Nuovi trattamenti per l' anemie a cellule falciformi

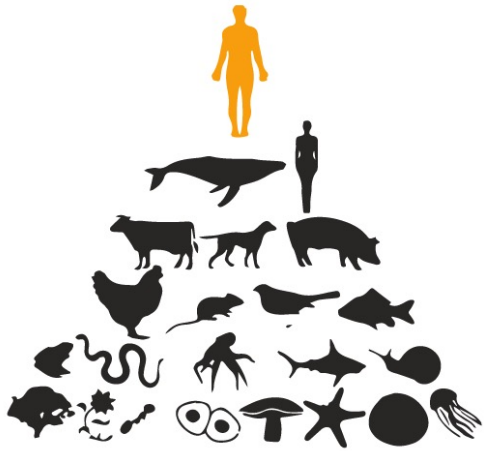
Lucia De Franceschi

Dept of Medicine, University of Verona & AOUI Verona, Verona, Italy

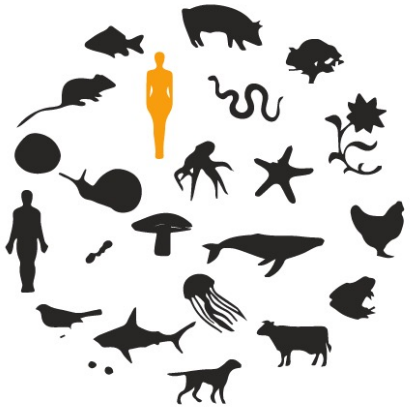
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						x	
Roche						x	
GSK						x	
Agios	x						
BMS	x						

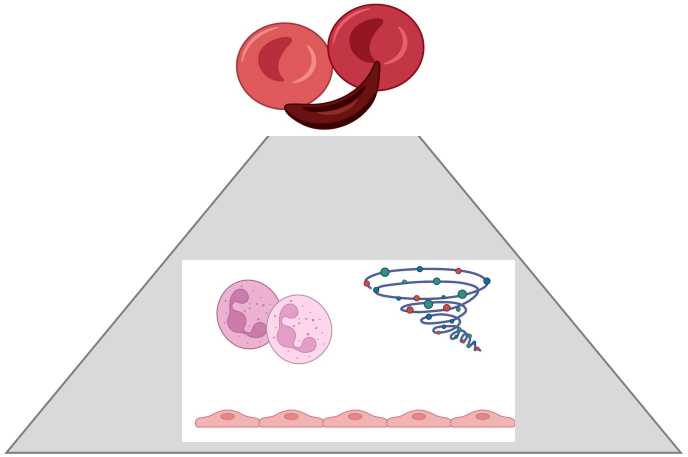
From Erythro-centric perspective to Multicellular perspective



