Tumor Immune Microenvironment: A Holistic Approach Workshop

April 21-22, 2022 • San Diego and Virtually

#SITCworkshop

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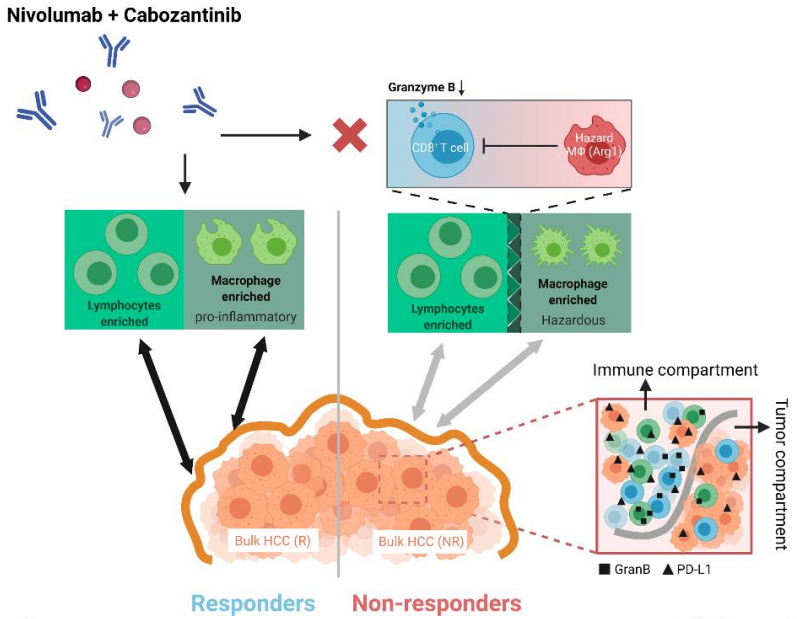
Society for Immunotherapy of Cancer

Quantitative immuno-oncology analysis of multiplex pathology images characterizes neoadjuvant cabozantinib and nivolumab efficacy in hepatocellular carcinoma



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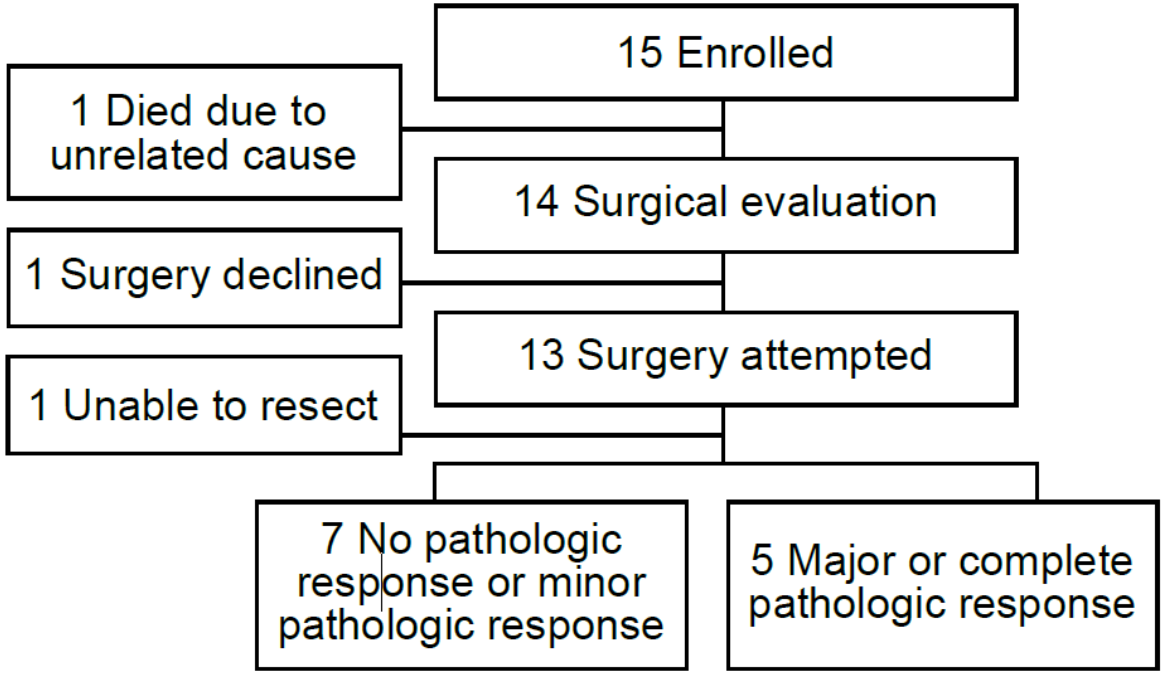
Hepatocellular Carcinoma (HCC)

- HCC is the fourth leading cause of cancer-related death in the United States.
- Globally, over 70% of HCCs are non-resectable when diagnosed.
- Poor long-term disease-free survival with high recurrence rates (54 – 100%).
- Development of novel treatment strategies is warranted.

Siegel et al, 2020, *Cancer J. Clin*
Yang et al, 2020, *Cancer J. Clin*
Tabrizian et al, 2015, *Ann. Surg*

Neoadjuvant cabozantinib and nivolumab in HCC patients

- First use of a targeted therapy in combination with an immune checkpoint inhibitor (anti-PD-1) in the neoadjuvant treatment of HCC.



