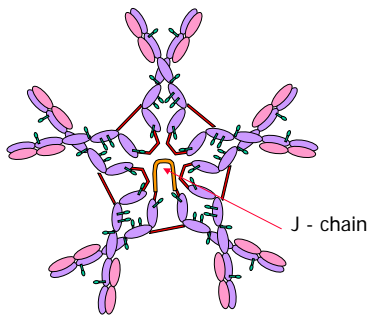


Grundläggande immunologi och immunologiska sjukdomar

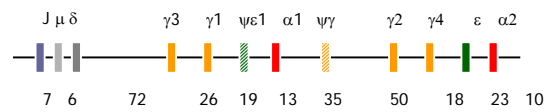
Prof. L. Hammarström

Ig classes

IgM
IgG
IgA
IgD
IgE



The human Ig heavy chain constant region gene locus



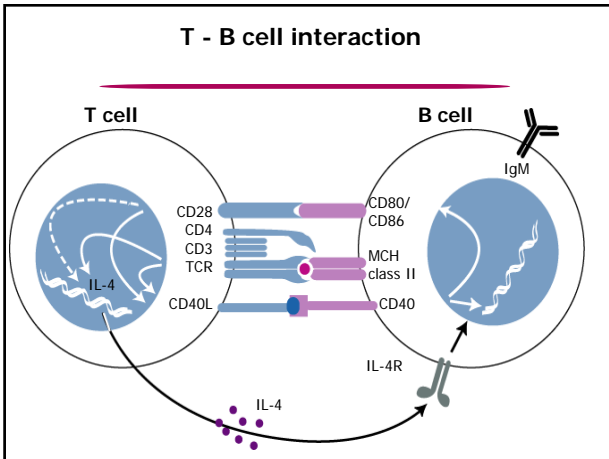
Infections in children

Form of care ratio	No (children)	Odds
At home with parents	1,4	1
At home with "other"	1,5	1,2
Private daycare	2,3	1,8
Communal daycare	3,4	2.6
Traditional daycare	19.3	6.8

Uldall 1990. Odds ratio 1 = 25 days

Cell activation

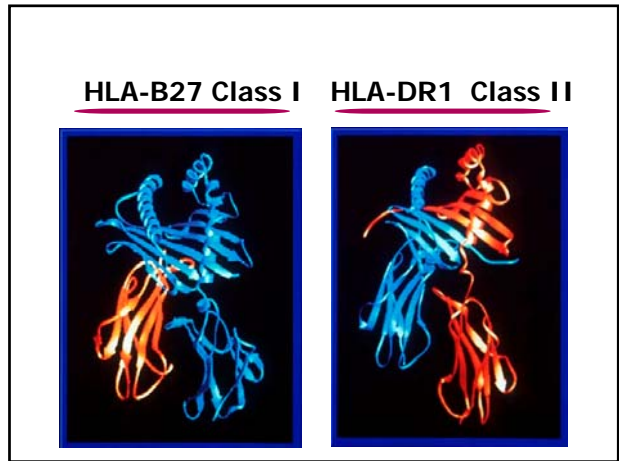
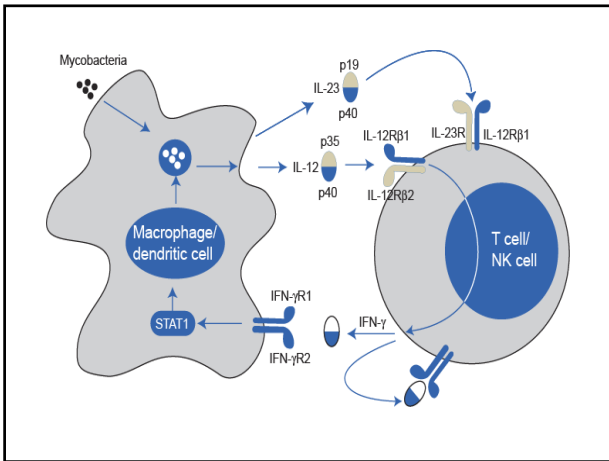
Physical binding
T - B cell collaboration
T - Macrophage collaboration
Chemical messengers



