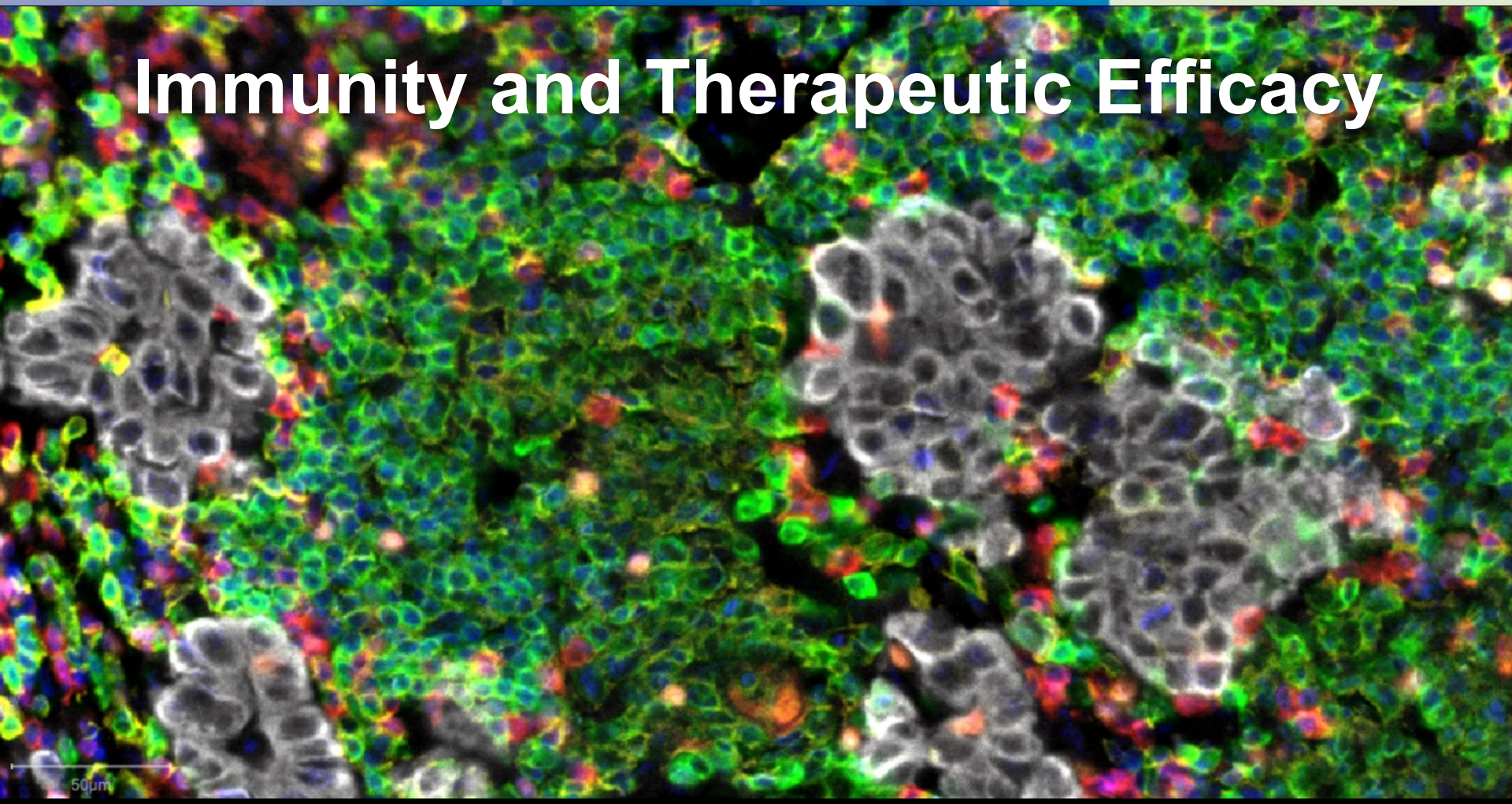
SITC Cancer Immunotherapy Winter School

A COMPREHENSIVE CANCER IMMUNOTHERAPY EDUCATION PROGRAM

sitc

Society for Immunotherapy of Cancer

Immunity and Therapeutic Efficacy



Brad Nelson, PhD
BC Cancer, Victoria BC

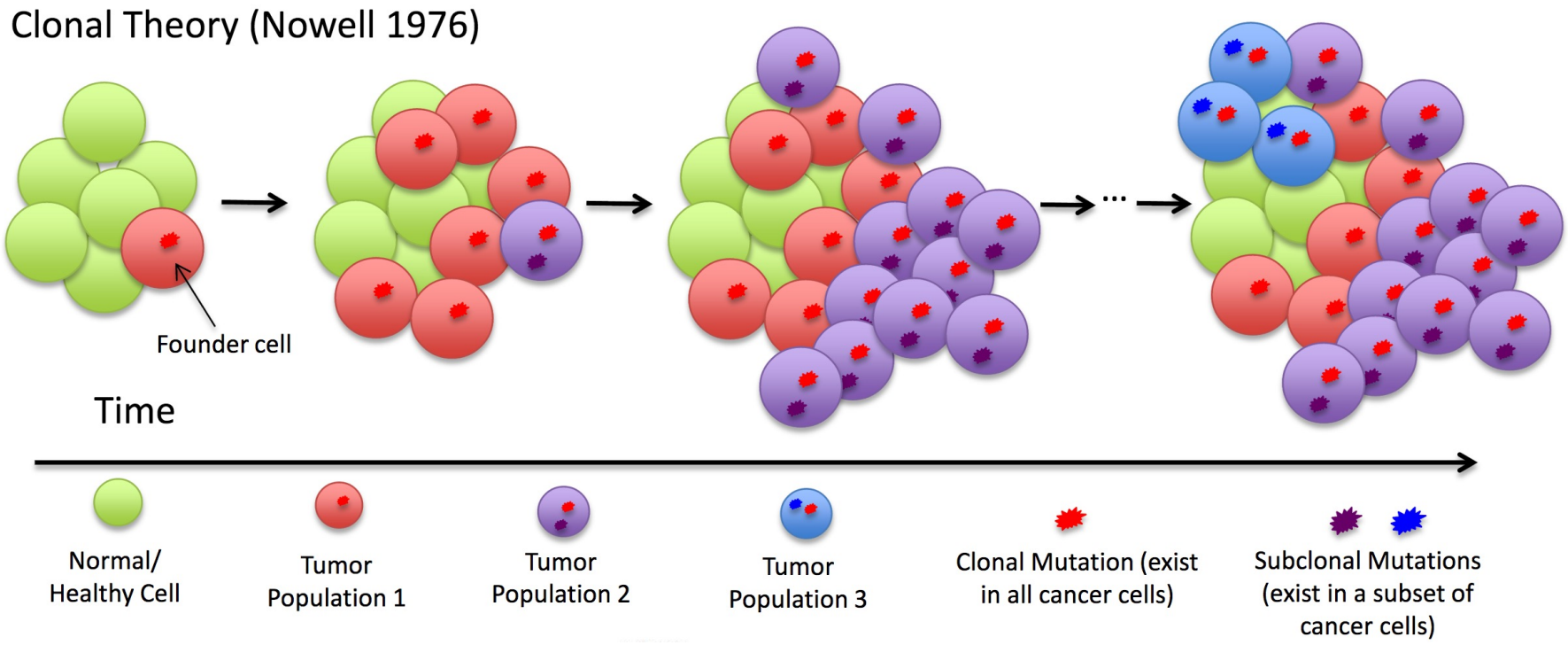
#SITCWinterSchool

January 25 2022

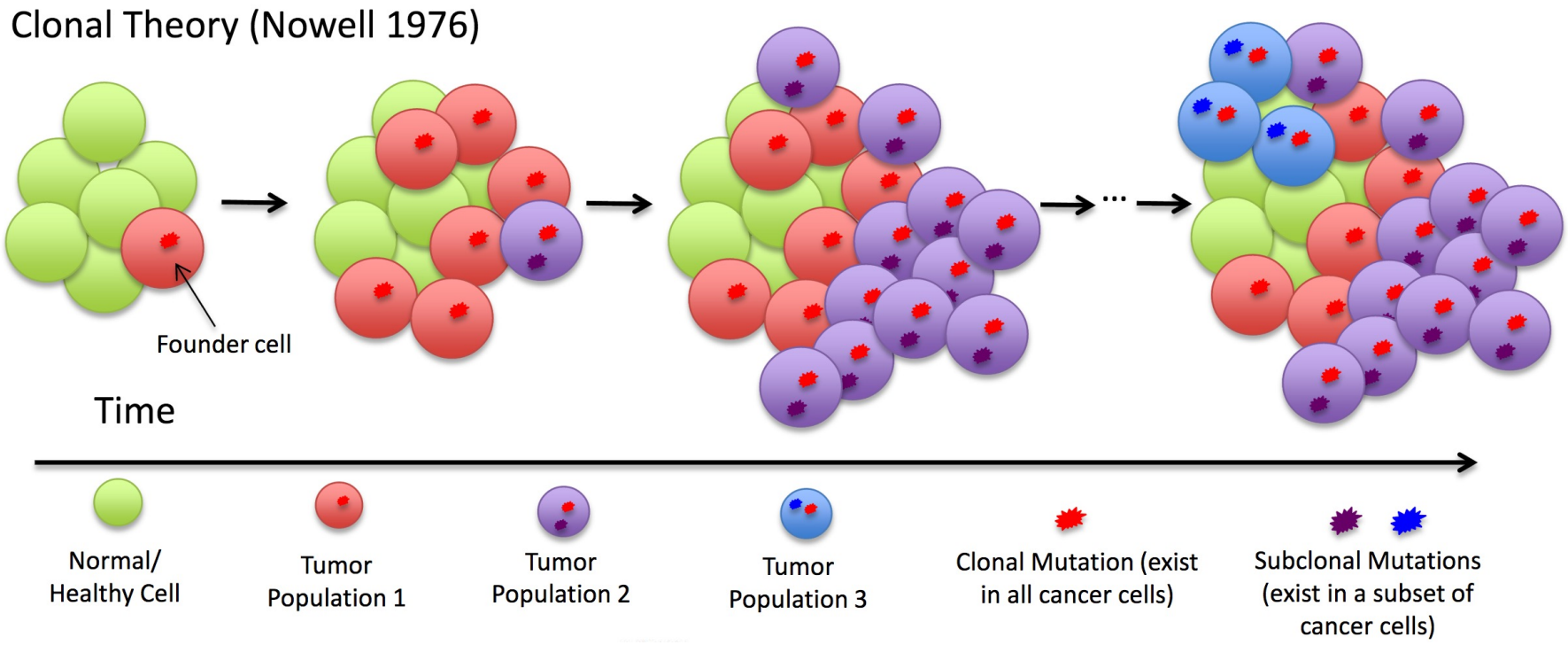
Disclosures

- Advisory Boards/Consulting: *Virogin*
- Contracted Research: *Zymeworks, Innovakine Therapeutics*
- Co-Founder, CEO: *Innovakine Therapeutics*

Tumor evolution gives rise to intratumoral heterogeneity

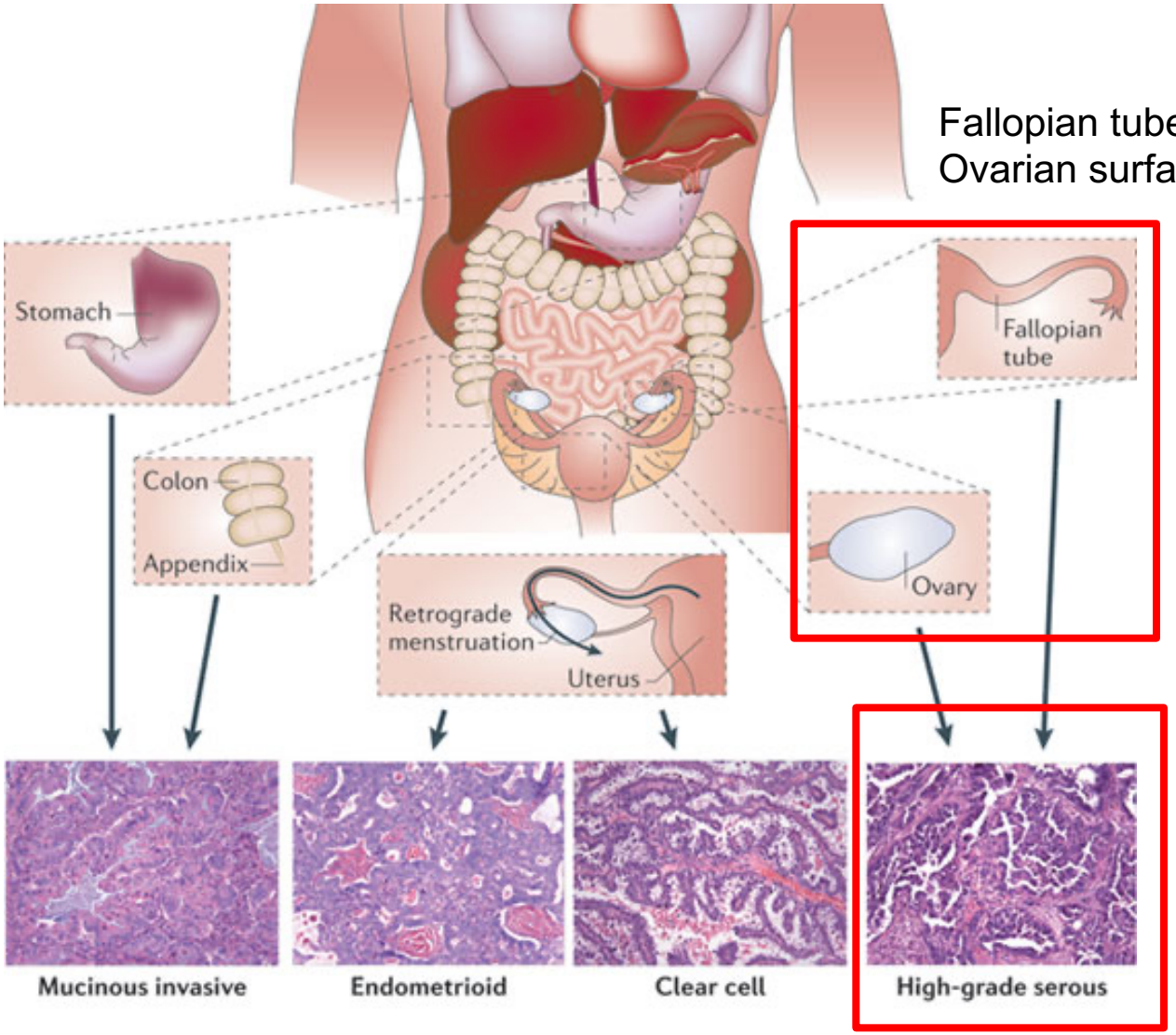


How does the immune system contend with tumor evolution?

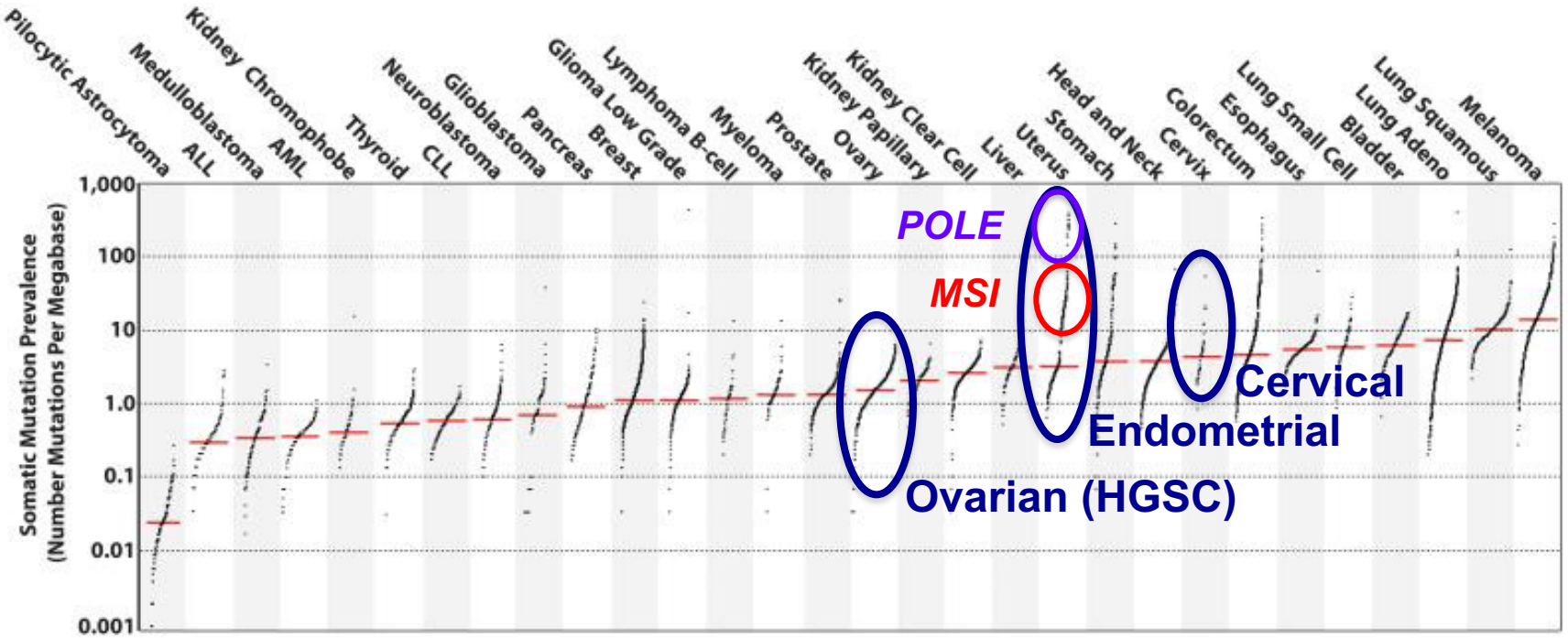


High-Grade Serous “Ovarian” Cancer (HGSC)