Ho et al, 2021, *Nature Cancer*

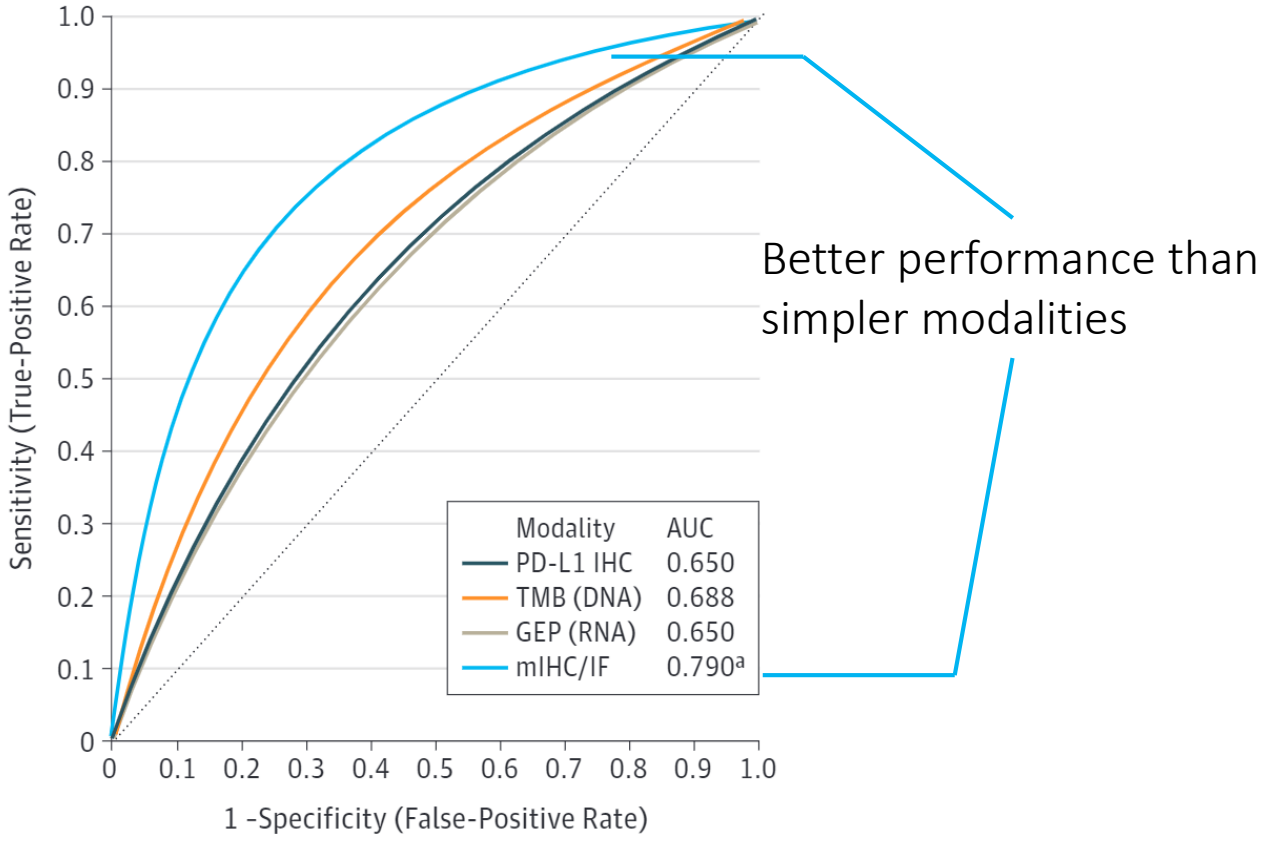
Specific aims

- Aim 1: Deep profiling the tumor microenvironment (TME). (*What* components and *Where* they are)

- Aim 2: Characterizing the spatial architectures of TME components to search response-modulating factors.(*How* they interact spatially)

Multiplex imaging offers better solution

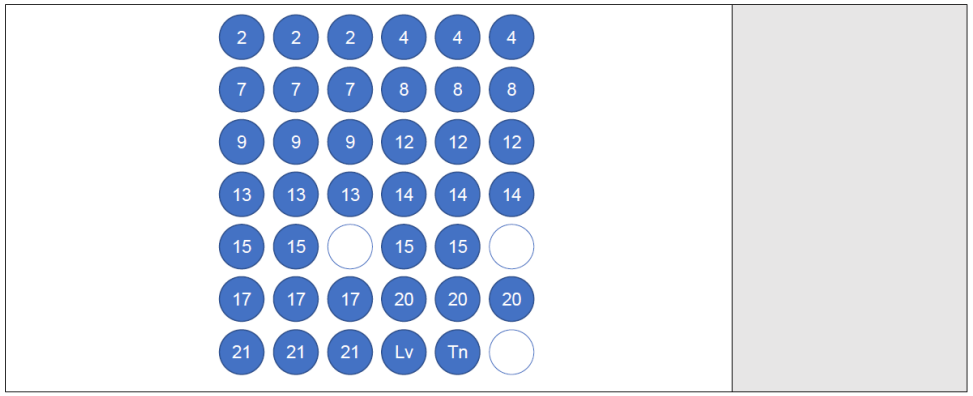
Simultaneous visualization of proteins



Better performance than simpler modalities

Lu et al, 2019, JAMA Oncology

Multiplex imaging and tissue microarray capture TME ecosystem



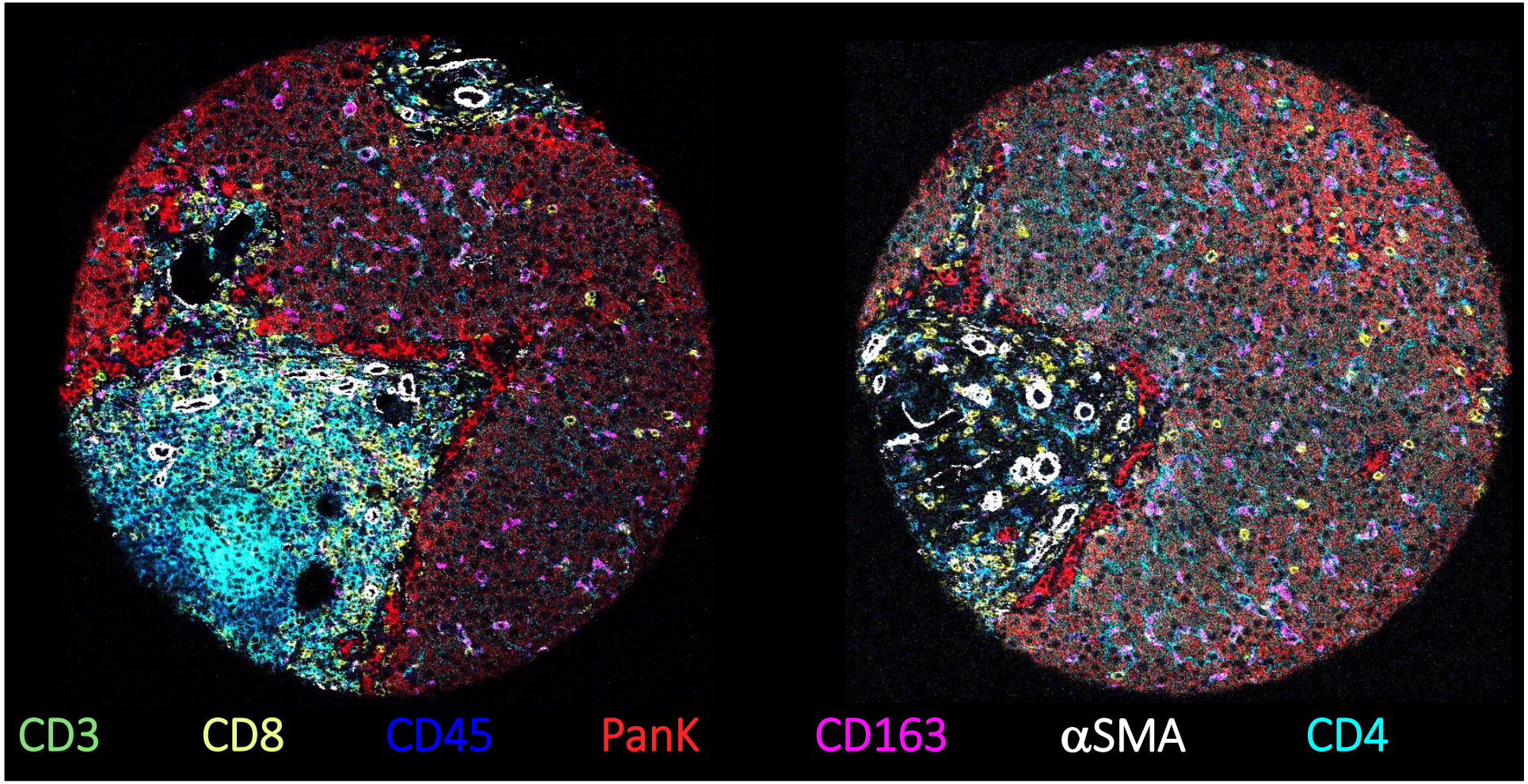
37 cores (12 patients)
15 responder cores (pt #2, 8, 13, 14, 17)
22 nonresponder cores (pt #4, 7, 9, 12, 15, 20, 21)
1 normal liver core, 1 normal tonsil core

