T-dependent humoral responses in mucosal sites

June 3, 2019
ECMIS, Ghent

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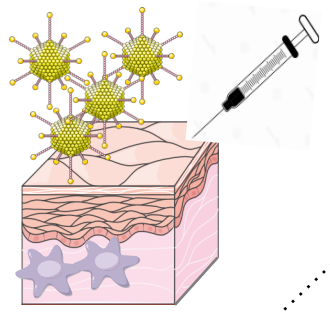
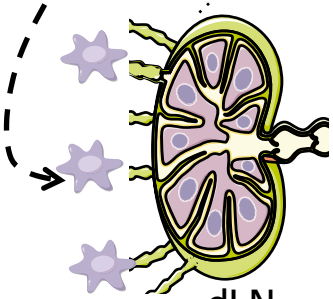
Regulation of B cell responses





dLN

B follicle

B cell

Dendritic cell

Naive Th cell

Th1

Th2

pTreg

Th17

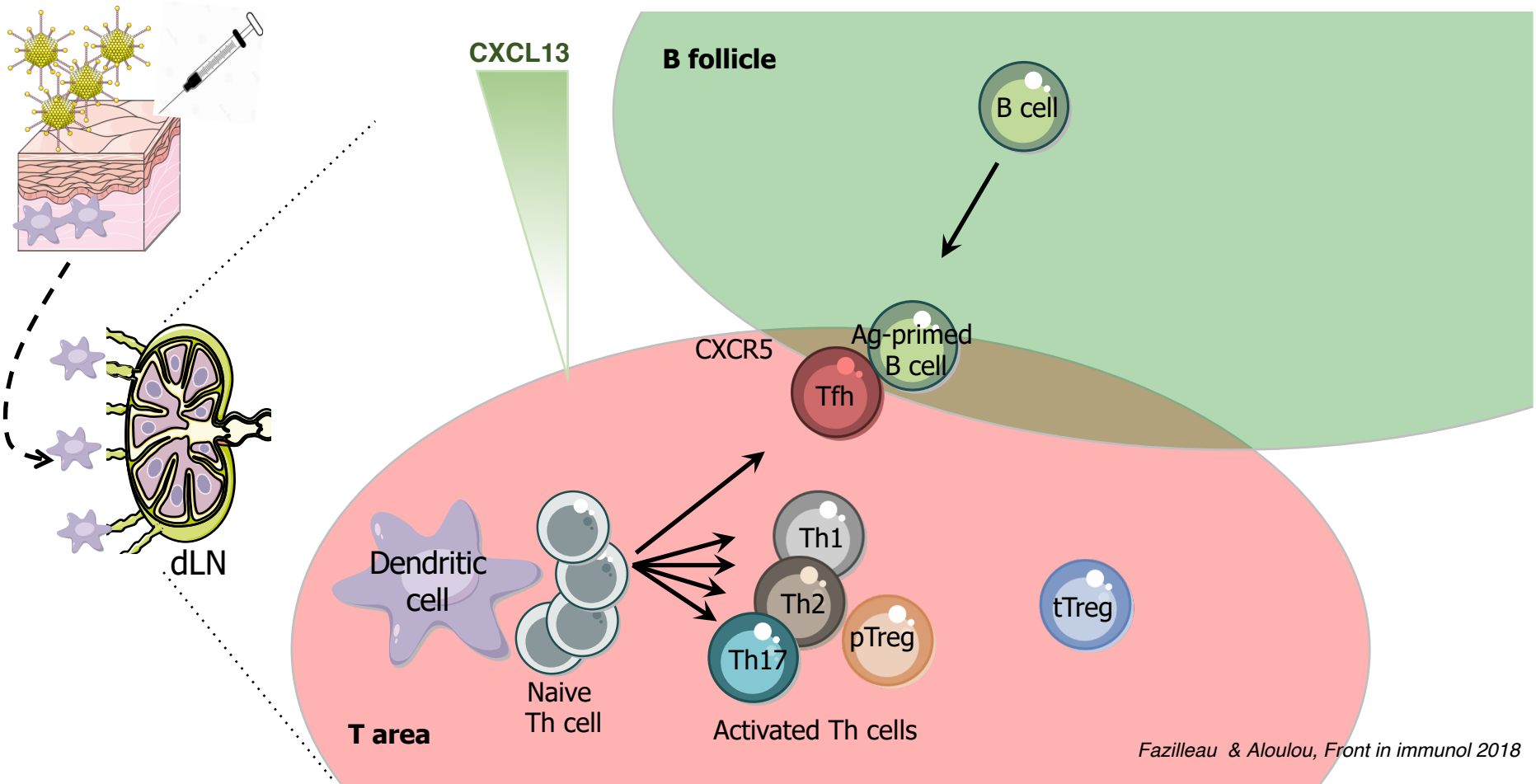
Activated Th cells

tTreg

T area

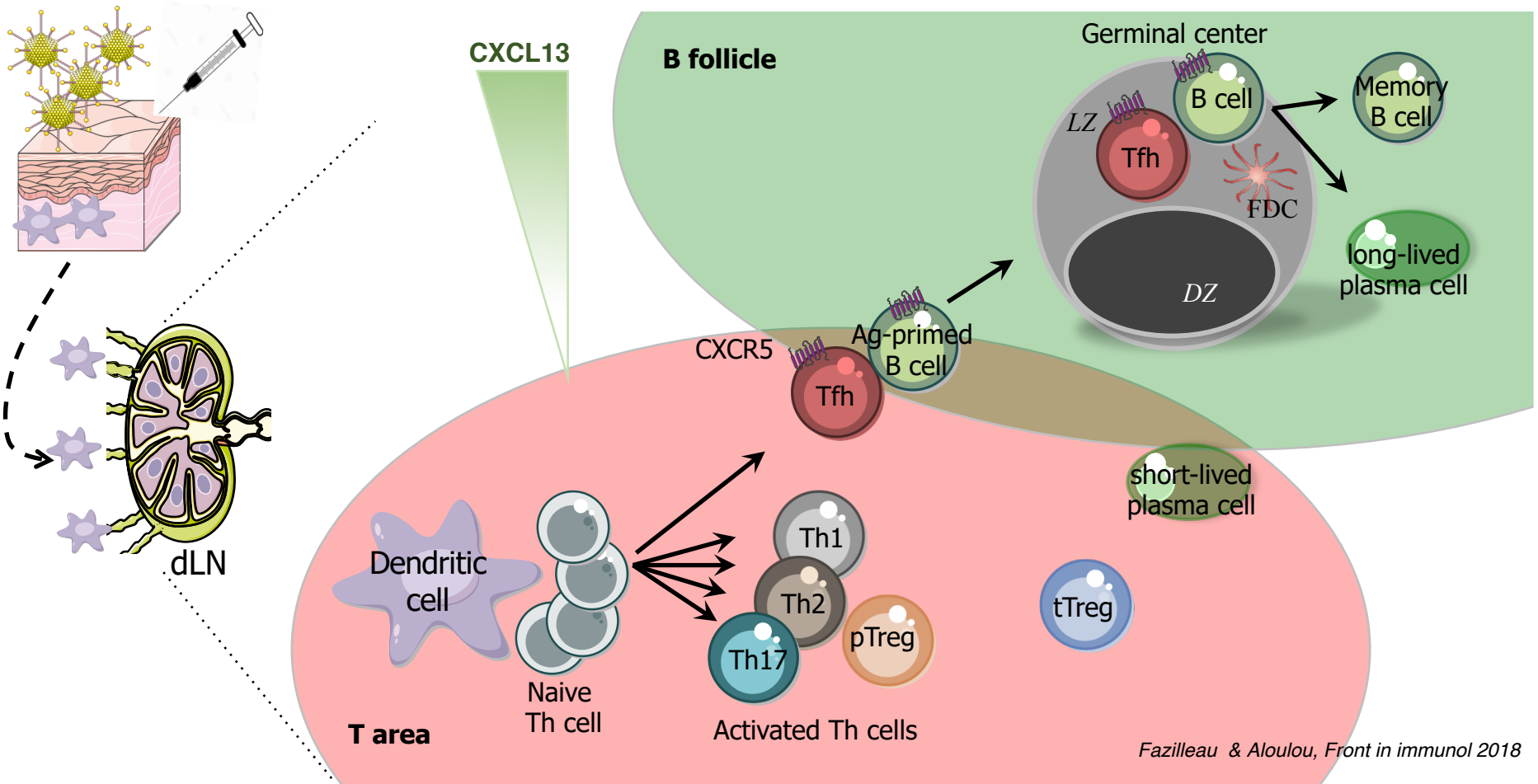
Fazilleau & Aloulou, Front in immunol 2018

Regulation of B cell responses



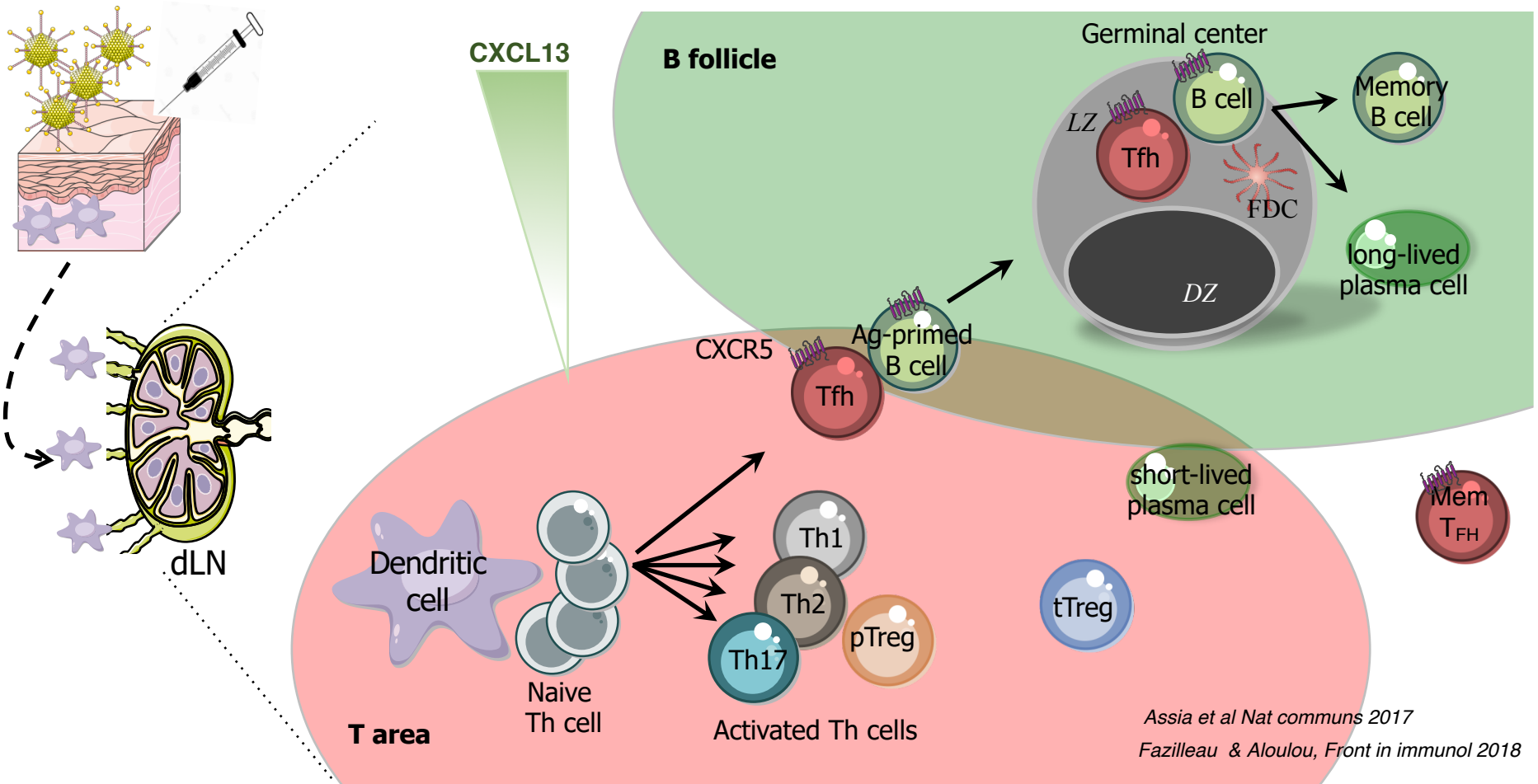
Fazilleau & Aloulou, Front in immunol 2018

