Potential Multiple Myeloma Therapeutic Strategies through Targeting Macrophages and Mesenchymal Stromal Cells

William Hu

Abstract:

Multiple Myeloma (MM), a bone marrow plasma cell hematopoietic cancer, remains a critical but incurable hematological malignancy, prone to deadly relapses even after existing treatment. Traditionally anti-tumor macrophages that home to the cancerous bone marrow are polarized into pro-tumor myeloma-associated macrophages. These myeloma-associated macrophages then play an important role in supporting multiple myeloma by enabling drug resistance, improved growth, angiogenesis and protection. Several treatments in development aim to sever the supportive link between myeloma-associated macrophages and MM by blocking signaling pathways, destroying or repolarizing macrophages and even preventing macrophage polarization in the first place. Careful study is needed to improve the reliability of these myeloma-associated macrophage treatments in order to reduce MM relapse and comprehensively treat this cancer.

Keywords:

Multiple myeloma, bone marrow, tumor associated macrophage, mesenchymal stromal cell, clodronate liposomes

Introduction:

MM is the 2nd most common hematological disease in the US and makes up 14.7% of worldwide hematological cancer cases.[1] It is an incurable hematopoietic plasma cell malignancy that causes 98,000 deaths and 139,000 diagnoses per year.[2] Existing treatments (e.g. immunotherapy and chemotherapy, thalidomide analogs, proteasome inhibitors) only delay the mortality by an average of 6 years. Ultimately patients suffer from renal insufficiency, bone lesions, hypercalcemia and anemia, leading to relapses (average refractory MM median survival is only 5-15 months) and death.[3]

---

[1] Bristol Myers Squibb. (n.d.). *Blood Cancers*. Retrieved from https://www.bms.com/assets/bms/us/en-us/pdf/Disease-State-Info/blood-cancers-at-a-glance.pdf; American Society of Clinical Oncology. (n.d.). *Multiple Myeloma: Statistics*. Cancer.Net. Retrieved from https://www.cancer.net/cancer-types/multiple-myeloma/statistics

[2] Kuehl WM , Bergsagel PL . Molecular pathogenesis of multiple myeloma and its premalignant precursor . J Clin Invest 2012 ; 122 : 3456 – 3463. ;
Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011 ; 364 : 1046 – 1060. ; Rajkumar SV . Treatment of multiple myeloma . Nat Rev Clin Oncol 2011 ; 8 : 479 – 491.

[3] International Myeloma Working, G. (2003). Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: A report of the International Myeloma Working Group. British Journal of Haematology, 121(5), 749– 757. ;

One major reason for this unsatisfactory situation is that existing treatments do not adequately account for myeloma-associated macrophage and bone marrow (BM) mesenchymal stromal cells' (MSCs) contributions to myeloma cell survival. Macrophages and MSCs are essential components of the tumor microenvironment and important tumor progression mediators. Over the last decade, scientists have more clearly defined the ways macrophages and MSCs worsen cancer. However, further research is needed to achieve a deeper understanding of the exact methods of macrophage-MM support. This understanding can help scientists discover ways to break this link and improve MM patients' survival chances.

In this review paper, I summarize 5 ways macrophages support myeloma cell growth including:

1. Homing
2. Tumor cell growth/proliferation
3. Drug Resistance
4. Angiogenesis
5. Immune Suppression.

I then explain 6 potential solutions to halt macrophage support for myeloma:

1. Clodronate Liposome Treatment
2. Colony Stimulating Factor 1 Receptor (CSF1R) Blockade
3. Restore Phagocytosis
4. Inhibit Polarization
5. Repolarization
6. Inhibit Monocyte Recruitment

Background: How Myeloma associated Macrophages Support MM Tumorigenesis

Monocytes normally polarize into 2 types of macrophages: M1 and M2.M1 macrophages (polarized by LPS and IFN-y) are at the forefront of fighting pathologen. M1 cells release IL1, IL6, IL8, IL12 and TNFa to promote inflammation, they secrete nitric oxide synthase and reactive oxygen species to destroy cancerous cells and they present antigens to activate anti tumor immune response.

