HHS Public Access

Author manuscript

Adv Drug Deliv Rev. Author manuscript; available in PMC 2018 May 15.

Published in final edited form as:

Adv Drug Deliv Rev. 2017 May 15; 114: 206–221. doi:10.1016/j.addr.2017.04.010.

Progress in tumor-associated macrophage (TAM)-targeted therapeutics

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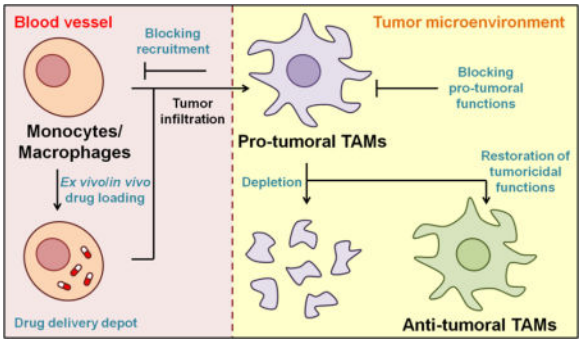
Abstract

As an essential innate immune population for maintaining body homeostasis and warding off foreign pathogens, macrophages display high plasticity and perform diverse supportive functions specialized to different tissue compartments. Consequently, aberrance in macrophage functions contributes substantially to progression of several diseases including cancer, fibrosis, and diabetes. In the context of cancer, tumor-associated macrophages (TAMs) in tumor microenvironment (TME) typically promote cancer cell proliferation, immunosuppression, and angiogenesis in support of tumor growth and metastasis. Oftentimes, the abundance of TAMs in tumor is correlated with poor disease prognosis. Hence, significant attention has been drawn towards development of cancer immunotherapies targeting these TAMs; either depleting them from tumor, blocking their pro-tumoral functions, or restoring their immunostimulatory/tumoricidal properties. This review aims to introduce readers to various aspects in development and evaluation of TAM-targeted therapeutics in pre-clinical and clinical stages.

Graphical abstract



Keywords

Tumor-associated macrophage; cancer immunotherapy; drug delivery; targeted therapy; tumor microenvironment

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1. Introduction

Macrophages, key cells in the innate immune system, are the main component of the mononuclear phagocyte system (MPS) [1], which also include bone marrow progenitors and blood monocytes. Recent studies have revealed that the different components of the MPS system are derived in various stages of embryotic development and are not all from the same progenitor lineage [2][3]. Macrophage functions are as diverse as their lineages and play important roles in normal homeostasis and disease development [4][5]. This is especially true in acute and chronic inflammatory disease states such as wounds, malignancy, and autoimmune disorders. There is increasing evidence that macrophages play a central role in both normal and diseased tissue remodeling including angiogenesis, basement membrane breakdown, leukocyte infiltration, and immune suppression [4]. As such, the macrophage has emerged as a central drug target in a variety of disease states, including the tumor microenvironment (TME). This review focuses on drug strategies in malignancies that affect macrophage, while the reader is referred to excellent recent reviews for more information on other aspects of macrophage biology, including macrophage physiological function [5], the role of the macrophage in tumorigenesis [6], and the clinical applicability and translation [7] of macrophage drug targets.

The review first provides an introduction to macrophage and the role of macrophage populations in tumor development. Cancer therapy strategies involving macrophages in the following three areas are then presented: 1) identifying drug targets for modulation of TAM activities, 2) engineering carriers that promote, in increasing order of cell specificity, effective delivery of drug cargos to systemic macrophages, tumor-localized TAMs, or subtype-specific pro-tumoral M2-TAMs, and 3) utilizing the tumor-homing property of macrophages for cell-based therapies.

1.1 Mononuclear phagocyte system

First described in the starfish by Ilya Ilyich Mechnikov in 1882, phagocytes are an evolutionarily conserved subset of leukocytes that maintain organismal homeostasis in all multicellular species, [8]. This cell type, especially within mammalian species, is distributed throughout the body and present within each tissue to perform specific functions [3]. Microglia, the tissue-resident macrophages within the brain, facilitate neurological synapse pruning for memory maintenance [9] and serve as an immunological defense in an immune privileged environment [10]. Kupffer cells in the liver clear foreign, pathogenic, and waste materials from circulation [11]. Splenic red pulp macrophages are responsible for the recycling process of red blood cells [11][12][13]. Specific macrophage subsets in protective barriers, such as the Langerhans cells in the skin [14] and the alveolar macrophages within the lung [15], are responsible for both clearing pathogenic material and raising local inflammatory responses. Intraglomerular mesangial cells in the kidneys regulate blood flow [16]. The monocytes in blood circulation provide a reservoir of macrophages for mounting immune and inflammatory responses [17]. Further, the monocytes are derived from the bone marrow where hematopoietic progenitors generate monocytes and also osteoclastic cells which maintain bone function. Finally, there is mounting evidence to suggest that Hofbauer

cells, the macrophages of the placenta, maintain signaling crosstalk from mother to baby during embryogenesis [18][19]. It is clear that MPS cells are part of a complex system that maintains the health and function of tissue and organs and therefore hold key roles in homeostasis and disease development. The complexities of different macrophage functions within different tissues are covered in several recent reviews [20][21][22].

1.2 Macrophage polarization

Macrophages are a plastic cell type capable of reacting to microenvironmental cues [23]. During pathogenesis, this cell type is among the first responders, recognizing pathogen-associated patterns (PAMPs) like lipopolysaccharide (LPS) [24]. LPS engages the Toll-like receptor 4 (TLR-4) on the surface of macrophages to activate transcription factors (e.g. interferon regulatory factors (IRFs) and nuclear factor kappaB (NF-κB)) to mount an inflammatory response [24][25]. These pro-inflammatory polarized macrophages (M(LPS)), release a variety cytokines, including IL-1β, IL-6, and TNF-α, facilitating the local recruitment of more macrophages and leukocyte infiltrate to fight against pathogenic insult [26]. In contrast, in wounding microenvironments, extensive release of inflammatory cytokines is potentially detrimental to overall tissue repair. Instead, macrophages respond to cytokines IL-4 and IL-13 released by damaged cells resulting in activation of the STAT6 transcription factor through the Janus kinase – signal transducers and activators of transcription (JAK-STAT) pathway, effectively turning on signature anti-inflammatory genes like arginase (Arg1) and resistin-like molecule α [26][27][28]. These gene regulatory pathways facilitate the recruitment of more immunoregulatory macrophages (M(IL-4)), release of immunoregulatory cytokines, and induction of processes like angiogenesis and basement membrane remodeling [29][30]. Based on pro-inflammatory and anti-inflammatory functions of macrophages under different stimuli, a broad classification has been proposed to generalize macrophages as classically activated M1 (pro-inflammatory, activated by LPS or interferon gamma (IFNγ)) or alternatively activated M2 (anti-inflammatory, activated by IL-4, IL-13, or IL-10) phenotypes [31]. Interestingly, these pro-inflammatory and anti-inflammatory pathways can converge with one another [32][33]. Oftentimes, wound sites are also susceptible to pathogen insult, so a balance between macrophage types is necessary for wound resolution. As such, both macrophage types exist within these environments, including macrophages that perform both functions and macrophages that are completely off the M1 and M2 spectrum [32][33]. Clearly, macrophage functions within a specific environment or in a specific disease or homeostatic state are complex. Nonetheless, macrophage activation within these environments and the key roles of macrophage in the development of resolution of complications or disease initiation are well-recognized. As such, macrophages are an important potential therapeutic target[26][34].

2. Macrophages in tumorigenesis

2.1 Macrophage polarization in tumor development

Macrophages are a large component of the leukocyte infiltrate into the TME. Over the last several decades, tumor-associated macrophages (TAMs) have been a subject of intense study for their impact on leukocytes, cytokines, and inflammatory mediators that either block or

propagate tumor progression. Interestingly, the macrophage has been identified as a driver for inflammation, not only in cancer but in other disease states. Indeed, chronic inflammation that arises from diseases such as inflammatory bowel disease, silicosis, and asbestosis, pre-dispose these sites to cancer development. Readers are directed to Elinav et al.'s excellent review on this topic [35].

