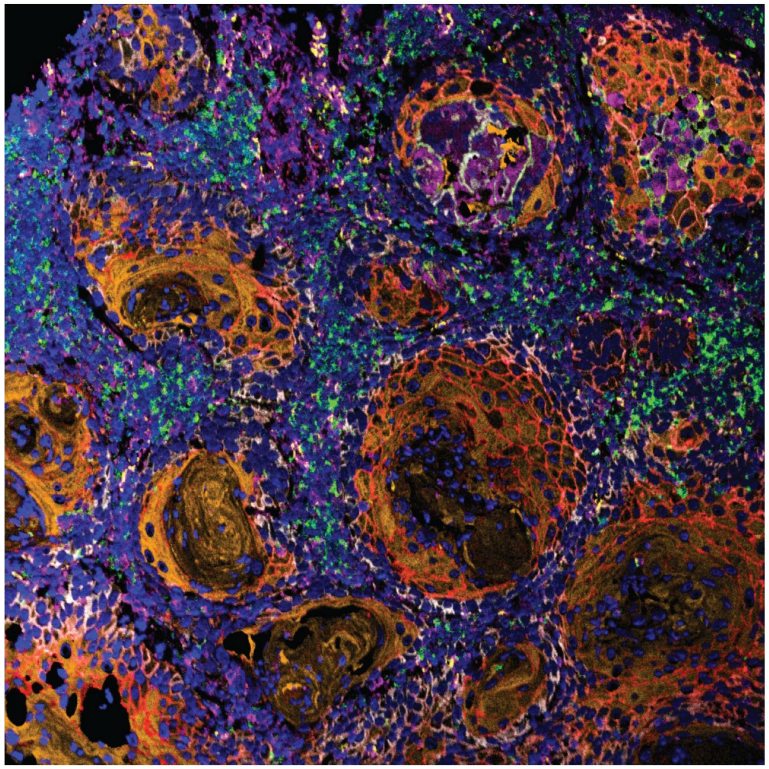
# The Tumor Microenvironment (TME):



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CHAN ZUCKERBERG BIOHUB

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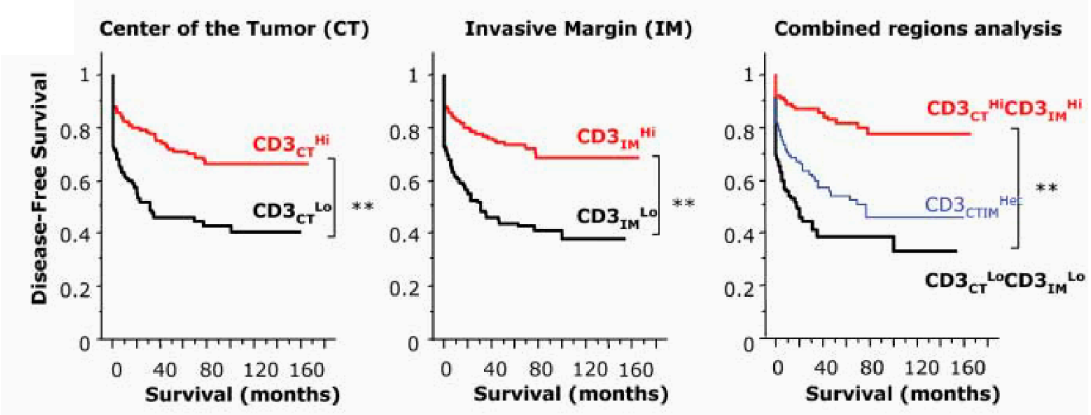
- and –

I will not discuss off label use and/or investigational use in my presentation.

# Properties of the TME are associated with prognosis

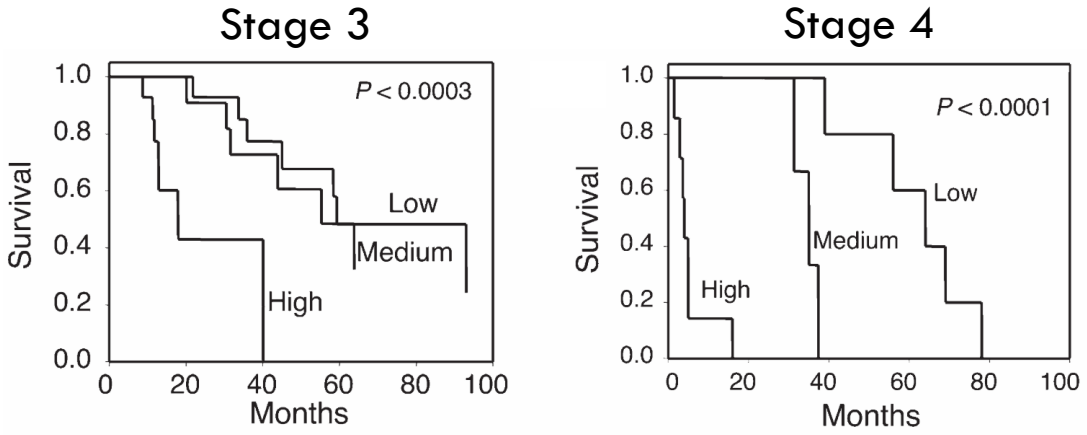
**Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome**

*Galon et al., Science, 2006*

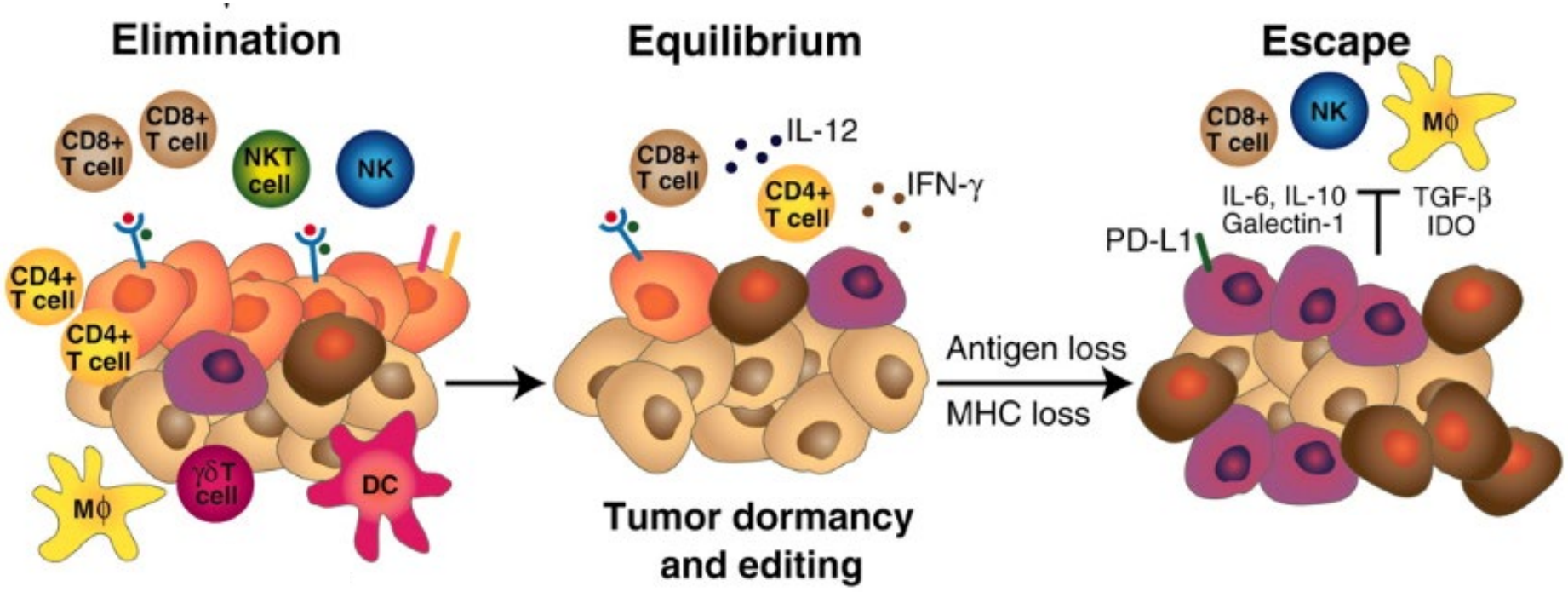



Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival

*Curiel et al., Nat. Med., 2004*



# The cancer immunoediting hypothesis: How tumor cells evade the immune system




**Elimination** → **Equilibrium** → **Escape**

Tumor cells recognized by immune cells are killed

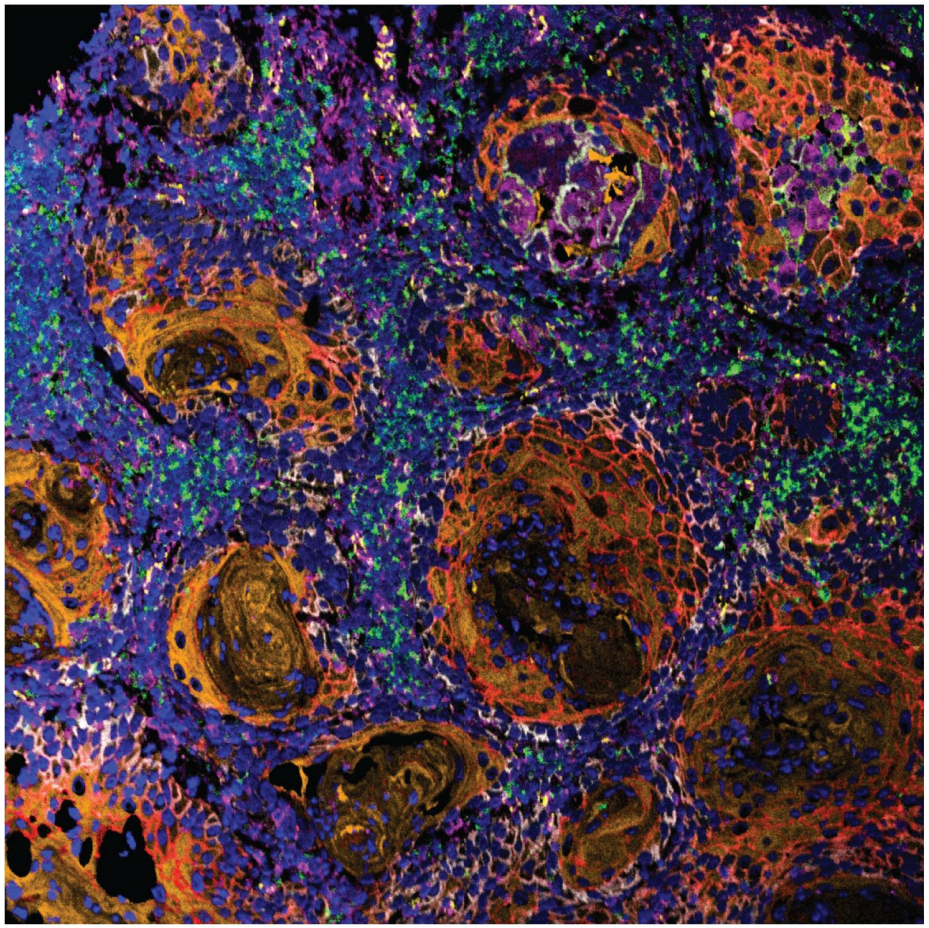
Tumor cells are selected that can suppress immune activity

Edited tumor cells evade immune responses and continue growing

Schreiber, Old and Smyth, *Science*, 2011

# Solid tumors are complex tissues with a broad diversity of cell types

Representative HNSCC



dsDNA, Keratin, E-Cadherin, CD45, Vimentin, CD31

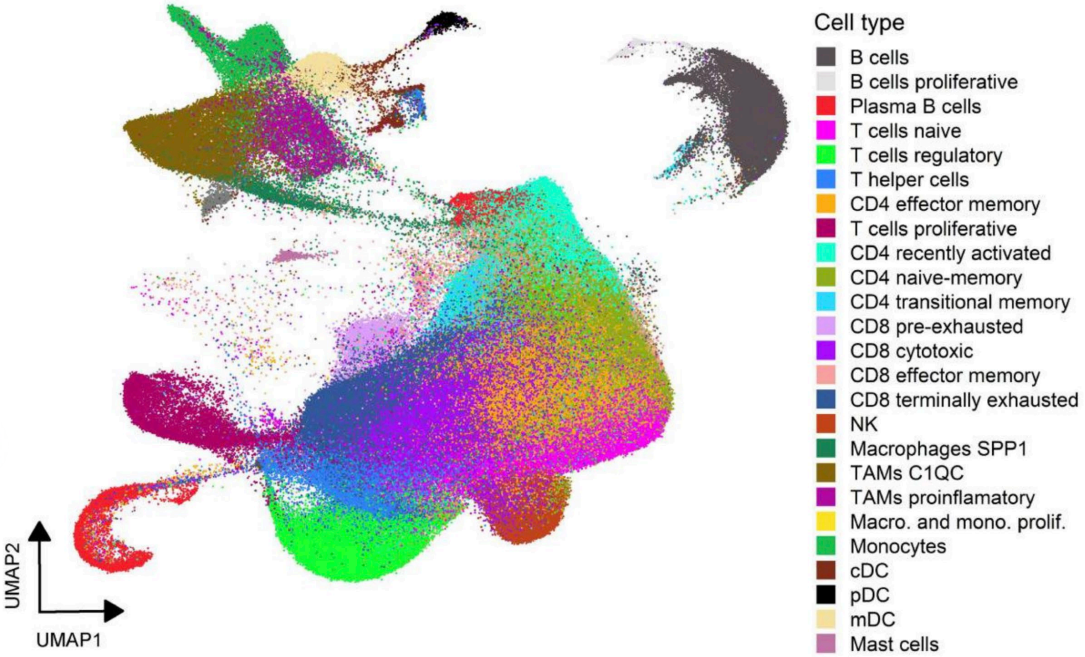
Maha Rahim, Kyle Jones

# Advances in single cell analysis provide new perspectives on this diversity

High-Dimensional Cytometry (CyTOF, spectral flow)

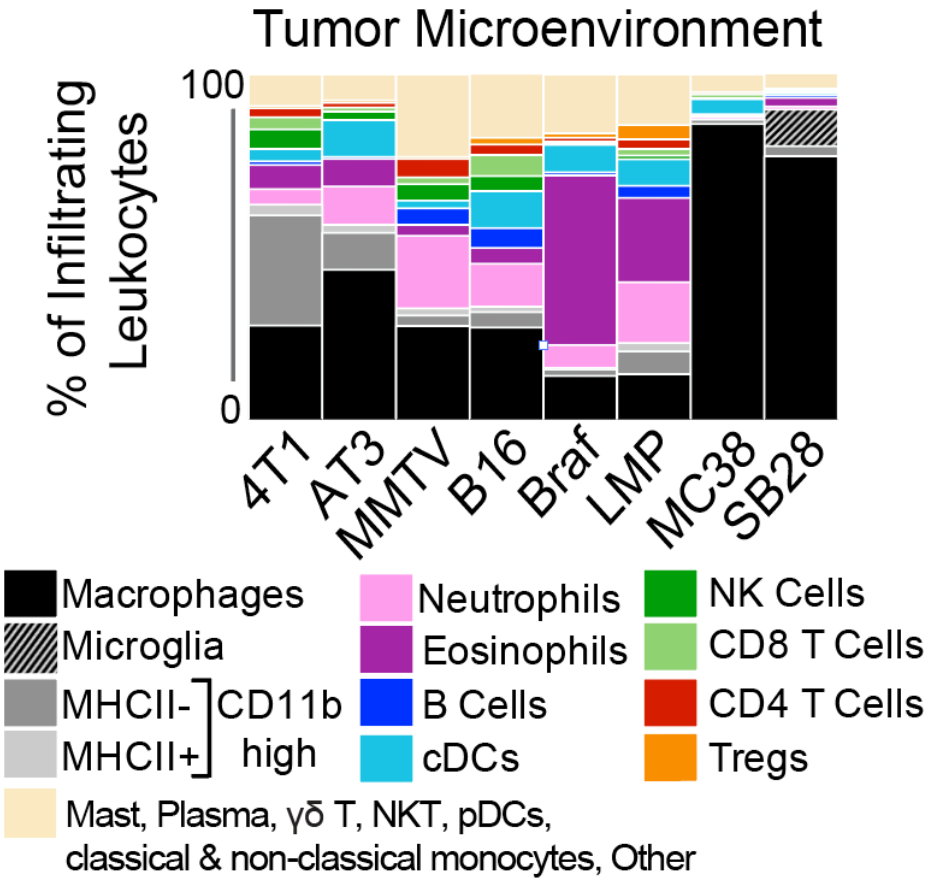
Single-Cell Sequencing (RNA, ATAC, multi-modal)

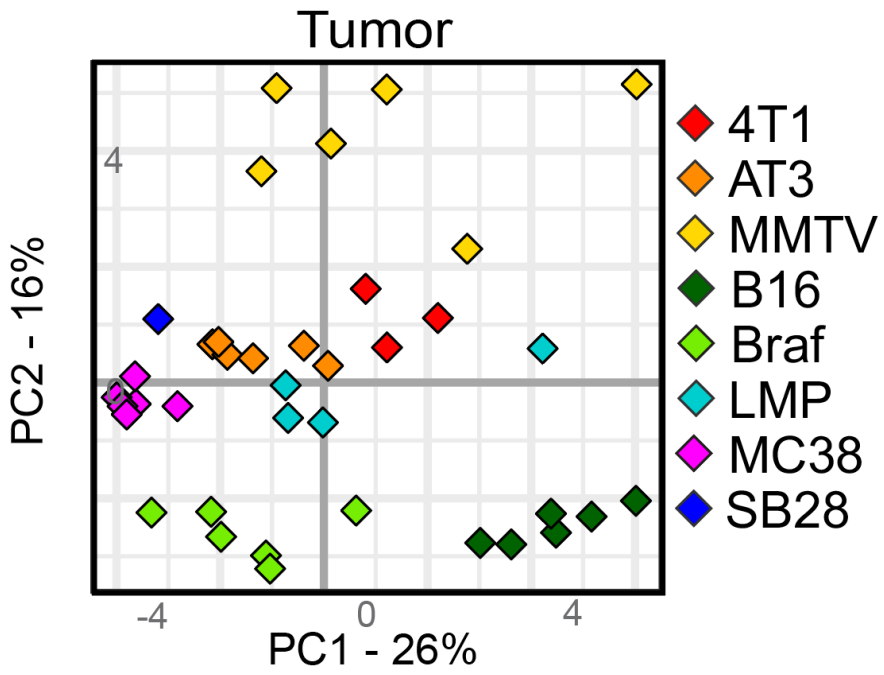
Multiplexed Imaging (MIBI, IMC, CODEX, MERSCOPE)




