EDIT-301: AN AUTOLOGOUS CELL THERAPY TO PROMOTE FETAL HEMOGLOBIN EXPRESSION FOR THE POTENTIAL TREATMENT OF SICKLE CELL DISEASE

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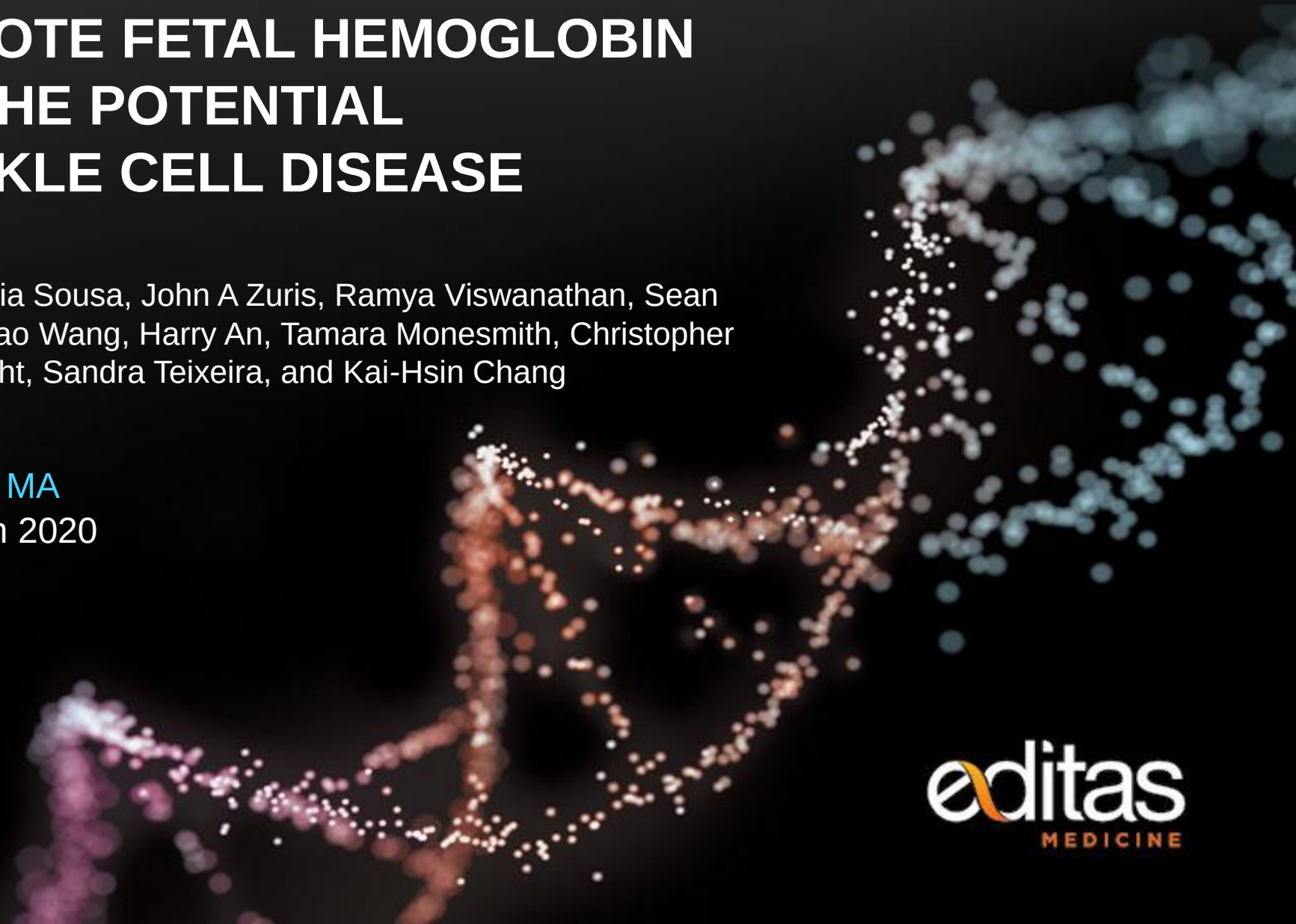
Editas Medicine, Inc., Cambridge, MA

