



Tumor Immune Microenvironment: A Holistic Approach Workshop

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#SITCworkshop



Society for Immunotherapy of Cancer

TREM2 associated signature defines a tumor-enriched macrophage subset associated with anti-PD-1 response in hepatocellular carcinoma

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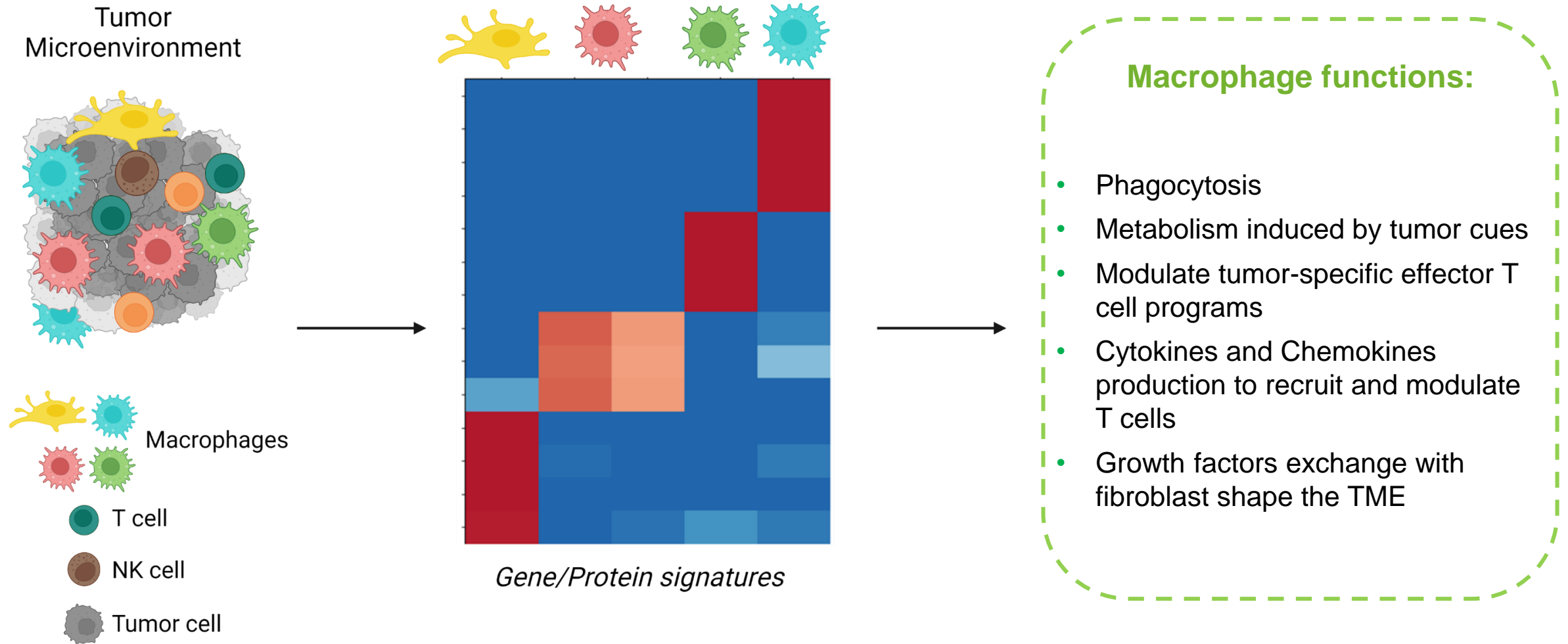
Disclosure information

Pauline Hamon, PhD

Clinical trial funded by Regeneron Pharmaceuticals.

ClinicalTrials.gov Identifier: **NCT03916627**

Identify how macrophage molecular programs define their functions in the TME



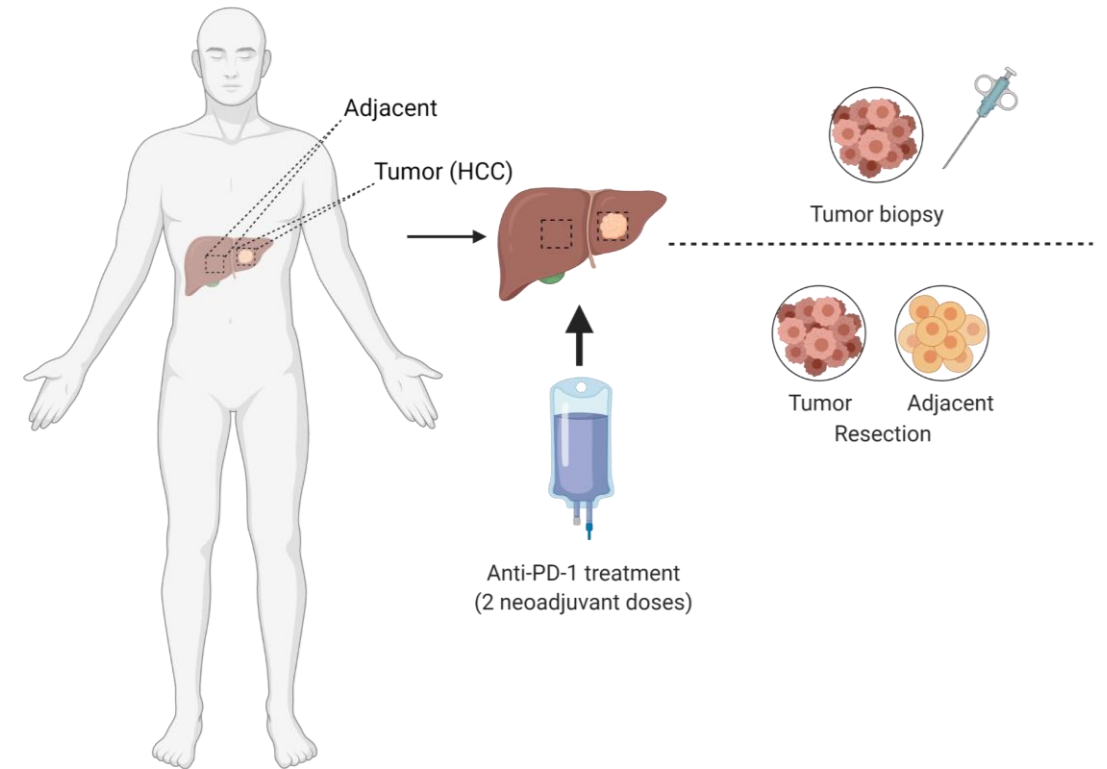
Largest cohort of neoadjuvant anti-PD-1 therapy in HCC

Hepatocellular carcinoma (HCC):

- 70% recurrence
- Early-stage HCC have 5-years survival rate of 34%
- 3 immunotherapy and combination had been FDA approved the past few years in advanced HCC

Neoadjuvant cemiplimab for resectable hepatocellular carcinoma: a single-arm, open-label, phase 2 trial

Thomas U Marron, Maria Isabel Fiel, Pauline Hamon, Nathalie Fiaschi, Edward Kim, Stephen C Ward, Zhen Zhao, Joel Kim, Paul Kennedy, Ganesh Gunasekaran, Parissa Tabrizian, Deborah Doroshov, Meredith Legg, Ashley Hammad, Assaf Magen, Alice O Kamphorst, Muhammed Shareef, Namita T Gupta, Raquel Deering, Wei Wang, Fang Wang, Pradeep Thanigaimani, Jayakumar Mani, Leanna Troncoso, Alexandra Tabachnikova, Christie Chang, Guray Akturk, Mark Buckup, Steven Hamel, Giorgio Ioannou, Clotilde Hennequin, Hajra Jamal, Haley Brown, Antoinette Bonaccorso, Daniel Labow, Umut Sarpel, Talia Rosenbloom, Max W Sung, Baijun Kou, Siyu Li, Vladimir Jankovic, Nicola James, Sara C Hamon, Hung Kam Cheung, Jennifer S Sims, Elizabeth Miller, Nina Bhardwaj, Gavin Thurston, Israel Lowy, Sacha Gnjatich, Bachir Taouli, Myron E Schwartz, Miriam Merad



- Cohort of 36 patients:
 - 8 Treatment-Naïve
 - 8 Responders to PD-1 blockade
 - 20 Non-responders to anti-PD-1 blockade

