

Impact of the immune landscape on Hodgkin lymphoma prognosis and treatment

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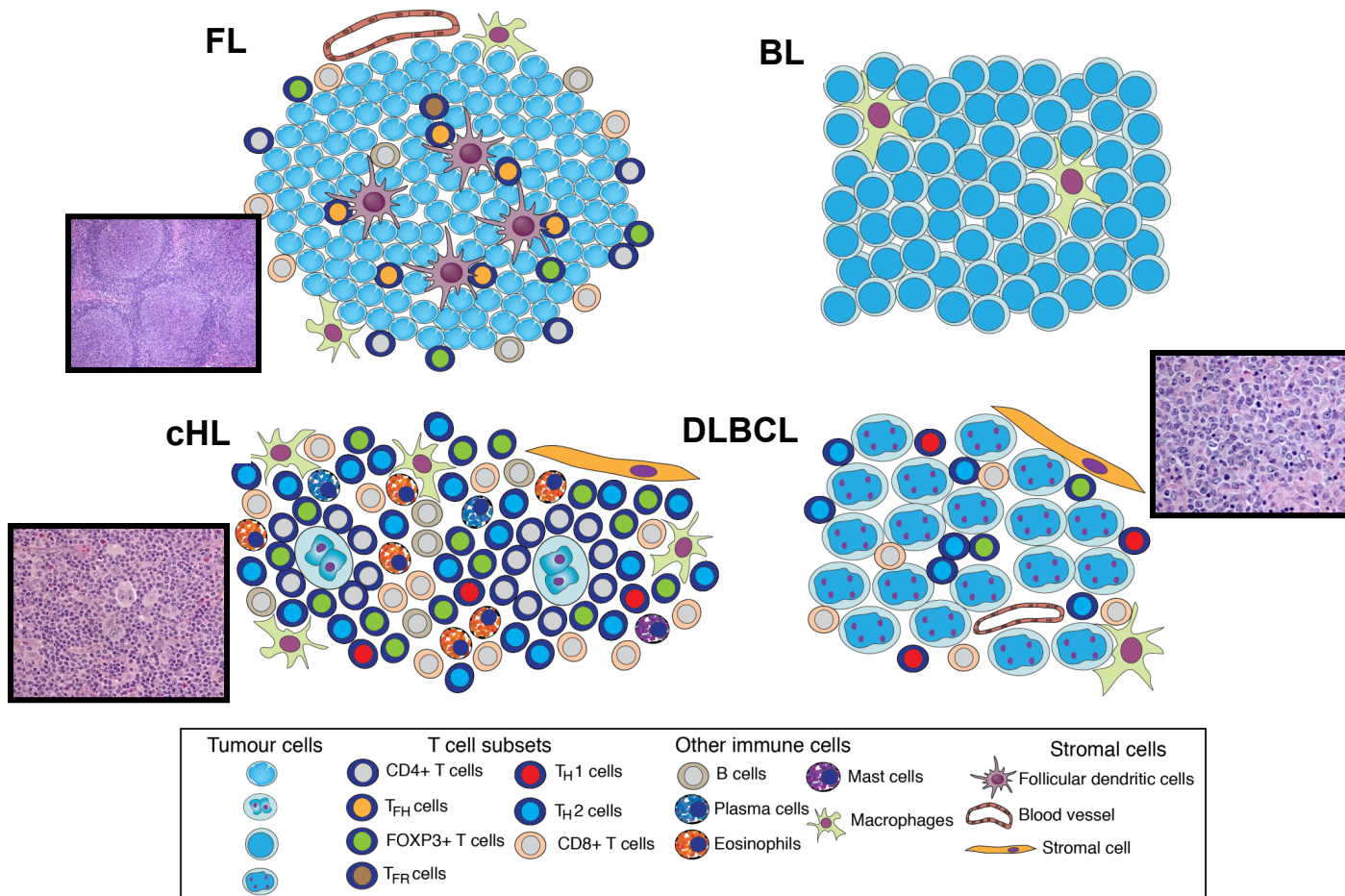


Disclosures

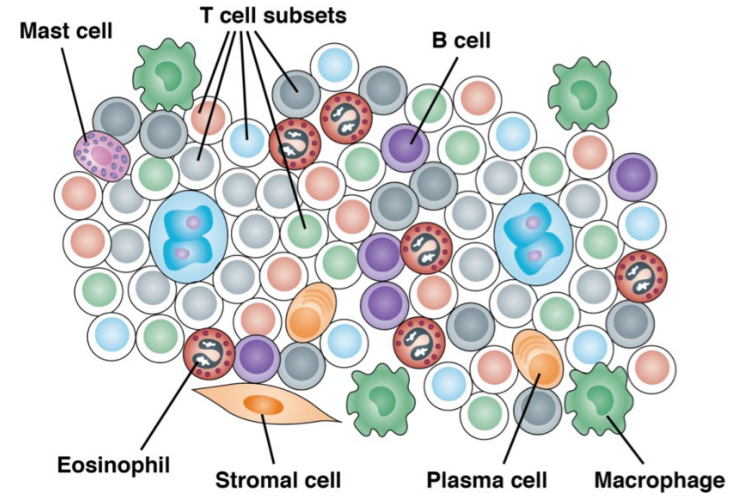
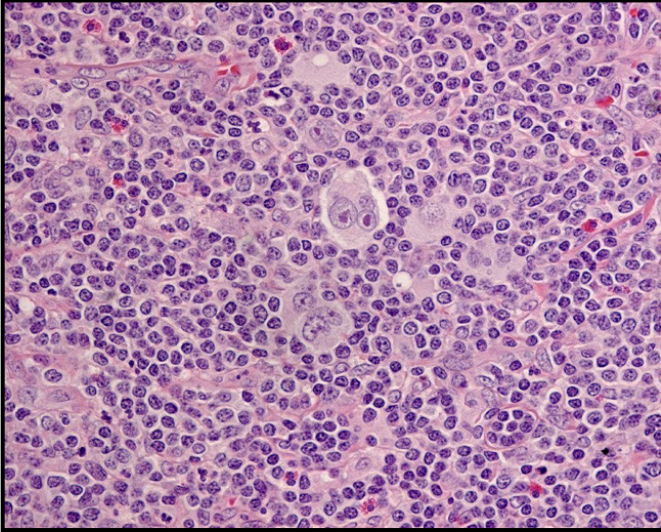
I have the following financial relationships to disclose:

- **Consultant for:** Seattle Genetics, Roche, Curis Inc, Bayer, AbbVie
- Speaker's Bureau for: N/A
- **Grant/Research support from:** Bristol-Myers Squibb, Trillium, Epizyme
- Stockholder in: N/A
- Honoraria from: N/A
- Employee of: N/A
- **Patents:** Lymph3Cx subtyping assay (Nanostring platform)

