Tumor Immune Microenvironment: A Holistic Approach Workshop

April 21-22, 2022 • San Diego and Virtually

#SITCworkshop

sitc

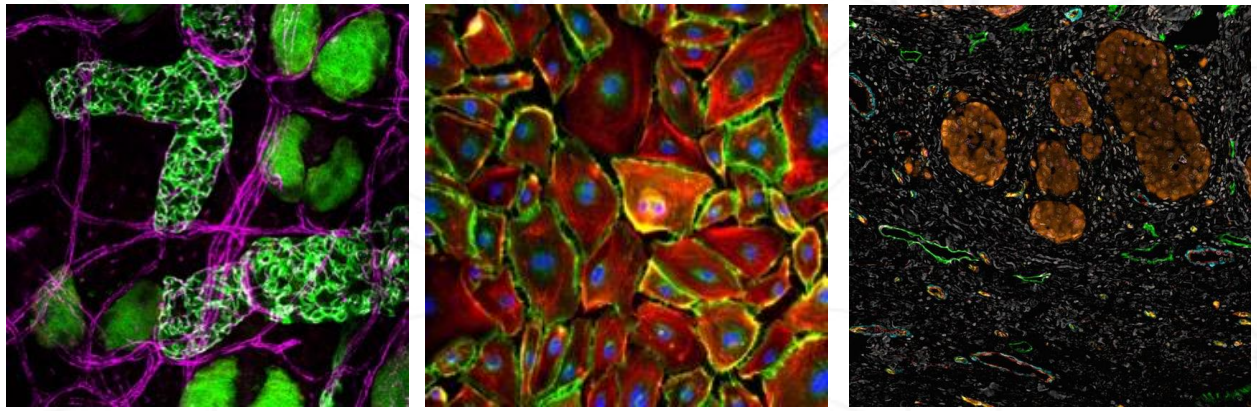
Society for Immunotherapy of Cancer

NYU Langone Health

Lymphatic transport, immune surveillance, and immune evasion

Amanda W. Lund, PhD

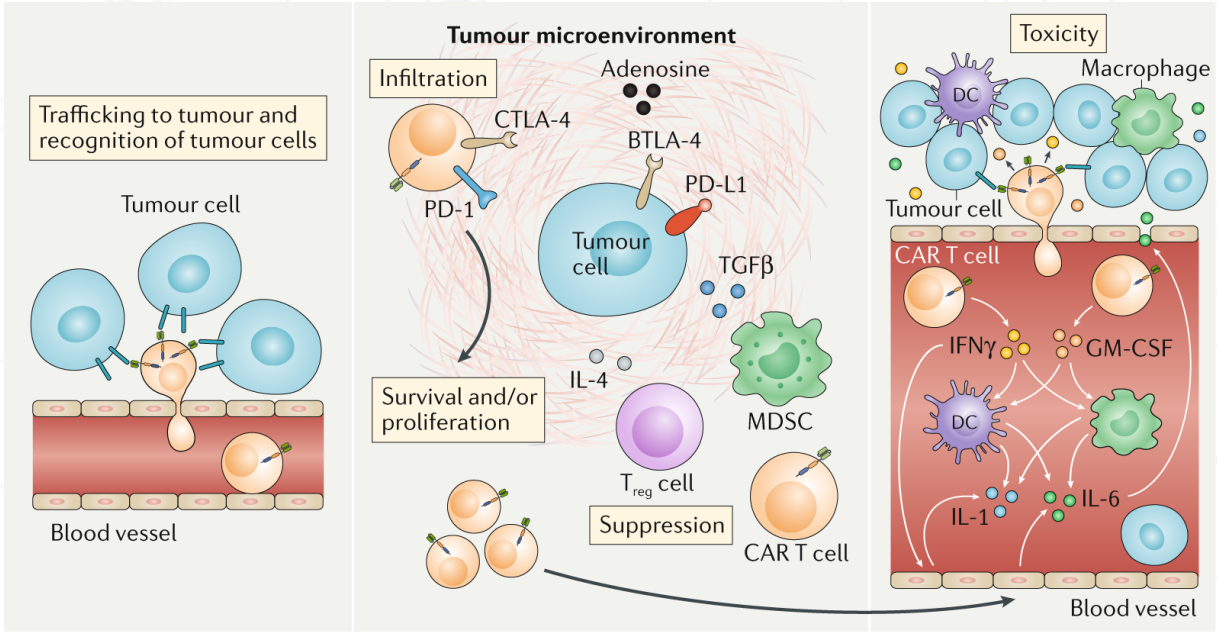
Friday April 22, 2022



Associate Professor, Ronald O. Perelman Department of Dermatology, Department of Pathology, and Laura and Isaac Perlmutter Cancer Center

Amanda W. Lund, PhD
No Disclosures

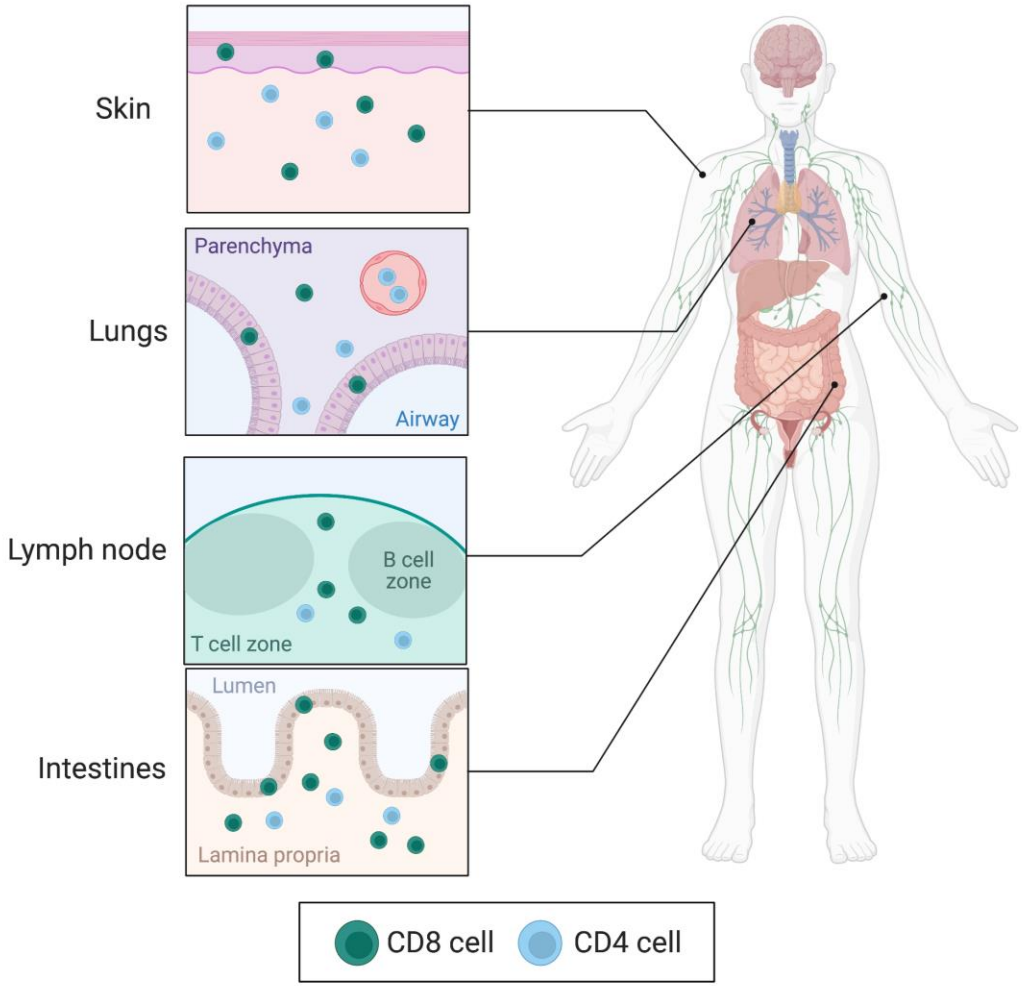
Microenvironmental barriers to T cell-based therapies

