B Cell Differentiation and Interaction with T cells

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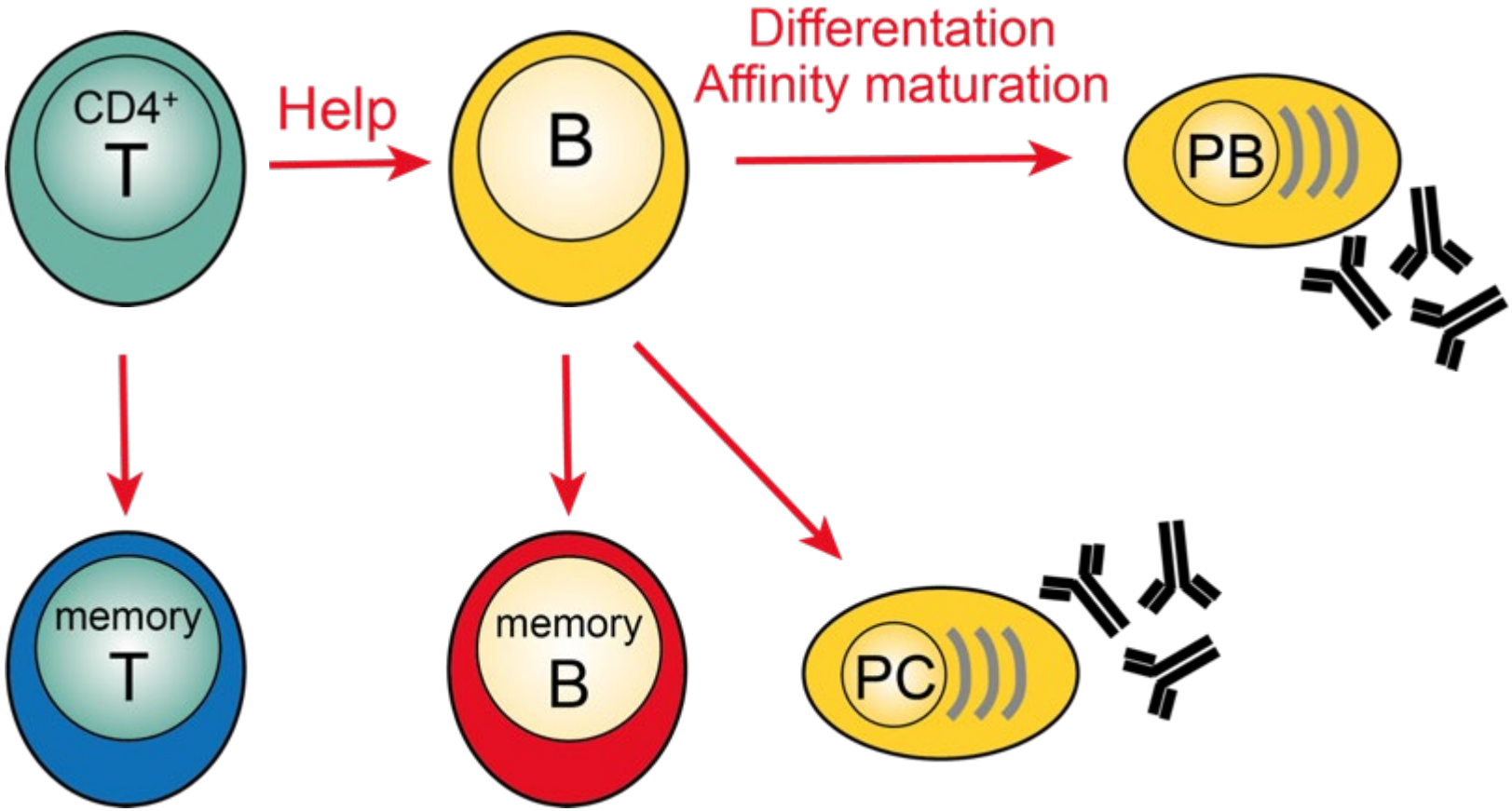
UK SH UNIVERSITÄTSKLINIKUM Schleswig-Holstein

DRFZ BERLIN Deutsches Rheuma-Forschungszentrum Ein Institut der Leibniz-Gemeinschaft

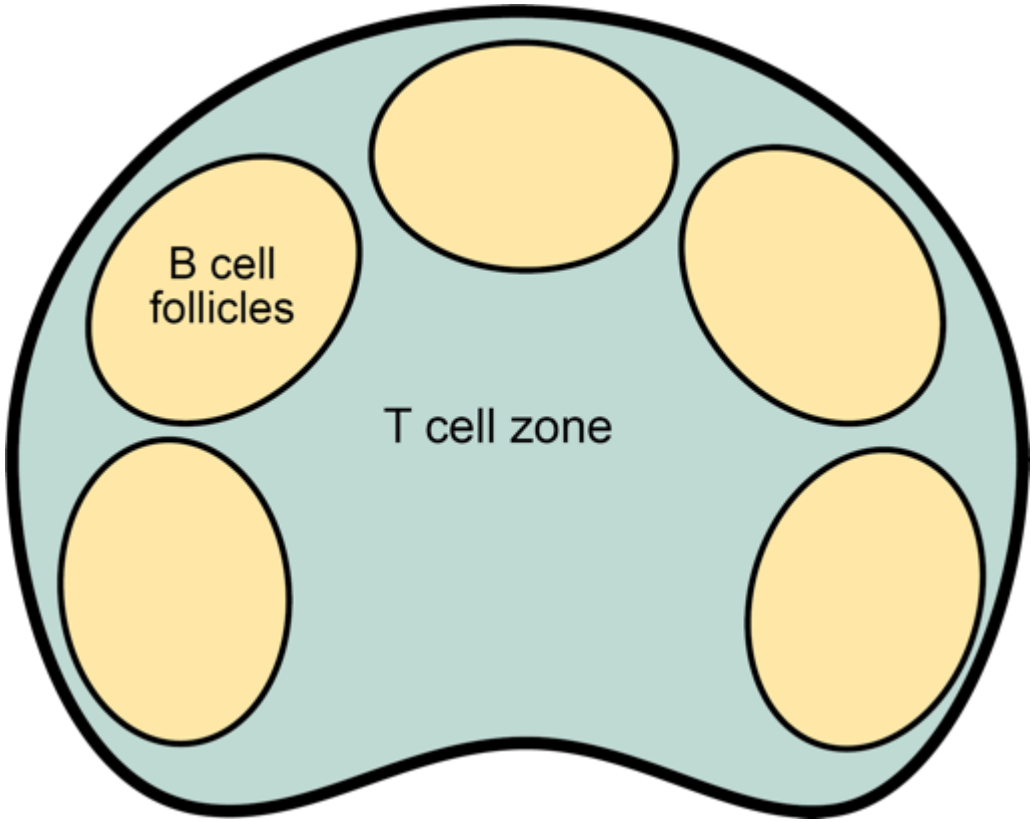
Leibniz WissenschaftsCampus Berlin CHRONISCHE ENTZÜNDUNG

ZIBI Center of Infection Biology and Immunity

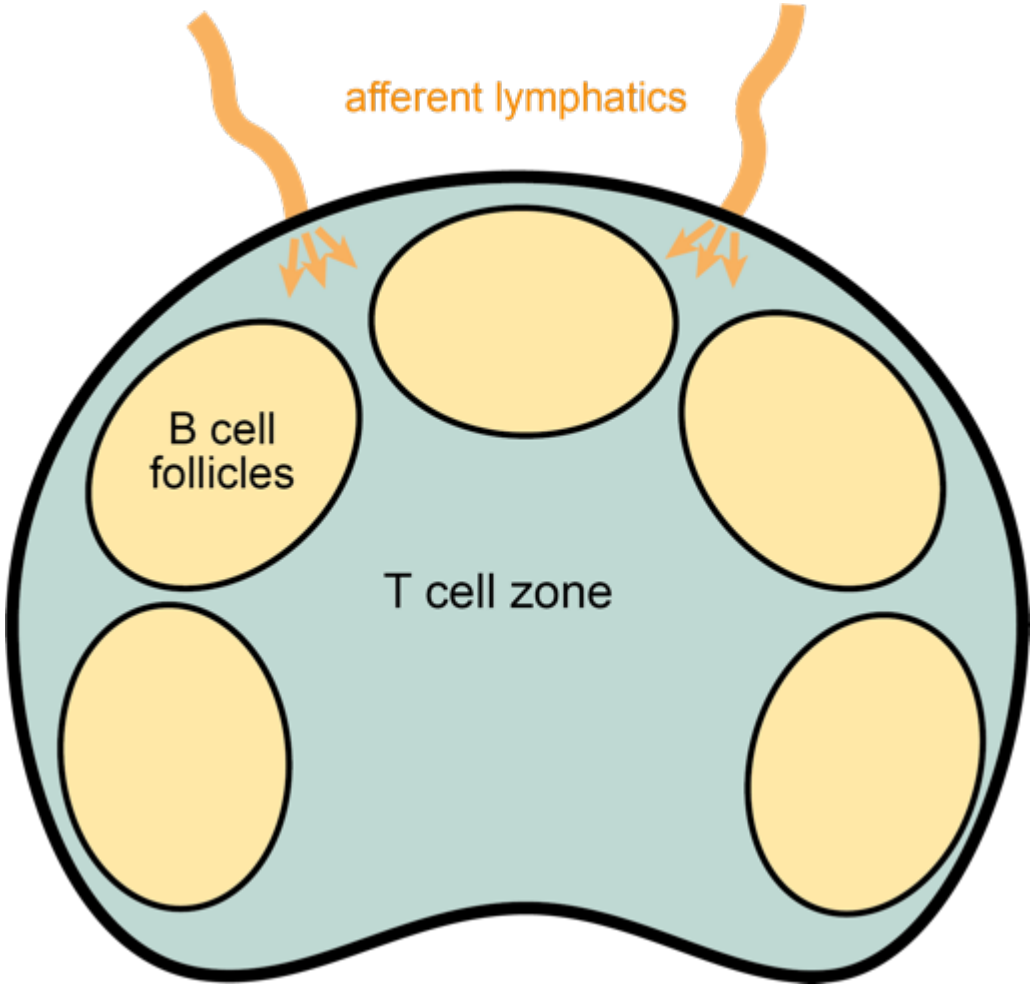
The adaptive immune system - Humoral immunity



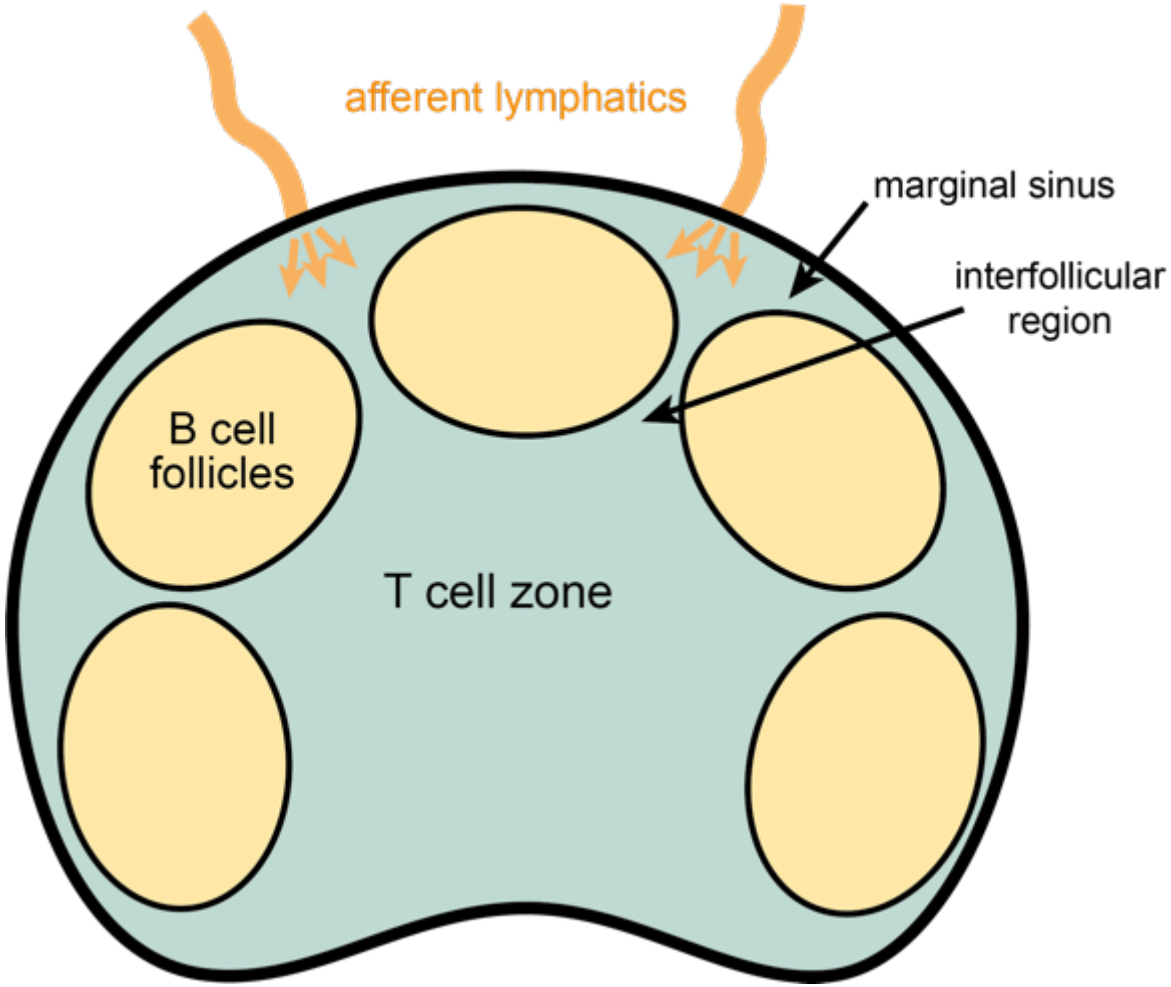
Secondary lymphoid organs as meeting point for T and B cells