Regulation of B cell responses



Fazilleau & Aloulou, Front in immunol 2018

Regulation of B cell responses



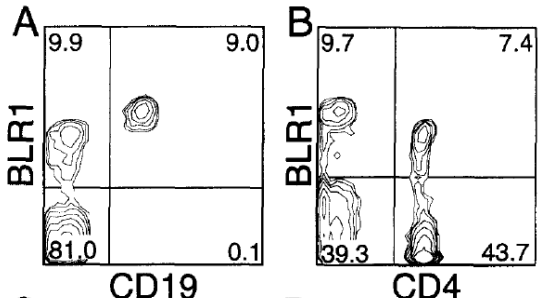
Assia et al Nat communs 2017

Fazilleau & Aloulou, Front in immunol 2018

Identification of Tfh cells

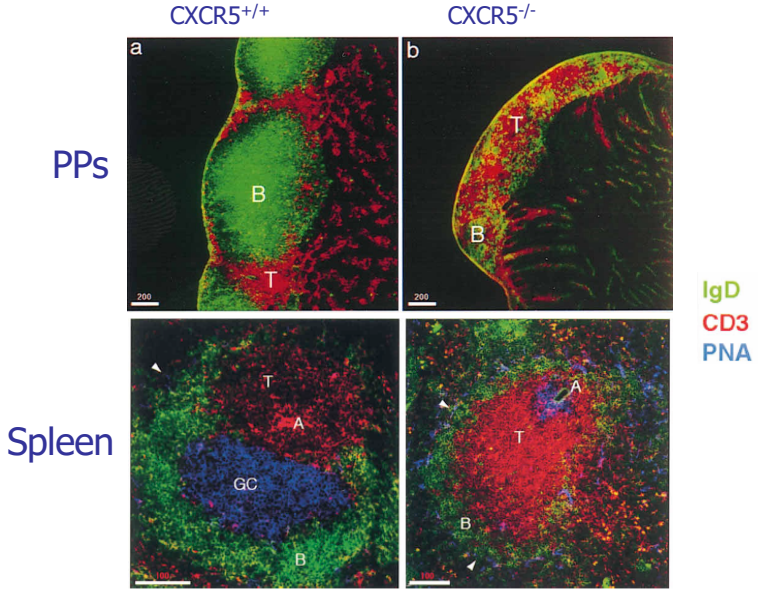
CXCR5-expressing T_H cells in human tonsils

CD44+CD25-CD62L-



Forster et al., Blood, 1994

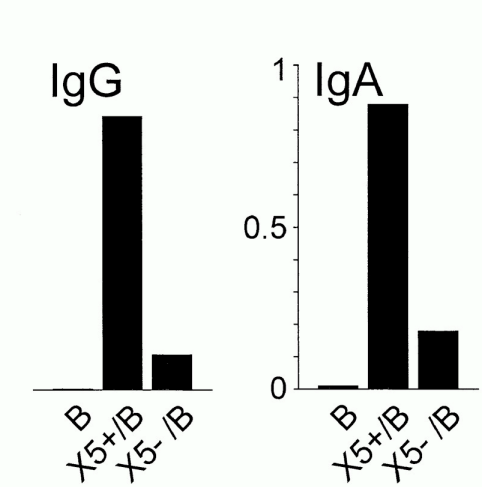
No Germinal center in CXCR5-deficient animals



Forster et al., Cell, 1996

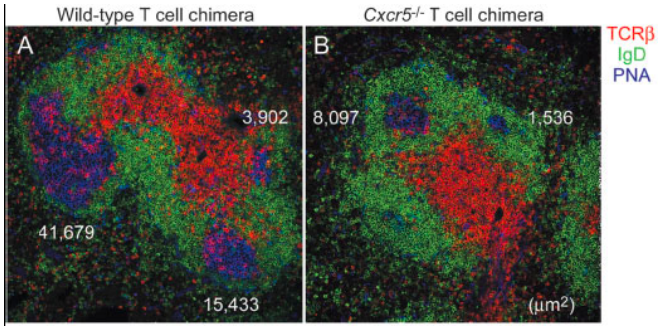
Only CXCR5+ Th cells control B cell responses

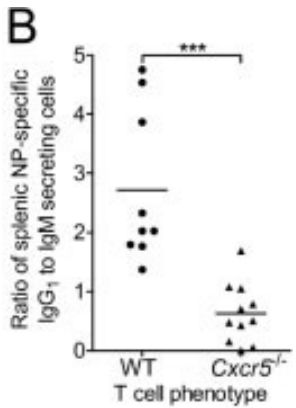
In vitro culture of human T lymphocytes and autologous B cells



Breitfeld et al., JEM, 2000
Schaerli et al., JEM, 2000

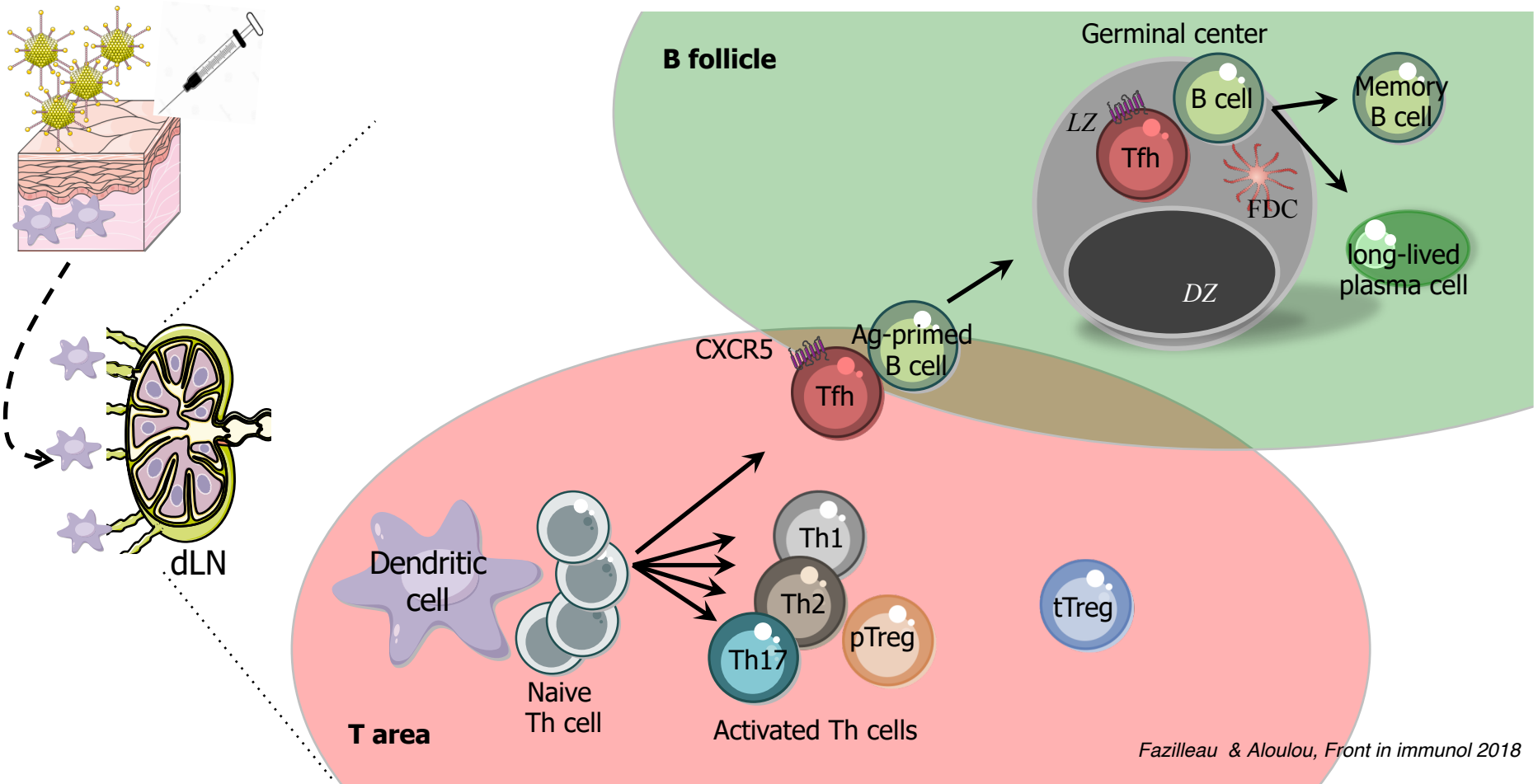
bone-marrow chimera in which all T cells are CXCR5 deficient





