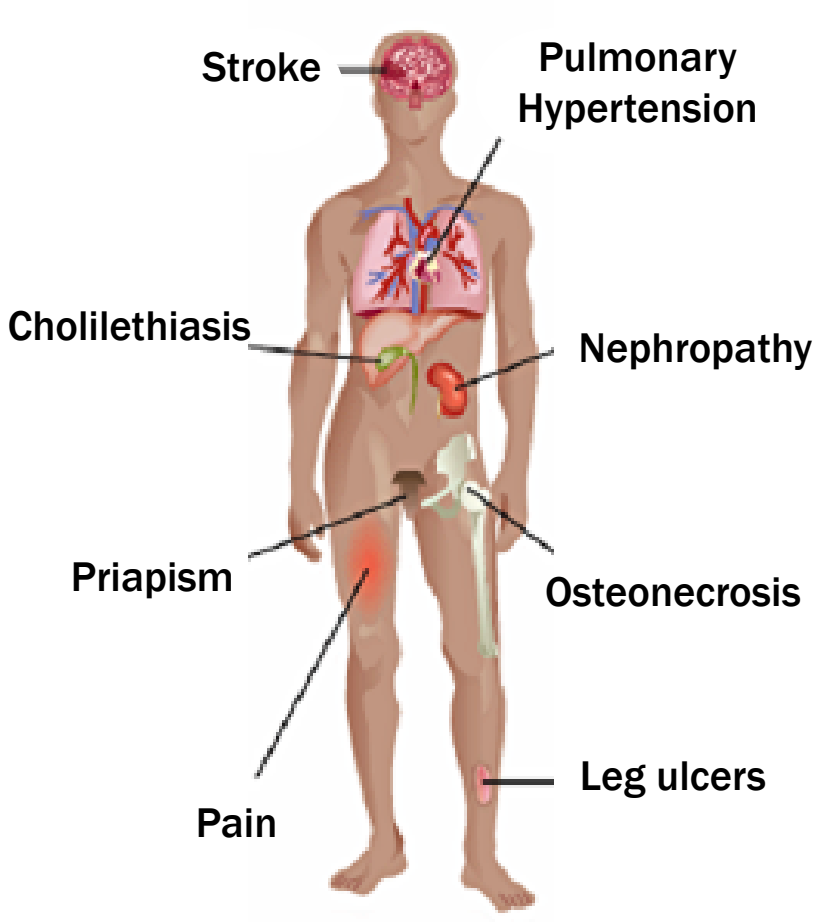
Mechanistic Basis of Hemolytic Anemia in Sickle Cell Disease

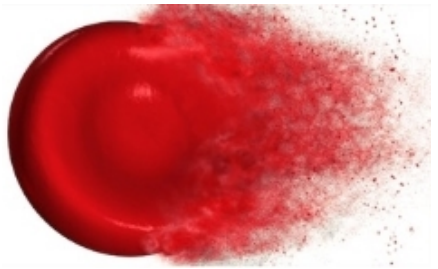
Narla Mohandas
New York Blood Center

Sickle cell disease clinical features

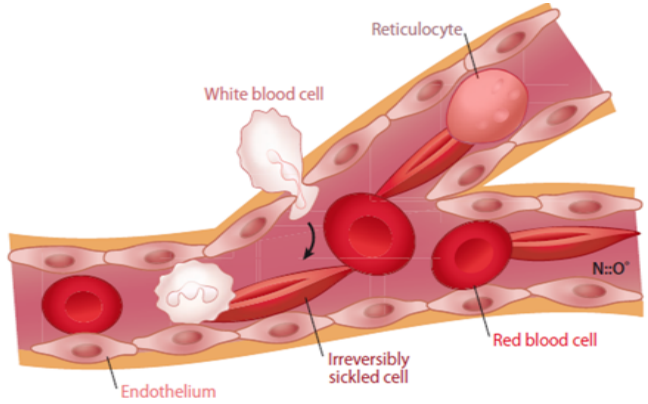


(Steinberg et al., 2008)

