# Genetic Therapies for Sickle Cell Disease

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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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at Boston Children's Hospital

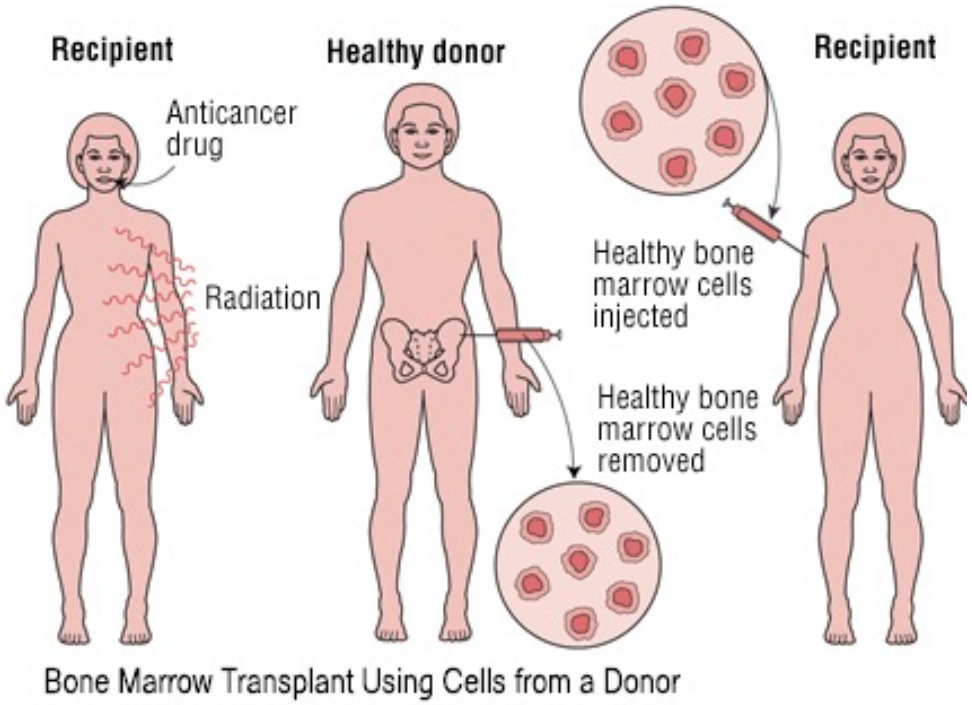
# Disclosures

- Consulting (Steering committee about thalassemia):  bluebird bio
- Research funding to institution:  Celgene, bluebird bio

# Sickle Cell Disease: Treatment options

| | |
|---|---|
| Early childhood | Difficult to predict future disease severity |
| Medical management | - Hydroxyurea since 1980s<br>- Chronic transfusion regimen<br>- Newly FDA-approved: Crizanlizumab, voxelotor, L-glutamine |
| Matched sibling donor stem cell transplant (SCT) | - **< 20%** of SCD patients have matched sibling<br>- Intensive chemotherapy preparation<br>- 85-90% Event-free survival<br>- Risk of Graft Versus Host Disease |
| Cell-based therapies | - Unrelated donor SCT: Risk of cGVHD<br>- Haplo-identical SCT: Risk of graft failure<br>- **Gene therapy** |

# Allogeneic hematopoietic stem cell transplant



Bone Marrow Transplant Using Cells from a Donor

Benefits
Potential cure

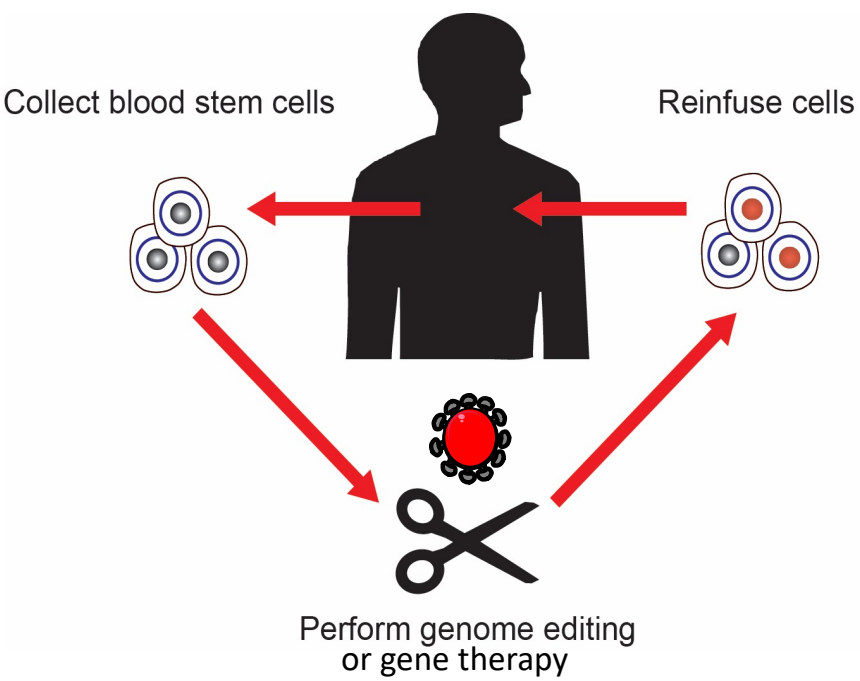
Challenges
Finding a donor
Intensive process

Risks
Myeloablative Conditioning:
- Infection
- Infertility

Transplant rejection
Graft vs. Host Disease

Image from Harvard Health Publications

# Gene Therapy or Gene Editing




Benefits

Potential cure

Challenges

~~Finding a donor~~

Intensive process

Risks

Myeloablative Conditioning

- Infection
- Infertility

Transplant rejection

~~Graft vs. Host Disease~~

Insertional mutagenesis

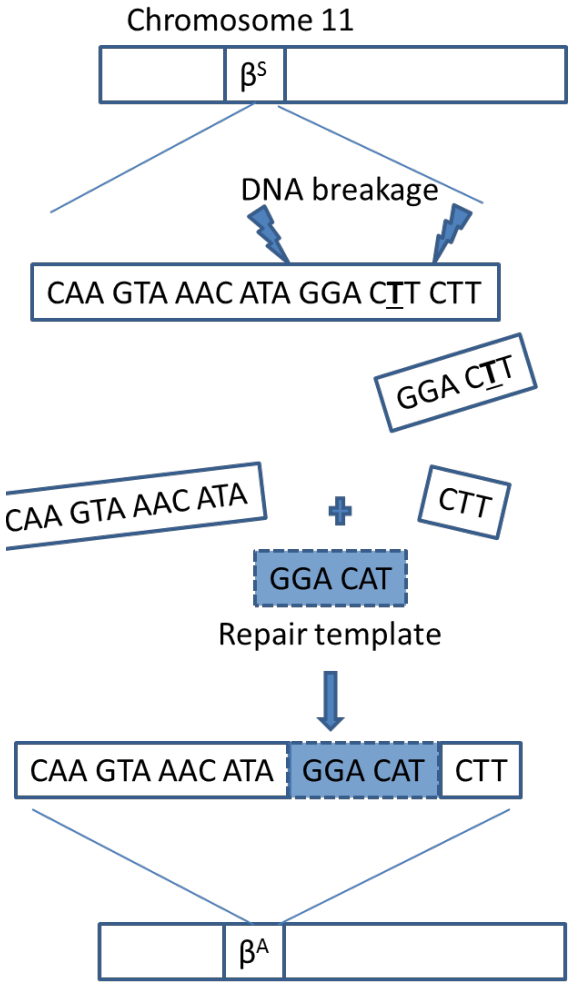
Off-target effects?