*Nieto et al., Genome Res., 2021*

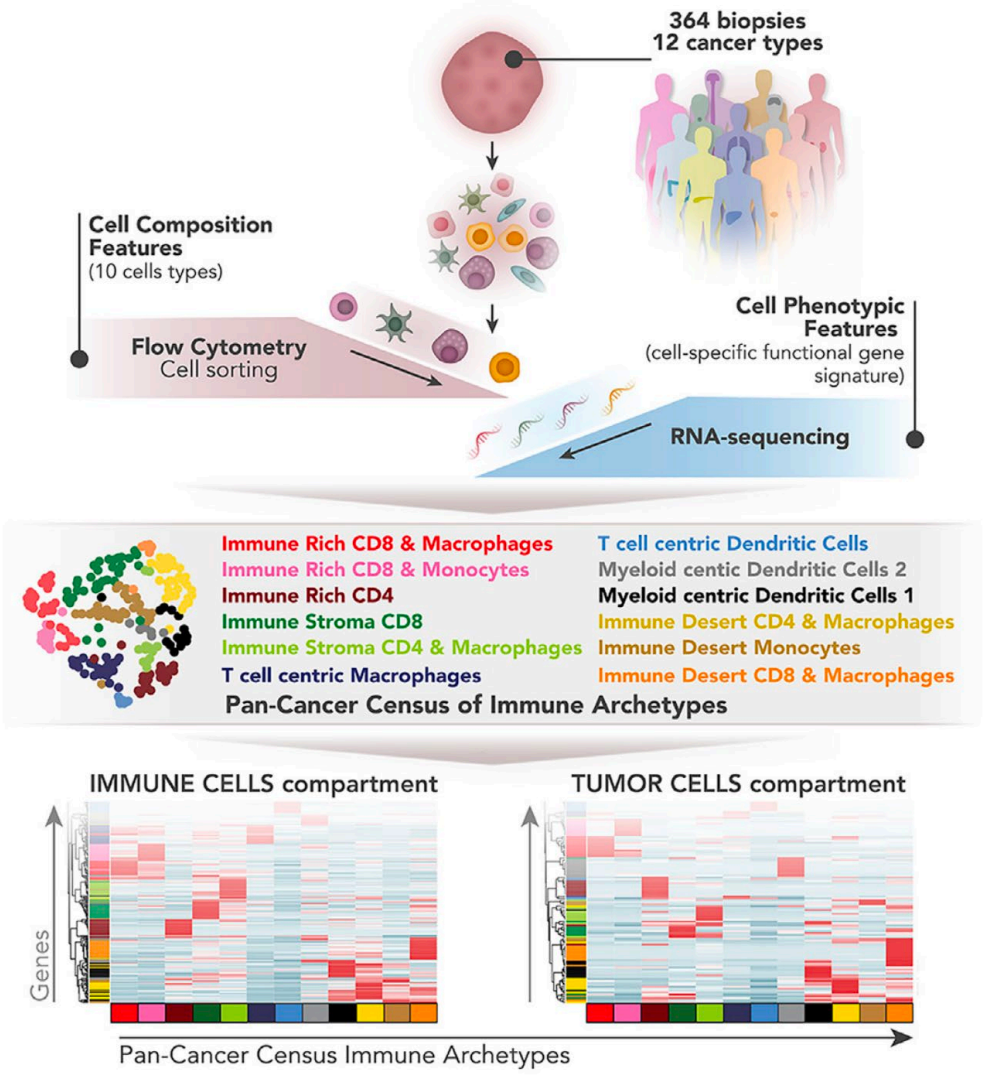
# Different tumors have unique TMEs




*Allen, Hiam et al., Nat. Med., 2020*

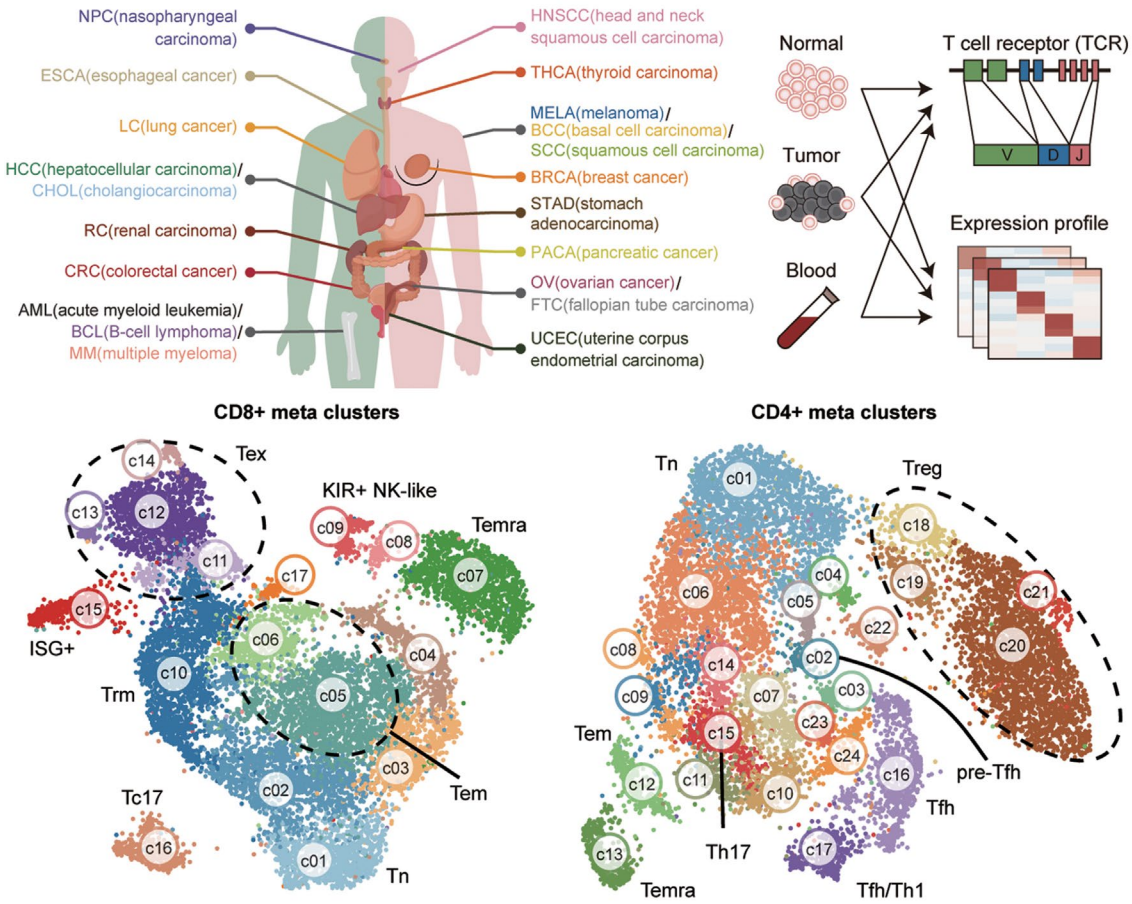
# Human TME archetypes defined by patterns of the cellular infiltrate




- Measuring the composition of immune cells in the tumor can classify into 12 groups
- These groups are independent of the cancer tissue-of-origin
- Associations with prognosis within the same tumor type

*Combes and Samad et al., Cell, 2022*

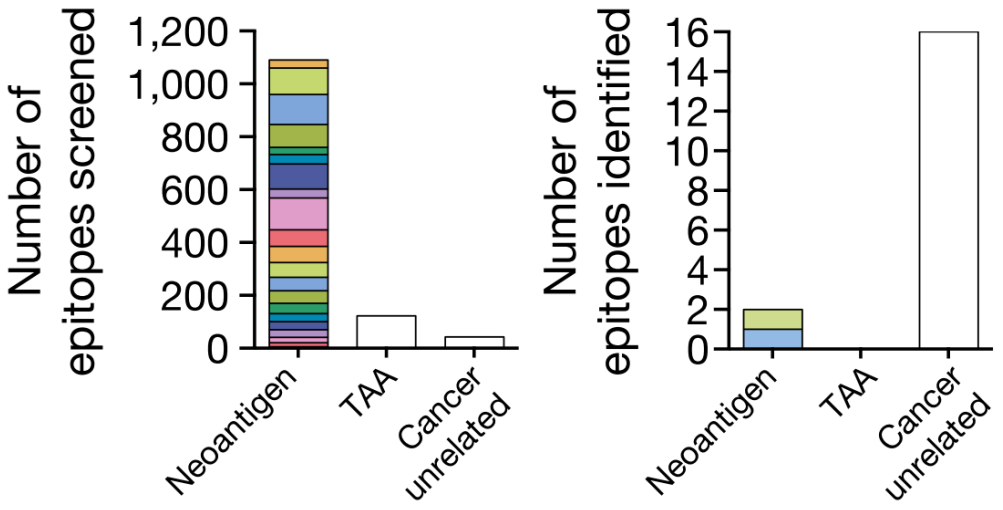
# Defining T cell subsets in the TME



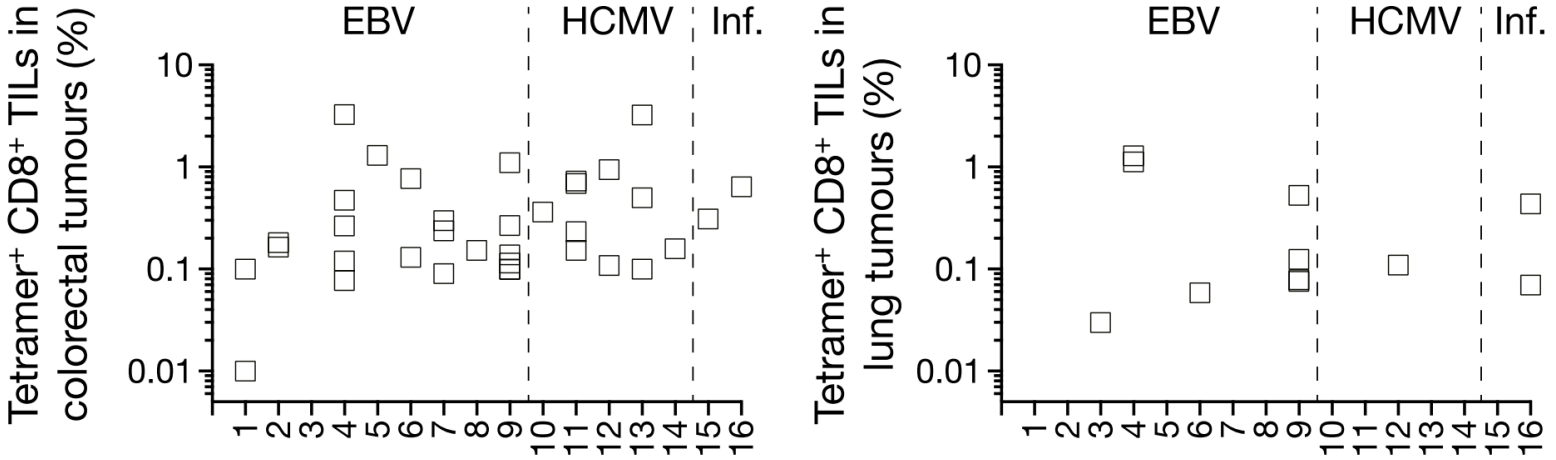

- Single-cell RNA-sequencing of tumor-infiltrating T cells
- Integrative analysis across 21 different tumor types
- The subsets of T cells are conserved across cancers, but significant variability across tumors

*Zheng et al., Science, 2021*

# Many CD8 T cells in the TME are bystanders

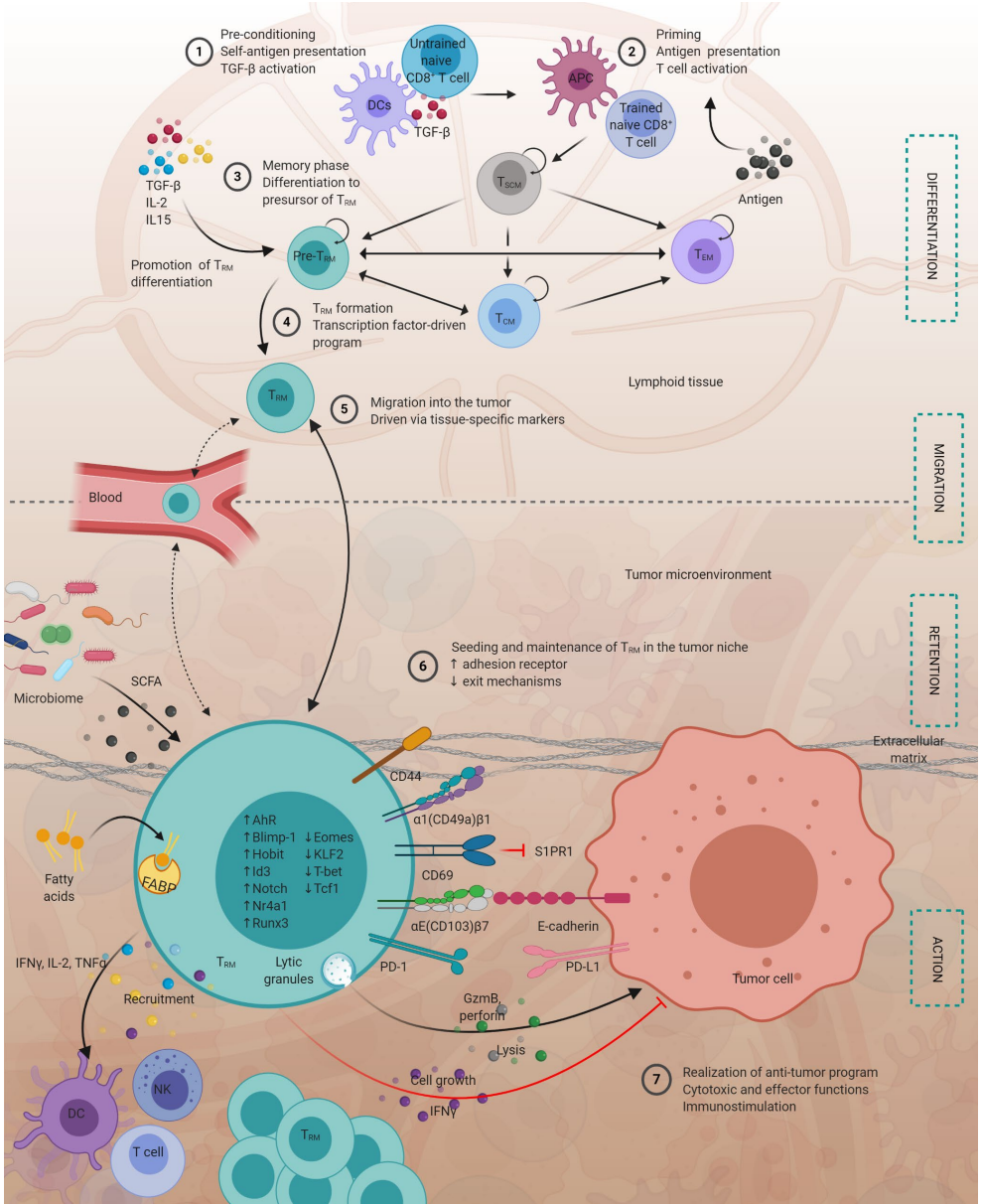



- Most predicted neoantigens did not have detectable T cell responses
- T cells specific to unrelated viruses can be abundant




*Simoni, Nature, 2018*

# Tissue resident memory T cells ($T_{RM}$) and newly infiltrating CD8 T cells

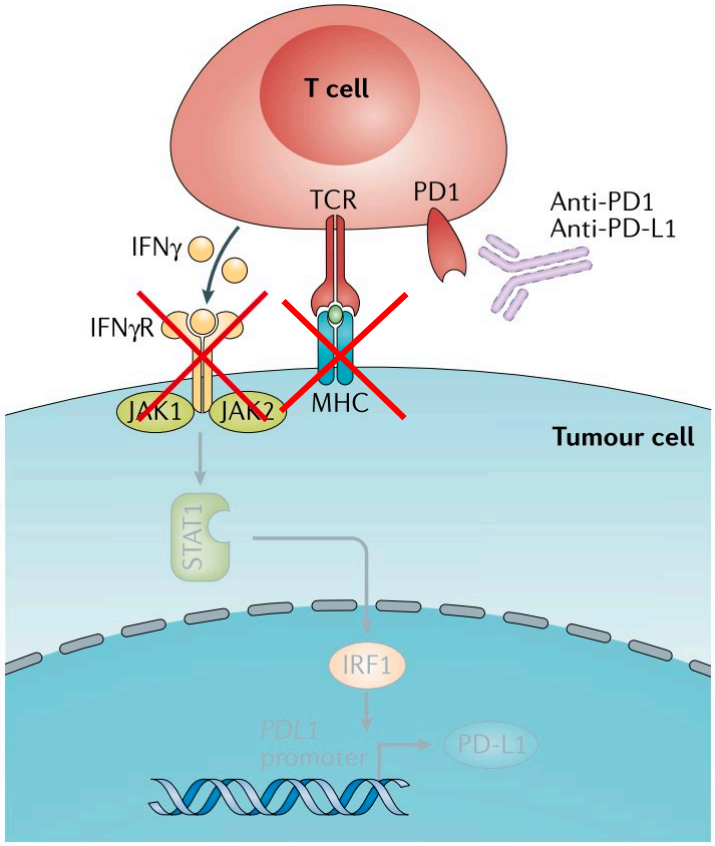



- $T_{RM}$ express molecules that mediate retention in tumors
  - CD103
  - CD69
- Recent studies suggest recirculation into lymph nodes after activation
- Cell trafficking dynamics between TME and periphery is under active investigation.

