# TUMOR TYPES AND IMMUNE MICROENVIRONMENT :

## UNDERSTANDING "HOT" AND "COLD" TUMORS IN CANCER THERAPY

*Author: Marie Tautou, Director of Scientific studies*

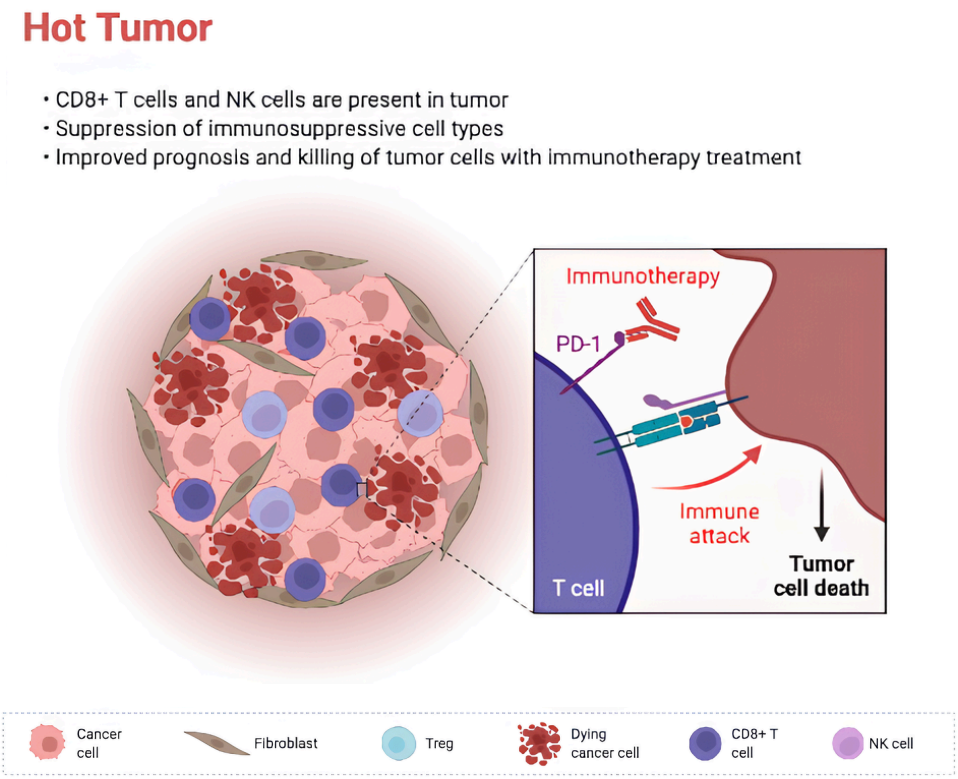
Cancer tumors can be categorized based on the presence of immune cells in the tumor microenvironment, a key factor in determining their behavior and response to treatments, especially immunotherapy.
Preclinical Contract Research Organizations (CROs) play a crucial role in this research by using murine models to simulate these immune environments and assess therapeutic responses.

### 1. Immuno-inflammatory Tumors - ("Hot Tumors")

**Immuno-inflammatory tumors,** or "hot tumors," are marked by a high infiltration of immune cells such as CD8+/CD4+ T cells and myeloid lymphocytes. These tumors are highly inflammatory, with elevated IFNγ signaling and a high mutational load. Despite the immune cell presence, tumor growth continues because the immune system is inhibited, often through mechanisms like PD-L1 overexpression. Patients with hot tumors tend to respond better to immunotherapies due to this active immune engagement.

