Sickle Cell Disease in North Carolina 2022: An Optimistic Update.

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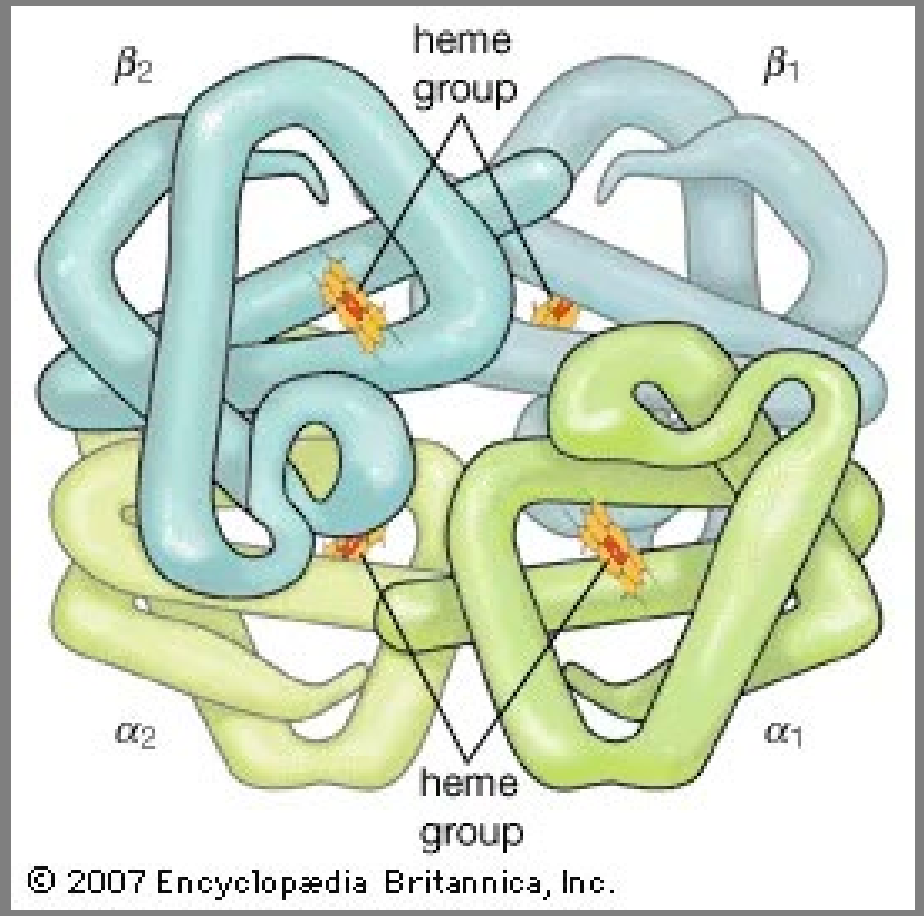
Disclosure of Conflicts of Interest

Jane Little, MD, has the following financial relationships to disclose:

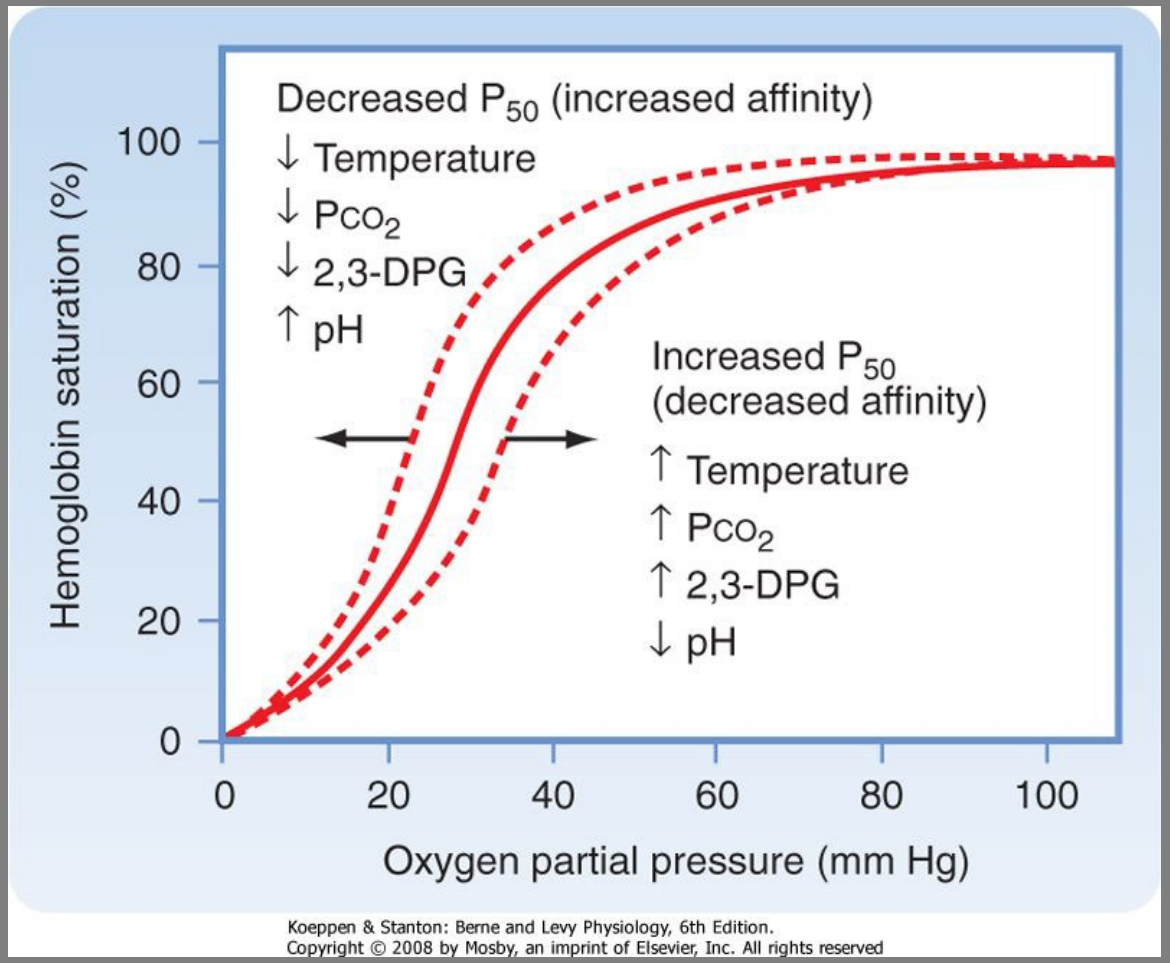
- Inventor on Hemex and SCD Biochip Patent
- Research support from Bluebird Bio
- Research support from GBT
- Adjudication for FORMA Hibiscus Trial
- Advisory Board, National Association of Sickle Cell Centers

Hemoglobin Delivers Oxygen



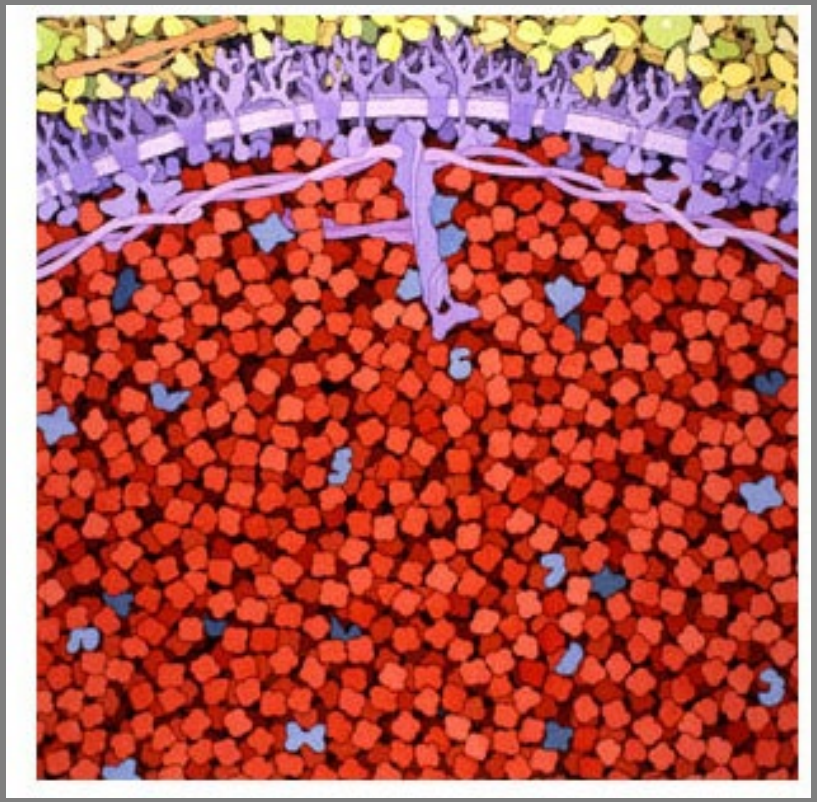
Hemoglobin A
($\alpha_2\beta_2$)

The cooperative α- & β-globin chains facilitate oxygen delivery



Adapted from MITCH WEISS & https://www.britannica.com/science/hemoglobin & Bernard and Levy Physiology, 6th Ed., 2008

Mature erythrocytes are loaded with hemoglobin



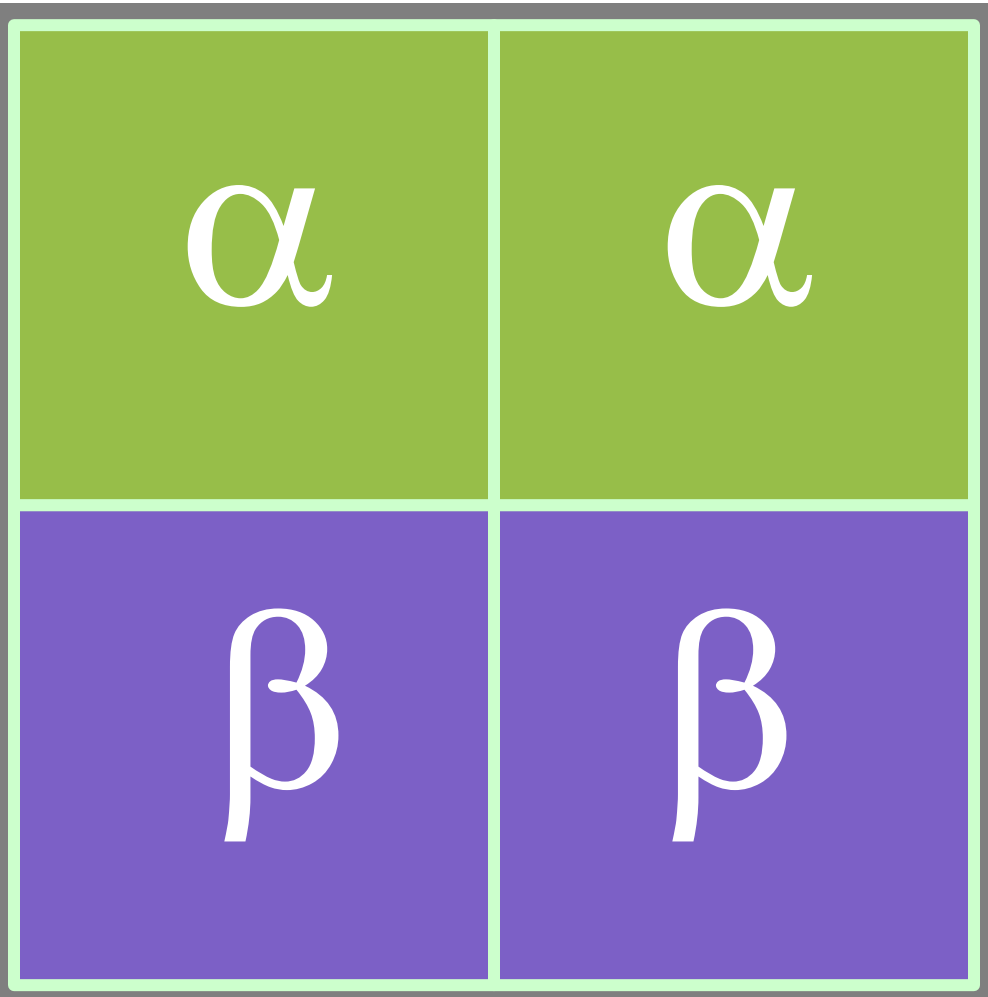
mature erythrocyte

- [Hb]= 35 g/dL= 350 mg/ml
- Hb and its intermediates produce ROS

Frydman, Ann Rev Bioch, 2001
David Goodsell
http://mgl.scripps.edu/people/goodsell

MITCH WEISS

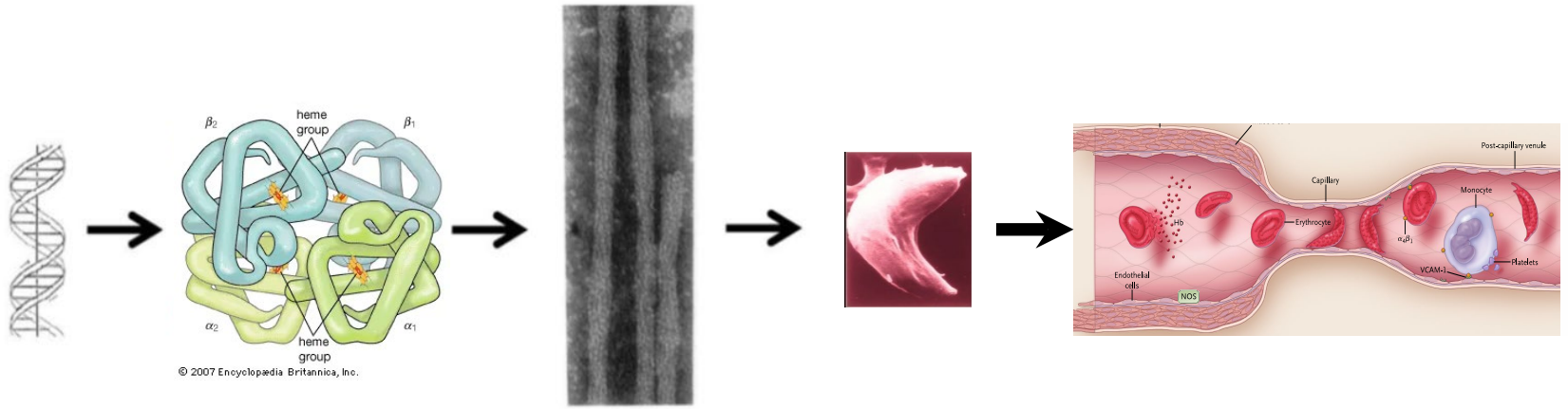
Hemoglobin-A



Most people have 2 normal β chains

HbA

SCD: The Problem



DNA

Hemoglobin

Deoxy HbS polymer.

