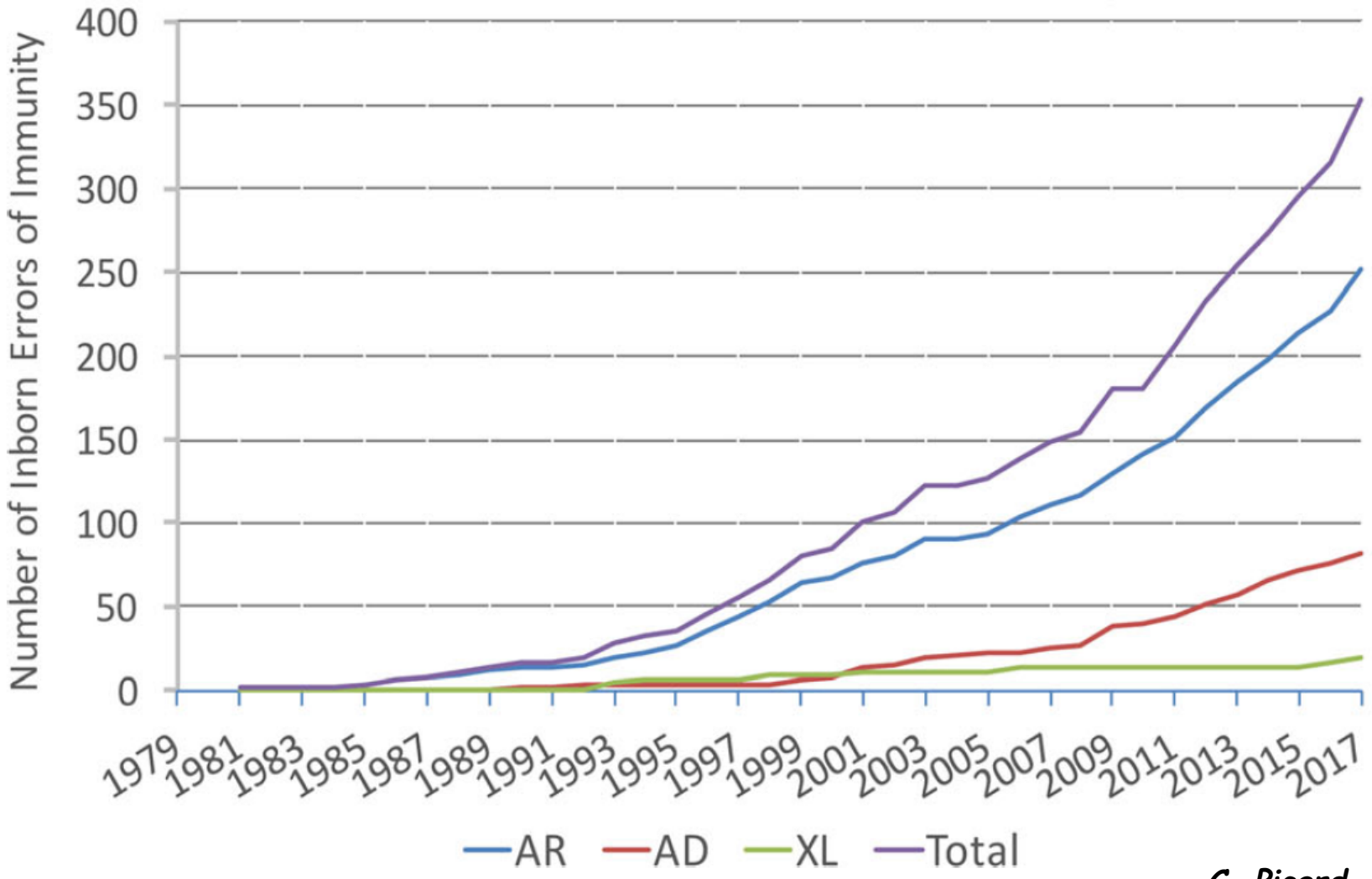
Transplantation and gene therapy for PID

Alain Fischer

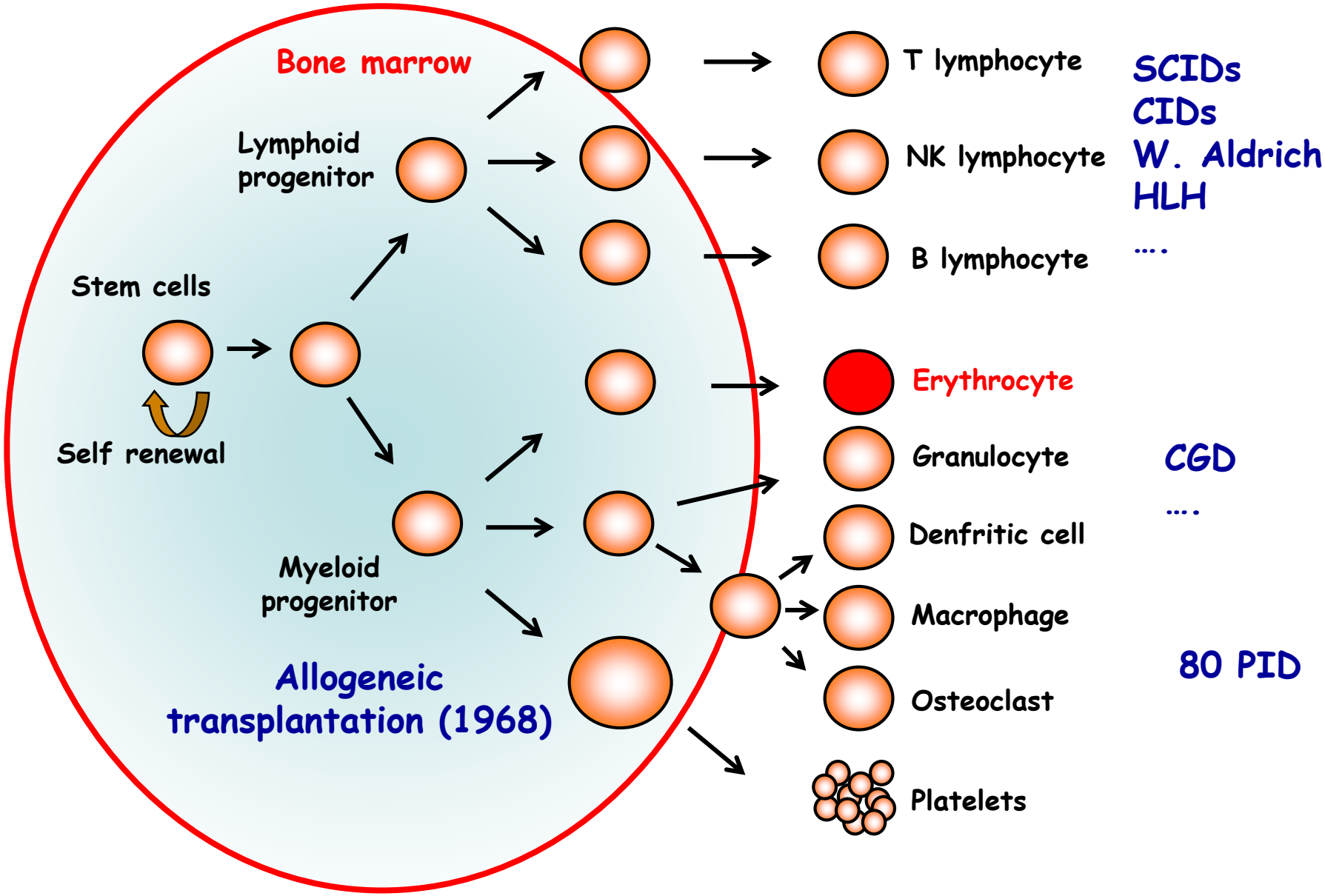
Hôpital Necker Enfants Malades, Inserm, Institut Imagine, Collège de France, Paris

Inherited disorders of the immune system



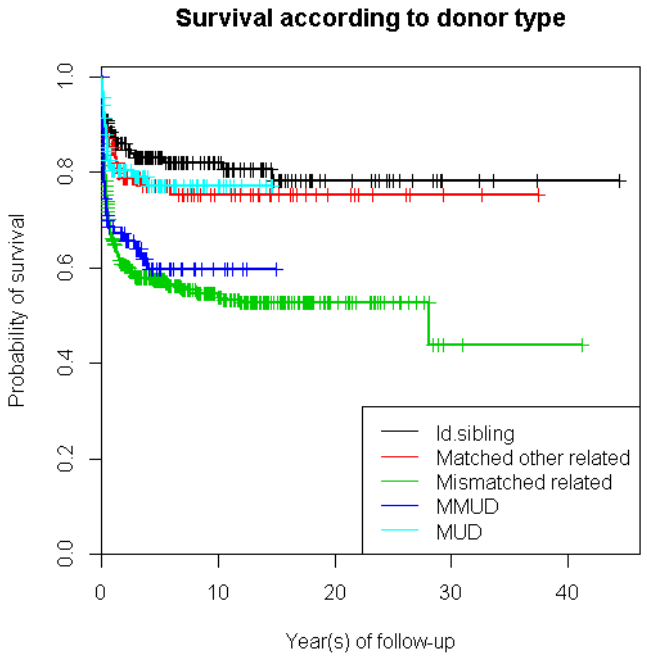
C. Picard

Allogeneic hematopoietic stem cell replacement (HSCT)



HSCT in SCID. Most recent results

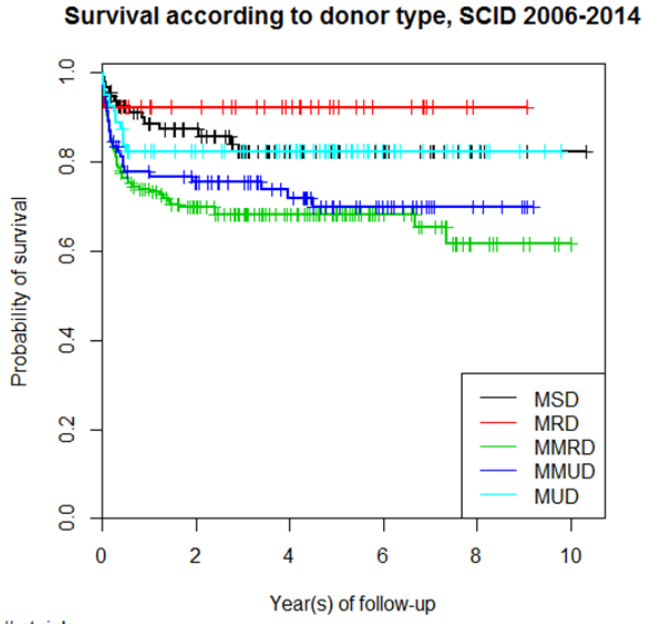
1968-2013



# at risk					
Id.sibling	193	55	18	4	1
Matched other related	108	27	9	2	0
Mismatched related	532	127	28	2	1
MMUD	91	6	0	0	0
MUD	117	13	0	0	0

Logrank *p*-value: <0.001

2006-2014

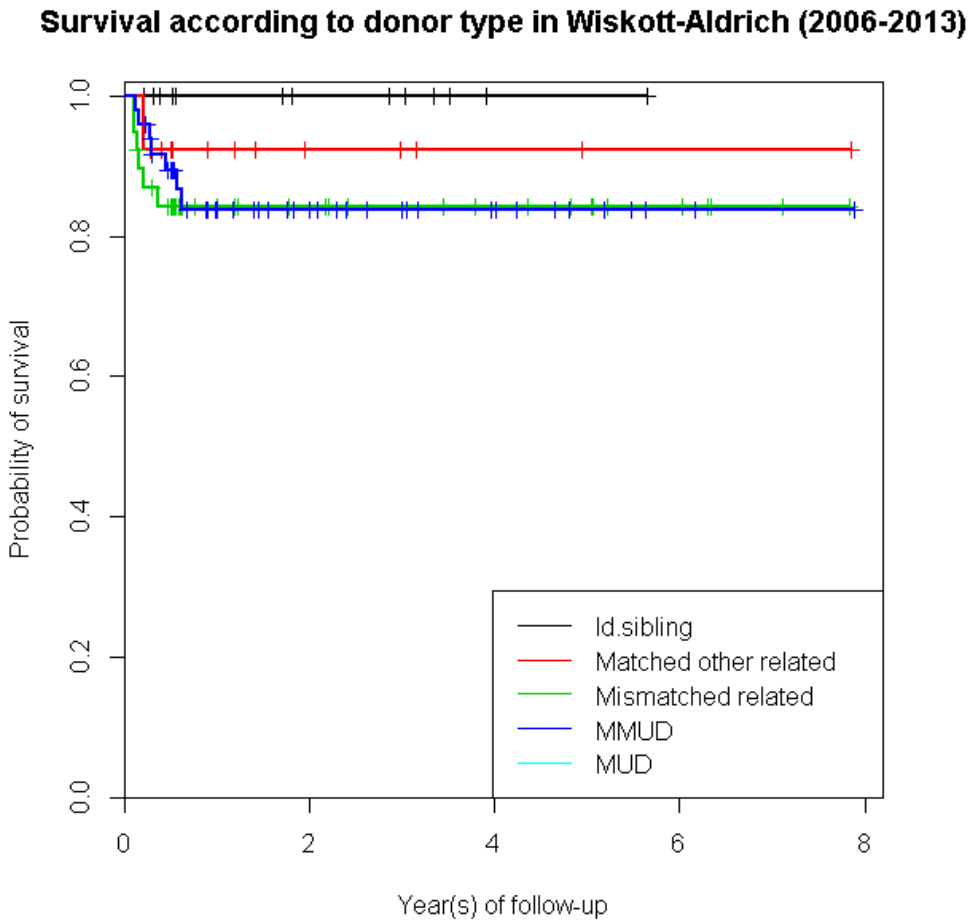


# at risk						
MSD	93	60	31	17	4	1
MRD	39	28	20	8	1	0
MMRD	169	93	62	29	10	1
MMUD	91	60	41	18	6	0
MUD	80	54	43	16	6	0

A. Lankaster

Wiskott Aldrich syndrome european data (2006-2013)

