

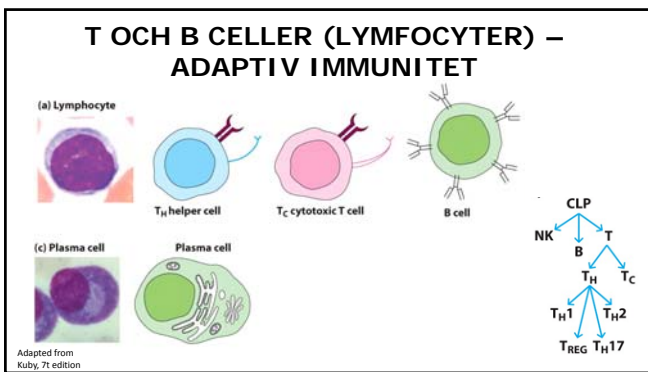
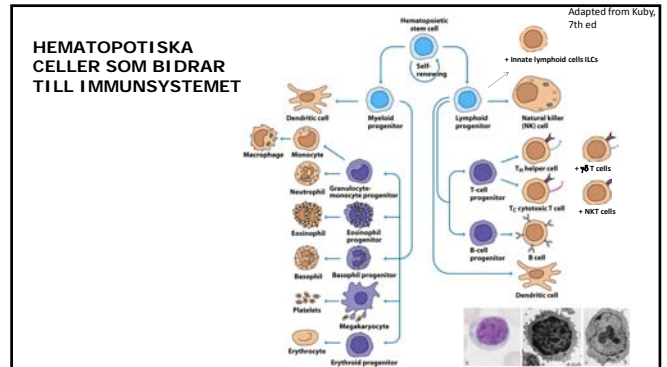
# BASAL IMMUNOLOGI UR NEUROLOGISKT PERSPEKTIV

2018-05-24

Kristina Lejon, PhD  
Docent  
Klinisk Mikrobiologi/Infektion&Immunologi  
Vicedekan, Utbildning Medicinska fakulteten

UMEÅ UNIVERSITET



### AUTOIMMUN SJUKDOM = AVSAKNAD AV IMMUNOLOGISK TOLERANS

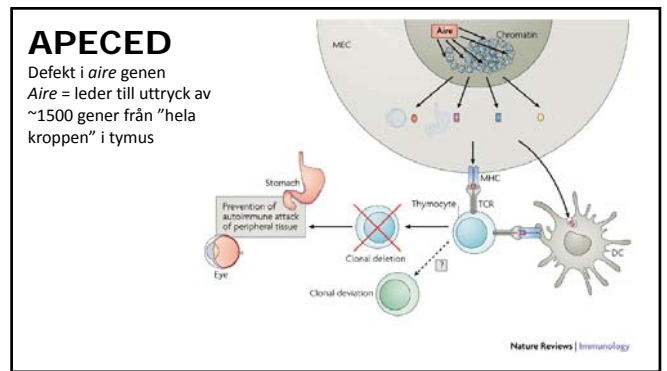
- Undermålig **selektion** mot autoreaktiva T- och B-celler i tymus och/eller benmärg
- Undermålig **perifer reglering** av autoreaktiva kloner med hjälp av Tregs och Bregs



### APECED

(Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy)

- Sällsynt monogen autoimmun sjukdom
- I Finland 1:25 000
- Många autoimmuna attacker
  - o Typ 1 diabetes
  - o Vitiligo
  - o Addisons sjukdom
  - o ...mm....

### PROBLEM APECED

Normal AIRE expression: Thymus. AIRE + TRIM21. Deletion of self-reactive T cells. Secondary lymphoid organs. Protective immunity.

APECED: Absence of AIRE. Survival of self-reactive T cells. Autoimmunity.

Legend:   
 ● Naive T cell   
 ● Autoreactive T cell   
 ● Regulatory T cell   
 ● CD4<sup>+</sup> T cell   
 ● CD8<sup>+</sup> T cell

### KOPPLING HLA ALLELER-AUTOIMMUNA SJUKDOMAR

- Vad som kan presenteras i tymus = selektion
- Vad som kan presenteras i periferin = immunsvär

① TCR signaling   
 ② Costimulatory interaction   
 ③ Cytokine signaling

Gene expression   
 Autocrine (e.g., IL-2)   
 Paracrine (e.g., IL-12)

Normal APC   
 Dendritisk cell   
 Makrofåg

Adapted from K 7th ed

### B CELLS URVAL (SELEKTIONEN) I BENMÄRGEN

50-75% av alla B celler som bildas i benmärgen är autoreaktiva

**Method:** single cell cloning and assay   
**IHC:** Hep-2 reactivity   
**ELISA:** ssDNA, dsDNA, insulin, LPS

Central tolerance checkpoint   
 Peripheral tolerance checkpoint

BM   
 Periphery

Early immat.   
 Immat.   
 New emigrant   
 Mature naive

CD54- CD54+   
 CD19+ CD19+   
 CD10+ CD10+   
 IgM- IgM+   
 CD27- CD27+

Meffre Wardemann 2008 Current Opinion in Immunology

### FEL I URVALET FRÅN BENMÄRG TILL PERIFERIN?

B  $P < 0.0001$    
 $P < 0.0001$    
 Controls MS T1D RA   
 n=11 n=7 n=8 n=10

C  $P < 0.0004$    
 $P = 0.0076$    
 Controls MS T1D RA   
 n=11 n=7 n=8 n=10

D  $P = 0.0298$    
 Controls MS   
 n=6 n=7

E  $P = 0.0286$    
 Controls MS T1D RA   
 n=6 n=7 n=8 n=10

Ja!   
 För T1D, RA & MS!

