Sickle Cell Disease Treatment Updates

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25th Advances in Oncology Conference

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University of California Davis School of Medicine, Center for Oncology Hematology Outcomes Research and Training (COHORT), Division of Hematology and Oncology, Sacramento, CA

NCI Designated Comprehensive Cancer Center

UCDAVIS COMPREHENSIVE CANCER CENTER

Outline

- Pathophysiology of sickle cell disease (SCD)
- SCD modifying therapies
- Gene therapies in SCD
- Future directions

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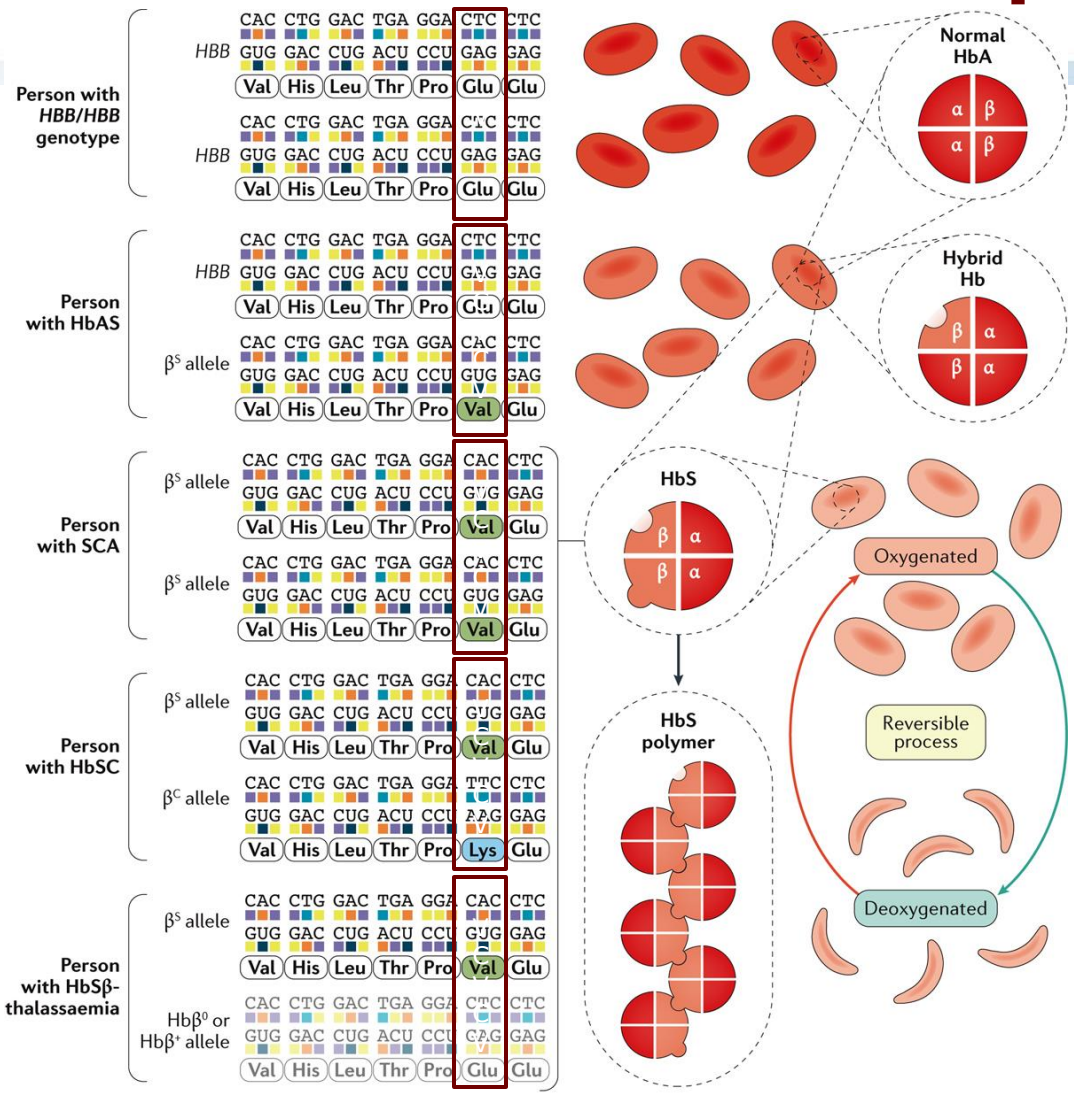
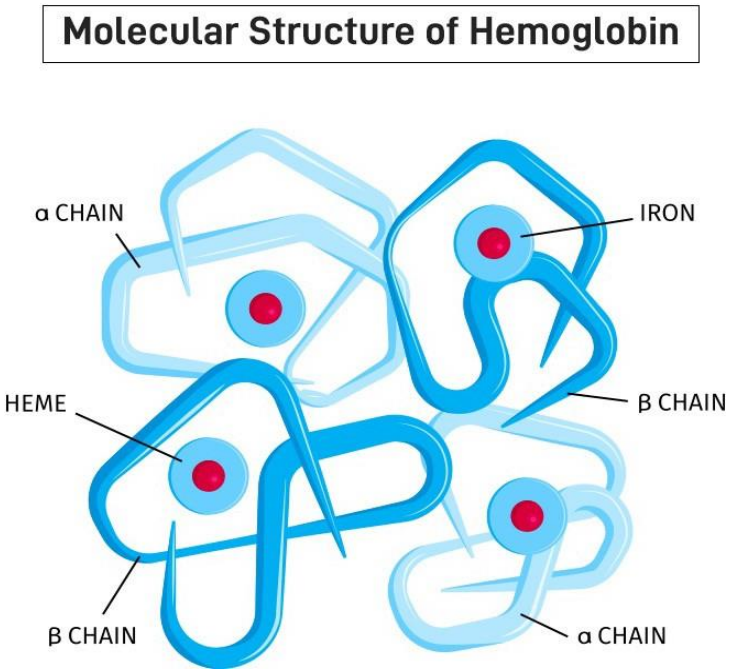
Genetic alterations in β globin gene (*HBB)*



Nature Reviews | Disease Primers



Kato, G.J., et al., *Sickle cell disease.* Nat Rev Dis Primers, 2018. **4**: p. 18010.

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Hemoglobin (Hb) packaging matters

Hb AA

$AAAAA_2$
A_2AAA
AA_2AAA_2

Hb AS

ASASA
AAA_2ASA
ASAAS

Hb SS

SSSSSS
S S S A_2
SSASSSS

Hb SS + HPFH*

$FSSSA_2$
SFSFFSS
$SSSSFA_2$

HbSS + RBC transfusions

SSA_2SSS
SSS S A_2
SSASSSS

$AAAAA_2$
A_2AAA
AA_2AAA_2

HbSS + Hydroxyurea

SSSSSS
S S S A_2
SSASSSS

FFF
F FF
FFFFFFF

Thousands of Hb molecules in every RBC

*Hereditary persistence of fetal hemoglobin

Slide courtesy of Dr. Julie Kanter (University of Alabama at Birmingham)

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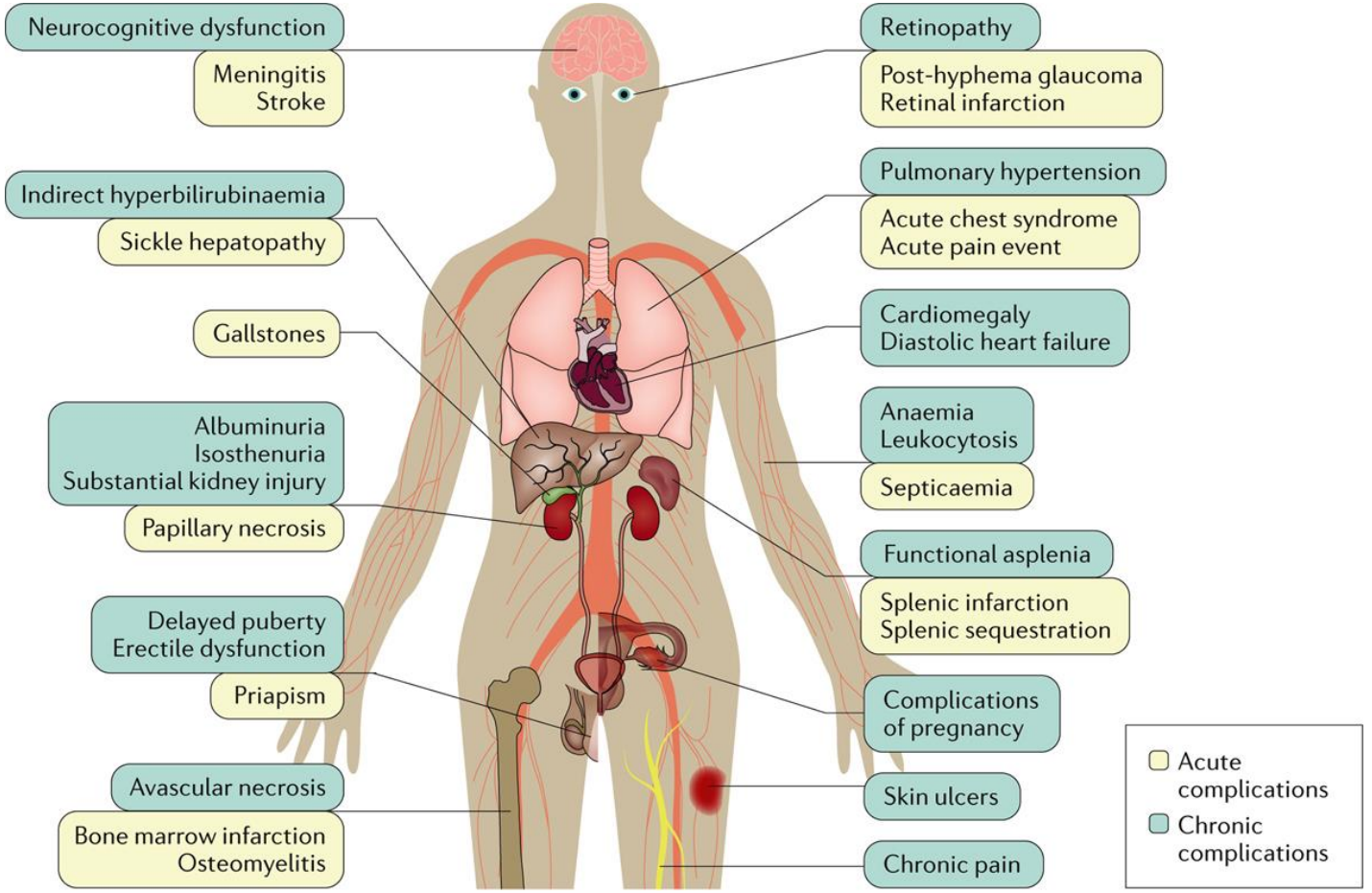
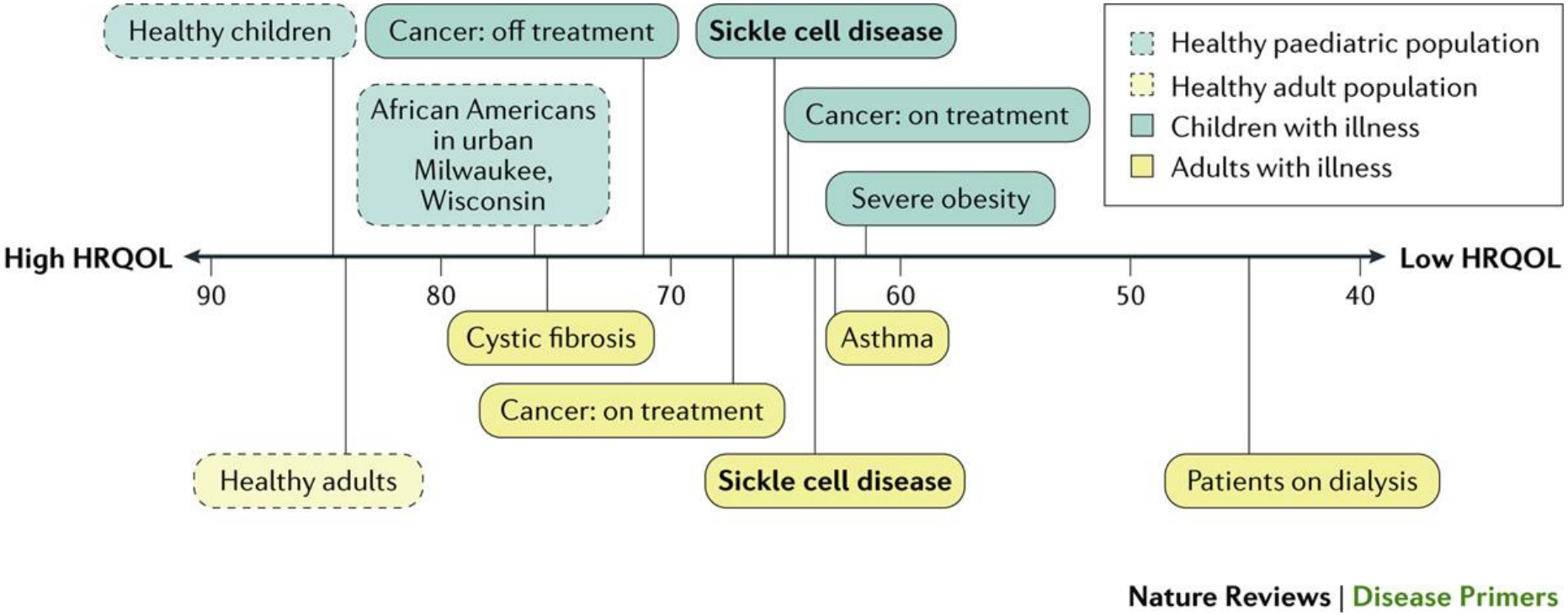
Sickle cell disease clinical complications



Kato, G.J., et al., *Sickle cell disease.* Nat Rev Dis Primers, 2018. **4**: p. 18010.

Health-related quality of life



Kato, G.J., et al., *Sickle cell disease.* Nat Rev Dis Primers, 2018. **4**: p. 18010.

