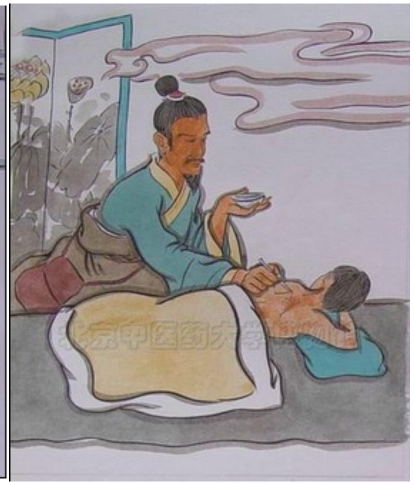
B cell activation and long-lived plasma cells

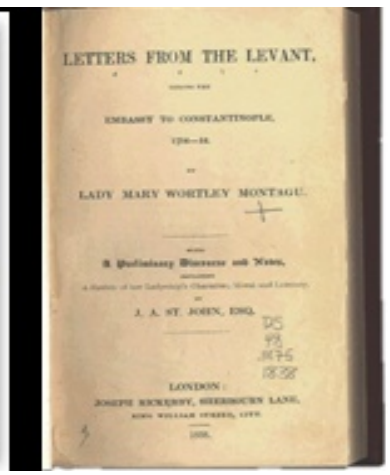
Dirk Mielenz
University of Erlangen-Nuremberg
Division of Molecular Immunology

molecular immunology

Generation of antibodies is the basis for the vast majority of succesful vaccination strategies



ca. 1000	Children were given dried pustules of convalescent Pock patients (Variolation, „*Variola*“ from lat. varius = blurry, checkered)
ca. 1500	variolation in Harems
1717	Mary Wortley Montagu introduces from Turkey variolation in Europe
1760	Variolation of the famillies of Maria Theresia and George III. make variolation popular
1776	Washington variolates its continental army



LETTERS FROM THE LEVANT,

EMBASSY TO CONSTANTINOPLE,

LADY MARY WORTLEY MONTAGU.

J. A. ST. JOHN, ESQ.

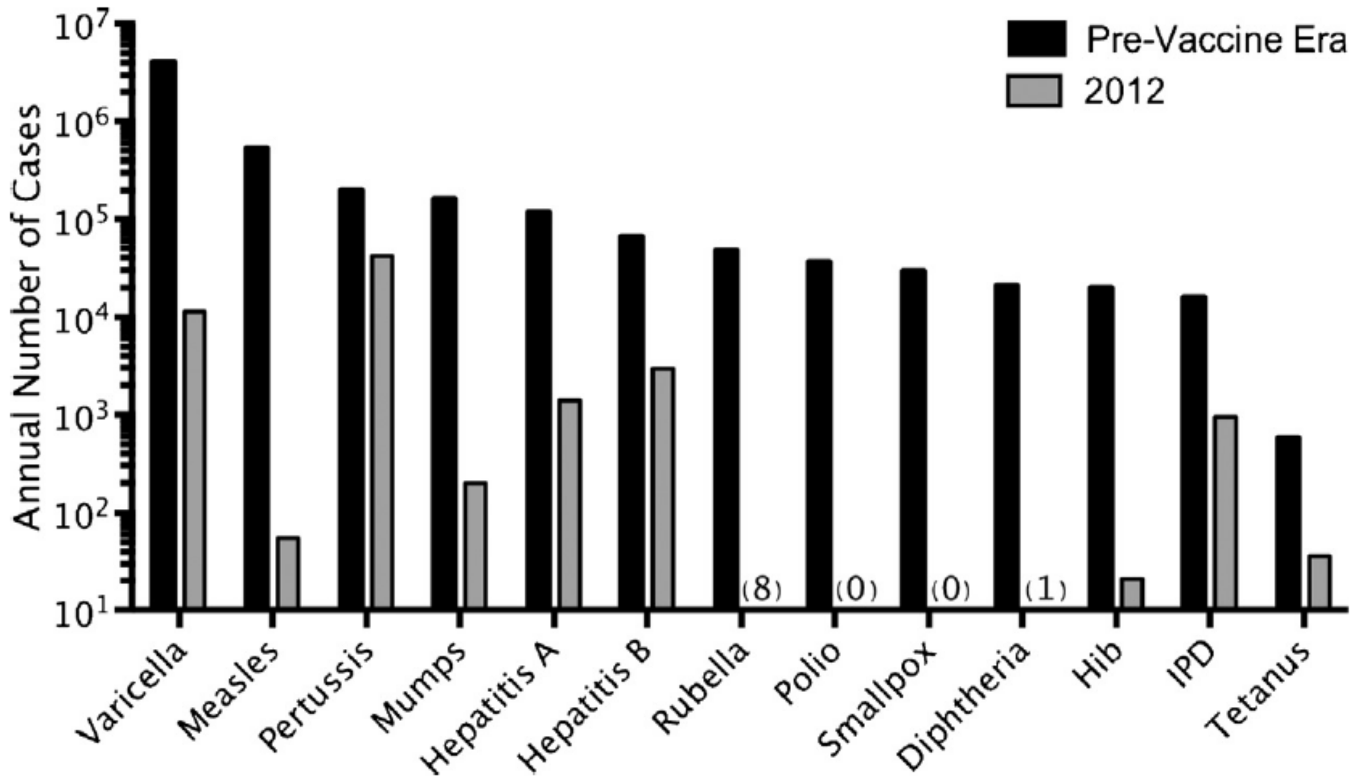
LONDON:

Lady Mary Montagu, wife of the British ambassodour to Turkey

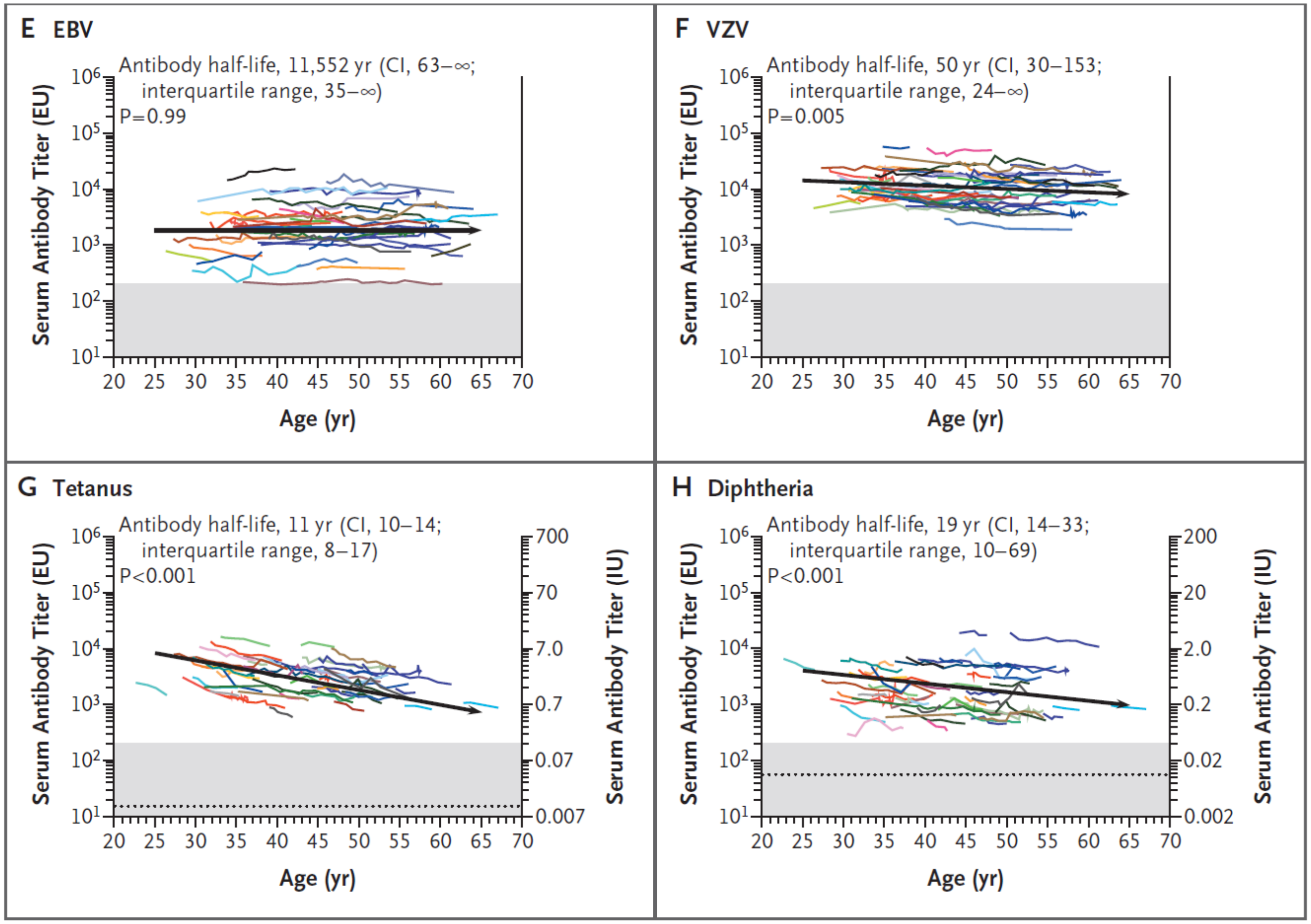
Nutt et al., Nat. Rev. Immunol., 2015
H.M. Jäck, Division of Molecular Immunology, Erlangen

How succesful vaccination reduced incidence of infectious diseases

M.K. Slifka, I. Amanna / Vaccine 32 (2014) 2948–2957



Duration of humoral immunity to common viral and vaccine antigens



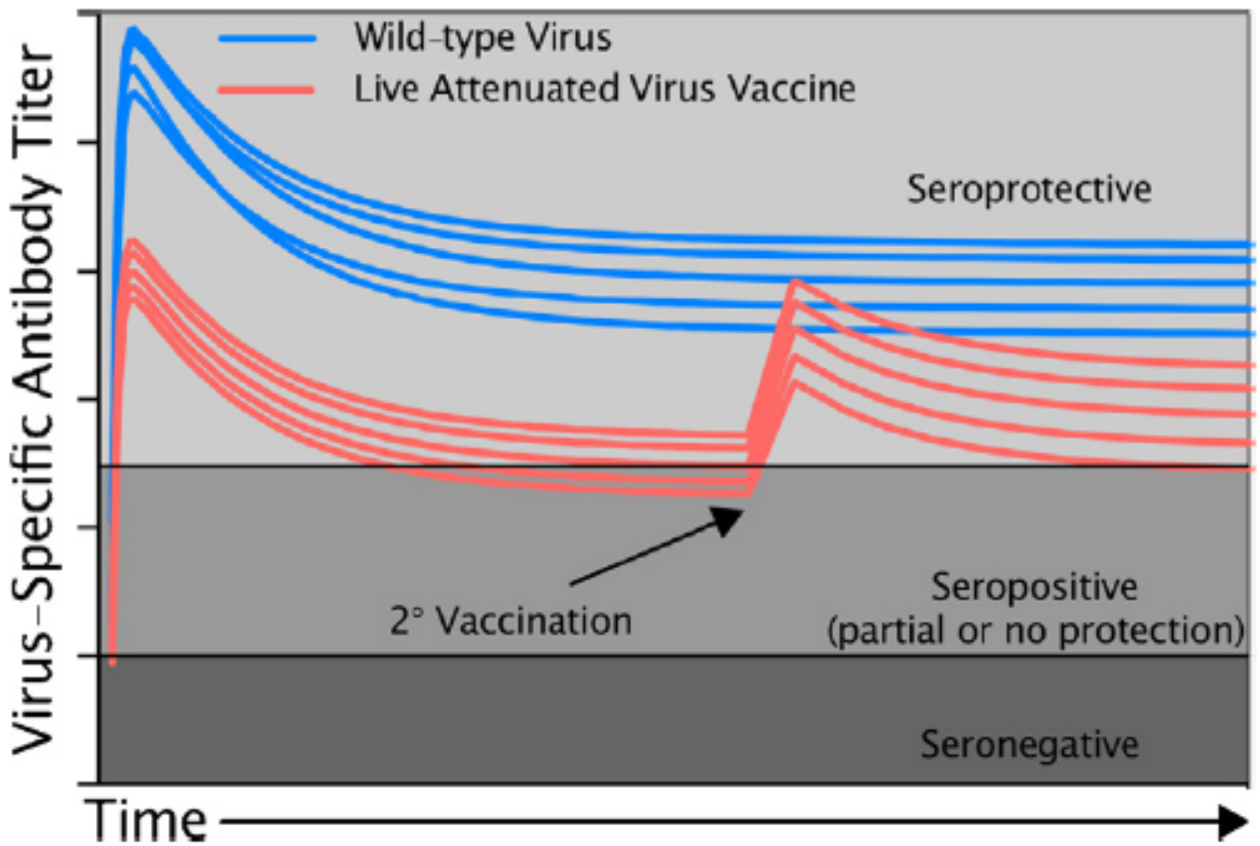
Viral antigens
Very long halflife

Protein antigens
Shorter half-life

Latent infection, recurrent re-exposure, repetitive infections, memory cell numbers or bystander memory is not necessarily an indicator for antibody titer longevity; **it is likely the nature of the antigen**

Amanna et al., NEJM, 2007

Relationship between long-term immunity and long term protection



M.K. Slifka, Vaccine, 2014

Questions – principles of antibody formation

Are there different kinds of antibodies?

What are the cells that secrete antibodies?

Is there only one type of B cells?

