Basic Immunology

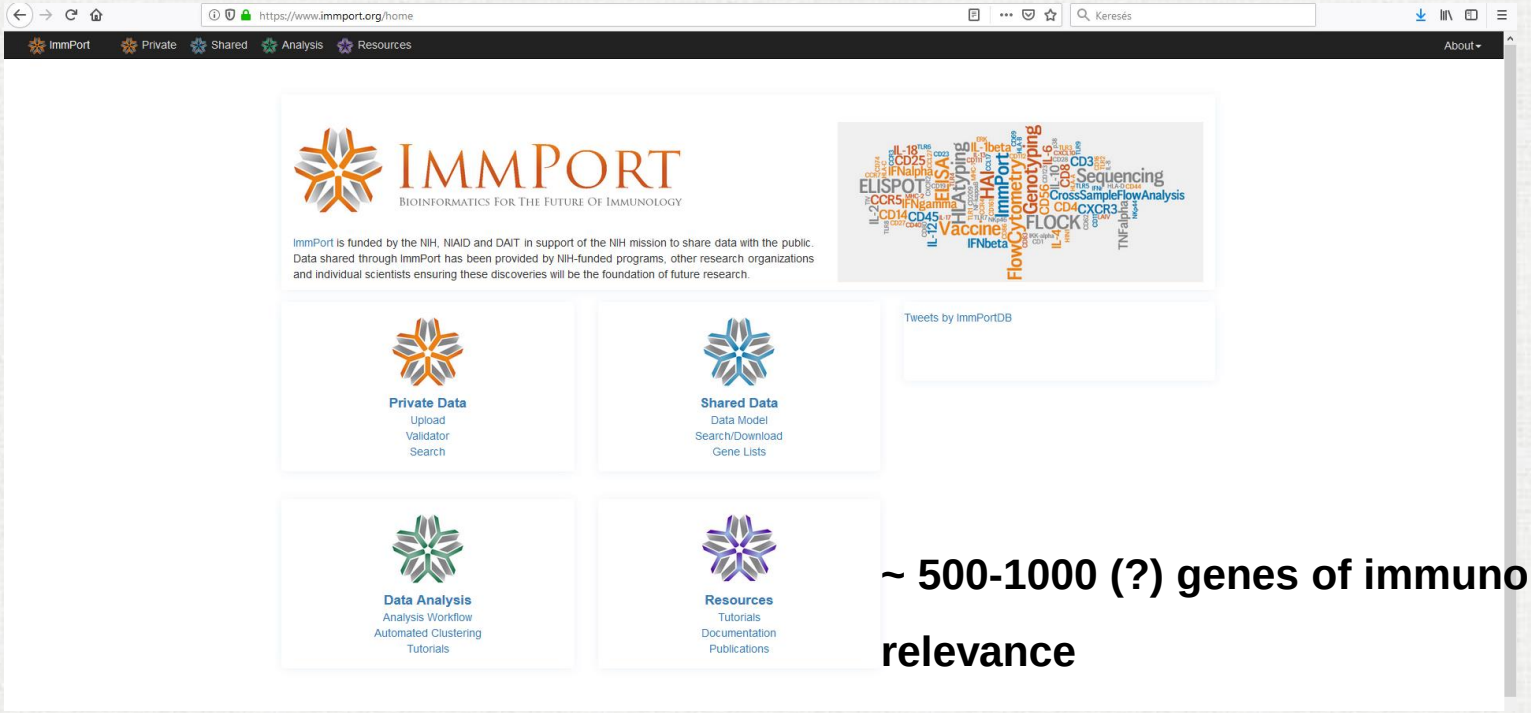
Lecture 25

Hereditary immunodeficiencies

Tolerance or immunodeficiency?

Tolerance: antigen-specific unresponsiveness **in the presence** of antigen-receptor bearing cells**.**

Immunodeficiency: Acquired (>400) or primary impaired/absent capacity to establish immune response **against various antigens in the absence** of ag-receptor bearing cells or effector components (also inborn error of immunity [IEI])**.**



~ 500-1000 (?) genes of immunological relevance

Main types of immunodeficiencies

PRIMARY

- **Innate** - *Humoral*: complement, cytokines
  - *Cellular:* Myeloid cells, NK cells
- **Adaptive** - *SCID*
  - *B-cell defects*
    - Primary (a/hypogammaglobulinaemias)
    - Secondary (dysgammaglobulinaemias)
  - *T-cell defects*
    - Primary
    - Secondary

ACQUIRED: infections (HIV), tumors, wasting, medical intervention, radioactive irradiation, etc.