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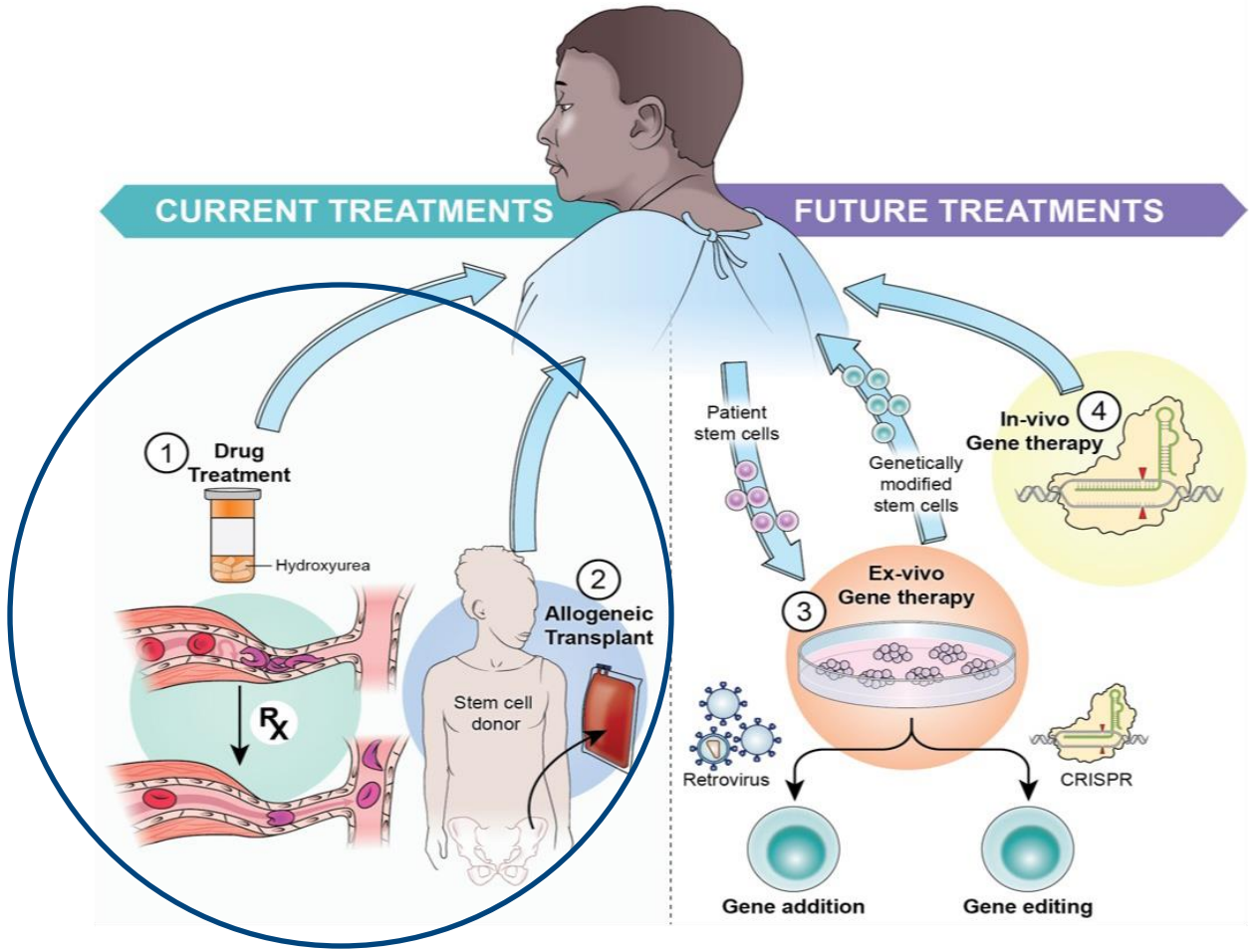
- SCD modifying therapies
- Gene therapies in SCD
- Future directions

Overview of SCD management



Slide courtesy of Dr. Julie Kanter (UAB)

Tisdale, Thein and Eaton, Science, 13 Mar, 2020

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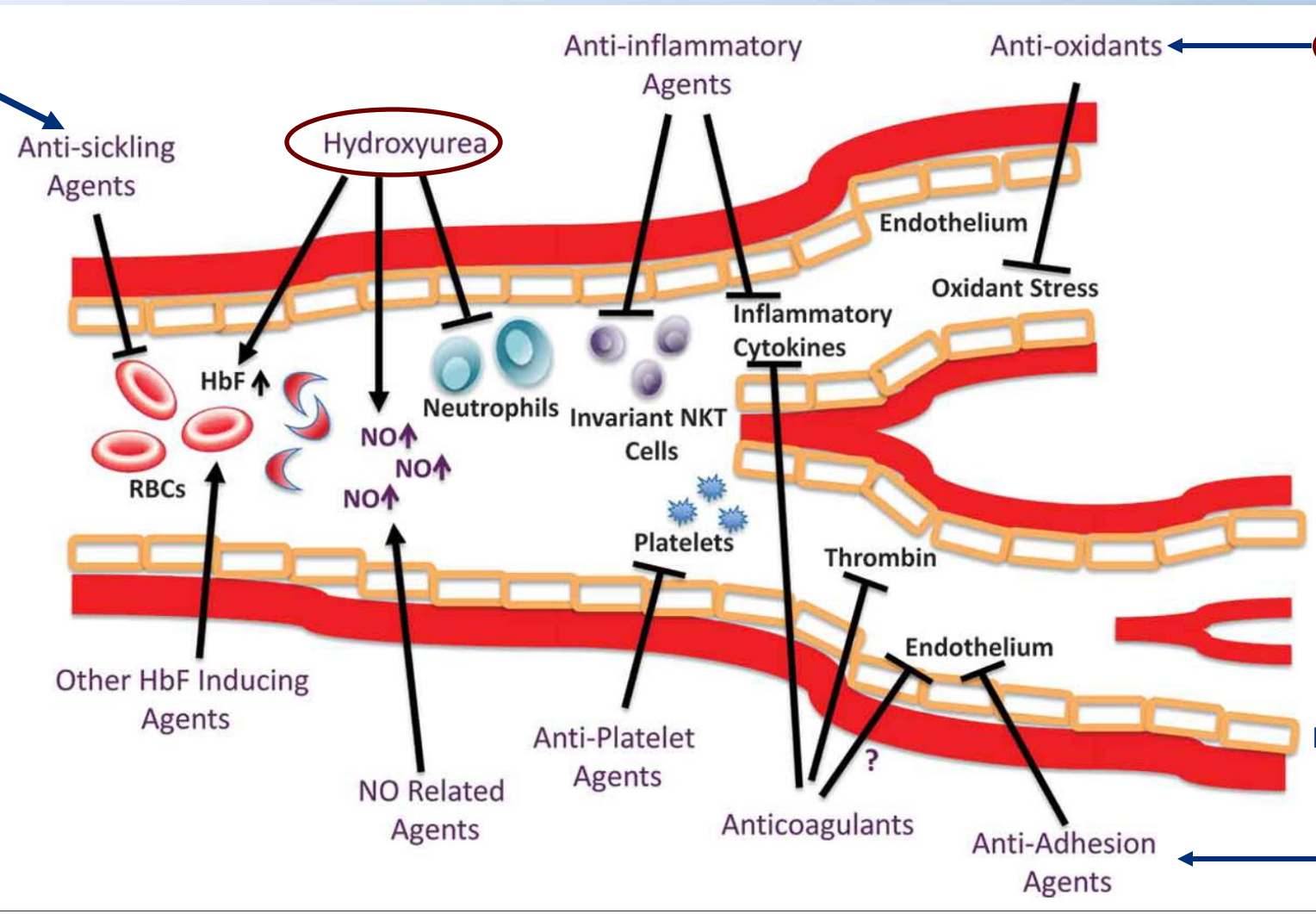
Drug therapies for SCD modification

~~Voxelator~~

Pfizer
(Sep 2024)



European Commission
(Aug 2023)

~~Crizanlizumab~~

Ataga, K.I., & Desai, P.C. (2018). *Expert Opinion on Orphan Drugs*, *6*(5), 329–343.

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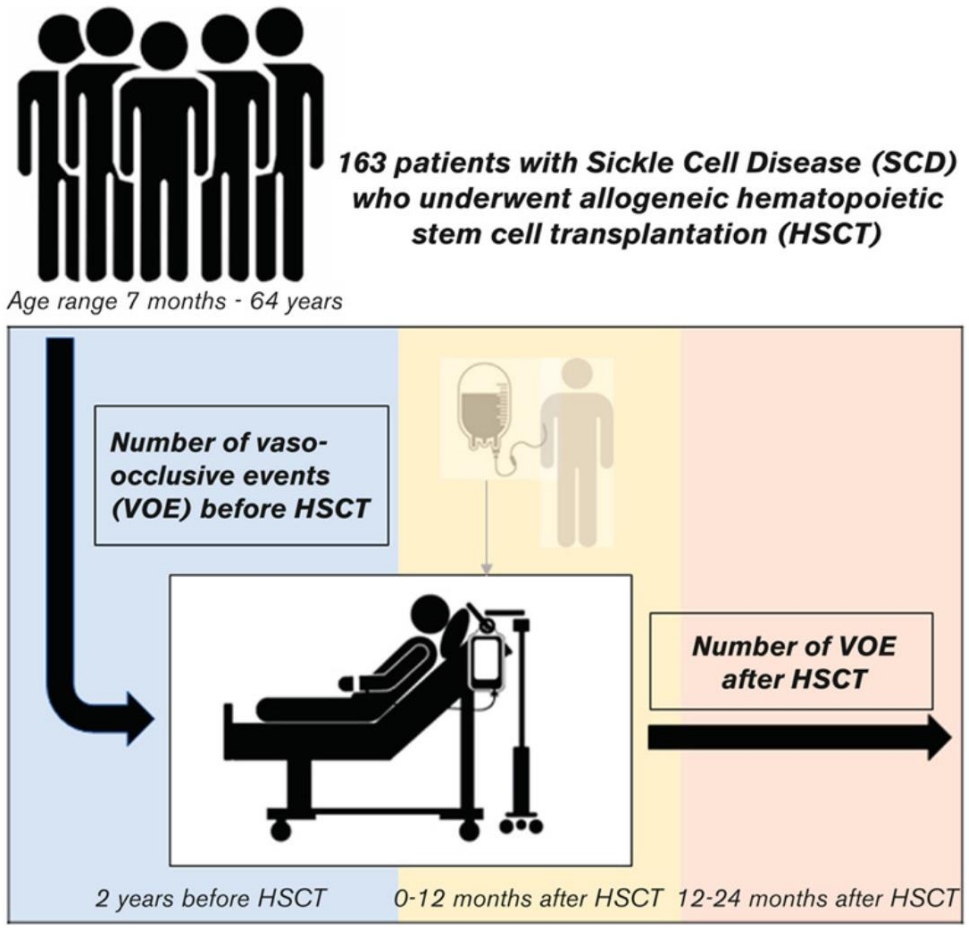
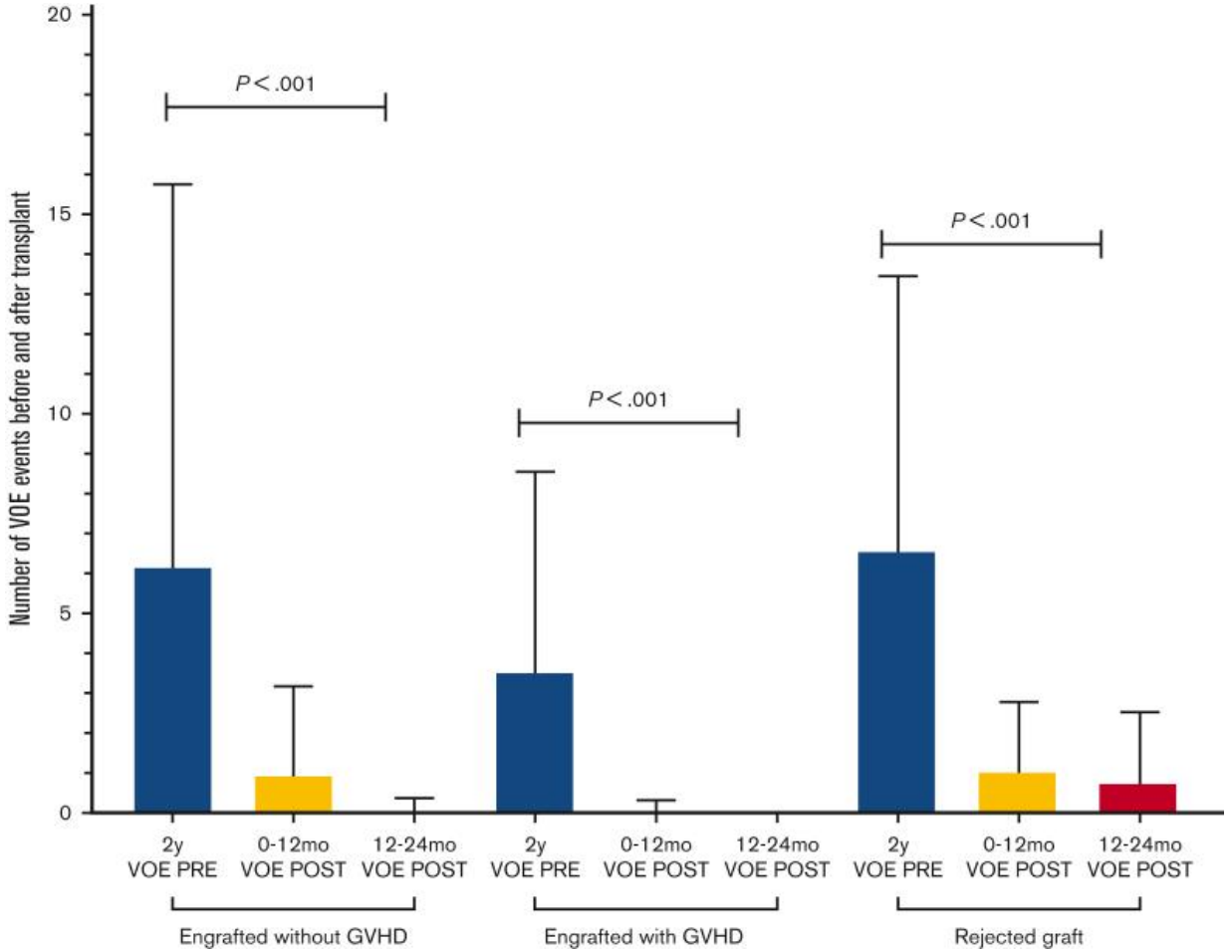
Allogeneic HSCT reduces vasoocclusive episodes (VOEs)





Leonard et al., Blood Adv. 2023 Jan 24;7(2):227-234.

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Haploidentical transplant in sickle cell disease

A Phase 2 Multicenter Trial of the Vanderbilt Global Haploidentical BMT Learning Collaborative to Optimize Curative Therapy for Sickle Cell Disease (SCD)

Context of Research

- Treatment-related mortality associated with myeloablative conditioning regimens represents a major barrier for adults with SCD
- A non-myeloablative conditioning regimen with PTCy has made related haploidentical BMT a promising alternative curative therapy for SCD
- **Hypothesis:** adding thiotepa (10 mg/kg) to the non-myeloablative related haploidentical BMT with post-transplant cyclophosphamide (PTCy) will improve engraftment in participants to at least 80%

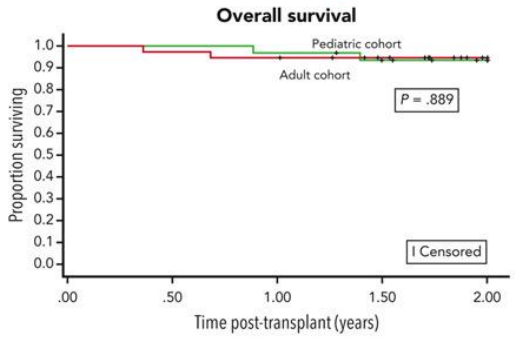
Methods

- A phase 2 multicenter trial using non-myeloablative haploidentical BMT to optimize curative therapy for SCD, Global Learning Collaborative (NCT01850108)

Results

- A total of 32 children and 38 adults were evaluable
- 2 year-overall survival was 94.1%
- 2-year event-free survival was 82.6%

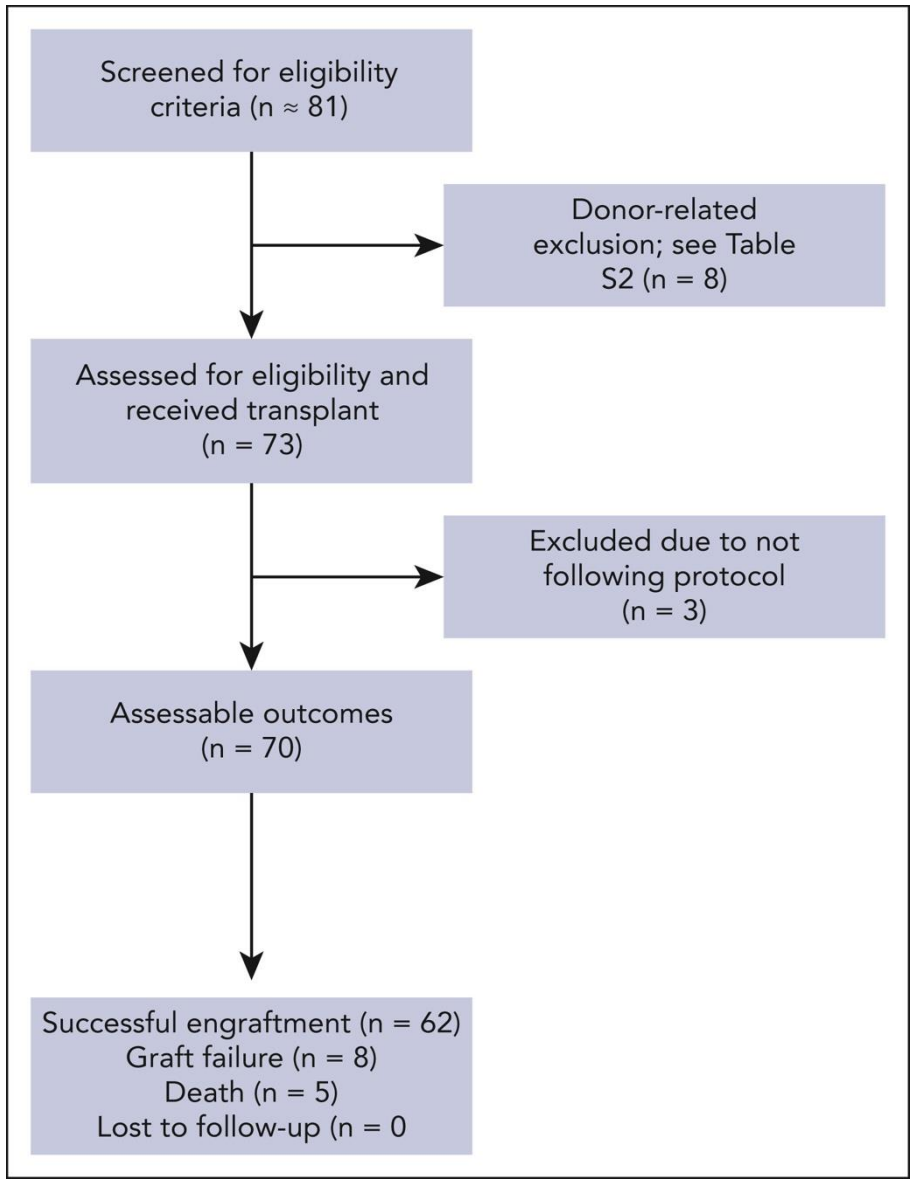
Main Findings



Conclusions: 1) For most adults with SCD, related haploidentical BMT with thiotepa + PTCy is now a widely available option with limited transplant-related morbidity and mortality. 2) For children, related haploidentical BMT with thiotepa + PTCy requires additional strategies to decrease the graft failure rate further.

