Nuove opportunità per chi non guarisce

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IRCCS Ospedale Policlinico San Martino
Genova

SITE
SOCIETA' ITALIANA TALASSEMIE ED EMOGLOBINOPATIE

XIV CONGRESSO NAZIONALE SITE

Roma, 11-13 Settembre 2025
Pontificia Università Urbaniana

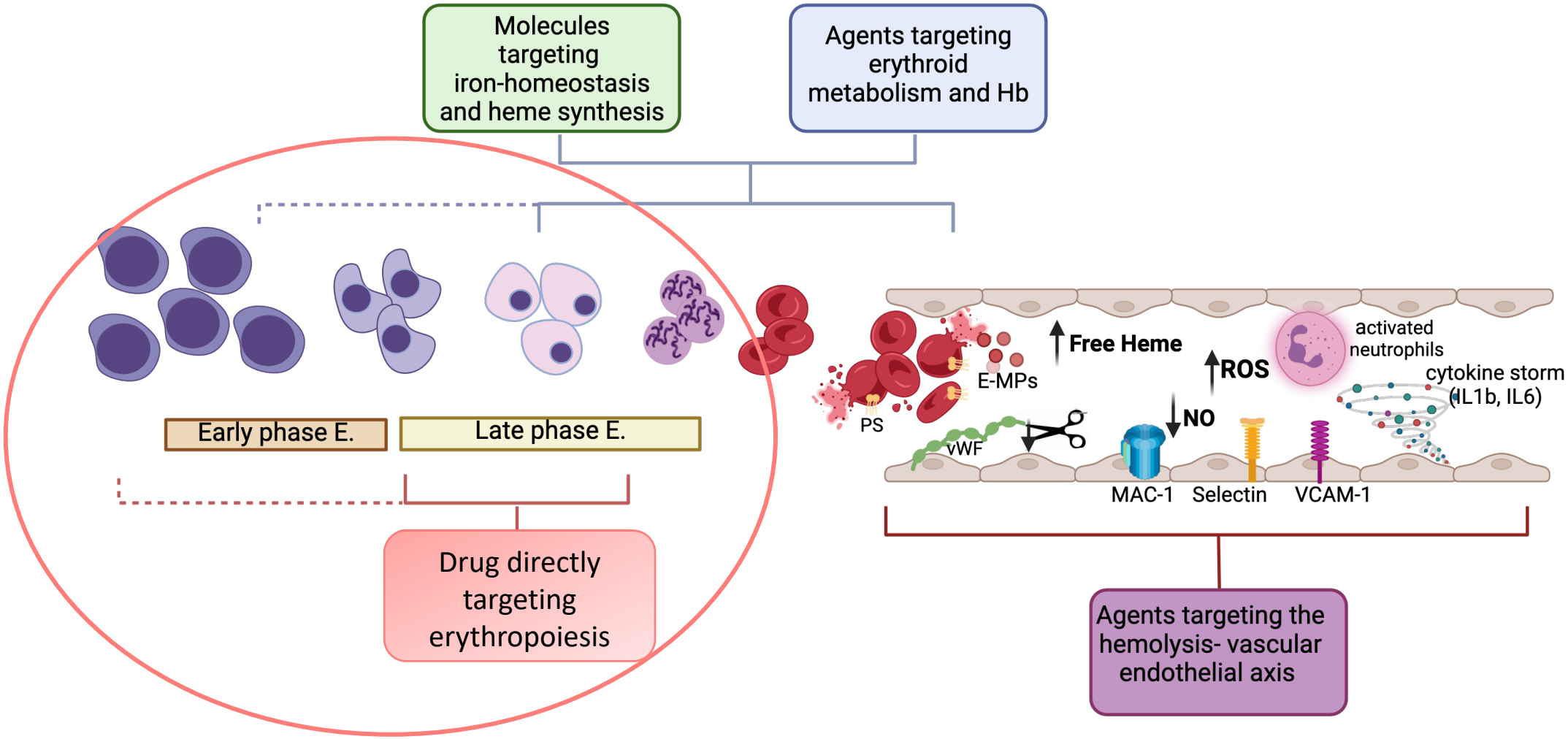
Disclosures of Valeria Maria Pinto

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BMS					x	x	
Vertex			x				

“non guarire” è una definizione in negativo che attraverso un stereotipo limita l’atto medico che è quello di transitare la speranza in nuovo stato di benessere che non necessariamente corrisponde a quello di un soggetto non affetto da malattia cronica.

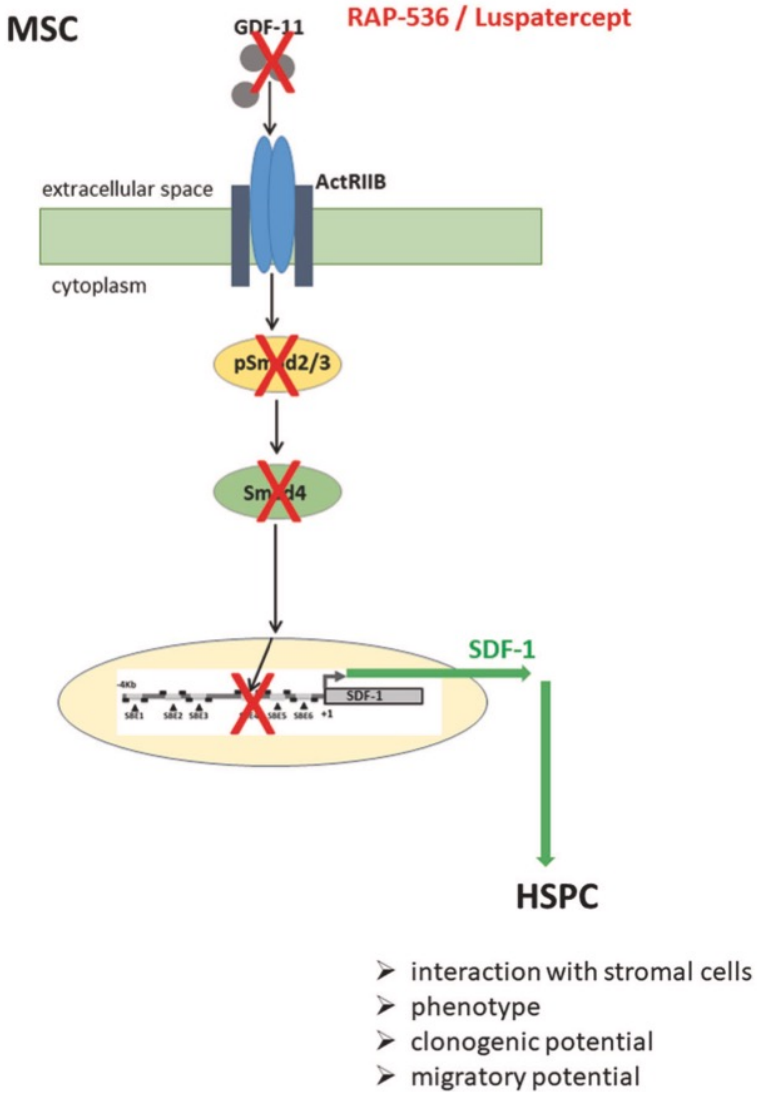
«Bene-essere»: ossia un’armonia dove tutto sia accorda”

1994



Pinto VM et al, Blood. 2024 Aug 22;144(8):853-866

Drug directly targeting erythropoiesis



- interaction with stromal cells
- phenotype
- clonogenic potential
- migratory potential

Wobus M et al, Leukemia 2021

HemaSphere eha

(PB2787) SINGLE CELL RNA-SEQ IDENTIFIES LUSPATERCEPT COULD SERVE AS A NOVEL THERAPEUTIC DRUG FOR APLASTIC ANEMIA

Topic: 11. Bone marrow failure syndromes incl. PNH - Biology & translational research

Zining Wang*[1], Liu Chunyan[1], Rong Fu[1]

[1]Tianjin Medical University General Hospital, Department of Hematology, Tianjin, China;

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(PB2789) RESEARCH ON THE EFFECT OF LUSPATERCEPT AND ERYTHROPOIETIN ON ERYTHROID DIFFERENTIATION IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