By contrast, M2 macrophages (polarized by IL4) exert healing and immunosuppressive functions. M2 cells release VEGF and TGF-b to activate fibroblasts and contribute to wound healing. When macrophages are polarized into M2 after the infection is controlled, they can be helpful in reducing inflammation and bringing surrounding tissue back to normality. When polarized into M2 within the tumor microenvironment, however, M2 macrophages inadvertently strengthen tumor cell survival, proliferation and growth, ultimately contributing to tumorigenesis.

Fonseca, R., Abouzaid, S., Bonafede, M., Cai, Q., Parikh, K., Cosler, L., & Richardson, P. (2017). Trends in overall survival and costs of multiple myeloma, 2000-2014. Leukemia, 31(9), 1915–1921. https://doi.org/10.1038/leu.2016.380.

MM cells hijack M2 macrophage function in order to strengthen the MM tumor. Myeloma cells recruit circulating monocytes to the myeloma microenvironment via monocyte attractant chemokines (CCL2, CSF-1, CXCL2, VEGF) and induce recruited monocytes to polarize into myeloma-associated macrophages.[4] Existing macrophages are also polarized from M1 into myeloma associated macrophage state. Myeloma associated macrophages function similarly to M2 macrophages, supporting growth rather then destroying cancerous cells (biomarkers: CD163, CD206, arginase expression).

Total BM macrophage count (including M1, M2 and myeloma associated types within) remains constant after patients develop MM.[5] However, IL4, IL13, IL10 and glucocorticoid signaling in the cancerous bone marrow causes the percentage and total number of myeloma associated macrophages to increase compared to M1 macrophages.[6] This is indicated by increased presence of M2 macrophage markers CD206+ and CD163.[7] In fully formed MM, myeloma cells make up 30% of the bone marrow and the myeloma associated macrophages supporting them make up another 10%.[8]

How Myeloma-associated Macrophages Support MM:

Consequently, M2 macrophages become critical to enabling MM survival through five main pathways: homing to the BM, tumor cell growth, drug resistance, angiogenesis and immune suppression.

1. Homing: BM Macrophages produce IGF-1, CCL2, CCL3 and IL8 chemotactic factors that, along with CXCL12/CXCR4 signaling from stromal cells, induce MM cells to migrate to the BM and adhere to endothelial cells.[9] In return, MM cells produce chemotactic factors that induce macrophage migration to the BM. This homing concentrates MM cells and macrophages into one microenvironment.

2. Myeloma-associated Macrophages release IL6, IL10, IL 1 beta, VEGF, TGF-b and IGF-1. These cytokines upregulate the JAK/STAT3 signaling pathway, which ultimately induces MM cell proliferation and promotes MM cell growth and survival.[10] Some of these cytokines also upregulate production of other related cytokines (e.g. IL6 leads to more IL10 production), amplifying the effect.[11]

   This correlation between myeloma associated macrophage presence and MM cell development has been proven through several studies. A 2020 National and Kapodistrian University of Athens study shows that the presence of myeloma-associated macrophages are one of the markers most correlated with patients failing to achieve cancer remission.[12] Furthermore, A 2014 Aarhus University experiment shows that the presence of soluble CD163 (a myeloma associated macrophage marker) in a patient's serum is associated with poor survival rates.[13]

3. Drug Resistance: Standard MM treatment drugs like melphalan, bortezomib, dexamethasone and lenalidomide directly destroy MM cells via inducing apoptosis.

Macrophages (especially M2) protect against this effect by emitting B cell activating factor(BAFF) cell survival factor via direct contact through the P-selectin ligand.[14] BAFF inhibits apoptotic signaler function to prevent MM cells from apoptosing. Furthermore, myeloma associated macrophages secrete IL-1B, which promotes increased MM stem cell differentiation.

4. Angiogenesis: Macrophages produce IL10, FGF2, MMPs, CCLs and most significantly: VEGF, which cause themselves (macrophages) to express VWK, TEK and VEGFR2 genes.[15] Expression of these genes allows macrophages (e.g. GFP+, Tie2+ types) to mimic vascular tissue (forming capillary-like vessels) and bring nutrients to the tumor. Other macrophage released molecules like iNOS (increases blood flow to tumor) and TNF alpha (remodels blood vessels) improve angiogenesis. This means the MM cancer tumor receives more nutrients and oxygen via blood, increasing its growth and diverting resources away from normally functioning cells.

