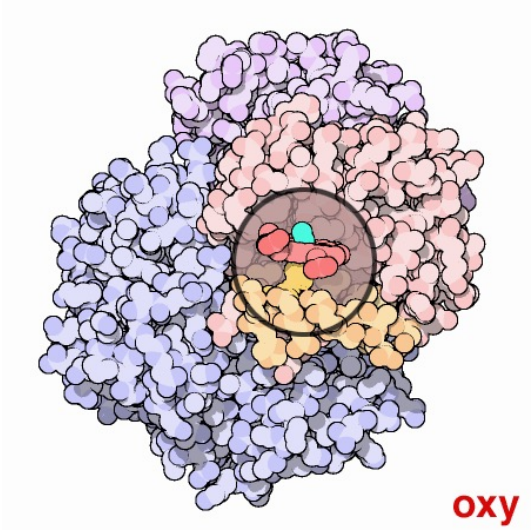
Sickle Cell Disease

New Drugs and Therapies.

NEPSCC
New England Pediatric Sickle Cell Consortium

12th Annual Symposium

October 7th, 2021



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Faculty Disclosure

Company	Relationship	Content Area
Vertex / CRISPR Therapeutics	Data Safety Monitoring Board / Consultant	Hemoglobinopathies
Novartis	Clinical Trial Funding / Consultant	Sickle cell
AstraZeneca	Clinical Trial Funding / Consultant	Sickle cell
Sancilio/Micelle Biopharma	Clinical Trial Funding / Consultant	Sickle cell
Ironwood / Cyclerion	Clinical Trial Funding / Consultant	Sickle cell
Pfizer	Clinical Trial Funding / Consultant	Sickle cell
FORMA Therapeutics	Consultant	Sickle cell
Global Blood Therapeutics	Consultant	Sickle Cell

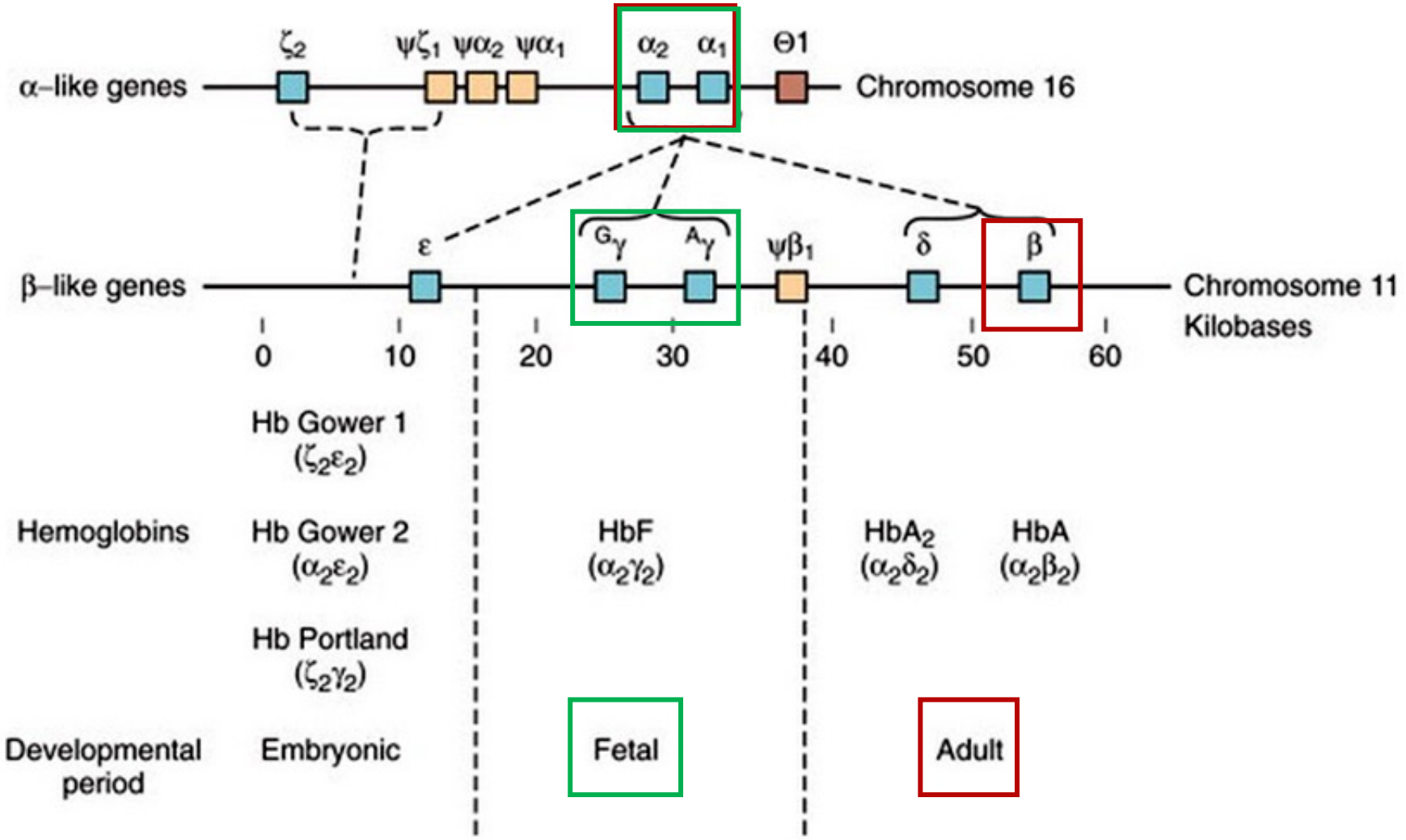
Faculty of this CE activity may include discussions of products or devices that are not currently labeled for use by the FDA. The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off label or investigational uses (any uses not approved by the FDA) of products or devices.

- **Brief Overview of Sickle Cell Pathophysiology**
- **Pathophysiologically-based Disease Modifying Therapies**

Hemoglobin

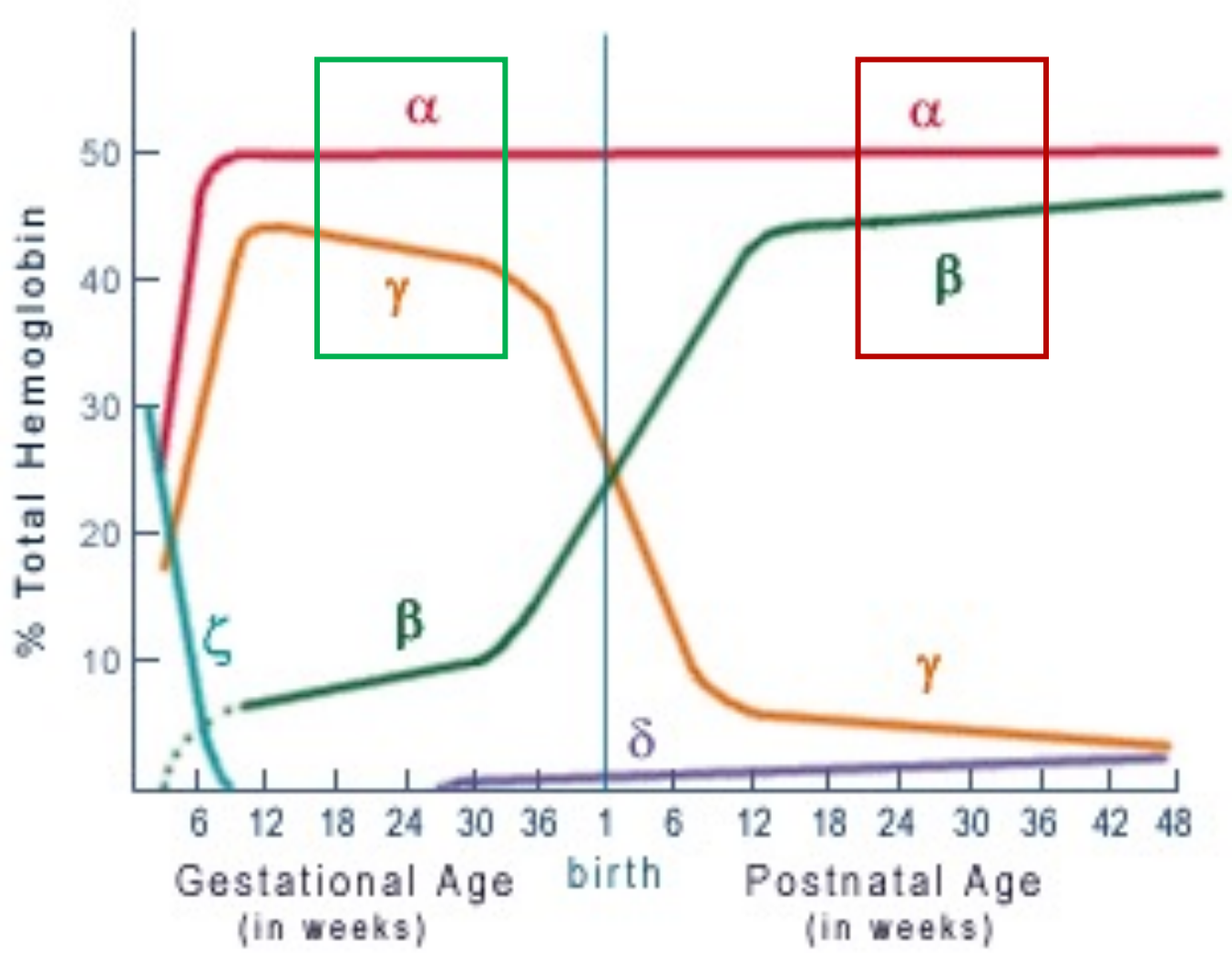
- Four globular proteins (globins)
  - 2 α-like globins
  - 2 β-like globins
- Four heme groups
  - One per globin chain
  - Reversibly bind O_2 (CO_2, NO)
- Hb synthesis must be balanced and coordinated
- All components are labile and toxic
  - globins, heme, iron

Globin Genes



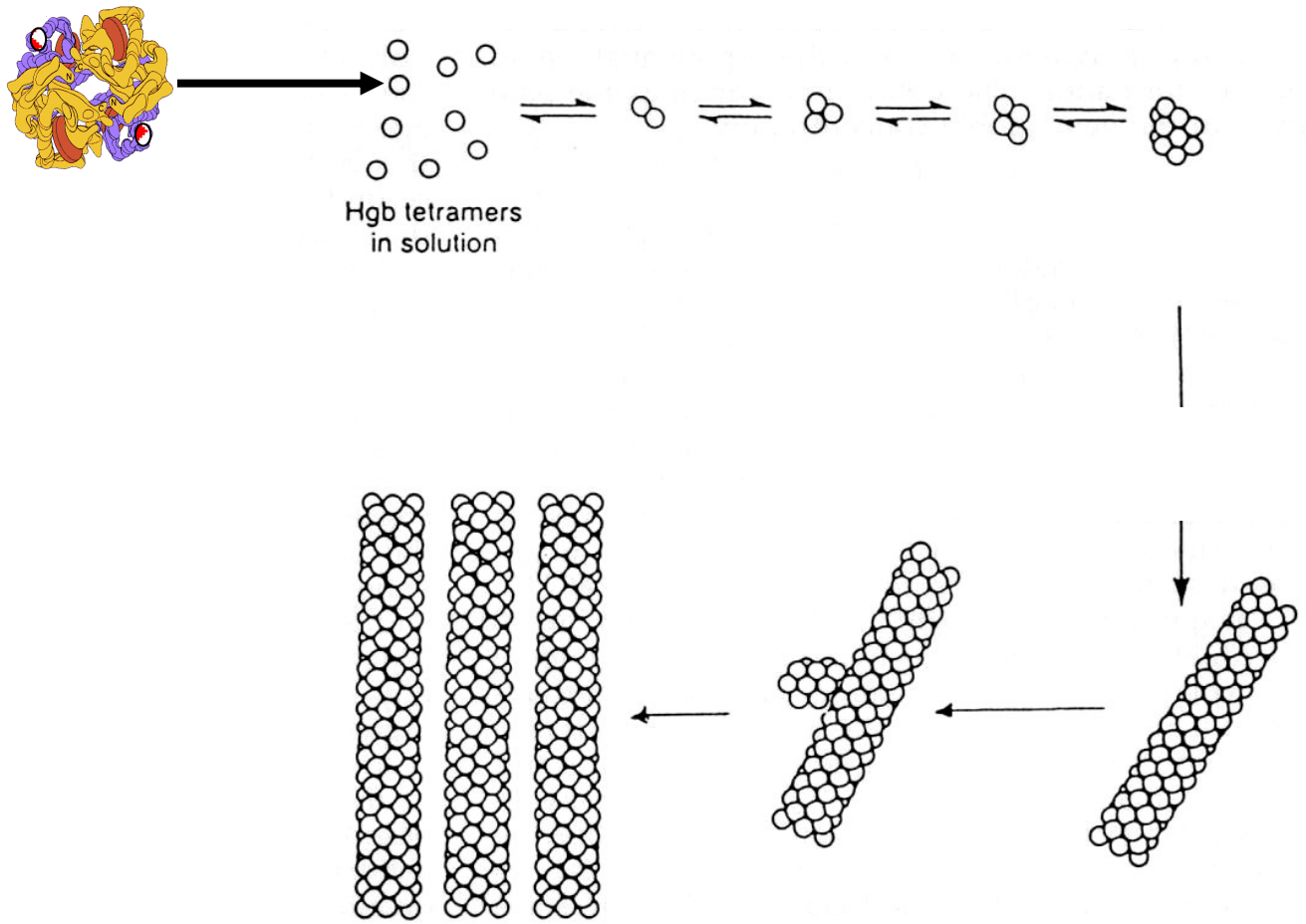
Nathan and Oski's Hematology of Infancy and Childhood, 7th Ed.

Globin Protein Synthesis



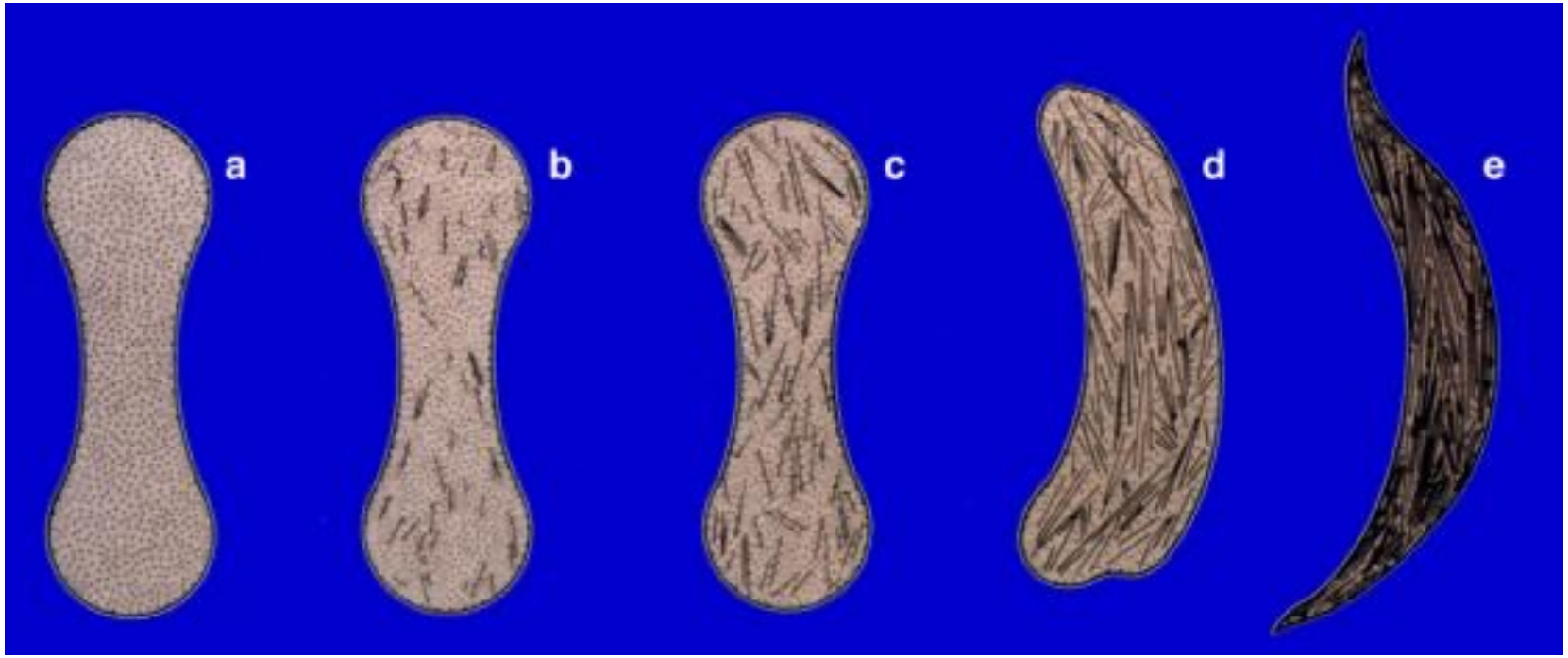
Sickle Cell - Molecular Pathophysiology

- HbS is the result of a single amino acid substitution (E6V) in β globin.
- Deoxygenation results in 'relaxation' of the β^S subunits and exposure of the hydrophobic valine.
- Valines form non-covalent bonds between β^S proteins
- Formation of 14-stranded helical polymers.