Hemolytic anemia

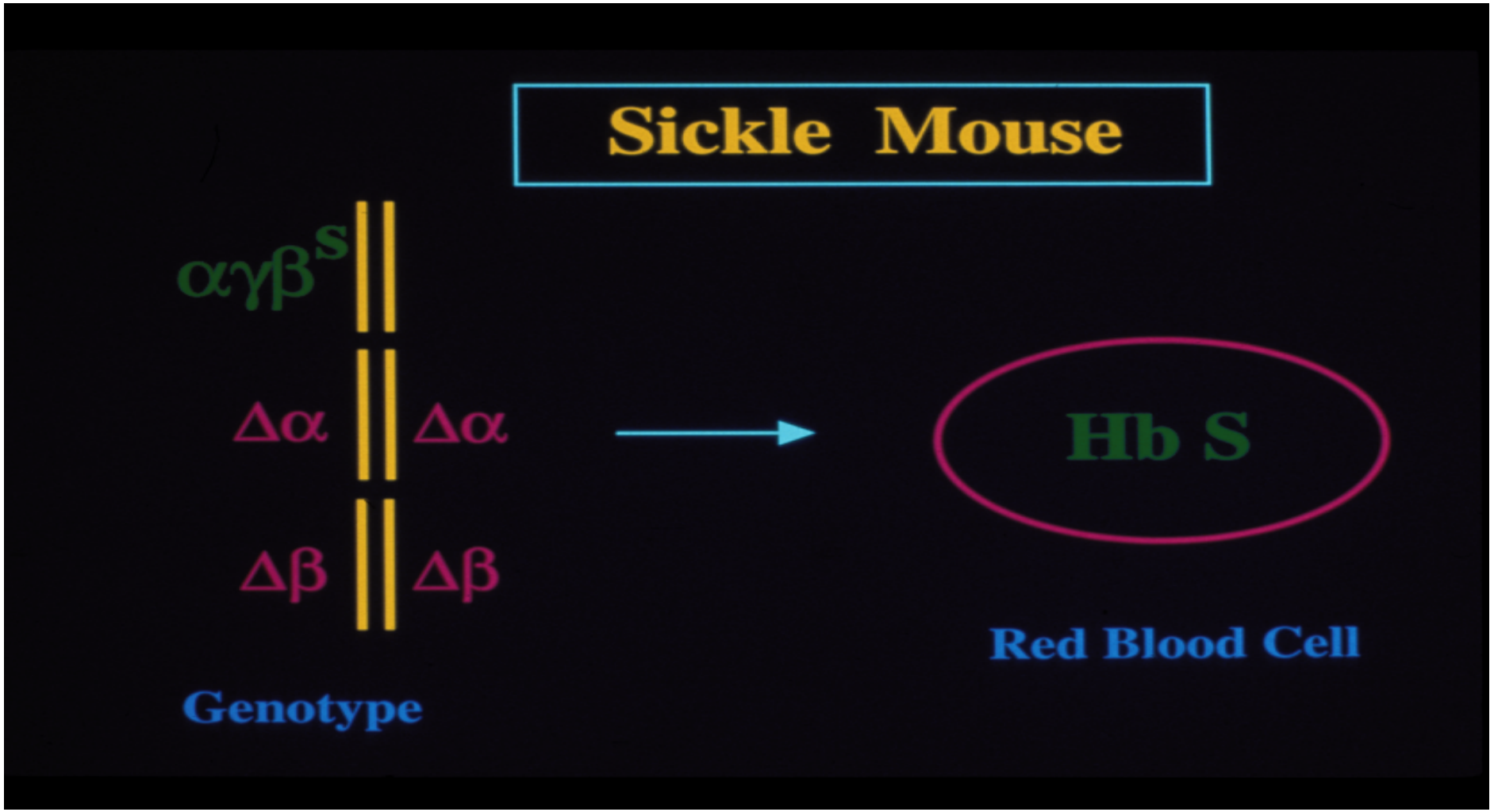


Vaso-occlusion

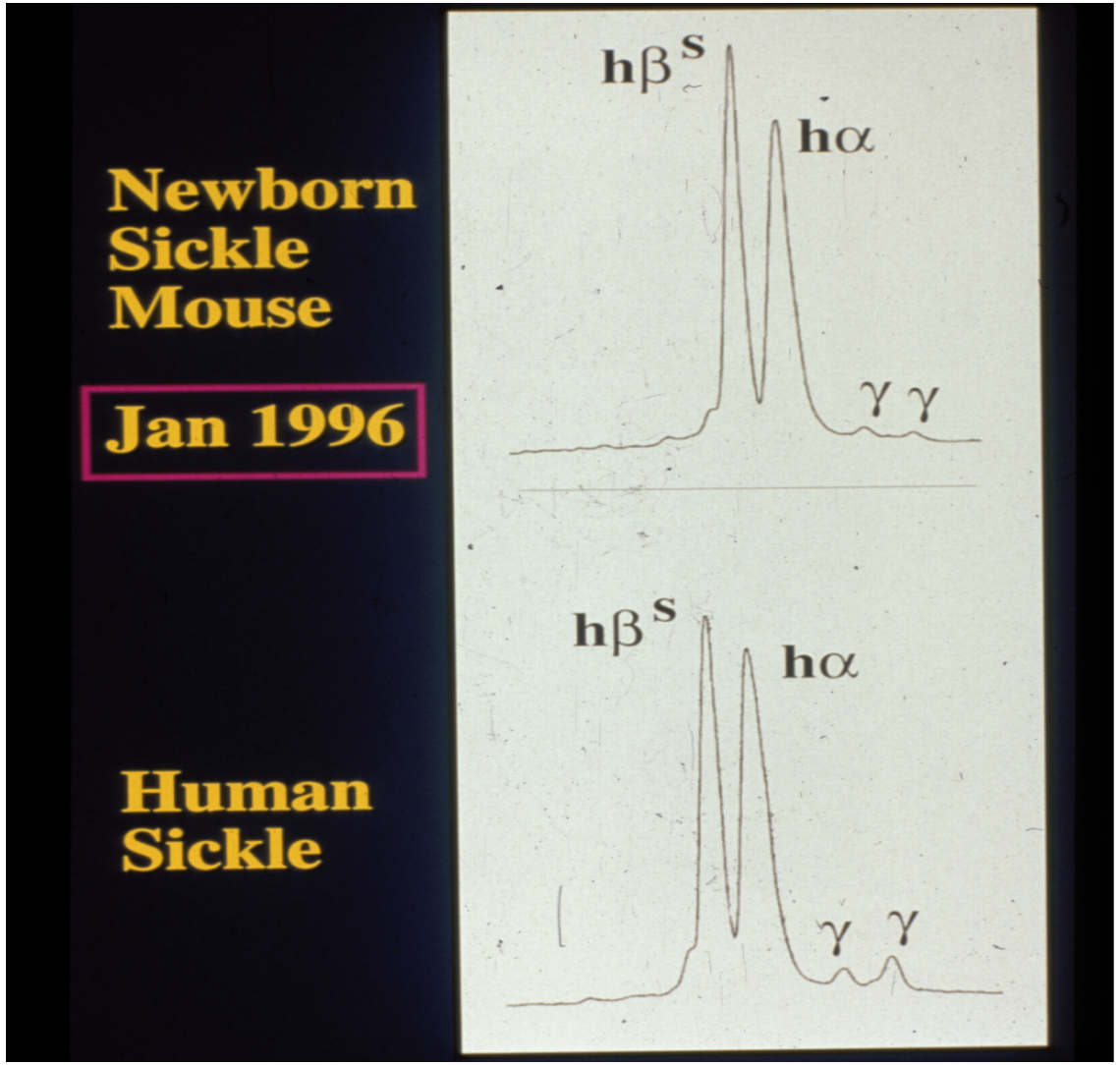


Mechanistic Basis of Hemolytic Anemia

- ***Extravascular hemolysis: Peripheral destruction of RBCs in the circulation leading to decreased red cell life span***
- ***Intravascular hemolysis***
- ***Ineffective erythropoiesis due to increased apoptosis of erythroblasts in the bone marrow***

