Re-creating Hereditary Persistence of Fetal Hemoglobin (HPFH) With CRISPR/Cas9 To Treat Sickle Cell Disease (SCD) And Beta-thalassemia (β-thal)

Transformative
Gene-based Medicines

for Serious Diseases

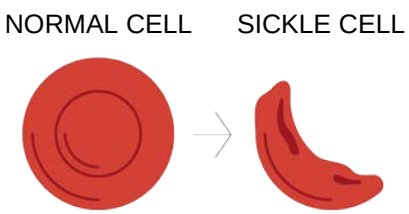
Forward Looking Statements

This document and the accompanying oral presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to statements concerning the timing of our preclinical studies and the intellectual property protection of our technology. All statements, other than statements of historical facts, contained in this document, including statements regarding the Company's strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, and objectives of management, are forward-looking statements. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "target," "should," "would," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. The Company may not actually achieve the plans, intentions, or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various factors, including: uncertainties inherent in the initiation and completion of preclinical studies for the Company's product candidates; availability and timing of results from preclinical studies; whether results from a preclinical trial will be predictive of future results of the future trials; expectations for regulatory approvals to conduct trials or to market products; uncertainties regarding the intellectual property protection for our technology; and other factors discussed in the "Risk Factors" section of the Company's most recent quarterly report on form 10-Q, which is on file with the Securities and Exchange Commission, and in other filings that the Company may make with the Securities and Exchange Commission in the future.

In addition, the forward-looking statements included in this document represent the Company's views as of the date of this document. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date of this document.

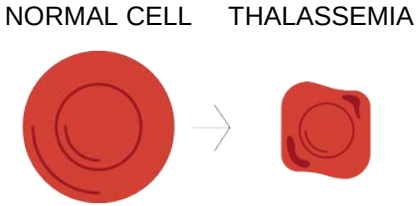
Sickle Cell Disease and β-thalassemia

SICKLE CELL DISEASE



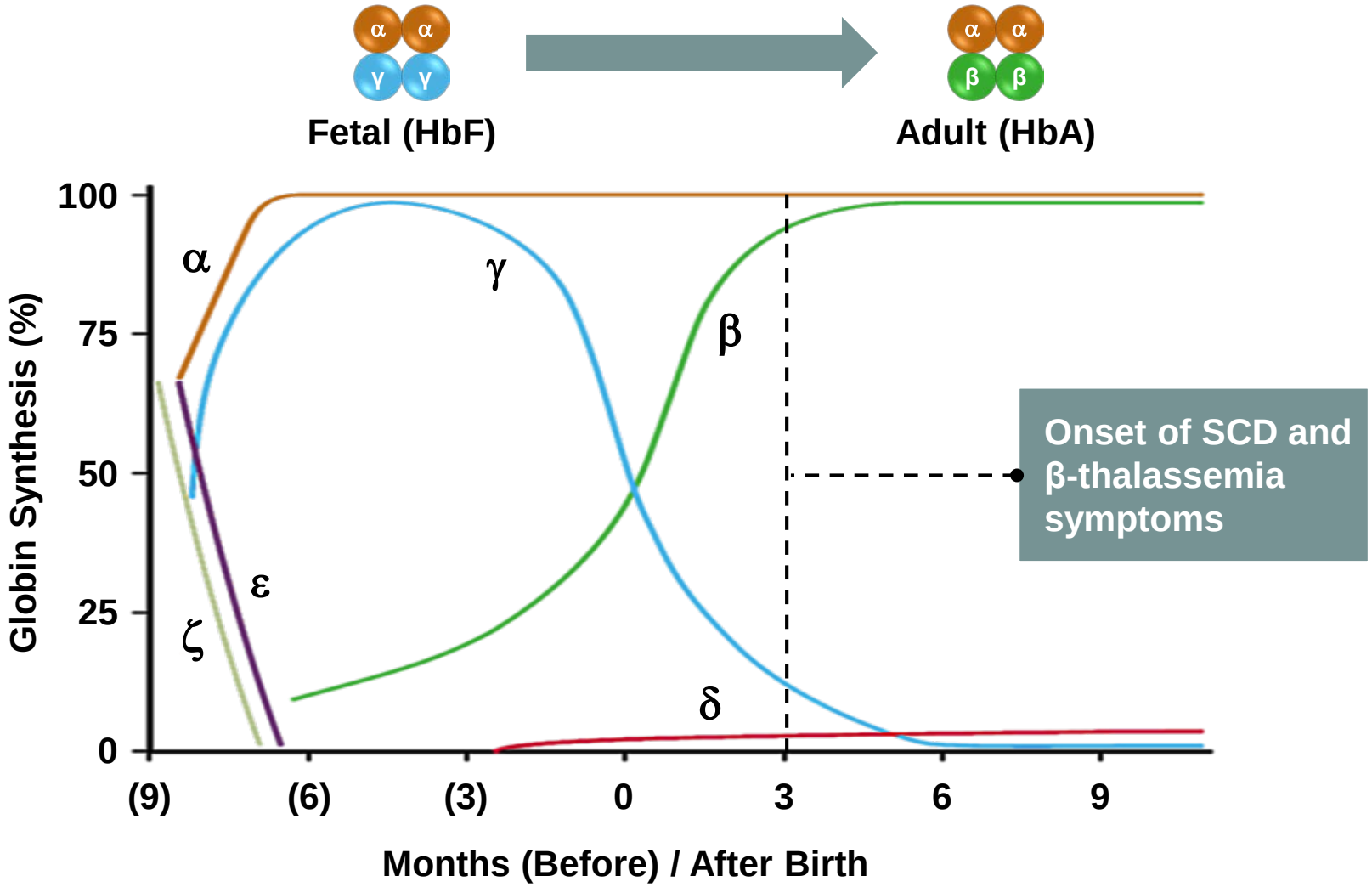
- Significant worldwide burden (300,000 births annually)
- Caused by a single DNA base pair mutation
- Devastating morbidity & mortality (anemia, pain, early death)
- High burden of patient care (sickle cell crises, chronic morbidity)