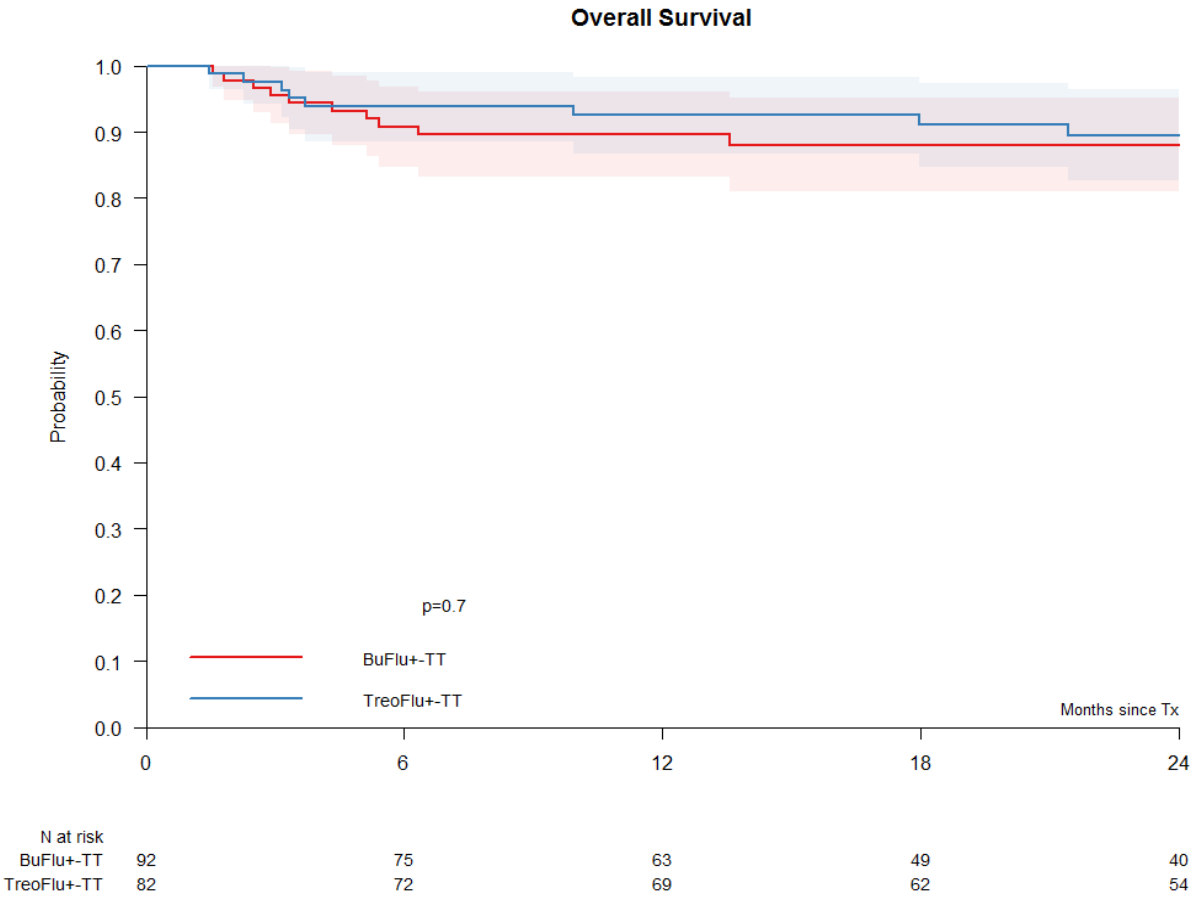
Survival



# at risk					
Id.sibling	15	6	1	0	0
Matched other related	13	4	2	1	0
Mismatched related	39	15	10	5	0
MMUD	49	17	9	2	0

SCETIDE/EBMT/ESID

W. Aldrich syndrome-Survival following HSCT

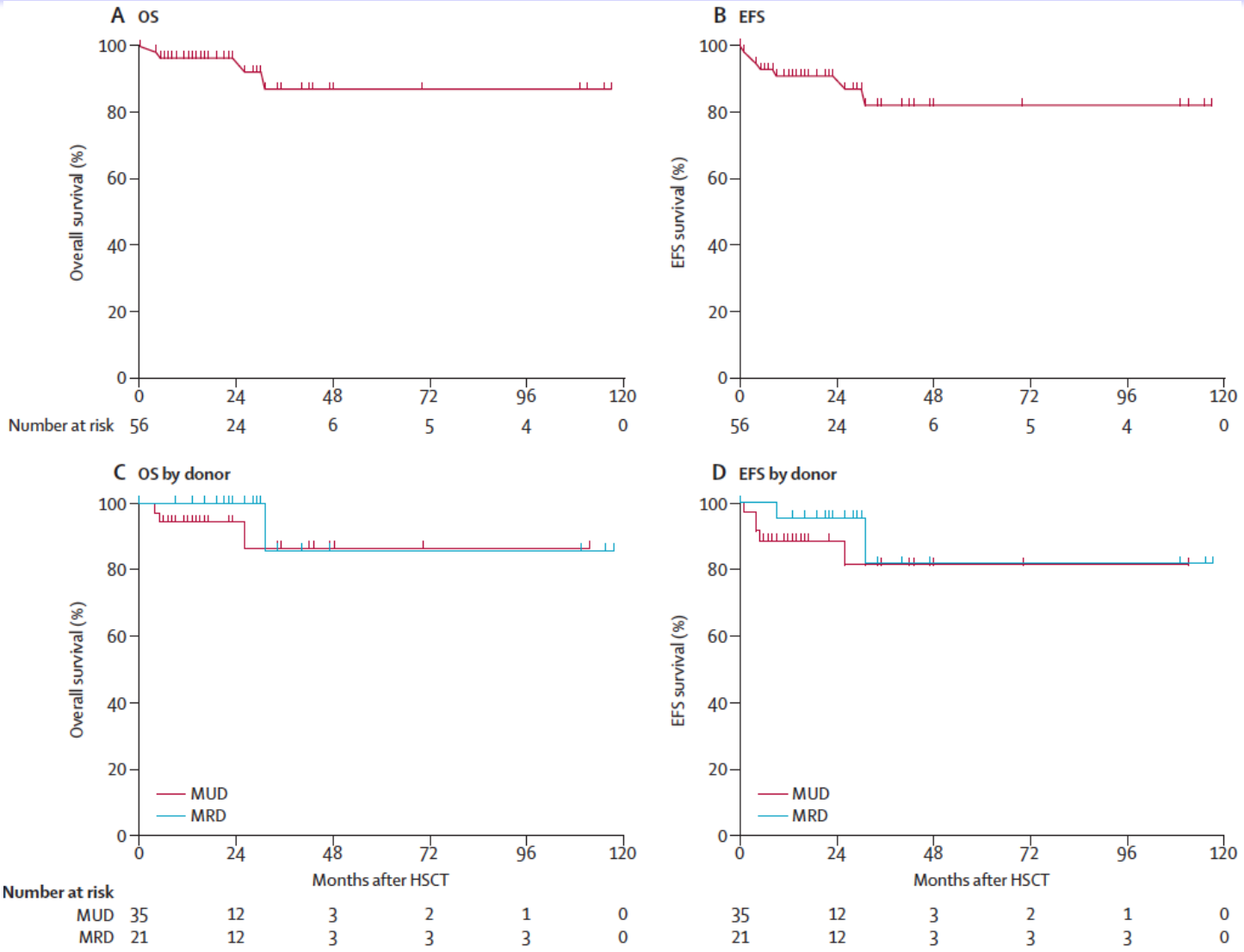


M. Albert et al, 2018

Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study

T. Güngör et al, The Lancet 2014

Survival



3 March 1972, Volume 175, Number 4025

SCIENCE

Gene Therapy for Human Genetic Disease?

Proposals for genetic manipulation in humans raise difficult scientific and ethical problems.

Theodore Friedmann and Richard Roblin

Schematic Model of Genetic Disease

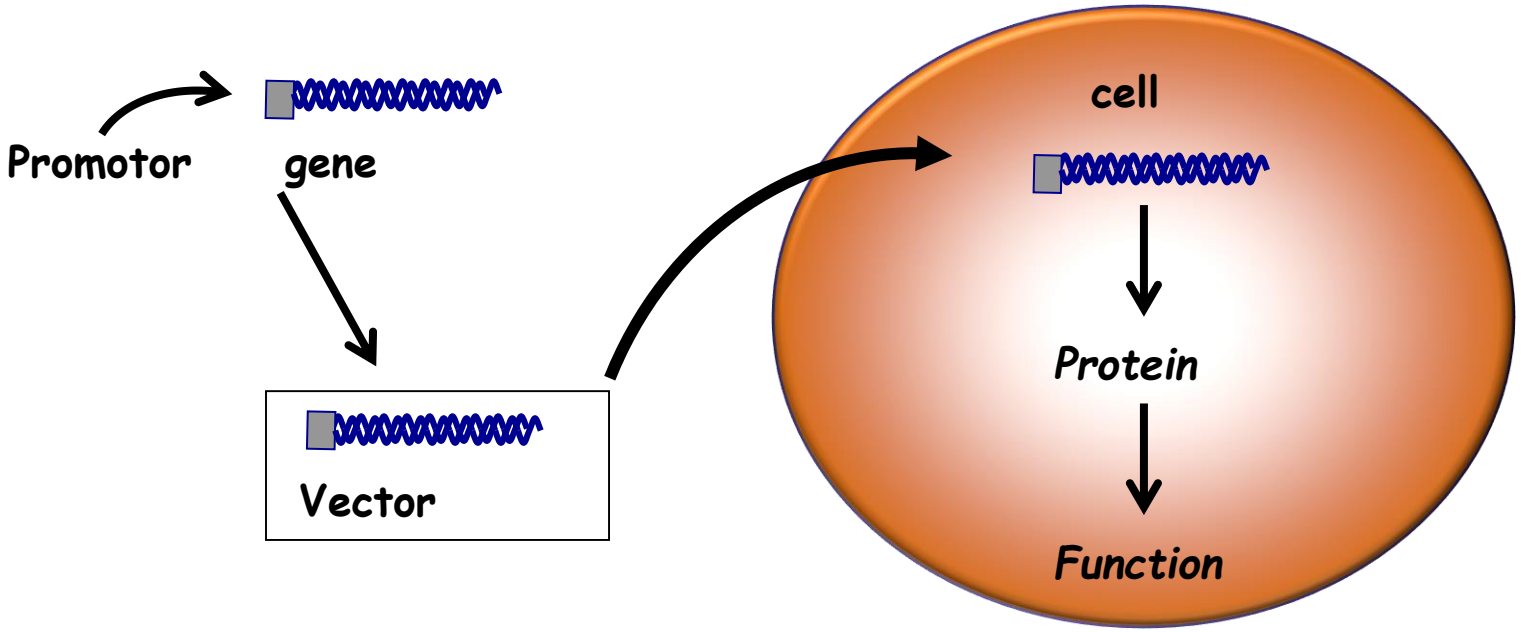
Some aspects of a hypothetical human genetic disease in which an enzyme is defective are shown in Fig. 1. The consequences of a gene mutation which renders enzyme E_3 defective could be (i) failure to synthesize required compounds D and F; (ii) accumulation of abnormally high concentrations of compound C and its further metabolites by other biochemical pathways; (iii) failure to regulate properly the activity of enzyme E_1, because of loss of the normal feedback inhibitor, compound F; and (iv) failure of a regulatory step in a linked pathway because