Interestingly, macrophages seem to have divided loyalties, on one hand promoting tumor resolution (M1/M(LPS)) and on the other propagating tumorigenesis (M2/M(IL-4)) (Fig. 1). Studies done almost a half century ago have shown that M1 macrophages have the capacity to kill and remove tumor cells, in line with the primary physiological function of M1 macrophages to remove foreign materials [36]. The M1 cells initiate cytokine production within the TME and facilitate tumor cell destruction through recruitment of pro-immunostimulating leukocytes and phagocytosis of tumor cells. However, studies within that same research period show that M2 macrophages have a central role in tumor propagation [37]. The M2 cells drive tumor development in both primary and metastatic sites through their contributions in basement membrane breakdown and deposition, angiogenesis, recruitment of leukocytes, and overall immune suppression [37][38][39]. It is important to note that, like normal homeostasis, macrophages within TME are not limited to M1/M(LPS) or M2/M(IL-4) states; they may reside in-between or off this spectrum. Removal of all macrophage populations regardless of polarization state has emerged as a potential therapeutic option, as there is a significant reduction in both primary and metastatic tumorigenesis [40]. However, as illustrated later within this review, the strategy has had a limited clinical impact, unless delivered in combination with other immunological agents, due to limitations in drug delivery and macrophage targeting [41]. On the other hand, the macrophage, regardless of polarization state retains the capacity for plasticity, including the ability to switch between phenotypes as a function of microenvironmental cues. Thus, altering the macrophage phenotype within TME from immune-suppressive to immune-promoting is currently being explored for therapeutic applications [41].

2.2 Clinical implication of TAMs

Clinically, the presence of macrophages within primary tumors have been shown to be correlated with poorer prognosis in almost all tumors [7][42], with the exception of colon cancers [43]. Interestingly in recent years, clinicians have expanded these studies to investigate both M1 and M2 phenotypes within these microenvironments. Increasing levels M1 macrophages within these sites indicate better prognosis [44][45] whereas increasing levels of M2 macrophages [42] or decreased lymphocyte to monocyte ratios [46] predict poor outcomes. While these correlation studies have yet to be linked to causation, emerging therapeutic strategies aiming to remove macrophages and/or alter macrophage phenotypes are facilitating promising therapeutic benefits [41].

3 Pharmacological modulation of macrophages/TAMs

3.1 Bisphosphonate

Bisphophonates are a family of compounds structurally composed of a central carbon linked by two phosphate groups, R1 and R2 side groups where R1 is H, OH, or Cl and R2

comprises diverse functional groups which determine the potency of the compounds [47]. The first generation non-nitrogen containing bisphosphonates (etidronate, clodronate, and tiludronate) are intracellularly converted to a non-hydrolyzable ATP analogue leading to apoptosis [48]. The second generation (aliphatic amine R2) and third generation (aromatic amine R2) bisphosphonates induce apoptosis by inhibiting the essential enzyme farnesyl diphosphate (FPP) synthase. Bisphosphonates have a high affinity for hydroxyapatite and are frequently used in management of bone diseases such as osteoporosis, Paget disease, and bone metastases. Moreover, pre-clinical studies in murine breast tumor models suggest that bisphosphonate may also exhibit an extraskeletal therapeutic effect [49][50]. In this case, the bisphosphonate (zoledronic acid) primarily binds to microcalcifications present in breast tumors and is subsequently phagocytosed by TAMs to both induce apoptosis and promote M2-to-M1 repolarization. To improve pharmacokinetics, reduce toxic side effects (e.g. osteonecrosis of the jaw), and alter biodistribution away from bone for extraskeletal applications, bisphosphonates are typically formulated into liposomes or nanoparticles [51] [52]. Although depletion of TAMs with liposomal clodronate (clodrolip) improves survival in some pre-clinical cancer models, to our knowledge, complete regression of tumors using bisphosphonate alone has not been achieved [51]. Some of the drugs shown to benefit from depletion of TAMs via bisphosphonates include anti-angiogenesis therapies (sorafenib and anti-VEGF antibody) and liposomal doxorubicin (Doxil) [51][53][54]. In addition to disrupting the pro-tumoral effect of TAMs, associated depletion of resident Kupffer cells has also been shown to reduce hepatic clearance of drug-loaded nanoparticles and hence prolong their plasma circulation time [54][55]. However, not all therapies benefit from depletion of macrophages/TAMs, especially immunotherapies designed to stimulate anti-tumor innate immunity [56][57][58]. In fact, an indiscriminate depletion of systemic macrophages such as via administration of clodronate liposomes may sometimes exacerbate the disease progression. As examples, depletion of subcapsular sinus $CD169^+$ macrophages in tumor-draining lymph nodes is linked to increased tumor burden in B16F10 tumor model while the density of $CD169^+$ macrophages in lymph nodes is also positively correlated with favorable prognosis in patients with colorectal and breast cancers [59][60][61]. These reports further suggest that TAM-targeted therapeutics that spare other potentially beneficial resident macrophages are more desirable than general macrophage depletion strategies. Clinically, bisphosphonates were among the first anti-cancer drug with reported activities on TAMs to be approved for human use, dating back to as early as 1995 for pamidronate and 2002 for zoledronic acid, where they were indicated for use in the management of multiple myeloma and bone-related metastasis (Table 1) [62].

3.2 Inhibition of growth factor signaling

3.2.1 CSF-1R inhibition—Colony stimulating factor 1 receptor (CSF-1R) is a tyrosine kinase receptor expressed on mononuclear phagocytes [64]. Dimerization of the receptor upon binding to CSF-1 or IL-34 leads to a cascade of signaling events which promote proliferation, function, and survival of macrophages [64][65]. Antibodies targeting CSF-1 or CSF-1R as well as CSF-1R kinase inhibitors have been developed for therapeutic modulation of resident macrophages and TAMs [66]. AFS98 and M279 anti-mouse CSF-1R antibodies, capable of blocking both CSF-1 and IL-34, are widely used to study the effect of macrophage depletion in mouse tumor models and have been shown to reduce tumor size

and improve survival in MMTV-PyMT spontaneous breast tumor model when administered both early and chronically [67][68][66]. While intraperitoneal administration of anti CSF-1R antibody systemically depletes resident macrophages in several major organs, a minimal effect is observed in brain, lung, ovary, and uterus likely due to anatomical accessibility (blood brain barrier), tissue turnover rate, or specific stimuli within the tissue environment [69]. On the other hand, a small molecule CSF-1R kinase inhibitor (BLZ945), which readily passes through blood brain barrier, has been shown to be effective in murine models of glioma, breast cancer, and cervical cancer [70][71]. It is worth noting that tumor recurrence in a murine glioma model following prolonged treatment with BLZ945 is attributed to increased level of IL-4 which enriches TAMs with the $CD206^+$ M2-like phenotype [72]. These IL-4 stimulated TAMs secrete insulin-like growth factor-1 (IGF-1) to enhance survival of rebound glioma cells via stimulation of the phosphatidylinositol 3-kinase (PI3k) pathway. A combination therapy of BLZ495 with IGF-1R inhibitor significantly prolonged survival of mice with rebound glioma compared to monotherapy of either BLZ495 or IGF-1R inhibitor highlighting the need for rational design of combinatorial therapy for maximized response to TAM-directed anti-cancer therapy. Due to structural similarities among different receptor tyrosine kinases, tyrosine kinase inhibitors typically recognize multiple targets [73] and as such, several FDA-approved, multi-target tyrosine kinase inhibitors (Table 1), initially developed for other targets such as c-KIT, VEGFR, and PDGFR (reviewed in [74]), have now been shown to exhibit activity on the CSF-1R kinase domain [75][76][77]. New developments of more CSF-1R-specific inhibitors (e.g. PLX3397, PLX7486, BLZ945, and ARRY-382) are also being investigated in clinical trials (Table 2). In particular, PLX3397, developed by structure-guided design against the CSF-1R target, exhibits higher affinity and selectivity to CSF-1R than imatinib and demonstrates better efficacy in treatment of tenosynovial giant cell tumor [78]. As a result, the drug has been designated breakthrough therapy status and advanced into clinical trial phase III for the indication. Antibodies targeting CSF-1R are also entering Phase I and II clinical trials for treatment of solid tumors.

3.2.2 RON inhibition—RON (Recepteur d'Origine Nantais) is a receptor tyrosine kinase expressed on tissue-resident macrophages that binds to macrophage-stimulating protein (MSP) after its proteolytic activation at inflammation sites [79]. RON signaling in macrophages promotes cell spreading and phagocytosis as well as enhances M2 polarization via stimulation of arginase expression and attenuation of responses to pro-inflammatory stimuli e.g. IFNγ and LPS [80][81][82][83]. In prostate and breast cancer models, RON signaling in macrophages has been shown to impair anti-tumor functions of $CD8^+$ T cells leading to promotion of tumor growth and metastatic outgrowth respectively [84][85]. Pharmacologic blockade of RON kinase with an inhibitor, BMS-777607/ASLAN002, boosts the population of pro-inflammatory TNF-α-secreting macrophages and reduces metastatic outgrowth in the lungs in the PyMT-MSP breast tumor model [85]. Alternatively, restoration of iNOS expression in MSP-stimulated macrophages may be achieved via inhibition of PI3k, one of the downstream targets of RON activation [83]. In fact, a synergistic therapeutic effect between the RON kinase inhibitor and a PI3k inhibitor NVP-BKM120 has been reported in a mouse xenograft model of patient-derived breast tumor where cancer cells

express constitutively active isoform of RON (short-form RON or sfRON) [86]. Both RON and PI3k inhibitors are being investigated in clinical trials [85][87].