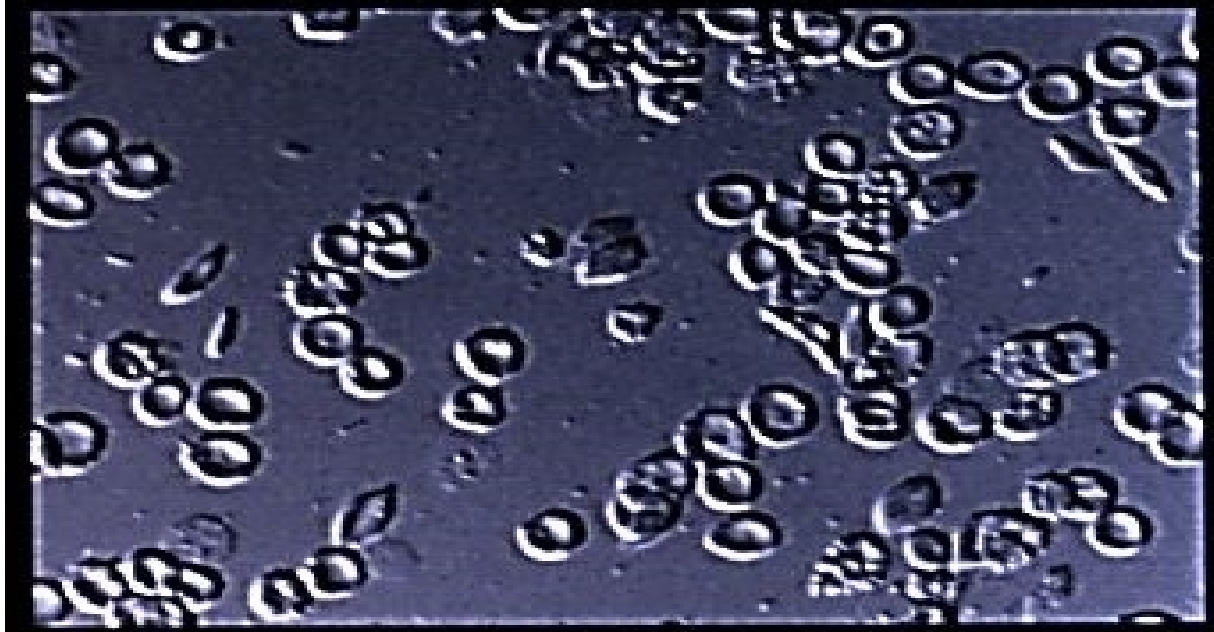


Paszty C et. Science 278: 876-878, 1997

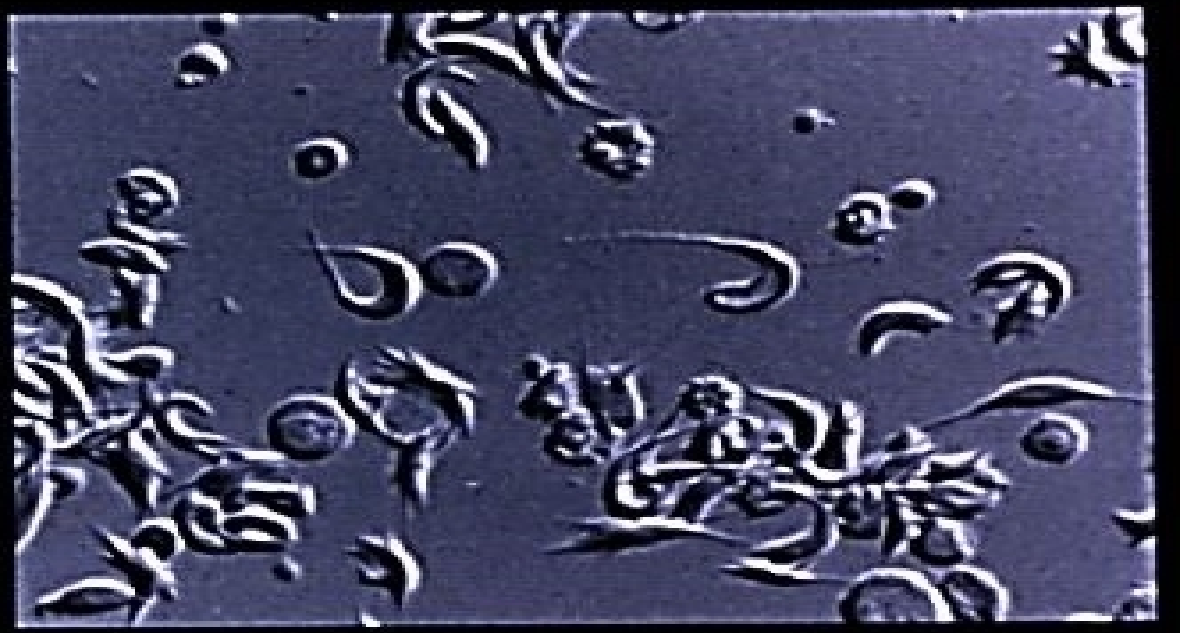


Paszty C et. Science 278: 876-878, 1997

Sickle Mouse RBCs



(oxygenated)

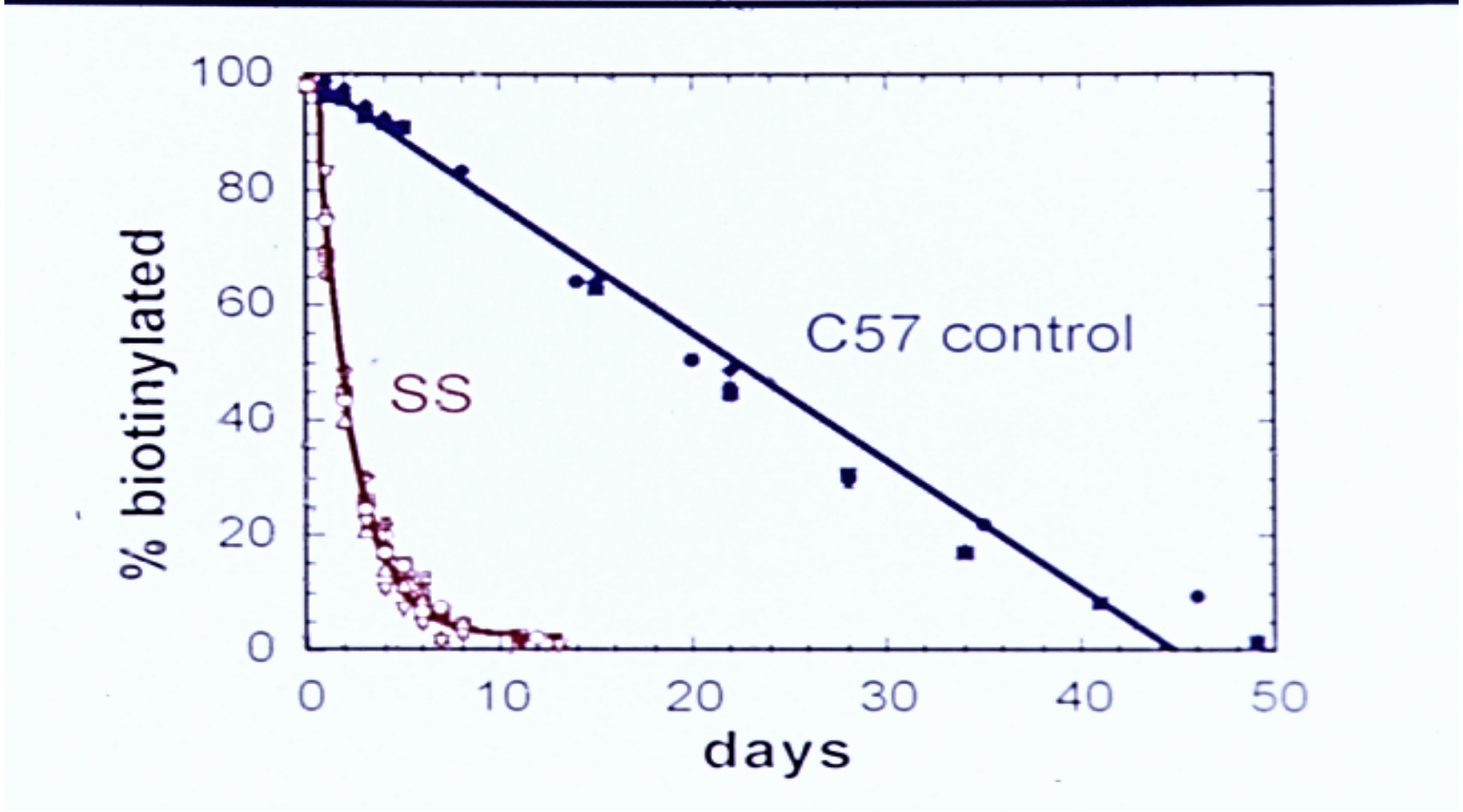


(de-oxygenated)

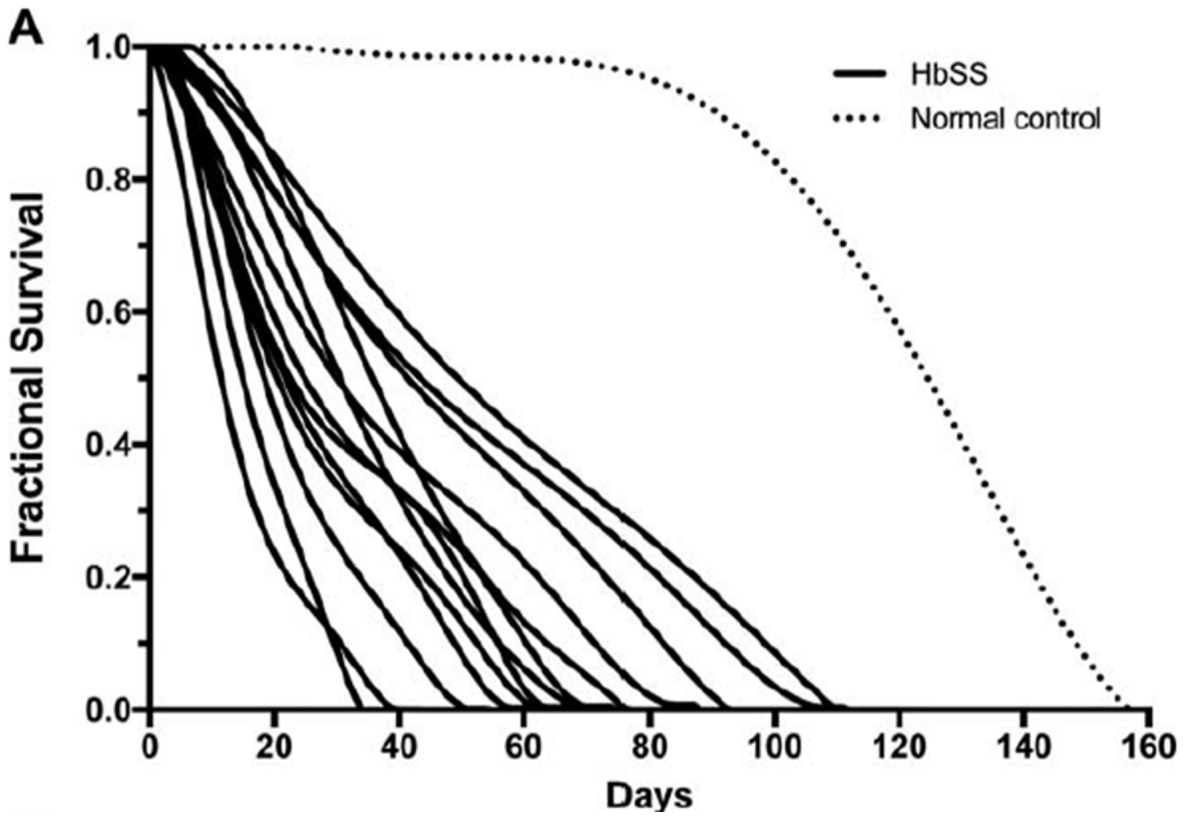
Hematologic data

		Hematocrit %	Reticulocyte %	Spleen % of body wt
Wild type	(n=6)	43.6 ±1.2	3.4 ±0.5	0.5
Sickle mouse	(n=6)	28.7 ±2.5	26.8 ±2.2	6.5

