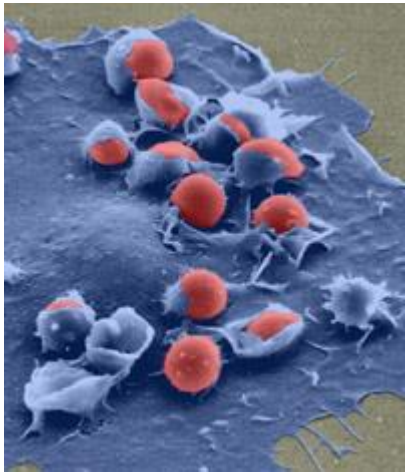
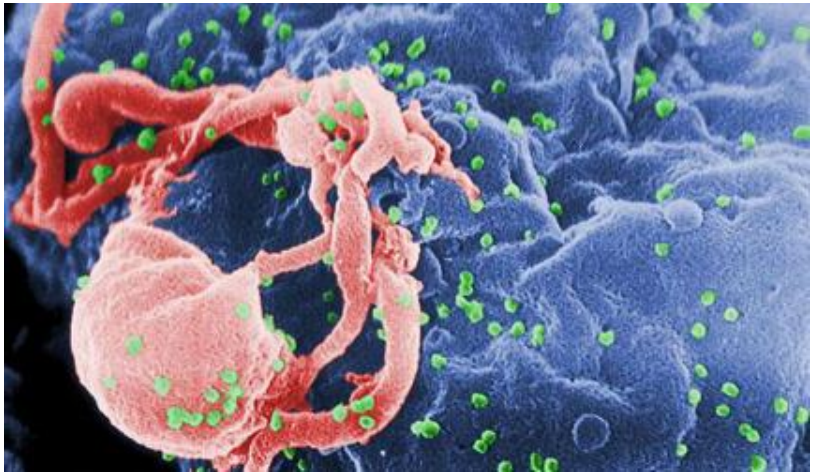
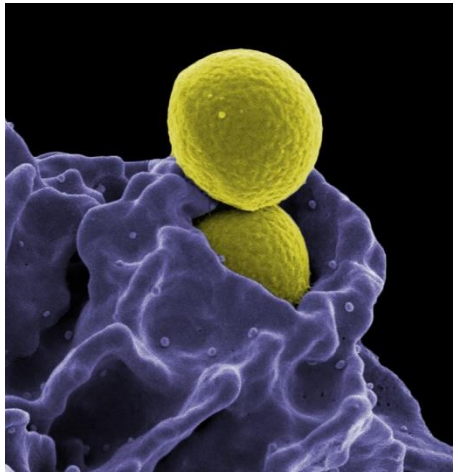
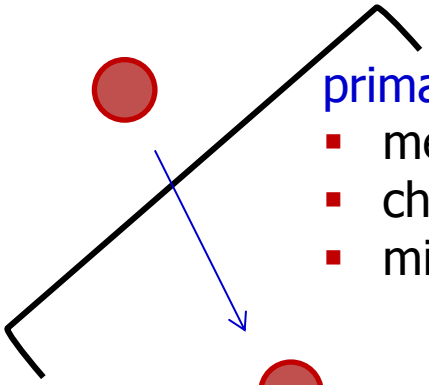
infection and immunity

Zsolt Illes
Department of Neurology
Odense University Hospital
University of Southern Denmark

antimicrobial immune responses



primary barriers

- mechanical (skin, lung, GI, eye)
- chemical (β-defensines, lysozyme, chatelicidin)
- microbial (microbiota)

innate immunity

- fast
- not always effective

cured

disease (microba)

adaptive immunity

- slower
- memory

cured

disease (prolonged immune responses)