3.3 Modulation of macrophage phagocytic activity

3.3.1 Antibody-dependent cellular phagocytosis (ADCP)—Two important innate immune functions of macrophages are phagocytosis of foreign bodies, apoptotic cells, as well as cancer cells and processing of the engulfed materials for antigen presentation to stimulate adaptive immunity [88]. Tumor-targeted antibodies are a powerful class of anti-cancer biologics that act through direct inhibition of survival signaling, mediation of antibody-dependent cellular cytotoxicity (ADCC) by natural killer (NK) cells, induction of complement-dependent cytotoxicity (CDC) via complement cascade activation, and facilitation of antibody-dependent cellular phagocytosis (ADCP) by macrophages [89]. Clinically approved anti-cancer monoclonal antibodies such as rituximab and trastuzumab have been demonstrated to exert their therapeutic effects, primarily or in part, through macrophage-mediated ADCP [90][91]. Contrary to their capability to promote tumor invasion, TAMs are also able to phagocytose cancer cells in the presence of the opsonizing tumor-targeted antibodies [92]. Nonetheless, the therapeutic efficacy of these antibodies may be limited by counter mechanisms including antigenic modulation and trogocytosis, both of which remove antibody-antigen complexes off target cell plasma membrane [90][93]. Of note, trogocytosis has recently been shown to induce cell death complimentary to whole cell phagocytosis [94]. To further improve ADCP activity, the Fc region of tumor-targeted antibodies could be engineered to increase its interaction with activatory Fc receptors, most importantly FcγRIIa, on macrophages [95]. While development of clinical antibodies is primarily focused on IgG, therapeutic potentials of other Ig isotypes (IgA and IgE) are being investigated in several pre-clinical studies where monocytes/macrophages are also important in effecting the ADCC/ADCP functions [96][97].

3.3.2 Inhibition of CD47-SIRPα signaling—Successful development and maturation of tumors require effective evasion from such immune-surveillance activities [98]. In several tumor types, cancer cells block phagocytosis by upregulating surface expression of CD47 which interacts with signal regulatory protein alpha (SIRPα) on macrophages to transmit the “don’t eat me” signal. Inhibiting the CD47-SIRPα signaling axis with anti-CD47 antibodies or an engineered SIRPα-Fc fusion has been shown to restore macrophage ability to phagocytose cancer cells and prime a cytotoxic $CD8^+$ T-cell response, leading to a significant reduction in tumor size and metastasis in several cancer models [98][99]. With promising results in pre-clinical studies, numerous clinical trials have been initiated in the past few years to investigate different therapeutic variants including anti-CD47 antibody (Hu5F9-G4 and CC-90002), engineered high affinity SIRPα (ALX148), and SIRPα-Fc fusion (TTI-621) (Table 2). One potential challenge in clinical translation of anti-CD47 therapies is the ubiquitous expression of CD47 on red blood cells and hematopoietic stem cells which may serve as an antibody sink to reduce efficacy while also causing transient anemia [100][101]. Alternative strategies have been investigated including targeted blocking of SIRPα with engineered high affinity CD47 ectodomain or development of bispecific antibody targeting both CD47 and tumor-associated antigen [102][101]. To minimize possible off-target toxicity, anti-CD47 antibody may be developed using the Fc scaffold of

IgG4 to reduce Fc effector functions, or the engineered SIRPα without Fc fusion may be used in combination with Fc-active tumor-targeted antibodies [100][103].

3.4 Inhibition of inflammatory monocyte/macrophage recruitment

3.4.1 Inhibition of CCR2-CCL2 signaling—The number of intratumoral TAMs increases with tumor growth due to self-proliferation as well as recruitment and differentiation from circulating inflammatory $Ly6C^+CCR2^+$ monocytes [104]. The latter is mediated by elevated secretion of CCL2 (also known as monocyte chemoattractant protein-1 (MCP-1)), the ligand for CCR2, by cancer and stromal cells in tumors and associated metastases [105][106][107]. As a chemotactic factor, CCL2 mobilizes bone marrow-resident inflammatory monocytes into circulation and subsequently into the tumors. High expression of CCL2 in tumors and high count of $CCR2^+$ monocytes in the peripheral blood are both correlated with poor prognosis in several cancer types [108][105][109]. Strategies to pharmacologically interrupt CCR2-CCL2 signaling axis (e.g. CCR2 small molecule inhibitor, anti-CCR2 antibody, and anti-CCL2 antibody) have been developed as anti-cancer therapies [110]. In a pancreatic mouse cancer model, a small molecule CCR2 inhibitor (PF-04136309) effectively reduces recruitment of inflammatory monocytes into the tumors resulting in reduced tumor growth and fewer liver metastases [105]. Anti-CCL2 antibodies have been shown to prevent metastasis in breast and prostate cancer models [111][112]. However, in the breast cancer model, discontinuation of the treatment accelerated metastases as a result of increased tumor localization of monocytes that were originally sequestered in bone marrow during the antibody treatment [111].

3.4.2 Inhibition of CXCR4-CXCL12 signaling—In addition to the CCR2-CCL2 signaling axis, CXCR4-CXCL12 (also known as stromal cell-derived factor-1 (SDF-1)) interaction is another signaling axis involved in recruitment of monocytes/macrophages and implicated in promotion of tumor invasiveness/regrowth [113][114]. Mechanistically, CXCL12 is secreted by both tumor and stromal cells including TAMs, and hence, mediates both autocrine and paracrine signaling in recruiting and differentiating monocytes expressing its receptor CXCR4 into tumor-infiltrating TAMs [115]. In glioma and breast cancer models, anti-cancer treatments with radiation therapy or chemotherapy have been shown to increase the level of CXCL12 in the perivascular region of tumors which in turn promotes accumulation of $CXCR4^+$ TAMs [115][114]. Secretion of vascular endothelial growth factor A (VEGF-A) by these TAMs stimulates formation of new tumor vasculature and tumor relapse, the effects of which could be inhibited by treatment with CXCR4 inhibitor (AMD3100). Given multiple signaling pathways in monocyte/macrophage recruitment, simultaneous blockades of different signaling axes may be necessary to achieve the optimal effect.

3.5 Immunostimulation by anti-CD40 agonistic antibody

CD40 is a member of the tumor necrotic factor (TNF) receptor family expressed on antigen-presenting cells (APCs), monocytes, B cells, as well as in some tumors [116]. Since ligation between CD40 on APCs and CD40 ligand (CD40L) on T cells stimulates these APCs to activate effector T cells for anti-tumor response, the therapeutic effect of anti-CD40 agonistic antibody was thought to act through a similar mechanism. However, in a KPC

mouse model of pancreatic ductal adenocarcinoma (PDA), depletion experiments of different immune cell populations revealed that the anti-tumor effect of the antibody could be mediated in a T cell-independent manner, requiring only the tumor infiltration of macrophages [117]. Mechanistically, systemic administration of anti-CD40 antibody raises the serum level of CCL2 and IFNγ where the former recruits inflammatory monocytes to the tumors, and the latter reprograms the recruited monocytes/macrophages for tumoricidal activities [118]. Interestingly, further optimization of anti-CD40 antibody by testing different IgG subclasses indicates that its agonistic immunostimulatory activity requires effective engagement of the antibody Fc domain with inhibitory FcγRIIb but not with other activatory Fc receptors (needed for ADCC/CDC) [119]. Consistent with the pre-clinical finding that the agonistic activity of anti-CD40 antibody is mediated more robustly when the activatory/inhibitory Fc receptor binding ratio (A/I) is lower [120], Pfizer's human anti-CD40 antibody of IgG2 subclass (CP-870,893) has been shown in clinical trials to be more agonistic in immunostimulation compared to the other candidates (e.g. dacetuzumab, Chi Lob 7/4, and HCD122), the rest of which have IgG1 subclass (Table S1) [116].