Reduced RBC survival in SS mice

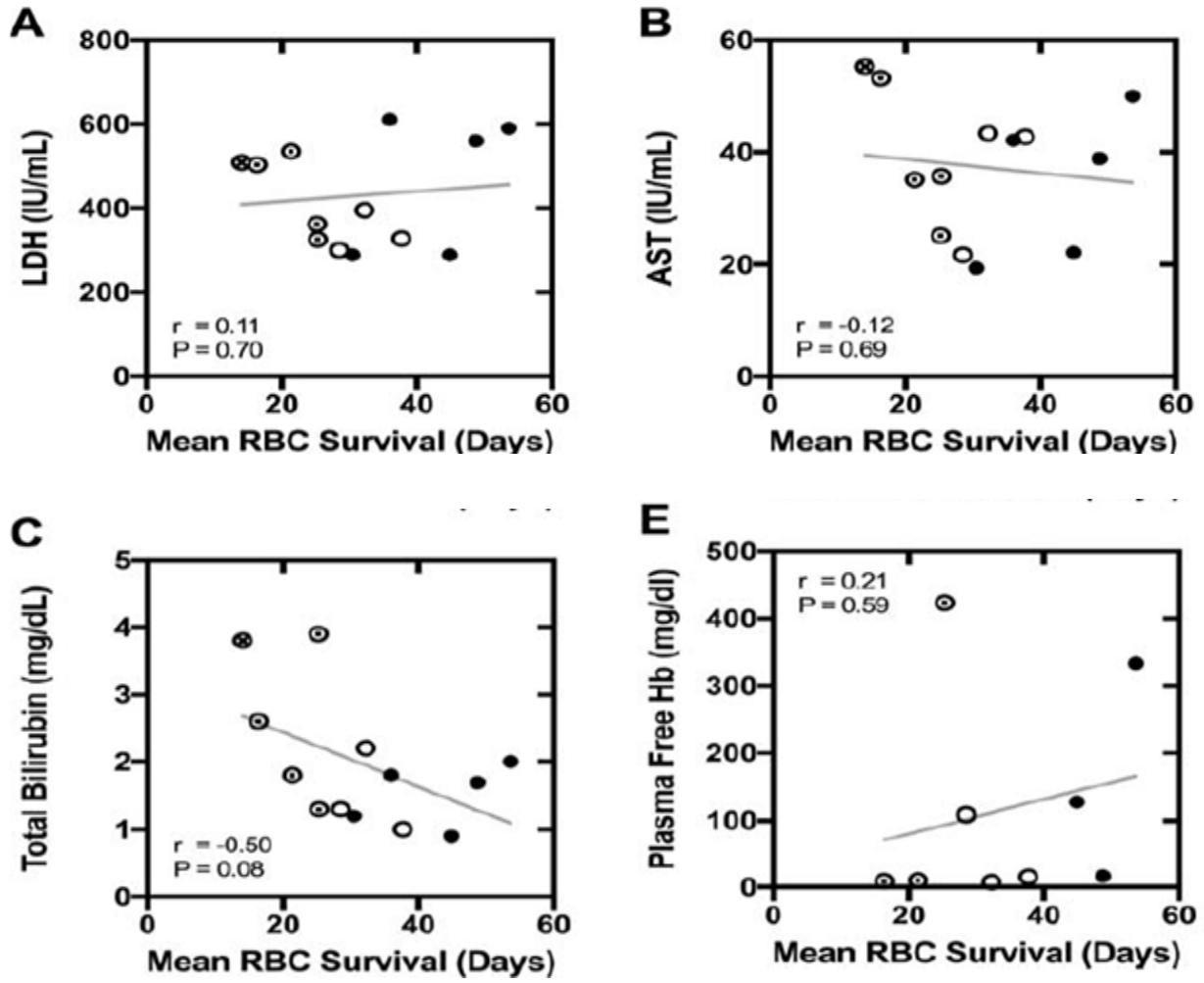


Marked Variability of Red Cell Life Span in SCD Patients



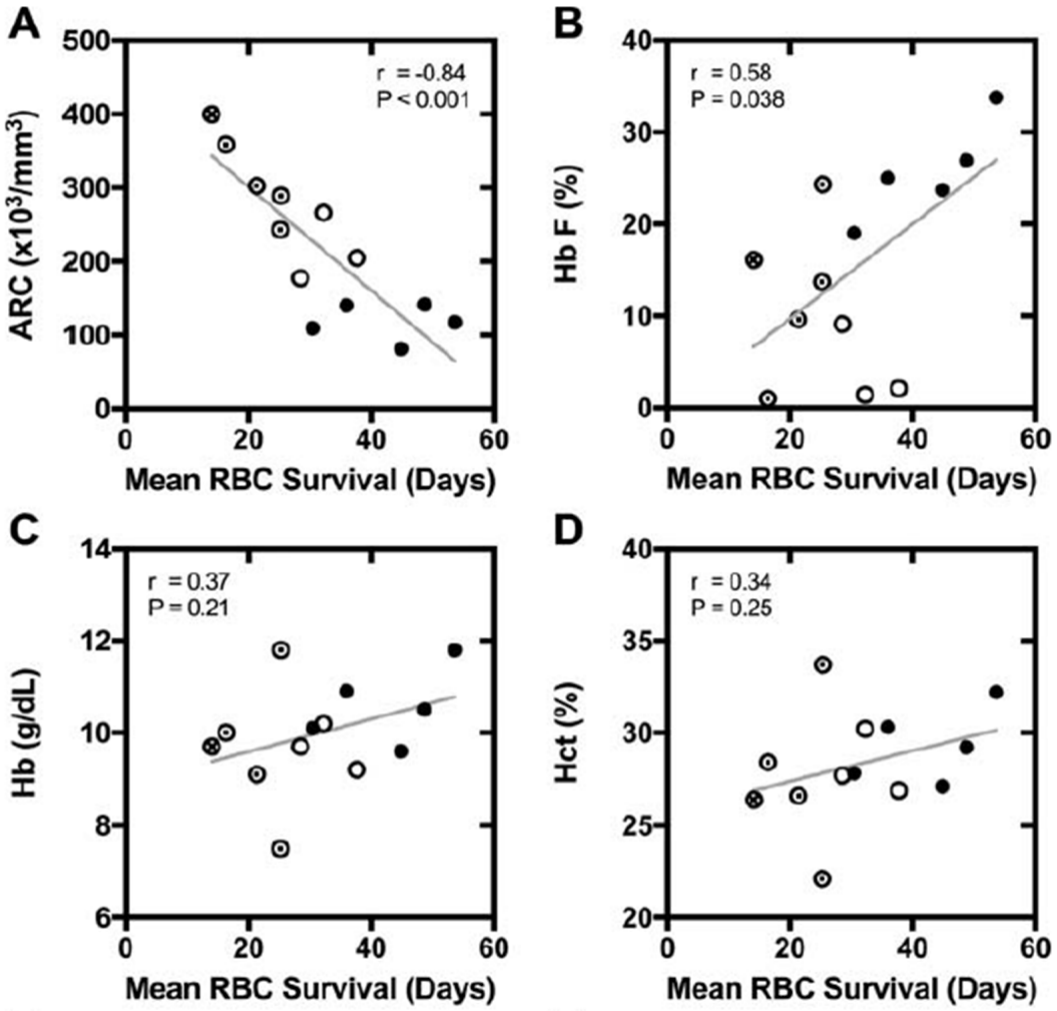
Quinn CT, et al. Am. J. Hematol. 2016

Conventional Markers of Hemolysis are not good predictors of Red Cell Lifespan



Quinn CT, et al. Am. J. Hematol. 2016

Absolute Reticulocyte Count is the best predictor of Red cell Lifespan



Quinn CT, et al. Am. J. Hematol. 2016

Extent of extravascular hemolysis is highly variable from individual to individual.

