

Gene Therapy for Severe Combined Immunodeficiency Disease

Medrano González, Laura. Genetics Degree (2012 – 2013). Facultat de Biociències, Universitat Autònoma de Barcelona. Catalonia, Spain.



Scientific Dissemination
<http://medranogonzalezlaura.wix.com/scid>

INTRODUCTION

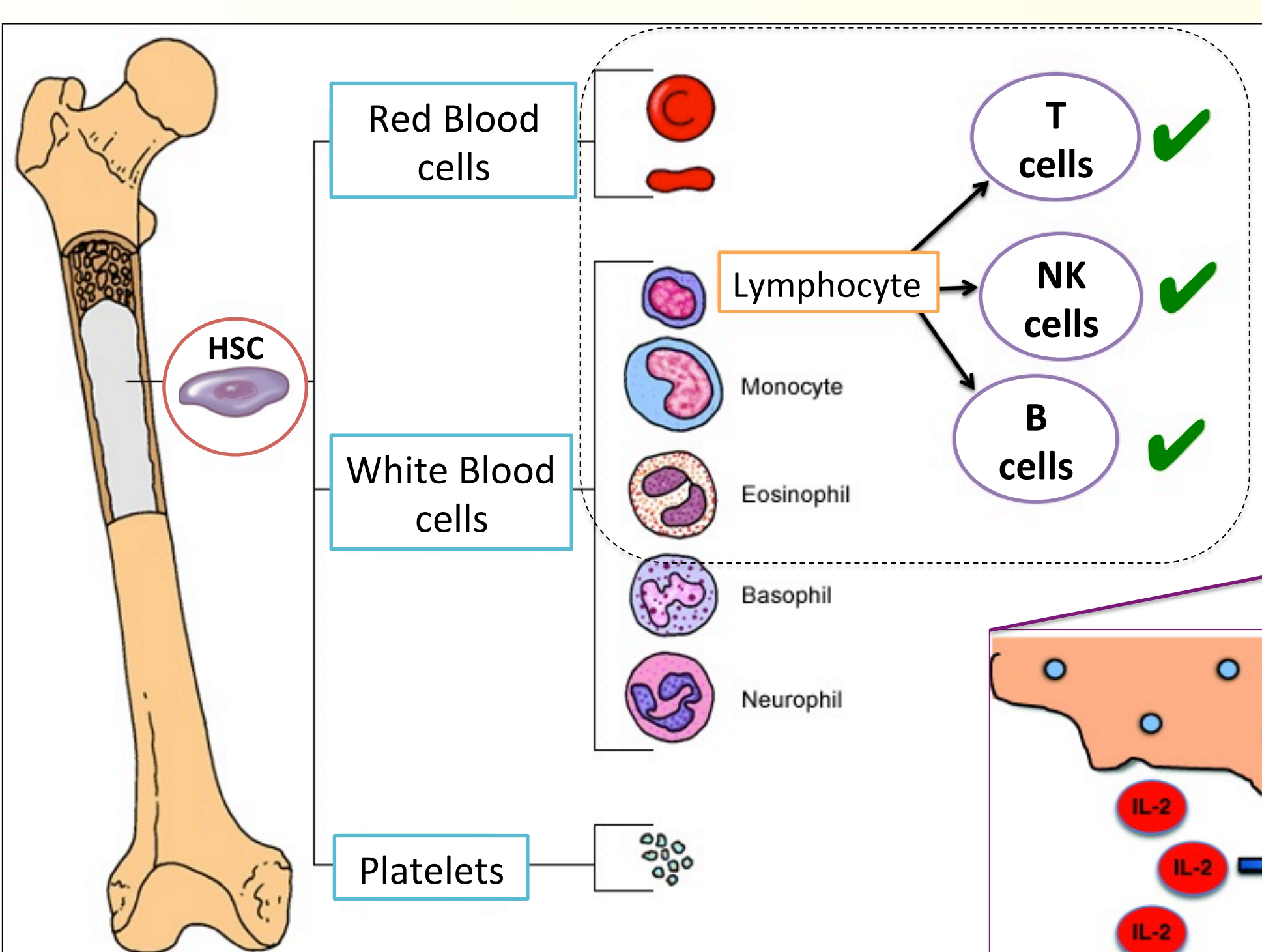
Severe combined immunodeficiency (SCID) is a syndrome caused by complex genetic disorders that usually results in the onset of one or more serious infections within the first few months of life. These infections are serious and could be lethal without treatment. SCID can be cured by allogeneic hematopoietic stem cell transplantation. This treatment strategy is highly successful when an HLA-matched sibling donor is available, but if not, few therapeutic options exist. Gene-modified, autologous bone marrow transplantation can circumvent the severe immunological complications that occur when a related HLA-mismatched donor is used and thus represents an attractive alternative. Several patients affected by SCID have received hematopoietic stem cell gene therapy in the last years. The aim of this work is summarize the advantages and limitations associated with the use of gene therapy to cure SCID and discuss the pros and cons of gene therapy in comparison to allogeneic transplantation.