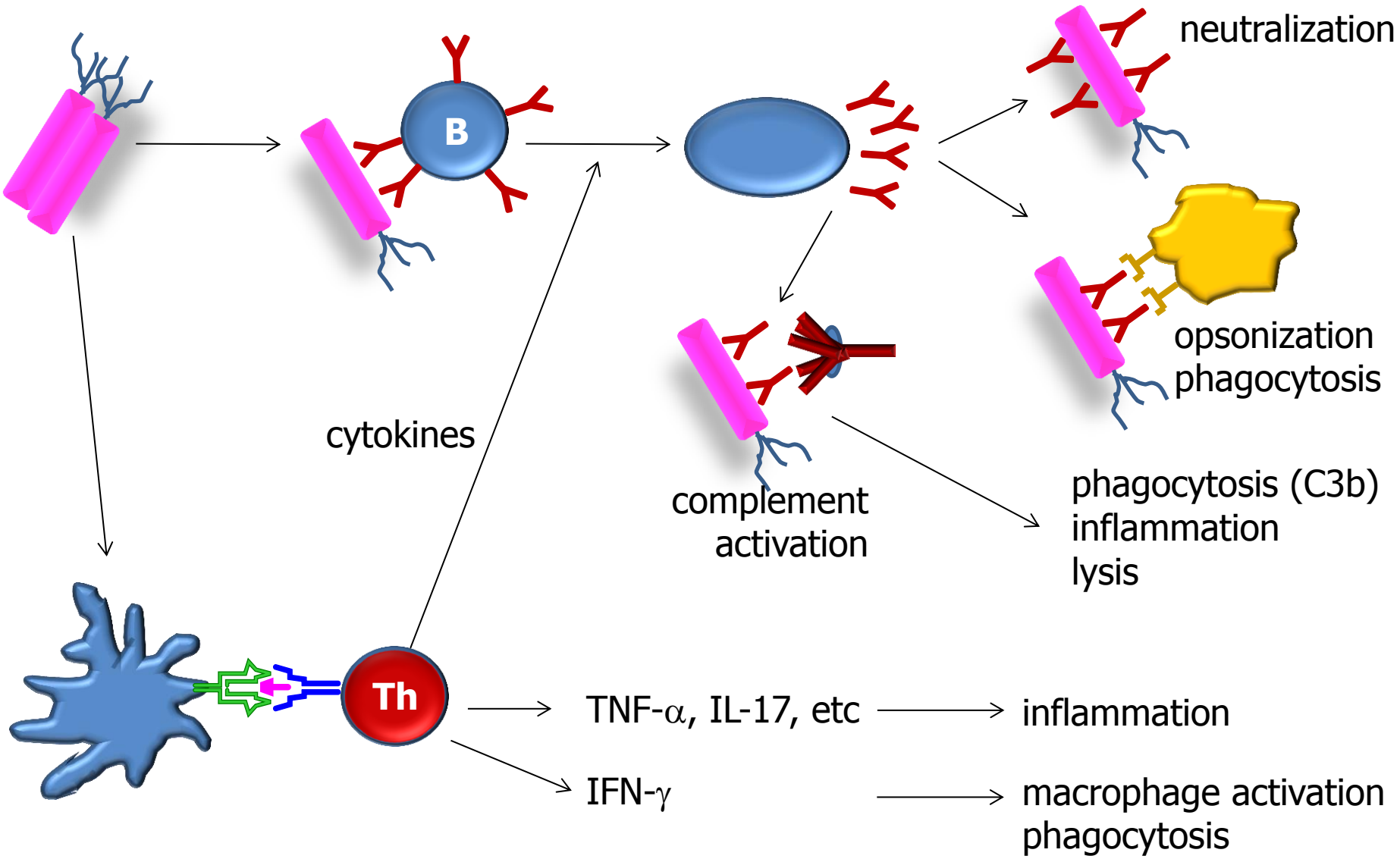
surviving strategies

latent infection

re-activation

disease

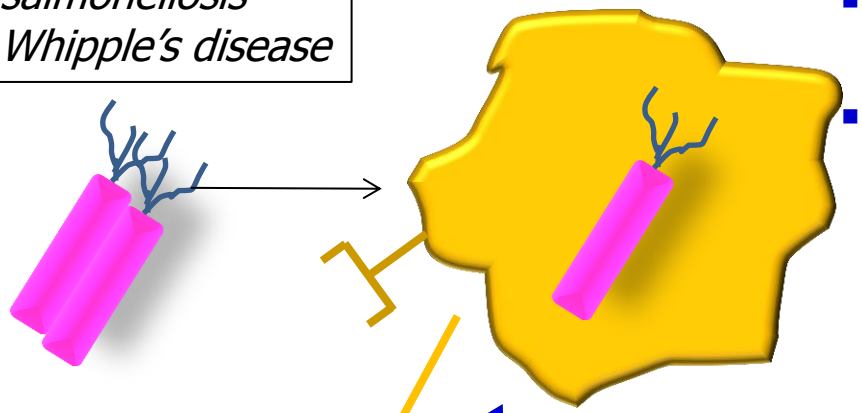
extracellular bacteria



listeriosis
tuberculosis
lepra
brucellosis
salmonellosis
Whipple's disease

intracellular bacteria

- mainly in macrophages
  - survive or/and proliferate
- antibodies can not reach them



IL-12

lysis
IFN-γ

adaptive

IFN-γ

ROS, NO

IL-12

CD4⁺ Th

MHC II

in phagosome

MHC I

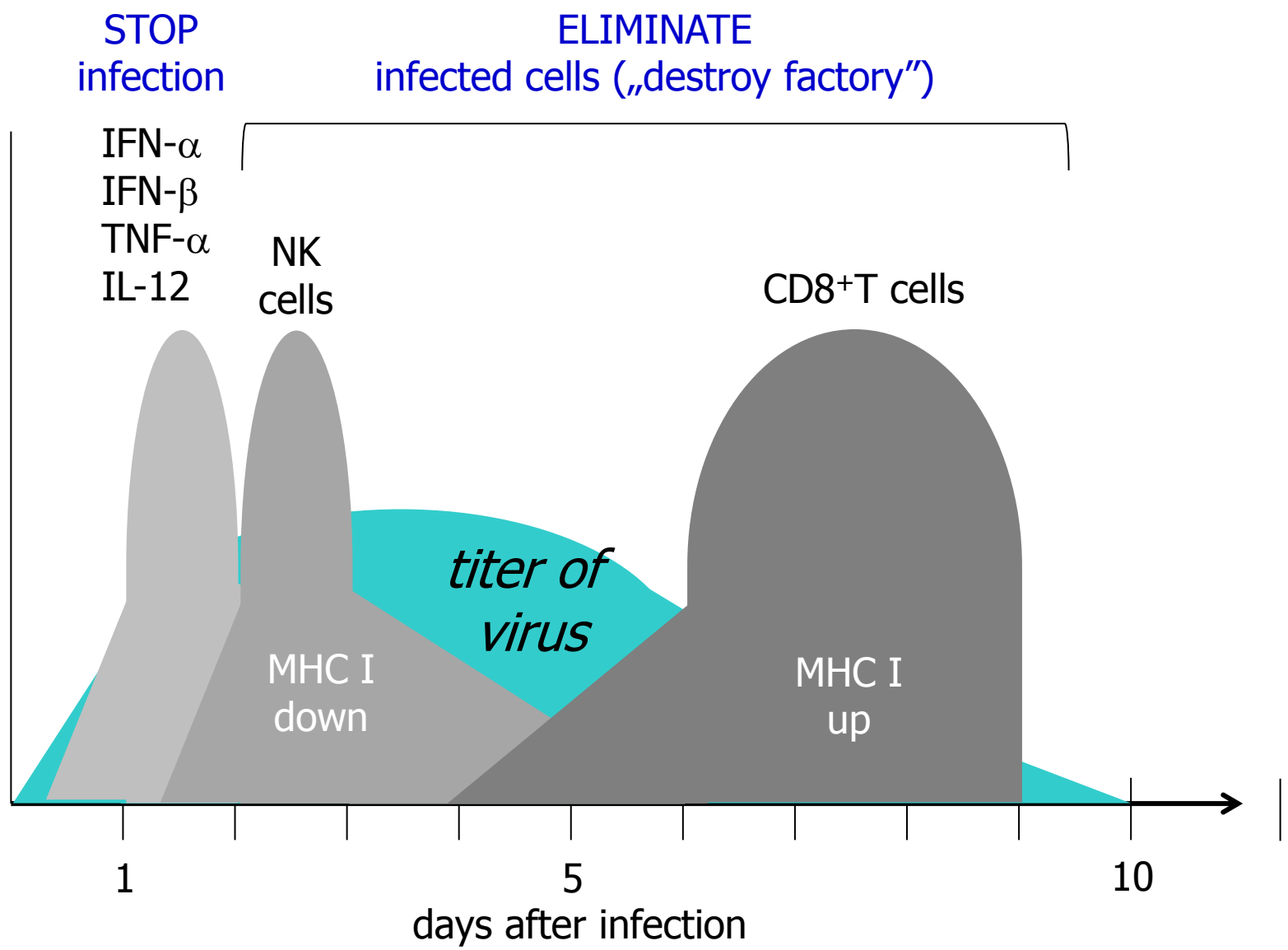
CD8⁺ Tc

in cytosol

innate

- not enough
- adaptive responses are needed

viruses


STOP
infection
ELIMINATE
infected cells („destroy factory")
IFN-α
IFN-β
TNF-α
IL-12
NK
cells
CD8+T cells
titer of
virus
MHC I
down
MHC I
up
1
5
10
days after infection

immunodeficiencies

- transient
- primary
- secondary
- acquired (HIV)

secondary immunodeficiencies

- Down syndrome
- SLE, liver cirrhosis, thymoma
- iatrogenic immunosuppression
- toxic (environmental)
- uraemia
- tumors of the immune system
- solid tumors with metastasis
- major surgery
- dysfunction or absence of spleen
- stress

