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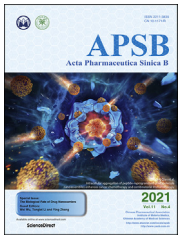

REVIEW

Biological drug and drug delivery-mediated immunotherapy

Qingqing Xiao[a,†], Xiaotong Li[a,†], Yi Li[a], Zhenfeng Wu[b], Chenjie Xu[c], Zhongjian Chen[d], Wei He[d,a,*]

[a]*School of Pharmacy, China Pharmaceutical University, Nanjing 210009, China*
[b]*Key Laboratory of Modern Preparation of TCM, Ministry of Education, Jiangxi University of Traditional Chinese Medicine, Nanchang 330004, China*
[c]*Department of Biomedical Engineering, City University of Hong Kong, Hong Kong 999077, China*
[d]*Shanghai Skin Disease Hospital, Tongji University School of Medicine, Shanghai 200443, China*

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Abbreviations: α1D-AR, α1D-adrenergic receptor; AAs, amino acids; ACT, adoptive T cell therapy; AHC, Chlamydia pneumonia; ALL, acute lymphoblastic leukemia; AP, ascorbyl palmitate; APCs, antigen-presenting cells; ApoA−I, apolipoprotein A−I; ApoB LPs, apolipoprotein-B-containing lipoproteins; AS, atherosclerosis; ASIT, antigen-specific immunotherapy; bDMARDs, biological DMARDs; BMPR-II, bone morphogenetic protein type II receptor; Bregs, regulatory B lymphocytes; CAR, chimeric antigen receptor; CCR9−CCL25, CC receptor 9−CC chemokine ligand 25; CD, Crohn's disease; CETP, cholesterol ester transfer protein; CpG ODNs, CpG oligodeoxynucleotides; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; CX3CL1, CXXXC-chemokine ligand 1; CXCL 16, CXC-chemokine ligand 16; CXCR 2, CXC-chemokine receptor 2; DAMPs, danger-associated molecular patterns; DCs, dendritic cells; DDS, drug delivery system; Dex, dexamethasone; DMARDs, disease-modifying antirheumatic drugs; DMPC, 1,2-dimyristoyl-sn-glycero-3-phosphatidylcholine; DSS, dextran sulfate sodium; ECs, endothelial cells; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EPR, enhanced permeability and retention effect; ET-1, endothelin-1; ETAR, endothelin-1 receptor type A; FAO, fatty acid oxidation; GM-CSF, granulocyte−macrophage colony-stimulating factor; HA, hyaluronic acid; HDL, high density lipoprotein; HER2, human epidermal growth factor-2; hsCRP, high-sensitivity C-reactive protein; IBD, inflammatory bowel diseases; ICOS, inducible co-stimulator; ICP, immune checkpoint; IFN, interferon; IL, interleukin; IT-hydrogel, inflammation-targeting hydrogel; JAK, Janus kinase; LAG-3, lymphocyte-activation gene 3; LDL, low density lipoprotein; LPS, lipopolysaccharide; LTB4, leukotriene B4; mAbs, monoclonal antibodies; MCP-1, monocyte chemotactic protein-1; MCT, monocrotaline; MDSC, myeloid-derived suppressor cell; MHCs, major histocompatibility complexes; MHPC, 1-myristoyl-2-hydroxy-sn-glycero-phosphocholine; MIF, migration inhibitory factor; MM, multiple myeloma; MMP, matrix metalloproteinase; mPAP, mean pulmonary artery pressure; MOF, metal−organic framework; MPO, myeloperoxidase; MSCs, mesenchymal stem cells; nCmP, nanocomposite microparticle; NF-κB, nuclear factor κ-B; NK, natural killer; NPs, nanoparticles; NSAIDs, nonsteroidal anti-inflammatory drugs; PAECs, pulmonary artery endothelial cells; PAH, pulmonary arterial hypertension; PASMCs, pulmonary arterial smooth muscle cells; PBMCs, peripheral blood mononuclear cells; PCSK9, proprotein convertase subtilisin kexin type 9; PD-1, programmed death protein-1; PD-L1, programmed cell death-ligand 1; PLGA, poly lactic-*co*-glycolic acid; RA, rheumatoid arthritis; rHDL, recombinant HDL; rhTNFRFc, recombinant human TNF-α receptor II-IgG Fc fusion protein; ROS, reactive oxygen species; scFv, single-chain variable fragment; SLE, systemic lupus erythematosus; SMCs, smooth muscle cells; Src, sarcoma gene; SHP-2, Src homology 2 domain−containing tyrosine phosphatase 2; TCR, T cell receptor; Teff, effector T cell; TGF-β, transforming growth factor β; Th17, T helper 17; TILs, tumor-infiltrating lymphocytes; TIM-3, T-cell immunoglobulin mucin 3; TLR, Toll-like receptor; TNF, tumor necrosis factor; T_{ph}, T peripheral helper; TRAF6, tumor necrosis factor receptor-associated factor 6; Tregs, regulatory T cells; UC, ulcerative colitis; VEC, vascular endothelial cadherin; VEGF, vascular endothelial growth factor; VISTA, V-domain immunoglobulin-containing suppressor of T-cell activation; YCs, yeast-derived microcapsules.

*Corresponding author.
E-mail address: weihe@cpu.edu.cn (Wei He).
†These authors made equal contributions to this work.

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KEY WORDS

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Drug delivery

Abstract The initiation and development of major inflammatory diseases, *i.e.*, cancer, vascular inflammation, and some autoimmune diseases are closely linked to the immune system. Biologics-based immunotherapy is exerting a critical role against these diseases, whereas the usage of the immunomodulators is always limited by various factors such as susceptibility to digestion by enzymes *in vivo*, poor penetration across biological barriers, and rapid clearance by the reticuloendothelial system. Drug delivery strategies are potent to promote their delivery. Herein, we reviewed the potential targets for immunotherapy against the major inflammatory diseases, discussed the biologics and drug delivery systems involved in the immunotherapy, particularly highlighted the approved therapy tactics, and finally offer perspectives in this field.

1. Introduction

Inflammatory diseases including cardiovascular diseases, cancer, allergies, autoimmune, and neuropsychiatric diseases commonly feature dysregulation of immune response[1]. For instance, atherosclerosis (AS) starting with dysfunctional alternation in the endothelium demonstrates increased recruitments of immune cells encompassing lymphocytes, antigen-presenting cells (APCs) and monocytes/macrophages[2]. Immunotherapy refers to disease treatment through activating or inhibiting the immune system. Unlike traditional treatments, the immunotherapy exerts therapeutic efficacy through modifying the endogenous immune response, or reversing the immunosuppression conditions of diseases[3], always characterized by changed infiltration of immune cells and modified expression of immune factors at the allergen[4]. Immunotherapy possesses significant advantages over traditional treatment regimes, such as higher efficacy against disease with fewer off-target effects and more durable response. Increasing evidence demonstrates immunotherapy is potent to treat malignant diseases, and cancer immunotherapy is becoming widely accepted in the clinic[5]. Furthermore, immunotherapy has promising potential to treat other inflammatory disorders, *e.g.*, AS[6], rheumatoid arthritis (RA)[7], intestinal inflammation[8], and pulmonary arterial hypertension (PAH)[9].

To target the pathogenesis of diseases, innate or adaptive immune system[10,11], numerous biological drugs were approved, including anti-tumor necrosis factor (anti-TNF) agents (etanercept, adalimumab, infliximab)[12], immune checkpoint (ICP) blockers (ipilimumab, tremelimumab, pembrolizumab)[13], and interleukin (IL)-family agonists (nivolumab) or antagonists (tocilizumab)[14,15]. The approved immunotherapy is present in Table 1[16−24]. However, the use of immunotherapies is always limited by several factors. For instance, repeated administration of the immunomodulators at high dose is always required and, as a result, may induce a series of autoimmune-mediated side effects[25], such as flu-like reactions, and vascular leak syndrome[26], and show a significant individual variation. Furthermore, most immunomodulators belong to biological drugs separated from or manufactured by biological systems and always are characterized by increased size, low stability, poor penetration into the diseased site and limited ability to cross cell membrane. Drug delivery using carriers including liposomes, hydrogels, living cells, microspheres, inorganic materials, polymeric micelles, drug crystals, and protein vehicles is robust to improve the treatment efficacy of biological drugs[27−32], owing to the advantages including extended blooded circulation, improved accumulation, promoted penetration in diseased tissues, increased uptake, and high drug-loading ability, large surface areas, and easy decoration of physicochemical properties[1,27,33−36]. Especially, more than 65 nanoscale drug delivery systems (DDSs) were marked for commercial use. In this review, we summarize the immunotherapy implications in major inflammatory diseases, highlight the biopharmaceuticals and DDS utilized to improve the delivery of immunomodulators, and finally provide perspectives in this field.

2. Cancer immunotherapy

2.1. Potential targets for cancer immunotherapy

Immunotherapy of cancer is attracting huge attention for its remarkable success in the clinic. *Via* targeting the immune system and overcoming the acquired drug resistance, the immunologically "cold" tumors lacking immune infiltrate can be converted into "hot" tumors having dense T cell infiltrate through efficient approaches[37], exhibiting as mobilization of the immune cells and eliminating the cancer cells[10]. In general, the immune response could be prompted by modulating the production of immune factors and ICPs and motivating the immune cells (Fig. 1).