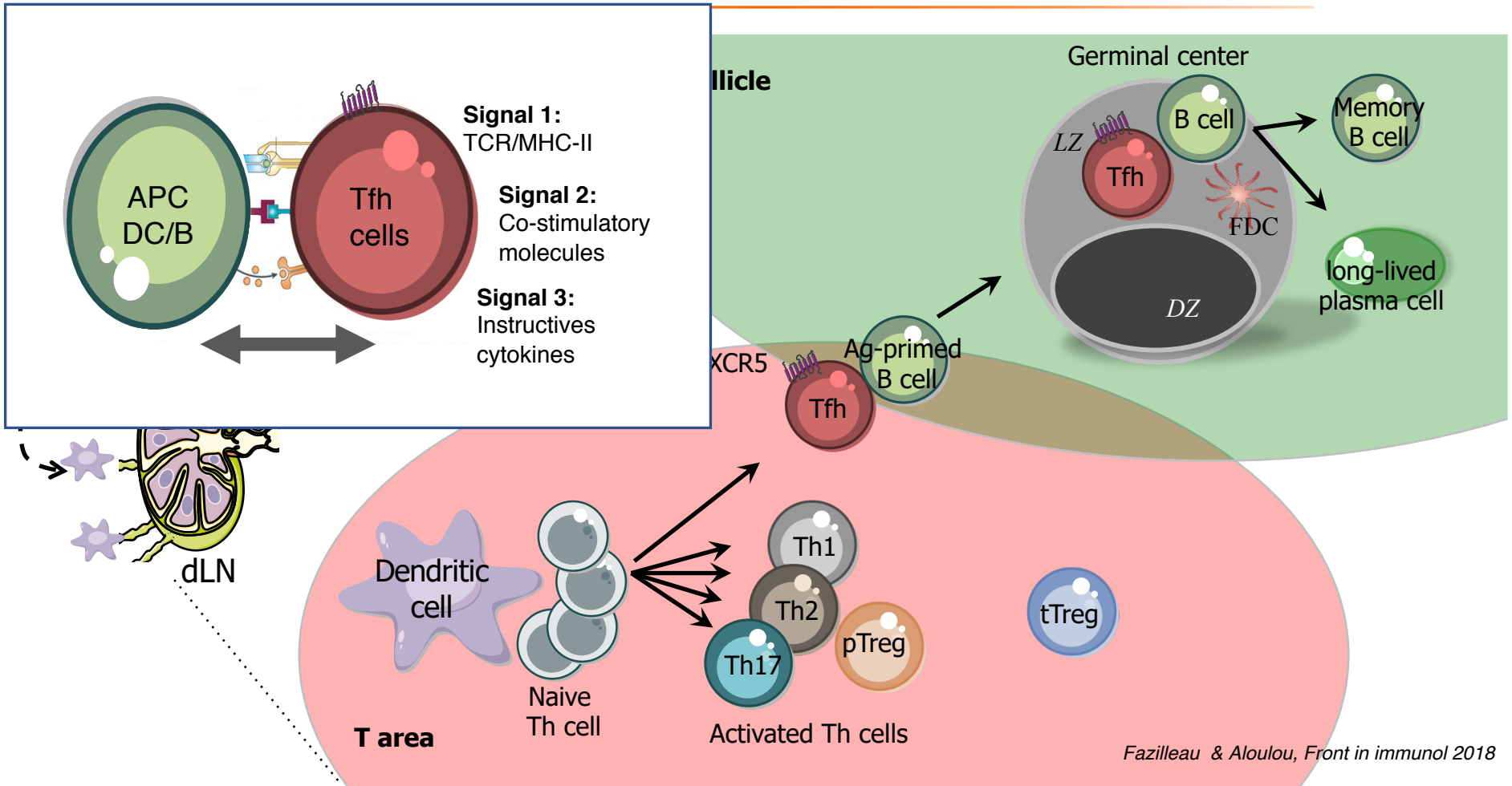
Arnold et al., EJI, 2007

Regulation of B cell responses



Fazilleau & Aloulou, Front in immunol 2018

Regulation of B cell responses



Fazilleau & Aloulou, Front in immunol 2018

2nd signal:
Expression of co-stimulatory molecules

- **CD28** and **OX40** engagements lead to
  CXCR5 expression by Th cells and GC formation

DC/Tfh

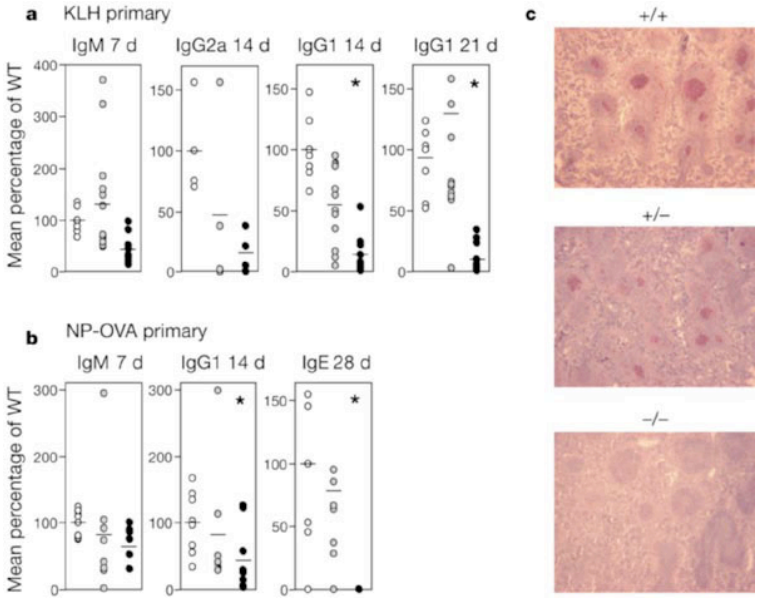
- **CD40L-CD40** interactions lead to
  B cell survival and BCR isotype switch

B/Tfh
GC-B/Tfh

Walker et al., JEM, 1999
Han et al., JI, 1995

2nd signal:
Expression of co-stimulatory molecules

Impaired primary Ab responses and GC formation in **ICOS**-/- mice challenged with T-cell-dependent Ag

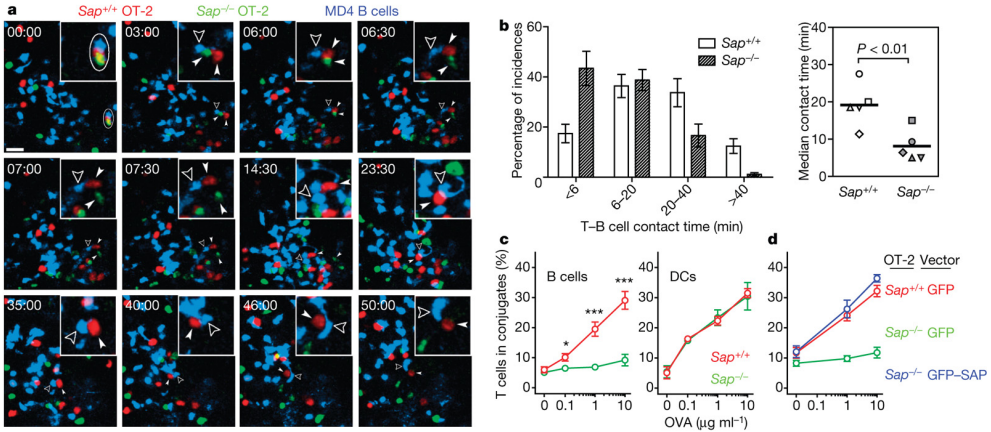


DC/Tfh
GC-B/Tfh

McAdam et al., Nature, 2001
Tafuri et al., Nature, 2001
Dong et al, Nature 2001

2nd signal:
Expression of co-stimulatory molecules

- **SAP** deficiency in T cells leads to impaired GC formation
- **SAP** is important to induce a prolonged T-B interaction

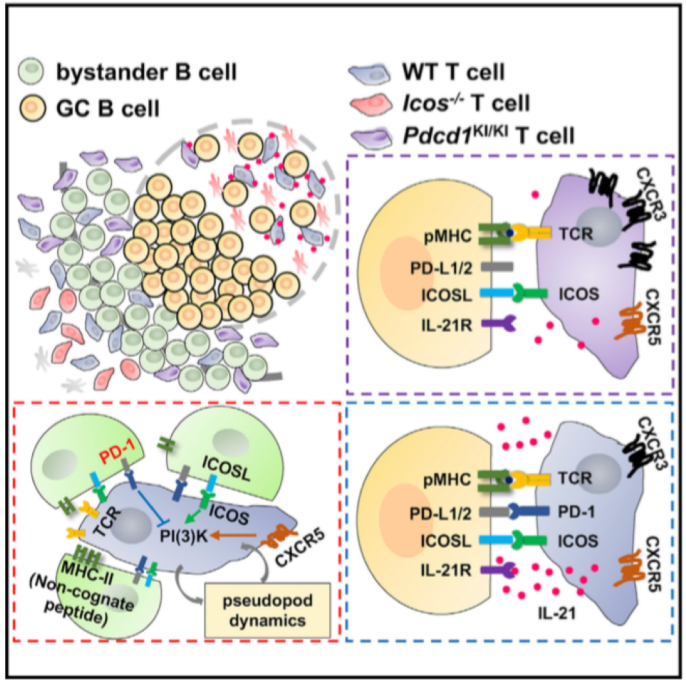


B/Tfh

Crotty et al., Nature, 2003
Veillette et al., PNAS, 2008
Qi et al, Nature 2008

PD-1, an inhibitory molecule, which allows positionning in GC

Graphical Abstract



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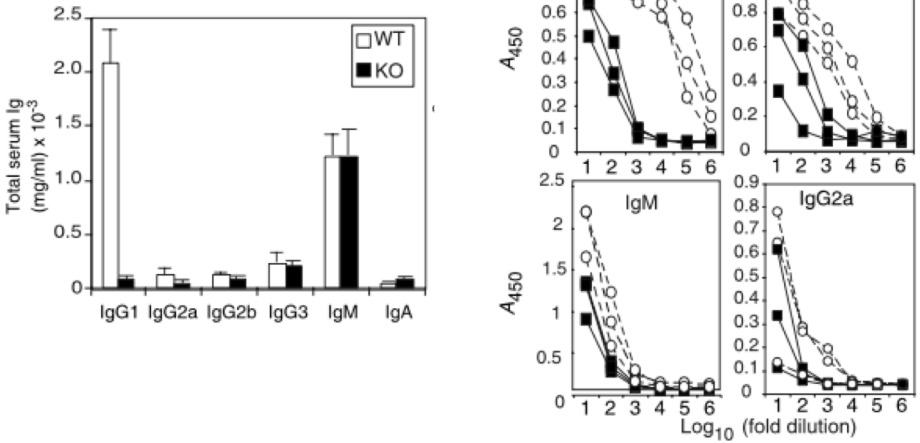
In Brief

Tfh cells highly express the inhibitory PD-1 molecule, although its function in the germinal center response is not well understood. Shi et al. show that, by operating in both costimulatory and bystander signaling mode, PD-1 suppresses follicular T cell recruitment but promotes Tfh cell concentration in the GC territory and helps maintain the stringency of GC affinity selection.

Shi et al., Immunity, 2018

Cytokine production by Tfh cells: IL-21

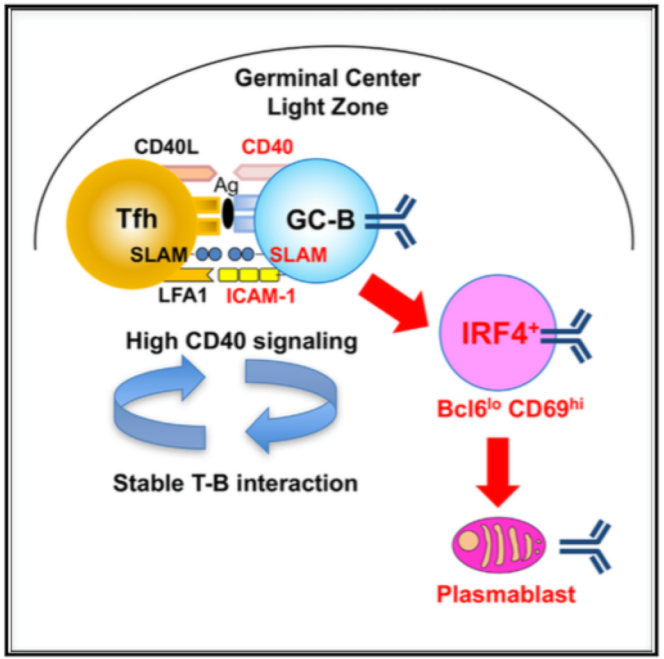
- High production of IL-21 by Tfh cells
- IL-21R is expressed by B cells
- IL21R-/- mice have impaired class switch



Ozaki et al, Science 2002

Strength of Tfh cell/GC B cell interaction regulates entry into Plasma cell or recycling GC fate

Graphical Abstract



Authors

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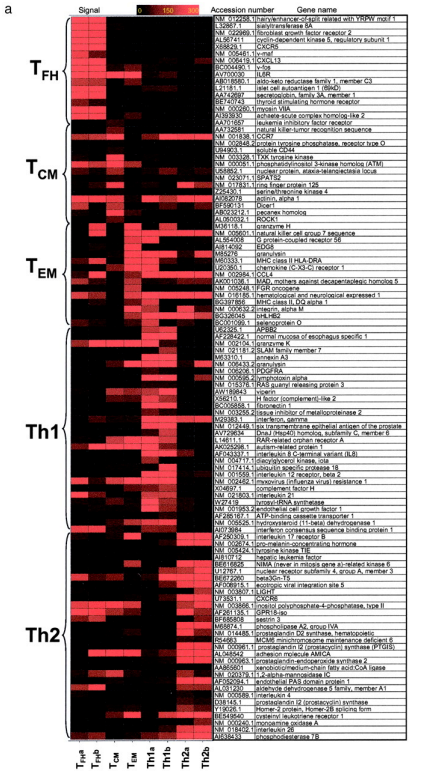
In Brief