Gene therapy compared to transplantation

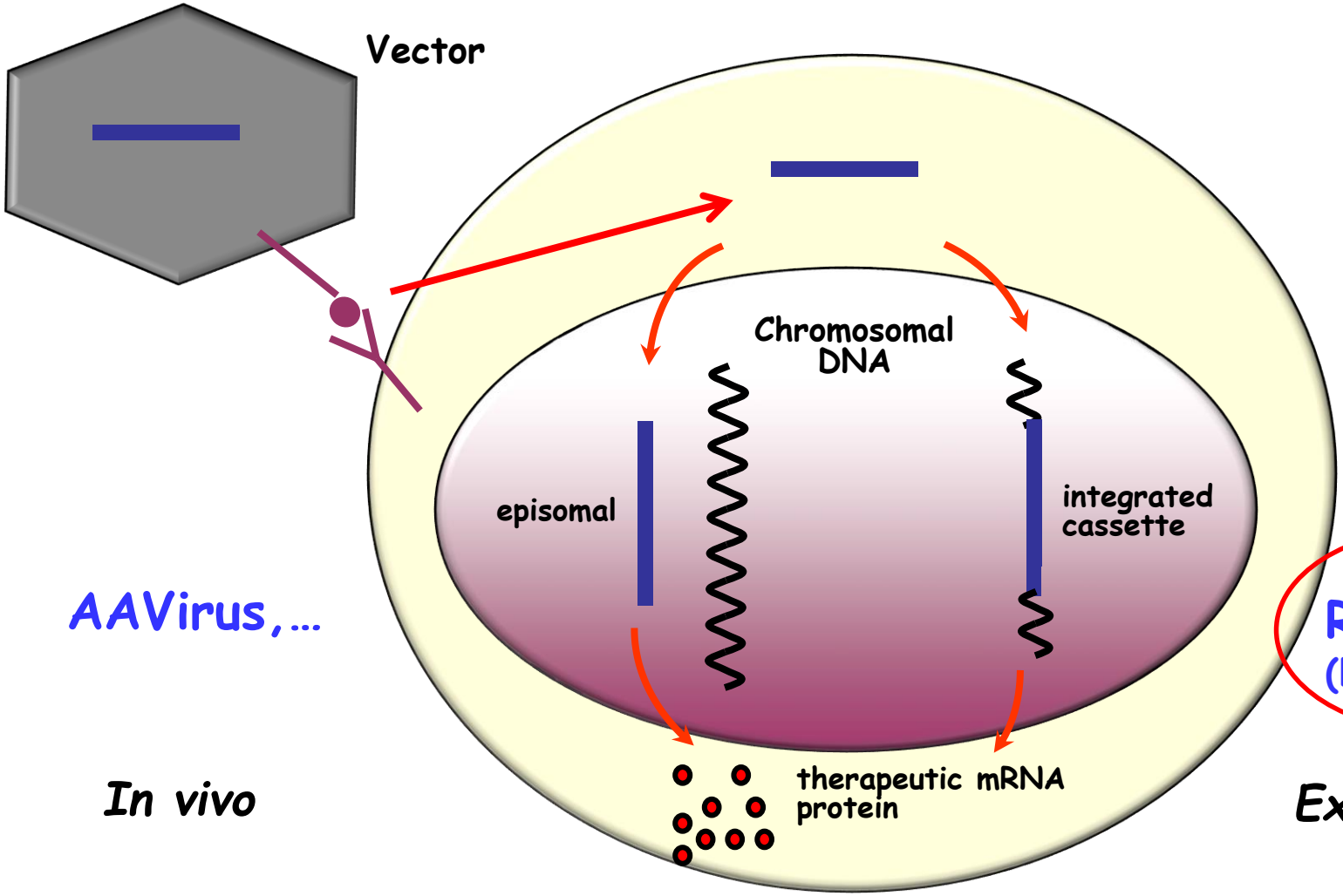
Gene Therapy	HSCT
• Autologous	• Allogeneic
• Cultured cells	• Non-cultured cells
• x% cell and gene-corrected	• 100% gene-normal

Strategies of gene therapy of PID

- to add a normal copy of the mutated gene
- to inhibit expression of a mutated gene with deleterious effects
- to fix a mutation



Gene therapy, how to do it ?
Integrative and non integrative vectors



AAVirus,…

Retrovirus (lentivirus)

In vivo

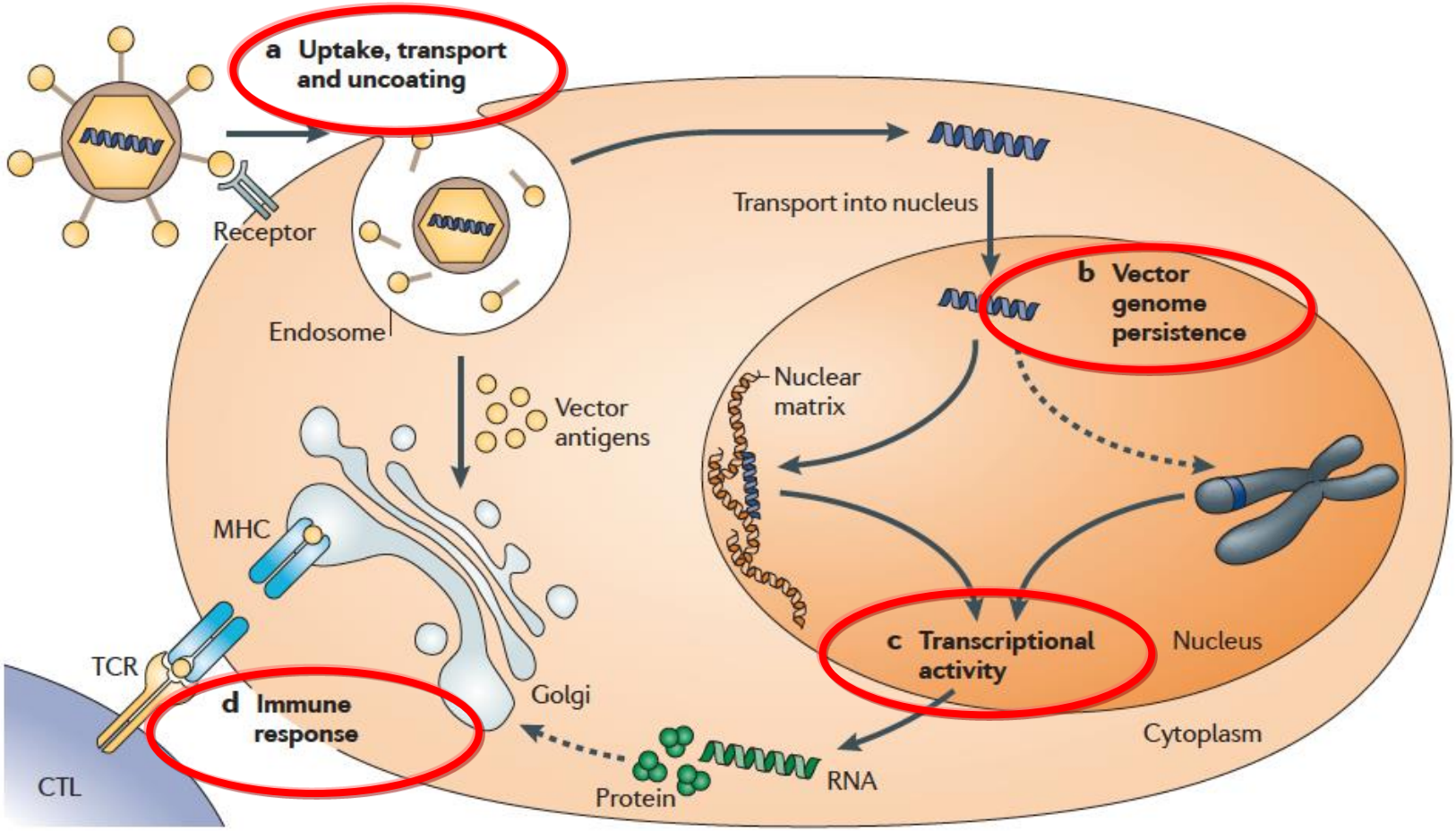
Ex vivo

post mitotic

target cell

mitotic

The hurdles, cause of so many failures !



Adapted from M.A. Kay, Nature Reviews Genetics 2011

Effective gene therapy

In vitro (RV)

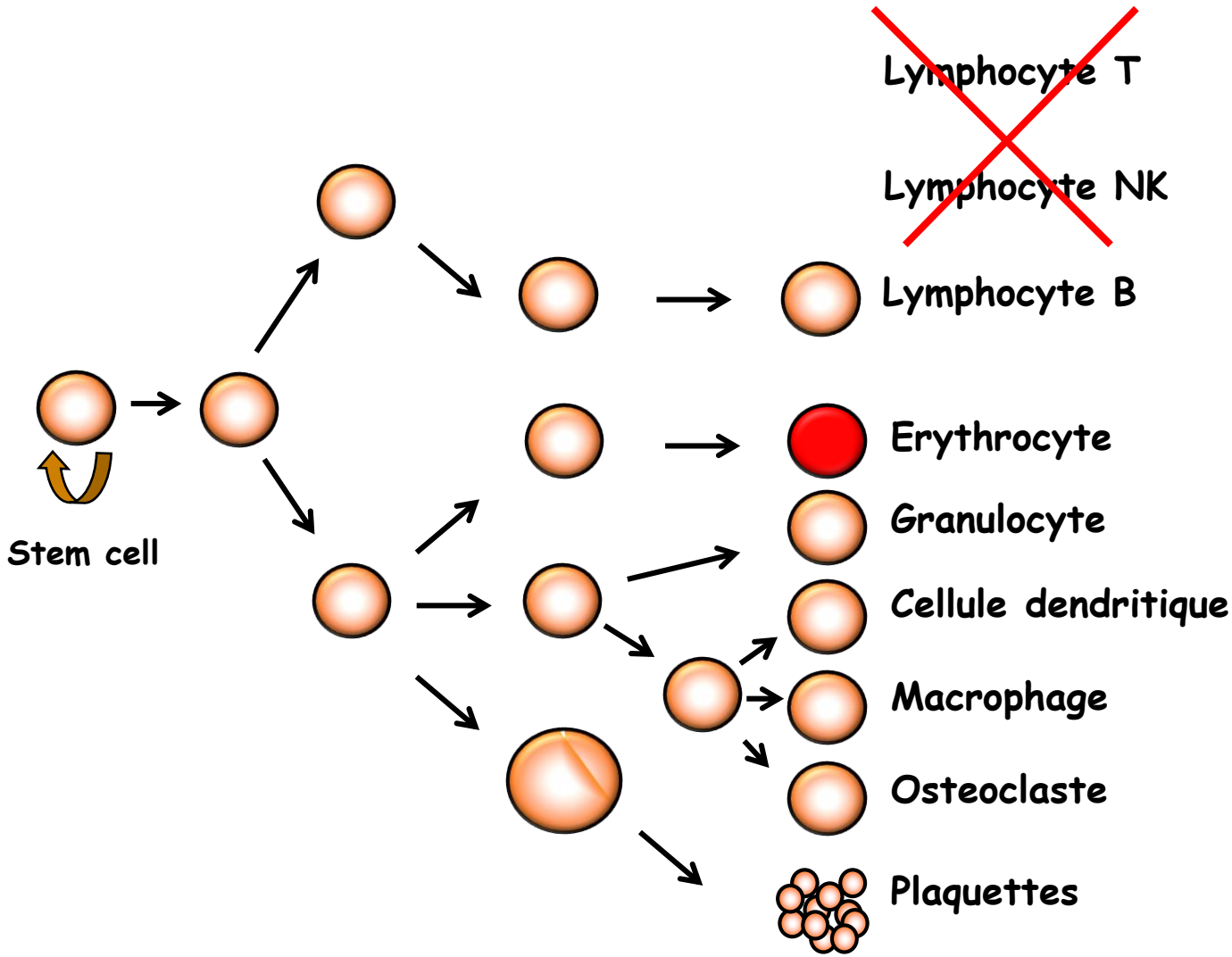
In vivo (AAV)

- 2000 SCID-X1
- 2002 SCID-ADA
- 2008 Amaurosis
- 2009 Adrenoleukodystrophy
- 2010 Beta thalassemia
- 2013 Wiskott-Aldrich syndrome
- 2013 Metachromatic leukodystrophy
- 2014 Hemophilia B
- 2017 Sickle cell disease
- 2017 Spinal muscular atrophy
- 2017 Epidermolysis bullosa
- 2017 Hemophilia A

