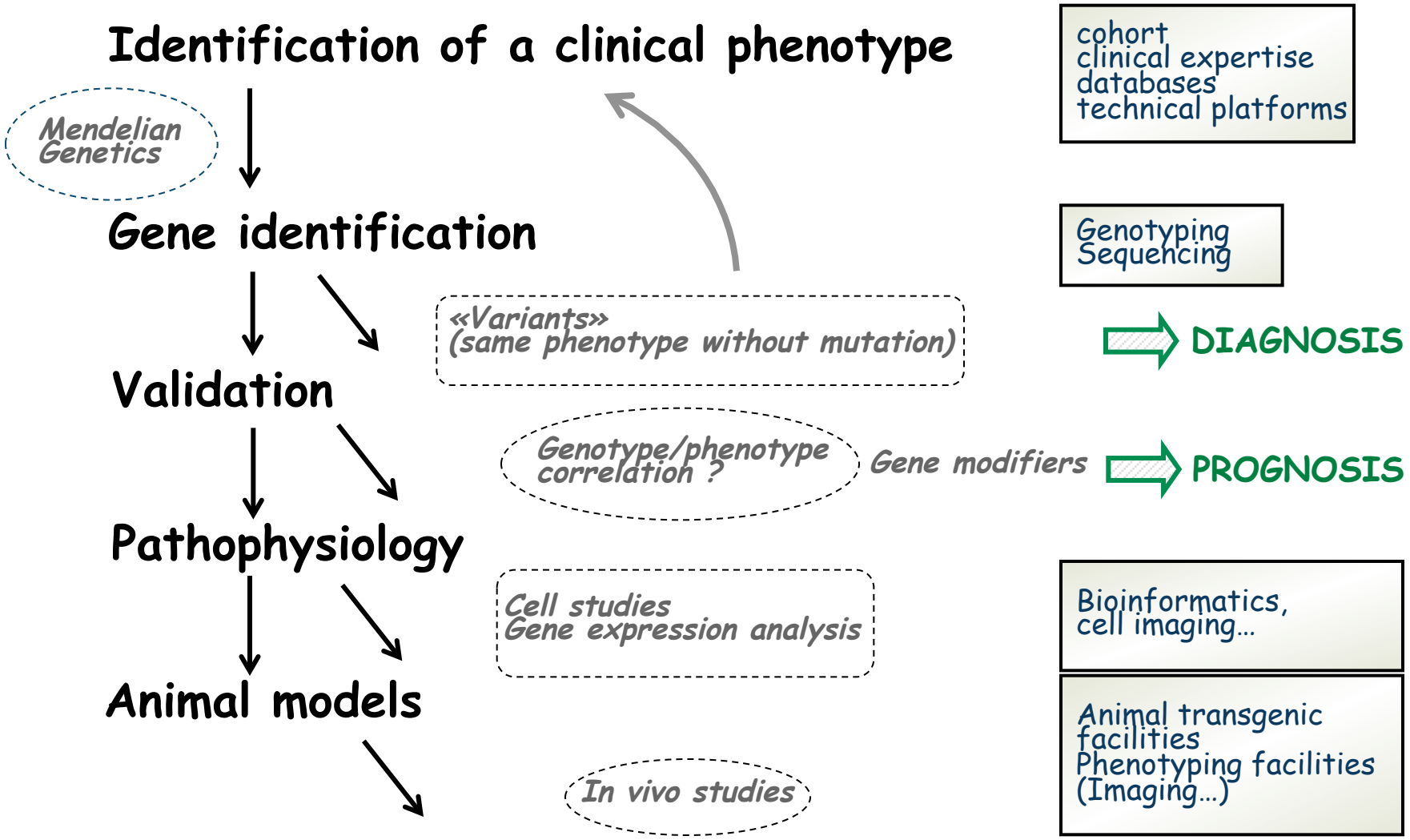
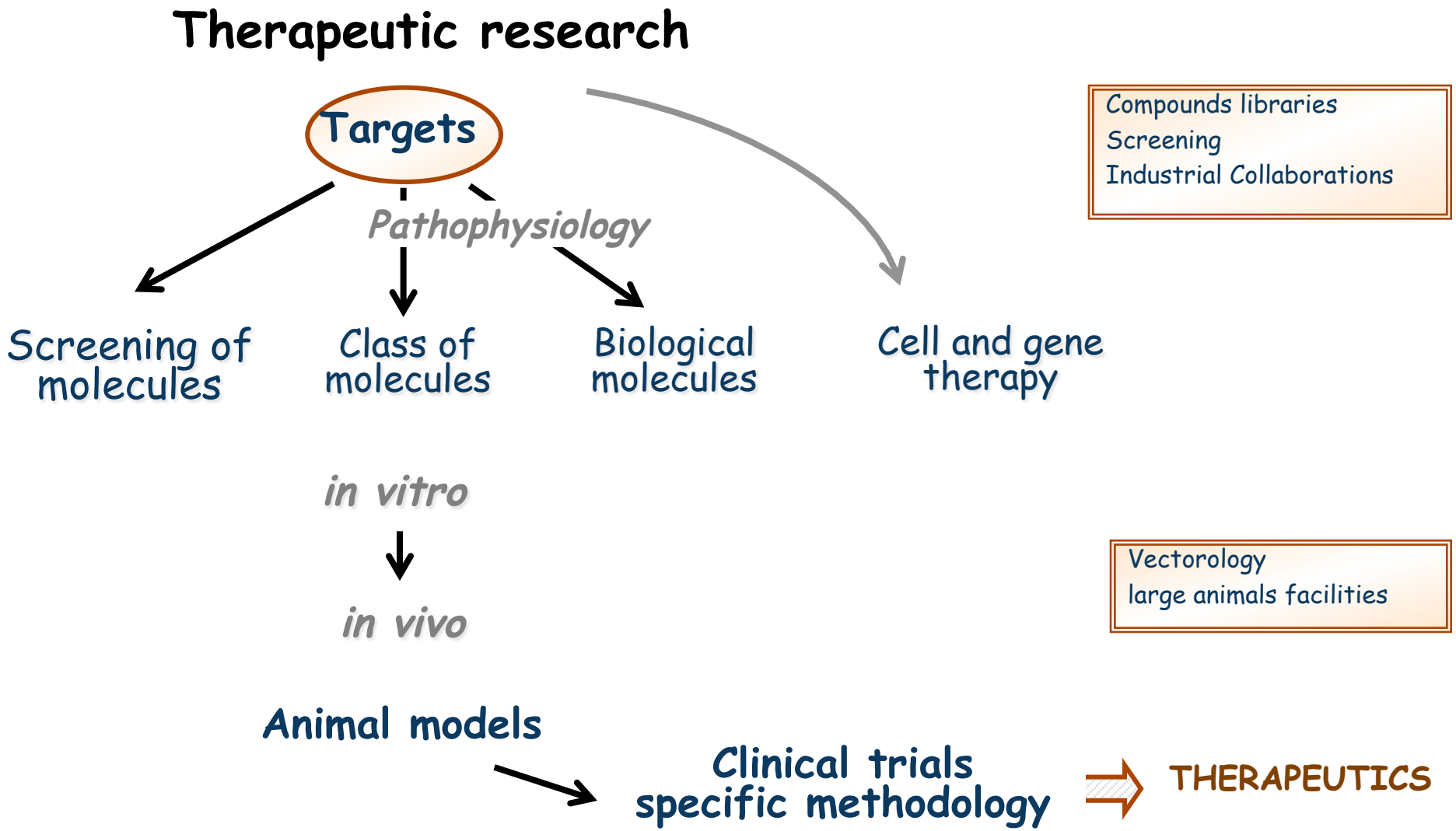
Research on rare diseases follows a long and complex pathway (1)



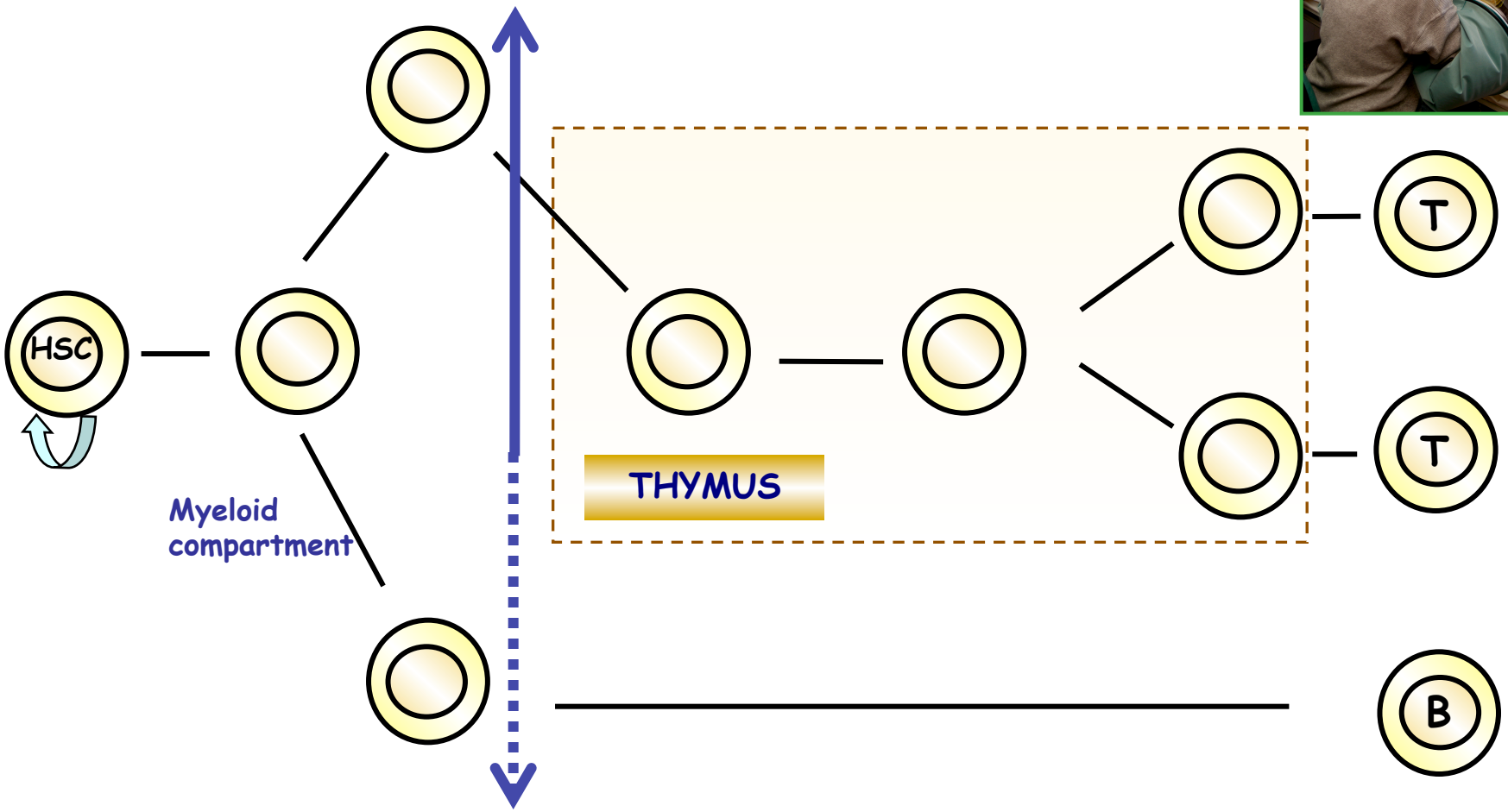
Research on rare diseases follows a long and complex pathway (2)