   Several studies demonstrate myeloma associated macrophages' roles in angiogenesis. A 2015 San Raffaele Scientific Institute study demonstrated that specific macrophage types, like CD206+ and Tie2+ expressing macrophages are correlated with an increase in microvessel density and angiogenesis-supporting cytokines.[16] Likewise, a University Hospital of Heraklion experiment in the same year showed that IL10 produced by myeloma associated macrophages is correlated with more angiogenic cytokine presence.[17] An in vitro study has also shown that both myeloma cells themselves and associated macrophages can promote human umbilical vein endothelial cell growth.[18] This lends credence to the idea that in vivo myeloma associated macrophages can promote vascular endothelial cells growth to bring blood vessels into the tumor.

5. Immune Suppression: When macrophages arrive in the BM tumor microenvironment, they (macrophages) lose the ability to present antigens, phagocytize and stimulate the adaptive immune response.

   How exactly does immunosuppression occur? Macrophages in the tumor microenvironment expresses Indoleamine 2,3-dioxygenase (IDO) and Interleukin 10 (IL10). IDO inhibits effector T cell function and promotes differentiation of T regulatory cells (which suppress phagocytosis) by degrading the tryptophan amino acid. IL10 in turn inhibits expression of MHC class 2, a lymphocyte surface protein critical to presenting antigens and alerting adaptive immunity. IL10 also increases cytotoxic T cell factor (e.g. granzyme B, IFN-y, eomesodermin), expression.

   Both IDO and IL10 function leads to less effector T cell activation and a weaker adaptive immune response against cancer, benefiting the tumor.[19] In addition, MM cells themselves express CD47 which inhibits phagocytosis.

Mesenchymal Stromal Cell Role:

Mesenchymal Stromal Cells(MSCs) provide contact-mediated support for MM via cytokines like IL-6, VEGF-a, IGF-1, CCL5, Interferon y and help MM development via cell adhesion.[20] MSCs also polarize macrophages into MSC-activated macrophages (express more IL10, IL6, less IL12, TNF-a).[21] The newly polarized myeloma associated macrophages display characteristics between M1 and M2 macrophages and promote angiogenesis and reduce LPS responsiveness.[22]

Myeloma-associated macrophages in return provide enhanced motility for MSCs and induce them to produce IL6, CCL5, Interferon-y. Myeloma cells also use TNF-alpha-mediated CCL2 induction to upregulate BM MSC function.[23]

Treatment Options:

How can medicine sever the support macrophages provide to MM and reduce minimal residual disease and relapse?[24] There are 6 potential solutions:

1. **Clodronate Liposome Treatment**

   Clodronate liposomes are double membranes containing a 5 mg/mL concentration of the drug clodronic acid (see Figure 1). When they are ingested to macrophages, these liposomes release the lethal clodronate drug, killing macrophages.[25] Clodronate liposomes can decrease both macrophage and myeloma 5TGM1 cell numbers, leading to decreased MM.

   For macrophages, clodronate liposome mediated treatment can cause body-wide macrophage depletion which leads to a >95% MM reduction vs the PBS control treatment[26]

   Clodronate liposome treatments have already been shown to decrease tumor expansion in other cancers (melanome, lymphoma, lung adenocarcinoma, ovarian).[26] This strengthens the case for using this treatment against multiple myeloma.

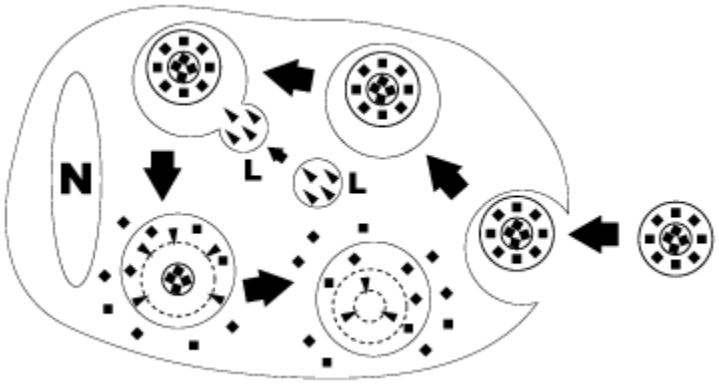

Figure 1: Clodronate Liposomes Function Lead to Macrophage Apoptosis After

Ingestion.