3.6 Inhibition of angiogenic signaling

One of the essential pro-tumoral functions of macrophages is promotion of angiogenesis. The $TIE2^+$ subpopulation, also called TIE2-expressing monocytes/macrophages (TEMs), has been shown to predominantly contribute to this role [6]. TEMs are typically recruited from circulation into the perivascular region of tumors where their pro-angiogenic activities are stimulated upon interaction of TIE2 with the corresponding ligand angiopoietin 2 (ANG2), secreted in several tumors [121][122]. Mazzieri et al. demonstrated that therapeutic blockade of ANG2 with an anti-ANG2 antibody reduced angiogenesis and tumor growth in mammary and pancreatic tumor models by preventing association between TEMs and angiogenic blood vessels as well as suppressing expression of TIE2 in TEMs [121]. Since upregulation of ANG2 is one of the resistance mechanisms to anti-VEGF therapy, dual targeting of both ANG2 and VEGF via either combination therapy or bispecific antibody has been investigated as a strategy to circumvent the therapeutic resistance [123][124]. Interestingly, in both highly vasculature-aberrant Gl261 as well as less aberrant MGG8 glioblastoma models, treatment with bispecific anti-ANG2/VEGF-A antibody (CrossMab, A2V) successfully improved survival the effect of which was attributed to the antibody-induced M2-to-M1 reprogramming of TAMs [124]. Similarly, a vascular-disrupting agent 5,6-dimethlxanthenone-4-acetic acid (DMXAA), initially developed for disrupting tumor vasculature, has also been shown to activate immunostimulatory functions of TAMs, which in turn orchestrate anti-tumor response of $CD8^+$ T cells [125].

3.7 Metabolic modulation of macrophages/TAMs

3.7.1 mTOR inhibition—Macrophages of different functional states vary in their use of metabolic pathways for energy and metabolite production to support their specialized cellular activities [126]. Mammalian target of rapamycin (mTOR) signaling through mTOR complex 1 (mTORC1) and mTORC2 serves a central role in sensing nutrients, oxygen, and metabolites to direct metabolic programming of these macrophages [127]. In addition to its direct cytotoxic effect on cancer cells [128], rapamycin, an mTORC1-specific inhibitor, has been shown to stimulate macrophages to the M1-like phenotype with an anti-tumor effect in

Huh-7 hepatocarcinoma mouse model [129]. Of note, other signaling molecules upstream of mTOR (e.g. PI3kγ, protein kinase B (Akt), and phosphatase and tensin homolog deleted on chromosome 10 (PTEN)) are also involved in shaping polarization and functions of macrophages/TAMs, making them potential targets for anti-cancer therapies [130][131][132]. As an example, Kaneda et al. recently showed that PI3kγ inhibitor (IPI-549) retarded tumor growth in implanted human papilloma virus positive head and neck squamous cell carcinoma (HPV^{+}HNSCC), lung carcinoma, and breast carcinoma models in a TAM-dependent manner by promoting TAM-immunostimulatory responses [130]. Similarly, expression of PTEN (PI3k suppressor) or silencing of Akt1 can also promote anti-tumor M1 macrophage polarization [131][132].

3.7.2 Modulation of PPARγ-Gpr132-lactate signaling—The TME is enriched for lactate which is secreted by cancer cells performing glycolysis [133]. It is now known that the recognition of lactate by Gpr132 (G-protein coupled receptor) on TAMs promotes M2 polarization of these TAMs while the expression of Gpr132 is under a suppressive control of peroxisome proliferator-activated receptor (PPARγ) transcription factor [134][135]. Several strategies have been developed to interrupt this signaling axis. For example, supply of lactate for M2-TAM polarization could be blocked using an inhibitor of lactate dehydrogenase (oxamic acid) [134]. Alternatively, PPARγ agonists (e.g. thiazolidinedione family of drugs) or siRNA silencing of Gpr132 have been successfully used to insensitize TAMs to lactate stimulation with a tumor-shrinking effect in EO771 breast tumor model [135].

3.7.3 Inhibition of metabolism of amino acids and lipids—In addition to competition for glucose, TAMs readily catabolize arginine and tryptophan which are essential amino acids required for anti-tumor T cell functions [126]. Restoration of these nutrients by inhibiting arginase, nitric oxide synthase, and indoleamine 2, 3-dioxygenase (IDO) constitutes another promising therapeutic intervention to improve T cell survival and functions [136][137]. Moreover, TAMs are also known to mediate immunosuppressive and metastasis-promoting functions in response to cancer cell/TAM-secreted lipid metabolites such as prostaglandin E_2 (PGE_2) and sphingosine-1-phosphate (S1P) [138][139][140]. Pharmacological inhibition of PGE_2-producing enzymes microsomal PGE_2 synthase 1 (mPGES1) and cyclooxygenase-2 (COX-2), with CAY10526 and celecoxib respectively, effectively reduced PGE_2 level in bone marrow cell/MBT-2 bladder cancer cell coculture with celecoxib being further shown to lower expression of T cell-suppressive programmed cell death ligand 1 (PD-L1) in an MBT-2 cancer model and also promote M2-to-M1 polarization of TAMs in an $Apc^{min/+}$ colon cancer model [139][141].

3.7.4 Modulation of essential elements and vitamins—Iron metabolism is vastly different between M1- and M2-polarized macrophages [142]. M1 macrophages upregulate ferritin to promote intracellular iron retention whereas M2 macrophages upregulate ferroportin to enhance iron efflux. Consistent with the M2-like phenotype, TAMs preferentially liberate iron and provide cancer cells with this essential element for promoting proliferation. Several iron chelators are being evaluated as anti-cancer agents [143]. Iron chelation therapy has recently been shown to reverse iron-processing function of M2 macrophages from iron release towards sequestration and block tumor-promoting effect of

the macrophages [144]. Conversely, external supply of iron through administration of ferumoxytol iron oxide nanoparticles has also been shown to be therapeutic at inhibiting tumor growth and metastasis by stimulating pro-inflammatory macrophage polarization and production of ROS [145]. These seemingly contradictory results regarding iron supply and macrophage response emphasize the need for further study in this area.

In another example, macrophages may secrete a host-defense peptide, cathelicidin, shown to readily lyse proliferating B cell lymphoma cells but not normal B cells [146]. Cathelicidin production requires intracellular metabolism of 25-hydroxyvitamin D (25D) into bioactive 1,25-dihydroxyvitamin D (1,25D3) by vitamin D-1-hydroxylase CYP27B1, which is expressed at lower levels in M2 macrophages and TAMs compared to M1 macrophages. Treating M2 macrophages with 1,25D3 successfully restores cathelicidin production and cytotoxicity against the B cell lymphoma cells[146].

3.8 Modulation of macrophage scavenger receptors

Scavenger receptors comprise a family of receptors that broadly recognize modified low-density lipoproteins, polyanions, endogeneous proteins, as well as conserved microbial structures and are important for clearing foreign particles, pathogens, and apoptotic cells from the body [147]. Several scavenger receptors (e.g. scavenger receptor class A (SR-A1), macrophage receptor with collagenous structure (MARCO), CD36, CD68, CD163, and receptor for advanced glycation endproducts (RAGE)) are expressed on macrophages, some of which are involved in regulation of tumor immunity and are therefore potential targets for therapeutic modulation [148][149]. As an example, apolipoprotein A-I mimetic peptide 4F, a competing ligand for SR-A1, has been shown to inhibit tumor growth and metastasis in ovarian and pancreatic tumor models [150]. The proposed mechanisms of action involve interrupting TAM/cancer cell crosstalk, blocking SR-A1 from scavenging ECM components that allow for cancer cell migration, and scavenging of pro-inflammatory/angiogenic lysophosphatidic acid (LPA) [151]. However, in the context of glioma model, Zhang et al. demonstrated that recognition of tumor-secreted heat shock protein 70 (HSP70) by SR-A1 is important in suppressing M2 polarization in TAMs and is needed for inhibition of glioma proliferation and angiogenesis [152]. These studies highlight the context-dependent effect in modulation of scavenger receptor activity as a result of its recognition of a broad range of ligands.