IUIS list of immunodeficiencies

Table 1. Summary of IUIS classification groups

IUIS classification groups	Primary Immunodeficiency Disease category	Number of genetic defects	New genetic defects[a]	Number of diseases	New diseases[b]
I	Cellular and humoral immunodeficiencies	60	9	52	8
II	Syndromic combined immunodeficiencies	65	15	61	13
III	Antibody deficiencies	43	13	50	11
IV	Immune dysregulatory diseases	47	9	46	9
V	Phagocytic diseases	42	4	35	2
VI	Innate immunodeficiencies	71	20	59	17
VII	Autoinflammatory diseases	49	15	50	12
VIII	Complement deficiencies	36	2	30	2
IX	Diseases due to bone marrow failure	43		43	
X	Phenocopies of PIDs	13[c]	1	13	1
Total	All IEI	469	88	439	75

Curr Opin Pediatr 2021 33:657-675.

Complement: main pathways

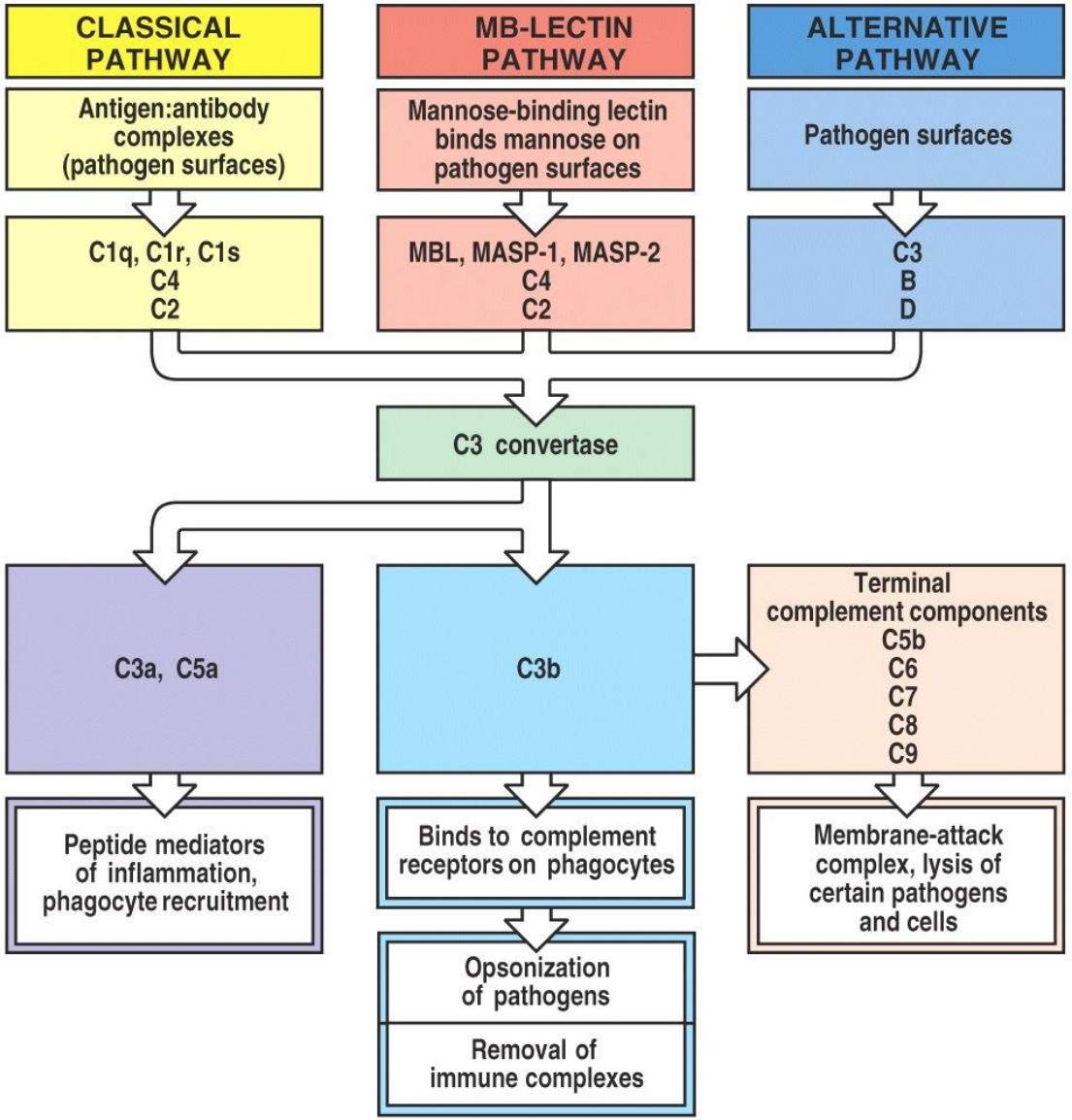


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

Complement defects: primary/secondary

- **5.2.1. Deficiencies of classical, alternative and terminal pathways**
- C1q deficiency - SLE.
- Deficiencies of C3 and alternative/classical pathway components - invasive bacterial infections with encapsulated bacteria such as *Pneumococcus, Streptococcus* or *Hemophilus*,
- Deficiencies of terminal pathway components/properdin - systemic neisserial infection,

- **5.2.2. Lectin pathway deficiencies**
- MBL- microbial infections in childhood (typically in the 6–18 month "susceptibility window"), and in adults, secondary to other immune deficiencies such as immunosuppression, AIDS and certain autoimmune diseases. MBL deficiency is common and most deficient individuals do not suffer from increased susceptibility to infection.