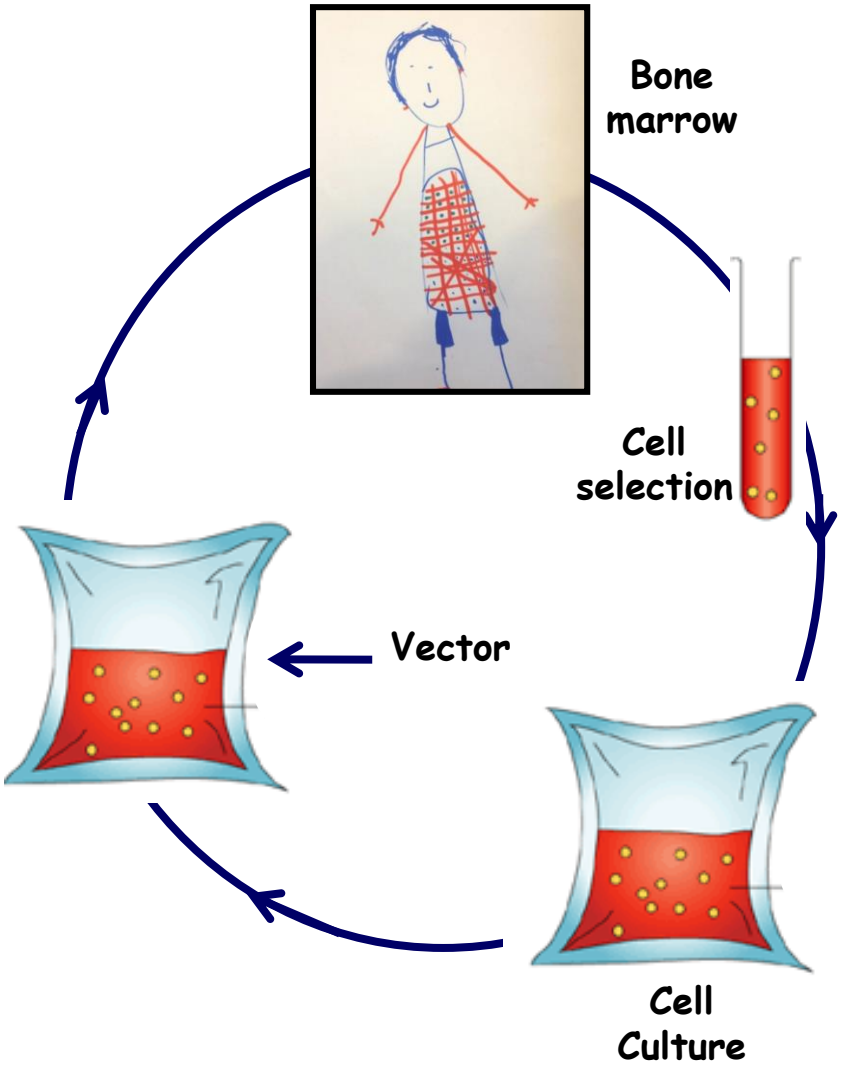
- 2014 B cell malignancies

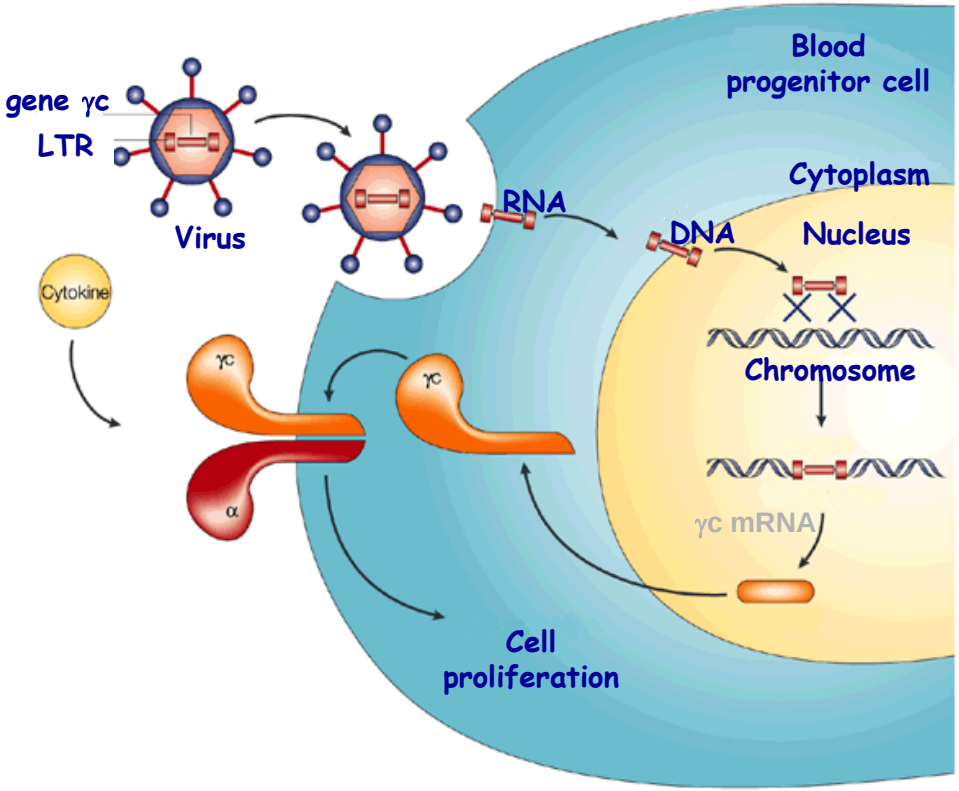
published results

SCID X1


Lymphocyte T
Lymphocyte NK
Lymphocyte B
Erythrocyte
Granulocyte
Cellule dendritique
Macrophage
Osteoclaste
Plaquettes
Stem cell

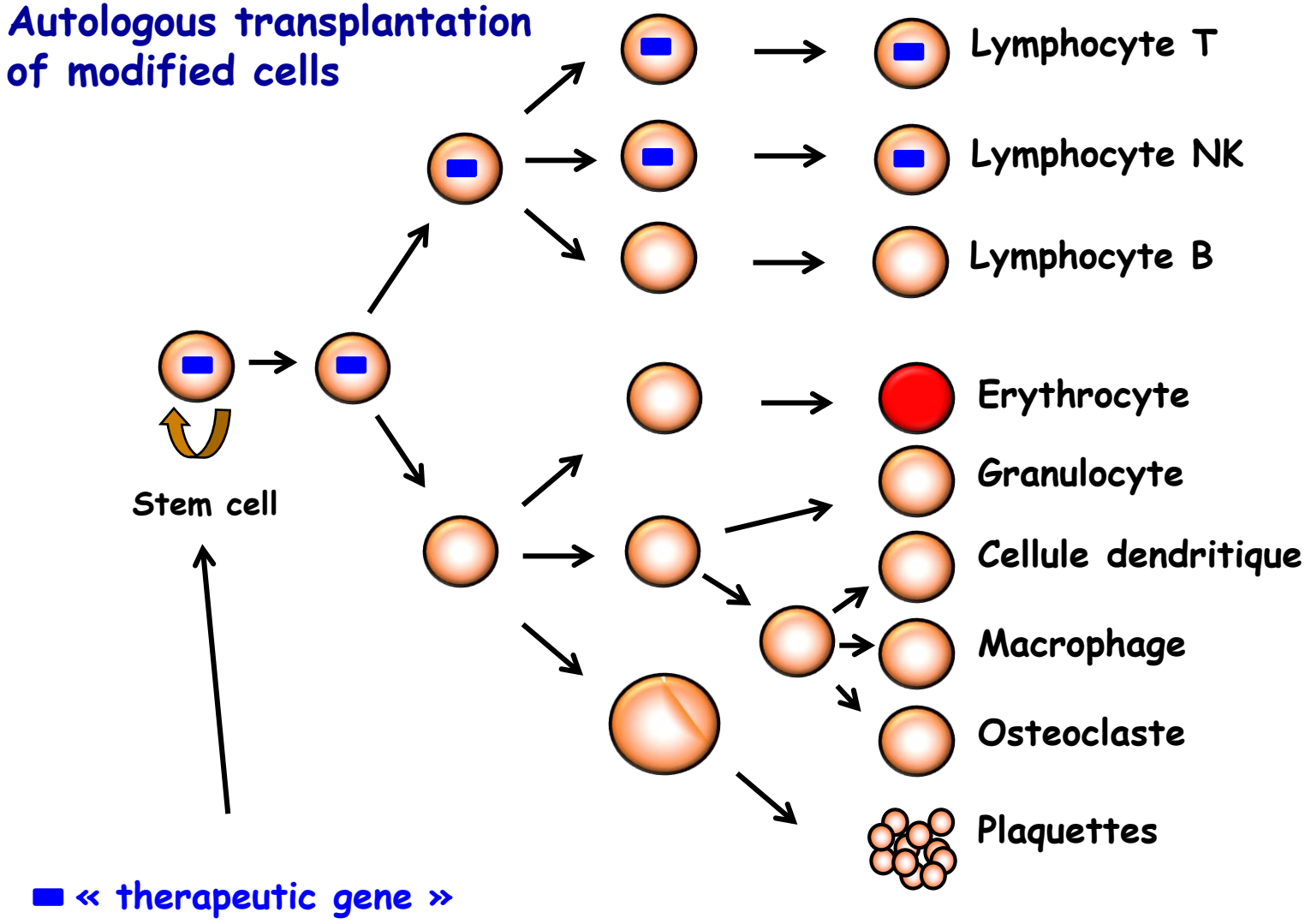
Ex vivo gene therapy of SCID - principle





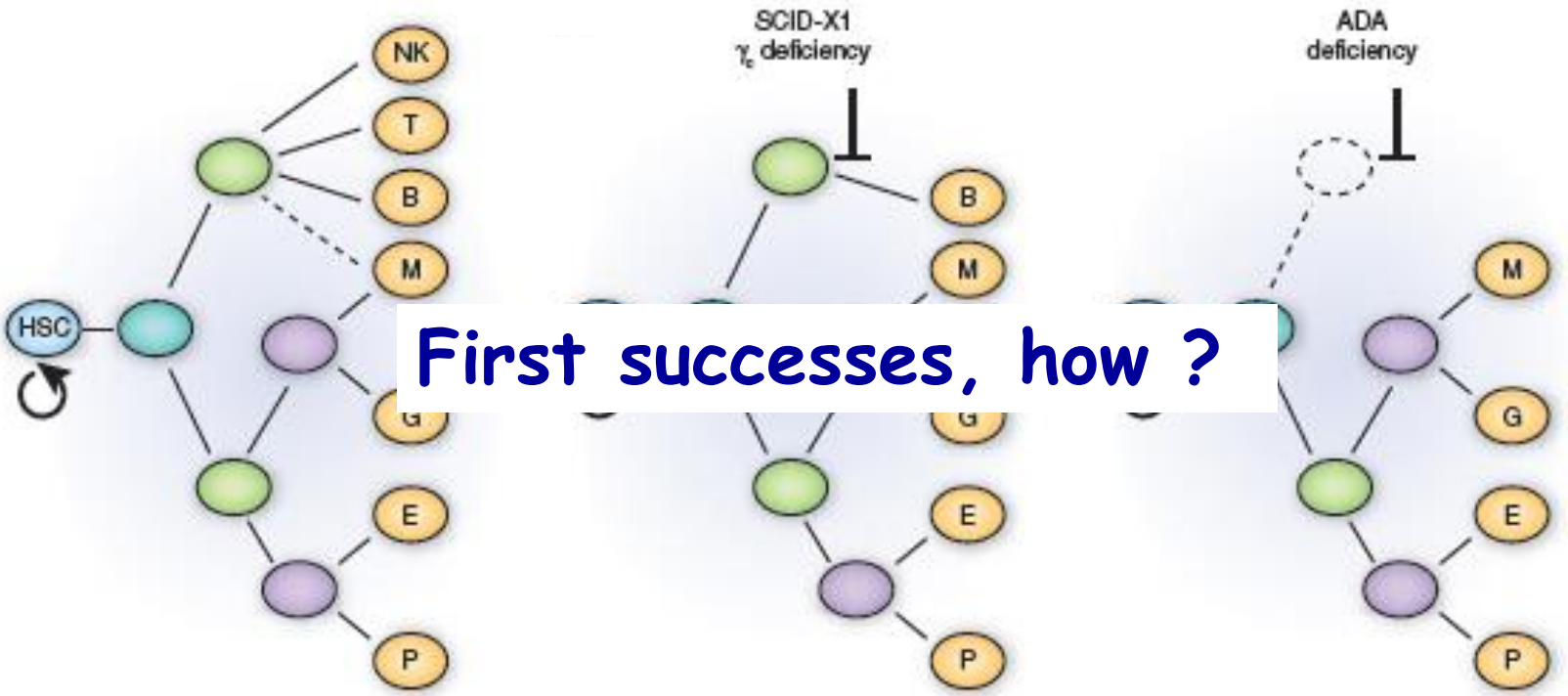
SCID : severe combined immunodeficiency

Gene therapy of SCID X1



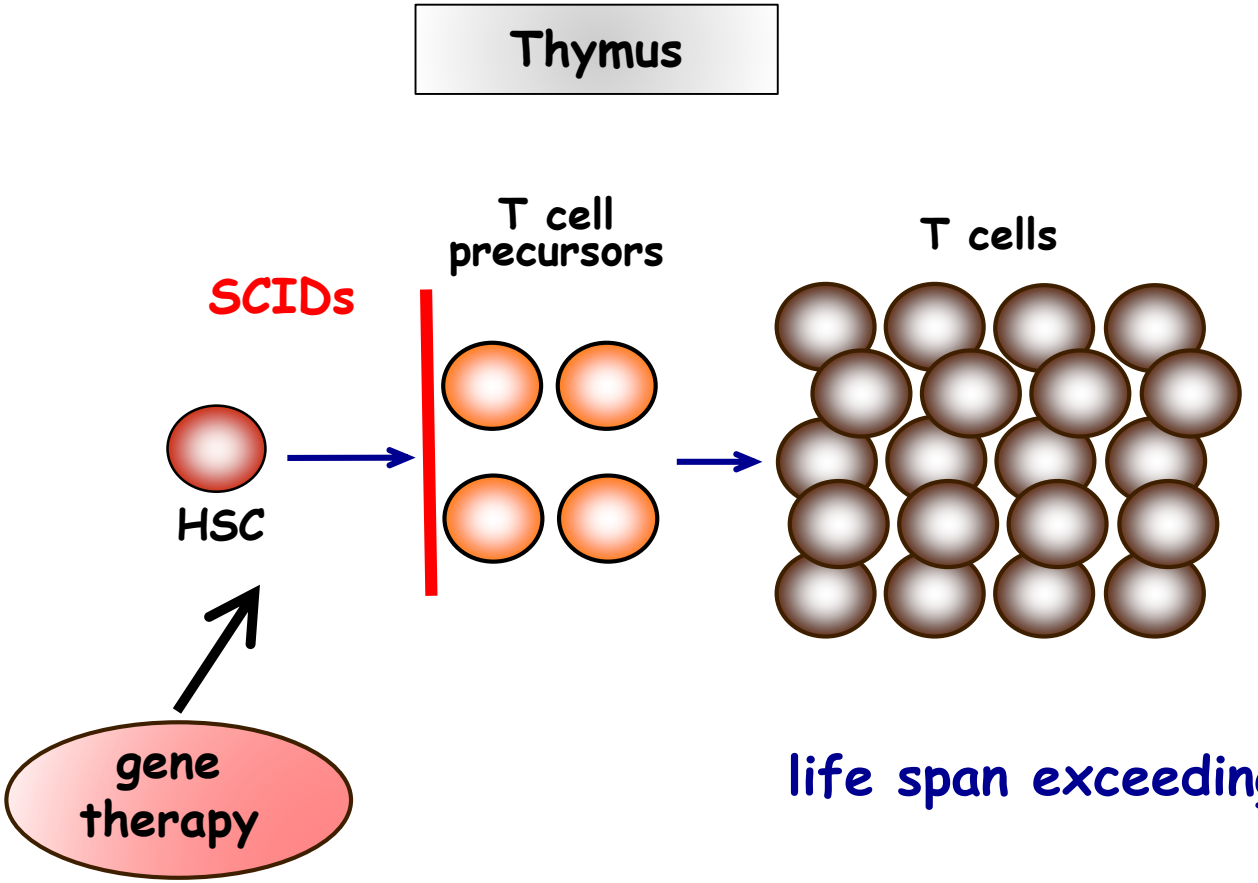
Gene therapy for severe combined immunodeficiencies (SCID)