Antigen	Description
Lymphoid markers	
CD45	Pan-Immphocytes
CD45RO	Memory T Cells
FoxP3	regulatory T Cells
CD3	T cells
CD4	Helper T cells
CD8	Cytotoxic T cells
CD20	B Cells
Architecture	
DNA	Single DNA strand
Histone H3	Chromatin
PM	Plasma membrane

Antigen	Description
Immune regulatory molecules	
Arginase-1	Hydolysis of argine
HLA-DR	Antigen presenting
CD28	T cell activation
CCR6	Metastasis
PDL1	Immune checkpoint
LAG3/CD223	T cell function
GranB	Mediate apoptosis
Cell Proliferation	
Ki67	Proliferation
Cell Death	
Caspase3	Apoptosis

Antigen	Description
Myeloid markers	
CD15	Granulocytic
CD16	Granulocytic
CD68	Pan-macrophage
CD163	M2-like macrophage
Mesenchymal markers	
Vimentin	Mesenchymal Cells
Collagen	Matrix
Adhesion molecules	
E-cadherin	Cell Adhesion
Hepatocyte/Tumor	
PanK	Pan-cancer

Multiplex imaging profiles tumor-immune landscape



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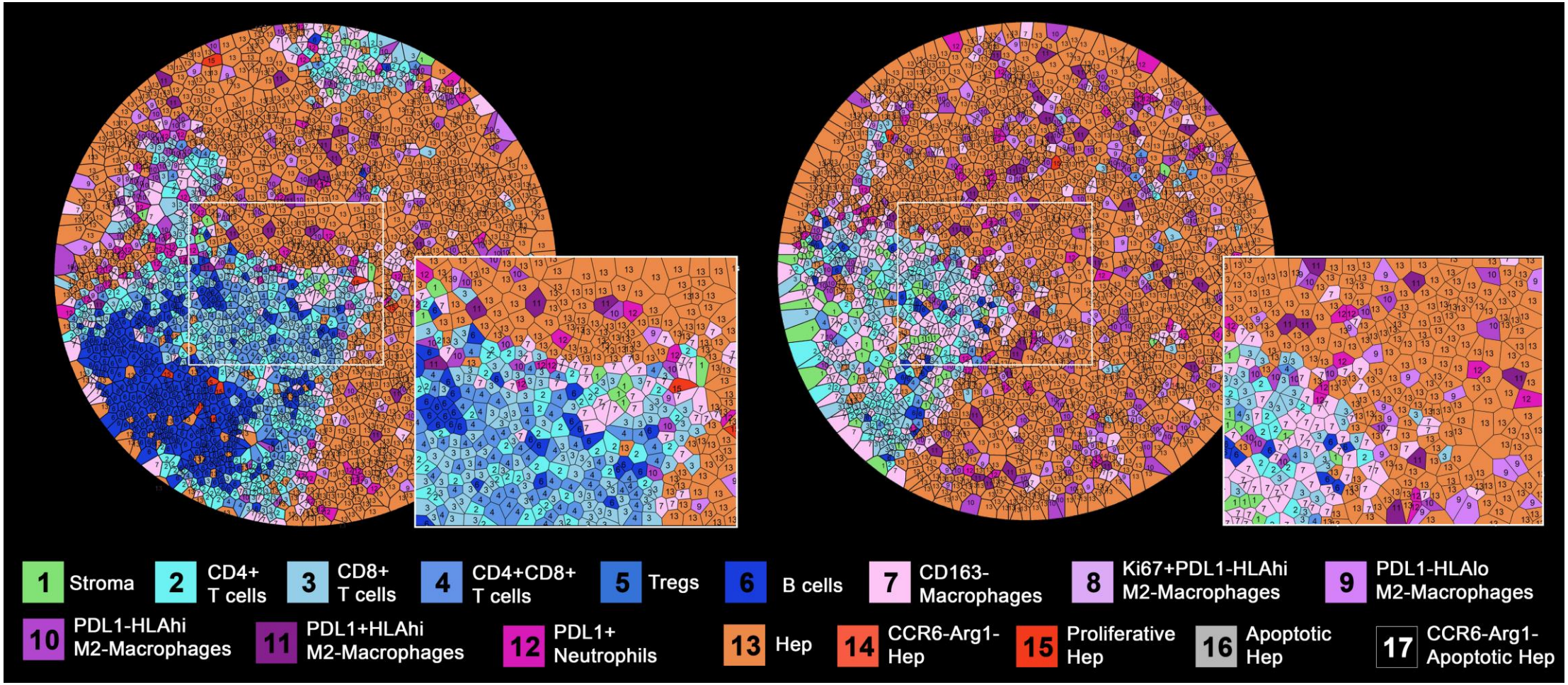

