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Macrophage-Based Therapeutic Strategies: Phenotypic Transition Control and Drug Delivery System Development

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ABSTRACT

Macrophages, being highly phenotypic changeable immune cells, have distinct functions in different clinical situations. Modifying and managing macrophage morphologies is seen as a unique possible therapeutic intervention. In the meanwhile, several transmembrane proteins that attach on the macrophage membrane's surface remain comparatively preserved, maintaining its functional characteristics including tumor targeting and inflammatory chemotaxis. As a result, a number of medication delivery mechanisms associated with certain macrophage membrane proteins are often used to treat chronic inflammatory disorders. The regulation of macrophage phenotypes and their polarization processes, the design and implementation of site-specific targeted drug delivery systems in vivo based on macrophages and their derived membrane receptors, and a summary of macrophage-based strategies for chronic diseases are all covered in this review. It seeks to advance knowledge of macrophages' role in immunoregulation and suggests tailored therapy strategies based on macrophages for chronic illnesses.

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1. Introduction

Immune cells called macrophages are essential for controlling the inflammatory response, encouraging tissue repair, and preserving dynamic homeostasis in the body via the regulation of innate immune responses [1]. The immunomodulatory effects are used to eliminate infections, inhale allergens, and lessen infection once they identify pathogen-associated molecules and link with pattern-recognition receptors to identify the damaged cells [2]. The occurrence and development of a number of chronic diseases, such as cancers, inflammatory diseases, metabolic diseases, and infectious diseases, are linked to the inappropriate activation or aberrant inflammatory response of macrophages, which can disrupt their homeostatic functions and produce uncontrollable inflammatory responses that can cause ongoing tissue and organ damage [3–8]. Macrophage-related immunotherapies have been extensively developed lately to target this aberrant immune milieu and combat the



processes of chronic illnesses, such as macrophage polarization, suppression of macrophage infiltration, and removal of the damaged macrophages [9–12]. Macrophages may move to inflammatory areas in response to certain chemotactic signals, including CCL2/CCR2, CSF-1/CSF-1R, and the $\alpha 4$ integrin/VCAM-1axis [13,14]. To target macrophages and mediate macrophage phagocytosis, membrane receptors such as scavenger receptors and phosphatidylserine receptors (PSR) are activated. Additionally, drug delivery systems that have been altered to include the appropriate ligands may be able to precisely deliver medications by targeting macrophages [15]. Due to the existence of particular receptors from the macrophage membrane (MM), macrophage-derived extracellular vehicles (EVs) that load with contents also function as the targeted delivery tools for cell-cell communication, including genes, endogenous proteins, and lipids [16,17]. Furthermore, to increase the administration effectiveness, drug-loaded nanoparticle coating with MM or macrophage-derived extracellular vesicle membrane (EVM), which may be passed off as macrophages or macrophageEVs, has been employed extensively [13,18,19]. These functionalized drug delivery systems associated with macrophages also combine the advantages of macrophages with nanoparticles to enhance effectiveness of drug delivery. Here, we provide therapeutic approaches based on the modulation of macrophage phenotype in chronic illnesses. We list the FDA-approved small molecule medications that influence macrophage polarization in light of our understanding of how to modify the macrophage phenotype. In order to get a better understanding of macrophage-based precise targeted drug delivery strategies for chronic inflammatory disorders, this review also attempts to provide a succinct summary of the macrophage-related drug delivery system that has been recently published.

2. Macrophages in the main illnesses

Macrophages are very malleable cells that release a variety of cytokines and chemokines and have a vast library of surface receptors that allow them to react to biological stimuli. Macrophages may primarily differentiate into two phenotypes based on the cues from the microenvironment: the alternative activated anti-inflammatory M2-like macrophages for anti-inflammation, tissue healing, and remodeling; a) the traditionally activated pro-inflammatory M1-like macrophages for phagocytosis and pathogen killing, tumor suppression, and tissue damage [20]. Because of the many transcriptional processes and stimuli involved, M2 may polarize into M2a (wound healing macrophages), M2b (regulatory macrophages), M2c (acquired inactivated macrophages), and M2d (tumor-associated macrophages, or TAMs) [21–24]. Interleukin-4 (IL-4) and interleukin-13 (IL-13) trigger M2a, which suppresses inflammation, stimulates T cell activation and angiogenesis, and releases paracrine substances to aid in tissue healing, cell proliferation, and remodeling [25–27]. Pro-inflammatory cytokines like interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumornecrosis factor- α (TNF- α) are produced by M2b after being stimulated by immune complexes and lipopolysaccharide (LPS). Additionally, M2b produces the anti-inflammatory cytokine interleukin-10 (IL-10), which is primarily involved in immunomodulation and Th2 activation, with potent immunomodulatory, pro-infectious, and pro-tumor effects [28–30]. Induced by transforming growth factor- β (TGF- β), glucocorticoids, or IL-10, M2c promotes tissue healing via angiogenesis and extracellular matrix remodeling and contributes to immunosuppression by negatively regulating pro-inflammatory cytokines [31, 32]. Toll-like receptors (TLR), adenosine receptors, and IL-6 all cause M2d, which increases immunosuppression, angiogenic tumor growth, and tumor tolerance by inhibiting anti-tumor T cell activity [33, 34]. The great degree of variation in macrophages' participation in pathogenic processes is due to their very changeable phenotype. Additionally, the body's immune responses and the onset of illness are strongly regulated by the balance of the M1 and M2-like macrophage phenotype [35]. Therefore, treatment approaches that modify the macrophage phenotype to influence the development of illness are very desirable [36–38]. The importance of comprehending the diversity and pleiotropic roles of macrophages in both health and illness has grown lately. In addition to having distinct functions in various tissues and organs, different macrophages are also implicated in the same illnesses. Inflammatory illnesses are intimately associated with macrophages that are drawn to the lesion site and remain in the tissue [39]. Here, we first go over the characteristics and management of macrophage polarization in chronic illnesses in order to provide an efficient method for treating inflammatory disorders. Macrophages in cancer Cytokines like IL-4, macrophage colony-stimulating factor-1 (MCSF-1), and granulocyte-macrophage colony-stimulating factor (GM-CSF) secreted by tumor cells cause macrophages to polarize into M2-like TAMs, a pro-tumor trait. They also increase the secretion of transforming



growth factor- β 1 (TGF- β 1) and Arginase-1 (Arg-1) to suppress immune responses, promote tumor development, invasion, and metastasis [40,41]. Targeting By inhibiting the release of KrasG12D protein from tumor cells, Dai et al. were able to delay the development of pancreatic ductal adenocarcinoma by preventing macrophages from polarizing into tumor-promoting M2-like TAMs [42]. Zhou et al. discovered that tumors that responded to immune checkpoint inhibitors had much higher expression of SLFN11, a member of the schlafen (SLFN) family. A tumor-specific SLFN11 loss exacerbated the development of hepatocellular carcinoma by increasing the polarization and infiltration of M2-like TAMs [43]. As a result, controlling the macrophage phenotype has emerged as a viable cancer immunotherapy strategy [44]. In inflammatory diseases, macrophages

Given the key role that macrophages play in the development of inflammatory disorders, targeting them to suppress M1 or increase M2-like macro-phage polarization may be a viable treatment option for conditions including atherosclerosis, colitis, and arthritis [45,46]. TLR and interferon (IFN) signaling dominate the inflammatory milieu in which M1-like macrophage activation takes place, causing tissue damage and the production of pro-inflammatory cytokines [45]. Conversely, M2-like macrophage activation encourages the release of anti-inflammatory cytokines and growth factors, which results in the clinical remission of diseases [47, 48]. M2-like macrophages control the inflammatory process and release IL-10, TGF- β , and chemokine ligand 18 in the late stages of inflammation and tissue repair. These substances stimulate the growth of fibroblasts and the production of collagen, which results in the development of organ fibrosis by creating a fibrous microenvironment [45]. In order to treat bleomycin-induced idiopathic pulmonary fibrosis (IPF), Pan et al. found that Sart1 depression can reduce M2-like macrophage polarization and infiltration in the lung [49]. M1-like macrophages also contribute to the development of other diseases, including colitis, arthritis, and atherosclerosis. Potential therapies for these illnesses include preventing M1-like macrophage infiltration and polarization and/or encouraging M2-like macrophage polarization [45,50,51]. Spermidine was used by Yuan et al. to slow the development of collagen-induced arthritis by reducing the polarization of M1-like macrophages and encouraging the production of anti-inflammatory molecules [47]. Tollip, a crucial negative regulator of TLR-mediated innate immunity, has been shown by Liu et al. to suppress the production of pro-inflammatory cytokines in colon tissues, induce macrophage polarization into an M2-like phenotype, and preserve the integrity of the mucosal barrier in the treatment of colitis [48]. In infectious diseases, macrophages

Macrophages can identify and absorb externally invading bacteria and viruses, and they may also release pro-inflammatory mediators including TNF- α , IL-1 β , IL-6, interleukin 12, and nitric oxide (NO) to destroy pathogens, according to emerging preclinical and clinical investigations of microbial or viral infection illnesses [52]. M1-like macrophages mediate antimicrobial resistance and antiviral immune response, exhibit potent cytotoxic effects on infected cells, and boost bactericidal activity and pro-inflammatory features in illnesses caused by microorganisms or viruses. M2-like macrophages enhance tissue healing, exhibit an immunosuppressive response, and block these effects [53–55]. Limetal discovered that M1-like macrophages produced more tumor suppressor p53 during mycobacterial infection, and that p53 successfully prevented Mycobacterium tuberculosis (Mtb) from surviving intracellularly in host cells [53]. Mannose-modified chitosan nanoparticles loaded with imatinib were developed by Gao et al. to efficiently target and induce macrophage siture modeling, boost M1, and block M2-like macro-phage polarization in order to eliminate the infection caused by the fungus Candida albicans [54]. Gengetal discovered that by encouraging M1-like macrophage polarization, baicalin can prevent influenza A virus infection [55]. As a result, preventing M2-like macrophage polarization and/or encouraging M1-like macrophage polarization have emerged as viable strategies for infectious disorders caused by microbes or viruses. Collectively, M1 and M2-like macrophages play distinct roles and maintain the balance between each other through polarization. Based on the significant plasticity of macrophages in phenotypes, an immuno-therapy that modulates macrophage phenotypes to maintain a coordinated inflammatory and anti-inflammatory balance has become an essential direction of various disease treatment researches.



2. Current status of FDA-approved drug targeting macrophages

FDA-approved small molecule drug that could regulate the

Table 1

Summary of small molecule drugs with their corresponding FDA-approved disease applications, and their effects on macrophage polarizations.

Drugs	FDA-approved application of disease	Macrophage polarization	Corresponding disease	Ref.
Cabazitaxel	Prostate cancer	M1↑	Triple-negative breast cancer	[56]
Mebendazole	Anthelmintic	M1↑	Colon cancer	[57]
Itraconazole	Anti-fungal	M1↑	Candida albicans infection	[58]
Zoledronic acid	Osteoporosis	M1↑, M2↓	Osteonecrosis of the jaw	[59]
Vitamin C	Scurvy	M1↑, M2↓	Bladder cancer	[60]
Pexidartinib	Tenosynovial giant cell tumor	M2↓	Osteosarcoma	[61]
Imatinib	Chronic myelogenous leukemia	M2↓	Lung cancer metastasis	[62]
Pirfenidone	Anti-fibrotic	M2↓	Pulmonary fibrosis	[63]
Niclosamide	Anti-helminthic	M2↓	Pulmonary fibrosis	[64]
Penfluridol	Schizophrenia	M1↓	Arthritis, Colitis	[65]

Table 1 summarizes the macrophage phenotype [56–79]. To treat disorders like cancer and organ fibrosis, some of them encourage the polarization of M1-like macrophages or prevent the polarization of M2-like macrophages. To successfully treat triple-negative breast cancer (TNBC), for instance, Cabazitaxel activates macrophages to the M1-like phenotype, which enhances its anti-tumor potential of programmed cell elimination [56]. Furthermore, vitamin C, a substance that is necessary for human health and can only be acquired via diet, may prevent bladder cancer by encouraging the polarization of M1-like TAMs [60]. Pirfenidone inhibited the infiltration and polarization of M2-like macrophages via the TGF-β1/Smad3 axis to improve pulmonary fibrosis, in addition to treating cancer by controlling macrophage phenotype [63]. Conversely, certain FDA-approved small molecule medications treat associated diseases including atherosclerosis, colitis, and arthritis by blocking M1 or encouraging the polarization of M2-like macrophages. Certain antihypertensive medications, such as Losartan [70] and Guanabenz [69], may prevent M1-like macrophage polarization. However, research has shown that medications used to treat type II diabetes, such as Gliclazide [67], Metformin [75], Glibenclamide [76], Dapagliflozin [77], and Saxagliptin [78], may enhance M2-like macrophage polarization, while some of them can also decrease M1-like macrophage polarization. Therefore, preventing obesity or diabetes-related disease may be achieved by managing the repolarization of macrophages from the M1 to M2-like phenotype [80]. Sclerosis fumarate

Developments in the use of medication delivery methods associated with macrophages

Cell surface receptor-based drug delivery systems have the potential to enhance drug bioavailability, decrease medication toxicity and adverse effects, and alter the immune microenvironment's equilibrium [81–83]. We separated these targeting systems into three primary groups based on the various macrophage components used in the development of delivery



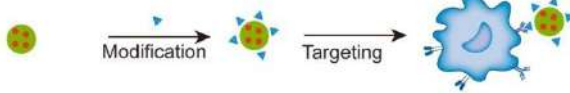
systems (Fig. 1): (1) Drug delivery system targeted by macrophages Gliclazide treats Type II diabetes M1↓ Atherosclerosis [67] by altering the ligand on drug delivery systems that can identify the receptor on macrophage surfaces, which can scan

Doxycycline Antibiotics M1↓ Hypertension of the pulmonary arteries [68] specifically target macrophages at the target locations to influence their Anti-hypertensive Guanabene M1↓, M2→ Autoimmune encephalomyelitis M1↓, M2↑ Losartan Anti-hypertensive Heart disease caused by sepsis. [69] [70] pathological process and halting the advancement of the illness; (2) Macrophage-based drug delivery systems that possess the traits of home and inflammatory microenvironment targeting, adapting to the macrophage or after functional modification as living macrophage drugs Chronic myelogenous leukemia with bosutinib MM coated biomimetic drug delivery system based on MM targeting and camouflage capabilities, as well as M1↓, M2↑ Silicosis [71] delivery system; (3) Ibrutinib Long-term lymphocytic leukemia M1↓, M2↑ [72] Chronic lymphocytic leukemia Extracellular vesicles (EVs) released by macrophages may be used as gene/drug targeted delivery systems or membrane-coated biomimetic drug delivery systems. Sulfasalazine Crohn's disease, ulcerative colitis, and rheumatoid arthritis M1↓, M2↑ Melanoma [73] can be built by doping or coating EV particles of mitonan. Mannose-modified nanoparticles were created by Ponpipom and Robbins et al as early as the 1980s in order to increase the effectiveness of the particles' absorption by alveolar macrophages [84,85] (Fig.2). And Miconazole Fungicide M1↓, M2↑ Damage to the peripheral nerves Metformin Type II diabetes M1↓, M2↑ Mellitus inflammation linked to obesity [74] [75] Other drug delivery methods linked to macrophages have also been recently created and implemented [86–90]. More selectivity and treatment options are offered by these drug delivery methods, where

Diabetes mellitus Type I Glibenclamide Diabetes mellitus, chronic kidney disease, and dapagliflozin type II M1↓, M2↑ TB [76] M2↑ Fibrosis of the heart [77] Below, a detailed description of how to create and identify ligand-receptor responsiveness will be provided. Drug delivery systems that target macrophages and are built via ligand-receptor specific binding

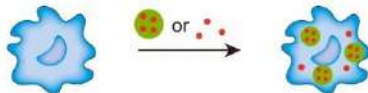
Type I diabetes mellitus with saxagliptin Fingolimod Multiple sclerosis with relapses M2↑ Non-alcoholic fatty liver disease M2↑ Damage from ischemic white matter Drug delivery systems that target macrophages are based on decorated nanoparticles that bind to cell surface receptors such as CD206, CD44, and Siglec-1 receptors with particular ligands. The decorated ligand on the nanoparticles such as mannose, chondroitin sulfate, and sialic "↑" means up-regulation; "↓" means down-regulation; and "→" means unchanged are the notes. β-dextran, human ferritin, and acid may all bind to macrophage membrane receptors [13,15]. As such an active targeted delivery system

A: Macrophage-targeted drug delivery systems



B: Macrophage-based drug delivery systems

(a) Living macrophage delivery system



(b) macrophage membrane coated delivery system



C: Macrophage-secreted drug delivery systems

(a) Macrophage extracellular vesicle delivery system



(b) macrophage extracellular vesicle membrane coated delivery system



Fig. 1.Macrophage-related drug delivery system. (A) Macrophage-targeted drug delivery systems; (B) Macrophage-based drug delivery systems. a) Macrophagemembrane coated delivery system and b) Macrophage extracellular vesicle delivery system; (C) Macrophage-secreted drug delivery systems. a) Macrophageextracellular vesicle and b) Macrophage extracellular vesicle membrane coated delivery system.