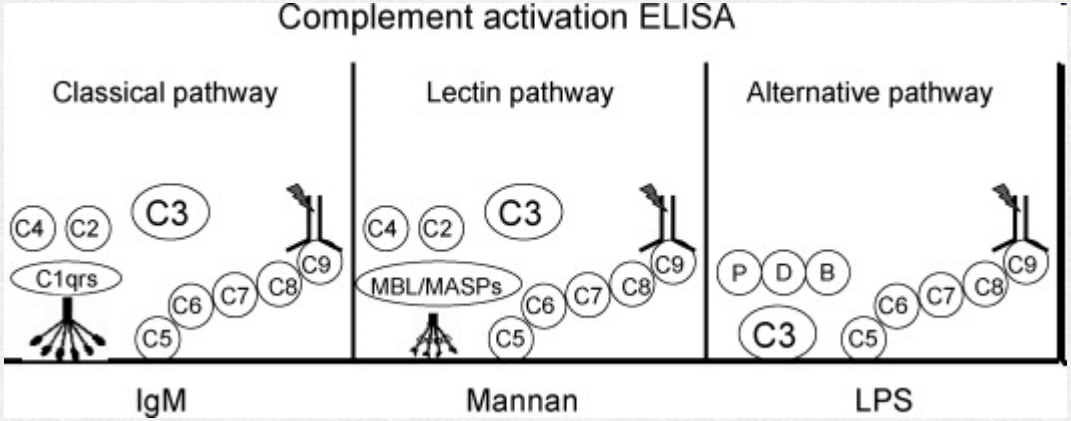
- **5.2.3. C1-inhibitor deficiency**
- C1-inhibitor deficiency - 2/100,000. It causes recurrent edema which may lead to death from suffocation if the larynx is involved. **The symptoms in HAE are caused by a failure of C1-inhibitor to control the contact activation system, leading to an increase in bradykinin,** which causes the capillary leakage. An acquired form of the disease (AAE) is frequently caused by autoantibodies to C1-inhibitor and an accompanying haematologic malignancy. In contrast to HAE, AAE is associated with a low concentration of C1q.

- **5.2.4. Paroxysmal nocturnal hemoglobulinuria (PNH)**
- Paroxysmal nocturnal hemoglobulinuria (PNH) is rare disease caused by a clonal somatic mutation affecting hematopoietic stem cells. **The mutation affects the PIG-A gene** which codes for the phosphoinositol glycosyltransferase that couples the first inositol to the phosphatidylinositol anchor that links numerous membrane proteins to the cell surface **Two of these proteins, DAF (CD55) and CD59**, **are important complement regulators** and deficiency causes spontaneous haemolytic attacks, thrombocytopenia and platelet activation leading to thrombosis.
- **5.2.5. aHUS** aHUS is a disease associated with microangiopatic haemolytic anemia, thrombocytopenia and acute renal failure, most probably due to **an inefficient regulation of complement at the surface of the endothelial cell. The disease is frequently associated with genetic variants of factor H and several other complement components and regulatory proteins.**

Diagnostic approaches

Soluble factors

ELISA: quantity and activity



Cell surface factors

Protein: FACS
mRNA: RT-PCR

- Primary factor deficiency – **lack** of degradation products
- Secondary factor deficiency – **accumulation** of degradation/split products