# What is gene editing?

Uses molecular tools to make breaks in the genome

Allows editing in the form of:

- Deletions that alter gene function or regulation
- Removal of DNA and replacement with a desired sequence of DNA called a repair template
- Techniques include
  - Zinc finger nucleases (ZFN)
  - Meganucleases
  - TALEN
  - CRISPR-Cas

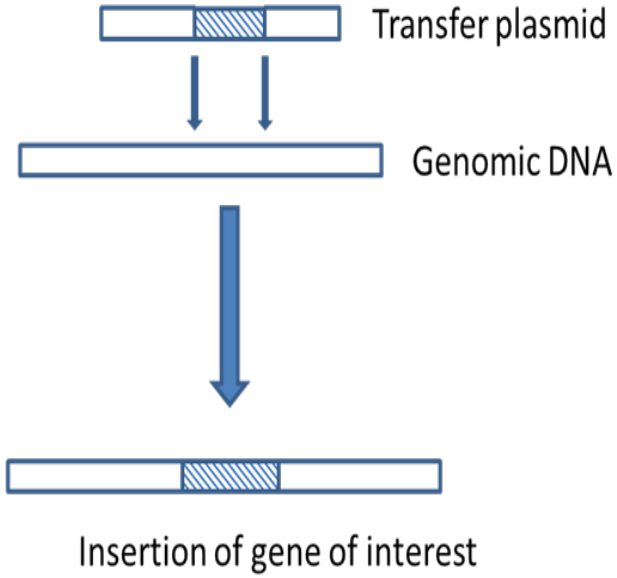



Slide adapted from Allistair Abraham

# What is gene therapy?

Viral vector transfers genetic material into cells

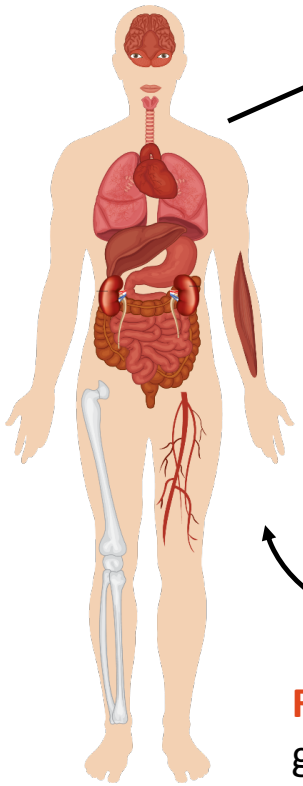
- **In vivo:** Genetic material (DNA/RNA) can remain in the cell but is not added to the cell's genome
  - ie, Hemophilia
- **Ex vivo:** Genetic material can be integrated into the genome
  - ie, Sickle Cell Disease



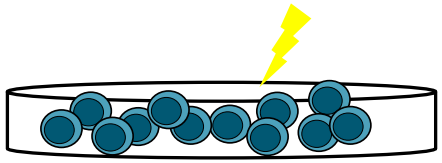

Slide adapted from Allistair Abraham

# Ex vivo gene therapy using lentiviral vector: Hemoglobinopathies

**HSC Collection:** HSCs harvested from bone marrow or by mobilization/apheresis



Hematopoietic stem cells



**Transduction:** HSC modified by transduction with a lentiviral vector

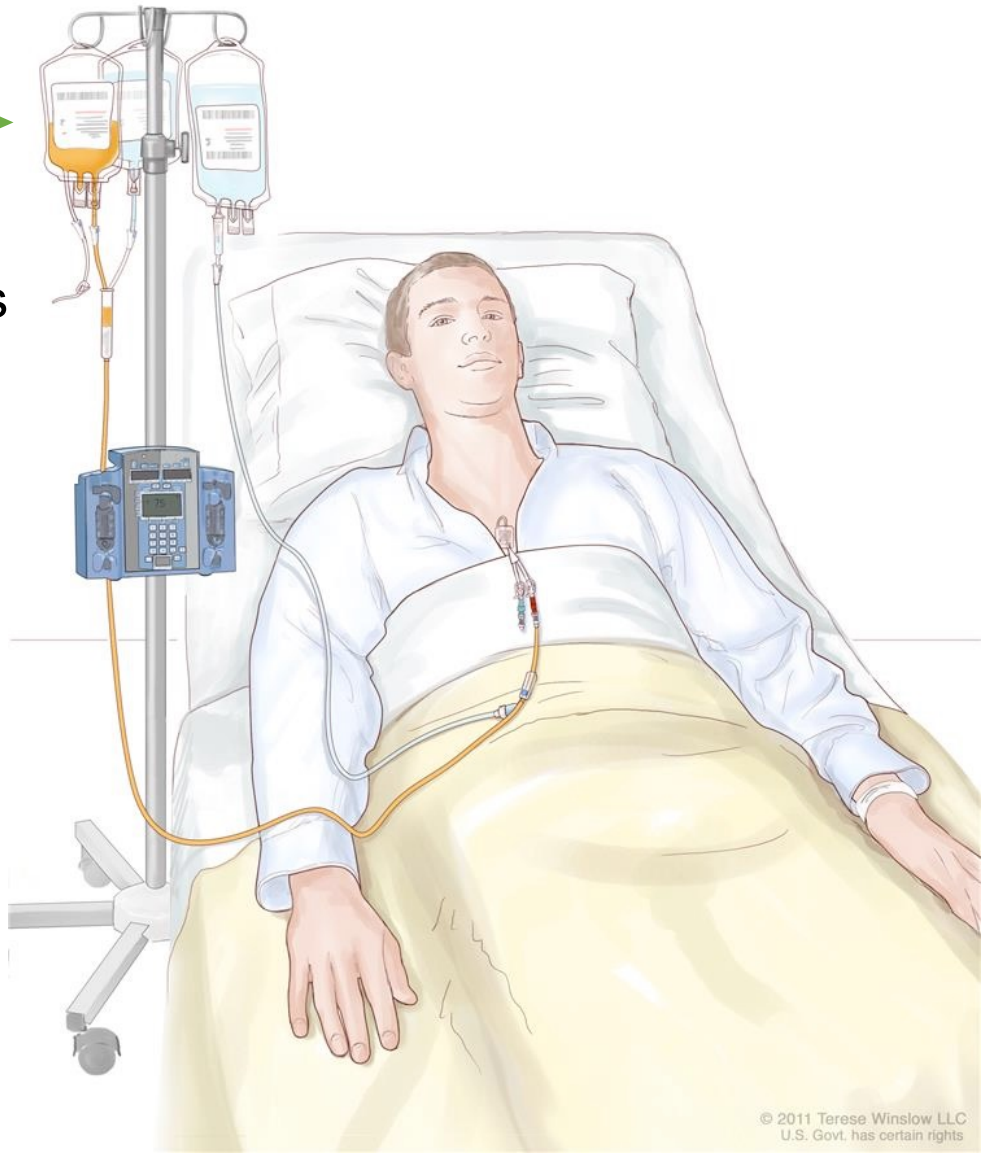
Modified hematopoietic stem cells

**Reinfusion:** Conditioning (myeloablation) and reinfusion of genetically modified HSC into bone marrow

Rivella. Haematologica. 2015;100:418.