The "reference center" for primary immunodeficiencies (PID). Necker University Hospital Paris

SCID diseases

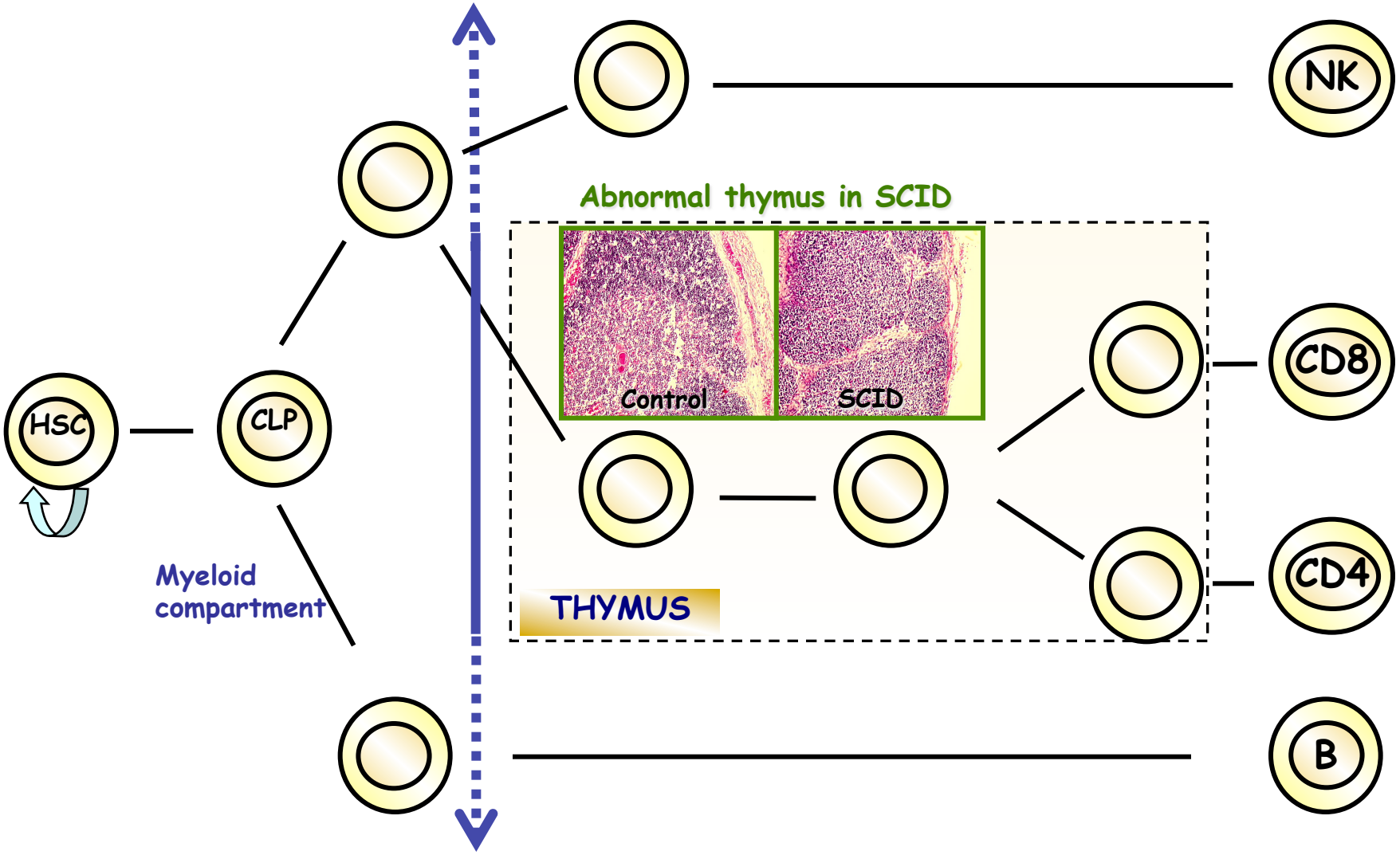
Fatal conditions early in life
X-linked or autosomal recessive inheritance