Higher Hb F levels and co-inheritance for alpha-thalassemia increase the circulatory life span of red cells.

Treatment with hydroxyurea by increasing HbF levels improves the circulatory life span of red cells and decreases the extent of extravascular hemolysis.

Phosphatidyl serine exposure is a determinant of red cell life span

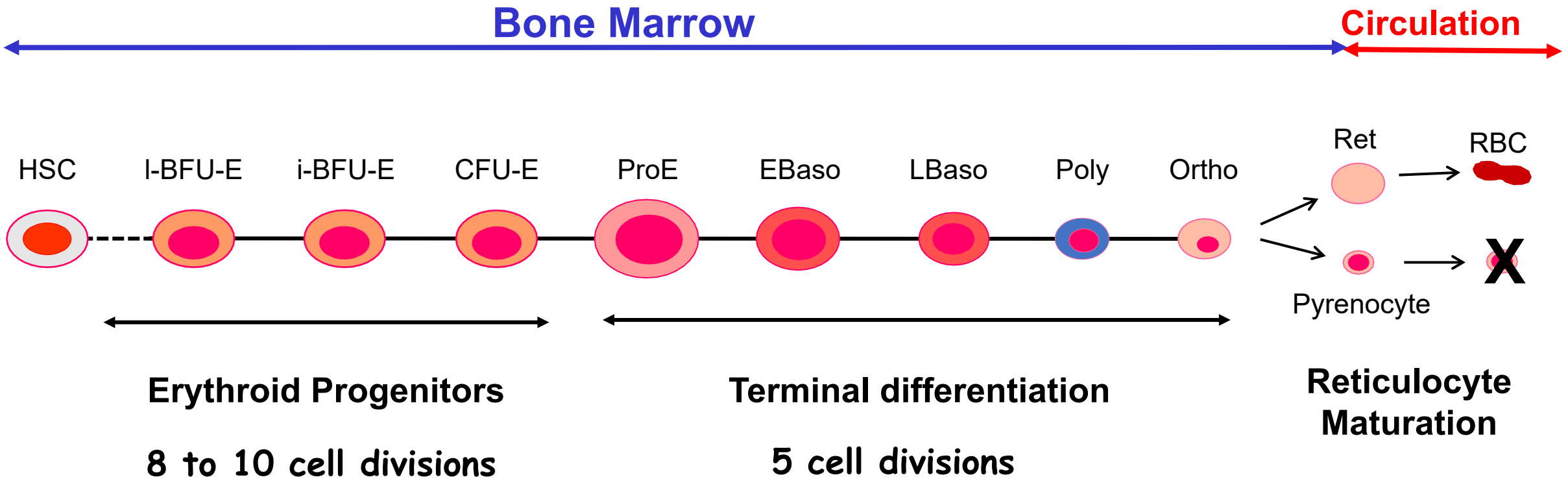
It is difficult to quantitate the extent of intravascular hemolysis in sickle cell disease

Ineffective Erythropoiesis in Sickle Cell Disease

Ineffective erythropoiesis due to increased apoptosis of erythroblasts in the bone marrow leading to decreased reticulocyte production has long been recognized to be a significant contributor to anemia in thalassemia.

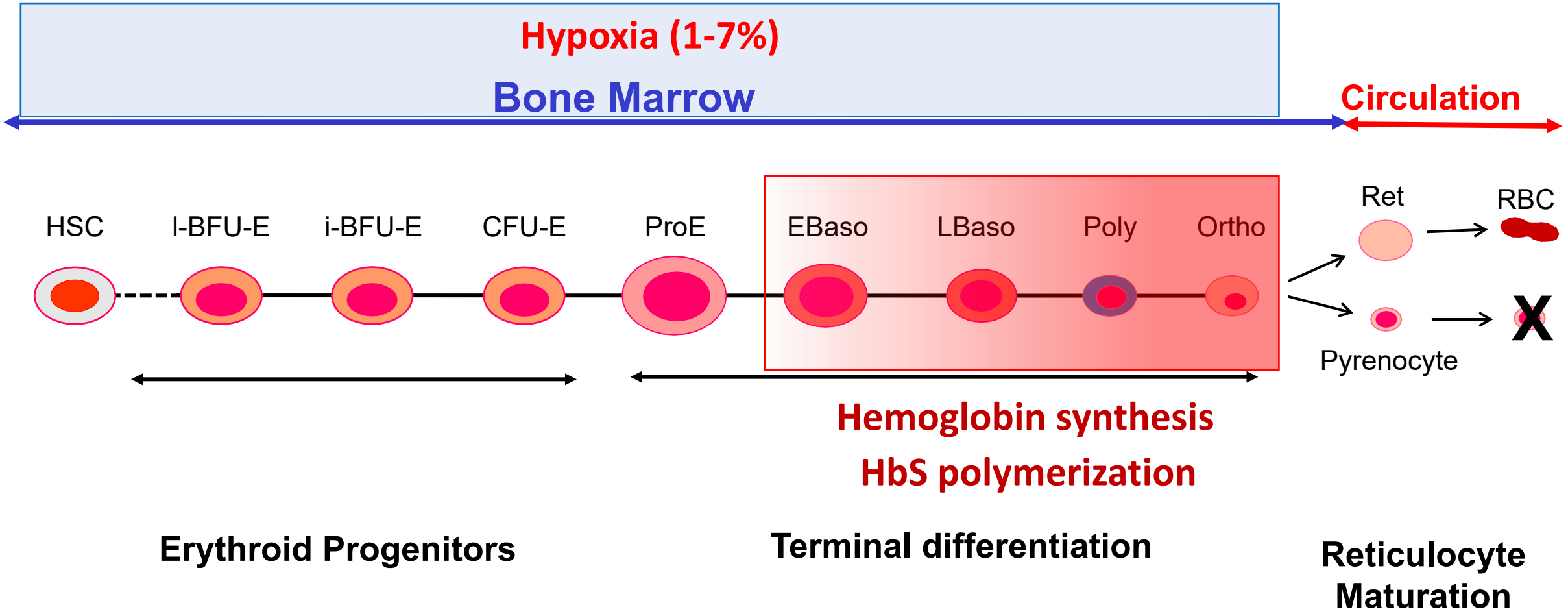
However, the contribution ineffective erythropoiesis to anemia in sickle cell disease has been less well studied.