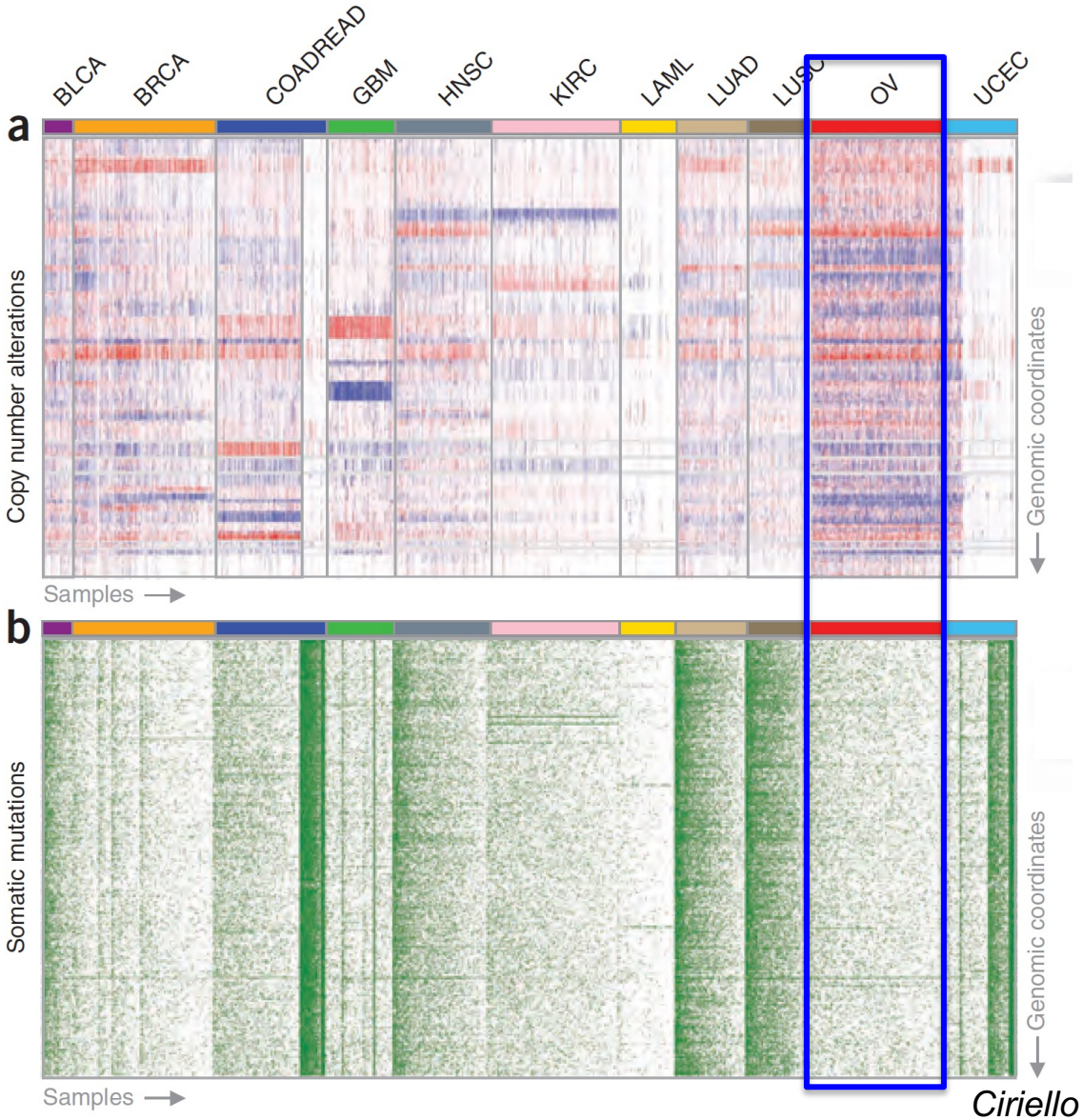
Fallopian tube
Ovarian surface epithelium



HGSC has an intermediate point mutation load

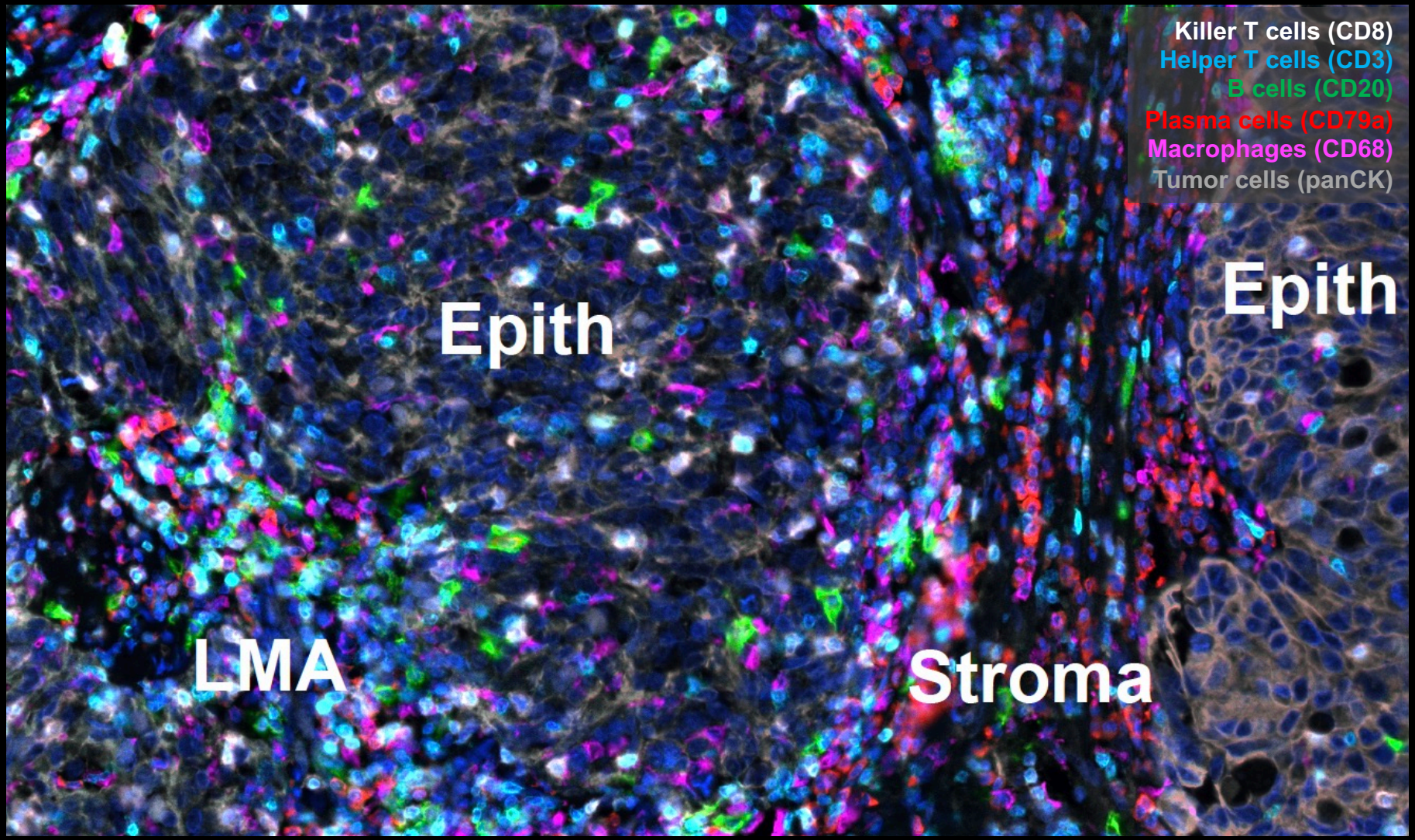


HGSC has extraordinarily high copy number alterations

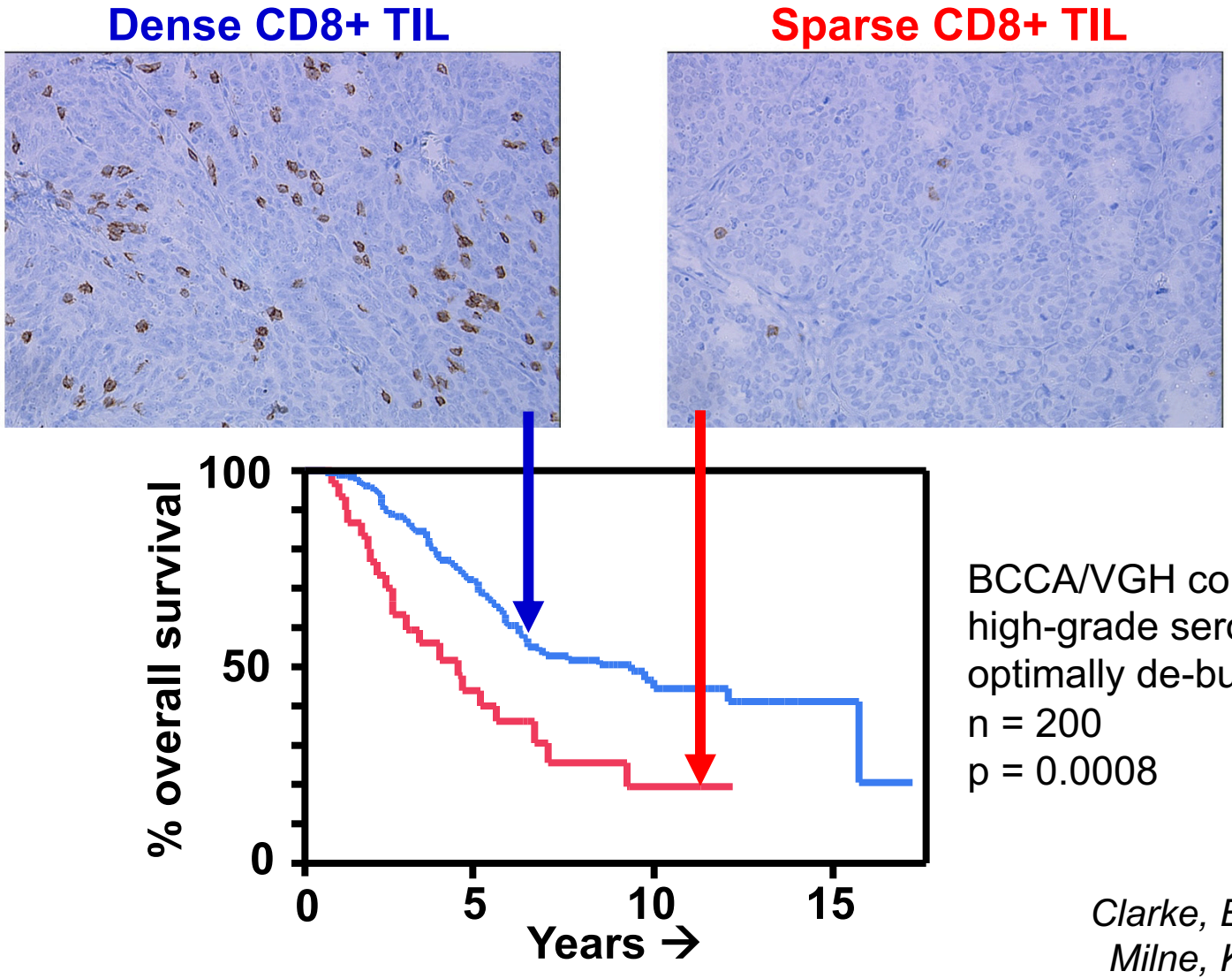


Ciriello et. al. Nat Gen 2013

HGSC tumors often exhibit robust TIL responses



TIL are strongly associated with survival in HGSC



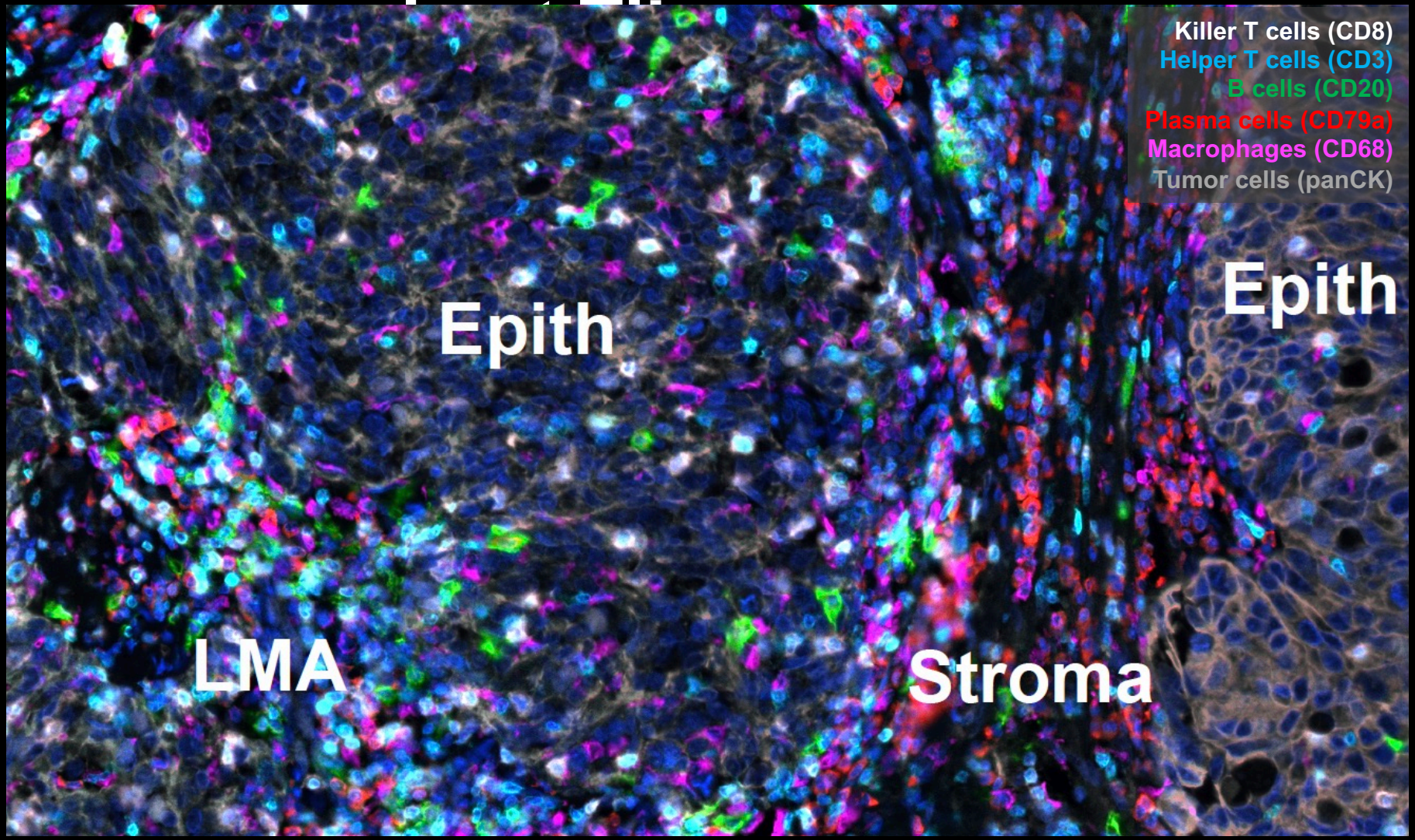
BCCA/VGH cohort
high-grade serous (HGSC)
optimally de-bulked
n = 200
p = 0.0008