β-THALASSEMIA



- Significant worldwide burden (60,000 births annually)
- Caused by a variety of different genetic mutations
- Severe cases have debilitating symptoms (anemia, heart failure)
- High burden of patient care (frequent transfusions, allo-HSCT)

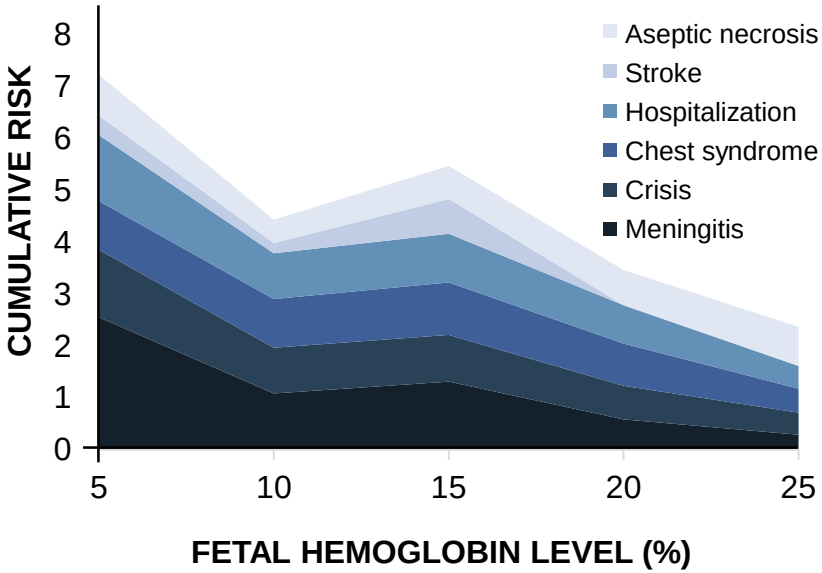
At Birth Hemoglobin Switches from Fetal to Adult



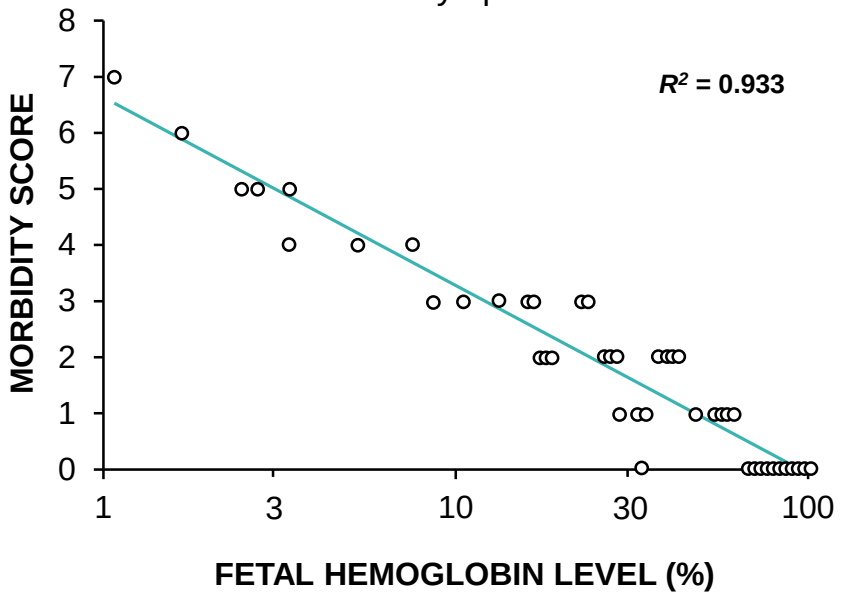
Modified from Canver & Orkin, Blood 2016

Fetal Hemoglobin Alleviates Symptoms

SICKLE CELL DISEASE
reduced risk of events[1]



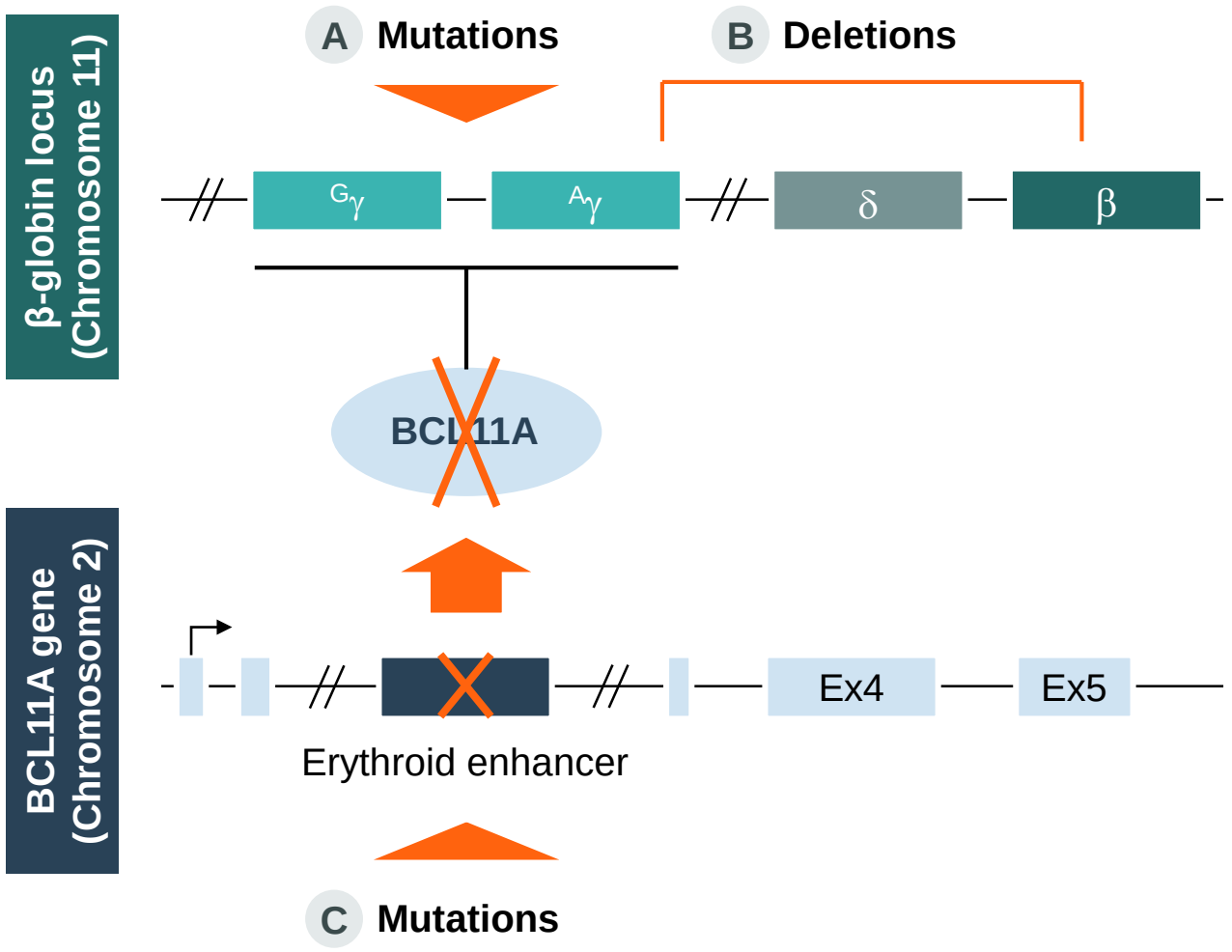
β-THALASSEMIA
reduced symptoms[2]