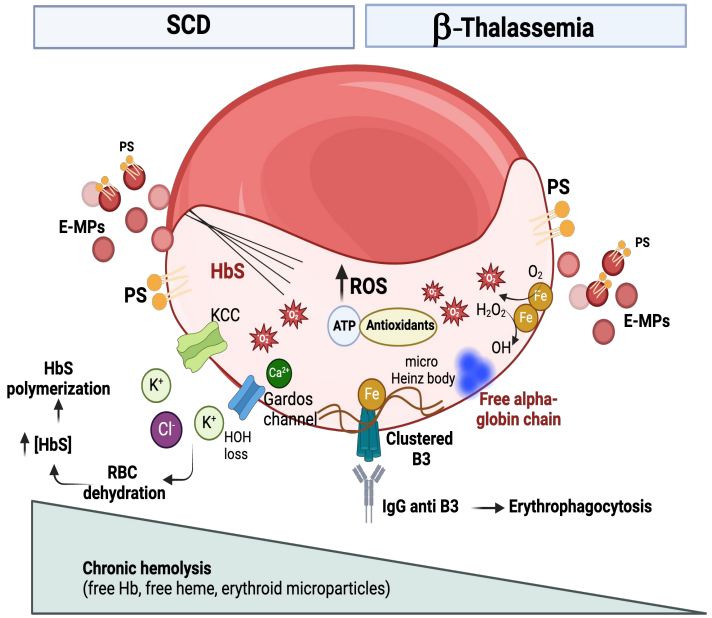
Topic: 11. Bone marrow failure syndromes incl. PNH - Biology & translational research

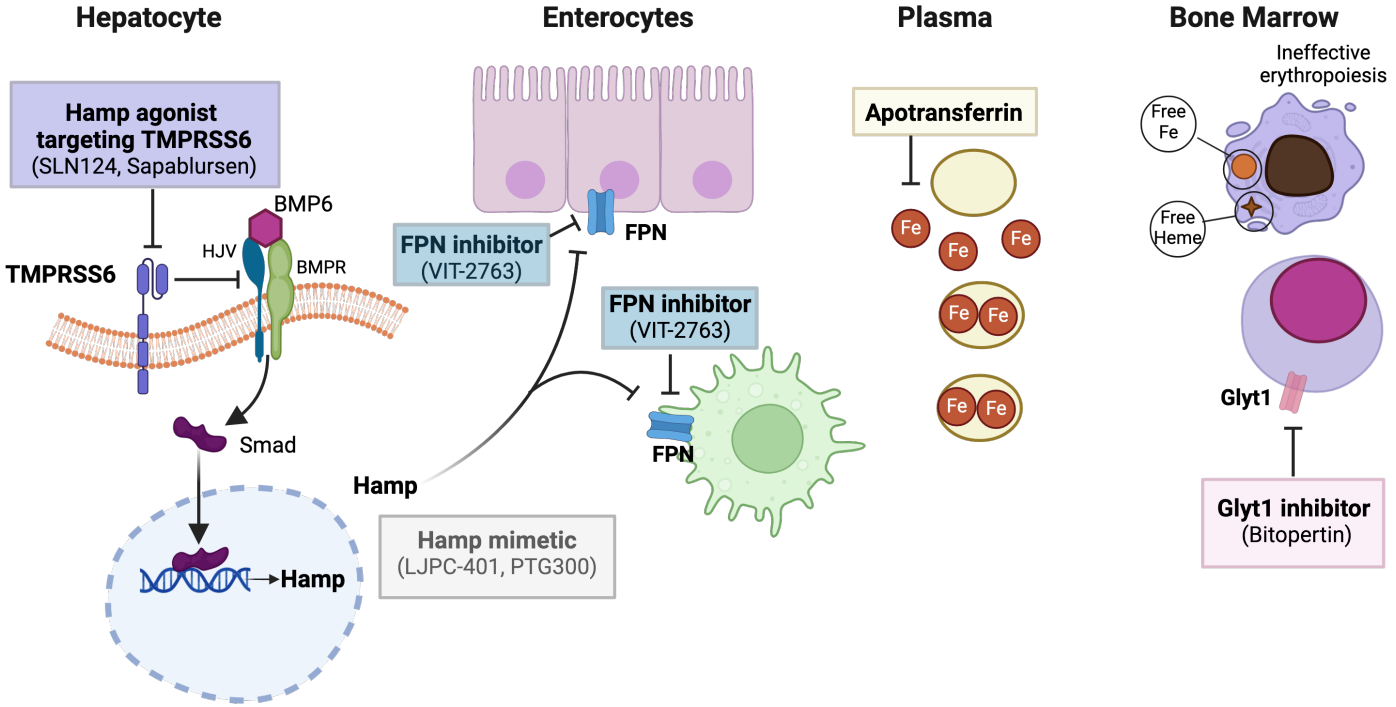
Liyan Li[1], Junshu Wu[1, 2], Hui Liu[1], Zhaoyun Liu[1], Rong Fu*[1]

[1]Tianjin Medical University General Hospital, Department of Hematology, Tianjin, China;[2]Tianjin Medical University General Hospital, Tianjin, China;

HemaSphere 2025;9(S1)

Molecules targeting iron homeostasis or heme synthesis



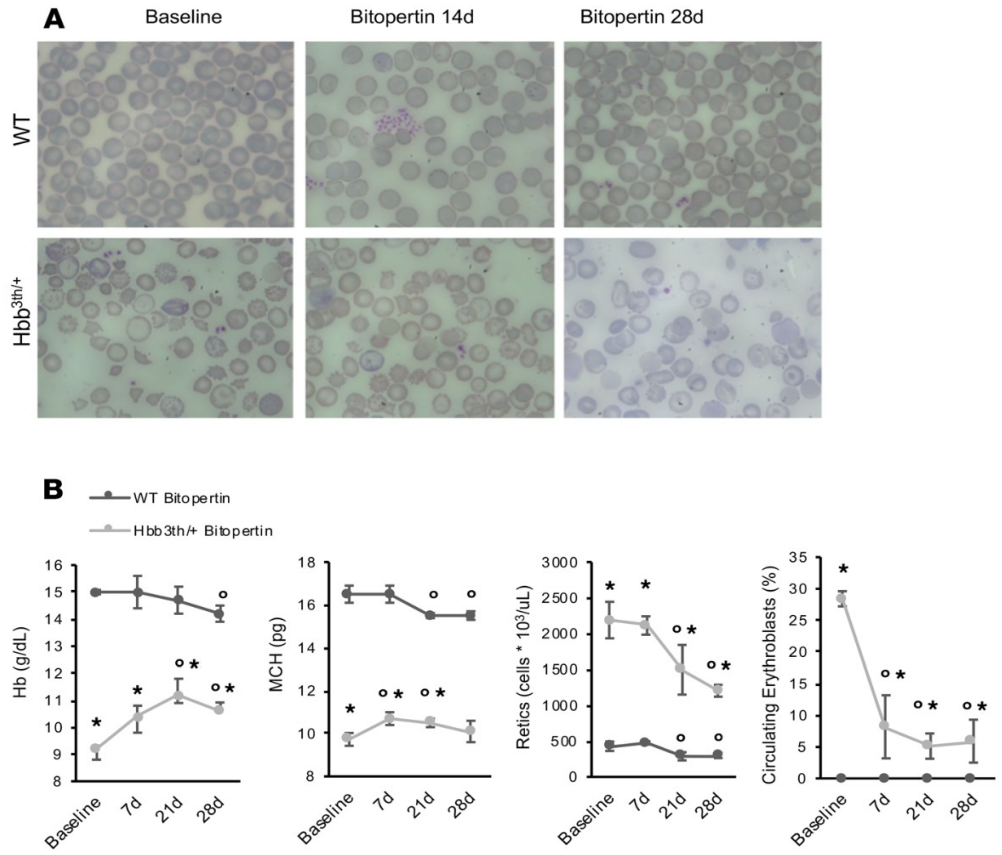


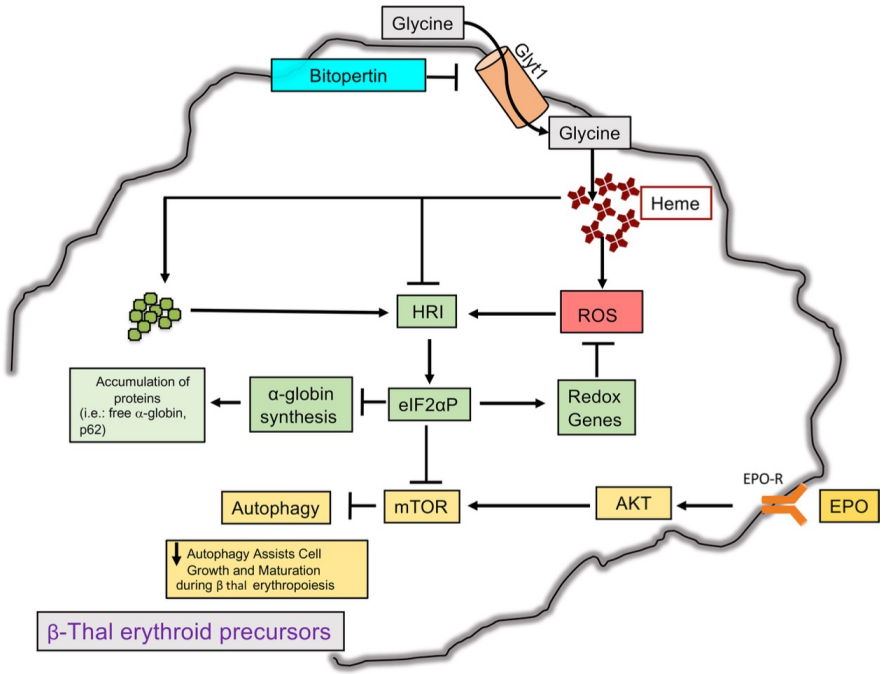
ViSionSerenity (NCT04817670)

