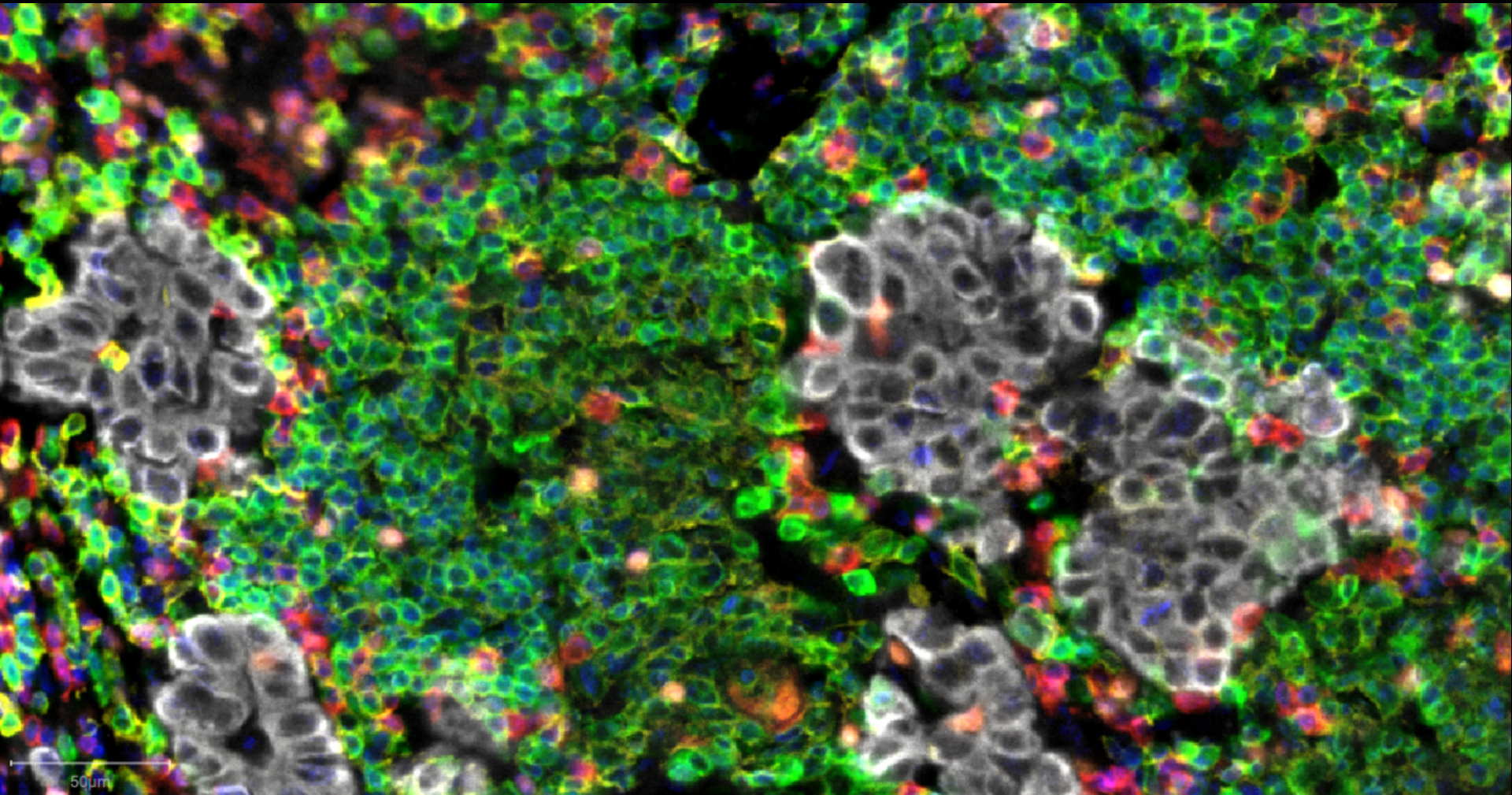


# Immunity and Therapeutic Efficacy



**Brad Nelson, PhD**  
**BC Cancer, Victoria BC**

**Cancer Immunotherapy Winter School**  
**February 22 2021**

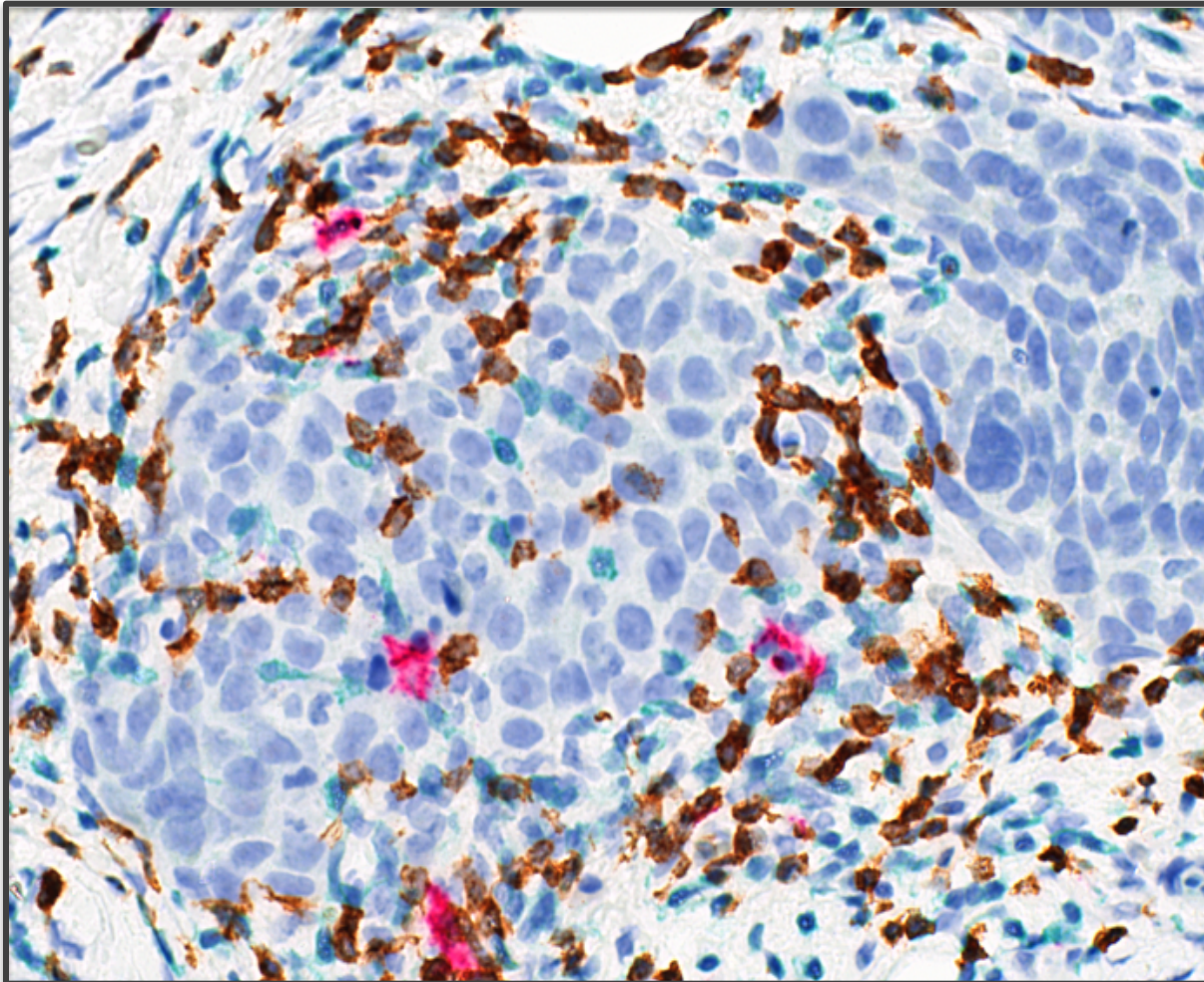
# Disclosures

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



# Tumor-infiltrating lymphocytes (TIL) in human cancer

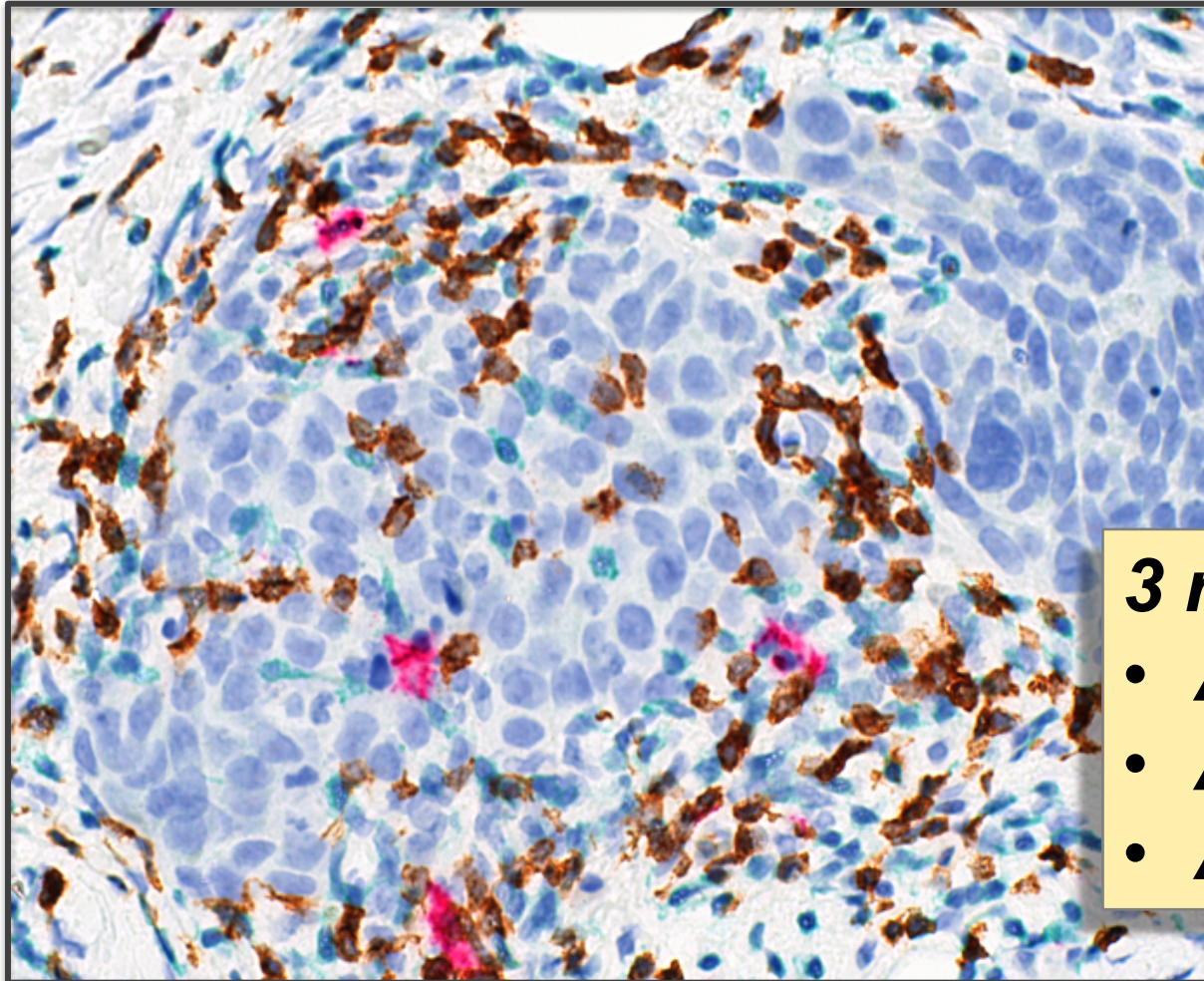
## *Ovarian cancer*



CD8+ killer T cells  
CD4+ T cells  
CD20+ B cells  
Tumor cells

# Tumor-infiltrating lymphocytes (TIL) in human cancer

## *Ovarian cancer*



CD8+ killer T cells  
CD4+ T cells  
CD20+ B cells  
Tumor cells

### ***3 requirements:***

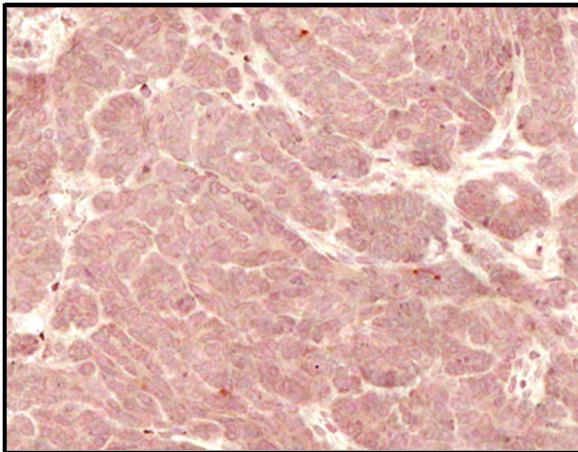