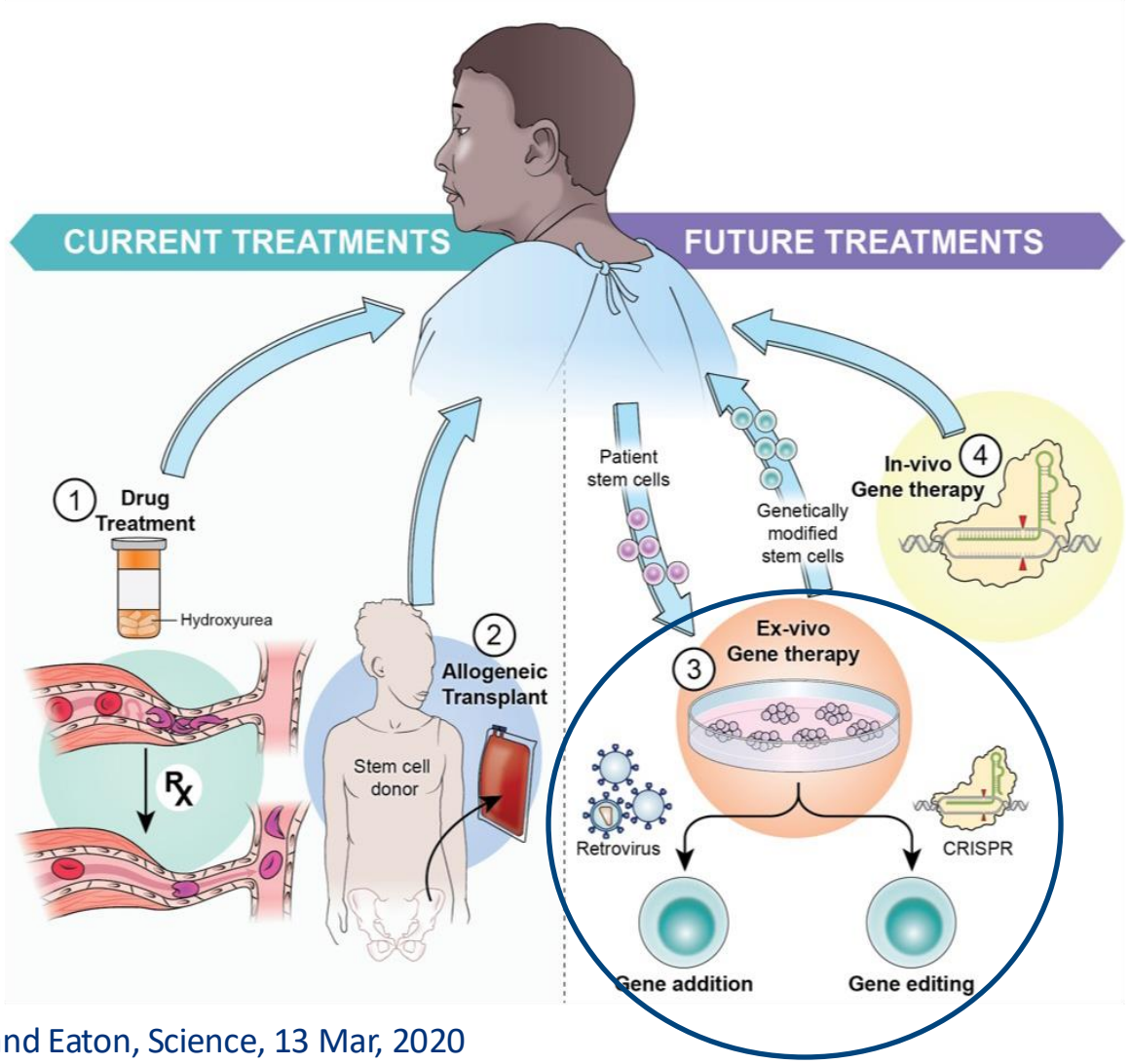
*Kassim et al. DOI: 10.1182/**blood**.2023023301*

blood Visual Abstract



Kassim, A.A., et al., Blood, 2024. **143**(25): p. 2654-2665.

Overview of SCD management



Tisdale, Thein and Eaton, Science, 13 Mar, 2020

FDA NEWS RELEASE

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

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For Immediate Release: December 08, 2023

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FDA Approves Two Cell-Based SCD Gene Therapies

February 2024

Keywords: February 2024, Latest & Greatest

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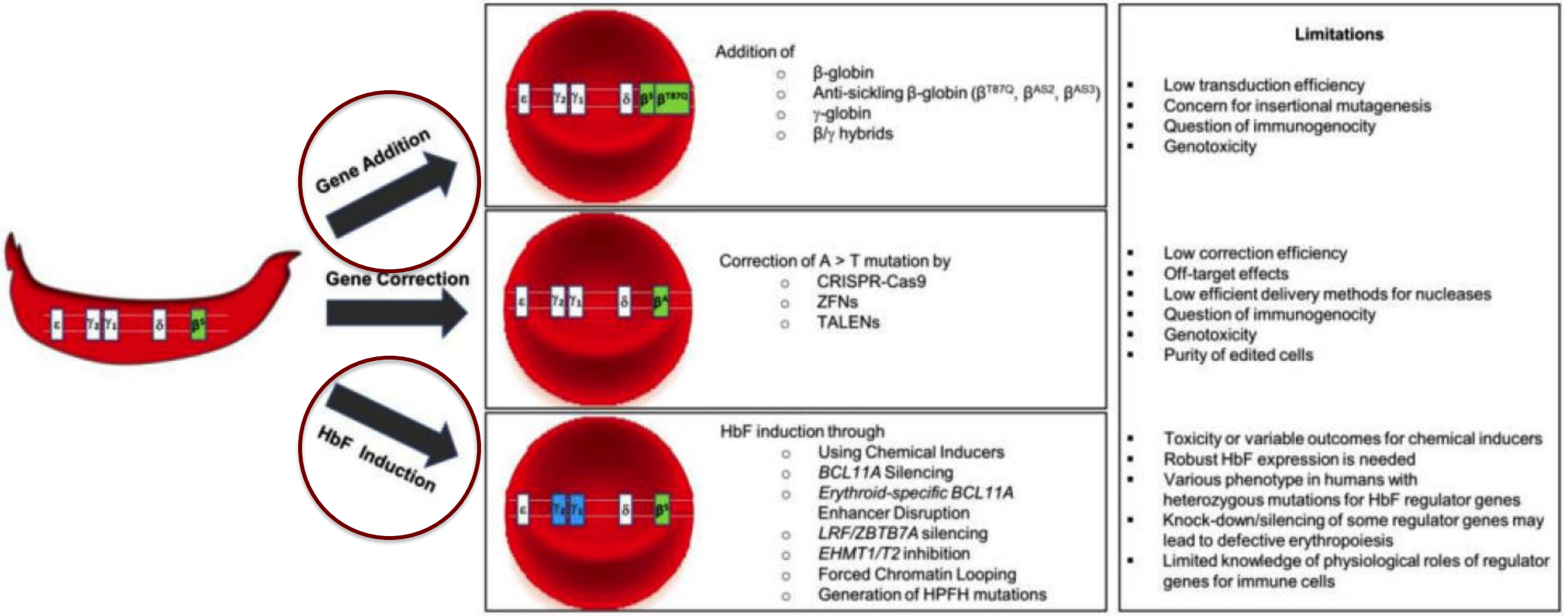
Overview of gene therapy options for sickle cell disease



Slide courtesy of Dr. Kleber Fertrin (University of Washington)

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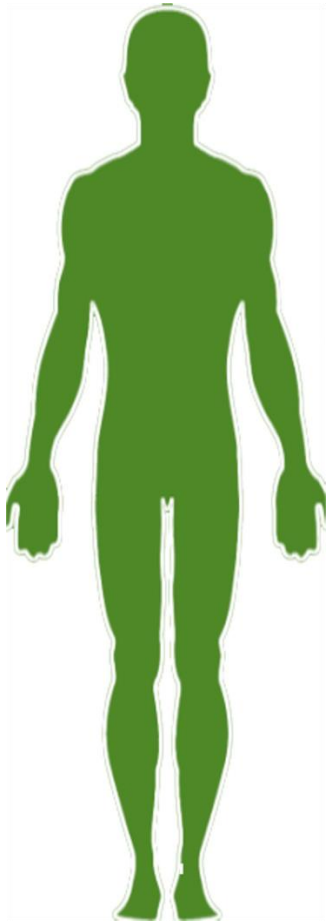
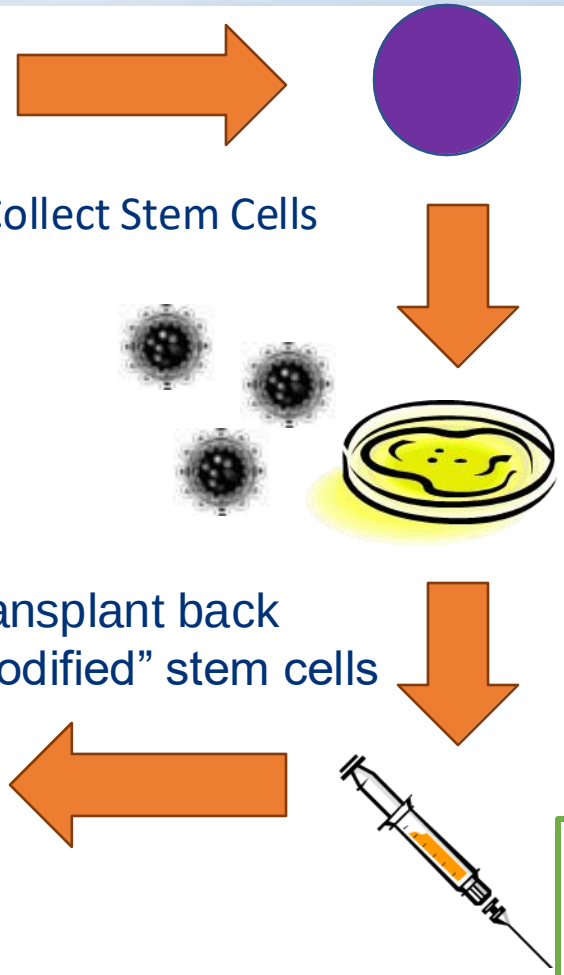
Current SCD gene therapy → autologous stem cells



Person with SCD



Patients' own stem cells

2 different gene therapy techniques to increase production of healthy (non-sickle) hemoglobin

- **Donor = Recipient**
- **Available for all patients**
- **No need for immunosuppression**
- **No risk of GVHD**

Slide courtesy of Dr. Julie Kanter (UAB)

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Transplantation and Cellular Therapy
Volume 30, Issue 2, Supplement, February 2024, Pages S230-S231

301

Efficacy and Safety in Patients (Pts) with Sickle Cell Disease (SCD) Who Have Received Lovotibeglogene Autotemcel (Lovo-cel) Gene Therapy: Up to 60 Months of Follow-up

Julie Kanter [1], Alexis A. Thompson MD, MPH [2 3], Janet L. Kwiatkowski MD, MSCE [3 4], Suhag Parikh MD [5], Markus Y. Mapara MD, PhD [6], Stacey Rifkin-Zenenberg [7], Banu Aygun [8 9], Kimberly A. Kasow DO [10], Ashish O. Gupta MD, MPH [11], Lixin Zhang [12], Emily Sheldon-Waniga [13], Meghan Gallagher [14], Katiana Gruppioni MPH [12], Anjulika Chawla [12], Heidi Elliot [12], Francis J. Pierciey Jr. [12], Mark C. Walters MD [15], John F. Tisdale MD [16]

Journal of Sickle Cell Disease, 2024, Vol. 1, No. S1 • 3

Clinical Research

Lovotibeglogene Autotemcel Gene Therapy for Sickle Cell Disease: 60 Months Follow-up

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RESEARCH ARTICLE

Lovo-cel gene therapy for sickle cell disease: Treatment process evolution and outcomes in the initial groups of the HGB-206 study

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Abstract

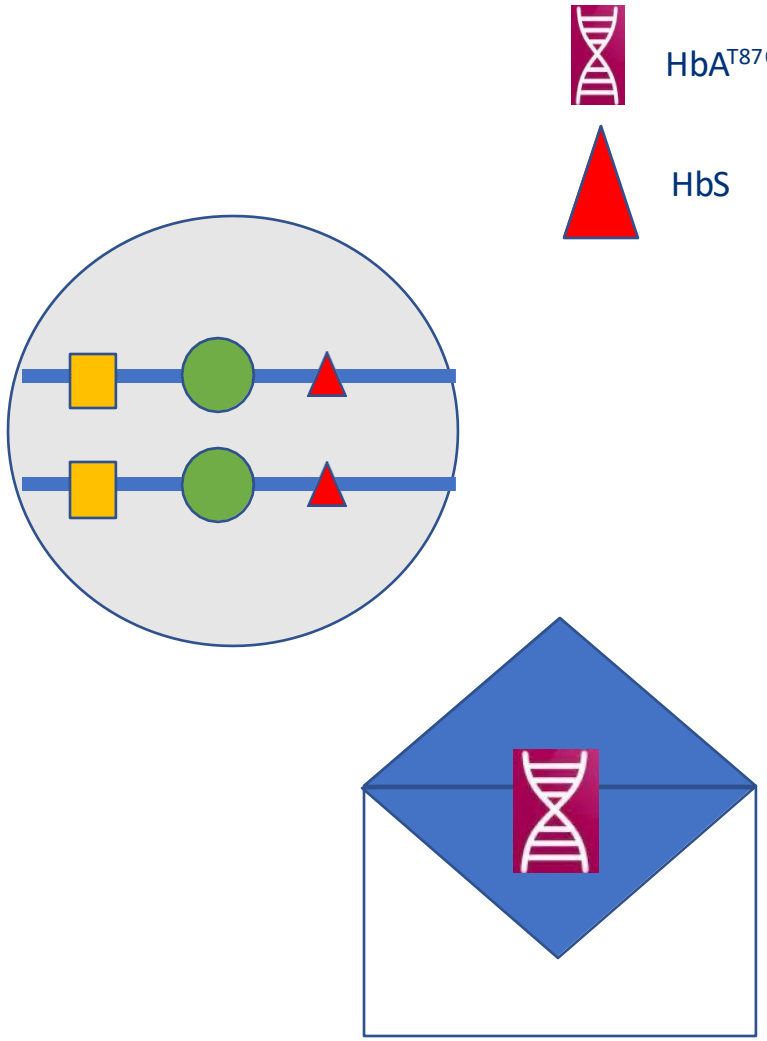
lovo-cel (bb1111; LentiGlobin for sickle cell disease [SCD]) gene therapy (GT) comprises autologous transplantation of hematopoietic stem and progenitor cells transduced with the BB305 lentiviral vector encoding a modified β-globin gene ($\beta^{A\text{-}T87Q}$) to produce anti-sickling hemoglobin (HbA^{T87Q}). The efficacy and safety of lovo-cel for SCD are being evaluated in the ongoing phase 1/2 HGB-206 study (ClinicalTrials.gov: NCT02140554). The treatment process evolved over time, using learnings from outcomes in the initial patients to optimize lovo-cel's benefit–risk profile. Following modest expression of HbA^{T87Q} in the initial patients (Group A, $n = 7$), alterations were made to the treatment process for patients subsequently enrolled in Group B ($n = 2$, patients B1 and B2), including improvements to cell collection and lovo-cel manufacturing. After 6 months, median Group A peripheral blood vector copy number (≥0.08 c/dg) and HbA^{T87Q} levels (≥0.46 g/dL) were inadequate for substantial clinical effect but stable and sustained over 5.5 years; both markedly improved in Group B (patient B1: ≥0.53 c/dg and ≥2.69 g/dL; patient B2: ≥2.14 c/dg and ≥6.40 g/dL, respectively) and generated improved biologic and clinical efficacy in Group B, including higher total hemoglobin and decreased hemolysis. The safety of the lovo-cel for SCD treatment regimen largely reflected the known side effects of HSPC collection, busulfan conditioning regimen, and underlying SCD; acute myeloid leukemia was observed in two patients in Group A and deemed unlikely related to insertional oncogenesis. Changes made during development of the lovo-cel treatment process were associated with improved outcomes and provide lessons for future SCD GT studies.