- Genetic variants occur naturally causing hereditary persistence of fetal hemoglobin (HPFH), and lead to reduced symptoms in patients with sickle cell disease and β-thalassemia
- Our gene editing strategy aims to recreate these variants in symptomatic patients — an approach supported by well-understood genetics

[1] Powars et al., Blood 1984; [2] Musallam et al., Blood 2012

Genetic Variants are Associated with Elevated HbF

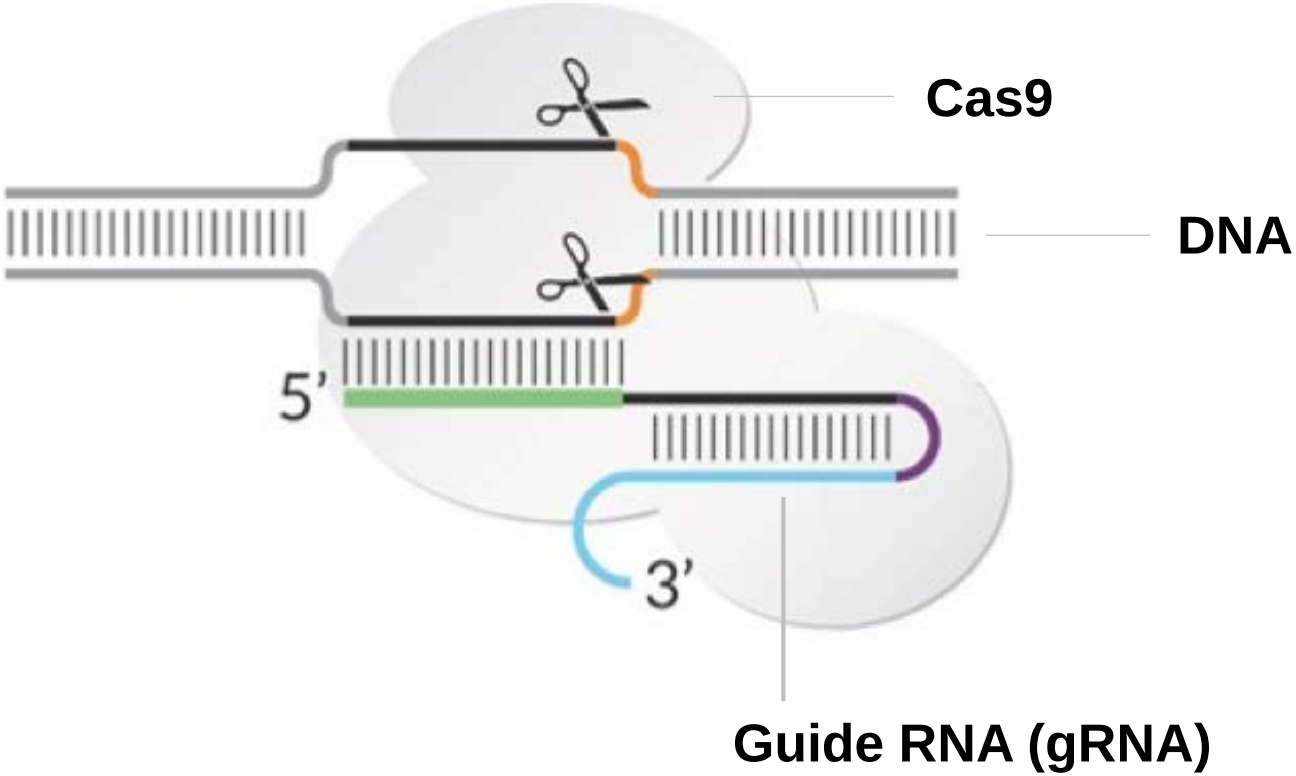


Variants associated with elevated HbF

- **A** Mutations in γ-globin regulatory regions
- **B** Partial deletions of the globin locus
- **C** Single nucleotide variants in the BCL11A erythroid enhancer region

