4th Global Congress
Sickle Cell Disease
In-person and on-line Congress
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Genetic Therapies for Sickle Cell Disease

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Disclosures

- **Consultancy:** Guide point Global, GLG, Graphite, Novartis, Fulcrum, Glycomimmetics, ORIC, Medscape, Bristol-Myers Squibb, Jansen
- **Research Funding:**
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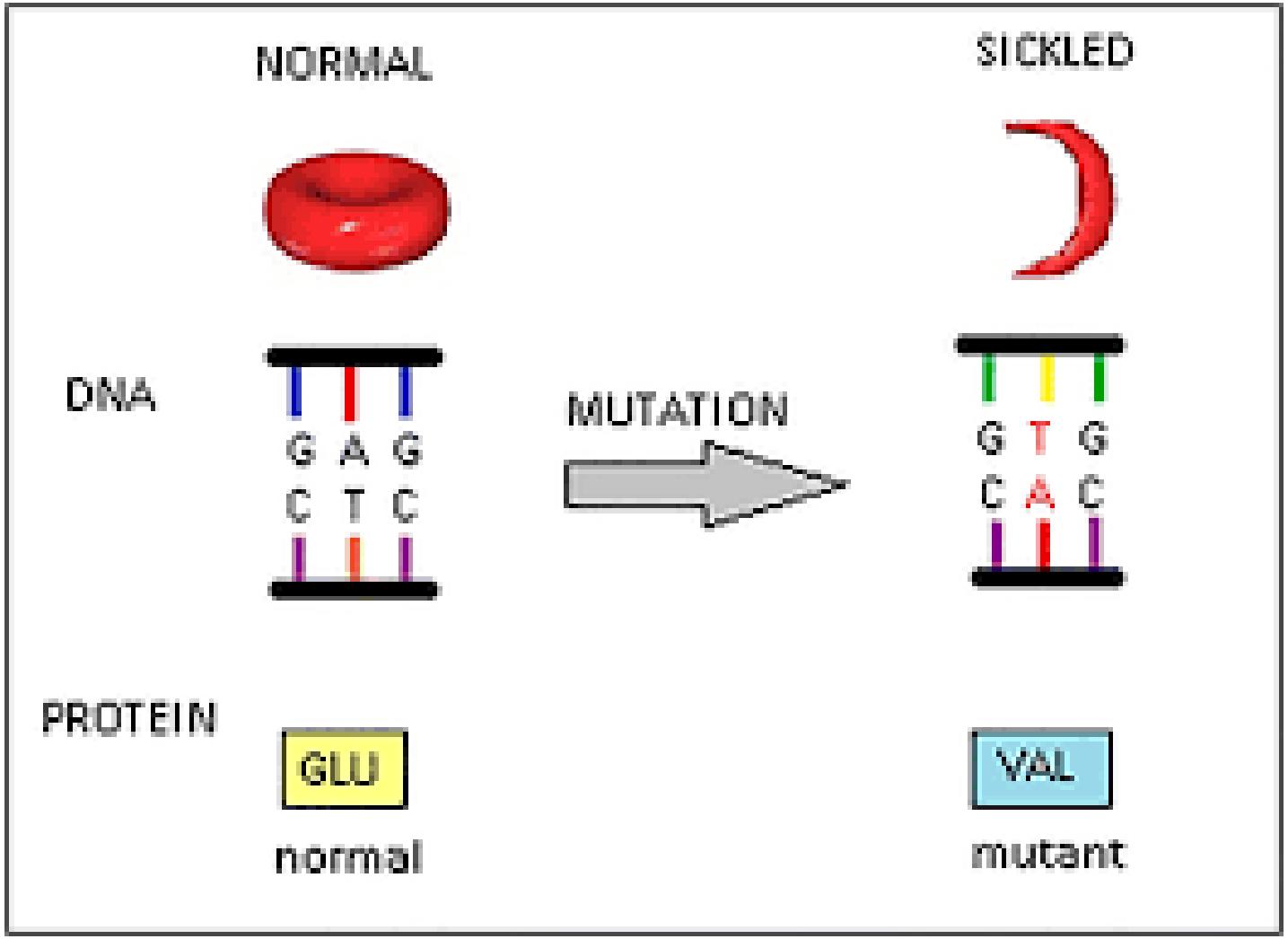
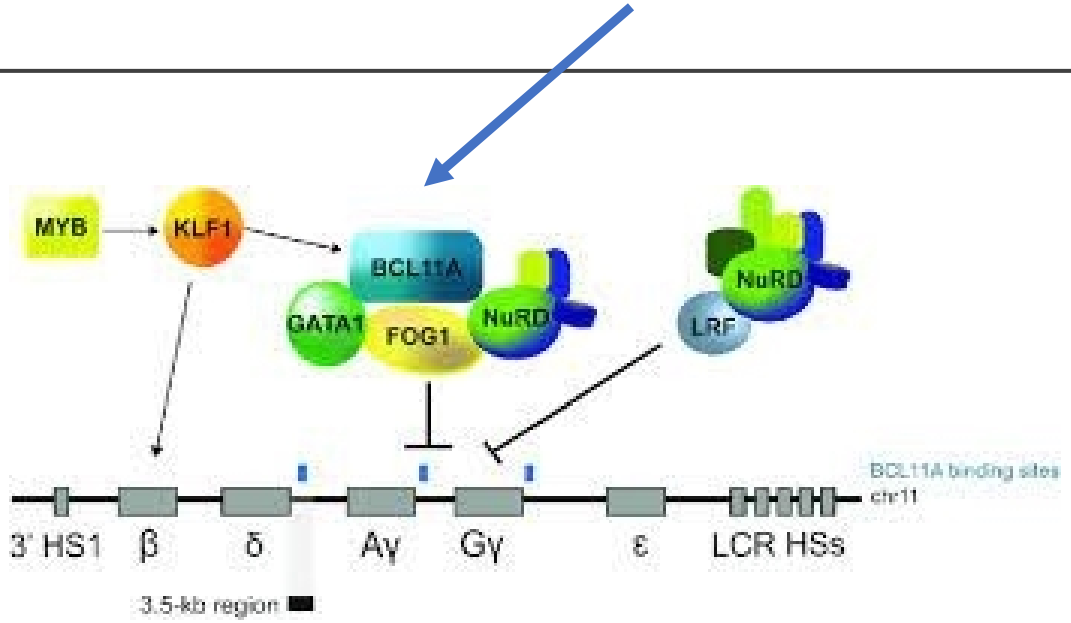
  - HRSA: U1EMC311080100
  - CDC: NU58DD0000009-01-00
- **Steering Committee:** Novartis, Astrazeneca
- **DSMB**: NovoNordisc, Magenta
- **Membership on a Scientific Advisory Committee:** Oric**,** Novartis, BEAM
- **Discussion of off-label drug use:** N/A

Discussion Objectives

-Review the pathogenesis of SCD
-Discuss current genetic therapy approaches in SCD
-Evaluate how we might compare outcomes across genetic therapies
-Discuss what a “cure” for sickle cell disease could look like (and why we are not there…**yet**)
-Consider implementation of genetic therapies

Pathogenesis of SCD

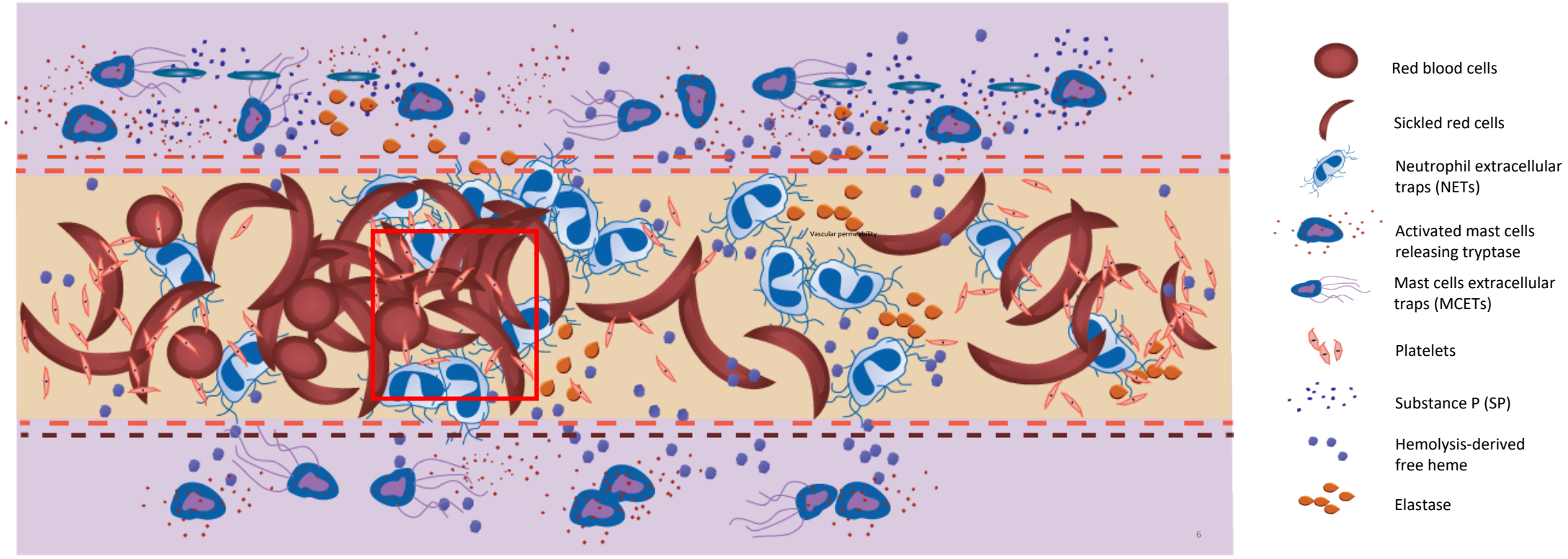




Fetal Hb is switched OFF

- BCL11A is one of the genes that acts as an “off” switch to fetal hemoglobin production shortly after birth for most people
- While most people with sickle cell disease switch to making HbS alone, some people keep making HbF

