Calling All Super Heroes

Emerging Gene Therapy Strategies - Challenges, Risks and Potential for Cure

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November 9, 2018

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Disclosures

The following faculty and planning committee staff have the following financial disclosures:

Name	Institution	Disclosure
Sung-Yun Pai, MD	Boston Children's Hospital/Dana-Farber Cancer Institute	None
Mark Walters, MD	UCSF Benioff Children's Hospital, Oakland	Bluebird bio, inc, Stipend, Consultant Sangamo Biotherapeutics, inc., Stipend, Consultant Bioverativ, Stipend, Consultant AllCells, inc., Stipend, Medical Director ViaCord Processing Lab, Stipend, Medical Director
Stephen Spellman	CIBMTR	None
Alexandra Erickson	CIBMTR	None
Misty Evans	Vanderbilt	Jazz Pharmaceuticals, Monetary, Speakers Bureau

Learning objectives

- At the conclusion of this session, attendees will be able to:
  - Define diseases that have the potential to be treated using gene therapy strategies
  - Analyze current strategies and methodologies such as CRISPR and viral vectors being used in gene therapy
  - Evaluate how these gene therapy strategies are being applied in current clinical trials

Boston Children's Hospital
Until every child is well™

Gene therapy for primary immunodeficiency: Important firsts and iterative progress

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NMDP Council Meeting 2018

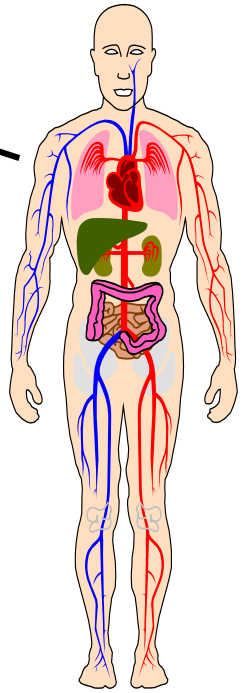
DANA-FARBER Boston Children's
CANCER AND BLOOD DISORDERS CENTER

HARVARD MEDICAL SCHOOL

Gene Therapy Medicinal Products

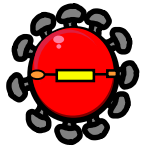
Ex vivo
genetically modified human ***cells***

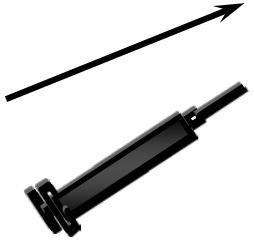
cell



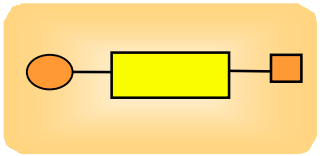
1) Isolation of the target cells (autologous or allogeneic)

2) Gene transfer





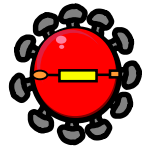
3) Re-Infusion of the genetically modified cells



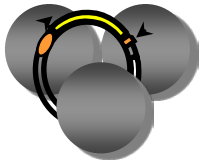
In vivo *delivered vectors, nucleic acids, replicating micro-organism (not including live vaccines)*

Direct application:

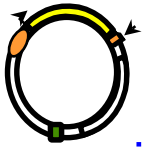
viral vector



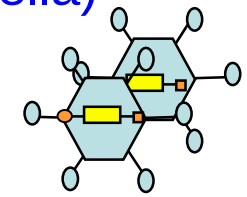
non-viral vector



naked DNA



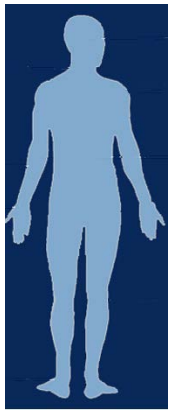
replicating rec. micro-organism (adenovirus, Salmonella)

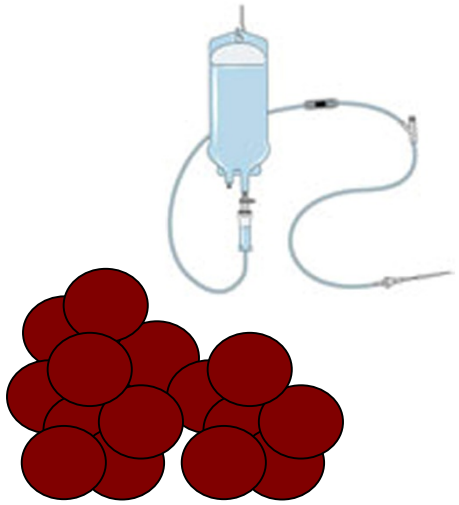


Chris Baum, David Williams

Limitations of allogeneic transplant for genetic blood disease

Healthy matched donor



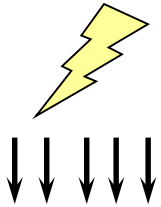


Problems:

- Most patients lack a matched sibling donor
- GVHD

Sick

prepare the patient

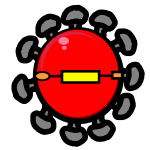


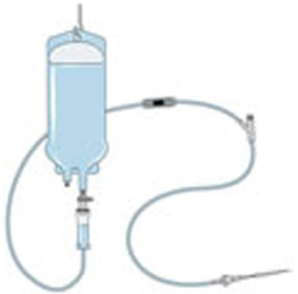
Transplant

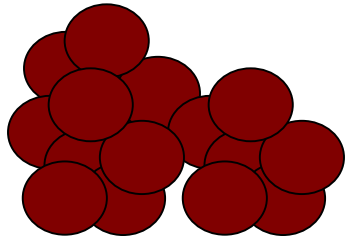
Well

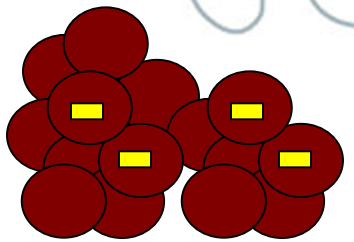
Gene therapy is an alternative to allogeneic transplant using the patient's own cells

γRV or LV





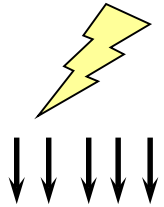




Transplant

Sick

prepare the patient

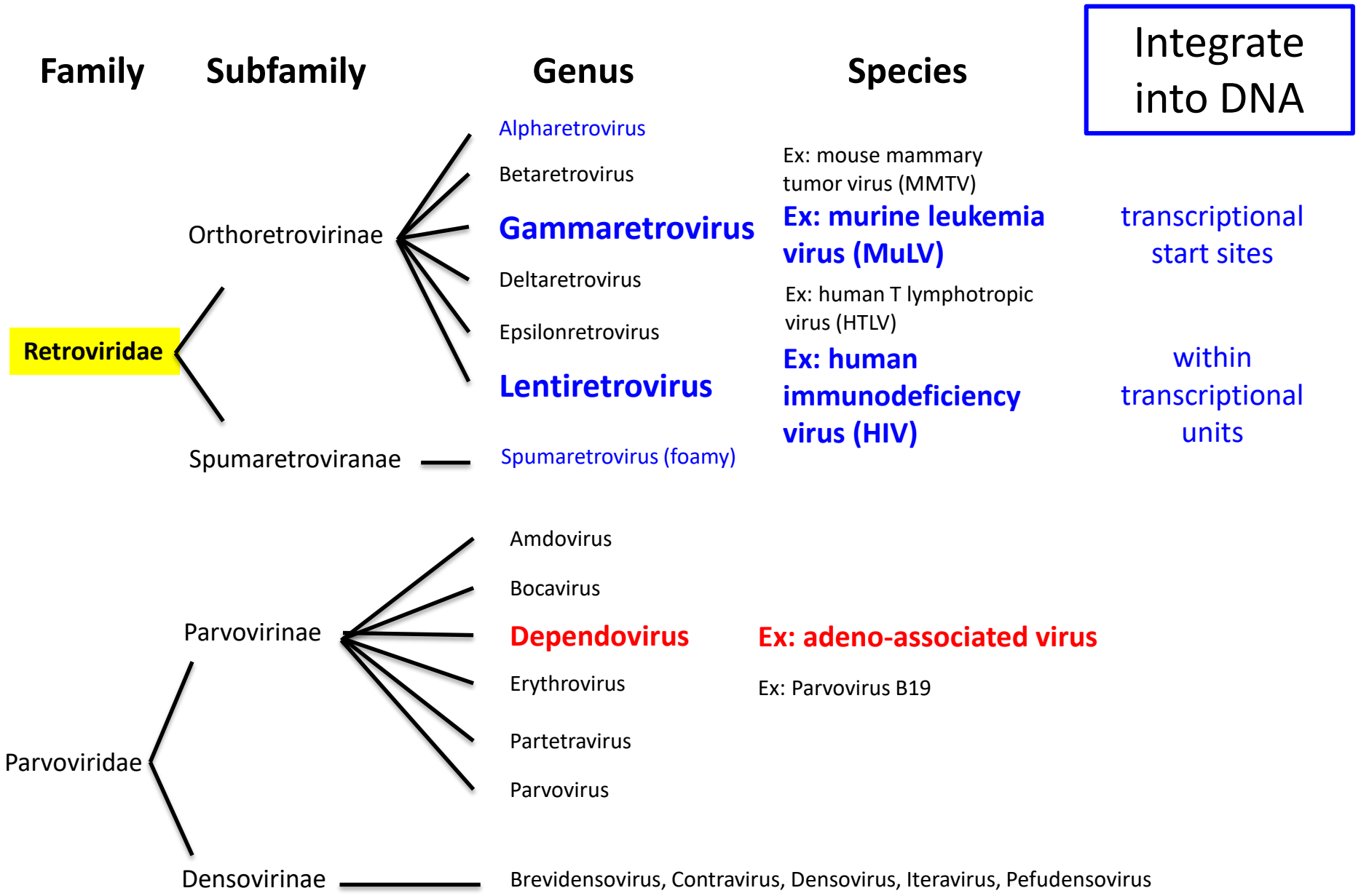


Well

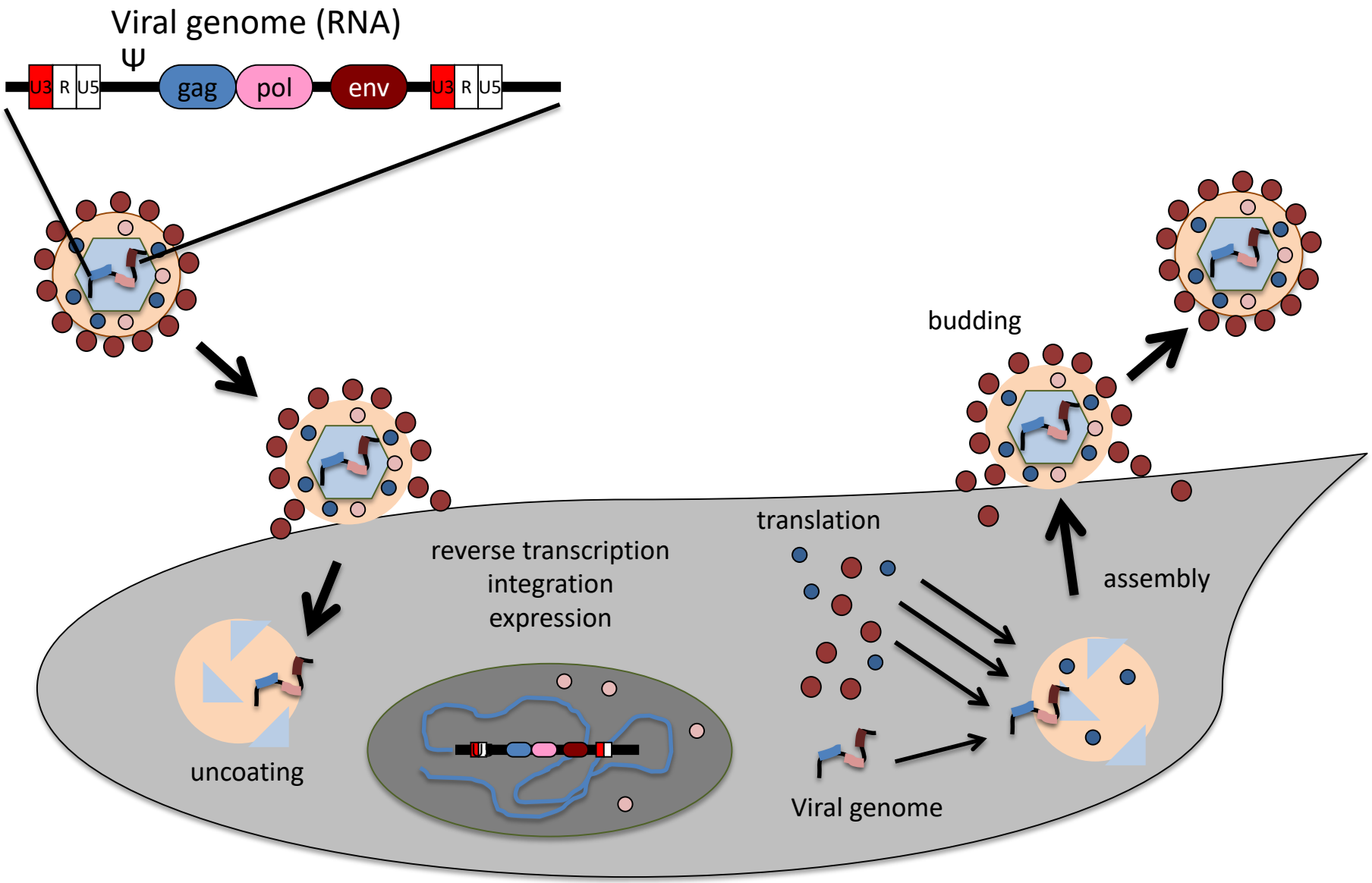
Advantages:

- Patient is own donor
- No GVHD
- Vector integrates into the DNA of the cell, and passes the gene to all progeny

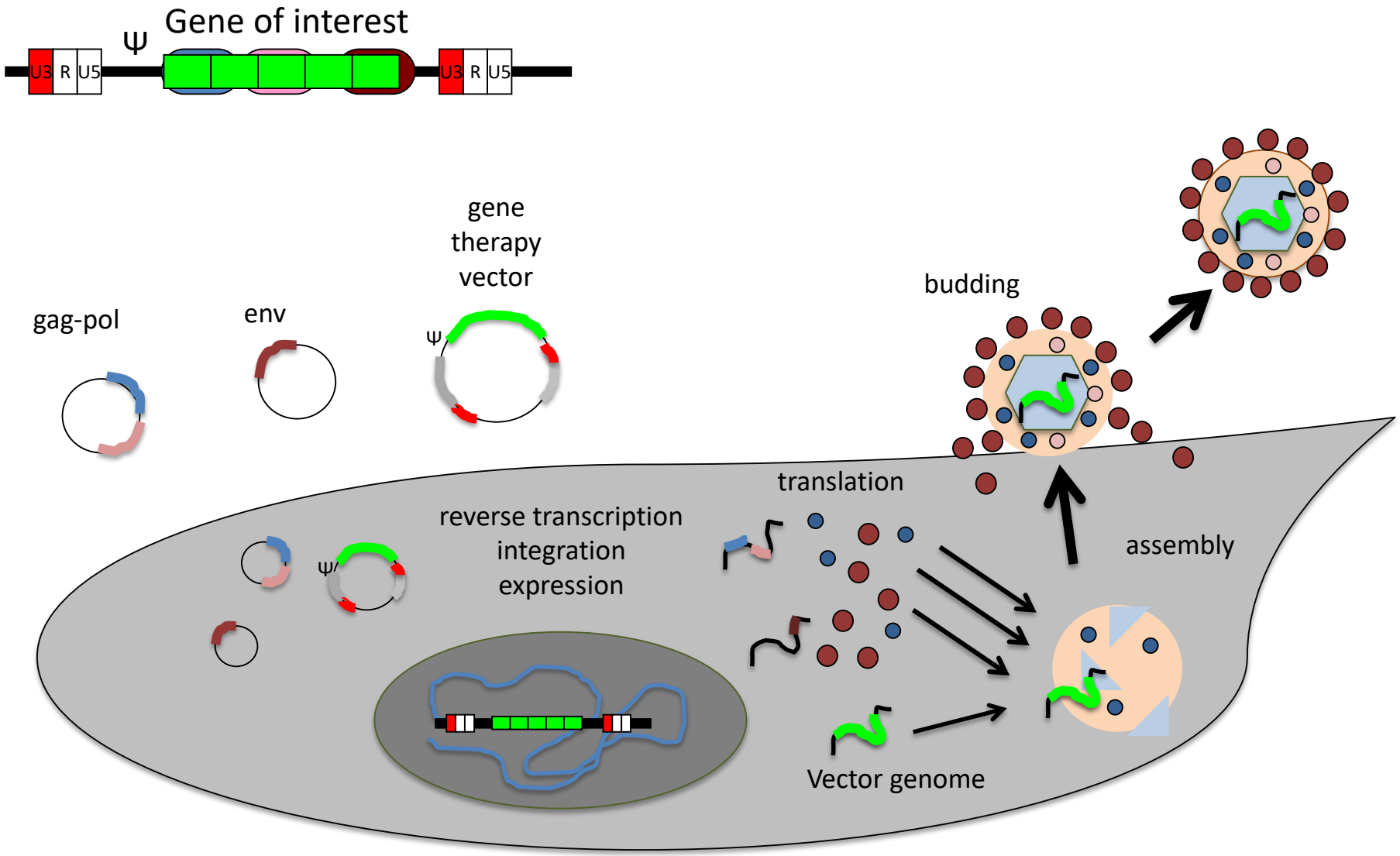
Retroviruses are used for ex vivo gene transfer into HSC