SCID X1 and ADA deficiencies



Fatal conditions < 1 year of age

Why SCIDs were the optimal condition to probe gene therapy



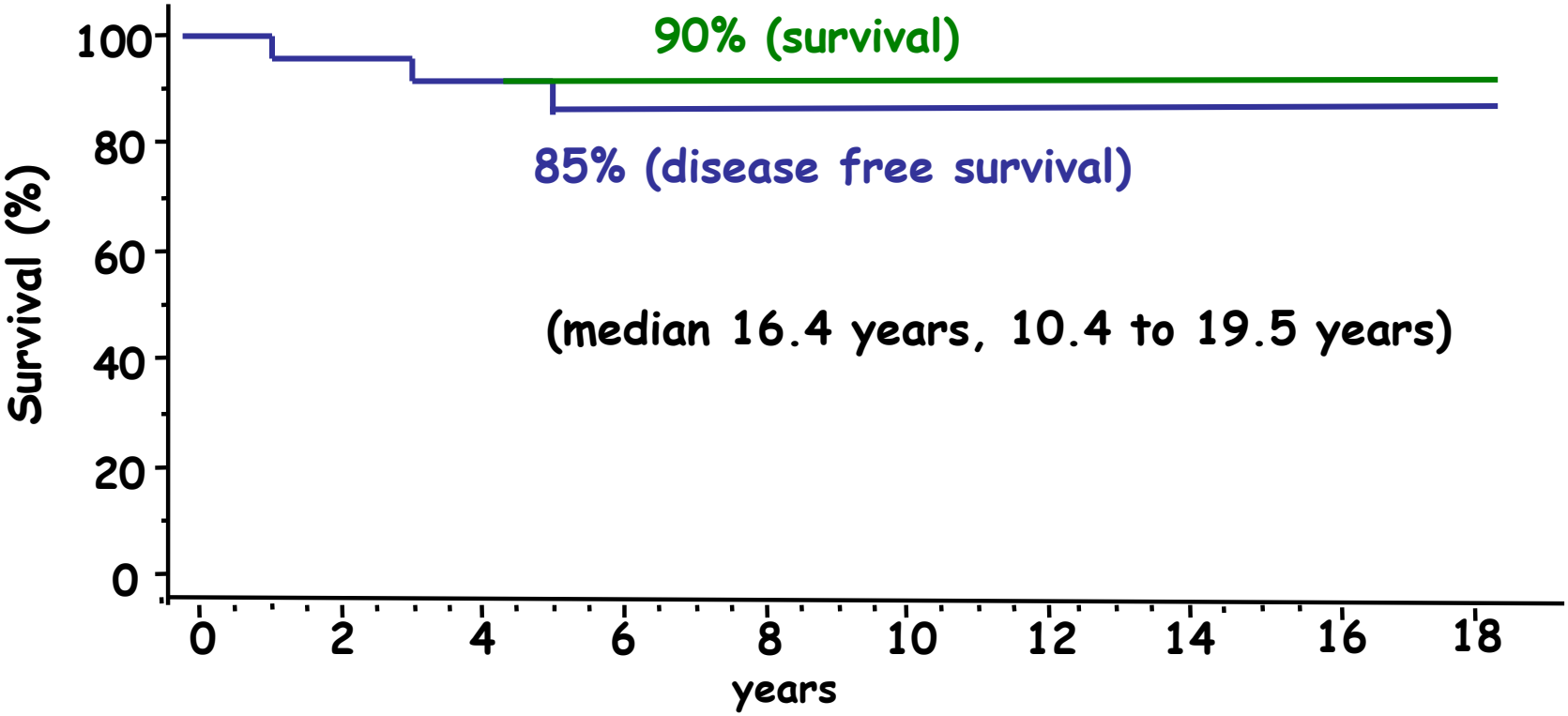
life span exceeding 50 years

Hypothesis:
autoamplified gene therapy with a long term effect !