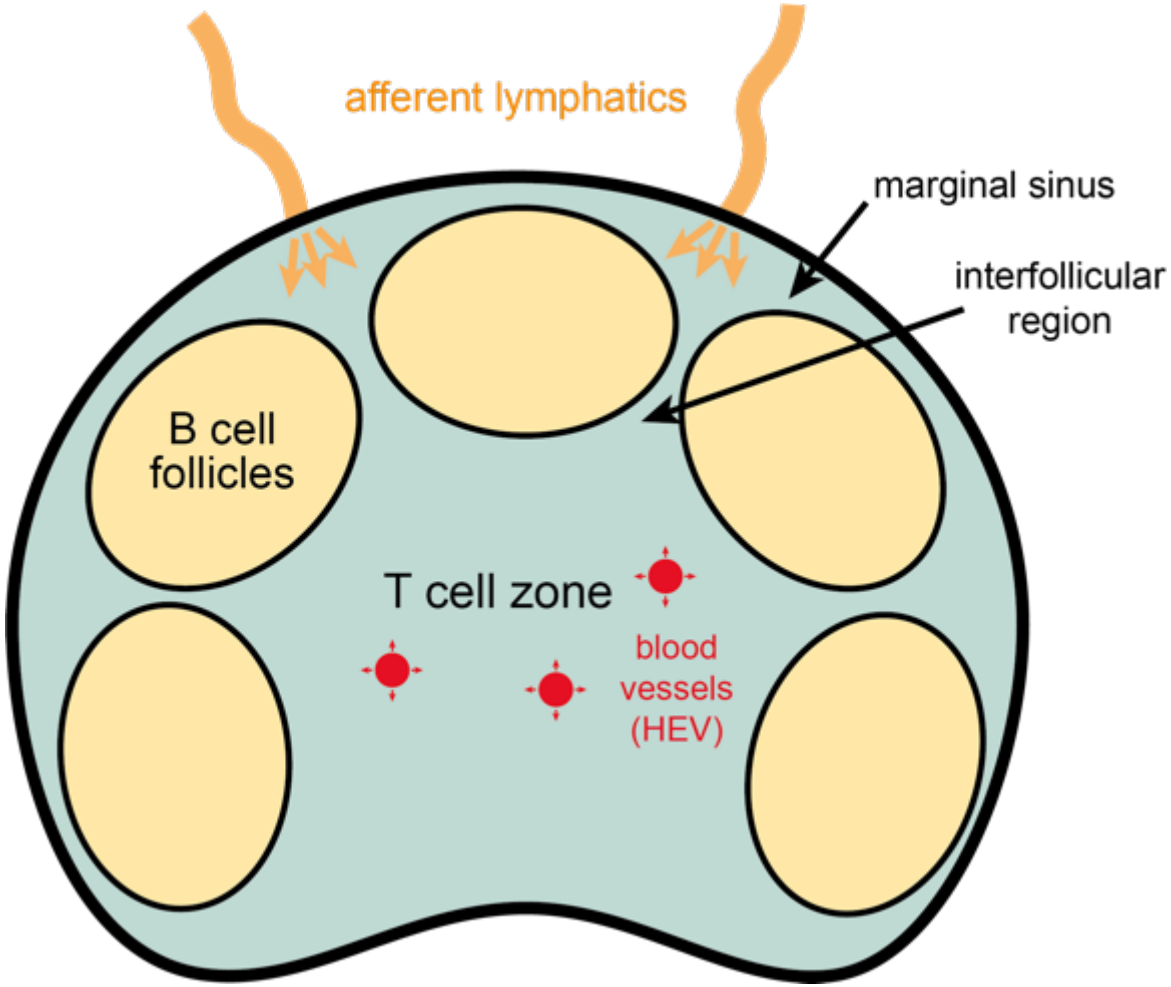
T and B cells enter the lymph node via afferent lymphatics ...



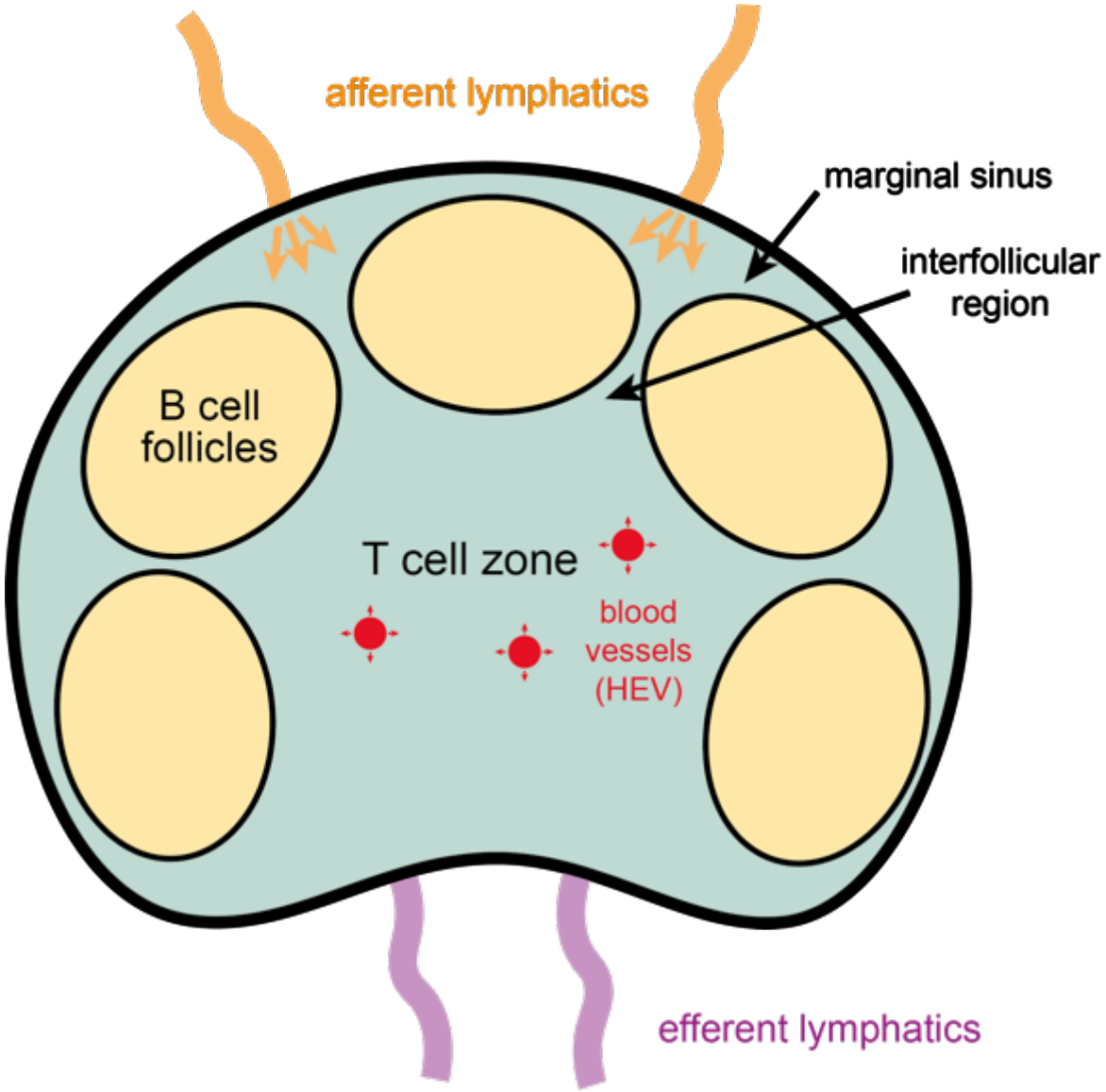
... and distrubute via the marginal sinus and interollicular regions



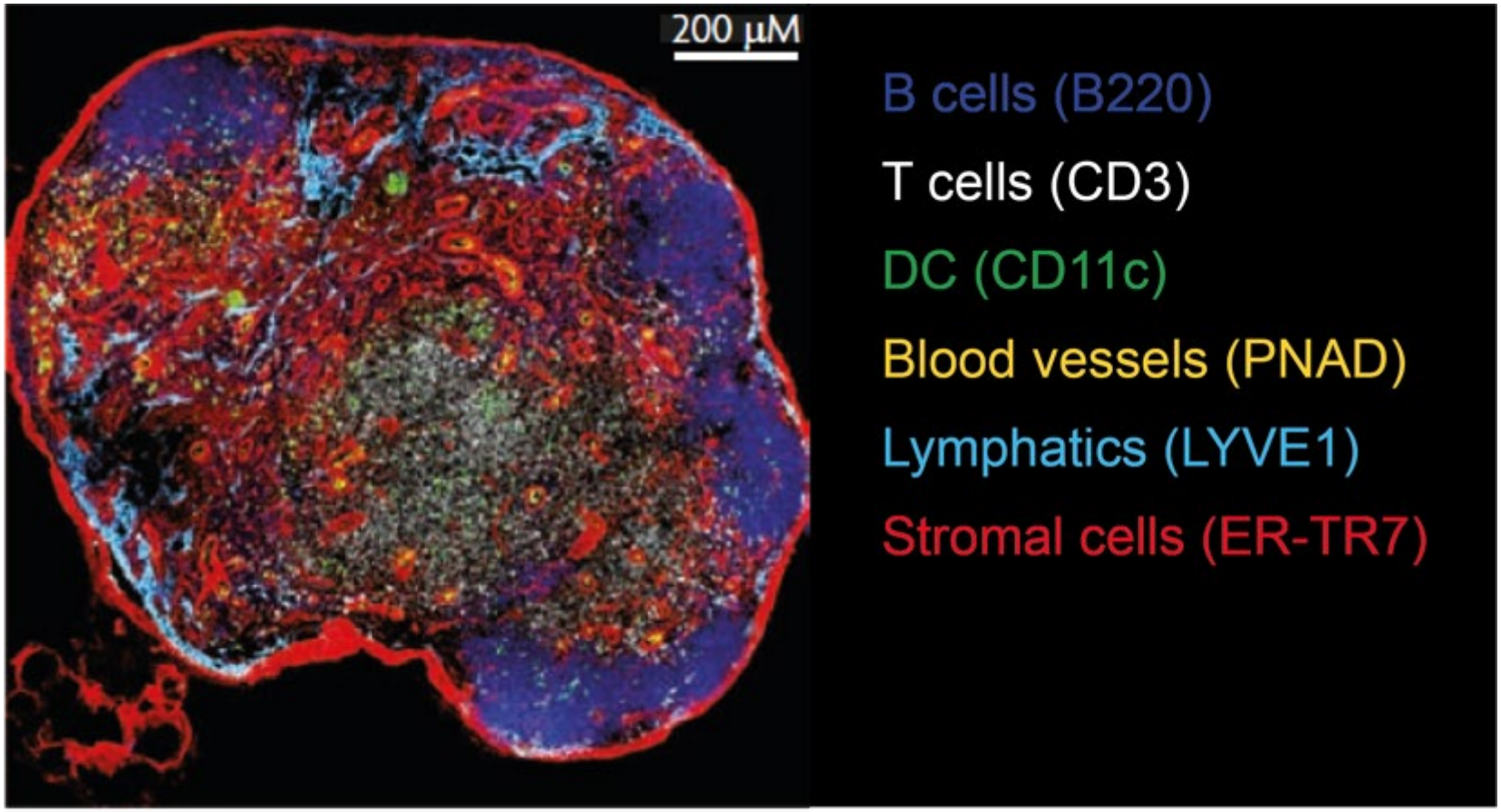
Alternatively, they can enter via the blood