- ***Antigens***
- ***Access***
- ***Activity***



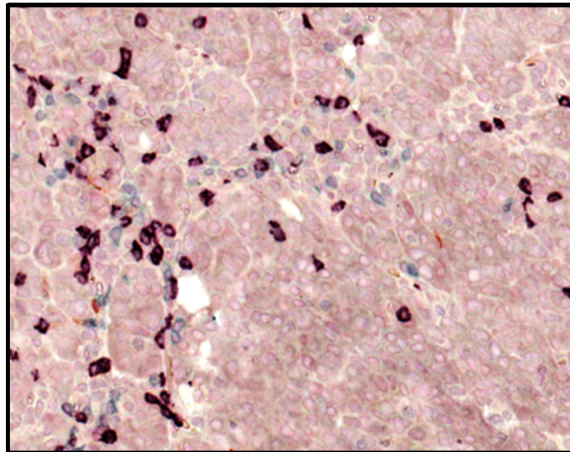
# Three major TIL patterns in cancer

*Three cases of ovarian cancer:*

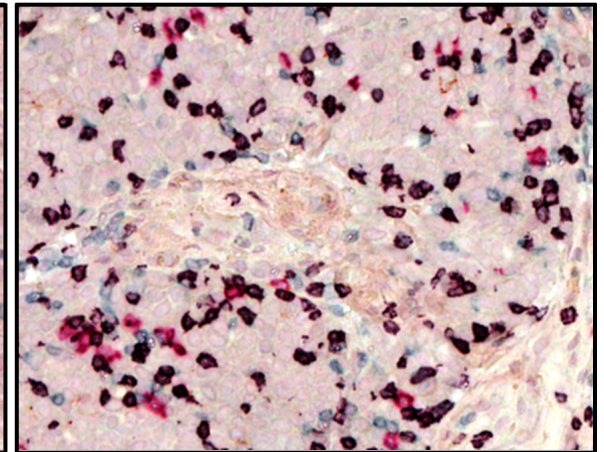
CD4+ T cells  
CD8+ T cells  
CD20+ B cells



**Cold**  
Few TIL



**Warm**  
Weak TIL  
*T cells in stroma*

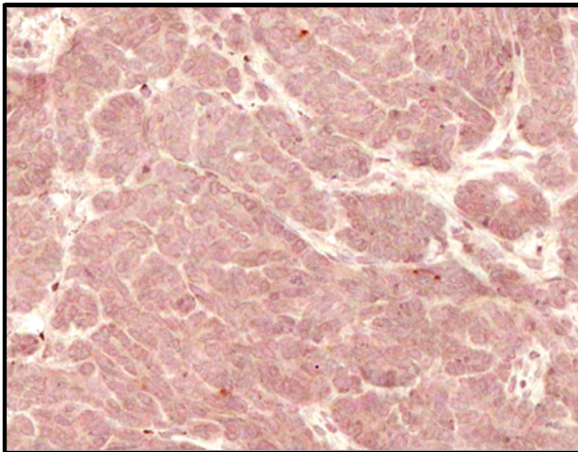


**Hot**  
Robust TIL  
*T cells and B cells  
in epithelium & stroma*

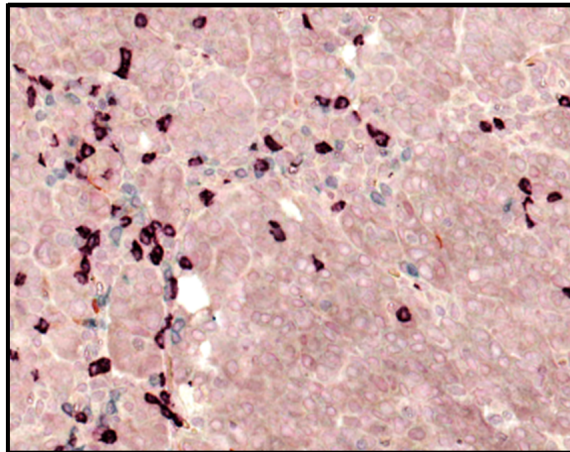
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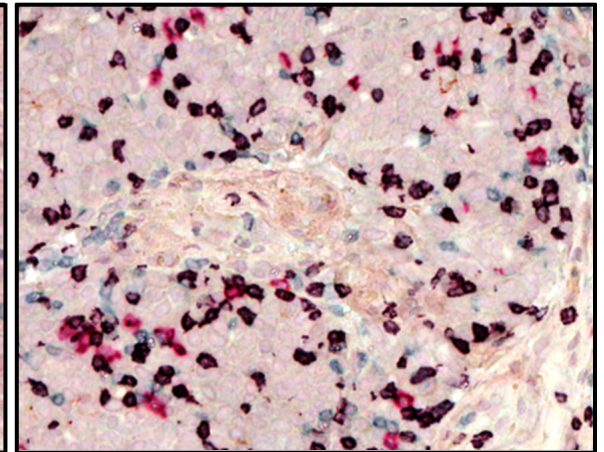
CD4+ T cells  
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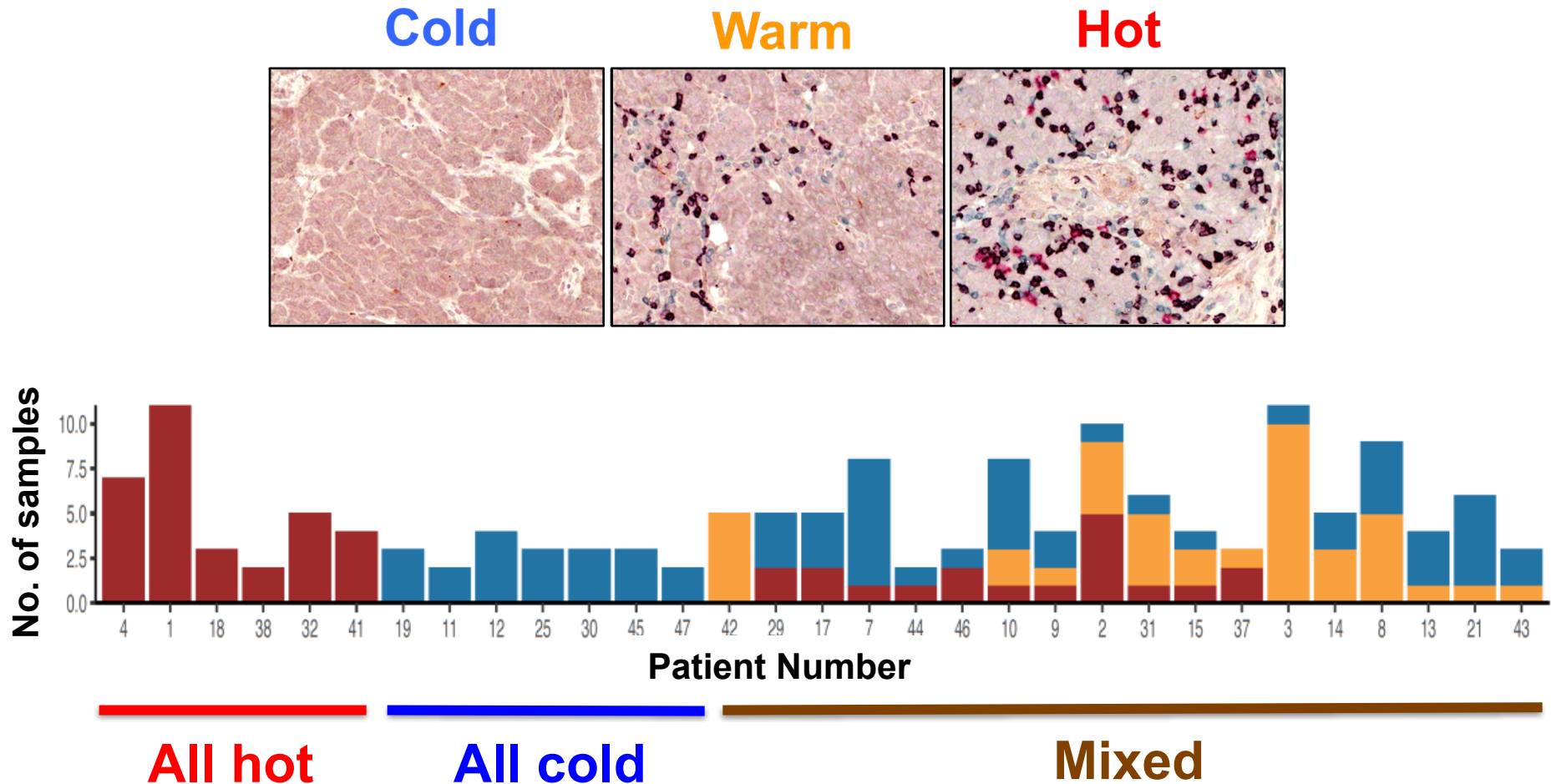
**Warm**  
Weak TIL  
*T cells in stroma*



