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

Presented by Christopher Moxham on behalf of:

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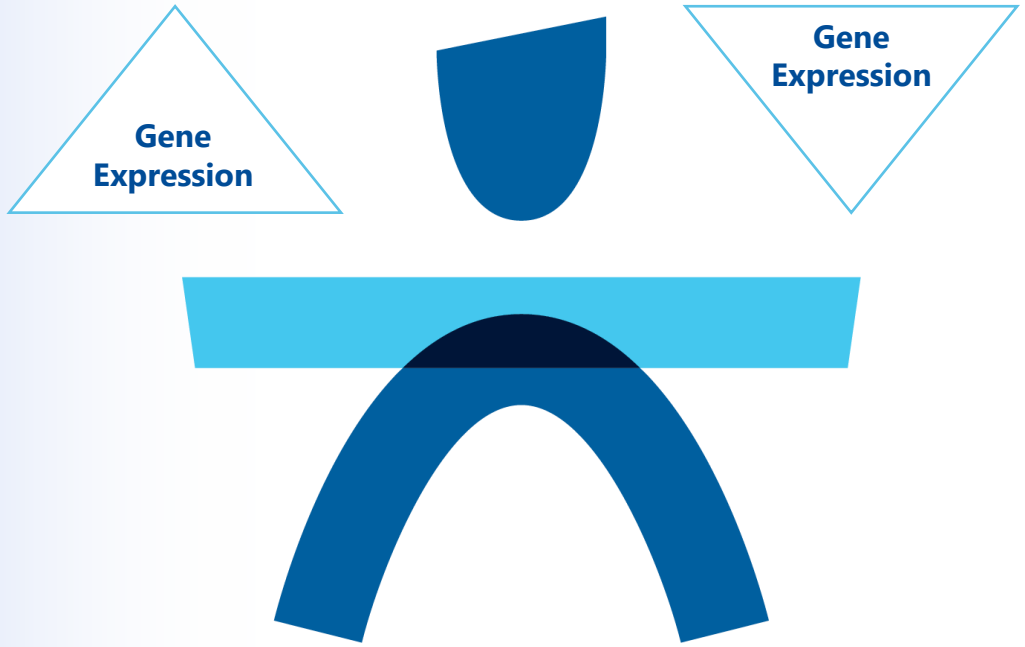
Disclosure

All authors are current or former employees and equity holders of Fulcrum Therapeutics.