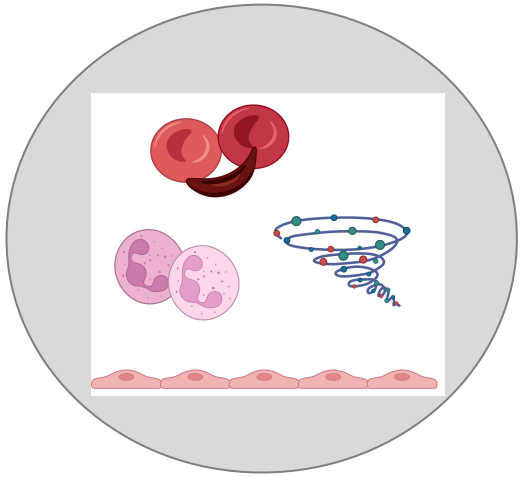
Anthropocentric



Non-Anthropocentric

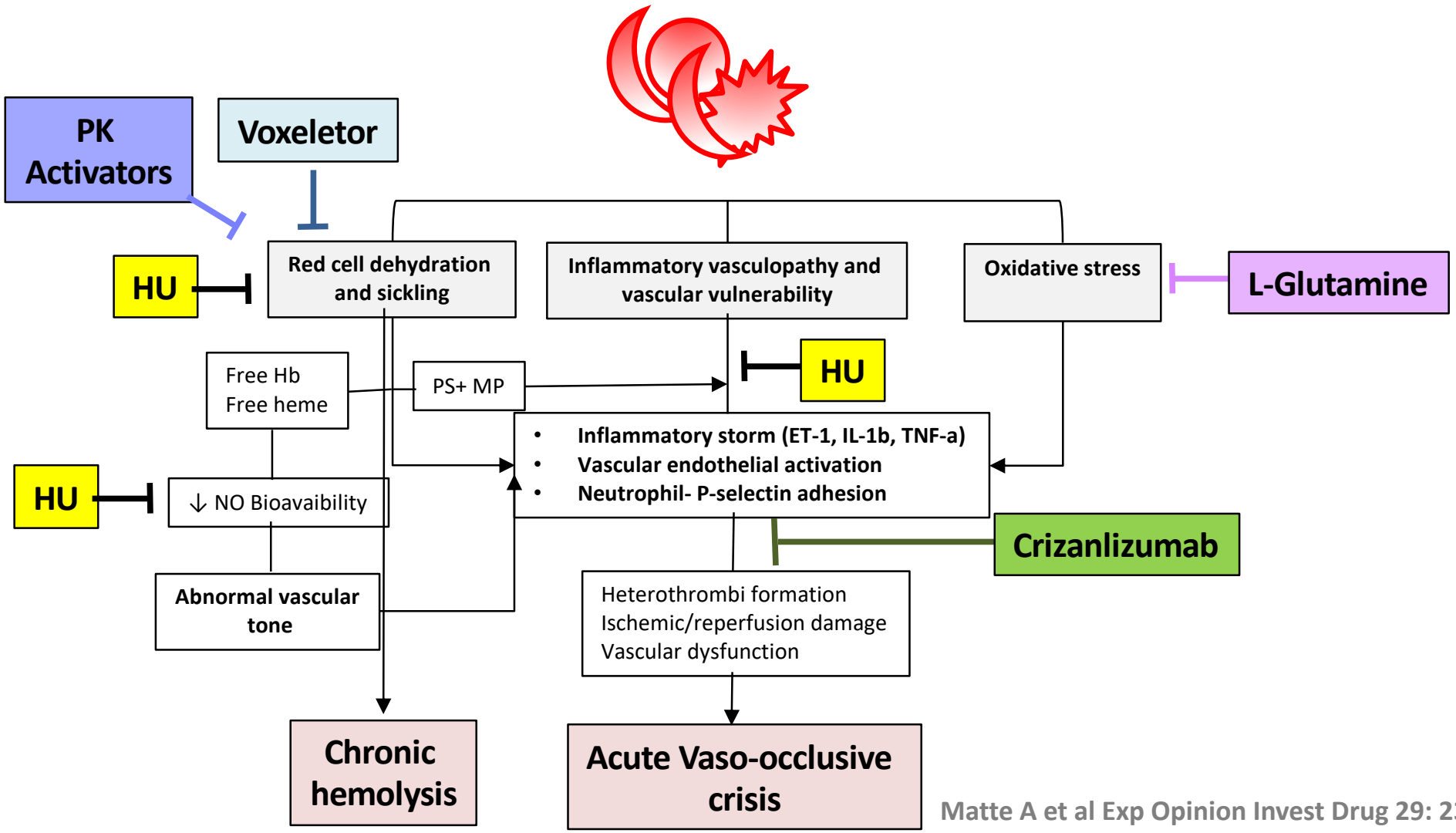


Erythro-centric perspective



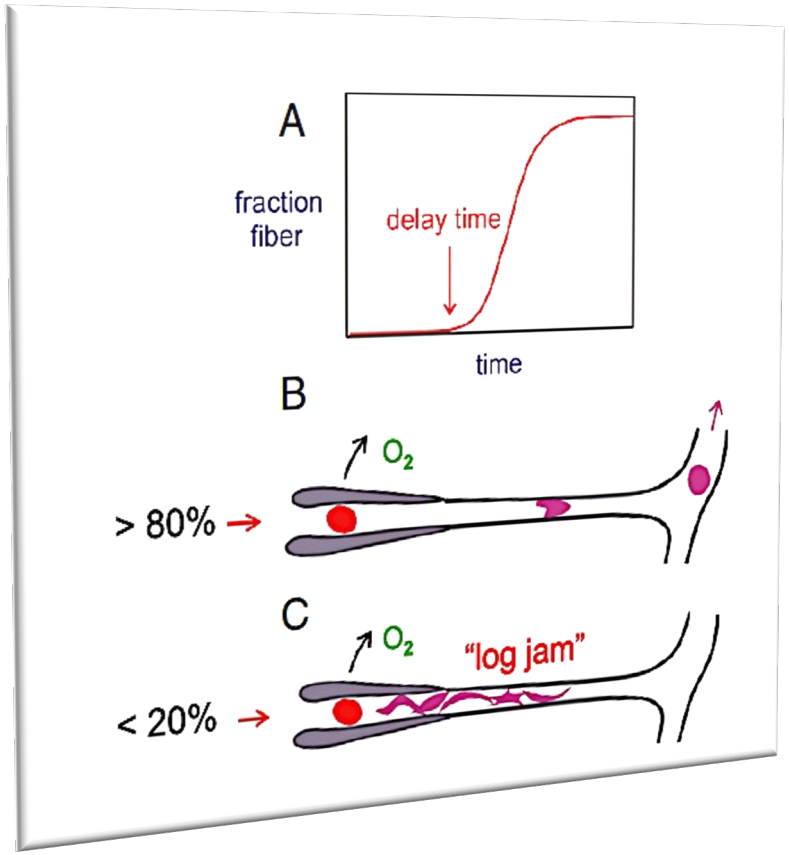
Multicellular perspective

Pathophysiology Based New Therapeutic Options for SCD



Matte A et al Exp Opinion Invest Drug 29: 23-31, 2020
Matte A et al Mediterr J Hematol Infect Dis 11: e22019002, 2019

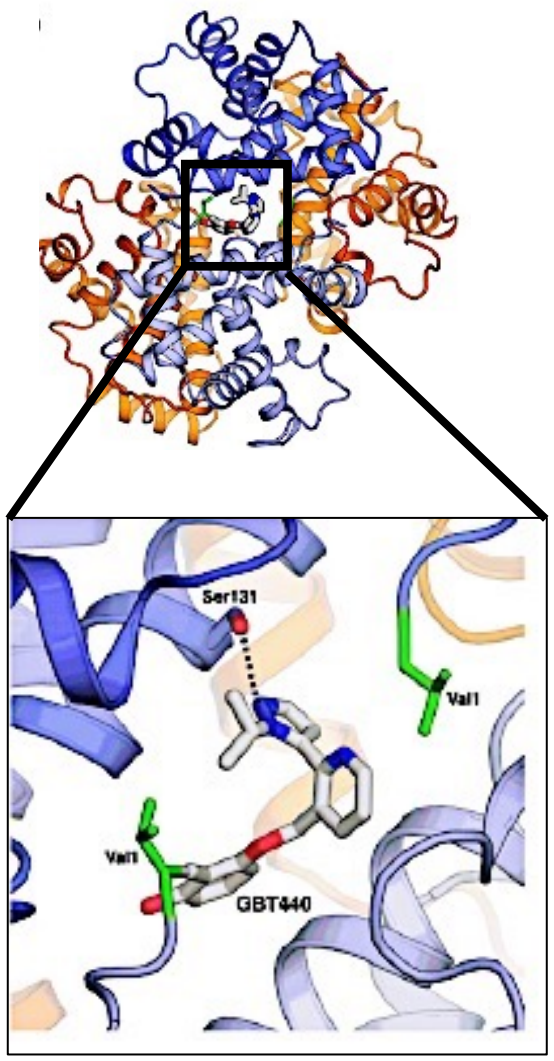
Generation of Sickle and Dense Red Cells



- **Block intermolecular contacts to prevent HbS fiber generation (Voxelotor)**
- **Decrease HbS concentration:**
  - **RBC volume increased (CLT, Senicapoc)**
  - **HbF induction (HU, Decitabine)**
- **Increase Hb oxygen affinity**
- **Weaken fiber contacts (intracellular pH or 2-3 DPG) (PK activator: Mitapivat and Etapivat)**

Li Q et al PNAS 11: e689, 2017; De Franceschi L et al Haematologica 89: 348, 2004; Telen MJ Blood Advance 4: 3457, 2020; Rai P et al F1000Research 592, 2020

Voxelotor (GBT440) and SCD

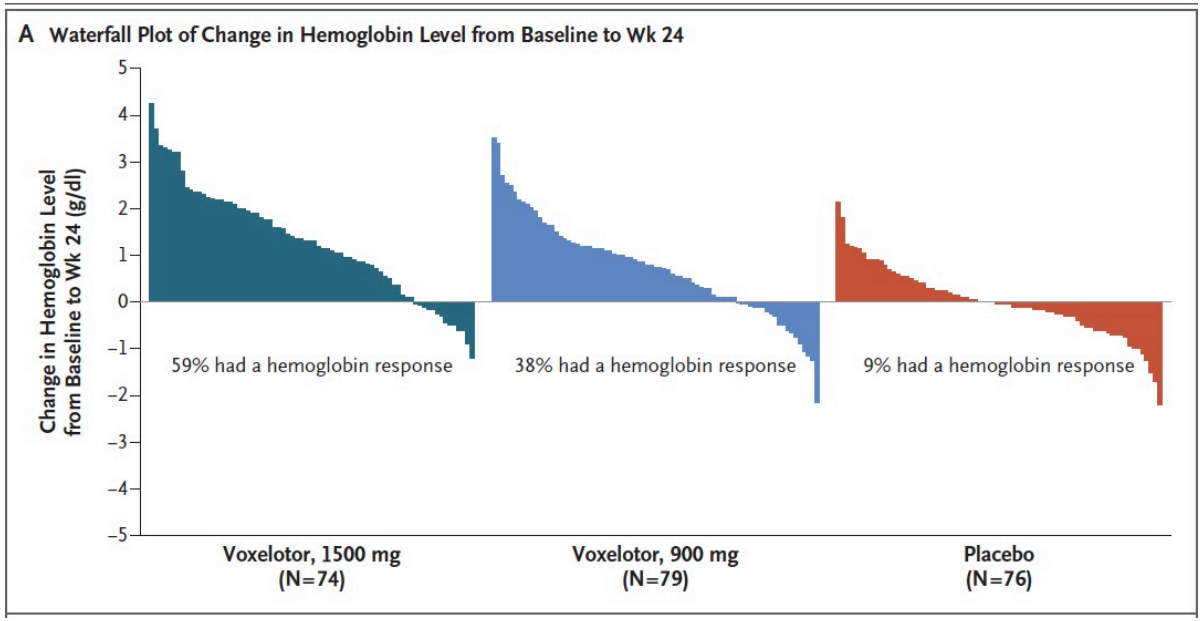


- **Voxelotor** is an oral available potent and direct anti-sickling agent

- **Voxelotor** binds to HbS and promotes a left shift in P_{50} of HbS, **delaying HbS polymerization and sickling**

Dufu K et al. . Blood. 2014;124:217; Oder E et al. BJH 175: 24, 2016; Oksenberg D et al BJH 175: 141, 2016; Li Q et al PNAS 11: e689, 2017;

Voxelotor and HOPE study (NCT03036813)



154 pts median age 28 years (SS or s/β^0) 12 months treatment (62-67% pts were on HU):

