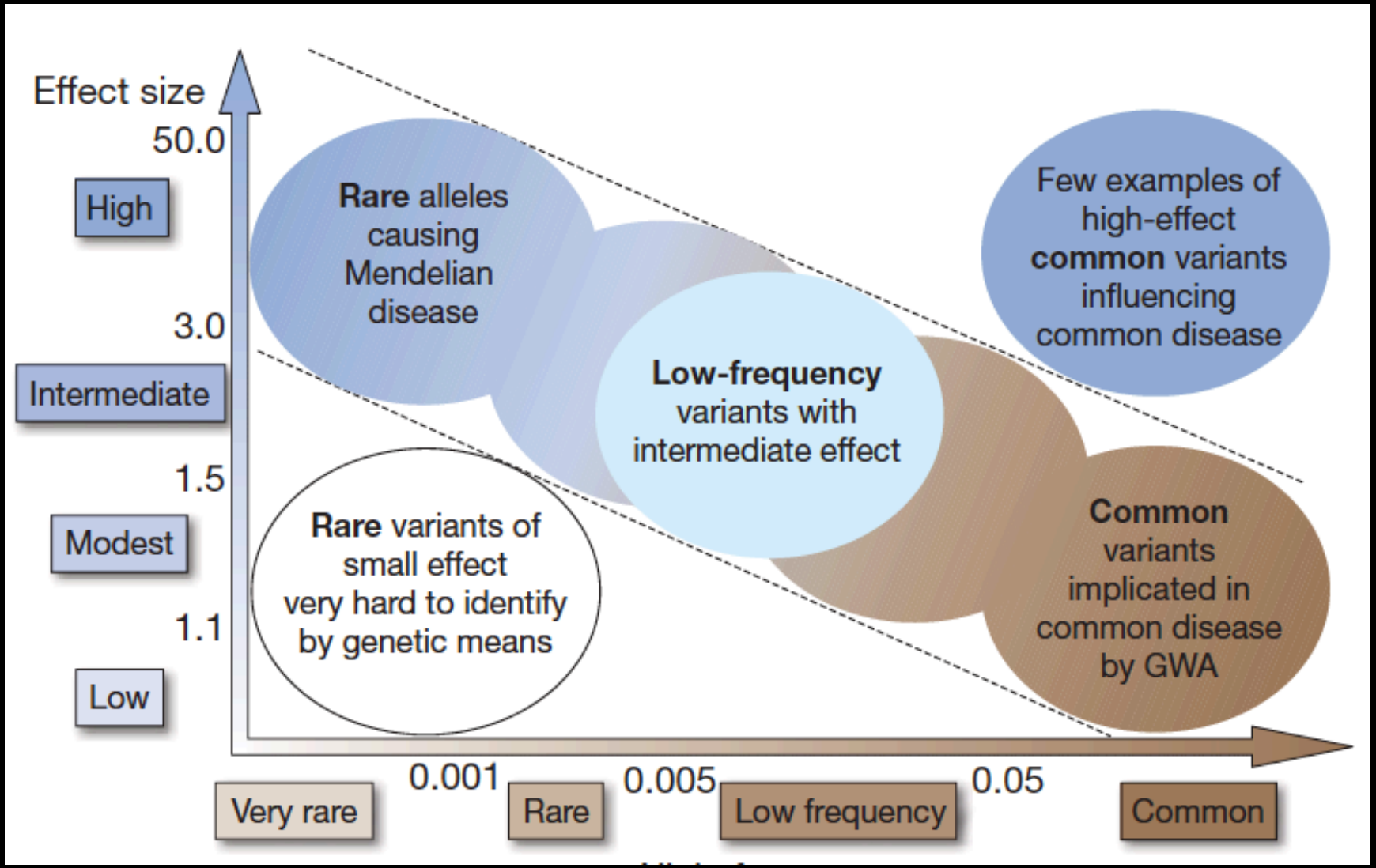
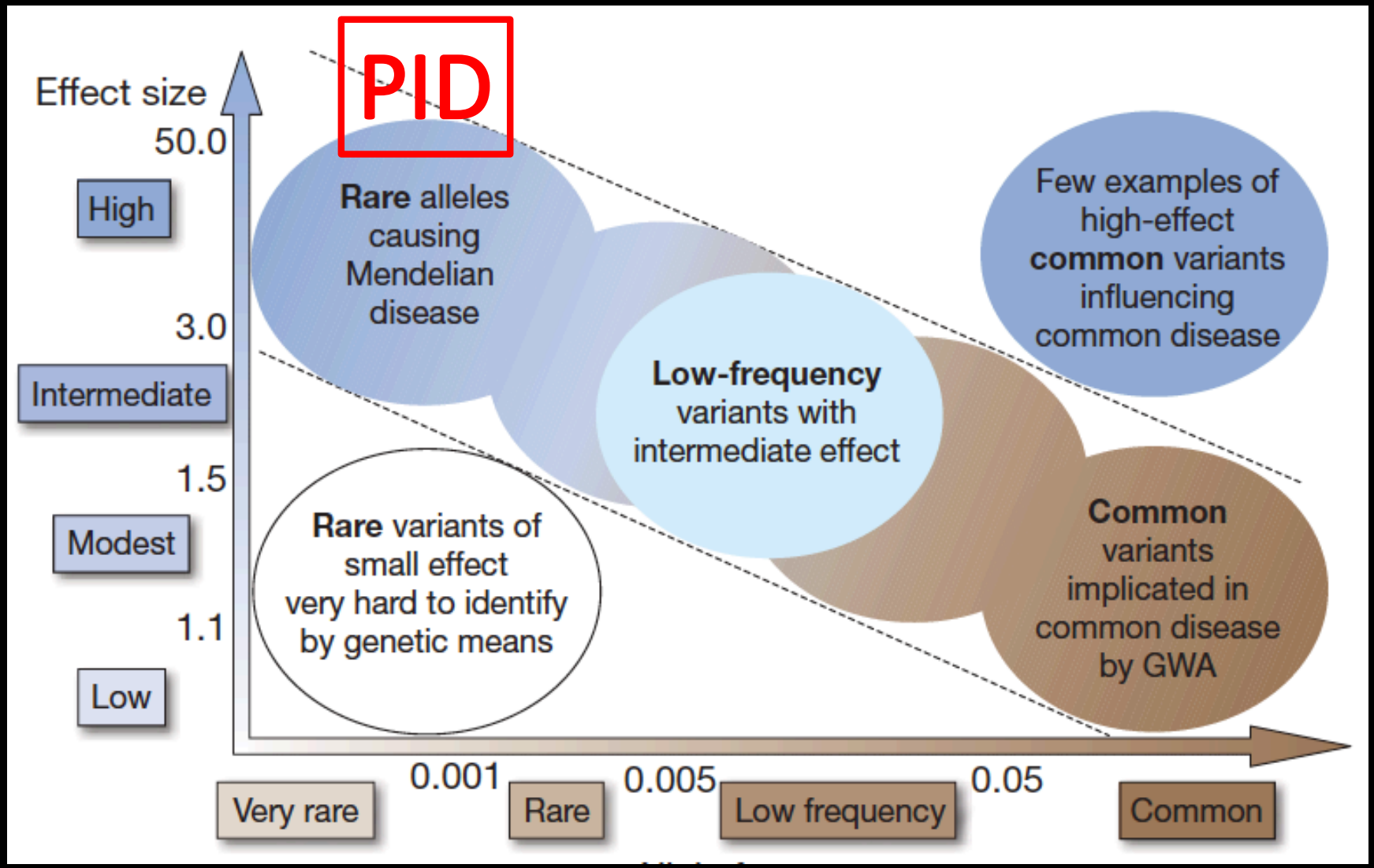
Primary Immunodeficiency Disorders

PERMANENT EDUCATION COURSE IN HUMAN GENETICS
Uliege

Stephanie Humblet-Baron, KU Leuven



Manolio TA et al., Nature, 2009



Manolio TA et al., Nature, 2009

Primary Immunodeficiency disorders (PID)/ Inborn errors of immunity (IEI)

- Rare Inherited Immunodeficiency
- Usually single mutation
- Unique immune phenotype
- Mild to severe immunodeficient patients
- Easy to explore (Blood test)
- First gene therapy success

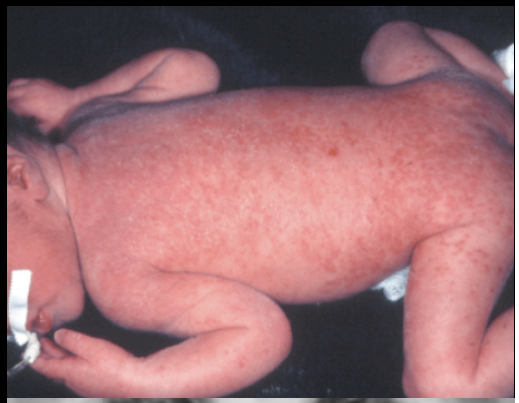
Mutations/inheritance

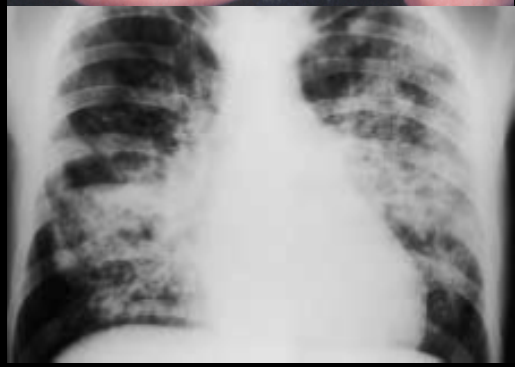
- Classical: AD, AR, X-L, de novo
- Particular:
  - Somatic mutation
  - Haploinsufficiency (GATA2)
  - Hypomorphic mutation (RAG, Artemis)

Exponential gene discovery in PID since WES application

PID previous classification : clinical presentation.

1. T cell defect. Acquired immunity/ Cell-mediated.





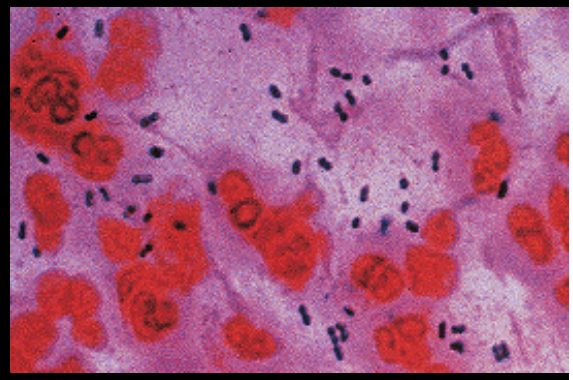
- Opportunistic infections: Pneumocystis jirovecii, candida systemic infection, HSV,VZV, EBV, CMV adenovirus, RSV infections.
- Failure to thrive
- Chronic diarrhea
- Small thymus, lymph node hypoplasia
- Graft-versus-host disease in neonates or after blood transfusion

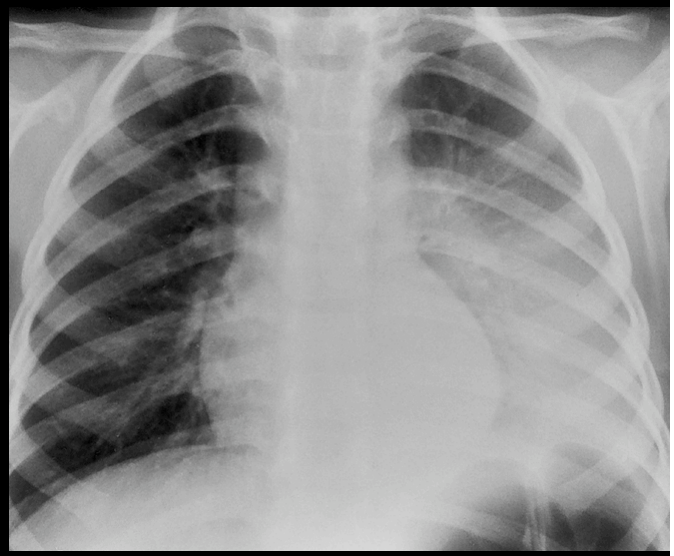
PID previous classification : clinical presentation.

2. B cell defect. Acquired immunity/ Antibody-mediated.

- Encapsulated Bacterial Infections:
  - -Meningitis, sepsis, pneumonia, sinusitis. (pneumococcus, meningococcus, haemophilius influenzae, staphylococcus,…)
- Viral Infections:
  - - Enterovirus
  - -Vaccine related infection (polio)

- Symptomatic after 4-6 first months of life.
- Tonsils and lymph node hypoplasia





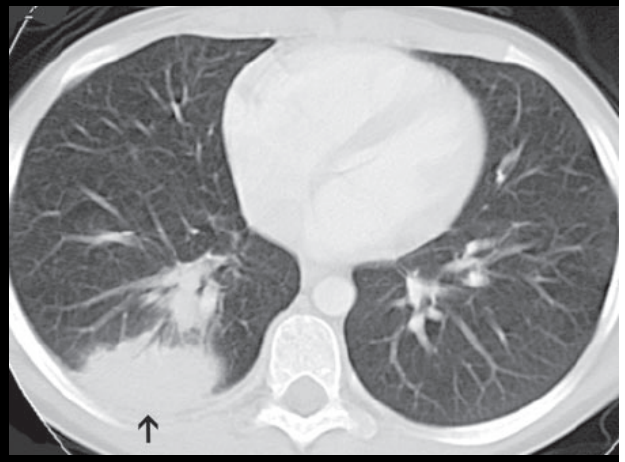
PID previous classification : clinical presentation.

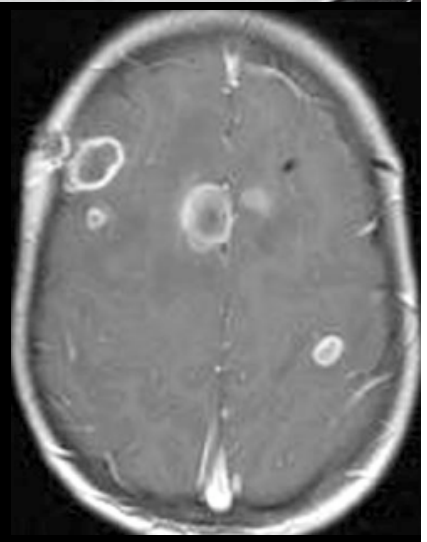
3. Myeloid defect.

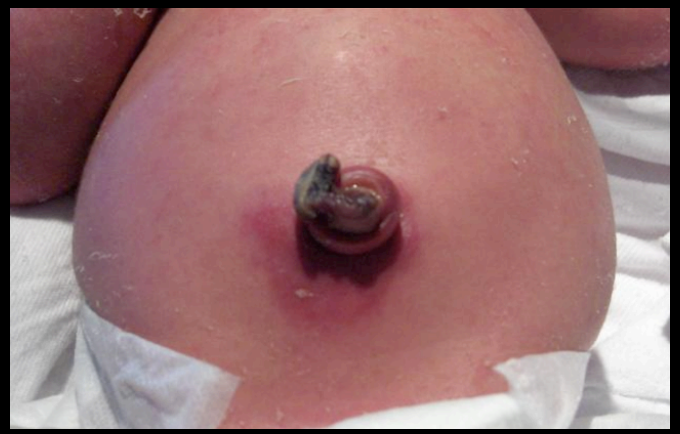
Innate immunity

-Bacterial/Fungal Infections- Abscess:

- Skin infection, omphalitis
- Mucosal infections
- Pneumonia (Aspergillus, Pseudomonas)
- Hepatic abscess (Staphylococcus)
- Granuloma.