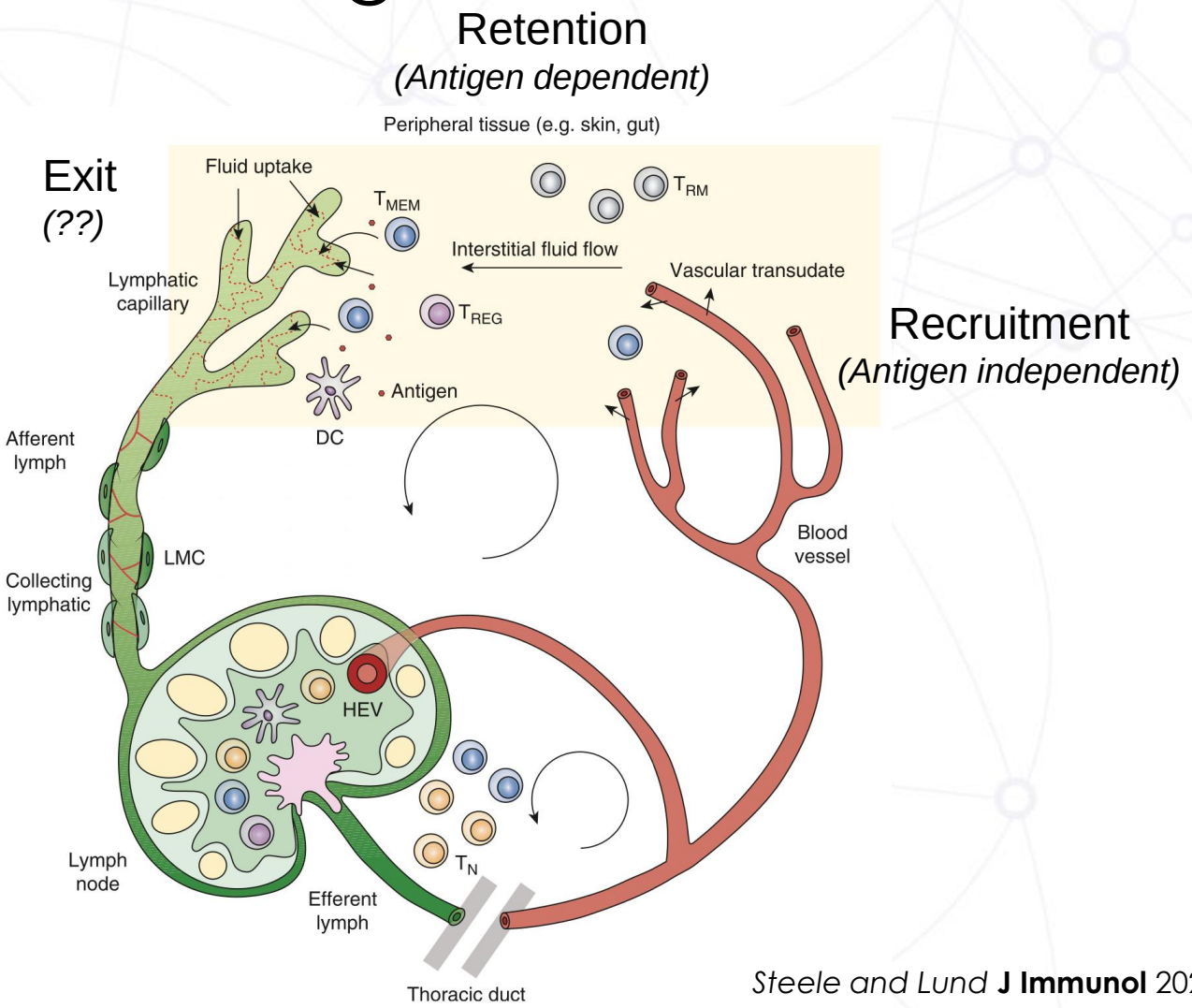


• Homing to tumour tissues • Tumour cell heterogeneity for antigen expression	• Physical barriers • Inhibitory ligands • Immunosuppressive cells (T_{reg} cells and MDSCs) • Antigen escape • Excessive co-stimulation	• On-target, off-tumour toxicities • CRS • ICANS
• Chemokines • Multispecific CARs • BiTEs	• Alter CAR structure • Cytokines • Ligands • Enzymes • BiTEs • scFv • Switch and/or dominant-negative receptors	• Alter CAR structure • Co-expression of factors • Safety switches • Logic gating and/or small-molecule adapters

Rafiq et al **Nat Rev Clin Oncol** 2019

Tissue/Tumor distribution of T cells depends on coordinated vascular and tissue signals