2.1.1. Cytokines and vaccines

Cytokines are potent to modulate the immune system. Three main types of cytokine are involved in cancer immunotherapy, including ILs such as IL-2, IL-12, IL-15, and IL-21, interferons (IFNs), and granulocyte−macrophage colony-stimulating factor (GM-CSF)[38]. The recombinant cytokine IFNα is the first approved for clinical use in 1986[39], followed by recombinant IL-2[40]. However, a high dose of cytokines was required for effective treatment efficacy, and frequently leads to a series of unwanted effects, *e.g.*, capillary-leak syndrome and cytokine-release syndrome[41]. The combined use of cytokines with checkpoint inhibitors or anticancer monoclonal antibodies (mAbs) might improve anti-tumor efficacy[42].

Therapeutic cancer vaccines whose activities closely rely on cytotoxic T cells combat the disease *via* abolishing cancer cells or abnormal cells[43]. The cancer vaccines are divided into four classes: peptide vaccines, cell-based vaccines, viral vector vaccines, and nucleic acid vaccines[44]. APCs, especially dendritic cells (DCs), are essential to the vaccination because they are

Table 1 Approved immunotherapy for clinical use.

Approved therapy	Active agent	Administration route	Manufacturer	Trade name	Therapy implication	Approved year	Ref.
mAbs	Abciximab	IV injection	Johnson & Johnson/Lilly	ReoPro®	Cardiovascular disease	1994	16
	Rituximab	IV injection	Genentech Inc.	Rituxan®	NHL, RA	1997	16
	Infliximab	IV injection	Johnson & Johnson	Remicade®	CRD, RA	1998	16
	Trastuzumab	IV injection	Genentech Inc.	Herceptin®	Breast cancer	1998	16
	Etanercept	SC injection	Amgen	Enbrel®	RA	1998	16
	Gemtuzumab ozogamicin	IV injection	Wyeth	Mylotarg®	Leukemia	2000	16
	Alemtuzumab	IV injection	Genzyme	Campath -1H®	Leukemia	2001	16
	Adalimumab	SC injection	CAT, Abbott	Humira®	RA, CRD	2002	16
	Abatacept	IV infusion	BMS	Orencia®	RA	2005	16
	Panitumumab	IV infusion	Amgen	Vectibix®	Colorectal cancer	2006	16
	Golimumab	SC injection	Centocor/Johnson & Johnson	Simponi®	RA	2009	16
	Certolizumab pegol	SC injection	UCB Inc.	Cimzia®	RA	2009	16
	Ofatumumab	IV injection	Novartis	Arzerra®	MCD, RA	2009	16
	Ipilimumab	IV injection	Bristol-Myers Squibb	Yervoy	Metastatic melanoma	2011	17
	Mogamulizumab	IV injection	Kyowa Hakko Kirin	POTELIGEO®	ATL	2012	16
	Pertuzumab	IV injection	Genentech	Perjeta®	Breast cancer	2012	16
	Ziv-aflibercept	IV injection	Sanofi/Regeneron	ZALTRAP®	MCRC	2012	16
	Trastuzumab emtansine	IV injection	Roche/Genentech	Kadcyla®	Breast cancer	2013	16
	Obinutuzumab	IV injection	Genentech	Gazyva®	CLL	2013	16
	Pembrolizumab	IV injection	Merck Sharp & Dohme Corp.	KEYTRUDA®	advanced melanoma, HNSCC	2014, 2016	17,18
	Nivolumab	IV injection	Bristol-Myers Squibb	Opdivo®	NSCLC, HNSCC, renal cell carcinoma	2015, 2016	17,18
	Atezolizumab	IV injection	Genentech Inc	Tecentriq	NSCLC, Urothelial Carcinoma	2016	18
	Avelumab	IV injection	Pfizer/Merck KGaA (EMD Serono)/Dyax	Bavencio™	Merkel cell carcinoma	2017	16
	Durvalumab	IV injection	AstraZeneca UK Limited	Imfinzi	Urothelial carcinoma	2017	19
Adoptive cell therapy	CAR-T therapy	IV infusion	Novartis	Kymriah®	B cell ALL	2017	20
		IV infusion	Kite Pharma/Gilead Sciences	Yescarta	Large B cell lymphoma	2017	21
		IV infusion	Kite Pharma	Yescarta®	Relapsed or refractory large B-cell lymphoma	2017	22
Cytokine-or chemokine-based therapy	Tofacitinib	Oral	Pfizer	Xeljanz	RA	2012	23
	Ruxolitinib Phosphate	Oral	Incyte corp	JAKAFI	RA	2011	24
	Daclizumab	SC injection	Biogen	Zinbryta	Multiple sclerosis	2016	24
	Sarilumab	SC injection	Sanofi Synthelabo	Kevzara	RA	2017	21
	Ribociclib	Oral	Novartis	Kisqali	Breast cancer	2017	21
	Brigatinib	Oral	Ariad Pharmaceuticals/Takeda	Alunbrig	ALK-positive NSCLC	2017	21
	Neratinib	Oral	Puma Biotechnology	Nerlynx	HER2-overexpressed breast cancer	2017	21
	Copanlisib dihydrochloride	IV injection	Bayer	Aliqopa	Follicular lymphoma	2017	21
	Baricitinib	Oral	Eli Lilly	OLUMIANT	RA	2017	21
	Sarilumab	SC injection	Sanofi Synthelabo	KEVZARA	RA	2018	24
	Tofacitinib citrate	Oral	Pfizer	XELJANZ XR	RA	2019	24

ALL, acute lymphoblastic leukemia; ALK, anaplastic lymphoma kinase; ATL, adult T-cell leukemia/lymphoma; CLL, chronic lymphocytic leukemia; CRD, Crohn's disease; HNSCC, head and neck squamous cell carcinoma; MCD, multicentric Castleman's disease; MCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; NHL, non-hodgkin lymphoma; RA, rheumatoid arthritis; IV Injection, intravenous injection; SC Injection, subcutaneous injection; IV Infusion, intravenous infusion.

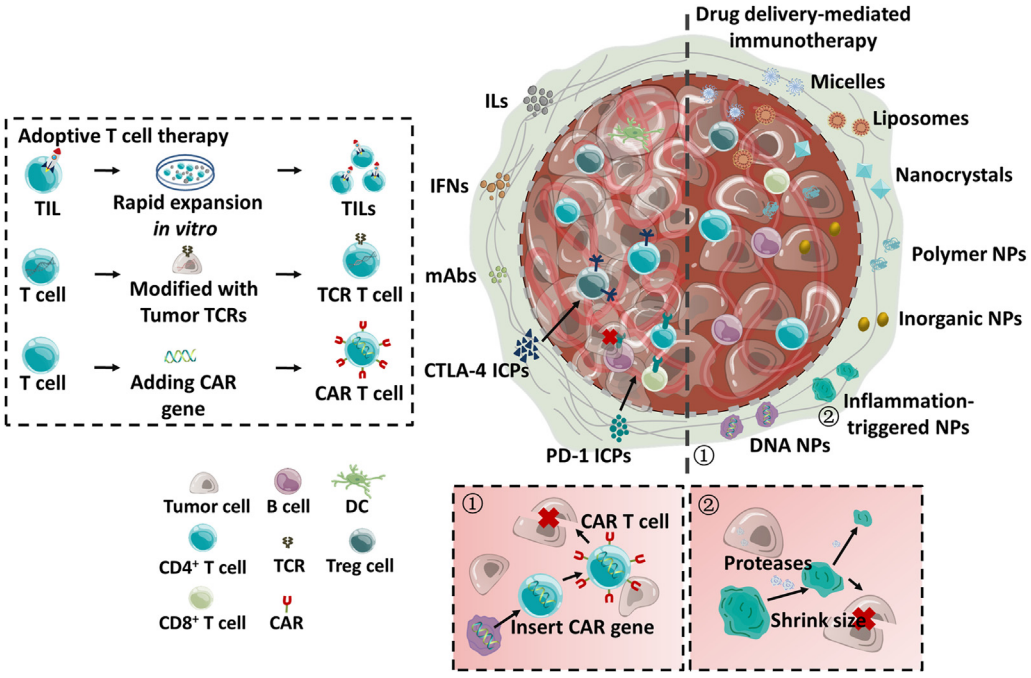

Figure 1 Immunotherapy for cancer and the used drug delivery systems (DDSs).

efficient to catch, refine, and present antigens to T cells[43]. Most reported cancer vaccines belong to the DC-based vaccines. Effective vaccine-elicited $CD8^+$ T cells should have properties as follows: (i) efficiently binding T-cell receptor, (ii) possessing robust T-cell affinity to the major histocompatibility complexes (MHCs) on cancer cells, (iii) producing a high level of granzymes and perforin (IV) potently recruiting T cells to site of tumor, and (V) modulating the release of costimulatory and inhibitory molecules[43]. Three cancer vaccines, Gardasil, Cervarix, and Sipuleucel-T were commercially marketed. However, the mutation of antigens is always unique to individuals and, therefore, compromises the treatment efficacy of the commonly used vaccine. The personalized vaccine is a potential route to overcome the shortage.

2.1.2. *mAb and ICP suppressors*

By targeting surface antigens differentially expressed on cancer cells, such as CD20, CD33, CD52, human epidermal growth factor-2 (HER2), vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), the antibody exerts cancer immunotherapy *via* means including the antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity[45]. mAbs represent the most frequently employed cancer immunotherapy in the clinic, and over 30 products were approved.