HbS-containing RBC (sRBC)

Vasculopathy

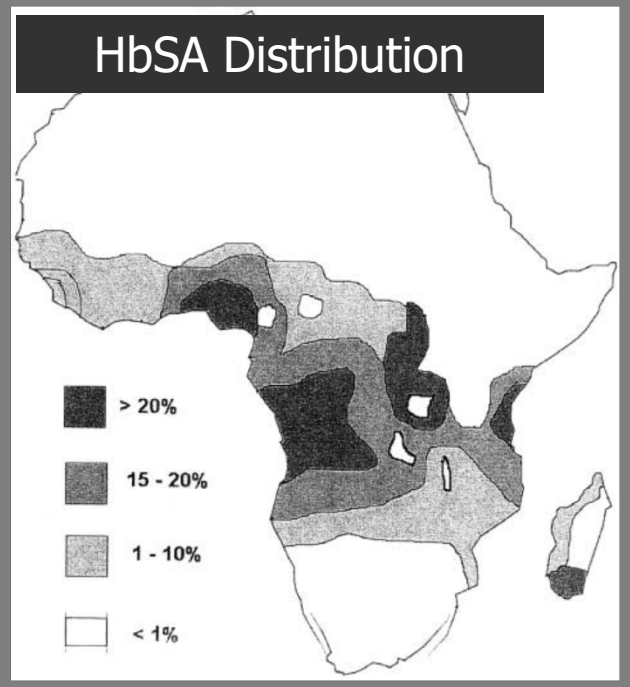
Watson & Crick, Nature 1953

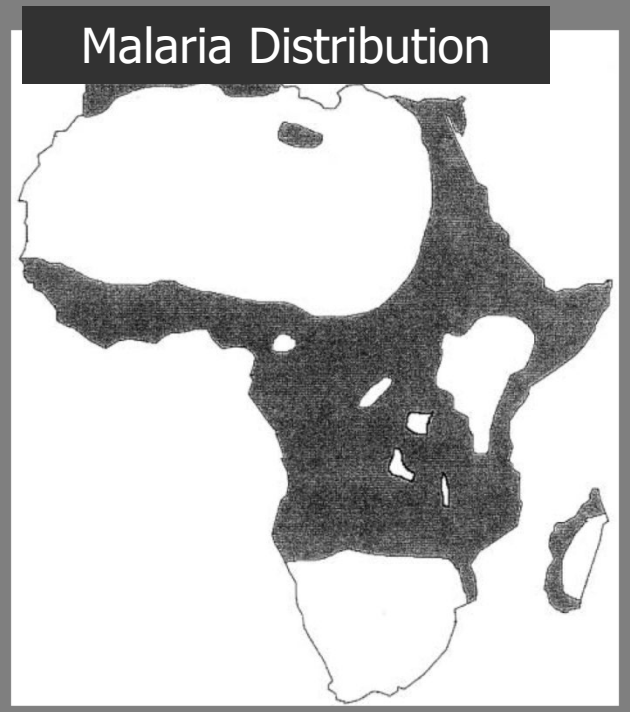
https://www.britannica.com/science/hemoglobin

Labie & Elion, Pathol Biol (Paris), 1999

Gladwin MT, Vichinsky E. N Engl J Med 2008;359:2254-2265.

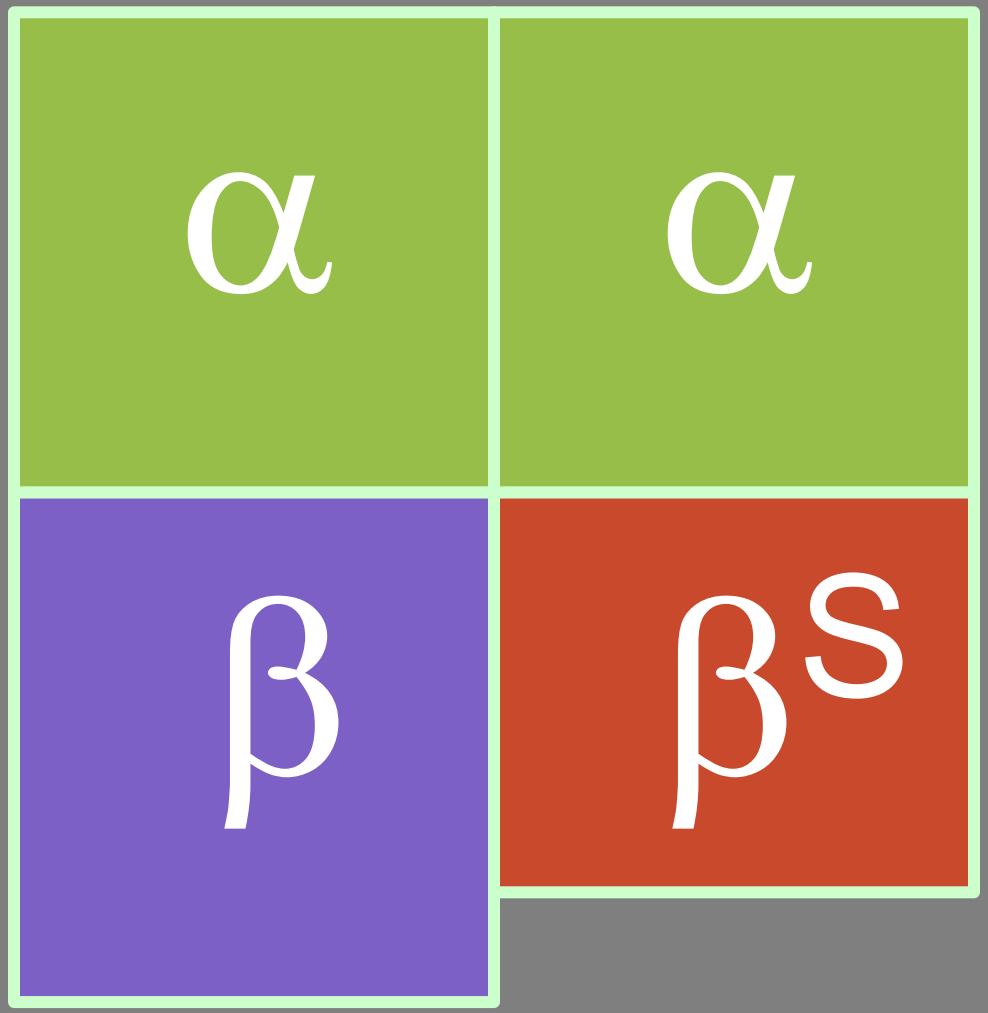
SCD is a biological “trade-off”





From Allison “Perspectives” *Genetics*, 2004

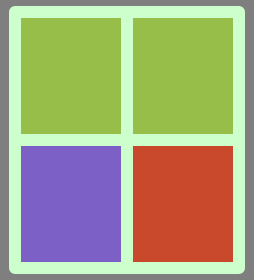
Hemoglobin-AS



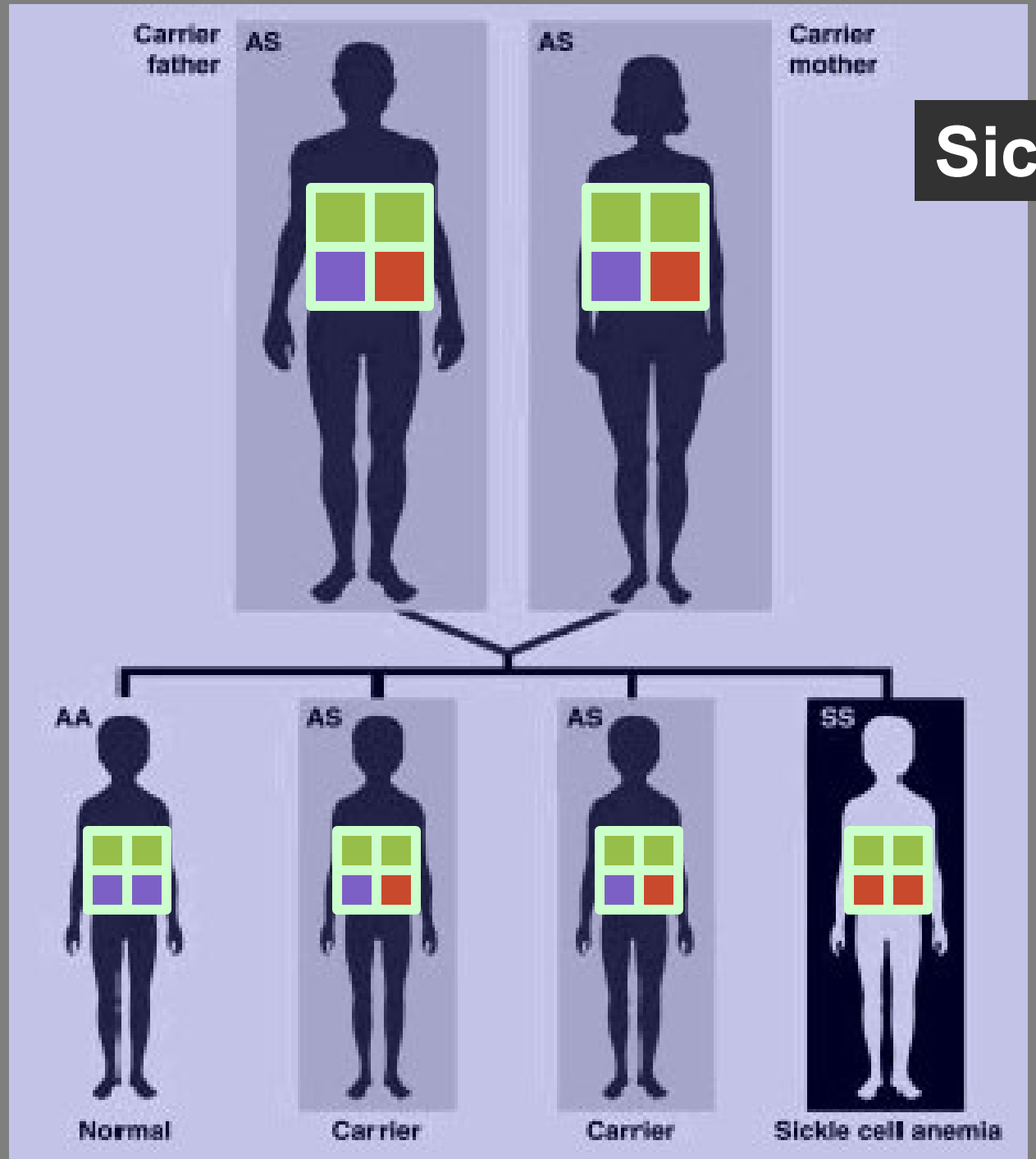
One β chain is abnormal in sickle cell trait

HbAS

Sickle Cell Trait is not a disease



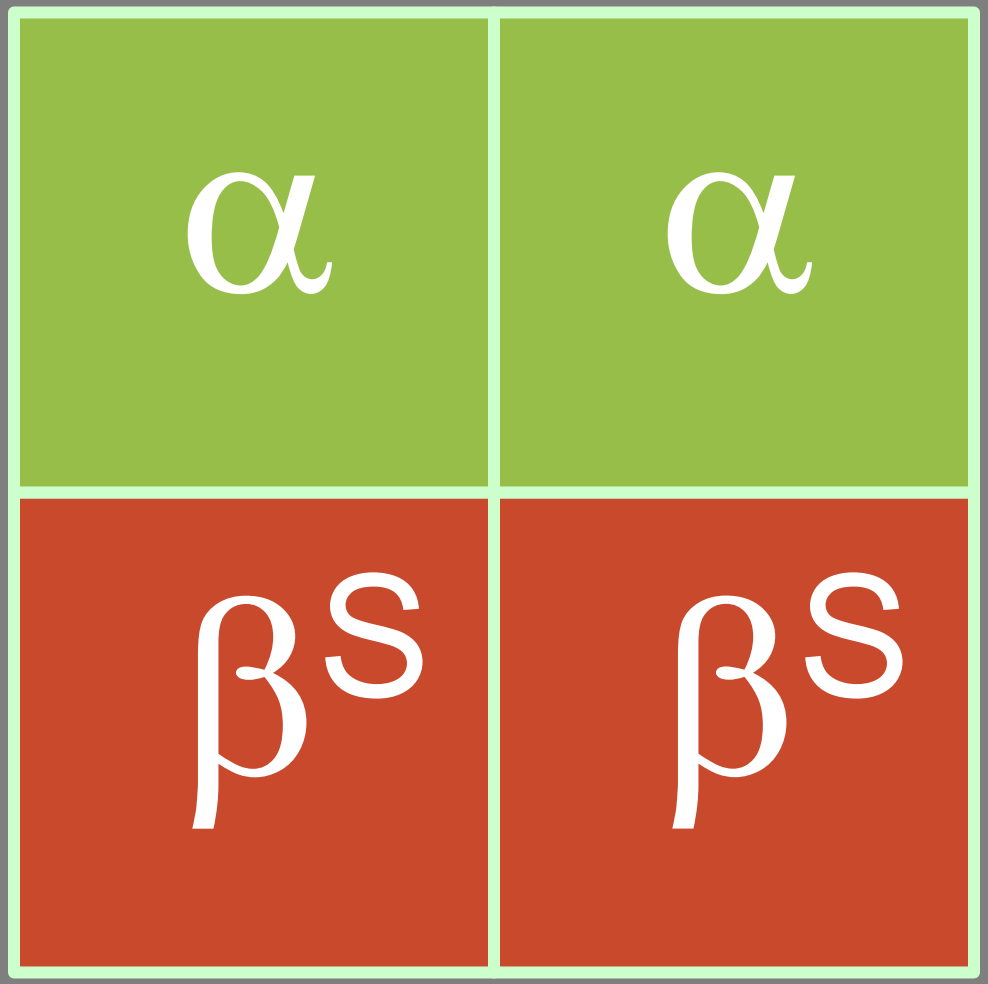
- 1 in 12 African Americans (up to 2 million Americans) have **HbAS (sickle cell trait)**
- Blood counts are normal
- Risks: Dilute Urine, Blood in the urine, ? Blood clots in the lung (Pulmonary Embolism), renal disease



