HÄMATOLOGIE HEUTE
KÖLN

Sichelzellerkrankung: Neue Möglichkeiten zur Induktion der HbF Synthese

Leo Kager

St. Anna Kinderspital, Abteilung für Kinder- und Jugendheilkunde, Medizinische Universität Wien

St. Anna Kinderkrebs Forschung

MEDICAL UNIVERSITY OF VIENNA

180 Jahre St. Anna kinderSpital

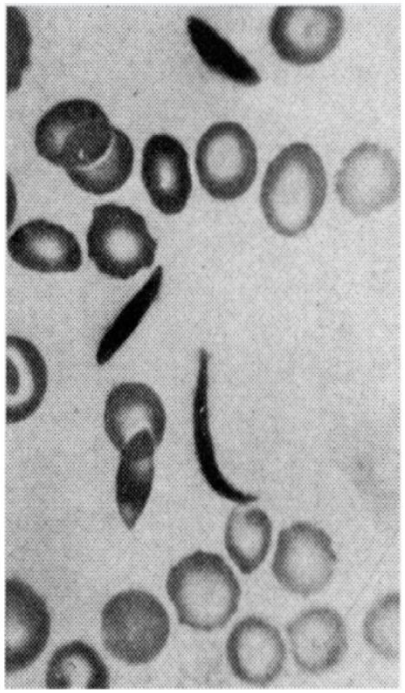
Novartis, Amgen und Bayer: Advisory Board

Sichelzellerkrankung – Phänotyp

Peculiar Elongated and Sickle-shaped Red Blood Corpuscles in a Case of Severe Anemia[a]

James B. Herrick, M.D.

1013 State Street, Chicago, Illinois



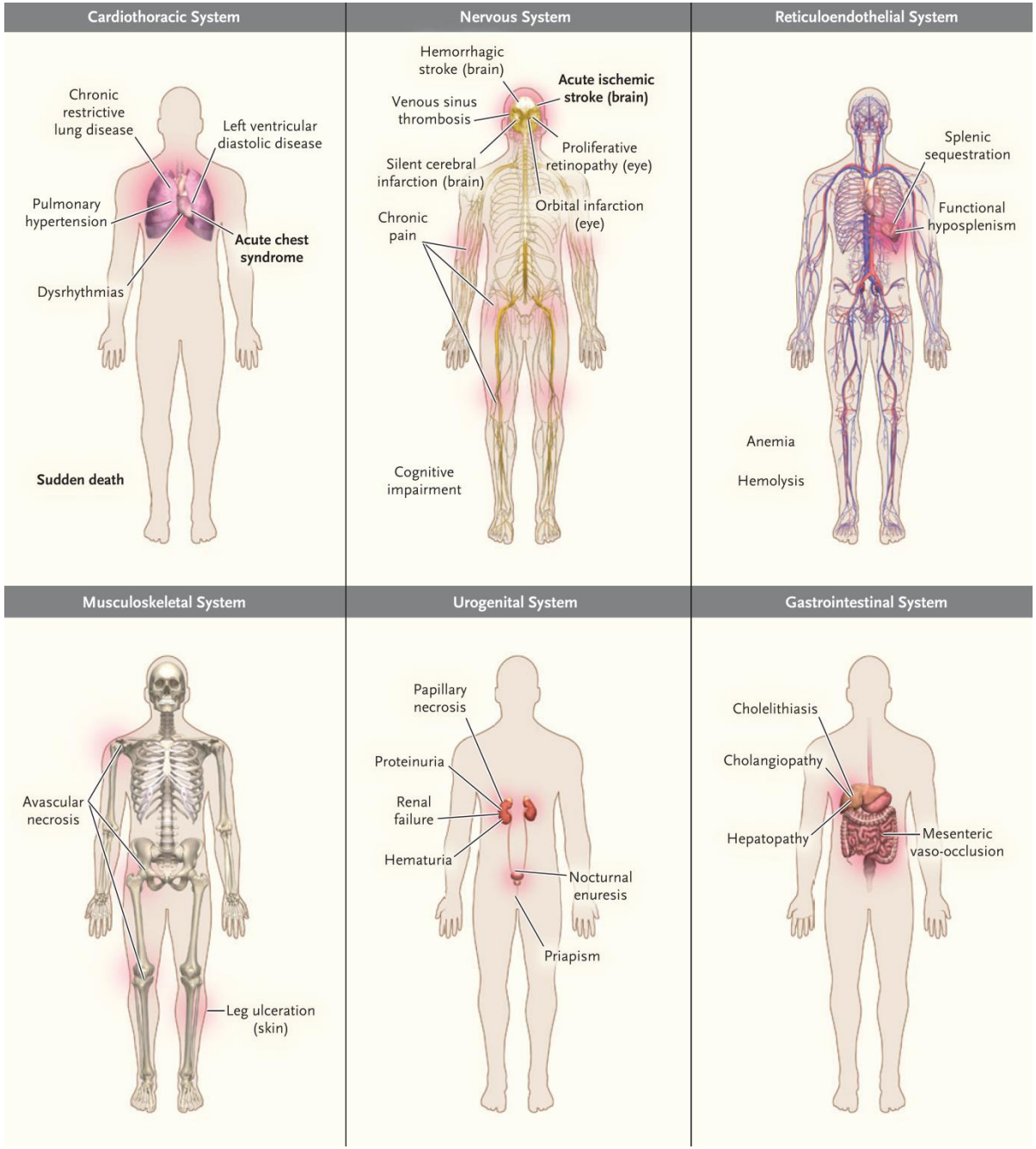
Ernest E. Iron, MD

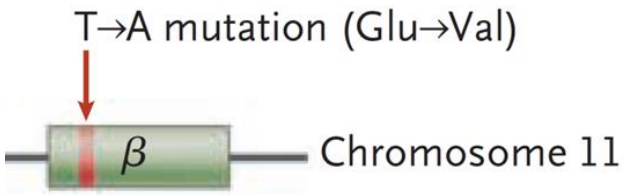
Dr. Herrick reported the first patient - Mr. Walter Clement Noel, a young black adult from Grenada, who studied Dentistry in Chicago - in 1910 and stated: ‚We were at a loss to account for this peculiar complex of symptoms…'.

‚…Wir waren nicht in der Lage, diesen besonderen Symptomkomplex zu erklären…'

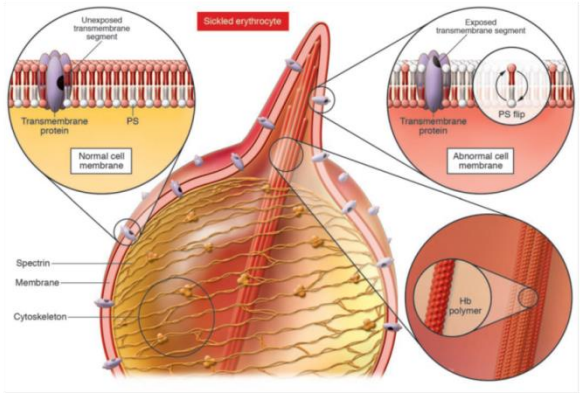
Arch Int Med 6:517-521, 1910

https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101419503-img

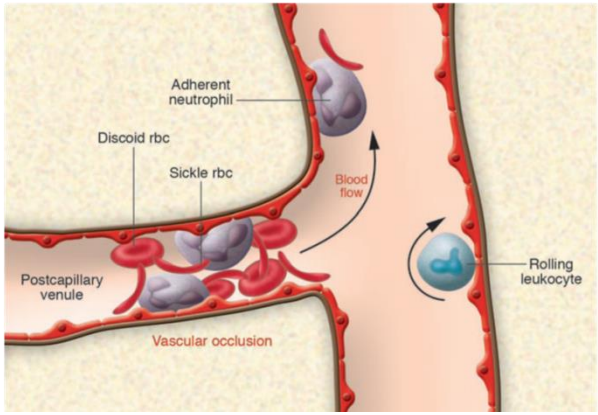




Formveränderung bei Deoxygenierung durch Polymerisierung von HbS



Sichelzellen generieren lokale Entzündungsreaktion – Gerinnungs und Leukozytenaktivierung - Vasookklusion