*Okla et al., J. Exp. Med., 2021*

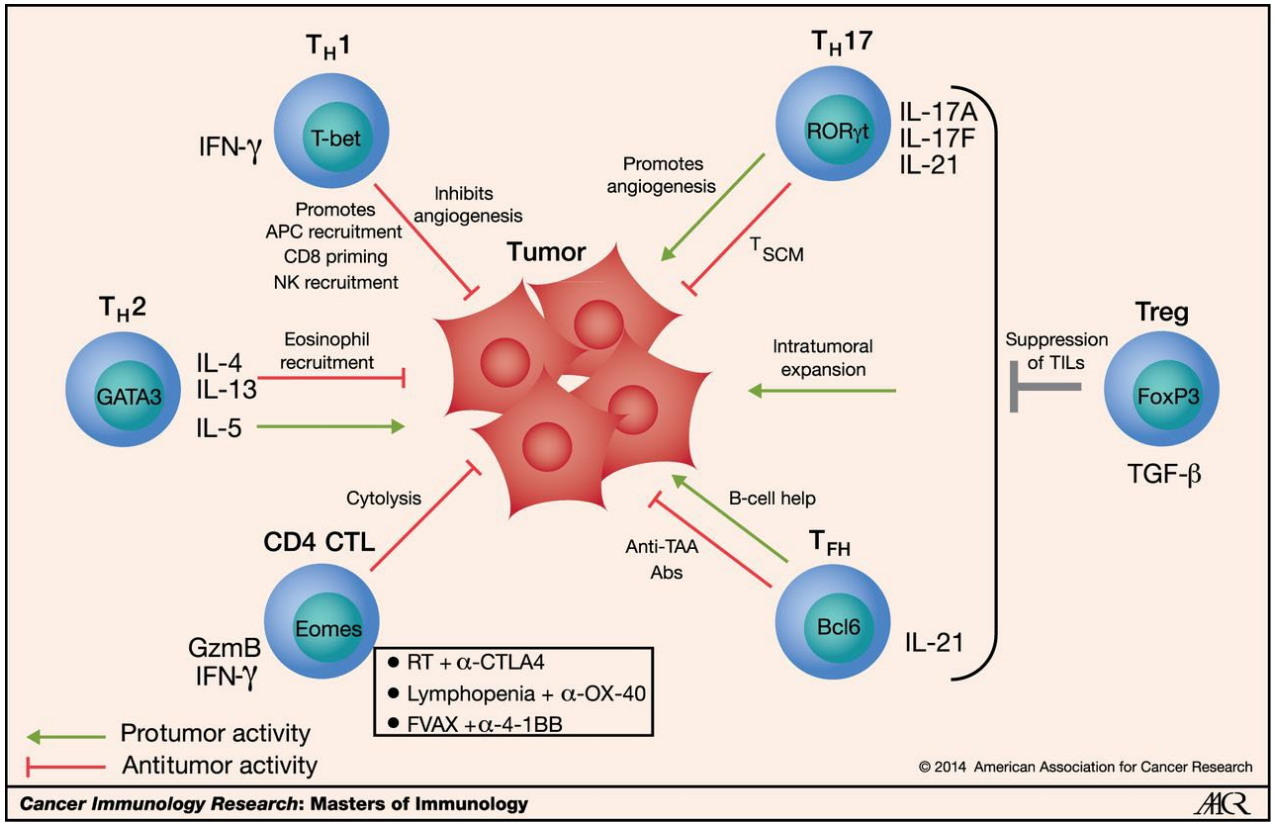
# Tumors can evolve to evade CD8 T cell responses

- Mutations, silencing, or degradation of MHC class I
- Loss of immunogenic neoantigens
- Mutations in antigen processing machinery
- Mutations in IFNγ signaling pathway




*Modified from Kalbasi and Ribas, Nat. Rev. Immunol., 2020*

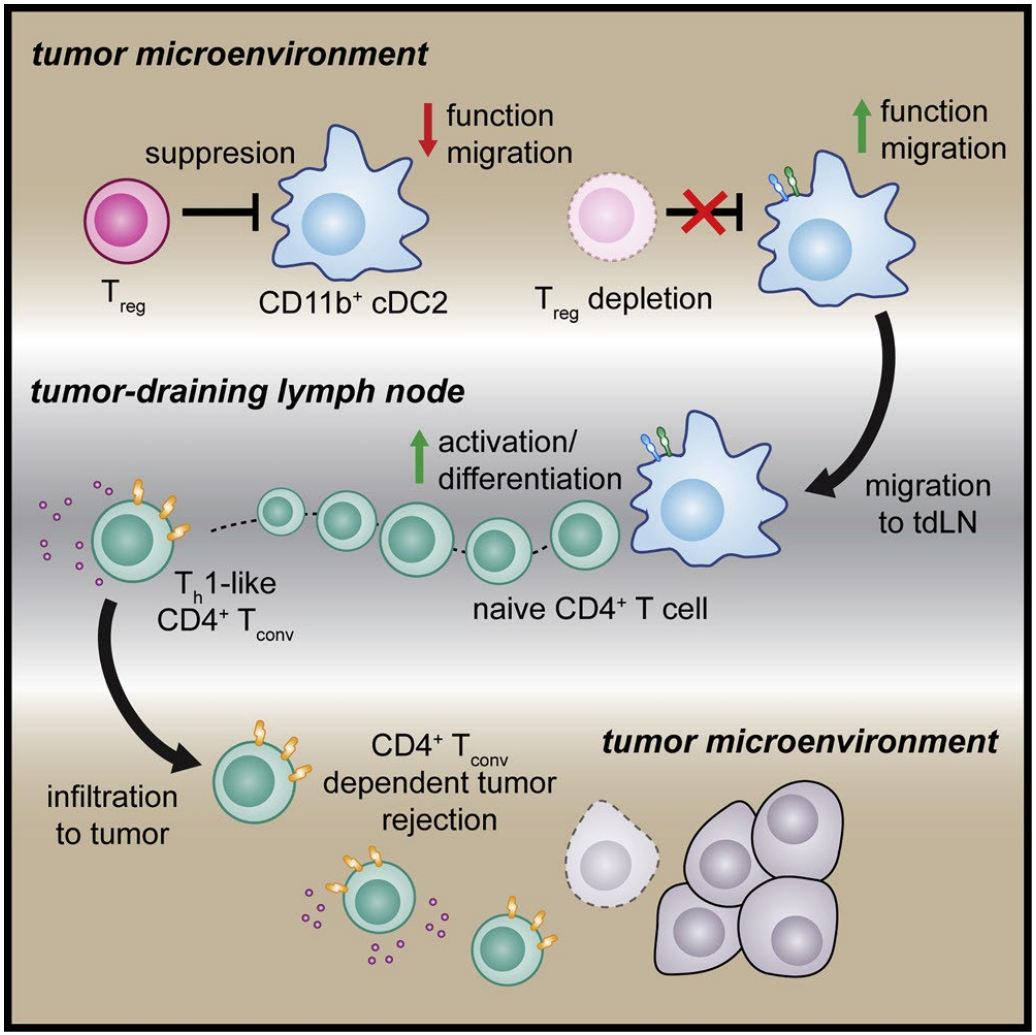
# CD4 T cells in the TME




- Different CD4 T cell subsets have opposing functions in the TME
- Recent studies identified importance for effective immunotherapy
- Direct recognition (MHC class II+ tumors) and "helper" functions

*Kim and Cantor, Cancer Immunol. Res., 2014*

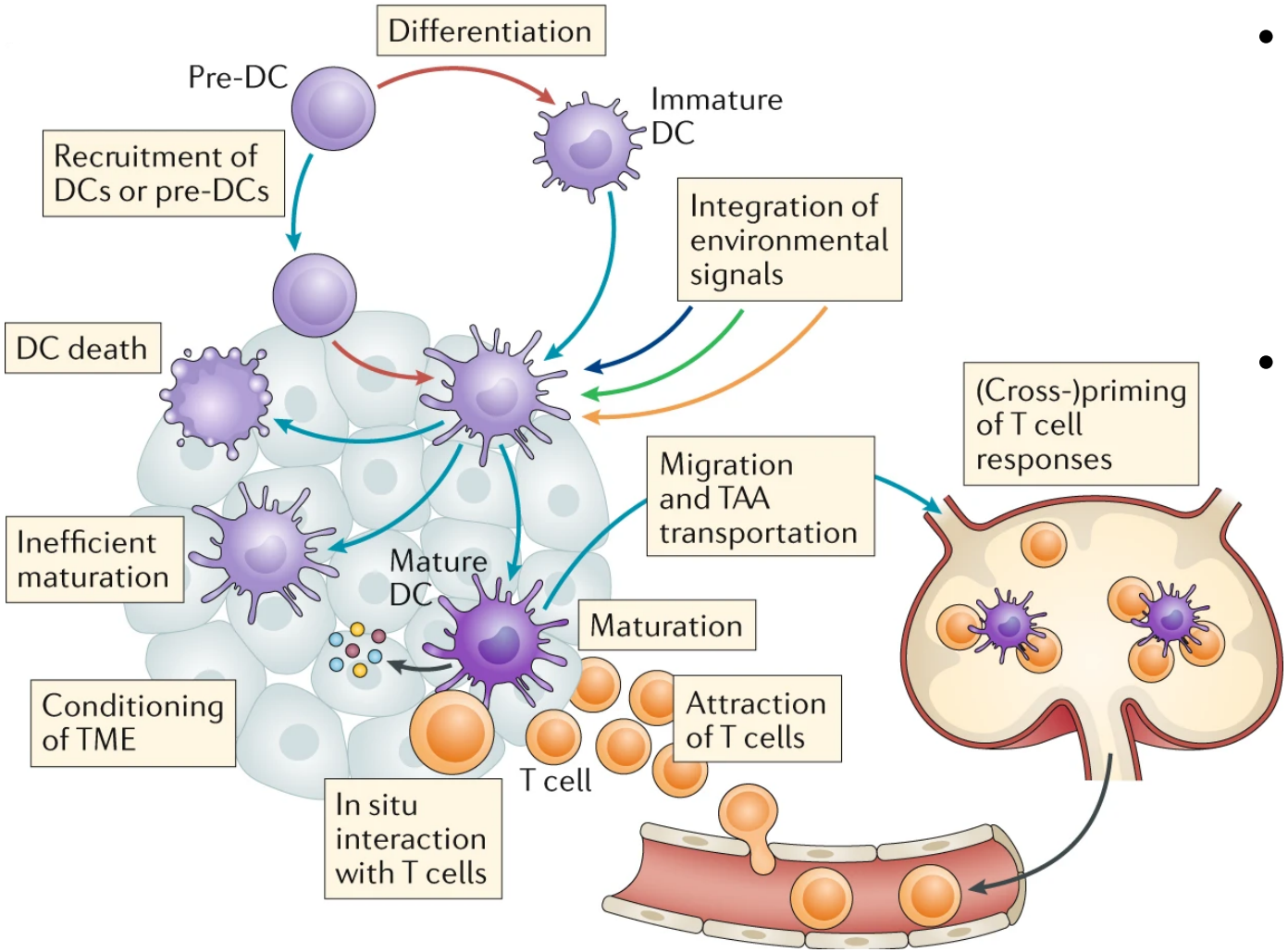
# CD4 T cells in the TME: Opposing functions and cross-regulation




- Treg depletion enables cDC2 trafficking to the lymph node
- Antigen presentation drives a CD4 effector cell response

*Binnewies, Cell, 2019*

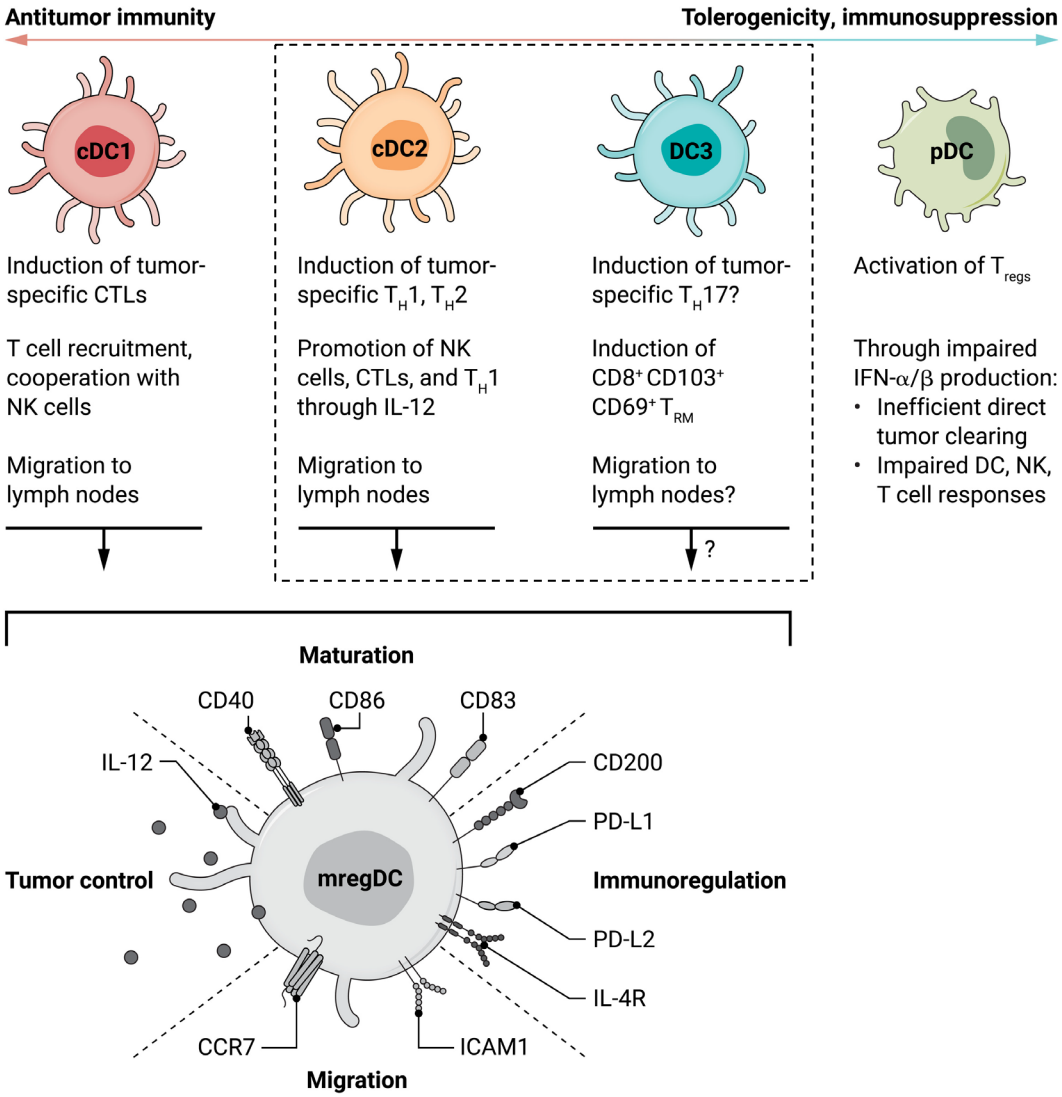
# Dendritic cells:
# Functions in the TME and in the tdLN




- Antigen uptake in TME and presentation in lymph nodes
- New studies identifying roles for supporting T cell responses in the TME

*Wculek et al., Nat. Rev. Immunol., 2020*

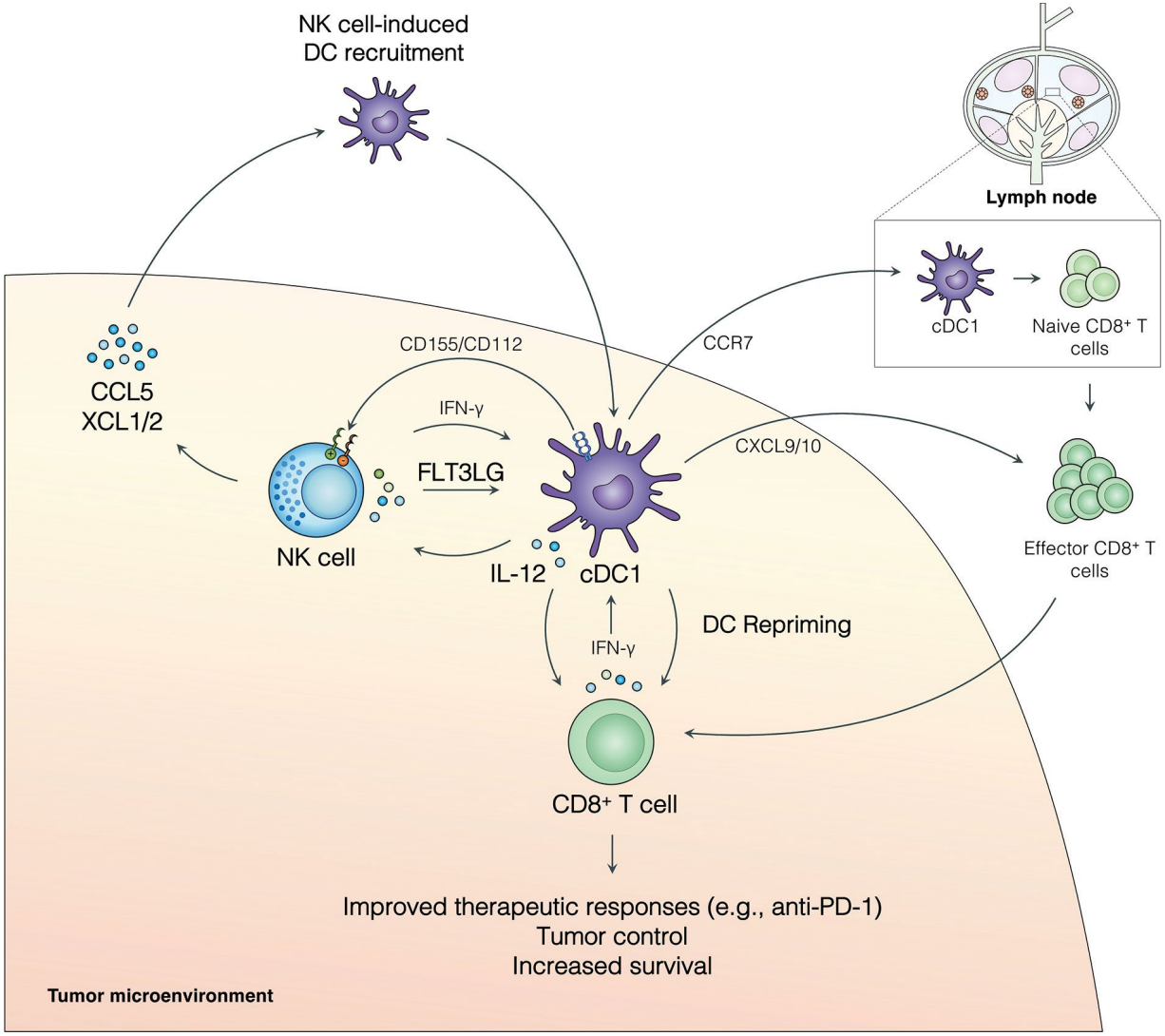
# Unique functions of dendritic cell subsets in the TME