Simplified retroviral life cycle

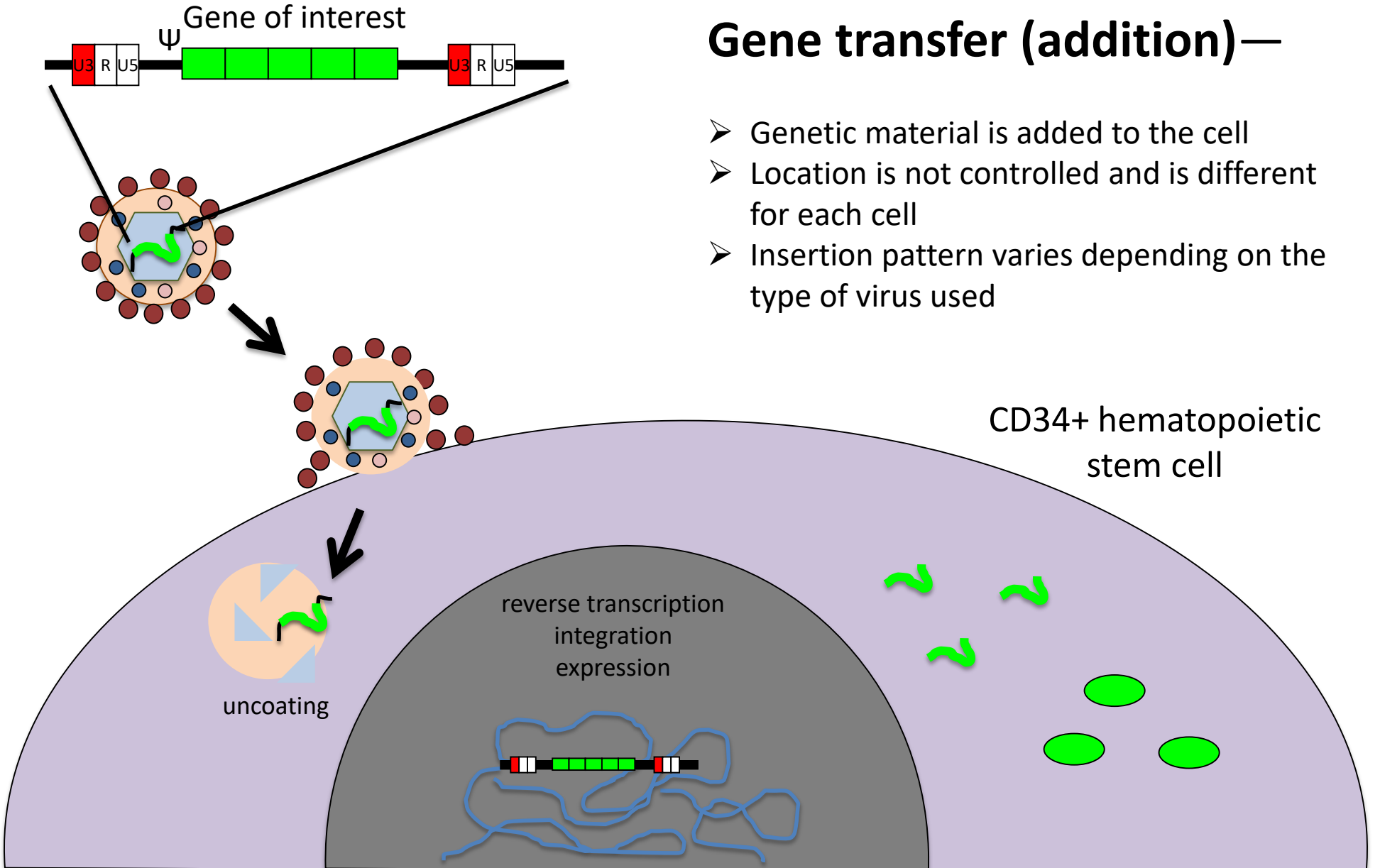


Gene transfer vectors are made to avoid replication competent retrovirus (RCR) by split packaging



Packaging cell line e.g. Human embryonic kidney 293T adherent cell line

Vector transduces stem cells without RCR



Gene transfer (addition)—

- Genetic material is added to the cell
- Location is not controlled and is different for each cell
- Insertion pattern varies depending on the type of virus used

What is severe combined immunodeficiency (SCID)?

A congenital disease in which babies are born without T lymphocytes

The first disease to be successfully treated with long-term engraftment of donor cells (Gatti 1968)

Multiple genetic causes

- IL2RG (X-linked)
- ADA (adenosine deaminase)

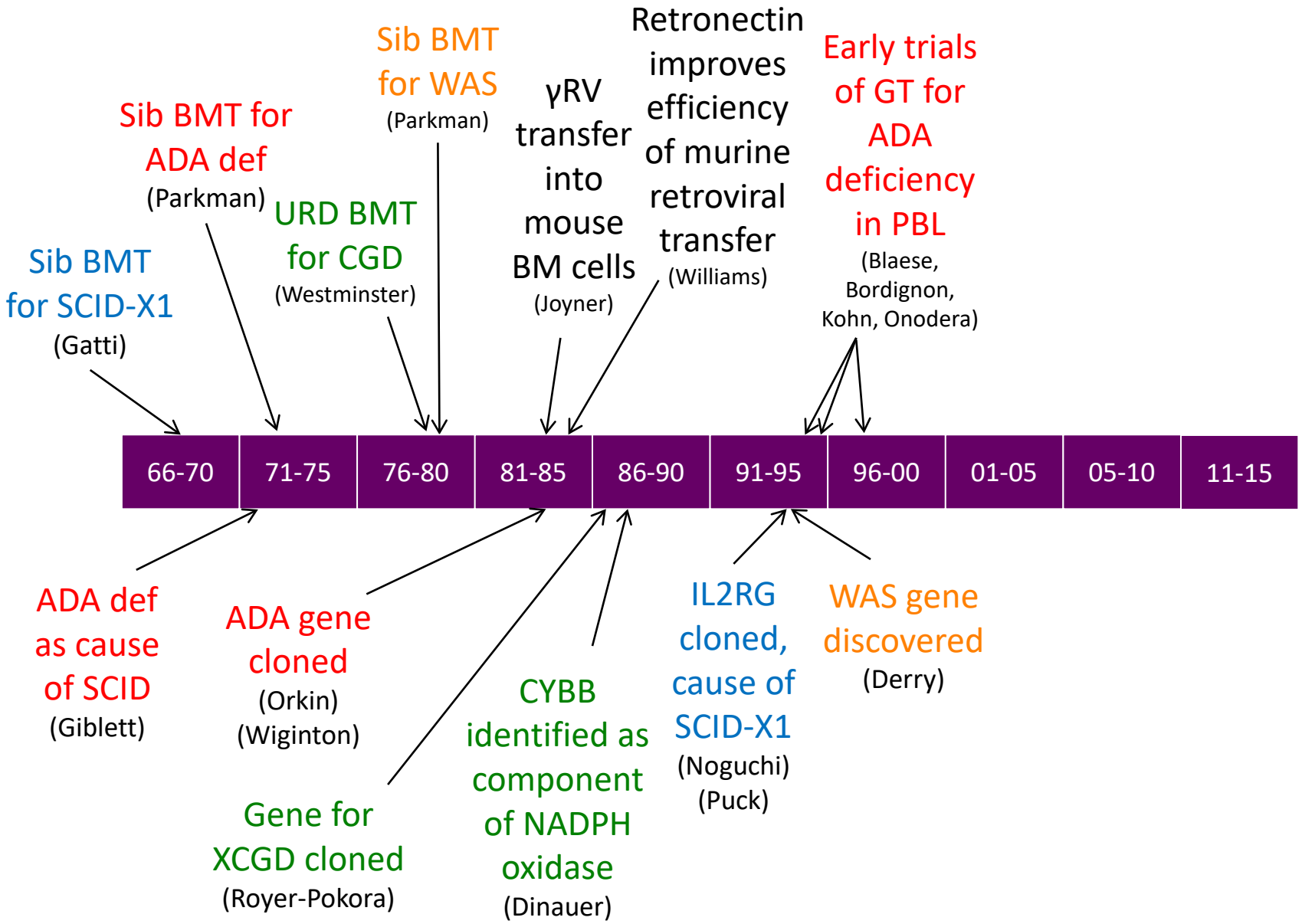
David Vetter, boy with X-linked SCID who lived in a bubble (1971-1984) with Dr. Bill Shearer (1937-2018)

Without treatment, death in the first year of life of infection

ADA SCID can be partially treated with enzyme replacement therapy which is expensive, non-curative and requires lifelong treatment

Standard treatment is allogeneic HSCT, can be performed without conditioning

The groundwork for successful gene therapy arose from HSCT for immunodeficiency



Gene therapy for primary immunodeficiency has led the way

Disease	Gene	Vector	Year	Groups	Efficacy?
Adenosine deaminase deficient SCID	ADA	γ-RV	2002 2009	Milan UCLA/NIH	Yes
X-linked SCID	IL2RG	γ-RV	2002 2004	Paris, London	Yes

Introduction of low dose conditioning propeled the success of gene therapy for ADA SCID

Year	Reference	Vector	Stop ADA?	Bu dose	N	Significant Gene Marking?	Off ADA?
1995	Bordignon et al	γ-RV	No	0	2	No	No
1995	Kohn et al	γ-RV	No	0	3	No	No
1996	Hoogerbrugge et al	γ-RV	No	0	3	No	No
2012	Candotti et al	γ-RV	No	0	4	No	No

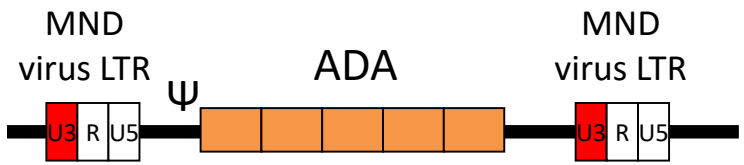
Rivat et al Hum Gene Therapy 2012, includes personal communications

Introduction of low dose conditioning propeled the success of gene therapy for ADA SCID

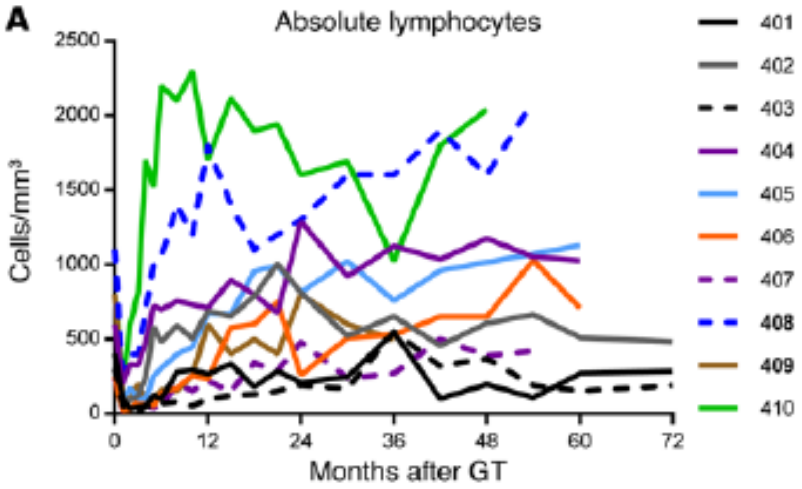
Year	Reference	Vector	Stop ADA?	Bu dose	N	Significant Gene Marking?	Off ADA?
1995	Bordignon et al	γ-RV	No	0	2	No	No
1995	Kohn et al	γ-RV	No	0	3	No	No
1996	Hoogerbrugge et al	γ-RV	No	0	3	No	No
2012	Candotti et al	γ-RV	No	0	4	No	No
2002	Aiuti et al	γ-RV	**Yes**	**4 mg/kg**	2	**Yes**	**1/2**
2009	Aiuti et al	γ-RV	**Yes**	**4 mg/kg**	18	**Yes**	**15/18**
2011b	Gaspar et al	γ-RV	**Yes**	**4 mg/kg (or Mel)**	8	**Yes**	**4/8**
2012	Candotti et al	γ-RV	**Yes**	**4 mg/kg**	14	**Yes**	**10/14**

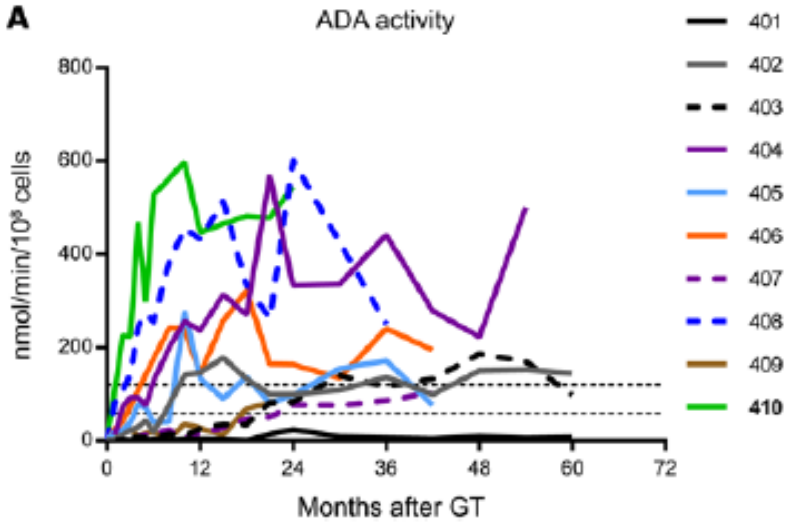
Rivat et al Hum Gene Therapy 2012, includes personal communications

Gammaretroviral gene therapy for ADA SCID is safe and effective



10 pts received with autologous CD34+ BM cells transduced with MND-ADA-γRV after 4 mg/kg busulfan





- 100% survival
- Excellent T cell reconstitution
- 9 of 10 off enzyme replacement
- 3 of 10 off of IVIG
- No gene therapy related SAE

Shaw et al JCI 2017

First generation gene therapy for X-linked SCID (SCID-X1) was efficacious but caused insertional oncogenesis

Gammaretroviral vector (with viral enhancers) (Paris, London)

- Viral promoter (Moloney leukemia virus) with strong expression of the IL2RG transgene
- Transduced autologous CD34+ bone marrow cells, infused without conditioning
- Excellent T cell reconstitution, 17/18 long-term survivors, no opportunistic infections

Safety concerns

Insertional oncogenesis:

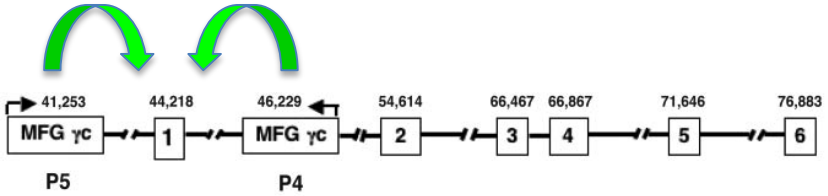
5/20 developed T cell leukemia at 2-5.6 years post-GT

1/20 developed T cell lymphoma at 15 years post-GT

1 patient died of leukemia

5 patients treated and in remission with normal T cells

Occurred due to insertion near and activation of oncogene (LMO2 in 5 of 6 cases)



TSS

LMO2 ⇧⇧

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

Gammaretroviral vectors were associated with insertional oncogenesis in multiple diseases

Disease	Gene	Vector	Year	Groups	Efficacy?	Safety?
Adenosine deaminase deficient SCID	ADA	γ-RV	2002 2009	Milan UCLA/NIH	Yes	Yes
X-linked SCID	IL2RG	γ-RV	2002 2004	Paris, London	Yes	**No** 6/20 ALL 1/20 T lymphoma
X-linked chronic granulomatous disease	CYBB	γ-RV	2006	Frankfurt	Transient (silencing)	**No** 2/2 MDS
Wiskott-Aldrich syndrome	WAS	γ-RV	2010	Hannover	Yes	**No** 7/9 ALL/AML

Possible strategies to avoid insertional oncogenesis

Strategies

Gene addition

- Modify vector
  - **promoter**
    - **- delete strong enhancers**
    - **- use weak cellular**
  - insulators
- Change vector class
  - lentiviral vector

Can modification of the SCID-X1 vector retain efficacy and improve safety?

(David Williams, Adrian Thrasher, Christopher Baum)

- No sibling donor
- No matched unrelated donor OR -active treatment-resistant infection at diagnosis

autologous BM harvest

CD34+ selection

d-4

SCF
IL3
TPO
Flt3L

3 rounds of transduction in retronectin coated bags

d-2 d-1 d0

24h 24h 6h

Infuse fresh

NO CONDITIONING

Boston (Pai, Notarangelo), **Los Angeles** (Kohn, DeOliveira), **Cincinnati** (Marsh, Malik), **Paris** (Hacein-Bey-Abina, Cavazzana, Fischer), **London** (Thrasher, Gaspar)

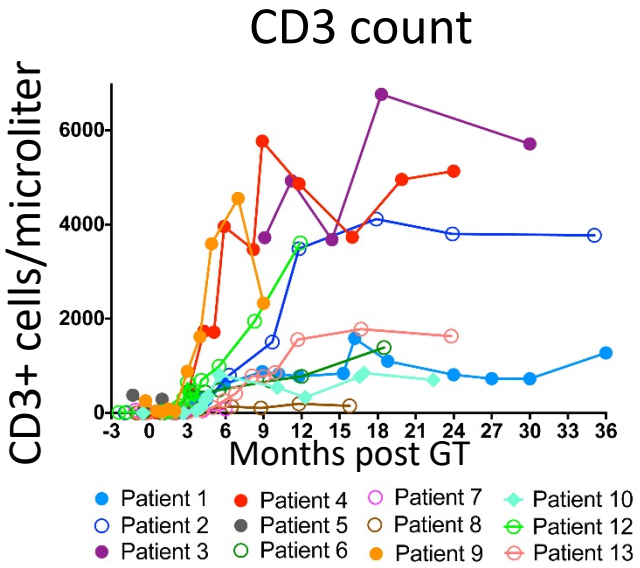
IND #14067, Sponsor David A. Williams, NCT01129544
Funding: NIAID U01-AI087628 (Williams/Pai)
Vector produced by Cincinnati Children's Hospital Medical Center

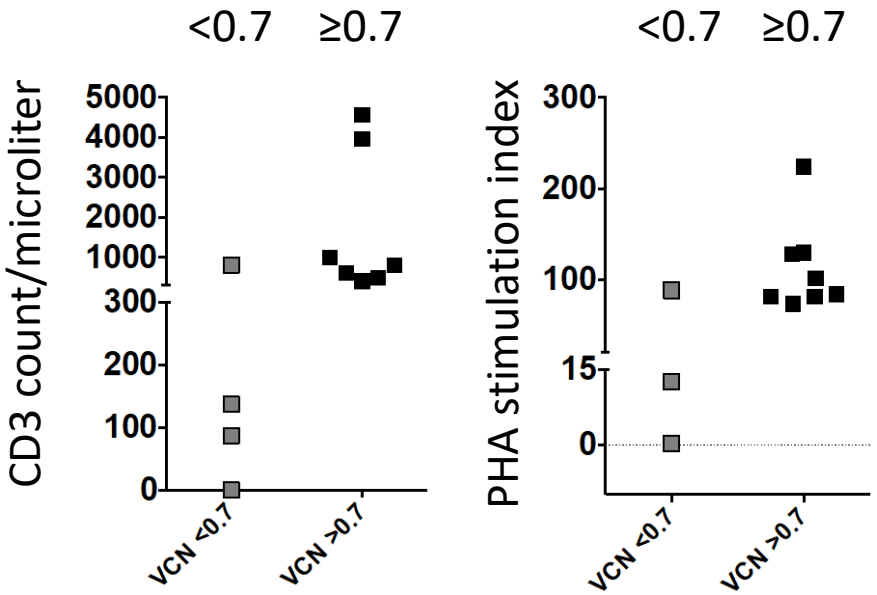
PACT Production Assistance for Cellular Therapies National Heart Lung and Blood Program

