Cellular Therapies Targeting Fetal Hemoglobin in Sickle Cell Disease

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Disclosures

Consultant, advisory boards:

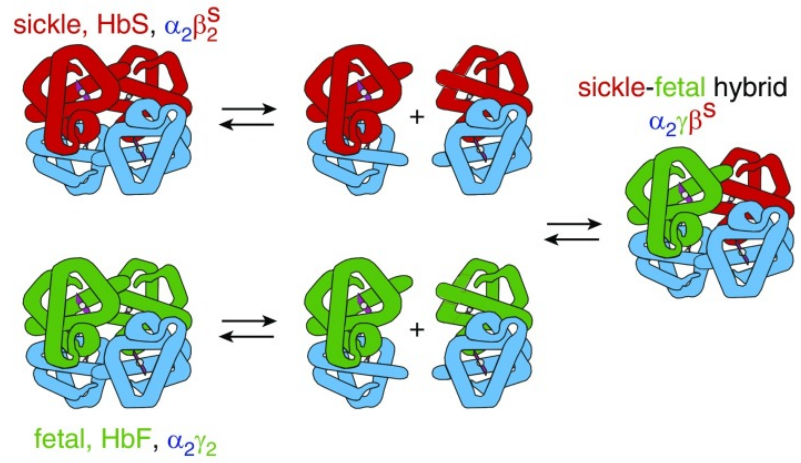
Vertex; Fulcrum; Alexion;

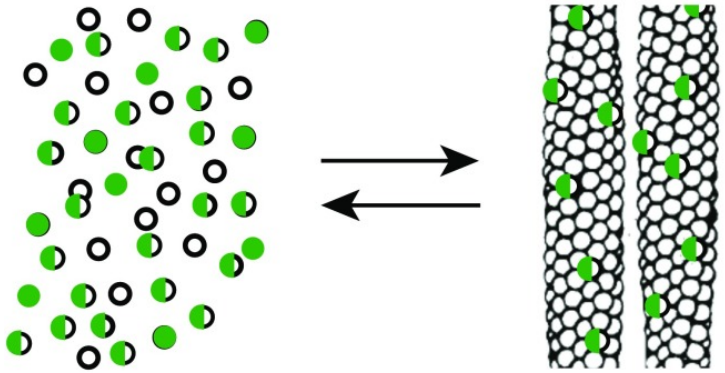
Astellas/Mitobridge

HbF

80% HbF at birth levels stabilize in SCD by 5-10 years

In adults, ~5% HbF in African SCD; ~16% in Arab-Indian haplotype SCD



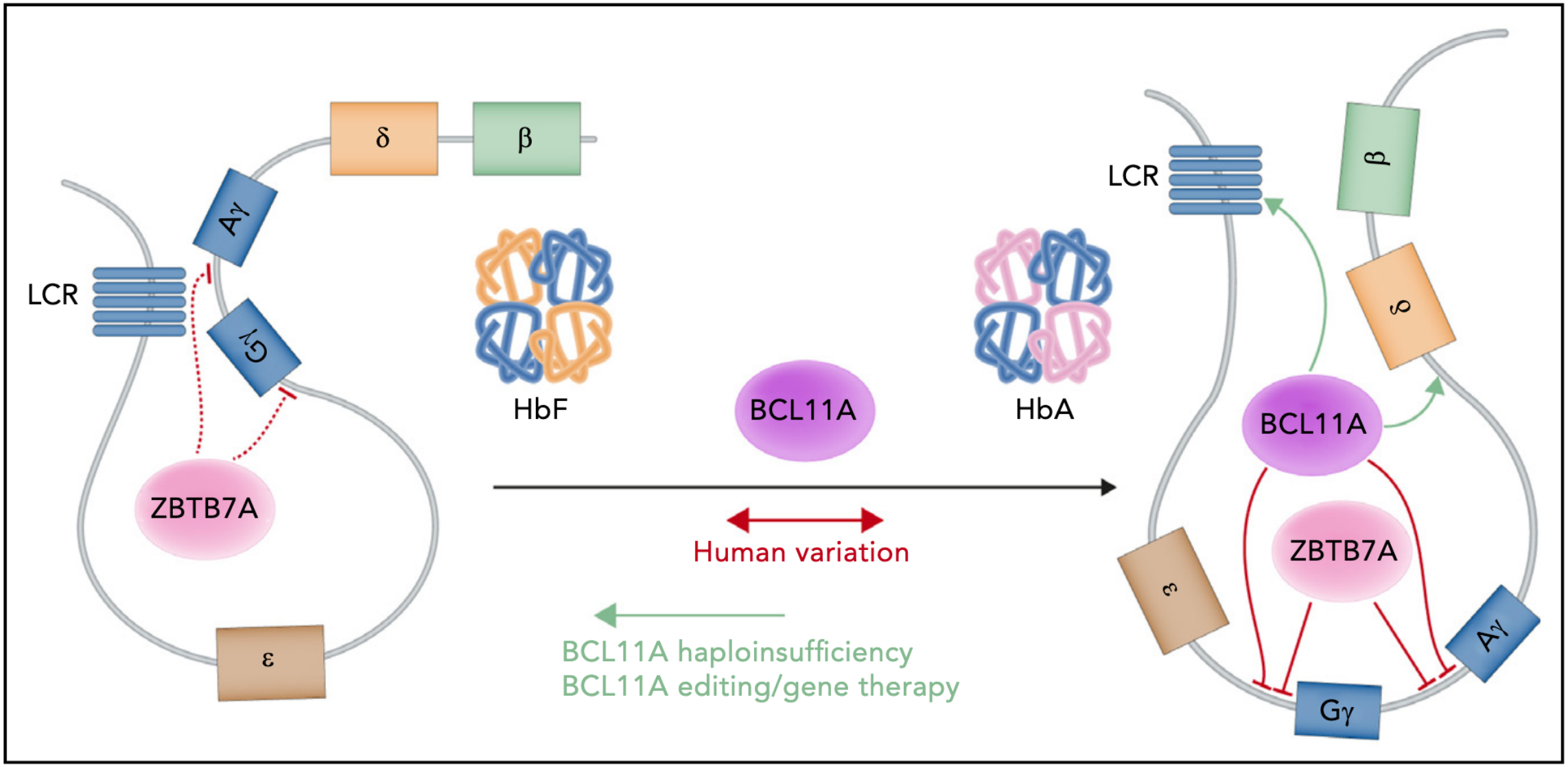


γ- differs from β-globin in ~39 amino acids; γ^{87Q} mainly responsible for the anti-polymerization effect of HbF

Both $\alpha_2\beta^S\gamma$ and $\alpha_2\gamma_2$, excluded from the HbS polymer

(Eaton & Bunn. Blood 2017)