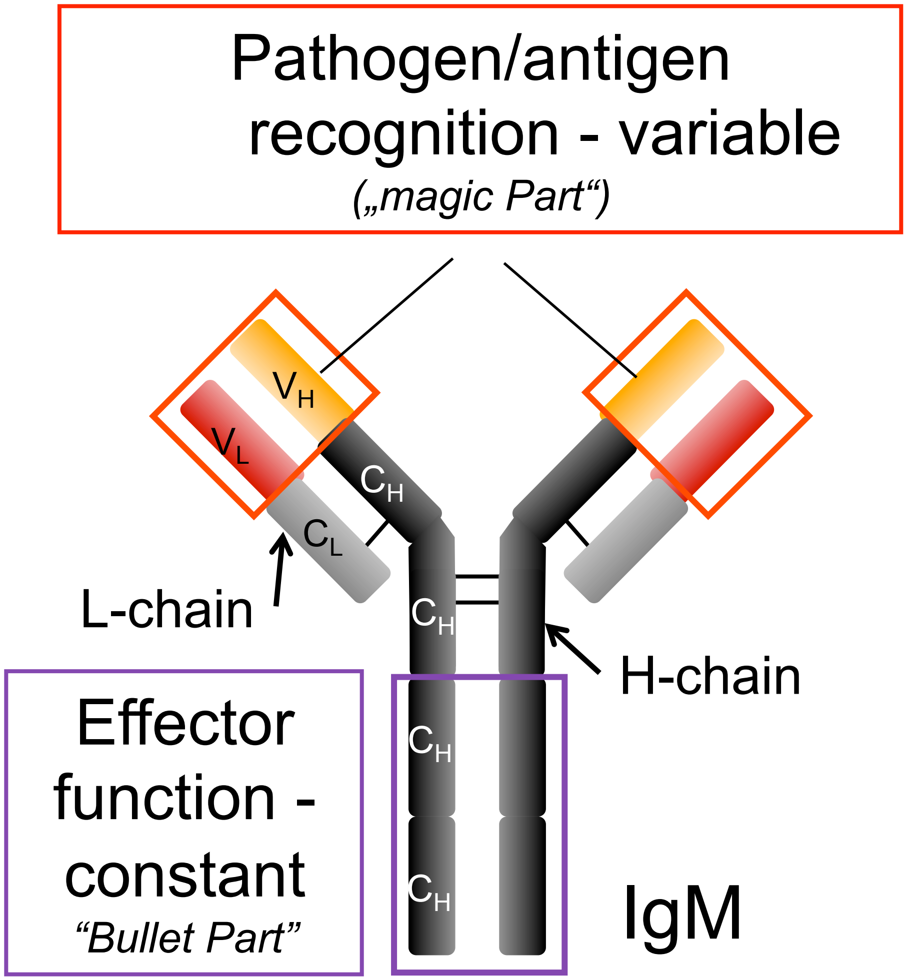
Is a B cell completely autonomous?

How does a B cell develop into a plasma cell?

How does a B cell sense an antigen – and where?

Does a normal B cell make „good“ antibodies?

Antibodies



Ig-Classes

IgM (penta/hexameric) - blood

IgG blood

[IgD]

IgA (dimer) - gut

IgE - mucosa

Antibodies are bifunctional molecules secreted by differentiated B cells

H.M. Jäck

Antibodies

IgM

- Antigen receptor on immature and naive/IgM memory B cells
- First line defense during immune reaction
- Very good agglutination
- anti-inflammatory (artherosclerosis)

IgD

- Antigen receptor on mature B cells

IgG

- Main antibody in blood → **Internal defense**
- Passes placenta

IgA

- Main Ab on mucosal and gut surfaces (lung, gut, urogenital tract) → **External defense**
- In tears, sputum, mother milk (passive immunity important for newbornes)

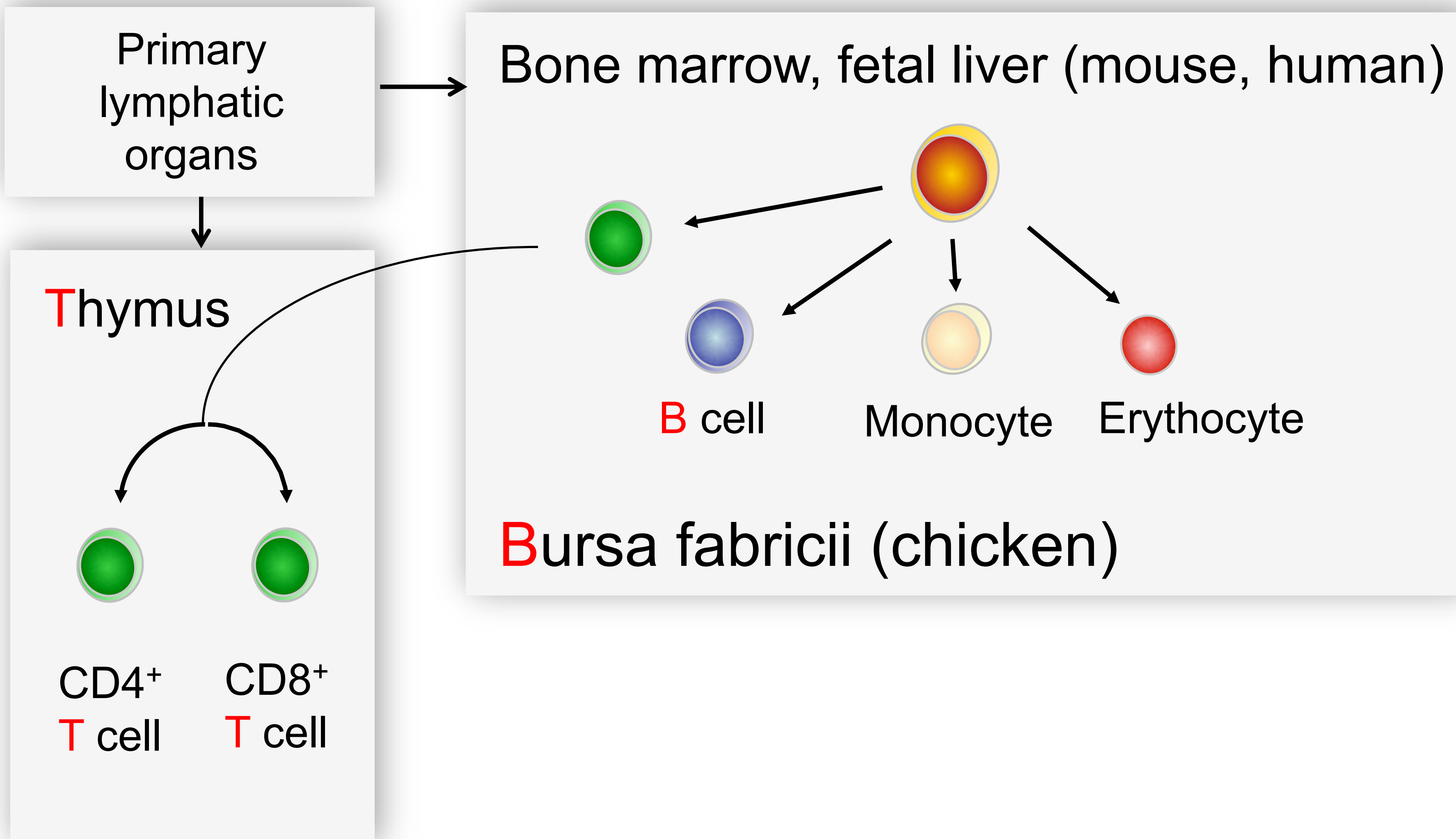
IgE

- activates effector cells (mast cells, eosinophils) during worm infection
- allergy

Antibody effector functions

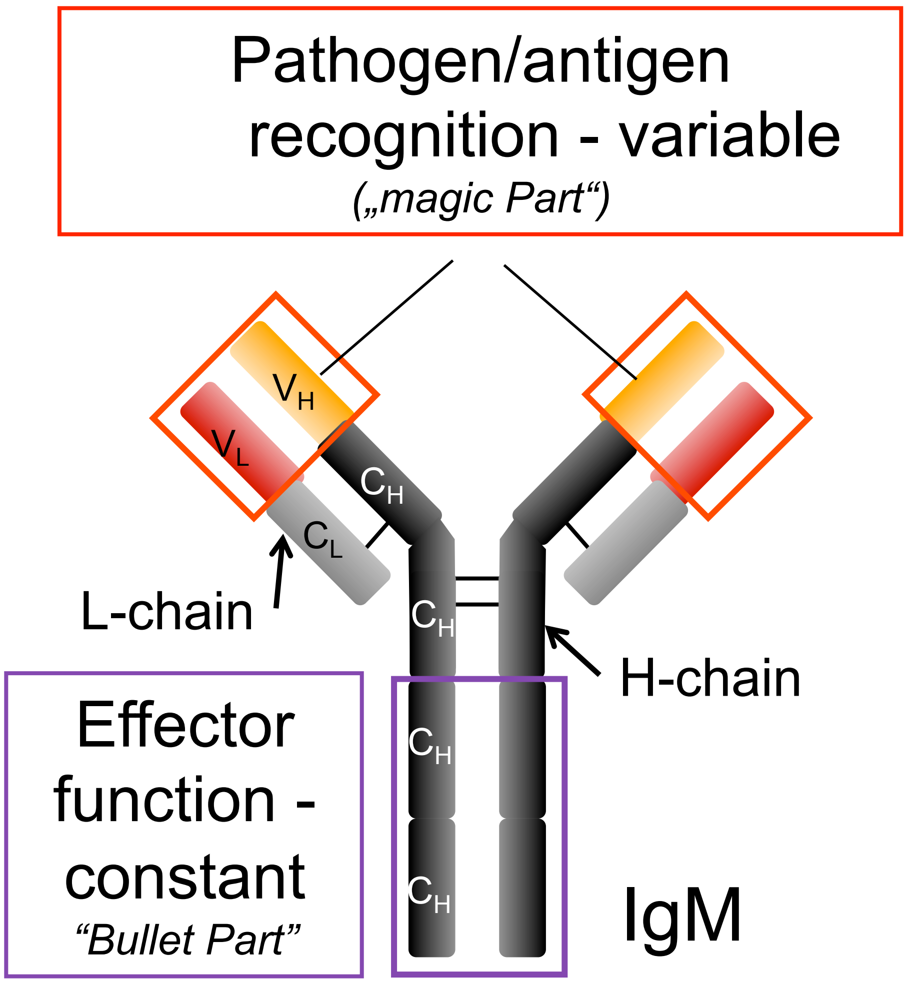
- Agglutination of bacteria (IgM)
- Neutralisation (IgG, IgA)
- Phagocytosis and Opsonization (IgM und IgG)
- Killing (antibody dependent cytotoxicity, ADCC; antibody dependent respiratory burst, ADRB)
- Mast cell activation (IgE) – inflammation
- Immune regulation via activating and inhibitory Fc receptors

Lymphocyte Maturation and Migration



H.M. Jäck

Antibodies



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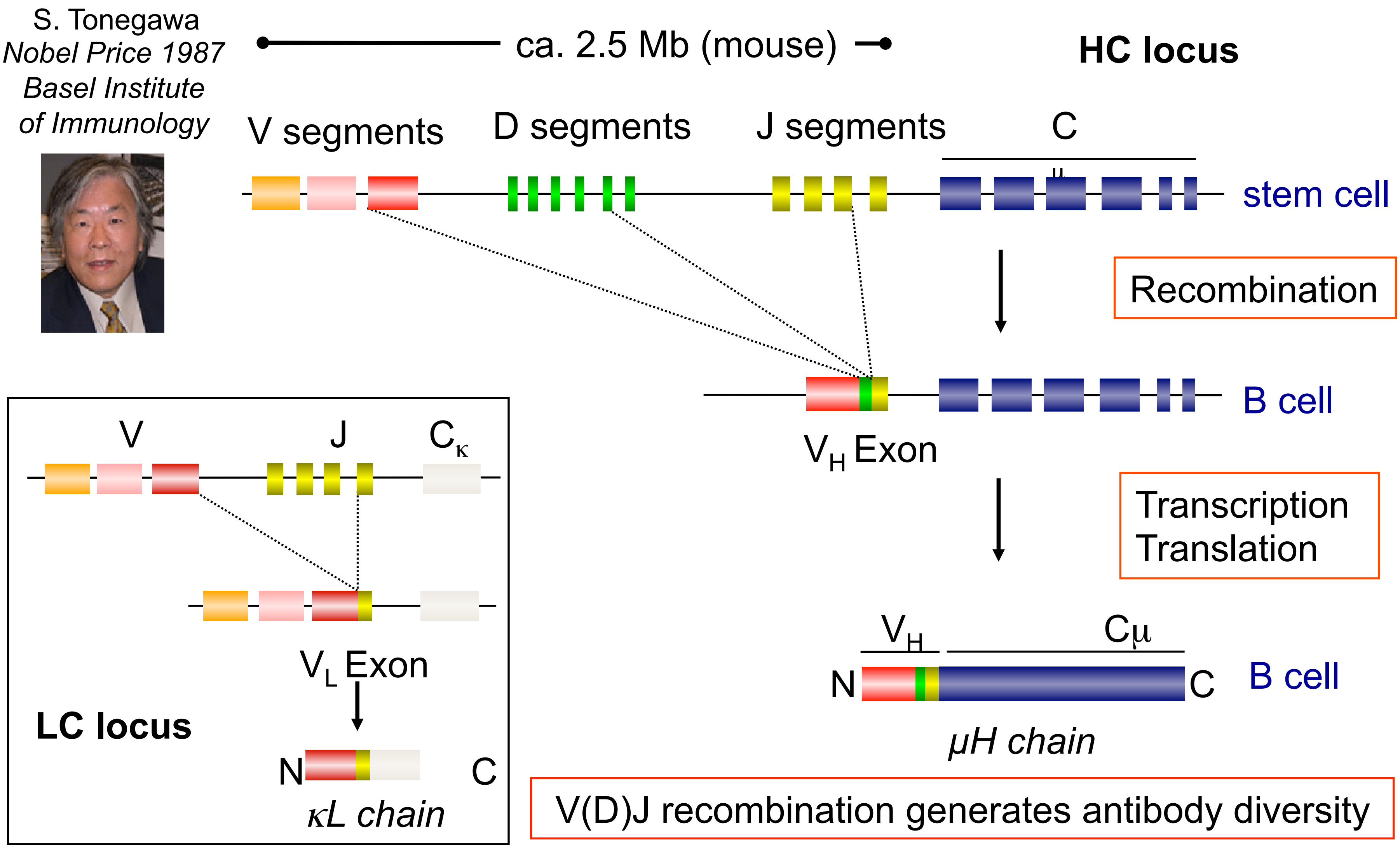
Antibodies are bifunctional molecules secreted by differentiated B cells