Double membraned liposomes containing the clodronate chemical lethal in high concentrations to macrophages are ingested by macrophages. The membrane lipids are digested by lysosome phospholipases, releasing clodronate. Once clodronate builds up to a certain concentration, it causes macrophage apoptosis.

2. **CSF1R Blockade**

Targeting or blocking the CSF1R (colony stimulating factor 1 receptor, see Figure 2) can decrease CD68+, CD103+ levels and restore macrophage apoptosis.[27] Two main methods of blocking CSF1R are 1) monoclonal anti-CSF1R like emactuzumab, CS7, IMC-CS4 and 2) CSF1R pharmacological inhibitors like ARRY382, JNJ-40346527, BLZ945. A 2018 preclinical study found CS7 can significantly reduce tumor burden.[28]

There are two things to note about CSF1R inhibition. Firstly, CSF1R inhibition has few toxic side effects, reducing patient harm. Secondly, CSF1R inhibitors work best when they are combined with drugs like bortezomib or melphalan, meaning they won't interfere with other treatment's function.[29]

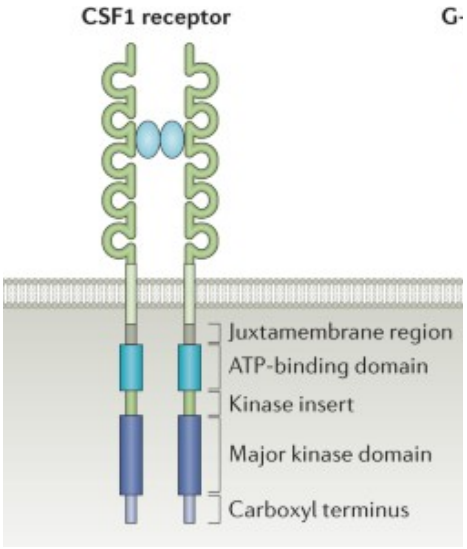

Figure 2: Structural Diagram of Colony Stimulating Factor 1 Receptor

3. **Repolarization**

Repolarizing M2 macrophages back to M1 via low doses of anti-CSF1R antibody CS7, Jak1/2 inhibitors (like ruxolitinib) or CRISPR/Cas9 reprogramming along with CD40 priming and TLR triggering can reduce M2 macrophage numbers.[30] This reduction is accompanied by an increase in M1 macrophages, leading to a beneficial CD4+ T cell immune response.

However, existing research on this method has been *in vitro* or using *in vivo* xenografts. Additional in vitro studies are needed to determine viability.

4. Restore Phagocytosis

Anti-CD47 antibodies (like Hv5F9-G4) can restore macrophages' ability to phagocytose MM cells like normal. These antibodies will inhibit “don’t eat me” signals and block the CD47 immune checkpoint protein.[31]

This method has led to reductions in other cancers like acute myeloid leukemia, non-Hodgkin lymphoma, pancreatic cancer and small lung cancer, indicating potential viability against MM.

Hv5F9-G4 currently has the most potential - it is entering phase 2 clinical trials.

5. Inhibit Polarization

Halting signals that shift macrophages to M2, keeping them as M1 macrophages (via IL10 inhibitor, TPL2 kinase blockade). The Tumor Progression Locus 2 (TPL2) kinase protein (Figure 3) makes an especially ideal target due to its unique structure in its ATP binding loop compared to other proteins which allows researchers to design specific proteins to target the kinase.[32]

TPL2 blocking molecules like luteolin have been in development for over a decade but further research to accurately determine the TPL2 crystal structure is needed.