Composition of the microenvironment in B cell lymphomas



The Hodgkin lymphoma tumor microenvironment



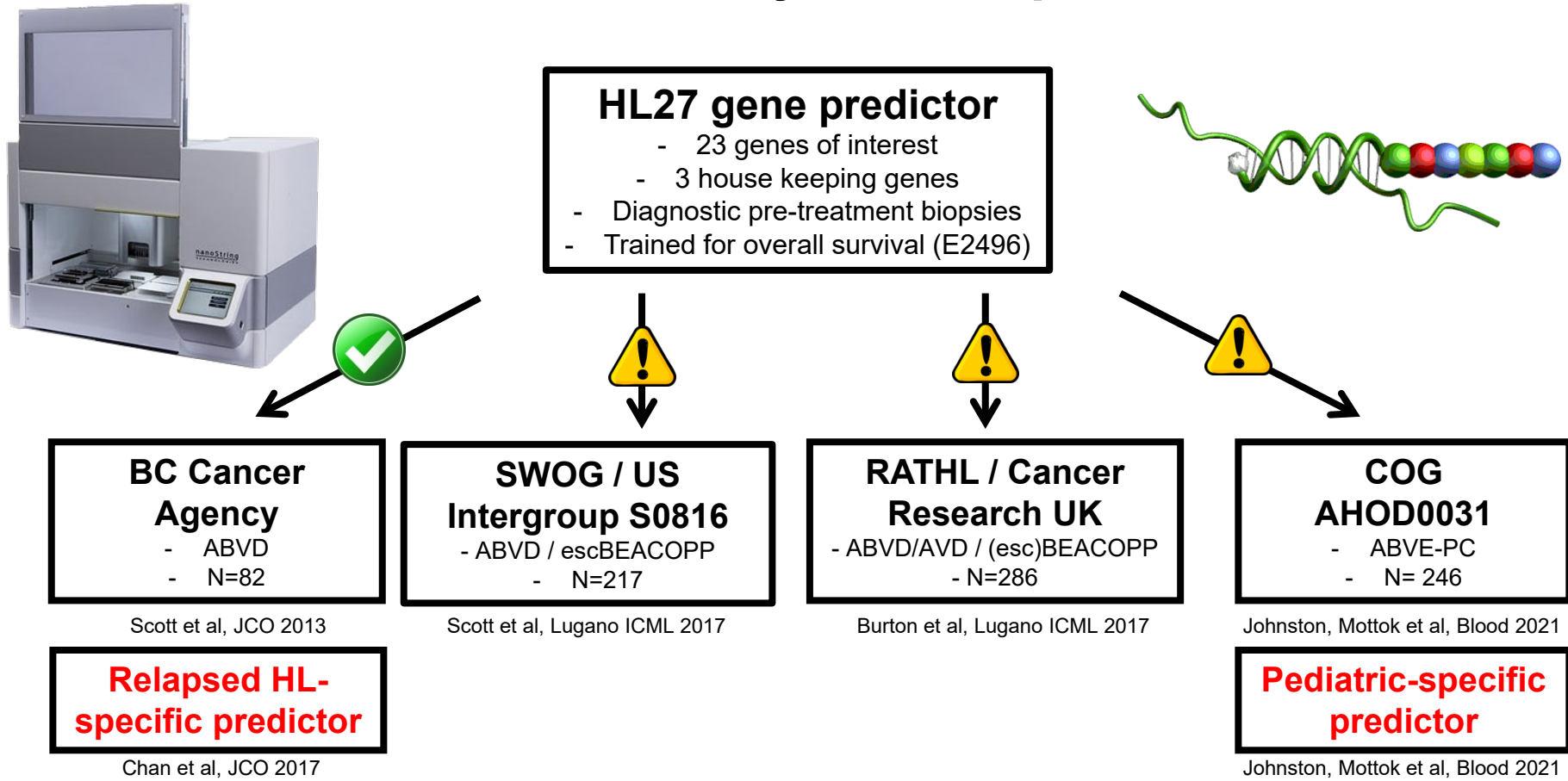
Scott and Gascoyne *Nat Rev Cancer* 2014

Microenvironment composition

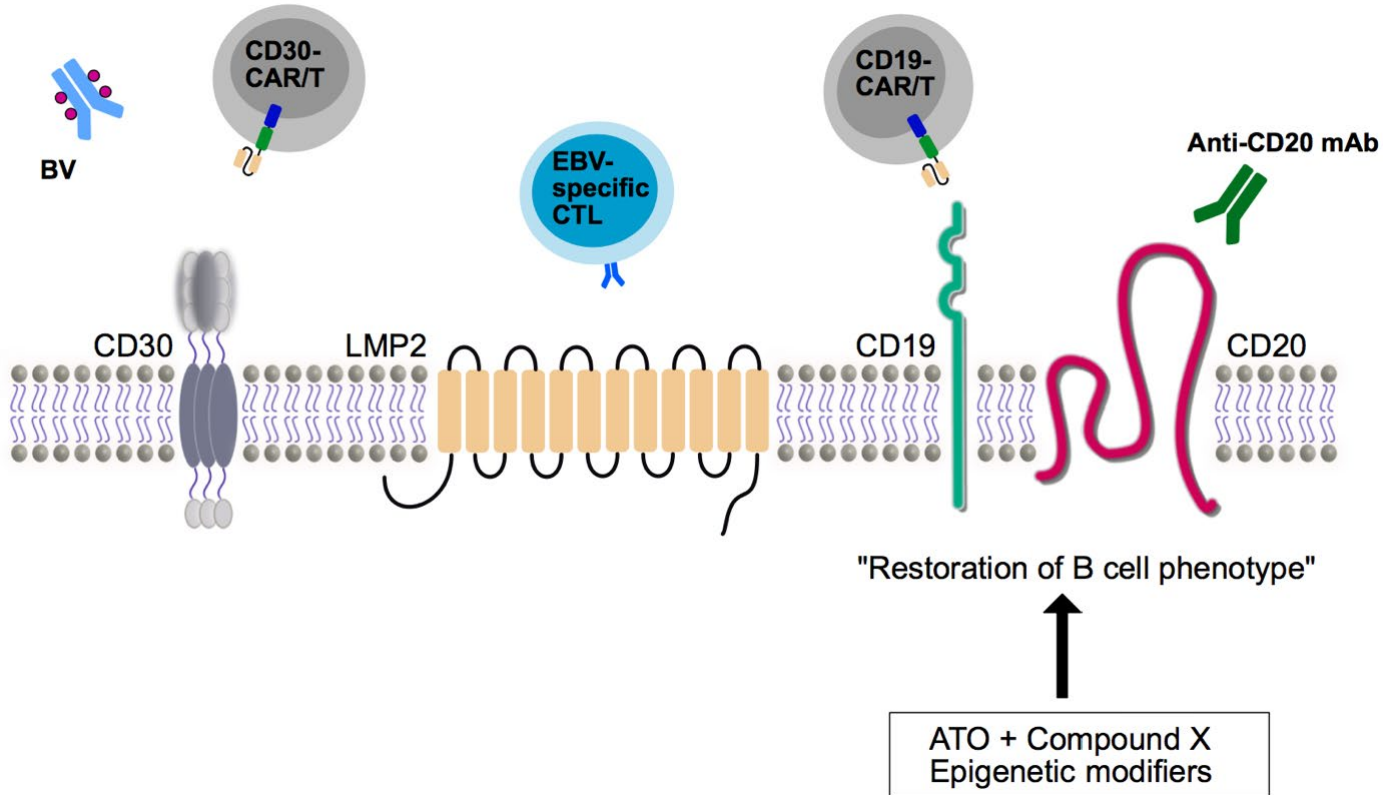
- (1) Defines subtypes
- (2) Prognostic for standard of care
- (3) Predictive for immunotherapy

Gene expression studies for outcome prediction

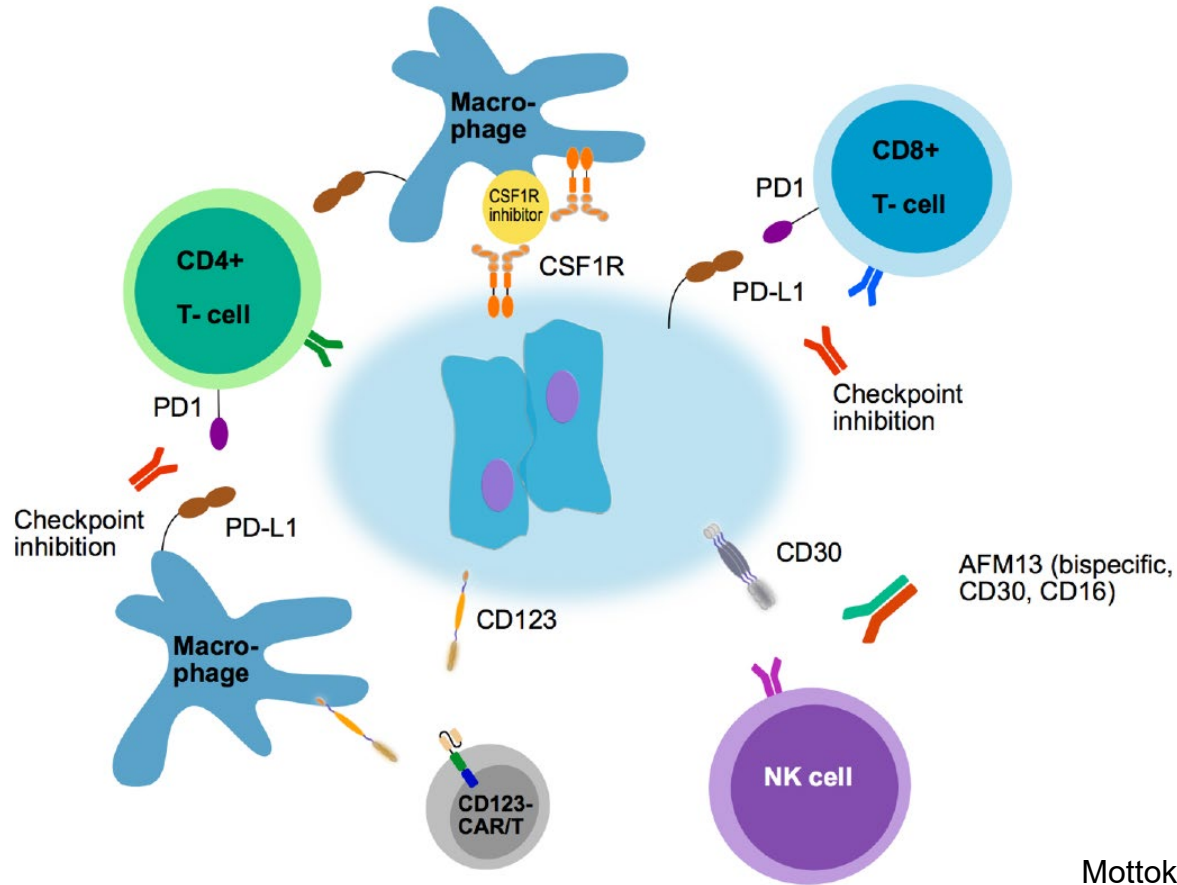
The HL27 assay in adult patient



Phenotypic features targetable by novel therapeutic agents



Can we guide treatment selection between immunotherapy options ?



