1-17-2017

Gene Therapy For Inherited Blood Diseases, From Viral Vectors To Gene Editing

Fulvio Mavilio
Genethon, Evry, France, fmavilio@genethon.fr

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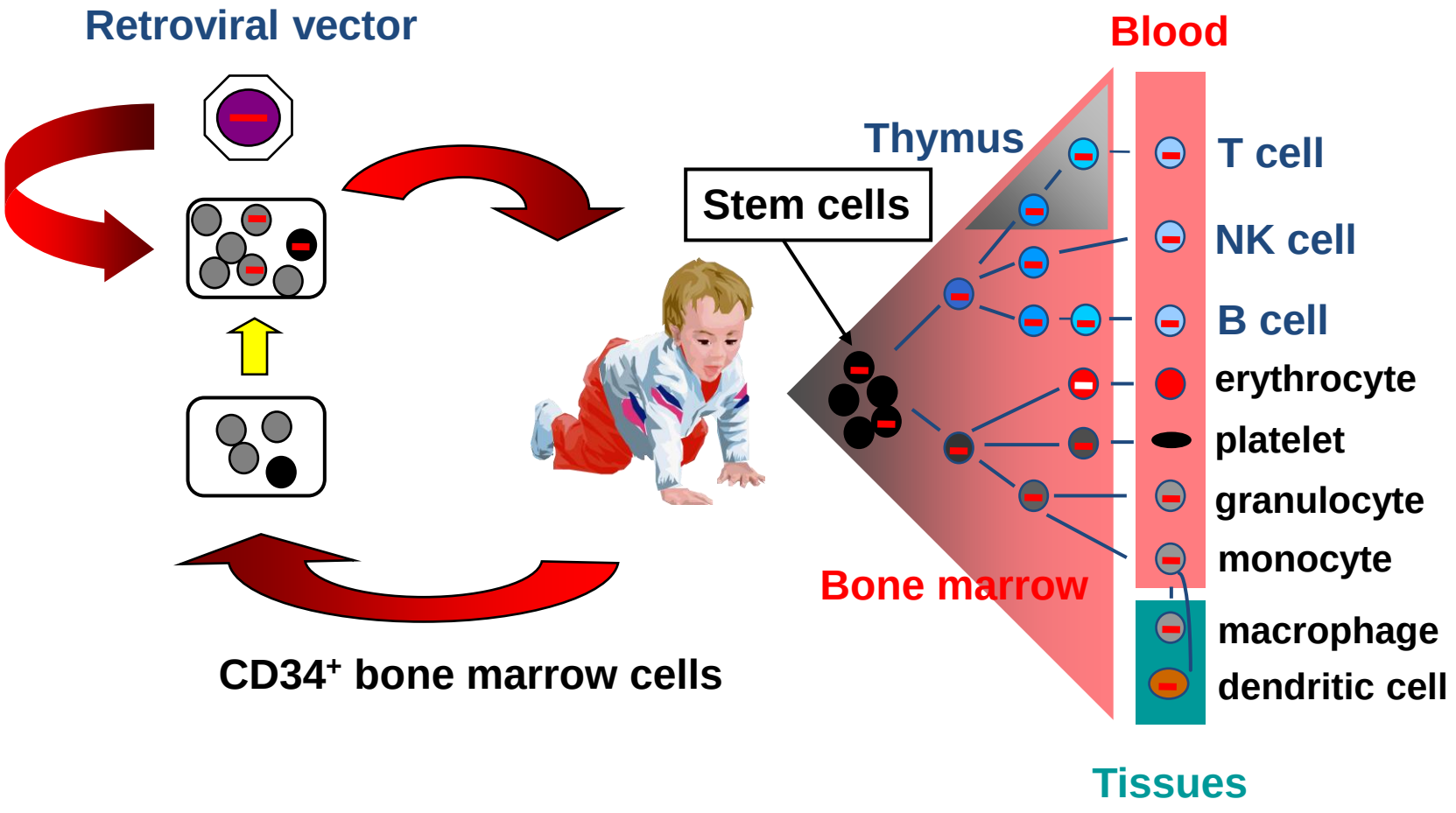
CURE THROUGH INNOVATION

Gene Therapy for Inherited Blood Diseases: from Viral Vectors to Gene Editing

Fulvio Mavilio
Genethon, Evry, France

Gene Therapy for blood genetic diseases



GÉNÉTHON
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ADA^{-} Severe combined immunodeficiency

Gene Therapy in Peripheral Blood Lymphocytes and Bone Marrow for ADA^{-} Immunodeficient Patients

Claudio Bordignon,* Luigi D. Notarangelo, Nadia Nobili, Giuliana Ferrari, Giulia Casorati, Paola Panina, Evelina Mazzolari, Daniela Maggioni, Claudia Rossi, Paolo Servida, Alberto G. Ugazio, Fulvio Mavilio

Adenosine deaminase (ADA) deficiency results in severe combined immunodeficiency, the first genetic disorder treated by gene therapy. Two different retroviral vectors were used to transfer ex vivo the human ADA minigene into bone marrow cells and peripheral blood lymphocytes from two patients undergoing exogenous enzyme replacement therapy. After 2 years of treatment, long-term survival of T and B lymphocytes, marrow cells, and granulocytes expressing the transferred ADA gene was demonstrated and resulted in normalization of the immune repertoire and restoration of cellular and humoral immunity. After discontinuation of treatment, T lymphocytes, derived from transduced peripheral blood lymphocytes, were progressively replaced by marrow-derived T cells in both patients. These results indicate successful gene transfer into long-lasting progenitor cells, producing a functional multilineage progeny.

SCIENCE • VOL. 270 • 20 OCTOBER 1995

- Rare genetic disorder characterized by loss of T, B and NK immune cells and metabolic defects, caused by lack of ADA
- Lethal in the first years of life, unless patients are kept in complete isolation; ERT available
- Fully matched allogeneic bone marrow transplantation available to less than 1/3 of patients

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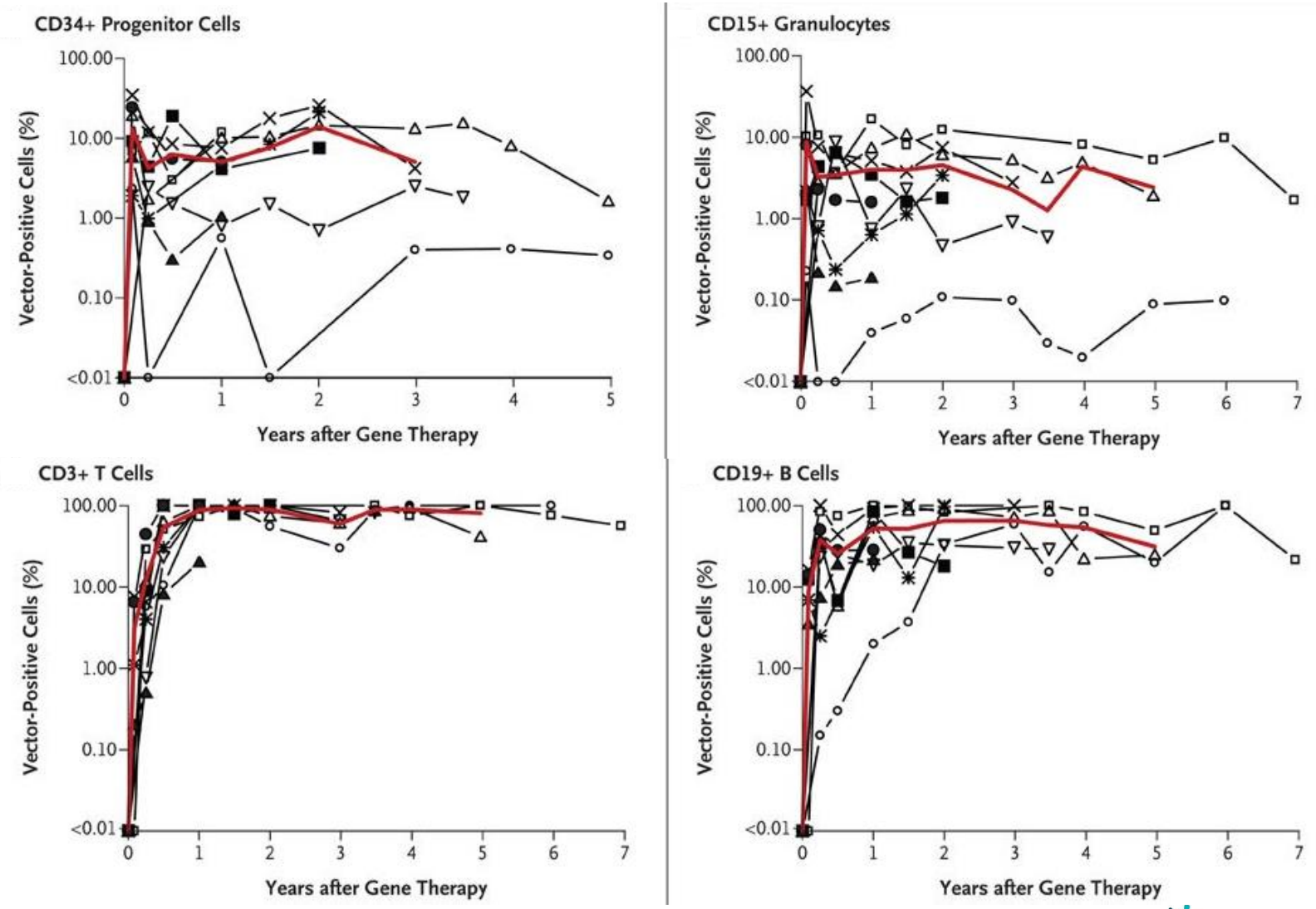
Gene therapy for ADA^{-} SCID



A. Aiuti et al., N. Engl. J. Med., 2009

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Gene therapy for ADA^{-} SCID

- 14 patients treated from 2000 to 2009
- 100% survival, 4 to 14 yrs follow-up. No side effects
- Engraftement of gene-corrected stem cells at 1% to >10% levels, selective advantage for gene-corrected T- cells
- Immunological reconstitution in all patients, and correction of the systemic metabolic defect in the majority of patients
- Protection from infections and normalization of growth parameters (height and weight) with no need for enzyme replacement therapy (12/14 patients)

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Gene therapy for ADA^{-} SCID

PRESS RELEASE

Issued: Friday 1 April London UK – LSE Announcement

GSK receives positive CHMP opinion in Europe for Strimvelis™, the first gene therapy to treat very rare disease, ADA-SCID

GlaxoSmithKline (LSE/NYSE: GSK) today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), in conjunction with the Committee for Advanced Therapies (CAT), has issued a positive opinion recommending marketing authorisation for Strimvelis to treat patients with a very rare disease called ADA-SCID (severe combined immunodeficiency due to adenosine deaminase deficiency). The medicine is a stem cell gene therapy created for an individual patient from their own cells which is intended to correct the root cause of the disease. If approved by the European Commission, the medicine - currently known as GSK2696273 (autologous CD34+ cells transduced to express ADA) - will be commercialised under the brand name Strimvelis, for the treatment of patients with ADA-SCID for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

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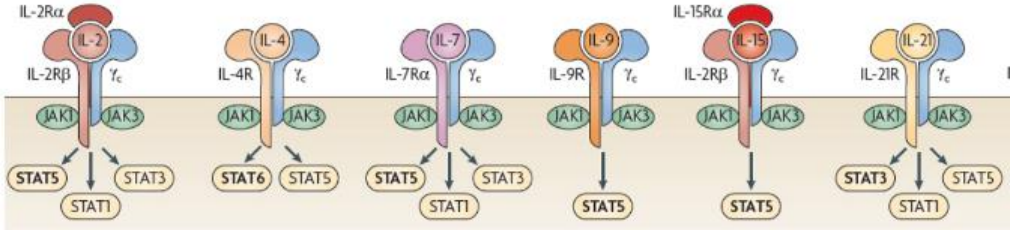
SCID-X1 (IL2RG deficiency)

- Rare genetic disorder characterized by loss of T, B and NK immune cells, caused by deficiency of the IL-2 common gamma receptor