Vasculopathy caused by adhesion & vaso-occlusion



Red blood cells

Sickled red cells

Neutrophil extracellular traps (NETs)

Activated mast cells releasing tryptase

Mast cells extracellular traps (MCETs)

Platelets

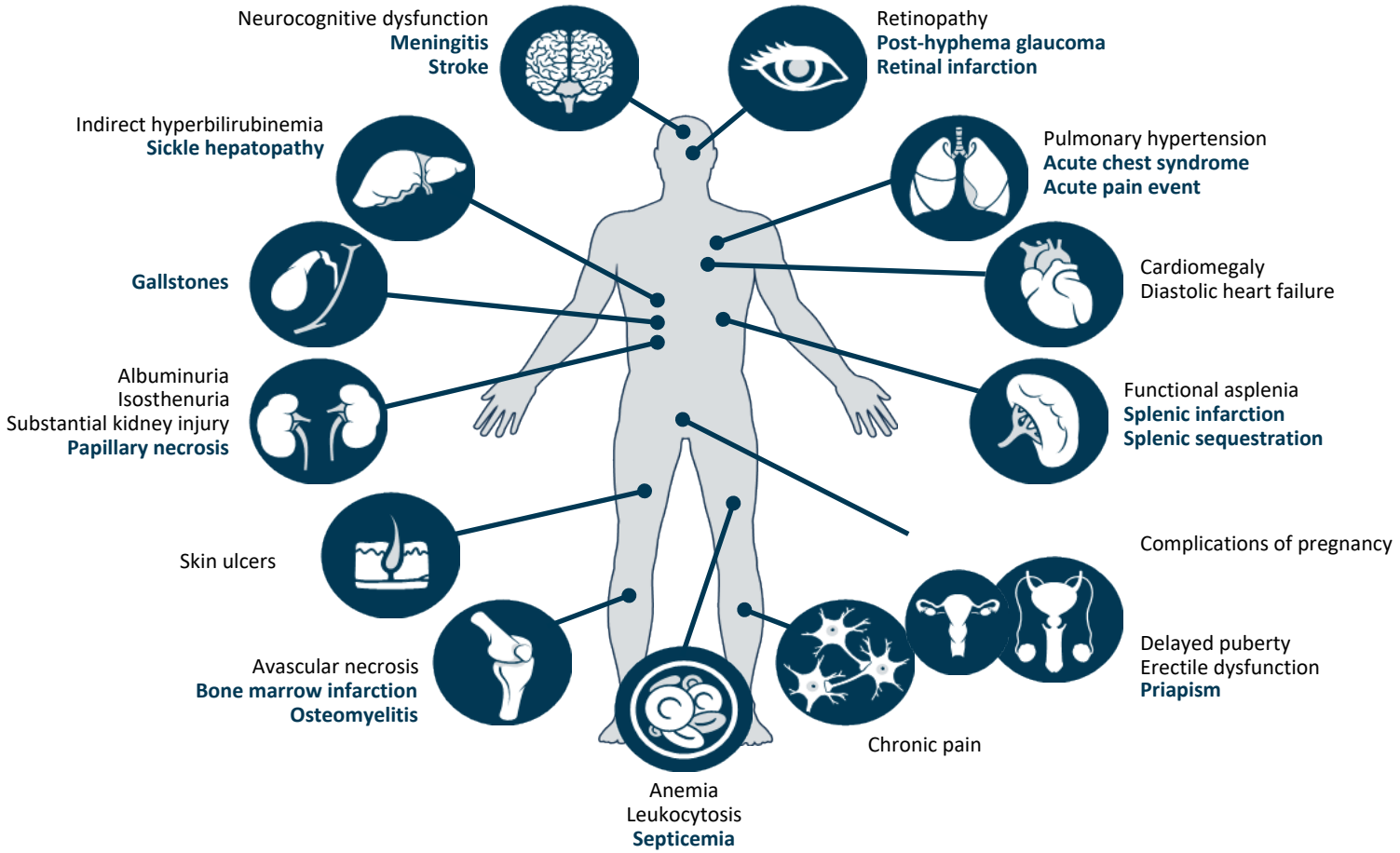
Substance P (SP)

Hemolysis-derived free heme

Elastase

Adapted from Aich A et al. *Curr Opin Hematol*. 2019;26(3):131-138.

SCD Is a Multi-System Disease



Kato GJ, et al. *Nature Reviews Disease Primers.* V4: 18010 (2018).

Why Gene Therapy?

Allogeneic Stem Cell Transplant for Sickle Cell Disease

- Curative for children >95% with a matched related donor
- Improving outcomes for adults with SCD
- Post-transplant Cytoxan and other immunosuppression changes have permitted improved outcomes with haplo-identical transplant with reduced GVHD and graft rejection
- So-why do we need other options?

Barriers to Allogeneic Stem Cell Transplant for Sickle Cell Disease

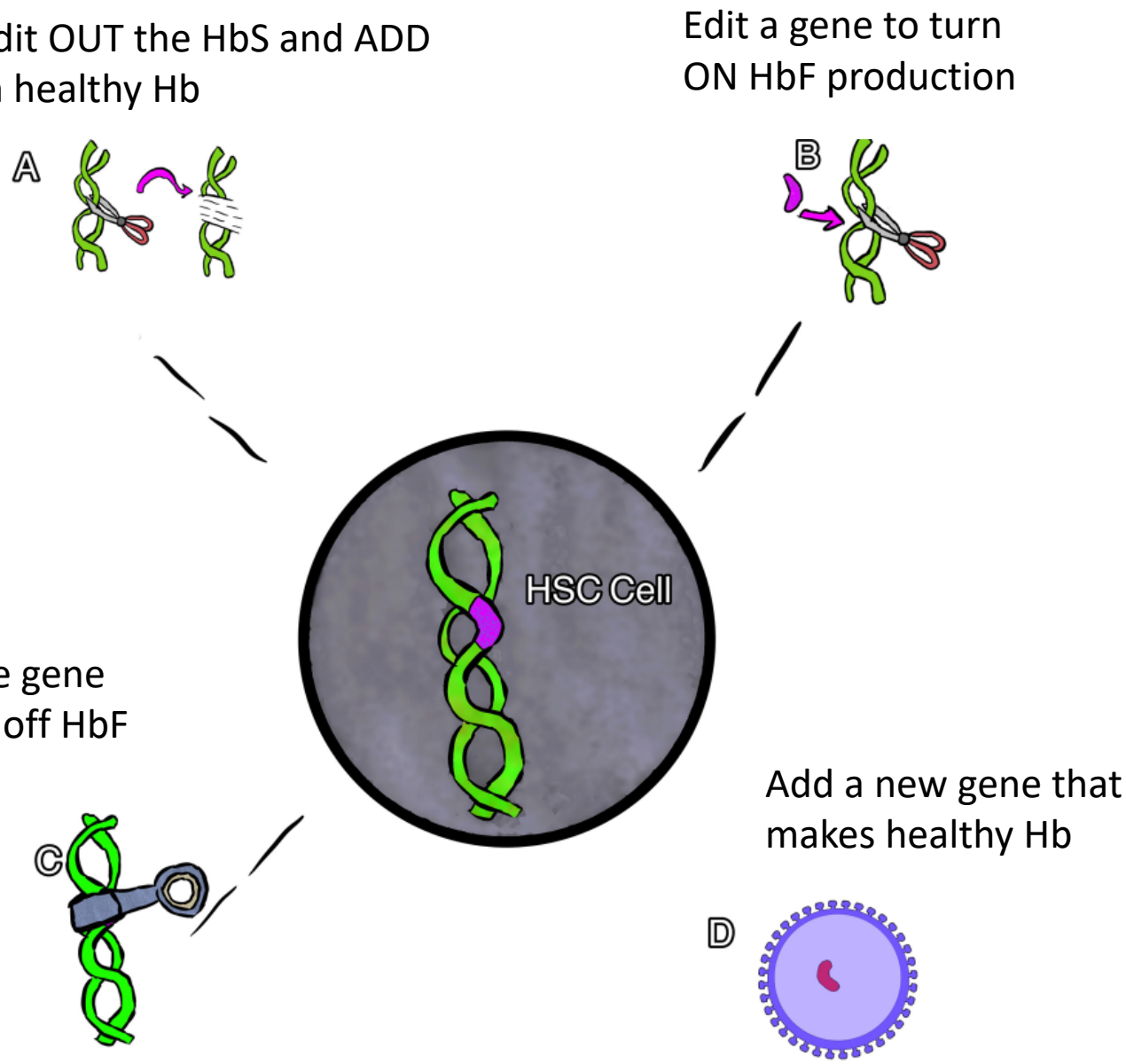
- Donor availability (matched donors and some haplo-identical donors)
- Risk of Graft Failure
- Risk of Graft Versus Host Disease
- Long Term Immune-suppression, viral reactivation, and complications
- ACCESS: Many individuals (ADULTS) don't even have access to a hematologist
  - **If people cannot get routine preventative treatment/care, how can they get a stem cell transplant?**
- So-it seems we DO need other options

