Fulcrum Therapeutics Virtual Sickle Cell Disease KOL Event

December 15th, 2020

Fulcrum Therapeutics




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Virtual Sickle Cell Disease KOL Event Agenda

December 15th, 2020

- **Opening Remarks and Corporate Overview** (Robert Gould)
- **SCD – A Physician's Perspective** (Dr. Maureen Achebe)
- **Pursuing HbF Elevation as a Therapeutic Strategy** (Dr. Gerd Blobel)
- **FTX-6058 SCD Program Overview** (Owen Wallace)
- **FTX-6058: Looking Ahead** (Bryan Stuart)
- **Q&A** (All)

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Corporate Overview

Robert Gould, CEO

December 15th, 2020

Fulcrum Therapeutics




Fulcrum Overview

Our vision is to treat genetically defined diseases by addressing their root cause

Clinical stage biopharmaceutical company using systematic approach to identify small molecules able to rebalance gene expression

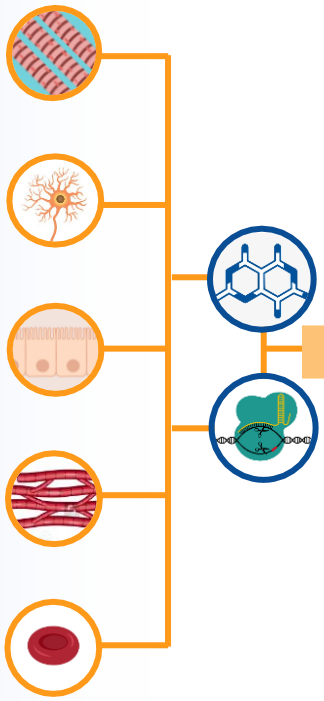
For Kadeem: **Increase** the protective protein, fetal hemoglobin

For Katelyn: **Decrease** the toxic protein, DUX4

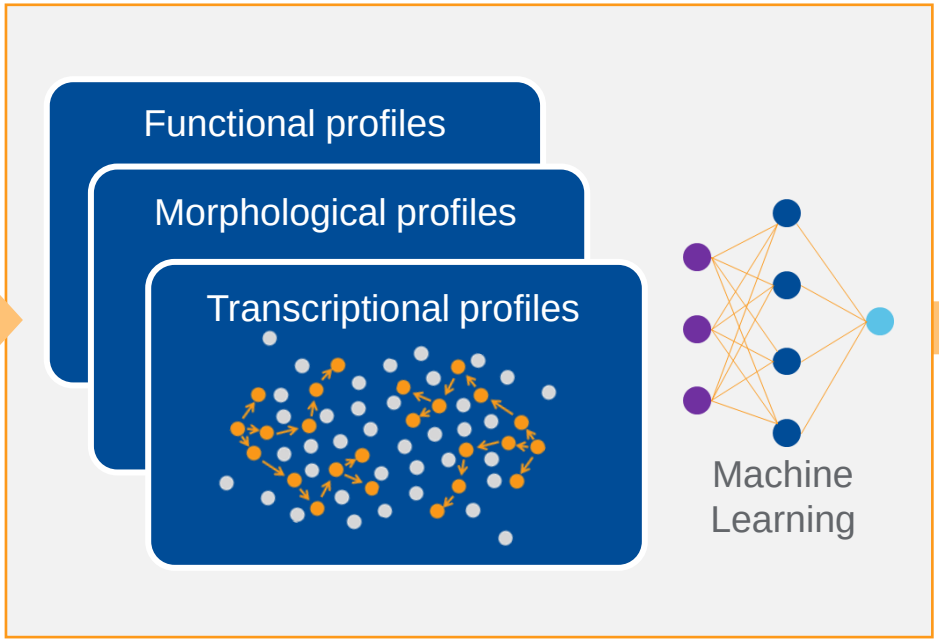
FulcrumSeek Discovery Approach

Intelligent drug discovery in disease relevant models through high dimensional data and machine learning

Discovery Engine



Computational Engine



Proprietary datasets in relevant cellular models that recapitulate tissue and disease biology

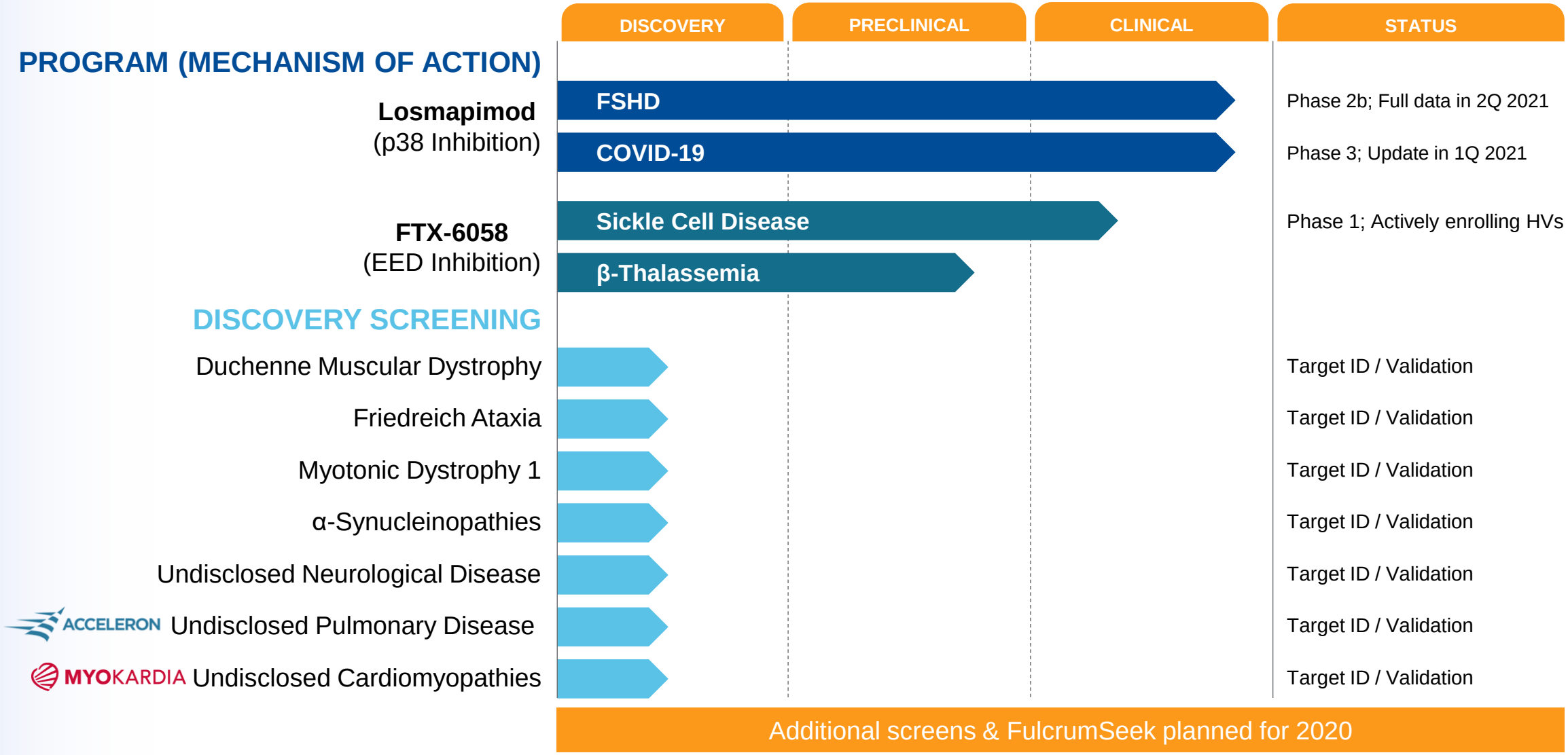
Accelerated Drug Discovery Programs

- Targets with desired profile of **specificity, selectivity and tolerability**
- Identification of tissue-relevant **translatable biomarkers**
- Characterization of lead candidates to understand **potential issues (toxicity or off-target activity)**

Data-rich target hypotheses and clinical candidates

Fulcrum Pipeline

Multiple clinical programs advancing



Focus of Today's Discussion

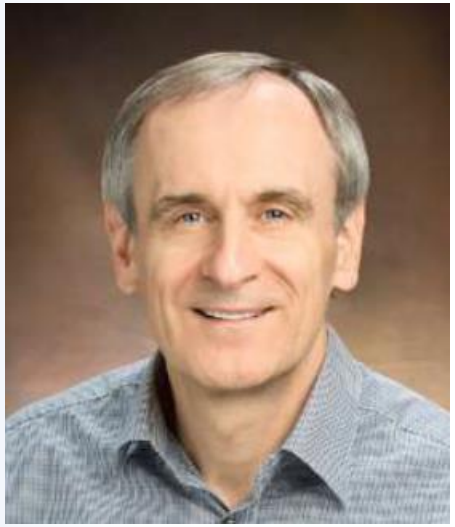
As a novel orally bioavailable HbF inducer, FTX-6058 has an opportunity to be a transformative therapy for patients with SCD and β-Thalassemia

- SCD and β-Thalassemia have significant unmet need, and require novel therapies
- An orally bioavailable compound that elevates fetal hemoglobin (HbF) has the potential to provide meaningful clinical benefit to a broad range of SCD and β-Thalassemia patients
- Fulcrum's Engine identified the EED protein as an HbF induction target
- FTX-6058 was designed by Fulcrum to be a novel, potent, selective, and effective EED inhibitor, with a composition of matter patent issued in November 2020
- Multiple pre-clinical studies show robust HbF elevation with FTX-6058 in human cells and genetically engineered SCD mice
- Oral, once-daily dosing with FTX-6058 is projected in humans from preclinical studies
- Actively enrolling healthy volunteers in Phase 1 SAD/MAD studies

Introduction to Today's KOLs

Maureen Achebe, MD, MPH

- Clinical Director, Non-malignant Hematology Clinic
- Assistant Director, Brigham and Women's Hospital Outpatient Infusion Center
- Director, Brigham and Women's Hospital Sickle Cell Program
- Assistant Professor of Medicine, Harvard Medical School



Gerd Blobel, MD, PhD

- Frank E. Weise III Professor of Pediatrics, University of Pennsylvania
- Co-director of Epigenetics Institute

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SICKLE CELL DISEASE
A PHYSICIAN'S PERSPECTIVE

Maureen M. Achebe, MD MPH

Director, Comprehensive Center for Sickle Cell Disorders

Brigham and Women's Hospital, Harvard Medical School

December 15, 2020

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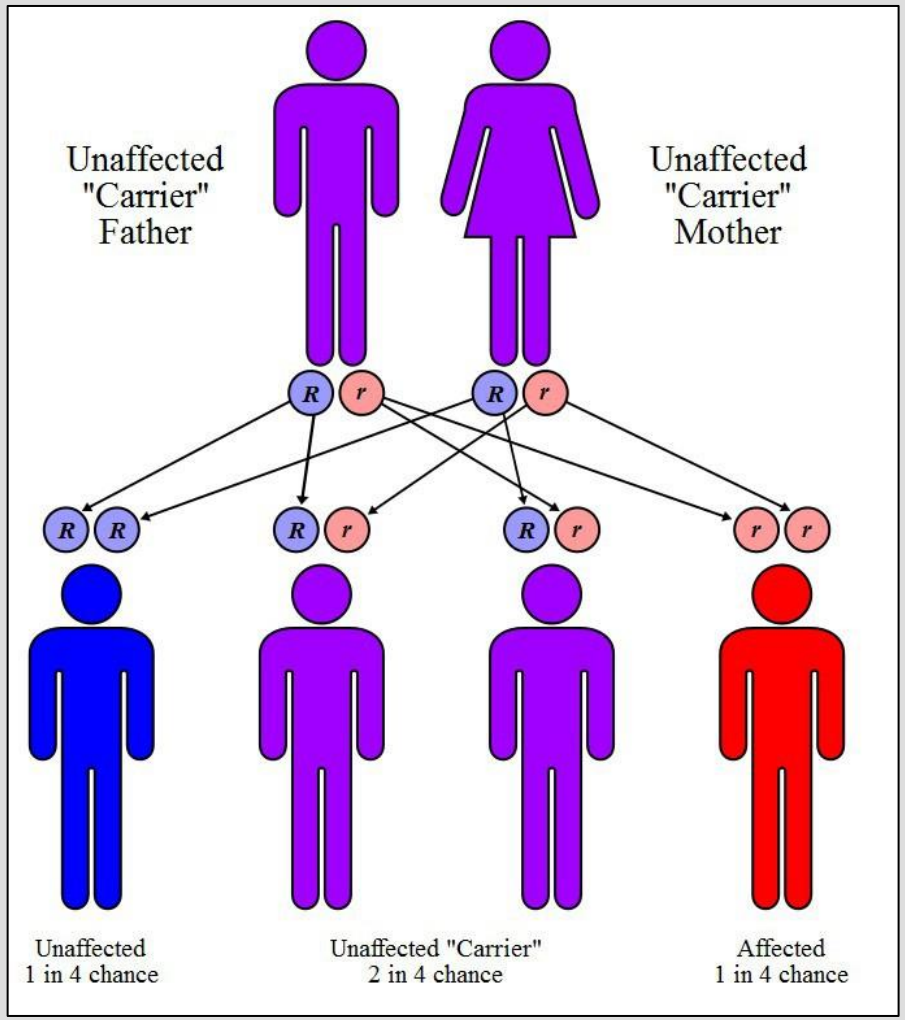
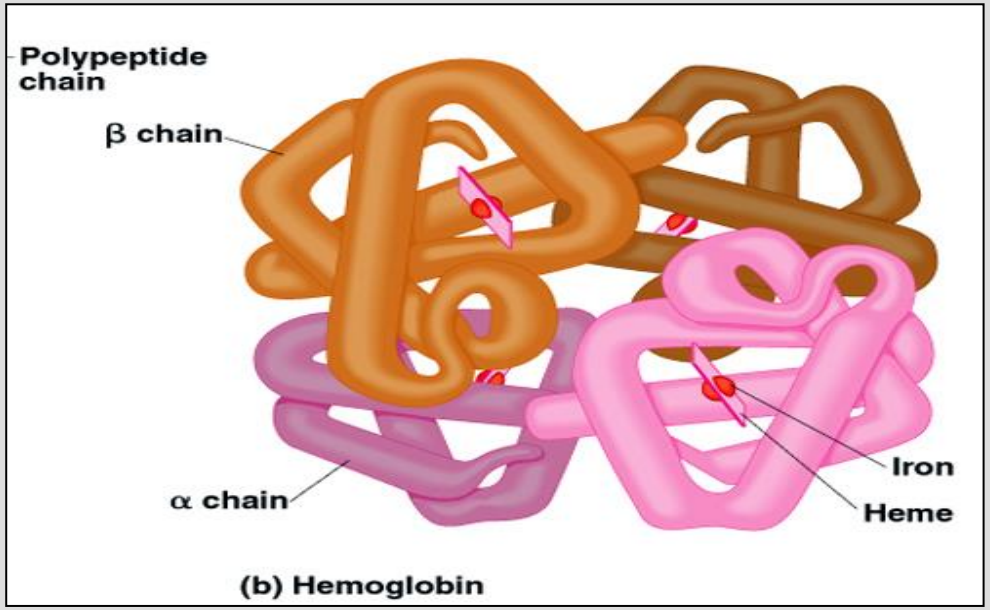
OUTLINE

- An Overview of Sickle Cell Disease
- The Patient with Sickle Cell Disease
- Pathophysiology
- Current Treatment Landscape
- Benefits of a Small Molecule

WHAT IS SICKLE CELL DISEASE?





Adult hemoglobin (HbA) - α_2 β_2

Sickle Hemoglobin(HbS) - α_2 β^s_2 (β6Glu → Val)

@MaureenAchebe

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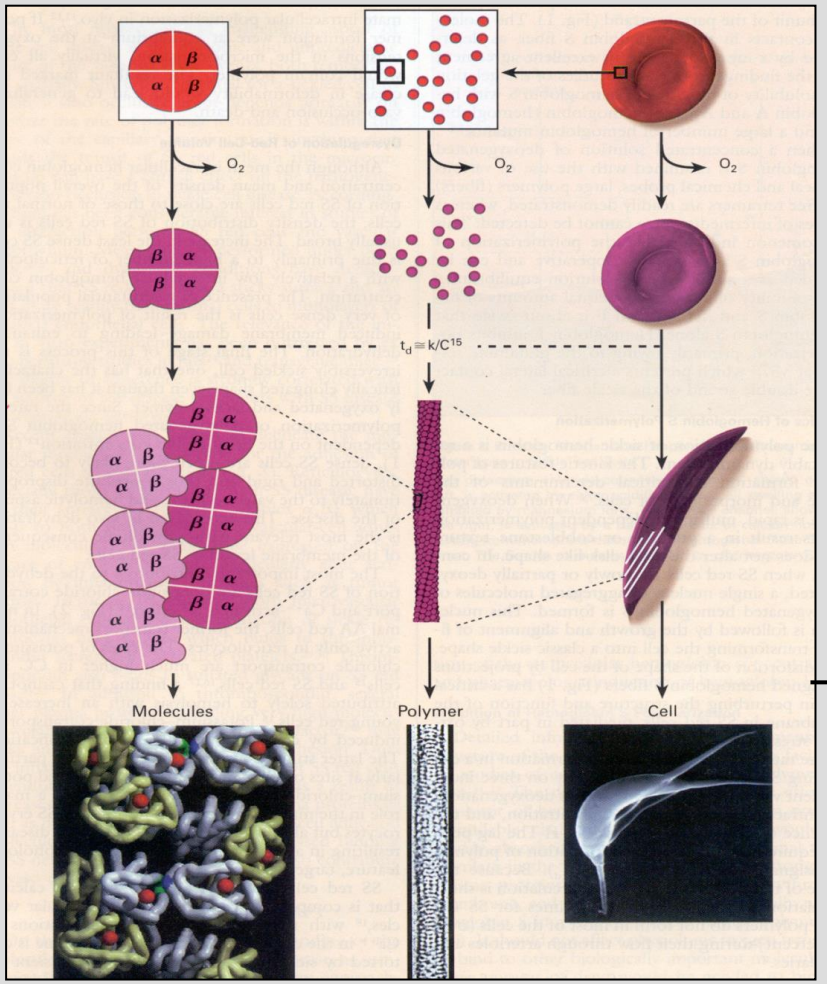
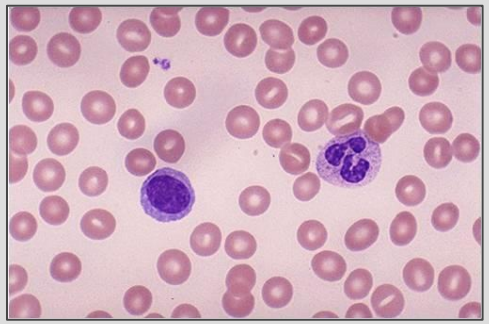
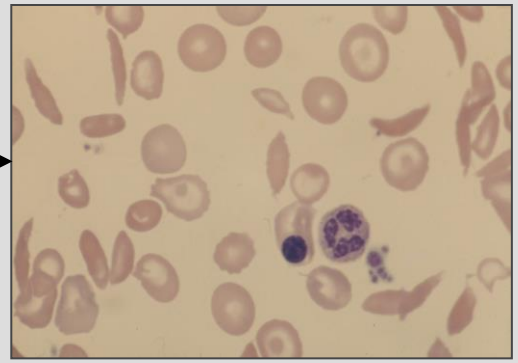
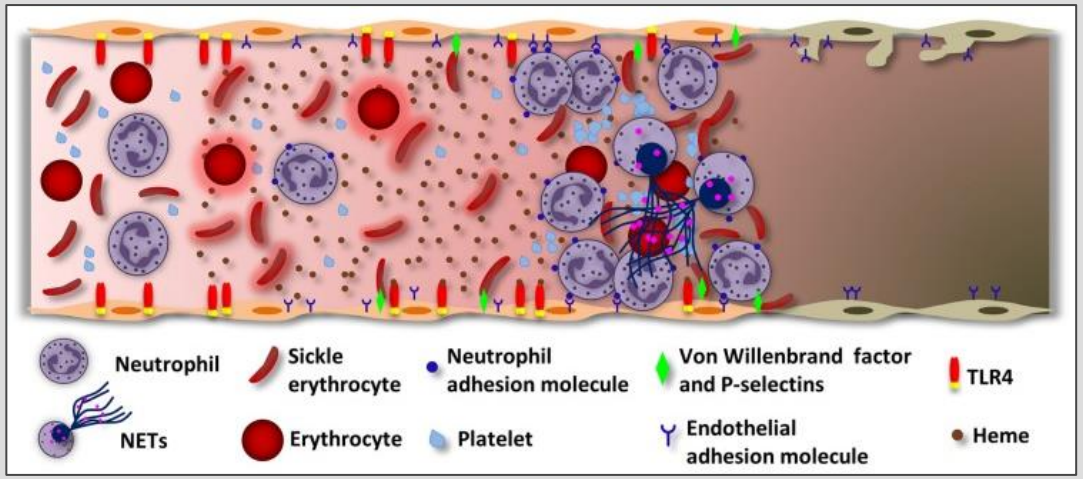
CENTRAL PATHOPHYSIOLOGY
HBS POLYMERIZATION