Fulcrum Overview

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

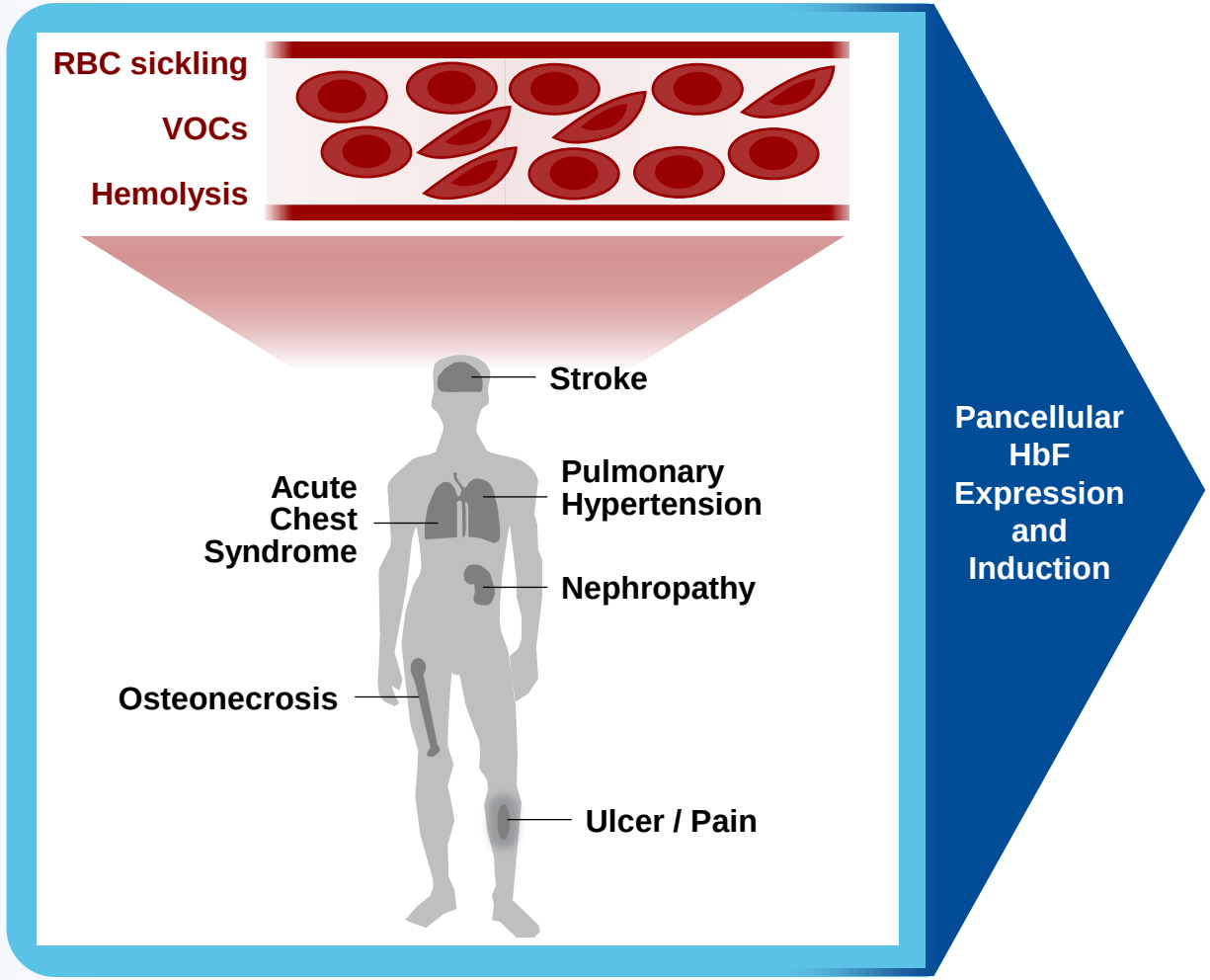


- ~7,000 genetically defined diseases today
- We are building on decades of research highlighting gene expression role in disease
- High-throughput product engine designed to rapidly identify and validate drug targets that can modulate gene expression and treat disease at its root cause
- Focus on small molecules as therapeutic modality