Loss or downregulation

- B2M* mutations and deletions
- NLRP5* mutations and deletions
- FAS* mutations and deletions
- CD58* mutations and deletions
- TNFSF7* mutations and deletions
- TNFRSF14* mutations and deletions
- CIITA* rearrangements, *CIITA* mutations, *CREBBP* mutations
- MHC class II CNV
- TNFSF9* mutations and deletions

Upregulation of surface molecules

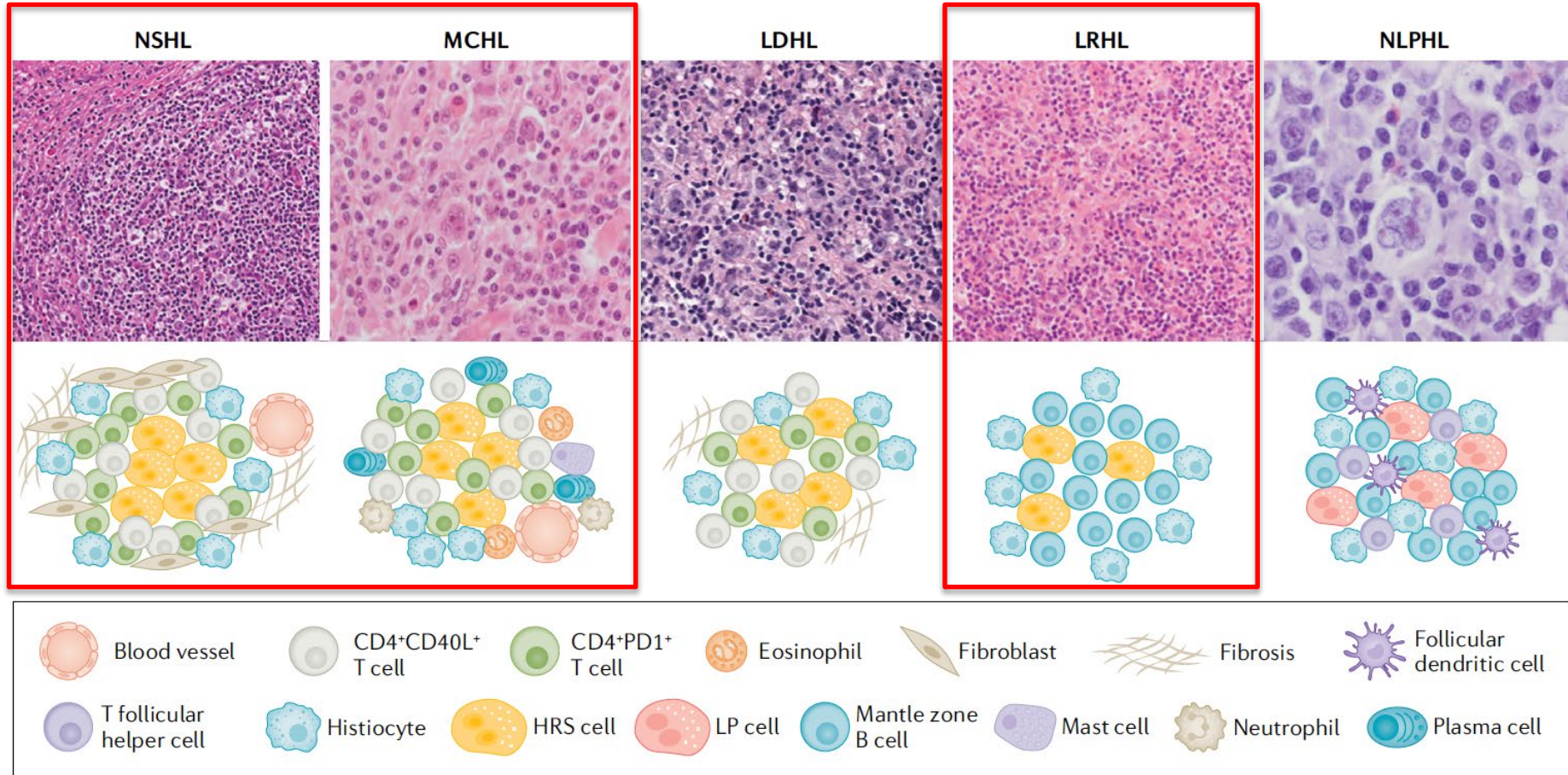
- PD-L1 copy number gain and amplification
- PD-L1 rearrangements

Immune Cells and Interactions:

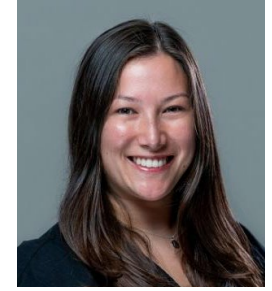
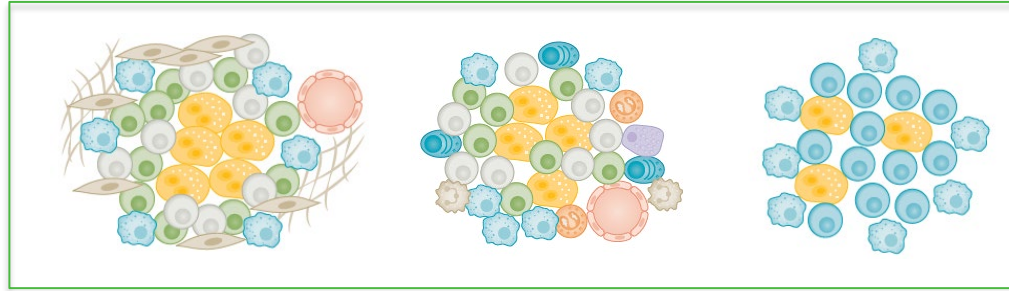
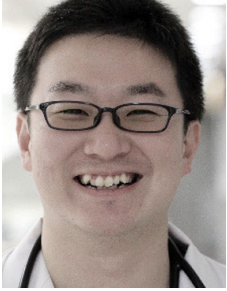
- CD8+ T cell:** Interacts with MHC I, FAS, and CD58.
- CD4+ T cell:** Interacts with MHC II, CD70, CD27, CD160, HVEM, BTLA, and LIGHT.
- NK cell:** Interacts with CD2 and CD137.
- regulatory T cell:** Interacts with PD-1 and PD-L1/2.