European Hematology Association 2020



Disclosures

Jack Heath is a full-time employee and shareholder in Editas Medicine

Overview

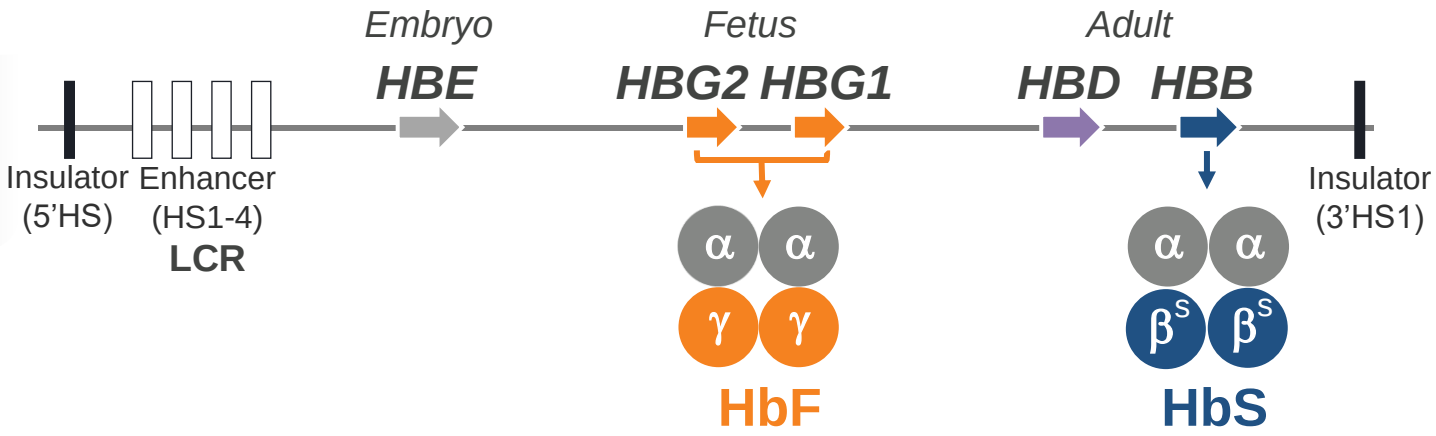
Inducing Anti-Sickling Fetal Hemoglobin to Treat Sickle Cell Disease

Desirable Editing with Cas12a at the *HBG1/2* Promoter in a Region Where Fetal Hemoglobin Inducing Mutations Naturally Occur

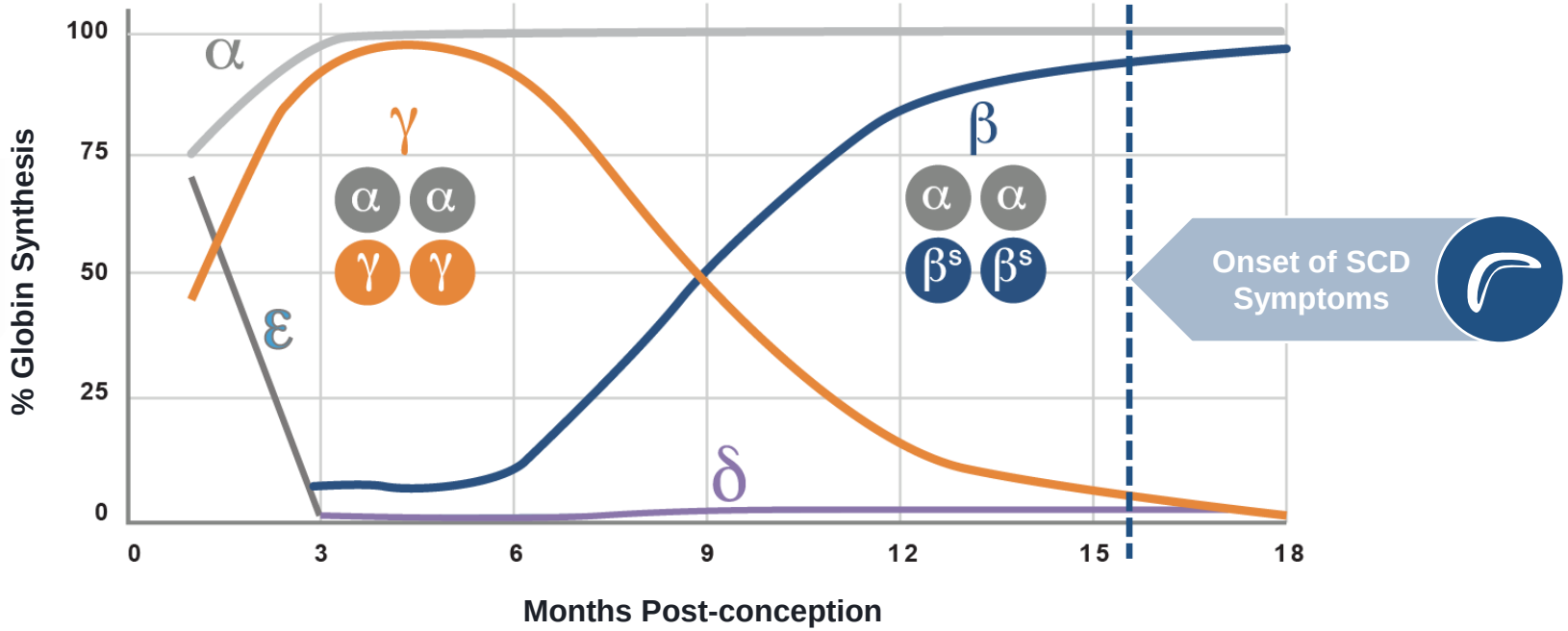
Highly Efficient, Productive and Durable Editing and an Improved Phenotype in Edited Sickle Patient Red Blood Cells

