

Research Previous Approaches

1. Igniting Hope for Tumor Immunotherapy: Promoting the “Hot and Cold” Tumor Transition

Chen Wei et al., DOI: 10.1177/11795549221120708

Sage Journal: Clinical Medicine Insights: Oncology Volume 16.

Good references on current approaches to driving T-cell proliferation in the TME (Table 1).

2. Advancing cellular immunotherapy with macrophages

Alok K. Mishra et al. DOI: <https://doi.org/10.1016/j.lfs.2023.121857>

- Review of chimeric antigen receptor-expressing macrophages (CAR-M) therapy. - - Discussion of the challenges and opportunities of this therapy.

3. Targeting tumor-associated macrophages in hepatocellular carcinoma: biology, strategy, and immunotherapy

Hongyu Zheng et al. Cell Death Discovery (2023(9: 65) Nature

Doi: <https://doi.org/10.1038/s41420-023-01356-7>

- This is study on targeting TAM for liver cancer (HCC), reviewing small molecule drug, immune checkpoint inhibitors strategies, antibodies, tumor vaccines, and nanocarriers for the drug delivery system.
- This review mentions the promising potential of adoptive cell therapy (CAR-M) for clinical application. However, it emphasizes that there are still major challenges to overcome, particularly in the realms of biosafety and understanding the intricate synergistic effects involving macrophages. This paper emphasizes that it is critical to ascertain whether depletion of TAMs can occur without adversely impacting monocytes/macrophages in normal tissue. Additionally, there is a pressing need to understand whether anti-tumor phenotypes can be regulated over the long term, ad to dig deeper into the complexities of macrophage subtypes beyond the simplistic “M1/M2” macrophage dichotomy.

4. CSF1R inhibitors are emerging immunotherapeutic drugs for cancer treatment

Jiachen Wen et al., DOI: 10.1016/j.ejmech.2022.114884

Elsevier - European Journal of Medicinal Chemistry

- Detailed review of a variety of CSF1R inhibitors completed and still active in clinical trials, with their limitations.

5. Targeting tumor-associated macrophages for successful immunotherapy of ovarian carcinoma

Iva Truxova et al., DOI: 10.1136/jitc-2022-005968

Journal for Immunotherapy 2023

- This article presents a detailed comparison of the characteristic of M-1like vs. M2-like macrophages (refer to Table 1).
- It then describes the TAMs antitumor response in ovarian TME, focusing on their involvement in angiogenesis, invasion and metastasis.
- The article highlights the critical impact of TAMs in recent immunotherapeutic advancements; emphasizing the need for further investigation into the detailed mechanisms by which TAMs affect the outcomes of these therapies.

- It categorizes TAM-targeting strategies into several approaches: (1) Preventing TAM recruitment through agents like CSF1(R)i, CCL2-CCR2i, CXCR4i, Ang2i (2) Depleting TAMs/ reducing their survival using CSF1(R)i, bisphosphonates, Trabectedin, CAR T therapy, Anti-TREM2 mAbs (3) TAM reprogramming/repolarization via TLR agnostic, PI3K inhibitors, and agonistic anti-CD40 mAbs, (4) Restoring the antitumor functions of TAMs with SIRP α i, and SIGLEC10 inhibitors, and (5) Limiting the tumor-promoting activity of TAMs through anti-PD-L1 mAbs, IDOi and VEGFi

6. Sophisticated genetically engineered macrophages, CAR-Macs, in hitting the bull's eye for solid cancer immunotherapy.

Nese Unver, DOI: <https://doi.org/10.1007/s10238-023-01106-0>

Clinical and Experimental Medicine 2023

- This review describes how CAR-Macrophages (CAR-Macs) , a novel approaches for manipulating M2-like or M2-like macrophages, the components of CAR-Macs platforms, and their approaches.

7. Engineering extracellular vesicles derived from macrophages for tumor therapy.

Ying Yan et al., DOI: 10.1039/D2MA00961G

Royal Society of Chemistry

- This article explores engineered macrophages-derived extracellular vesicles (EVs) designed to mimic natural EVs but with enhanced yield, and efficient targeting capabilities. These advancements can make them ideal for targeted drug delivery, and immunotherapy.