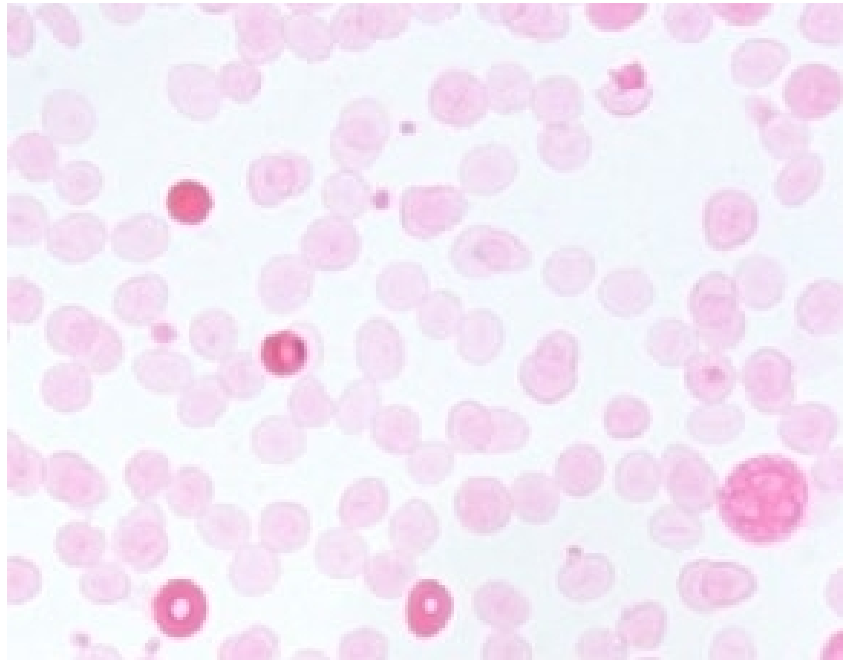
Hemoglobin switching



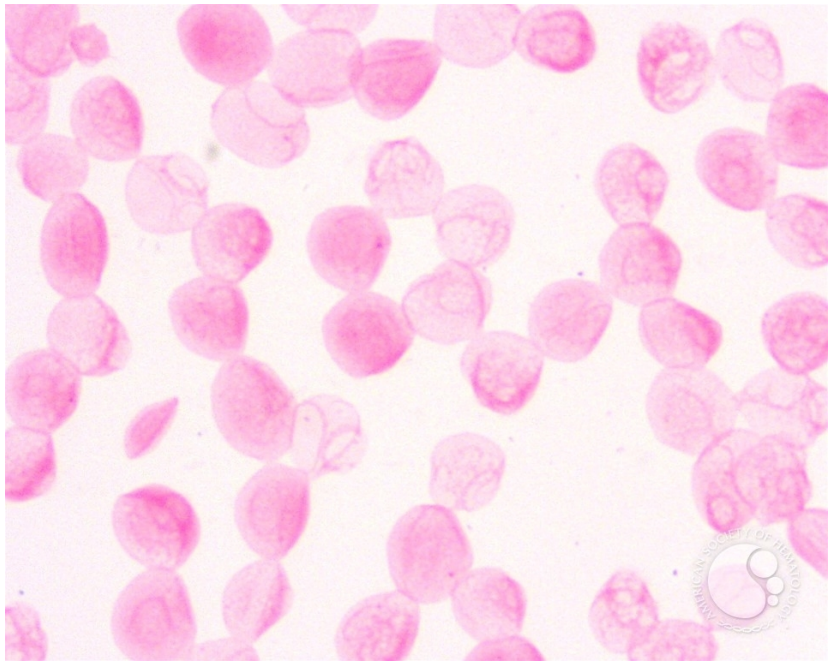
(Caulier & Sankaran, Blood, 2022)

Pancellular vs. heterocellular HbF: ? artifact of measurement and function of *HBG* expression

Heterocellular



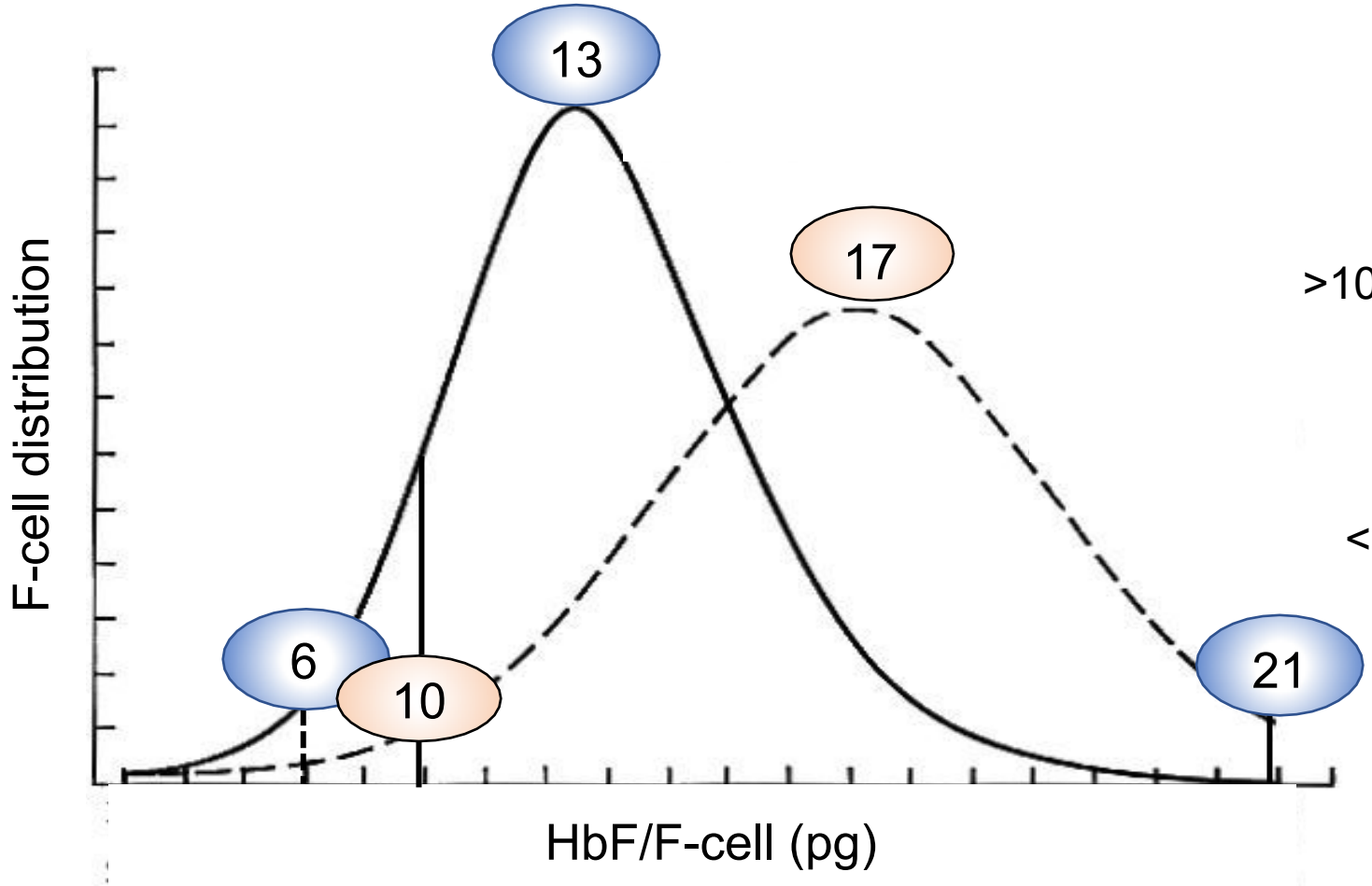
Pancellular (pancellular ≠ uniform)

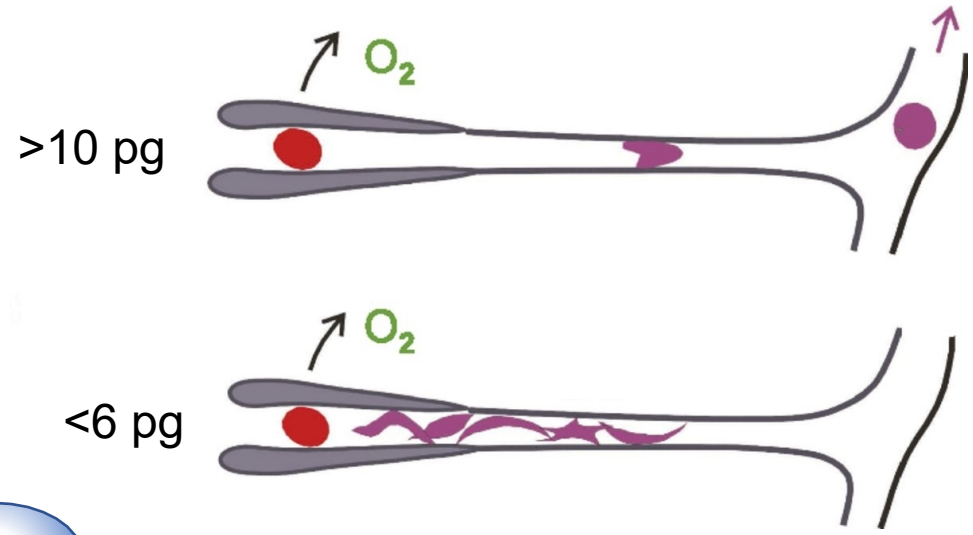


HbF/F-cell varies within and amongst patients
Sickle F-cells average ~6 pgs. HbF/F-cell
HbS polymerization inhibited by ~10 pgs. HbF/F-cell

(https://imagebank.hematology.org/image/3061/hemoglobin-shpfh)