- Lethal in the first years of life, unless patients are kept in complete isolation
- Fully matched allogeneic bone marrow transplantation available to only 1/3 of patients

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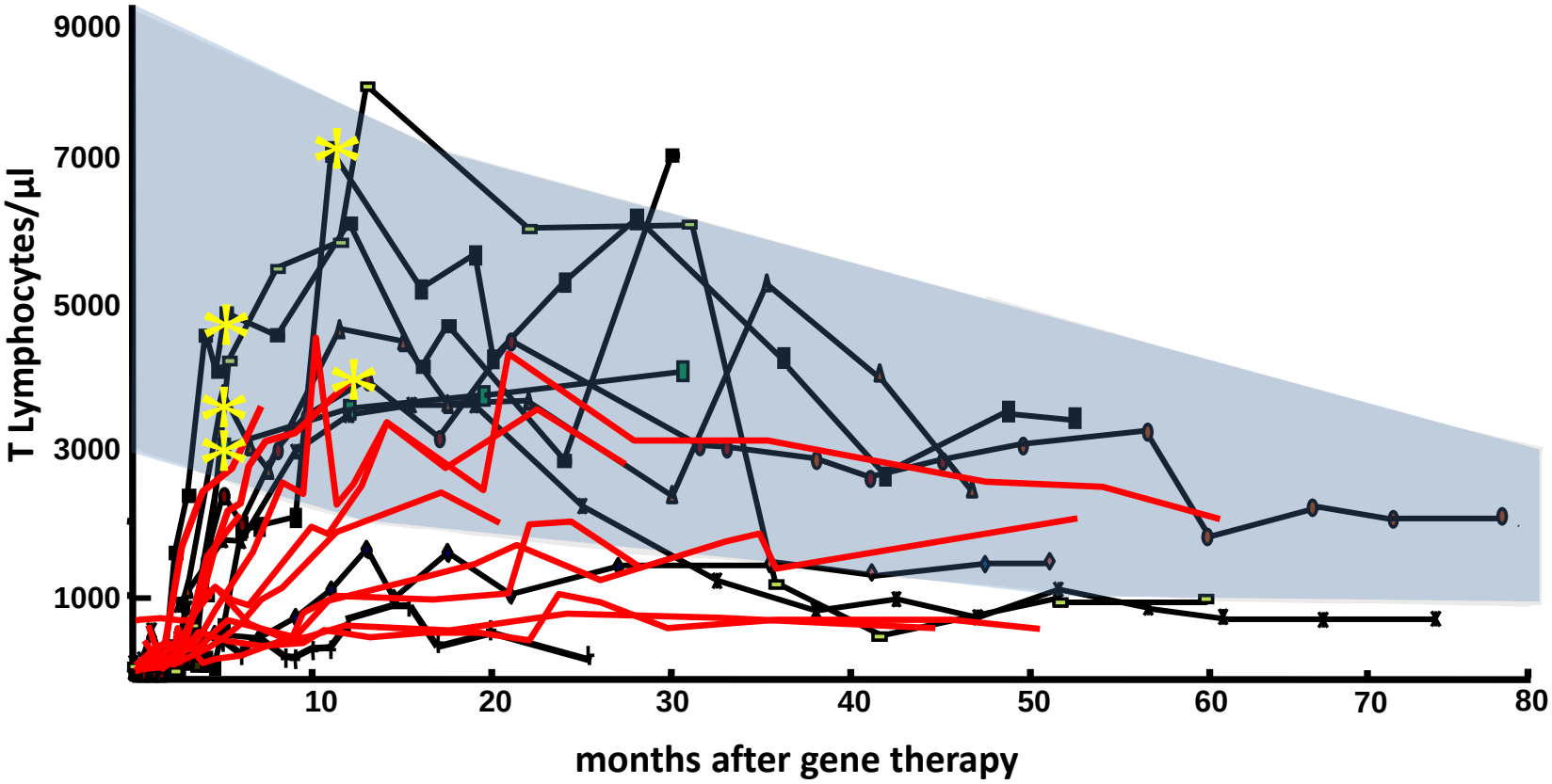
Gene therapy for SCID-X1 (IL2RG deficiency)



Hacein-Bey-Abina et al Science 2003; Hacein-Bey-Abina et al JCI 2008; Howe et al JCI 2008;
Hacein-Bey-Abina et al NEJM 2010; Gaspar et al Sci Transl Med 2011;
+ unpublished data courtesy of Salima Hacein-Bey and Adrian Thrasher

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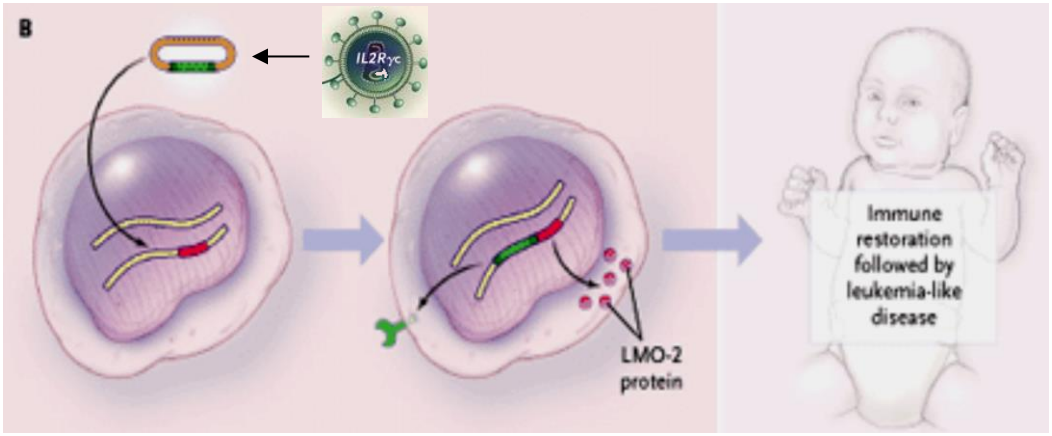
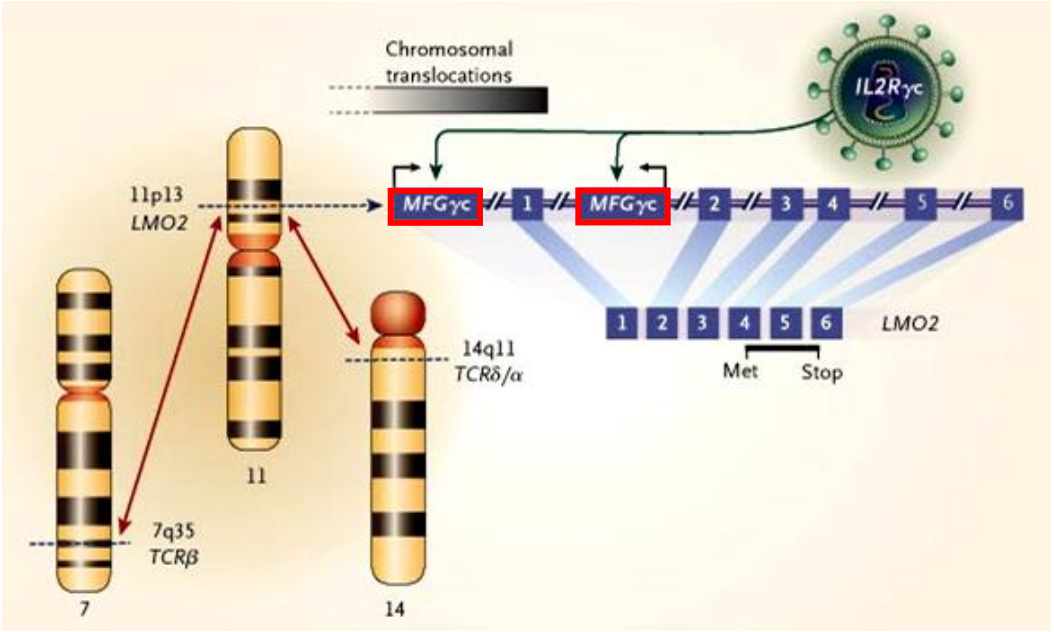
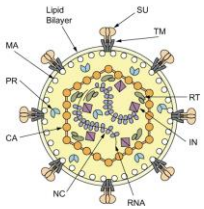
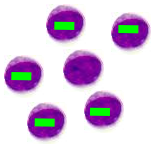
Side effects of gene therapy: insertional oncogenesis





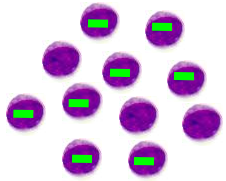
Mapping viral integration sites in the genome





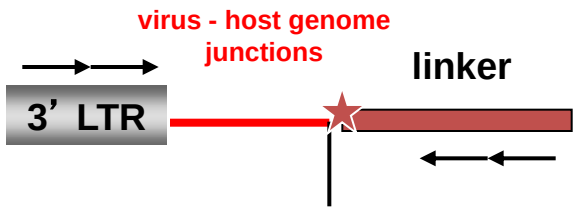
CD34⁺ cells

~3 doublings



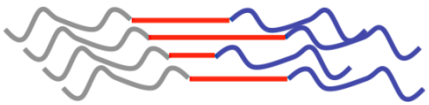
>90% CD34⁺
>40% CD133⁺

LM-PCR



Illumina sequencing

Analysis



Library of virus - host genome junction amplicons

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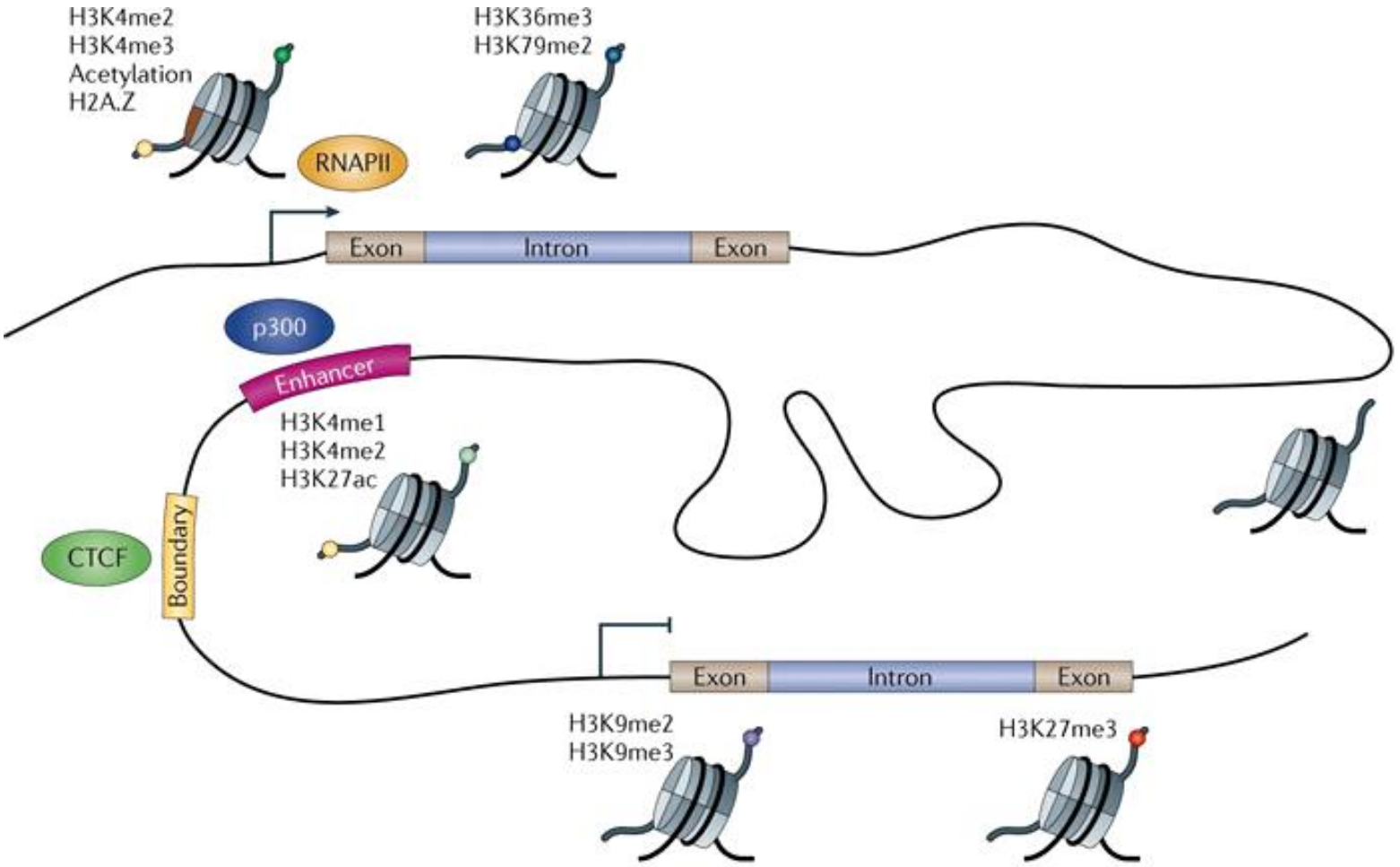
The epigenetic landscape of mammalian chromatin