Clarke, B. et al. 2009
Milne, K. et al. 2009

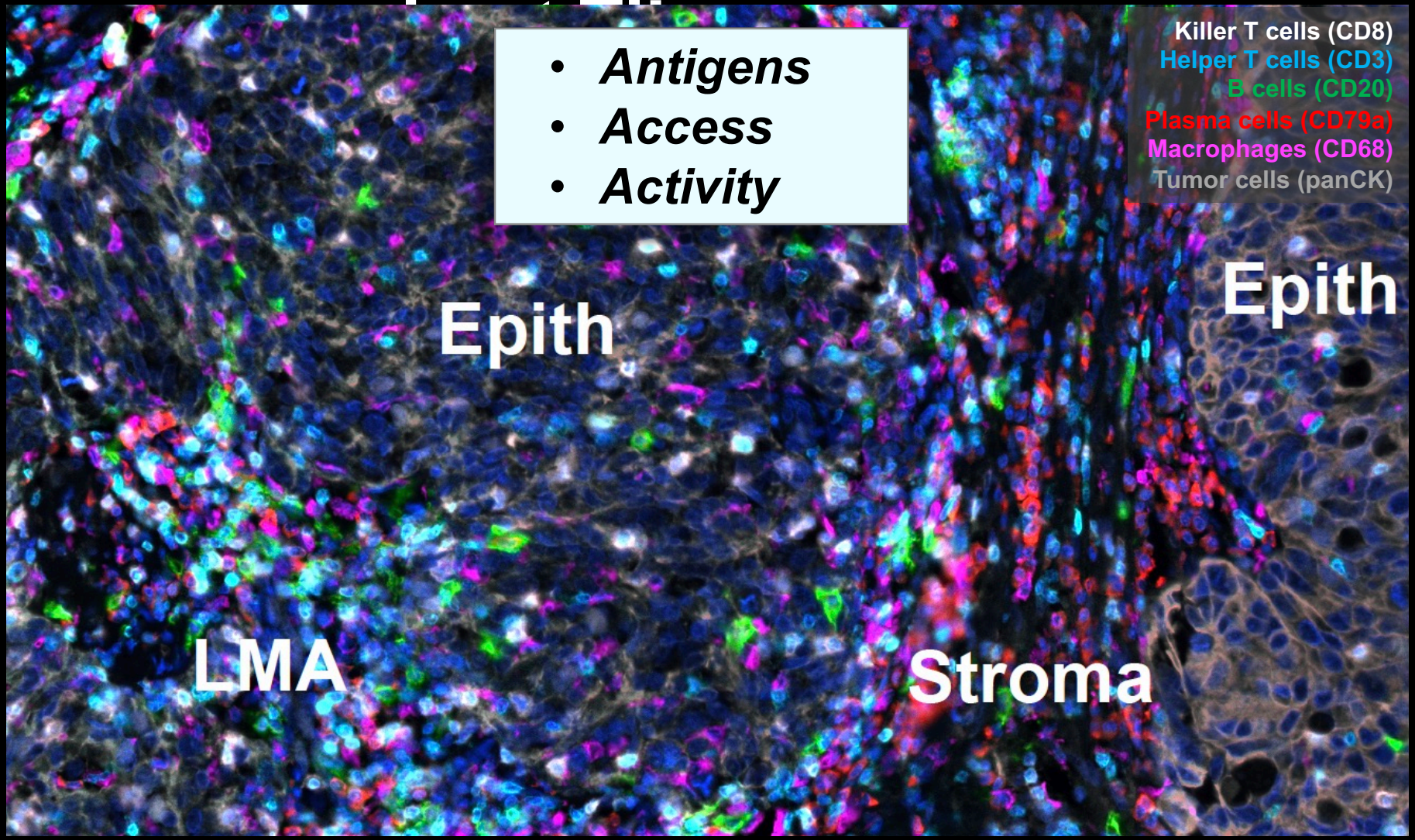
Conundrum

- **Hot tumors are common and favorably prognostic in HGSC**
- **Yet response rates to current immunotherapies are low:**
  - **checkpoint blockade: 10-15% OR**
  - **TIL/CAR-T therapy: best response is stable disease**

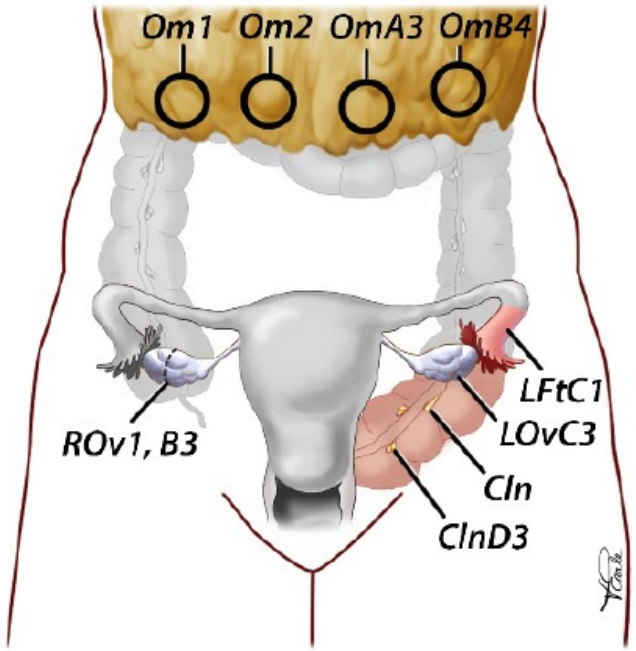
Three requirements for a successful immune response



Three requirements for a successful immune response



Extensive spatial profiling of 212 primary tumors from 38 HGSC patients



Whole genome sequencing
→ ***clonal architecture & mutation signatures***

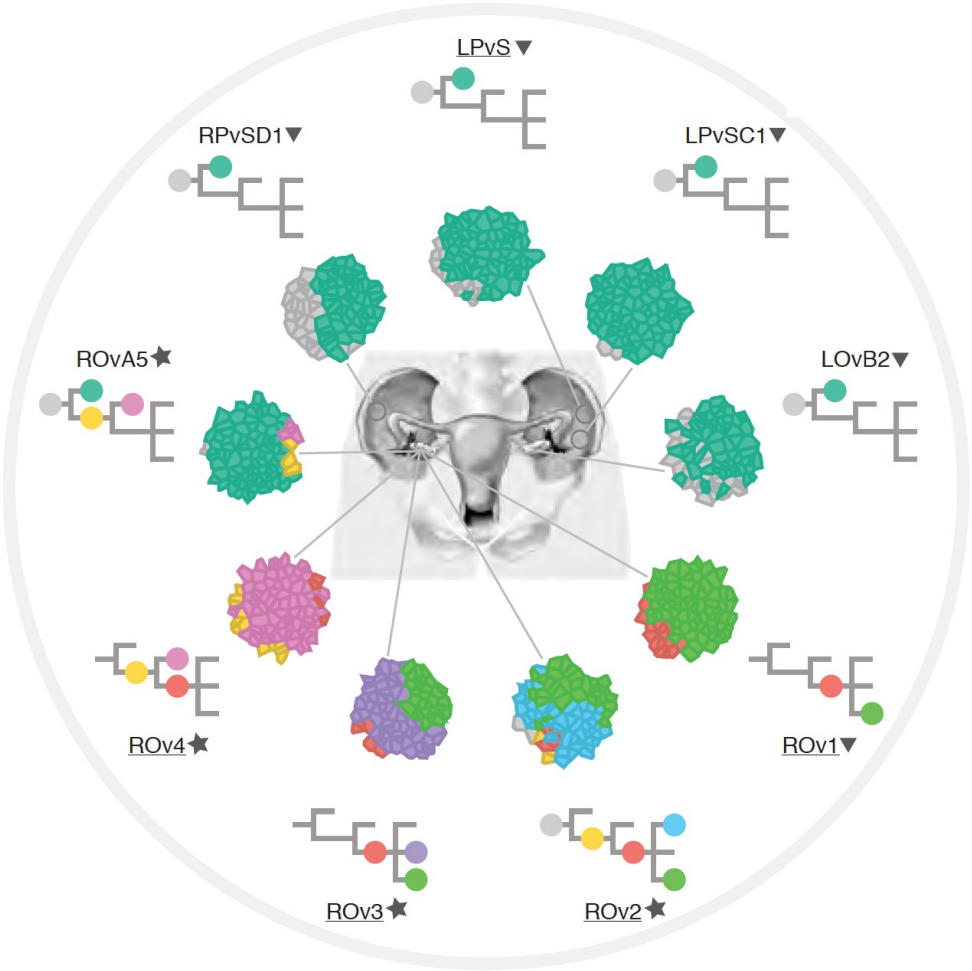
Multi-colour IHC
→ ***TIL patterns: T cells, B cells, plasma cells***

Nanostring profiling
→ ***molecular subtype, immune gene expression***

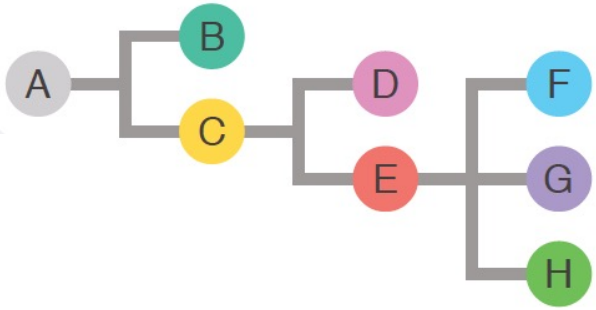
TCR & BCR sequencing
→ ***T cell and B cell clonal distributions***

Allen Zhang, Rob Holt, Sohrab Shah, et al. Cell 2018

Tumor evolution leads to intratumoral heterogeneity



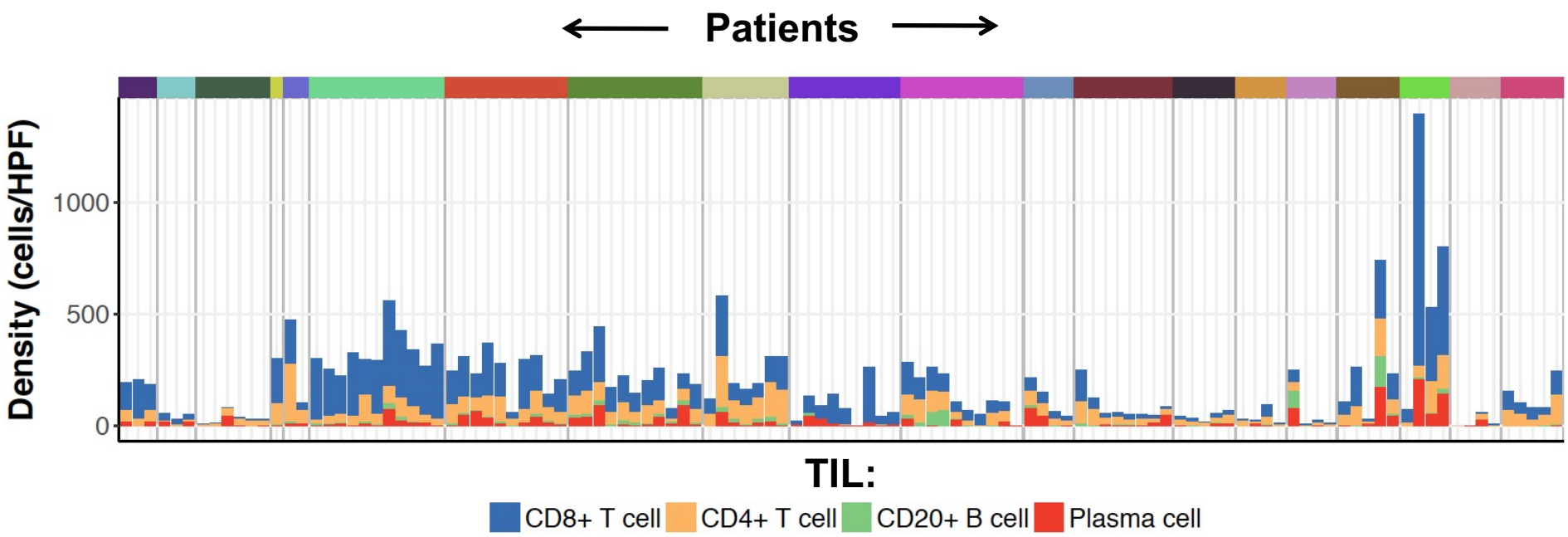
Clonal phylogeny in ovarian cancer (patient 4)



A McPherson...S Shah, Nature Genetics 2016

Patients show a range of TIL “temperatures”

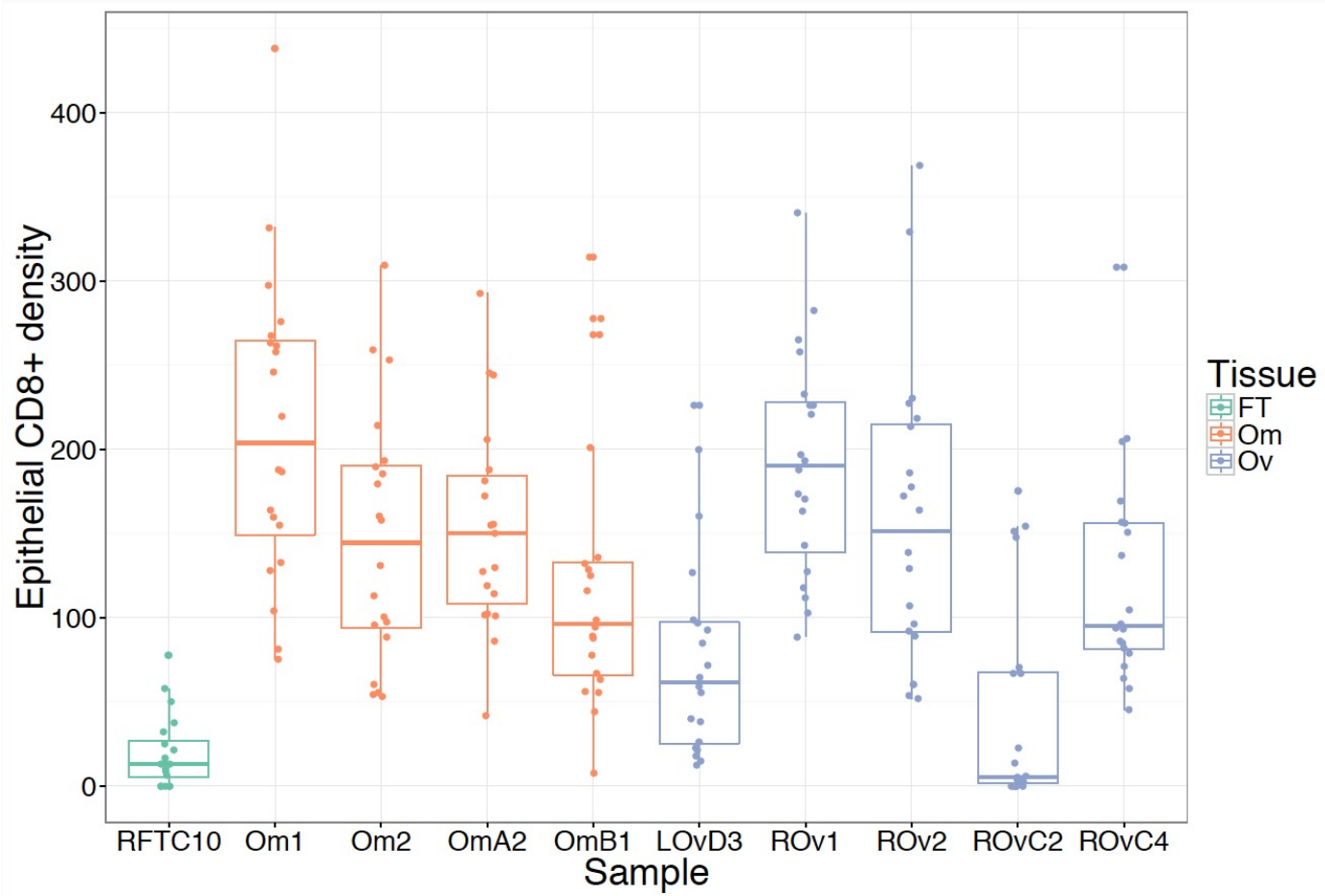
Immunohistochemistry data for 4 TIL subsets



Allen Zhang, Rob Holt, Sohrab Shah, et al. Cell 2018

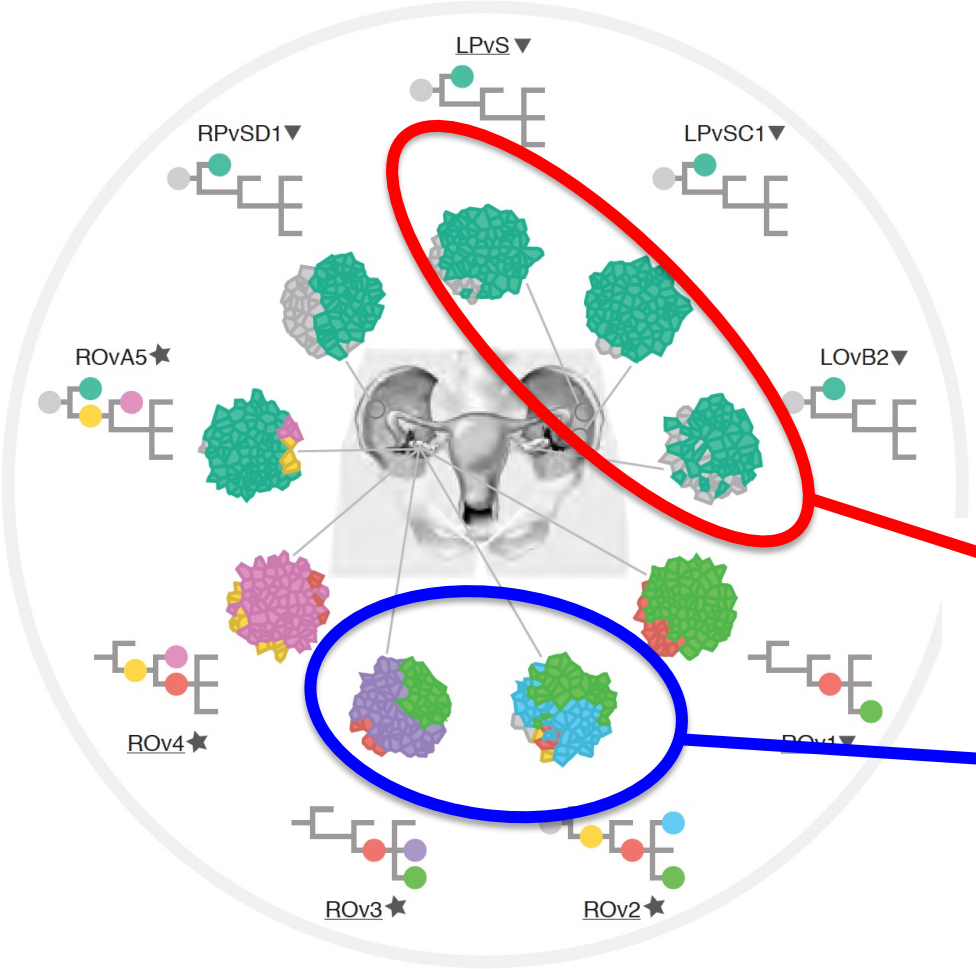
TIL densities can vary widely within a patient