They leave via medulla and efferent lymphatics

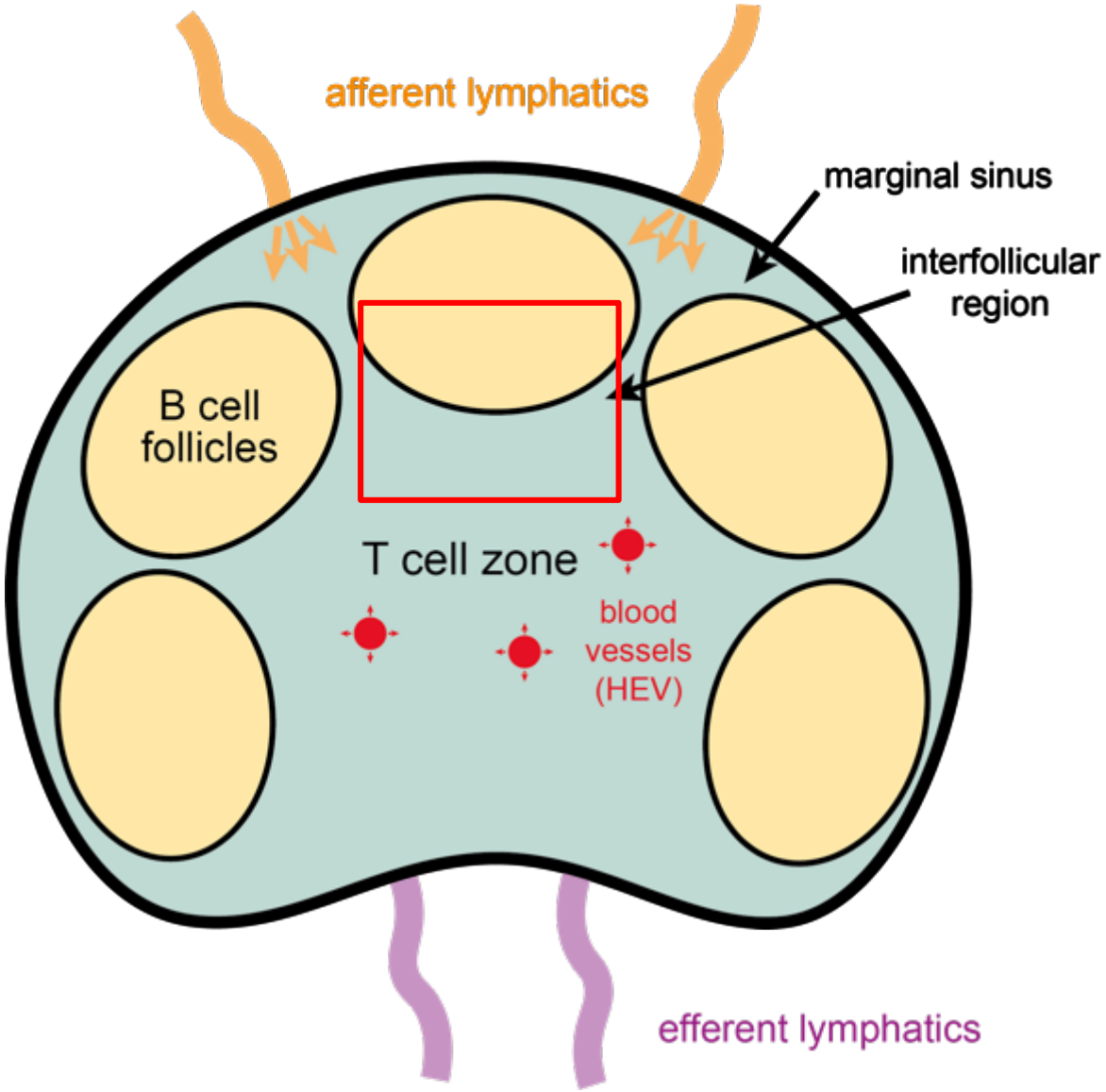


Additional cell types provide a unique micro environment

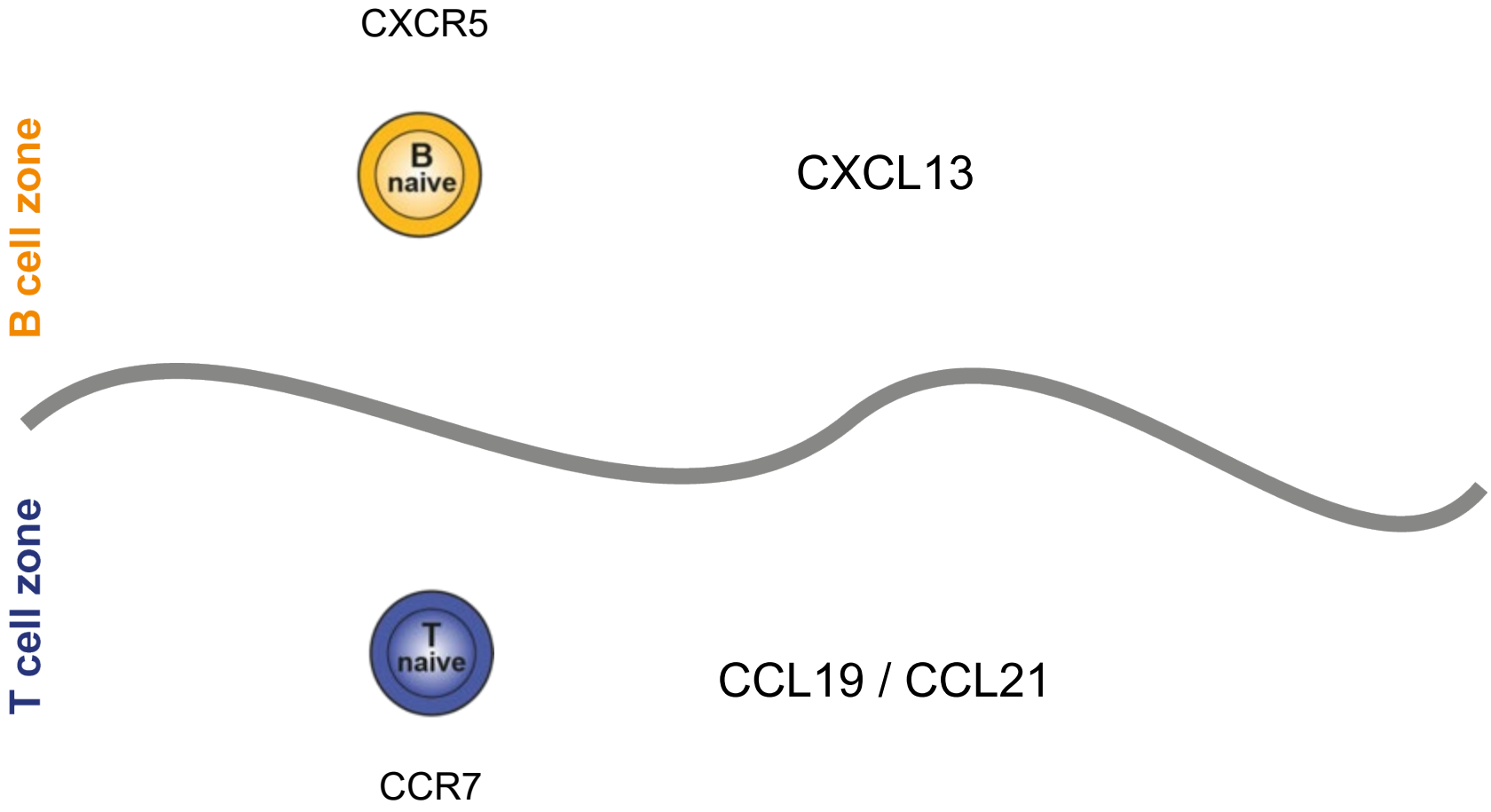


from: Mueller and Germain, Nat Rev Immunol (2009)

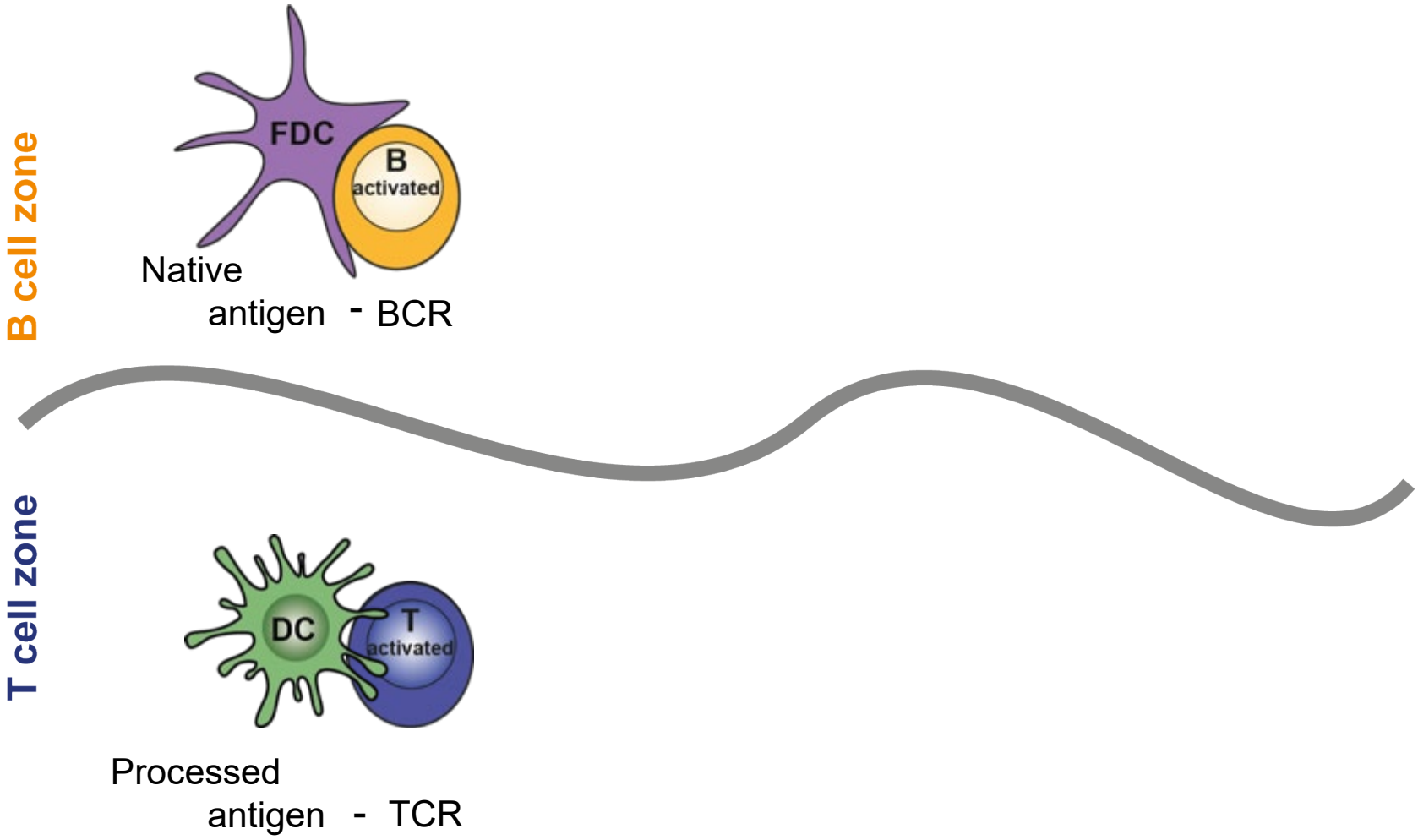
What happens during an antigen-specific immune response?



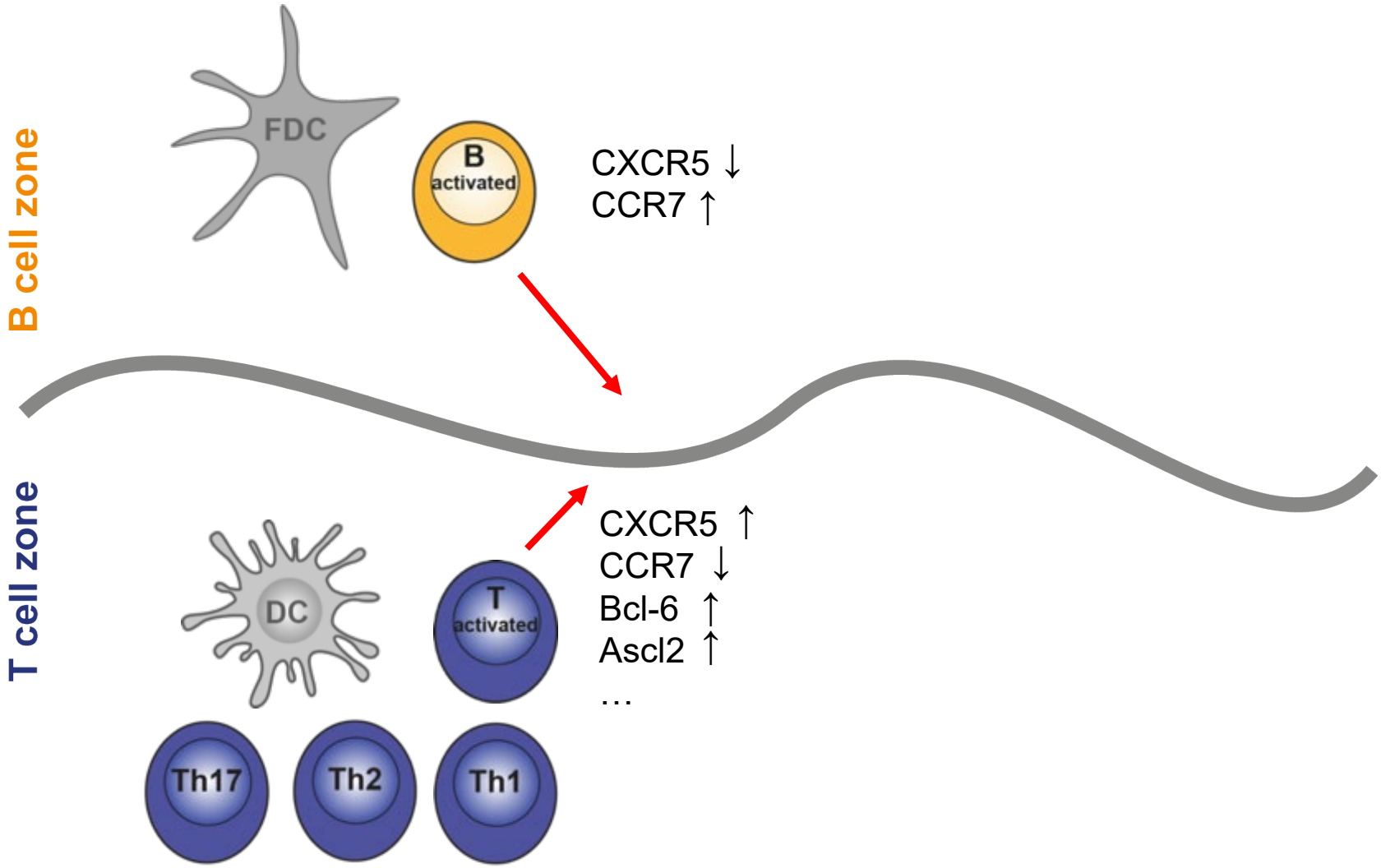
SLO provide a highly organized microenvironment for T/B interaction