Nature Reviews | Genetics

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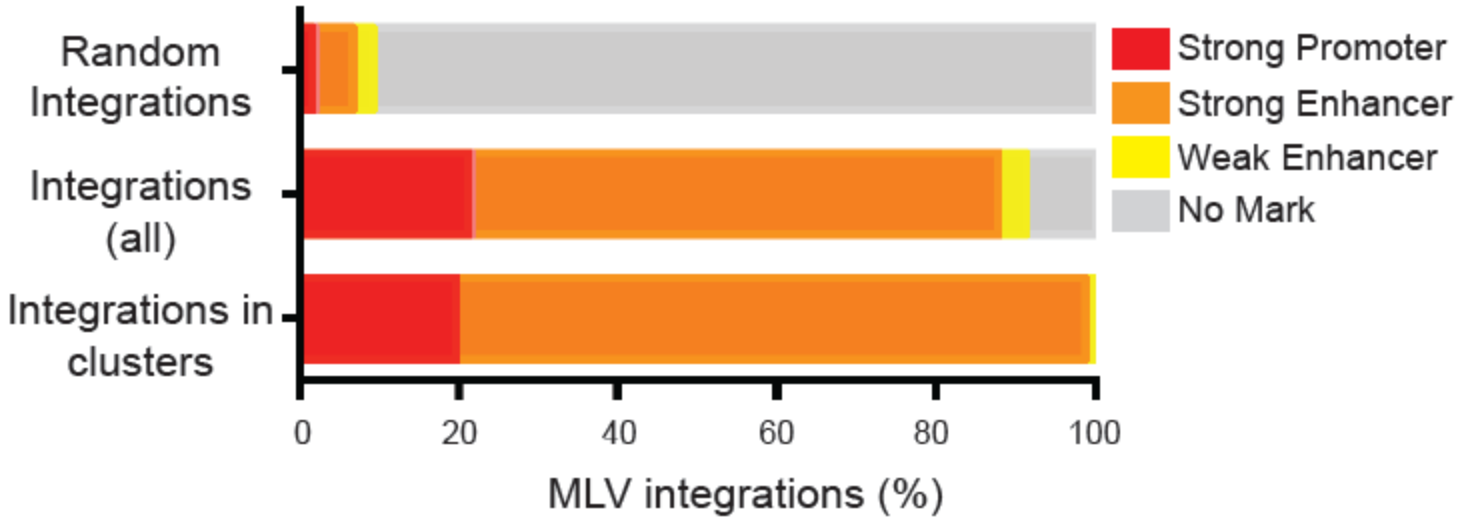
MLV integrates in regulatory regions



A. Cavazza et al., Stem Cell Reports, 2016

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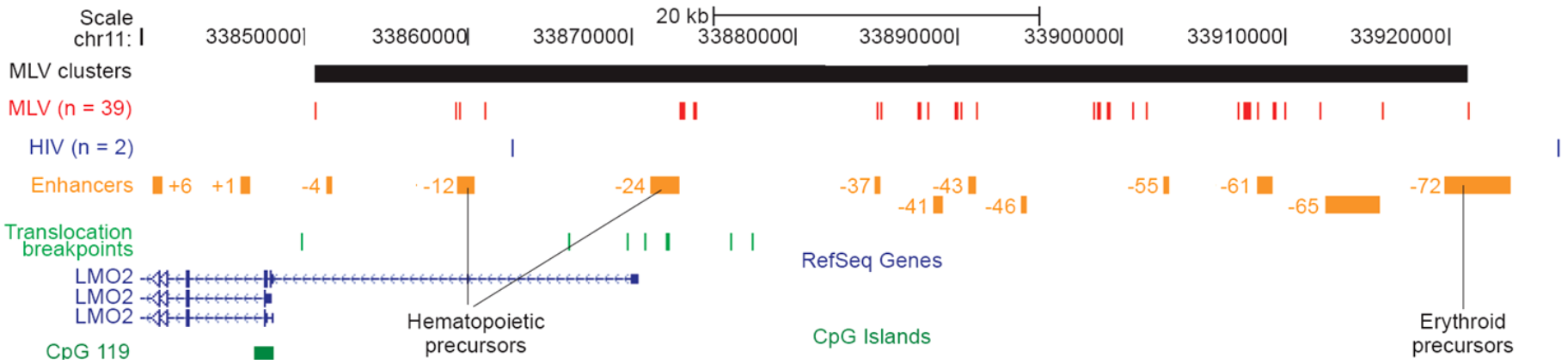
MLV integrates in regulatory regions: the LMO2 locus



Frequency of integration in the LMO2 locus: 1:1,200

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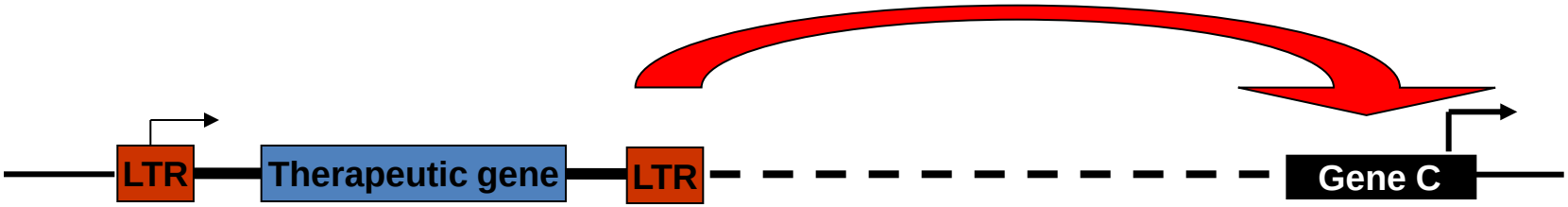
MLV interferes with normal gene function

Retroviral vector



Retroviral vector

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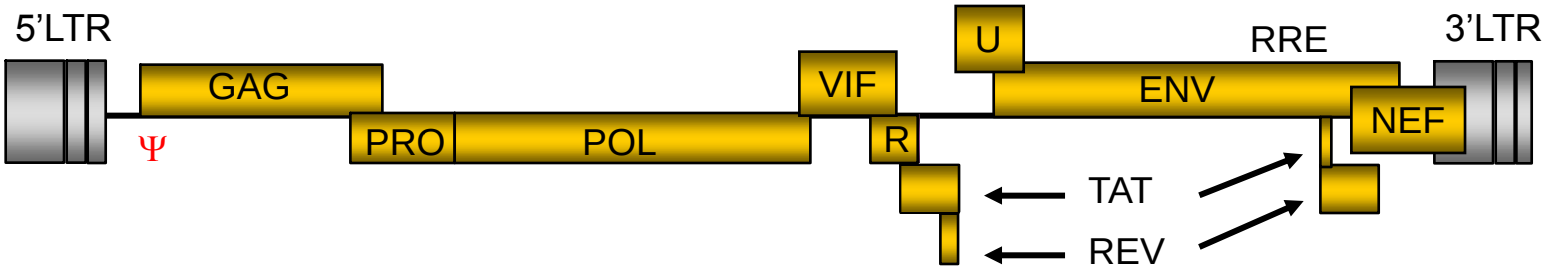
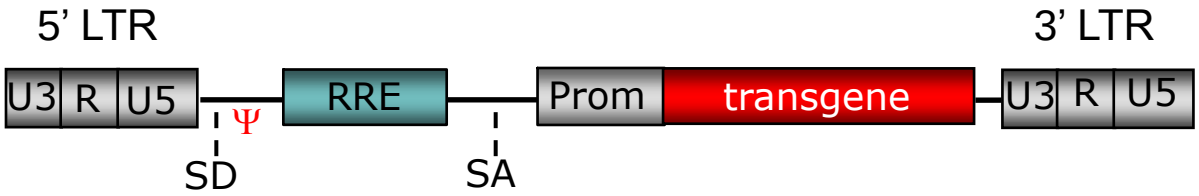
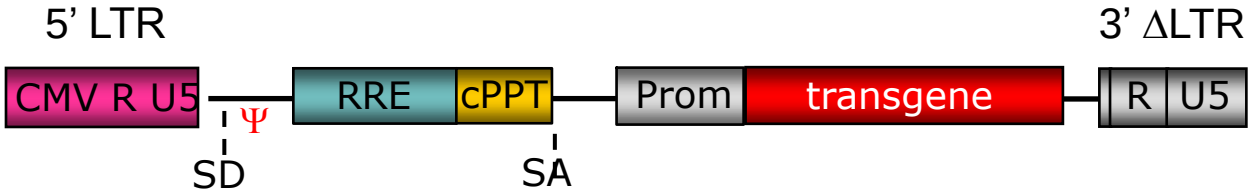
HIV-derived Lentiviral Vectors



HIV provirus



LTR transfer vector (Tat-dependent)



SIN transfer vector (Tat-independent)

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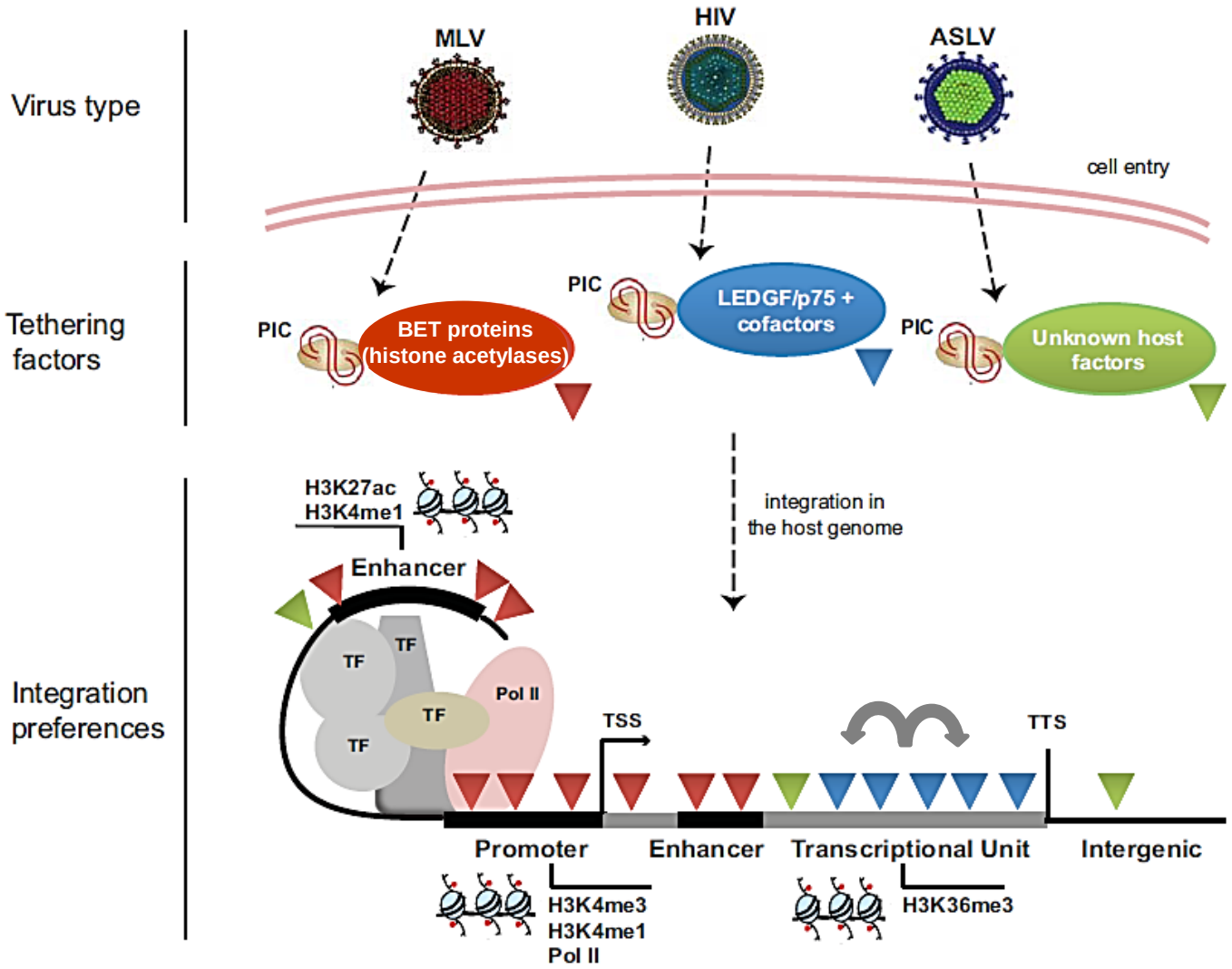
Retrovirus-genome interactions