SECONDARY PATHOPHYSIOLOGY
SICKLE VASCULOPATHY









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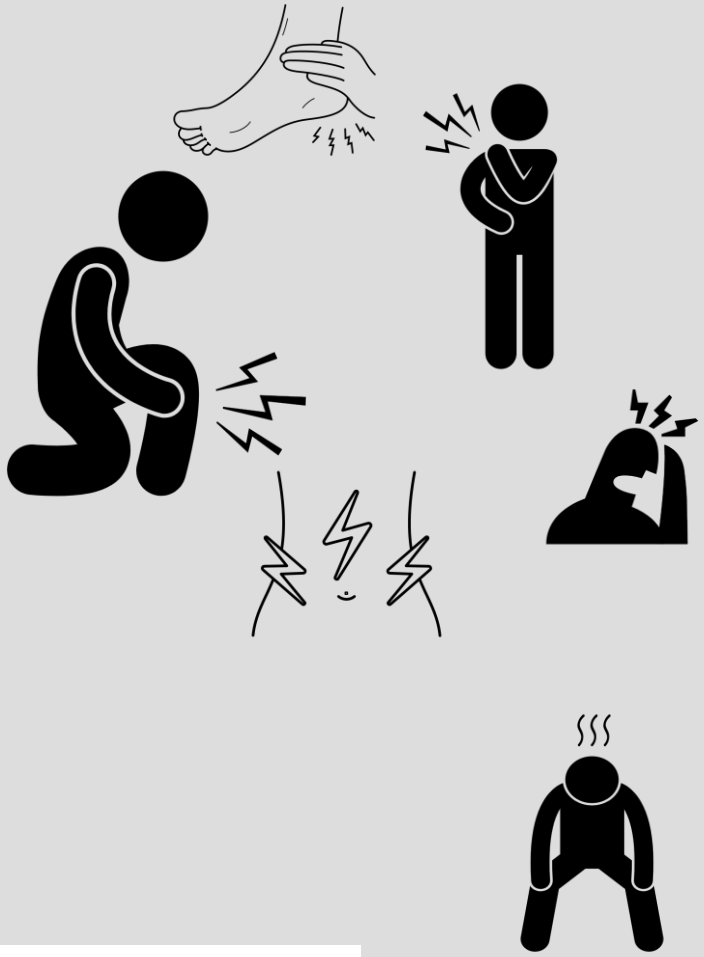
Bunn, NEJM 1997;337:762

SICKLE CELL PATIENT PRESENTS WITH EXCRUCIATING PAIN



- Vaso-occlusive episodes (VOE)
- Vaso-occlusive crisis
- Pain crisis
- Fatigue

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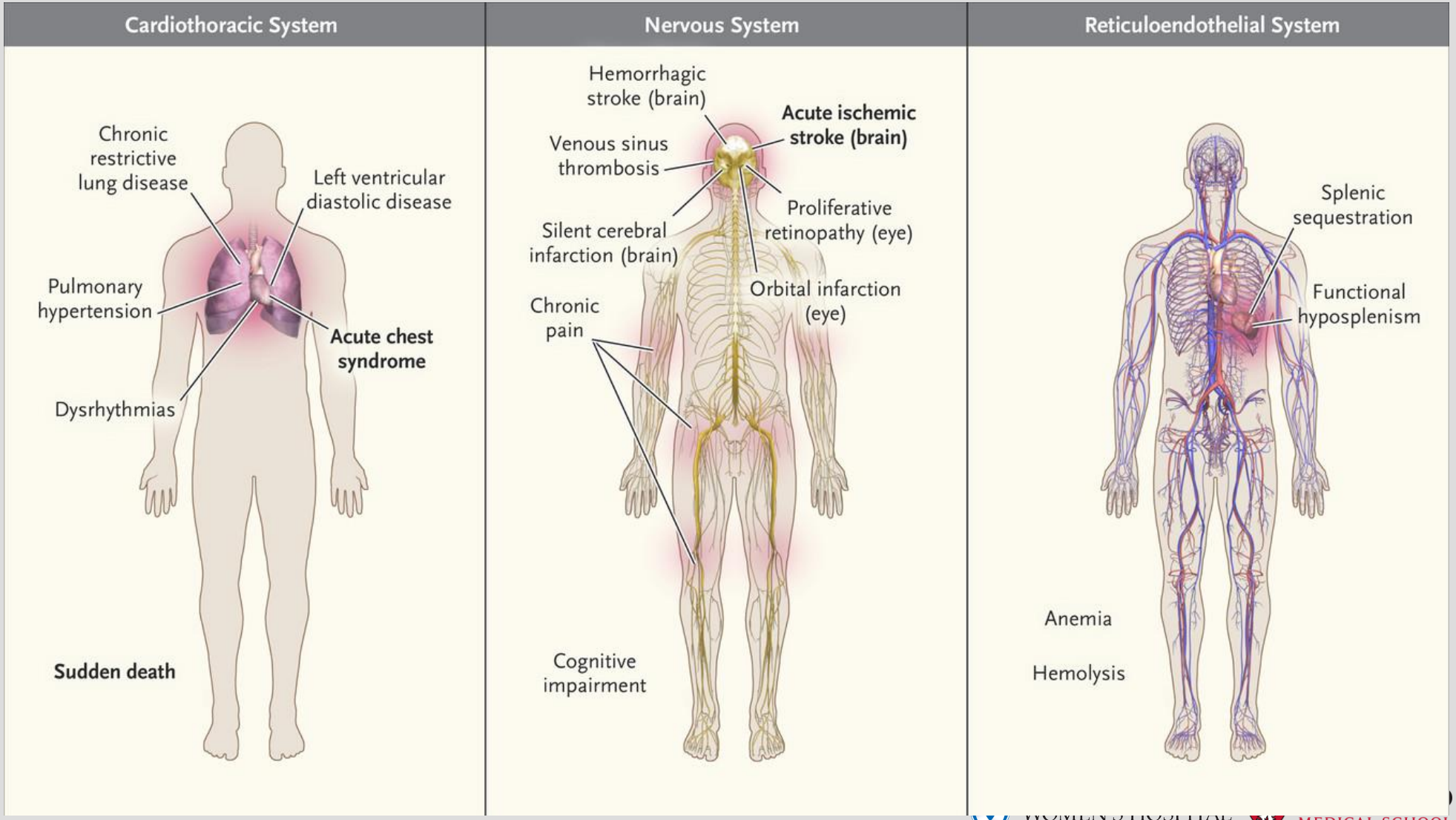
SCD AFFECTS ALL ORGAN SYSTEMS



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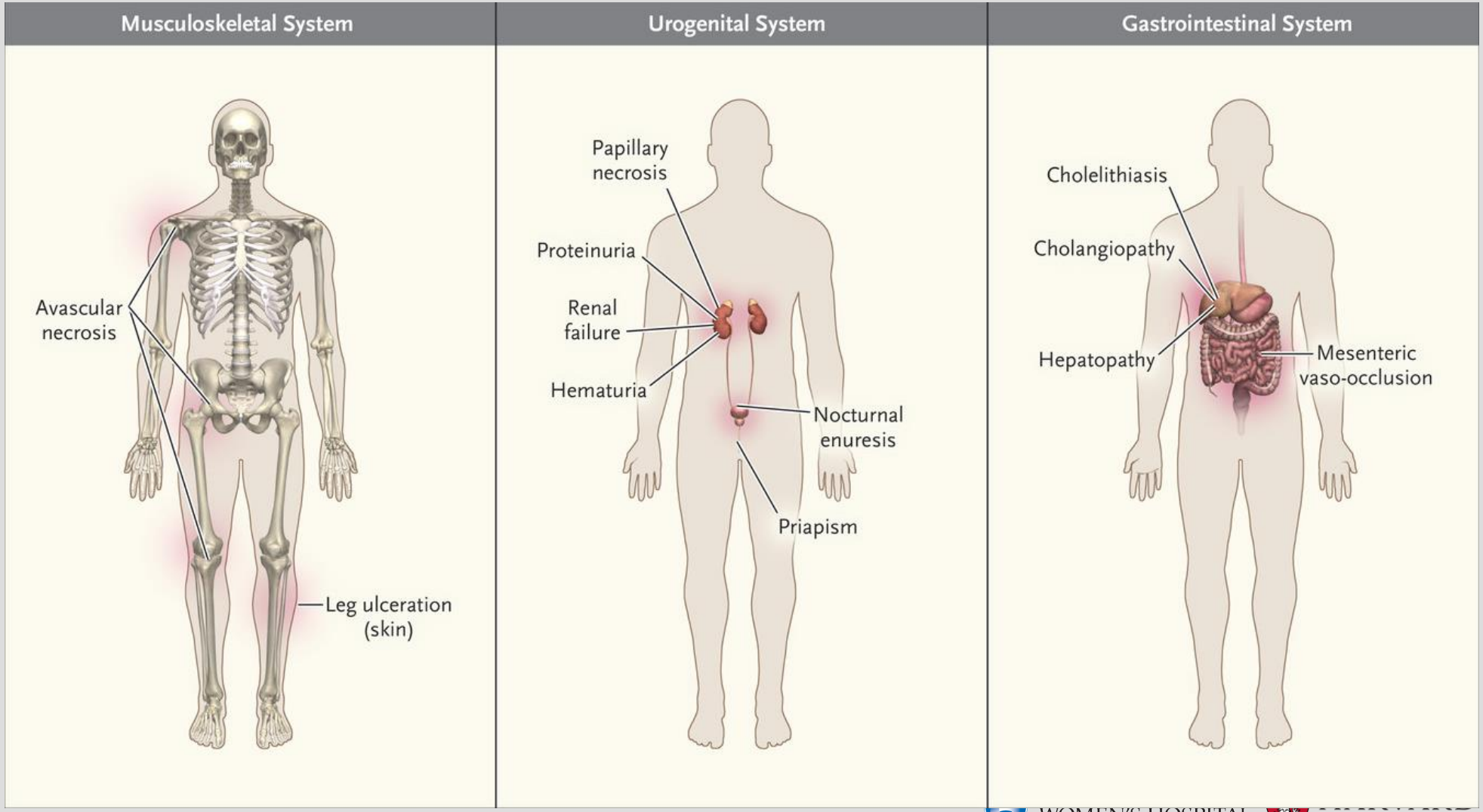
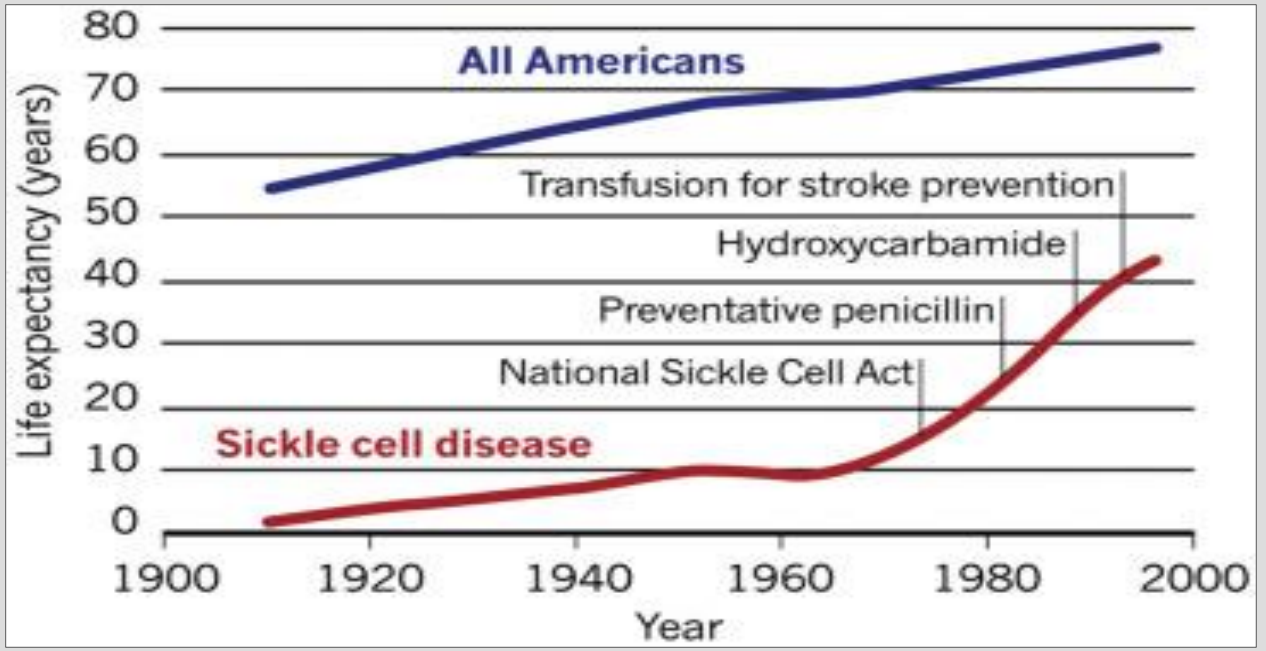


@MaureenAchebe

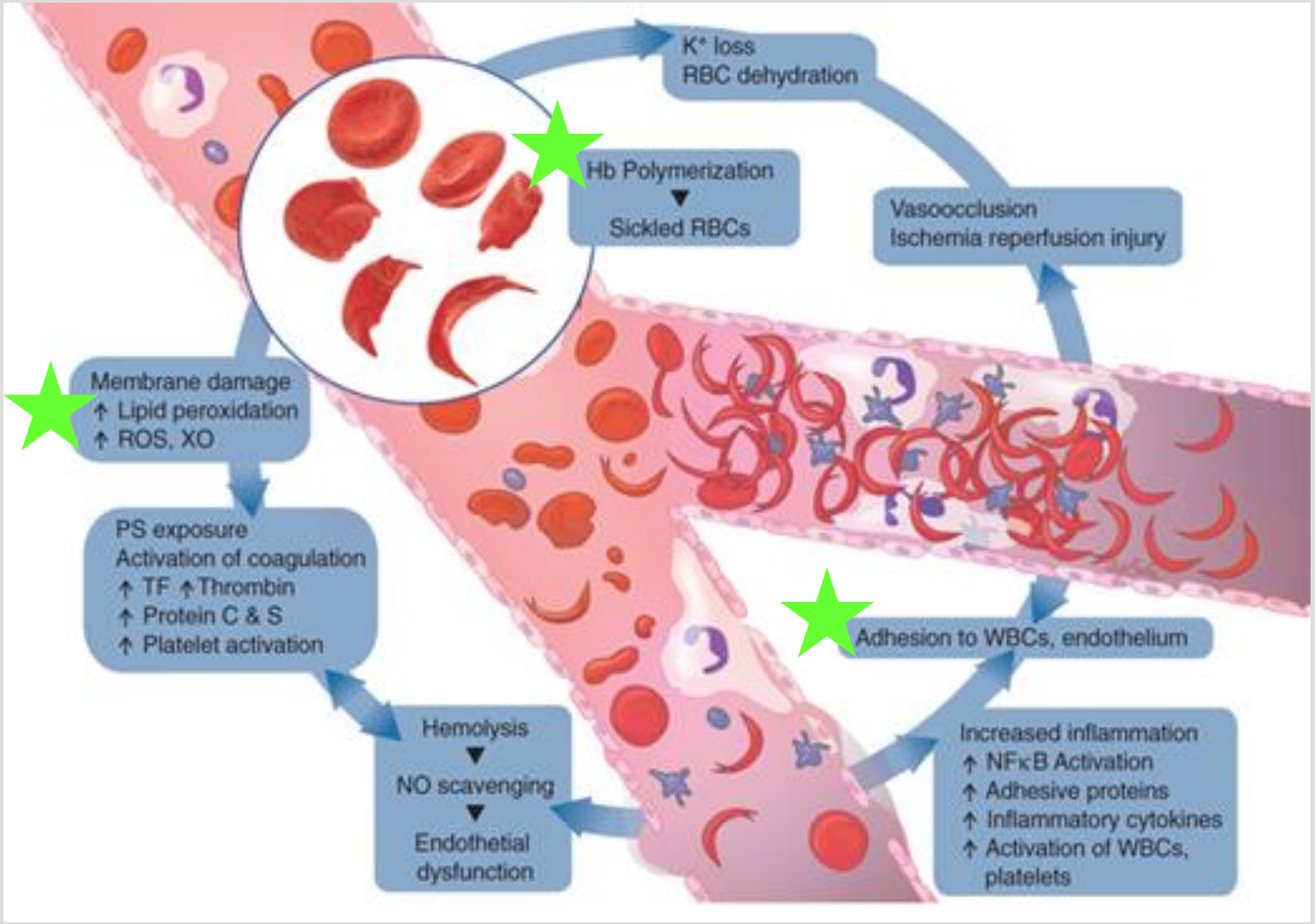
LIFE EXPECTANCY OF SCD IN US MUCH WORSE THAN THE GENERAL PUBLIC

- Worldwide, > 300,000 babies is born with SCD.
- Over 90,000 people in the USA have SCD
- Over 90% SCD children with SCD in USA reach adulthood



Thein, M. Pathology. Volume 49, Issue 1, Pages 1-9 (January 2017)