Double-blind, randomized, placebo- controlled, efficacy, and safety study of multiple doses of VIT-2763 in subjects with SCD

Pinto VM et al, Blood. 2024 Aug 22;144(8):853-866

Bitopertin blocks Glycine Transporter-1 (Glyt-1), which is important in heme





Matte A, JCI Insight. 2019 Nov 14;4(22):e130111

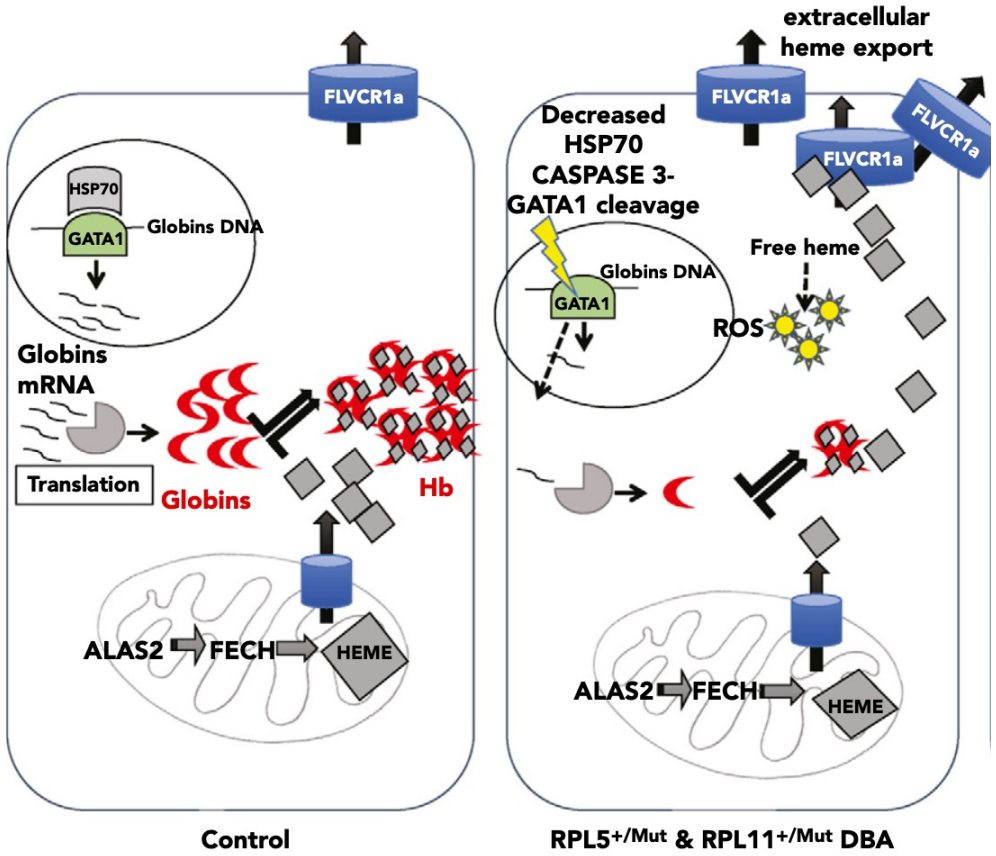
NCT03271541: Bitopertin in NTDT patients was discontinued due to lack of efficacy

Taher A et al, BJH 194:474,2021

Bitopertin may limit the detrimental effect of free heme in Diamond-Blackfan anemia (DBA)

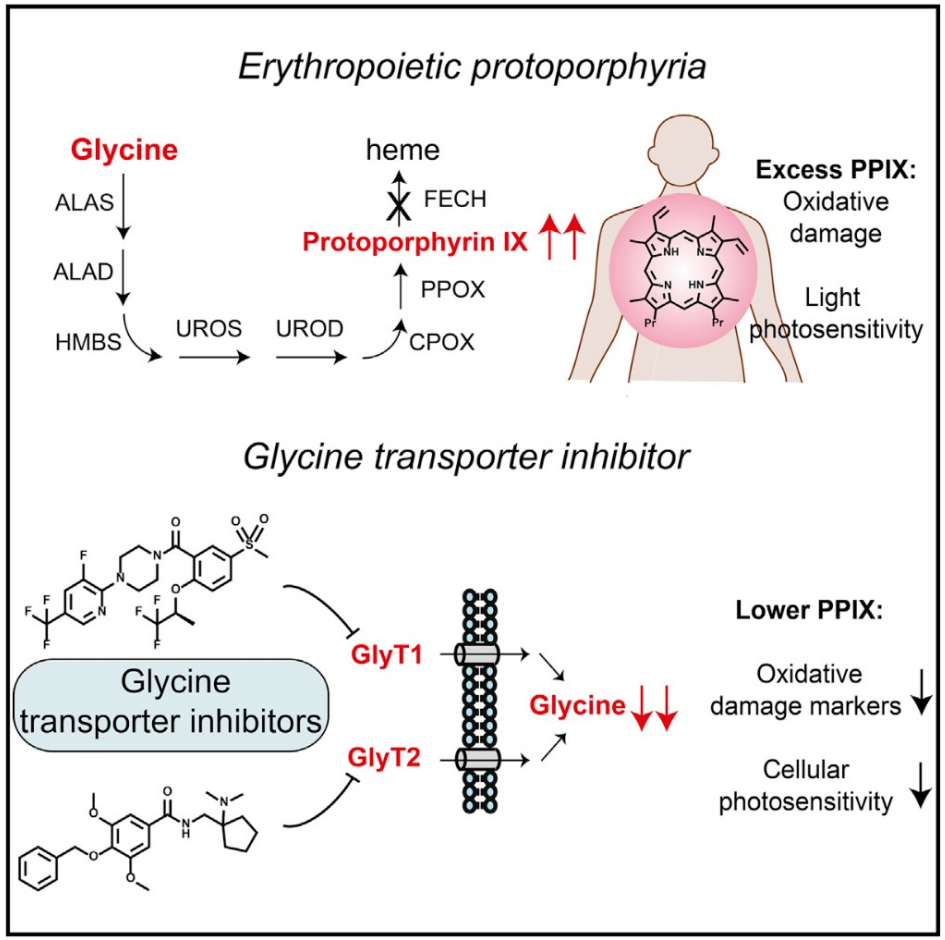
Ex vivo in CD34+ derived cells from patients with DBA display accumulation of free heme overcoming the expression of cyto-protective systems and contributing to the pathophysiology of DBA

A phase 1-2 intra-patient dose-escalation study of bitopertin for steroid-refractory DBA (NCT05828108) has recently activated



Rio S et al. , Blood. 2019 Mar 21;133(12):1358-1370; Mercurio S et al.. Eur J Haematol. 2016 Apr;96(4):367-74;
Pinto VM et al, Blood. 2024 Aug 22;144(8):853-866

Repurposing of glycine transport inhibitors for the treatment of erythropoietic protoporphyria



Halloy F. et al Cell Chem Biol. 2021 Aug 19;28(8):1221-1234.e6

In EPP, in vitro evidence of improvement of EPP cell metabolism and reduced protoporphyrin IX (PPIX) synthesis in presence of bitopertin