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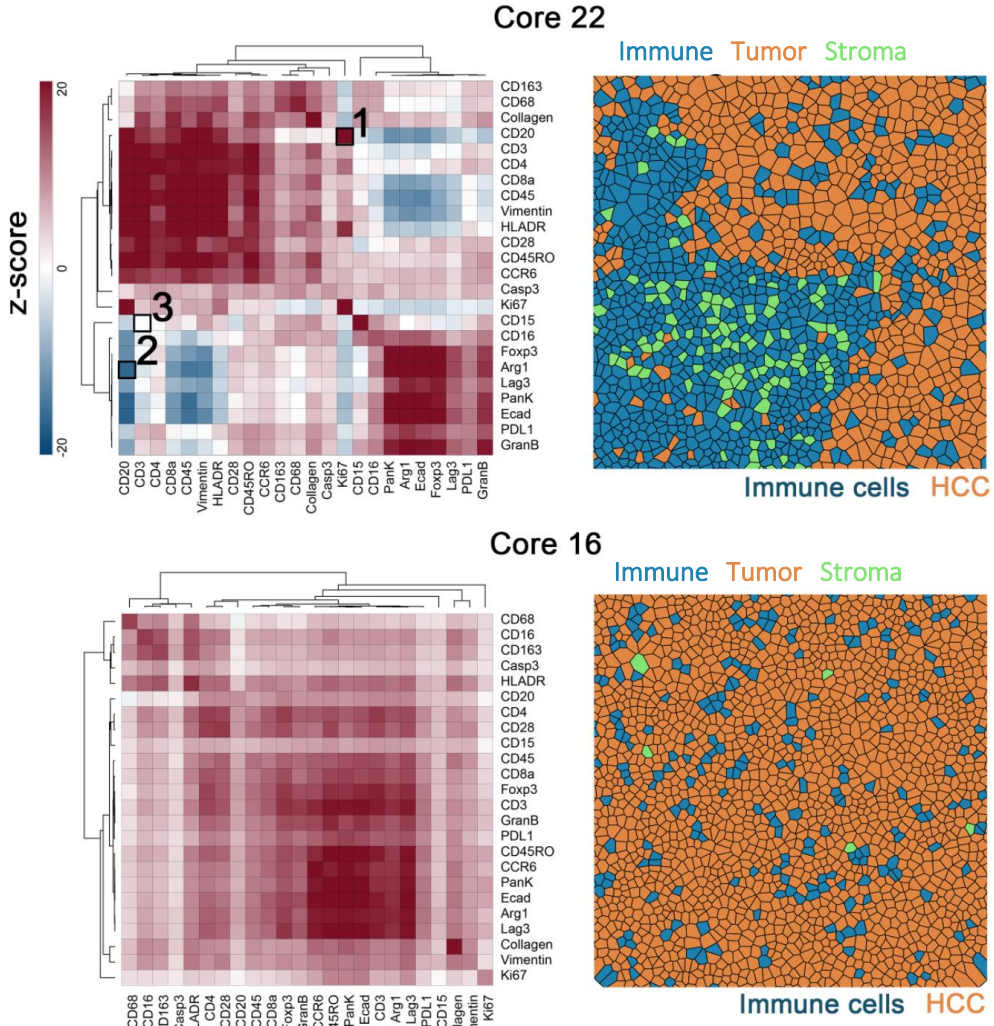
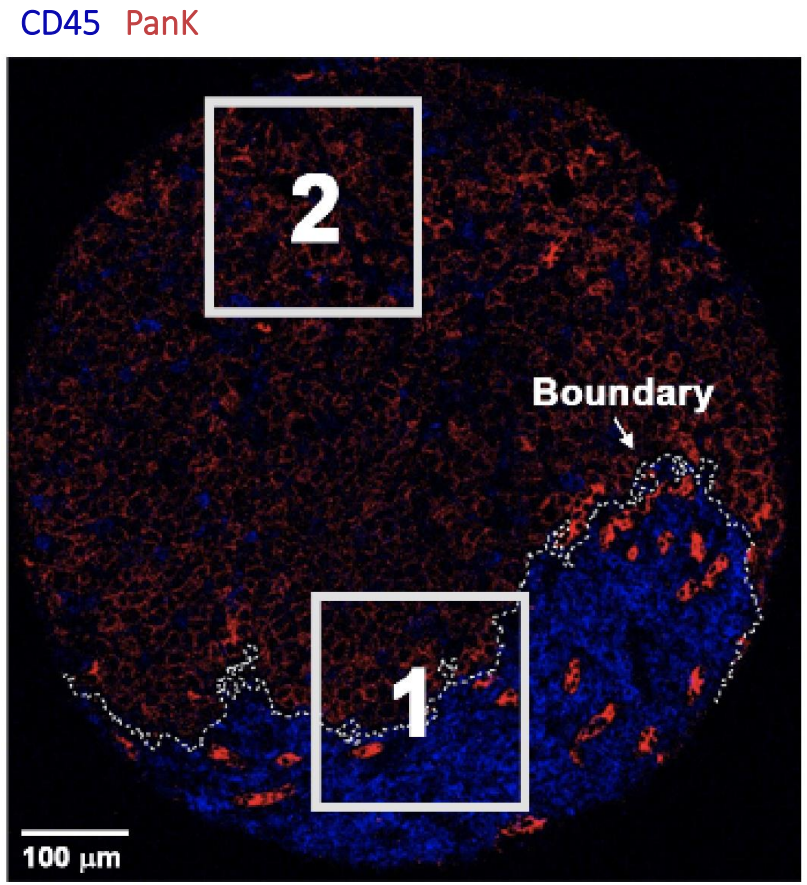
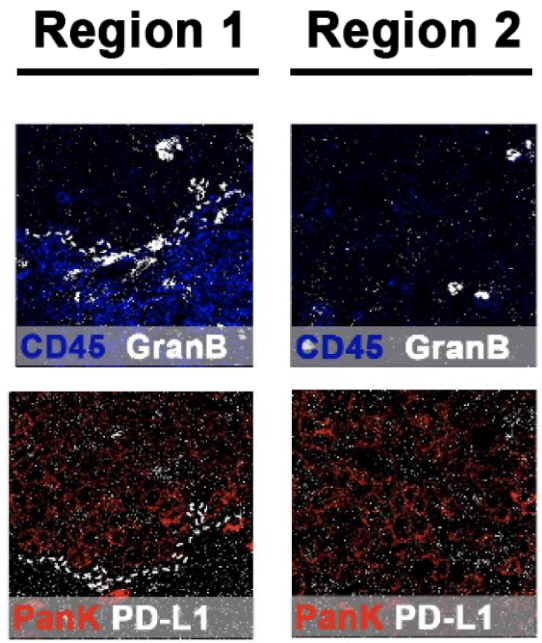