Cavazza et al., Hum. Gene Ther. 2013

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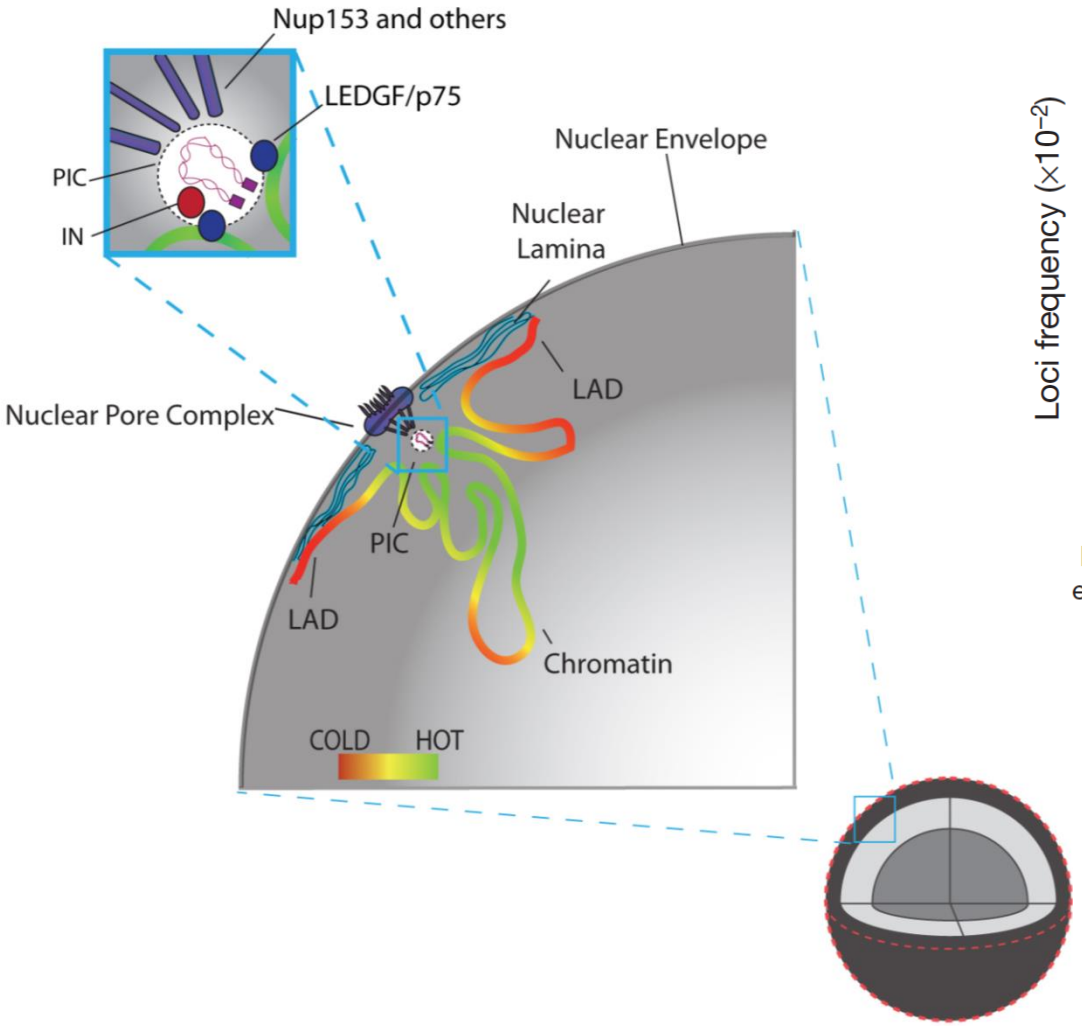
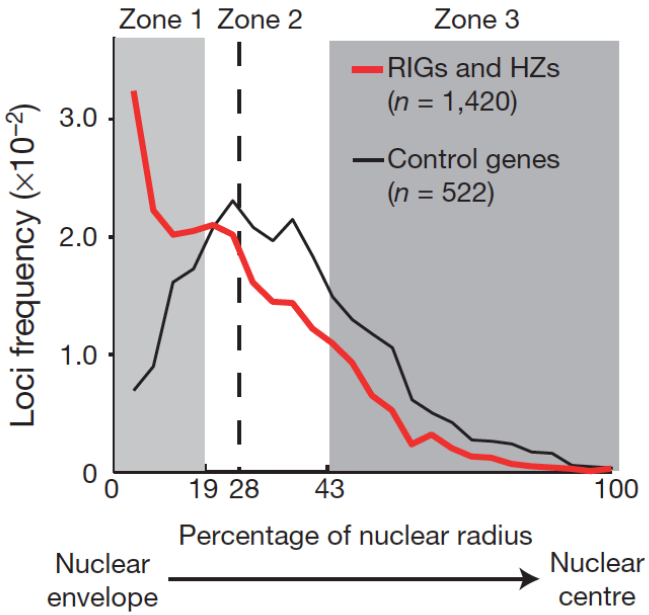
HIV targets genes at the nuclear periphery





Marini et al., Nature 2015

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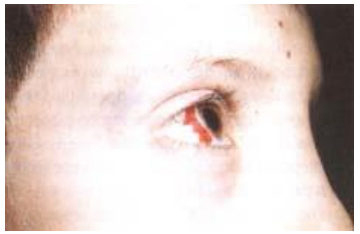
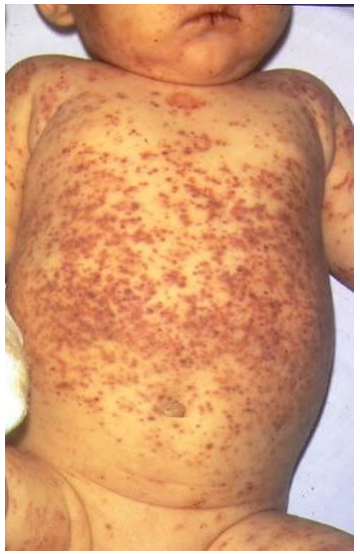
Gene Therapy for Wiskott-Aldrich Syndrome

- X-linked, rare primary immunodeficiency
- Multiple symptoms:
  - Hemorrhage (microthrombocytopenia)
  - Immunodeficiency
  - Eczema
  - Auto-immune disorders
  - Lymphoreticular malignancies
- Lack of WASP, a cytoskeletal component
- Treated by transplantation of allogeneic HSC





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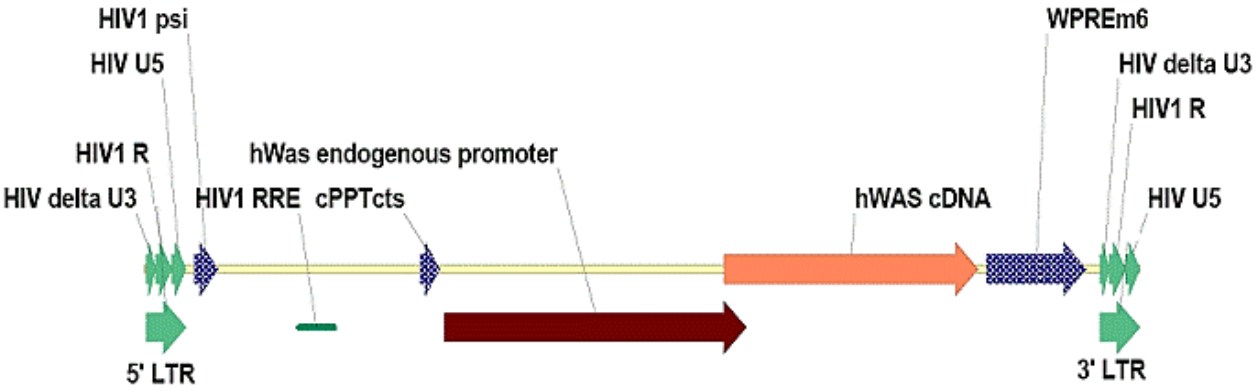
Gene Therapy for Wiskott-Aldrich Syndrome

- pCCL-Wp-WAS is a replication-defective, self-inactivating lentiviral vector derived from HIV1 and pseudotyped with VSV-G
- The vector contains the human WAS cDNA driven by its endogenous 1.6-kb promoter.



w1.6_hWASP_WPRE integrated sequence

5905 bp

Gene Therapy for WAS: results

- 13 patients 0.8 to 15.5 years of age treated in three centers in Europe and the US
- 12/13 patients alive with follow-up of 4-50 months
- rapid and sustained immune reconstitution, substantial clinical improvement (cleared eczema), sustained though slower, and in some patients incomplete, platelet reconstitution
- no treatment-related severe adverse events
- polyclonal vector integration pattern, no evidence for skewed hematopoietic reconstitution or clonal dominance

Great Ormond Street Hospital for Children NHS Trust

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Boston Children's Hospital
Until every child is well™

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The WAS gene therapy trials

RESEARCH ARTICLE

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

Alessandro Aiuti,[1,2,3,4]* Luca Biasco,[1]† Samantha Scaramuzza,[1]† Francesca Ferrua,[2,3,5] Maria Pia Cicalese,[2,3] Cristina Baricordi,[1] Francesca Dionisio,[1] Andrea Calabria,[1] Stefania Giannelli,[1] Maria Carmina Castiello,[1,5] Marita Bosticardo,[1] Costanza Evangelio,[2,3] Andrea Assanelli,[3,6] Miriam Casiraghi,[2] Sara Di Nunzio,[2] Luciano Callegaro,[2] Claudia Benati,[7] Paolo Rizzardi,[7] Danilo Pellin,[8] Clelia Di Serio,[8] Manfred Schmidt,[9] Christof Von Kalle,[9] Jason Gardner,[10] Nalini Mehta,[11] Victor Neduva,[11] David J. Dow,[11] Anne Galy,[12] Roberto Miniero,[13] Andrea Finocchi,[4] Ayse Metin,[14] Pinaki P. Banerjee,[15] Jordan S. Orange,[15] Stefania Galimberti,[16] Maria Grazia Valsecchi,[16] Alessandra Biffi,[1,2,3] Eugenio Montini,[1] Anna Villa,[1,17] Fabio Ciceri,[3,6] Maria Grazia Roncarolo,[1,2,3,5]‡ Luigi Naldini[1,5]‡

Wiskott-Aldrich syndrome (WAS) is an inherited immunodeficiency caused by mutations in the gene encoding WASP, a protein regulating the cytoskeleton. Hematopoietic stem/progenitor cell (HSPC) transplants can be curative, but, when matched donors are unavailable, infusion of autologous HSPCs modified ex vivo by gene therapy is an alternative approach. We used a lentiviral vector encoding functional WASP to genetically correct HSPCs from three WAS patients and reinfused the cells after a reduced-intensity conditioning regimen. All three patients showed stable engraftment of WASP-expressing cells and improvements in platelet counts, immune functions, and clinical scores. Vector integration analyses revealed highly polyclonal and multilineage haematopoiesis resulting from the gene-corrected HSPCs. Lentiviral gene therapy did not induce selection of integrations near oncogenes, and no aberrant clonal expansion was observed after 20 to 32 months. Although extended clinical observation is required to establish long-term safety, lentiviral gene therapy represents a promising treatment for WAS.

