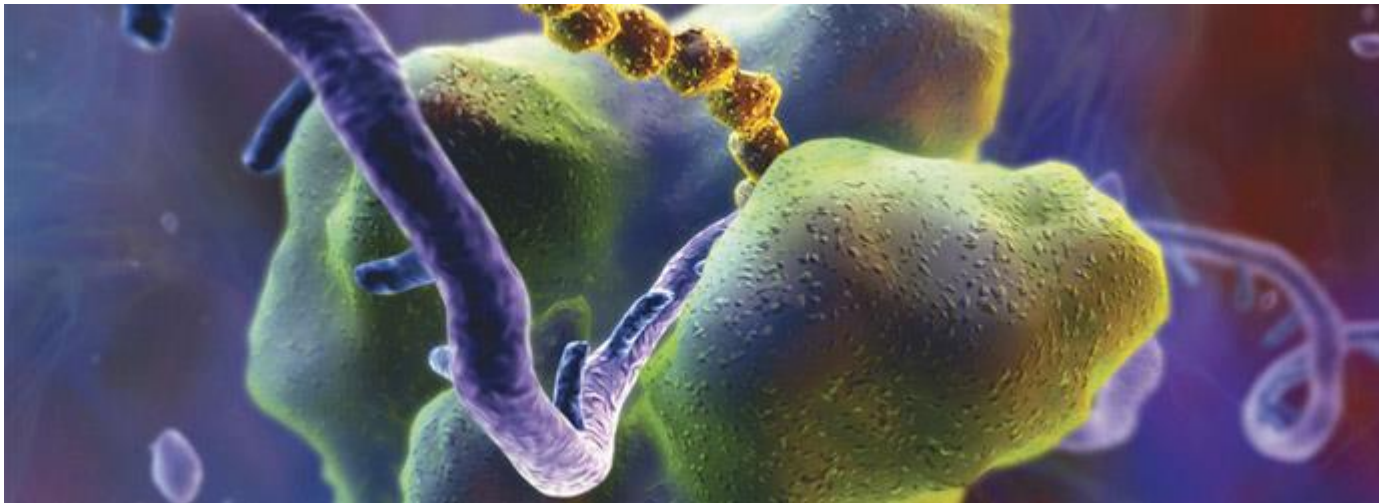


# the immune system; pathogenesis of neuroimmune diseases



Zsolt Illes

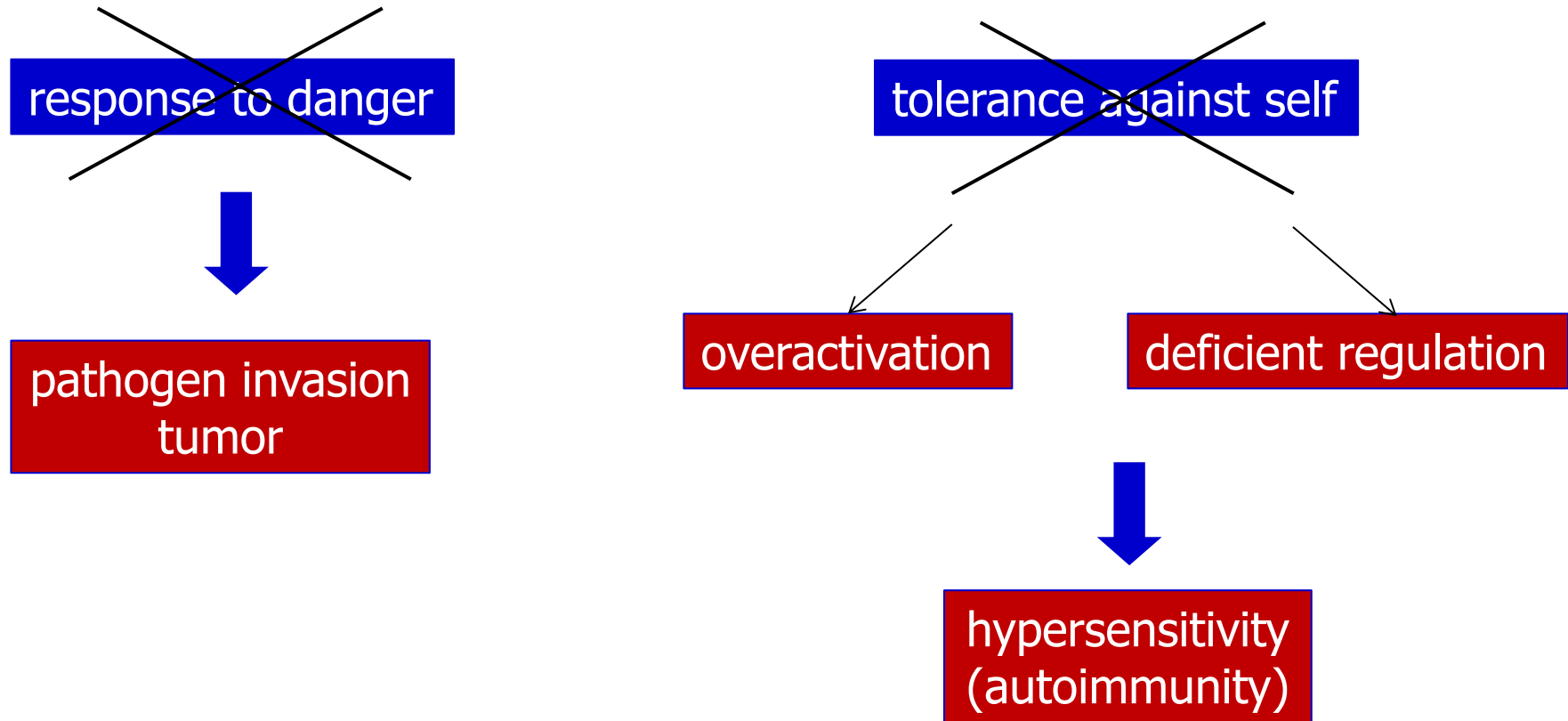
Department of Neurology  
Odense University Hospital  
University of Southern Denmark

# novelties in neuroimmunology, 2014

- novel treatments in MS: oral, biological
- anti-AQP4 in NMO, then anti-MOG in NMO
- novel pathogenic antibodies in myasthenia gravis: anti-Lrp4, anti-agrin
- antibody-mediated encephalitis and epilepsy syndromes

*MOG: myelin oligodendrocyte glycoprotein*

# immune system



# components of the immune system

innate



adaptive  
(„acquired“)