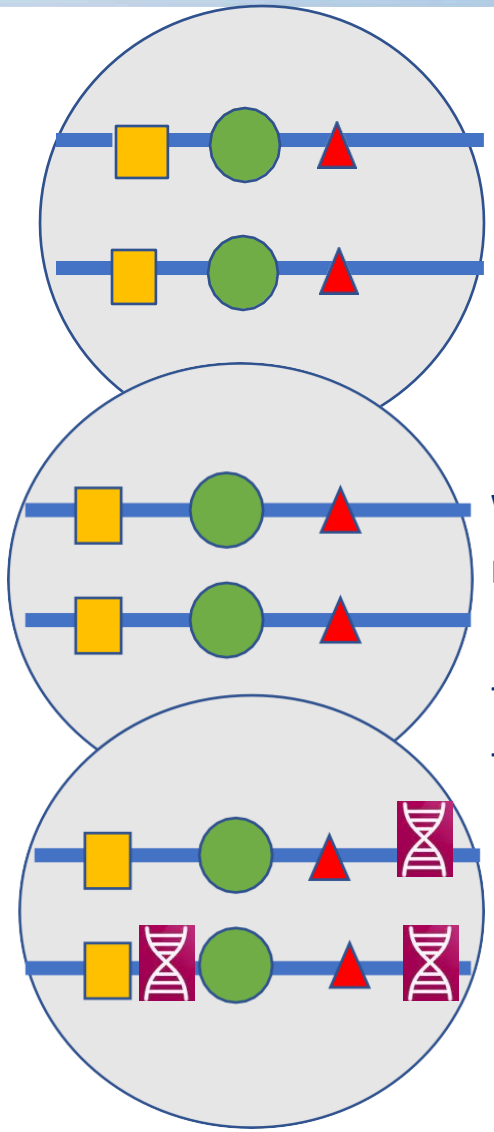
Lovotibeglogene autotemcel (lovo-cel) therapy

- Lovo-cel inserts A NEW GENE using a viral vector to deliver a non-sickling globin gene to the stem cells
- A virus is chosen as a vector because it can get inside the cell – but the viral genes are fully removed and replaced with the anti-sickling gene
- Gene addition does not remove or change any of the existing genes

Slide courtesy of Dr. Julie Kanter (UAB)

Lovo-Cel mechanism of action





What type of Hb do these new stem cells make?

-Hb A^{T87Q}

-Hb S

Slide courtesy of Dr. Julie Kanter (UAB)

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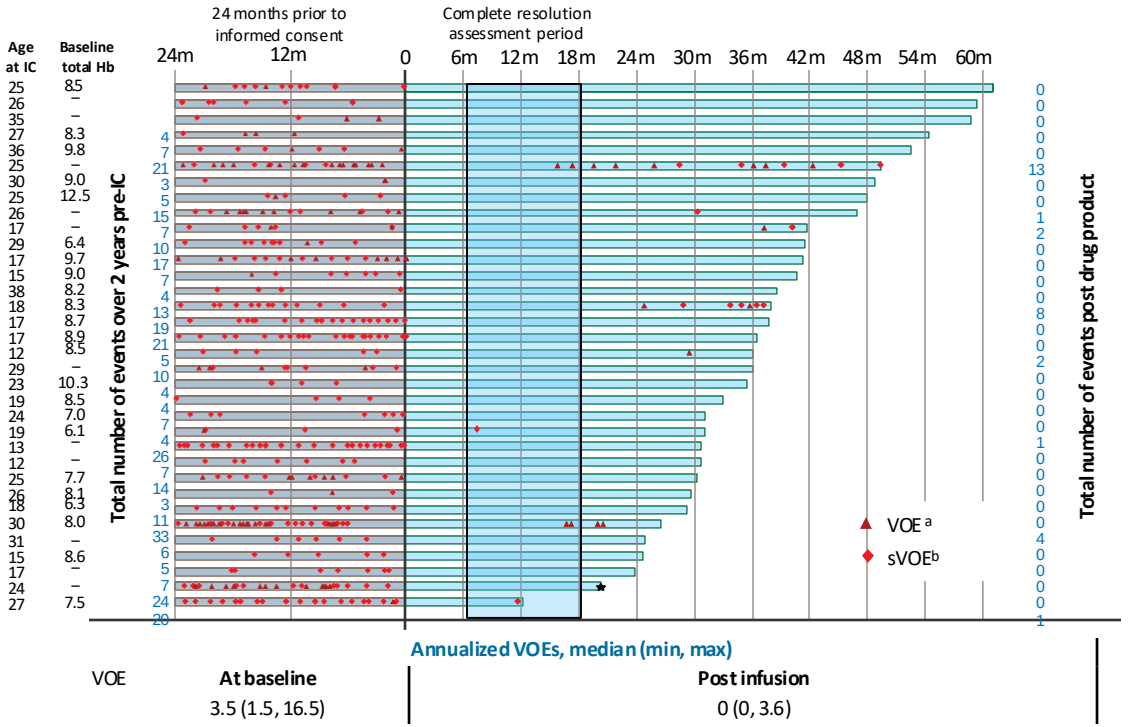
Table 1: Lovo-cel patient characteristics

Characteristics	Total N=47
Age at enrollment in years, median (min, max)	23 (12, 38)
Adult, ≥18 y, n (%)	37 (78.7)
Adolescent, ≥12 to <18 y, n (%)	10 (21.3)
Sex, n (%)	
Male	28 (59.6)
Female	19 (40.4)
Follow-up post infusion in months, median (min, max)	35.5 (0.3, 61.0)
Genotype for β-globin, n (%)	
β^S/β^S	46 (97.9)
β^S/β^0	1 (2.1)
Genotype for α-globin, n (%)	
αα/αα	32 (68.1)
αα/-α3.7	13 (27.7)
-α3.7/-α3.7	2 (4.3)
Annualized number of adjudicated VOEs,[a,b] median (min, max)	3.5 (0.0, 16.5)
Annualized number of adjudicated sVOEs,[a,b] median (min, max)	3.0 (0.0, 13.0)
History of stroke, n (%)	6 (12.8)
Annualized number of packed RBC transfusions,[a] median (min, max)	3.0 (0.0, 17.0)
Baseline total Hb, median (min, max),[c] g/dL	8.70 (6.1, 12.5)
Prior hydroxyurea use, n (%)	40 (85.1)

Hb, hemoglobin; RBC, red blood cell; sVOE, severe vaso-occlusive event; VOE, vaso-occlusive event.

Kanter, J., et al., Transplantation and Cellular Therapy, 2024. **30**(2, Supplement): p. S230-S231.

Lovo-cel 1º endpoint: 88% of evaluable patients achieved Complete Resolution of all vasoocclusive events (VOEs)



Hb, hemoglobin; HbA^{T87Q}, anti-sickling Hb; IC, informed consent; SCD, sickle cell disease; sVOE, severe vaso-occlusive event; VCN, vector copy number; VOE, vaso-occlusive event

During Complete Resolution Period:

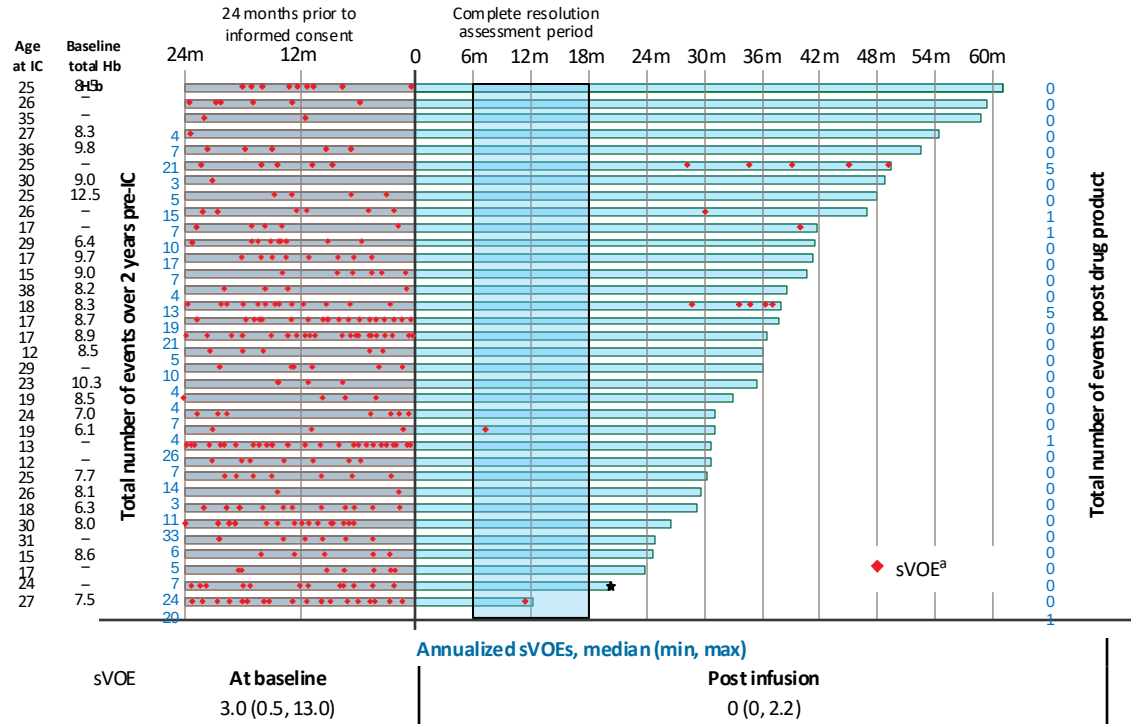
- **88.2%** (30/34; 95% CI: 72.5-96.7) of patients achieved complete resolution of all VOEs
- **100%** (10/10) of adolescent patients demonstrated complete resolution of VOEs

Through Long Term Follow Up:

- Most **(7/8)** patients who experienced VOEs post treatment experienced a reduction of at least 75% compared with before treatment
- All patients had stable peripheral blood VCN, total Hb, and HbA^{T87Q} after lovo-cel infusion, including those who had VOEs (n=8)

*VOEs= Any acute episode of pain with no medically determined cause other than a vasoocclusion lasting 2 hours and requiring care at a medical facility

Lovo-cel 2º endpoint: 94% of evaluable patients achieved Complete Resolution of all severe VOEs*



Hb, hemoglobin; HbA^{T87Q}, anti-sickling Hb; IC, informed consent; SCD, sickle cell disease; sVOE, severe vaso-occlusive event; VCN, vector copy number; VOE, vasoocclusive event

Severe VOE Resolution

- **94%** (32/34; 95% CI, 80.3-99.3) of patients experienced **complete resolution of sVOEs**

Hospital Admissions & Days

- **85%** (29/34) of patients had no VOE-related hospital admissions from 6 months post infusion to last follow-up

Among patients with VOEs post lovo-cel infusion, annualized median (min, max):

- **Hospital admissions** were reduced from **2.5**(1, 13) →**0.41** (0, 2)
- **Hospital days** were reduced from **15.75** (3.5, 136.0) → **2.20** (0.0, 25.4)

*Severe VOE=VOE requiring ≥24-hour hospital or ER observation unit visit or ≥≥ 2 visits to a day unit or ER over a 72-hour period, with both visits requiring intravenous pain management

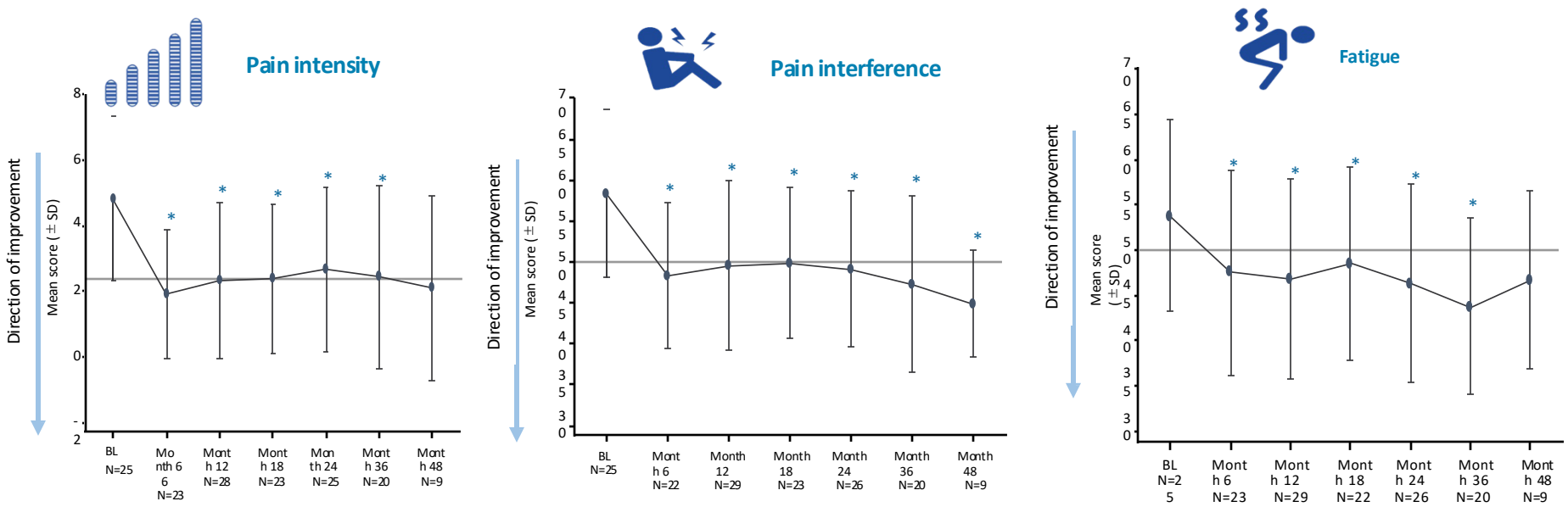
Figure. Total Hb and HbA^{T87Q} fraction for HGB-206 Group C and HGB-210 combined

Data are reported as of Feb 13, 2023. Percentages represent the median HbA^{T87Q} fraction as a percentage of nontransfused total Hb. Values above each bar represent the median total Hb at each visit and are not equivalent to the sum of the individual Hb fraction medians. The baseline was an average of 2 qualified, total Hb values (measured in g/dL) during the 24 mo before study enrollment.

Hb, hemoglobin; HbA, adult Hb; HbA^{T87Q}, anti-sickling Hb.

Kanter, J., et al., Transplantation and Cellular Therapy, 2024. **30**(2, Supplement): p. S230-S231.