Our approach is to mimic these variants using CRISPR/Cas9

CRISPR/Cas9 Gene Editing Mechanism

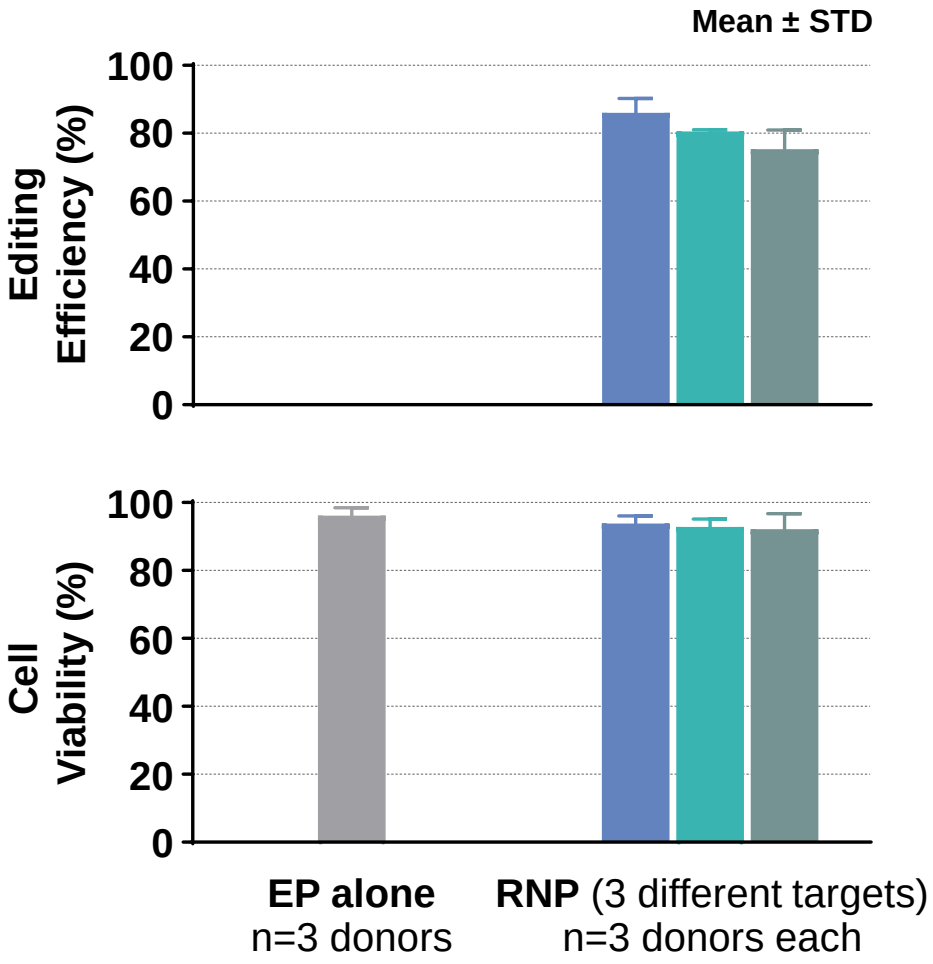


High Editing Efficiency and Cell Viability with Cas9 RNP

Multiple CRISPR/Cas9 delivery parameters were tested:

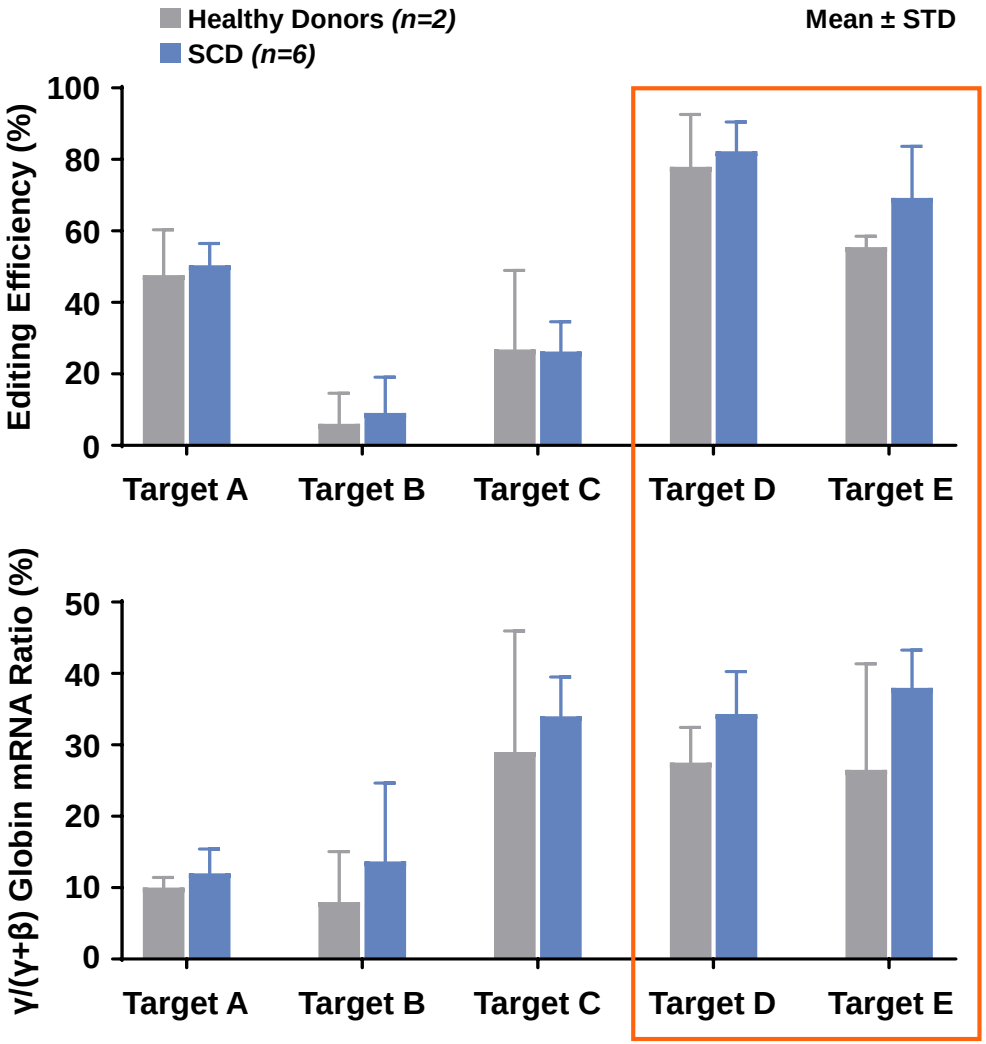
- Cas9 ribonucleoprotein (RNP) vs. mRNA delivery
- gRNA backbone sequences and chemical modifications
- Nuclear localization sequences
- Synthesis and purification methods
- Multiple different CMO vendors