ICPs are regulators often expressed on lymphocytes and classified into inhibitors and stimulators, such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), programmed death protein-1 (PD-1), programmed cell death-ligand 1 (PD-L1), lymphocyte-activation gene-3 (LAG-3), OX40 (a potent costimulatory receptor), B7-H3 belonging to a member of B7 superfamily, 4-1BB categorized into a member of TNF receptor superfamily, V-domain immunoglobulin-containing suppressor of T-cell activation (VISTA), T-cell immunoglobulin mucin 3 (TIM-3), and inducible co-stimulator (ICOS)[46]. Several inhibitors of ICPs, *i.e.*, anti-PD-1, anti-PD-L1, and anti-CTLA-4, were approved for the clinical use[47,48]. Nonetheless, their application may be limited for acquired-resistance to monotherapy[49].

2.1.2.1. CTLA-4. T cells are activated *via* binding their surface CD28 with B7-1 (CD80) or B7-2 (CD86) on the APCs[50]. However, the CD28 homolog CTLA-4, possesses a significantly greater binding affinity toward B7[51] and, as a result, leads to blockade of T cell upregulation and activation. Anti-CTLA-4 acts through blocking the connection between B7 and CTLA-4. Human CTLA-4 antibodies, ipilimumab, was approved to treat advanced metastatic cancer; and while another CLTLA-4 blockade, tremelimumab, is under clinical trial. The long-lasting anti-tumor response always occurs after dosing, yet accompanying unwanted effects, such as enterocolitis, inflammatory hepatitis, and dermatitis; however, it was argued these toxicities could be discounted by using corticosteroids and whereas did not reduce the anti-tumor effects[52].

2.1.2.2. PD-1 and PD-L1. PD-1 is categorized into the CD28 superfamily as well, whereas PD-L1 and PD-L2 are classified as the B7 family. The expression of the PD-1 was found predominantly on three immune cells in the periphery, activated $CD8^+$ and $CD4^+$ T cells and B cells[53]. The binding with the ligand, PD-L1 or PD-L2, allow PD-1 to recruit the sarcoma gene (Src) homology 2 domain-containing tyrosine phosphatase 2 (SHP-2) and inhibit the T-cell activities[54], *e.g.*, T-cell expansion and effector functions including release of IFN-γ and cytotoxicity[55]. It should be noteworthy that PD-1 mainly reduce effector T-cell functions at the later-phase of immune reaction while CTLA-4 engages at the early stage[56].

By targeting the PD-1, PD-L1, or PD-1PD-L1 axis, numerous mAbs were fabricated, including nivolumab, pembrolizumab,

tislelizumab, camrelizumab and sintilimab, durvalumab, avelumab, and atezolizumab[57]. Nivolumab (Opdivo®) and pembrolizumab (Keytruda®) have been commercially marked.

Blockades of CTLA-4 or PD-1-based signaling are effective to combat cancer, however, monotherapy may induce adverse effects occasionally probably due to the individual variations[25,58]. Combinatorial treatment, *e.g.*, anti-CTLA-4 plus anti-PD-1 and PD-1 plus PD-L1 antibodies, provides the potential to eliminate or alleviate the side effects.

2.1.3. *Adoptive T cell therapy (ACT)*

ACT refers to the transfer of isolated T cells from the patient that are genetically engineered *in vitro* to the same patient[59], including tumor-infiltrating lymphocytes (TILs), T cell receptor (TCR) T cells, and chimeric antigen receptor (CAR) T cells[60] (Fig. 1). The FDA has approved CAR therapy for adult patients with leukemia and lymphoma.

For TIL therapy, the TILs are extracted from the separated tumors, sorted with endogenous TCRs, purified, and ultimately undergo a rapid expansion protocol *in vitro* using with IL-2 and CD3 antibody[61]. For TCR therapy, TCR composed of an α- and a β-chains is anchored on T cells through noncovalently binding with CD3 complex. T cells become cytotoxic T cells when the anchored TCR is recognized and binds with the MHC on APCs or tumor cells[60]. Rapoport et al.[62] developed NY-ESO-1/LAGE-1 TCR-engineered T cells to treat multiple myeloma (MM). The engineered T cells were infused into twenty patients with MM at a cell number of 2.4×10^9 two days after dosing autologous stem cell[62]. The results indicated that the engineered T cells could proliferate, move to the marrow, and kill the cancer cells selectively, with clinical response of up to 80% and median survival of 19.1 months[62].

To overcome the limitations of TCR therapy, *e.g.*, the requirement of MHC expression, MHC identity, and costimulation, CAR therapy was developed *via* adding CAR genes on T cells comprised of an extracellular single-chain variable fragment (scFv), a transmembrane spacer, and intracellular signaling/activation domain(s)[63].

ACT therapy has demonstrated its success in the treatment of cancers and several products were approved for clinical use. However, increasing limitations of the therapy are revealed as well, *i.e.*, on-target/off-tumor toxicity, cytokine-release syndrome, neurologic toxicities, off-targeting reactivity, complicated fabrication, extremely high cost, etc.[64–66].

2.2. *Drug delivery-mediated cancer immunotherapy*

To promote the immune response toward cancer, repeated administration of immunomodulators at a high dose is always required because most immunostimulants are unstable in physiological conditions, have the poor tumor-targeting ability, and can't translocate the plasma membrane, etc.[27]. Such a dosing approach frequently induces side effects and compromises the patient's compliance. As a result, dosing the immunomodulators in a controllable and safe way is highly expected. Drug carriers, *e.g.*, liposomes[67] and dendrimers[68], are effective to improve the delivery due to their well-known advantages (Fig. 1). Numerous drug carriers were reported to improve the efficacy of immunotherapeutic agents such as T cell activators, ICP inhibitors, and cytokines[69], *via* increasing their circulation time[70] and targetability to immune cells[71]. Several reviews summarized the use of a drug delivery strategy to improve cancer immunotherapy[69,72–75]. The most commonly used carriers include polymer nanoparticles (NPs), inorganic NPs, and lipid-based NPs[72,76,77]. Recently, to lower the cost and facilitate the expansion of T lymphocytes for CAR therapy without complicated procedures, Smith et al.[78] developed plasmid DNA-loaded polymeric nanocarriers decorated with T-cell-targeting anti-CD3e f(ab')2 fragments to deliver leukemia-specific CAR genes into host T cells *in situ.* They found that the 155-nm NPs were able to rapidly and selectively program circulating T cells *in vivo* and demonstrated improved leukemia regression over the treatment with conventional CAR therapy[78]. This work represents a new use of the DDS aiming to reduce the cost of ACT and avoid complications of clinical-scale manufacturing. Furthermore, changing the basic properties of NPs, *e.g.*, diameter, shape and surface charge, are potent to modulate the immunotherapy[73]. For instance, smaller NPs (<50 nm) have enhanced ability to elicit the immune activities over the large NPs (>100 nm) because the smaller ones tend to traffic to lymph nodes *via* DCs, whereas the larger ones are difficult to move once accumulating at the diseased site[72]. The NPs with a diameter of over 500 nm can target macrophages and are internalized *via* phagocytosis[74].

Another significant advantage of using drug carriers is the efficiency to facilitate the combinational therapy. The durable immune response is only indicated in limited cancer types when an immunostimulant is used alone. Such that immunomodulator and other anti-tumor inhibitors are always combined for use in the clinic; however, their active targets are spatio-temporarily discrepant and, as a result, often leads to sub-optimized treatment efficacy. Drug carriers have a remarkable potential to deliver the agents to their respective active sites precisely by co-delivery approach or physicochemical triggering means. For example, by using nanoclews based on long-chain single-strand DNA as a carrier that could be enzymatically degraded in inflammation conditions, CpG oligodeoxynucleotides (CpG ODNs) and anti-PD-1 antibody were released in a sustained pattern[79]. The results demonstrated that the codelivery system synergistically induced long-lasting anti-tumor T lymphocyte responses in a melanoma model[79].

The nanocarriers demonstrated their promising potential to promote the treatment efficacy of cancer immunotherapy. Nonetheless, few of them are translated, mainly owing to the poor reproducibility and scalability, unpredictable toxicity *in vivo*, etc[80]. Several techniques such as bubble blown assembly, capillary-force-assisted assembly, electric-field-assisted assembly, and Langmuir–Blodgett assembly were developed to scale up the nanomaterials[81]. Yet, it is difficult to acquire a commonly used approach to fabricate the devices since they always have their unique features. Furthermore, many studies for cancer immunotherapy was performed on the mouse models while there are huge discrepancy between the animal and human immune systems, the efficacy appeared on mouse may have poor correlation with human patients[82].

3. Immunotherapy for autoimmune disease therapy

Autoimmune diseases encompassing RA, multiple sclerosis, inflammatory bowel diseases (IBD), mainly results from dysregulation of the T cell checkpoint pathways[83]. Especially, the helper T

cells have profound effect on the progression of these diseases, since they often affect the function of other immune cells, *e.g.*, regulatory T cells (Tregs), monocytes and macrophages[84].

3.1. RA

RA is a chronic inflammation and frequently demonstrates damage of both articular cartilage and bone[85]. The exact pathological mechanism of RA is unclear, but it is well accepted that RA is closely linked to the breakdown of immune tolerance[86]. The immunotherapy by modulating the differentiation of lymphocytes and secretion of cytokines may combat RA (Fig. 2).

3.1.1. Implications for immunotherapy in RA

3.1.1.1. Regulation of lymphocytes. Four lymphocyte subpopulations, Tregs, T helper 17 (Th17) cells, and regulatory B lymphocytes (Bregs), affect the process of RA[87]. Furthermore, Lamas et al.[88] discovered that the activation extends of peripheral blood mononuclear cells (PBMCs) and the disease activity allowed for immunomodulatory effect of bone marrow-derived mesenchymal stem cells (MSCs) on T-cell activation. Accordingly, the immunotherapy should concentrate on the modulation of these lymphocytes.