Improvement in Pain Intensity, Pain Interference, and Fatigue (PROMIS-57)



BL, baseline; HRQOL, health-related quality of life; PROMIS-57, Patient-Reported Outcomes Measurement Information System questionnaire

Clinically meaningful improvements in pain intensity (57%), pain interference (64%), and fatigue (64%) sustained up to 36 months

Slide courtesy of Dr. Julie Kanter (UAB)

Lovo-cel safety outcomes

TEAEs	Events, N (%)
Any grade	47 (100)
Grade ≥ 3	44 (93.6)
Lovo-cel–related AEs	**6 (12.8)**
Anemia[a]	2 (3.4)
Abdominal discomfort	1 (1.7)
Blood pressure diastolic decreased	1 (1.7)
Myelodysplastic syndrome[b]	1 (1.7)
Nasal congestion	1 (1.7)
Patients with any serious AE	**26 (55.3)**
Patients with lovo-cel–related serious AEs	2 (3.4)

[a] Sponsor assessed, [b] Serious AE

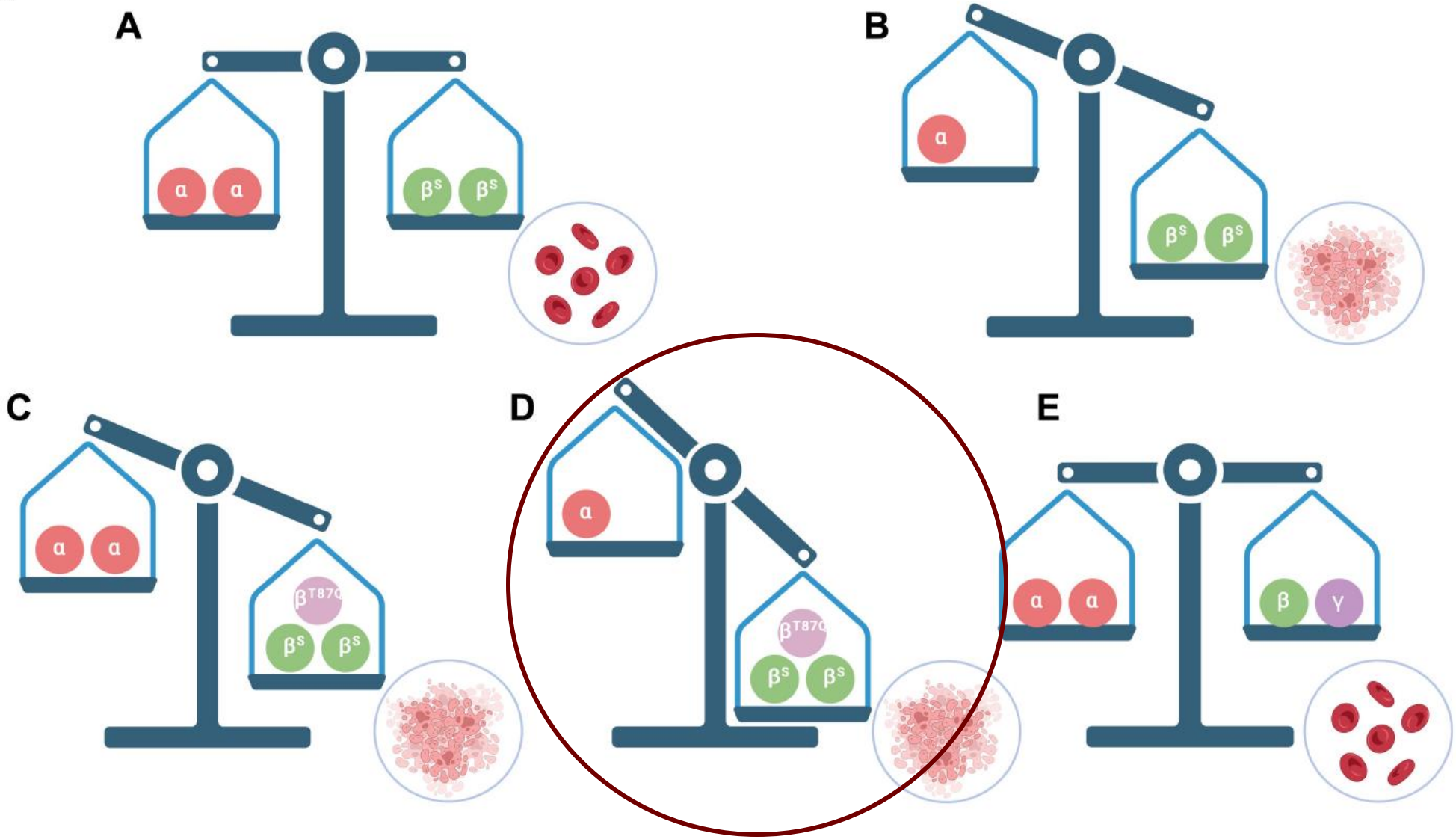
TEAEs, treatment-emergent adverse events, AE, adverse event; SCD, sickle cell disease

- Most TEAEs occurred in the 1st year post-lovo-cel infusion and mostly due to **busulfan conditioning**
- No cases of veno-occlusive liver disease, graft failure, or graft-versus-host disease
- No vector-related complications e.g., insertional oncogenesis or vector-mediated replication-competent lentivirus
- **One death** due to significant baseline SCD-related cardiopulmonary disease, not considered related to study drug

Hsieh, M.M., et al., Blood Adv, 2020. **4**(9): p. 2058-2063.

Kanter, J., et al., Transplantation and Cellular Therapy, 2024. **30**(2, Supplement): p. S230-S231.

Lovo-cel contraindicated in SCD patients with ≥2 alpha gene deletions



Sharma, A., *How I Treat Sickle Cell Disease with Gene Therapy.* Blood, 2024.

BRIEF REPORT

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia

H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace, J. Foell, J. de la Fuente, S. Grupp, R. Handgretinger, T.W. Ho, A. Kattamis, A. Kernytsky, J. Lekstrom-Himes, A.M. Li, F. Locatelli, M.Y. Mapara, M. de Montalembert, D. Rondelli, A. Sharma, S. Sheth, S. Soni, M.H. Steinberg, D. Wall, A. Yen, and S. Corbacioglu

SUMMARY

Transfusion-dependent β-thalassemia (TDT) and sickle cell disease (SCD) are severe monogenic diseases with severe and potentially life-threatening manifestations. BCL11A is a transcription factor that represses γ-globin expression and fetal hemoglobin in erythroid cells. We performed electroporation of CD34+ hematopoietic stem and progenitor cells obtained from healthy donors, with CRISPR-Cas9 targeting the *BCL11A* erythroid-specific enhancer. Approximately 80% of the alleles at this locus were modified, with no evidence of off-target editing. After undergoing myeloablation, two patients — one with TDT and the other with SCD — received autologous CD34+ cells edited with CRISPR-Cas9 targeting the same *BCL11A* enhancer. More than a year later, both patients had high levels of allelic editing in bone marrow and blood, increases in fetal hemoglobin that were distributed pancellularly, transfusion independence, and (in the patient with SCD) elimination of vaso-occlusive episodes. (Funded by CRISPR Therapeutics and Vertex Pharmaceuticals; ClinicalTrials.gov numbers, NCT03655678 for CLIMB THAL-111 and NCT03745287 for CLIMB SCD-121.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Frangoul at the Sarah Cannon Center for Blood Cancer at the Children's Hospital at TriStar Centennial, 330 23rd Ave. N., Suite 450, Nashville, TN 37203, or at haydar.frangoul@hcahealthcare.com; or to Dr. Corbacioglu at Children's Hospital Regensburg, University of Regensburg, Franz-Josef Strauss Allee 11, 93053 Regensburg, Germany, or at selim.corbacioglu@mac.com.

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A Quick Take is available at NEJM.org

Transfusion-dependent β-thalassemia (TDT) and sickle cell disease (SCD) are the most common monogenic diseases worldwide, with an annual diagnosis in approximately 60,000 patients with TDT and 300,000 patients with SCD.[1-3] Both diseases are caused by mutations in the hemoglobin β subunit gene (*HBB*). Mutations in *HBB* that cause TDT[a] result in reduced (β^+) or absent (β^0) β-globin synthesis and an imbalance between the α-like and β-like globin (e.g., β, γ, and δ) chains of hemoglobin, which causes ineffective erythropoiesis.[5,6] Sickle hemoglobin is the result of a point mutation in *HBB* that replaces glutamic acid with valine at amino acid position 6. Polymerization of deoxygenated sickle hemoglobin causes erythrocyte deformation, hemolysis, anemia, painful vaso-occlusive episodes, irreversible end-organ damage, and a reduced life expectancy.[5]

Treatment options primarily consist of transfusion and iron chelation in patients with TDT[7] and pain management, transfusion, and hydroxyurea in those with SCD.[8] Recently approved therapies, including luspatercept[9] and crizanlizumab,[10] have reduced transfusion requirements in patients with TDT and the incidence of vaso-occlusive episodes in those with SCD, respectively, but neither treatment addresses the underlying cause of the disease nor fully ameliorates disease manifestations. Allogeneic bone marrow transplantation can cure both TDT and

ORIGINAL ARTICLE

Exagamglogene Autotemcel for Severe Sickle Cell Disease

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ABSTRACT

BACKGROUND

Exagamglogene autotemcel (exa-cel) is a nonviral cell therapy designed to reactivate fetal hemoglobin synthesis by means of ex vivo clustered regularly interspaced short palindromic repeats (CRISPR)–Cas9 gene editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) at the erythroid-specific enhancer region of *BCL11A*.

METHODS

We conducted a phase 3, single-group, open-label study of exa-cel in patients 12 to 35 years of age with sickle cell disease who had had at least two severe vaso-occlusive crises in each of the 2 years before screening. CD34+ HSPCs were edited with the use of CRISPR-Cas9. Before the exa-cel infusion, patients underwent myeloablative conditioning with pharmacokinetically dose-adjusted busulfan. The primary end point was freedom from severe vaso-occlusive crises for at least 12 consecutive months. A key secondary end point was freedom from inpatient hospitalization for severe vaso-occlusive crises for at least 12 consecutive months. The safety of exa-cel was also assessed.

RESULTS

A total of 44 patients received exa-cel, and the median follow-up was 19.3 months (range, 0.8 to 48.1). Neutrophils and platelets engrafted in each patient. Of the 30 patients who had sufficient follow-up to be evaluated, 29 (97%; 95% confidence interval [CI], 83 to 100) were free from vaso-occlusive crises for at least 12 consecutive months, and all 30 (100%; 95% CI, 88 to 100) were free from hospitalizations for vaso-occlusive crises for at least 12 consecutive months (P<0.001 for both comparisons against the null hypothesis of a 50% response). The safety profile of exa-cel was generally consistent with that of myeloablative busulfan conditioning and autologous HSPC transplantation. No cancers occurred.

CONCLUSIONS

Treatment with exa-cel eliminated vaso-occlusive crises in 97% of patients with sickle cell disease for a period of 12 months or more. (CLIMB SCD-121; ClinicalTrials.gov number, NCT03745287.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Frangoul can be contacted at haydar.frangoul@hcahealthcare.com or at Sarah Cannon Pediatric Hematology–Oncology and Cellular Therapy at TriStar Centennial, 330 23rd Ave. N., Suite 450, Nashville, TN 37203.

*A list of the site investigators and coordinators in the CLIMB SCD-121 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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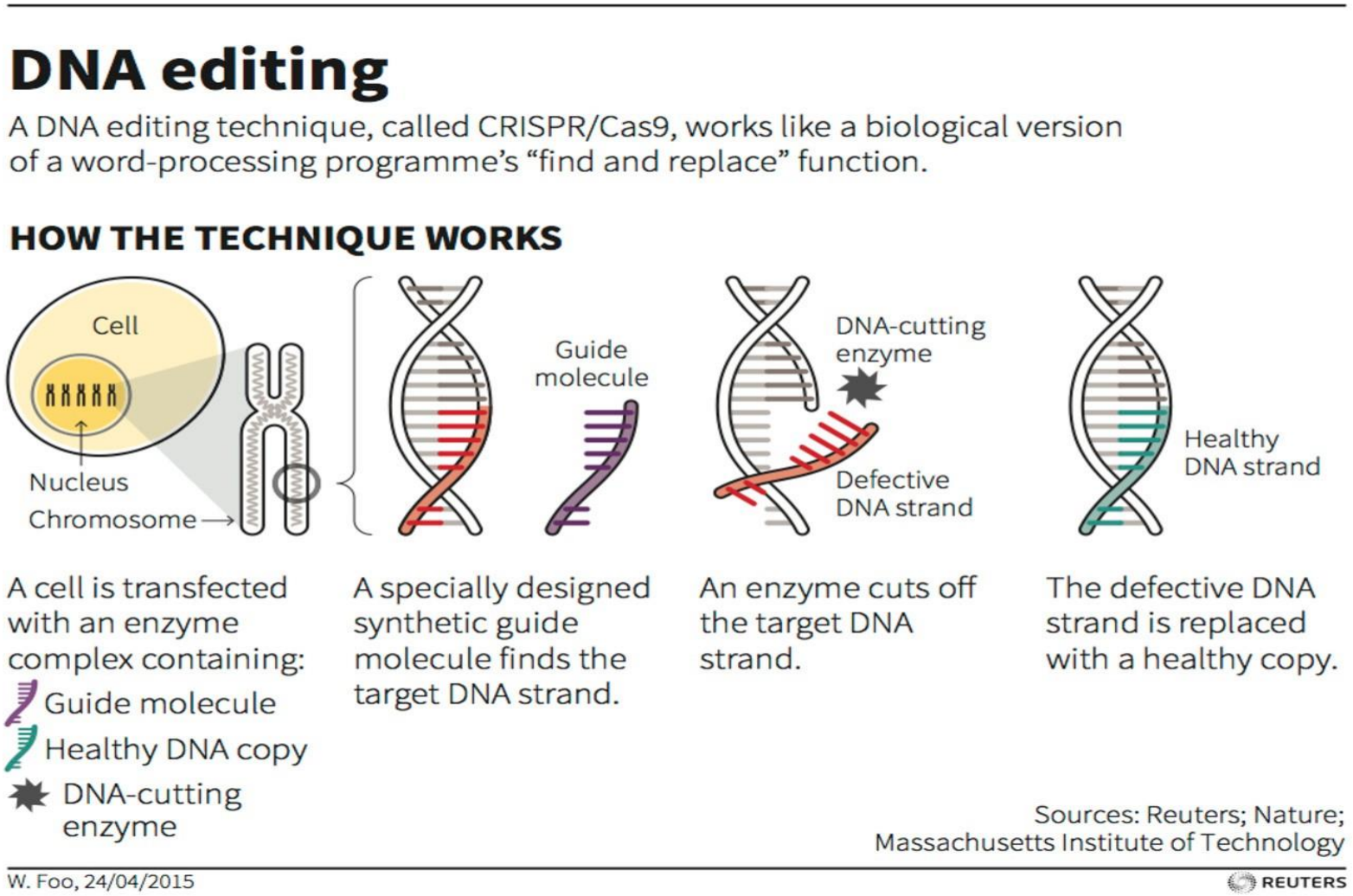
How does gene editing work?