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

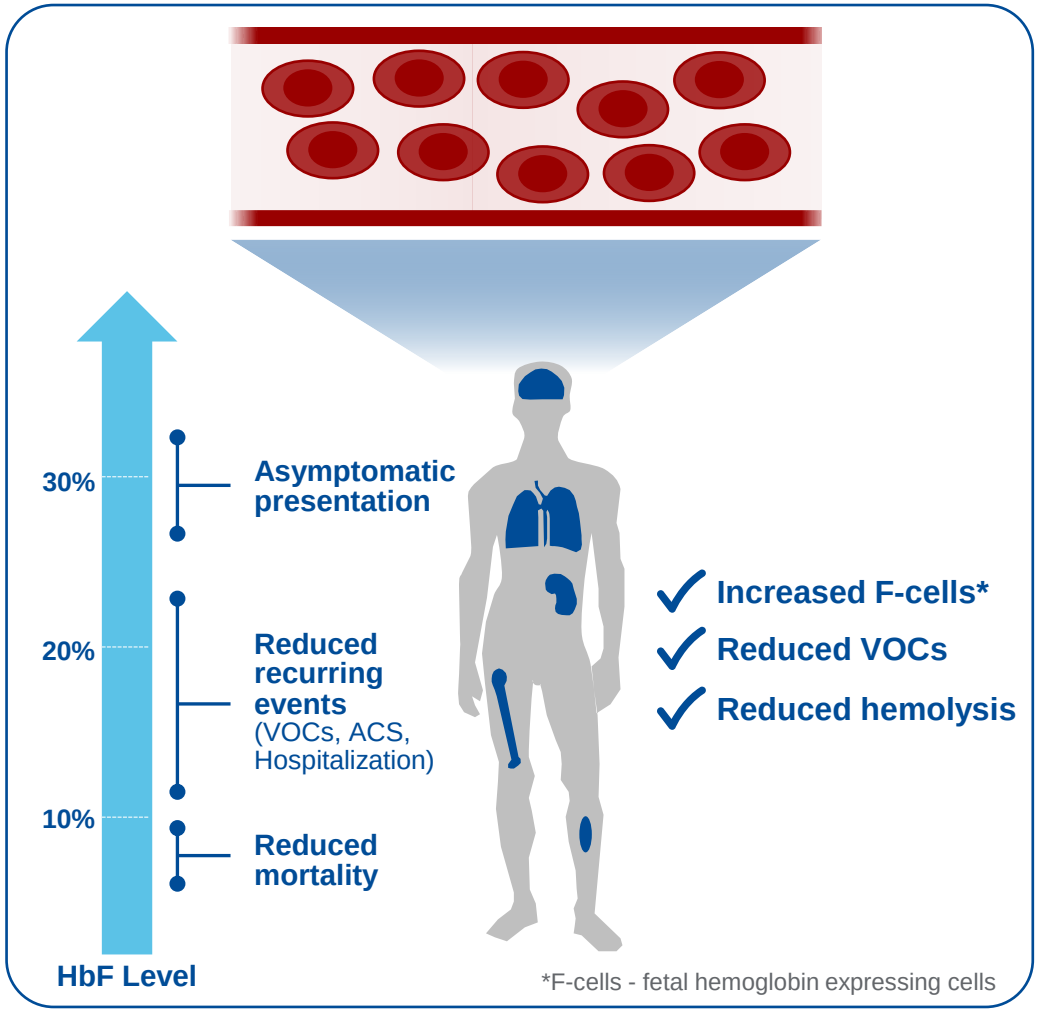
Fetal Hemoglobin Mitigates Mortality and Morbidity Risks Associated with Sickle Cell Disease (SCD)

SCD Patient



Pancellular HbF Expression and Induction

SCD Patient with High Fetal Hemoglobin (HbF)



Powars, DR. Blood. 1984; Estepp, JH. Br J Haematol. 2013; Platt, OS. NEJM. 1994; Akinsheye, I. Blood. 2011.

Preclinical Executive Summary: FTX-6058 for Sickle Cell Disease

- Highly potent (~1 nM) and selective small molecule with clean off-target profile
- Superior pre-clinical activity relative to SOC and competitor compounds
- Potent upregulation of HBG mRNA and pancellular induction of HbF protein in primary human erythroid cells
- Clinically desirable globin profile (e.g., % HbF) in differentiated CD34+ cells from multiple healthy and SCD donors
- PK/Target Engagement relationship established
- Elevation of human fetal hemoglobin mRNA (HBG1), protein (HbF), and F-cells in Townes mouse model of SCD
- 28-day GLP toxicology studies completed, and GMP material scale-up for Phase 1 is complete
- PK and human dose projections support once-daily, oral dosage of FTX-6058

FTX-6058: A Product of Fulcrum Research Laboratories

CRISPR + Compound Screening Engine
Experimentally screened candidate targets

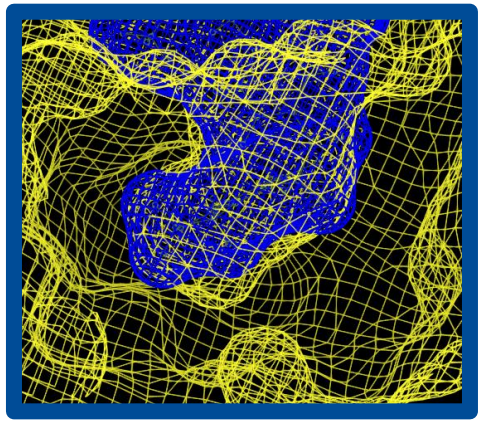
Computational Data Mining
Computationally mined candidate targets