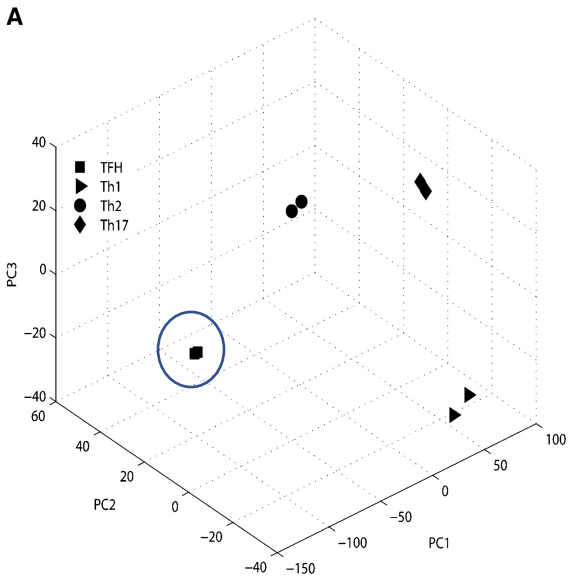
Ise et al. identify the plasma cell-prone LZ GC B cells whose generation relies on the amount of CD40 signal. Higher expression of ICAM-1 and SLAM in those cells facilitates more stable contacts with Tfh cells, suggesting that strength of Tfh-GC B cell interaction critically regulates formation of plasma cell precursors.

Ise et al, Immunity 2018

Genetic program of Tfh cells

Tfh express a distinct signature when compared to Th1, Th2, Th17, Tem and Tcm



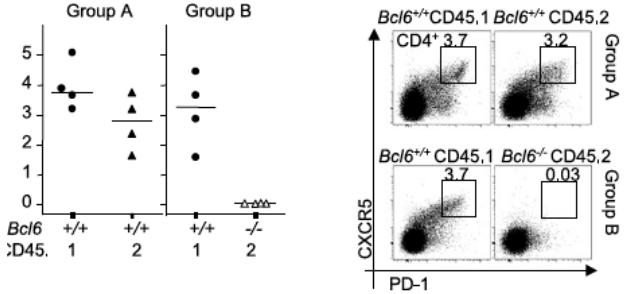


Kim et al., JEM, 2001
Chtanova et al., JI, 2004
Nurieva et al., Immunity, 2008

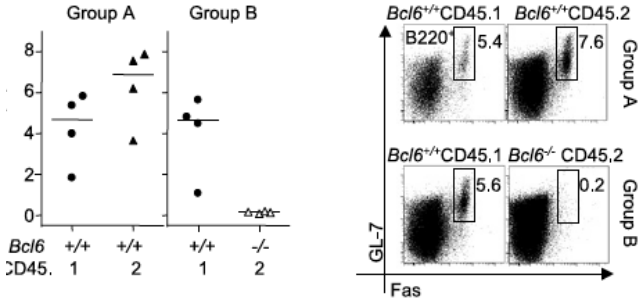
Bcl-6 is required for Tfh cell formation

In vivo differentiation of Tfh and GC B cells in bone-marrow chimera

Tfh



GC B cells

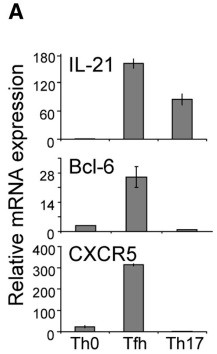


Jonhston et al., Science, 2009
Nurieva et al., Science, 2009
Yu et al., Immunity, 2009
Kitano et al., Immunity, 2011
Choi et al., Immunity, 2011
Lee et al., JEM 2011

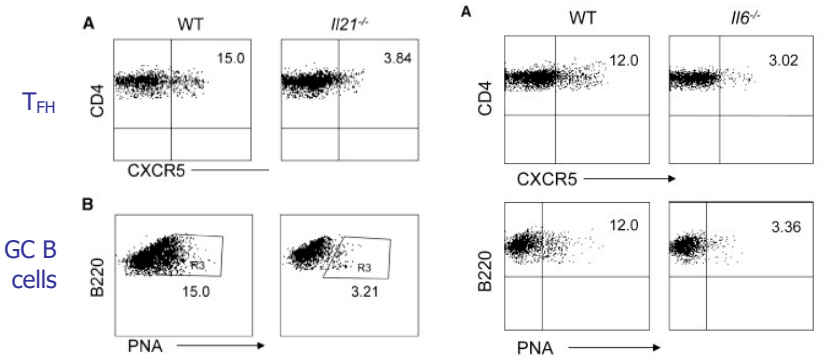
Tfh differentiation

IL-6 and IL-21 promote Tfh cell differentiation *in vitro* and *in vivo*

In vitro culture of stimulated T lymphocytes



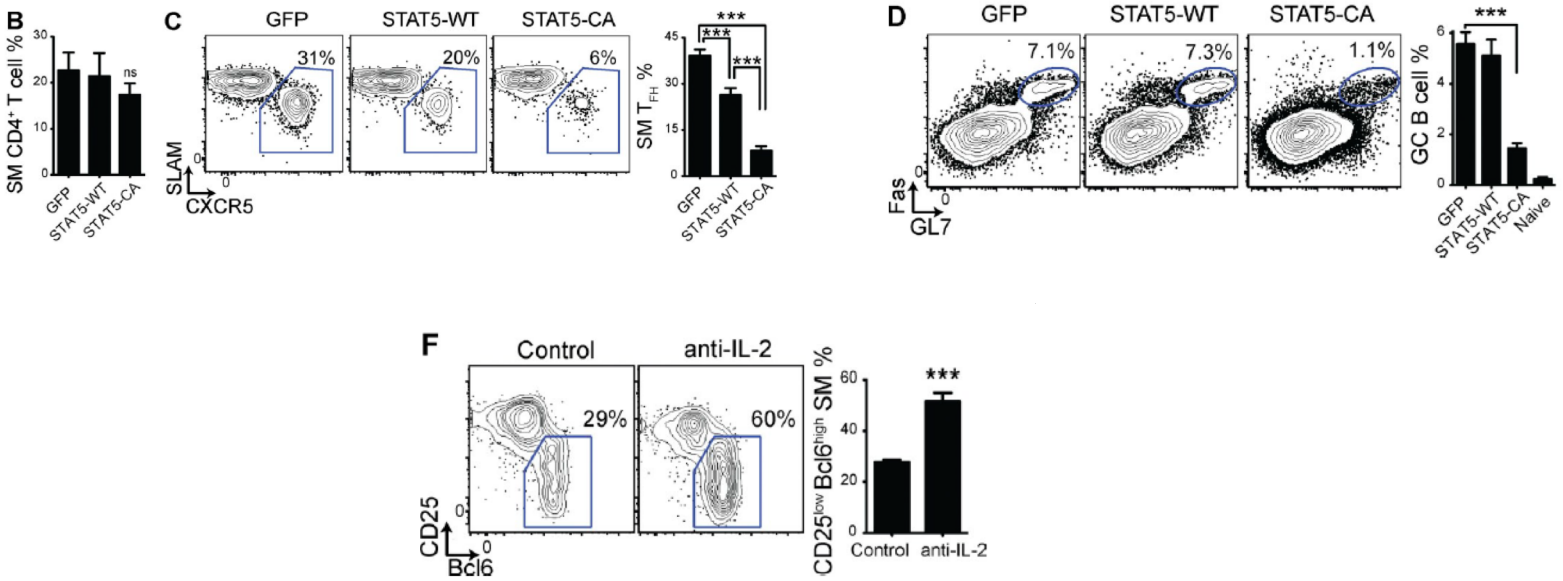
In vivo differentiation of Tfh and GC B cells in deficient animals



Nurieva et al., Immunity, 2008
Vogelzang et al., Immunity, 2008

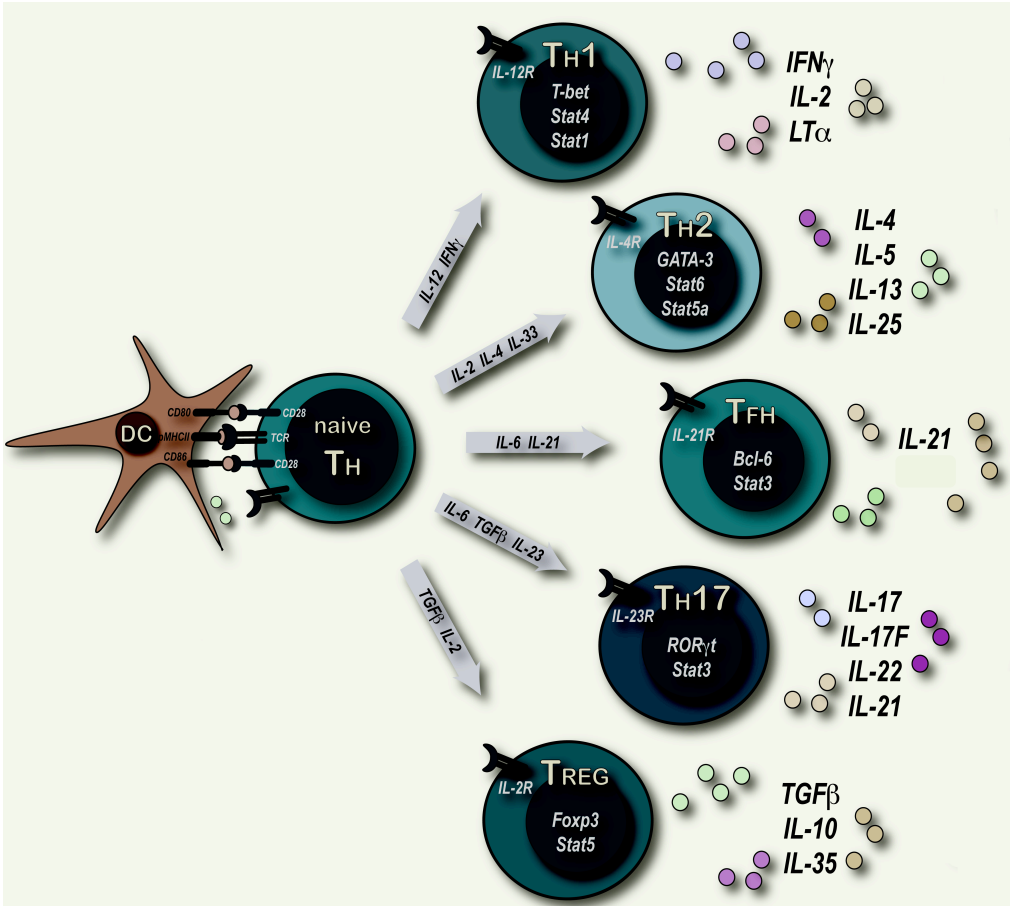
Tfh differentiation

IL-2 inhibits Tfh cell differentiation *in vitro* and *in vivo*



Ballesteros-Tato et al, Immunity, 2012
Johnston et al, J Exp Med, 2012

Tfh differentiation



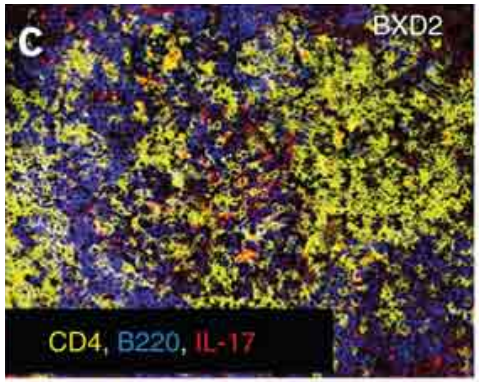
Fazilleau N et al., Immunity, 2009

Unfortunately,
it is not that trivial…

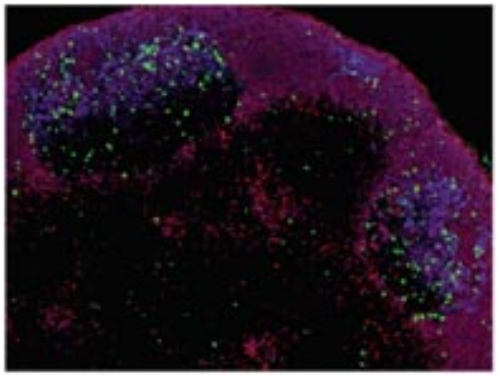
Tfh can secrete cytokines associated to other Th lineages