Severe Combined Immunodeficiency Disease

SCID is considered one of the most serious primary immunodeficiency diseases. SCID is a rare, inherited condition resulting in a weak immune system that is unable to fight off even mild infections. Comprise a number of rare genetic disorders that affects the function of T cells. There are several forms of SCID. Depending on the type of SCID, B cells and NK cells can also be affected. These cells play important roles in helping the immune system battle bacteria, viruses and fungi that cause infections. The overall frequency of SCIDs is estimated at 1:100,000 live births. The most common type is linked to a mutation in a gene localized on the X chromosome (SCID-X1). Other common form of SCID is caused by a deficiency of the enzyme adenosine deaminase (ADA).

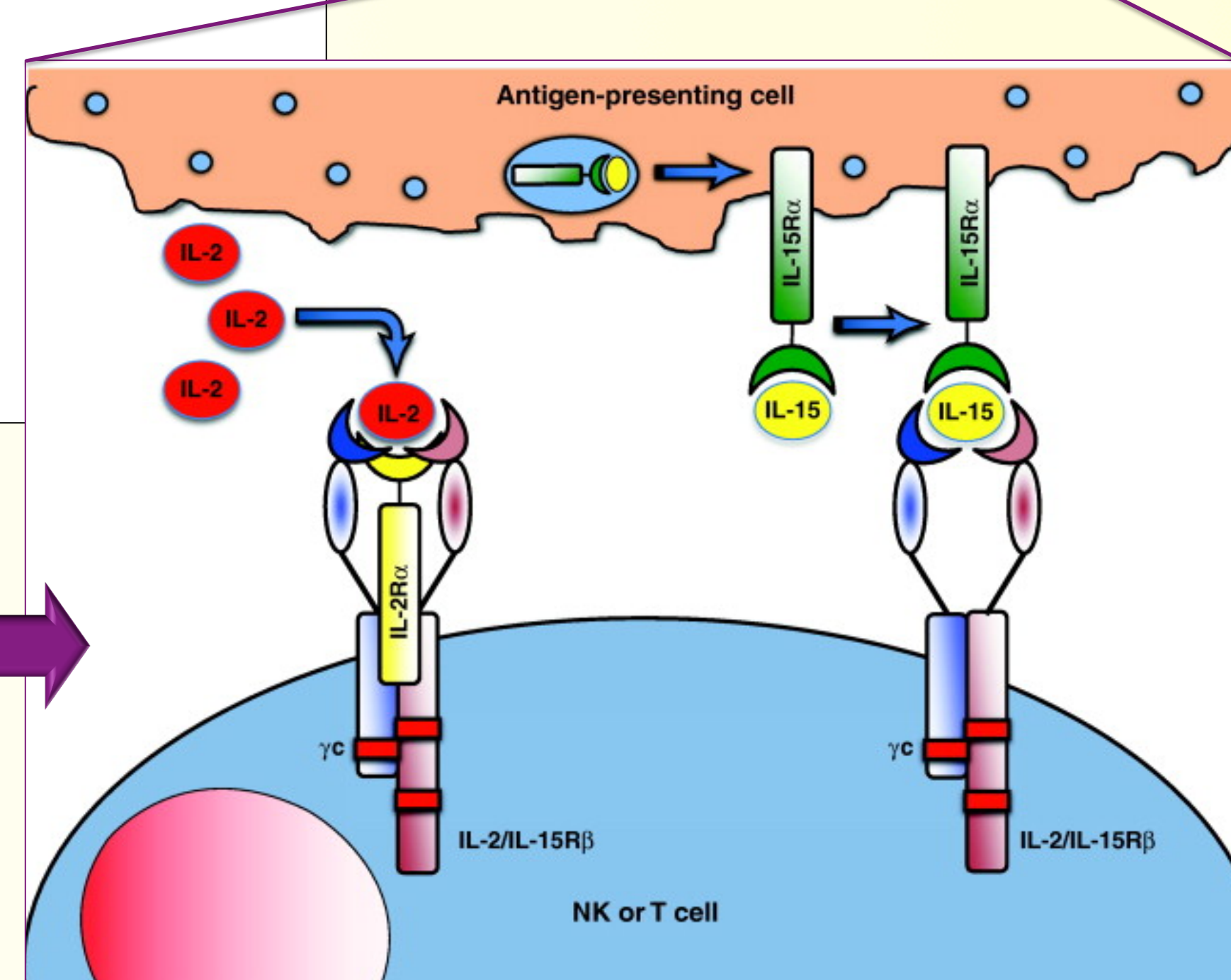
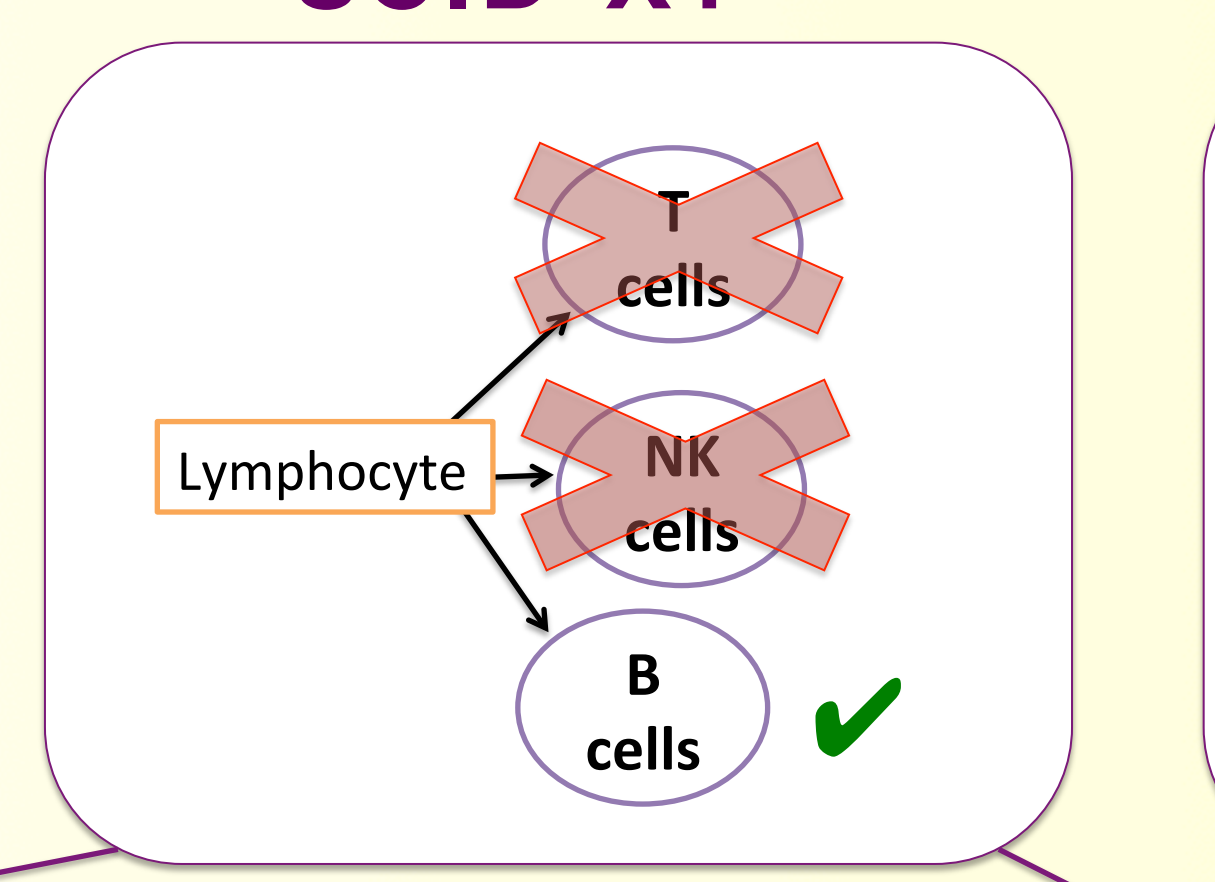
Gene therapy is a form of molecular medicine based on the addition of a corrected copy of a gene to the somatic cells of an individual in order to cure or to alleviate his/her disease. This strategy may provide new treatments for a large number of inherited diseases in the near future. The practical use of gene therapy is currently limited to 2 cell types: accessible stem cells and terminally differentiated, postmitotic, long-lived cells.