HSC: hematopoietic stem cells

SCID-X1 gene therapy

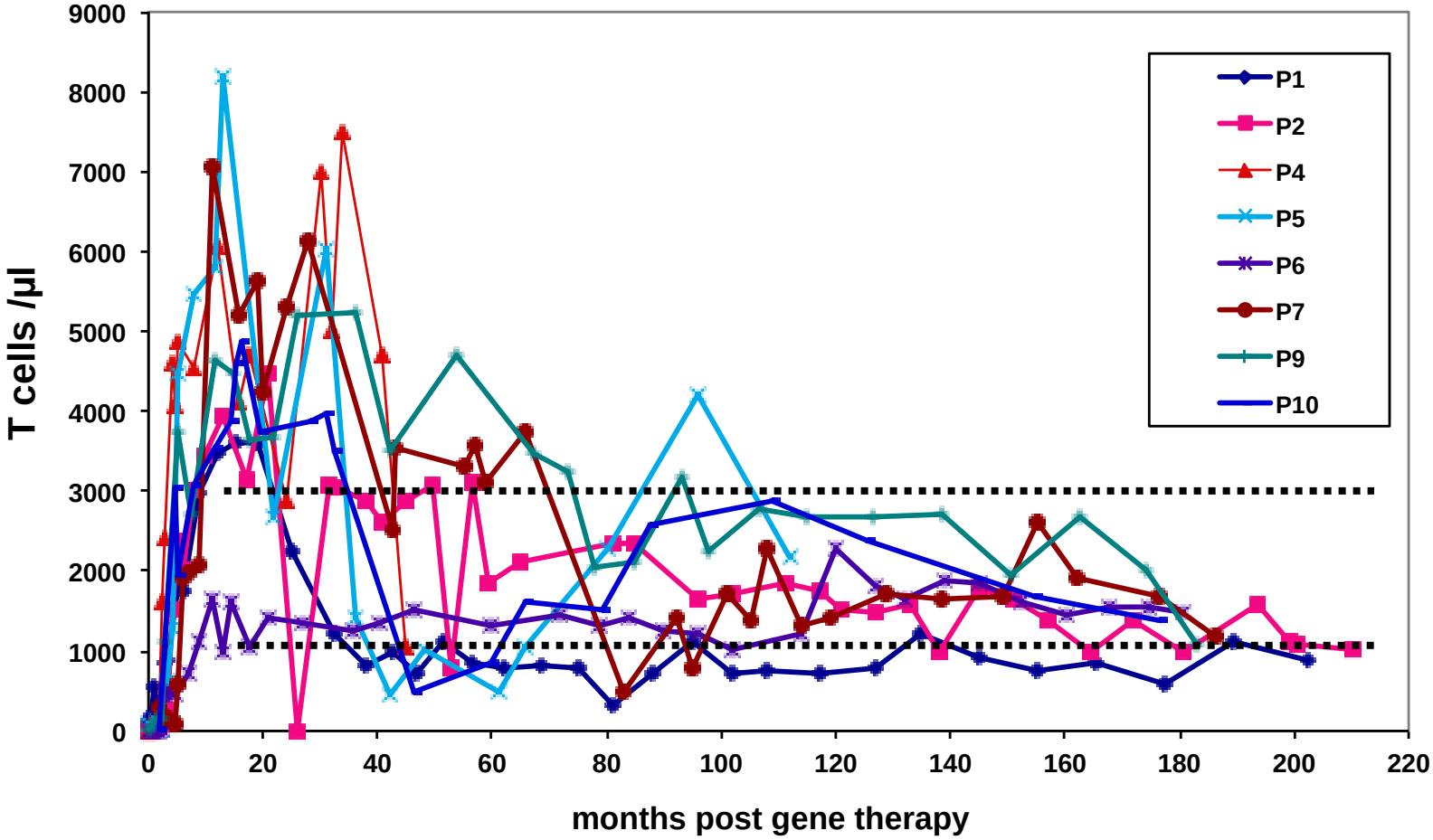
First results: efficacy



Correction of T cell-mediated immune functions, normal quality of life

SCID-XI trial 1: sustained T cell detection

blood

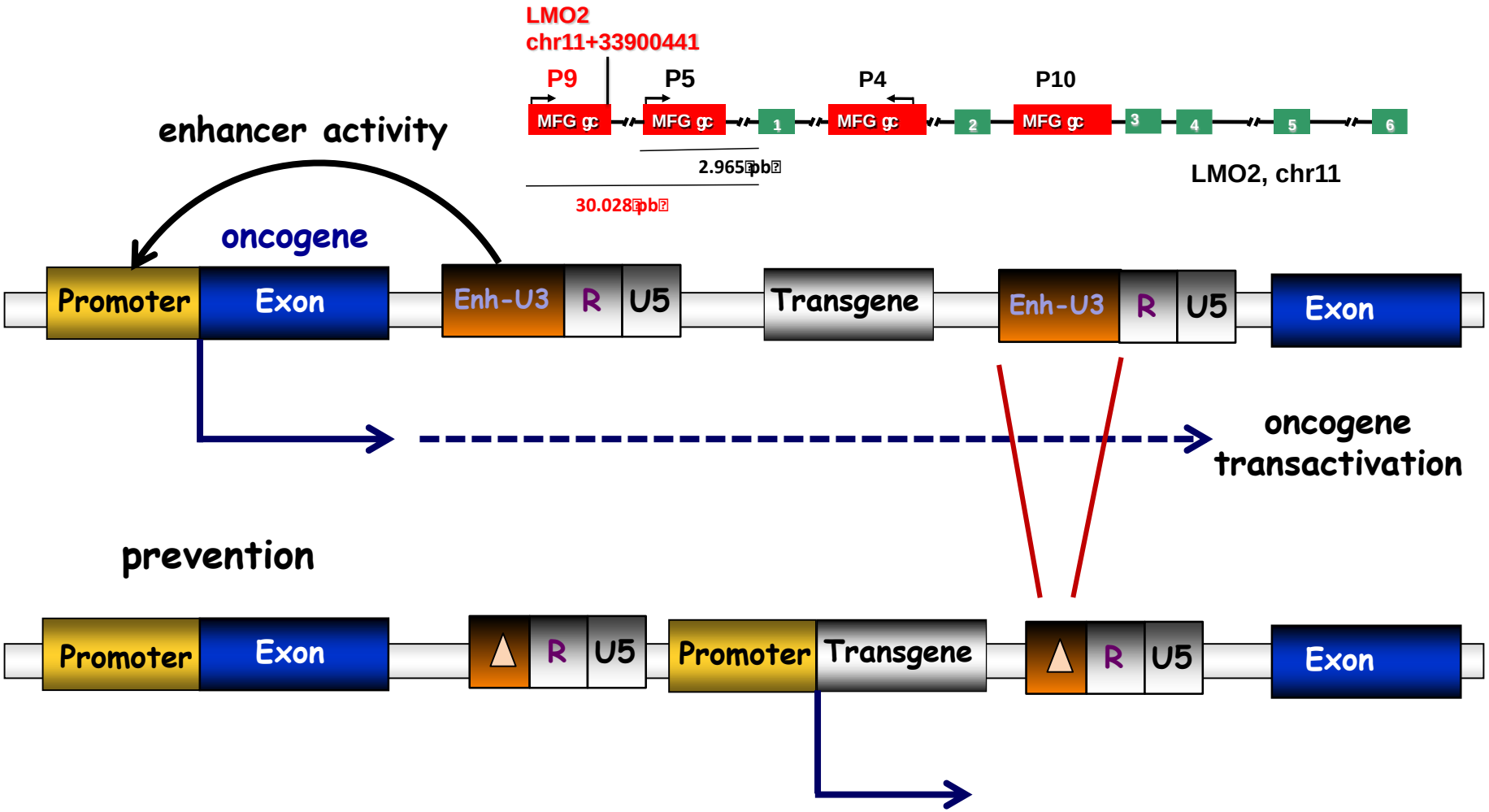


Functional T cells, broad repertoire, sustained production over time

…, but genotoxicity causing (curable) leukemias in one fourth

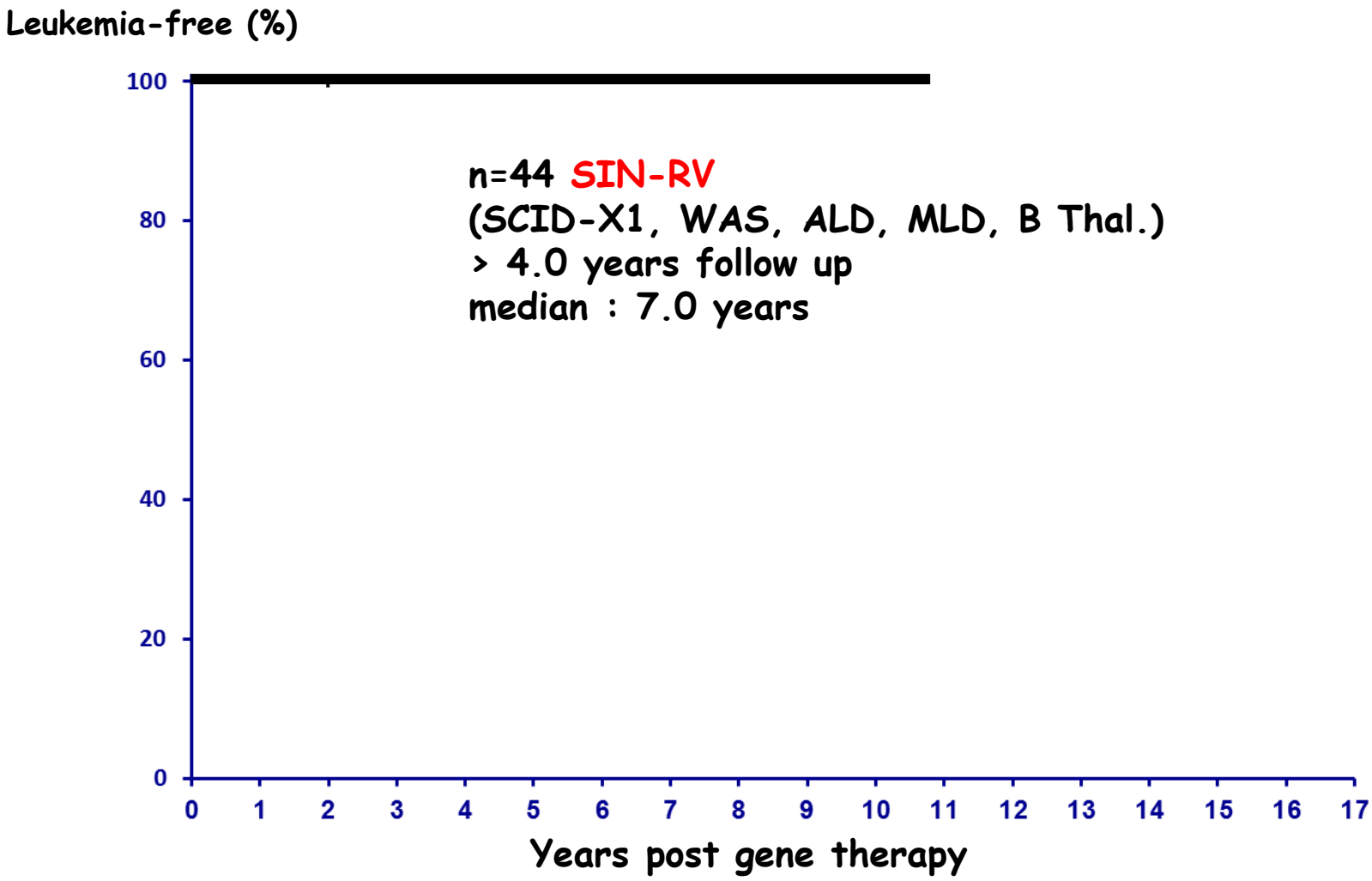
Insertional mutagenesis, cause and prevention

Virus enhancer-mediated (onco)gene transactivation

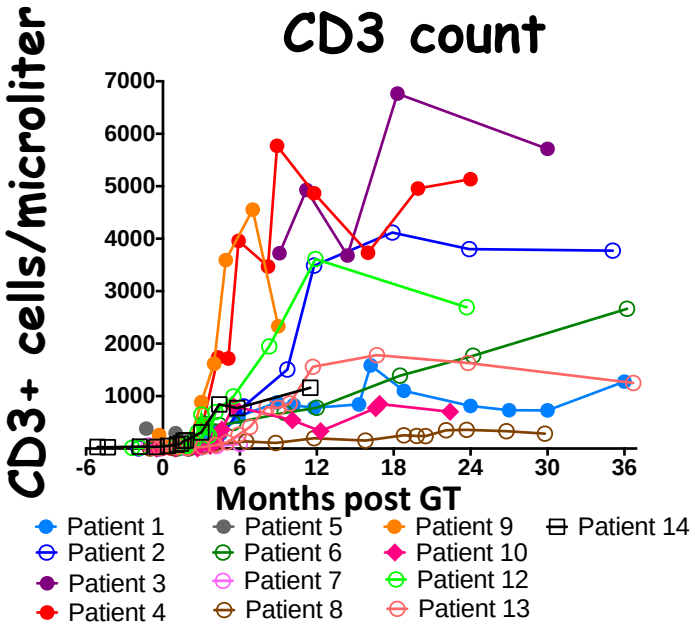


Self inactivating vector (SIN) → new clinical trials

Safety of SIN vectors



SCID X1, trial #2

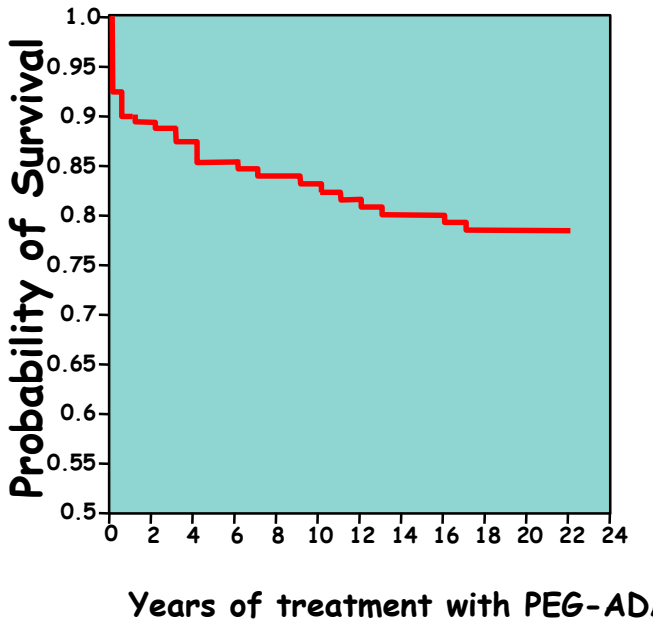


- 14 patients enrolled
- 13/14 alive (1 died of infection)
- 11/13 patients have T cells
- 0.8-7.5y follow-up (median 6 years)

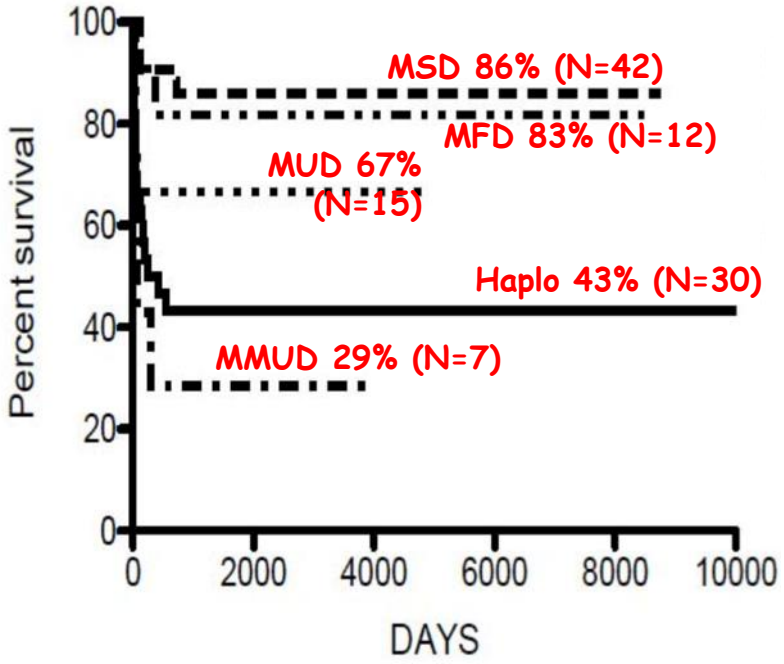
Hacein-Bey-Abina, Pai et al NEJM 2014 and unpublished

ADA-SCID – Standard Treatments

PEG-ADA Enzyme Replacement Therapy
(Gaspar et al., BLOOD 2009)



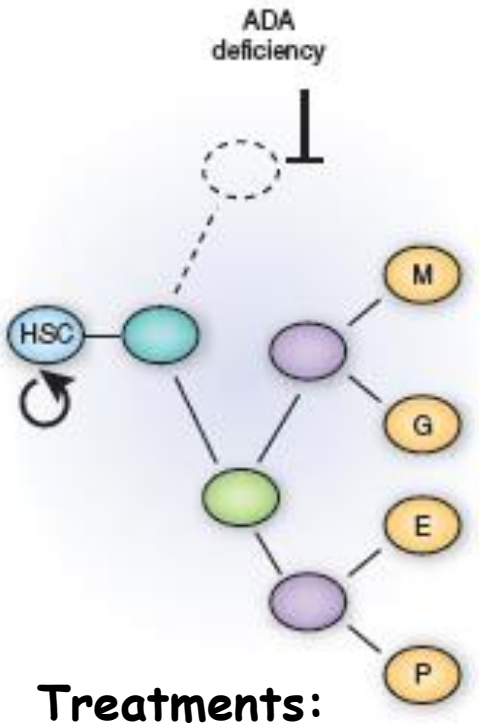
Hematopoietic Stem Cell Transplantation
(Hassan et al., BLOOD 2012)



F. Candotti

Gene therapy of ADA-SCID

ADA deficiency



Treatments:
Allotransplantation
Enzymotherapy

2002-2013, 3 trials (Italy, US, UK)
γRV vectors
mild myeloablation (space for reinjected stem cells)
no genotoxicity ! (disease related)
55 patients, all alive,
38 off enzymotherapy
median 9.5 years (4.0-17.0 years)
one approved drug product !

Since 2013, 1 trial (US, UK),
SIN LV* vectors
53 patients, all alive
51 off enzymotherapy

A. Aiuti, B. Gaspar, A. Thrasher D. Kohn, F. Candotti

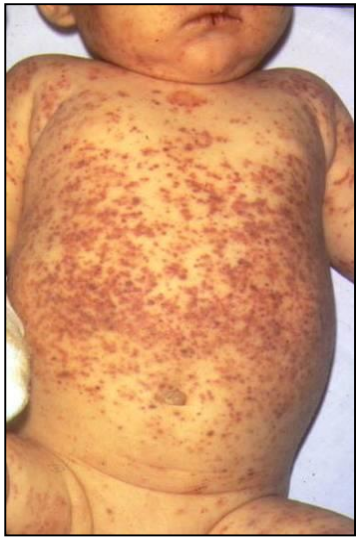
*LV : lentiviral vectors

Gene Therapy vs. HSCT in ADA-SCID

	MSD HSCT	Gene Therapy
Minimum time to procedure (months)	0.5-1	3-6
Performed at local specialized centers	Yes	Not currently
Donor availability	<20%	100%
Cost of procedure	<120,000 dollars	594,000 euro +120,000
Chemotherapy conditioning	No	Yes
ERT prior to procedure	Usually not given	Usually given
Bone marrow/PBSC harvest from patient	No	Yes
Bone marrow/PBSC harvest from donor	Yes	No
Years of successful experience	>40	6 (LV) - 17 (γRV)
Procedure failure frequency	10-20%	5-20%
Potential for graft versus host disease	Yes	No
Procedure-related mortality	5.6%	0%
Time to immune reconstitution	3-6 months	6-24 months
Immunoglobulin replacement need	4%	7-10%

Modified from DB. Kohn et al., F. Candotti JACI 2018, in press.