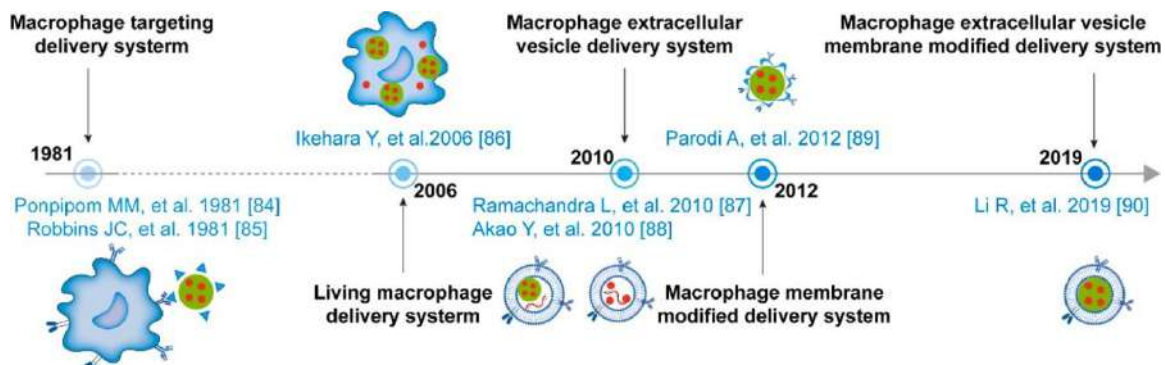


Fig. 2.Historical milestone for macrophage-related drug delivery systems. References: Ponpipom MM, et al.[84]; Robbins JC, et al.[85]; Ikehara Y, et Akao Y et al. [88]; Parodi A et al. [89]; Ramachandra L et al. [87]; LiR et al. [90]. capitalizes on the robust ligand-receptor interaction to perform controlled drug release, imaging of cells, tissues, or organs, and active targeting of macrophages through receptor-dependent internalization, further achieving the goal of disease tracking and treatment. These particular ligands were



categorized and shown in Table 2 and Figure 3. These consist of proteins and polypeptides, lipids, vitamins, and mono- and poly-saccharides. Both mono- and polysaccharides Monosaccharides and polysaccharides are examples of carbohydrate-based ligands that have the ability to selectively target macrophages. A common monosaccharide-targeting ligand that binds mannose receptors (MR/CD206) is mannose. Wang et al. placed mannose-modified magnetic nanoparticles on the surface of the drug-loaded liposomes to create a functionalized dual-targeted drug delivery system with magnetic targeting and macrophage targeting for the treatment of IPF [91]. Certain mannose derivatives, such as galactomannans, and mannose residues, such as methyl α -D-mannopyranoside, may also selectively target the CD206 that macrophages express [112,113]. Tang et al. synthesized functionalized liposomes modified with a galactose ligand that could target the galactose-specific C-typelectin (MGL) expressed on M2-like TAMs and a CD47-derived self-peptide ligand that demonstrated active escape from M1-like TAMs. The surface of liposomes was altered to include higher amounts of galactose (0.5%, 1%, and 2%), and M2-like macrophages subsequently absorbed these liposomes more readily [92]. In order to connect with sialic acid-binding type II lectin receptor (Siglec-1), which is overexpressed on M2-like macrophages, Qiu et al. created sialic acid (a 9-carbon monosaccharide derivative) modified nanocarriers. When compared to unmodified sialic acid nanoparticles in vivo, it accumulated almost three times as much in tumors. It then preferentially transported medicines to TAMs for controlling the immune responses against cancers [93]. Additionally, polysaccharides can be altered on the surface of nanoparticles.

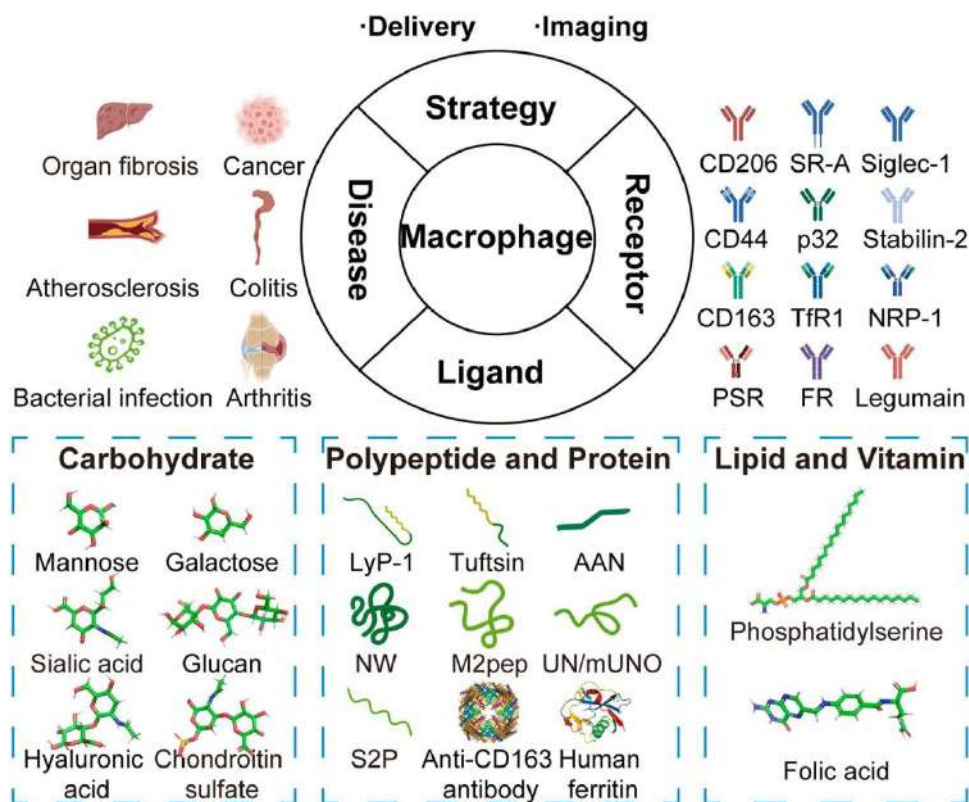


Fig.3.Summary of macrophage-targeted drug delivery systems involving modified ligands, corresponding receptors, treated diseases, and application strategies.



Table2

Summary of macrophage-targeted drug delivery systems.

Function	Ligand types	Targeted macrophages (Type)	Receptor or	Ligand	Disease	Ref.
For delivery	Monosaccharides and polysaccharides	RAW264.7, invivo (M2)	CD206	Mannose	IPF	[91]
		RAW264.7, BMDMs (M2)	MGL	Galactose	Lymphoma	[92]
	Polypeptides	RAW264.7, invivo (M2)	Siglec-1	Sialic acid	Sarcoma	[93]
		RAW264.7, invivo (M1)	CD44	Chondroitin sulfate	Ulcerative colitis	[94]
		RAW264.7, invivo (M1)	CD44	Hyaluronic acid	Colitis	[95]
		RAW264.7, invivo (M1)	SR-A	β -Dextran	Gliomas	[96]
		Invivo (M)	p32	LyP-1 peptide	Atherosclerosis	[97]
		BMDMs (M)	Stabilin-2	S2P peptide	Atherosclerosis	[98]
		BMDMs (M)	/	NW peptide	Fracture	[99]
		Peritoneal macrophages, invivo (M2)	CD206	UN peptide	Breast cancer	[100]
		Human primary blood mononuclear cells (M2)	CD206	mUNO peptide	Breast cancer	[101]
		BMDMs, invivo (M2)	/	M2 peptide	Melanoma	[102]
		(M)	SR-B1	α -peptide	Atherosclerosis	[103]
		J774A.1, RAW264.7, invivo (M)	SR-B1	peptide 37pA	Atherosclerosis	[103]
		RAW264.7 (M)	SR-B1	R4F peptide	Breast cancer	[104]
		Invivo (M)	Legumin	AAN peptide	Breast cancer	[105]
			NRP-1	Tufts in peptide		
	proteins	BMDMs (M2)	IL-4	IL4RPep-1	Breast cancer	[106]
		Human primary blood mononuclear cells (M2)	CD163	Anti-CD163	/	[107]
		BMDMs, invivo (M1)	LRP-1	antibody Lactoferrin	Inflammatory bowel diseases	[108]
For imaging	Lipids	RAW264.7, invivo (M)	PSR	Phosphatidylserine	Atherosclerosis	[109]
	Vitamin	RAW264.7 (M1)	FR	Folic acid	Rheumatoid arthritis	[110]
	Polypeptides	Invivo (M)	p32	LyP-1 peptide	Atherosclerosis	[97]
		Peritoneal macrophages, invivo (M2)	CD206	UN peptide	Breast cancer	[100]



	Human primary blood mononuclear cells (M2)	CD206	mUNOpeptide	Breast cancer	[101]
proteins	Invivo (M)	TfR1	Ferritin	Atherosclerosis	[111]

acting as nanoparticles for oral delivery that target macrophages. After incubating modified silk fibroin nanoparticles for 1, 2, and 4 hours, the cell internalization efficiency increased by 1.5-, 1.3-, and 1.1-folds compared to non-modified silk fibroin nanoparticles. Gouet al. synthesized chondroitin sulfate, a glycosaminoglycan, modified silk fibroin nanoparticles that could target CD44 on the macrophages. Additionally, intravenous injection of NPs resulted in a larger buildup of curcumin than oral administration of NPs.

the colon and considerably extended the duration of curcumin's retention in the bloodstream [94]. Polysaccharides, such as β -dextran (a homopolysaccharide made of glucose as a monosaccharide) and hyaluronic acid (HA, a glycosaminoglycan) nanoparticles, may be employed as a structural foundation to create nanoparticles due to their significant molecular weight. In order to control the dysregulated intestinal barrier, microbiota, and immunological responses in colitis, Lee et al. created HA-bilirubin nanomedicine, which targeted CD44 and delivered bilirubin to the inflammatory colonic epithelium and M1-like macrophages [95]. Miao et al. used a prodrug coupled with dextran that specifically targeted intestinal macrophages and was subsequently phagocytized by these cells. In order to treat gliomas specifically, the macrophages were then delivered to the circulatory system via the lymphatic system and penetrated the blood-brain barrier (BBB) [96]. Proteins and polypeptides Macrophage-expressed receptors, such as CD206 and folic acid receptors, are also extensively expressed on dendritic and epithelial cells. On the other hand, macrophage-targeting peptides are more precise [114]. The structural units that adorn the surface of drug delivery systems are peptides made of amino acids (Aa), which are primarily made up of dozens or even hundreds of amino acids. One cyclic and tumor-homing peptide that may preferentially bind to the p32 receptor protein, which is overexpressed on the macrophages in atherosclerotic plaque, is the LyP-1 peptide (amino acid (Aa) sequence: CGNKRTRGC) [97]. Based on the trifunctional simian virus 40, Sun et al. created an ananocarrier that was loaded with quantum dots and the thrombin inhibitor Hirulog. This ananocarrier was able to effectively target the macrophages in the vascular wall and increased by 3.4 times after being modified with LyP-1 peptide for imaging and drug-targeted delivery to atherosclerotic plaque [97]. Tao et al. created poly (lactic-co-glycolic acid) (PLGA) nanoparticles loaded with siRNA and modified with S2p peptide (Aa sequence: CRTLTVRKC) that could target macrophage-expressed scavenger receptor stabilin-2 and increase macrophage uptake of PLGA by almost three times. By silencing genes, they were able to prevent atherosclerotic plaque necrosis [98]. Zhou et al. created magnetic mesoporous silica nanoparticles modified with the NW peptide (Aa sequence: NWYLPWLGTNDW) to target macrophages at the fracture site, control the polarization of M2-like macrophages, and stimulate the differentiation of bone marrow mesenchymal stem cells in conjunction with magnetic targeting and macrophage targeting [99]. According to other research, NW peptide may interact with the surface of macrophages' PHB1 (prohibitin) [115]. Scodelle et al. examined a number of peptide phages in the mouse model of metastatic breast tumors and discovered that UNO peptide (Aa sequence: CSPGAKVRC), a redox-responsive peptide that targets CD206, may specifically target TAMs that express CD206 [100]. Nevertheless, the reducing tumor microenvironment had to linearize the UNO peptider, a reducing capacity absent from smaller tumors. Thus, based on the proposed UNO peptide, the mUNOpeptide (Aa sequence: CSPGAK) may also target the CD206 without the need for a decreasing tumor microenvironment [101]. Similarly, the same receptor on the surface of macrophages may be targeted by peptides with entirely distinct sequences [102–105]. Qian et al. created a new M2-like TAMs dual-targeted nasal



cavity that included M2pep (an M2-like macrophage binding peptide, Aa sequence: YEQDPWGVKWWY) and α -peptide (ascavenger receptor Btype1 (SR-B1) targeting peptide, Aa sequence: FAEKFKEAVKDYFAKFWD). When bone marrow-derived macrophages (BMDMs) were exposed to these nanoparticles at concentrations of 0.1, 1, and 10 μ M, they produced M2-like macrophages that were noticeably greater than M1-like macrophages. This led to the accumulation of 7.9-, 7.2-, and 5.3-folds, respectively. For the treatment of melanoma, it may precisely suppress the survival signal of M2-like TAMs and target the distribution of siRNA [102]. Furthermore, the apolipoprotein A-I was the source of 37pA peptide (Aa sequence: DWLKAFYDKVAEKLKEAFPDWLKA-FYDKVAEKLKEAF) and R4F peptide (Aa sequence: FAEKFKEAVKDY-FAKFWD), which may also target the SR-B1 receptor [103,104]. When many polypeptides are modified at the same time, the nanoparticles perform more complex tasks than when just one kind of peptide is modified. To improve drug absorption efficiency, Peng et al. combined tuft-sin peptide (Aa sequence: TKPR) with alanine-alanine-asparagine (AAN, Aa sequence: AAN) peptide. The AAN peptide may target legumain that is overexpressed on TAMs and then cleaved by pod protease, and then the exposed tuftsintargeted neuropil-1 (NRP-1) receptor to induce the phagocytosis of TAMs [105].

Peptide-based proteins may also be used to target macrophages. A long-circulating liposome modified with a monoclonal anti-CD163 antibody was created by Rafique et al. in order to target the CD163 receptor expressed on macrophage membranes [107]. For the treatment of inflammatory bowel disease, Zhao et al. made lactoferrin-modified drug-loaded liposomes that actively target M1-like macrophages at the disease site (low-density lipoprotein receptor-related protein-1, LRP-1), lower inflammatory cytokine and reactive oxygen species (ROS) levels, and block the MAPK/NF- κ B pathway. The uptake efficiency of M1-like macrophages is 2.5 times higher in vivo and 2.2 times higher in vitro following lactoferrin modification [108]. Some proteins can be used directly as nanoparticles for drug delivery because of their significant molecular weight, similar to the polysaccharide-based nanoparticles we discussed above. A technetium-99m labeled natural human ferritin (Hfn) nanocage was built by Lian et al. By targeting transferrin receptor 1 (TfR1), Hfn facilitated macrophages' selective absorption of neutrophils in atherosclerotic plaque. Using a combination of computed tomography imaging and single-photon emission computed tomography, the atherosclerotic plaque infiltrates with macrophages in living mice [111].