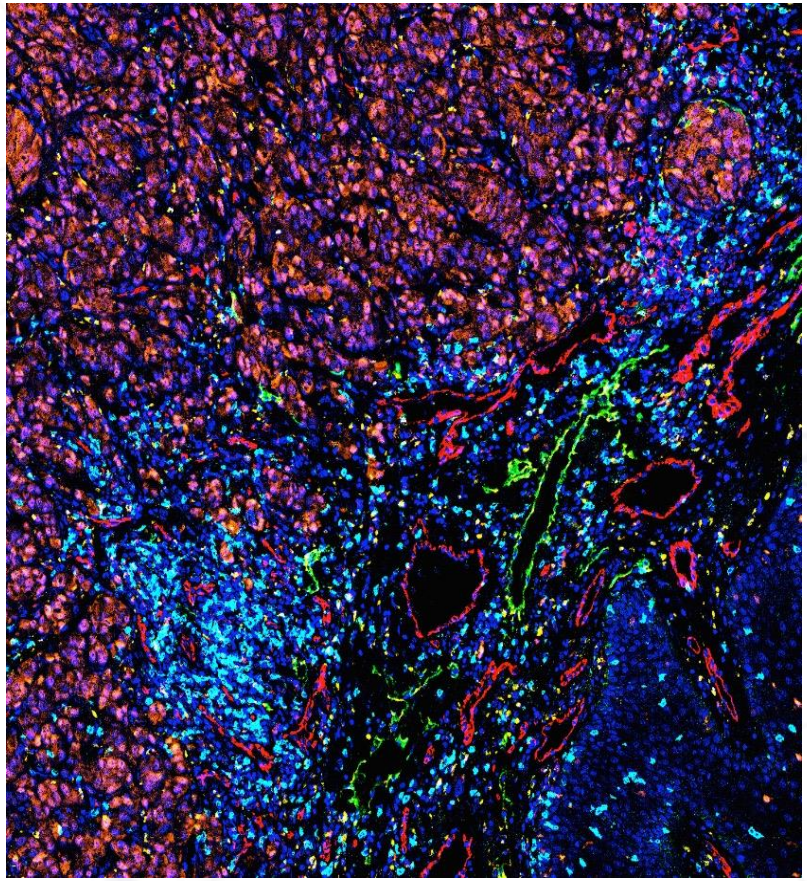




Steele and Lund **J Immunol** 2021

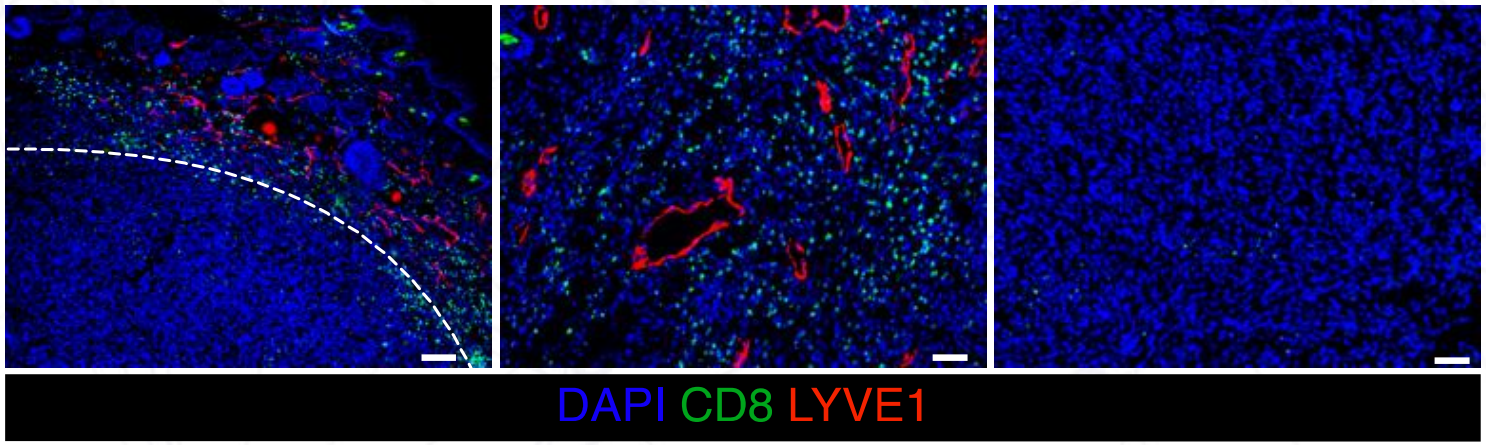
CD8+ T cells are restricted to the activated peritumoral stroma

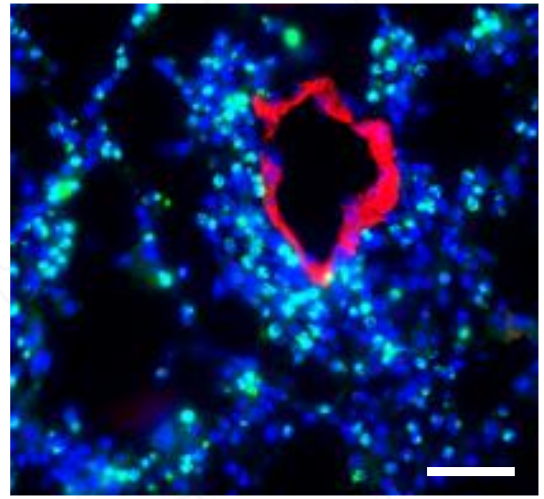
Human Cutaneous Primary Melanoma



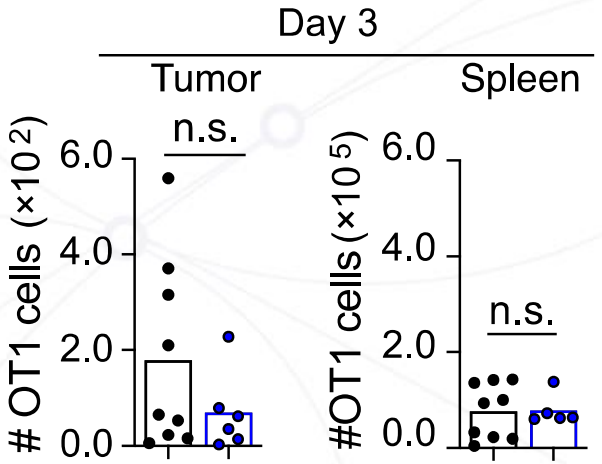
S100 CD8 PDPN AQP1 CD68

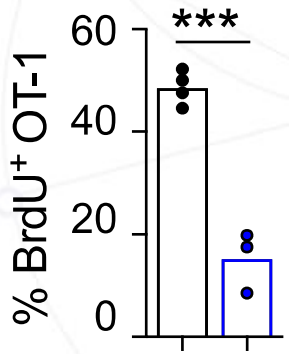
Primary Murine Melanoma

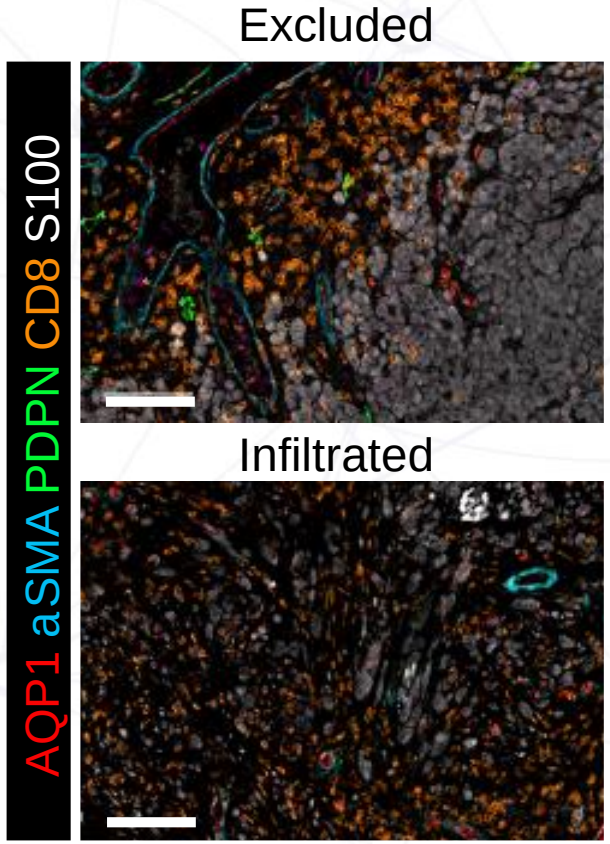


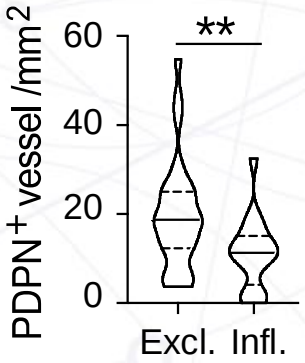


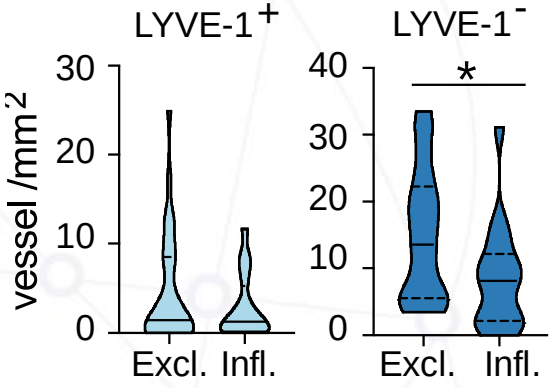
Dermal lymphatic vessels limit CD8+ T cell accumulation in melanoma