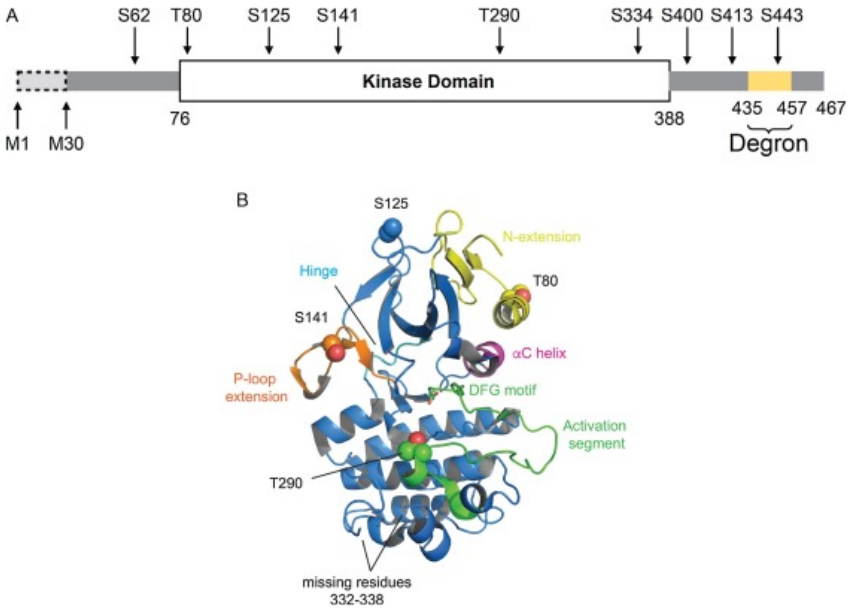

Figure 3: Tumor Progression Locus 2 Structure.

6. **Inhibit Monocyte Recruitment**

   Interfering with monocyte recruitment to the MM niche via CCL2-CCR2 axis inhibition.[33] Both CCR2 inhibitors and anti-CCL2 antibodies can achieve this function.

   CCR2 (C-Chemokine Receptor 2) is the receptor for CCL2 (C-Chemokine Motif Chemokine Ligand 2), a ligand released by monocytes to trigger their recruitment to the tumor and commonly in the myeloma BM vascular network. Research on CCR2/CCL2 inhibition has only recently entered the cancer field, but if proven, it could help MM recovery.

Conclusion:

Rather than solely focusing on tumor eradication, oncologists should also consider simultaneously targeting the myeloma-associated macrophages that provide cancer cells with support. Therefore, further research to clarify the efficacy of the above 6 treatments is needed.

Endnotes:

[1] Bristol Myers Squibb. (n.d.). *Blood Cancers*. Retrieved from https://www.bms.com/assets/bms/us/en-us/pdf/Disease-State-Info/blood-cancers-at-a-glance.pdf; American Society of Clinical Oncology. (n.d.). *Multiple Myeloma: Statistics*. Cancer.Net. Retrieved from https://www.cancer.net/cancer-types/multiple-myeloma/statistics

[2] Kuehl WM , Bergsagel PL . Molecular pathogenesis of multiple myeloma and its premalignant precursor . J Clin Invest 2012 ; 122 : 3456 – 3463. ;
Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011 ; 364 : 1046 – 1060. ; Rajkumar SV . Treatment of multiple myeloma . Nat Rev Clin Oncol 2011 ; 8 : 479 – 491.

[3] International Myeloma Working, G. (2003). Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: A report of the International Myeloma Working Group. British Journal of Haematology, 121(5), 749– 757. ;
Fonseca, R., Abouzaid, S., Bonafede, M., Cai, Q., Parikh, K., Cosler, L., & Richardson, P. (2017). Trends in overall survival and costs of multiple myeloma, 2000-2014. Leukemia, 31(9), 1915–1921. https://doi.org/10.1038/leu.2016.380.

[4] Pollard JW . Trophic macrophages in development and disease . Nat Rev Immunol 2009 ; 9 : 259 – 270.