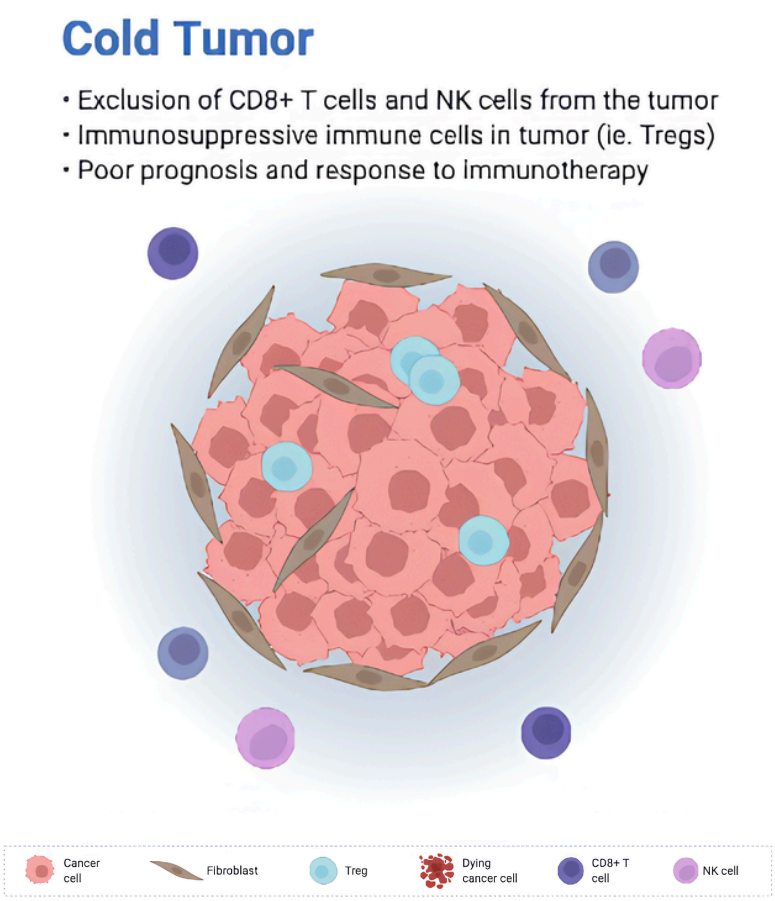
### 2. Immuno-excluded Tumors

**Immuno-excluded tumors** contain immune cells, but these cells remain confined to the tumor's periphery, unable to penetrate the core. This exclusion occurs due to factors such as abnormal chemokine levels, a hypoxic environment, or a stromal barrier. These obstacles prevent T lymphocytes from reaching and destroying tumor cells. Utilizing in vivo models, preclinical CROs are able to mimic these conditions to test interventions aimed at enhancing immune cell infiltration.



### 3. Immuno-deprived Tumors - (“Cold Tumors”)

In contrast, **immuno-deprived tumors**, often referred to as "cold tumors," exhibit minimal or no immune cell presence, indicating a lack of immune response. The absence of immune cells can stem from poor antigen presentation, lack of tumor antigens, or the failure of dendritic cells (DCs) to activate T lymphocytes. These cold tumors have low mutational loads and weak responses to immunotherapies. By leveraging murine models, preclinical CROs can investigate ways to stimulate immune responses in cold tumors, offering hope for patients with tumors unresponsive to conventional treatments.




### Tumor Evasion Mechanisms

#### A. Failure to Recognize Neo-antigens

Even in hot tumor environments, cancer cells can avoid immune detection by presenting tumor antigens defectively. The downregulation of MHC I molecules is a common evasion strategy, preventing recognition by the immune system. An estimated 40-90% of solid tumors employ this tactic. Tumor cells also secrete cytokines like TGFβ, IL-10, and IL-6, which suppress DC maturation, rendering them ineffective in activating T lymphocytes. **Preclinical models** provided by **CROs** help explore how these immune evasion mechanisms can be disrupted.

#### B. Mimicking of Immunosuppressive Mechanisms

Tumor cells also mimic immunosuppressive functions to deactivate effector immune cells and recruit immunosuppressive cells.

##### 1. Secretion of Immunosuppressive Molecules

Tumor cells secrete molecules such as TGFβ, VEGF, and PGE2, which significantly affect the tumor microenvironment. For example:

- **VEGF**

Promotes blood vessel formation while inhibiting DC maturation and promoting immune checkpoint expression.

- **TGFβ**

Regulates cell growth but can suppress the activity of T lymphocytes, NK cells, and B lymphocytes, promoting tumor growth.

- **PGE2**

Inhibits the proliferation of NK cells and macrophages while fostering the expansion of Tregs and MDSCs.

##### 2. Immune Checkpoints

Tumor cells often exploit inhibitory immune checkpoints like PD-1 to escape immune surveillance. These checkpoints are essential for maintaining immune system balance but are hijacked by cancer cells to limit effector cell activation. Targeting these checkpoints has become a central strategy in immunotherapy, and **resistant murine models** are essential for preclinical testing of these therapies.

### Conclusion

Understanding the distinction between **hot tumors and cold tumors**, as well as the sophisticated immune evasion mechanisms used by cancer cells, is crucial in developing effective cancer therapies. **Preclinical CROs** utilizing novel murine models are at the forefront of this research, helping to identify novel approaches to enhance the immune system's ability to fight cancer. By focusing on reactivating immune responses in cold tumors and targeting the suppressive mechanisms in hot tumors, new cancer treatment avenues are being explored, offering greater hope in the battle against this disease.

*For more information on the latest research and advancements in cancer drug resistance and TME, contact our team of experts.*