Wiskott-Aldrich syndrome (WAS) is an X-linked primary immunodeficiency characterized by infections, microthrombocytopenia, eczema, autoimmunity, and lymphoid malignancies (*1*, *2*). The disorder is caused by mutations in the *WAS* gene, which codes for WASP, a protein that regulates the cytoskeleton. WASP-defective immune cells display alterations in proliferative responses after activation, cell migration, immunological synapsis formation, and cytotoxicity (*3*–*5*). Allogeneic hematopoietic stem/progenitor cell (HSPC) transplantation can be curative, but it is often associated with substantial morbidity and mortality, particularly in the absence of fully matched donors (*6*–*8*).

For patients without matched donors, an alternative therapeutic strategy is the infusion of autologous HSPCs that have been genetically corrected ex vivo. This gene therapy approach has been successful in more than 50 patients affected by primary immunodeficiencies, including 10 WAS patients treated with HSPCs transduced with a γ-retroviral vector encoding a functional WAS gene (*9*–*15*). Gene therapy combined with a reduced intensity conditioning regimen proved to be effective and safe in patients with severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency, who were followed up to 13 years after treatment (*9*, *15*, *16*). In contrast, despite the initial clinical benefit, gene therapy with γ-retroviral–transduced HSPC was associated with the development of leukemia or myelodysplasia in patients with SCID-X1, chronic granulomatosis disease, and WAS (*14*, *17*–*20*). These adverse events were ascribed to vector insertion sites (ISs) near specific proto-oncogenes, leading to their transactivation by enhancer/promoter sequences within the long-terminal repeat (LTR) of the retroviral vector (*10*–*12*, *21*–*23*). In the case of WAS, characterization of ISs over the first 2 years of follow-up revealed a highly skewed insertion profile in vivo, resulting in the expansion of clones with insertions in proto-oncogenes such as *LMO2* (*12*), some of which progressed to leukemias (*14*, *24*). The possibility of vector-driven leukemogenesis is a particular concern for WAS patients, who are cancer-prone (*1*).

Lentiviral vectors with self-inactivating (SIN) LTRs integrate efficiently in HSPC, allow robust transgene expression from a promoter of choice inserted within the vector, and could potentially be safer for gene therapy applications (*24*–*26*). Lentiviral-based HSPC gene therapy combined with full conditioning has been used to treat three patients with adrenoleukodystrophy (ALD) (*27*) and one patient with β-thalassemia (*28*), resulting in 10 to 15% progenitor cell marking with therapeutic benefit. Although a relative expansion of a clone harboring an insertion in the *HMGA2* gene was observed in the β-thalassemia patient (*28*), no aberrant clonal proliferation has been reported for the lentiviral-based trials up to 5 years after treatment (*27*, *29*).

We developed a SIN lentiviral vector coding for human WASP under the control of a 1.6-kb reconstituted WAS gene promoter (LV-w1.6W) (*3*). The use of this endogenous promoter ensures that the transgene is expressed in a physiological manner (*4*), restoring WASP expression and function in human and murine WAS cells (*3*, *30*–*34*). Its moderate enhancer activity combined with the SIN LTR design reduces the risk of insertional mutagenesis (*35*), as shown by in vitro transformation assays (*36*) and preclinical in vivo studies in WASP-deficient mice (*34*, *37*). These data provided the rationale for a phase I/II clinical trial in which LV-w1.6W was used as a gene therapy vector for treatment of patients with WAS (*38*).

Results

Lentiviral Transduction of HSPC and Infusion of Gene-Corrected Cells into Patients Pretreated with Reduced Intensity Conditioning

Three children with WAS, who had been shown by genotyping to carry severe mutations in the X-linked *WAS* gene and who did not have compatible allogeneic donors, were enrolled in the phase I/II clinical trial (Table 1). All patients suffered from recurrent infections, eczema, bleeding, and thrombocytopenia, with a disease score ranging from 3 to 4 (*39*) (Table 1). Autologous bone-marrow (BM)–derived CD34$^+$ cells were collected, transduced twice with purified LV-w1.6W vector using an optimized protocol (fig. S1) (*34*), and reinfused intravenously back into the patients 3 days after collection. The vector and genetically modified

[1]San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Division of Regenerative Medicine, Stem Cells, and Gene Therapy, San Raffaele Scientific Institute, 20132 Milan, Italy. [2]HSR-TIGET Pediatric Clinical Research Unit, San Raffaele Scientific Institute, 20132 Milan, Italy. [3]Pediatric Immunohematology and Bone Marrow Transplant Unit, San Raffaele Scientific Institute, 20132 Milan, Italy. [4]University Department of Pediatrics (DPUO), Bambino Gesù Children's Hospital and Tor Vergata University, School of Medicine, 00165 Rome. [5]Vita-Salute San Raffaele University, 20132 Milan, Italy. [6]Hematology and Bone Marrow Transplant Unit, San Raffaele Scientific Institute, 20132 Milan, Italy. [7]MolMed S.p.A., 20132 Milan, Italy. [8]University Centre of Statistics in the Biomedical Sciences (CUSSB), Vita-Salute San Raffaele University, 20132 Milan, Italy. [9]Nationales Zentrum für Tumorerkrankungen (NCT), Deutsches Krebsforschungszentrum (DKFZ), 69120 Heidelberg, Germany. [10]Regenerative Medicine Discovery Performance Unit, GlaxoSmithKline Research and Development, King of Prussia, 19406 PA, USA. [11]Molecular and Cellular Technologies, GlaxoSmithKline, Stevenage Herts SG1 2NY, UK. [12]Unité Mixte de Recherche (UMR) 951, Molecular Immunology and Biotherapies, Genethon, 91002 Evry, France. [13]Dipartimento di Scienze Mediche e Chirurgiche, Università Magna Graecia di Catanzaro, 88100 Catanzaro, Italy. [14]Ankara Children's Hospital, 06050 Ankara, Turkey. [15]Texas Children's Hospital, Baylor College of Medicine, Houston, TX 73030, USA. [16]Dipartimento di Medicina Clinica e Prevenzione, University of Milano-Bicocca, 20126 Monza, Italy. [17]Istituto di Ricerca Genetica e Biomedica (IRGB)-Consiglio Nazionale delle Ricerche (CNR), 20138 Milan, Italy.

*Corresponding author. E-mail: aiuti.alessandro@hsr.it
†These authors contributed equally to this work.
‡These authors contributed equally to this work.

Research

Preliminary Communication

Outcomes Following Gene Therapy in Patients With Severe Wiskott-Aldrich Syndrome

Salima Hacein-Bey Abina, PharmD, PhD; H. Bobby Gaspar, MRCP, PhD; Johanna Blondeau, MS; Laure Caccavelli, PhD; Sabine Charrier, PhD; Karen Buckland, PhD; Capucine Picard, MD, PhD; Emmanuelle Six, PhD; Nourredine Himoudi, PhD; Kimberly Gilmour, PhD; Anne-Marie McNicol, PhD; Havinder Hara, MS; Jinhua Xu-Bayford, DipHE; Christine Rivat, PhD; Fabien Touzot, MD, PhD; Fulvio Mavilio, PhD; Annick Lim, MS; Jean-Marc Treluyer, MD, PhD; Sébastien Héritier, MD; Francois Lefrère, MD; Jeremy Magalon, PharmD; Isabelle Pengue-Koyi, PharmD, PhD; Géraldine Honnet, MD; Stéphane Blanche, MD; Eric A. Sherman, BA; Frances Male, BA; Charles Berry, PhD; Nirav Malani, MS; Frederic D. Bushman, PhD; Alain Fischer, MD, PhD; Adrian J. Thrasher, MB, BS, PhD; Anne Galy, PhD; Marina Cavazzana, MD, PhD

IMPORTANCE Wiskott-Aldrich syndrome is a rare primary immunodeficiency associated with severe microthrombocytopenia. Partially HLA antigen–matched allogeneic hematopoietic stem cell (HSC) transplantation is often curative but is associated with significant comorbidity.

OBJECTIVE To assess the outcomes and safety of autologous HSC gene therapy in Wiskott-Aldrich syndrome.

DESIGN, SETTING, AND PARTICIPANTS Gene-corrected autologous HSCs were infused in 7 consecutive patients with severe Wiskott-Aldrich syndrome lacking HLA antigen–matched related or unrelated HSC donors (age range, 0.8-15.5 years; mean, 7 years) following myeloablative conditioning. Patients were enrolled in France and England and treated between December 2010 and January 2014. Follow-up of patients in this intermediate analysis ranged from 9 to 42 months.

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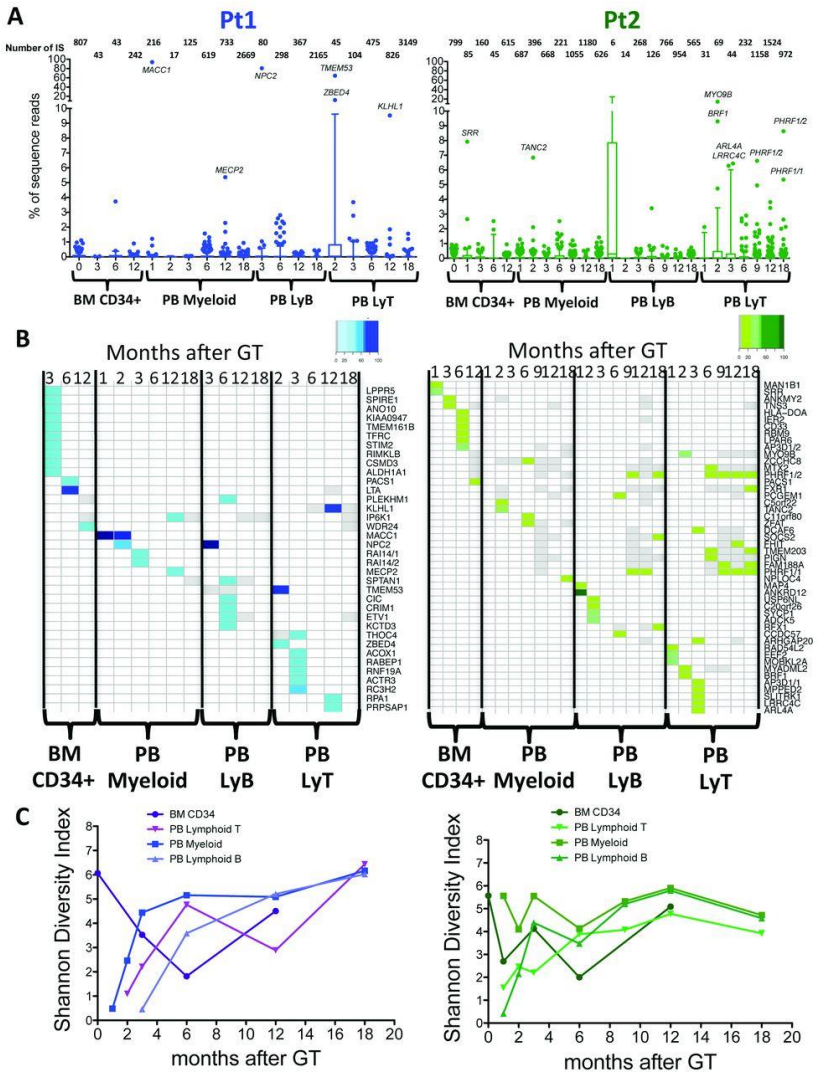
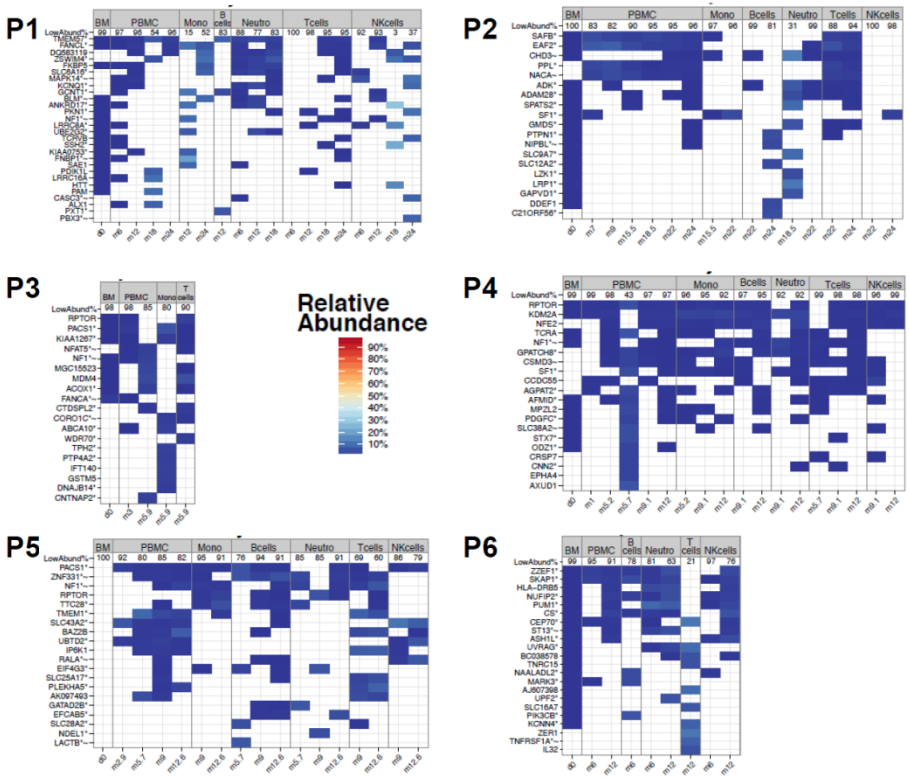
Gene therapy for WAS: insertion site analysis