H.M. Jäck

Generation of primary antibody diversity (repertoire)



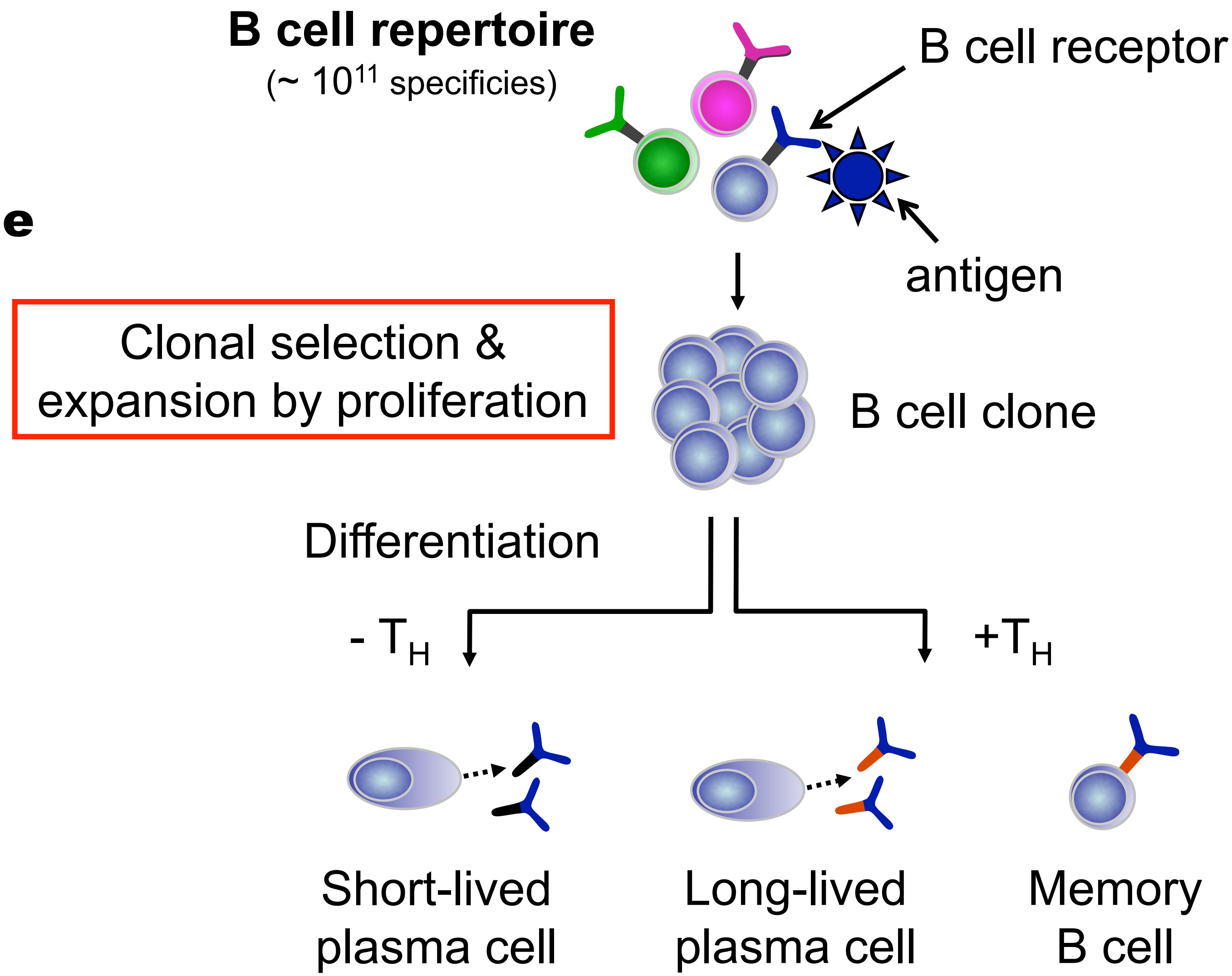
H.M. Jäck

CLONAL Selection Theories (1956-58)

Burnet

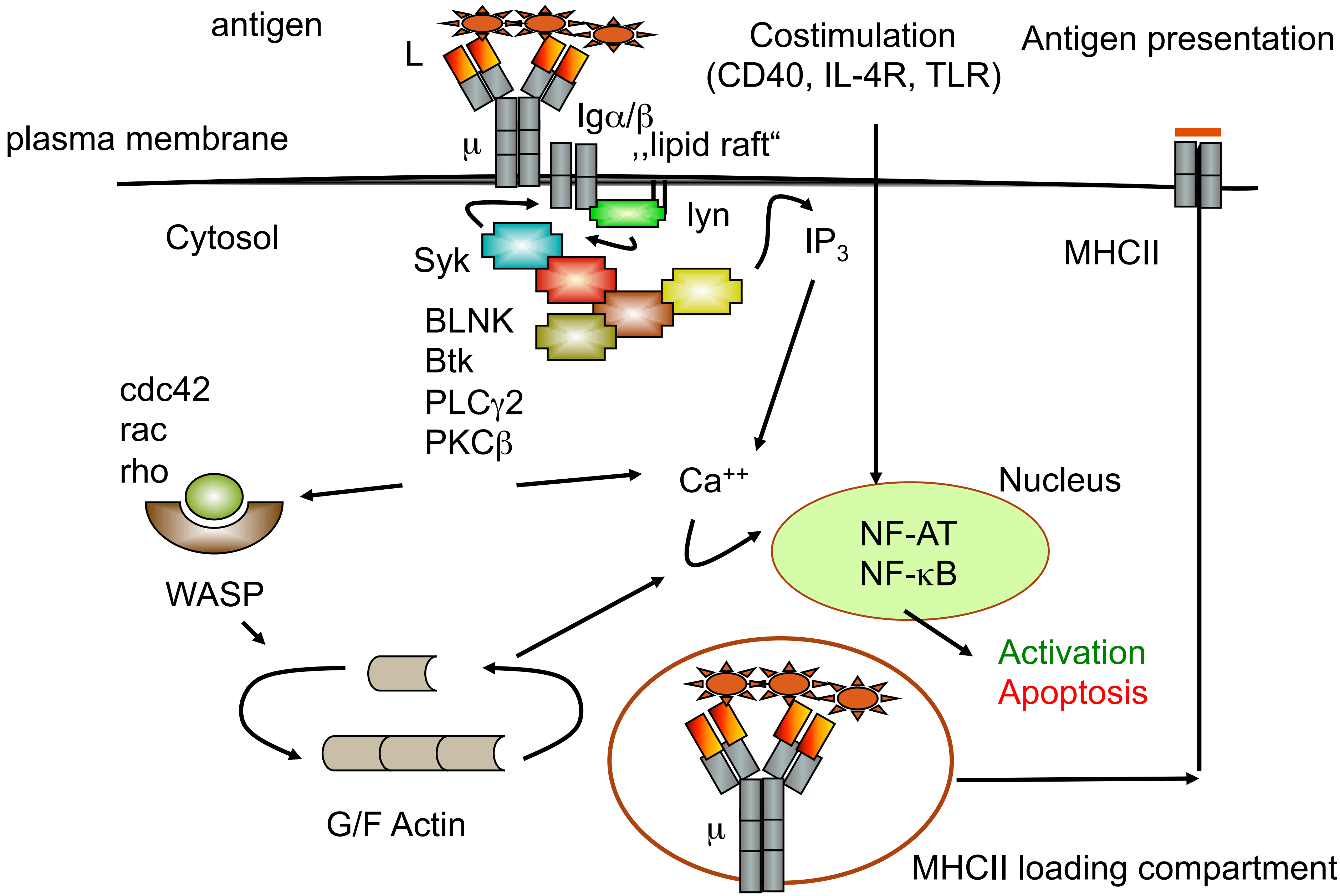
Jerne

Talmage

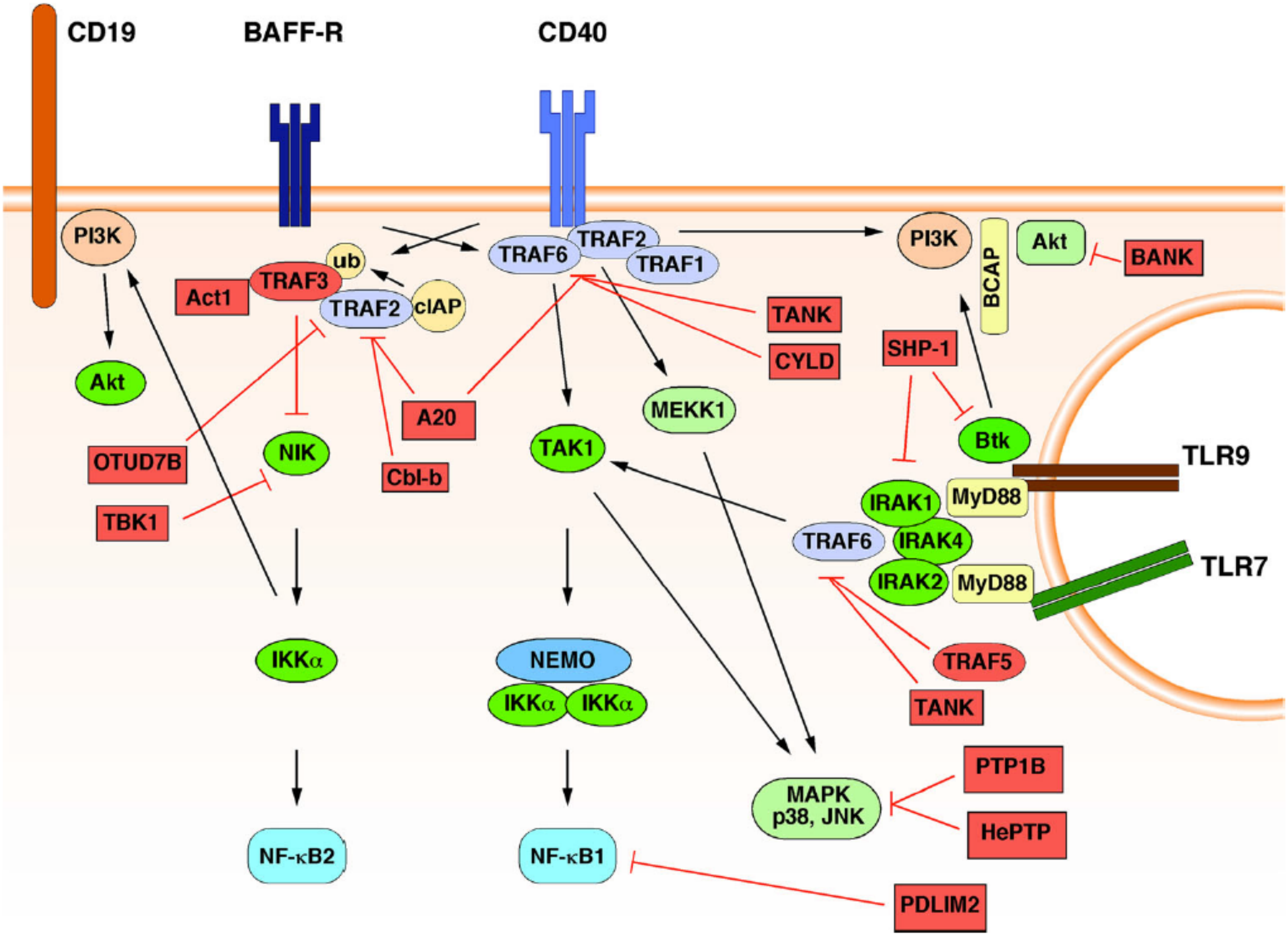


H.M. Jäck

The IgM BCR is a signaling machine and an endocytotic receptor



Integration of adaptive and innate signals in B cells – relevance for antiviral immunity and autoimmunity