Sustained ↑ 1gr/dL Hb in both 900 and 1500 mg groups

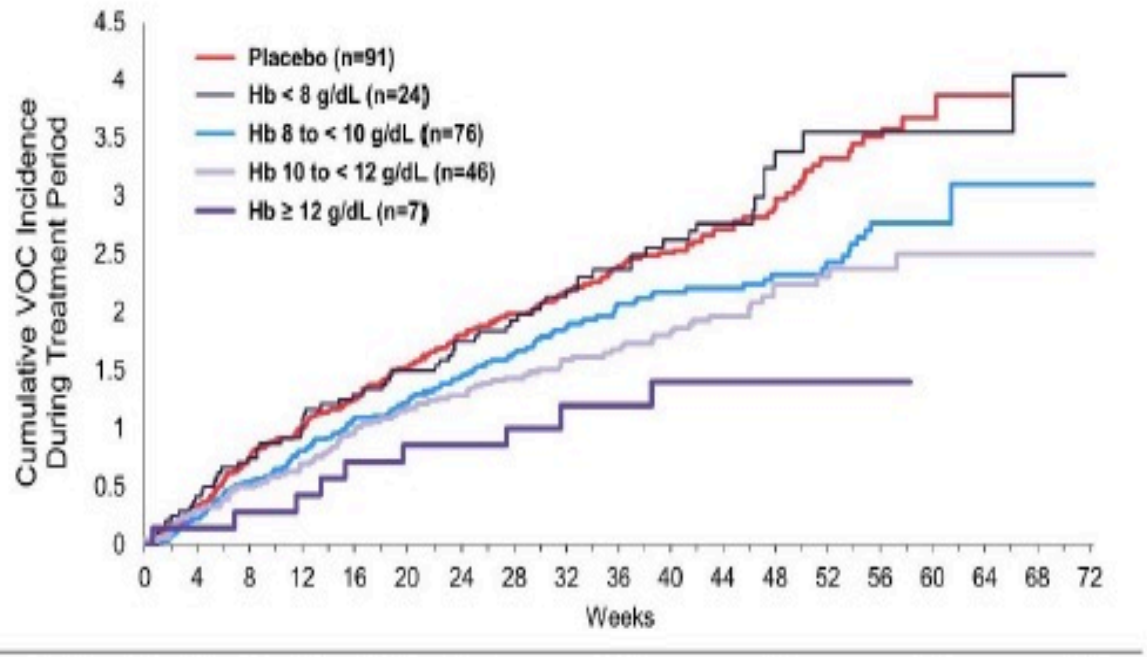
Sustained ↓hemolysis

AE: Diarrhea (n=3 pts), nausea (n=2-3 pts), vomiting (n=3 pts)

Vichinsky E et al Blood 132: 505, 2018; Vichinsky E et al. NEJM 381: 509, 2019; Osunkwo I et al BJH 30 Agust 2022 1-3, 2022

- **Voxeletor 900-1500 mg/die ≥24 sett.**
- **Persitent increased in Hb in Voxeletor treated group**
- **No effect on blood viscosity**

Long-term open study on SCD patients enrolled in HOPE trial

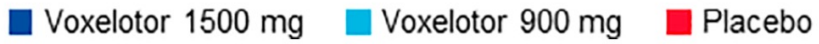


Vichinsky E et al ASH 2019; abstract #2313

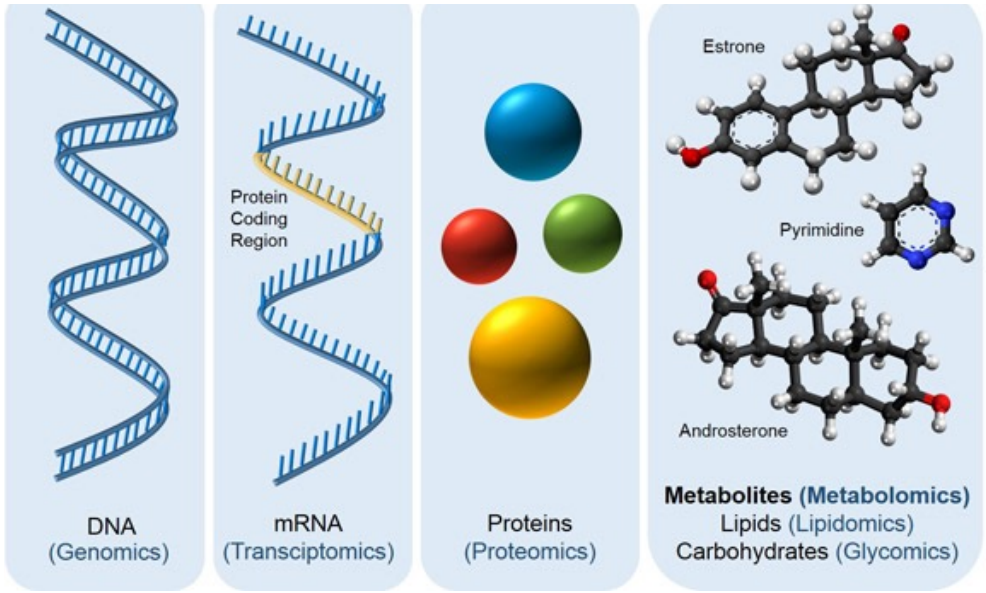
Voxelotor improves Leg Ulcers in patients with SCD

SCD (1500 mg/d-> patient improvement evaluated by CGI-C

(clinical global impression scale-change)



Minniti C et al Am J Hematol 96: Ee126, 2021; Smith WR et al ASH 2020, abstract# 802



RBCs
metabolomic

ATP
2-3, DPG

Normal red blood cell

A sickle-shaped red blood cell of sickle cell disease

ESTIMATE, Mitapivat (AG-348) improves anemia in patients with SCD (phase 2 open label study)

- SCD: SS, Sβ^+, Sβ^0 on HU (n=9)
- Mitapivat: multiple ascending dose 20-50-100 mg BID

Table 1. Mean Response in Sickling, Hemolysis and Biochemical Parameters at Treatment Week 8 compared to Baseline in the Dose Finding Period (n=6)

	Baseline	Treatment week 8	
Sickling parameters			*p-value**
PoS (mmHg)	40.3 (7.3)	31.3 (6.0)	0.009
p50 (mmHg)	22.7 (1.5)	20.9 (1.3)	0.009
Hemolysis parameters			
Hb (g/dL)	9.3 (0.9)	10.5 (1.1)	0.004
ARC (10^9/L)	274 (84)	168 (34)	0.005
RETC (%)	9.2 (1.5)	4.9 (0.8)	0.001
Bilirubin, total (mg/dL)	2.43 (1.09)	1.11 (0.58)	0.004
LDH (U/L)	402 (32)	312 (47)	0.007
Biochemical parameters			
2,3-DPG (10^3 µg/gHb)	11.5 (1.1)	8.1 (1.3)	0.001
ATP (10^3 µg/gHb)	3.0 (0.9)	3.5 (0.6)	0.173
ATP/2,3-DPG ratio	0.26 (0.05)	0.45 (0.11)	0.003

Data are presented as mean (standard deviation) for baseline and treatment week 8 results (n=6). *Paired t-tests or Wilcoxon signed-rank tests are used when appropriate. PoS point of sickling; p50 oxygen pressure at an oxygen saturation of 50%; Hb hemoglobin; ARC absolute reticulocyte count; RETC reticulocytes; LDH lactate dehydrogenase; 2,3-DPG 2,3-diphosphyglycerate; ATP adenosine triphosphate.

van Dijk J et al 2047, 2021

- **Mitapivat** significantly increases Hb **(> 1 g/dL in 75% of SCD patients**) with associated reduction of markers of hemolysis

- ESTIMATE study shows a reduction **in the mean annualized SCD-related hospital admission days**

- Mitapivat was well tolerated, and the recorded adverse events were mainly grade 1-2 (*e.g.* headache, increase AST, ALT, dyspepsia).

van Dijk MJ Am J Hematol 2022; 97:E226-E229; Matte A et al Curr Opin Hematol 2023 Feb 10. doi: 10.1097/MOH.0000000000000758.

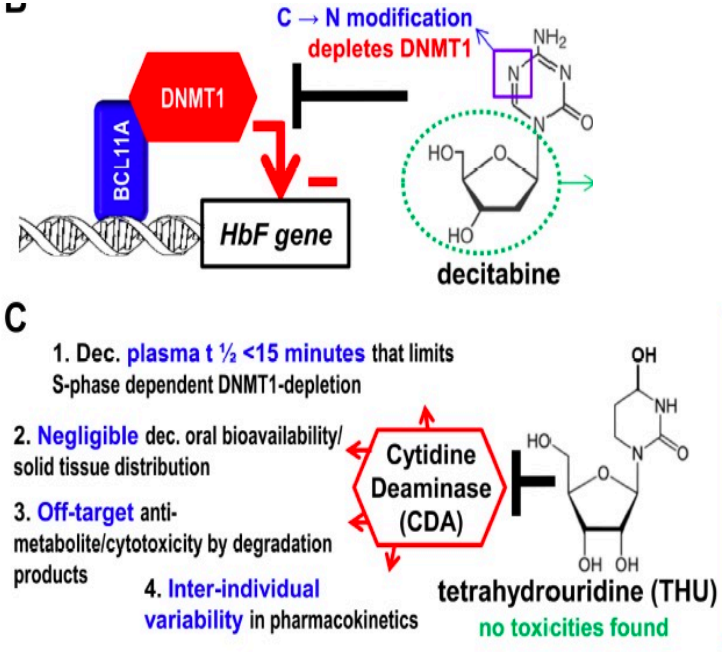
In adult patents with SCD the following studies with PK activator are on-going:

(i) RISE-UP (NCT 05031780), a phase 2/3 clinical trial with mitapivat (50-100 mg twice a day);
(ii) HIBISCUS (NCT 04624659) phase 2/3 clinical trial with etavopivat comparing 200-400 mg dosage;
(iii) GLADIOLUS, a phase 2 clinical study with etavopivat (400mg/d) (NCT 04987489) in SCD patients under chronic transfusion regimen.