Tfh cells can secrete IFN-γ, IL-4, IL-17 and TGF-β that will control isotype switch

IL-17 secreting GC Th cells

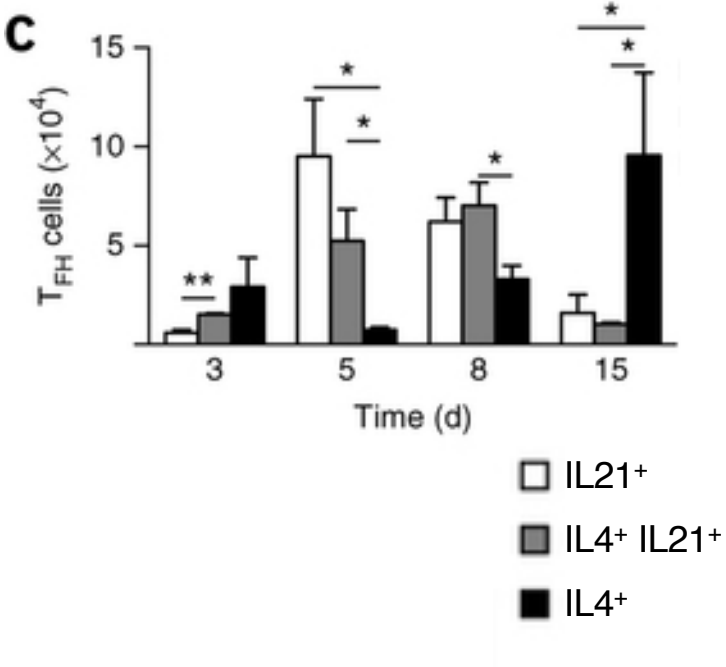


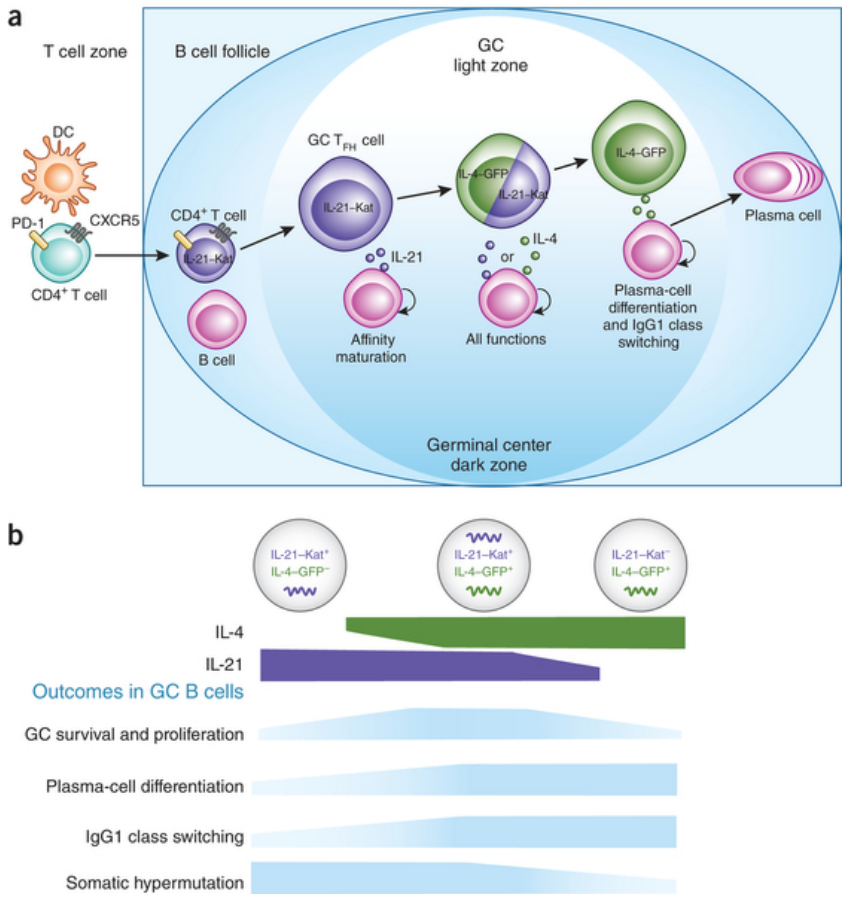
IL-4 secreting GC Th cells



Vijayanand et al., Immunity , 2012
Tsuji et al. Science, 2009
Bauquet et al., Nature Immunol, 2009
Fazilleau et al., Nature Immunol, 2009
Reinhardt et al., Nature Immunol, 2009

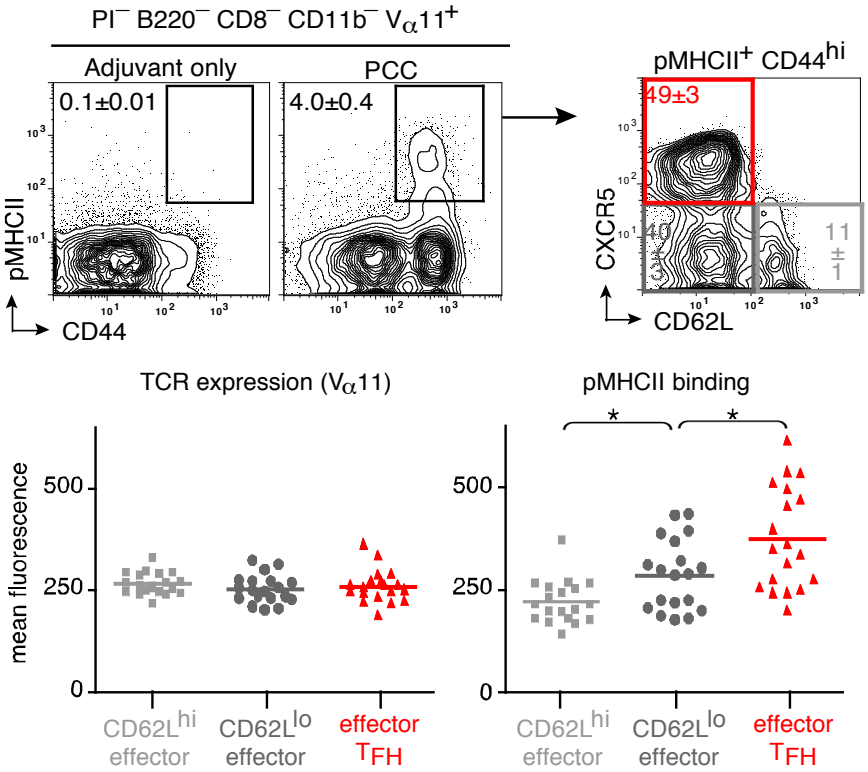
Tfh progressively differentiate to regulate the GC response





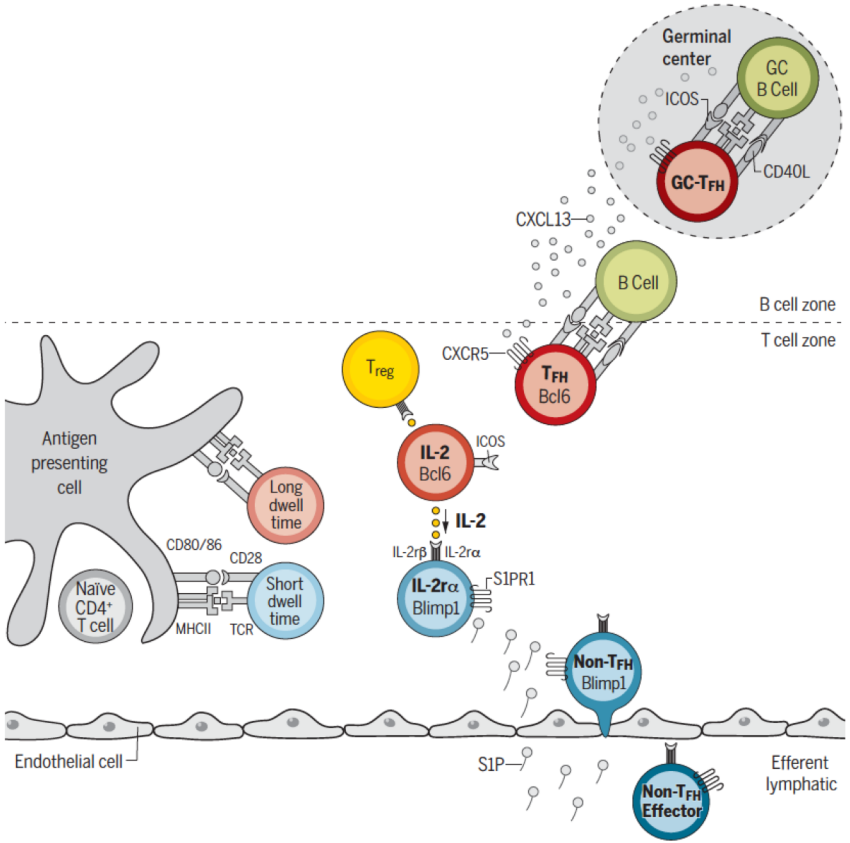
Weinstein et al., Nature Immunol, 2016

Tfh cell preferentially express high-affinity TCR



Fazilleau N et al., Nat Immunol, 2009

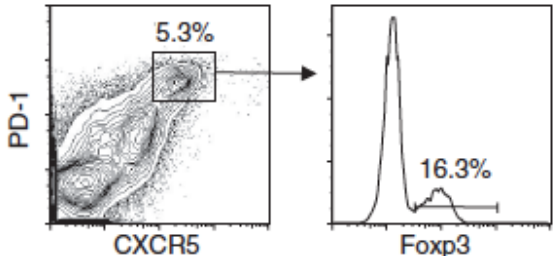
Differential IL-2 expression defines developmental fates Tfh vs non Tfh