*limited (pattern)*

*antigen specificity*

*yes*

*linear*

*propagation, enhancement*

*exponential*

*no*

*memory*

*yes*

*random*

*interaction with antigen*

*selective*

*no*

*latency*

*yes*

*complement*

*soluble*

*antibodies*

*phagocytes, NK, DC*

*cellular*

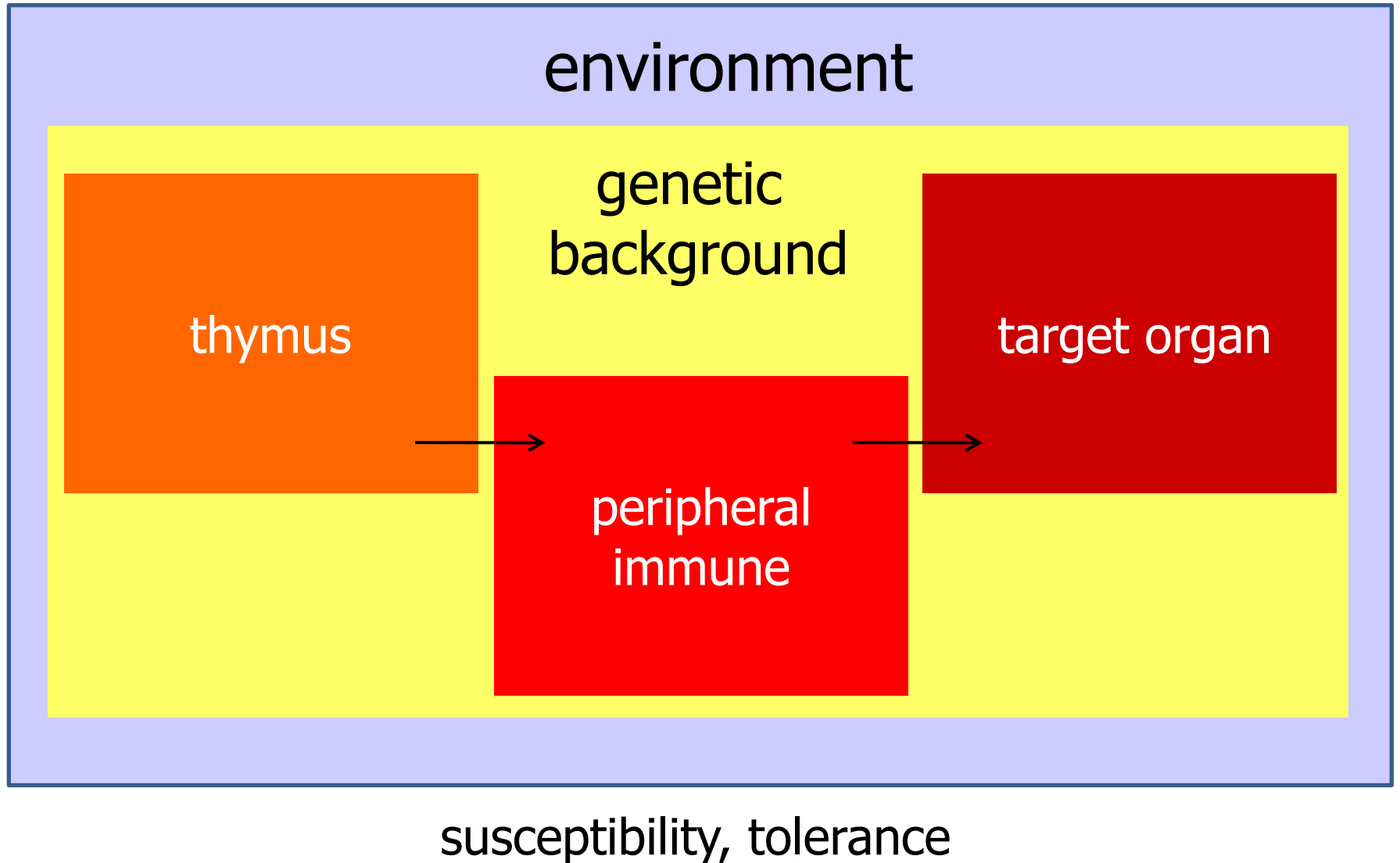
*lymphocytes*

*FcR, CR, cytokine rec*

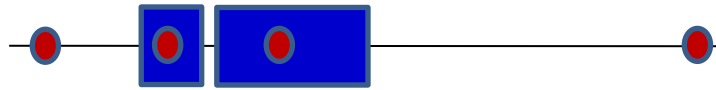
*receptors*

*BCR, TCR*

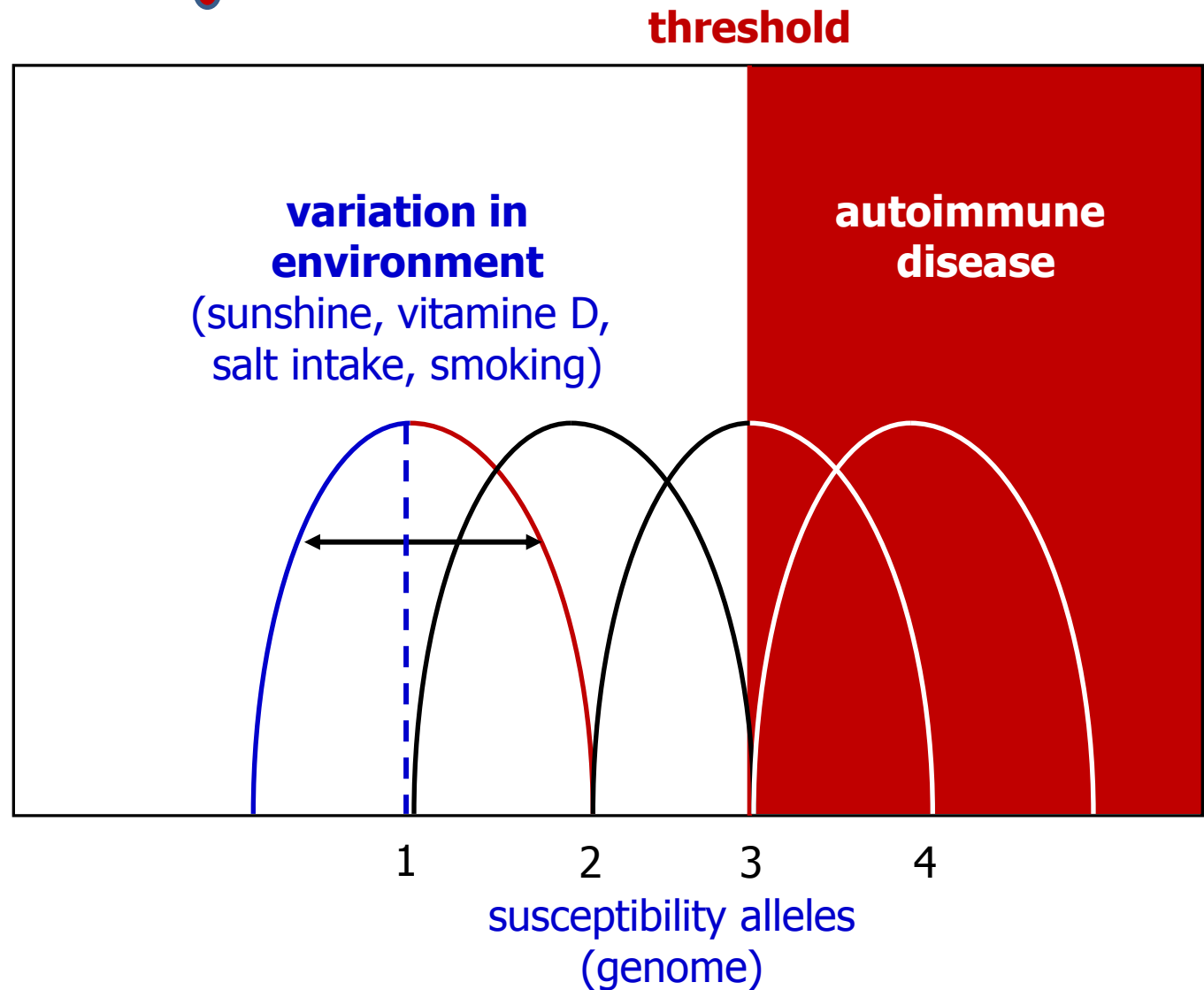