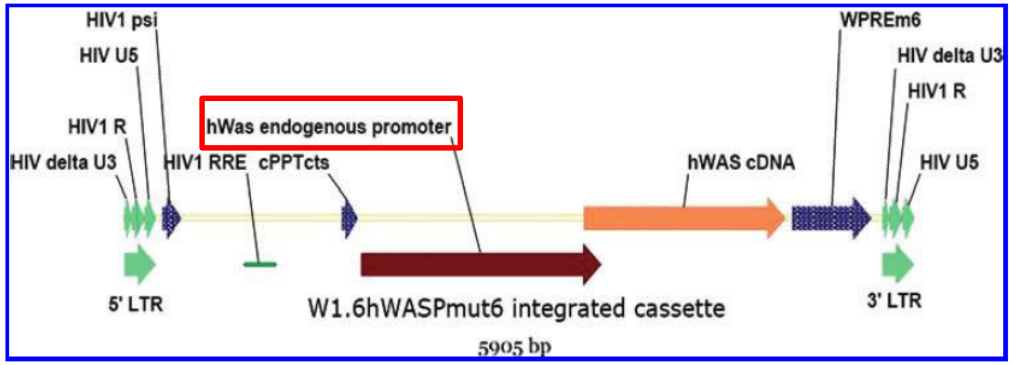
Gene therapy of the Wiskott Aldrich syndrome (WAS)



bone marrow
progenitor cells

myeloablation
(Bu/Flu)

ex vivo gene transfer
SIN LV-WAS



Immunodeficiency:T+B
Thrombocytopenia
Autoimmunity
WASp deficiency
Protein controling actin cytoskeleton in blood cells

L. Naldini, M.G. Roncarolo, A. Aiuti, A. Thrasher, A. Galy, et al

Lentiviral Hematopoietic Stem Cell Gene Therapy in Patients with Wiskott-Aldrich Syndrome

Alessandro Aiuti,* Luca Biasco, Samantha Scaramuzza, Francesca Ferrua, Maria Pia Cicalese, Cristina Baricordi, Francesca Dionisio, Andrea Calabria, Stefania Giannelli, Maria Carmina Castiello, Marita Bosticardo, Costanza Evangelio, Andrea Assanelli, Miriam Casiraghi, Sara Di Nunzio, Luciano Callegaro, Claudia Benati, Paolo Rizzardi, Danilo Pellin, Clelia Di Serio, Manfred Schmidt, Christof Von Kalle, Jason Gardner, Nalini Mehta, Victor Neduva, David J. Dow, Anne Galy, Roberto Miniero, Andrea Finocchi, Ayse Metin, Pinaki P. Banerjee, Jordan S. Orange, Stefania Galimberti, Maria Grazia Valsecchi, Alessandra Biffi, Eugenio Montini, Anna Villa, Fabio Ciceri, Maria Grazia Roncarolo, Luigi Naldini

SCIENCE VOL 341 23 AUGUST 2013

Close to 8 years of follow follow up
Safe, effective

Gene therapy of WAS

7 patients (Paris/London)

- Failure in one (overwhelming infections)
- Clinical benefit :

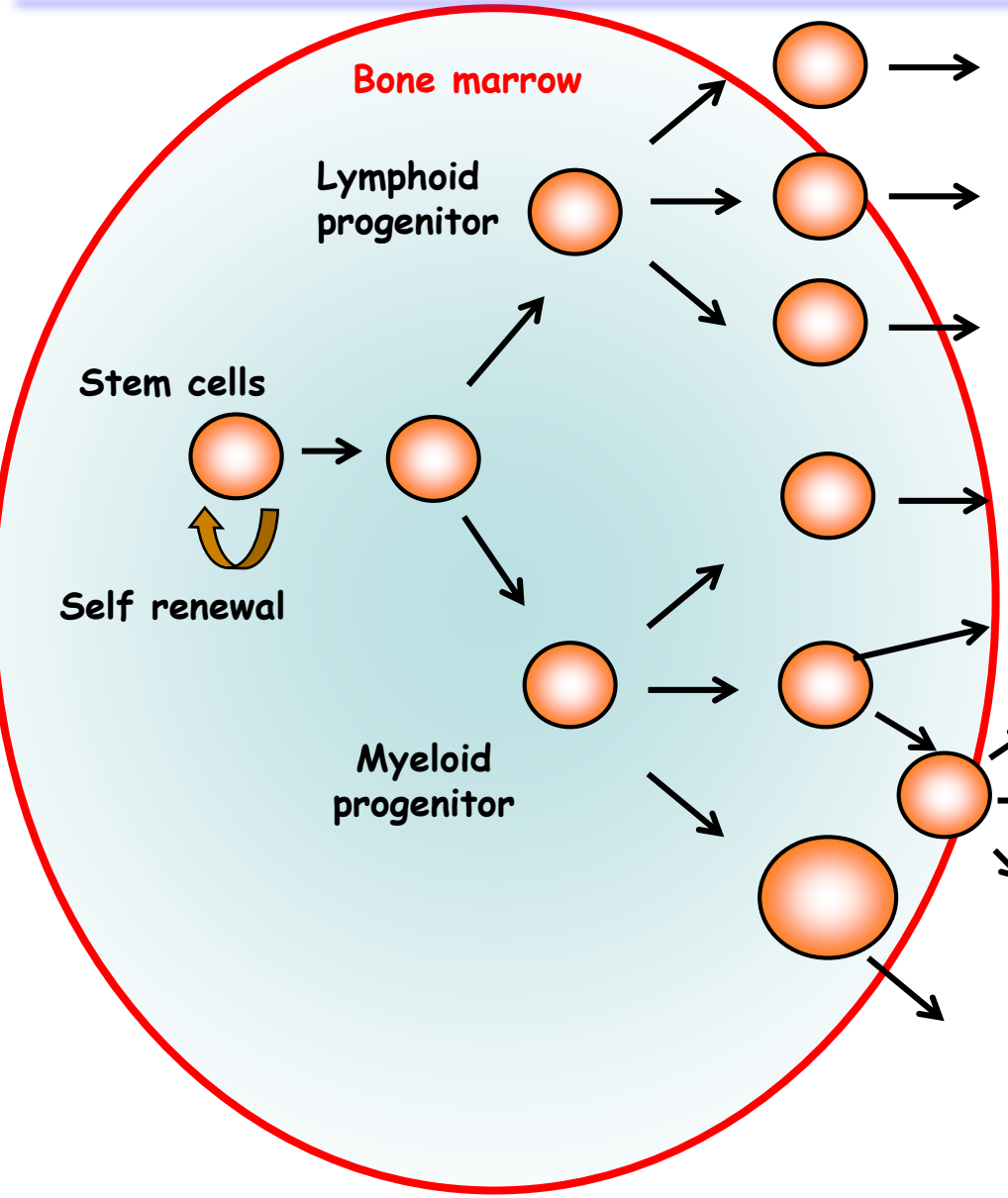
	score	Follow up
in 6	4.7 → 0.3	48-84 months

Resolution of infections, autoimmunity, eczema, severe bleedings

- Absence of toxicity
- No clonal dominance
- Multilineage engraftment

Overall 30 pts treated
(Milan, Paris, London, Boston)

Perspectives of gene therapy for PID

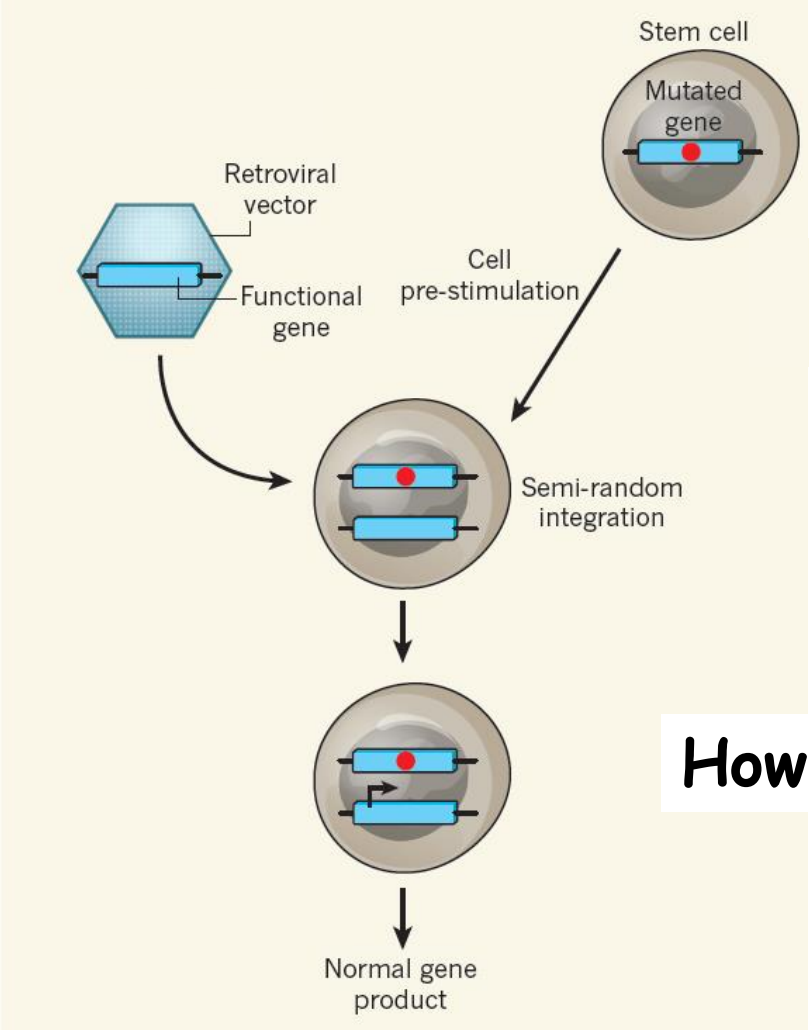


SCID X1
ADA SCID
WAS

ongoing projects :
other SCID,
CGD,LAD,HLH,IPEX,
...

international collaboration

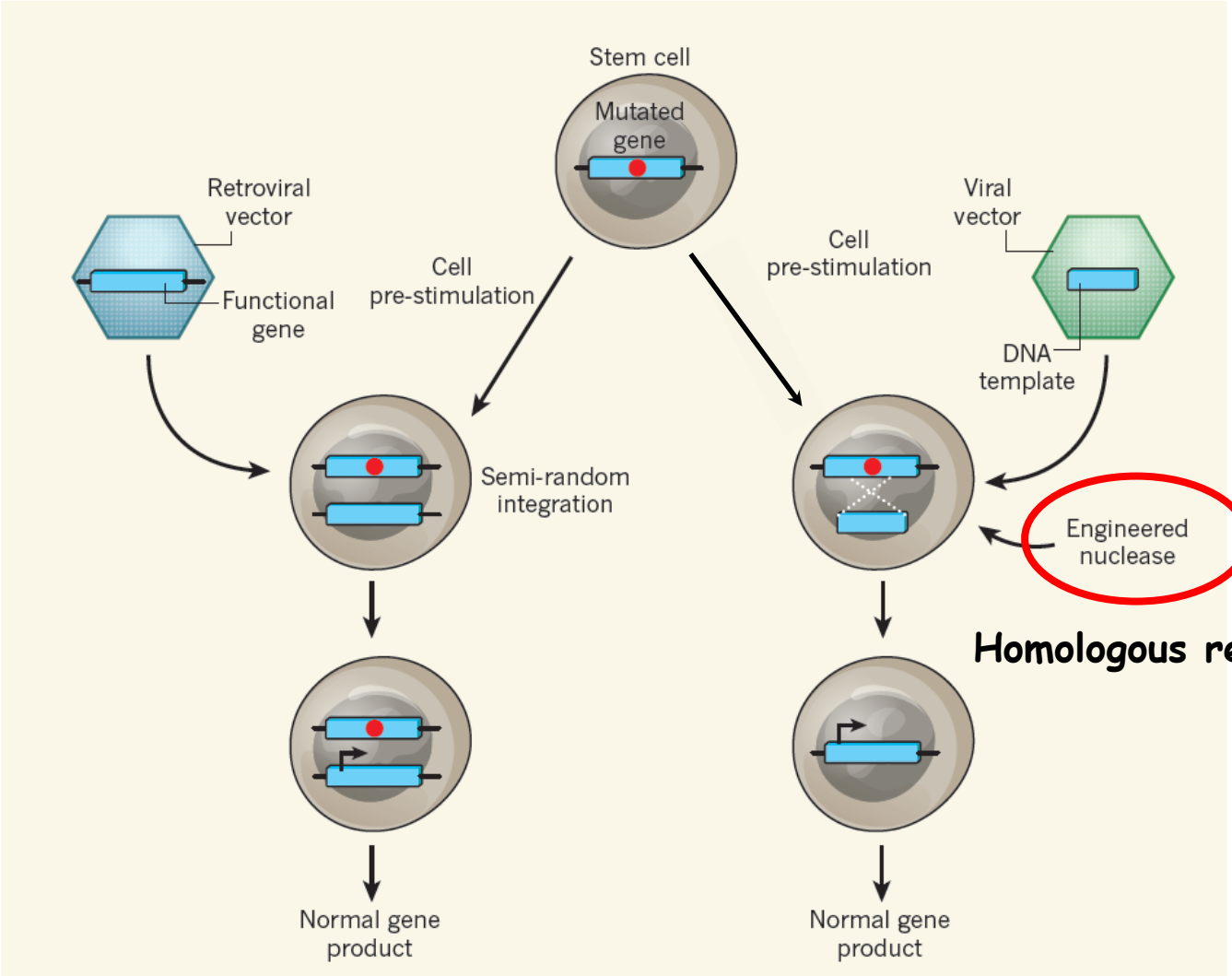
Present status of gene therapy



How to do better ?

Expression control of the transgene is not physiological

Gene therapy by gene editing ?



