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Graphical Abstract

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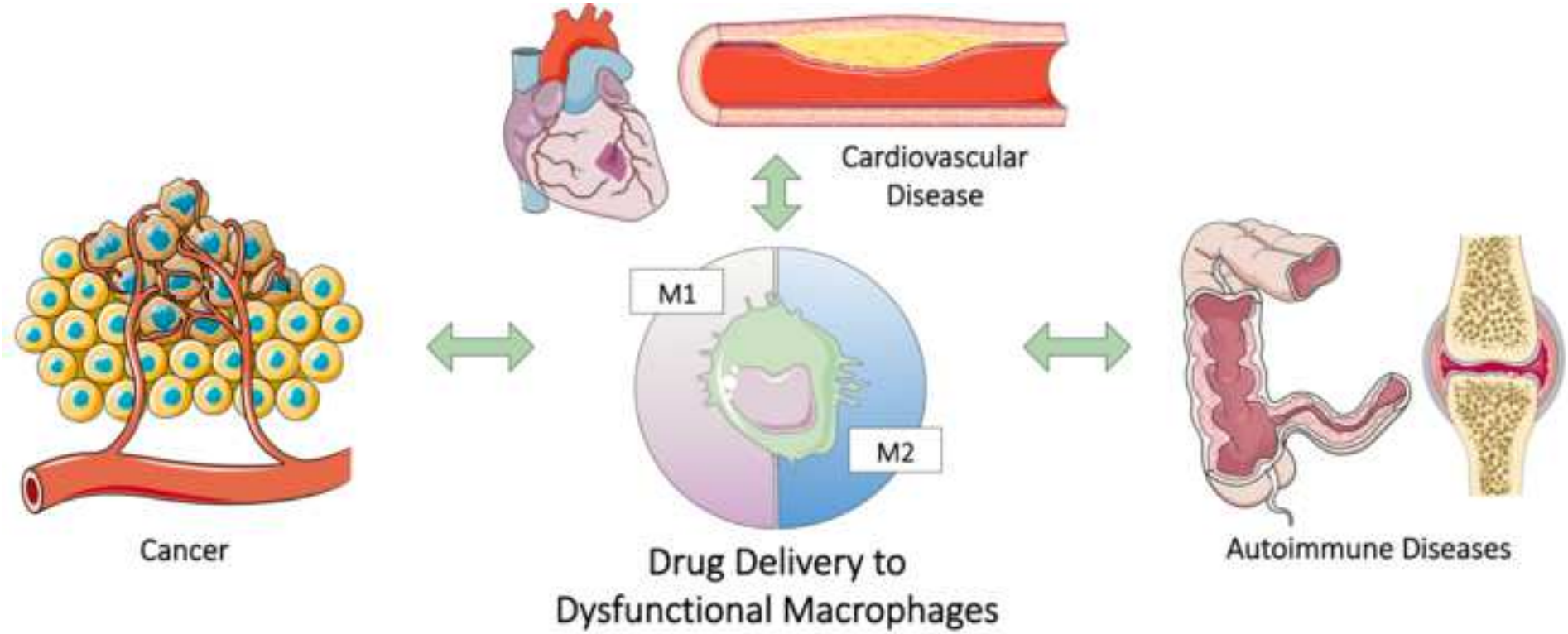

Drug Delivery to Macrophages for Inflammatory Diseases

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ABSTRACT

Macrophages play a key role in defending against foreign pathogens, healing wounds, and regulating tissue homeostasis. Driving this versatility is their phenotypic plasticity, which enables macrophages to respond to subtle cues in tightly coordinated ways. However, when this coordination is disrupted, macrophages can aid the progression of numerous diseases, including cancer, cardiovascular disease, and autoimmune disease. The central link between these disorders is aberrant macrophage polarization, which misguides their functional programs, secretory products, and regulation of the surrounding tissue microenvironment. As a result of their important and deterministic roles in both health and disease, macrophages have gained considerable attention as targets for drug delivery. Here, we discuss the role of macrophages in the initiation and progression of various inflammatory diseases, summarize the leading drugs used to regulate macrophages, and review drug delivery systems designed to target macrophages. We emphasize strategies that are approved for clinical use or are poised for clinical investigation. Finally, we provide a perspective on the future of macrophage-targeted drug delivery systems.

*Keywords***:** Inflammation; Macrophages; Drug delivery; Solid tumors; Cardiovascular disease; Autoimmune disease

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Glossary of Terms

AhR, aryl hydrocarbon receptor; ALN, alendronate; AMPK, AMP-activated protein kinase; APAH, associated pulmonary artery hypertension; ARG1, arginase 1; BAFF, B cell activating factor; c-KIT, receptor tyrosine kinase; cAMP, adenosine 3',5' cyclic monophosphate; CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; CD, Crohn's disease; CO, carbon monoxide; cRGD, cyclic RGD (arginylglycylaspartic acid) peptide; CSF-1, colony stimulating factor 1; CSF-1R, CSF-1 receptor; CTGF, connective tissue growth factor; CXCR, CXC chemokine receptor; DOTAP, dioleoyl-3-trimethylammonium propane; DSPC, distearoylphosphatidylcholine; EAM, experimental autoimmune myocarditis; EC, endothelial cell; Flt3, FMS-like tyrosine kinase 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; H_2S, hydrogen sulfide; HA-PLA, hyaluronate-polylactide; HDAC, histone deacetylase; HLA, human leukocyte antigen; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A reductase; HMGB1, high mobility group box-1 protein; HPAH, heritable pulmonary artery hypertension; HPH, hypoxia-induced pulmonary hypertension; hsCRP, high-sensitivity C-reactive protein; HySU, hypoxia plus Sugen 5416 (SU5416); ICAM-1, intercellular adhesion molecule 1; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IRF1, IFN regulatory factor 1; Kv1.3, voltage-gated potassium channel 1.3; LDL, low-density lipoprotein; LOX, lysyl oxidase; LTB4, leukotriene B4; MARCO, macrophage receptor with collagenous structure; MCP-1, monocyte chemoattractant protein-1; mCSF, macrophage colony-stimulating factor; MHC, major histocompatibility complex; MIP-1α, macrophage inflammatory protein-1 alpha; MMP, matrix metalloproteinase; MP, mononuclear phagocyte; mRNA, messenger RNA; MS, multiple sclerosis; MSC, mesenchymal stem cell; NALP3, NACHT, LRR and PYD domains-containing protein 3; NLR, NOD-like receptor; *NLRP3*, gene encoding for NALP3; NO, nitric oxide; NOD, nucleotide-binding oligomerization domain; *Nr4a1*, nuclear receptor subfamily 4 group A member 1; NSAID, nonsteroidal anti-inflammatory drug; ODN, oligonucleotide; OxLDL, oxidized low-density lipoprotein; PADRE, pan HLA DR-binding epitope; PAEC, pulmonary artery EC; PAH, pulmonary artery hypertension; PAP, pulmonary artery pressure; PASMC, pulmonary artery smooth muscle cell; PBAP, phenylboronic acid pinacol ester; PDE4, phosphodiesterase-4;

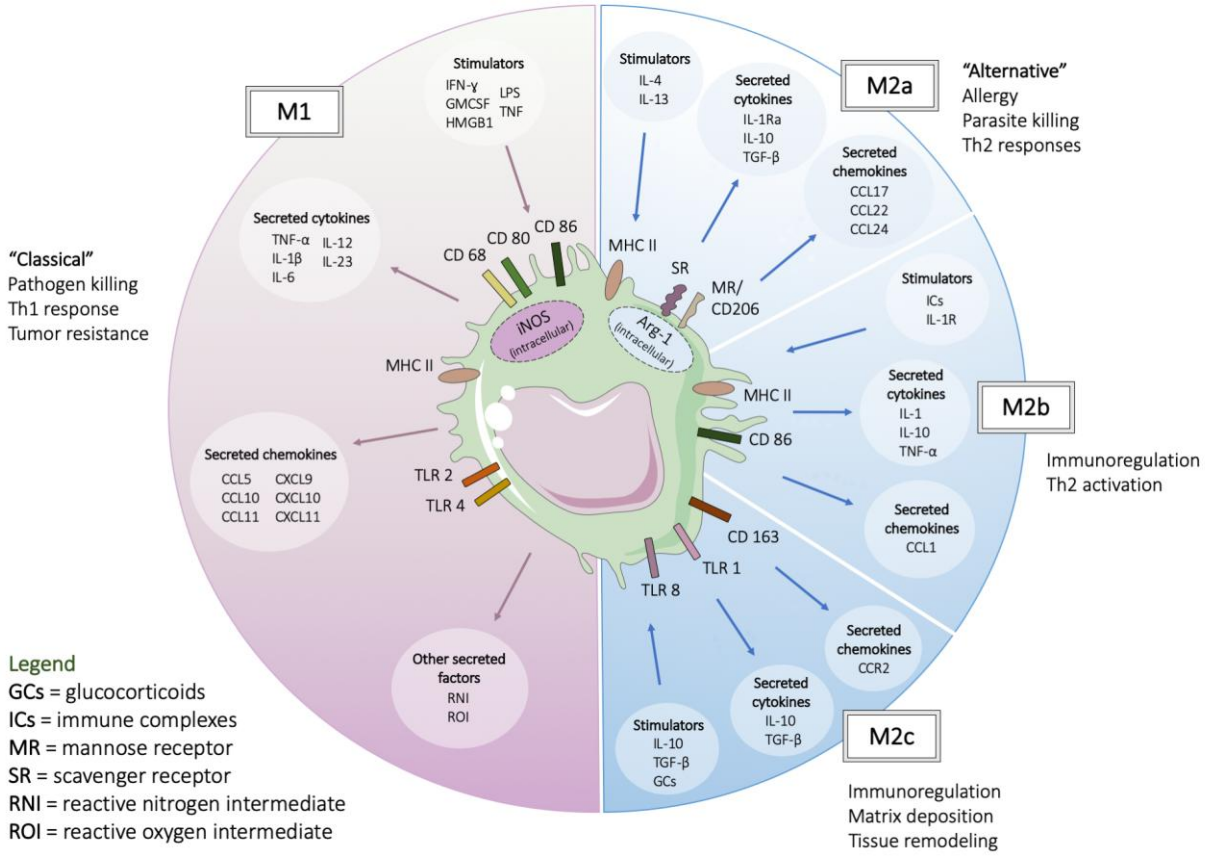
PDGF, platelet-derived growth factor; PEG-DMG, polyethylene glycol/dimyristoyl-rac-glycero; PI3Kγ, phosphoinositide 3-kinase-gamma; PPARγ, peroxisome proliferator-activated receptor-gamma; PS, phosphatidylserine; RELMα, resistin-like molecule-alpha; rhASB, recombinant human arylsulfatase B; RNI, reactive nitrogen intermediate; Siglec-1, sialic acid binding Ig-like lectin 1; SIRPα, signal regulatory protein-alpha; SLE, systemic lupus erythematosus; SOCS1, suppressor of cytokine signaling 1; SPARC, secreted protein acidic and rich in cysteine; SPM, specialized pro-resolving mediator; STAT3, signal transducer and activator of transcription 3; T1D, type 1 diabetes; TAM, tumor-associated macrophage; TEMPOL, 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl radical; THAP, thapsigargin; TIMP-3, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; Trk, tropomyosin kinase receptor; TSG-6, tumor necrosis factor-alpha-stimulated gene 6 protein; TSLP, thymic stromal lymphopoietin; UC, ulcerative colitis.

1. Introduction

Inflammation is a natural form of "life insurance", protecting the body from invasion by pathogens and other threats that may impose cellular damage. However, chronic inflammation can contribute to, and even accelerate, the progression of numerous diseases [1]. Macrophages are important regulators of inflammation, as they can adopt a range of phenotypes that support inflammatory or anti-inflammatory programs **(Figure 1)**. Macrophage polarization is best characterized by a multidimensional spectrum [2], but it is often simplified to an ostensible M1/M2 dichotomy. M1 macrophages (classically activated) are pro-inflammatory, characterized by the secretion of pro-inflammatory cytokines, reactive nitrogen intermediates (RNIs), and reactive oxygen species (ROS), all of which act to clear pathogens and damage unhealthy tissues. However, macrophages with sustained M1 phenotypes have been shown to promote autoimmune diseases due to chronic secretion of Th1 response elements, iNOS-dependent RNIs, chemokines, and cytokines such as IFN-1β, IL-12, IL-23, and TNF-α [3]. M1 macrophages are also characterized by low expressions of IL-10. Conversely, M2 macrophages (alternatively activated) are anti-inflammatory, characterized by high expressions of scavenging molecules, mannose and galactose receptors, ornithine, and polyamines. Yet, macrophages with M2 phenotypes in neoplastic tissues have been linked to tumor growth and metastasis [4]. The M2 phenotype has several sub-types (M2a, M2b, and M2c) that have distinct physiological roles. M2 macrophages are generally characterized by increased secretion of IL-10 and decreased secretion of IL-12 and IL-23 [3], promoting tissue remodeling and healing, extracellular matrix (ECM) deposition, responses to fungal infections *via* decreased autophagy, and regulation of other immune cells, particularly Th2 responses, in a highly adaptable manner [5].