Normal

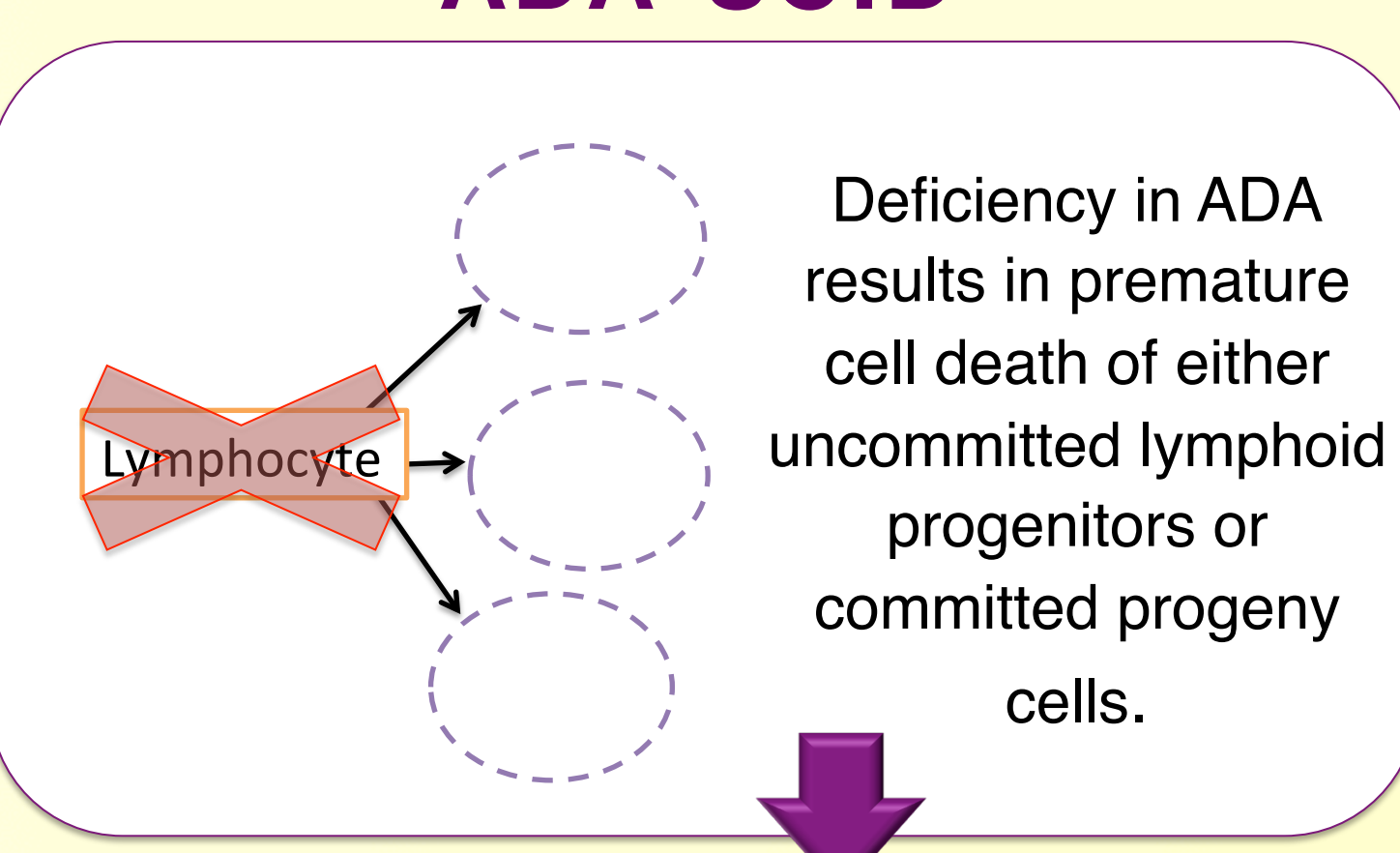


IL2RG gene encodes the protein IL-2RG (interleukin-2 receptor subunit gamma), its mutation produce a lack of the common gamma cytokine receptor subunit, which causes a complete block in T-cell and natural killer (NK) cell development.