Largest cohort of neoadjuvant anti-PD-1 therapy in HCC

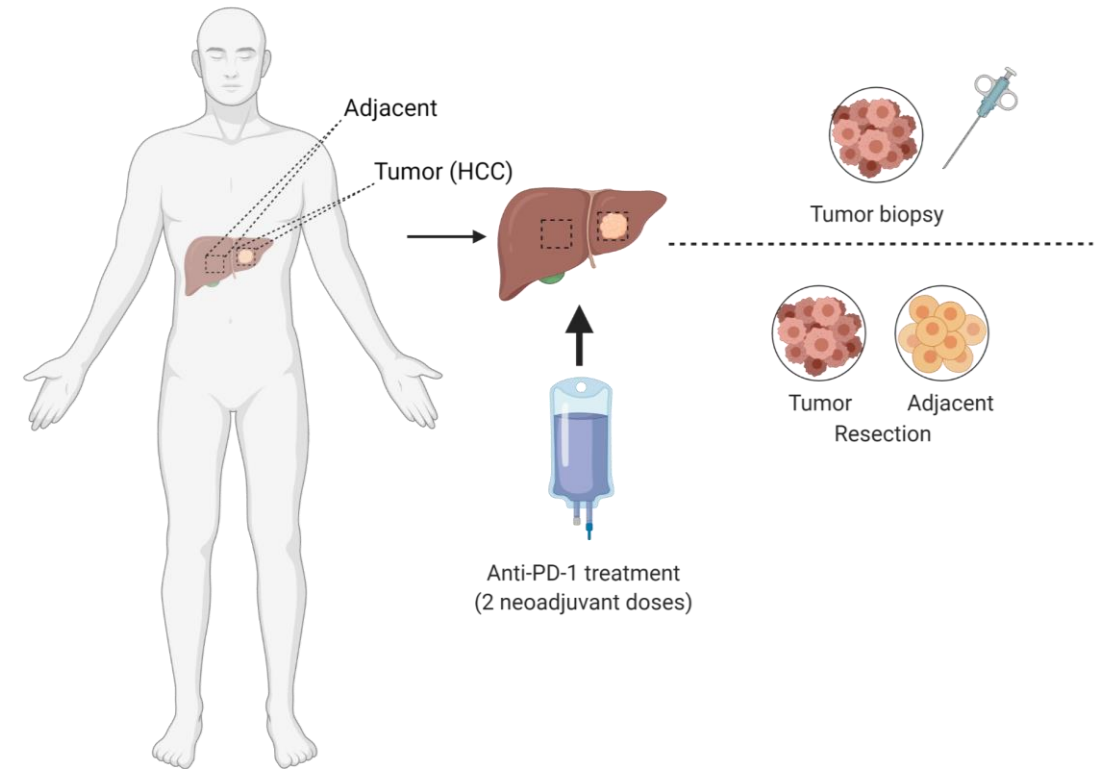
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➤ Identify the key players of the anti-tumor immune response to PD-1 blockade



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Unbiased profiling of immune cells that accumulate in HCC lesions and adjacent tissues during treatment with PD-1 blockade

Unbiased clustering analysis:

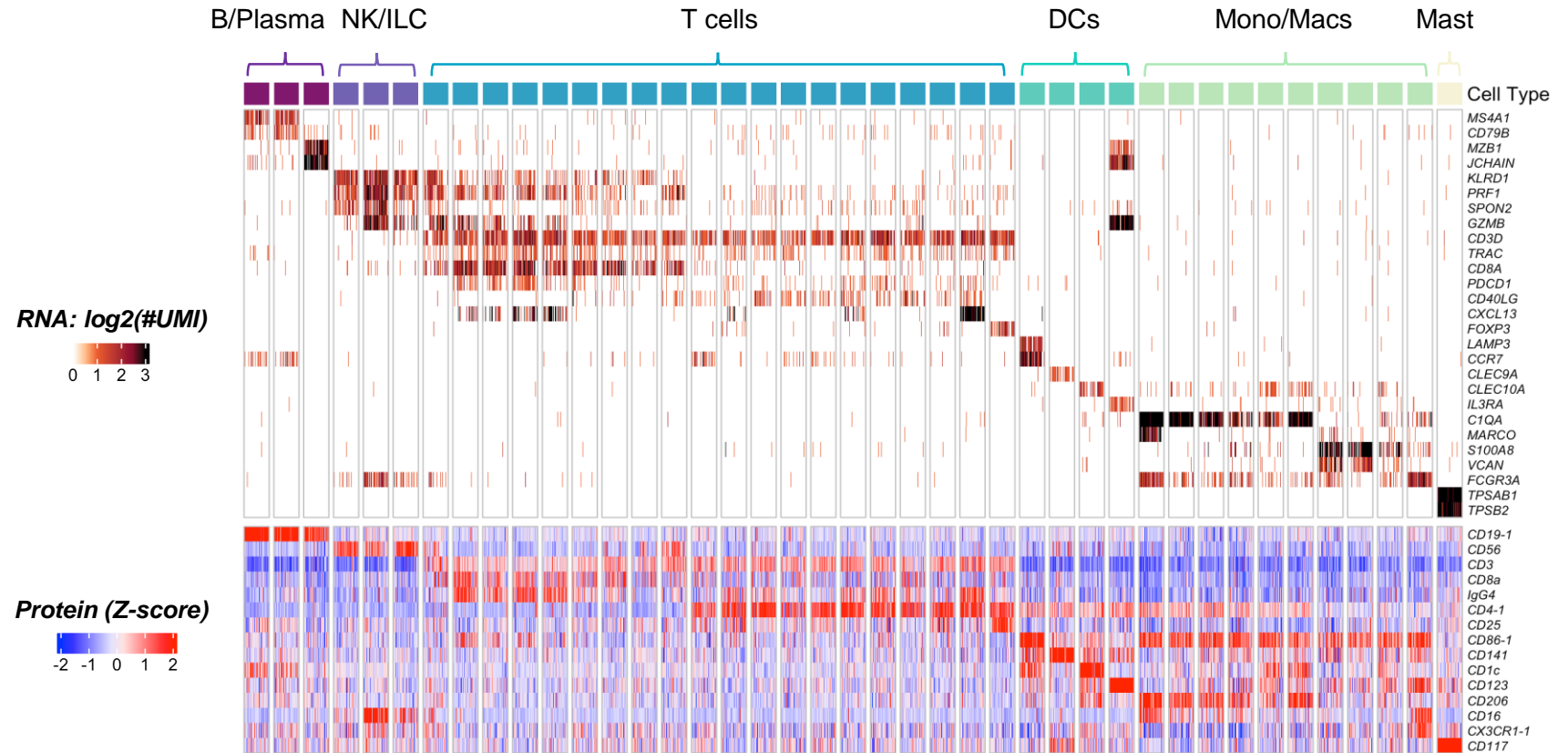
120 clusters

More than 900,000 total cells

41,381 macrophages

32,329 monocytes

22,838 DCs



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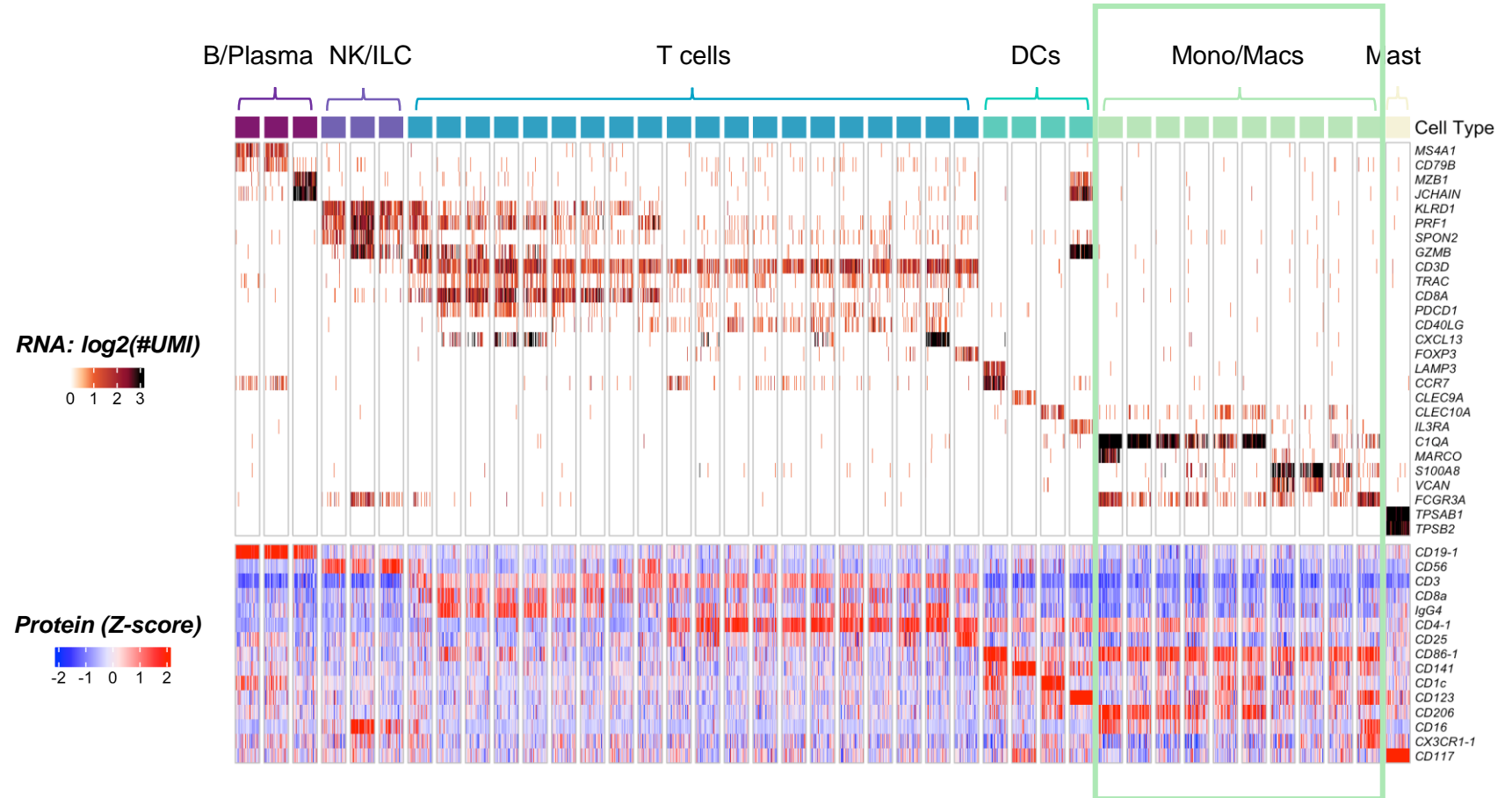
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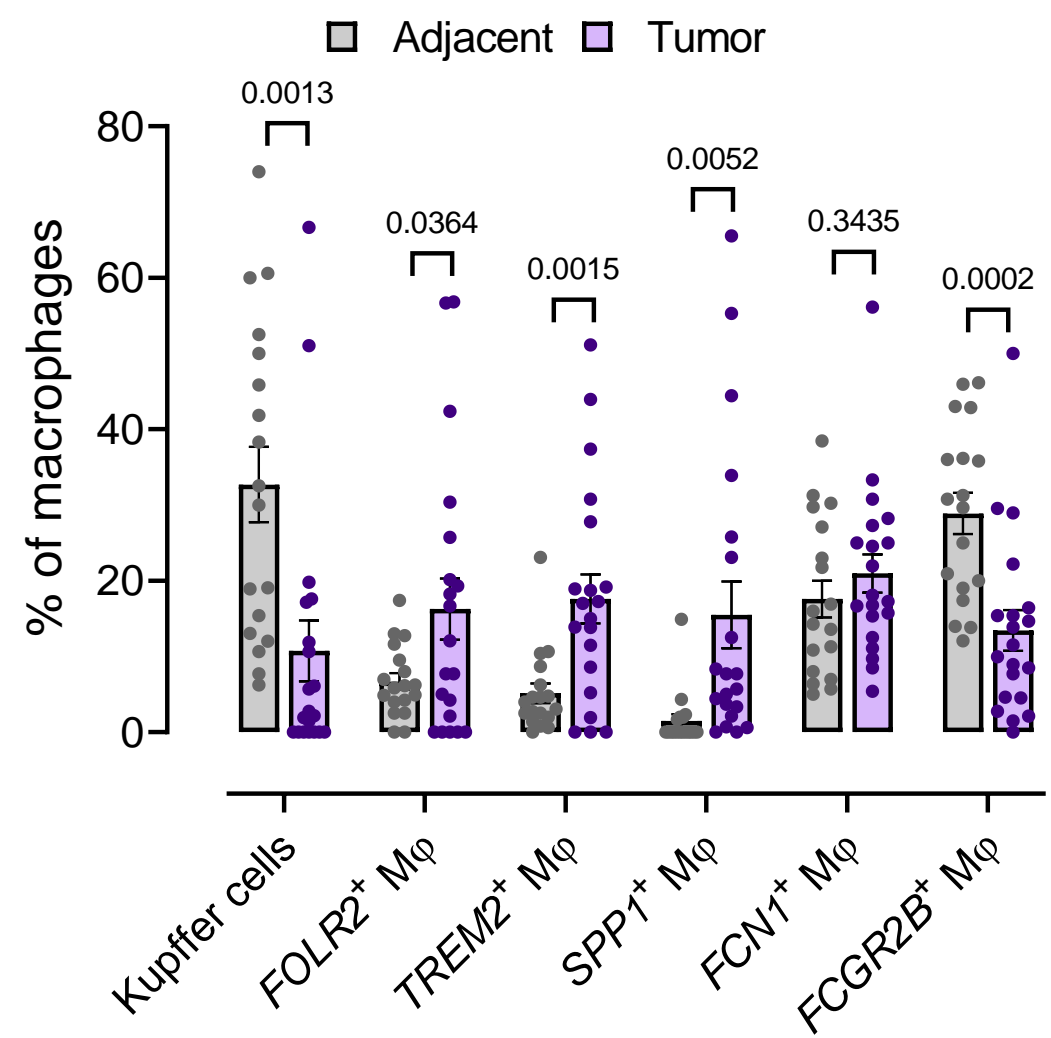
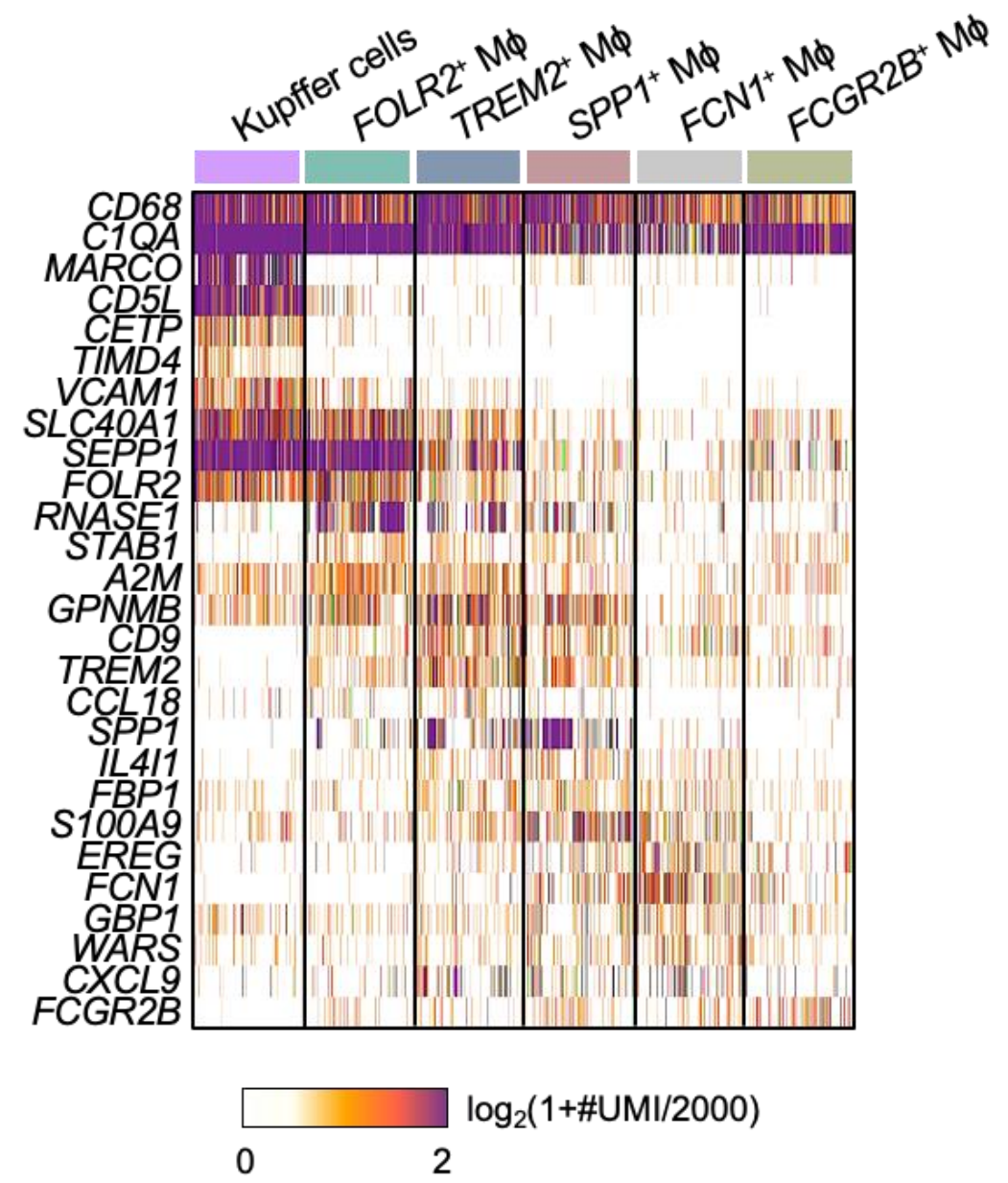
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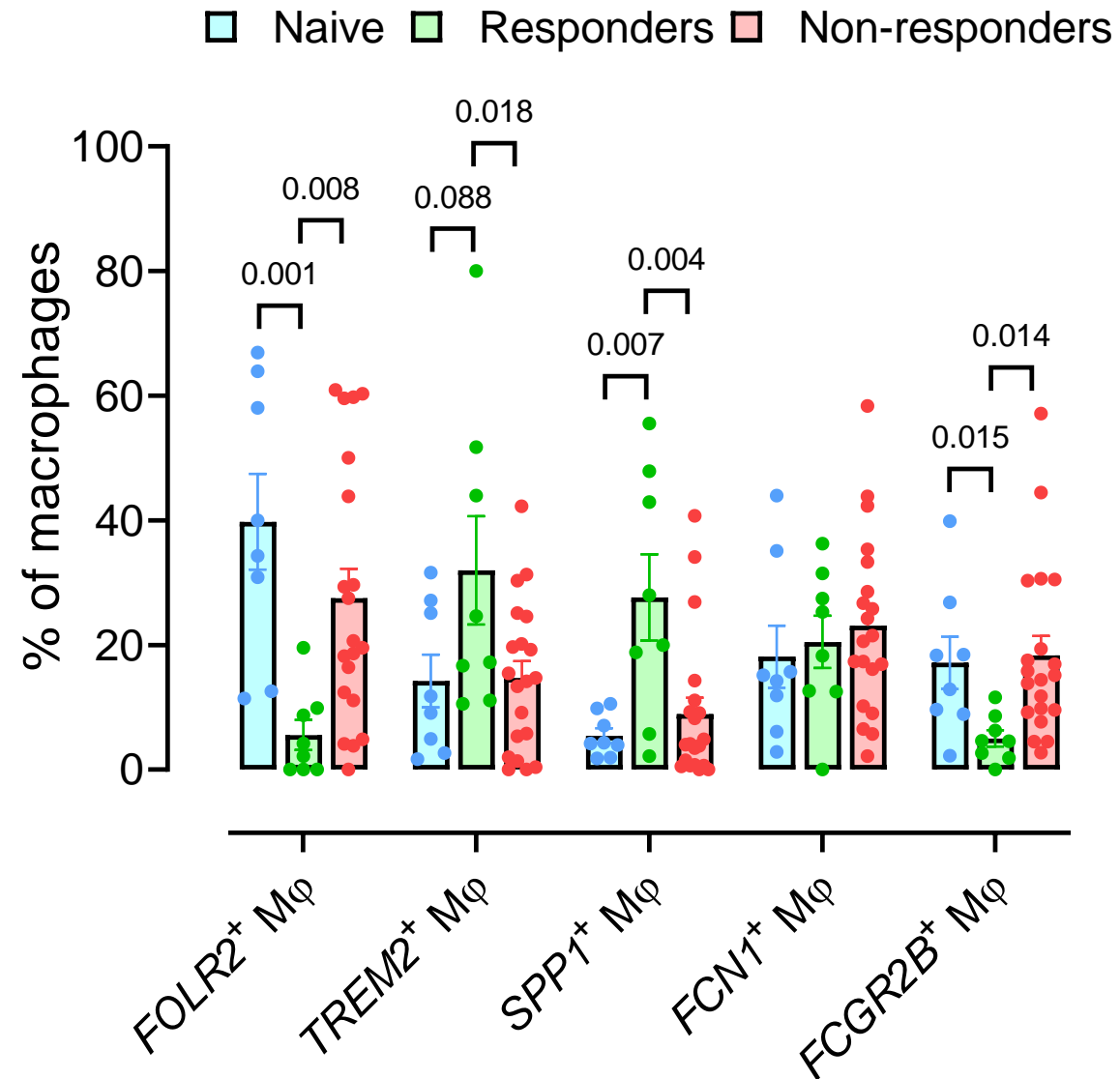
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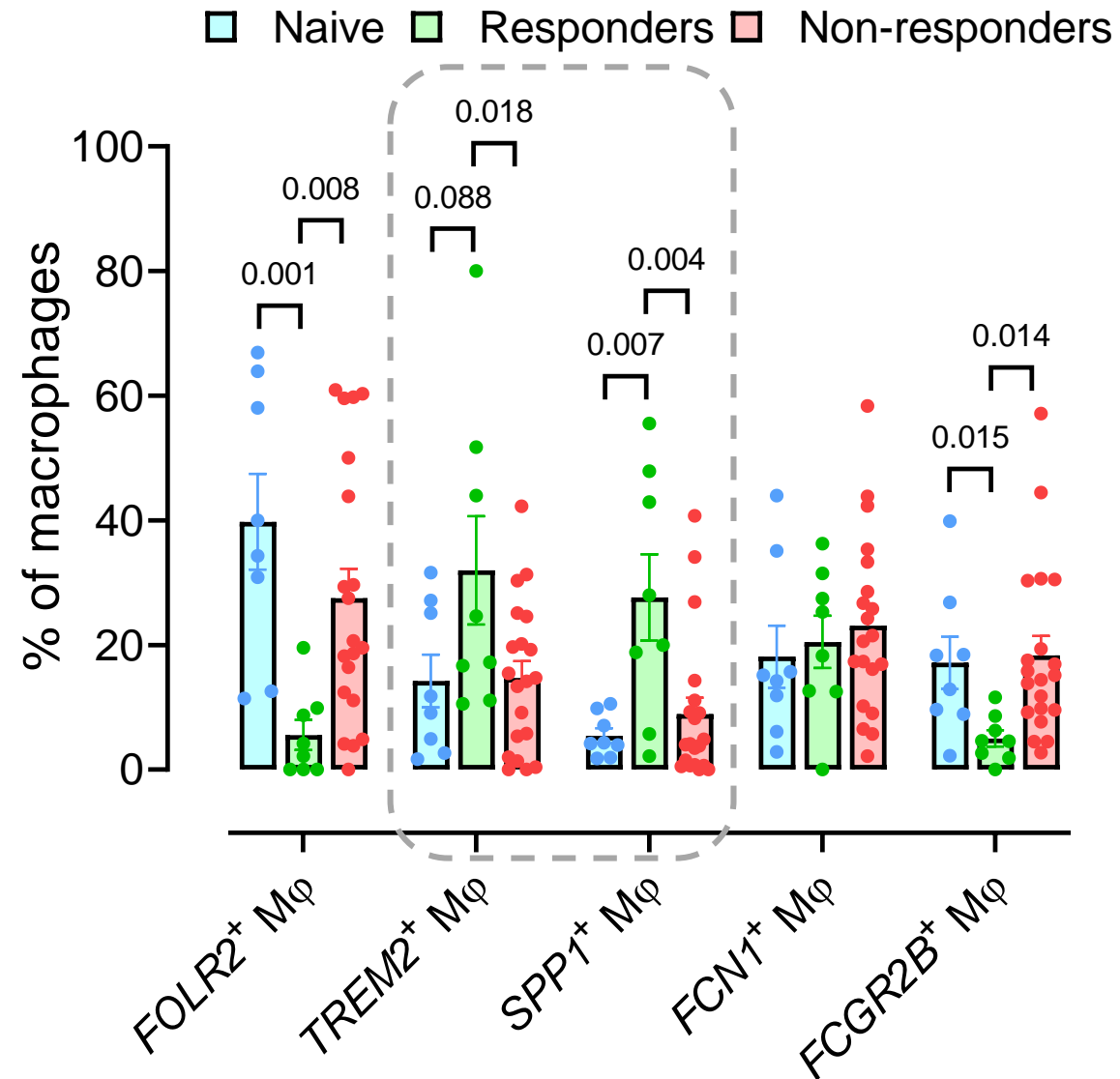
Macrophage subsets specifically accumulate in HCC lesions during PD-1 blockade