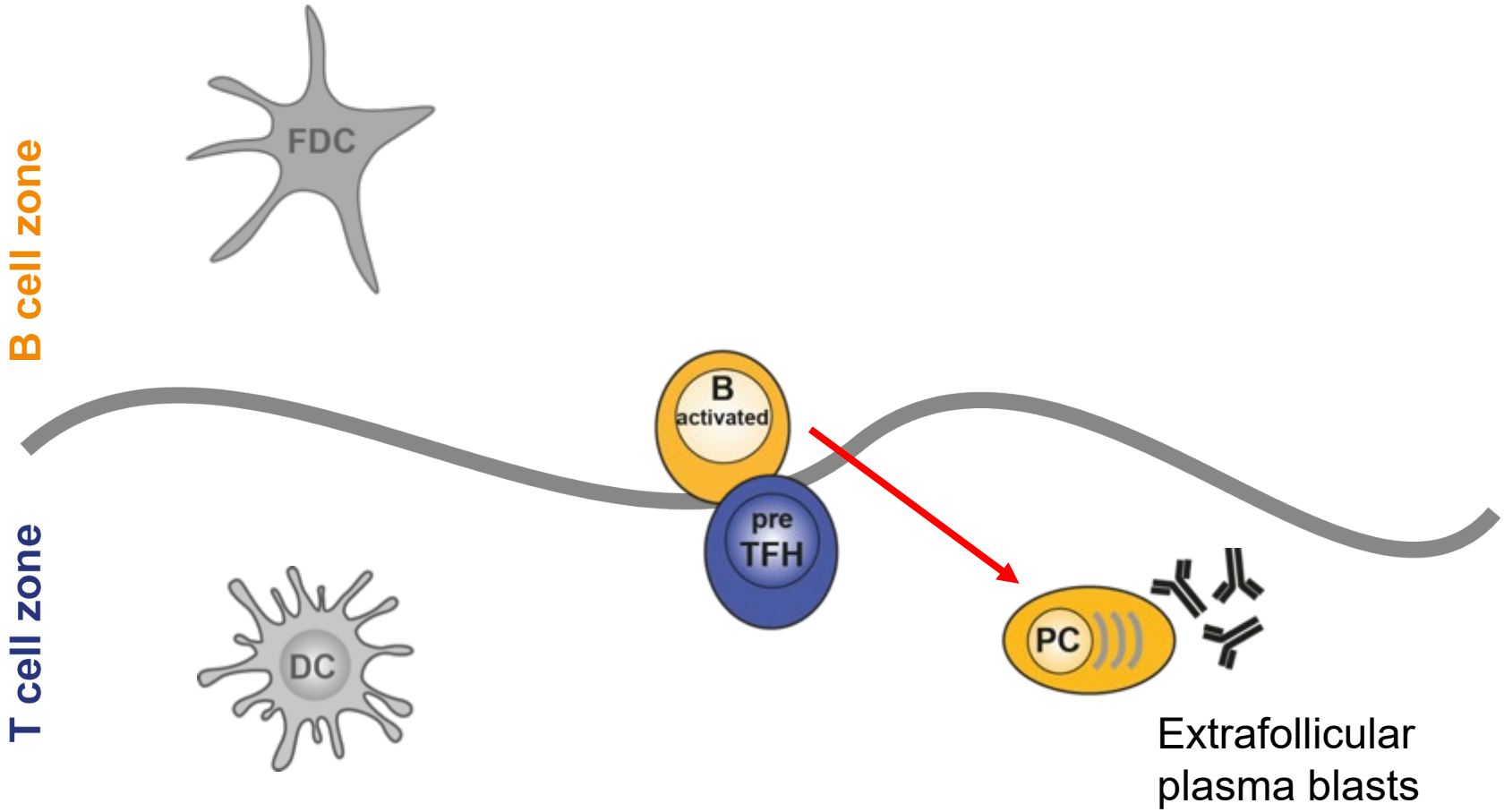
Antigen-specific T and B cells both recognize their antigen



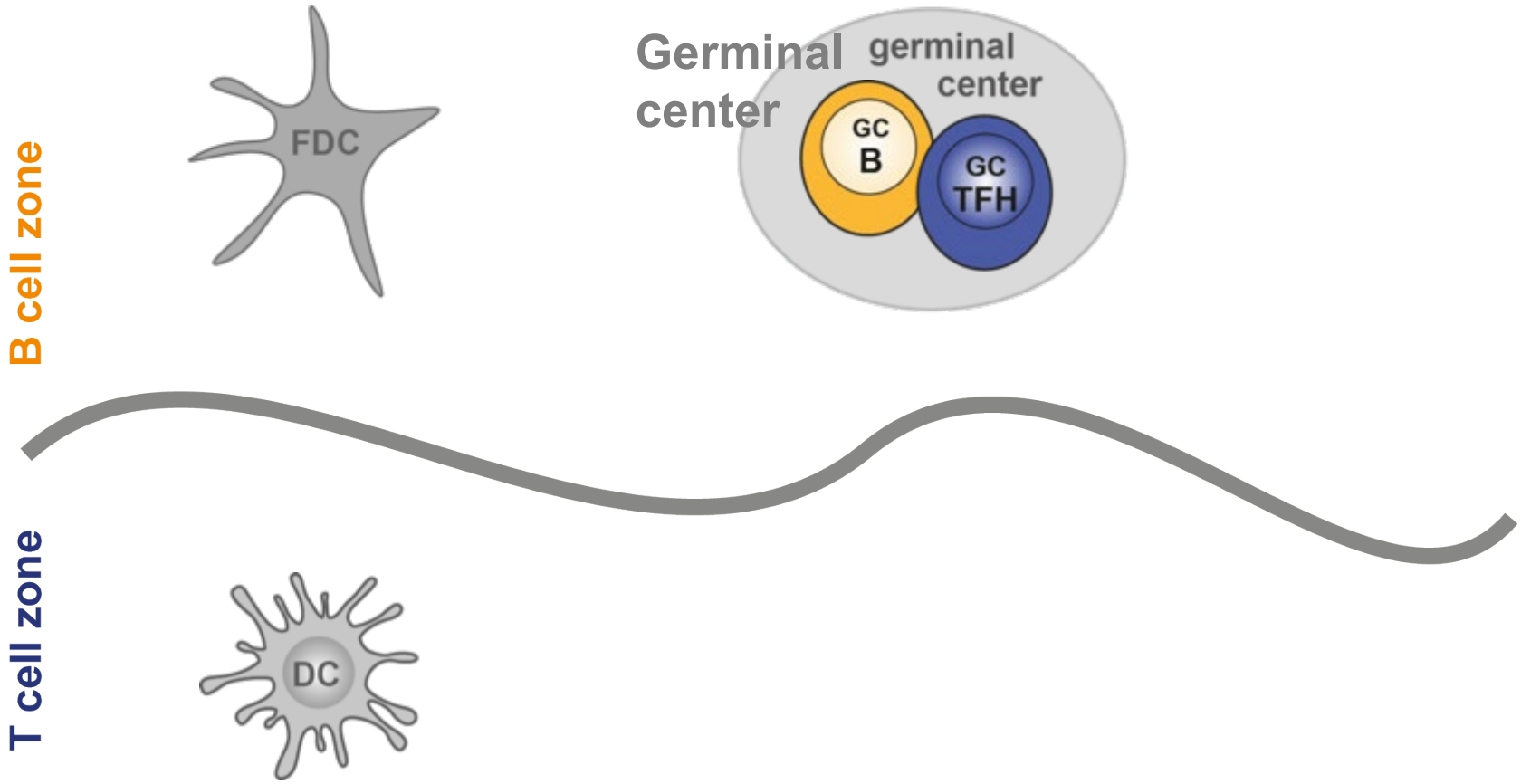
T cells can differentiate into different lineages



The subset of Tfh cells interacts with antigen-specific B cells



Tfh cells drive B cell differentiation in the germinal center



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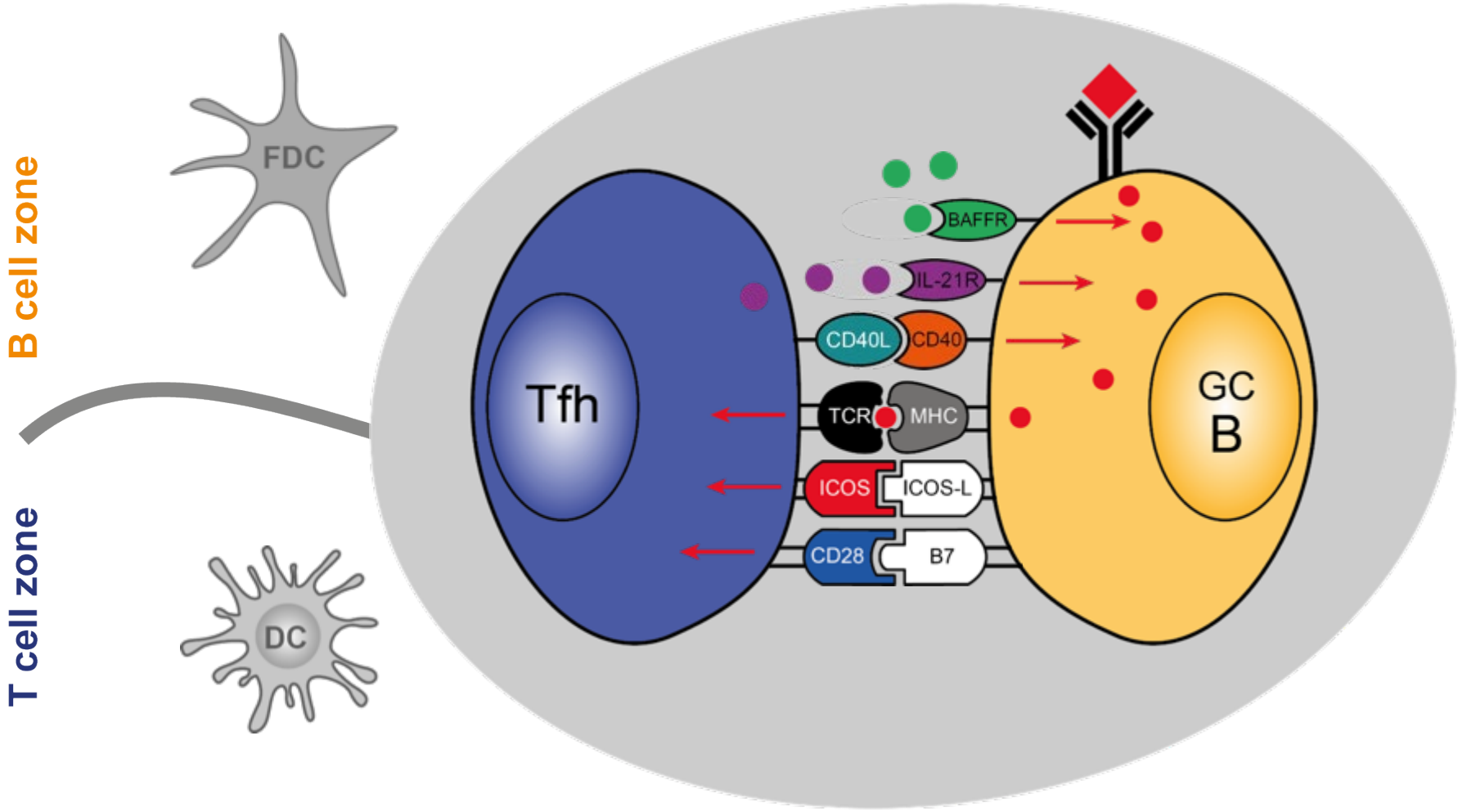
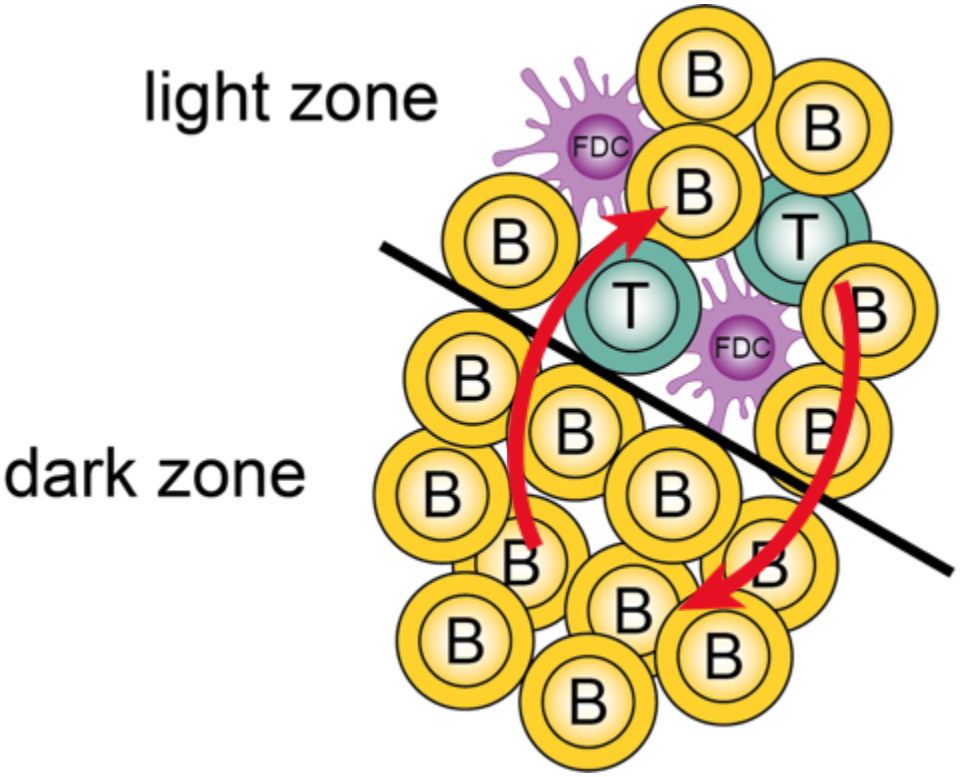
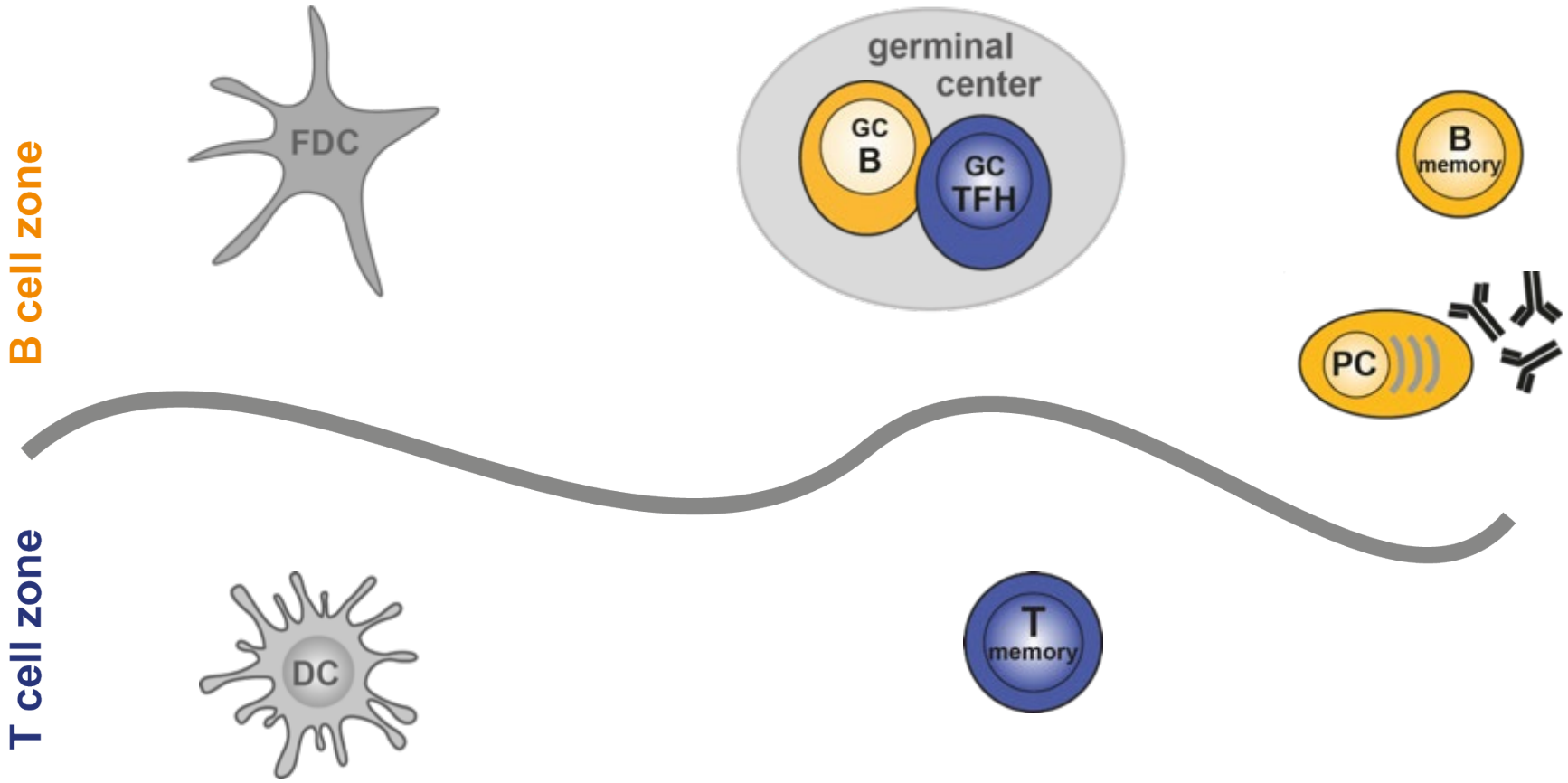