J. Clin. Invest. **117**:850–858 (2007).

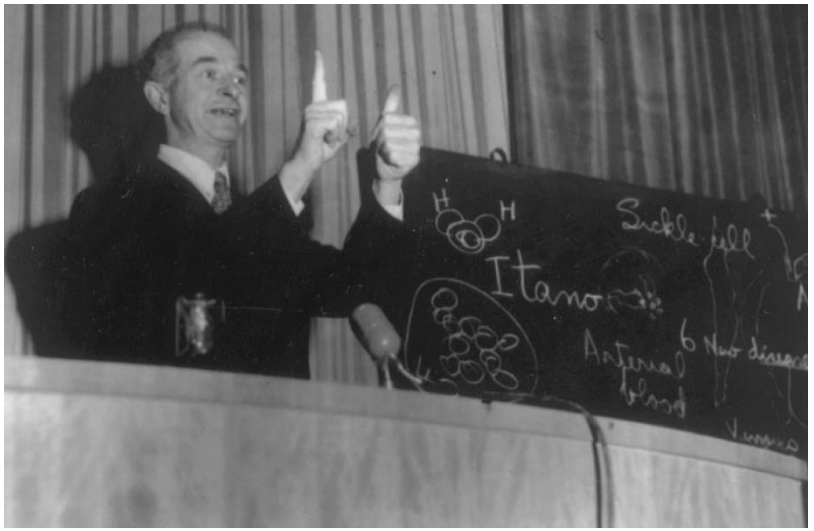
Sichelzellerkrankung
Die erste molekulare Erkrankung

SCIENCE April 29, 1949, Vol. 109

Sickle Cell Anemia, a Molecular Disease[1]

Linus Pauling, Harvey A. Itano,[2] S. J. Singer,[2] and Ibert C. Wells[3]

Gates and Crellin Laboratories of Chemistry,
California Institute of Technology, Pasadena, California[4]



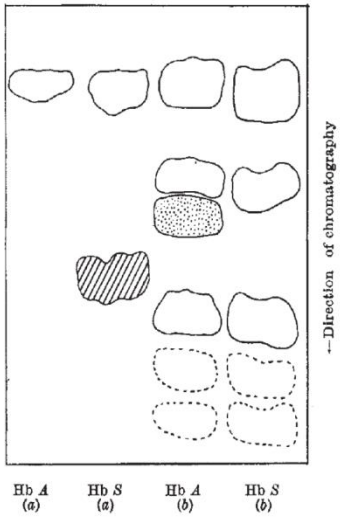
Linus Pauling

A SPECIFIC CHEMICAL DIFFERENCE BETWEEN THE GLOBINS OF NORMAL HUMAN AND SICKLE-CELL ANÆMIA HÆMOGLOBIN

By Dr. V. M. INGRAM

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, University of Cambridge

October 13, 1956 NATURE

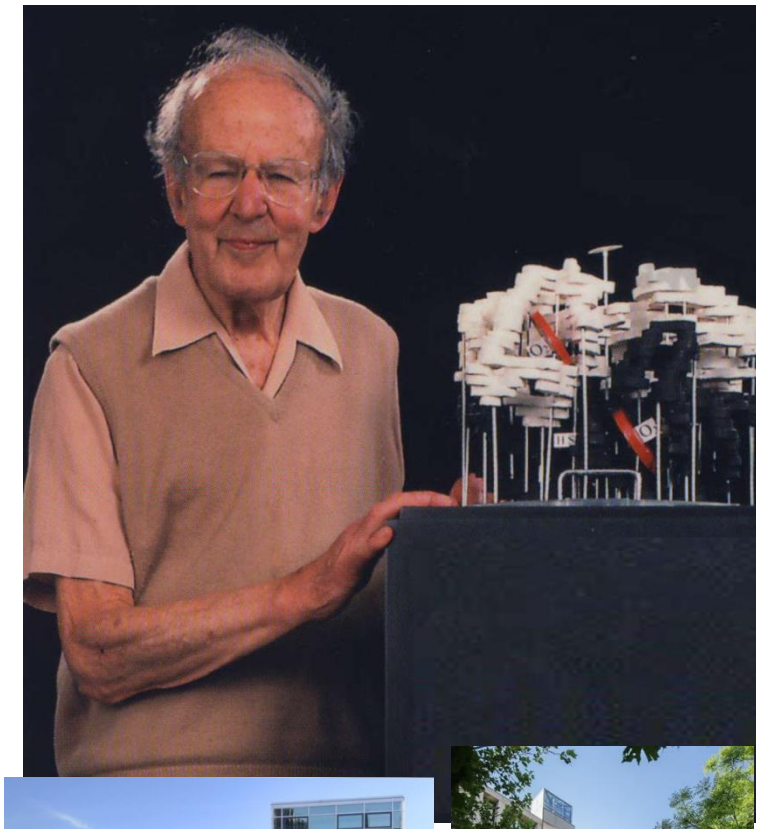


HbA Val-His-Leu-Thr-Pro-Glu-Glu-Lys....

HbS Val-His-Leu-Thr-Pro-Val-Glu-Lys....

American Journal of Medical Genetics (Semin. Med. Genet.) 115:83–93 (2002)