1970s

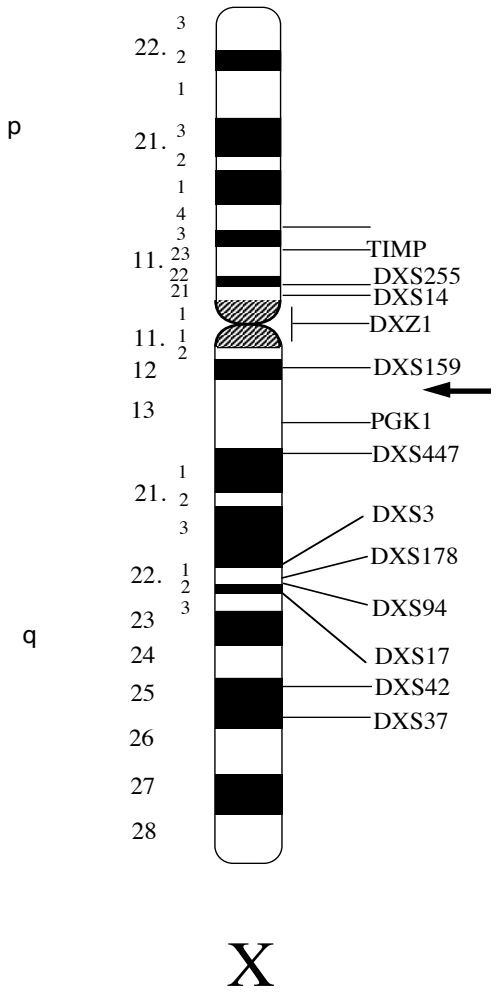
SCID diseases

1985

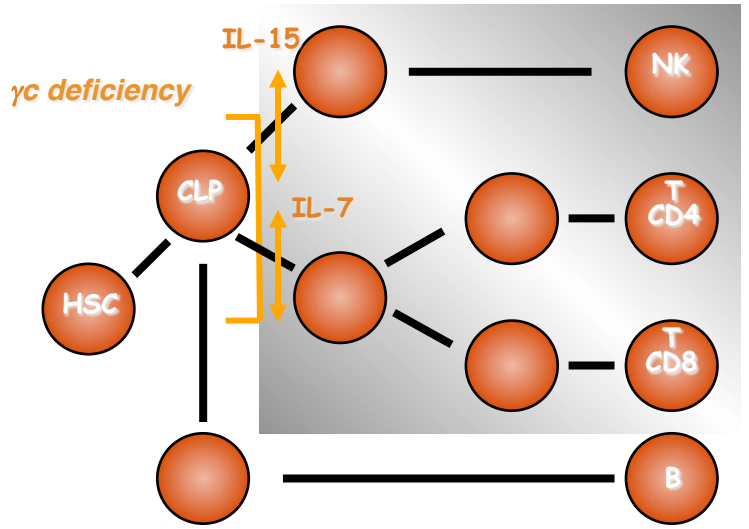


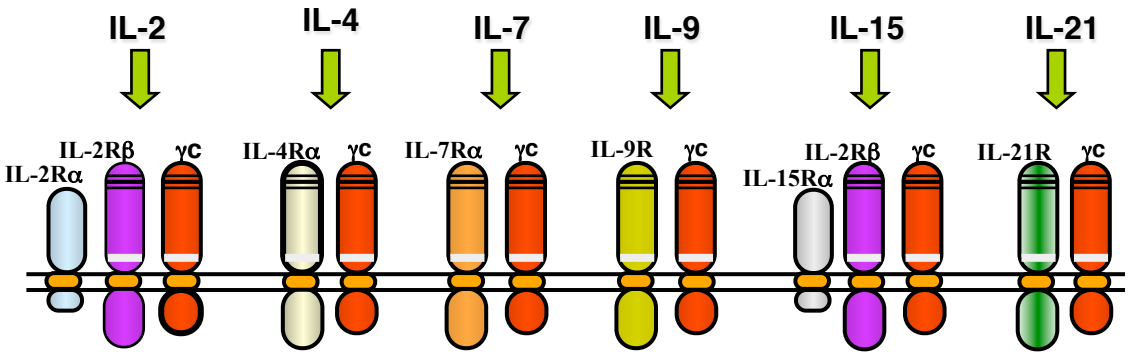
X-linked SCID

1985-1995

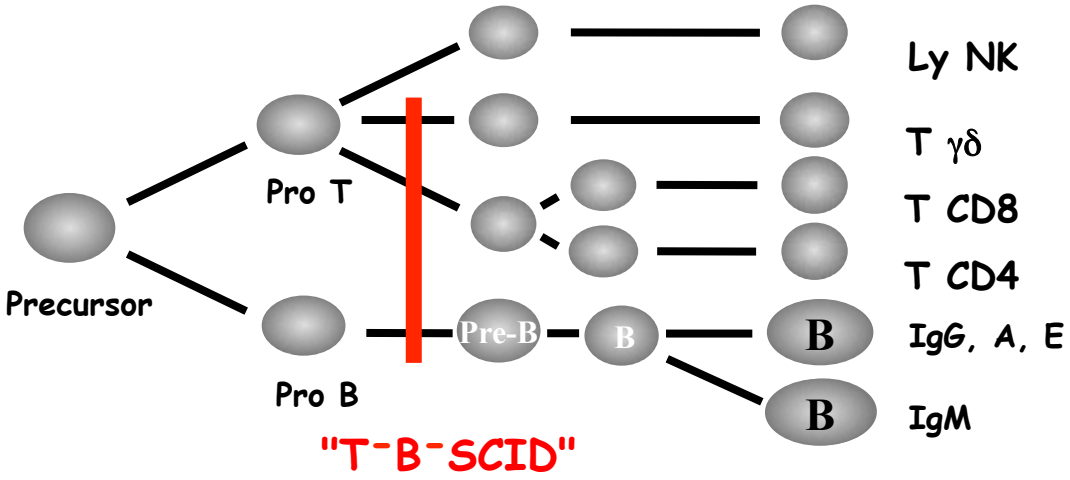


XL-SCID
γc gene

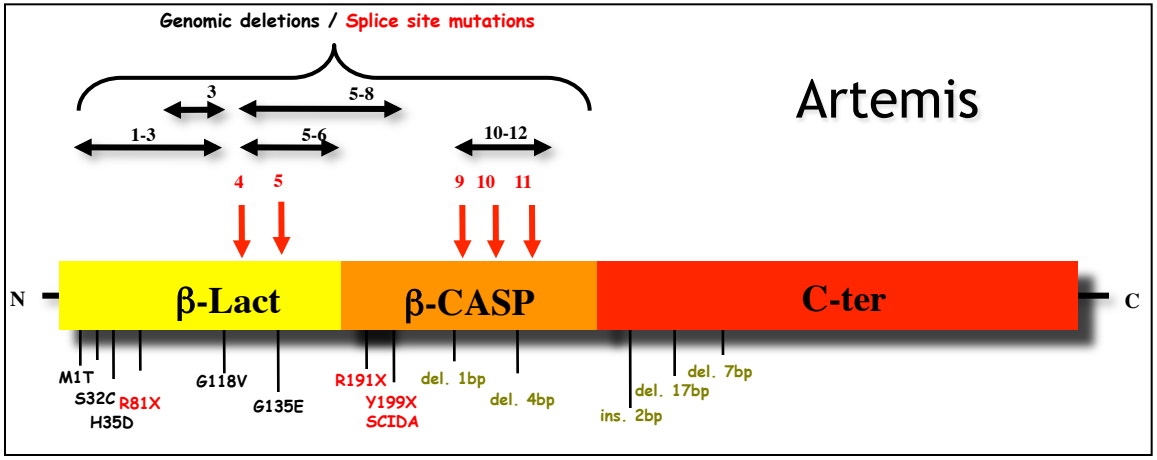


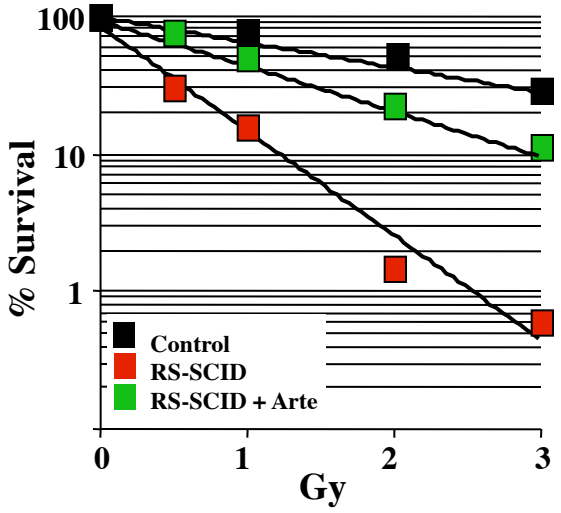


T-B-SCID



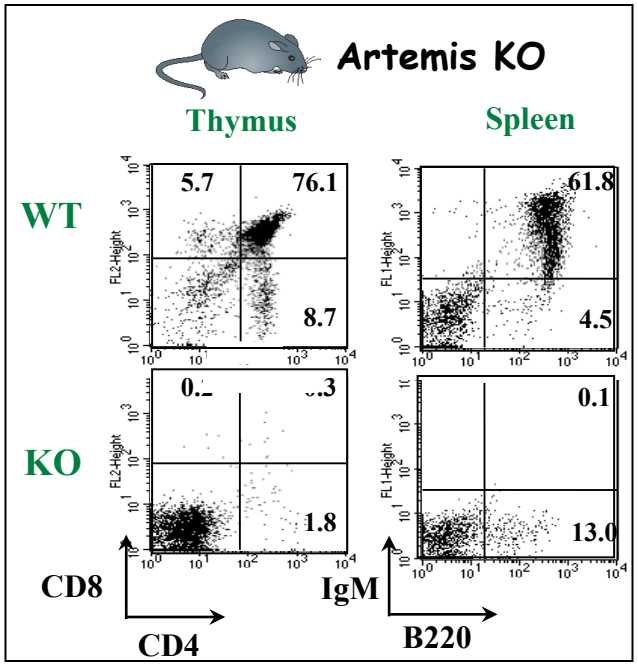
Chr. 10



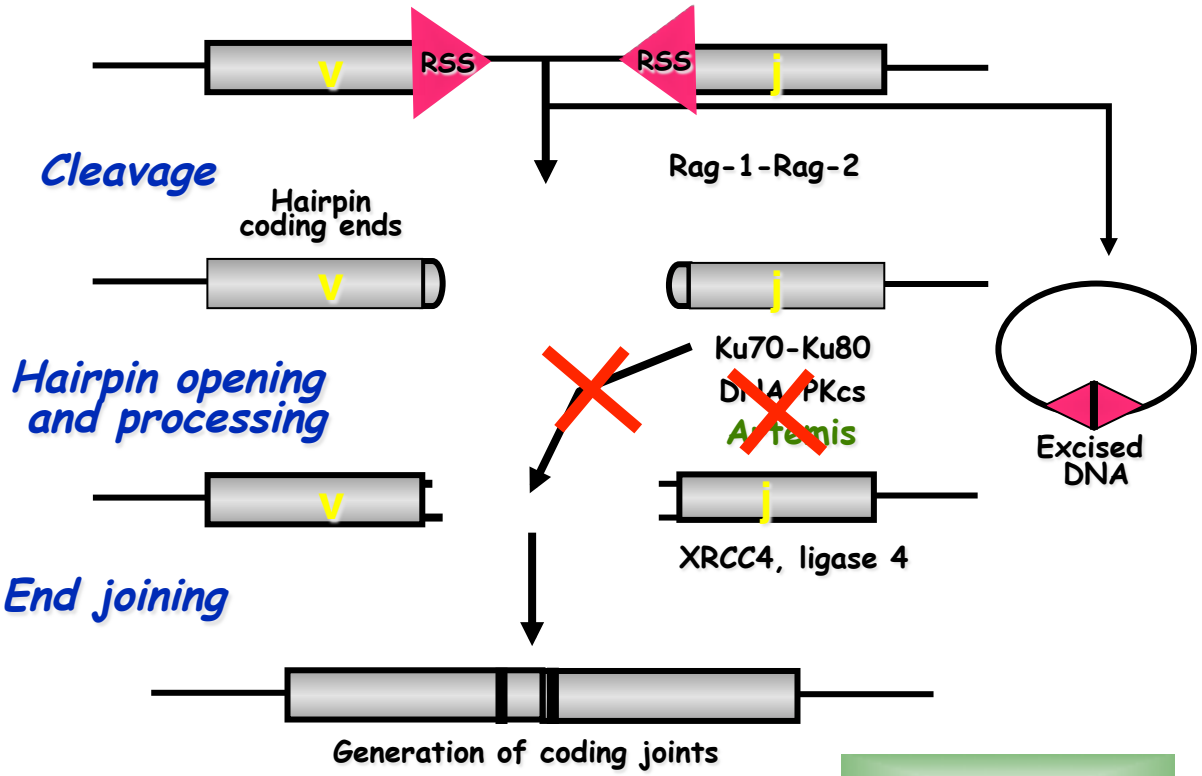


1990-2001

T-B-SCID



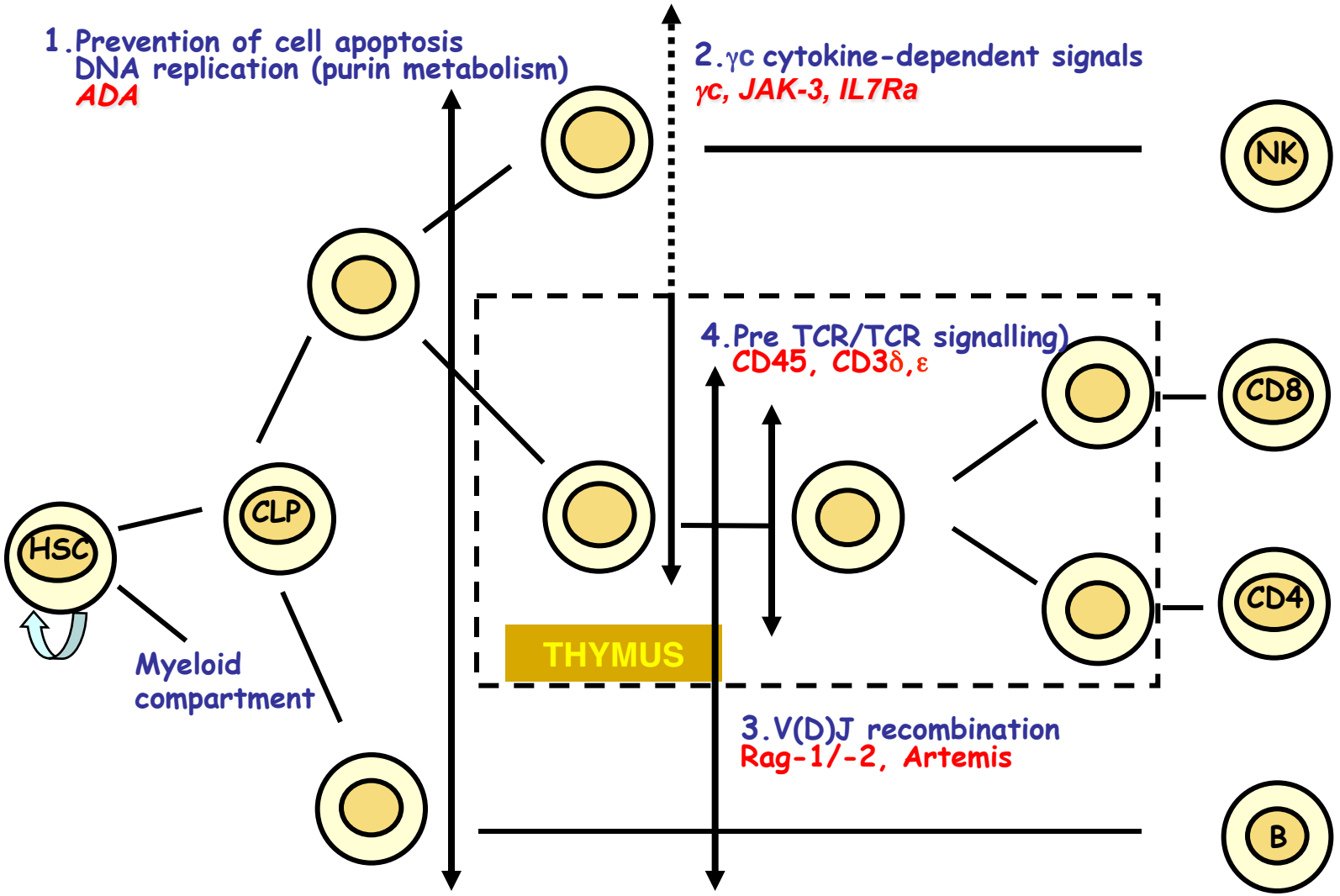
TCR and BCR genes rearrangements during T and B cell differentiation