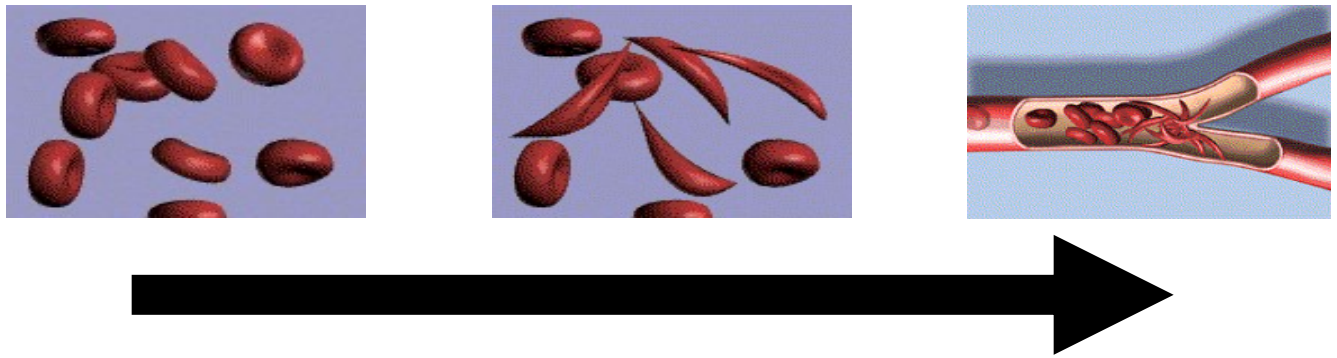
Delay time

- Delay time: period during which hemoglobin is deoxygenated, but not yet polymerized
- If passage through the capillaries exceeds the delay time, hemoglobin will aggregate, initiate polymerization, and sickling.



Sickle Cell - Cellular Pathophysiology

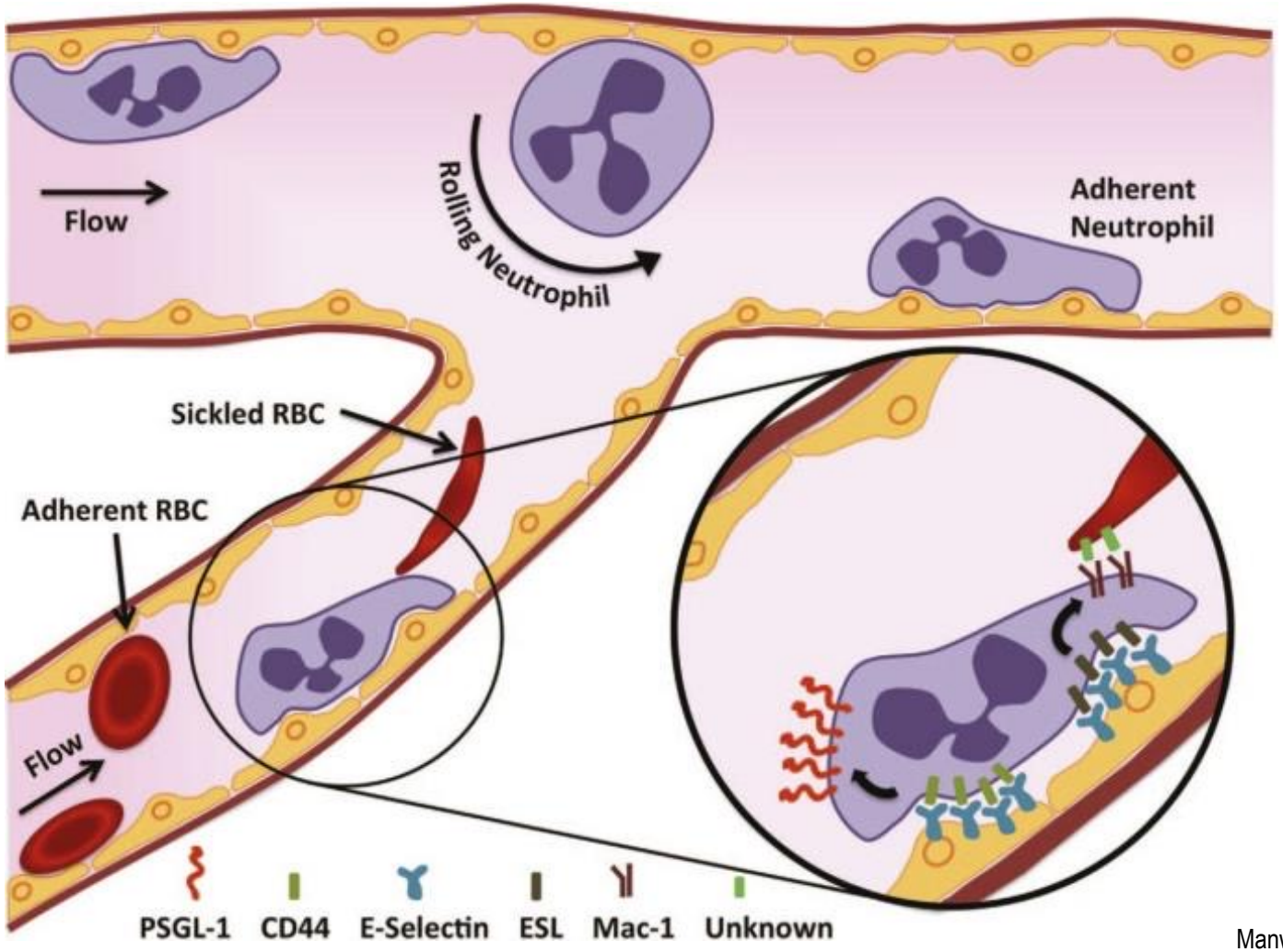
- Polymerization leads to:
    - Distortion of cell shape
    - Damage to RBC membrane
    - Abnormal permeability
    - Irreversible sickling
- Premature hemolysis = Anemia
- Impairment of RBC flow = Ischemia / Infarction



Cellular Pathophysiology - Beyond the Red Cell

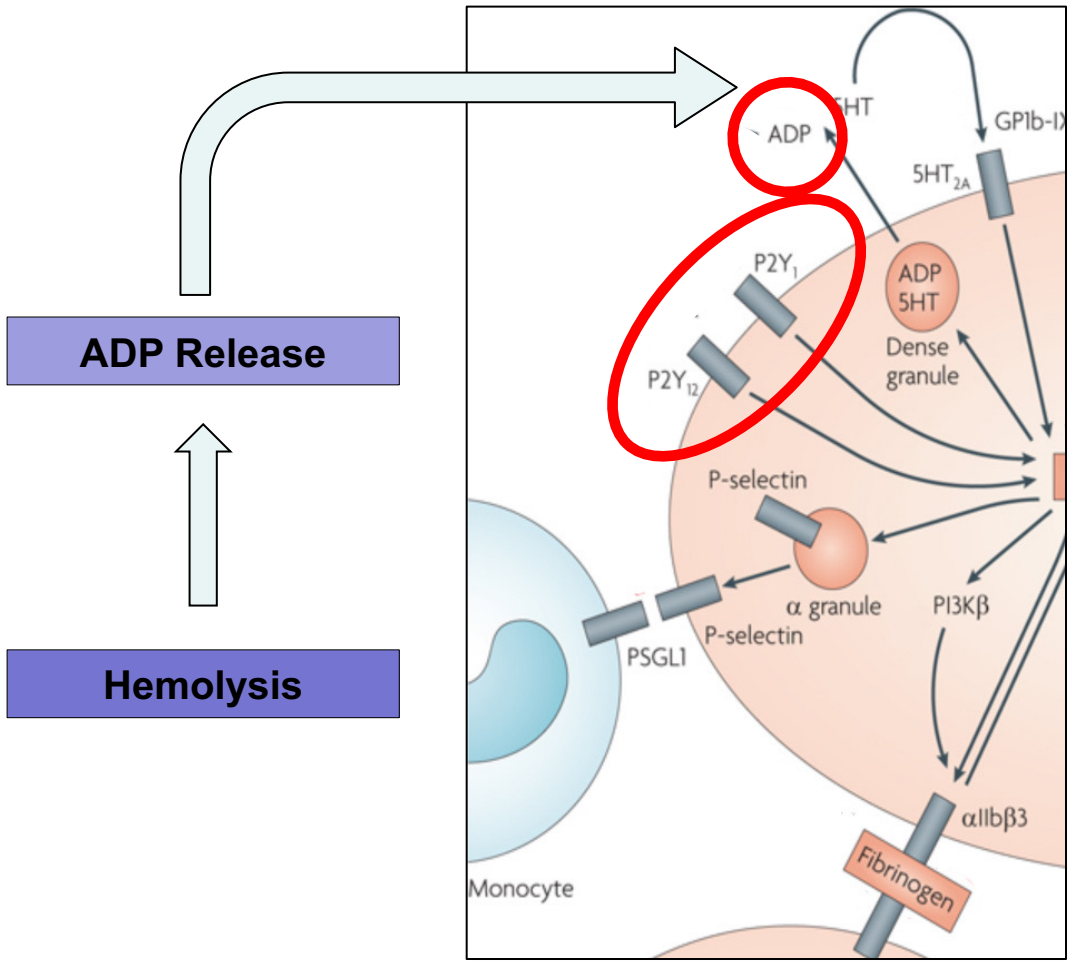
- Vascular endothelial dysfunction
- Sickle RBC binds endothelium more readily.
- Dysregulation of vascular tone (NO mediated)
  - ↑ red blood cell transit time
  - ↑ oxygen extraction
  - ↑ sickling and vaso-occlusion.
- Role of
  - WBC
  - Reticulocytes
  - Platelets
  - Coagulation cascade (Thrombin)

Beyond the Red Cell - Leukocytes



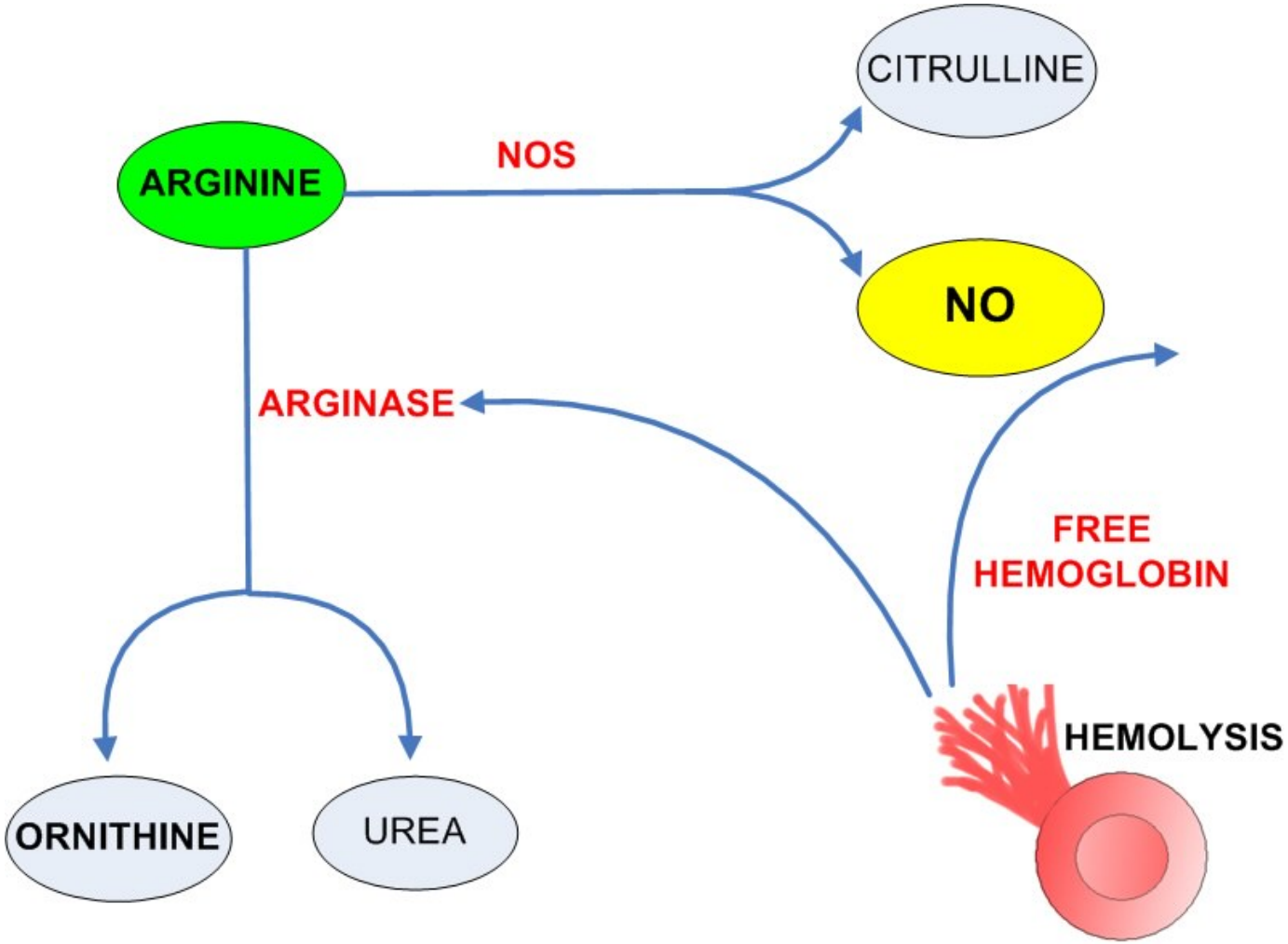
Manwani D and Frenette PS Blood. 2013:122(24):3892-3898