New Classification: Molecular diagnosis

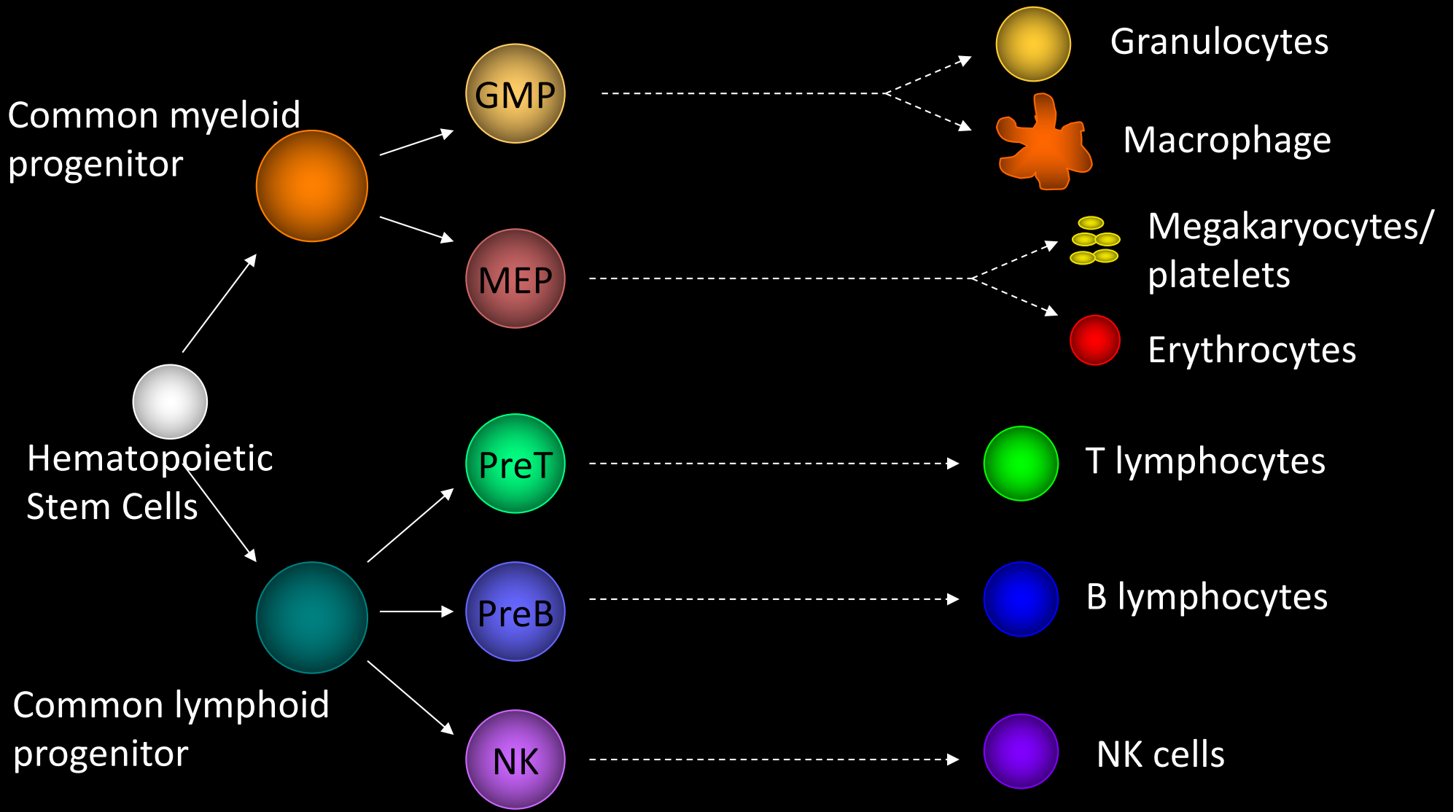
More than 430 clinical primary immunodeficiency diseases have been described.

Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee

Stuart G. Tangye et al.

J Clin Immunol.. 2020 Jan;40(1):66-81. doi: 10.1007/s10875-020-00758-x. Epub 2020 Feb 11.

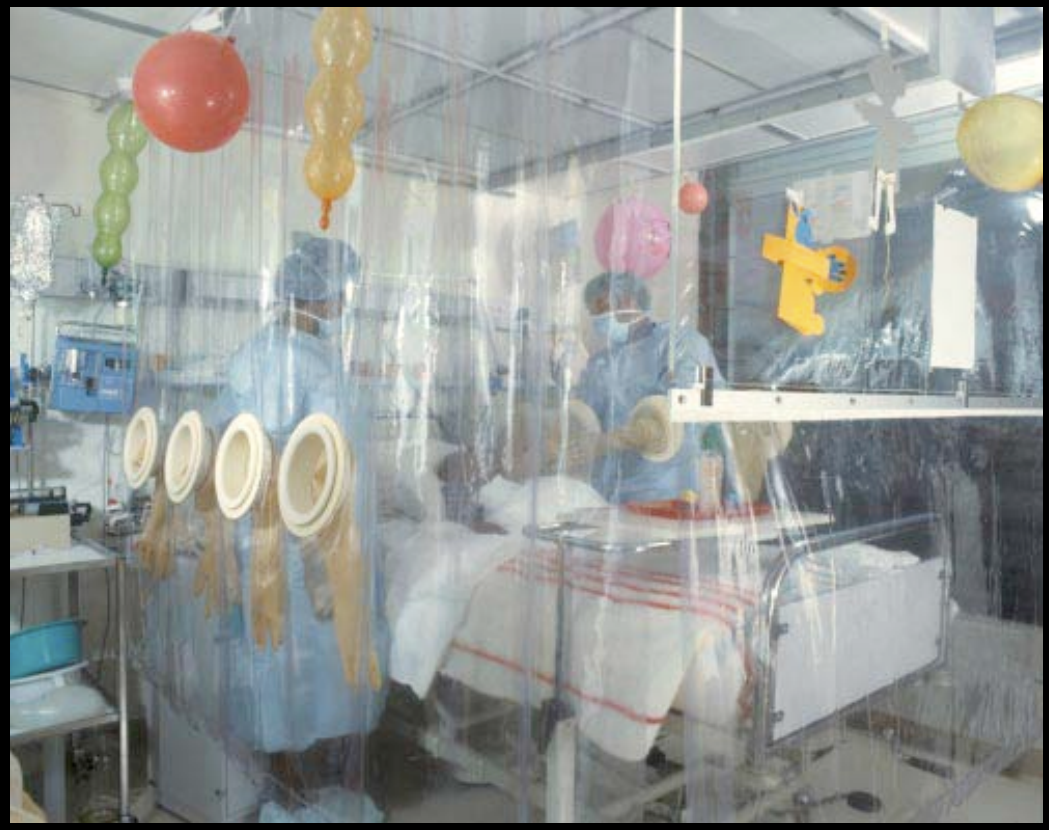
Brief immune system development overview



T cells

Developmental block

SCID
Severe Combined ImmunoDeficiency



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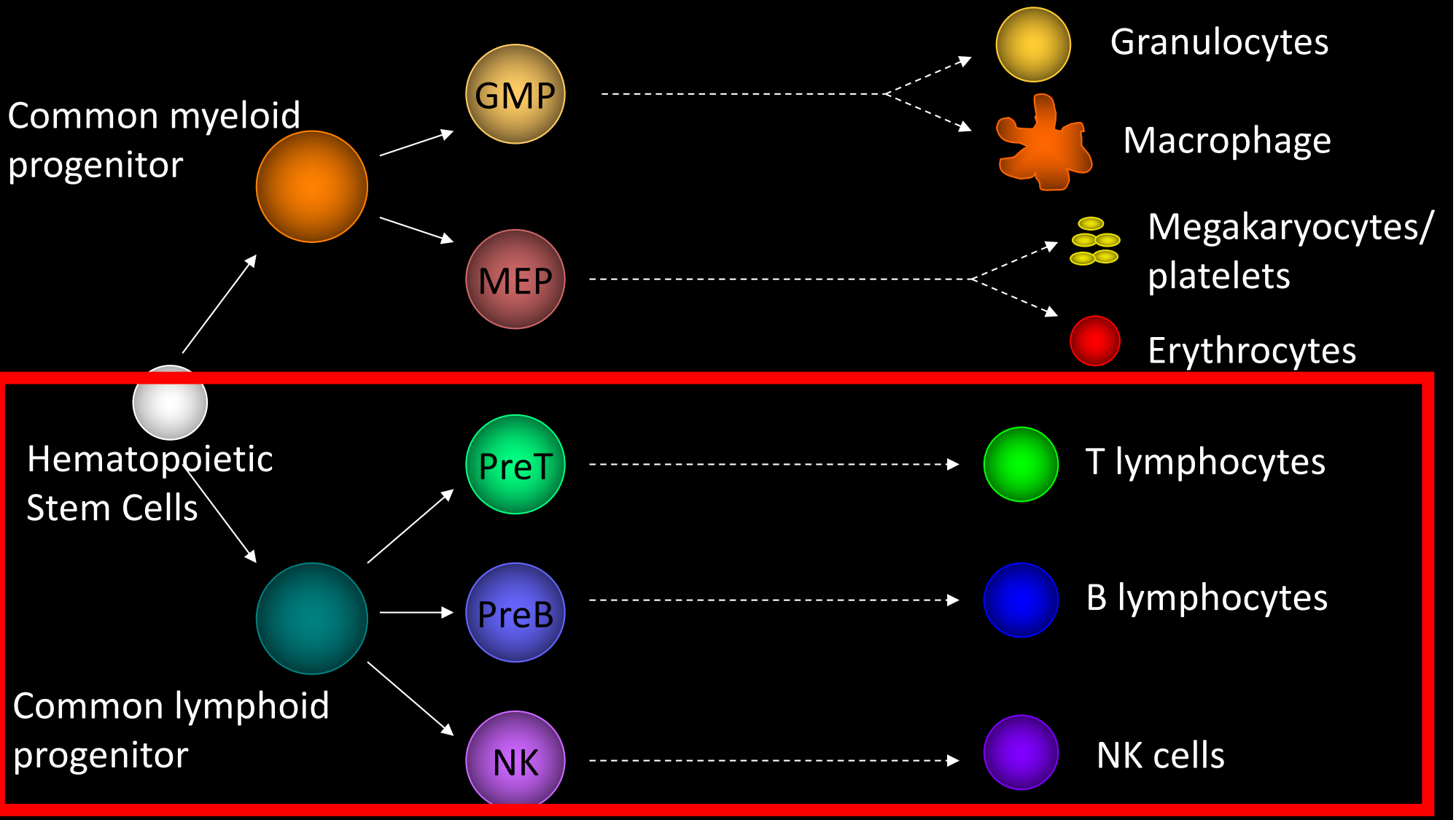

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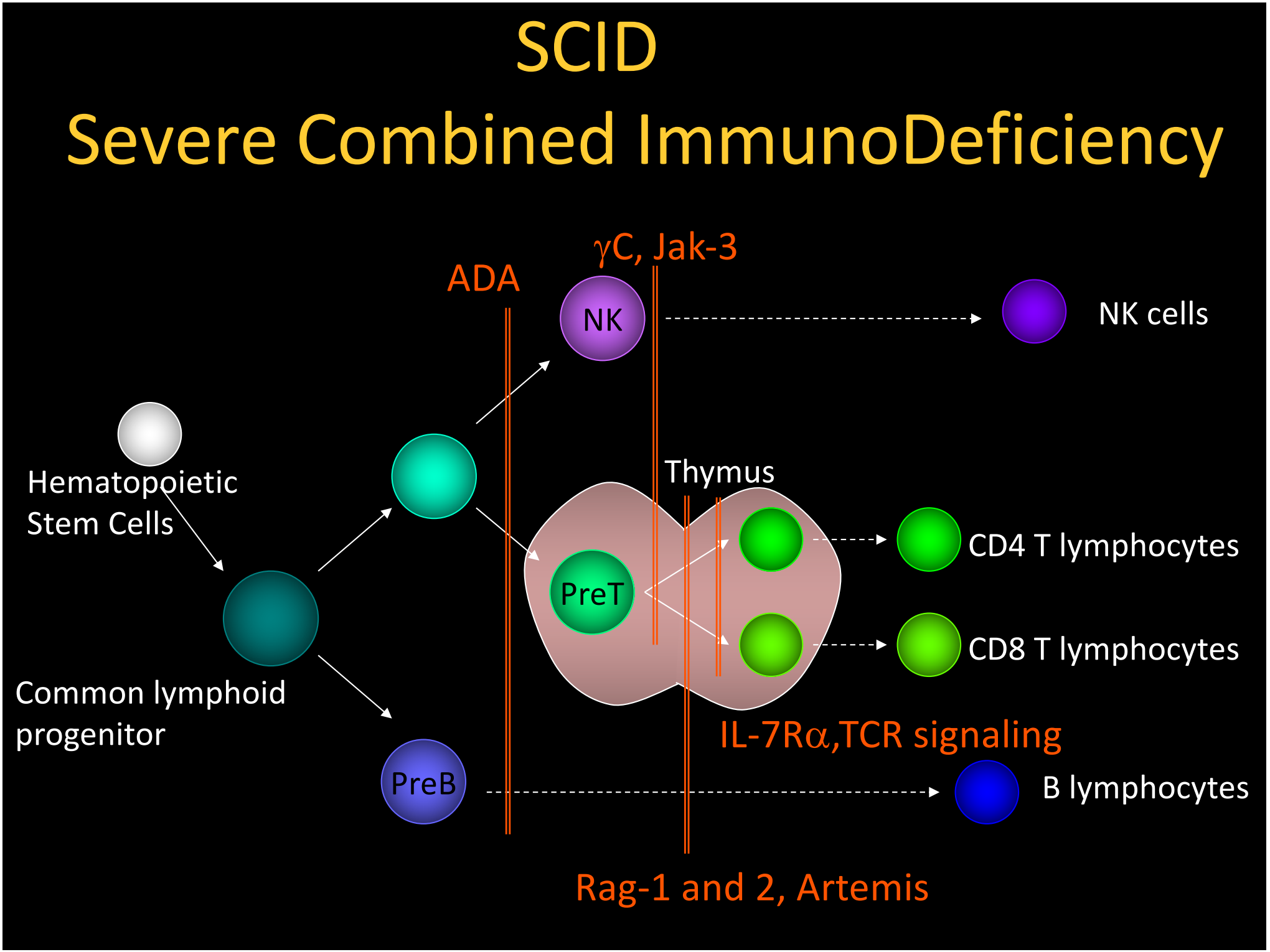
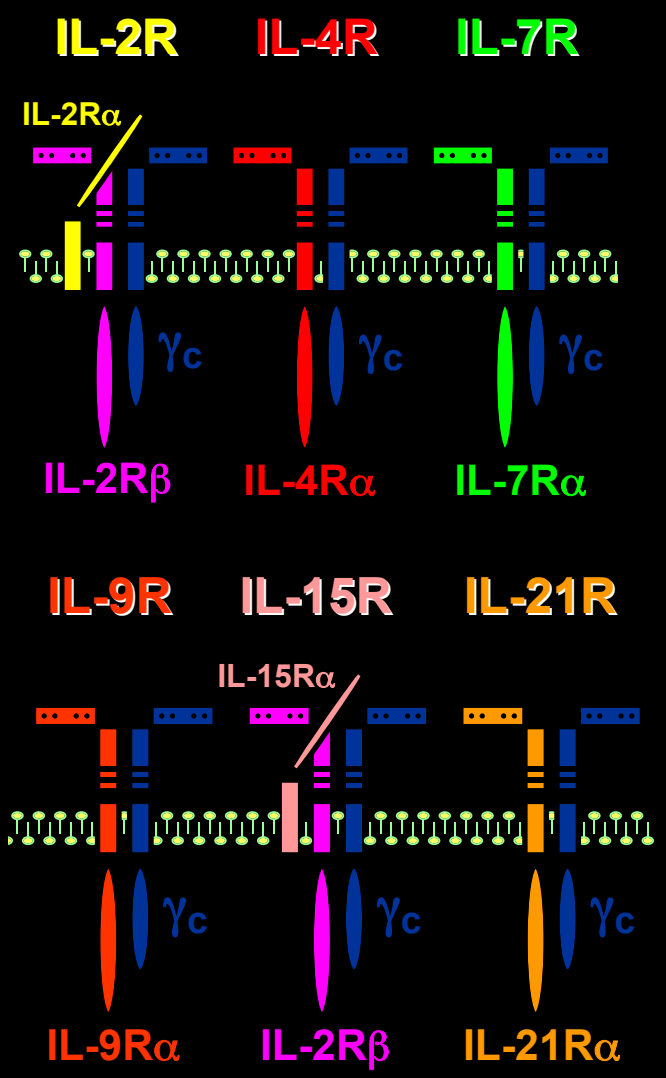


