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Development and translation of novel therapeutics targeting tumor-associated macrophages

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Abstract

Tumor-associated macrophages (TAMs) regulate an array of tumor functions and have critical roles in both the progression as well as the eradication of cancer. Numerous therapies targeting TAMs are under development in cancer and many have demonstrated success at the preclinical and clinical levels. Most of these therapies fall within three main categories: systemic depletion of TAMs, inhibition of TAM recruitment and polarization, and promoting the anti-tumor functions of TAMs. In this article, the rationale behind these various therapies and approaches are reviewed along with supporting preclinical and clinical data.

Introduction:

Macrophages are myeloid immune cells with integral roles in a wide range of physiologic processes. Within these roles, macrophages can perform a diverse range of functions including matrix remodeling, growth factor secretion, angiogenesis, pathogen eradication and immune regulation[1–42,5–7]. In cancer, this broad functional capacity enables critical roles in both tumor progression and tumor destruction. These roles are dependent on their phenotype, which are grouped into two main categories, termed M1 and M2. M1 macrophages support tumor eradication through stimulation of innate and adaptive immune responses. M2 macrophages promote tumor growth, invasion, and therapeutic resistance through their roles in growth factor secretion, angiogenesis, and immune suppression. Within the tumor microenvironment (TME), the phenotype of these tumor-associated macrophages (TAMs) is regulated in large part by an array of factors, which are secreted by tumor, immune and stromal cells as well as physical interactions with the extracellular matrix (ECM).

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In both solid and hematologic malignancies, the extent of TAM infiltration within the TME as well as the predominant TAM phenotype has direct correlation with patient outcomes[8]. In cancers where TAMs are predominantly of the M2 phenotype, increased TAM infiltration is associated with more advanced disease at diagnosis as well as worse progression free and overall survival[9]. However, when TAMs are skewed more towards an M1 phenotype, their infiltration is associated with better cancer-related outcomes, including a decreased risk of death.

Given their numerous tumor supportive functions, their potential anti-tumor properties, and their strong correlation with patient outcomes, TAMs represent an attractive therapeutic target with vast potential. An array of approaches for targeting TAMs in cancer are under investigation and have demonstrated success at both the preclinical and clinical levels.

Systemic Depletion of TAMs:

Several TAM-directed strategies have focused on the systemic depletion of monocyte/macrophage populations through the administration of compounds that have macrophage-selective toxicity. Among these is trabectedin, a DNA binding agent that promotes apoptosis of macrophages through TNF-related apoptosis-inducing ligand (TRAIL) receptors 1 and 2[10]. In both Europe and the US, trabectedin has been approved for treatment of sarcomas based on improvements in progression-free survival and clinical benefit rates. This therapy was overall well tolerated in phase III studies, with hematologic toxicity and transient transaminitis as the most frequent complications. Rates of alopecia, cardiotoxicity, and neurotoxicity were notably low. The macrophage-directed toxicity has been found to be a key component of the antitumor effect of trabectadin[10,11] and multiple clinical trials are now investigating trabectedin as an anti-neoplastic agent with a focus on its macrophage-mediated effects (Table 1).

Bisphosphonates are another class of drugs that induce macrophage apoptosis[12]. Their effect is mediated through multiple pathways, which include impairing mitochondrial function and inhibiting protein prenylation, both of which lead to induction of cellular apoptosis. While these agents have roles in the prevention of skeletal related events as anti-resorptive agents in multiple cancers including breast and prostate cancer, their impact on PFS and OS is limited. In an effort to maximize the antitumor activity of these agents, numerous approaches have been developed which enhance their macrophage toxicity. This includes the loading of bisphosphonates into liposomes, which are preferentially endocytosed by macrophages following systemic administration. In preclinical studies, which include murine teratocarcinoma models, this strategy has resulted in depletion of systemic and tumor macrophage populations with associated slowed tumor growth, decreased vascular density[13] and delayed tumor recovery from radiation[14].

Immunotherapy has also been utilized to target macrophages in cancer and has demonstrated success at the preclinical level. Legumain is an endopeptidase that is upregulated in M2 macrophages with little to no expression in M1 macrophages. Vaccination against legumain in murine cancer models has resulted in CD8-mediated depletion of M2 macrophages with resultant decreased metastatic burden and increased survival[1,15]. Other surface molecules

have also been targeted. Alemtuzumab, a monoclonal antibody directed against CD52, a surface glycoprotein expressed by monocyte/macrophage, has been found to induce complement-mediated lysis of monocytes *in vitro*. In a murine ovarian tumor model, administration of alemtuzumab resulted in decreased angiogenesis as well as slowed tumor growth[16].