The balance of pro-inflammatory and anti-inflammatory programs is often key to the outcome of inflammatory diseases (IDs) [6]. Accordingly, drug delivery strategies that target macrophages are gaining traction as a means to treat IDs. In general, two strategies are used, those that target: (i) extracellular signals secreted by, or intended for, macrophages and (ii) receptors on, or within, macrophages. However, perhaps the main factor that determines the efficacy of these

immunomodulatory strategies is targeting precision, which can be improved by using drug delivery systems (DDS). Nanoscale delivery systems in particular are promising platforms for macrophage-based immunomodulation due to their large surface areas, high drug-loading capacities, drug stabilizing potential, prolonged circulation, and potentially enhanced accumulation and penetration in diseased tissues [7]. Furthermore, modifying delivery systems with ligands specific to macrophage receptors, such as $\alpha v\beta_3$ integrin, collagen type IV, CD36, CD44, mannose receptors, class A scavenger receptors, and macrophage galactose type C-type lectin (MGL, CD301) have been shown to improve targeting efficacy [8-16]. In this review, we focus on cutting-edge drug delivery systems to macrophages in the three major classes of IDs: cancer, cardiovascular disease



(CVD), and autoimmune diseases.

Figure 1. Macrophage subsets and their corresponding stimulators, markers, and secretory outputs. M1 macrophages (classically activated) promote inflammatory responses, encompassing pathogen killing, Th1 activation, and tumor resistance. M2 macrophages (alternatively activated) generally promote an anti-inflammatory response and are further categorized as M2a (allergy, parasite killing, Th2 responses), M2b (immunoregulation, Th2 activation), and M2c (immunoregulation, matrix deposition, tissue remodeling). Adapted from Martinez and Gordon [2].

2. Targeting Macrophages for Cancer Therapy

2.1 Implications for macrophage targeting in cancer

Cancer progression is strongly correlated with macrophage residence and polarization; yet the role of these cells has been historically overlooked. A preponderance of work has shown that the fate of solid tumors can be orchestrated by tumor associated macrophages (TAMs) [17], which constitute up to 50% of the tumor mass in some cases [18]. Association of these cells with solid tumors has been linked to chemotherapy resistance, metastasis, and resultantly, poor patient prognoses [19]. Furthermore, the presence of TAMs has been shown to interfere with the efficacy of immunotherapy in solid tumors [20].

Combinations of proliferating cancer cells, stromal cells, and infiltrating immune cells lead to the establishment of solid tumors. During initiation, chronic inflammation activates key transcriptional factors such as nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), STAT3, and HIF1α, which direct macrophages to adopt pro-inflammatory phenotypes [18] and secrete pro-inflammatory mediators that are linked to a mutagenic microenvironment [21]. This is believed to be the primary reason why early inflammatory cells in diseases like inflammatory bowel syndrome are associated with an elevated risk for cancer contraction [22]. During chronic inflammation, these mediators act to recruit large numbers of myeloid cells, such as monocytes, which differentiate into macrophages upon their arrival [18]. Once established, TAMs adopt anti-inflammatory phenotypes, providing surrounding cells and tissues with signals to promote tumor growth and metastasis [23]. Thus, solid tumors with higher densities of TAMs tend to positively correlate with poor patient prognoses; although, some exceptions exist, including colorectal and non-small cell lung cancers [24, 25].

TAMs promote tumor growth and dissemination by numerous mechanisms, but perhaps most prominently *via* angiogenesis, which reduces the barriers necessary for cancer cells to extravasate and form metastatic colonies. Metastases are especially effective at attracting circulatory monocytes and directing their infiltration, differentiation, and polarization into

protumoral macrophages. Given their indelible role in cancer initiation and progression, macrophages have emerged as an important target for cancer therapy.

2.2 Targeting macrophages in solid tumors

Primarily three strategies are used to target macrophages for cancer therapy, those that: (i) inhibit monocyte infiltration into solid tumors, (ii) repolarize TAMs to reject solid tumors and (iii) eliminate TAMs from the tumor milieu [18]. These strategies represent a significant departure from traditional oncological treatments, which have previously focused on the administration of small molecule drugs [26]. More recent strategies in immunotherapy, which have improved clinical outcomes in many cancers [27], have largely focused on directing adaptive immune responses. Given the central role of macrophages and monocytes in cancer pathogenesis, there remains a clear opportunity to target innate immune cells to eradicate cancer. This section will discuss the key advances, limitations, and future opportunities for macrophage and monocyte-targeting drug delivery strategies for cancer therapy.

2.2.1 Blocking monocyte infiltration

Recent evidence has revealed that tissue-resident macrophages have origins derived from the yolk sac or fetal liver [28, 29]. In contrast, TAMs mostly originate from infiltrating bone marrow progenitor cells, such as circulating monocytes [18]. Thus, pathways to block monocyte infiltration to inflamed tissues associated with neoplastic tumors has emerged as an excellent strategy to treat primary tumors and inhibit the formation of metastatic colonies. TAMs typically recruit monocytes to solid tumors by the secretion of CSF-1, mCSF, CCL2, CCL3, CCL4, CCL5, CCL8, and VEGF [30, 31]. CCL2 in particular is a potent chemoattractant that has garnered significant attention as an important mediator of myeloid cell recruitment, as CC-chemokine receptor (CCR)2^{+} monocytes are the inflammatory precursors of M2-polarized TAMs [32]. Thus, strategies aimed at inhibiting the CCL2/CCR2 chemokine axis have become central to many therapeutic regimens [33, 34].

Two drugs that inhibit the CCL2/CCR2 chemokine axis are currently undergoing clinical investigation: PF-04136309 and CNTO 888 (carlumab) (**Table 1**). PF-04136309 is an inhibitor of CCR2, which was studied in Phase Ib clinical trials in combination with FOLFIRINOX, a chemotherapeutic drug combination comprising oxaliplatin and irinotecan with leucovorin and fluorouracil [35]. The study found that the combination was safe and effective compared to just FOLFIRINOX alone. Carlumab, on the other hand, is an antibody that binds to CCL2. When injected intravenously, carlumab was shown to induce regression of prostate cancer tumors by reducing monocyte and macrophage infiltration into the tumor microenvironment [36, 37]. Phase I and II clinical trials were performed with carlumab; however, the suppression of CCL2 was temporary and no therapeutic benefits were found [38]. One study found that cessation of CCL2 inhibition resulted in accelerated metastasis of breast carcinomas *via* angiogenesis [39]. Thus, further work is needed to evaluate the safety and efficacy of CCL2 inhibitors as monotherapies. Despite this, the use of CCL2 inhibitors in combination therapies is promising. Blockades against CCL2 were found to improve the efficacy of chemotherapy with carboplatin and paclitaxel in a mouse ovarian cancer model [40]. It is worth noting that several drugs that target the CSF-1 receptor (CSF-1R) have been shown to affect monocyte infiltration, including PLX3397, PLX7486, JNJ-40346527, ARRY-382, BLZ945, IMC-CS4, RG7155, and FPA008; however, these drugs are reviewed elsewhere [41, 42]. Another potential target to inhibit monocyte infiltration may be through blocking the angiopoietin receptor Tie-2 on monocytes. One study found knocking out Tie-2-expressing cells *in vivo* markedly reduced angiogenesis in human glioma xenografts and prompted considerable tumor regression [43]. Despite these advancements, an increased biological understanding of monocyte recruitment to primary or metastatic tumors is necessary before this strategy can reach its full potential [18].

2.2.2 Repolarizing TAMs

Restoring pro-inflammatory phenotypes in TAMs represents the fastest growing strategy for targeting macrophages in cancer therapy [44]. This approach directly leverages endogenous cells to mount a potent antitumor response, which can act synergistically with drugs that enhance T cell

infiltration (e.g., checkpoint inhibitors) [45]. Numerous strategies have been proposed to alter the phenotype of TAMs toward M1 phenotypes (**Figure 2**), including blockades against CD47 and macrophage receptor with collagenous structure (MARCO), agonists for CD40 and toll-like receptors (TLRs), and inhibitors of histone deacetylase (HDAC), phosphoinositide 3-kinase-γ (PI3Kγ), and microRNA (miR) activity. We discuss a few of the prominent examples of each below.

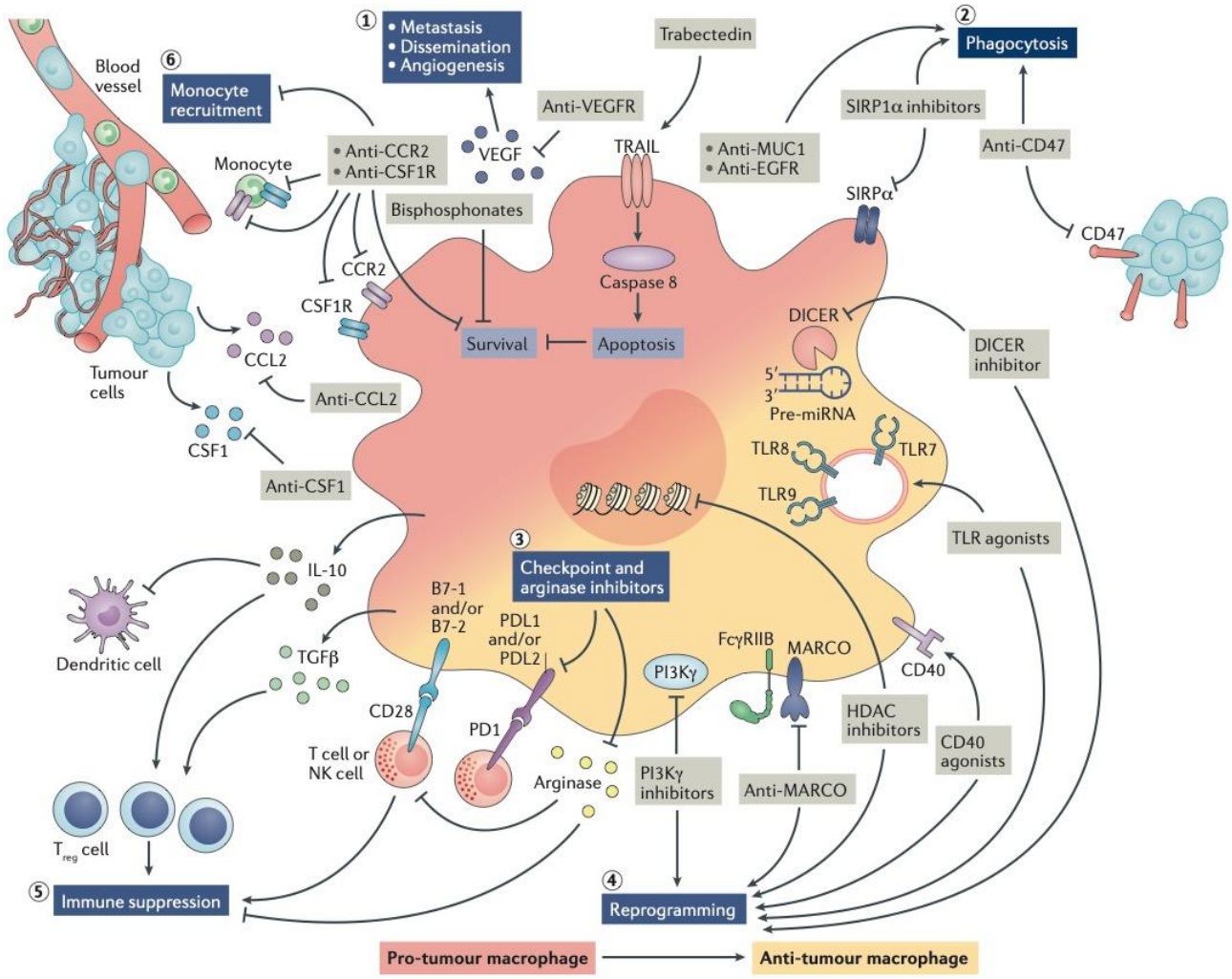


Figure 2. Strategies for targeting TAMs in cancer therapy. Schematic illustration of the main activities of TAMs that have been targeted in preclinical or clinical studies. Strategies fall into six categories: (1) blocking protumoral functions, including those that promote tumor growth, angiogenesis, and metastasis; (2) promoting phagocytosis of tumor cells; (3) employing checkpoints inhibitors, anti-immunosuppressive cytokines, or protein inhibitors to enable T cell infiltration; (4) reprogramming the polarization of TAMs; (5) inhibiting the suppressive microenvironment of tumors; and (6) inhibiting recruitment of monocytes. Reproduced with permission from Cassetta and Pollard [18], *Nature Publishing Group* 2018.