Aiuti A. et al., Science 2014



Hacein-Bey Abina et al., JAMA 2015

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Gene Therapy for blood genetic diseases

Active clinical trials

- SCID-X1 (BCH, UCL, Necker)
- Adrenoleukodystrophy (Bluebird Bio)
- Metachromatic Leucodystrophy (TIGET)
- Chronic Granulomatous Disease (Genethon, UCLA, BCH, NIH)
- Fanconi Anemia (CIEMAT, FHCC)
- β-thalassmia/HbE (Bluebird Bio)
- β-thalassemia (TIGET)
- Sickle-Cell Disease (Bluebird Bio)
- Sickle-Cell Disease (UCLA)

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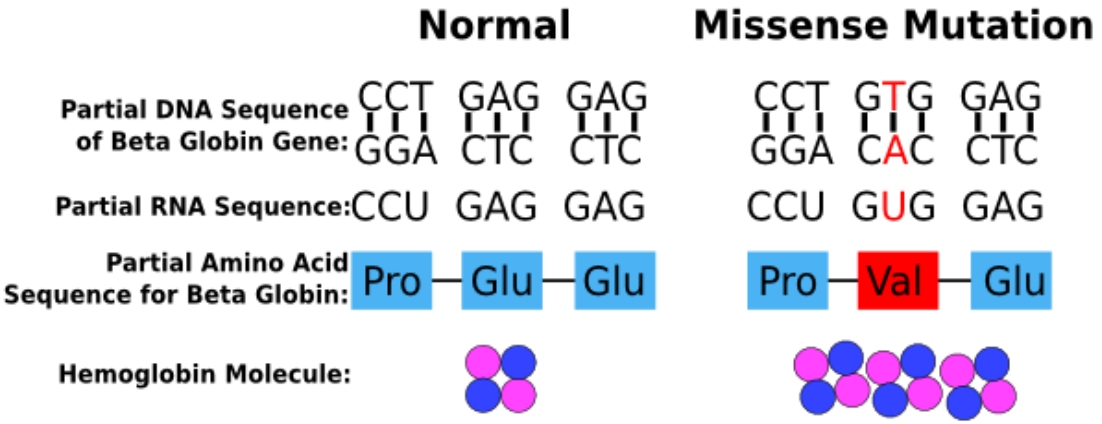
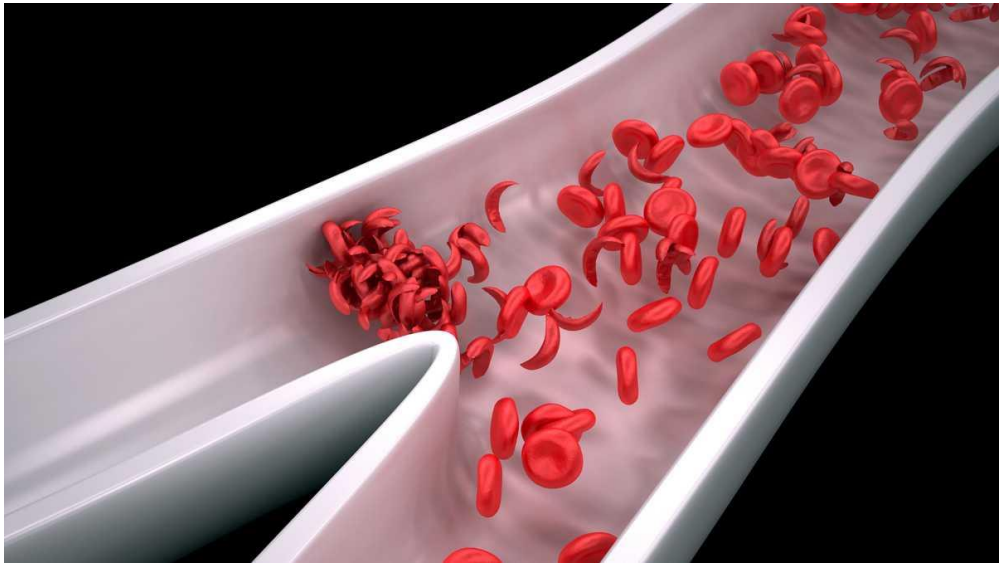
Sickle cell disease





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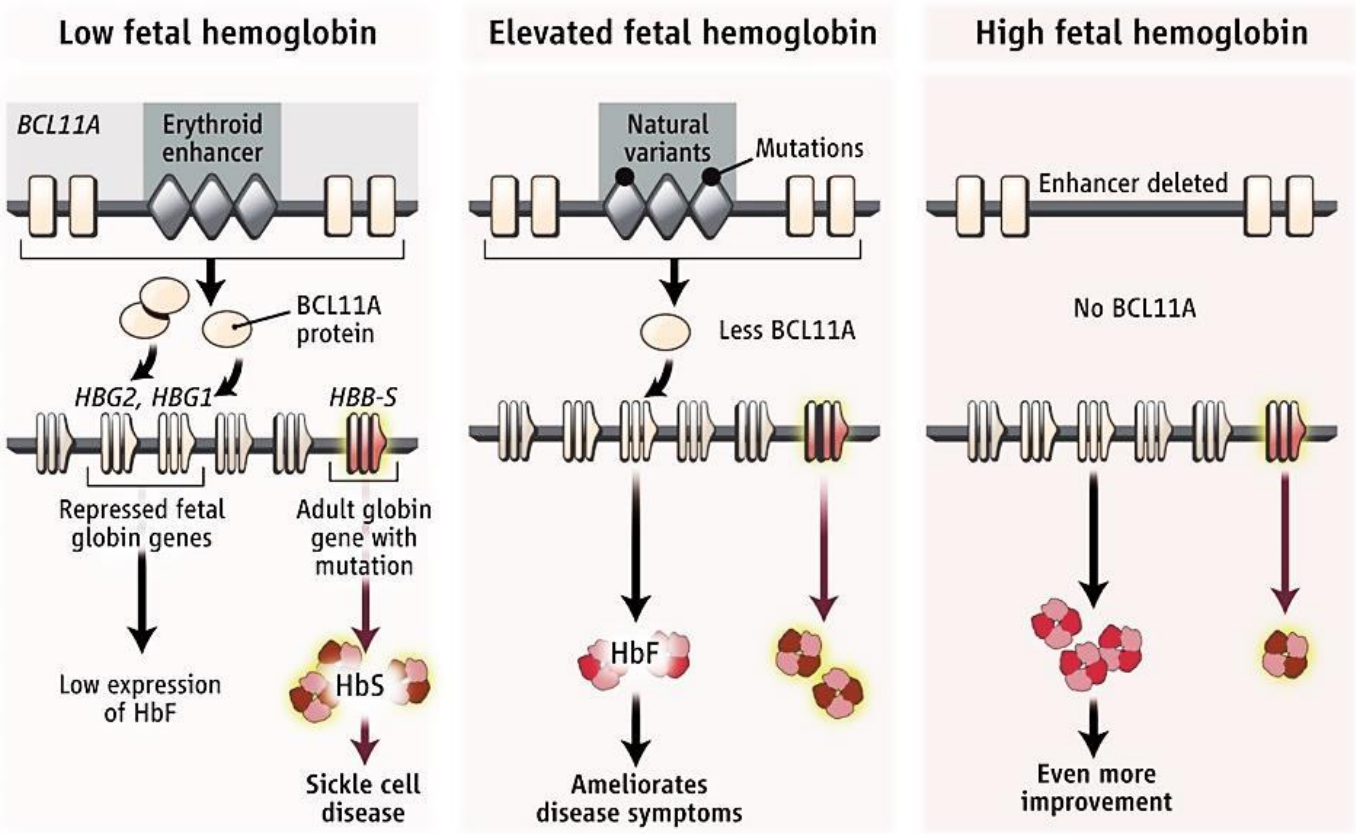
HbF ameliorates the symptoms of sickle-cell disease



From: Hardison & Blobel, Science 342:206, 2013

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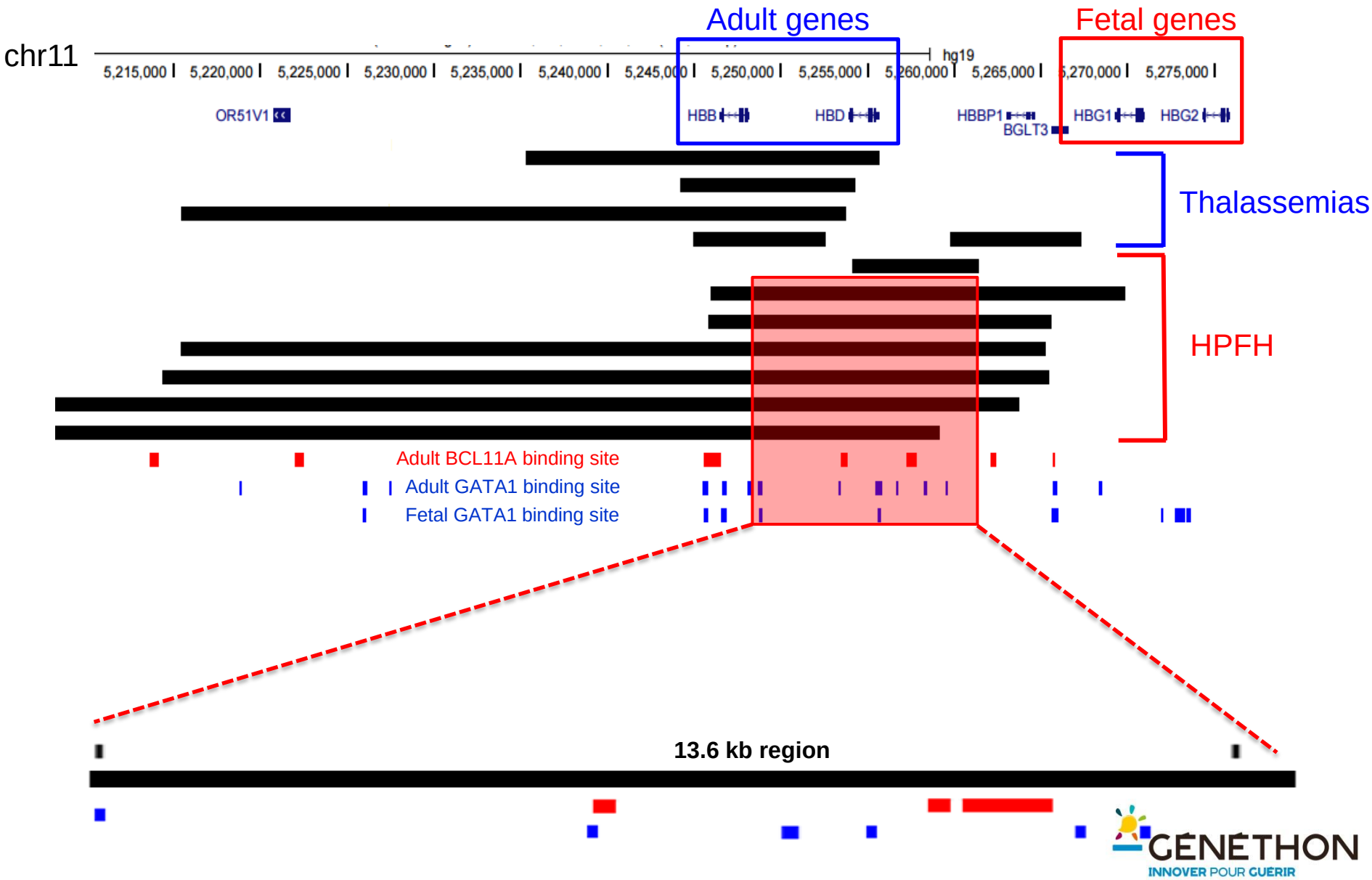
HPFH is caused by gene deletion