CD8+ TIL densities at 10 anatomical sites, 20 high-powered fields each

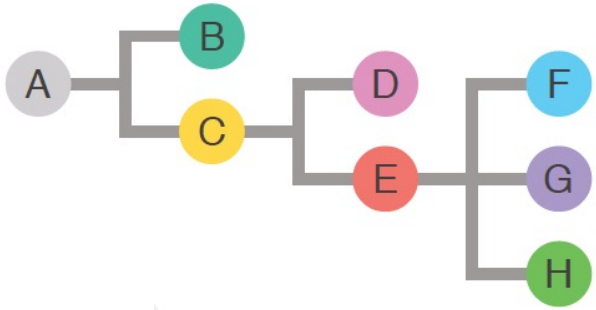


Allen Zhang, Rob Holt, Sohrab Shah, et al. Cell 2018

TIL are negatively associated with intratumoral heterogeneity



Clonal phylogeny in ovarian cancer (patient 4)



Monoclonal tumors tend to be hot

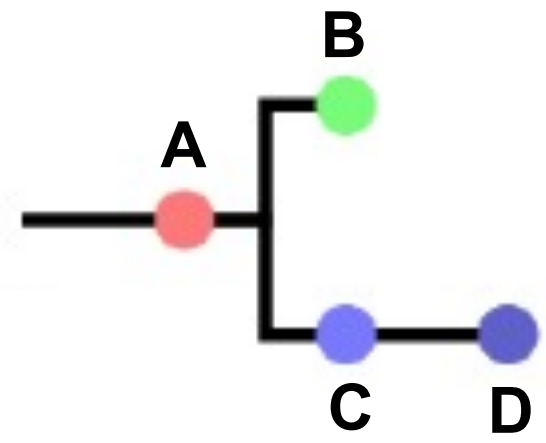
Polyclonal tumors tend to be cold

Allen Zhang, Rob Holt, Sohrab Shah, et al. Cell 2018

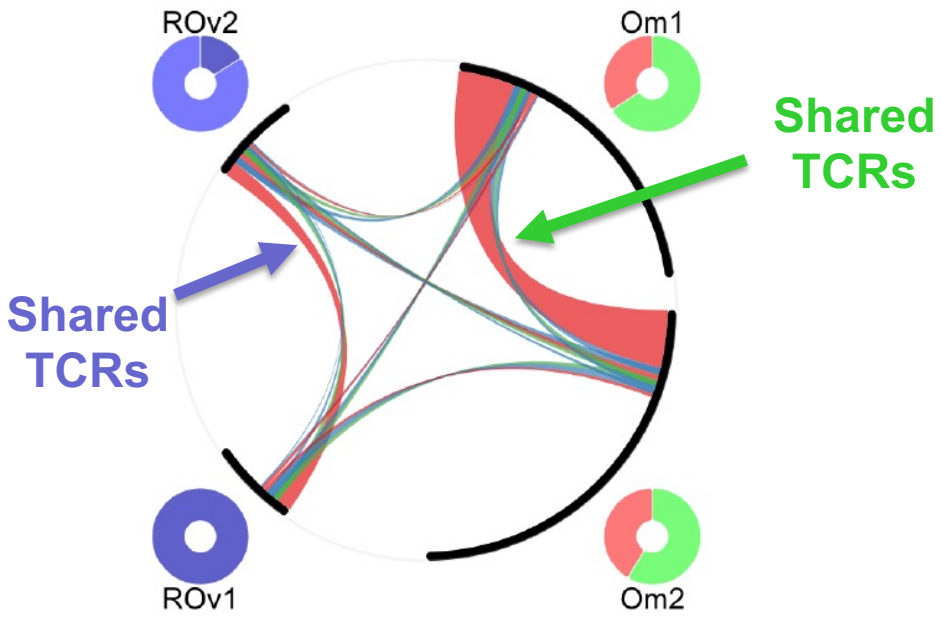
T cell clones track spatially with tumor clones

Example from ovarian cancer patient #2

Tumor clone phylogeny:



TCR sharing at 4 tumor sites:

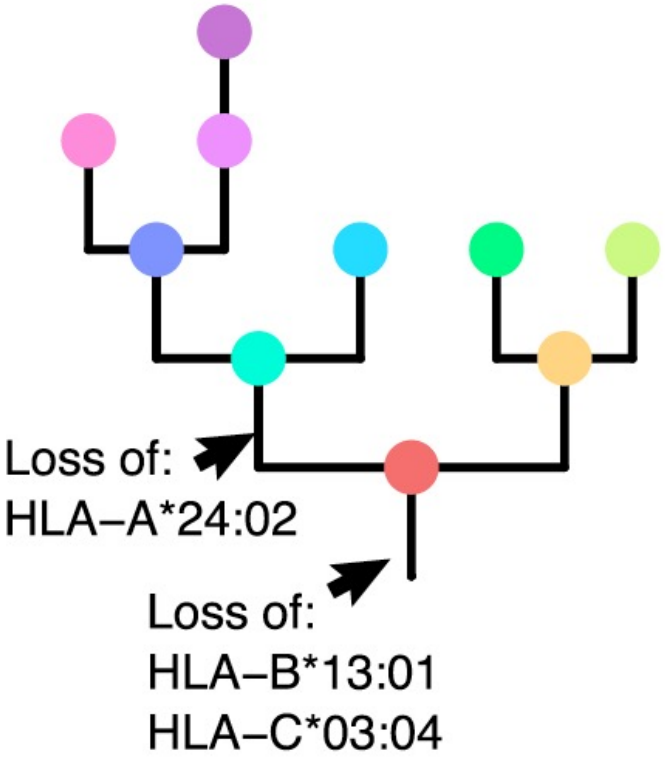


Allen Zhang, Rob Holt, Sohrab Shah, et al. Cell 2018

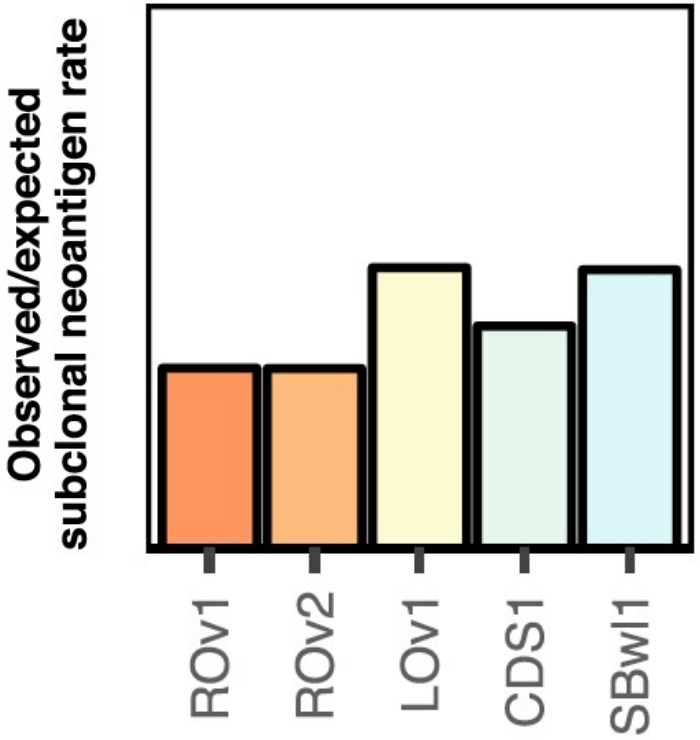
Hot tumors show signs of immune editing

Example from ovarian cancer patient #15

HLA allelic loss:



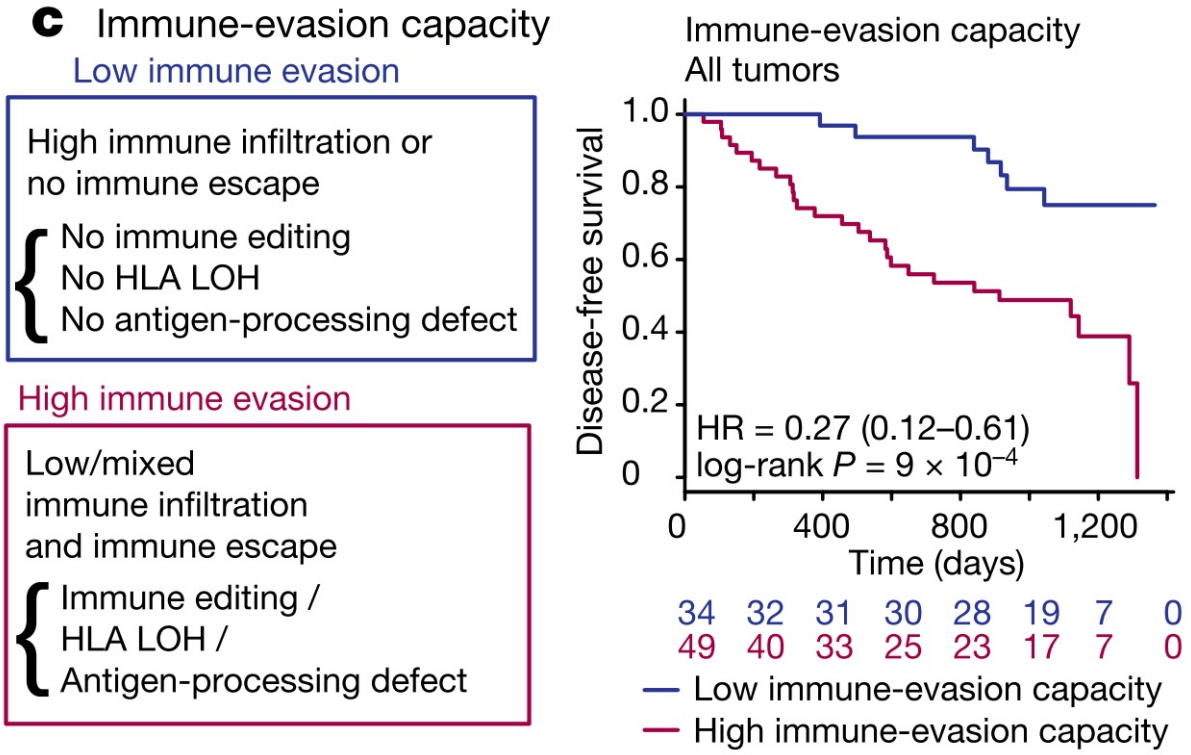
Neoantigen depletion:



Allen Zhang, Rob Holt, Sohrab Shah, et al. Cell 2018

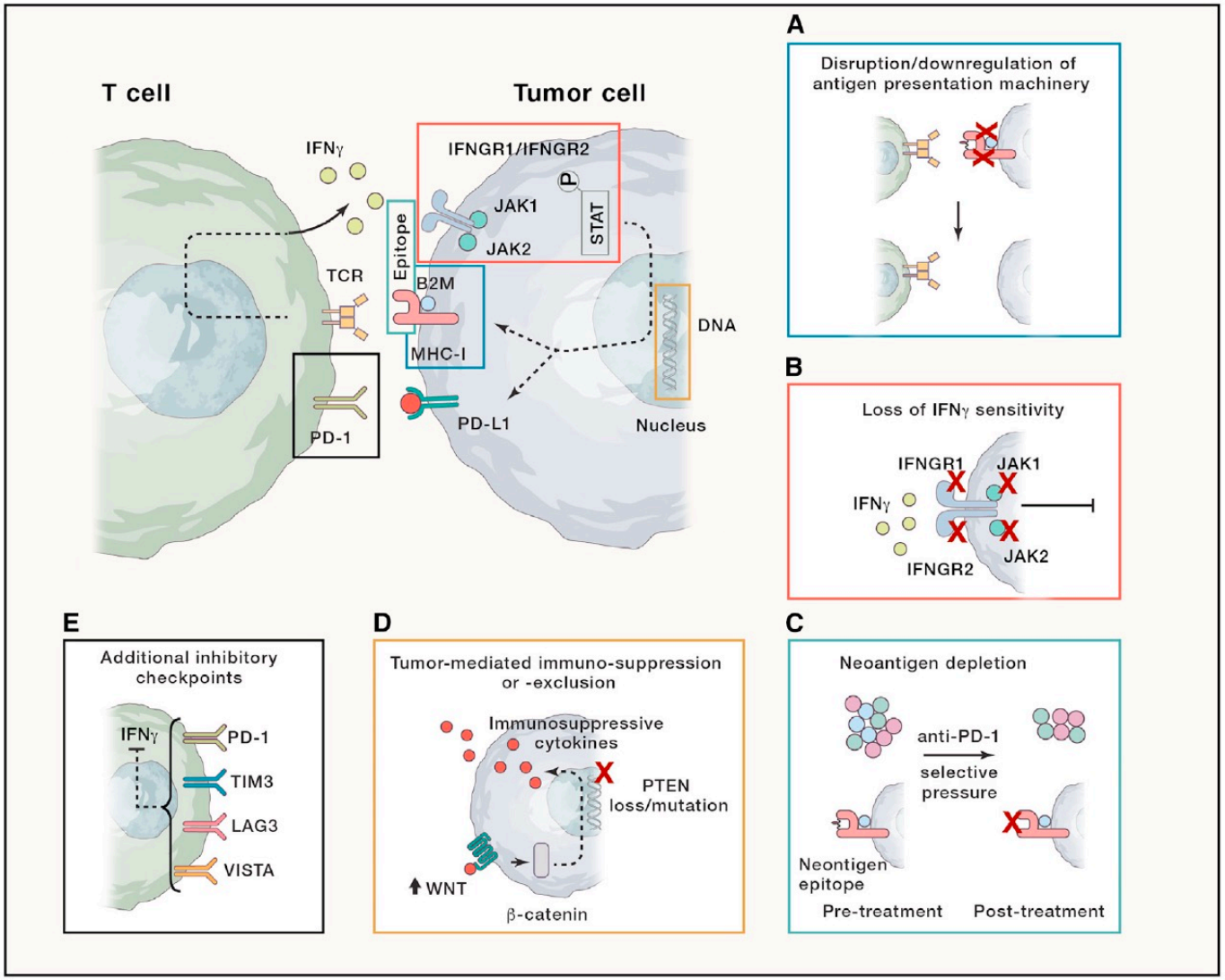
Lung cancer: immune evasion is linked to prognosis

- **Non-small-cell lung cancer: 88 cases and 258 specimens**
- **Hot tumors show decreased clonal diversity and increased immune editing (neoantigen and/or HLA loss)**
- **The extent of immune evasion was key to prognosis**



Rosenthal R…Swanton C. Nature 2019

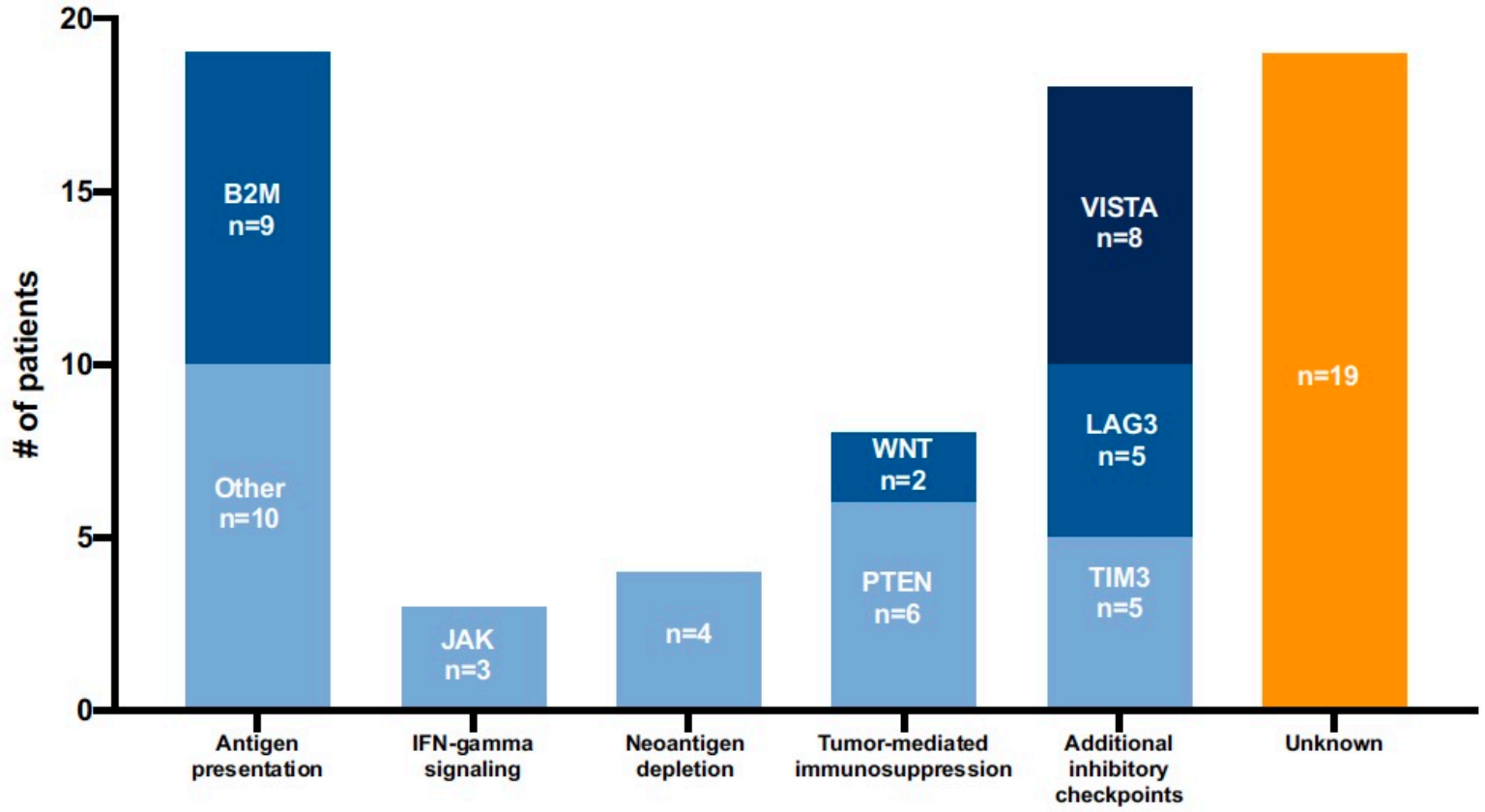
Checkpoint blockade can select for a variety of immune evasion mechanisms