case

nephrosis syndrome for 12 years
membranous glomerulonephritis

3 months ago:
- cyclophosphamide + steroid

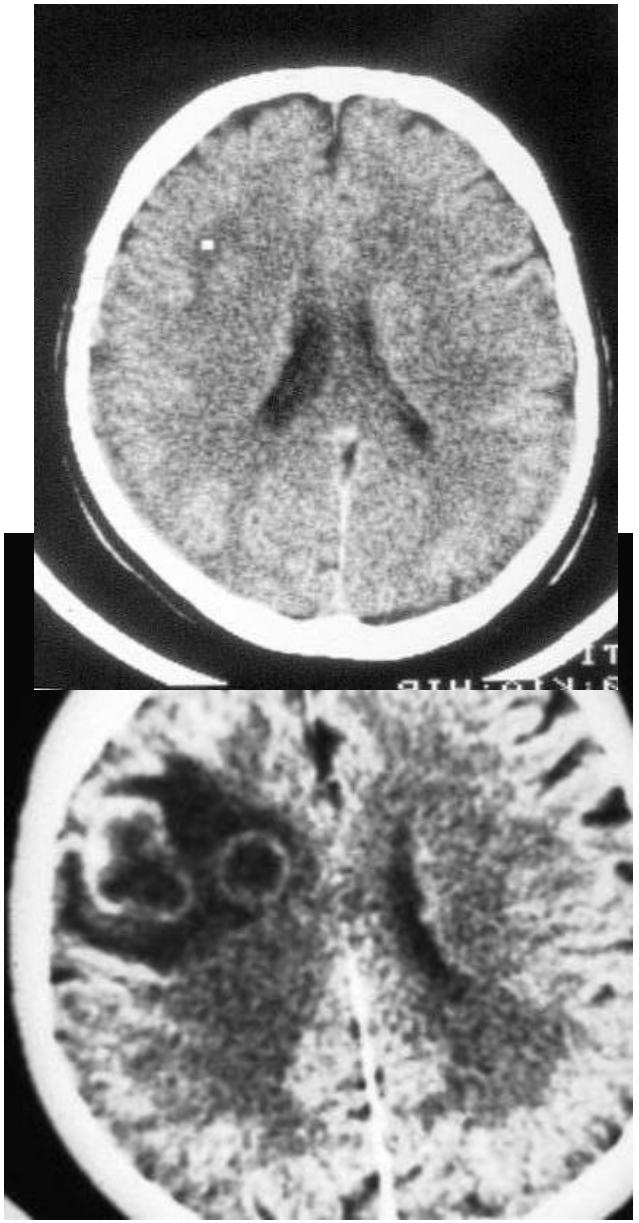
3 weeks ago:
- weakness of the right lower extremity

1 day ago:
- stupor
- no fever

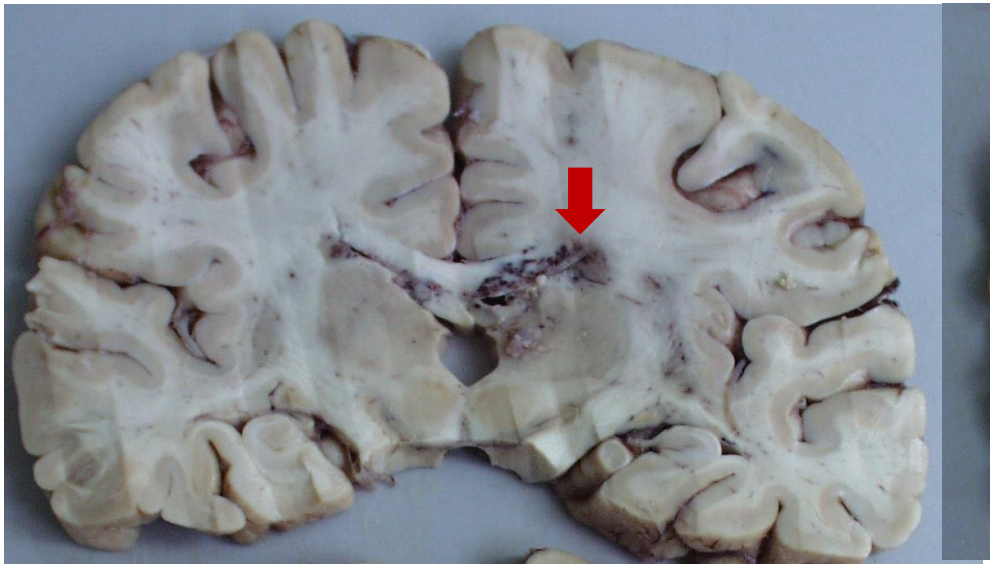
- CRP: 51 mg/L
- ESR: 130 mm/h

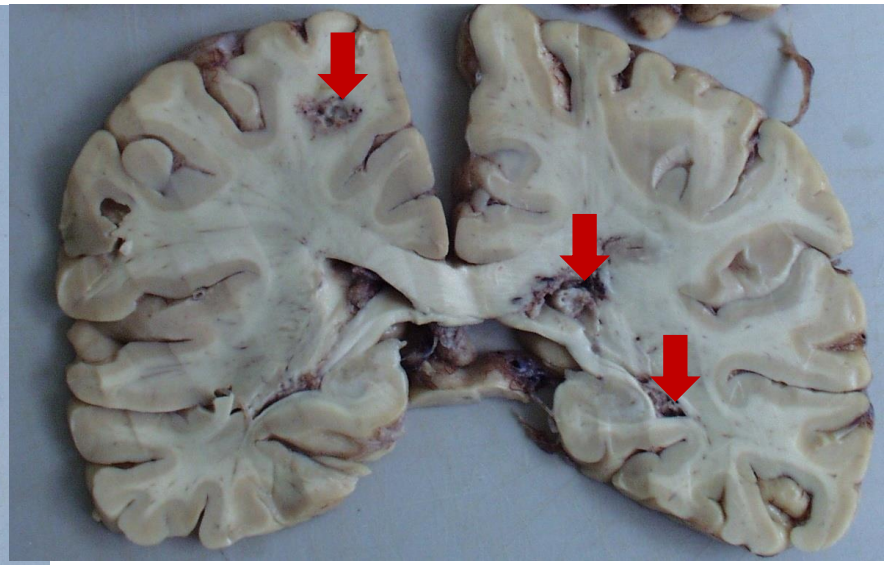
- Hgb: 88.6 g/L
- Htc: 24.9 %

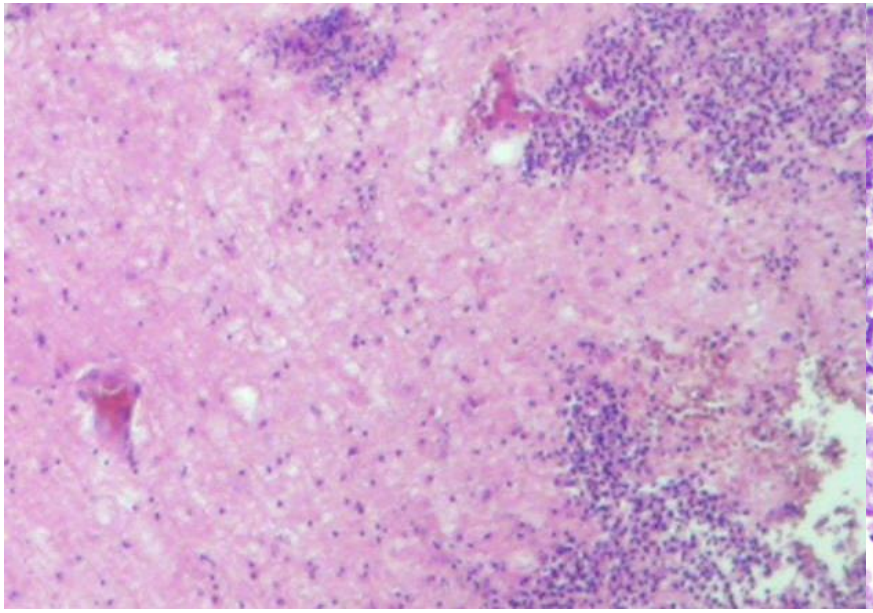
- WBC: 13.9 G/L
- CN: 25.3 mmol/L
- LDH: 667 U/L