T cell help in the germinal center has to be strictly controlled

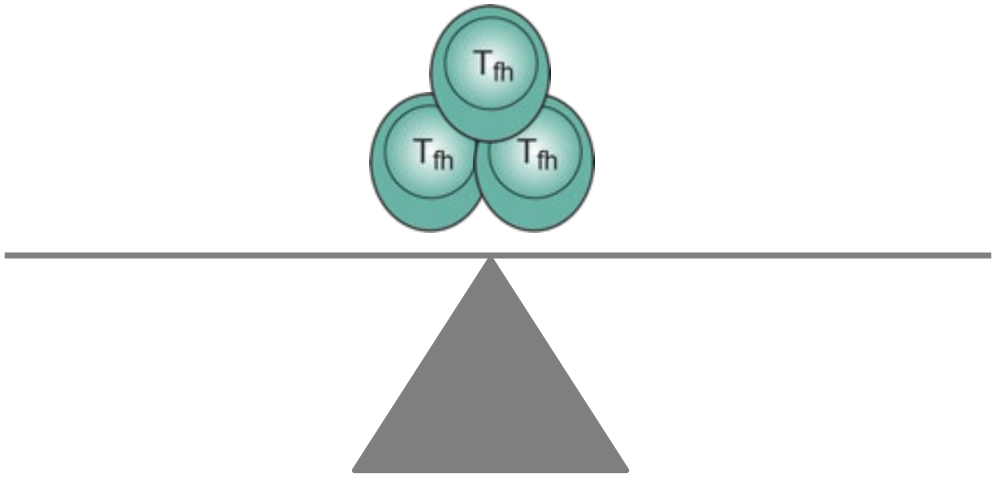


The GC reaction produces high-affinity memory B cells and PC



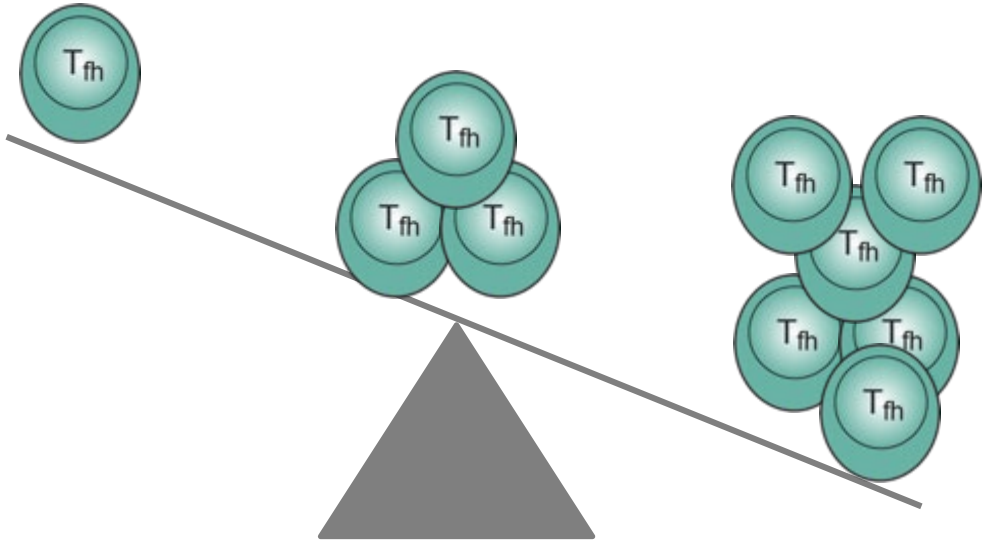
Tfh cells are critical regulators of immunity versus autoimmunity

Protection



Tfh cells are critical regulators of immunity versus autoimmunity

Immunodeficiency Protection Autoimmunity



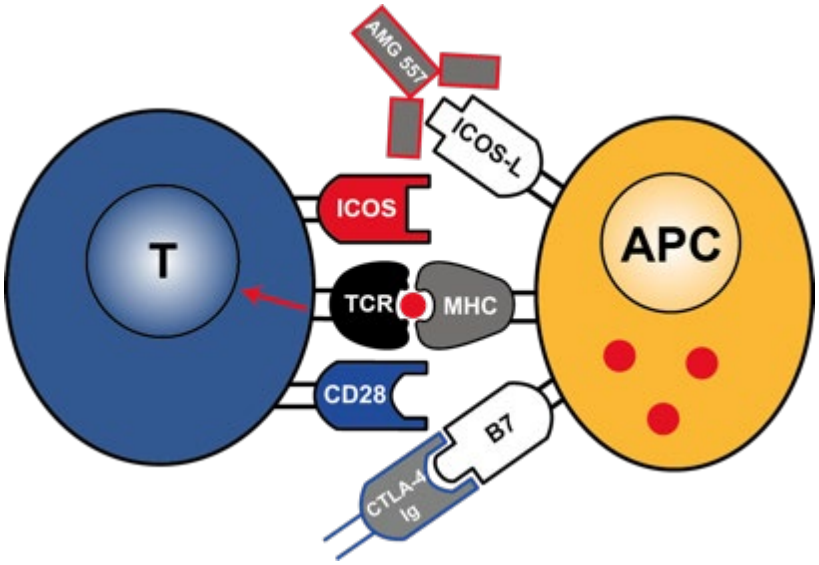
ICOS deficient patients
(CVID)

Rheumatoid arthritis
Systemic lupus erythematosus
Type I diabetes

Grimbacher, Hutloff et al. Nat Immunol 2003

Hutloff et al. Arthr Rheum 2004

Costimulation blockade as therapeutic target



Abatacept (Orencia™) Bristol-Myers-Squibb

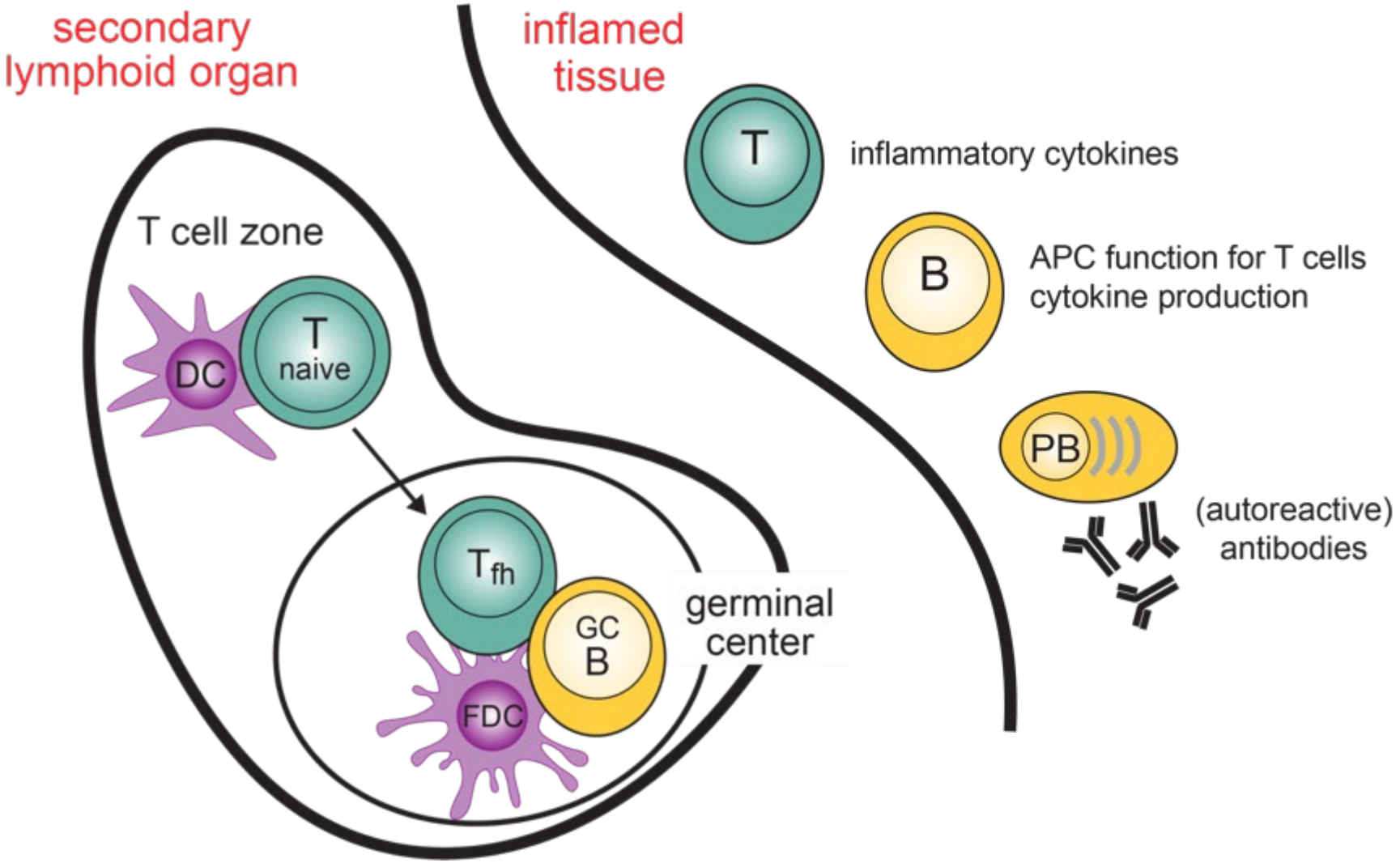
- CTLA-4-Ig fusion protein
- higher affinity to B7 than CD28
- blocks CD28 signaling
- approved for treatment of RA