3.9 Chemotherapy drugs

Although chemotherapy drugs are primarily developed to induce cell death in rapidly dividing cancer cells, many also have pharmacological effects on non-cancer cell populations. In particular, trabectedin and its second generation lurbinectedin are effective at killing TAMs in addition to cancer cells [153][154]. Mechanistically, trabectedin interacts with tumor necrosis factor-related apoptosis inducing ligand receptor 2 (TRAIL-R2) on mononuclear phagocytes leading to receptor clustering and subsequent caspase-8 dependent activation of apoptosis [154][155]. Its selective toxicity in TAMs over neutrophils and lymphocytes has been attributed to higher expression of the receptor in conjunction with lower expression of non-signaling decoy TRAIL-R3. In addition, trabectedin also inhibits production of chemoattractant cytokine CCL2 by TAMs and tumor cells [156]. Apart from

exerting a cytotoxic effect, several chemotherapy drugs modulate macrophage responses to tumor [157,158]. In murine fibrosarcoma and mammary tumor models, microtubule-stabilizing agents such as docetaxel and paclitaxel have been shown to promote polarization of myeloid-derived suppresser cells (MDSCs) to macrophages with anti-tumor M1-phenotype via suppression of STAT3 phosphorylation [159,160]. Cyclophosphamide treatment promotes infiltration of macrophages, enhances secretion of pro-inflammatory cytokines (IL-6 and IL-12), and suppresses production of pro-tumoral M2-related cytokines (IL-4, IL-10, and IL-13) [161][162]. As a self-protective mechanism against chemotherapies, chemo-resistant cancer cells secrete IL-34 which enhances their survival as well as promotes M2 polarization of TAMs to further reinforce immunosuppressive functions [163]. In addition, chemotherapy treatments may also increase intratumoral level of CXCL12, which serves as a chemotactic factor in recruiting $TIE2^{+}CXCR4^{+}$ macrophages to the perivascular region of the tumor where they preferentially promote angiogenesis and tumor regrowth [113]. To combat these resistance mechanisms, an integration of chemotherapy and immunotherapy may allow for a more effective tumor regression. Of note, paclitaxel and gemcitabine are two chemotherapy drugs commonly investigated in a combination therapy with other TAM-modulating therapeutics due to their possible promotion of antigen release following cancer cell death (Table 2 and S1).

3.10 Activation of Toll-like receptors (TLRs)

Toll-like receptors (TLRs), expressed on either plasma membranes (TLR1, 2, 4, 5, 6, and 10) or endosomal membranes (TLR3, 7, 8, and 9) of APCs, recognize various PAMPs and damage-associated molecular patterns (DAMPs), constituting an indispensable system for innate immune surveillance [164]. In regard to modulation of TAMs, several TLR agonists (e.g. polyinosinic:polycytidylic acid (polyI:C) for TLR3, LPS for TLR4, imiquimod for TLR7, and CpG-olionucleotide for TLR9) have been shown to activate NF-κB leading to pro-inflammatory M1 polarization (reviewed in [165]). Moreover, TLR signaling may also be initiated by chemotherapy drugs via induction of immunogenic cell death (ICD) [166]. Oftentimes, engaging multiple TLRs is essential to effect a more potent anti-tumor response. As an example, a recent study by Zheng et al. reported development of a dual TLR4/5 stimulating bacterial cell therapy (BCT) based on attenuated ΔppGpp *Salmonella typhimurium* (TLR4 agonist) with inducible production of *Vibrio vulnificus* flagellin B (FlaB, TLR5 agonist) [167]. The dual stimulation was more effective at reprogramming TAMs from $CD206^{+}$ M2 phenotype to immunostimulating $CD86^{+}$ M1 phenotype. Despite the anti-tumor effect of NF-κB activation being observed in TLR agonistic therapies, an opposite finding has also been reported where inhibition of IκB kinase β (IKKβ), the main downstream activator molecule of NF-κB, repolarizes TAMs to IL-12-secreting, NO-producing M1 phenotype with a growth inhibition effect in an ID8 ovarian tumor model [168]. These opposing reports on pro-tumoral/anti-tumoral effects of NF-κB activation may imply involvement of other determining parameters (e.g. the presence of other signaling factors that shape TLR responses or the effects of TLR signaling on other cell populations in TME) that collectively dictate the overall response to the therapies and highlight the need to thoroughly understand the immunological context of tumor for effective tailoring of anti-cancer therapy.

4 Targeted drug delivery systems to macrophages/TAMs

With promising drugs for different molecular targets being identified that could potentially modulate TAMs to effect an anti-tumor response, the next challenge has been how to deliver these immunomodulating drugs effectively and selectively to TAMs while minimizing off-target side effects. The extensive number of studies in the cancer nanomedicine field investigating passive targeting to tumor via the enhanced permeability and retention (EPR) effect has provided information regarding the biodistribution of nanoparticle systems i*n vivo*. From this work, we have also gained more understanding about parameters that influence internalization by macrophages (e.g. Kupffer cells), the main player in the mononuclear phagocyte system responsible for clearance of nanomedicines. This section describes parameters that dictate passive targeting of macrophages/TAMs as well as targeting ligands being investigated pre-clinically for active targeting of macrophages/TAMs.

4.1 Passive targeting to macrophages/TAMs

Due to their primary role in clearing cellular debris, pathogens, and foreign substances, macrophages possess high phagocytic capability. Micro/nanoparticles are relatively indiscriminately internalized by macrophages, although the rate and extent of uptake is affected by properties such as shape, size, rigidity, contact angle, and surface charge (Fig. 2) [169][170][171][172]. For nanoparticles/liposomes larger than 100 nm, most studies report increased uptake with increasing particle size up to about 1 - 3 μm, after which uptake declines [169][173]. On the other hand, for nanoparticles/liposomes smaller than 100 nm, most studies report increased uptake with decreasing particle size [174][175][176]. Contrasting trends are also observed which may be partially attributed to differences in nanoparticle composition and macrophage source, as well as involvement of other uptake mechanisms [177][178][179]. In term of charge, nanoparticles with either highly positive or highly negative zeta potentials are preferentially internalized compared to the ones with near neutral or slightly negative zeta potentials [169][177]. In general, rigid and spherical nanoparticles are more readily uptaken by macrophages than soft and cylindrical nanoparticles [172][180][181][182][183].

Recently, MacParland et al. reported a comparative study on nanoparticle uptake by human monocyte-derived macrophages of different phenotypic polarization [184]. In general, M2-polarized human macrophages exhibit higher internalization of gold nanoparticles than the M1-polarized cells, and the extent of uptake is positively correlated with the expression of M2 markers CD163 and CD206. Further investigation on the nanoparticle uptake by unstimulated and stimulated M1- or M2-polarized Kupffer cells from deceased donors showed that the unstimulated Kupffer cells, possessing a mixed M1/M2 phenotype, exhibited comparable internalization of nanoparticles to the M2-polarized cells, both of which ingested more nanoparticles than the M1-polarized cells did.

While the natural tendency of M2 macrophages to more readily internalize nanoparticles could be beneficial for designing TAM-targeted therapy, the resident macrophages' penchant for internalizing nanoparticles is still an important challenge in developing TAM-targeted therapies [185][186][181][187]. While this ability might be exploited to target TAMs in liver

cancer or metastasis, delivery of NP-based formulations to TAMs at other sites must compete with avid internalization by hepatic and splenic macrophages [188][180]. In fact, the current mainstay for depletion of TAMs in animal cancer models utilizes liposomal clodronate, which relies on passive accumulation of liposomes in the macrophages and therefore indiscriminately affects both TAMs and resident macrophages [189][52].

4.2 Active targeting to macrophages/TAMs

Targeting ligands are also employed to facilitate preferential delivery to TAMs via specific ligand-receptor interaction (Fig. 2). Mannose receptor (CD206) is one of the most commonly targeted receptors for macrophage delivery due to its overexpression on M2 macrophages [190]. As a simple sugar, the native ligand mannose can be easily conjugated to carriers but binds with low affinity. Thus, anti-CD206 antibody has also been developed for targeting TAMs [191]. Although CD206-targeted drug delivery systems can achieve high M2/M1 selectivity, they are readily sequestered in liver by resident macrophages and liver sinusoidal endothelial cells which also express high level of the receptor [192].

TAMs also overexpress folate receptor beta (FRβ), which can be targeted using its ligand, folic acid [193][194]. To improve selectivity over folate receptor alpha (FRα), reduced folate carrier (RFC), and proton-coupled folate transporter (PCFT) which are expressed on both cancerous and non-cancerous tissues, various antifolate analogs have been developed a few of which exhibit significant FRβ selectivity over the rest [195]. Anti-FRβ Fv is also successfully used to selectively target $FR\beta^{+}$ TAMs [196]. While expression of FRβ is more restricted than FRα, several studies have reported that FRβ is also expressed on pro-inflammatory activated M1 macrophages [197][198][199].

Legumain and transferrin receptor are two other target receptors overexpressed on M2-TAMs compared to M1-TAMs but that are also present on several cancer cell types [200][201][202]. The proteolytic activity of legumain specific to the Ala-Ala-Asn substrate sequence has been used in the design of pro-drugs or smart drug delivery systems that target both TAMs and cancer cells [200][203][204]. Although many drug delivery systems targeting transferrin receptor have been reported, to our knowledge, all these systems are tailored toward targeting cancer cells expressing the receptor or enhancing transcytosis across blood brain barrier, and neither the effect on nor the application to affect TAMs has been reported [205][206][207].