Hobeika et al., J. Mol. Med., 2015

IgM BCR signaling

The BCR provides a „tonic“ survival signal

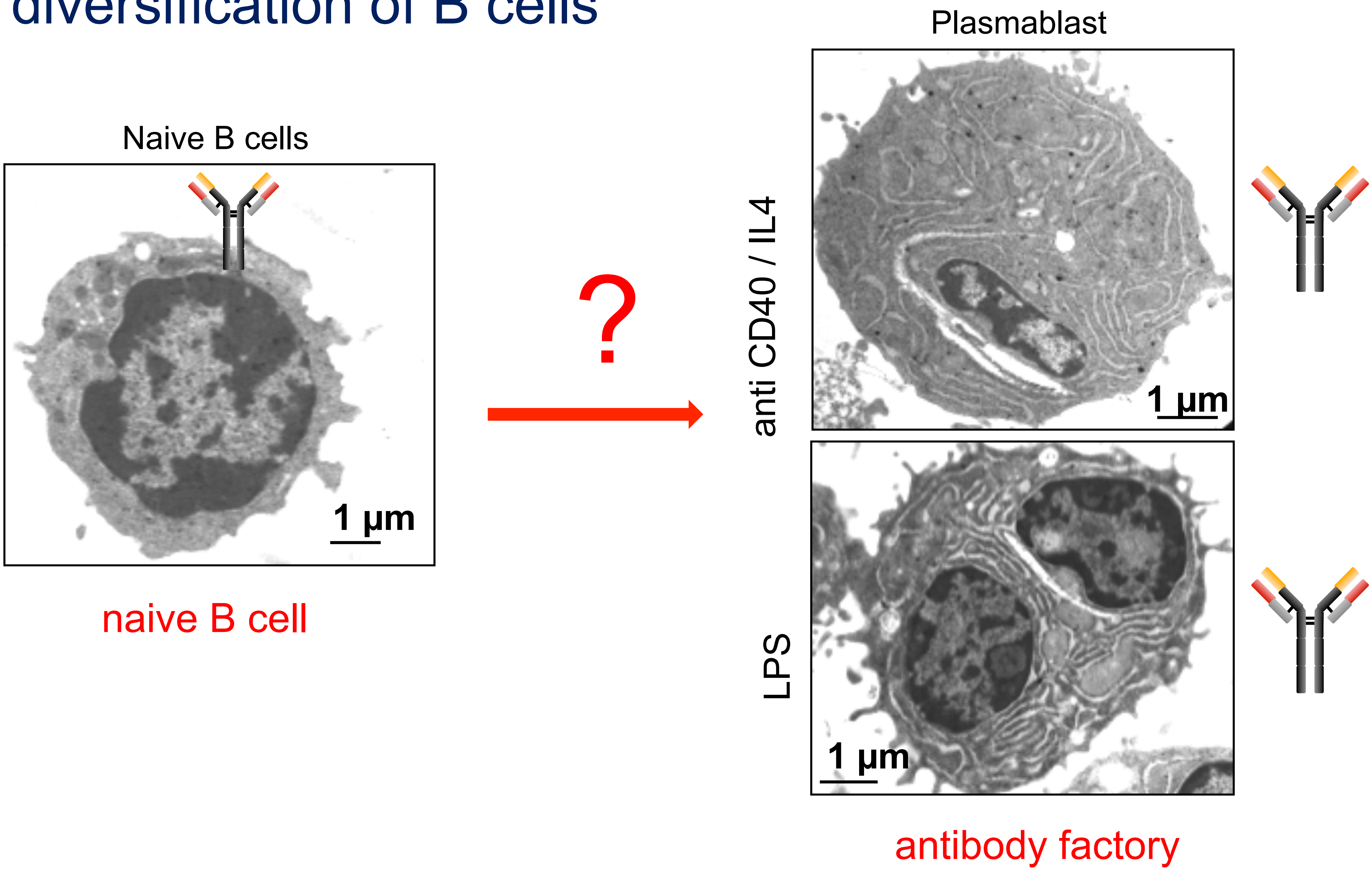
The BCR provides signals for B cell activation by ultimatively triggering transcription factors

The BCR organizes B cell signaling and its machinery integrates signals from CD40 and TLRs

The BCR is an endocytotic receptor which delivers antigen super-efficiently into the MHCII loading compartment

B cell receptor signaling, CTMI, 2016, Kurosaki, Wienands (eds.)

Morphological and functional diversification of B cells



Grötsch B et. al, JEM 2014

Morphological and functional diversification of B cells

Mature B cells are resting and have a low metabolic activity, consuming mainly fatty acids

Activated B cells proliferate and have a high metabolic activity

Plasma cells are quiescent but have an enormous energy turnover and a high, very specific metabolic activity

Plasma cells need a good redox balance

10^3 IgM molecules / s **x** 10^2 disulfide bonds/IgM = 10^5 disulfide bonds / s / cell!!

10^5 sugar molecules / s / cell!

Caro-Maldonado et al., J. Immunol., 2014
Anelli et al., Free Rad. Biol. Med., 2015
Lam et al., Immunity, 2016

Naive B cell subsets: B1 and B2 (marginal zone, MZ, and follicular, FO)

B1 (pleura) and MZ (spleen)

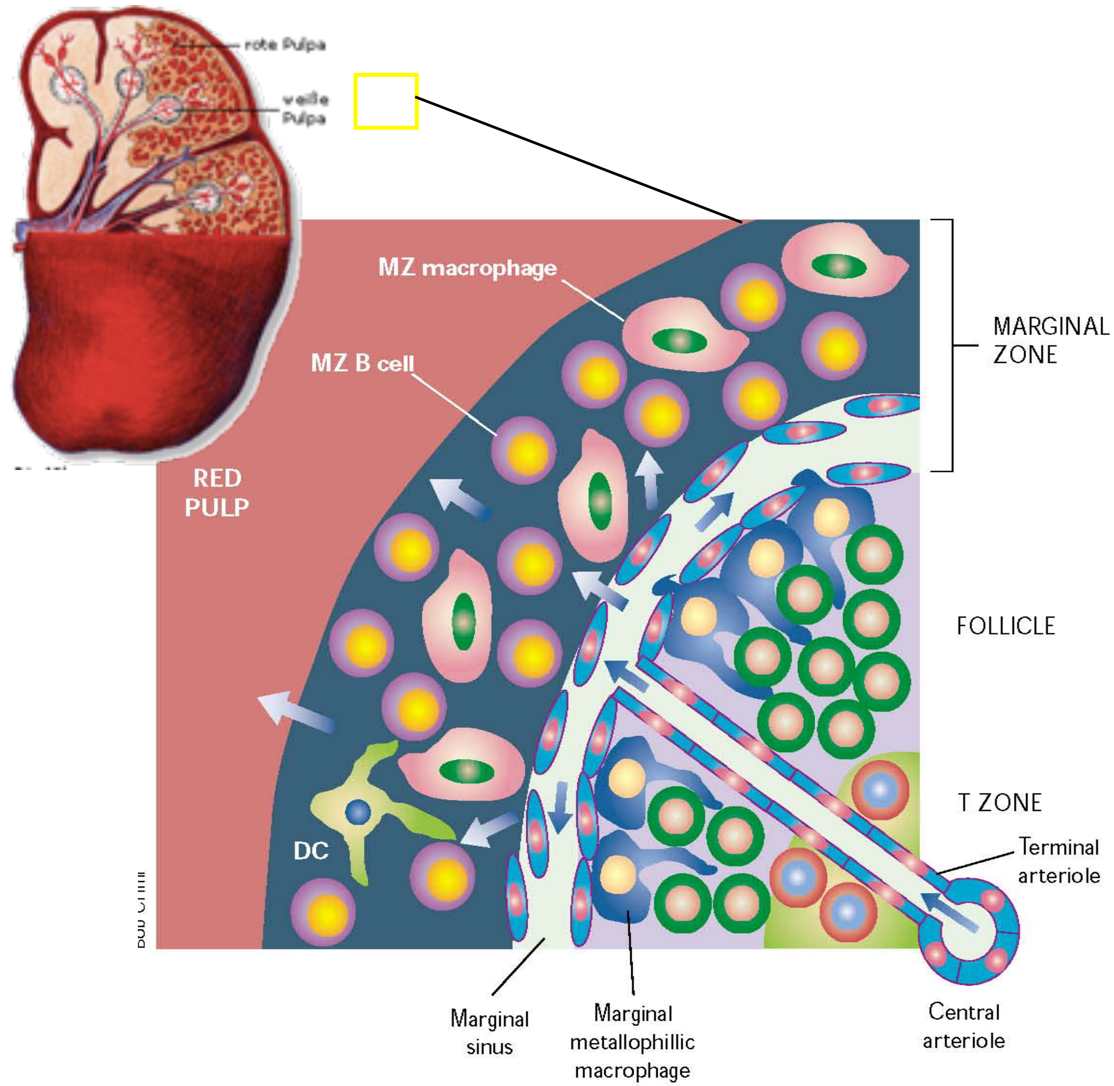
- Rapid T independent response against polysaccharides (encapsulated bacteria) (TLR)
- Natural IgM
- Very rapid differentiation into plasma cells

MZ

- Shuttle between MZ and follicle; transport antigen

FO

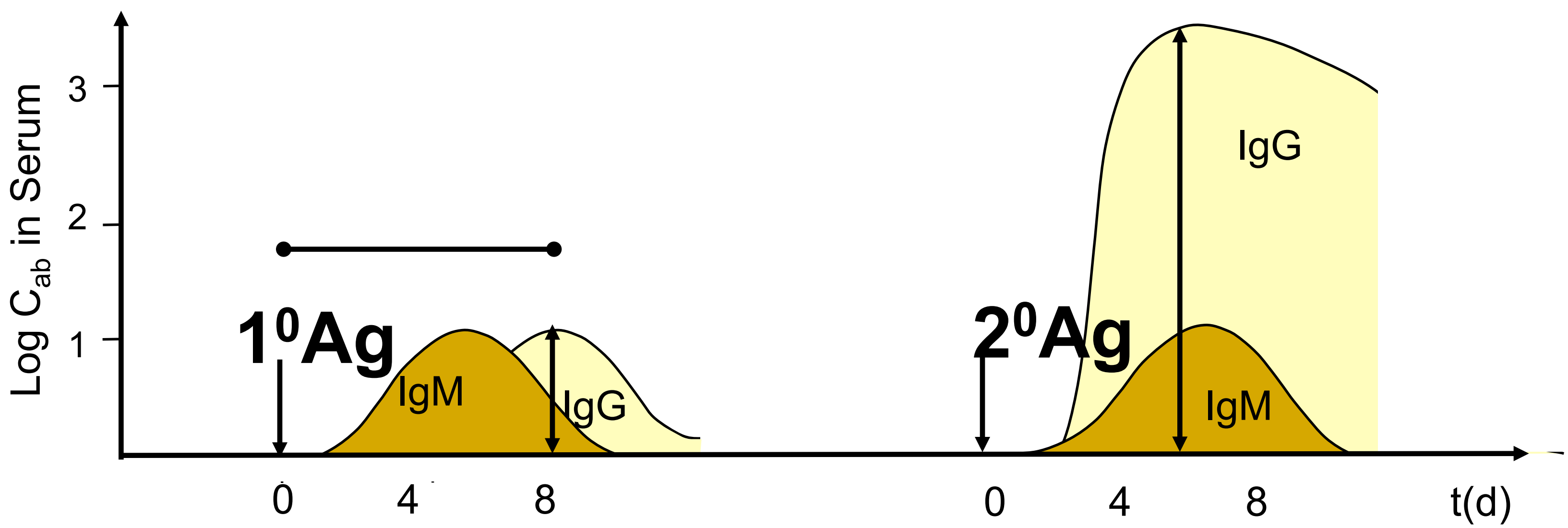
- Prone to interact with T cells
- Give rise to class switched (IgG, IgA, IgE) antibodies + memory



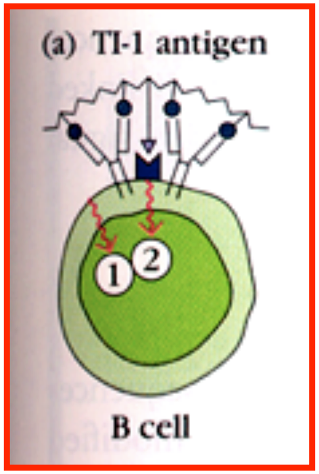
Cyster et al., Nat. Immunol., 2000

Primary and secondary antibody responses

primary **secondary**



Thymus-independent (TI) and dependent (TD) activation - The nature of the antigen matters!

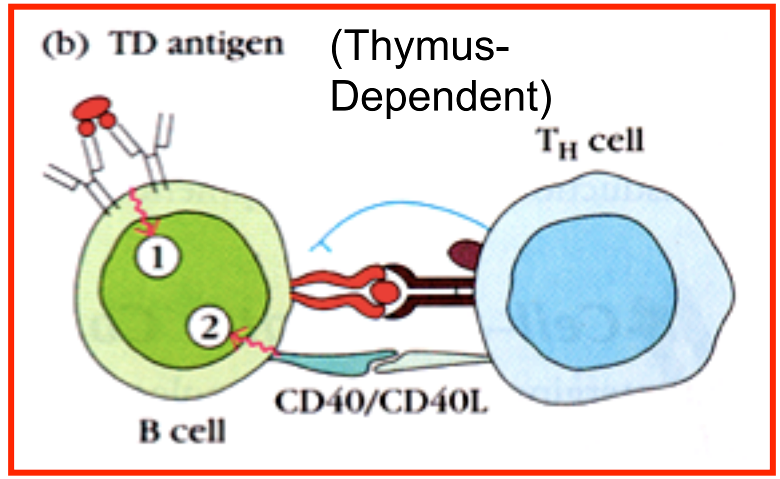


(Thymus-Independent)

- Normally not T cell help
- Bacterial components (PAMPs)
  (i.e., LPS=Lipopolysaccharide)

