



6th POSTGRADUATE
**Lymphoma
Conference**

Signaling pathways & Immune evasion in Hodgkin's

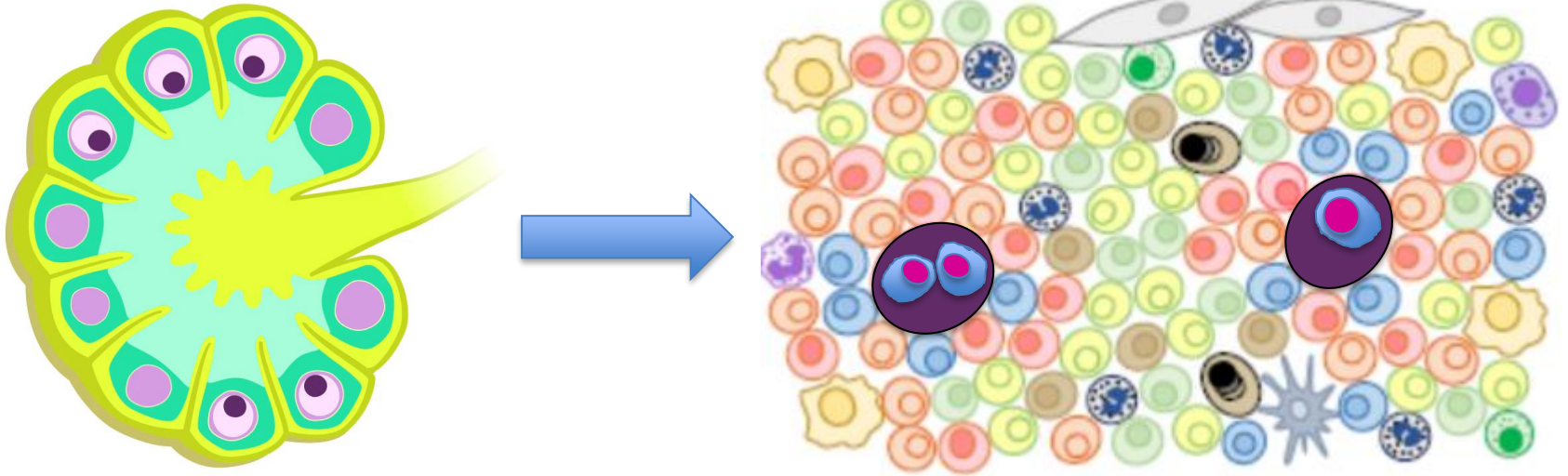
Arjan Diepstra

University Medical Center Groningen, the Netherlands

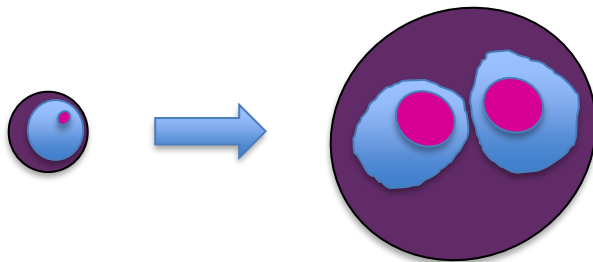
Rome,
September 7-9
2022

President:
P.L. Zinzani

VOI Donna Camilla Savelli Hotel



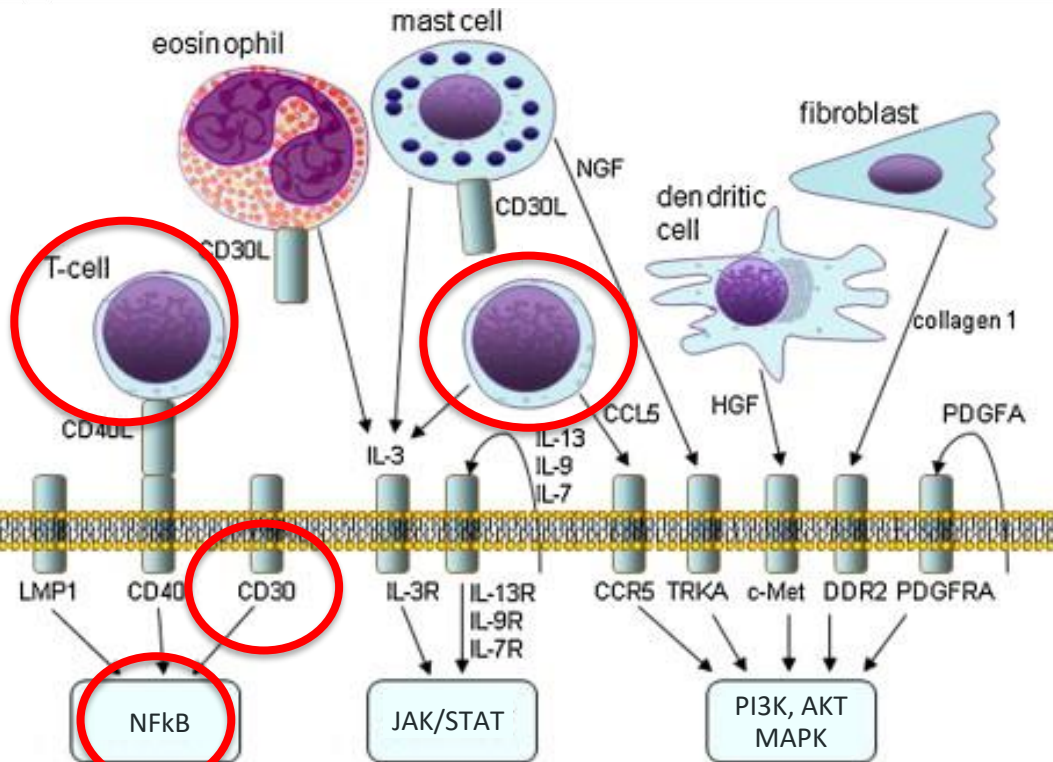
Adapted from:
www.lymphomaresearchgroningen.nl
Tan GW, *Pathogens* 2018; 7:40



- High extent of transformation
 - Loss of B cell phenotype
- Extremely strongly activated
 - Aberrant signalling pathways
- Bizarre phenotype
 - Immune escape mechanisms