# autoimmunity: compartments



# threshold liability model: gene-environment

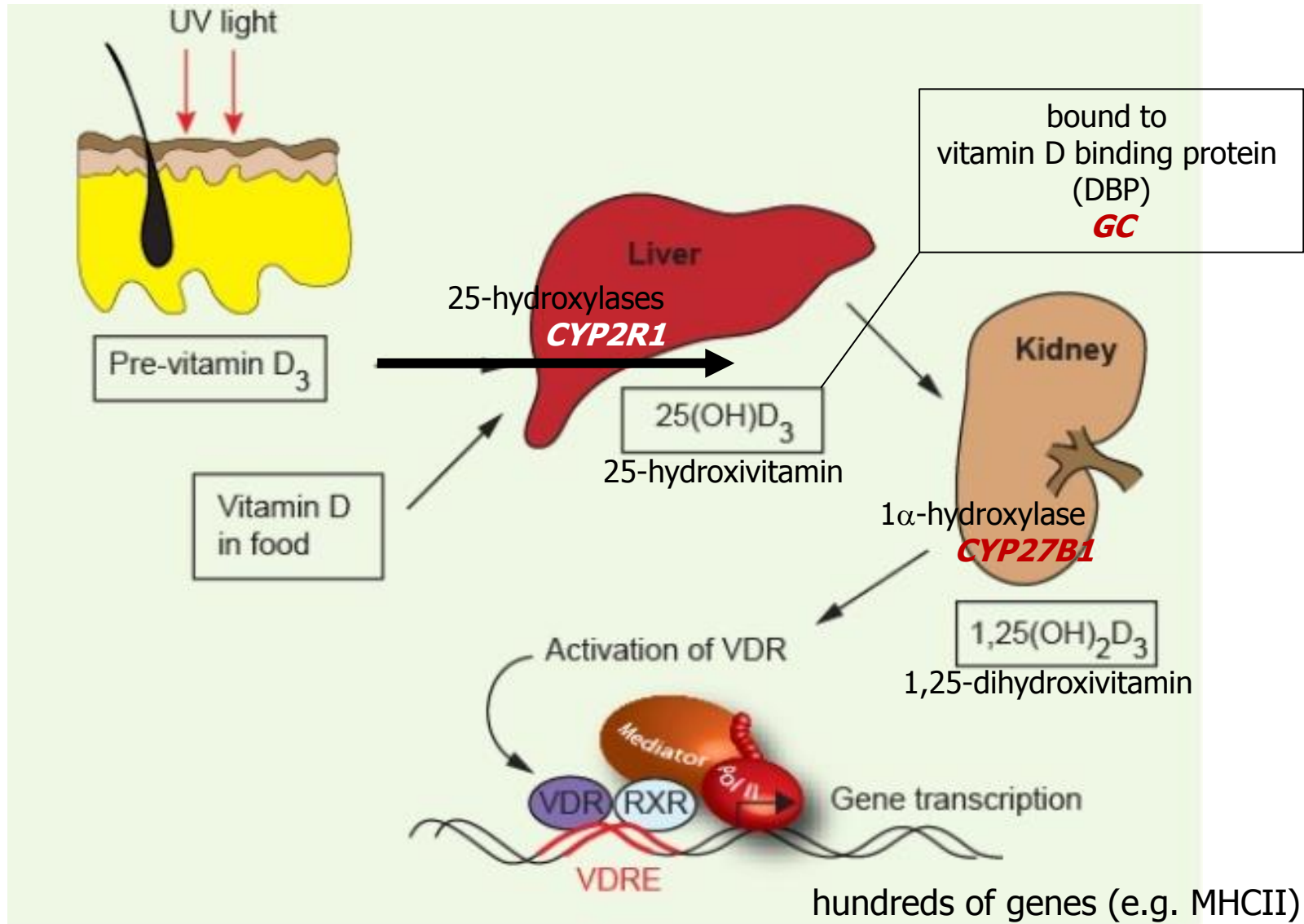


80% SNPs  
*single nucleotide  
polymorphisms*



# vitamin D levels: genes and environment

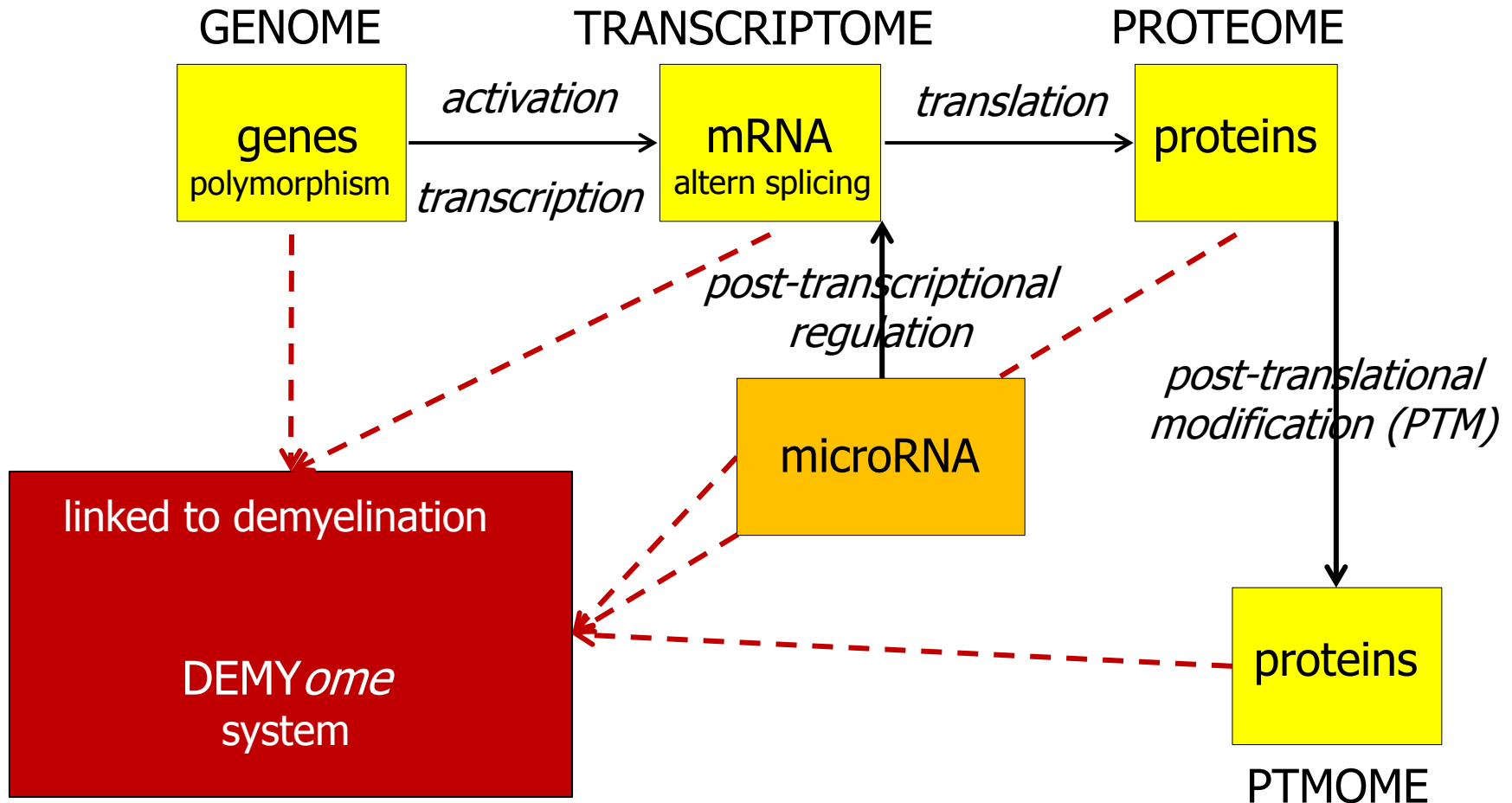
Laursen, JH, Mult Scler, 2014



# levels: systems biology approach

## epigenetic modifications:

- do not involve a change in DNA sequence
- alter gene expression
- heritable changes, environmental effects
- DNA methylation, histone modification, nucleosome position, non-coding RNA