Harnessing Natural Anti-Sickling Hemoglobin to Treat Sickle Cell Disease

β-globin locus



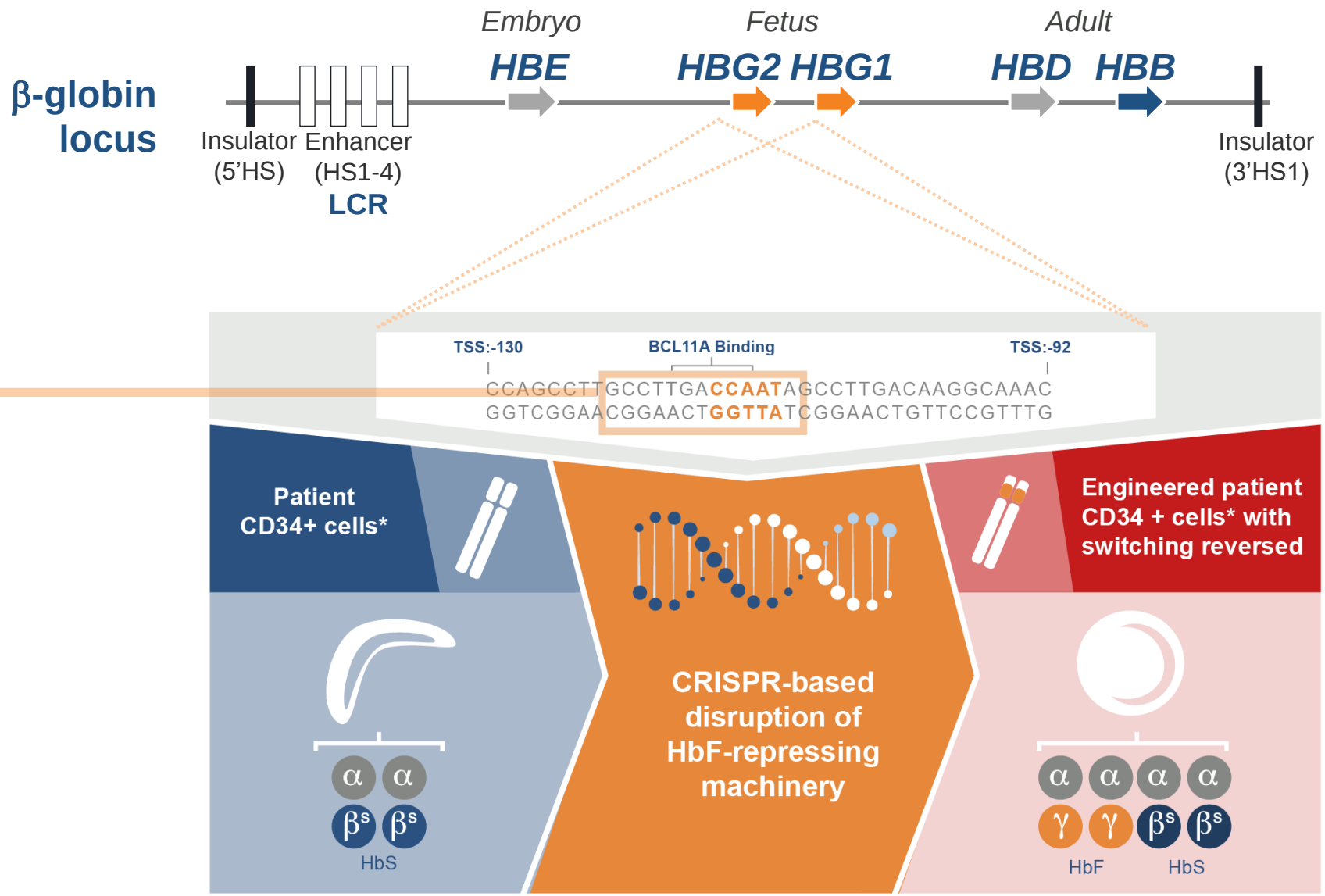
Globin switch



Adapted from Canver and Orkin, *Blood*, 2016.

Naturally Occurring Mutations Support Clinical Relevance and Safety of Editing at the *HBG1/2* Promoter Region

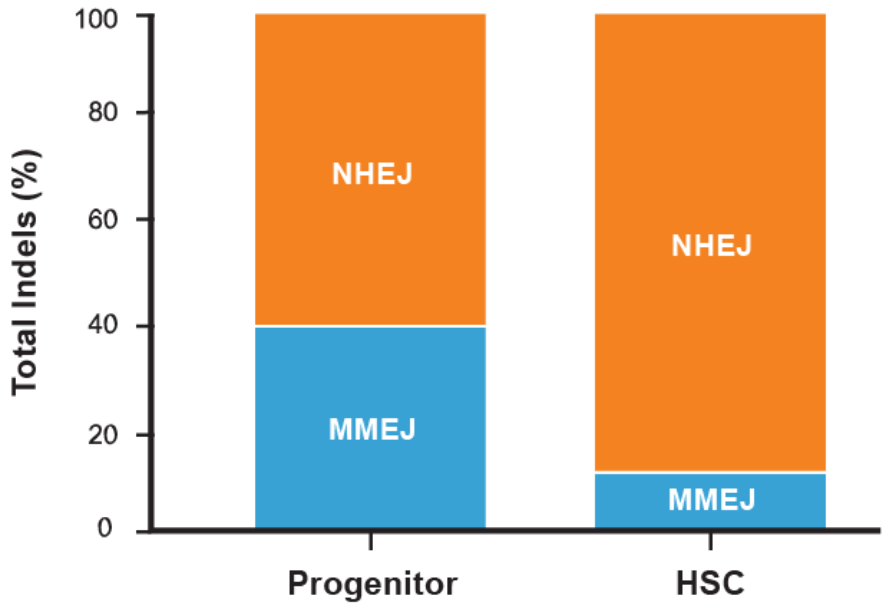
Multiple Naturally Occurring HbF Inducing Mutations located in *HBG* Distal CCAAT Box