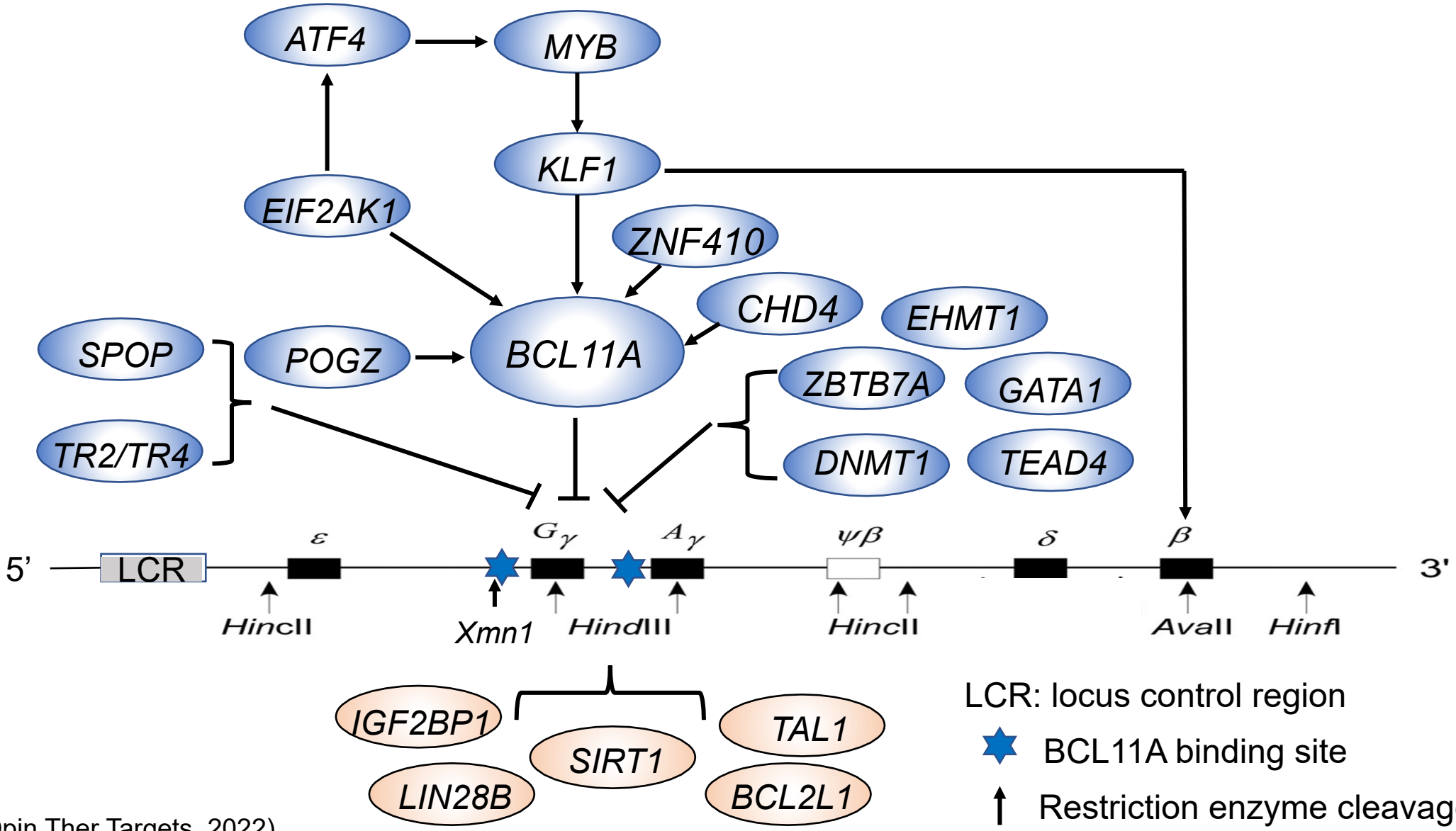
Distributions of HbF/F-cell





(Steinberg Exp Opin Ther Targets 2022; Sunshine et al, J Mol Biol 1979)

Modulators of HbF gene expression



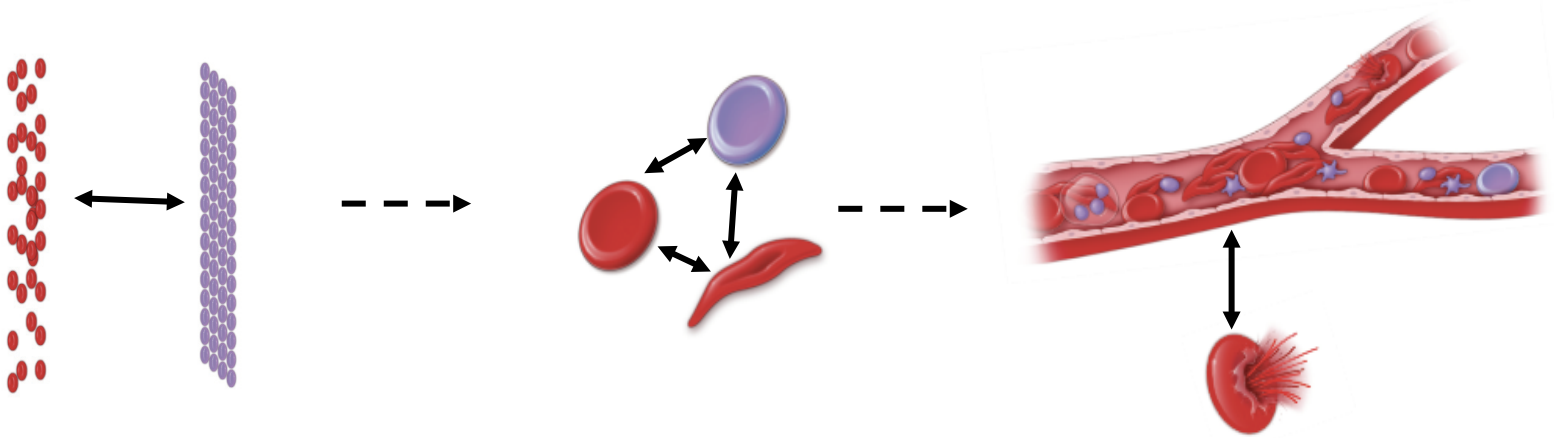
(Steinberg, Exp Opin Ther Targets, 2022)

Aspirational goal: ~10 pg. of HbF/RBC should inhibit pathophysiology and “cure” SCD