Chemical messengers

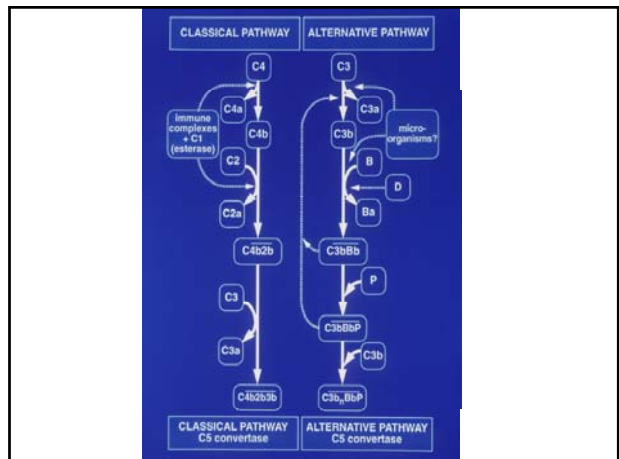
Cytokines
(IL- 1-29, TNF, interferons)

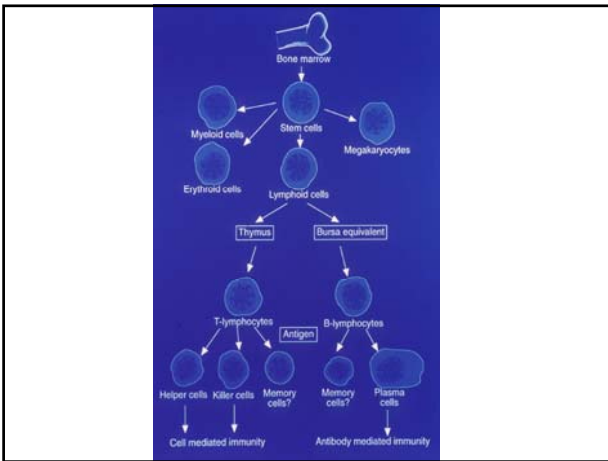
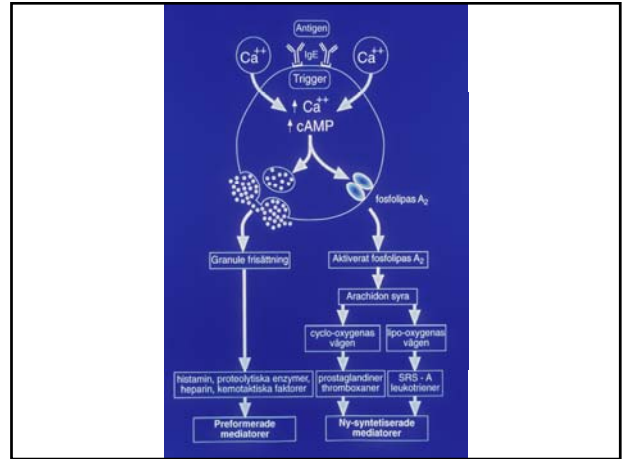
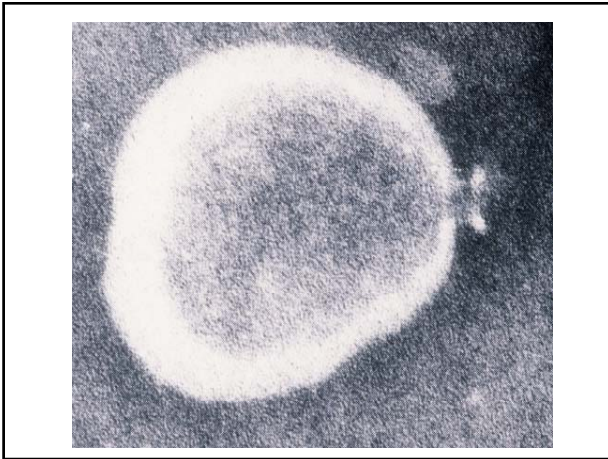
Chemokines
(CXCL, CCL, C, CX3C, ELR)