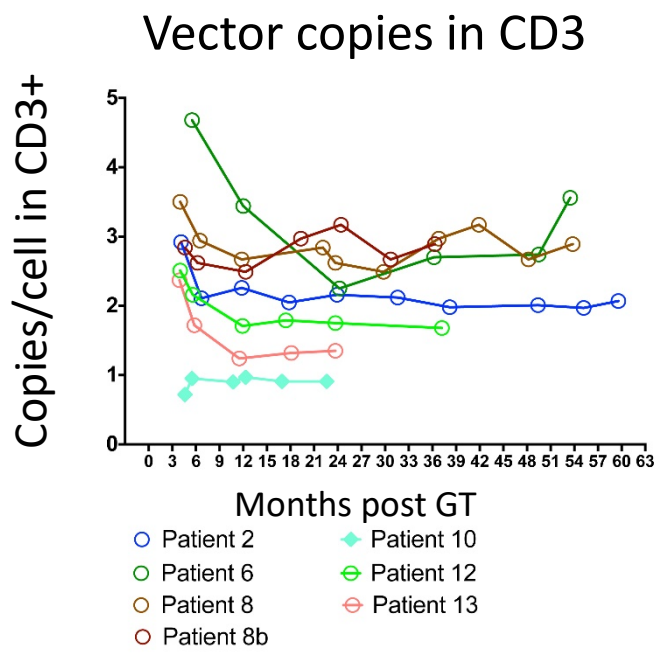
NIH National Institute of Allergy and Infectious Diseases

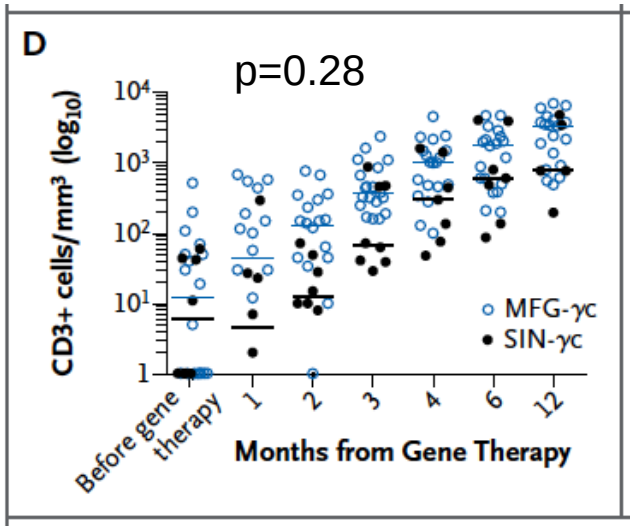
Translational Research Program Children's Hospital Boston

Robust reconstitution equivalent to previous vector









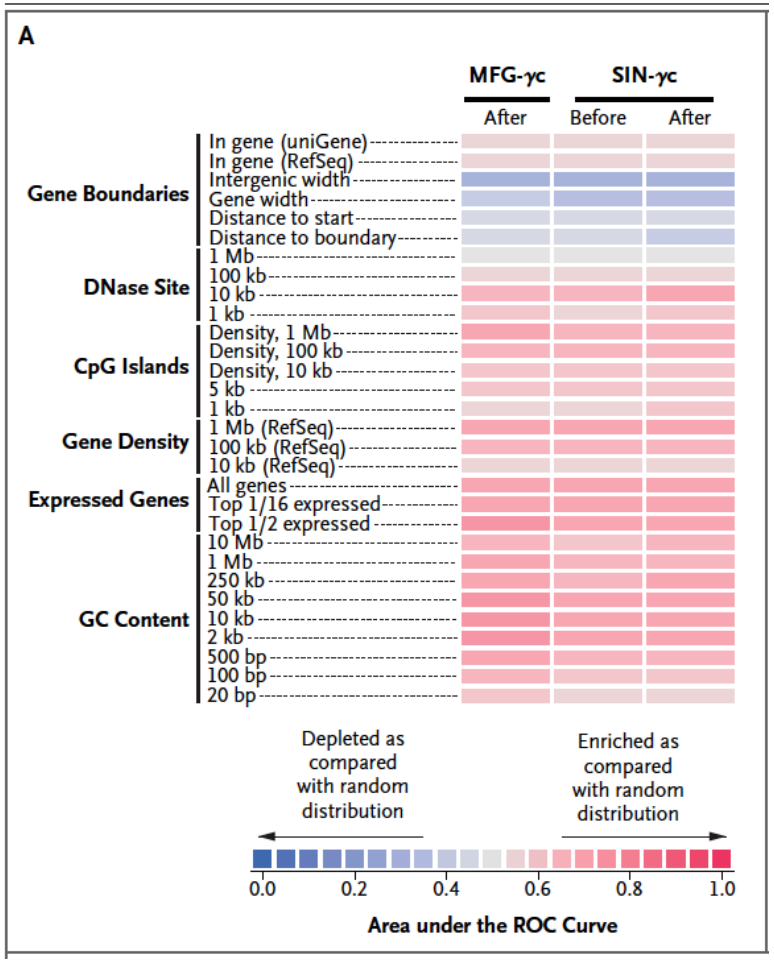
10/13 patients successful

Kinetics of T cell reconstitution similar between vectors

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

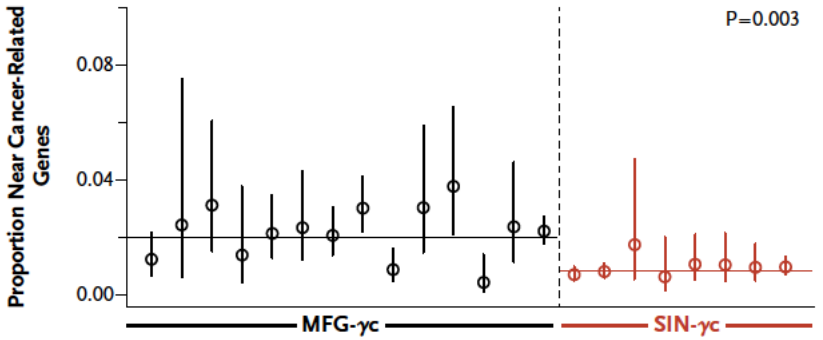
SIN-γRV appears to be safer than γRV

Insertion pattern of SIN-γRV still typical for γRV

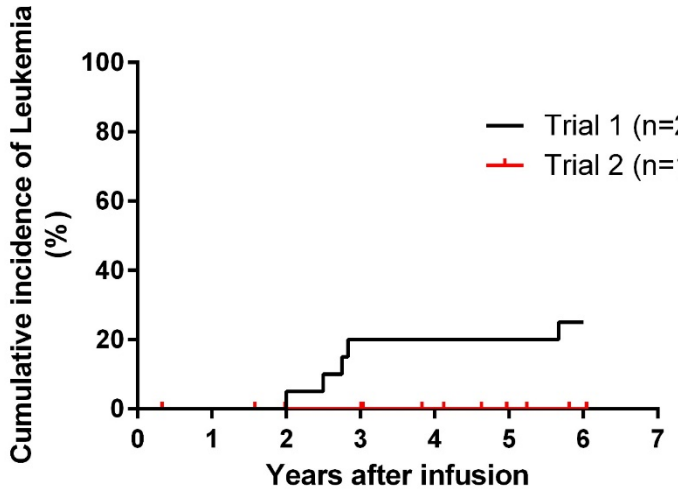


Frederic Bushman, University of Pennsylvania (studies of all sites including European patients)

Proportion of insertions near cancer-causing genes decreased in SIN-γRV pts



No leukemias to date, median 6.5y (1.3 to 7.9y)



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

Possible strategies to avoid insertional oncogenesis

Strategies

Gene addition

- Modify vector
  - **- self-inactivating format**
  - **- use cellular promoter**
  - insulators
- Change vector class
  - lentiviral vector

Next generation trials all use lentiviral vectors (US only)

	ADA SCID		X-linked SCID			Wiskott-Aldrich	X-linked CGD
Promoter	EFS		EFS			Human WAS 1.6kB	Chimeric myeloid specific
Codon optimized?	Yes		Yes			No	No
Frozen cells?	No	Yes	Yes	Yes	Yes	No	No➔Yes
Year open	2013	2016	2011	2012	2017	2011	2014
Centers	UCLA, NIH		NIH	St. Jude, UCSF, Seattle	Boston, UCLA	Boston	UCLA, NIH, Boston
N treated	20	10	8	9	2	5	6
Longest follow-up	~5y	~2y	>5y	~2y	0.5y	5y	2.7y
Efficacy?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Oncogenesis?	**No**	**No**	**No**	**No**	**-**	**No**	**No**

Unpublished data, Kohn, UCLA; Sorrentino, St. Jude/Cowan, UCSF; Pai/Williams, Boston; Malech, NIH

What about gene editing?

Gene editing methods seek to modify or repair endogenous genes, rather than adding a new copy of the relevant gene.

Advantages of editing over addition:

1. Regulation in native context
2. Avoid insertional oncogenesis

Strategy:
Target a double stranded break (DSB) to gene of interest
Repair the break

- with or without a donor template
- using nonhomologous or homologous recombination

Two double stranded break repair pathways

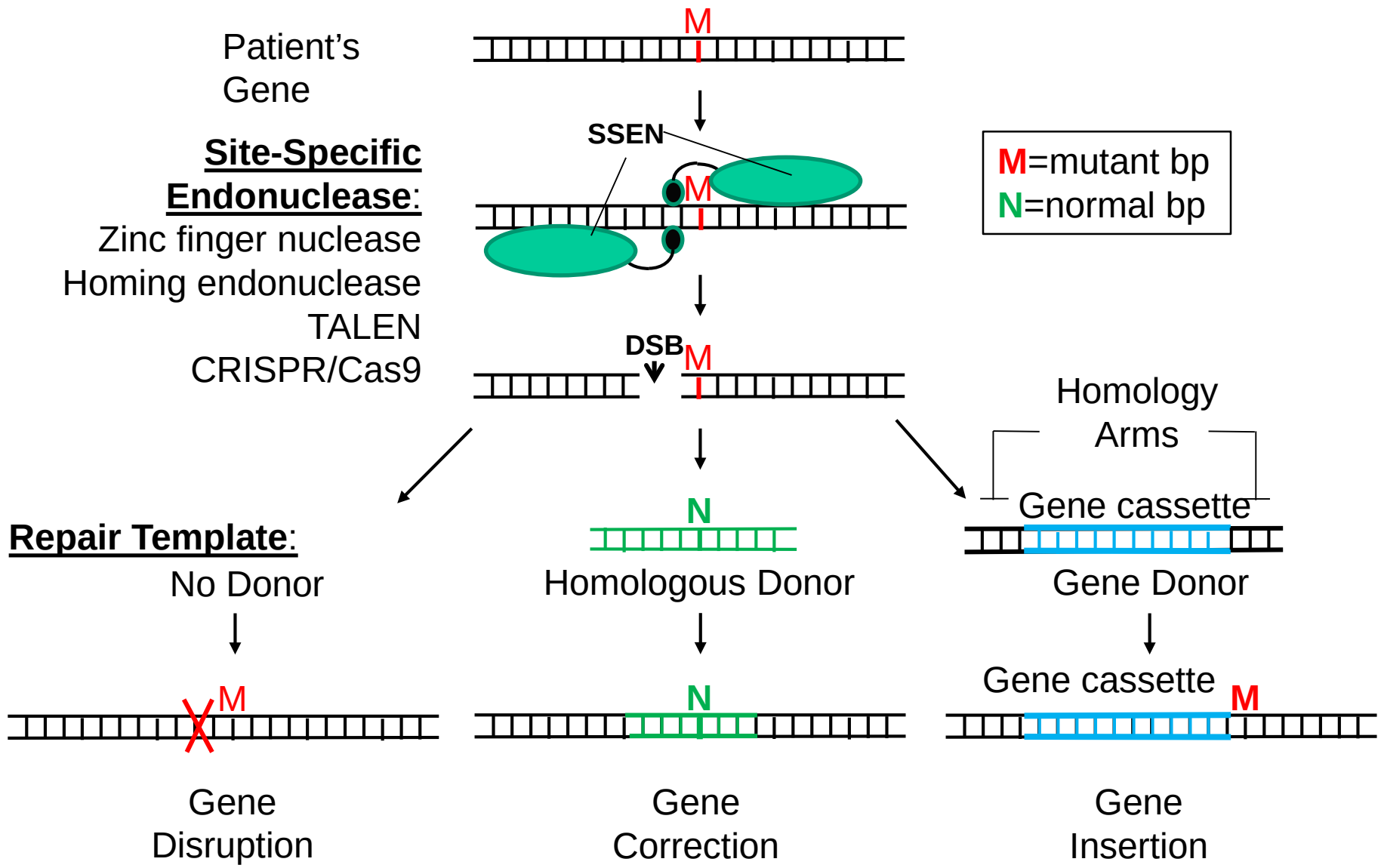
- Non-Homologous End Joining (NHEJ)
  - Inaccurate repair
  - No donor template required

- Homologous Recombination (HR)
  - Accurate repair
  - Homologous donor template required

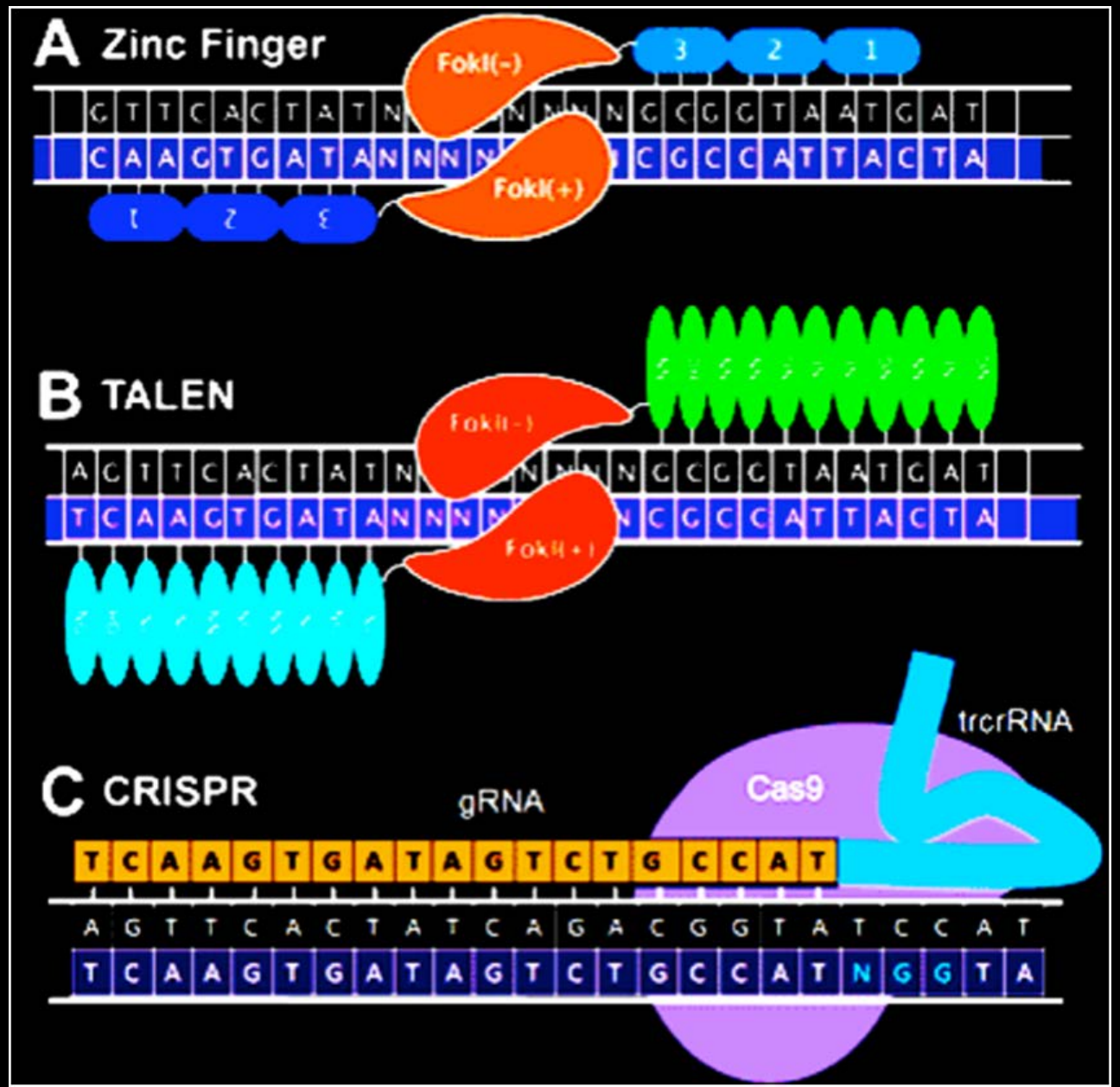
NHEJ:HR ratio depends on:

Cell type
Cell cycle phase
Presence of donor template

Different outcomes of gene repair



ZFN, TALENs and CRISPRs– Oh My!