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

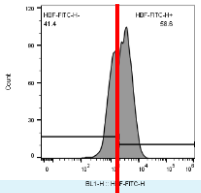
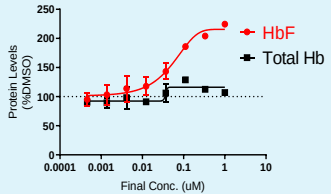
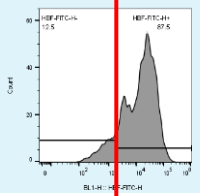
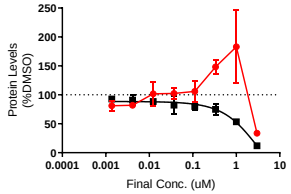
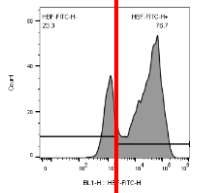
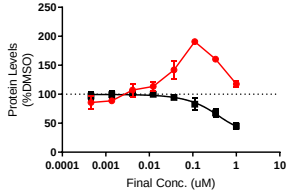
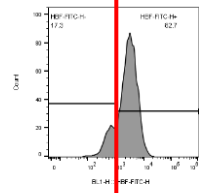
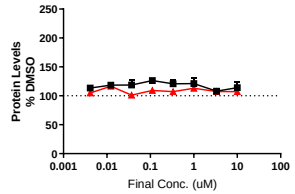
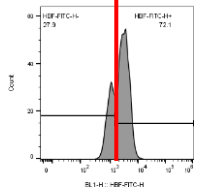


FTX-6058

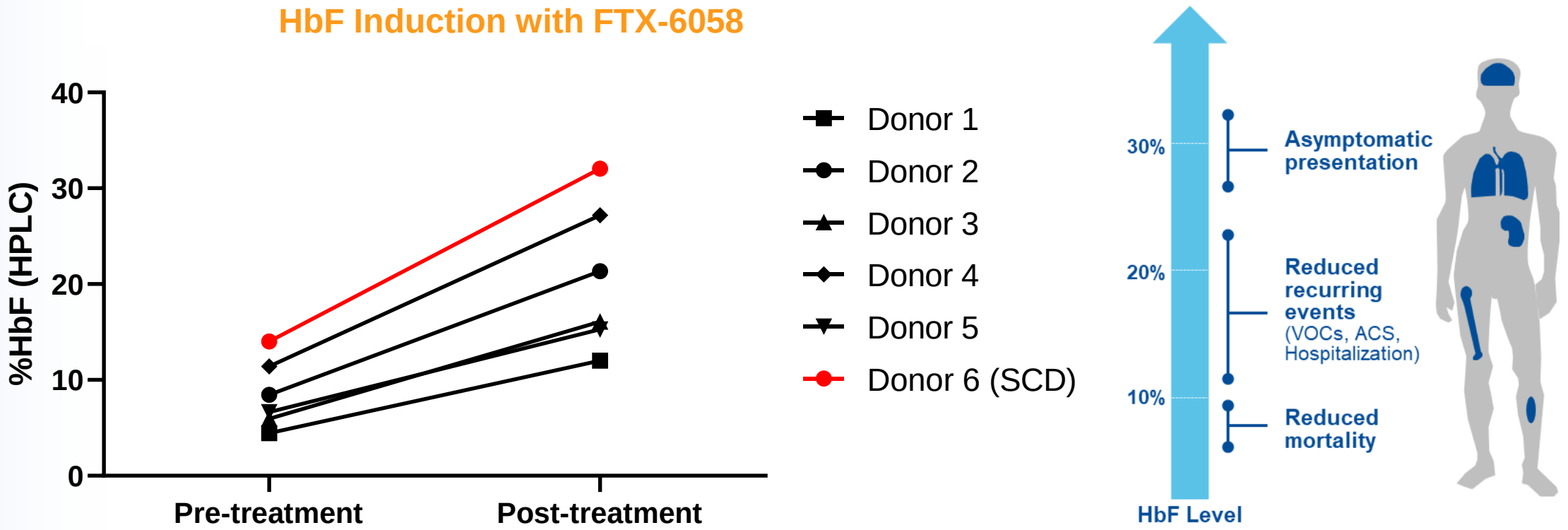
- EED K_D = 0.163 nM
- PRC2 IC_{50} < 5 nM
- Highly Selective
- Clean Off-target Profile