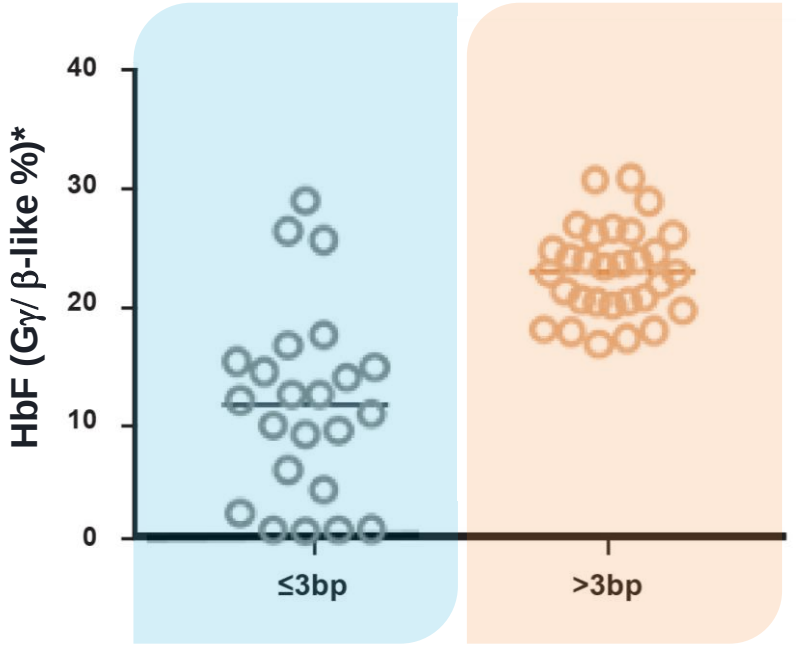
*CD34+ hematopoietic stem and progenitor cells (HSPCs)

Large NHEJ Deletions at *HBG* Distal CCAAT Box Region Are Durable and Induce High Levels of HbF

Long-Term HSCs Rely Heavily on NHEJ-mediated Editing



Larger Deletions are More Productive

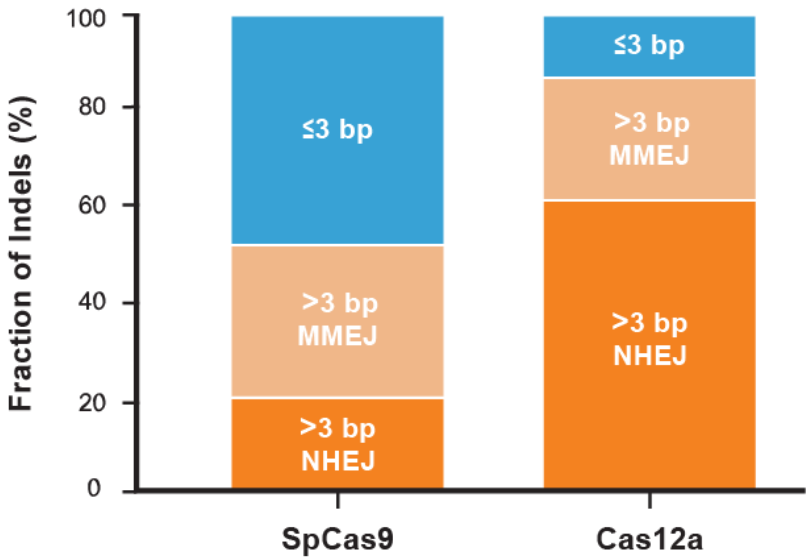


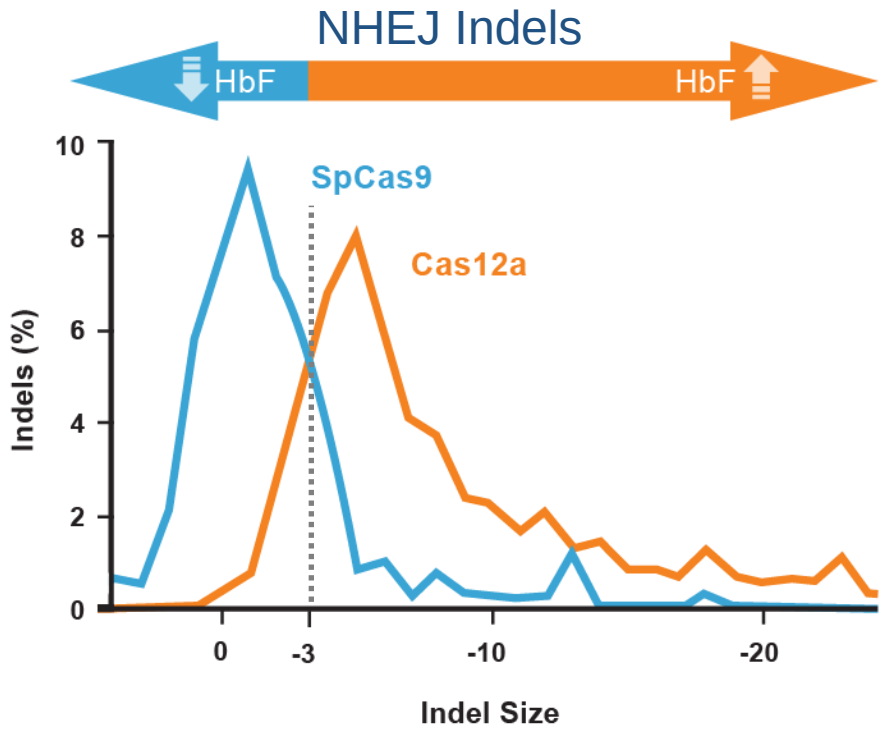
> 3bp NHEJ deletions induce long-term, robust HbF expression