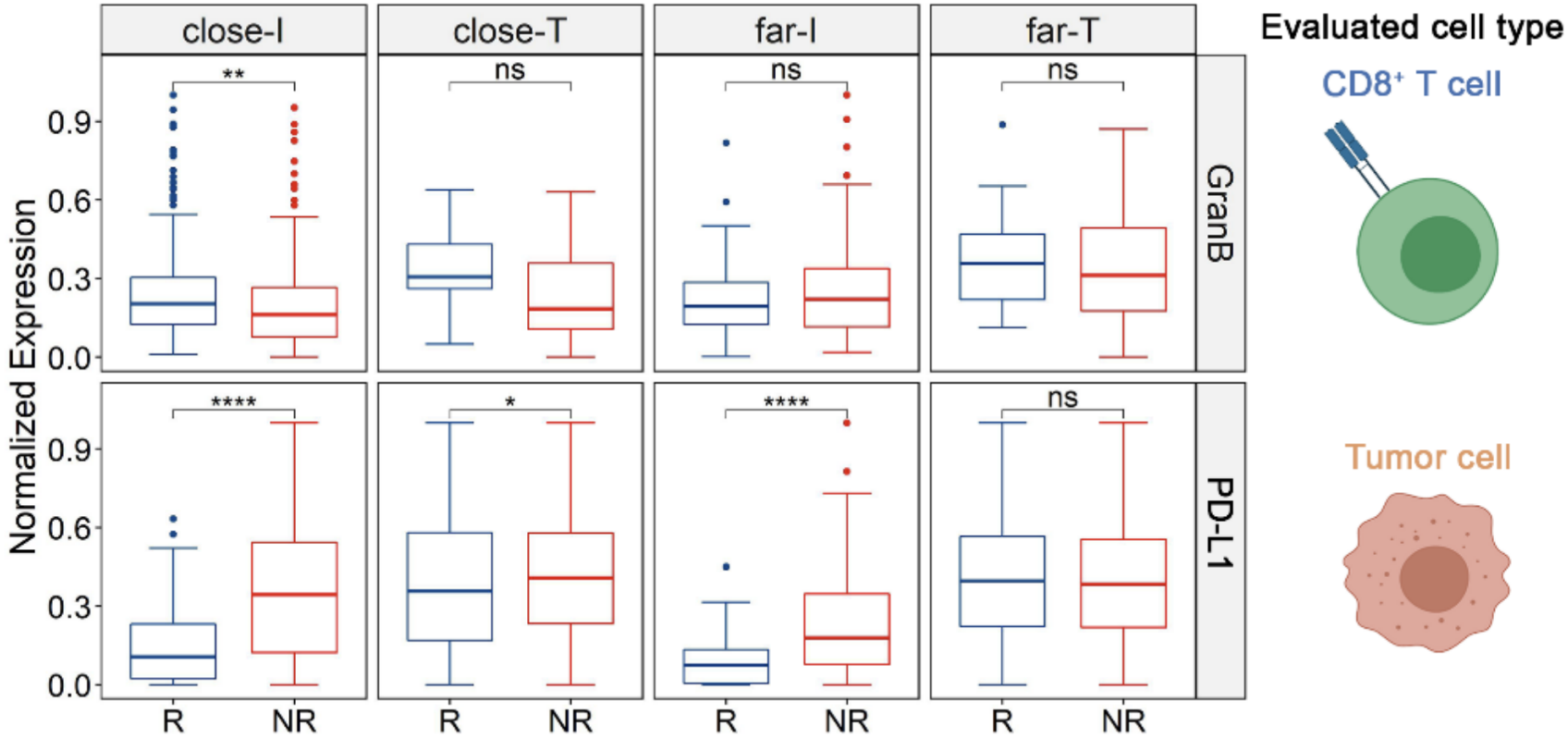
Checkpoint expressions exhibit response-dependent, location-sensitive pattern

close-I: Regions **within 40 μm** towards boundary in **Immune compartment**

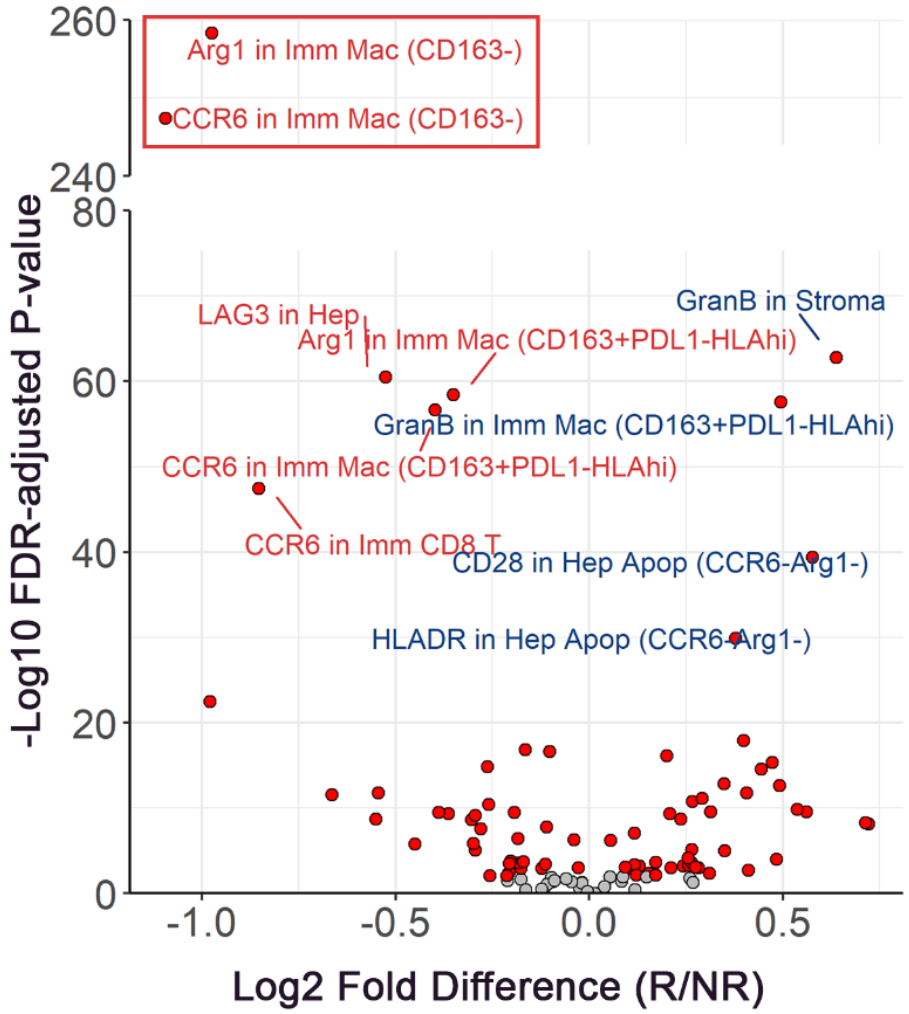
far-I: Regions **beyond 40 μm** towards boundary in **Immune compartment**

close-T: Regions **within 40 μm** towards boundary in **Tumor compartment**

far-T: Regions **beyond 40 μm** towards boundary in **Tumor compartment**

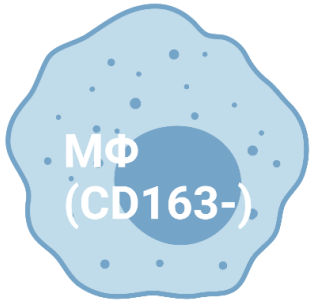


Macrophage-T cell mediates immune therapy resistance



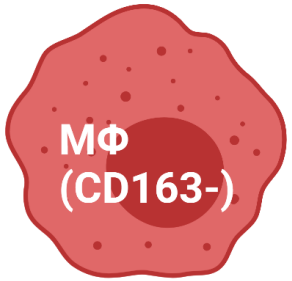
Non-Hazard

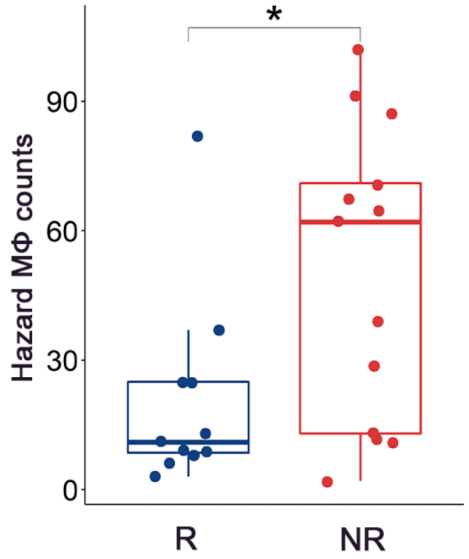
Arginase-1 and CCR6 are both non-upregulated