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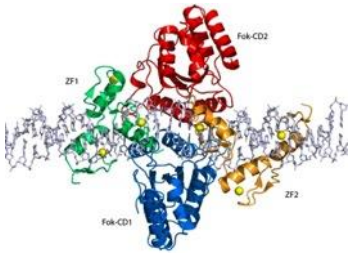
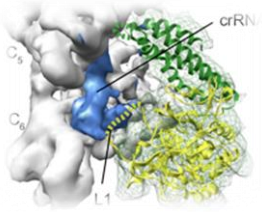
Targeted genome editing

ZFN

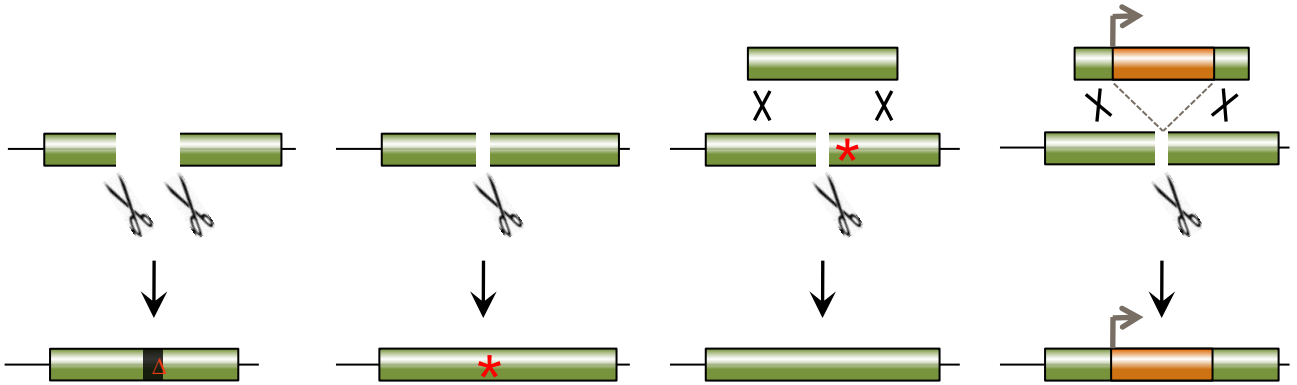




CRISPR-Cas9

Editing via
non-homologous end-joining
(NHEJ ≈ *error prone*)

Editing via
homologous recombination
(HR ≈ *accurate*)



targeted deletion

targeted disruption

targeted correction

targeted integration

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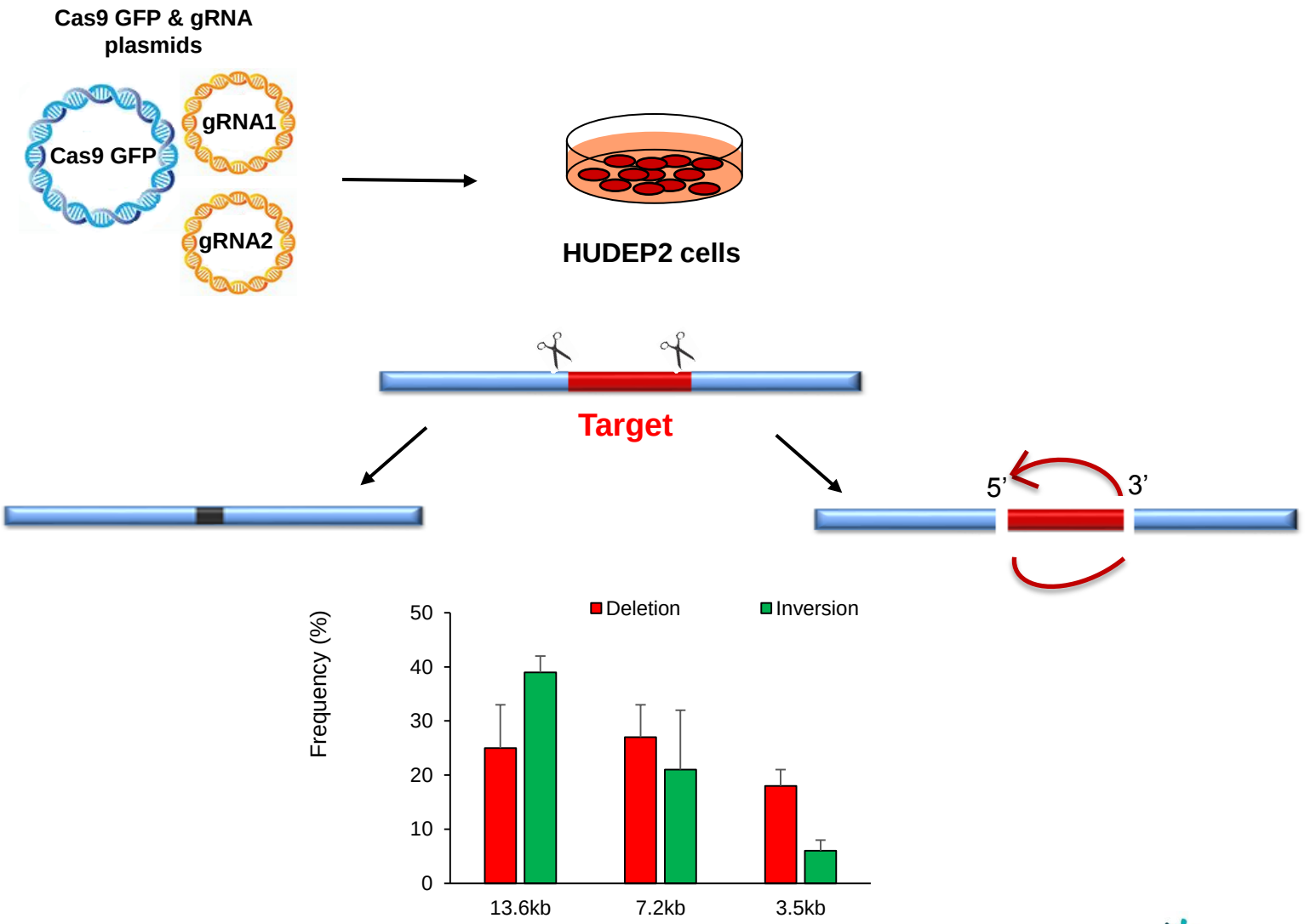
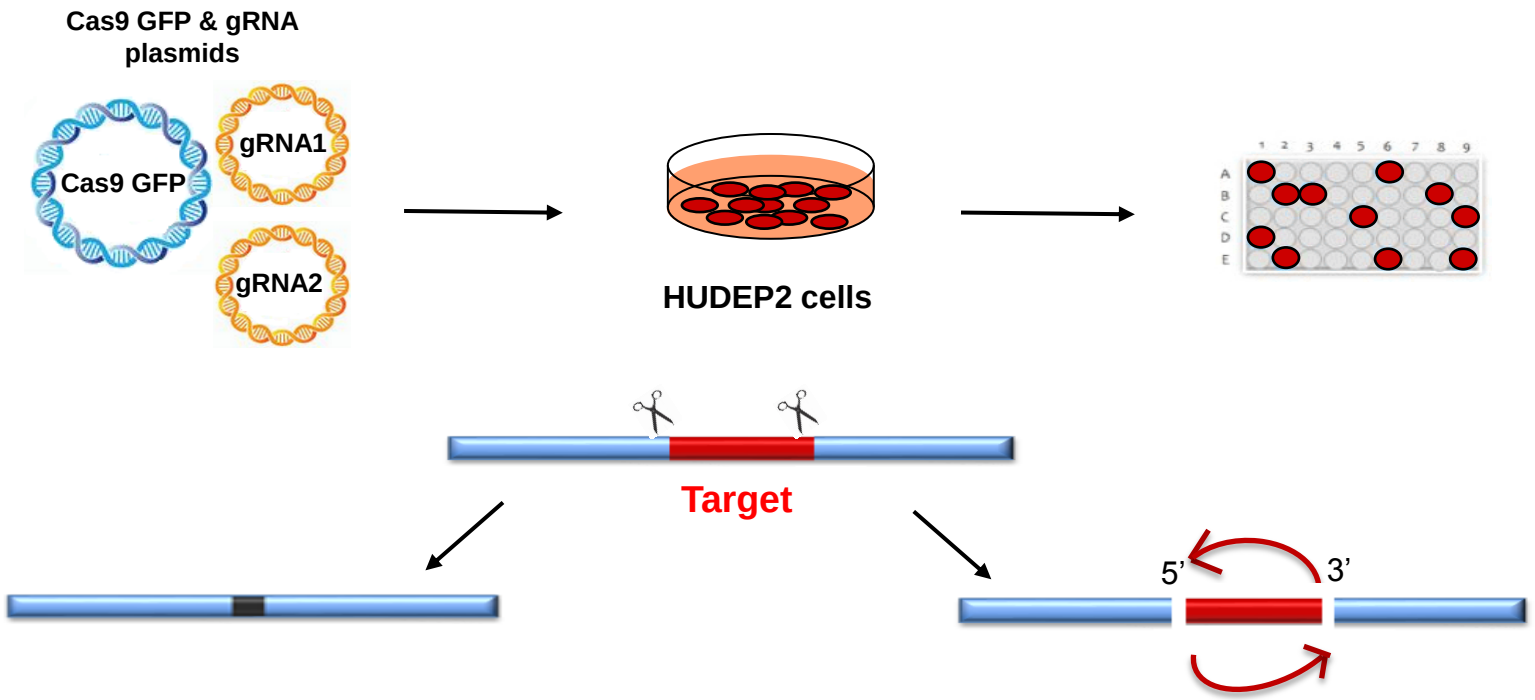
Targeted deletion in HUDEP2 cells



Targeted deletion in HUDEP2 cells (13.6 kb)



Deletion junction

AACCCAAGAGTCTTCTCTGTCTCCACATCTAAGGGTCTTGGGTACAGGAGTTTGA	**Del**
AACCCAAGAGTCTTCTCTGTCTCCACATCTAAGGGTCTTGGGTACAGGAGTTTGA	50.0%
AACCCAAGAGTCTTCTCTGTCTCCACAT--AAGGGTCTTGGGTACAGGAGTTTGA	35.7%
AACCCAAGAGTCTTCTCTGTCTCCACATGCTAAGGGTCTTGGGTACAGGAGTTTA	7.1%
AACCCAAGAGTCTTCTCTGTCTCCACATCG-AGGGTCTTGGGTACAGGAGTTTGA	7.1%