Sickle Cell Disease

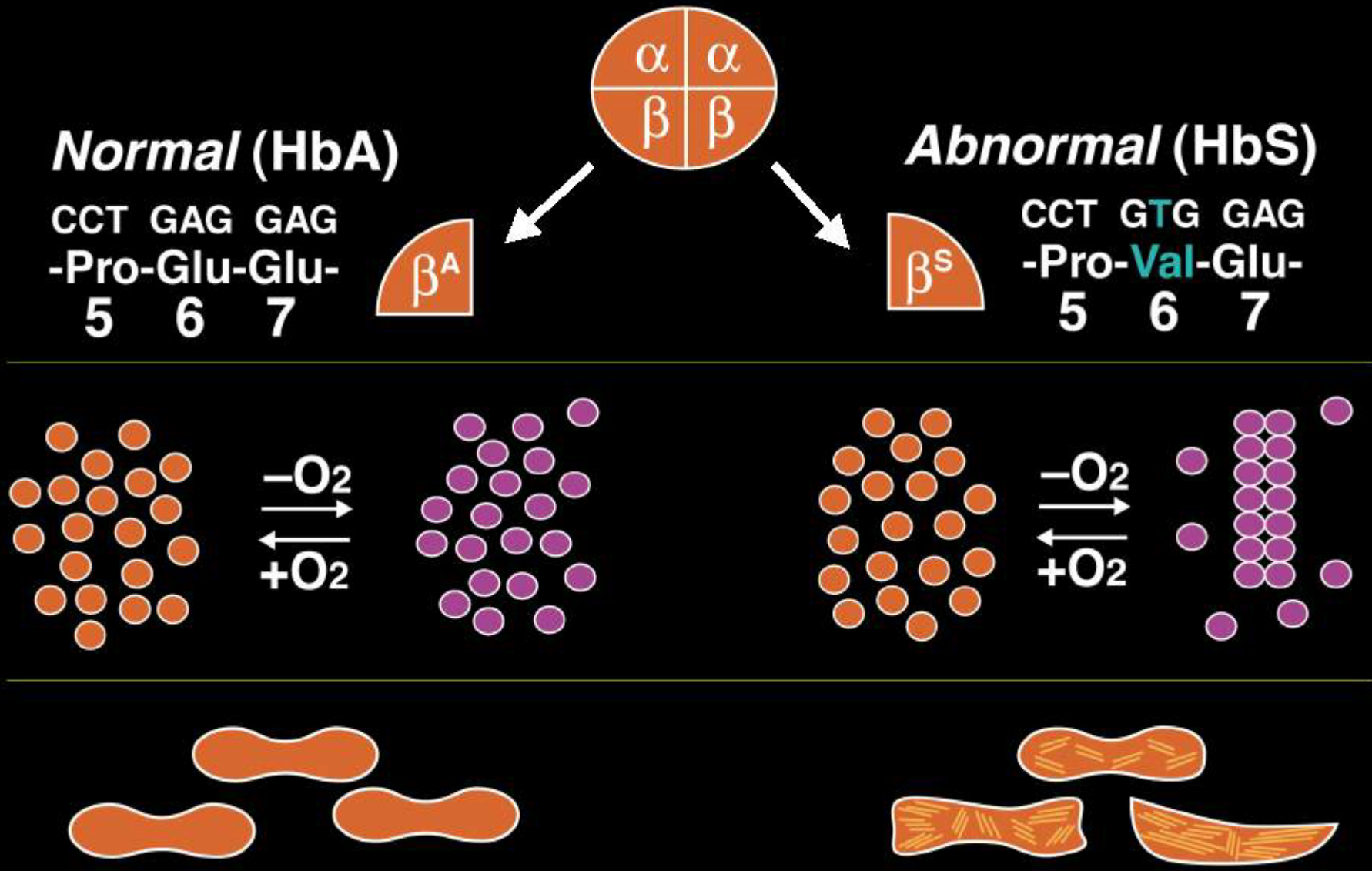
- 1:400-600 African American children are born with HbSS
- 1:835 African Americans are born with HbSC
- 1:1000-1400 Hispanic Americans are born with HbSS
- 100,000 Americans have SCD
- >6 million sub-Saharan Africans have SCD

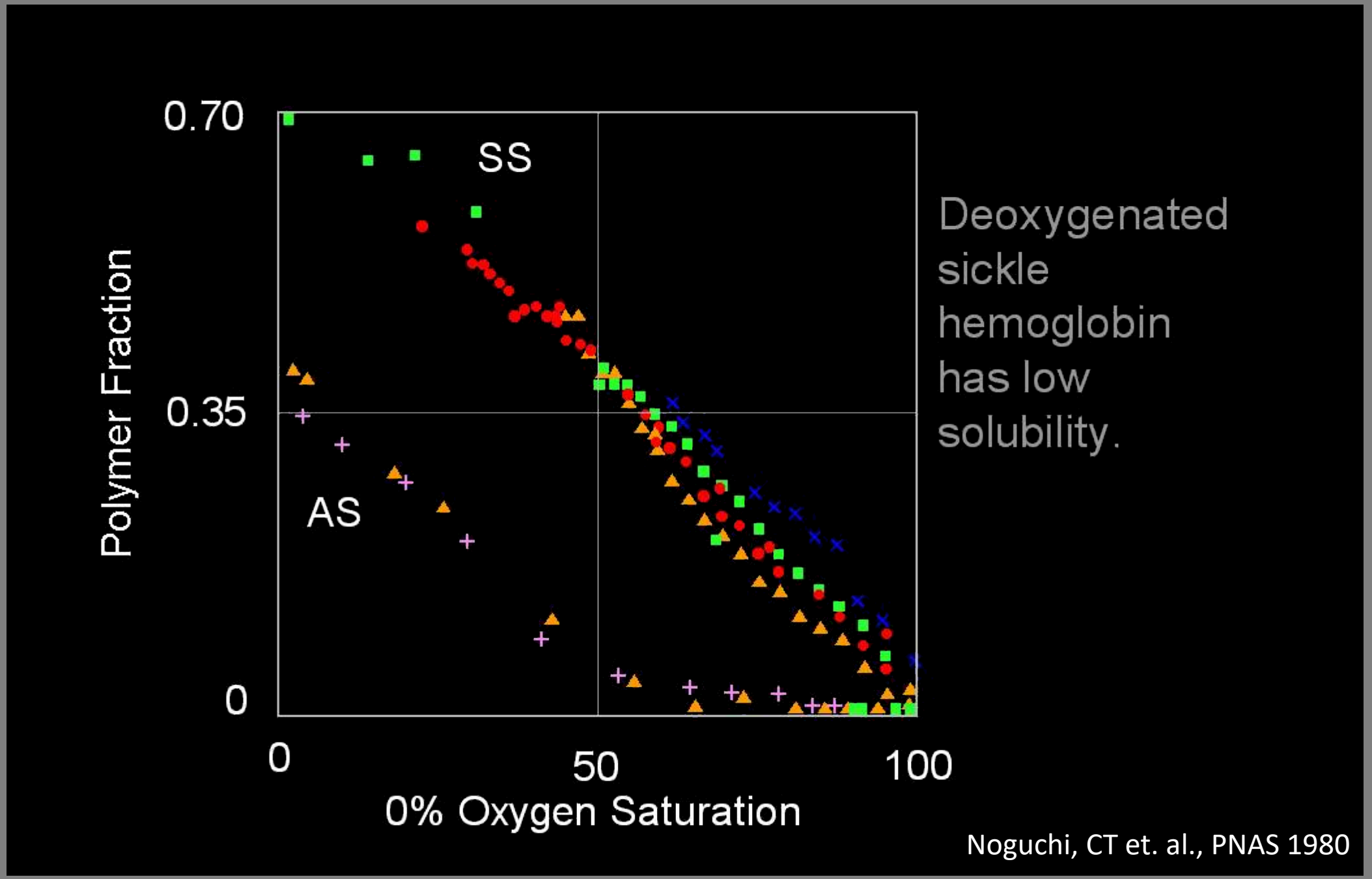
Hemoglobin-SS

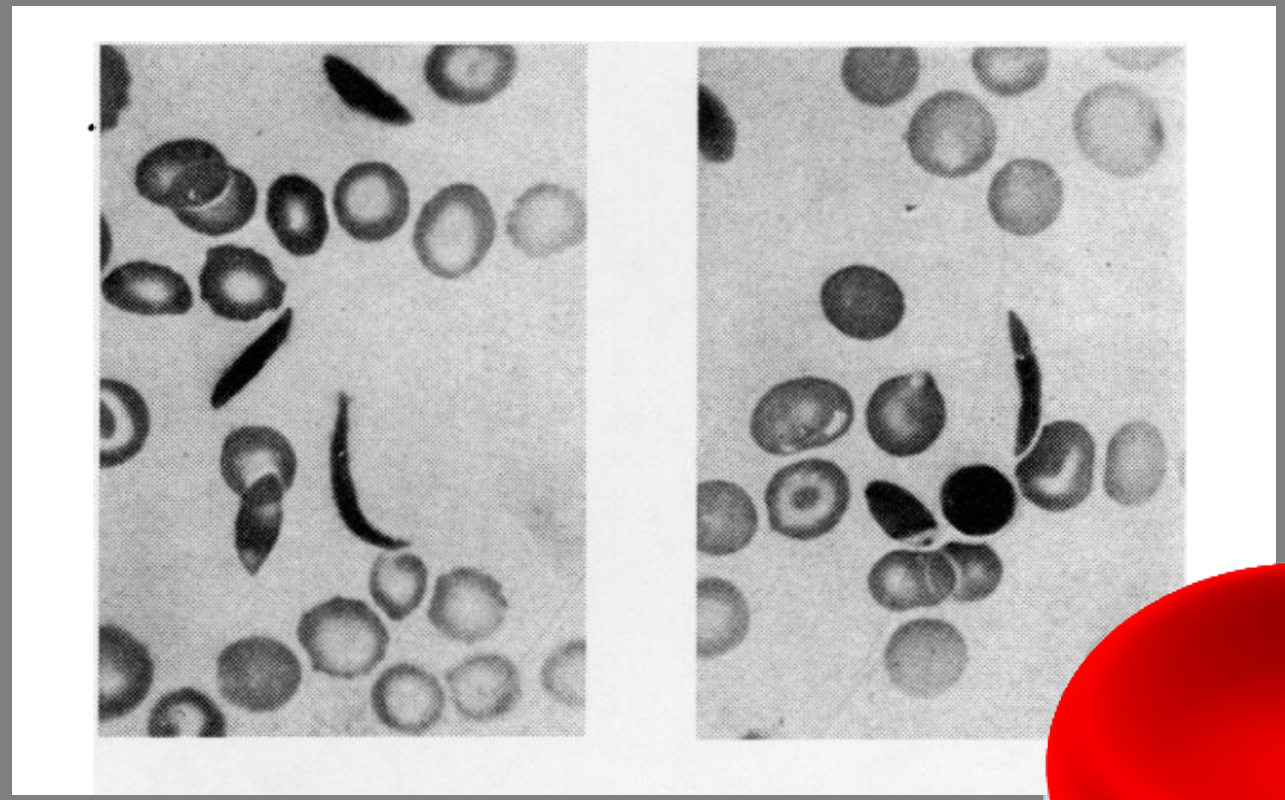


Both β chains are abnormal in
HbSS, sickle cell anemia (2/3 of SCD in US)

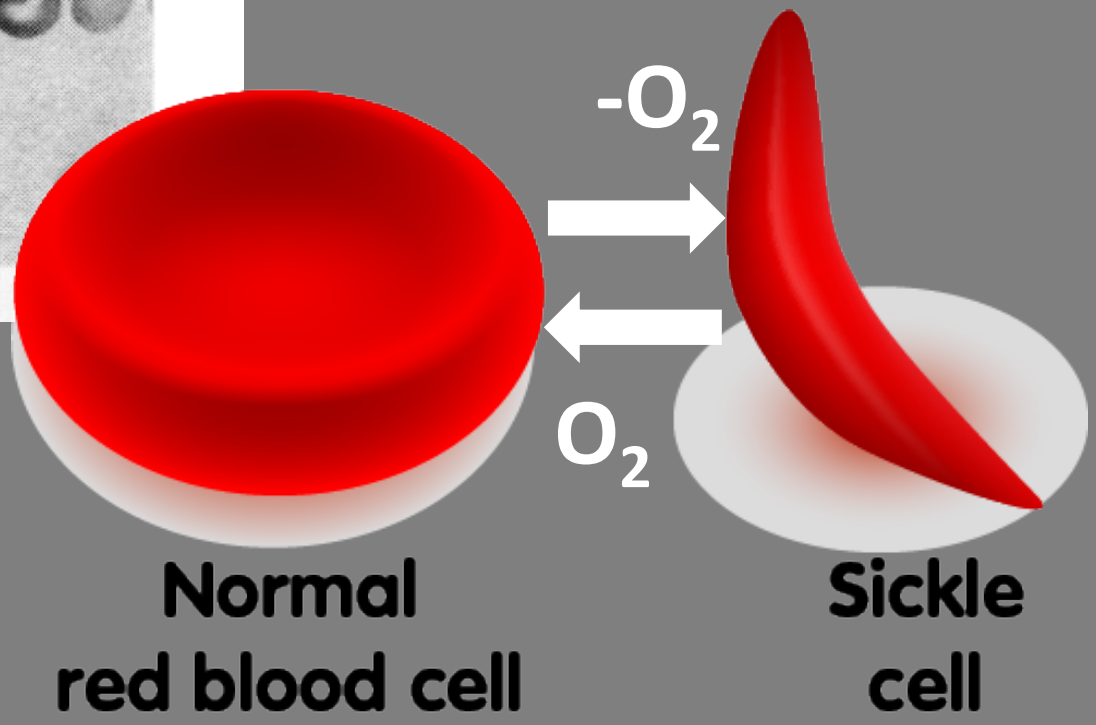
SCD: The Problem




0.70
0.35
0
Polymer Fraction
SS
AS
0
50
100
0% Oxygen Saturation
Deoxygenated sickle hemoglobin has low solubility.
Noguchi, CT et. al., PNAS 1980

