

### *Overview*

Hot and cold tumor are crucial in assessing the efficacy of existing cancer immunotherapies. A hot tumor is rich in tumor immune microenvironment (TME), PD-L1 overexpression, genomic instability. Example of hot tumors include melanoma and lung cancer. In contrast, non-T- cell inflamed cancers, such as Triple Negative Breast Cancer (TNBC), prostate or pancreas cancers fall into the category of “cold tumors”. Simultaneously, tumor-associated macrophages (TAMs), T/B regulatory cells (T/Bregs), myeloid-derived suppressor cells (MDSCs) have been identified as contributor to the formation of a specific TME in “cold tumors”. Factors affecting tumor virulence include immune checkpoints (PD-1, PD-L1, CTL4, TIM-3, and LAG-3), tumor infiltrating lymphocytes (TIL), tertiary lymphoid tissue (TLS), microsatellite status (MSI), tumor mutational burden (TMB) and gene mutations (for ex.TP53, BRCA1).

Immune checkpoint inhibitors (ICIs) have shown success in improving the survival of cancer patient. ICI-mediated antitumor responses depend on the infiltration of T cells that identify and eliminate cancer cells. Therefore, ICIs are less efficacious in “cold tumors” which are characterized by the lack of T-cell infiltration.

### *Specific Aims*

The aims of this project are to analyze the current landscape of strategies designed in “warming up” cold tumors to immune checkpoint inhibitors (ICIs); and to introduce an innovative approach utilizing nanoparticles, viral vectors, or polymeric particles as potential solutions.

### *Significance*

#### **1. Turning cold tumors into hot tumors by improving T cell infiltration**

Yuan-Tong Liu, Zhi-Jun Sun doi: 10.7150/thno.58390

- a) Summarizes the mechanisms in “cold tumors”, and factors that influence T-cell priming, and deficient T-cell homing.
- b) Discuss existing strategies and recent advances, promoting the transformation of “cold” tumor into “hot tumors” and the mechanisms by which these strategies lead to increased T-cell infiltration.
- c) Discuss the application of nanomaterial and the potential of combining nanomedicines with ICIs.

#### **2. Turning cold tumors hot: form molecular mechanisms to clinical applications**

Jiahui Zang et al. Trend in Immunology

- a) Proposes the concept of 'effector immune cell deployment (EICD)' for predicting prognoses and guiding immunotherapy regimens by understanding local and systemic regulator mechanisms of immune response in cold and hot tumors.
- b) The authors discuss a multivariable modeling using diagnostic techniques and biomarkers to predict tumor immunogenicity, antigen presentation, trafficking and infiltration efficiency, tumor microenvironment heterogeneity and cytolytic activity.

### **3. Strategies for Heating Up Cold Tumors to Boost Immunotherapies**

Danie Zabranksy et al. Annual Review of Cancer Biology

- a) This paper reviews key factors that create resistance to ICIs
- b) It explores novel strategies which addresses each of them, including approved drugs, ongoing or failed clinical trials.
- c) It also mentions the potential immunogenicity of cellular necrosis triggered by chemotherapies and the importance of studying combinations of immunotherapies with chemotherapies to improve patient outcomes.

### **4. Hot and cold tumors: Immunological features and the therapeutic strategies**

L Wang, H Geng, Y Liu, L Liu, Y Chen, F Wu, Z Liu

<https://doi.org/10.1002/mco2.343>

- a) Detailed review of what separates hot and cold tumors in terms of molecular profile, key factors, tumor microenvironment, and signaling pathways.
- b) This paper might provide a good review of existing therapeutic strategies addressing this problem.

### **5. Combining in site vaccination and immunogenic apoptosis to treat cancer.**

Arman Lamai, Mehdi Shalgolzari – Future Medecine – Immunotherapy – Vol.15, Issue 5

- a) This review discusses the combination of immunogenic cell death (ICD) and in situ vaccination (ISV), ISV applies directly antigens to the tumor.
- b) It might be interesting to understand the limitations of this research, investigate the optimal strategy for combining ICD and ISV loaded with checkpoint blockade therapies and the benefits.

### **6. Dendritic cells and natural killer cells: The road to a successful oncolytic virotherapy**

Matin Ghasemi et al. Frontiers in Immunology

- a) This article mentions oncolytic viruses (OVs) which can enhance immune responses by stimulation the activation and recruitment of DCs and NK cells.
- b) We can investigate them in combination of OV with ICIs

### **7. Pouring Petrol on the flames: Using oncolytic virotherapies to enhance tumor immunogenicity.**

Alicia Teijeira Crespo et al. Wiley Library, Immunology

- a) Another article about OV but compared to the previous one more specifically related to cold tumor.
- b) This paper reviews existing therapies and ongoing clinical trials.

### **8. Unlocking the potential of antibody-drug conjugates for cancer therapy**

Joshua Z. Drago et al. doi:10.1038/s41571-021-00470-8.

- a) This paper discusses the current state of antibody-drug conjugates (ADCs) including their limitations.
- b) This might be useful to understand their mechanisms of action and how to use them to enhance T cell trafficking or priming in cold tumors.

**9. Tumor Targeting of a Sting Antagonist with an Antibody-Drug Conjugate Elicits Potent Anti-Tumor Immune Responses.**

- a) Poster from Mersana Therapeutics targeting the Stimulator of Interferon Genes (STING) pathway which plays a critical role in innate immune response.
- b) It might be interesting to understand the validation of this drug using ADC.
- c) STING might be a promising target.

**10. Antibody-Drug Conjugates: A Review of Approved Drugs and Their Clinical Level of Evidence**

Review by Pooja Gogi et al. Cancers

- a) Describes the key components of antibody-drug conjugates (ADCs)
- b) Provides an overview of failed or approved by FDA ADCs in different cancer indications.
- c) Investigates existing limitations associated with each drug and discusses future directions.

**11. The Evolution of Antibody-Drug Conjugates: A Positive Inflexion Point**

Anthony W. Tolcher - ASCO Educational Book

- a) This paper discusses mechanisms of action of ADCs.
- b) It explores the challenges associated with the four components of ADCs: the target antigen, the antibody construct, the linker for the payload and the payload itself.
- c) It describes recent advances to address the limitations of ADCs, and promising future usages of ADCs.