Chosen format yields high editing rate and viability in human CD34+ cells



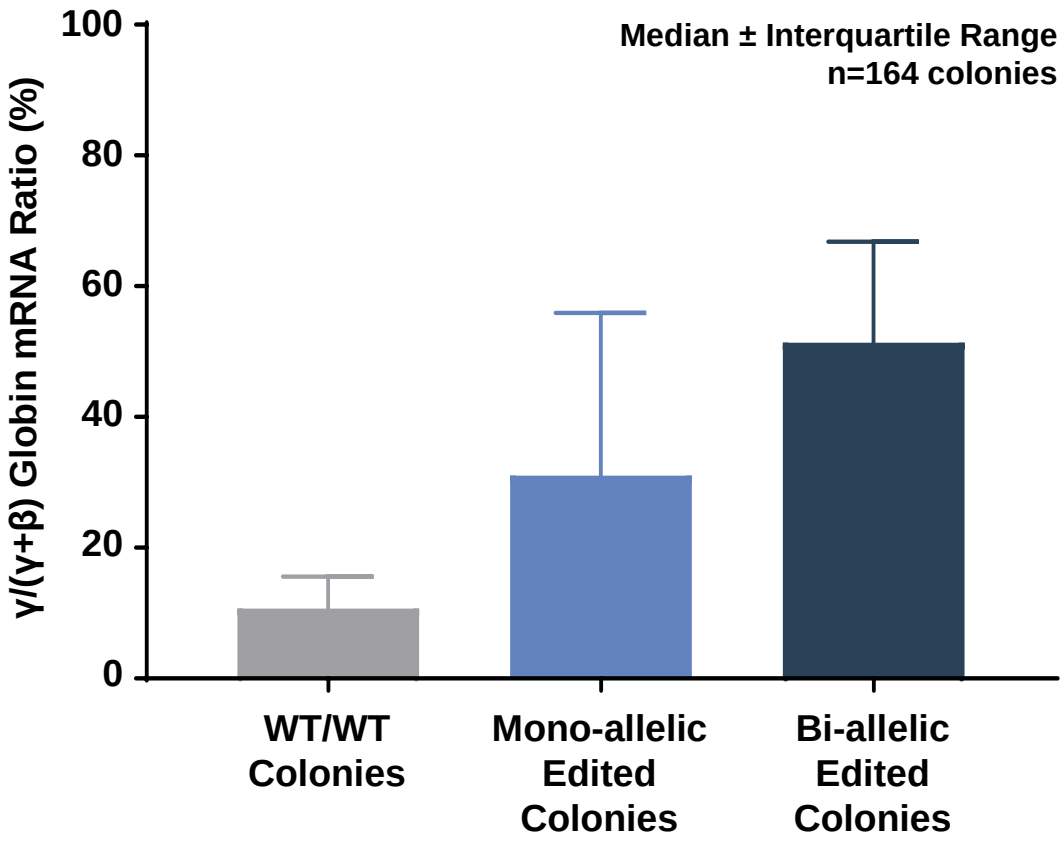
CRISPR/Cas9 Can Re-Create HPFH Variants in Human Cells

High γ-globin expression upon erythroid differentiation



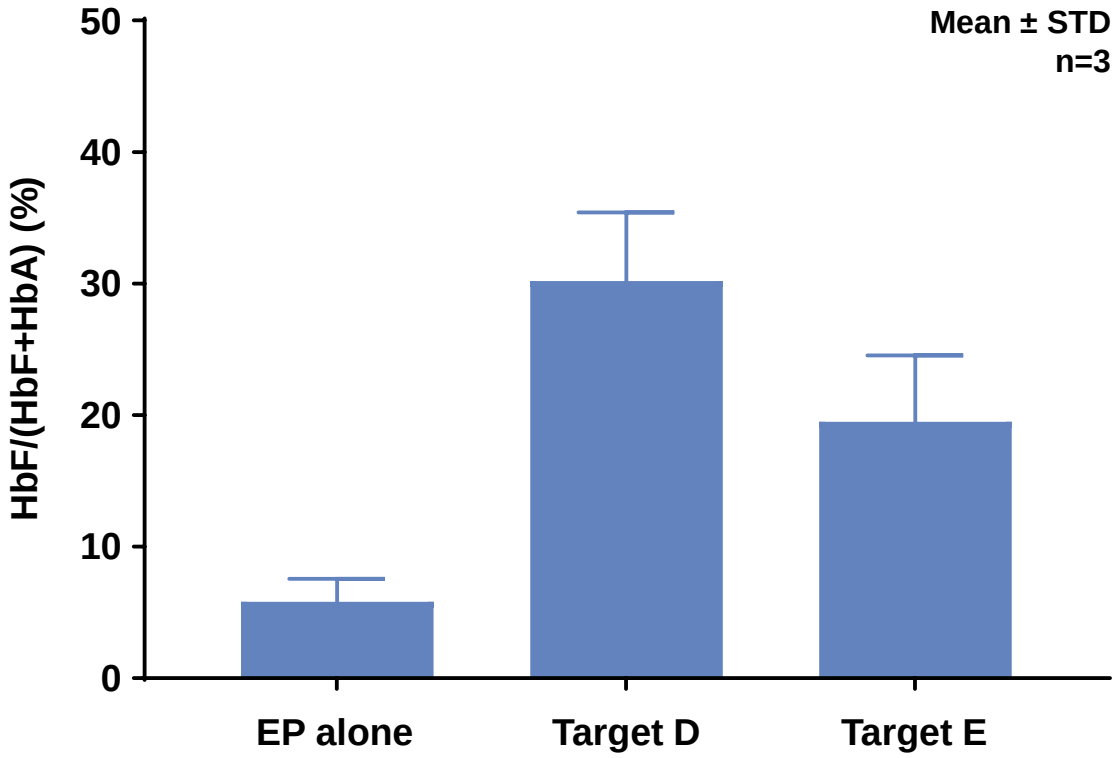
Editing Genotype Correlates with γ-Globin Expression