Antibodies against CD47 are powerful tools to modulate macrophage phenotypes. During homeostasis, the role of CD47 is to inhibit phagocytosis by interacting with thrombospondin 1 and signal regulatory protein-α (SIRPα), which are expressed on phagocytic myeloid cells like dendritic cells and macrophages [46]. However, CD47 is generally overexpressed by all solid tumors, providing a 'do not eat me signal' to the surrounding environment. Antibodies against CD47 have shown outstanding progress in xenograft mouse models through mechanisms related to activating phagocytosis pathways in TAMs [47, 48]. Several innovative delivery systems have been developed to deliver anti-CD47. One group developed a class of liposome-like particles to simultaneously inhibit the mCSF-CSF-1R signaling axis *via* blocking CSF-1R while inhibiting the CD47-SPIRα signaling axis *via* SIRPα-blocking antibodies [49]. The combination therapy repolarized TAMs toward M1 phenotypes to improve antitumor and anti-metastasis effects in murine breast and melanoma models. Another group developed a sprayable gel containing calcium carbonate NPs to slowly release anti-CD47 in the surgical bed after melanoma resection in mice [50].

Currently two antibodies against CD47 are undergoing clinical investigation: Hu5F9-G4 and CC-90002, for malignant brain tumors and hematological malignancies, respectively (**Table 1**) [51, 52]. Another drug currently undergoing clinical testing is a recombinant fusion protein that blocks the CD47-SIRPα axis, which produced promising results in a xenograft model for acute myeloid leukemia and B lymphoma [53]. Recently, monoclonal antibodies targeting the MARCO was shown to reprogram TAMs toward pro-inflammatory phenotypes [54], rendering MARCO as a promising target for future therapies aimed at repolarizing TAMs.

Antibodies against CD40 are another class of drugs with TAM-repolarizing capabilities. CD40 is expressed by antigen-presenting cells and binds to CD40L, which is mainly expressed on $CD4^+$ T cells. CD40-CD40L interactions generate phenotypic shifts toward M1 phenotypes by increased major histocompatibility complex (MHC) expression and increased production of pro-inflammatory cytokines [55]. Agonists for CD40, especially in combination with anti-programmed cell death 1 (anti-PD-1), have shown excellent antitumor activity in subcutaneous and metastatic pancreatic cancer mouse models [56]. Two agonist drugs for CD40 are currently undergoing

clinical investigation: CP-870,893 and RO7009789, both as a monotherapy and in combination with chemotherapeutic drugs [57-61].

A popular strategy to shift TAMs toward pro-inflammatory phenotypes is to deliver TLR agonists [62]. TLRs are a class of proteins that play a key role in innate immunity as a type of pathogen recognition receptor. Numerous TLR agonists have been investigated in preclinical models. One group found that β-cyclodextrin (β-CD) nanoparticles (NPs) loaded with R848, a TLR7/8 agonist, were able to shift TAM polarization toward M1 phenotypes in multiple mouse models and synergize with anti-PD-1 [63]. Two small molecule TLR7 ligands (imiquimod and 852A) and one TLR9 ligand (IMO-2055) are currently undergoing clinical investigation [64-66]. Numerous clinical trials are still ongoing, especially several in combination with other drugs [62].

Two other inhibitors that potentiate pro-inflammatory shifts in macrophage polarization are HDAC inhibitors and PI3Kγ inhibitors. Posttranslational modification of histones is believed to play a role in cancer progression. HDACs are responsible for epigenetic regulation of gene expression and inhibiting certain classes of HDACs, particularly class IIA, which has been shown to alter CCL1 and CCL2 expression to enhance M1 phenotypes [67]. TMP195, a small molecule HDAC inhibitor that induces the recruitment and differentiation of highly phagocytic and stimulatory macrophages, was shown to effectively shift TAMs toward pro-inflammatory phenotypes in a mouse breast cancer model [68]. PI3Kγ was recently shown to act as a switch for regulating immunosuppression in solid tumors [69]. Inhibiting PI3Kγ *via* IPI-549 was found to increase expression of MHCII and increase secretion of IL-12, shifting the polarization of TAMs toward M1 phenotypes in mouse models and synergizing with anti-PD-1.

Another strategy to affect TAM polarization is through siRNA to interfere with intracellular mRNAs [70]. NPs coated with mannose (i.e., mannosylated NPs) have been used in several preclinical studies to deliver siRNA to TAMs. One group delivered siRNA to manipulate the NF-κB pathway to induce antitumor phenotypes [71]. Another study used mannosylated NPs capable of escaping endosomal compartments to deliver siRNA to TAMs in an ovarian tumor mouse model and lung metastases [72]. One group found that conditional deletion of miR-processing enzyme

DICER in macrophages prompts M1-like TAM programming, which eventually recruited cytotoxic T lymphocytes (CTLs) and eradicated tumors in mouse models when used in combination with anti-PD-1 or CD40 agonists [73].

Numerous materials systems have been investigated to potentiate shifts in TAMs toward M1 phenotypes in preclinical studies [7, 74] One group created complexes formed from cationic dextran with nucleic acid drugs, comprising combinations of ODNs, anti-IL-10, and anti-IL-10 receptor ODNs [75]. Similar to the mannosylated NPs described before, another group coated mannosylated NPs with hyaluronic acid to shift TAMs toward M1 phenotypes in mice with breast cancer [76]. Ferumoxytol, an iron oxide-based NP, was used to induce shifts toward M1 phenotypes in murine mammary tumors and lung metastases [77]. NP gels encapsulating IL-12, which has anti-angiogenic properties, was used to repolarize TAMs in murine melanoma models [78]. One group developed NPs that generate ROS *via* photogeneration, which provided superior efficiency and efficacy over lipopolysaccharide stimulation and promoted infiltration of CTLs in mouse tumor models [79]. In a unique demonstration, one group synthesized NPs from M1 polarized macrophages that mimicked exosomes, which shifted the polarization of TAMs in murine colon carcinomas toward M1 phenotypes and led to tumor reduction in combination with anti-PD-L1 [80].

One other potential strategy to repolarize TAMs is *via* fractional radiotherapy. Traditional ablative radiotherapy is one of the most widely adopted approaches to kill tumorous tissues; however, their effect at lower doses to potentiate antitumor phenotypes is still undergoing investigation. After a single ablative dose of 10 Gy, the innate immune system is generally activated by inflammatory cytokines and pro-fibrotic factors that recruit macrophages with a tissue-reparative phenotype and contribute to tumor progression [81]. However, one group recently showed that, after a fractional dose of 2 Gy/fraction/day, radiotherapy generated pro-inflammatory phenotypes, yet with preserved pro-invasive and pro-angiogenic capacities [82]. More work must be done to evaluate the safety and efficacy of this approach before clinical testing. In a similar vein, low dose

chemotherapy has been shown to enhance the effect of immunotherapies to retrain the immune to adopt antitumor phenotypes. These works have been reviewed elsewhere [83].

Overall, while their phenotypic plasticity makes macrophages attractive targets for cancer therapy, it also makes the design of durable therapeutic interventions a major challenge. Macrophages continuously adapt their polarization in response to the surrounding tissue microenvironment. Thus, delivery vehicles with short-lived release profiles often result in minimal potencies. Resultantly, we anticipate that controlled release strategies through materials design will become increasingly important [7].

2.2.3 Depleting TAMs

The elimination of TAMs is a strategy aimed at eradicating macrophages at tumor sites, with the intention to interrupt the network of signals that favors tumor growth and progression [22]. The most common routes to date to achieve depletion of TAMs are *via* depleting antibodies or clodronate-containing liposomes.

The CSF-1R signaling pathway drives the recruitment of TAMs to tumors and promotes the differentiation of TAMs toward protumoral phenotypes. CSF-1R is a transmembrane tyrosine kinase class III receptor that is required for the presence of the vast majority of macrophages. It binds to two ligands, CSF-1 and IL-34, and regulates macrophage differentiation, proliferation, and survival in humans and mice [18]. Thus, a blockade against this pathway has become a major area of interest for halting TAM recruitment and promoting their depletion.

Several small molecule drugs have been developed against CSF-1R, many of which are undergoing clinical investigation (**Table 1**). PLX3397 (pexidartinib) has been shown to block the progression of gliomas, suppress tumor cell proliferation, and reduce tumor grade [84]. CSF-1R blockades with PLX3397 also rendered tumor cells more susceptible to receptor tyrosine kinase inhibition in a preclinical glioblastoma model. PLX3397 has been tested in Phase I and II clinical trials, demonstrating an antitumor response in 52% of patients as a monotherapy [85]. BLZ945, another small molecule inhibitor against CSF-1R, was shown to delay cervical and mammary tumor growth in murine models by attenuating the turnover of TAMs and enhancing infiltration by $CD8^+$

T cells [86]. One study found that BLZ945 alters macrophage polarization and blocks glioma progression in mice, leading to increased survival and regressed established tumors [87]. JNJ-40346527 entered clinical trials as a monotherapy for patients with relapsed or refractory Hodgkin lymphoma, which was well-tolerated and led complete remission in one patient [88]. Other small molecule drugs that inhibit CSF-1R have also been investigated, including PLX7486, which can also block tropomyosin kinase receptors (Trks), and ARRY-382, both of which are undergoing clinical investigation [42].

Antibody blockades have been developed for CSF-1R. RG7155 (emactuzumab) binds to CSF-1R and blocks its dimerization. Preclinical studies found that RG7155 led to increased $CD8^+$ / $CD4^+$ T cell ratios, which reduced CSF-$1R^+$ $CD163^+$ macrophages in solid tumors [89]. This antibody was well-tolerated in Phase I clinical trials in patients with advanced and metastatic tumors [90]. Both IMC-CS4 and FPA008 (cabiralizumab) are antibodies against CSF-1R that are currently undergoing three sets of independent clinical trials [42, 91]. AMG 820 has also progressed to clinical trials, but limited antitumor activity was observed [92]. Overall, CSF-1R inhibitors are a promising approach to deplete TAMs; however, findings from these trials have limited dose escalations due to toxicity issues that result from clearing macrophages in healthy tissues. For this reason, we anticipate that CSF-1R inhibitors in combination with other drugs may be a promising path forward.

The second approach to deplete TAMs is *via* bisphosphonates (e.g., clodronate, alendronate), which can exert toxicity against macrophages due to their specific interactions with mononuclear cells. Nanotechnology has emerged as a powerful tool to formulate and deliver bisphosphonates [7], typically as liposomes. Liposomes generally comprise one or more phospholipid bilayers with an aqueous core. They are typically 100−200 nm in size, allowing them to infiltrate solid tumors. Clodronate liposomes (sometimes called clodrolip) are effective at selectively inducing macrophage ‘suicide’, as (i) the natural fate of liposomes is phagocytosis, (ii) the lipid bilayer is then disrupted by lysosomal phospholipases, (iii) the clodronate does not easily exit the cell, and (iv) the clodronate released from dead cells does not enter new phagocytic cells,

and it has an extremely short half-life in circulation [93]. Storm and co-workers found that liposomes containing clodronate inhibited tumor growth by 55% compared to untreated controls while preventing chemoattraction of new monocytes from the bloodstream [94]. A potential mechanism behind the inhibited chemoattraction of new monocytes is suppressed angiogenesis, which was found later by another group [95]. Liposomal clodronate made from DOTAP, a positively charged surfactant commonly used to form cationic liposomes, was later used to inhibit proliferation and induce apoptosis of macrophages in a dose and time-dependent manner, leading to reduced tumor volumes in mouse melanoma models [96]. One group enhanced the affinity of clodronate to macrophages by conjugating ALN to free glucomannan, a polysaccharide with high affinity for the mannose receptor, for the efficient depletion of TAMs [97]. Clodronate liposomes have also been used against lung carcinomas [98], colon cancer [99], T cell lymphoma [100], pancreatic cancer [101], and multiple myeloma [102], among others. Most studies involving clodronate liposomes and other bisphosphonates to deplete TAMs have been performed in mice; however, the handful of clinical trials that have been produced have shown inconsistent results, suggesting a need to optimize particle design and administration [103]. Other studies are investigating the effect of combining clodronate as a neoadjuvant with chemotherapeutics and hormonal therapies [18].

A third, and relatively less-studied, mechanism to deplete TAMs is through trabectedin, which is a small molecule chemotherapeutic agent capable of targeting tumor cells and inducing apoptosis of macrophages and monocytes [104]. Trabectedin activates caspase 8 through TRAIL [105]. Overall, while promising in many preclinical and clinical studies, a broader concern of the general strategy to deplete TAMs is that the protective functions of macrophages will be compromised, which can increase the risk for infection [106]. Thus, we believe that careful consideration must be given to drug delivery strategies and dosing to enhance targeting and minimize off-target effects.

Table 1. Macrophage-targeting and monocyte-targeting drugs for cancer therapy in preclinical or clinical studies (non-exhaustive).