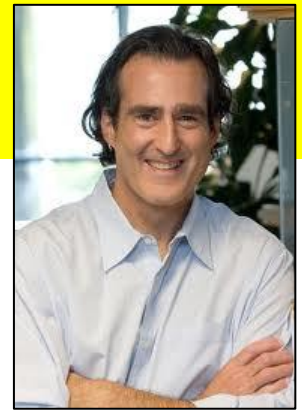






Andrew Z. Fire

# microRNA



Craig C. Mello

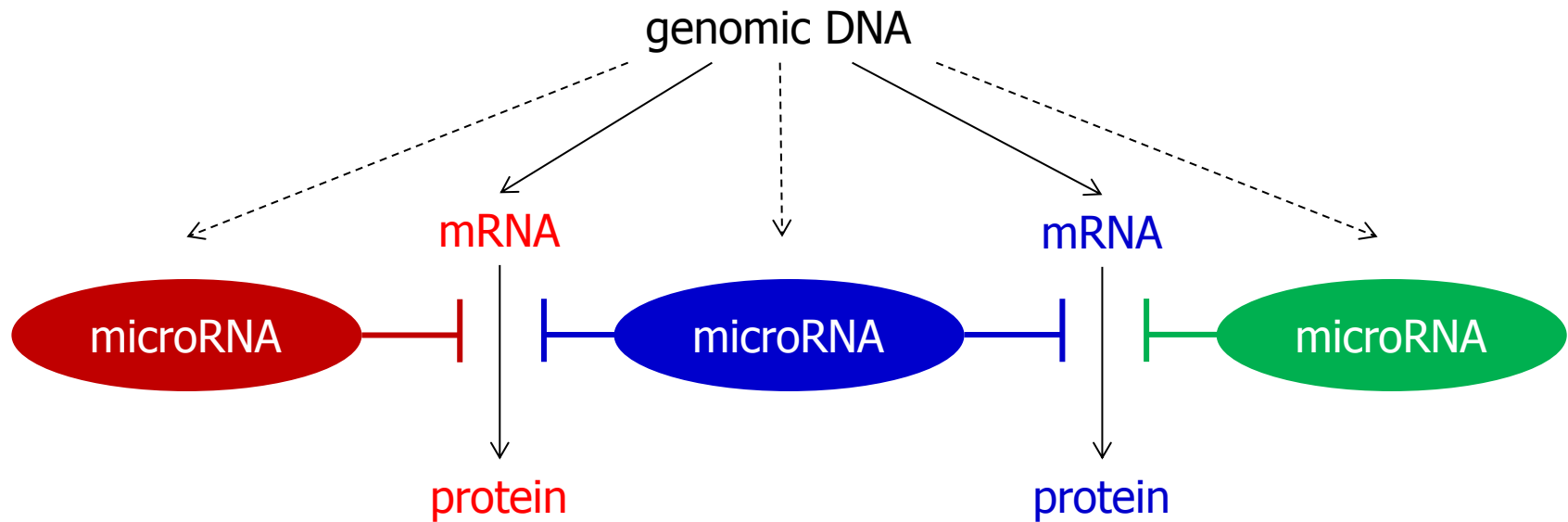
Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello, CC

"Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*"  
1998, *Nature* 391 (6669): 806–811

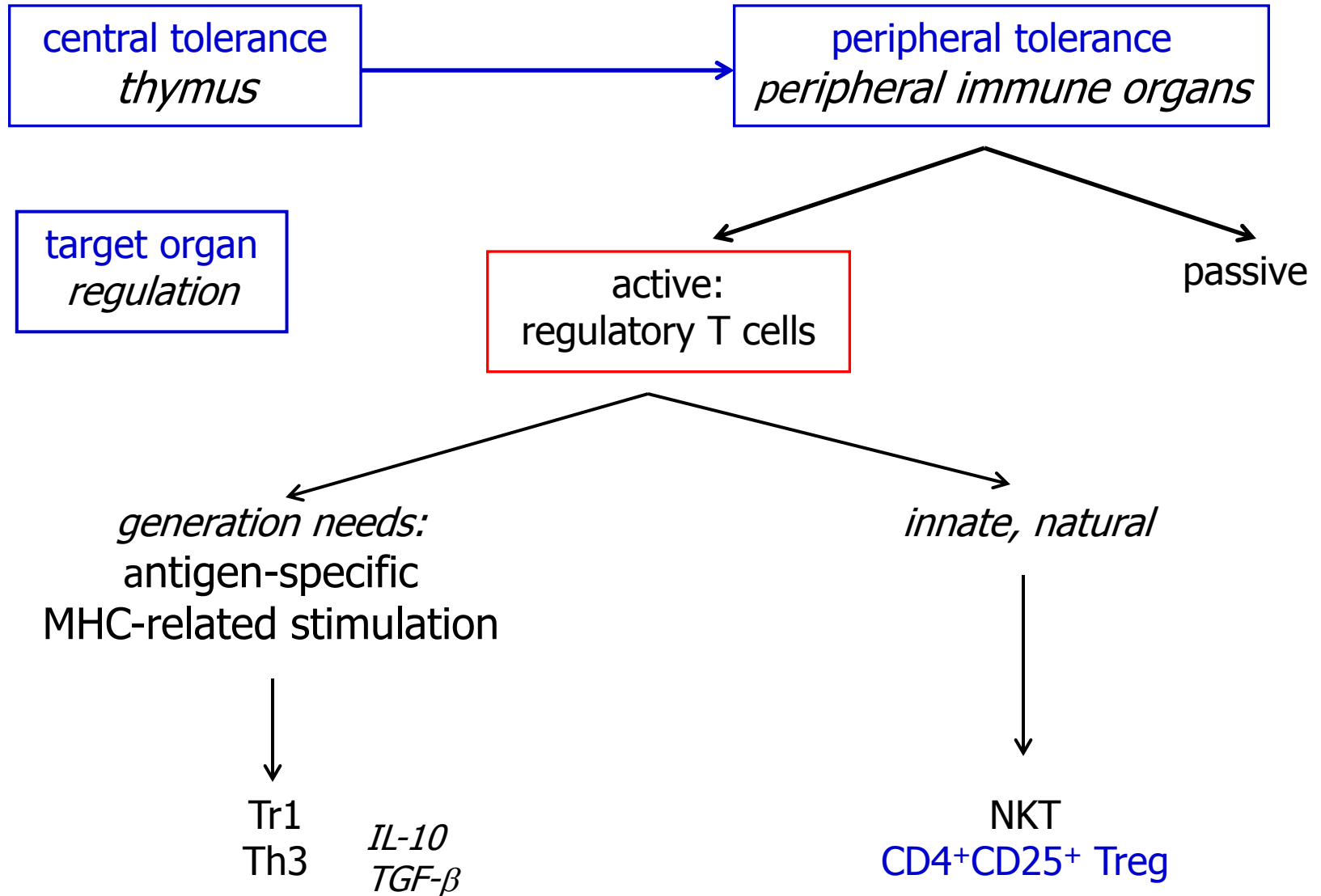
Dr. Mello recounted the phone call that he received announcing that he had won the prize.

He recalls that it was shortly after 4:30 am and he had just finished checking on his daughter, and returned to his bedroom. The phone rang (or rather the green light was blinking) and his wife told him not to answer, as it was a crank call. Upon questioning his wife, she revealed that it had rung while he was out of the room and *someone was playing a bad joke on them* by saying that he had won the Nobel prize. When he told her that they were actually announcing the Nobel prize winners on this very day, he said "her jaw dropped."