Beyond the Red Cell – Platelets



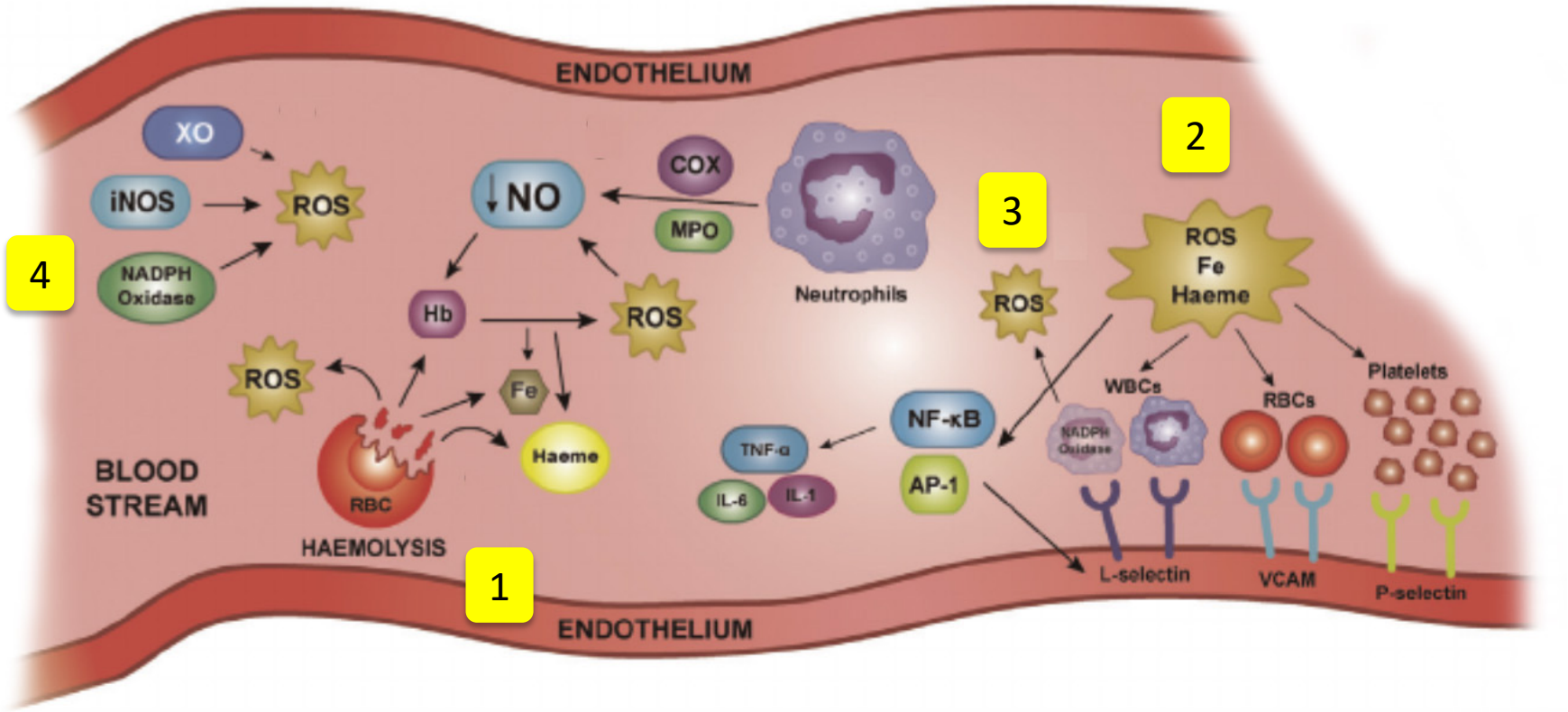
Michelson AD. Nat Rev Drug Discov. 2010 Feb;9(2):154-69.

Beyond the Red Cell – Nitric Oxide Consumption

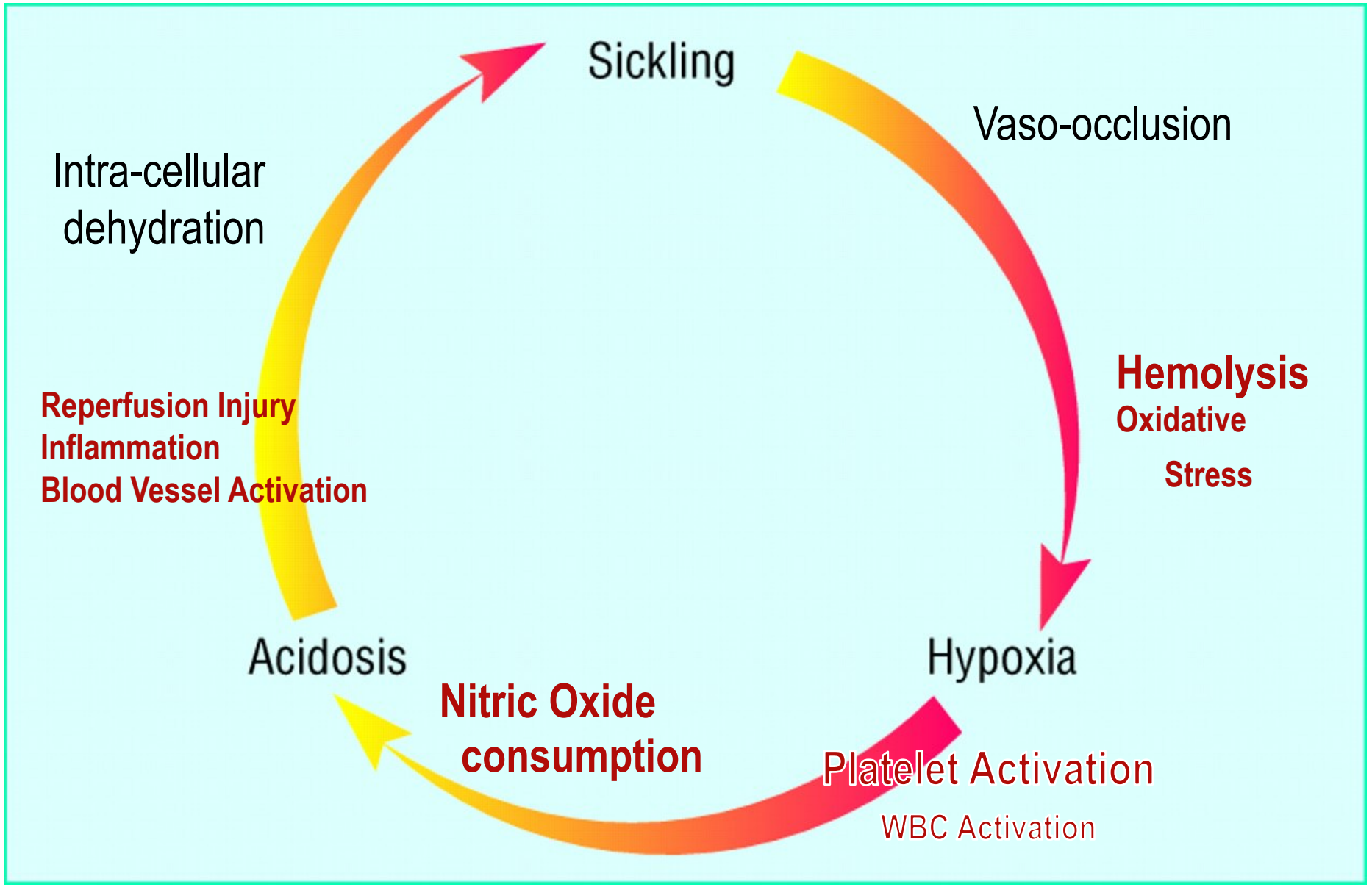


- ↓ NO bioavailability
- Endothelial cell dysfunction

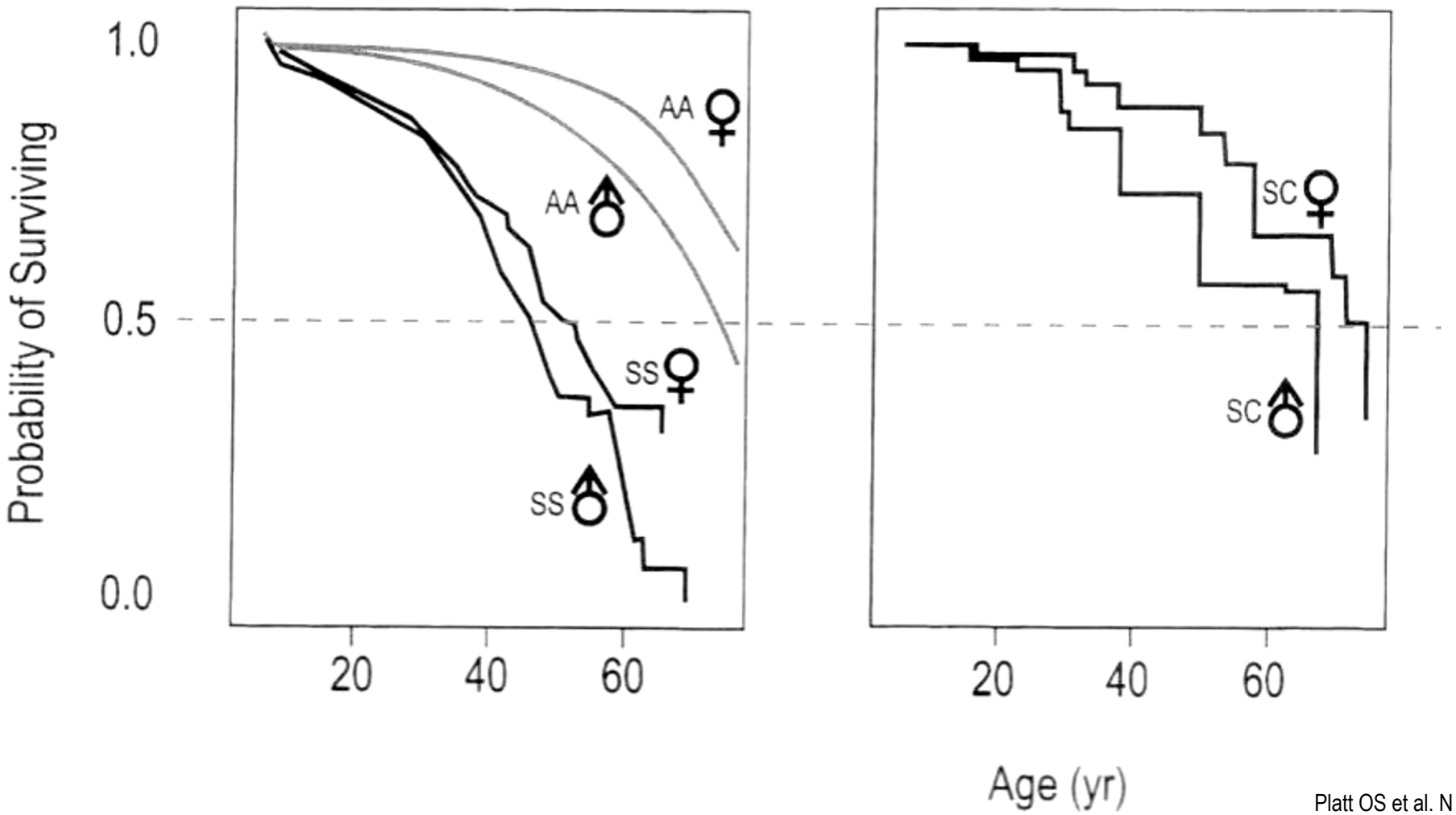
Beyond the Red Cell – Oxidative Stress



1. Hemolysis → free Hb autooxidation → ↑ plasma **ROS**, Heme, Iron
2. ROS/Heme/Fe →
   - damage hematopoietic/endothelial cell membranes
   - activate NF-κB → ↑ pro-inflammatory cytokines (IL-1, IL-6, TNFα)
   - activate AP-1 → ↑ endothelial adhesion
3. Activated leukocytes produce ↑**ROS** via their NADPH oxidase
4. Reperfusion ↑ plasma Xanthine oxidase/NADPH oxidase → ↑**ROS**

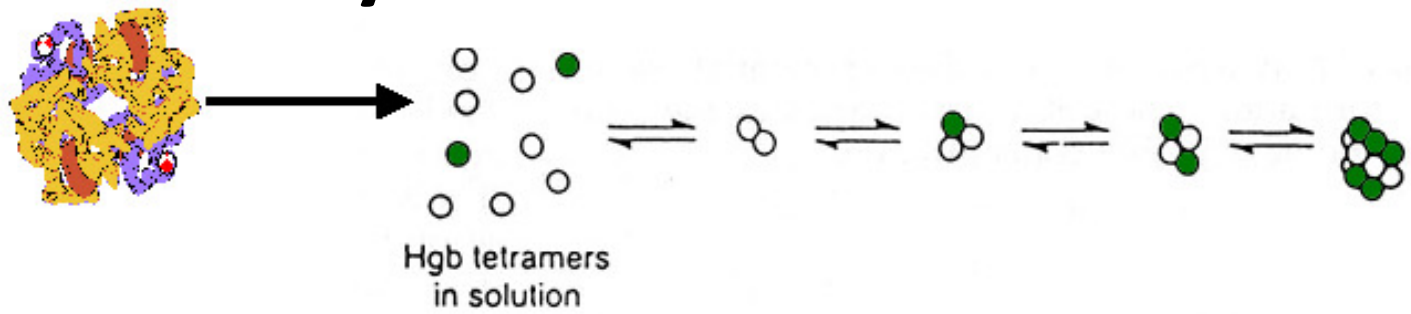

Sickling
Vaso-occlusion
Hemolysis
Oxidative
Stress
Hypoxia
Platelet Activation
WBC Activation
Nitric Oxide
consumption
Acidosis
Reperfusion Injury
Inflammation
Blood Vessel Activation
Intra-cellular
dehydration