In order to improve TAM selectivity over resident macrophages, a few groups have employed unique physical properties of TME to rationally design their targeting systems [203][190][208]. As an example, Zhu et al. reported the development of mannosylated PLGA nanoparticles that are masked with acid-sensitive PEG(2000) that prevents recognition by resident macrophages but is cleaved in the acidic TME to expose mannose for intratumoral TAM targeting [190]. In another study, Movahedi and Schoonooghe et al. demonstrated the use of excess unlabeled bivalent anti-MMR nanobody as a decoy to reduce background signal of 99mTc-labeled monovalent anti-MMR nanobody in liver and spleen [208]. The bivalent nanobody competitively binds to resident macrophages with higher avidity over the monovalent nanobody but has poor tumor penetration due to its bigger size, whereas the monovalent nanobody can diffuse into tumor to label M2-TAMs for imaging.

On our part, we have developed an M2 macrophage-targeting peptide (M2pep) via peptide phage display screening [209]. The peptide binds to M2 macrophages and M2-TAMs selectively over M1 and M0 macrophages as well as over other leukocytes. Further optimization of the peptide improves its serum stability and affinity, and enables enhanced targeting to M2-TAMs in syngeneic CT26 colon cancer and 4T1 breast cancer models [210] [211]. Multivalent display of the peptide further improves binding avidity to M2 macrophages[212]. The small size and easy production of M2pep make it a promising and attractive targeting ligand for developing M2-TAM-targeted therapeutics.

5 Macrophages as a therapeutic depot

Macrophages receive considerable interest as a drug delivery carrier due to their tumor-homing property, high phagocytic capability of drug-loaded nanoparticles, and ability to directly kill cancer cells given the right immunostimulating environment [213]. For examples, peritoneal macrophages may be harvested, incubated with drugs, typically in nanoparticle/liposome formulations, for loading, and then infused back to animals/patients [214][215], or nanoparticles with appropriate size and/or ligand may be directly injected *in vivo* and get uptaken by resident macrophages/TAMs in the body for subsequent sustained release [216][217][188]. While both strategies significantly improve the circulation half-life of the drugs, the long-term survival of the macrophage host is limited by toxicity of the drug, and hence, most of the drugs are loaded in the nanoparticle or liposome formulations to reduce acute toxicity to the macrophage carrier [214,216]. Interestingly, Tanei et al. observed increased expression of p-glycoprotein efflux pump in albumin-bound paclitaxel nanoparticle-loaded macrophages compared to the unloaded control and attributed this as one of the possible mechanisms to preserve macrophage viability as well as to enable drug release to the surrounding e.g. TME [188]. In the case where drug is not toxic to macrophages, appropriate formulation enables sustained release of the loaded drug from macrophages for up to at least 2 weeks as demonstrated by Dou et al. for indinavir nanoparticle-loaded macrophages [218][219]. With proper nanoparticle encapsulation strategies to achieve intracellular stability, it is even possible to load biologics such as proteins into macrophages [220,221]. Equally important to effective drug loading is the ability of drug-laden macrophages to migrate to tumor. A study by Chang and Guo et al. shows that the size of nanoparticles internalized by macrophages can significantly alter locomotivity of the macrophages, with smaller nanoparticles (30 and 50 nm) having higher uptake into macrophages than larger nanoparticles (100 and 500 nm) but also more readily retarding the migration rate of the macrophages; this study suggests that 100 nm nanoparticles provide a good balance for effective drug loading and macrophage migration [174]. To increase control over drug activity from macrophage carriers, macrophage have been loaded with temperature-responsive liposomes for triggered release [216], with gold-silica nanoshells for photothermal therapy [215], and with iron oxide nanoparticles for dual tracking and trafficking using electromagnetic actuation [214][222][223].

Recently, an additional role of TAMs as a processing factory for antibody-drug conjugates (ADCs) has been reported [224]. Specifically, Li et al. observed an anti-tumor activity of non-targeted humanized IgG conjugated to protease-cleavable monomethyl auristatin E (hIgG-vaMMAE) in L-82 anaplastic large cell lymphoma and MCF-7 breast cancer

xenograft models and further demonstrated, in a panel of xenograft models, that the efficacy is positively correlated with the extent of $F4/80^+$ TAM infiltrate. Mechanistic investigation revealed the two key parameters for the TAM-mediated, antigen-independent, anti-tumor activity; (1) binding and internalization of ADCs to FcγR on TAMs for processing and release of drug and (2) membrane permeability of drug to mediate the by-stander effect once released from TAMs. This report provides the first evidence on the possible contribution of TAMs on efficacy of ADCs and presents an underexplored opportunity of TAM-targeted ADC engineering.

Instead of loading drugs into macrophages, it is also possible to genetically engineer them to produce therapeutic proteins. As an example, Palma and Mazzieri et al. transduced hematopoietic/progenitor stem cells (HPSCs) with lentiviral vector encoding *Ifna1* under control of *Tie2* promoter/enhancer elements. When transplanted into tumor-bearing mice, a subpopulation of these cells matured into TEMs and homed to the tumor where their TIE2 expression was further heightened resulting in localized production of IFNα that provided an anti-tumor effect and without systemic toxicity [225].

Since macrophages may exhibit both pro-tumoral and anti-tumoral activities in TME, it is important to fully understand the *in vivo* fate/functional state of these macrophages as well as ideally be able to promote and maintain the anti-tumor functional state of the macrophage carrier in order to maximize this cell-directed therapy. Although the early days of research were devoted to loading macrophages with cytotoxic drugs, it should be possible to load drugs/nanoparticles that may enhance *in vivo* anti-tumor properties of these macrophages or other immune cells. In light with the recent report on M1-inducing property of clinically approved iron oxide nanoparticles [145], it would be interesting to study how the iron oxide nanoparticle-loaded macrophages, already developed for diagnostic purpose, may exhibit enhanced anti-tumor properties. Finally, further development of the technology for delivery of biologics such as peptide or proteins drugs would greatly expand the utility of this technology in cancer therapy.

6 Perspectives on TAM-targeted therapeutics

With deeper understanding of cancer immunology, diverse strategies for modulation of TAMs are being uncovered and explored for therapeutic applications. Due to the complexity of tumors, combination therapy is typically needed to maximize an anti-tumor response. Thus, a clear understanding of the modes of drug action as well as mechanisms of resistance is needed in order to design an efficacious combination therapy that minimizes antagonistic effects. For example, identification of PI3k up-regulation in tumor as a resistance mechanism for CSF-1R kinase inhibitor in recurrent glioma suggests that a combination therapy between PI3k and CSF-1R inhibitors could be more beneficial [72]. Conversely, the therapeutics aiming to block macrophage recruitment signals (e.g. CCL2 or CXCL12 inhibition) may not be compatible with the ones that require the presence of macrophages for anti-tumor actions (e.g. anti-CD40 antibody) [118]. In congruence with the well-appreciated immunosuppressive roles of TAMs, a consensus was observed regarding the potential benefits of TAM-targeted therapies in potentiating immune checkpoint blockade therapies (anti PD-1/PD-L1/CTLA-4 antibodies) as evidenced in the race among

pharmaceutical companies to investigate such combination therapies (Table 2). Improvement in gene sequencing and analysis technologies greatly facilitates the adoption of precision medicine where patients could be examined for genetic makeup and matched with appropriate therapeutic regimens. Documenting patients' genetic profile and the corresponding therapeutic outcome are also beneficial in correlation studies to better predict patient response as well as in refining drug development. In the case of CSF-1R inhibition therapy, certain single nucleotide polymorphisms (SNPs) in CSF-1R have been identified that reduce the potency of emactuzumab [226]. Nonetheless, the study may help in the future design of the next-generation CSF-1R blockade therapy. To reap the benefit of a steady rise in molecularly targeted therapies that are promising for clinical translation, it is more than ever important to be resource-efficient. This may be possible through careful validation of pre-clinical studies and innovative design of clinical trials as seen, for example, in the I-SPY 2 trial (NCT01042379) [227]. With numerous therapeutic targets being identified and drug candidates being explored for modulation of TAMs, drug delivery technologies will soon come into play to further enhance therapeutic efficacy of these drugs, for example, by improving pharmacokinetics, stability, selectivity, or intracellular delivery while limiting systemic toxicity. Together with advancement in gene-editing technology, effective silencing of genes that promote pro-tumoral functions of TAMs (e.g. STAT3, SIRPα, PI3k, or Gpr132) may one day be a practicable therapeutic option. Finally, a cost barrier is another factor that could impede the clinical translation especially when multiple antibodies are used in a combination therapy as currently investigated in several trials. The problem may be alleviated with improvement in manufacturing efficiency or development of cheaper alternatives such as small molecule drugs or peptide analogs.

