SCD: La Terapia Oggi

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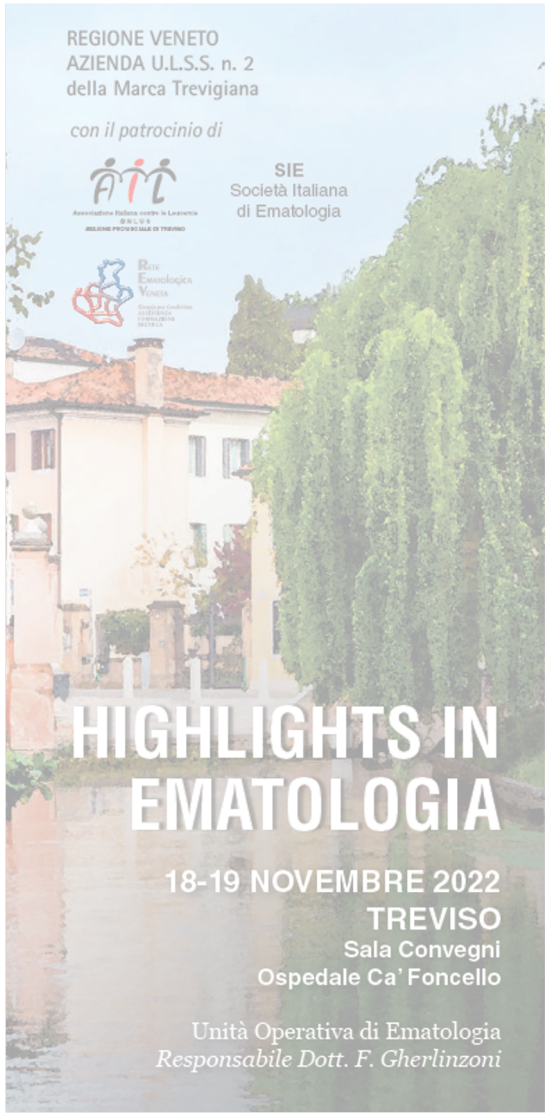
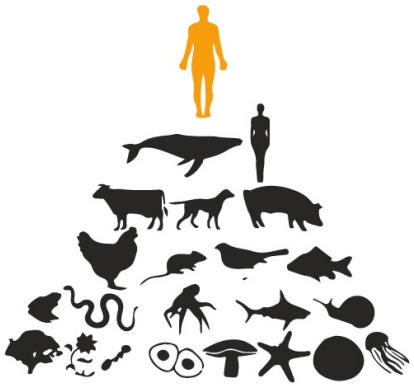
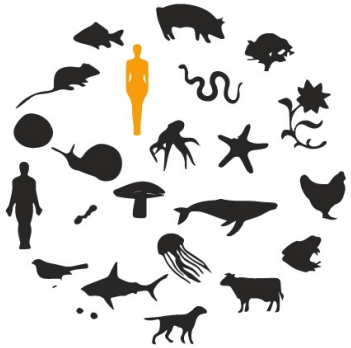


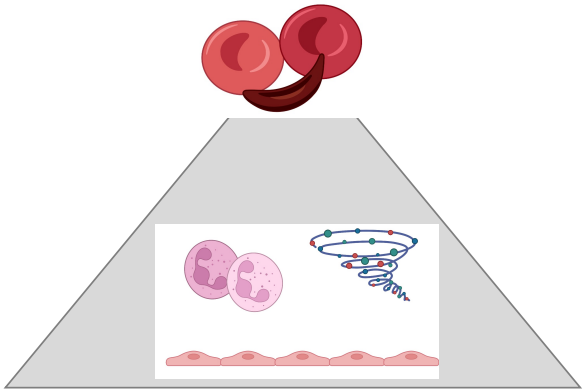
From Erythro-centric perspective to Multicellular perspective