2001-2004

SCID diseases

2005



More diseases to be described…

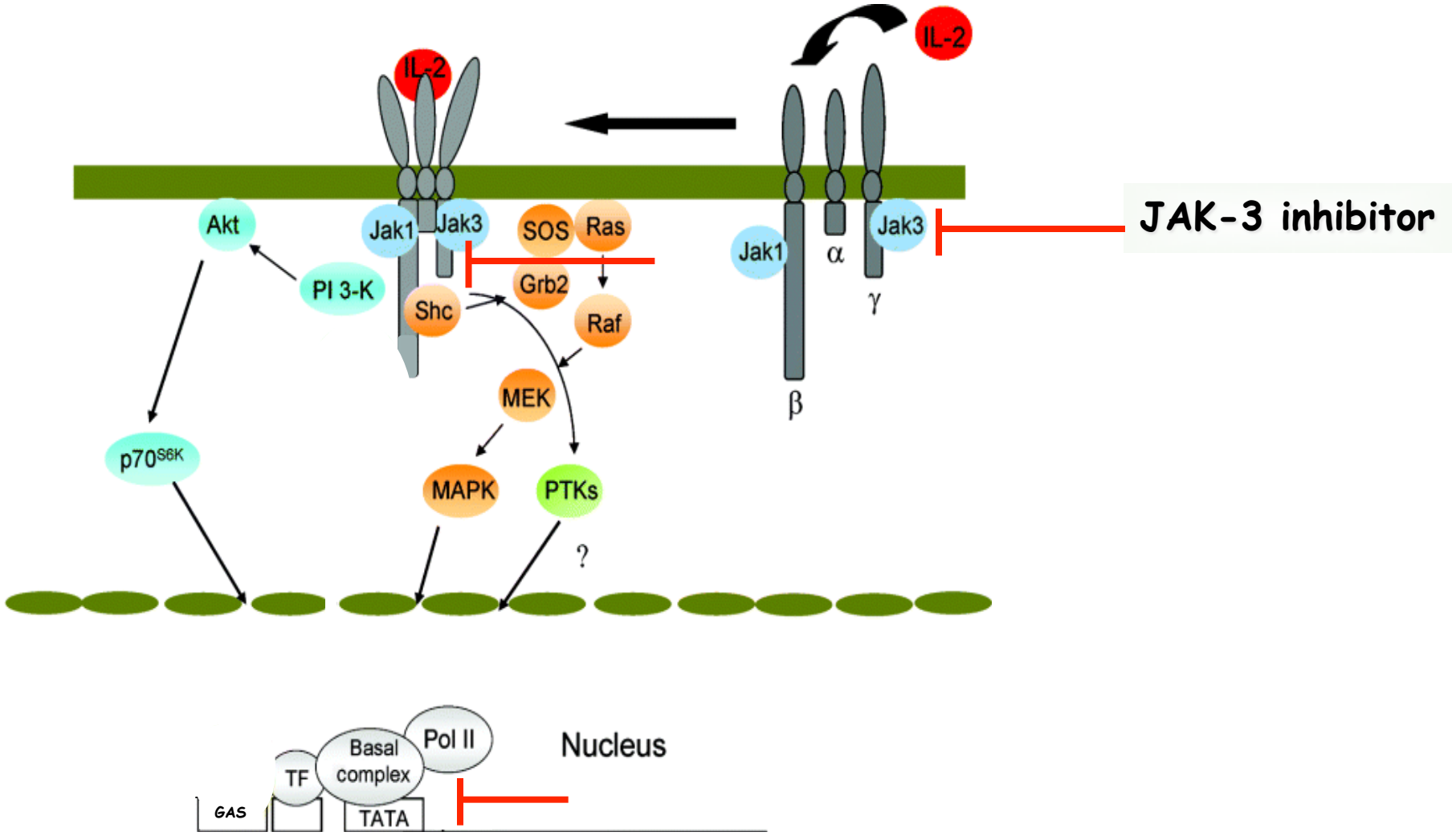
Molecular analysis of SCID conditions, what for ?

1. Basic science: lymphocyte development
2. Molecular diagnosis/genetic counseling
3. Specific therapies: ADA enzyme substitution, gene therapy

4. Design of new drugs:
   . ADA deficiency ⇨ lymphotoxic role of deoxyadenosine
   ↳ 2 chloro deoxyadenosine, a cytotoxic drug used in the treatment of lymphomas

   . γc/JAK-3 deficiencies ⇨ role of JAK-3 in lymphocyte development/survival/function
   ↳ JAK-3 inhibitor as a new immunosuppressive agent used in transplantation…

Schematic representation of a major signaling pathway activated by IL-2

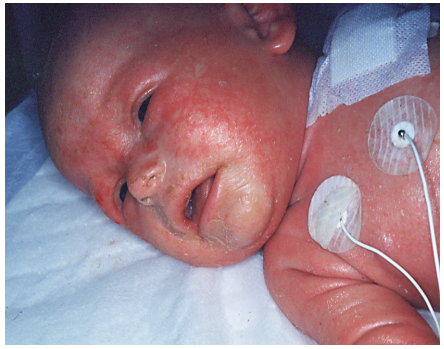


Description of multiple SCID variants

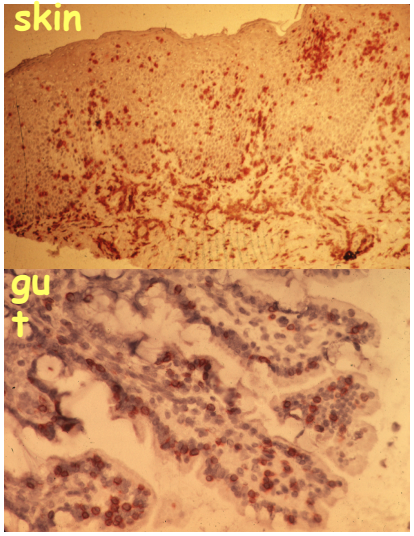
Three examples:

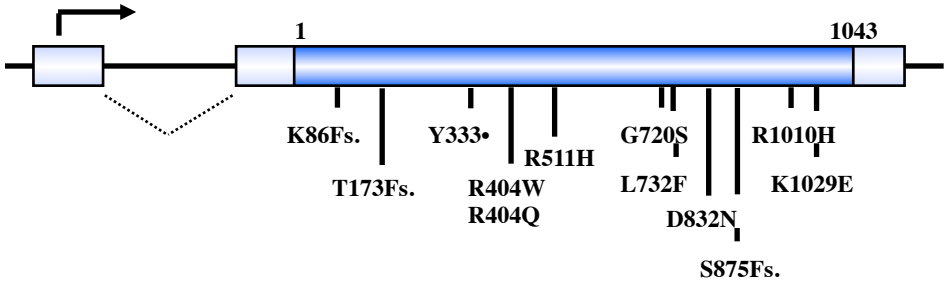
- ⇨ Omenn's syndrome
- ⇨ Hypomorphic mutations of Artemis
- ⇨ Revertant in XL-SCID

Omenn's Syndrome: hypomorphic mutations in Rag-1/2 emergence of autoreactive T cell clones