Genetic therapies are:

Designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein (healthy hemoglobin)

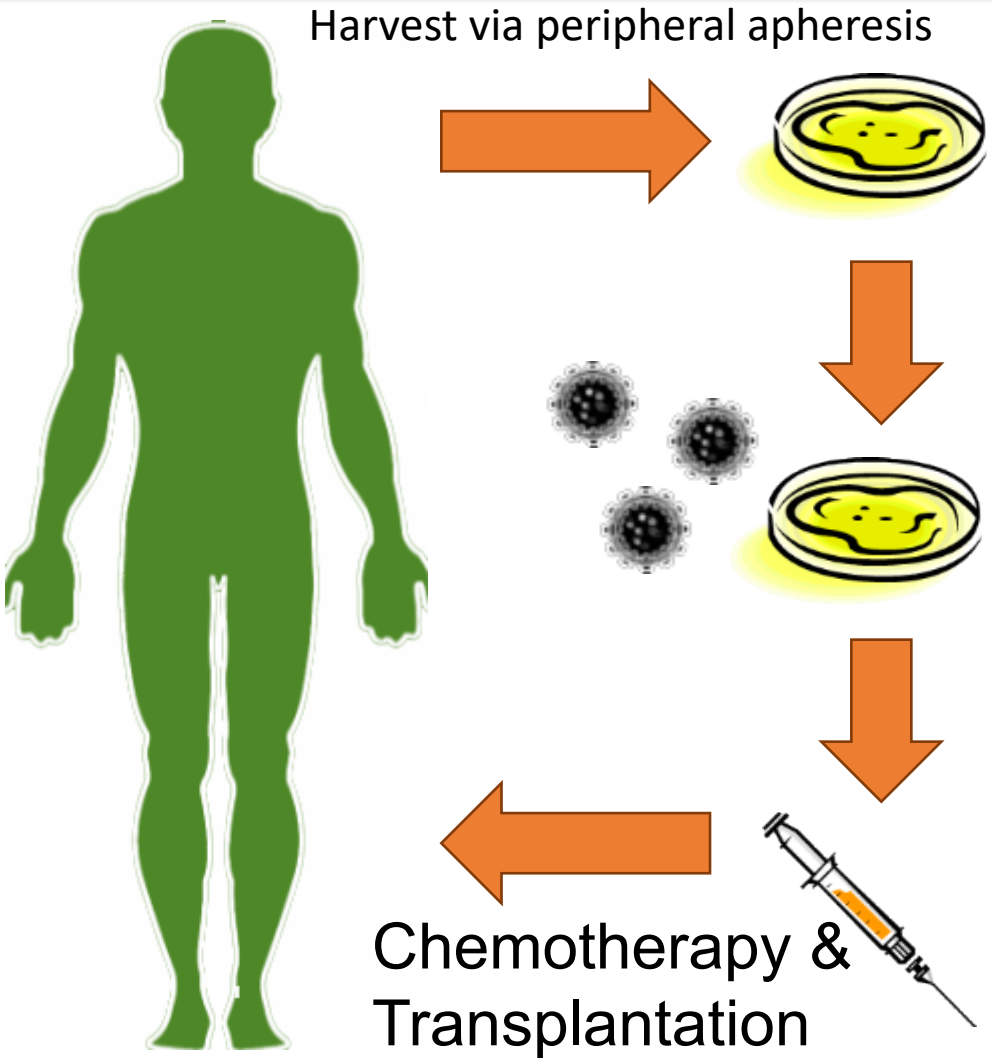
Different types of Gene Therapy

- Gene Correction or base editing (A)
- Gene Editing (B)
- Gene Silencing (C)
- Gene Addition(D)



Art by Samuel Washko
Kanter et al, Hematology ASH Education 2021

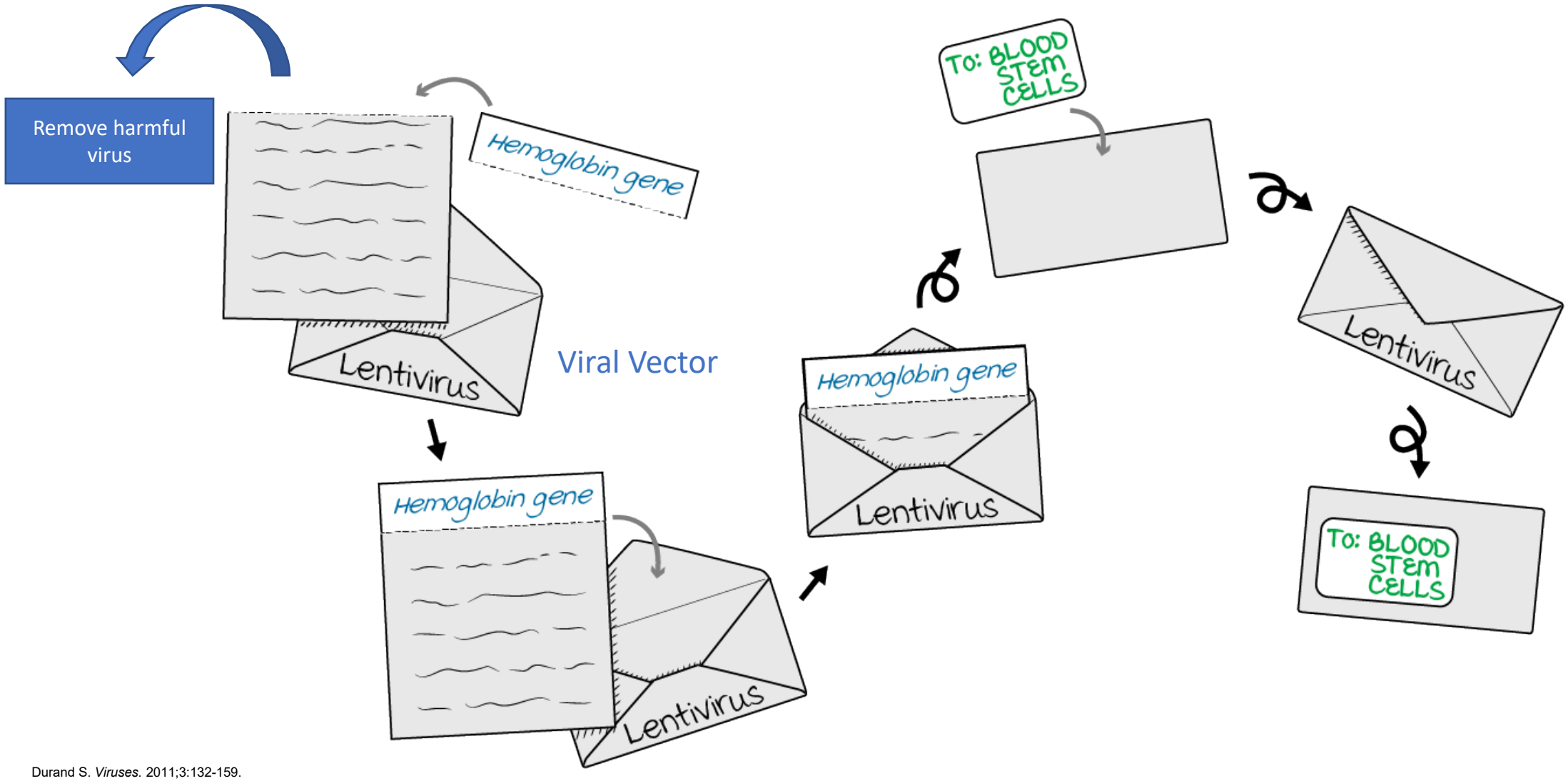
Autologous bone marrow stem cell-targeted gene therapy