Drug Name	Type	Target	Effect	Ref
PF-04136309	Small molecule	CCR2	Inhibit monocyte infiltration	[35]
CNTO 888 (carlumab)	Antibody	CCL2	Inhibit monocyte infiltration	[36, 37]
Hu5F9-G4	Antibody	CD47	Repolarize TAMs	[51]
CC-90002	Antibody	CD47	Repolarize TAMs	[52]
TTI-621	Fusion protein	SIRPα	Repolarize TAMs	[53]
HPA063793	Antibody	MARCO	Repolarize TAMs	[54]
CP-870,893	Agonistic antibody	CD40	Repolarize TAMs	[57-60]
RO7009789	Agonistic antibody	CD40	Repolarize TAMs	[61]
R848	Small molecule	TLR7/8	Repolarize TAMs	[63]
Imiquimod	Small molecule	TLR7	Repolarize TAMs	[64]
852A	Small molecule	TLR7	Repolarize TAMs	[65]
IMO-2055	Small molecule	TLR9	Repolarize TAMs	[66]
TMP195	Small molecule	HDAC	Repolarize TAMs	[68]
IPI-549	Small molecule	PI3Kγ	Repolarize TAMs	[69]
PLX3397, PLX108-01 (pexidartinib)	Small molecule	CSF-1R, c-KIT, Flt3	Deplete macrophages	[42, 84, 85]
BLZ945	Small molecule	CSF-1R	Deplete macrophages/ Repolarize TAMs	[86, 87]
JNJ-40346527	Small molecule	CSF-1R	Deplete macrophages	[88]
PLX7486	Small molecule	CSF-1R, Trk	Deplete macrophages	[41, 42]
ARRY-382	Small molecule	CSF-1R	Deplete macrophages	[41, 42]
RG7155 (emactuzumab)	Antibody	CSF-1R	Deplete macrophages	[89]
IMC-CS4	Antibody	CSF-1R	Deplete macrophages	[41, 42]
FPA008 (cabiralizumab)	Antibody	CSF-1R	Deplete macrophages	[42, 91]
AMG 820	Antibody	CSF-1R	Deplete macrophages	[92]
Bisphosphonates (e.g., clodronate, alendronate)	Small molecule in liposomes	Phagocytes	Deplete macrophages	[95, 97]
Trabectedin	Small molecule	Caspase 8	Deplete macrophages	[104]

3. Targeting Macrophages for Cardiovascular Disease (CVD) Therapy

Macrophage-induced inflammation is involved in nearly all CVDs, including myocarditis,

atherosclerosis (AS), pulmonary arterial hypertension (PAH), stroke, and cardiac disease. Therefore, targeting dysfunctional macrophages is an encouraging strategy to treat CVDs. This section will highlight the recent advances using DDS to target vascular macrophages for CVD treatment. The reported active drugs for treatment are summarized in **Table 2**. The targeting strategies are summarized in **Figure 3.**

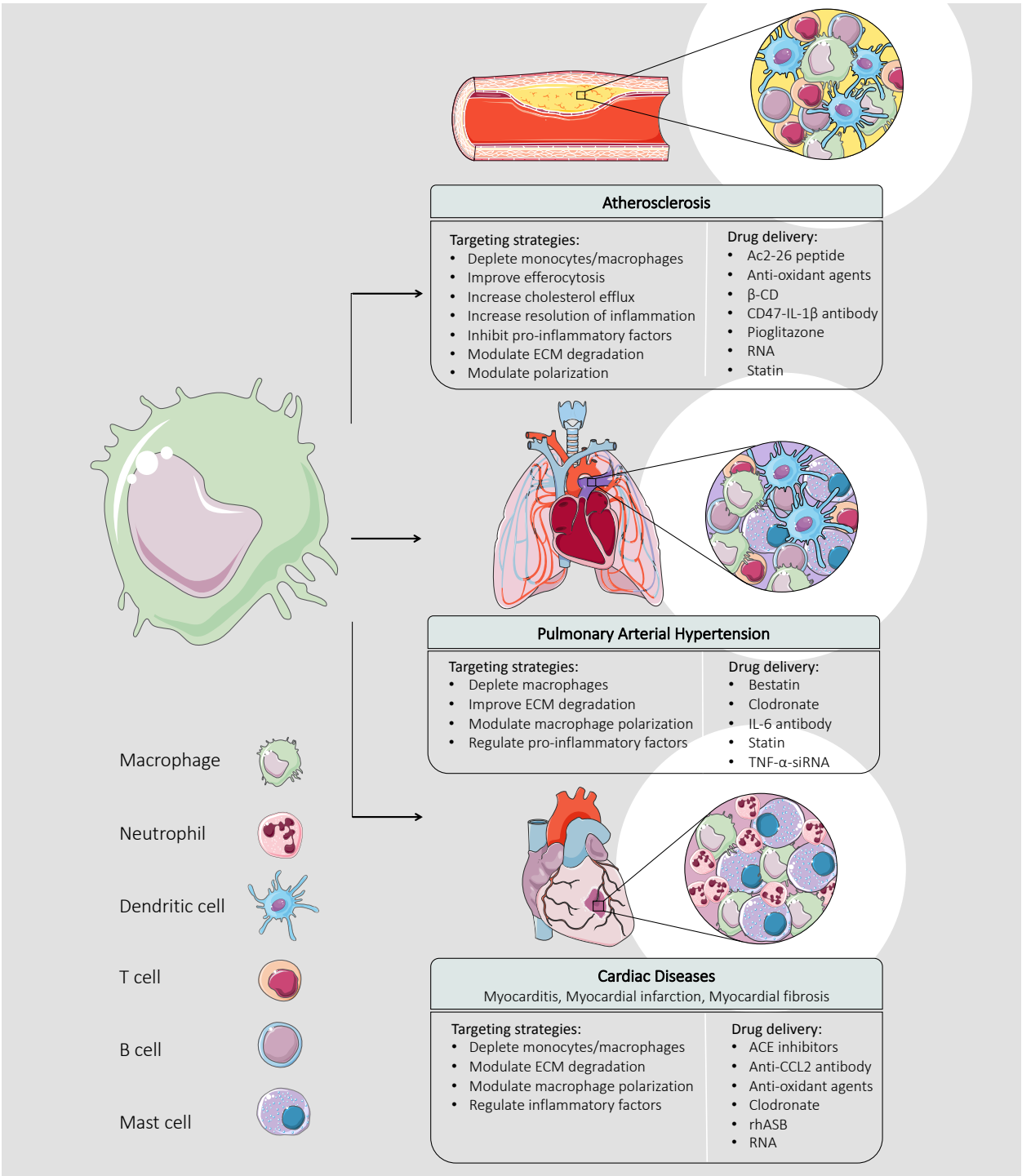


Figure 3. Strategies for targeting macrophages in CVD therapy. (Top) For atherosclerosis (AS), macrophages play a central role in disease development *via* proliferation, formation of foam cells (promoted by cholesteryl ester), and phenotypic shifts to M1 polarizations. (Middle) For pulmonary arterial hypertension (PAH), recruited macrophages in the perivascular space exacerbate inflammation and promote crosstalk with pulmonary artery

(PA) SMCS and PAECs, leading to remodeling of pulmonary arteries. (Bottom) For cardiac diseases including myocarditis, myocardial infract (MI), and myocardial fibrosis (MF) induced by MI, increased accumulation of M1 macrophages is a common feature. For each class of CVD, common drugs and targeting strategies used to potentiate therapeutic effects are shown.

3.1 Atherosclerosis (AS)

3.1.1 Implications of macrophage targeting in AS

AS is a lipid-driven inflammatory disease of the arterial wall characterized by plaque buildup. This occurs due to the accumulation of diseased cells (e.g., monocytes, macrophages, endothelial cells (ECs), smooth muscle cells (SMCs), and neutrophils), lipids, and ECM components, whereby accumulation of cholesteryl ester (oxLDL) is characteristic [107, 108]. The pathogenesis of AS is not fully understood, but increasing evidence suggests that the presence of macrophages and macrophage-derived pro-inflammatory cytokines, such as IL-1β, IL-18, and macrophage inflammatory protein-1α (MIP-1α) [109, 110], play a critical role [109]. As a result, targeting lesional macrophages is a promising method to retard plaque progression. Macrophage-targeted strategies include facilitating cholesterol efflux, preventing foam cell formation, improving resolution of inflammation, shifting macrophage polarizations from M1 to M2 phenotypes, and promoting efferocytosis [109-111].

3.1.2 Strategies for targeting macrophages in AS

In the clinic, increasing cholesterol efflux from macrophages or decreasing lipid uptake into macrophages are commonly adopted methods to delay the development of AS. One class of drugs used to induce these responses is 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors, commonly known as statins (e.g., simvastatin, lovastatin, and atorvastatin). However, statins are conventionally delivered as a capsule or tablet, which have potential liver toxicity due to limited targeting capabilities. To improve delivery of the statins, several targeted DDS, such as HDL-mimicking NPs [112, 113], solid lipid NPs, polymer micelles, and eletrospun fibers, have been proposed [114].

Delivery of nucleic acids is another effective strategy to regulate cholesterol efflux [115-118]. Chitosan NPs with a diameter of 150−200 nm were designed to deliver miR-33 mimic to naïve macrophages, resulting in a 5% increase in cholesterol efflux and an overall decrease in reverse cholesterol transport to the plasma, liver, and feces [115]. Interestingly, Henrich *et al*. reported that spherical HDL mimics made from lipid-conjugated organic cores promoted cholesterol efflux from immortalized macrophages loaded with tritium-labeled cholesterol [119]. Another strategy to promote cholesterol efflux is β-CD, commonly used in pharmaceutical applications to deliver hydrophobic drugs. Zimmer *et al*. reported that administration of β-CD significantly improved cholesterol efflux by promoting LXR activation in plaque macrophages and potentiating anti-inflammatory effects [120, 121]. Increased cholesterol efflux also has been shown to inhibit foam cell formation [122]. These findings suggest that increasing the solubility and removal of cholesterol crystals could be an effective and potentially translatable strategy for AS treatment, which has elicited follow-up studies [120, 121].

Targeted delivery of anti-oxidative agents to macrophages to inhibit the secretion of pro-inflammatory factors, such as ROS, TNF-α, IL-1β, and monocyte chemoattractant protein-1 (MCP-1), is a well-demonstrated strategy to induce regression of AS [122-125]. It should be mentioned that the delivered anti-oxidative agents can protect the plaque matrix as well, preventing MMP [122] and collagen [126] from degradation. In particular, anti-inflammatory treatment by administration of canakinumab, an approved IL-1β-antibody to treat arthritis, was shown to produce significant anti-AS effects by decreasing high-sensitivity C-reactive protein (hsCRP) levels in the span of 3 months in a clinical trial containing over 1,000 patients [127].

Modulating the polarity of monocytes and macrophages toward anti-inflammatory phenotypes can alleviate inflammatory activity and prevent plaque rupture [128-131]. This has been shown by modulation of Ly-6C^{high} to Ly-6C^{low} in monocytes, CD14^{+} CD16^{++} to CD14^{++} CD16^{-} in monocytes, and M1 to M2 phenotypes in macrophages [128-131]. One group loaded pioglitazone into bioabsorbable poly(lactic-co-glycolic-acid) (PLGA) NPs for intravenous injection into ApoE$^{-/-}$ mice [128]. The pioglitazone-NPs polarized macrophages toward M2 phenotypes, as

indicated by lower expressions of CD206 and suppressed MMP activity, inhibiting atherosclerotic plaque destabilization and rupture more effectively than oral pioglitazone [128].

Resolution of inflammation by systemic delivery of mediators reduces leukocyte recruitment, improves efferocytosis, and repairs tissue damage, representing a new approach to treat AS [110]. These mediators include IL-10, annexin A1, specialized pro-resolving mediators (SPMs) (e.g., resolvins, lipoxins, maresins, and protectins), endogenous gases (e.g., NO, H_2S, and CO), and Tregs [110]. To improve delivery of these mediators, type IV collagen (ColIV)-targeted NPs and other delivery methods have been developed [126, 132-134]. Addition of ColIV binding peptides to the formulation allowed polymeric NPs loaded with Ac2-26 peptides (an SPM) to selectively target the AS lesion and sustainably release Ac2-26 over 5 days [126].

Depletion of plaque-associated macrophages is a potential route to reduce inflammation and delay the progression of AS [114, 135, 136]. The LyP-1 peptide has known tumor-penetrating abilities. She *et al*. demonstrated that LyP-1 could target atherosclerotic plaques, penetrate the interior of plaques, accumulate in macrophages, and trigger their apoptosis, which effectively reduced burdens associated with advanced hypoxic plaques [135]. Another group designed TRAF6i (protein)–HDL to moderate CD40–CD40L signaling in monocytes and macrophages by blocking the interaction between CD40 and TRAF6 [137]. TRAF6i–HDL was well taken up by monocytes and macrophages in an $Apoe^{-/-}$ mouse model, resulting in decreased monocyte recruitment and inflammation [137].