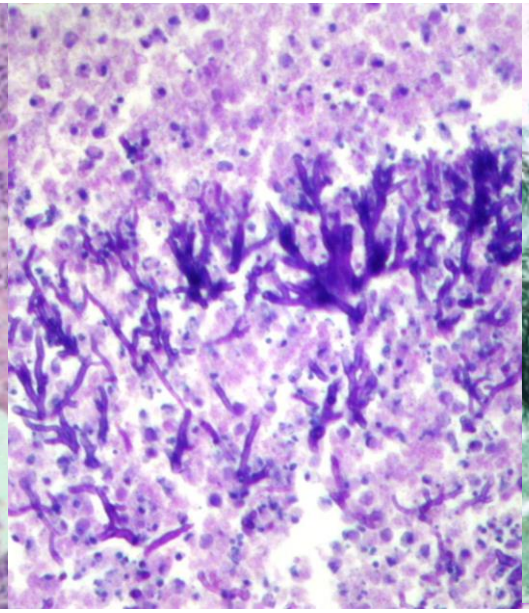


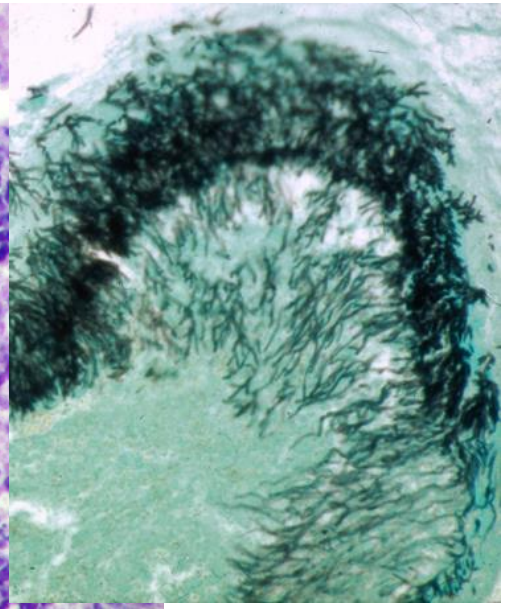
case invasive CNS aspergillosis











primary immune deficiencies

1:250-500

infections	normal	pathological
frequency	<8-12/year	>8-12/year
severity	mild	severe
course	acute	chronic, relapses
residual signs	no	yes, chronic
relapse – same microbe	rare	yes
opportunistic infection	no	yes

10 red flags

1 ≥8 otitis within a year	6 recurrent abscesses (skin, organs)
2 ≥2 severe sinusitis within a year	7 persistent soor oris or other skin mucosis beyond 1 year of age
3 ≥2 antibiotic course for months without major effect	8 infections respond only to intravenous antibiotics
4 ≥2 pneumonia within a year	9 ≥2 progressing infections
5 infant does not grow, does not gain weight	10 positive family history

common variable immunodeficiency syndrome

34-year old female

- decreased IgG and IgA: IVIG monthly

$CD19^+$ B cells:
1,9% (11.8±4.6)
$CD4^+$ Th cells:
32,3% (45.2±8.7)

common variable immunodeficiency syndrome (CVID)

late-onset hypogammaglobulinemia
Giedion-Scheidigger deficiency
dysgammaglobulinemia

- heterogeneous group
- 1/25-66.000
- deficient Ab synthesis: IgA and IgG
- B cell number can be decreased
- deficient T cell function 50%

- mean age 25 years
- mortality 24 %

- recurrent pneumonia, bronchiectasy

role of immune system?

- malignancy 11-13 %
  - lymphoma 18 %
- autoimmune disease 22 %
  - granulomatous diseases
  - can mimic sarcoidosis

common variable immunodeficiency syndrome

34-year old female

- decreased IgG and IgA: IVIG monthly

$CD19^+$ B cells:
1,9% (11.8±4.6)
$CD4^+$ Th cells:
32,3% (45.2±8.7)

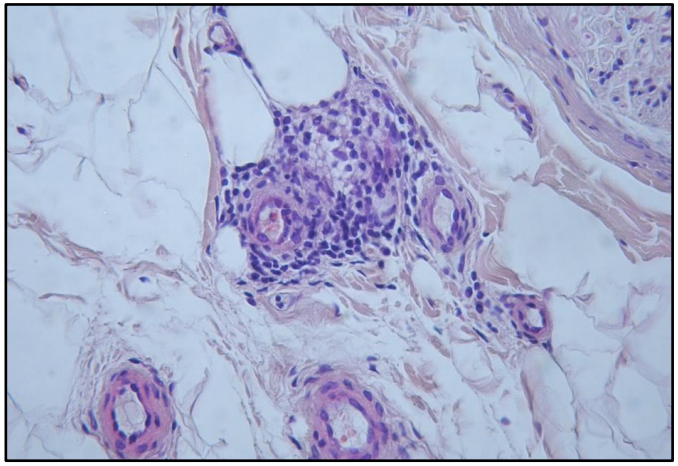
- constant subfebrility, intermittent fever
- arthralgia
- ESR and hsCRP elevated, procalcitonine normal
- antibiotics are ineffective, steroid stops fever
- leukopenia, anaemia
- proteinuria
- abnormal liver and thyroid function

CVID + PNS vasculitis
(ANCA negative)

- asymmetric paresis
- distal muscle atrophy
- absent deep reflexes
- almost normal sensation

EMG
- axonal
- motor
- asymmmetric

sural nerve



case CVID plus vasculitis

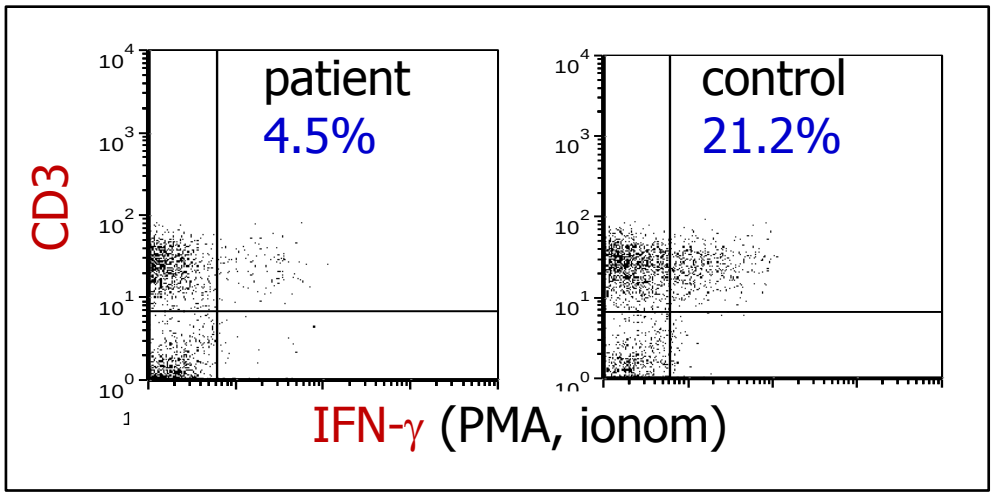
azathioprine
3 months later:
- acute aphasia, convulsion
- loss of consciousness
- temporal MRI activity
- ????