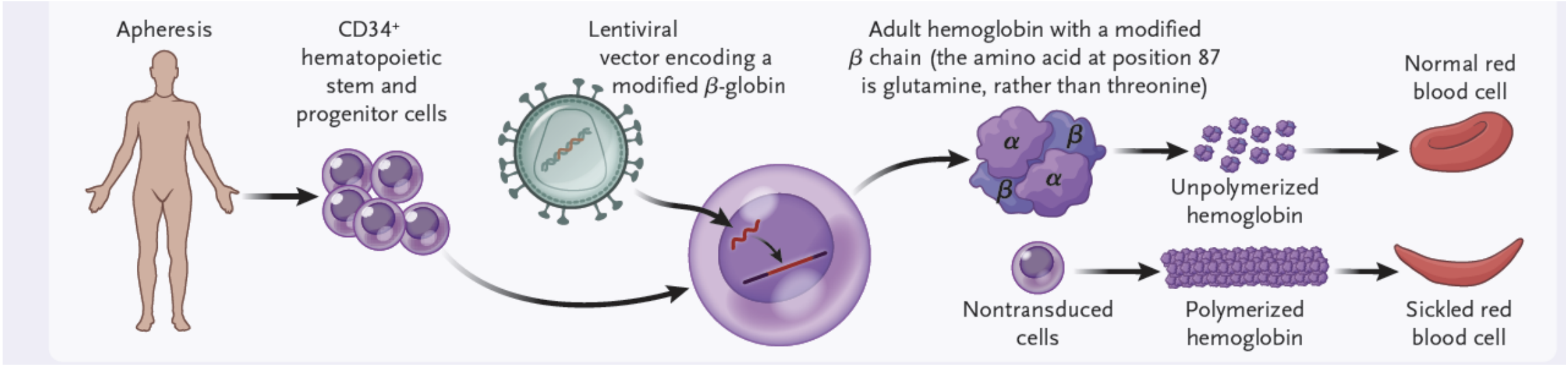
1^0: prevents HbS polymerization

2^0: prevents RBC damage

3^0: prevents vasoocclusion and hemolysis

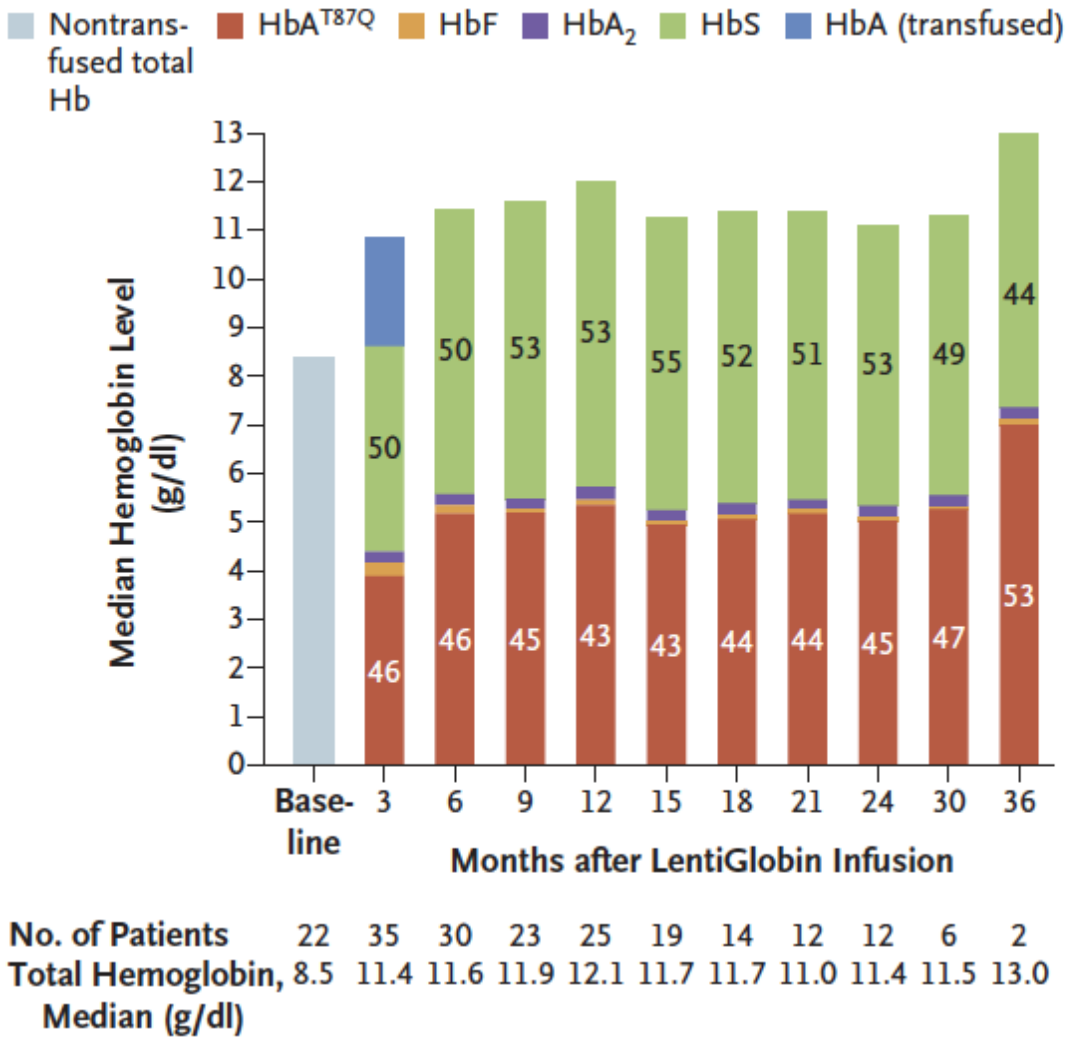


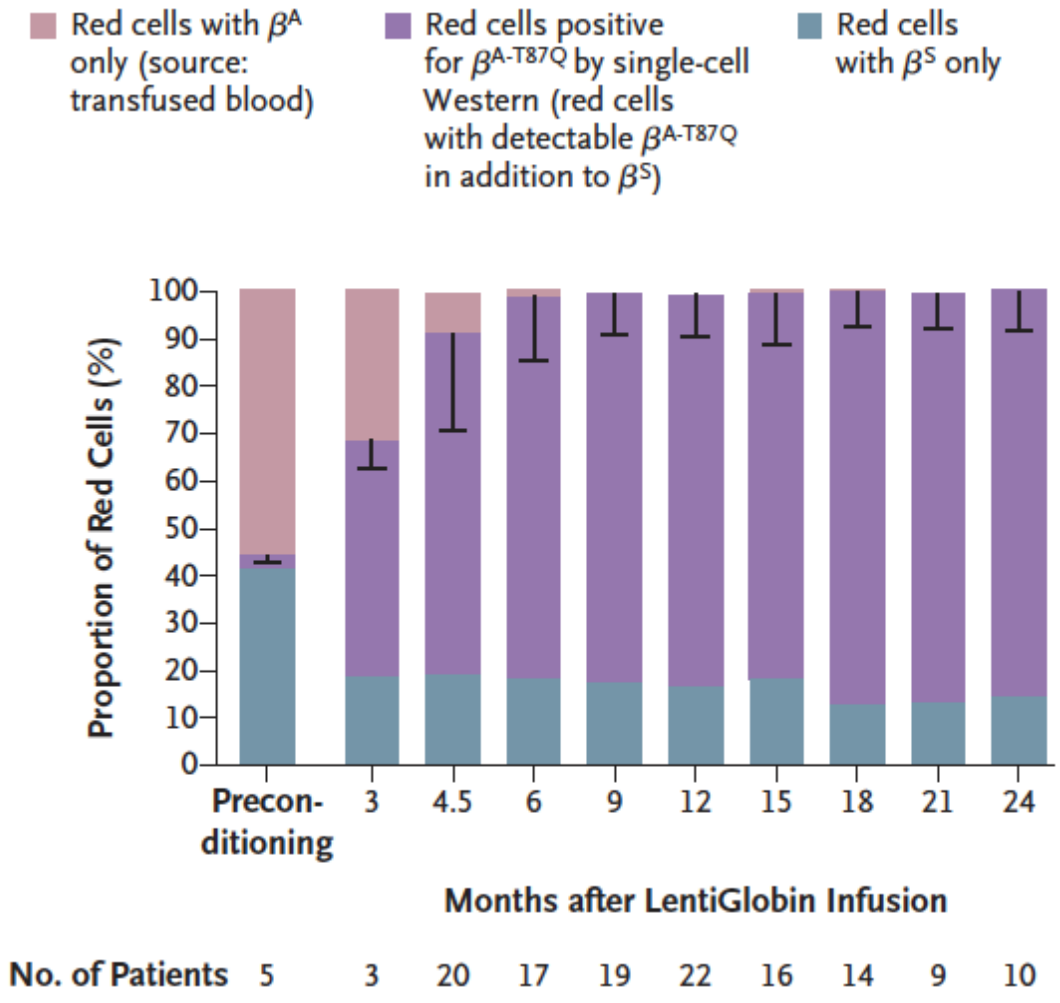
Transduction of CD34+ cells with a “HbF-like” HbA gene



(Steinberg, NEJM 2022)