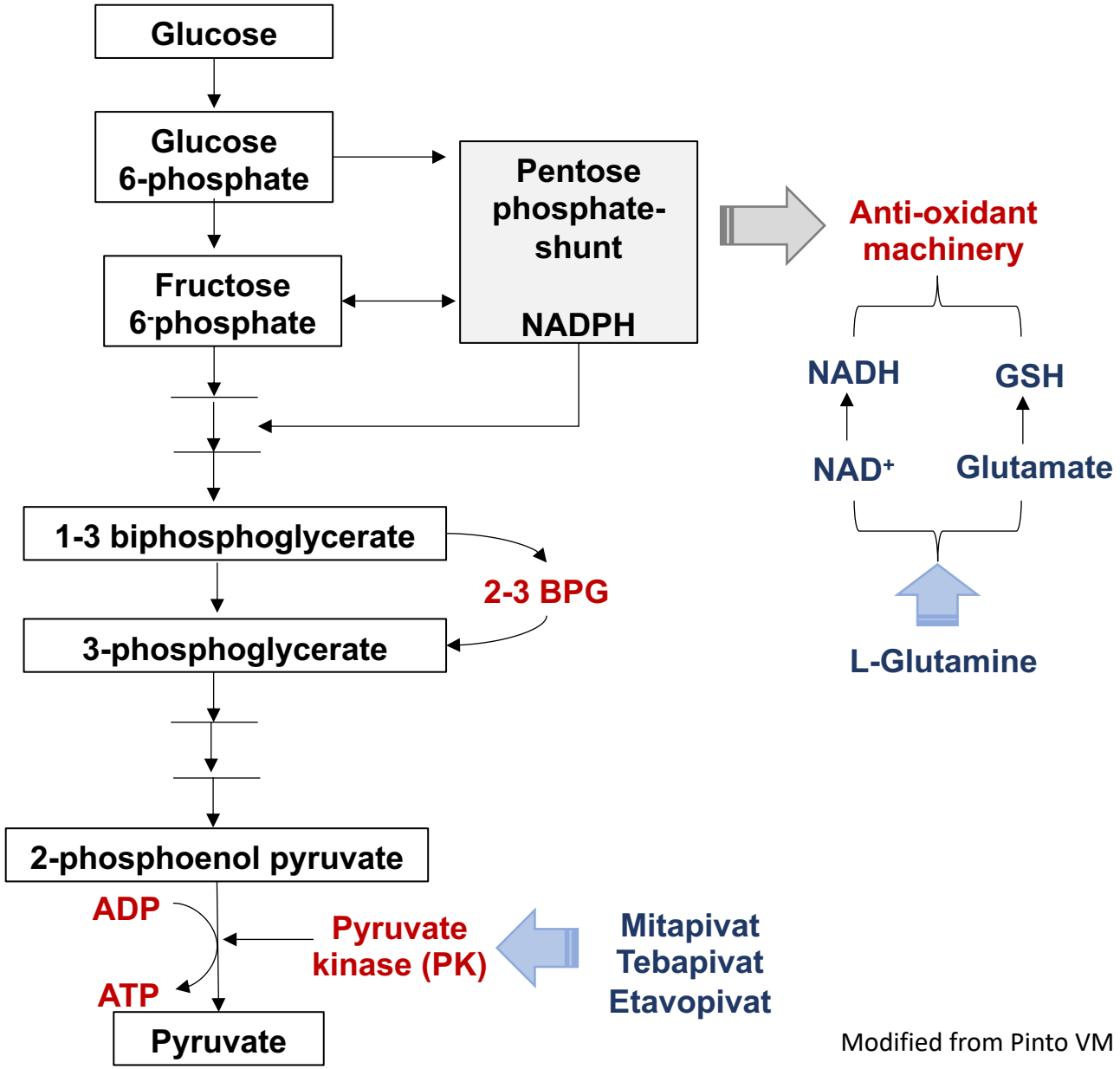
BEACON (ACTRN12622000799752) and AURORA (NCT05308472) phase-2 studies with bitopertin in adut subjects with EPP and X-linked porphyria

BEACON and AURORA studies show a dose-dependent, and sustained reductions of plasma PPIX levels, amelioration of sunlight tolerance, stable Hb and grade 1-2 adverse event (e.g. limited dizziness, lightheadedness, headache and nausea)

In AURORA study, a significant improvement in the patient global impression of change (PGIC) was also reported in EPP patients treated with bitopertin 60 mg once daily compared to placebo group

(ad interim data)

Agents targeting erythroid metabolism



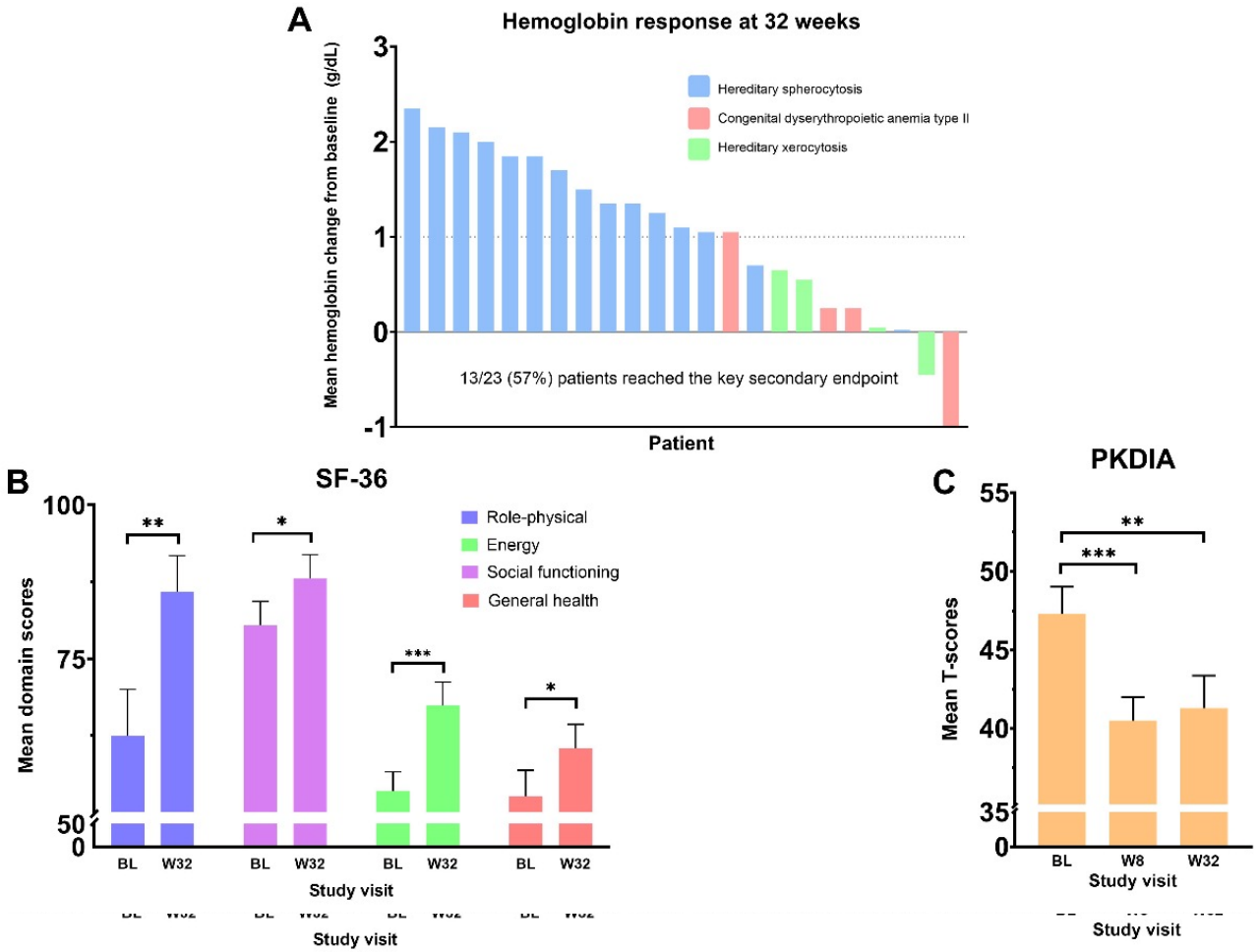
Modified from Pinto VM et al, Blood. 2024 Aug 22;144(8):853-866