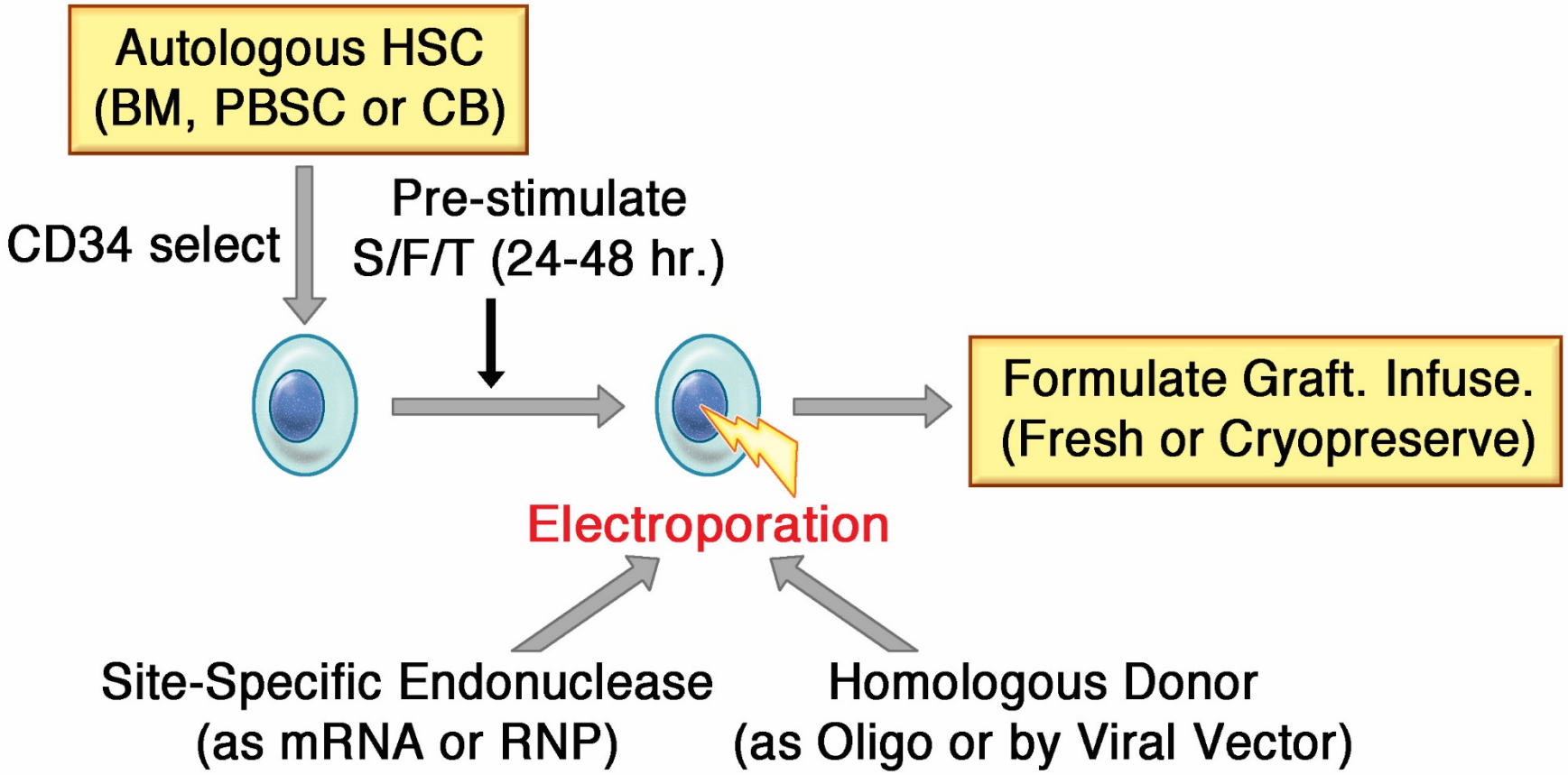
Artificial protein with ZnF array, each recognizing 3-4 nt, connected to FokI nuclease

Artificial protein with TAL effector protein array, each recognizing 1 nt, connected to FokI nuclease

Bacterial system in which the Cas9 protein nuclease is guided to target by bacterial trcrRNA fused to guide RNA (gRNA) with specificity

Donald B. Kohn

Site-specific Gene Editing of Autologous Hematopoietic Stem Cells for Gene Therapy



Kohn & Kuo, JACI 2017.

Practical considerations in gene editing

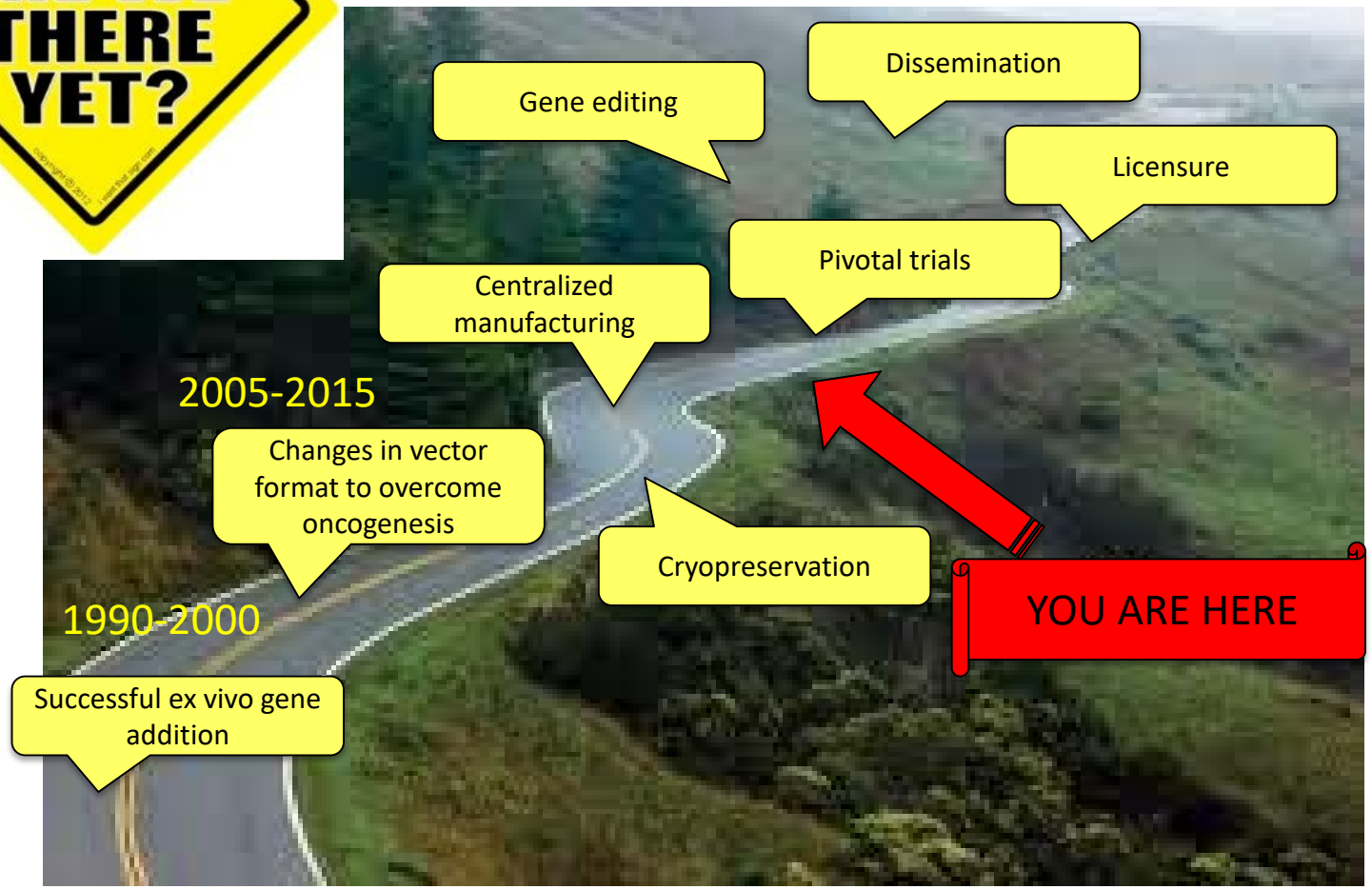
Similar to gene addition

- Efficiency, efficiency, efficiency
- Delivery into appropriate cell type
- Toxicity of the process to HSC, maintaining pluripotency
- Ethical issues of somatic versus germline manipulation

Distinct from gene addition

- ✧ Off target cutting
- ✧ Delivery that is transient yet effective (no integration)
- ✧ Need to deliver both the nuclease and for HR, donor template
- ✧ If strategy is mutation specific, need personalized materials for each patient

On the road to gene therapy as standard care



UCSF Benioff Children's Hospital Oakland

Principals of gene therapy for transfusion-dependent β-thalassemia and severe sickle cell disease

C·H·O·R·I
Children's Hospital Oakland Research Institute

Mark Walters, MD

Financial Disclosure

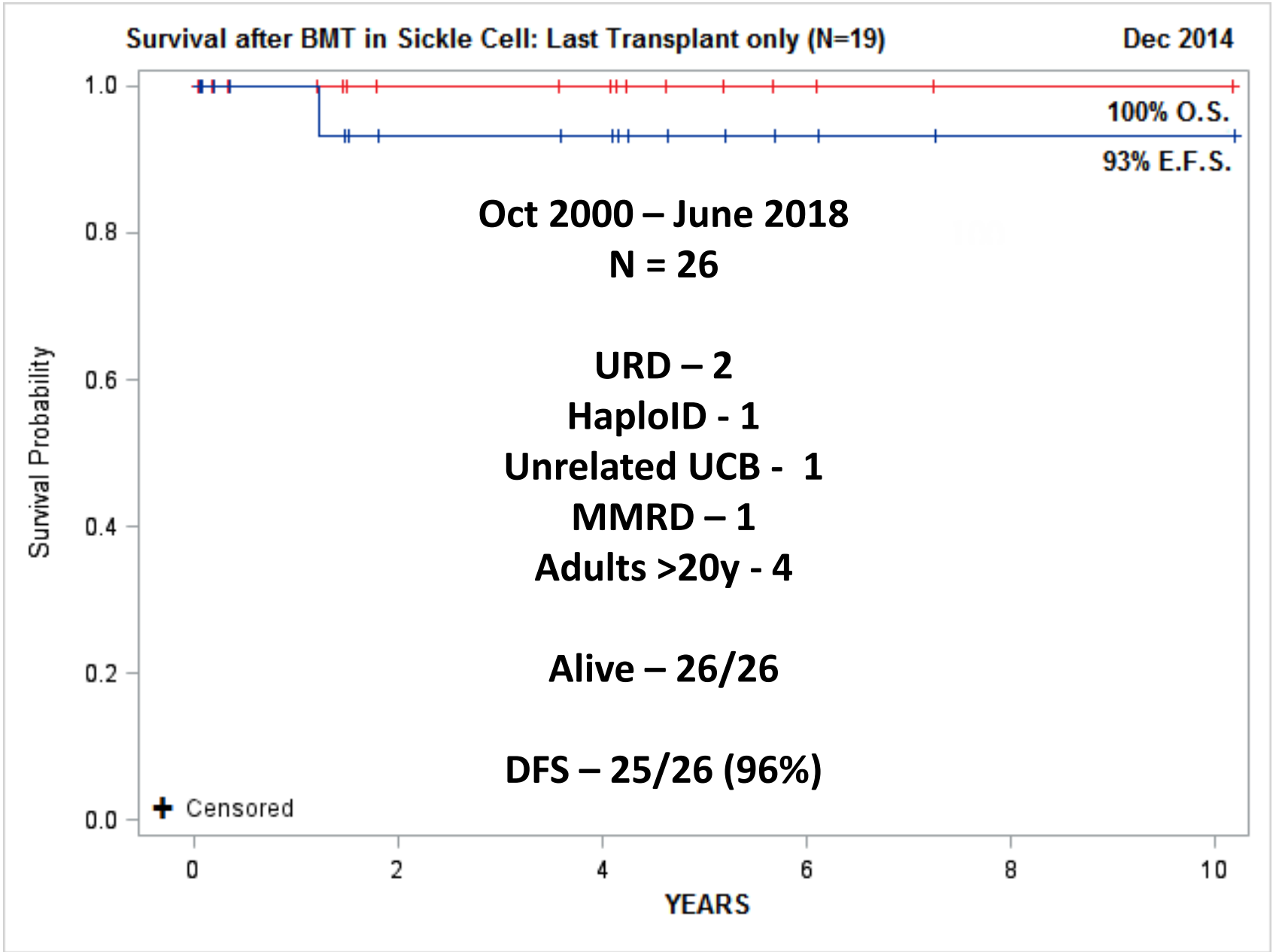
In accordance with the ACCME® standards for Commercial Support Number 6, my relevant financial relationships are disclosed:

Medical Director:
ViaCord Processing Lab
AllCells, Inc

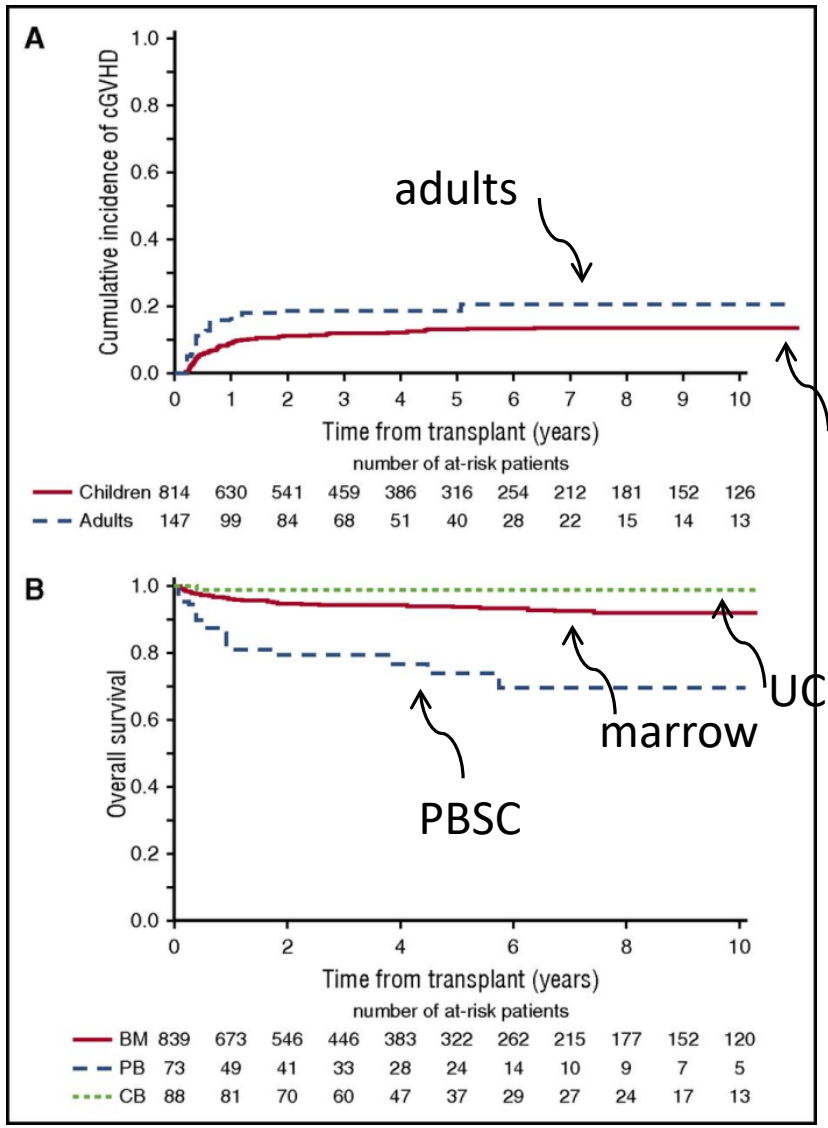
Consultant:
bluebird bio, Inc
Sangamo Biosciences/Bioverativ
Global Blood Therapeutics
Trucode

BMT for SCD at UCSF BCHO

UCSF Benioff Children's Hospitals



How is a curative outcome depicted – HLA-ID sibling HCT?



Complication incidence – Graft-versus-host disease

Successful outcome – overall survival

E Gluckman et al Blood 2017 129:1548-1556

Barriers to Transplant for SCD

- Only 18% of families have HLA-ID sibling donor
- Only 19% have well-matched unrelated donor
- Clinicians do not refer patients because of GVHD and risks of dying/long-term toxicity
- The problem of graft rejection/recurrent SCD has not been eliminated, especially in mismatched donor HCT

‘Genomic’ therapies for hgb disorders

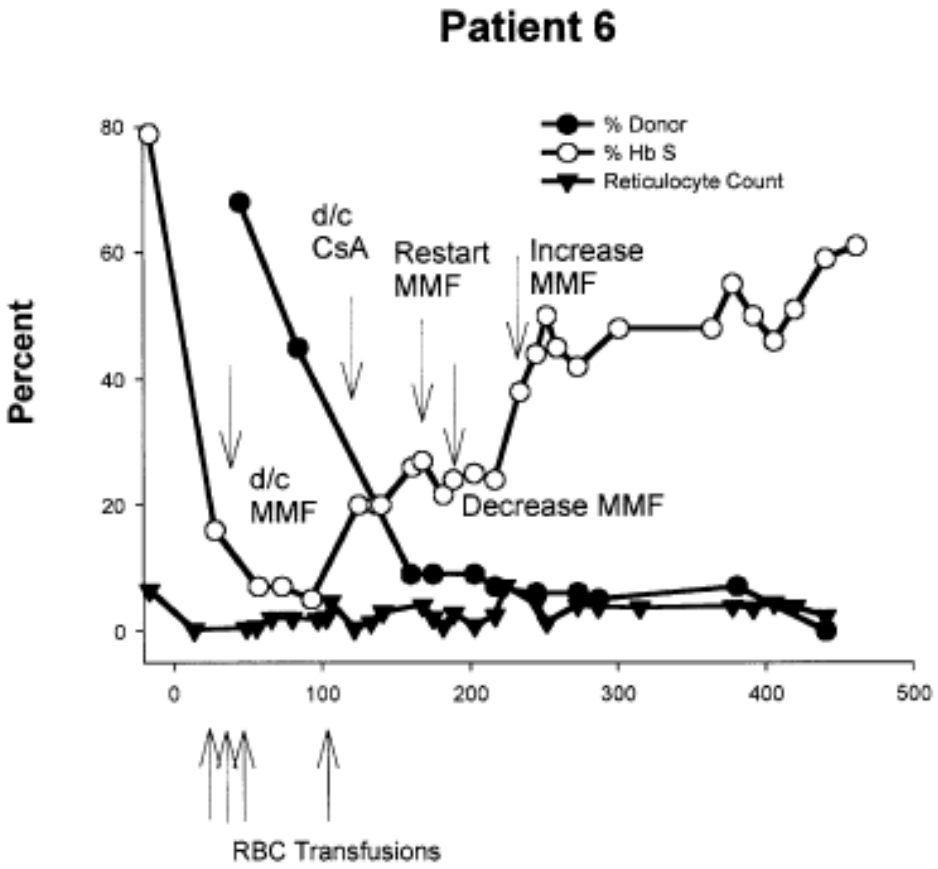
- Gene addition therapy (anti-sickling β-globin or γ-globin) in autologous HCT
- Gene editing for γ-globin expression in autologous HCT
- Gene editing for sickle allele correction in autologous HCT
- In vivo gene editing