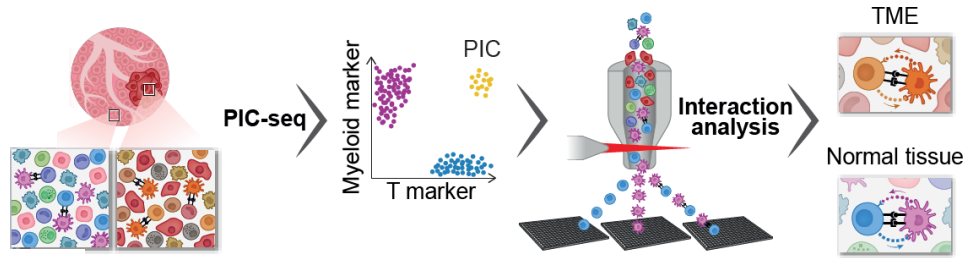
TREM2 and SPP1 associated macrophages accumulate in responder patients



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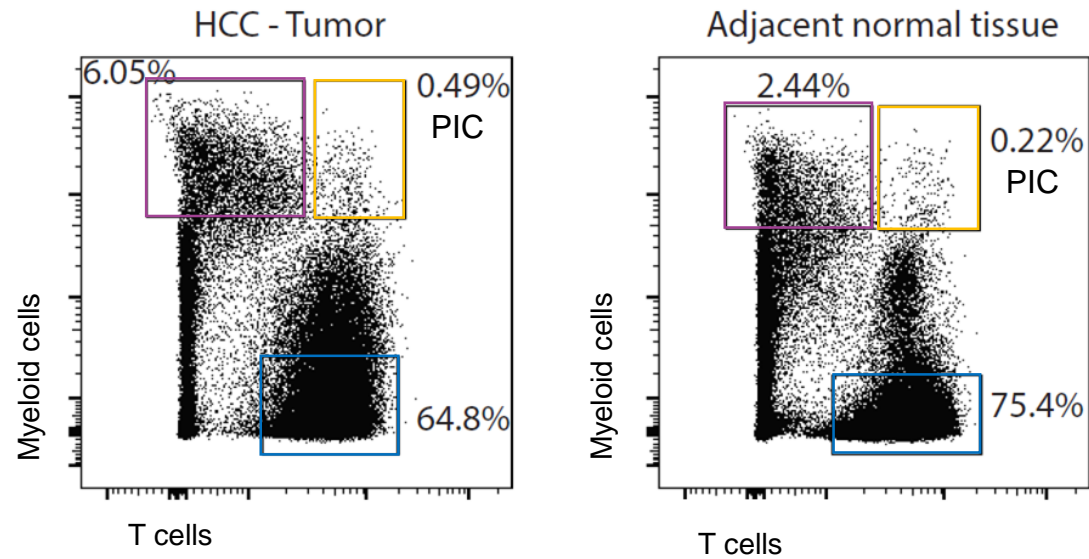