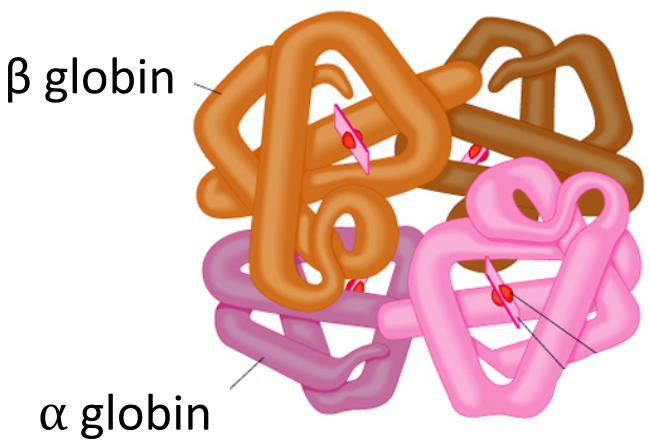
Slide credit: clinicaloptions.com

> 250 million cells



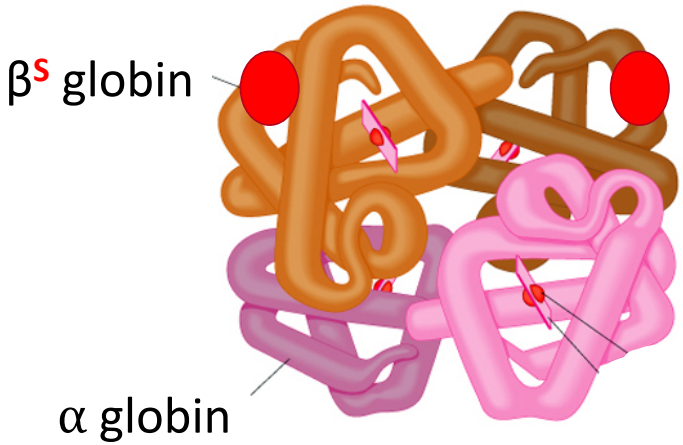

https://www.cancer.gov/publications/

# Lentiviral *ex vivo* gene therapy for hemoglobinopathies




$\alpha_2\beta_2$

Normal adult Hb = HbA

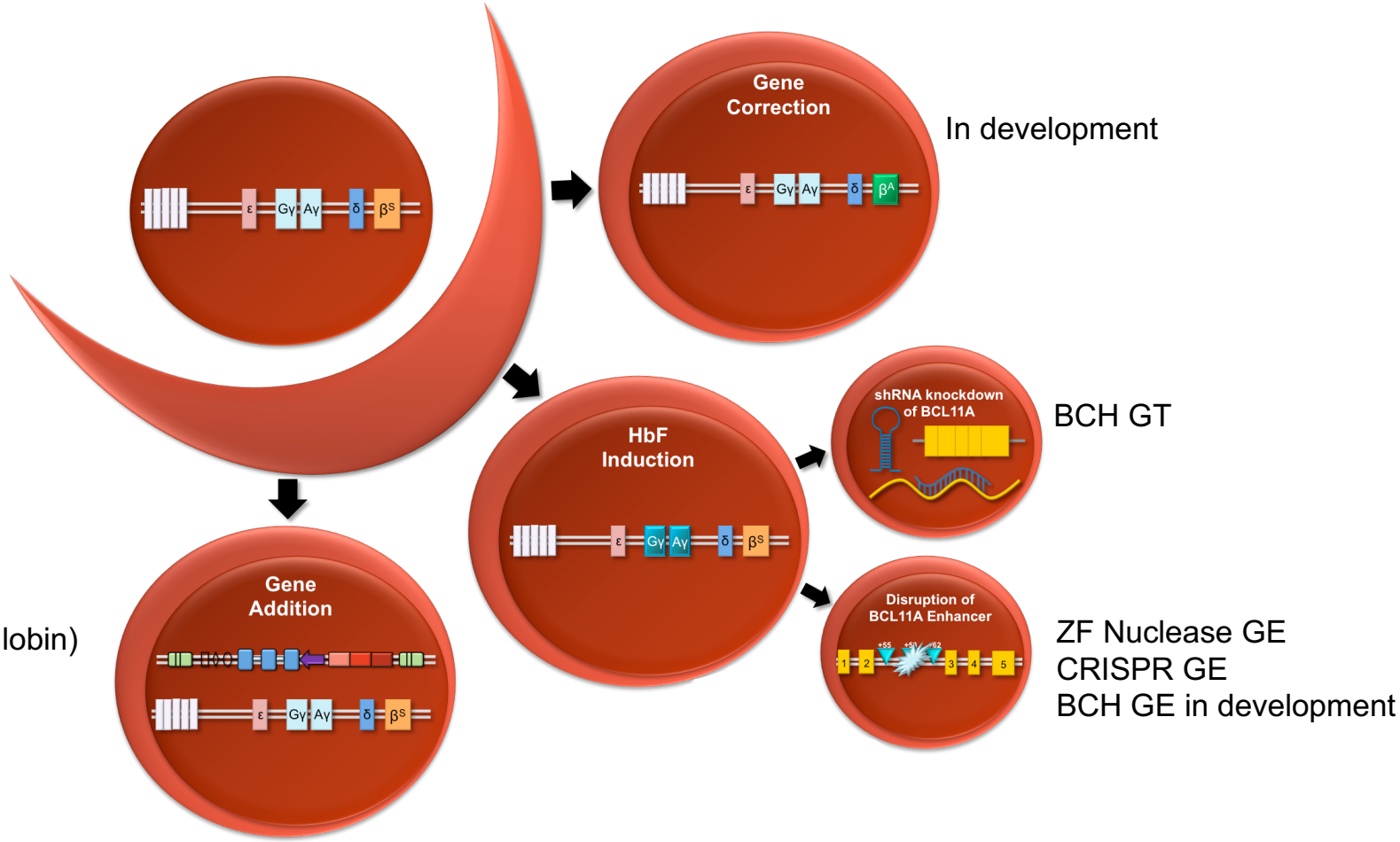



$\alpha_2\beta^S_2$

Sickle Hb = HbS

The "genetic payload" needs to yield an alternative to $\beta^S$ globin

# Autologous gene therapy approaches for β-hemoglobinopathies



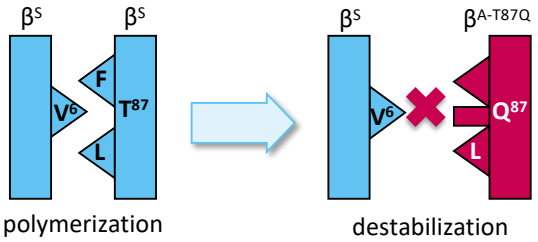

Hoban *et al.* Blood (2016) 127:839.

# Sickle cell disease lentiviral gene therapy: active clinical trials

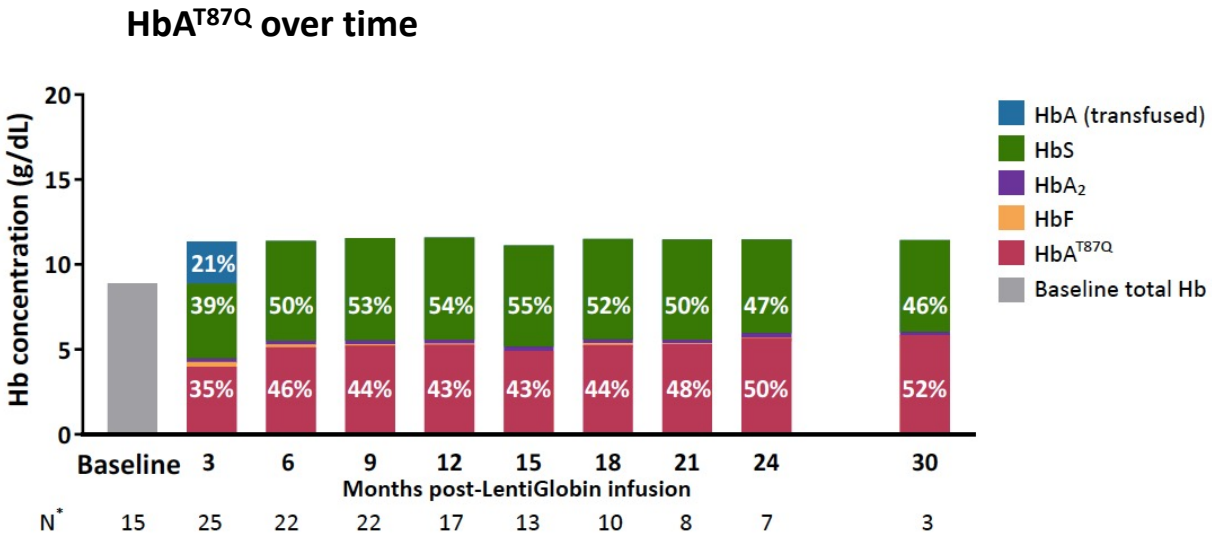
| Vector | Sponsor | NCT | Sites | Patient ages | Patients treated |
|---|---|---|---|---|---|
| ARU 1801:<br>Modified gamma globin gene | Aruvant Sciences | NCT 02186418 | Cincinnati, NC, Jamaica, (NY, Philly, Toronto) | 18-45 | 3 |
| LentiGlobin:<br>Modified beta globin gene | bluebird bio | NCT 04293185 | Boston, Minn, NJ, NC, Houston | 2-35 | > 40 |
| Modified beta globin | Donald Kohn / UCLA | NCT 02247843 | UCLA | > 18 | ? |
| Modified beta globin | Marina Cavazzana / Assistance Publique – Hôpitaux de Paris | NCT 03964792 | Paris | 5-35 | ? |
| shRNA targeting BCL11A | David Williams / Boston Children's Hospital | NCT 03282656 | Boston, Los Angeles | 3-40 | 9 |
| Modified gamma globin | CSL Behring | NCT 04091737 | City of Hope (Duarte, CA) | 18-45 | ? |