- cDC1s specialized in antigen cross-presentation
- cDC2s are better at priming CD4 T cell responses
- cDC3s recently described but may be a subset of cDC2s
- pDCs can make type 1 IFN but mixed functions

*Kvedaraite and Ginhoux, Sci. Immunol., 2022*

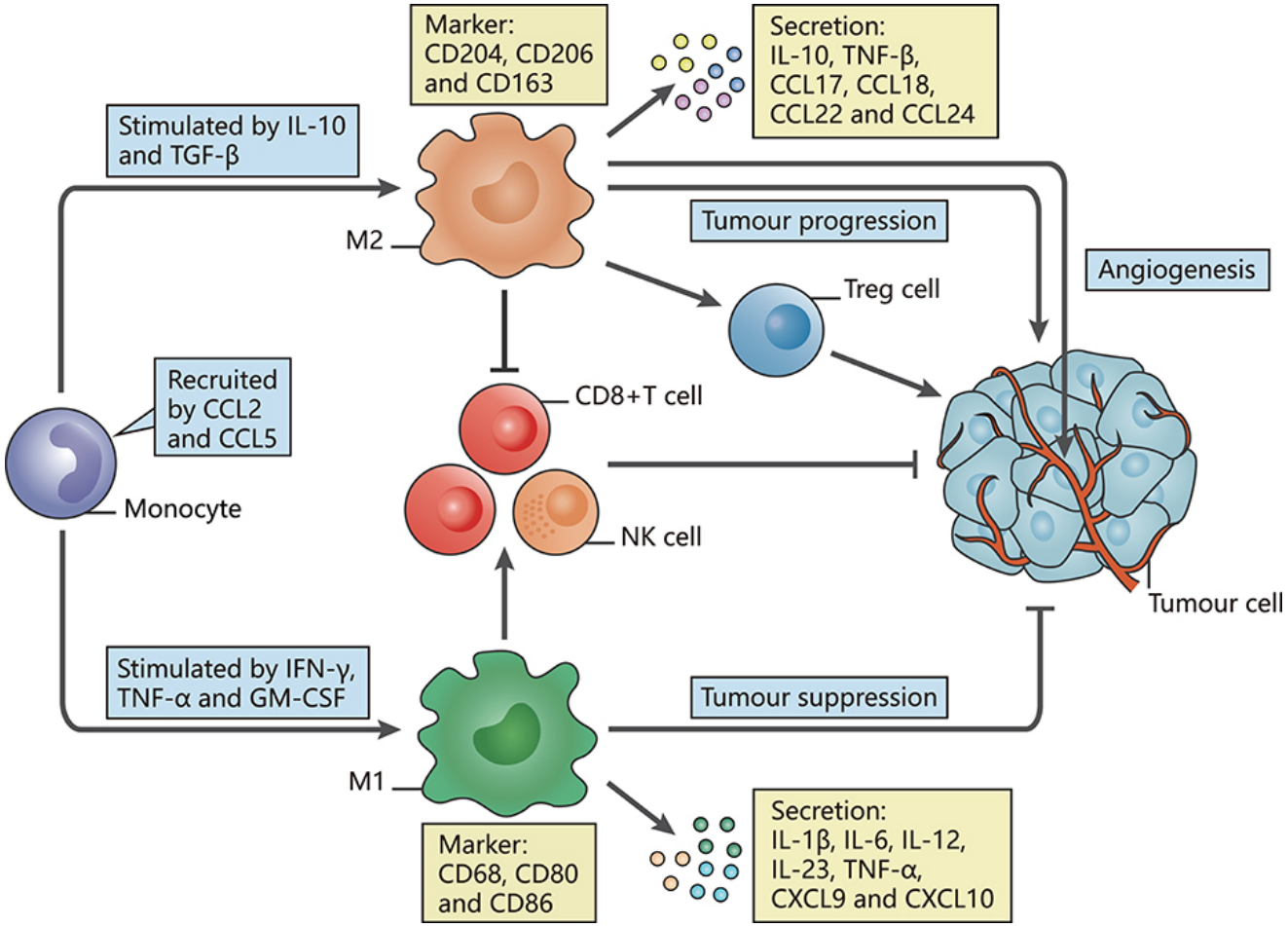
# NK cells can drive a cDC1-CD8 T cell circuit in the TME




*Bottcher et al., Cell, 2018; Barry et al., Cancer Cell, 2018*

*Figure from review: Peterson and Barry, Front. Immunol., 2021*

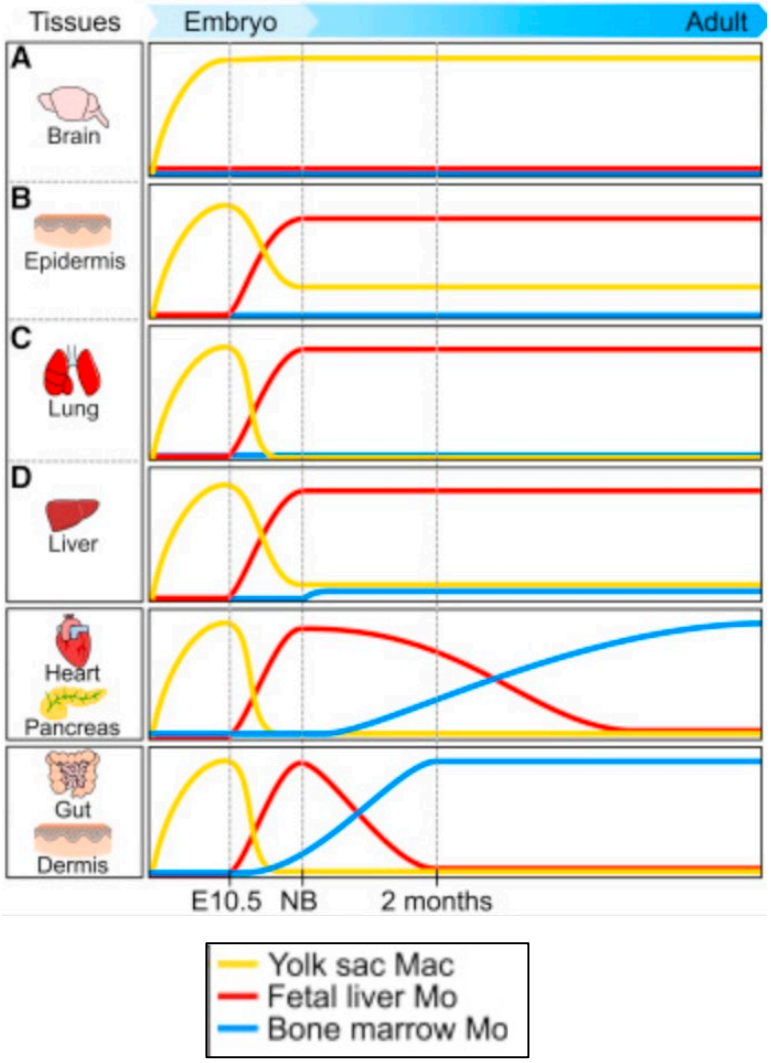
# Macrophages in the TME: The M1/M2 Paradigm




- Classically defined from in vitro polarization studies
- Extrapolation to in vivo immune responses

*Wu et al., Front. Immunol., 2020*

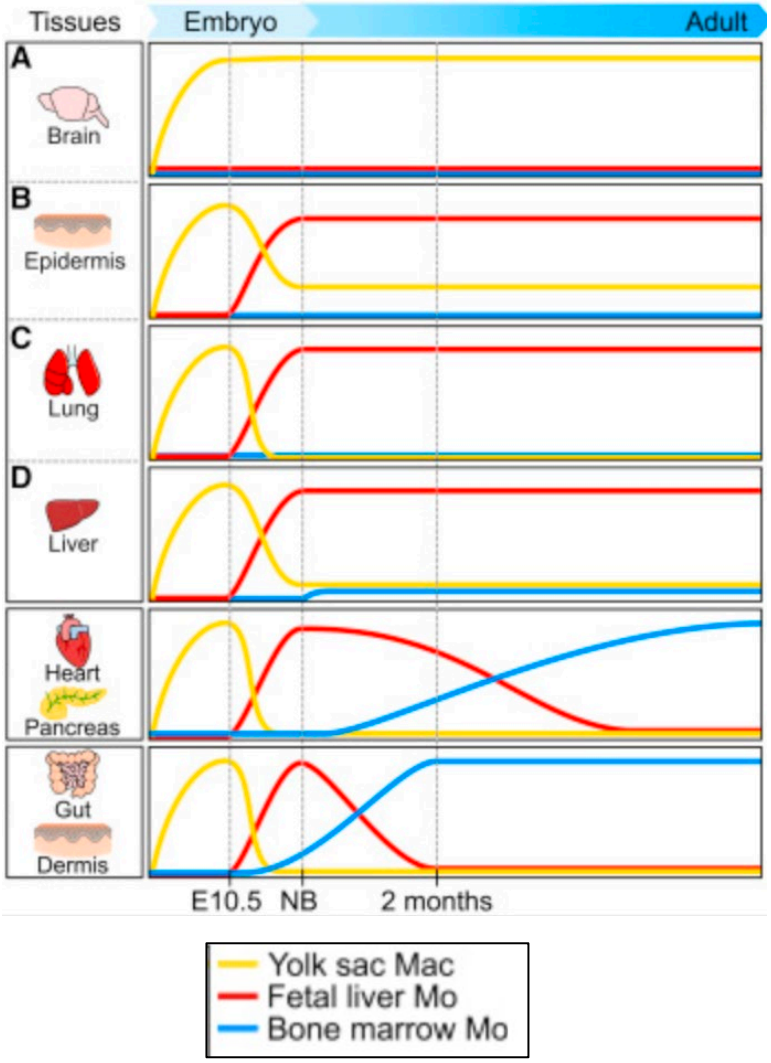
# Macrophage ontogeny: tissue- or bone marrow-derived?

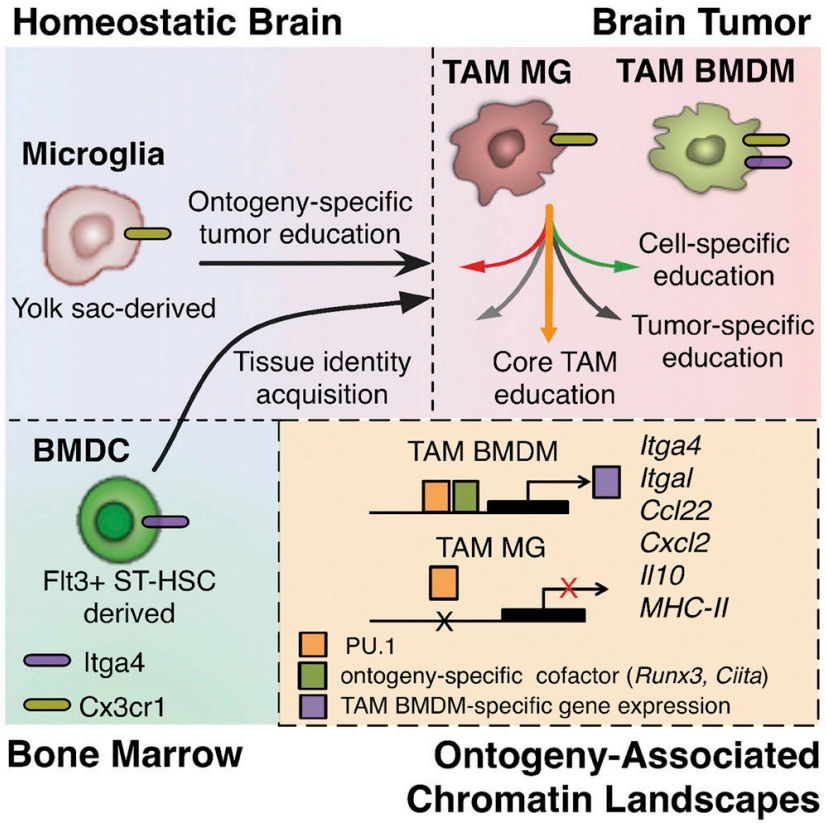



- Macrophages can be replenished from bone marrow-derived monocytes
- Early tissue macrophages are derived from embryonic sources
- The balance of these sources of cells is highly tissue-specific