Survival



Platt OS et al. N Engl J Med 1994; 330:1639-1644

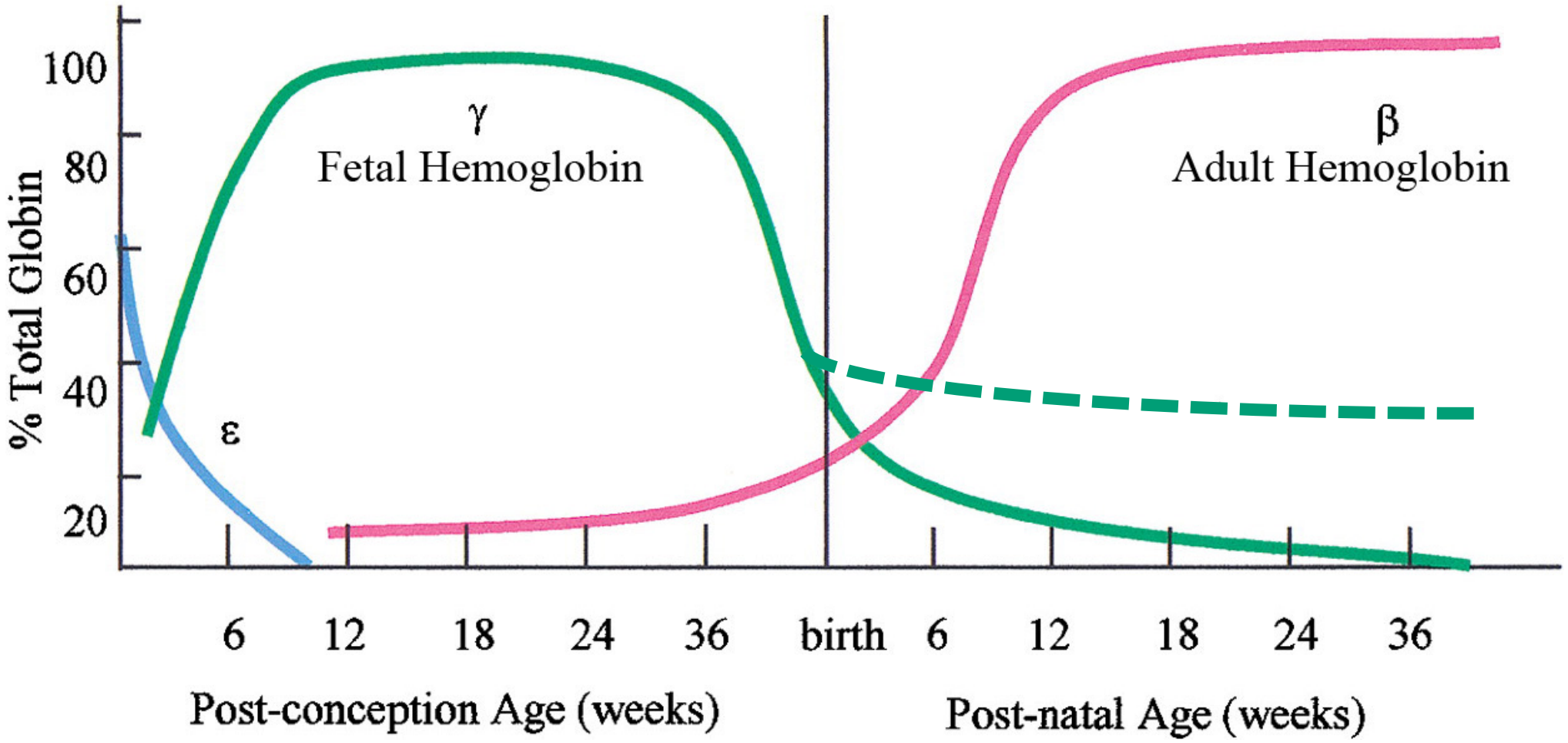
HbS Polymerization blocked by HbF



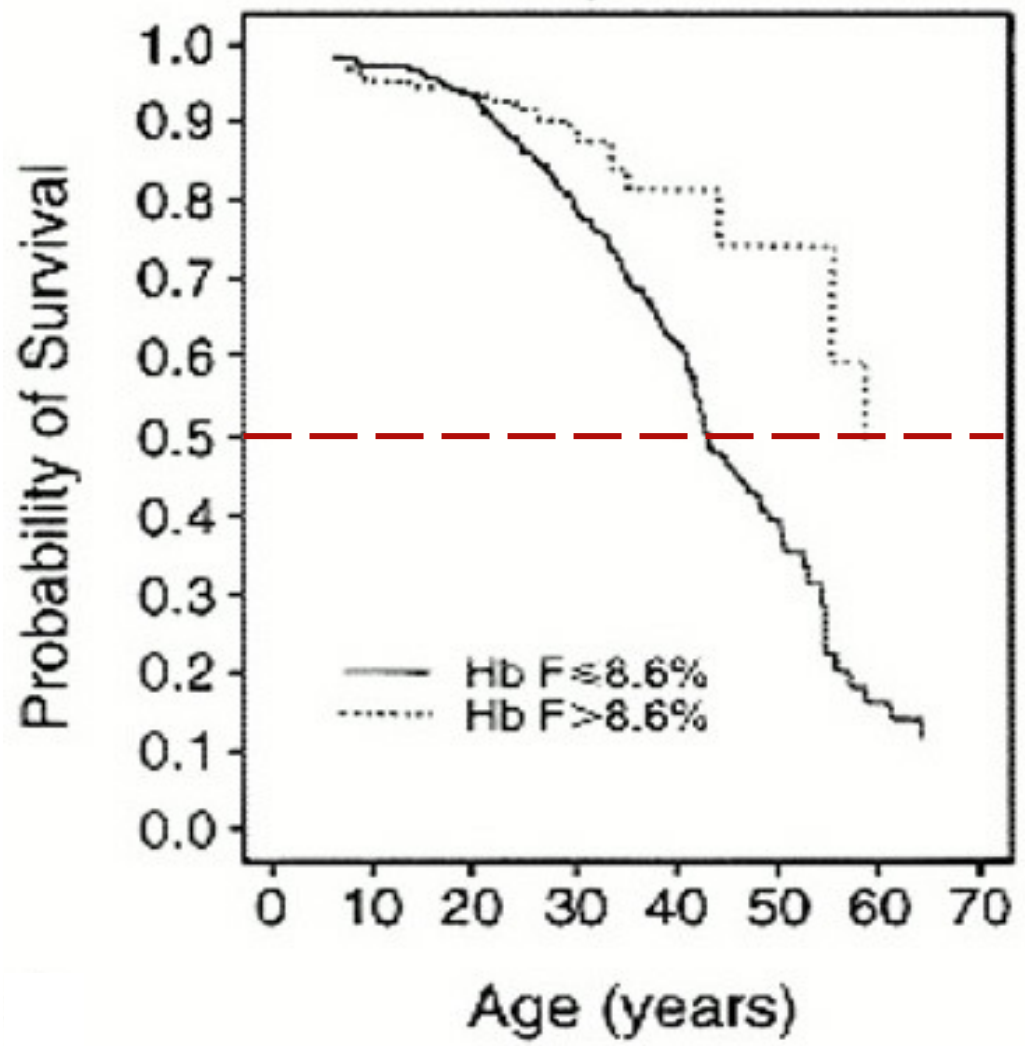
- Fetal life and early infancy are a “Honeymoon period” for sickle cell disease.

- Very few VOC complications observed due to Hemoglobin F

“Leaky” Beta globin “Switch” at Birth → HPFH



Survival improved with ↑ HbF %



Platt OS et al. N Engl J Med 1994; 330:1639-1644

- **Brief Overview of Sickle Cell Pathophysiology**

- **Pathophysiologically-based Disease Modifying Therapies**

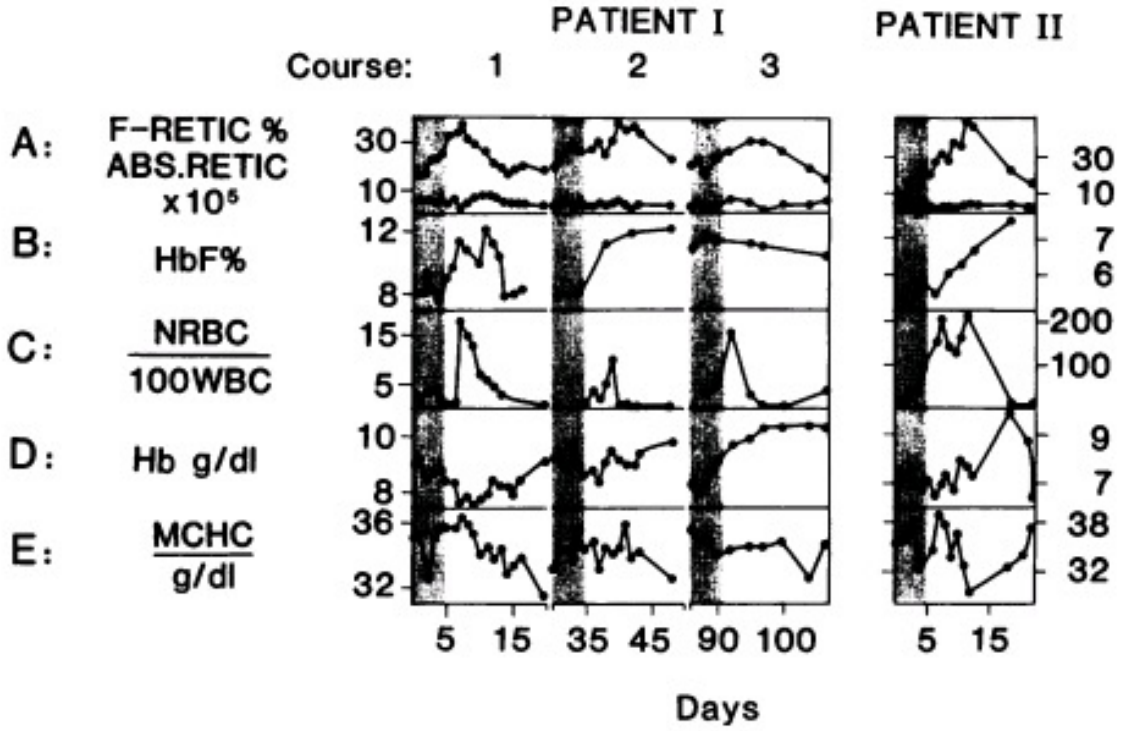
Hydroxyurea – A Fortuitous Observation

Hydroxyurea Enhances Fetal Hemoglobin Production in Sickle Cell Anemia

Orah S. Platt, Stuart H. Orkin, George Dover, G. Peter Beardsley, Barbara Miller, and David G. Nathan
Division of Hematology and Oncology, Children's Hospital, Division of Pediatric Oncology, Dana Farber Cancer Institute, Department of Pediatrics of the Harvard Medical School, Boston, Massachusetts 02115, and Department of Pediatrics, Johns Hopkins University and Hospital, Baltimore, Maryland 21205

Two patients
Four, 5-day courses
(50mg/kg/d).

Pt I HbF% 7.9 → 12.3%
Pt II HbF% 5.4 → 7.4%



Platt OS et al. J Clin Invest. 1984;74(2):652–656

Hydroxyurea – Adult Clinical Trials

MultiCenter Study of Hydroxyurea (MSH) (1992-1995)

- ↑ Hemoglobin F; ↓ Hemolysis & Anemia; ↓ white blood cells
- ↓ pain crises by 40%; ↓ acute chest syndrome by 50%; ↓ transfusions by 50%

Charache S et al. N Engl J Med 1995;332:1317-1322.

MSH Follow-Up (1996-2001)

- 40% reduction in mortality after 9 years of follow-up

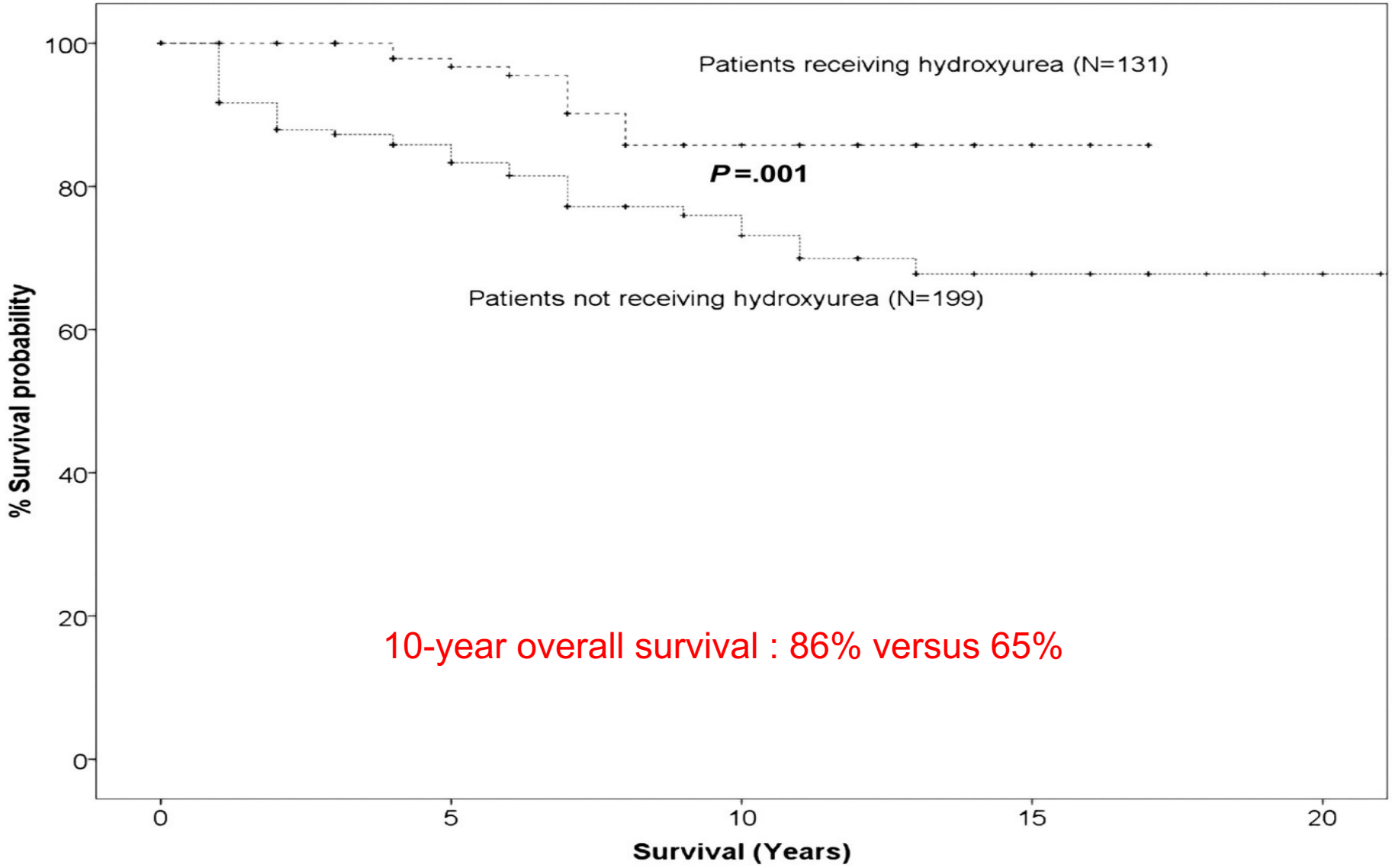
Steinberg MH et al JAMA. 2003;289(13):1645-1651

Laikon Study of Hydroxyurea in Sickle Cell (LaSHS)(1991-2008)

- after 17 years of follow-up
- ↓ pain crises; ↓ admissions; ↓ acute chest syndrome; ↓ transfusions

Voskaridou E et al. Blood 2010;115:2354-2363

LaSHS



10-year overall survival : 86% versus 65%

Voskaridou E et al. Blood 2010;115:2354-2363

Hydroxyurea – Pediatric Clinical Trials

HUG-KIDS (1994-1996)

- Children 5-15 y.o. with severe disease.
- Similar laboratory and clinical results as MSH

Kinney TR et al. Blood 1999 94:1550-1554

HU-SOFT (1996-2001)

- Age >2 y.o. Good Laboratory & Clinical effect.
- Normal growth/development.

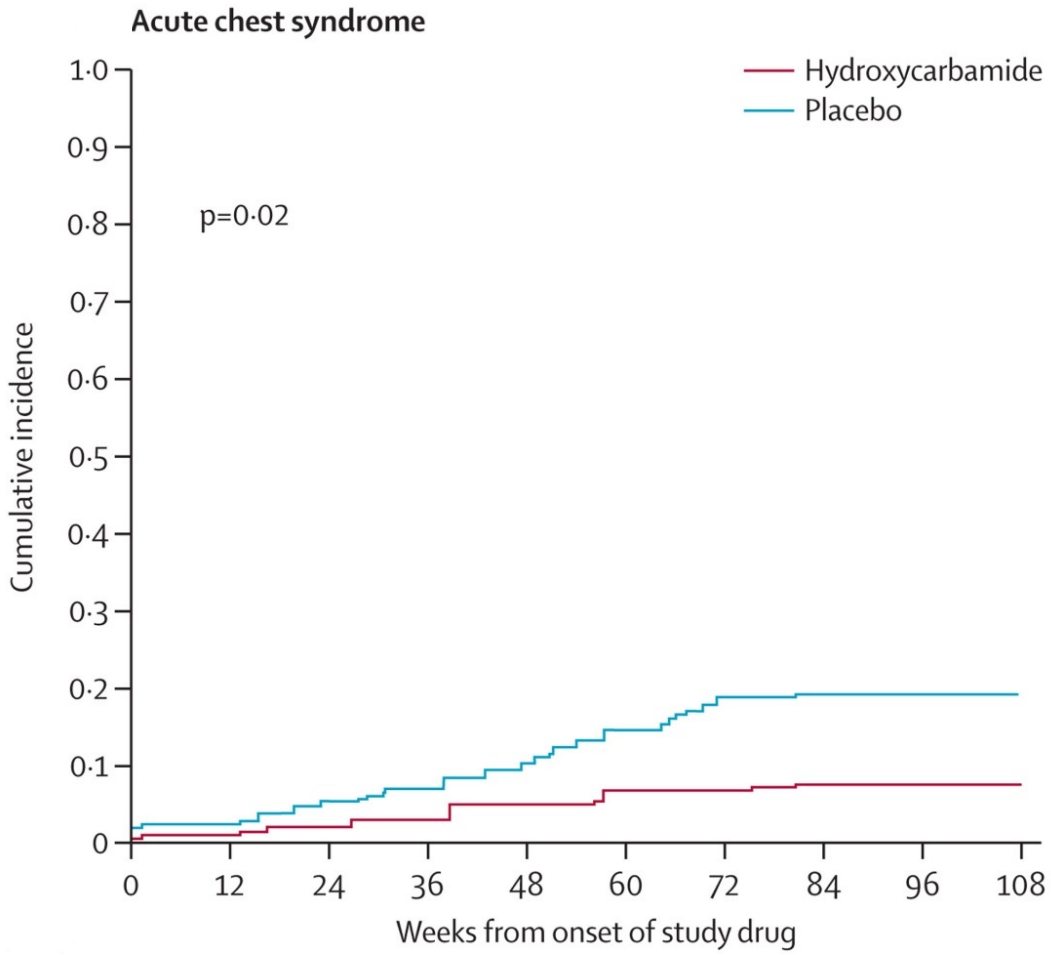
Hankins JS et al. Blood. 2005 Oct 1;106(7):2269-75.