8. Recent advances in macrophage-derived exosomes as delivery vehicles

Shumin Wang et al. DOI: <https://doi.org/10.26599/NTM.2022.9130013>

- This article describes recent advances using extracellular vesicles derived from macrophages as drug delivery.
- Gunassekaran et al. developed a targeted cancer immunotherapy based on the biological properties of exosomes derived from M1 macrophages.

9. Therapeutic Targeting of DNA Damage Repair in the Era of Precision Oncology and Immune Checkpoint Inhibitors

Curis Clark et al., DOI: <https://doi.org/10.36401/JIPO-22-15>

- Elaboration on DNA-damage response (DDR) mechanisms the impact of DNA single-strand break (SSB) damage in cancer.
- Review of loss of functions in hallmark genes such as BRCA1/2, ATM, ATR, CHEK1/2, BRD4, PALB2, RAD51, BARD1, FANC, PTEN, or TP53.
- Overview of current PARP inhibitors (including Olaparib, rucaparib, niraparib, talazoparib) along with ongoing clinical trials.
- Discussion of immunotherapies and strategies targeting DDR pathways.
- Examination of innate and/or acquired resistance mechanisms to single-agent PARPi therapies.

10. Dual antitumor immunomodulatory effects of PARP inhibitor on the tumor microenvironment: A counterbalance between anti-tumor and pro-tumor

Xiao-Fang Yi et al., DOI: 10.1016/j.biopha.2023.114770

- The article provides an overview of the dual immunomodulatory effects of PARP inhibitors (PARPi) within the tumor microenvironment (TME).
- PARPi enhances the TME by fostering the activation, mobilization, and efficacy of immune cells while reducing tumor angiogenesis.
- Conversely, PARPi exert a negative regulatory influence on the TME by disrupting DNA repair mechanisms in immune cells and inducing upregulation of PD-L1 expression in tumor cells.
- There is a need for further investigation into the potential synergistic effects of combining PARPi with immune checkpoint inhibitors (ICIs) and other agents known to modulate the TME.

Outline Method to Tackle Problem

Colony-Stimulating Factor-1 Receptor (CSF1R) and its binding molecule CSF1 are prevalently observed in many cancers, including breast, prostate, pancreas, renal and ovary cancers. The inhibition of the CSF-1/CSF1R axis has demonstrated significant impact on the recruitment, and transformation of M2-like TAMs, showcasing potential therapeutic effects that could be contingent upon specific TME and cancer subtype.

The Poly (ADP-ribose) polymerase (PARP) family has many crucial functions in cellular processes, including the regulation of transcription, apoptosis and promote the repair of DNA. PARP inhibitor (PARPi) have been shown to be efficient against homologous recombination repair of cancer cells. Additionally, PARPi can upregulate PD-L1 expression and PD-L1 upregulation can contribute to an inflammatory feedback loop that enhances T cell infiltration. This can trigger the release of additional inflammatory cytokines and chemokines by activated T cells, further promoting T cell recruitment into the tumor microenvironment.

Using an antibody-drug conjugate (ADC) or a macrophage-derived exosome to combine CSF-1R inhibition and PARP inhibition (PARPi) could be a promising strategy for targeting associated macrophages (TAMs) and cancer cells within the TME.

This project presents significant challenges: first, designing an effective delivery mechanism and second, devising an experiment encompassing aspects such as mouse model selection, cell line or tissue selection, CSF-1R knock out in animal model, monitoring tumor growth, TAMs infiltration, and antigen expression analysis. Additionally, the success of this innovative approach is not guaranteed, and integrating with PD-1 inhibitor therapies poses additional complexities.

Questions for professors:

1. How can we effectively structure an experiment to ensure its success?

2. What strategies can be employed to develop an efficient novel drug therapy that enhances survival rates when used in conjunction with checkpoint immunotherapy inhibitors?