Prezalumab (AMG 557) Amgen

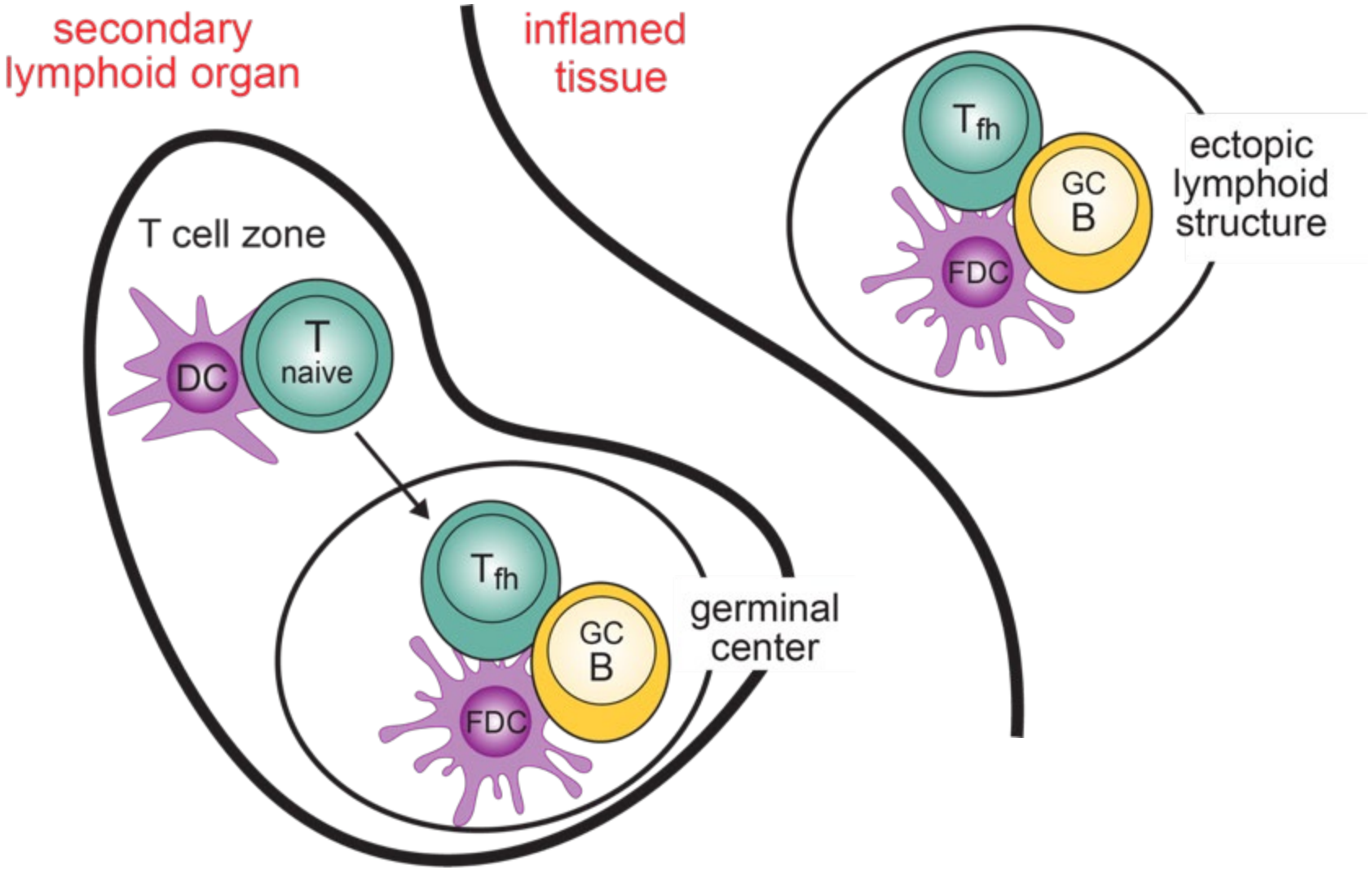
- fully human mAb against ICOS-L
- blocks ICOS signaling
- phase Ib study in patients with mild SLE sucessfully completed
- phase II study for lupus did not meet expectations

T cell / B cell cooperation in inflamed non-lymphoid tissues

T and B cell infiltrates are frequently found in inflamed tissues



Special case: Ectopic lymphoid structures (ELS)



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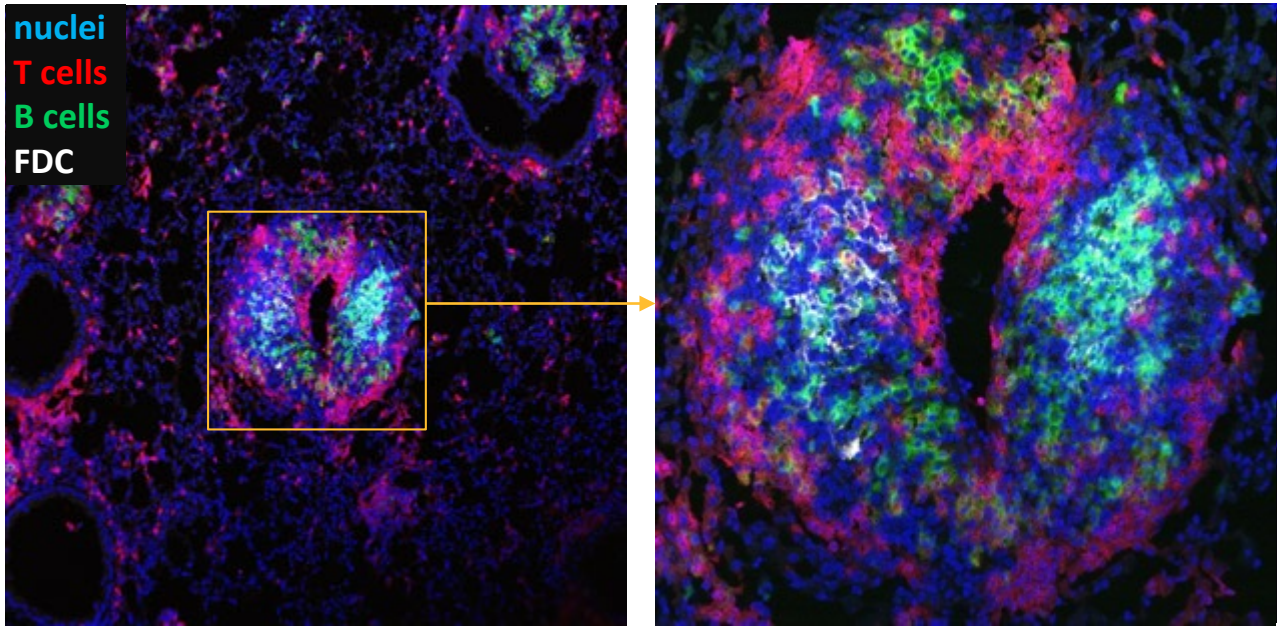


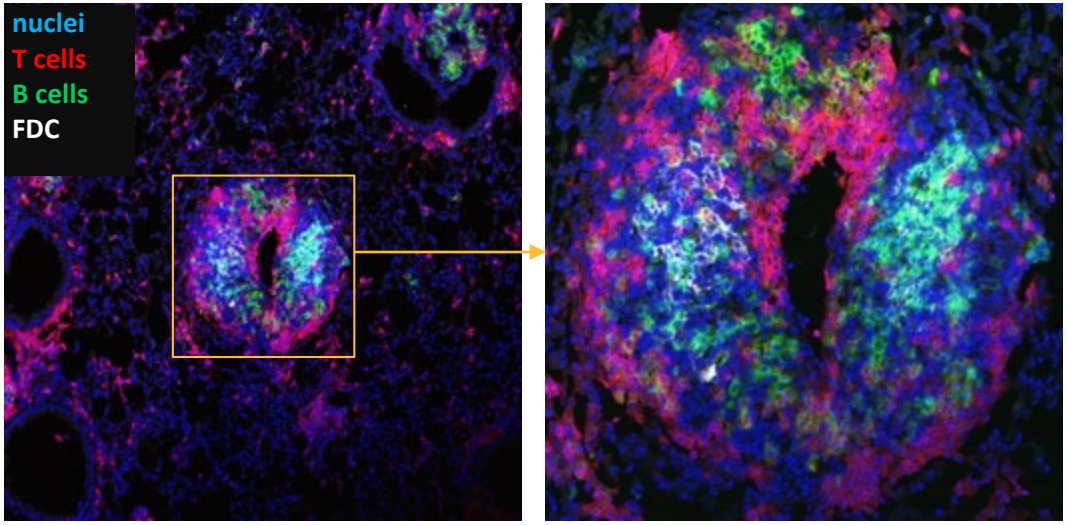
Fully resemble germinal centers in SLO with

- separate T and B cell zones
- follicular dendritic cells (FDC)
- GC B cells and Tfh cells

➢ Require strong stimuli like viral infection

Hutloff, Front Immunol 2018

Special case: Ectopic lymphoid structures (ELS)

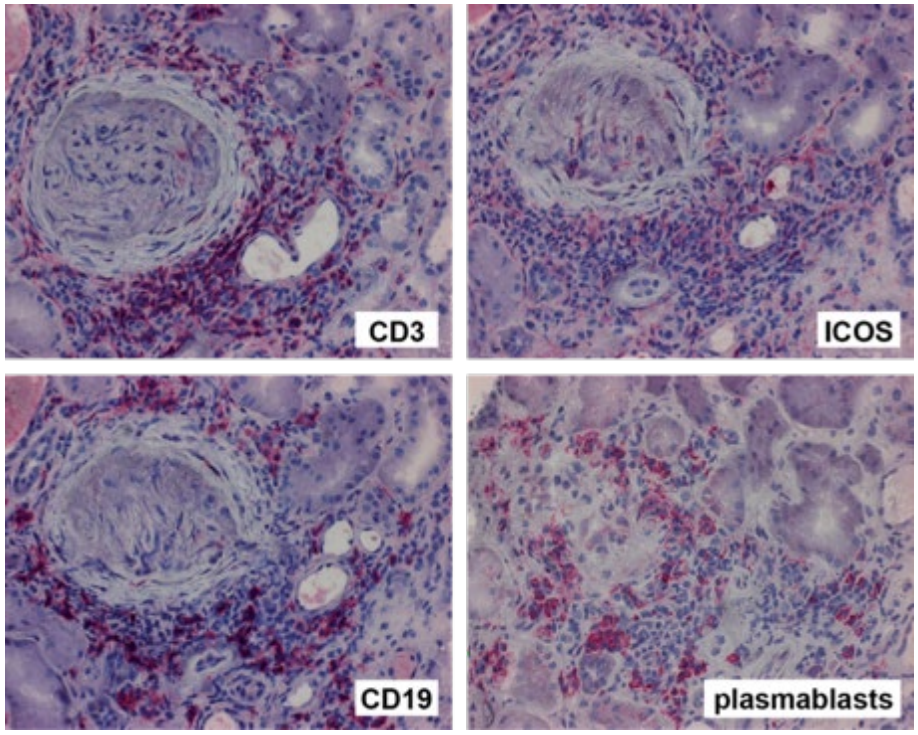


Prevalence of fully developed ELS in autoimmune diseases

Disease	Organ	Prevalence
Rheumatoid arthritis	synovial joint	6% - 25%
Rheumatoid arthritis	lung	11%
Sjögren syndrome	salivary glands	20%
Systemic lupus erythematosus	kidney	6%
Myositis (adult)	muscle	0%