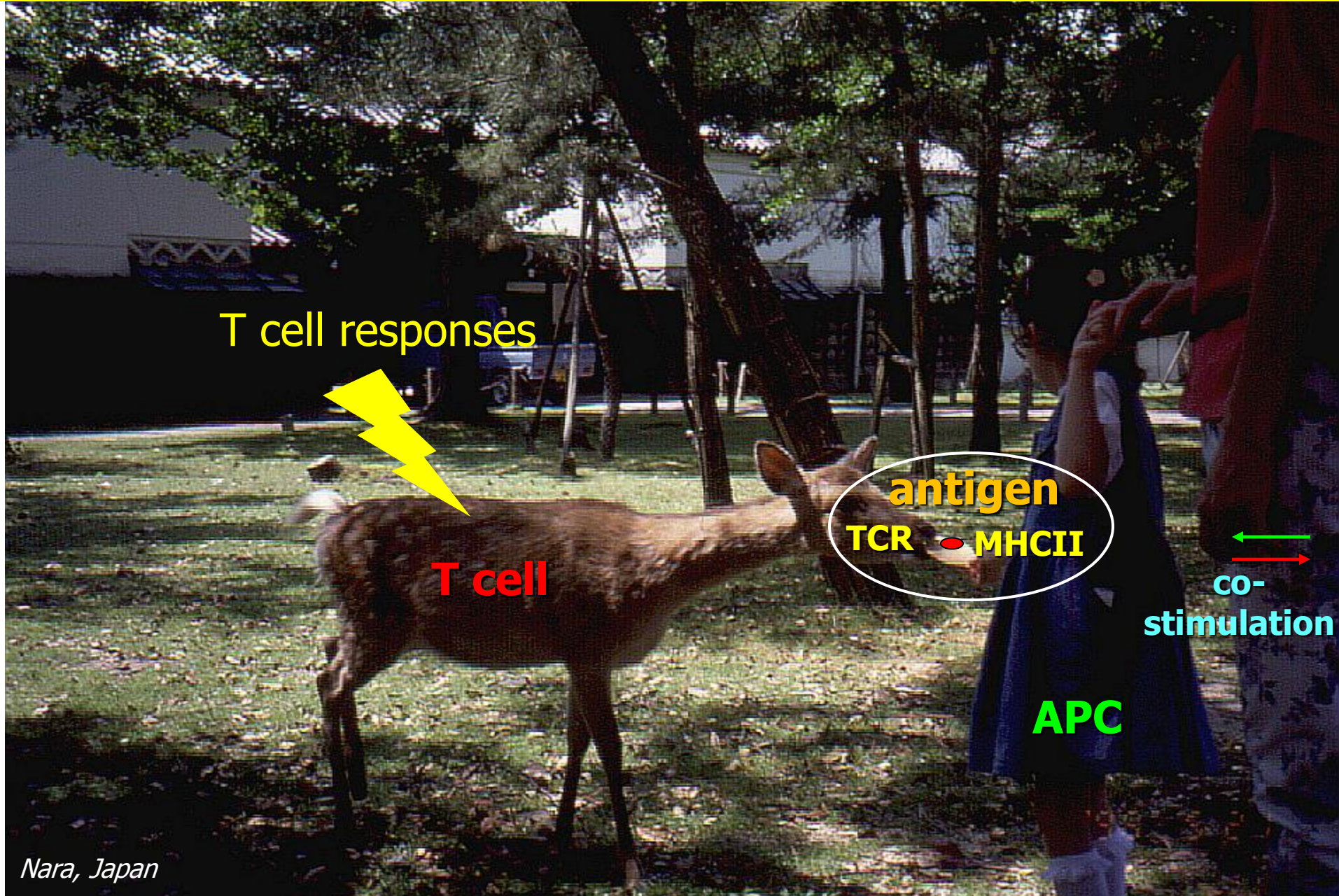
# microRNA: complexity



# self-tolerance: protection against autoimmunity



# antigen presentation: MHC and T cell receptor



# MHC I, MHC II, MHC III: chromosome 6

## III

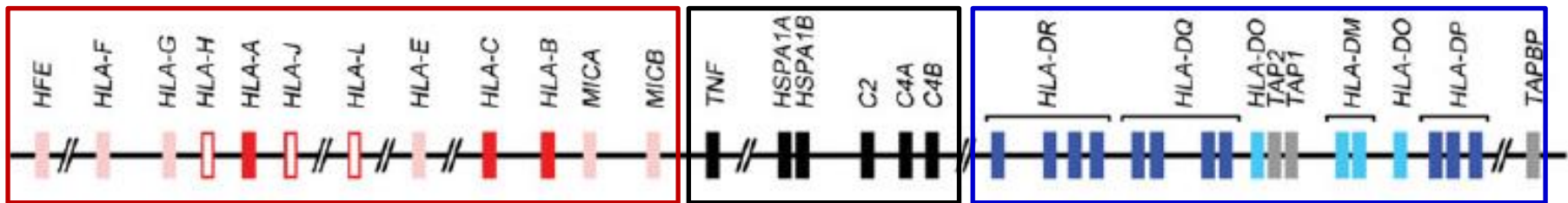
classical complement C2 C4  
 cytokine TNF- $\alpha$  and  $\beta$   
 heat shock proteins

brain:

C1q and C3 tag synapses for elimination

TNF- $\alpha$  regulates expression of AMPARs, increases connectivity

hsp: chaperons, elimination of misfolding proteins



## I on all nucleated cell

presented peptides: **intracellular**

MHC-peptide monitored by **CD8<sup>+</sup> Tc**

binds to inhibitory receptors of **NK**

brain:

modulate synaptic plasticity

(negatively NMDAR function and AMPAR trafficking)

expression regulated by neuronal activity

## II on antigen presenting cells

presented peptides: **extracellular**

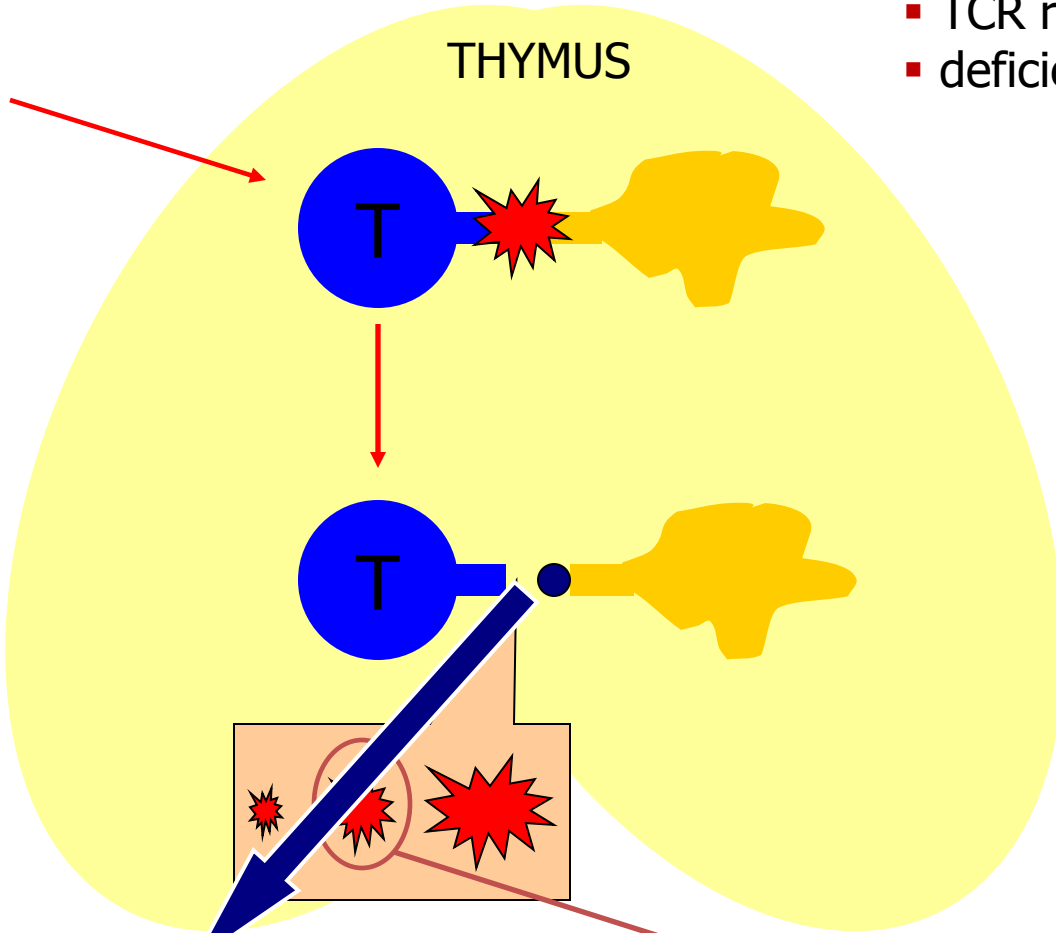
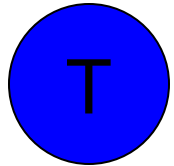
MHC-peptide monitored by **CD4<sup>+</sup> Th**

brain:

microglia, astrocyte,  
 perivascular monocyte

# central tolerance

bone marrow



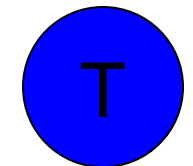
THYMUS

- MHC repertoire?
- TCR repertoire?
- deficient selection (apoptosis)?

positive selection  
MHCII

negative selection  
MHCII + Ag

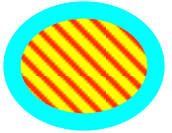
- expressed in thymus?



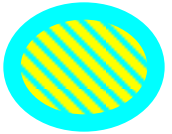
blood

# antigen in the thymus and autoimmune susceptibility

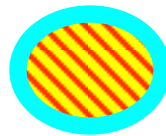
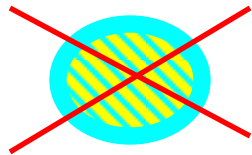
PLP



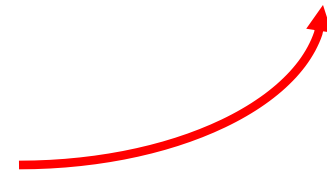
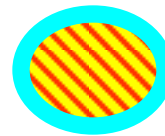
DM20