Target E example – healthy donor cells

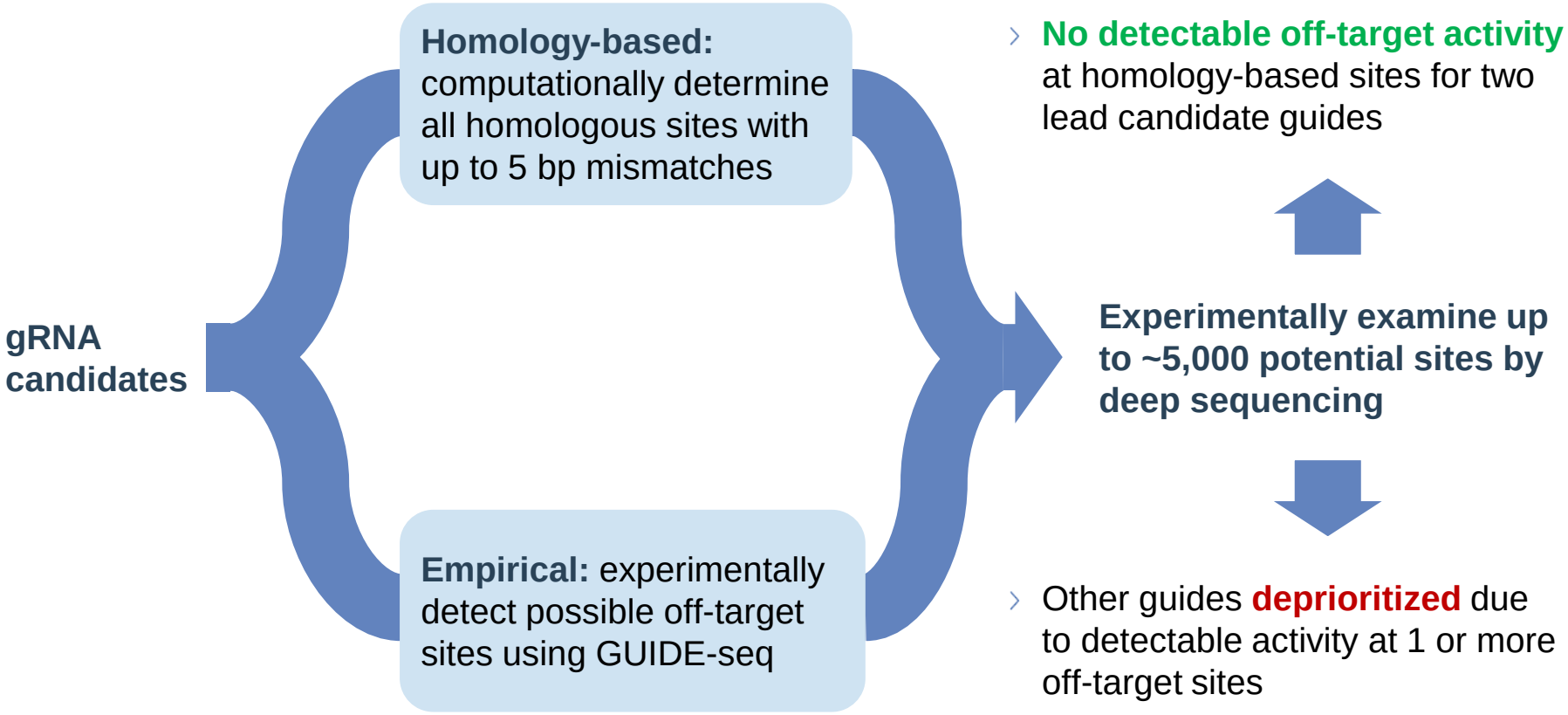


Re-Creating HPFH Increases HbF Protein Level

HbF protein as % of total hemoglobin – healthy donor cells



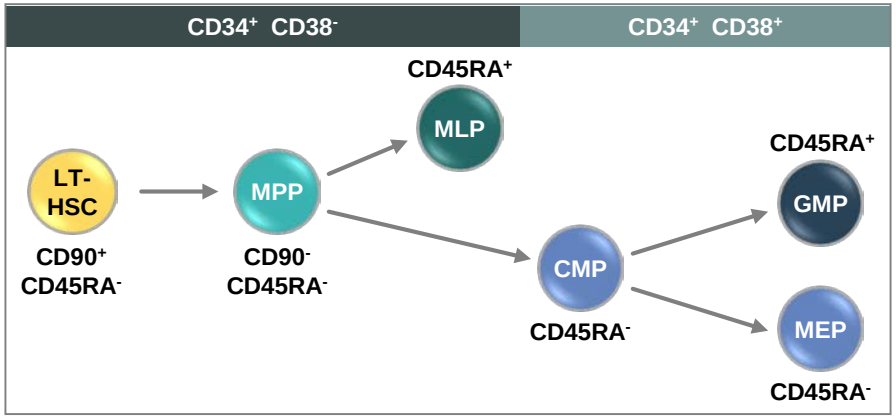
Extensive Testing Reveals No Off-Target for Lead Guides