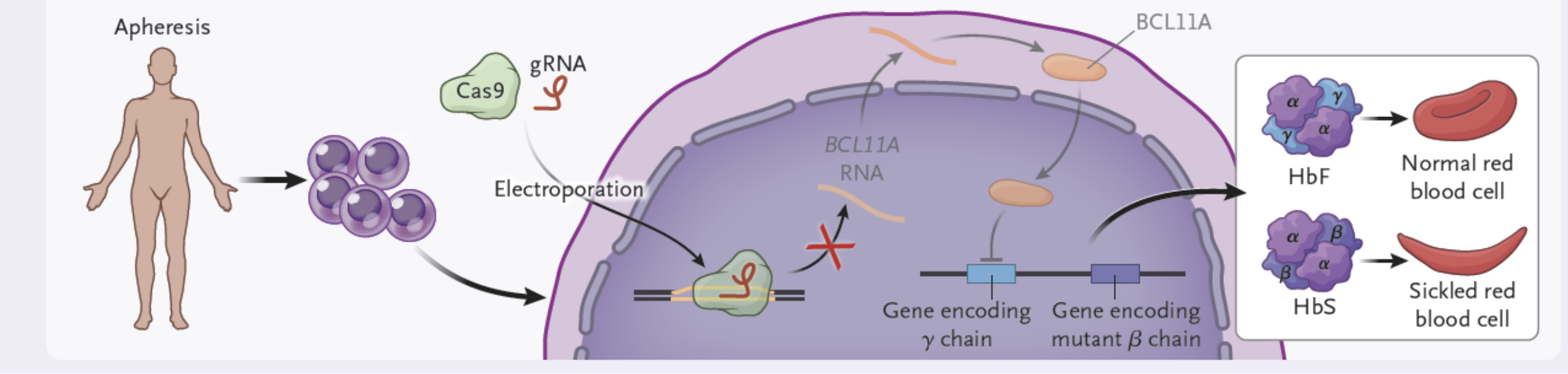
Lentivirus-mediated (β^{T87Q}) gene therapy in SCD: "HbF-like" HbA





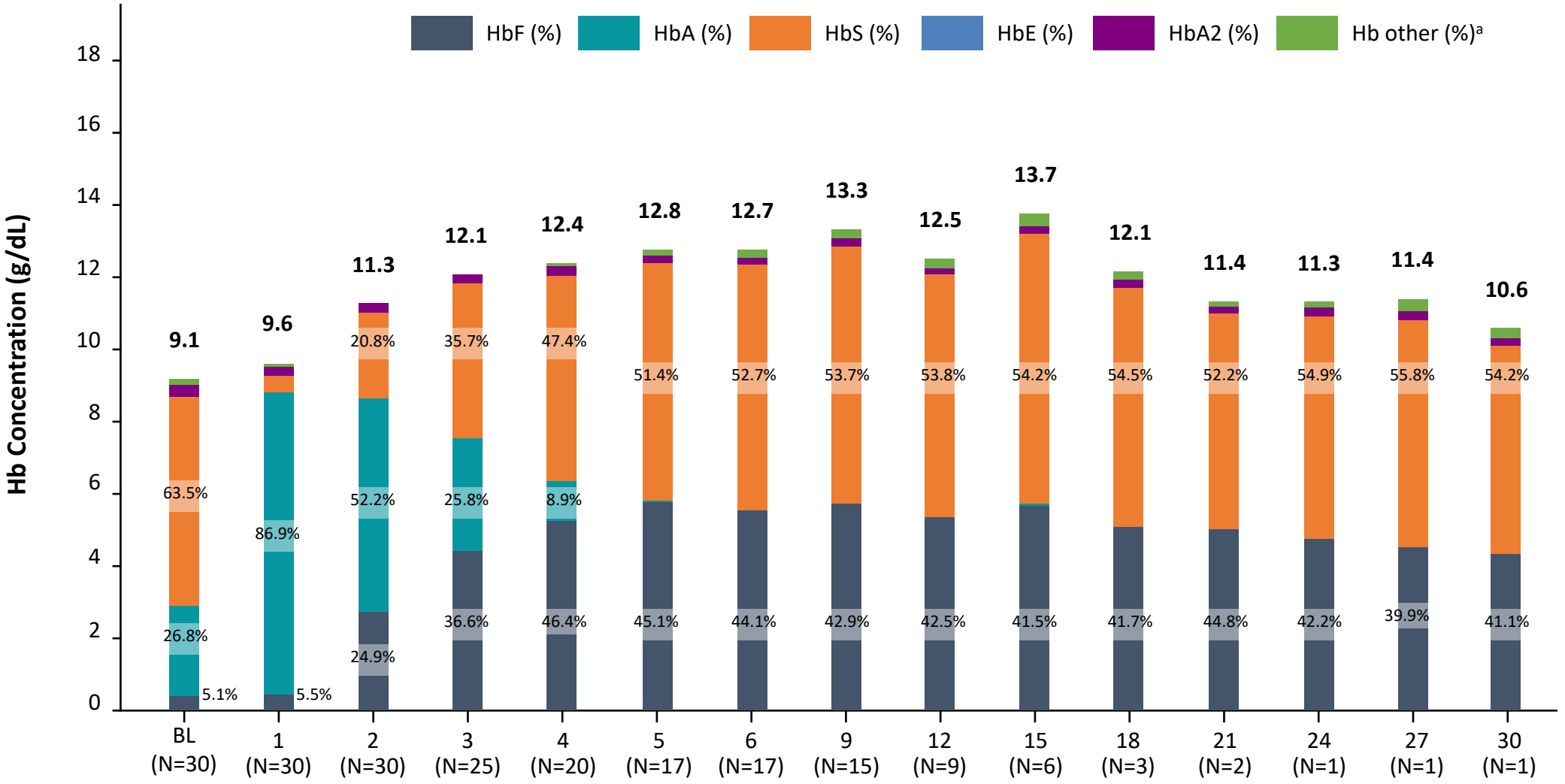
(Kanter et al. NEJM 2022)

Editing the erythroid enhancer of *BCL11A*



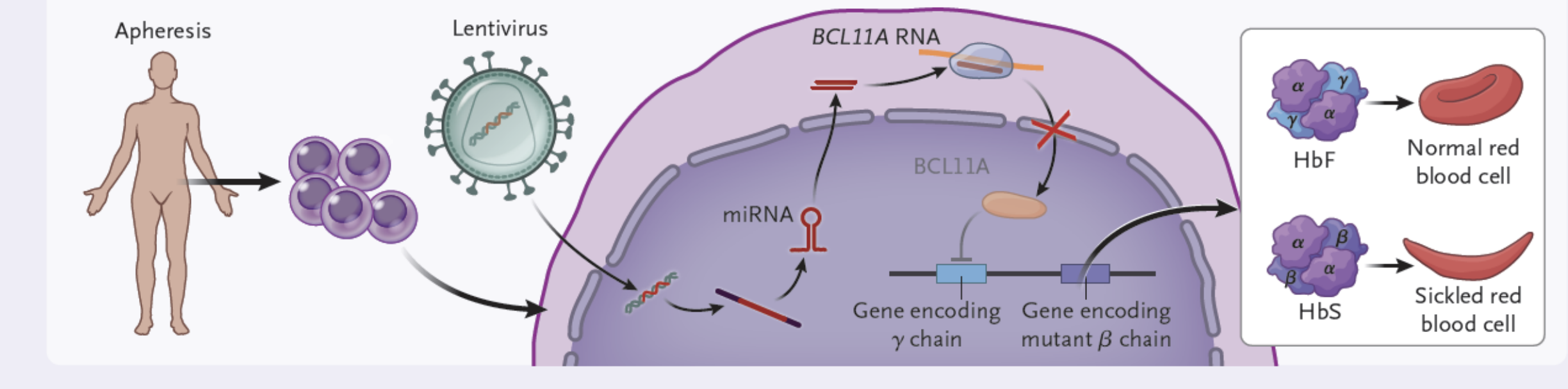
(Steinberg, NEJM 2022)

Hemoglobin fractions after *BCL11A* enhancer editing in sickle HPSCs



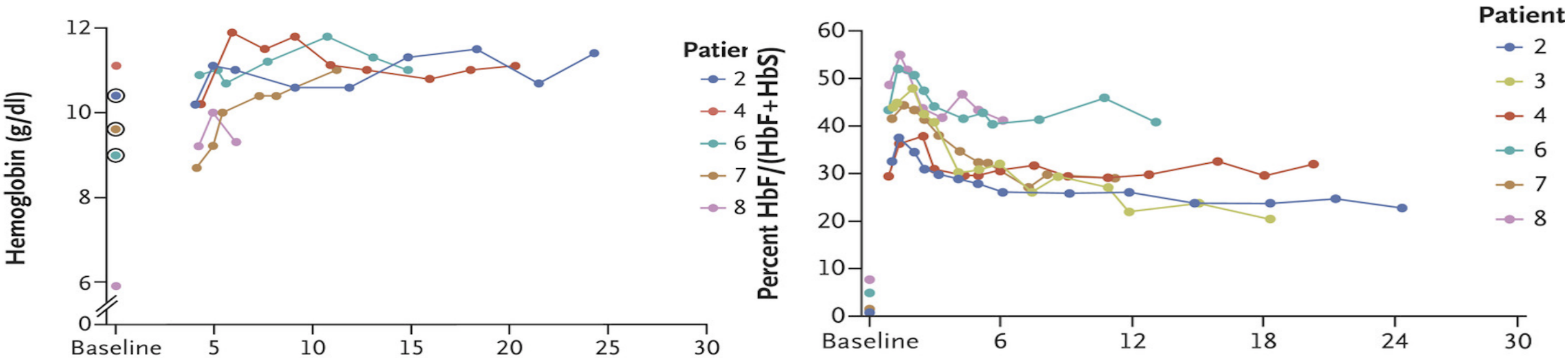
(Locatelli et al, EHA 2022)