Vernon Ingram

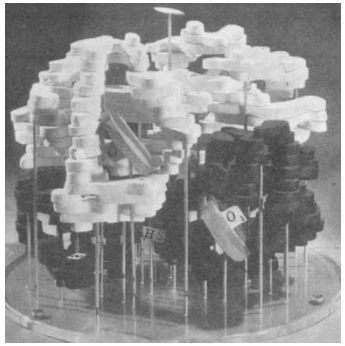


mfpl
MAX F. PERUTZ LABORATORIES

https://de.wikipedia.org/wiki/Max_F._Perutz_Laboratories

Max Ferdinand Perutz

Laboratory of Molecular Biology, Cambridge
Nobelpreis für Chemie 1962



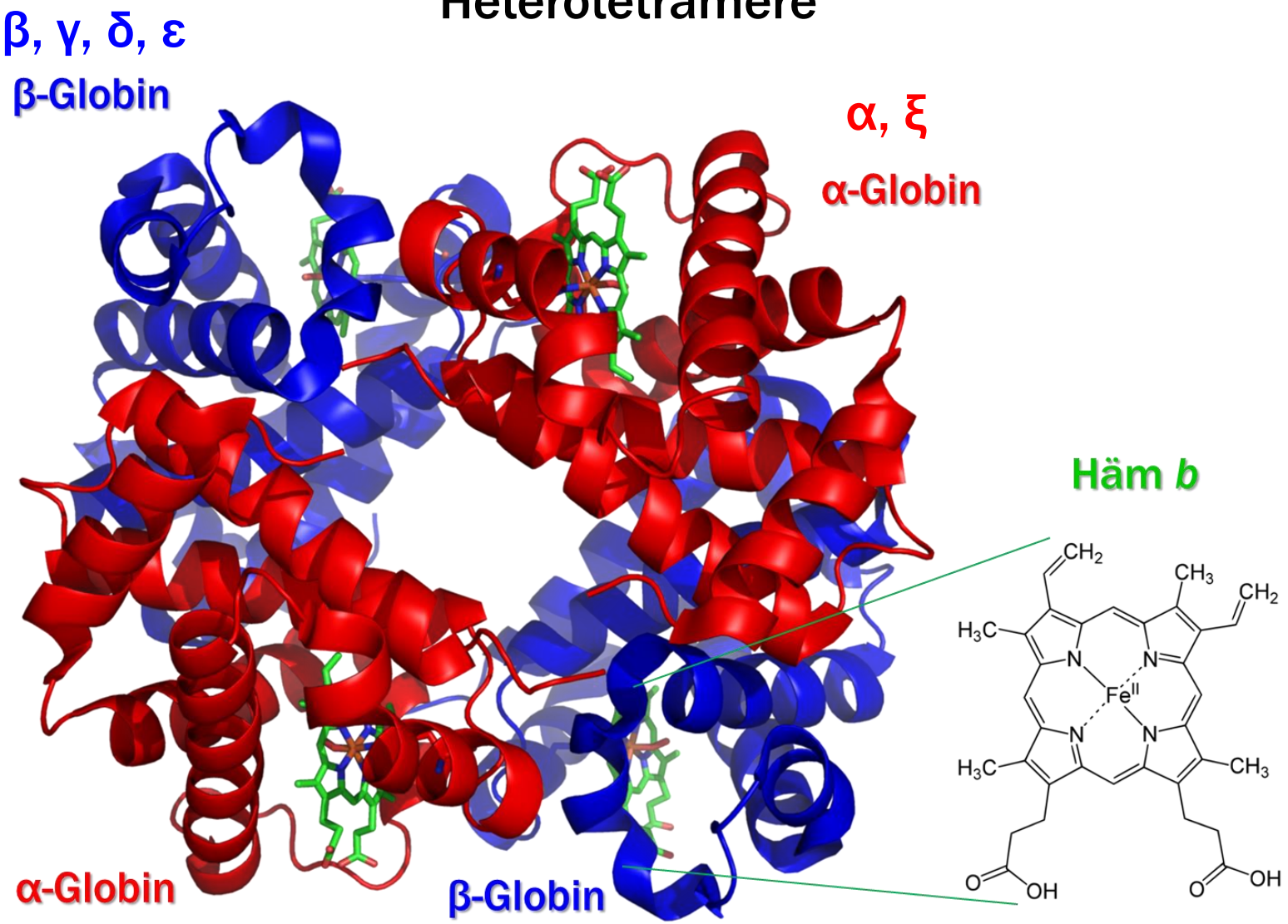
NATURE February 13, 1960 VOL. 185

https://www.geschichtewiki.wien.gv.at/Theresianische_Akademie

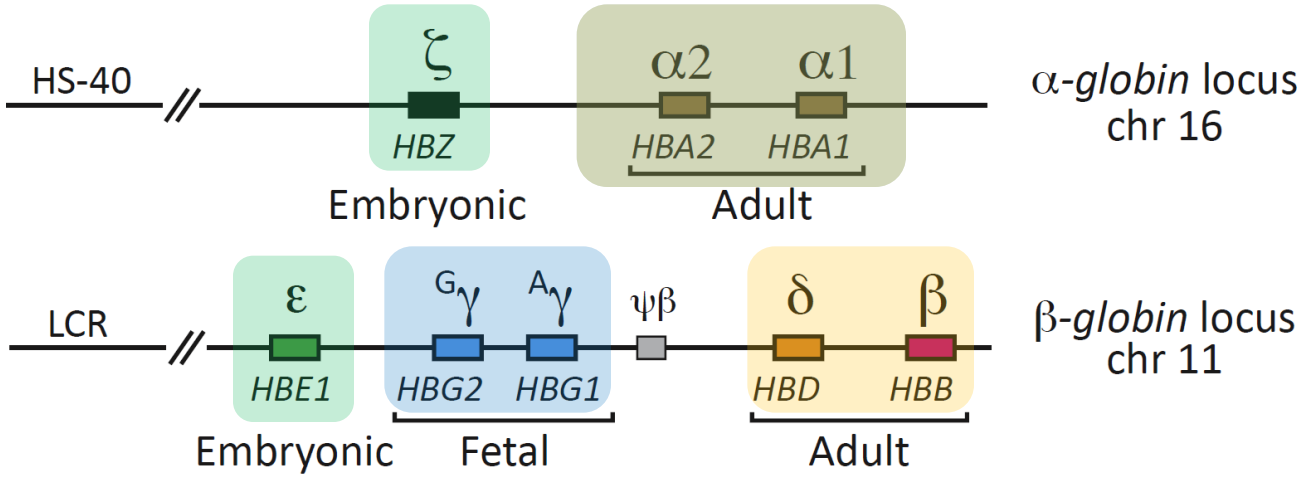
BLOOD, 15 NOVEMBER 2008 • VOLUME 112, NUMBER 10

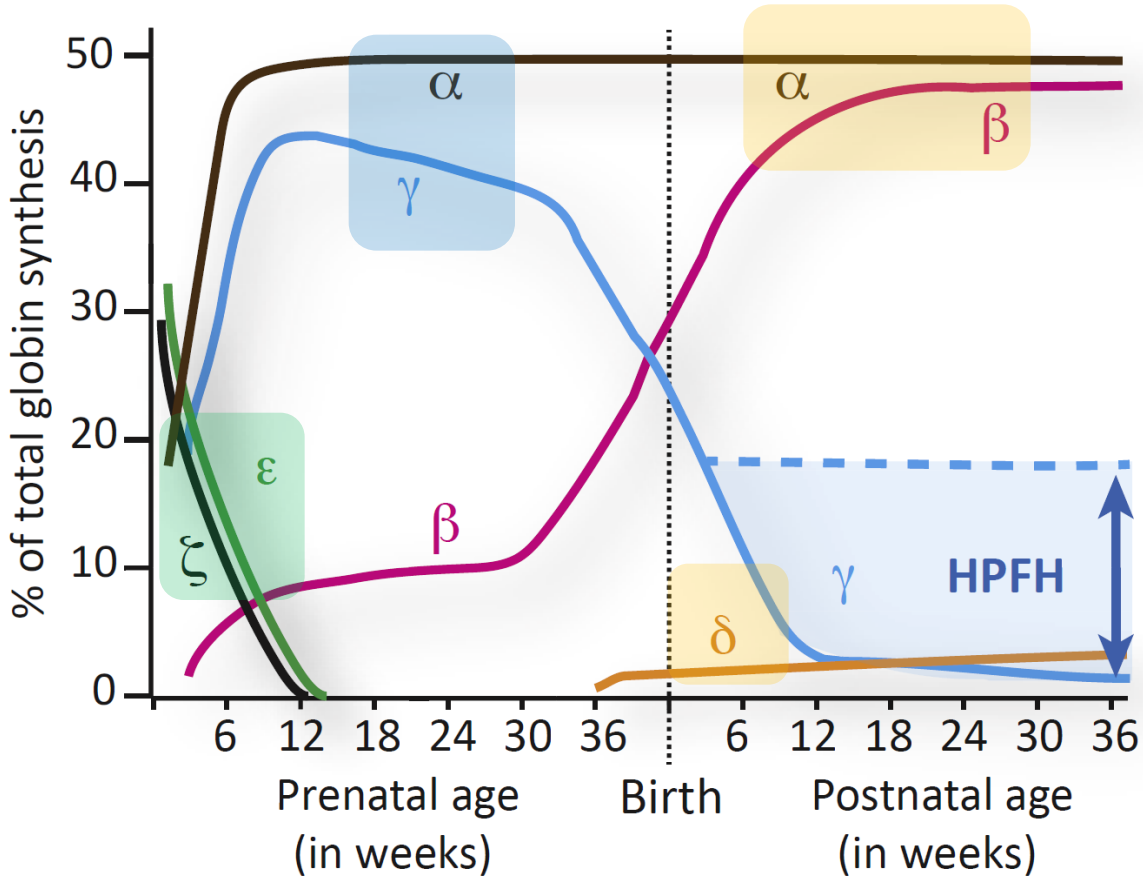
Molekulare Struktur von Hämoglobinen

Heterotetramere



https://de.wikipedia.org/wiki/Hämoglobin





HbA (2α2β) >95%
HbA2 (2α2δ) <3,5%
HbF (2α2γ) <1%

HbF > 1%
Hereditäre Persistenz von fetalem Hämoglobin

Trends in Genetics
December 2018, Vol. 34, No. 12

HbF ($\alpha_2\gamma_2$) modifiziert den Schweregrad von β-Globin Erkrankungen

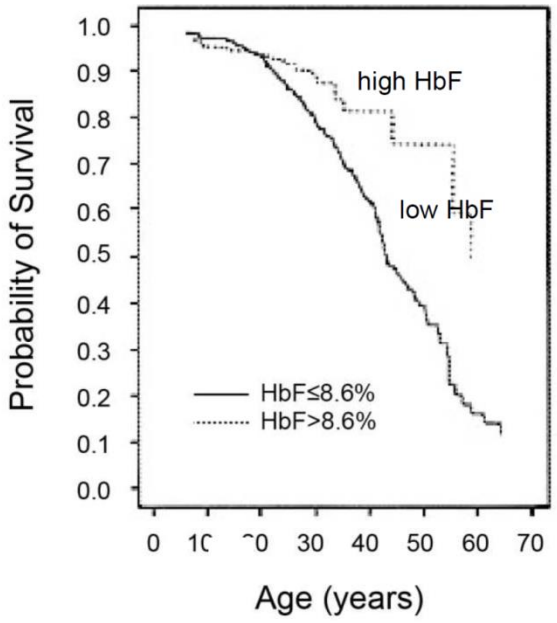
THE SIGNIFICANCE OF THE PAUCITY OF SICKLE CELLS IN NEWBORN [AA] INFANTS

By Janet Watson, M.D.*

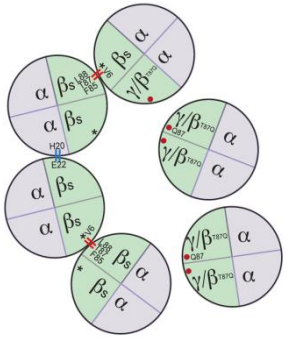
Brit. J. Haemat., 1958, **4**, 138.