γC SCID (SCID-X1)

- Most common form of SCID (50%)
- X-linked inherited, Xq13.1
- Defect in γ chain common to different interleukin receptors

(IL-2, 4, 7, 9,15 and 21 receptors)

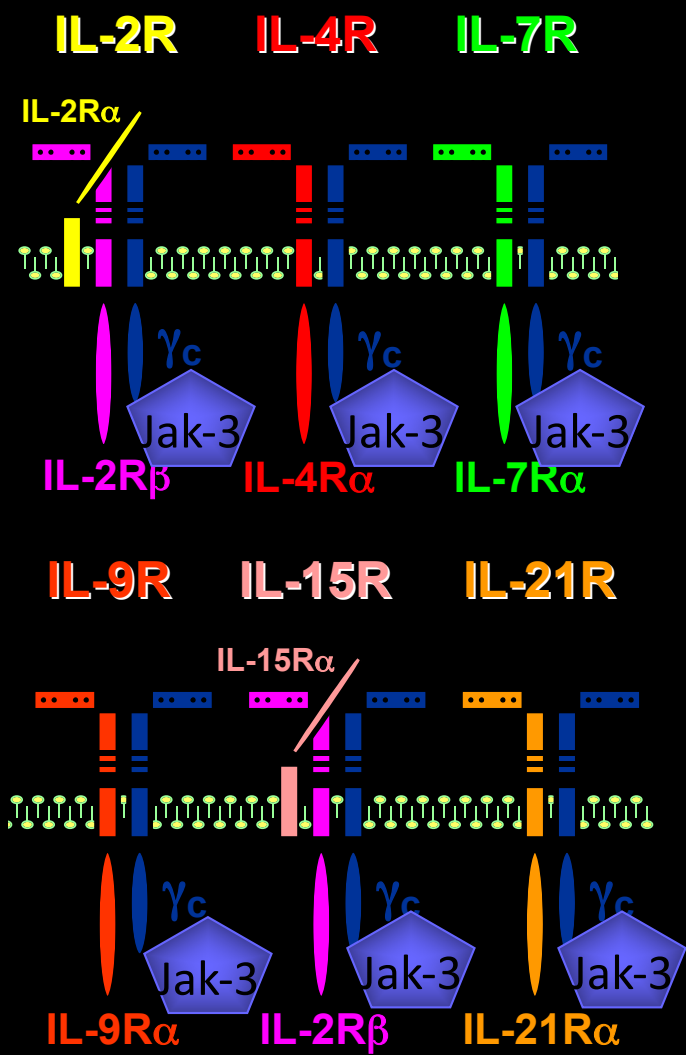
- 2/3 abnormal protein, 1/3 no protein
- T -, NK -, B +.
- Could be diagnosed at birth.(Journal of Allergy and Clinical Immunology Volume 115, Issue 2, February 2005, Pages 391-398)
- Patients are lymphopenic with normal number of B cells but have low to no detectable levels of Igs.
- Treatment : early BMT/gene therapy



Jak3 deficiency-SCID

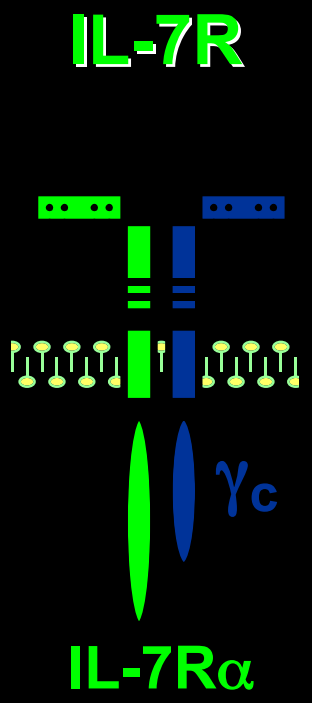
- 7% of SCID
- AR, 19p13.1
- Defect in Janus kinase 3 (Jak3).

  Tyrosine kinase binding the tail γC. Once activated phosphorylates STAT-5.
- T -, NK -, B +.
- Identical features as X-SCID
- Treatment : early BMT



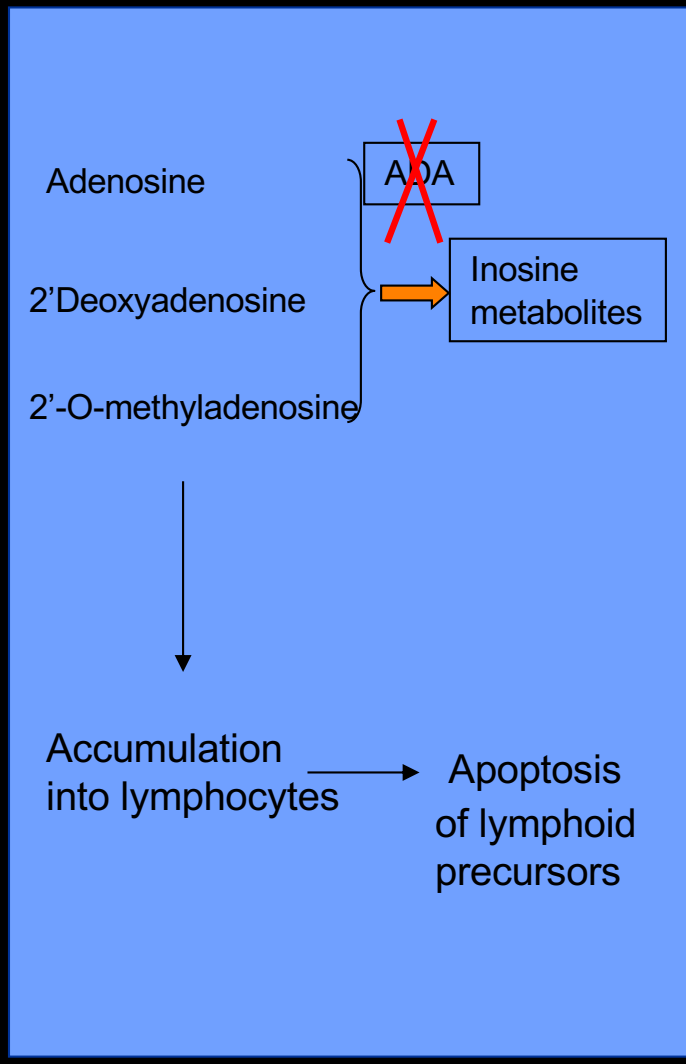
IL7Rα-SCID

- 10% of SCID
- AR, 5q13
- Defect in Interleukin-7 receptor (αchain)
- T -, NK +, B +.
- Severe T cell defect with normal and functional B cells
- Treatment : early BMT

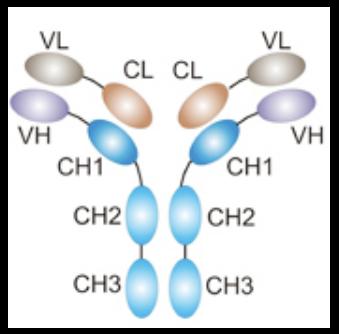


ADA-SCID

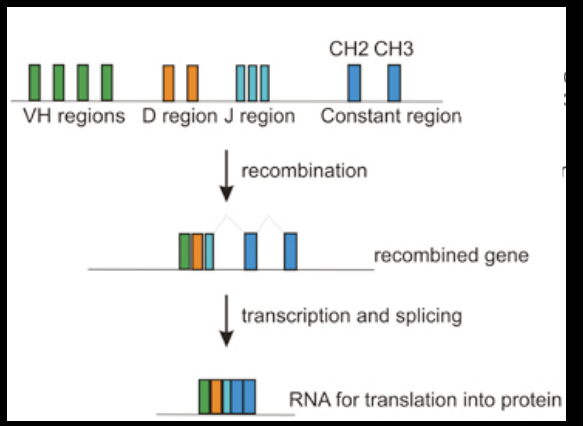
- From 8-20% of SCID
- AR, 20q13.11
- Defect in adenosine deaminase (ADA)
- T -, NK -, B -.
- Early onset, diagnosed at birth.
- Patients are deeply lymphopenic.
- Additional feature : Chondro osseous dysplasia (ribs and pelvic bone), some have neurological signs.
- Treatment :
  - PEG-ADA
  - early BMT/gene therapy



RAG deficiency SCID



- 2-10% of SCID
- AR, 11q13
- Defect in RAG 1 or 2 (Recombinase activating gene). During the TCR or BCR rearrangement RAG is mediating the double stranded DNA break during the VDJ rearrangement.



- T -, NK +, B -.
- Treatment : early BMT/ (gene therapy)
- Omenn's Syndrome: partial defect in VDJ recombinant activity.
  - Oligoclonal T cells expansion, generalized erythrodermia at birth, diarrhea, hepatosplenomegaly.
  - Corrected by BMT (conditioning needed)

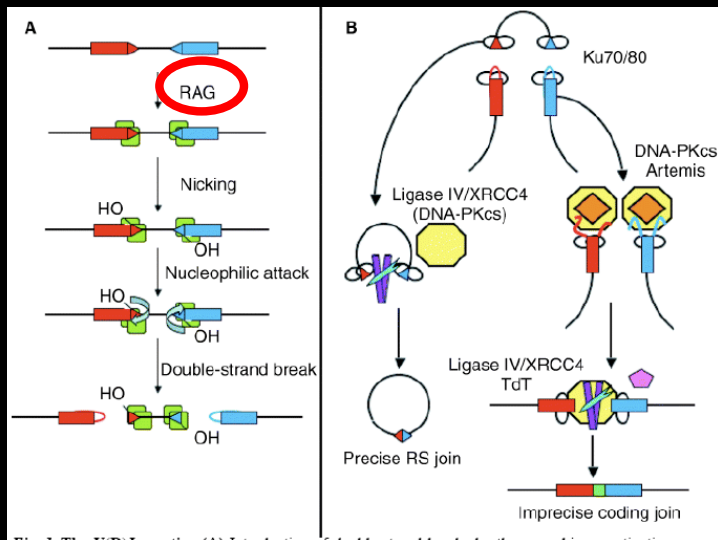


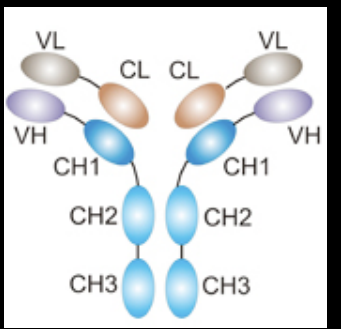
Fig. 1. **The V(D)J reaction.**(A) Introduction of double-strand breaks by the recombinase-activating gene (RAG) endonuclease.(B) The non-homologous end-joining (NHEJ) factors responsible for recombination signal (RS) and coding joining.

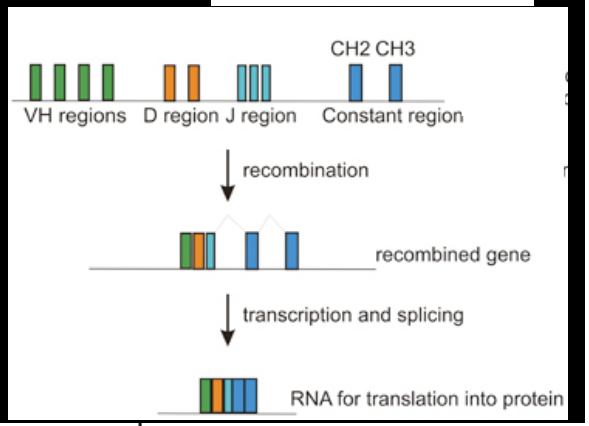
Rooney S, Immuno Rev, 2004

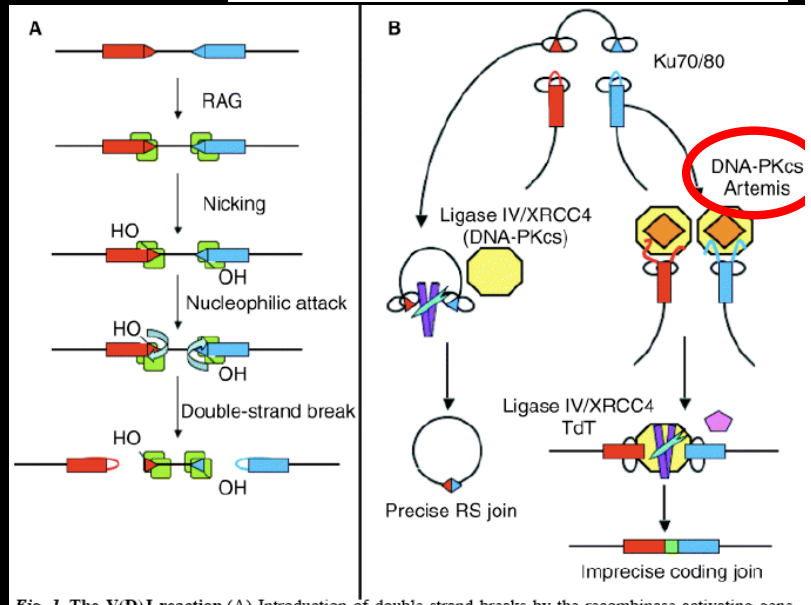
Artemis deficiency-SCID

- 10% of SCID
- AR, 10p13
- Defect in Artemis.

  DNA repair factor after doubled strained DNA cut made by RAG during the VDJ rearrangement.
- T -, NK +, B -.
- Sensitivity to radiation (skin and bone marrow)
- Treatment : early BMT (no conditioning!)