SCID-X1



ADA-SCID

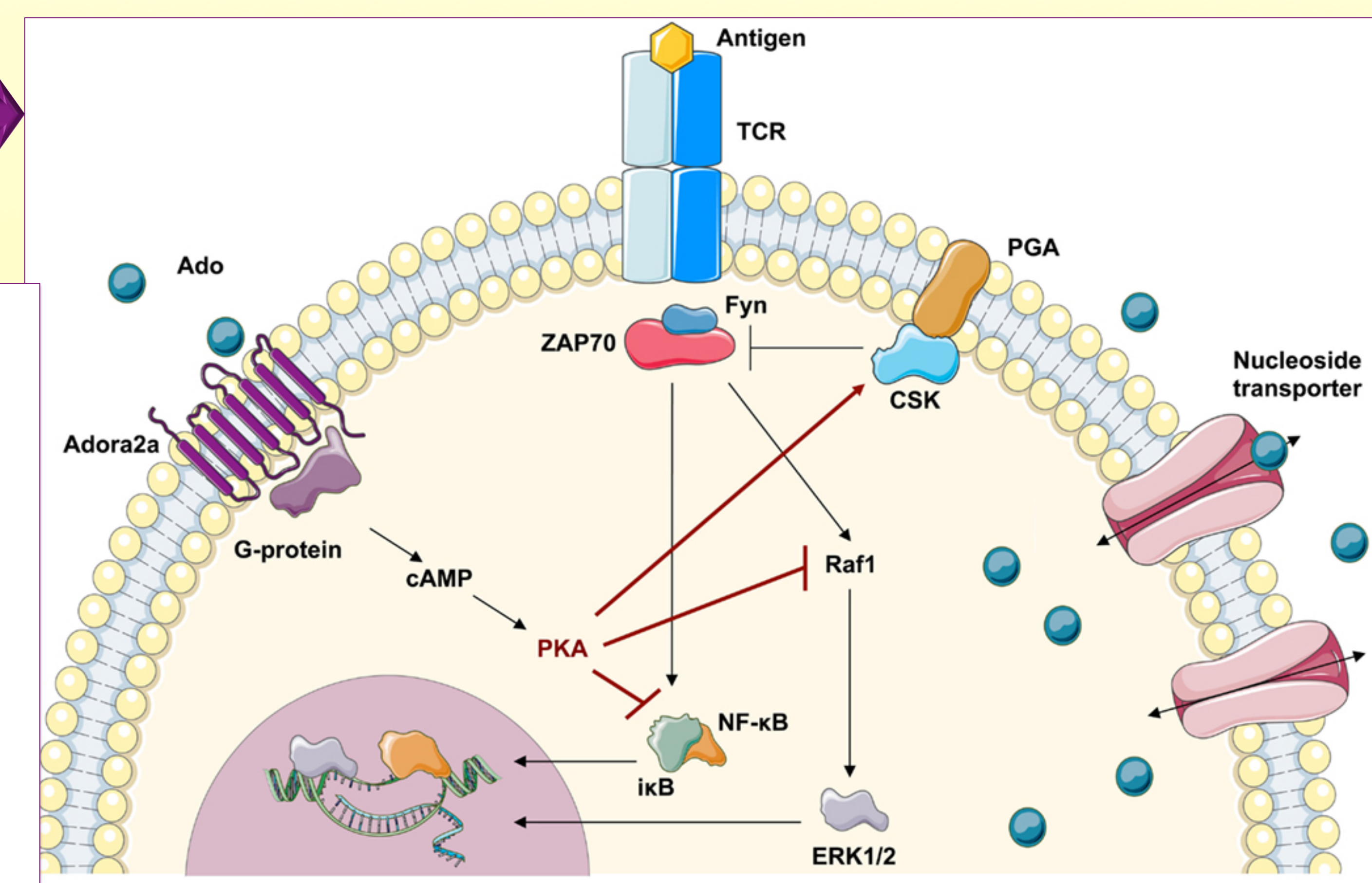


The gene encodes for the enzyme adenosine deaminase (ADA). ADA is an enzyme expressed in all tissues of the body, which catalyses the toxic substance deoxyadenosine.

Without this enzyme, the body is unable to break down the toxic substance. The toxin builds up and destroys infection-fighting immune cells. The absence of ADA leads to an accumulation of toxic metabolic by products within lymphocytes that cause cells to die.

Extracellular adenosine accumulations produce:

- block of cell cycle progression and proliferation
- inhibition of activation pathways
- reduced IL-2 and cytokine production



MATERIAL & METHODS

A typical protocol for *ex vivo* hematopoietic stem cell gene therapy for SCID-X1 and/or ADA-SCID

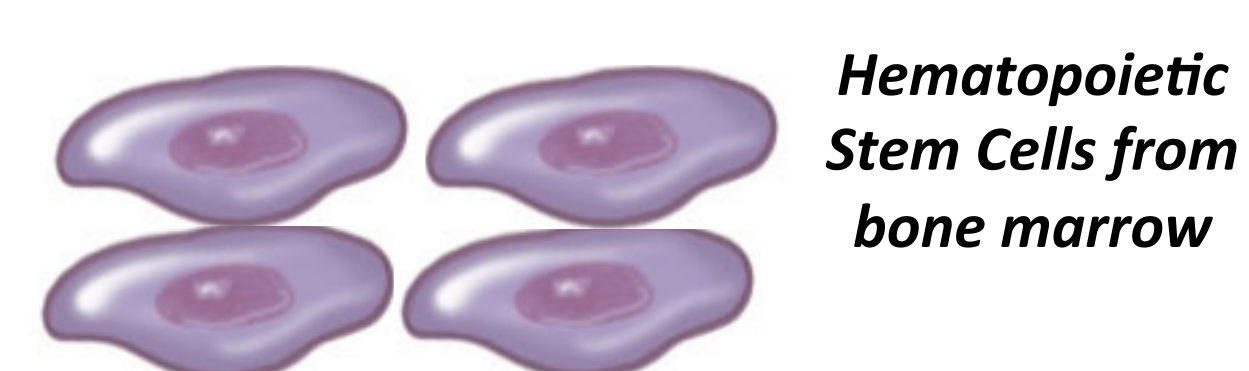
Step 1

Laboratory

- Design of the retroviral (RV) vector depending the type of SCID
- **SCID-X1** → γ -RV expressing IL-2R common gamma chain
- **ADA-SCID** → γ -RV carrying a functional ADA
- Gene inserted into viral DNA
- Placed under the transcriptional control of the long terminal repeat (LTR)