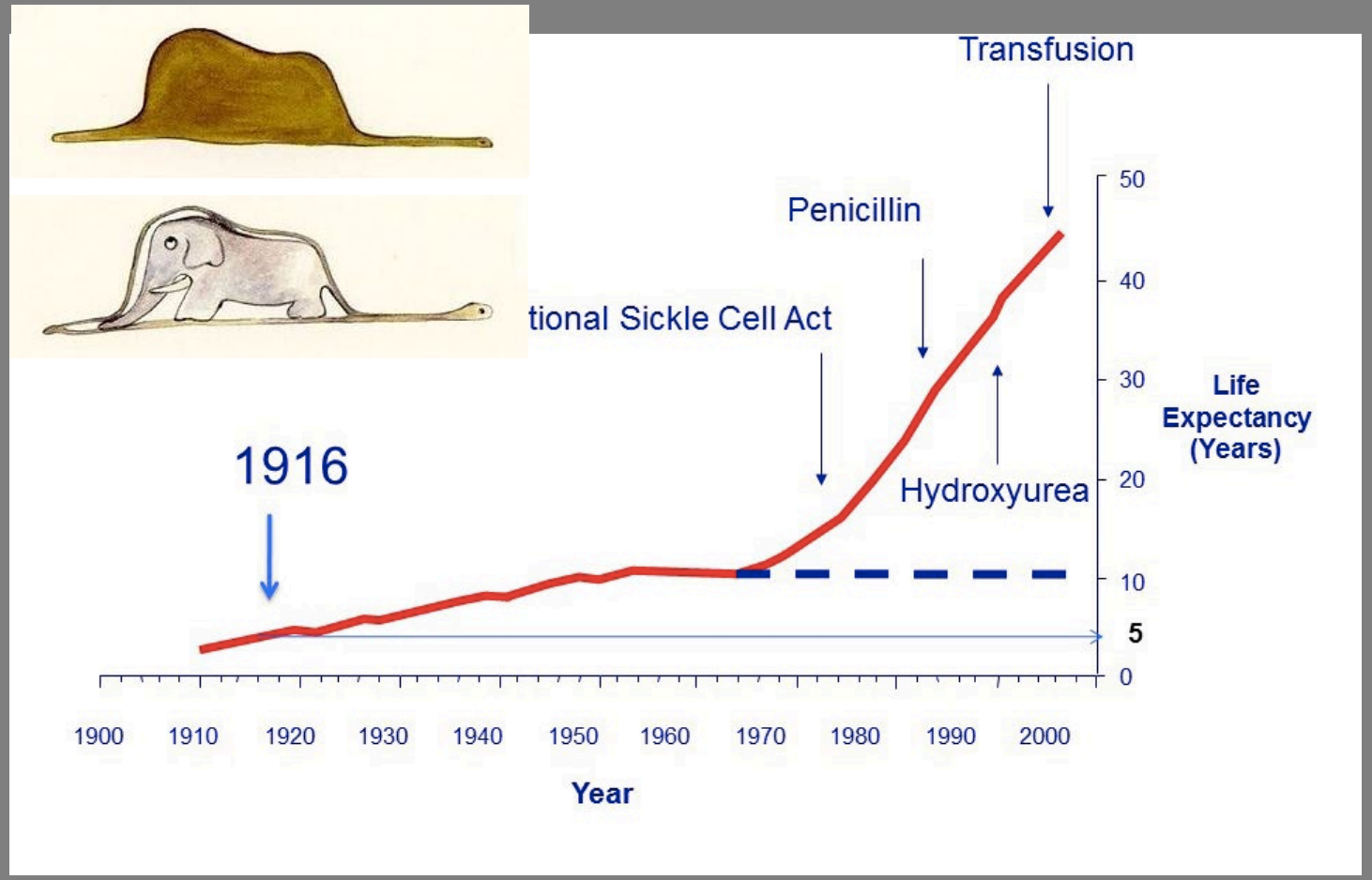


Polymerization results in abnormal adhesion and in hemolysis.



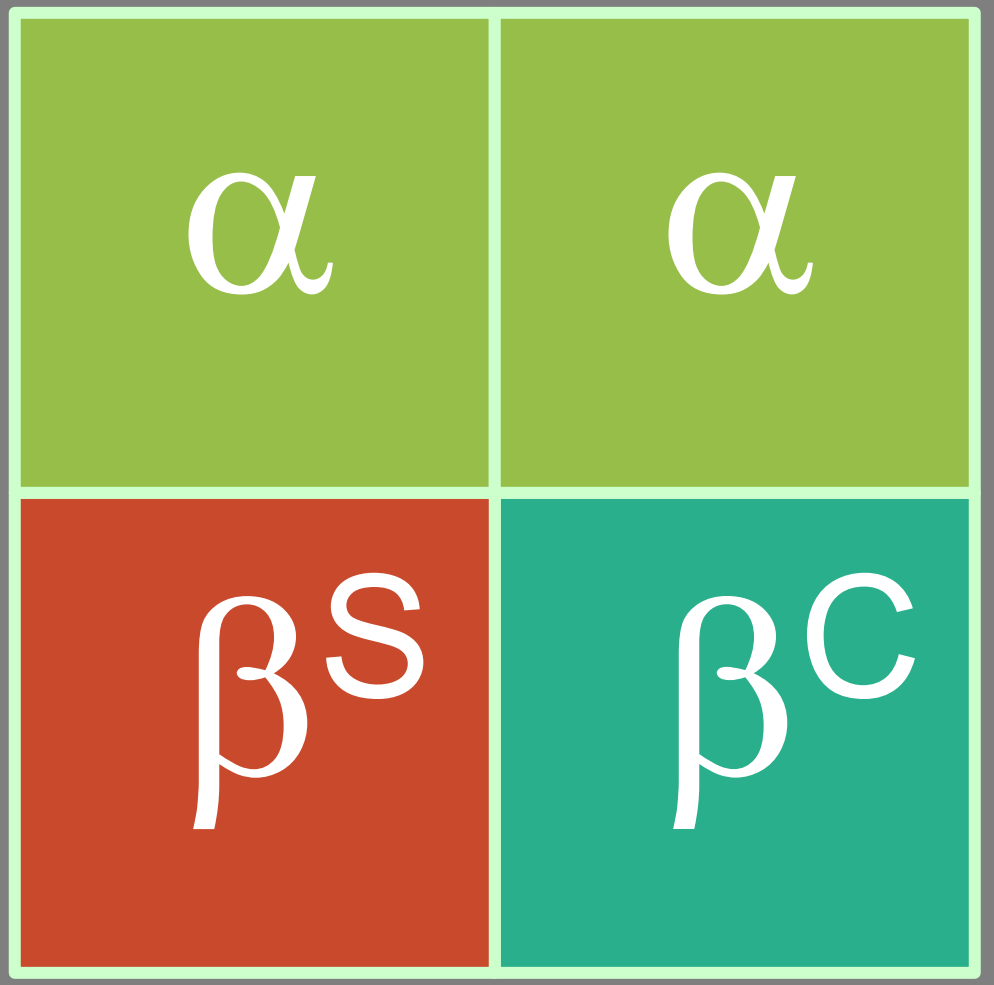
Herrick, JB, Arch Int Med, 1910 & Office of Minority Health, HHS.gov

A new population in SCD



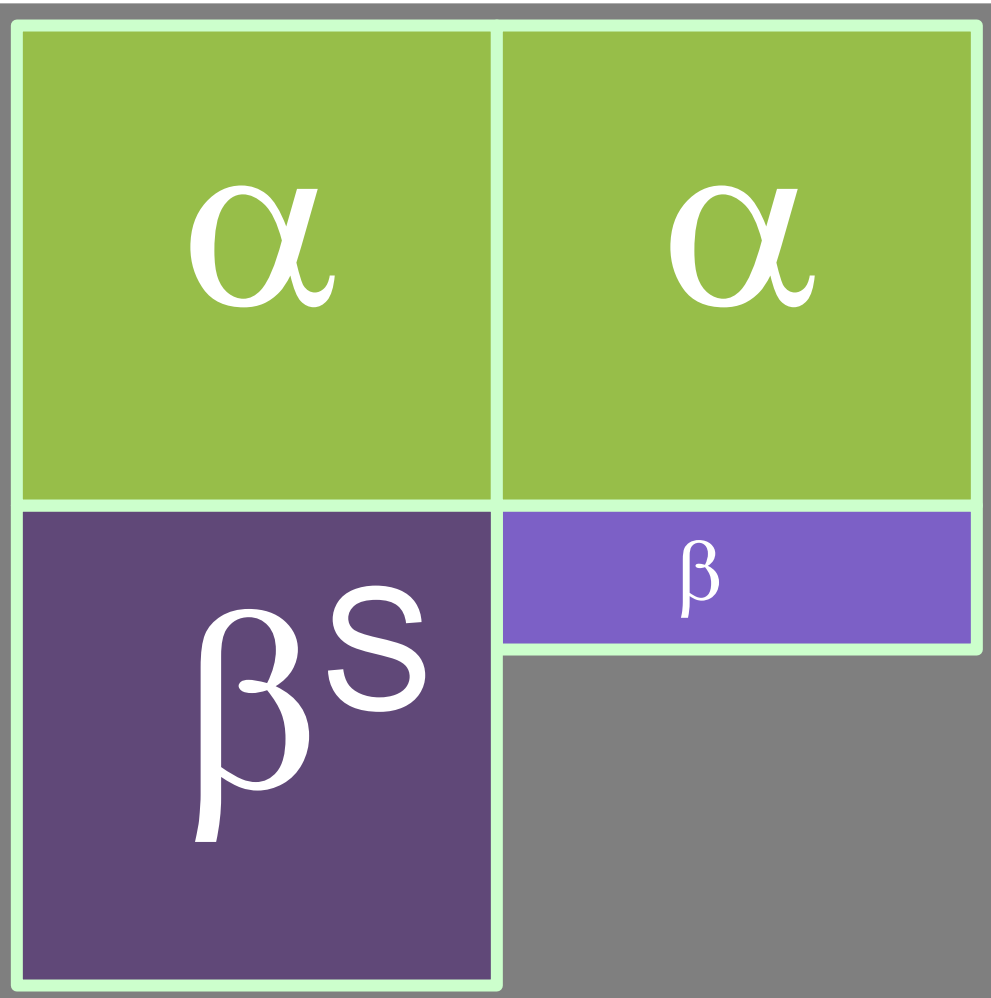
Le Petit Prince,de St Exupery, Sntoine,1943 & https://www.nhlbi.nih.gov/health/health-topics/topics/sca/research

Hemoglobin-SC



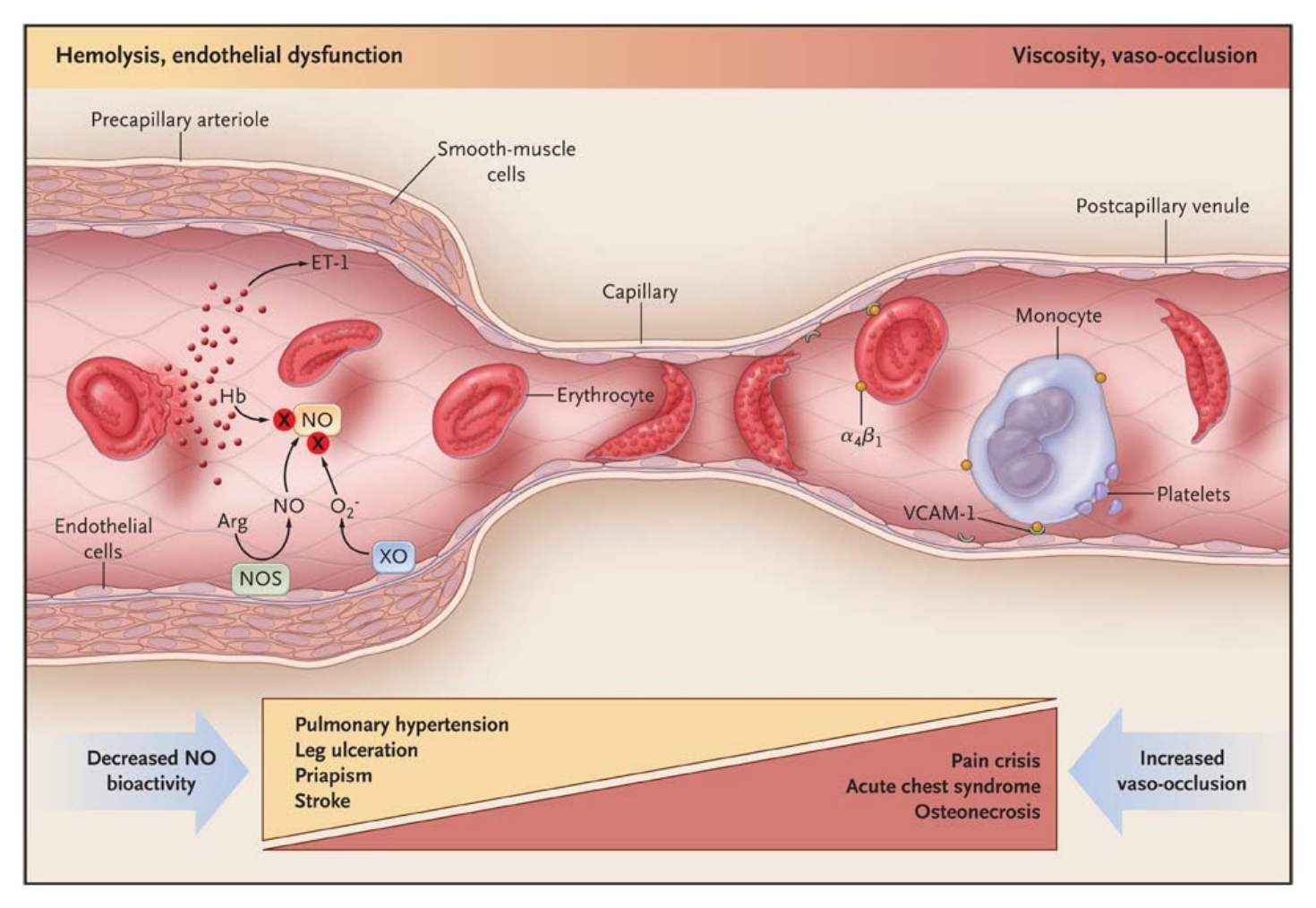
Both β chains are abnormal in
SC Disease (HbSC, 1/4 SCD in US)

Hemoglobin-Sβ–thalassemia



Both β chains are abnormal in HbSβ^{+}–thalassemia
(1/10th of SCD in US)

Pathogenesis of SCD: Hemolysis and Adhesion



Gladwin MT, Vichinsky E. N Engl J Med 2008;359:2254-2265.