**Hot**  
Robust TIL  
*T cells and B cells  
in epithelium & stroma*  
→ favorable prognosis



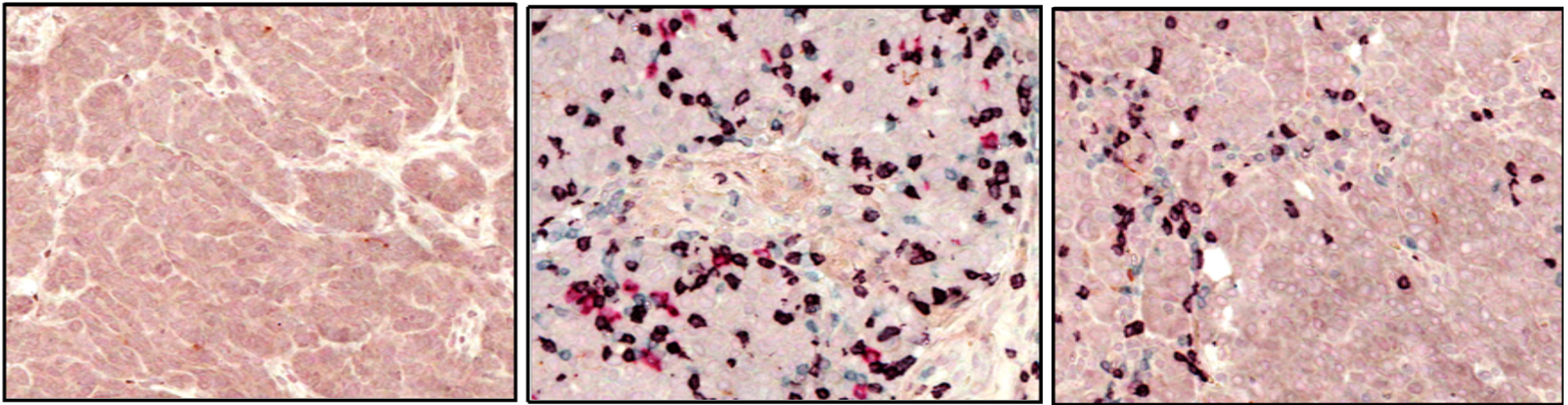
# Patients often present with a mixture of hot, warm and/or cold tumors



# Hypothesis: do TIL patterns represent a temporal sequence?

*Ovarian cancer:*

CD4+ T cells  
CD8+ T cells  
CD20+ B cells



Cold



Hot



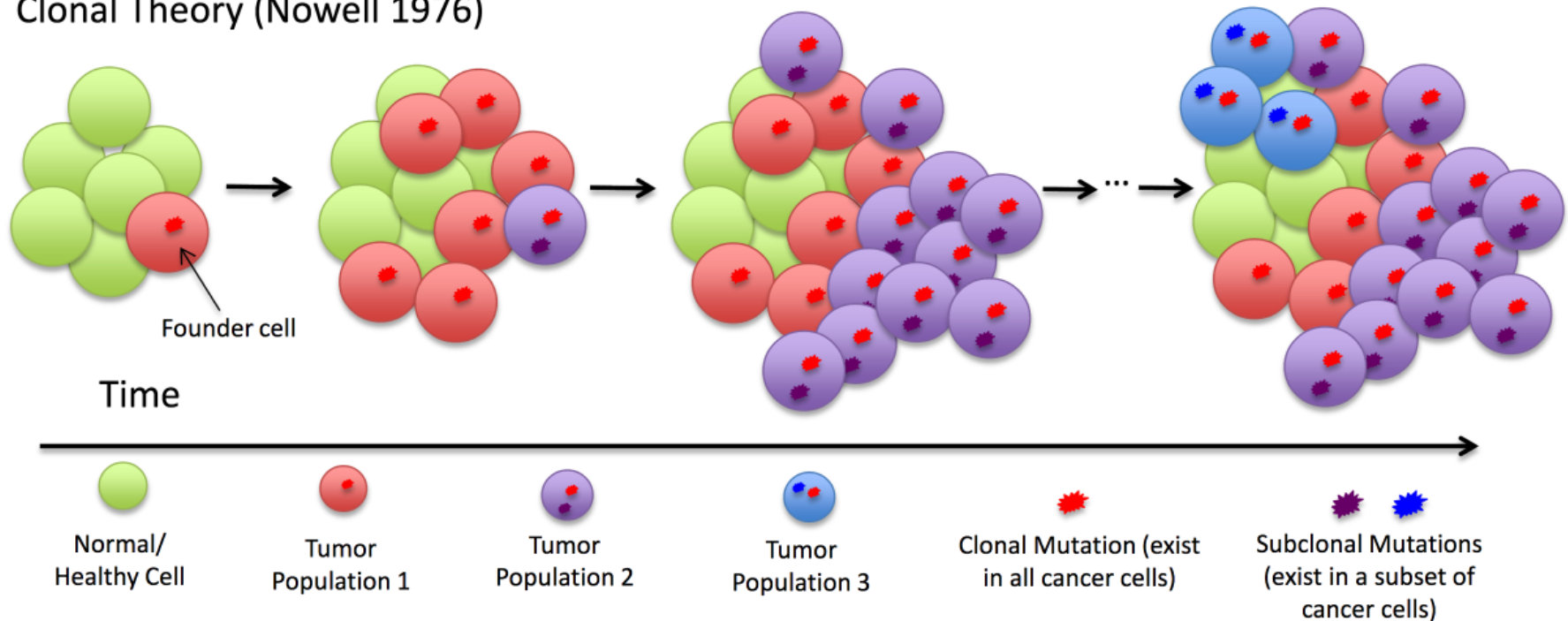
Warm





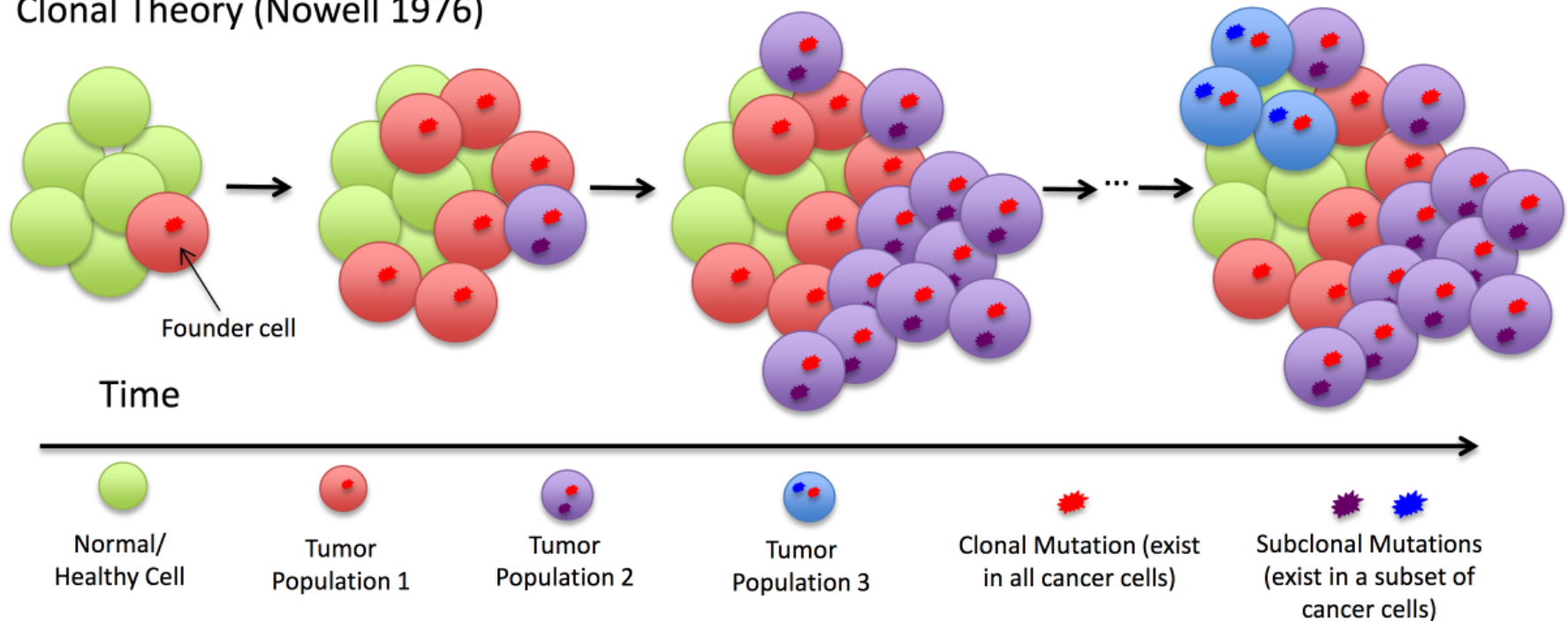
# Tumor evolution gives rise to intratumoral heterogeneity

Clonal Theory (Nowell 1976)