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

Superior in vitro Activity Relative to Other Mechanisms

	HUDEP2	CD34+ Cells		
Agent	**HbF Elisa**	**HbF HPLC**	**%F-cells**	**HbF/cell**
Vehicle	N/A	N/A	59%	
FTX-6058		**2 – 3 Fold** ↑	**88%** ↑	 ↑
DNMT inhibitor (5-azacytidine)		1.5 – 2 Fold	77%	
G9a inhibitor (EPZ-35544)		1.5 – 2 Fold	83%	
PDE9 inhibitor (PF-04447943 / IMR-687)		None	72%	

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



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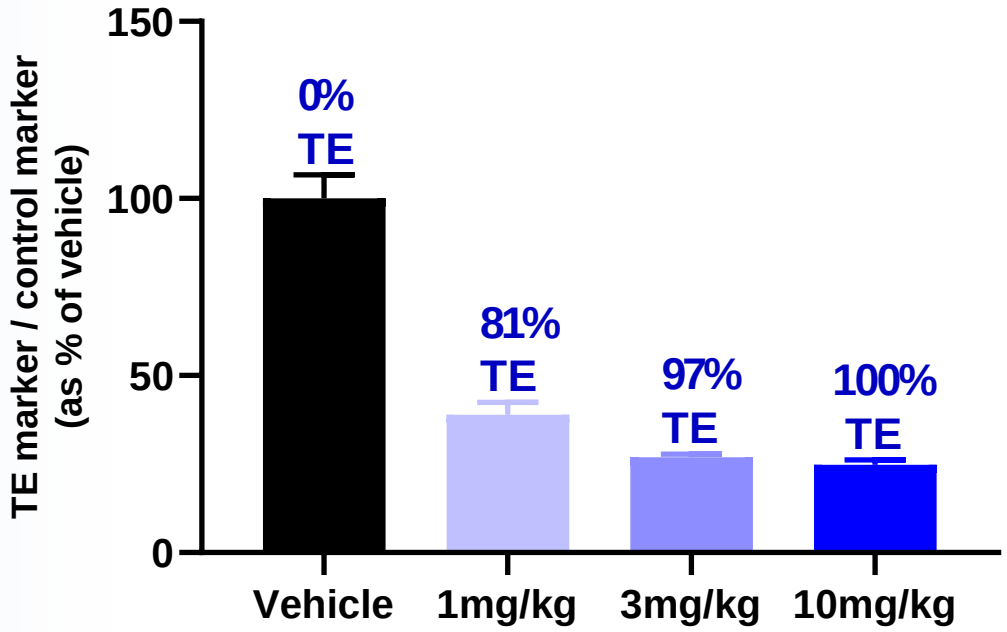
- **Observe an absolute 8 – 18% increase in HbF upon treatment with FTX-6058, which has the potential to address mortality risk and recurring events in SCD patients**
- **Small increases in HbF (1 – 5%) have the potential to provide clinical benefits to all SCD patients**