The NEW ENGLAND JOURNAL of MEDICINE

Major Complications of SCD-HbSS & HbSC

HbSS 2/3 of SCD	HbSC 1/4 of SCD
•Painful Crises •Central Nervous system disease-strokes, bleeds •Lung disease-ACS, ↑ TRV •Bone Disease-AVN •Infection •Kidney disease •Obstetrical Complications •Priapism •Asplenia •Thrombophilia •Shortened life expectancy •Candidate for Symptom or Disease Modifying Therapy (Hydroxyurea, RBC transfusions, vox, gene therapy or HSCT)	•Painful Crises •Retinal Disease •Lung Disease-ACS •Bone Disease-AVN •Infection •Kidney disease •Obstetrical Complications •Priapism •'Hypersplenism' •Thrombophilia->25% lifetime prevalence •Near normal life expectancy •Candidate for Symptom Management Therapy (Crizanlizumab, glutamine, red blood cell transfusions)

Our Current Practice

- All pain is real. Compassion is highly therapeutic. (Labs that are unchanged from baseline do not change this.)
- Knowing baseline labs is very important.
- Subtle cognitive (executive function) impairment may make complicated recommendations difficult for some patients (HbSS) to follow. Be clear.
- Pain is critically important, but is the tip of the pathophysiologic iceberg.
- Caveat: ‘Sickler’ is an outmoded knickname.

SCD: The Solution?

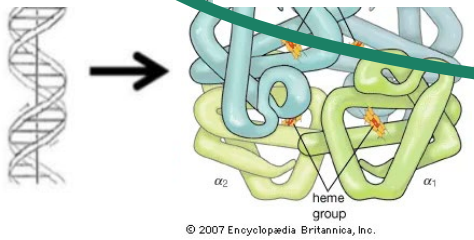
Gene therapy &HSCT

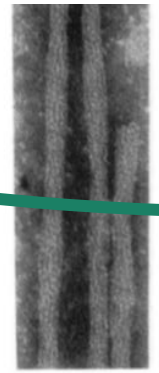
Voxelator & PK Activators

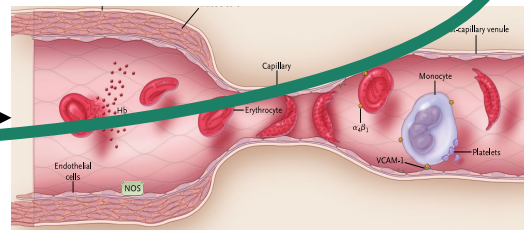
Hydroxyurea

Glutamine

Crizanlizumab







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The many tributaries of SCD

The many tributaries of SCD

Disease Modifying Therapies

Go.Grolier.com

+/-Symptom-Modifying Therapy

Go.Grolier.com

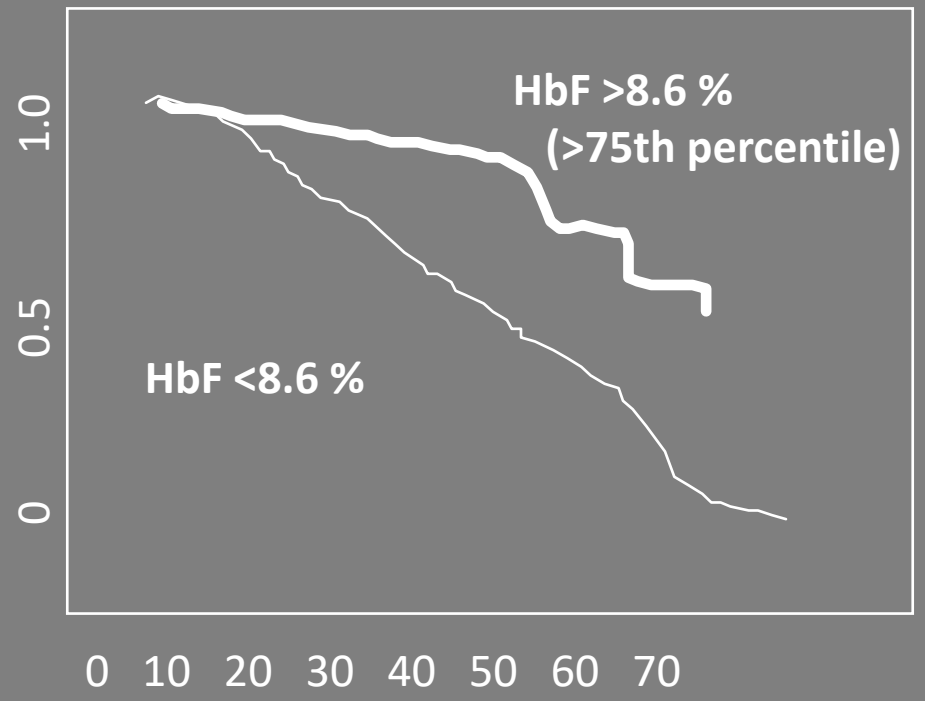
1. Amelioration of SCD by HbF

Hemoglobin	N	Total Hb, g/dL	Reticulocyte, %	HbF, %	HbS, %
HbAS	34	14.3	2.0	0.8	40.5
HbSS-HPFH (Saudi Arabia)	22	10.9	5.2	28.5	69.4
HbSS	88	7.8	11.9	5.3	91.1

From Brittenham et al, Blood 1985

Amelioration of SCD by HbF

- 1991: Platt, et al. (NEJM) studied pain in SS disease
  - Inverse correlation between pain and HbF
- 1994: Platt, et al. (NEJM) Mortality in SS disease
  - Higher HbF was associated with survival



Standard of Care in HbSS

The New England
Journal of Medicine

Volume 332 MAY 18, 1995 Number 20

EFFECT OF HYDROXYUREA ON THE FREQUENCY OF PAINFUL CRISES IN SICKLE CELL ANEMIA

SAMUEL CHARACHE, M.D., MICHAEL L. TERRIN, M.D., RICHARD D. MOORE, M.D., GEORGE J. DOVER, M.D., FRANCA B. BARTON, M.S., SUSAN V. ECKERT, ROBERT P. MCMAHON, PH.D., DUANE R. BONDS, M.D., AND THE INVESTIGATORS OF THE MULTICENTER STUDY OF HYDROXYUREA IN SICKLE CELL ANEMIA*

Results:

Crises (**2.5** vs. 4.5 per year ($p<.05$)

Median time to 1st crisis (mos.): **3.0** vs. 1.5 ($p<.05$)

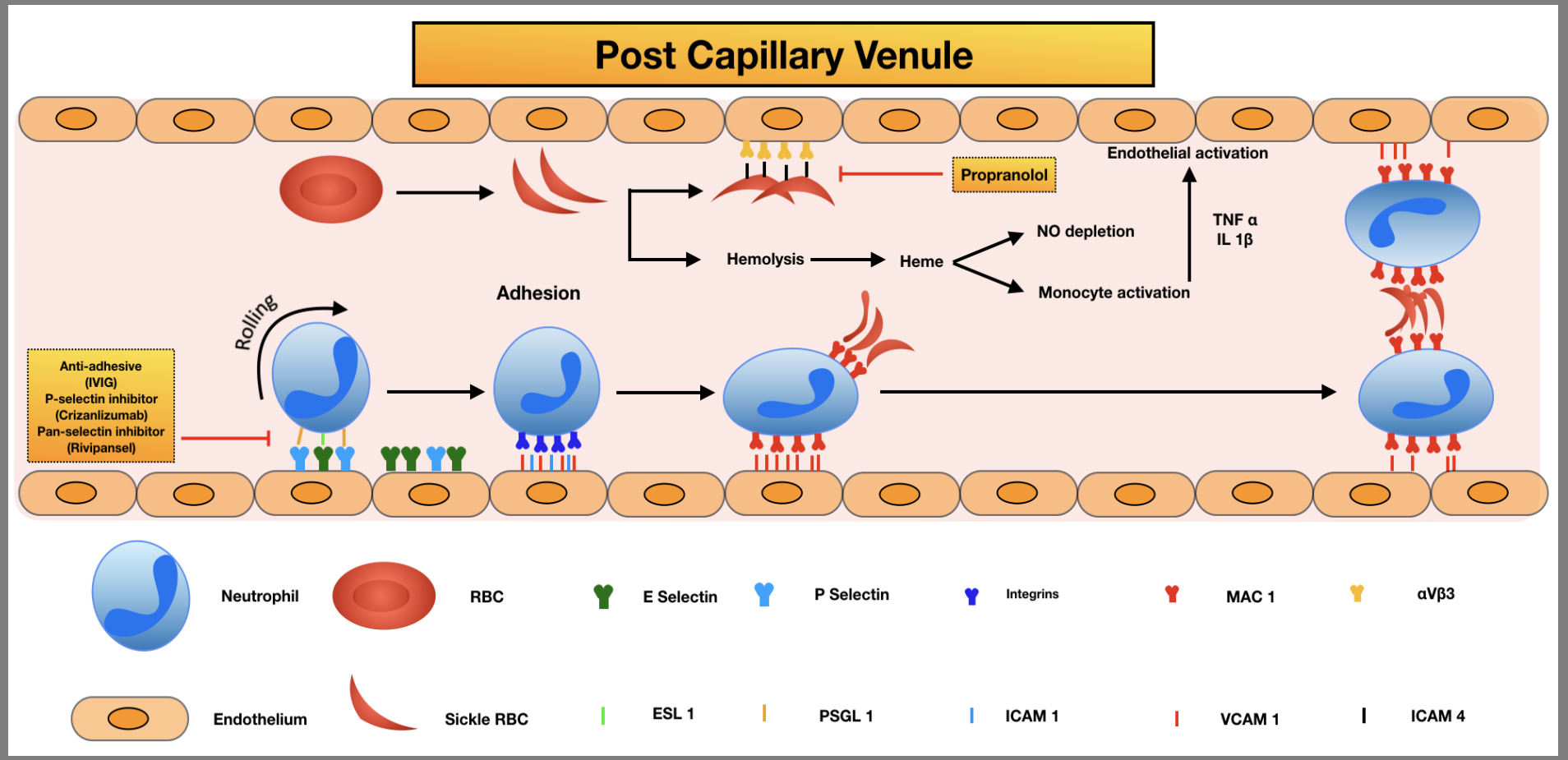
Median time to 2nd crisis (mos.): **8.8** vs. 4.6 ($p<.05$)

ACS episodes (total): **25** vs. 51 ($p<.05$)