Transduction with DNA encoding shmRNA targeting *BCL11A* mRNA



(Steinberg, NEJM 2022)

shmRNA directed to the *BCL11A* enhancer increases HbF in SCD



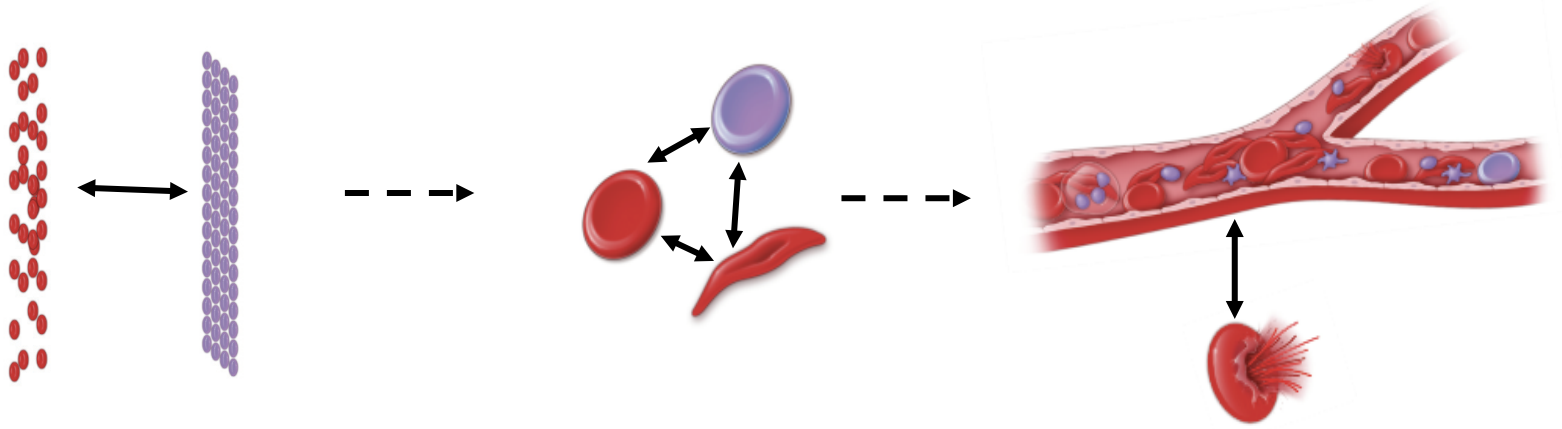
(Esrick et al, N Engl J Med 2021)

Current results of gene therapy suggest sufficient HbF/RBC for potential "cure"

1^0: prevents HbS polymerization

2^0: prevents RBC damage

3^0: prevents vasoocclusion and perhaps hemolysis



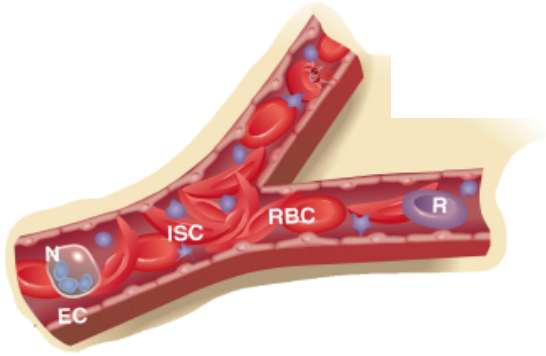
Up to 3 yrs: No VOC, little or no hemolysis