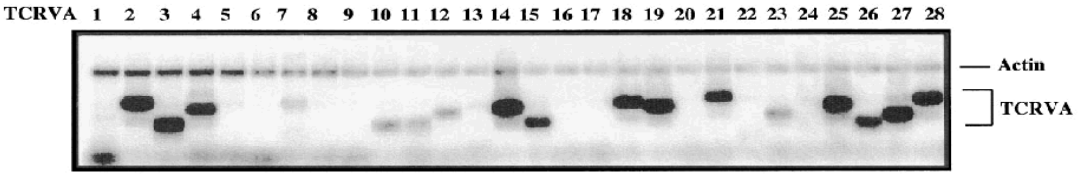


CD3 staining



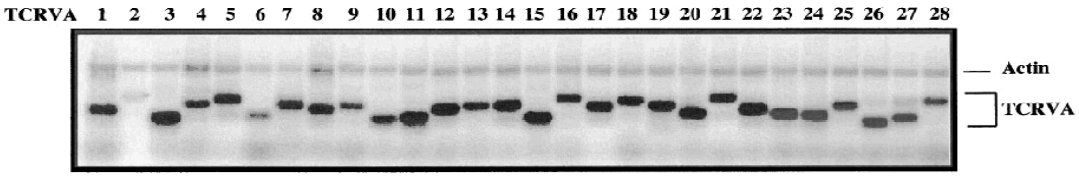


Hypomorphic mutations of Rag-1



Patient

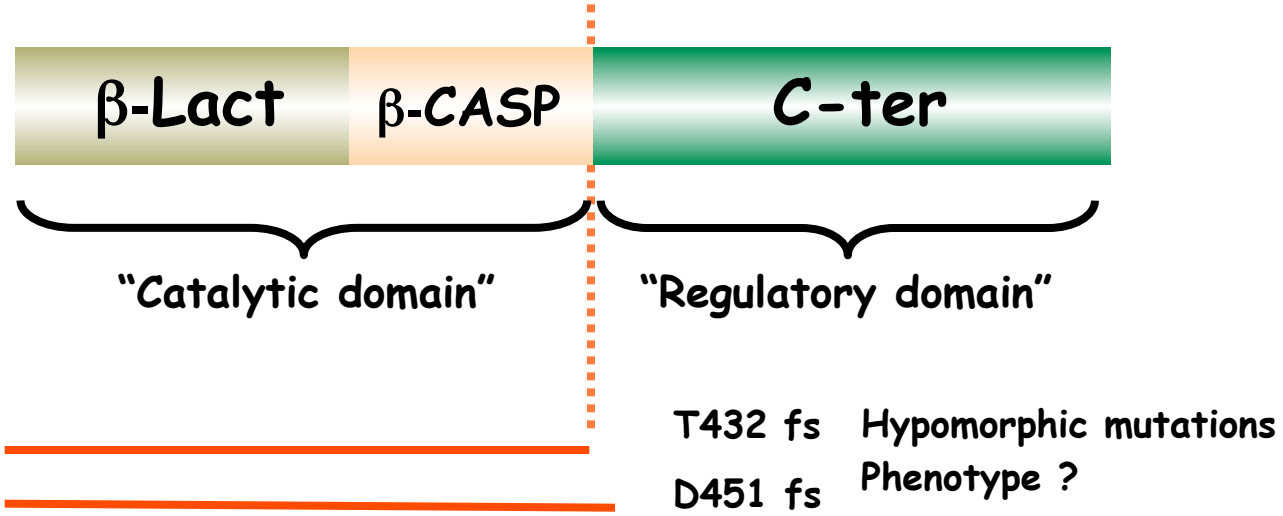
Defective central T cell tolerance



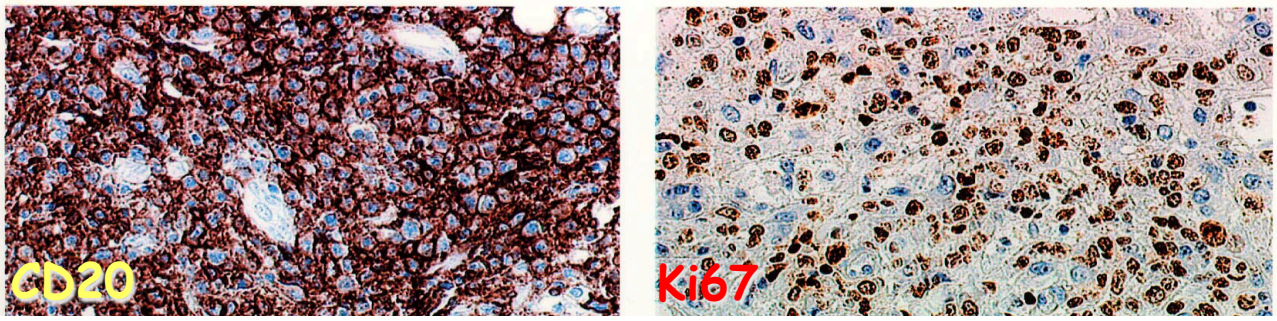
Control

Oligoclonal T cell expansion

Hypomorphic mutations of Artemis associated with B cell lymphomas

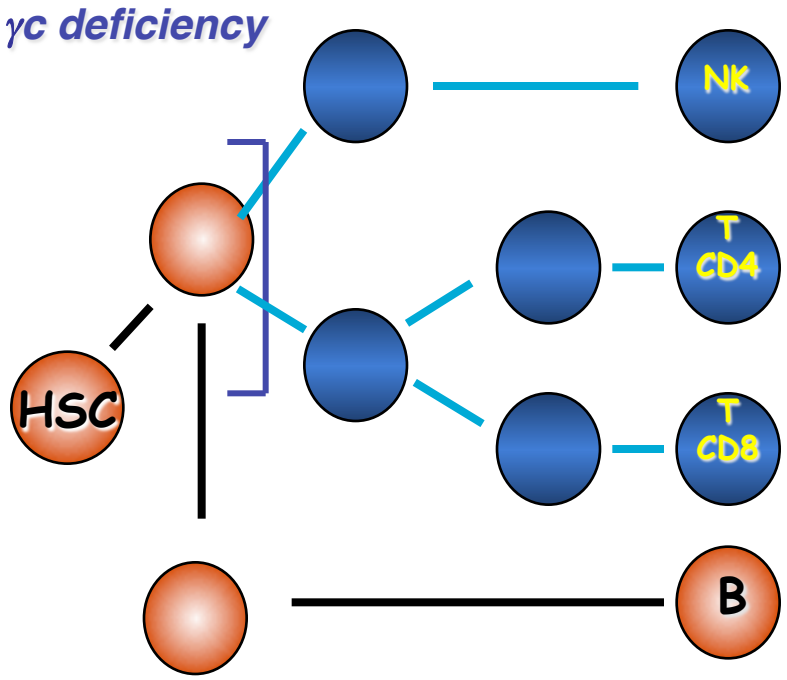


Occurrence of B cell lymphomas

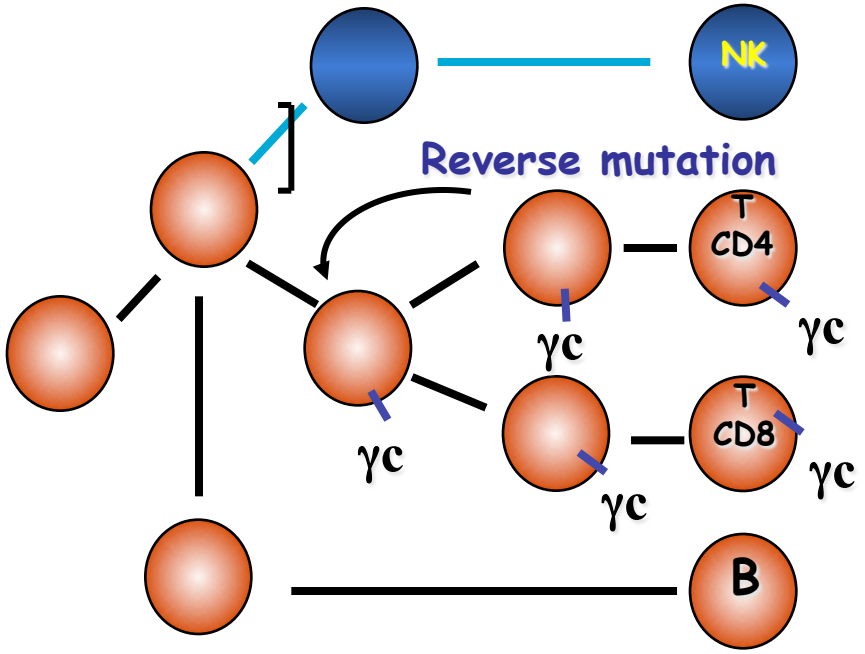


Role of Artemis as a genome caretaker

An atypical case of XL-SCID



Absence of T cells
Absence of NK cells



T cell counts = 50 % of control
memory phenotype
Repertoire diversity generated from one precursor (revertant cell) ?

Revertant analysis

- 1 T cell precursor ⇨ 1 x 10^3 TCRVB clones

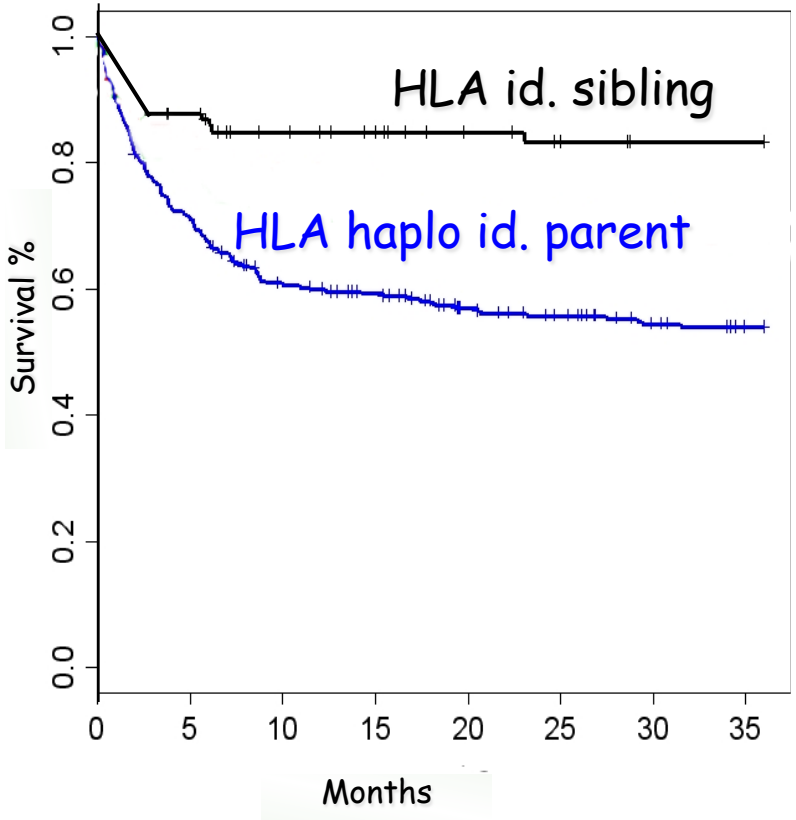
  ≥ 10 to 11 cell division cycles

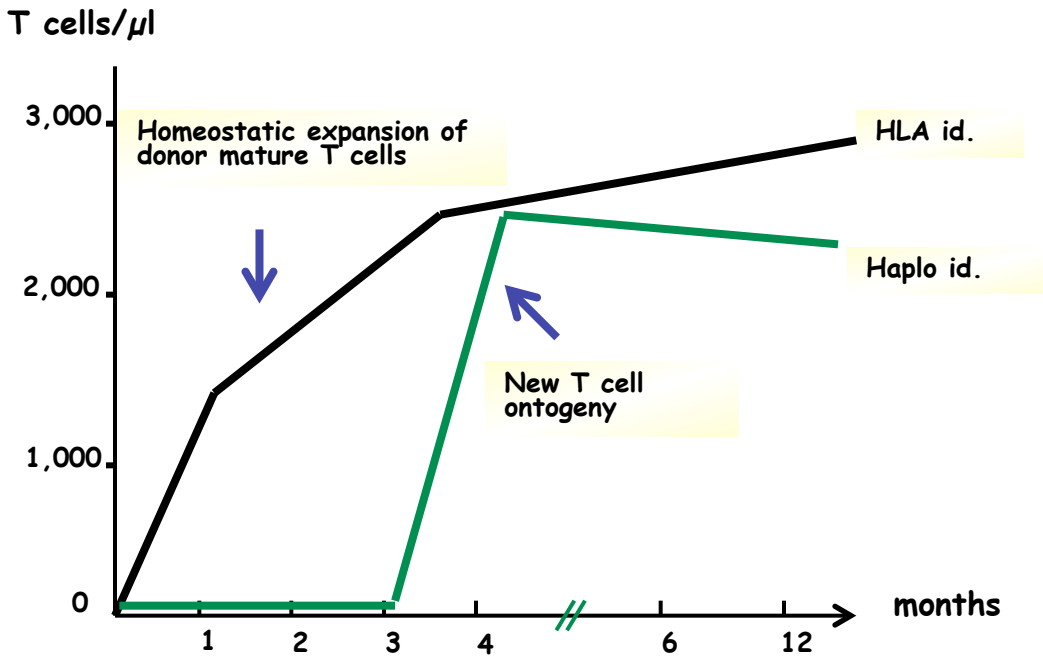
  ~ 1 % of T cell repertoire diversity

A form of natural gene therapy !