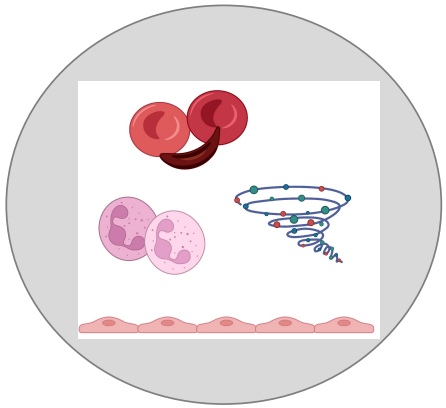
Anthropocentric



Non-Anthropocentric

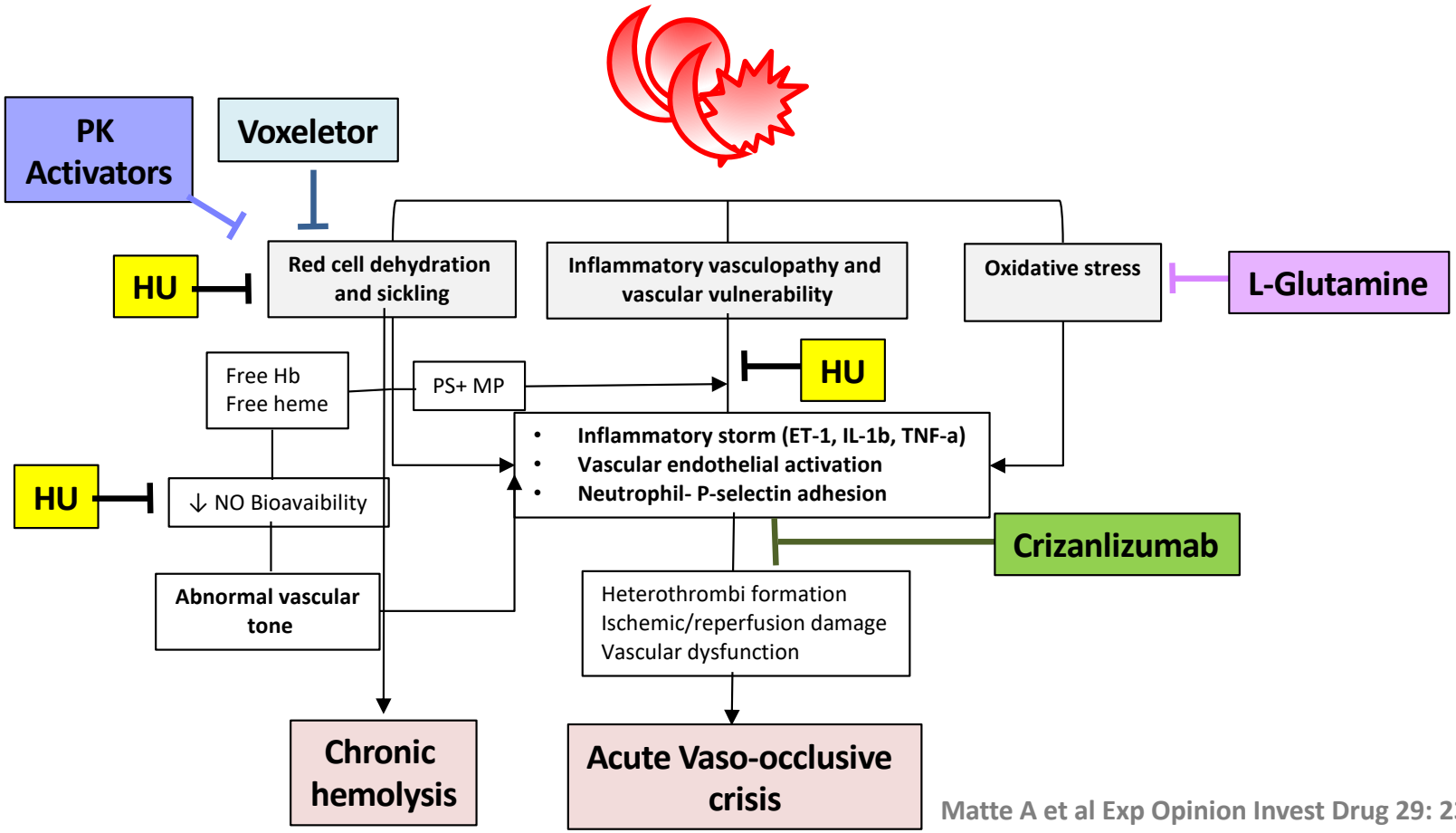


Erythro-centric perspective



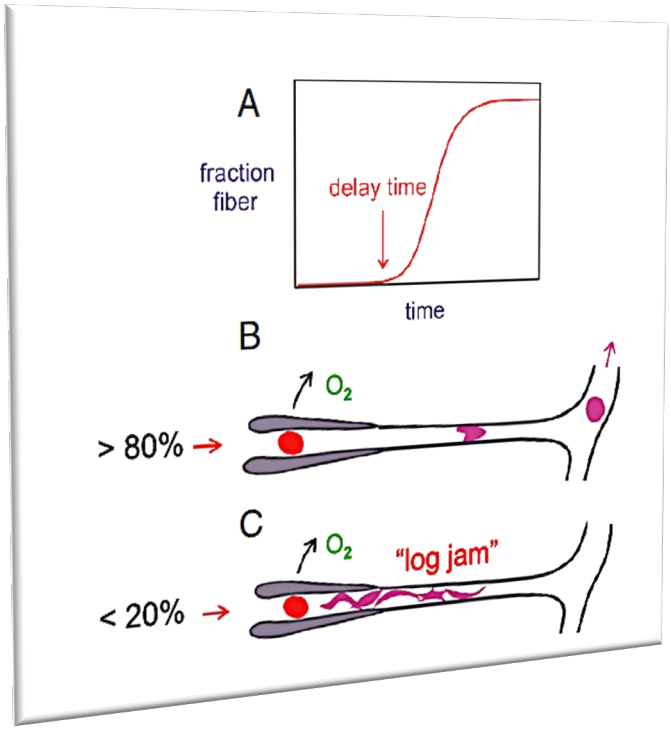
Multicellular perspective

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

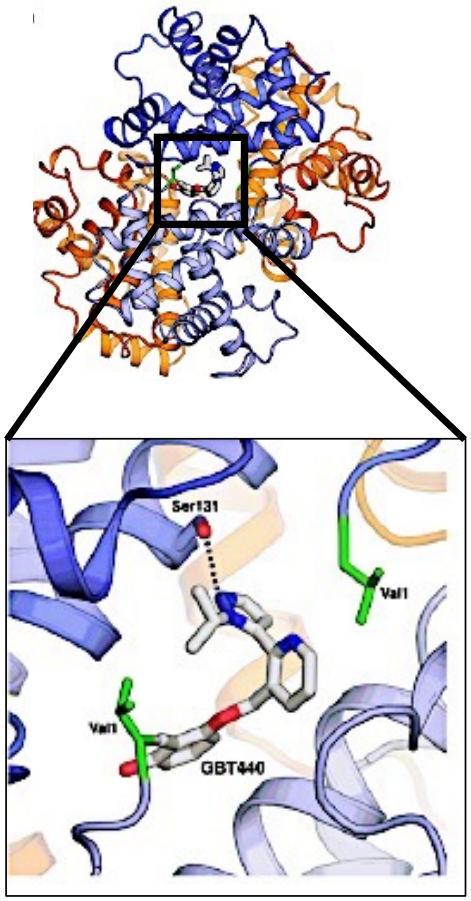
Generation of Sickle and Dense Red Cells



- **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)

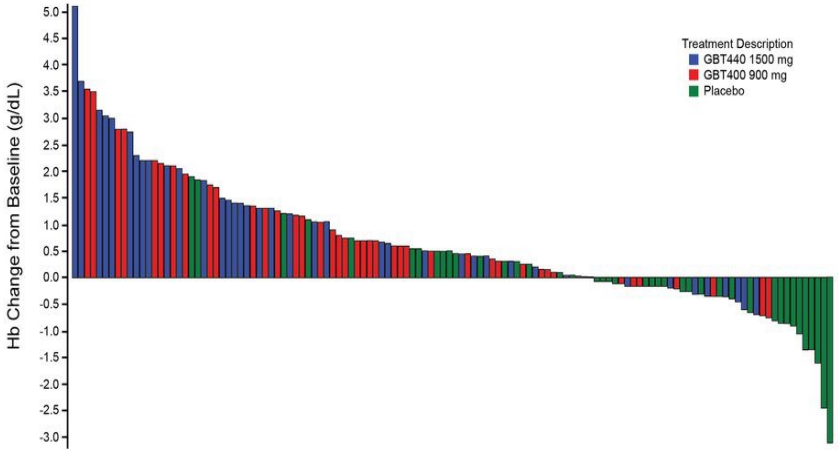
Phase III randomized double-blind placebo controlled multicentric study:

- **<u>Primary endopoint:</u> ↑ 1gr/dL Hb**
- **<u>Secondary endopoints</u>: rate VOC, ↓hemolysis**

Vichinsky E et al Blood 132: 505, 2018; Telen MJ Blood Advance 4: 3457, 2020; Rai P et al F1000Research 592, 2020

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

Figure1: Study from GBT440-031 (Part A): Observed Week 12 Change in Hemoglobin (g/dL) from Baseline