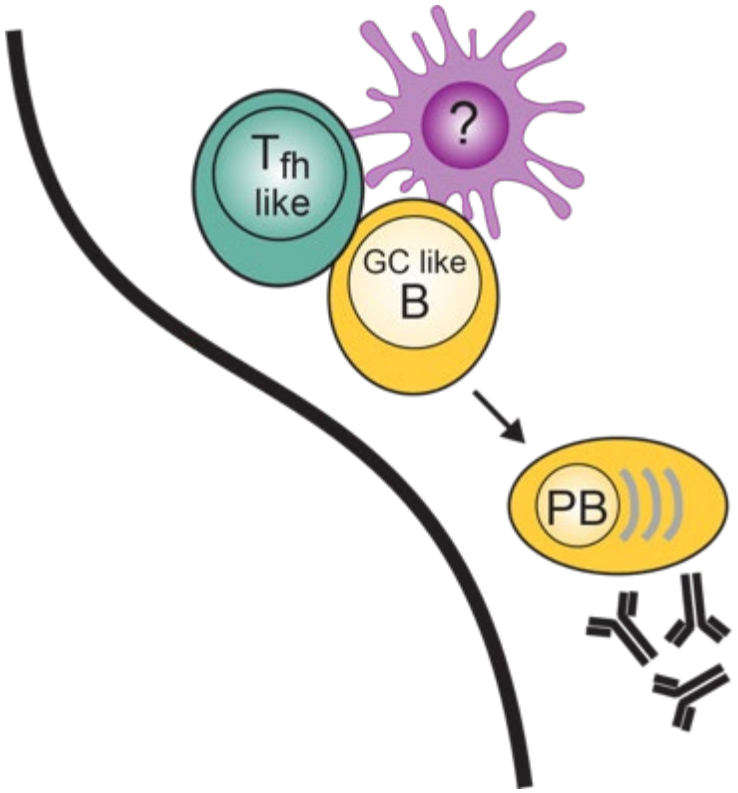
Hutloff, Front Immunol 2018

Unstructured T/B infiltrates are a typical finding in autoimmune diseases



Kidney from SLE patient

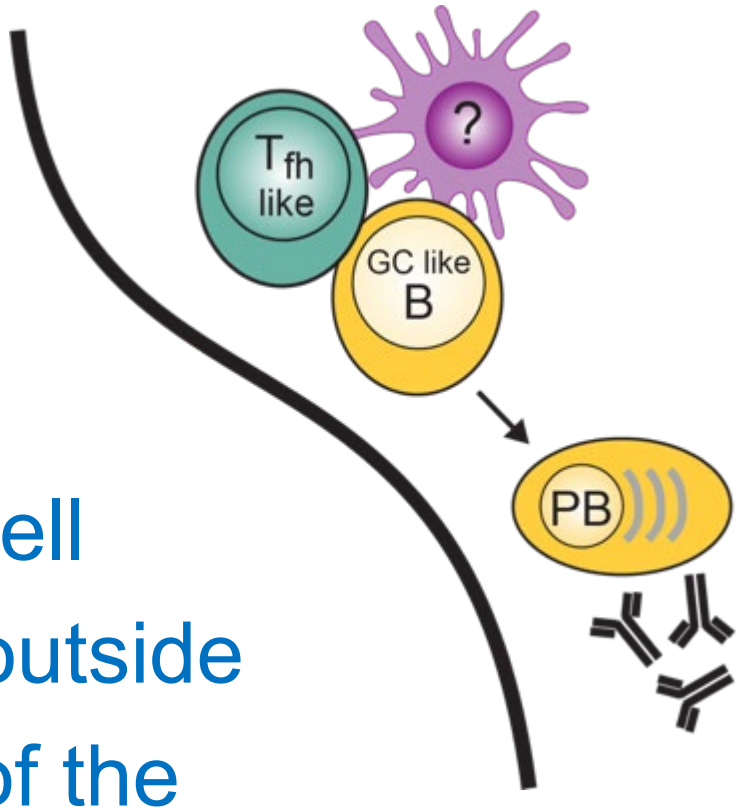
Hutloff et al. Arthr Rheum 2004



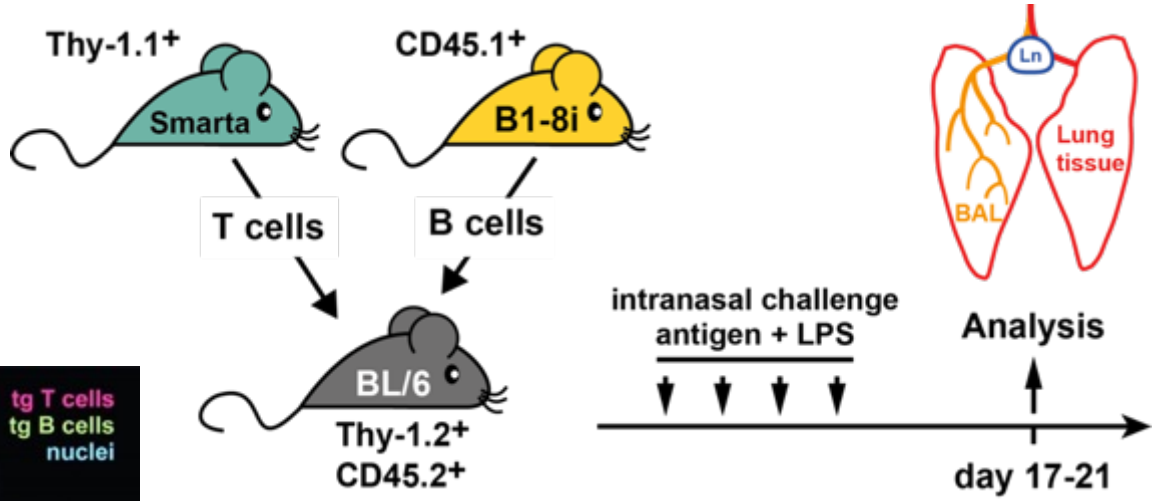
Unstructured T cell / B cell infiltrates are also found in:

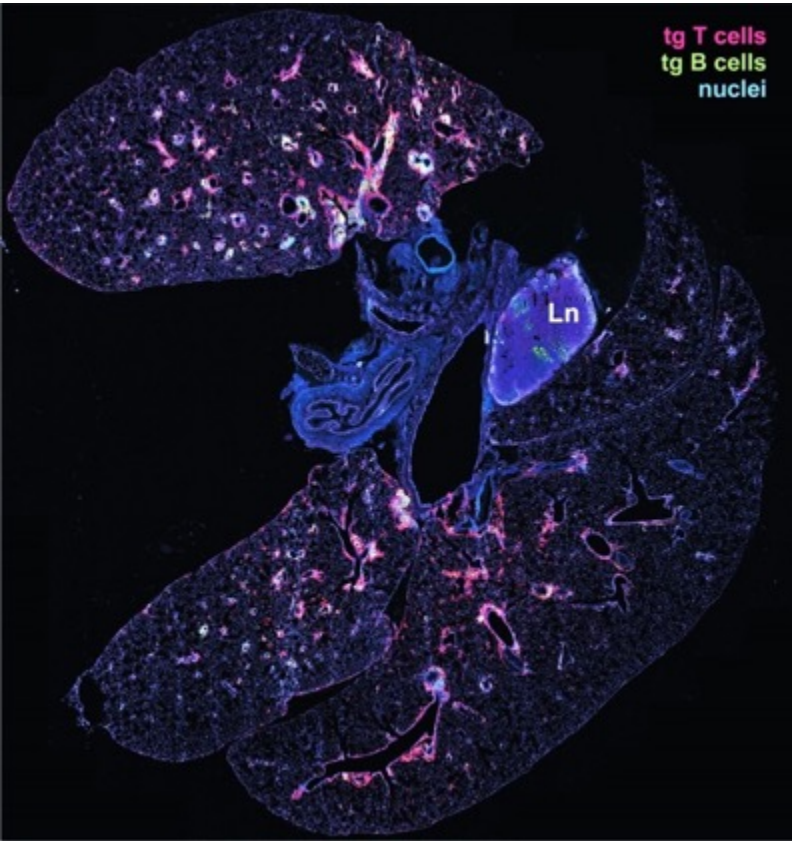
- inflamed synovium of RA patients
- inflamed gut, e.g. inflammatory bowel disease
- inflamed lung, e.g. asthma, rheumatic lung disease (up to 70% of RA patients)

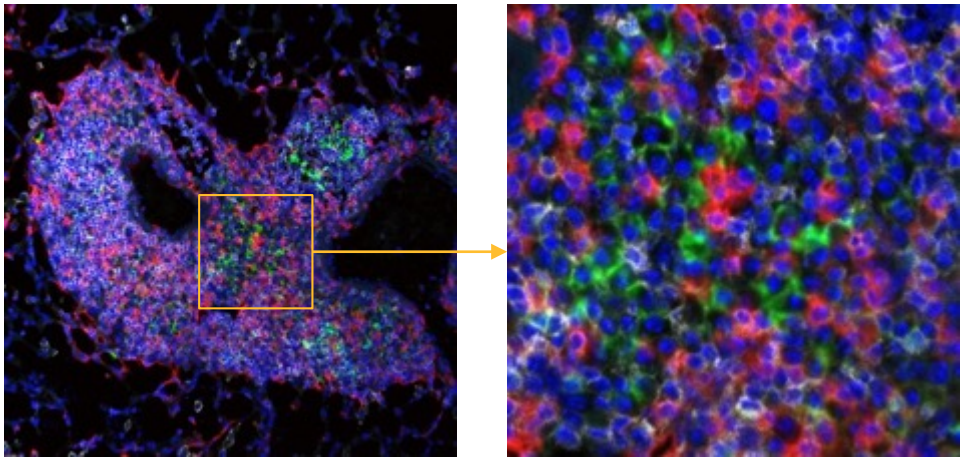
How can T cell / B cell cooperation take place outside the ordered structure of the germinal center?



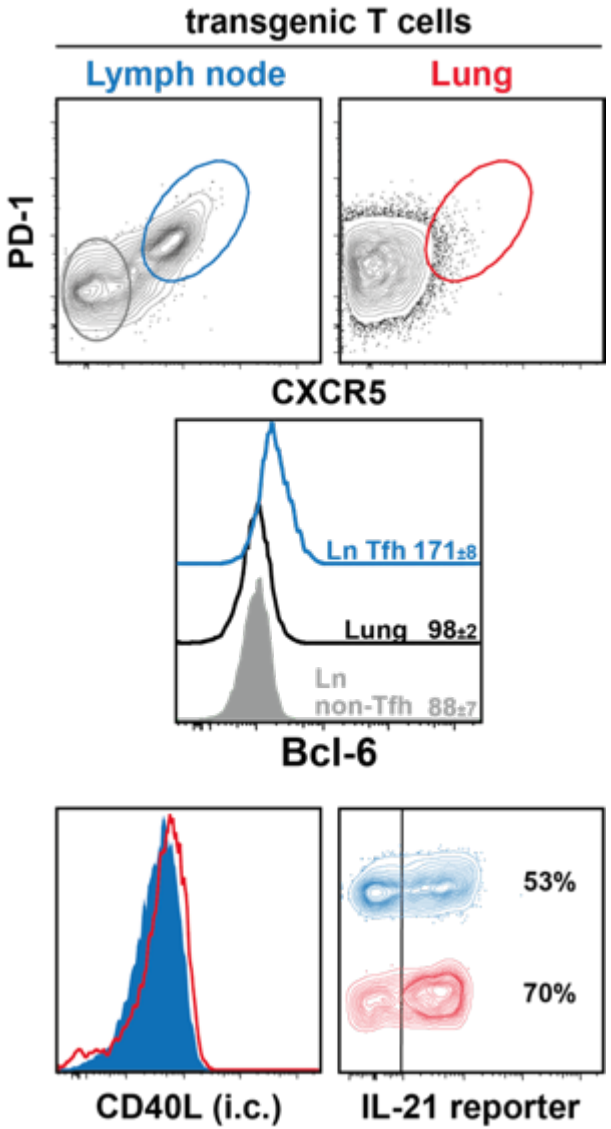
Mouse model to study T/B cooperation in inflamed tissues



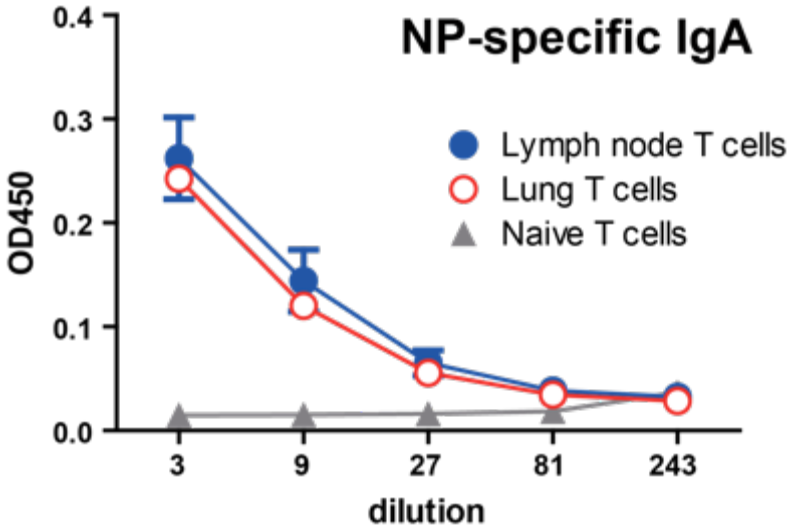




Lung T cells lack a classical Tfh phenotype but are potent B cell helpers

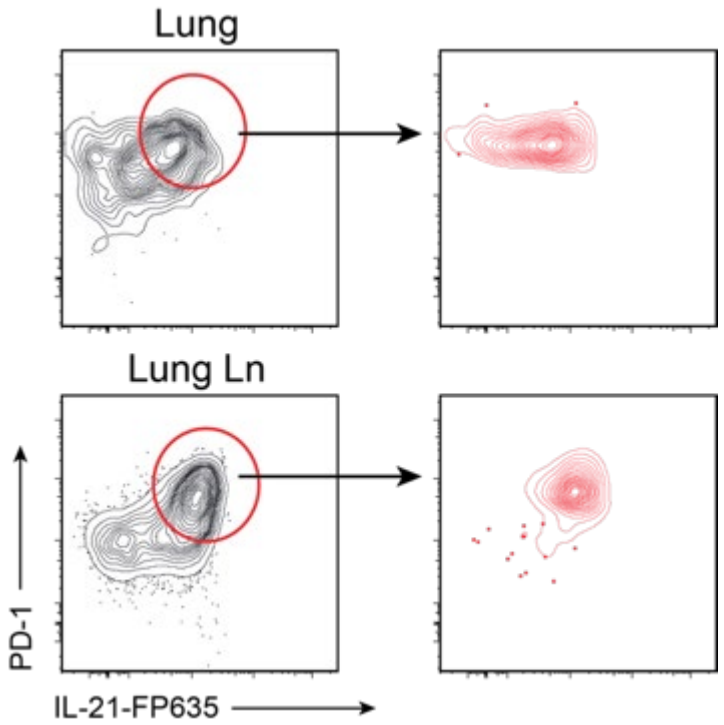


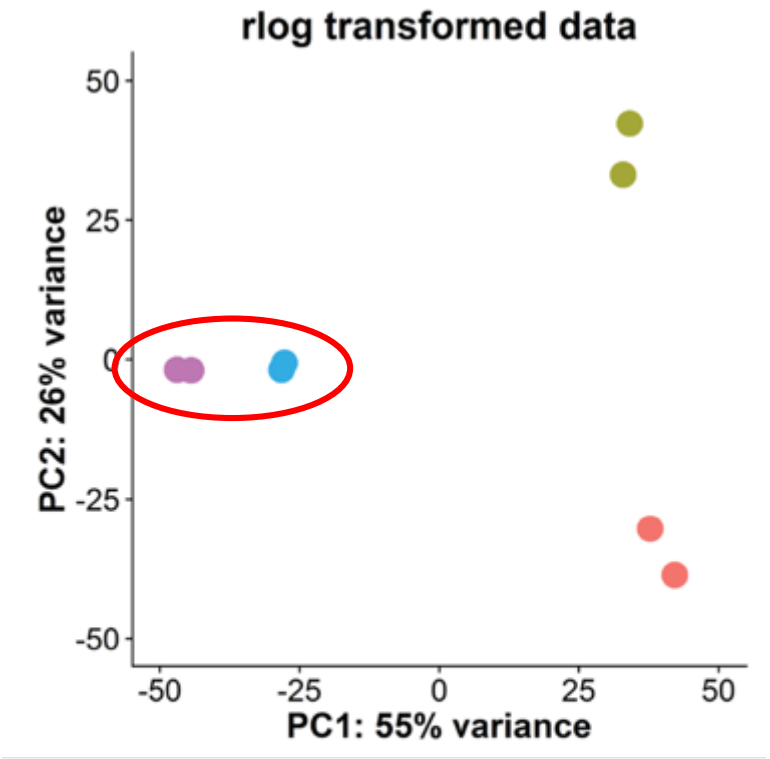
Co-culture of *ex-vivo* lung or lymph node T cells with naive B1-8i B cells in the presence of antigen for 7 days