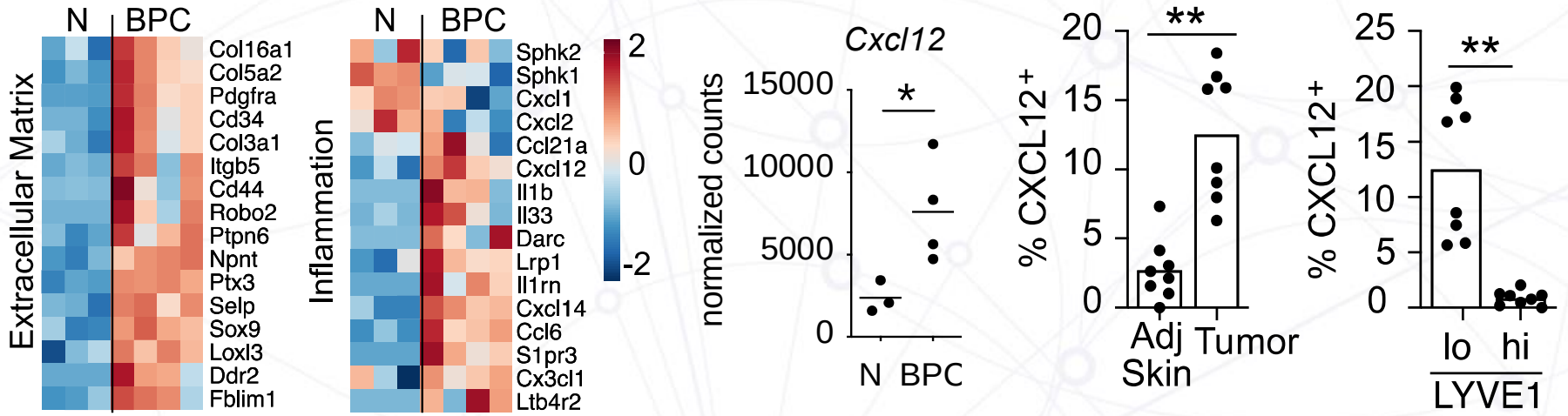


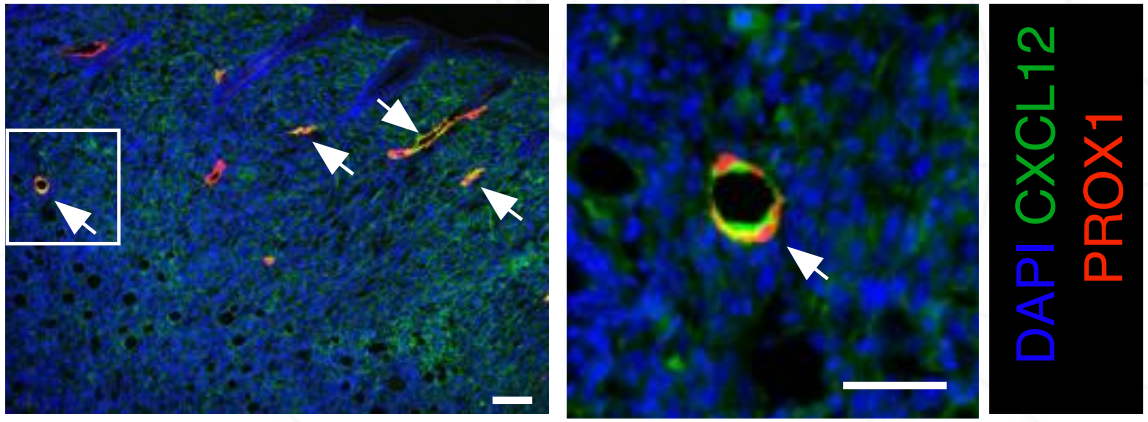




Steele et al *under review* 2022

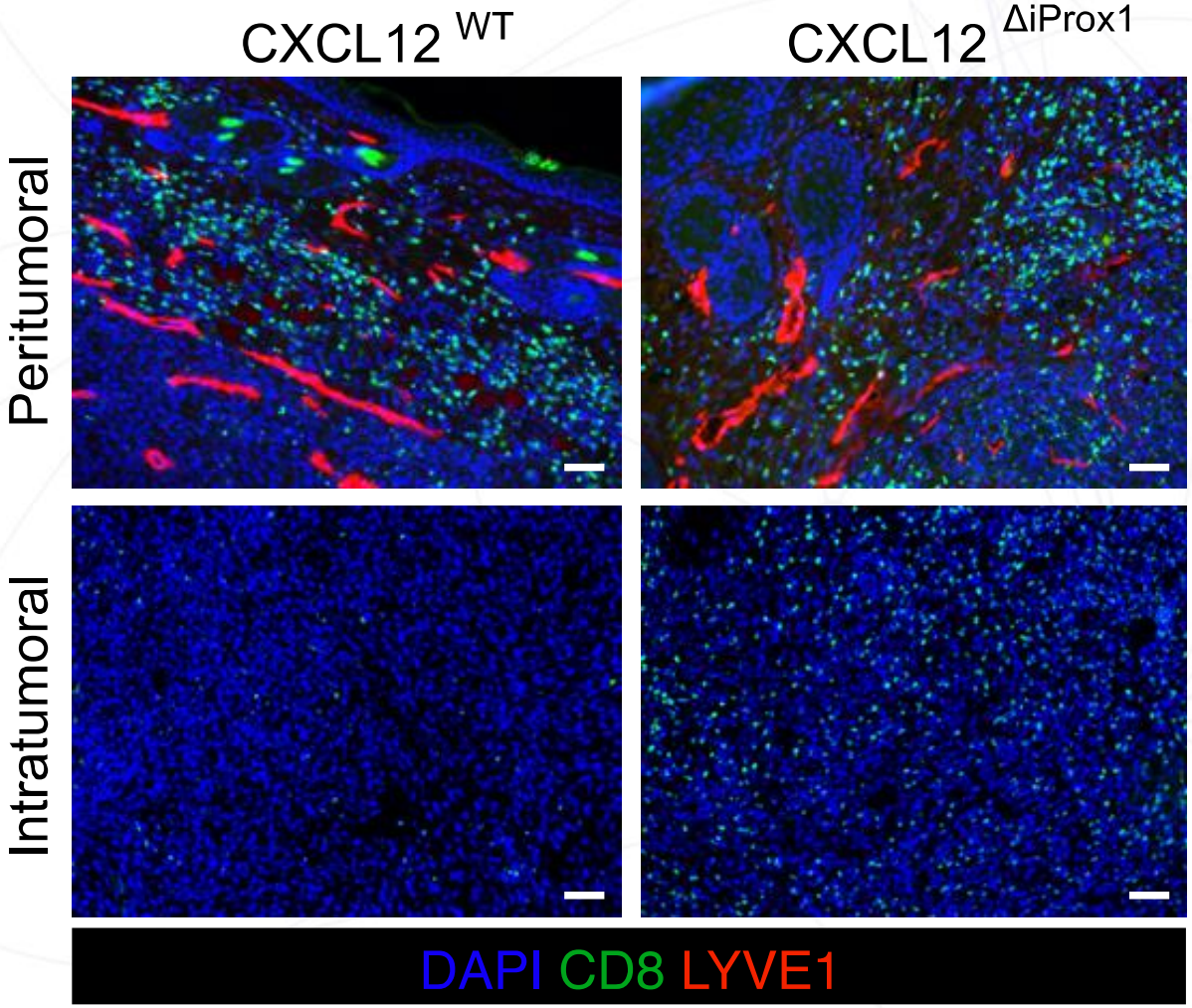
Lymphatic endothelial cells are transcriptionally reprogrammed in the tumor microenvironment

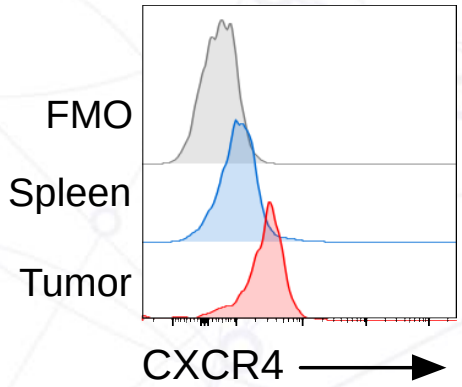


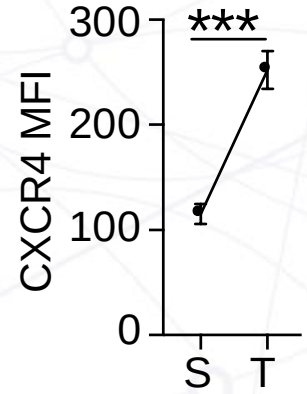


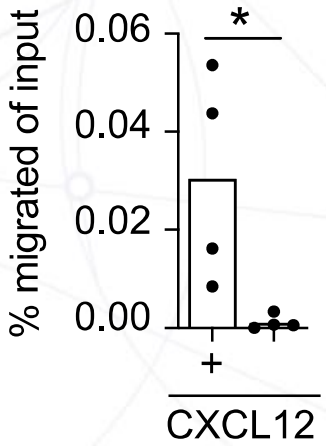
Steele et al *under review* 2022

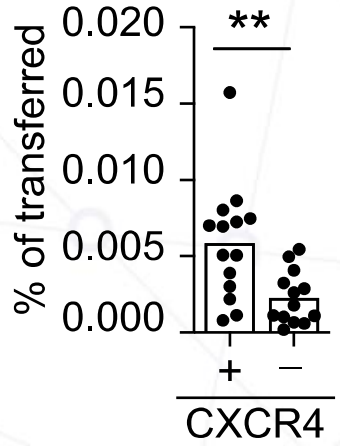
Lymphatic-secreted CXCL12 sequesters CD8+ T cells in the tumor periphery