**Mottok and Steidl,
Current Opinion in Hematology 2015**

Histology subtypes of Hodgkin lymphoma

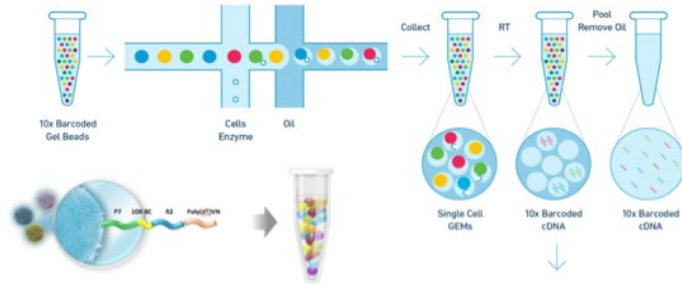


Study of the Hodgkin lymphoma tumor microenvironment

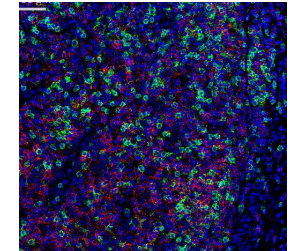
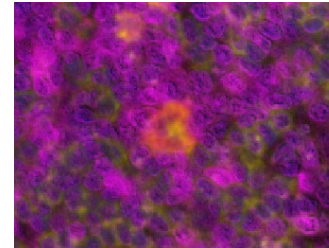


Single cell RNA sequencing (scRNA-seq)
(10X Genomics)

Multi-color immunohistochemistry (MC-IHC)
and **Imaging mass cytometry (IMC)**

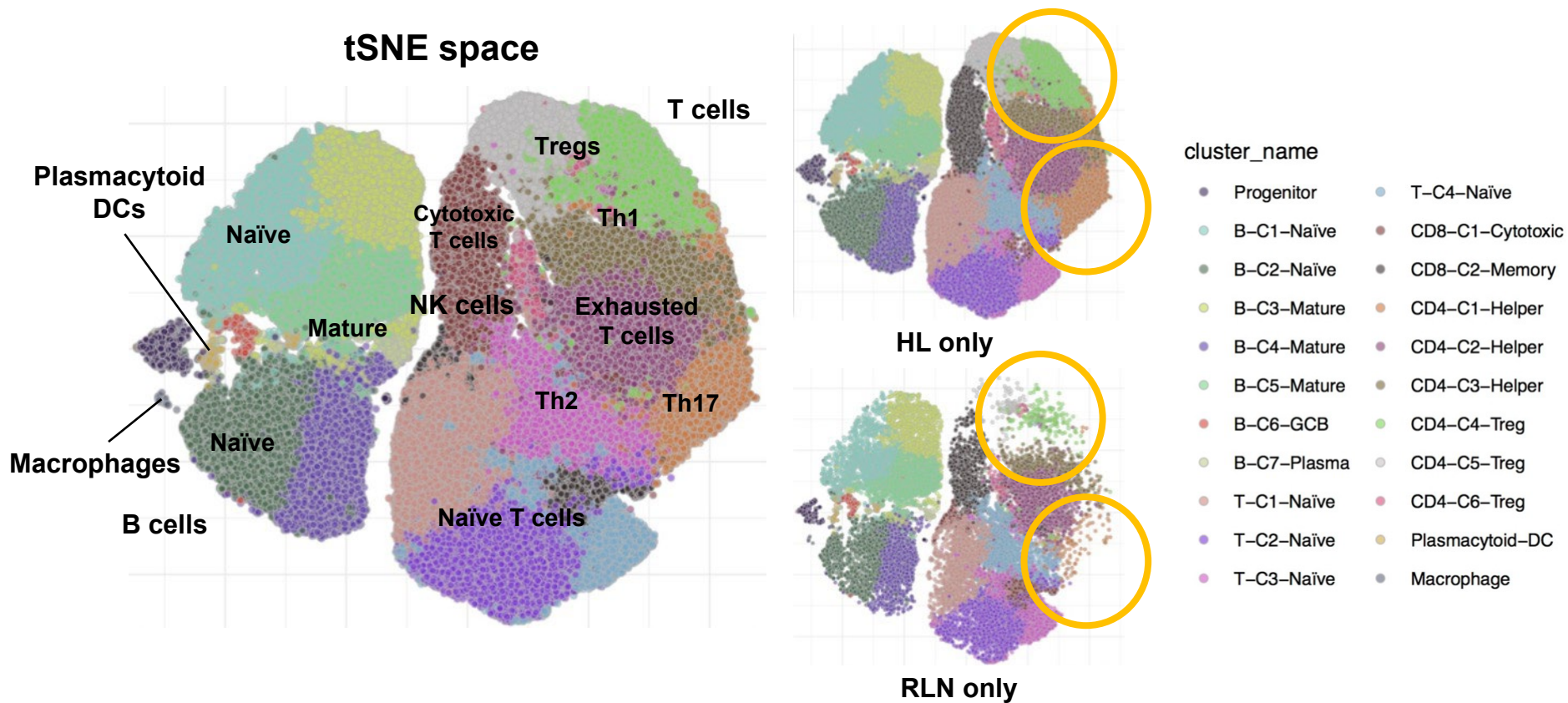


Total cells after filtering = **146,437**

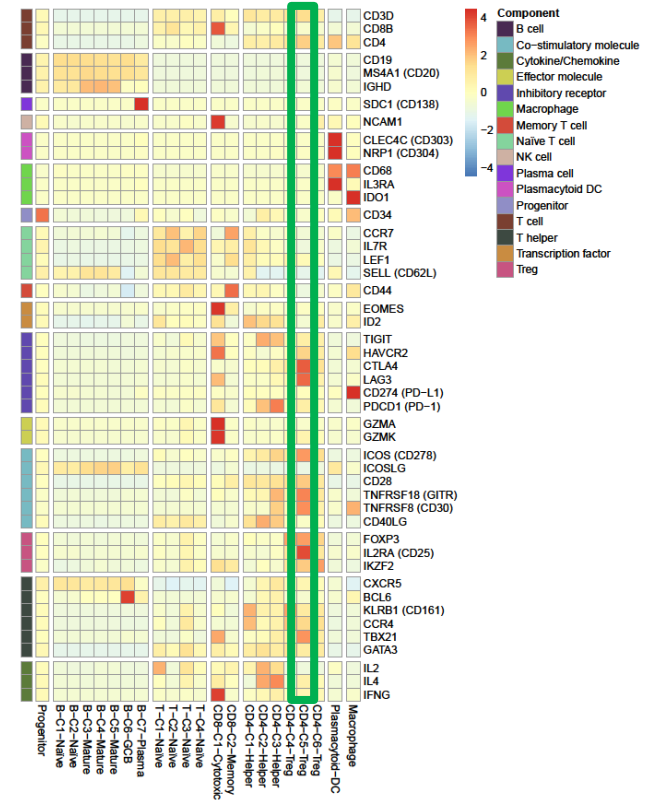
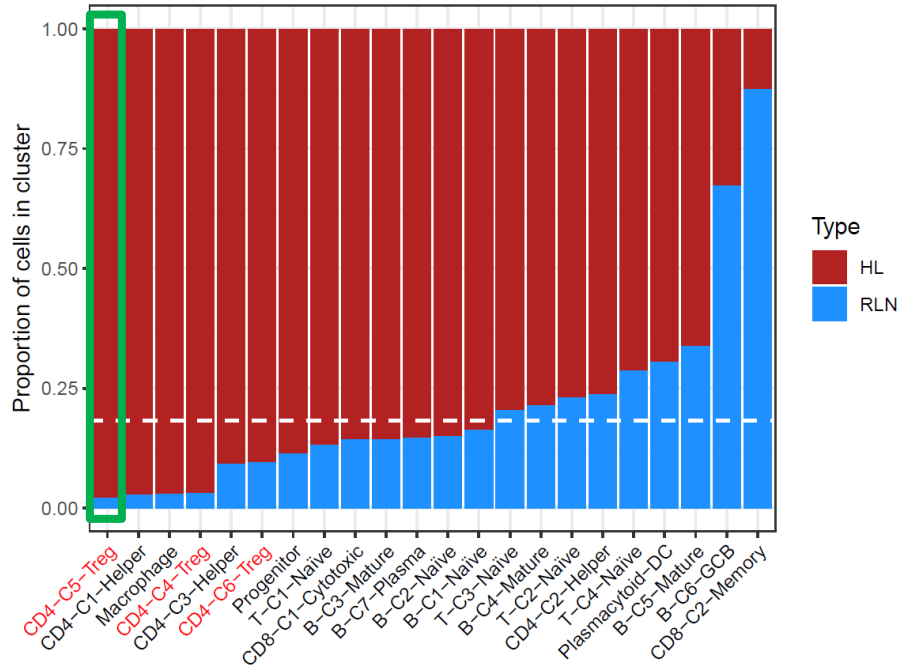


Visualization in the spatial context of the TME

Single cell RNAseq of classical Hodgkin lymphoma (n=22)



The cHL-specific Treg subsets



Previous Literature on LAG3 T cells

IMMUNOBIOLOGY

Expression of LAG-3 by tumor-infiltrating lymphocytes is coincident with the suppression of latent membrane antigen-specific CD8⁺ T-cell function in Hodgkin lymphoma patients