# Tumor evolution gives rise to intratumoral heterogeneity

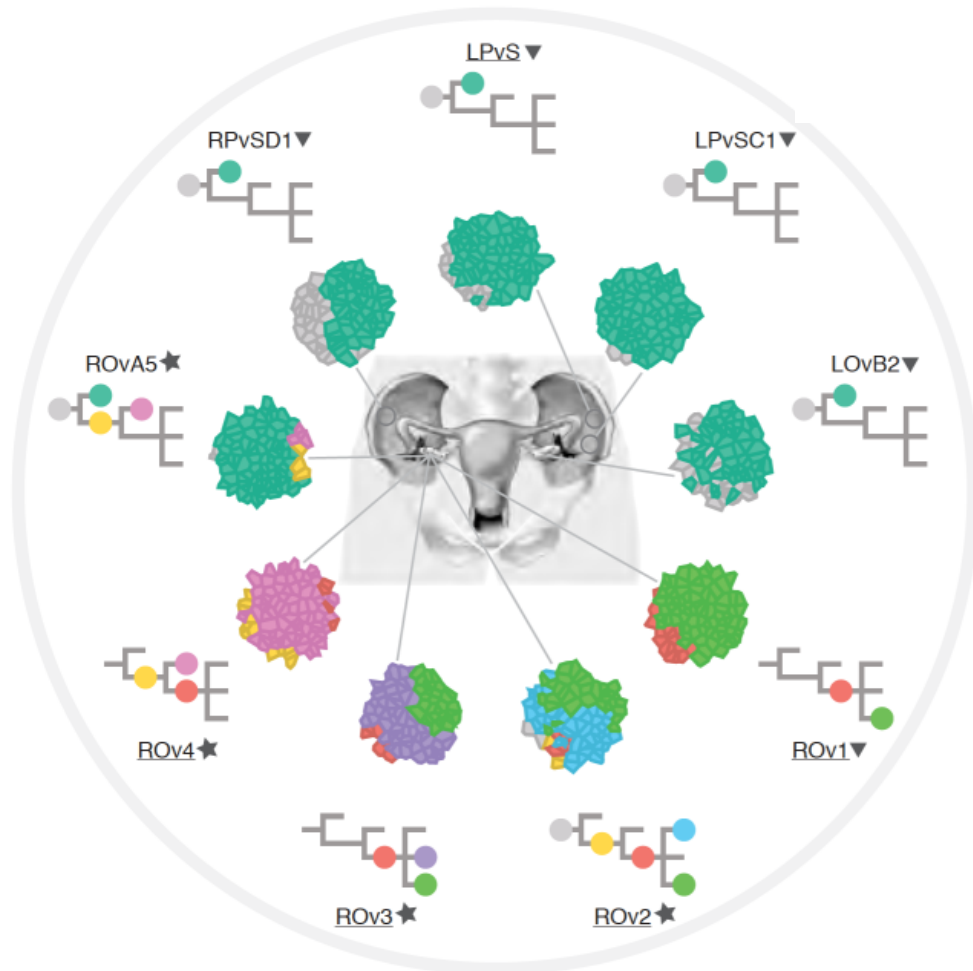
Clonal Theory (Nowell 1976)



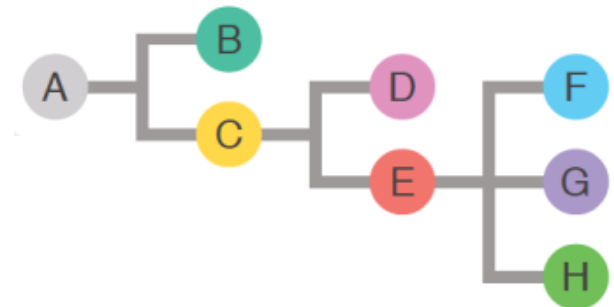
***Somatic mutations provide an “arrow of time” for tumor evolution***



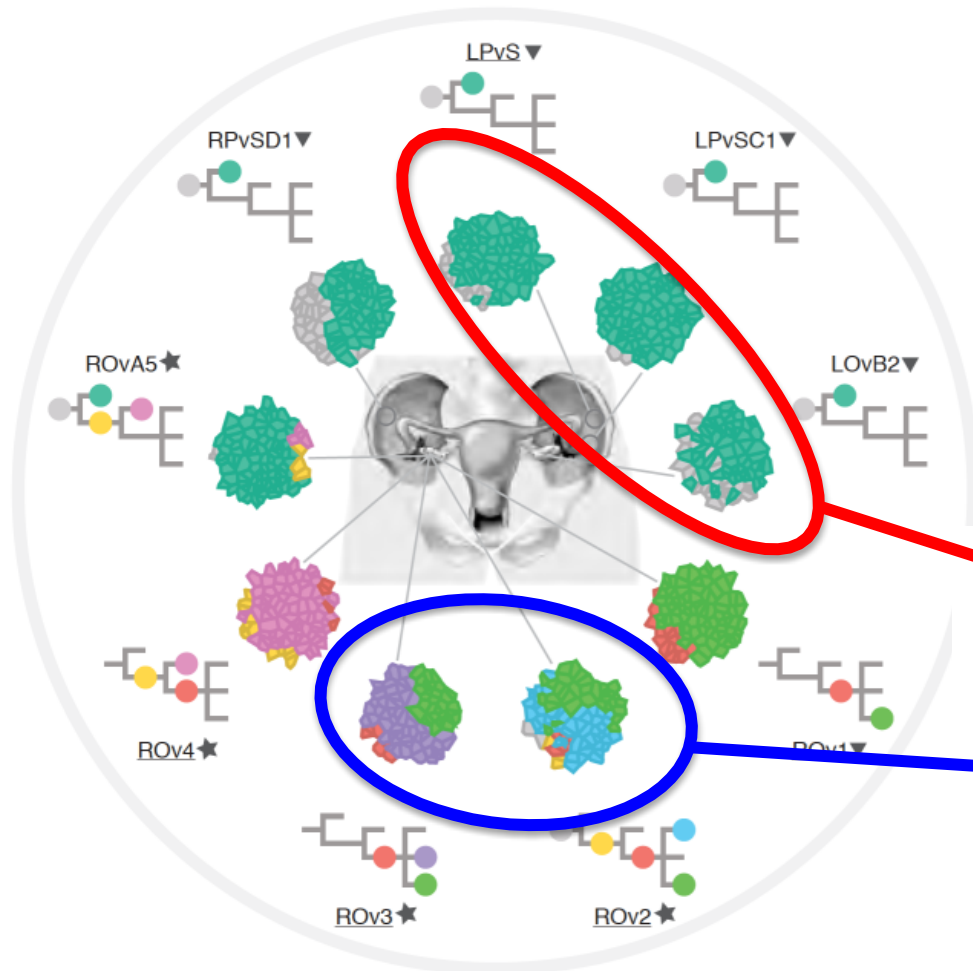
# Tumor evolution leads to intratumoral heterogeneity



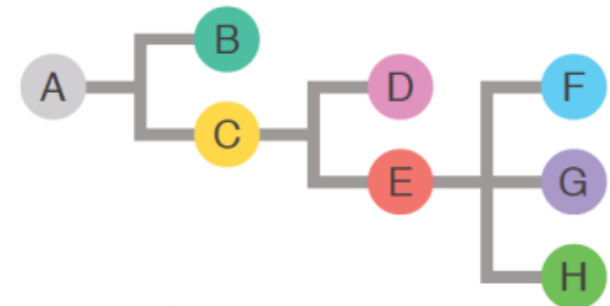
## Clonal phylogeny in ovarian cancer (patient 4)



# 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**

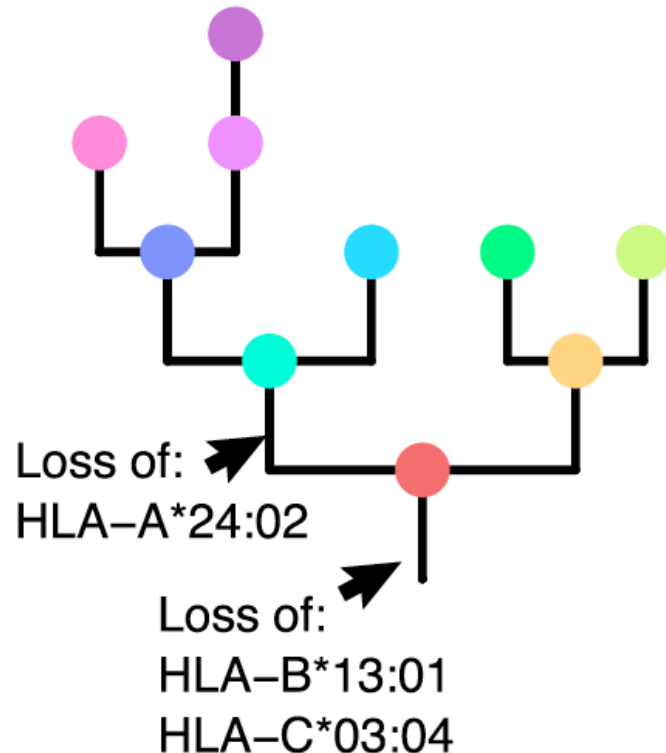




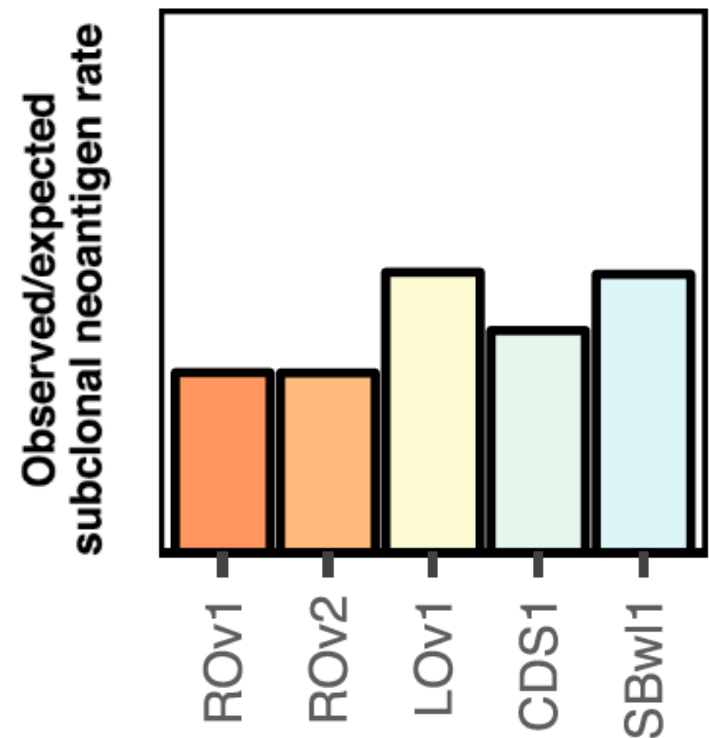
# Hot tumors show signs of immune editing