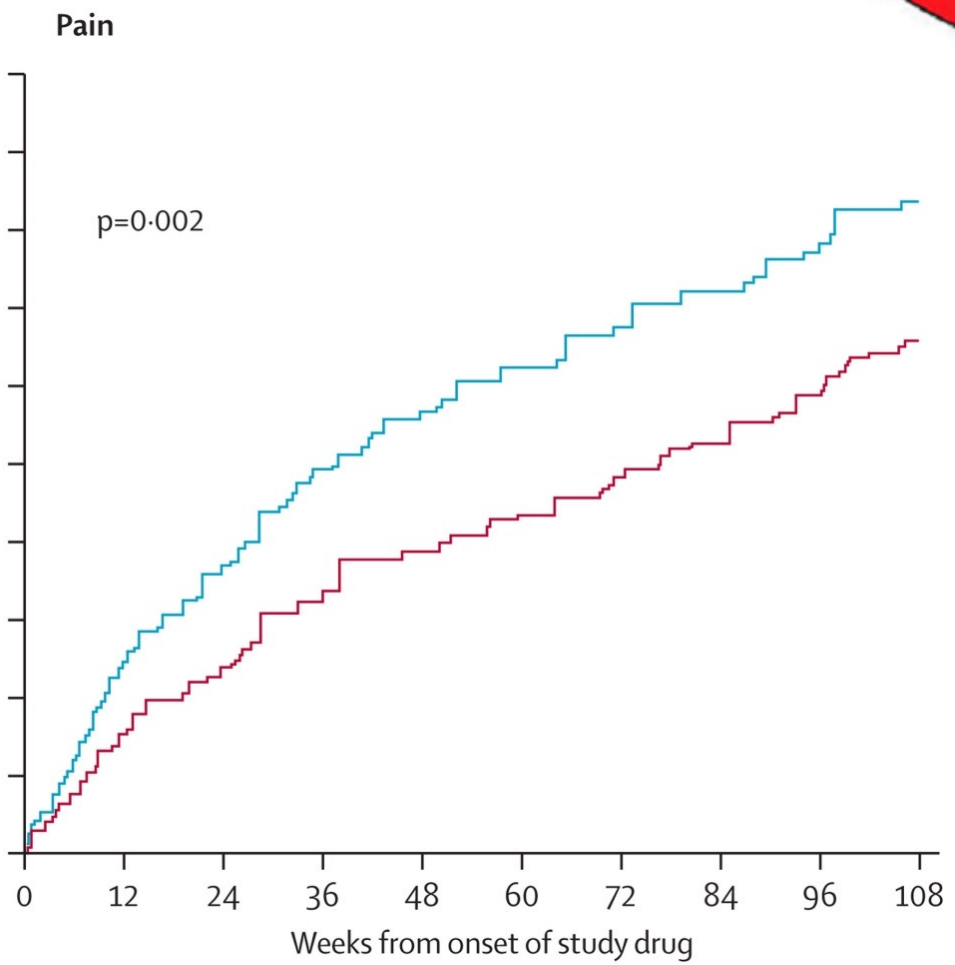
Baby HUG (2003-2007)

- Age 9–18months.
- Dose limited to 20 mg/kg/day for 2 years.

Wang WC et al. Lancet. 2011 377(9778):1663-72.

Baby HUG





Wang WC et al., Lancet 2011 377:1663 - 1672

Fetal Hemoglobin Induction

FDA granted Hydroxyurea:

- New Drug Application accepted
- Indication: to reduce the frequency of painful crises and the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises.
  - 03/04/1998 Adults
  - 12/21/2017 Pediatric patients >2 years

Who should get Hydroxyurea? 2021

Indications:

a) Frequent pain crises?

b) Acute chest syndrome?

c) **?? age** HbSS, HbSβ^0 + **?? HbSC**.

Expert Panel Report, 2014

Management of Sickle Cell Disease
Summary of the 2014 Evidence-Based Report by Expert Panel Members

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

http://www.nhlbi.nih.gov/guidelines

Table 6. Evidence-Based Recommendations for Use of Hydroxyurea Therapy

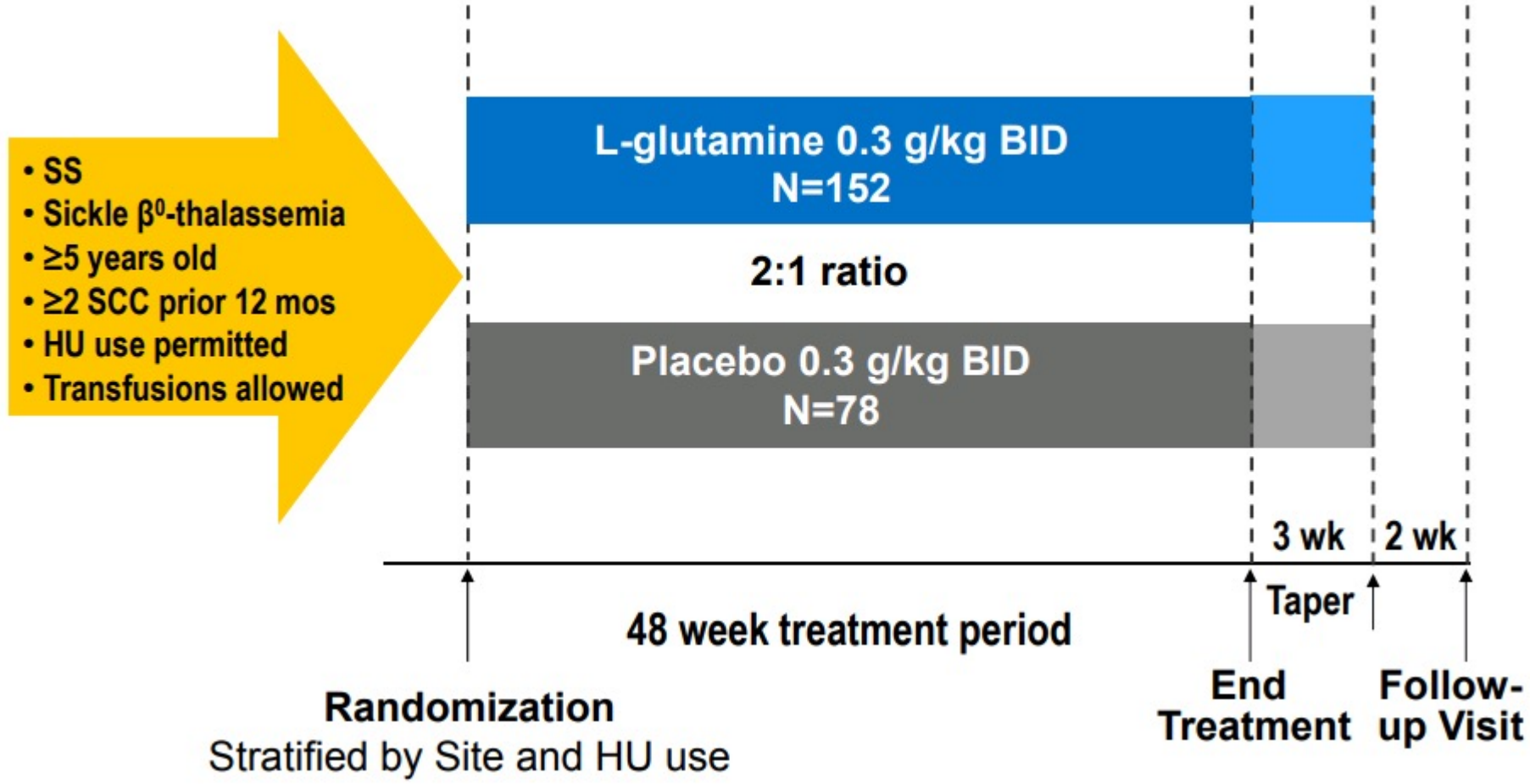
Evidence-Based Recommendations for Use of Hydroxyurea Therapy	Strength of Recommendation	Quality of Evidence
In infants 9 mo of age or older, in children, and in adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce complications (eg, pain, dactylitis, ACS, anemia) related to SCD	Strong[b] and moderate[c]	High[b] and moderate[c]

Anti-oxidant Therapy L-glutamine

- Oxidative stress damage is believed to be involved in the pathophysiology of SCD. Sickle RBCs are more susceptible to oxidative damage than normal RBCs.

- L-glutamine is an amino acid and precursor for the synthesis of essential metabolic redox cofactors.
- L-glutamine utilization in SCD exceeds the ability to produce it and its depletion played a role in oxidative stress.

L-glutamine Phase 3 Study Design (NCT01179217)



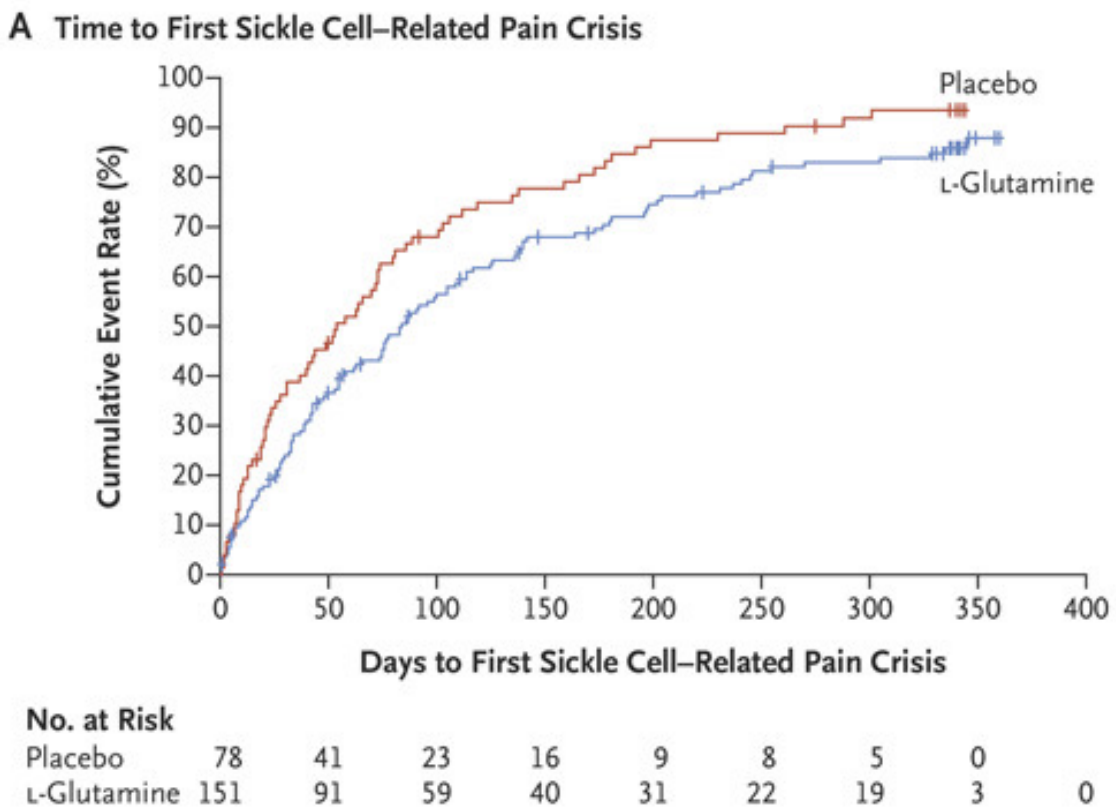
L-glutamine Summary (NCT01179217)

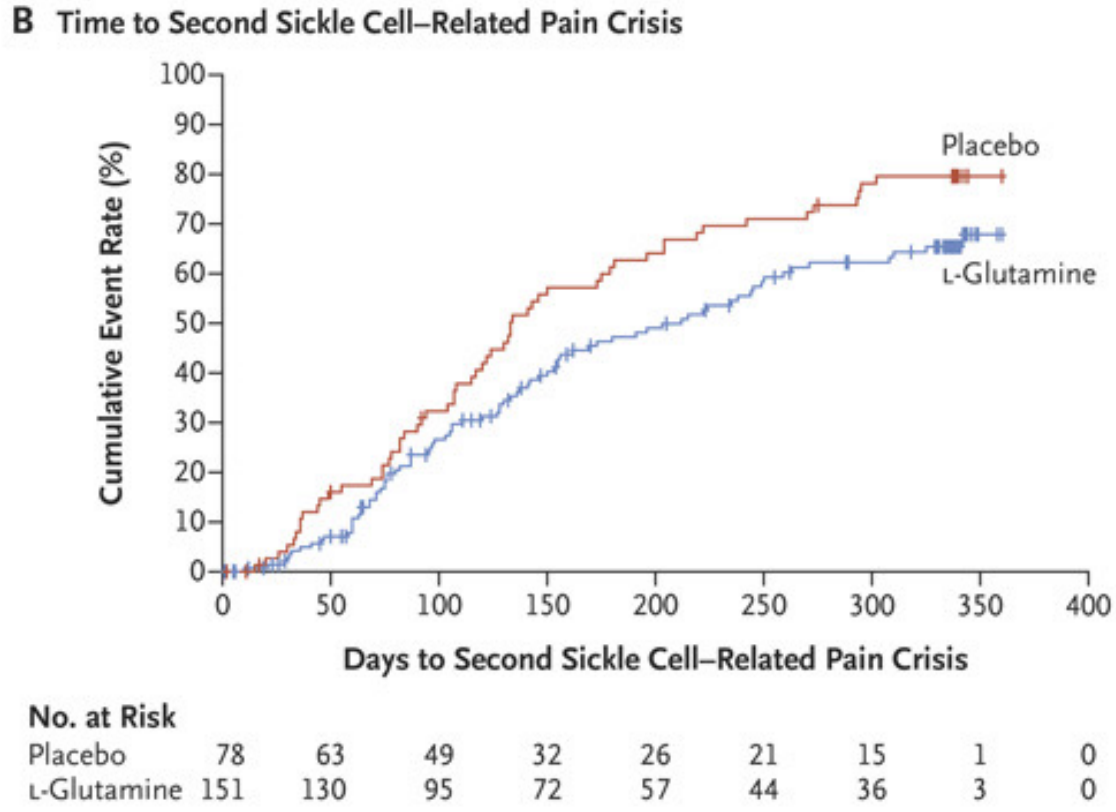
Descriptive Results	SCCs (median)	Days to First Crisis (median)	Acute Chest Syndrome (mean)	Hospitalizations (median)	Cumulative Days in Hospital (median)	Blood Transfusion Events (mean)
L-glutamine	3	84	0.1	2	6.5	1.42
Placebo	4	54	0.3	3	11	2.32
Difference from placebo	25%	56%	67%	33%	41%	39%
p-value for between group difference	0.0052[a]	0.0152[b]	0.0028[a]	0.0045[a]	0.022[c]	na