Clark Clark Brown R et al 9, 2021; Kalfa T et al 8, 2021

Fetal Hb inducers commentary to HU: decitabine and THU-Decitabine

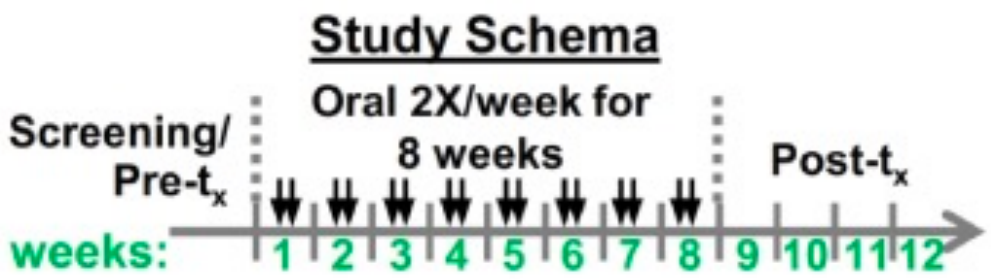
Decitabine (Dec), a 5-azacitidine related molecule, induces HbF through inhibition of DNA methyl transferase (DNMT)-> major limitation: **bioavailability**



Tetrahydrouridine (THU)
inhibitor of cytadine deaminase (CDA)

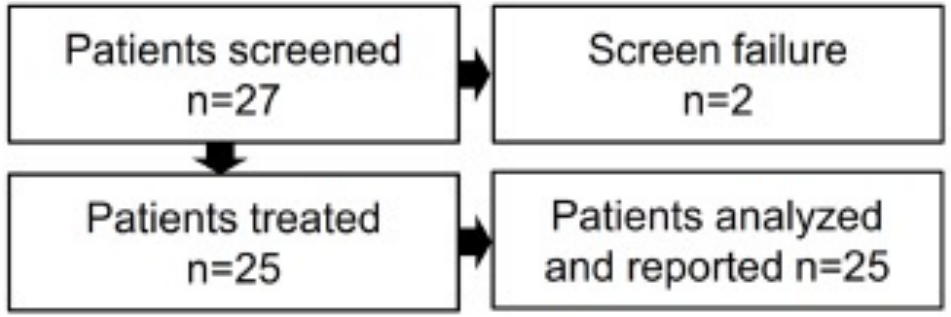
Fard AD et al. Int J Hematol Oncol Stem Cell Res. 7:47; 2013; Lavelle D et al. Blood 119:1240; 2012; Sauntharajah Y et al. Br J Haematol 141:126; 2008; Okam MM et al Blood 125: 3668; 2015; Musallam K et al Blood 121: 2199, 2013, Oliveri NF et al Blood 118: 2708, 2011; Molokie R et al Plos Medicine 14: e1002382, 2017;

Study Schema



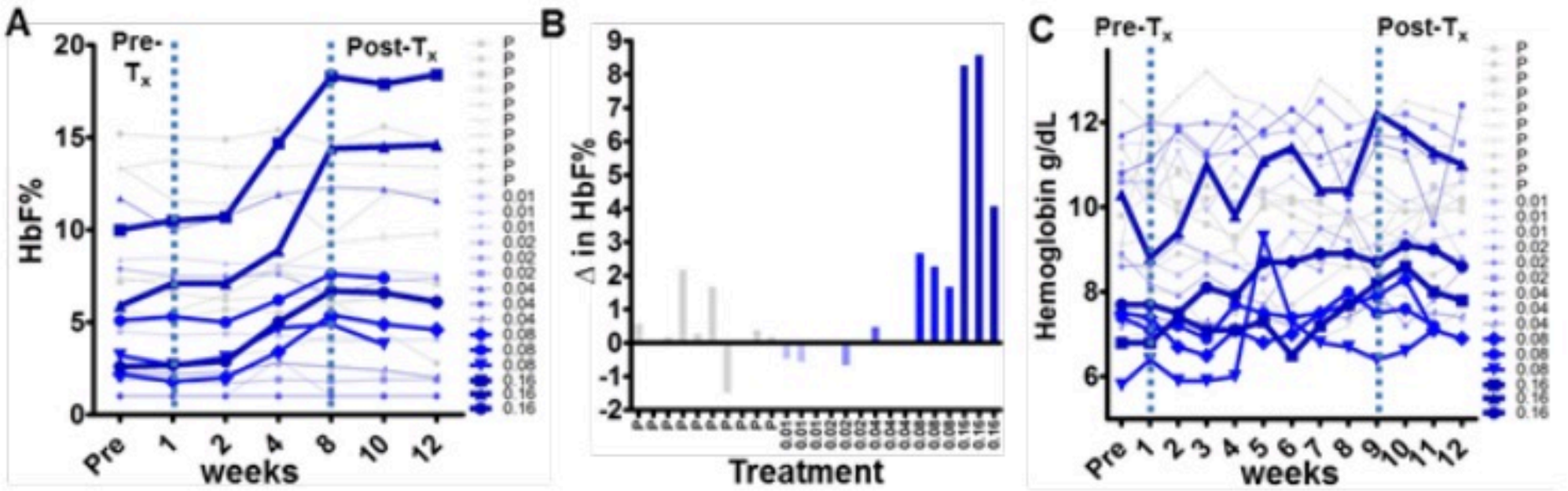
- **Randomized:** Placebo v THU-Dec (2:3)
- **5 cohorts -**
  THU fixed dose 10 mg/kg followed by
  decitabine 0.01, 0.02, 0.04, **0.08**, **0.16** mg/kg

SS or Sβ genotypes



Patient	Cohort	ED/Hosp Admits prior 12m	ACS (events)	PE/DVT (events)	CVA (events)	AVN (joints)
101	1	0	≥1	≥1		
106		1				
107		0				
103	2	1				
110		4	≥1	≥1		≥1
111		1	≥1			
112	3	10	≥1	≥1	≥1	
115		2	≥1			
116		2	≥1		≥1	≥1
117	4	7	≥1	≥1		≥1
120		18			≥1	
122		1	≥1			
124	5	7	≥1		≥1	
125		6	≥1		≥1	
127		3				≥1
102	P	1	≥1	≥1		≥1
105		4				≥1
108		4	≥1	≥1	≥1	
109		8	≥1	≥1		≥1
104		5	≥1	≥1		
114		3	≥1			≥1
119		4	≥1		≥1	
121		1				
123		4				
126		9	≥1	≥1		≥1