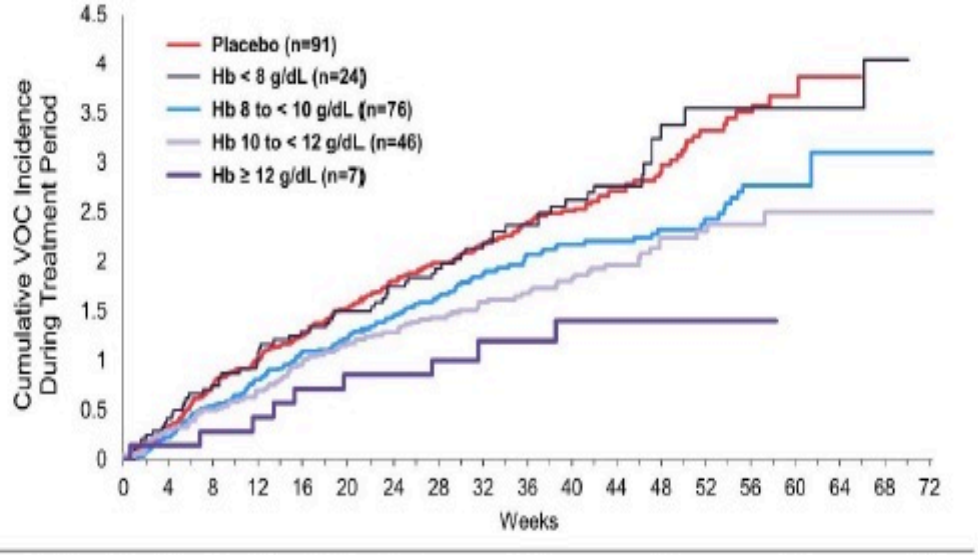


- **Sustained ↑ 1gr/dL Hb in both 900 and 1500 mg groups**
- **Sustained ↓hemolysis and in reticulocyte count**
- **AE: Diarrhea (n=3 pts), nausea (n=2-3 pts), vomiting (n=3 pts)**

Vichinsky E et al Blood 132: 505, 2018; Telen MJ Blood Advance 4: 3457, 2020; Rai P et al F1000Research 592, 2020; Osunkwo I et al Therapeutic Sdvances in Hematol 11: 1-15, 2020

- **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

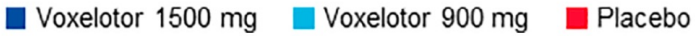


Vichinsky E et al ASH 2019; abstract #2313

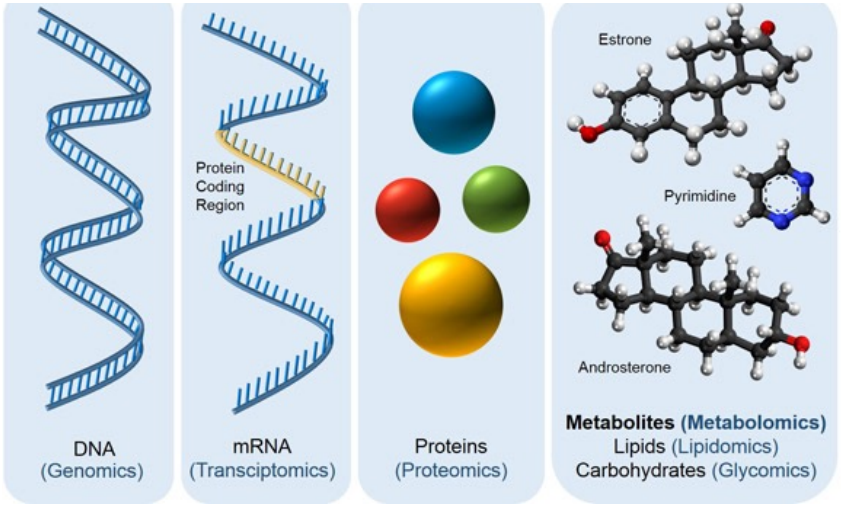
Voxelotor improves Leg Ulcers in patients with SCD

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, Miatpivat (AG-348) improves anemia in patients with SCD

- 9 pts with SCD: SS, $S\beta^{+}$, $S\beta^{0}$ on HU
- 20 mg BID, 52 weeks observation (*ad interim* 8 weeks)
- Mitapivat was safe and well tolerate

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

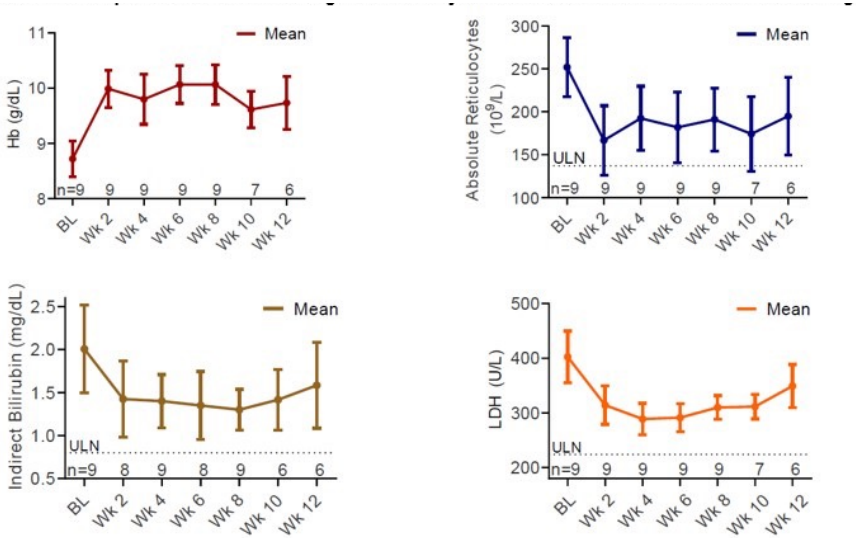
Miatpivat (AG-348) improves hemolysis and sickling in patients with SCD (NCT04610866)

- 17 pts SCD (with or without HO or L-glutamine) range age: 25-35 ys
- Dose escalation 20-50-100 mg BID
- Improvement of hemolysis, reduction in sickling rate
- AE grade 1-2: insomnia, arthralgia, grade 3: hypertension