Improved efferocytosis of apoptotic foam cells is another strategy to remove lesional macrophages [138]. A previous review described detailed signaling pathways to regulate efferocytosis [110]. It was reported that CD47 was overexpressed in plaque macrophages, which negatively affected phagocytosis [139]. Delivery of CD47 antibodies to block cognate receptor SIRPα improved efferocytosis, normalized the clearance of diseased vascular tissue, and ameliorated AS in multiple mouse models [139].

3.2 Pulmonary arterial hypertension (PAH)

3.2.1 Implications of macrophage targeting in PAH

PAH is a progressive disease characterized by vascular remodeling of precapillary pulmonary arteries resulting from overgrowth of SMCs, apoptosis-resistant ECs, fibroblasts, macrophages, increased ECM deposition, and chronic inflammation [140-142]. PAH is classified into the following categories: (i) idiopathic PAH, (ii) heritable PAH (HPAH), (iii) drug- and toxin-induced PAH, (iv) associated PAH (APAH), and (v) persistent pulmonary hypertension of the newborn (PPHN) [143]. Although it is believed that inflammation is central to the development of PAH, the precise mechanism is unclear. Many factors, such as infections, cytokines (e.g., IL-1β, IL-6, IL-8, and TNF-α), chemokines (e.g., MCP-1), and immune cells (e.g., monocytes, macrophages, mast cells, dendritic cells, and T cells) may contribute [144]. The increased recruitment of monocytes and macrophages in the perivascular space is a prominent feature of PAH [145, 146]. In particular, the presence of $CD68^+$ macrophages is closely related to PAH progression [146]. Furthermore, the crosstalk between macrophages and pulmonary artery ECs (PAECs) mediated by CCR2/CCR5 promotes proliferation of pulmonary artery SMCs (PASMCs) and remodeling of the pulmonary artery [5].

3.2.2 Strategies for targeting macrophages in PAH

Accumulation of mannose receptor (MR)-positive macrophages in the lungs is a hallmark of PAH [147]. Depletion or inactivation of such macrophages has shown promise to treat PAH in several models, including experimentally induced hypoxia and portopulmonary hypertension models [146, 148-150]. Crosswhite *et al*. reported that intravenous delivery of recombinant adeno-associated virus (AAV)-2-carrying TNF-α short hairpin RNA (shRNA) significantly reduced macrophage infiltration and inflammation in cold-induced PAH [151]. In another case, 7-day doxycycline treatment significantly upregulated heme oxygenase-1 (*HMOX1*) during the entire period of hypoxic inflammation, inhibited macrophage accumulation and activation, induced IL-10 expression, and prevented the development of hypoxia-induced PAH [148]. In a monocrotaline

(MCT)-induced model, inhalation of PLGA-NPs loaded with pitavastatin or cerivastatin-liposomes eliminated macrophages, reduced inflammation, and delayed the development of PAH [152, 153]. In particular, inhaled cerivastatin-liposomes exhibited sustained release profiles over 12 hours, inhibited the proliferation of PASMCs, and significantly reduced $CD68^+$ macrophages, which are prominent in advanced obliterative plexiform lesions. This effect resulted in reduced occlusion of small arteries and declined pulmonary alveolar proteinosis [153]. Two other reports demonstrated that the delivery of clodronate by liposomes eliminated macrophages and inhibited remodeling of pulmonary arteries [154, 155].

In response to hypoxia, alveolar macrophages undergo M2 polarization. The presence of M2 macrophages is associated with the development of hypoxia-induced pulmonary hypertension (HPH) and PASMC proliferation [148]. IL-6 is a well-known pro-inflammatory factor in HPAH due to its potentiation of M2 phenotypes. One group showed that IL-6 blockade by tocilizumab, a monoclonal antibody approved for clinical use for RA treatment, prevented the hypoxia-induced accumulation of Th17 cells and M2 macrophages by reduced expression of IL-21, ameliorating HPH [156]. Treatment of PAH with tocilizumab is undergoing a Phase II clinical trial [156].

Blockage of macrophage-derived cytokines is another potential approach to remove $CD68^+$ macrophages and retard PAH development [157]. One group found that macrophage-derived leukotriene B4 (LTB4) resulted in EC death, induced PASMC proliferation, and hypertrophy in a dose-dependent and BLT1-dependent manner, contributing to the development of immune dysregulation-associated pulmonary hypertension [145]. LTB4 blockage with bestatin-induced apoptosis of SMCs enabled effective treatment for PH in immune-dysregulated rats [145]. In another study, Bai *et al*. reported that macrophage-derived legumain could promote pulmonary hypertension by activating the MMP-2/transforming growth factor-β1 (TGF-β1) signaling pathway. The intraperitoneal administration of legumain inhibitor RR-11a delayed PAH progression in hypoxia and SU5416 (HySU)-induced PAH mice and MCT-induced PAH rats [158].

3.3. Cardiac diseases

3.3.1 Strategies for targeting macrophages for myocarditis treatment

Myocarditis is an inflammatory disease of the muscular portion of the heart. Massive infiltration of immune cells, particularly macrophages, is a typical feature in acute and chronic myocarditis [159]. Macrophage polarization toward M2 phenotypes is one potential strategy to treat myocarditis [160]. Gold NPs (AuNPs) coated with miR-155 antagonist promoted M2 polarizations and reduced inflammation, thereby restoring cardiac function in an ovariectomized diabetic mouse model [161]. To facilitate phenotypic shifts toward M2 polarizations, Farajzadeh *et al*. developed curcumin-encapsulated hyaluronic-polylactic acid (HA-PLA) NPs to target CD44 [162]. Curcumin is an approved drug to combat inflammation by inhibiting NF-κB and TLR4 as well as by activating PPRγ, thus suppressing the production of pro-inflammatory cytokines like TNF-α and IL-1β [163]. To improve the targeting and delivery of curcumin, several DDS have been developed, such as micelles, ovalbumin NPs, and covalent organic frameworks [163, 164].

$CD11b^+$ monocytes/macrophages regulated by CCR2 are believed to contribute to the development of myocarditis [165]. One group loaded lipidoid NPs with siRNA for CCR2 (siCCR2) prepared from distearoylphosphatidylcholine (DSPC), cholesterol, and polyethylene glycol/dimyristoyl-rac-glycero (PEG-DMG). NPs were administered to patients with myocarditis twice per week and showed reduced myocarditis [166]. Since myocarditis occurs after acute inflammation, the group administered NPs during the peak of disease and later found an enhanced ejection fraction as well as a 10-fold reduction in collagen and myocardial fibrosis [166]. The study represents one of the most promising strategies to treat myocarditis by using DDS.

Downregulation of macrophage-secreted factors, including MMPs, TGF-β, TNF-α, IL-10, IL-13, IL-4, and IL-1, facilitates the suppression of myocarditis [167]. One group demonstrated that PEGylated liposomes accumulate in ischemic/reperfused myocardia [168]. Another group used PEGylated liposomes loaded with FK506 (tacrolimus), an immunosuppressive drug, in an experimental autoimmune myocarditis rat model, which markedly suppressed the expression of INF-γ and TNF-α and reduced cardiac inflammation and fibrosis [169].

3.3.2 Strategies for targeting macrophages for myocardial infarction (MI) treatment

MI is a serious cardiovascular disorder that frequently results in death. After MI, macrophages are recruited to the site of injury, resulting in substantial inflammation and leading to adverse cardiac remodeling and dysfunction [170]. The cardiac ECM predominantly consists of fibronectin, glycosaminoglycans, and proteoglycans, which provide mechanical support to the heart [171]. Following MI, increased inflammation upregulates proteases, such as MMP-2 and MMP-9, resulting in ECM decomposition, reduced mechanical properties of cardiac tissues, and decreased ventricular wall thicknesses, thereby inhibiting cardiac function [170].

Inhibition of monocyte and macrophage accumulation is a primary treatment approach for cardiac tissue healing after MI [172]. Following MI, increased serum levels of IL-1β typically exist in patients [173]. Administration of IL-1β antibodies allowed for a reduction of both monocytes and neutrophils in blood and infarct regions of the heart, which led to markedly attenuated left ventricular remodeling in MI-mice model with AS [174]. Administration of canakinumab (FDA-approved IL-1β antibody) to a patient with a history of MI and elevated hsCRP effectively prevented adverse cardiac events over a 3.7-year median [175]. In another study, PLGA-based NP-mediated delivery of TAK-242 to block TLR4 inhibited cardiac accumulation of Ly-6C^{high} monocytes, while decreasing circulating high mobility group box-1 protein (HMGB1), NF-κB activation, and expression of IL-6 and MCP-1 in the heart after MI [172].

Inducing a phenotypic shift toward regenerative phenotypes is a promising strategy to improve myocardial remodeling after MI [176-179]. miR-155 in macrophages results in cardiac inflammation, hypertrophy, and failure in response to pressure overload [180]. miR-155 inhibition has been shown to downregulate nerve growth factor (NGF) expression and diminish MI-induced sympathetic neural remodeling by decreasing M1 polarization and suppressing the cytokine signaling 1(SOCS1)/NF-κB pathway [181]. miR-21 is another nucleic acid to modulate polarization of macrophages. Bejenora *et al*. demonstrated that NP-facilitated delivery of miR-21 to cardiac macrophages after MI induced polarization towards reparative phenotypes, which was correlated with angiogenesis, a lower number of apoptotic cells, and attenuation in left ventricle remodeling

[177]. Also, delivery of a protein, neuregulin-1, by using PLGA microparticles induced macrophage polarization toward a regenerative phenotype ($CD206^+$ cells) and promoted cardiac tissue repair [182, 183]. Alternatively, inhibiting the secretion of NO and other pro-inflammatory factors from macrophages enabled cardiac repair [184]. One group showed that liposomes loaded with berberine, an anti-inflammatory drug, efficiently accumulated in infarcted zones and were taken up by macrophages, resulting in a significant inhibition of IL-6 secretion and improved cardiac ejection fractions [185].

Locally administrated DDS that can sustain drug release have been shown to facilitate cardiac repair after MI, particularly *via* enhanced shifts from M1 macrophages towards reparative phenotypes [176, 186-190]. To prolong retention of NPs in infarcted myocardia after MI, a group designed NPs that respond to upregulated MMPs present in acute MI and accumulate in infarcts at 28 days post injection [191]. Similarly, Carlini *et al*. reported another enzyme-response hydrogel that improves drug accumulation and retention in infarcts [192].

3.3.3 Strategies for targeting macrophages for myocardial fibrosis (MF) treatment

MF is a cardiovascular disease mainly resulting from abnormal accumulation of ECM proteins such as collagen, elastins, fibronectin, and laminins [193]. MF can be classified into reactive interstitial fibrosis, infiltrative interstitial fibrosis, and replacement fibrosis [194]. Two proteases, MMPs and lysyl oxidases (LOXs) that covalently cross-link collagen, are critical to fibrosis development; and in MI-induced MF, MMPs are overexpressed, inducing tissue remodeling, and promoting disease development [193]. One group demonstrated that sustained local delivery of an MMP inhibitor, recombinant tissue inhibitor of metalloproteinase (TIMP-3), to the infarct zone using an MMP-degradable hydrogel ameliorated MF caused by MI [195].

MF is characterized by monocyte-derived macrophage accumulation in the myocardia that interacts with fibroblasts and induces the secretion of matricellular proteins, like secreted protein acidic and rich in cysteine (SPARC) [196, 197]. In replacement fibrosis induced by heart injury, M1 macrophage-mediated inflammation damages tissues and increases fibrotic responses; for other types of MF, M2 macrophages secrete anti-inflammatory and pro-fibrotic factors, including IL-10,

TGF-β, connective tissue growth factor (CTGF), and platelet-derived growth factor (PDGF), which promote fibroblast proliferation and ECM production [198]. To combat circulating monocytes that infiltrate the myocardia and contribute to MF, one group developed cytotoxic clodronate liposomes [196]. After intravenous injection of the liposomes, monocyte infiltration was significantly reduced in angiotensin II-infused mice [196]. Targeting of phosphatidylserine (PS)-presenting liposomes to infarct macrophages after intravenous injection promoted anti-inflammatory polarizations of tissue-resident macrophages, as evidenced by increased expressions of CD206, which facilitated angiogenesis and prevented ventricular dilatation and remodeling [199]. Another group reported that delivery of recombinant human arylsulfatase B (rhASB) to the myocardium in a transverse aortic constriction rat model reduced TNF-α secretion and decreased inflammation and fibrosis [200]. Additionally, delivery of anti-oxidative agents to macrophages using NPs has generated similar effects for reducing fibrosis [178, 201].

The use of hydrogels to regenerate cardiac tissue is another approach to treat MF [202-205]. Recently, several groups reported that the injection of hyaluronic acid-based microrods with anti-inflammatory properties decreased ECM deposition, attenuated myocardial wall thinning, and improved left ventricle function [206, 207].

Table 2. Macrophage-targeting and monocyte-targeting drugs for CVD in preclinical or clinical studies (non-exhaustive).