a. Cochran Mantel Haenszel
b. Log Rank Test
c. Wilcoxon Test

Emmaus FDA ODAC Meeting Presentation May 24, 2017

L-glutamine - Times to the 1st and 2nd Pain Crises





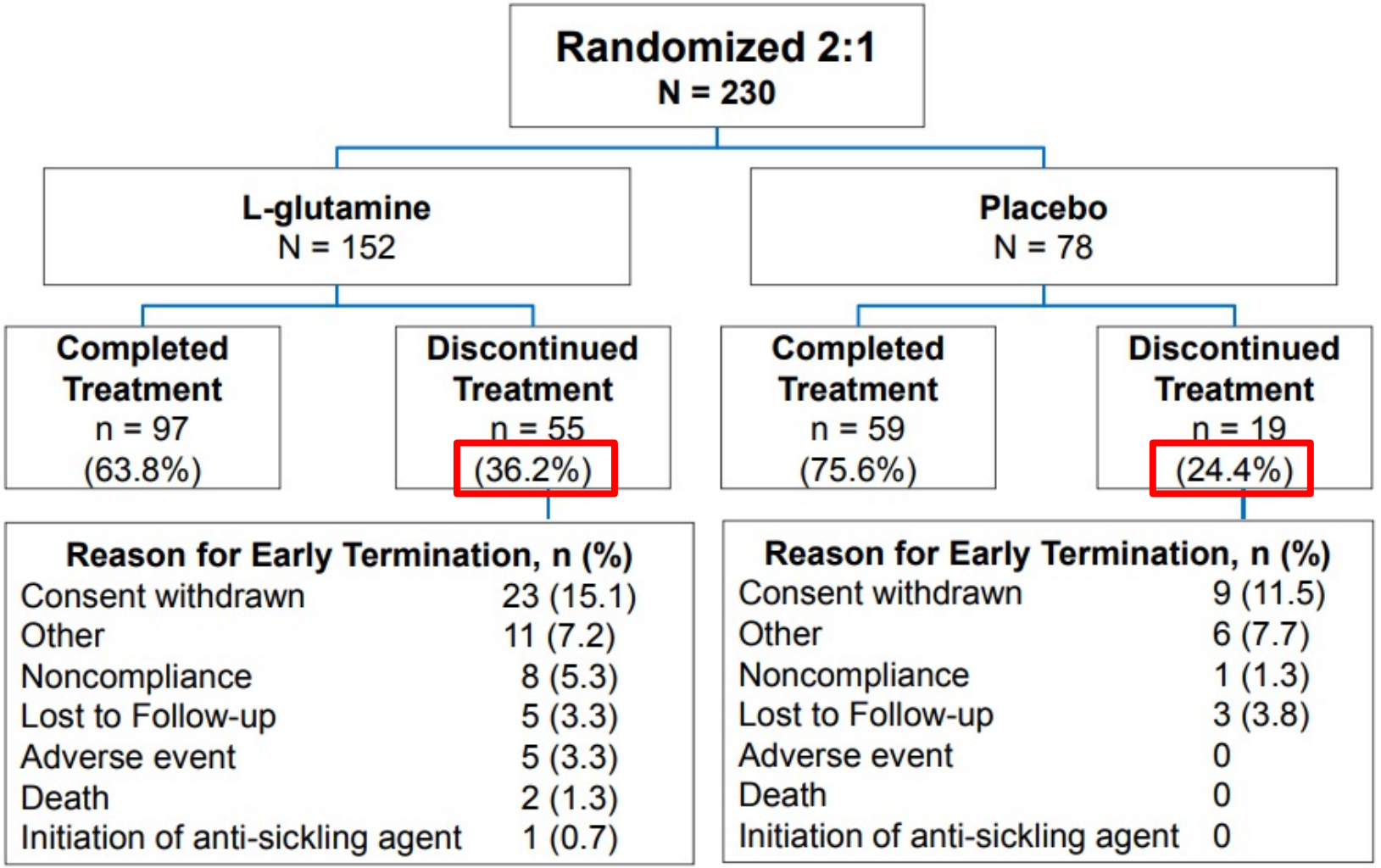
Median time to the first pain crisis was 84 days (95% CI, 62 to 109) in the L-glutamine group, as compared with 54 days (95% CI, 31 to 73) in the placebo group. (Hazard Ratio, 0.69; 95% CI, 0.52 to 0.93; P=0.02)

Niihara Y et al et al. NEJM. 2018 Jul 19;379(3):226-235.

Patient Disposition (NCT01179217)

- Sites: 31 in USA
- Enrollment: 230
- Randomization: 2 : 1

- Start Date: May 2010
- Completion: March 2014



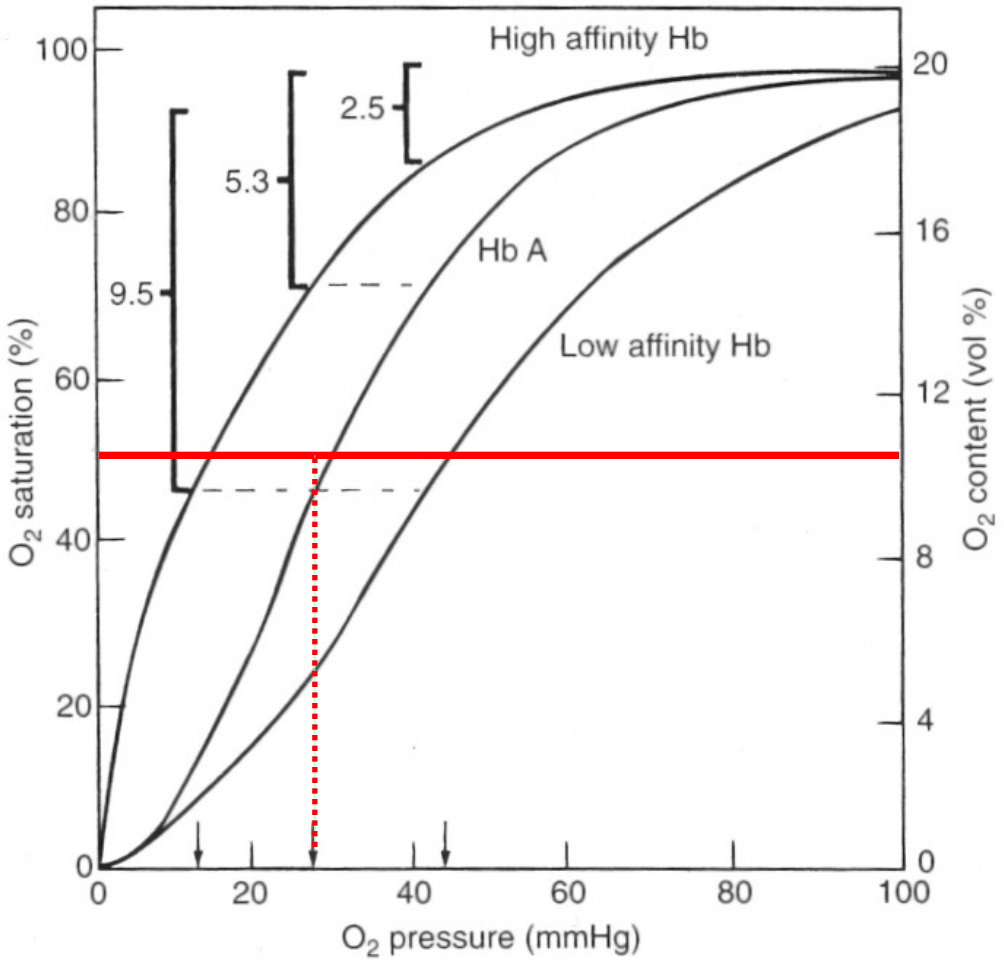
Emmaus FDA ODAC Meeting Presentation May 24, 2017

Anti-oxidant Therapy

FDA granted L-glutamine:

- Orphan Drug designation
- Rare Pediatric Disease designation.
- New Drug Application accepted (7/7/2017)
- Indication: to reduce the acute complications of sickle cell disease in adult and pediatric patients > 5 years of age.

Hemoglobins with altered oxygen affinity



P50

- P50 describes the affinity of a given Hb for oxygen.
- P50 is the PO_2 at which the Hb is 50% saturated with oxygen.
- As the P50 ↓,
  oxygen affinity ↑.

- Hb A 26.5 mmHg
- Hb F 20 mmHg
- ***Hb S 34 mmHg***

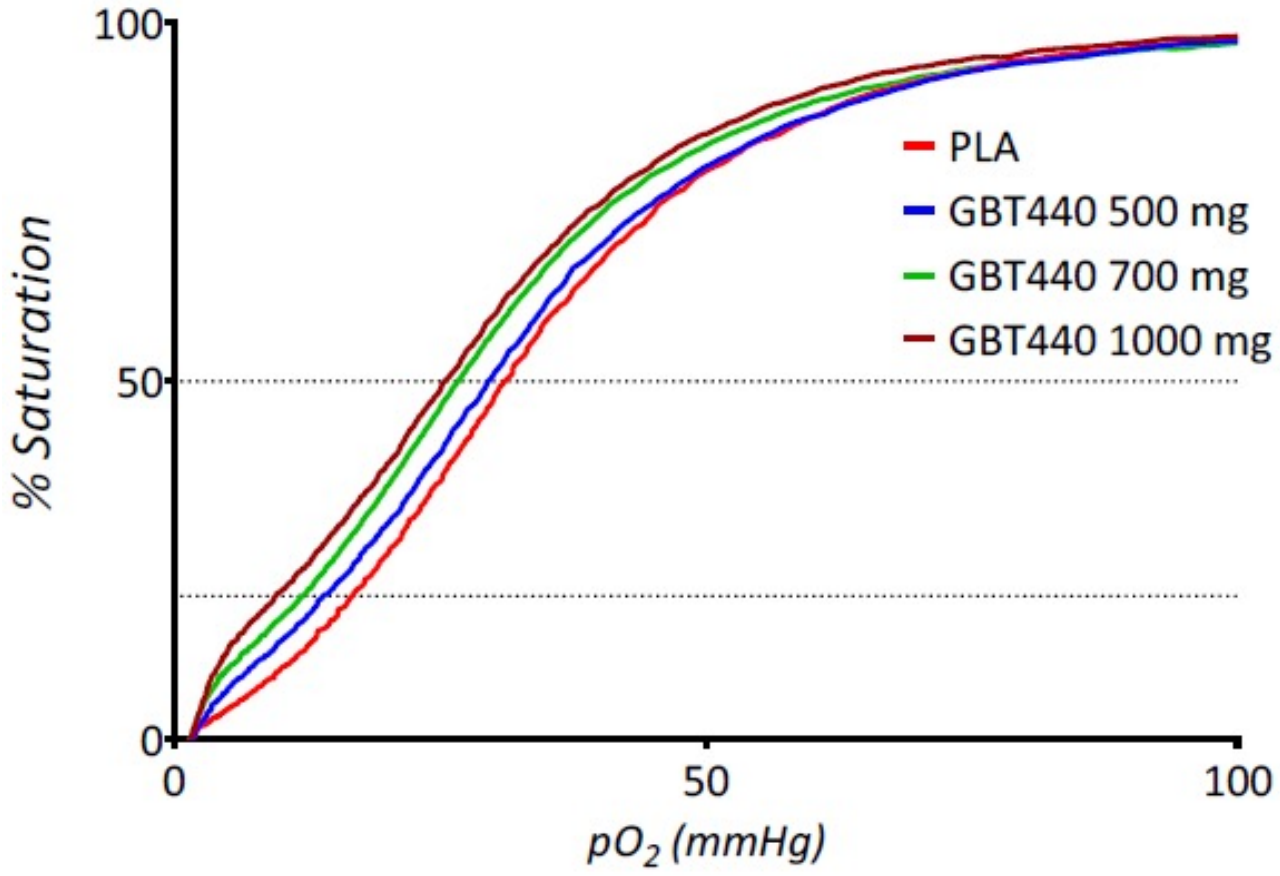
Manipulation of Oxygen Binding

Voxelotor

- A rationally designed small molecule.
- Stabilizes Hb in the oxygen bound formation.
- Dose-dependent increase in oxygen binding.
- Highly selective for alpha globin.
- Oral, once daily.

- Prevents RBC sickling and prolongs RBC half-life in a mouse model of sickle cell disease.

Manipulation of Oxygen Binding



Lehrer-Graiwer J et al. EHA 2016

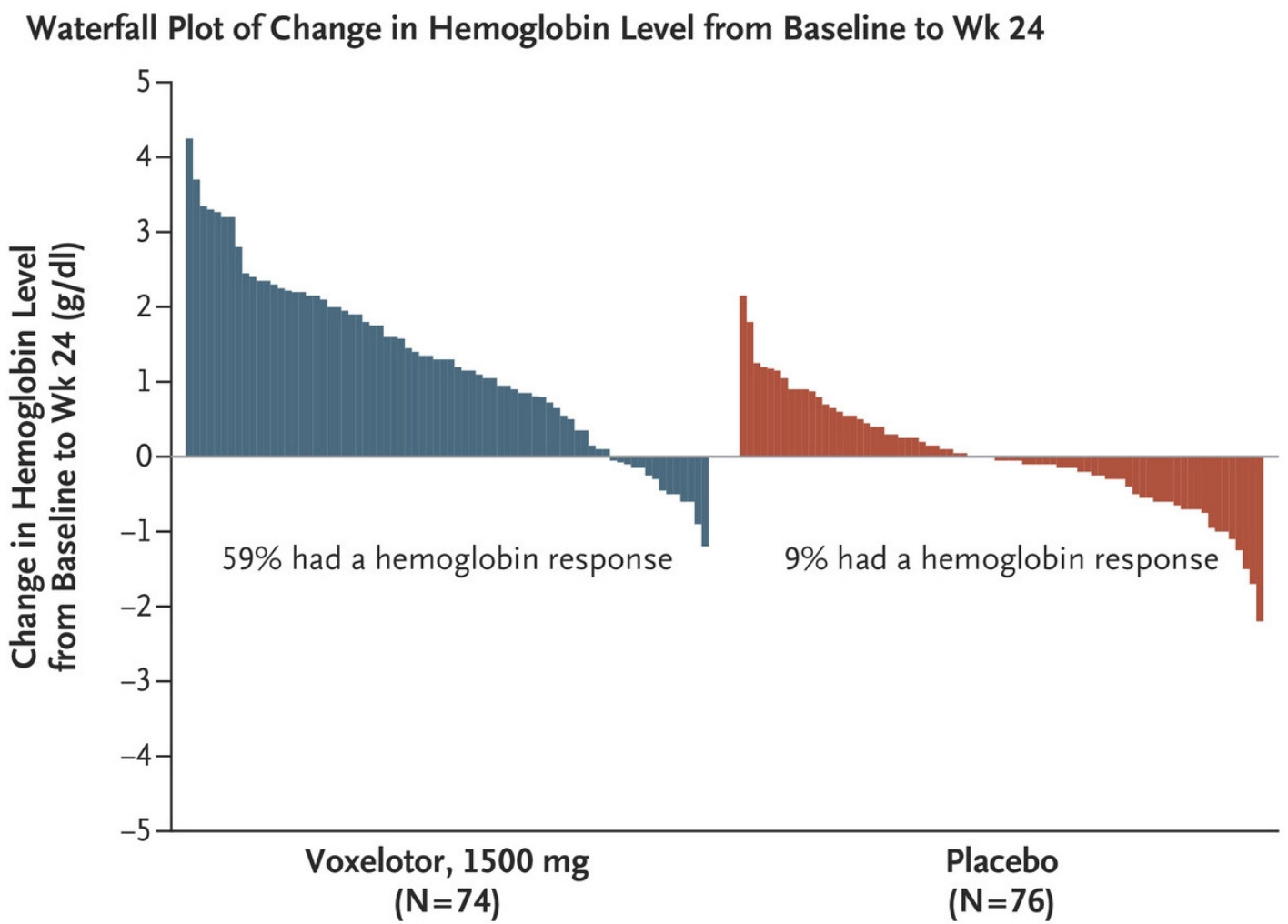
Voxelotor – Phase 2 Study Design (NCT03036813)

- Phase 2 Randomized, placebo-controlled, double blind, parallel group, multicenter study of Voxelotor Administered Orally to Patients With Sickle Cell Disease.