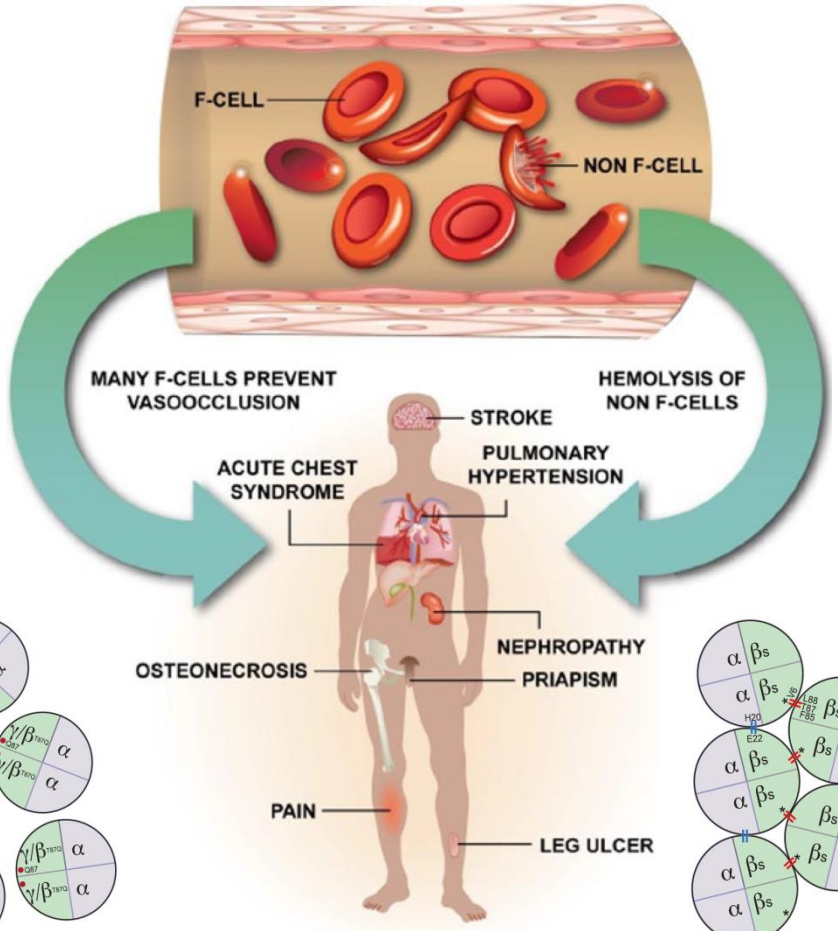
Hereditary Persistence of Foetal Haemoglobin Production, and its Interaction with the Sickle-Cell Trait

Gillian F. Jacob and Alan B. Raper*



Platt *et al*, NEJM (1994) 330:1639.





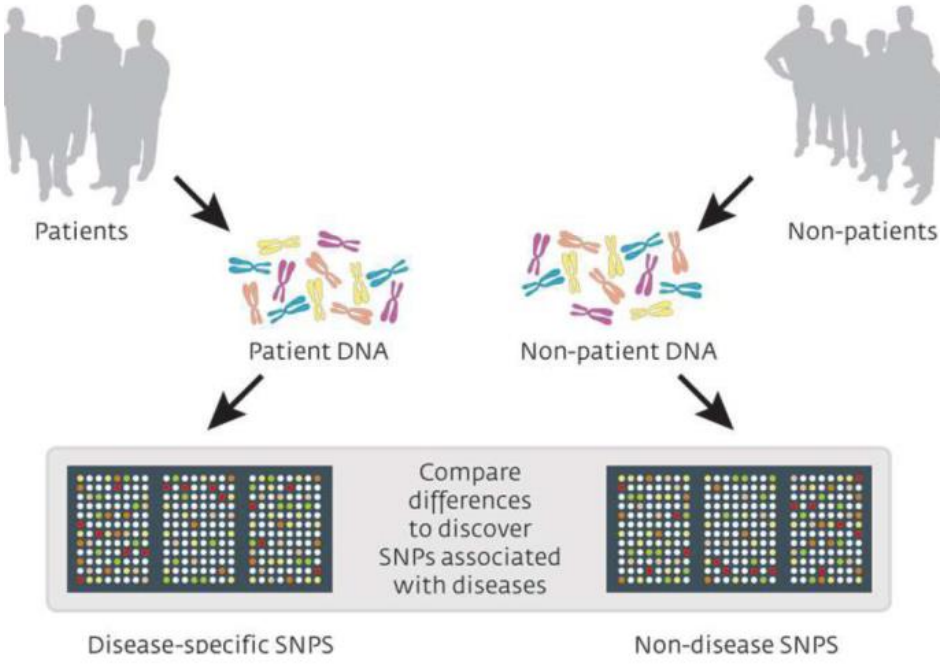
***Blood*. 2011;118(1):19-27**

Molecular Therapy Vol. 25 No 5 May 2017

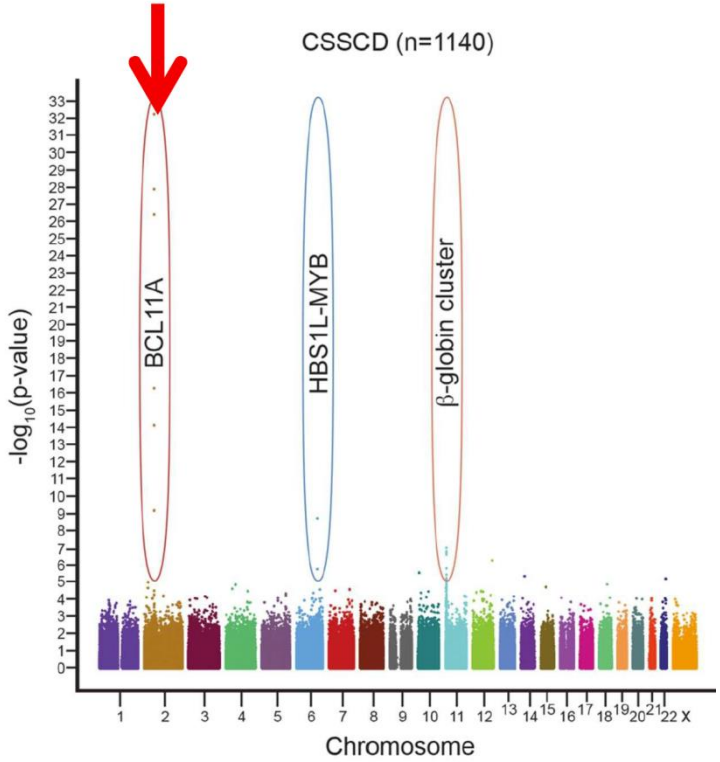
HbS polymer

Wie hoch muss der Anteil an HbF sein, um die Erkrankung zu heilen oder zu verhindern (20%)?

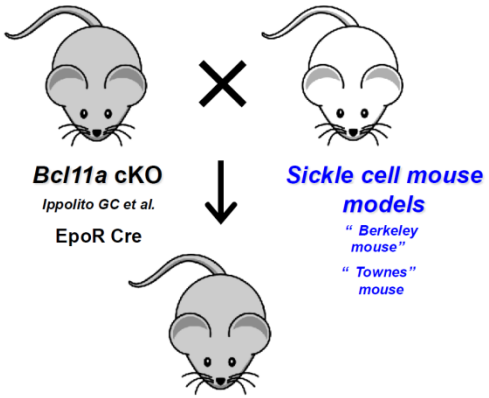
Identifikation von Mechanismen, welche den Hämogobin-Switch regulieren – Genomweite Assoziation Studien (GWAS)



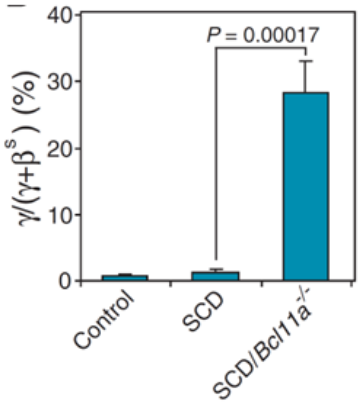
© Pasieka, Science Photo Library
https://www.mpg.de/10680/Modern_psychiatry