HLA interaction

T cells		
CD8+	A, B, C	
CD4+	DR, DQ, DP	
NK cells		
	E, F, G	





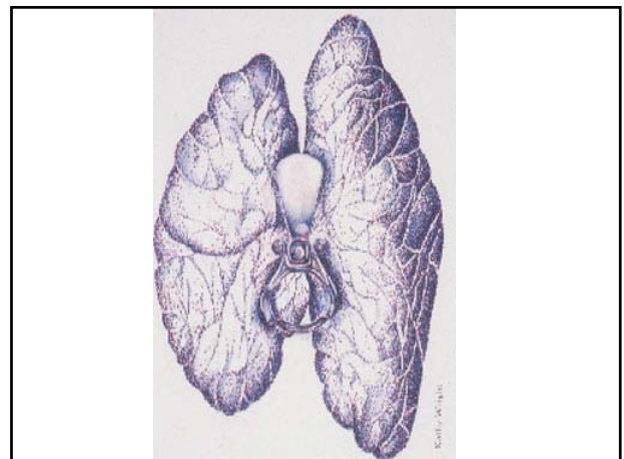
Immunity

Innate

Monocytes, macrophages, granulocytes

Adaptive

T and B lymphocytes



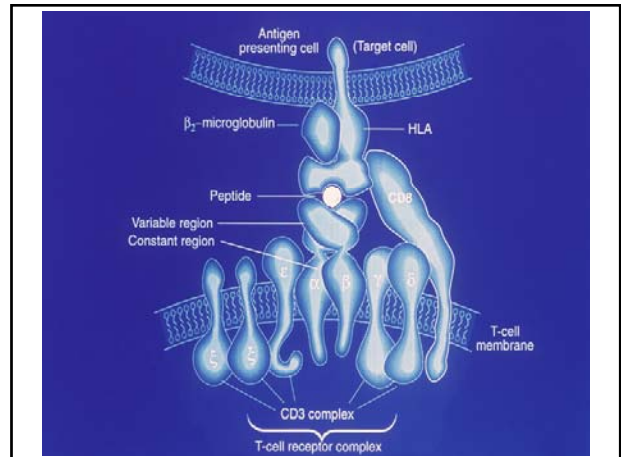
T cell subsets

Helper T cells (CD4)

Th1

Th2

Cytotoxic T cells (CD8)



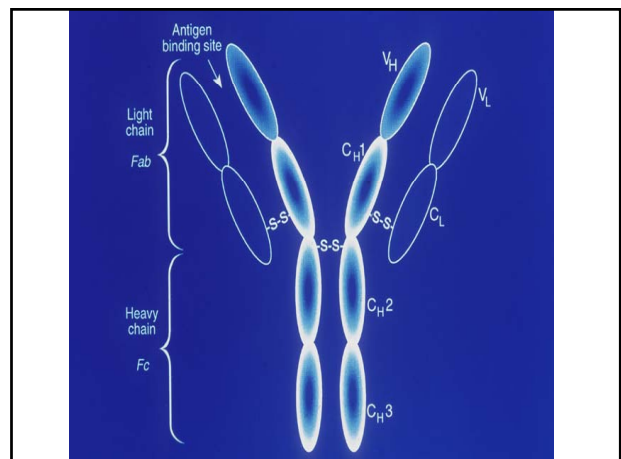
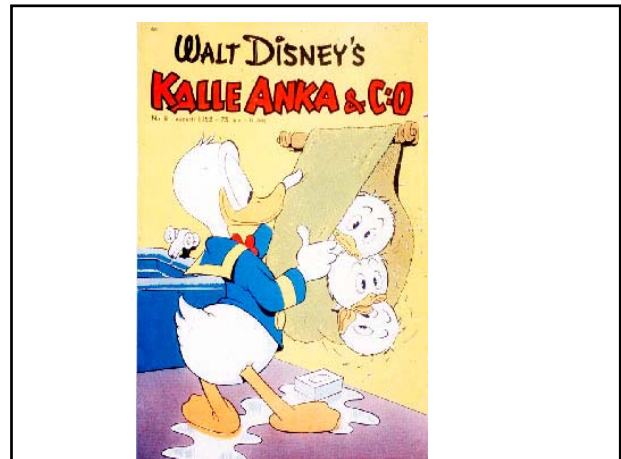
T cell receptors