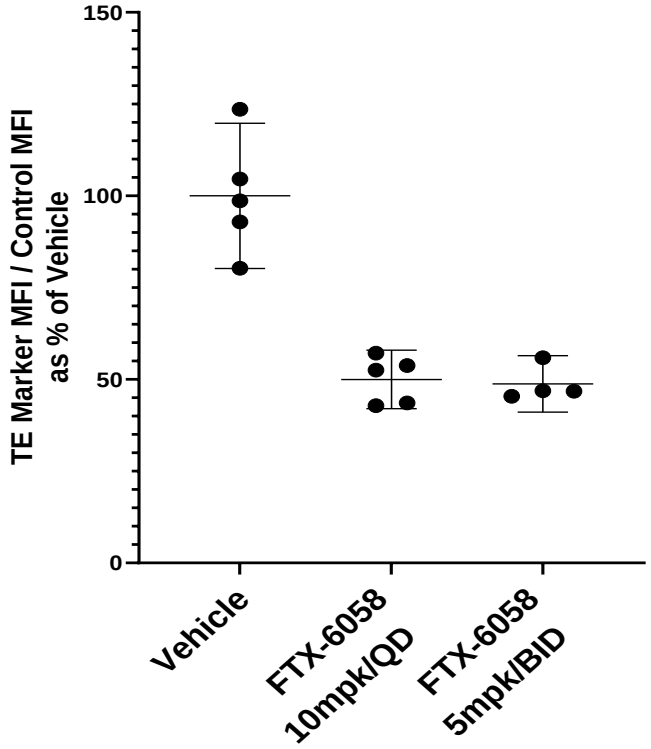
Meaningful Target Engagement is Anticipated in Clinic

Target Engagement
(Bone Marrow)



WT CD1 mice; 5 days of QD PO treatment

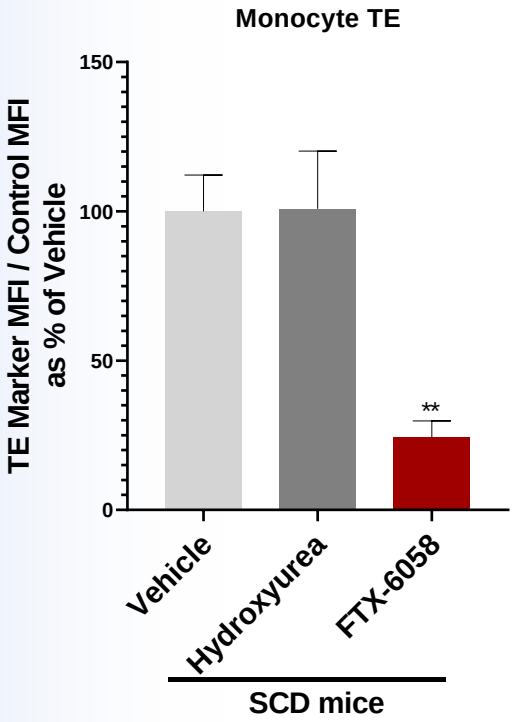
Target Engagement
(Blood Monocytes)



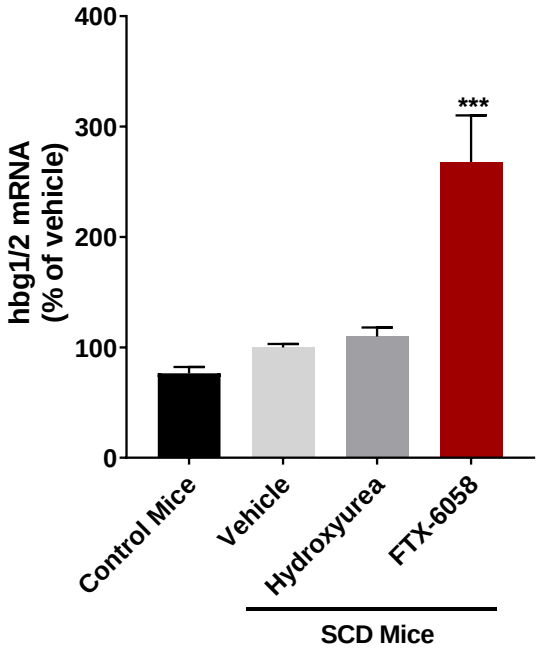
- **Provides Fulcrum a facile way to measure target engagement in peripheral blood**

Superior Induction of Human Fetal Hemoglobin mRNA and Protein Versus HU in Townes SCD Mice