*Ginhoux and Guilliams, Immunity, 2016*

# Macrophage ontogeny: tissue- or bone marrow-derived?



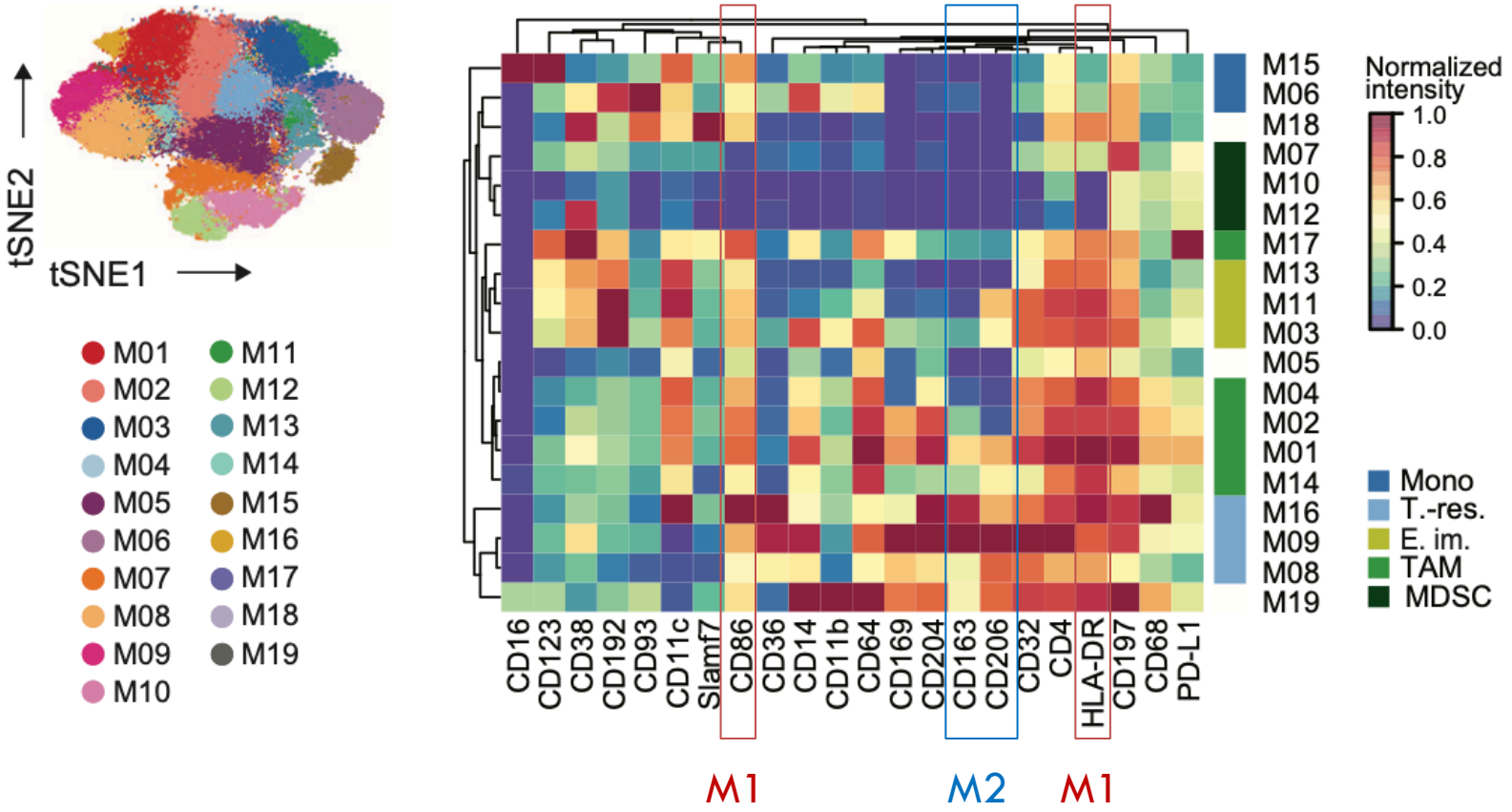




*Ginhoux and Guilliams, Immunity, 2016*

*Bowman, Cell Rep., 2016*

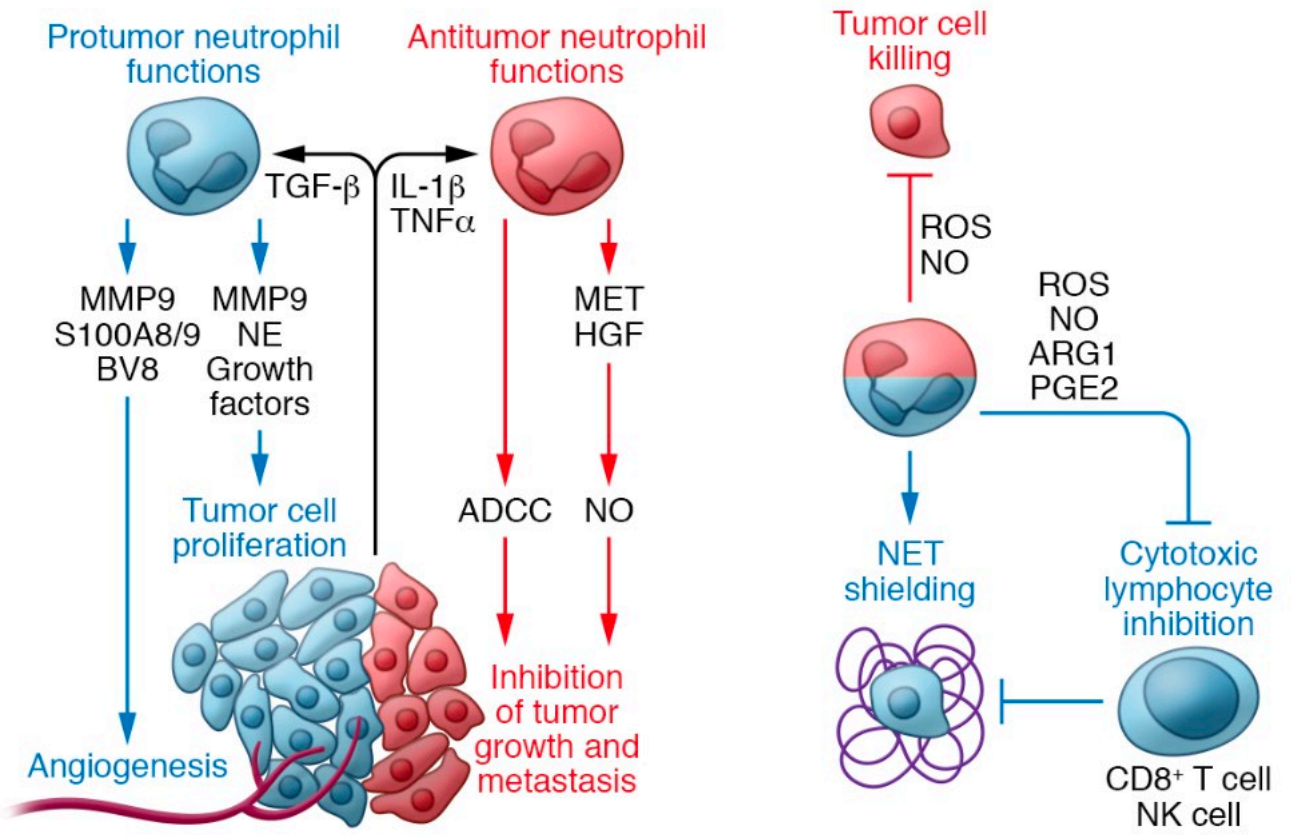
# Revisiting Macrophages in the TME: A diversity of cell states

Human Breast Cancers:




*Wagner et al., Cell, 2019*

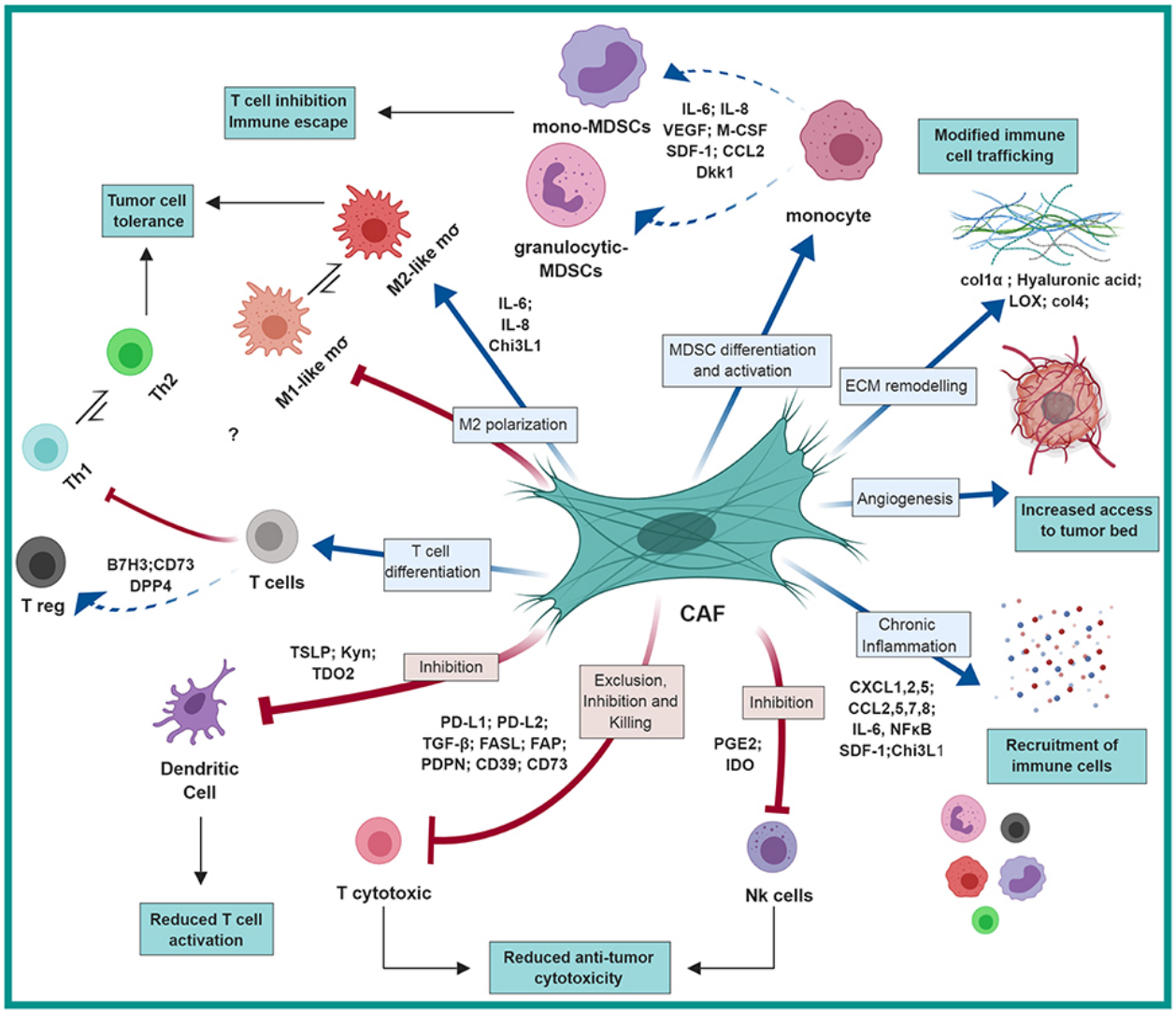
# Neutrophils in the TME




- Inflammatory functions can be pro- or anti-tumor
- Cytokines can promote tumor cell growth
- Other mechanisms can be tumoricidal
- Suppression of T cell responses

*MacFarlane et al., J. Clin. Invest., 2021*

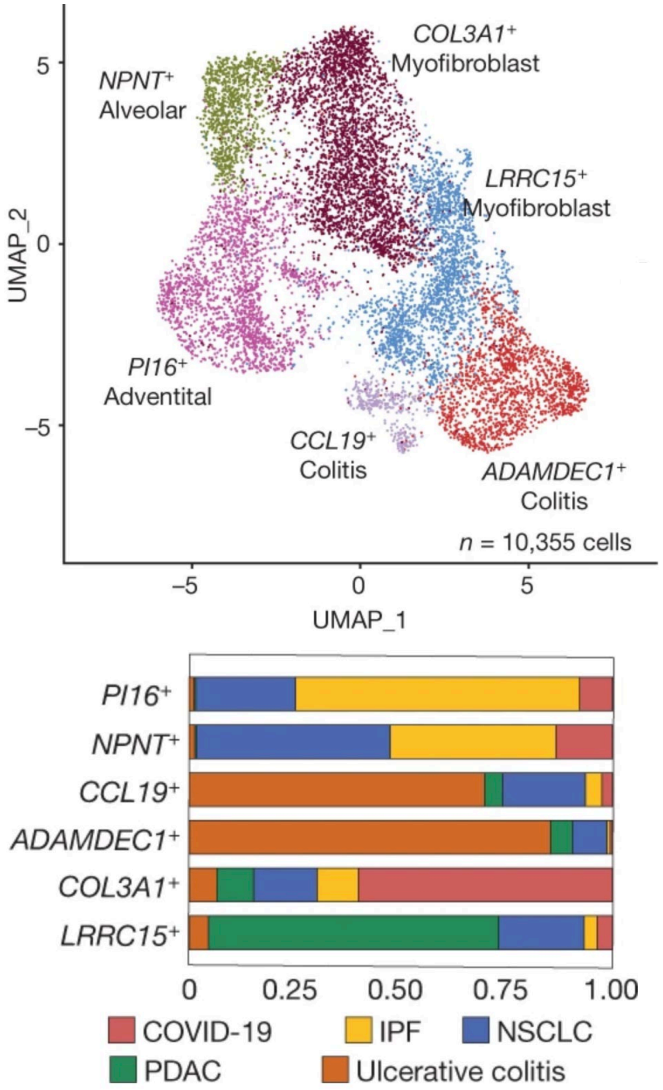
# Fibroblasts in the TME

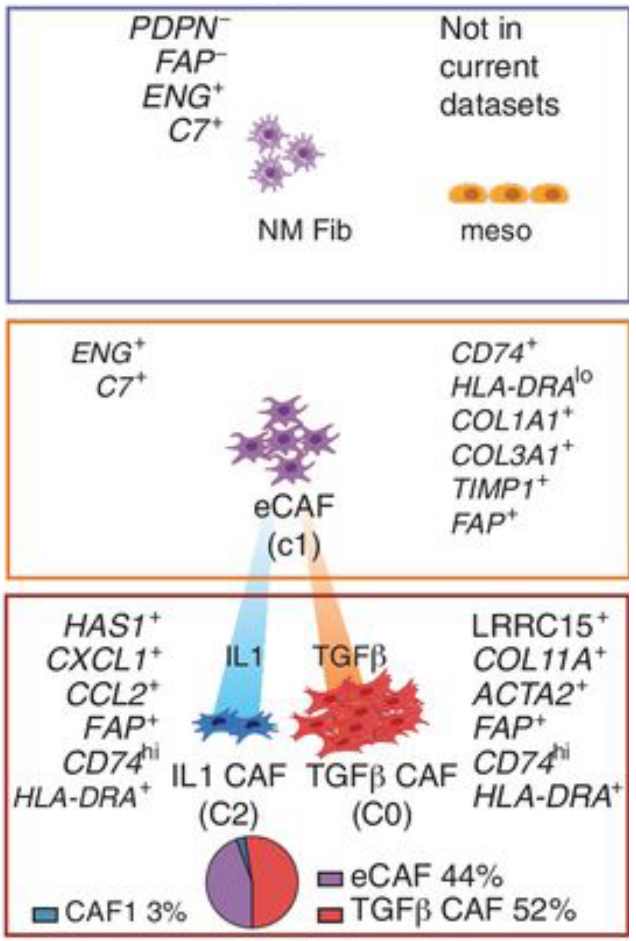



- Substantial focus on tumor-promoting properties of cancer-associated fibroblasts (CAFs)
- Data suggest that fibroblasts can play anti-tumor roles in some contexts

*Monteran and Erez, Front. Immunol., 2019*

# Dissecting fibroblast diversity in the TME

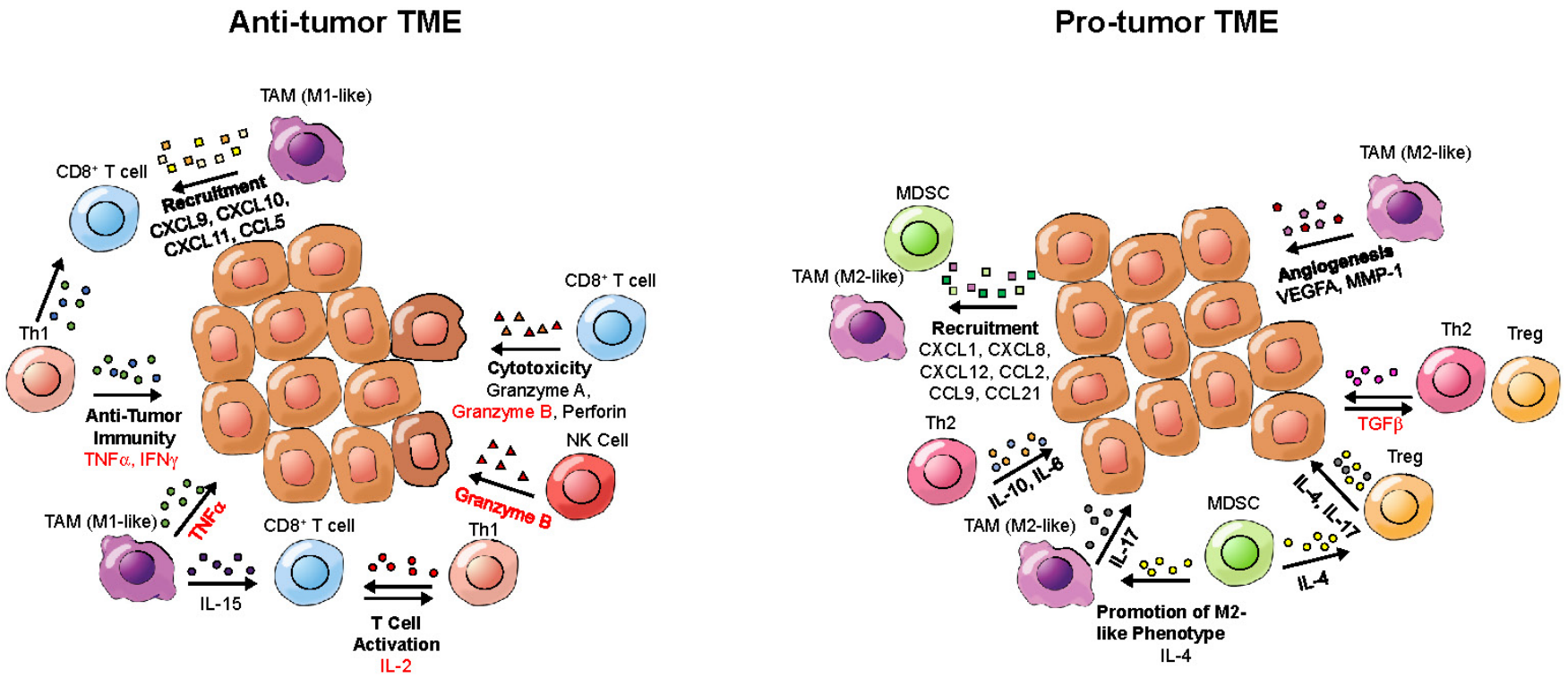



*Buechler and Pradhan et al., Nature, 2021;*

*Dominguez et al., Cancer Discov., 2020*

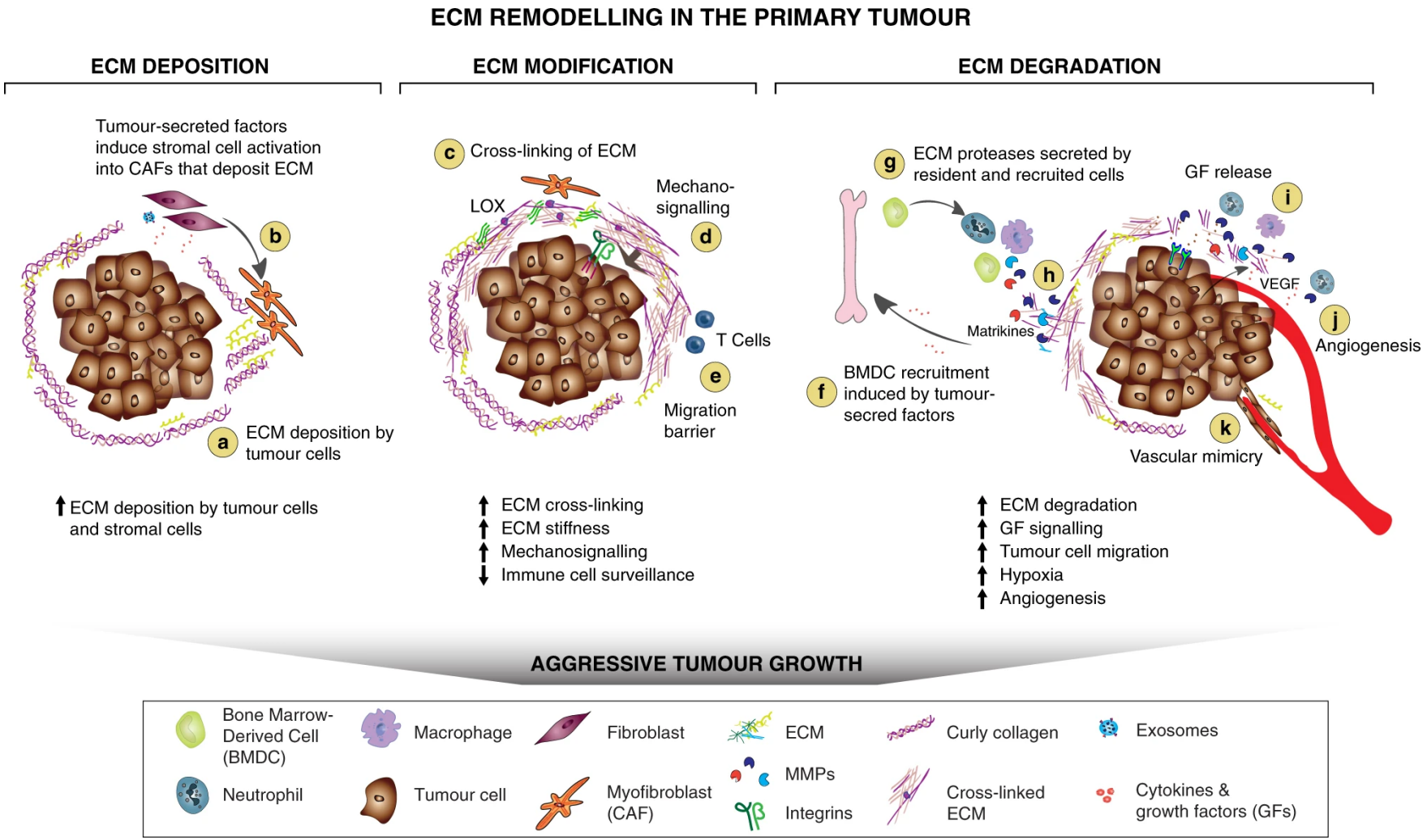
# Soluble factors in the TME




- Complex cytokine networks mediate cell-cell communication and migration in the TME
- Shape the polarization, differentiation and effector function of each cell type