Targeting Recruitment and Reprogramming:

Aiming to limit or even alter the role of macrophages within the TME, multiple TAM-directed strategies have focused on targeting the pathways involved in TAM recruitment and polarization. One of the most extensively studied targets of macrophage recruitment is the CCL2. CCL2 is a chemokine that is secreted by cells within the TME that recruits TAMs into tumors through interaction with the macrophage CCR2 receptor. Targeting CCL2 has shown considerable promise at the preclinical level, resulting in enhanced tumor responses and improved survival through a reduction in TAM infiltration[17–20]. Other strategies targeting this pathway include inhibition of the CCR2 receptor on macrophages. This strategy offers theoretical benefit over CCL2-directed therapies as CCR2 is the receptor for multiple macrophage chemoattractant proteins and recruitment pathways. PF-04136309 is a potent antagonist of the CCR2 receptor that is currently under investigation as a cancer therapy. After successful preclinical evaluation, administration of PF-04136309 in combination with FOLFIRINOX chemotherapy resulted in objective response rates approaching 50% in a phase 1b study of patients with locally advanced pancreatic adenocarcinoma[21]. Additional trials targeting CCR2 in cancer patients are ongoing (Table 1).

The CSF-1 pathway is another target for TAM-directed therapies that has shown considerable promise in preclinical and clinical investigation. In addition to involvement in TAM recruitment, CSF-1 also promotes M2 polarization of TAMs within the TME. This pathway is of particular value as CSF-1R is expressed exclusively on myeloid cells and may potentially be targeted with lower toxicity. Numerous agents are under development targeting this pathway and preclinical studies have demonstrated efficacy in a range of cancers, including prostate, brain, breast, pancreas, ovaries, sarcomas, and hematologic malignancies[22–25]. A number of these therapies have been further evaluated at the clinical level and have already demonstrated anti-tumor efficacy. In early phase trials, emactuzumab (RG7155), a monoclonal antibody against the CSF-1R, elicited objective responses in up to 93% of patient with Diffuse-Type Giant Cell tumors[22]. Pexidartinib (PLX3397), a CSF-1R TKI, was also evaluated in patients with Diffuse-Type Giant Cell tumors in a phase I/II dose expansion study and objected responses were demonstrated in 52% of patients[26]. Based on this data, pexidartinib was granted breakthrough status by the FDA for treatment of patients with tenosynovial giant cell tumors.

CSF-1R targeted therapies such as GW2580 and pexidartinib, have been combined with chemotherapy in preclinical cancer models, including pancreatic and breast cancers. This combination resulted in an increase in cytotoxic immune responses, decreased metastases, and improved survival compared with chemotherapy alone[27–29]. Administration of pexidartinib has also improved the efficacy of immunotherapies, including adoptive cell-

transfer immunotherapy in melanoma and PDL-1 therapy in pancreatic cancer[30,31]. This exciting preclinical data has led to numerous clinical trials, which are currently investigating combinations of CSF-1 directed therapies with hormone therapies, chemotherapies, and immunotherapy (Table 1). Specific examples include NCT02452424, which is evaluating the combination pexidartinib and the immune checkpoint inhibitor, pembrolizumab, in a phase 1/2 trial of melanoma and other solid tumors. Checkpoint inhibitors, which promote antitumor immune responses, have gained considerable momentum recently due to their ability to induce durable responses and improve survival in a range of cancers. This trial and others, such as NCT02777710, evaluating pexidartinib in combination with durvalumab in pancreas and colon cancers, and NCT02323191, evaluating RG7155 in combination with atezolizumab in solid tumors, are seeking to enhance the effectiveness of these checkpoint inhibitors through the combinatorial targeting of macrophages, which are well known suppressors T-cell immune responses.

In addition to systemic therapies, radiation therapy is also augmented by the administration of CSF-1 directed therapies. In murine cancer models, tumor responses were significantly improved when CSF-1 therapies were combined with XRT[32,33]. In a glioblastoma model, this combination even resulted in improved survival compared with XRT alone. The combination of pexidartinib and XRT is now also being evaluated in NCT01790503, which is combining pexidartinib with standard of care radiation and temozolamide (chemotherapy) in patients with newly diagnosed glioblastoma (Table 1).