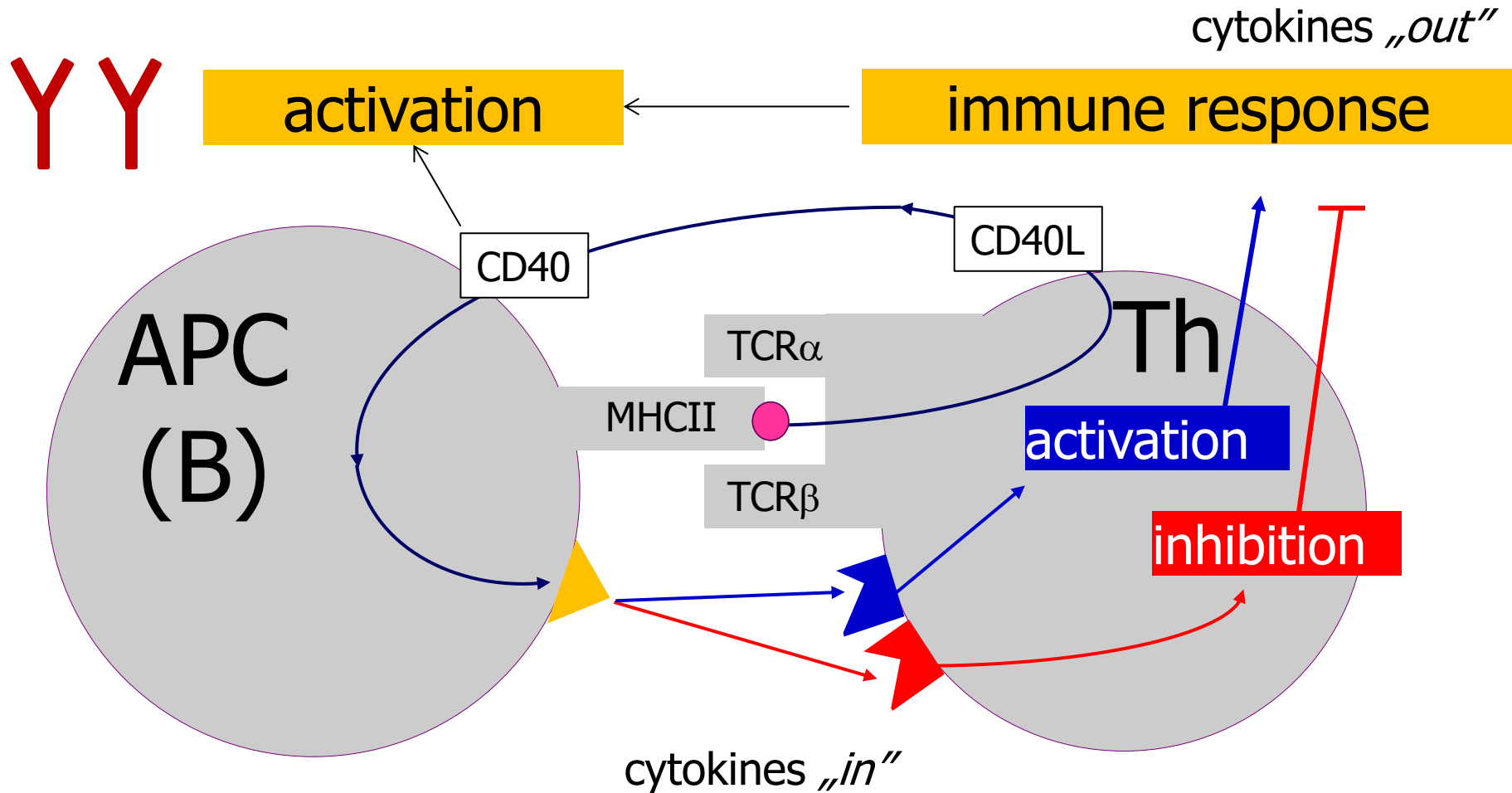
thymus



brain



# T cell activation and signals



APC: antigen presenting cell

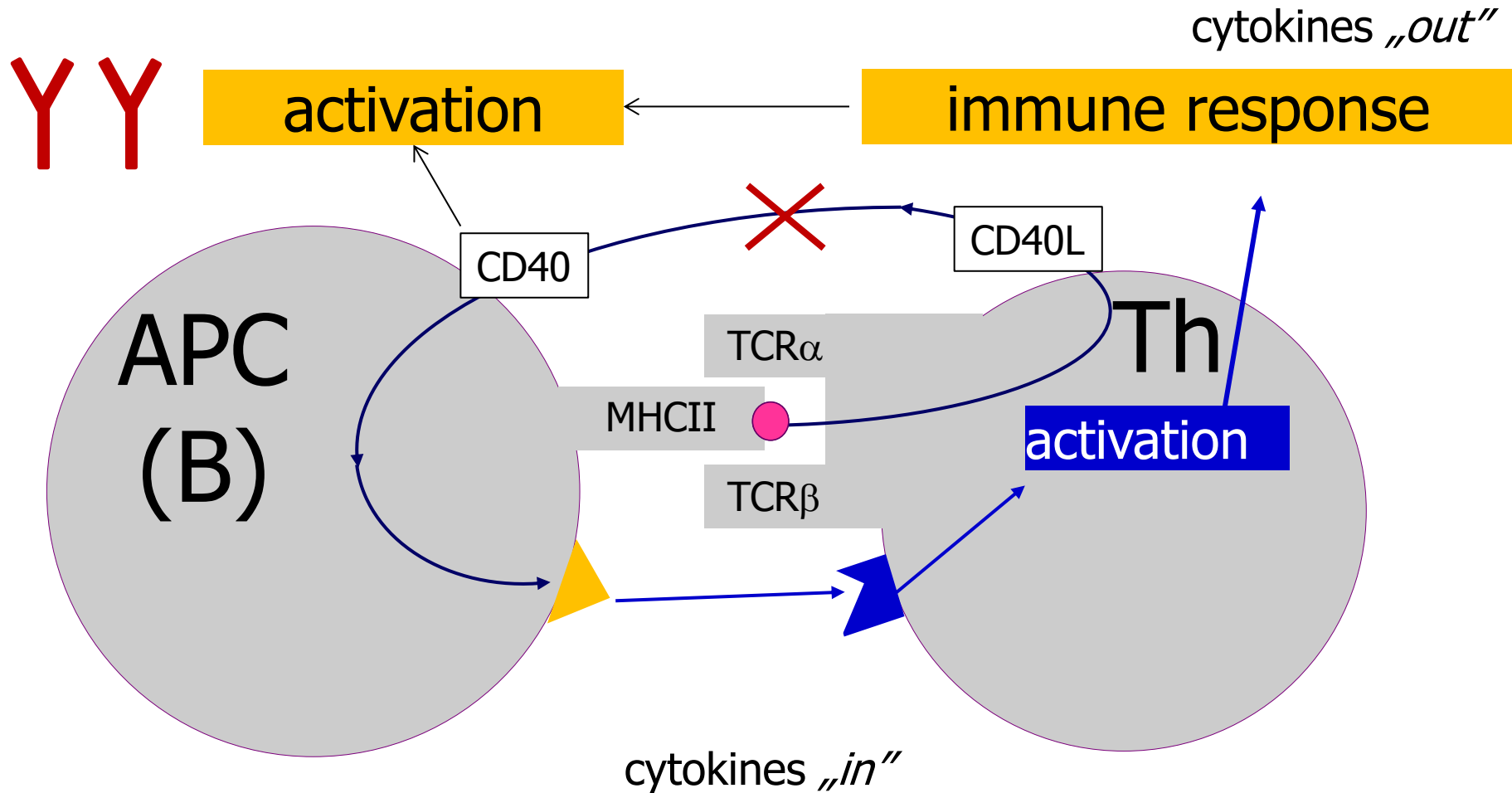


# hyper-IgM syndrome

19-year old male

- CD40L deficiency
- hyper-IgM syndrome
- monthly IVIG since age of 3

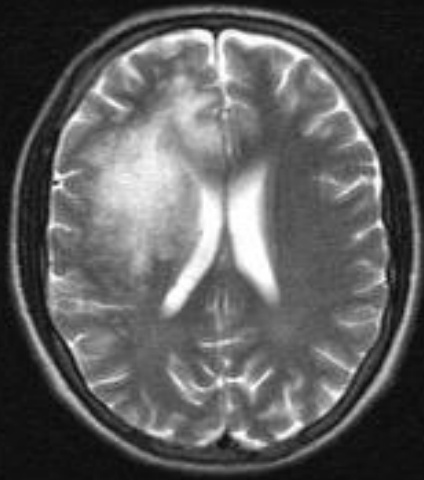
# T cell activation and signals



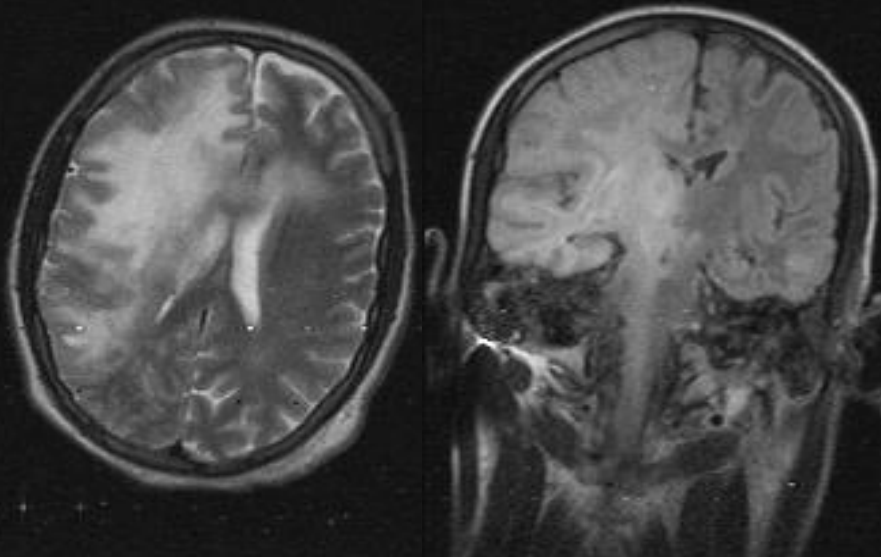
APC: antigen presenting cell

# PML – progressive multifocal leukoencephalopathy

no enhance

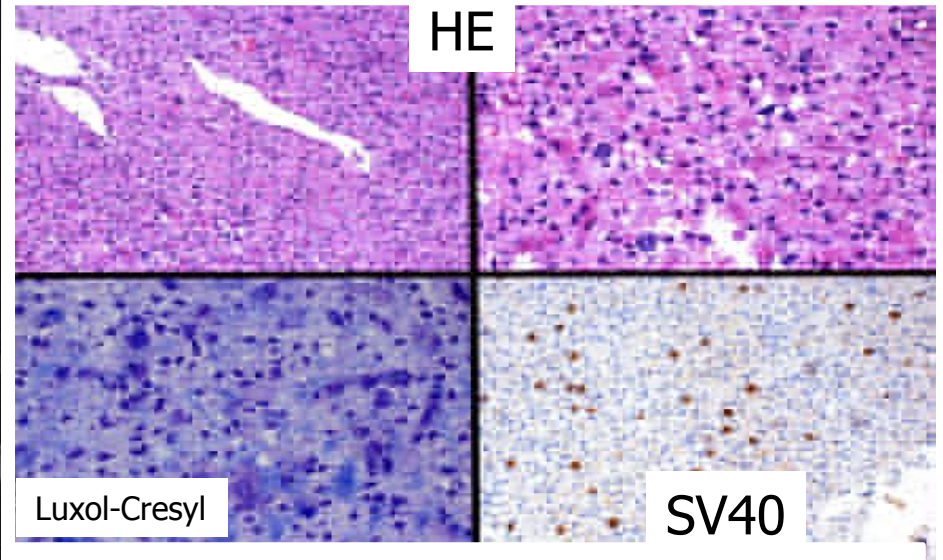


2 weeks later

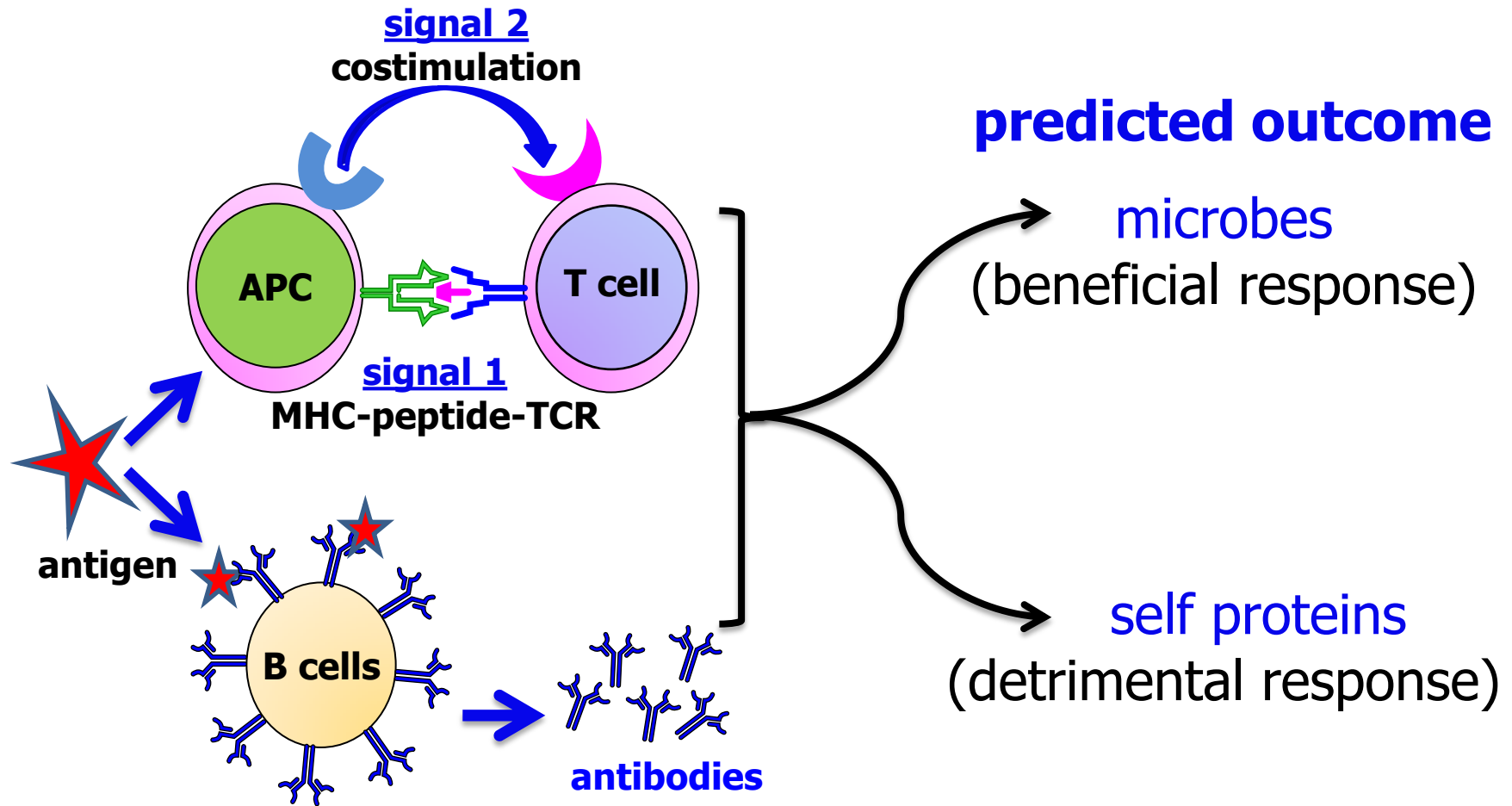


19-year old male

- CD40L deficiency
- hyper-IgM syndrome
- monthly IVIG since age of 3
- concentration and memory problems
- progressive hemiparesis
- normal CSF
- coma in 6 weeks