*Abousaway et al., Nanotheranostics, 2021*

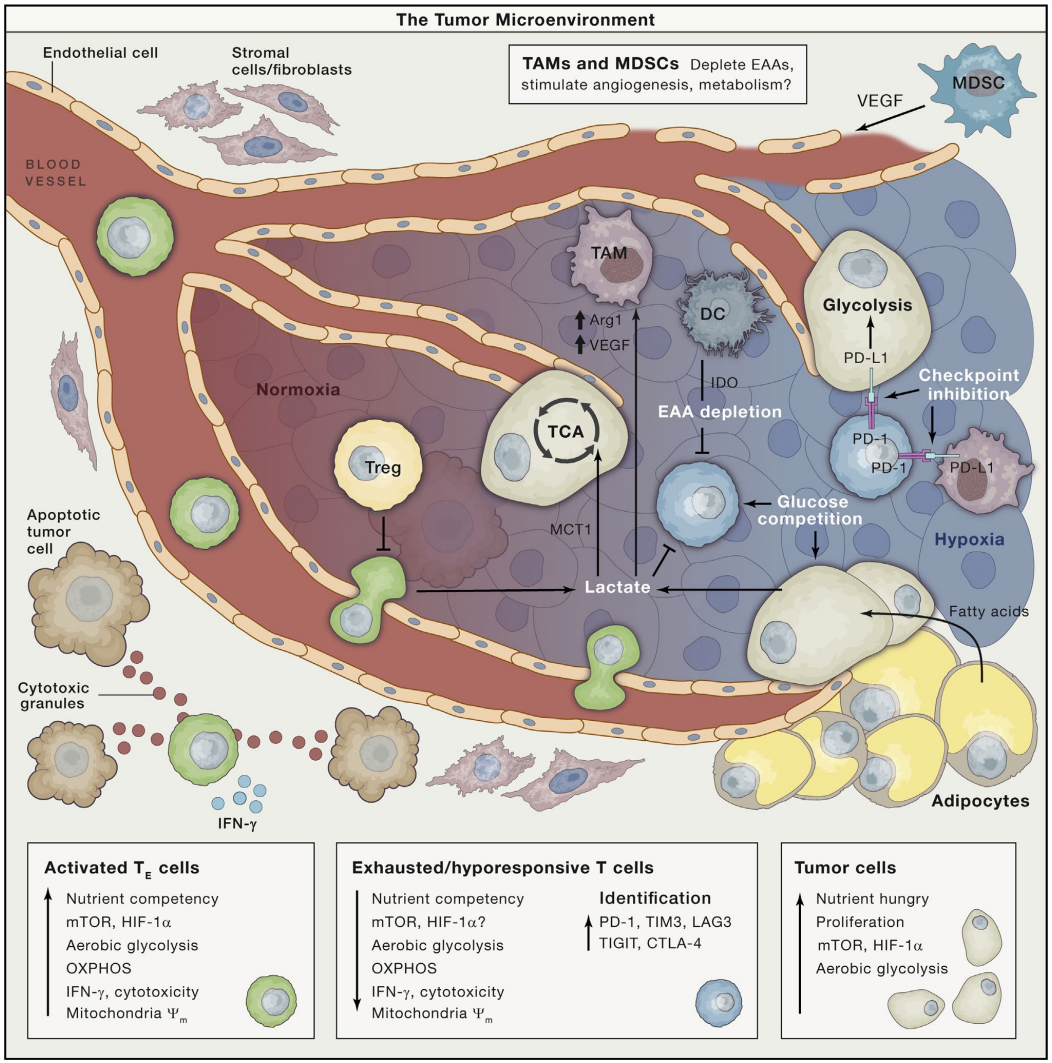
# Extracellular matrix in the TME




*Winkler et al., Nat. Comm., 2020*

# The metabolic environment of the TME

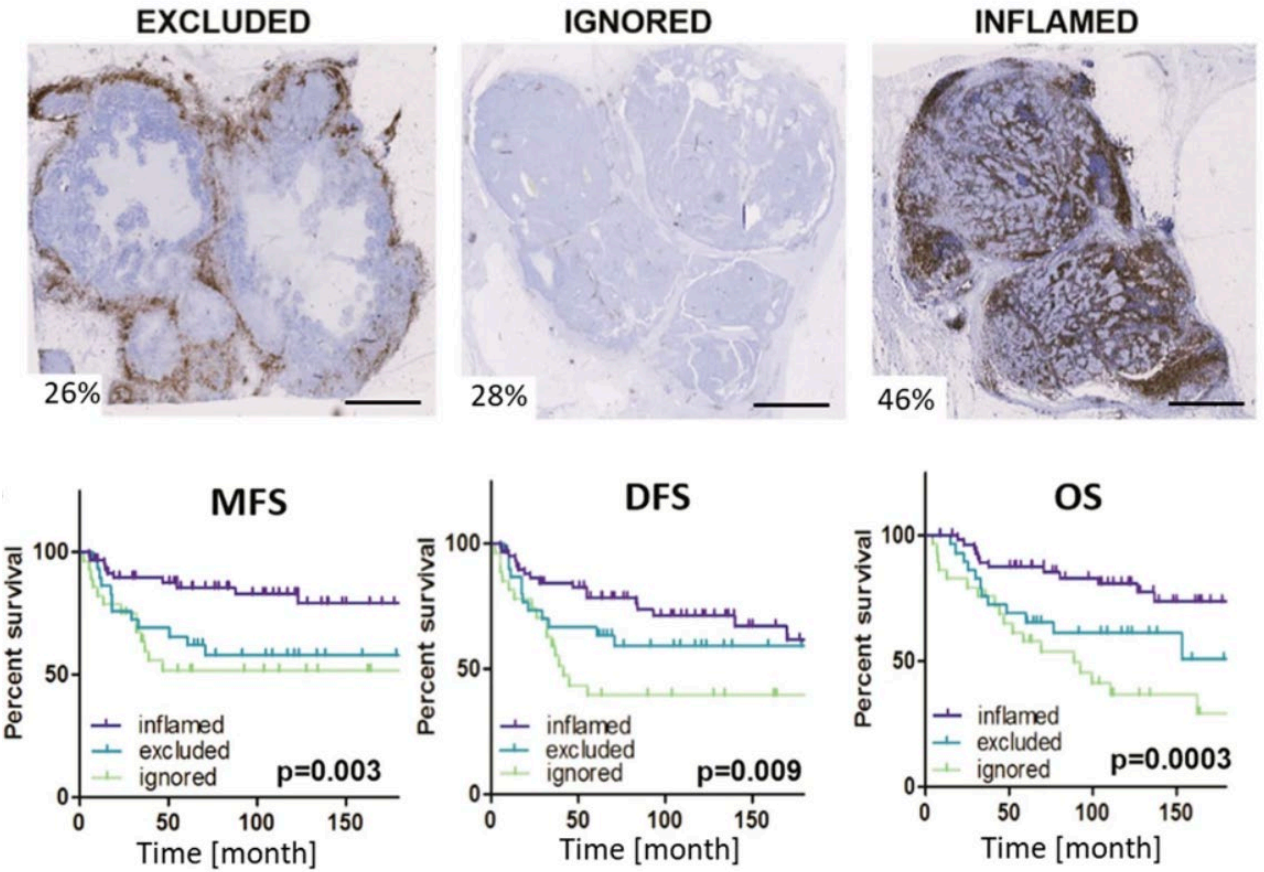
- Hypoxia
  - Induces HIF1α
- Nutrient poor
  - e.g., glucose consumption, arginine and tryptophan depletion)
- Immunomodulatory metabolites
  - e.g., kynurenine, adenosine




*Buck et al., Cell, 2017*

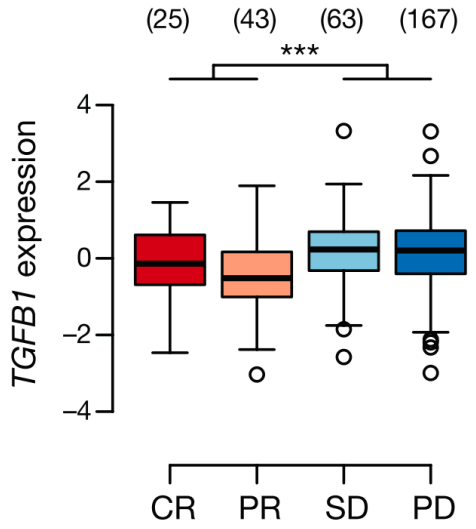
# The spatial organization of the TME is associated with prognosis

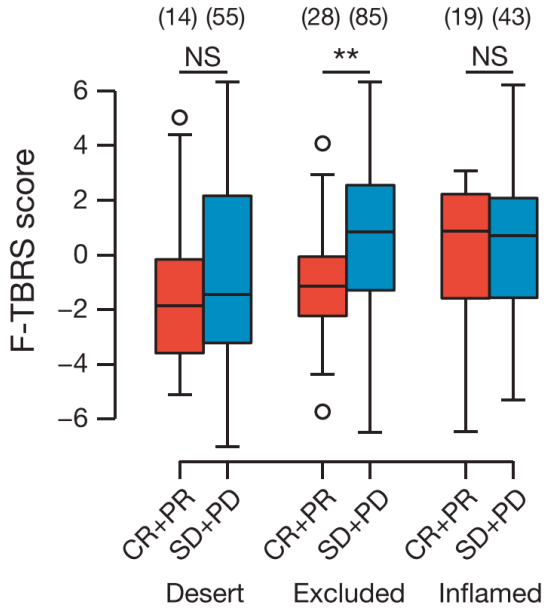
*Triple-negative breast cancer:*

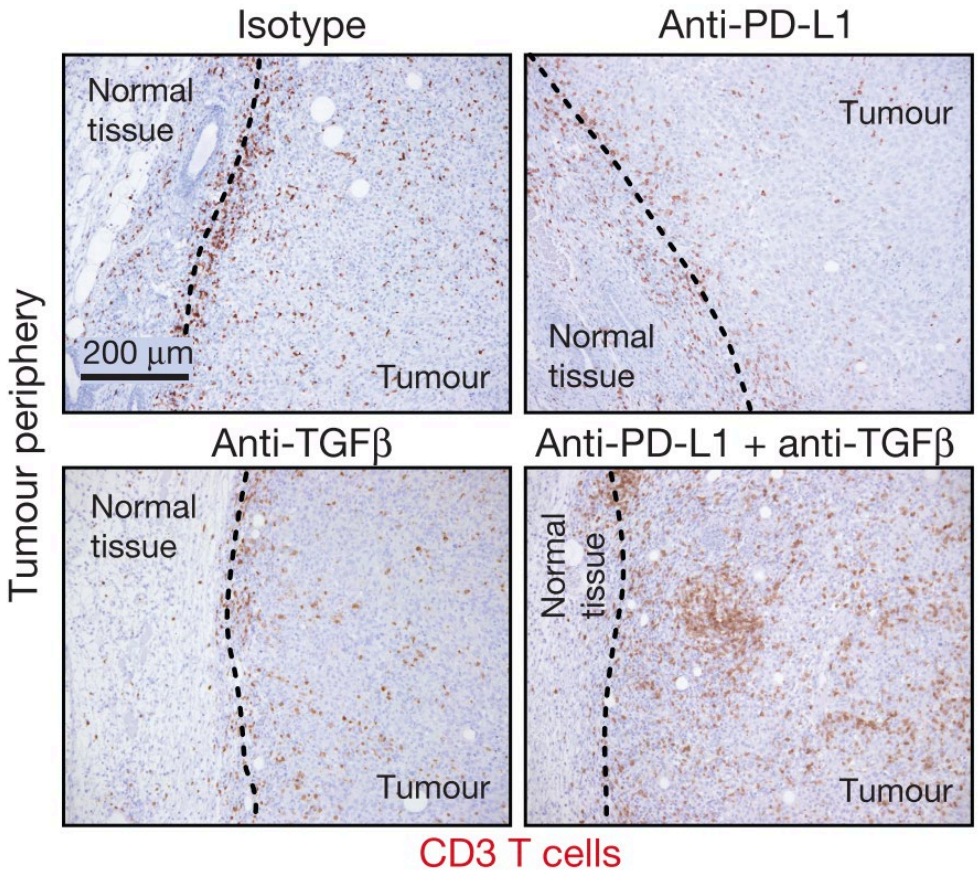



*Hammerl et al., Nat. Comm., 2021*

# TGFβ is a regulator of the "excluded" phenotype

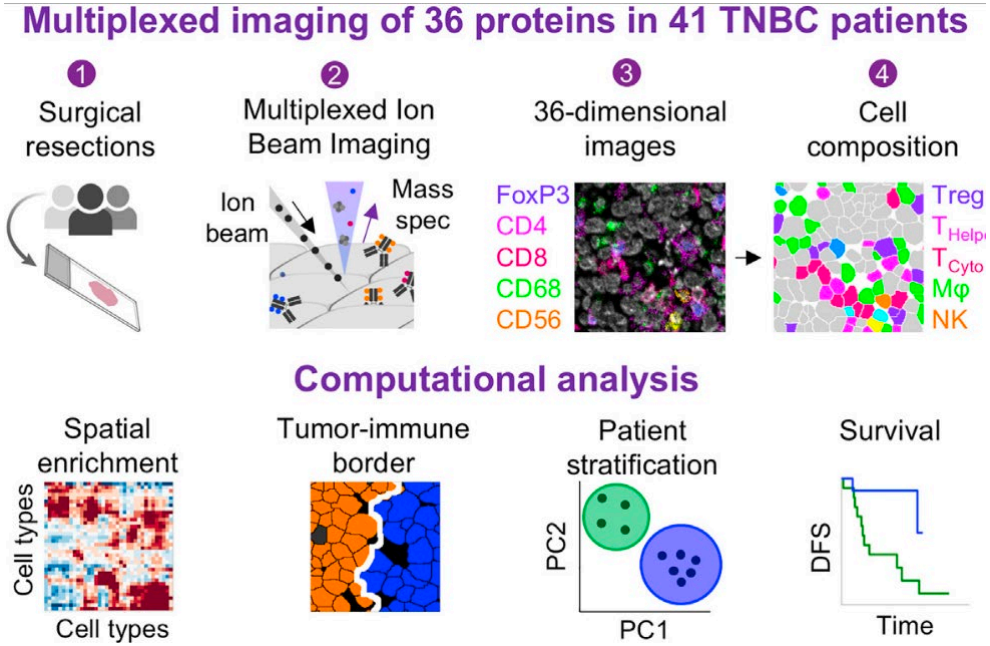


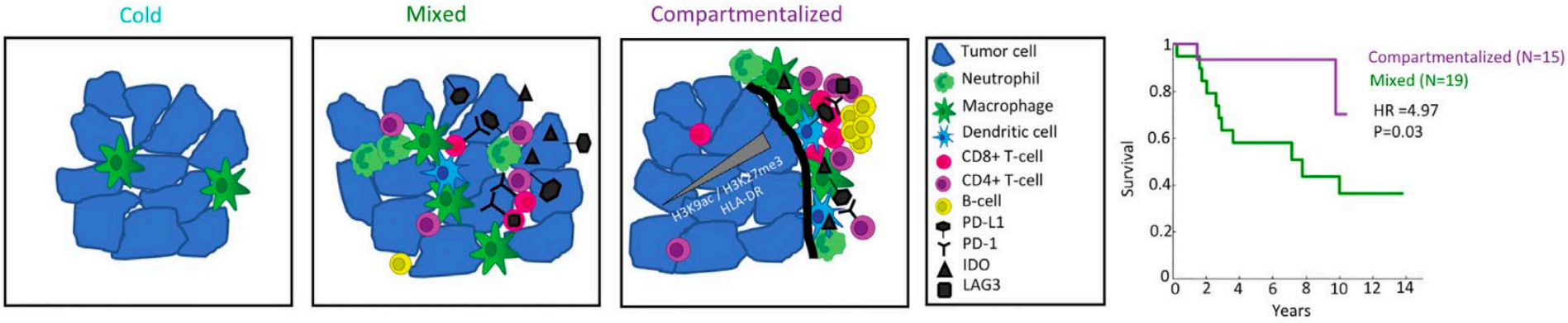




*Mariathasan et al., Nature, 2018*

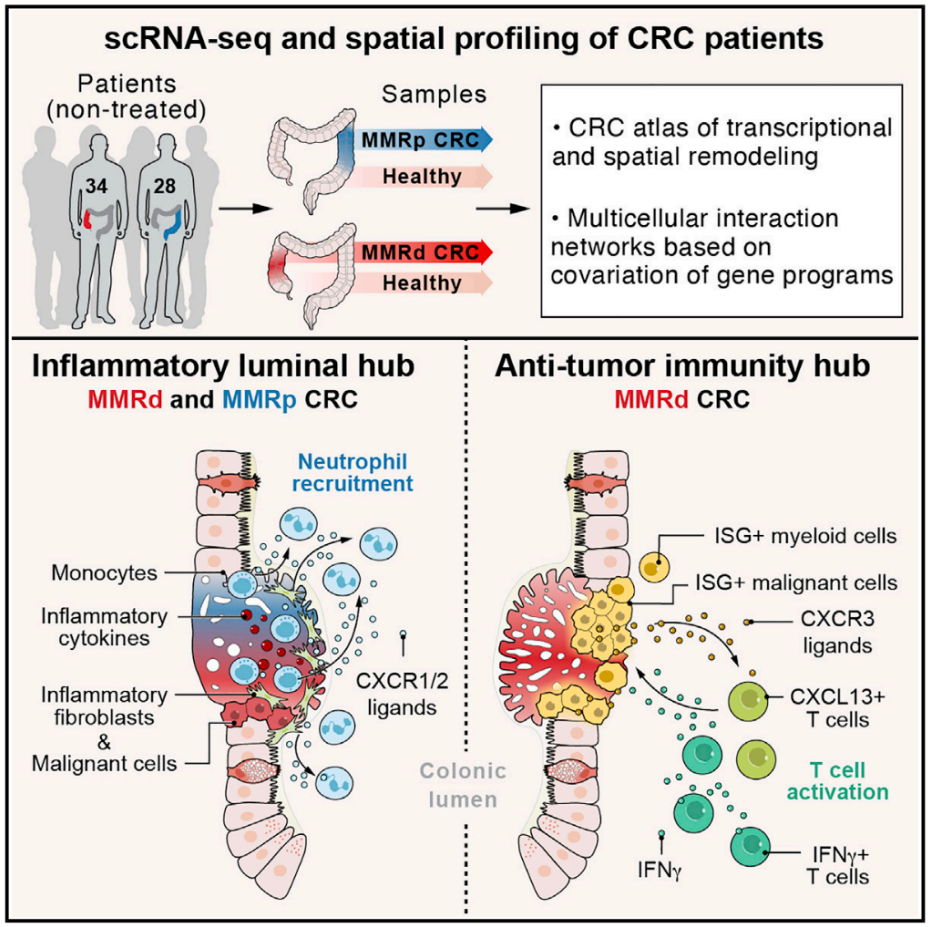
# The spatial organization of the TME is associated with prognosis