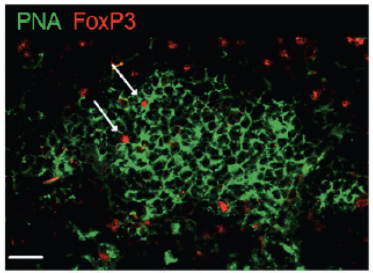
DiToro et al, Science, 2018

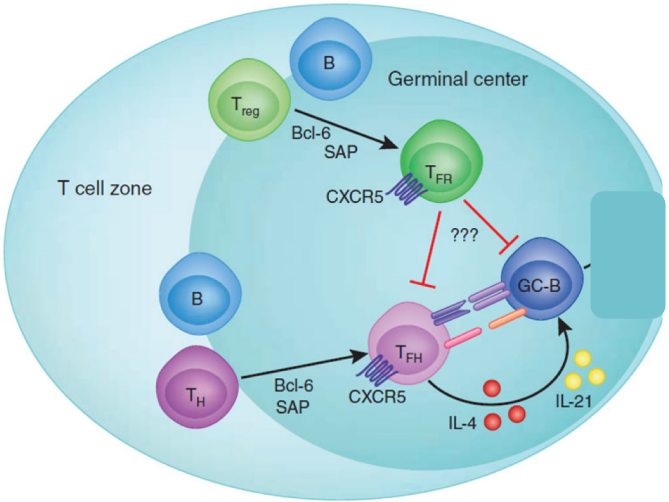
Regulation of B cell reponse

Some Tfh express Foxp3



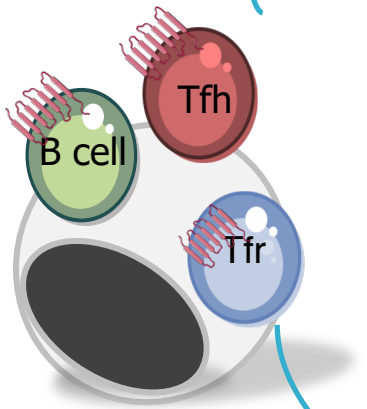
Tfr participate to GC reaction



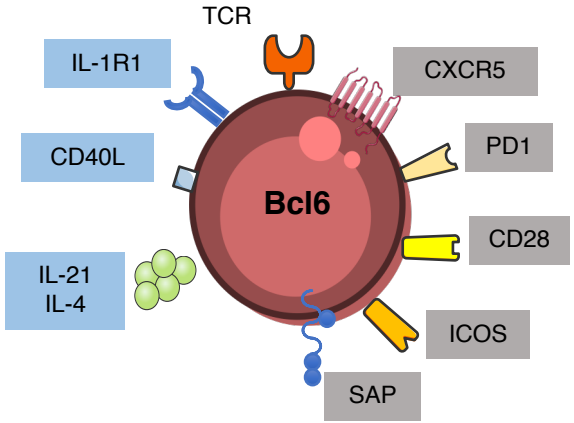


Linterman et al., Nature Medicine, 2011
Chung et al., Nature Medicine, 2011
Amé-Thomas et al., Leukemia, 2011
Wollenberg et al., Journal of Immunology, 2011

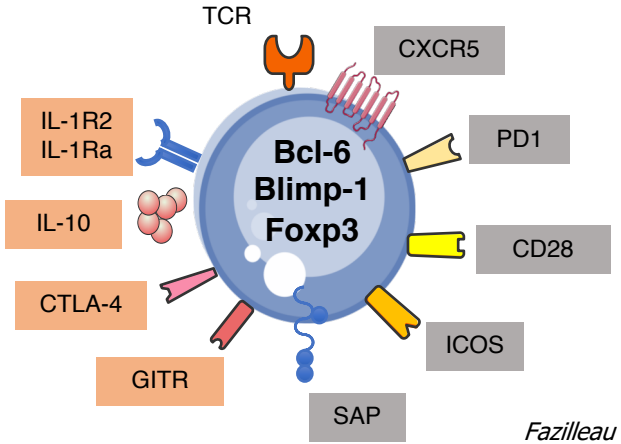
Regulation of B cell reponse



Germinal Center



Tfh cells
Positive regulator

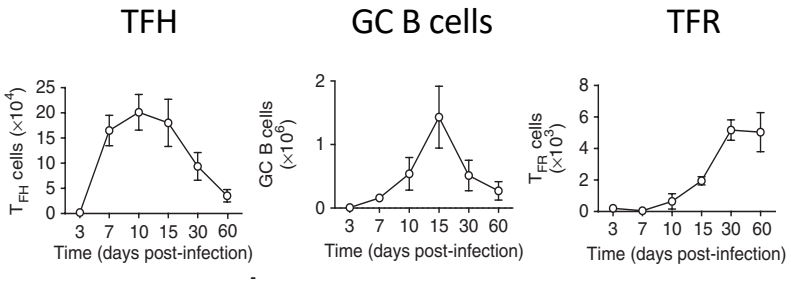


Tfr cells

Fazilleau & Aloulou Front Immunol 2018
Ritvo & Klatzmann Front Immunol 2019

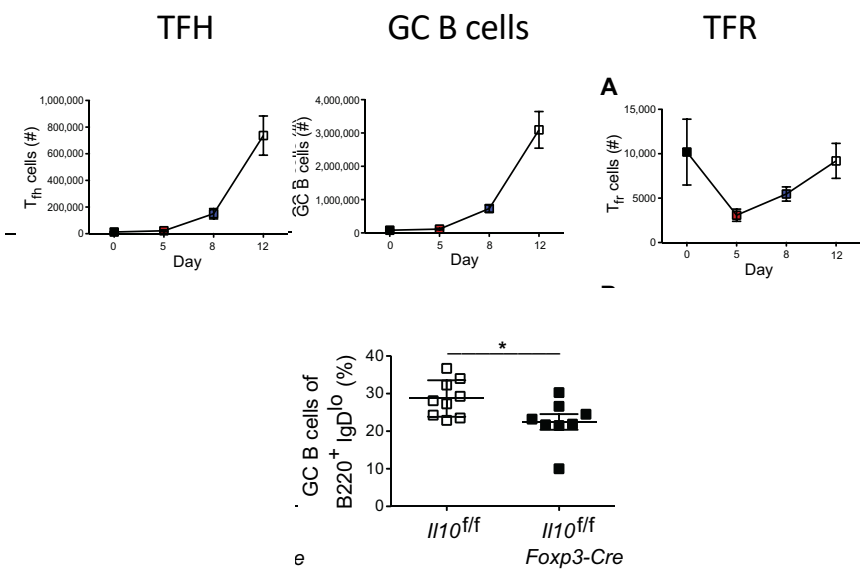
Distinct functin of Tfr cells

TFR prevent the expansion of self-reactive B cell clones (Influenza infection)



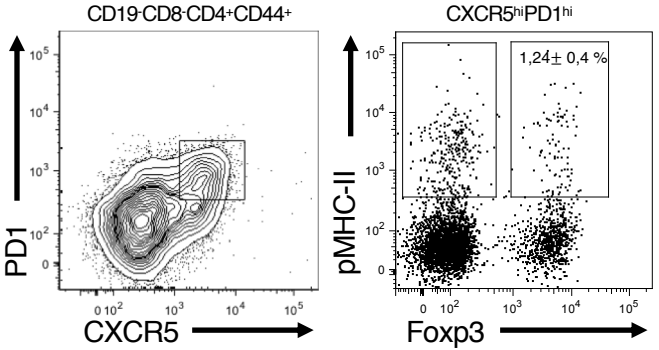
Botta et al, Nat Immunol 2017

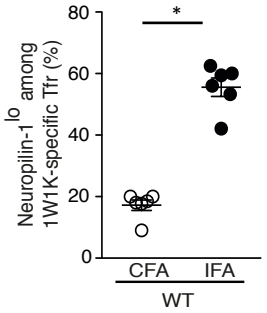
Tfr cells promote GC response through the production of IL-10 (LCMV infection)