COMPLEX PATHOPHYSIOLOGY OF SCD



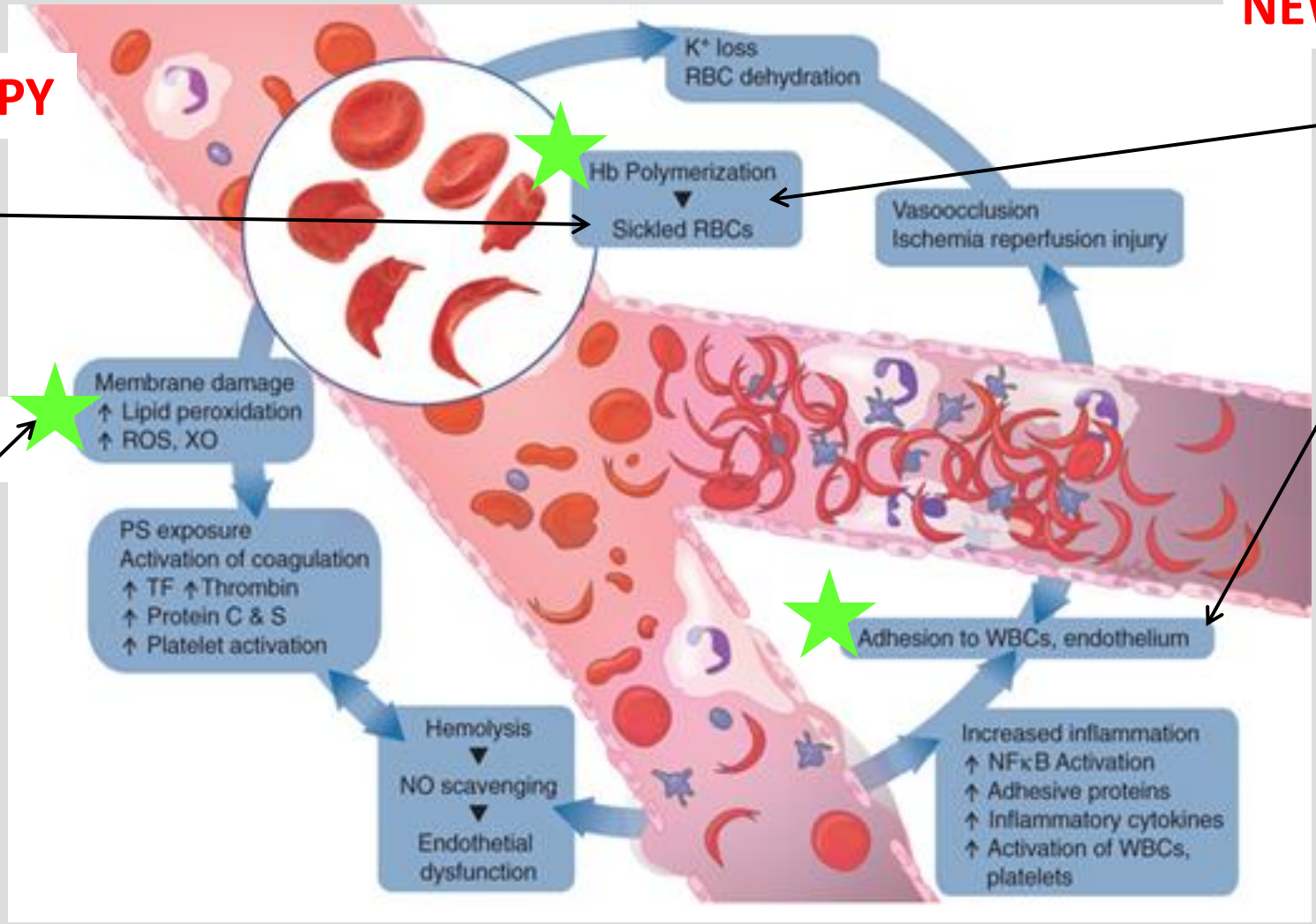
CURRENT LANDSCAPE OF TREATMENTS IN SCD

MAINSTAY THERAPY

Hydroxyurea
FDA 1998

NEWER THERAPY

L-glutamine
(Endari)



NEWEST THERAPIES

Voxelotor
(Oxbryta)

Crizanlizumab
(Adakveo)

Stem cell transplant

Gene therapy

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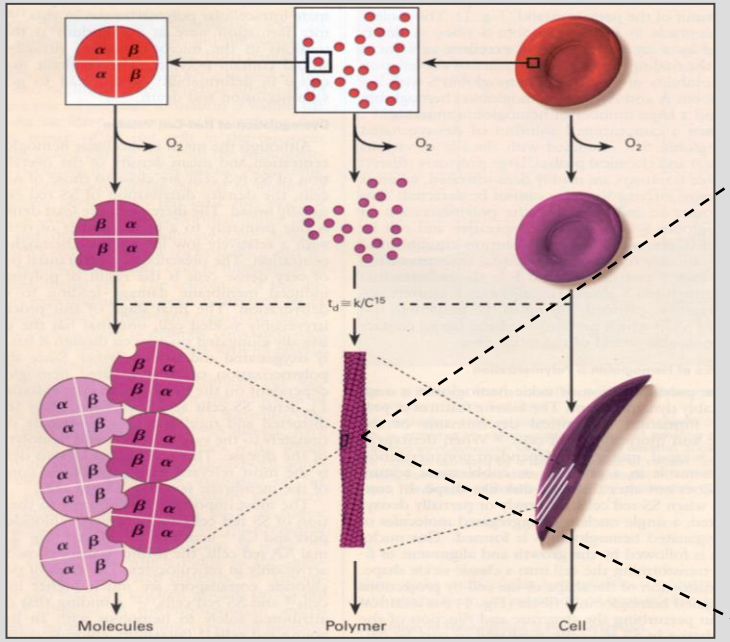
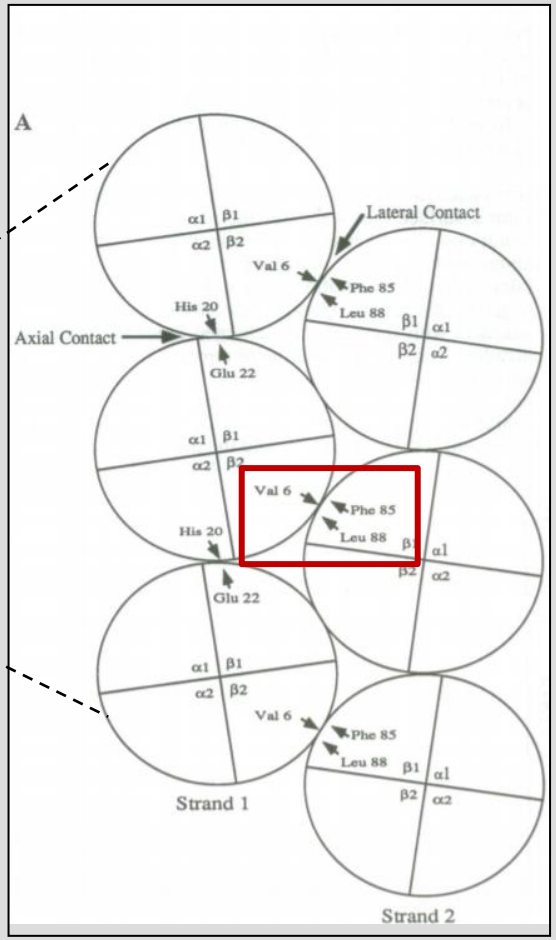
INDUCTION OF FETAL HEMOGLOBIN IN SCD

- Hydroxyurea was investigated based on its ability to induce HbF



Bunn, NEJM 1997;337:762



Adachi, J Biol Chem 1994;269(50):31563

Adult hemoglobin (HbA) - α_2 **β 87** threonine
Sickle Hemoglobin(HbS) - α_2 β^s **87** threonine
Fetal Hemoglobin (HbF) - α_2 **γ 87** glutamine

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WHAT DO SCD PATIENTS **HAVE** NOW?

Drug (FDA *)	Target	MOA	Hb	Pain	Benefits	Disadvantages
Hydroxyurea 1998	↓ polymer	heterocellular ↑ HbF	✓	✓	Oral 💰	chemotherapy, inconsistently effective in adults
L-glutamine 2017	rbc REDOX	↓ RBC oxidative stress	✓	✓	Oral 💰 💰	15 G, non-compliance
Crizanlizumab 2019	vasculopathy	P selectin mAb	-	✓	monthly	IV, 💰 💰 💰
Voxelotor 2019	↓ polymer	↑O_2 affinity	✓	-	Oral	💰 💰 💰
SCT gene therapy Phase 3	Gene	Gene modification	✓	✓	cure	chemotherapy, infertility 💰 💰 💰 💰 💰

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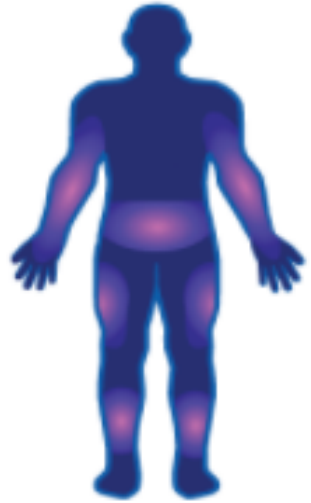
THERE IS **SIGNIFICANT** UNMET NEED IN SCD

Go to the hospital more than once a year, with an average stay of 5 days per hospitalization.

Go to the ED an average of 2–3 times a year.



Go to the ED and hospital most commonly for VOEs.

WHAT DO SCD PATIENTS **NEED** NOW?

Oral therapy, once daily, safe, effective, inhibits HbS polymerization

- Effective ---------- Pancellular HbF induction
- Safe ---------- minimal off-target effects
- Well tolerated ---------- oral therapy, minimal side effects
- Affordable ---------- oral therapy

THANK YOU

@MaureenAchebe

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Pursuing HbF elevation as a therapeutic strategy

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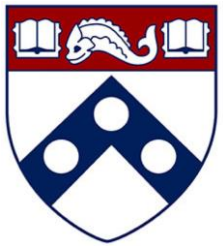
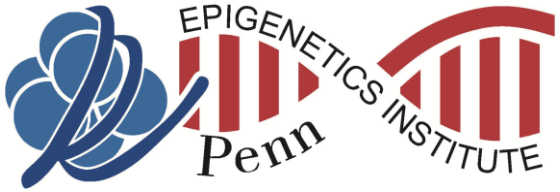
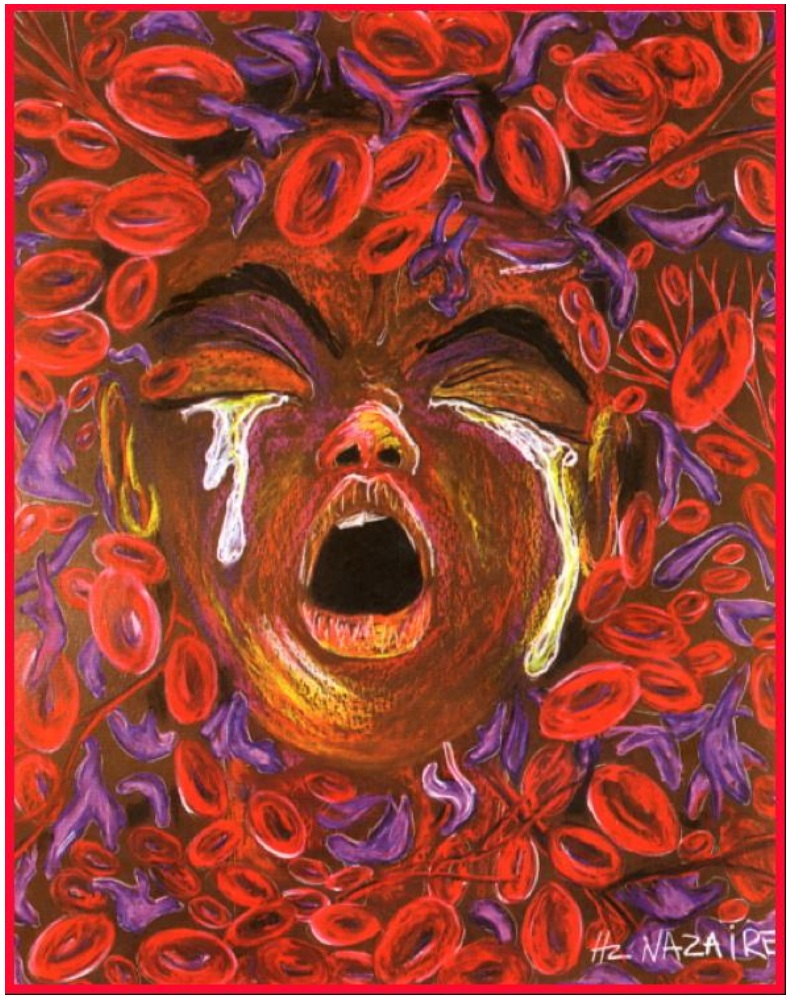
Gerd Blobel, M.D., Ph.D.
Frank E. Weise III Professor of Pediatrics
The Children's Hospital of Philadelphia
Co-director U-Penn Epigenetics Institute
Perelman School of Medicine
University of Pennsylvania

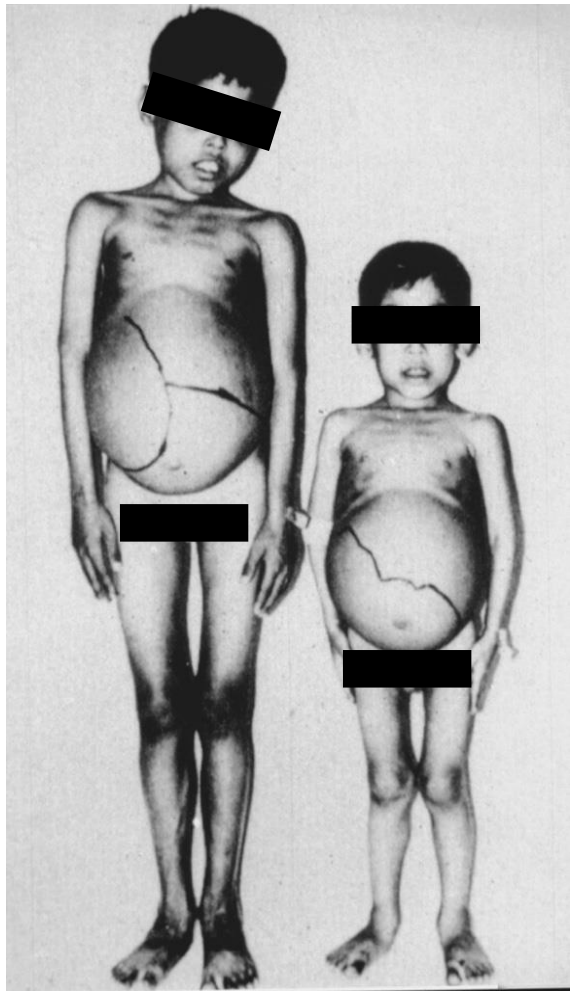




Hemoglobinopathies:
A disease of multi-system complications

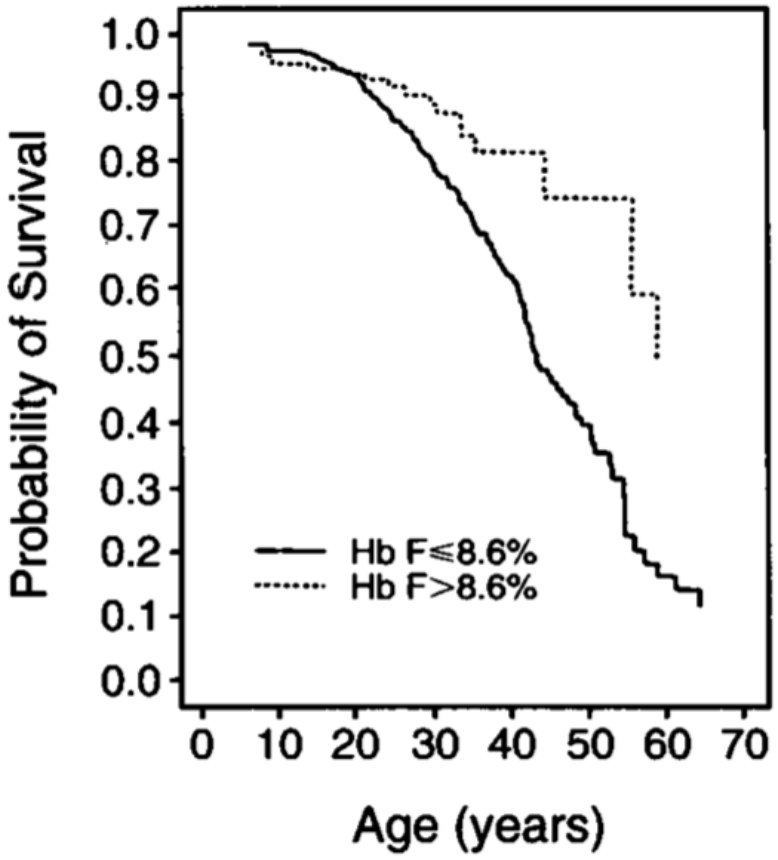


Sickle cell disease



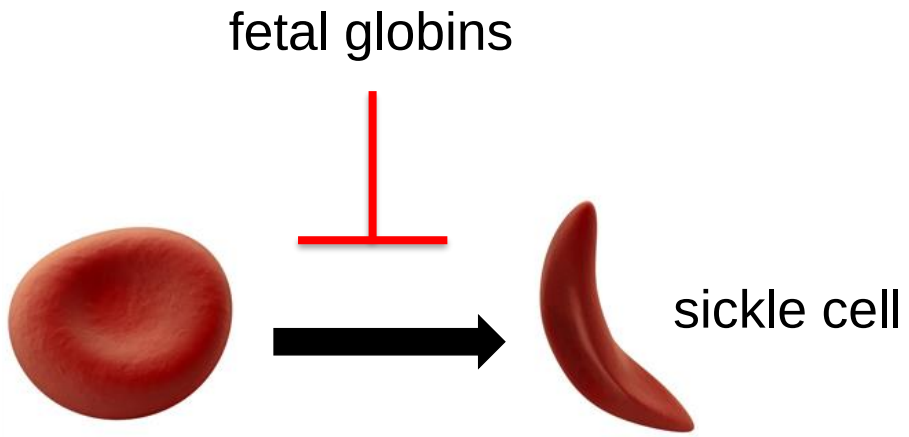
Thalassemia intermedia

Elevated levels of fetal hemoglobin (HbF) improve the clinical course of patients with sickle cell disease



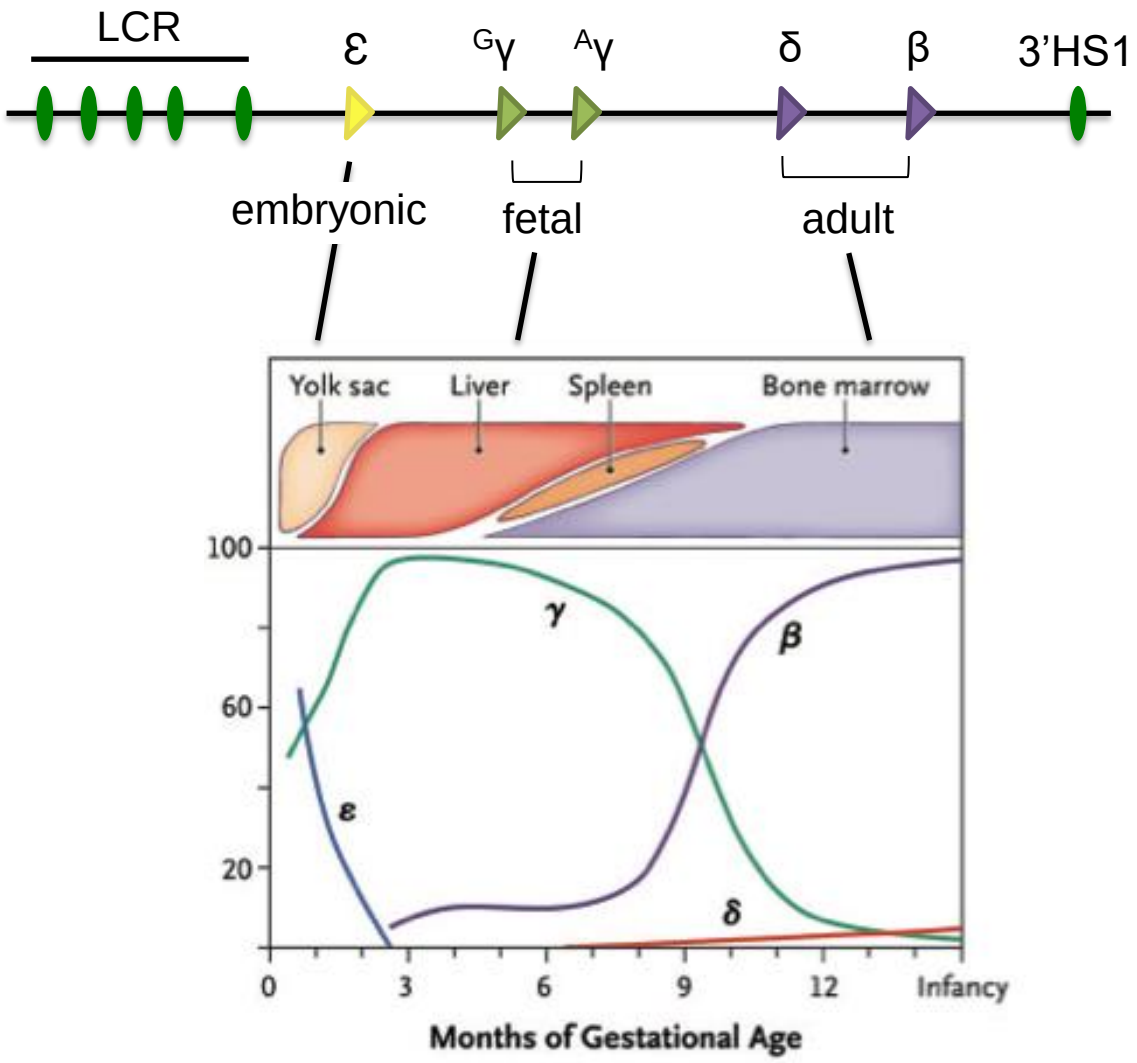
Platt, O. S. et al. N. Engl. J. Med. 1994