Efficient Editing Occurs in Long-Term Stem Cells

Target E example – healthy donor cells

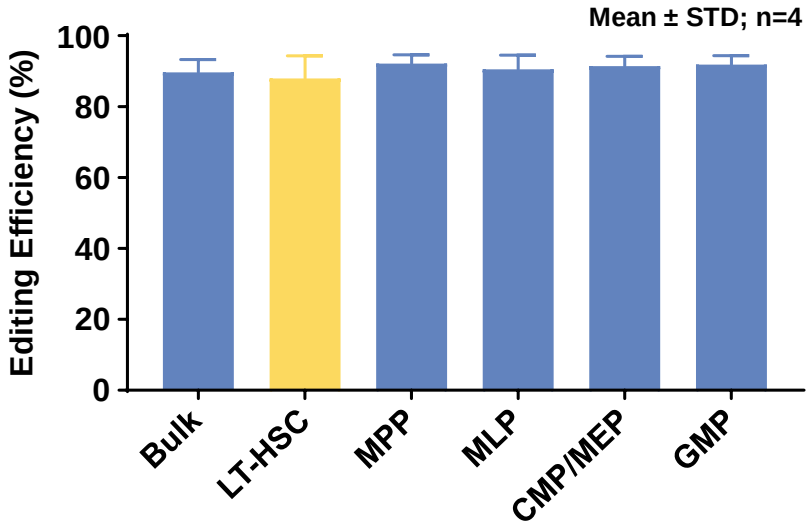
LT-HSC differentiate into numerous cell types



Editing does not affect the prevalence of LT-HSCs

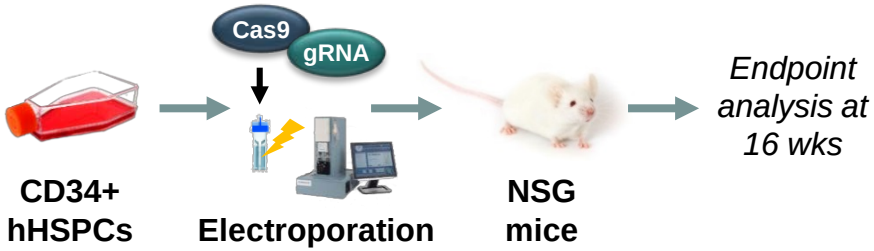
Population	Frequency	
	Mock	*Edited*
Bulk	94.83	94.30
LT-HSC	7.82	7.98
MPP	18.97	16.38
MLP	13.23	8.47
CMP/MEP	11.23	11.32
GMP	8.39	13.26

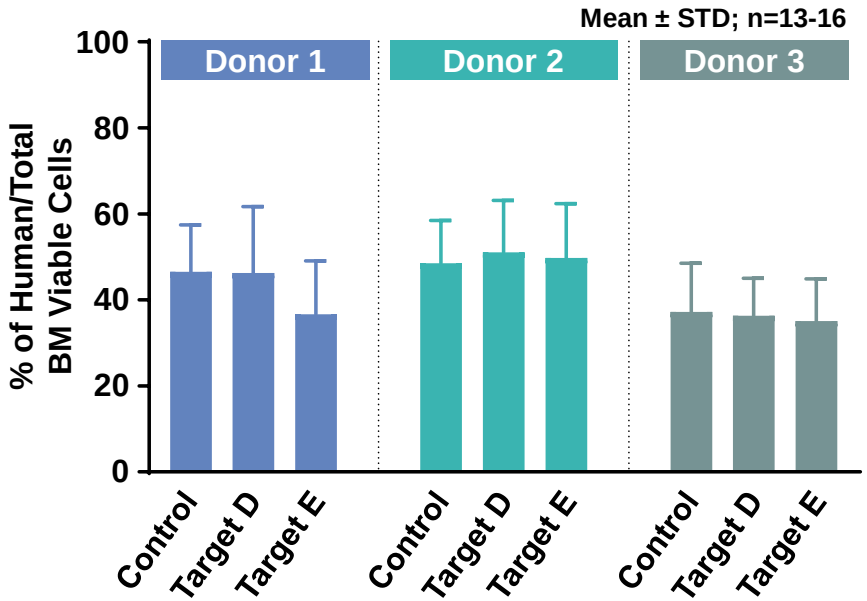
High editing in all cell types including LT-HSC



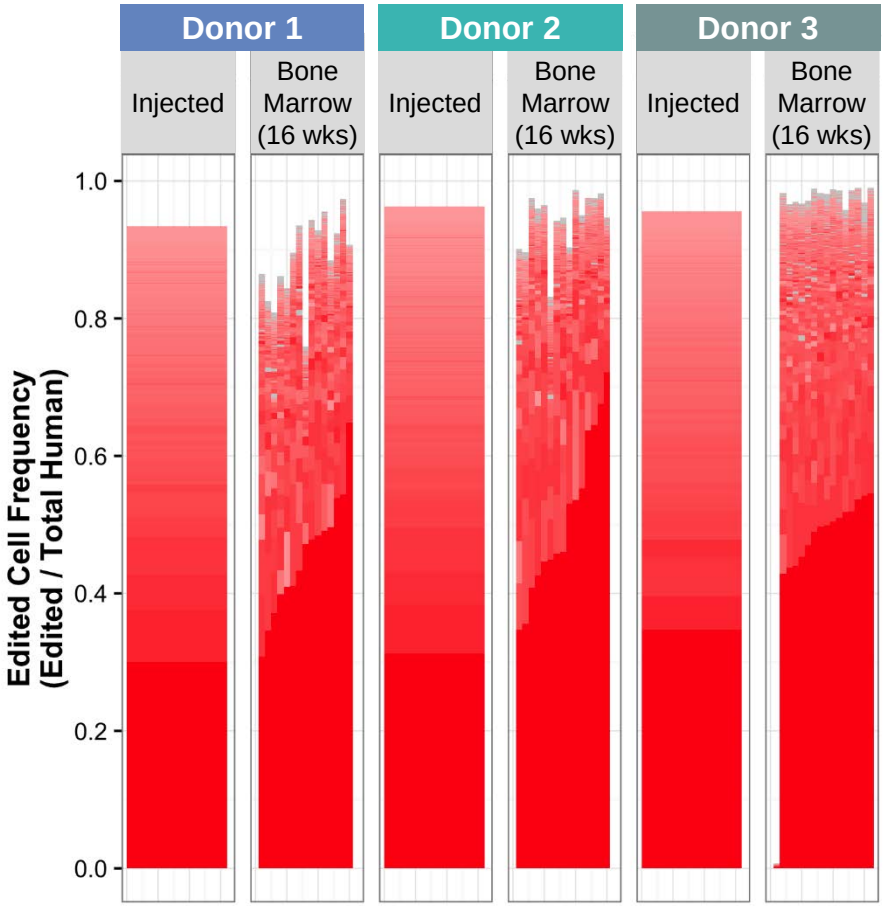
High Editing Efficiency Persists *In Vivo*