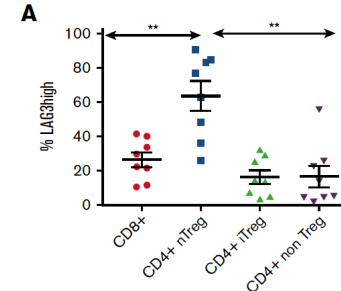
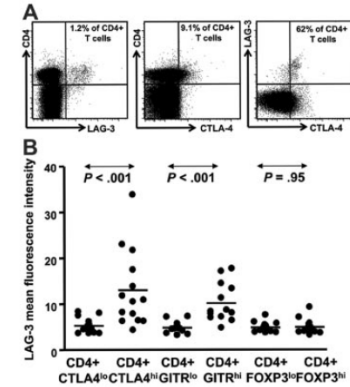
Maheer K. Gandhi, Eleanore Lambley, Jaikumar Duraiswamy, Ujjwal Dua, Corey Smith, Suzanne Elliott, Devinder Gill, Paula Marlton, John Seymour, and Rajiv Khanna

REGULAR ARTICLE

blood advances

LAG3: a novel immune checkpoint expressed by multiple lymphocyte subsets in diffuse large B-cell lymphoma

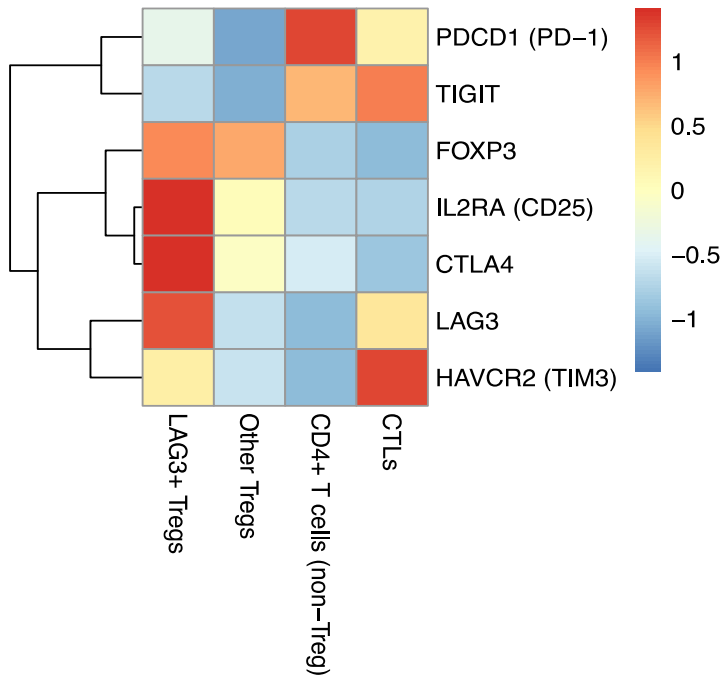
Colm Keane,^{1,2} Soi C. Law,¹ Clare Gould,³ Simone Birch,⁴ Muhammed B. Sabdia,¹ Lilia Merida de Long,¹ Gayathri Thillaiyampalam,³ Emad Abro,² Joshua W. Tobin,¹ Xiaohong Tan,⁵ Zijun Y. Xu-Monette,⁵ Ken H. Young,⁵ Grace Gifford,^{6,7} Sara Gabreilli,^{6,7} William S. Stevenson,^{6,7} Anthony Gill,⁸ Dipti Talaulikar,^{9,10} Sanjiv Jain,^{9,10} Annette Hernandez,⁴ Sarah-Jane Halliday,⁴ Robert Bird,^{2,4} Donna Cross,⁴ Mark Hertzberg,¹¹ and Maheer K. Gandhi^{1,2}



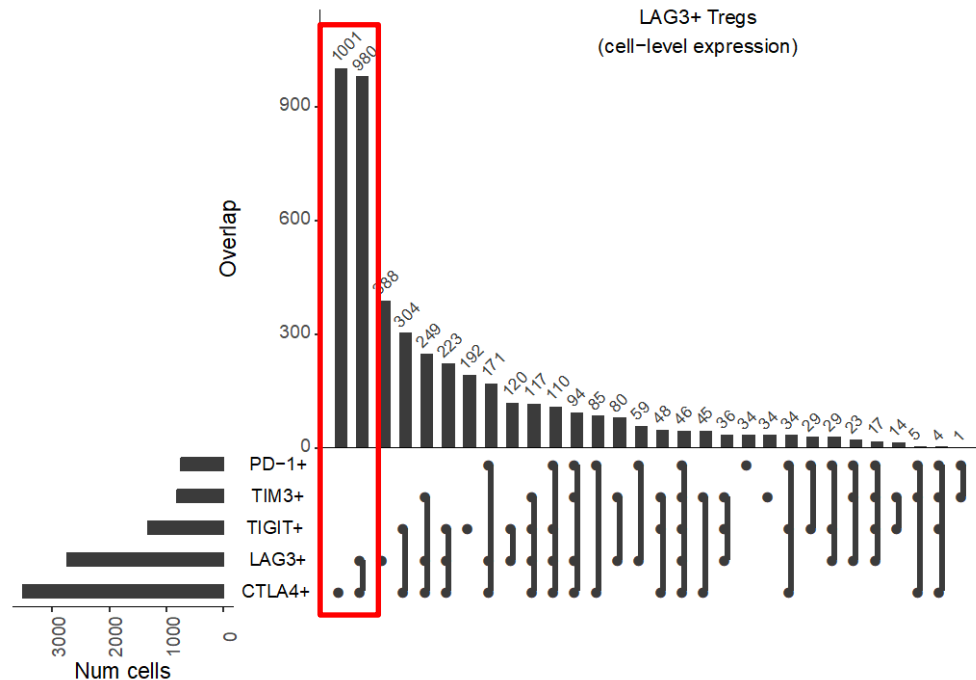
Gandhi et al, Blood 2006
Kaene et al, Blood Advances 2020

Co-expression patterns of inhibitory markers

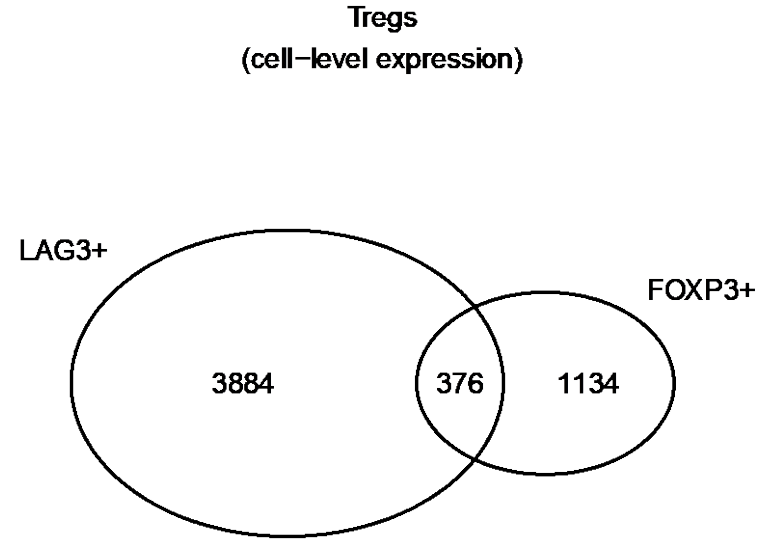
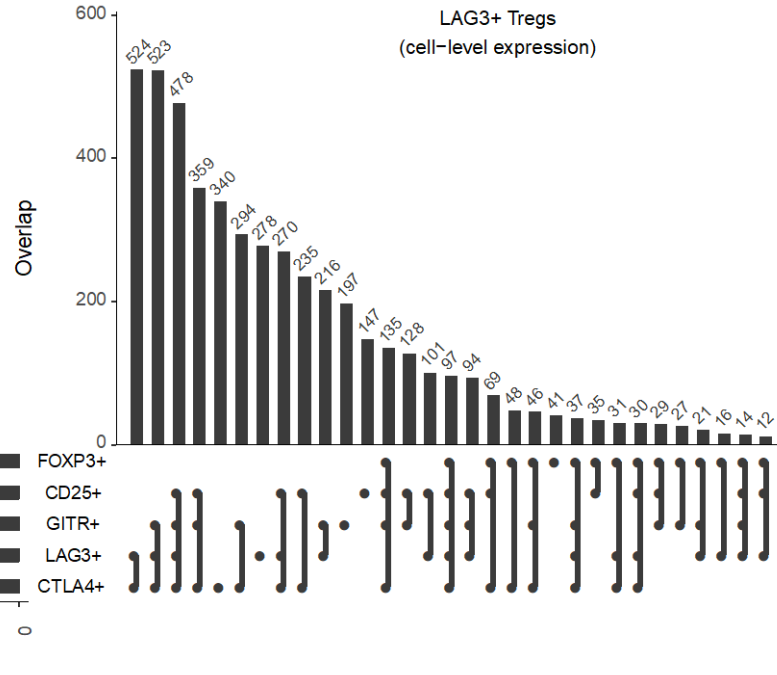
Cluster level