Curative therapies – fraction of ‘corrected’ HSCs

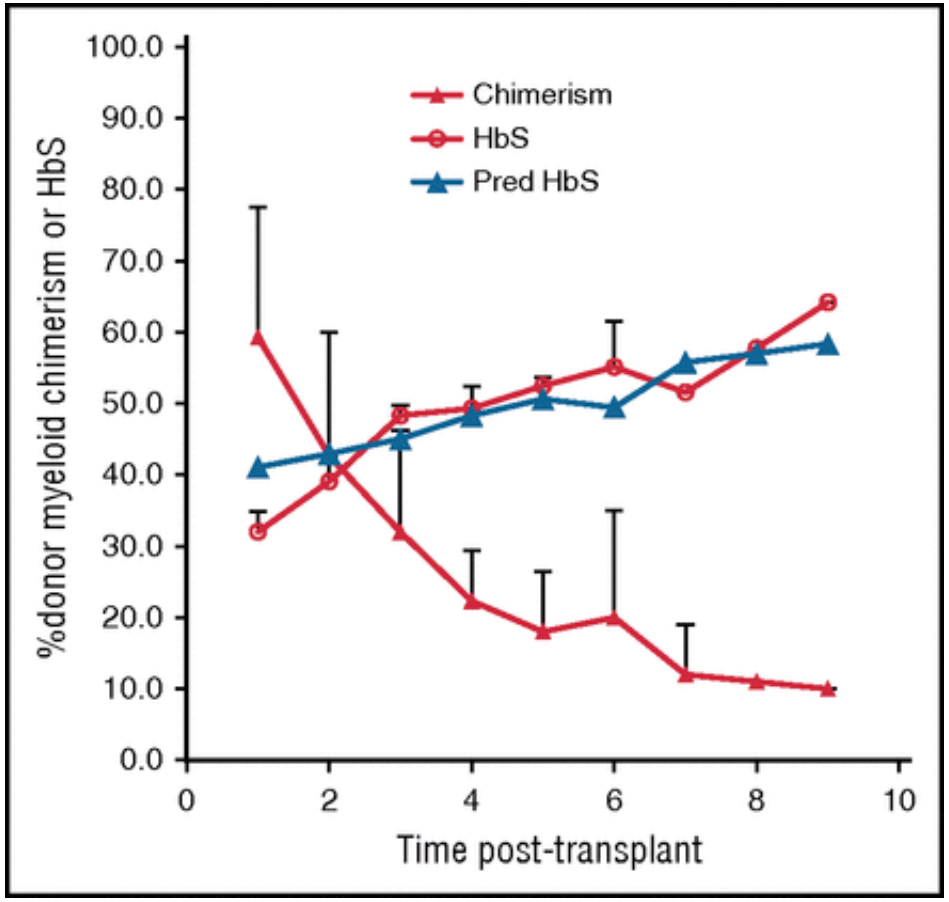
- After allogeneic HCT, stable mixed hematopoietic chimerism is sufficient to establish a curative effect
- Benchmark of >20-25% donor myeloid chimerism has been suggested, but there is inter-individual variability
- Ideally, fraction of corrected HSPCs might be even higher

Fitzhugh CD, et al Blood 130:1946, 2017
Abraham A, et al BBMT 12:2178, 2017

Curative therapies – stable mixed chimerism after allo-HCT

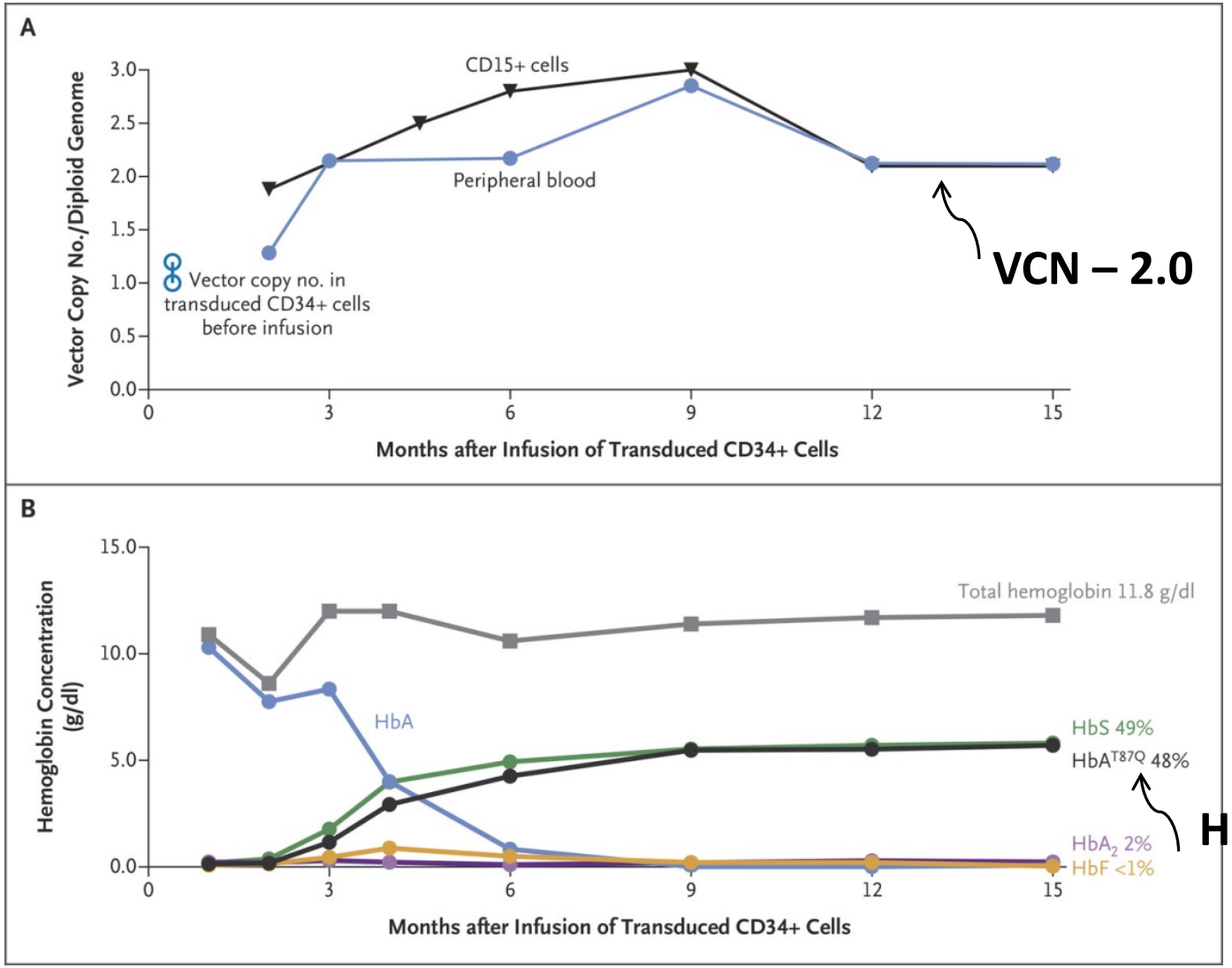


Iannone R, et al. BBMT. 2003;9(8):519-28.



Fitzhugh CD, et al Blood 130:1946, 2017

How a curative outcome is depicted – Gene therapy



VCN – 2.0

Avg vector copy number (VCN) is surrogate for fraction HSCs transduced

Dilution of HbS by 50%

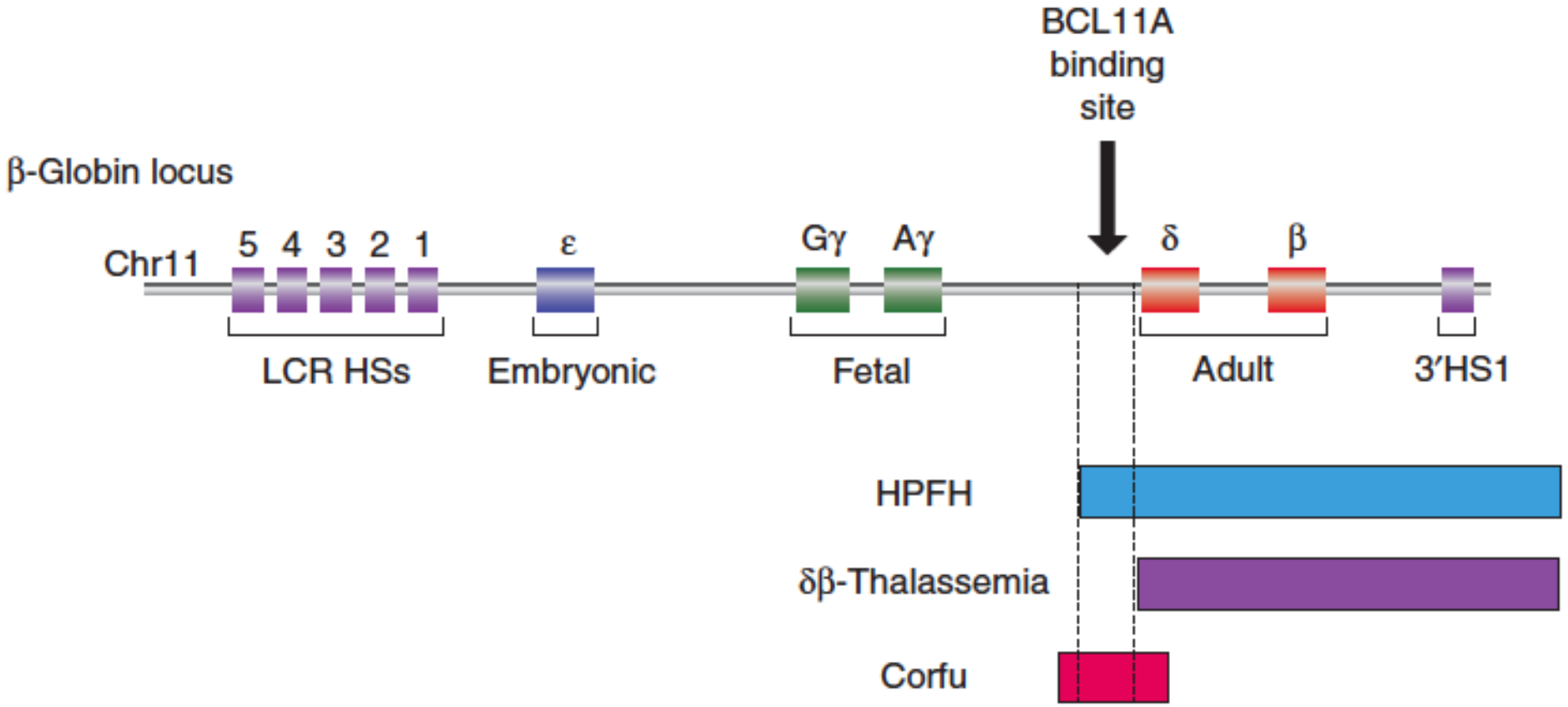
HbA ^{T87Q} ~50%

Rebeil et al. NEJM 2017; 376:848-55

Modulators of HbF expression

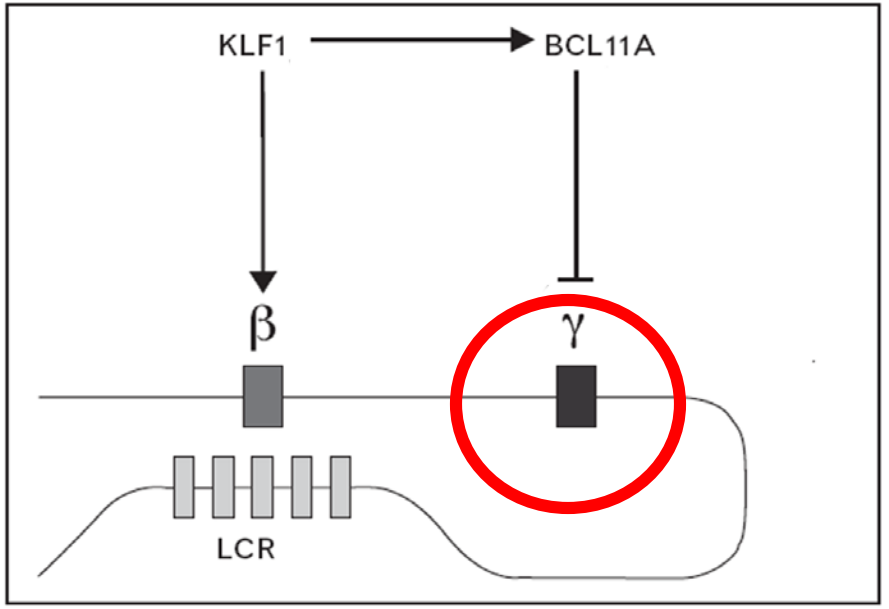
GWAS observations

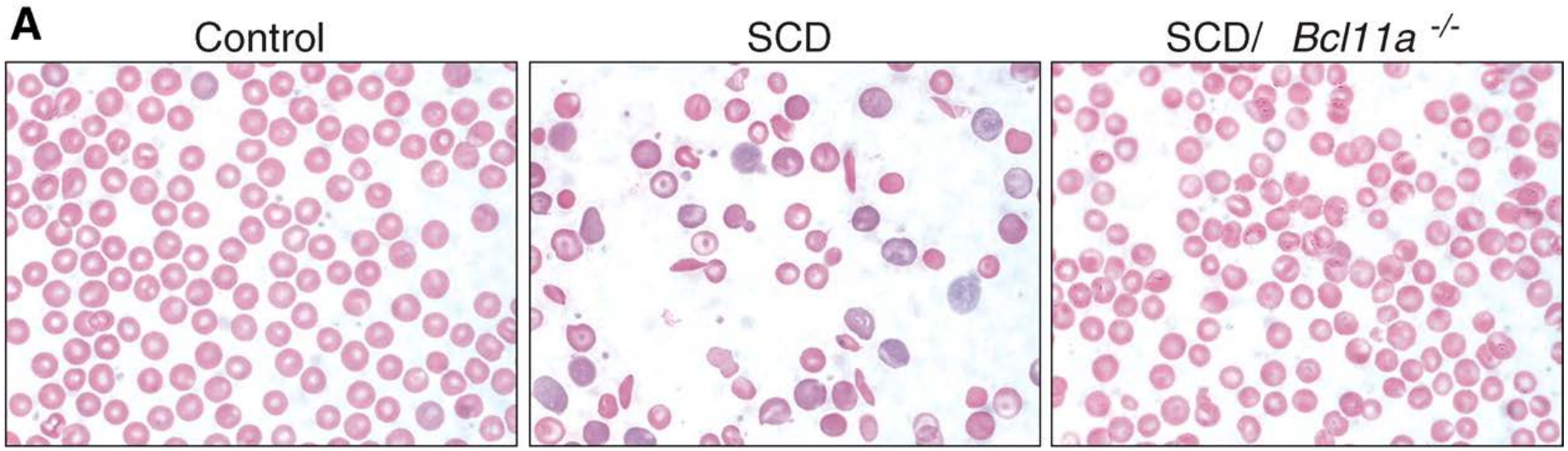
1. β-globin locus (chromo 11)
2. HBS1L-MYB intergenic region (chromo 6)
3. BCL11a (chromo 2)



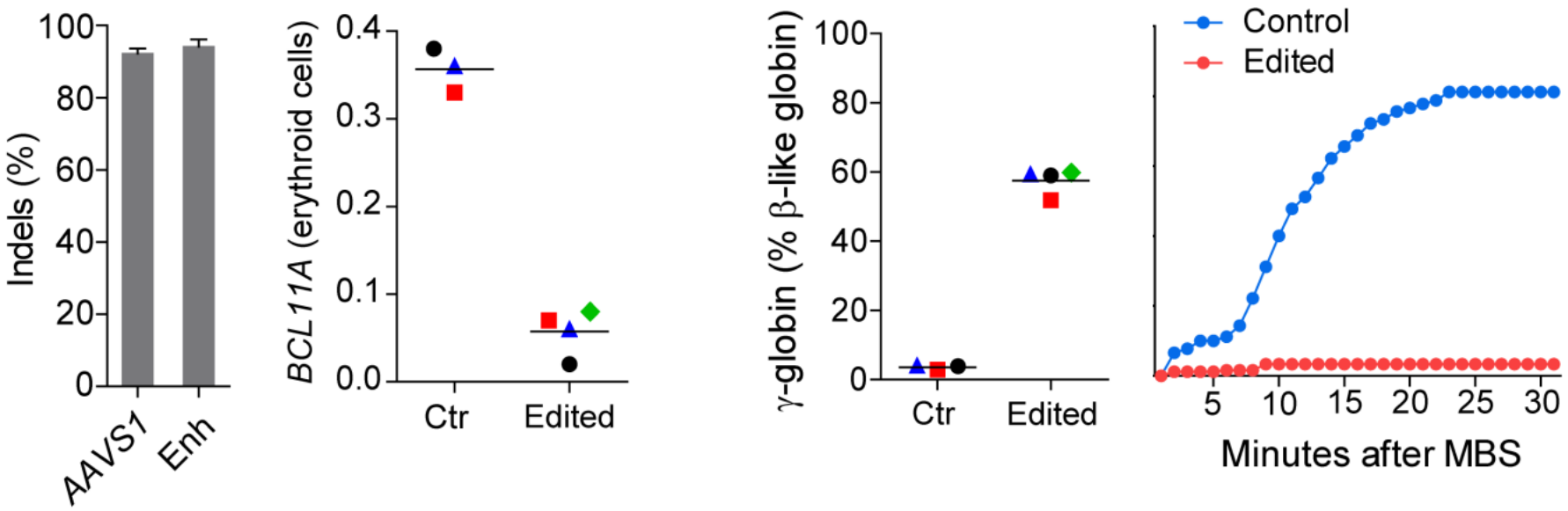
BCL11A is an epistatic suppressor fetal Hb

Data from: Xu J, et al. Correction of sickle cell disease in adult mice by interference with fetal hemoglobin silencing. *Science*. 2011 334:993-6.





How is a curative outcome depicted – Hb F induction after gene editing?



What is the HbF and F-cell induction target?