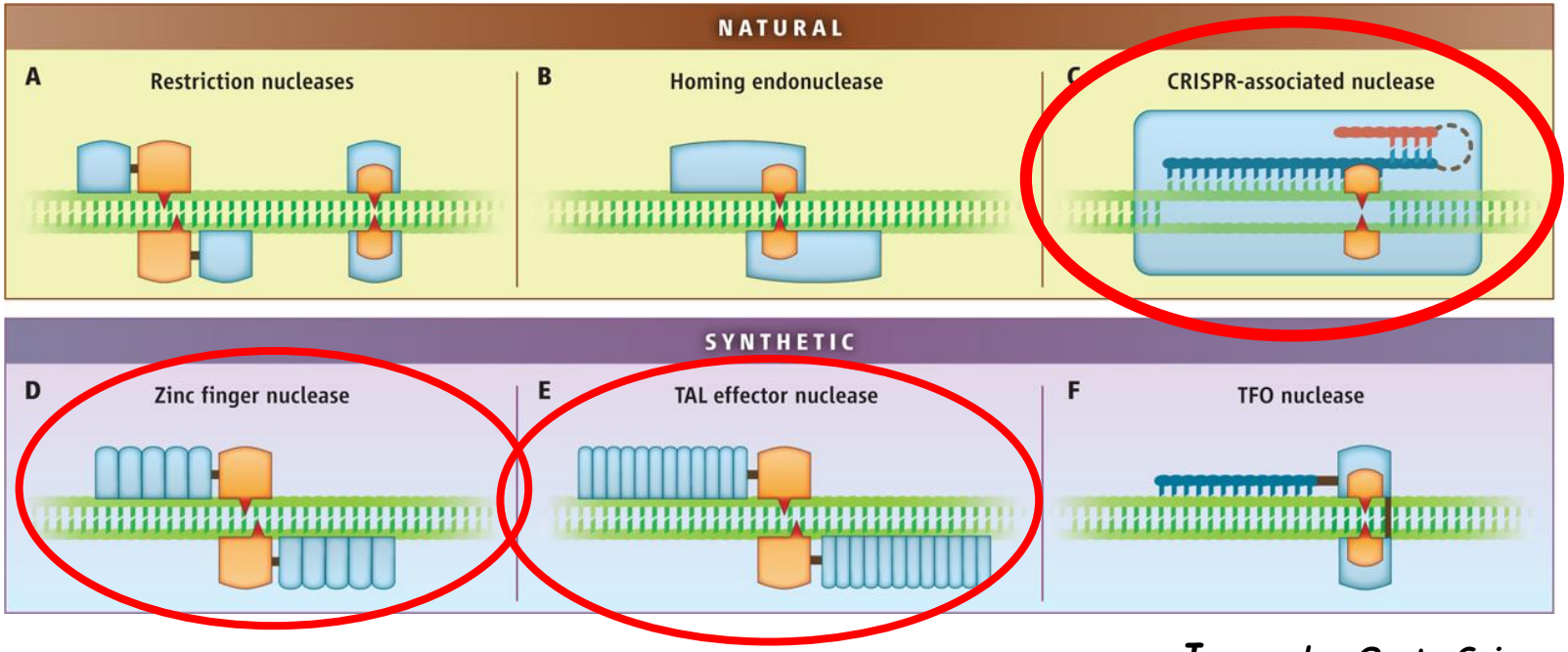
Homologous recombination

non physiological gene control

corrected gene
under physiological regulation !

Tools for genome editing

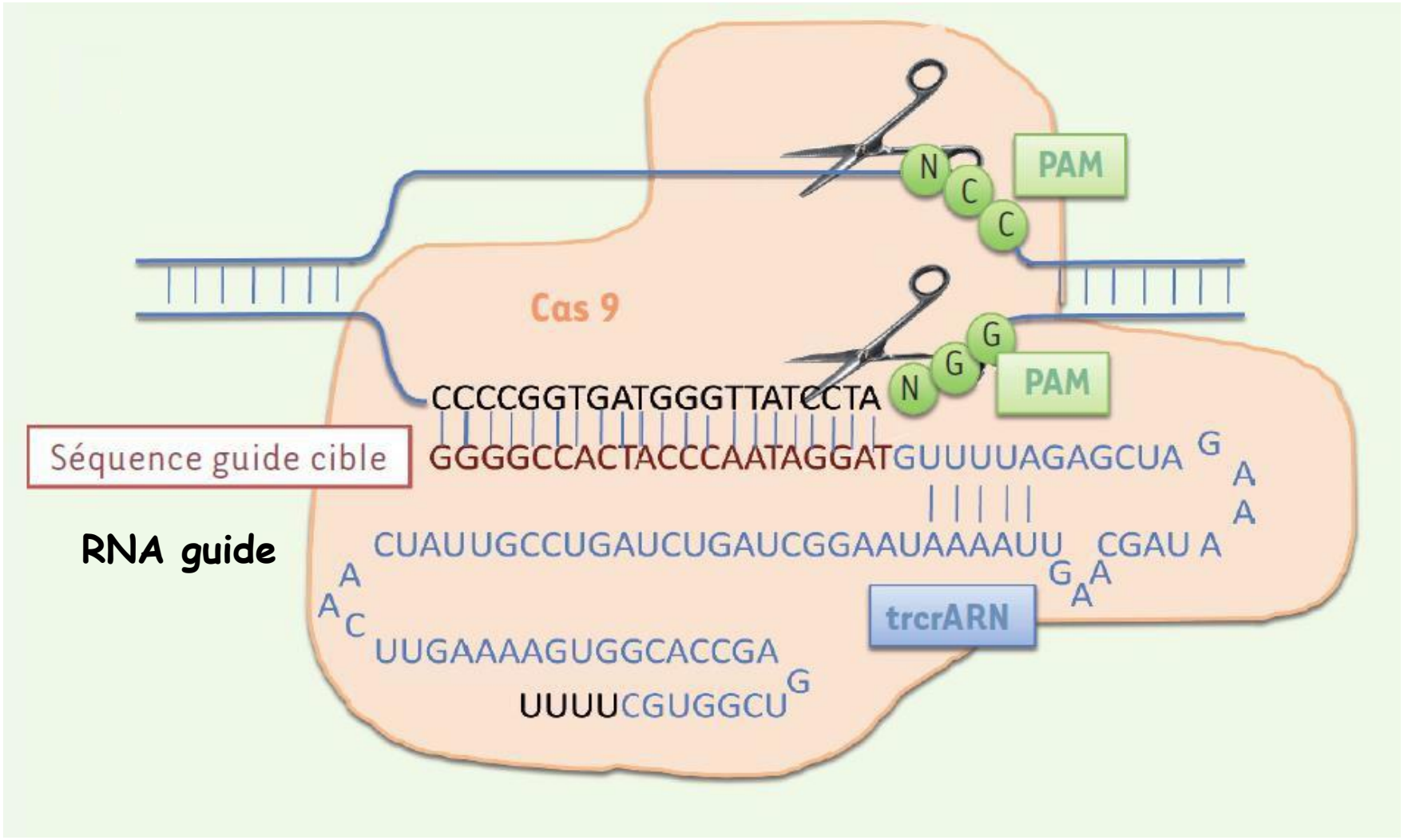
engineered RNA guided-nuclease
simple code
easy to design



J. van der Oost, Science 2013

engineered protein guided-nucleases
complex code
cumbersome to design

CRISPR-Cas9



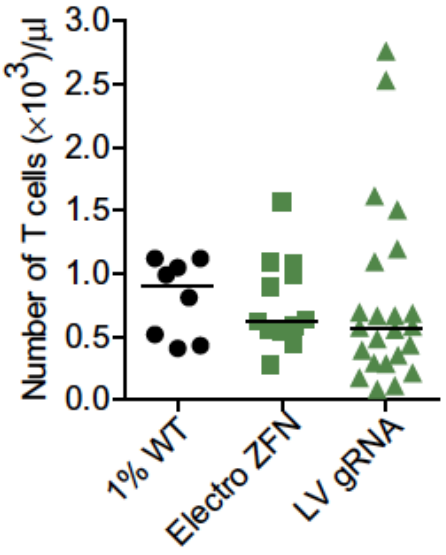
Gilgenkrantz, Med Sci, 2014

First preclinical tests for SCID X1

Preclinical modeling highlights the therapeutic potential of hematopoietic stem cell gene editing for correction of SCID-X1

Giulia Schiroli,[1,2] Samuele Ferrari,[1,2] Anthony Conway,[3] Aurelien Jacob,[1] Valentina Capo,[1] Luisa Albano,[1] Tiziana Plati,[1] Maria C. Castiello,[1] Francesca Sanvito,[4] Andrew R. Gennery,[5] Chiara Bovolenta,[6] Rahul Palchaudhuri,[7,8] David T. Scadden,[8] Michael C. Holmes,[3] Anna Villa,[1,9] Giovanni Sitia,[10] Angelo Lombardo,[1,2] Pietro Genovese,[1*†] Luigi Naldini[1,2*†]

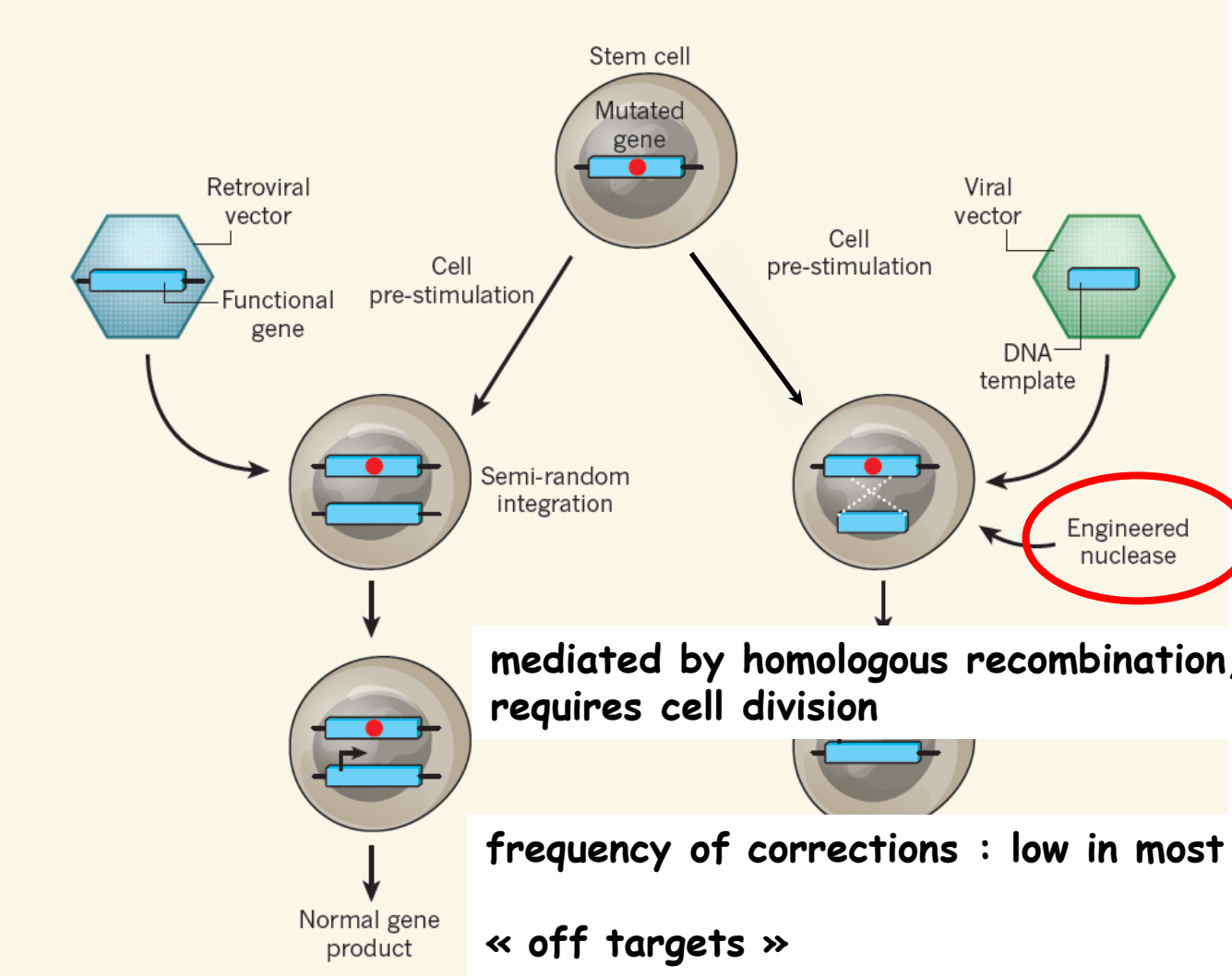
Schiroli *et al.*, *Sci. Transl. Med.* **9**, eaan0820 (2017) 11 October 2017



Patients cells edited and transplanted into immunodeficient mice
2 editing enzymes tested (ZFN, CRISPR)
Results equivalent to the transfer of 1% normal bone marrow

May be sufficient to treat SCID X1.., but not non SCID diseases

Gene therapy by gene editing



mediated by homologous recombination, requires cell division

frequency of corrections : low in most stem cells

« off targets »

Conclusions

- Major advances of HSCT to treat PID (80 diseases)
- Donor availability is no longer an issue in most cases
- Over the last 20 years, emergence of gene therapy that has proven to be efficacious and now safe, applicable to a number of PID
- Genome editing may be a future development of great value for some complex PID
- Choice of therapeutic strategy may in part depend on economical ressources