- Patients serve as their own donor
- Could be available for all patients
- No need for immunosuppression
- No risk of GVHD

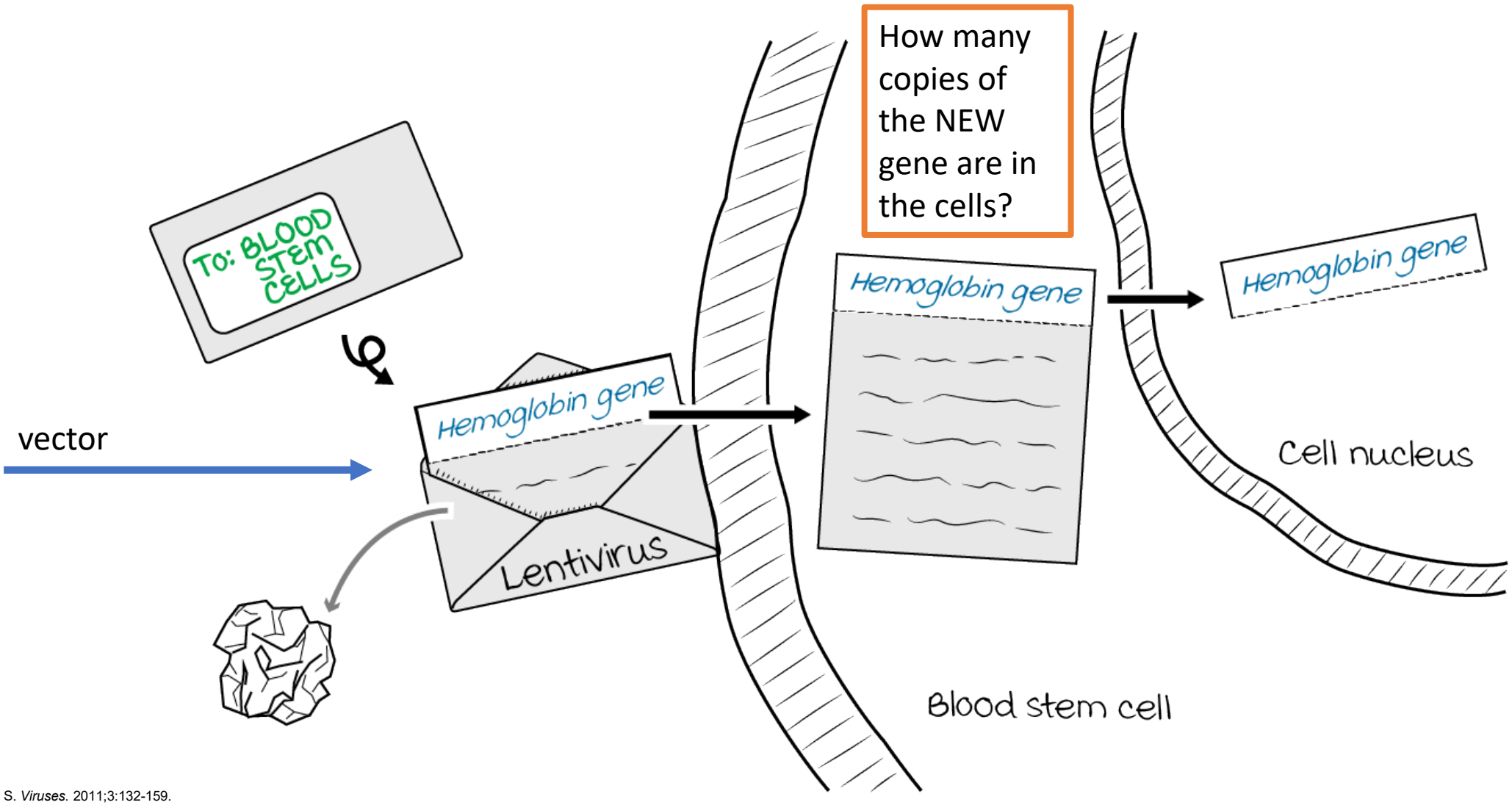
The Language of Gene Therapy

Some gene therapies use viral vectors for gene delivery



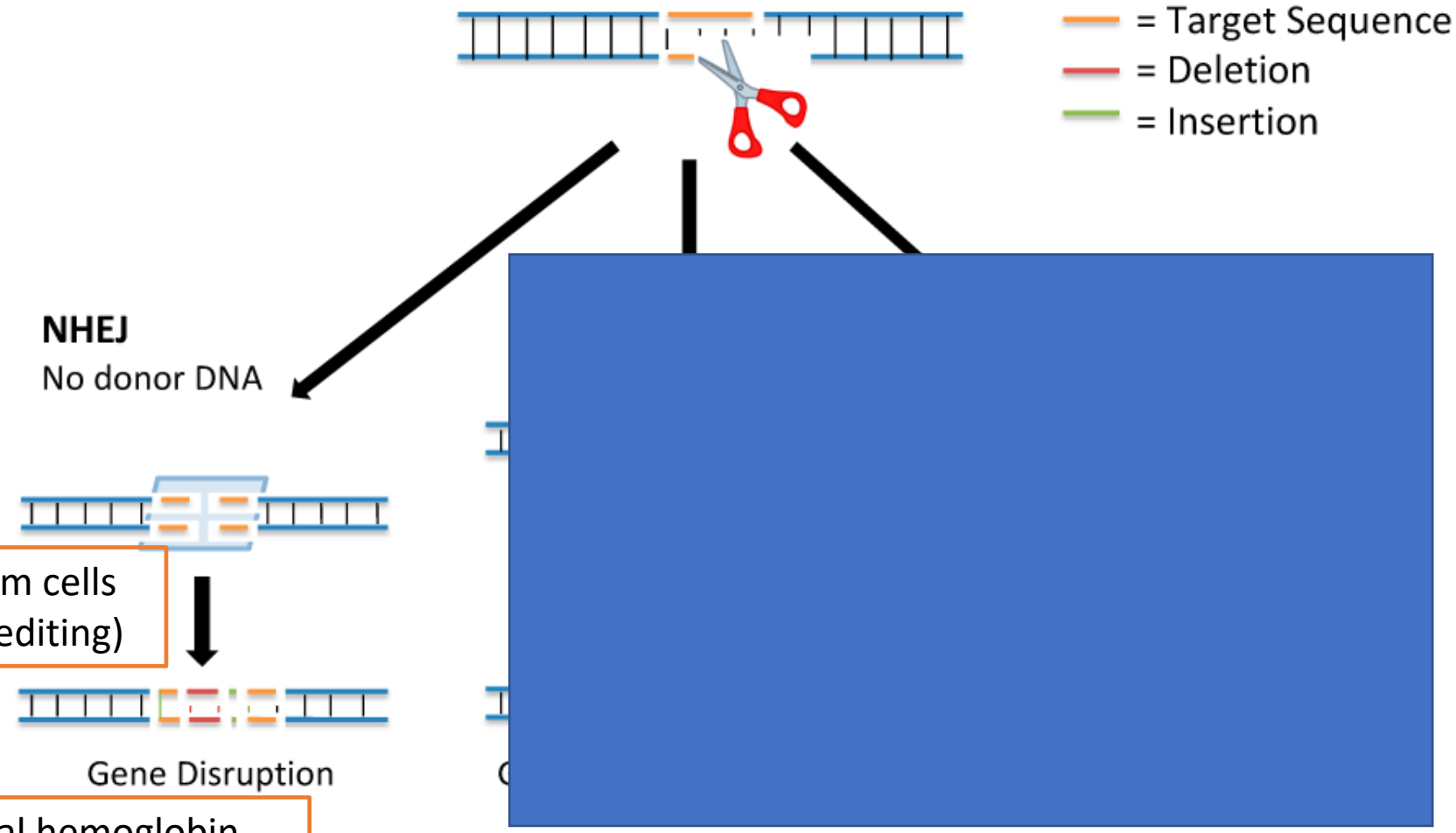
Durand S. *Viruses.* 2011;3:132-159.
Dong AC. *Adv Exp Med Biol.* 2017;1013:155-176.

Gene addition therapy uses viral vectors for gene delivery



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

Gene Editing



How many stem cells are edited (% editing)

How many stem cells are edited AND corrected

How much healthy Hb does the edit+correction cause?