e.g. Patient 15

*HLA allelic loss:*

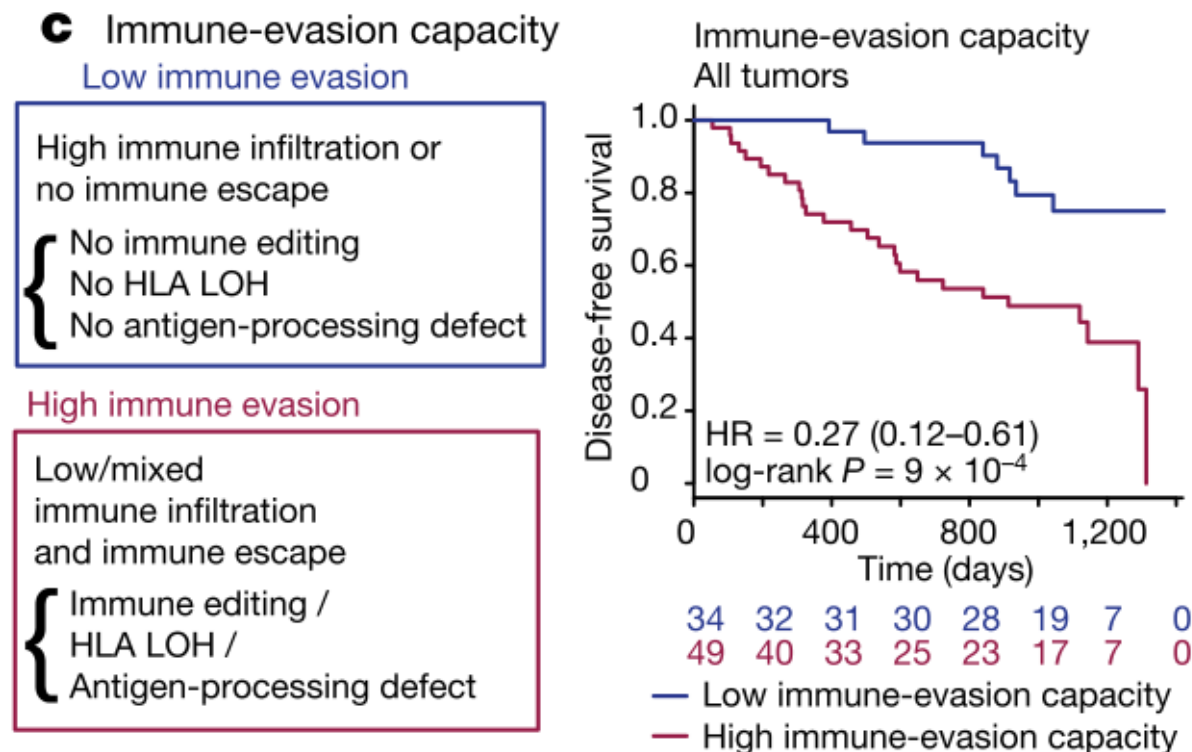


*Neoantigen depletion:*



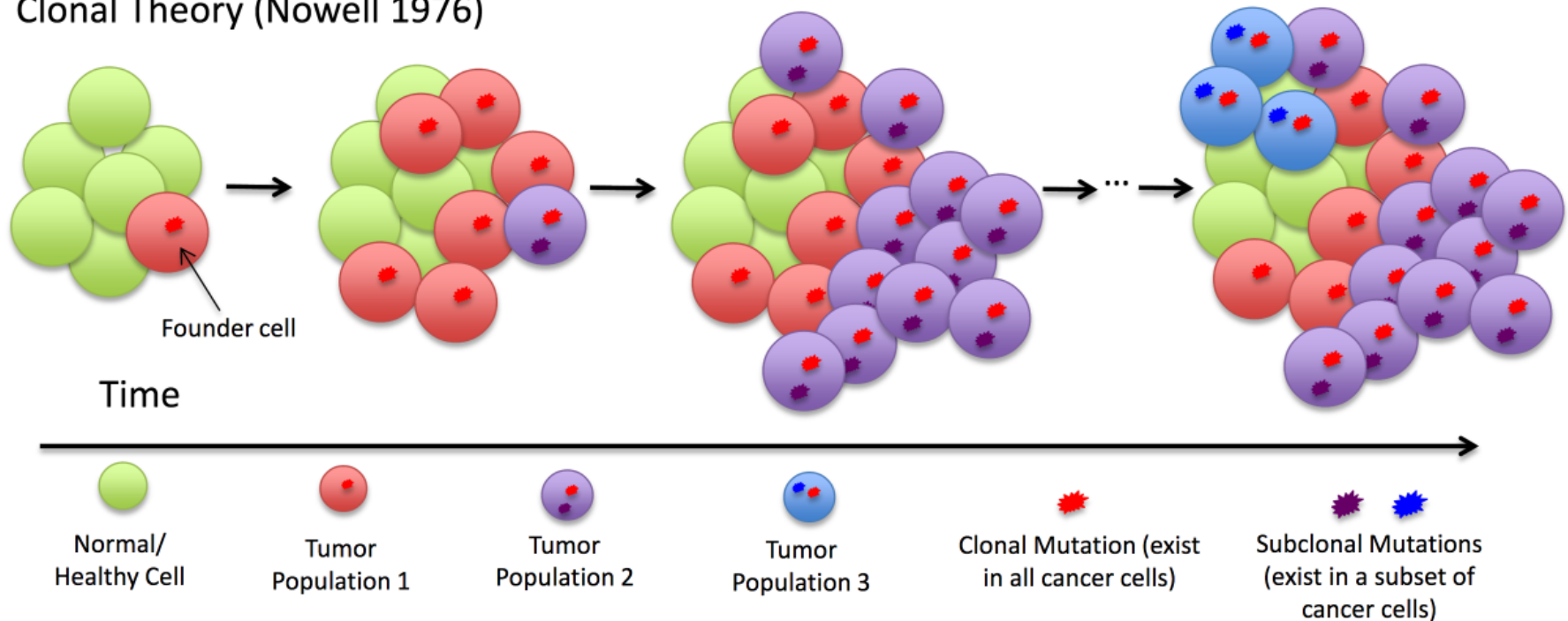
# Lung cancer: immune evasion is linked to prognosis

- 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



# How does the immune response change over time and treatment?

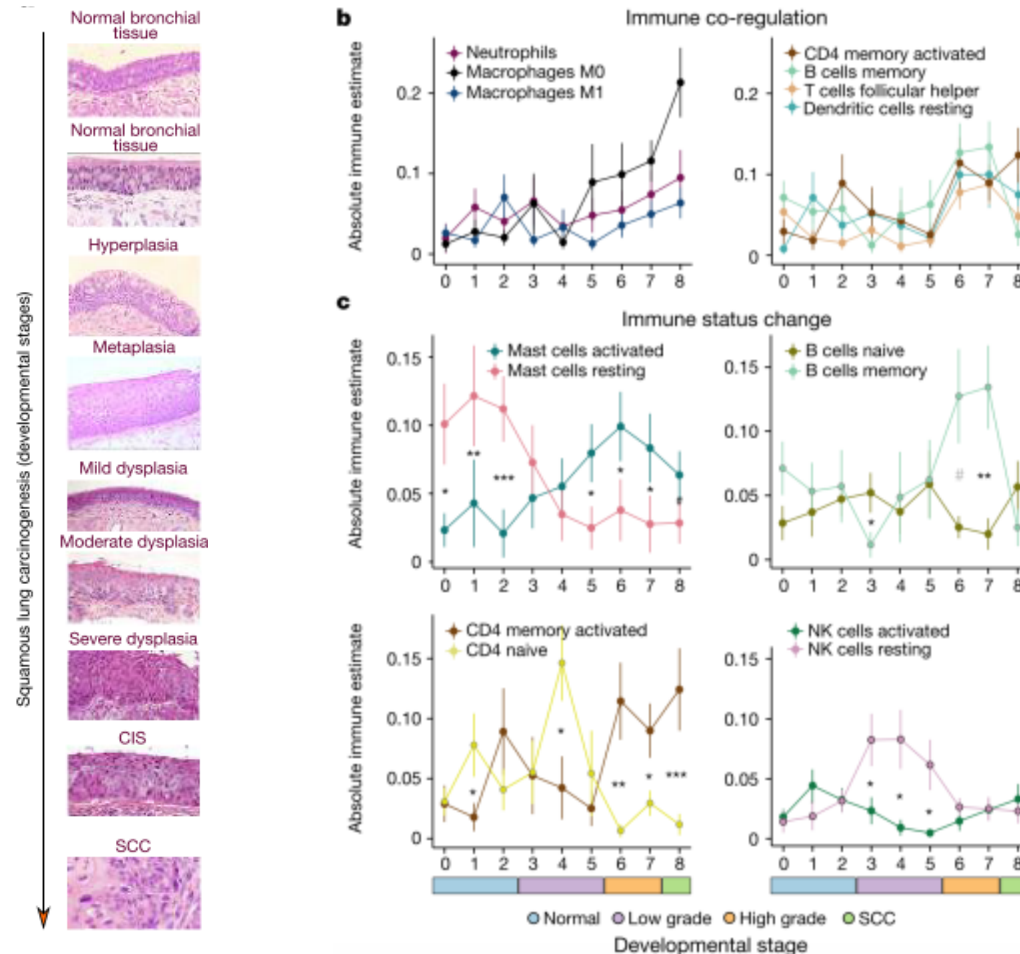
Clonal Theory (Nowell 1976)