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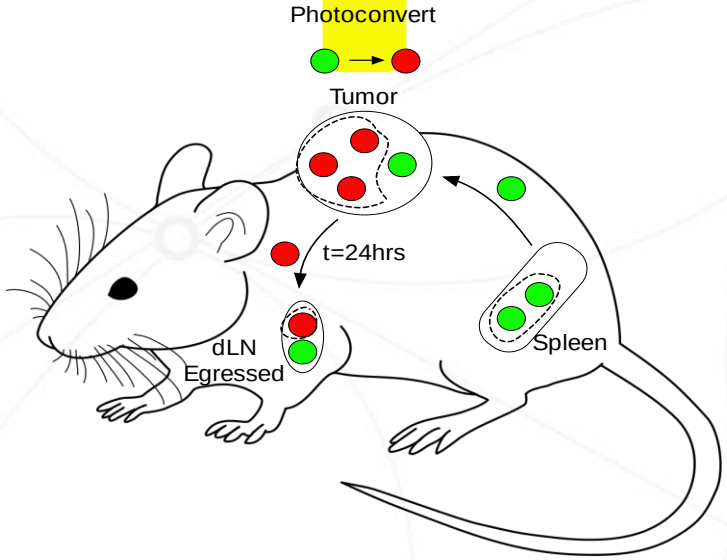
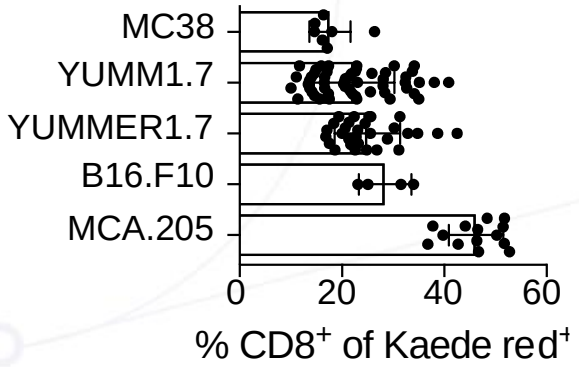
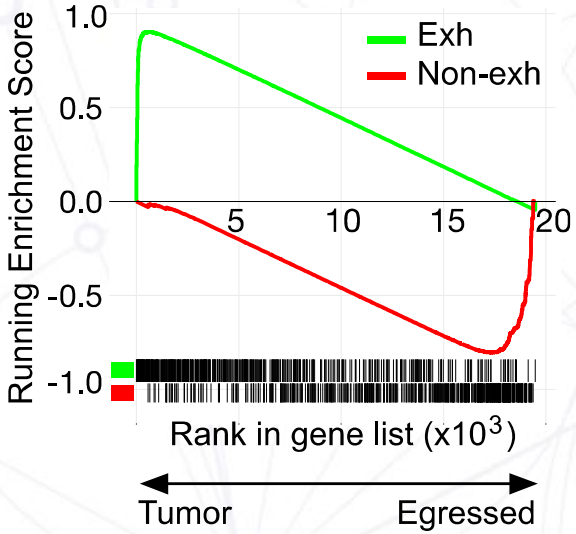
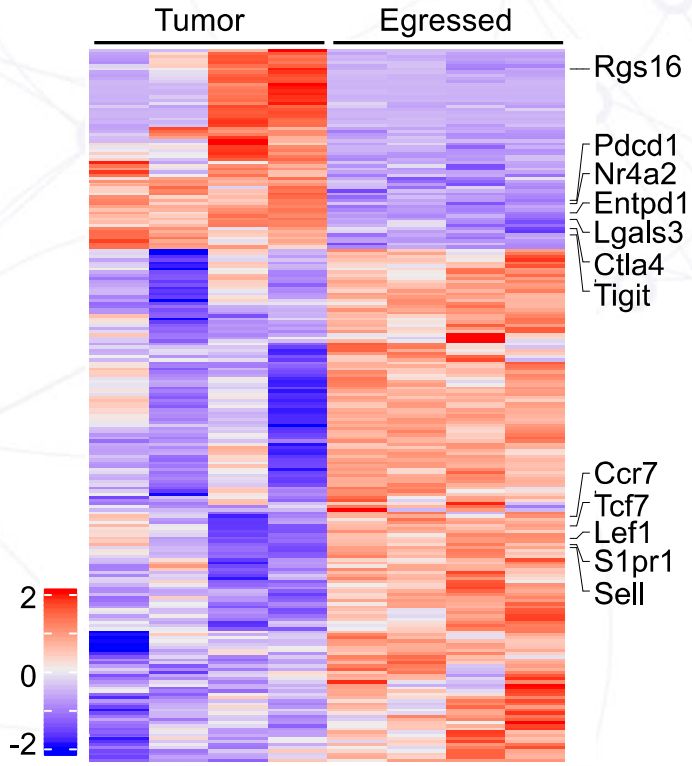
Functional CD8+ T cells exit the tumor microenvironment









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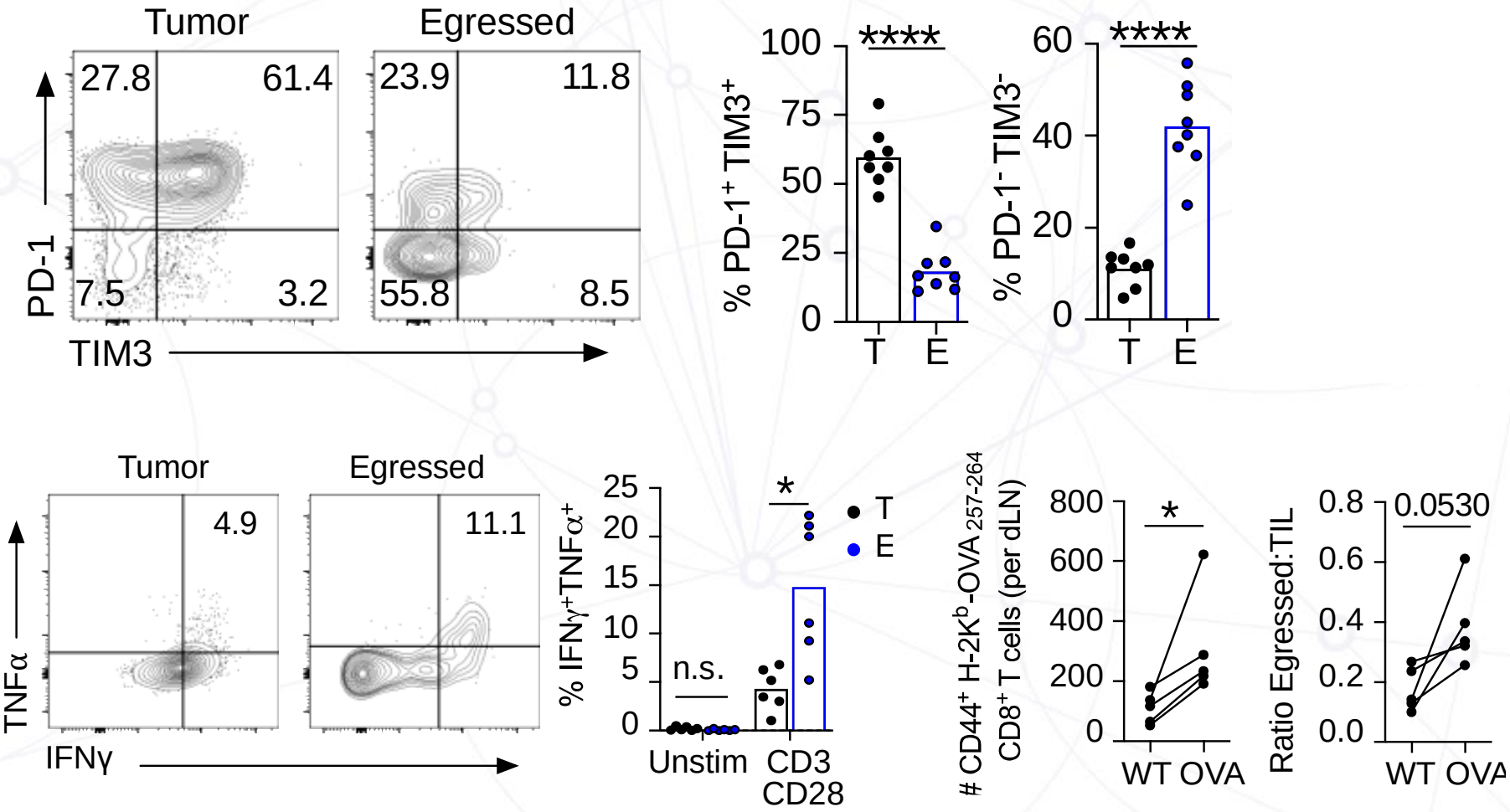
Tumor-specific, functional CD8+ T cells are expelled from the tumor microenvironment