Human erythropoiesis

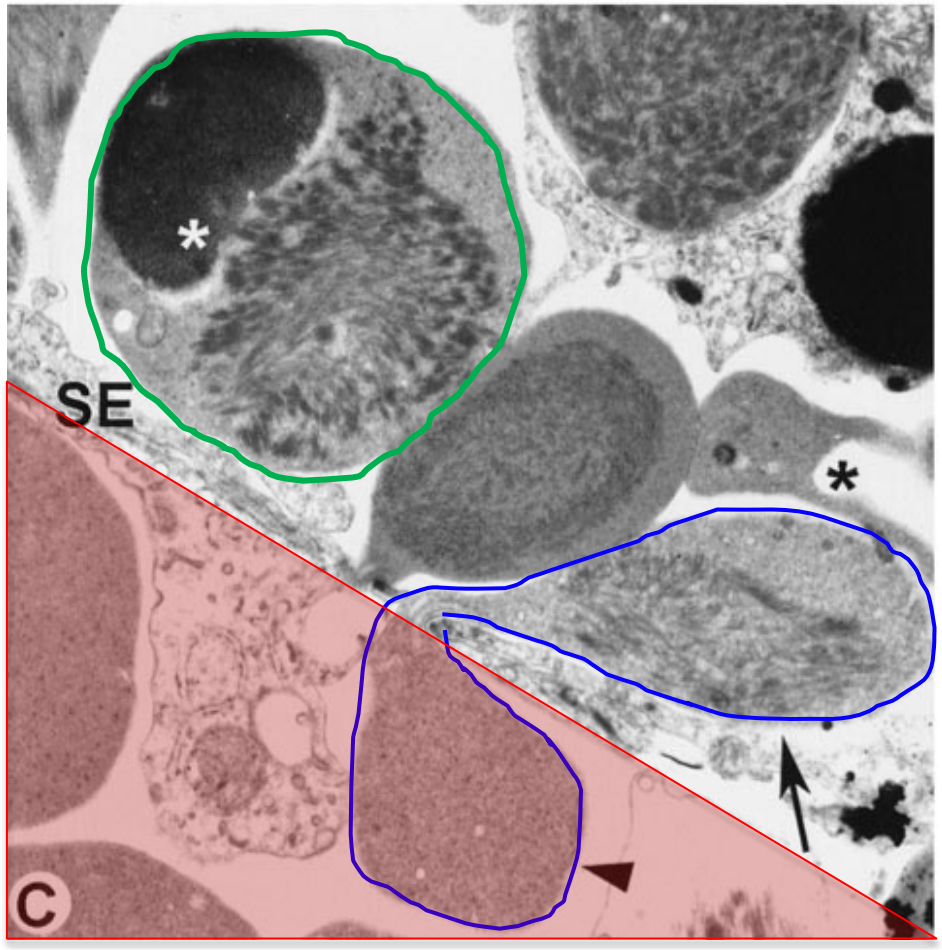


2.5 million reticulocytes are generated every second in the human bone marrow

Erythropoiesis in SCD marrow



Bone marrow of SAD mice

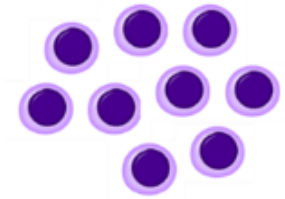


Blouin MJ, et al. Blood 1999

In vitro erythropoiesis

Patient and **control**

peripheral blood



CD34+ cells

Phase I (SCF, IL3, IL6)