Molokie R et al Plos Medicine 14: e1002382, 2017

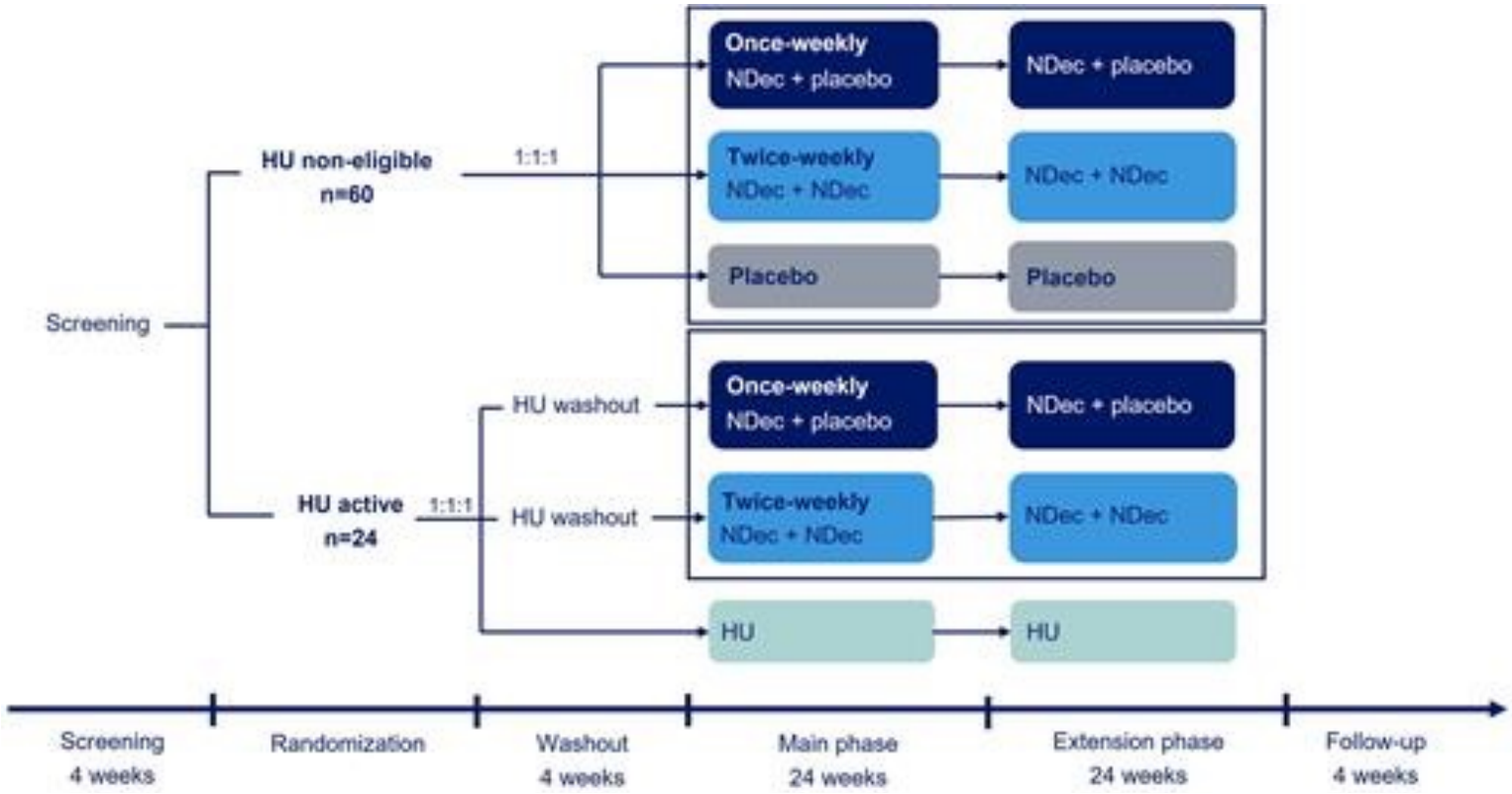


- **Phase 1/2 trials with Decitabine (0.01-0.16 mg/Kg) followed by tetrahydrouridine (THU, 10 mg/Kg), an inhibitor of cytadine deaminase,** has shown promising pharmacokinetic effects in patients with SCD

- **Phase 2 clincal trial reports increased total Hb and % HbF associated with reduced hemolysis and rate of VOCs except for cohort 4**

Molokie R et al Plos Medicine 14: e1002382, 2017

ASCENT1: multicenter, randomized, parallel-group, double blind, double-dummy placebo-controlled trial (all SCD genotypes)

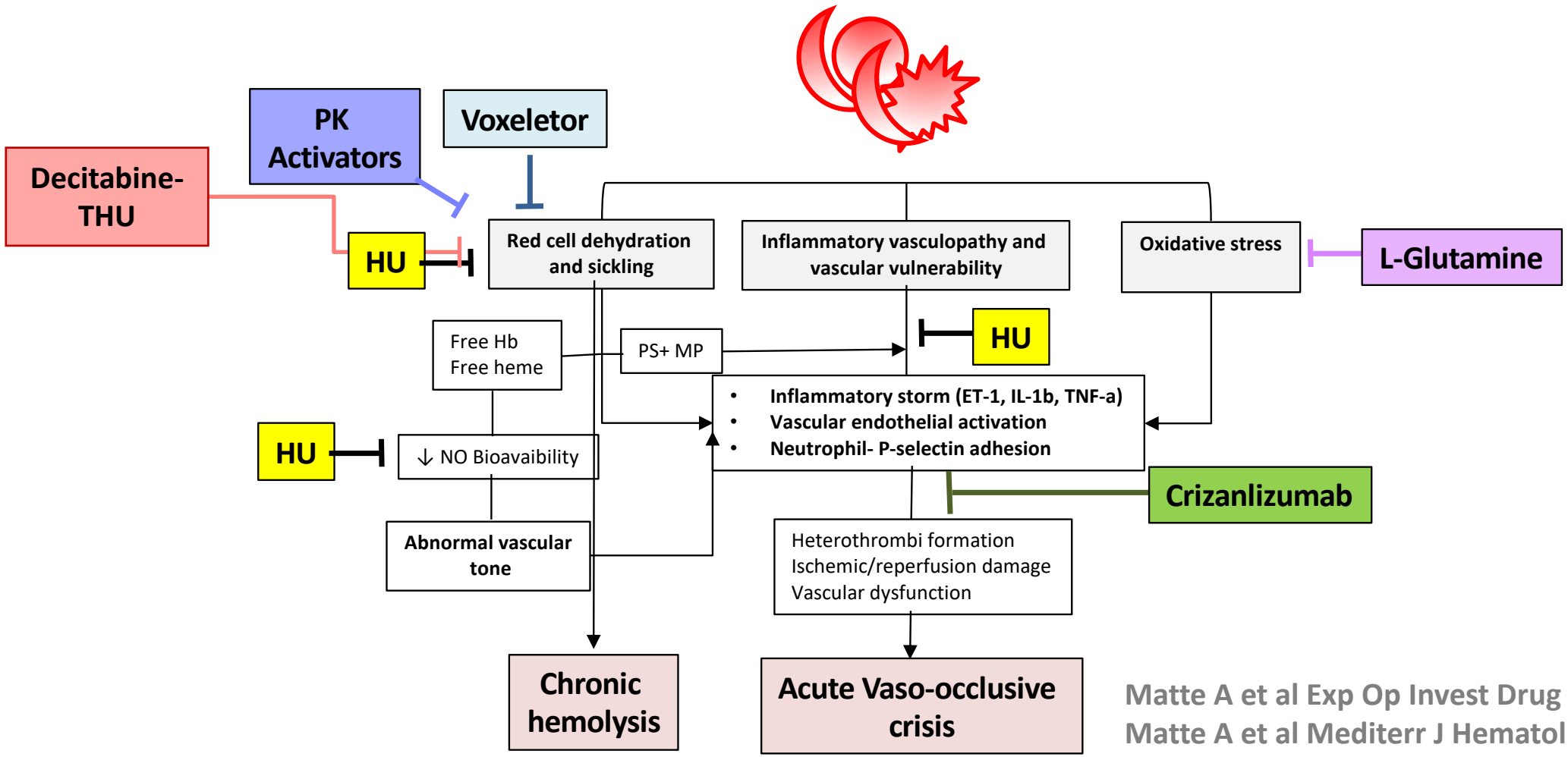


Primary endpoint is change in total Hb (g/dL) from baseline (BL) to Week 24.

Secondary efficacy endpoints include change in HbF (change in %F-cells of total RBCs, and change in hemolysis markers from BL to Week 24. Secondary efficacy endpoints also include numbers of VOCs, acute chest syndrome and transfused RBC units from BL to Week 48.