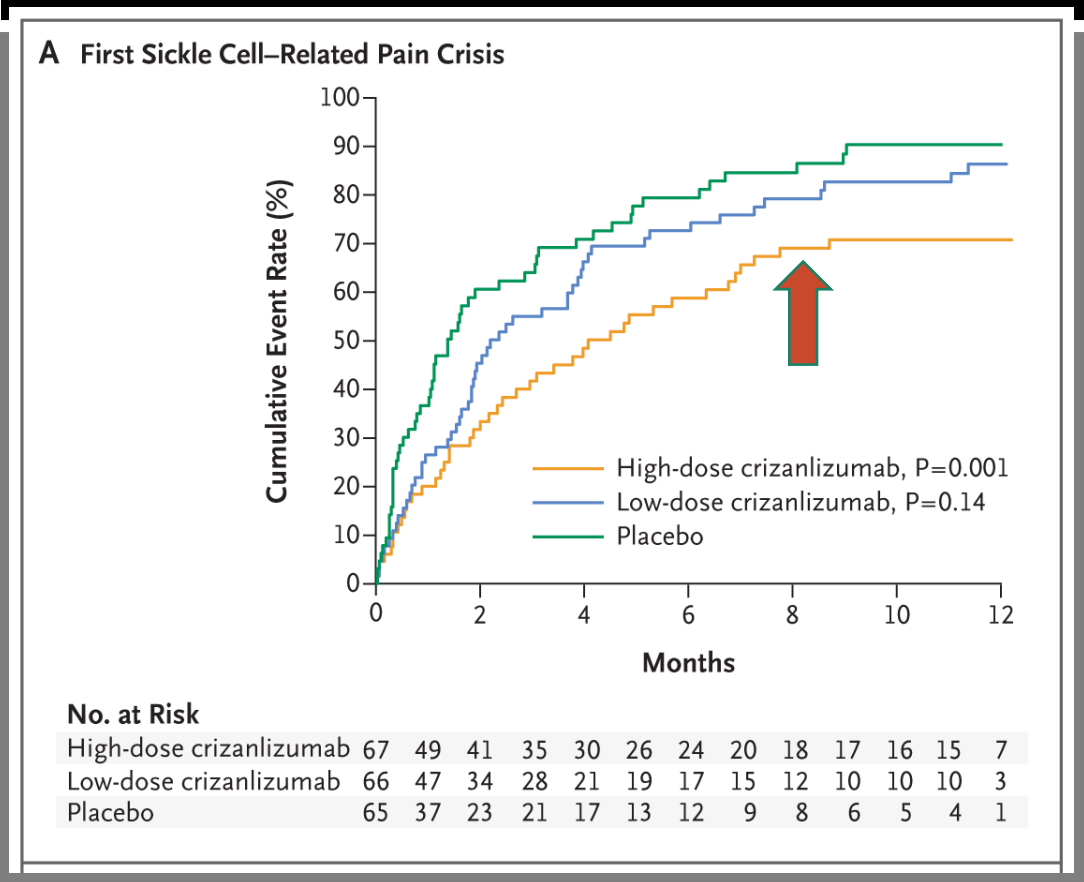
Caveats: Hydroxyurea

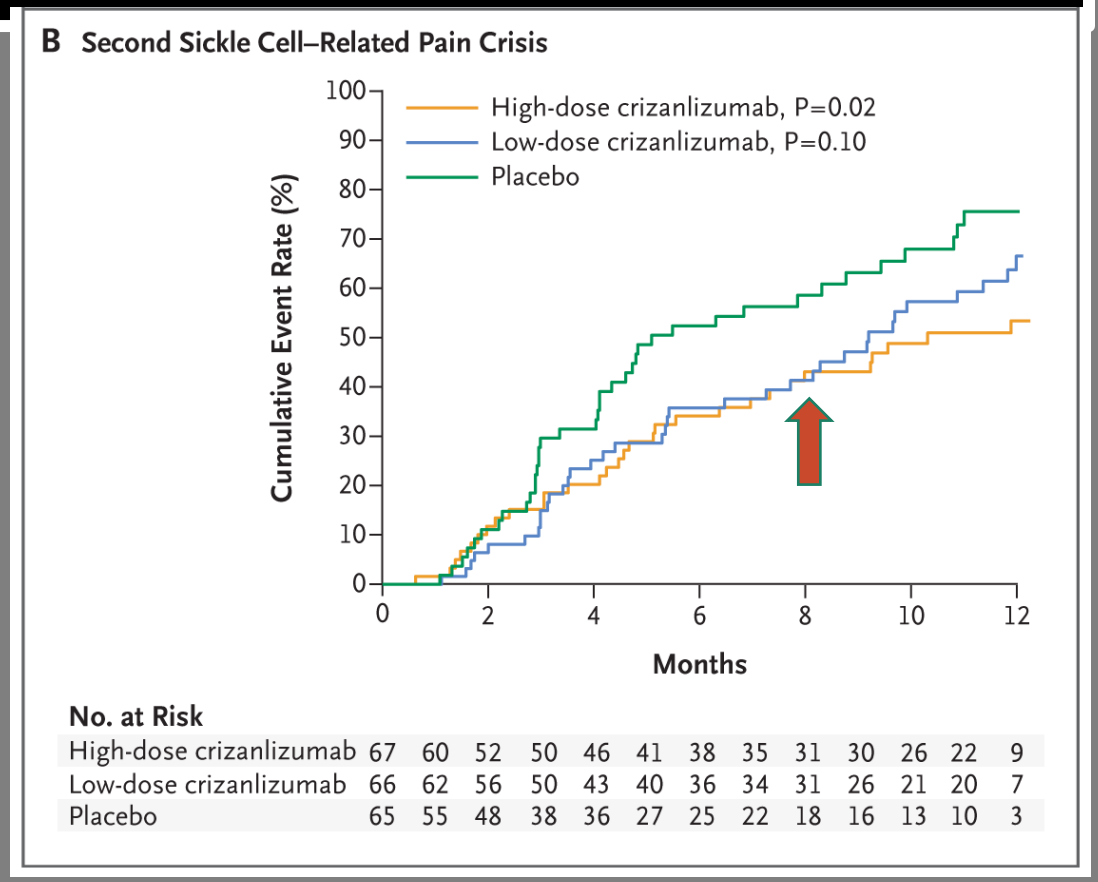
- Morbidity and Mortality, Decreased
- Adherence, difficult, missing a dose here and there OK
- Monitoring: q2-4 weeks at start, then quarterly. MTD yes
- Fertility effects: probable but poorly defined/ use during pregnancy, case-by-case
- Cancer risk: No change
- Lab changes? Inc HbF and Inc Hgb, dec WBC/ANC, inc MCV, decrease hemolytic markers (LDH, reticulocyte)
- Risks: Hair loss, nail changes, weight gain

- 2. Amelioration of Pain by anti-adhesive therapy



Anti-P Selectin





- Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease K.I. Ataga,et. Al. NEJM, 2017.

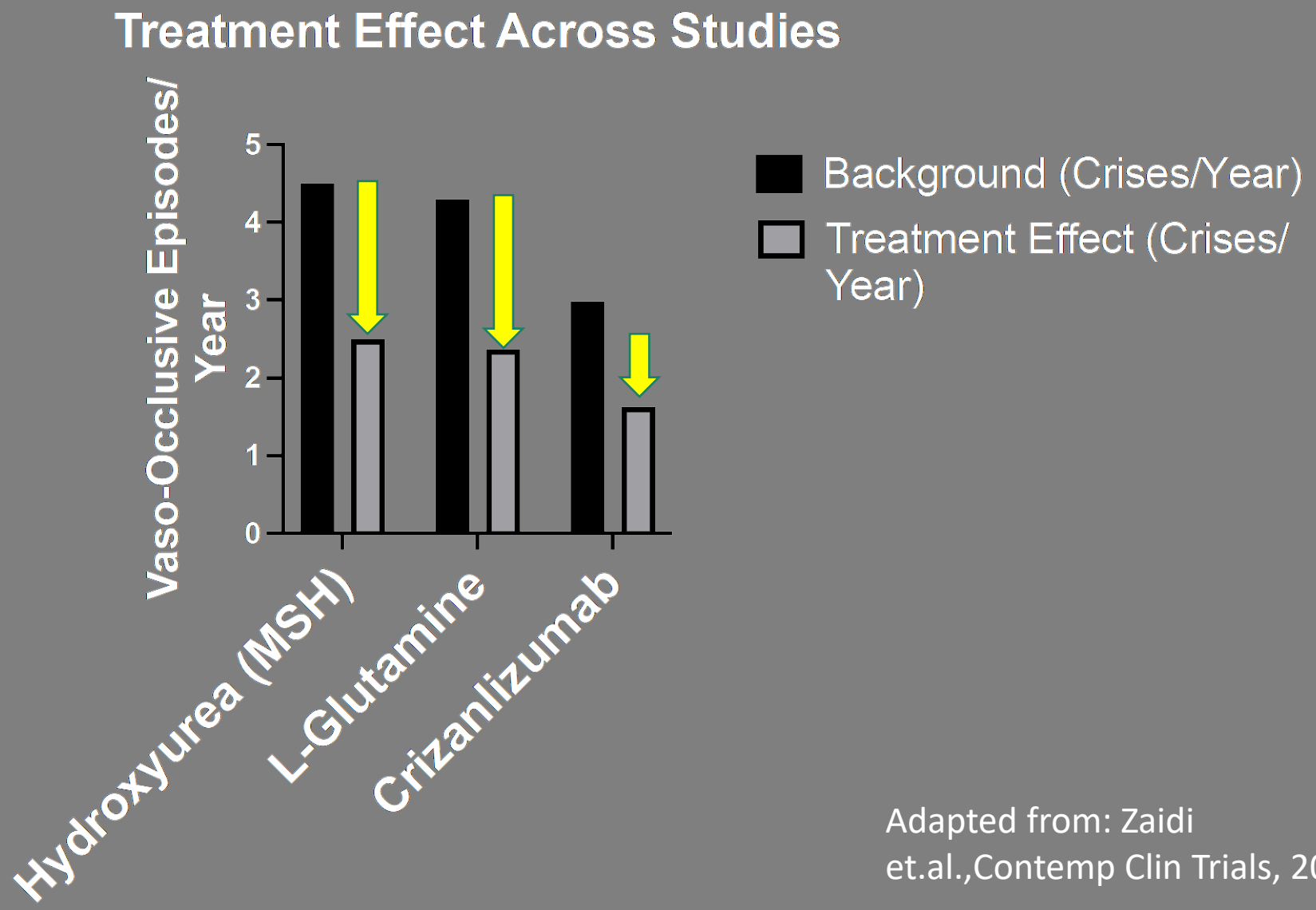
Caveats: Crizanlizumab

- Morbidity Decreased
- Mortality, Unknown
- Adherence, easier, monthly.
- Fertility effects: Avoid during pregnancy
- Cancer risk: No change
- Changes? No lab changes
- Risks: infusion related reactions* **CAN BE SEVERE** (34.8% versus 21%), arthralgia (18.2% versus 8.1%), diarrhea (10.6% versus 3.2%), and nausea (18.2% versus 11.3%), DelGado et. al., 2021 *Hemasphere*.

Caveats: Voxelotor

- Morbidity Unclear
- Mortality Unknown
- Adherence difficult, daily-can be catastrophic-hard to continue while hospitalized; Avoid during pregnancy
- Changes? Increase in Hgb, decrease in hemolytic markers
- Risks: Headache 26% vs. 22%, diarrhea or rash 20% vs. 10%, nausea 17% vs. 10% (Vichinsky, et. al., NEJM 2019; **stopping suddenly can be catastrophic; especially a risk when hospitalized, given insurance constraints (Nagalapuram & Kanter, Am J Heme, 2022).**

Symptom Relief in SCD, mostly SCA

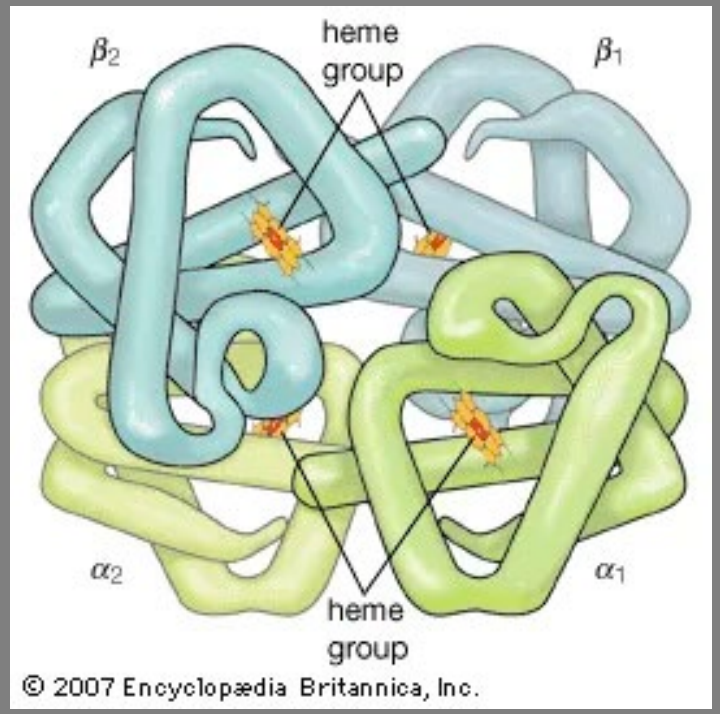


Adapted from: Zaidi et.al.,Contemp Clin Trials, 2021

Current Therapeutics in SCD

Treatment	How it works	How it is given	What it costs	Tested in variant disease?
HYDROXYUREA	Increases HbF Decreases inflammation Increases MCV	Oral	$	Limited, but possible benefit
L-Glutamine (Endari)	?Anti-oxidant	Oral	$$	No, theoretically useful
Crizanlizumab (Advakeo)	Anti-adhesive (P-selectin)	IV (Monthly)	$$$	Yes
Voxelotor (Oxbryta)	Increase Hb affinity	Oral	$$$	No

• 3. Increasing Hb through inhibition of polymerization



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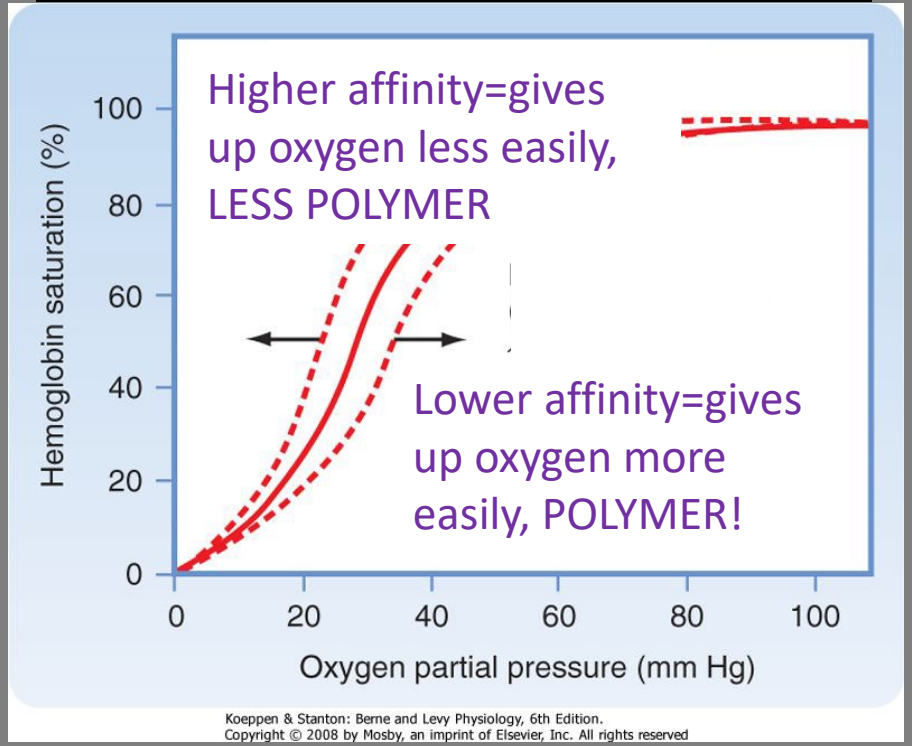


Adapted from MITCH WEISS & https://www.britannica.com/science/hemoglobin & Bernard and Levy Physiology, 6th Ed., 2008

