# Overview of the Current Mechanistic Understanding of Immune Exclusion

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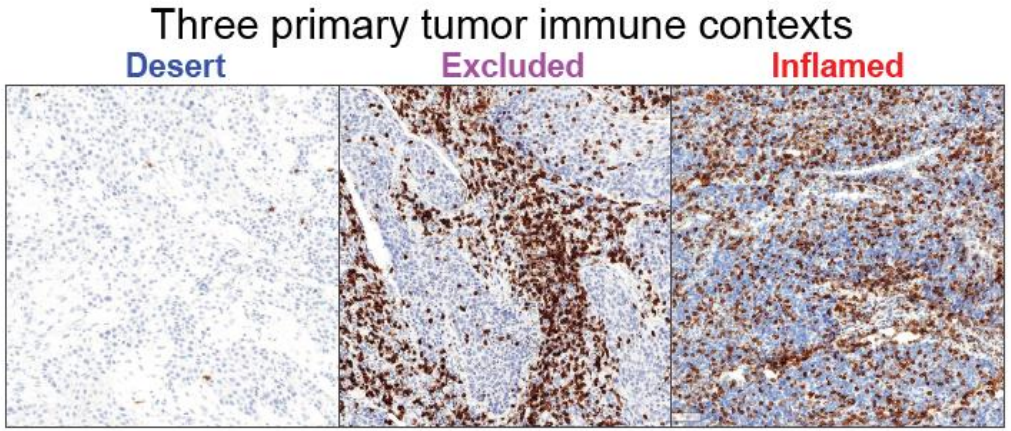
# Immune Context Features and Definition




*Key features*

| | | |
|---|---|---|
| **Low CD8 infiltration**<br>Low neoantigen burden<br>Genomic instability | **Moderate/high CD8 infiltration**<br>**CD8 mostly limited to stroma**<br>Heterogeneous neoantigen burden<br>TGF-B polarization in stroma | **High CD8 infiltration**<br>**CD8 pervasive throughout tumor**<br>PD-L1 amplifications<br>Highest neoantigen burden |

| Analysis Platform | Desert | | Excluded | | Inflamed | |
|---|---|---|---|---|---|---|
| | # cells/mm² | Tum/Stroma Ratio | # cells/mm² | Tum/Stroma Ratio | # cells/mm² | Tum/Stroma Ratio |
| HALO | <500 | N/A | >500cells | <0.5 | ≥500cells | ≥0.5 |
| Visual Evaluation | <5% total immune cells observed | | >50% more cells observed in stroma | | >5% cells observed across tumor and stroma | |

*IHC performed with CD8 Ab (C8/144B, Cell Signaling); HALO Image analysis software purchased from Indica Lab; Visual evaluation done by two independent scientists

Pai SI et al, Presentation at ASCO 2018 Annual Meeting, Chicago, IL

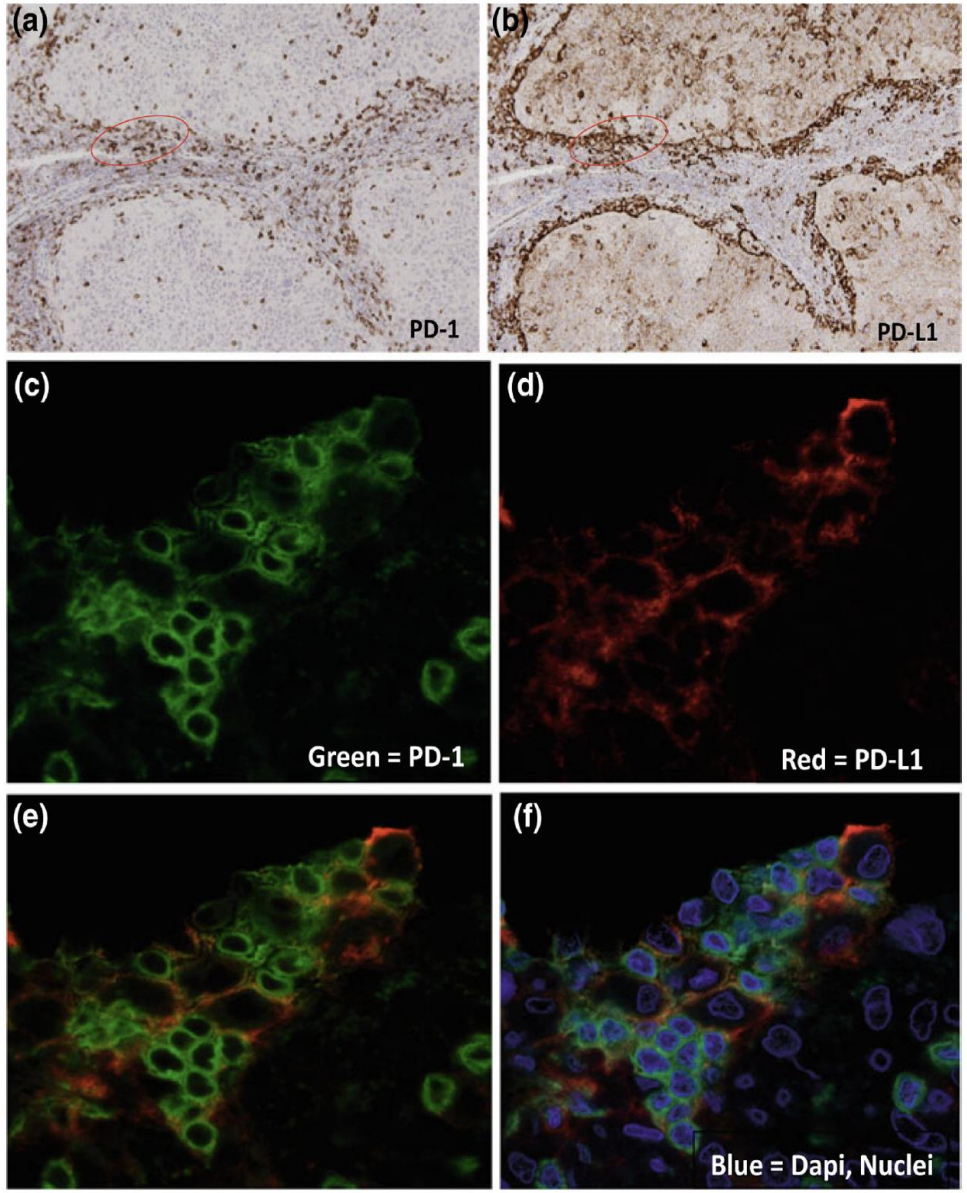
# Consensus on Immune Exclusion Statements