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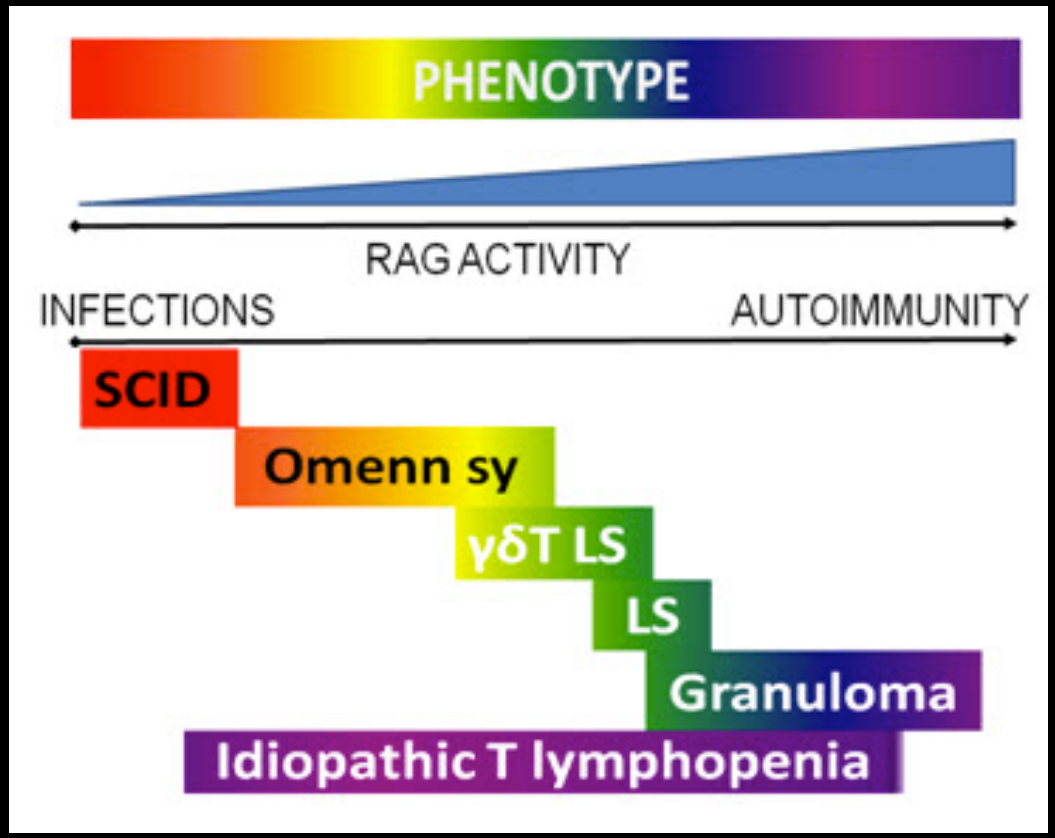
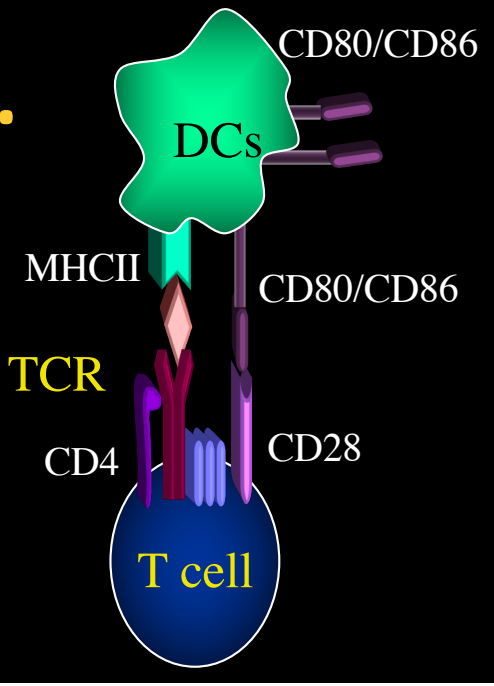
RAG and Artemis deficiency: an heterogeneous phenotype



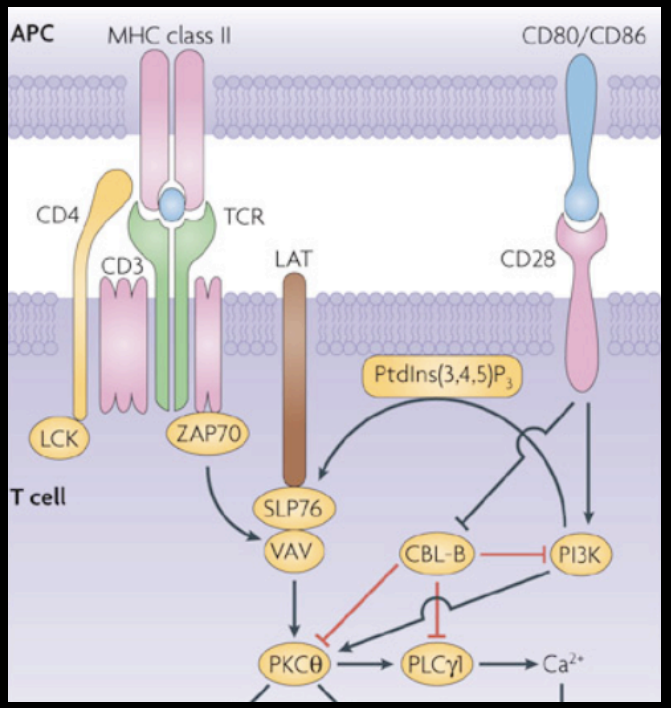
Notarangelo L

TCR mediated defect.



Highly variable presentation, from severe to negligible immune dysfunction

- CD3 δ, ζ, ε, (γ): severe T cell defect (no CD4 or CD8 cells)
- CD45 (regulates Src kinase protein): low T and NK cells, normal B cells
- MHCII defect: severe immune defect, low CD4 and normal CD8 cells
- ZAP70 defect: CD8 lymphopenia
- MHCI defect: milder defect, low CD8, normal CD4
- CD8 defect



T cells

Loss of function

Cytotoxicity defect :FHL

Severe inflammatory lymphoprolipherative disorder

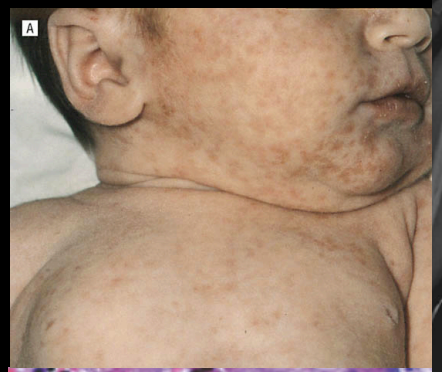
Familial hemophagocytic lymphohistiocytosis (primary HLH)

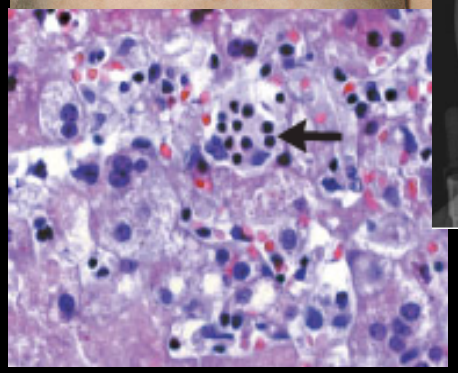
Clinical presentation:

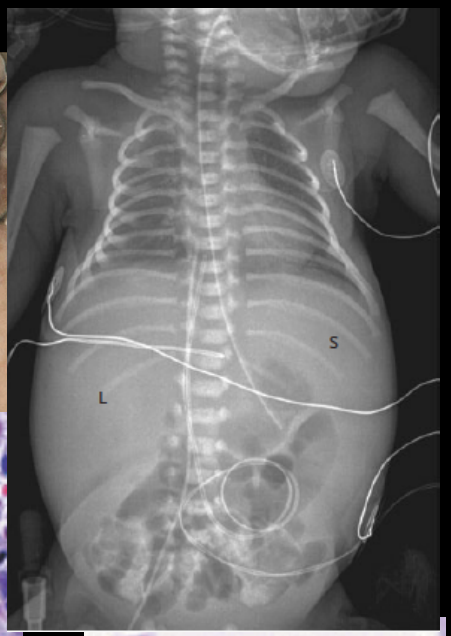
- Some early onset (<1year old)
- Fever
- Hepatosplenomegaly
- Cytopenia (anemia, thrombocytopenia)
- Hepatitis
- Neurological symptoms

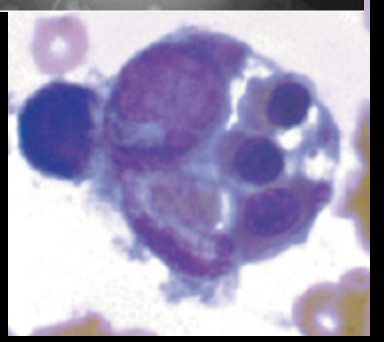
Biological features:

- Cytopenia (low RC, plts, PMN)
- Elevated ferritin
- HyperTG, Hypofibrinogenemia
- BM hyperplasia
- Hemophagocytes (histiocytes) infiltration (BM, spleen, LN, CSF)
- Defective NK cells function







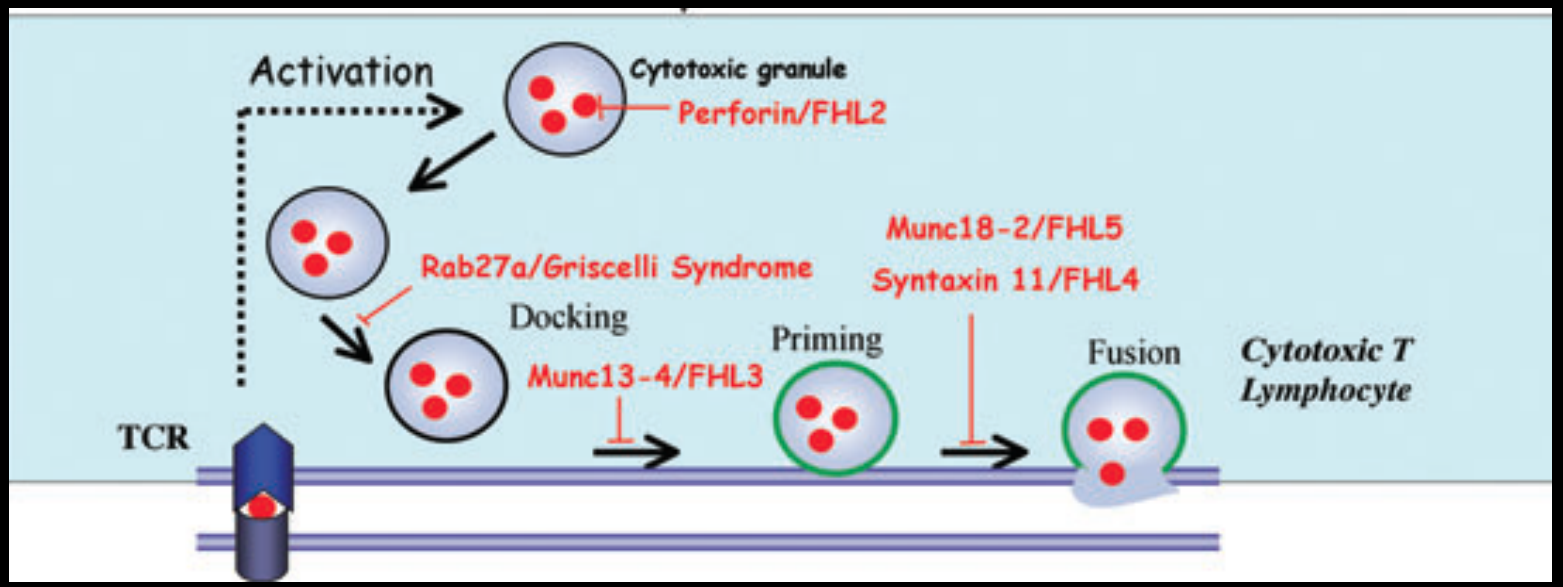


FHL: etiology

Autosomal recessif disease.
Incidence: 1/50000

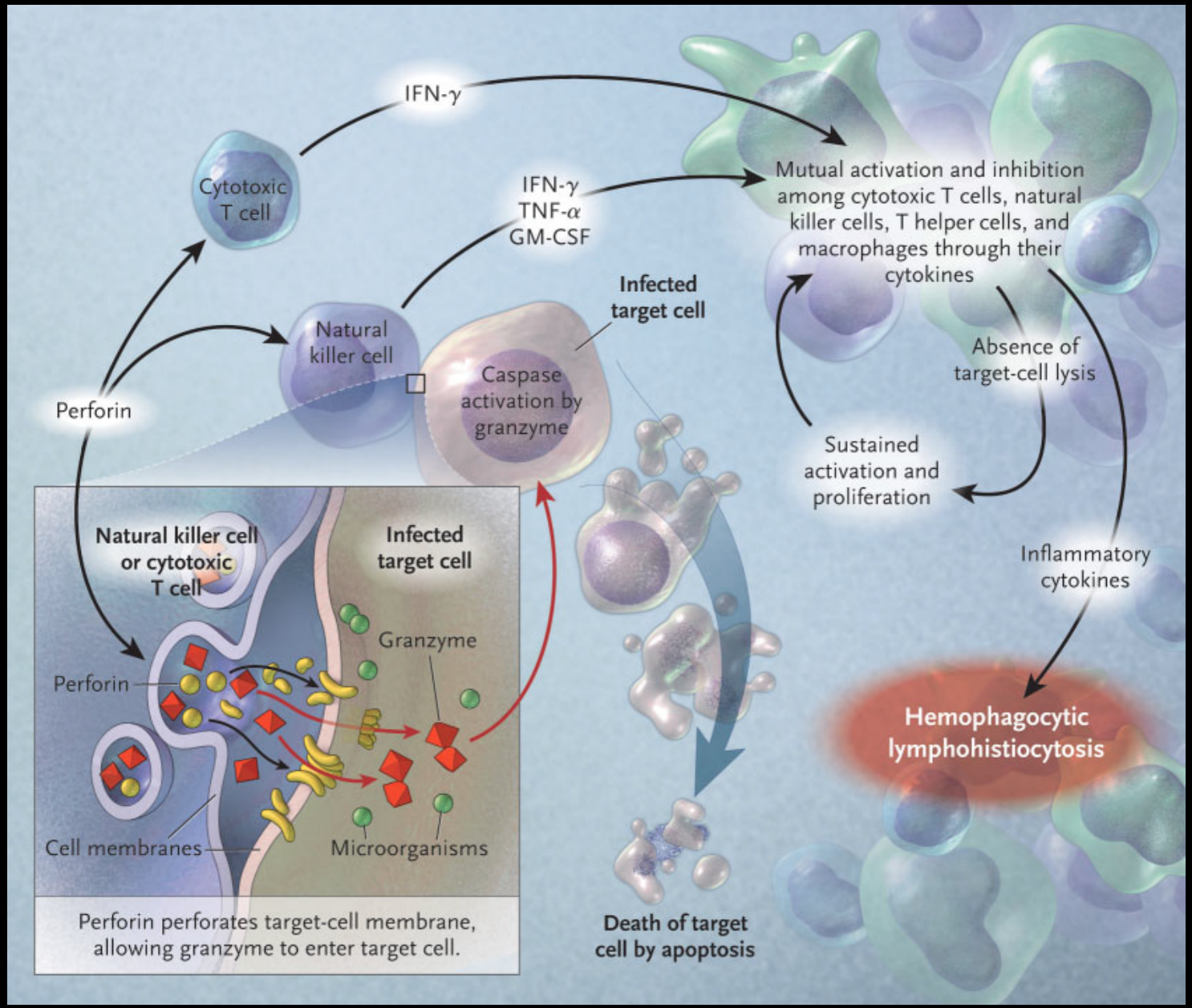
Cytotoxicity defect

-FHL1: unknown mapped at 9q21.3-22 locus
-FHL2: Perforin deficiency: 30%
-FHL3: MUNC 13-4 deficiency
-FHL4: Syntaxin 11
-FHL5: Munc 18-2
+ Griscelli syndrome, Chediak-Higahsi syndrome and Hermansky-Pudlak syndrome.