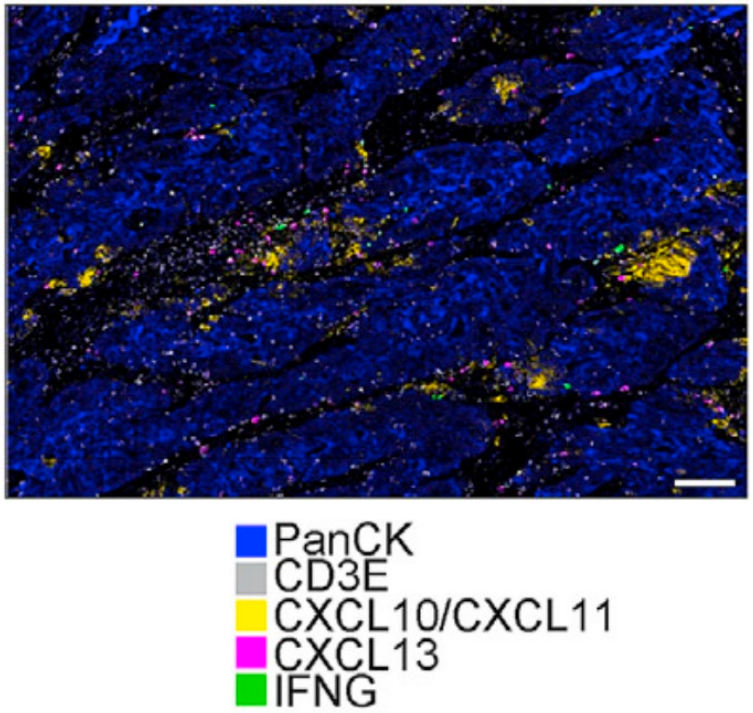



*Keren et al., Cell, 2018*

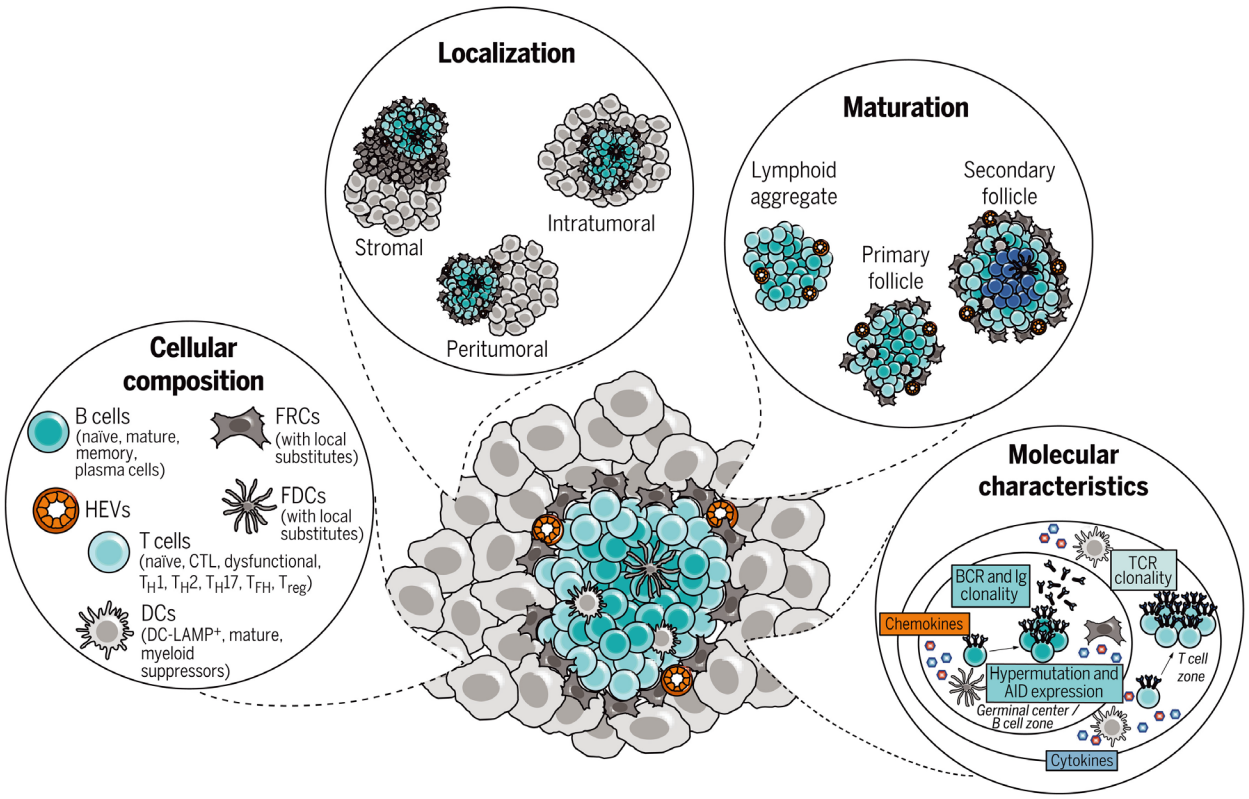
# Cellular hubs with coordinated activity in the TME




*Pelka et al., Cell, 2021*

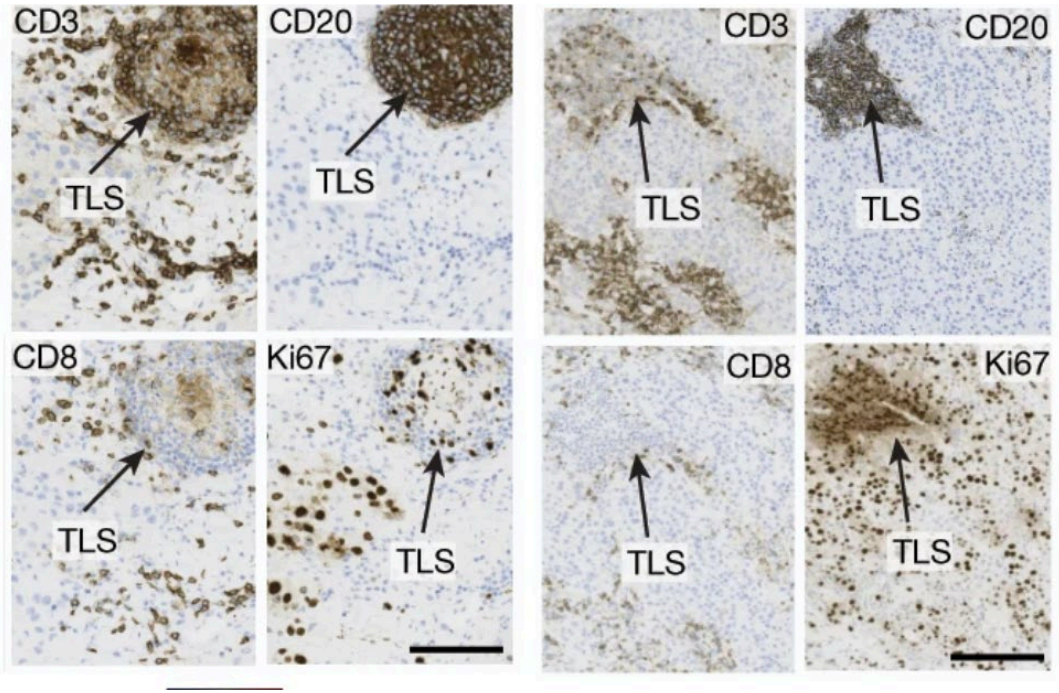
# Tertiary lymphoid structures in the TME

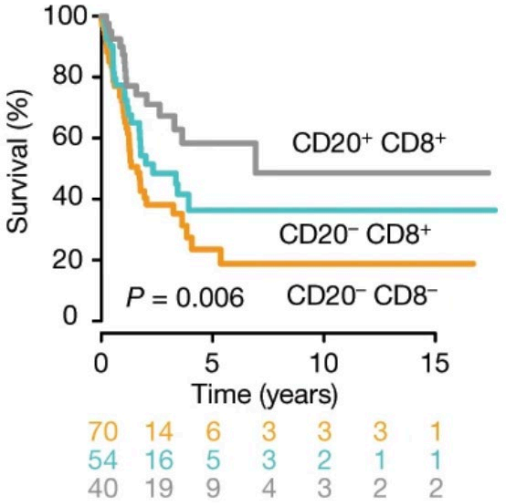


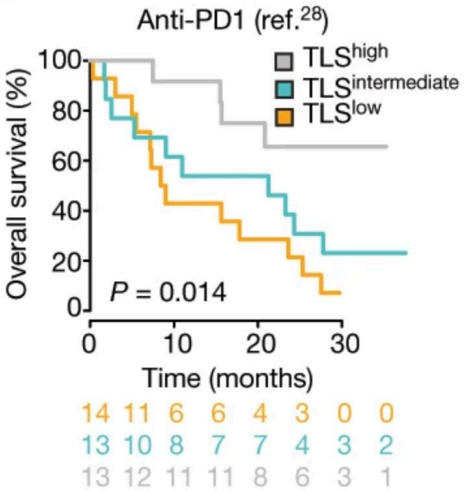

- TLS are lymph node-like structures that form ectopically in inflamed tissues
- Variable in their composition, localization and maturation state
- Poorly modeled in mice

*Schumacher and Thommen, Science, 2022*

# Tertiary lymphoid structures associate with response to checkpoint inhibitor immunotherapy

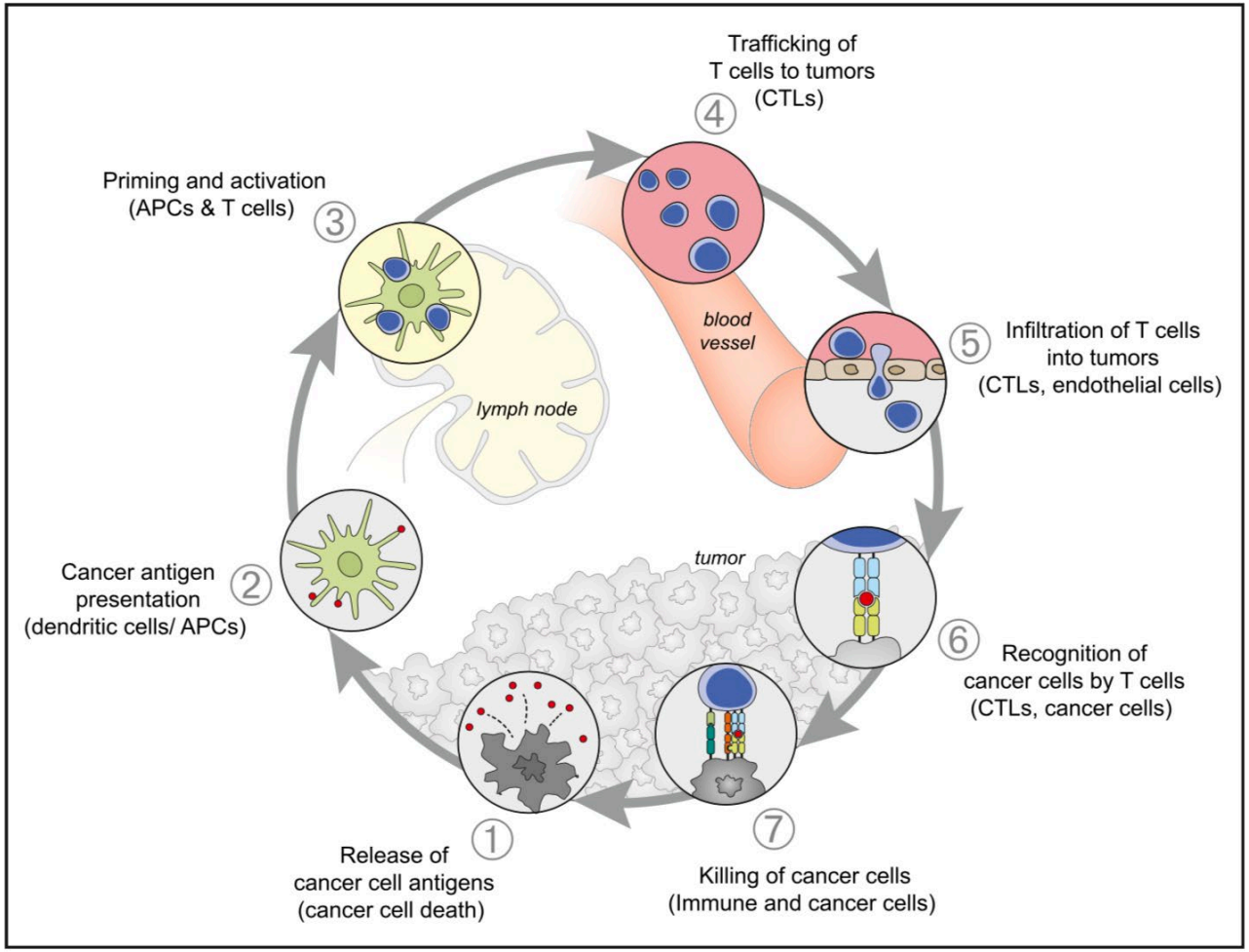


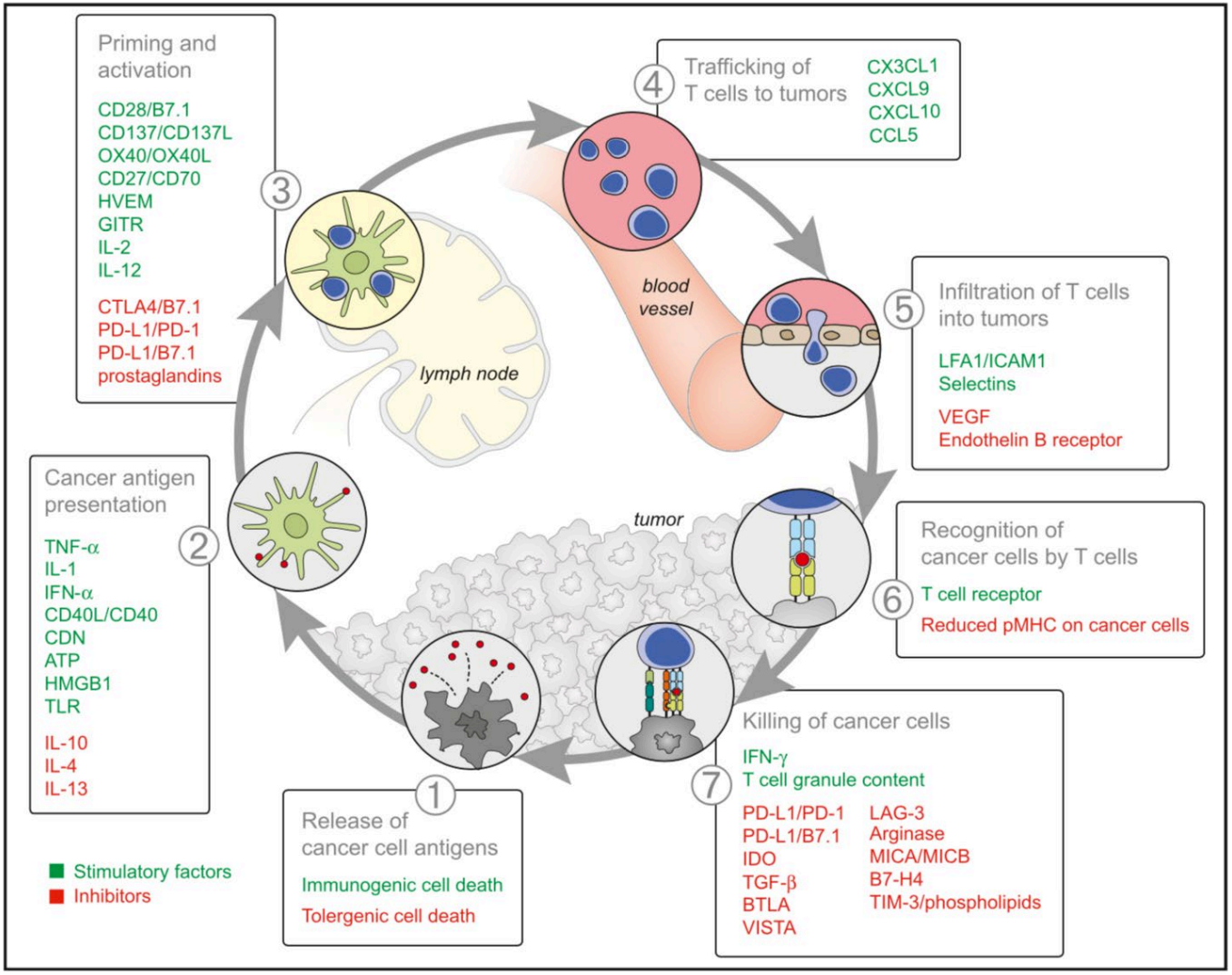

*Cabrita et al., Nature, 2020 (figures)*
*Helmink et al., Nature, 2020*
*Petitprez et al., Nature, 2020*