Lipids The phospholipid bilayer cell membrane depends on phosphatidylserine (PS). When macrophages identify and phagocytize apoptotic cells, it may exhibit a "eat me" signal on their surface [109]. PS may attach itself to soluble bridging protein receptors and the phosphatidylserine receptor (PSR) on macrophages [109]. A carrier-free nanomotor powered by NO and modified with PS was created by Wu et al. Atherosclerosis locations with high ROS and iNOS expression function as chemotactic agents to trigger the chemotactic activity of nanomotors. PS then sends "eat-me" signals to specifically target macrophages in atherosclerosis plaques [116].

Vitamin Four members of the folate receptor (FR) gene family—FR α /FOLR1, FR β /FOLR2, FR γ /FOLR3, and FR δ /FOLR4—have a strong affinity for folic acid, often referred to as vitamin B9, a water-soluble vitamin [15]. Silver nanoparticles modified with folic acid were created by Yang et al. to specifically target M1-like macrophages, which demonstrated a five-fold increase in absorption compared to M0 macrophages. The internalized silver nanoparticles without any medication lowered the number of M1-like macrophages and M1 polarization, significantly retarding rheumatoid arthritis [110].

Macrophage-based drug delivery systems: development of living macrophage delivery system and macrophage membrane coated delivery system Some specific membrane proteins expressed on the surface of the macrophage membrane (MM) like the integrin (α 4 and α 4 β 1 integrin), C-C chemokine receptor type 2 (CCL2), and colony-stimulating factor-1 receptor (CSF-1R), make macrophages have the ability to chemotactic migration to inflammatory and tumor microenvironment sites. Therefore, using living macrophages as a delivery system and MM-coated drug delivery systems possess this functionality of targeting and inflammatory chemotaxis [13,117]. Delivery system for living macrophages



Functional nanoparticles are modified on the surface of the MM, or drugs or nanoparticles are delivered into macrophages via incubation, infiltration, and electroporation. Infrared light irradiation and enzyme activation trigger the release of the medication, and living macrophages are used as direct carriers. The gathered macrophages are then administered intravenously [118–120]. Macrophages often co-incubate with medicines or nanoparticles and load them by endocytosis due to their solid phagocytic capabilities. Compared to adhesion or electroporation techniques, the co-incubation approach will not harm the cell membrane and will prevent any potential off-target interactions with various biological components in vivo [118,119]. However, we should keep in mind that excessive drug loading may impact the immune system, cause macrophage death, and compromise the stability of medications within macrophages. Although these problems can be minimized by physically and chemically altering drug-loaded nanoparticles on the surface of the macrophage membrane, this may obscure membrane proteins and interfere with the regular operation of cell membranes [120]. Using living macrophages loaded with dexamethasone-loaded liposomes (Dex-LP), Sang et al. achieved maximum effective uptake following a 4-hour incubation period. Approximately 2, 6, 13, and 25 pg/cell of macrophages were loaded with the Dex-LP at 5, 25, 50, and

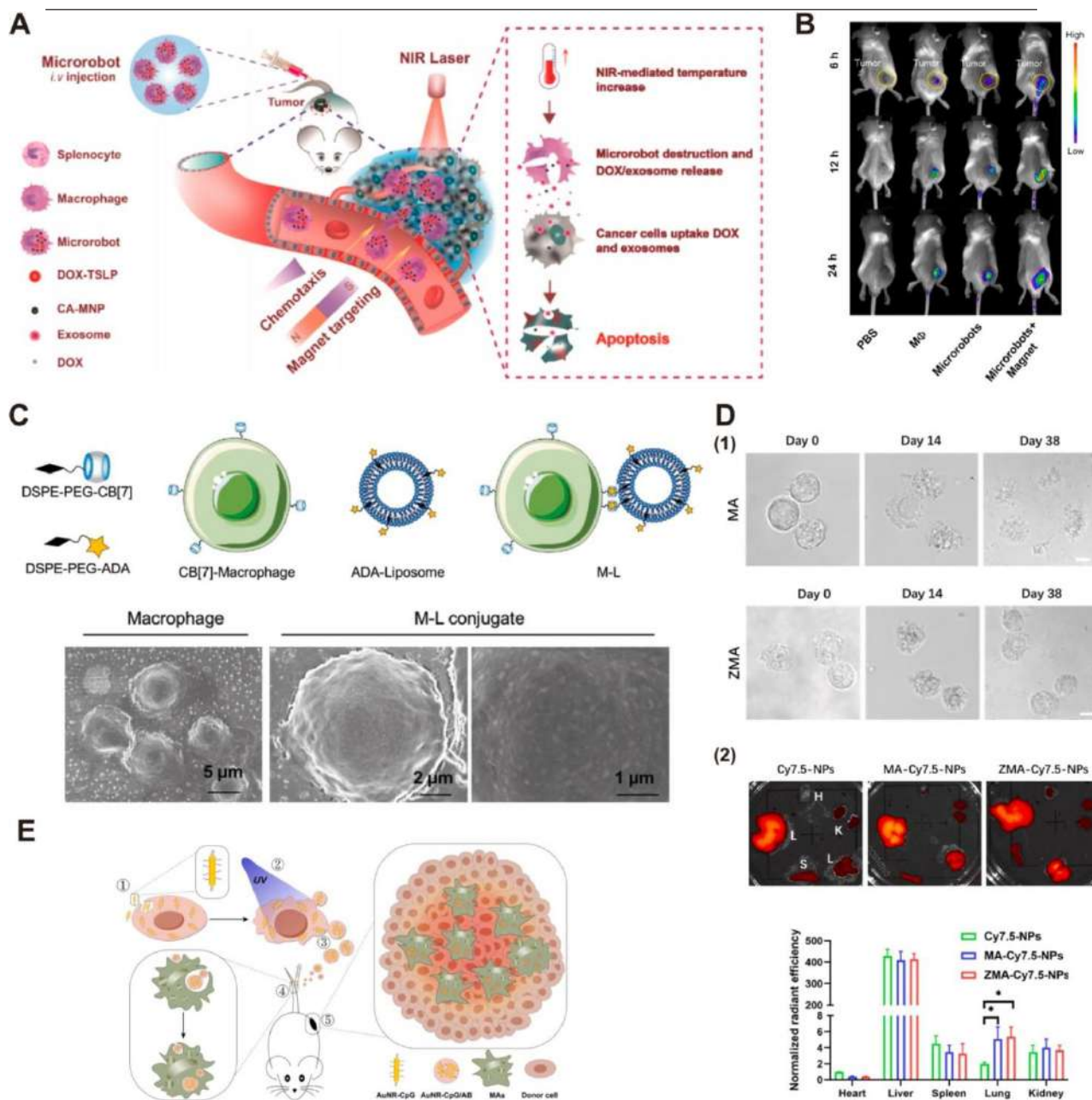


Fig. 4. Living macrophage delivery system.

(A) Diagram showing how the microrobots used chemotaxis and a magnetic field to target the tumor spots before using NIR-mediated medication release to eliminate the tumor. and (B) fluorescence pictures of mice with 4T1 tumors. Reproduced [122] with permission. American Chemical Society, copyright 2021. (C) A schematic representation of the supramolecular macrophage-liposome drug delivery system's production and characterization. Reproduced [123] with permission. By John Wiley and Sons, copyright 2021. (D) ZMA ("zombie" macrophages) and MA (living macrophages) suspended in PBS during 0, 14, and 38 days were observed using bright-field microscopy. Cy7.5-labeled macrophage biodistribution in different mouse tissues and quantitative analysis. Reproduced [124] with permission. American Chemical Society, copyright 2023. (E) Schematics of the increased tumor photo-thermal



immunotherapy using the macrophage "hitchhike" drug delivery method. Reproduced [125] with permission. American Chemical Society, copyright 2020.

100 μM after a 4-hour incubation period, respectively. Dexamethasone (Dex) release characteristics from macrophages also increased in a time-dependent way, reaching about 90% at 10 hours [121]. Additionally, it must guarantee that macrophages are capable of accurately releasing medicines at the intended location. Nguyen et al. used thermosensitive liposomes loaded with doxorubicin (DOX) and primary mouse spleen-derived macrophages as carriers loaded with superparamagnetic nanoparticles modified with citric acid to increase the targeting efficiency (Fig. 4A). The co-incubation approach was used to encapsulate 107 microrobots with 319.2 μg of Fe (EE% = 22.98%) and 56 μg of DOX (EE% = 12.45%). Through the use of a magnetic field controllability, active targeting, and responsiveness to infrared radiation, the microrobot was able to successfully navigate through the 3D cancer cell microspheres and, after applying a magnet, expanded the tumor site by about 1.5 times (Fig. 4B). Additionally, the microspheres' migratory ability is lower than that of main macrophages, which may be because of nanoparticle loading [122]. However, using macrophages' robust phagocytic ability to build the drug delivery system would be vulnerable to intracellular enzyme breakdown, which might result in early drug leakage and cell death. Premature deterioration may be prevented by altering the nanoparticles on the MM's surface by chemical bonding. By injecting lipid-modified cucurbit[7]uril (CB[7]) into MM and then allowing host-guest interactions with adamantane (AD) modified drug-loaded liposomes attached to the surface of living macrophage membranes, Gao et al. created a unique supramolecular macrophage-liposomes drug delivery system (Fig. 4C). When compared to drug-loaded liposomes, this supramolecular modified macrophage drug delivery system can remain stable for several hours and increase the drug amount by approximately 3.02 and 4.1 times for pneumonia sites and tumors, respectively. This has been shown to be an effective immunotherapy for treating acute pneumonia and melanoma [123]. Furthermore, the activity and function of macrophages will not be impacted by surface alteration. Certain nanoparticles may physically stick to the surface of macrophages in addition to modifying them chemically to achieve high bioactivity [126,127]. In contrast to the traditional cellular loading via endocytosis, Zhu et al. created an adivalent metal ion-phenolic network (MPN) that allows adhesion of PLA nanoparticles, which can adhere to the surface of MM by co-incubating under an ice bath for just two minutes. This enhances the cell viability and migrating chemotaxisability of the macrophages. In comparison to trivalent ions (Fe^{3+} and Cr^{3+}), they discovered that MPN nanoparticles containing divalent ions (Cu^{2+} , Mn^{2+} , Zn^{2+} , and Co^{2+}) showed reduced cellular absorption and improved cell surface adherence over 10 days. Compared to intracellular loading by cell absorption for three hours, this approach obtained greater drug loading (about 1 $\mu\text{g}/106$ cells). Furthermore, after being loaded onto macrophages, the concentration of nanoparticles at the tumor location may rise by 3.7 times, thereby preventing lung metastasis and tumor progression [127].

It's interesting to note that macrophages, as carriers, may accomplish targeted medication delivery while simultaneously having immuno-modulatory effects at the target region. By loading polyinosinic-polycytidylic acid (Poly I: C, PIC) encapsulated poly (lactic-co-glycolic acid) nanoparticles (PLP NPs) on the surface of BMDMs using the maleimide-thiol conjugation, Zhou et al. created a biomimetic system that could effectively deliver PIC to re-program BMDMs into tumor-killing M1-like macrophages and trigger insitu tumor-specific immune responses [128].

Maintaining drug loading and macrophage activity over prolonged storage is a difficult task for living macrophage drug delivery systems. Xu et al. used cyclodextrin-modified "zombie" macrophages supramolecularly attached to adamantane-functionalized nanodrugs to create a cryo-shock macrophage-based drug delivery system in order to overcome these problems. Over the course of a 38-day observation period, the "zombie" macrophages maintained their full cell shape, membranes, and biological capabilities while demonstrating superior storage stability compared to real macrophages (Fig. 4D) [124]. Rapid exocytosis of nanoparticles from live macrophages is possible, particularly for tiny particles such as sub-5 nm Au nanoparticles, which may attain 45.6% exocytosis from live macrophages in under 24 hours [129]. In order to assure the efficient transport of Au nanoparticles to the tumor, Xu et al. obtained "half-dead" and "dead" macrophages loaded with Au nanoparticles. This significantly decreased the exocytosis of Au nanoparticles below 5 nm in the live macrophage delivery system in vivo. When compared to free Au nanoparticles, the "dead" macrophage delivery mechanism also considerably lowered the toxicity to unwanted organs and reduced the number of Au nanoparticles that crossed the blood-brain barrier by about 39.2 times [129]. Furthermore, intracellular hydrogel technology may be used to transform live macrophages into hard



gel macrophage particles while maintaining MM and capacity integrity [130]. Apart from exogenous macrophage delivery techniques, nanoparticles may also "hitchhike" into the body's circulation to target lesion sites in vivo by using host macrophages [131]. By aggressively targeting and delivering medications to the illness site, the macrophage "hitchhiking" technique may partially avoid the immune system's clearance. Crucially, real-world bench testing is still a long way off [131]. Depending on the type of nanoparticle, TAMs may actively move in the direction of the extravasated nanoparticles from blood vessels, engulfing and redistributing them into the tumor stroma. The depth of penetration attained will then vary. For instance, macrophages carrying nanoparticles were transported into the tumor site at a rate that was two to five times higher than that of passive diffusion of nanoparticles [132]. Drugs encapsulated by apoptotic vesicles were reported by Zheng et al. to be able to be taken up by monocytes or macrophages following intravenous injection and then actively penetrating the central tumorsite in vivo (Fig. 4E) [125]. Sofias et al. made the significant observation that targeting ligand-modified nanoparticles accumulated at the tumor site through a variety of targeting delivery methods, including the "hitchhiking" of mono-cytes/macrophages, which is a crucial mechanism for active tumor targeting [133]. Delivery system with macrophage membrane coating

The membrane camouflaged nanoparticles coated with MM can have or increase the ability of active targeted delivery by using the antigen-antibody specific binding to intervene in the immune response and inherit the homing and chemotaxis of macrophages. These nanoparticles typically exhibit higher tumor penetration and accumulation, longer blood circulation time, and more effective immune escape [134]. Cell membranes are typically obtained by a multi-step process that includes sonication, freeze-thaw, extrusion, hypotonic lysis buffer, and dounce homogenizer. Sonication, co-extrusion, and microfluidic electroporation are then used to coat the cell membranes on drug-loaded nanoparticles [135,136]. Drugs are often put into nanoparticles in this method, and the cell membrane is either fused with drug-laden liposomes or coated to create a traditional core-shell structure. A thorough explanation and comparison of MM extraction, separation, and coating methods were given by Khatoon et al. [136]. The coated nanoparticles, not the method used to prepare the membrane-coated drug delivery systems, are the primary determinant of the encapsulation efficiency.