Aberrant signaling

Tumor microenvironment



HRS cell membrane

HRS cell interior

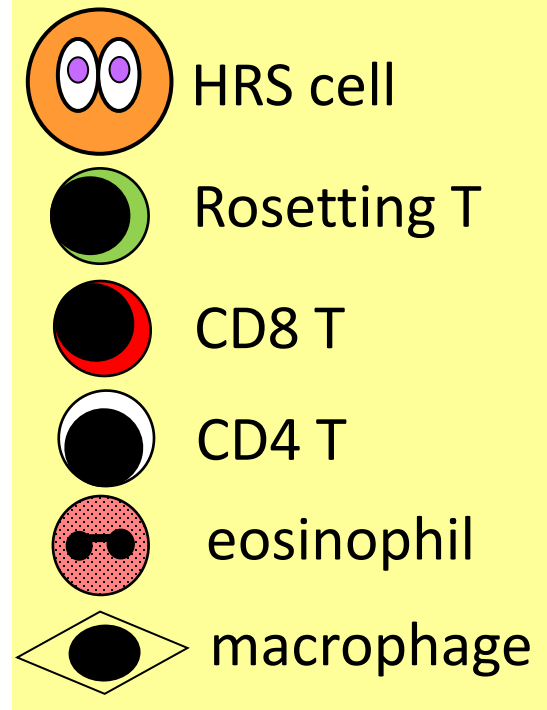
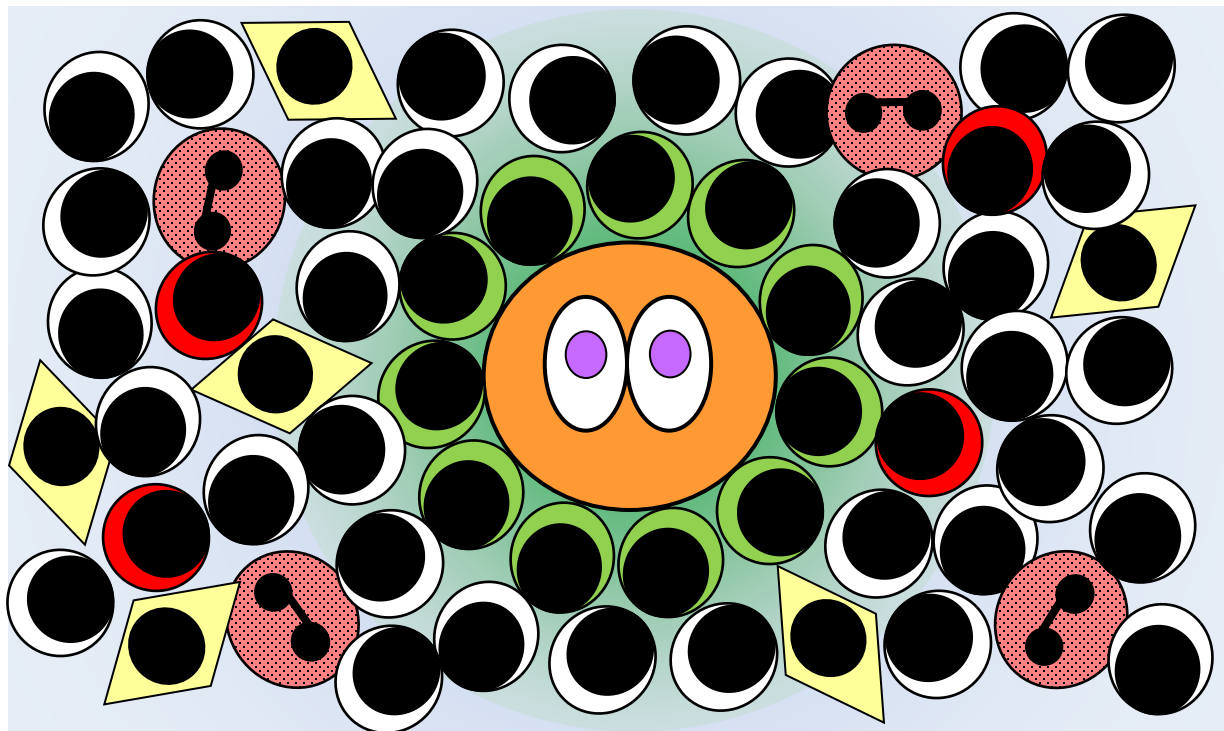
Genetic aberrations

Activating mutations*
Gains/amplifications*
Translocations

Activating mutations*
Gains/amplifications*

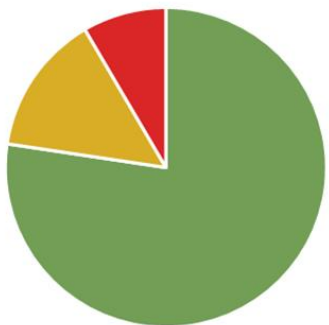
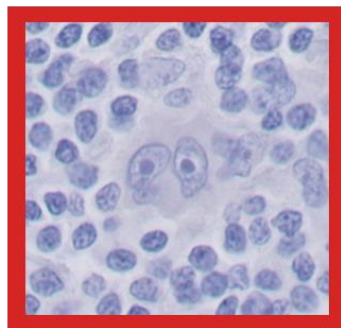
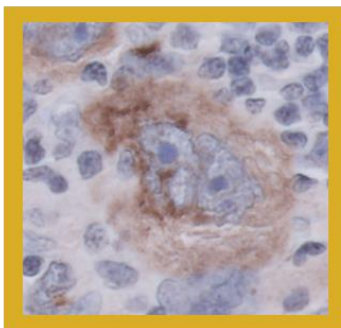
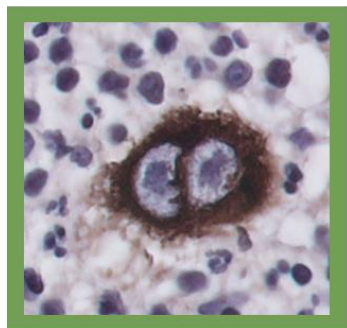
Activating mutations

Liu Y, *Sem Cancer Biol* 2014; 24:15-22
Weniger MA, *Leukemia* 2021; 35:968-81
*Sobesky S, *Med* 2021; 2:1171-93