$\alpha\beta$

VJ- α /VDJ- β

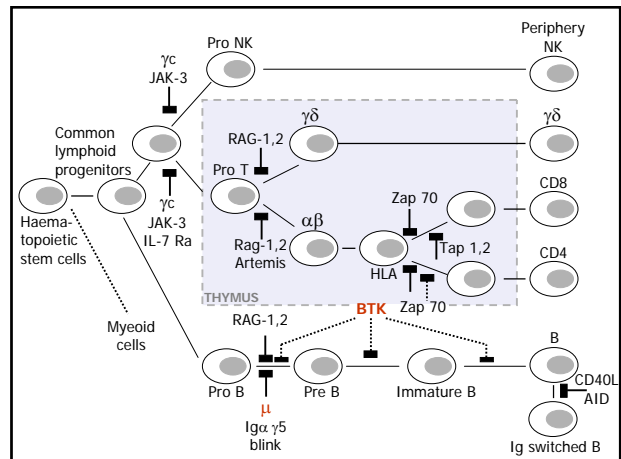
$\gamma\delta$

VJ- γ /VDJ- δ



Primary Immunodeficiency Diseases

- T cell defects
- B cell defects
- Phagocytic disorders
- Complement defects

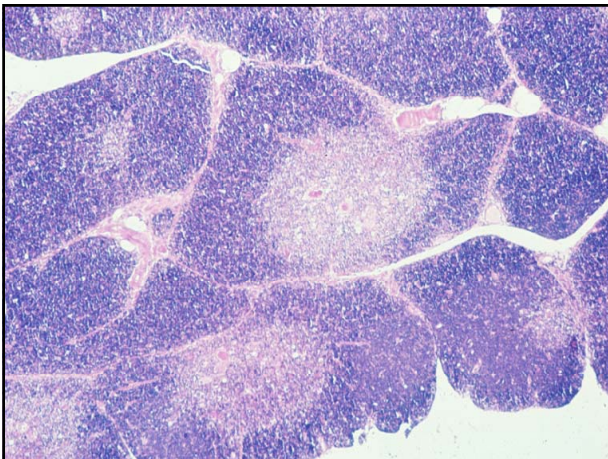


Diagnostic tools

- Clinical history
Clinical picture/infections, associated features, inheritance
- Protein analysis
Nephelometry, Western blot, FACS, histopathology
- Genetic analysis
Southern blot, Northern blot, PCR amplification, sequencing

Primary Immunodeficiency Diseases

- **T cell defects**
- B cell defects
- Phagocytic disorders
- Complement defects



T cell defects

- Di George syndrome

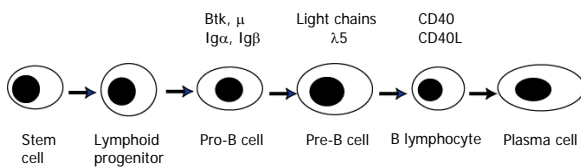
Severe combined immunodeficiencies

Reticular dysgenesis (AR)	M, T, B, NK	?
ADA (AR)	T, B, NK	ADA
B (-) SCID (AR)	T, B	Rag-1/Rag-2
B (-) SCID (AR)(radiation sens)	T, B	Artemis
NK (-) SCID (X-linked)	T, NK	γ c
NK (-) SCID (AR)	T, NK	Jak-3
SCID (AR)	T	IL-7R α
SCID (AR)	T	CD45