[5] De Beule, N., De Veirman, K., Maes, K., De Bruyne, E., Menu, E., Breckpot, K., et al. (2017). Tumour-associated macrophage mediated survival of myeloma cells through STAT3 activation. The Journal of Pathology, 241(4), 534–546.https://onlinelibrary.wiley.com/doi/10.1002/path.4860

[6] Mantovani, A., Sica, A., Sozzani, S., Allavena, P., Vecchi, A., & Locati, M. (2004). The chemokine system in diverse forms of macrophage activation and polarization. Trends in Immunology, 25(12), 677–686. https://doi.org/10.1016/j.it.2004.09.015.

[7] Andersen, M. N., Abildgaard, N., Maniecki, M. B., Moller, H. J., & Andersen, N. F. (2014). Monocyte/macrophage-derived soluble CD163: A novel biomarker in multiple myeloma. European Journal of Haematology, 93(1), 41–47. https://doi.org/10.1111/ ejh.12296

[8] Zheng Y, Cai Z, Wang S, et al. Macrophages are an abundant component of myeloma microenvironment and protect myeloma cells from chemotherapy drug-induced apoptosis. Blood 2009;114:3625–8.

[9] Wang, Q., Lu, Y., Li, R., Jiang, Y., Zheng, Y., Qian, J., Bi, E., Zheng, C., Hou, J., Wang, S., & Yi, Q. (2018). Therapeutic effects of CSF1R-blocking antibodies in multiple myeloma. Leukemia, 32(1), 176–183. https://doi.org/10.1038/leu.2017.193.
[10] Wang et al. (2018). Therapeutic effects of CSF1R-blocking antibodies in multiple myeloma. Leukemia, 32(1), 176–183. https://doi.org/10.1038/leu.2017.193.
[11] Kim J, Denu RA, Dollar BA, et al. Macrophages and mesenchymal stromal cells support survival and proliferation of multiple myeloma cells. Br J Haematol 2012;158:336–46
[12] Papadimitriou K, Tsakirakis N, Malandrakis P, et al. Deep phenotyping reveals distinct immune signatures correlating with prognostication, treatment responses, and MRD status in multiple myeloma. Cancers 2020;12:3245.
[13] Andersen MN, Abildgaard N, Maniecki MB, et al. Monocyte/ macrophage-derived soluble CD163: a novel biomarker in multiple myeloma. Eur J Haematol 2014;93:41–7.
[14] Zheng, Y., Cai, Z., Wang, S., Zhang, X., Qian, J., Hong, S., Li, H., Wang, M., Yang, J., & Yi, Q. (2009). Macrophages are an abundant component of myeloma microenvironment and protect myeloma cells from chemotherapy drug-induced apoptosis. Blood, 114(17), 3625–3628. https://doi.org/10.1182/blood-2009-05- 220285.
[15] Sunderkotter, C., Goebeler, M., Schulze-Osthoff, K., Bhardwaj, R., & Sorg, C. (1991). Macrophage-derived angiogenesis factors. Pharmacology & Therapeutics, 51(2), 195–216. https://doi.org/10.1016/0163-7258(91)90077-y.
[16] Calcinotto A, Ponzoni M, Ria R, et al. Modifications of the mouse bone marrow microenvironment favor angiogenesis and correlate with disease progression from asymptomatic to symptomatic multiple myeloma. Oncoimmunology 2015;4:e1008850
[17] Alexandrakis MG, Goulidaki N, Pappa CA, et al. Interleukin-10 induces both plasma cell proliferation and angiogenesis in multiple myeloma. Pathol Oncol Res 2015;21:929–34
[18] Sun M, Qiu S, Xiao Q, et al. Synergistic effects of multiple myeloma cells and tumor-associated macrophages on vascular endothelial cells in vitro. Med Oncol 2020;37:99.
[19] Smith LK, Boukhaled GM, Condotta SA, et al. Interleukin-10 Directly Inhibits CD8+ T Cell Function by Enhancing NGlycan Branching to Decrease Antigen Sensitivity. Immunity 2018;48:299–312.
[20] Lewis JS , Landers RJ , Underwood JC , et al . Expression of vascular endothelial growth factor by macrophages is up-regulated in poorly vascularized areas of breast carcinomas . J Pathol 2000 ; 192 : 150 – 158
[21] Karin M , Greten FR . NF-kappaB: linking inflammation and immunity to cancer development and progression . Nat Rev Immunol 2005 ; 5 : 749 – 759.
[22] Lin EY , Pollard JW . Tumor-associated macrophages press the angiogenic switch in breast cancer . Cancer Res 2007 ; 67 : 5064 – 5066.
[23] Anton K , Banerjee D , Glod J . Macrophage-associated mesenchymal stem cells assume an activated, migratory, proinflammatory phenotype with increased IL-6 and CXCL10 secretion . PLoS One 2012 ; 7 : e35036.
[24] Chanan-Khan AA , Giralt S . Importance of achieving a complete response in multiple myeloma, and the impact of novel agents . J Clin Oncol 2010 ; 28 : 2612 – 2624
[25] Van Rooijen, N., & Sanders, A. (1994). Liposome mediated depletion of macrophages: mechanism of action, preparation of liposomes and applications. Journal of immunological methods, 174(1-2), 83-93.
[26] Shen, L., Li, H., Shi, Y. *et al.* M2 tumour-associated macrophages contribute to tumour progression via legumain remodelling the extracellular matrix in diffuse large B cell lymphoma. *Sci Rep* 6, 30347 (2016). https://doi.org/10.1038/srep30347 ;
Fritz, J. M., Tennis, M. A., Orlicky, D. J., Lin, H., Ju, C., Redente, E. F., Choo, K. S., Staab, T. A., Bouchard, R. J., Merrick, D. T., Malkinson, A. M., & Dwyer-Nield, L. D. (2014). Depletion of tumor-associated macrophages slows the growth of chemically induced mouse lung adenocarcinomas. *Frontiers in Immunology, 5*, 587. https://doi.org/10.3389/fimmu.2014.00587.