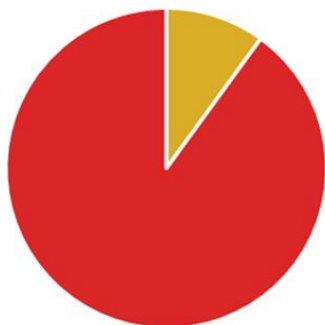


 = TARC/CCL17

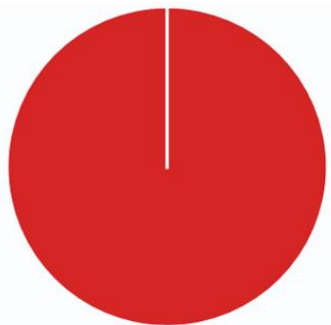
TARC immunohistochemistry



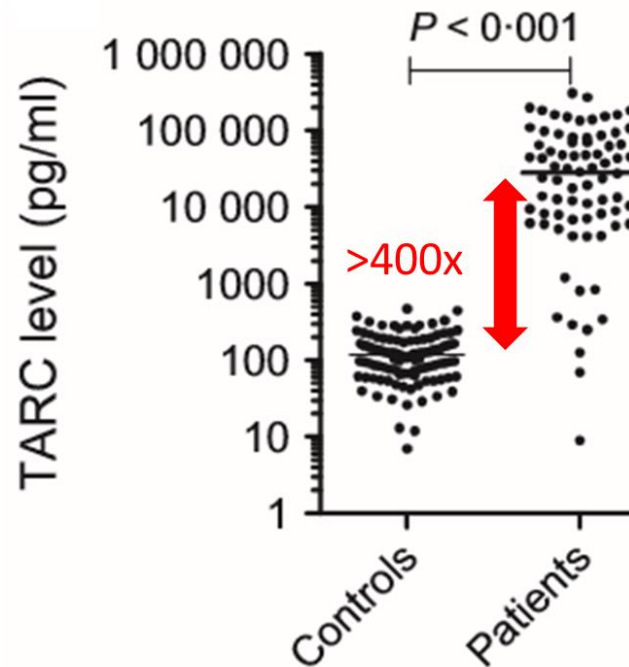
Classic Hodgkin lymphoma
N=190



Nodular lymphocyte
predominant Hodgkin Lymphoma
N=20

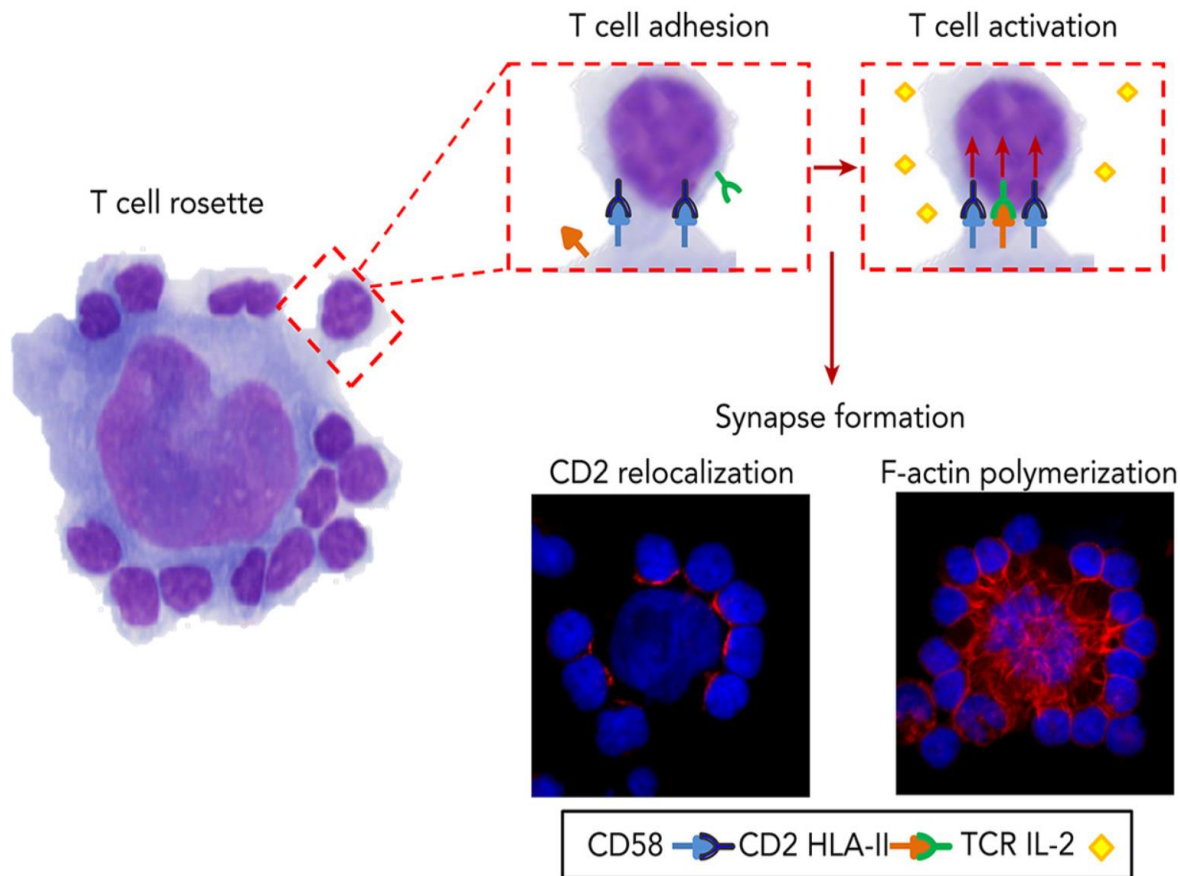


Reactive