Elevated levels of fetal hemoglobin (HbF) improve the clinical course of patients with sickle cell disease

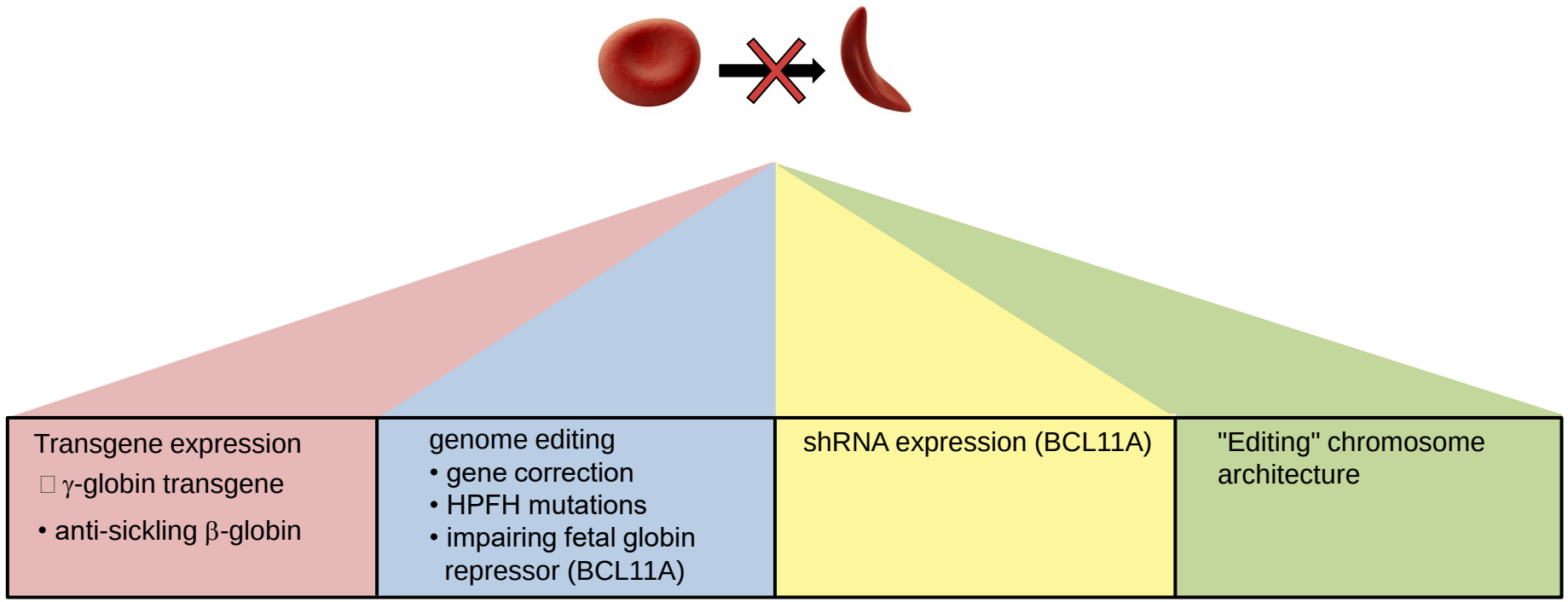


hereditary persistence of fetal hemoglobin (HPFH)

Human hemoglobin switching

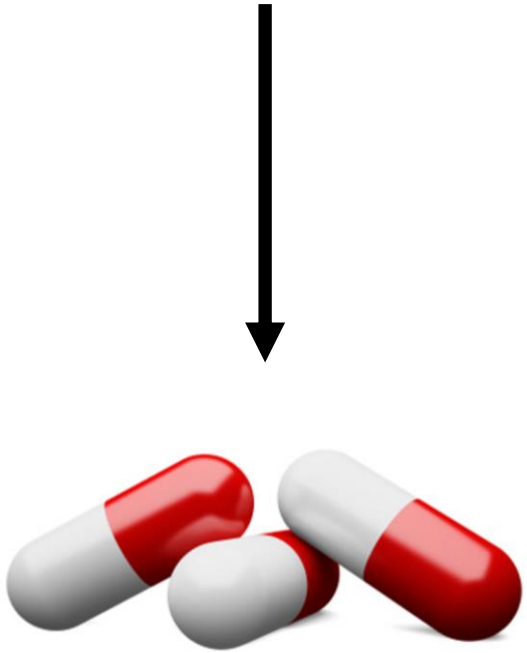


Therapeutic approaches for sickle cell disease (a brief scenic tour)

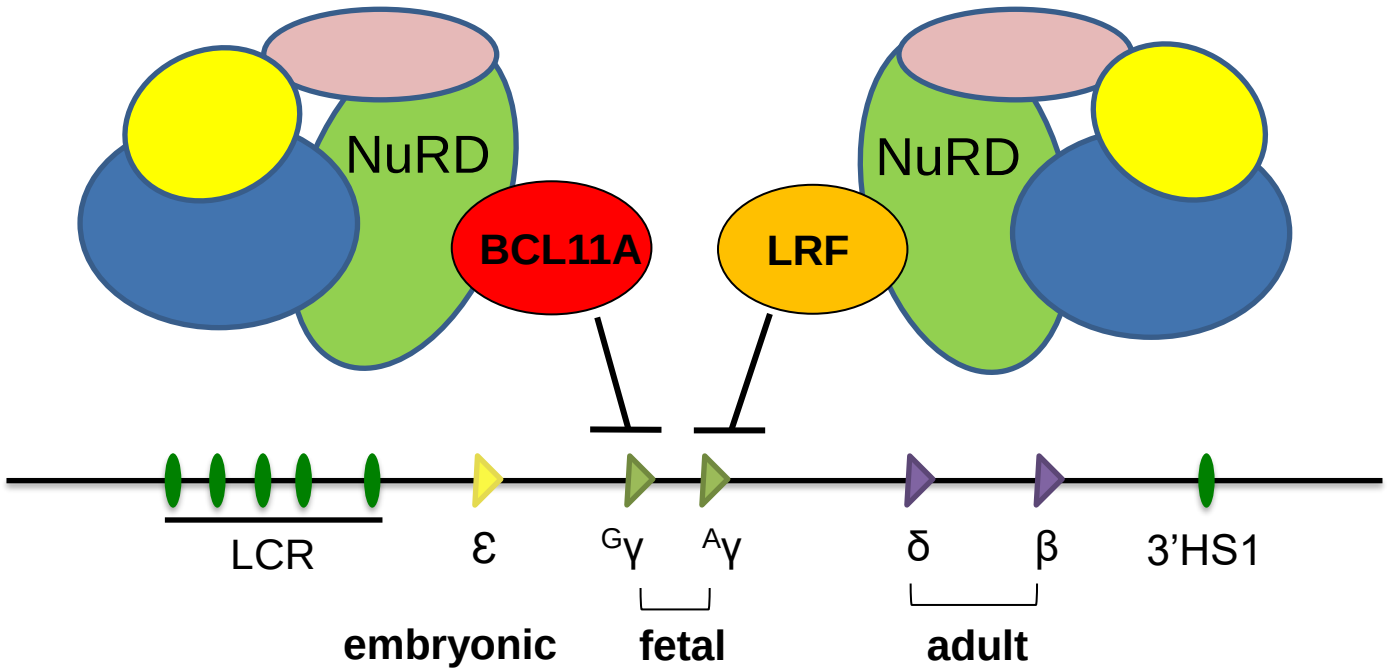


All of these approaches require autologous BM transplants

Goal: Identify HbF regulators that could be targeted with small molecules



Hemoglobin switching involves widely expressed co-regulators

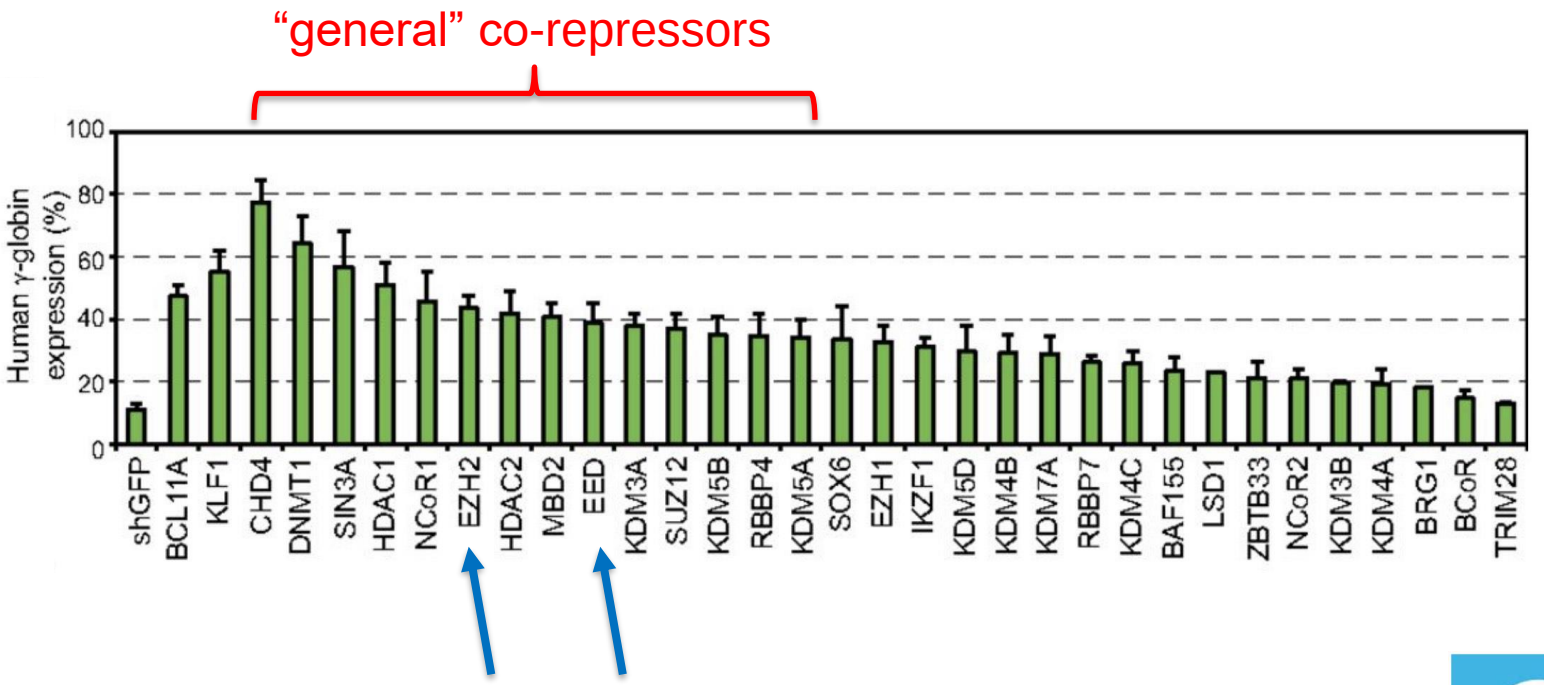


Hemoglobin switching involves widely expressed co-regulators

Corepressor-dependent silencing of fetal hemoglobin expression by BCL11A

Jian Xu[a], Daniel E. Bauer[a], Marc A. Kerenyi[a], Thuy D. Vo[a], Serena Hou[a], Yu-Jung Hsu[a], Huilan Yao[b], Jennifer J. Trowbridge[a], Gail Mandel[b], and Stuart H. Orkin[a,c,1]

PNAS 2013



CHD4-NuRD is a critical fetal hemoglobin co-repressor

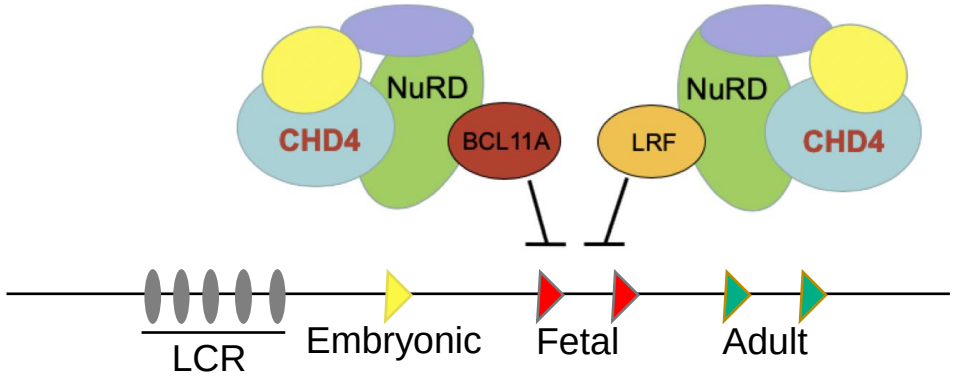
nature genetics

ARTICLES

https://doi.org/10.1038/s41588-019-0453-4

Rational targeting of a NuRD subcomplex guided by comprehensive in situ mutagenesis

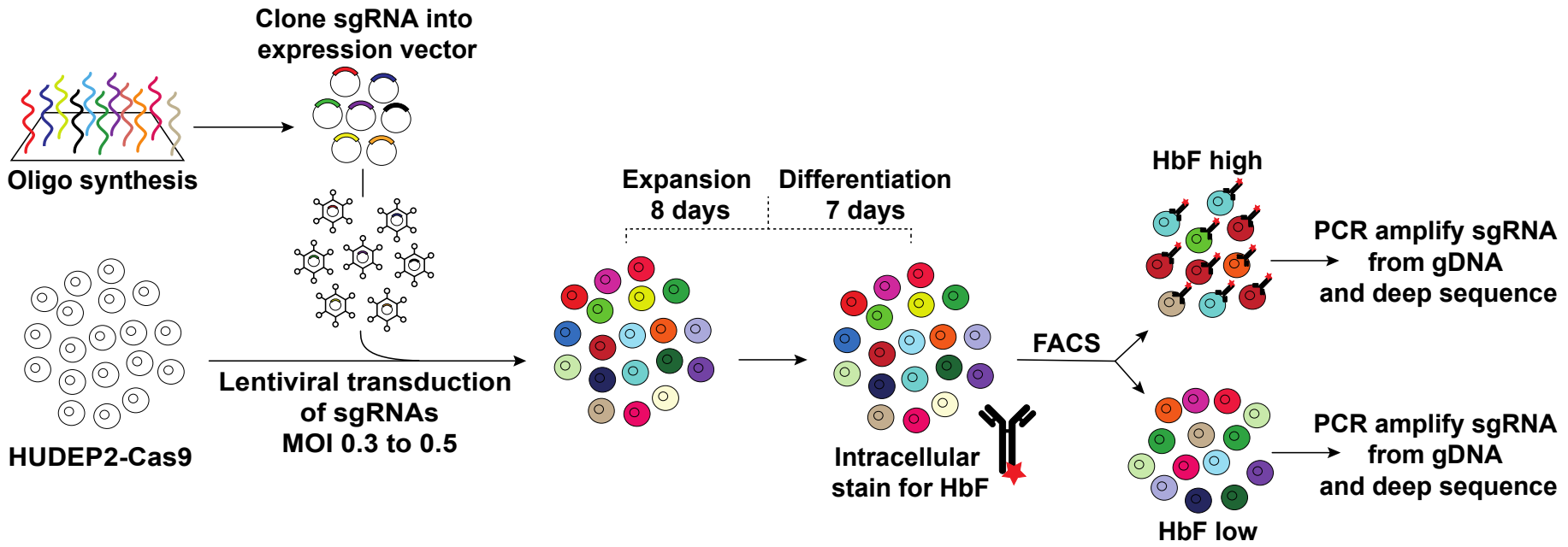
Falak Sher[1,2,11], Mir Hossain[1,11], Davide Seruggia[1,11], Vivien A. C. Schoonenberg[1,3], Qiuming Yao[1,4], Paolo Cifani[5], Laura M. K. Dassama[1], Mitchel A. Cole[1], Chunyan Ren[1], Divya S. Vinjamur[1], Claudio Macias-Trevino[1], Kevin Luk[6], Connor McGuckin[1], Patrick G. Schupp[1], Matthew C. Canver[1], Ryo Kurita[7], Yukio Nakamura[8], Yuko Fujiwara[1], Scot A. Wolfe[6], Luca Pinello[4], Takahiro Maeda[9], Alex Kentsis[5], Stuart H. Orkin[1,10] and Daniel E. Bauer[1*]



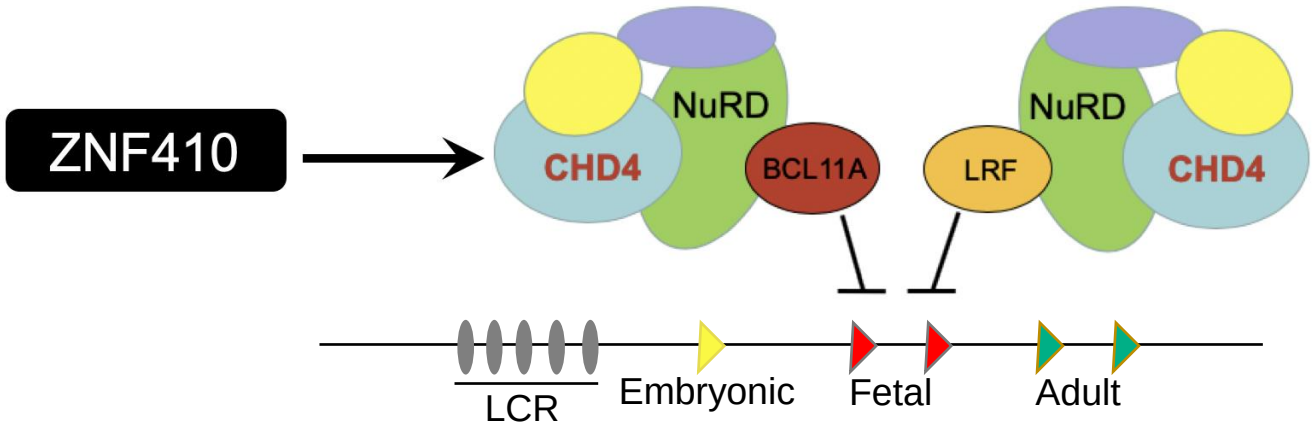
β-globin locus

CRISPR-Cas9 screen to identify druggable genes involved in fetal globin repression

(HUDEP2 cells)



CRISPR screen identifies transcription factor ZNF410 as novel HbF repressor



β-globin locus

Lan et al., Mol Cell in press

Hemoglobin switching involves widely expressed co-regulators

Our screens also identified several PRC2 components as fetal hemoglobin regulators, providing independent validation of PcG as targets.

Validation standards in the field:

1. Validation in HUDEP2 cells with individual sgRNAs

2. Validation in cultured primary human cells from normal and SCD donors

3. Mouse models (Townes, BERK, NBSGW)

Questions you might ask

1) Does it make sense to “drug” a widely expressed protein such as PcG proteins?

Numerous inhibitors are in clinical trials/use do exactly that (HDACs, BETs, kinases, etc)

Questions you might ask

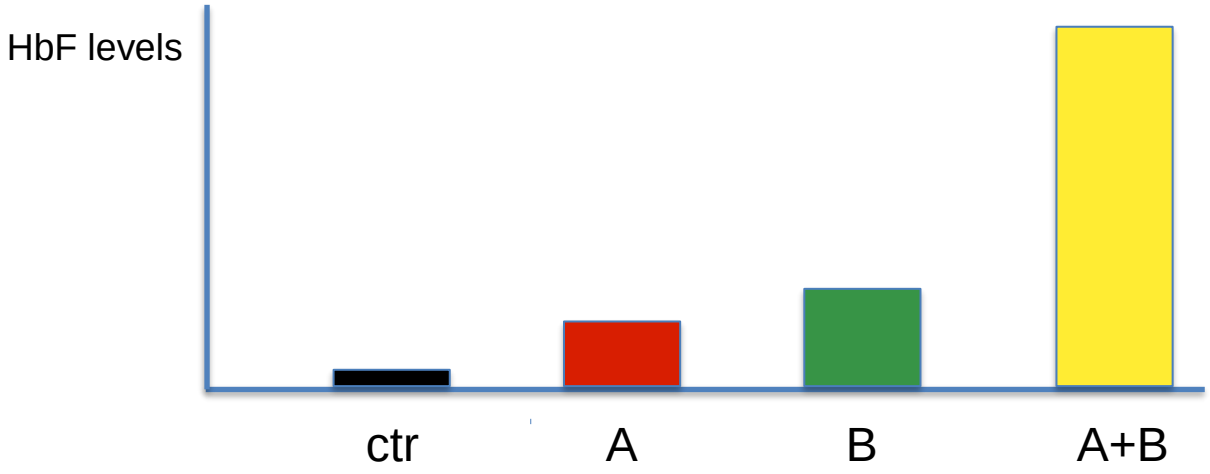
2) Do beneficial effects have to be direct?