Unknown: Freedom from myelodysplasia, leukemia

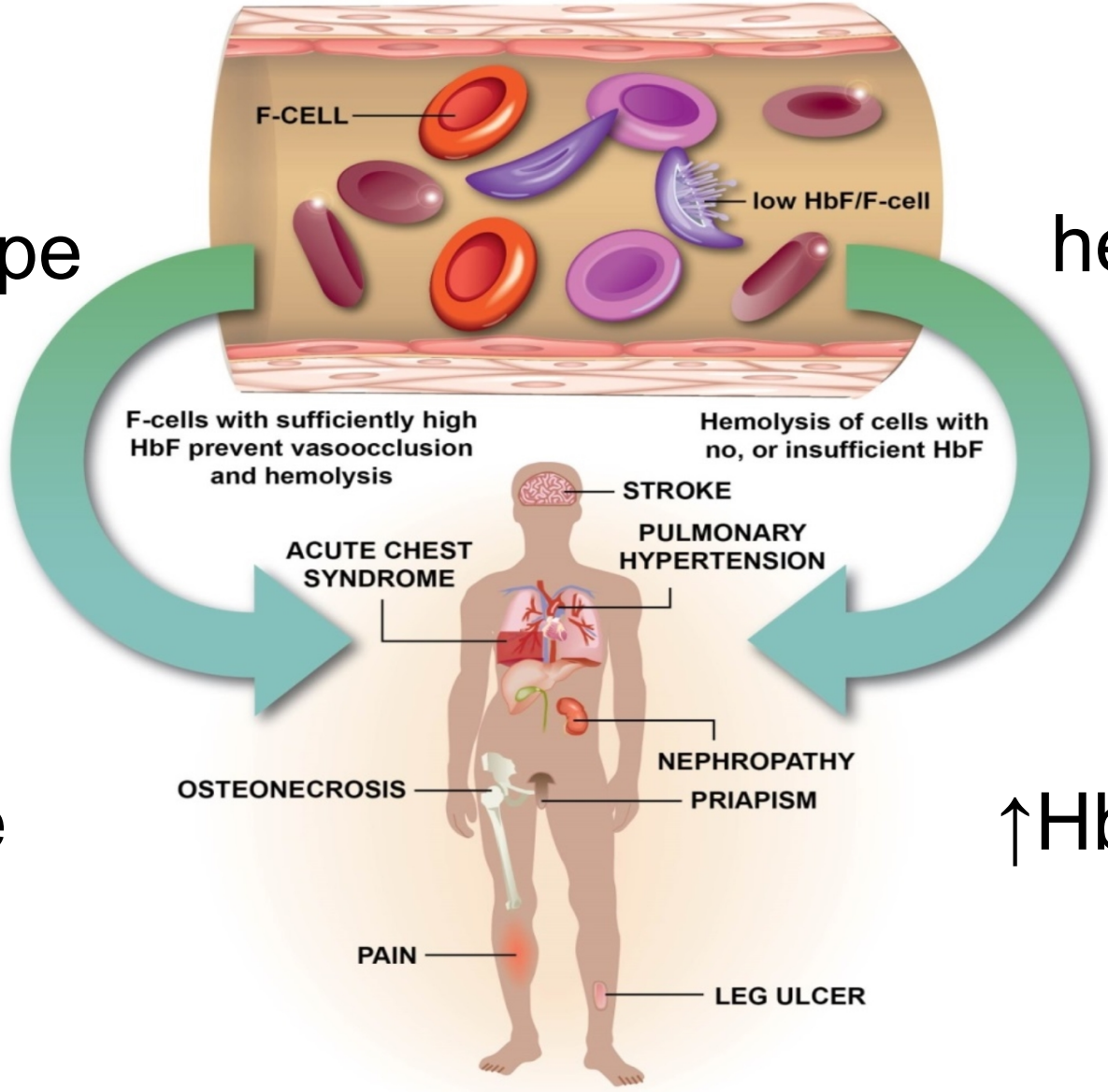
Lifelong persistence

“Apparent” differential effects of HbF on SCD phenotypes

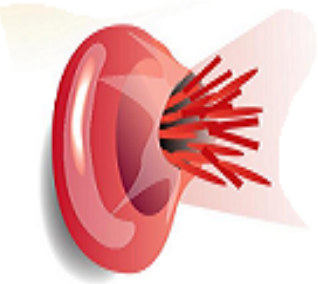
vasoocclusive ϕtype



↑HbF ↓ incidence

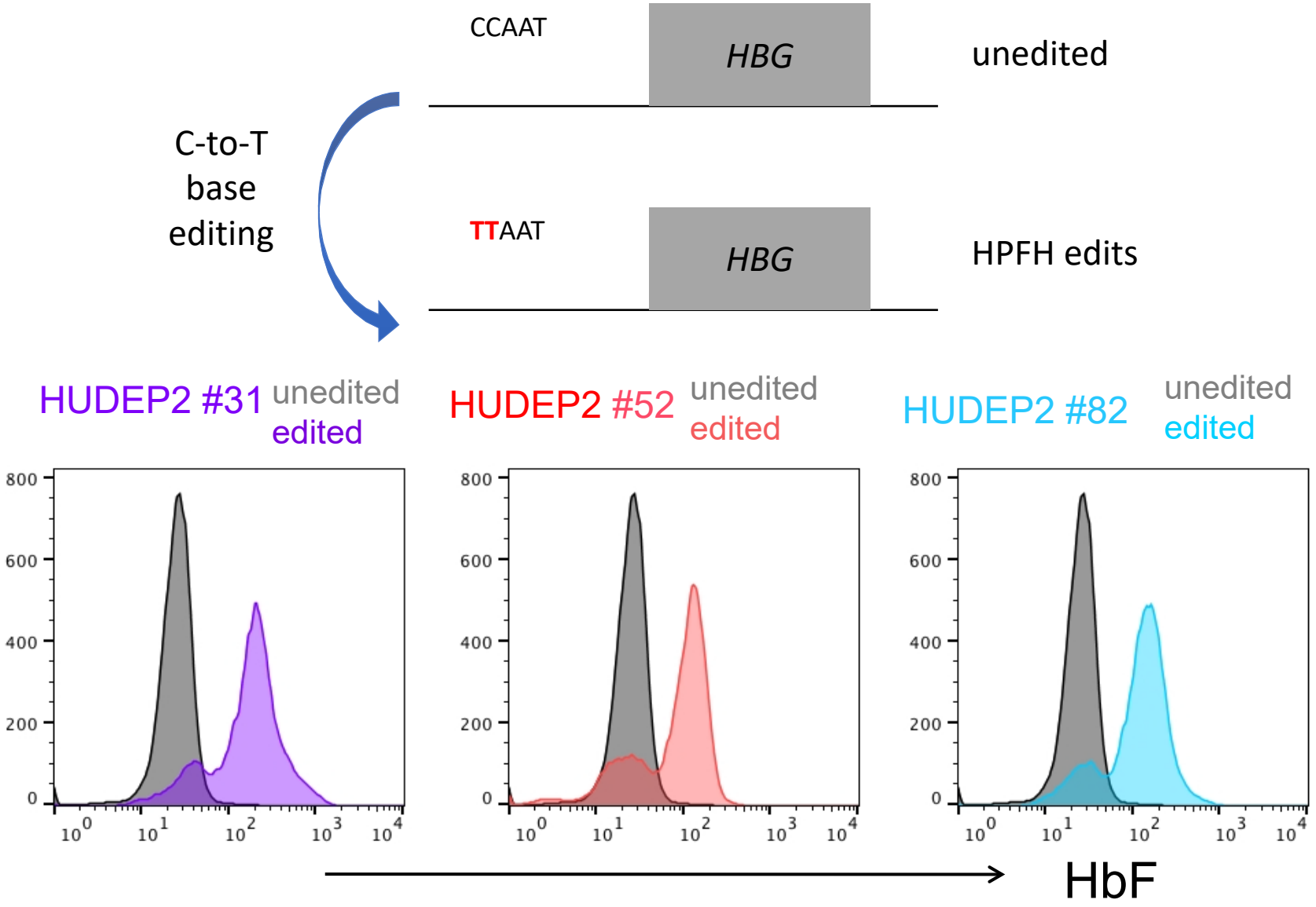


hemolytic ϕtype



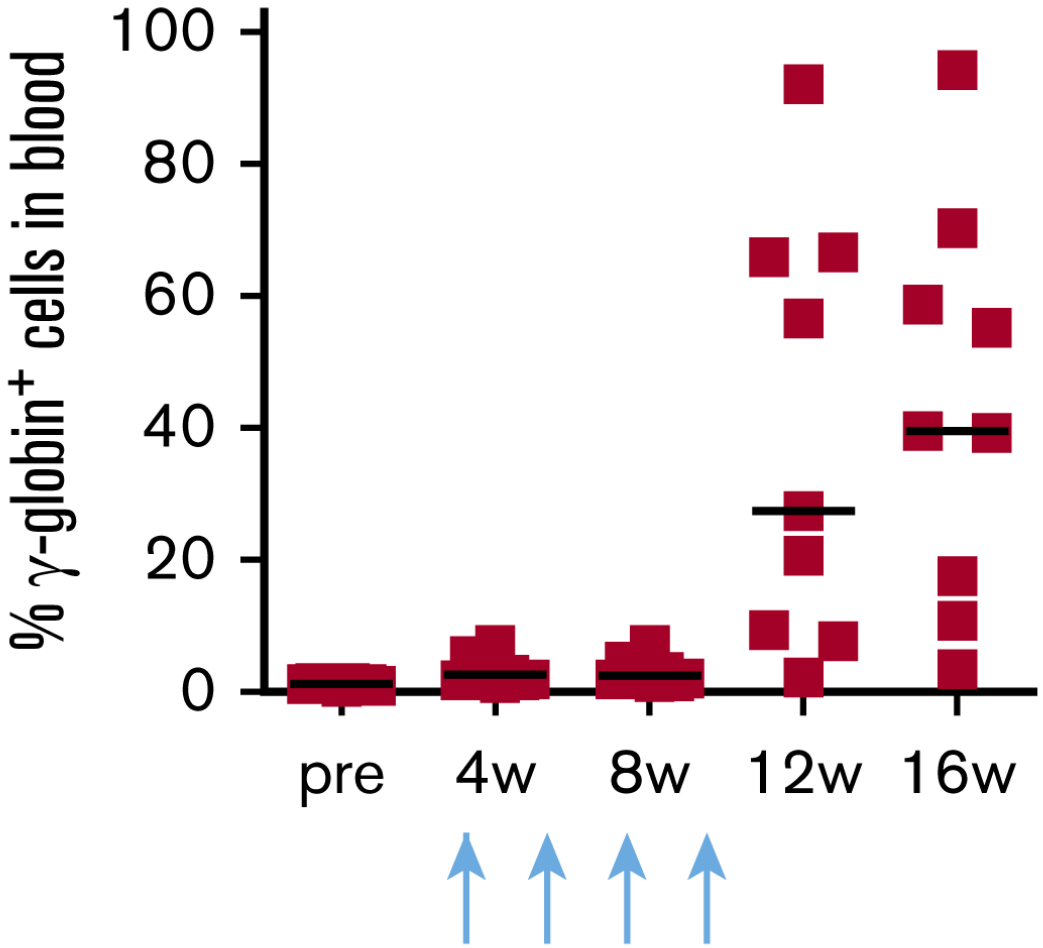
↑HbF ± incidence

BCL11A binding motif base-editing increases HbF



(Vanuytsel et al, 2020)

In vivo base editing of BCL11A binding motif in β-YAC mice increases HbF expression