[27] Wang et al. (2018). Therapeutic effects of CSF1R-blocking antibodies in multiple myeloma. Leukemia, 32(1), 176–183. https://doi.org/10.1038/leu.2017.193.
[28] Wang et al. (2018). Therapeutic effects of CSF1R-blocking antibodies in multiple myeloma. Leukemia, 32(1), 176–183. https://doi.org/10.1038/leu.2017.193.
[29] Gomez-Roca, C. A., Italiano, A., Le Tourneau, C., Cassier, P. A., Toulmonde, M., D'Angelo, S. P., et al. (2019). Phase I study of emactuzumab single agent or in combination with paclitaxel in patients with advanced/metastatic solid tumors reveals depletion of immunosuppressive M2-like macrophages. *Annals of Oncology, 30*(8), 1381–1392. https://doi.org/10.1093/annonc/mdz163.
[30] Chen, H., Li, M., Sanchez, E., Soof, C. M., Bujarski, S., Ng, N., Cao, J., Hekmati, T., Zahab, B., Nosrati, J. D., Wen, M., Wang, C. S., Tang, G., Xu, N., Spektor, T. M., & Berenson, J. R. (2019). JAK1/2 pathway inhibition suppresses M2 polarization and overcomes resistance of myeloma to lenalidomide by reducing TRIB1, MUC1, CD44, CXCL12, and CXCR4 expression. *British Journal of Haematology, 188*, 283–294. https://doi.org/10.1111/bjh.16158.
[31] Ries, C. H., Cannarile, M. A., Hoves, S., Benz, J., Wartha, K., Runza, V., Rey-Giraud, F., Pradel, L. P., Feuerhake, F., Klaman, I., Jones, T., Jucknischke, U., Scheiblich, S., Kaluza, K., Gorr, I. H., Walz, A., Abiraj, K., Cassier, P. A., Sica, A., Gomez-Roca, C., de Visser, K. E., Italiano, A., le Tourneau, C., Delord, J. P., Levitsky, H., Blay, J. Y., & Rüttinger, D. (2014). Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer Cell, 25(6), 846–859. https://doi.org/10.1016/j.ccr.2014.05.016.
[32] Gantke T , Sriskantharajah S , Ley SC . Regulation and function of TPL-2, an IkappaB kinase-regulated MAP kinase kinase kinase . Cell Res 2011 ; 21 : 131 – 145
[33] Majeti R , Chao MP , Alizadeh AA , et al . CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells . Cell 2009 ; 138 : 286 – 299.