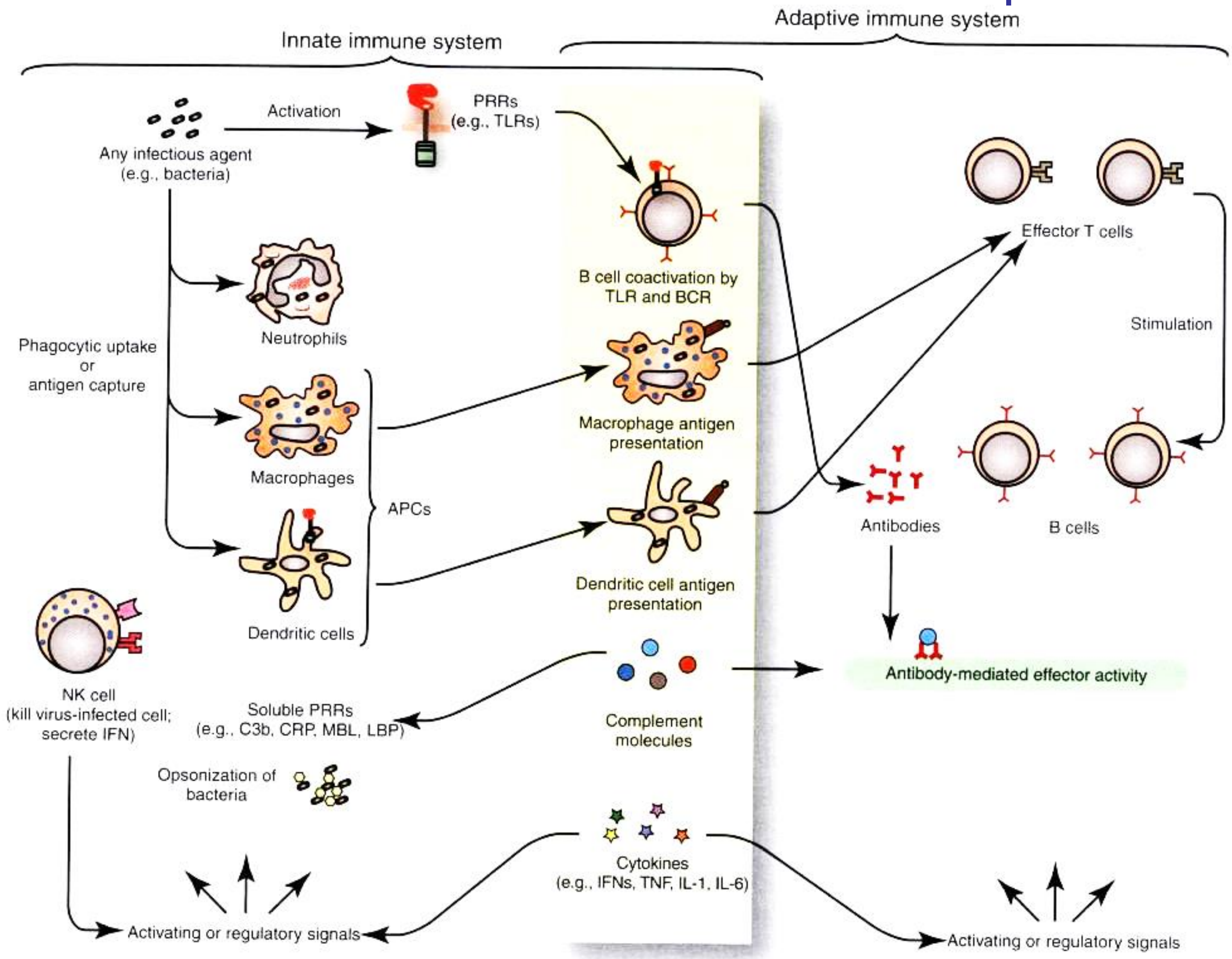
  TLR3/7/9 (mouse)
- Highly repetitive antigens
- B1- and MZ B cells

→ **No memory**



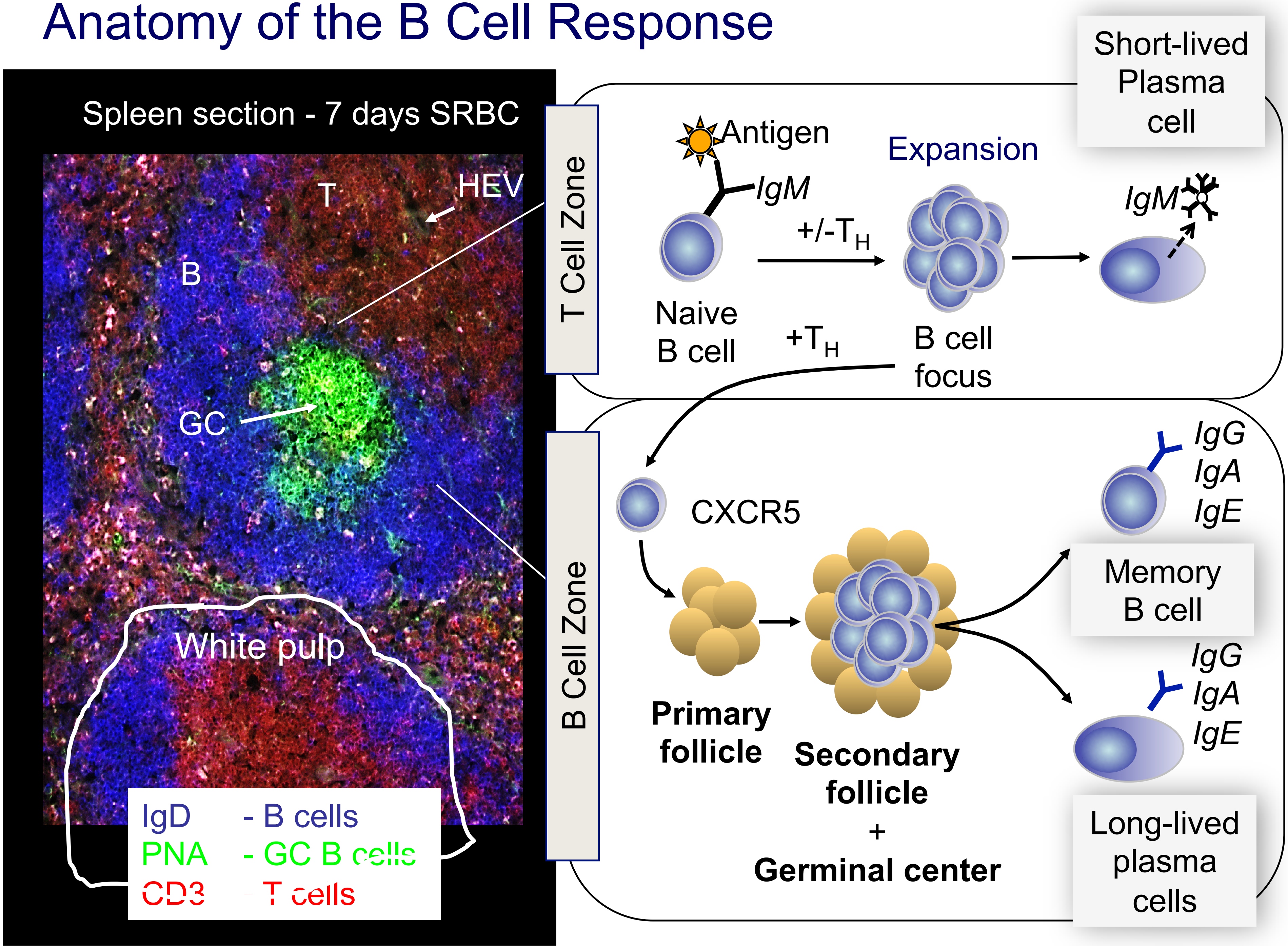
- T cell help
- <u>**Antigen needs to contain protein in a digestable and presentable form**</u>
- Mainly FO B cells
- High affine IgG
- → **Memory**

B cells at the crossroads of innate and adaptive immunity

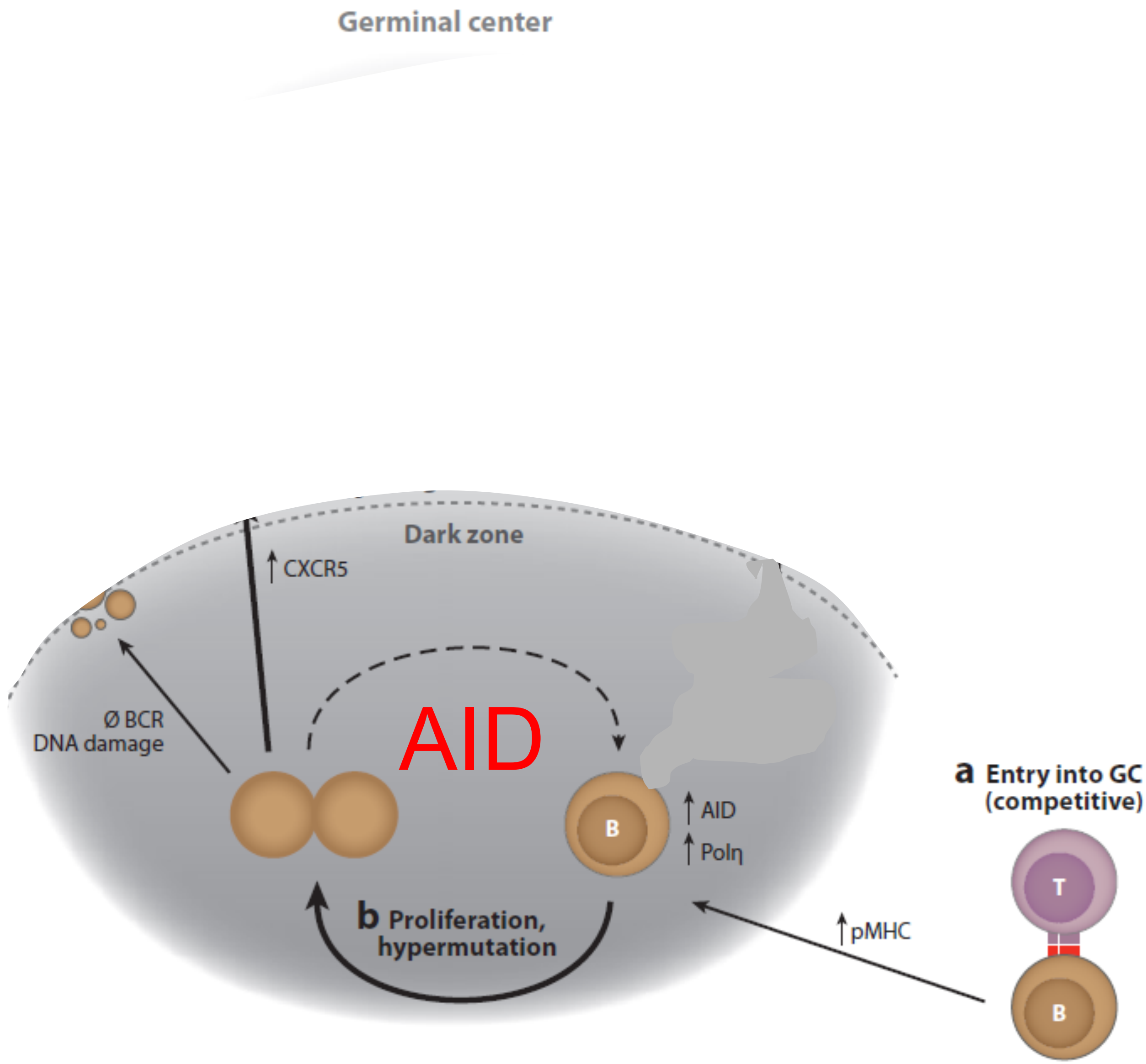


Klaus D. Elgert: „Immunology“, 2nd ed., WILEY-Blackwell, Hoboken, NJ, 2009

Anatomy of the B Cell Response



Fates of activated B cells

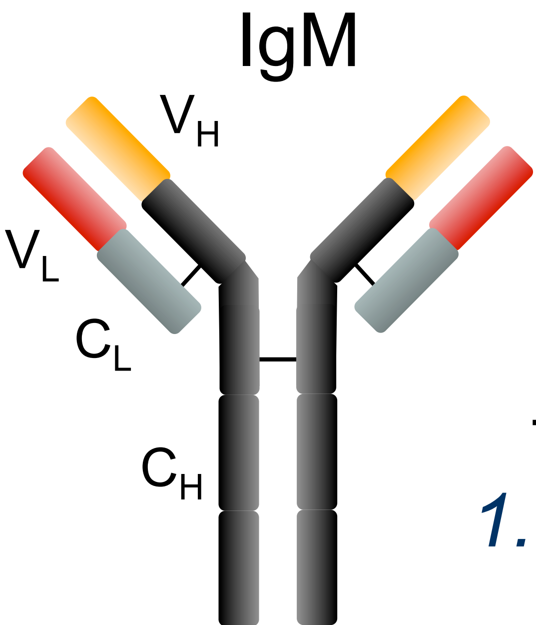


competition for T cells

Muramatsu et al., Cell, 2016
Victora & Nussenzweig, Ann. Rev. Immunology, 2012
Weisel et al., Immunity, 2016

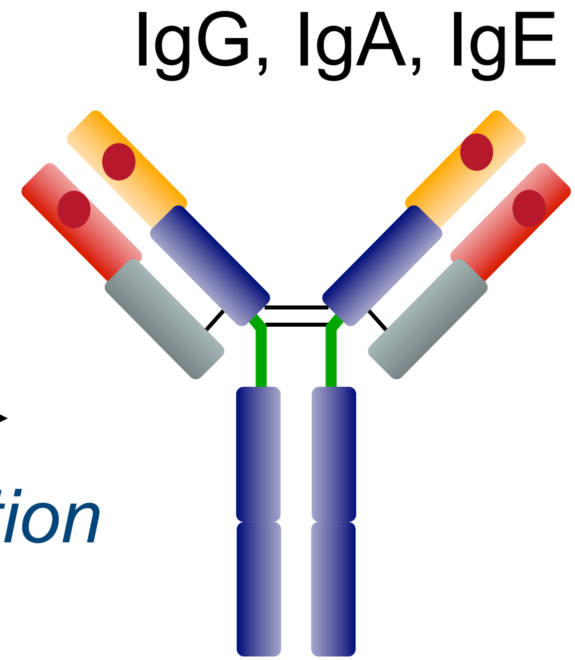
AID: activation induced deaminase

Molecular Changes at the Ig locus (pre GC/dark zone)