A deficit of Tregs was demonstrated to promote the RA development and increasing proliferation of Tregs *via* anti-TNF treatment benefits to the suppression of RA[89]. Consequently, the activation of Tregs is the potential to ameliorate RA. These activators include IL-2[90], T cell superagonists (CD28SAs), and non-depleting anti-CD4 mAbs[91]. Second, the subsets of B cells, *i.e.*, Bregs[92], memory B cells ($CD24^{hi}CD27^{+}$ phenotype)[93], and $B10^{+}$ cells[94], are potential targets to treat RA due to increased secretion of IL-10[92], improved proliferating of Tregs[94], or reduced expansion of Th1, Th17, $TNF\alpha^{+}$ T cells[95]. However, it was reported that, in patients with RA, the $CD24^{hi}CD27^{+}$ and the $CD24^{hi}CD38^{hi}$ B cells may not enhance the Treg's proliferation or decrease Th1 and $TNF\alpha^{+}$ T cells although the abundance of the two sets is similar to that in the healthy[96]. In this situation, the adoptive transfer of Bregs has the potential to alleviate the symptoms of the disease[97]. Besides, the synovial macrophages advance the process of RA *via* the secreting IL-6 and TNF-α and the resultant damage of the joint[1].

Overall, *via* reeducating or depleting the autoreactive cells, the process of RA can be inhibited *via* inducing immune tolerance to self-antigens[98]. The antigen-specific immunotherapy (ASIT) using peptides, antibodies, vaccines, etc. is extensively employed to target the autoreactive cells, *i.e.*, T and B cells and DCs[98]. Recently, a pcDNA-CCOL2A1 DNA vaccine was developed to treat collagen-induced RA[99]. The administration *via* intramuscular injection at 300 μg/kg pcDNA-CCOL2A1 enabled decreased percentages of $CD4^{+}CD29^{+}$ and transferred Th1 to Th2 and Tc1 to Tc2, along with the reduced level of Th1 cytokines and downregulation of proinflammatory modulators IL-10 and transforming growth factor β (TGF-β) derived from Th2 and Th3, respectively[99].

3.1.1.2. Cytokines and chemokines. Cytokines and chemokines have a robust ability to regulate intercellular interactions, cell activation, localization, and phenotype in the lymphoid environment[100]. The cytokines, in particular TNF and IL-6[101], IL family, and GM-CSF[101], promote the process of RA[102].

TNF, a multifunctional cytokine, often exacerbates inflammation *via* increasing T-cell proliferation and differentiation

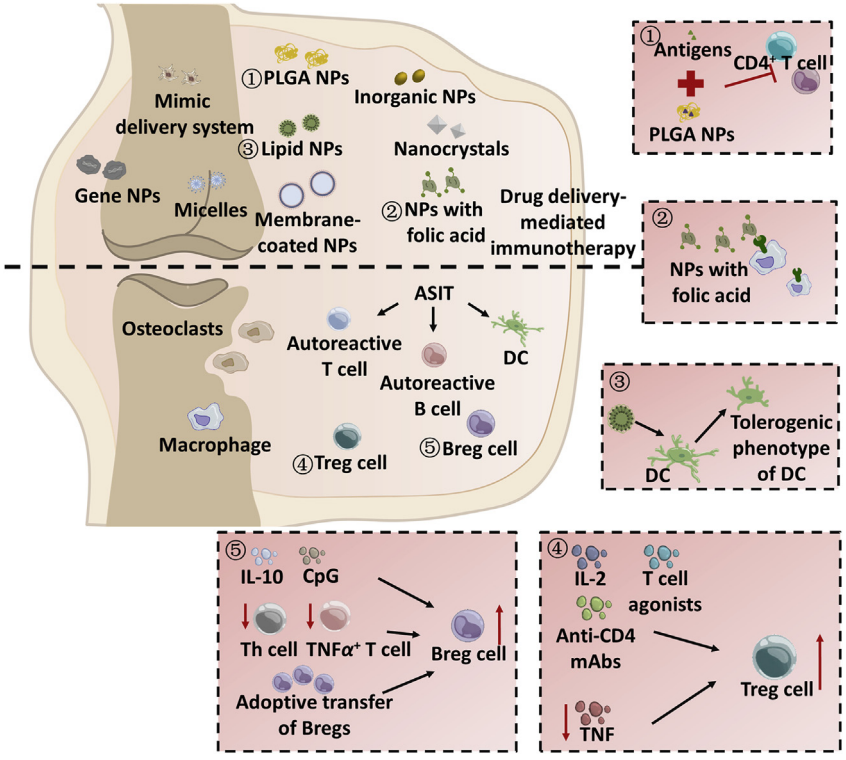

Figure 2 Immunotherapy for rheumatoid arthritis (RA) and the used DDSs.

at various stages[103], *i.e.*, single positive thymocytes and CD3/CD4/CD8 (triple-negative) T cells[104], and activating the immune system *via* the control of secondary lymphoid organs structures[103]. Anti-TNF-α treatment is potent to treat RA *via* increasing Treg proportion and suppressing effector T cell (T_{eff})[105], affecting T peripheral helper (T_{ph}) cells that may prevent the differentiation of plasma-blasts[106], decreasing activated B cells, and expanding regulatory B10 cells[107].

IL-6, an activator of B and T cells, facilitates the differentiation of B cells into lg-producing plasmablasts, directs the expansion of antigen inexperienced $CD4^+$ T cells, as a consequence, promotes the transition of innate immunity to adaptive immunity[108]. IL-6 inhibitors, such as IL-6 mAbs and miRNA targeting IL-6[108], toll-like receptor (TLR) 4 inhibitor[109], demonstrated promising inhibition of RA[109]. In particular, the IL-6 mAbs exhibited outstanding efficacy against RA[108].

So far, some mAbs capable of neutralizing TNF-α have been approved for the clinical use, including etanercept, infliximab, certolizumab pegol, golimumab, adalimumab, and other blockers such as mAbs IL-6 (tocilizumab) and IL-1R (anakinra)[110]. The turbulence of immune cells, and the immune response is closely linked to RA progression. Consequently, the regulation of immune cells or immune response is promising to alleviate RA. However, individual treatment should not be ignored, since the gene expression and sensitivities are differentiated among person to person.

3.1.1.3. Janus kinase (JAK) inhibitors. The JAK pathway also links to the development of diverse immune-dependent disorders, *e.g.*, RA and IBD, by promoting the signal transduction of immunostimulators[111]. The JAK, mainly composed of JAK1, JAK2, JAK3, and TYK2, acts through the receptors of type I and II. Type-I receptor generally associates with ILs, hormones and colony-stimulating factors, whereas Type-II receptor binds with IL-10-family cytokines including IL-10, IL-19, IL-20, IL-22 and IL-26[112] and IFNs. Two inhibitors of JAK, tofacitinib and baricitinib, were marked in 2018 and 2012, respectively, to treat RA[113].

3.1.2. Drug delivery-mediated immunotherapy in RA

The used drugs against RA mainly consist of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biological DMARDs (bDMARDs), and are always dosed *via* oral delivery or injection. Various DDSs were adopted to improve the delivery of modulators to the immune cells, *e.g.*, lipid-based NPs[114–116], polymeric NPs[117,118], hydrogels[119], gold NPs[120], pH-sensitive NPs[118], and biological membrane-coated NPs[121–123]. Surface modification with ligands or peptide modification allows for improved targeting-ability to immune cells[124], and cytokines and chemokines pathways, such as nuclear factor κ-B (NF-κB), ERK signal pathway, IL related pathway, etc[91]. Nonetheless, the most frequently reported ligand is folate receptor β that is overexpressed on the activated macrophages[125].

Liposomes or liposome-like NPs are the most widely used DDS for RA treatment due to their excellent encapsulation-ability and biocompatibility[126]. Recently, lipidoid-polymer hybrid NPs were designed to deliver siRNA against IL-1β to the activated macrophages to inhibit the pathogenesis of RA induced by collagen antibody[115]. Dosing *via* intravenous injection of the NPs enabled the efficient delivery of siRNA to macrophages inhibiting in the arthritic joints, downregulation of inflammation-induced modulators in the joints, and a significant reduction in the cartilage destruction, swelling of ankle and bone damage[115]. Furthermore, such DDS facilitates codelivery for combined therapy. For instance, hybrid-NPs consisted of calcium phosphate/liposomes were developed to deliver methotrexate and NF-κB-specific siRNA to the lipopolysaccharide (LPS)-activated macrophages at the diseased site[127]. Egg phosphatidylcholine liposomes were used to co-load an antigen, OVA or methylated BSA, and a water-insoluble inhibitor of NF-κB, curcumin or quercetin, and targeted APCs[116], demonstrating as suppressing the response of the cells to proinflammatory pathway and promoting the proliferation of Ag-specific $Foxp3^+$ Tregs[116].