Schoenfeld AJ and Hellmann MD, Cancer Cell 2020

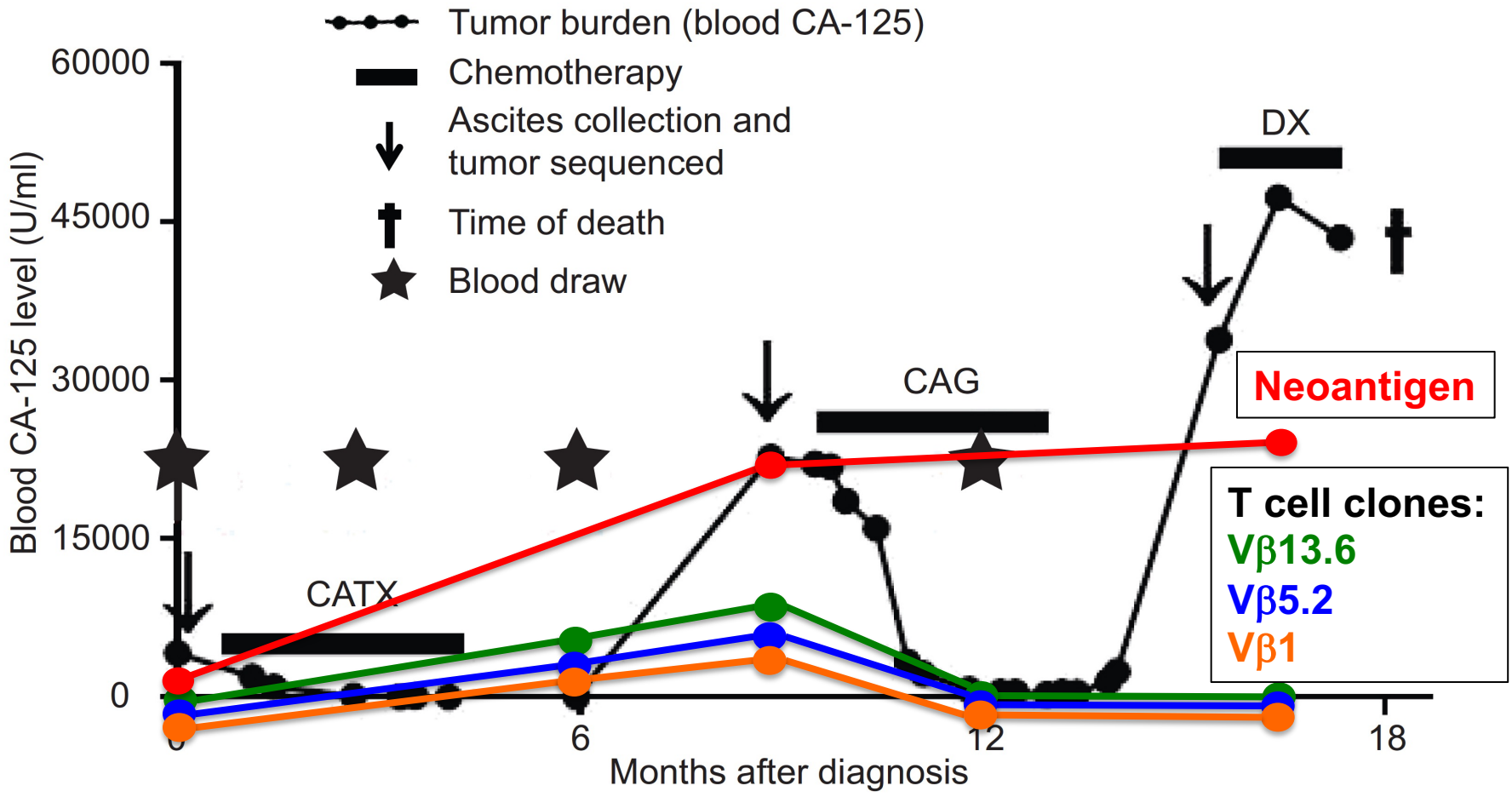
Checkpoint blockade can select for a variety of immune evasion mechanisms

Number of cases showing a given resistance mechanism



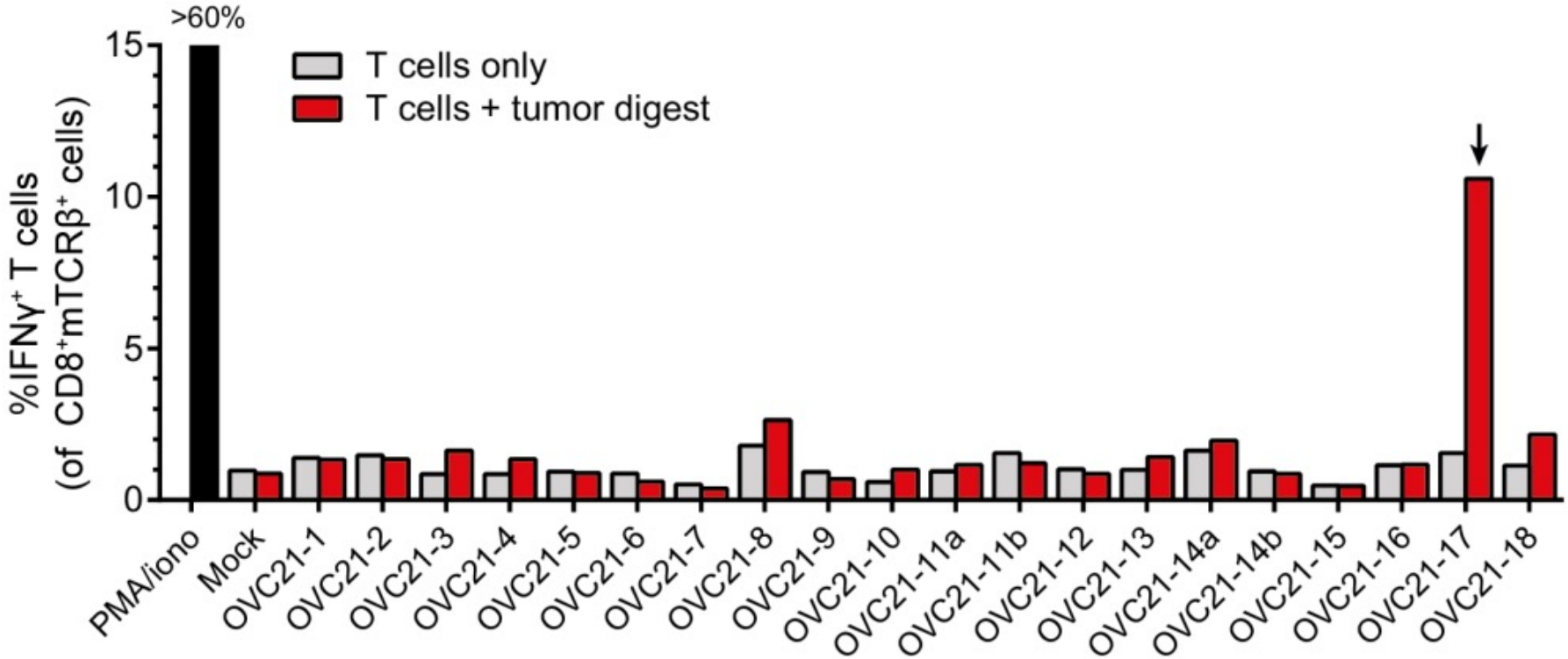
Schoenfeld AJ and Hellmann MD, Cancer Cell 2020

Tumor-specific CD8+ T cells can emerge & then disappear during tumor progression



Darin Wick et al, Clin Can Res 2014
Spencer Martin et al, Oncoimm 2017

Only a small minority of CD8+ TIL are tumor reactive in HGSC



Scheper, Kelderman…Schumacher, Nat Med, 2018

Tumor-infiltrating T cells exhibit major limitations

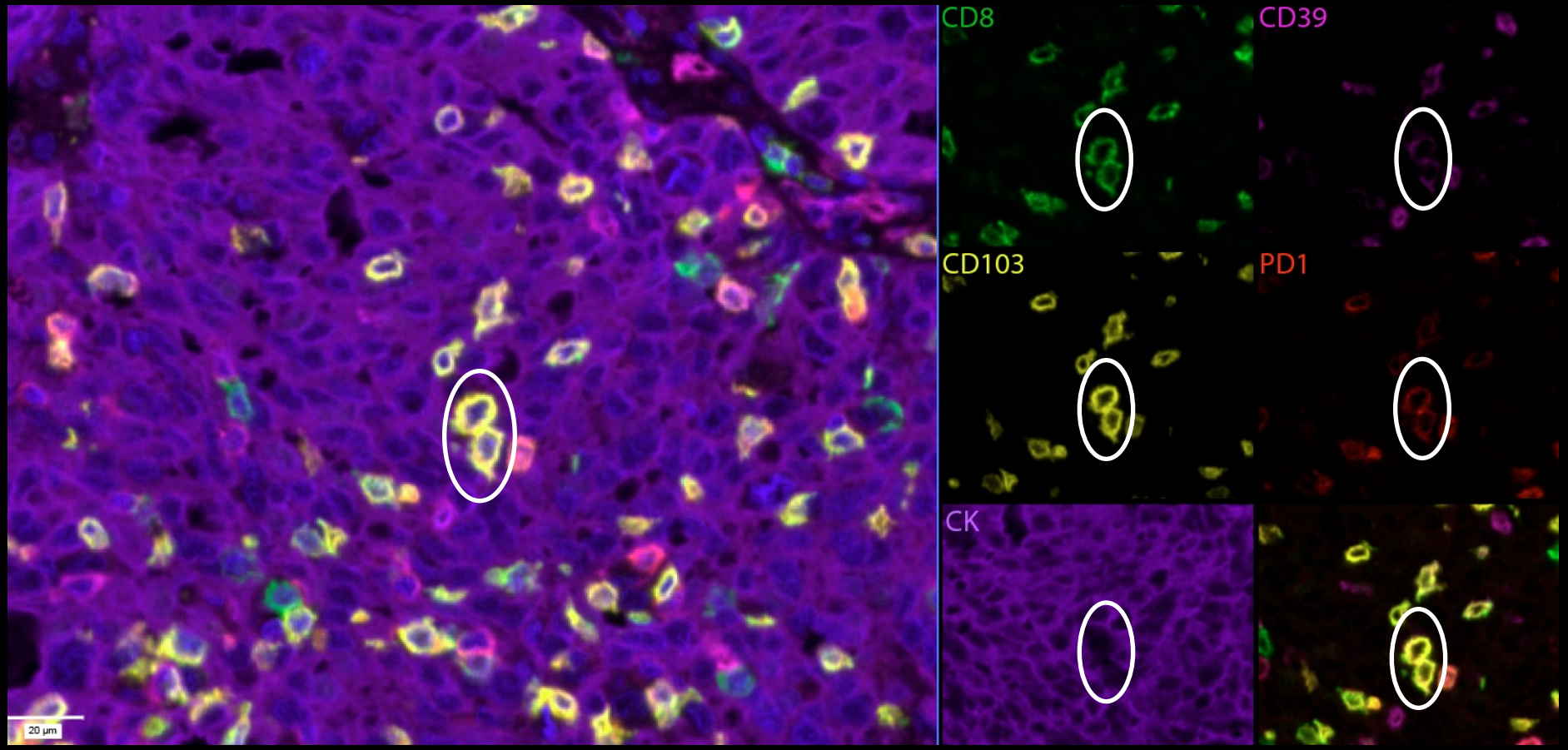
Despite their prognostic benefit, hot tumors can exhibit:

- **Antigen loss**
- **MHC loss**
- **Loss of tumor-reactive T cells over time**
- **Multiple immune suppressive factors**
- **High proportion of bystander T cells**
- **Mixture of hot & cold sites in individual patients**
- **Progression toward colder tumors at end stage**

What is the phenotype of tumor-reactive TIL and how can we help them?

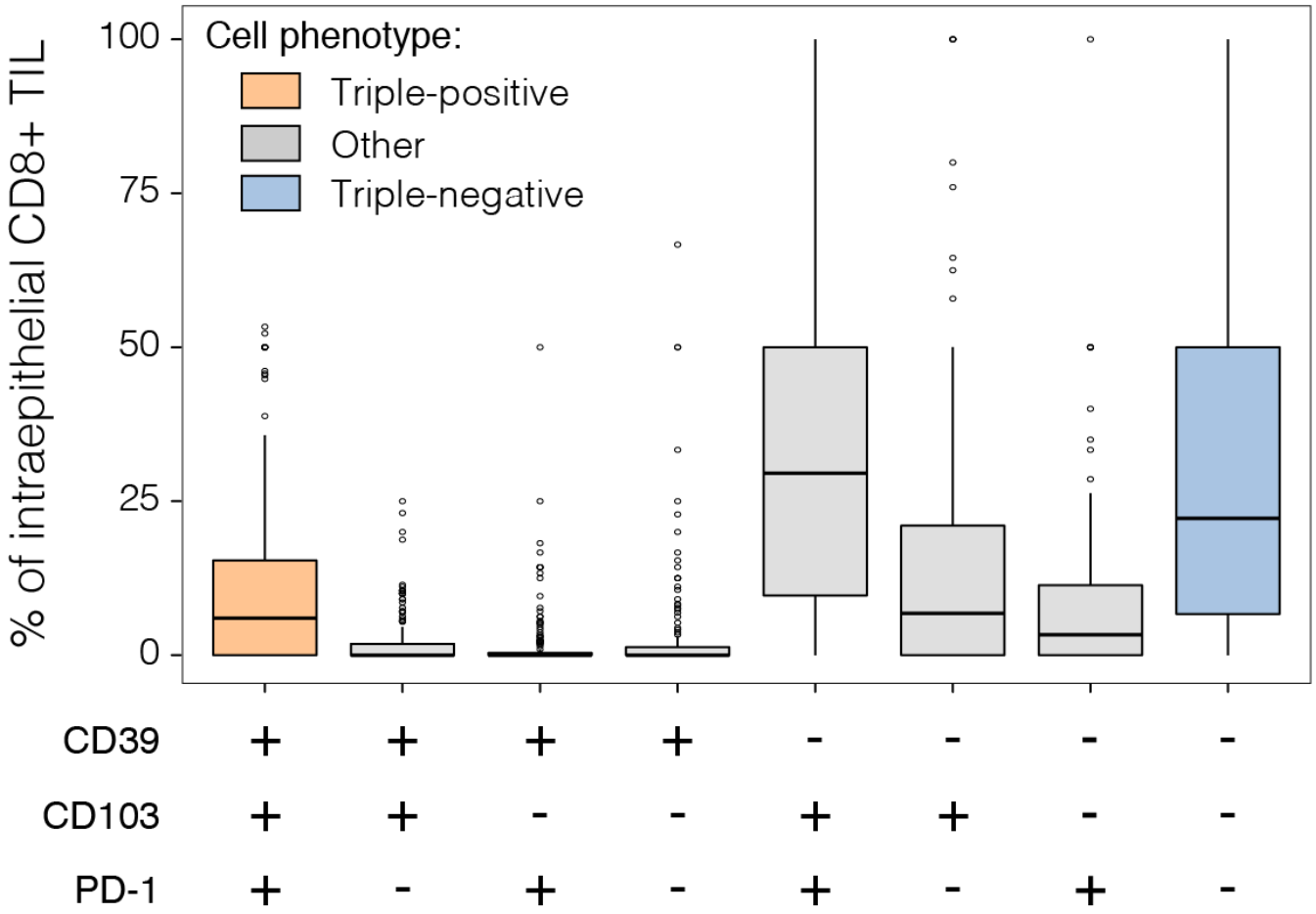
Defining the phenotype of tumor-reactive CD8 TIL in HGSC