Hazard

Arginase-1 upregulation
or
CCR6 upregulation

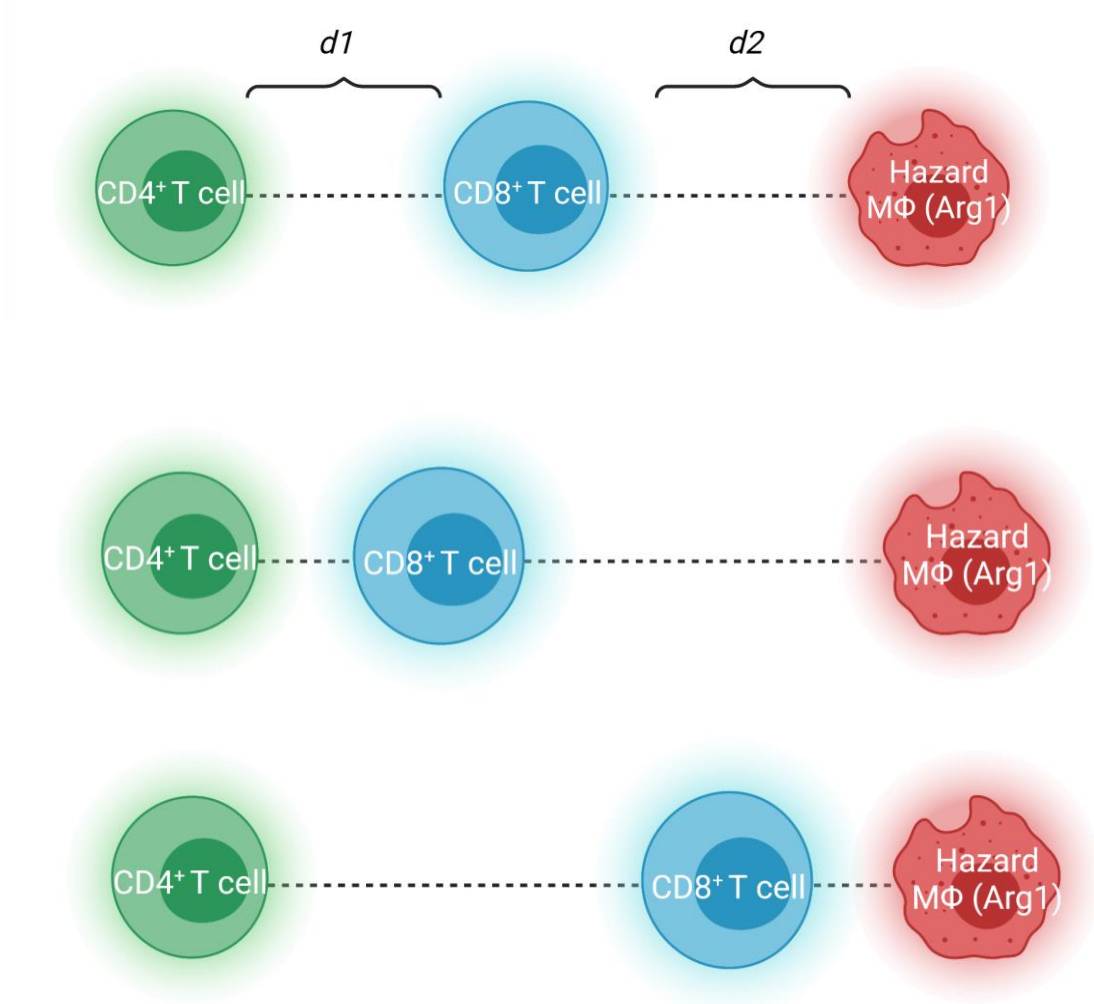


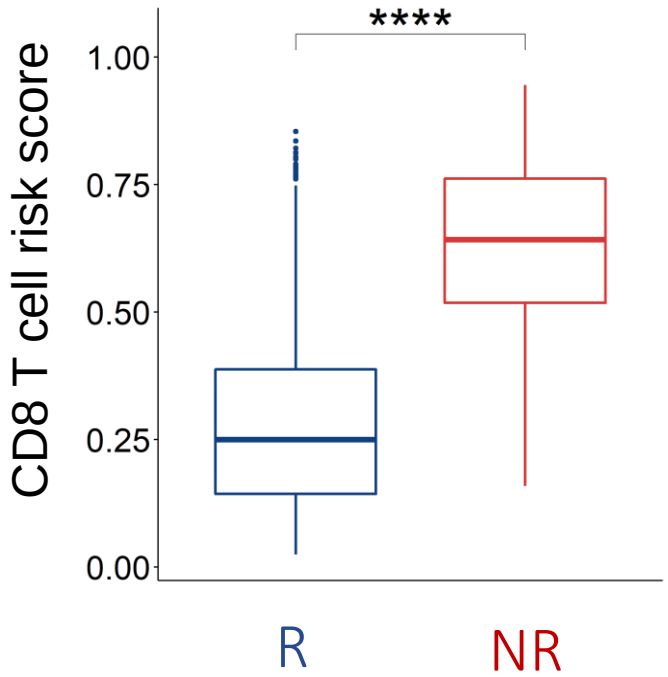


Macrophage-T cell mediates immune therapy resistance

CD8⁺ T cell risk score

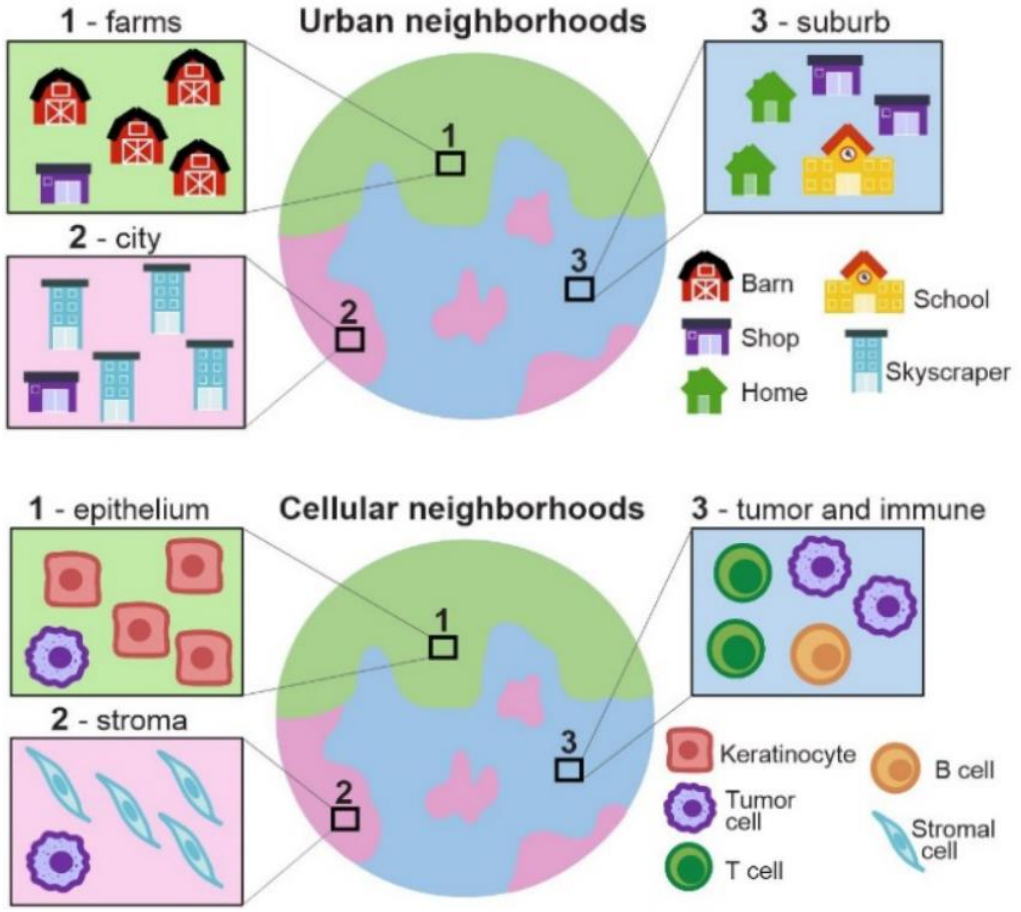