Schmid JP et al., Immuno Rev, May 2010

FHL: pathogenesis

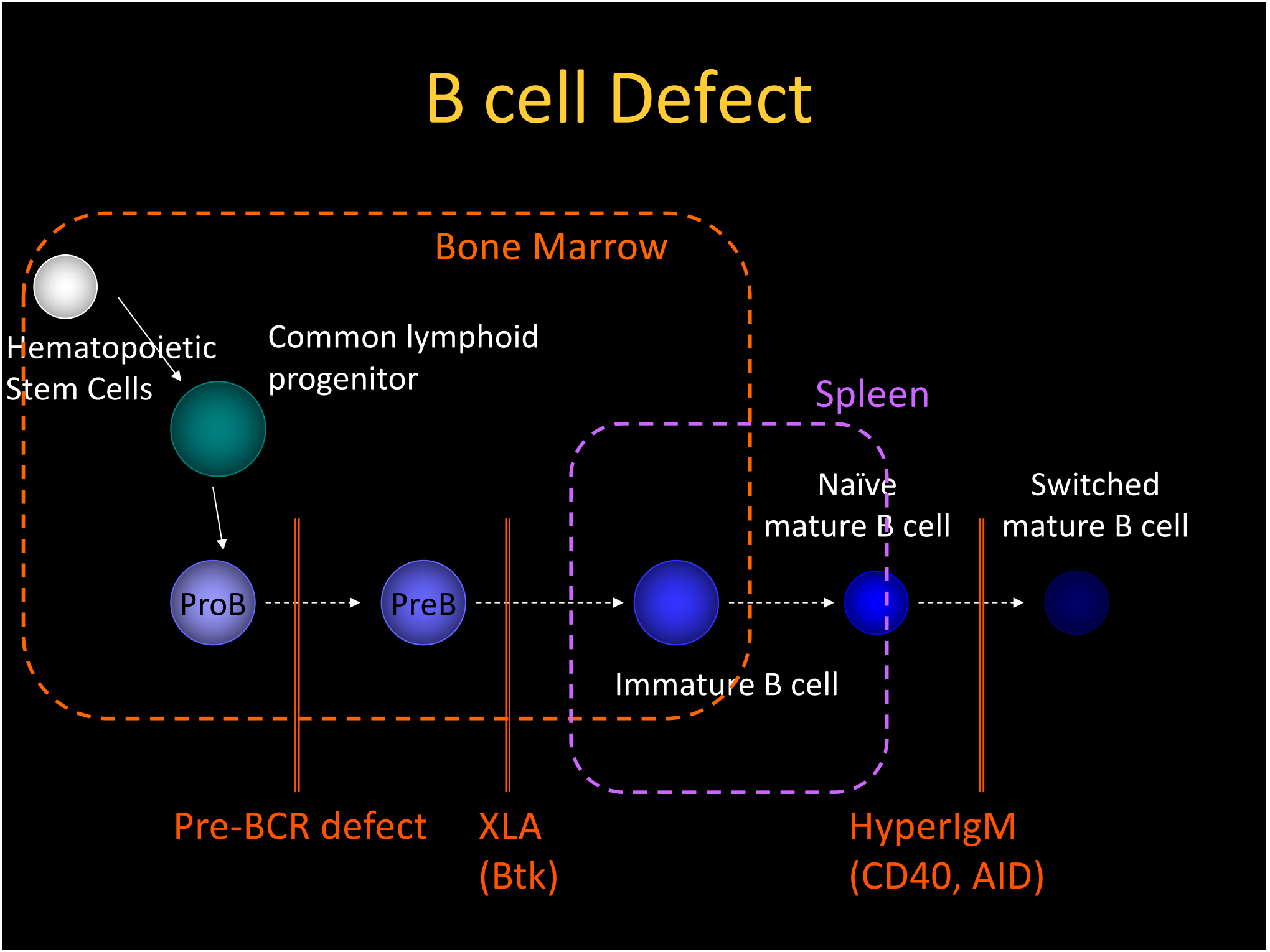


Lipton JM et al., NEJM, 2004

B cells

Developmental block

B cell Defect



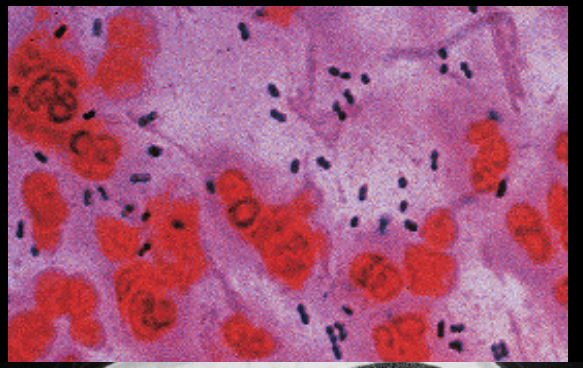
X-linked Agammaglobulinemia (XLA)

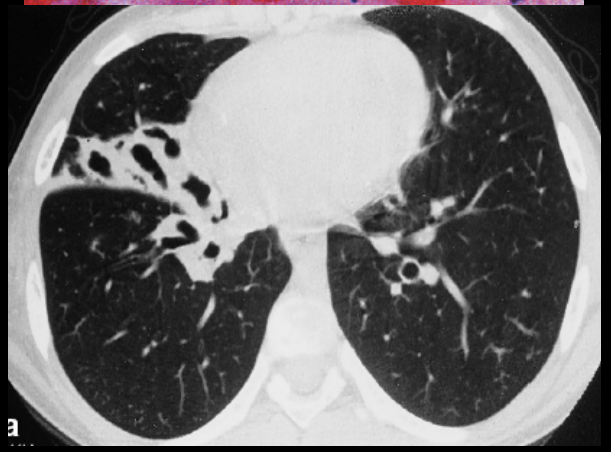
Primary humoral immunodeficiency

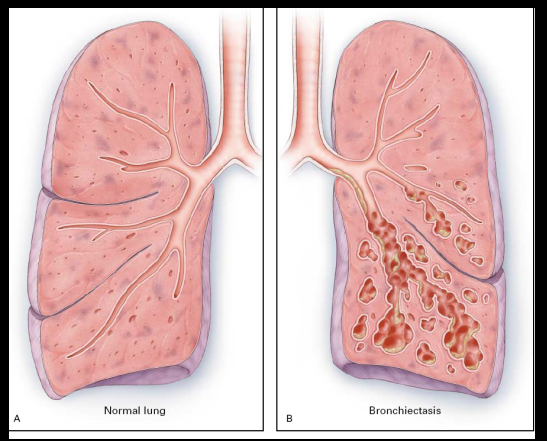
- Lack of immunoglobulins, mature B cells and plasma cells.
-Btk defect (tyrosine kinase downstream the BCR signal pathway.)

- Incidence of 1/100000.
- Symptomatic after the 6 first months:
  - recurrent bacterial infections, sepsis.
  - enteroviral infections
  - others: arthritis, GI disease.

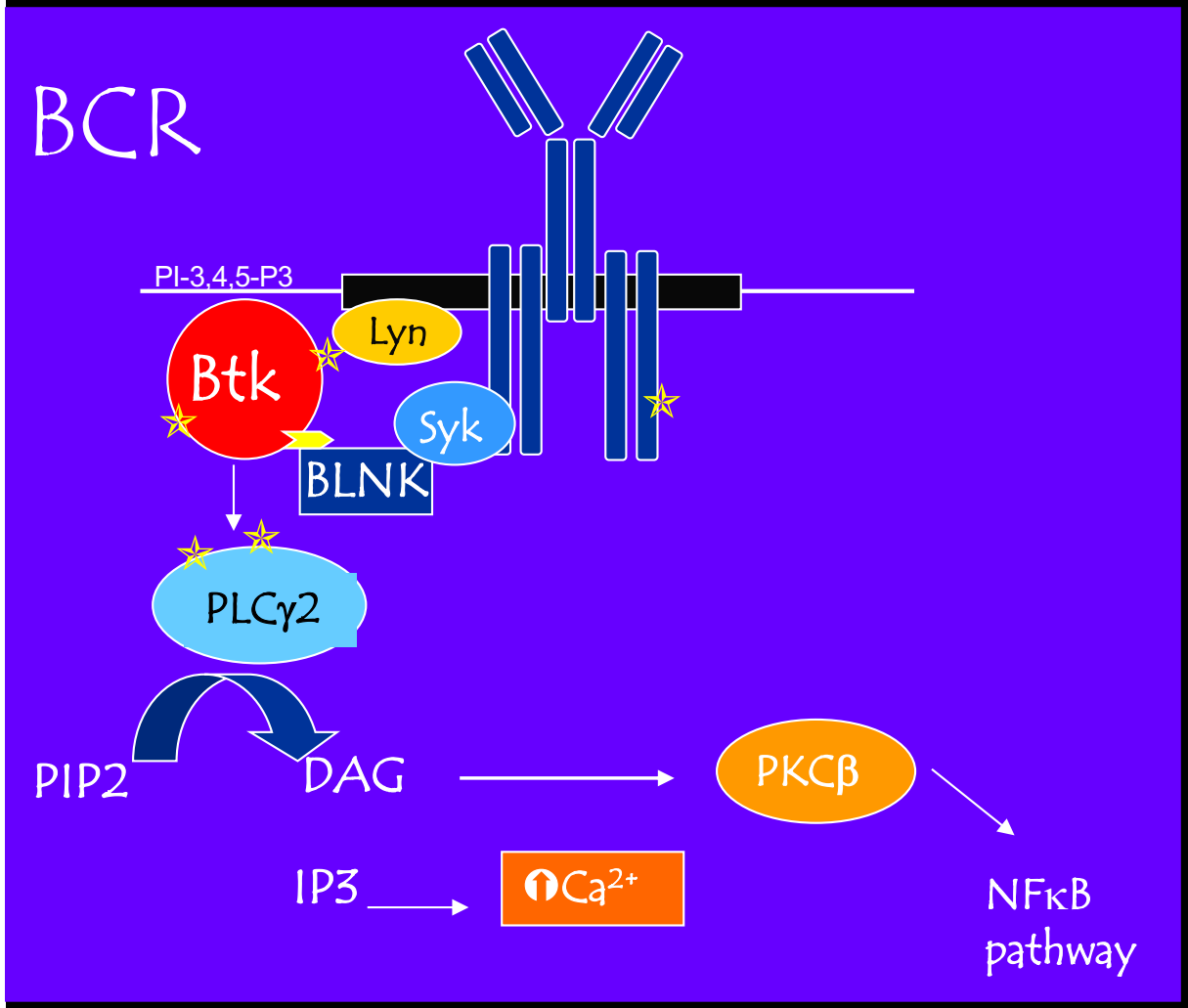
-Treatment: IV Igs and AB. (gene therapy)
-Complications and long term prognosis:
  - mortality 30% over 10 years
  - long term lung complications (bronchiectasis)
  - increase risk of malignancy







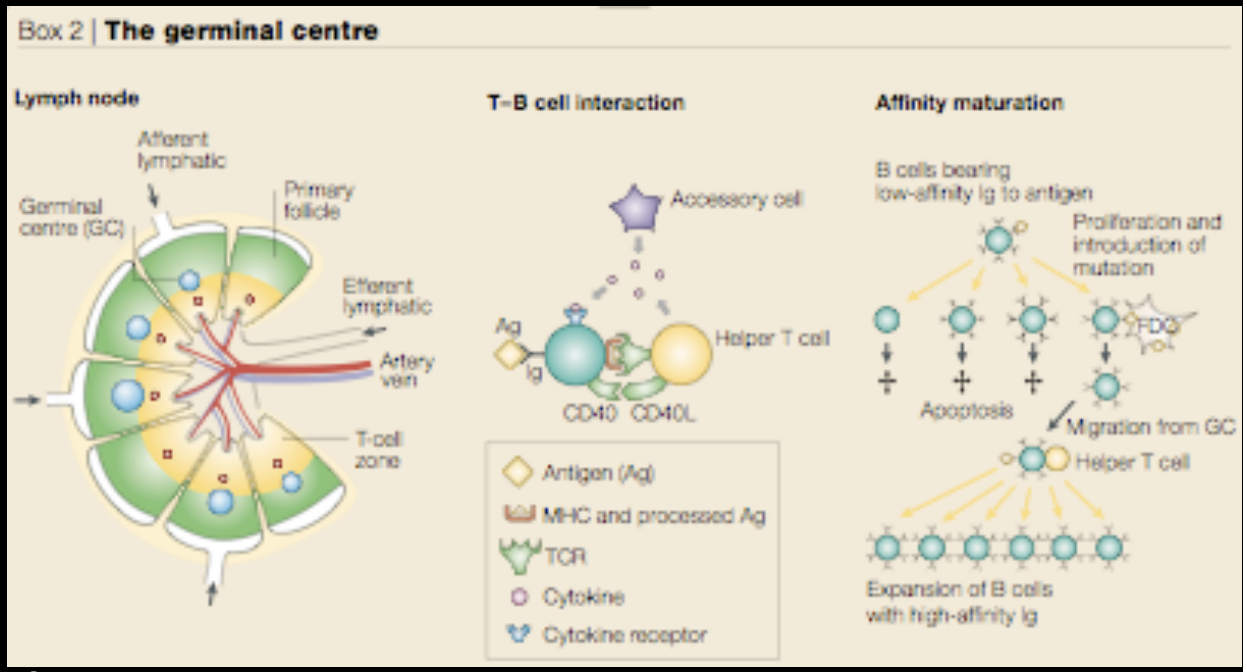
Btk plays a role in the BCR signalosome



Other agammaglobulinemia without Btk defect have been described. (10%)
They involved other BCR molecules which are important in B cell life as early as the Pro/PreB cell step.
(Igα, Igβ, BLNK, …)

HyperIgM Syndrome (HIGM)

Characterized by impaired Immunoglobulin Class-Switch Recombination and Somatic Hypermutation



Kinoshita K et al., Nat Rev Mol cell Bio, 2001

- Patients have low/no IgG, IgA and IgE. High level of IgM. Normal B cells (decreased memory B cells)
- Recurrent bacterial infection

  (CD40L deficient have opportunistic disease 50% have Pn j)
- Autoimmunity
- Treatment: BMT/AB/IVIGs

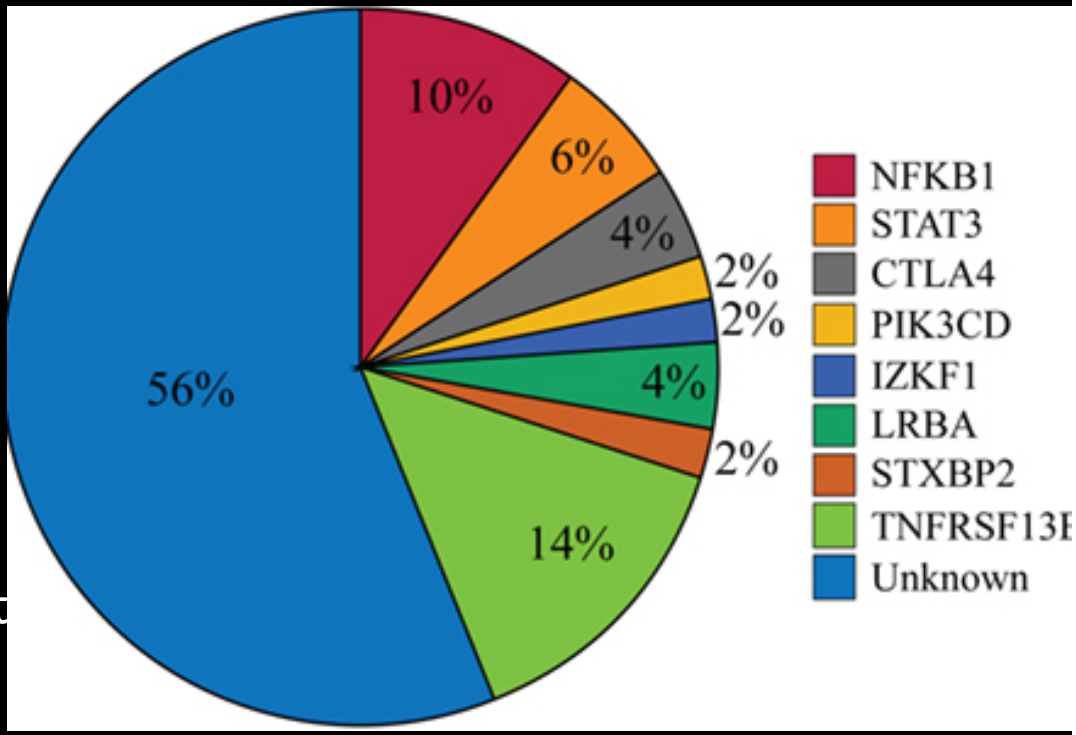
- HIGM1: Defect in CD40L

  (X-linked, Xq26, T cell defect, 2/3 of patients with HIGM)
- HIGM2: Defect in AID (activation induce cytidine deaminase)
- HIGM3: Defect in CD40

Common variable immunodeficiency (CVID)

Definition (ESID 2014):
At least one of the following:

*increased infection rate
*autoimmune manifestations
*granulomatous disease
*unexplained polyclonal lymphoproliferation
*affected family members with antibody deficiency
AND relevant decrease of IgG and IgA wit
or w/o IgM reduction
AND at least one of the following:
*poor antibody response to vaccination
reduced switched memory B cells