TREM2 macrophages interact with T cells in the TME



PIC = Physically Interacting Cells

From Cohen, Giladi et al, Nature Cancer 2022
Giladi, Nature Biotech 2020



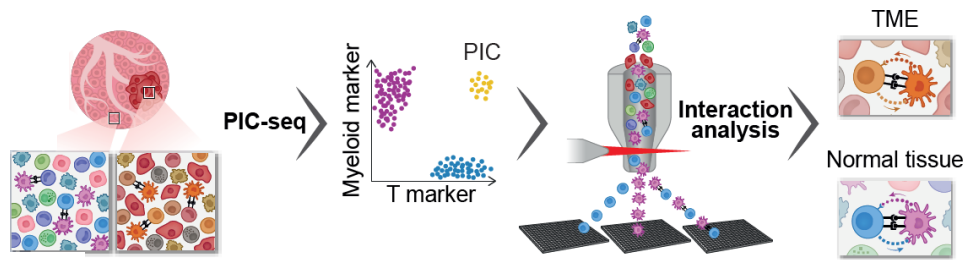
Merav Cohen, PhD



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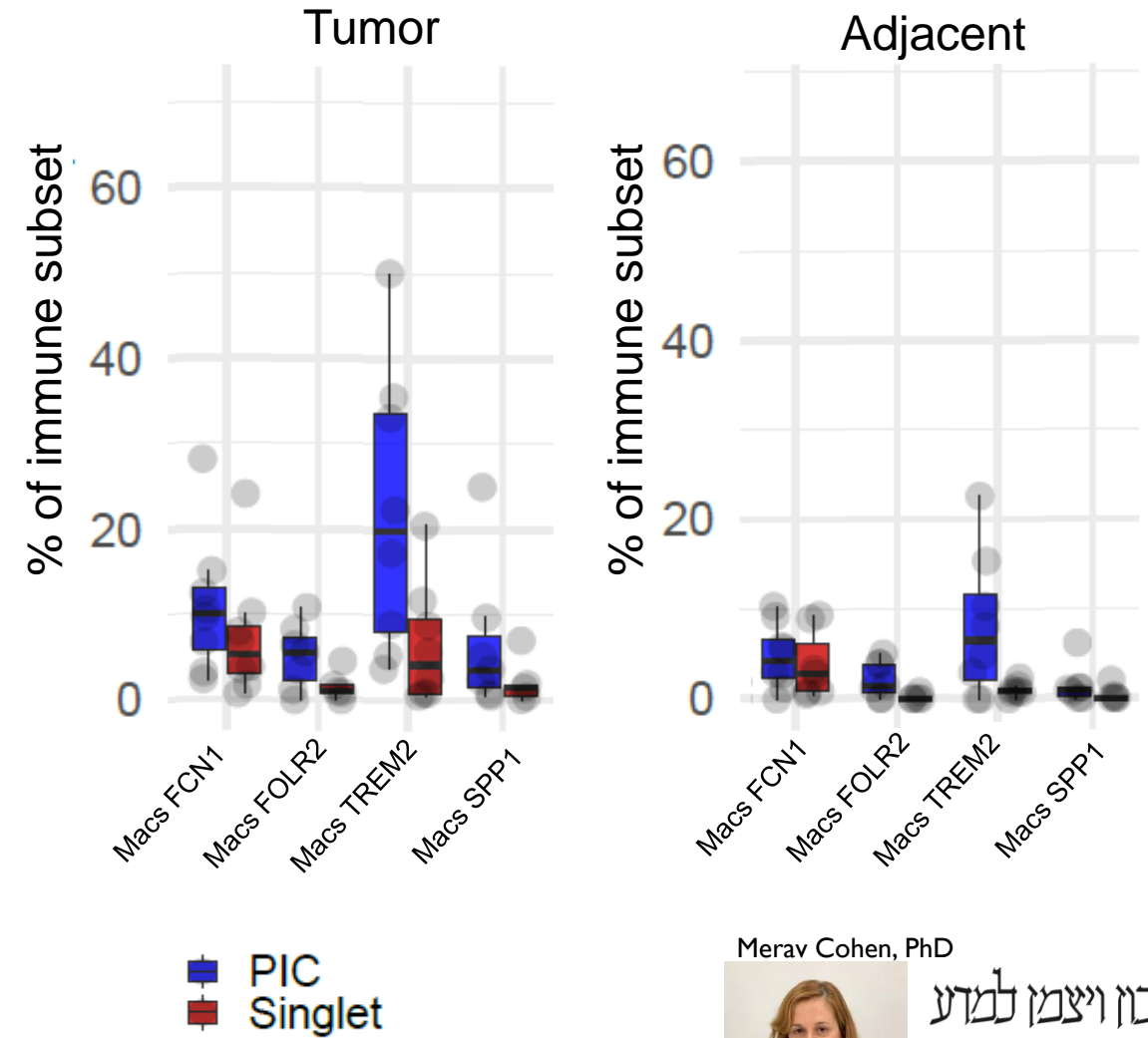
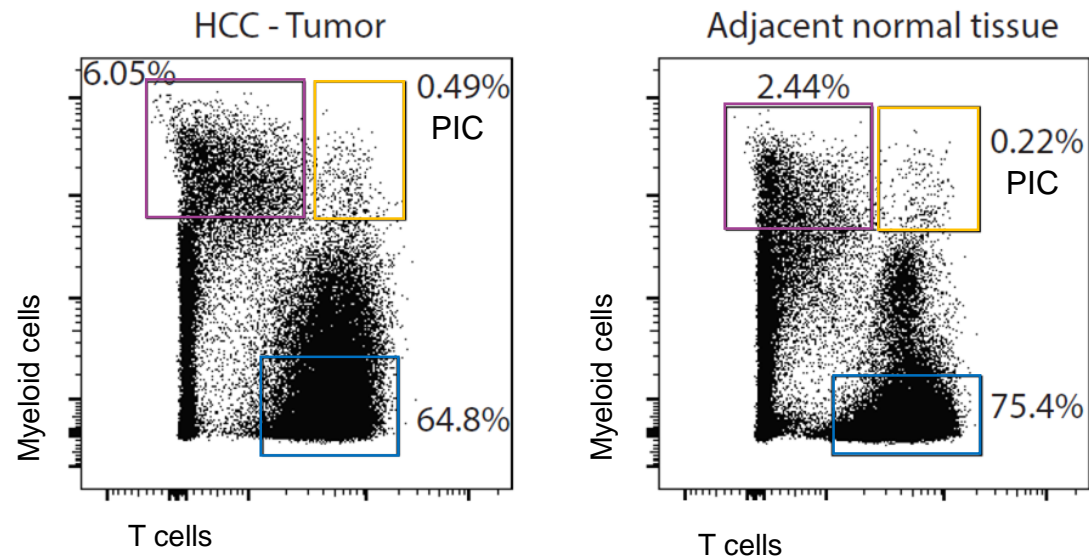
Icahn School of Medicine at
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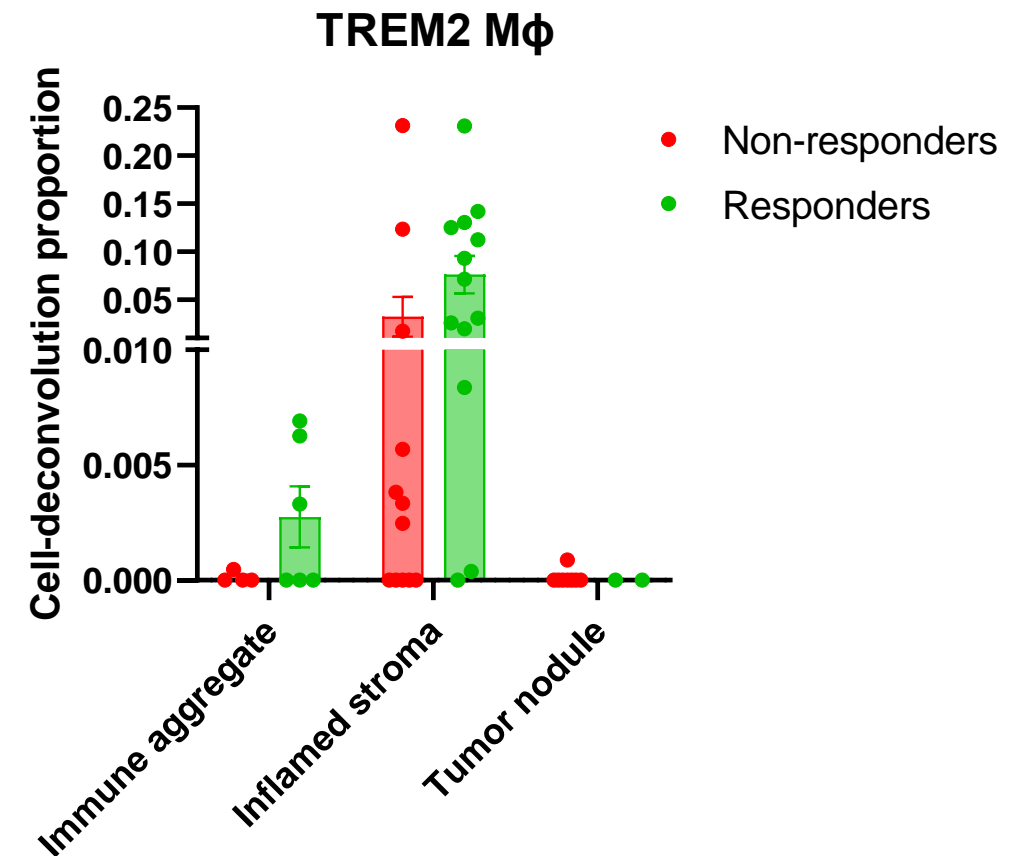
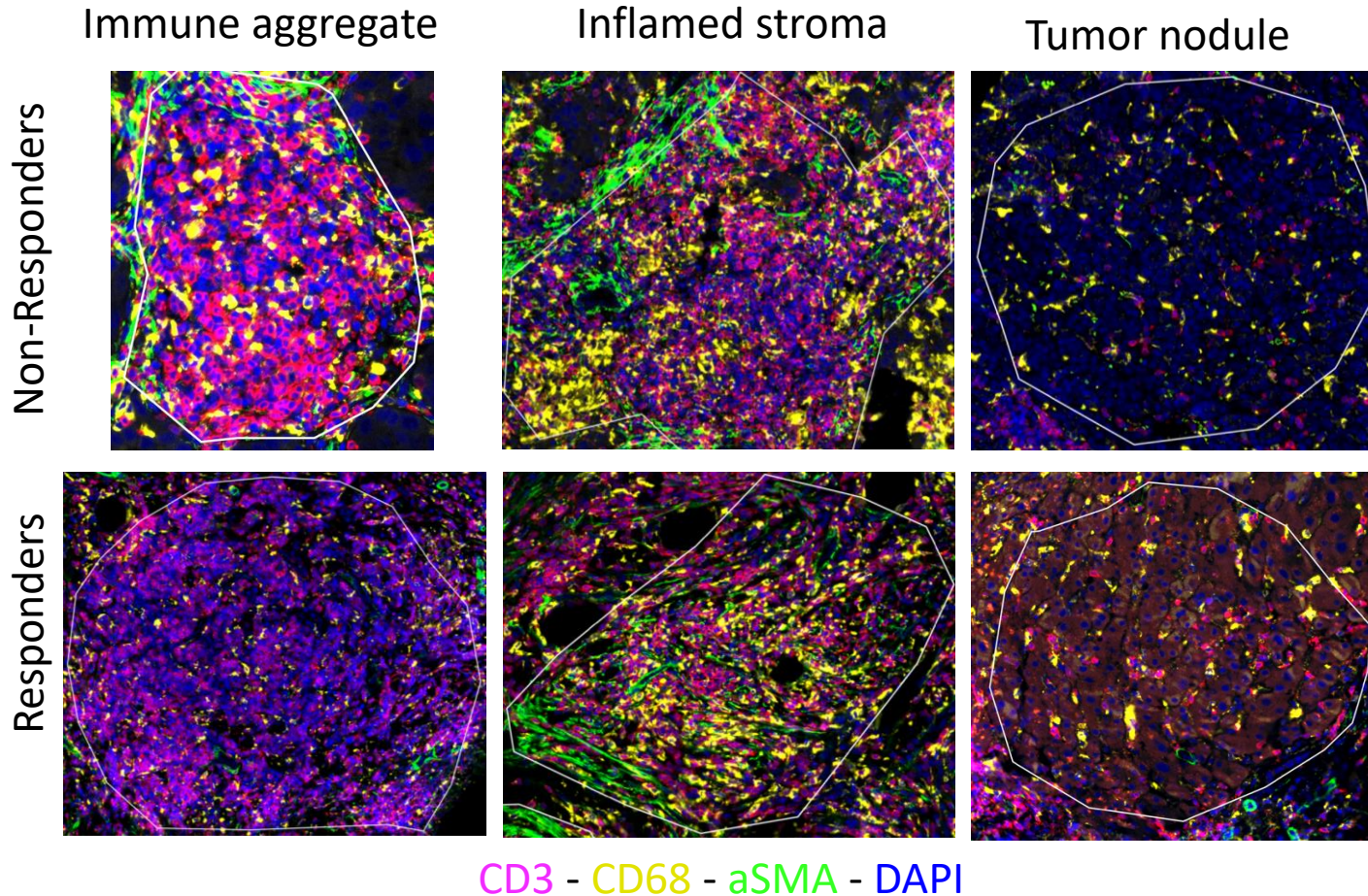
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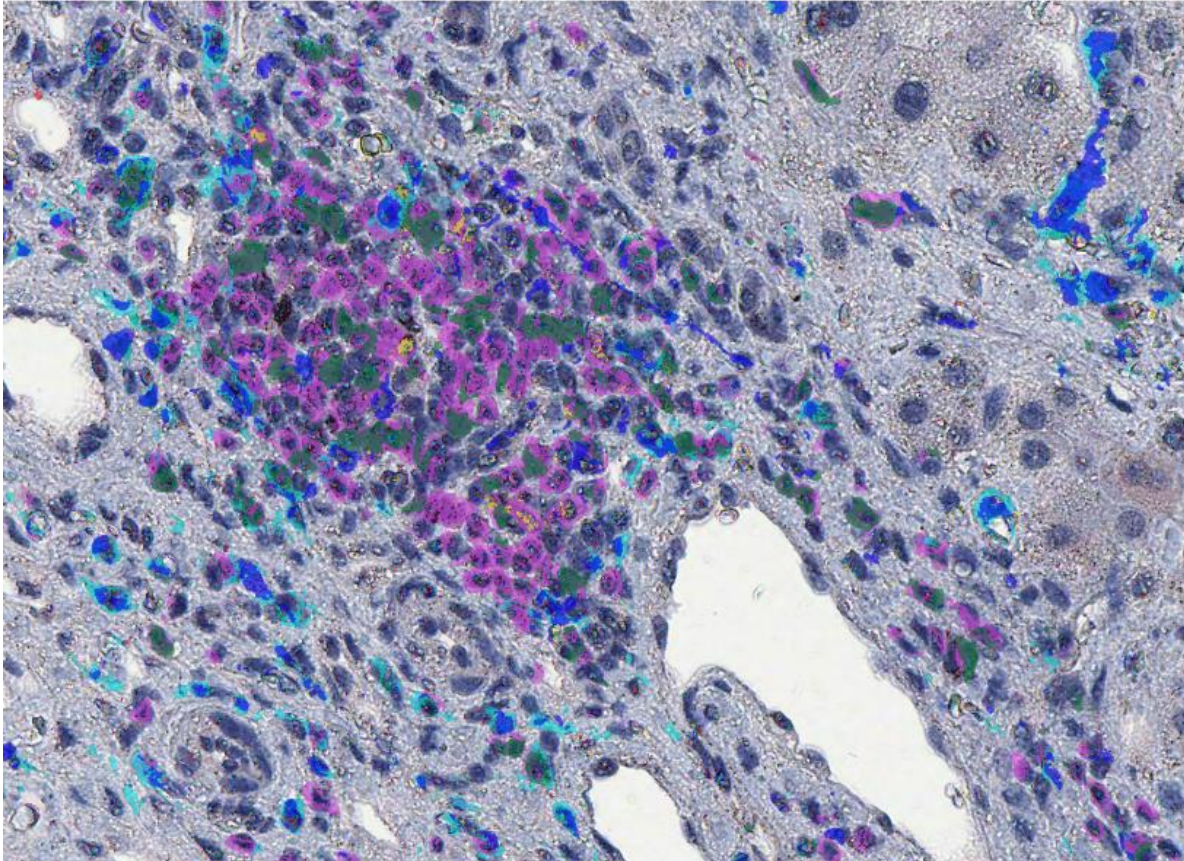
Spatial transcriptomic reveals enrichment of TREM2 Mac program in inflamed stroma and immune aggregates in response to PD-1 blockade