* Only showing levels of Gγ chain which represents the gene product of *HBG2*

Cas12a Demonstrates a Superior Editing Profile to SpCas9 at *HBG* Distal CCAAT Box Region for Persistent and High HbF Expression

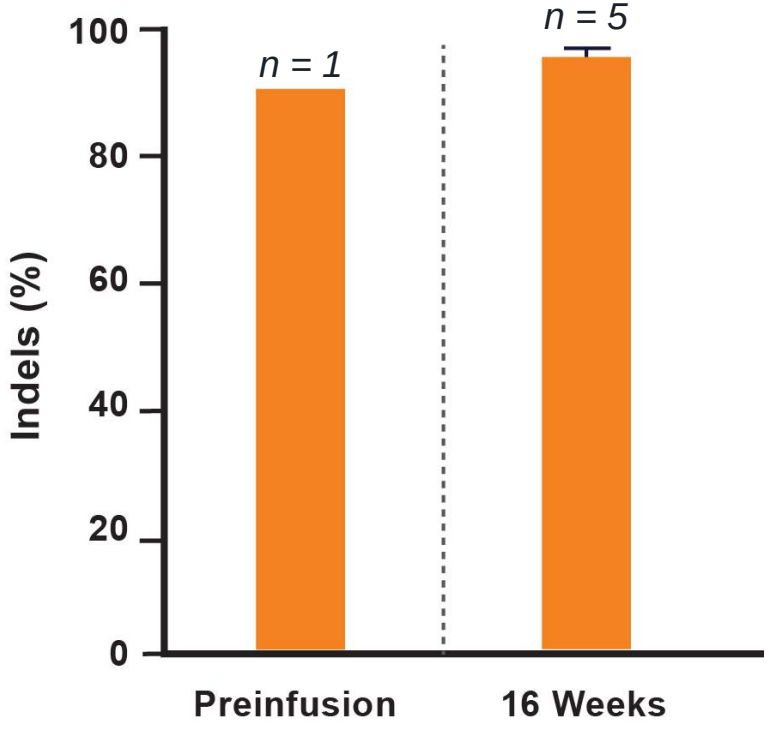
Enzyme Cleavage Sites





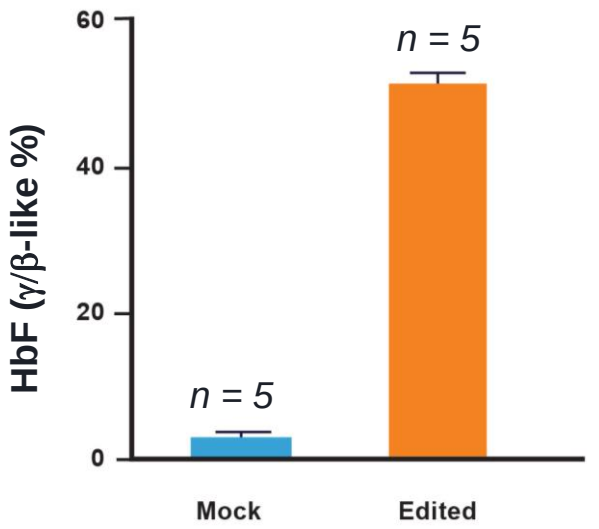
Cas12a Editing is Efficient and Results in Long-Term Robust and Pancellular HbF Expression *In Vivo*