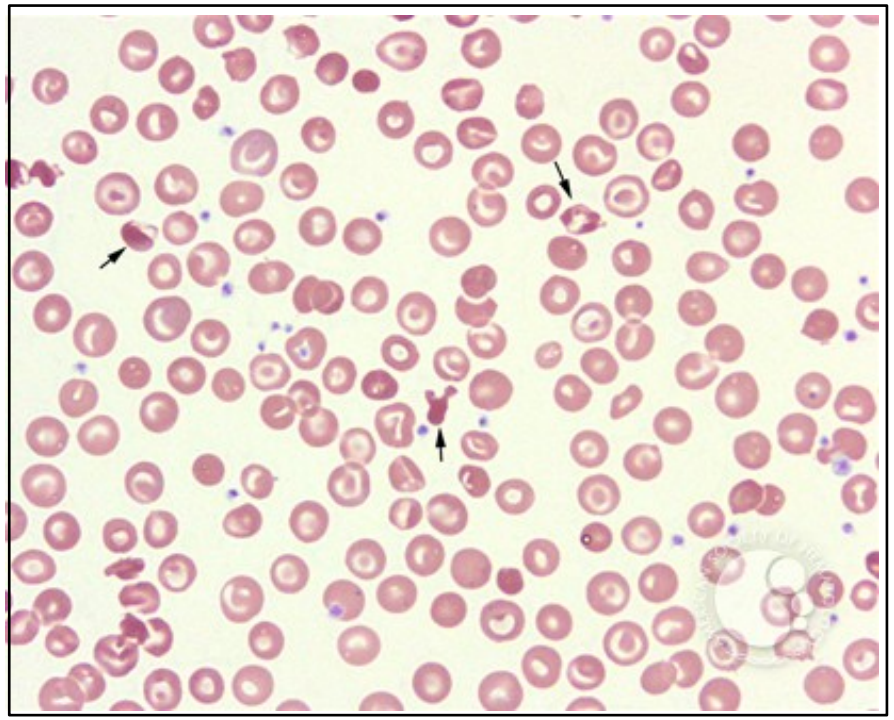


(Li et al, Blood Adv 2021)

Gene therapy for HbSC disease

Loss of K^+ and H_2O, increases cell density promoting HbS polymerization

Asymmetric hybrids are the favored tetramer in hemoglobin mixtures



$\alpha_2\beta^C\gamma \approx \alpha_2\beta^S\gamma$, and as with $\alpha_2\gamma_2$, is likely excluded from the polymer

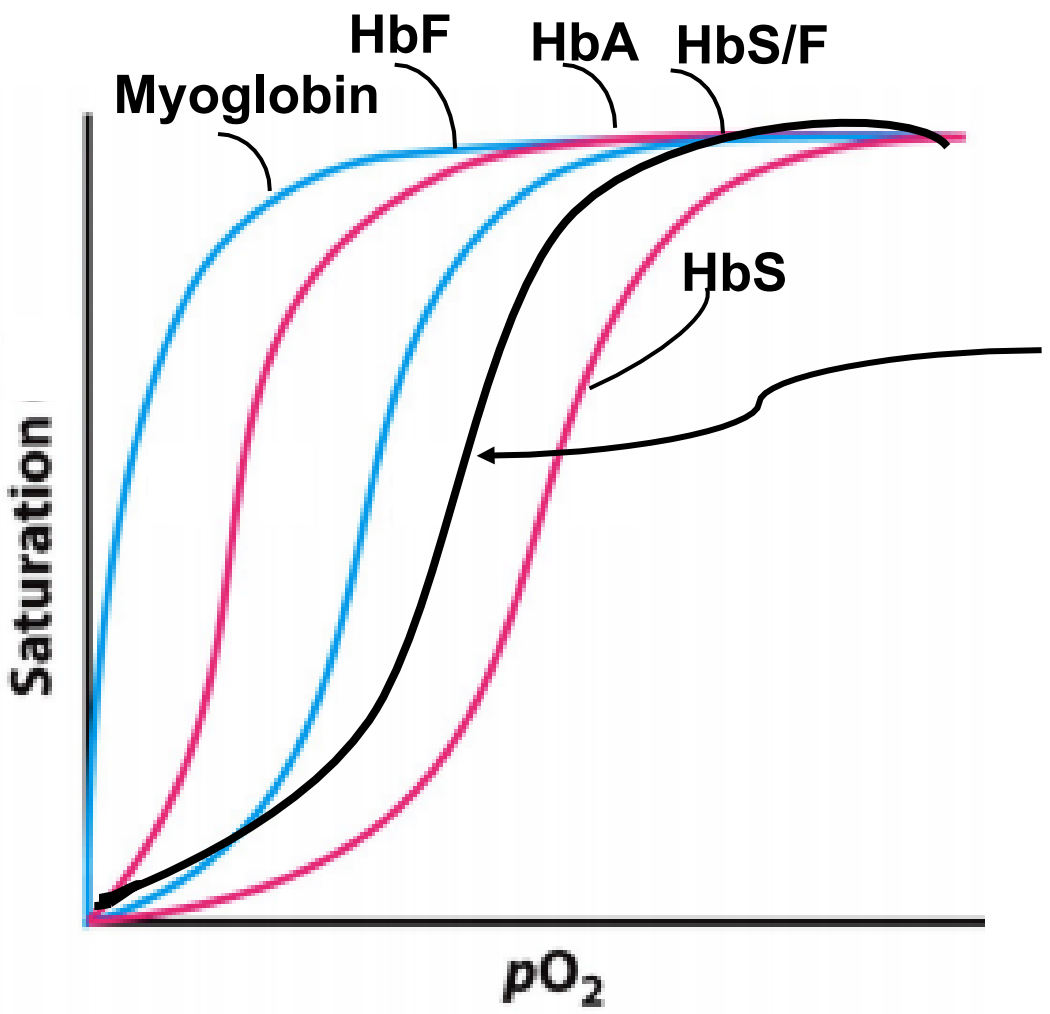
$\alpha_2\beta_2{}^C$ and $\alpha_2\beta^C\gamma$ could increase cell density

↑HbF to levels ≈ to those achieved in sickle cell anemia should be therapeutic as $\alpha_2\beta^C\gamma$, $\alpha_2\beta^S\gamma$, and $\alpha_2\gamma_2$ are “anti-sickling”

Can enough HbF be too much?

HPFH homozygotes with100% HbF are normal, pregnancy experience limited

Carriers of ↑O_2 affinity variants (? HbF surrogates) can have normal fetuses and normal exercise responses to altitude



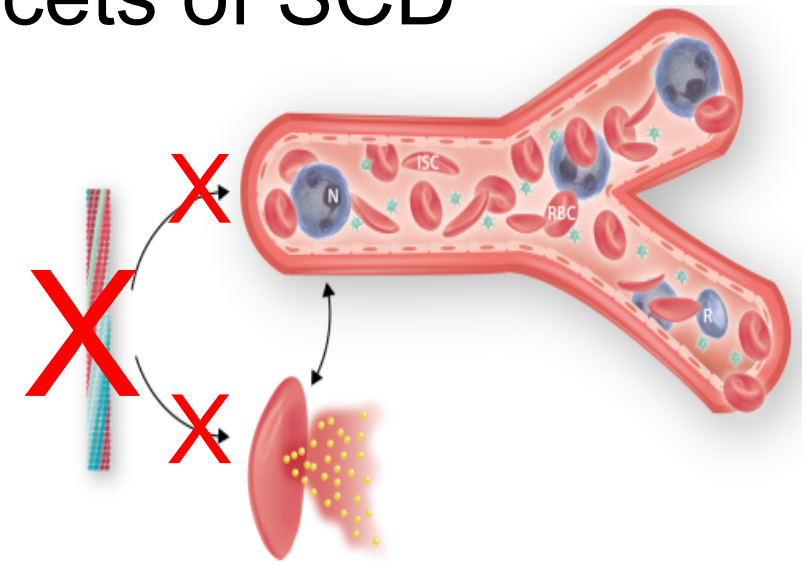
P_{50} and O_2 delivery in HbS/F (35% F) was normal; with 40% HbF and ~50% $\alpha_2\beta^S\gamma$, blood P_{50} is a composite $\alpha_2\beta^S\gamma$, HbF, HbS

↓ P_{50} in β thalassemia with 100% HbF and normal hemoglobin could ↓birth weight

(Charache & Conley, 1969; Charache et al, 1985; Marda et al, 1994; Rangat et al, 2021;Hebbel et al, 1978, Henry et al, 2021)

Summary

40-50% HbF “forces” a therapeutically “curative” level of HbF into nearly all RBCs abolishing vasoocclusive and hemolytic facets of SCD



Pancellularly distributed lower levels of HbF are apt to be therapeutically useful

Even heterocellular HbF expression, as exemplified by HU in children with SCD, can be useful, albeit not “curative”

Acknowledgement: Arlie House, 1988

(Steinberg & Schechter, Am J Hematol 2018)