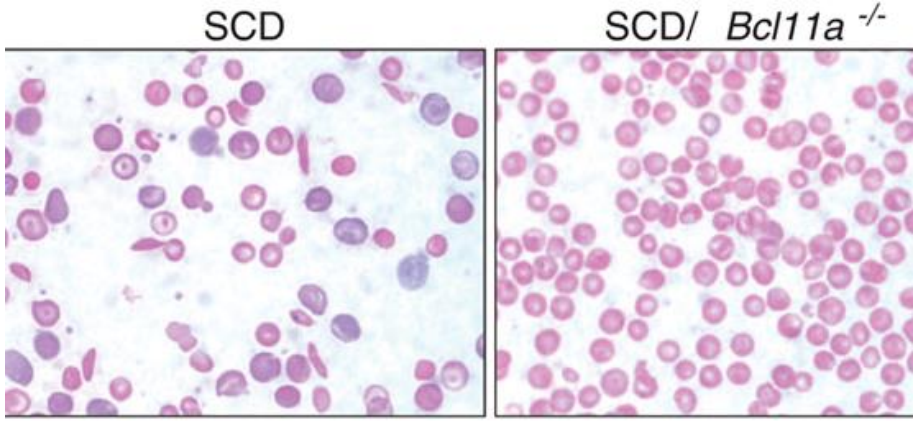


Mausmodell SCD, *BCL11A* und HbF



Genetic rescue experiment

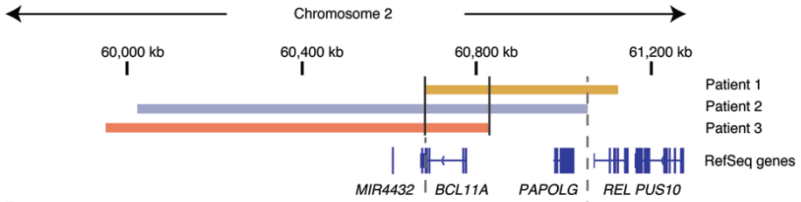


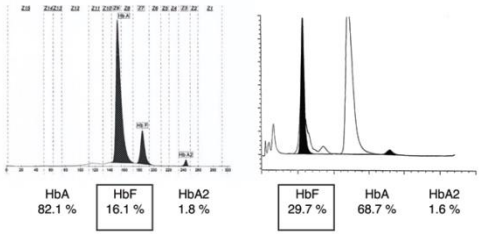


SCIENCE VOL 334 18 NOVEMBER 2011

Stuart H. Orkin, MD

***BCL11A* deletions result in fetal hemoglobin persistence and neurodevelopmental alterations**





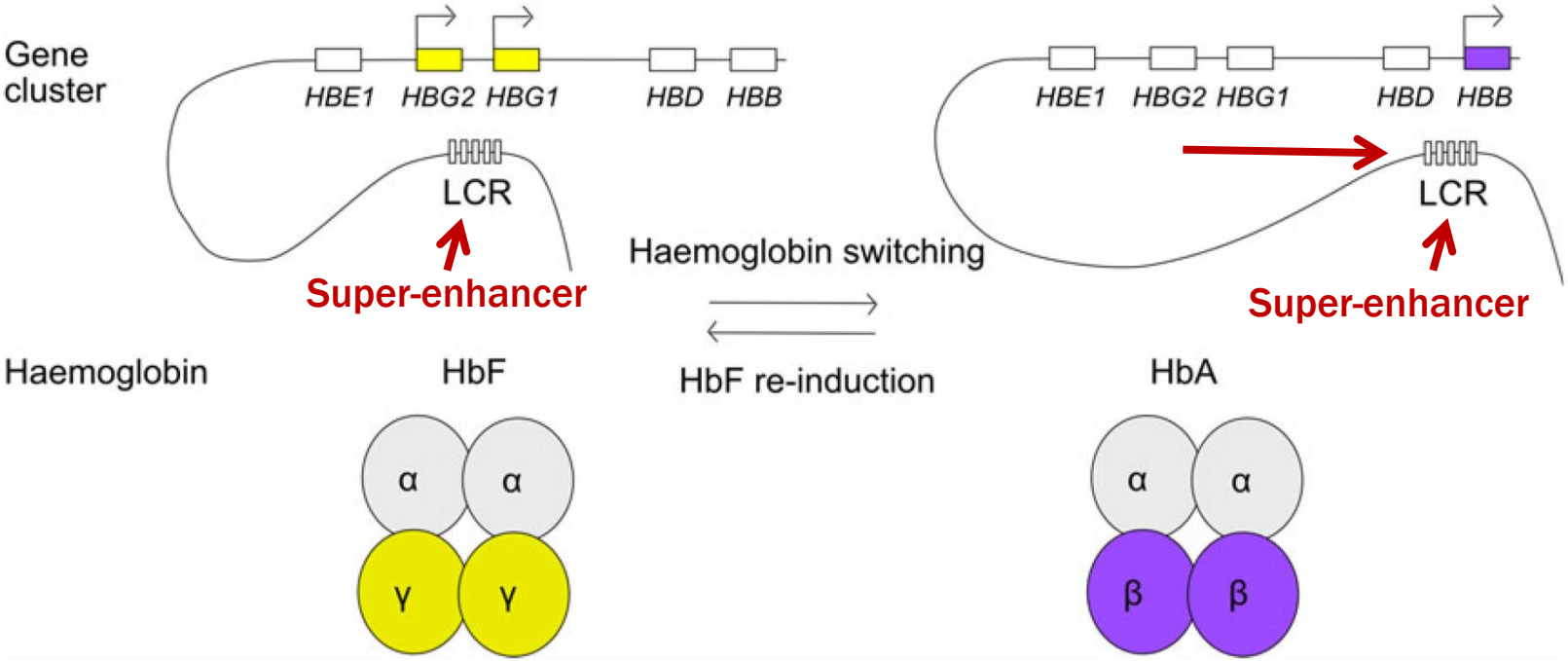
J Clin Invest. 2015;125(6):2363–2368

Am J Med Genet Part A 161A:865–870

BCL11 ist ein quantitativer Regulator von HbF

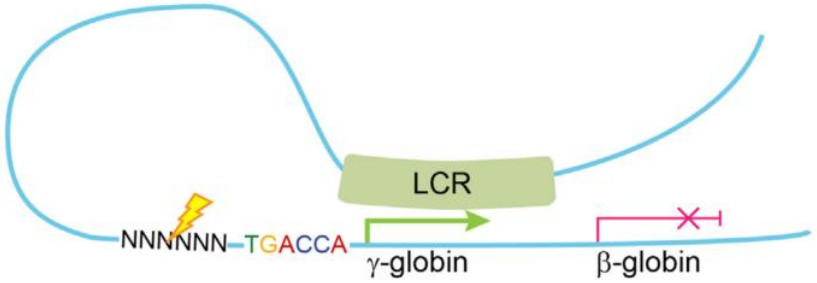
Ann. N.Y. Acad. Sci. 1368 (2016) 5–10