Single cell level



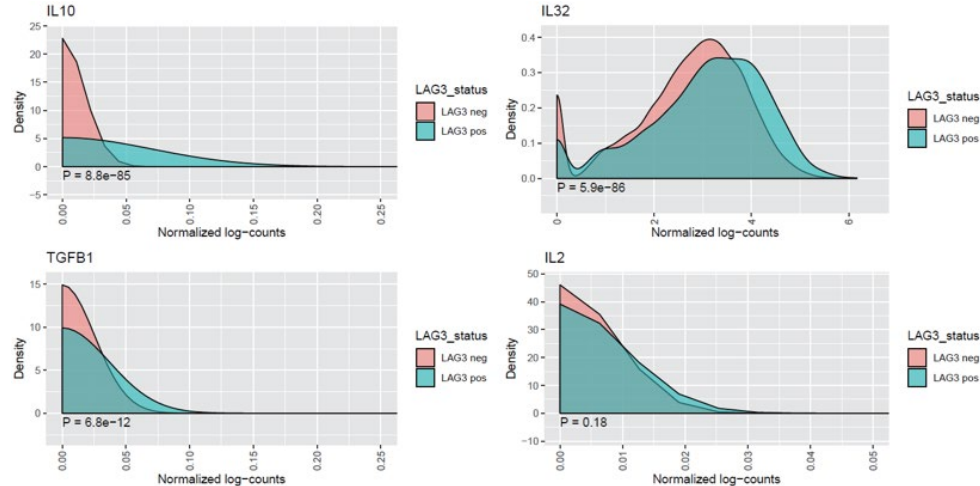
Co-expression patterns of Treg markers (single cell level)



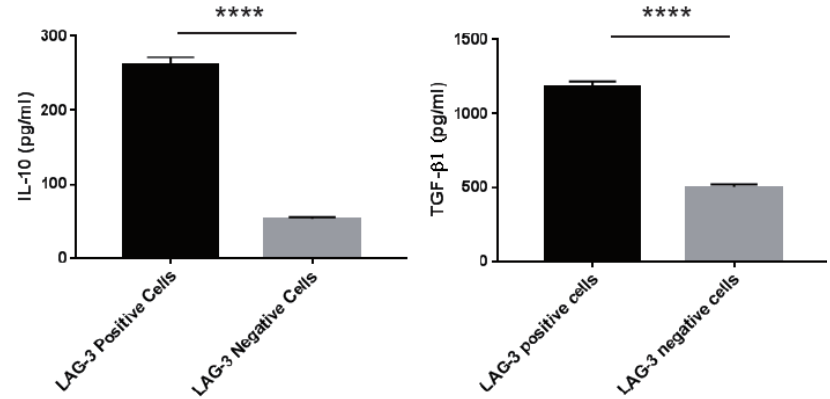
- LAG3 and FOXP3 expression is mostly mutually exclusive
- Cellular phenotype is consistent with type 1 regulatory (Tr1) T cells

Cytokine co-expression in LAG3+ T cells

Primary HL biopsies (10X data)

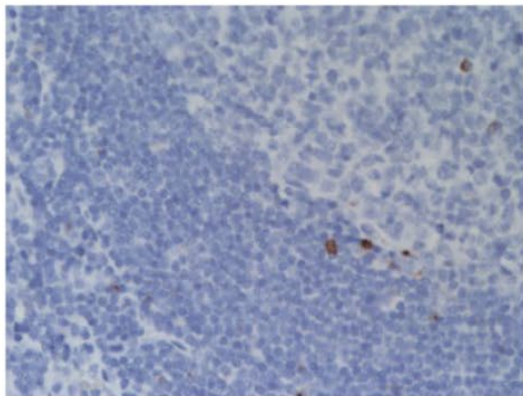


In vitro induced LAG3+ cells (L1236 supernatant transfer)

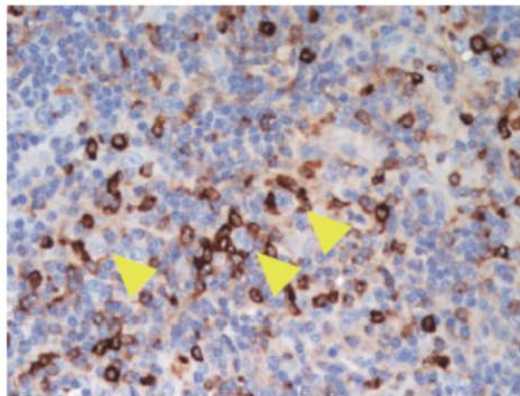


LAG3+ T cells had higher expression of immunosuppressive cytokines.

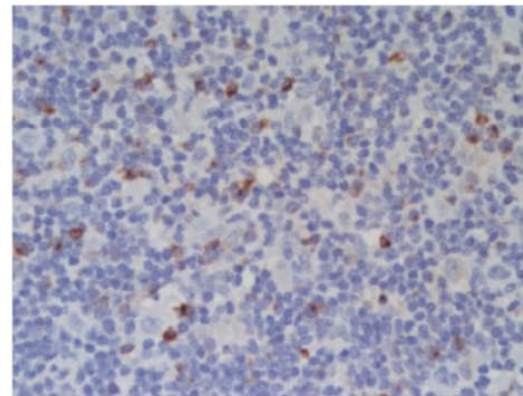
LAG-3 single IHC staining



RLN



HL surrounded

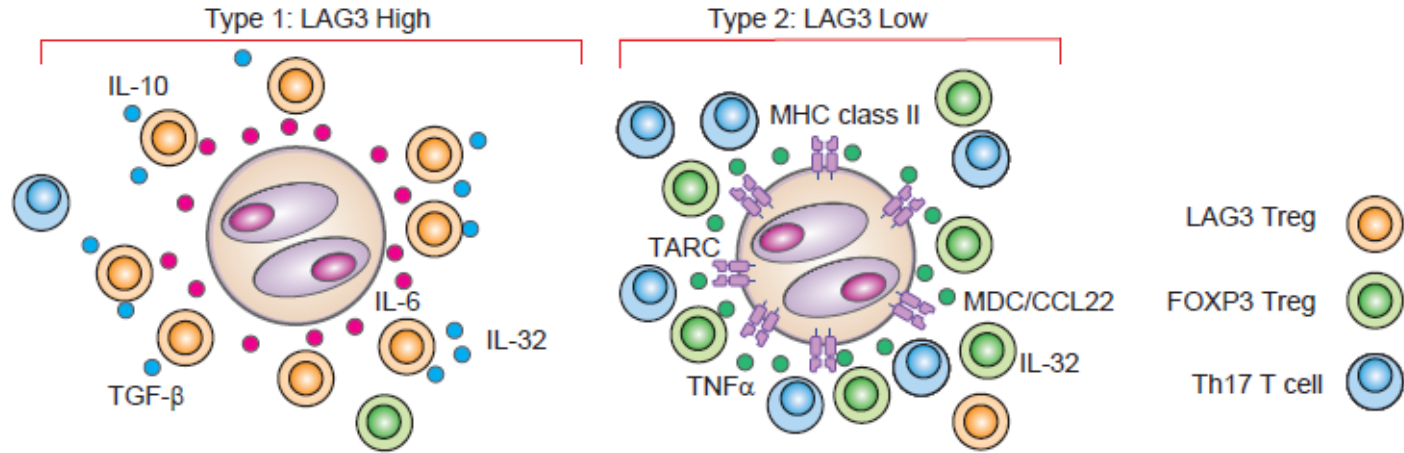


HL non-surrounded

- cHL cases have **more LAG3+ cells** than RLN
- In some cHL cases, LAG3+ cells are located **surrounding HRS cells**



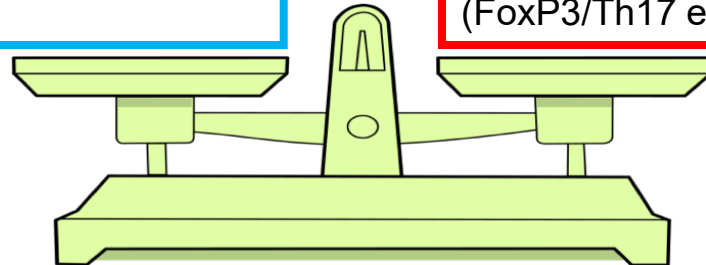
Subgroups based on tumor microenvironment composition in cHL



“Mediated immunosuppression” through induced regulatory cells (LAG-3-positive Tr-1 cells)

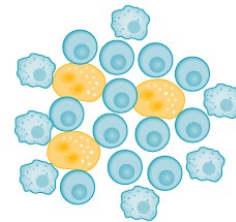
“Inflammatory HRS cell support” through natural Tregs and T-helper cells (FoxP3/Th17 enriched environments)

LAG3/CTLA antibodies ?