Andemariam B et al Blood Abstract 140: 520, 2022

Pathophysiology Based New Therapeutic Options for SCD

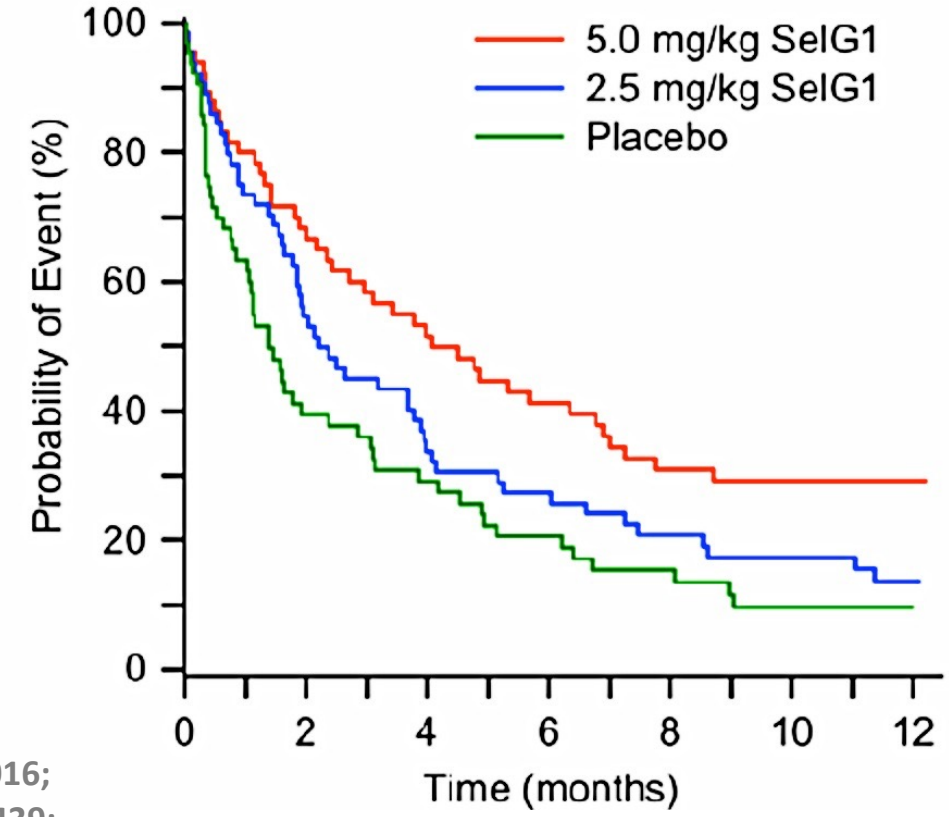


Matte A et al Exp Op Invest Drug 29: 23-31, 2020
Matte A et al Mediterr J Hematol Infect Dis 11: e22019002, 2019

Humanized Monoclonal Ab against P-selectin (Crizanlizumab)

In a double blind placebo-controlled multinational trial, Crizanlizumab:

- **was safe and well tollerated**
- **Induced a 1 month P-selectin block**
- **Reduced pain crisis**
- **Increased the time between pain crisis**



Mandarino D et al Blood 122: abstract 970, 2013; Telen MJ Blood 127: 810-19, 2016; Ataga KI et al abstract 1, 2016 (Dec 4); Ataga KI et al N Engl J Med 2017;376:429-439; Ataga KI et al. N Engl J Med 2017;376:1796.; Slomski A. JAMA 2017;317:798.

SUSTAIN: double blind placebo-controlled phase II study (NCT0185361) with P-selectin inhibitor-Crizanlizumab

- **Genopyte: SS, SC, S/β0, S/β+**
- **66 pts on 2.5 mg/Kg every 4 weeks and 67 pts on 5 mg/Kg every 4 weeks**
- **Crizanlizumab (5 mg/Kg every 4):**
  - increases the likelihood of SCD adult patients being sickle cell pain crisis free
  - is effective also in patients under HU -> (44% median rate of VOCs *vs* 32% on low dose crizanlizumab): ADDITIVE EFFECT

Kutlar A et al Haematologica S454, 2017; Telen MJ Blood Advance 4: 3457, 2020; Rai P et al F1000Research 592, 2020; Matte A et al Exp Opinion Invest Drug 29: 23-31, 2020; Matte A et al Mediterr J Hematol Infect Dis 11: e22019002, 2019 Ataga K et al NEJM 376: 429, 2017; Kutlar A et al Am J Hematol 94: 55, 2019; Yu Z et al. NEJM 376: 1795, 2017

Crizanlizumab: SUSTAIN and SOLANCE studies

- 111 pts from SUSTAIN and SOLANCE trial (NCT03264989, on going adult open label PK/PD study) 5 mg/Kg/ month

- Genotype: SS/SC, 75% in HU

- AE:
- **85% grade 1-2:** headache (15%), nausea (19%), backpain (15.3%)
- **45.9% experiences infection:** upper respiratory tract and urinary infection
- **No bleeding**

Kanter J et al ASH 2019, abstract #991; Kutlar A et al Am J Hematol 94: 55, 2019

SUSTAIN study: Crizanlizumab reduces days requiring opioid use

Analysis of Parenteral Opioids

- For this analysis, only parenteral opioids were included, with two assumptions tested:
  1. All parenteral fixed doses were taken as prescribed
  2. Both parenteral fixed or PRN doses were taken as prescribed.
- Under both assumptions tested, the median annual rate of opioid days were lower for patients in the Crizanlizumab 5 mg/kg arm compared with patients in the Placebo arm (**Table 3**).
- The absolute difference ranged from 2.01 to 2.03 median days per year and the relative reduction ranged from 50% to 67%.
- The 2.01 fewer median annual opioid days for patients treated with Crizanlizumab 5 mg/kg compared to Placebo was statistically significant (p=0.0470).

Table 3

	Median Annualized Opioid Days (Min., Max)				
Assumption	**Crizanlizumab 5 mg/kg (n = 40)**	**Placebo (n = 41)**	**Abs. Diff.**	**Rel. Red.**	**MW p-value**
Fixed	0.99 (0, 30.5)	3.02 (0, 37.0)	2.03	67%	0.0740
Fixed & PRN	1.98 (0, 32.6)	3.99 (0, 37.0)	2.01	50%	0.0470

Abbreviations: Abs. Diff. = absolute difference; MW = Mann-Whitney; n = number; PRN = pro re nata (administration of medication is not scheduled) Rel. Red. = relative reduction.

SCD patients treated with Crizanlizumb show a statistic significant 50% reduction in days per year on parental opioids compared to placebo group

Combination therapy Crizanlizumab and voxelotor: real life data

- As of July 2022, there were **18 patients** eligible for analysis.
- Median age: 30.5 (range, 19–47) years, 7 men and 11 women; 8 patients had the HbSS genotype, 7 HbSC, and 3 HbSB null.
- The **median duration** of exposure to crizanlizumab was **53.6 weeks**; **16** patients received crizanlizumab for **≥26 weeks**.

Improvement of VOCs related hospitalization in SCD patients under crizanlizumab associated with voxelotor.

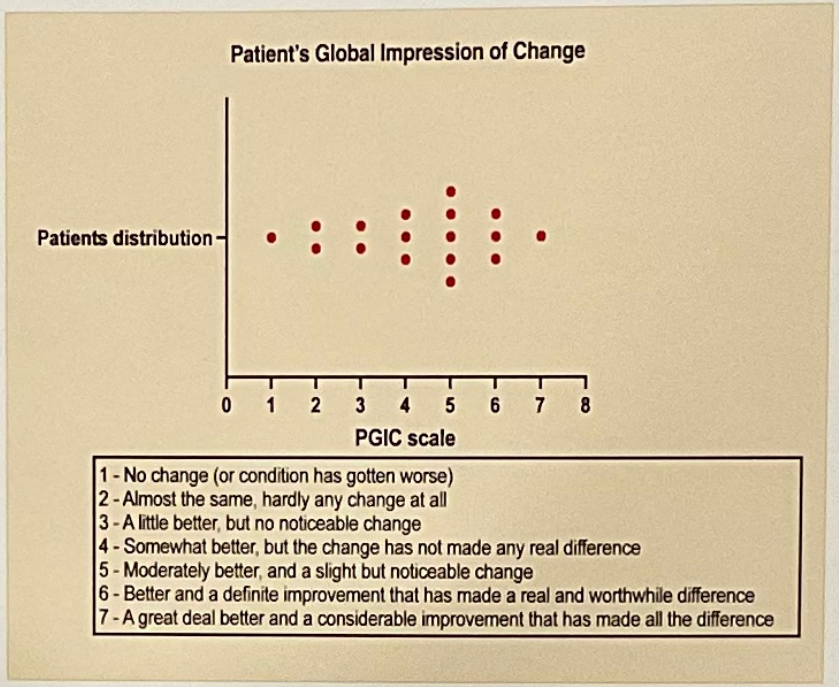
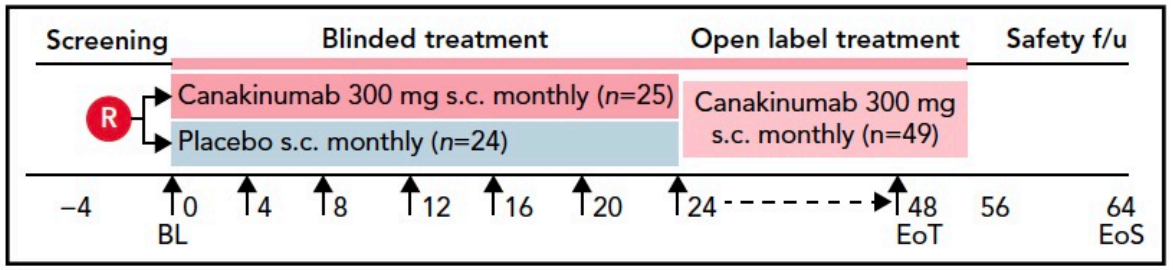