Biological membrane from living cells, *e.g.*, red blood cells, platelet, neutrophils, and macrophages, is always rich in various biomarkers and receptors; and as a result, its coating is able to alter the biological properties of DDSs and elevate their cell-targeting ability[121]. Motivated by the association of platelet with RA, platelet-like NPs were fabricated to deliver the anti-inflammatory tacrolimus to the joints of a collagen-induced arthritis[122]. Through GVPI recognition and P-selectin, these NPs allowed for efficient drug accumulation in the joint and inhibited RA's development[122]. Interestingly, drug-free neutrophil membrane-coated poly lactic-*co*-glycolic acid (PLGA) based NPs were developed recently[123]. *Via* neutralizing the inflammation-induced TNF-α and IL-1β, these neutrophil-NPs exhibited synovial inflammation, robust chondroprotection against joint damage, and enhanced penetration into the cartilage matrix[123]. Furthermore, their anti-RA effectiveness in both human-transgenic arthritic model and collagen-induced model is comparable to that from the treatment with anti-TNF-α or anti-IL-1β[123]. These biomimetic-targeting DDSs, due to their natural targeting-ability to the inflamed sites, represent a promising approach against RA and may have the potential of clinical translation because of the simple preparation process. Nevertheless, their translation is still limited by the scalability of DDS.

3.2. Intestinal inflammation

3.2.1. Potential targets for IBD immunotherapy

IBD is always characterized by long-lasting inflammation and divided into ulcerative colitis (UC) and Crohn's disease (CD). The IBD pathogenesis has not been illustrated fully, however, is often characterized by an imbalance between the mucosal immune system and the commensal ecosystem[128]. The regulatory immune cells including intestinal intraepithelial lymphocytes, T and B cells, macrophages, DCs and innate lymphoid cells could affect the progression of IBD[129]. DCs contribute the maintaining of immune environment homeostasis in the intestine *via* connecting humoral and cellular immune response. Especially, Tregs play a critical role in limiting the populations of Teffs and innate inflammatory signaling[130]. Antigen-specific T-helper cells and natural killer (NK) cells contribute to inflammation in IBD as well and their influx can be used as a potential treatment target[131]. In addition, agitations in intestinal epithelial cells, in particular Paneth cells, may initiate intestinal inflammation[131]. The therapy strategies toward IBD are classified into anti-inflammatory treatment with mesalazine and glucocorticoids, antibiotics therapy using ciprofloxacin and metronidazole, gene therapy, and immunotherapy with immunosuppressants and anti-TNF agents[8]. The immunotherapy is acquired through interfering with IL-12/23 axis, JAK and TGF-β/Smad 7 pathways, and modulating IL-6, IL-13, chemokines and chemokine receptors CC receptor 9–CC

chemokine ligand 25 (CCR9−CCL25)[132], and cell adhesion and leukocyte recruitment[133]. The IBD immunotherapy can also be achieved by using adoptive cell transfer, such as MSCs and engineered Tregs[8]. Previous reviews summarized the use of biological drugs for IBD immunotherapy[133,134]. Currently, about seven mAbs were approved for IBD immunotherapy, including ustekinumab, natalizumab, infliximab, vedolizumab, golimumab, certolizumab pegol and adalimumab. The implication of immunotherapy for IBD is illustrated in Fig. 3.

3.2.2. *Drug delivery-mediated immunotherapy in IBD*

The mAbs are effective to treat IBD; however, the response rate to initial treatment is only 50% and their use is always limited by systematic side-effects including immunogenicity, the induction of anti-drug antibodies, serum sickness, etc., induced by administration *via* intravenous injection[135]. DDS-mediated therapy may elevate treatment outcomes and reduce systemic toxicity. A previous review summarized various approaches and devices for targeting treatment of IBD using DDS, encompassing meanings of ligand-receptor-, charge-, degradation-, size- and microbiome-mediation[136]. Another review discussed intestine targeting strategies, *e.g.*, conventional DDS-mediated treatment, disease-mediated delivery of active agents by synthetic and biological DDS[137]. Given that oral administration is a well-accepted delivery route for both patients and physicians[138], herein we mainly discuss targeted oral delivery of immunomodulators to the inflamed sites in the large intestine. The site-specific DDSs are often designed according to (i) the physiological changes in the gastrointestinal tract such as pH, microflora, transit time, pressure, and osmotic potential[139,140] or (ii) disease-induced alterations, *i.e.*, increased permeability, changes in tight junctions and mucus composition and amount, reduced antimicrobial secretions and numbers of secretory cells and loss of the area of ulcerated epithelium[141−145]. The recently reported DDSs include hydrogel platform[146−149], redox- and pH-sensitive NPs[150−155], hyaluronic-based NPs[148,156,157], macrophage-targeted DDSs[1,156,158−160], polyphenol-based delivery[161,162], etc.

Recently, an oral inflammation-targeting hydrogel (IT-hydrogel) assembled from ascorbyl palmitate (AP) was developed to treat IBD[149]. IT-hydrogel microfibers encapsulating corticosteroid dexamethasone (Dex) could adhere to the inflamed mucosa from animal and human colon and exhibited increased drug release at the inflammation site due to the degradation by the enzymes secreted from active-macrophages and other immune cells. In clitic ulcerative mice administrated *via* a single enema with free Dex as control, dosing with the drug-loaded IT-hydrogel enabled significant reduction of colon weight, myeloperoxidase (MPO) activity, and expression of TNF in the distal colon, and lowered the systemic drug exposure[149]. Another reactive oxygen species (ROS) responsive assembles prepared from HA-bilirubin conjugate were fabricated to combat dextran sulfate sodium (DSS)-induced acute colitis[156]. *In vitro*, the assembles dissociated rapidly after exposure to ROS, were well taken up by macrophages and granulocytes due to the hyaluronic acid (HA)-CD44 affinity, polarized pro-inflammatory M1 macrophages into the M2 phenotype. *In vivo*, in contrast with treatment with clinically used drugs, the treatment had remarkably boosted efficiency to combat DSS-induced acute colitis *via* decreasing the impairment of colon and MPO activity, recovering the body weight, and keeping the length of colon[156]. In addition, the treatment markedly reduced the infiltration of pro-inflammatory phenotypes, $CD11b^{+}Ly6C^{+}Ly6G^{+}$ neutrophils and $CD11b^{+}Ly6C^{+}Ly6G^{-}$ monocytes, in the layer of lamina propria in DSS-induced model, and increased the accumulation of anti-inflammatory phenotypes including $CD3^{+}CD4^{+}Foxp3^{+}$ Tregs, $MHCII^{+}CD11c^{+}CD11b^{-}$ DCs and $CD11b^{+}Ly6C^{-}Ly6G\text{-}MHCII^{+}$ tissue-resident macrophages[156]. Overall, increasing oral DDSs against IBD is emerging, such as polymer-drug prodrug formulations[152,163],microspheric vehicles to suppress TNF-α[154,164], thermoreversible mucoadhesive polymer-drug dispersion with prolonged retention at the inflamed site[165], and biomimetic NPs, *i.e.*, cell membrane-coated NPs and liposomes engineered with cell membrane proteins[166]. These oral inflammation-targeting DDSs represent a promising strategy to treat IBD, owing to their scalability, biocompatibility, and potent therapeutic efficacy.

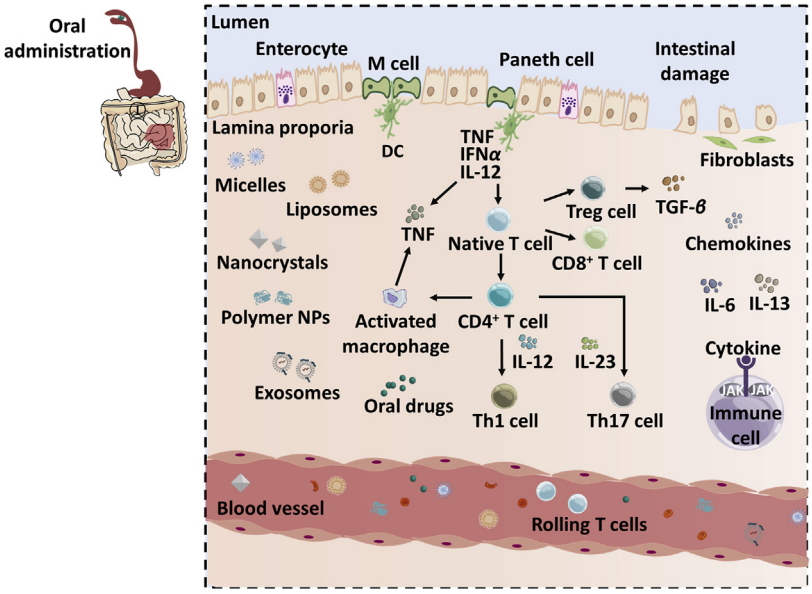

Figure 3 Immunotherapy for inflammatory bowel diseases (IBD) and the used DDSs.

Numerous DDSs were designed to treat IBD *via* targeting macrophages[167,168], whereas exosomes isolated from the TGF-β1 gene-modified DCs was demonstrated to inhibit the progression of IBD *via* eliciting immunosuppression[169]. The 50−100-nm exosomes can efficiently block the advance of DSS-triggered IBD *via* inducing Tregs through the TGF-β1 pathway and reducing the Th17 in the inflammatory site, mesentery lymph nodes[169].

4. Immunotherapy for vascular disease

4.1. AS

In AS, the immune cells encompassing monocytes, T cells, DCs, neutrophils, NK cells and innate lymphoid cells are recruited to these sites[170−173], due to the elicited local inflammation by apolipoprotein-B-containing lipoproteins (ApoB LPs) that deposit in the artery wall and are liable to modification by oxidation, enzymes and aggregation[174]. The recruited monocytes constantly differentiate into macrophages, a major cell population in the atherosclerotic plaques, and finally become cholesterol-loaded macrophage foam cells, facilitating the plaque formation[175,176]. Whereas the factors, *e.g.*, pro-inflammatory modulators, cholesterol crystals, oxidative stress, oxidized lipids, and danger-associated molecular patterns (DAMPs) predominantly stemmed from the macrophage foam cells, construct a complicated micro-environment that maintains the local inflammation[177]. A previous review highlighted the role of macrophages in AS development[1]. Here, we mainly focus on other immune cells involved in AS and related treatment approaches.