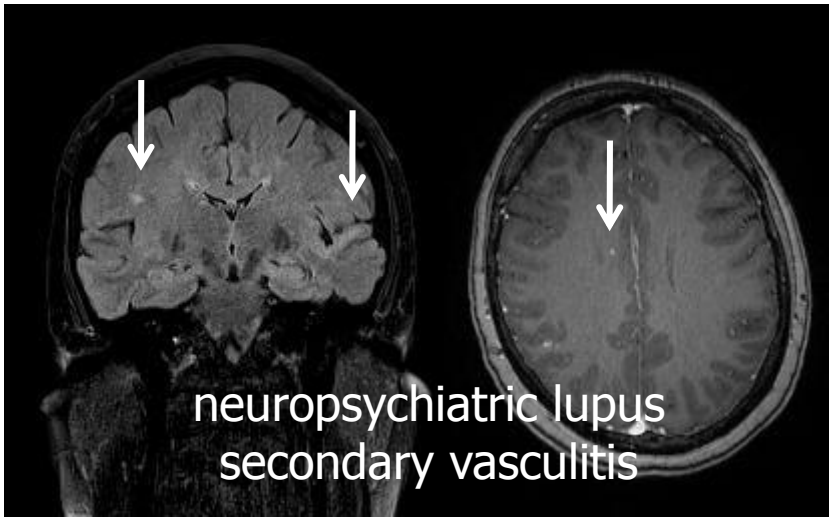
HSE

42-year old female

- right loss of vision, retinal hemorrhage
- 3 months later generalized convulsion
- aphasia, right hemiparesis: recovery in 4 days after steroid
- CSF: 200/3 mononucl, 0.9 g/l, OCB
- brain MRI: small enhancing lesions

- CRP: 75 mg/l, mild anemia
- ANA, dsDNA increased
- chest CT: mild pulmonary fibrosis

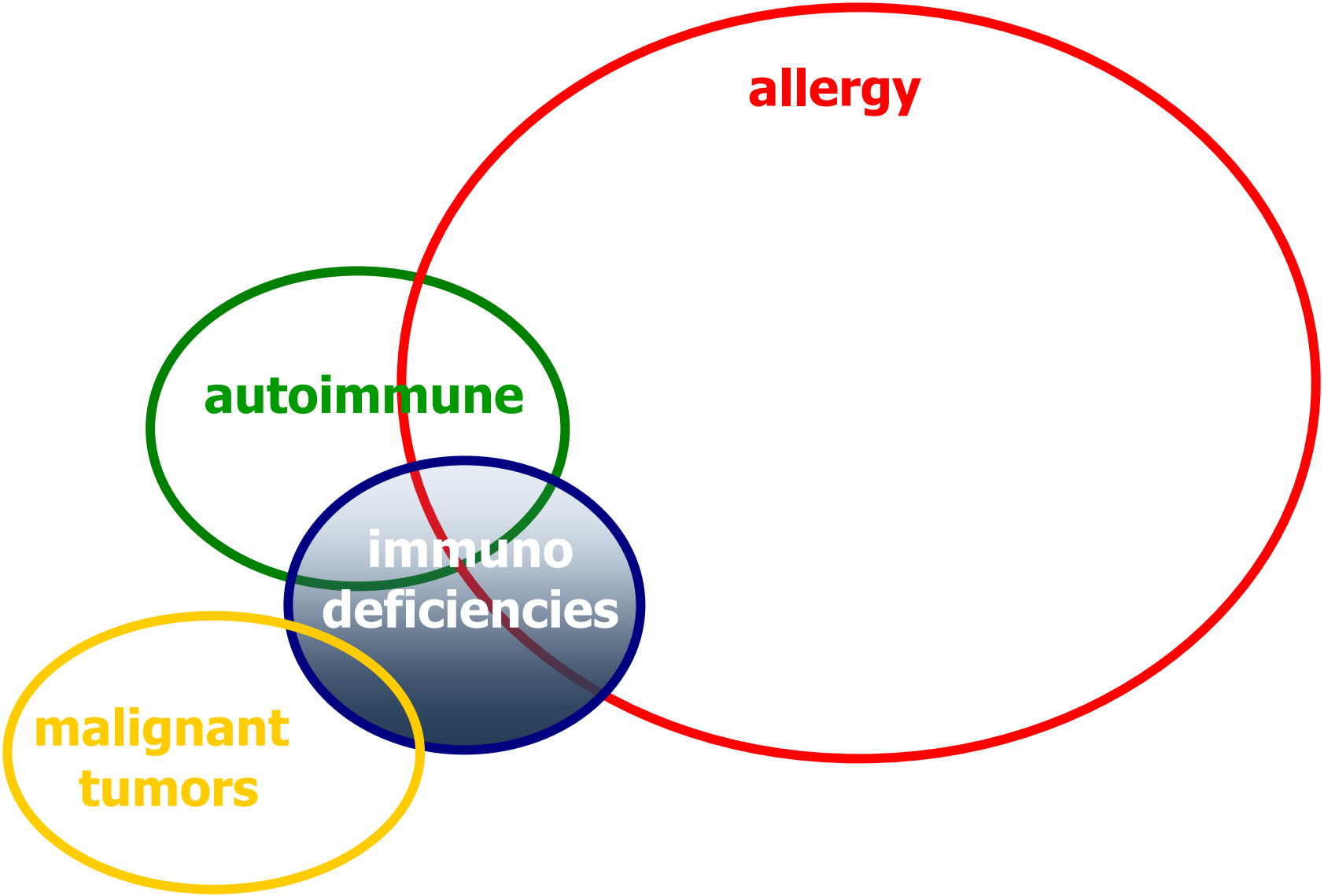




normal IgM
low IgG
low IgA

is it expecteed?
????

immunological diseases in children



immunodeficiencies: consequences

- infections
- lymphoproliferative diseases
  - mainly in T- and NK cell deficiencies
- allergy
- autoimmune diseases
  - arthritis, SLE, inflammatory bowel diseases
  - T-, B- and complement deficiencies

WHO classification

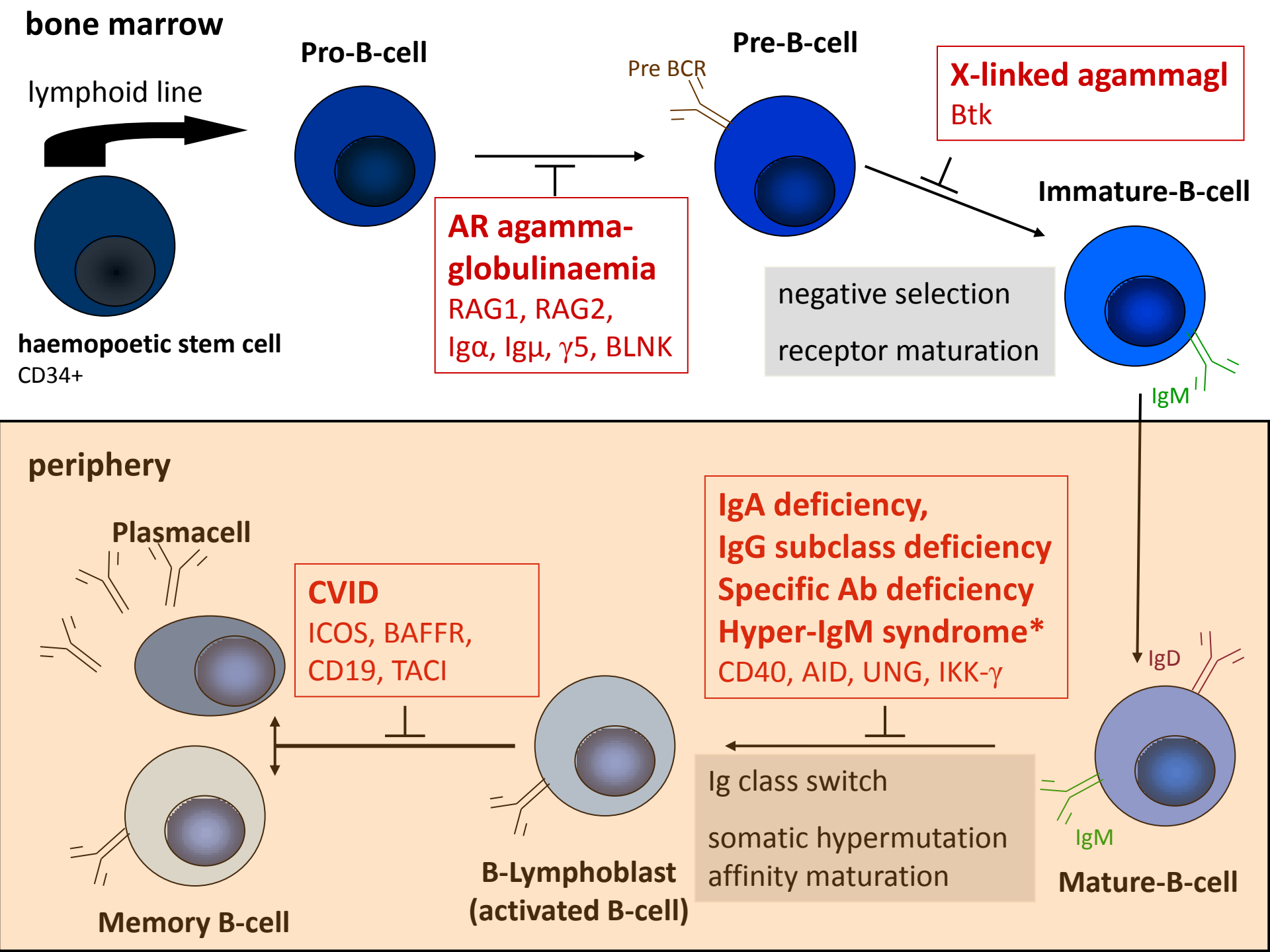
about 200 primary immunodeficiency syndrome