Drug name	Type	Target	Effect	Disease	Ref
LXR-L T0901317	Antibody	LXR	Increase cholesterol efflux, inhibit pro-inflammatory factors	AS	[12]
Simvastatin	Small molecule in HDL mimic NPs	HMG-CoA	Deplete macrophages or monocytes	AS, PAH	[112, 114]
miR-33	Nucleic acid in chitosan NPs	ABCA1	Increase cholesterol efflux	AS	[115]
miR-181b	Nucleic acid	Importin-α3, NF-κB	Inhibit pro-inflammatory factors	AS	[116]
miR-378a	Nucleic acid	SIRPα	Increase cholesterol efflux	AS	[118]
β-CD	Small molecule	Cholesterol crystals	Increase cholesterol efflux	AS	[120]

TEMPOL plus PBAP	β-CD-based NPs	ROS	Increase cholesterol efflux	AS	[122]
Lovastatin	Small molecule in HDL mimic NPs	HMG-CoA	Inhibit pro-inflammatory factors, increase cholesterol efflux	AS	[123]
Anti-miR-155	Nucleic acid in HDL mimic NPs	HBP1	Inhibit ROS, increase cholesterol efflux	AS, PAH, myocarditis, MI	[124, 181]
Ac2-26	Peptide in polymeric NPs	Collagen	Regulate FPR2/ALX receptor	AS	[126]
Pioglitazone	Small molecule in PLGA NPs	PPARγ	Modulate macrophage polarity	AS	[128]
LyP-1	Peptide	p32	Depletion of macrophages	AS	[135]
Rapamycin	Small molecule in red blood cell-based NPs	mTOR	Depletion of macrophages	AS	[136, 208]
SMI 6877002	Small molecule in HDL mimic NPs	CD40–CD40L signaling axis	Depletion of macrophages	AS	[137]
CD47 antibody	Antibody	CD47	Inhibit pro-inflammatory factors	AS	[139]
LXR agonist GW3965	Small molecule in NPs	LXR	Increase cholesterol efflux	AS	[209]
Pitavastatin	Small molecule in PLGA NPs	HMG-CoA	Inhibit pro-inflammatory factors, increase cholesterol efflux	PAH	[129]
Bestatin	Small molecule	LTA4H	Block macrophage-derived cytokines	PAH	[145]
Clodronate	Small molecule in liposomes	CX3CR1 signaling	Deplete macrophages or monocytes	PAH, MF	[196]
Tocilizumab	Antibody	IL-6	Modulate macrophage polarity	PAH	[156]
Antagomir-130a	Nucleic acid	phosphatase/PI3K /protien kinase B	Block macrophage-derived factors	PAH	[210]
Curcumin	Small molecule in HA/ovalbumin NPs	NF-κB, STAT1	Modulate macrophage polarity	Myocarditis	[162, 164, 211]
siCCR2	Nucleic acid in lipidoid NPs	IL-1β	Modulate macrophage polarity	Myocarditis	[166]
Canakinumab	Antibody	IL-1β	Depletion of macrophages	MI	[174]
Neuregulin-1	Protein in microparticles	α-SMA	Modulate macrophage polarity	MI	[176]

miR-21	Nucleic acid in hyaluronan-sulfate NPs	TGF-β, TNF-α	Modulate macrophage polarity	MI	[177]
IL-4 pDNA	Nucleic acid in graphene oxide NPs	ROS	Modulate macrophage polarity	MI	[178]
Dexamethasone	Small molecule in albumin fibers	NO	Inhibit pro-inflammatory factors	MI	[184]
Hyaluronic acid oligosaccharides	Polysaccharide-hydrogels	CCL2/CXCL5	Modulate macrophage polarity	MI	[207]
Recombinant TIMP-3	Protein in MMP-response hydrogels	MMP-3	Modulate macrophage	MF	[195]
Phosphatidylserine (PS)	Liposomes	Macrophages	Modulate macrophage polarity, inhibit pro-inflammatory factors	MF	[199]
rhASB	Protein	Chondroitin sulfate glycosaminoglycans	Inhibit pro-inflammatory factors	MF	[200]

4. Targeting Macrophages for Autoimmune Disease Therapy

Many autoimmune diseases are characterized by high macrophage infiltration [44, 212, 213]. Although macrophage recruitment and activation follow canonical pathways, each autoimmune disorder is unique in its pathology [214]. Through aberrant secretions of cytokines, chemokines, and transduction factors and resultant irregular crosstalk with dendritic cells or regulatory T cells, macrophages can directly contribute to the progression of autoimmune diseases [44, 215]. Ma *et al*. reviewed the role of monocytes and macrophages in autoimmune disease, underlining the phenotypic and functional role of these cells in disease pathogenesis [212]. Here, we seek to delve into macrophage-targeting treatments for autoimmune diseases, specifically in the context of rheumatoid arthiritis (RA), inflammatory bowel diseases (IBD), multiple sclerosis (MS), systemic lupus erythematous (SLE), and type 1 diabetes (T1D). The targeting strategies are summarized in **Figure 4**.

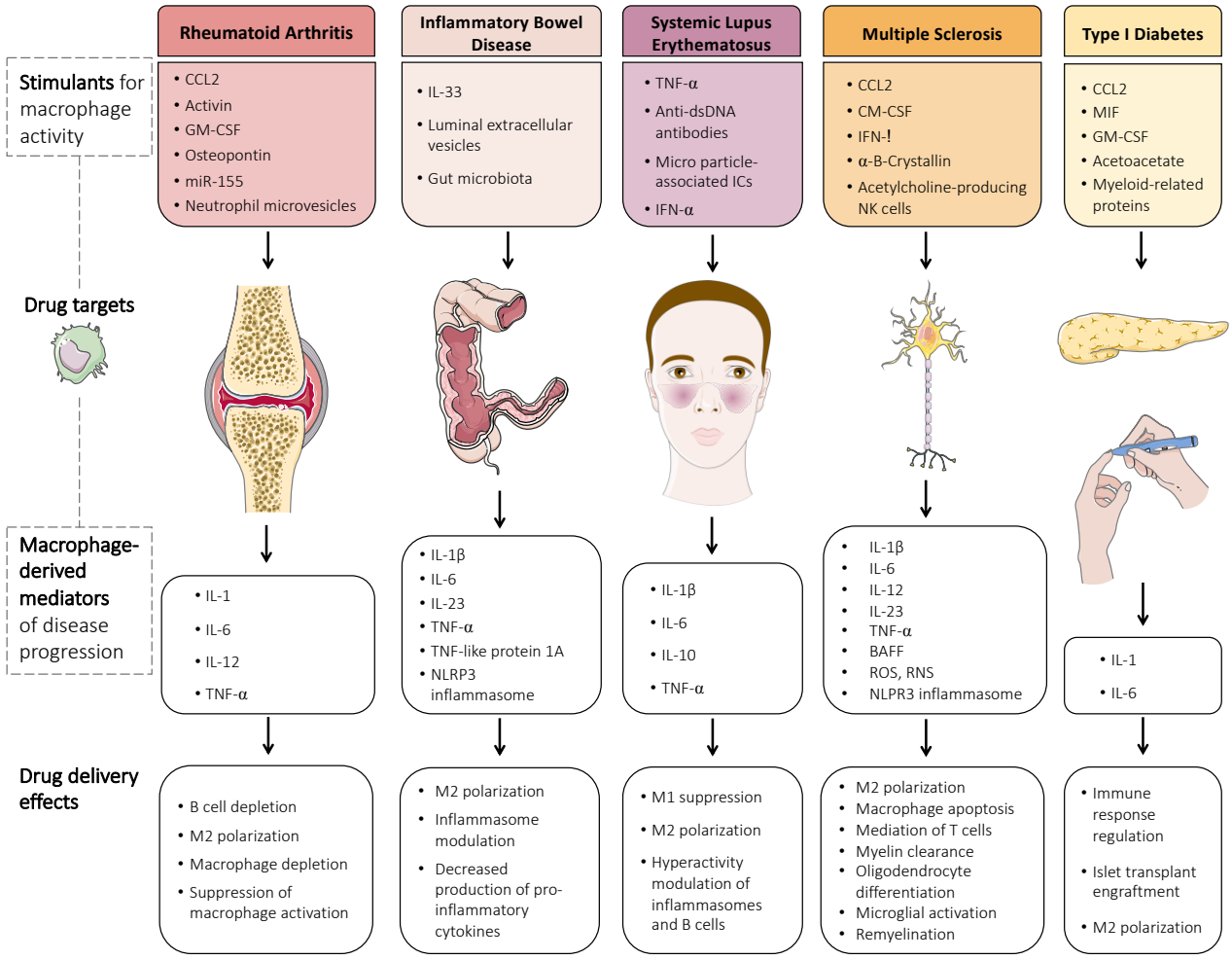


Figure 4. Macrophage activity in the progression and treatment of autoimmune diseases. Drug targets for autoimmune diseases include stimulants for macrophage activity, which promote recruitment and activation, and subsequent macrophage-derived mediators of disease progression. These contributors to disease activity are outlined for rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, and type 1 diabetes. The resulting drug delivery effects modulate the activity of macrophages, pro-inflammatory cytokines, and associated immune cells.

4.1 Rheumatoid arthritis (RA)

4.1.1 Implications of macrophage targeting in RA

RA involves chronic inflammation in the joints and can lead to cartilage destruction and bone erosion. It is characterized by an accumulation of macrophages in synovial tissues [216]. Increased infiltration of synovial macrophages leads to greater IL-6 and TNF-α secretion, resulting in increased degrees of joint erosion [215, 217]. The polarization of macrophages in RA favors a high M1/M2 ratio, coupling unrestrained, pro-inflammatory M1 polarization with incomplete M2

polarization [218]. Increased expressions of CD50 and CD36 are also coupled with decreased expressions of CD163 and CD209 [219]. The exaggerated M1 polarization results in elevated levels of TNF-α, IL-1, IL-6, and IL-12 [212, 220-222]. Key macrophage-derived mediators in disease progression are IL-1, IL-6, and TNF-α, which are secreted by activated macrophages and mediate local and systemic inflammation and cartilage degradation [223]. IL-12 also mediates local and systemic inflammation [212]. Synovial membrane-resident macrophages and monocyte-derived macrophages have different functions in RA, which is an important consideration when designing targeted therapies [224].

4.1.2 Strategies for targeting macrophages for RA treatment

4.1.2.1 Modulation of macrophages

The current standard of care for RA involves disease-modifying anti-rheumatic drugs, which most commonly include methotrexate, steroids, and nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs are not specific to macrophages, but they mitigate some of the inflammatory effects related to macrophage activation [225]. One macrophage-based strategy to treat RA is the elimination of inflammatory synovial macrophages. Synovial inflammation in experimental arthritis has been shown to improve (i) after injection of chlodronate liposomes to selectively deplete local macrophages [226], (ii) after *SIRT1* inhibition to block monocyte differentiation into macrophages [227], and (iii) after introduction of a CD64-directed immunotoxin [228, 229]. Another strategy to treat RA is by repolarizing macrophages toward anti-inflammatory phenotypes. IL-10 was shown to suppress M1 phenotypes in experimental arthritis [230, 231], while activation of SIRT1/AMPKα signaling [232] and administration of THAP, a Notch inhibitor, reduced inflammation in knee joints [233]. In a similar vein, mesenchymal stem cells (MSCs), which have immunomodulatory capacities, were systemically delivered into mice with collagen-induced arthritis and improved disease severity [234].

4.1.2.2 Modulation of cytokines and associated disease-mediators

Blockades against cytokines and other pro-inflammatory factors are attractive therapeutic targets for RA. Blockades of TNF-α using monoclonal antibodies (infliximab, adalimumab, certolizumab, or golimumab) or a TNF receptor 2 (p75) fusion protein with human IgG1 (etanercept), have been shown to suppress arthritis in various rodent models and has shown clinical efficacy in patients with established RA [215, 235-237]. Anti-IL-6 (tocilizumab) is an antibody that blocks the IL-6 receptor, which was effective in Phase II clinical trials [221]. Human anti-IL-15 was shown to neutralize IL-15 activity *in vitro* and lead to substantial improvements in disease activity in Phase I-II clinical trials [238, 239]. IL-10 has also been shown to mediate RA pathogenesis. For example, alginate NPs containing IL-10 pDNA repolarized macrophages in an arthritic mouse model, resulting in reduced joint damage and inflammation [230, 231, 240]. Depletion and blockade studies for granulocyte-macrophage colony-stimulating factor (GM-CSF) are being assessed in preclinical studies and clinical trials, with the GM-CSF receptor antagonist mavrilimumab showing promising results in patients with RA in Phase II trials [241-243]. IL-12 holds promise due to its role in negating the IL-23/IL-17 cascade, which is responsible for leukocyte migration, bone erosion, and angiogenesis [222]. Similarly, IFN regulatory factor 5 (IRF5) is a promising target due to its involvement in monocyte differentiation, spurring inflammatory phenotypes in macrophages, and promoting the secretion of neutrophil attractants [215, 244]. Finally, the first oral Janus kinase (JAK) inhibitor, tofacitinib, has been approved for the treatment of RA [245], paving the way for a new class of small molecule drug inhibitors.