Xu J et al 10, 2021

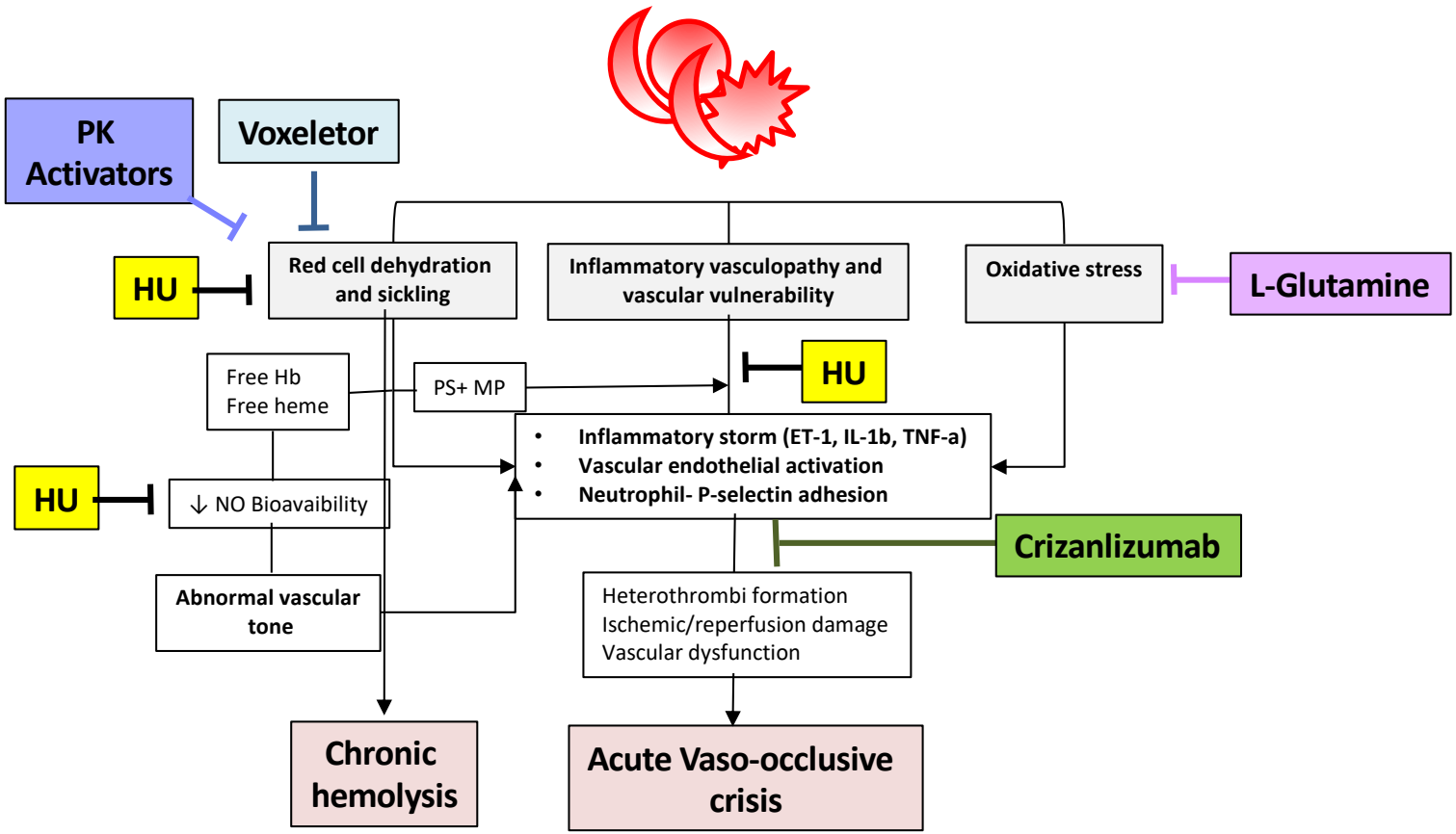
Etavapivat, a PKr activator improves hematologic parameters and red cell features in patients with SCD (NCT03815695)

- Multiple dose ascending study 300-> 600 mg *vs* placebo
- 20 SCD pts (17 SS, 2 Sβ, 1 SC)
- Improved Hb, reduction indices of hemolys
- ↓ PS+ RBCs
- ↓ soluble TNFa and D-dimer
- AE: < grade 3: headache, nausea



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

Pathophysiology Based New Therapeutic Options for SCD

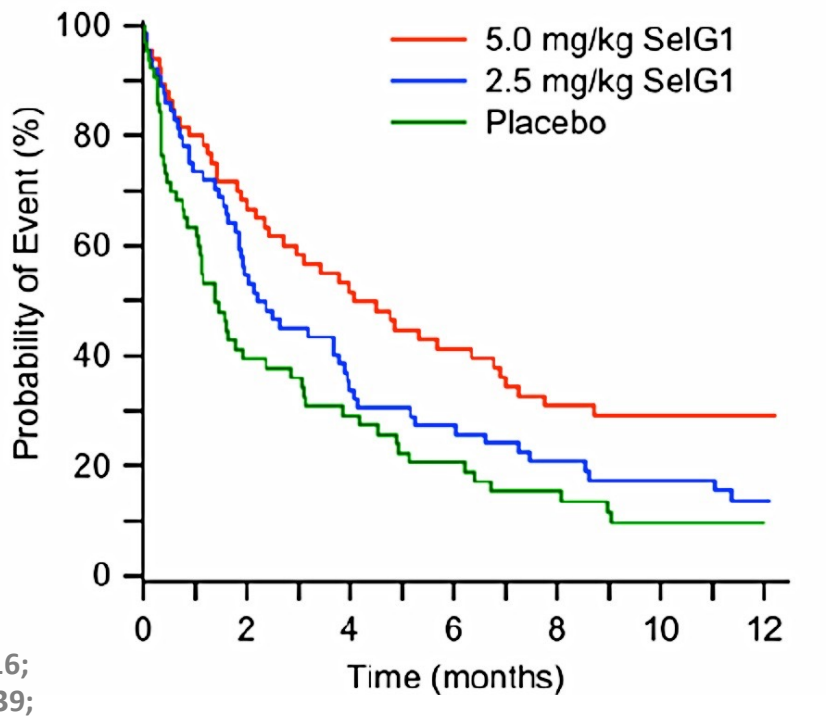


Matte A et al Exp Opinion Invest Drug 29: 23-31, 2020
Matte A et al Mediterr J Hematol Infect Dis 11: e22019002, 2019

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

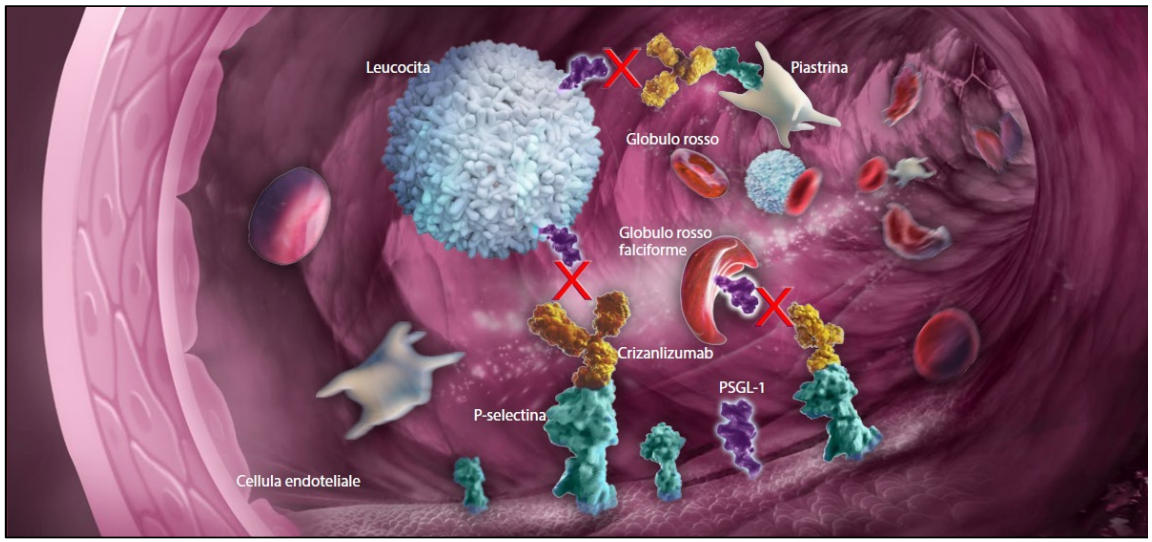
	Median Annualized Opioid Days (Min., Max)				
Assumption	**Crizanlizumab 5 mg/kg (n = 40)**	**Placebo (n = 41)**	**Abs. Diff.**	**Rel. Red.**	**MW p-value**
Fixed	0.99 (0, 30.5)	3.02 (0, 37.0)	2.03	67%	0.0740
Fixed & PRN	1.98 (0, 32.6)	3.99 (0, 37.0)	2.01	50%	0.0470