- B cell defect (antibodies) 65%
- T cell/combined immunodeficiency 20%
- phagocyte defects 9%
- complement deficiency 4%
- other 2%

- most common: IgA deficiency 1/400-700
  (IVIG!)

antibody deficiencies (B cells)

- manifests at the age of 4-6 months or later (no maternal Igs)
- infections:
  - with polysaccharide capsules
  - S. pneumoniae, H. infleunzae, Mycoplasma catarrhalis, S. pyogenes, P aeruginosa
  - otitis media, sinusitis, bronchitis, pneumonia, deeep pustulous abscess
  -
- hypoplasy of lymphoid tissues:
  - autoimmune diseases
  - diffuse bronchiectasia


bone marrow
lymphoid line
haemopoetic stem cell
CD34+
Pro-B-cell
AR agamma-globulinaemia
RAG1, RAG2,
Igα, Igμ, γ5, BLNK
Pre-B-cell
Pre BCR
X-linked agammagl
Btk
Immature-B-cell
negative selection
receptor maturation
IgM
periphery
Plasmacell
CVID
ICOS, BAFFR,
CD19, TACI
IgA deficiency,
IgG subclass deficiency
Specific Ab deficiency
Hyper-IgM syndrome*
CD40, AID, UNG, IKK-γ
IgD
IgM
Ig class switch
somatic hypermutation
affinity maturation
Memory B-cell
B-Lymphoblast
(activated B-cell)
Mature-B-cell

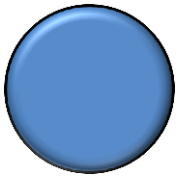
severe combined immunodeficiencies (SCID)

- no gain of weight
- unusual or unusually severe infections
- uncontrollable diarrhoe
- eczema, soor
- abnormal bones
- hepatosplenomegalia
- malignant tumors

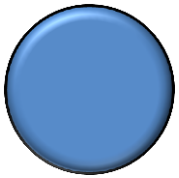
check:

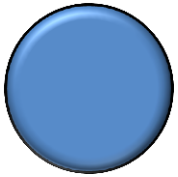
- immunoglobulins
- T cell number and function
- NK cell number and function