HU is likely indirect; so are experimental HbF inducers (pomalidomide, G9a inhibitors, Aza)

Questions you might ask

3) Can one drug do it all?

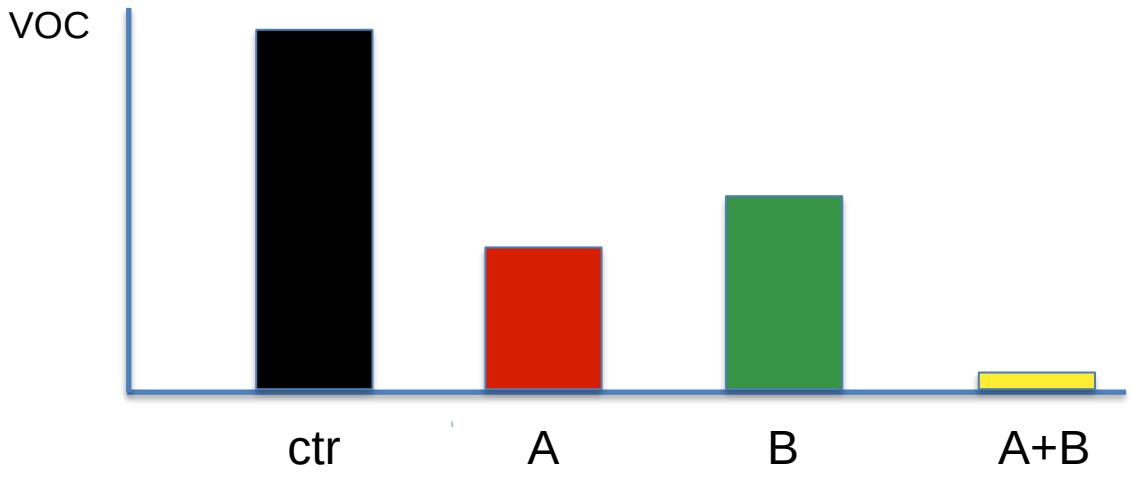
Drug combinations might produce cooperative HbF induction while reducing off target effects



Questions you might ask

3b) Can one drug do it all?

Drug combinations converging on entirely different mechanisms might provide cooperative patient benefit



Questions you might ask

4) Do we have to know the mechanism of action?

While the molecular targets for many effective drugs are known, a precise and detailed mapping of the various intermediary effector pathways that link target modulation to the demonstrated therapeutic effect (e.g HbF induction) is unclear in most cases

Thank you!

Questions?

Fulcrum Therapeutics

Virtual Sickle Cell Disease KOL Event Agenda

December 15th, 2020

- **Opening Remarks and Corporate Overview** (Robert Gould)
- **SCD – A Physician's Perspective** (Dr. Maureen Achebe)
- **Pursuing HbF Elevation as a Therapeutic Strategy** (Dr. Gerd Blobel)
- **FTX-6058 SCD Program Overview** (Owen Wallace)
- **FTX-6058: Looking Ahead** (Bryan Stuart)
- **Q&A** (All)

FTX-6058, a novel HbF-inducing agent for the treatment of Sickle Cell Disease and β-Thalassemia

Owen Wallace, CSO

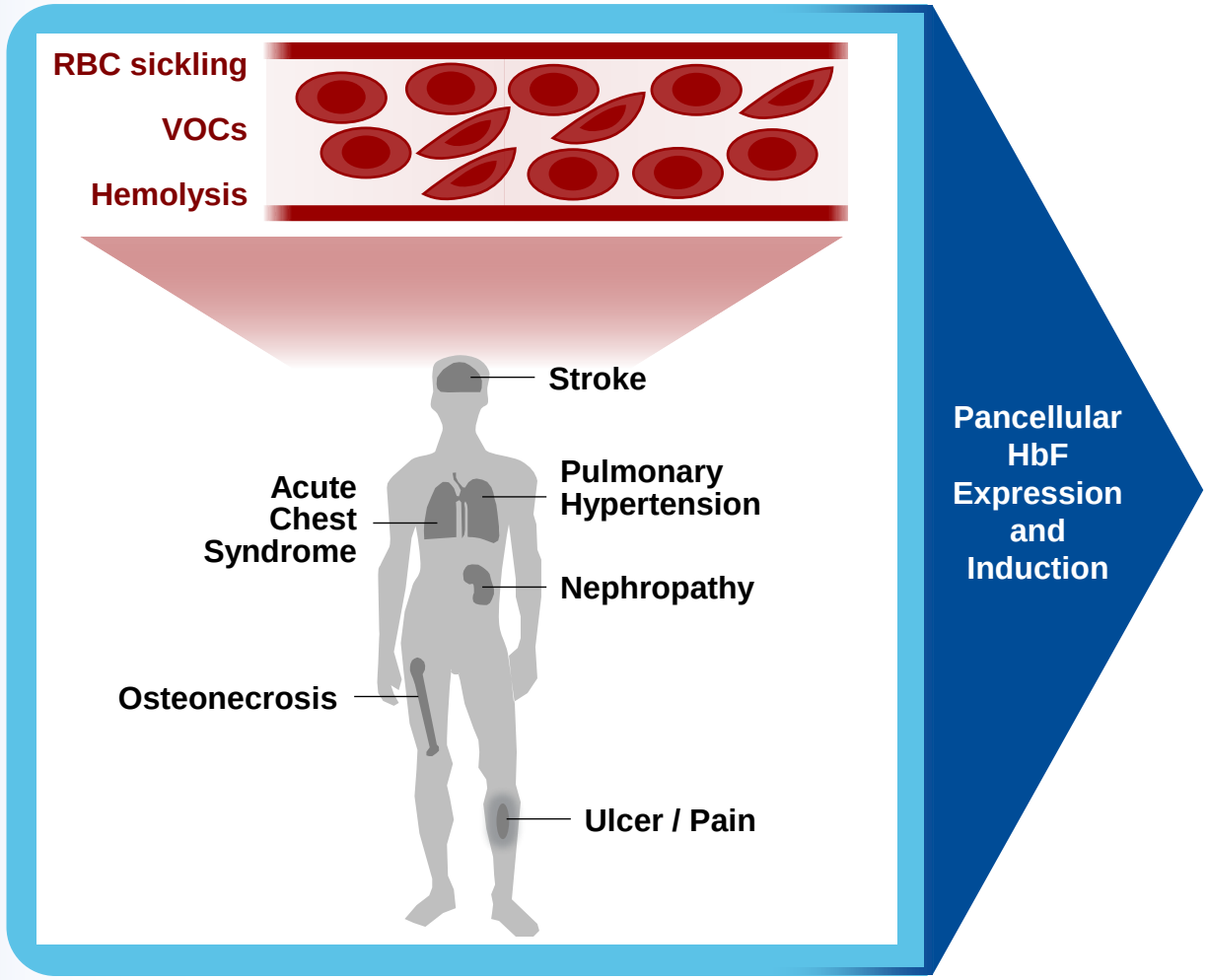
December 15th, 2020

Fulcrum Therapeutics



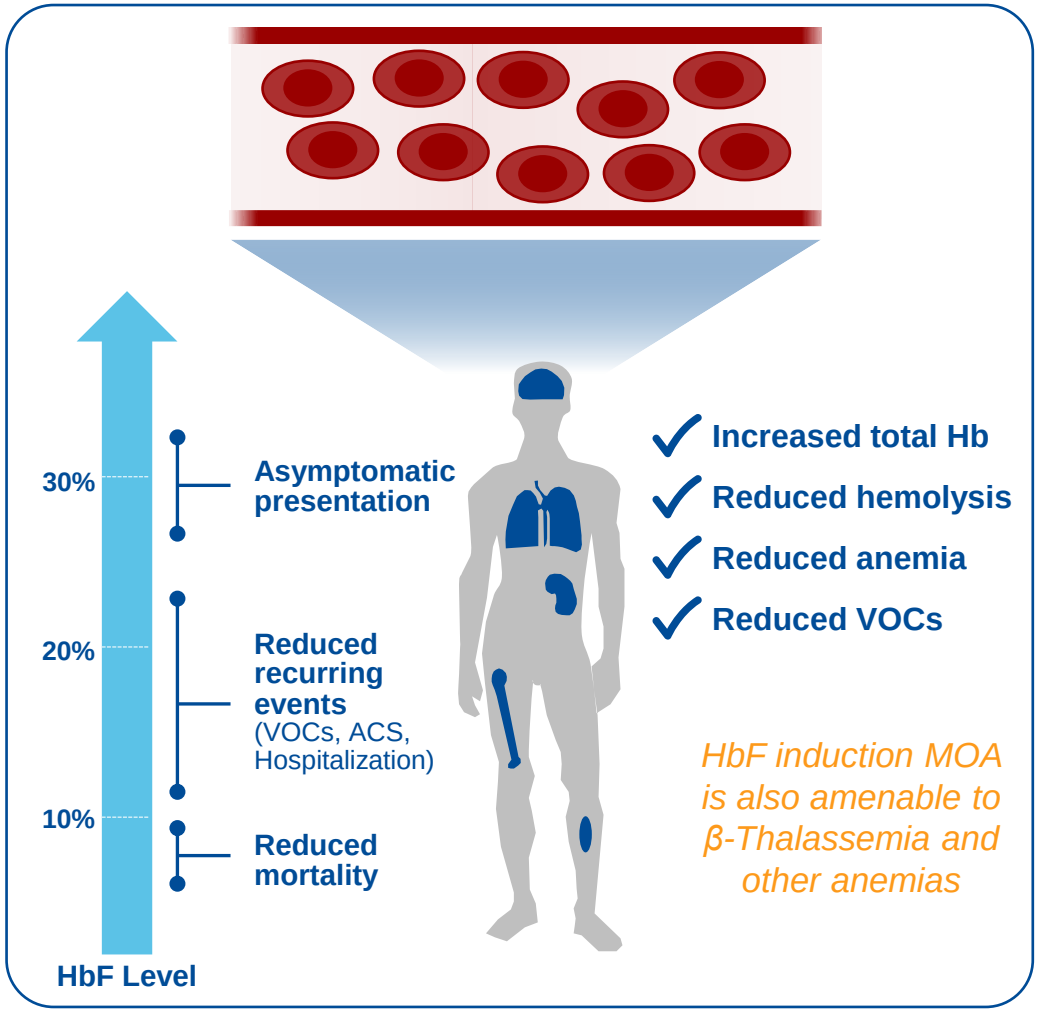

Fetal Hemoglobin Mitigates Mortality and Morbidity Risks Associated with Sickle Cell Disease (SCD)

SCD Patient



Pancellular HbF Expression and Induction

SCD Patient with High Fetal Hemoglobin (HbF) and F Cells



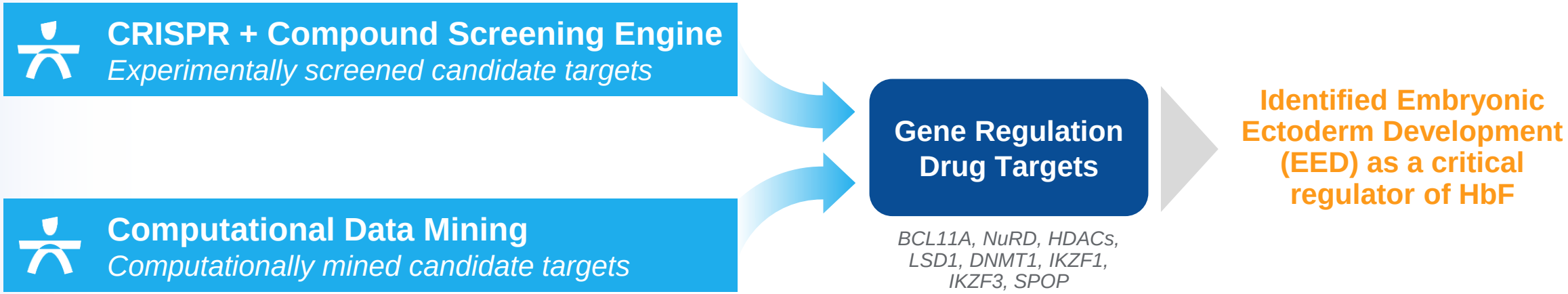
*F cells - fetal hemoglobin expressing cells; Hb: Hemoglobin; VOCs: Vaso-occlusive crisis; *Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.*

FTX-6058 has Potential to be a Transformative Therapy for SCD

Actively enrolling healthy volunteers in Phase 1 SAD/MAD studies

- Target identified from Fulcrum Product Engine
- Developed a potent and selective EED Inhibitor
- Oral, once-daily dosing supported by PK and human dose projections
- Anticipated plasma exposures required to elevate HbF in clinic are predicted to be achievable
- Demonstrates impressive preclinical pharmacological profile to potentially act as disease-modifying therapeutic
- Composition of matter patent issued

FTX-6058: A Product of Fulcrum Research Laboratories



FTX-6058: A Product of Fulcrum Research Laboratories

CRISPR + Compound Screening Engine
Experimentally screened candidate targets

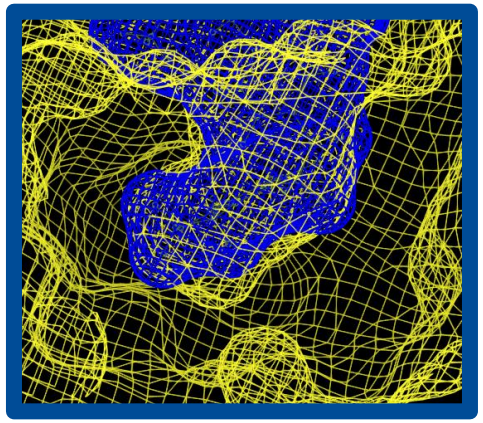
Computational Data Mining
Computationally mined candidate targets

Gene Regulation Drug Targets

BCL11A, NuRD, HDACs, LSD1, DNMT1, IKZF1, IKZF3, SPOP

Identified Embryonic Ectoderm Development (EED) as a critical regulator of HbF

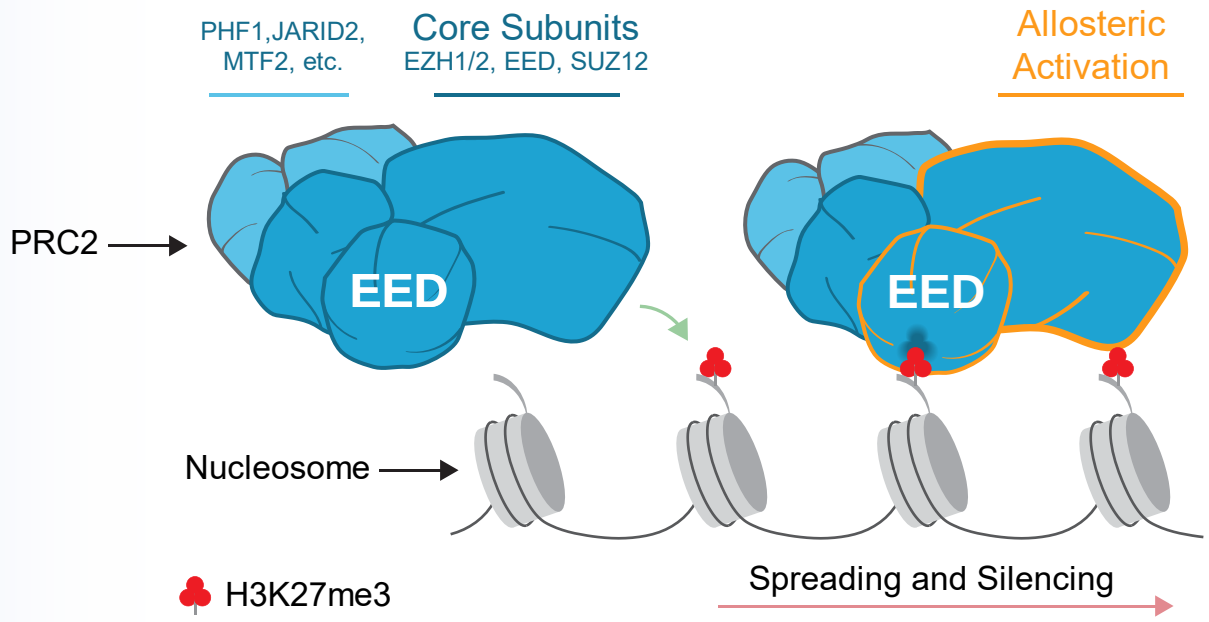
Structure-Based Drug Design



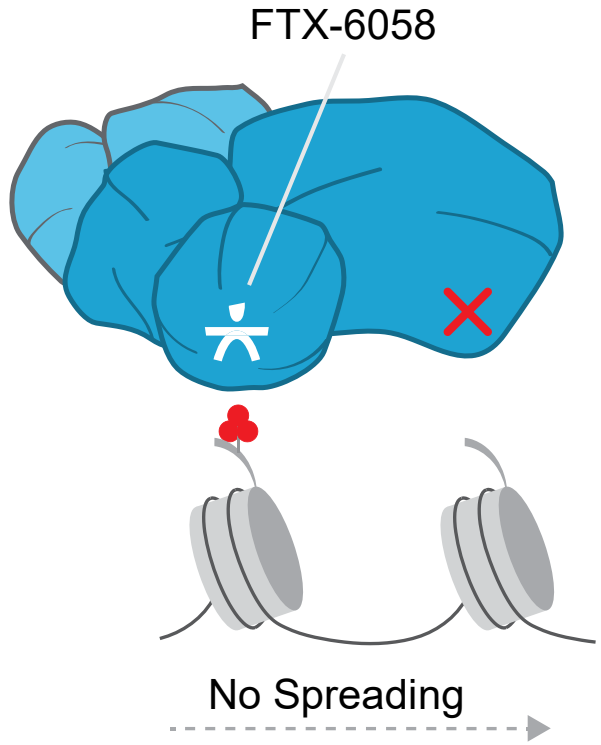
FTX-6058

- EED K_D = 0.163 nM
- PRC2 IC_{50} < 5 nM
- Highly Selective
- Clean Off-target Profile
- Composition of Matter Patent Issued Nov 2020

FTX-6058 Binds EED and Inhibits PRC2 Activity

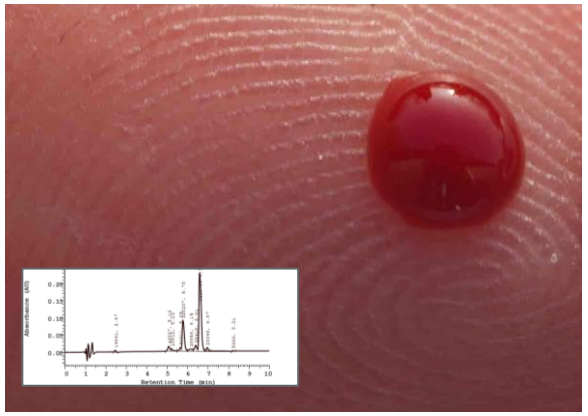
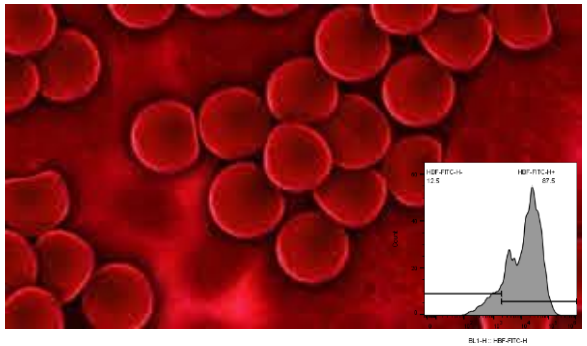
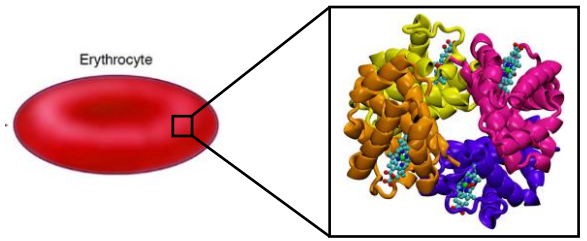