Patient

- SCID-X1 or ADA-SCID disease
- Target cells removed from patient
- Autologous bone marrow-derived HSC extraction



Step 2

Ex vivo culture

- Transduction with γ -retroviral vector
- Cultured cells are infected with genetically-altered virus
- Cells grow in culture

Step 3

Reinfusion of HSC with gene transduction to the patient

- Patient's sample target cells are now genetically altered with therapeutic gene
- Cells are reintroduced into body
- Inside the body, the genetically altered cells produce the desired proteins encoded by therapeutic DNA

RESULTS

ADA-SCID

- The expression of the recombinant ADA gene in 20% of lymphocytes ten years after the treatment.
- The functions of their immune system were resorted:
 - ✦ Increase of lymphocytes counts.
 - ✦ Improvements of cellular and humoral responses.
 - ✦ Adequate metabolic detoxification.
 - ✦ Gene corrected cells were detected in myeloid and lymphoid subsets.
- The cumulative experience on these studies did not reveal leukemic or oncogenic events indicating that ADA-SCID gene therapy has a better risk/benefit profile.
- The use of self-inactivating lentiviral vector may reduce the risk of insertional mutagenesis and at the same time increases gene transfer efficiency into hematopoietic stem/progenitor cells in their progeny.

SCID-X1

- After 2.5-5 years, 5 of 20 patients develop T-cell leukemia. In four cases, chemotherapy was easily able to destroy abnormal clones. However, one of them died.
 - ✦ Full or nearly full correction of the T cells immunodeficiency.
 - ✦ NK cells fell o very low values (same for patients treated with HSCT).
 - ✦ B cells poorly transduced and non detected in the blood.
- RV-mediated gene transfer could deregulate proto-oncogen expression (LMO-2) through the LTR's enhancer activity.
- Now they are using a self-inactivating (SIN) RV vector which should reduce the risk of insertional mutagenesis.

CONCLUSIONS

- ✓ Gene therapy has shown promising results for some patients with ADA deficiency SCID. ADA-SCID was an ideal target for the first gene therapy trials because of:
 - the pathological effects of ADA disease are reversible and the disease results from the loss of function of a single gene
 - ADA levels vary widely in the normal population so tight control of the introduced gene is not important
 - ADA gene is very small and easy to manipulate in the laboratory
 - the target cells for the therapy are lymphocytes, which are accessible, easy to culture and easy to put back into the body of the patient
 - the alternative treatments are expensive and/or hazardous
- ✓ Gene therapy also appeared to be a promising treatment for X-linked SCID but some children treated with gene therapy developed leukemia.
 - Gene therapy for SCID-X1 should be reserved for SCID patients aged over 1 month and for whom an HLA-identical sibling donor or a perfectly matched unrelated donor of bone marrow or cord blood will not be available in the coming three months.
- ✓ HSCT represents the treatment of choice depending the donor type, the age at transplant, the SCID diagnosis and the recipient/donor compatibility.
- ✓ The only cure currently and routinely available for SCID is bone marrow transplant, which provides a new immune system to the patient.
- ✓ Gene therapy treatment of SCID has also been successful in clinical trials, but not without complications.
- ✓ Research on gene therapy for SCID is continuing and may one day be a good option.

REFERENCES

- Cavazzana-Calvo, M. *et al.* Gene therapy for primary immunodeficiencies: Part 1. *Curr Opin Immunol.* 2012 Oct; 24(5):580-4.
- Naldini L. Ex vivo gene transfer and correction for cell-based therapies. *Nat Rev Genet.* 2011 May; 12(5):301-15.
- Fischer, A. *et al.* 20 years of gene therapy for SCID. *Nat Immunol.* 2010 Jun; 11(6):457-60.
- Aiuti, A. *et al.* Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning. *Science.* 2002 Jun.
- Cavazzana-Calvo, M. *et al.* Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. *Science.* 2000 Apr 28; 288(5466):669-72.