NK-cell

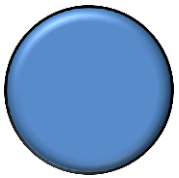


CD8^{+} T-cell

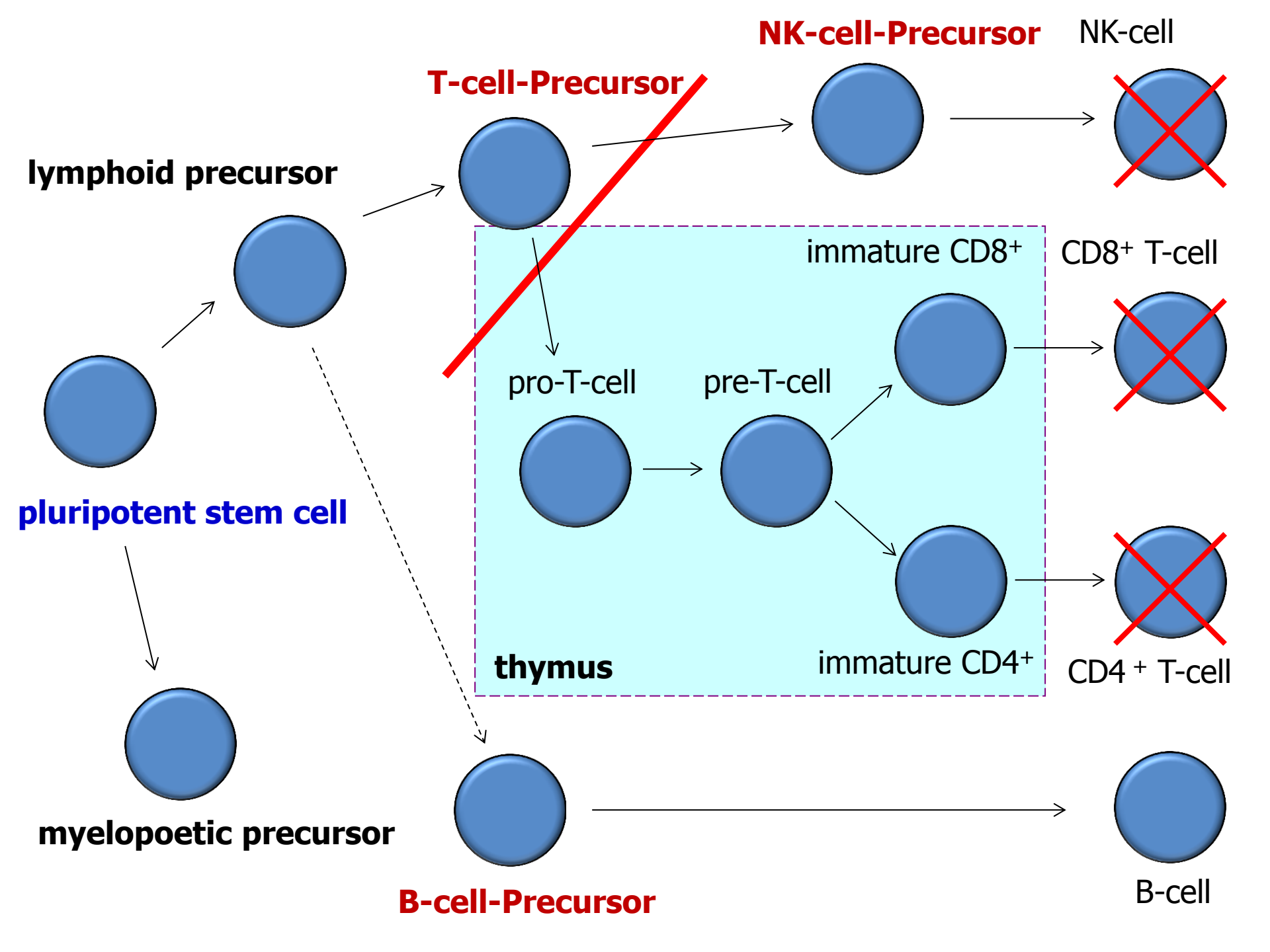


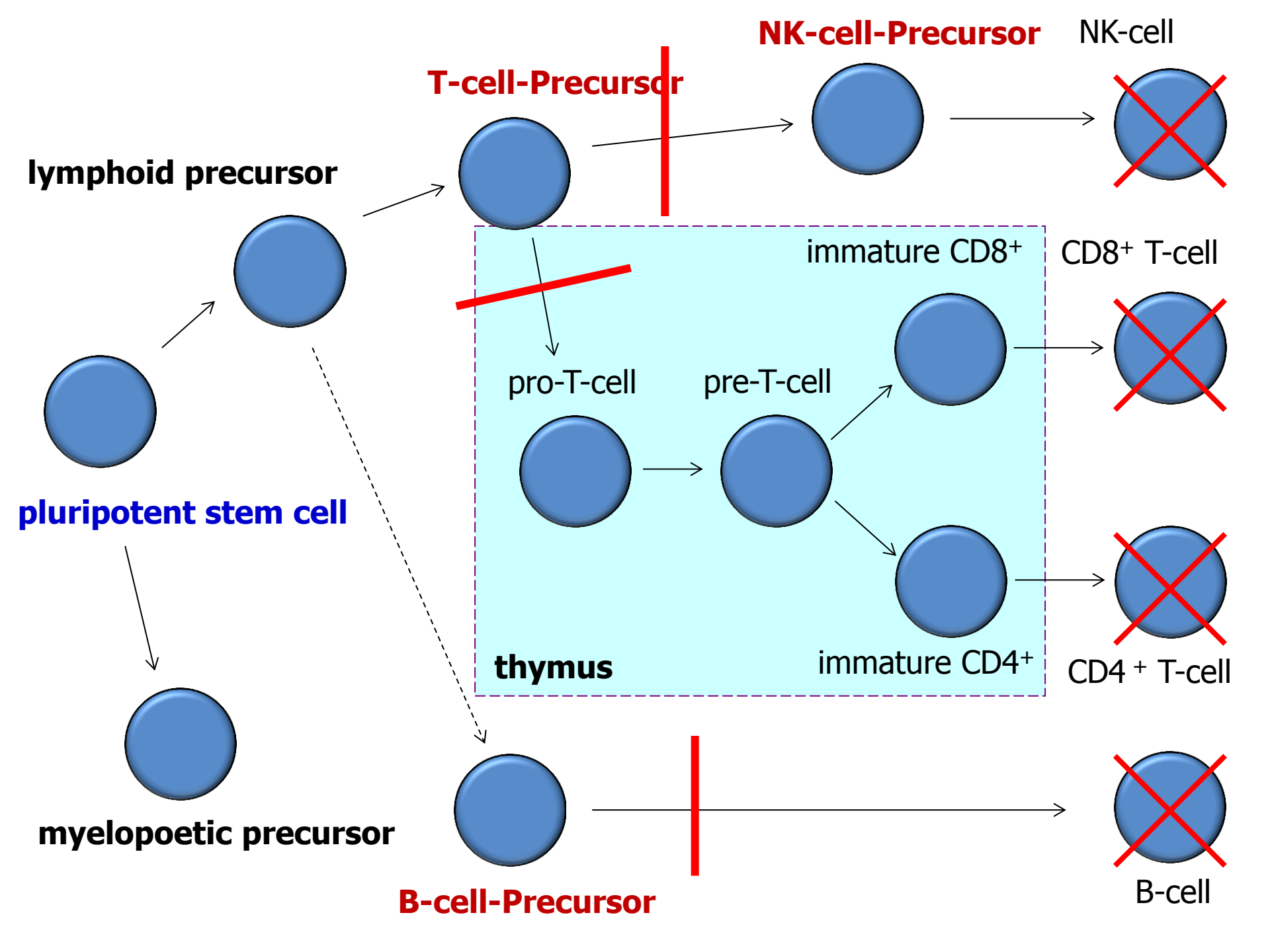


CD4 $^{+}$ T-cell



B-cell


NK-cell-Precursor
NK-cell
T-cell-Precursor
lymphoid precursor
immature CD8+
CD8+ T-cell
pro-T-cell
pre-T-cell
pluripotent stem cell
thymus
immature CD4+
CD4 + T-cell
myelopoetic precursor
B-cell-Precursor
B-cell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NK-cell
T-cell-Precursor
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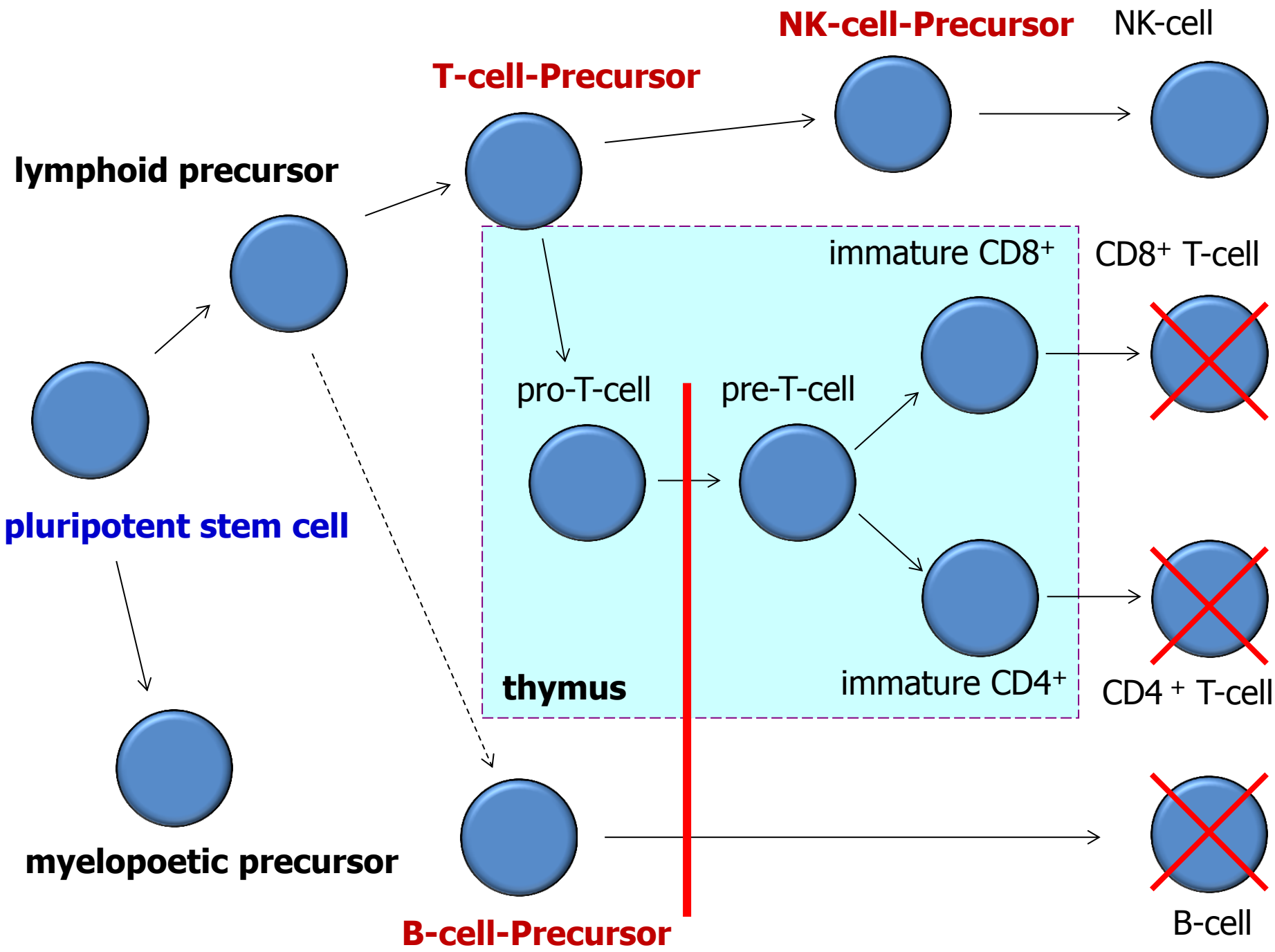
CD8+ T-cell
pro-T-cell
pre-T-cell
pluripotent stem cell
thymus
immature CD4+
CD4 + T-cell
myelopoetic precursor
B-cell-Precursor
B-cell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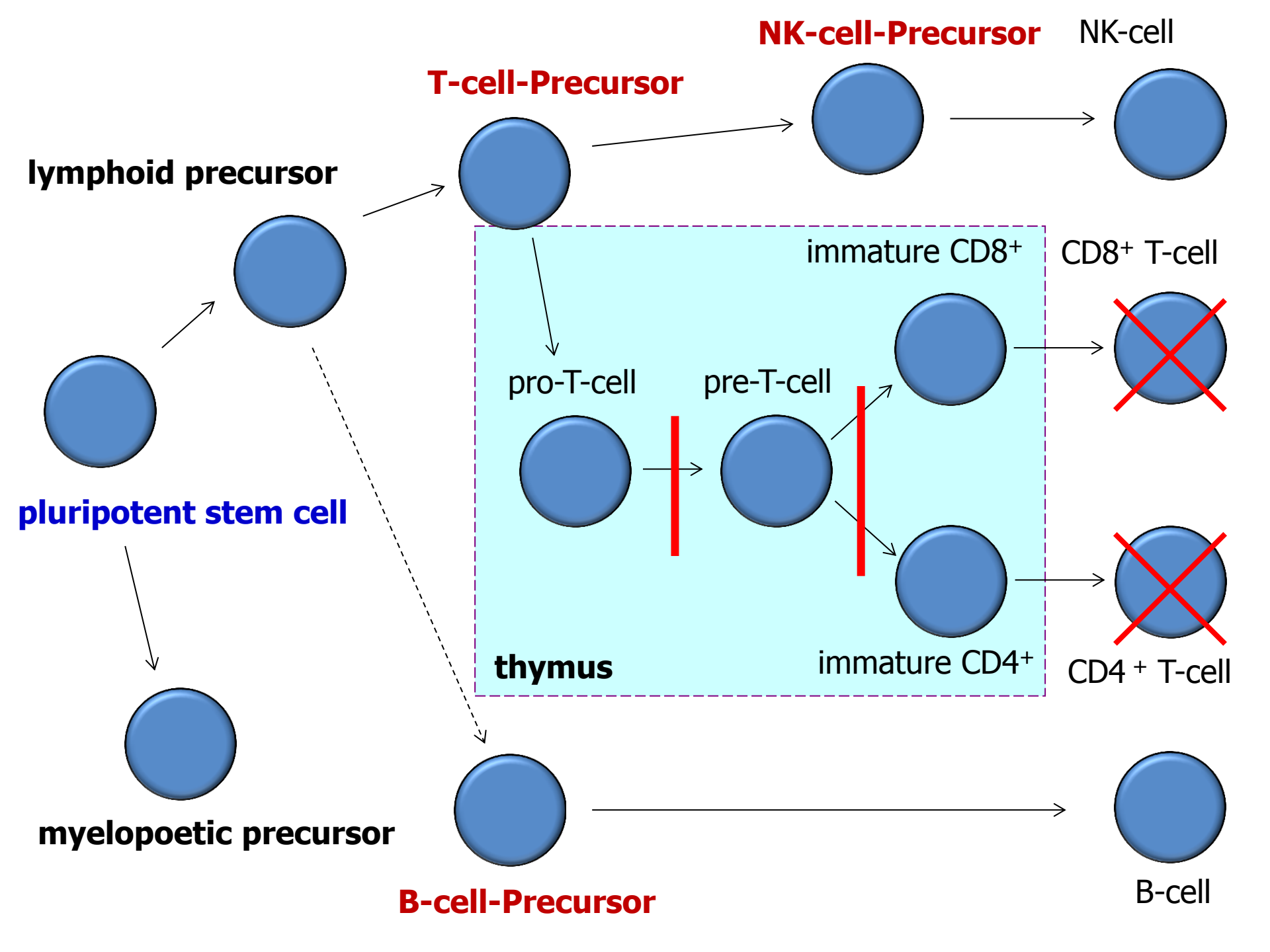
B-cell-Precursor
B-cell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pre-T-cell
pluripotent stem cell
thymus
immature CD4+
CD4 + T-cell
myelopoetic precursor
B-cell-Precursor
B-cell

„secondary" NMDA receptor encephalitis

69-year old male

- herpes simplex encephalitis: fever, aphasia

5 months later: epilepsy, aphasia, cognitive decline, desorientation

CSF

- OCB
- elevated IgG index

?

anti-NMDAR IgG antibodies

- CSF strongly positive
- serum weakly positive

PLEX 5x
methylprednisolone

- rapid improvement

another case:
NMDAR encephalitis after brain trauma

secondary autoimmunity: herpes simplex encephalitis