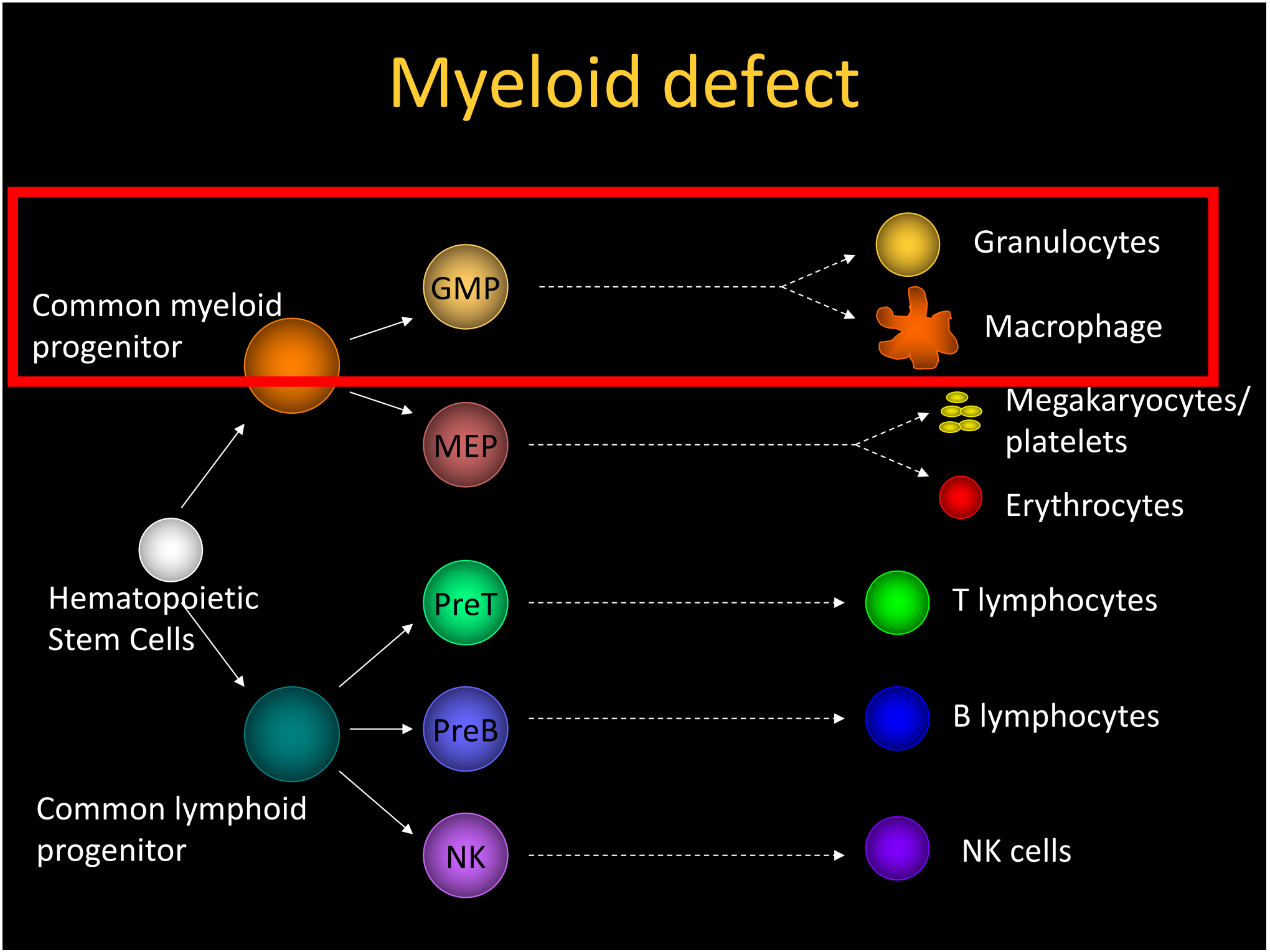
Maffucci P et al., frontiers immuno, 2016

+ TACI, ICOS, BAFF-R, CD19, CD20….

Myeloid cells

Developmental block

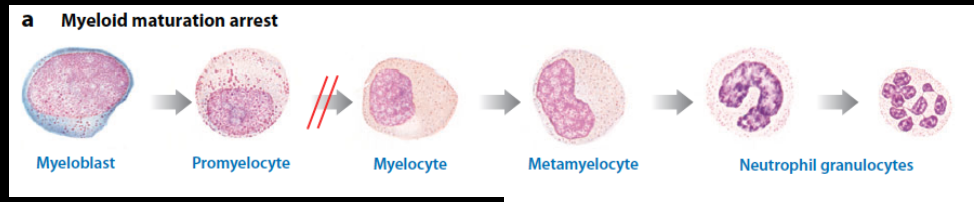
Myeloid defect



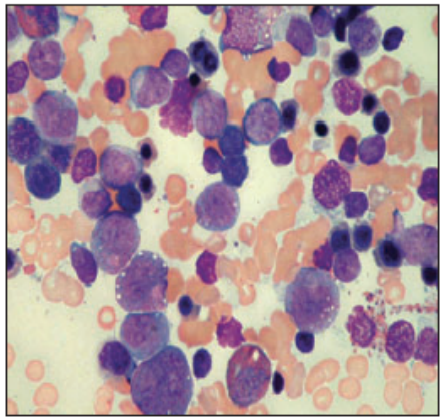
Severe Congenital Neutropenia

Clinical presentation:
- Recurrent infections (fungal/bacterial)
- Osteopenia
- Susceptibility to myelodysplasia

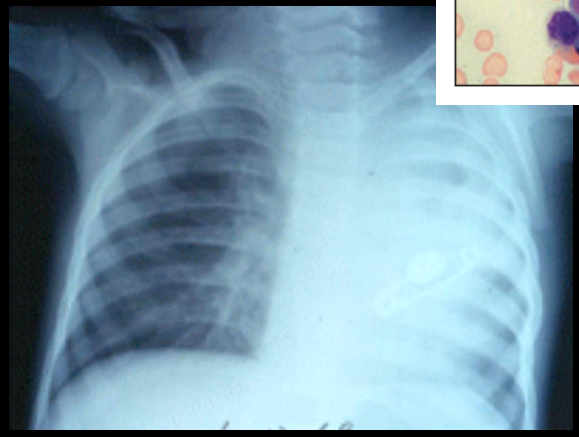
Treatment: supportive, G-CSF, Allo-HSCT.



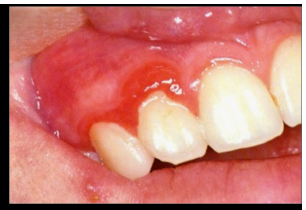
Klein C., Ann Rev Immuno, 2011



- SCN1: Defect in ELANE/ELA2 (AD,19p13.3, 50% of the patients)
- SCN2: Defect in GFI1 (AD,1p22.1, rare)
- SCN3: Defect in HAX-1 (Kostmann disease) (AR,1q21.3, 20% of patients)
- SCN4: Defect in G6PC3 (AR,17q21.31, 5% of patients)
- Additional : Defect in GSD1b, dominant mutation in WASp



Pickering LK., American Academy of Pediatrics; 2012



Myeloid cells

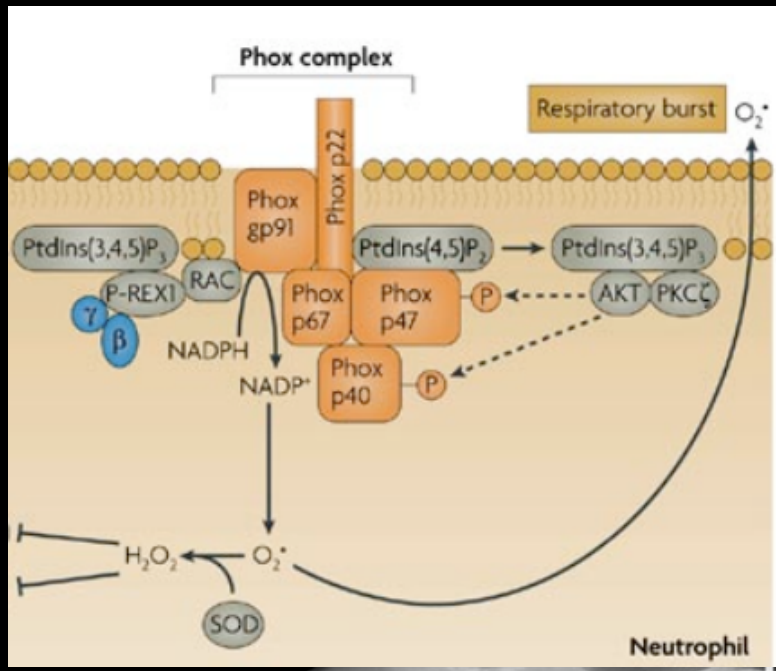
Loss of function

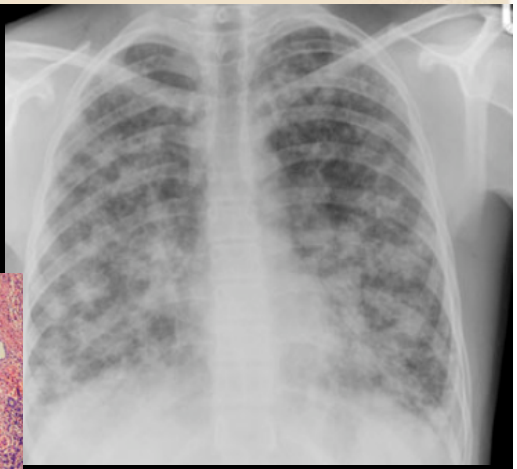
Chronic Granulomatous Disease (CGD)

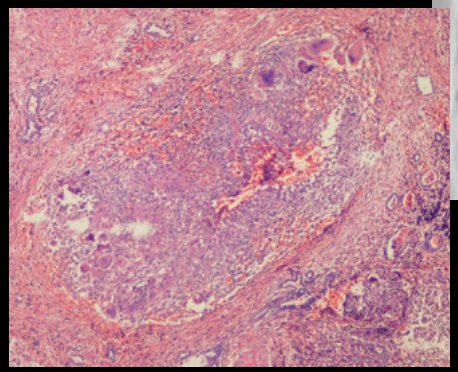
Defect in superoxyde generating phagocyte oxidase (phox)

Unability to degrade pathogen by formation of active oxydase in phagosome.

- 5 identified defective proteins
  -gp91phox, X-linked (75%)
  -p22phox, p47phox, p67phox and p40phox(AR)
- Clinical presentation:
  -Early ulcerus, omphalitis
  -Recurrent infection (fungal/bacterial)
  -granuloma
- Treatment: supportive, BMT, gene therapy







Other PIDs

Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee

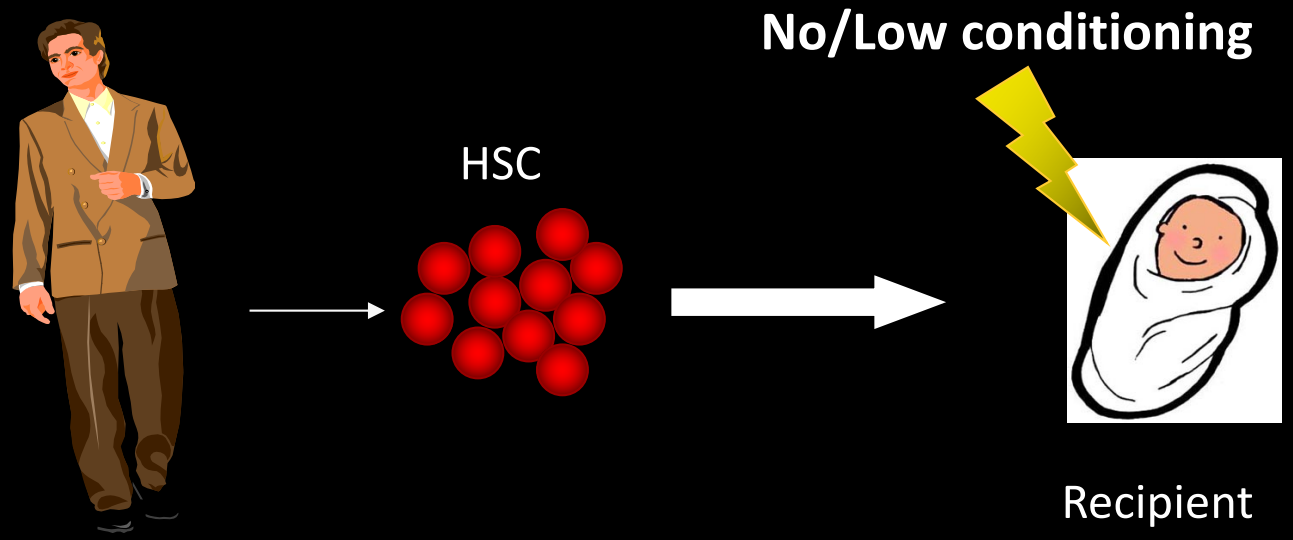
Stuart G. Tangye et al.

J Clin Immunol.. 2020 Jan;40(1):66-81. doi: 10.1007/s10875-020-00758-x. Epub 2020 Feb 11.

Gene therapy for primary immundeficiency disorders

Standard treatment : HSCT

Until recently, hematopoietic stem cells transplantation was the only curative treatment.



Donor: - sibiling donor
- unrelated HLA identical donor
- haploidentical donor

Outcome of HSCT

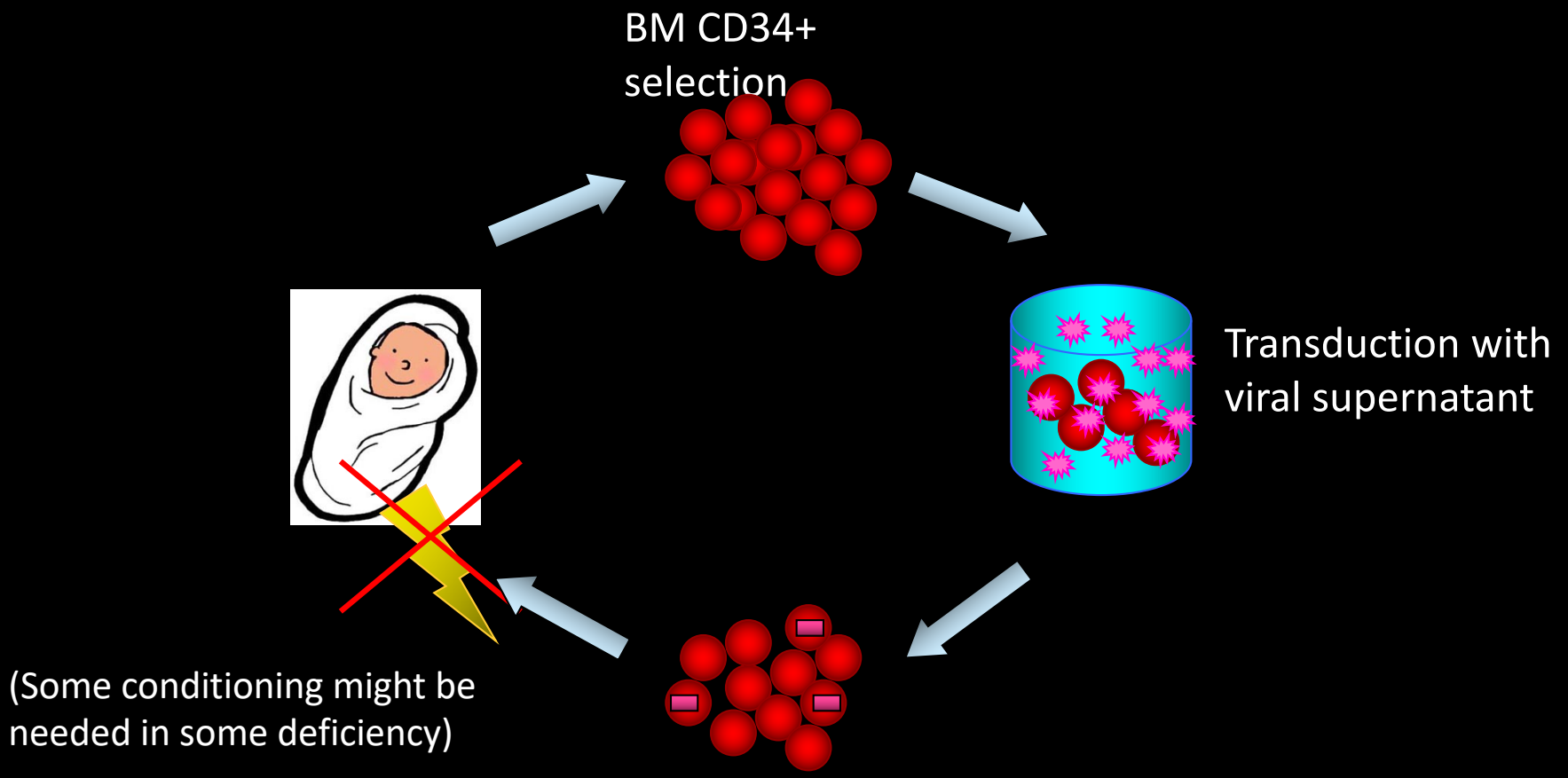
- In SCID patients the long term survival rate after transplantation is more than 90% for sibilingHSCT and between 60 -80% for patients transplanted with other donors.