Co-expression of CD39, PD1 and CD103



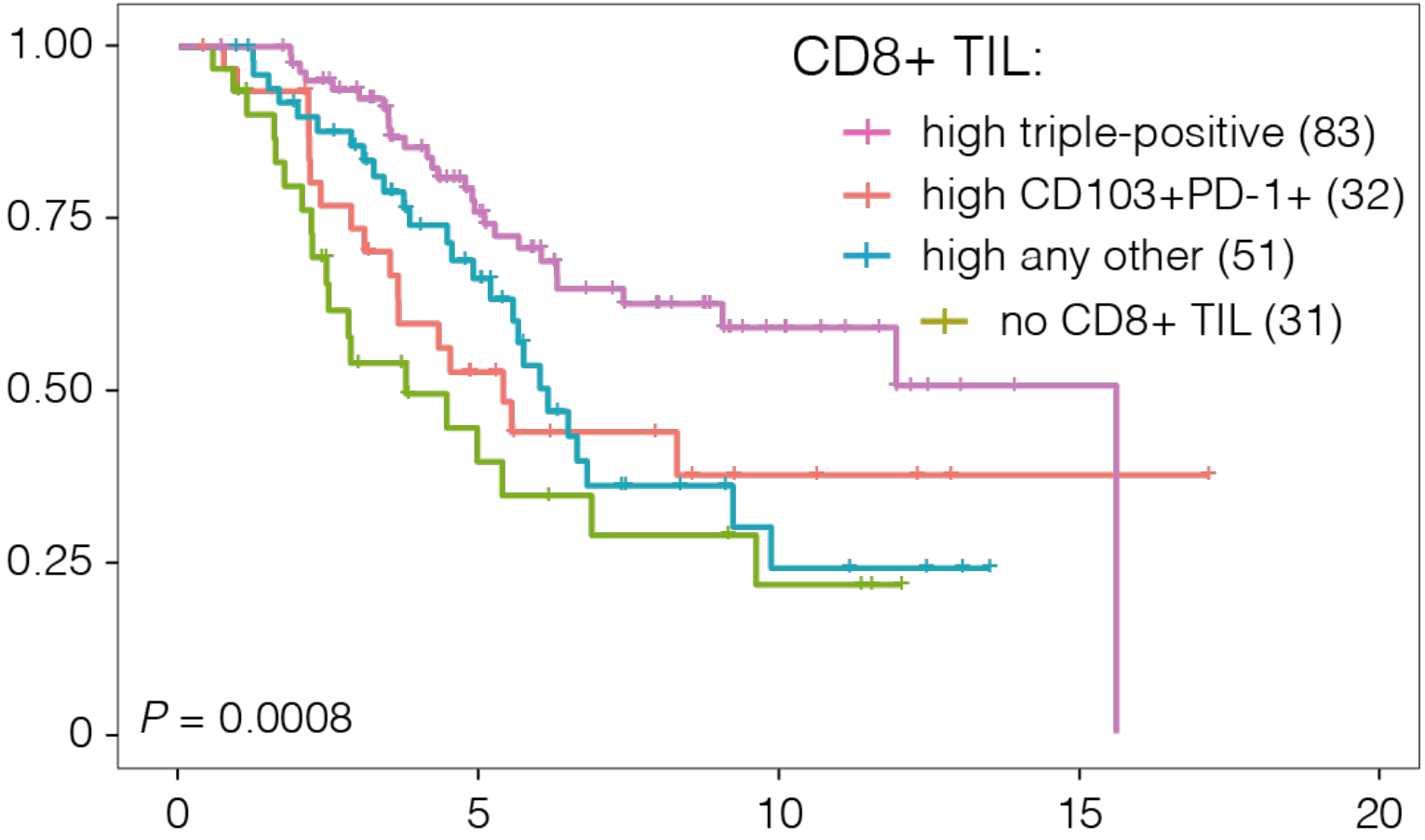
Céline Laumont, Maartje Wouters, Julian Smazynski et al. Clin Can Res 2021

A small subset of CD8+ TIL co-express CD39, PD1 & CD103



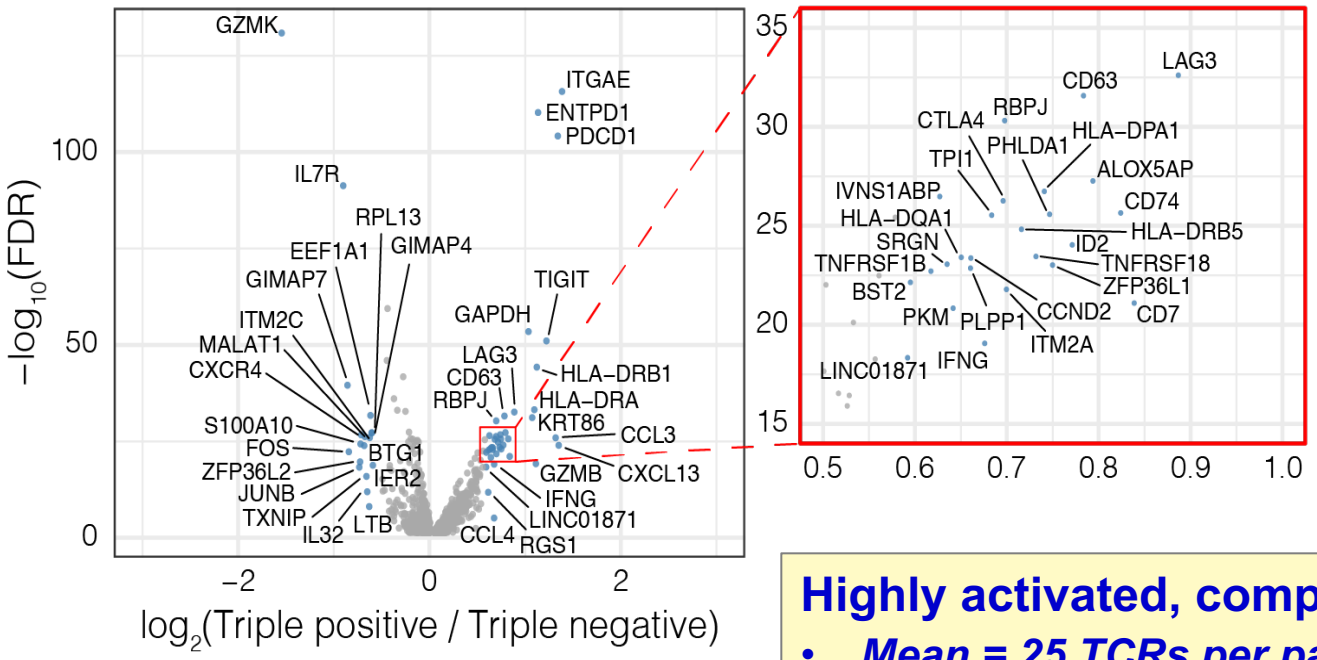
Céline Laumont, Maartje Wouters, Julian Smazynski et al. Clin Can Res 2021

Co-expression of CD39, CD103 & PD-1 defines the most prognostically favourable CD8 TIL



Céline Laumont, Maartje Wouters, Julian Smazynski et al. Clin Can Res 2021

Single-cell profile of CD8 TIL co-expressing CD39, PD1 & CD103



Highly activated, complex phenotype:

- ***Mean = 25 TCRs per patient***
- ***Granzyme B – killing***
- ***PD-1, CD39, TIGIT, LAG-3, TIM-3 – inhibitory***
- ***CXCL13 – B cell recruitment***

Céline Laumont, Maartje Wouters, Julian Smazynski et al. Clin Can Res 2021

Hallmarks of tumor-reactive CD8 T cells

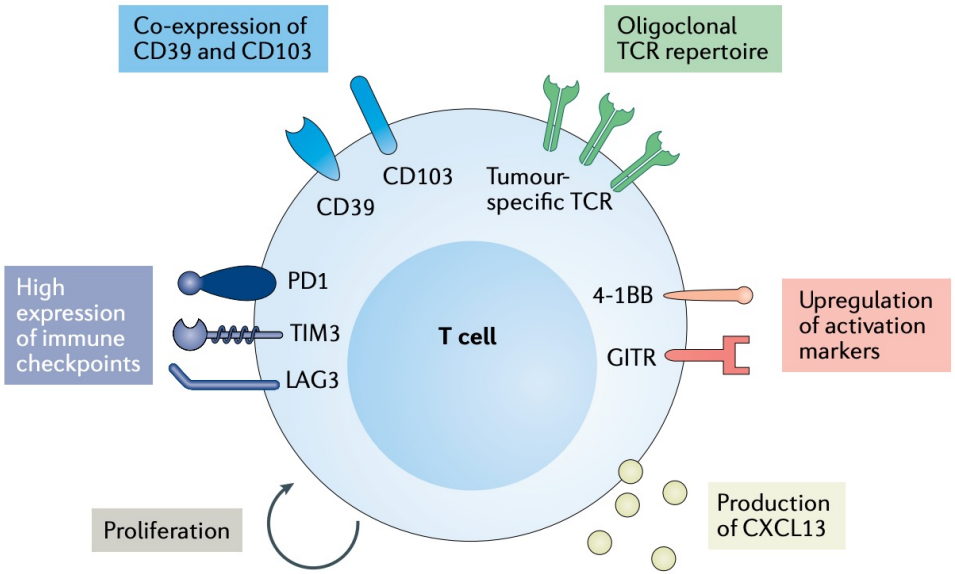
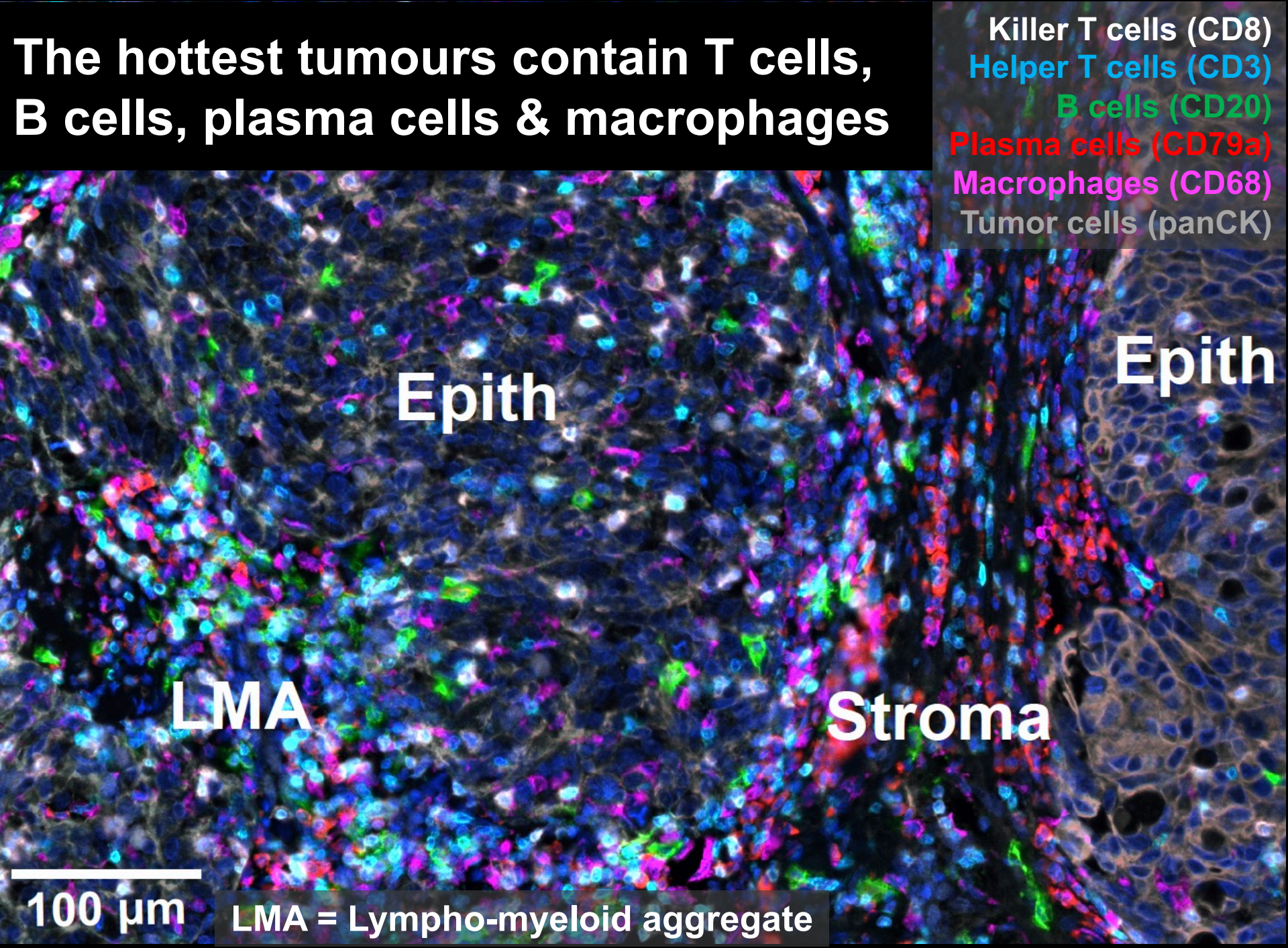


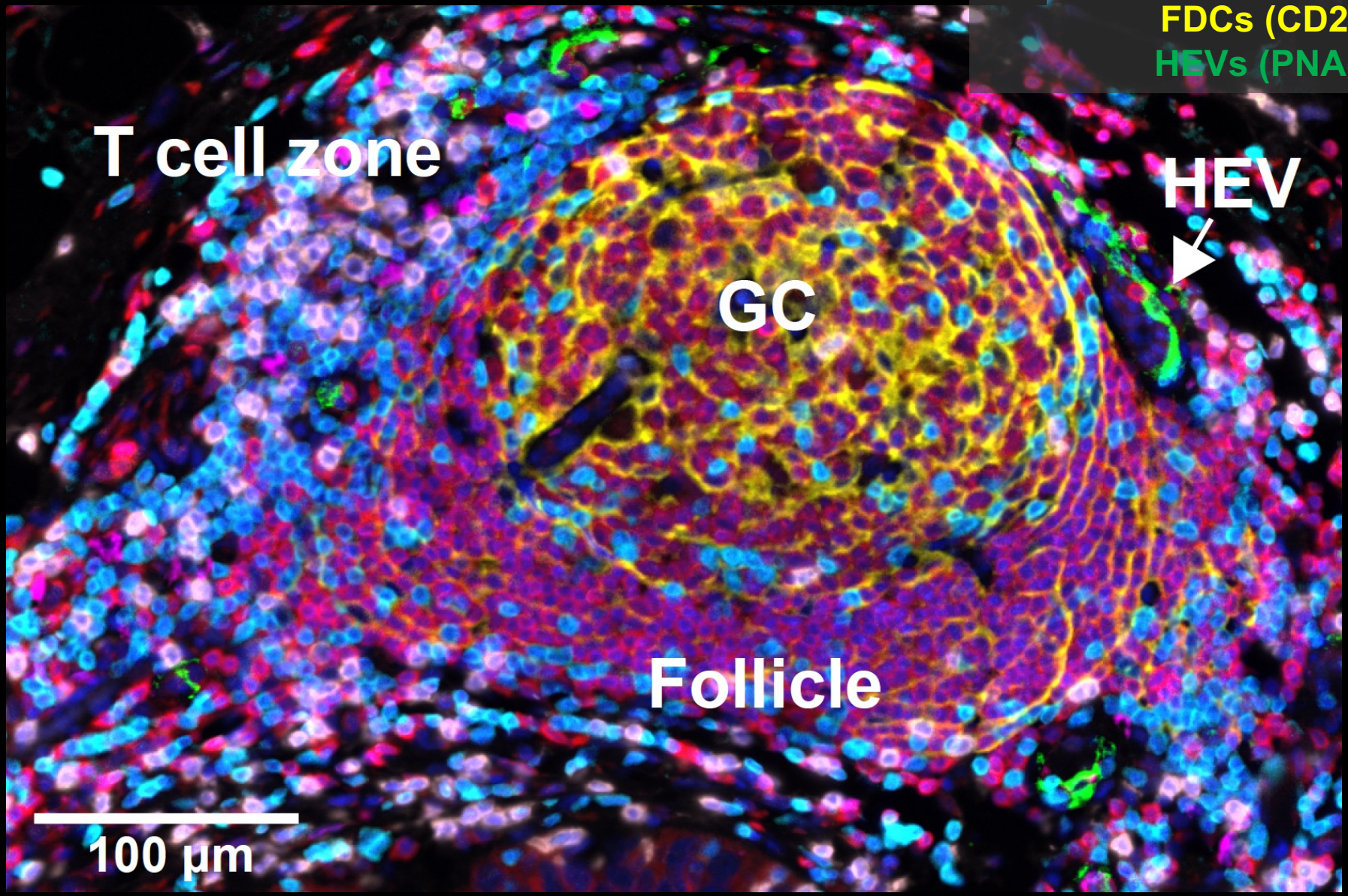
Fig. 3 | **Hallmarks of intratumoural tumour-reactive CD8⁺ T cells.** The schematic depicts protein markers and functional properties that are enriched in tumour-reactive CD8⁺ T cells (that is, T cells that express a tumour-reactive T cell receptor (TCR), irrespective of their functional capacity) relative to bystander CD8⁺ T cells at the tumour site. Note that none of these characteristics alone identifies tumour-reactive CD8⁺ T cells with absolute precision and that for some of these markers (4-1BB, glucocorticoid-induced tumor necrosis factor-related protein (GITR) and CXC chemokine ligand 13 (CXCL13)), the evidence is less well established. LAG3, lymphocyte activation gene 3 protein; PD1, programmed cell death protein 1; TIM3, T cell immunoglobulin mucin receptor 3.

van der Leun AM, Thommen DS, Schumacher TN. CD8⁺ T cell states in human cancer: insights from single-cell analysis. Nat Rev Cancer. 2020 Apr;20(4):218-232. PMID: 32024970.