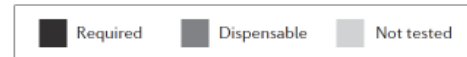
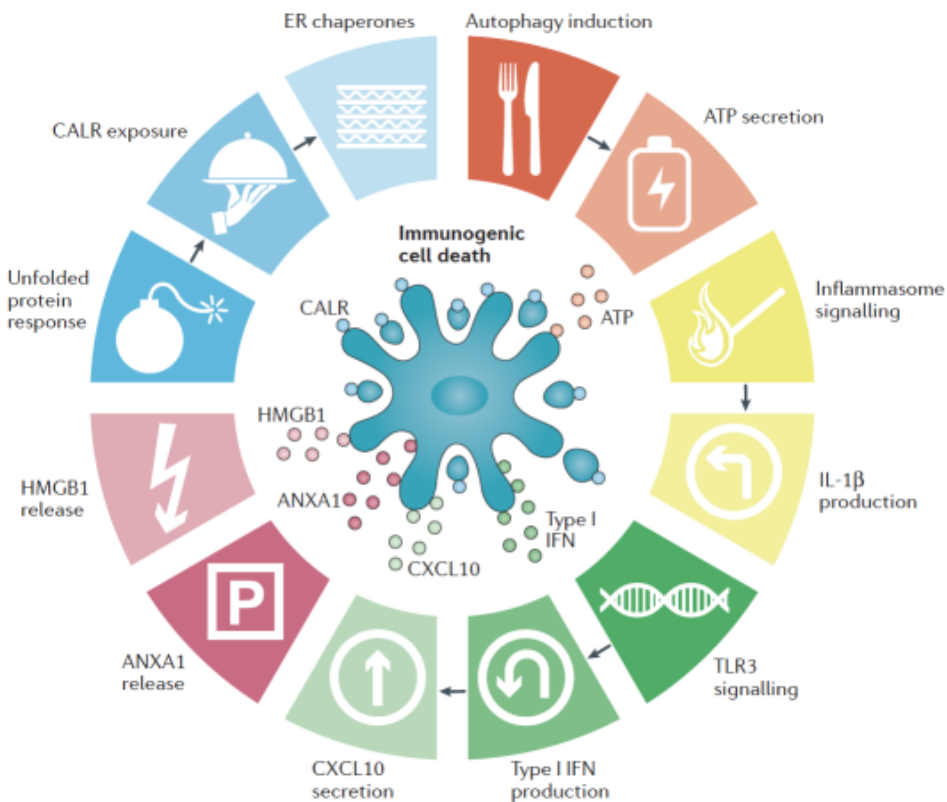


# Immune cell composition in the TME changes dramatically during cancer progression

## Lung squamous cell carcinoma 77 cases, 122 biopsies, 9 stages



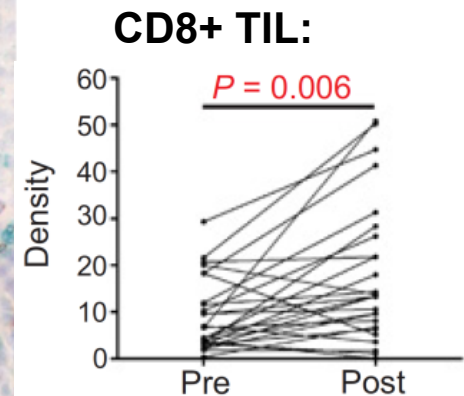
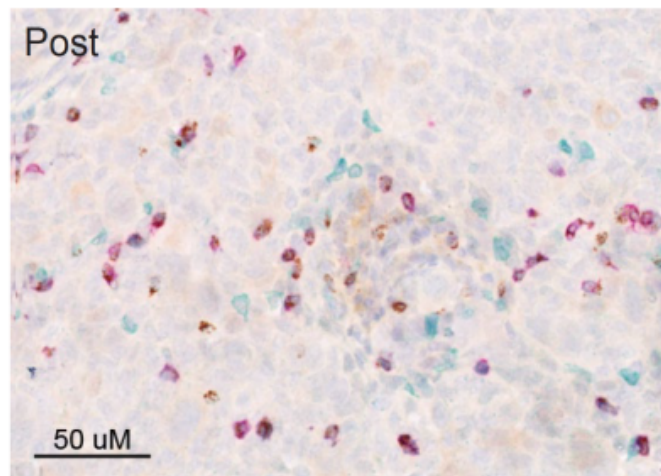
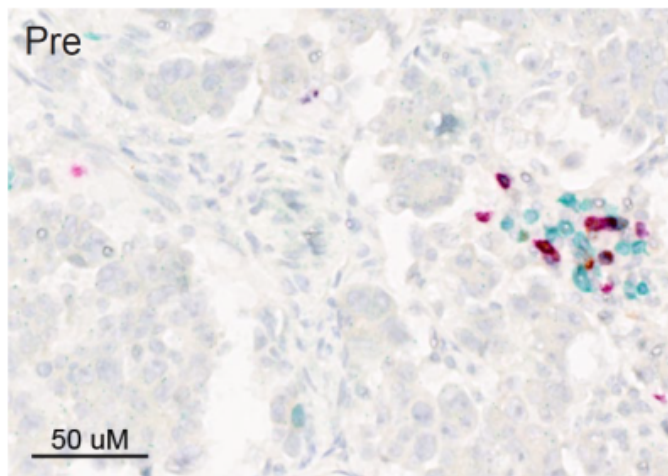
# Mechanisms of immunogenic cell death