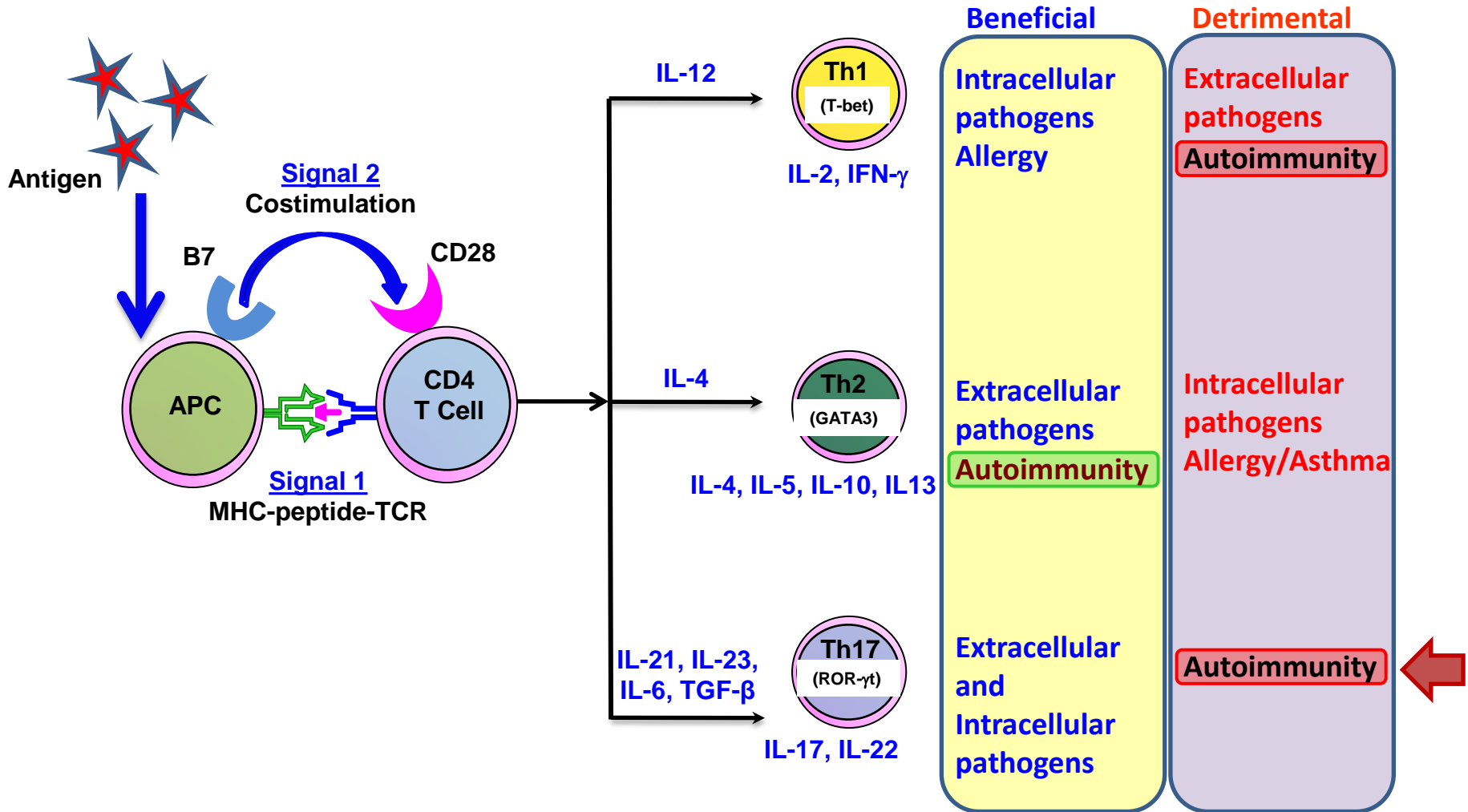


# immune response and autoimmunity

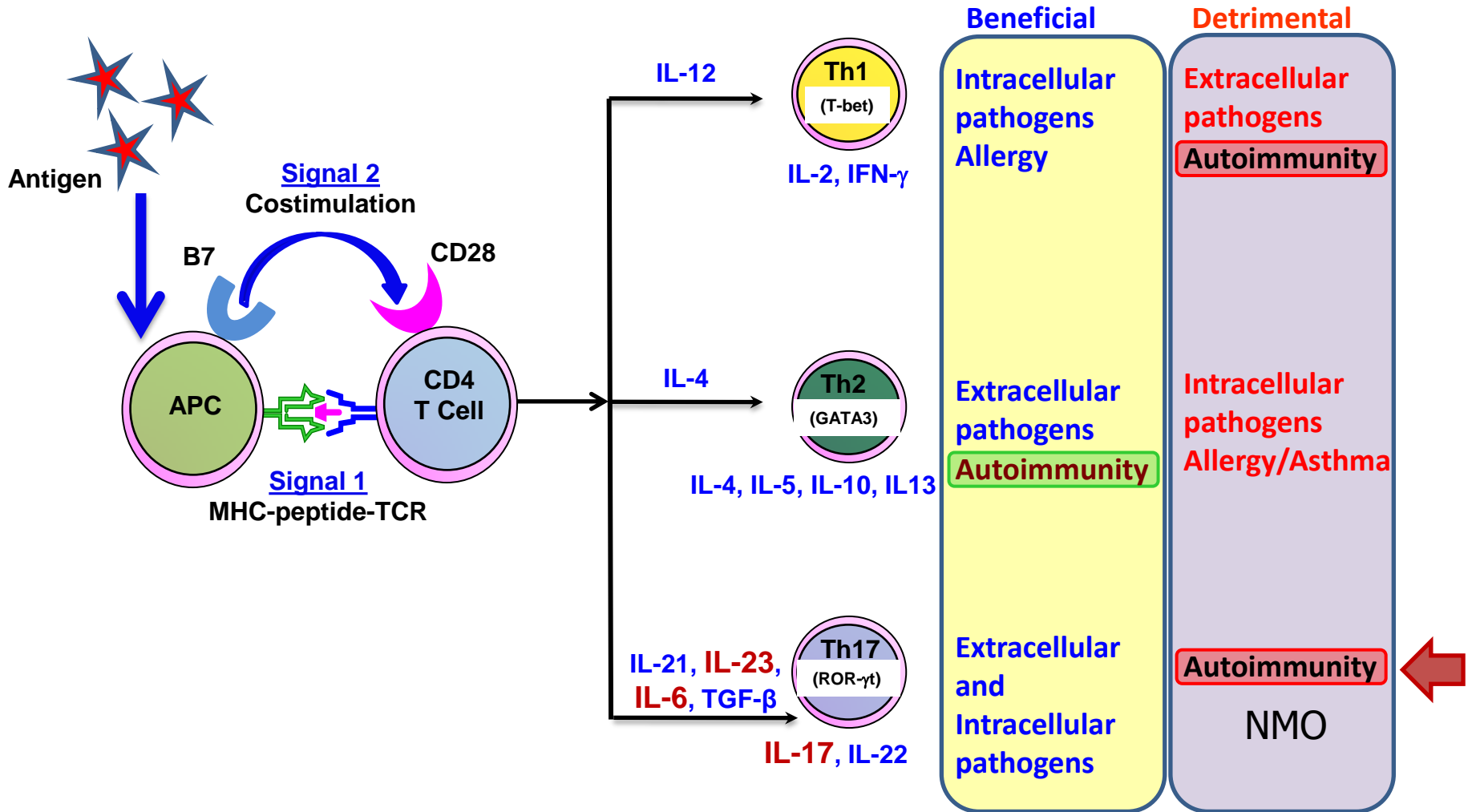


break in self-tolerance leads to autoimmunity

# immune response to self- vs. foreign-antigens



# immune response to self- vs. foreign-antigens



# interference with IL23-IL17

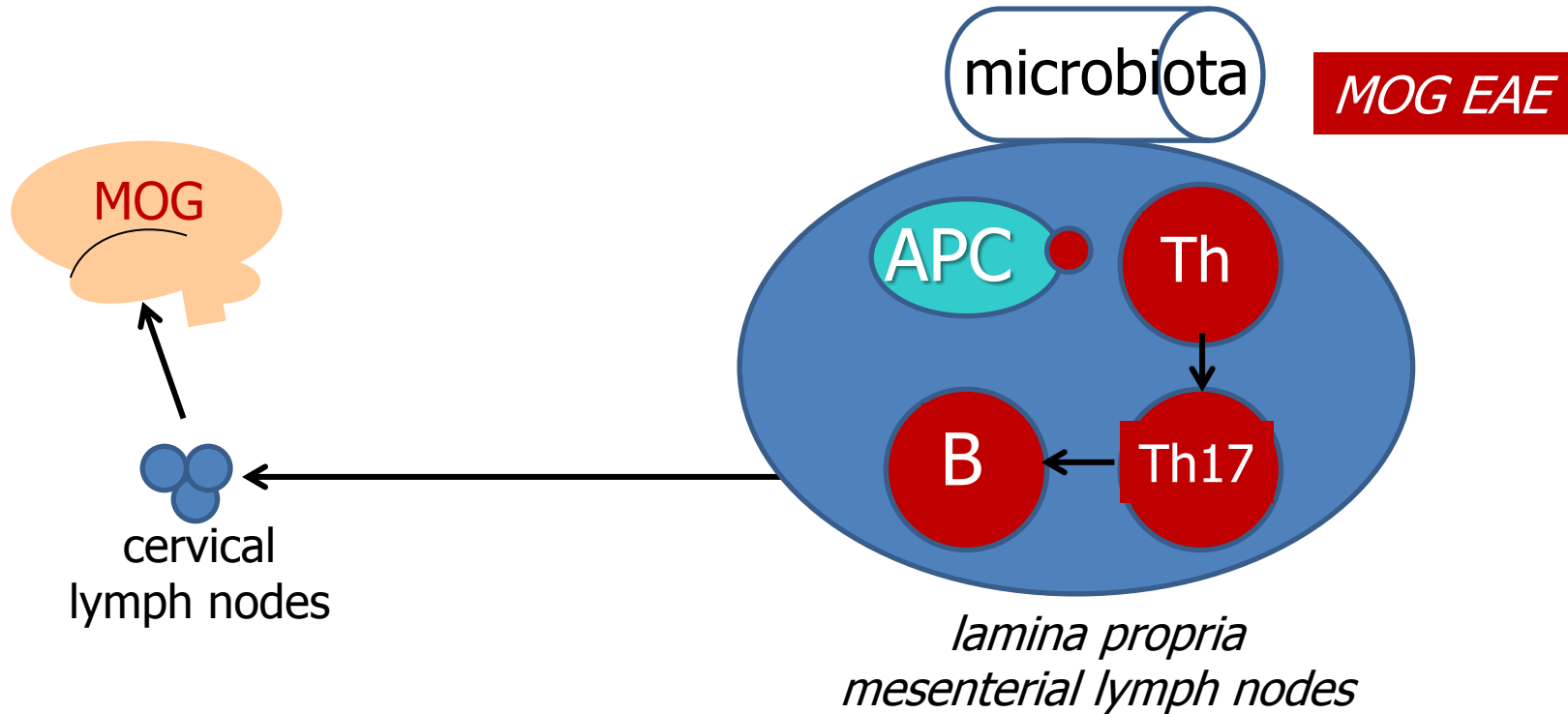
agent	target	company	clinical trial
ixekizumab	IL-17A	Eli Lilly	psoriasis, RA
secukinumab	IL-17A	Novartis	MS (II) and many
brodalumab	IL-17RA	Amgen, MedImmune	psoriasis, CD, asthma
ABT-122	IL-17A and TNF	Abbott, AbbVie	RA
ustekinumab	p40 IL-12 and IL-23	Johnson&Johnson, Janssen Biotech	MS (II) and many
briakinumab	p40 IL-12 and IL-23	Abbott	MS (II), CD, psoriasis
tildrakizumab	IL-23p19	Merck	psoriasis
guselkumab	IL-23p19	Johnson&Johnson, Janssen Biotech	psoriasis, RA
AMG-139	IL-23p19	Amgen, MedImmune	psoriasis, CD
LY-3074828	IL-23p19	Eli Lilly	psoriasis
BI-655066	IL-23p19	Boehringer Ingelheim	psoriasis, CD, AS

CD: Crohn's disease, RA: rheumatoid arthritis, AS: ankylosing spondylitis

# microbiome

*Am J Pathol 2008, PNAS 2011, Nature 2011*

microbiome: microbial ecosystem (microbiota)  
plus its entire genetic content



absence of microbial flora: milder EAE (MOG)



# microbiota in early infancy

## ***hygiene hypothesis:***

lack of microbial exposure – immune dysregulation (Th2)

## ***microflora hypothesis:***

microbiota alteration – disrupt immune tolerance

## ***vanishing microbiota hypothesis:***

changes in microbiota – allergy/immune diseases

## postnatal

- feeding (breast/bottle)
- solid food introduction
- pre/probiotics
- antibiotics

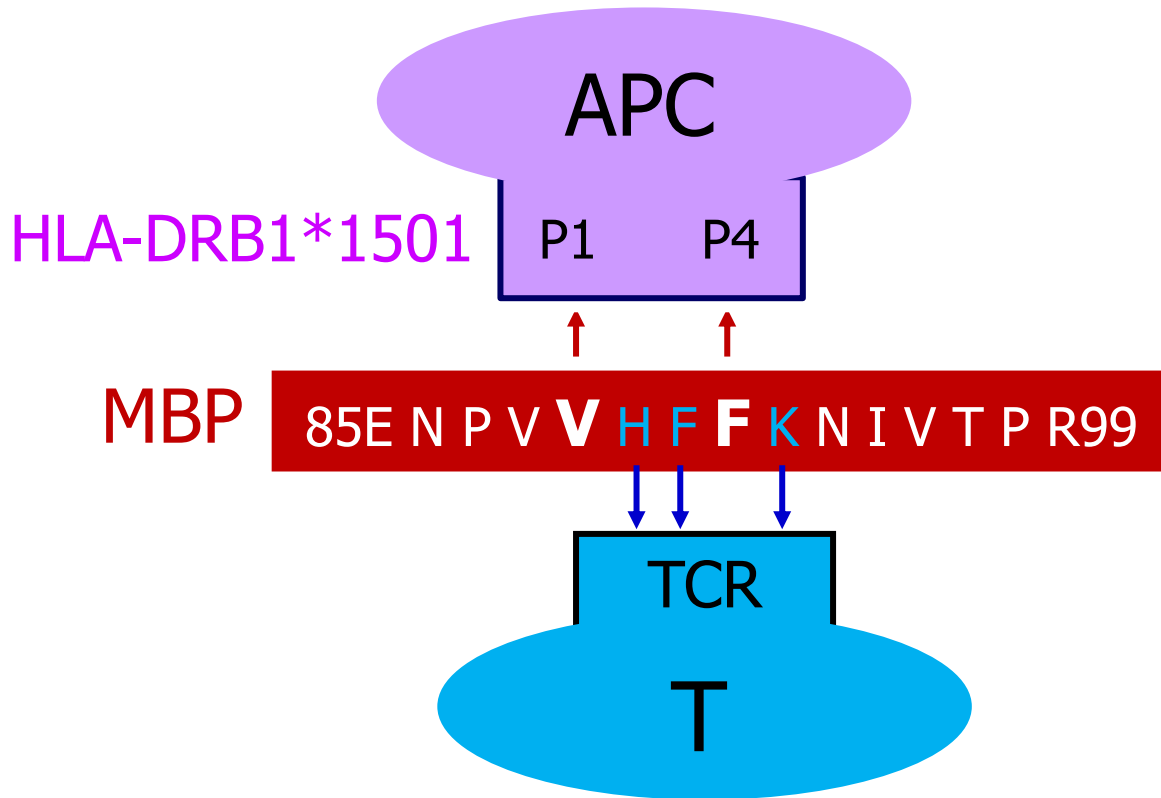
## perinatal

- delivery (vaginal/cesarean)
- gestation time (preterm/term)
- maternal nutrition (pre/probiotics)
- antibiotics

## prenatal

- intrauterine colonization
- host genetics
- maternal nutrition (pre/probiotics)
- antibiotics