Unpublished, Daniel Bauer

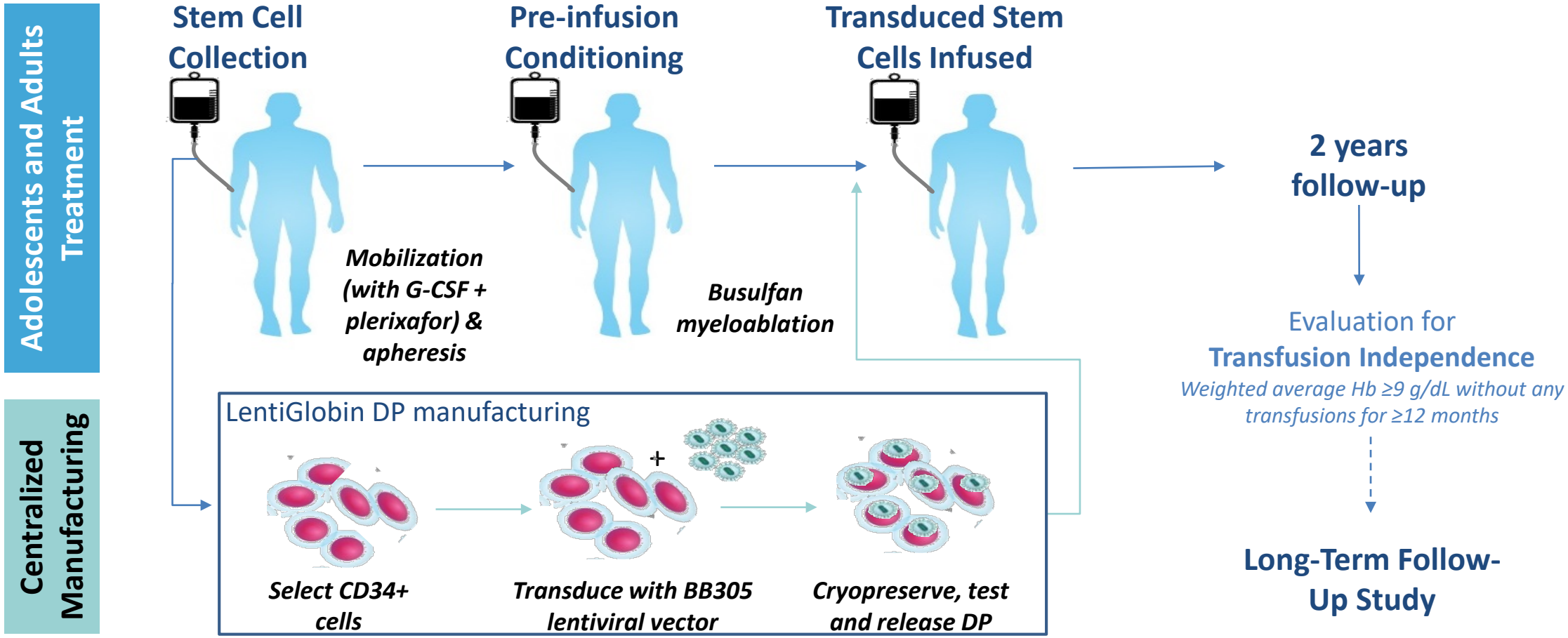
Curative therapies – VCN

- After vector transduction, VCN and % transduced HPSCs directly proportional
- VCN of 0.5 – 1 corresponds to 20-30% HSPC transduction
- Stochastic nature of HSPC contribution to erythropoiesis challenges a direct prediction
- However, VCN and %transduction are important endpoints that should be tracked in the short- and long-term

Thompson AA et al NEJM 378:1479, 2018

LentiGlobin gene therapy for transfusion-dependent β-thalassemia

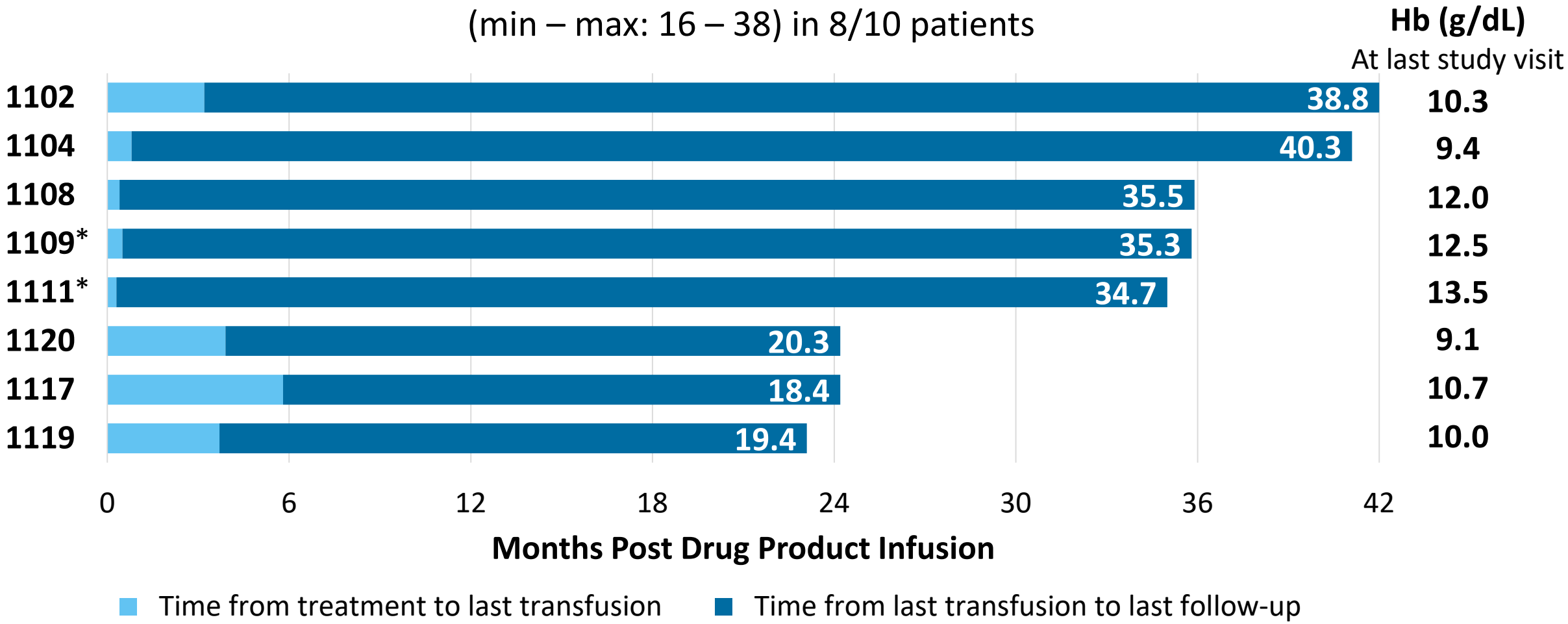
LentiGlobin gene therapy contains autologous CD34+ HSCs transduced ex vivo with the BB305 lentiviral vector encoding β-globin with a T87Q amino acid substitution



Locatelli, et al. EHA 2018. Abstract 1510.

HGB-204: 8/10 patients with non-β^0/β^0 genotypes achieved and maintain transfusion independence

Median duration of transfusion independence to date of **33 months**
(min – max: 16 – 38) in 8/10 patients

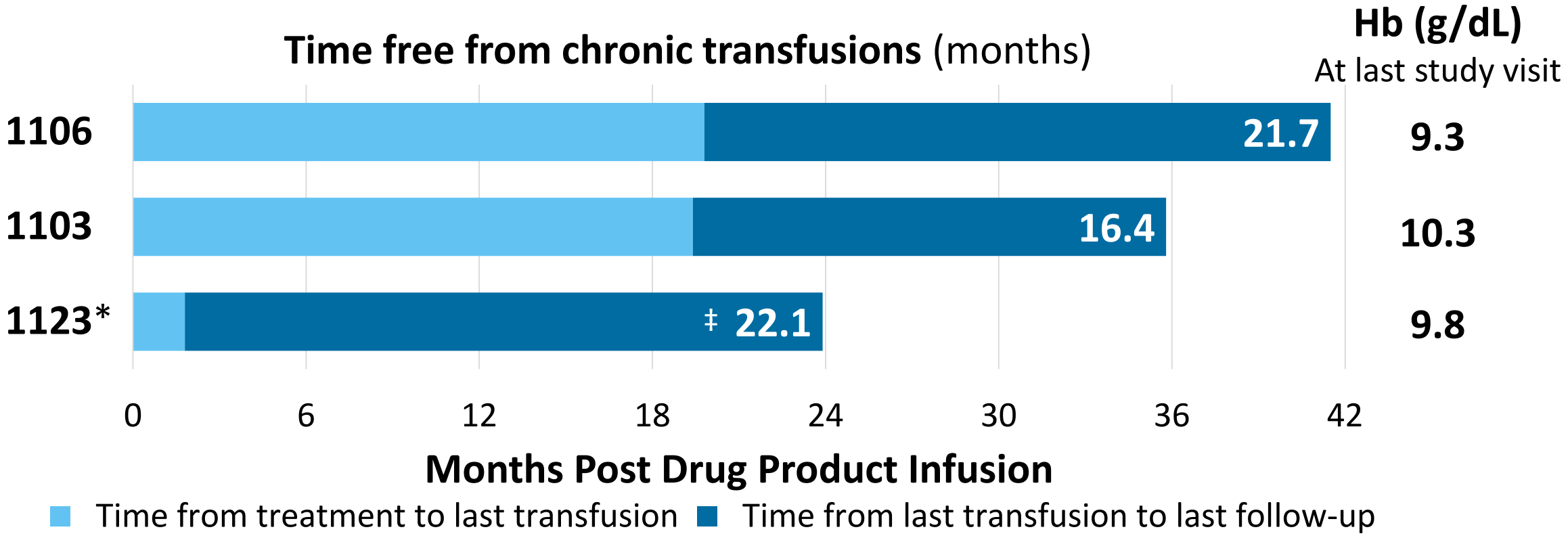


*Indicates male patients. Transfusion independence is defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months. Hb, hemoglobin

Rasko, et al. ISCT-EU 2018. Abstract 1.

Data as of 7 March 2018

HGB-204: 3/8 patients with β^0/β^0 genotypes are free from chronic transfusions



Patients 1103 and 1123 achieved transfusion independence with a duration to date of 14 and 16 months, respectively

* Indicates male patient

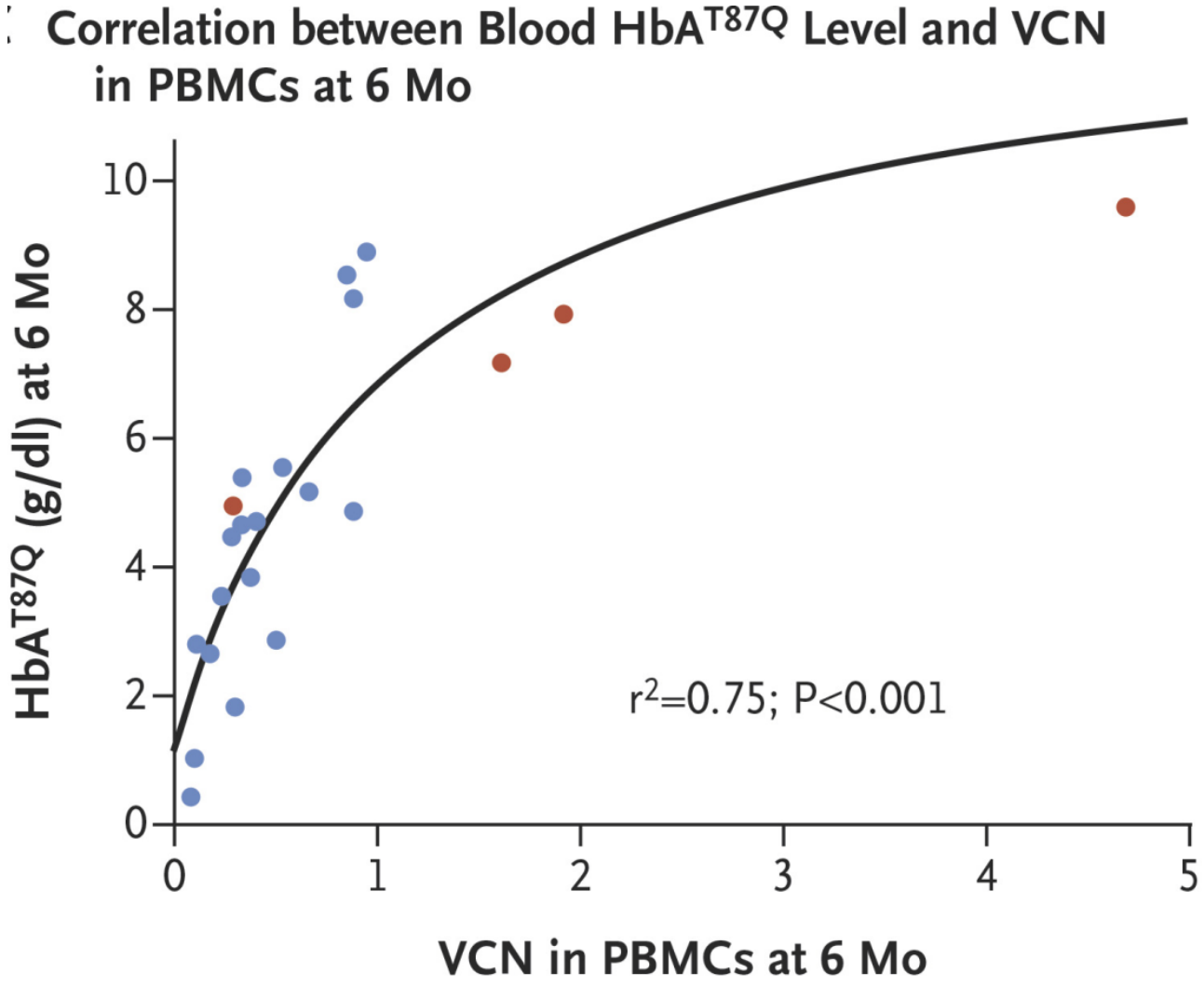
‡ Patient had a single transfusion for an acute event of cat scratch disease

Transfusion independence is defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months. Hb, hemoglobin

Rasko, et al. ISCT-EU 2018. Abstract 1.