Rather than blocking M2 polarization, another approach to reprogramming macrophages is to utilize therapeutic agents that promote M1 polarization. In clinical trials, administration of IFN-γ, which has been shown to stimulate transformation from M2 to M1 in vitro, resulted in objective responses in minimal residual ovarian cancer[34–36]. Therapies that activate CD40 have upregulated MHC class II and CD86 on macrophages in a mouse model of pancreatic cancer along with increased systemic levels of M1 cytokines[37]. Furthermore, when a fully human CD40 agonist antibody CP-870,893 was administered in combination with gemcitabine chemotherapy in a phase I trial for patients with pancreatic cancer, partial responses were identified in approximately 20% of patients[38].

In genitourinary cancers, numerous studies have also demonstrated a promising role for targeting macrophage recruitment/reprogramming and this has led to further research at both the preclinical and clinical levels. Combining GW2580, a CSF-1R kinase inhibitor, with hormonal therapy (enzalutamide) resulted in slowed tumor growth and delayed development of therapeutic resistance in a murine prostate cancer model[23]. The combination of hormone therapy with CSF-1 directed therapy is now being investigated at the clinical level in NCT02472275. This trial combines pexidartinib with anti-androgen therapy in patients with prostate cancer without distant metastases. CSF-1 directed therapies (pexidartinib) have also been shown to improve the efficacy of radiation therapy in prostate cancer. In these mice, the addition of pexidartinib decreased macrophage infiltration following radiotherapy and slowed the growth of tumors[32].

Other investigated approaches that have demonstrated success in genitourinary cancers include the targeting of macrophage recruitment. The CCL2 inhibitor, carlumab,

demonstrated efficacy in numerous preclinical studies, leading to the evaluation of this therapy at the clinical level[17–19]. Phase I and phase II trials have investigated carlumab as both a monotherapy in prostate cancer and in combination with chemotherapy in a range of malignancies[20]. Although these trials failed to demonstrated antitumor responses, CCL2 levels were noted not to be effectively suppressed following carlumab administration. Thus, the limited efficacy of carlumab in the clinical setting may have been primarily driven by suboptimal pharmacokinetics or ineffective dosing.

Supporting the Anti-Tumor Functions of TAMs:

Direct phagocytosis of malignant cells is an important mechanism of TAM-mediated tumor eradication[25]. Unfortunately, tumor cells are able to avoid this method of destruction through upregulation of surface receptors, such as CD47, which inhibit macrophage phagocytic activity[39]. Multiple therapies are under development, which target this defense mechanism by tumors. This includes monoclonal antibodies, which can block surface CD47. At the preclinical level, administration of these agents has resulted in increased macrophage phagocytosis as well as impressive anti-tumor effect in both solid and hematologic malignancies. Included among these is bladder cancer, which has been found to express high levels of CD47. In *in vitro* models using human bladder cancer cells, blocking CD47 increased the phagocytosis of these cells by macrophages[40]. Clinical investigation of these agents in a range of cancers is now under way (Table 1).

Discussion:

While tumor-directed therapies, such as hormone therapies, chemotherapies, and radiation therapies remain the foundation of cancer treatment, therapies that target the TME are rapidly becoming an invaluable component of oncologic care. This includes genitourinary malignancies, where a number of these therapies are now standard of care and even frontline treatments. Notable examples include checkpoint inhibitors in renal and bladder cancers, anti-angiogenic agents in renal cell carcinoma, and sipuleucel-T in prostate cancer. The continued development of novel, TME-directed therapies holds great potential for the further advancement of cancer treatment and TAMs, which are an integral component of the TME, are a promising target. Numerous therapies targeting TAMs have already demonstrated success at the preclinical level in cancers of renal, bladder, prostate, and testicular origin. The effective clinical translation of these therapies will rely on identifying the contexts of use for which these therapies are able to improve patient outcomes, such as disease morbidity, PFS, and OS, as well as optimizing dosing to achieve maximum biologic effect.