- Age: 12 to 65 years
- 62 sites
- HbSS, HbSC, HbSβ^0- and HbSβ^+-thalassemia.
- 274 subjects randomized.

- 1^o endpoint - % subjects Hb rise > 1.0g/dL

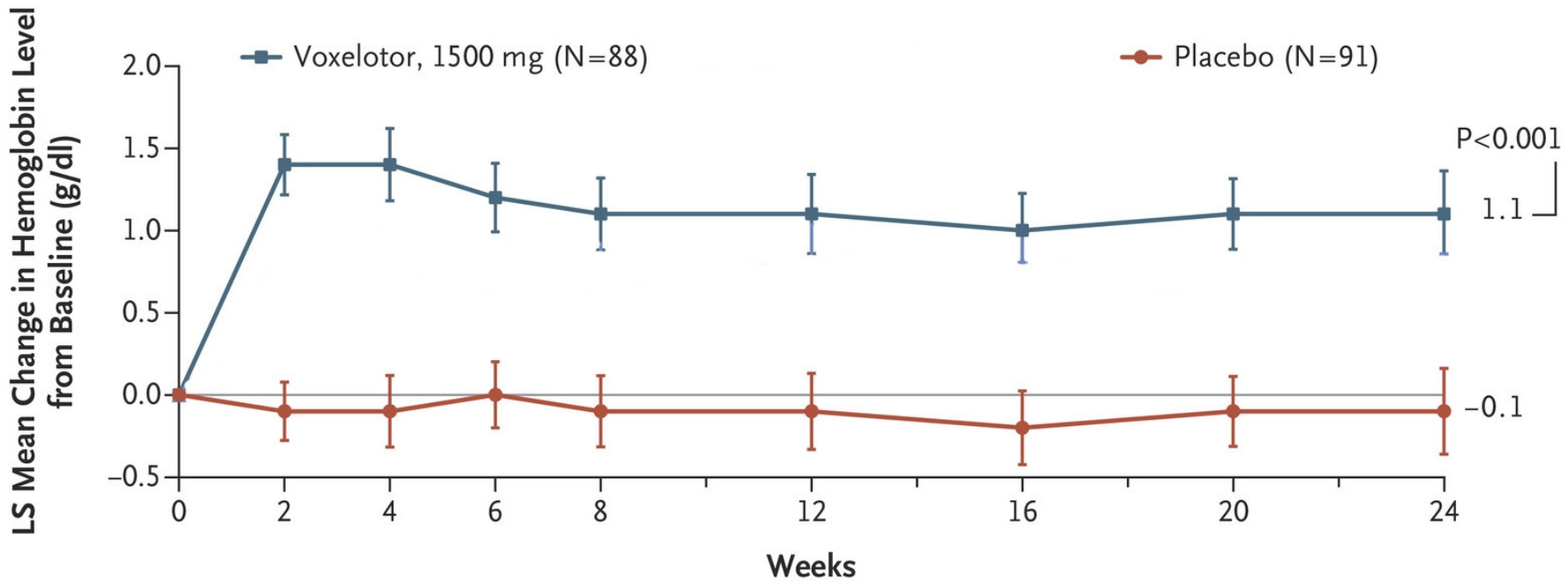
Voxelotor – Effect on Anemia



Adapted from Vichinsky E et al. NEJM 2019;381:509-519.

Voxelotor – Effect on Anemia

LS Mean Change in Hemoglobin Level from Baseline to Wk 24



No. at Risk

Voxelotor, 1500 mg	76	78	74	74	71	76	77	72
Voxelotor, 900 mg	82	78	69	74	76	77	73	78
Placebo	82	79	81	74	81	77	78	72

Adapted from Vichinsky E et al. NEJM 2019;381:509-519.

Voxelotor - Pain

Table 3. Annualized Incidence Rate of Vaso-Occlusive Crisis and the Most Common Adverse Events That Occurred or Worsened during the Treatment Period.

Variable	Voxelotor, 1500 mg (N = 88)	Placebo (N = 91)
Annualized incidence rate of vaso-occlusive crisis — no. of crises per person-yr (95% CI)*	2.77 (2.15 to 3.57)	3.19 (2.50 to 4.07)
Participants with ≥1 vaso-occlusive crisis — no. (%)	59 (67)	63 (69)
Total no. of vaso-occlusive crises	179	219

Vichinsky E et al. NEJM 2019;381:509-519.

Voxelotor - Adverse Events

Table 3. Most Common Adverse Events That Occurred or Worsened during the Treatment Period.

Variable	Voxelotor, 1500 mg (N=88)	Placebo (N=91)
Adverse events not related to sickle cell disease — no. (%)†		
Incidence of adverse events of any grade	83 (94)	81 (89)
Adverse events with ≥10% incidence		
Headache	23 (26)	20 (22)
Diarrhea	18 (20)	9 (10)
Nausea	15 (17)	9 (10)
Arthralgia	13 (15)	11 (12)
Upper respiratory tract infection	12 (14)	10 (11)
Abdominal pain	12 (14)	7 (8)
Fatigue	12 (14)	9 (10)
Rash‡	12 (14)	9 (10)
Pyrexia	11 (12)	6 (7)
Pain in extremity	10 (11)	16 (18)
Back pain	10 (11)	10 (11)
Vomiting	10 (11)	11 (12)
Pain	8 (9)	6 (7)
Noncardiac chest pain	7 (8)	8 (9)
Upper abdominal pain	6 (7)	6 (7)

Predominantly GI adverse events
Diarrhea usually resolves in days/weeks

Vichinsky E et al. NEJM 2019;381:509-519.

Manipulation of Oxygen Binding

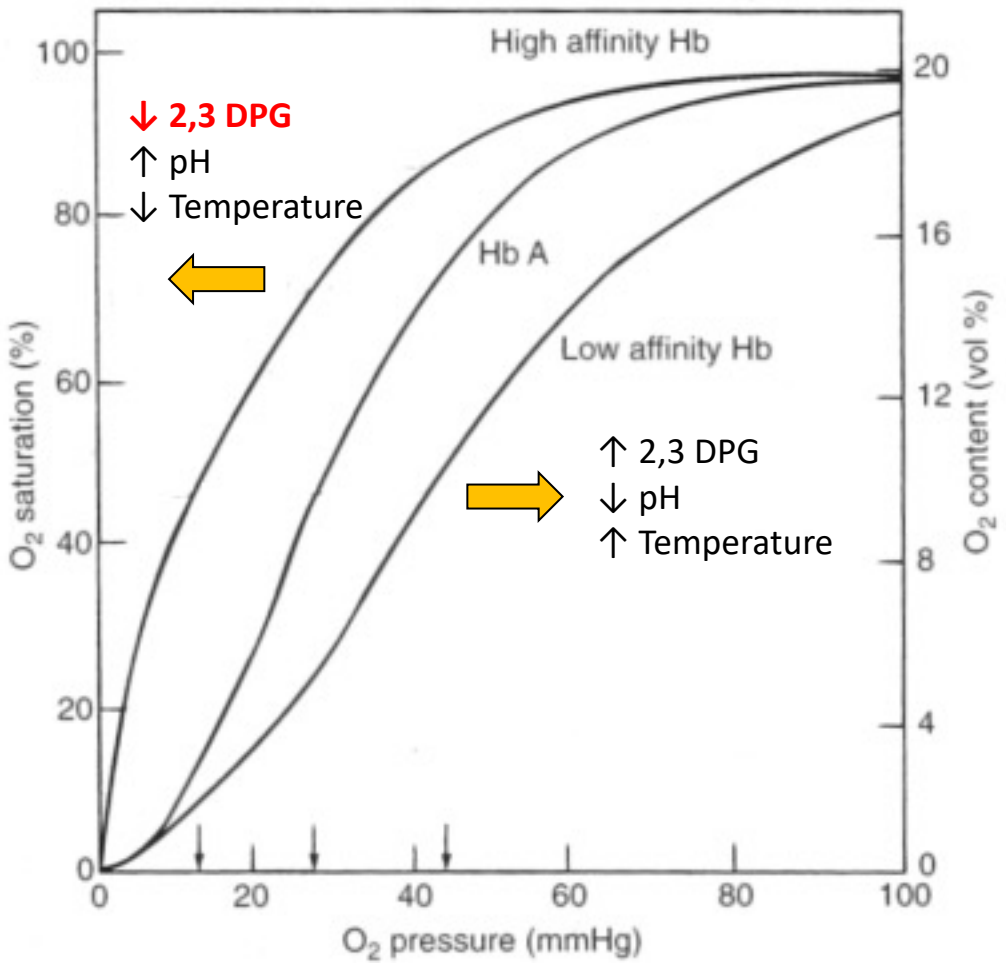
FDA granted Voxelotor:

- Breakthrough Therapy designation
- Fast Track designations
- Orphan Drug designation
- Rare Pediatric Disease designation.
- New Drug Application accepted (9/5/19)
- Indication: for the “treatment of sickle cell disease” in age > 12 y.o. Accelerated approval based on increase in hemoglobin (Hb). Contingent upon verification and description of clinical benefit in confirmatory trial(s)

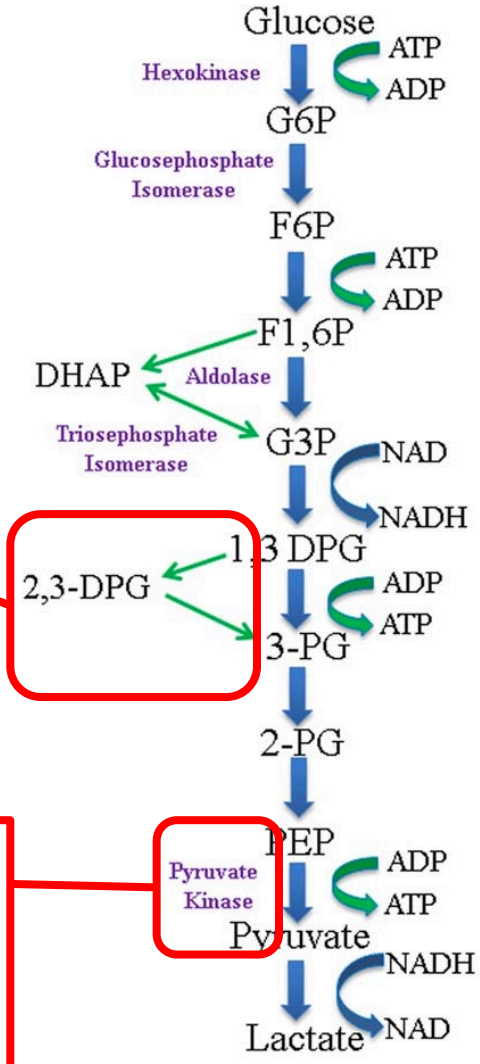
HOPEKids2
GBT Sickle Cell Disease Clinical Study

Coming Soon !