# LentiGlobin HGB-206 Group C Study

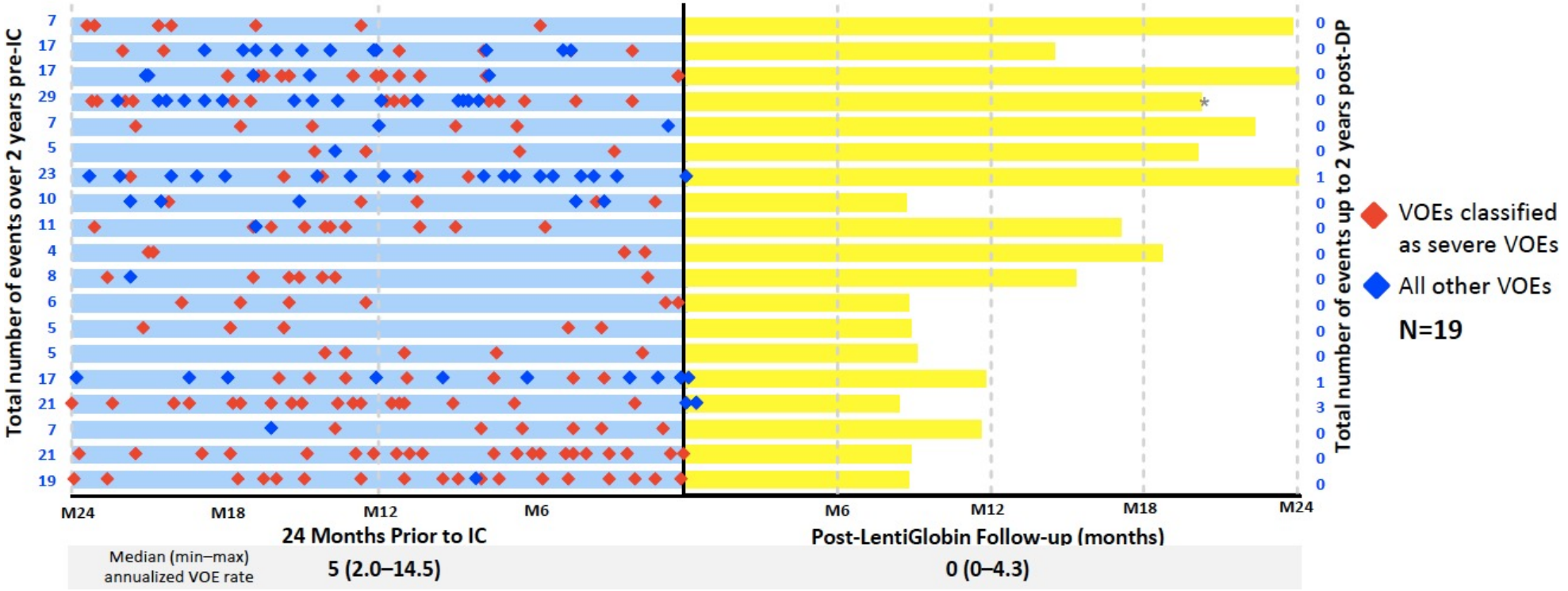
"Genetic payload" in this trial is a modified beta globin gene that prevents sickling: **HbA$^{T87Q}$**




**Modified RBCs express gene therapy-derived HbA$^{T87Q}$**



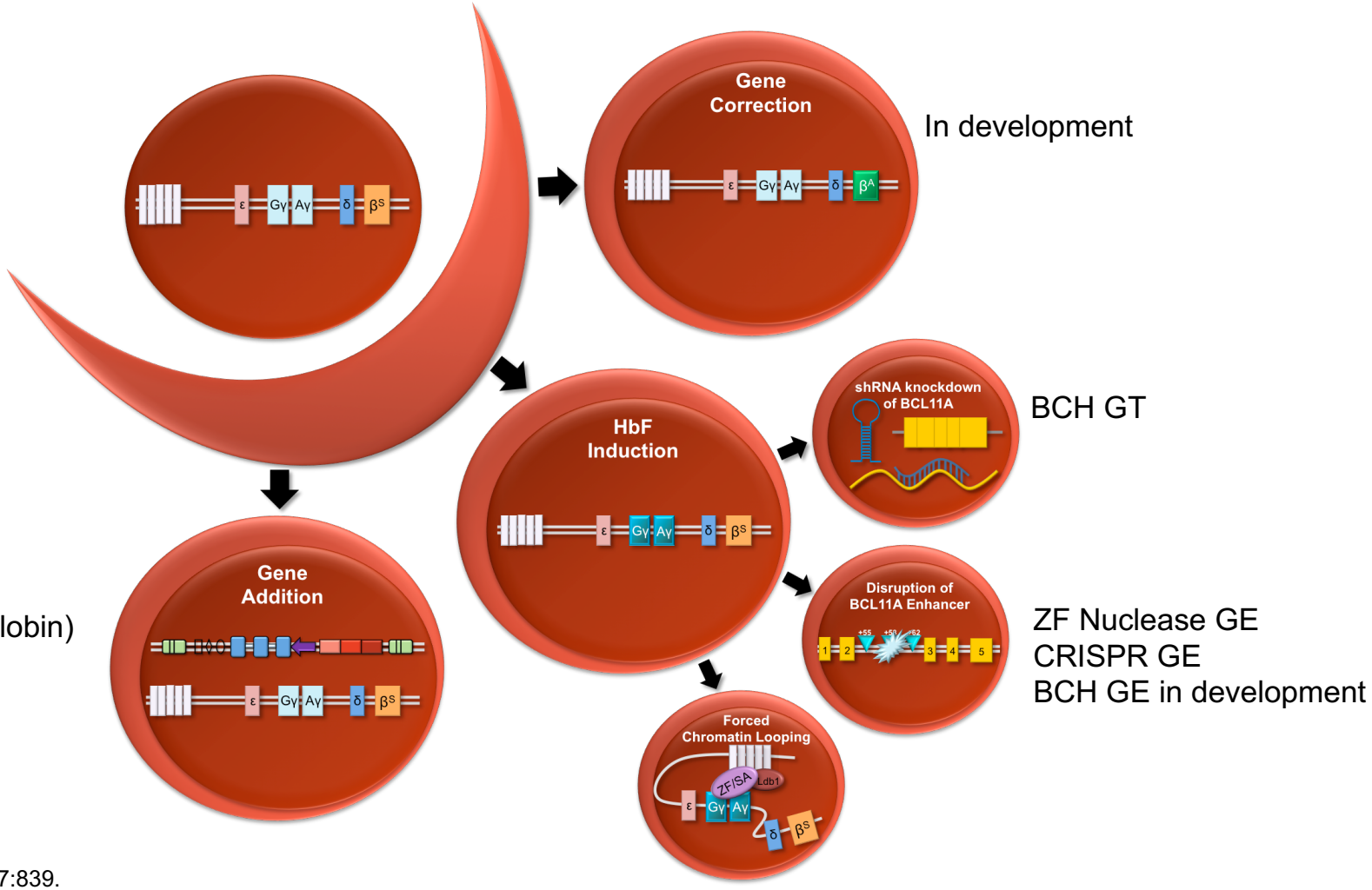
# LentiGlobin HGB-206 Group C Study: Clinical improvement after gene therapy




Patients with ≥ 4 VOC/ACS at baseline before IC and with ≥ 6 months of follow-up post-DP infusion are included
VOE includes episodes of acute pain with no medically determined cause other than a vaso-occlusion, lasting more than 2 hours and severe enough to require care at a medical facility, a VOE includes acute episodes of pain, acute chest syndrome, acute hepatic sequestration, and acute splenic sequestration.
IC, informed consent

Slide courtesy of bluebird bio, data as of August 2020

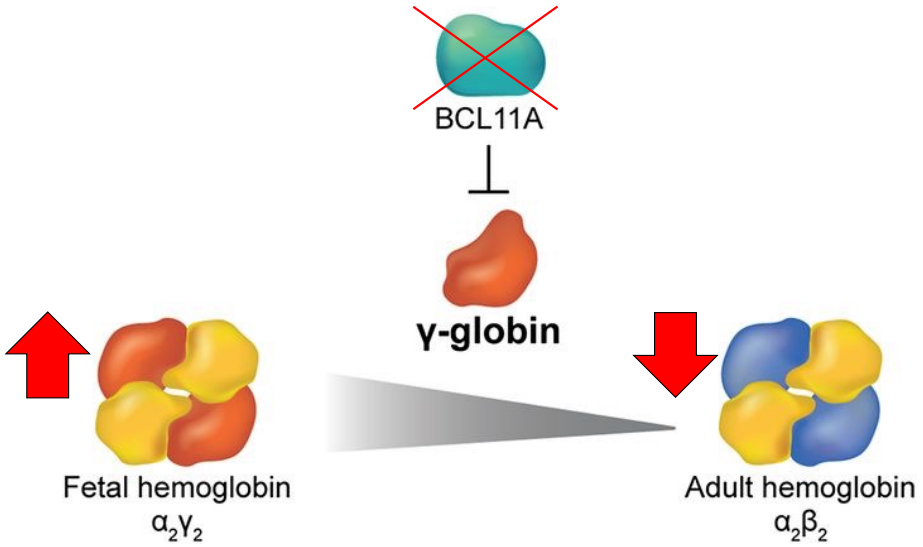
# Autologous gene therapy approaches for β-hemoglobinopathies




Hoban *et al.* Blood (2016) 127:839.