Probability of survival in SCID patients after hematopoietic stem cell transplantation according to donor-recipient compatibility

1968: the 1st successful HSCT was achieved in a patient with SCID

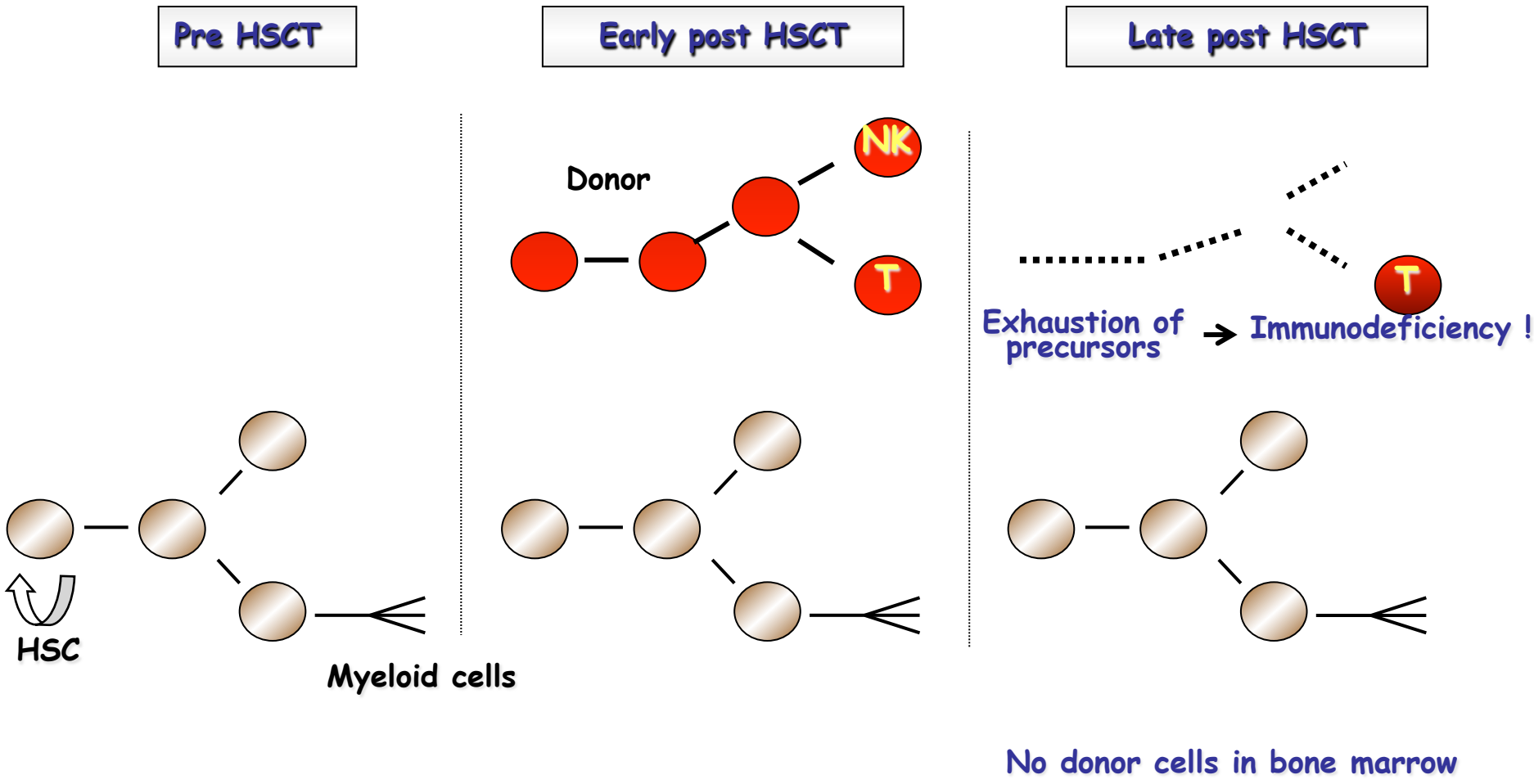




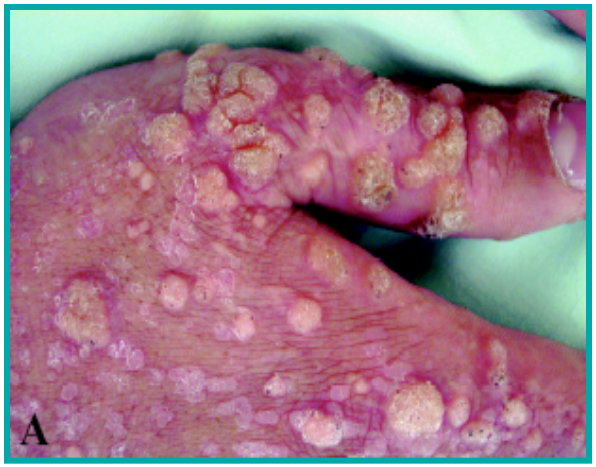
European registry - 464 pts

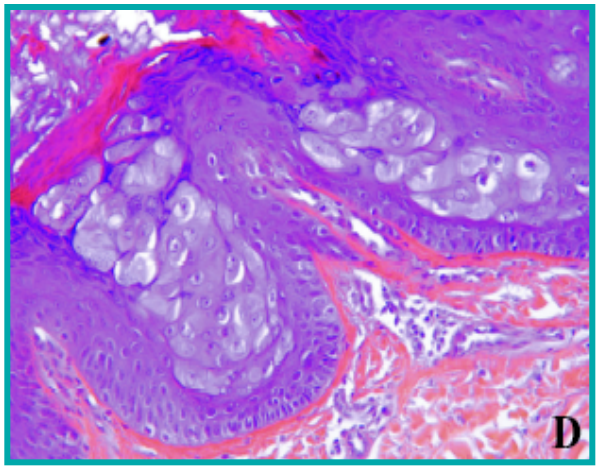
Persisting severe immunodeficiency

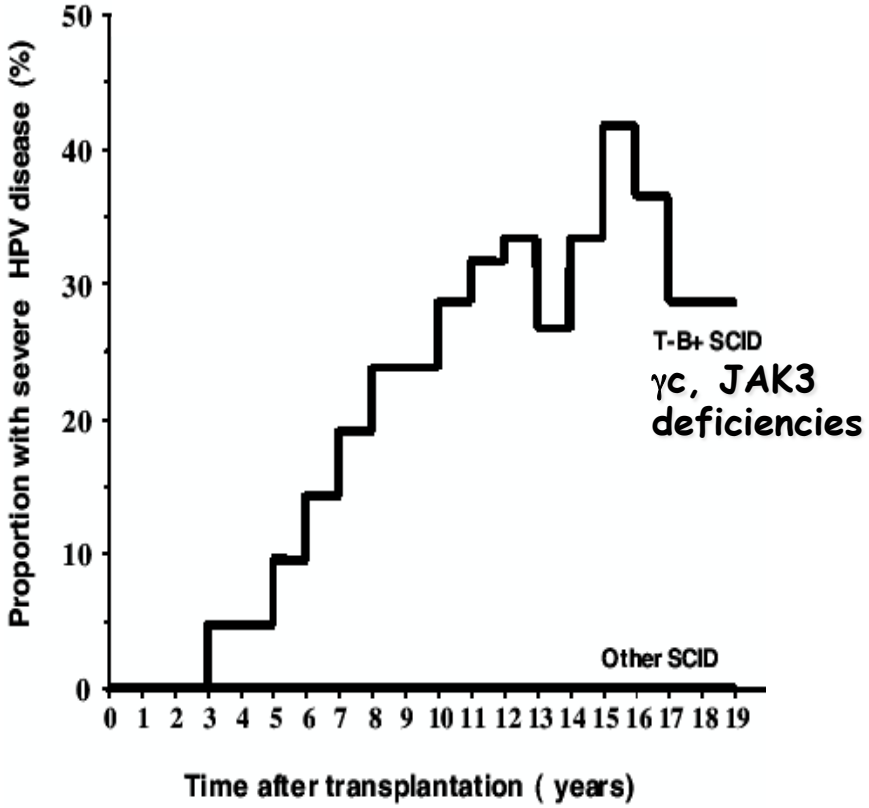
Lymphopoiesis in SCID patients pre/post hematopoietic stem celltransplantation (HSCT)



Occurrence of severe chronic skin HPV disease in SCID patients after HSCT







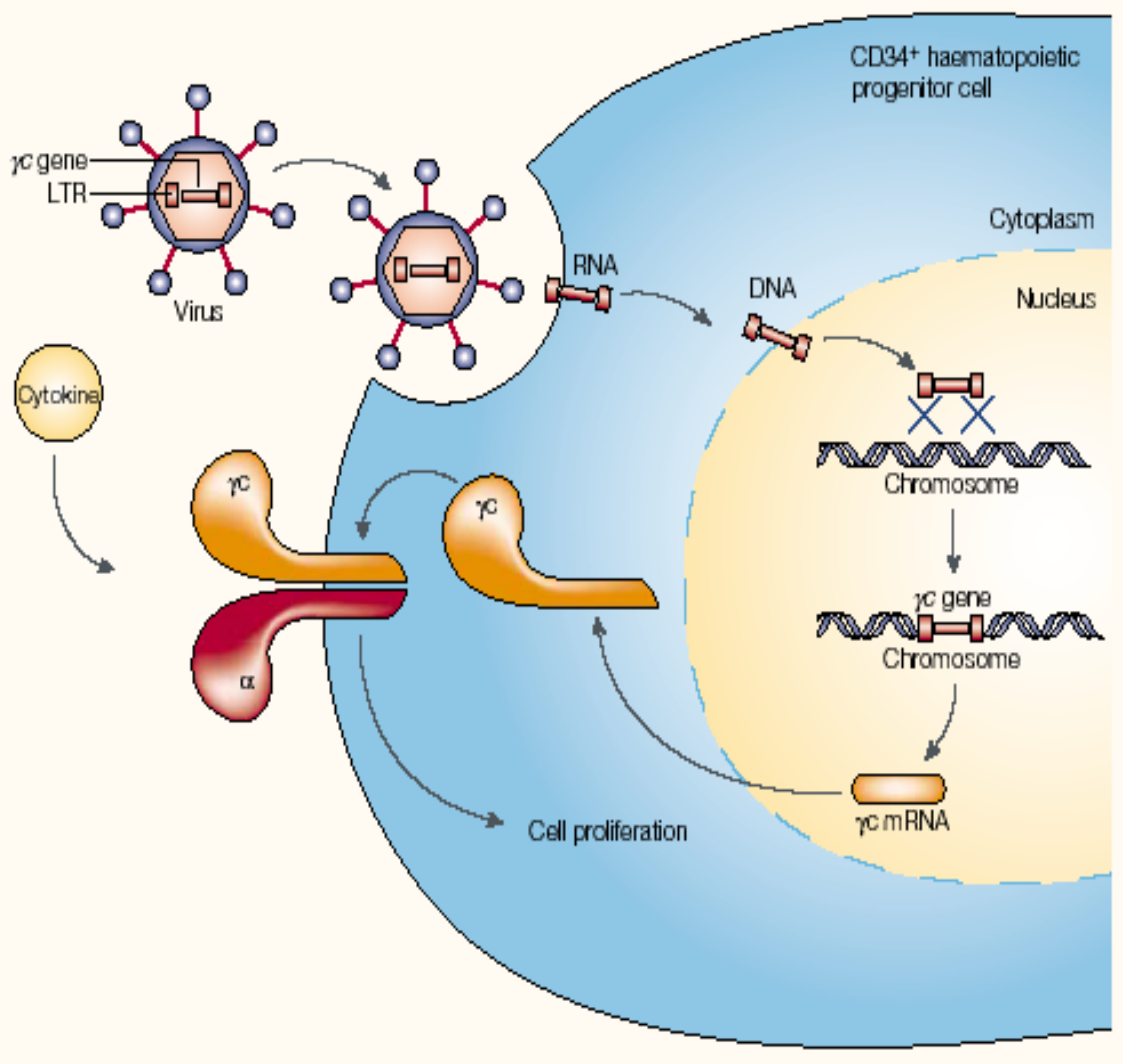
Occurrence of severe chronic skin HPV disease in SCID patients after HSCT