Primary Immunodeficiency Diseases

- T cell defects
- **B cell defects**
- Phagocytic disorders
- Complement defects

B lymphocyte development



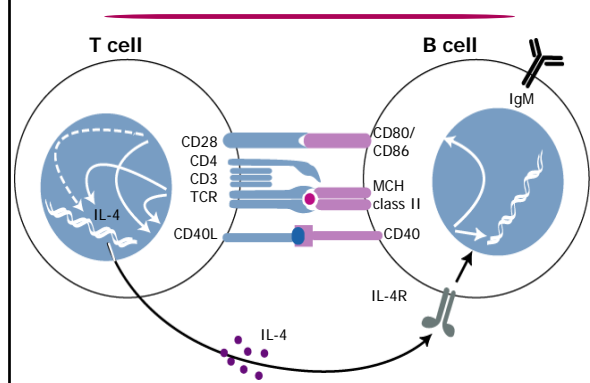
Defects in early B cell development

- Mu (μ) gene mutation
- Ig α / β (CD79a/b) mutations
- Lambda (λ) 5/VpreB mutations
- BLNK mutations
- Btk mutations (XLA)

Defects in late B cell development

- **Hyper IgM**
- Common variable immunodeficiency
- IgA deficiency
- IgG subclass deficiency

T - B cell interaction



Ig class switch defects

- Hyper IgM type I (CD40L)
- Hyper IgM type II (AID)
- Hyper IgM type III (CD40)
- Hyper IgM type IV (NEMO)
- Hyper IgM type V (UNG)

Defects in late B cell development

- Hyper IgM
- **Common variable immunodeficiency**
- **IgA deficiency**
- IgG subclass deficiency

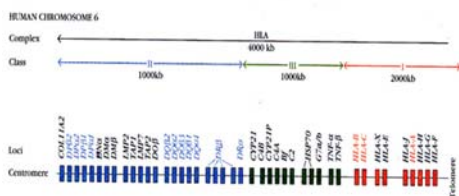
IgAD and CVID Polar ends of the same disease ?

- Presence of both disorders in the same family
- Progression of IgAD to CVID in selected patients
- Multiple etiologies/multiple genetic defects (?)

Susceptibility genes in "CVID/IgAD"

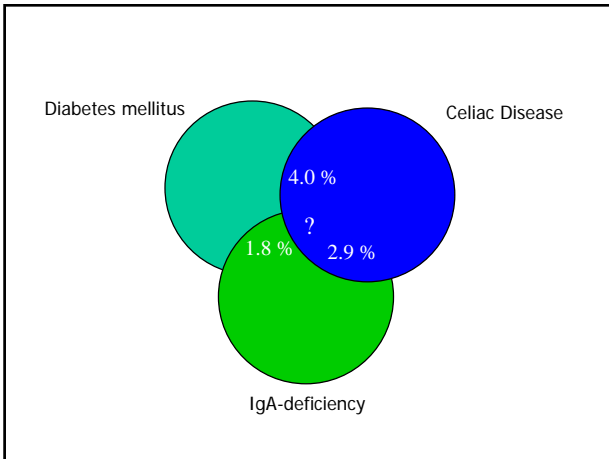
- **MHC**
- non-MHC

The human MHC region



Genetic strategies

- Multicase families
- **Disease associations**
- Different ethnic groups
- Twin studies
- Genome wide scan