How many stem cells are edited (% editing)

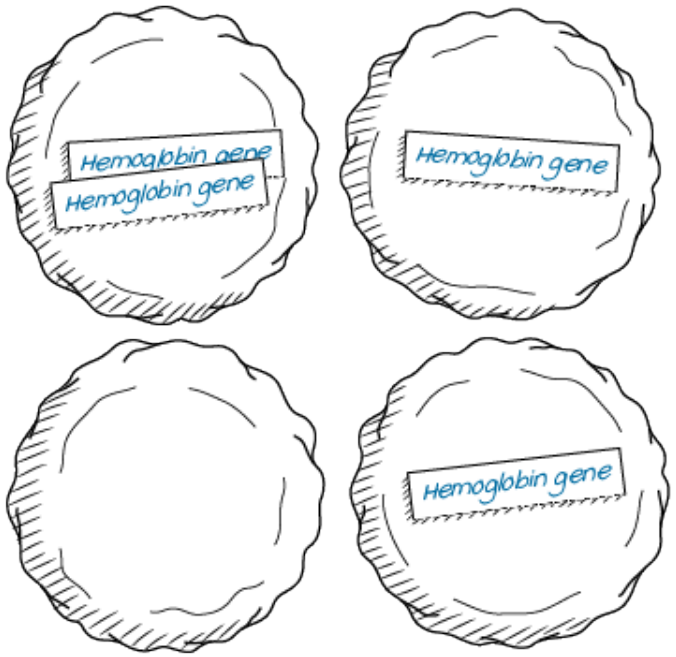
How much fetal hemoglobin does the edit cause?

Ates et al. *Genes* **2020**, *11*(10), 1113; https://doi.org/10.3390/genes11101113

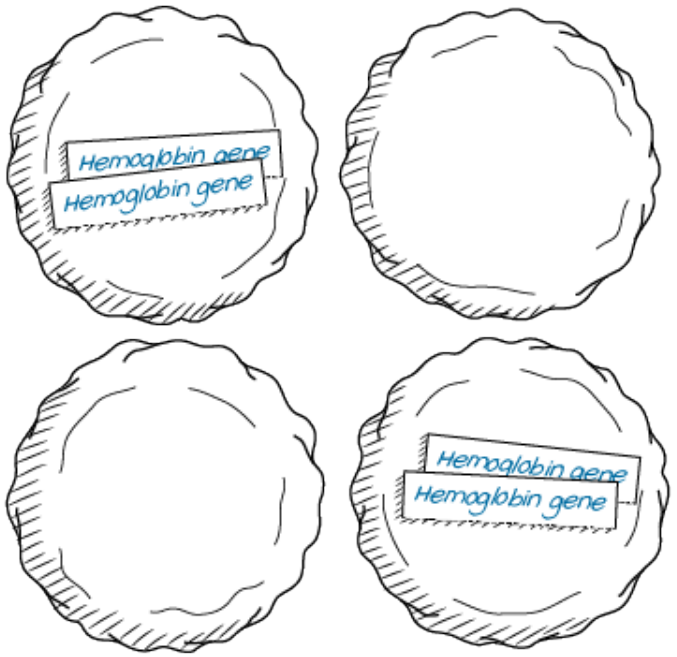
Vector copy number (VCN) calculation

All have VCN = 1

%LVV+ = 100%

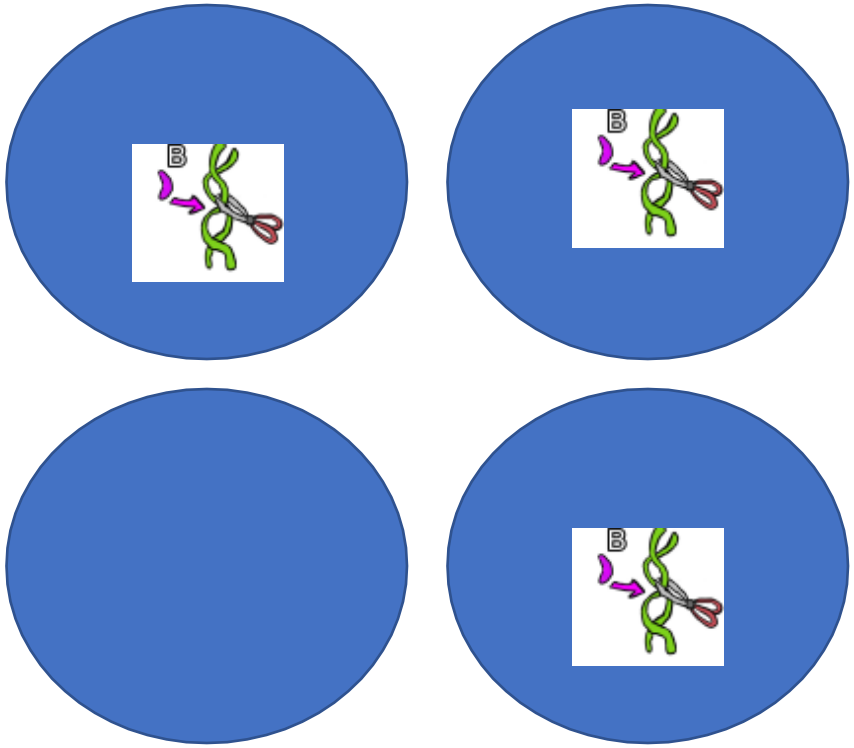


%LVV+ = 75%

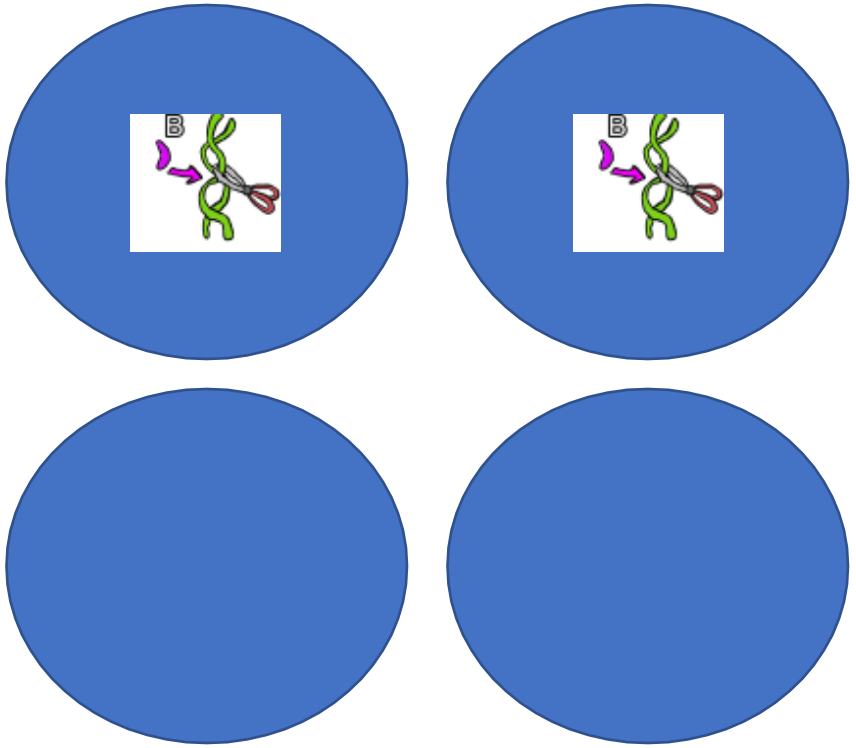


%LVV+ = 50%

Editing efficiency in stem cells

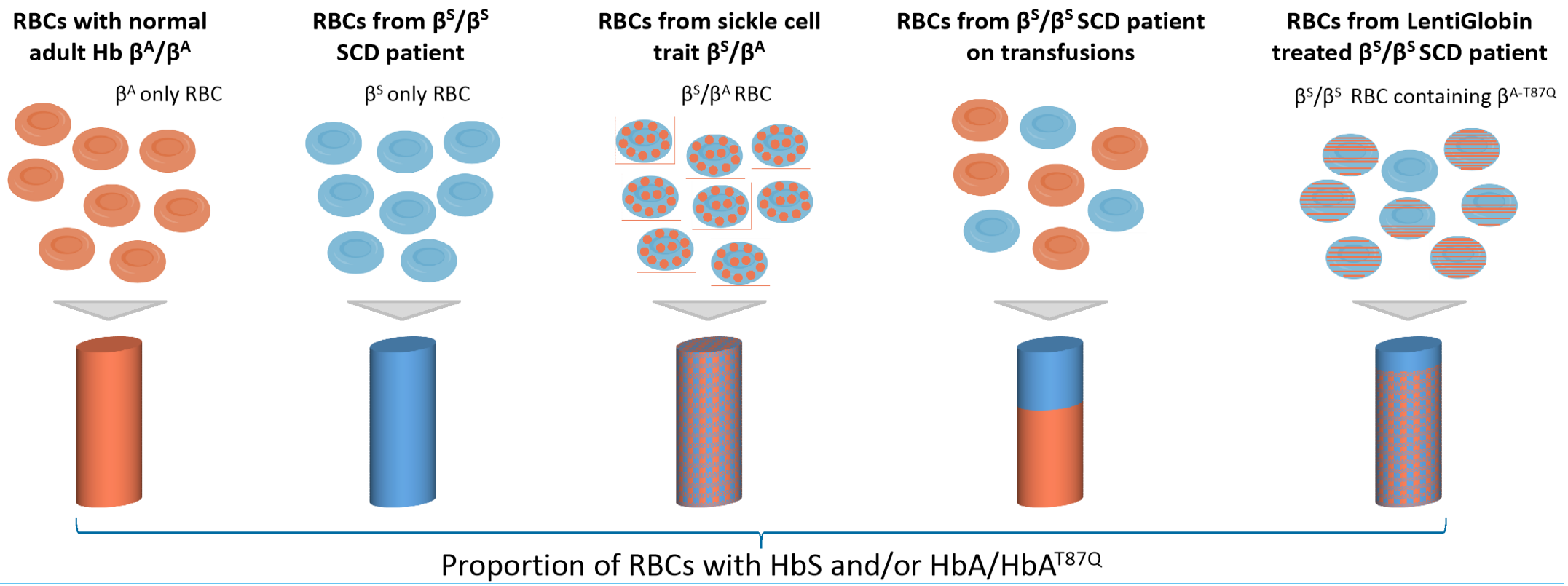


75% of cells are edited



50% of cells are edited

Measuring pancellularity



How do we measure gene therapy?