Phase II Normoxia (Epo, SCF, IL3) 20% O_2

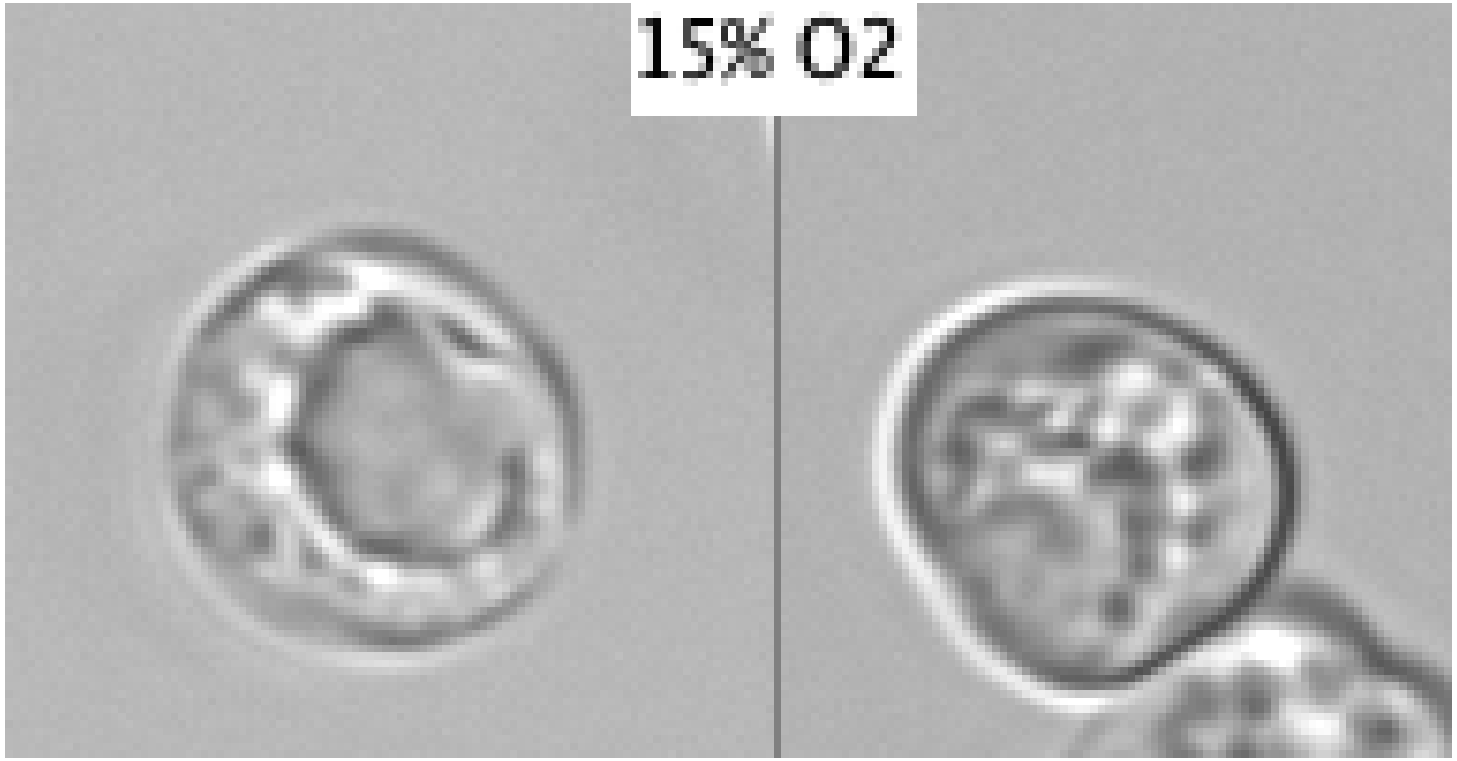
Hypoxia (Epo, SCF, IL3) 5% O_2

Erythropoietin

D3 **D5** **D7** **D9** **D11**

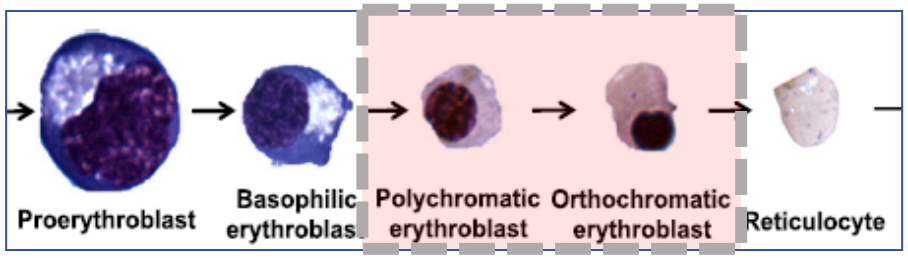
Analysis

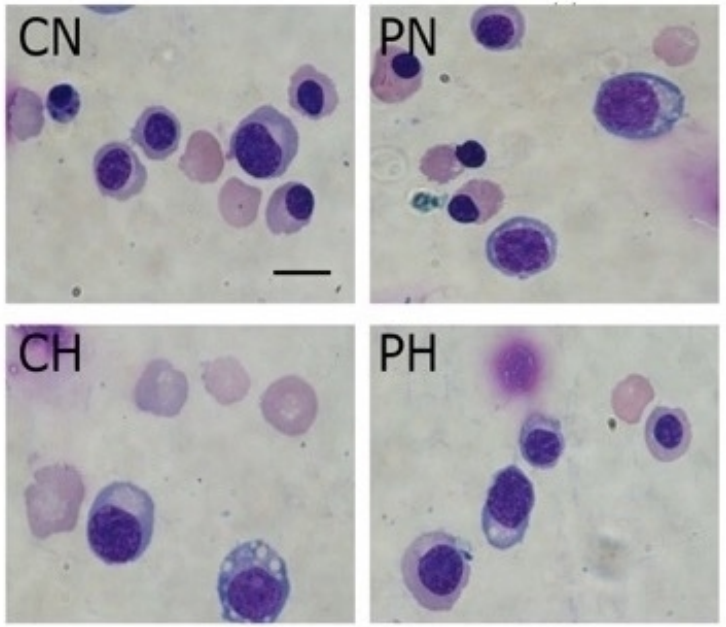
In vitro sickling of SS erythroblasts

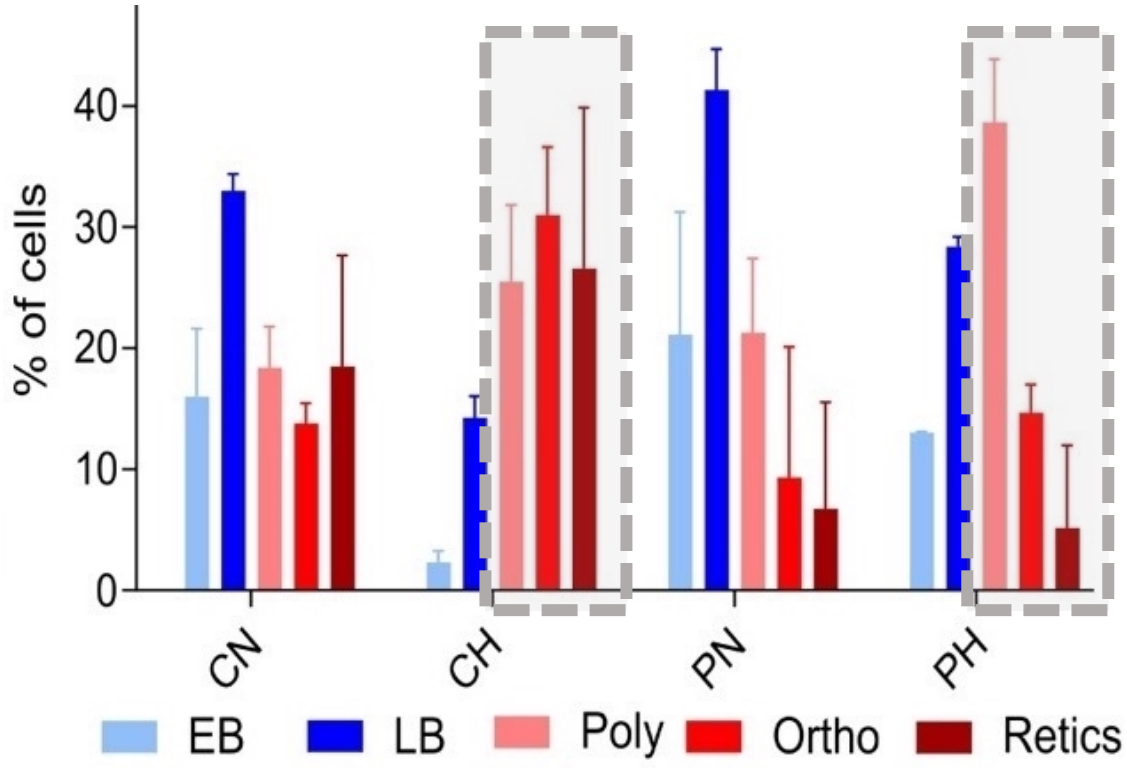


(El Hoss et al., Haematologica 2021)