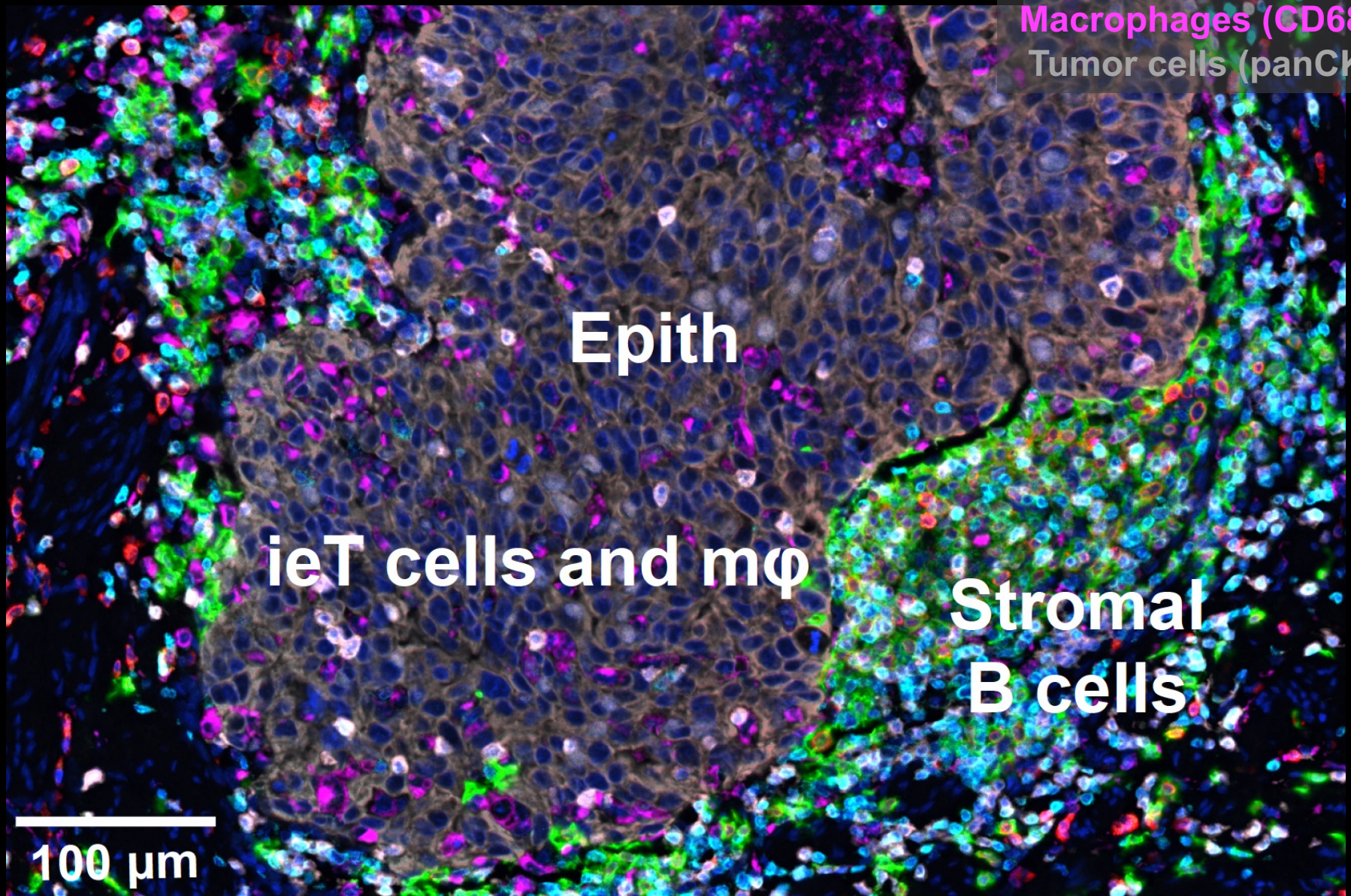
The hottest tumours contain T cells, B cells, plasma cells & macrophages



The hottest tumours contain tertiary lymphoid structures

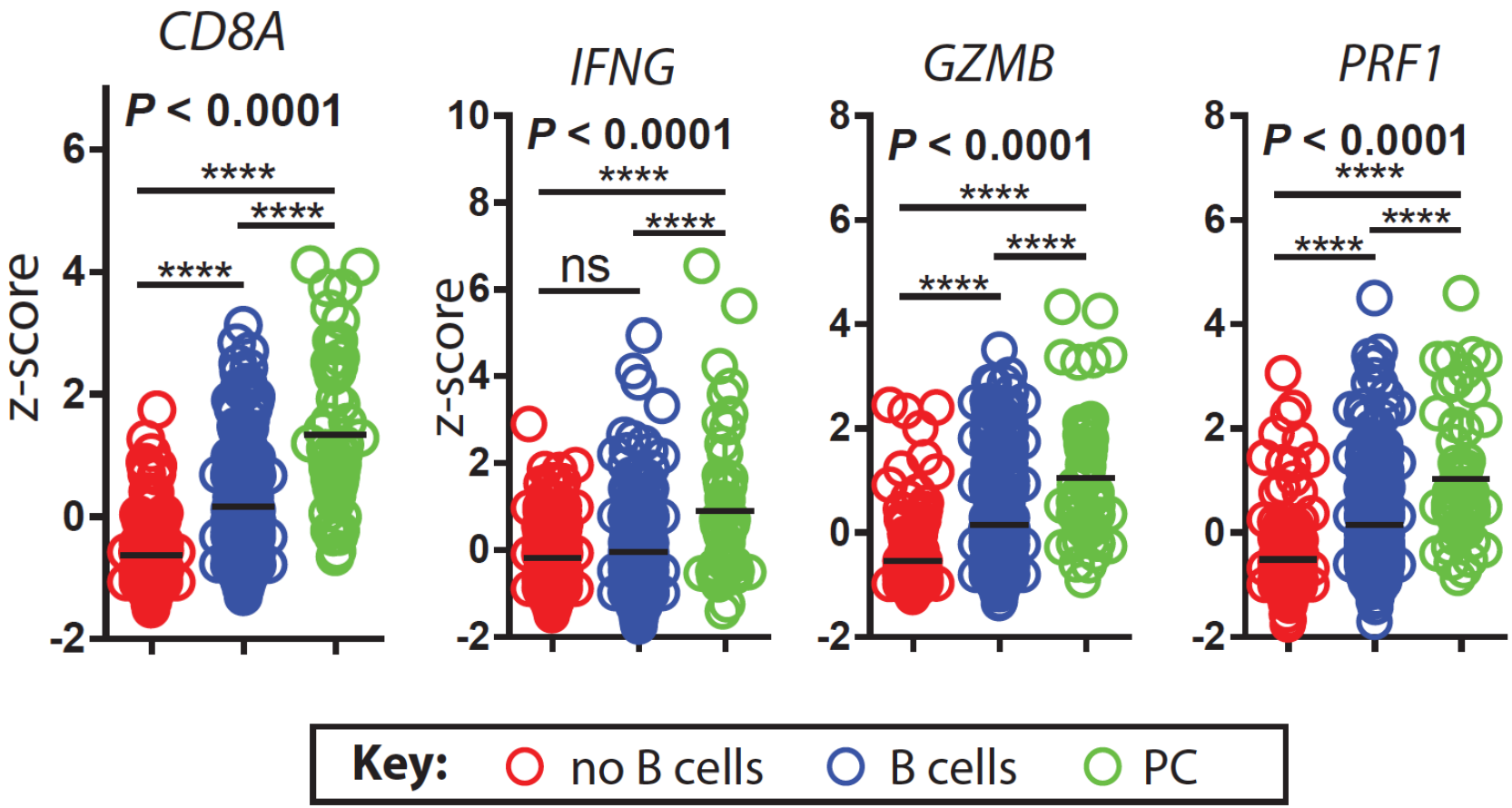


Some hot-ish tumours contain T cells and macs but not B cells



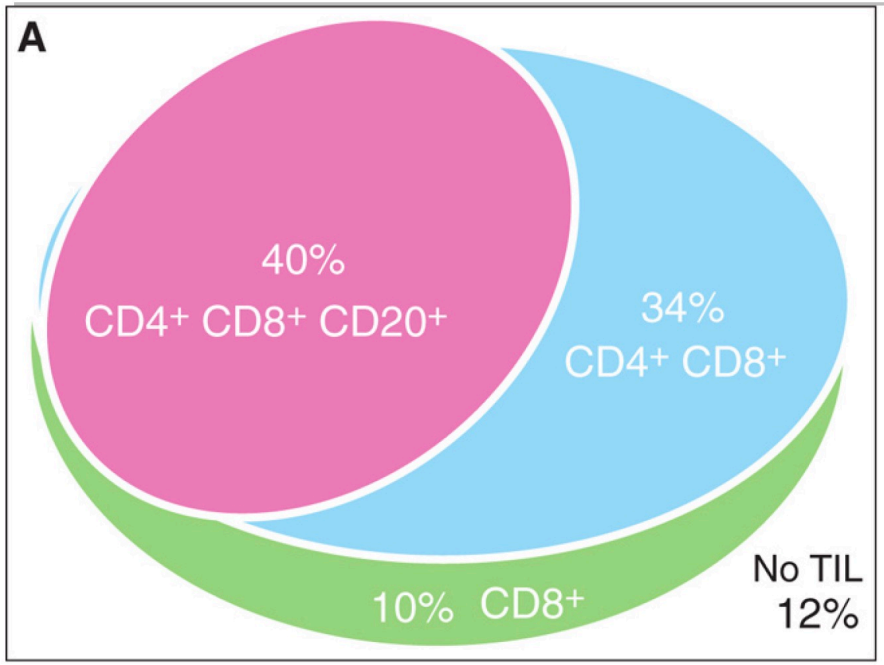
TIL-B responses are associated with stronger cytolytic signatures

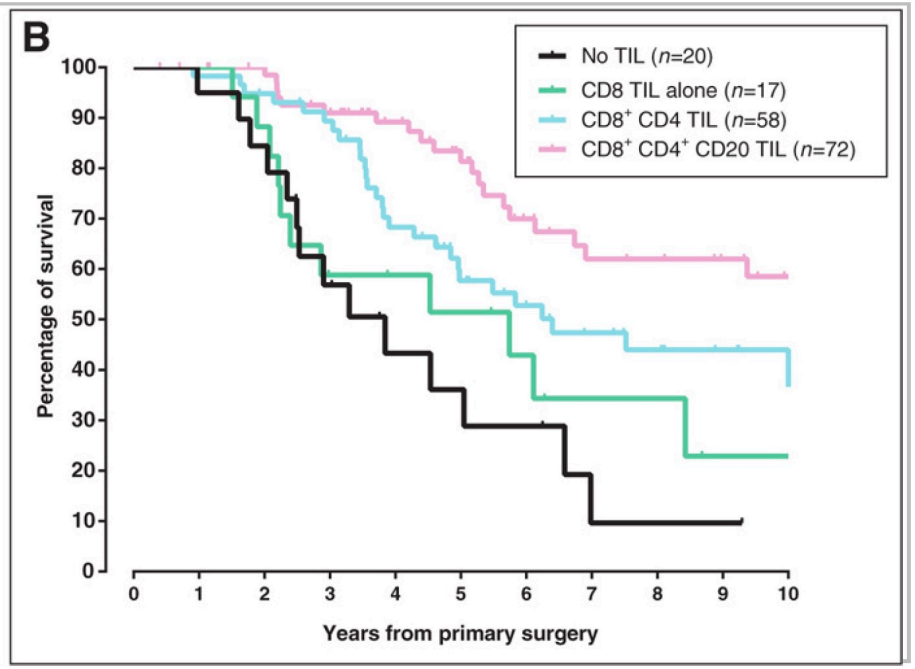
TCGA ovarian cancer dataset



David Kroeger et al, Clin Can Res 2016

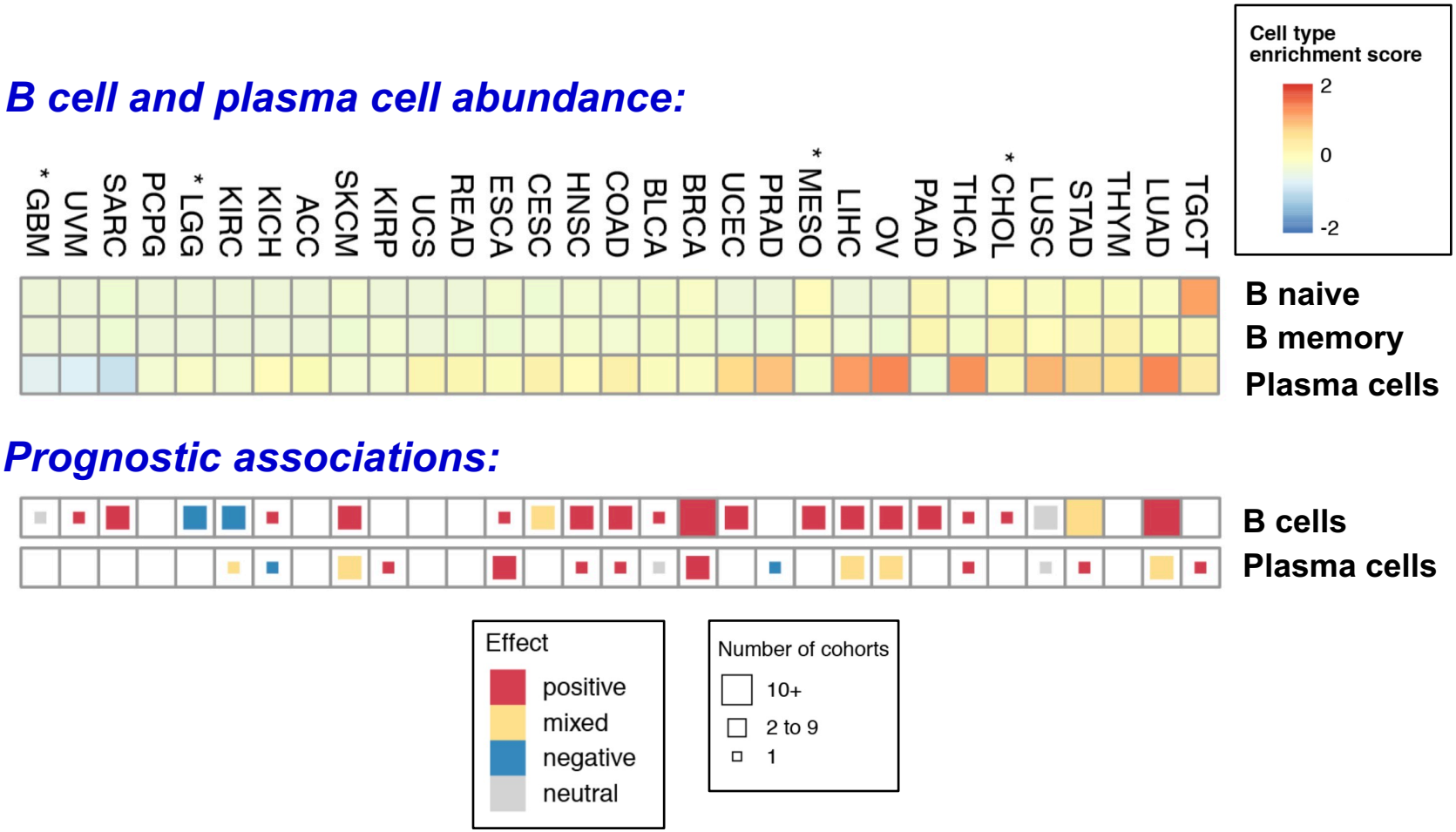
Tumor-infiltrating T cells and B cells show a combined effect on survival





Julie Nielsen et al. Clin Can Res 2012
Ron deLeeuw et al. Can Imm Res 2015
David Kroeger et al. Clin Can Res 2016
Wouters & Nelson SITC 2017