HemaSphere eha

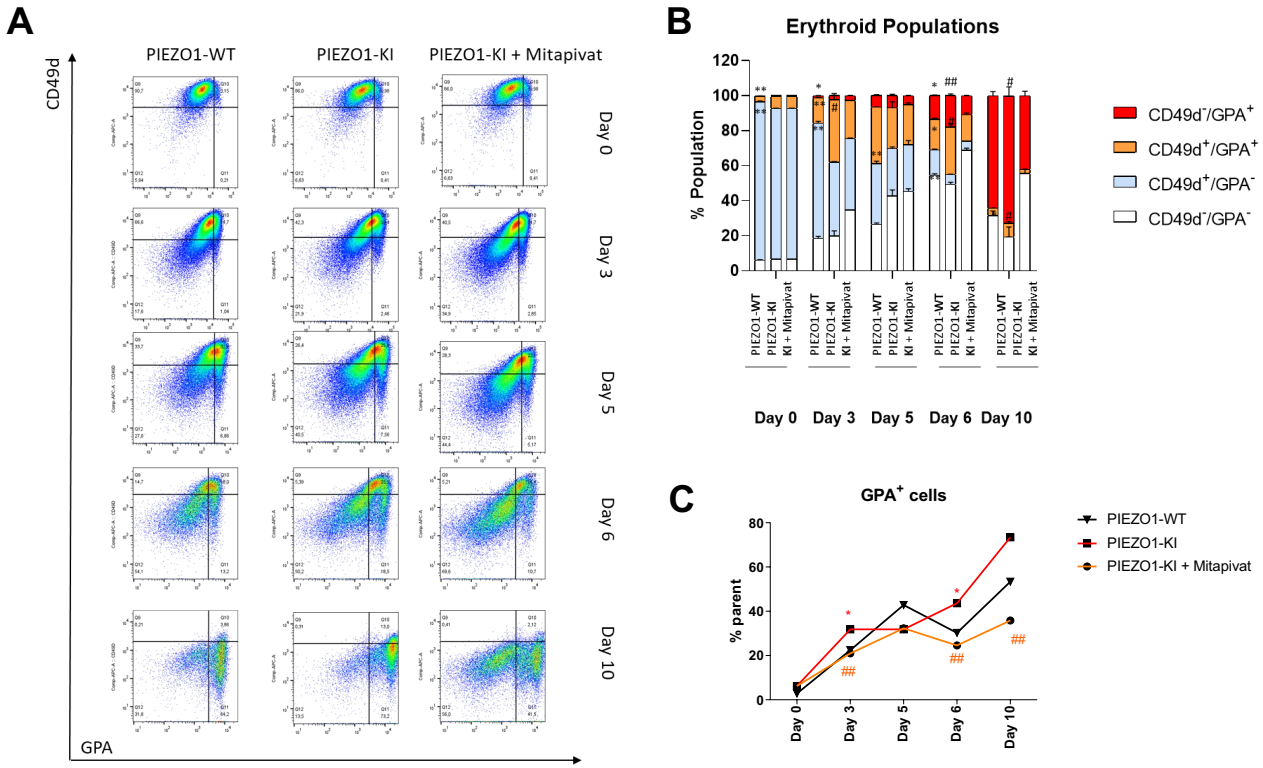
(S297) SATISFY: MITAPIVAT IN ADULTS WITH ERYTHROCYTE MEMBRANOPATHIES AND CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE II: A EUROBLOODNET, MULTICENTER, SINGLE-ARM, PHASE 2 STUDY

Topic: 28. Enzymopathies, membranopathies and other anemias

Thomas Doeven*[1], Eduard J. van Beers[1], Richard van Wijk[2], Evelyn Groot[1], Joline Saes[1], Jennifer Bos[2], Jonathan de Wilde[2], Minke Rab[2], Selma Bendtsen[3], Jesper Brix Petersen[3], Niels Vejlstrup[4], Jens Helby[3], Adeline Gladieux[5], Fatiha Chermat[5], Pierre Fenaux[5], Kevin H.M. Kuo[6], Andreas Glenthøj[3]



Mitapivat restores alterations of erythropoiesis in the PIEZO1 GoF erythroid model

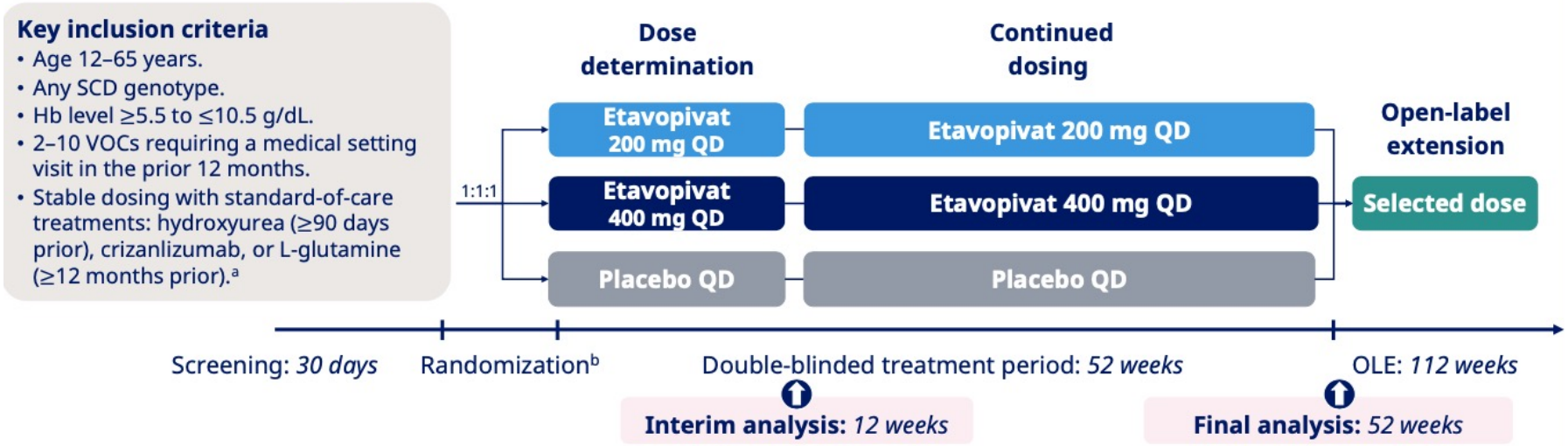


Mitapivat treatment during the erythroid differentiation is able to restore the percentage of GPA+ cells (differentiated cells) in HUDEP2-PIEZO1-KI cells (FACS analysis)

HemaSphere 2025;9(S1)

Etavopivat Reduces Incidence of Vaso-Occlusive Crises in Patients With Sickle Cell Disease: HIBISCUS Trial Phase 2 Results Through 52 Weeks

Dose determination study design.



Demographics and baseline characteristics.

	Etavopivat 200 mg (n=21)	Etavopivat 400 mg (n=20)	Placebo (n=19)
Age in years, mean (min, max)	35.7 (14, 57)	34.0 (12, 59)	30.6 (13, 57)
Adolescents (12–17 years), n (%)	3 (14.3)	2 (10.0)	2 (10.5)
Female, n (%)	17 (81.0)	14 (70.0)	10 (52.6)
Hispanic or Latino, n (%)	5 (23.8)	6 (30.0)	0
Black or African American, n (%)	13 (61.9)	15 (75.0)	16 (84.2)
VOC frequency in year prior to study, mean (min, max)	3.0 (2, 7)	3.5 (2, 9)	3.3 (2, 9)
2 or 3, n (%)	15 (71.4)	14 (70.0)	13 (68.4)
4–10, n (%)	6 (28.6)	6 (30.0)	6 (31.6)
Baseline Hb in g/dL,[a] mean (SD)	8.16 (1.17)	8.26 (1.07)	8.78 (1.20)
Hb SS, n (%)	18 (85.7)	18 (90.0)	18 (94.7)
On-trial use of SCD therapies, n (%)			
Hydroxyurea	16 (76.2)	13 (65.0)	14 (73.7)
Crizanlizumab	1 (4.8)	2 (10.0)	1 (5.3)
L-glutamine	0	0	1 (5.3)

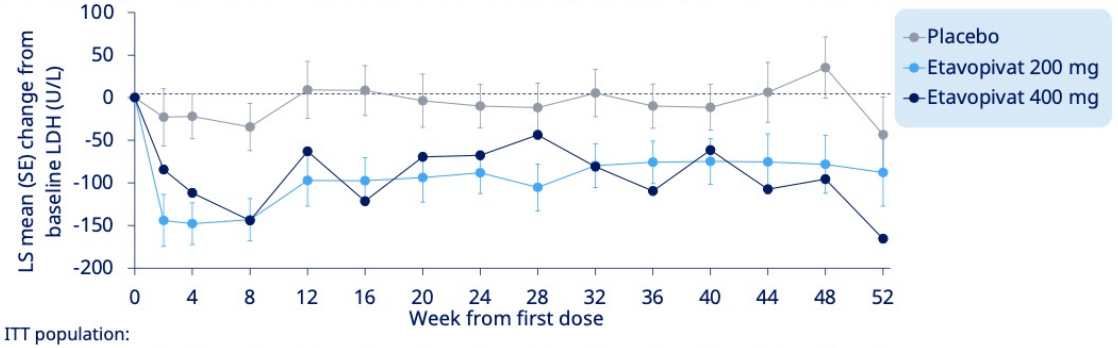
Global Sickle Cell Disease Network (GSCDN 2025)

Etavopivat Reduces Incidence of Vaso-Occlusive Crises in Patients With Sickle Cell Disease: HIBISCUS Trial Phase 2 Results Through 52 Weeks

Both doses of etavopivat reduced annualized VOC rate, compared with placebo, in the ITT and PP populations. Both doses also delayed the median time to first adjudicated VOC vs placebo (33.6 weeks for either dose of etavopivat vs 16.9 weeks for placebo, ITT population, data not shown).