In evaluating for the most effective contexts of use for TAM-directed therapies, key questions that must be addressed by current and future trials include: in which cancers will TAM-directed therapies improved patient outcomes, in which stage of disease (i.e. localized, locally advanced, metastatic) are they most effective, where do TAM-directed therapies fit best among the current sequencing of therapies, and should these therapies be administered as a monotherapy or can they be combined with other therapeutic modalities for maximum efficacy? Many early phase clinical trials are currently investigating TAM-directed therapies through cohort designs, which include patients with a wide range of solid and hematologic

malignancies. This strategy provides a convenient and cost-effective way to screen these drugs in an array of cancers and may potentially identify useful roles for TAM-directed therapies. Caution in the interpretation of these results, however, must be exercised as often times in these types of trials, very limited numbers of patients in each cancer type are exposed to a drug that may not be optimally dosed. In this setting, it can be easy to miss a potentially valuable role for these agents if there are not enough patients or if the signal isn't strong enough in the small number of patients who were treated. Disease-focused phase II and III trials are therefore also needed, particularly in GU malignancies where immunotherapies have already demonstrated efficacy at the clinical level.

Successful clinical translation of TAM-directed therapies will also include identifying whether each agent should be utilized as a monotherapy or if they can be more effective as part of a combination approach with hormonal therapies, chemotherapies, radiation therapies, or immune therapies. The majority of clinical trials now under way are investigating TAM-directed therapies alone and in combination with other modalities. They key for these trials moving forward will need to be a continued focus on rational therapeutic combinations. Important questions should focus on where mechanisms of resistance for these therapies lie. Many clinical trials are addressing this question from the standpoint of traditional therapies, which are known to have resistance mechanisms that are mediated by TAMs. However, a focus on the resistance pathways for TAM-directed therapies is also important, such as how PDL-1 expression by macrophages may limit immune-mediated depletion of TAMs. Future trials will need to focus on these questions at the preclinical level as well as in clinical trials.

Furthermore, it is critical to address where TAM-directed therapies fit within the sequencing of therapies for each cancer. Rational arguments can certainly be made that TAM-directed therapies have the potential to be effective throughout the stages of disease treatment. However, in genitourinary cancers, there is compelling data that these therapies may be able to play a particularly influential role when administered early on in cancer treatment. In prostate cancer, the development of castrate-resistant disease is a critical phase of disease progression, which signifies the development of more aggressive, treatment resistant disease and poorer prognosis for patients. Escamilla et al. demonstrated that in murine models of prostate cancer, the administration of TAM-directed delayed the development of castrate-resistance[23]. Studies such as this one provide strong rationale for administering TAM-directed therapies up front in the treatment of patients with prostate cancer as a strategy to prevent or delay the development of castrate-resistant disease and improve both morbidity and mortality. In other cancers, such as renal cell carcinoma and urothelial bladder cancer, immune checkpoint inhibitors are gaining approval for use in earlier lines of treatment, including in the first line. Zhu et al. demonstrated that TAM-directed therapies can improve the efficacy of these checkpoint inhibitors[31]. Given the potential of checkpoint inhibition to induce complete and durable responses in patients, combining TAM-directed therapies early in the course of the disease may ultimately be able to increase the number of patients who experience these impressive responses and dramatically delay the need for subsequent therapies.

While the inclusion of a broad range of malignancies can be an effective strategy for identifying contexts of use, most of these trials are still relying on traditional dosing strategies such as dosing to the maximum tolerated dose. Unfortunately, in the age of biologic therapies, this type of trial design frequently fails to identify the most effective therapeutic doses. In the case of carlumab, the phase II trial evaluating this medication in men with metastatic prostate cancer failed to demonstrate a significant antitumor effect. The dosing of carlumab in this trial, however, was derived from the highest doses investigated in phase I trials despite the fact that this dose was noted to ineffectively neutralize CCL2 in patients[41]. In the phase I study, this predefined maximal dose of 15 mg/kg every 2 weeks was based on a number of factors including pharmacokinetics and preclinical data. This dose, however, was ultimately not found to be the maximum tolerated dose based on safety and tolerability analysis in the trial. While the authors did consider evaluating higher doses of carlumab, due to preclinical data in non-human primates demonstrating ineffective suppression of CCL2 even at considerably higher doses, this investigation was ultimately not pursued. It is therefore not known if higher doses of carlumab could be tolerable as well as effectively suppress CCL2 and/or improve patient outcomes. Carlumab still holds considerable promise for the treatment of prostate cancer and future clinical trials must identify doses that are biologically relevant and able to improve patient outcomes. Biomarkers, in particular those that are predictive or pharmacodynamic, can be an invaluable asset in this pursuit. For carlumab, titrating the dose to demonstrated suppression of systemic CCL2 will be an important next step in the clinical investigation of this drug and one that may ultimately identify a role for this therapy in cancer treatment. The development and validation of biomarker assays will certainly be a critical step in this process and the focus of such research should include the biologic relevance of the assays as well as reliability and reproducibility[42].