Vector copy number (VCN) per cell: Average number of new genes (in their vector envelope) delivered to a sample of blood stem cells

Transduction efficacy: Percentage of blood stems cells which have been successfully transduced (gotten the new gene)

Editing efficiency: Percentage of the stem cells are edited and/or corrected

Cell dose: total amount of patient's own blood stem cells returned to the patient after production

Healthy Hemoglobin production: How much of the new non-sickling hemoglobin is being produced?

Pancellularity: What percent of the red blood cells contain the healthy hemoglobin

How do we measure safety in gene therapy?

Vector copy number (VCN) insertion: Ensuring the vector+new gene don't insert in the wrong place

Off target assessment: Evaluating for "off-target" edits

Correction assessment: making sure that cells with edited genes for HbS are making healthy hemglobin

Monitoring for abnormal cell bone marrow: bone marrow assessments to make sure the there are not abnormal (dysplatic cells)

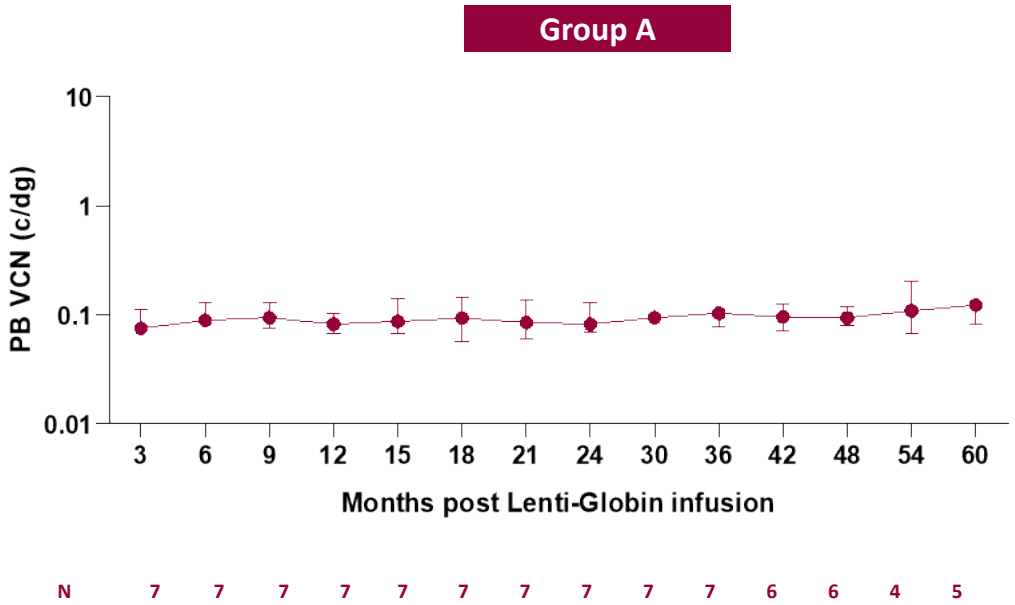
Evaluating for side effects or complications: Chemotherapy effect (mouth sores, fever), infertility, infections

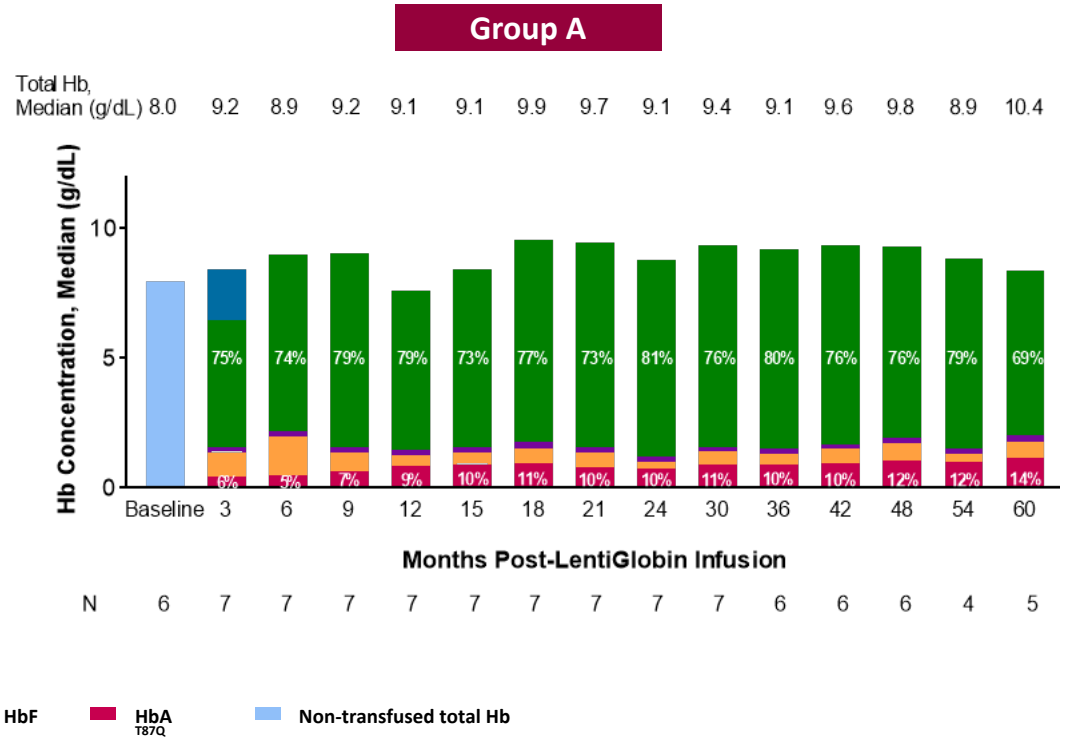
Continue to monitor for sickle cell related issues: VOC but ALSO kidney, heart, lung and organ dysfunction

How will we compare all the different types of gene therapy?

- OVERALL GOAL: Enough healthy hemoglobin in every cell that allows red blood cells to work as they should
  - Deliver oxygen
  - Flow through the blood stream
- Understanding how the edits/changes/additions predict the amount of hemoglobin produced
- Ensuring side effects and complications are measured in the same way so we can compare across trials

HGB-206 Groups A shows low PB VCN that persists over time but leads to minimal HbA^{t87q} production





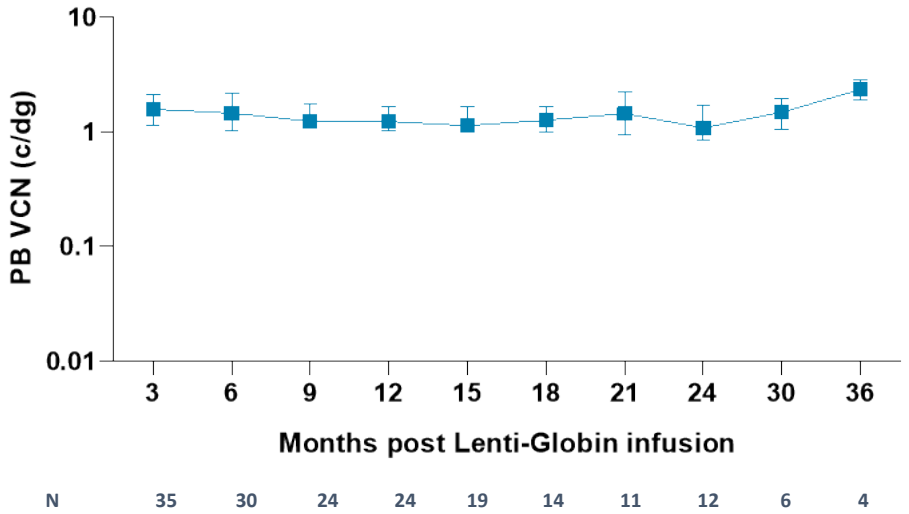
HbA (transfused) HbS HbA_2 HbF HbA_{T87Q} Non-transfused total Hb

c/dg, copies per diploid genome; PB, peripheral blood; VCN, vector copy number.