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

SOLANCE: Crizanlizumab in children-adolescent with SCD

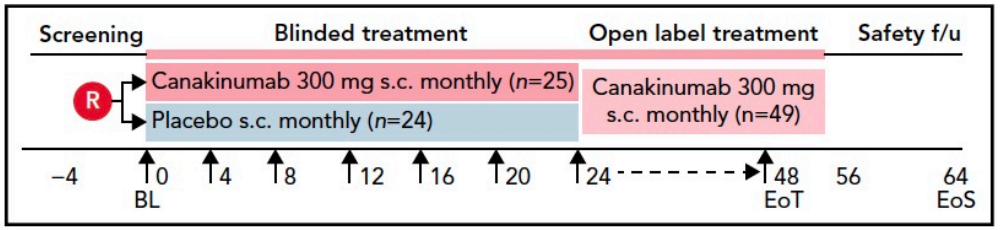
- Expected 100 pts-> enrolled 50 pts
  - 88% SS genotype;
  - 84% on HU
- Ad interim results->
- mean reduction of 1 VOCs

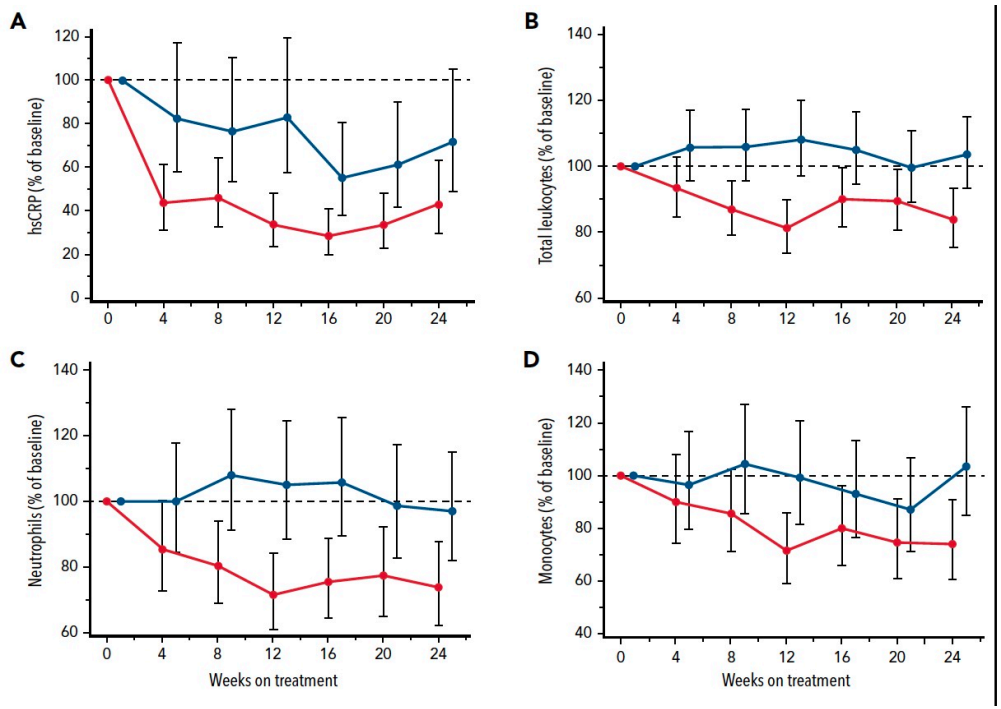


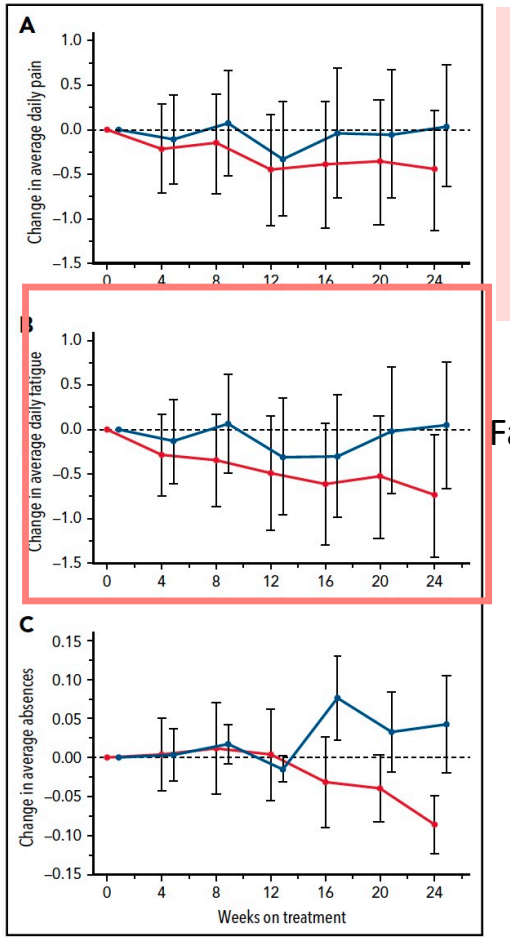
Inclacumab: fully human IgG4 anti P-Selectin Ab
(20-40 mg/Kg every 12 weeks)

Heeney M et al abstract# 12, 2021; Heeney M et al abstract# 12, 2021; Mayer C et al abstract #977, 2021