Abundance and prognostic significance of B cells and plasma cells across cancers



Céline Laumont et al, in revision

Article

B cells are associated with survival and immunotherapy response in sarcoma

Florent Petitprez…Wolf H. Fridman, *Nature* Jan 23 2020

Article

Tertiary lymphoid structures improve immunotherapy and survival in melanoma

Rita Cabrita…Goran Jonsson, *Nature* Jan 23 2020

Article

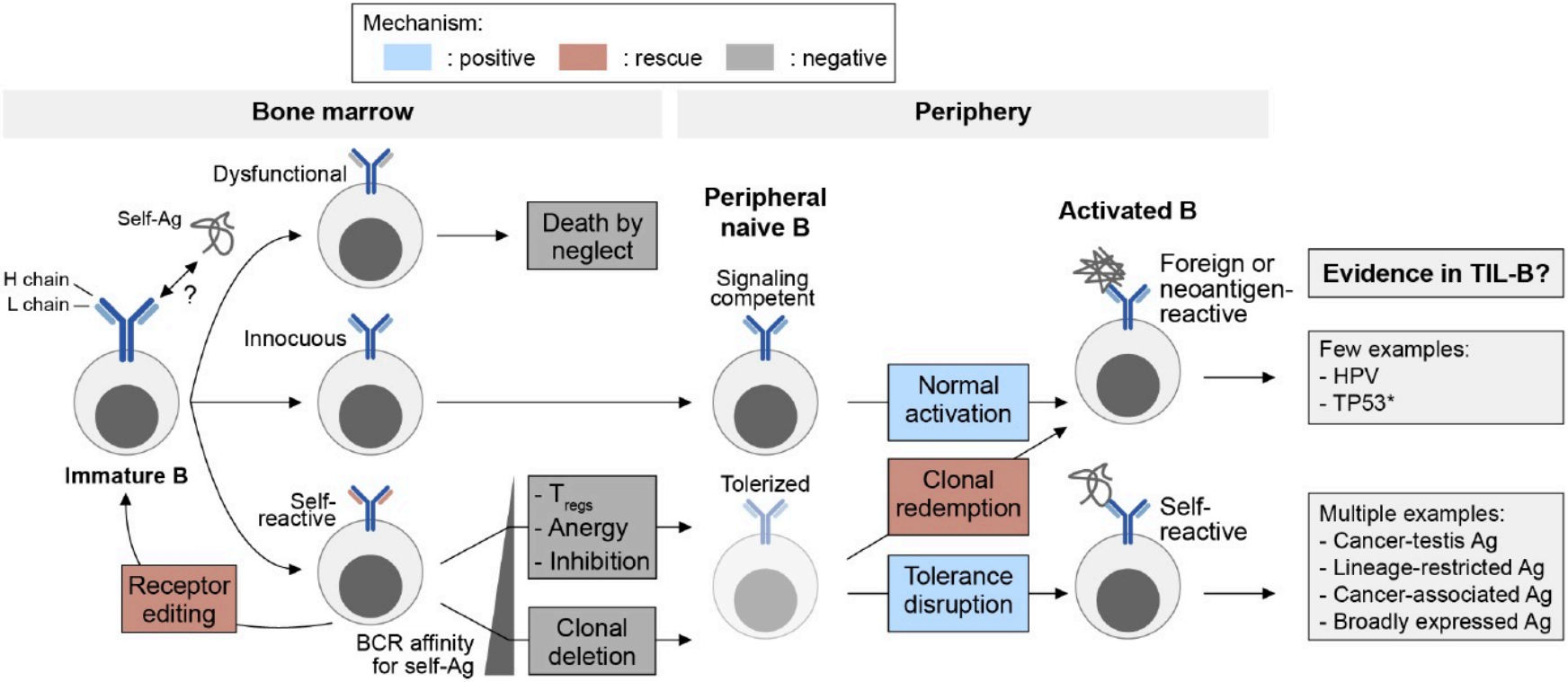
B cells and tertiary lymphoid structures promote immunotherapy response

Beth A. Helmink…Jennifer A. Wargo, *Nature* Jan 23 2020

Mature tertiary lymphoid structures predict immune checkpoint inhibitor efficacy in solid tumors independently of PD-L1 expression

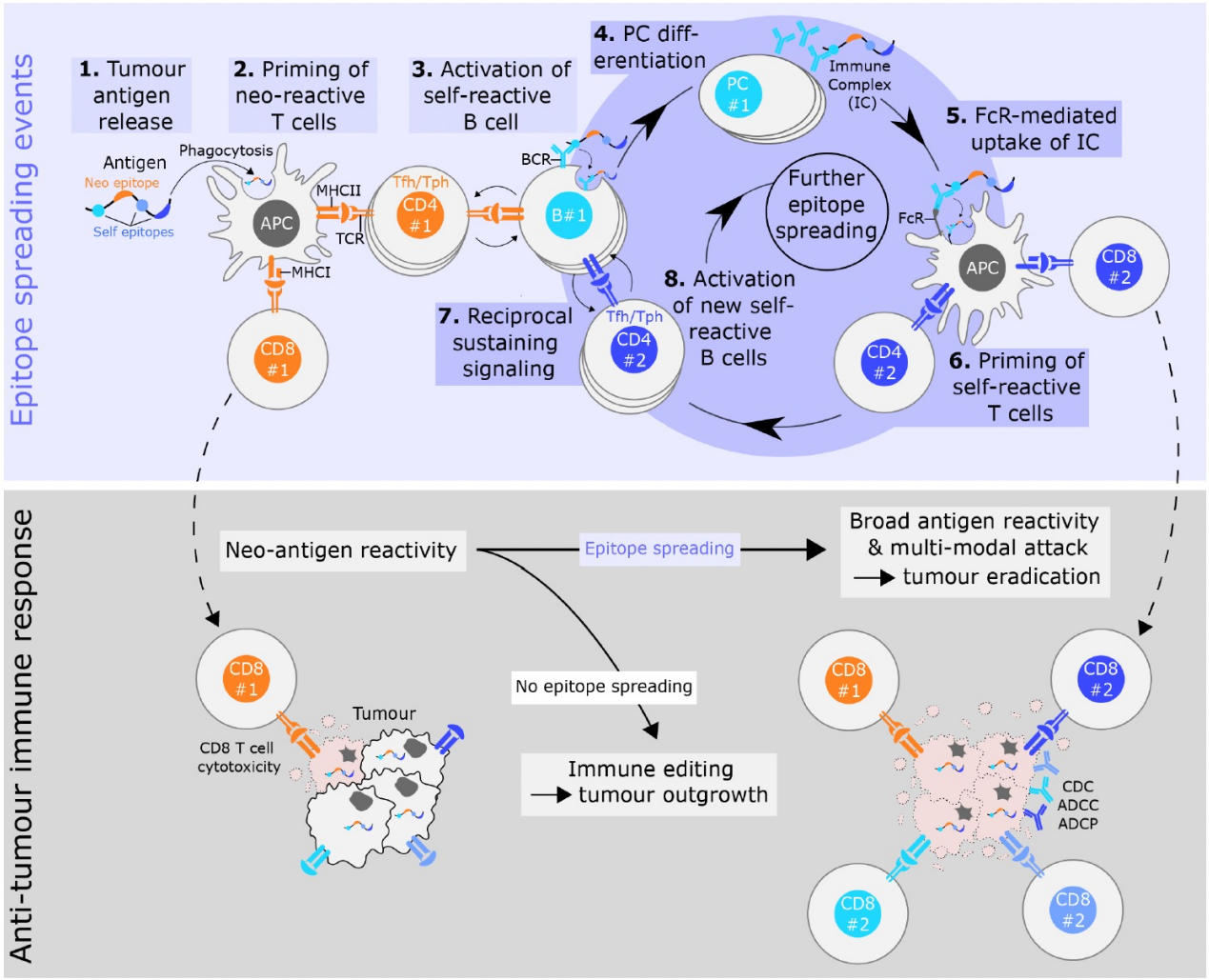
Lucile Vanhersecke…Antoine Italiano, *Nature Cancer* Aug 2021

B cells & T cells have complementary definitions of ‘self’



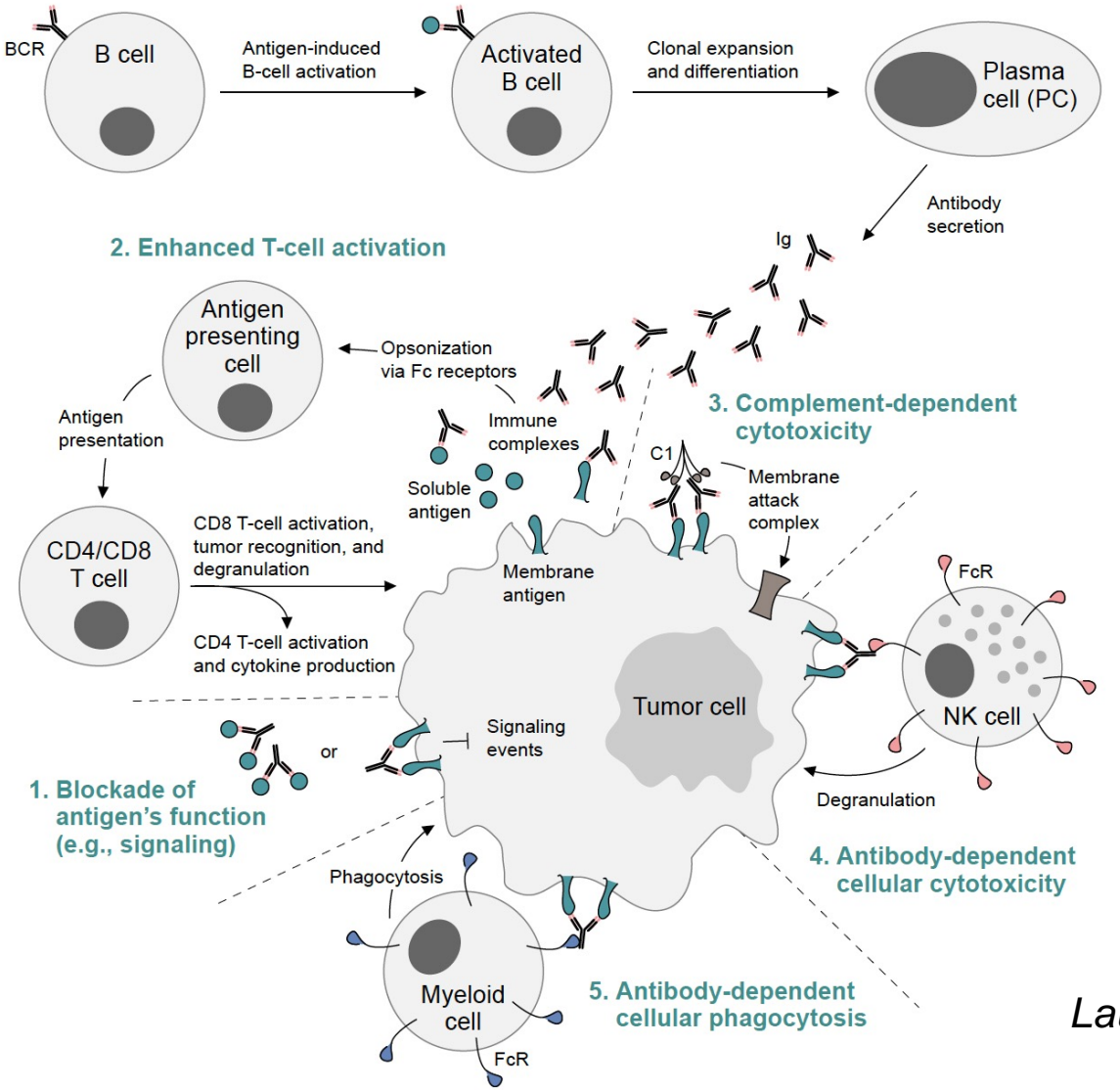
Céline Laumont et al, in revision

B cells can promote antigen spreading, a holy grail of immunotherapy



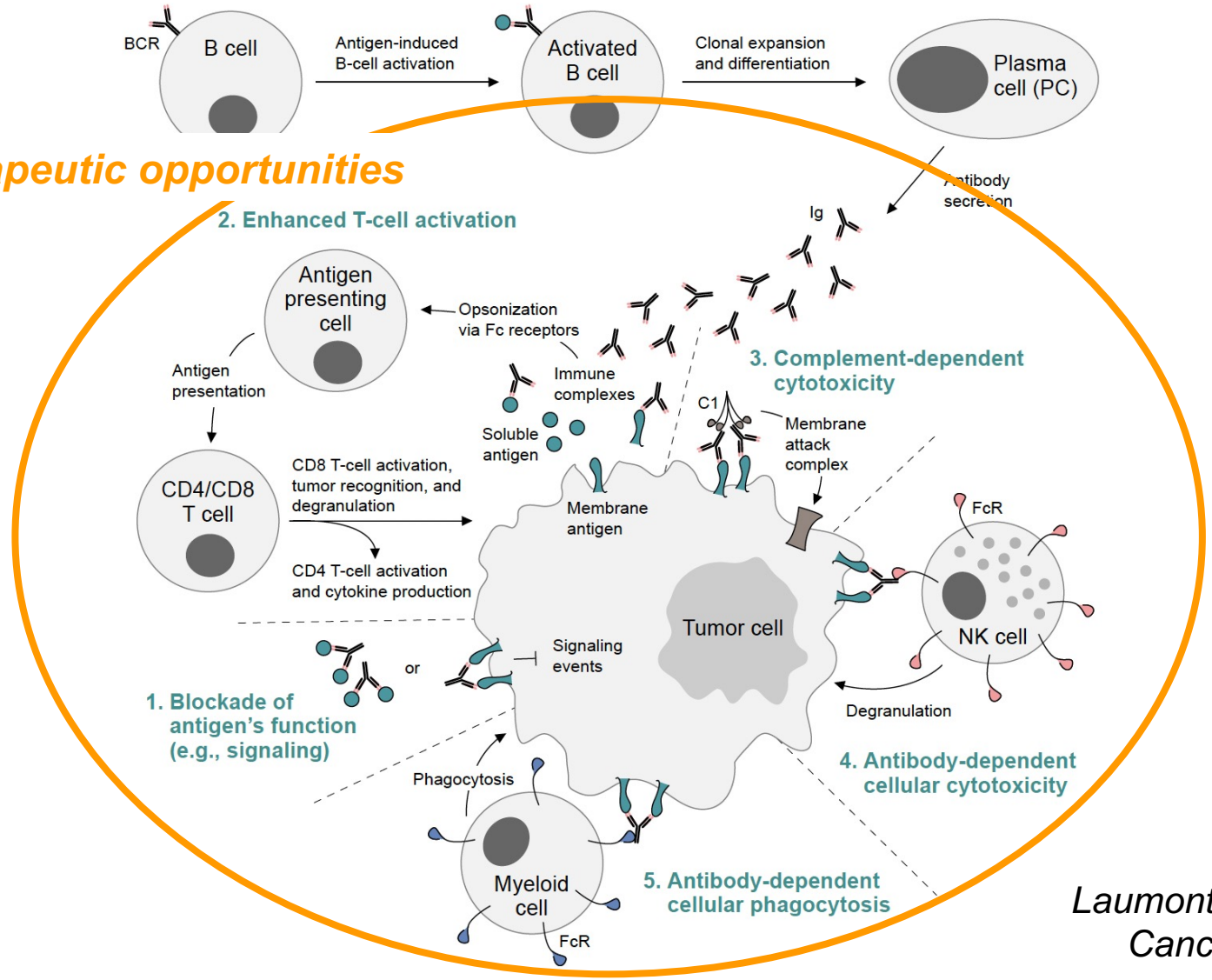
Céline Laumont et al, in revision

B cells and plasma cells have an impressive anti-tumor armamentarium



Laumont and Nelson Cancer Cell 2021

B cells and plasma cells have an impressive anti-tumor armamentarium



Laumont and Nelson Cancer Cell 2021

Take home messages

- Tumors evolve under numerous selective pressures, including the immune response
- Like all treatments, immunotherapy can shape tumor evolution significantly
- T cell responses are important yet fragile
- The strongest, most prognostic, durable TIL responses involve T cell, B cells and macrophages
- B cells and antibodies use diverse effector mechanisms which are orthogonal to T cells
- A more holistic understanding of TIL cell types and mechanisms will inspire new approaches to immunotherapy

BC Cancer Agency
CARE + RESEARCH

University of Victoria

THE UNIVERSITY OF BRITISH COLUMBIA

OVCARE
BC'S OVARIAN CANCER RESEARCH TEAM

Nelson Lab:
Alex Rodriguez, PhD
Phineas Hamilton, PhD
Céline Laumont, PhD
Julian Smazynski
Allyson Banville
Monica Fuss
Shreena Kalaria
Megan Fuller
Alexi Pearson-Lund
Mitchell Adamson
Sam Preshaw

Key Alumni:
Maartje Wouters, PhD
David Kroeger, PhD
Nicole Little, MSc
Darin Wick
Ron deLeeuw, PhD
Charlotte Lo
Spencer Martin
Kwame Twumasi-Boateng, PhD

MCIC (Histo Core):
Katy Milne
Bronwyn Gibson-Wright
Heather Derocher
Sonya Laan
Stacey LeDoux
Hannah McCarter
Chanel Ghesquiere
Daniel Kos
Talia Goodyear

Genomics - Vancouver:
Sohrab Shah, PhD
Allen Zhang
Rob Holt, PhD
Scott Brown

MOCOG/OTTA/AOCS:
Leigh Pearce, PhD
Malcolm Pike, PhD
Susan Ramus, PhD
David Bowtell, PhD
Dale Garsed, PhD
Anna DeFazio, PhD

Immunotherapy Program:
Rob Holt, PhD
Kevin Hay, MD
John Webb, PhD
Julie Nielsen, PhD
David Bond, PhD
Mhairi Sigrist, PhD
Miruna Bala, PhD
Nicole Little, MSc
Bianca Loveless, MSc
Kayla Clark
Tyler Dyer
Richard Hogg
Maria Chapman
Leah McCormick
Michael Gignac

Collaborators - Victoria:
Peter Watson, MD
Julian Lum PhD
Sindy Babinsky

Collaborators - Ottawa:
John Bell, PhD
Harry Atkins, MD
Natasha Kekre, MD

Collaborators - Toronto:
Pam Ohashi, PhD
Linh Nguyen, PhD
Marcus Butler, MD

Collaborators - Vancouver:
Anna Tinker, MD
Blake Gilks, MD
David Huntsman, MD
Jessica McAlpine, MD
Dianne Miller, MD
Michael Anglesio, PhD
Christian Steidl, MD
Liz Chavez
Lauren Chong

Collaborators - Montréal:
John Stagg, PhD
Réjean Lapointe, PhD
Anne-Marie Mes-Masson, PhD

Funding:
BC Cancer Foundation
CCSRI
CIHR
TFRI
US DOD
CRS
Genome BC
BioCanRx NCE
Conconi Family
CFI
MSFHR
Innovakine Therapeutics

Special thanks to our patients