# Chemotherapy can enhance TIL density

## *Neoadjuvant chemotherapy of ovarian cancer*

CD3 CD8 TIA-1

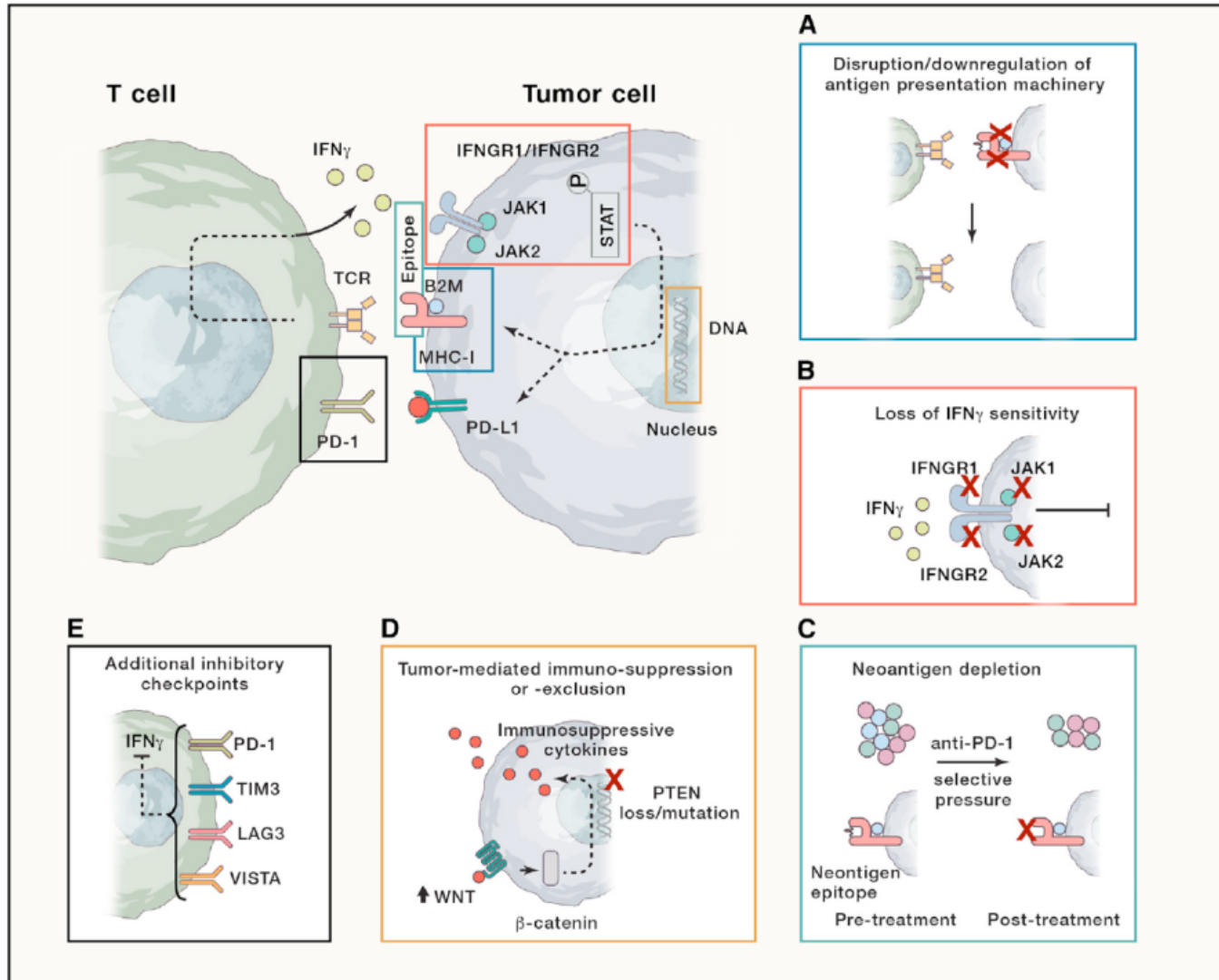


*Charlotte Lo et al, Clin Can Res 2016*

***Similar effects reported for hormone, radiation  
and targeted therapies in other cancers***

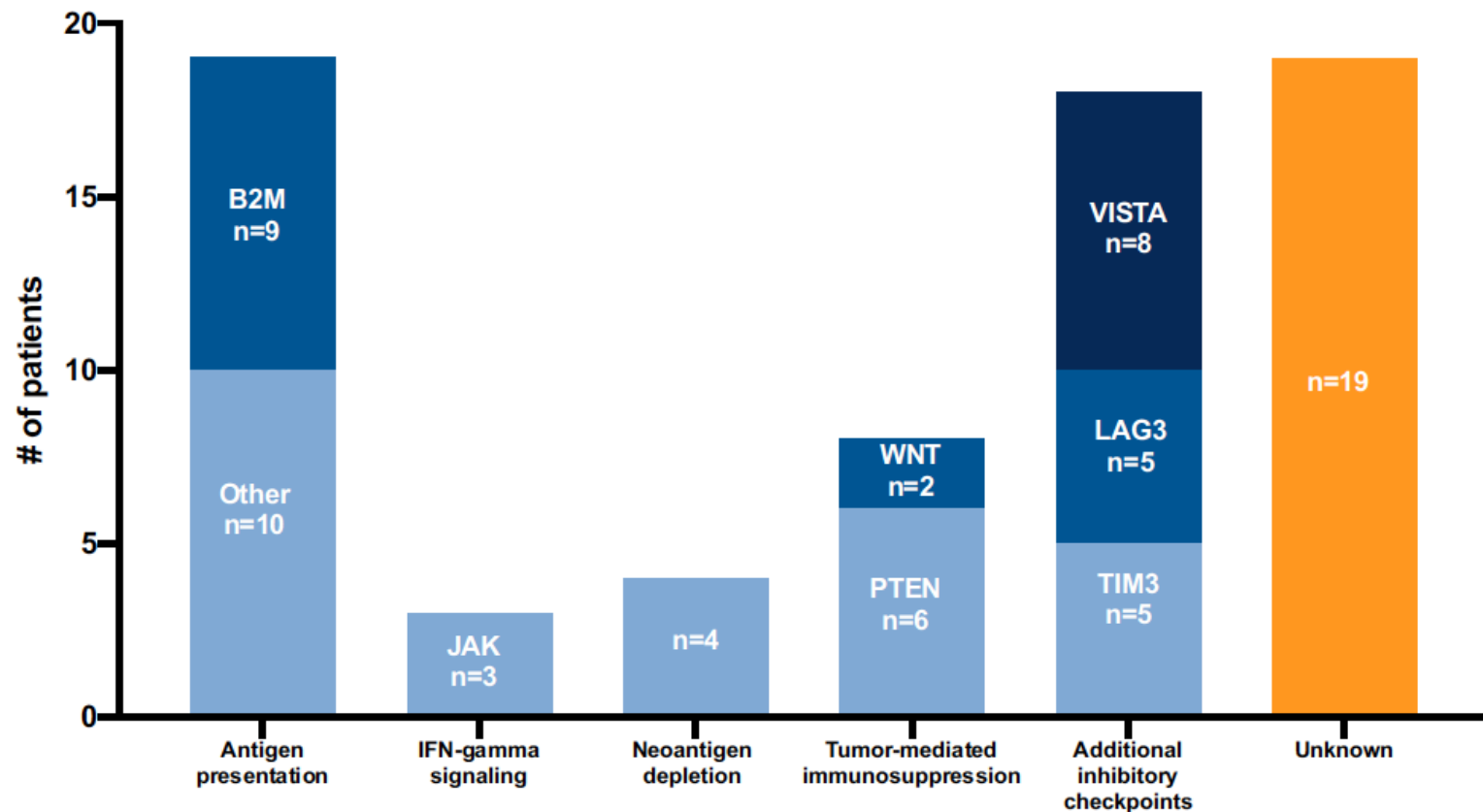


# Checkpoint blockade can select for a variety of immune evasion mechanisms



# Checkpoint blockade can select for a variety of immune evasion mechanisms

*Number of cases showing a given resistance mechanism*



# Tumor-infiltrating T cells exhibit major limitations

**Despite their prognostic benefit, hot tumors can exhibit:**

- **Antigen loss**
- **MHC loss**
- **High proportion of bystander T cells**
- **Multiple immune suppressive factors**
  - ***PD-1, TIGIT, LAG3, CD39, Tregs etc.***
- **Loss of tumor-reactive T cells over time**



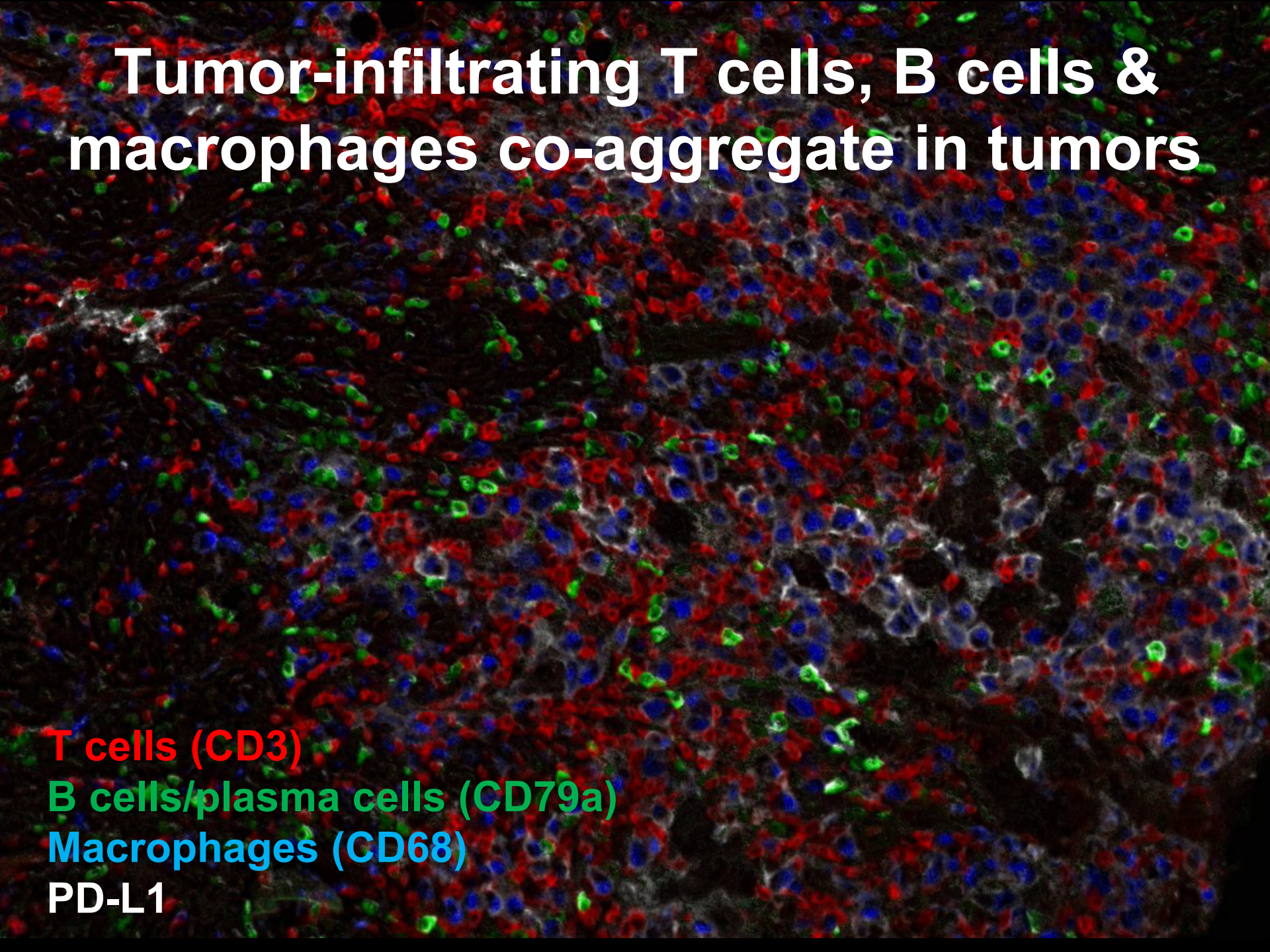
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- **Multiple immune suppressive factors**
  - ***PD-1, TIGIT, LAG3, CD39, Tregs etc.***
- **Loss of tumor-reactive T cells over time**

***How do TIL promote patient survival???***

# Tumor-infiltrating T cells, B cells & macrophages co-aggregate in tumors



T cells (CD3)

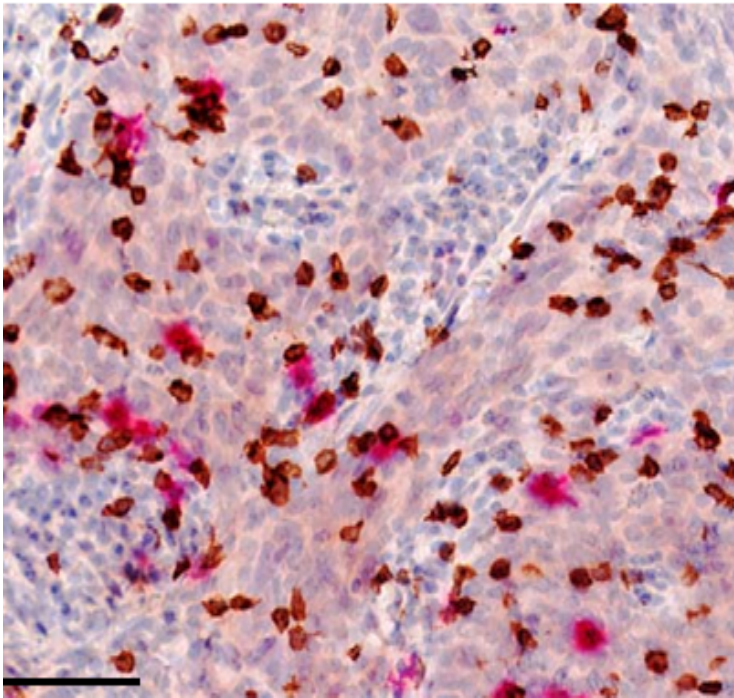
B cells/plasma cells (CD79a)

Macrophages (CD68)