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







25 pts:Canakinumab
24 pts: placebo

SS, Sβ⁰
8-20 years of age

Fatigue

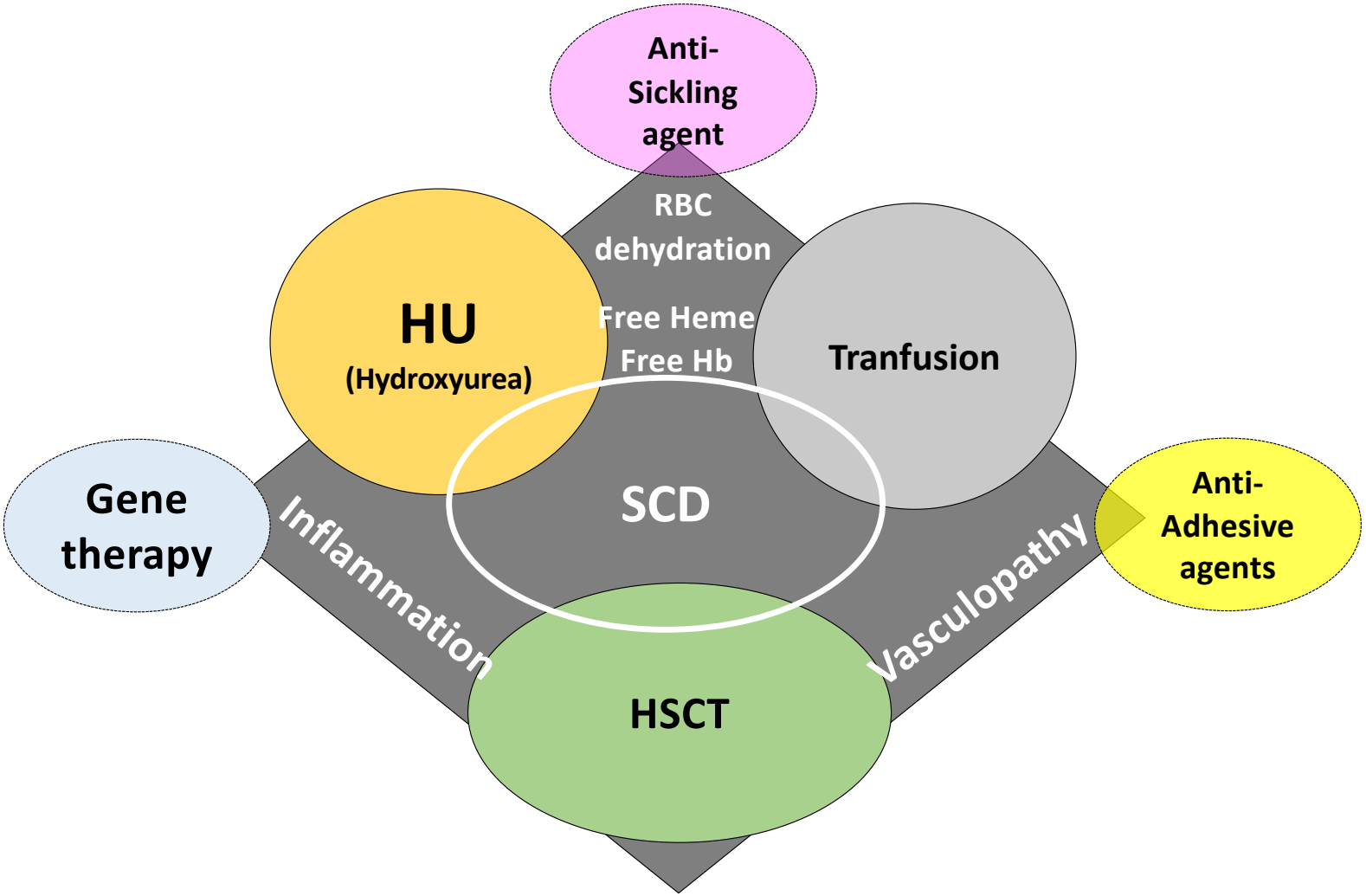
Rees DC et al Blood 139: 2642, 2022

Perspectives: Combination Therapies for SCD

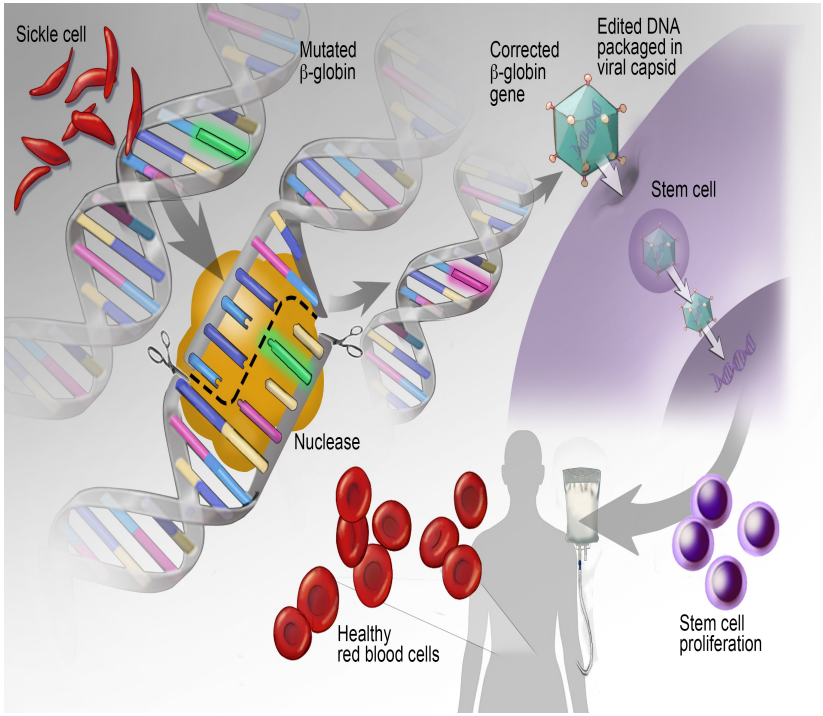
- HU in combination with:
  - Chronic P-selectin blockade (Ataga KI et al. abstract #1, 2016; Telen MJ et al doi 10.111/BJH14303, 2016)
  - PK activators, Nutritional/dietary supplementation (i.e.: ω-3 fatty acid, Mg2+ supplementation) (Kalish B et al Haematologica 100:870-80, 2015; Daak AA et al. AJCN 97: 37, 2013; Hankins JS et al. BJH 140: 80, 2008)
- Combination treatment without HU:
  - Anti-sickling agent(s) combined with P-selectin blockade (Swift R et al abstract #121, 2016; Lehrer J et al. abstract #2488, 2016; Ataga KI et al. abstract #1, 2016; Telen MJ et al doi 10.111/BJH14303, 2016)
  - Anti-sickling agent(s) and anti-inflammatory/anti-oxidant agents

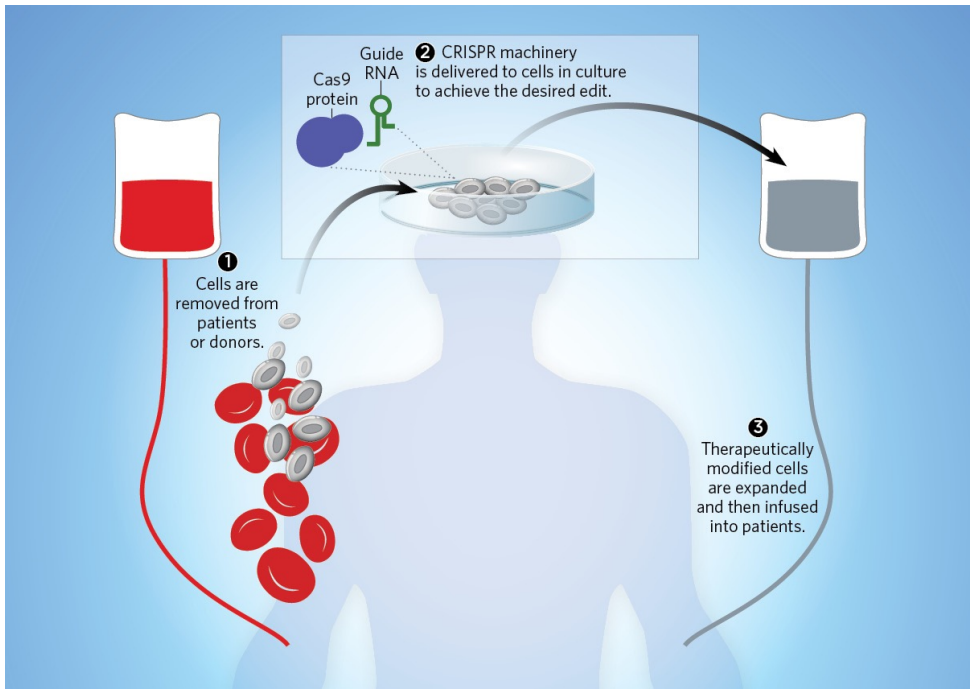
Telen MJ Blood Advance 4: 3457, 2020; Rai P et al F1000Research 592, 2020; Matte A et al Exp Opinion Invest Drug 29: 23-31, 2020; Matte A et al Mediterr J Hematol Infect Dis 11: e22019002, 2019