Vu Van et al. Nat Commun 2016

Transriptome analysis confirms Tfh-like phenotype

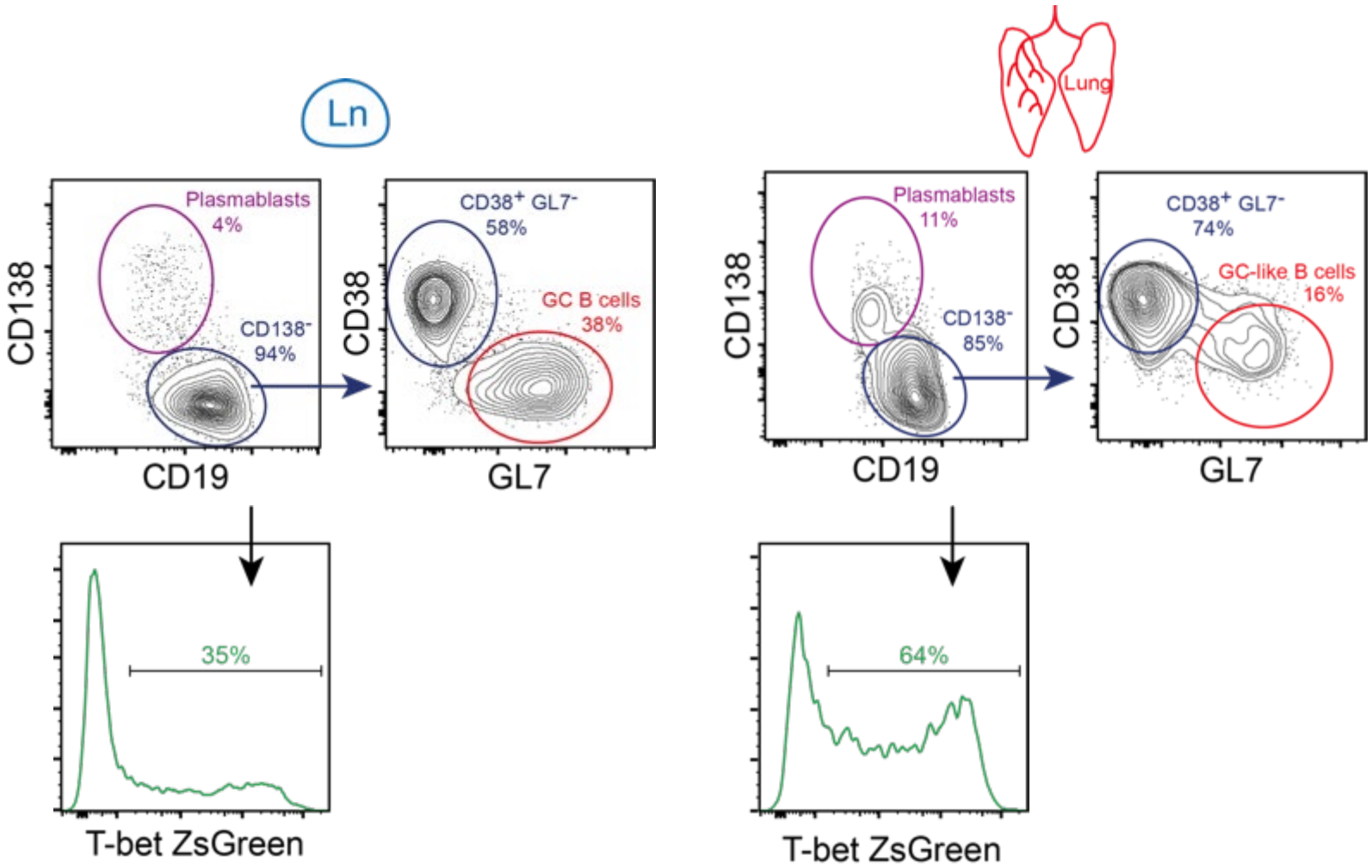




- Sort of antigen-specific T cells from lung and lung-draining lymph node on day 15
- Transcriptome analysis by RNAseq

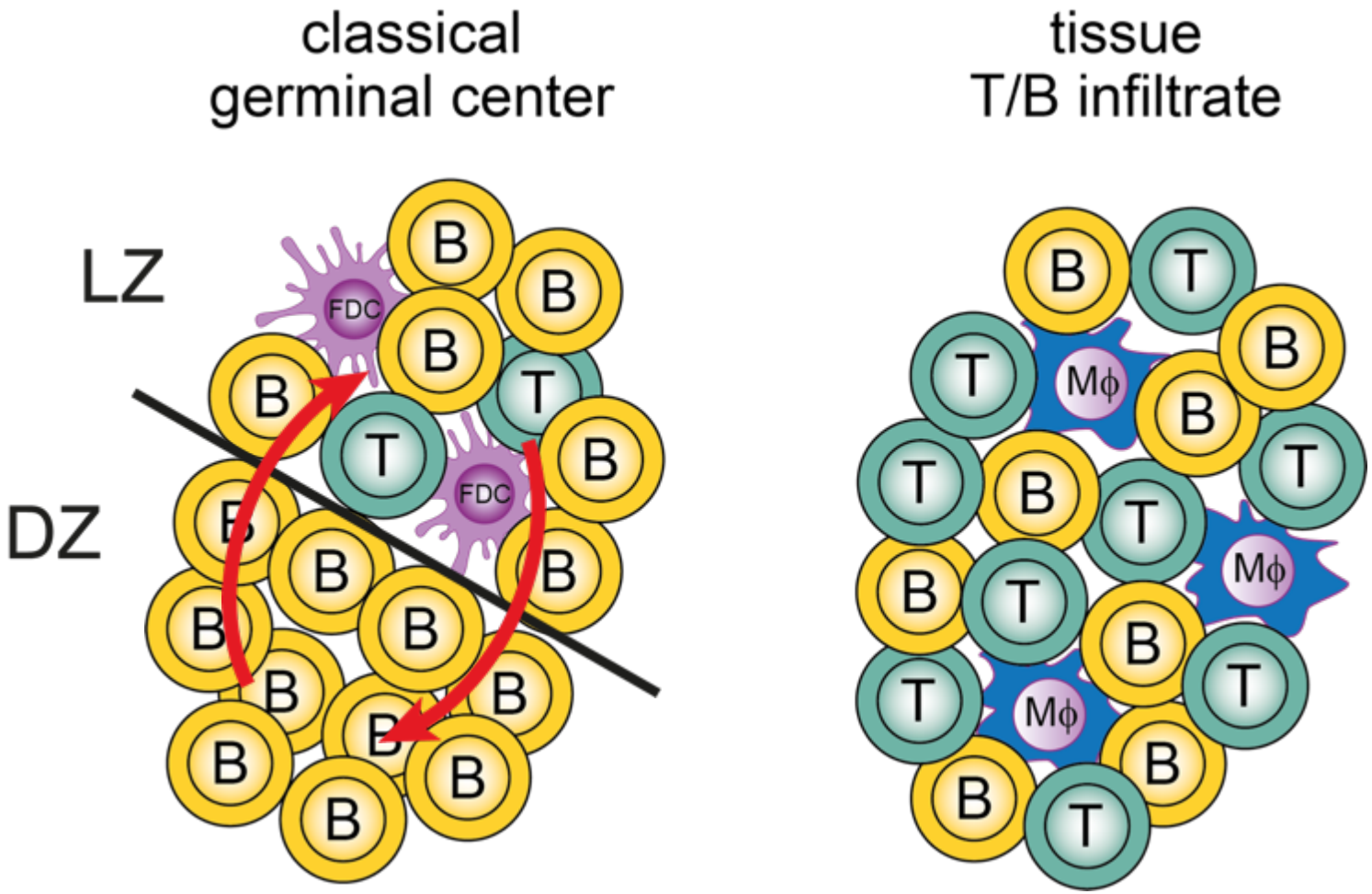
Laura Bauer, Lisa Müller, unpublished

The lung contains three distinct B cell populations



Vu Van et al. Nat Commun 2016 Marcel Finke, unpublished

Uncontrolled T/B interaction poses a high risk for development of autoreactive clones



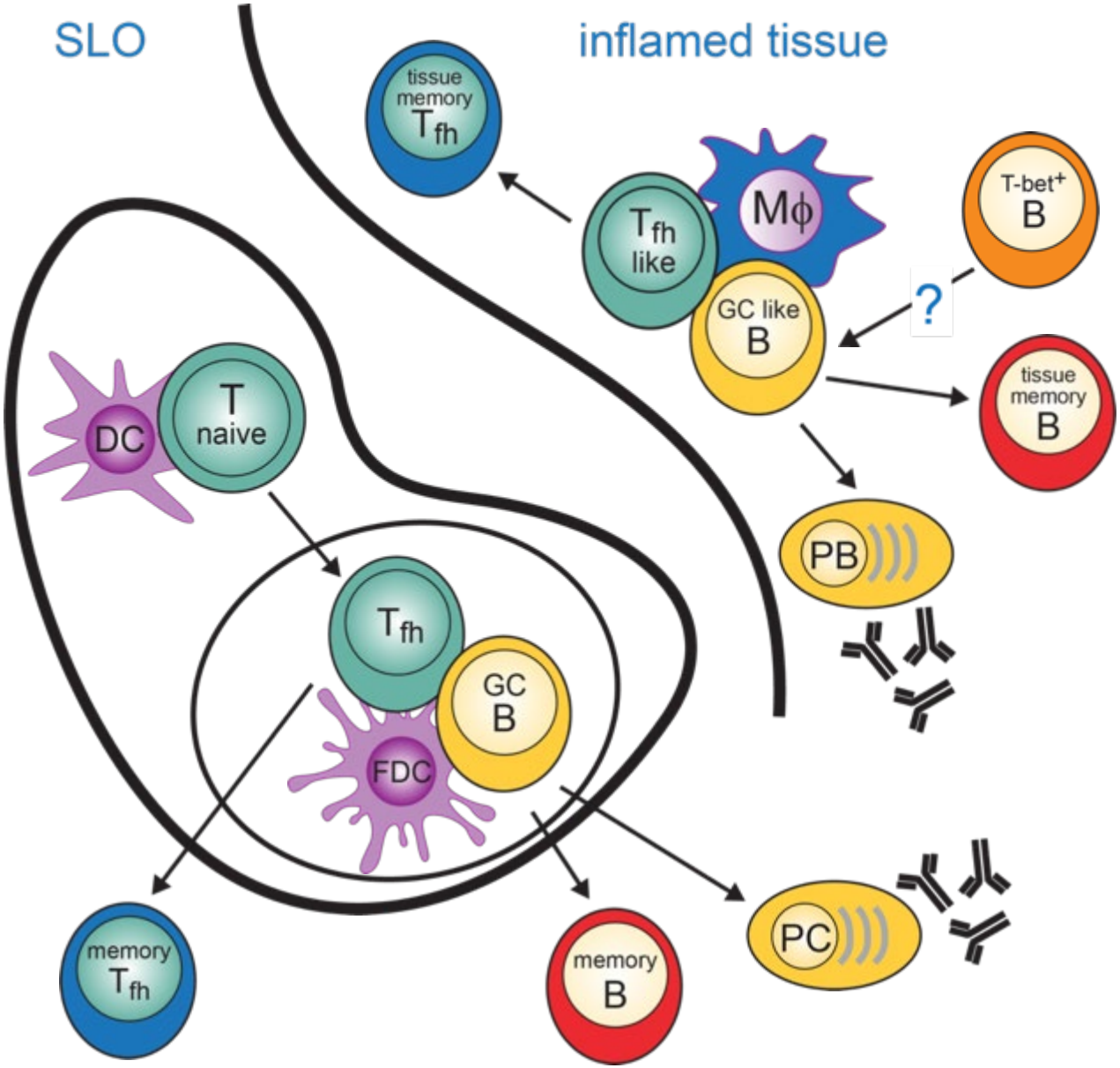
Tfh-like cells recently identified in autoimmune patients

General phenotype in comparison to classical Tfh cells

- distinct: lack of Bcl-6 and CXCR5
- similar: high expression of IL-21, CD40L, CXCL13

- Rheumatoid arthritis (Manzo *Arthr Rheum* 2008, Rao *Nature* 2017) > peripheral T helper cells
- Lupus nephritis (Hutloff *Arthr Rheum* 2004, Lin *Rheumatol* 2019, Bocharnikov *JCI Insight* 2019)
- Sjögren's syndrome (Haskett *J Immunol* 2016, Blokland *Arthr Rheum* 2017)
- Systemic sclerosis (Taylor *Sci Transl Med* 2018, Christophersen *Nat Med* 2019)
- Pemphigus (Yuan J Inv Derm 2017)
- Breast cancer (Gu-Trantien *JCI Insight* 2017) > $T_{FH}X13$ cells

SUMMARY


SLO
inflamed tissue
tissue memory Tfh
Tfh like
Mϕ
T-bet+ B
?
GC like B
tissue memory B
DC
T naive
PB
Tfh
GC B
FDC
memory Tfh
memory B
PC

Recommended reading

Michael McHeyzer-Williams, Shinji Okitsu, Nathaniel Wang and Louise McHeyzer-Williams.
Molecular programming of B cell memory.
Nat Rev Immunol (2012) 12:24

Abhinav Seth and Joe Craft.
Spatial and functional heterogeneity of follicular helper T cells in autoimmunity.
Curr Opin Immunol (2019) 61:1

Andreas Hutloff.
T follicular helper-like cells in inflamed non-lymphoid tissues.
Front Immunol (2018) 9:1707.