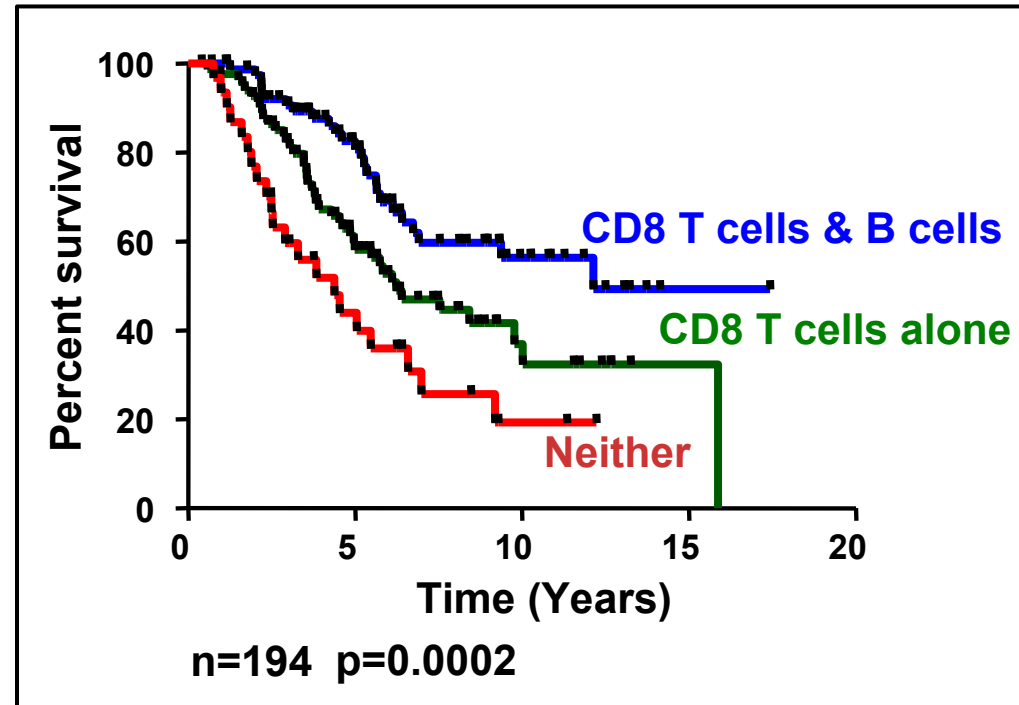
PD-L1



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



T cells (CD8)  
B cells (CD20)



*Julie Nielsen et al. Clin Can Res 2012*  
*David Kroeger et al, Clin Can Res 2016*



Article

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## **B cells are associated with survival and immunotherapy response in sarcoma**

[Florent Petitprez...Wolf H. Fridman, \*Nature\* Jan 23 2020](#)

Article

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## **Tertiary lymphoid structures improve immunotherapy and survival in melanoma**

[Rita Cabrita...Goran Jonsson, \*Nature\* Jan 23 2020](#)

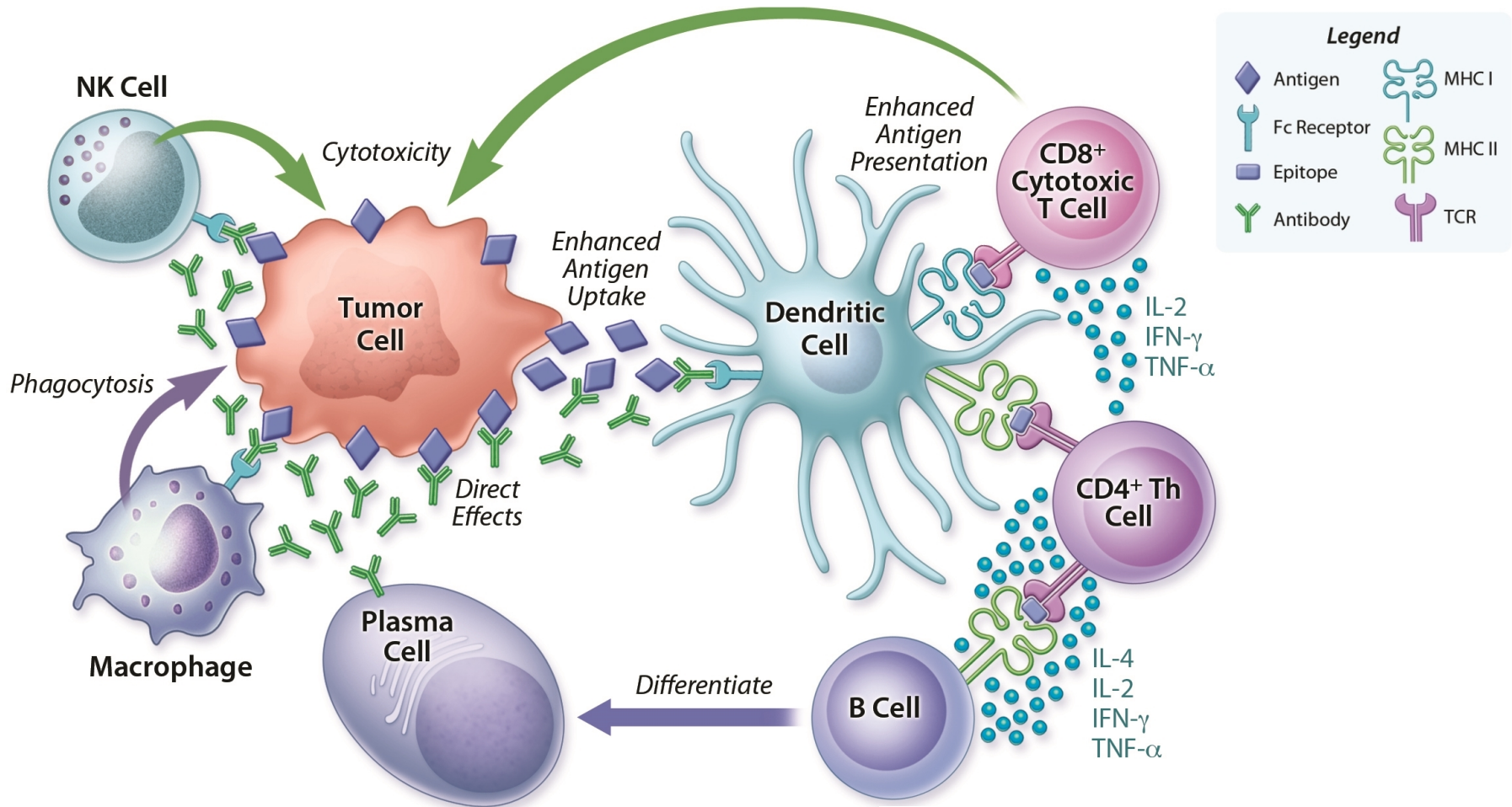
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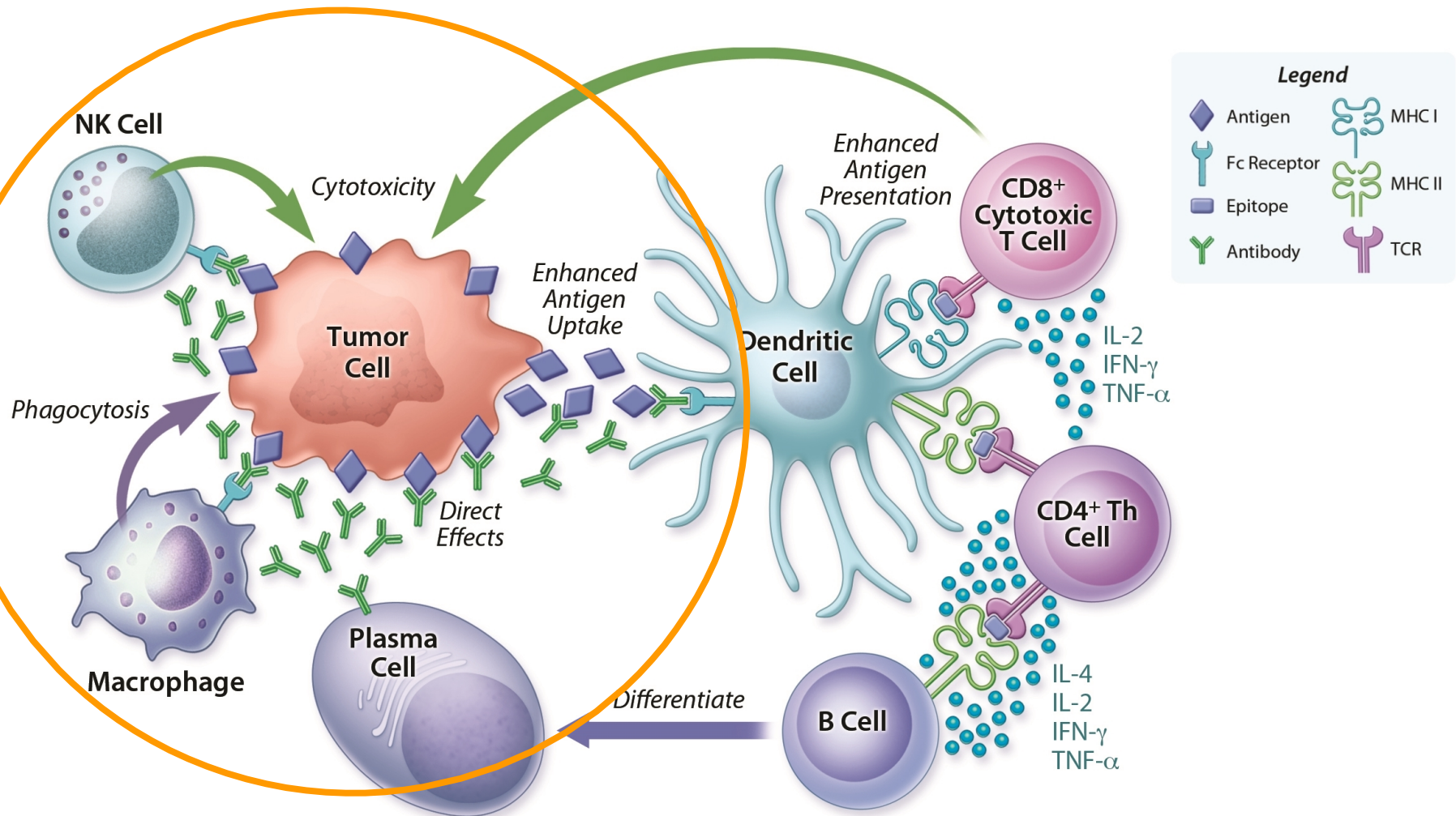
## **B cells and tertiary lymphoid structures promote immunotherapy response**

[Beth A. Helmink...Jennifer A. Wargo, \*Nature\* Jan 23 2020](#)

# Optimal TIL responses involve both cytolytic and antibody-based mechanisms



# Optimal TIL responses involve both cytolytic and antibody-based mechanisms



**New therapeutic opportunities**

Wouters and Nelson  
Clin Can Res 2018

# Take home messages

- Tumor microenvironment is a **complex ecosystem** with multiple effector & regulatory cell types & factors
  - *Ecological principles apply*
- Tumors evolve under numerous **selective pressures**, including the immune response
  - *Evolutionary principles apply*
- Our challenge is to devise therapeutic strategies that force the **extinction of tumor cells** while sparing host tissues
  - *Today's immunotherapies are achieving this in some patients and inspiring the next generation of strategies!*