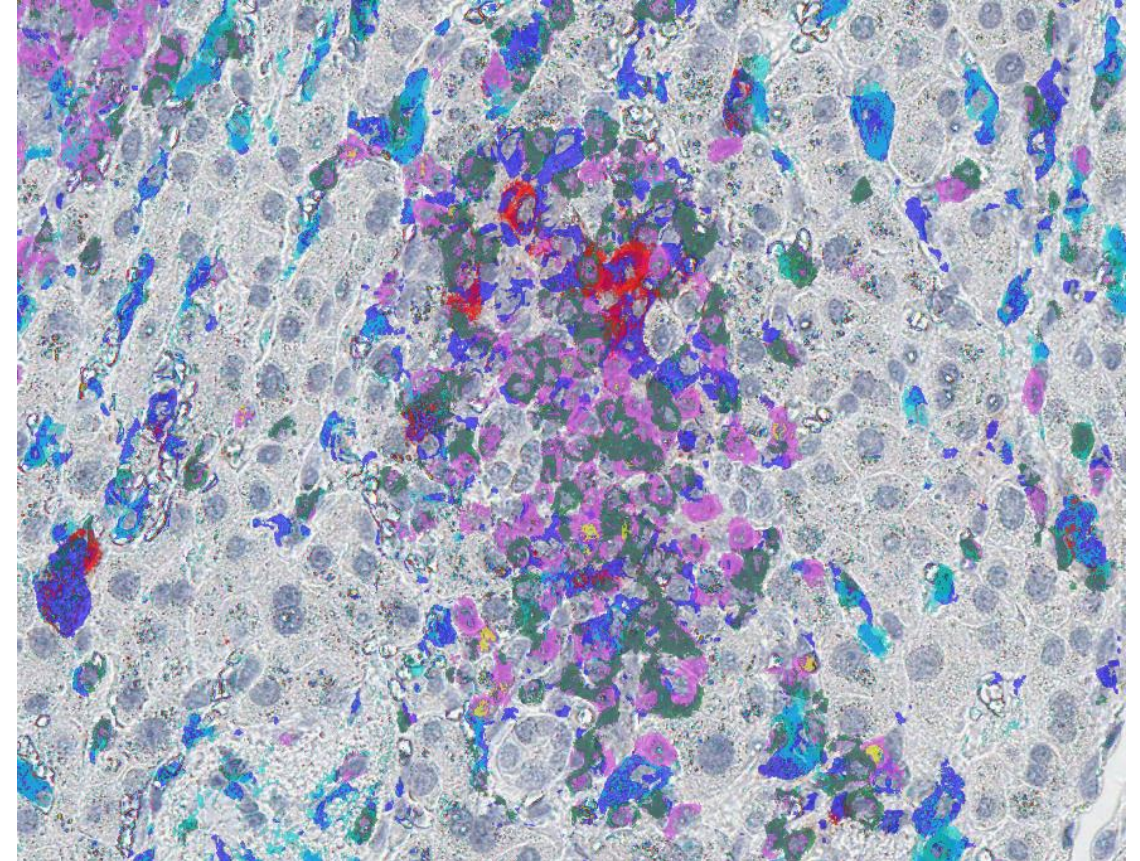
SITC-NanoString Technology Award

TREM2 Macs are enriched in the immune aggregates of patients responding to PD-1 blockade