Wie unterdrückt BCL11 die Expression von HbF

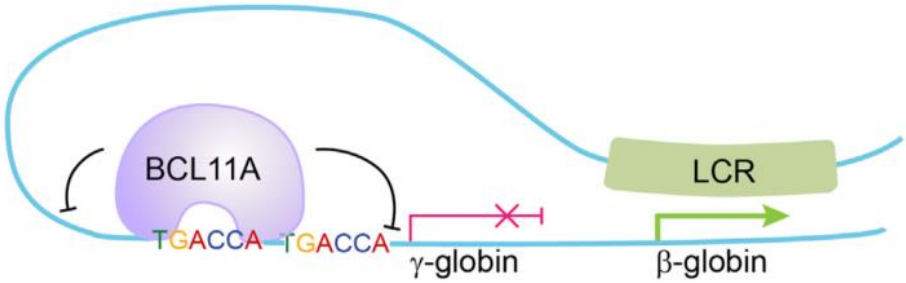


British Journal of Haematology, 2018, **180,** 630–643

HPFH or CRISPR edited erythroid cells

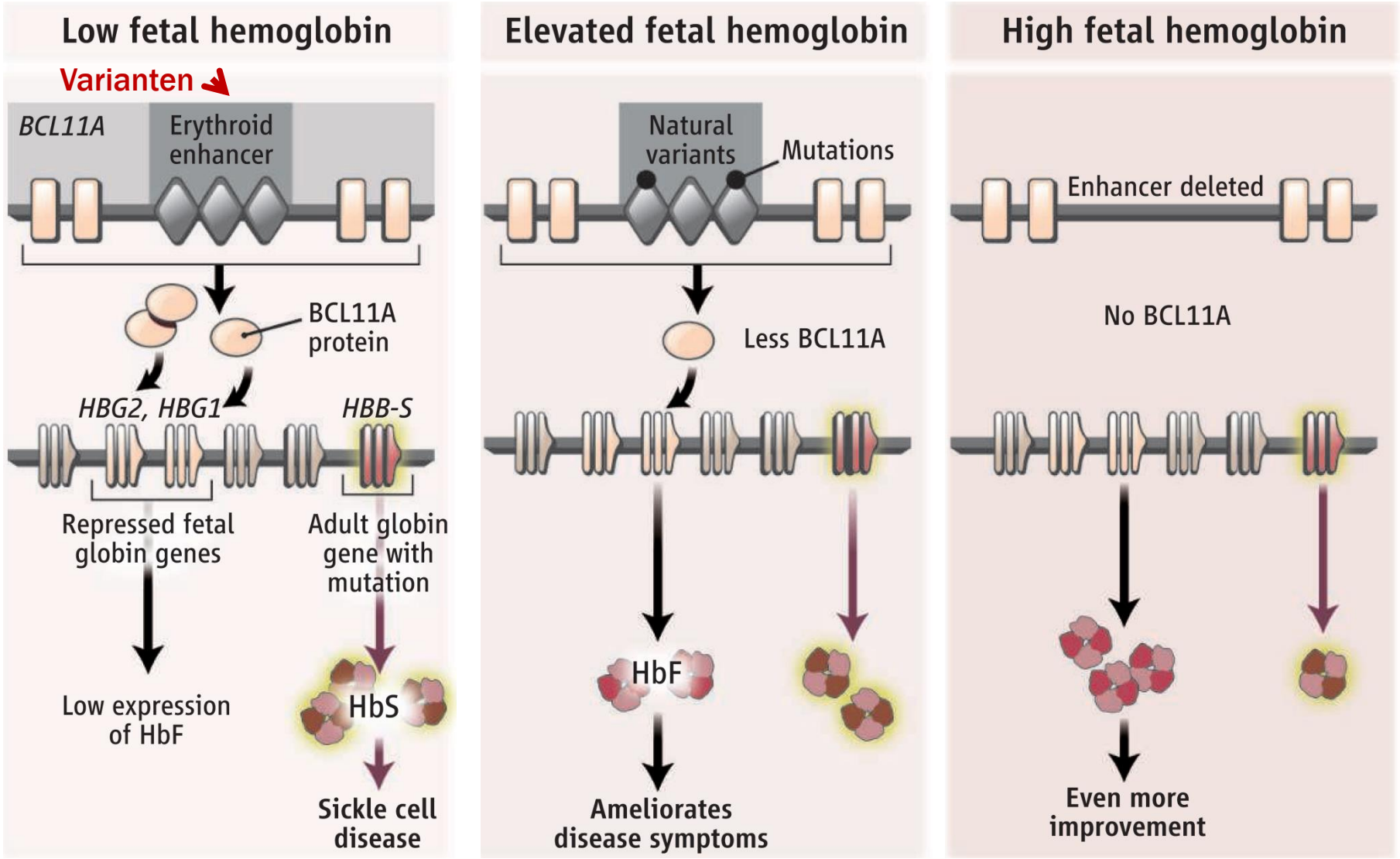


Normal adult human erythroid cells



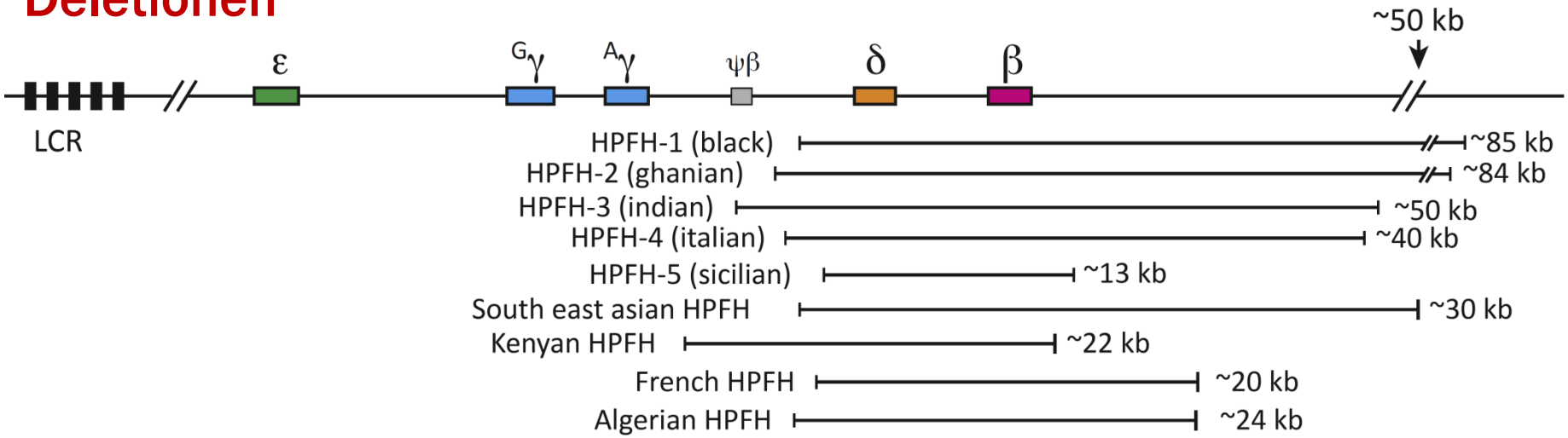
Cell *173*, 430–442, April 5, 2018

Mutationen, welche bei Individuen mit erhöhtem HbF gefunden werden, liegen in einer Enhancer Region in der intergenischen Region von BCL11A

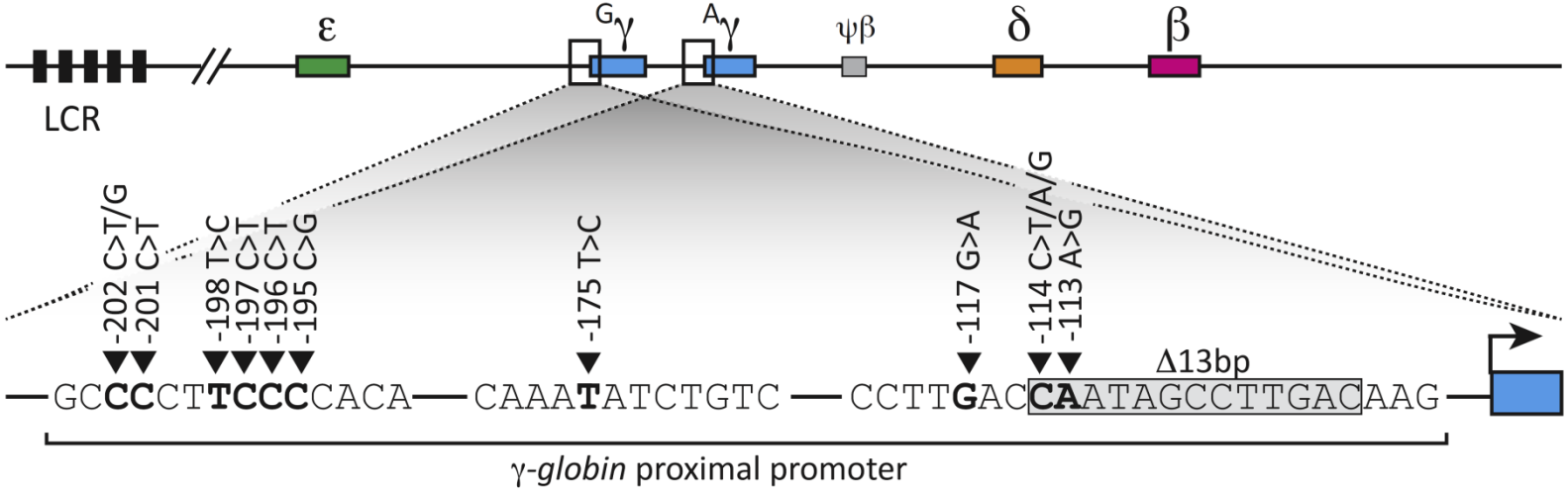


Kausale genomische Varianten bei Individuen mit hereditärer Persistenz von fetalem Hämoglobin (HPFH)