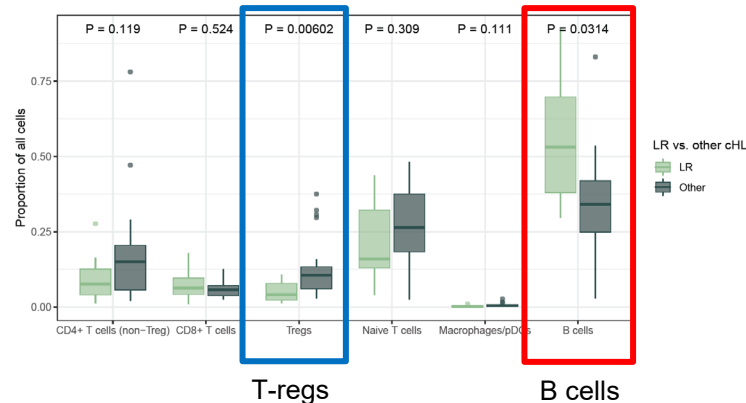
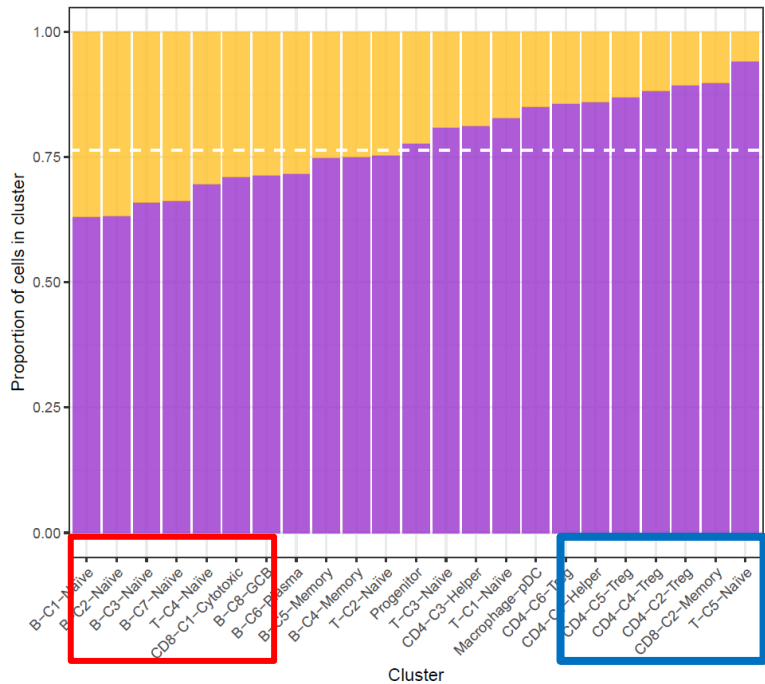


PD-1 blockade ?

Lymphocyte-rich Hodgkin lymphoma (n=8)



Significant differences in microenvironment composition between lymphocyte-rich and other subtypes

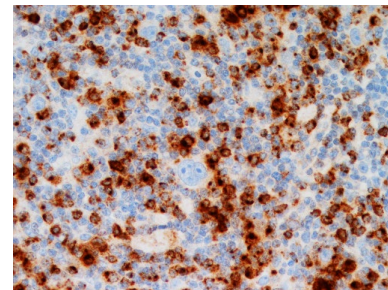


B cell phenotype:

- Naïve: CD27-IgD+ (unswitched)
- High CXCR5+ expression

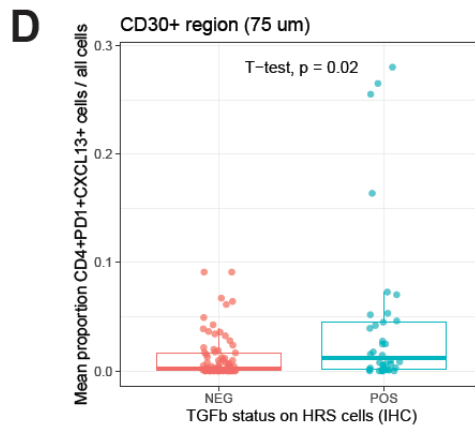
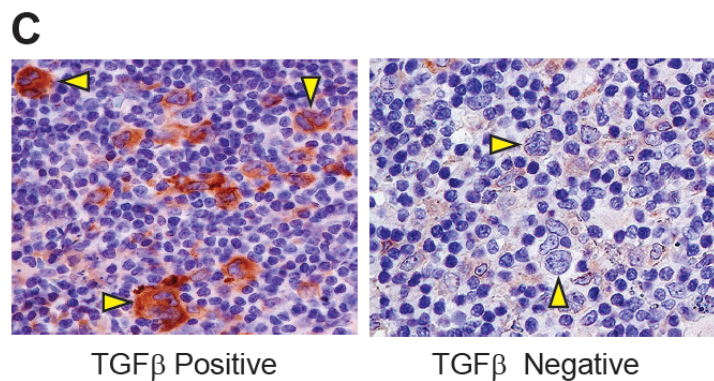
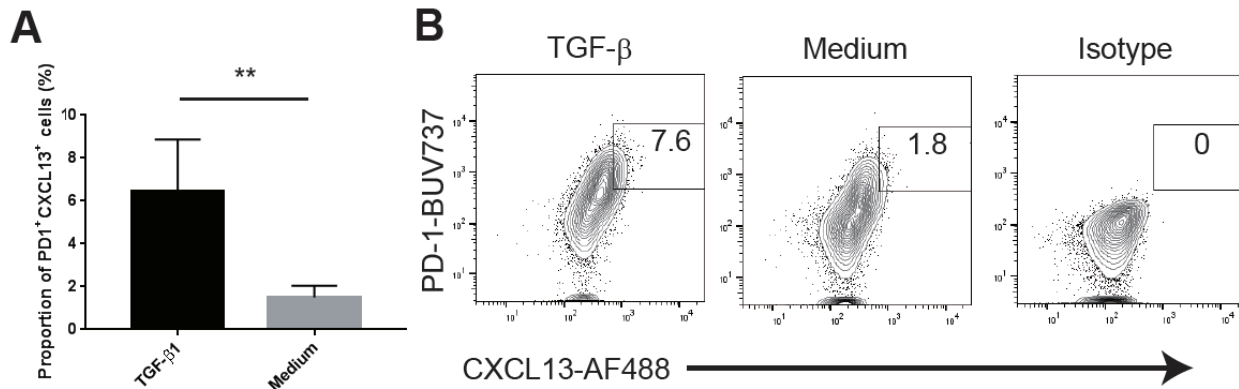
Aberrant 'TFH cell' phenotype:

- CXCL13+ ICOS+ PD1+ BCL6+

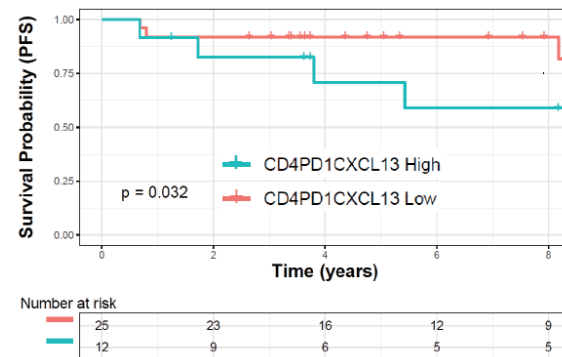


CXCL13 IHC

PD1+CXCL13+ T cells are induced by TGF β

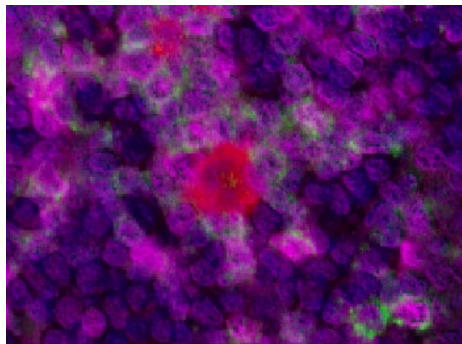


Progression-free survival In LR-CHL



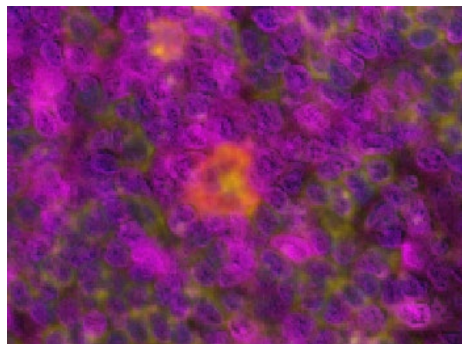
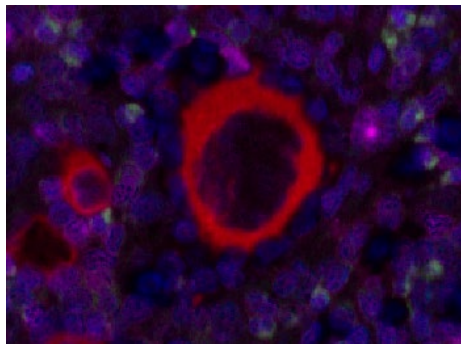
MC-IHC revealed CXCL13+ CD4 T cells surrounding HRS cells

LRCHL

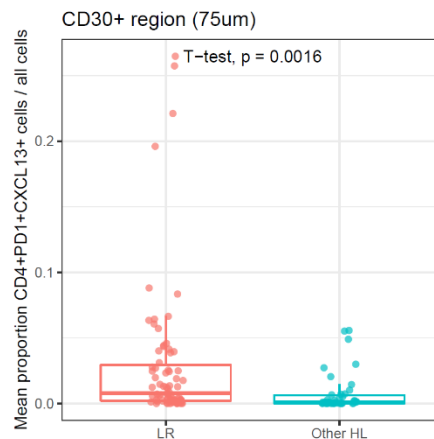
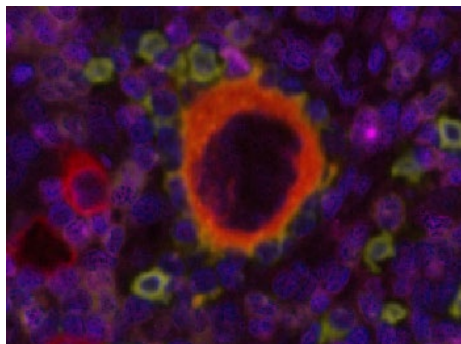


CD30 (Red) / PD1 (Green) / CXCL13 (Magenta)

Other CHL

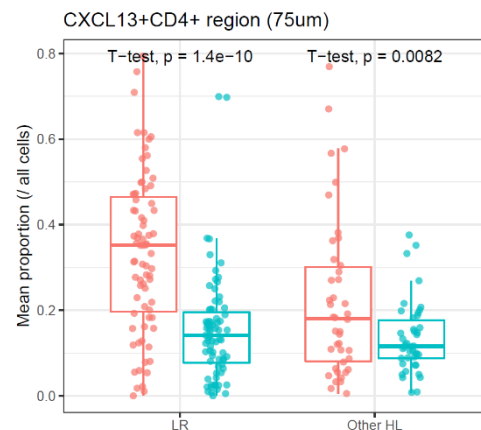


CD30 (Red) / CXCL13 (Magenta) / CXCR5 (yellow)



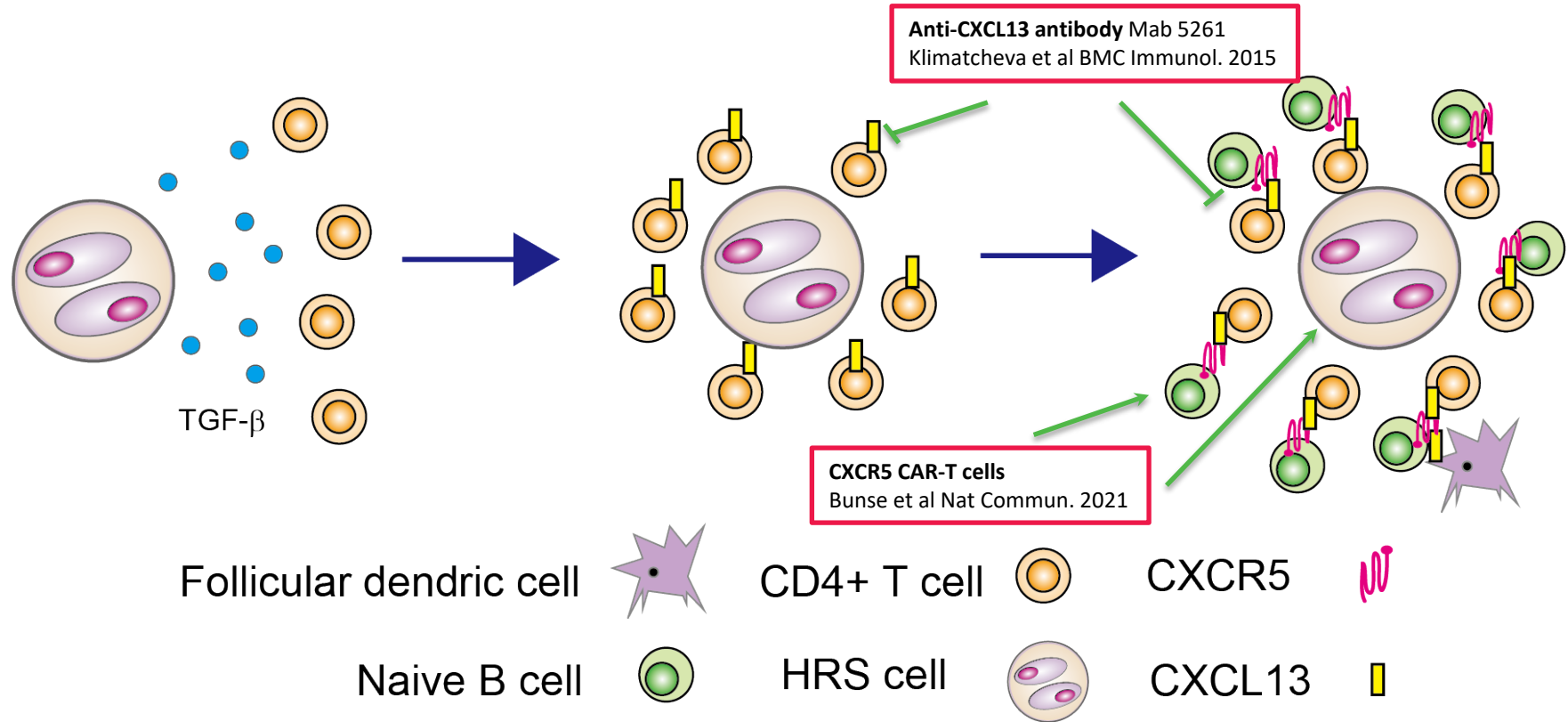
HRS cells (CD30+) are in close contact with CD4+CXCL13+ cells in LRCHL, but not other CHL

CD20+CXCR5+ cells are abundant in the region surrounding CXCL13+CD4+ cells



Collaboration with Brad Nelson, BC Cancer

Model for lymphocyte-rich Hodgkin lymphoma



Summary and conclusions

- Detailed **functional and spatial characteristics of immune cells** in the cHL microenvironment at single cell resolution.
- **LAG3+ T-cells** (consistent with a Tr1 phenotype) represents immuno-suppressive phenotype in cHL, particularly in cases with MHC class II negative HRS cells.
- LAG3 is a cancer **immuno-therapeutic target in ongoing clinical trials** in malignant lymphoma, including cHL.
- Lymphocyte-rich classic cHL is characterized by **CD4+ PD1+ CXCL13+ cells** (consistent with aberrant TFH cells) in close proximity to CXCR5+ B cells.
- Opportunity for **refinement of microenvironment-based classification** of cHL with implications for therapeutic decision making.



Canadian Cancer Society
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