- PRC2 catalyzes tri-methylation of histone H3 at lysine 27 (H3K27me3), which results in transcriptional silencing
- EED, a subunit of PRC2, binds to H3K27me3 and increases the activity of PRC2



- FTX-6058 is a small molecule inhibitor of PRC2 activity

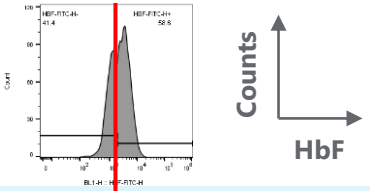
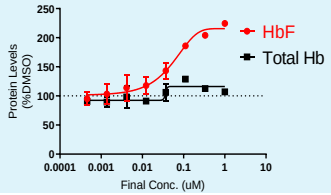
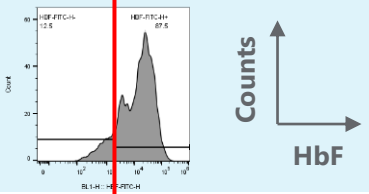
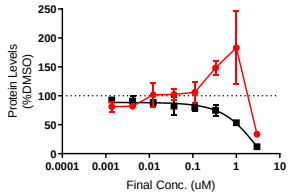
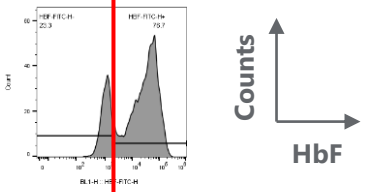
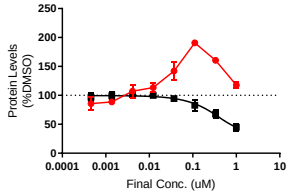
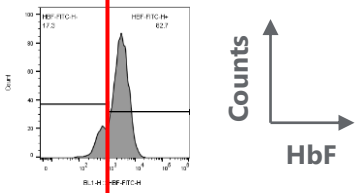
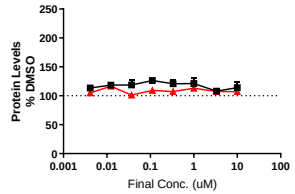
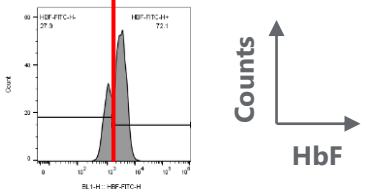
FTX-6058 Robustly Induces HbF in a Pancellular Manner

Whole Blood Parameters	Pancellular HbF Expression & Cellular Distribution	Cell-level Quantitation Methods
		
% HbF	%F cells	% Globin Chains
HPLC	Flow Cytometry	Mass Spectrometry

Hattangadi, SM. J Clin Invest. 2007; Kirk, R. Nature. 2014.

FTX-6058 Displays Robust Increases in HbF *and* F-cells

Superior in vitro Activity Relative to Other Mechanisms

Agent	HUDEP2 HbF Elisa	CD34⁺ Cells %HbF (HPLC)	CD34⁺ Cells %F-cells	CD34⁺ Cells HbF Enrichment
Vehicle	No Change	No Change	59%	
FTX-6058		↑ **2 – 3 Fold**	↑ **88%**	↑ 
DNMT1 inhibitor (5-azacytidine)		1.5 – 2 Fold	77%	
G9a inhibitor (EPZ-35544)		1.5 – 2 Fold	83%	
PDE9 inhibitor (PF-04447943 / IMR-687)		No Change	72%	

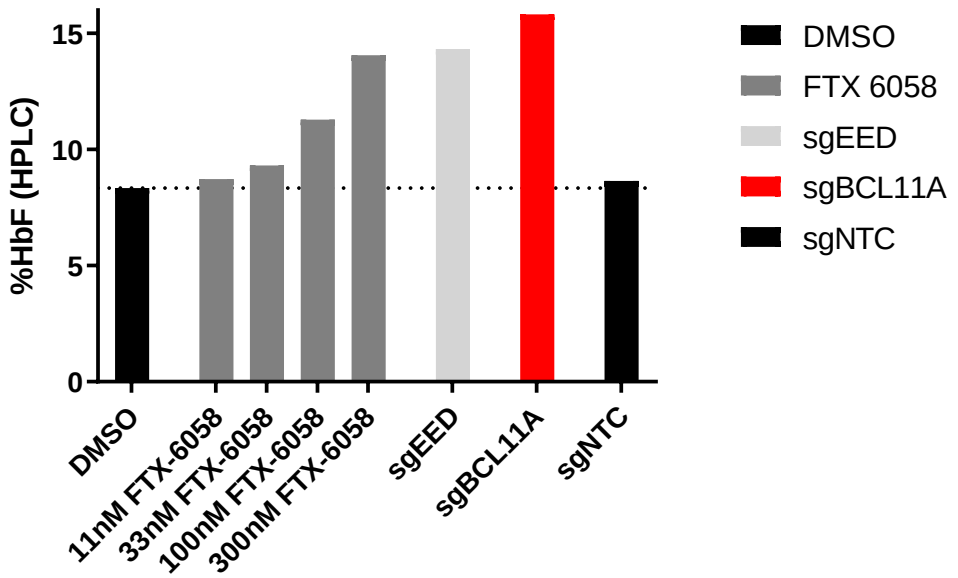
Fulcrum generated data

FTX-6058 Has Superior Pharmacologic Activity Relative to Other MOAs

EEDi has Superior Preclinical Activity Compared to Other Small Molecule HbF Inducers

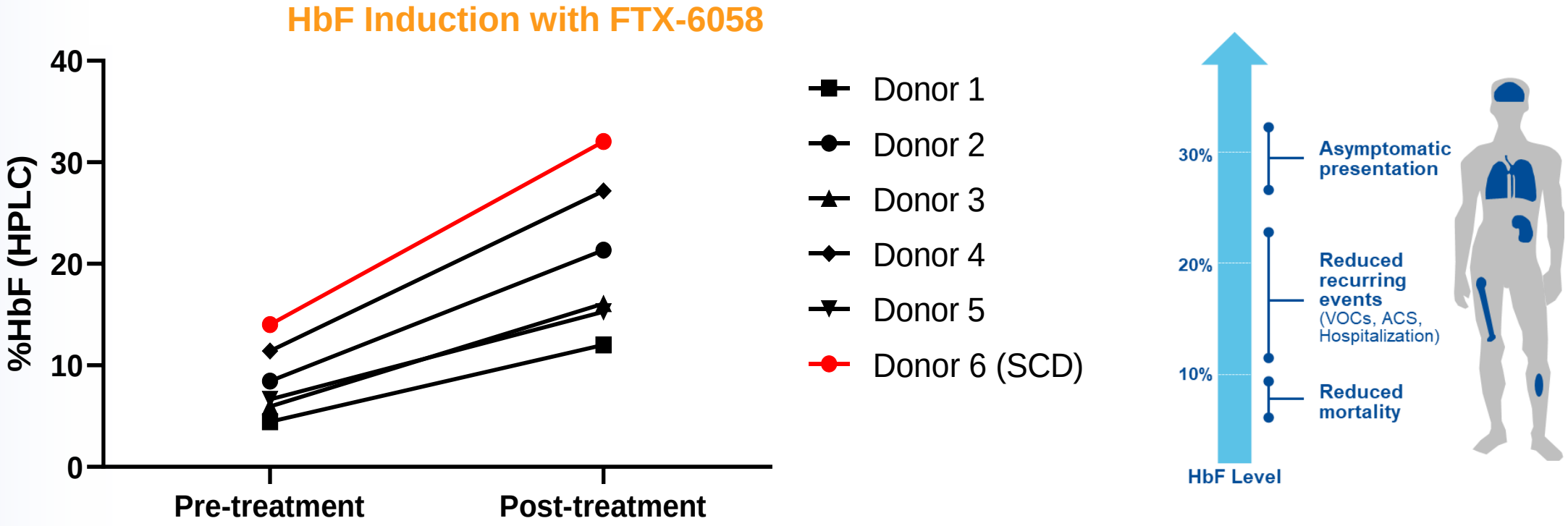
Mechanism/compound	HbF elevation detected	% HbF increase (HPLC)
FTX-6058 / FTX-6274	**Yes**	**2 – 3 fold**
Hydroxyurea (HU)	Yes	1.1 – 2 fold
DNMT1 inhibitor	Yes	1.5 – 2 fold
G9a inhibitor	Yes	1.5 – 2 fold
PDE9 inhibitor	No	None
sGC agonist	No	None
Metformin	No	None
LSD1 inhibitor	No	Toxic
DOPA Decarboxylase Inh	No	None

EEDi and EED Knock-Down (KD) Elicit Comparable HbF Induction to BCL11A KD



Fulcrum generated data; NTC: Non-targeting control

FTX-6058 Robustly Induces Fetal Hemoglobin in CD34+ Cells from Healthy and SCD Donors

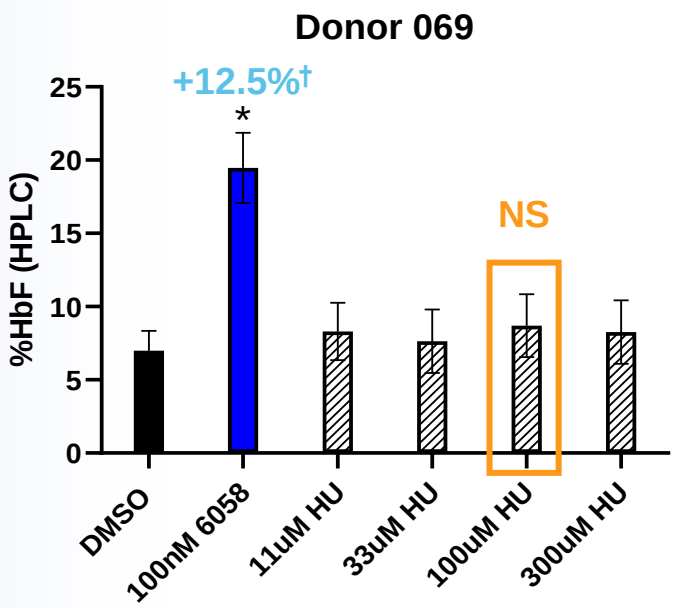


- **Observe an absolute 8 – 18% increase in HbF upon treatment with FTX-6058, which has the potential to address mortality risk and recurring events in SCD patients**
- **Small increases in HbF (1 – 5%) have the potential to provide clinical benefits to all SCD patients**
- **FTX-6058 selectively upregulates fetal globin, phenocopying Hereditary Persistence of Fetal Hemoglobin**

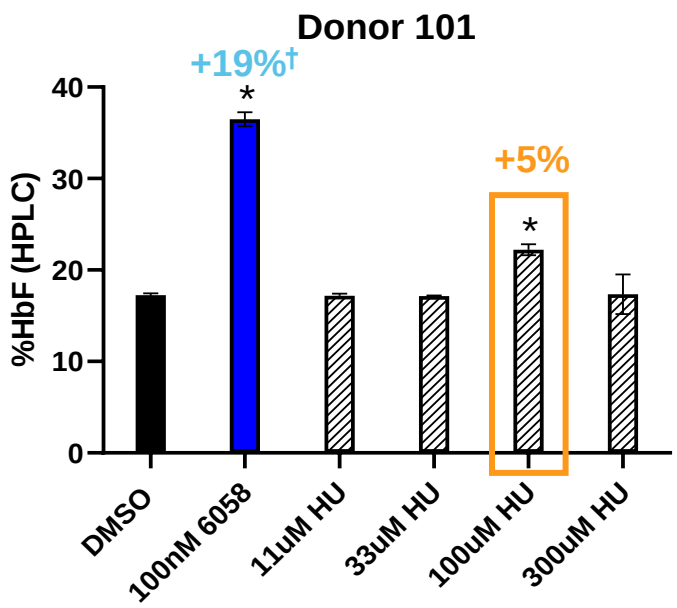
Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011; Fulcrum generated data.

FTX-6058 Induces Potent HbF Induction in Both HU Responsive and Non-responsive CD34+ Cells from Healthy Donors

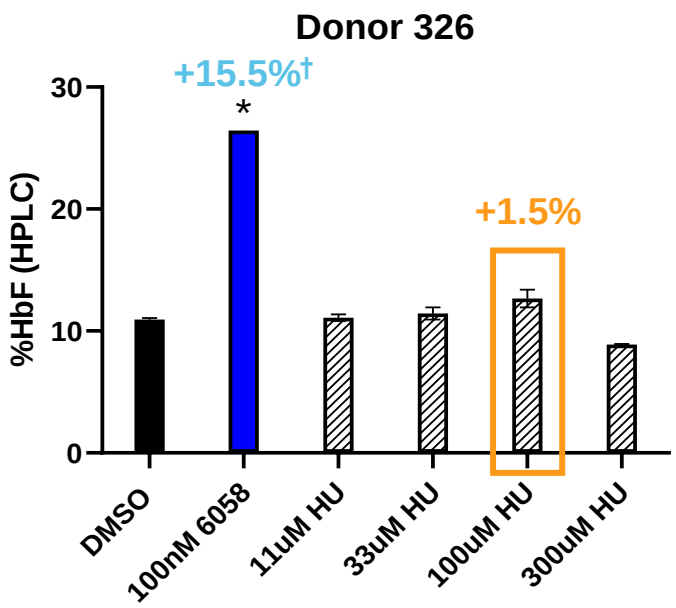
HU Non-responsive



HU Responsive

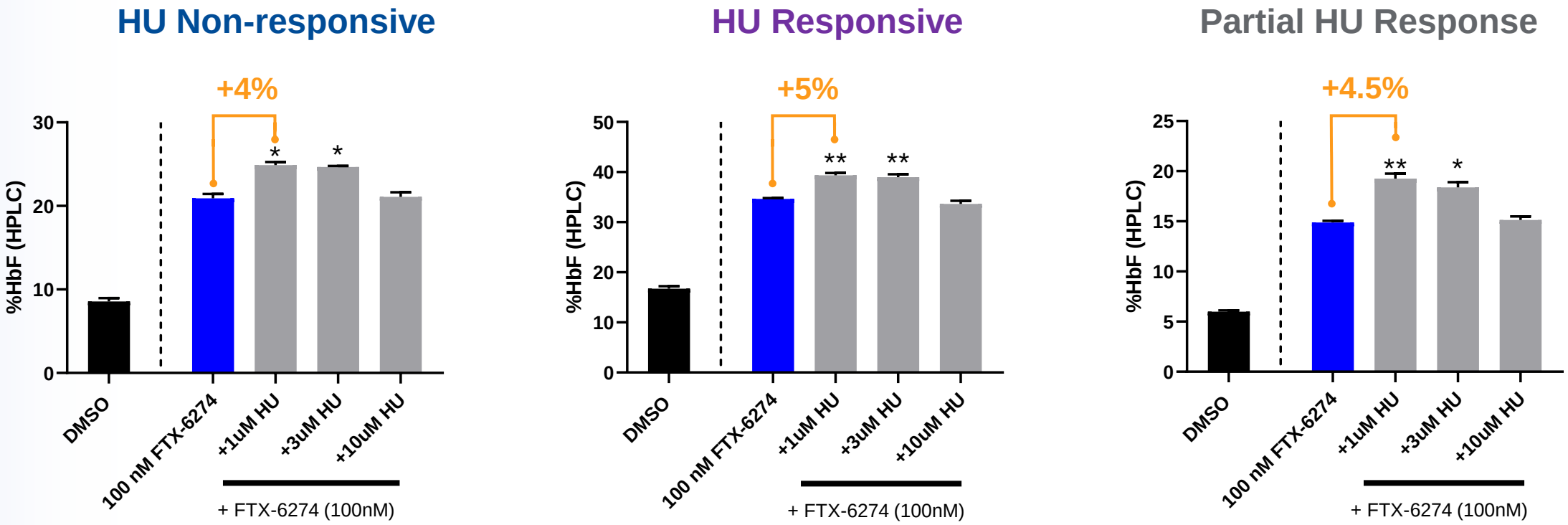


Partial HU Response



NS: Not significant; HU: Hydroxyurea; Fulcrum generated data; * p<0.05 one-way ANOVA in comparison to DMSO;
† Absolute increase in %HbF FTX-6058 vs. DMSO

Combinations with EEDi and Subclinical Concentrations of HU Enhance HbF Induction in CD34+ Cells from Healthy Donors

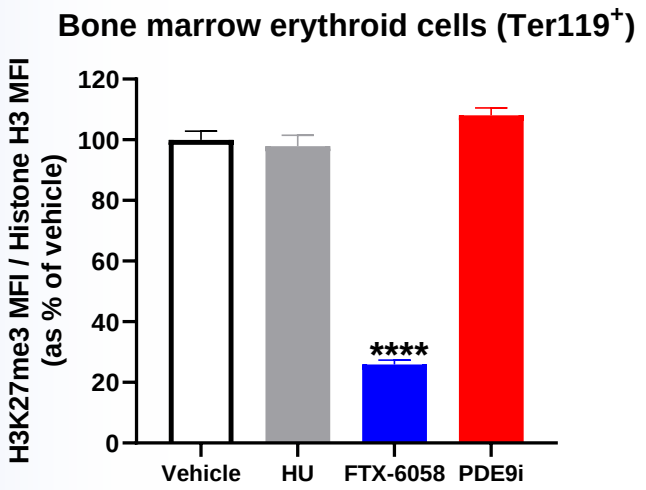


- **FTX-6274 is a structurally-related analog of FTX-6058, with a nearly identical pharmacological profile**

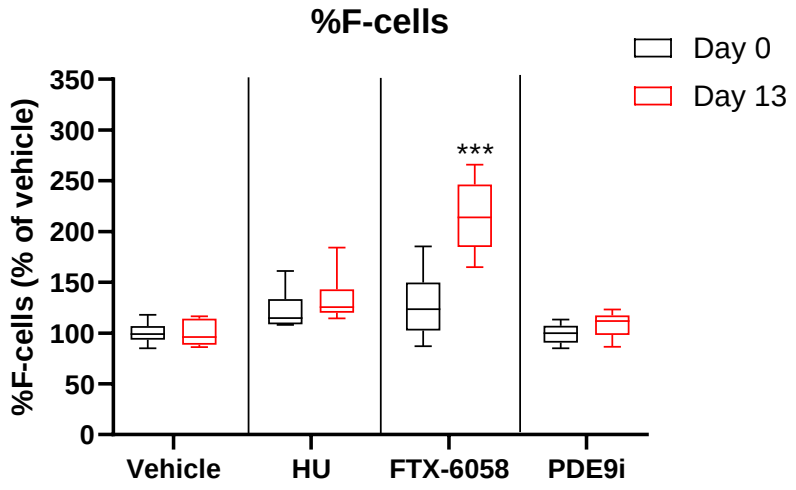
HU: Hydroxyurea; Fulcrum generated data; * p<0.05, ** p<0.01 one-way ANOVA in comparison to 100nM FTX-6274

FTX-6058 Induces HbF and Increases F-cells in the SCD Townes Mouse Model

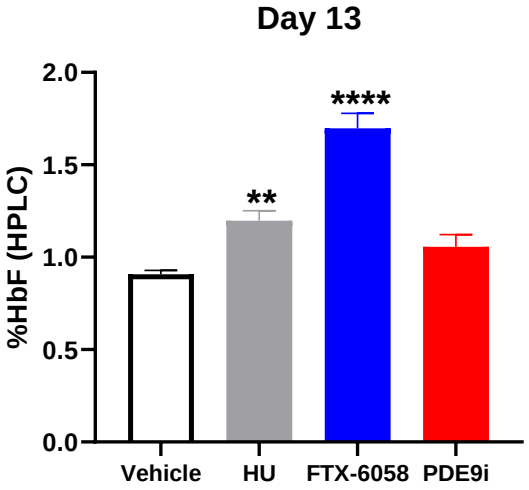
Robust Target Engagement



Increased F-cells (Flow Cytometry)