Gao et al. created a biomimetic MM-coated drug delivery device that changed its functionality in response to ROS. MM gave nanoparticles the capacity to aggressively target inflammatory areas while avoiding their movement via the ticuloendothelial system. Then the ROS responsiveness nanoparticles released the loaded medicines to treat atherosclerosis [137]. Interestingly, MM may be changed using functionalized membrane coatings of live materials. Gao et al. employed MM coated with modified drug-loaded liposomes and live chlorella (Chl, green algae) on the exterior of the cell membrane via a host-guest interaction. Through photosynthesis, the CHL might enhance the oxygen-deficient environment at the tumor location, and this delivery mechanism could have the inflammatory homeostatic function of macrophages [138]. Additionally, MM could act as membrane-based cellular nanosponge coatings. receptors on the surface that bind viruses or cytokines [139–144]. Tan and Li et al. created alveolar MM-coated lopi-navir-loaded PLGA nanocarriers (PLGA-LPV@M), as seen in Fig. 5A. These nanocarriers exhibited the same surface receptors, such as coronavirus receptors and other cytokine receptors. PLGA-LPV@M were employed as baits that could inhibit coronavirus from entering host cells and particularly bind pro-inflammatory factors such as IL-6, IL-1 β , and TNF- α for the adjuvant therapy of anti-inflammatory and anti-viral (Fig. 5B) [139,140]. Interestingly, compared to nanoparticles coated with M0 and M1-like MM, nano-particles coated with M2-like MM may absorb more inflammatory factors, such as IL-1 β and TNF- α [141]. This is comparable to the use of MM surface protein receptors to adsorb and neutralize the globally prevalent severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). An MM-coated PLGA cellular nanosponge was created by Zhang et al. to neutralize SARS-CoV-2, which was unable to infect normal cells, demonstrating an antiviral effect that was observable in vitro (Fig. 5C). They discovered that human angiotensin-converting enzyme 2 (ACE2) receptors are expressed by membrane-coated epithelial cells and MM-coated nanosponges, and that CD147 receptors exhibit a higher capacity for neutralization against SARS-CoV-2 infection than membrane-coated red blood cells (Fig. 5D) [143]. Through the spike glycoprotein S protein, which may attach to ACE2 and glycosaminoglycans like heparin, SARS-CoV-2 attaches and penetrates cells [145]. In order to increase the density of heparin on the surface of MM, Ai et al. functionalized the surface of MM using the cellular nanosponge structure of MM-coated PLGA (Fig. 5E). While the IC₅₀ was lower at 0.0254 μ g/mL than that of MM-coated PLGA, where it was 170 μ g/mL (Fig. 5F), the heparin-functionalized MM-coated PLGA demonstrated a more substantial binding ability with the virus S protein, which significantly enhanced the inhibitory effect on the infection of SARS-CoV-2 [144]. It should be noted that there is no connection between the cellular nanosponge platform and viral mutation or possible virus species. Once the virus infects host

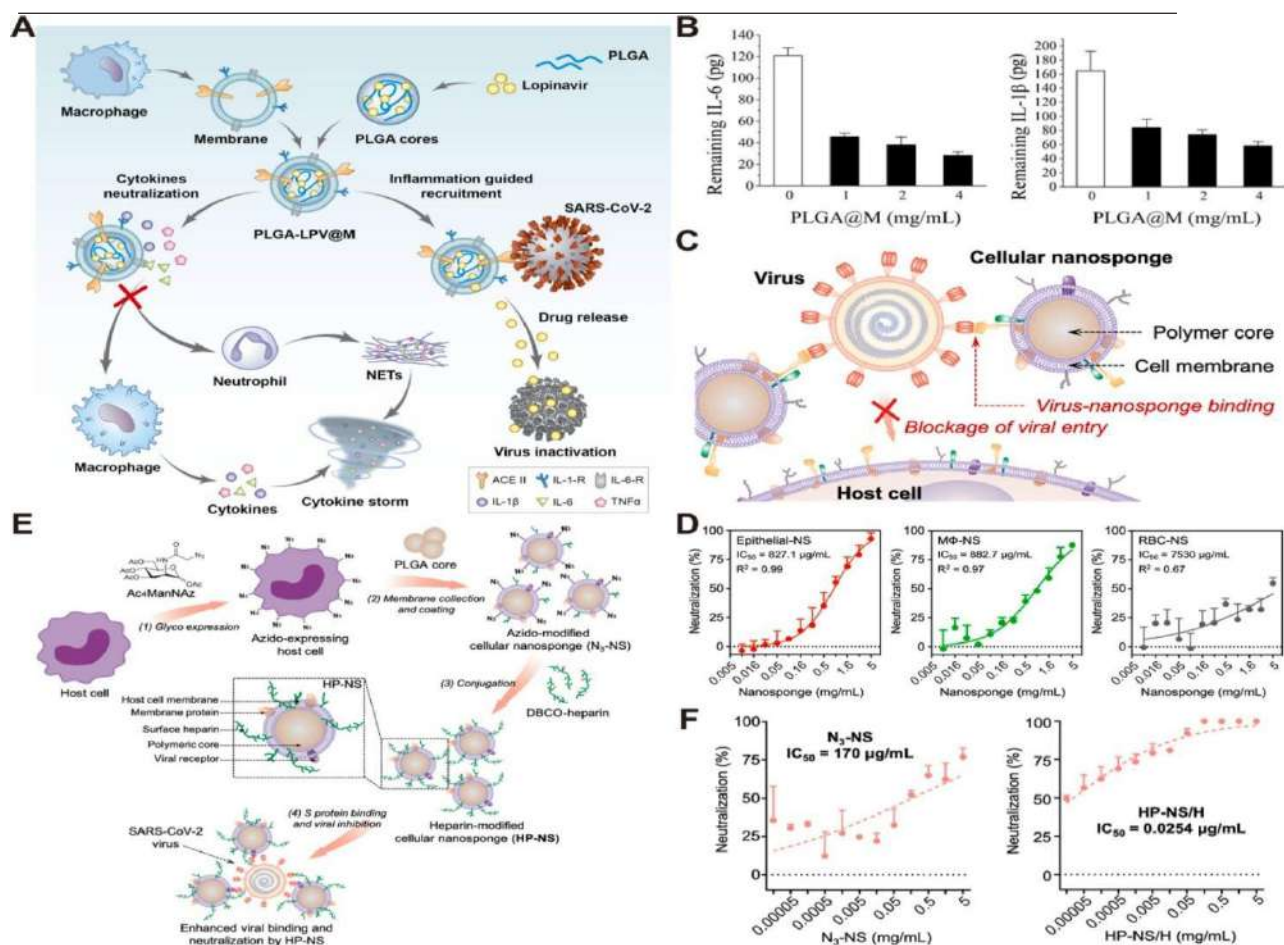


Fig. 5. Macrophage membrane coated delivery system.

(A) Schematic illustration of macrophage biomimetic nanoparticle-based drug delivery system (PLGA-LPV@M) for anti-inflammation and targeted anti-viral treatment in COVID-19. And (B) the result of the binding capacity of PLGA@M to recombinant pro-inflammatory factor of human IL-6 and IL-1β. Reproduced with permission[139]. Copyright 2021, Springer Nature. (C) Schematic mechanism of cellular nano-sponges inhibiting SARS-CoV-2 infectivity. And (D) the result of neutralization against SARS-CoV-2 infection by epithelial cells membrane-coated nanosponges (Epithelial-NS), macrophages membrane-coated nanosponges (MΦ-NS), and red blood cells membrane-coated nanosponges (RBC-NS, used as a control). Reproduced with permission [143]. Copyright 2020, American Chemical Society. (E) Schematic illustration of engineering surface glycans onto cellular nanosponges to promote SARS-CoV-2 inhibition. And (F) neutralization of live SARS-CoV-2 infectivity by HP-NS. Reproduced with permission [144]. Copyright 2021, American Chemical Society. cells, the cellular nanosponge can neutralize the virus showing broad-spectrum anti-viral potential applications [146].

Taking advantages of a simple and efficient membrane modification method, the lipidated modification of peptides or protein can help them anchored on the cell membrane. Han et al. anchored lipidated rabies virus glycoprotein and triphenylphosphine cation to the MM coated with solid lipid nanoparticles (SLN). The MM modified SLN could significantly cross the BBB more than un-modified SLN and then target neuronal mitochondria for the treatment of sporadic Alzheimer's disease [147]. In addition, there is also an effective membrane modification method, employing an inducer that encourages macrophages to express



specific receptors to get the required function before the extraction of MM from live macrophages. Yan et al. utilized LPS to stimulate macrophages to express toll-like receptor TLR2/1 complexes. The MM was coated on the surface of the nanoparticles to give them the capacity to target *Porphyromonas gingivalis*, which was encapsulated in hydrogel for the treatment of periodontitis [148]. Similarly, Hou et al. obtained MM-PLGA that the MM isolated from the IFN- γ stimulated macrophages produced large amounts of programmed death-ligand 1 (PD-1), adhesion molecule receptors, and pro-inflammatory cytokine receptors. The MM-PLGA can be accumulated to the arthritis site show 3.6-folds higher than that of PLGA coated with un-induced native MM, and stimulate effective synergistic anti-inflammatory, immunosuppressive effects for arthritis treatment [149]. Furthermore, a large number of studies have shown that the mixed membrane obtained by fusing cell membranes from different cells could be used to camouflage nanoparticles, which could give full play to the advantages and integrate the benefits of various cell membranes, and increase the functionality of nanoparticles [150–153]. For example, Zhang et al. created a hybrid-sensitized nanosystem with a mixed breast cancer cell membrane and MM. By combining the homologous adhesion detection capacity of breast cancer cells and the immune escape ability of macrophages, this nanosystem may successfully target breast cancer and increase the bioavailability of photodynamic therapy in vivo [152]. Yin et al. designed a PLGA coated with MM and neutrophil membrane by way of sonication and extrusion (NM-PLGA) (Fig. 6A,B), which combined the stimulating homing response of macrophages with strong inflammatory chemotaxis of neutrophils, which could effectively cross the BBB (285.36-folds over the standard condition that did not add chemoattractant in BBB model in vitro), respond to inflammatory stimuli and specifically accumulate 24.4-folds than PLGA in mouse brain inflammatory model in vivo (Fig. 6A,C) [153]. Modifying diverse characteristics and functions of phospholipid materials on the cell membrane coating to manage the coating's integrity, fluidity, and permeability is one of the most efficient techniques to improve the targeted delivery efficiency of cell membrane-coated nanoparticles. Liu et al. found that the integrity of cell membrane coating influences the internalization process of biomimetic nanoparticles. Nanoparticles coated with cell membrane that a coverage area was higher than 50% may enter cells alone, and nanoparticles need to gather together before internalization to achieve a reasonably large coverage area when the covering area of the cell membrane is less than 50% (Fig. 6D, E) [154]. This is presumably owing to the enormous quantity of membrane proteins on the cell membrane and saturated phospholipids,

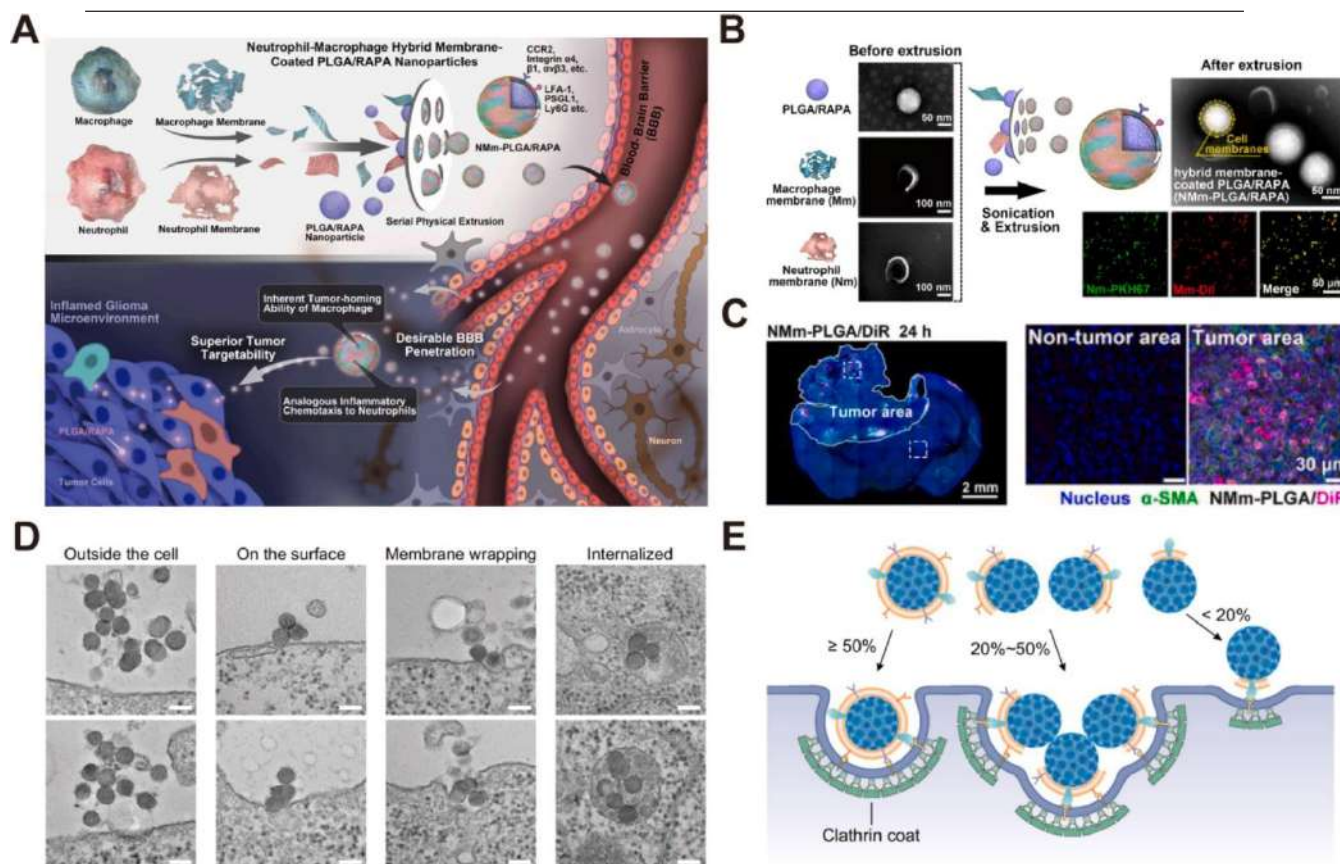


Fig. 6. The hybrid macrophage membrane coated delivery system and the endocytic entry mechanism about the membrane coating integrity. (A) Schematic illustration of preparing a neutrophil-macrophage hybrid membrane-coated PLGA/RAPA nanoplatform (NMm-PLGA/RAPA); (B) The representative transmission electron microscope (TEM) images of nanoparticle and cell membranes before and after extrusion. (C) Representative fluorescence images of NMm-PLGA/DiR (red) and α-SMA (green) in brain tumor at 24 h after NMm-PLGA/DiR administration. Reproduced with permission [153]. Copyright 2022, Elsevier. (D) TEM images showing the process of cell membrane-coated nanoparticles being absorbed by cells. (E) schematic illustration of a possible endocytic entry mechanism for partially cell membrane-coated nanoparticles. Reproduced with permission [154]. Copyright 2021, Springer Nature. resulting in low membrane fluidity for the inability of adjacent cell membrane segments to fuse spontaneously. The introduction of exogenous phospholipids fused to cell membranes can improve cell membrane fluidity, then promote the fusion of cell membrane fragments and increase the percentages of nanoparticles that fully coated with cell membrane from 6% to 23%, thereby increasing the targeting efficiency of the cell membrane coated nanoparticles [155]. However, artificial phospholipids also need to be chosen with great care. Wang et al. found that cholesterol depleting of cell membranes significantly enhanced the enzymatic activity when treating with fabricated RBC-membrane-coated nanoparticles containing therapeutic CAT enzymes, which is possibly due to the enhanced membrane permeability [156].

Macrophage-secreted drug delivery systems: construction of macrophage extracellular vesicles delivery system and macrophage extracellular vesicle membrane coated delivery system



Macrophage-secreted extracellular vesicles (EVs) are plasmamembrane-derived vesicles fusing and released by macrophages into the extracellular space, which contains specific membrane proteins from MM, they are capable of inheriting the inflammatory chemotaxis, immune escape, and stimulating homing response ability of macrophages. EVs show less immunogenic than their host cell membranes due to the more negligible number of expressions of transmembrane proteins like major histocompatibility complex (MHC) on their surface, but the exact amount depends on the cellular origin [157,158]. EVs carry a variety of bioactive substances (such as protein, lipid, and nucleic acid). As a way of cell interaction, EVs are the primary chemical messengers of inter-cellular communication and can affect the biological function of recipient cells. According to the source and particle size, the EVs are mainly divided into three categories: a) Small EVs with a diameter of 50–150 nm, such as exosomes (Exos), small exosomes, and ciliary ectosomes; b) Medium EVs with a diameter of 200–800 nm, such as microvesicles, FDC-derived iccosomes, and T cell microvilli particles; c) Large EVs with a diameter of ≥ 1000 nm include apoptotic bodies, large oncosomes, and beaded apoptopodia, etc [159]. Similar to MM and macrophages, the extracellular vesicle membrane (EVM) prepared from EVs secreted by macrophages has the same membrane protein as EVs, so the drug delivery system coated with EVM shows the same membrane surface characteristics as EVs.

