

## **Essay Title 7 – Dr Veenu Manoharan**

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The potential of therapeutic strategies targeting tumour associated phagocytic macrophages in the tumour microenvironment: a critical evaluation.

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In the complex landscape of the tumour microenvironment, tumour associated phagocytic macrophages (TAMs) have emerged as major players. They influence cancer progression and treatment outcomes (Basak et al., 2023). This critical literature review delves into the potential therapeutic avenues that target TAMs, attempting to recognise their multifaceted roles in tumour development, metastasis, and therapeutic resistance. TAMs have dynamic plasticity and diverse functional phenotypes, significantly impact immune responses. Examples include angiogenesis, tissue remodelling, and immune evasion mechanisms within the tumour milieu (Safir et al., 2023). Understanding the relationship between TAMs and the tumour microenvironment is vital in developing new strategies to reprogram TAM behaviour. This is done to enhance anti-tumour immune responses to existing therapies. This review will critically evaluate current research, exploring benefits, challenges, and limitations and aiming to find potential future research directions in cancer therapy.

One potential therapeutic strategy that stands out against TAMs is targeting the CSF1R signalling pathway. CSF1R plays a significant role by pulling macrophages to the tumour area and moulding them into TAMs (Moeller et al., 2023). In clinical trials, using AMG 820 to block CSF1R notably reduced the presence of immune suppressing TAMs in solid tumours. A genetic change in CSF1R makes it more responsive to CSF1R inhibitors (Papadopoulos et al., 2017). BLZ945 is a specific

CSF1R inhibitor. Experimental studies with BLZ945 demonstrated its ability to hinder TAM recruitment in breast and cervical cancers and restrain neuroblastoma growth (Webb et al., 2018).

Another Monoclonal antibody, RG7155, also deactivates CSF1R, reducing the number of specific macrophages in tumours and slowing cancer growth (Zhang and Mouldy Sioud, 2023). Yet, using only CSF1R blockers to treat tumours showed limited success in mouse studies and human trials. Combining these blockers with chemotherapy or checkpoint inhibitors significantly enhanced their effectiveness (Cannarile et al., 2017).

In pancreatic cancer studies, CSF1R blockers helped macrophages present antigens and prompted T cells to combat tumours (Zhu et al., 2014). However, CSF1R inhibitors increased the PD-1 protein in these T cells, weakening the inhibitors' anti-tumour effect. Nevertheless, combining CSF1R blockers with ICB strengthened their effectiveness (Neubert et al., 2018).

In melanoma, CSF1 production correlated with CD8+ T cells and TAM abundance. Combining anti-PD1 and anti-CSF1R antibodies led to mouse melanoma regression by eliminating tumour associated macrophages (Reis-Sobreiro et al., 2021).

However, while targeting CSF1R to tackle TAMs seems promising, it has shown limited effectiveness against tumours (Mar et al., 2023). A challenge arises from how tumour cells, via CSF1, limit granulocyte migration to tumours. Combining CSF1R inhibitors with CXCR2 antagonists effectively blocked granulocyte infiltration and exhibited anti-tumour solid effects (Kumar et al., 2017).

Targeting chemokines is a crucial strategy to tackle TAMs in the tumour environment (TME). CCL2, for instance, brings in monocytes that transform into TAMs at the tumour site (Cendrowicz et al., 2021). When a protein like liver kinase B1 is not working right, it messes up CCL2 production, leading to more tumour macrophages. Stopping CCL2 release or using small molecule inhibitors for CCR2, a receptor for CCL2, can block macrophage entry into the TME (Tu et al., 2020).

Blocking the CCL2/CCR2 pathway in liver cancer helps the immune response against tumours. Zoledronic acid, a compound, can also cut CCL2 production in tumours, reducing TAMs and boosting killer T cells (Teng et al., 2016).

However, interrupting CCL2 might worsen metastasis. It can release monocytes from the bone marrow, amp up cancer cell movement from the primary tumour, form more blood vessels, and boost lung metastatic cell growth. This relies on IL-6 and VEGF-A (Batoon and McCauley, 2021).

CCL5, another chemokine, also recruits TAMs, promoting tumour spread. However, blocking its receptor with maraviroc or a protein inhibitor can limit this effect (Zhang et al., 2023). In colorectal cancer, macrophage made CCL5 helps cancer cells dodge the immune system through a specific pathway, significantly activated by macrophage infiltration caused by certain triggers in an animal model of CRC (Liu et al., 2019).