lymphadenopathy
N=64

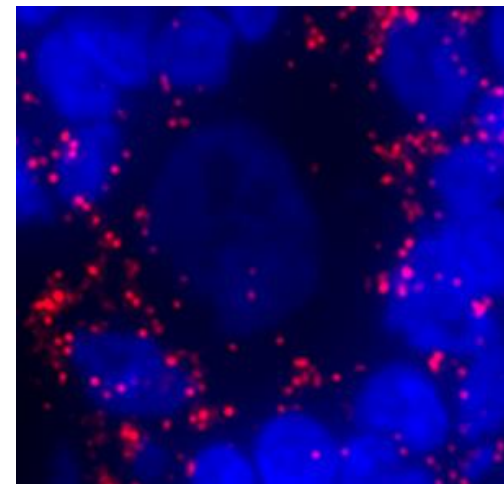


Kilsdonk M, under review
Plattel W, *BrJHaem* 2016;175:868-75

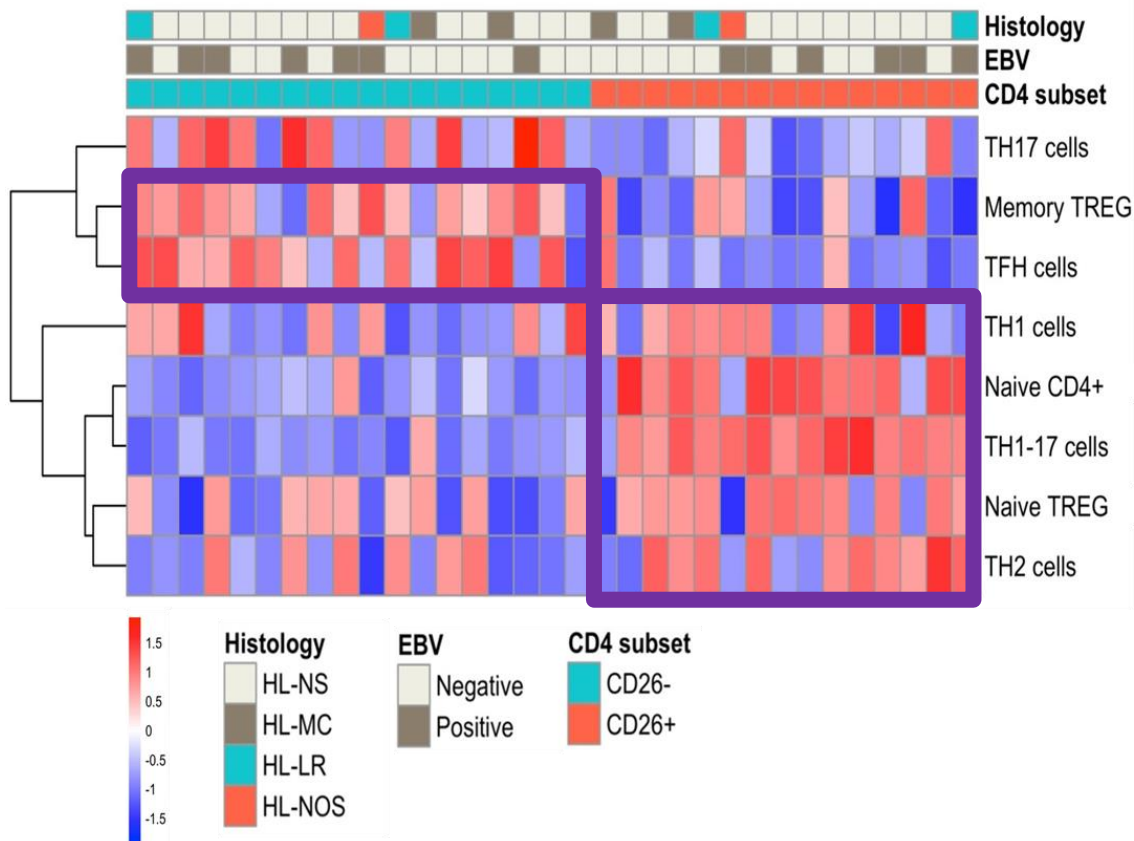
Aberrant signaling



TCR-HLA II interaction in tissue

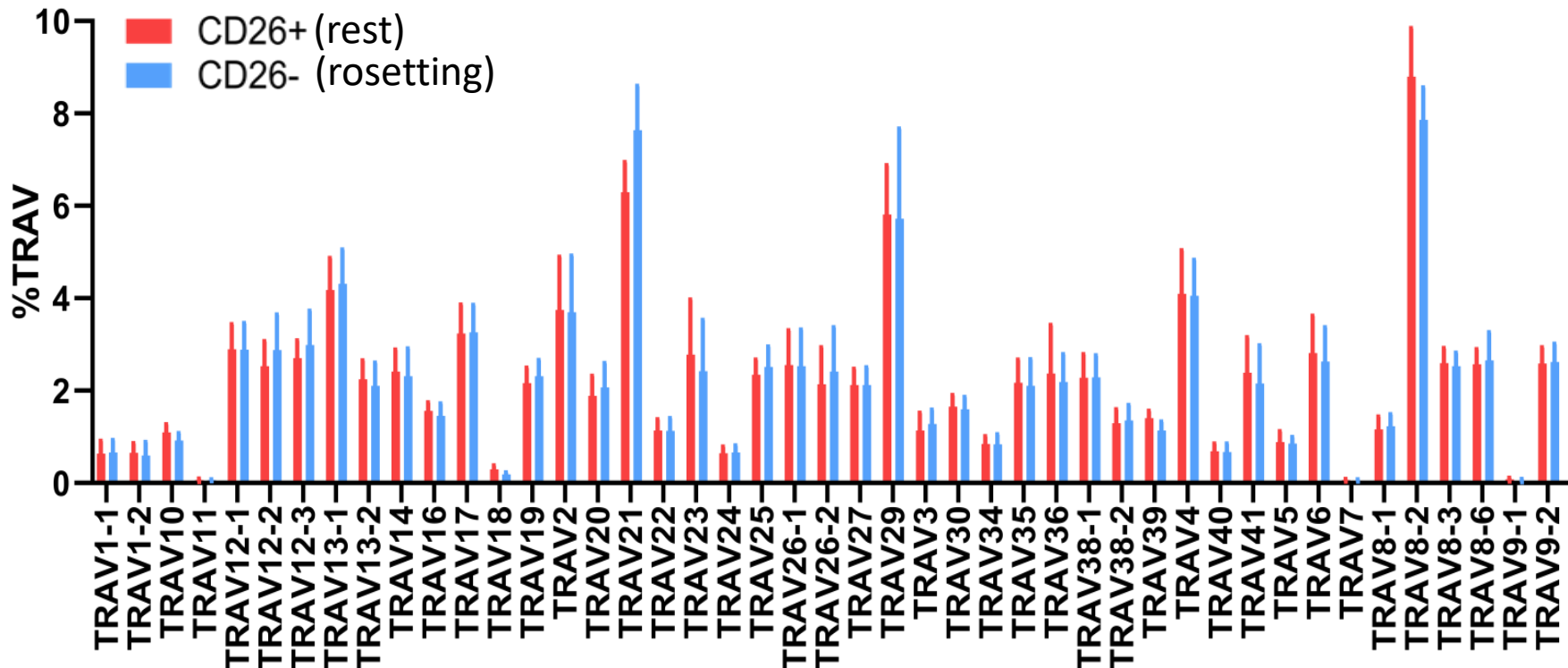


Veldman J, *Blood* 2020, 136:2437-41.