Macrophage extracellular vesicle delivery system

Macrophage-derived EVs are often used to target delivery drugs or genes attributed to similar surface membrane receptors from macrophages. Kimiz Gebologlu et al. provided a detailed description and comparison of various methods for EVs isolation and drug loading efficiency [160]. They mentioned that pre-loading contents into macrophages is mainly via co-inclusion, transfer and electroporation methods, while separation of EVs and post-loading methods of the drug are containing the ways of sonication, extrusion, surface treatment, and hypo-tonic dialysis, while incubation, freeze-loading, and pH gradient [160]. Compare to the pre-loading methods, post-loading approaches are not so simple and easy, and they may lead to EVs membrane damage, inactivation of proteins, or EVs aggregation risk, but they can result in controlled and higher drug loading efficiency [160–162].

While selecting macrophage-secreted EVs as carriers, it is necessary to consider the different phenotypes of macrophages. There are some variabilities in the composition of EVs secreted by macrophages with different phenotypes, such as protein, lipid, and RNA. Dechantsreiter et al. taken the proteomic analysis revealed significant differences in protein profiles between large and small EVs from macrophages, and between EVs secreted by macrophages with different phenotypes. HLA-DR (class II MHC protein) was expressed on 40% of M1-like macrophages secreted EVs (M1-EVs) which was 2-folds more than that of M0-like macrophages secreted EVs (M0-EVs) and M2-like macrophages secreted EVs (M2-EVs). Some pro-inflammatory related proteins such as IL-18 and IL-1 β are only expressed on M1-EVs, while CD163, folate receptor β are only defined on M2-EVs [163]. Reinicke et al. used quantitative mass spectrometry to determine the differences in lipid composition of M1-EVs and M2-EVs. They found that some pro-inflammatory lipids like tetra-*n*-12-HETE and 8-HETE/12-HETE were significantly decreased or not detected in the M2-EVs [164]. Pantazi et al. used small RNA sequencing revealed a different miRNA profile in M1-EVs and M2-EVs, a higher relative abundance of miRNA and a lower quantity of tRNA fragments in M2-EVs compared to M1-EVs [165].

Since EVs secreted by different phenotypes of macrophages show different surface receptors and contents, different phenotypes of macrophage Exos can be used depending on the diseases. The EVs secreted by the different phenotypes of macrophages used in the subsequent studies showed reverse inflammatory regulation



and macro-phage polarization effects [166–169]. Li et al. isolated Exos from M2-like macrophages (M2-Exos) transfected the IL-10 plasmid, and then loaded with betamethasone sodium phosphate (BSP) using the electroporation method. The encapsulation efficiency (EE%) was 6.97% for IL-10 pDNA and 29.03% for BSP, and M2-Exo releases about 75% of BSP within 20 h. Importantly, the M2-Exos were significantly uptaken by M1-like macrophages compared to M0-like macrophages. M2-Exos can target to inflamed joint sites and promote M1 polarization into M2-like macrophages by reducing the secretion of pro-inflammatory cytokines to retard rheumatoid arthritis [168]. On the contrary, Wang et al. developed M1-like macrophage-derived EVs that loaded hydrophobic agents and hydrophilic hypoxia-activated prodrug (Fig. 7A). The EVs penetrated the BBB, polarized M2 into M1-like macrophages to modulate the immunosuppressive tumor microenvironment, then activated the prodrug to generate ROS to achieve chemiexcited photodynamic therapy [169]. Also, M1-like macrophage-derived exosomes (M1-Exos) alone can be used as a cancer vaccine adjuvant owing to its pro-inflammatory function [170].

After modifying macrophage-derived EVs with small molecules, macromolecules, and peptides, EVs will achieve more functions, such as higher targeting efficiency and immunoregulation ability [171,175]. Li et al. designed M2-Exos modified with cell-penetrating peptide R9 peptide (A sequence: RRRRRRRRR) loaded with curcumin by the method of sonication (EE% = 27.52%). The Exos showed a more vital ability to target inflammation sites after modifying the R9 peptide *in vitro* and *in vivo* [175]. As shown in Fig. 7B, Wei et al. developed mannose-modified macrophage-derived microvesicles (MVs) loaded with metformin to effectively target M2-like TAMs and repolarized into M1-like TAMs, and reshaped the tumor immune microenvironment by increasing the recruitment of CD8⁺ T cells, reduced the immune-suppressive infiltration of myeloid suppressor cells, regulatory T cells, promoted anti-PD-1 antibody treatment, and enhanced memory immunity after the combined treatment [171].

In addition to the direct modification of Exos, exosome-liposome fusion strategies can be used as a potential method to ameliorate the problems of insufficient Exos loading efficiency, uncontrollable poly-dispersity, and difficulty in maintaining long-term stability [176,177] (Lopes et al. compared the advantages and disadvantages between natural Exos and synthetic liposomes [178]). Han et al. established the M1-Exo fused with photothermal sensitive liposomes (ELP) loaded with

Granzyme B (GrB) and siSB9 (Fig. 7C). The EE% of GrB was $36.3 \pm 4.3\%$ and siSB9 was $49.9 \pm 3.8\%$ significant improvement compared to pure M1 Exo ($23.9 \pm 1.6\%$ for GrB and $37.3 \pm 9.3\%$ for siSB9). Interestingly, B16F10 and 4T1 tumor cells internalized more ELP than liposomes that not fused with M1-Exos, but no significant differences in normal liver cells, and significantly higher liposomes cell uptake than ELP were observed in RAW 264.7 *in vitro*. The liposomes fused Exos helped the nanoparticles targeting drug delivery to the tumor site and escaping capture of macrophages *in vivo* [172]. Similarly, fused liposomes can be used for MM to improve the properties and function of nanoparticles.

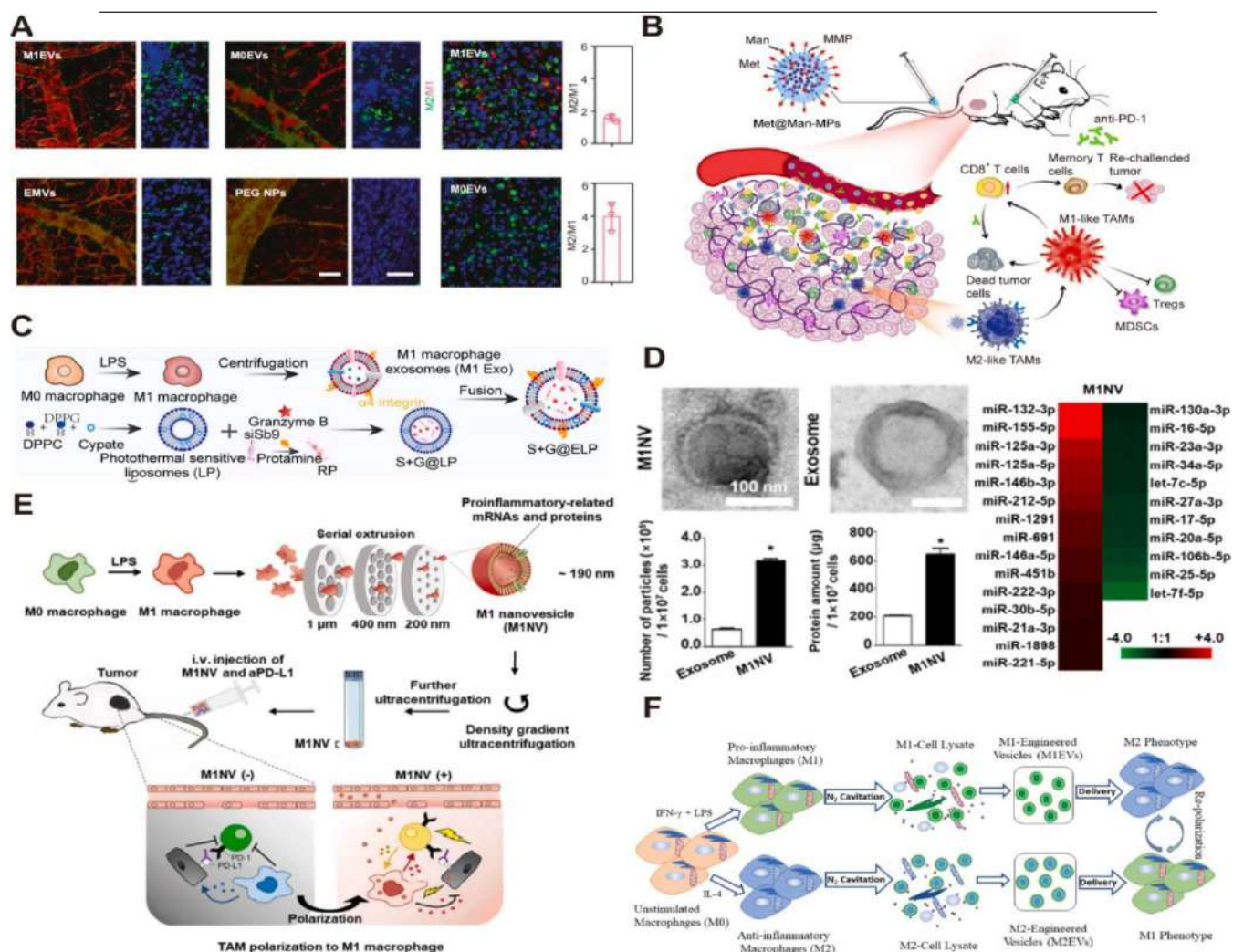


Fig. 7. Macrophage-secreted delivery system.

(A) Time-lapse two-photon pictures of the diffusion of M1EVs, M0EVs, EMVs (erythrocytes), and PEG NPs across the brain microvascular endothelial cells in vivo. blood vessels (red); M1EVs, M0EVs, and EMVs, PEG NPs tagged with FITC (green). And immunofluorescence photos of M2 and M1-like macrophages, and quantitative analysis of M2/M1 ratios. Reproduced with permission [169]. Copyright 2022, Springer Nature. (B) Schematic illustration of mannose-modified macrophage-derived microparticles loading metformin (Met-Man-MPs) to increase tumor resistance of anti-PD-1 treatment. Reproduced [171] with permission. Copyright 2022, Springer Nature. (C) A schematic representation of the nanoparticles that merged photothermally sensitive liposomes with M1-Exos. Reproduced [172] with consent. Copyright Elsevier, 2022. (D) TEM comparison of M1-like macrophage exosome-mimetic vesicles (M1NVs) and M1-Exos shape, number, and protein content. M1NVs and their miRNAs. The manufacture of M1NVs and their therapeutic effects, including their capacity to enhance the anti-cancer effectiveness of checkpoint inhibitors in cancer treatment, are shown in (E). Reproduced [173] with permission. American Chemical Society, 2018. All rights reserved. (F) Diagram showing the process of producing exosome-mimetic vesicles for M1 and M2-like macrophages and the polarization ability of the macrophage phenotypes. Reproduced [174] with permission. American Chemical Society, copyright 2020. Additionally, by altering the lipid



bilayer composition of liposomes, cellular uptake behavior may be modulated [179]. The low yield of exos produced by macrophages is a challenge for macrophage-secreted exos, but this can be addressed by creating macrophage-exos-mimetic vesicles [180,181]. The extrusion approach primarily creates macrophage Exos-mimetic vesicles, however the starting material may be sourced from various macrophage components, excluding extracellular vesicles [182,173,183,174]. The protein content of these macrophage Exos-mimetic vesicles is much greater than that of Exos (Fig. 7D), and they exhibit a comparable structure and miRNA to Exos [173]. In the colon cancer model, Jang et al. discovered that drug-loaded Exos-mimetic vesicles had a greater transport efficiency than free drug, drug-loaded Exos, or drug-loaded micro-sized cells [181]. Beak et al. found that macrophage Exos-mimetic vesicles generated from equal number of cells exhibited 25-folds greater protein content than macrophage-secreted Exos [182], and comparable findings were also demonstrated in the work by Choo et al. (Fig. 7D) [173]. This might be one of the causes of the Exos-mimetic vesicles' increased delivery efficiency. Like M1-Exos, M1-like macrophage Exos-mimetic vesicles may also polarize M1 and repolarize M2-like macrophages, which is advantageous for treating organ fibrosis, cancer, and other illnesses (Fig. 7E, F) [173,183,174]. On the other hand, in light of M2-like macrophages' anti-inflammatory properties [174,184], Qiao et al. created novel particles that included M2-like macrophage

Exos-mimetic vesicles and liposomes, which could be phagocytosed by infiltrating neutrophils and macrophages and target pneumonia symptomatic areas, drastically decreased inflammatory cell infiltration, accomplished control of cytokine storm, and inhibited oxidative stress [184]. Different cell membrane functions may be merged by fusion with cell membranes, and EVs can also go through the same functionalization modification. In order to inherit the source cells, Rao prepared Exos-mimetic vesicles mixed with the membrane of cancer cells, M1-like macrophages, and platelets could effectively accumulate at the surgical wound site, interact with circulating tumor cells in the blood, repolarize TAM towards the M1-like phenotype, and block CD47-SIRP α interactions, which in turn effectively inhibited local recurrence and distant metastasis of malignant melanoma [185]. Delivery method influenced by the membrane of macrophage extracellular vesicles. Like cell membrane coatings, extracellular vesicular membranes (EVMs) are made from EVs and then applied to the surface of nanoparticles. While overcoming their drawbacks, EVM-encapsulated nanoparticles combine the pharmaceutical benefits of nanoparticles (higher drug-carrying capacity, ease of scalability, greater flexibility for surface modification, and controlled drug release) with the advantages of endogenous EVs (improved biocompatibility, decreased clearance by mononuclear phagocyte systems, and tissue specificity) [178,186,187]. Improved interfacial characteristics, enhanced cell/tissue targeting, immune evasion capacity, and a longer to-body circulation length are all conferred to the nanoparticles by this modified approach with macrophage EVM coating [187–190]. For example, in order to treat glioblastoma multiforme, Wu et al. created a membrane coating for macrophage exosomes that was altered using AS1411 aptamers. This allowed catalase-encapsulated silica nanoparticles to demonstrate efficient BBB penetration and cancer cell targeting capabilities [191]. Intrinsic targeting, cell-specific absorption, prolonged somatic circulation, improved biocompatibility, stability, and immune evasion are only a few benefits of encapsulating nanoparticles with naturally occurring Exos membranes [178]. Remarkably, the protein content of the MM was five times lower than that of the macrophage-secreted microvesicle membrane (MMVs) from the same number of macrophages (Fig. 8A). These vital membrane proteins, along with 151 other membrane proteins from the MMVs, were also discovered in the MM and may provide them comparable biological activities (Fig. 8A,B). Following coating

In order to treat rheumatoid arthritis, PLGA nanoparticles with MMVs can efficiently target the inflammatory site



of osteoarthritis [90]. Additionally, compared to the identical cell membrane coated nanoparticles, the cancer cells' produced Exos membrane coated nanoparticles demonstrated superior homologous targeting ability. After preparing A549 cells with both cell membrane and exos membrane, Liu et al. found that in A549 tumors in vivo, exosmembrane-coated PLGA accumulated one-fold more than cell membrane-coated PLGA and 5.5 times more than uncoated PLGA [192]. Depending mostly on the variable expression of membrane proteins, the functionalities of Exos membrane-coated nanoparticles made from Exos released by macrophages with distinct phenotypes also vary. To load suberoylanilide hydroxamic acid, Li et al. created mesoporous silica-modified upconversion (SUC) nanoparticles, which were subsequently concealed by an Exos membrane made from M1-like macrophages. In order to produce a superior anti-tumor effect, they discovered that the nanocarriers that retained the integrin $\alpha 4 \beta 1$ expressed on the Exos membrane could help target and homing the VCAM-1 on the tumor, exhibit temporal and spatial resolution, and encourage drug accumulation in the tumor (Fig. 8C) [193]. Exos from M2-like macrophages were obtained by Pei et al., who then coated the Exos membrane on the surface of PLGA nanoparticles loaded with siRNA. By reducing lung inflammation, the biomimetic nanoparticles delayed allergic asthma by targeting M2-like macrophages in the inflammatory region of the lung, downregulating their percentage and inflammatory cytokine production via gene silencing [194]. According to cell membrane coating, the proteins expressed on the surface of Exos membranes are also crucial. The integrity of membrane protein structure is maintained while modulating the expression of Exos membrane proteins by adding appropriate inducers and modifying the membrane with synthetic target ligands to achieve receptor or in-situ targeting functions.