But:

- All the patients don't have the chance to have a HLA-identical donor.
- Some patients can experience GVHD (destruction of recipient organs by immune cells from the graft.)
- In most SCID-X1 patients, NK cells remain low and deficient B cells function persists after transplantation.
  Some T cell deficiency may persist too.

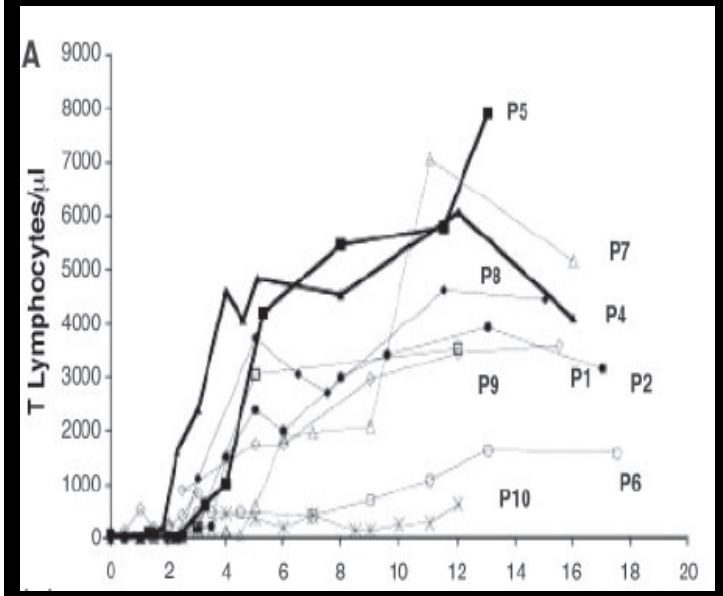
Alternative therapeutic approach : Gene Therapy.

- Ex vivo transfer of the defective gene into autologous hematopoietic stem cells.



Clinical trials (1)

SCID-X1

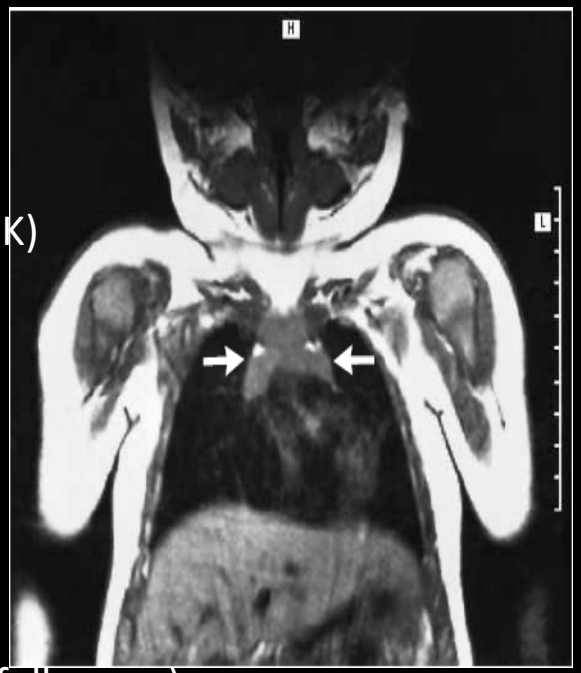


- Total patient number :
> 20
(1st trials:10 in the french trial, 10 in UK)

- Vector : retrovirus carrying γC gene

- No conditioning

- Results : success in 17/20 treated patients
(some patients with more than 10y follow-up)



- Side effect : lymphoproliferative diseases (leukemia) in 5/20 patients due to insertional mutagenesis
In addition Trial is ongoing using SIN-RT virus.

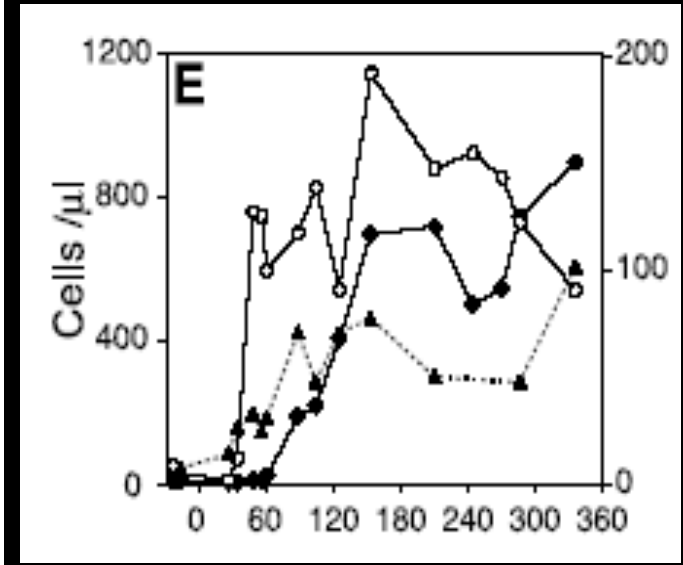
LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1.
Hacein-Bey-Abina S et al., Science. 2003 Oct 17;302(5644):415-9. Erratum in: Science. 2003 Oct 24;302(5645):568.

Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease.
Cavazzana-Calvo M etal.,Science. 2000 Apr 28;288(5466):669-72.

Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy.Hacein-Bey-Abina S,et al., N Engl J Med. 2002 Apr 18;346(16):1185-93.

Clinical trials (2)

ADA-SCID

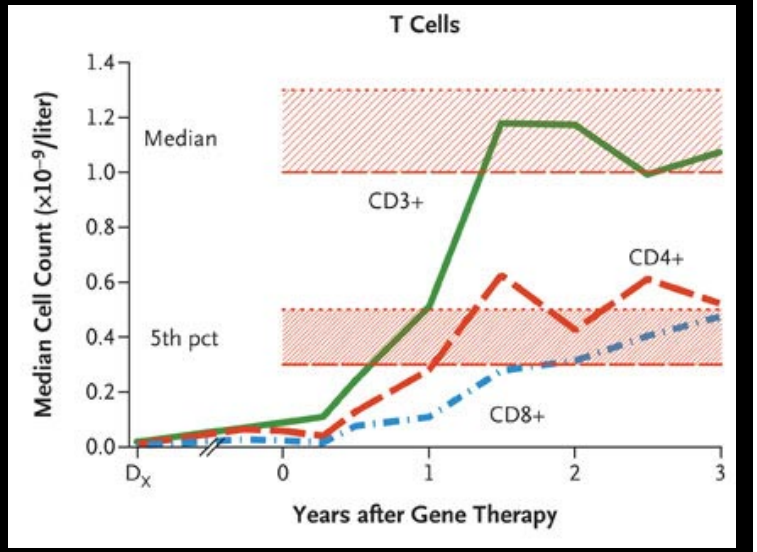


◆ T cells (left scale)
▲ NK cells (right scale)
◯ B cells (left scale)

- Total patient number : > 40
(18 in the italian trial, 8 in UK, 14 in the NIH, +2 with LV)

-Vector : retrovirus carrying ADA gene

- Mild conditioning (Bu)



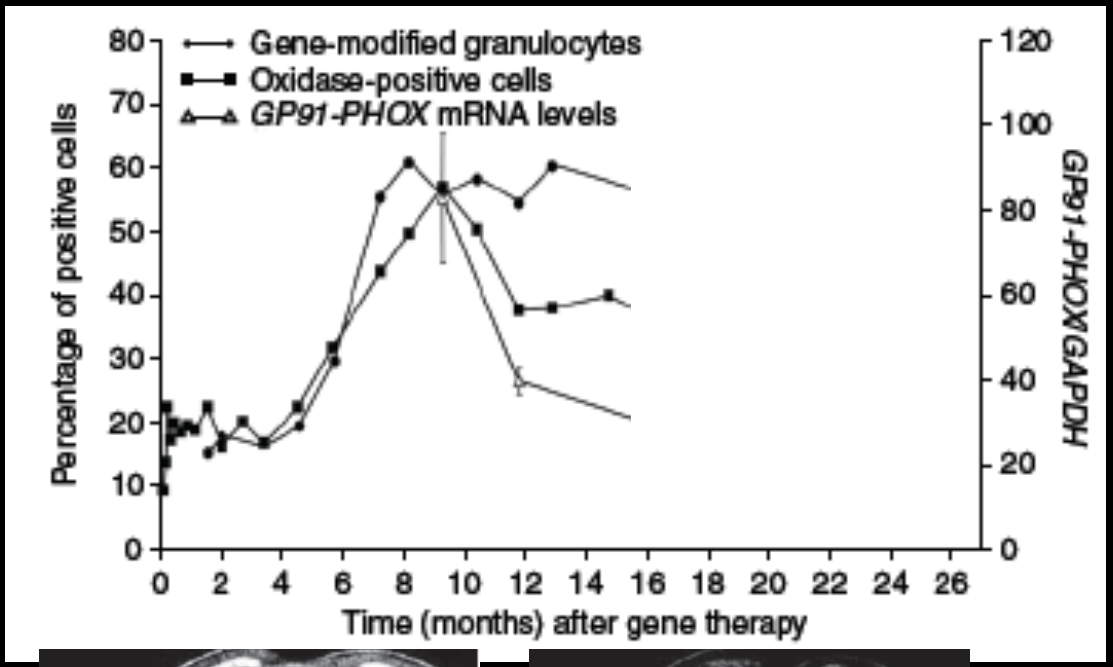
- Results : success in 50-80% of treated patients (off enzyme replacement)
(some patients with 10y follow-up)

- Side effect : no side effect due to insertional mutgenesis so far

Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning.
Aiuti A et al., Science. 2002 Jun 28;296(5577):2410-3.
Gene therapy for immunodeficiency due to adenosine deaminase deficiency.Aiuti A et al.,
N Engl J Med. 2009 Jan 29;360(5):447-58.

Clinical trials (3)

CGD



- Total patient number : 24
(4 in the german trial, 3 at the NIH (13 total in US), 4 in UK,and 2 in Korea)

-Vector : retrovirus carrying gp91phox gene

- Moderate conditioning (Bu)

- Results : transient innate immune system improvement

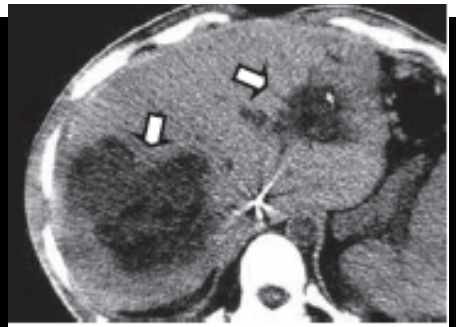


Image 2 pre gene therapy

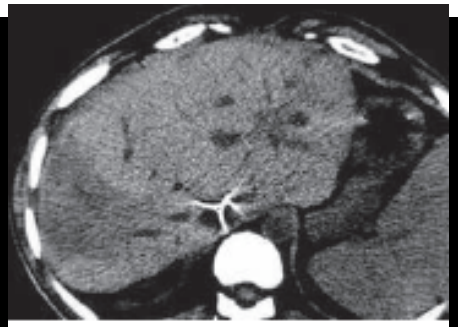
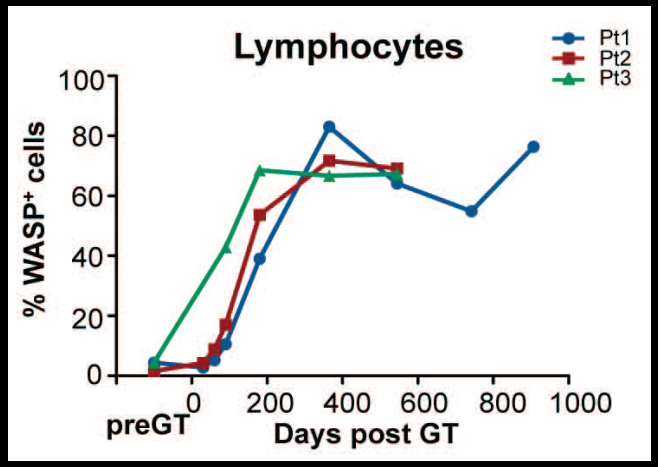


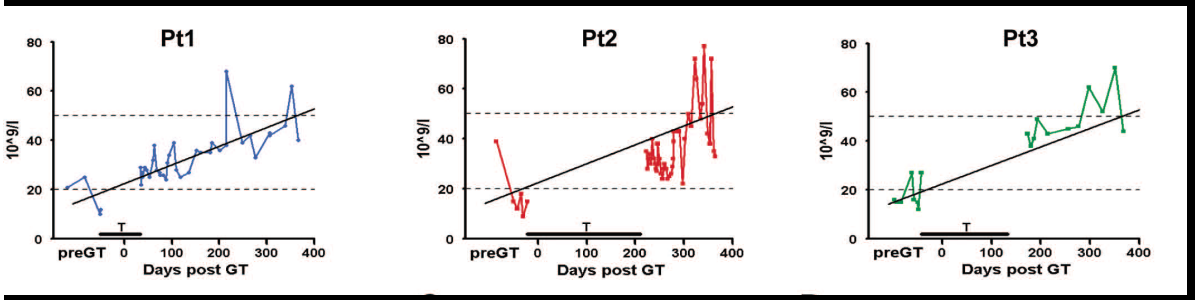
Image 2 post gene therapy

- Side effect : myelodysplasia (MDS) In 3/4 patients (german trial) due to insertional mutagenesis

Retrovirus gene therapy for X-linked chronic granulomatous disease can achieve stable long-term correction of oxidase activity in peripheral blood neutrophils. Kang EM et al., Blood. 2010 Jan 28;115(4):783-91. Epub 2009 Dec 1.
Genomic instability and myelodysplasia with monosomy 7 consequent to EVI1 activation after gene therapy for chronic granulomatous disease. Stein S et al.,Nat Med. 2010 Feb;16(2):198-204. Epub 2010 Jan 24.

Clinical trials (4)
Wiskott-Aldrich Syndrome





- Total patient number in this study: >21 (Italy)

- Vector : lentivirus
carrying WASp gene and promoter

- Conditioning: RIC

- Results : Clinical and biological improvement

- The first open trial was in Germany in which they used RT-virus with well-known risk of insertional mutagenesis. So did the patients developed myelodysplasia and leukemia (7/10).