# molecular mimicry



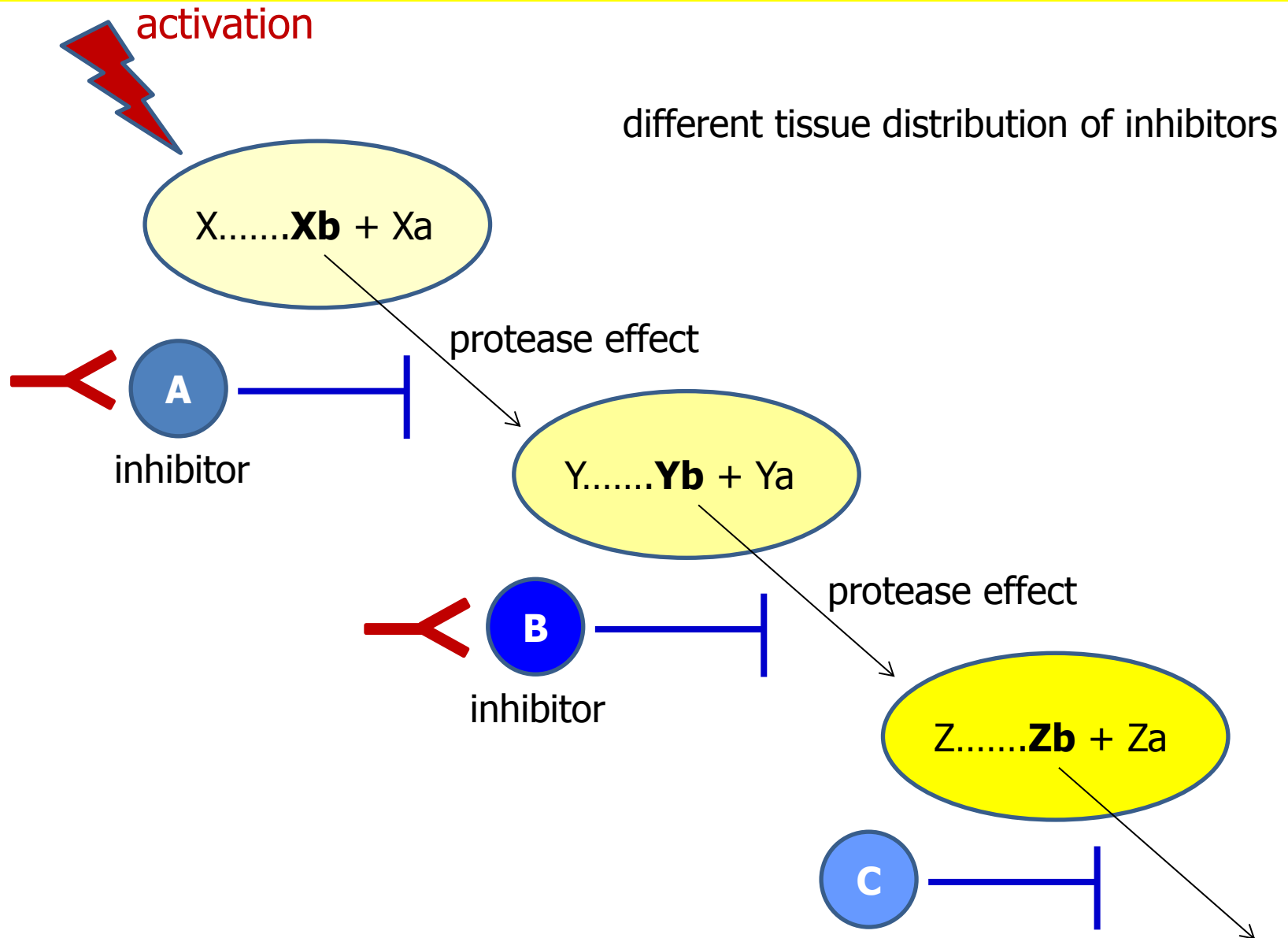
degenerate T cell responses

- millions of peptides
- affinity differs

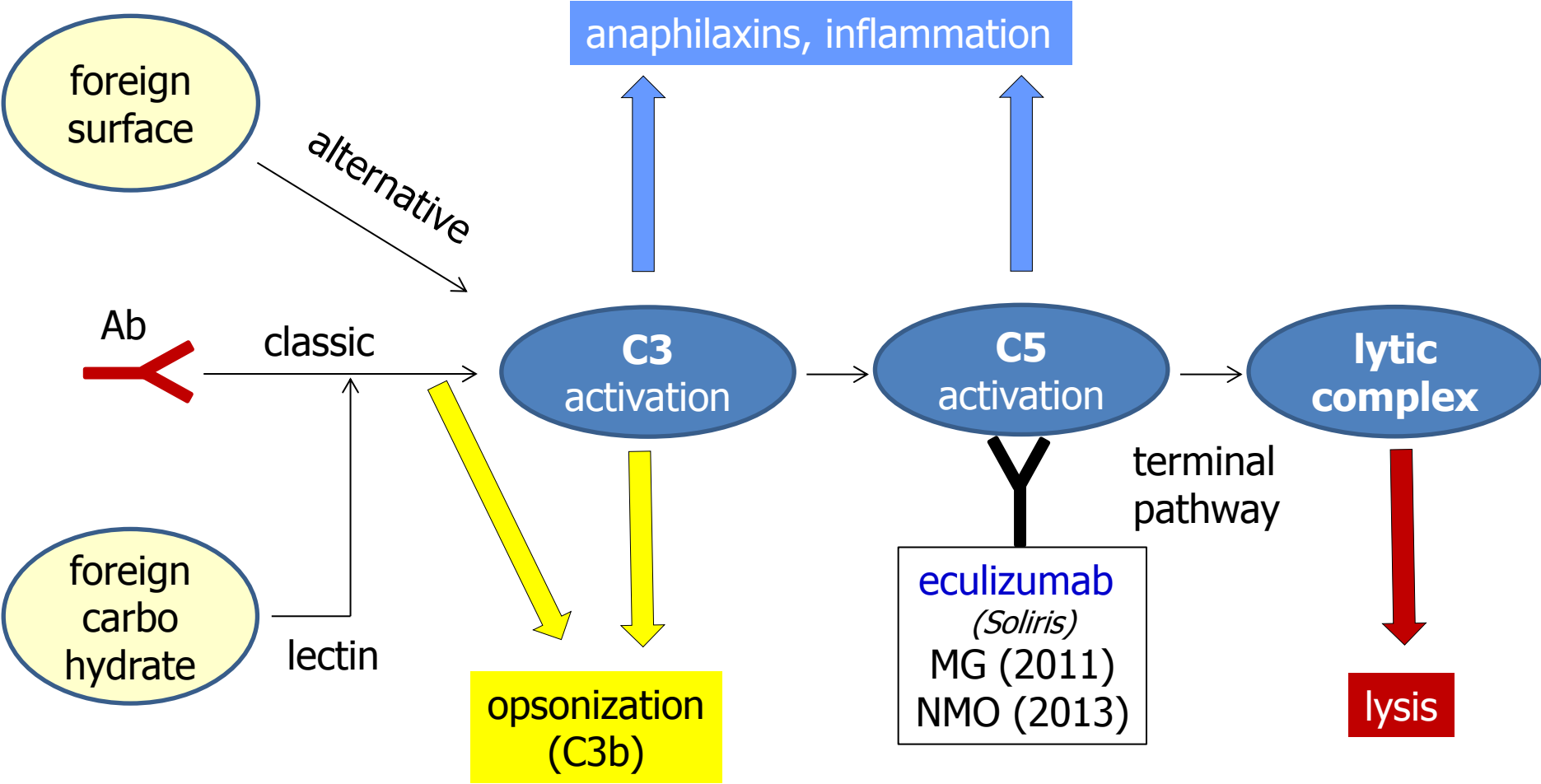
molecular mimicry

- linear: 1-2 amino acids
- charge, conformation

# the complement cascade



# the complement cascade

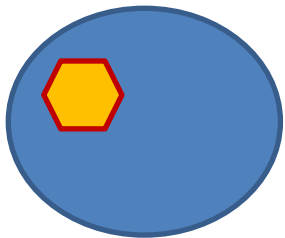


# B cell functions

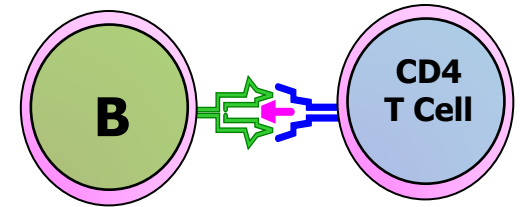
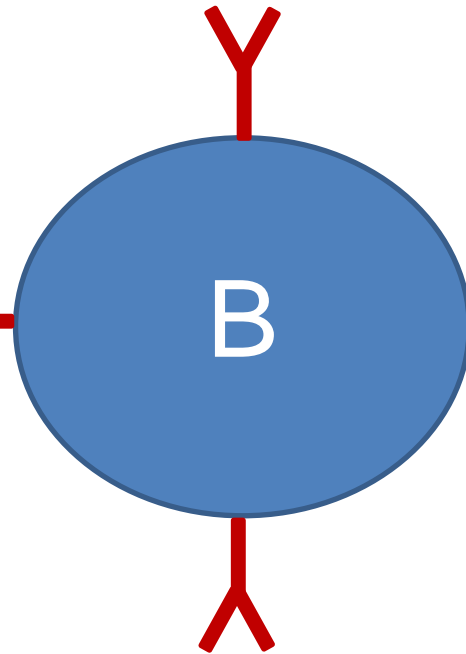
NK, macrophage  
complement



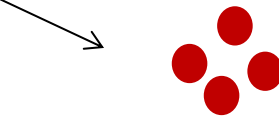
autoantibody production  
(plasma cell)



host for EBV



antigen presentation  
T cell activation

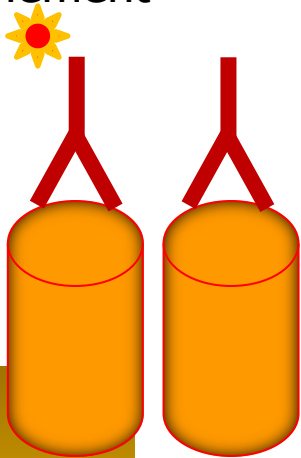


cytokine production  
IL-10, IL-6, TGF- $\beta$ ,  
TNF- $\alpha$ , TNF- $\beta$

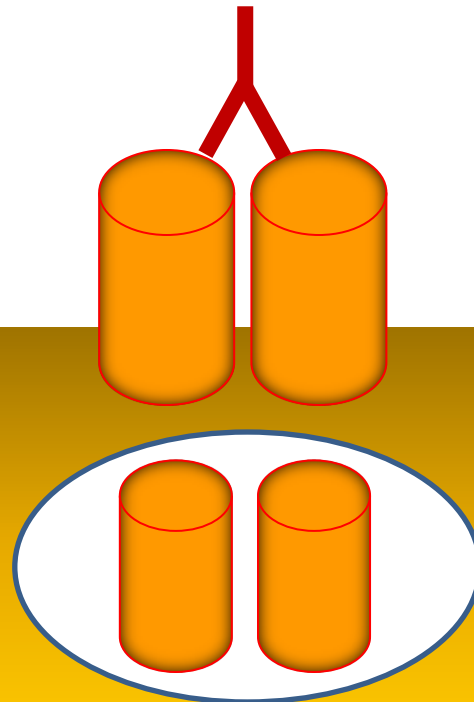
# effect of Abs: treatment consideration!

AchR  
AQP4 M23

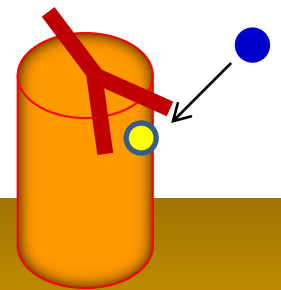
complement



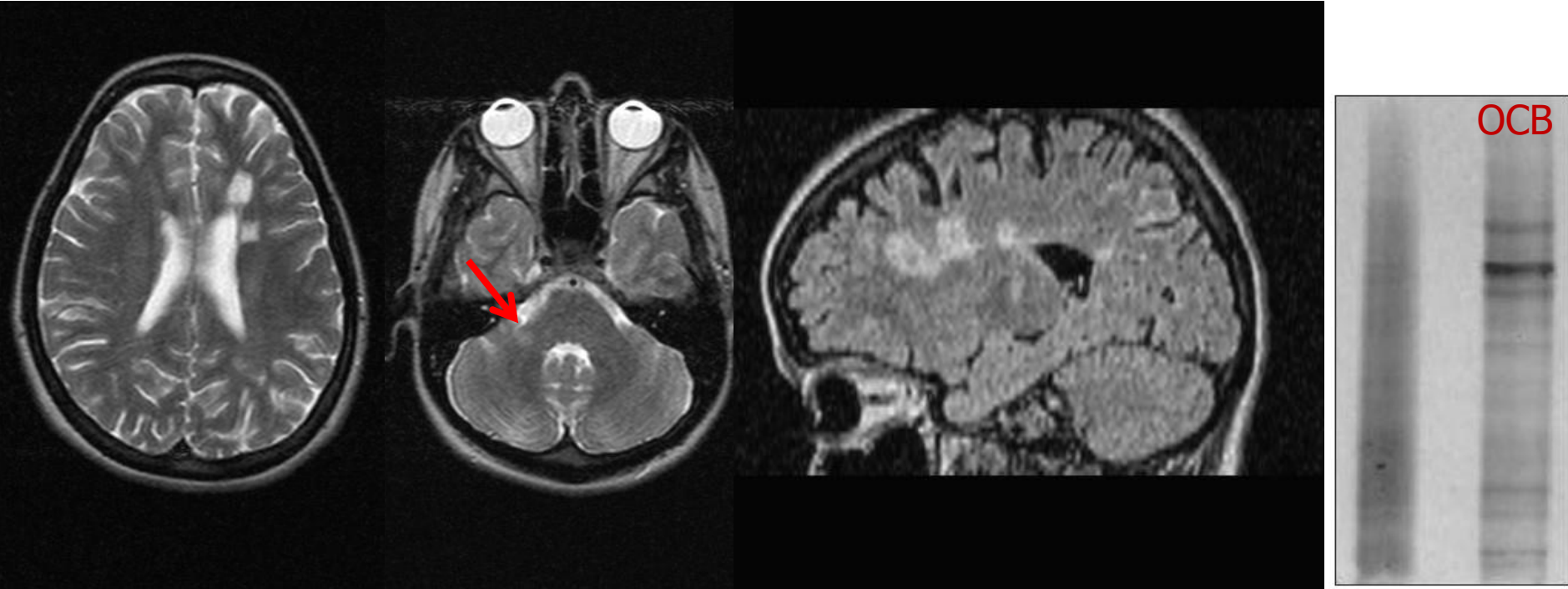
AchR  
AQP4 M1  
LGI1  
NMDAR



AQP4 M1, M23  
AchR?  
LGI1?  
NMDAR?



# when does autoimmunity start?



age  
10-12?

*radiologically isolated syndrome  
childhood MS...*

girl, age 15, migraine headache:  
▪ no focal neurological sign/symptom  
▪ SC-MRI, VEP, SEP, MEP negative

MRI  
DIT  
DIS

*CDMS  
adult MS...*

age 21:  
▪ first symptom

# THANK YOU



*Island Fyn, Denmark - Egeskov Castle*