4.1.1. Implications for AS immunotherapy

According to the pathological mechanism of AS, the treatment with anti-hypertensive or cholesterol-lowering drugs is far from to cure AS. Several experimental results demonstrated the essential roles of immune activation in the AS development[178,179]. Always, the innate response to AS mediated by stimulating macrophages and endothelial cells (ECs) in the walls of the coronary arteries allows for adaptive immune reactions to the antigens presented to Teff by APCs, *i.e.*, DCs[180]. As a result, targeting inflammation to modulate immune responses against plaque antigens may treat AS fundamentally. The potential targets and used DDSs are displayed in Fig. 4.

4.1.1.1. Cytokine-based therapy. Two types of cytokines are involved in AS progression, pro-atherogenic and anti-atherogenic cytokines[181]. Pro-atherogenic cytokines always promote the development of AS, including various ILs such as IL-4, IL-6, IL-8, IL-12, IL-15, IL-18, IL-20, IL-21, IL-23 and IL-32, GM-CSF, TNF-α, monocyte chemotactic protein-1 (MCP-1), IFN-α, β, and γ, etc. Whereas the anti-atherogenic ones can inhibit AS development, such as IL-5, IL-10, IL-13, IL-19, IL-27, IL-33, IL-35, IL-37, TGF-β, etc[181]. In general, cytokine-based treatment drugs are mainly categorized into broad-based immunomodulatory agents, blockade of pro-inflammatory cytokines and activators to induce anti-inflammatory cytokines[182]. Clinical trials uncovered the administration of Canakinumab, a mAb targeting IL-1β, at 150-mg dose every 3 months reduced the inflammation and rate of cardiovascular events, though, did not lower the lipid-level[183]. Another clinical test demonstrated that dosing Canakinumab with the same regimen allowed for decreased levels of IL-6 and inflammatory biomarker high-sensitivity C-reactive protein (hsCRP), an indicator that the mAb works *via* inhibiting the IL-1β−IL-6 signaling of innate immunity[184]. Accordingly, pro-inflammatory cytokines can be effective targets for AS therapy and IL-1β−IL-6−CRP signaling axis is a credible AS-associated inflammatory pathway[185].

4.1.1.2. ICPs. Due to a surplus of ICPs, *e.g.*, CD27, CD28, CTLA-4, CD40, CD40L, CD70, CD80/86, Ox40, Ox40 L, PD-1, PD-L1/2, the costimulatory molecules derived from T cells, CD30 and CD137L, can be induced and facilitate atherogenesis[186]. For instance, blocking the CD80/86−CD28 axis alleviates the symptoms of AS that have occurred or are about to occur in both mice and humans[187−189]. In addition, the dyad CD40L−CD40 is closely associated with plaque's vulnerability and formation[190−193]. Treatment with anti-CD40L or CD40 allowed for plaque suppression[191].

4.1.1.3. Chemokines. Over 20 chemokines produced mainly from ECs, smooth muscle cells (SMCs), leukocytes[194] and their receptors are involved in AS progression[195]. The chemokines, CCL5, CCL2, CXC-chemokine receptor 2 (CXCR 2) and CXCR3 and their ligands, CXXXC-chemokine ligand 1 (CX3CL1) and CXC-chemokine ligand 16 (CXCL16), CXCL12/CXCR4 axis, and macrophage migration inhibitory factor (MIF), are linked to the plaque development[196]. The main AS-treatment strategies based on the chemokines are divided into small molecule chemokine receptor antagonists, modified chemokine, chemokine-neutralizing protein and chemokine heteromer formation-antagonists[196]. For example, the treatment with CCR5 antagonist enabled size reduction of plaque in *ApoE*$^{-/-}$ mice[197]. Furthermore, inhibition of CXCL12 is promising to prevent and alleviate AS-associated diseases. CXCL12 inhibitors, AMD3100, AMD3465, and POL551, showed inhibition of CXCL12-damaged vascular wall[198,199].

4.1.1.4. Metabolic regulation of immune cells. Besides the specific target substances, the altered metabolism of cells in AS may be used as therapeutic potential. The changed metabolism includes upregulated inflammatory activities, the elevated vulnerability of plaque, downregulated fatty acid oxidation (FAO), increased consumption of amino acids (AAs) and upregulated glycolysis in plaque[200]. Abnormal glycolysis always fosters the production of the inflammation-stimulated IL-1β and IL-6[201,202]. Accordingly, supplementary of FAO, during the activation of M2 macrophages[203] and T cells[204], may stimulate anti-inflammation signals directly or make $CD8^+$ T cells exert indirect anti-inflammatory activity[203−205]. Reduced metabolism of AAs may decrease foam cell formation and reduce plaque size[206,207].

4.1.1.5. Vaccination against low density lipoprotein (LDL) particles. AS does not belong to an autoimmune disease, however, ApoB is always known as AS antigens. As a result, autoimmune responses against ApoB *via* vaccination can be a potential therapeutic implication for AS[171]. The vaccination therapy includes using mAbs against the cholesterol ester transfer protein (CETP) or proprotein convertase subtilisin kexin type 9 (PCSK9) and induction of antigen-specific Tregs. PCSK9 is able to damage the LDL receptor and raise plasma LDL cholesterol level[208], whereas CETP strengthens the change of high density lipoprotein (HDL)-LDL[209]. Consequently, anti-PCSK9 allows for reductions

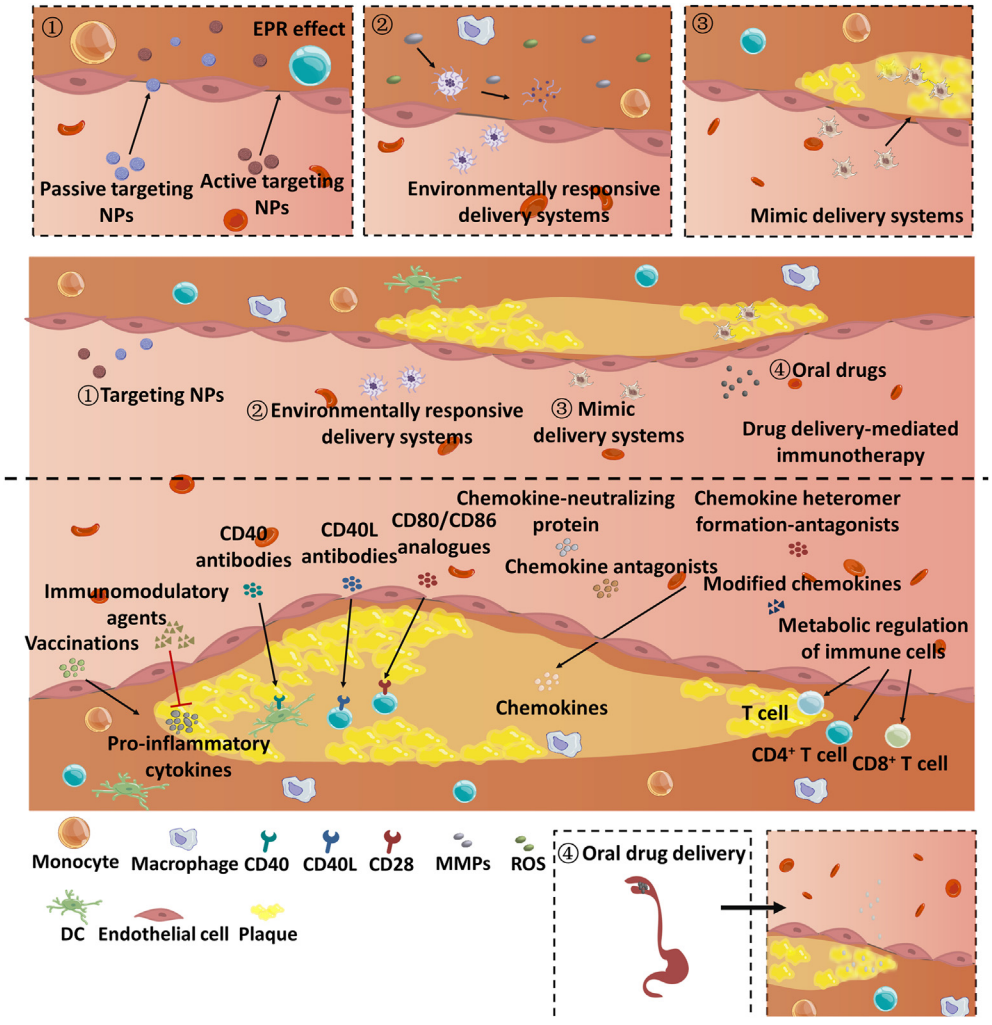

Figure 4 Immunotherapy for atherosclerosis (AS) and the used DDSs.

of LDL cholesterol[210,211], and vaccination with CETP could promote HDL cholesterol levels and decrease the plaque size[212]. In addition, Tregs can suppress the plaque development through limiting Teffs expansion, especially Th1 cells, and reduced production of inflammatory cytokine[213,214]. Accordingly, stimulation of the Tregs may inhibit AS progression by suppressing the activities of immune cells including T cells, NK cells, monocytes, B cells, and DCs and by inducing suppressive modulators such as IL-10, TGF-β and IL-35[215].