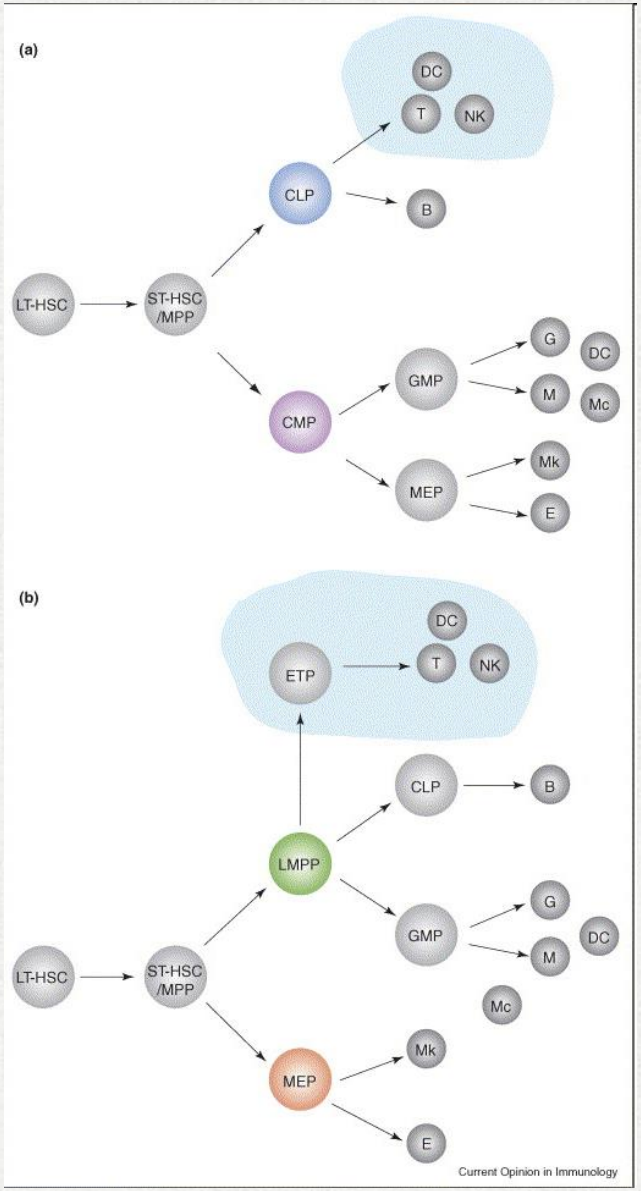
„Frequent” deficiciencies of the cellular innate immune system

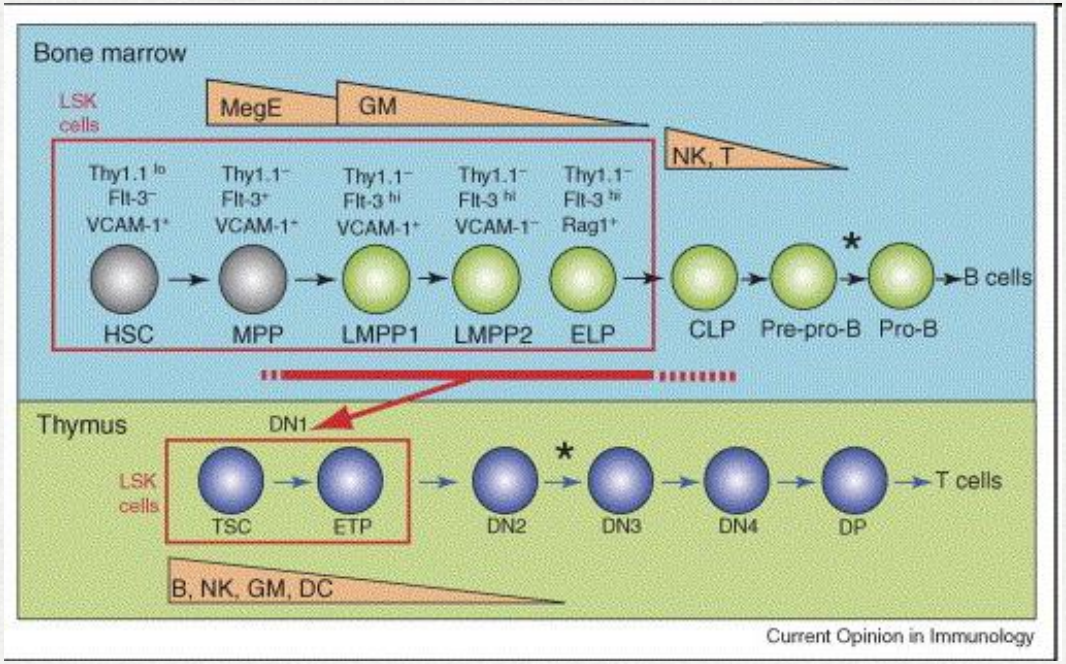
- Granulocyta/monocyta granule-defects
- Intracellular killing defects
- Adhesion-chemotaxis abnormalities
- PAMP/TLR-defects
- NK-cell defects

Immunodeficiencies of the cellular elements of the adaptive immune system I.