Data as of 7 March 2018

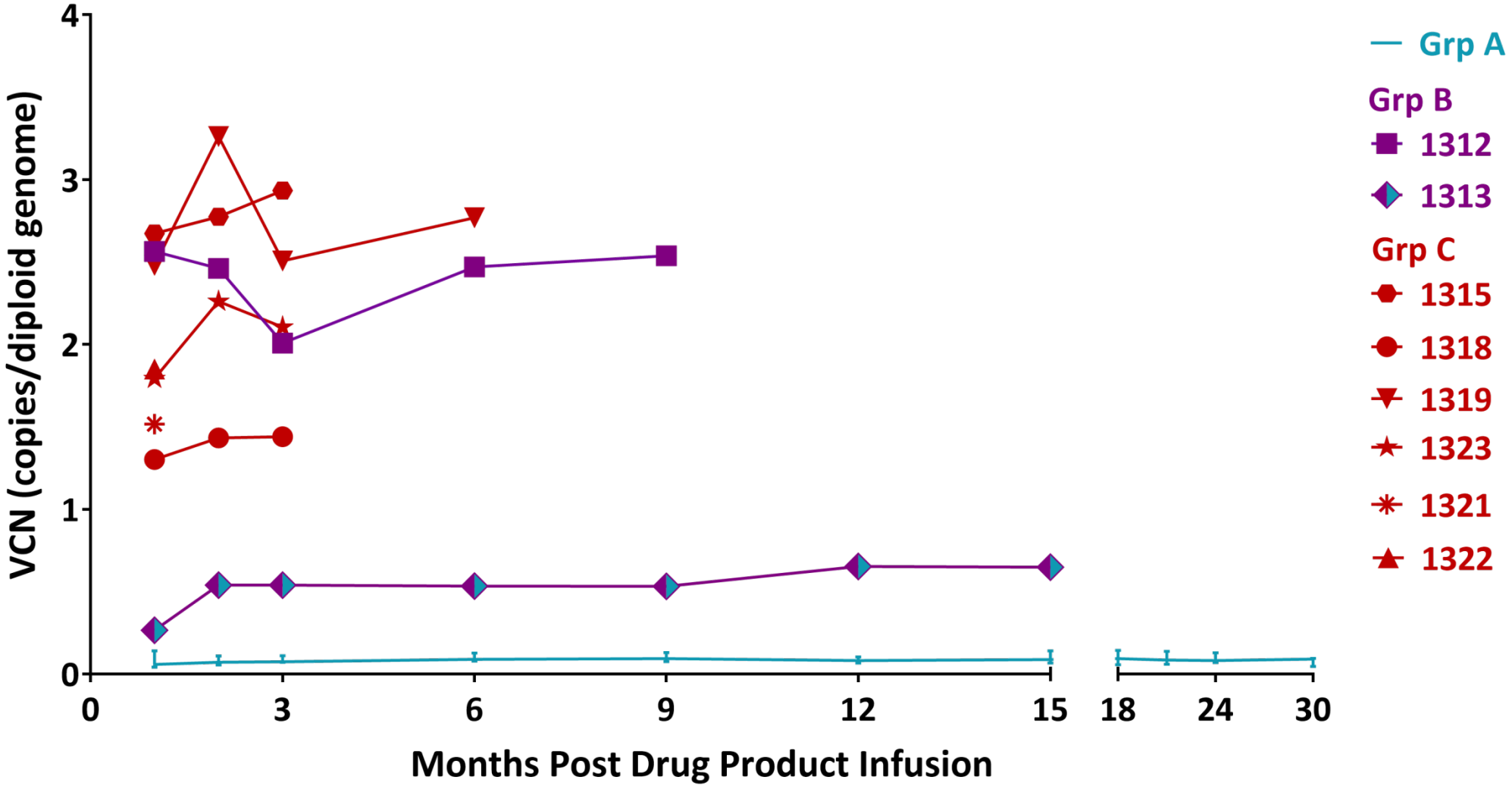
Curative therapies – VCN



Blue dots: US/Austr/Thai
Red dots: France

Thompson AA et al NEJM 378:1479, 2018

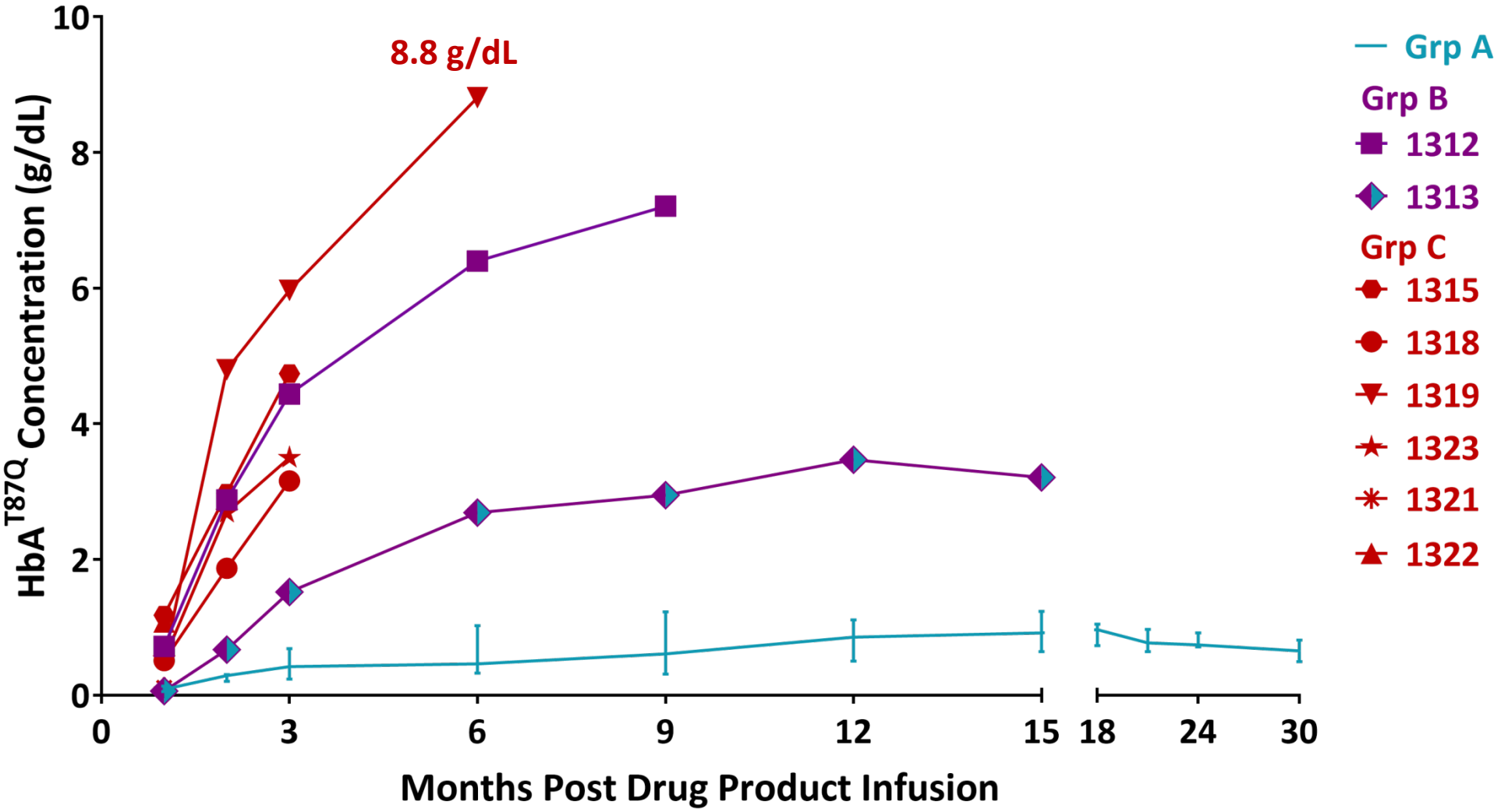
Peripheral blood VCN is higher in patients in Group B and C



For Group A patients, medians (Q1, Q3) depicted; Group A patients with month 30 study visit (N=3)
VCN, vector copy number (vector copies/diploid genome)
Kanter, et al. EHA 2018. Abstract S836.

Data as of May 15, 2018

Patients in Group B and C demonstrate higher HbA^{T87Q} production



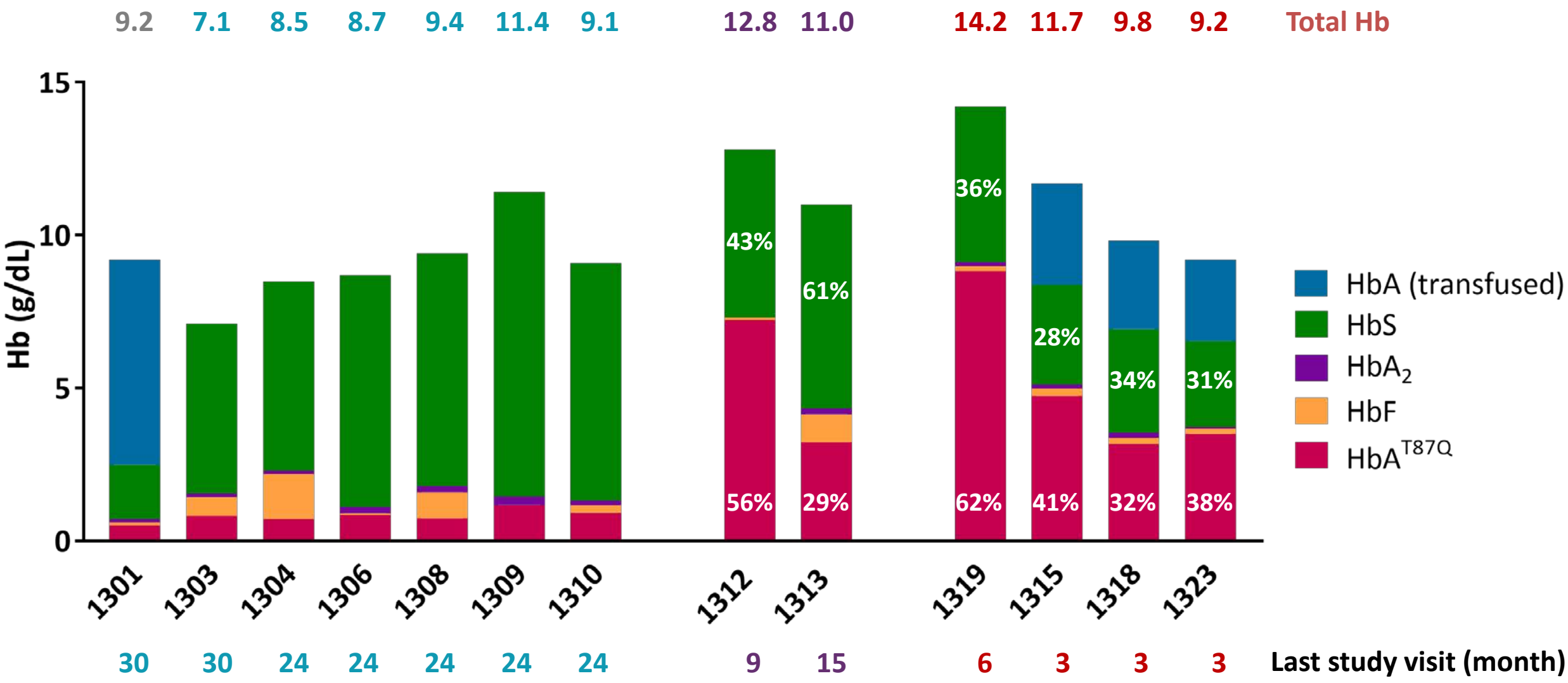
For Group A patients, medians (Q1, Q3) depicted; Group A patients with month 30 study visit (N=2)

HbA^{T87Q}, vector derived hemoglobin

Kanter, et al. EHA 2018. Abstract S836.

Data as of May 15, 2018

Vector-derived hemoglobin in treated patients

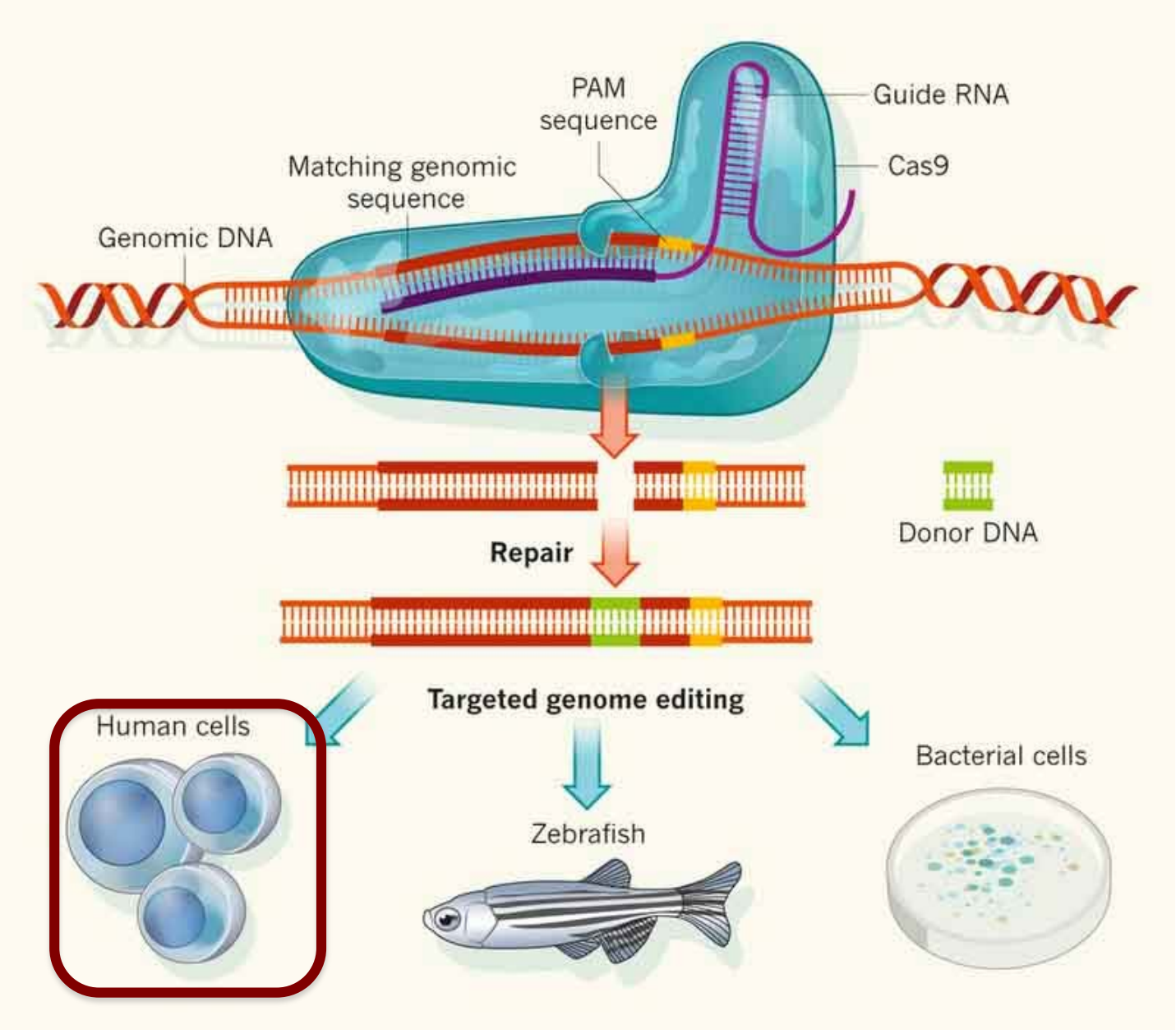


Hb, hemoglobin; HbA, adult hemoglobin; HbA^{T87Q}, vector derived hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin

Kanter, et al. EHA 2018. Abstract S836.

Data as of May 15, 2018

Cas9 for programmable gene correction



targeted

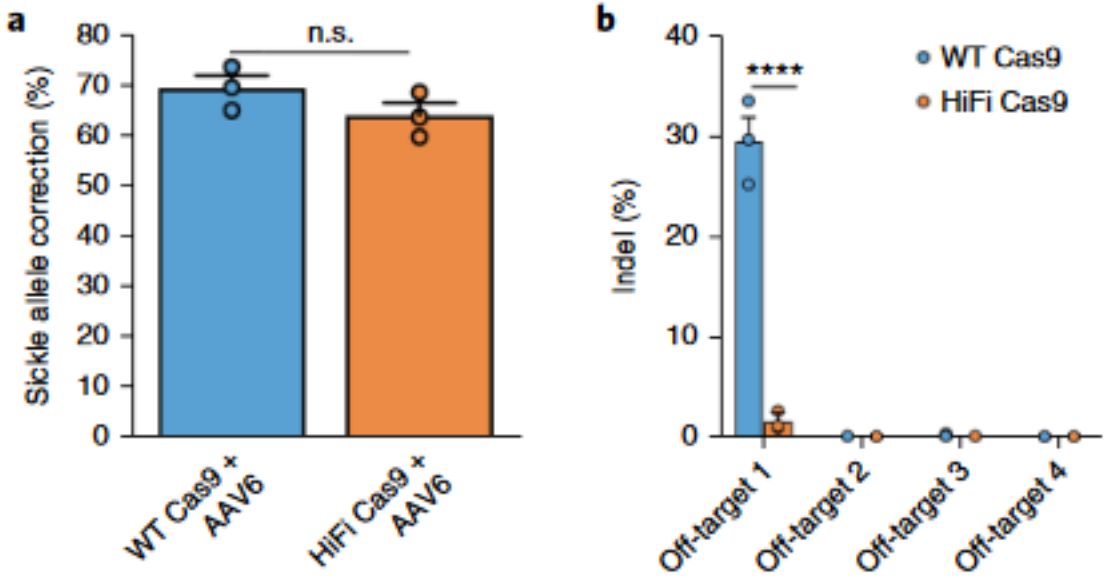
fast

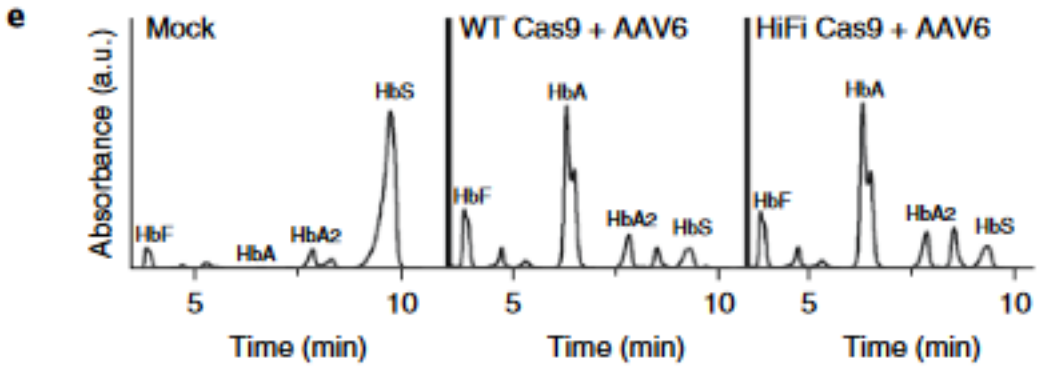
efficient

simple

inexpensive

How is a curative outcome depicted – Gene editing?





Fraction of Sickle allele corrected

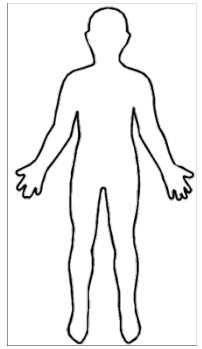
Frequency of off-target modification

Dilution of HbS by 50%

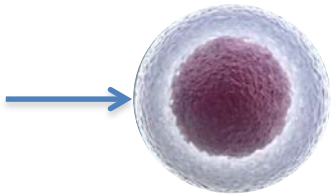
Vakulskas CA et al, Nat Med 24:1216, 2018

In vivo and *in vitro* experiments

Do edited HSCs produce non-sickle hgb?

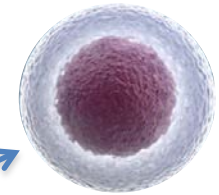


sickle donors



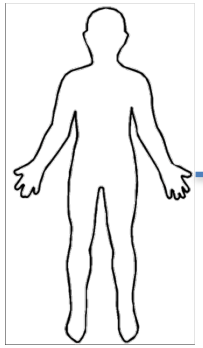
correct

In Vitro Erythroid Expansion conditions

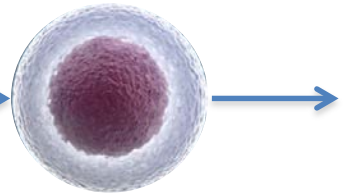


edited erythrocytes?
Ameliorate sickle globin?

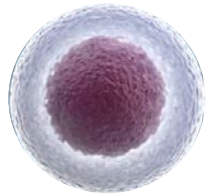
Are human edited cells true HSCs?



sickle donors

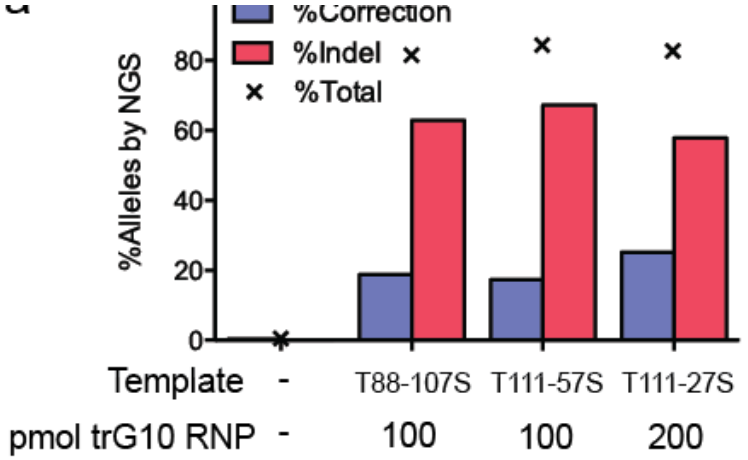


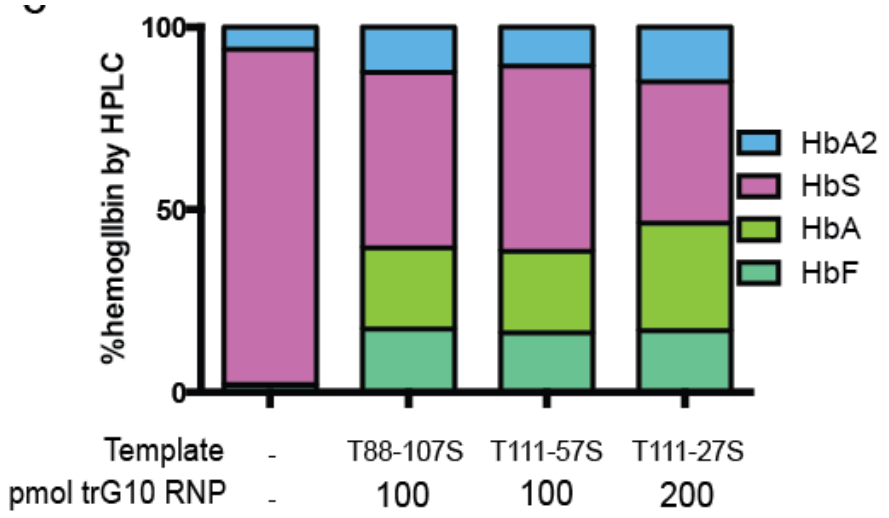
correct

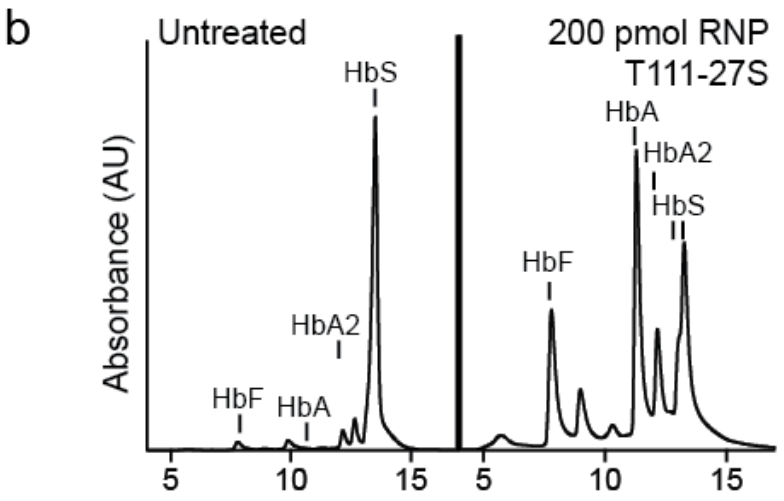


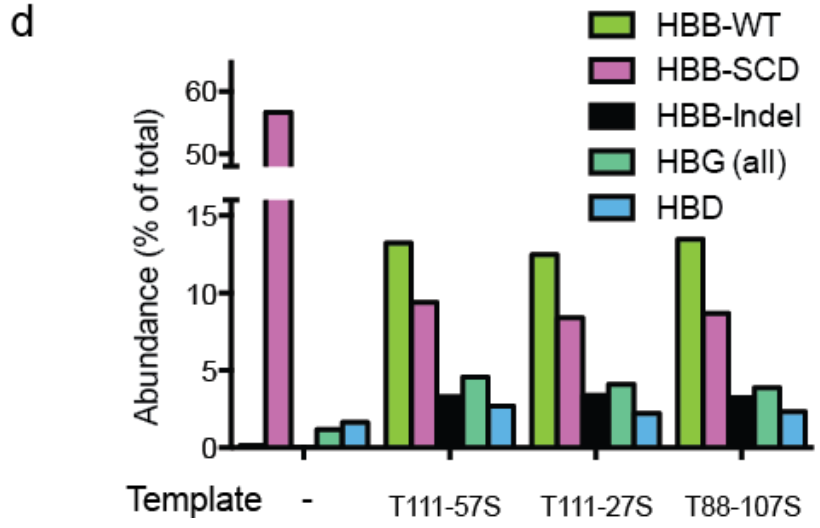
engraftment?
edited blood lineages?