Meffre JCI 2013

### INITIERING AV ETT T-CELLS BEROENDE B-CELLS SVAR

Secondary lymphoid organ   
 B cell follicle   
 T cell zone   
 Germinal center   
 Light zone   
 Dark zone   
 T cell   
 B cell   
 Memory B cell   
 Long-lived plasma cell   
 Antibody-secreting cell

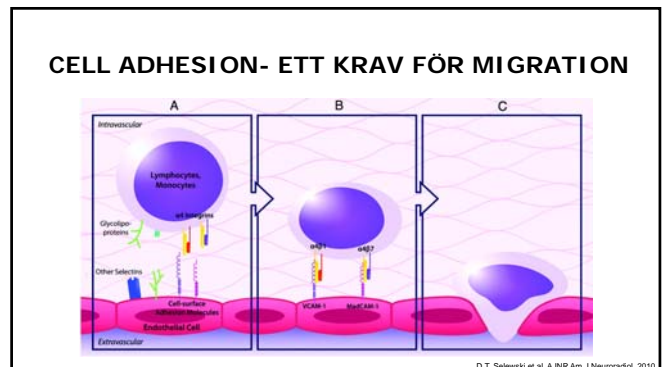
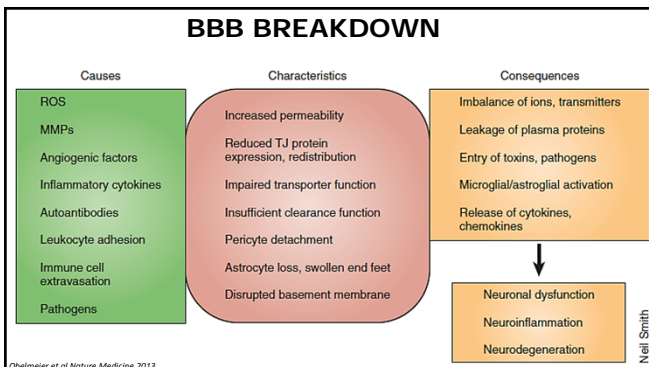
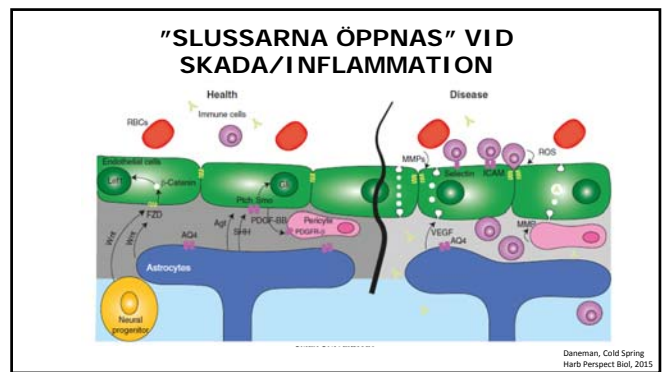
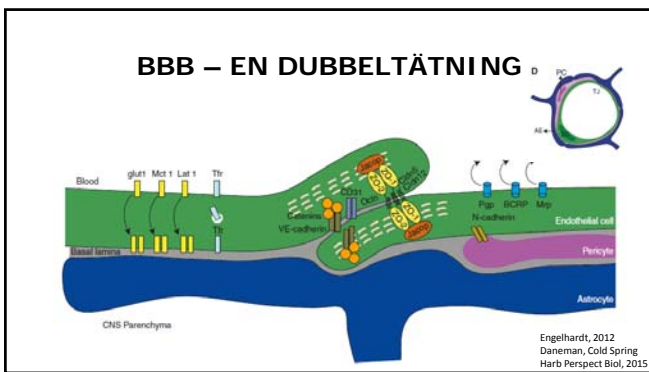
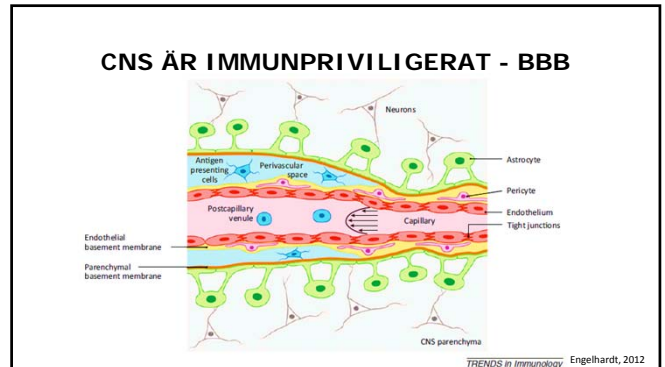
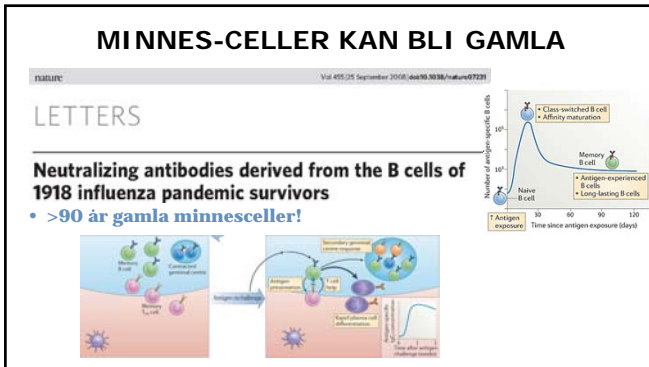
Adapted from Nat Rev Imm