Figure 1: Patient's Global Impression of Change (PGIC) after crizanlizumab administration.

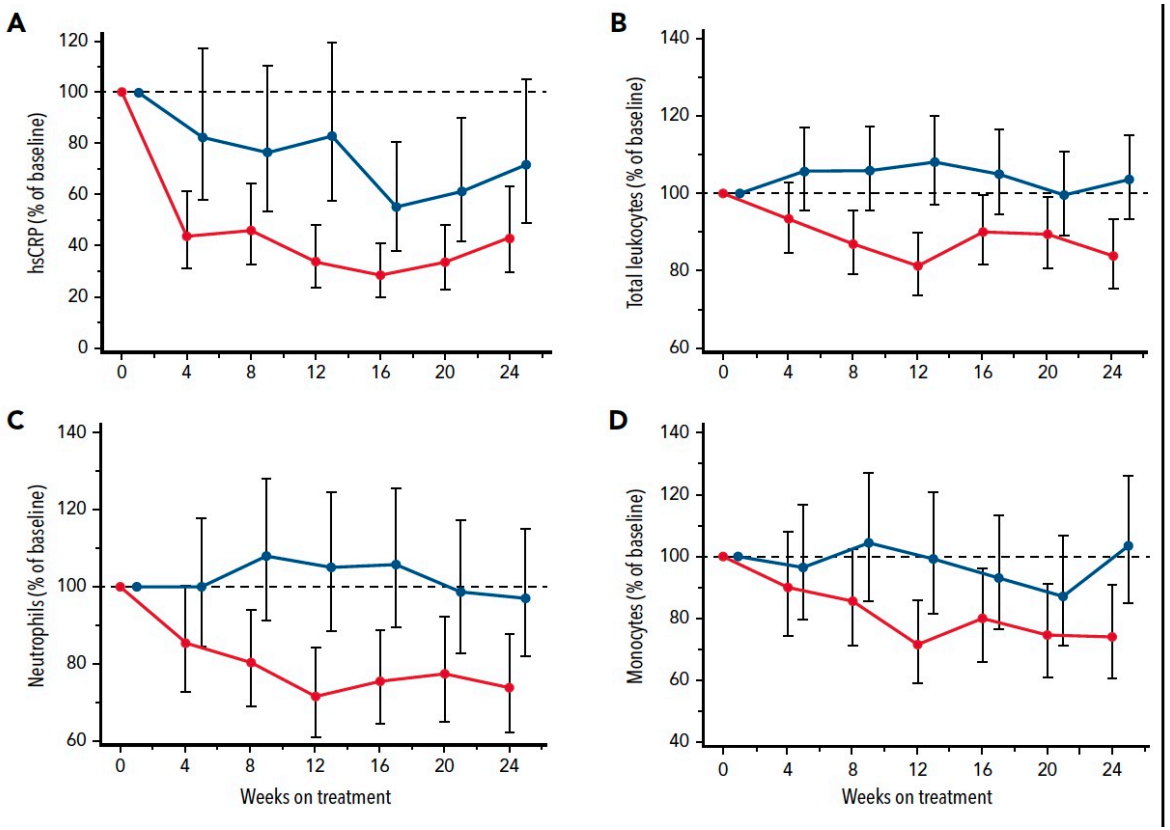
- There was a **remarkable improvement** in patients' subjective response after crizanlizumab infusion.
- The **median PGIC score of our patients was 5**, signifying moderately better with noticeable changes, although slight.
- **12 patients provided a score of ≥4**, which signifies feeling better with changes.

Chan KH et al. 8292-93, Blood 140 (S1), 2022

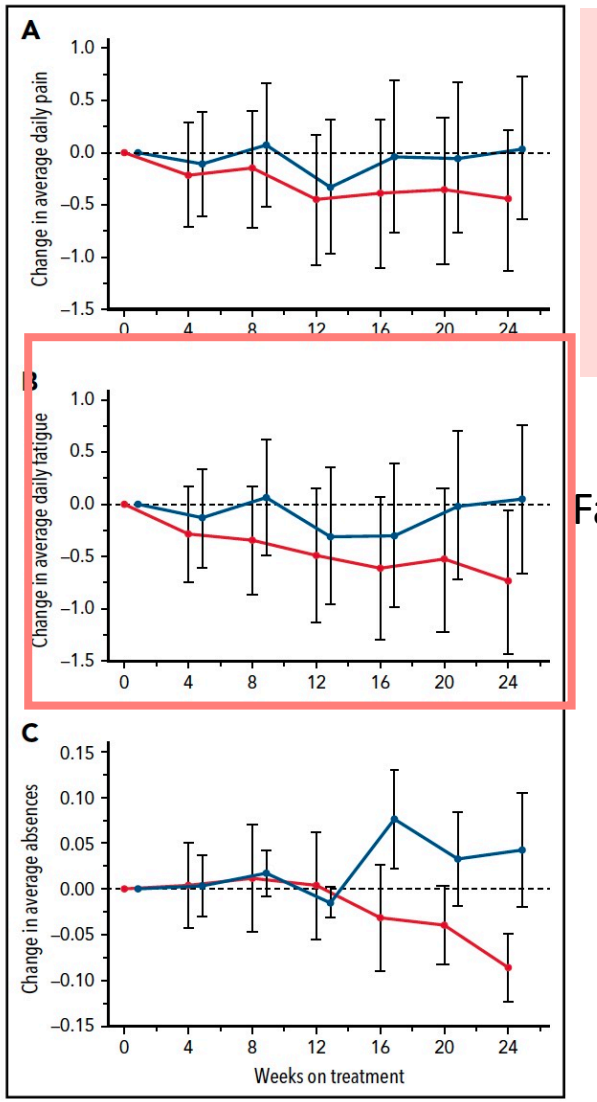
In SCD Canakinumab-Ab anti-IL1β reduces makers of system inflammation and fatigues