Available Treatments for SCD



Gene Therapy/Gene Editing As New Perspective For SCD

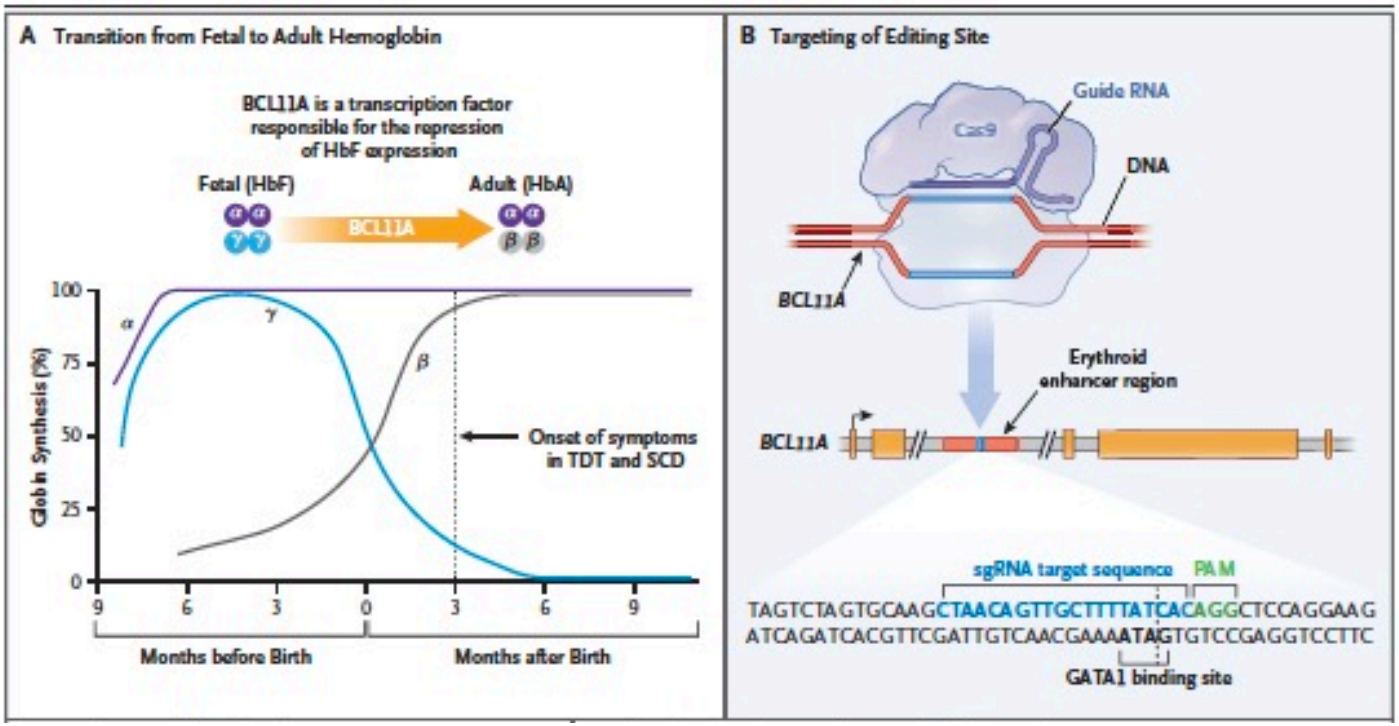


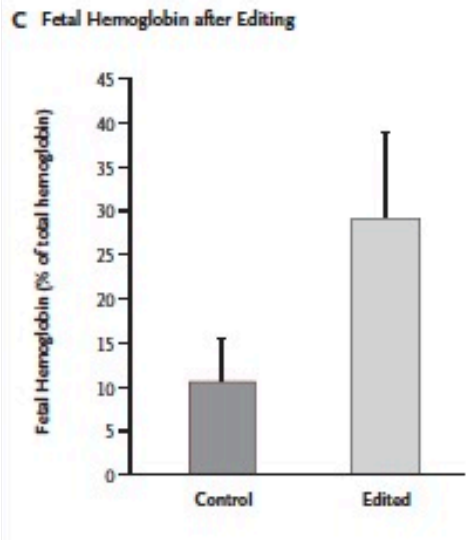


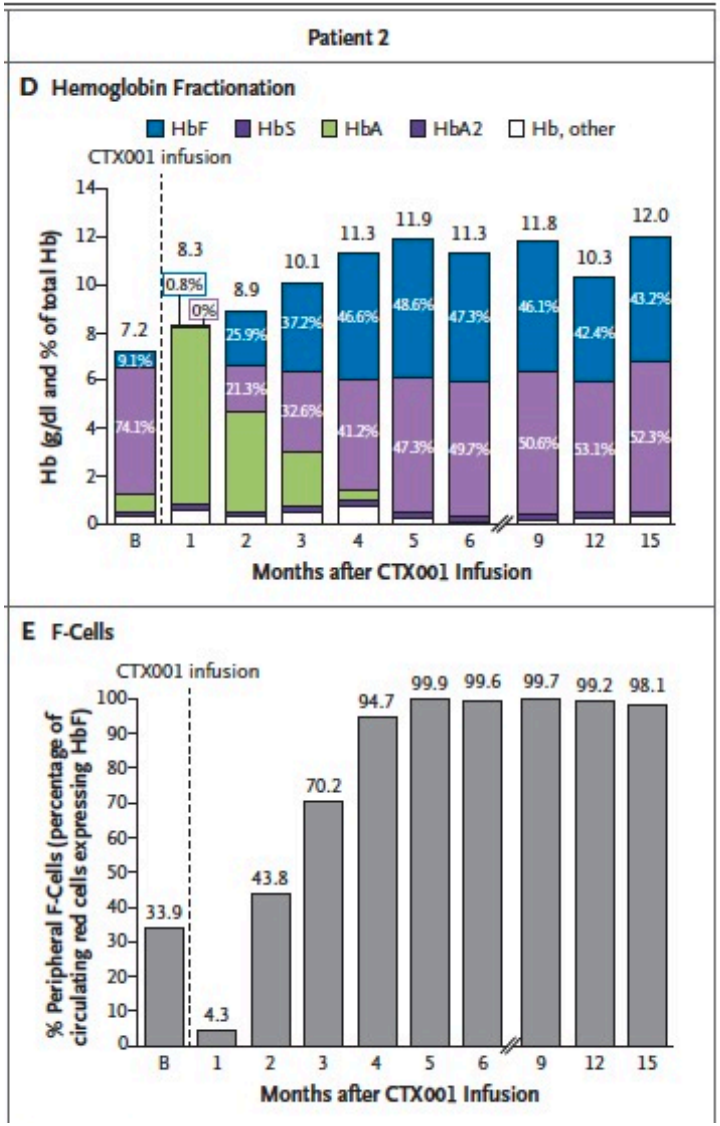
Malik P et al Blood 132: 1021, 2018; Nfazel HM et al. al Blood 132: 2194, 2018; Kanter P et al Blood 132: 1021, 2018;Ribel JA et al NEJM 376: 848, 2017; Frangoul H et al NEJM doi 10.1056/nejma2031054, 2020