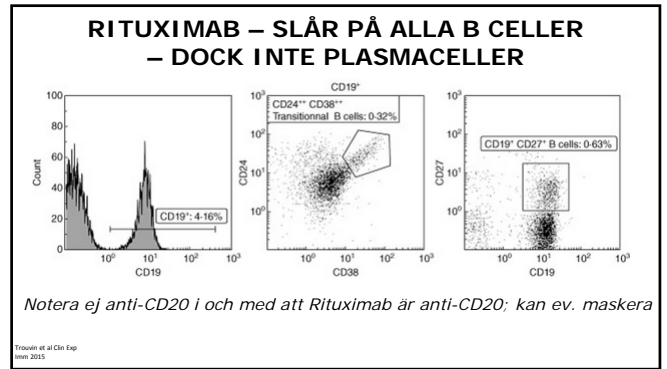
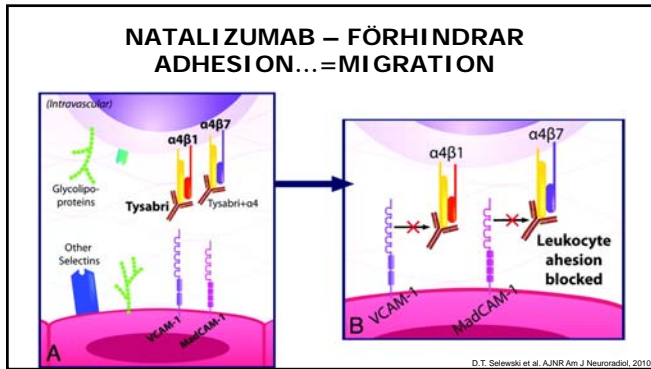
### ÖVERLEVAD AV PLASMACELLER

Periphery   
 Germinal center   
 B cell   
 Plasma cell (CXCR4+)   
 High-affinity antibodies   
 CXCR4   
 Eosinophil (CXCR4+)   
 APRIL   
 Plasma cell   
 Stromal cells (CXCL12+)   
 Megakaryocyte   
 Bone marrow

Långlivande plasma celler - återfinns i benmärgen - tas hand om av flera celltyper

Adapted from Kuby, 7th ed





Notera ej anti-CD20 i och med att Rituximab är anti-CD20; kan ev. maskera

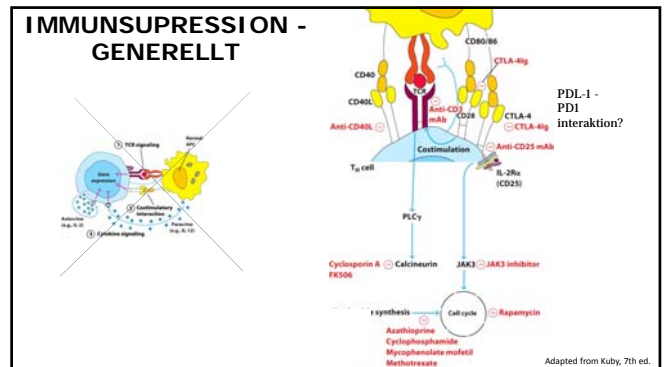
### RITUXIMAB BEHANDLING - UTSLAGNING AV B<sub>REGS</sub>?

Development of Psoriasis After B Cell Depletion With Rituximab  
Shoenk & Dan, Edward M. Vitai, and Paul Iversy

ARTHRITIS & RHEUMATISM  
Vol. 50, No. 6, August 2008, pp 2715-2718  
DOI 10.1002/art.23081  
© 2008, American College of Rheumatology

RA patient (52-y old), no effect anti-TNF - Rituximab treatment, development of psoriasis after second round of treatment

SLE patient (26-y old), severe SLE, Rituximab treatment, development of psoriasis



**Tack för att du lyssnade!**

**Frågor? At your service!**

UMEÅ UNIVERSITET

Angel of the West, Julian Voss-Andrea