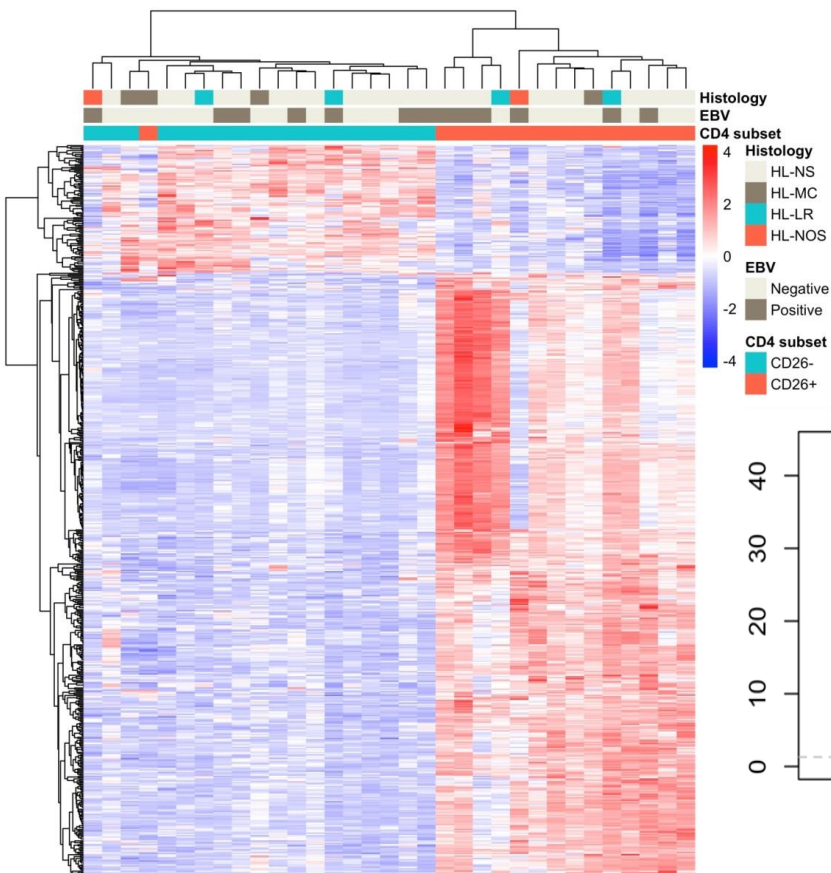


- 19 HL cell suspensions
- Flow sorting:
 - CD4+CD26- (rosetting)
 - CD4+CD26+ (rest)
- RNA sequencing
- Gene Set Variation Analysis
- T cell subset correlation*
- CD26- = memory Treg / Tfh
- CD26+ = naïve, Th1/Th2

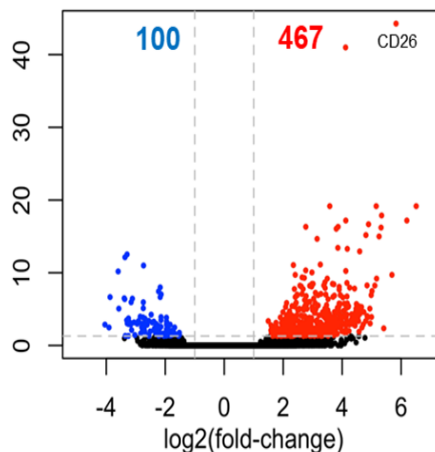
* Schmiedel et al. *Cell* 2018
Veldman J, *Oncoimmunology* 2022, 11:2033433



- V segment usage TCR alpha CD4 cells (TCR beta similar result)