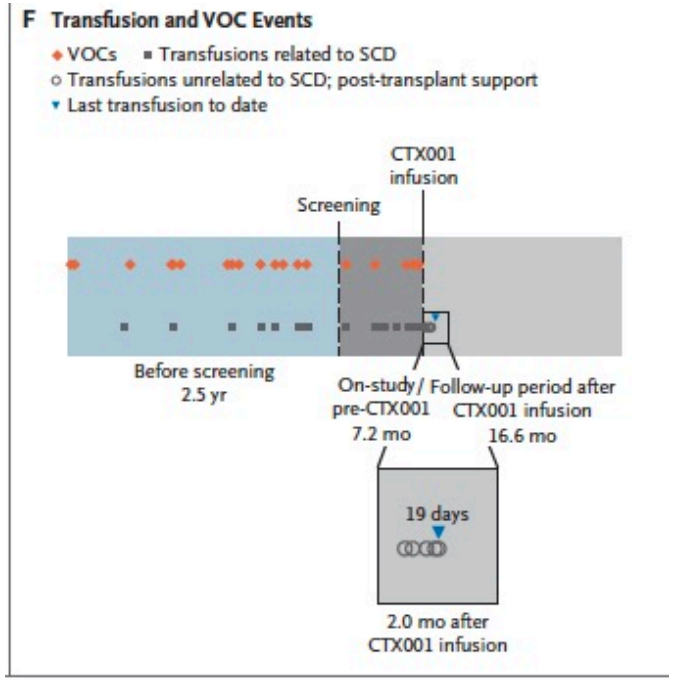
Gene Editing Approaches

CRISPR-Cas9 gene editing targeting Bcl11a in SCD

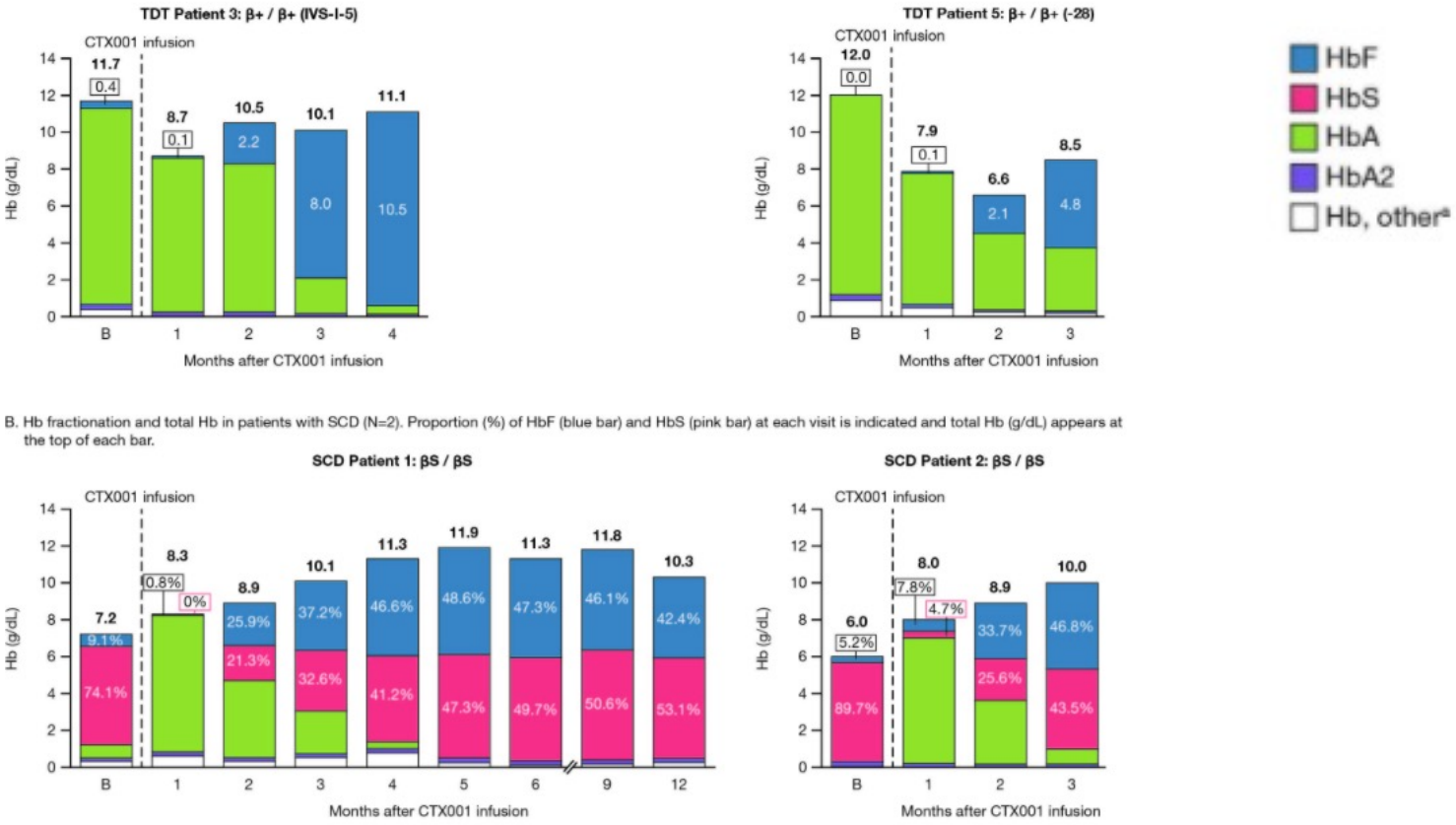








Frangoul H et al NEJM doi 10.1056/nejma2031054, 2020



B. Hb fractionation and total Hb in patients with SCD (N=2). Proportion (%) of HbF (blue bar) and HbS (pink bar) at each visit is indicated and total Hb (g/dL) appears at the top of each bar.

B: Baseline; Hb: hemoglobin; HbA: adult hemoglobin; HbF: fetal hemoglobin; HbS: sickle hemoglobin: SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia.
[a]Hb adducts and other variants; [b]Total Hb from local laboratory and Hb fraction from central laboratory.

Frangoul H, ASH 2020

Guidelines/Reccomendations; gene therapy/gene editing

Coordinators

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-Mariane de Montalembert (France)-C

Writters

- Jean-Hugues Dalle (France)
- Josu de la Fuente (UK)
- Pagona Flevari (Greece)
- Stephan Lobitz (Germany)
- David Rees (UK)
- Stefano Rivella (USA)

Reviewers panel (anonimous)

Pateints' advocacies

- N
- N
  h
  c
- A
  c
  d