# Background: Targeting BCL11A to increase HbF

- Fetal hemoglobin (HbF)
  - Prevents HbS polymer formation
  - High HbF → Low SCD severity
- Pancellular distribution of HbF is goal
- BCL11A
  - Major repressor of γ-globin in adult cells
  - Essential in B lymphoid and hematopoietic stem cell lineages

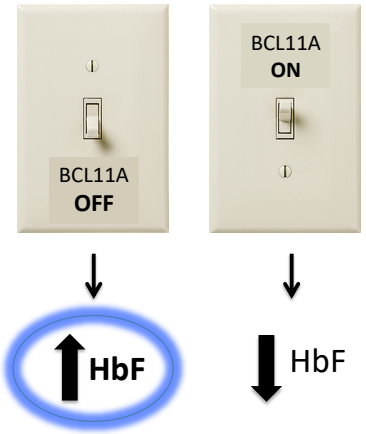



→ **Our approach:** Knock down BCL11A via RNAi to induce γ-globin expression
→ **Advantage:** Harness the physiologic switch machinery → Simultaneously increase HbF and decrease HbS (maintain α:β ratio)

Sankaran et al., *Science*, 2008; Sankaran et al., *Nature*, 2009; Basak et al., *JCI*, 2015; Liu et al., *Cell*, 2018; Martyn et al., *Nat. Genet*., 2018

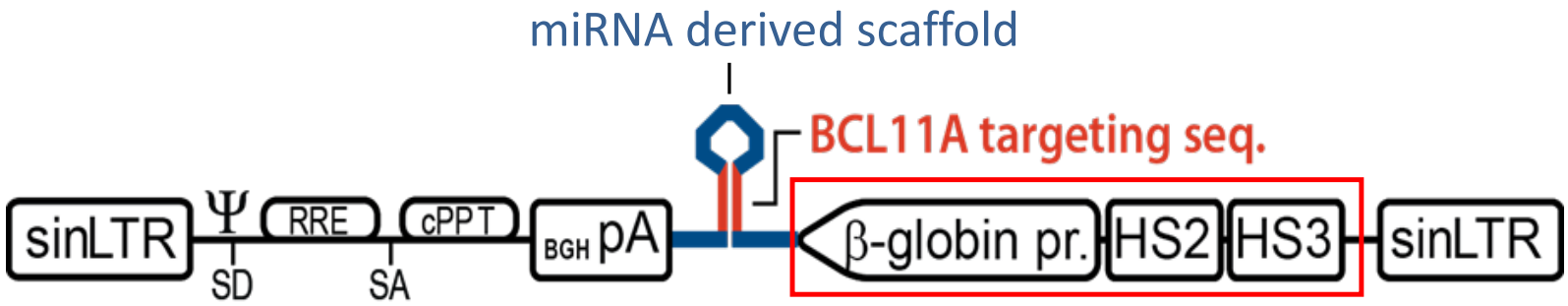
# Boston Children's Hospital study: Inactivate BCL11A→ increase HbF

The gene BCL11A is a regulator of HbF




"Genetic payload" in this trial is a genetic structure called an shRNA that targets BCL11A.

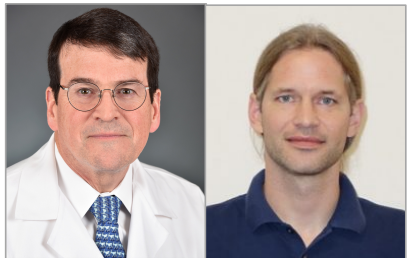
# Development of lentiviral vector shmiR targeting BCL11A




**shmiR vector** = BCL11A targeting sequence embedded in microRNA derived scaffold

- Delivers a more **physiologic** "payload", resembling an endogenous microRNA
- Allows for regulated **erythroid expression:** avoids toxicity in HSCs and B cells

**HSC** = hematopoietic stem cell

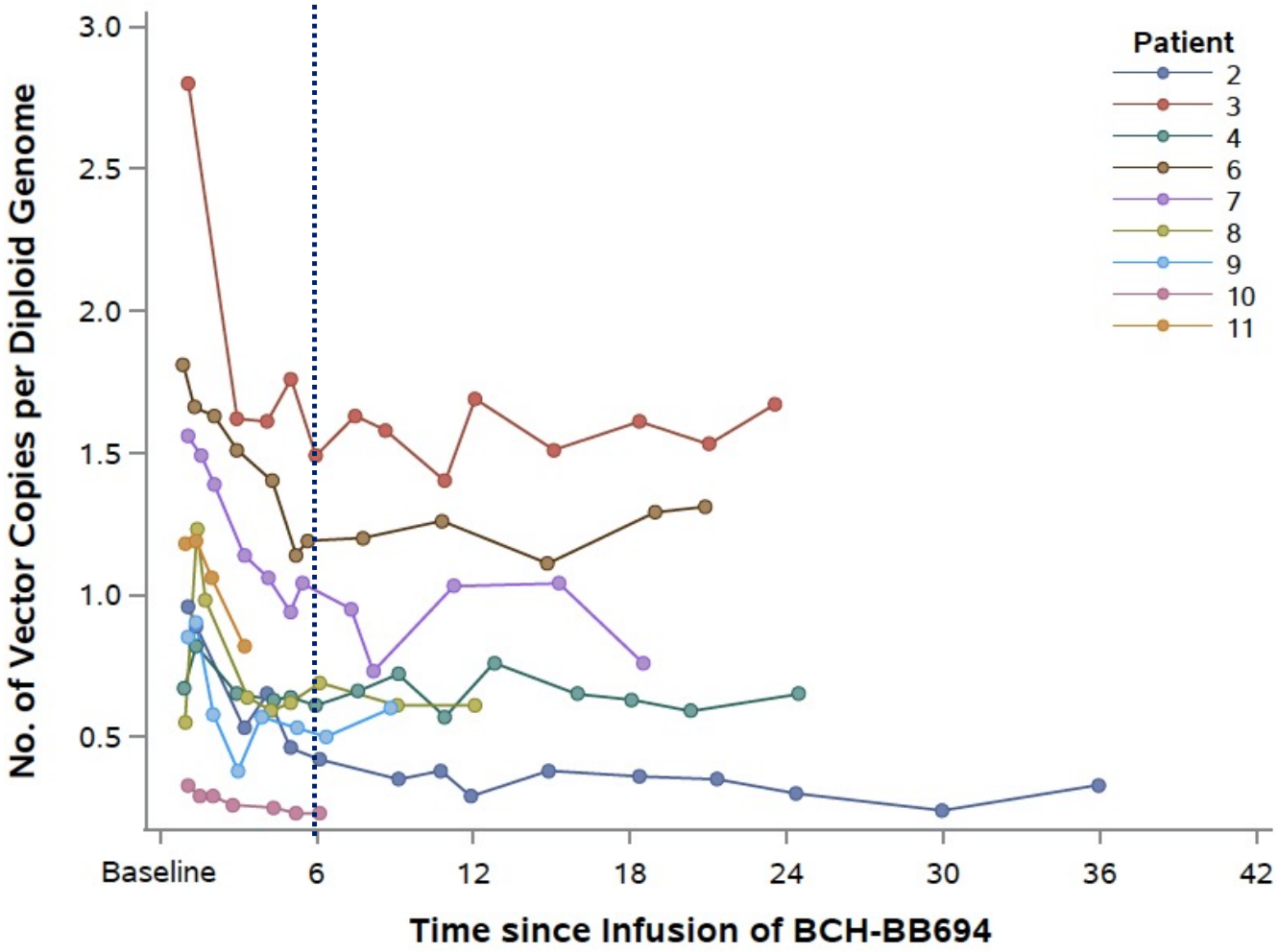


Guda et al. *Mol Ther* 2015; Brendel et al. *JCI*, 2016
Brendel et al. *Methods & Clinical Development*, 2020