HbF Induction (HPLC)

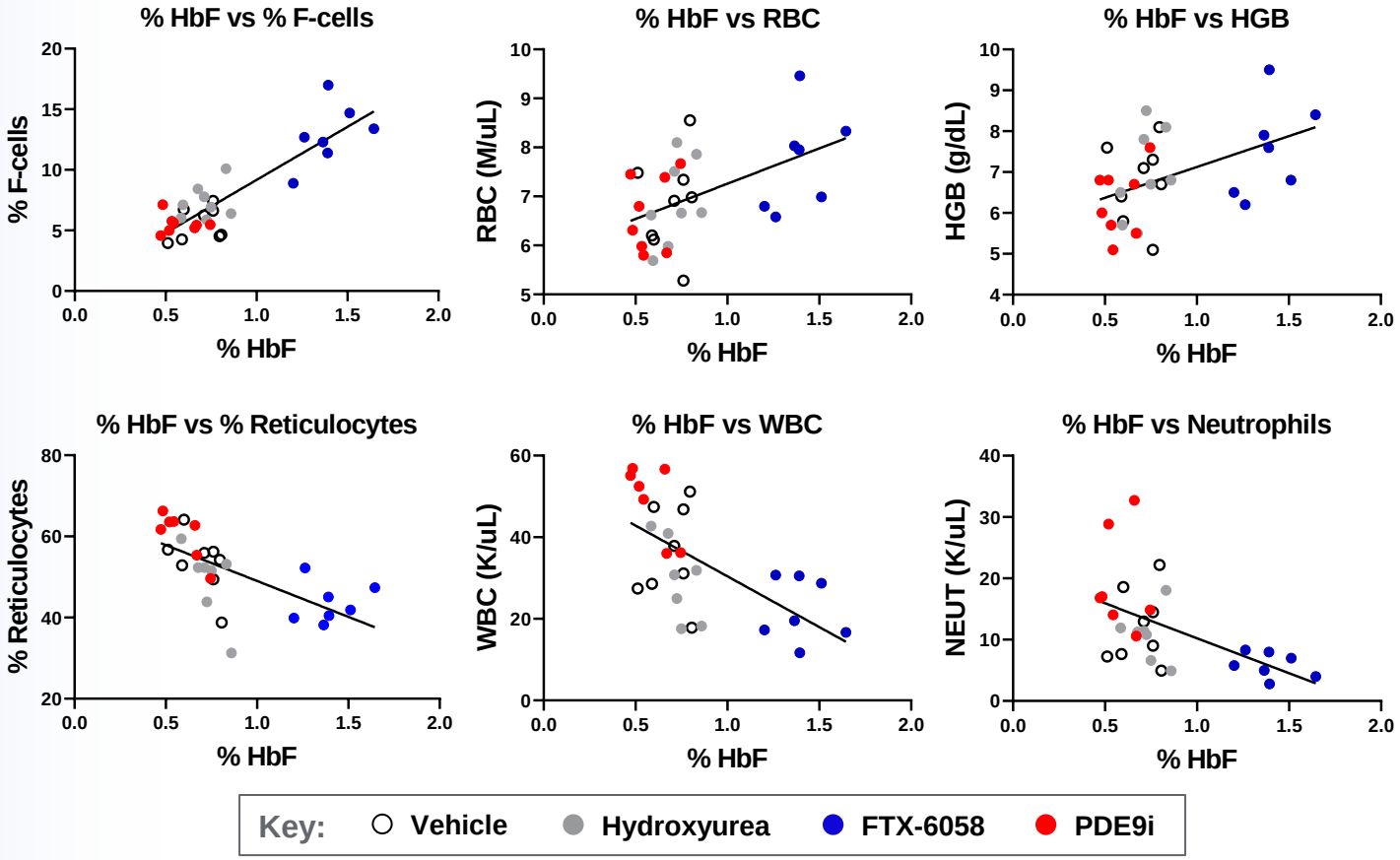


- **Observe 3-fold increase in HbF mRNA (HBG1) levels with FTX-6058**
- **Maximal target engagement maintains ~30% of H3K27me3 mark**

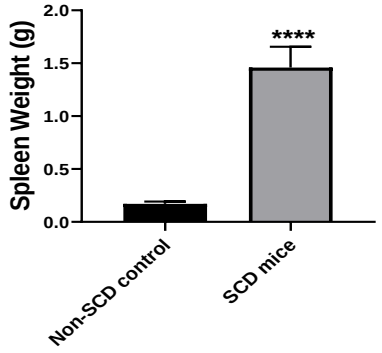
Fulcrum generated data; Townes SCD mice were orally dosed (QD) with vehicle, HU (100 mg/kg), FTX-6058 (5 mg/kg) or PDE9i (30mg/kg). ** p<0.01, *** p<0.001, **** p<0.0001, one-way ANOVA in comparison to pre-dose (Day 0) level (%F-cells) or vehicle group (target engagement and %HbF)

FTX-6058 Modifies Disease Severity in Townes SCD Mice

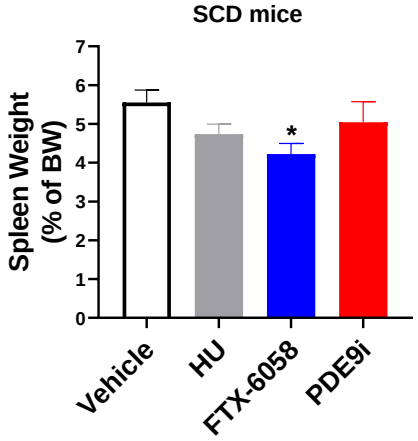
FTX-6058 Positively Impacts Hematological Parameters



FTX-6058 Reduces Splenomegaly



Splenomegaly in SCD mice is consistent with disease presentation

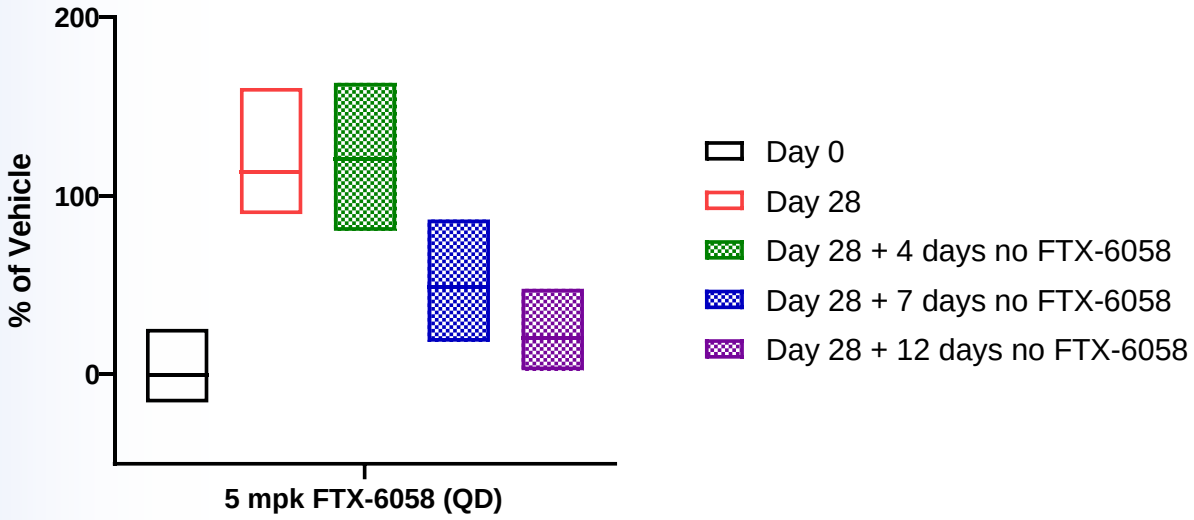


Reduction of splenomegaly is consistent with FTX-6058 hematological effects

Fulcrum generated data; RBC: Red Blood Cell; HGB: Hemoglobin; WBC: White Blood Cell; Control mice: Hb-AA mice; SCD mice: Hb-SS mice
* p<0.05 one-way ANOVA in comparison to vehicle group; **** p<0.0001 t-test in comparison to Control mice

Durability of FTX-6058 Pharmacologic Response in SCD Mice is Consistent with MOA

Persistent F-Cell Increases Following FTX-6058 Dosing Cessation at Day 28 (Flow Cytometry)



- Dose-dependent increases in F-cells and HbF protein were observed (data not shown)
- F-cell increases detected with QD dosing as low as 2.5 mg/kg (data not shown)
- FTX-6058 demonstrates time-dependent increases in F-cell and HbF expression
- Consistent with MOA and RBC half-life, F-cell increases demonstrate robust persistence, with no loss of effect up to 4 days after dosing cessation

Fulcrum generated data; FTX-6058 was administered once per day at the indicated dose in Townes SCD mice

Consistent HbF Induction Observed with FTX-6058 Across Preclinical Studies

Preclinical Models Utilized

- **HUDEP-2 Cells** (Human)
- **Healthy CD34+ Cells** (Human)
- **SCD CD34+ Cells** (Human)
- **Wild-type Mouse***
- **SCD Townes Mouse**

Key Takeaways

- ✓ **Consistent 2 – 3 fold HbF induction observed across preclinical studies**
- ✓ **Similar levels of HbF induction observed in both healthy and SCD cell models**
- ✓ **Reliable HbF induction observed in both wild-type and SCD mouse models**
- ✓ **Robustness of 2–3 fold HbF induction has the potential to translate to clinically meaningful benefits for patients with SCD**

*Assessment based on embryonic ortholog in wild-type mouse

Phase 1 Doses Will Enable Assessment of HbF Induction and Target Engagement in Healthy Volunteers

SAD Cohorts	Dose (mg)	MAD Cohorts	Expected TE level	Expected PD effect
Cohort 1	2	Cohort 1		
Cohort 2	4			
	6	Cohort 2	TE80	
Cohort 3	10	Cohort 3	TE100	HbF EC50-EC80
	20	Cohort 4	TE100	HbF EC80-EC100
Cohort 4	30			
Cohort 5	60			
Cohort 6	90			

- *Predicted human dose from PK/PD modeling is 4mg, and supports QD dosing*
- *The 6, 10, and 20mg doses are projected to achieve maximal target engagement and HbF induction*
- *Maximal target engagement maintains ~30% of H3K27me3 mark in preclinical studies*

FTX-6058 Clinical and Regulatory Strategy

Clinical Considerations

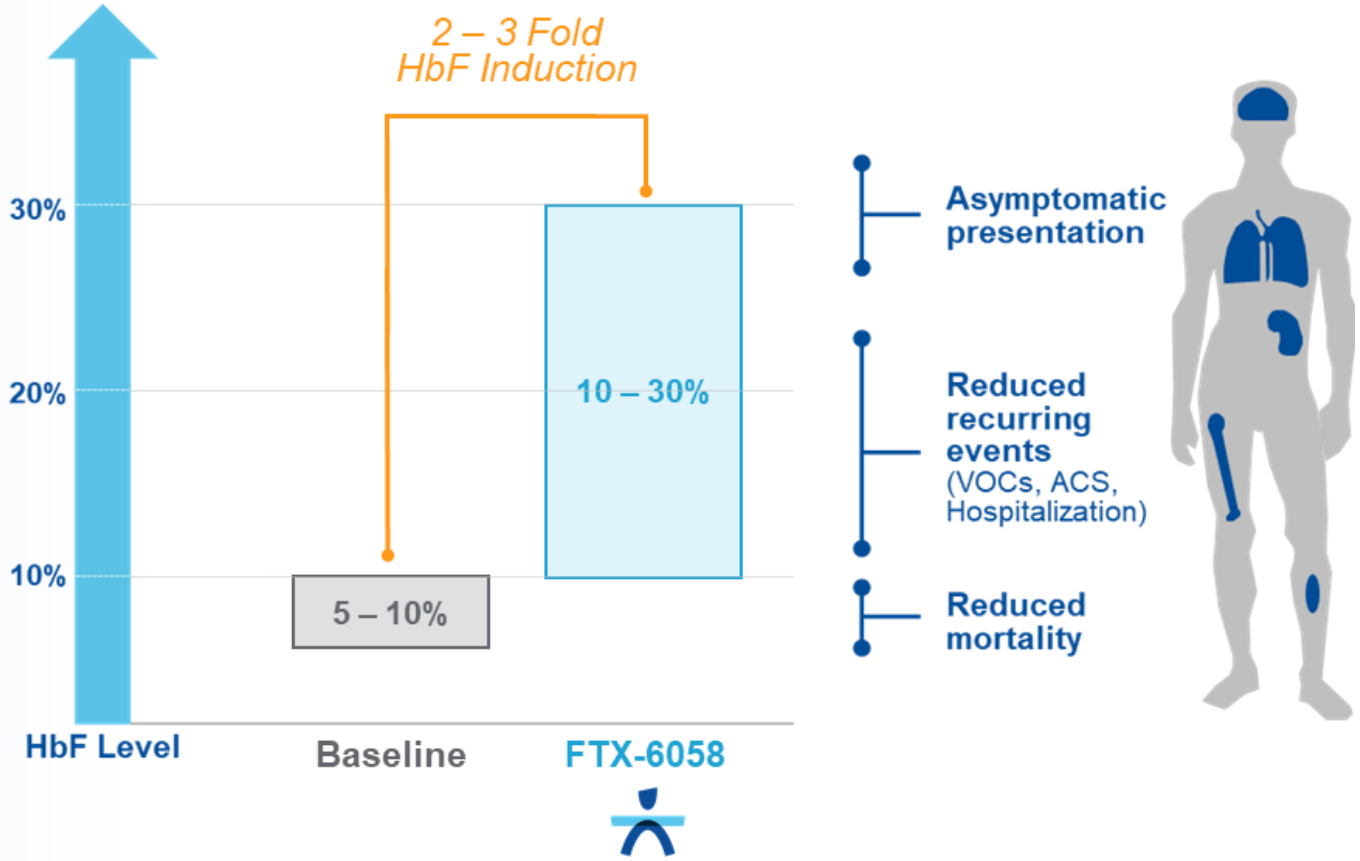
- **IND open – Phase 1 SAD/MAD actively enrolling healthy volunteers**
  - Anticipate sharing data in mid-2021
- **Anticipate initiation of trial in patients with SCD in 2021**
  - Clinical trial design currently being developed
- **Advancing clinical strategy for use in patients with β-Thalassemia**

Regulatory Considerations

- **With the first accelerated approval in SCD in the last year, the FDA has shown they are open to use of a surrogate endpoint reasonably likely to predict clinical benefit in SCD**
- **The Phase 1 study with FTX-6058 in healthy volunteers is being conducted under an open US IND following productive discussion Pre-IND**
  - Fulcrum intends to continue the dialogue with FDA and other health authorities over the course of the clinical development program
  - Fulcrum intends to seek orphan drug, Fast Track and/or Breakthrough Therapy designations as the data may warrant

Preclinical HbF Induction Observed with FTX-6058 Has the Potential to Translate to Meaningful Clinical Benefits

Robust HbF Induction May Translate to Meaningful Clinical Benefits



- EED Target identified with Fulcrum Product Engine
- Developed a potent and selective EED Inhibitor
- Oral, once-daily dosing supported by PK and human dose projections
- Impressive pharmacological profile, with potential to be a disease-modifying therapeutic
- Composition of matter patent issued
- **Actively enrolling healthy volunteers in Phase 1 SAD/MAD studies**

Powars, DR. Blood. 1984; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.

Fulcrum Therapeutics

Virtual Sickle Cell Disease KOL Event Agenda

December 15th, 2020

- **Opening Remarks and Corporate Overview** (Robert Gould)
- **SCD – A Physician's Perspective** (Dr. Maureen Achebe)
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FTX-6058: Looking Ahead

Bryan Stuart, COO

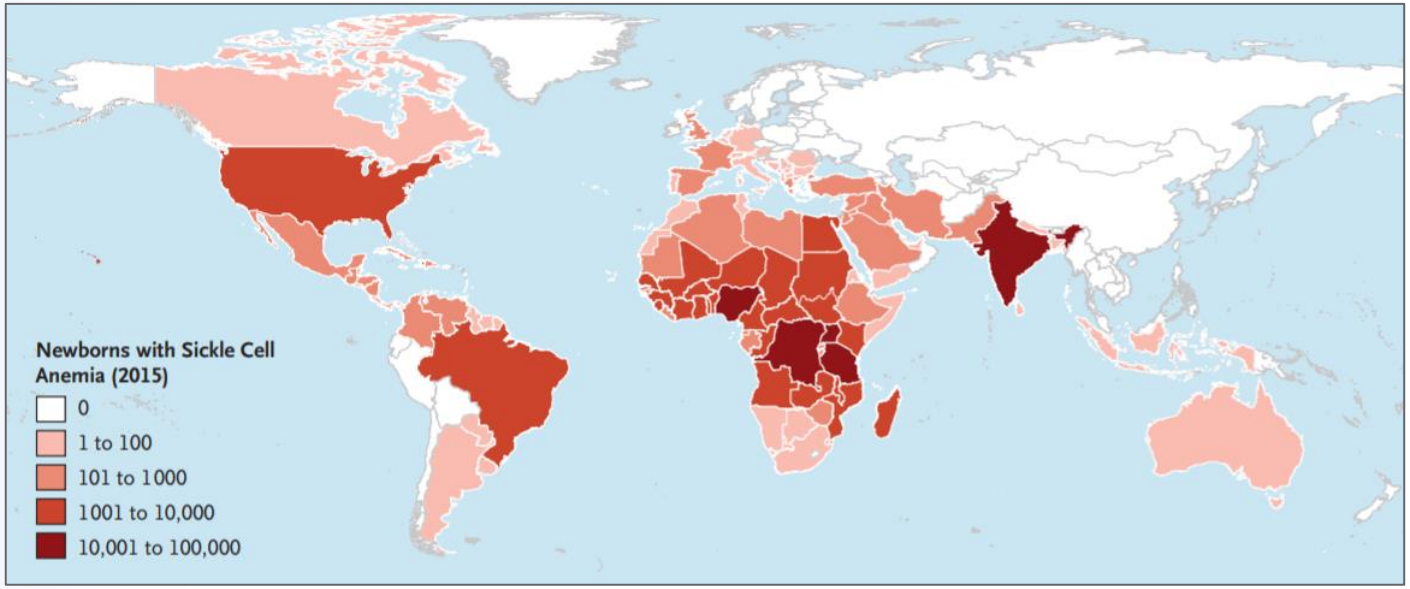
December 15th, 2020

Fulcrum Therapeutics




Sickle Cell Disease is Prevalent Globally, with Large Patient Populations in the Americas, Africa, and Middle East

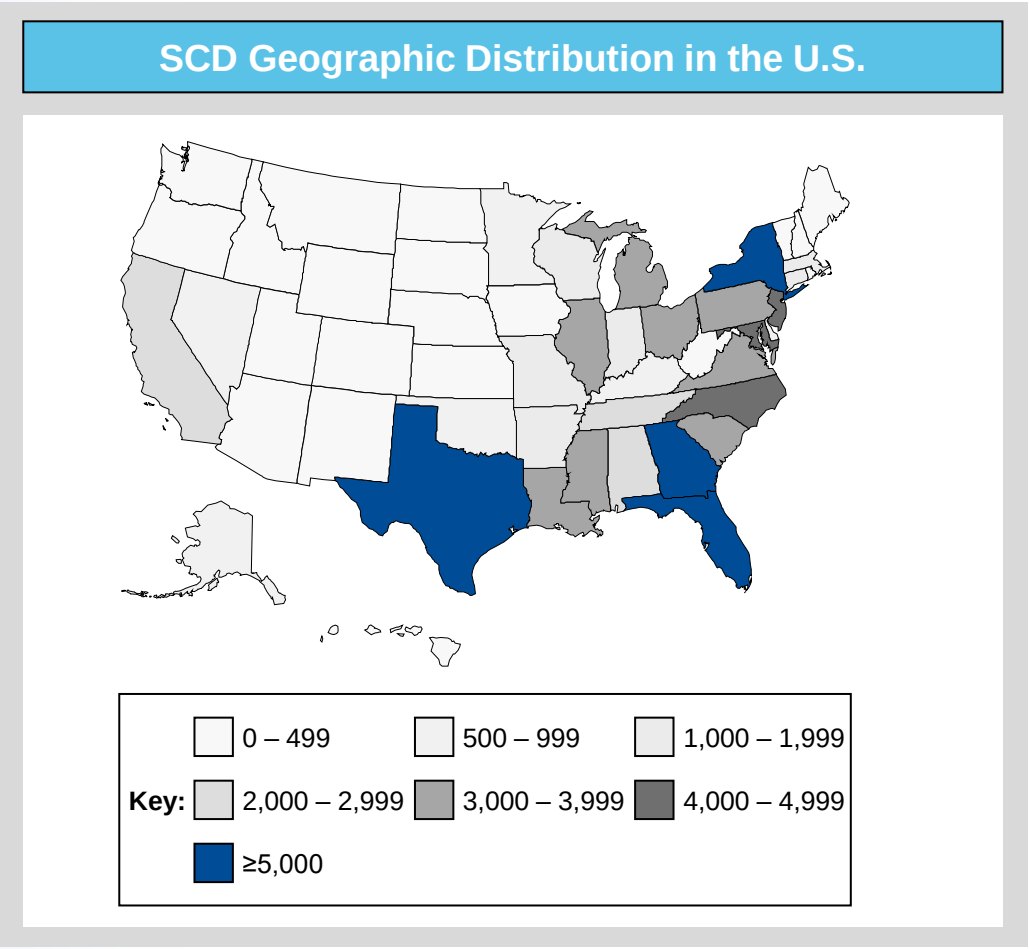
Number of Newborns with Sickle Cell Disease (SCD) in 2015



- Globally, ~300,000 babies are born with a severe hemoglobin disorder per year
- Estimated that ~1,000 children are born with SCD in Africa every day
- Approximately 5% of the world's population is a carrier for SCD or β-thalassemia
- **An estimated 100K patients in the U.S. and 50K patients in EU are currently diagnosed with SCD**

Source: Piel, FB. N Engl J Med 2017; Piel, FB. PLoS Med 2013; SCD Coalition, ASH Infographic 2016; WHO, Sickle Cell Disease, 2020, EMA Orphan Designation (EU/3/18/2125).