Editing

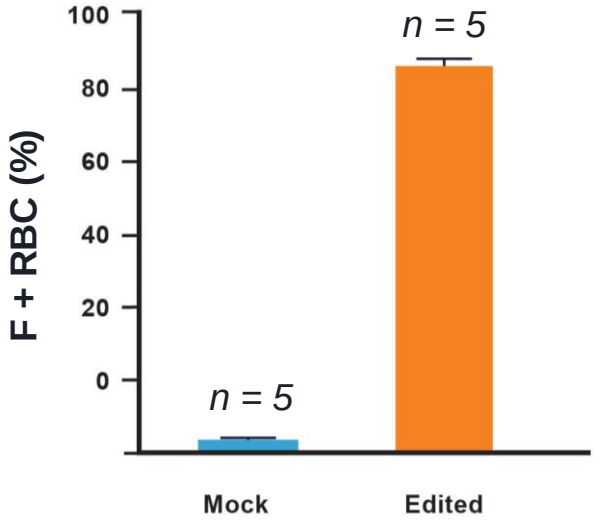


Data from one representative experiment

In vivo HbF Expression

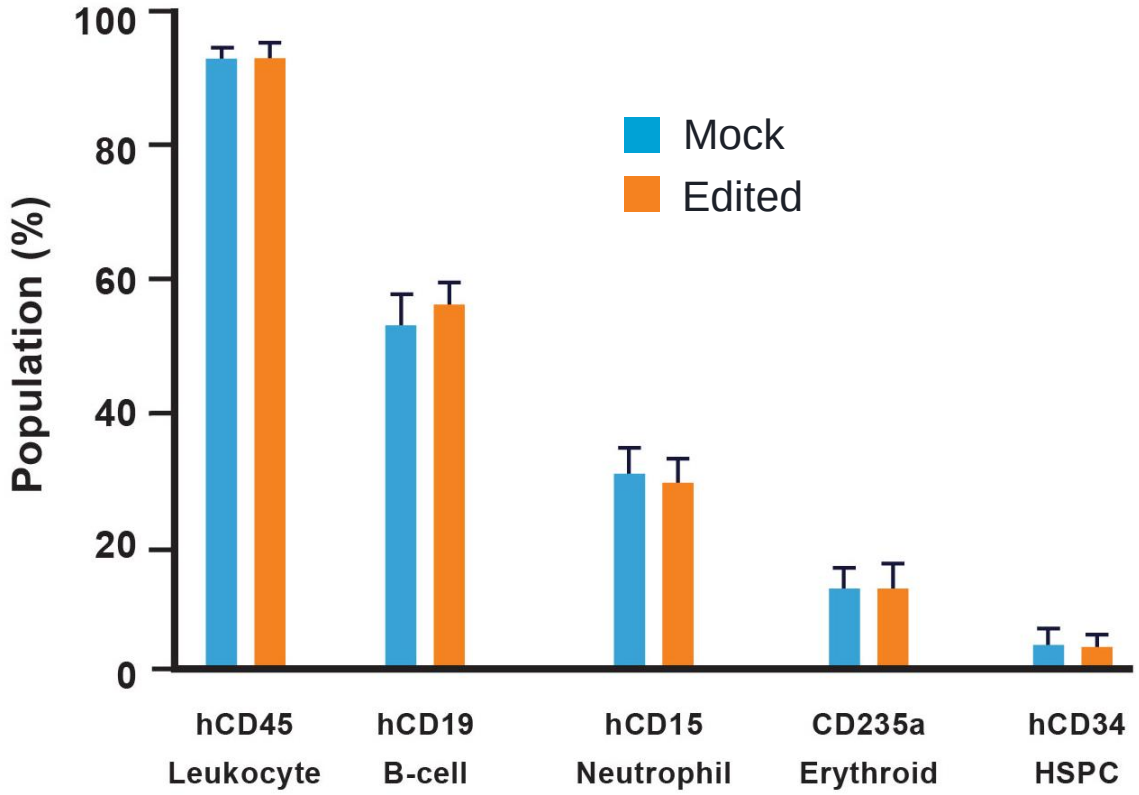


In vivo HbF-positive RBCs (F-cells)



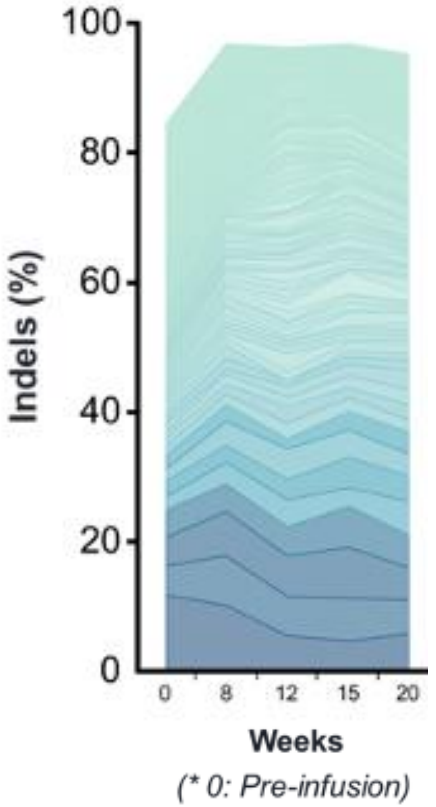
Cas12a Edited CD34+ Hematopoietic Stem Cells Provide Stable, Polyclonal Engraftment with No Lineage Skewing