# Boston Children's Sickle Cell Gene Therapy Trial

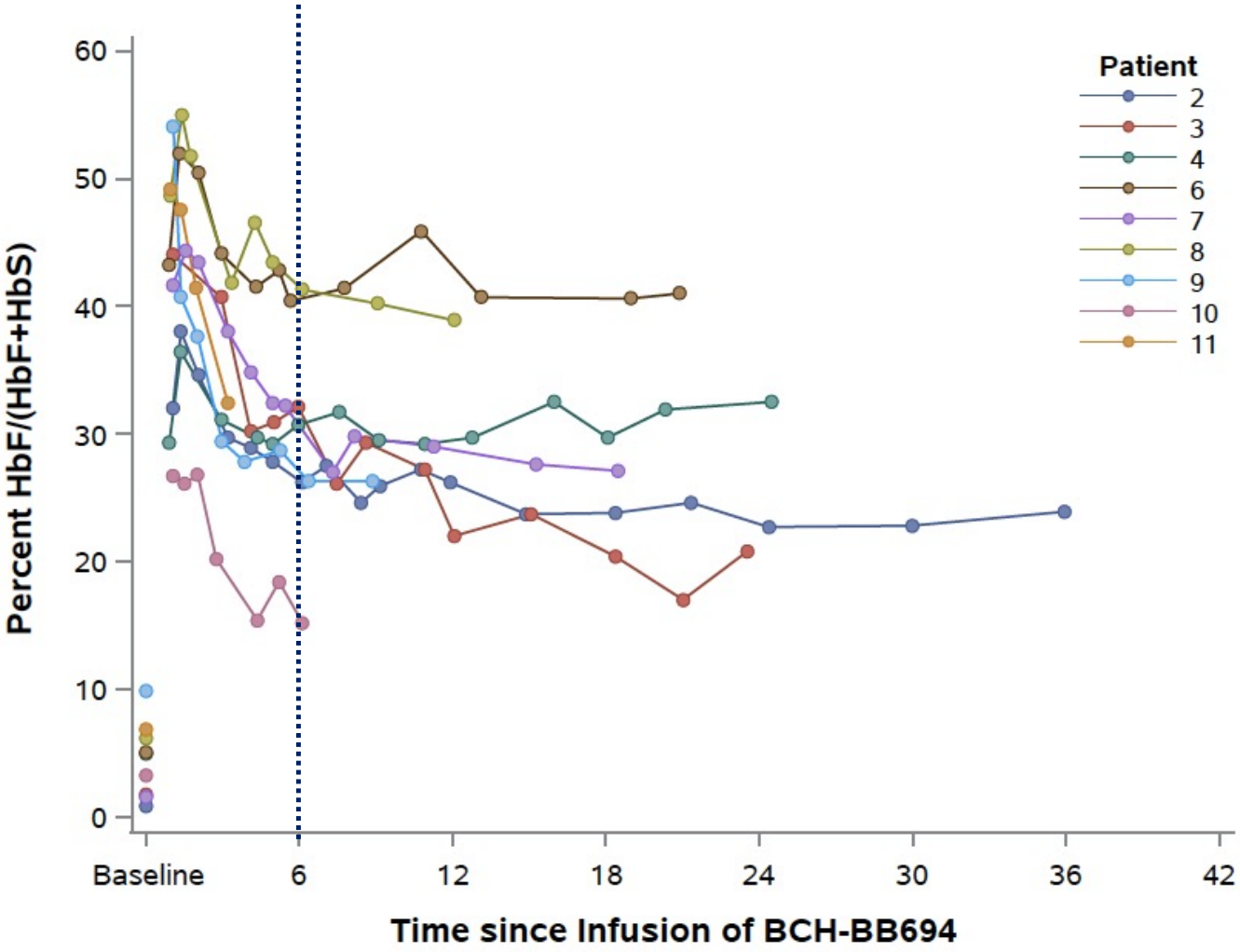
- 9 patients treated
  - Age at enrollment: 7 – 26 years
  - Sex: 5 males, 4 females
  - Genotype: HbSS (8) and HbS/$\beta^0$ (1)
- Follow-up: 8 – 40 months since gene therapy
- Cell product details (median, min-max)
  - Cell dose: 5.2 (3.3 - 8.3) x $10^6$/kg CD34+ cells
  - Vector copy number (VCN): 3.3 (1.8 – 6.9) copies per cell