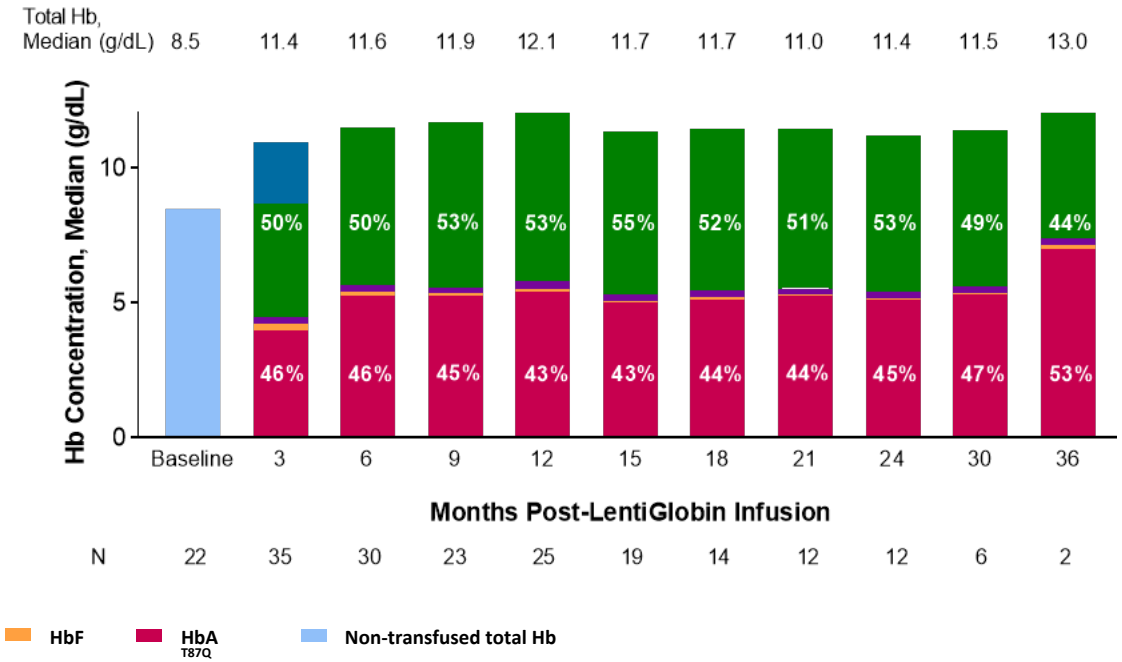
Data as of 17 February 2021

HGB-206 Groups C: Increased VCN and subsequent HbA^{T87Q} observed post-LentiGlobin infusion

Group C†



Group C†



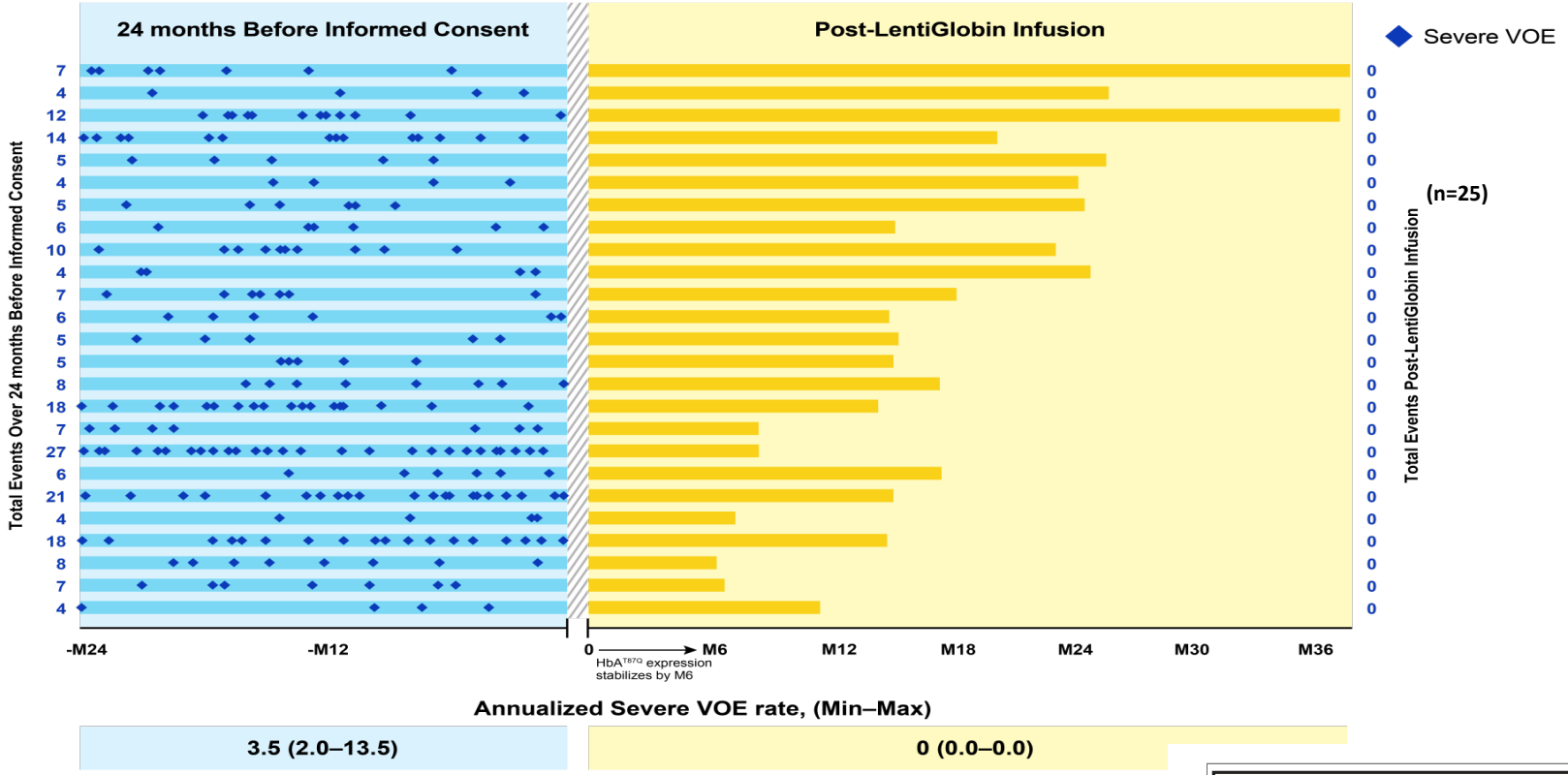
*Two patients in Group A received transfusions post-LentiGlobin infusion for an extended period of time with an additional patient receiving transfusions at the M60 visit; †total Hb values include transfused Hb while bar graph values indicate non-transfused Hb at ≥6 months post-LentiGlobin infusion. Percentages represent median Hb fraction as a percentage of non-transfused total Hb; baseline is average of 2 qualified non-transfused total Hb (g/dL) in 24 months before informed consent.

Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease

J. Kanter, M.C. Walters, L. Krishnamurti, M.Y. Mapara, J.L. Kwiatkowski, S. Rifkin-Zenenberg, B. Aygun, K.A. Kasow, F.J. Pierciey, Jr., M. Bonner, A. Miller, X. Zhang, J. Lynch, D. Kim, J.-A. Ribeil, M. Asmal, S. Goyal, A.A. Thompson, and J.F. Tisdale

g/dL, grams per deciliter; Hb, hemoglobin; HbA, adult hemoglobin; HbS, sickle hemoglobin; HbF, fetal hemoglobin

HGB-206 Group C: Complete resolution of severe VOEs ≥ 6 months post-LentiGlobin infusion



Severe VOEs were assessed in 25 patients who met the TPVOE population criterion of ≥4 severe VOEs in the 24 months before informed consent, and also met the minimum follow-up of 6 months post-LentiGlobin infusion required for VOE analysis. The hatched area represents the time between informed consent and LentiGlobin infusion, during which VOE and severe VOE data are not reported because patients received pre-harvest transfusions. A VOE was defined as an episode of acute pain with no medically determined cause other than a vaso-occlusion, including acute episodes of pain, acute chest syndrome, acute hepatic sequestration, acute splenic sequestration, and acute priapism. A severe VOE is a subset of VOEs requiring a ≥24-hour hospital or emergency room observation unit visit or ≥2 visits to a day unit or emergency room over 72 hours with both visits requiring intravenous treatment, or priapism episodes lasting >2 hours and requiring a medical facility visit. Adjudication of severe VOEs is pending.

*One death, unlikely related to LentiGlobin, 20 months post-infusion in a patient with significant baseline SCD-related cardiopulmonary disease.
max, maximum; min, minimum; SCD, sickle cell disease; TPVOE, transplant vaso-occlusive event; VOE, vaso-occlusive event.