Bisphosphonates are another example of the importance of dosing. In clinical trials, these medications have had little to no anti-tumor activity despite demonstrated efficacy at the preclinical level. However, the dosing for bisphosphonates in these trials were based on approved dosing for prevention of bone resorption and not for anti-tumor activity. As a consequence, this strategy resulted in far lower and less frequent exposure to active drug than has been shown to be effective at the preclinical level. Thus, the limited anti-tumor effect in patients may also be attributable to how this medication is administered and not a lack of biologic efficacy. Therefore, tailoring the dosing to the context of use (ie treatment of cancer) with higher or more frequent dosing may lead to a more effective role for these agents in cancer treatment.

Continued development of novel TAM-directed therapeutic strategies is critical as well.An array of alternative targets, such as IL-4, CXCL12/CXCR4, Toll-like receptor (TLR), STAT3, STAT6, anti-phosphatidylserine antibodies, Nrp1 [28,43–47] are under investigation. The identification of high-value therapeutic targets with robust likelihood of clinical translation will be supported by improved TME modeling *in vitro*. The TME is a complex, multicellular environment governed by coordinated signaling pathways. Investigation and analysis of such a multifaceted environment is limited by traditional preclinical platforms, such as mouse models and commercial cell culture devices, which have a restricted ability to model and analyze such a multifaceted environment. An array of new tools such as

microfluidic cell culture platforms are under development, which have the capacity for multicellular tumor modeling in both 2D and 3D using primary, patient-derived cells. These platforms, as well as others in development, hold great potential for future drug development, which will ultimately be realized through high quality translational research.

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Highlights

- Tumor-associated macrophages (TAMs) have critical roles in cancer
- Therapies targeting TAMs are in development at the preclinical and clinical level
- This review summarizes current data and ongoing trials for TAM-directed therapies

Table 1.

Ongoing clinic trials for TAM-targeted agents

Target	TAM-Directed Therapy	Cancer	Combination Therapy	Phase	Trial
TRAIL 1,2	Trabectedin	Sarcoma	-	2	NCT03397186
		Mesothelioma	-	2	NCT02194231
CCR2	PF-04136309	Pancreatic	Nab-Paclitaxel/ Gemcitabine	1 b/2	NCT02732938
CCR2/5	BMS 813160	Pancreatic	Nivolumab/Gemcitabine/Nab-paclitaxel	1/2	NCT03496662
CSF-1R	Pexidartinib	Solid Tumors	PLX9486	1/2	NCT02401815
		Solid Tumors	-	1	NCT01004861
		Solid/Hematologic	-	1/2	NCT02390752
		Melanoma	-	1/2	NCT02975700
		Glioblastoma	Radiation/Temozolamide	1/2	NCT01790503
		Pancreatic/Colon	Durvalumab	1	NCT02777710
		Breast	Eribulin	1/2	NCT01596751
		Prostate	Antiandrogen/Hormone	1	NCT02472275
		Peripheral Nerve Sheath Tumors	Sirolimus	1/2	NCT02584647
		Melanoma	Pembrolizumab	1/2	NCT02452424
		Melanoma	-	2	NCT02071940
		Solid Tumors	Atezolizumab	1	NCT02323191
	RG7155	Female Genital	Paclitaxel/Bevacizumab	2	NCT02923739
		Female Genital	Paclitaxel/Bevacizumab	2	NCT02923739
CD40	CP-870,893	Melanoma	Tremelimumab	1	NCT01103635
CD47	CC-90002	Hematologic	-	1	NCT02641002
		Solid/Hematologic	Rituximab	1	NCT02367196
	Hu5F9-G4	Solid/Hematologic	-	1	NCT02678338
	TTI-621	Hematologic	Rituximab/PD-1 Inhibitor/Proteasome Inhibitor	1	NCT03530683
		Solid/Hematologic	Rituximab/Nivolumab	1	NCT02663518
	SRF231	Solid/Hematologic	-	1	NCT03512340
	ALX148	Solid/Hematologic	Rituximab/Trastuzumab/Pembrolizumab	1	NCT03013218
	Hu5F9-G4	Hematologic	Azacitidine	1	NCT03248479
		Solid Tumors	Cetuximab	1/2	NCT02953782