Engraftment

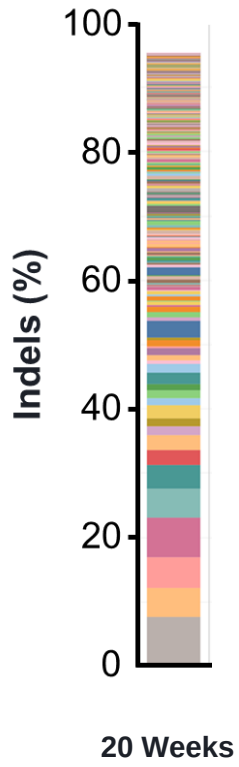


16 weeks post infusion. n = 5 mice / group

Blood



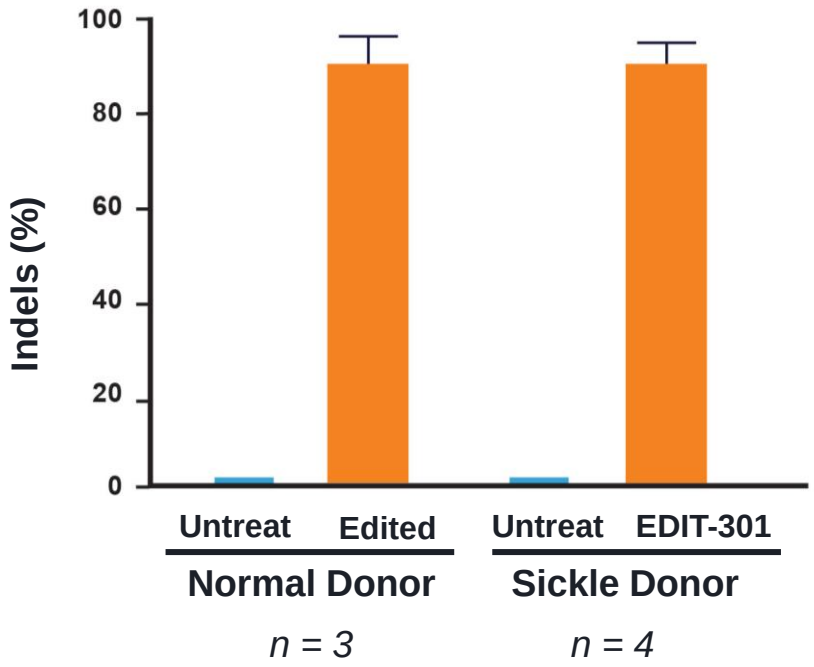
Bone Marrow



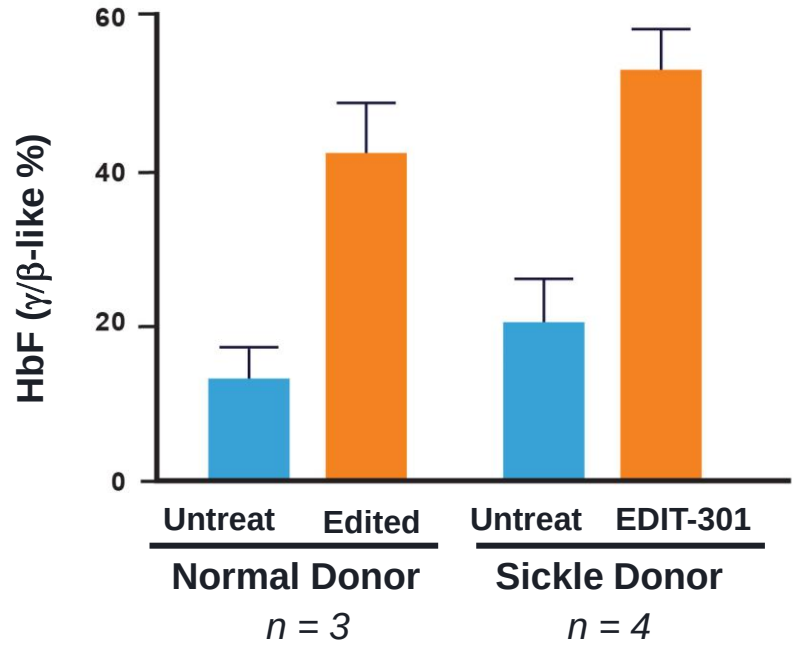
Representative data from one mouse

Comparable Editing and Robust HbF Induction Achieved in Normal and Sickle Donor CD34+ Cells (EDIT-301)

Editing



Ex vivo HbF Expression

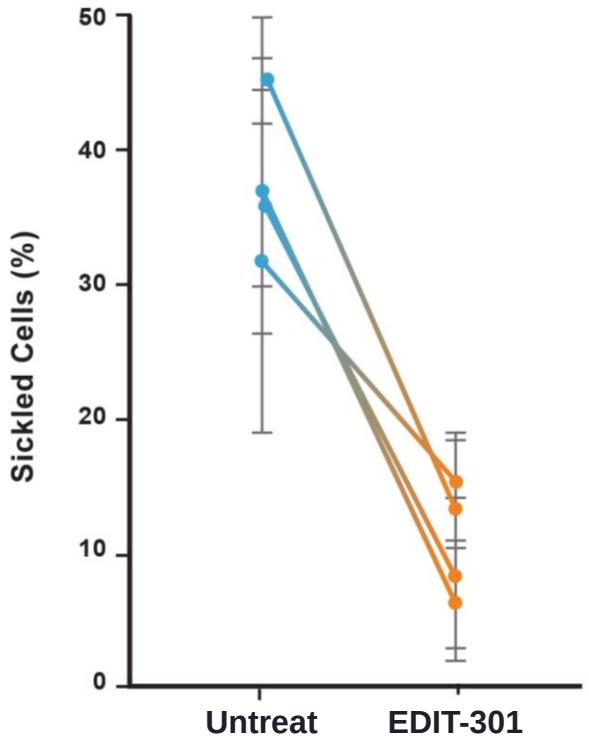


Efficient editing and robust HbF induction observed in normal donors translate to sickle patient derived CD34+ cells and their progeny