Slide courtesy of Dr. Julie Kanter (UAB)

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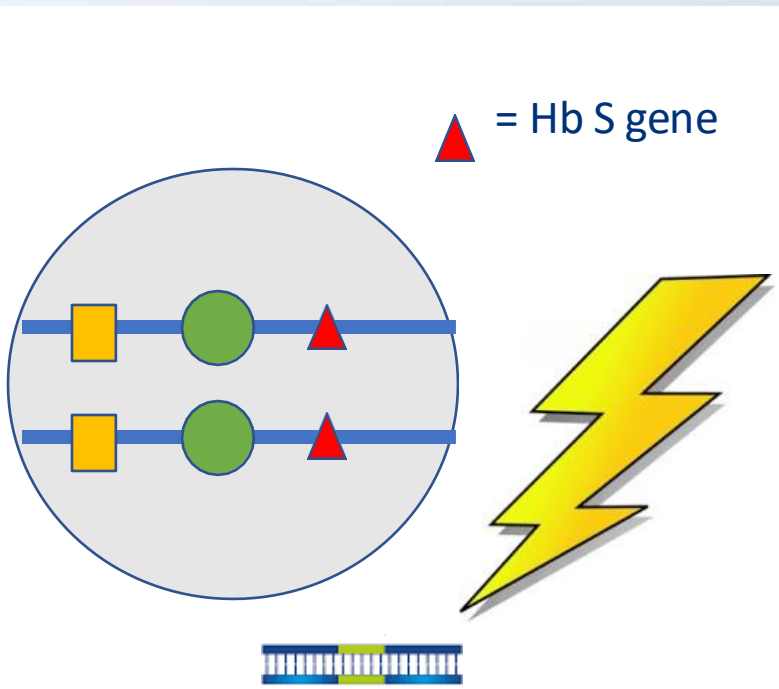
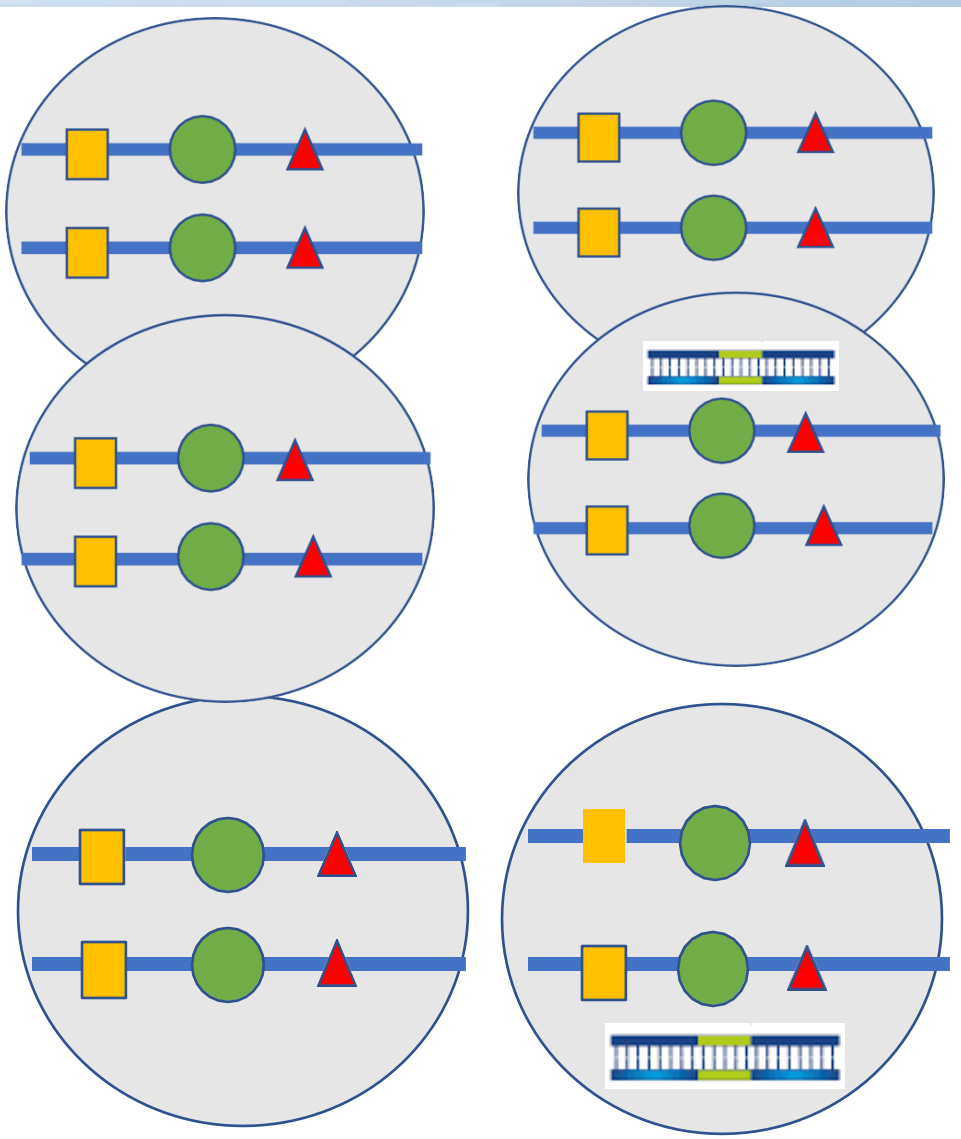
Exagamglogene autotemcel (exa-cel) mechanism of action



Cut out BCL11a aka Hb F "off" switch
(turns Hb F production back on)



What type of Hb do these new stem cells make?

-Hb S

-Hb F

Slide courtesy of Dr. Julie Kanter (UAB)

Table 1: Exa-cel patient characteristics

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Full Analysis Population (N=44)	Primary Efficacy Population (N=30)
Sex — no. (%)		
Male	24 (55)	16 (53)
Female	20 (45)	14 (47)
Age at screening		
Mean — yr	21.2±6.1	22.1±6.0
Distribution — no. (%)		
12 to <18 yr	12 (27)	6 (20)
18 to 35 yr	32 (73)	24 (80)
Race — no. (%)†		
White	3 (7)	1 (3)
Black	38 (86)	26 (87)
Other	3 (7)	3 (10)
Genotype — no. (%)		
β^S/β^S	40 (91)	29 (97)
Non-β^S/β^S		
β^S/β^0	3 (7)	1 (3)
β^S/β^+	1 (2)	0
Annualized rate of severe vaso-occlusive crises‡		
No. of severe vaso-occlusive crises/yr	4.1±3.0	3.9±2.1
Distribution — no. (%)		
≥3 vaso-occlusive crises/yr	26 (59)	17 (57)
<3 vaso-occlusive crises/yr	18 (41)	13 (43)
Total hemoglobin — g/dl§	9.1±1.6	9.0±1.6
Total fetal hemoglobin — %§	5.4±3.9	5.2±3.8
Median no. of mobilization cycles (range)	2 (1–6)	2 (1–5)
Median exa-cel dose (range) — CD34+ cells/kg	4.0×10^6 (2.9×10^6–14.4×10^6)	4.0×10^6 (2.9×10^6–14.4×10^6)

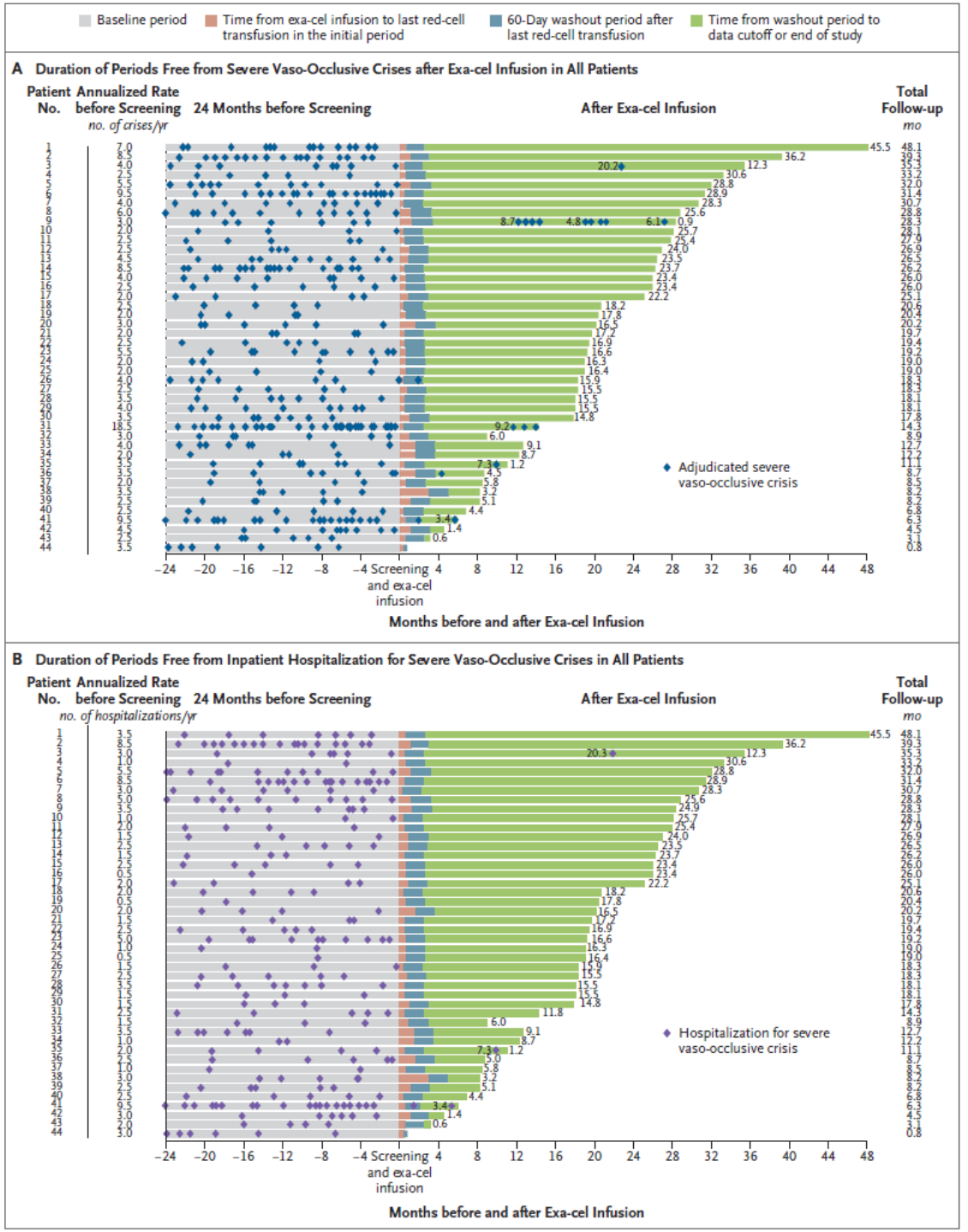
Primary efficacy population had >12 months of follow up after transitional washout period

Frangoul, H., et al., N Engl J Med, 2024.

Exa-cel clinical outcomes

Table 2. Primary and Key Secondary Efficacy Results in Patients in the Primary Efficacy Population and the Early Efficacy Population.*

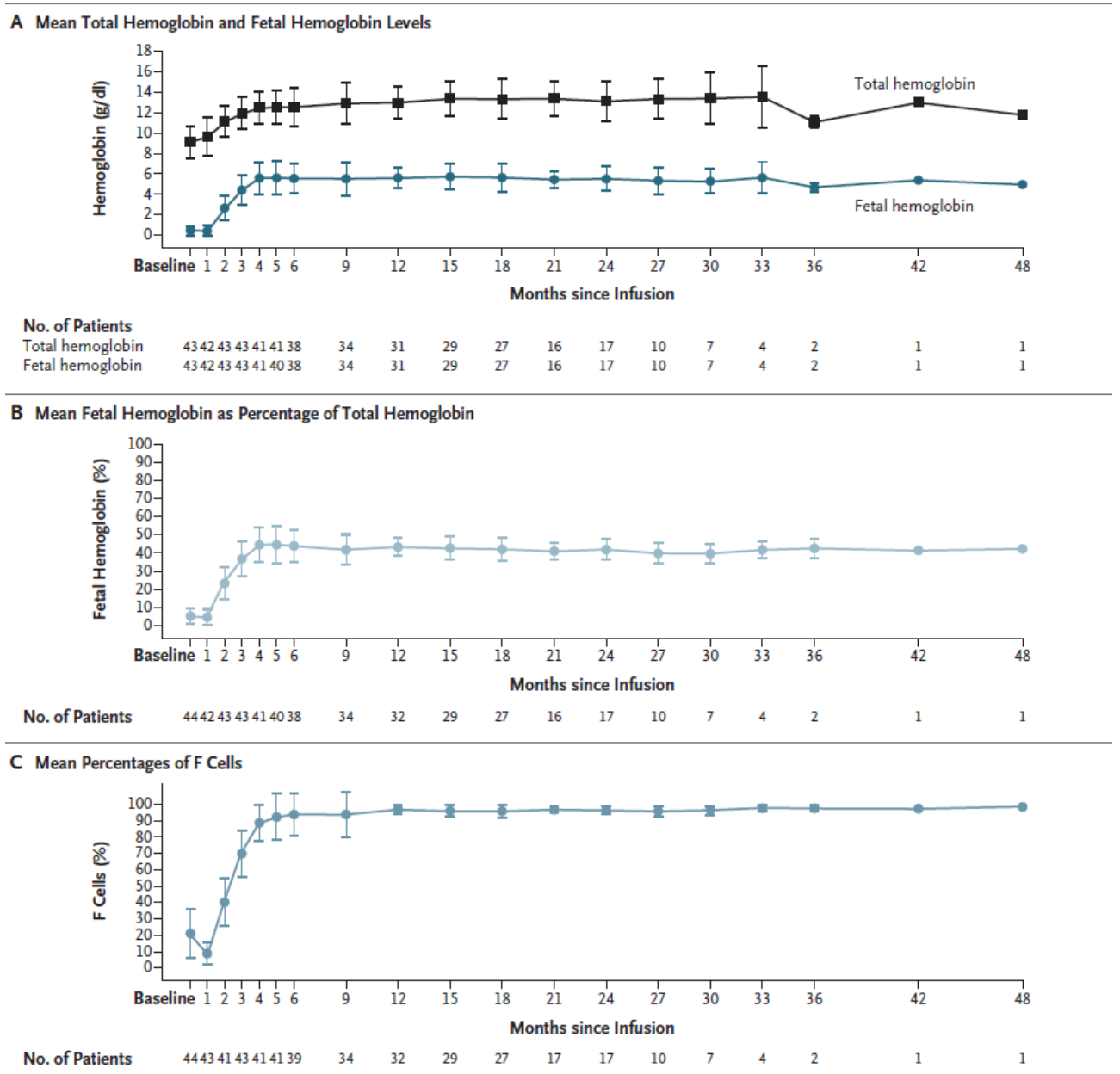
End Point	Value
Primary end point	
Freedom from severe vaso-occlusive crises for ≥12 mo	
No. of patients who met end-point criteria/total no.	29/30
Percentage of patients (95% CI)	97 (83–100)
P value	<0.001
Key secondary efficacy end points	
Freedom from inpatient hospitalization for severe vaso-occlusive crises for ≥12 mo	
No. of patients who met end-point criteria/total no.	30/30
Percentage of patients (95% CI)	100 (88–100)
P value	<0.001
Freedom from vaso-occlusive crises for ≥9 mo	
No. of patients who met end-point criteria/total no.	31/32
Percentage of patients (95% CI)	97 (84–100)
P value	<0.001



Frangoul, H., et al., N Engl J Med, 2024.

Exa-cel secondary outcomes

- Hb 9 g/dL → 11.9 ± 1.5g/dL at 3 months
- Decrease in hemolysis indices
- BCL11A edits in CD34+ HPSCs in bone marrow → 86% at 6 months
- Improvement in patient reported outcomes
- Edited alleles detected in the 1 patient not meeting the primary clinical endpoint



Frangoul, H., et al., N Engl J Med, 2024.

Exa-cel safety outcomes

- VOD in 1 patient improved with defibrotide
- 1 death due to COVID
- No graft failure or hematologic malignancy

Table 3. Grade 3 or 4 Adverse Events after Exa-Cel Infusion.

Event	Full Analysis Population (N=44)
	no. of patients (%)
Grade 3 or 4 adverse event	42 (95)
Grade 3 or 4 adverse event occurring in ≥5% of patients*	
Stomatitis	24 (55)
Febrile neutropenia	21 (48)
Platelet count decrease	21 (48)
Appetite decrease	18 (41)
Neutrophil count decrease	17 (39)
Mucosal inflammation	14 (32)
Anemia	11 (25)
Thrombocytopenia	11 (25)
Neutropenia	10 (23)
White-cell count decrease	6 (14)
Abdominal pain	5 (11)
CD4 lymphocyte count decrease	5 (11)
Cholelithiasis	5 (11)
Pruritus	5 (11)
Constipation	4 (9)
Headache	4 (9)
Nausea	4 (9)
Noncardiac chest pain	4 (9)
Pneumonia	4 (9)
Upper abdominal pain	3 (7)
Arthralgia	3 (7)
Back pain	3 (7)
Deep-vein thrombosis	3 (7)
Oropharyngeal pain	3 (7)
Pain	3 (7)
Weight decreased	3 (7)

Frangoul, H., et al., N Engl J Med, 2024.