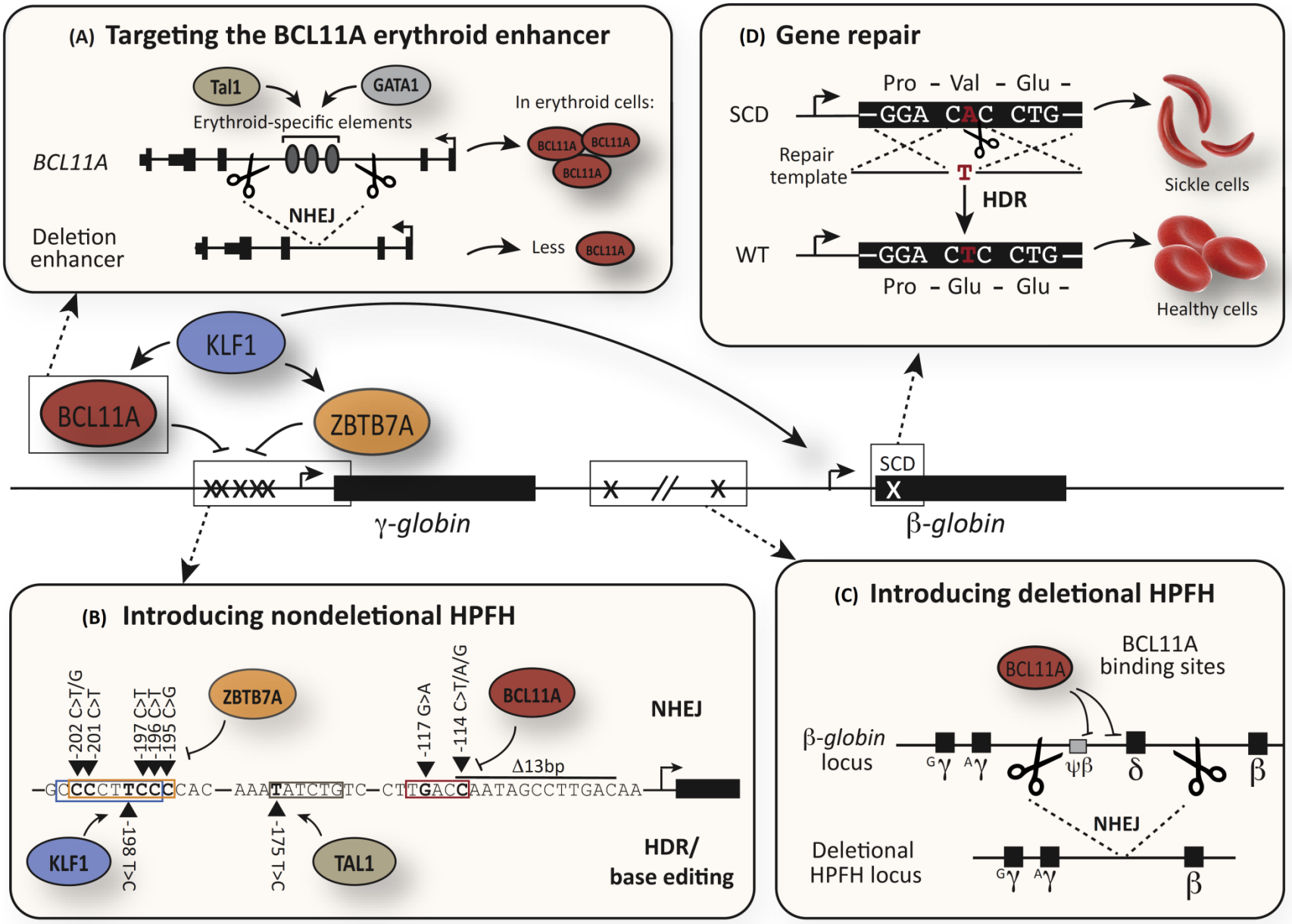
Deletionen



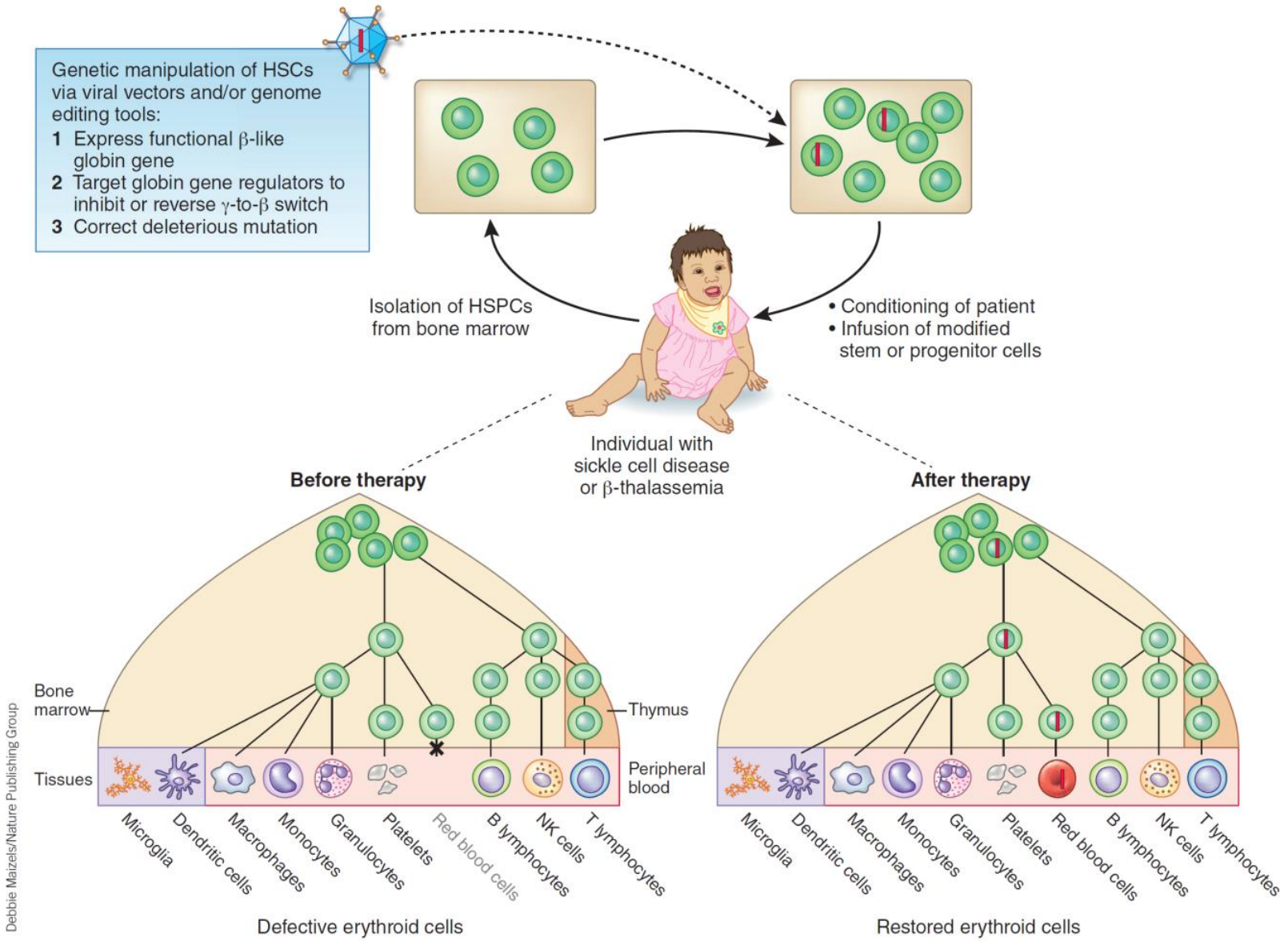
Mutationen



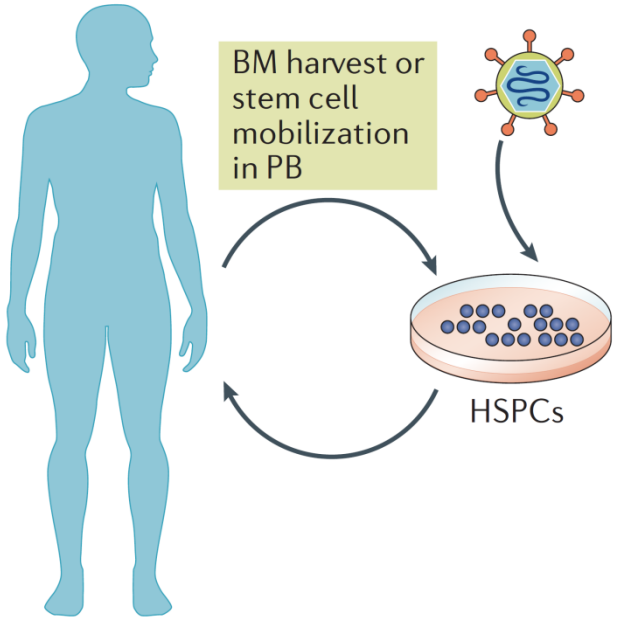
Trends in Genetics

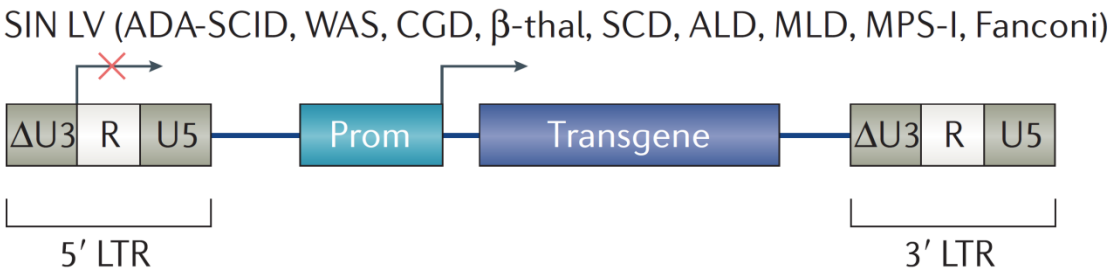

(A) Targeting the BCL11A erythroid enhancer
Tal1
GATA1
Erythroid-specific elements
BCL11A
NHEJ
Deletion enhancer
In erythroid cells:
BCL11A
Less
(D) Gene repair
Pro – Val – Glu –
SCD
GGA CAC CTG
Repair template
T
HDR
WT
GGA CTC CTG
Pro – Glu – Glu –
Sickle cells
Healthy cells
KLF1
BCL11A
ZBTB7A
γ-globin
SCD
β-globin
(B) Introducing nondeletional HPFH
-202 C>T/G
-201 C>T
-197 C>T
-196 C>T
-195 C>G
ZBTB7A
-117 G>A
-114 C>T/A/G
BCL11A
NHEJ
Δ13bp
GCCCCTTCCCCCAC—AAATATCTGTC—CTTGACCAATAGCCTTGACAA
-198 T>C
-175 T>C
KLF1
TAL1
HDR/
base editing
(C) Introducing deletional HPFH
BCL11A
BCL11A
binding sites
β-globin
locus
Gγ
Aγ
ψβ
δ
β
NHEJ
Deletional
HPFH locus
Gγ
Aγ
β