Inversion junctions

AACCCAAGAGTCTTCTCTGTCTCCACATGAAGTATGTAGCACCCTCAAACCTAAA	**5' Inv**
AACCCAAGAGTCTTCTCTGTCTCCACATGAAGTATGTAGCACCCTCAAACCTAAA	56.2%
AACCCAAGAGTCTTCTCTGTCTCCACATG--GTATGTAGCACCCTCAAACCTAAA	25.0%
AACCCAAGAGTCTTCTCTGTCTCCACATGGAAGTATGTAGCACCCTCAAACCTAA	18.8%
GGTTTAAGGAGACCAATAGAAACTGGGCCTAAGGGTCTTGGGTACAGGAGTTTGA	**3' Inv**
GGTTTAAGGAGACCAATAGAAACTGGGCCTAAGGGTCTTGGGTACAGGAGTTTGA	42.9%
GGTTTAAGGAGACCAATAGAAACTGGGC-TAAGGGTCTTGGGTACAGGAGTTTGA	35.7%
GGTTTAAGGAGACCAATAGAAACTGGG------GGTCTTGGGTACAGGAGTTTGA	14.3%
GGTTTAAGGAGACCAATAGAAACTGG--CTAAGGGTCTTGGGTACAGGAGTTTGA	7.1%

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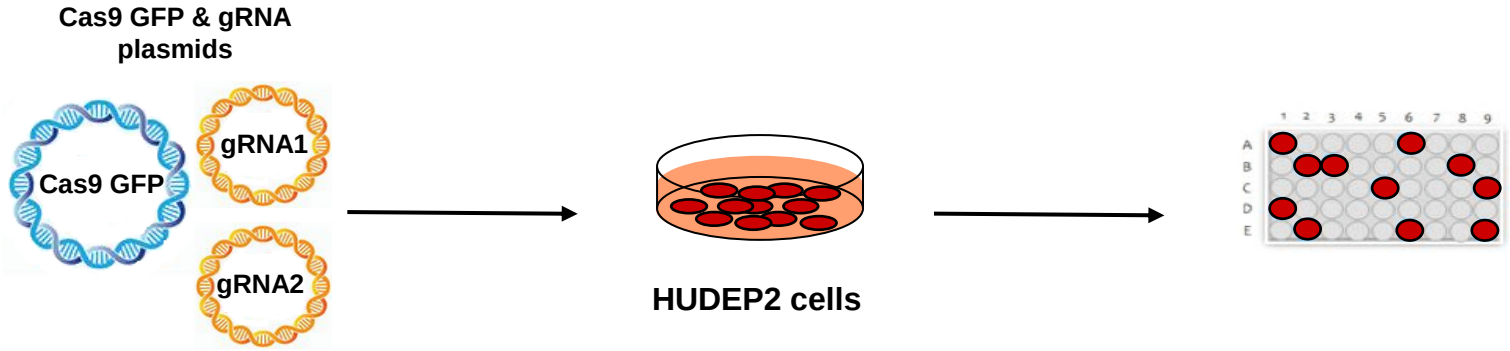
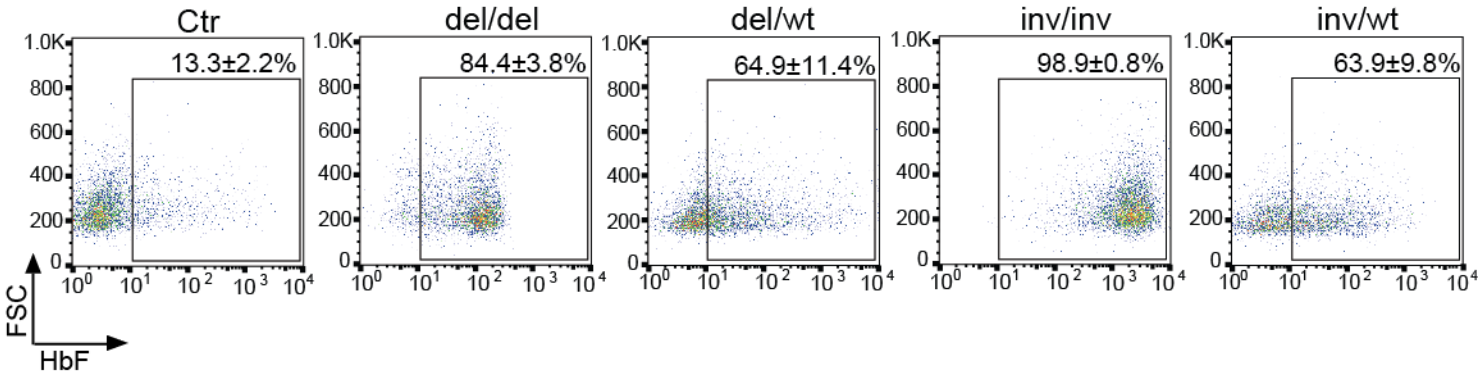
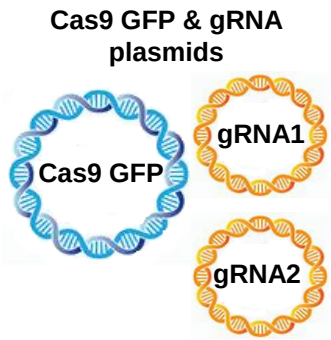
HbF reactivation in HUDEP2 clones (13.6kb)

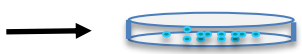


F cells(%)

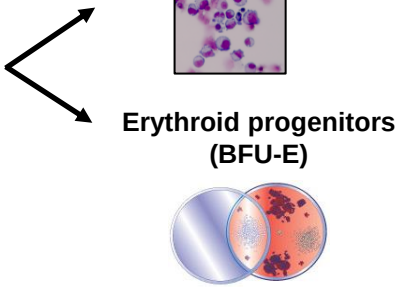


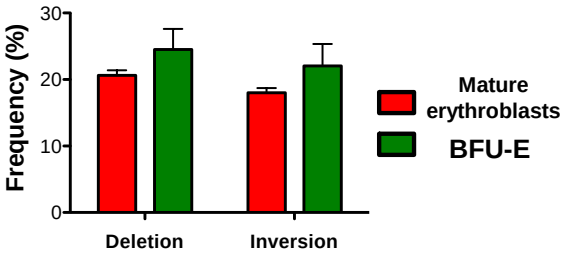
HbF induction in primary erythroblasts

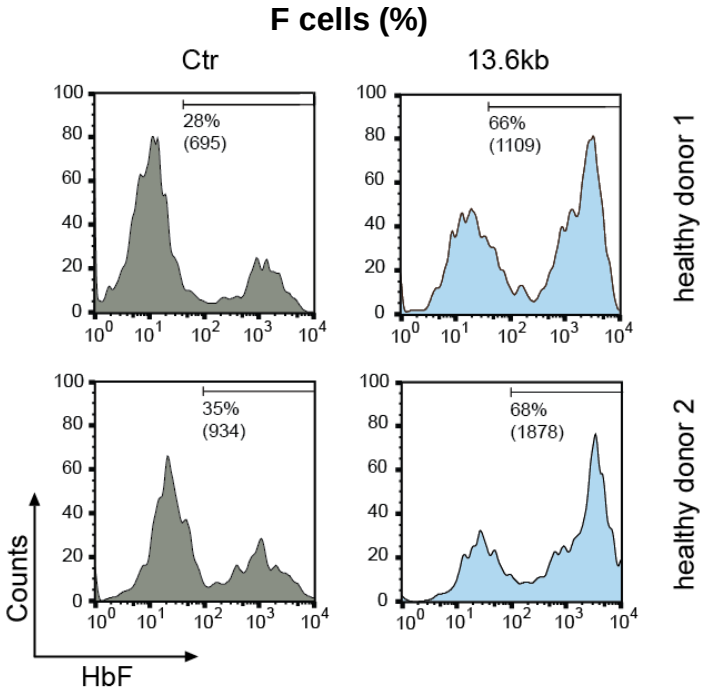


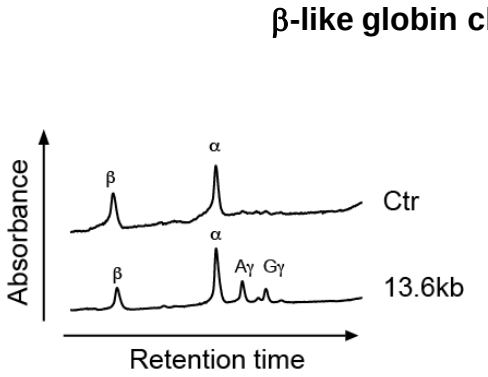


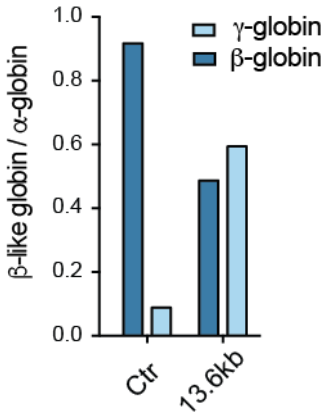
Adult HSPC from healthy donors











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Genome editing *vs*. gene replacement therapy

- Gene knock-out and genomic deletions are relatively efficient in hematopoietic stem cells. In a few indications, these could be effective forms of therapy (e.g., CCR5 KO in AIDS gene therapy)
- Gene correction by HR-mediated DNA repair requires a different therapeutic for each mutation in any given gene, a complex and very expensive approach; in addition, HR has an exceedingly low efficiency in somatic stem cells, far from what would be required for medical application, with few exceptions (e.g., a strong selective advantage for corrected cells)
- Gene deletions are not an obvious target for the existing gene editing technology
- The consequences of introducing double-stranded DNA breaks in somatic stem cells are far from being understood: gene editing is not necessarily safer than viral-mediated gene addition

Gene Therapy for WAS: the teams

GENETHON
CURE THROUGH INNOVATION

A Galy, S. Charrier, A Viornery, K. Seye, G. Cedrone,

HIV-vector development
O.Merten F. Barnay-Toutain, E. Galene

Regulatory-Clinical Affairs, QA
G. Honnet*,* D. Caizergues, M. Keen, M. Souquieres , H. Haddad, A. Kobrine

GENOSAFE, Evry, France
M. Audit, A. Botrel, M. Dessainte

MHH, Hannover, Germany
C. Baum, U. Modlich, S. Knoss

TIGET, Milan , Italy
L. Naldini, MG Roncarolo, A. Aiuti

INSTITUTE OF CHILD HEALTH –
GREAT ORMOND STREET HOSPITAL, London
A. Thrasher, B. Gaspar
C. Rivat, E. De Falco, K. Buckland, K. Parsley
A.M. McNichol, S. Swift, M. Blundell, G. Bouma
N. Himmoudi

Great Ormond Street Hospital for Children NHS Trust

NECKER HOSPITAL, Paris
M. Cavazzana, S. Hacein-Bey Abina,
A. Fischer, *S. Blanche,* J. Blondeau,
L. Caccavelli

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

CHILDREN'S HOSPITAL, Boston, MA
D. Williams, SY. Pai, L. Notarangelo
M. Armant, G. Kao, M. Wladkovski, O. Sturtevant

Children's Hospital Boston

UNIVERSITY OF PENNSYLVANIA, Philadelphia
F. Bushman, *N. Malani, C. Berry*

Perelman School of Medicine
University of Pennsylvania

GEORG SPEYER HAUS, Frankfurt, Germany
M. Grez

GENETHON
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Gene editing: the team

Annalisa Lattanzi
Giulia Pavani
Mario Amendola
Fulvio Mavilio

Annarita Miccio
Vasco Meneghini
Chiara Antoniani
Oriana Romano
Tristan Felix

Elisa Magrin
Leslie Weber
Marina Cavazzana

Wassim El-Nemer

Yukio Nakamura

Matthew Porteus

Thomas J Cradick
Ante S Lundberg