Outline

- Pathophysiology of sickle cell disease (SCD)
- SCD modifying therapies
- Gene therapies in SCD
- Future directions

Summary of key clinical trials of selected gene therapies for SCD

	Lovotibeglogene autotemcel[25]	Exagamglogene autotemcel[15,24]	Renizgamglogene autogedtemcel[17]	BCH BB694[14,94]	BEAM-101
Gene modification modality	Gene addition, Lentiviral Vector (BB305) encoding HbA^{T87Q}.	Cas9 editing of the BCL11A erythroid specific enhancer.	AsCas12a editing of the HBG1/2 promoters.	shRNA encoding Lentiviral Vector suppressing BCL11A .	Base editing, target undisclosed.
Number of patients infused	47 (median age 23, range 12-38 years) (HGB-206 Group C and HGB-210)	46 (34 adults, 12 children)	18 (all adults)	10 (children and adults)	Unknown
Duration of follow-up	Median, 35.5 months (range, 0.3–61.0 months)	Median, 22.3 months (range, 2.1–41.3 months)	Mean, 6.2 months (standard deviation, 5.8 months)	Median, 30.5 months (range, 2–50 months)	Unknown

[#]At least three more clinical trials have been reported as having enrolled more than one participant. These trials are (1) NCT02186418 (a trial of an HSC product transduced with an LVV, ARU-1801, expressing a modified fetal hemoglobin [HbF^{G16D}])[13]; (2) PRECIZN-1/NCT03653247 (a trial of *BCL11A* erythroid-specific enhancer disruption using ZFN-BIVV003 to increase fetal hemoglobin)[95]; and (3) NCT04443907 (a trial of CRISPR/Cas9 disruption of a regulatory element in the *HBG1* and *HBG2* promoters to increase fetal hemoglobin).[16] To the best of my knowledge, further clinical development of these approaches has been abandoned. Hence, they are mentioned only for enumeration purposes.

Sharma, A., *How I Treat Sickle Cell Disease with Gene Therapy.* Blood, 2024.

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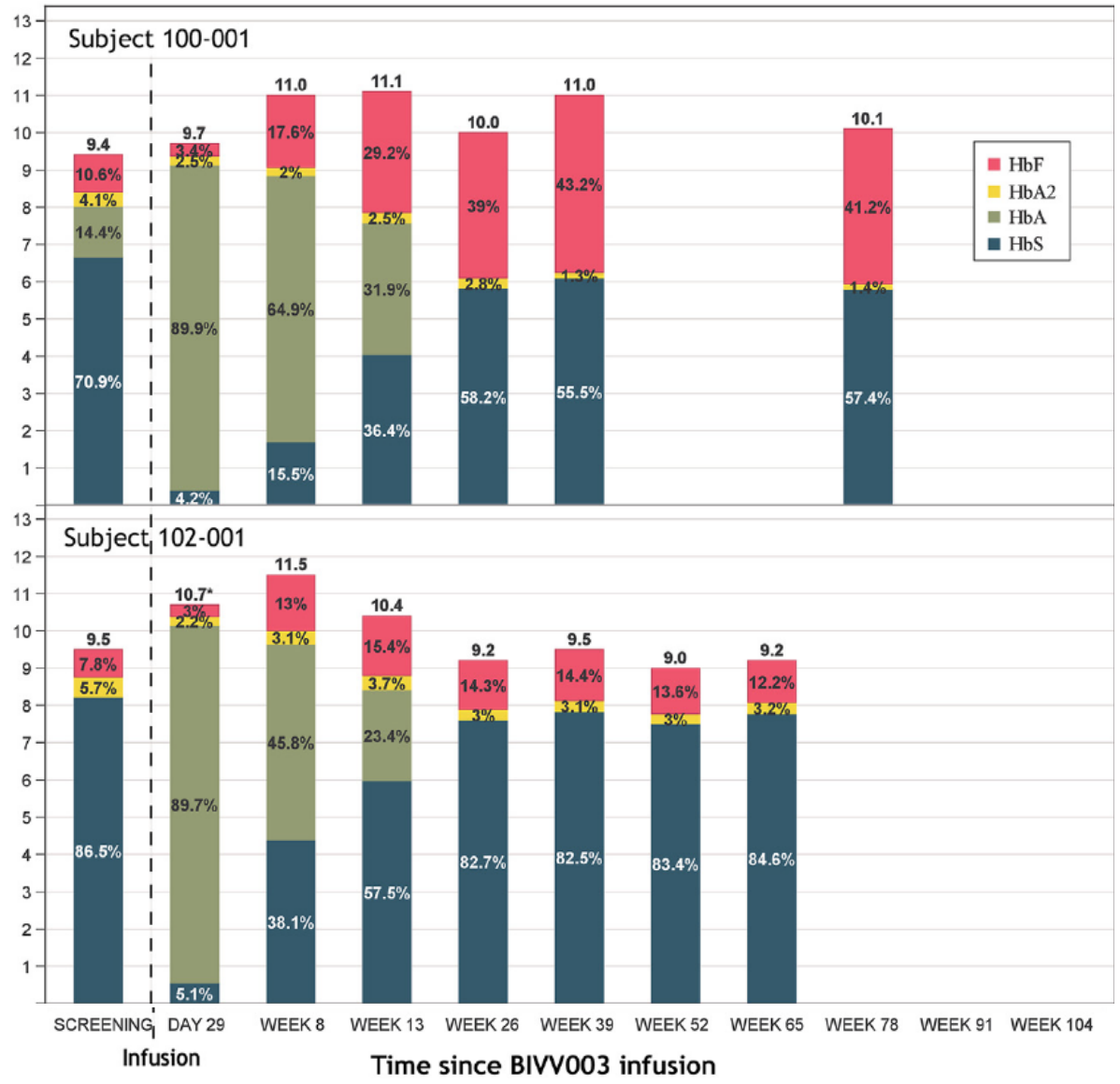
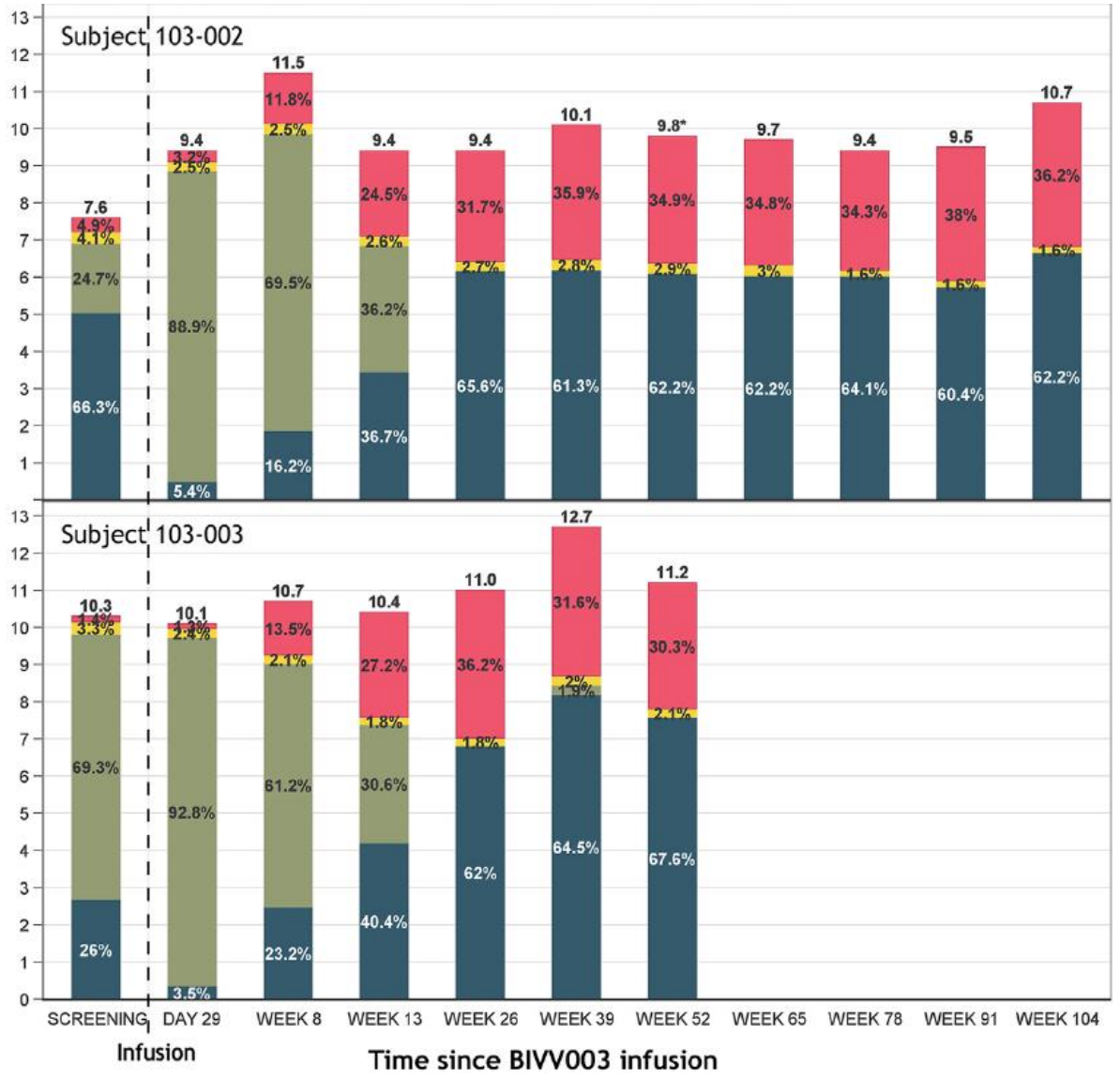
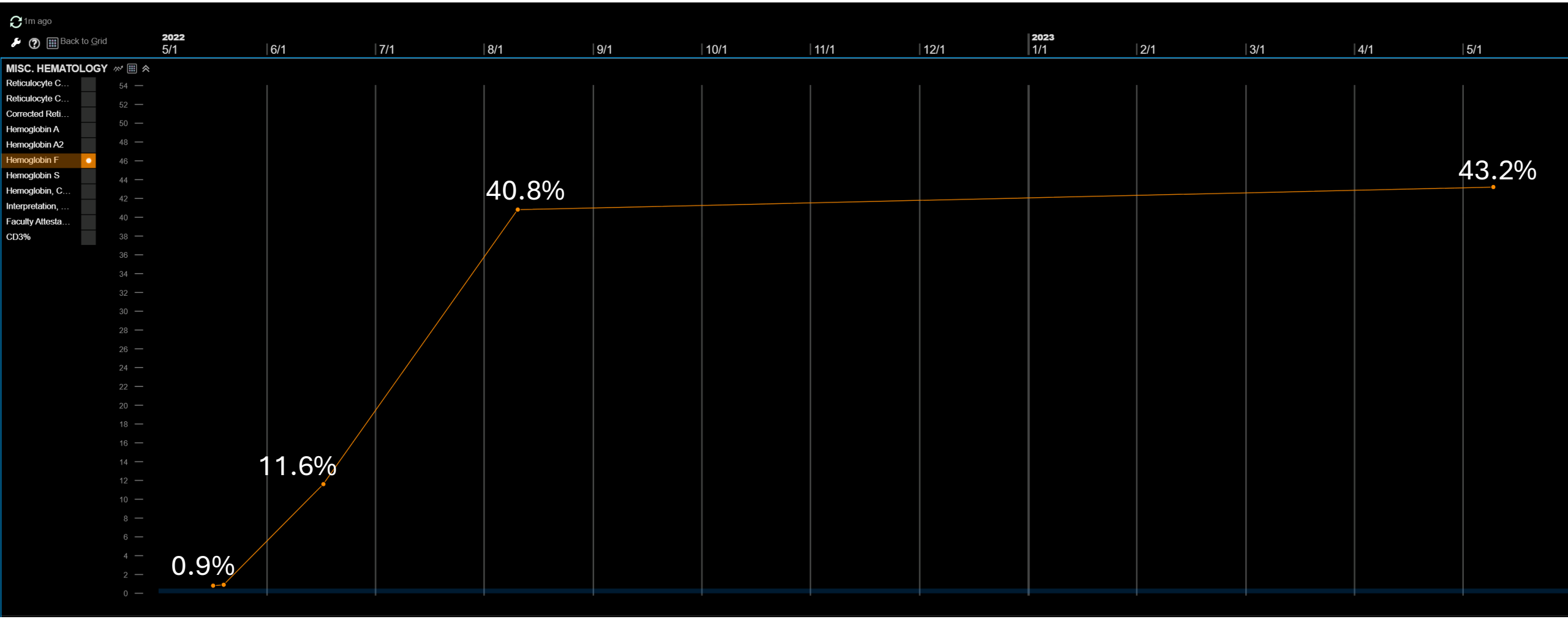
PRECIZN-1: Phase 1/2 Study of Zinc Finger Nuclease-Modified Autologous Hematopoietic Stem for Sickle Cell Disease (BIVV003)