# The “Cancer Immunity” cycle connects the TME with the rest of the body



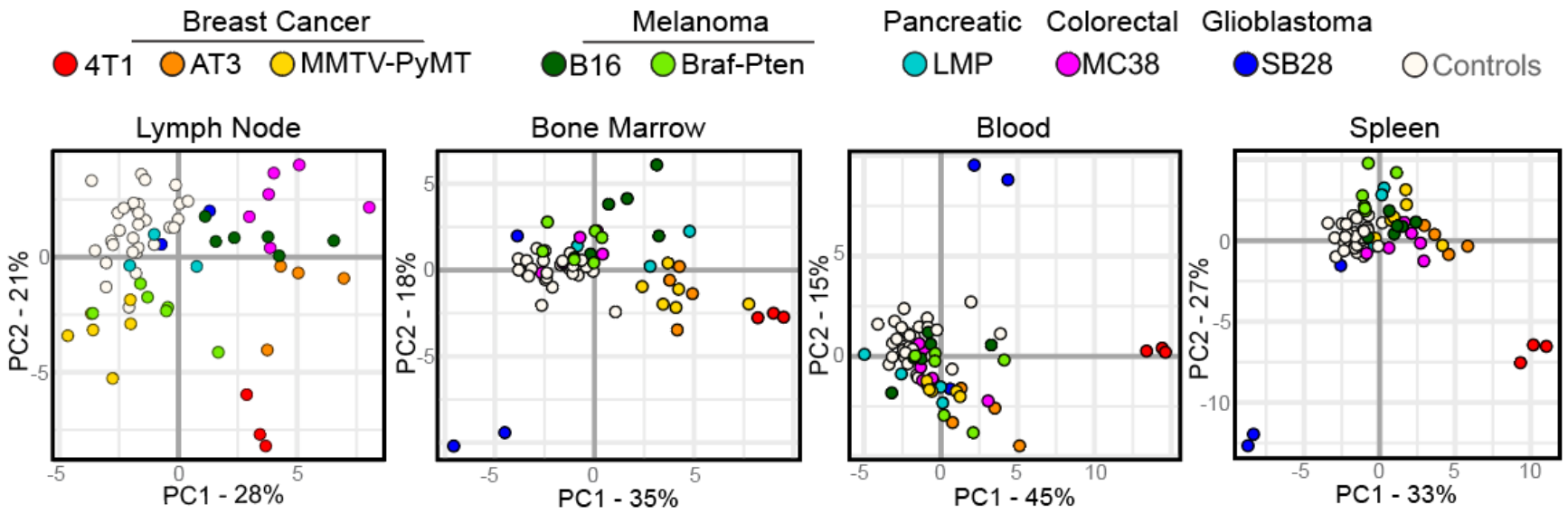

*Chen and Mellman, Immunity, 2013*

# The "Cancer Immunity" cycle connects the TME with the rest of the body




*Chen and Mellman, Immunity, 2013*

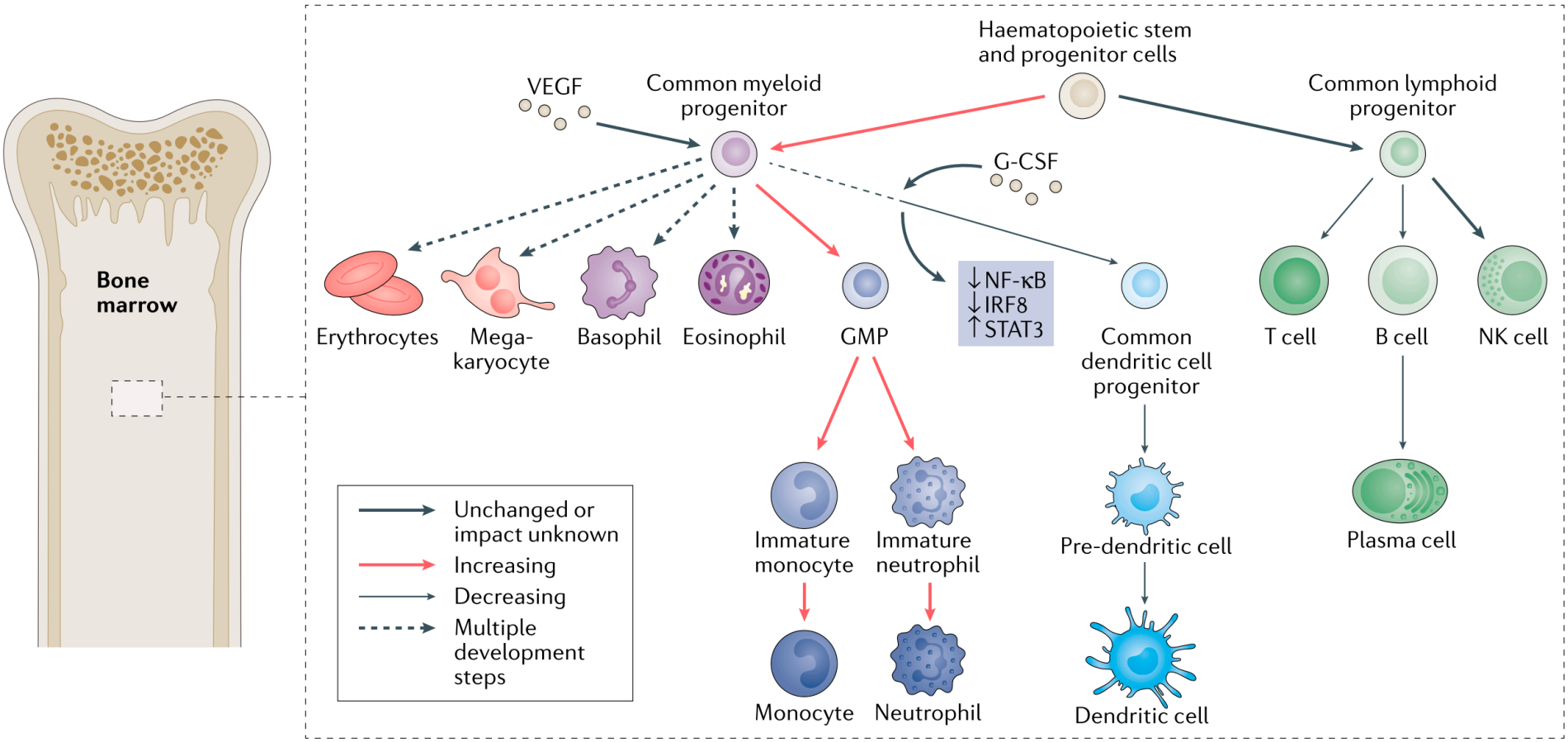
# The TME communicates with the rest of the body




- Different mouse models of cancer change the peripheral immune system in distinct ways
- Some have dramatic effects across all tissues, while some predominantly impact the tumor-draining lymph node

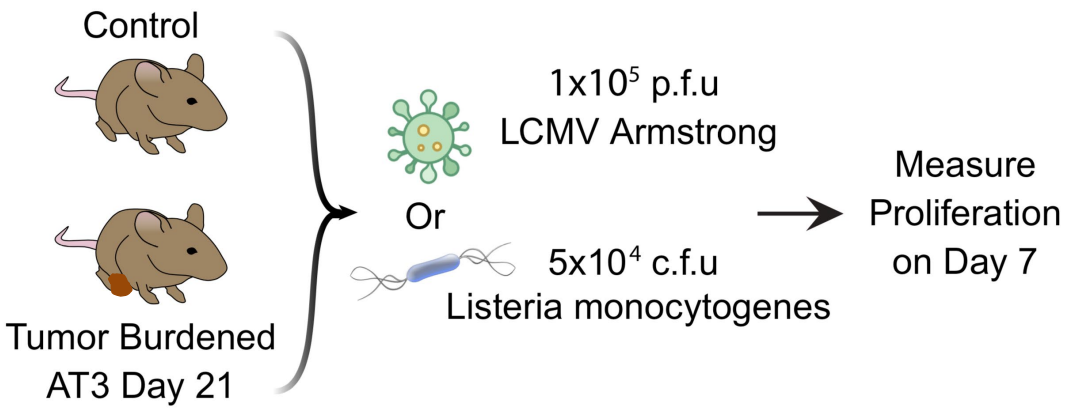
*Allen, Hiam et al., Nat. Med., 2020*

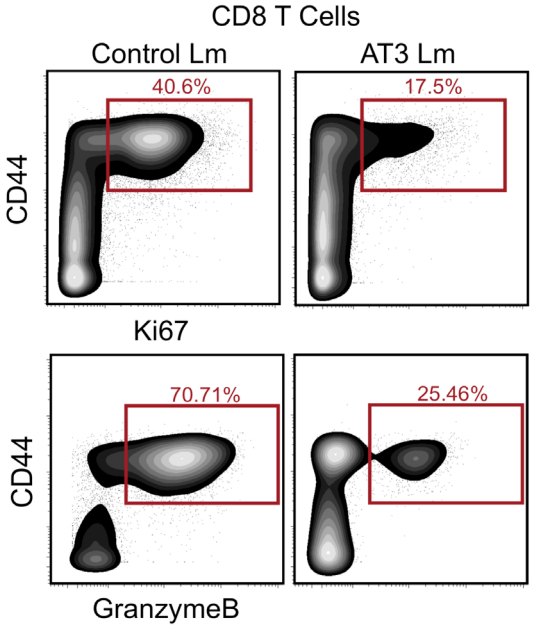
# Tumors can alter immune cell development in the bone marrow




*Casbon et al., PNAS, 2015; Meyer et al., 2018, Nat. Comm.*
*Figure from review: Hiam-Galvez et al., Nat. Rev. Cancer, 2021*

# Tumors can alter new immune responses

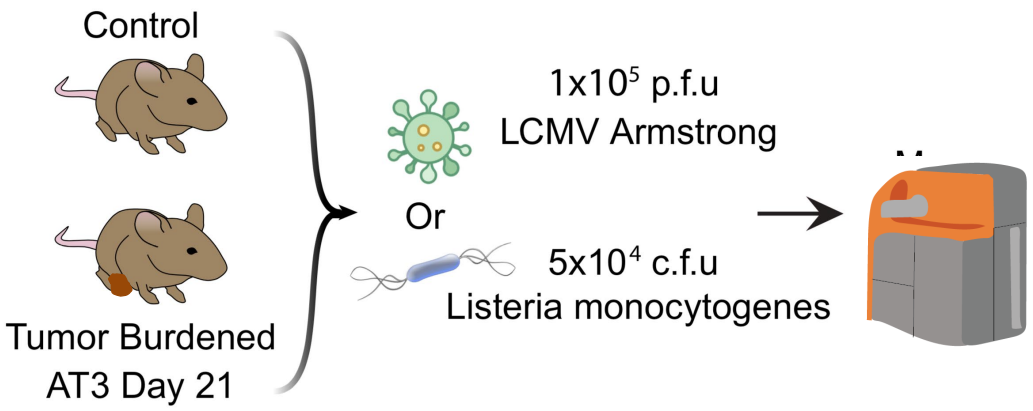


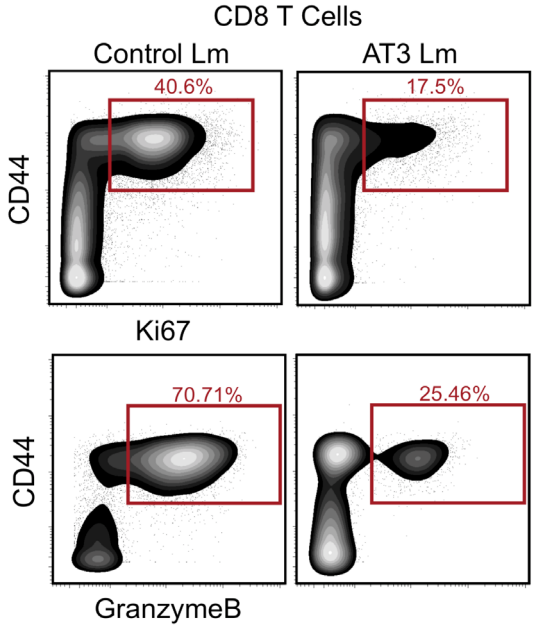




*Allen, Hiam et al., Nat. Med., 2020*

- Mice with established cancers make poor T cell response to new stimuli, such as pathogens.

# Tumors can alter new immune responses




*Allen, Hiam et al., Nat. Med., 2020*

CellPress

Cancer Cell

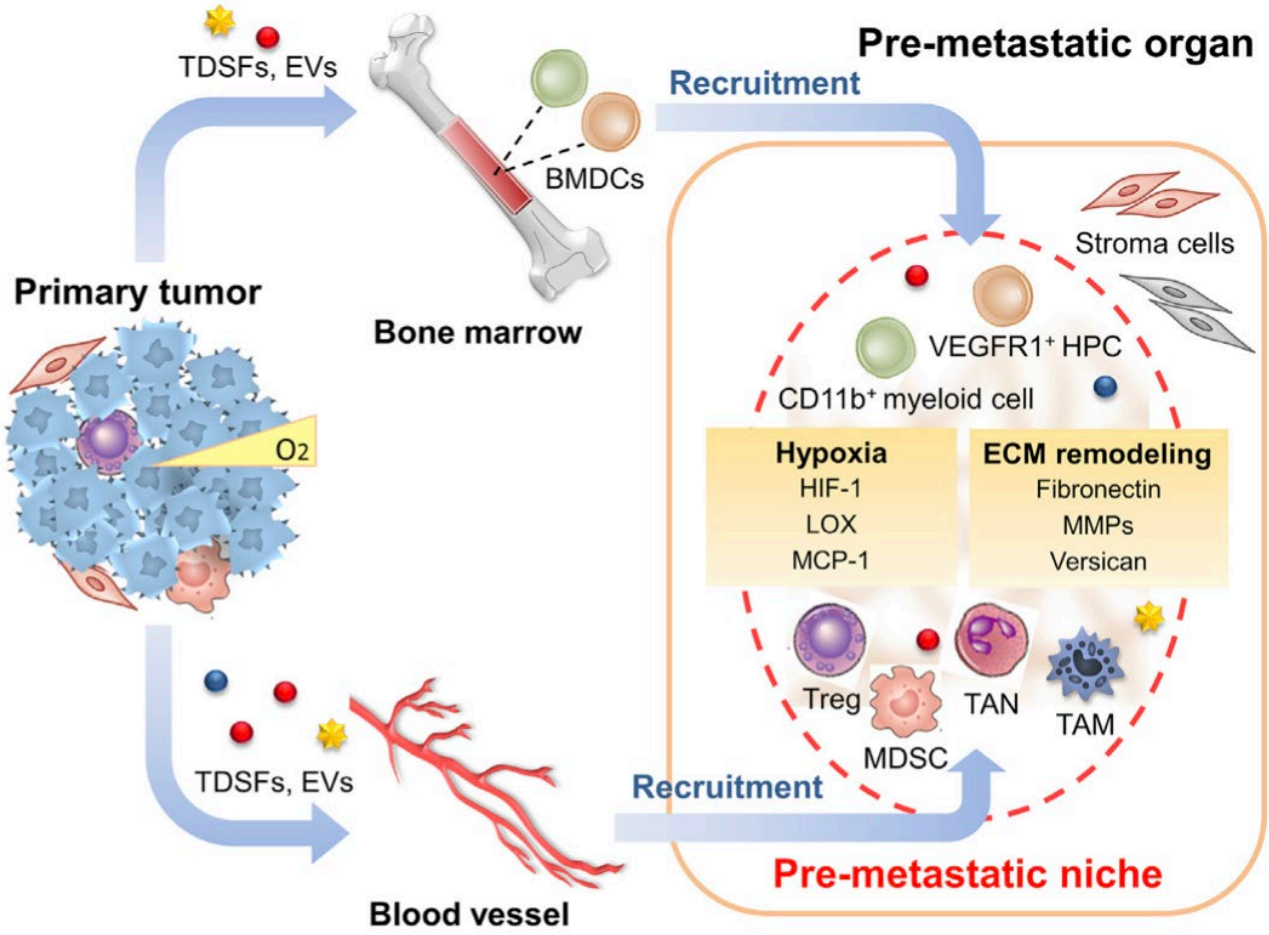
Letter

## Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer

Sidse Ehmsen,[1,2,3] Anders Asmussen,[4] Stefan S. Jeppesen,[1,2,3] Anna Christine Nilsson,[2,5] Sabina Østerlev,[1] Hanne Vestergaard,[4] Ulrik S. Justesen,[2,6] Isik S. Johansen,[2,7] Henrik Frederiksen,[2,3,4] and Henrik J. Ditzel[1,2,3,8,9,*]

[1]Department of Oncology, Odense University Hospital, Odense, Denmark

# Pre-metastatic niches create a hospitable environment for tumor cells to disseminate




- Before tumor cells metastasize, targeted tissues begin to change
- Infiltration of myeloid cells that drive inflammation and suppress T cells
- Remodeling of ECM and vasculature

*Liu and Cao, Cancer Cell, 2106*

# Questions?