		Annualized VOC rate [95% CI]	VOC rate ratio [95% CI] (etavopivat vs placebo)	Reduction	p value
ITT population	**Etavopivat 200 mg** (n=21)	**1.07** [0.49, 2.37]	**0.55** [0.24, 1.26]	**45%**	0.154
	Etavopivat 400 mg (n=20)	**1.06** [0.46, 2.46]	**0.54** [0.23, 1.26]	**46%**	0.154
	Placebo (n=19)	**1.97** [0.89, 4.36]			
PP population	**Etavopivat 200 mg** (n=13)	**0.66** [0.28, 1.58]	**0.37** [0.16, 0.85]	**63%**	0.020
	Etavopivat 400 mg (n=12)	**0.70** [0.29, 1.66]	**0.39** [0.17, 0.90]	**61%**	0.028
	Placebo (n=15)	**1.77** [0.90, 3.50]			

Hemolysis markers (LDH, absolute reticulocyte count, and indirect bilirubin) were decreased by Week 2 following initiation of both doses of etavopivat vs placebo. Data shown for LDH only.

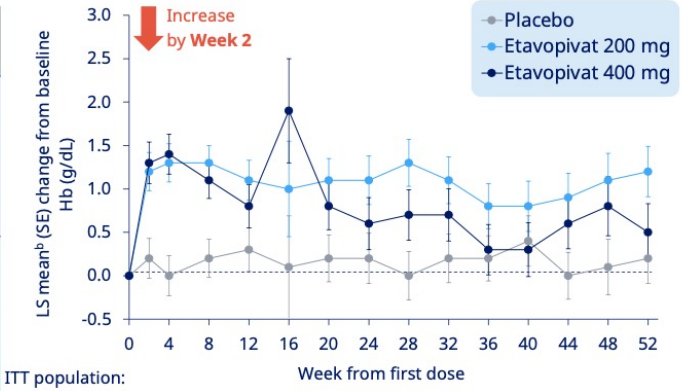


ITT population:

Placebo (n=18)	12	16	11	14	15	12	14	14	13	15	13	14	13	11
Etavopivat 200 mg (n=21)	17	20	19	20	18	16	16	15	15	14	12	13	13	14
Etavopivat 400 mg (n=19)	14	17	14	15	15	14	12	13	12	13	13	12	10	12

Increased Hb response rates at Week 24 were observed with both doses of etavopivat vs placebo, in the ITT and PP populations. Increased Hb was observed by Week 2 and maintained over 52 weeks in patients receiving etavopivat vs placebo.

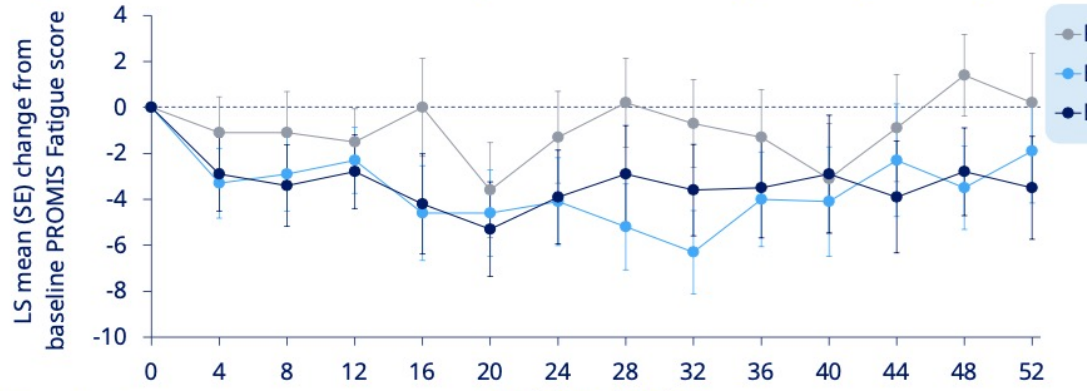
	Etavopivat 200 mg	Etavopivat 400 mg	Placebo
ITT population	n=21	n=20	n=19
Hb responders at Week 24,[a] %	**38.1**	**25.0**	**10.5**
Rate difference vs placebo	27.6	14.5	
p value	p=0.187	p=0.660	
PP population	n=13	n=12	n=15
Hb responders at Week 24,[a] %	**46.2**	**33.3**	**13.3**
Rate difference vs placebo	32.8	20.0	
p value	p=0.248	p=0.680	



ITT population:

Placebo (n=19)	16	17	13	15	15	13	15	14	15	16	15	16	13	13
Etavopivat 200 mg (n=21)	20	19	17	18	17	17	14	15	15	14	14	12	14	13
Etavopivat 400 mg (n=19)	14	15	14	15	14	12	13	12	10	11	11	12	10	9

PROMIS Fatigue score was decreased for patients receiving etavopivat vs placebo.



ITT population:

Placebo (n=17)	14	12	14	13	11	12	13	13	13	12	13	11	12	
Etavopivat 200 mg (n=18)	15	16	15	14	14	13	14	14	13	11	10	11	9	
Etavopivat 400 mg (n=18)	13	12	11	12	11	11	10	10	11	9	11	9	10	

Results from a Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Tebapivat (AG-946) in Patients with Sickle Cell Disease

NCT06924970

Blood 144 (2024) 2496–2497

16 adult pts with SCD received at least one dose of either 2 mg QD (n=8) or 5 mg QD (n=8) oral tebapivat.

At the end of the 28-day treatment period, the mean (SD) **change from baseline for Hb was 1.2 (0.41) g/dL in the 2 mg cohort and 1.9 (0.69) g/dL in the 5 mg cohort**. Improvements in markers of hemolysis and erythropoiesis were also observed at Day 28.

Tebapivat was well tolerated in pts with SCD receiving either 2 mg or 5 mg QD for 28 days.

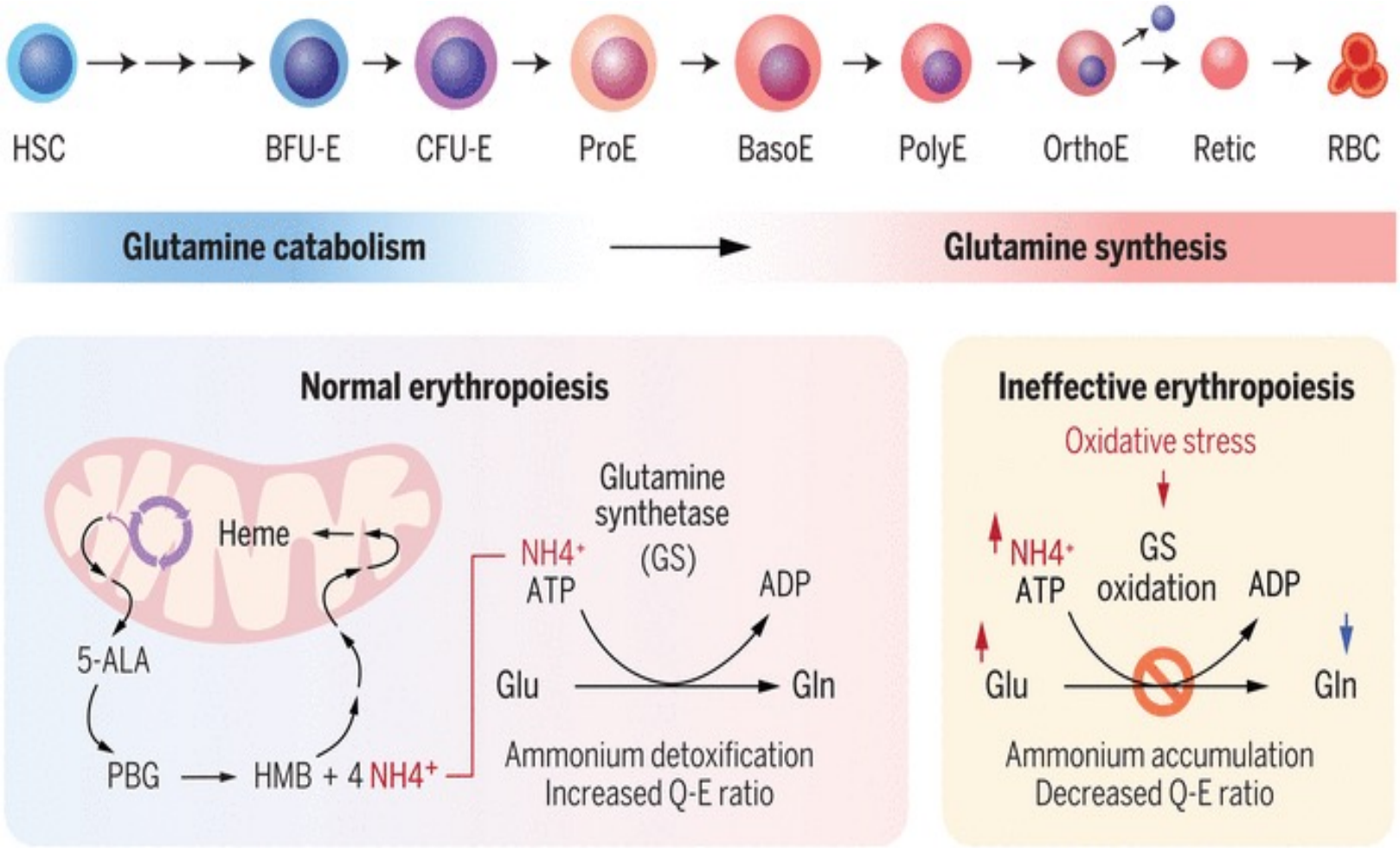
A Phase 2B, Open-Label Multicenter Study of Tebapivat (AG-946), a Potent Pyruvate Kinase Activator, in Patients with Anemia Due to Lower-Risk Myelodysplastic Syndromes