Blockade at the polychromatic stage





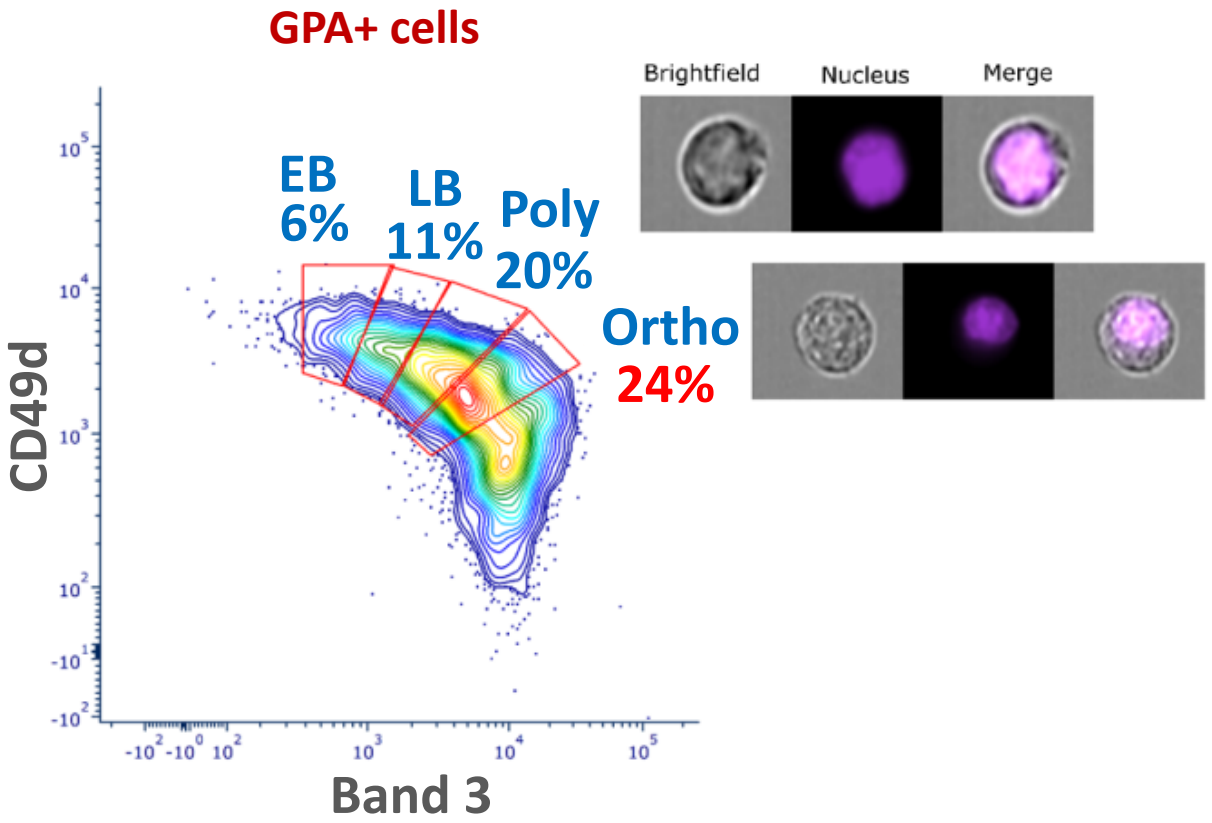


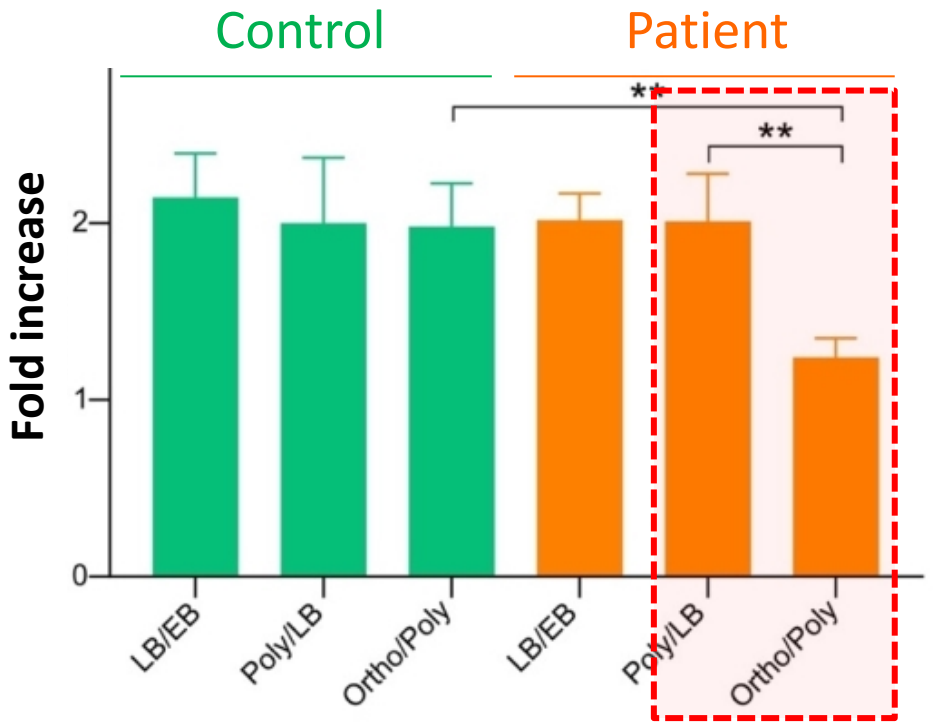
This decrease in proliferation is due to apoptosis

El Hoss et al., Haematologica 2021

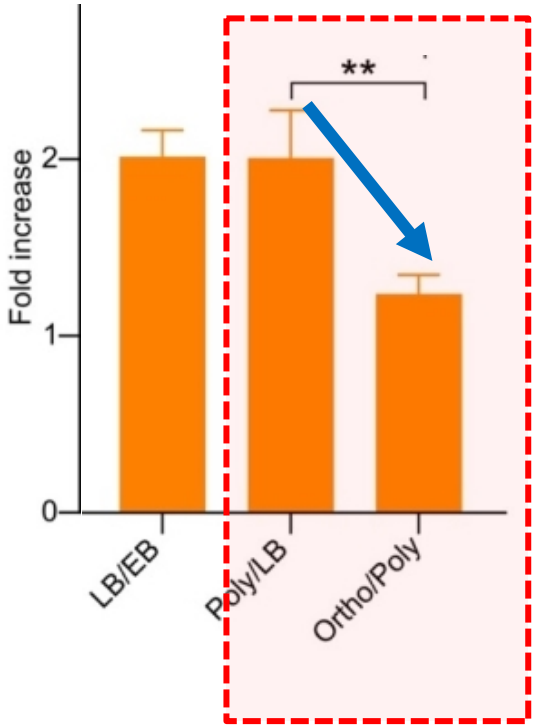
Terminal erythroid differentiation in vivo

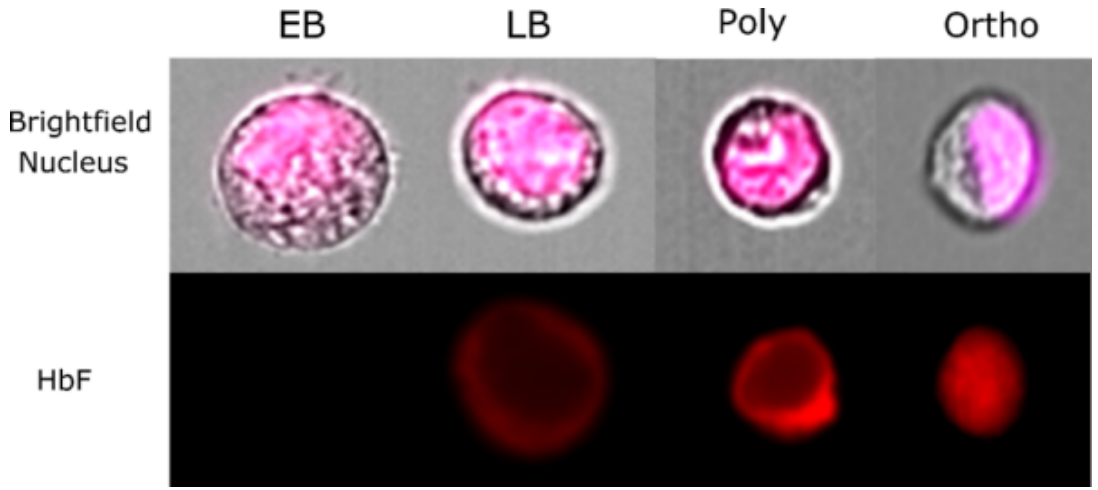
SCD bone marrow

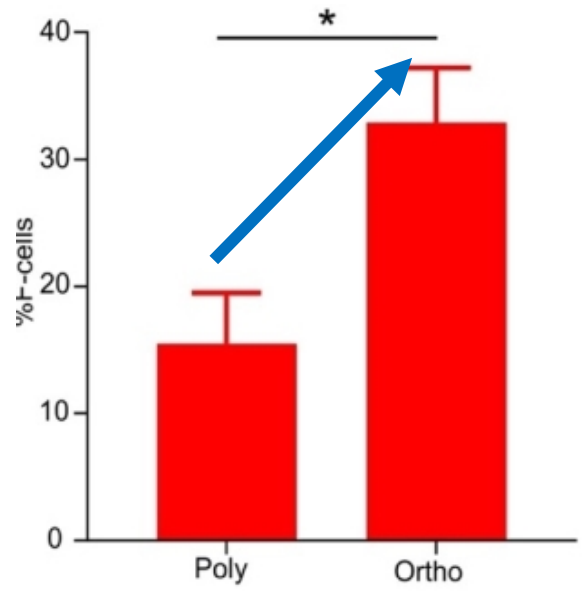




F-cells in SCD bone marrow in vivo







Positive selection of F-cells during erythroid differentiation *in vivo*

Ineffective erythropoiesis is a feature of sickle cell disease.

Hemoglobin polymerization and sickling of polychromatic erythroblasts in the hypoxic bone marrow environment leads to apoptosis.

Increased HbF levels by reducing the extent of sickling of erythroblasts decreases ineffective erythropoiesis.

Treatment with hydroxyurea by increasing HbF levels could lead to more effective erythropoiesis.

Summary

- *Hemolytic anemia of sickle cell disease in multifactorial with contributions from extravascular hemolysis, intravascular hemolysis and ineffective erythropoiesis.*

- *Hypoxia induced sickling is a contributors to all three features of hemolysis.*

- *Reduced sickling due to induction of fetal hemoglobin or changing oxygen affinity by inhibiting sickling reduces severity of anemia.*

Current Scientific collaborators

NYBC : Red Cell Physiology lab
Hongxia Yan
Chris Hillyer

Feinstein Institute, NY
Lionel Blanc

Yale University
Patrick Gallagher

France
Wassim El Nemer
Emilie-Fleur Gautier
Marjorie Leduc
Patrick Mayeux
Lydie Da Costa
Olivier Hermine
Naomi Taylor
Sandrina Kinet

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