Lentiviral Hematopoietic Stem Cell Gene Therapy in Patients with Wiskott-Aldrich Syndrome,
Aiuti A et al., Science. 2012 Aug 23;341(6148):1233158

However…

RESEARCH ARTICLE

LMO2-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1

S. Hacein-Bey-Abina,[1,2*] C. Von Kalle,[6,7,8] M. Schmidt,[6,7] M. P. McCormack,[9] N. Wulffraat,[10] P. Leboulch,[11] A. Lim,[12] C. S. Osborne,[13] R. Pawliuk,[11] E. Morillon,[2] R. Sorensen,[19] A. Forster,[9] P. Fraser,[13] J. I. Cohen,[15] G. de Saint Basile,[1] I. Alexander,[16] U. Wintergerst,[17] T. Frebourg,[18] A. Aurias,[19] D. Stoppa-Lyonnet,[20] S. Romana,[3] I. Radford-Weiss,[3] F. Gross,[2] F. Valensi,[4] E. Delabesse,[4] E. Macintyre,[4] F. Sigaux,[20] J. Soulier,[21] L. E. Leiva,[14] M. Wissler,[6,7] C. Prinz,[6,7] T. H. Rabbitts,[9] F. Le Deist,[1] A. Fischer,[1,5]†‡ M. Cavazzana-Calvo[1,2]†

We have previously shown correction of X-linked severe combined immunodeficiency [SCID-X1, also known as γ chain (γc) deficiency] in 9 out of 10 patients by retrovirus-mediated γc gene transfer into autologous CD34 bone marrow cells. However, almost 3 years after gene therapy, uncontrolled exponential clonal proliferation of mature T cells (with γδ+ or αβ+ T cell receptors) has occurred in the two youngest patients. Both patients' clones showed retrovirus vector integration in proximity to the *LMO2* proto-oncogene promoter, leading to aberrant transcription and expression of *LMO2*. Thus, retrovirus vector insertion can trigger deregulated premalignant cell proliferation with unexpected frequency, most likely driven by retrovirus enhancer activity on the *LMO2* gene promoter.

Ex vivo retrovirus-mediated gene transfer into hematopoietic progenitor cells has been shown to be an efficient strategy to correct inherited diseases of the lymphohematopoietic system, provided that a strong selective advantage is conferred to transduced cells (*1*–*3*). Indeed, in 9 out of 10 patients with typical X-linked severe combined immunodeficiency [SCID-X1, or γ chain (γc) deficiency], ex vivo γc gene transfer into autologous bone marrow–derived CD34+ cells with a long terminal repeat (LTR)–driven MFG vector (*4*) resulted in the development of a functional adaptive immune system (Fig. 1A) (*2*). The clinical benefit has been so far sustained for more than 4 years in the first two treated patients; potentially, this sustained efficacy could be explained in part by the transduction of pluripotent progenitors with self-renewal capacity (*5*, *6*). The main potential risk of retrovirus-mediated gene transfer is insertional mutagenesis resulting from random retroviral integration. This could either activate proto-oncogenes over long distances (up to 100 kbp) or inactivate tumor-suppressor genes, ultimately leading to malignancies. To date, this risk has been considered very low, because it has never been observed in a clinical trial. Furthermore, only recently has evidence become available that insertion of replication-defective retrovirus vectors could contribute to malignancy in a single experimental setting (*7*). This risk assessment is now seriously challenged by our report of the occurrence of two severe adverse events in our SCID-X1 gene therapy trial.

Clinical findings. Two children (patients P4 and P5) have developed an uncontrolled clonal proliferation of mature T lymphocytes 30 and 34 months after gene therapy, respectively (*8*). These two children, 1 and 3 months old at the time of treatment, received 18×10^6 and 20×10^6 CD34(+) γc(+) cells per kg of body weight, respectively. These values are in the high range compared with those of other treated patients (range, 1.1×10^6 to 22×10^6; median, 4.3×10^6) (*1*, *2*).

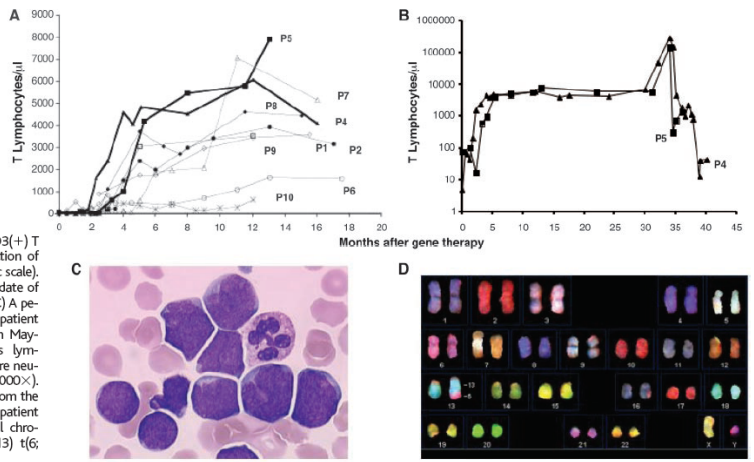


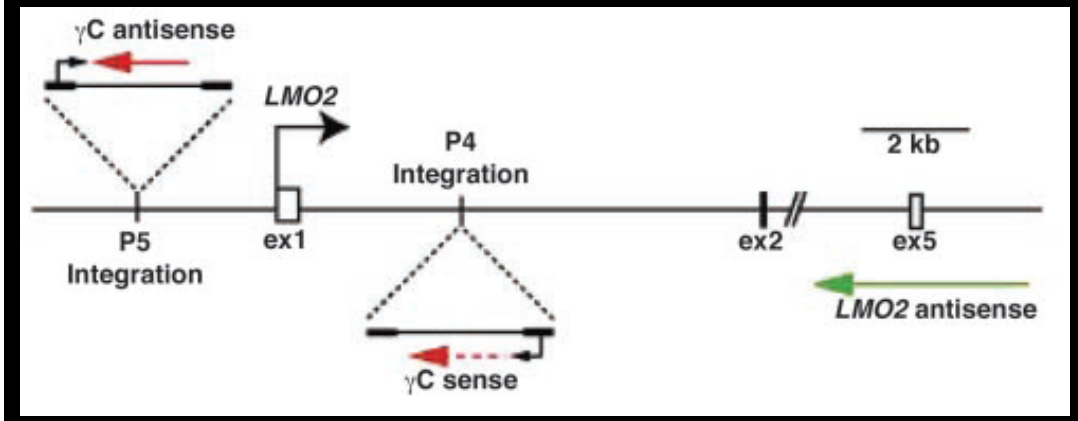
Fig. 1. Kinetics and characteristics of P4 and P5 abnormal T cells. (**A**) Longitudinal kinetics of blood T lymphocyte (CD3+) counts in treated patients (P1, P2, and P4 to P10), who recovered T cell immunity. (**B**) T cell kinetics of patients P4 (triangles) and P5 (squares), who developed an uncontrolled T lymphocyte proliferation. Absolute counts of CD3(+) T cells are shown as a function of time (on a semilogarithmic scale). Day 0 corresponds to the date of gene therapy treatment. (**C**) A peripheral blood smear from patient P4 at M+34, stained with May-Grünwald Giemsa, shows lymphoid blasts and one mature neutrophil (magnification, 1000×). (**D**) A spectral karyotype from the unstimulated blast cells of patient P4, showing the abnormal chromosome 13, derivative (13) t(6; 13) at M+34.

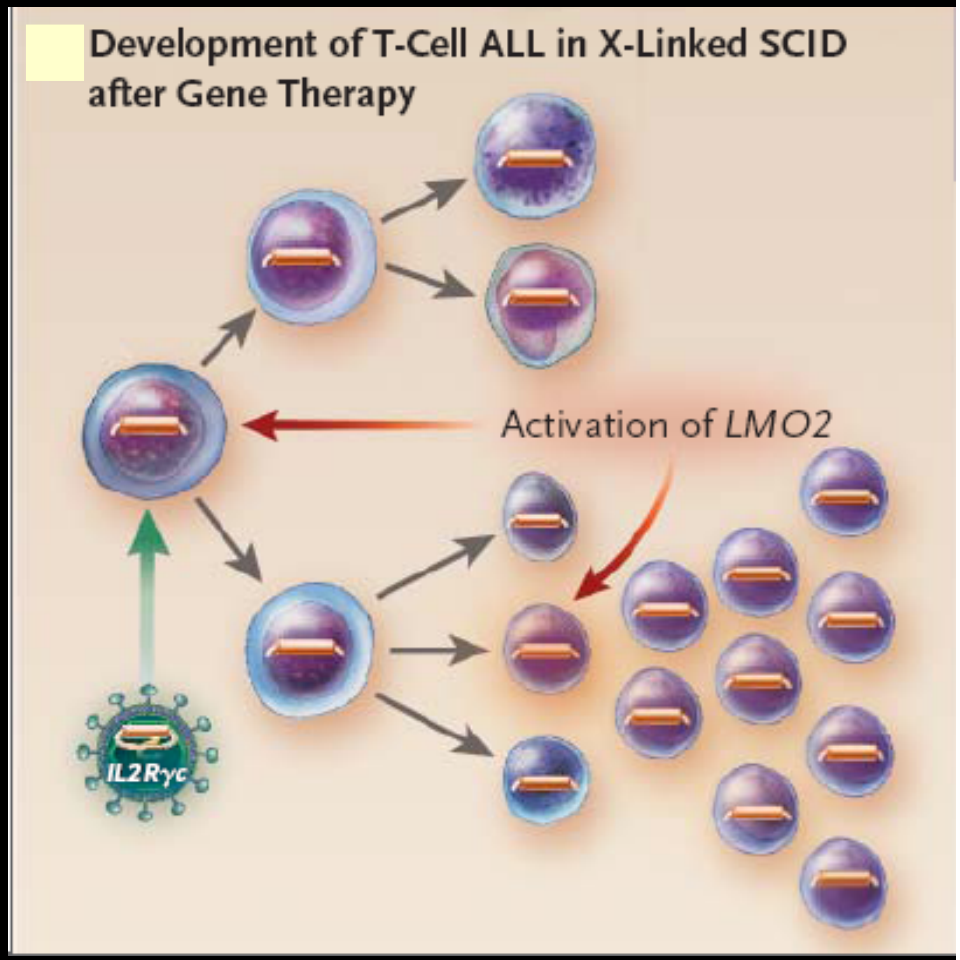
Severe side effects occur in 16 treated patients as they developed a proliferative disorder.

Why this happened ?

Insertional mutagenesis

Retrovirus preferentially integrate into active genes and indeed, near gene promoters.





SCID-X1

Towards a safer procedure

- **Gene :** avoid oncogene, insert suicide gene.
- **Vector selection :** better vector design,

  virus: Use lentivirus instead of RV

  ⇒ self-inactivating vector

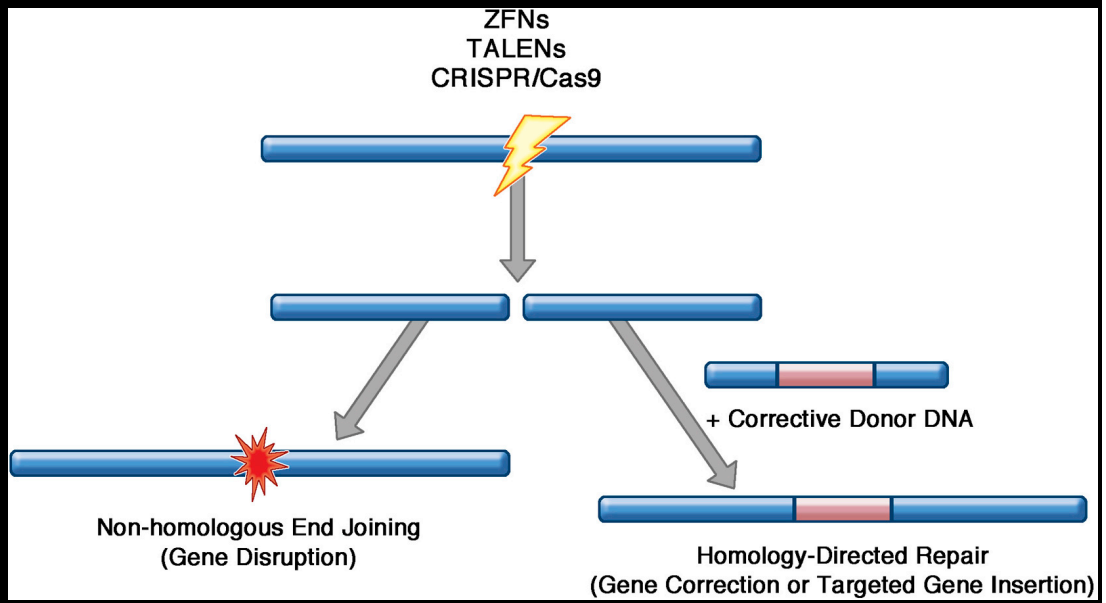
  ⇒ selective internal promoter

  ⇒ use of insulator

  new methods: Homologous recombination

  (zinc finger nucleases, homing endonucleases/TALEN, CRISPR/Cas9)

- **Genome related toxicity studies**



Kohn DB et al., JACI, March 2017

On going PID gene therapy trials

Booth C, Romano R, Roncarolo MG, Thrasher AJ. Gene therapy for primary immunodeficiency. *Hum Mol Genet*. 2019;28(R1):R15–R23. doi:10.1093/hmg/ddz170

Table 1. Current and closed gene therapy trials for PIDs

Disease	Centre	Trial No	Vector	Cryopreserved	Start date	Recruiting	Refs
ADA-SCID	Milan Jerusalem	NCT00599781 NCT00598481	GRV		1992 2002		(23–26)
	Bethesda	NCT00018018	GRV		2001		
	London	NCT01279720	GRV		2003		(97)
	LA	NCT00794508	GRV		2008		(98)
	London	NCT01380990	LV		2012 2013		
	LA/Bethesda	NCT01852071					
	Bethesda	NCT02022696	LV		2013		
	LA London	NCT02999984 NCT03765632	LV	Yes	2016 2018	Yes	
X-SCID	London Paris		GRV		2003		(27,28,97)
	Bethesda	NCT00028236	GRV		2001		
	Boston/LA	NCT01129544	SIN-GRV		2010		
	Paris	NCT01410019			2010		
	London	NCT01175239			2011		(99)
	Memphis	NCT01306019	LV		2011		
	Bethesda	NCT03315078	LV		2012		(39)
	Memphis/Seattle/San Francisco	NCT01512888	LV		2016		(33)
	Beijing	NCT03217617	LV		2017		
	Boston/LA/London	NCT03311503	LV		2018	Yes	
CGD	Frankfurt	NCT00564759	GRV		2004		(30)
	Zurich	NCT00927134	GRV		2004		(31)
	Bethesda	NCT00394316	GRV		2006		(100)
	Seoul	NCT00778882	GRV		2007		(101)
	Frankfurt	NCT01906541	SIN-GRV		2013	Yes	
	London	NCT01855685	LV		2013		
	LA/Boston/Bethesda	NCT02234934	LV		2015	Yes	
	Paris	NCT02757911	LV		2016	Yes	
	Beijing	NCT03645486	LV		2018	Yes	
WAS	Hannover	DRKS00000330	GRV		2006		(29)
	Milan	NCT01515462	LV		2010		(34,36)
	London	NCT01347242	LV		2011	Yes	(35)
	Paris	NCT01347346				Yes	
	Boston	NCT01410825	LV		2011		
	Milan	NCT03837483	LV	Yes	2019	Yes	
LAD	Bethesda	NCT00023010	GRV/PBL		2001		
	Madrid	NCT03825783	LV	Yes	2019	Yes	
	LA	NCT03812263				Yes	

ADA, adenosine deaminase; SCID, severe combined immune deficiency; GRV, gammaretroviral vector; LV, lentiviral vector; SIN-GRV, self inactivating gammaretroviral vector; X-CGD. X-linked chronic granulomatous disease; WAS, Wiskott–Aldrich syndrome; LAD, leukocyte adhesion deficiency; PBL, peripheral blood leukocytes.

Importantly, Gene Therapy has already cured up to 150 patients with a long term follow-up!