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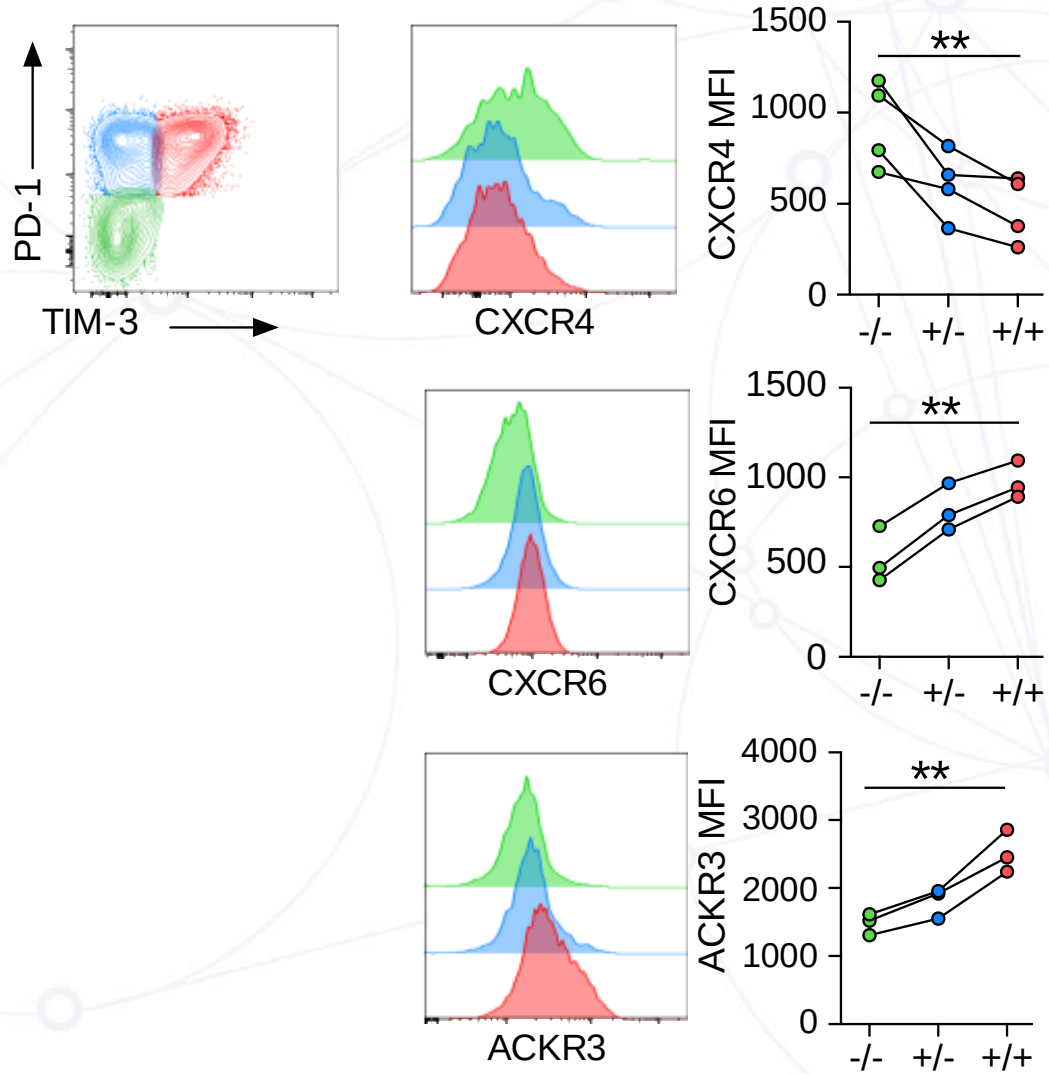
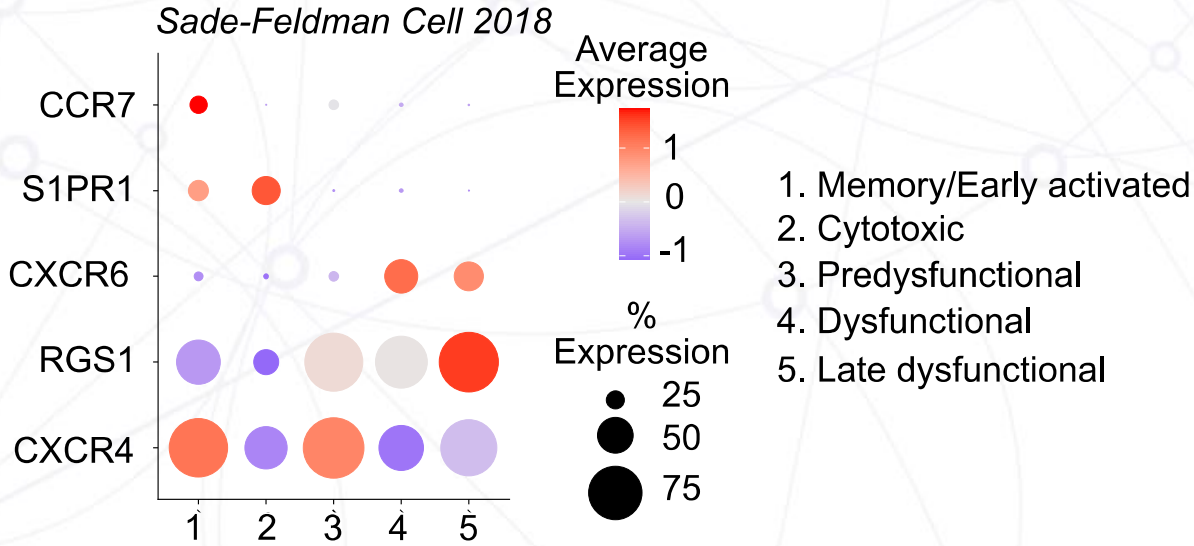
Linking migration potential and T cell state in tumors