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Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease

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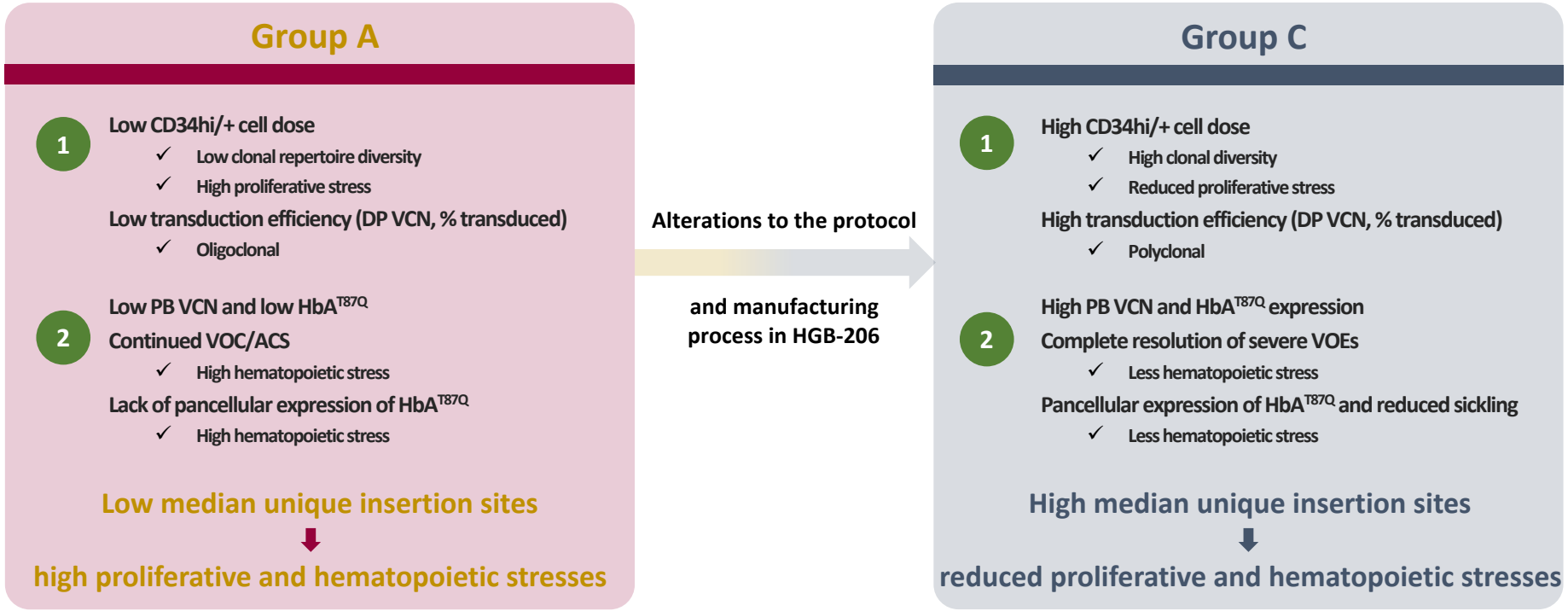
HGB-206 group A had two cases of MDS/leukemia

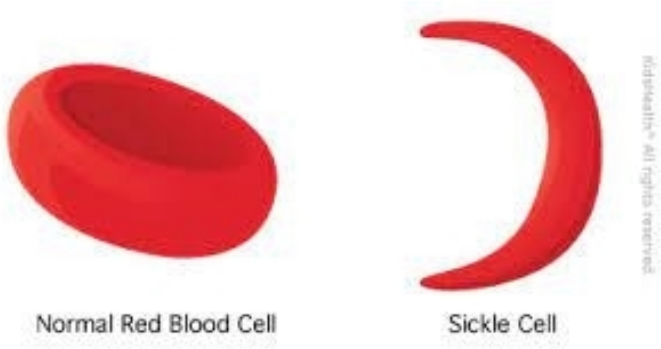


The safety profile post-LentiGlobin for all treated patients with SCD remains generally consistent with the risks of autologous stem cell transplant, myeloablative busulfan conditioning, and underlying SCD

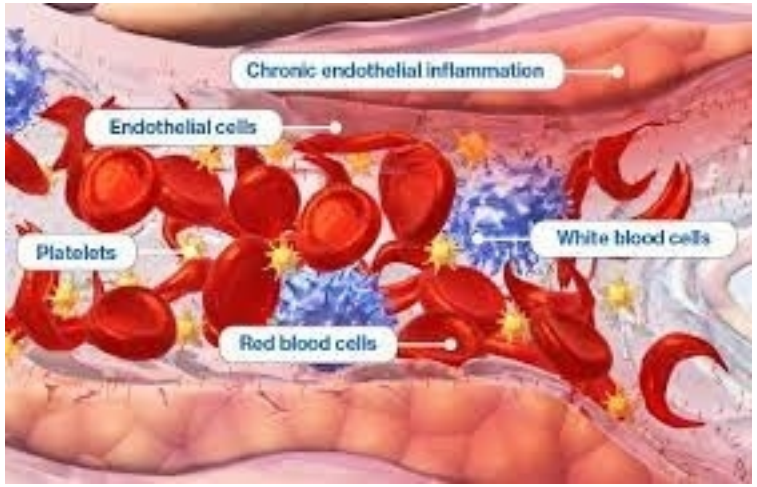
ACS, acute chest syndrome; DP, drug product; PB, peripheral blood; SCD, sickle cell disease; VOC, vaso-occlusive crisis; VOE, vaso-occlusive event.

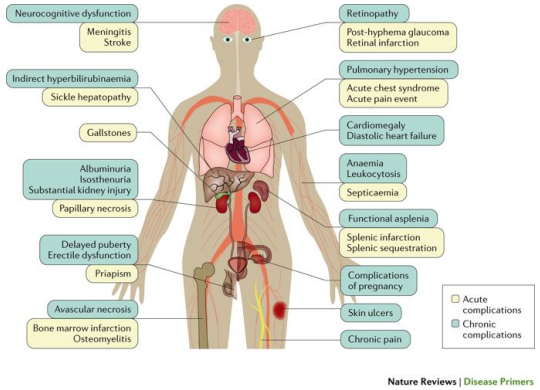
Data as of 17 February 2021

What will define a cure:

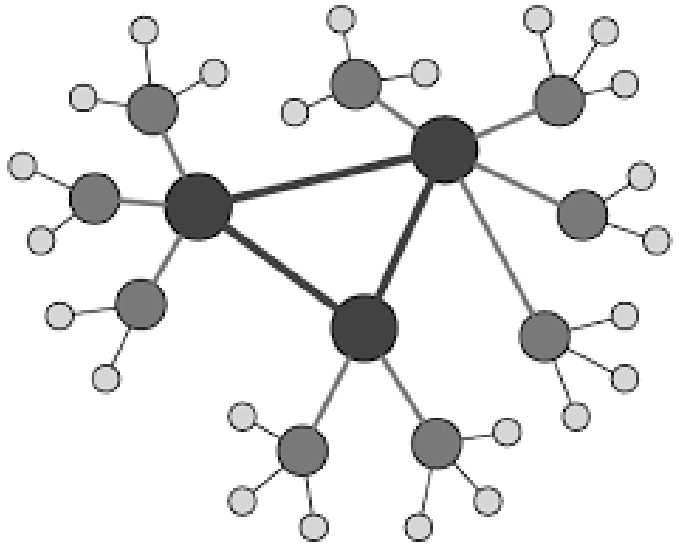


- We must see sufficient “new” hemoglobin to prevent sickling
- Resolution of hemolysis
- Lack of adhesion to blood vessels
- Stabilization (or improvement of organ function)
- Resolution of acute painful events





How will we deliver gene therapy safely, efficiently and appropriately?



- We have to ensure people with SCD are seen by **sickle cell specialists** prior to gene therapy
- We have to ensure potential patients understand the impact of the therapy (what it can and cannot do)
- We have to follow patients long term for SCD and transplant related issues
- We have to make sure that patients receive appropriate counseling on their terms

What is the future of genetic therapies?

- We have to define a grade of cure
- We have to ensure we are honest with patients about the options and outcomes
- We need FDA (and similar agencies) to ensure that studies that are not working well-are stopped
- We have to monitor LONG TERM to see if these therapies give LONG TERM DISEASE MANAGEMENT/CURE
- We also have to use a comparative registry of patients treated without stem cell therapy to understand the impact of these treatments
- We have to ensure safe, ethical implementation
- We have to work to figure out how to make this type of therapy available, affordable and universal.

What did we talk about?

- Pathobiology of Sickle Cell Disease
- Allogeneic Stem Cell Transplant for sickle cell disease
- Genetic therapies for sickle cell disease.
- The language of gene therapy
- Understanding the impact of gene therapy
- Long-term implementation of gene therapy

Thank you!

#togetherwecan

#sicklecell

#sicklecellmatters

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