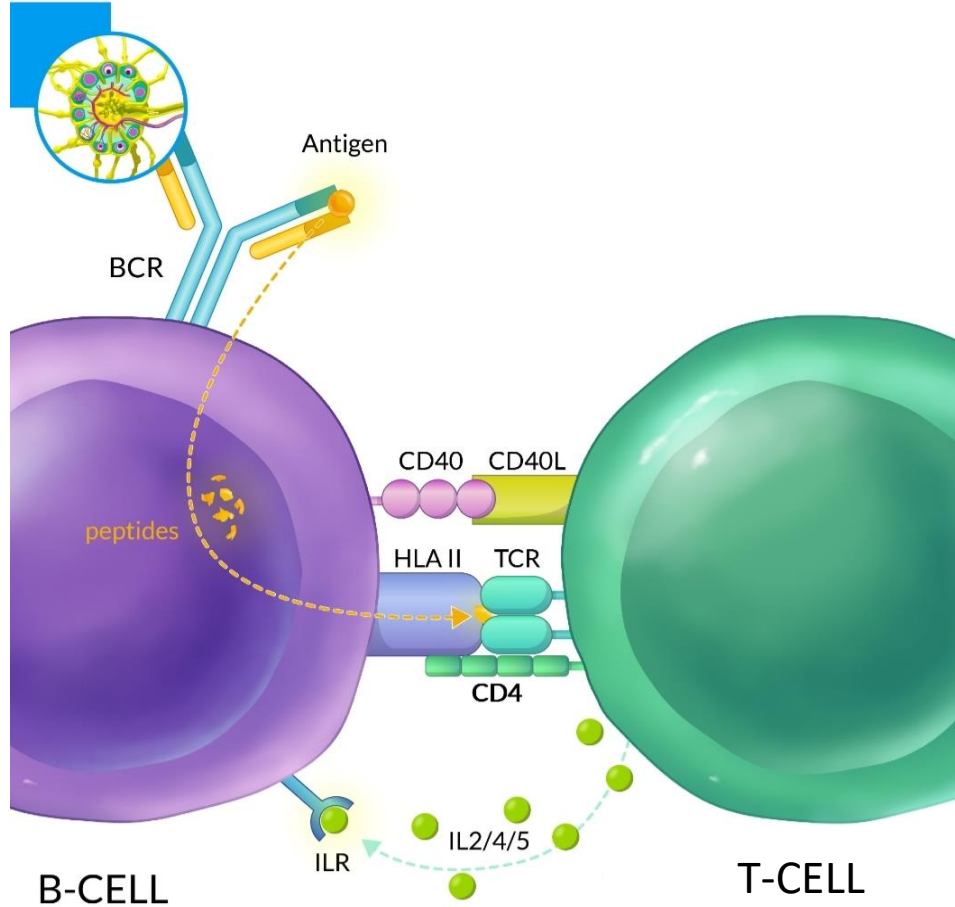
CD26- vs. CD26+

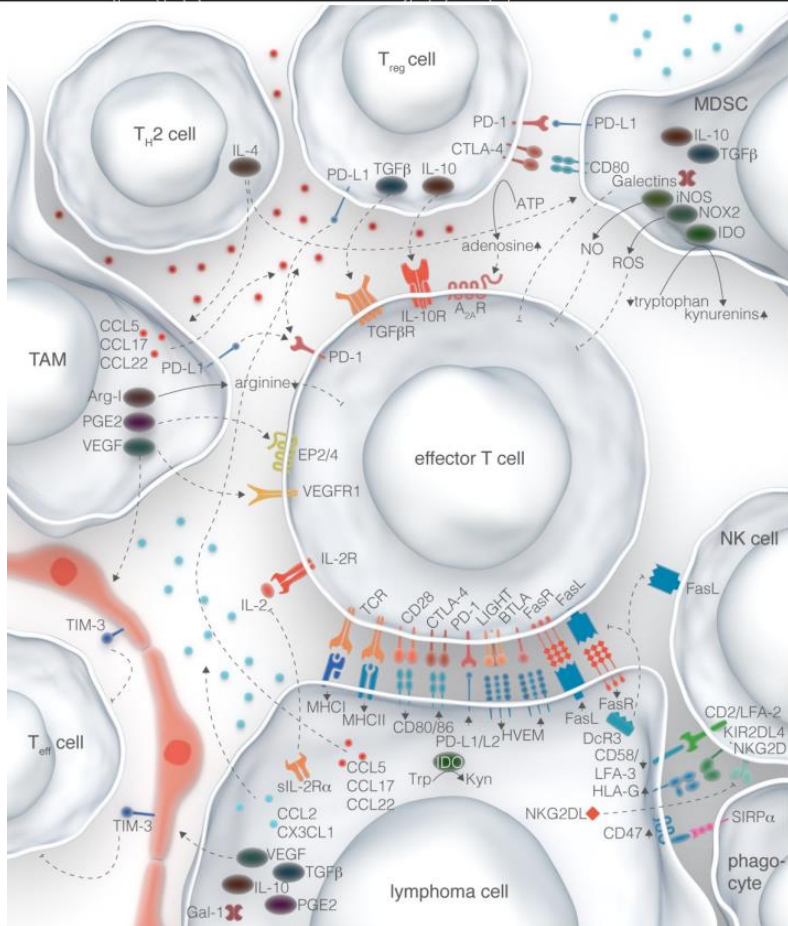


- 567 DEG: 100 up, 467 down
- Among genes up + validated:
 - TOX
 - TOX2
 - PDCD1 (PD1)

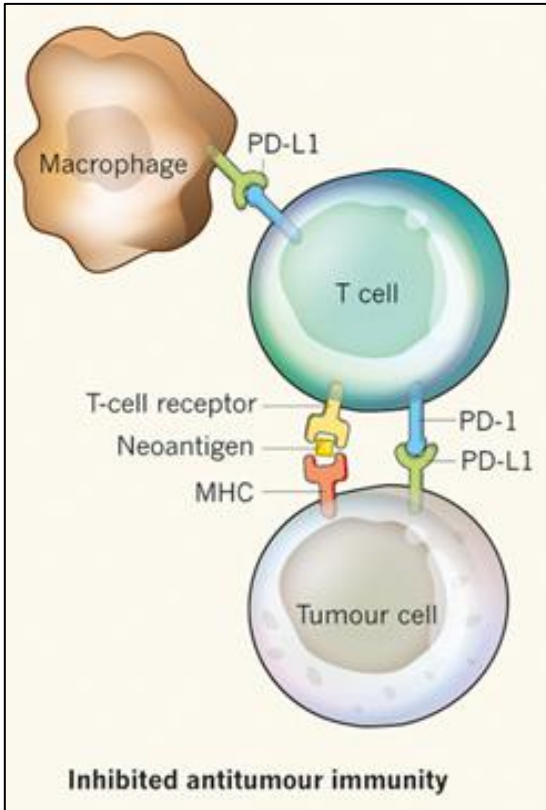


Chronic T cell stimulation!