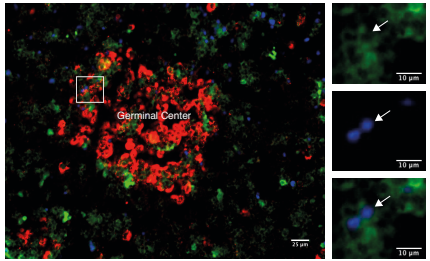
Laidlaw et al, Sci Immunol 2017

Tfr compartment is heterogeneous





bone-marrow chimera
in which all T cells are CXCR5 deficient
+ iv naive T cells

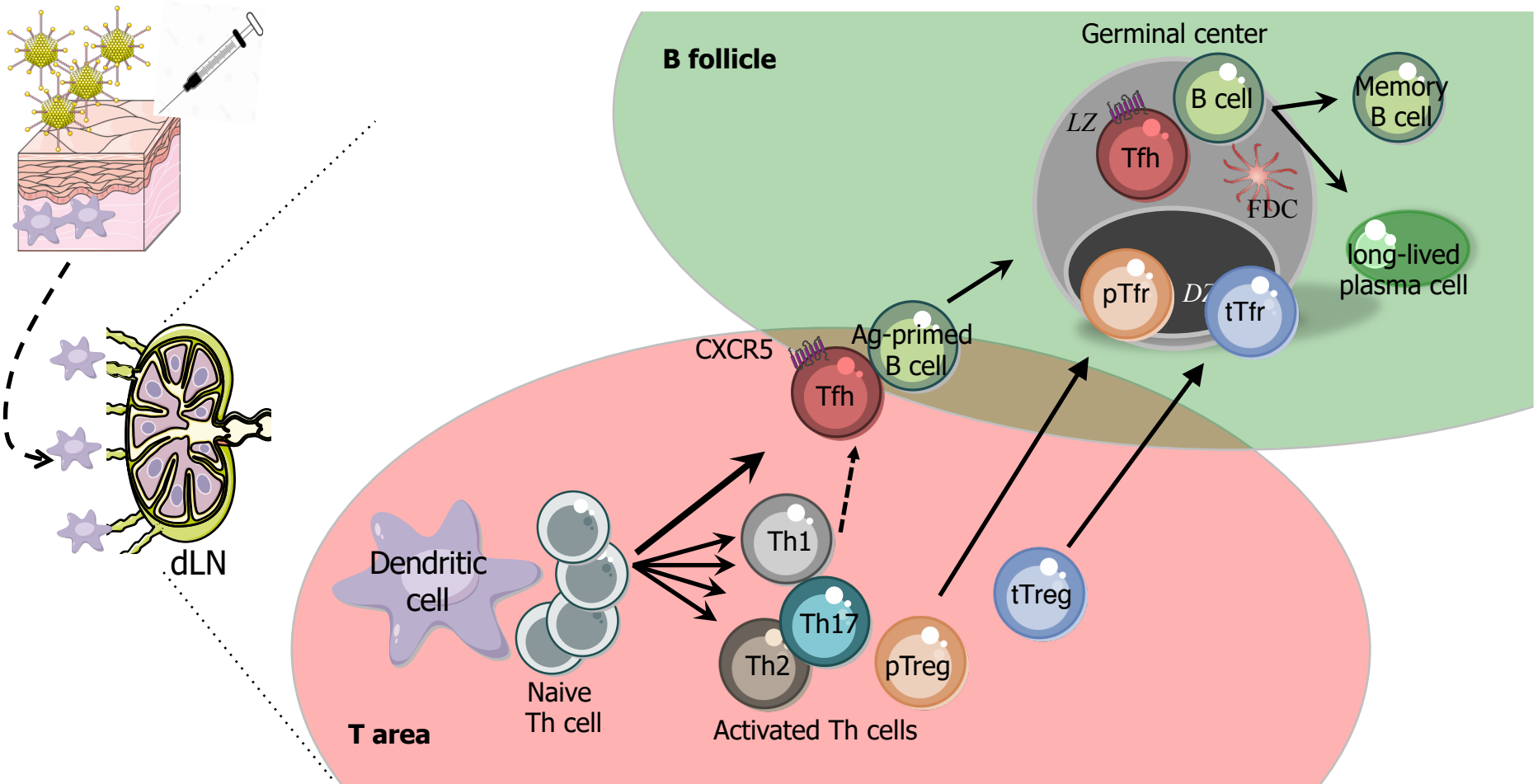


CD45.1 Foxp3 GL-7

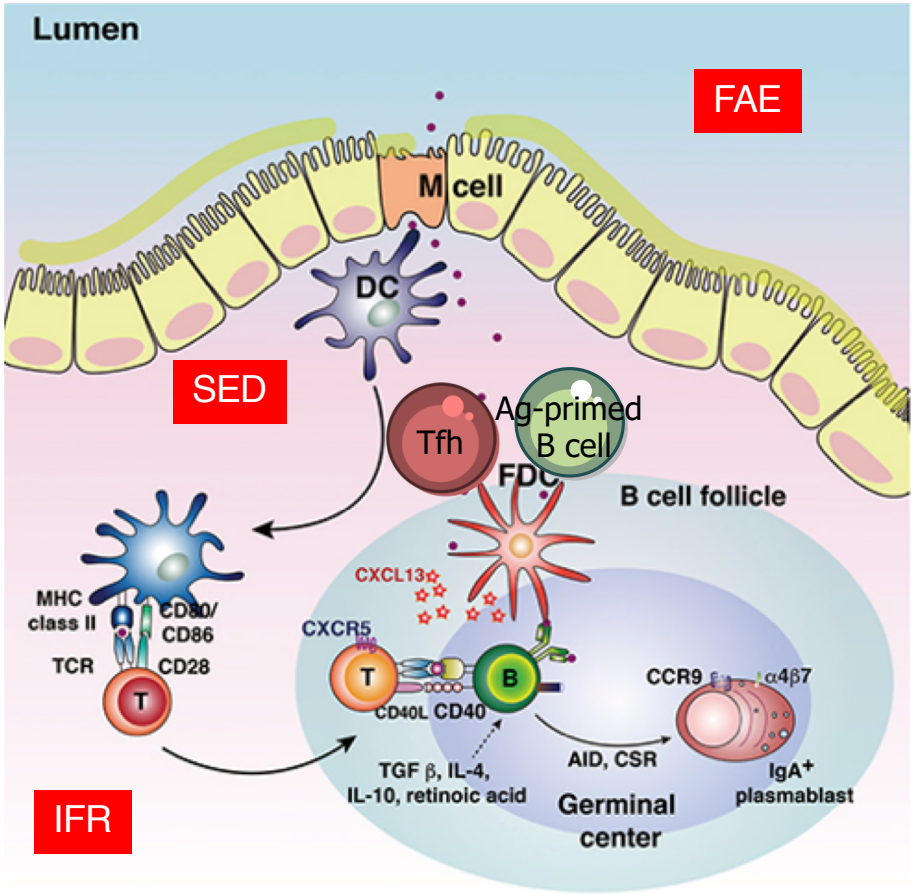
- Tfr compartment is heterogenous based on:
  - antigen-specificity
  - ontogeny: thymic versus peripheral

Aloulou et al Nat communs 2016

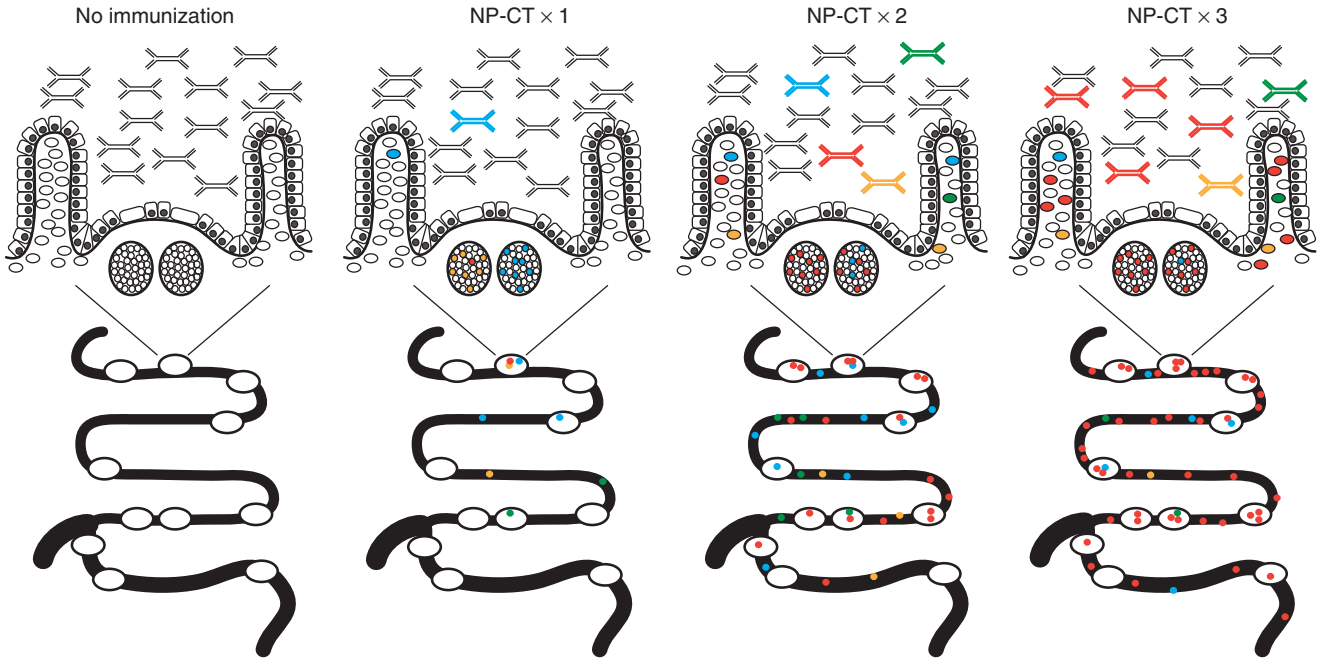
Regulation of B cell responses



B cell responses in mucosal sites

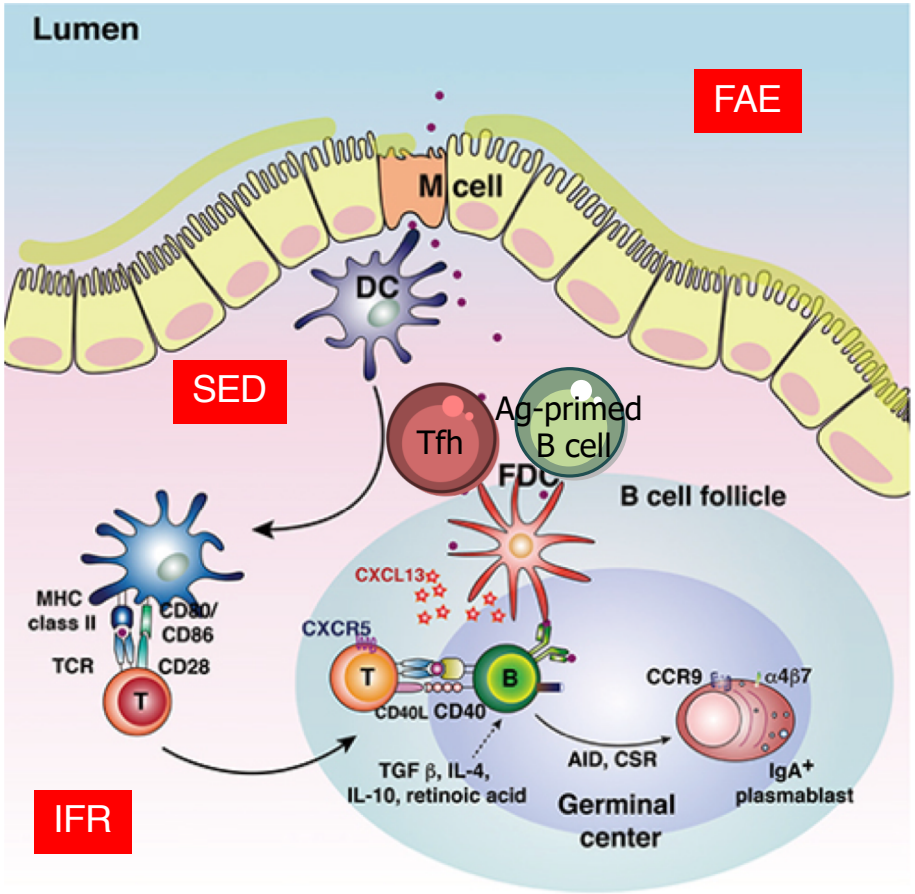


Re-utilization of GCs in multiple PPs results in highly synchronized, oligoclonal, and affinity-matured gut IgA responses