SCID variants

Commitment and/or limited choice





DN1: $CD44^{+}$
$CD25^{-}$
$CD4^{lo}/CD8^{-}$

MPP	Multipotent progenitor
LMPP	Lymphoid-primed MPP
CLP	Common lymphocyte progenitor
CMP	Common myeloid progenitor
MEP	Megakaryocyte-erythroid progenitor

SCID variant I. SCID *genotype* with lymphocyte developmental abnormalities

Defective cytokine signaling

X-linked: Cytokine receptor common γ chain

Autosomal recessive: IL-2 receptor α chain, IL-7 receptor α chain, Janus kinase 3 (JAK3)

Defective T-cell receptor signaling: CD45, CD3γ, CD3δ, CD3

Defective receptor gene recombination: RAG1, RAG2, DNA cross-link repair 1C (DCLRE1C, ARTEMIS)

Defective nucleotide salvage pathway: Adenosine deaminase (ADA), purine nucleoside phosphorylase (PNP)

Defective MHC class I expression: Transporter of antigenic peptides 1 and 2 (TAP1, TAP2), TAP-binding protein

Defective MHC class II transcription complementation groups A-D (Four components of the MHC class II gene transcription complex: CIITA, RFXANK, RFX5, and RFXAP

Other: Winged-helix nude transcription factor

SCID variants II. SCID *phenotype* with other abnormalities

22q11 deletion – DiGeorge syndrome (complete/incomplete - 22q11.2 deletion)

Omenn syndrome: SCID, erythrodermia, hepatosplenomegaly, lymph node swelling, eosinophilia, increased IgE production and oligoclonal T-cell proliferation (RAG1/2 mutation)

Diagnostic and therapeutic approaches in SCID variants

- Diagnostics: lymphocyte-composition/number, phenotype (other laboratory parameters)
- Supplementation (ADA, PNP)
- Bone marrow transplantation
- ADA-SCID, IL2r-SCID – gene therapy (retroviral, or rAAV)

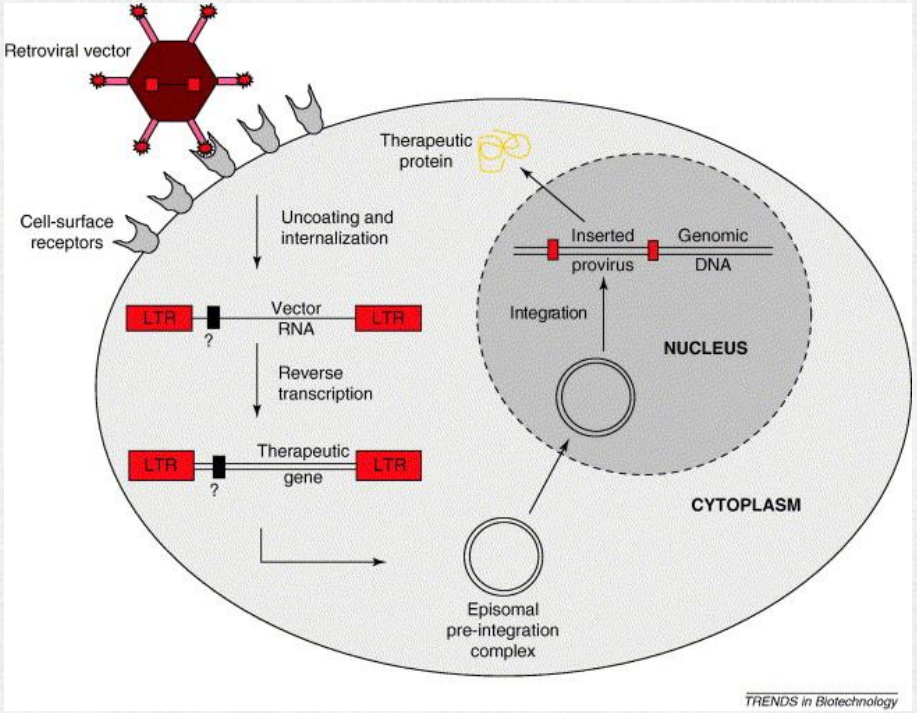
Altered lymphocyte composition in the „frequent" variants of SCID

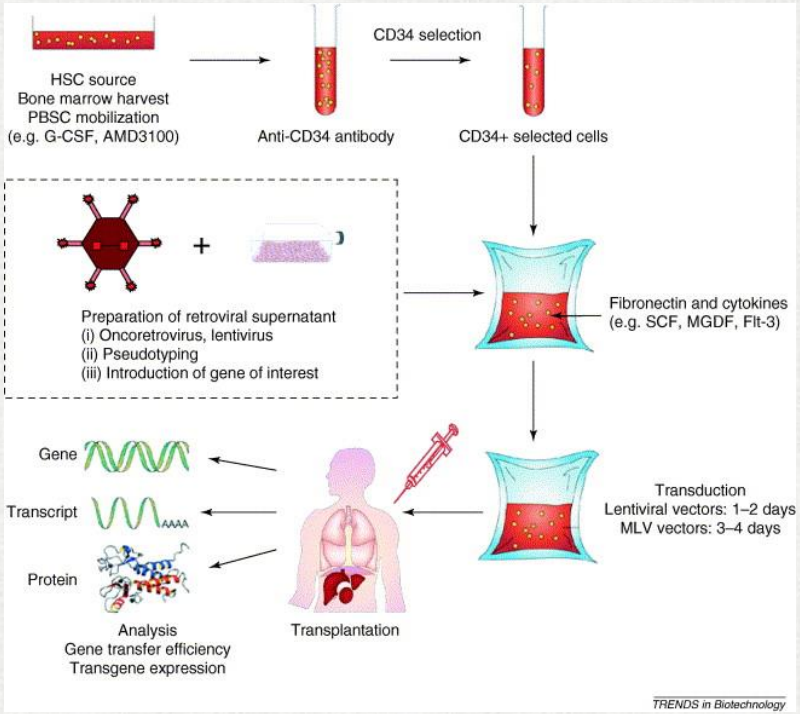
TABLE III. Lymphocyte phenotypes characteristically associated with particular forms of SCID