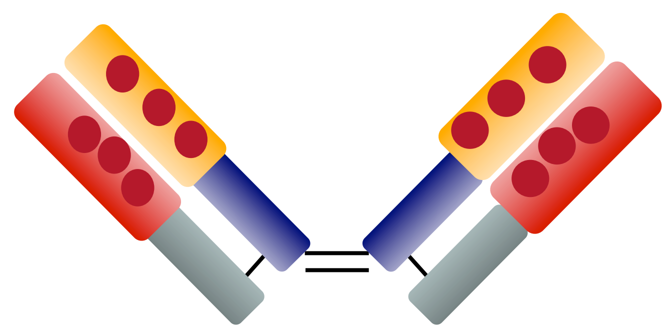
AID

1. *Somatic hypermutation*
2. *IgH class switch*



Escolano et al., Cell, 2016
Tian et al., Cell, 2016

Anti HIV broadly neutralizing Ab (bnAb) are highly mutated and have long CDR3



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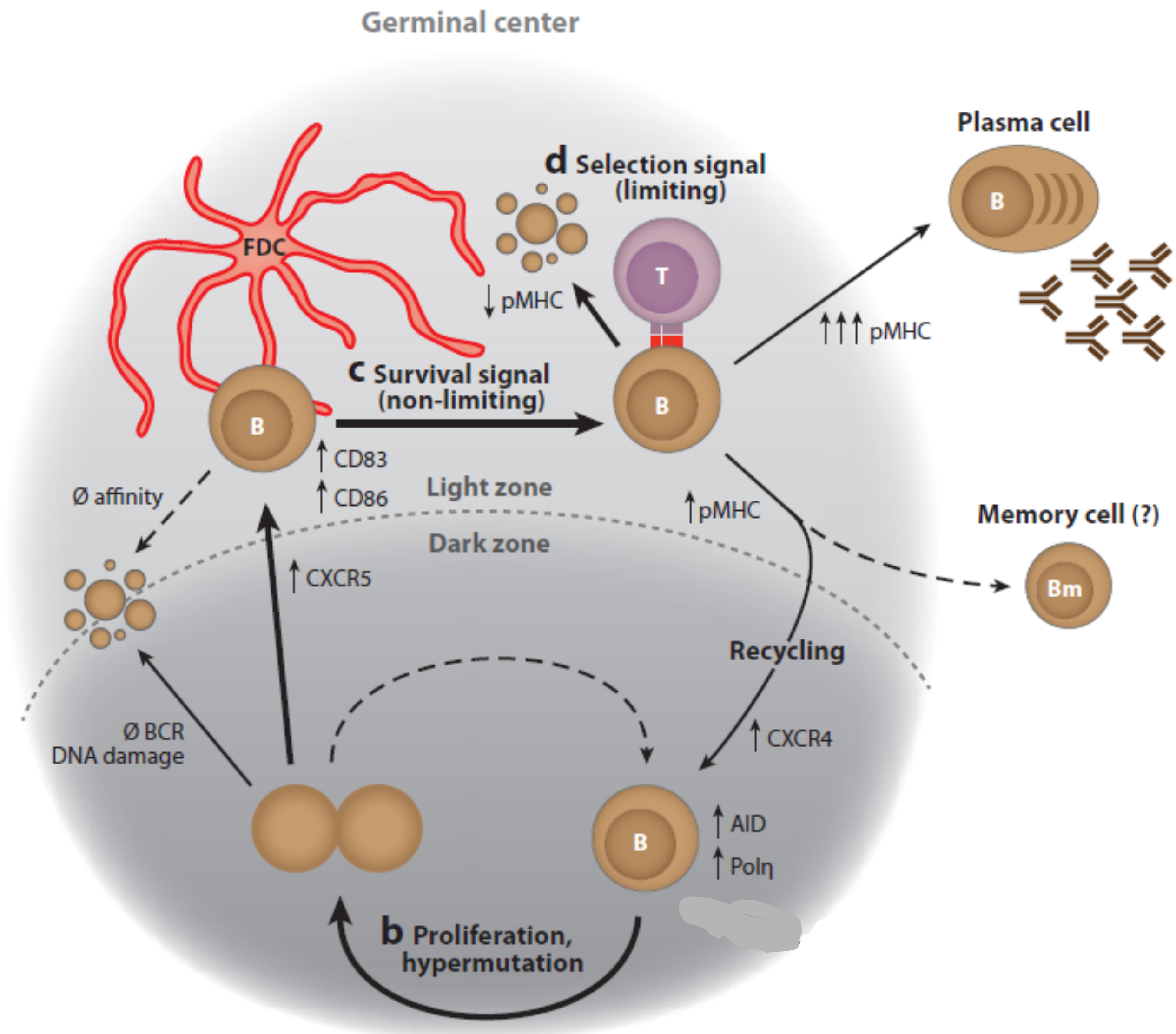
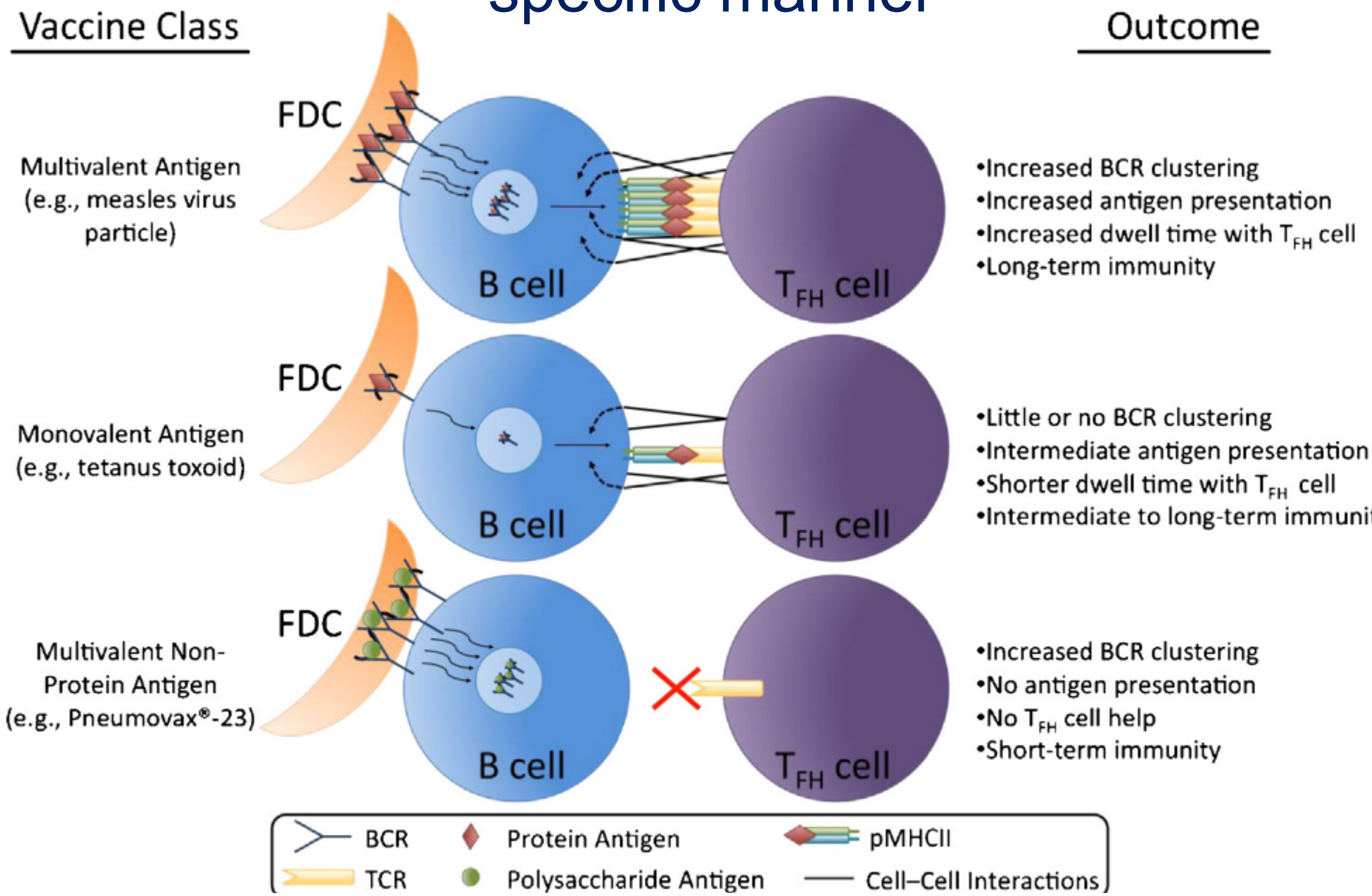


high affine antibodies
class switched
late

lower affinity
class switched
early

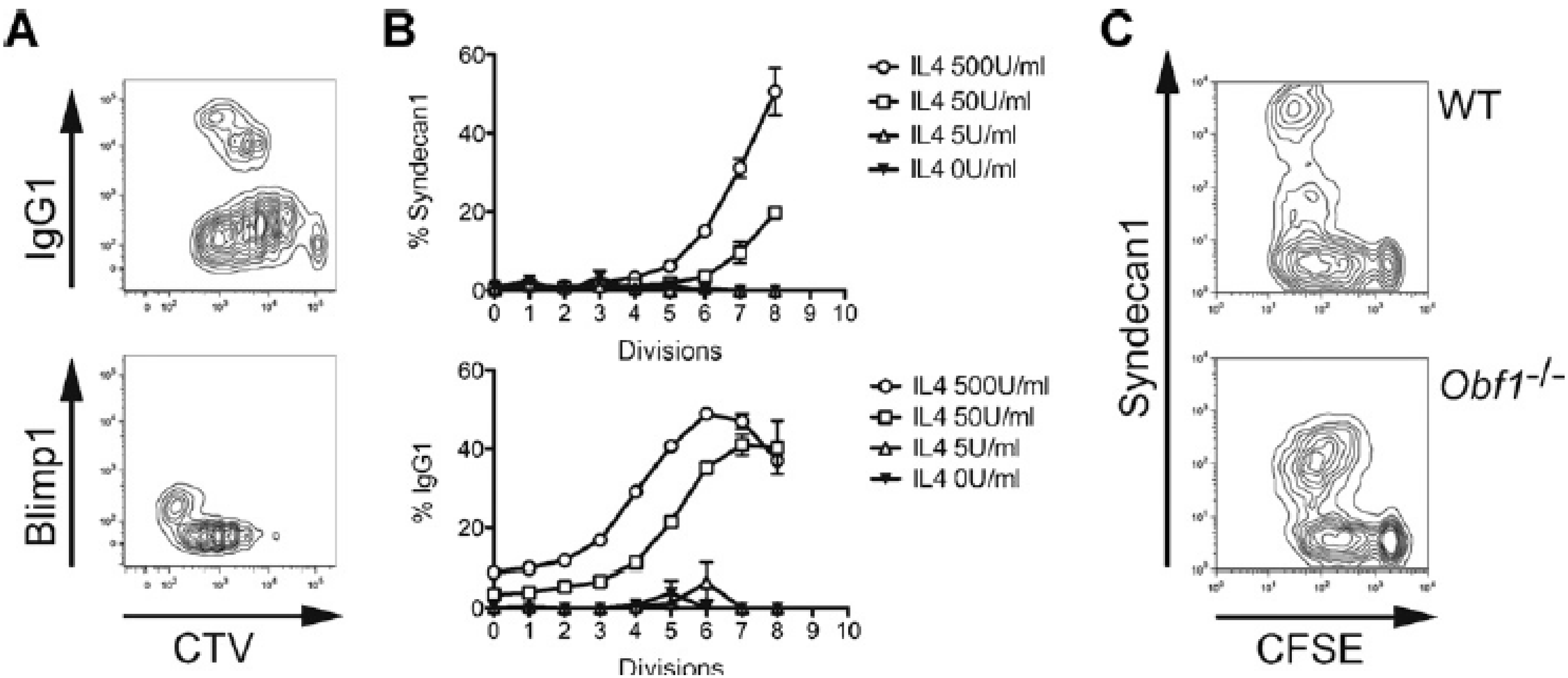
Victora & Nussenzweig, Ann. Rev. Immunology, 2012
Weisel et al., Immunity, 2016

Characteristics of a vaccine antigen determine subsequent levels and duration of immunity – or: the antigen has to go THROUGH the B cell in a BCR specific manner



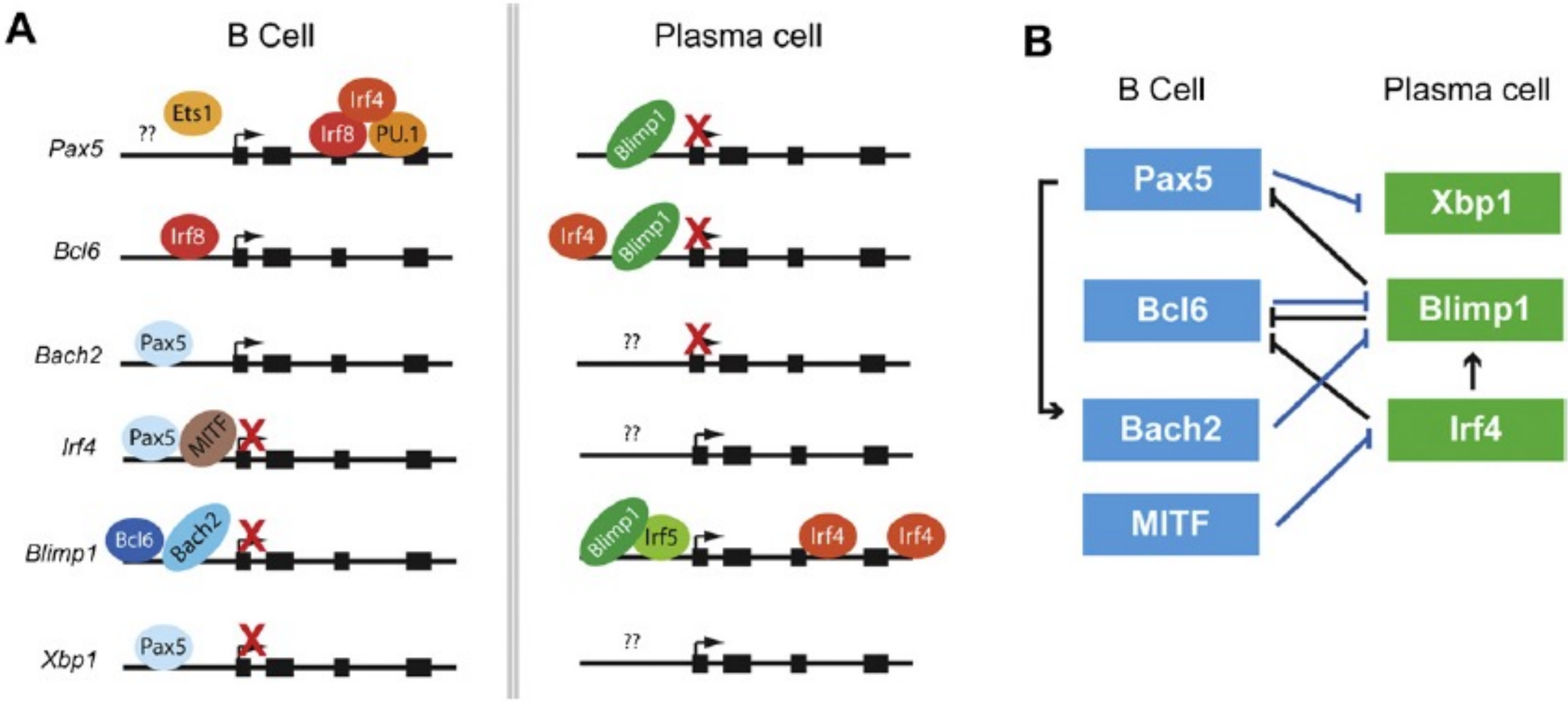
M.K. Slifka, Vaccine, 2014

A principle of plasma cell differentiation is proliferation, increasing the probability for plasma cell differentiation