$$\frac{d1}{d1 + d2}$$





Darci et al, 2021, *Nature Comm*

Network analysis of cellular community pictures communication landscape in TME



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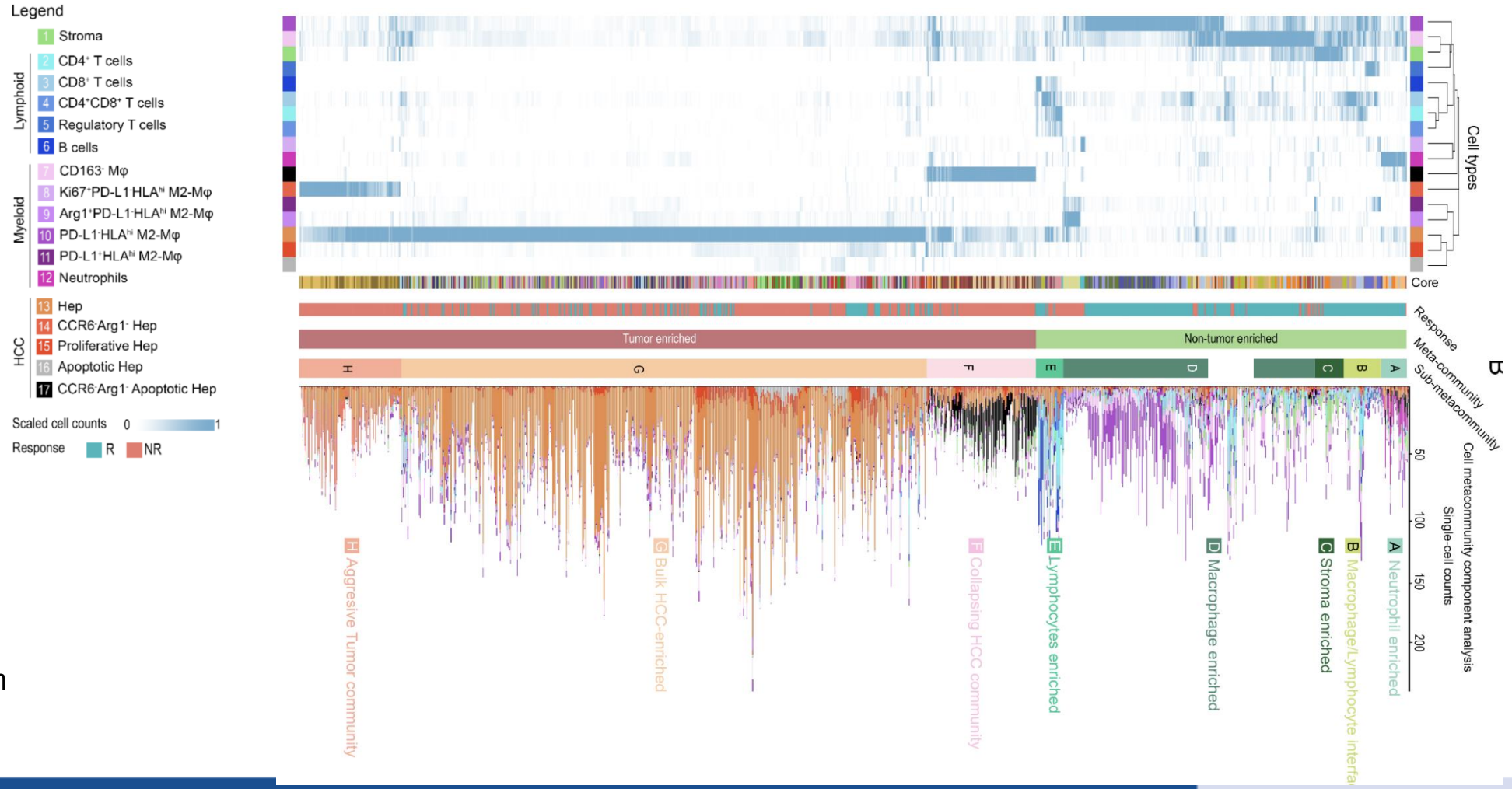
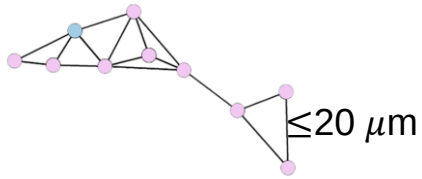