NCT05490446

Blood 144 (2024) 6708–6710

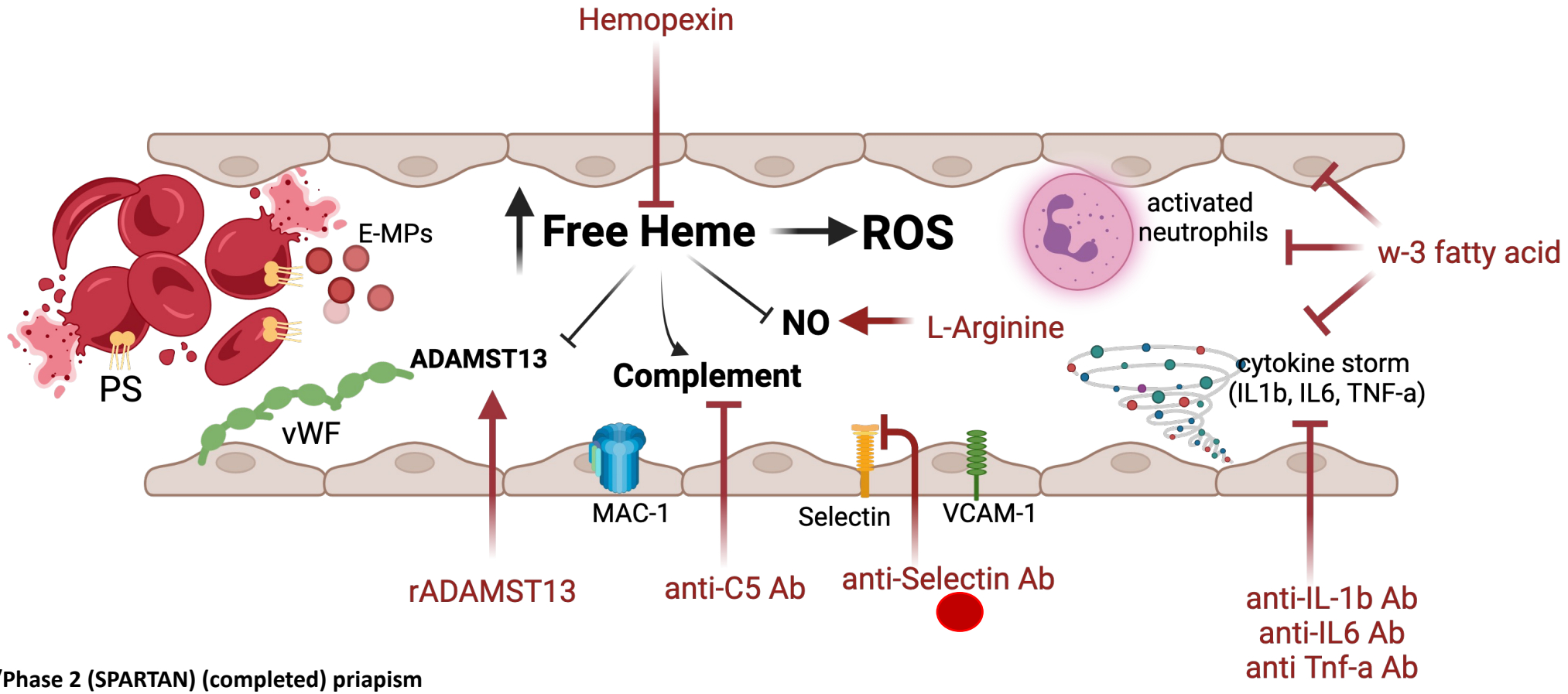
Given that the 5 mg daily dose was well tolerated in the phase 2a part of the study, this phase 2b, open-label, multicenter trial will explore efficacy at 3 additional higher dose levels. Patients will receive 1 of 3 dose levels (Dose Levels 1-3) for up to 24 weeks (Core Period).

Dynamic changes in glutamine metabolism during erythopoiesis further support metabolic-reprogramming as novel therapeutic strategy in pathologic erythropoiesis



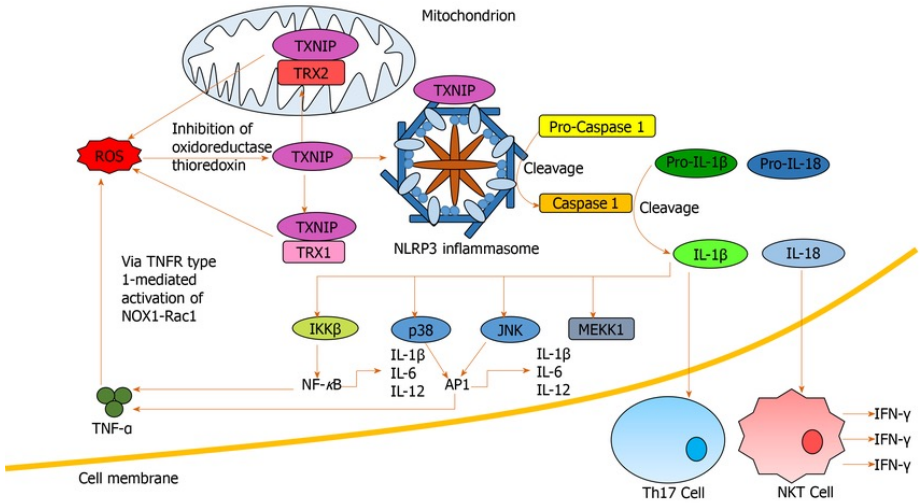
A glutamine metabolic switch supports erythropoiesis, Volume: 386, Issue: 6723, DOI: (10.1126/science.adh9215)

Agents targeting the hemolysis-vascular endothelial axis



NCT03938454/Phase 2 (SPARTAN) (completed) priapism
NCT04053764/Phase 2 (STEADFAST) (completed) chronic kidney disease due to sickle cell nephropathy
NCT05334576/ Interventional (CRIZ)(unknown status) prevention of silent cerebral infarcts
NCT03474965/Phase 2 (completed) ages 2 to <18 years VOC

Pinto VM et al, Blood. 2024 Aug 22;144(8):853-866.



NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3)

Blood 144 (2024) 2482–2483

The 66th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

113.SICKLE CELL DISEASE, SICKLE CELL TRAIT, AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

Bruton Tyrosine Kinase Inhibitor Rilzabrutinib Reduces Vaso-Occlusion and Markers of Inflammation and Adhesion in Transgenic Mice with Sickle Cell Disease

Ahmed Daak, MDPhDMSc, DPM/MFPM[1], David R. Light, PhD[2], Fuad Abdulla[3], Chunsheng Chen, PhD[3], Julia Nguyen, B.S.[4], Conglin Ruan, B.S.[4], Michael Storek[5], Dimitry Ofengeim[6], Alexandra Hicks[6], Michelle Lee[5], Vincent Mikol[6], Gregory M. Vercellotti, MD[3], John D. Belcher, PhD[3]

The Efficacy and Safety of Rilzabrutinib in Patients Aged 10 to 65 Years With Sickle-cell Disease (LIBRA)

NCT06975865

A 52-week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Group Sequential Study to Evaluate the Efficacy and Safety of Rilzabrutinib in Patients Aged 10 to 65 Years With Sickle-cell Disease

Phase 3, N patients enrollment (estimated) = 192, Recruiting

Molecules targeting Hb are still on track in SCD

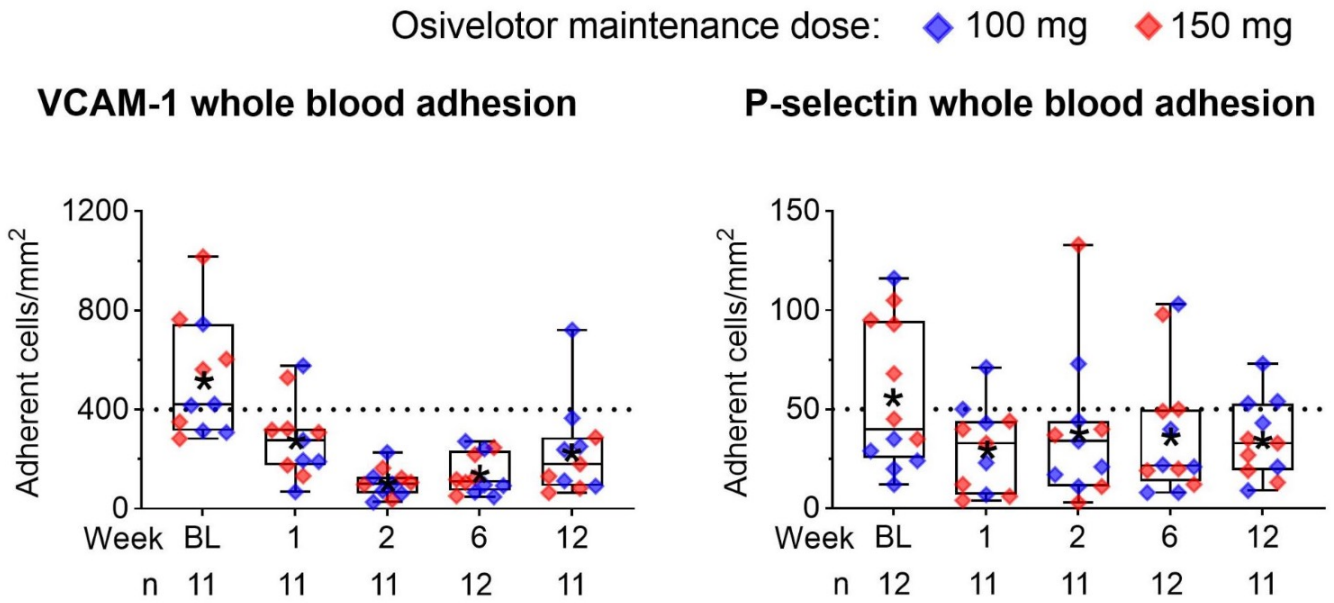
(PS2166) PRELIMINARY PHARMACODYNAMIC BIOMARKER RESULTS IN PATIENTS WITH SICKLE CELL DISEASE FOLLOWING TREATMENT WITH OSIVELOTOR IN A MULTICENTER PHASE 2/3 TRIAL

Topic: 26. Sickle cell disease

GBT021601

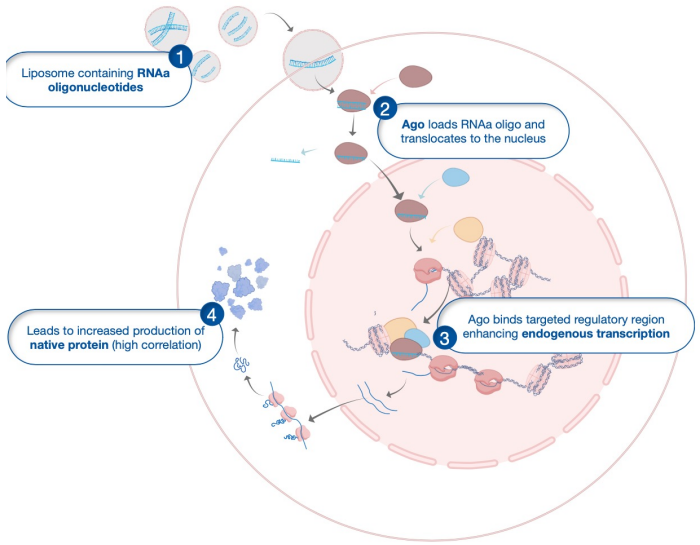
Mira Pochron*[1], Kelly Fader[2], Samantha Braxton[3], Chiara Federici[3], Umut Gurkan[3], John Zak[3], Xiufeng Gao[4], Aliya Zaidi[4], Patrick Hines[4], Yuvika Paliwal[5], Adeyemi Adenola[5], Eleanor Lisbon[5]

Figure. Biomarkers over the 12-week osivelotor treatment period

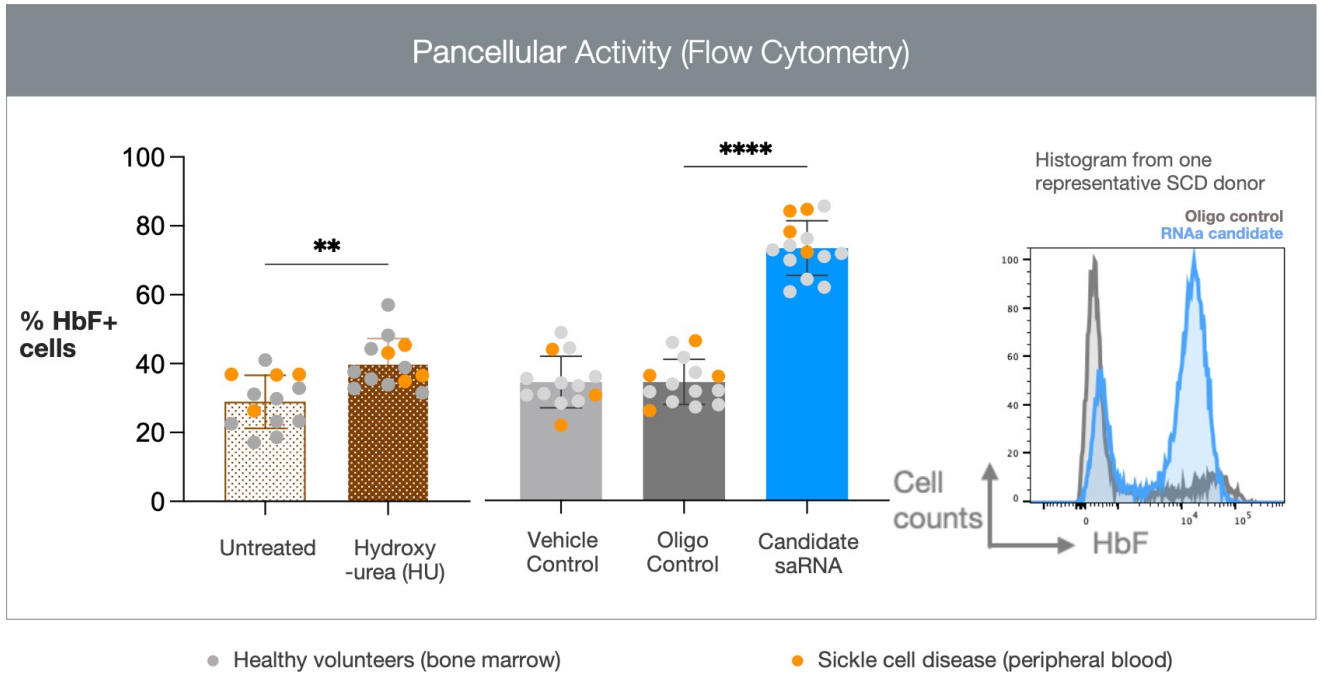


HemaSphere 2025;9(S1)

Small activating Rna-mediated induction of Hbg via liposome delivery for *in vivo* treatment of Sickle Cell Disease



- Candidate saRNA induces HbF in pancellular manner in committed erythroid progenitor cells
- Healthy donors: RNAa induces HbF in 73% of cells (vs 35% for oligo control)
- SCD donors: RNAa induces HbF in 82% of cells (vs 37% for oligo control)



HemaSphere 2025;9(S1)

Take home messages

The therapeutic landscape for erythroid disorders is evolving toward a more integrated approach

Single agents may be used to treat multiple erythroid diseases

This shift offers an opportunity to expand available treatment options, especially in the field of rare diseases

Developing new therapies will require a holistic and multidisciplinary approach

Patient quality of life should become a central endpoint in future clinical trial design