4.2 Inflammatory bowel disease (IBD)

4.2.1 Implications of macrophage targeting in IBD

IBD is characterized by inflammation in the digestive tract. Increased $CD68^+$ macrophages are present in both ulcerative colitis (UC) and Crohn's disease (CD), with increased $CD163^+$ also present in CD [246-248]. Macrophages in CD show decreased synthesis of retinoic acid and abnormally accelerated lysosomal degradation of cytokines, while macrophages in both CD and UC

show defective CM-CSF receptor expression and function [246, 249, 250]. In CD, macrophage-derived TNF-α increases the secretion of other pro-inflammatory cytokines and recruits other immune cells to the local tissue microenvironment, promoting the formation of granulomas [251]. The polarization of macrophages in IBD is complex, with CD macrophages favoring M2 polarizations, as observed by increased production of IL-13 and increased expression of CD163 [247, 252]. In UC, however, M1 macrophages secrete higher levels of IL-23 and TNF-α and lower levels of IL-10, while M2 macrophages express higher levels of CD163 and CD206 [247, 253-255]. Key macrophage-derived mediators in disease progression are IL-1β, IL-6, IL-23, TNF-α, and TNF-like protein 1A, which promote Th1 and Th17 cellular responses [256-259]. IL-23 also promotes Th17 cell differentiation and NK cell activation [260-262].

4.2.2 Strategies for targeting macrophages for IBD treatment

4.2.2.1 Modulation of macrophages

Many standard IBD therapies influence macrophage functions by inhibiting inflammatory signaling pathways or inducing polarization of alternatively activated macrophages [251]. Suppression of the pro-inflammatory M1 phenotype and/or induction of the tissue-repairing and anti-inflammatory M2 phenotype has been shown to attenuate IBD [212]. This has been demonstrated through the adoptive transfer of M2a macrophages [263, 264], oral administration of pentacyclic triterpene lupeol [265], TNF-α-simulated gene 6 protein (TSG-6) [266], IL-33 [267], and the probiotic *C. butyricum* as a probiotic [268]. The adoptive transfer of peritoneal cells also has been shown to control regulatory B cells and macrophages in experimental colitis [269].

4.2.2.2 Modulation of cytokines and associated disease-mediators

Since the approval of infliximab, the main focus for treatment of IBD is anti-TNF, which has been followed by many other new anti-TNF biologics [251]. Anti-TNF treatment induces regulatory macrophages that reduce intestinal inflammation and induces alternative macrophage polarization *via* Fcγ receptor ligation [270-274]. Selective inhibition of MMP-9 reduced disease severity in a dextran sodium sulfate-induced mouse model of UC [275]. Monoclonal antibodies targeting IL-6

and IL-12 receptors were well tolerated in Phase I clinical trials [276, 277]. Suppression of *NLRP3* inflammasome expression and activation by Glyburide, an FDA-approved drug, led to ameliorated colitis and also delayed disease onset [278]. Blockades of IL-23 may also be an attractive strategy, as IL-23 differentially regulates the Th1/Th17 balance [260, 261]. Another emerging strategy for treating IBD are small molecules that target JAK signaling [251]. Tofacitinib, a pan-JAK inhibitor, has been successfully tested in three Phase III clinical trials with a total of 1,732 patients displaying moderately to severely active UC, but similar results have not been seen in patients with CD [251, 279, 280]. An emerging therapeutic target is phosphodiesterase-4 (PDE4), a key enzyme that modulates intracellular signaling by degrading adenosine 3′,5′ cyclic monophosphate (cAMP). PDE4 inhibitors, like apremilast and roflumilast, increase cAMP levels, thereby blocking pro-inflammatory mediators and producing anti-inflammatory proteins [281, 282]. A recent Phase II study of patients with active UC treated with apremilast displayed meaningful improvements in symptoms, endoscopic scores, and associated biomarkers [251, 283].

4.3 Multiple sclerosis (MS)

4.3.1 Implications of macrophage targeting in MS

MS is a multifocal demyelinating disease of the central nervous system (CNS) with progressive neurodegeneration caused by an autoimmune response to self-antigens. Macrophages enhance the pro-inflammatory response of T cells and B cells, leading to damage of myelin tissue [284, 285]. MS is characterized by increased total mononuclear phagocyte (MP) number, including monocyte-derived macrophages and tissue-resident microglia [286-288]. MP infiltration is associated with chronic tissue damage and formation of microglial nodules [286, 289]. In murine models, the degree of MP infiltration correlates with brain atrophy, impaired neuronal function, and decreased regenerative responses [212, 289-291]. The presence of $CD68^+$ macrophages contributes to the staging of MS lesions [288]. Functional abnormalities of MS macrophages consist of increased expressions of CD68, human leukocyte antigen (HLA), CD86, and iNOS as well as abnormal metabolic switches from oxidative phosphorylation to glycolysis [292, 293]. These factors

contribute to higher antigen-presenting abilities, impaired remediation of myelin damage, and impaired remediation of neurotoxicity [292, 294]. The polarizations of macrophages in active MS lesions show intermediate phenotypes, with co-expressions of M1 and M2-markers, such as CD40 and MR [295]. Key macrophage-derived mediators in disease progression are *NLRP3* inflammasomes, which induce autoreactive T cell migration [296] and secretion of IL-1β, IL-6, and IL-23, which promote generation and maintenance of Th17 cells [297-299]. TNF-β, IL-1β, IL-6, IL-12, and ROS mediate inflammatory responses [300, 301], while IL-6 and BAFF mediate B cell survival and differentiation [302].

4.3.2 Targeting macrophages for MS treatment

4.3.2.1 Modulation of macrophages/microglia

Macrophage depletion was shown to suppress CNS damage and reduce clinical signs of autoimmune encephalomyelitis (EAE) in murine models by inhibiting the induction of myelin-specific T cells [298, 303-306]. Although the depletion of macrophages, specifically monocyte-derived macrophages, has been shown to arrest disease progression, it is not sufficient to promote recovery [305]. Thus, inducing anti-inflammatory M2 phenotypes is another approach that demonstrates promise, particularly because M2 macrophages are essential for oligodendrocyte differentiation [294, 307]. The use of fasudil (a selective Rho-kinase inhibitor), inhibition of succinate release, and the adoptive transfer of IL-33-treated macrophages all potentiated anti-inflammatory M2 phenotypes and ameliorated EAE [308-310]. Glatiramer acetate, a drug approved for MS, also promotes the development of M2 phenotypes in macrophages and increases IL-1 receptor antagonism, while decreasing T cell-induced IL-1β in human monocytes and MS [311, 312]. Other clinically used drugs that promote M2 polarizations include dimethyl fumarate, natalizumab, and fingolimod [313]. Prevention of microglial activation to repress inflammatory effects has also been explored *via* microglial paralysis [304], suppression of CXCR7 [314], treatment with hydroxychloroquine (an antimalarial drug [315]), and administration of 18β-glycyrrhetinic [254]. *Nr4a1*, a gene encoding for an orphan nuclear receptor, also induces M2

phenotypes in macrophages and is a critical inhibitory molecule for Th1/Th17 cell differentiation, indicating therapeutic potential [299]. More recently, compounds that influence macrophage and microglial functions are undergoing preclinical testing [316]. Ethyl pyruvate can inhibit the activation of macrophages and microglia within the CNS to protect against EAE [317]. Forskolin alleviates EAE by suppressing macrophage expression of CD86 and enhancing macrophage expression of arginase 1 (ARG1) [318]. Bryostatin-1 acts on macrophages to promote the differentiation of lymphocytes into Th2 cells, which improved symptoms of EAE in mice [319]. Furthermore, the pan HLA DR-binding epitope (PADRE)-Kv1.3 vaccine has been applied to treat EAE, demonstrating the presence of therapeutic antibodies and M2 macrophage infiltration in the CNS [320]. Another potential target is mineralocorticoid receptors expressed on macrophages, as mice selectively lacking mineralocorticoid receptors demonstrate fewer clinical symptoms of EAE [321]. Glucocorticoids, the current standard of care for MS, were packaged in inorganic-organic hybrid NPs and were preferentially taken up by macrophages, allowing for improved therapeutic efficacy in EAE models [322].

4.3.2.2 Modulation of pro-remyelination *via* microglia

Current therapies are targeted to mitigate adverse immune responses in MS, but they do not target remyelination or tissue repair [323]. In a cuprizone-induced mouse model of demyelination, quetiapine, an antipsychotic drug, significantly reduced recruitment and activation of microglia and promoted remyelination [324], while mCSF-induced microglial activation prevented myelin loss and promoted its repair [325]. Endogenous factors also may be targeted for remyelination. The retinoid X receptor (RXR) pathway is a positive regulator of myelin debris clearance. Thus, RXR agonists, such as bexarotene, hold promise to reverse deficiencies in phagocytosis and remyelination [326].

MS is also characterized by abnormal levels of thyroid hormones. During remission, thyroid hormones were found to alleviate demyelination by promoting the development of oligodendrocyte lineage cells and remyelination [327-329]. It also has roles in microglial phagocytosis *in vitro* and microglial migration *in vivo* [327]. Human IgM antibody rHIgM22 accelerated remyelination and

increased differentiation of oligodendrocyte precursor cells into mature oligodendrocytes in a cuprizone murine model and increased myelin debris uptake *in vitro* by a microglial cell line [330, 331].

4.3.2.3 Modulation of cytokines and associated disease-mediators

Targeting molecules that mediate immune cell migration may also be an effective approach to treat MS. An IL-6 blockade using an anti-IL-6 receptor antibody contributed to reduced infiltration of T cells in the CNS and inhibited EAE development [332]. IFN-β is another therapeutic target that modulates crosstalk between B cells and monocytes *via* TLR7, primes macrophages for apoptosis upon activation or differentiation, and has shown success in clinical trials [302, 333]. Gc protein-derived macrophage activating factor (GcMAF), which has many immunomodulatory effects, has shown therapeutic potency in the treatment of MS in a study with one patient [334]. Using chemically modified and specific siRNAs delivered by NPs, Zhang *et al*. silenced the expression of transcription factor c-Rel in macrophages of EAE mice, resulting in diminished T cell infiltration in the CNS, reduced clinical symptoms, and downregulated pathogenic Th1 and Th17 responses [297]. Another attractive target may be gp130 cytokines, which regulate the Th17 inflammation of EAE [298].

4.4 Systemic lupus erythematous (SLE)

4.4.1 Implications of macrophage targeting in SLE

SLE is characterized by widespread inflammation in connective tissues, and it has no known cure [335]. Macrophages found in SLE have defective phagocytic abilities, leading to impaired clearance of apoptotic cells and immune complexes [336-338]. SLE macrophages also have higher antigen-presenting abilities and are involved in the modulation of the adaptive immune system through an enhanced ability to activate autoreactive T cells and B cells [339-343]. Overexpression of adhesion molecules, intercellular adhesion molecule 1 (ICAM-1), may also lead to impaired macrophage activation [344]. SLE macrophages also overexpress CD40 [341], CD86 [339, 340], and sialic acid binding Ig like lectin 1 (Siglec-1) [345]. There is a predominance of pro-inflammatory macrophages

in SLE, resulting in increased levels of IL-1β [346], IFN-γ [347], CXCL10 [348], CCL2 [349], and GM-CSF [350]. This M1-dominance is coupled with insufficient M2-polarization, characterized by higher levels of IL-10 [351, 352]. IL-10 canonically has anti-inflammatory functions, but in SLE, IL-10 acquires pro-inflammatory features, conferred by type 1 IFNs [353]. Overall, the main cytokine mediators in SLE progression are IL-1β, IL-6, TNF-α, and IL-10, all of which contribute to local and systemic inflammation [353-356]. Intriguingly, in lupus-prone mice, monocyte-derived macrophages were more responsive to cytokine stimulation than renal macrophages [357].

4.4.2 Strategies for targeting macrophages for SLE treatment

4.4.2.1 Modulation of macrophages

Adoptive transfer of M2a macrophages, induced by IL-4, in a murine model of SLE significantly decreased SLE activity [358]. Induction of M2 polarization in patients with pioglitazone treatment also suppressed the production of inflammatory cytokines [359]. Recent work by Mohammadi *et al*. found that sodium valproate, a HDAC inhibitor, can alternatively activate macrophages *ex vivo* and prevent M1 inflammatory phenotypes *in vitro*, indicating that epigenetic modifications may play a role in macrophage polarization [360]. The aryl hydrocarbon receptor (AhR)-mediated signaling pathway and expression of PPARγ also contributes to the secretion of anti-inflammatory cytokines and expression of M2 markers from monocyte-derived macrophages of SLE patients [359, 361].