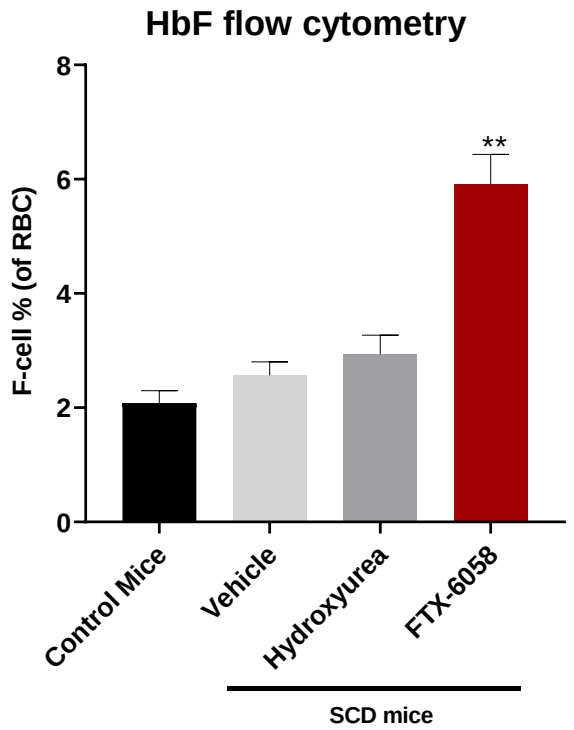
Target Engagement

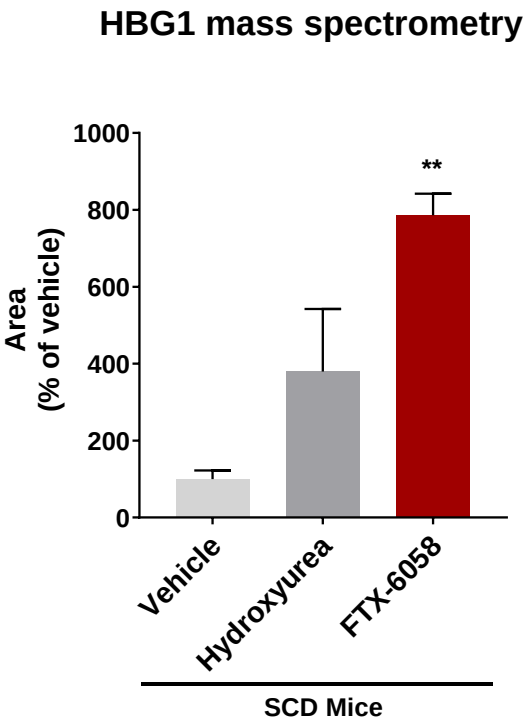


HBG1 mRNA levels



Fetal hemoglobin protein levels



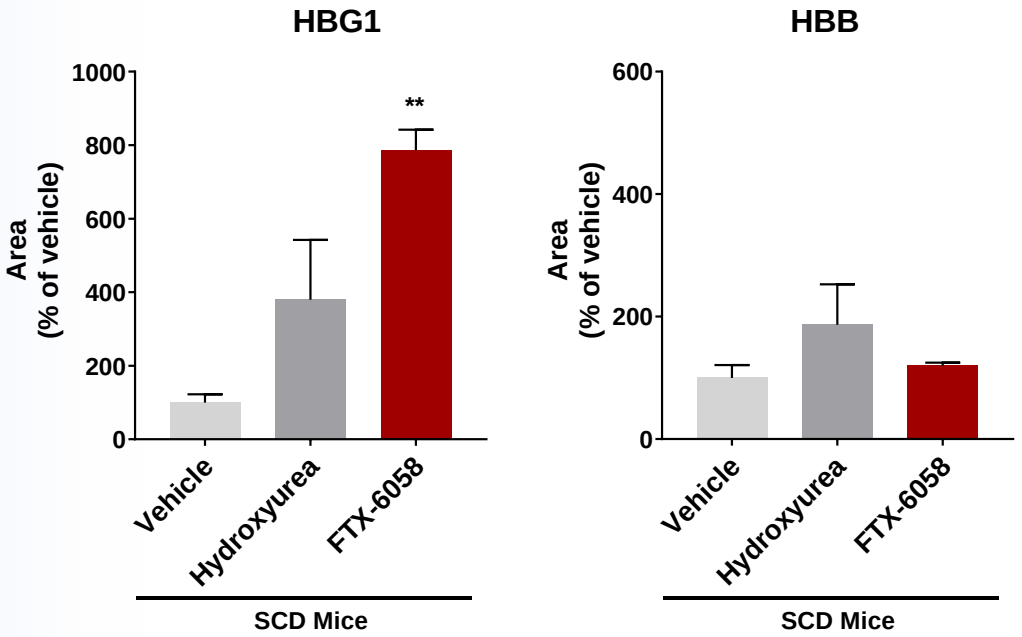


Hydroxyurea was administered once daily at 100 mg/kg for 28 days;
FTX-6058 was administered twice per day at 5 mg/kg for 28 days

**p<0.01; ***p<0.001

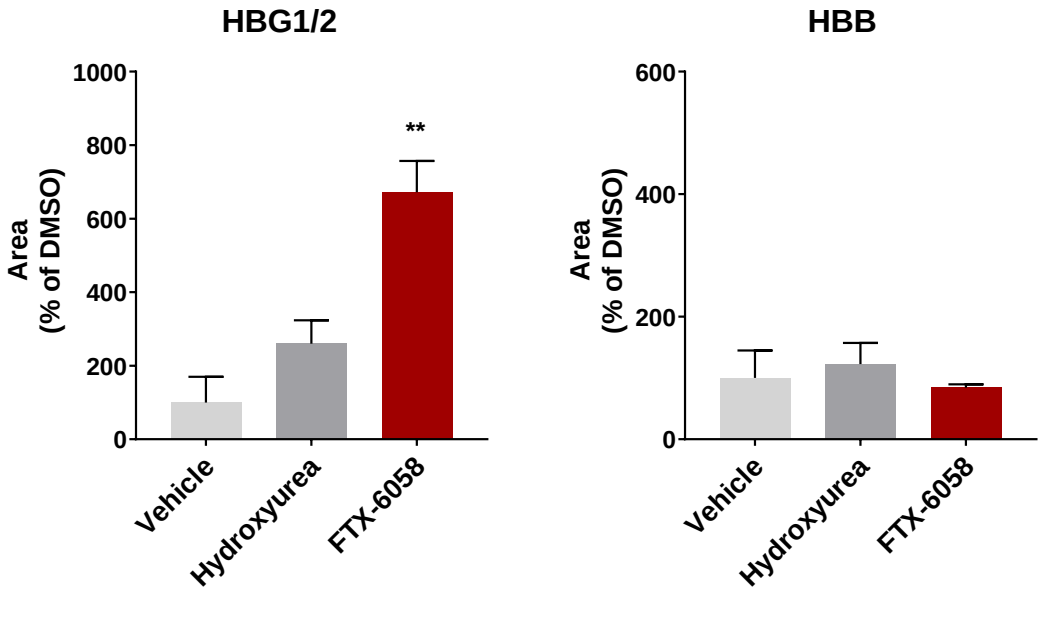
FTX-6058 Selectively Upregulates Fetal Globin, with No Observed Effect on Beta Globin Expression

In vivo pharmacology
(Townes SCD mouse model)



Townes mouse model (28 days treatment):
Hydroxyurea was administered once daily at 100 mg/kg;
FTX-6058 was administered twice per day at 5 mg/kg

In vitro pharmacology
(Human CD34+ cells)



Human primary CD34+ cells (Donor 224):
CD34+ cells expanded and differentiated for 14 days
in a two-phase culture system; treated for final 7 days

FTX-6058 Has Potential to be Transformative Therapy for SCD

Open IND - Phase 1 in healthy volunteers initiated 4Q2020

- Target identified from Fulcrum Product Engine
- Delivered 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 act as disease-modifying therapeutic (See abstracts #789 and #2612)

Thank you!

Additional questions:

Please contact us at **info@fulcrumtx.com**

fulcrumtx.com