• 3. Increasing Hb through inhibition of polymerization

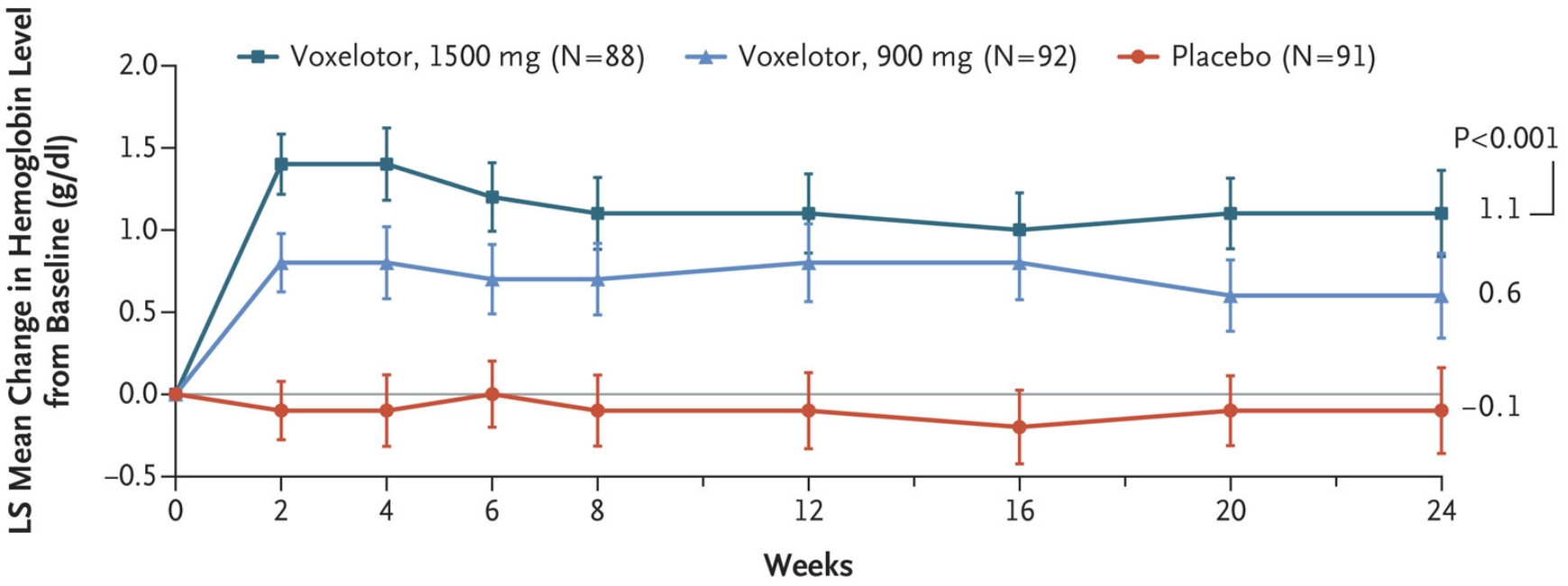
Voxelotor:

- Favors the R-state or OXY-Hb configuration
- Binds to 30% of Hb molecules in the sickle RBC
- Increases Hb in people with HbSS and a Hb>7g/dL

- A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. E. Vichinsky et. al., NEJM 2019.

Voxelotor Increases Total Hgb in people with SCD

B LS Mean Change in Hemoglobin Level from Baseline to Wk 24



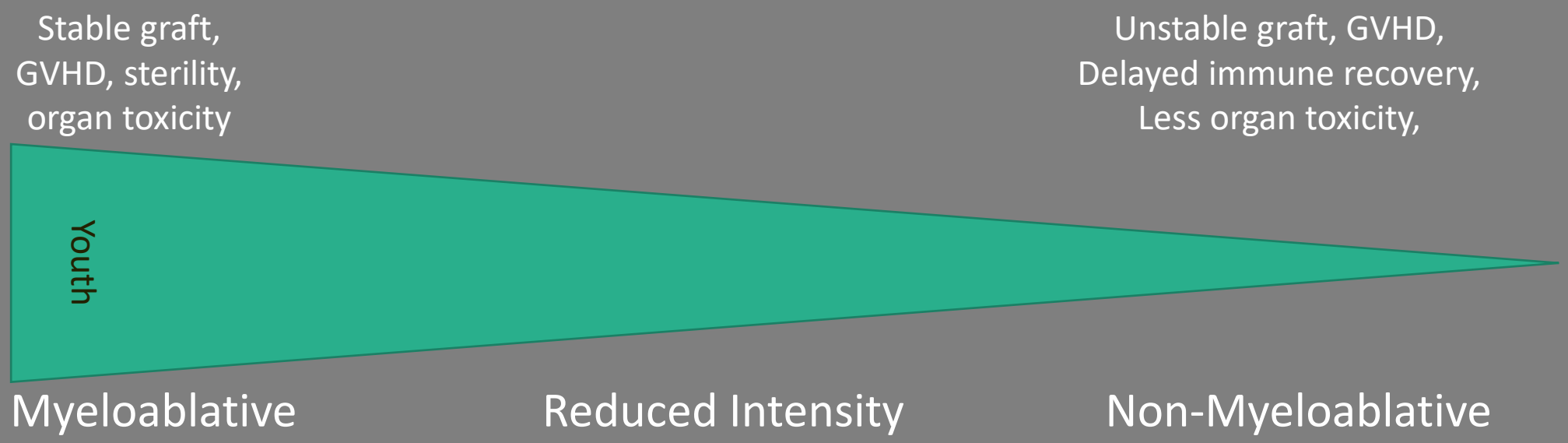
No. at Risk								
Voxelotor, 1500 mg	76	78	74	74	71	76	77	72
Voxelotor, 900 mg	82	78	69	74	76	77	73	78
Placebo	82	79	81	74	81	77	78	72

Vichinsky et. al., NEJM 2019.

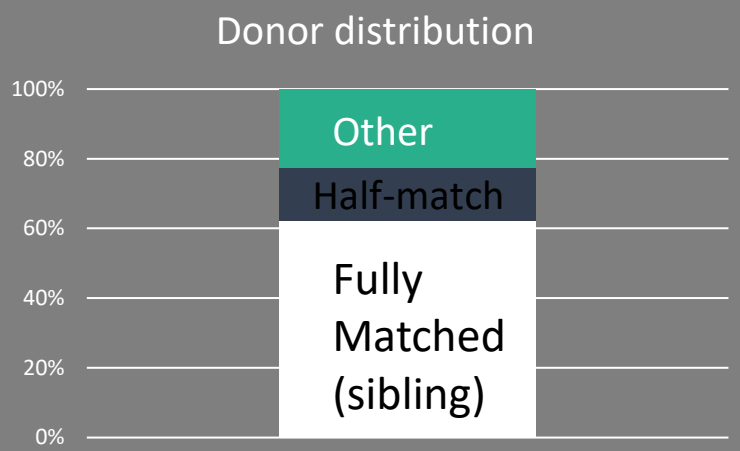
What about CURE?

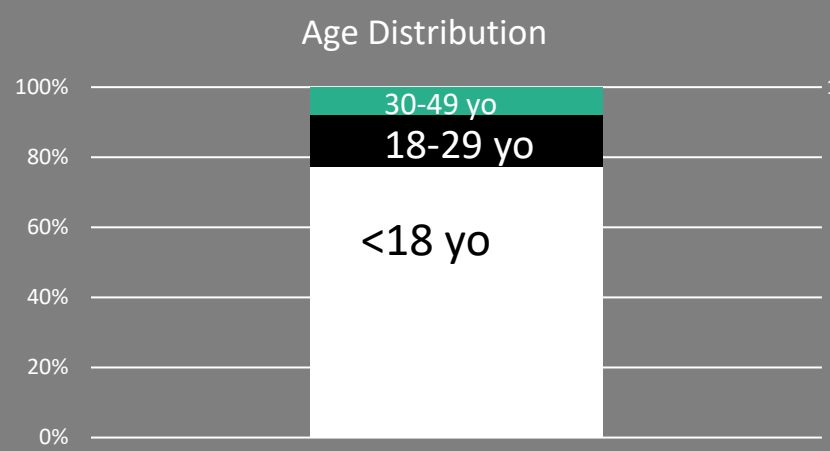
- ALLOGENEIC Transplant, or
- Gene Therapy