# Vector copy number (VCN)



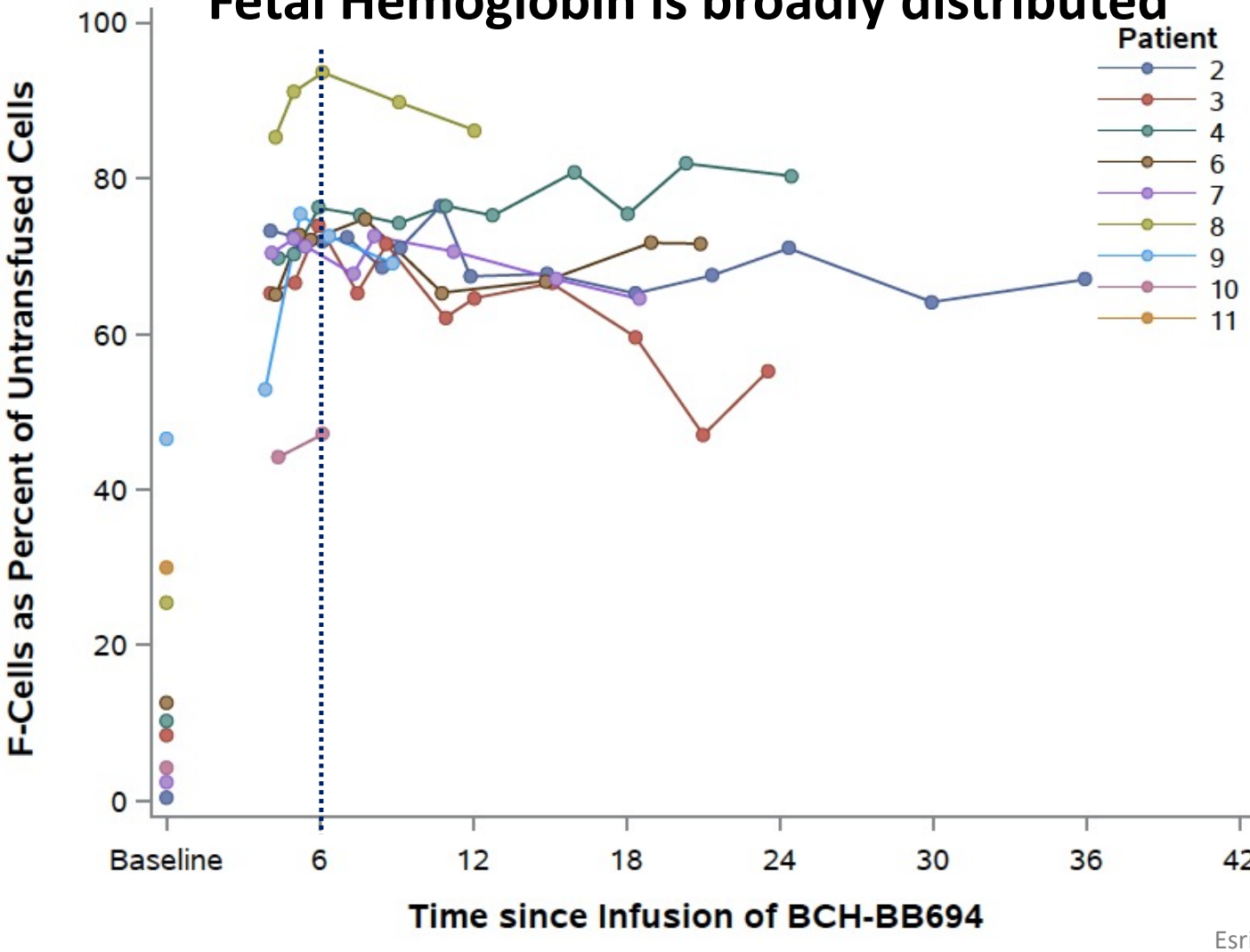

Esrick et al, *NEJM* 2020 + updates

# Induction of Fetal Hemoglobin



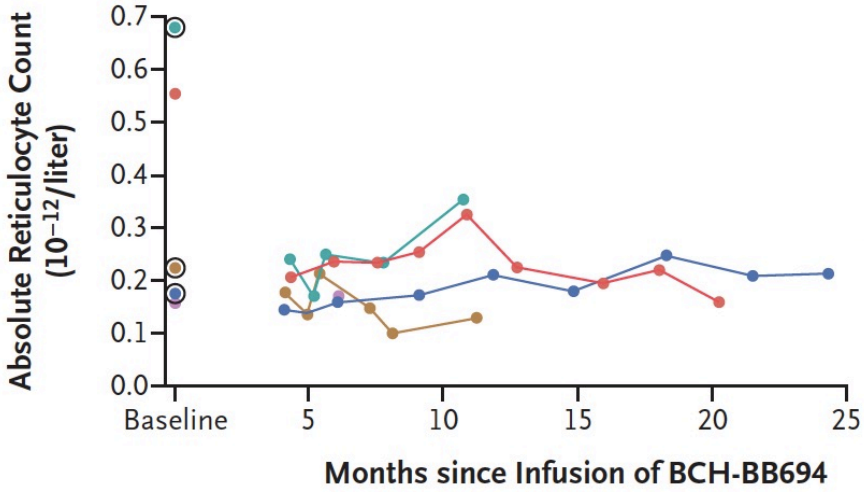

Esrick et al, *NEJM* 2020 + updates

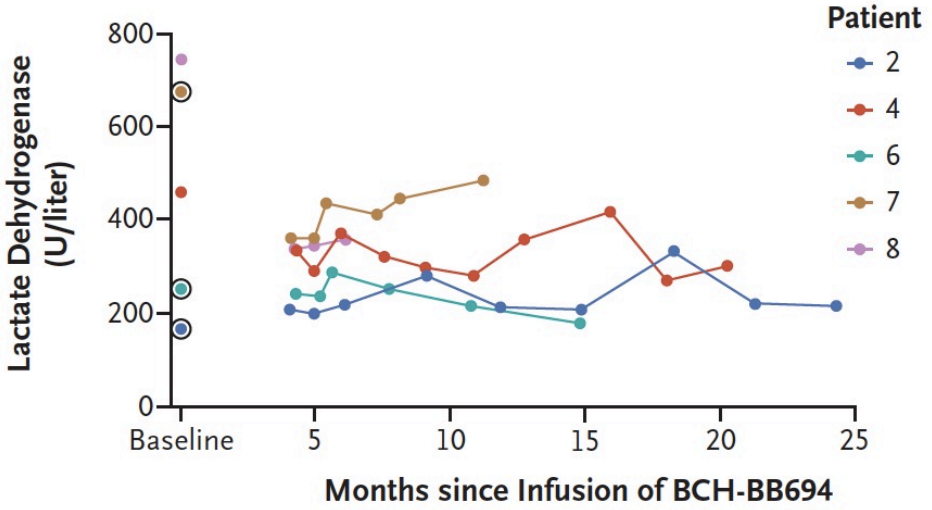
# Fetal Hemoglobin is broadly distributed




Esrick et al, *NEJM* 2020 + updates

# Markers of Hemolysis




Esrick et al, *NEJM* 2020

# Safety data

| Subject | Neutrophil engraftment* (Days) | Platelet engraftment# (Days) | Non-lab ≥ Gr 3 AEs during transplant admission | Serious AEs post-infusion |
|---|---|---|---|---|
| BCL-002 | 22 | 31 | Nausea | |
| BCL-003 | 22 | 26 | Febrile neutropenia | |
| BCL-004 | 22 | 25 | Mucositis | - Influenza<br>- Priapism episodes[1] |
| BCL-006 | 26 | 27 | Nausea, vomiting, mucositis, febrile neutropenia | - Non-sickle ankle pain |
| BCL-007 | 22 | 62 | Mucositis, febrile neutropenia | |
| BCL-008 | 16 | 52 | Nausea, mucositis, febrile neutropenia, ileus, parainfluenza / hypoxia, T1DM | - Type 1 diabetes |
| BCL-010 | 24 | 27 | Nausea, mucositis, febrile neutropenia | - VOC admissions x 3[2] |
| BCL-009 | 30 | 41 | Mucositis, nausea, anorexia, CVL infection, febrile neutropenia | - VOC/ACS x 1, now improved |
| BCL-011 | 21 | 33 | Febrile neutropenia | |

*Absolute neutrophil count [ANC] ≥ 500 cells/µL for 3 consecutive days. #Unsupported platelet count ≥ 50,000/µL

[1]Has received priapism-directed meds, no admissions since 8 mo post-GT. [2]No admissions since 8 mo post-GT; started on voxelotor by hematologist.

- Pre-infusion: Grade 3+ AEs were CVL-related (thrombus, infection, pneumothorax).
- No grade 3+ AEs associated related to mobilization or collection procedures.
- No adverse events associated with medicinal product; no clonal dominance on insertional site analysis.

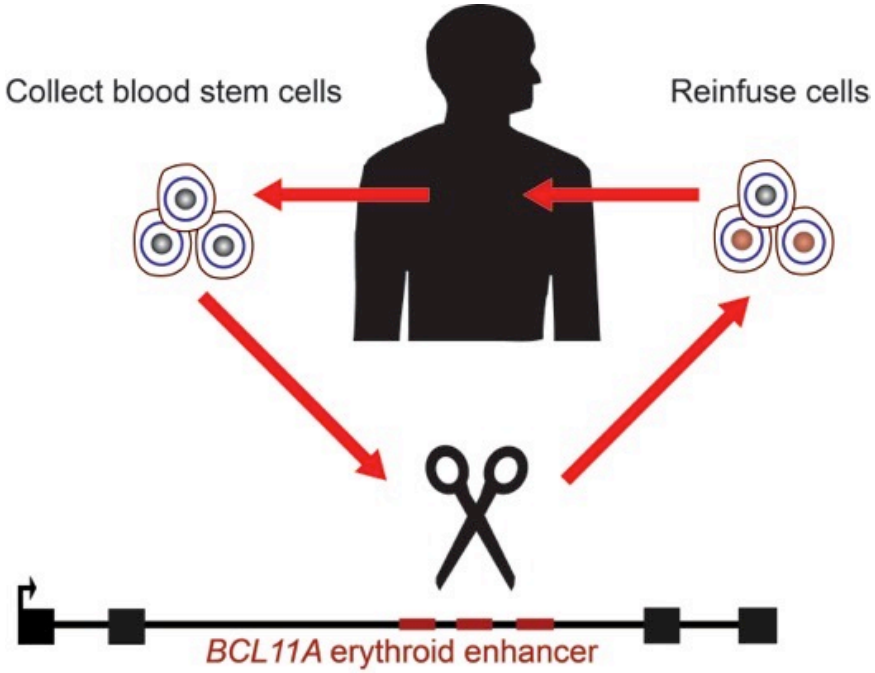
**AE** = adverse event ; **CVL** = central venous line

# Clinical sickle phenotype

- VOC pain:  7 with no pain, 1 with mild pain, 1 with severe pain
- Acute chest syndrome:  1 episode (in patient w/ underlying lung disease)
- No neurologic or other events
- Priapism post-GT in 1 subject:  improved but recurred intermittently, no ED/hospitalization after 8 months
- Anemia:  Clear improvement in most; ongoing hemolysis

**VOC** = vaso-occlusive crisis; **GT** = gene therapy

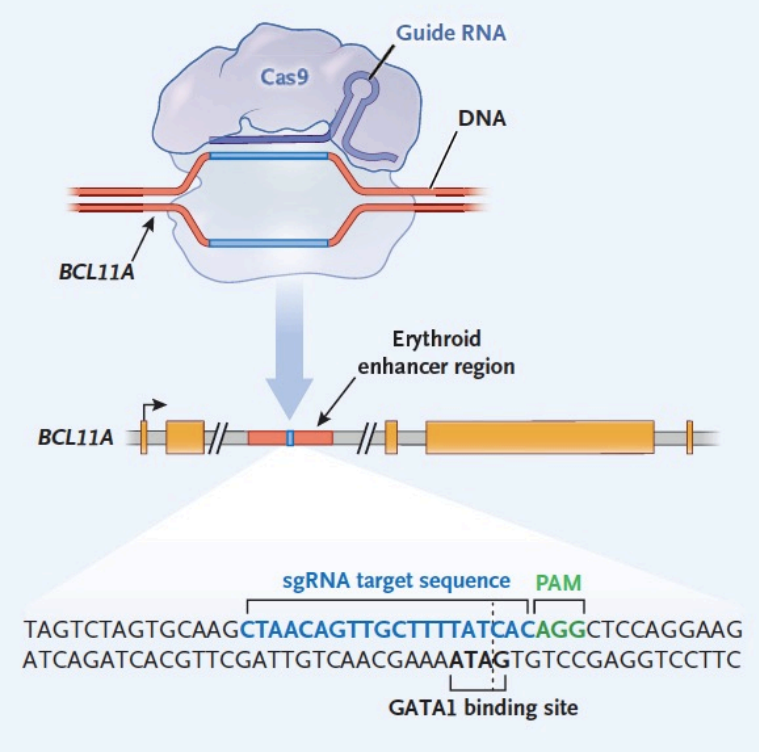
# Therapeutic genome editing of the *BCL11A* erythroid enhancer