Form of SCID	T cells			B cells	NK cells
	CD3	CD4	CD8		
Common γ chain, JAK3, IL-2R α chain, CD45	↓	↓	↓	NL	↓
IL-7R α chain, CD3δ	↓	↓	↓	NL	NL
RAG1, RAG2	↓	↓	↓	↓	NL
Adenosine deaminase	↓	↓	↓	↓	↓
MHC class II	NL	↓	NL	NL	NL
ZAP70, MHC class I	NL	NL	↓	NL	NL

↓, Decreased; *NL*, normal; *ZAP70*, ζ-associated protein, 70 kd.

Big dream: gene therapy





Big success: ADA

Big failure: X-SCID (T-ALL)

Vector-dependent insertion preference

Low-level transduction – augmented repopulation

Table 1

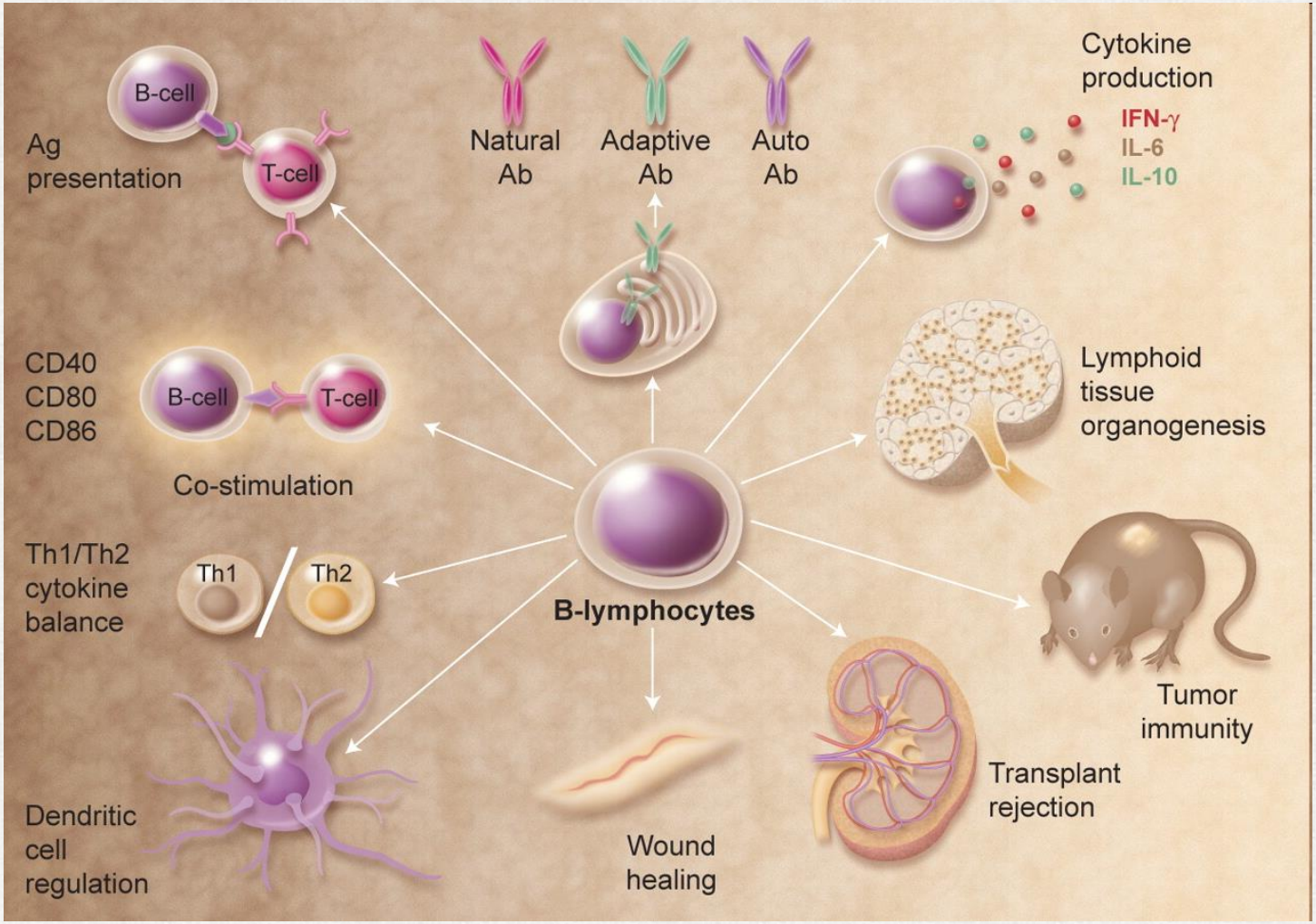
Gene therapy clinical trials recruiting patients for the treatment of SCID-X1 registered in https://clinicaltrials.gov/.