4.1.2. Drug delivery-mediated immunotherapy in AS

The formation of plaque offers numerous opportunities for targeting therapy of AS by using DDS. The commonly reported DDSs are summarized in Fig. 4. The targeting approaches include enhanced accumulation of DDS in the plaque through enhanced permeability and retention effect (EPR)-like or biomimetic mechanism and promoted drug release from DDS in the plaque by microenvironment-responsive strategy. Beldman and coworkers[216] used a kind of HA-NPs to investigate the EPR effect in the plaque of AS progression. They found that the endothelial junction architecture normalized at the later period of AS compared with early AS and the accumulated HA-NPs was decreased. However, the HA-NPs can enter the plaque *via* endothelial junctions, distribute throughout the extracellular matrix (ECM) and eventually phagocytized by plaque-associated macrophages.

A recent study indicated the unusual and condensed cell morphology and junction irregularities in arterial endothelial layer of *ApoE*$^{-/-}$ mouse observed by transmission electron microscopy[216]. In the endothelial junctions of AS, the distance between vascular endothelial cadherin (VEC) units is up to 3 μm[216]. Whereas, in the normal vascular endothelial layer, the VEC units were firmly ranked and the space between the VEC units is only about 0.5 μm[216]. Nonetheless, advanced plaques have a small recovery of endothelial junction[216]. Whereas, in the normal vascular endothelial layer, the VEC units were firmly ranked and the space between the VEC units is only about 0.5 μm[216]. However, the stage of AS affects the accumulation and the trafficking pathway of NPs. In advanced plaque, the accumulation of NPs at the AS lesions was closely relied on the transcellular route and was reduced around 30% compared with that in early plaque[216]. Anyway, the findings rationalize the use of nanoscaled DDS for target treatment of AS. So far, DDSs have been widely utilized for AS immunotherapy, such as liposomes[217,218], recombinant HDL (rHDL) NPs[219], nanofiber[220], membrane-coated NPs[221], polymersomes[222], and injectable filamentous hydrogel loaded micelles[81].

Targeting macrophages are the most commonly used strategy in AS immunotherapy[1,167,219]. The ligand signaling of CD40−CD40L is a widely known enhancer of AS and other chronic inflammatory diseases; consequently, its inhibition allows

for inhibition of AS[223]. Whereas tumor necrosis factor receptor-associated factor 6 (TRAF6) is potent to boost CD40's signaling cascade inside monocytes and macrophages[190]. As a result, disruption of CD40-TRAF6 interactions can reduce monocyte recruitment to plaques and inhibition the formation of plaque[190]. Recently, to suppress the interplay between CD40 and TRAF6 in macrophages and monocytes, a CD40-TRAF6 inhibitor 6877002 was loaded into 20-nm TRAF6i-rHDL NPs consisted of apolipoprotein A−I (ApoA−I), the 1,2-dimyristoyl-*sn*-glycero-3-phosphatidylcholine (DMPC) and 1-myristoyl-2-hydroxy-*sn*-glycero-phosphocholine (MHPC)[224]. The results demonstrated that TRAF6i-HDL NPs could bind well to monocytes and macrophages in the lesion site. The one-week treatment decreased the content of plaque macrophage content and plaque inflammation through the reduction of monocyte accumulation instead of decrement of local macrophage proliferation[224]. The results demonstrated that TRAF6i-HDL NPs could bind well to monocytes and macrophages in the lesion site. The one-week treatment decreased the content of plaque macrophage content and plaque inflammation through the reduction of monocyte accumulation instead of decrement of local macrophage proliferation[219]. TRAF-STOPs enabled AS inhibition by limiting chemokine-induced accumulation of leukocyte to the plaques and suppressing release of cytokine from macrophages. Upon encapsulation in the rHDL NPs, their treatment efficacy was improved, displayed as reduced administration times and total dose over treatment with free TRAF-STOP[219].

Targeting Tregs or DCs are promising for AS immunotherapy[215,225−227]. DCs have an extremely lower concentration compared with monocytes and macrophages within AS plaque, however, they have an unignored role in promoting the inflammation and AS advance[228−230]. Yi et al.[222] prepared three types NPs, 20 nm-micelles, 100-nm polymersomes, and 50 nm × micron-length filomicelles using PEG-bl-PPS block copolymers. The results demonstrated that, among the NPs, the 100-nm polymersomes had the highest targeting ability to DCs in the arterial wall and lymphoid organs of animal model[222]. By surface decoration with a P-D2 peptide, the polymersomes could well target DCs and enhance the cytosolic delivery of anti-inflammatory agent 1,25-dihydroxy vitamin D3-(aVD)[231]. Low-dose intravenous administration for a week markedly inhibits the progression of plaque in a high-fat-diet-fed *ApoE*$^{-/-}$ mice[231].

AS immunotherapy acquired *via* activating Tregs include adoptive transfer Tregs, AS relevant antigens such as x-LDL, HSP60, and ApoB100, pharmacological agents such as rapamycin, vitamin D3 and cholesterol-lowering drugs, and antibodies and cytokines such as IL-2 and anti-CD3 antibody[215]. To improve the delivery of the immunostimulators to Tregs, liposomes formulated with the anionic phospholipid 1,2-distearoyl-*sn*-glycero-3-phosphoglycerol[232], pH-responsive NPs[233] and filomicelles[81] were developed to selectively deliver LDL-derived peptide antigen, miR-33, and vitamin D to Tregs.

AS immunotherapy displays promising treatment efficacy in preclinical studies, and some of them are undergoing clinical trials[234]. However, their translation is still hampered by various factors, *e.g.*, unknown side effects and immunogenicity, poor scalability of DDS, high cost, and poor patient compliance because the injection is always required. AS immunotherapy obtained *via* oral administration benefits the translation, whereas it is challenged to prevent the degradation of the biopharmaceuticals or DDS in the gastrointestinal tract. Nonetheless, several oral formulations for AS immunotherapy have been investigated in preclinical studies, such as yeast-derived microcapsules (YCs) encapsulated an inhibitor of MCP-1/CCL2 bindarit[235], recombinant *Mycobacterium smegmatis*, a live bacterial vector, that allowed to produce cloned Chlamydia pneumonia (AHC) antigen and induce regulatory immune response to self-proteins[236,237], low-dose oral cyclophosphamide formulation[238], algae-based vaccine[239], and carrot-cell vaccine platform[240].

4.2. PAH

PAH is characterized by an average pulmonary arterial pressure of >25 mmHg while a capillary wedge pressure of ≤15 mmHg. PAH is an uncommon and serious disease demonstrated as pulmonary vascular remodeling, endothelial abnormality, vasoconstriction and *in situ* inflammation and thrombosis[241]. Most immune cells, *i.e.*, T cells, DCs, NK cells, macrophages, B cells, mast cells, and eosinophils, are involved in the progression of PAH[1,242]. Accordingly, these immunity pathways can be potential targets for treat PAH. Implications of immunotherapy in PAH are illustrated in Fig. 5.

4.2.1. Implications for immunotherapy in PAH

4.2.1.1. Cell-based therapy. Increasing evidence indicates Tregs involve in all stages of PAH pathogenesis, and reducing their number and activities always execrate PAH[243,244]. A previous review summarized the function of Tregs in PAH[245]. Tregs inhibit the development of PAH through producing cytokines and chemokines such as IL-10, bone morphogenetic protein type II receptor (BMPR-II) and CXCL12−CXCR4, relating with other immune cells to suppress the immune activity and, as a result, repair injured pulmonary artery endothelial cells (PAECs), control proliferation and apoptosis of pulmonary arterial smooth muscle cells (PASMCs), limit proliferation and activation of fibroblast, and stay immune homeostasis[245]. Consequently, Tregs is a potential treatment target against PAH. The Tregs-targeted treatment includes adoptive Treg therapy acquired by exogenous Treg transplantation and expansion of intrinsic Tregs induced by stimulators including Liver kinase B1[246], IL-2[247,248], vitamin D[249], and CD28 superagonist[250]. Of the stimulators, IL-2 is most frequently applied and is demonstrated roust ability to promote the proliferation of Tregs. Until now, approximately fifty one clinical tests using Treg therapy have been recorded in ClinicalTrials.gov[251]. A phase I trial demonstrated that the infused Tregs in patients with T1D could last one year[252], indicating safety and tolerance. Recently, adoptive Treg cell therapy was used on a patient with systemic lupus erythematosus (SLE)[253]. The results displayed that the treatment could increase activated Treg cells in inflamed skin and promote a shift from Th1 toward Th17 reactions[253]. Another clinical trial using rituximab to delete B cells for PAH immunotherapy is ongoing[254].

Myeloid-derived suppressor cells (MDSCs) were reported to be involved in the development of PAH and several inflammatory diseases[255]. PD-L1 is overexpressed on MDSC from PAH patients[255], and PD-1/PD-L1 interactions exacerbate the inflammation in PAH in animal model[256]. A report displayed that therapy using anti-PD-1 or PD-L1 might inhibit MDSC and alleviate the progression of PAH[256].