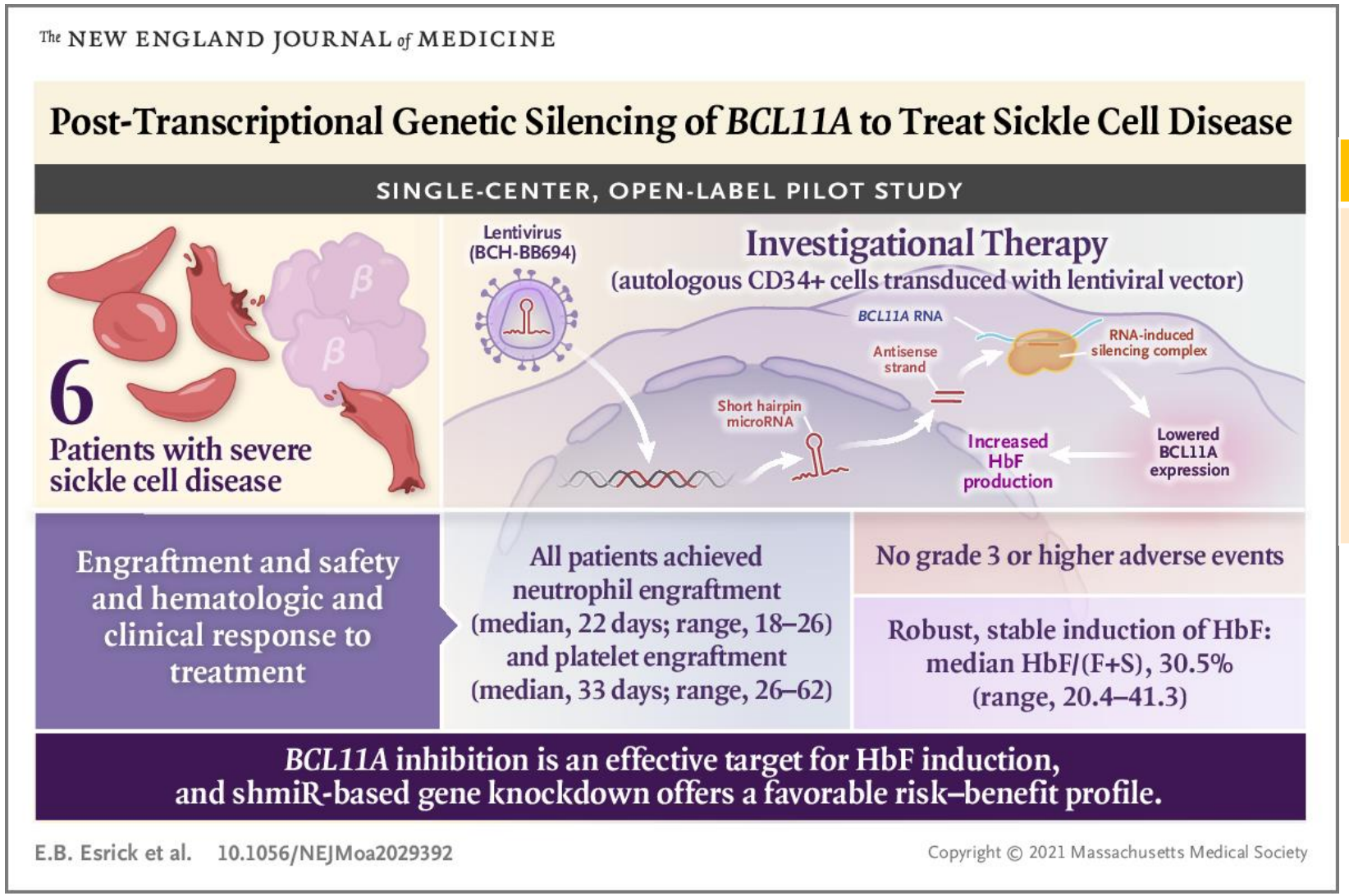


Alavi et al., *Blood* 2022; 140 (Supplement 1): 4907–4909

BIVV003 study participant



Gene Transfer Study Inducing Fetal Hemoglobin in SCD (GRASP) STUDY



Phase 2 Trial (NCT05353647) – active, enrolling

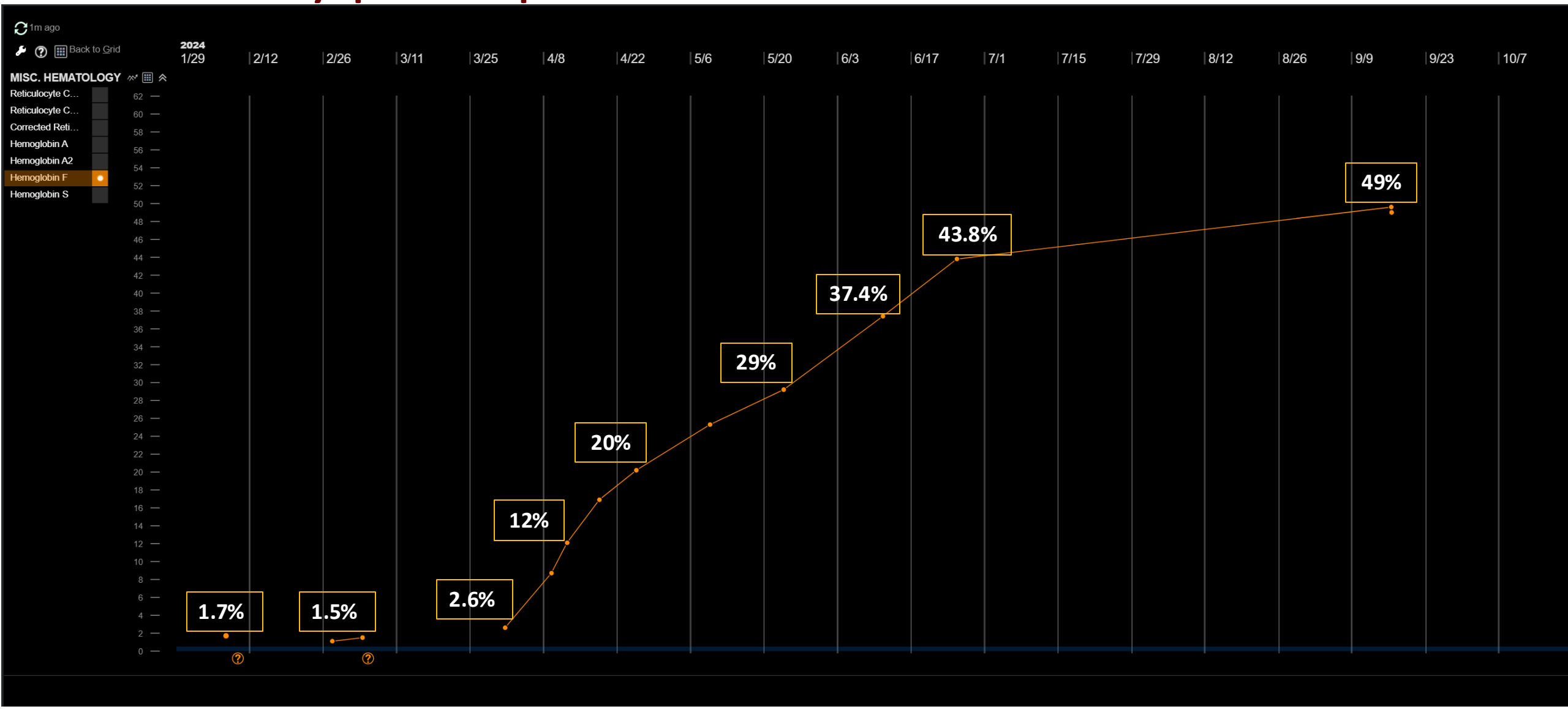
- BMT CTN 2001 (PI: David Williams)
- Primary endpoint: Elimination of VOEs
- 25 total patients, ages 13 – 40 years old
- 9 sites (4 in California)

GRASP

Gene therapy to Reduce All Sickle Pain

Funded in part by the National Heart, Lung, and Blood Institute and the California Institute for Regenerative Medicine

GRASP study participant



In summary….

Lovo-cel and Exa-cel gene therapies improve clinical outcomes and quality of life:

- INCREASE total Hb and non-sickle Hb
- ALMOST normalize hemolysis markers
- DECREASE or eliminate acute pain episodes
- IMPROVE fatigue and other patient-reported health-related quality of life measures

What we do NOT know about these 2 gene therapies for SCD:

- Prevent end-organ damage e.g., stroke, retinopathy, nephropathy, hepatopathy, etc.,
- Reverse current end-organ damage e.g., osteonecrosis, leg ulcers, etc.,
- Durability of response e.g., will hematologic effects of Exa-Cel last > 3 years?

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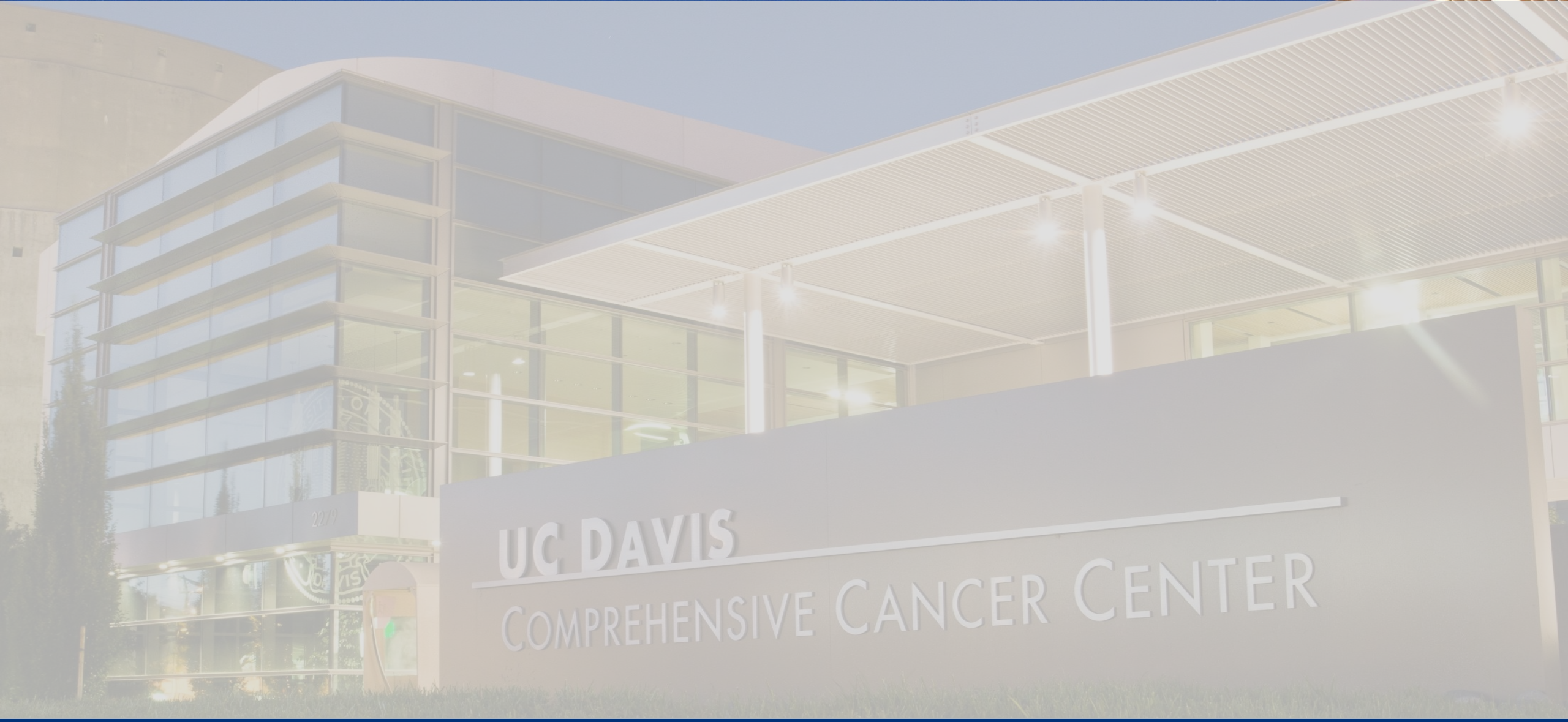
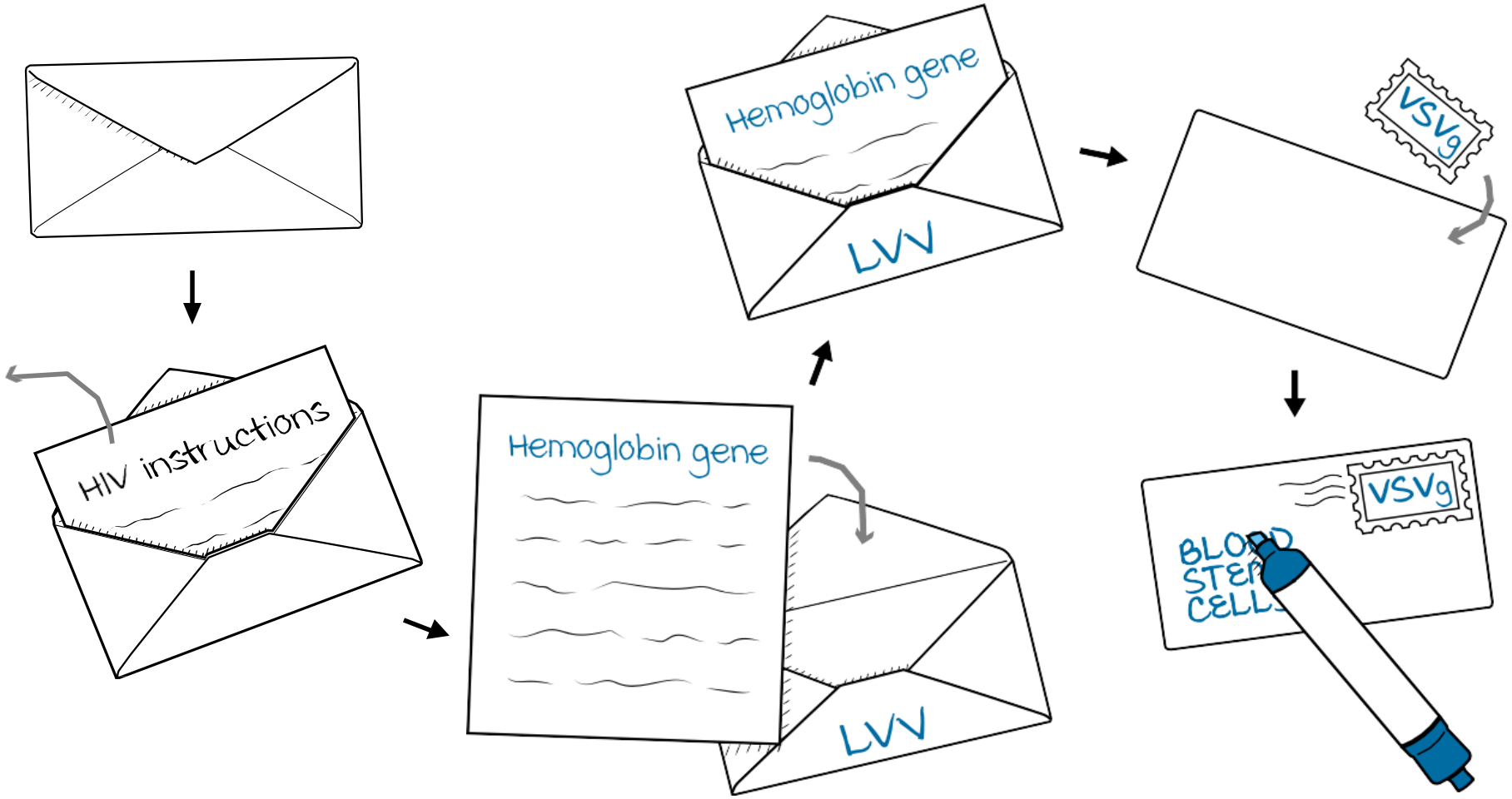


Thank you

Lentiviral vector (LVV) for Hb gene delivery



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Durand S. *Viruses*. 2011;3:132-159.
Dong AC. *Adv Exp Med Biol.* 2017;1013:155-176.

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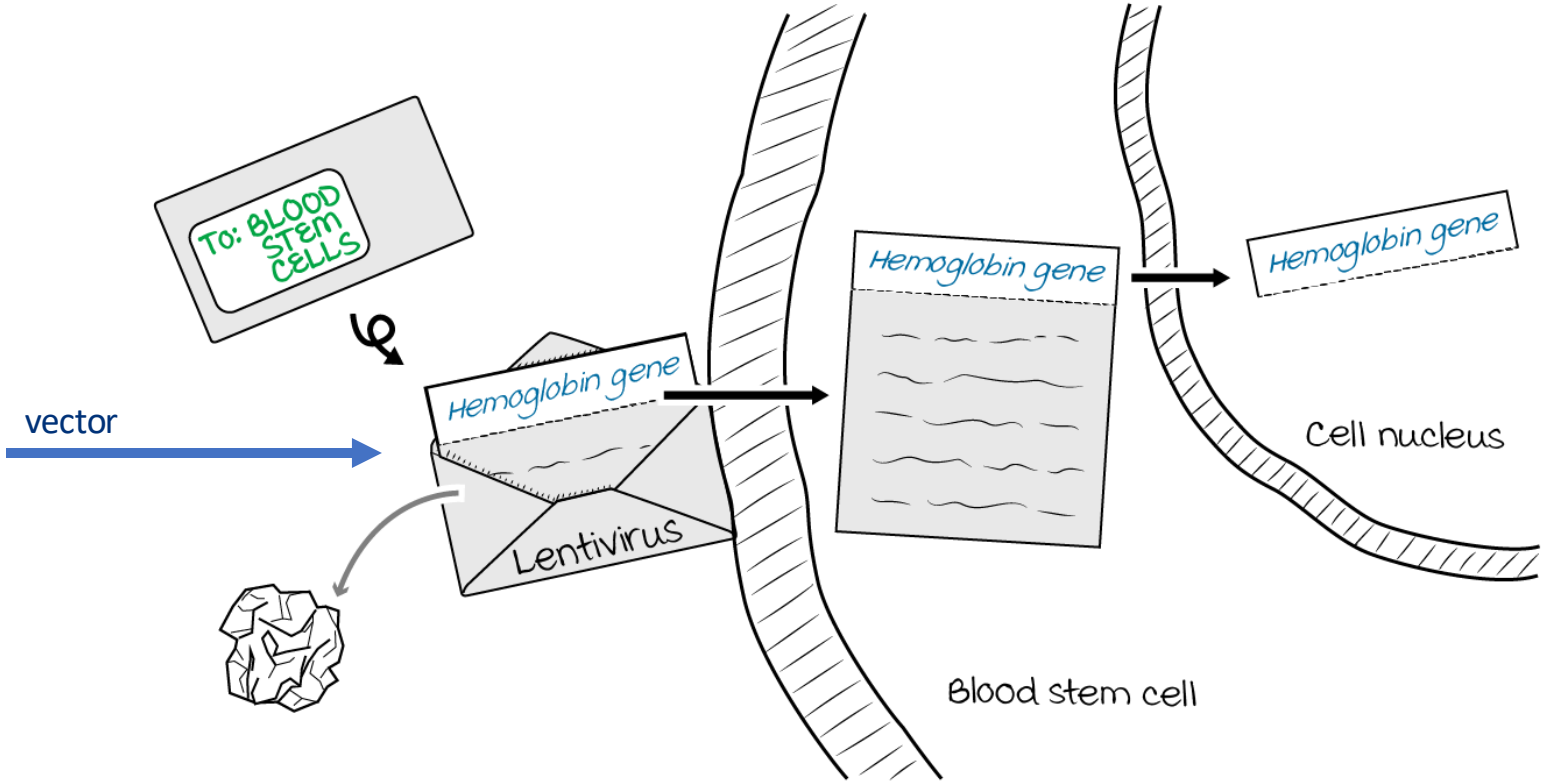
Lentiviral vector (LVV) for Hb gene delivery



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