The last century of research has revealed that the mononuclear phagocyte system and macrophages play an essential role in normal physiological processes and disease development. Targeting TAMs has proven to be a promising strategy as TAM targeting agents are rapidly advancing to the clinic, both in combination with traditional therapeutics and with other immunomodulatory agents. With the increasing depth of TAM targeting agents within pre-clinical development and new research developments in understanding mechanistic TAM pathways, it is clear that TAM targeted therapies will be an important addition to the anti-cancer armamentarium.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIH 1R01CA177272. Chayanon Ngambenjawong was supported by an Anandamahidol Foundation Fellowship. Heather H. Gustafson was supported by the Cardiovascular Pathology Training Grant (5 T32 HL 007312-37).

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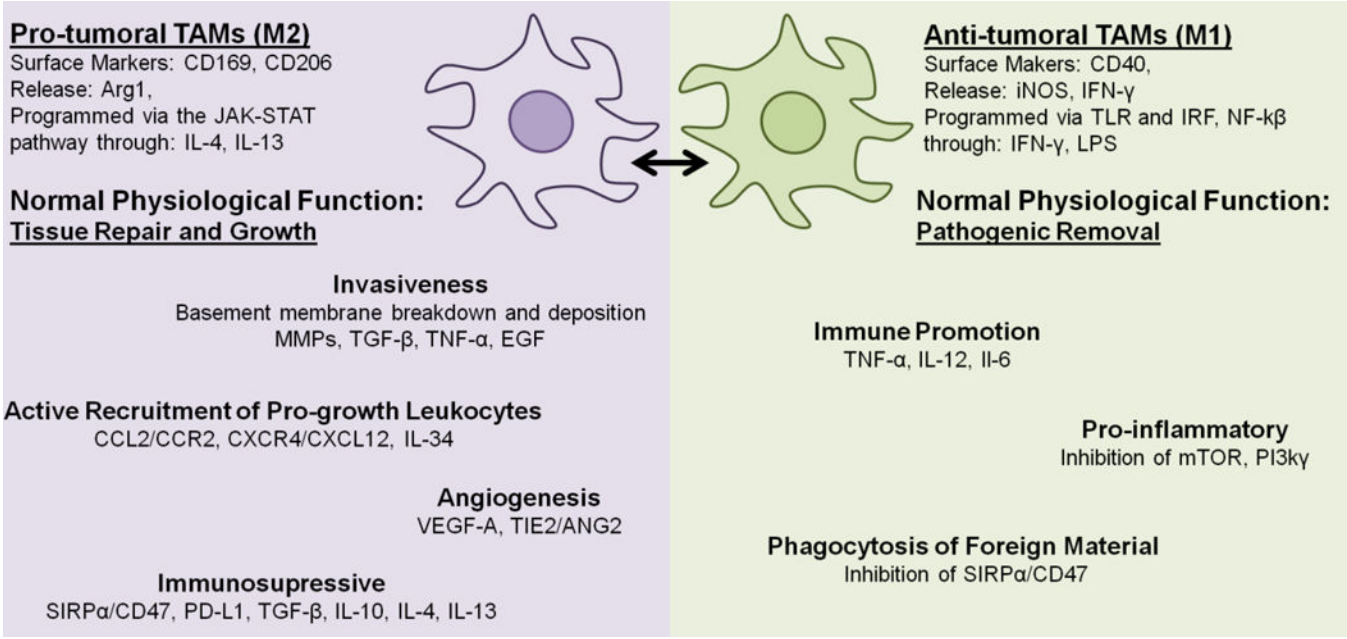

Fig. 1.

Normal physiological macrophage functions that can promote (M2) or reduce tumor growth (M1).

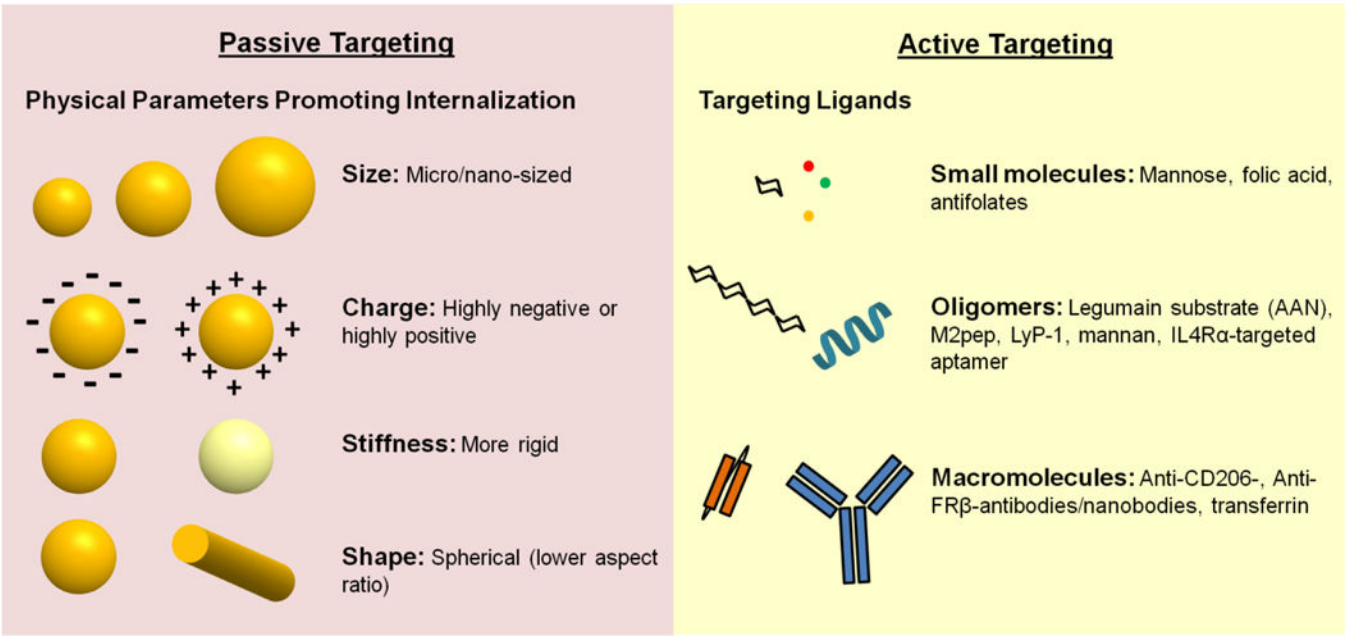

Fig. 2.
Strategies to promote passive and active targeting of macrophages/TAMs.

Table 1

FDA-approved drugs whose mechanisms of action may involve modulation of macrophages/TAMs

Drug	Treatment	Year approved (US FDA)
Bisphosphonate		
Pamidronate/Aredia	Multiple myeloma, metastatic breast cancer	1995
Zoledronic acid/Zometa	Multiple myeloma, bone metastases from solid tumors	2002
Alkylating agent		
Trabectedin/Yondelis	Advanced soft-tissue sarcoma	2007 (EU) [63]
		2015 (US)
	Ovarian cancer	2009 (EU) [63]
Tyrosine kinase inhibitor		
Imatinib/Gleevec	Chronic myelogenous leukemia (CML)	2001
Dasatinib/Sprycel	CML,Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL)	2006
	Chronic phase CML	2007
	Chronic phase Philadelphia chromosome-positive CML	2010
Sunitinib/Sutent	Gastrointestinal stromal tumor (GIST), advanced kidney cancer	2006
	Pancreatic neuroendorcrine tumors	2011
Nilotinib/Tasigna	CML	2007
Imaging agent		
Tc 99m tilmanocept/Lymphoseek (CD206 targeting)	Lymphatic mapping in breast cancer and melanoma	2013
	Guiding Sentinel Lymph Node (SLN) Biopsy in squamous cell carcinoma of the oral cavity	2014

Source: www.fda.gov, www.cancer.gov

These drugs were not necessarily approved due to their actions on TAMs.