In the United States, Geographic Distribution of SCD Patients is Highly Concentrated

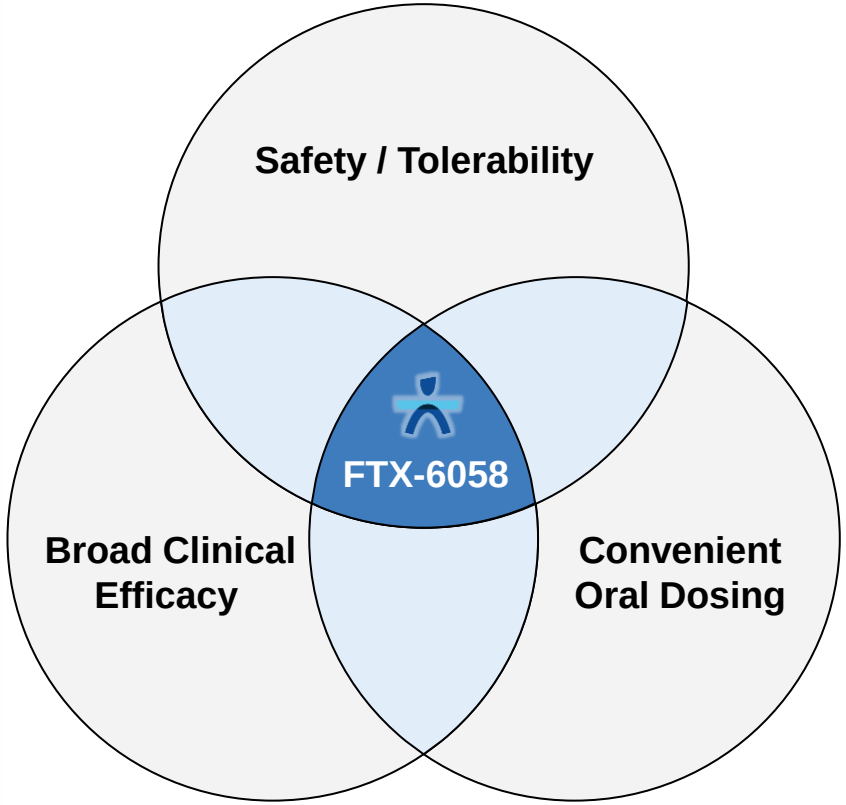


- **In the U.S. and Europe, robust prenatal and newborn screening programs enable early diagnosis of SCD patients**
- **Approximately 100K SCD patients in the U.S.**
- **Majority of the ~100K SCD patients in the U.S. are concentrated in urban areas of several key states**
  - Enables a streamlined approach to patient outreach, clinical trial recruitment, and commercial launch strategy

Source: HCUP Database 2014; Hassell. Am J Prev Med. 2010;38(4S):S512-21.

FTX-6058 Has the Potential to be Uniquely Positioned as a Best-in-Class Treatment

HbF Induction is a Compelling Opportunity for Therapeutic Differentiation



The FTX-6058 MOA has the potential to address both anemia- and VOC-driven disease

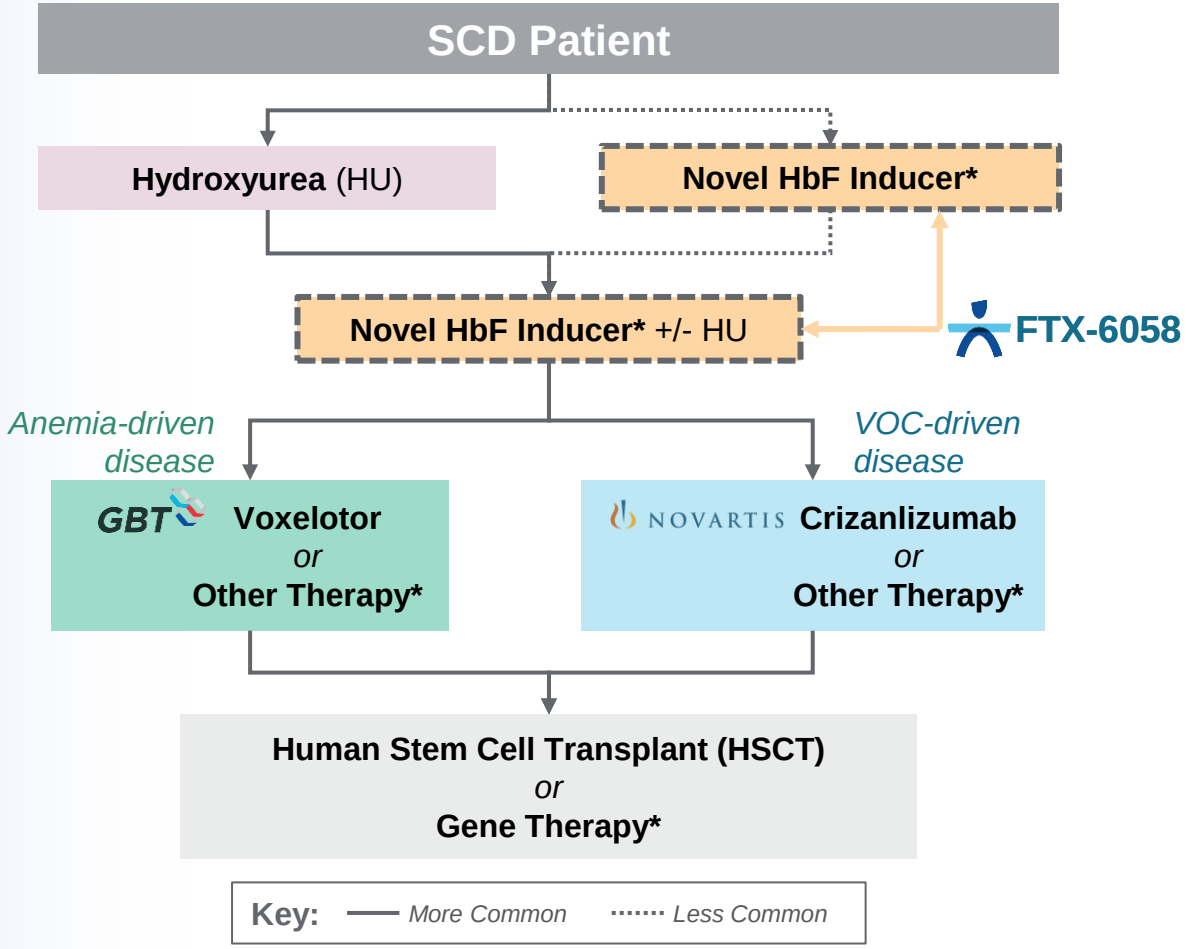
HU tolerability issues and HSCT/gene therapy safety risks provide FTX-6058 an opportunity to differentiate on safety and tolerability

The projected once-daily, oral dosing of FTX-6058 is likely advantageous over other methods such as IV infusion and bone marrow transplant

HU: Hydroxyurea; HSCT: Human Stem Cell Transplant

Novel Therapies are Necessary Given the Enduring Unmet Needs of SCD Patients

Potential Future SCD Treatment Paradigm

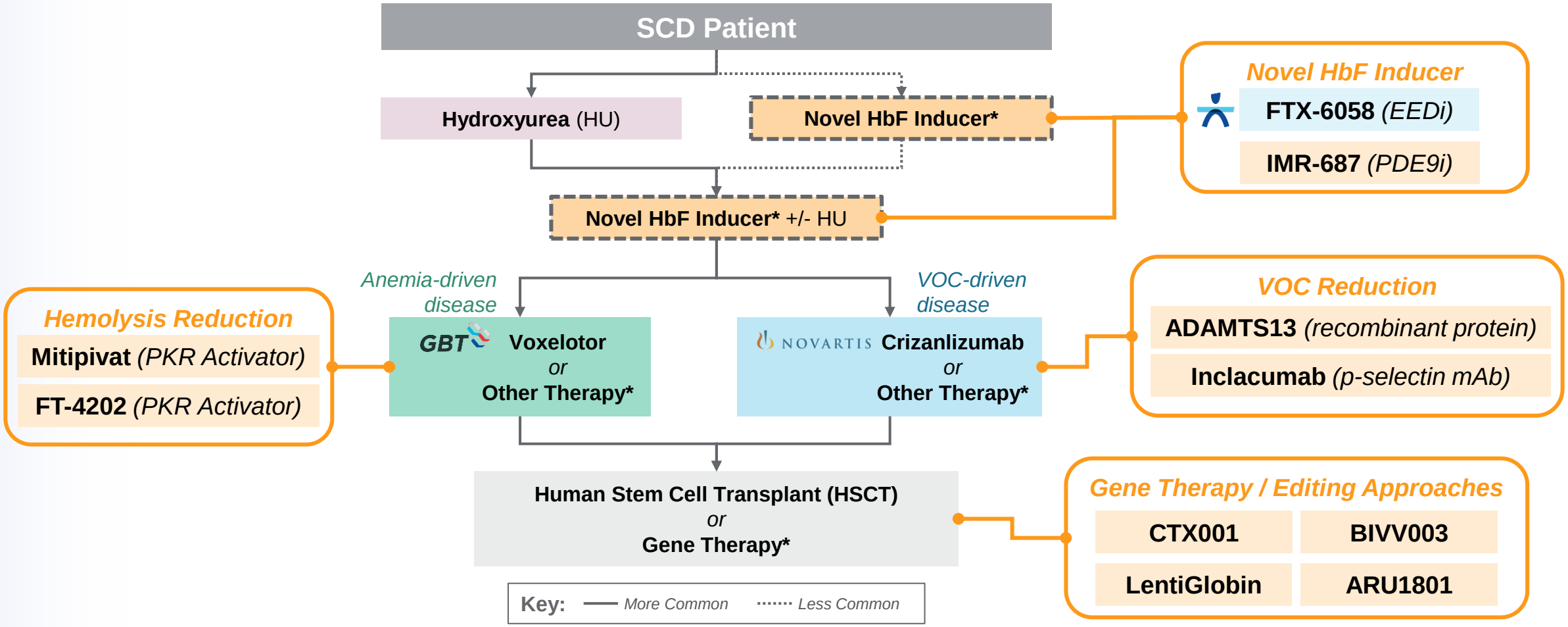


- **Majority of SCD patients experience shortcomings with HU treatment**
  - Limited clinical efficacy, tolerability issues, and safety risks
- **SCD therapies are primarily focused on addressing either anemia- or VOC-driven disease**
- **Given the safety risks associated with conditioning regimens and access limitations, HSCT and gene therapy is likely to be utilized as a last-line treatment**
- **Novel HbF inducers have the potential to address both anemia- and VOC-driven disease**
  - May be utilized as monotherapy or combination therapy with HU

* Therapies currently in clinical development; Endari has FDA approval, but was not included due to limited current and anticipated physician utilization

Key Clinical-stage Assets are Primarily Focused on Specific Aspects of Disease, with Gene Therapy Becoming Increasingly Competitive

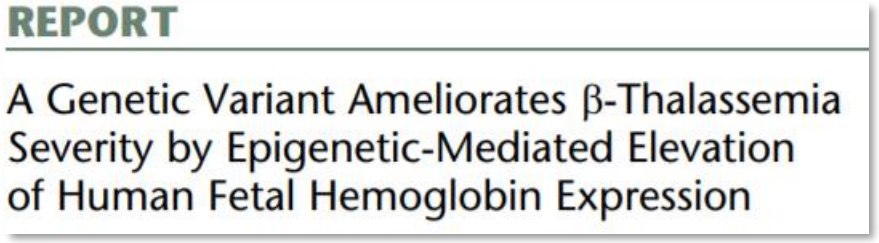
Potential Future SCD Treatment Paradigm



* Includes select therapies currently in clinical development; Endari has FDA approval, but was not included due to limited current and anticipated physician utilization

HbF Induction is an Attractive Therapeutic Approach in β-Thalassemia

HbF is a Known Disease Modifier of β-Thalassemia


REPORT

A Genetic Variant Ameliorates β-Thalassemia Severity by Epigenetic-Mediated Elevation of Human Fetal Hemoglobin Expression


Targeted Fetal Hemoglobin Induction for Treatment of Beta Hemoglobinopathies

Susan P. Perrine, MD[a,*], Betty S. Pace, MD[b], Douglas V. Faller, MD, PhD[c]


Manipulation of developmental gamma-globin gene expression: an approach for healing hemoglobinopathies

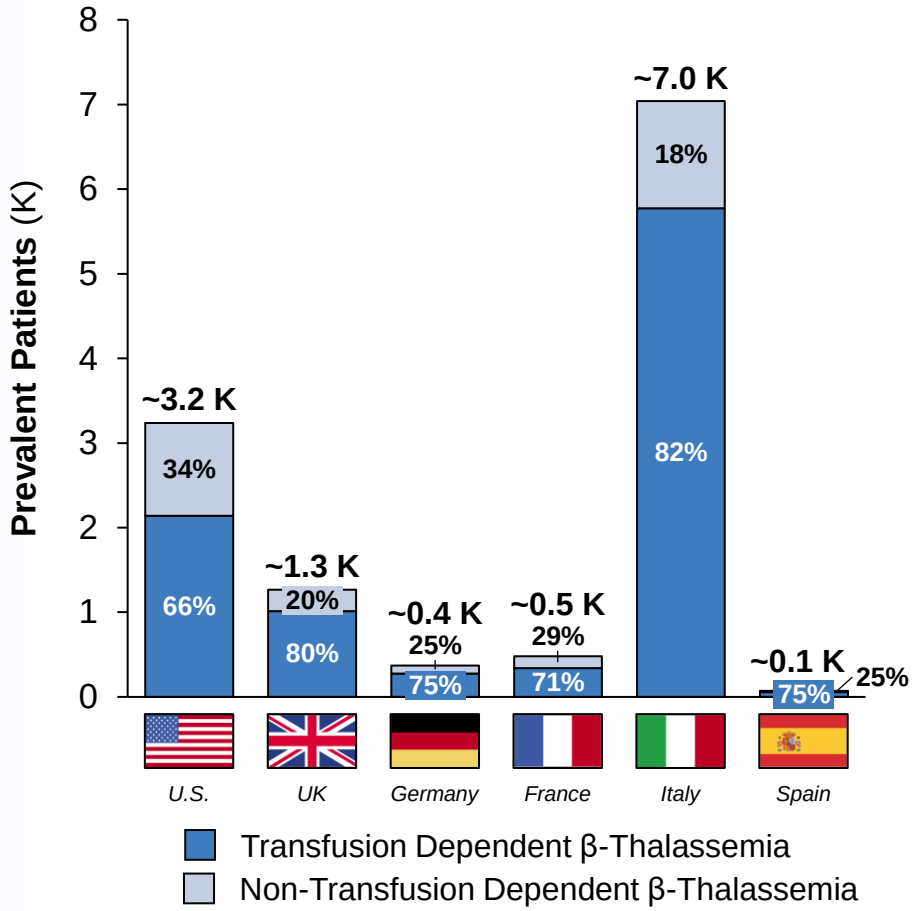
Vigneshwaran Venkatesan, Saranya Srinivasan, Prathibha Babu, Saravanabhavan Thangavel

- **β-Thalassemia patients often experience numerous morbidities during disease progression, such as:**
  - Abnormal hematopoiesis
  - Pulmonary hypertension
  - Venous thromboembolism
  - Heart Failure
  - Leg Ulcers
  - Others (e.g., diabetes, osteoporosis)
- **Increased HbF levels are associated with a milder disease course in β-Thalassemia patients**
- **Novel therapeutics capable of inducing HbF and total Hb have the potential to address β-Thalassemia and other anemias**

Musallam, KM. Blood. 2012; Chen, D. Am J Hum Genet. 2017; Perrine, SP. Hematol Oncol Clin North Am. 2014; Venkatesan, V. Mol Cell Biol. 2020

There are >12K Patients Diagnosed with β-Thalassemia in the U.S. and EU5

β-thalassemia Prevalence in U.S. and EU5 (2019)



- **β-Thalassemia has a higher prevalence in Mediterranean and Asian populations**
- **Studies in the U.S., Italy, UK, and France suggest that on average ~75% of affected patients may be Transfusion Dependent β-Thalassemia (TDT)**
  - TDT rates vary between 50 – 80% due to differences in inter-study ethnic composition, design, and dependence definition
- **Fulcrum is advancing a clinical strategy for FTX-6058 in patients with β-Thalassemia**

Source: Maserejian. Blood. 2015.; UK National Haemoglobinopathy Registry; Cario. Ann Hematol. 2000.; Thuret. Haematologica 2010.; Angelucci. Blood. 2016.; Cela. Pediatric Blood Cancer National registry of hemoglobinopathies in Spain (REPHem). 2016.; UN World Population Prospects.

Summary and Next Steps

As a novel orally bioavailable HbF inducer, FTX-6058 has an opportunity to be a transformative therapy for patients with SCD and β-Thalassemia

- SCD and β-Thalassemia have significant unmet need, and require novel therapies
- An orally bioavailable compound that elevates fetal hemoglobin (HbF) has the potential to provide meaningful clinical benefit to a broad range of SCD and β-Thalassemia patients
- Fulcrum's Engine identified the EED target, and developed FTX-6058, a potent small molecule HbF inducer in both human cells and genetically engineered SCD mice
- Oral, once-daily dosing with FTX-6058 is projected in humans from preclinical studies
- Actively enrolling healthy volunteers in Phase 1 SAD/MAD studies

Next Steps

- **Anticipate initiating an FTX-6058 clinical trial in patients with SCD in 2021**
- **Advancing a clinical strategy for FTX-6058 in patients with β-Thalassemia**

Fulcrum Therapeutics

Virtual Sickle Cell Disease KOL Event Agenda

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Thank you!

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Q&A

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