44 patients with HSE

- 30%: NMDAR antibodies in sera *or* CSF
- 14%: only in CSF
- Ig downregulate NMDA receptors in culture

children: relapse in 25%

9 children, 3 relapsing with chorea
Abs against NMDAR, D2R or both

response to acyclovir: viral reactivation

no response to acyclovir, no virus

- sometimes new symptoms (choreoathetosis)

HSV triggers brain autoimmunity:

- NMDAR antibodies after HSV, before relapse
- such relapses respond to immunotherapy
- antibodies against other uncharacterized neuronal cell surface antigens

Ann Neurol, 2012, 72:902-911; Mov Disord, 2014, 29:117

„if you hear hoofbeats think of horses not zebras”
…use your common sense…

Sherlock Holmes and Dr. Watson are hiking. They set up the tent, and go to sleep. Holmes wakes his friend up in a few hours:
„Watson, please, look up at the sky and tell me what you see!”
„I see millions of stars.”
„And what does it mean?”
Watson is thinking, then replies:
„From astronomical point it means that millions of galaxis and billions of stars are existing. From astrological point it meand that the Saturn is in the Lion. As for time, it is 4 am. From teological point it means that the Lord is almighty, and we are small and insignificant. From meteorological point we can hope a nice weather tomorrow. And what does it tell *you*?”

„Watson, you idiot. Somebody stole our tent.”

„differential diagnostic tent effect”

THANK YOU

Fyn - Egeskov Castle