3. Overview and Prospect

This research examines the immunomodulatory effects of macrophage phenotype and macrophage-related treatment techniques with the control of phenotypic switching and the development of drug delivery systems, based on the functional variety and phenotypic plasticity of macrophages. Using macrophage phenotypic regulation as a basis, we first examined disease treatment approaches and macrophage heterogeneity. Next, we included FDA-approved small-molecule medications in Table 1 and

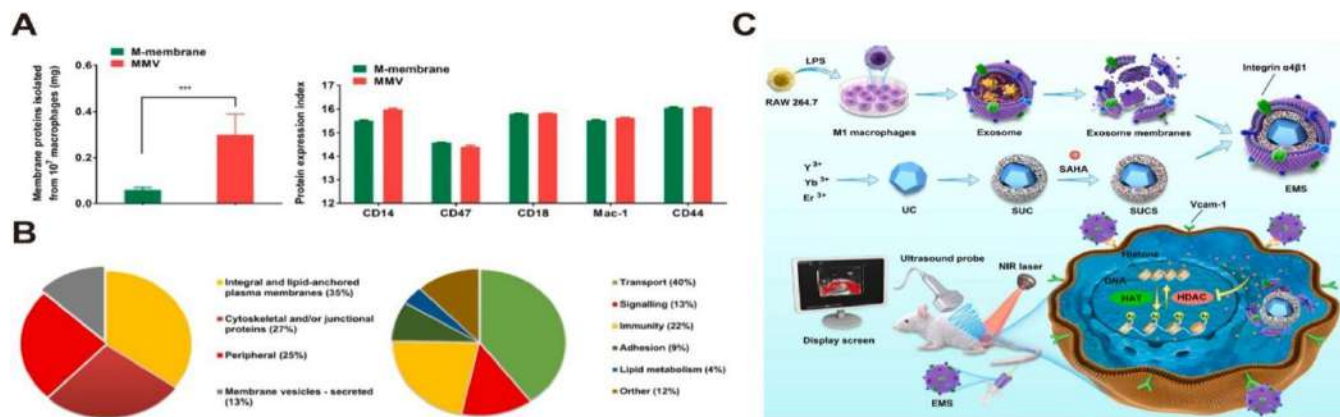


Fig. 8.Macrophage extracellular vesicle membrane coated delivery system.

(A) Purified MMV and macrophage membrane (M-membrane) protein content and crucial protein extracted from the same number of macrophages. Additionally, the pie charts in (B) display the MMV protein categorization according to molecular function and cellular location, respectively. Reproduced [90] with permission. American Chemical Society, 2019. All rights reserved. (C) Diagrammatic representations of the macrophage exosome membrane-coated nanoparticle (EMS) production procedure and the in vivo biological effects. Reproduced [193] with permission. All rights reserved. SpringerNature.

emphasized their clinical uses in the primary chronic illnesses. Finally, a number of drug delivery methods connected to macrophages that are used to treat the condition were reviewed and presented. The drug delivery system can actively target macrophages, inflammatory chemotaxis, tumor homing, immunomodulation, neutralization of viruses/inflammatory factors, and more. These three types of macrophage drug delivery systems, as illustrated in Fig. 1, mainly use MM surface receptors. In order to address associated disorders, this review attempts to provide a stronger scientific foundation for regulating macrophage morphologies and precisely targeting medication delivery linked to macrophages. The practical design of macrophage-based immunotherapy strategies includes, but is not limited to, the use of highly biocompatible carriers and the sensible application of physical properties like light, heat, and magnetism because of the intricate inflammatory microenvironment, macrophage recruitment, and polarization mechanism in various diseases. Additionally, to increase the affinity between ligands and MM receptors, ligands' quantity, density, spacing, spatial direction, and valence are optimized [15,112]. Additionally, improving the targeting efficiency and specificity of macrophages may be achieved by real-time monitoring of macrophages to elucidate their dispersion and polarization process within the inflammatory milieu [133]. The use of M1 or M2 dichotomies for naming macrophages may be overly simplistic, according to a growing body of research, which suggests that macrophages have a comprehensive identity and activation status. Instead, researchers suggest naming macrophages based on their behavior in their natural habitat, which may be more reasonable [20,195,196]. A more accurate and detailed classification of macrophages might provide a more useful roadmap for therapeutic approaches using macrophages. Despite the fact that different drug-loading strategies have their own benefits and drawbacks [119,135,160], effort should be placed on increasing drug loading effectiveness and reducing membrane damage to the surface functional proteins. In order to include the benefits of the aforementioned approaches and minimize their drawbacks, it is advisable to broaden the area of the investigation. Recent reviews have compiled a list of several macrophage-related targets and pharmaceutical drugs. We reclassified these delivery mechanisms associated with macrophages into three primary delivery systems. Despite the widespread usage of macrophage-derived vesicles, a few issues still need to be resolved in order to bridge the gap between the bench and the clinic. 1) The ambiguous relationship between macrophages and loads, which might negatively impact physiological processes as adhesion, migration, and cell signal transduction [13,117]. 2) Imminent issues include the diversity and variety of macrophages as well as their potential immunoregulating and therapeutic roles [118,120]. 3) various phenotypes or states of cells that express various membrane proteins, as well as non-standardized or inappropriate membrane extraction and



coating techniques, may result in varying therapeutic outcomes [134,152,154]. 4) Effective methods are needed to address the issues with the large-scale production, extraction, purification, screening, effectiveness, and safety assessment of macrophages and their derived nanoparticles in biomaterials [158,192]. As of right now, targeting macrophages may be a promising immune-modulating response strategy for chronic diseases. If these obstacles can be addressed and standardized procedures are established, the design of these kinds of drug delivery systems related to macrophages will also offer more potential options for future clinical therapeutic applications.

References

- A. Mantovani, P. Allavena, F. Marchesi, C. Garlanda, Macrophages as tools and targets in cancer therapy, *Nat. Rev. Drug Discov.* 21 (11) (2022) 799–820.
- L. Kraehenbuehl, C.H. Weng, S. Eghbali, J.D. Wolchok, T. Merghoub, Enhancing immunotherapy in cancer by targeting emerging immunomodulatory pathways, *Nat. Rev. Clin. Oncol.* 19 (1) (2022) 37–50.
- J. Ochando, W.J.M. Mulder, J.C. Madsen, M.G. Netea, R. Duivenvoorden, Trained immunity - basic concepts and contributions to immunopathology, *Nat. Rev. Nephrol.* 19 (1) (2023) 23–37.
- R.N. Ramos, Y. Missolo-Koussou, Y. Gerber-Ferder, C.P. Bromley, M. Bugatti, N. G. Núñez, J. Tosello Boari, W. Richer, L. Menger, J. Denizeau, C. Sedlik, P. Caudana, F. Kotsias, L.L. Niborski, S. Viel, M. Bohec, S. Lameiras, S. Baulande, L. Lesage, A. Nicolas, D. Meseure, A. Vincent-Salomon, F. Rey, C.A. Dutertre, F. Ginhoux, L. Vimeux, E. Donnadieu, B. Buttard, J. Galon, S. Zelenay, W. Vermi, P. Guermonprez, E. Piaggio, J. Helft, Tissue-resident FOLR2+ macrophages associate with CD8+ T cell infiltration in human breast cancer, *Cell* 185(7)(2022) 1189–1207.e25.
- E. Barreby, P. Chen, M. Aouadi, Macrophage functional diversity in NAFLD -more than inflammation, *Nat. Rev. Endocrinol.* 18 (8) (2022) 461–472.
- J.G. Rurik, H. Aghajanian, J.A. Epstein, Immune cells and immunotherapy for cardiac injury and repair, *Circ. Res.* 128 (11) (2021) 1766–1779.
- S. Li, J. Yu, A. Huber, I. Kryczek, Z. Wang, L. Jiang, X. Li, W. Du, G. Li, S. Wei, L. Vatan, W. Szeliga, A.M. Chinnaiyan, M.D. Green, M. Cieslik, W. Zou, Metabolism drives macrophage heterogeneity in the tumor microenvironment, *Cell Rep.* 39 (1) (2022), 110609.
- M.D. Park, A. Silvín, F. Ginhoux, M. Merad, Macrophages in health and disease, *Cell* 185 (23) (2022) 4259–4279.
- Y. Wang, R. Shi, R. Zhai, S. Yang, T. Peng, F. Zheng, Y. Shen, M. Li, L. Li, Matrix stiffness regulates macrophage polarization in atherosclerosis, *Pharmacol. Res.* 179 (2022), 106236.
- H. Xiang, H. Yu, Q. Zhou, Y. Wu, J. Ren, Z. Zhao, X. Tao, D. Dong, Macrophages: arising star in immunotherapy for chronic pancreatitis, *Pharmacol. Res.* 185 (2022), 106508.
- D.G. DeNardo, B. Ruffell, Macrophages as regulators of tumour immunity and immunotherapy, *Nat. Rev. Immunol.* 19 (6) (2019) 369–382.
- L. Parisi, E. Gini, D. Baci, M. Tremolati, M. Fanuli, B. Bassani, G. Farronato, A. Bruno, L. Mortara, Macrophage polarization in chronic inflammatory diseases: killers or builders? *J. Immunol. Res.* 2018 (2018) 8917804.
- Y. Xia, L. Rao, H. Yao, Z. Wang, P. Ning, X. Chen, Engineering macrophages for cancer immunotherapy and drug delivery, *Adv. Mater.* 32(40)(2020), e2002054.
- W. He, N. Kapate, C.W. Shields 4th Mitragotri, Drug delivery to macrophages: a review of targeting drugs and drug carriers to macrophages for inflammatory diseases, *Adv. Drug Deliv. Rev.* 165–166 (2020) 15–40.
- N. Gaspar, G. Zambito, C.M.W.G. Loñik, L. Mezzanotte, Active nano-targeting of macrophages, *Curr. Pharm. Des.* 25(17)(2019) 1951–1961.



- Y.Xing,X.Sun,Y.Dou,M.Wang,Y.Zhao,Q.Yang,Y.Zhao,Theimmuno-modulation effect of macrophage-derived extracellular vesicles in chronicinflammatory diseases, *Front. Immunol.* 12 (2021), 785728.
- C.Liu,Y.Wang,L.Li,D.He,J.Chi,Q.Li,Y.Wu,Y.Zhao,S.Zhang,L.Wang,Z. Fan, Y. Liao, Engineered extracellular vesicles and their mimetics forcancerimmunotherapy,*J.Control. Release* 349 (2022) 679–698.
- Y.Wu,S.Wan,S.Yang,H.Hu,C.Zhang,J.Lai,J.Zhou,W.Chen,X.Tang,J.Luo,X.Zhou,L.Yu,L.Wang,A.Wu,Q.Fan,J.Wu,Macrophagecellmembrane-basednanoparticles:anewpromisingbiomimeticplatformfortargeteddeliveryandtreatment,*J.Nano biotechnol.* 20 (1) (2022) 542.
- J.Lopes,D.Lopes,M.Pereira-Silva,D.Peixoto,F.Veiga,M.R.Hamblin,J.Conde,C.Corbo,E.N.Zare,M.Ashrafizadeh,F.R.Tay,C.Chen,R.F.Donnelly,X.Wang,P. Makvandi, A.C. Paiva-Santos, Macrophage cell membrane-cloakednanoplatforms for biomedical applications, *Small Methods* 6 (8)(2022),e2200289.
- C. Bl'eriot, S. Chakarov, F. Ginhoux, Determinants of resident tissuemacrophageidentity and function, *Immunity* 52 (6) (2020) 957–970.
- C.B.Anders,T.M.W.Lawton,H.L.Smith,J.Garret,M.M.Doucette,M.C. B. Ammons, Use of integrated metabolomics, transcriptomics, and signal proteinprofile to characterize the effector function and associated metabotype ofpolarized macrophage phenotypes,*J.Leukoc. Biol.* 111 (3) (2022) 667–693.
- S. Gordon, F.O. Martinez, Alternative activation of macrophages: mechanism andfunctions, *Immunity* 32 (5) (2010) 593–604.
- Q. Sun, S. Hu, Z. Lou,J.Gao, The macrophage polarization in inflammatorydermatosisanditspotentialdrugcandidates,*Biomed.Pharmacother.*161(2023),114469.
- K.E. Martin, A.J. García, Macrophage phenotypes in tissue repair and the foreignbody response: implications for biomaterial-based regenerative medicinestrategies, *Acta Biomater.* 133 (2021) 4–16.
- R.Bianchini,F.Roth-Walter,A.Ohradanova-Repic,S.Flicker,K.Hufnagl,M. B. Fischer, H. Stockinger, E. Jensen-Jarolim, IgG4 drives M2a macrophages toaregulatory M2b-like phenotype: potential implication in immune tolerance,*Allergy* 74 (3) (2019) 483–494.
- T.Kubota,M.Inoue,N.Kubota,I.Takamoto,T.Mineyama,K.Iwayama,K. Tokuyama, M.Moroi, K. Ueki, T. Yamauchi,T. Kadowaki, Downregulationofmacrophage Irs2 by hyperinsulinemia impairs IL-4-induced M2a-subtypemacrophage activation in obesity, *Nat. Commun.* 9 (1) (2018), 4863.
- C. Liang, S. Wu, G. Xia,J.Huang, Z. Wen, W. Zhang, X. Cao, Engineered M2amacrophagesforthetreatmentofosteoarthritis,*Front.Immunol.*13(2022)1054938.
- L.X.Wang,S.X.Zhang,H.J.Wu,X.L.Rong,J.Guo,M2bmacrophagepolarizationand its roles in diseases,*J.Leukoc. Biol.* 106 (2) (2019) 345–358.
- Y.Liu,X. Ji,N.Kang, J.Zhou,X.Liang, J.Li,T.Han,C.Zhao,T.Yang,Tumornecrosis factor α inhibition overcomes immunosuppressive M2b macrophage-induced bevacizumab resistance in triple-negative breast cancer, *Cell Death. Dis.*11 (11) (2020) 993.
- D. Philipp, L. Suhr, T. Wahlers, Y.H. Choi, A. Paunel-Go'rgülü, Preconditioning ofbonemarrow-derivedmesenchymalstemcellshighlystrengthenstheirpotentialtopromoteIL-6-DependentM2bpolarization,*StemCellRes.Ther.*9(1)(2018),286.
- S.M.Ohlsson,C.P.Linge,B.Gullstrand,C.Lood,A.Johansson,S.Ohlsson,A. Lundqvist, A.A. Bengtsson, F. Carlsson, T. Hellmark, Serum from patients withsystemicvasculitisinducesalternativelyactivatedmacrophageM2cpolarization,*Clin. Immunol.* 152 (1–2) (2014) 10–19.
- S. Lu, Y. Luo, G.B. Sun, X.B.Sun Traditional, Chinese medicines treatingmacrophage: a particular strategy for atherosclerosis, *Chin. Herb. Med.* 11 (1)(2019) 3–9.