4.2.1.2. Cytokine- and chemokine-based and vaccination therapy. The cytokines, *e.g.*, IL-6, IL-8, IL-10, IL-13, IL-18, IL-1β and TNFα, are intimately associated with development of

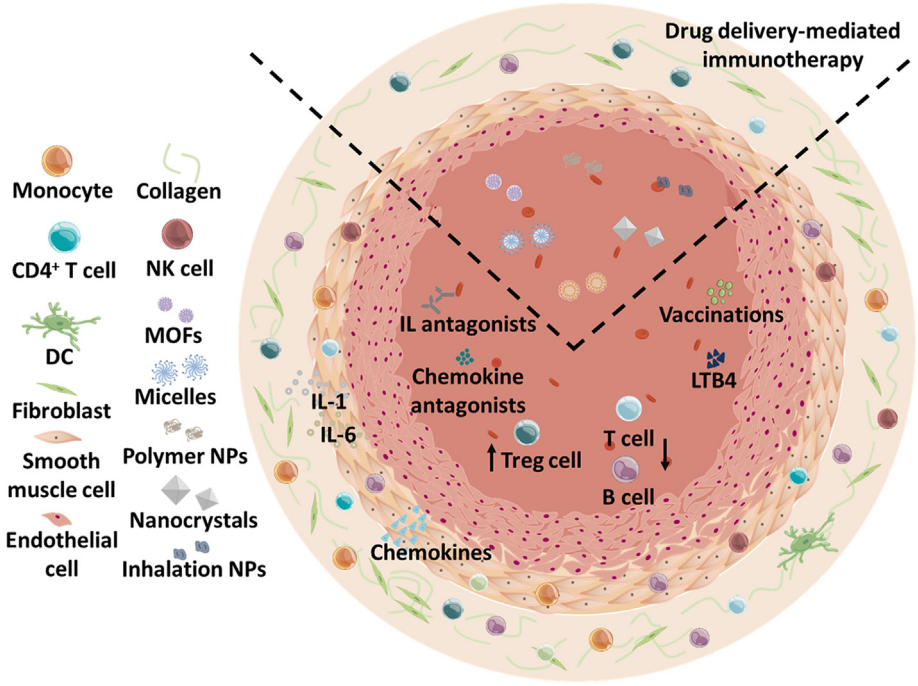

Figure 5 Immunotherapy for pulmonary arterial hypertension (PAH) and the used DDSs.

PAH[257−259]. Inhibition of the proinflammatory cytokines is potential to treat PAH. Clinical test was performed to study the effictiveness against PAH using a IL-6 receptor antagonist, tocilizumab[260]. The results revealed that the treatment with tocilizumab was safe and improved pulmonary hemodynamic parameters[260]. Dosing a TNF-α antagonist, recombinant human TNF-α receptor II-IgG Fc fusion protein (rhTNFRFc), alleviated PAH *via* lowering mean pulmonary artery pressure (mPAP) and inhibiting pulmonary vascular remodeling[261]. Furthermore, disruption of the IL-6/Th17/IL-21 pathway is promising to selectively treat PAH[262].

Numerous chemokines are involved in inflammation and pulmonary vascular remodeling, including CXCL8/CXCR1/CXCR2, CXCL10/CXCR3, CXCL12/CXCR4/ACKR3, CCL2/CCR2, CCL5/CCR5/CCR1, CX3CL1/CX3CR1, etc.[263]. In particular, leukotriene B4 (LTB4) has robust ability to promote inflammatory immune response *via* increasing neutrophil recruitment and, as a result, induce apoptosis of ECs[264,265]. Inhibition of LTB4 with bestatin allows reversing established PAH *via* increasing the numbers of open arterioles and reducing arteriolar wall thickness and muscularization[264].

Endothelin-1 (ET-1) receptor type A (ETAR) can activate the endothelin system and facilitate the initiation and development of PAH[266]. A vaccine against ETAR was designed by conjugating an ETR-002 peptide with a Qβ bacteriophage virus-like particle[267]. The vaccination approach has potent efficacy to combat PAH in the monocrotaline (MCT)-induced- and Sugen/hypoxia-induced models by suppressing the pulmonary arterial remodeling and the RV hypertrophy through inhibition of Ca^{2+}-dependent signal transduction events[267]. In addition, disruption of theα1D-adrenergic receptor (α1D-AR) might be a vaccination strategy against hypertension by using ADRQβ-004 vaccine[268].

4.2.2. *Drug delivery-mediated immunotherapy in PAH*

Numerous DDSs are applied to improve immunotherapy; however, their use in PAH immunotherapy moves forward slowly. The most commonly used DDSs to elevate pulmonary delivery are liposomes[152,269,270] and polymeric NPs[269,271−273] dosed *via* intravenous injection or inhalation[274]. Loss of endothelial BMPR-II facilitates the initiation and development of PAH, enabling BMPR-II to be a therapeutic target[275]. Tacrolimus, an immunosuppressor, is able to activate BMPR-II and is allowed to repair the endothelial function in PAH patient cells and inhibit the remodeling of the pulmonary artery in animal model[276]. A clinical test demonstrated that administration of tacrolimus at a low dose to three patients with advanced PAH for twelve months, which the trough concentration was 1.5−5 ng/mL, upregulated BMPR-II in PBMCs and, as a result, ameliorated PAH through elevating heart function, prolonging 6-min walk distance, and inducing N-terminal pro-brain natriuretic peptide[277]. Another clinical trial displayed that this administration regimen was safe and could promote the expression of BMPR-II in subsets of PAH patients[278]. To improve the pulmonary delivery of tacrolimus, nanocomposite microparticles (nCmPs) were prepared by formulating 200-nm drug-loaded polymeric NPs into microparticles through spray drying. After administration *via* inhalation, the nCmP could deposit in the lung regions, penetrate through the mucus barrier, and control drug release over time[279]. In addition, other immunomodulators, *e.g.*, rapamycin, everolimus, anti-TNFα, TGF-β antagonist, rituximab, and tocilizumab[280], were used to combat PAH as well.

5. Conclusions and outlook

We summarized the potential immune targets in several major inflammatory diseases, reviewed the biological drugs and DDSs used for immunotherapy. Immunotherapy is updating the concept of disease treatment and has acquired rapid development in the past five years, evident by that several products such as mAbs and adoptive cell transfer were approved for clinical use. In particular, immunotherapy is being developed as a most effective strategy

against cancer. For RA and IBD immunotherapy, the progression is being promoted smoothly, along with several mAbs against TNF-α and IL-6 and two JAK inhibitors, baricitinib and tofacitinib, being marked, whereas there are seven mAbs approved for IBD immunotherapy. For immunotherapy of vascular diseases such as AS and PAH, the clinical test demonstrated promising potential, *e.g.*, the treatment efficacy against AS with a mAb targeting IL-1β can persist three months[183], bringing significant connivance to patients who have to take lipid-lowering drugs daily. So far, there is no report regarding clinical trials to ameliorate PAH. Always, the patients with the advanced PAH possess poor response to the frequently applied vasodilator agents probably due to the loss of elasticity in the remodeling pulmonary arteries. Such that the utilization of immunotherapy may reverse PAH; however, the rationalization is required from the physician. Overall, immunotherapy against serious vascular diseases don't move forward smoothly compared with cancer immunotherapy, mainly owing to the factors: (1) in pathogenesis lacking sufficiently understanding toward the immune pathways involved in these diseases; (2) absence of legitimacy from the clinic; (3) the potential immune-related adverse events[281]; (4) remarkably high cost compared with the conventionally used treatment regimens; (5) patients' compliance because dosing *via* injection is always required in most immunotherapy.

In general, the strategies for immunotherapy are predominantly categorized into several types, including mAbs against cytokines or chemokines, inhibitory ICPs, JAK inhibitors, adoptive cell transfer, metabolic regulation of immune cells and vaccination. mAb-immunotherapy is the most widely applied approach and has gained huge success, evident by over seventy-four formulations have entered the market. Second, ACT, especially T cell-based transplantation, is attracting increasing attention and advances rapidly. The milestone event of this technique is the approval use of CAR therapy to treat for relapsed/refractory acute lymphoblastic leukemia (ALL)[282]. After that, other ACTs are constantly emerging, such as TIL-, TCR-, NK Cell-, Treg-, and MDSC-therapies. Although several problems regarding ACT, such as safety, efficacy, and persistence, are needed to be addressed, the ACT will be concentrated continuously and an increasing number of commercial products will be approved, mainly due to its advantages such as simple composition and controllable scalability. Particularly, Tregs are demonstrating potent efficacy to combat serious inflammation and over 50 of Treg techniques were registered for clinical trial[251]. This technique deserves much more attention and we believe increasing products will be marked for clinical usage.

Most of the immunomodulators belong to biological drugs and their application is always limited by their large size, poor stability, humble penetration ability across physiological barriers, rapid clearance by the reticuloendothelial system, etc. To improve immunotherapy, repeatedly dosings at high doses of the biological drugs *via* intravenous injection are always required, leading to safety concerns and significantly reducing patient's compliance. The drug delivery approach through engineering biomaterials is robust to enhance delivery of the biologics to the targeted site. Tremendous DDSs demonstrated their amazing immunotherapy efficacy toward various inflammatory diseases in pre-clinical studies. Nonetheless, extremely limited DDS-mediated immunotherapy is approved frequently due to DDS's potential toxicity to the body, unknown *in vivo* fate[283], modest scale-up ability, and unfriendly dosing route. In this case, the selection of DDS is critical to the translation. As a result, DDSs with excellent safety and promising industrial perspectives may be an optional choice for the DDS immunotherapy. These DDSs include liposomes or liposome-like NPs, degradable polymeric carriers such as PLGA-NPs or microspheres, albumin-based NPs, cell carriers like red blood cells, etc. In addition, the dosing routes are of the essence to the translation, and well-accepted delivery pathways should be first choice, encompassing oral, buccal, transdermal, nasal, inhalation and subcutaneous routes[284].

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Author contributions

Wei He conceived the work. Qingqing Xiao, Xiaotong Li, Yi Li, Zhengfeng Wu, Chenjie Xu, Zhongjian Chen, and Wei He co-wrote the paper. Xiaotong Li prepared the figures. All of the authors discussed the results and commented on the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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