1. Memory/Early activated
2. Cytotoxic
3. Predysfunctional
4. Dysfunctional
5. Late dysfunctional

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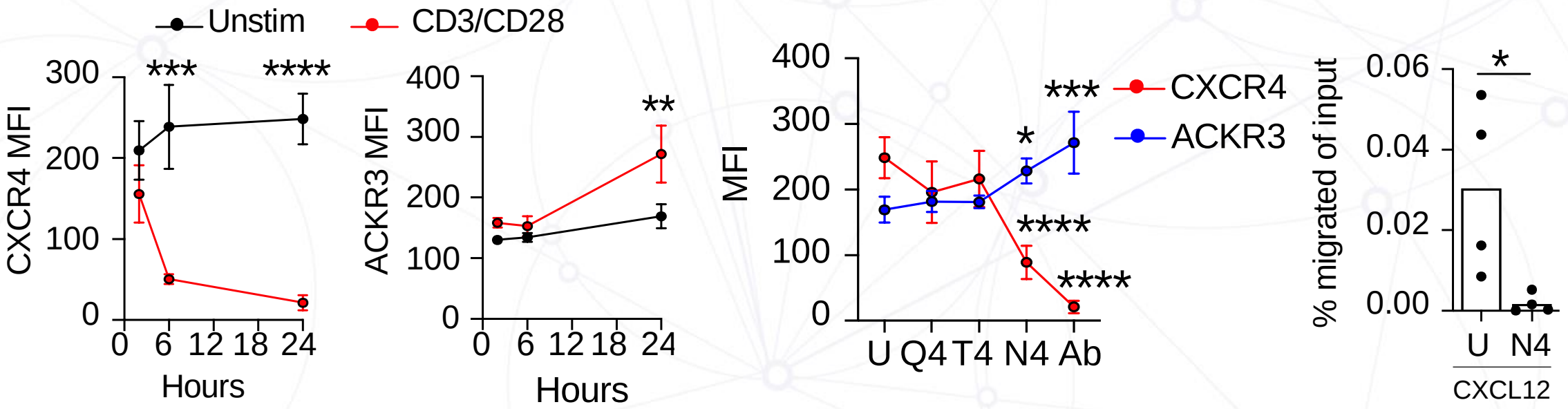
Antigen encounter regulates CXCL12 sensitivity and migration ex *vivo*



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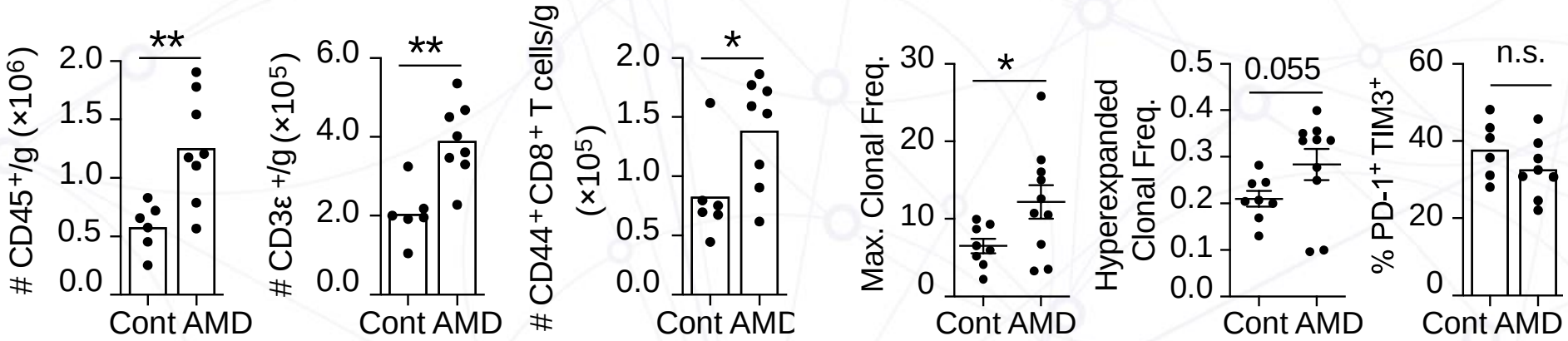
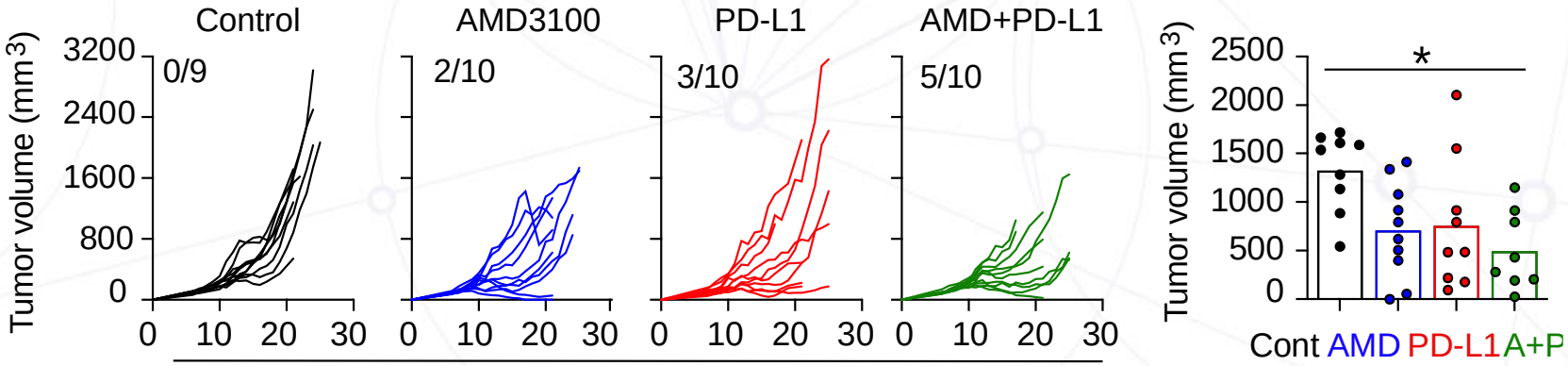
CXCR4 inhibition synergizes with immune checkpoint blockade in immunogenic melanoma