| Statement | | Panelist agreement n/N (%) |
|---|---|---|
| 1 | Cancer immune exclusion is a descriptive definition of a cancer phenotype characterized by a spatial imbalance with more immunologic cells in proximity to the tumor but fewer immune cells in physical contact with tumor cells. | 12/13 (92) |
| 2 | The degree of imbalance that is necessary to distinguish immune excluded tumors from immune deserted or immune inflamed tumors is yet to be determined. | 13/13 (100) |
| 3 | A relative paucity of physical contact between immune cells and tumor cells is a hallmark of this descriptive definition. | 13/13 (100) |
| 4 | Fibrosis is often present in excluded tumors but not essential to the definition. | 12/13 (92) |
| 5 | There are multiple mechanisms that likely play a part in immune exclusion to include: | |
| | A mechanical barrier | 11/12 (92) |
| | Lack of chemotactic factors | 12/13 (92) |
| | Immunosuppressive cytokines | 12/13 (92) |
| | Apoptosis of T cells | 9/12 (75) |
| | Disordered vasculature | 11/13 (85) |
| | Cancer-associated fibroblast subtypes | 11/12 (92) |

Clifton GT et al *J Immunother Cancer* 2023 11(6):eoo6774; Published online June 2023

# Three Potential Mechanisms

- Mechanical Barriers
- Functional Barriers
- Dynamic Barrier




Pai SI, Cesano A, Marincola FM. *Cancer Treat Res* 2020 180:173-195

# Mechanical Barrier

- Physical impediment preventing contact between T cells and cancer cells
  - Stromal Fibrosis
    - Filaggrin and desmosomal proteins
    - Endothelin B Receptor
    - Transforming growth factor (TGF)-β-induced fibrosis
    - Epithelial mesenchymal transition
  - Vascular access/Disorder
    - VEGF

Pai SI, Cesano A, Marincola FM. *Cancer Treat Res* 2020 180:173-195

# Functional Barrier

- Pre-existing biological and/or metabolic interactions between cancer, stromal, and immune cells limiting the migration, function and/or survival of T cells

  - Metabolic barriers
  - Soluble factors (Cytokine/chemokines, TGF-β)
  - Danger sensing
  - Tumor cell-intrinsic signaling (β-catenin, PI3K, STAT-3, MAPK signaling)

Pai SI, Cesano A, Marincola FM. *Cancer Treat Res* 2020 180:173-195

# Dynamic Barrier

- Biological interactions between cancer and T cells that result in limited function
  - Immune checkpoint pathway activation

Pai SI, Cesano A, Marincola FM. *Cancer Treat Res* 2020 180:173-195

# Clinical Implications

- Immune-excluded cancers are much more prevalent across cancer histologies than generally perceived.

- Improved understanding of the mechanisms that drive immune exclusion has important clinical implications in the development of novel therapeutic strategies aimed to overcome immune resistance.

- Efforts to enhance the host anti-tumor immune response or improve the immunogenicity of cancers are important but plays only a limited role when other mechanisms of immune exclusion are in play.

# Panel Discussion

| | |
|---|---|
| • Hartmut Koeppen, MD, PhD | Genentech |
| • Jakob Kather, MD, MSc | Else Kroener Fresenius Center for Digital Health |
| • Ryan Sullivan, MD | Massachusetts General Hospital |
| • Karin Jooss, PhD | Gritstone Oncology |
| • Steve Katz, MD | TriSalus Life Sciences |
| • Myriam Chalabi, MD | Netherlands Cancer Institute |

# Potential Research Focus Areas for Immune Exclusion

| Area of research | Panelist rank of importance |
|---|---|
| Repulsion/rejection of T cells | 2.5±1.2 |
| Spatial profiling of T-cell cancer interaction | 2.6±2.3 |
| Understanding the role of cancer-associated fibroblasts | 2.8±2.2 |
| Immunosuppressive cytokines | 3.3±1.7 |
| Cancer-associated fibroblast subtypes | 3.5±2.5 |
| Disordered angiogenesis or vasculature | 3.8±1.9 |
| Apoptosis of T cells | 3.9±1.8 |

Panelists were asked to provide a rank based on how important the topic was to the field of immune exclusion with 1 being the most important and 7 being least important. Data presented as mean±SD.

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