- Q.Wang,H.Ni,L.Lan,X.Wei,R.Xiang,Y.Wang,Fra-1 protooncogene regulates il-6 expression in macrophages and promotes the generation of M2 macrophages, *Cell Res* 20 (6) (2010) 701–712.
- C.Lu,W.Shi,W.Hu,Y.Zhao,X.Zhao,F.Dong,Y.Xin,T.Peng,C.Liu, Endoplasmic reticulum stress promotes breast cancer cells to release exosomes Circ_0001142 and induces M2 polarization of macrophages to regulate tumor progression, *Pharmacol. Res.* 177 (2022), 106098.
- P.J. Murray, T.A. Wynn, Protective and pathogenic functions of macrophage subsets, *Nat. Rev. Immunol.* 11 (11) (2011) 723–737.
- C. Kerneir, C.E. Cano, D. Olive, Major pathways involved in macrophage polarization in cancer, *Front. Immunol.* 13 (2022) 1026954.
- Q. Sun, Q. Liu, X. Zhou, X. Wang, H. Li, W. Zhang, H. Yuan, C. Sun, Flavonoids regulate tumor-associated macrophages - from structure-activity relationship to clinical potential (review), *Pharmacol. Res.* 184 (2022), 106419.
- Y. Song, Y. Huang, F. Zhou, J. Ding, W. Zhou, Macrophage-targeted nanomedicine for chronic diseases immunotherapy, *Chin. Chem. Lett.* 33(2) (2022) 597–612.
- A.T. Gharavi, N.A. Hanjani, E. Movahed, M. Doroudian, The role of macrophage subtypes and exosomes in immunomodulation, *Cell. Mol. Biol. Lett.* 27 (1) (2022), 83.
- X. Zhang, L. Ji, M.O. Li, Control of tumor-associated macrophage responses by nutrient acquisition and metabolism, *Immunity* 56 (1) (2023) 14–31.
- L. Ren, J. Yi, Y. Yang, W. Li, X. Zheng, J. Liu, S. Li, H. Yang, Y. Zhang, B. Ge, S. Zhang, W. Fu, D. Dong, G. Du, X. Wang, J. Wang, Systematic pan-cancer analysis identifies APOC1 as an immunological biomarker which regulates macrophage polarization and promotes tumor metastasis, *Pharmacol. Res.* 183 (2022), 106376.
- E. Dai, L. Han, J. Liu, Y. Xie, G. Kroemer, D.J. Klionsky, Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization via release and uptake of oncogenic KRAS protein, *Autophagy* 16 (11) (2020) 2069–2083.
- C. Zhou, J. Weng, C. Liu, S. Liu, Z. Hu, X. Xie, D. Gao, Q. Zhou, J. Sun, R. Xu, H. Li, Y. Shen, Y. Yi, Y. Shi, X. Sheng, Q. Dong, M.C. Hung, N. Ren, Disruption of SLFN11 deficiency-induced CCL2 signaling and macrophage M2 polarization potentiates Anti-PD-1 therapy efficacy in hepatocellular carcinoma, *Gastroenterology* 164 (7) (2023) 1261–1278.
- C. Li, X. Xu, S. Wei, P. Jiang, L. Xue, J. Wang, Tumor-associated macrophages: potential therapeutic strategies and future prospects in cancer, *J. Immunother. Cancer* 9 (1) (2021), e001341.
- D. Yang, L. Yang, J. Cai, X. Hu, H. Li, X. Zhang, X. Zhang, X. Chen, H. Dong, H. Nie, Y. Li, A sweet spot for macrophages: focusing on polarization, *Pharmacol. Res.* 167 (2021), 105576.
- Y. Wang, X. Wang, Y. Li, Z. Xue, R. Shao, L. Li, Y. Zhu, H. Zhang, J. Yang, Xuanfei Baidude decoction reduces acute lung injury by regulating infiltration of neutrophils and macrophages via PD-1/IL17A pathway, *Pharmacol. Res.* 176 (2022), 106083.
- H. Yuan, S.X. Wu, Y.F. Zhou, F. Peng, Spermidine inhibits joint inflammation and macrophage activation in mice with collagen-induced arthritis, *J. Inflamm. Res.* 14 (2021) 2713–2721.
- X. Liu, X. Ren, L. Zhou, K. Liu, L. Deng, Q. Qing, J. Li, F. Zhi, M. Li, Tolliporchestrates macrophage polarization to alleviate intestinal mucosal inflammation, *J. Crohns Colitis* 16 (7) (2022) 1151–1167.
- T. Pan, Q. Zhou, K. Miao, L. Zhang, G. Wu, J. Yu, Y. Xu, W. Xiong, Y. Li, Y. Wang, Suppressing Sart1 to modulate macrophage polarization by siRNA-loaded liposomes: a promising therapeutic strategy for pulmonary fibrosis, *Theranostics* 11 (3) (2021) 1192–1206.
- S. Huang, D. Xu, L. Zhang, L. Hao, Y. Jia, X. Zhang, T. Cheng,



- J.Chen,Therapeutic effectsofcurcuminliposomesandnanocrystalsoninflammatoryosteolysis: in vitro and in vivo comparative study, Pharmacol. Res. 192(2023),106778.
- K.J. Moore, F.J. Sheedy, E.A. Fisher, Macrophages in atherosclerosis: a dynamicbalance, Nat. Rev. Immunol. 13 (10) (2013) 709–721.
- C. Atri, F.Z. Guerfali, D. Laouini, Role of human macrophage polarization ininflammationduringinfectiousdiseases,Int.J.Mol.Sci.19(6)(2018)1801.
- Y.J.Lim,J.Lee,J.A.Choi,S.N.Cho,S.H.Son,S.J.Kwon,J.W.Son,C.H.Song,M1 macrophage dependent-p53 regulates the intracellular survival ofmycobacteria,Apoptosis 25 (1–2) (2020) 42–55.
- Q.Gao,J.Zhang,C.Chen,M.Chen,P.Sun,W.Du,S.Zhang,Y.Liu,R.Zhang, M. Bai, C. Fan,J.Wu, T. Men, X. Jiang, In situ mannosylated nanotrinity-mediated macrophage remodeling combats candida albicans infection,ACS Nano14 (4) (2020) 3980–3990.
- P.Geng,H.Zhu,W.Zhou,C.Su,M.Chen,C.Huang,C.Xia,H.Huang,Y.Cao, X. Shi, Baicalin inhibits Influenza A virus infection via promotion ofM1 macrophage polarization, Front. Pharmacol. 11 (2020) 01298.
- X.Cao,B.Li,J.Chen,J.Dang,S.Chen,E.G.Gunes,B.Xu,L.Tian,S.Muend, M. Raoof, C. Querfeld, J.Yu, S.T. Rosen, Y. Wang, M. Feng, Effect of cabazitaxelon macrophages improves CD47-targeted immunotherapy for triple-negativebreast cancer,J.Immunother. Cancer 9 (3) (2021), e002022.
- K.Blom,W.Senkowski,M.Jarvius,M.Berglund,J.Rubin,L.Lenhammar, V. Parrow, C. Andersson, A. Loskog, M. Fryknäs, P. Nygren, R. Larsson, Theanticancer effect of mebendazole may be due to M1 monocyte/macrophageactivation via ERK1/2 and TLR8-DEpendent Inflammasome Activation,Immunopharmacol. Immunotoxicol. 39 (4) (2017) 199–210.
- X.L.Zheng,G.Z.Liang,D.M.Shi,H.P.Yao,L.Zhang,W.D.Liu,G.Z.Chen,Itraconazole promotes macrophage M1 polarization and phagocytic capacityofmacrophage to Candida albicans, Int.J.Dermatol. Venereol. 2 (4) (2019) 193–201.
- W.Zhu,R.Xu, J.Du,Y.Fu,S.Li,P.Zhang,L.Liu,H.Jiang,Zoledronicacidpromotes TLR-4-mediated M1 macrophage polarization in bisphosphonate-related osteonecrosis of the jaw, FASEBJ.33 (4) (2019) 5208–5219.
- Z.Ma,M.Yang,M.F.Foda,K.Zhang,S.Li,H.Liang,Y.Zhao,H.Han,Polarizationof tumor-associated macrophages promoted by vitamin C-loaded liposomes forcancer immunotherapy, ACS Nano 16 (10) (2022) 17389–17401.
- T.Fujiwara,M.A.Yakoub,A.Chandler,A.B.Christ,G.Yang,O.Ouerfelli,V. K.Rajasekhar,A.Yoshida,H.Kondo,T.Hata,H.Tazawa,Y.Dogan,M.A. S.Moore,T.Fujiwara,T.Ozaki,E.Purdue,J.H.Healey,CSF1/CSF1Rsignalinginhibitor pexidartinib (PLX3397) reprograms tumor-associated macrophages and stimulatesT-cellinfiltrationinthesarcomamicroenvironment,Mol.CancerTher.20 (8) (2021) 1388–1399.
- Z.Yao,J.Zhang,B.Zhang,G.Liang,X.Chen,F.Yao,X.Xu,H.Wu,Q.He,L.Ding, B. Yang, Imatinib prevents lung cancer metastasis by inhibiting M2-likepolarization of macrophages, Pharmacol. Res. 133 (2018) 121–131.
- H. Ying, M. Fang, Q.Q. Hang, Y. Chen, X. Qian, M. Chen, Pirfenidone modulatesmacrophage polarization and ameliorates radiation-induced lung fibrosis byinhibiting the TGF-β1/Smad3 pathway,J.Cell. Mol. Med. 25 (18) (2021)8662–8675.
- W.Zhang,S.Ohno,B.Steer,S.Klee,C.A.Staab-Weijnitz,D.Wagner, M. Lehmann, T. Stoeger, M. Koönigshoff, H. Adler, S100a4 is secreted byalternatively activated alveolar macrophages and promotes activation oflungfibroblasts in pulmonary fibrosis, Front. Immunol. 9



(2018) 1216.

Y.H.Chen,R.H.Liu,Y.Z.Cui,A.Hettinghouse,W.Y.Fu,L.Zhang,C.Zhang,C.

J.Liu, Penfluridol targets acid sphingomyelinase to inhibit TNF signaling and is a therapeutic against inflammatory autoimmune diseases, *Arthritis Res. Ther.* 24

(1)(2022)27.

M.D.Kornberg,P.Bhargava,P.M.Kim,V.Putluri,A.M.Snowman,N.Putluri,P.

A. Calabresi, S.H. Snyder, Dimethyl fumarate targets GAPDH and aerobic glycolysis to modulate immunity, *Science* 360 (6387) (2018) 449–453.

H. Jahan, M.I. Choudhary, Gliclazide alters macrophages polarization state in diabetic atherosclerosis in vitro via blocking AGE-RAGE/TLR4-reactive oxygen species-activated NF- κ B nexus, *Eur.J.Pharmacol.* 894 (2021), 173874.

A.Zawia,N.D.Arnold,L.West,J.A.Pickworth,H.Turton,J.Iremonger,A.

T. Braithwaite, J. Can˜edo, S.A. Johnston, A.A.R. Thompson, G. Miller, A. Lawrie, Altered macrophage polarization induces experimental pulmonary hypertension and is observed in patients with pulmonary arterial hypertension, *Arter.Throm.Vas.* 41 (1) (2021) 430–445.

K.K. Thompson, S.E. Tsirka, Guanabenz modulates microglia and macrophages during demyelination, *Sci. Rep.* 10 (1) (2020), 19333.

X.S.Chen,S.H.Wang,C.Y.Liu,Y.L.Gao,X.L.Meng,W.Wei,S.T.Shou,Y.C.Liu,

Y.F. Chai, Losartan attenuates sepsis-induced cardiomyopathy by regulating macrophage polarization via TLR4-mediated NF- κ B and MAPK signaling, *Pharmacol. Res.* 185 (2022), 106473.

P.J.Carneiro,A.L.Clevelario,G.A.Padilha,J.D.Silva,J.Z.Kitoko,P.C.Olsen,V.

L. Capelozzi, P.R. Rocco, F.F. Cruz, Bosutinib therapy ameliorates lung inflammation and fibrosis in experimental silicosis, *Front. Physiol.* 8 (2017) 159.

A.Colado,M.Genoula,C.Cougoule,J.L.MarínFranco,M.B.Almejún,D.Risnik,

D.Kviatcovsky,E.Podaza,E.E.Elfás,F.Fuentes,I.Maridonneau-Parini,F.

R.Bezares,H.FernandezGrecco,M.Cabrejo,C.Jancic,M.D.C.Sasiain,

M.Giordano, R. Gamberale, L.Balboa, M.Borge, Effect of the BTK inhibitor ibrutinib on macrophage- and $\gamma\delta$ T cell-mediated response against mycobacterium tuberculosis, *Blood Cancer J.* 8 (11) (2018), 100.

N.Liu,J.Zhang,M.Yin,H.Liu,X.Zhang,J.Li,B.Yan,Y.Guo,J.Zhou,J.Tao,

S. Hu, X. Chen, C. Peng, Inhibition of xCT suppresses the efficacy of Anti-PD-1/L1 melanoma treatment through exosomal PD-L1-induced macrophage M2 polarization, *Mol. Ther.* 29 (7) (2021) 2321–2334.

L.Zhang,X.Chen,Z.Liu,Q.Han,L.Tang,Z.Tian,Z.Ren,C.Rong,H.Xu,Miconazole alleviates peripheral nerve crush injury by mediating a macrophage phenotype change through the NF- κ B pathway, *Brain Behav.* 9 (10) (2019), e01400.

Y. Jing, F. Wu, D. Li, L. Yang, Q. Li, R. Li, Metformin improves obesity-associated inflammation by altering macrophages polarization, *Mol. Cell Endocrinol.* 461 (2018) 256–264.

C.Kewcharoenwong,S.A.Prabowo,G.J.Bancroft,H.A.Fletcher,

G. Lertmemongkolkhai, Glibenclamide reduces primary human monocyte functions against tuberculosis infection by enhancing M2 polarization, *Front.Immunol.* 9 (2018) 2109.

T.M.Lee,N.C.Chang,S.Z.LinDapagliflozin,A selective SGLT2 inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts, *Free Radic. Biol. Med.* 104 (2017) 298–310.

Y.Yang,Y.Lu,F.Han,Y.Chang,X.Li,Z.Han,M.Xue,Y.Cheng,B.Sun,L.Chen,Saxagliptin regulates M1/M2 macrophage polarization via CaMKK β /AMPK pathway to attenuate NAFLD, *Biochem. Biophys. Res. Commun.* 503 (3) (2018) 1618–1624.

C.Qin,W.H.Fan,Q.Liu,K.Shang,M.Murugan,L.J.Wu,W.Wang,D.S.Tian,Fingolimod protects against ischemic white matter damage by modulating microglia toward M2 polarization via STAT3 pathway, *Stroke* 48 (12) (2017) 3336–3346.