4.4.2.2 Modulation of cytokines and associated disease mediators

Several macrophage-derived and mediated cytokines have been targeted to treat SLE. IL-10 is thought to be a potential prognostic biomarker for SLE [351]. In a 6-month study with a small sample size, administration of IL-10 antagonist ameliorated SLE severity [362]. Inhibition of IL-10 was also tested in a Phase I dosage escalation study. The study generated significant improvements in SLE, along with a significant decrease in the frequency of circulating plasma cells and reduced autoantibody levels in the serum [363, 364]. A blockade of TNF-α with infliximab, a chimeric TNF-α antibody, in addition to immunosuppression with azathioprine or methotrexate was shown to reduce disease severity in patients, but induced the formation of autoantibodies to double-stranded

DNA and cardiolipin [354, 365, 366]. Targeting type I IFNs for their regulation of the inflammasome complex, which is a driver of SLE organ damage, has also been assessed using IRF1 [367]. Reduction of IRF1 expression *via* siRNA significantly reduced hyperactivity of inflammasomes in monocytes of SLE patients, suggesting that IRF1 inhibition may serve as a novel target for treatment of SLE [367]. Other promising therapeutic targets include the CSF-1/CSF-1R signaling axis, CX3CR1, MCP-1, and Bruton's tyrosine kinase for their roles in recruitment of monocytes, macrophage polarization, and macrophage activation [368].

4.5 Type 1 diabetes (T1D)

4.5.1 Implications of macrophages in T1D

T1D is characterized the by destruction of beta cells in the pancreas, preventing insulin from being produced and manifesting in elevated blood glucose levels. Compared to the previously discussed disorders, there is relatively less data clearly elucidating the role of macrophages in T1D progression. Two studies have shown that macrophages from non-obese diabetic mice display defective phagocytic abilities, resulting in impaired clearance of apoptotic cells [369-371]. Macrophages from non-obese diabetic mice were also abnormally activated, mediating the death of islet beta cells *via* cytolytic activity and producing ROS [369, 372]. Furthermore, macrophages display crosstalk with cells in the adaptive immune system and are involved in the trafficking of $CD4^+$ and $CD8^+$ T cells, notably through type-1 IFN signaling [373, 374]. The polarization of T1D macrophages favors pro-inflammatory phenotypes, which is associated with higher levels of C reactive protein (CRP) [375], IFN-γ [376], CXCL10 [377], and CCL2 [377], resulting in greater secretions of IL-6 [375, 378], IL-1β [375, 378], and TNF-α [379, 380]. It has been proposed that elevated IL-1 and IL-6 levels generate Th17 cells [378]. Similar to the other diseases discussed, monocyte-derived macrophages and pancreas-resident macrophages in T1D possess different functions, which is an important consideration when developing macrophage-targeted therapies [381-383].

4.5.2 Strategies for targeting macrophages for T1D treatment

Preliminary treatments for T1D have focused on removing or repolarizing macrophages. Targeted depletion of macrophages by clodronate liposomes was shown to abolish diabetes in non-obese diabetic mice, although inflammation persisted [369]. To limit macrophage-derived TNF-α, TNF-α blockades have demonstrated clinical efficacy, but they remain controversial because other cases have shown disturbance of glycemic control [384, 385]. Efforts to suppress M1 phenotypes through the adoptive transfer of M2 macrophages reduced T1D onset in non-obese diabetic mice and induced M2 reduced hyperglycemia, kidney injury, and insulitis *in vitro* [386, 387]. Another group sought to employ the immunomodulatory effects of MSCs by engineering MSCs with the TGF-β gene, which were found to restore regulation of adverse immune responses and other T1D features in murine studies [388]. Treatment of non-obese diabetic mice with monoclonal antibodies against CSF-1 receptors reduced diabetes incidence and promoted a regulatory pathway for autoimmune progression in non-obese diabetic mice [389]. Furthermore, local scaffold release of dexamethasone, an anti-inflammatory drug, promoted phenotypic shifts toward M2 macrophages and accelerated islet transplant engraftment [390].

4.6 Other applications for autoimmune disease therapy

Other autoimmune diseases in which macrophages are implicated include systemic sclerosis, primary biliary cholangitis, Sjögren's syndrome, autoimmune hepatitis, and celiac disease [212]. Similar principles for targeting macrophage for therapies may apply.

Table 3. Macrophage-targeting drugs for autoimmune diseases in preclinical or clinical studies (non-exhaustive).

Drug name	Type	Target	Effect	Disease	Ref
Chlodronate	Small molecule in liposomes	Phagocytes	Deplete macrophages	RA, T1D, MS	[226, 369]
CP-690,550 (tofacitinib)	Small molecule	JAK1, JAK2	Inhibit macrophages	RA, UC	[237, 245, 251, 279, 280]
Infliximab	Antibody	TNF	M2 polarization	RA, IBD, SLE	[235, 237, 245, 251,

					270-274, 279, 280]
Adoptive transfer of M2 macrophages	Cell	T cells, Macrophages	Reduce T cells/M2 polarization	IBD, T1D, SLE, MS	[263, 264, 308-310, 358, 386, 387]
Anti-miR-449a	Nucleic acid	*SIRT1*	Deplete macrophages	RA	[227]
Toxin-conjugated antibody CD64-ricin A (CD64-RiA)	Antibody	IgG receptor FcRI	Deplete macrophages	RA	[228, 229]
Thapsigargin	Small molecule	Notch	M2 polarization	RA	[233]
Human umbilical cord blood-derived MSCs	Cell	Macrophages	M2 polarization	RA	[234]
INCB018424 (ruxolitinib)	Small molecule	JAK1, JAK2	Inhibit macrophages	RA	[237]
Baricitinib	Small molecule	JAK1, JAK2	Inhibit macrophages	RA	[391]
Adalimumab	Antibody	TNF	M2 polarization	RA	[235, 392]
Certolizumab	Antibody	TNF	M2 polarization	RA	[235, 392]
Golimumab	Antibody	TNF	M2 polarization	RA	[235]
Etanercept	Antibody	TNF	M2 polarization	RA	[235, 392]
Rituximab	Antibody	CD20	Deplete B cells	RA	[392]
Tocilizumab	Antibody	IL-6 receptor	M2 polarization	RA	[221, 235, 392]
HuMax-IL15	Antibody	IL-15	M2 polarization	RA	[238, 239]
IL-10 pDNA	Nucleic acid in alginate NPs	IL-10	M2 polarization	RA	[230, 231, 240]
Mavrilimumab	Antibody	GM-CSF	M2 polarization	RA	[241-243]
Lupeol, pentacyclic triterpene	Small molecule	Macrophages	M2 polarization	IBD	[265]
TSG-6	Protein	Macrophages	M2 polarization	IBD	[266]
IL-33	Protein	Macrophages	M2 polarization	IBD	[267]
Clostridium butyricum	Probiotic	IL-10	M2 polarization	IBD	[268]
Apremilast	Small molecule	PDE4	M2 polarization	IBD	[251, 283]
Roflumilast	Small molecule	PDE4	M2 polarization	IBD	[251, 283]
GS-5745	Antibody	MMP-9	M2 polarization	UC	[275]
Glyburide	Small molecule	*NLRP3*	Inhibit pro-inflammatory factors	UC	[278]
MRA	Antibody	IL-6 receptor	Inhibit pro-inflammatory factors	CD	[276, 277]
Anti-IL-12	Antibody	IL-12	M2 polarization	CD	[276, 277]
Fasudil	Small molecule	Rho kinase	M2 polarization	MS	[308-310]
Neural stem cell	Cell	Succinate	M2 polarization	MS	[308-310]

Glatiramer acetate	Small molecule	IL-1	M2 polarization	MS	[311, 312]
Dimethyl fumarate	Small molecule	NRF-2, NF-κB	M2 polarization	MS	[313]
Natalizumab	Small molecule	α4 integrin antagonist, T cells	M2 polarization/ mediate T cell migration	MS	[313]
Fingolimod	Small molecule	Sphingosine-1-phosphate, lymphocytes	M2 polarization/ suppress lymphocyte migration	MS	[313]
Anti-CXCR7	Antibody	CXCR7	Prevent microglial activation	MS	[104]
Hydroxychloroquine	Small molecule	Microglia	Prevent microglial activation	MS	[315]
18β-glycyrrhetinic	Small molecule	Microglia	Prevent microglial activation/ promote remyelination	MS	[254]
Ethyl pyruvate	Small molecule	Microglia	Prevent microglial activation	MS	[317]
Forskolin	Small molecule	CD86, ARG1	M2 polarization	MS	[318]
Bryostatin-1	Small molecule	Lymphocytes	Th2 differentiation	MS	[319]
PADRE-Kv1.3	Protein	KV 1.3	M2 polarization	MS	[320]
Glucocorticoids	Small molecule in inorganic-organic hybrid NPs	Macrophages	Improve targeting	MS	[322]
Quetiapine	Small molecule	STIM1	Promote remyelination	MS	[324]
mCSF	Protein	Macrophages	Clear myelin	MS	[325]
rHIgM22	Antibody	CNS myelin	Promote remyelination/ differentiate oligodendrocytes	MS	[330, 331]
Anti-IL-6	Antibody	IL-6	Mediate Th1 and Th17 cellular responses	MS	[332]
IFN-β	Protein	Macrophages	Deplete macrophages	MS	[302, 333]
siRNA	Nucleic acid in NPs	NF-κB	Inhibit T cell infiltration	MS	[297]
Pioglitazone	Small molecule	PPARγ	M2 polarization	SLE	[359]
Sodium valproate	Small molecule	Histone deacetylase	M1 suppression	SLE	[360]
Tocilizumab	Antibody	IL-10	Modulate B cell hyperactivity/ M1 suppression	SLE	[362-364]
siRNA	Nucleic acid	IRF-1	Reduce hyperactivity of the inflammasome	SLE	[367]
TGF-β-engineered MSCs	Cell	-	Regulate immune responses	T1D	[388]
Anti-CSF-1	Antibody	CSF-1	Control autoimmune	T1D	[363, 364,

			progression		389]
Dexamethasone	Small Molecule	Macrophages	M2 polarization and improve islet transplant engraftment	T1D	[390]

5. Conclusions and Outlook

As a result of their plasticity, macrophages contribute to the development and progression of IDs by numerous pathways [393]. Thus, targeting macrophages with modulatory drugs has emerged as a popular and potentially disruptive strategy to combat IDs. Yet, the efficacies of these strategies can vary significantly across disease subtypes. For example, modulating macrophages in solid tumors often does not fully eradicate cancer due to the presence of an overwhelming number of cancer cells. Accordingly, combination therapies with other immunomodulatory or chemotherapeutic agents can be useful, particularly those that instruct adaptive immune responses. For CVDs and autoimmune diseases, reducing inflammation and monocyte infiltration has generally improved therapeutic outcomes; however, the long-term durability of these approaches is still undergoing clinical evaluation.

Numerous small molecules and biological regulators, encompassing antibodies, cells, proteins, and nucleic acids, have been reported to modulate macrophage phenotypes in IDs. The most commonly reported approach is the use of small molecule or antibody antagonists that target cell-surface receptors or extracellular chemokines/cytokines. Biologics constitute a majority of these regulators due to their potency and high selectivity of action. Several of such drugs are in clinical trials or have recently gained regulatory approval, including the CD47-antibody, IL-6-antibody, natalizumab, fingolimod, glyburide, and canakinumab [127, 394, 395]. However, frequent administrations with high doses of these drugs are often necessary due to the timescales for restoring tissue health, resulting in safety concerns and potentially limiting translational potential.

Targeted DDS have improved the performance of macrophage regulators in preclinical studies by enabling their controlled release at diseased sites. As a result, a handful of macrophage-targeting DDS have progressed into the clinic. For example, clodronate liposomes have been shown

to regulate several IDs, including cancer, CVDs, and autoimmune diseases; siCCR2-loaded NPs have shown promising results in a number of studies [5]; HDL-mimicking NPs have been shown to deliver a range of regulators [119]; and siRNA-liposomes (patisiran) have been approved by FDA. However, beyond these examples, few macrophage-targeting DDS have gained approval for clinical use. This is likely due to cost and poor scalability. Additionally, the *in vivo* fate of many DDS, the physicochemical properties of the carrier, and interactions between the carrier and the surrounding biological environment are not fully understood [396]. These challenges represent the most critical barriers that must be addressed to develop the next generation of DDS with improved targeting and immunomodulatory properties.

Overall, the notion of treating IDs by targeting macrophages with drugs and tailored DDS is still in its early years, thus its long-term potential is promising. Liposomes and HDL mimic NPs in particular have been successful in the clinic. To date, over 20 liposomal formulations have been approved for clinical use [397], demonstrating a promising translational path. We anticipate that other DDS that specifically target macrophages in diseased sites will also have a high likelihood for clinical investigation and adoption after issues related to poor stability and limited penetration across biological barriers have been resolved. To accelerate the translation of new DDS into the clinic, we emphasize that it is important to (i) involve in researchers across fields of study, including materials science, engineering, pharmacology, and immunology and (ii) collaborate with clinicians early on to understand patient needs, select appropriate animal models, and confirm the role of macrophages in disease progression and treatment.

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