Clodronate, a chemical, can slash the number of TAMs in the TME. In trials, it wiped out these macrophages in mice with chronic hepatitis and HCC, seriously dropping F4/80+ cells in their livers and spleens (Wu et al., 2022). With subcutaneous melanoma, clodronate made tumours smaller and lowered F4/80 and  $\alpha$ -SMA

expression. In lung metastatic melanoma, it cuts the number of lung nodules and reduces F4/80+ cells and microvascular density (Comunanza et al., 2016).

Cancer has been seen to resist treatments due to factors like tumour hypoxia (low oxygen) and aerobic glycolysis. TAMs can promote these issues by releasing  $\text{TNF}\alpha$  for tumour cell glycolysis and amping up some other factors. Clodronate knocking out TAMs helped fix these problems, making tumours respond better to treatments (Chen et al., 2023).

Without tumour associated macrophages, cancer cells showed more PD-L1, and more T cells got into tumours. This made anti-PD-L1 antibodies work against tumours, which they could not do before (Pu and Ji, 2022).

Examining therapeutic strategies targeting tumour associated phagocytic macrophages in the tumour microenvironment reveals promising prospects for cancer treatment. Approaches like targeting chemokines, using clodronate for TAM depletion, and understanding TAM mediated resistance mechanisms demonstrate potential benefits (Anfray et al., 2019). These therapeutic strategies show efficiency in reducing TAM infiltration, altering tumour growth, and sensitising tumours to existing therapies, highlighting their significance in cancer treatment (Li et al., 2022).

Nevertheless, limitations persist within these studies. While TAM focused, therapies offer promise, their sole use might only partially eradicate tumours. Studies highlight complexities like potential exacerbation of metastasis upon treatment interruption and the need for combination therapies to maximise efficacy (Esposito et al., 2021). Moreover, various cancers might respond differently to TAM targeted treatments, necessitating tailored approaches (Krzyszczuk et al., 2018).

In conclusion, targeting TAMs presents a valuable therapeutic avenue for cancer treatment. Research gaps lie in clarifying TAM complexity, the long term effects of TAM focused treatments, and how existing therapies work together simultaneously. Overall, TAM directed strategies hold promise, yet a multifocal approach is vital for successful cancer therapy strategies. Further research understanding the complexities of TAM interactions and optimising combination strategies is crucial for realising their full potential in clinical settings.

## Reference list

Anfray, C., Ummarino, A., Andón, F.T. and Allavena, P. (2019). Current Strategies to Target Tumor-Associated-Macrophages to Improve Anti-Tumor Immune Responses. *Cells*, 9(1), p.46. doi:<https://doi.org/10.3390/cells9010046>.

Basak, U., Sarkar, T., Mukherjee, S., Chakraborty, S., Dutta, A., Dutta, S., Nayak, D., Kaushik, S., Das, T. and Sa, G. (2023). Tumor-associated macrophages: an effective player of the tumor microenvironment. *Frontiers in Immunology*, [online] 14. doi:<https://doi.org/10.3389/fimmu.2023.1295257>.

Batoon, L. and McCauley, L.K. (2021). Cross Talk Between Macrophages and Cancer Cells in the Bone Metastatic Environment. *Frontiers in Endocrinology*, [online] 12, p.763846. doi:<https://doi.org/10.3389/fendo.2021.763846>.

Cannarile, M.A., Weisser, M., Jacob, W., Jegg, A.-M., Ries, C.H. and Rüttinger, D. (2017). Colony-stimulating factor 1 receptor (CSF1R) inhibitors in cancer therapy. *Journal for ImmunoTherapy of Cancer*, 5(1). doi:<https://doi.org/10.1186/s40425-017-0257-y>.

Cendrowicz, E., Sas, Z., Bremer, E. and Rygiel, T.P. (2021). The Role of Macrophages in Cancer Development and Therapy. *Cancers*, 13(8), p.1946. doi:<https://doi.org/10.3390/cancers13081946>.

Chen, Z., Han, F., Du, Y., Shi, H. and Zhou, W. (2023). Hypoxic microenvironment in cancer: molecular mechanisms and therapeutic interventions. *Signal Transduction and Targeted Therapy*, 8(1). doi:<https://doi.org/10.1038/s41392-023-01332-8>.