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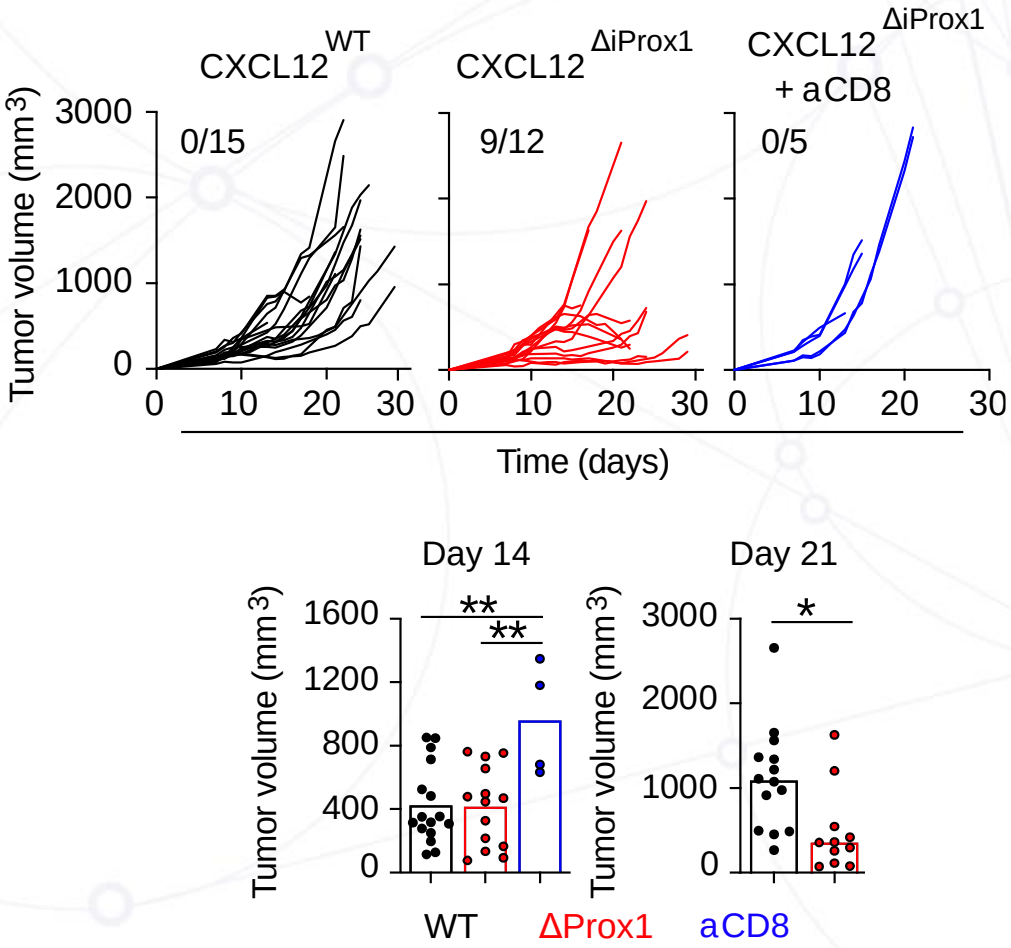
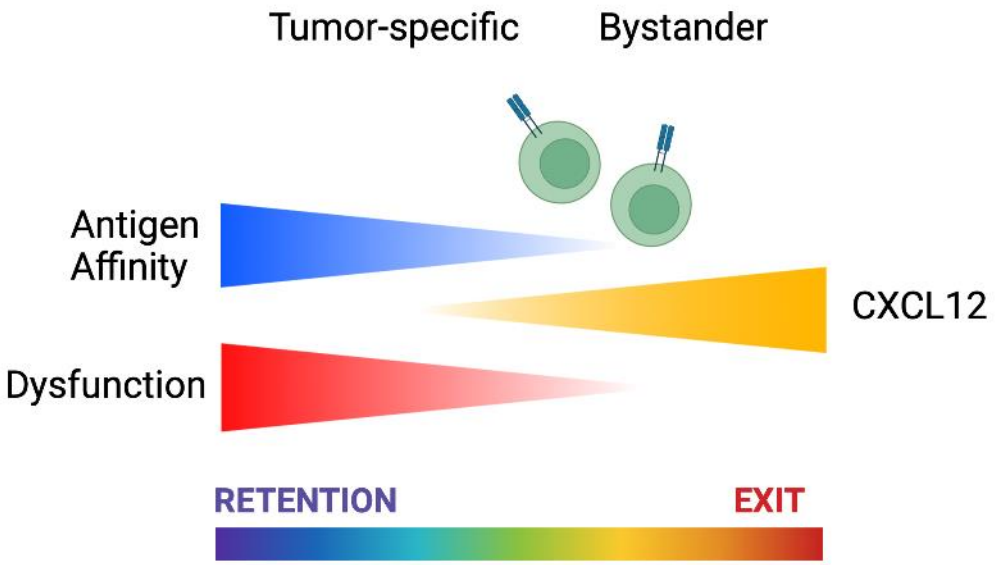
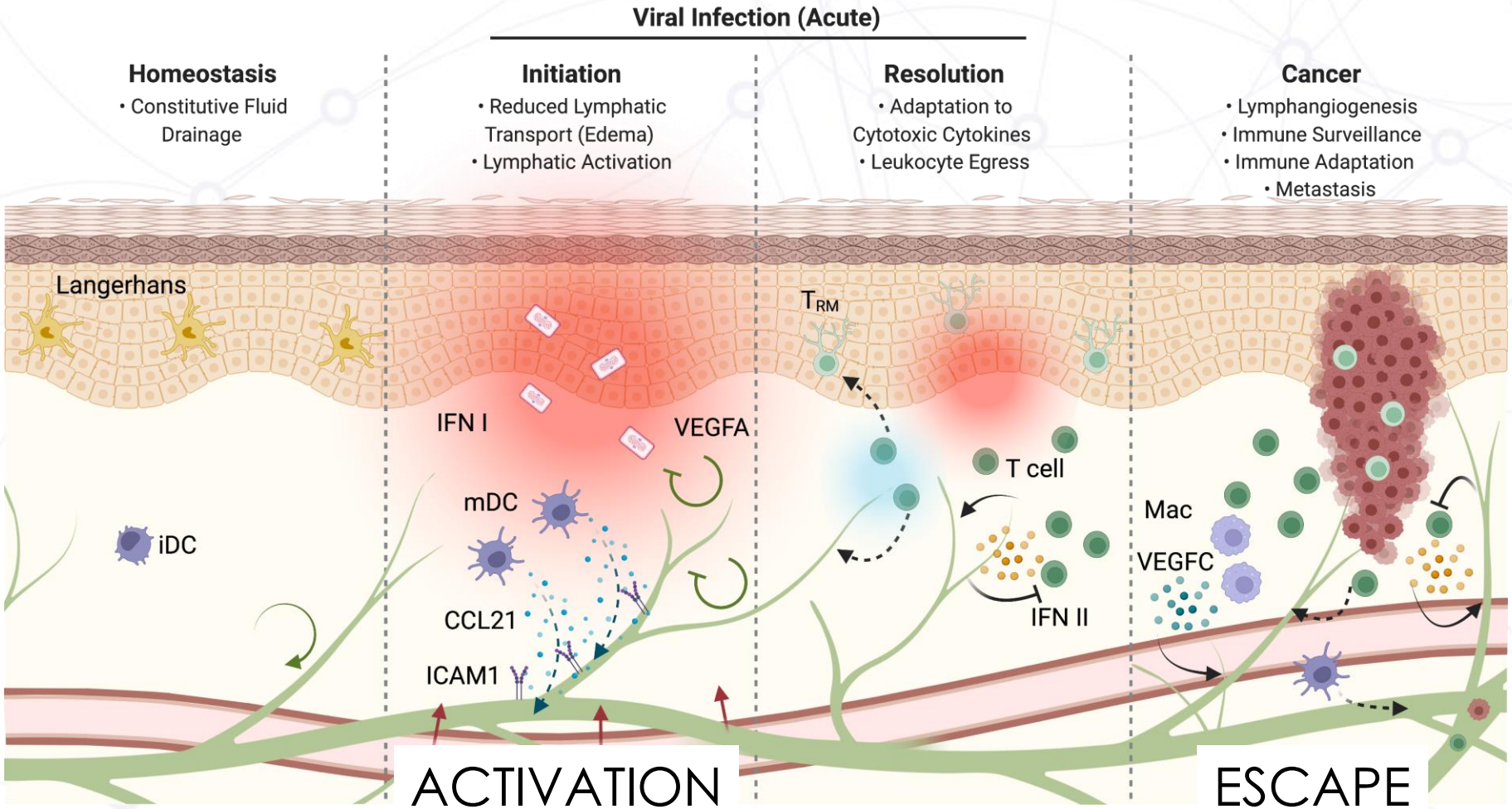
Lymphatic-secreted CXCL12 restricts CD8+ T cell-mediated tumor control in immunogenic melanoma





Steele et al *under review* 2022

The lymphatic vasculature as a dynamic, immunological scaffold and immunotherapy target



Lund et al *Cell Reports* 2012
Lund et al *JCI* 2016
Loo, Nelson et al *Cell Reports* 2017
Lane et al *JEM* 2018
Steele et al *JOVE* 2019
Churchill et al *JEM* 2022
Steele et al *under review* 2022

LEVERAGE LYMPHATIC VASCULATURE FOR CANCER IMMUNOTHERAPY

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