Non-Responders



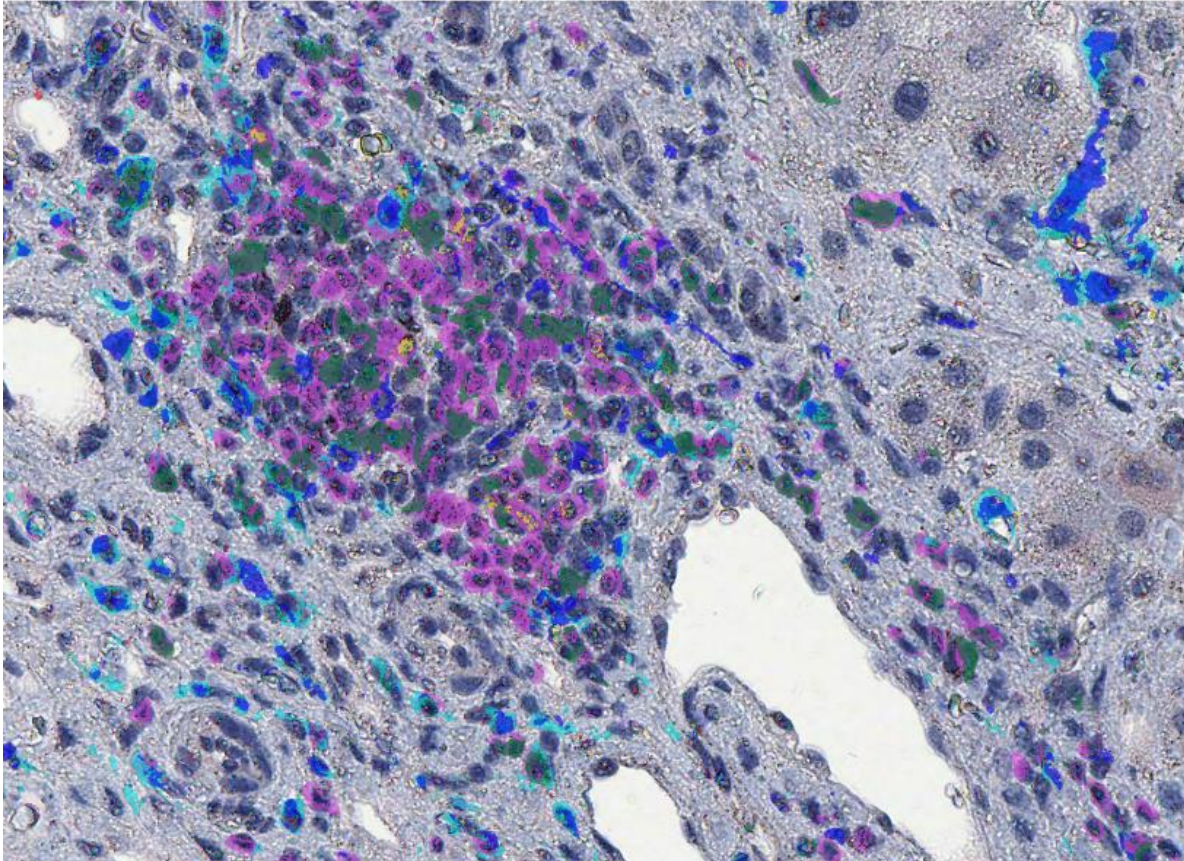
Responders



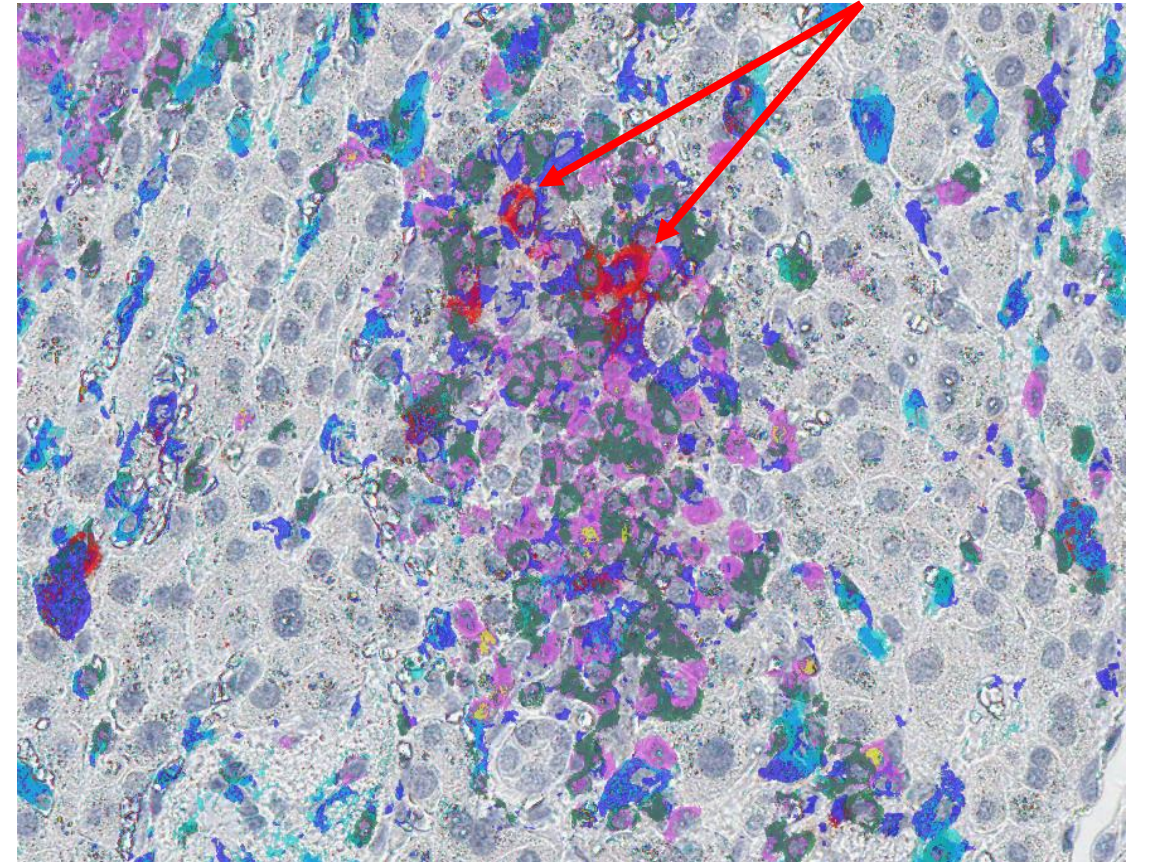
CD68 FOLR2 TREM2 CD3 CD8 FOXP3

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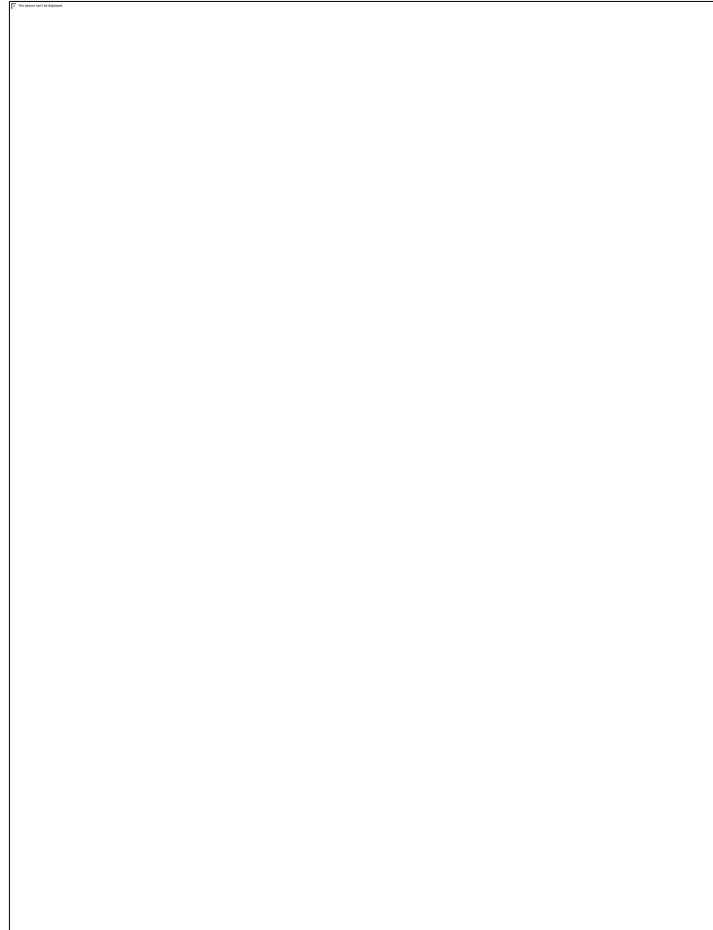
Responders