Comunanza, V., Corà, D., Orso, F., Consonni, F.M., Middonti, E., Di Nicolantonio, F., Buzdin, A., Sica, A., Medico, E., Sangiolo, D., Taverna, D. and Bussolino, F. (2016). VEGF blockade enhances the antitumor effect of BRAF<sup>V 600E</sup> inhibition. *EMBO Molecular Medicine*, [online] 9(2), pp.219–237. doi:<https://doi.org/10.15252/emmm.201505774>.

Esposito, M., Ganesan, S. and Kang, Y. (2021). Emerging strategies for treating metastasis. *Nature Cancer*, 2(3), pp.258–270. doi:<https://doi.org/10.1038/s43018->

[021-00181-0.](#)

Krzyszczczyk, P., Acevedo, A., Davidoff, E.J., Timmins, L.M., Marrero-Berrios, I., Patel, M., White, C., Lowe, C., Sherba, J.J., Hartmanshenn, C., O'Neill, K.M., Balter, M.L., Fritz, Z.R., Androulakis, I.P., Schloss, R.S. and Yarmush, M.L. (2018). The growing role of precision and personalized medicine for cancer treatment. *TECHNOLOGY*, [online] 06(03n04), pp.79–100. doi:<https://doi.org/10.1142/s2339547818300020>.

Kumar, V., Donthireddy, L., Marvel, D., Condamine, T., Wang, F., Lavilla-Alonso, S., Hashimoto, A., Vonteddu, P., Behera, R., Goins, M.A., Mulligan, C., Nam, B., Hockstein, N., Denstman, F., Shakamuri, S., Speicher, D.W., Weeraratna, A.T., Chao, T., Vonderheide, R.H. and Languino, L.R. (2017). Cancer-Associated Fibroblasts Neutralize the Anti-tumor Effect of CSF1 Receptor Blockade by Inducing PMN-MDSC Infiltration of Tumors. *Cancer Cell*, 32(5), pp.654-668.e5. doi:<https://doi.org/10.1016/j.ccell.2017.10.005>.

Li, Y., Chen, Z., Han, J., Ma, X., Zheng, X. and Chen, J. (2022). Functional and Therapeutic Significance of Tumor-Associated Macrophages in Colorectal Cancer. *Frontiers in Oncology*, 12. doi:<https://doi.org/10.3389/fonc.2022.781233>.

Liu, C., Yao, Z., Wang, J., Zhang, W., Yang, Y., Zhang, Y., Qu, X., Zhu, Y., Zou, J., Peng, S., Zhao, Y., Zhao, S., He, B., Mi, Q.-Y., Liu, X., Zhang, X. and Du, Q. (2019). Macrophage-derived CCL5 facilitates immune escape of colorectal cancer cells via the p65/STAT3-CSN5-PD-L1 pathway. *Cell Death & Differentiation*, [online] 27(6), pp.1765–1781. doi:<https://doi.org/10.1038/s41418-019-0460-0>.

Mar, del, Schlom, J. and Hamilton, D.H. (2023). Blockade of tumor-derived colony-stimulating factor 1 (CSF1) promotes an immune-permissive tumor microenvironment. *Cancer Immunology, Immunotherapy*, [online] 72(10), pp.3349–3362. doi:<https://doi.org/10.1007/s00262-023-03496-2>.

Moeller, A., Kurzrock, R., Botta, G.P., Adashek, J.J., Patel, H., Lee, S., Pabla, S., Nesline, M.K., Conroy, J., Sicklick, J.K. and Kato, S. (2023). Challenges and prospects of CSF1R targeting for advanced malignancies. *American journal of cancer research*, [online] 13(7), pp.3257–3265. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10408490/> [Accessed 8 Dec. 2023].

Neubert, N.J., Schmittnaegel, M., Bordry, N., Nassiri, S., Wald, N., Martignier, C., Tillé, L., Homicsko, K., Damsky, W., Maby-El Hajjami, H., Klamann, I., Danenberg, E., Ioannidou, K., Kandalaft, L., Coukos, G., Hoves, S., Ries, C.H., Fuertes Marraco, S.A., Foukas, P.G. and De Palma, M. (2018). T cell-induced CSF1 promotes melanoma resistance to PD1 blockade. *Science Translational Medicine*, 10(436). doi:<https://doi.org/10.1126/scitranslmed.aan3311>.