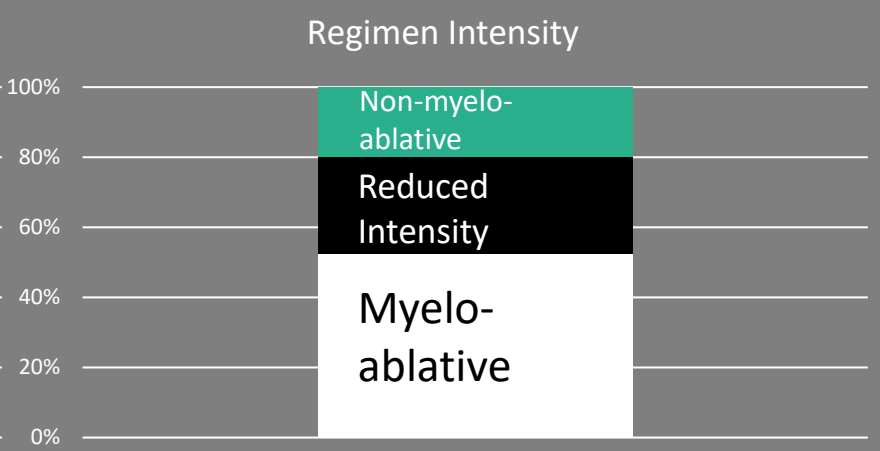
Allogeneic Transplant is a trade-off



So Far, most transplants are 1. Matched Sibling and 2. In Children

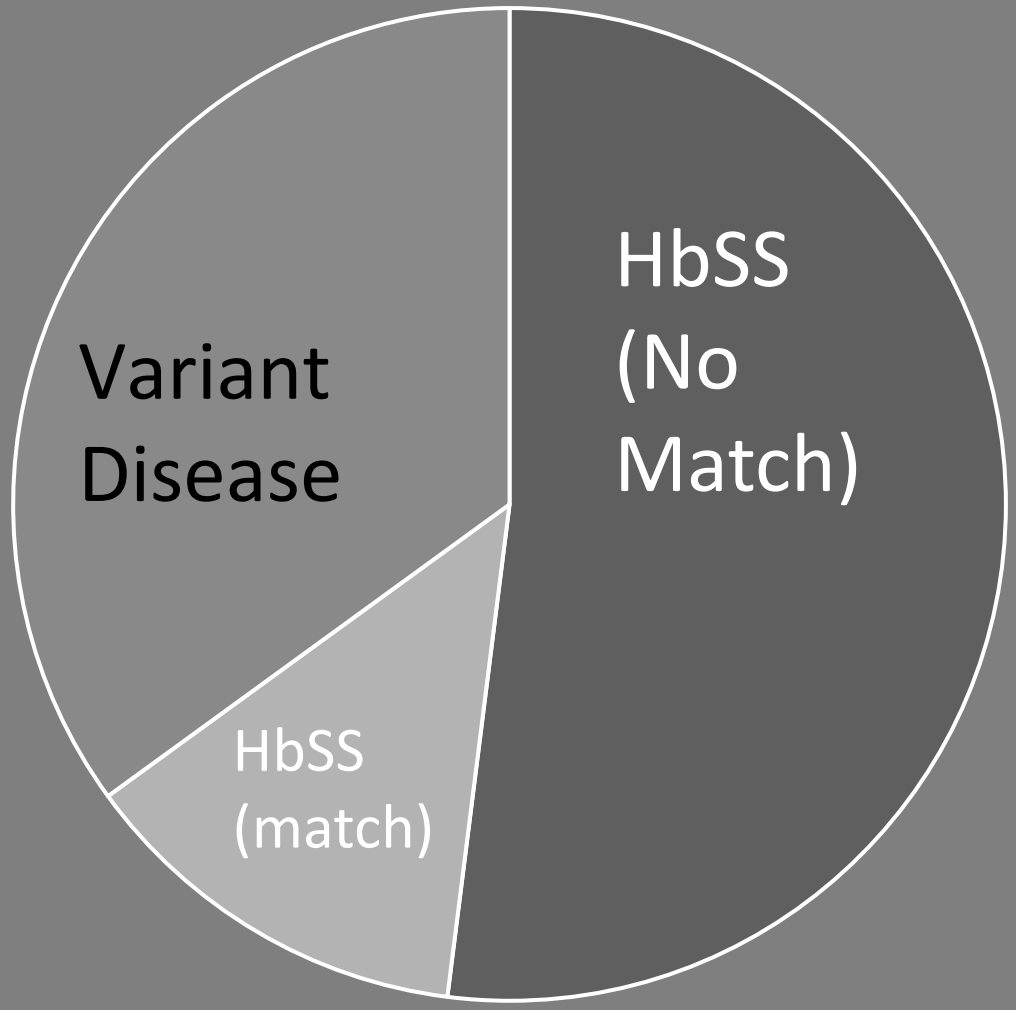




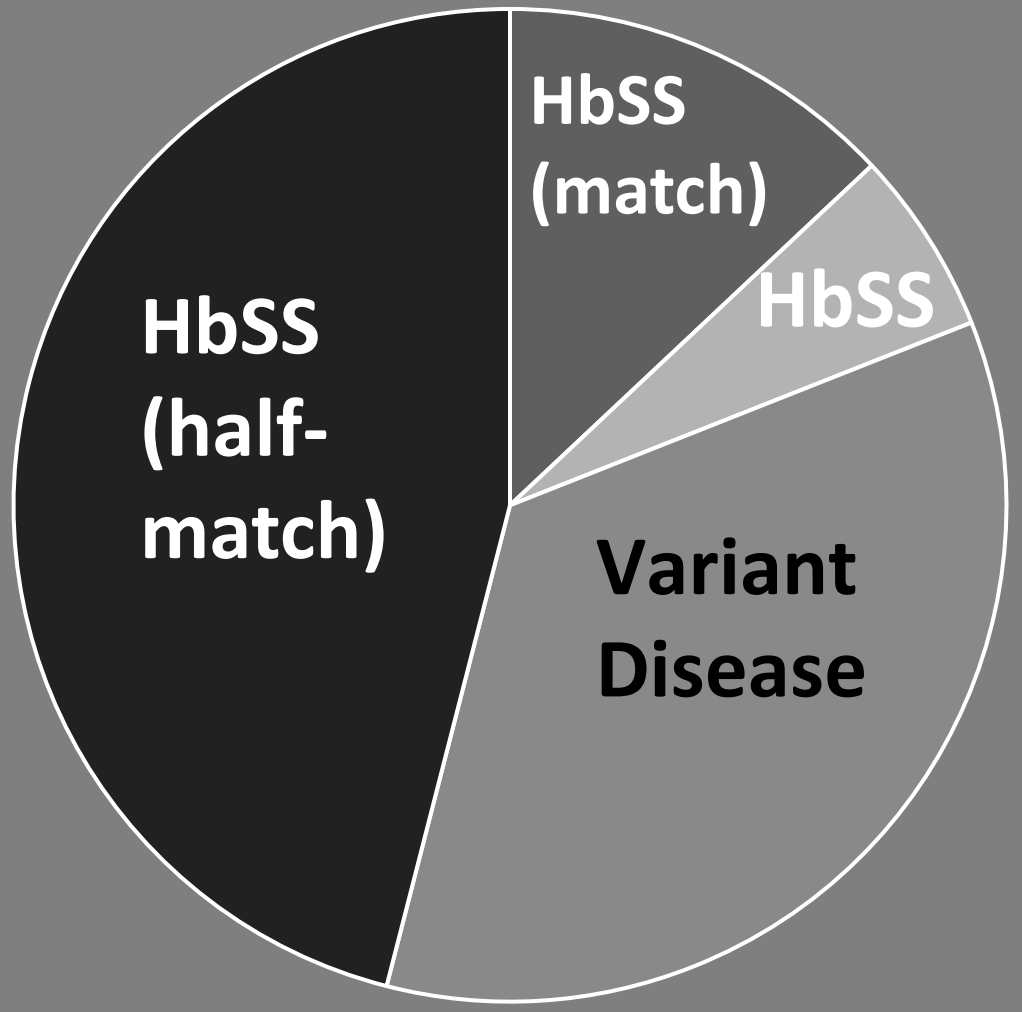


Eapen M, et al. The Lancet Vol 6, Nov 2019

Only 13/100 people with HbSS have a matched sibling

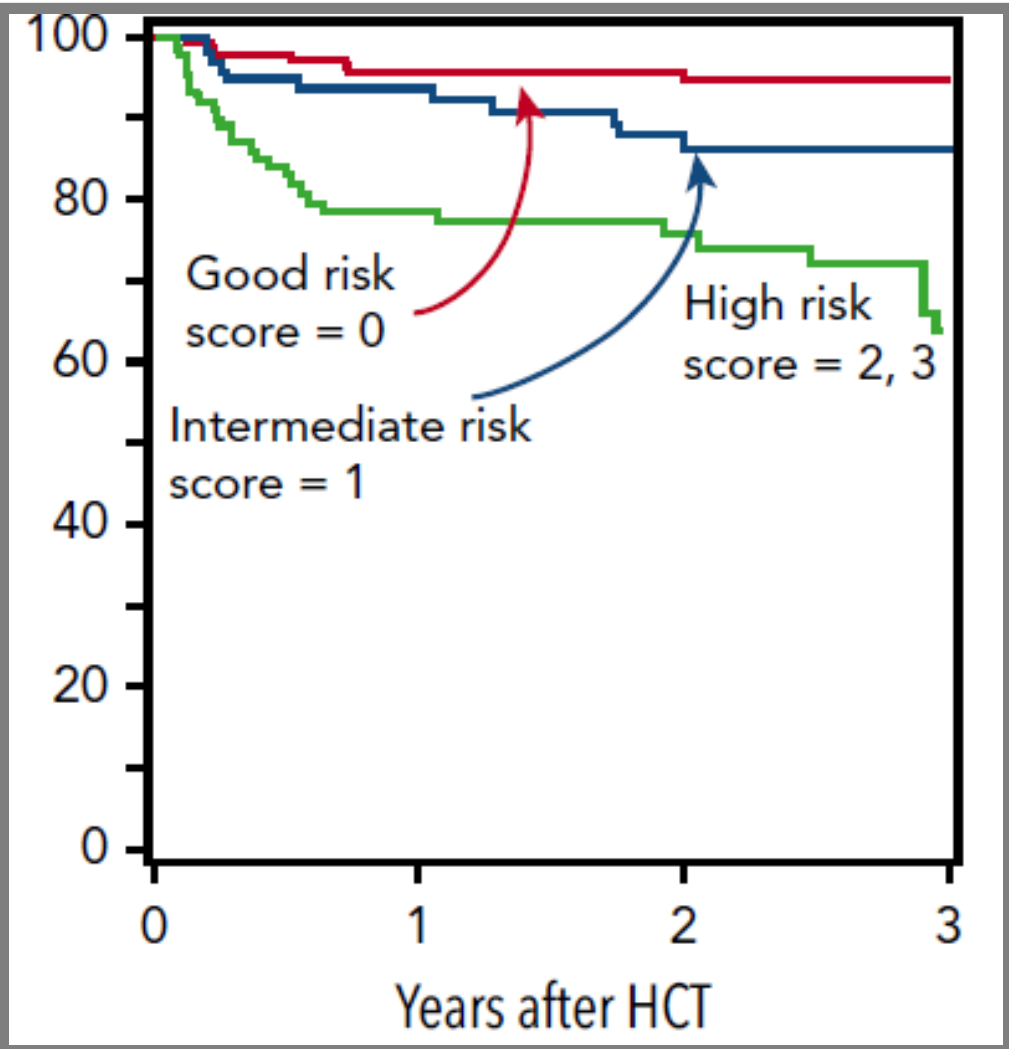


Most people with HbSS have a possible donor



Donor type and age matter

Age Score	Matched Sibling	Matched Unrelated	Mis-matched Related or unrelated (HAPLO)
<13 yo	0	1	2
0			
13+ yo	0	1	2
1			

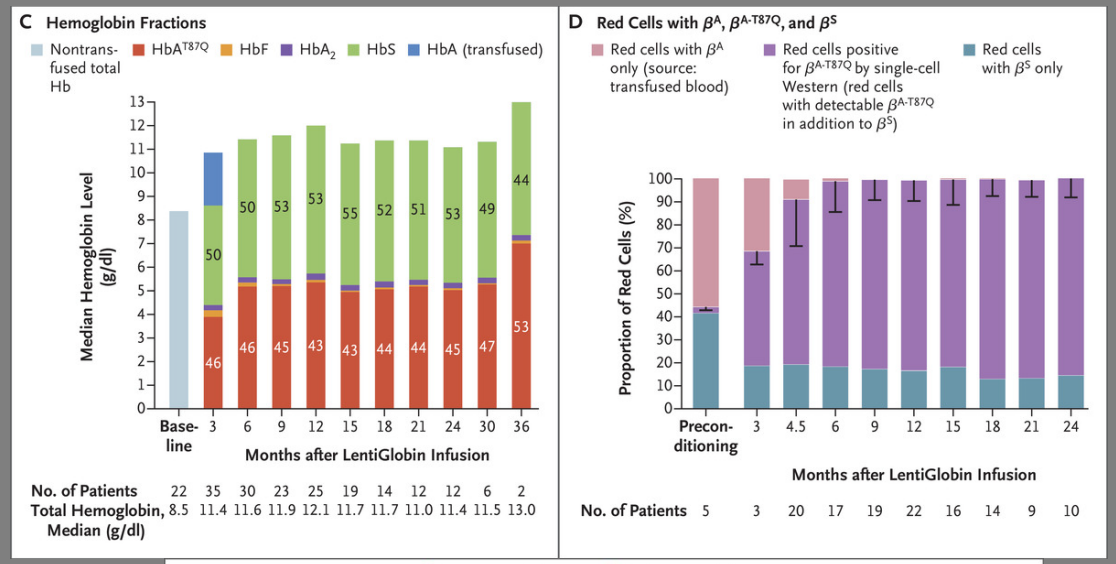


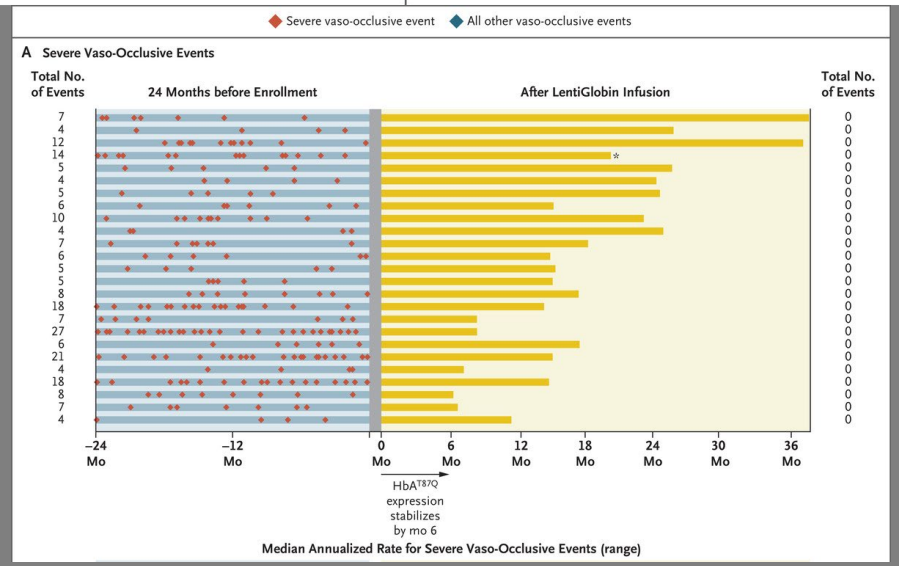
Brazauskas, R Blood, July 2020

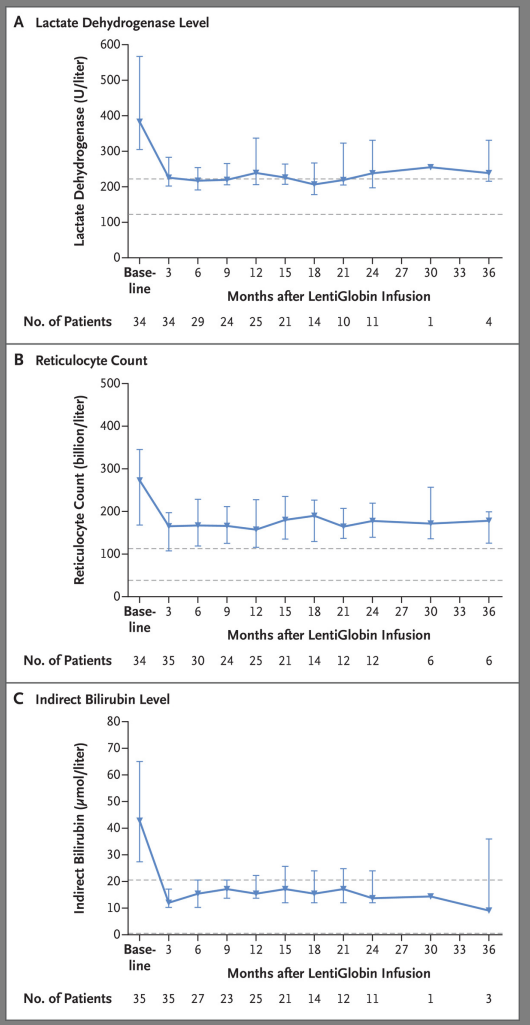
Caveats: Allogeneic transplant

- Fertility and CNS Bleed/seizures are risks
- 10% Mortality (underlying organ damage)
- Intolerant of tacrolimus (PRES)
- Uncommon MSD, estimated <25% (e.g. Hsieh, et. Al., 2013 NEJM)
- Rare MUD, <20% (Justus et.al., 2015)
- Haploidentical widespread, but 50% rejection using Reduced intensity
- Recruitment can be a challenge
- At the NIH, 3/76 recipients developed MDS/AML, all had rejected their transplant (Ghannam, et.al., Blood 2020)

Gene Therapy has an impact in SCD







J Kanter et al. N Engl J Med 2022;386:617-628.

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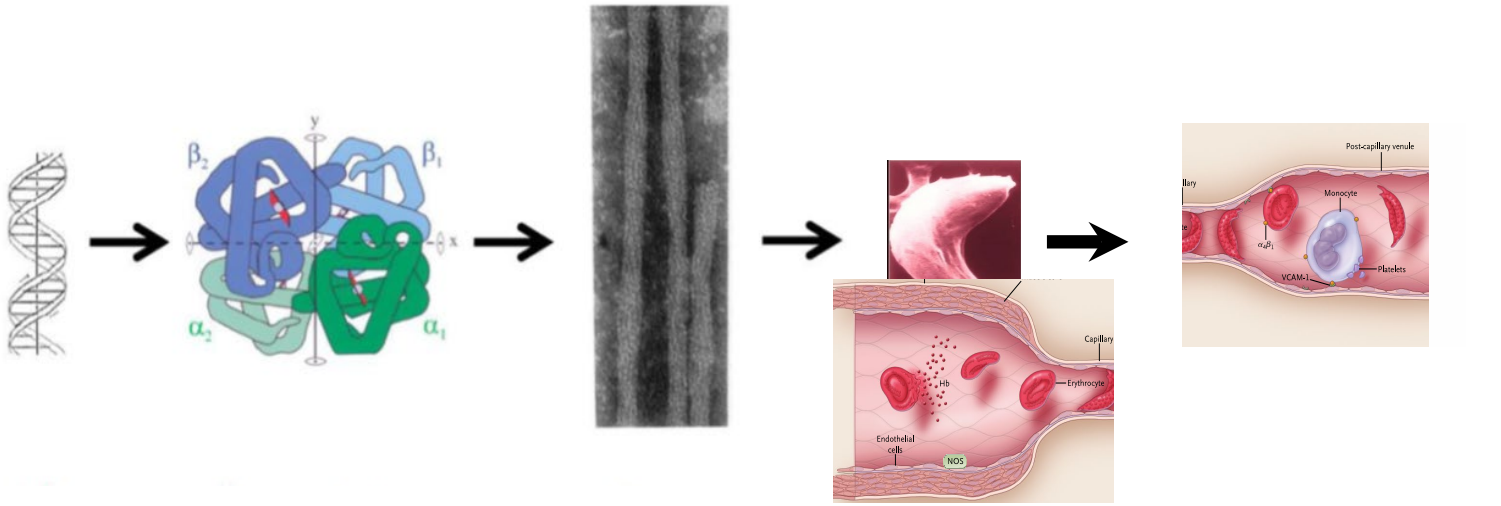
Caveats-Autologous (gene therapy)

- Stressed marrow
- Only Cincinnati (Dr. Malik) non-Myeloablative (fertility, cost, applicability to resource-constrained settings)
- Cost: e.g. 1.8 Million (Bluebird)
- Cannot use GCSF, must use plerixafor
- 2/47 recipients with SCD developed MDS/AML (vs. 0/63 2ith Beta Thalassemia treated with the same vector, Leonard & Tisdale, Mol Ther, 2021)

SCD: Balancing Act



DNA → Hemoglobin → Deoxy HbS polymer. → Hemolysis & & Vasculopathy → Abnormal adhesion

RISK TOLERANCE

Questions?