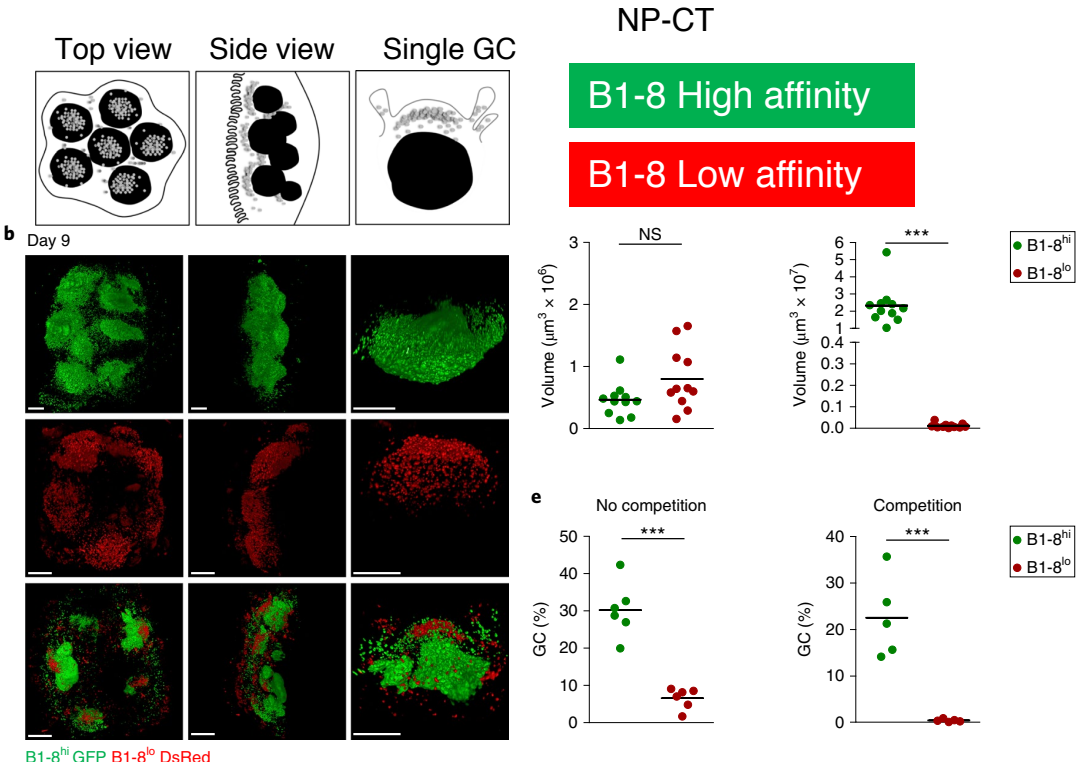


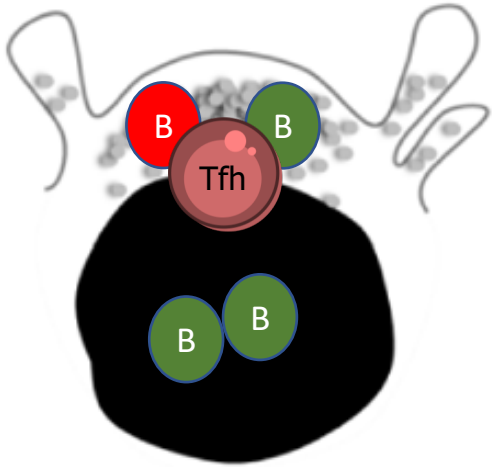
Bergqvist et al Mucosal Immunol 2013

B cell responses in mucosal sites



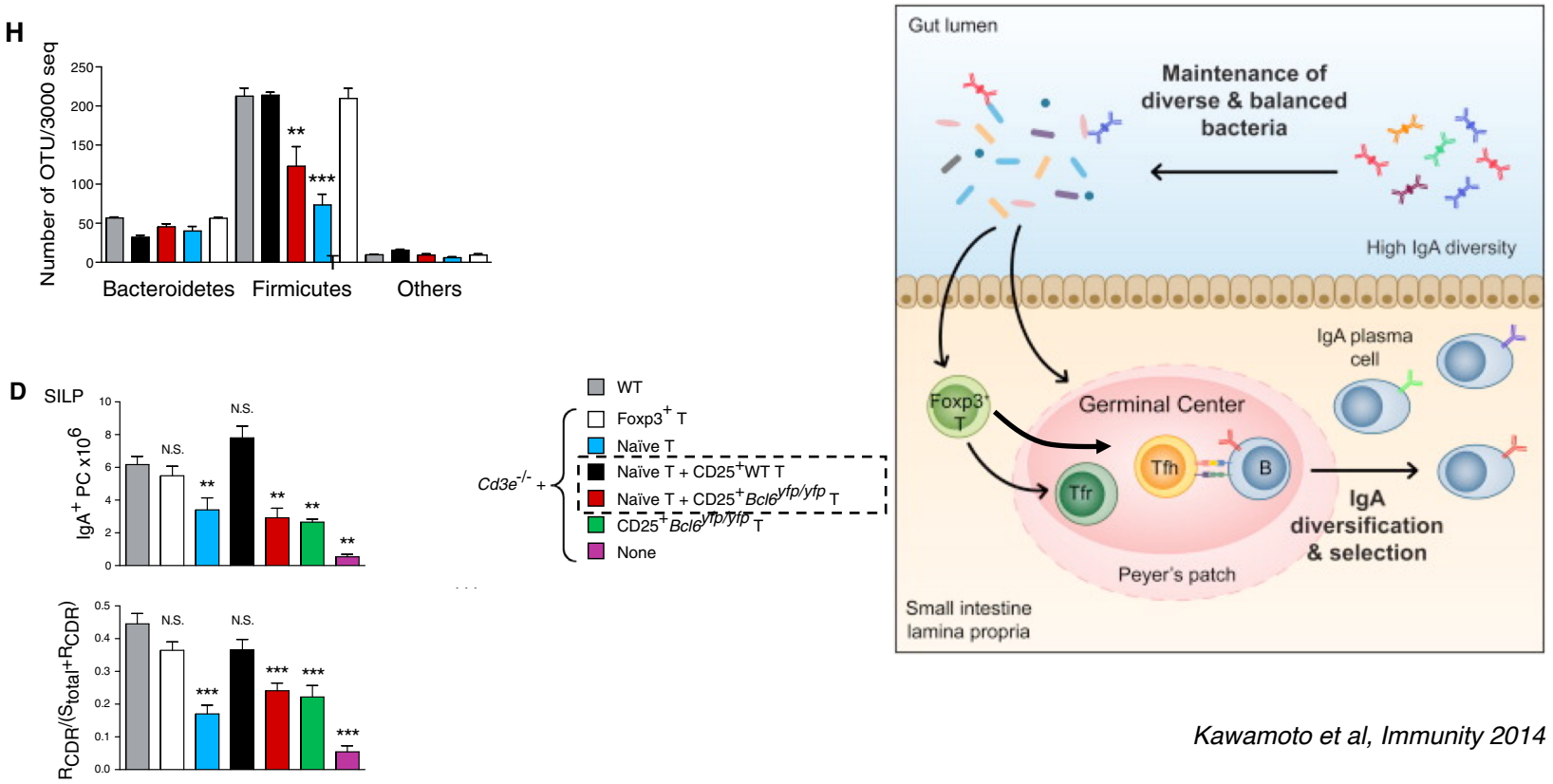
BCR affinity controls GC infiltration but neither proliferation nor early plasmablast formation in the SED





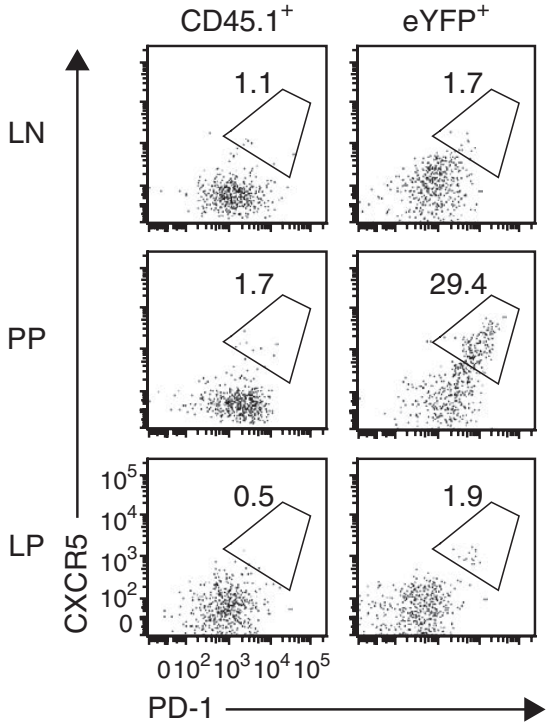
Biram et al, Nat Immunol 2019

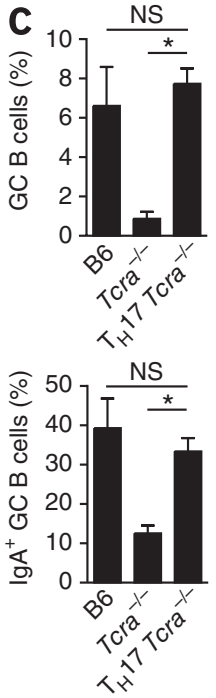
Foxp3-Regulated Microbiota Induces Maturation of Gut Immune System



Kawamoto et al, Immunity 2014

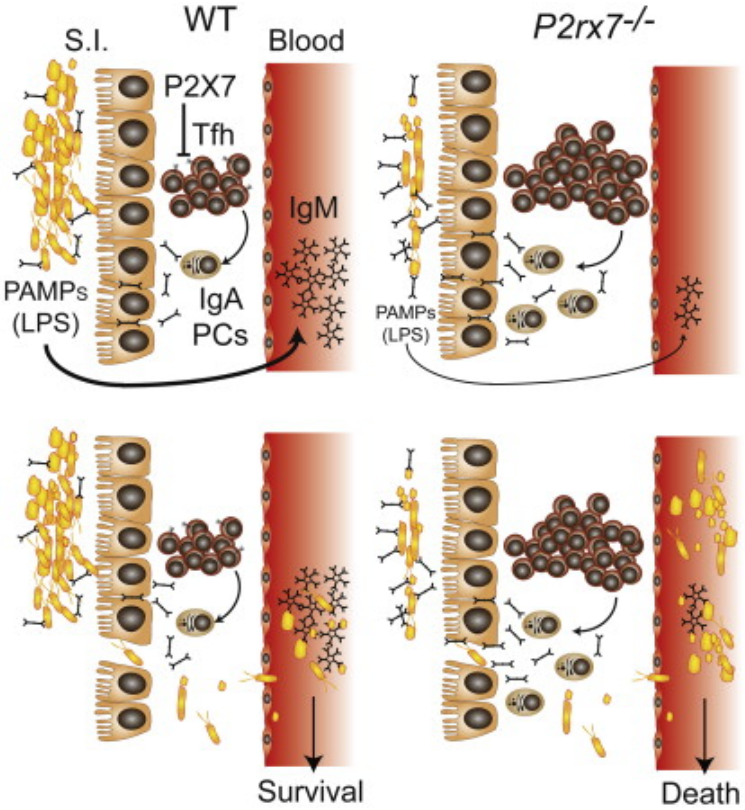
High affinity IgA need Th17 plasticity





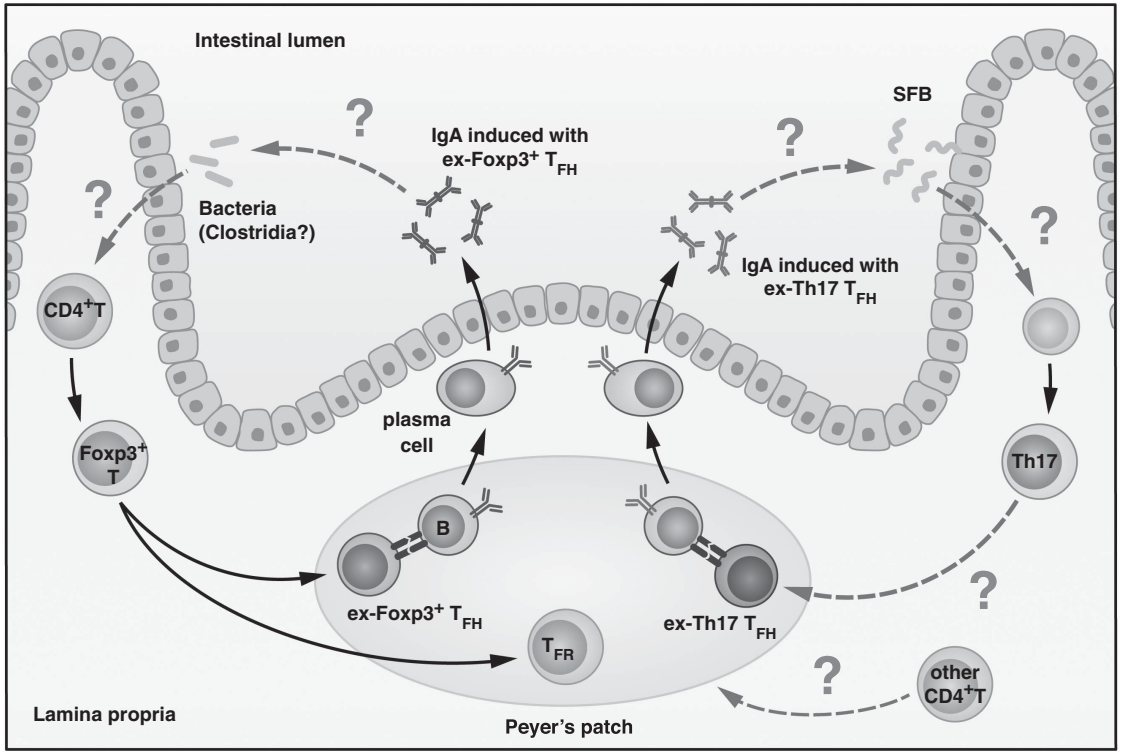
Horota et al, Nat Immunol 2013

P2X7 receptor controls T-cell-dependent IgA response to preserve commensalism



Proietti M et al Immunity 2014
Proietti et al Nat commus 2019

Regulatory loop between Tfh cells, IgA and gut microbiota



Kato et al, Immunology and Cell biology 2014

Cebula et al Nature 2013

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