Markers of systemic inflammation



Assesment fo pain in SCD patients



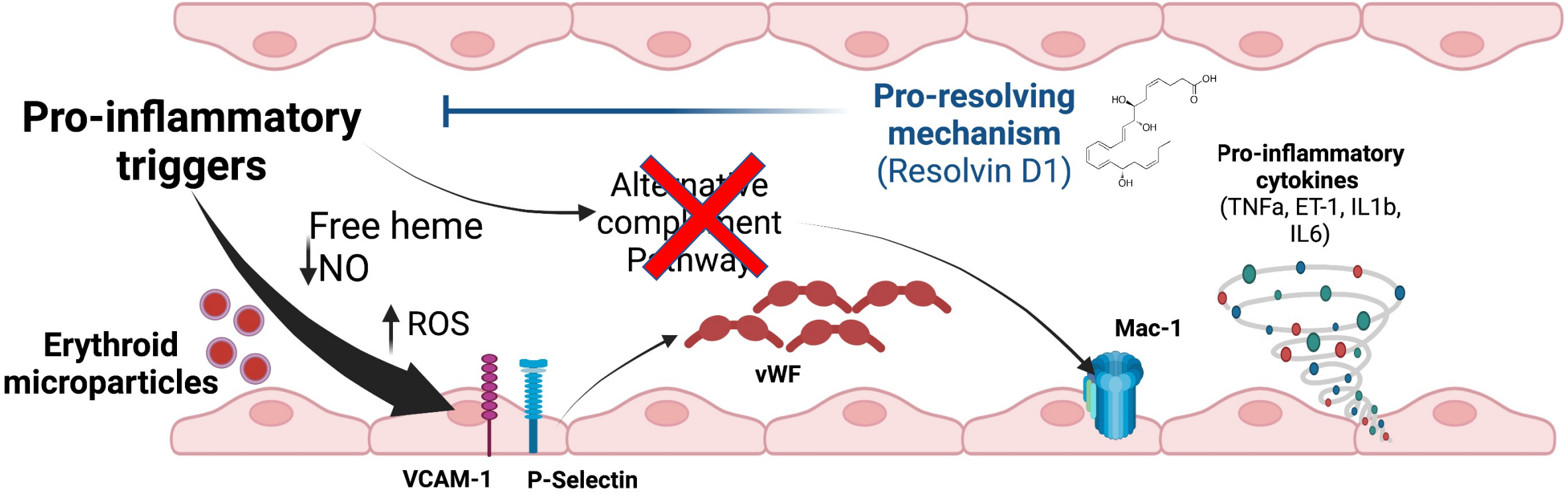
25 pts:Canakinumab
24 pts: placebo

SS, Sβ⁰
8-20 years of age

Fatigue

Rees DC et al Blood 139: 2642, 2022

Behind Sickle Red Cells: Vascular Vulnerability and Amplified Inflammatory Response



AP and SCD-I: Anti-complement 5 monoclonal Ab

114.HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIA: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 5, 2021

Trial in Progress: The Randomized, Double-Blind, Placebo-Controlled Phase Ib CROSSWALK-a Trial Evaluating the Safety of Crovalimab for the Management of Acute Uncomplicated Vaso-Occlusive Episodes (VOEs) in Patients with Sickle Cell Disease (SCD)

Pablo Bartolucci, Kenneth I. Ataga, Michael U. Callaghan, Lucia De Franceschi, Caterina Minniti, Ari Alexandrou, Diane-Charlotte Imbs, Richard Fox, Himika Patel, Alexandre Sostelly, Jonathan Schimmel

Blood (2021) 138 (Supplement 1): 3108.

https://doi.org/10.1182/blood-2021-147854

114.HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIA: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 5, 2021

Trial in Progress: The Randomized, Double-Blind, Placebo-Controlled Phase IIa CROSSWALK-c Trial Evaluating the Efficacy of Crovalimab As Adjunct Treatment in the Prevention of Vaso-Occlusive Episodes (VOEs) in Patients with Sickle Cell Disease (SCD)

Michael Callaghan, Kenneth I. Ataga, Lucia De Franceschi, Caterina Minniti, Nadiesh Balachandran, Diane-Charlotte Imbs, Thomas Perretti, Julia Ramos, Alexandre Sostelly, Pablo Bartolucci

Blood (2021) 138 (Supplement 1): 3111.

https://doi.org/10.1182/blood-2021-151222

AP and SCD-II: ALXN1820 is a humanized bispecific VHH antibody that simultaneously binds albumin and properdin

114.HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIA: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 15, 2022

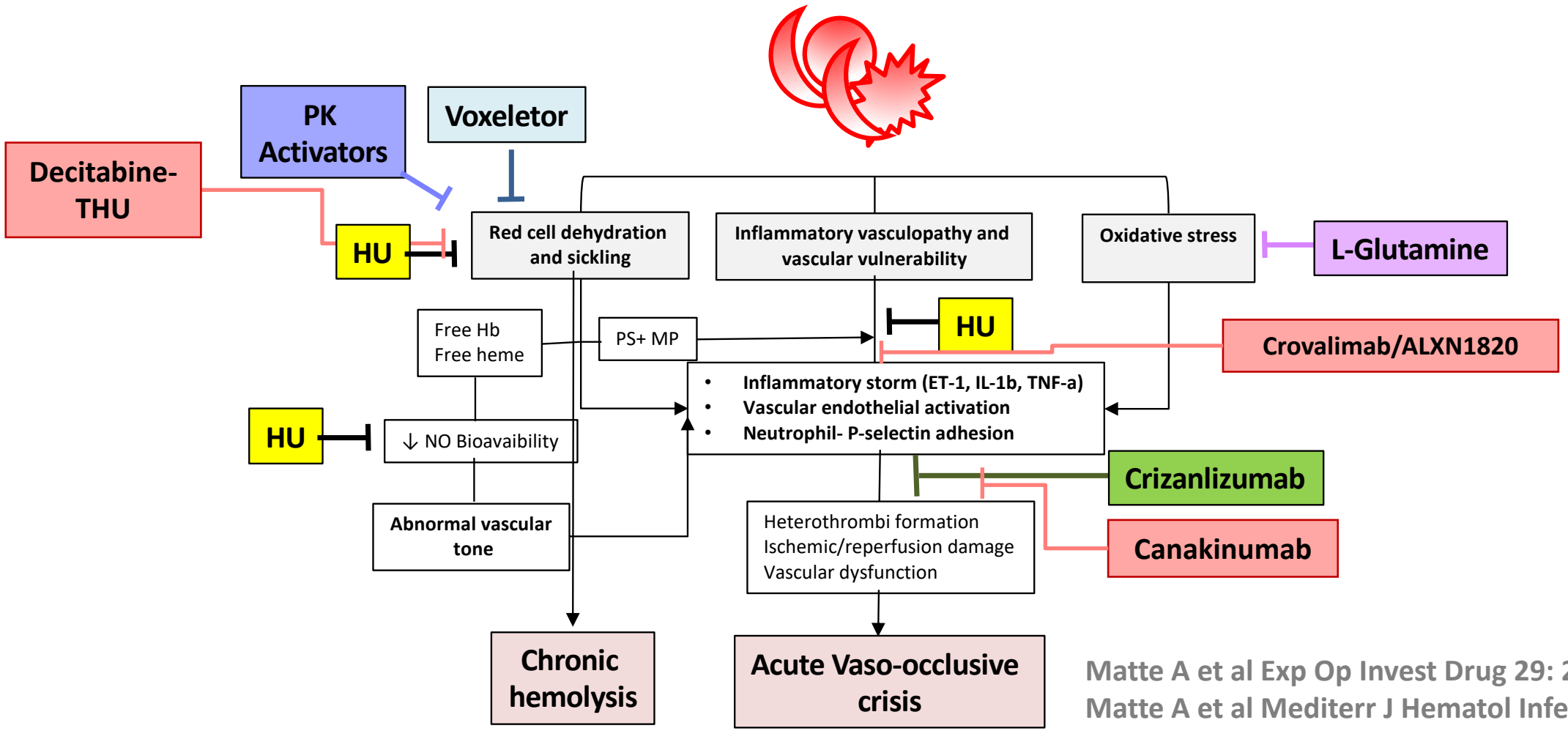
A Phase 2a, Randomized, Open-Label Study to Evaluate Multiple Dosing Regimens of Subcutaneous ALXN1820 in Adult Patients with Sickle Cell Disease

Yang Dai, Kelley Hill, Daniel Harris, Tong Shen, Chao-Xing Yuan, Christoph Gasteyger

Blood (2022) 140 (Supplement 1): 8298–8299.

https://doi.org/10.1182/blood-2022-166694

Pathophysiology Based New Therapeutic Options for SCD



Matte A et al Exp Op Invest Drug 29: 23-31, 2020
Matte A et al Mediterr J Hematol Infect Dis 11: e22019002, 2019

L-Glutamine and SCD

Since no information are available on log-term use of L-glutamine supplementation as well on the systemic effects of L-glutamine, the sickle cell scientific community should **use caution** in prescribing L-glutamine supplement for both adult and pediatric SCD patients

Niihara Y et al Blood 132: 1065, 2018; Niihara Y et al NEJM 379: 226, 2018 Quinn TC Blood 132:689, 2018; Matte A et al Mediterr J Hematol Infect Disease 11: e2019002, 2019

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