Editing of human blood stem cells does not affect engraftment in a mouse



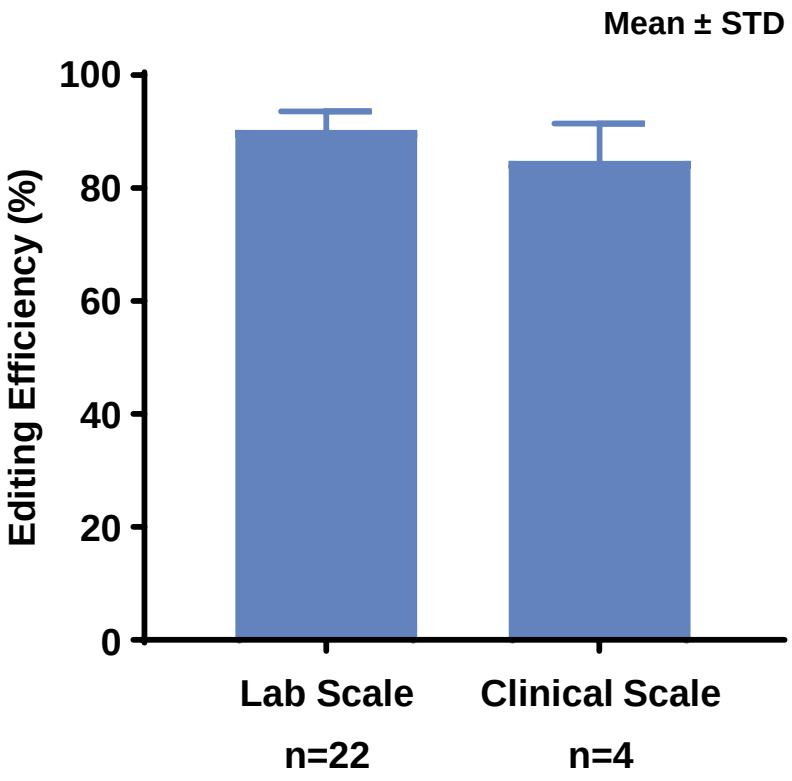


Editing efficiency maintained 16 weeks after engraftment – *Target E example*

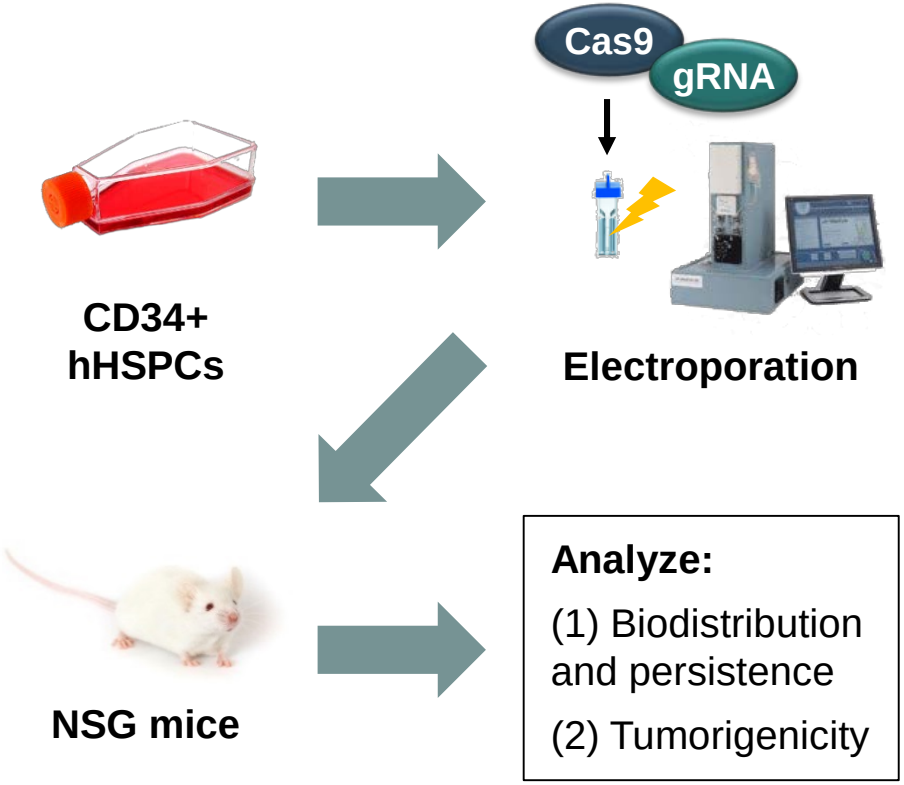


Progressing Toward Clinical Studies

Successful transition to GMP facility



IND/CTA-enabling studies are underway



Conclusions

- We have **re-created naturally occurring HPFH genetic variants with high efficiency** in human blood stem cells
- Editing of healthy donor, β-thalassemia, and sickle cells results in **clinically relevant increases in the γ-globin** component of protective HbF
- **No detectable off-target modifications** seen by targeted deep sequencing for the two lead guides
- Edited blood stem cells **engraft and reconstitute long-term hematopoiesis** in the NSG model
- We have established a highly effective CRISPR/Cas9 editing **process at clinical scale** at a GMP compliant contract manufacturing facility
- We have **GLP toxicology studies ongoing** to support a Clinical Trial Application in 2017 to start clinical testing next year

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