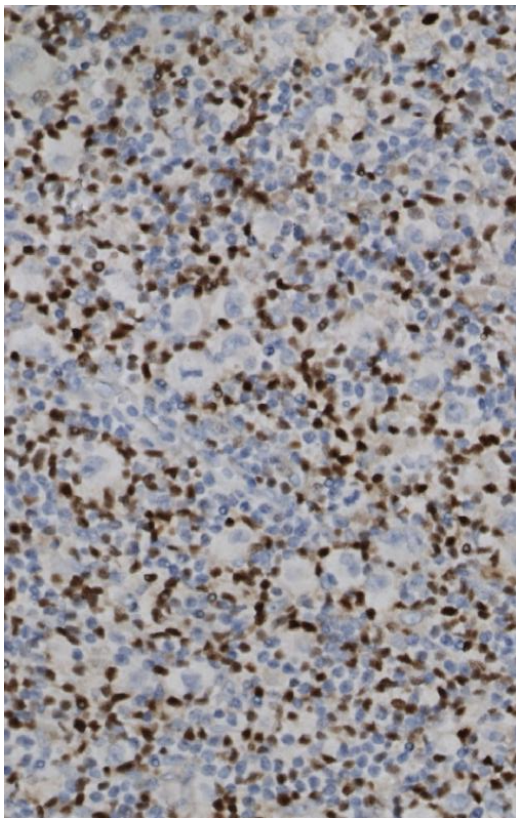




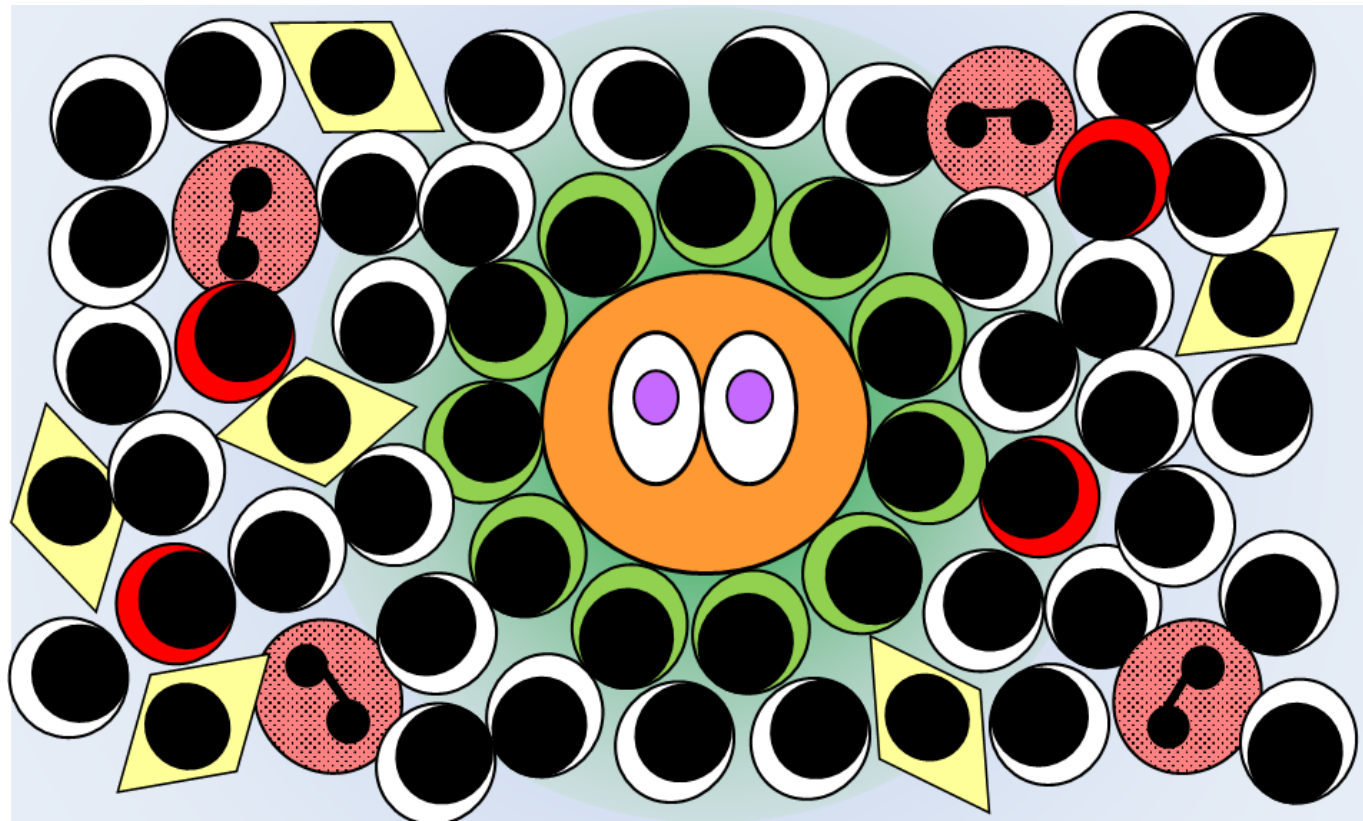
- Immune checkpoints: PD-L1, CTLA4, LAG3
- Downregulation MHC/HLA class I: B2M
- Upregulation HLA-G
- Immunosupp. cytokines: IL-10, TGFβ
- Death inducing ligands: FasL
- TME modulating chemokines
- IDO, adenosine
- Alteration immunological synapse



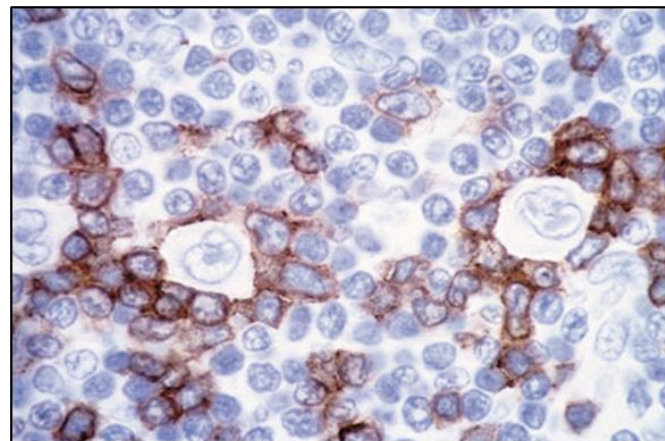
- PD-L1 strongly involved:
 - high expression on HRS cells
 - 9p24.1 genetic aberrations
- However, effector cell not CD8:
 - >70% of cases no HLA/MHC class I
 - No PD-1 expression on CD8 cells
- Alternative effector cells:
 - CD4+ T cells
 - NK cells
 - Macrophages



TOX



- Hodgkin lymphoma is very heterogeneous:
 - signaling pathways
 - microenvironment interactions
- Targets for treatment:
 - CD30, immune checkpoints
 - Experimental: TARC, small molecules
- Renewed focus on T cell rosettes