TREM2 Macs

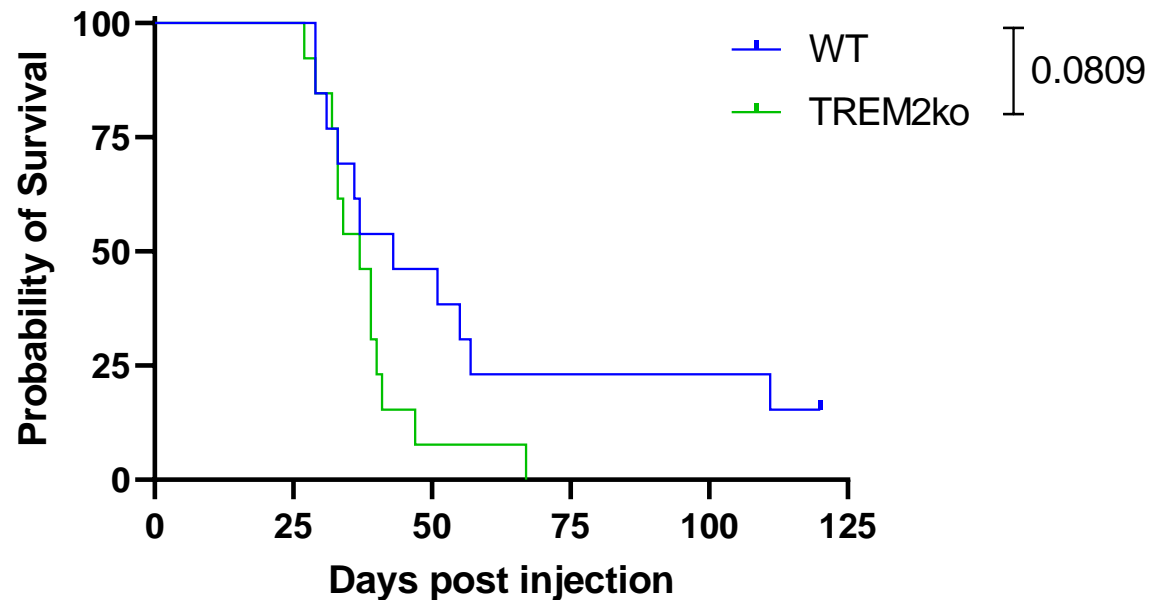
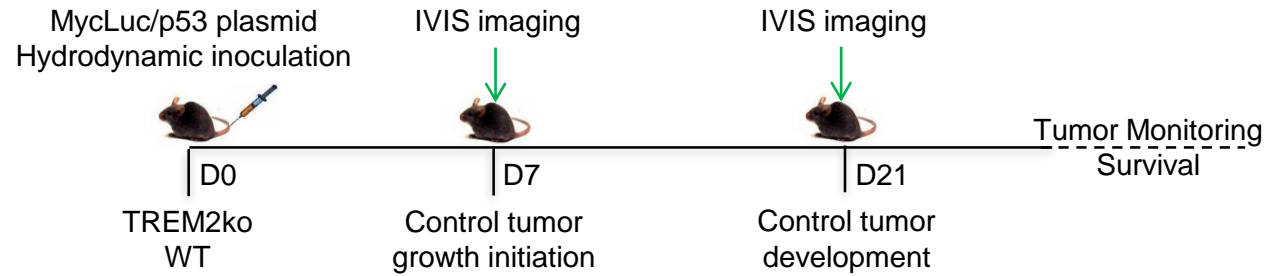
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TREM2 signaling pathway and role in disease



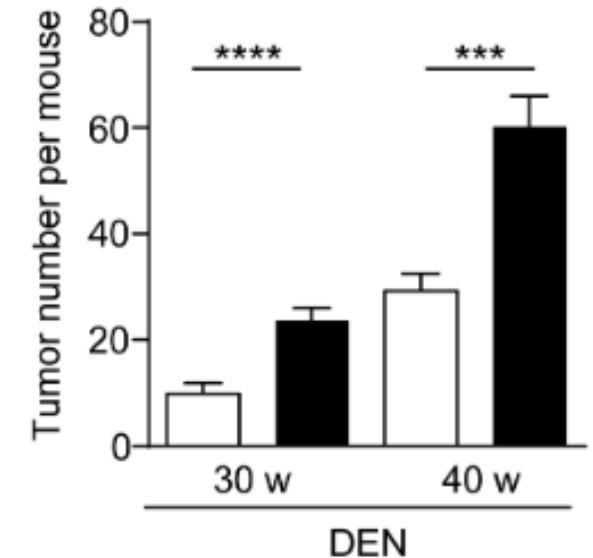
- TREM2 signaling is propagated via DAP12 and results in activation of PI3K
- In human, TREM2 macrophages have a protective role in Alzheimer and metabolic diseases including obesity and NAFLD
- TREM2 Macs are associated with bad prognosis in multiple cancer types
- TREM2ko mice exhibit increased liver damage and inflammation in acute and chronic liver damage mouse models

Protective role of TREM2 in HCC mouse models

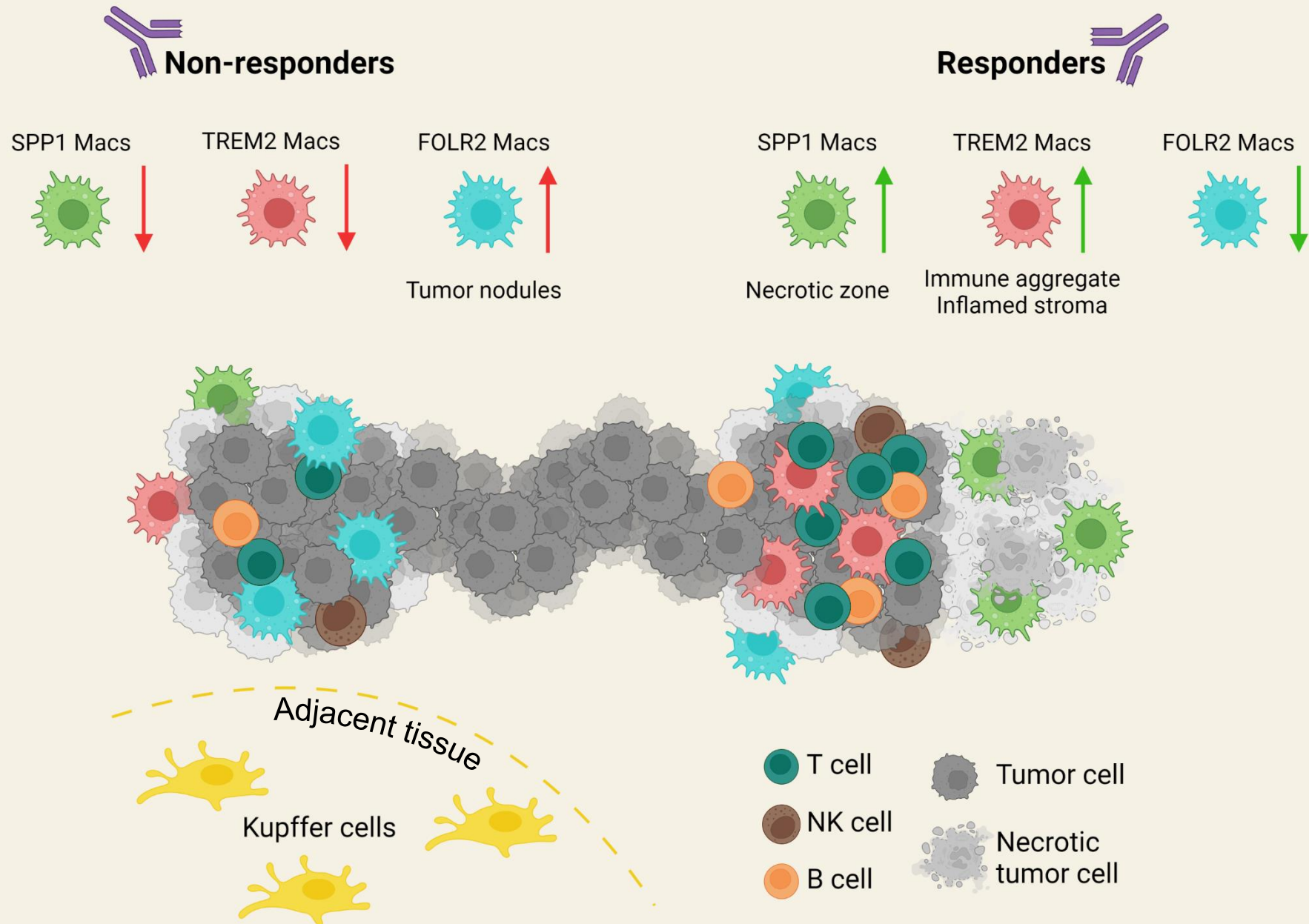


□ WT mice
■ *Trem-2^{-/-}* mice

Tumor number



Conclusion



Acknowledgement

Merad lab

Miriam Merad

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Christie Chang

Alona Lansky

Andrew Leader

Nausicaa Malissen

Yonit Lavin

Fiona Desland



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Darwin D'souza

& members

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Thomas Marron

Myron Schwartz

& clinical research coordinators

*Thank you to the patients
and their families!*