Oxygen Affinity and PK activation



Embden Meyerhoff glycolytic pathway

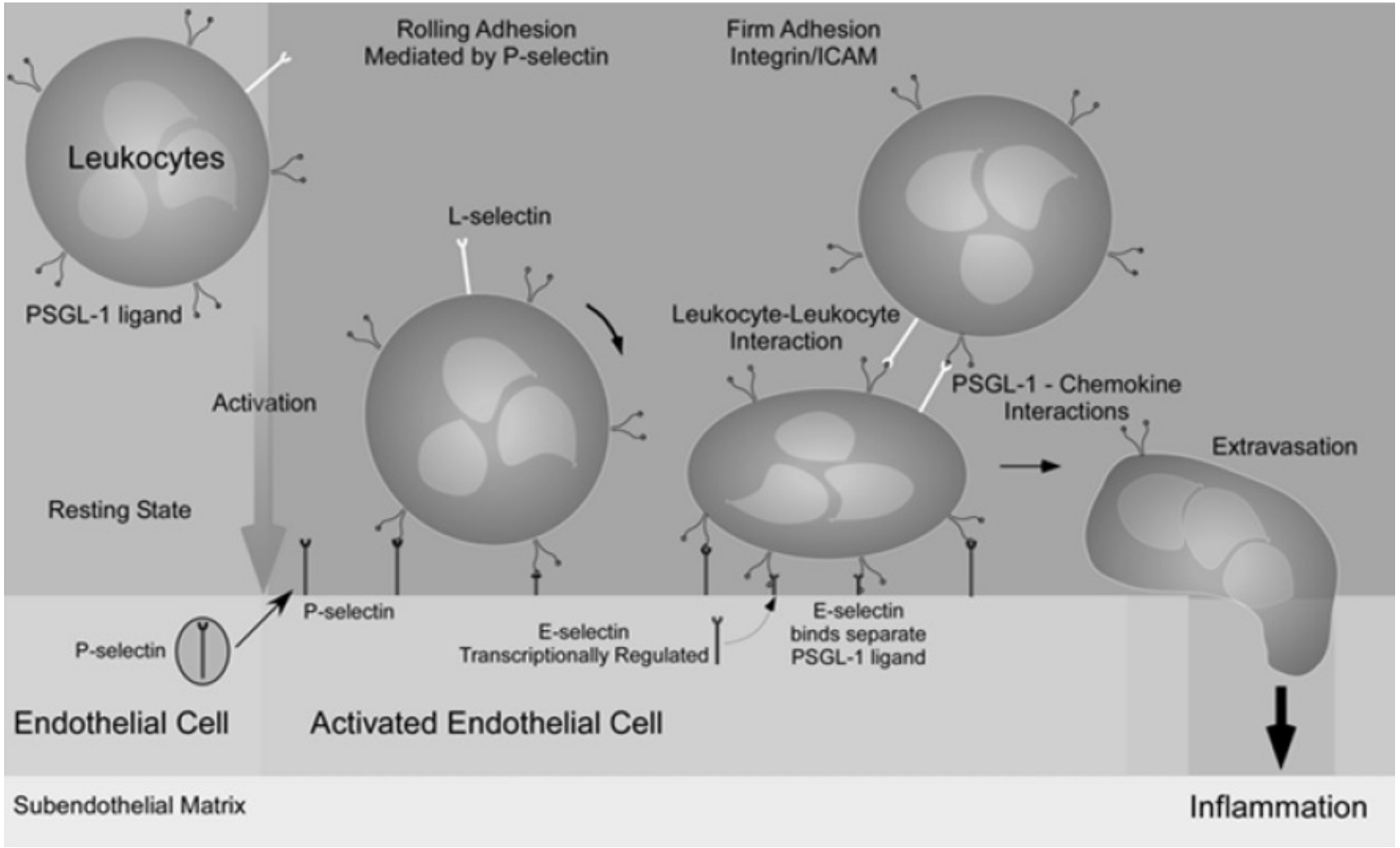


Rapoport Luebering shunt

Pyruvate Kinase activators

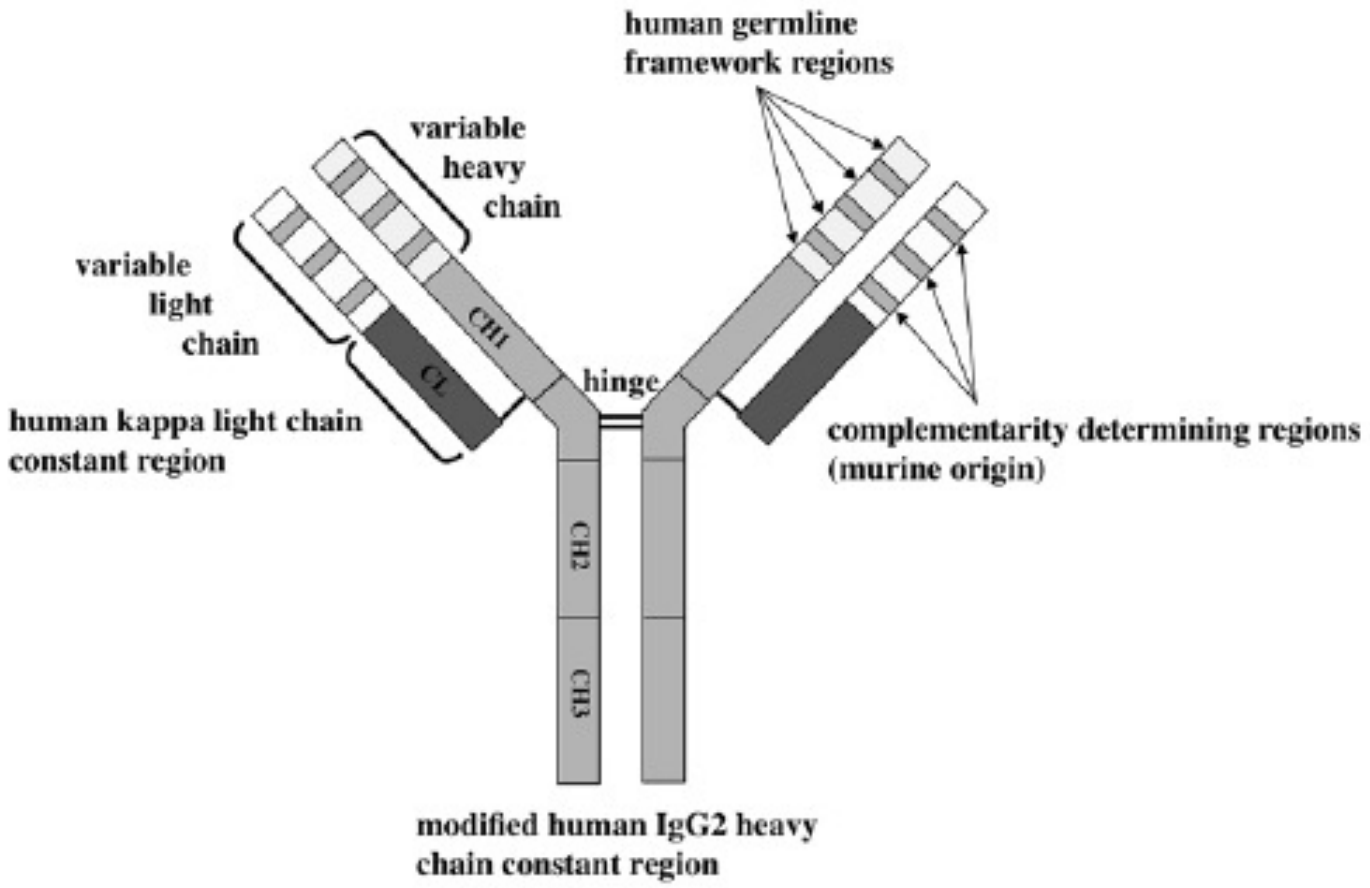
- **AG-348 (Mitapivat)**
- **FT-4202 (Etavopivat)**

White Blood Cell / Selectin Biology



Crizanlizumab - White Blood Cell / Selectin blocking

- A humanized antibody that binds to human P-selectin and blocks the interactions with its binding partners.



Crizanlizumab - Phase 2 Trial Design (NCT01895361)

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A SICKLE CELL PAIN CRISIS STUDY

Phase 2, multicenter, randomized, placebo-controlled, double-blind, **St**u**d**y to Assess **S**afety and Efficacy of SelG1 With or Without Hydroxyurea **T**herapy in Sickle Cell Disease Patients with Sickle Cell-Related P**ain** Crises.

- 198 randomized subjects
- 60 sites
    - US (151), Brazil (40), and Jamaica (7)
- Age 16 - 65 years
- HbSS, HbSC, HbSβ^0- and HbSβ^+-thalassemia.
- Administered IV over 30 min. followed by 60 min. monitoring.
- *Loading Dose:* Day 1 and Day 15 $\pm$ 3 days
- *Maintenance Dose:* continuing every 4 weeks.

Crizanlizumab - Annual Rates of Sickle Cell Pain

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Table 2. Annual Rates of Sickle Cell–Related Pain Crises.*

Variable	High-Dose Crizanlizumab	Low-Dose Crizanlizumab	Placebo
Primary end point: annual rate of crises in the intention-to-treat population			
No. of patients	67	66	65
Median rate of crises per year (IQR)	1.63 (0.00–3.97)	2.01 (1.00–3.98)	2.98 (1.25–5.87)
Difference from placebo — %	−45.3	−32.6	—
P value	0.01	0.18	—
No. of patients with crisis rate of zero at end of trial	24	12	11
Annual rate of crises in the per-protocol population			
No. of patients	40	44	41
Median rate of crises per year (IQR)	1.04 (0.00–3.42)	2.00 (1.00–3.02)	2.18 (1.96–4.96)
Difference from placebo — %	−52.3	−8.3	—
P value	0.02	0.13	—
No. of patients with crisis rate of zero at end of trial	15	7	5

Ataga KI et al. N Engl J Med 2017; 376:429-439.

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Crizanlizumab - Times to the 1st and 2nd Pain Crises

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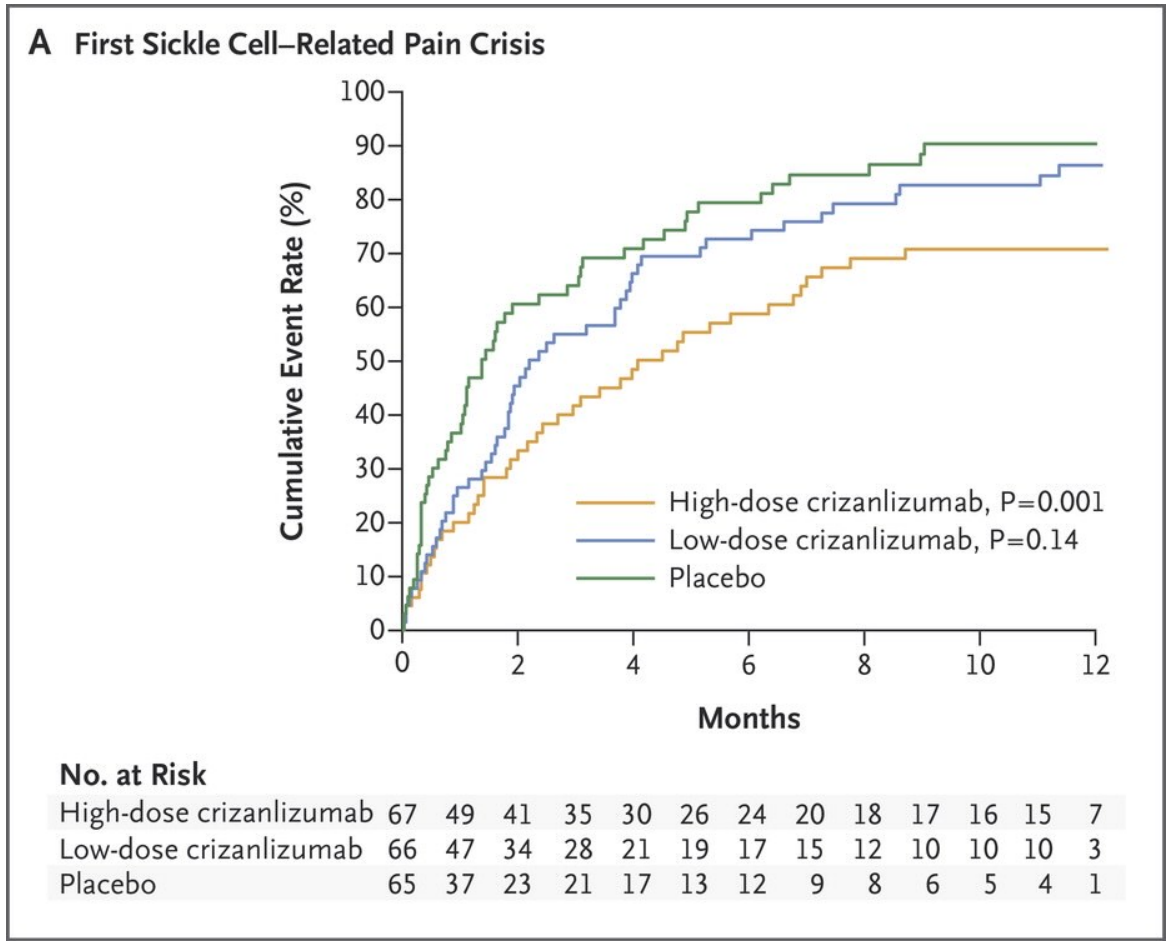

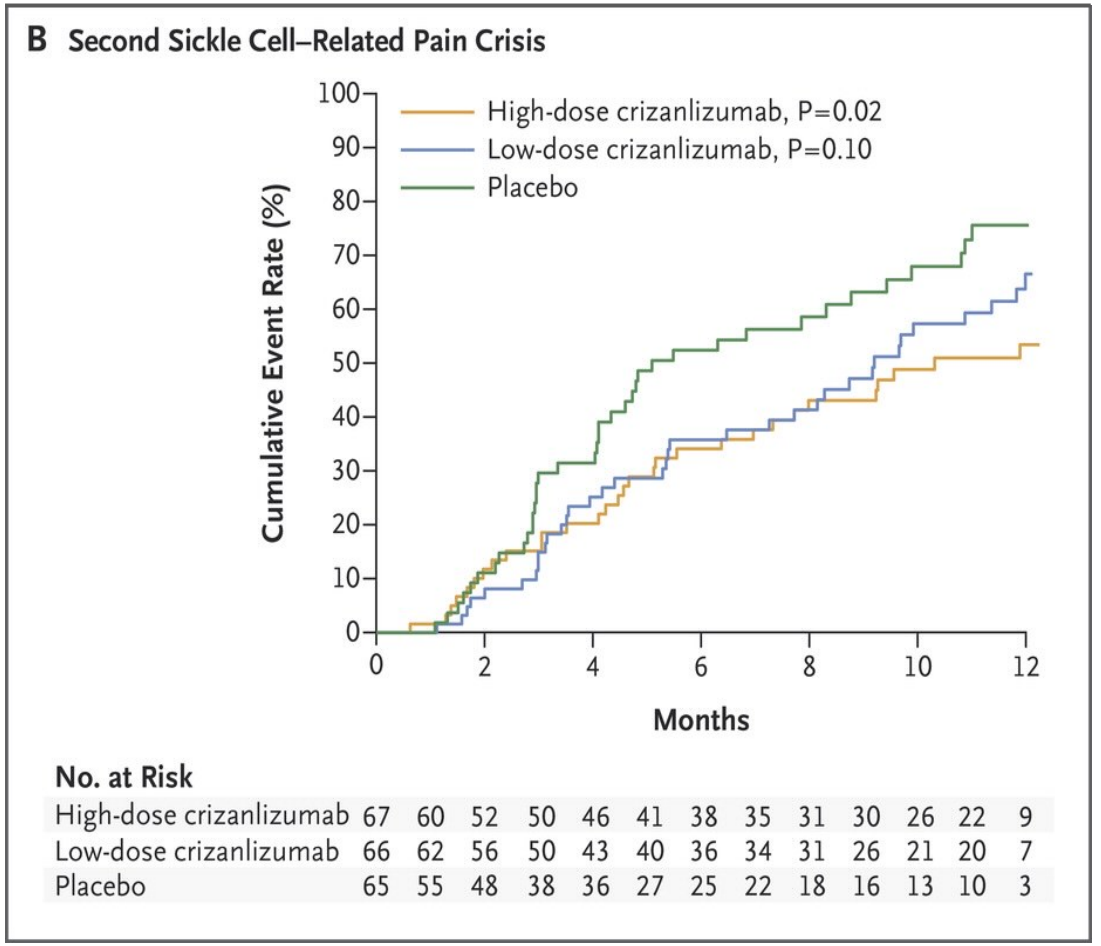

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Adverse Events

Table 4. Adverse Events in the Safety Population.*

Variable	High-Dose Crizanlizumab (N=66)	Placebo (N=62)
Serious adverse events		
No. of patients with ≥1 serious adverse event	17 (26)	17 (27)
Most frequent serious adverse events†		
Pyrexia	2 (3)	1 (2)
Influenza	0	0
Pneumonia	3 (5)	3 (5)
Adverse events		
No. of patients with ≥1 adverse event	57 (86)	55 (89)
Most frequent adverse events‡		
Headache	11 (17)	10 (16)
Back pain	10 (15)	7 (11)
Nausea	12 (18)	7 (11)
Arthralgia	12 (18)	5 (8)
Pain in extremity	11 (17)	10 (16)
Urinary tract infection	9 (14)	7 (11)
Upper respiratory tract infection	7 (11)	6 (10)
Pyrexia	7 (11)	4 (6)
Diarrhea	7 (11)	2 (3)
Musculoskeletal pain	8 (12)	6 (10)
Pruritus	5 (8)	3 (5)
Vomiting	5 (8)	3 (5)
Chest pain	1 (2)	1 (2)

Ataga KI et al. N Engl J Med 2017; 376:429-439.

Infusion-related reactions (IRRs) were observed in 3 patients (2.7%), neither of which was serious or required discontinuation.

Post-marketing IRR cases, including severe pain events.

- Majority occurring during the 1st and 2nd infusion.

- Secondary complications such as ACS / fat embolism, particularly those treated with steroids.

Patients should be monitored for IRR.
In the event of a severe IRR, discontinue infusion, supportive care, and caution with corticosteroids unless clinically indicated (e.g. anaphylaxis).

https://www.report.novartis.com

Selectin Blockade

FDA granted Crizanlizumab:

- Breakthrough Therapy designation
- Orphan Drug designation
- Priority Review designation

- New Drug Application accepted (11/15/19)
- Indication: reduce the frequency of VOCs in patients aged > 16 y.o. with sickle cell disease.

Crizanlizumab SENTRY Program

STEADFAST NCT04053764

- A Phase II, Multicenter, Randomized, Open Label Two Arm Study Comparing the Effect of Crizanlizumab + Standard of Care to Standard of Care Alone on Renal Function in Sickle Cell Disease Patients ≥ 16 Years With Chronic Kidney Disease Due to **Sickle Cell Nephropathy**

SPARTAN NCT03938454

- A Prospective Phase II, Open-Label, Single-arm, Multicenter, Study to Assess Efficacy and Safety of SEG101 (crizanlizumab), in Sickle Cell Disease Patients with **Priapism**