CD3



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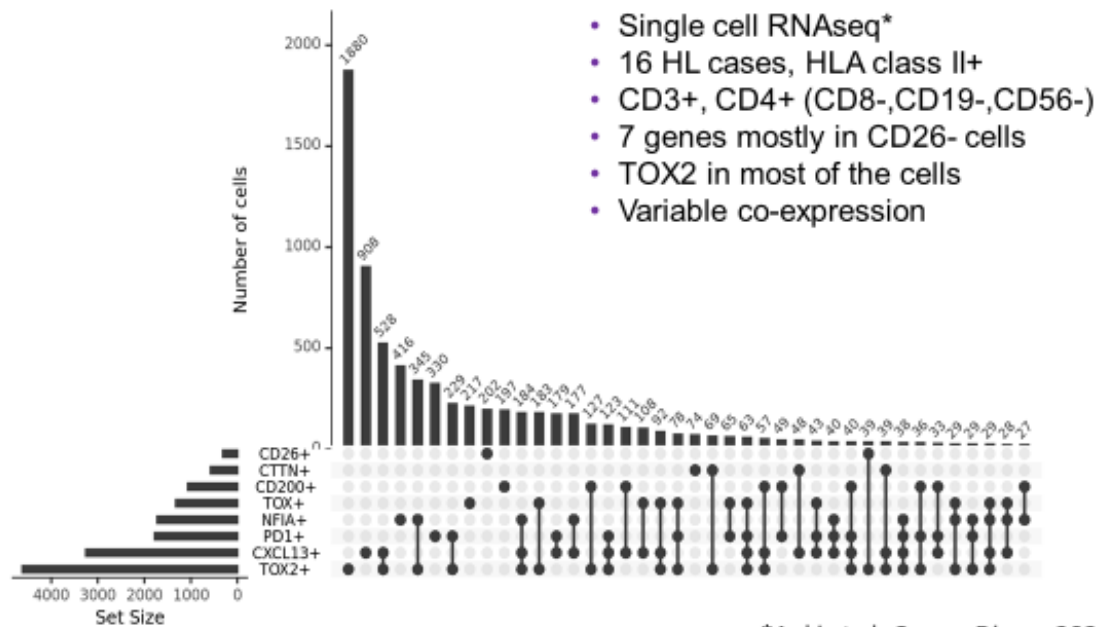


university of
groningen

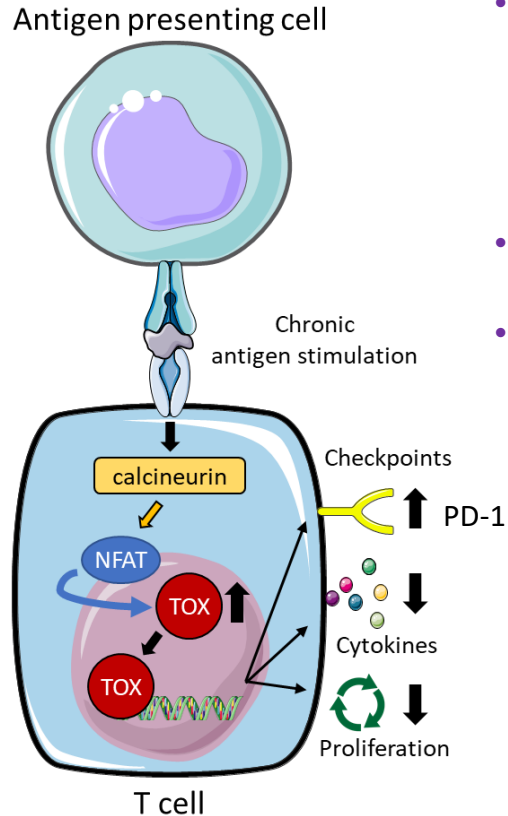


umcg

7 genes in scRNAseq



*Aoki et al. *Cancer Discov.* 2020



- TOX and TOX2:
 - transcription factors
 - Induced by chronic antigen stimulation
 - Induce and maintain exhaustion in T cells
 - Essential for the development of Tfh cells
- CXCL13:
 - Chemokine induced by TOX
- PD-1 and CD200:
 - Immune checkpoints induced by TOX

Yoshitomi et al. *Nat Commun.* 2018

Alfei et al. *Nature* 2019

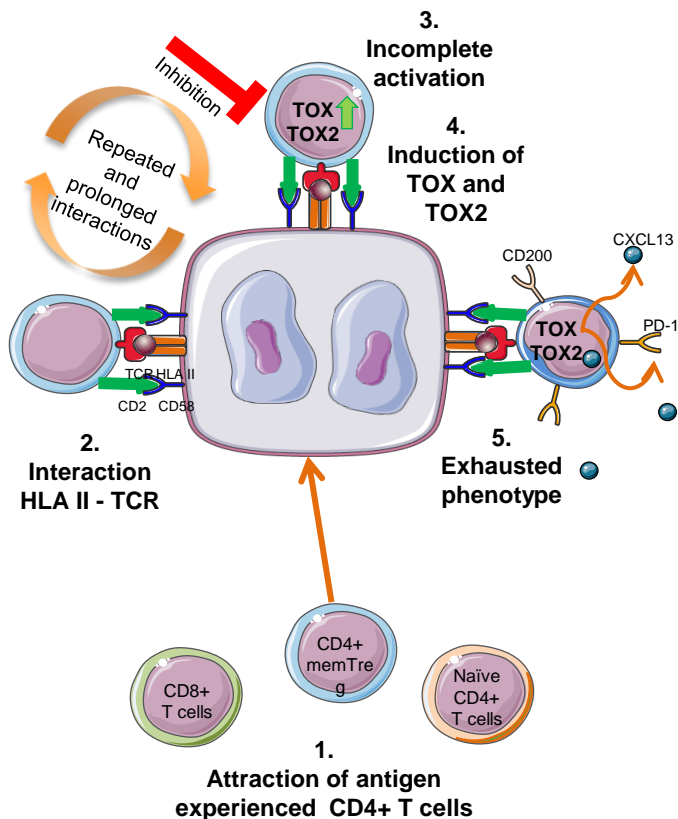
Scott et al. *Nature* 2019

Seo et al. *PNAS* 2019

Yao et al. *Nat Immunol.* 2019

Xu et al. *Immunity.* 2019

Balanca et al. *JCI Insight* 2021



1. TARC/MDC attract memory Tregs
2. memTregs interact with HLA class II
3. Activation is incomplete and repeated
4. TOX/TOX2 induction + exhaustion
5. Markers of Tfh appear

Conclusions

- Tumor cell associated CD4+ T cells are CD26- and form rosettes
- These cells are:
 - Important for HRS cell survival
 - Antigen experienced
 - Polyclonal
 - Recruited Memory Treg cells with induced Tfh characteristics
 - Expressing TOX and TOX2, markers of exhaustion
- TOX and TOX2 may be attractive as:
 - Diagnostic markers
 - Predictive markers in immune checkpoint inhibitor therapy
 - Novel targets in Hodgkin lymphoma treatment