- A significant problem with no simple solution

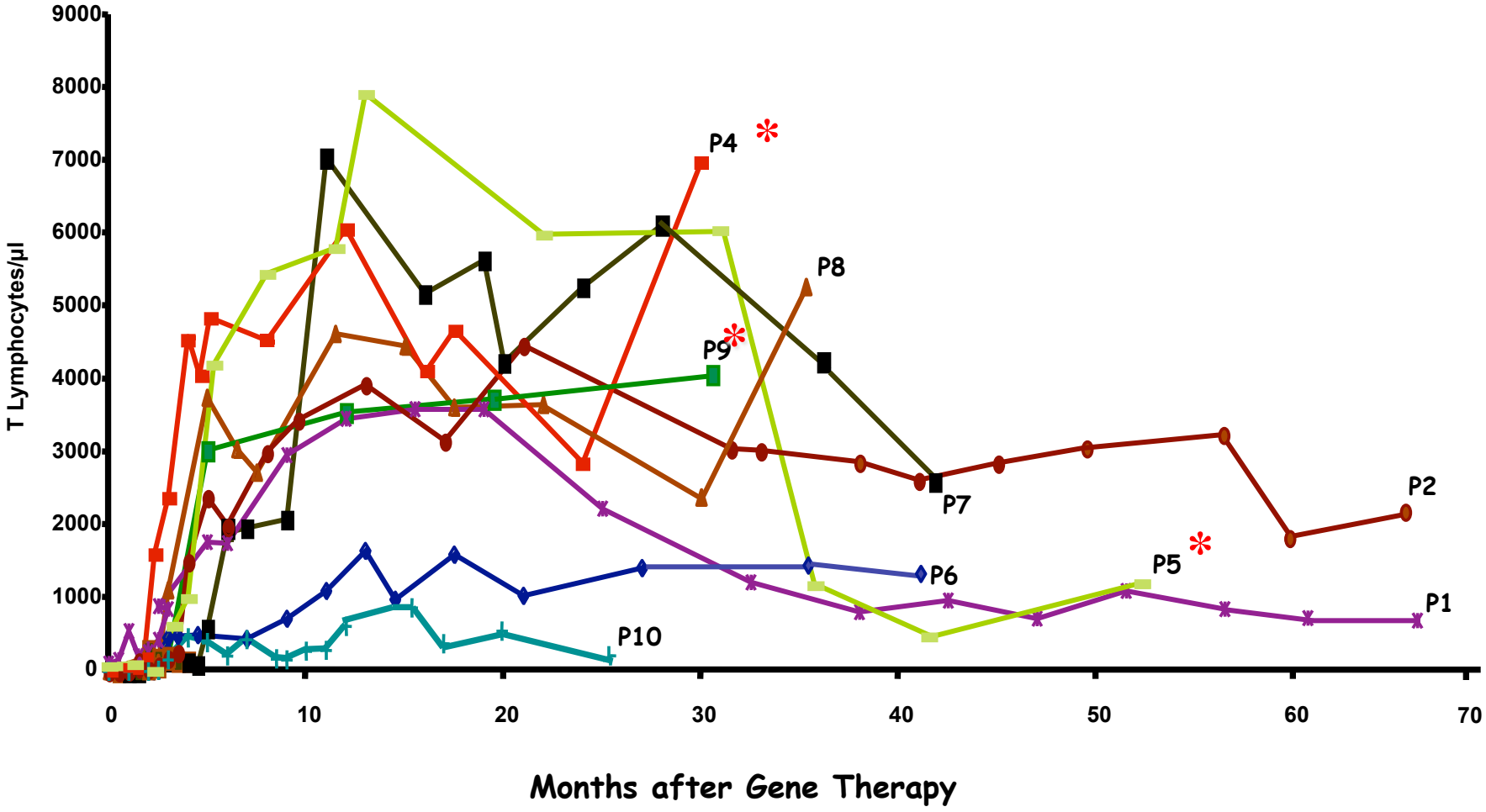
- An unexpected role for γc/JAK-3 cytokine receptor signaling pathways in defense of keratinocytes against papilloma virus

⇨ New therapeutics ?

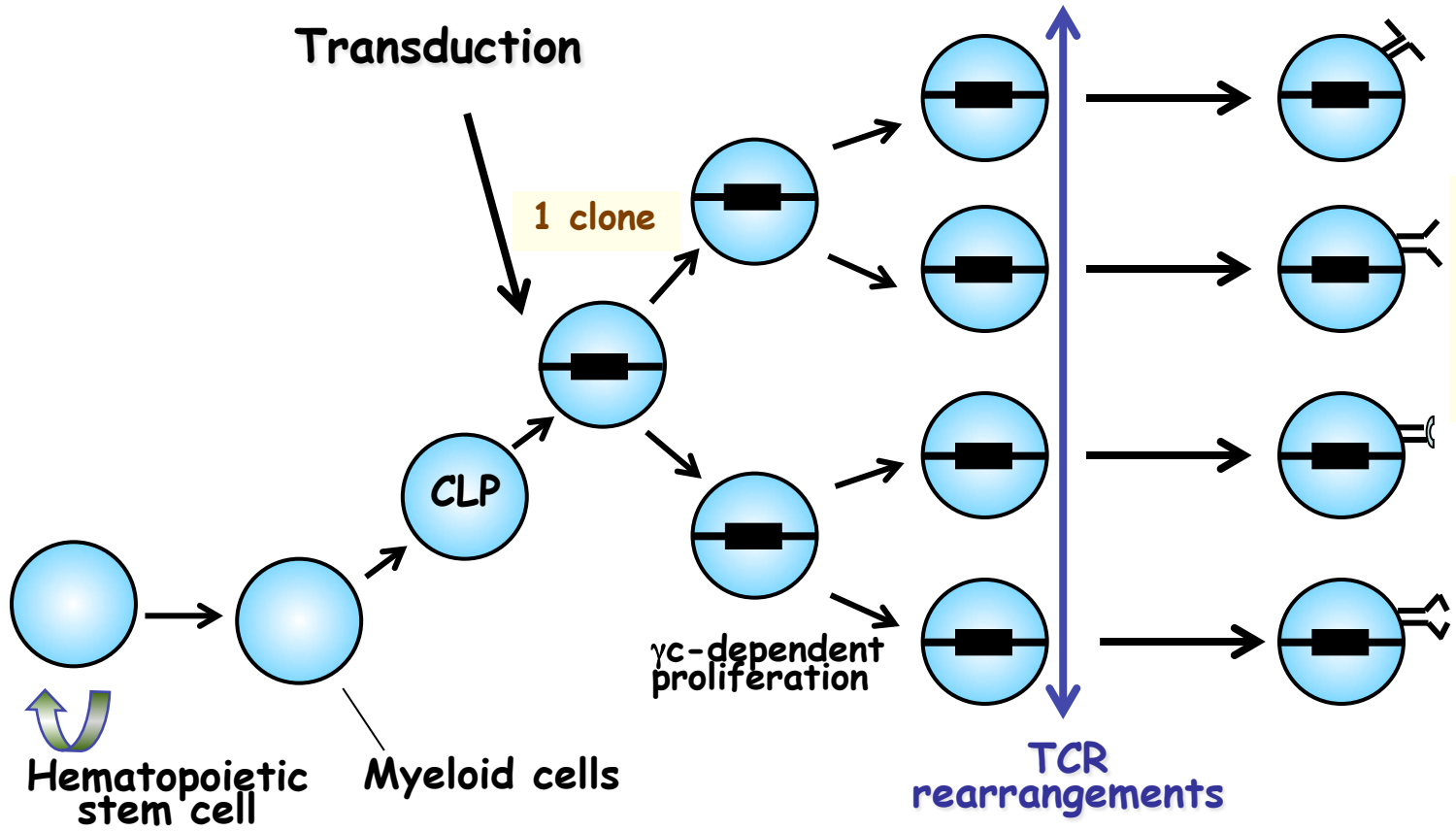
Principle of ex vivo gene therapy of the SCID-X1 condition



T Lymphocytes development after gene therapy of SCID-X1

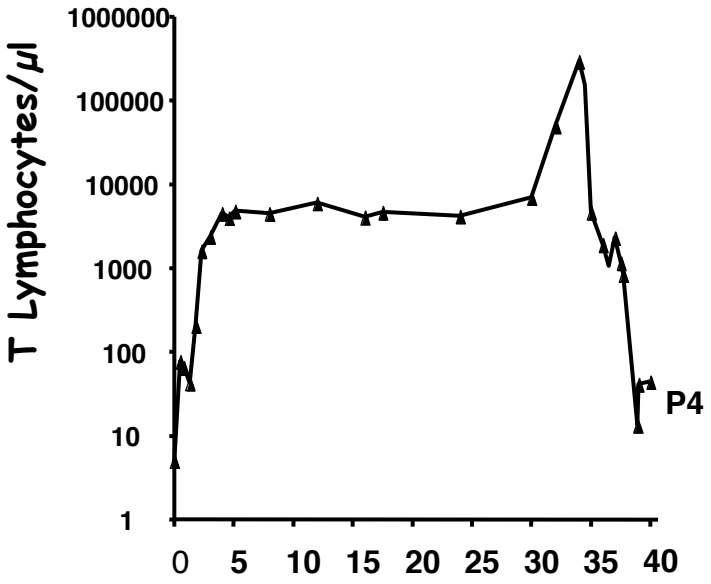


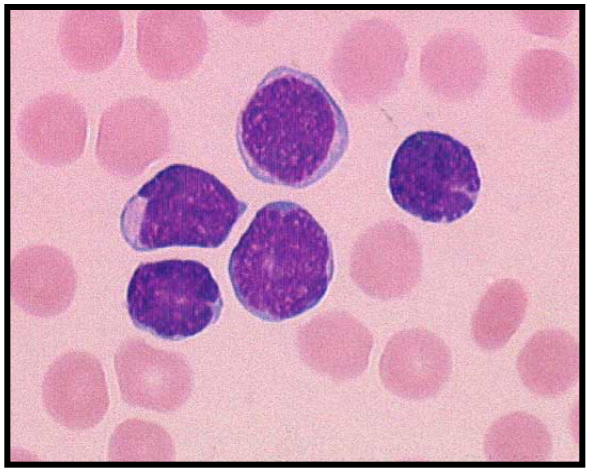
High proliferation rate enables T cell diversification from a few precursors