Untreated cells did not undergo electroporation

EDIT-301 RBCs from Sickle Patient Donors Have Significantly Reduced Sickling, Lower Point of Sickling and Improved Deformability

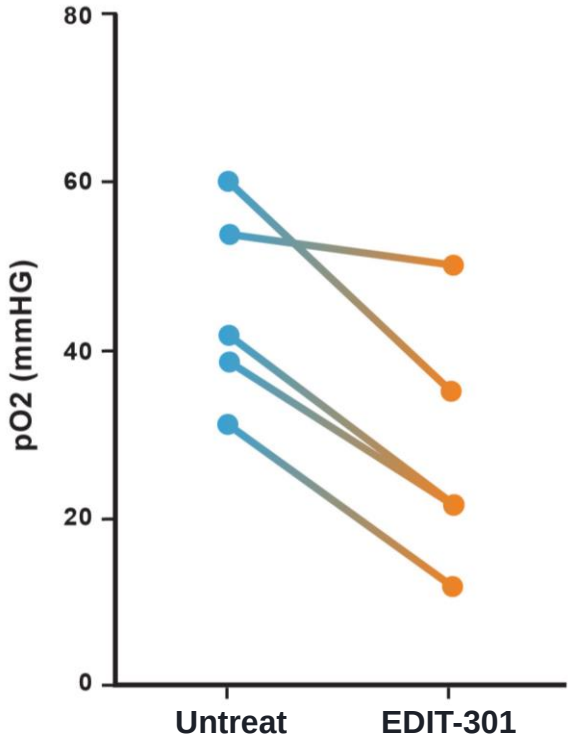
Reduced Sickling



HbF 19.9% HbF 53.8%

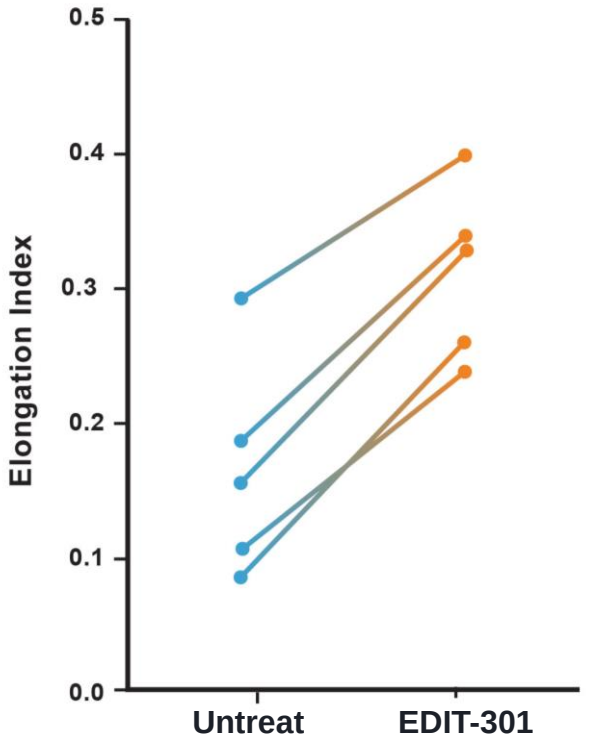
When exposed to sodium metabisulfite

Lowered Point of Sickling



HbF 19.9% HbF 53.8%

Improved Deformability at Low O_2



HbF 19.9% HbF 53.8%

Measured with Lorrca Oxygenscan

Conclusions

Cas12a demonstrates a superior editing profile to SpCas9 at *HBG* distal CCAAT box region for persistent and high HbF expression

Potentially therapeutically-relevant levels of HbF were expressed long-term with pancellular distribution *in vivo*

High levels of editing were achieved with EDIT-301, leading to a **significant reduction in sickling**, lowered point of sickling and improved deformability of sickle patient RBCs

Plan to file IND for EDIT-301 by end of 2020

Acknowledgements

Editas Medicine

Mingli Li, Francis Awokang, Pratik Randeria, Daniel Nguyen, Gwen Wilmes, Emmett Hedblom, Daniel Leblanc, Ash Mondkar, Jacqueline Nelson, Krithika Murali, Gwynneth Borges, Mingli Li, Arun Bhattathiri, Deep Majithia, Faith Barnard, Raisa Lowe, Shahzad Master, Benjamin Hutchins, Zeke Johnston, Harry Gill, Stephen Arold, John Hornyak, Gregory Gotta, Georgia Giannoukos, Diana Tabbaa, Dawn Ciulla, Racheal Dsouza, Swati Mukherjee, Emily Brennan, Chris Borges, Jared Nasser, Michael Dinsmore, Damien Fenske-Corbiere, Eugenio Marco

NIH

John Tisdale

UCSF

Mark Walters