In vitro erythroid expansion



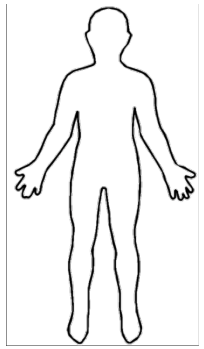






In vivo experiments: xenografts

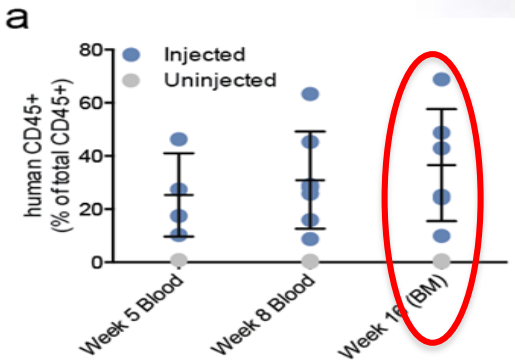
Are human edited cells true HSCs?

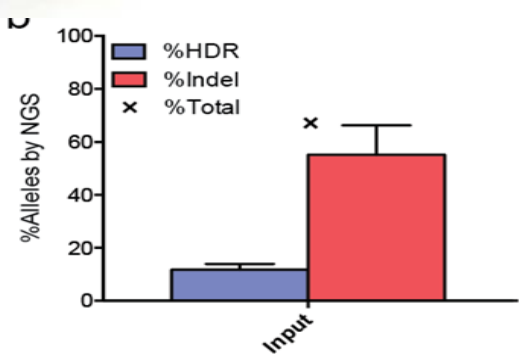


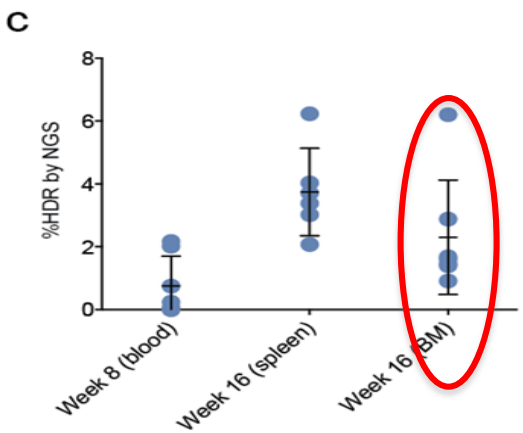
sickle donors

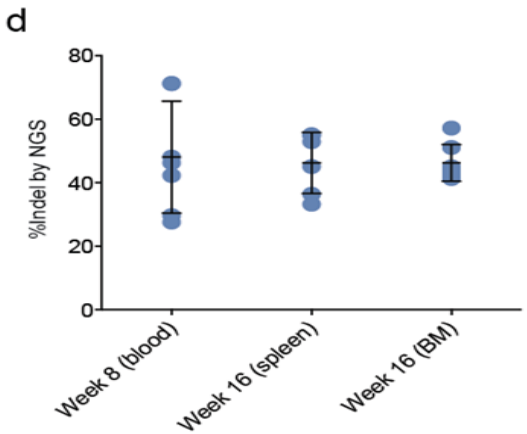
correct

engraftment?
edited blood lineages?

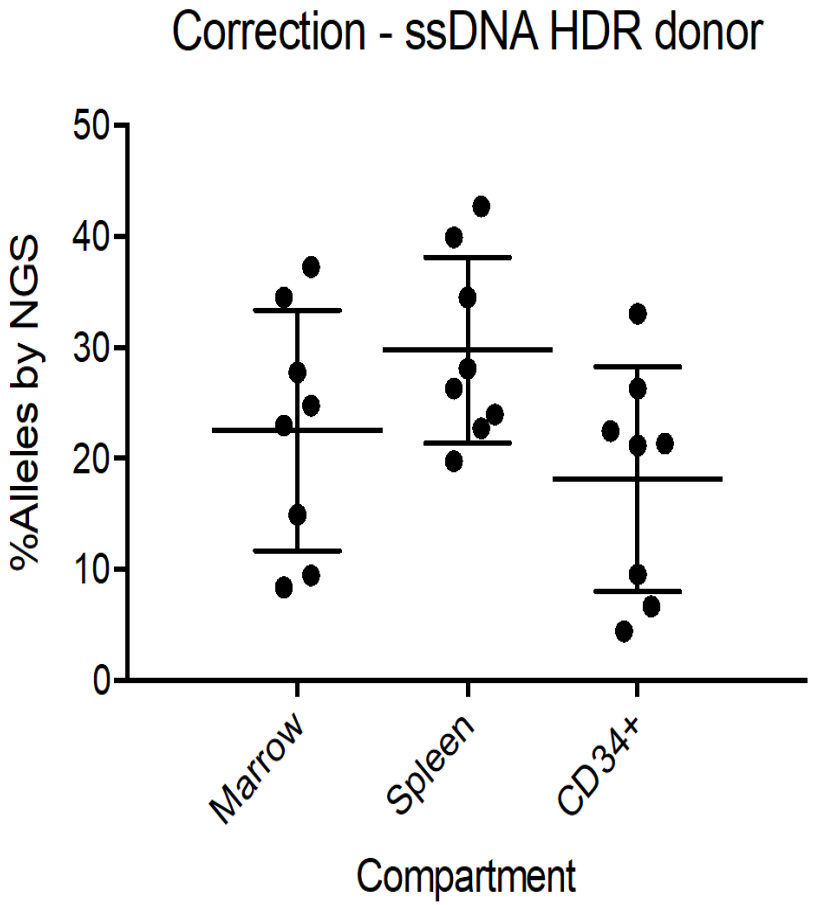


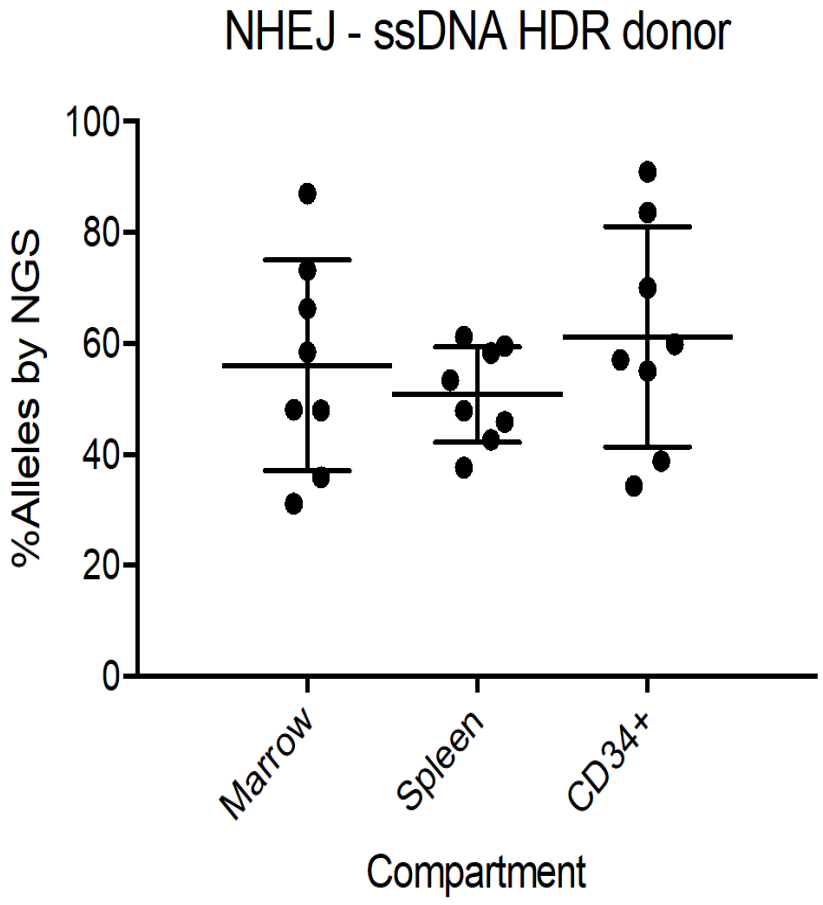






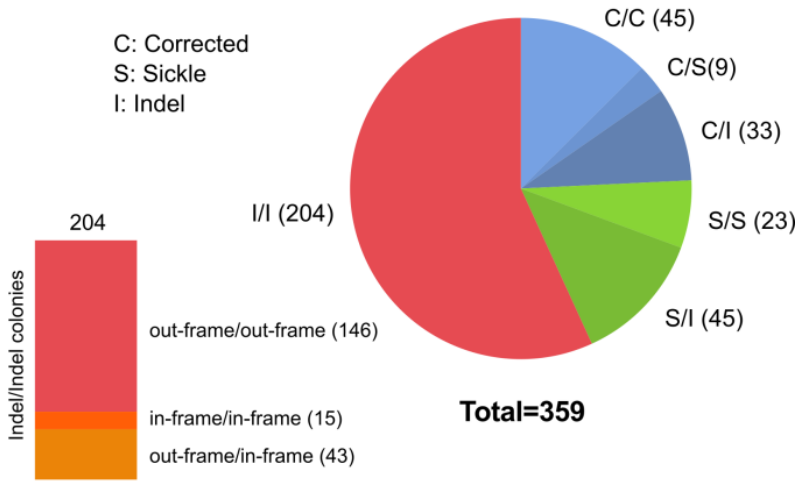
Optimized sickle correction in xenotransplant model with plerixafor-mobilized HbSS CD34+ cells

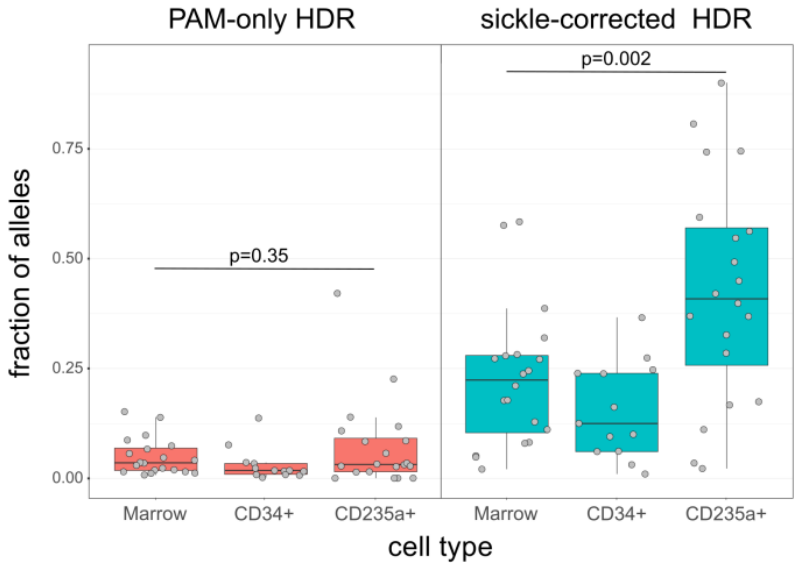




ssDNA donor directed editing had an average of 22.15% ± 7.66% correction in marrow

Curative therapies – % allele





Magis W et al.; bioRxiv 432716; doi: https://doi.org/10.1101/432716

Summary

- **LentiGlobin BB305 gene therapy shows promising results in TDT**
- **LentiGlobin VCN strongly correlated with HbA^{T87Q} level**
- **Clinical benefit in SCD has been appears to follow HbA^{T87Q} levels – approach 50% non-HbS**
- **The future of curative therapies that will have broad availability might follow advances in gene therapy and genomic correction of the sickle mutation in HSCs – availability of the treatment will be a limiting factor**

Acknowledgements

- **HGB-206:** Julie Kanter, Mark C. Walters, Matthew Hsieh, Lakshmanan Krishnamurti, Janet Kwiatkowski, Rammurti T. Kamble, Christof von Kalle, Frans A. Kuypers, Marina Cavazzana, Philippe Leboulch, Marcelyne Joseney-Antoine, Mohammed Asmal, Alexis A. Thompson, John F. Tisdale
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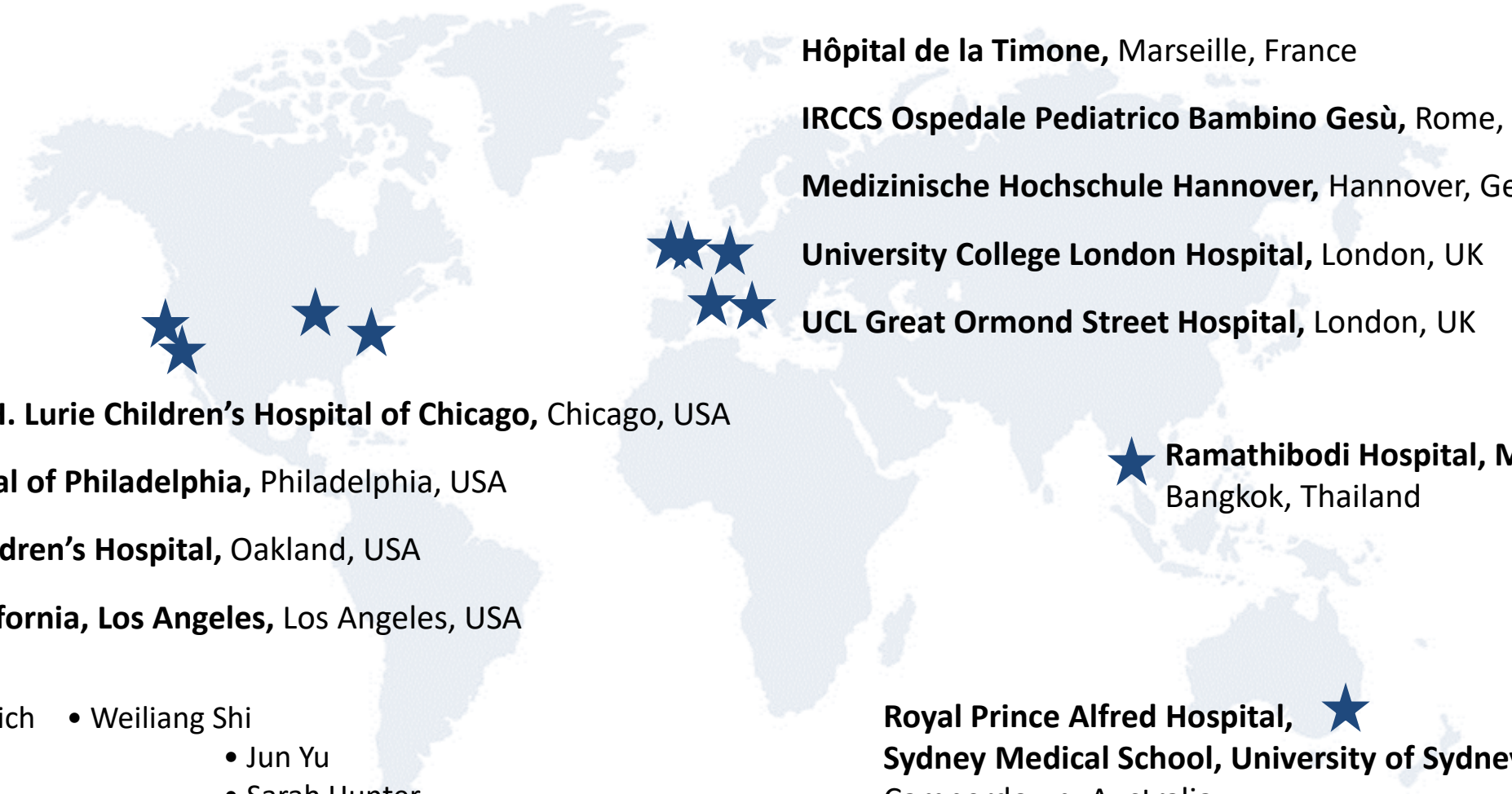
HGB-204 and HGB-207: Study sites and investigators



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Children's Hospital of Philadelphia, Philadelphia, USA

UCSF Benioff Children's Hospital, Oakland, USA

University of California, Los Angeles, Los Angeles, USA

Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

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- UCLA

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Thank you!

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