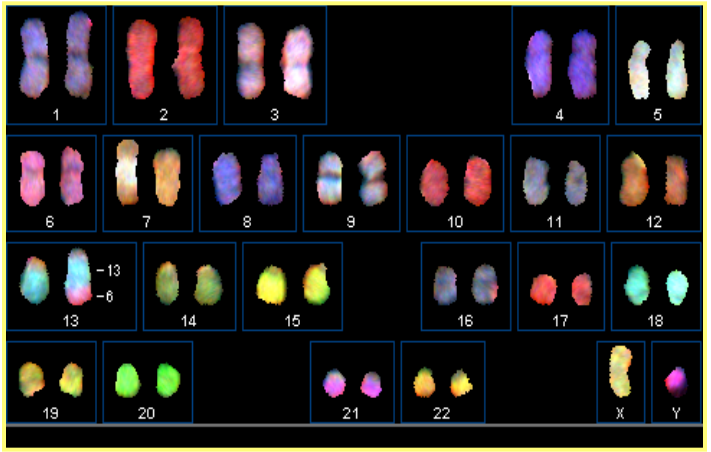


As in the reversion case, oligoclonal lymphopoiesis
⇨ polyclonal repertoire

Monoclonal γδ T cell proliferation P4



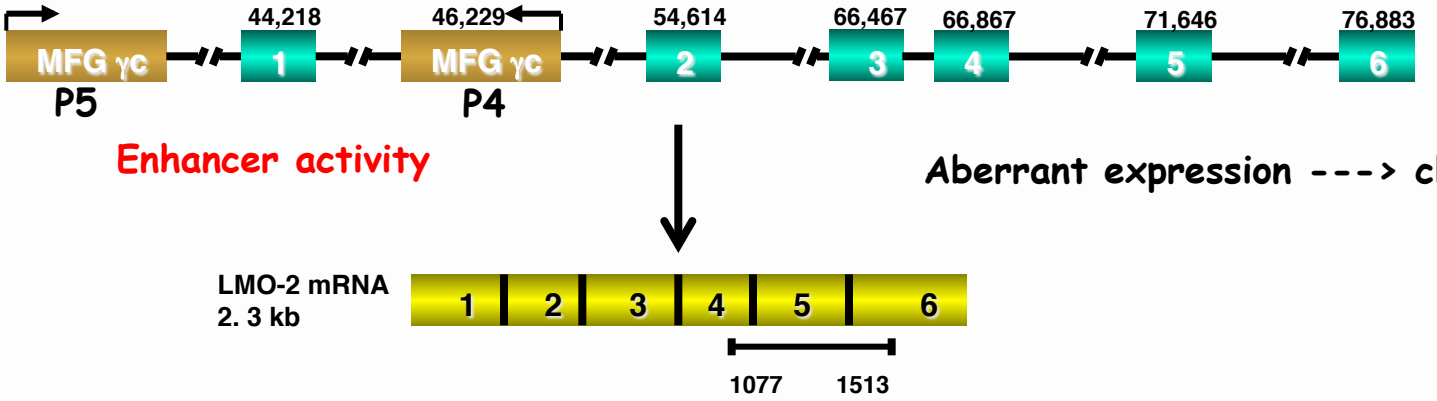


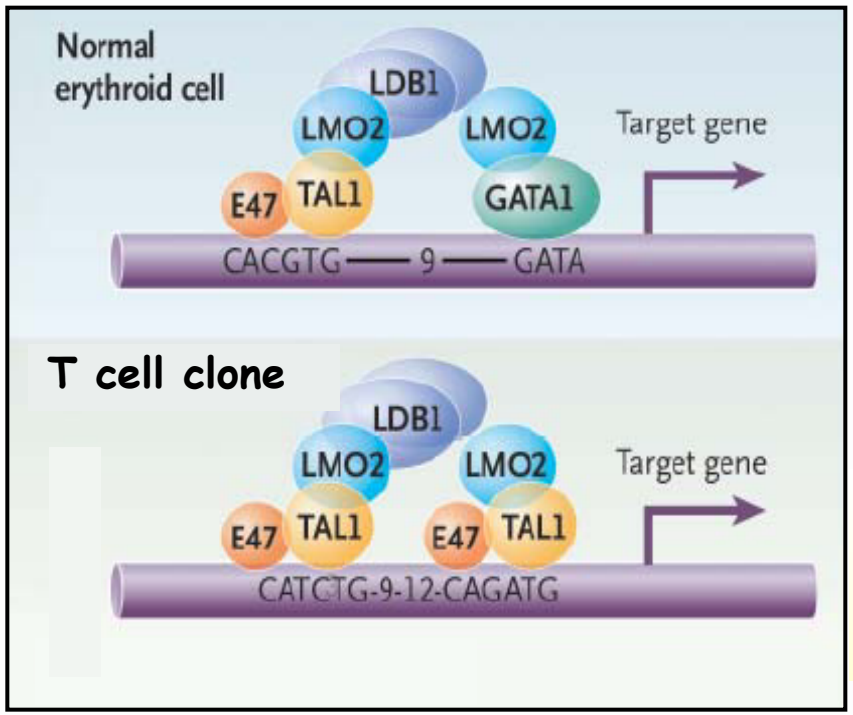


46, XY, 6q21;13qter

- **Monoclonal γ δ T cell clone**

Serious adverse effect caused by retroviral insertional mutagenesis in a protooncogene



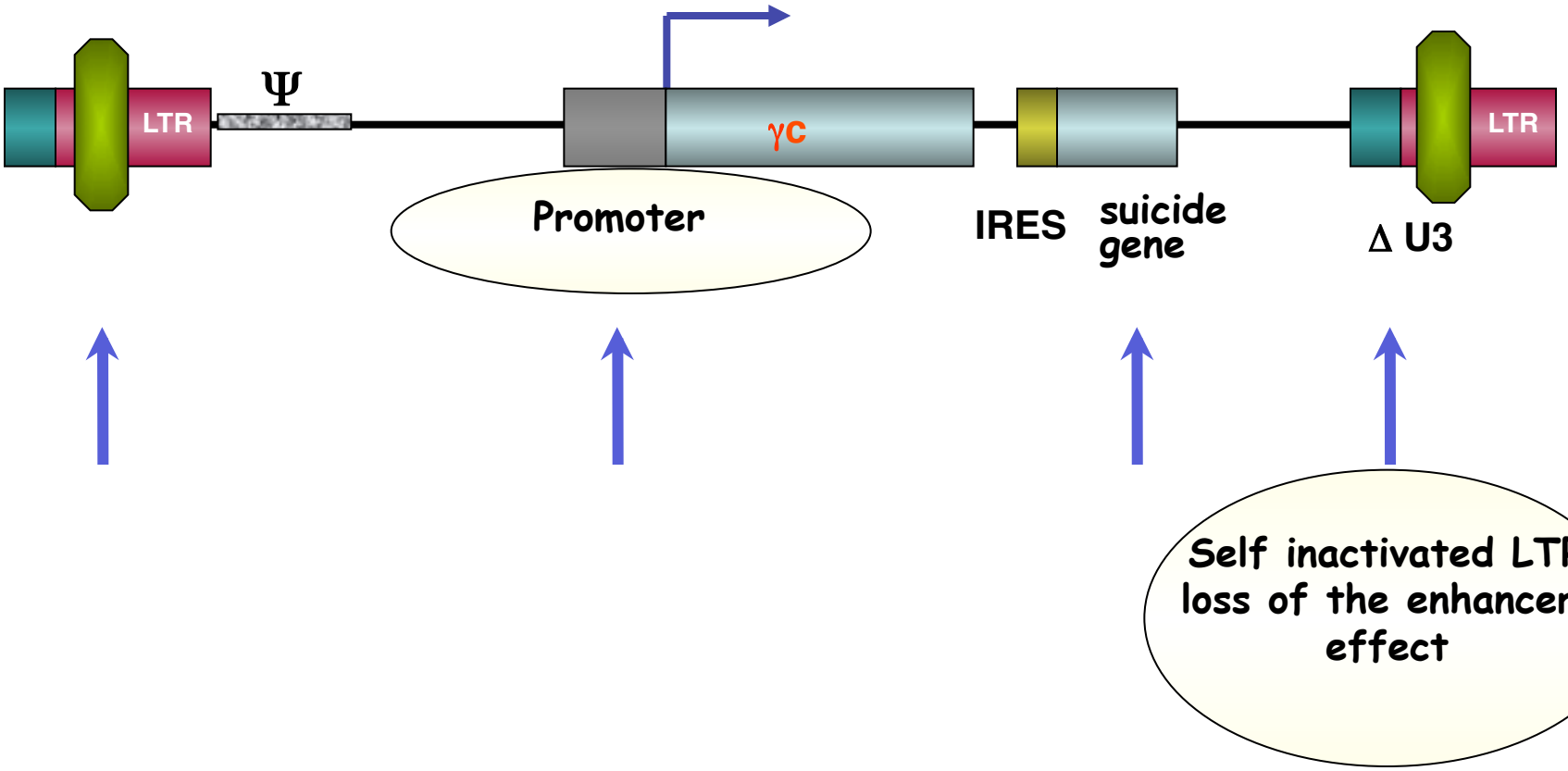


Clonal lymphoproliferation
Synergistic effect with the γc transgene

Conclusion

- Clinical benefit with sustained efficacy
- 6 additional successfully treated patients in UK (A.Thrasher)
  - ⇨ extension to other SCID ?
  - ⇨ ADA deficiency, Rag-1, Rag-2, Artemis deficiencies…
- But… a serious adverse effect
  - ⇨ vector modifications

Vector modifications



Principles for research on rare diseases

- Clinical centers of expertise in limited numbers
  - well studied cohorts of patients
- International collaborative effort
- Multidisciplinary approach
- Impact ⇨
  - basic science
    - . lymphocyte development
  - knowledge and therapy of more common diseases
    - . pathophysiology of papilloma virus disease,
    - . hematopoietic stem cell transplantation,
    - . gene therapy
  - new drugs
    - . treatment of lymphomas, prevention of graft rejection

An European institute supporting research on rare diseases

- To organize disease-reference centers (national/regional), in an european network
- To build a network of platforms available for research projects on rare diseases (genomics,animal house, post genomics, molecular screening…)
- To foster collaboration with pharmaceutical companies.
  - example: the ERDITI initiative

ERDITI: European Rare Diseases Therapeutic Initiative

A public/private partnership

- ⇨ To provide academic teams with an access to a variety of compounds from pharmaceutical companies
  - based on pathophysiological hypotheses
- ⇨ To provide a collaboration process between academic teams and pharma partners

Under the European Science Foundation
Coordinated by GIS – Institut des maladies rares

Partners and supporting institutions

Pharmaceutical partners

- Aventis
- Glaxosmithkline
- Roche
- Servier

Supporting institutions

- **Austria**, *Medical University Vienna*
- **Belgium**, FNRS - *Fonds national de la Recherche Scientifique*
- **Croatia**, *Academy of Science ans Arts*
- **Denmark**, *Medical research council*
- **France**, *CNRS and Inserm*
- **Germany**, *DLR Project managment Organisations – Health research*
- **Netherlands**, *ZonMw, Steering committee on Orphan Drugs*
- **Spain**, *Rare diseases Institute (IIER)*
- **Slovakia**, *Academy of sciences*

A charter of collaboration

- Partnership based on a charter of collaboration
- The charter has 3 sections:
  - working procedure
  - standard material transfer agreement (MTA)
  - standard intellectual property rights agreement
- Assessment by a scientific advisory board
  - analysis of the accuracy of the proposal
  - advices

www.erditi.org

GIS Institut des maladies rares

www.institutmaladiesrares.net