Table 2

Selected compilation of drugs in clinical trials whose mechanisms of action may involve modulation of macrophages/TAMs

Drug/Description	Sponsors and collaborators	Phase/Status	Tumor type	Treatment	ClinicalTrials.govIdentifier	First received
CSF1R inhibitor						
Pexidartinib/PLX3397 (Oral c-fms/KIT/FLT3 tyrosine kinase inhibitor)	Centre Leon Berard and Plexxikon, AstraZeneca	1 Ongoing	Advanced/metastatic colorectal or pancreatic cancer	With Durvalumab (Anti-PD-L1 antibody)	NCT02777710	May 12, 2016
	Plexxikon and Merck Sharp & Dohme Corp.	1/2a Ongoing	Advanced melanoma and other solid tumors	With Pembrolizumab (Anti-PD-1 antibody)	NCT02452424	May 20, 2015
	Daiichi Sankyo Inc.	3 Ongoing	Pigmented villonodular synovitis (PVNS), giant cell tumors of the tendon sheath (GCT-TS), or tenosynovial giant cell tumor (TGCT)	Monotherapy	NCT02371369	February 19, 2015
PLX7486 (Oral c-fms/Trk tyrosine kinase inhibitor, tosylate salt form)	Plexxikon	1 Ongoing	Solid tumors or tumors of any history with activating Trk point or NTRK fusion mutation	Monotherapy	NCT01804530	March 1, 2013
BLZ945 (Oral c-fms tyrosine kinase inhibitor)	Novatis Pharmaceuticals	1/2 Ongoing	Advanced solid tumors	Monotherapy and with PDR001 (Anti-PD-1 antibody)	NCT02829723	July 8, 2016
ARRY-382 (Oral c-fms tyrosine kinase inhibitor)	Array BioPharma	1b/2 Ongoing	Advanced solid tumors	With Pembrolizumab (Anti-PD-1 antibody)	NCT02880371	August 2, 2016
AMG 820 (Human IgG2 anti-CSF-1R antibody)	Amgen	1b/2 Ongoing	Advanced solid tumors	With Pembrolizumab (Anti-PD-1 antibody)	NCT02713529	March 3, 2016
Emactuzumab/RO5509554/RG7155 (Human IgG1 anti-CSF-1R antibody)	Hoffmann-La Roche	1 Ongoing	Solid cancers	With MPDL3280A (Tecentriq/anti-PD-L1 antibody)	NCT02323191	December 5, 2014
	Hoffmann-La Roche	1 Ongoing	Solid tumors	With RO7009789 (Anti-CD40 agonistic antibody)	NCT02760797	April 14, 2016
	M.D. Anderson Cancer Center and Genentech Inc.	2 Ongoing	Platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal Cancer	With paclitaxel and Bevacizumab	NCT02923739	September 30, 2016

Drug/Description	Sponsors and collaborators	Phase/Status	Tumor type	Treatment	ClinicalTrials.govIdentifier	First received
				(Avastin/anti-VEGF antibody)		
LY3022855/IMC-CS4 (Human IgG1 anti-CSF-1R antibody)	Eli Lilly and Company and AstraZeneca	1a/1b Ongoing	Advanced solid tumors	With Durvalumab (Anti-PD-L1 antibody) or Tremelimumab (Anti-CTLA-4 antibody)	NCT02718911	March 21, 2016
Cabiralizumab/FPA008 (Anti-CSF-1R antibody)	Five Prime Therapeutics Inc. and Bristol-Myers Squibb	1a/1b Ongoing	Advanced solid tumors	Wth BMS-936558 (Nivolumab/ anti-PD-1 antibody)	NCT02526017	August 13, 2015
RON/MET inhibition						
ASLAN002/BMS777607 (Oral RON/MET receptor tyrosine kinase inhibitor)	Aslan Pharmaceuticals	1 Completed	Malignant solid tumors	Monotherapy	NCT01721148	November 1, 2012
CD47-SIRPα inhibitor						
Hu5F9-G4 (Human IgG4 Anti-CD47 antibody)	Forty Seven Inc.	1b/2 Ongoing	Colorectal neoplasms or solid tumors	With Cetuximab (Erbitux/anti-EGFR antibody)	NCT02953782	November 1, 2016
	Forty Seven Inc.	1b/2 Ongoing	Non-Hodgkin's lymphoma or diffuse large B-cell diffuse lymphoma, indolent lymphoma	With Rituximab (Anti-CD20 antibody)	NCT02953509	November 1, 2016
CC-90002 (Anti-CD47 antibody)	Celgene	1 Ongoing	Acute myeloid leukemia or myelodysplastic syndromes	Monotherapy	NCT02641002	November 12, 2015
TTI-621 (SIRPα-Fc fusion)	Trillium Therapeutics Inc.	1 Ongoing	Solid tumors or mycosis fungoides	Monotherapy	NCT02890368	August 26, 2016
ALX148 (High affinity SIRPα variant)	Alexo Therapeutics Inc.	1 Ongoing	Metastatic cancer, solid tumor, advanced cancer, or non-Hodgkin's lymphoma	Monotherepay, with Atezolizumab (Tecentriq/anti-PD-L1 antibody) or Transtuzumab (Herceptin/ anti-HER2 antibody)	NCT03013218	December 15, 2016
CCR2-CCL2 inhibitor						
PF-04136309/PF6309 (Small molecule CCR2 antagonist)	Pfizer	1b/2 Ongoing	Metastatic pancreatic ductal adenocarcinoma	With Nab-paclitaxel and gemcitabine	NCT02732938	February 29, 2016

Drug/Description	Sponsors and collaborators	Phase/Status	Tumor type	Treatment	ClinicalTrials.govIdentifier	First received
MLN1202/S0916/plozalizumab (Human anti-CCR2 antibody)	Millennium Pharmaceuticals Inc.	1 Ongoing	Melanoma	With Nivolumab (Anti-PD-1 antibody)	NCT02723006	March 25, 2016
Carlumab/CNTO 888 (Human IgG1κ anti-CCL2 antibody)	Centocor Inc.	1 Completed	Cancer	With DOXIL, gemcitabine, paclitaxel + carboplatin, or docetaxel	NCT01204996	September 16, 2010
CXCR4-CXCL12 inhibitor						
Mozobil/AMD-3100/plerixafor* (Small molecule CXCR4 antagonist)	CCTU-Cancer Theme, Sanofi, Stand Up To Cancer, CRUK Cambridge Institute, Lustgarten Foundation, and National Institute for Health Research (UK)	1 Ongoing	Metastatic pancreatic adenocarcinoma, ovarian serous adenocarcinoma, or metastatic colorectal cancer	Monotherapy	NCT02179970	July 1, 2014
LY2510924 (CXCR4 agonistic peptide)	Eli Lilly and Company and AstraZeneca	1 Ongoing	Solid tumors	With Durvalumab (Anti-PD-L1 antibody)	NCT02737072	April 8, 2016
CD40 agonist						
CP-870,893/RO7009789 (Human IgG2 anti-CD40 antibody)	Abramson Cancer Center of the University of Pennsylvania	1 Ongoing	Recurrent/stage IV melanoma	with Tremelimumab (Anti-CTLA-4 antibody)	NCT01103635	April 12, 2010
	Hoffmann-La Roche	1 Ongoing	Solid cancers	with MPDL3280A (Tecentriq/anti-PD-L1 antibody)	NCT02304393	November 26, 2014
	Abramson Cancer Center of the University of Pennsylvania	1 Ongoing	Pancreatic cancer	With nab-paclitaxel and gemcitabine	NCT02588443	October 21, 2015
	Hoffmann-La Roche	1 Ongoing	Advanced/metastatic solid tumors	With Vanucizumab (Bispecific anti-Ang2/ VEGF-A antibody)	NCT02665416	January 15, 2016
	Hoffmann-La Roche	1 Ongoing	Solid tumors	With Emactuzumab (Anti-CSF-1R antibody)	NCT02760797	April 14, 2016
Vasculature-modulating agent						
Vanucizumab (Human bispecific anti-Ang2/ VEGF antibody)	Hoffmann-La Roche	1 Ongoing	Neoplasms	With Atezolizumab	NCT01688206	September 13, 2012

Drug/Description	Sponsors and collaborators	Phase/Status	Tumor type	Treatment	ClinicalTrials.govIdentifier	First received
				(Anti-PD-L1 antibody)		
	Hoffmann-La Roche	1 Ongoing	Advanced/metastatic solid tumors	With RO7009789 (Anti-CD40 antibody)	NCT02665416	January 15, 2016
Vadimezan/5,6-dimethylxanthenone-4-acetic acid (DMXAA) (Vasculature-disrupting agent)	Swiss Group for Clinical Cancer Research	2 Completed	Lung cancer	With carboplatin and paclitaxel	NCT01057342	January 26, 2010
PI3kγ inhibitor						
Duvelisib/IPI-549 (Oral PI3kδ/γ inhibitor)	Infinity Pharmaceuticals Inc.	1 Ongoing	Advanced solid tumors, non-small cell lung cancer (NSCLC), melanoma, or squamous cell cancer of the head and neck	With Nivolumab (Anti-PD-1 antibody)	NCT02637531	December 16, 2015

Source: clinicaltrials.gov, www.cancer.gov

This compilation highlights the recently-initiated clinical trials with emphasis on combination therapy.

"Ongoing" includes both recruiting and non-recruiting stages.

* Approved for use in combination with G-MCSF to mobilize hematopoietic stem cells to peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma.

Adv Drug Deliv Rev. Author manuscript; available in PMC 2018 May 15.