Papadopoulos, K.P., Gluck, L., Martin, L.P., Olszanski, A.J., Tolcher, A.W., Ngarmchamnanrith, G., Rasmussen, E., Amore, B.M., Nagorsen, D., Hill, J.S. and Stephenson, J. (2017). First-in-Human Study of AMG 820, a Monoclonal Anti-Colony-Stimulating Factor 1 Receptor Antibody, in Patients with Advanced Solid Tumors. *Clinical Cancer Research*, [online] 23(19), pp.5703–5710. doi:<https://doi.org/10.1158/1078-0432.CCR-16-3261>.

Pu, Y. and Ji, Q. (2022). Tumor-Associated Macrophages Regulate PD-1/PD-L1 Immunosuppression. *Frontiers in Immunology*, 13. doi:<https://doi.org/10.3389/fimmu.2022.874589>.

Reis-Sobreiro, M., Teixeira da Mota, A., Jardim, C. and Serre, K. (2021). Bringing Macrophages to the Frontline against Cancer: Current Immunotherapies Targeting Macrophages. *Cells*, 10(9), p.2364. doi:<https://doi.org/10.3390/cells10092364>.

Safir Ullah Khan, Munir Ullah Khan, Muhammad, Ibrar Muhammad Khan, Muhammad Imran Khan, Bungău, S. and Hassan (2023). Reprogramming tumor-associated macrophages as a unique approach to target tumor immunotherapy. *Frontiers in Immunology*, 14. doi:<https://doi.org/10.3389/fimmu.2023.1166487>.

Teng, K.-Y., Han, J., Zhang, X., Hsu, S.-H., He, S., Wani, N.A., Barajas, J.M., Snyder, L.A., Frankel, W.L., Caligiuri, M.A., Jacob, S.T., Yu, J. and Ghoshal, K. (2016). Blocking the CCL2–CCR2 Axis Using CCL2-Neutralizing Antibody Is an Effective Therapy for Hepatocellular Cancer in a Mouse Model. *Molecular Cancer Therapeutics*, 16(2), pp.312–322. doi:<https://doi.org/10.1158/1535-7163.mct-16-0124>.

Tu, M.M., Abdel-Hafiz, H.A., Jones, R.T., Jean, A., Hoff, K.J., Duex, J.E., Chauca-Diaz, A., Costello, J.C., Dancik, G.M., Tamburini, B.A.J., Czerniak, B., Kaye, J. and

Theodorescu, D. (2020). Inhibition of the CCL2 receptor, CCR2, enhances tumor response to immune checkpoint therapy. *Communications Biology*, [online] 3(1), pp.1–12. doi:<https://doi.org/10.1038/s42003-020-01441-y>.

Webb, M.W., Sun, J., Sheard, M.A., Liu, W., Wu, H., Jackson, J.R., Malvar, J., Sposto, R., Daniel, D. and Seeger, R.C. (2018). Colony stimulating factor 1 receptor blockade improves the efficacy of chemotherapy against human neuroblastoma in the absence of T lymphocytes. *International Journal of Cancer*, [online] 143(6), pp.1483–1493. doi:<https://doi.org/10.1002/ijc.31532>.

Wu, D., Liu, X., Mu, J., Yang, J., Wu, F. and Zhou, H. (2022). Therapeutic Approaches Targeting Proteins in Tumor-Associated Macrophages and Their Applications in Cancers. *Biomolecules*, 12(3), p.392. doi:<https://doi.org/10.3390/biom12030392>.

Zhang, Q. and Mouldy Sioud (2023). Tumor-Associated Macrophage Subsets: Shaping Polarization and Targeting. *International Journal of Molecular Sciences*, 24(8), pp.7493–7493. doi:<https://doi.org/10.3390/ijms24087493>.

Zhang, X., Zhang, X., Wang, Y., Fang, Y., Li, M.-L., Liu, X., Luo, H. and Tian, Y. (2023). The regulatory network of the chemokine CCL5 in colorectal cancer. *Annals of Medicine*, [online] 55(1). doi:<https://doi.org/10.1080/07853890.2023.2205168>.

Zhu, Y., Knolhoff, B.L., Meyer, M.A., Nywening, T.M., West, B.L., Luo, J., Wang-Gillam, A., Goedegebuure, S.P., Linehan, D.C. and DeNardo, D.G. (2014). CSF1/CSF1R Blockade Reprograms Tumor-Infiltrating Macrophages and Improves Response to T-cell Checkpoint Immunotherapy in Pancreatic Cancer Models. *Cancer Research*, 74(18), pp.5057–5069. doi:<https://doi.org/10.1158/0008-5472.can-13-3723>.