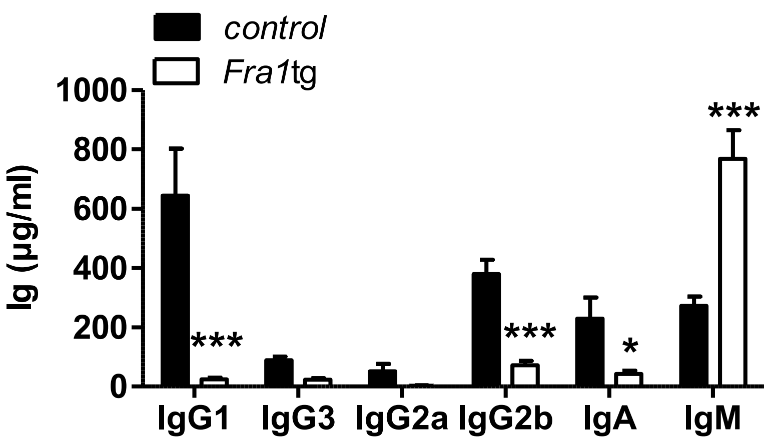
Nutt et al., Sem. Immunology, 2011

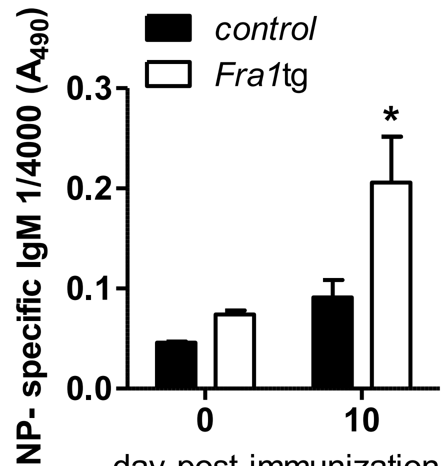
The gene network controlling terminal plasma cell differentiation

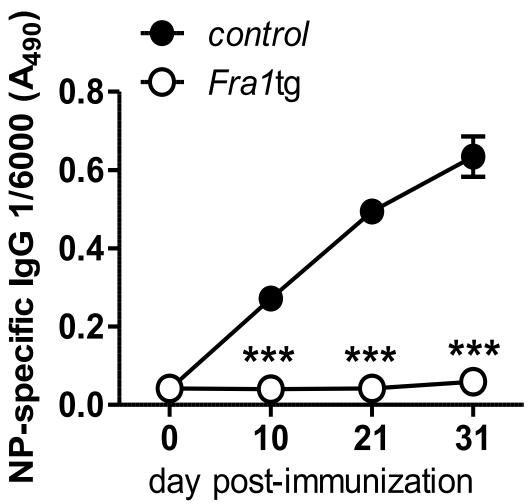


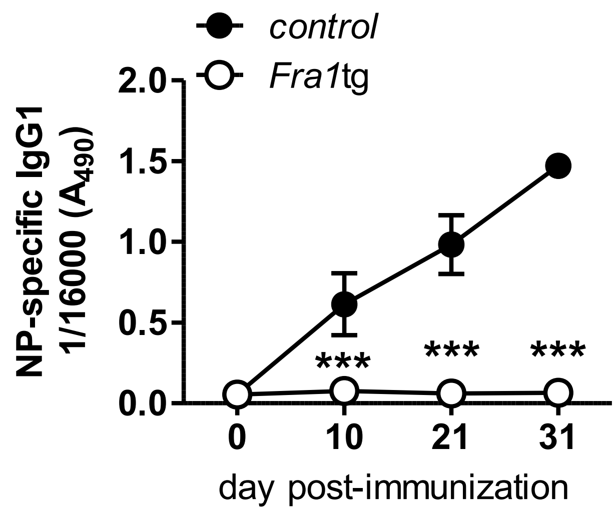
Nutt et al.,Sem. Immunology, 2011
Ochiai et al., Immunity, 2013

Fra1(FosL1) *tg* mice do not respond well to immunization





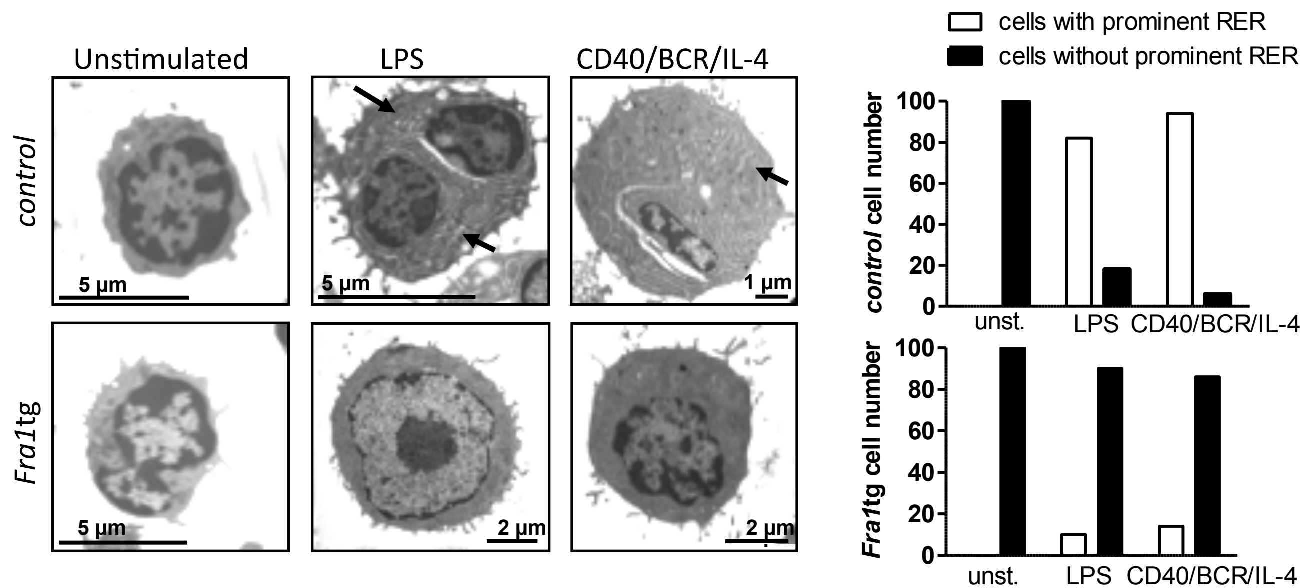




H2-Fra1-LTR*tg*

Grötsch et al., JEM, 2014

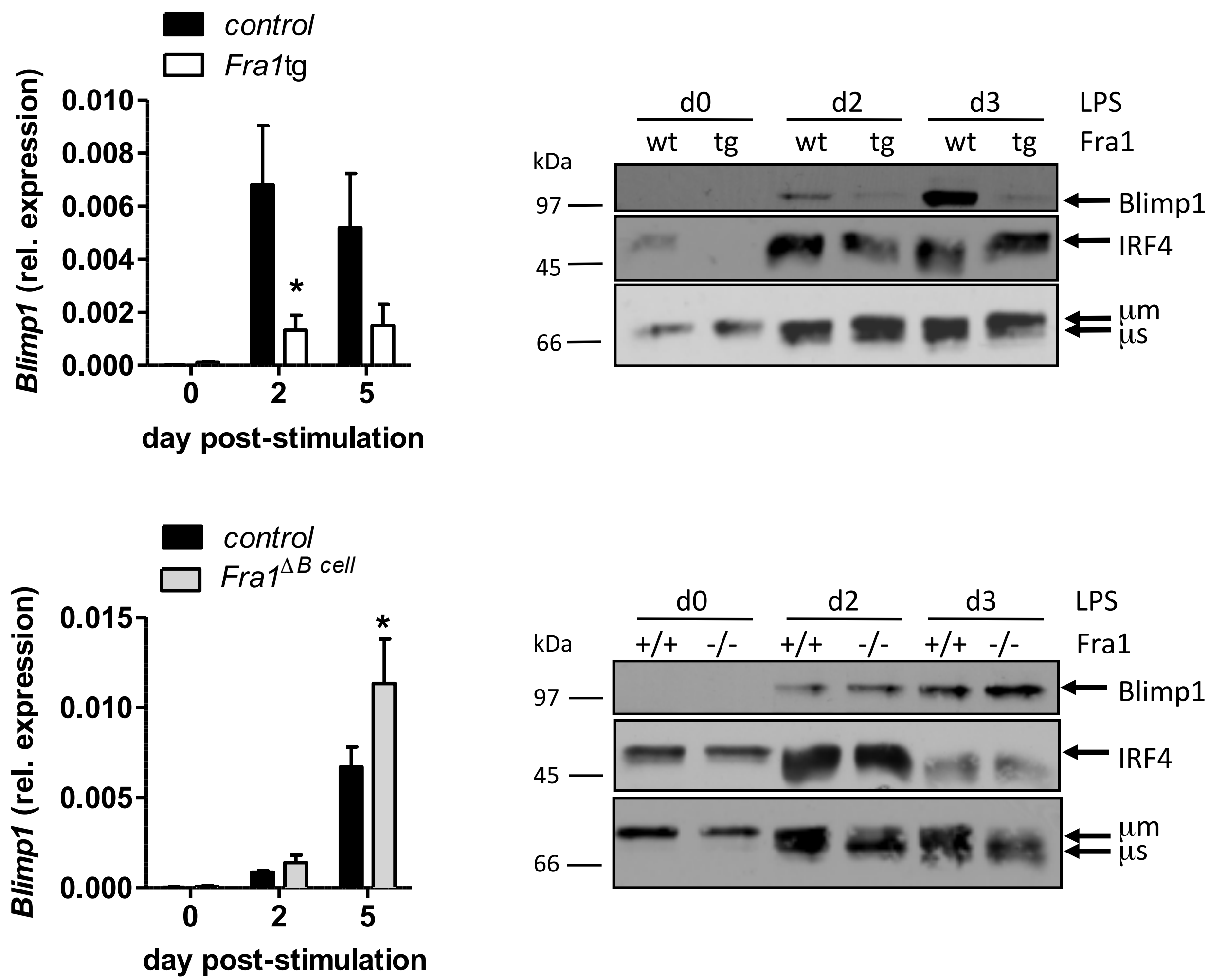
Fra1 inhibits the formation of RER containing plasmablasts in vitro



Ficoll purified cells

Grötsch et al.,JEM, 2014

Fra1 controls Blimp1 and μs expression in vitro



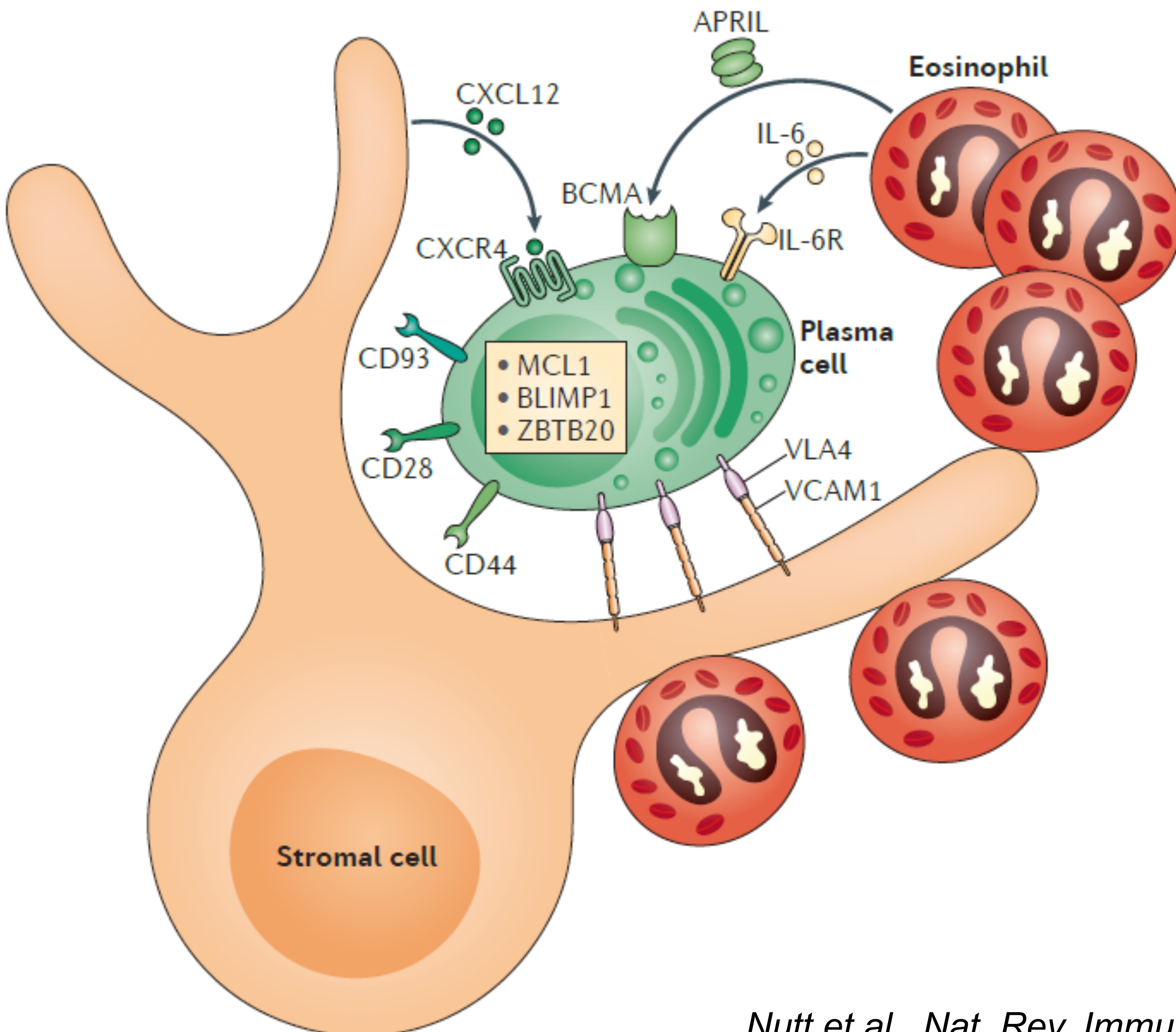
Grötsch et al., JEM, 2014

Different kinds of plasma cells

	Naive B cell	Plasmablast	Immature plasma cell	Mature plasma cell
Lifespan	++	+	+	++++
Proliferation	–	++	–	–
CD27*, CD38*, CD138 and CXCR4 expression	–	+	++	+++
CD19, CD20, CD45 and MHC class II expression	+++	++	+/–	+/–
Location	Lymphoid organs	Lymphoid organs and blood	Lymphoid organs	Bone marrow
Isotype	IgM and IgD	All‡	IgM=IgG>IgA	IgG>>IgA>IgM
BLIMP1 expression	–	+	+	++