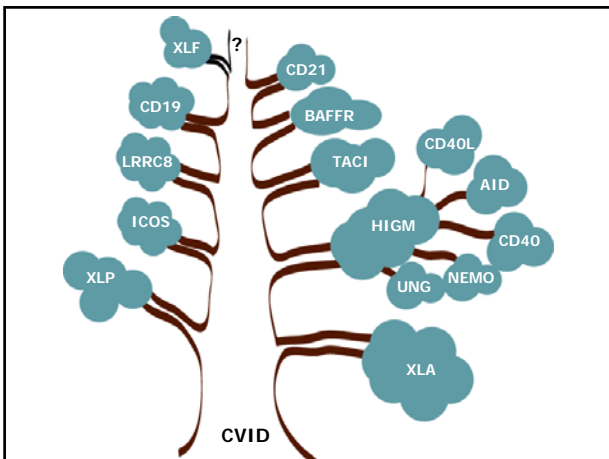
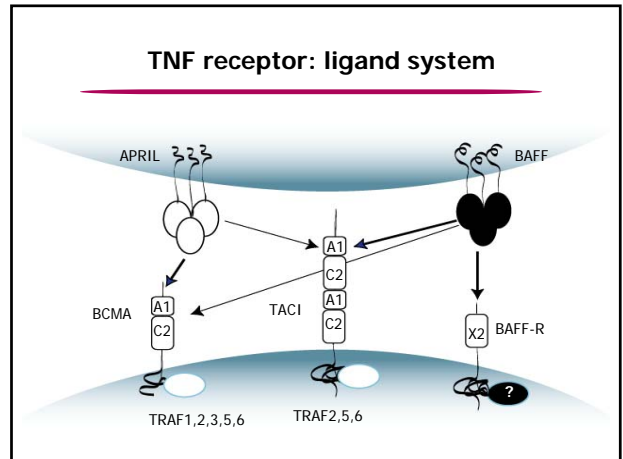


Susceptibility genes in "CVID/IgAD"

- MHC
- non-MHC

Rare causes of "CVID/IgAD"

- XLA (btk)
- XLP (SH2D1A)
- Hyper-IgM (CD40L)
- Hyper IgM (AID)
- ICOS
- CD19
- TACI



Defects in late B cell development

- Hyper IgM
- Common variable immunodeficiency
- IgA deficiency
- IgG subclass deficiency

The human Ig heavy chain constant region gene locus



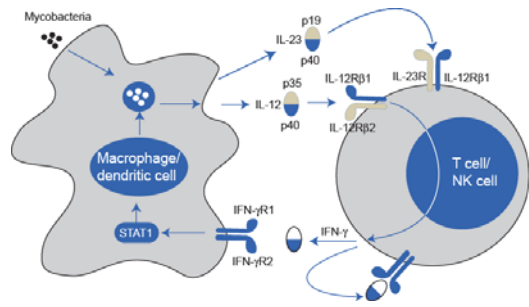
Primary Immunodeficiency Diseases

- T cell defects
- B cell defects
- **Phagocytic disorders**
- Complement defects

Phagocytic disorders

- Chronic granulomatous disease
gp91phox (XL), gp22, 47,67 (AR)
- Congenital neutropenia (Kostmann)
Elastase 2 (AD), HAX1
- LAD1/2
CD18 of LFA-1, Mac 1, p150.95 (AR) and GDP fucose transporter (AR)
- Leucocyte mycobactericidal defects
γ-IFN, γ-IFNR, IL-12, IL-12 R (AR)

Mycobacterial susceptibility circuit



Primary Immunodeficiency Diseases

- T cell defects
- B cell defects
- Phagocytic disorders
- **Complement defects**

Complement defects

- Classical pathway defects
C1, C2, C3, C4, C5, C6, C7, C8, C9
- Lectin pathway defects
MBL, MASP-2
- Alternative pathway defects
FD, FB, Properdin

Patients with PID in Sweden

SCID	19	30
μ defects	2	<5
CD40L	10	20
AID	1	<5
CVID	250	300 -
500		
IgAD	1500	15000
A-T	18	20 - 25

Patients with PID in Sweden

C1q	2	<5
C4	2	<5
C2	42	200 -
700		
C3	3	<5
C6	3	<5
Properdin	9	?
MBL	50	?
MASP-2	5	1350
C1 esterase I	100	180