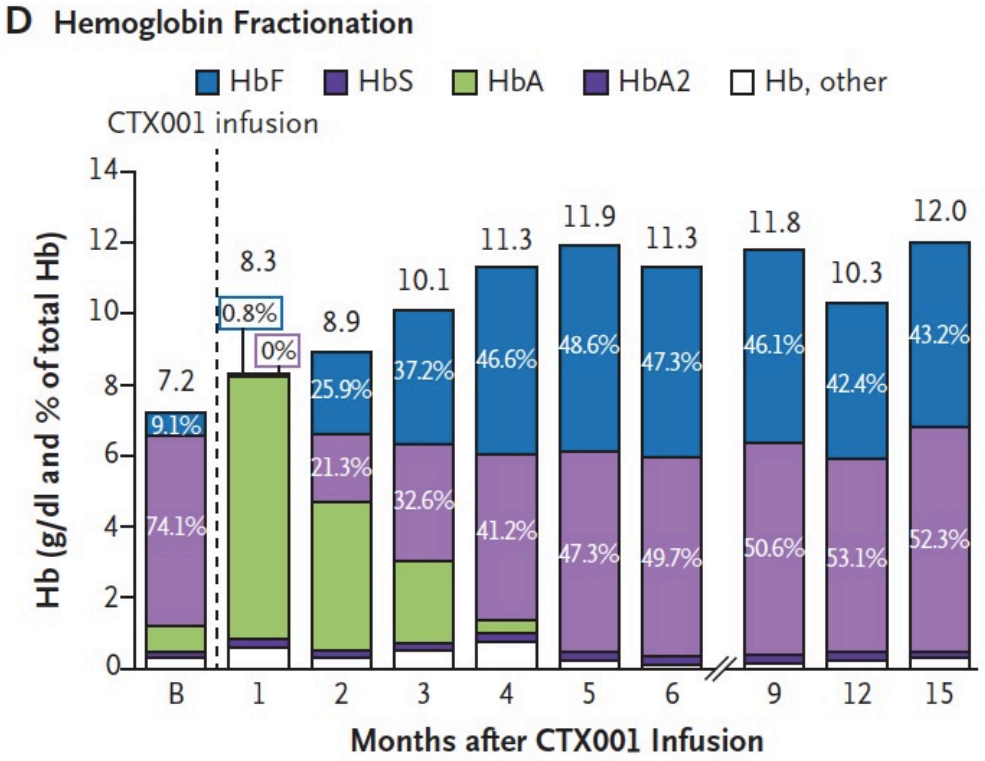


# Sickle cell disease gene editing: active clinical trials

| Product | Sponsor | NCT | Sites | Patient ages | Patients treated |
|---|---|---|---|---|---|
| OTQ923 or HIX763 Targeting BCL11A | Novartis | NCT 04443907 | Memphis | 2-40 | ? |
| CTX001 Targeting erythroid enhancer of BCL11A | Vertex / CRISPR Therapeutics | NCT 03745287 | CA, Chicago, NYC, Philly, Tenn, TX, Toronto, Europe | 12-35 | 2 |
| BIVV003 Targeting erythroid enhancer of BCL11A | Sanofi / Bioverativ | NCT 03653247 | CA, Atlanta, NIH, Detroit | 18-40 | ? |

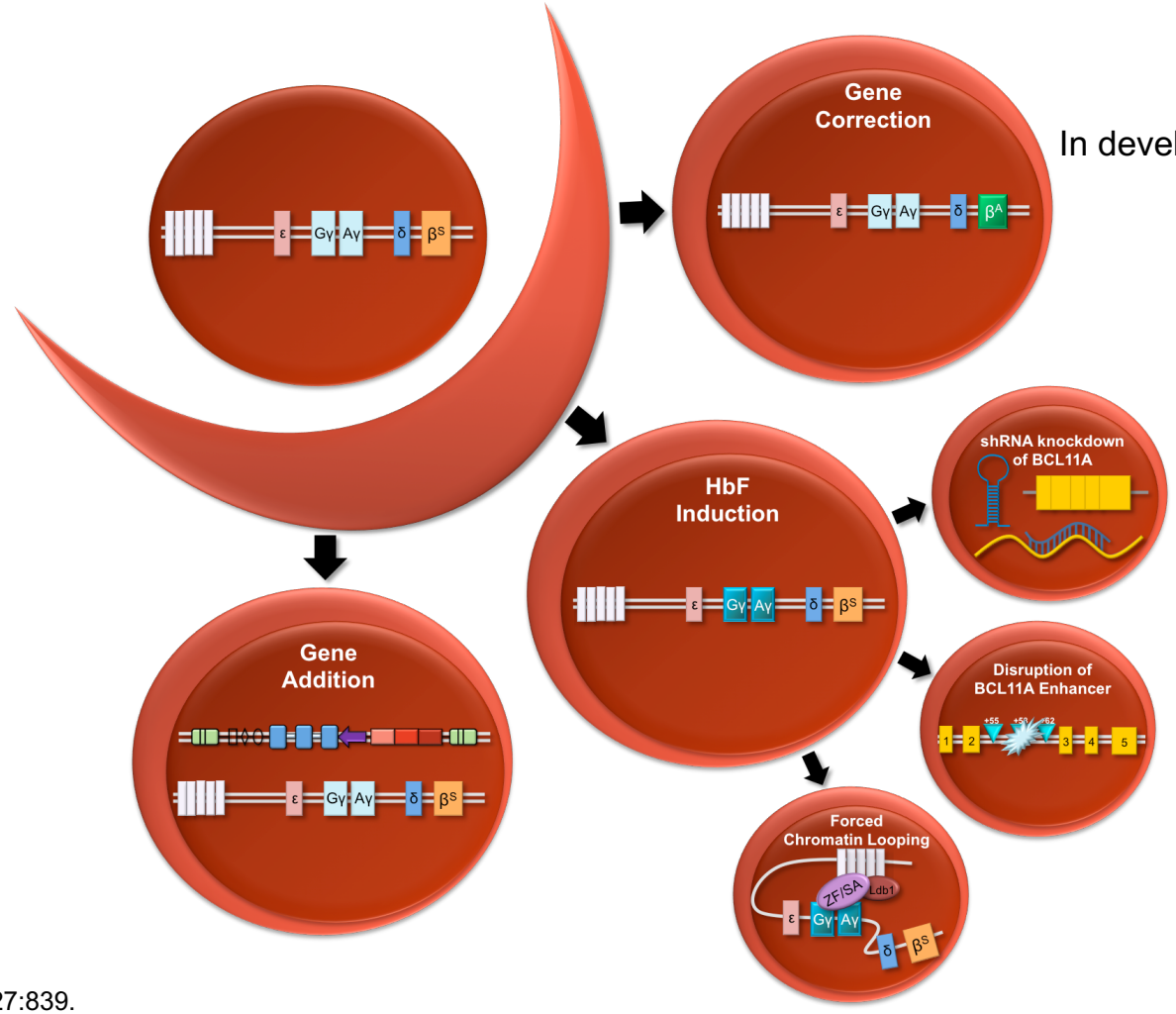
# CRISPR-Cas9 Gene Editing: First published data = CTX001




Frangoul et al, *NEJM* 2021

# Autologous gene therapy approaches for β-hemoglobinopathies




Hoban *et al.* Blood (2016) 127:839.

# Unexpected safety event in LentiGlobin trial

**bluebird bio Announces Temporary Suspension on Phase 1/2 and Phase 3 Studies of LentiGlobin Gene Therapy for Sickle Cell Disease (bb1111)**

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Feb. 16, 2021-- **bluebird bio, Inc.** (Nasdaq: BLUE) announced today that the company has placed its Phase 1/2 (HGB-206) and Phase 3 (HGB-210) studies of LentiGlobin gene therapy for sickle cell disease (SCD) (bb1111) on a temporary suspension due to a reported Suspected Unexpected Serious Adverse Reaction (SUSAR) of acute myeloid leukemia (AML).

- BCH trial remains on hold by NIH
- What was the cause of these cases?
- Are SCD patients at higher risk for myeloid malignancy?
- Are there ways to mitigate risk of malignancy?

# Proposed amendments based on leukemia cases

- Add screening for existing MDS features and exclude eligibility if present (morphology, FISH, cytogenetics)
- Add molecular screening (Rapid Heme Panel = RHP) for pathogenic mutations in genes associated with heme malignancies
- Add longitudinal screening for MDS and genetic alterations
  - Bone marrow at 6 and 24 months;  RHP every 6 months
- Add expert genomics/leukemia review

# Future considerations

- Continual evaluation of safety and efficacy
- Expansion of educational materials for patients and referring providers
- Expanded focus on mental health and psychological support
  - Before, during, and after gene therapy / gene editing
- Long-term follow-up:
  - Clinical care (distinct from post allo transplant): patients return to sickle cell programs
  - Research: harmonize endpoints between trials

# Patients/Families: How to learn more

- Discuss with your hematologist
- HLA typing of siblings
- Consultation with Stem Cell Transplant team
- **www.clinicaltrials.gov**

Thank you!
Questions?