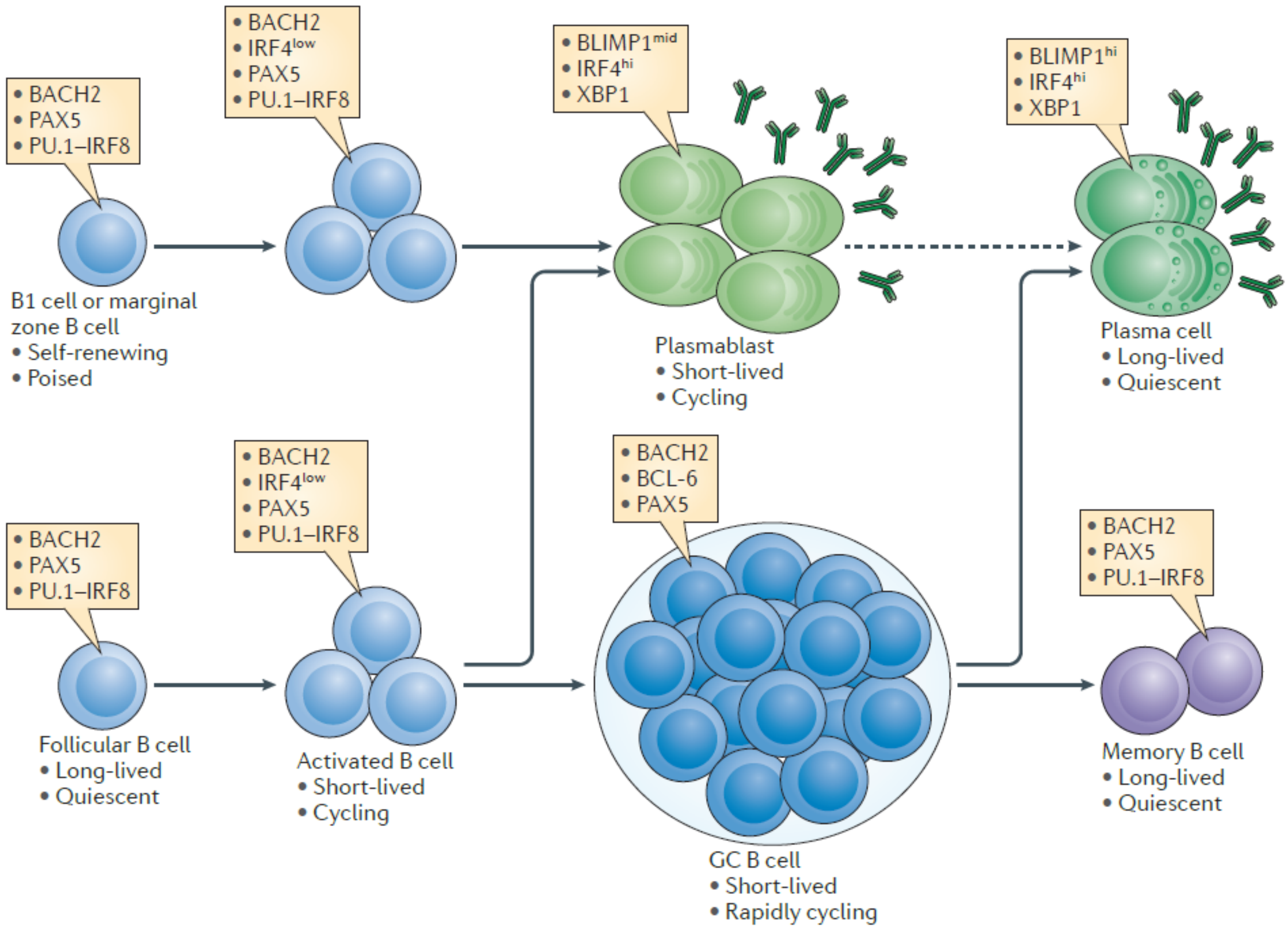
Nutt et al., Nat. Rev. Immunol., 2015

Plasma cells need a niche



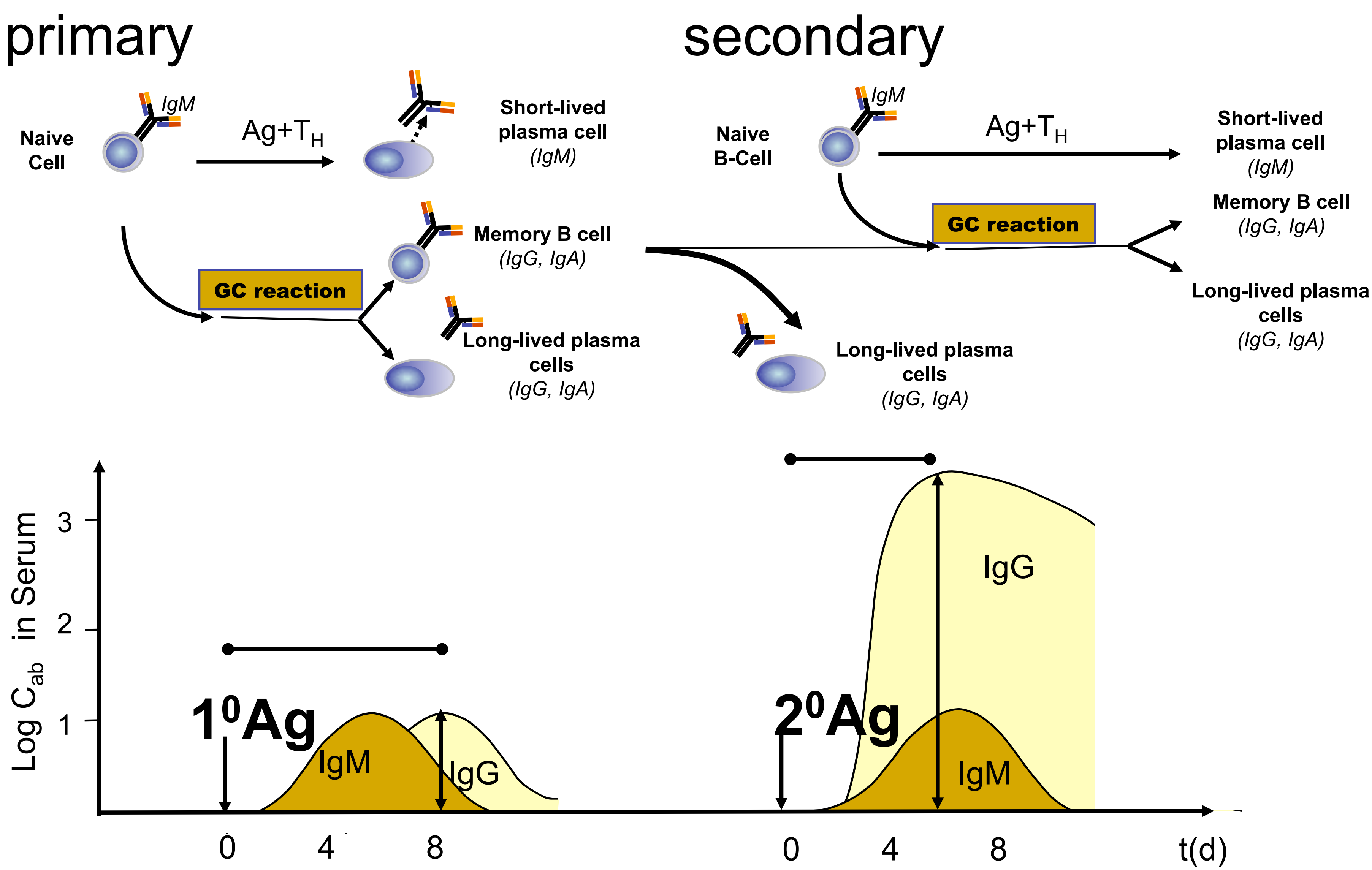
Nutt et al., Nat. Rev. Immunol., 2015

Generation of long lived plasma cells - overview



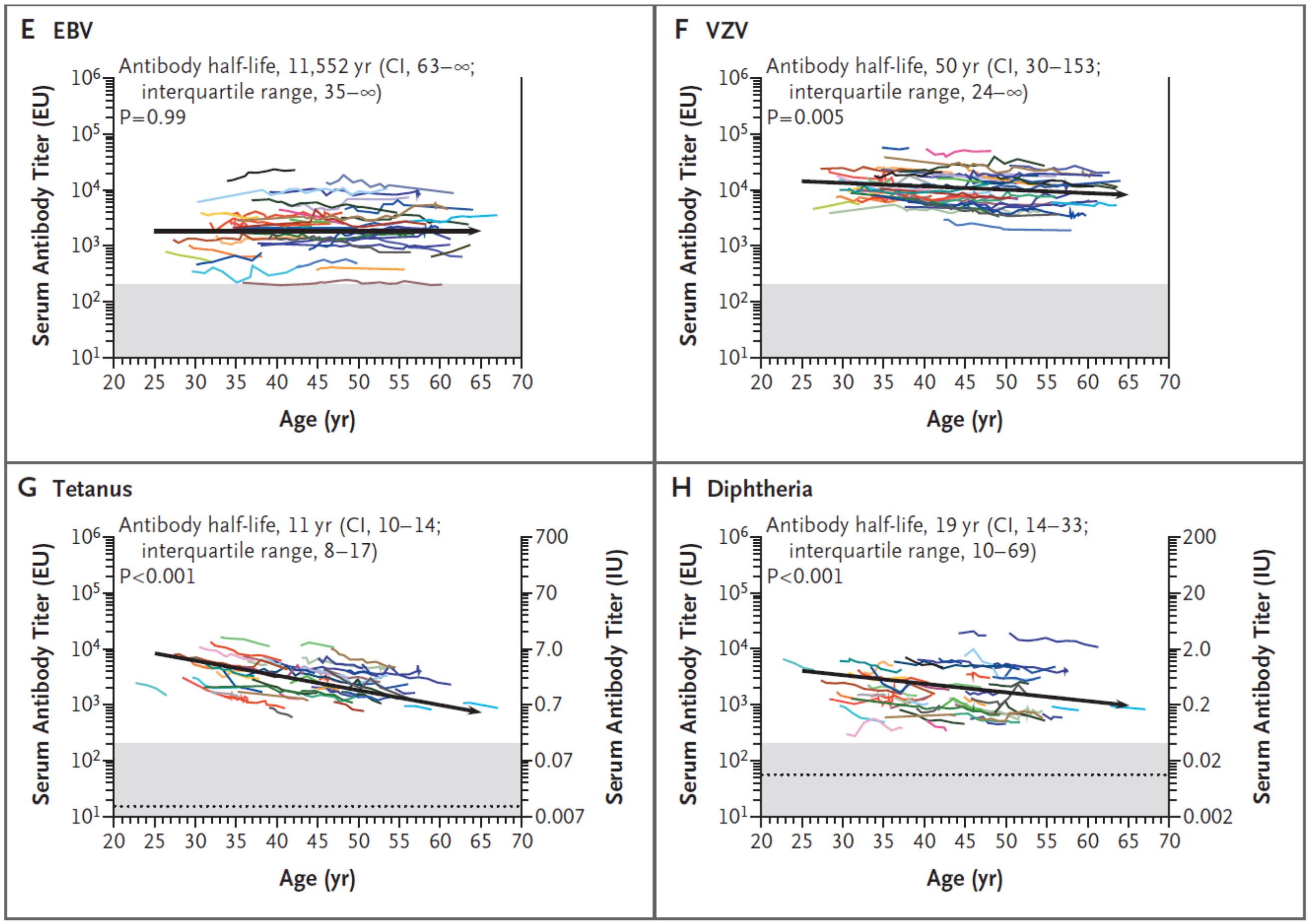
Nutt et al., Nat. Rev. Immunol., 2015

Summary



primary
secondary
Naive Cell
IgM
Ag+T$_H$
Short-lived plasma cell
(IgM)
GC reaction
Memory B cell
(IgG, IgA)
Long-lived plasma cells
(IgG, IgA)
Naive B-Cell
IgM
Ag+T$_H$
Short-lived plasma cell
(IgM)
GC reaction
Memory B cell
(IgG, IgA)
Long-lived plasma cells
(IgG, IgA)
Long-lived plasma cells
(IgG, IgA)
Log C_{ab} in Serum
3
2
1
1^0Ag
IgM
IgG
2^0Ag
IgG
IgM
0
4
8
0
4
8
t(d)

Duration of humoral immunity to common viral and vaccine antigens



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