Number	Estimated number of patients	Locations	Start date	Treatment	Age
NCT01306019	30	Bethesda	2012	Vector: Lentivirus Conditioning: Busulfan Other drugs: Palifermin (to prevent side effects of busulfan)	2–40 y
NCT03315078	13	Bethesda	2012	Vector: Lentivirus Conditioning: Busulfan Other drugs: Palifermin (to prevent side effects of busulfan)	2–40 y
NCT01512888	28	San Francisco Memphis, Seattle	2016	Vector: Lentivirus Conditioning: Busulfan	<24 m
NCT03217617	10	Beijing Shenzhen	2017	Vector: Lentivirus	1 m–10 y
NCT03601286	5	London	2018	Vector: Lentivirus Conditioning: Busulfan	2 m–5 y
NCT03311503	10	Los Angeles Boston London	2018	Vector: Lentivirus Conditioning: Busulfan	<5 y
NCT04286815	10	Chongqing	2020*	Vector: Lentivirus	<18 y

*Estimated start date. m, months; y, years.

Immunodeficiency of the cellular elements of adaptive immune system II. B- or T-cell immunodeficiencies

Consequences of the impairment of B-cell functions



Primary B-cell differentiation defects – hypo/agammaglobulinaemias

XLA: X-linked agammaglobulinaemia (Btk-mutation ~ 600 variants) pre-

BcR/BcR signaling defects, with various severities – 85%

Autosomal mutations: IgM μ-chain, Igβ/Igα, VpreB/λ5, BLNK – 15%

Secondary B-cell differentiation abnormalities – dysgammaglobulinaemias

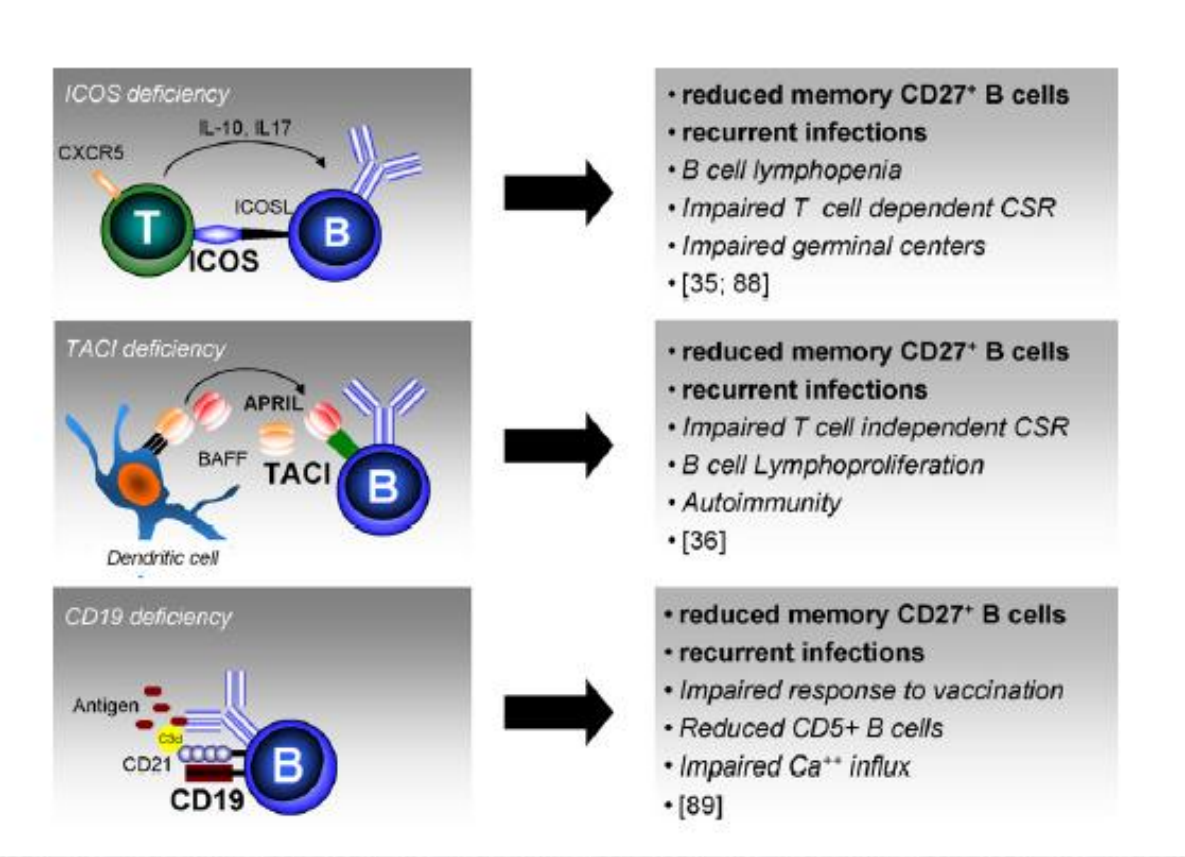
CVID

Hyper-IgM syndrome:

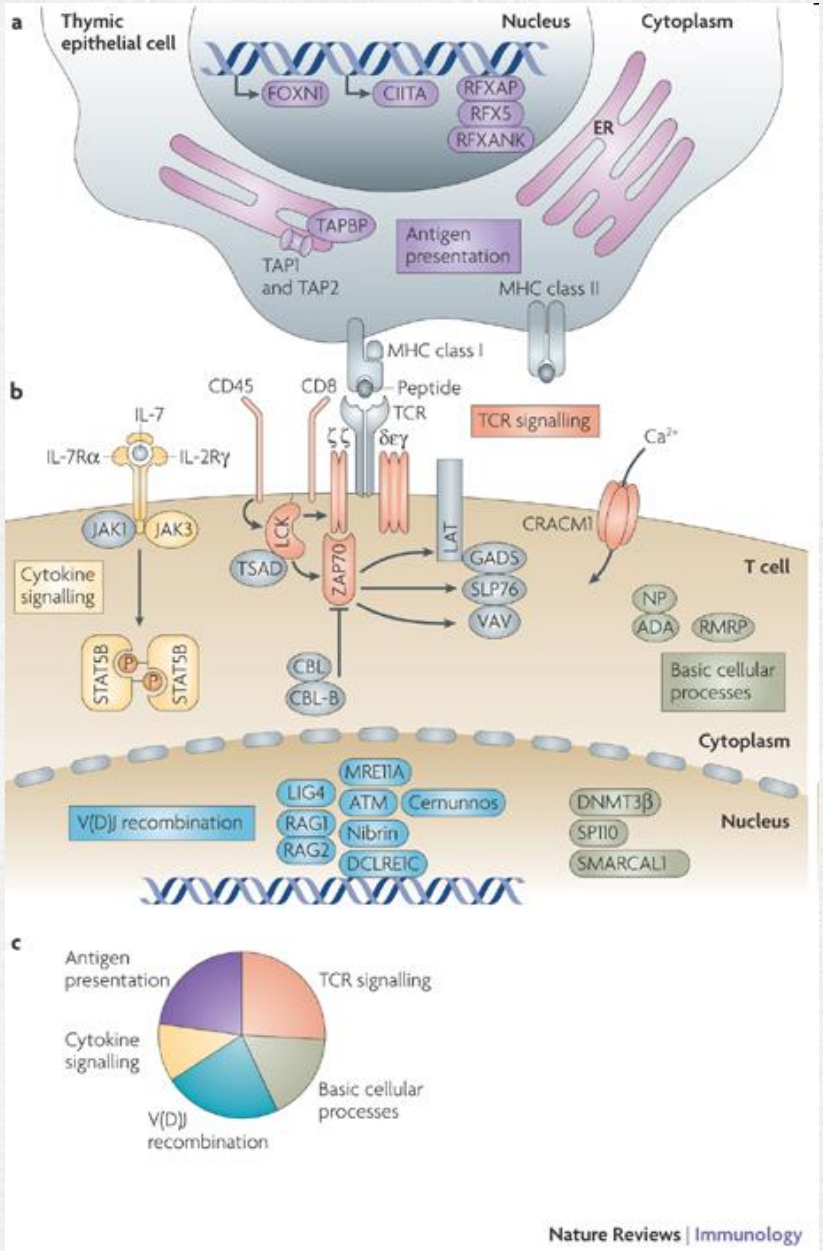
X-linked: CD40L

Autosomal: Ig-CSR def 1: AID (C→U)

Ig-CSR def 2: UNG (U-DNS-repair)



T-cell differentiation defects - causes



Diagnostic and therapeutic approaches in T/B lymphocyte-defects

- Diagnostics: lymphocyte composition/number/phenotype, Ig levels, molecular screening
- Therapy: Supplementation (IVIG)
- Bone marow transplantation, monitoring for lymphoid malignancies
- **Frequent association with autoimmune diseases and lymphoproliferation**