cell-cell network



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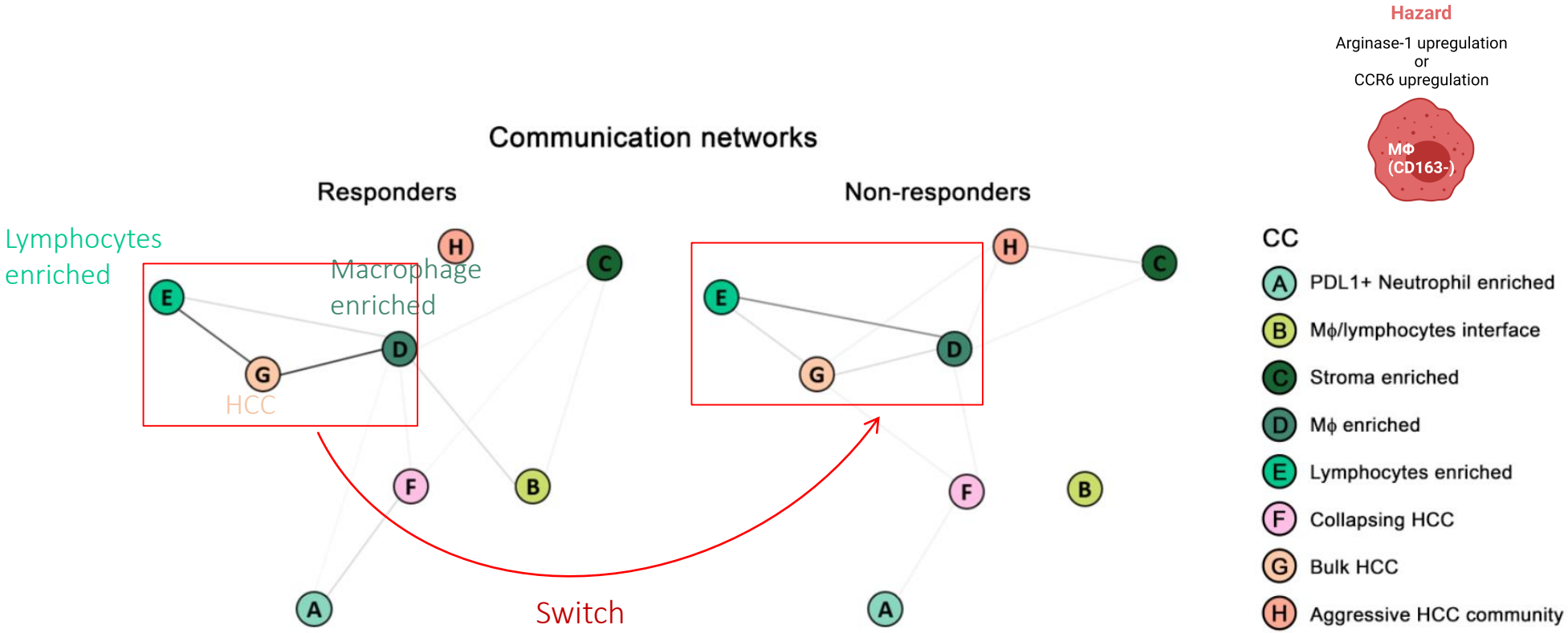

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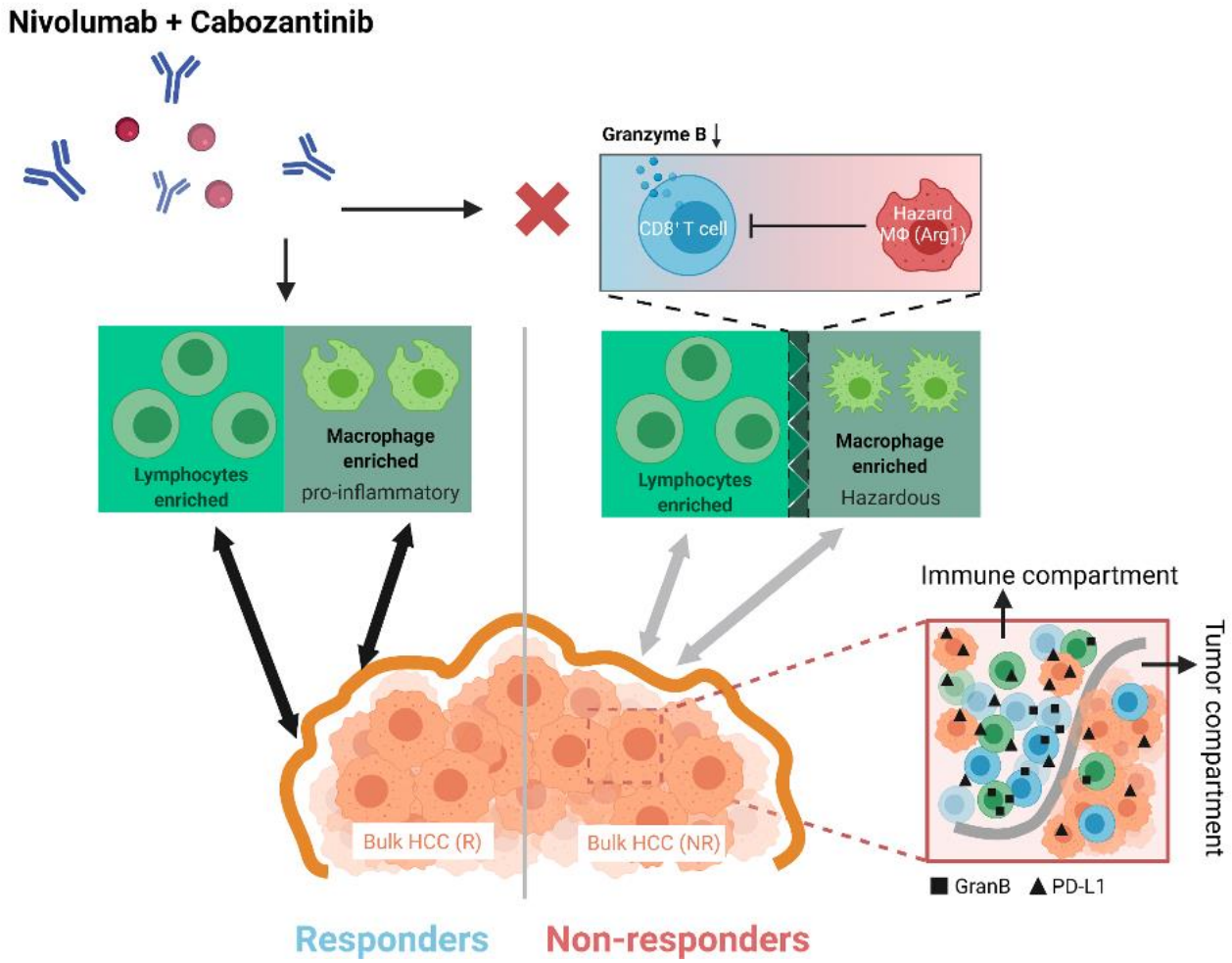

Conclusion

- PDL1 and Granzyme B upregulations in immune compartment within TME is a key indicator of response to Cabo-Nivo.
- Arg-1 and CCR6 expressions on CD163- macrophages contribute to therapy resistance by compromising CD8 T cells cytotoxicity.
- Components within TMEs are orchestrated. Specifically, joint anti-tumor immunity of macrophage and lymphocytes neighborhoods favors response to therapy.

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