- W.Ren,Y.Xia,S.Chen,G.Wu,F.W.Bazer,B.Zhou,B.Tan,G.Zhu,J.Deng,
 Y. Yin, Glutamine metabolism in macrophages: a novel target for obesity/type2 diabetes, *Adv. Nutr.* 10 (2) (2019) 321–330.
- Z.Liu,X.Wang,X.Chen,L.Cui,Z.Li,Z.Bai,K.Lin,J.Yang,F.Tian,Construction of pH-responsive polydopamine-coated magnetic layered hydroxide nanostructure for intracellular drug delivery, *Eur.J.Pharm. Biopharm.* 182(2023) 12–20.
- L. Cui, X. Wang, Z. Liu, Z. Li, Z. Bai, K. Lin, J. Yang, Y. Cui, F. Tian, Metal-organic framework decorated with glycyrrhetic acid conjugated chitosan as a pH-responsive nanocarrier for targeted drug delivery, *Int.J.Biol. Macromol.* 240(2023), 124370.
- Z.Li,W.Wan,Z.Bai,B.Peng,X.Wang,L.Cui,Z.Liu,K.Lin,J.Yang,J.Hao,
 F. Tian, Construction of pH-responsive nanoplateform from stable magnetic nanoparticles for targeted drug delivery and intracellular imaging, *Sens.Actuators B Chem.* 375 (2023), 132869.
- M.M. Ponpipom, R.L. Bugianesi, J.C. Robbins, T.W. Doebber, T.Y. Shen, Cell-specific ligands for selective drug delivery to tissues and organs, *J.Med.Chem.* 24 (12)(1981)1388–1395.
- J.C.Robbins,M.H.Lam,C.S.Tripp,R.L.Bugianesi,M.M.Ponpipom,T.Y.Shen,Synthetic glycopeptide substrates for receptor-mediated endocytosis by macrophages, *PNAS* 78 (12) (1981) 7294–7298.
- Y.Ikehara,T.Niwa,L.Biao,S.K.Ikehara,N.Ohashi,T.Kobayashi,Y.Shimizu,
 N. Kojima, H. Nakanishi, A carbohydrate recognition-based drug delivery and controlled release system using intraperitoneal macrophages as a cellular vehicle, *Cancer Res* 66 (17) (2006) 8740–8748.
- L.Ramachandra,Y.Qu,Y.Wang,C.J.Lewis,B.A.Cobb,K.Takatsu,W.H.Boom,
 G.R. Dubyak, C.V. Harding, Mycobacterium tuberculosis synergizes with ATP to induce release of microvesicles and exosomes containing major histocompatibility complex class II molecules capable of antigen presentation, *Infect. Immun.* 78 (12) (2010) 5116–5125.
- Y.Akao,A.Iio,T.Itoh,S.Noguchi,Y.Itoh,Y.Ohtsuki,T.Naoe, Microvesicle-mediated RNA molecule delivery system using monocytes/macrophages, *Mol.Ther.* 19 (2) (2011) 395–399.
- A.Parodi,N.Quattrocchi,A.L.vandeVen,C.Chiappini,M.Evangelopoulos,J.
 O.Martinez,B.S.Brown,S.Z.Khaled,I.K.Yazdi,M.V.Enzo,L.Isenhardt,
 M. Ferrari, E. Tasciotti, Synthetic nanoparticles functionalized with biomimetic leukocyte membranes possess cell-like functions, *Nat. Nanotechnol.* 8 (1) (2013) 61–68.
- R.Li,Y.He,Y.Zhu,L.Jiang,S.Zhang,J.Qin,Q.Wu,W.Dai,S.Shen,Z.Pang,
 J.Wang, Route to rheumatoid arthritis by macrophage-derived microvesicle-coated nanoparticles, *Nano Lett.* 19 (1) (2019) 124–134.
- X.Wang,Y.Wang,Z.Xue,W.Wan,Y.Li,H.Qin,Y.Zhu,F.Tian, J.Yang, Magnetic liposome as a dual-targeting delivery system for idiopathic pulmonary fibrosis treatment, *J.Colloid Interface Sci.* 636 (2023) 388–400.
- Y.Tang,Z.Tang,P.Li,K.Tang,Z.Ma,Y.Wang,X.Wang,C.Li, Precise delivery of nanomedicine to M2 macrophages by combining "eat me/don't eat me" signals and its anticancer application, *ACS Nano* 15 (11) (2021) 18100–18112.
- Q.Qiu,C.Li,Y.Song,T.Shi,X.Luo,H.Zhang,L.Hu,X.Yan,H.Zheng,M.Liu,
 M. Liu, M. Liu, S. Yang, X. Liu, G. Chen, Y. Deng, Targeted delivery of ibrutinib to tumor-associated macrophages by sialic acid-stearic acid conjugate modified nanocomplexes for cancer immunotherapy, *Acta Biomater.* 92 (2019) 184–195.
- S.Gou,Y.Huang,Y.Wan,Y.Ma,X.Zhou,X.Tong,J.Huang,Y.Kang,G.Pan,
 F. Da, B. Xiao, Multi-bioresponsive silk fibroin-based nanoparticles with on-demand cytoplasmic drug release capacity for CD44-targeted alleviation of ulcerative colitis, *Biomaterials* 212 (2019) 39–54.
- Y. Lee, K. Sugihara, M.G. Gilliland, S. Jon, N. Kamada, J.J. Moon, Hyaluronic acid-bilirubin



- nanomedicine for targeted modulation of dysregulated intestinal barrier, microbiome and immune responses in colitis, *Nat. Mater.* 19 (1)(2020) 118–126.
- Y.B.Miao,K.H.Chen,C.T.Chen,F.L.Mi,Y.J.Lin,Y.Chang,C.S.Chiang,J.
T. Wang, K.J. Lin, H.W. Sung, A noninvasive gut-to-brain oral drug delivery system for treating brain tumors, *Adv. Mater.* 33 (34) (2021), e2100701.
- X.Sun,W.Li,X.Zhang,M.Qi,Z.Zhang,X.E.Zhang,Z.Cui, In vivo targeting and imaging of atherosclerosis using multifunctional virus-like particles of simian virus 40, *Nano Lett.* 16 (10) (2016) 6164–6171.
- W.Tao,A.JrYurdagul,N.Kong,W.Li,X.Wang,A.C.Doran,C.Feng,J.Wang,M.
A. Islam, O.C. Farokhzad, I. Tabas, J. Shi, siRNA nanoparticles targeting CaMKII γ in lesional macrophages improve atherosclerotic plaque stability in mice, *Sci. Transl. Med.* 12 (553) (2020), eaay1063.
- W.Zhou,Z.Lin,Y.Xiong,H.Xue,W.Song,T.Yu,L.Chen,Y.Hu,A.C.Panayi,
Y. Sun, F. Cao, G. Liu, L. Hu, C. Yan, X. Xie, W. Qiu, B. Mi, G. Liu, Dual-targeted nanoplateform regulating the bone immune microenvironment enhances fracture healing, *ACS Appl. Mater. Interfaces* 13 (48) (2021) 56944–56960.
- P.Scodeller, L. Simo $\acute{n}$ -Gracia,S.Kopanchuk, A. Tobin, K.Kilk,P.S $\ddot{a}$ lik, K.Kurm,
M.L. Squadrito, V.R. Kotamraju, A. Rinken, M. De Palma, E. Ruoslahti, T. Teesalu, Precision targeting of tumor macrophages with a CD206 Binding Peptide, *Sci. Rep.* 7 (1) (2017), 14655.
- A.Lepland,E.K.Asciutto,A.Malfanti,L.Simo $\acute{n}$ -Gracia,V.Sidorenko,M.J.Vicent,
T.Teesalu,P.Scodeller, Targeting pro-tumoral macrophages in early primary and metastatic breast tumors with the CD206-binding mUNO peptide, *Mol. Pharm.* 17 (7)(2020) 2518–2531.
- Y.Qian,S.Qiao,Y.Dai,G.Xu,B.Dai,L.Lu,X.Yu,Q.Luo,Z.Zhang, Molecular-targeted immunotherapeutic strategy for melanoma via dual-targeting nanoparticles delivering small interfering RNA to tumor-associated macrophages, *ACS Nano* 11 (9) (2017) 9536–9549.
- Q.Yang,H.Jiang,Y.Wang,X.Leng,Y.Wang,J.Tong,Y.Zhou,C.Mo, J.Peng,
H. Gao, Plaque macrophage-targeting nanosystems with cooperative Co-regulation of ROS and TRAF6 for stabilization of atherosclerotic plaques, *Adv. Funct. Mater.* (2023), 2301053.
- J.Wang, X.Peng, J. Wei, Y.Dai, S. Huang, D. Deng, Z.Fan, Y.Leng, J.Ai, Z. Cai,
M.Qiu,S.Chen,X.Yang,Z.Zhang, In situ phagocyte-mediated deep tumor penetration assisted by ApoA-1 mimetic peptide-modified silicasome, *Nano Today* 50 (2023), 101864.
- H. Peng, J.H. Wang, F. Guo, F.F. Zhu, Z.J. Wen, H.J. Zhong, D.S. Liang, Legumain protease-activated tuftsin-functionalized nanoparticles for dual-targeting TAMs and cancer chemotherapy, *Colloid Surf. B.* 197 (2021), 111442.
- G.R.Gunasekaran,S.M.Poongkavithai Vadevoo,M.C.Baek,B.Lee, M1 macrophage exosomes engineered to foster M1 polarization and target the IL-4 receptor inhibit tumor growth by reprogramming tumor-associated macrophages into M1-like macrophages, *Biomaterials* 278 (2021), 121137.
- A.Rafique,A. Etzerodt, J.H. Graversen, S.K.Moestrup, F. Dagnæs-Hansen, H.
J.Møller, Targeted lipid nanoparticle delivery of calcitriol to human monocyte-derived macrophages in vitro and in vivo: investigation of the anti-inflammatory effects of calcitriol, *Int. J. Nanomed.* 14 (2019) 2829–2846.
- Y.Zhao, Y.Yang, J. Zhang, R. Wang, B. Cheng, D. Kalambhe, Y. Wang, Z. Gu,
D. Chen, B. Wang, Y. Huang, Lactoferrin-mediated macrophage targeting delivery and patchouli alcohol-based therapeutic strategy for inflammatory bowel diseases, *Acta Pharm. Sin. B* 10 (10) (2020) 1966–1976.
- G. Lemke, How macrophages deal with death, *Nat. Rev. Immunol.* 19 (9)(2019) 539–549.
- Y. Yang, L. Guo, Z. Wang, P. Liu, X. Liu, J. Ding, W. Zhou, Targeted



- silver nanoparticles for rheumatoid arthritis therapy via macrophage apoptosis and Re-polarization, *Biomaterials* 264 (2021), 120390.
- M. Liang, H. Tan, J. Zhou, T. Wang, D. Duan, K. Fan, J. He, D. Cheng, H. Shi, H. S. Choi, X. Yan, Bioengineered H-ferritin nanocages for quantitative imaging of vulnerable plaques in atherosclerosis, *ACS Nano* 12 (9) (2018) 9300–9308.
- E. Maretti, L. Costantino, C. Rustichelli, E. Leo, M. A. Croce, F. Buttini, E. Truzzi, V. Iannuccelli, Surface engineering of solid lipid nanoparticle assemblies by methyl α -D-mannopyranoside for the active targeting to macrophages in anti-tuberculosis inhalation therapy, *Int. J. Pharm.* 528 (1–2) (2017) 440–451.
- E. Peled, A. Sosnik, Amphiphilic galactomannan nanoparticles trigger the alternative activation of murine macrophages, *J. Control. Release* 339 (2021) 473–483.
- Y. Cao, B. Qiao, Q. Chen, Z. Xie, X. Dou, L. Xu, H. Ran, L. Zhang, Z. Wang, Tumor microenvironment remodeling via targeted depletion of M2-like tumor-associated macrophages for cancer immunotherapy, *Acta Biomater.* S1742–7061 (23) (2023), 00076-4.
- Q. Zhang, A. Olberg, M. Sioud, Structural requirements for the binding of a peptide to prohibitins on the cell surface of monocytes/macrophages, *Int. J. Mol. Sci.* 23 (8) (2022) 4282.
- Z. Wu, M. Zhou, X. Tang, J. Zeng, Y. Li, Y. Sun, J. Huang, L. Chen, M. Wan, C. Mao, Carrier-free trehalose-based nanomotor targeting macrophages in inflammatory plaque for treatment of atherosclerosis, *ACS Nano* 16 (3) (2022) 3808–3820.
- C. J. Chao, E. Zhang, Z. Zhao, Engineering cells for precision drug delivery: new advances, clinical translation, and emerging strategies, *Adv. Drug Deliv. Rev.* 197 (2023), 114840.
- Y. Chen, D. Qin, J. Zou, X. Li, X. D. Guo, Y. Tang, C. Liu, W. Chen, N. Kong, C. Y. Zhang, W. Tao, Living leukocyte-based drug delivery systems, *Adv. Mater.* (2022), e2207787.
- Y. Wu, Y. Liu, T. Wang, Q. Jiang, F. Xu, Z. Liu, Living cell for drug delivery, *Eng. Regen.* 3 (2) (2022) 131–148.
- Y. Huang, X. Gao, J. Chen, Leukocyte-derived biomimetic nanoparticulated drug delivery systems for cancer therapy, *Acta Pharm. Sin. B.* 8 (1) (2018) 4–13.
- X. Sang, Y. Wang, Z. Xue, D. Qi, G. Fan, F. Tian, Y. Zhu, J. Yang, Macrophage-targeted lung delivery of dexamethasone improves pulmonary fibrosis therapy via regulating the immune microenvironment, *Front. Immunol.* 12 (2021), 613907.
- V. D. Nguyen, H. K. Min, H. Y. Kim, J. Han, Y. H. Choi, C. S. Kim, J. O. Park, E. Choi, Primary macrophage-based microrobots: an effective tumor therapy in vivo by dual-targeting function and near-infrared-triggered drug release, *ACS Nano* 15 (5) (2021) 8492–8506.
- C. Gao, Q. Cheng, J. Li, J. Chen, Q. Wang, J. Wei, Q. Huang, S. M. Y. Lee, D. Gu, R. Wang, Supramolecular macrophage-liposome marriage for cell-hitchhiking delivery and immunotherapy of acute pneumonia and melanoma, *Adv. Funct. Mater.* 31 (37) (2021), 2102440.
- X. Xu, C. H. T. Kwong, J. Li, J. Wei, R. Wang, "Zombie" macrophages for targeted drug delivery to treat acute pneumonia, *ACS Appl. Mater. Interfaces* 15 (24) (2023) 29012–29022.
- L. Zheng, X. Hu, H. Wu, L. Mo, S. Xie, J. Li, C. Peng, S. Xu, L. Qiu, W. Tan, In vivo monocyte/macrophage hitchhike in tumor accumulation of nanomedicines, *Enhanc. Tumor Ther. J. Am. Chem. Soc.* 142 (1) (2020) 382–391.
- C. W. Shields 4th, M. A. Evans, L. L. Wang, N. Baugh, S. Iyer, D. Wu, Z. Zhao, A. Pusuluri, A. Ukidve, D. C. Pan, S. Mitragotri, Cellular backpacks for macrophage immunotherapy, *Sci. Adv.* 6 (18) (2020), eaaz6579.
- M. H. Zhu, X. D. Zhu, M. Long, X. Lai, Y. Yuan, Y. Huang, L. Zhang, Y. Gao, J. Shi, Q. Lu, P. Sun, J. F. Lovell, H. Z. Chen, C. Fang, Metal-coordinated adsorption of nanoparticles to macrophages for targeted cancer therapy, *Adv. Funct. Mater.* (2023), 2214842.



- H.Zhou,H.He,R.Liang,H.Pan,Z.Chen,G.Deng,S.Zhang,Y.Ma,L.Liu,L.Cai, In situ poly I:C released from living cell drug nanocarriers for macrophage-mediated antitumor immunotherapy, *Biomaterials* 269 (2021), 120670.
- L. Xu, X. Wang, R. Wang, S. Liu, M. Xu, Engineered macrophages: a safe-by-design approach for the tumor targeting delivery of Sub-5 nm gold nanoparticles, *Small* 19 (1) (2023), e2205474.
- Y. Gui, Y. Zeng, B. Chen, Y. Yang, J. Ma, C. Li, A smart pathogen detector engineered from intracellular hydrogelation of DNA-decorated macrophages, *Nat. Commun.* 14 (1) (2023), 2927.
- A. Padmakumar, N.P. Koyande, A.K. Rengan, The role of Hitchhiking in cancer therapeutics—a review, *Adv. Ther.* 5 (9) (2022), 2200042.
- Z.P.Lin,L.N.M.Nguyen,B.Ouyang,P.MacMillan,J.Ngai,B.R.Kingston, S. M. Mladjenovic, W.C.W. Chan, Macrophages actively transport nanoparticles in tumors after extravasation, *ACS Nano* 16 (4) (2022) 6080–6092.
- A.M.Sofias,Y.C.Toner,A.E.Meerwaldt,M.M.T.vanLeent,G.Soultanidis, M.Elschot,H.Gonai,K.Grendstad,Å.Flobak,U.Neckmann,C.Wolowczyk,E. L.Fisher,T.Reiner,C.L.Davies,G.Bjørkøy,A.J.P.Teunissen,J.Ochando, C.Pe´rez-Medina,W.J.M.Mulder,S.Hak, Tumor targeting by $\alpha v \beta 3$ -integrin- specific lipid nanoparticles occurs via phagocyte Hitchhiking, *ACS Nano* 14(7) (2020) 7832–7846.
- N.Dhas,M.C.García,R.Kudarha,A.Pandey,A.N.Nikam,D.Gopalan,