Stammzelltransplantation und genetische Manipulation von HSCs



Genetische Manipulation von HSCs bei SZE

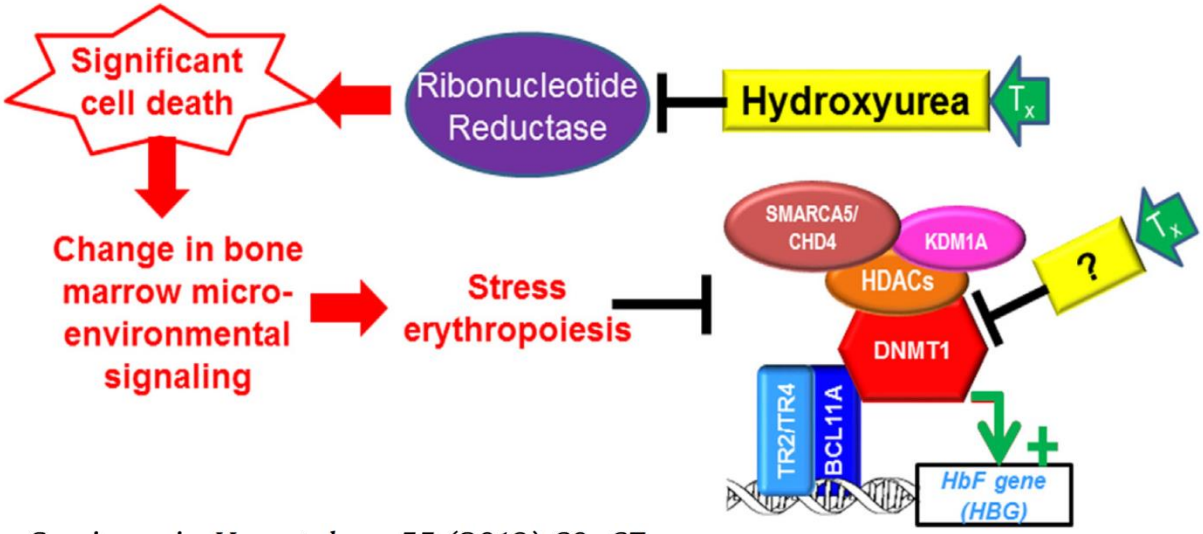




Trial number (phase)	Starting year; sites	Vector	Conditioning	Number of patients
NCT02151526 or HGB205 (phase I/II)	2013; France	SIN LV LCR-βprom-β-globin	Yes	3
NCT02140554 or HGB206 (phase I)	2014; USA	SIN LV LCR-βprom-β-globin	Yes	9
NCT02247843 (phase I)	2014; USA	SIN LV LCR-βprom-β-globin	Yes	1
NCT03282656 (phase I)	2018; USA	SIN LV LCR-βprom-BCL11A shRNA	Yes	1
NCT02186418-phase I/II	2014; USA, Jamaica	SIN LV LCR-βprom-β-globin	Yes	2

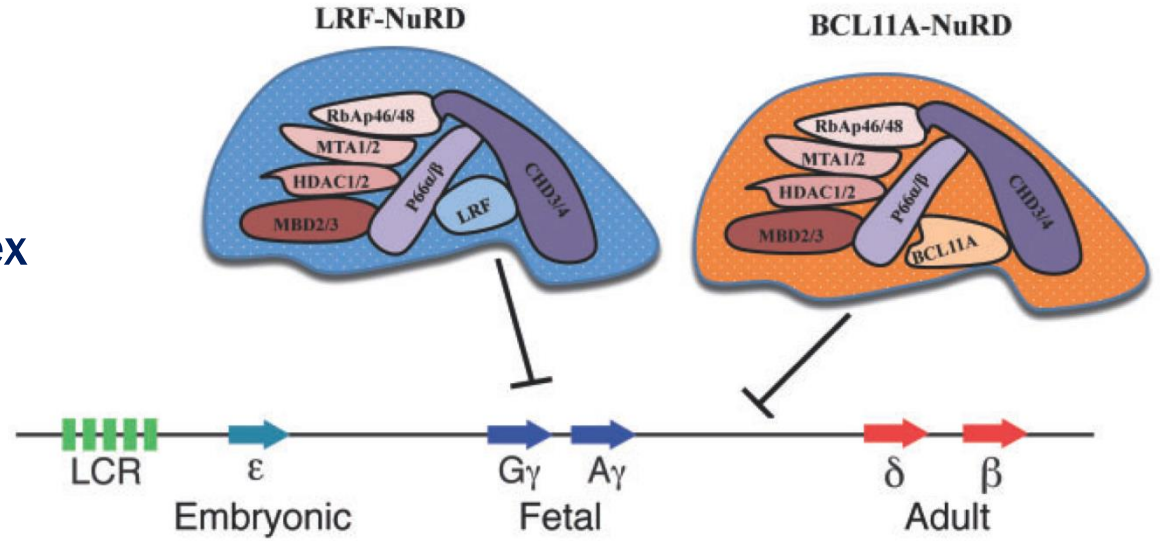
https://doi.org/10.1038/s41573-019-0020-9

Medikamentöse Erhöhung der F-Zellen



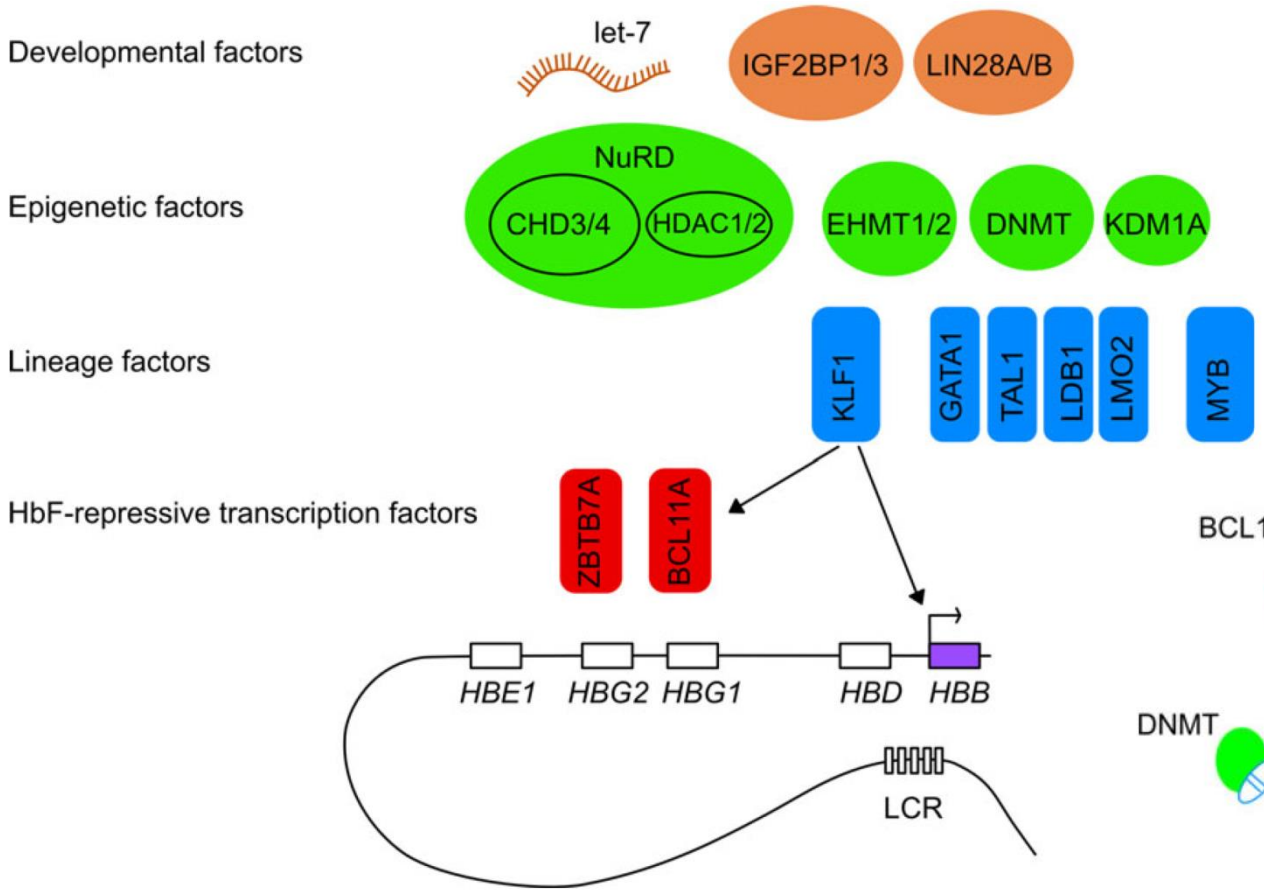
Seminars in Hematology 55 (2018) 60–67

The Nucleosome Remodeling and Deacetylase Complex NuRD

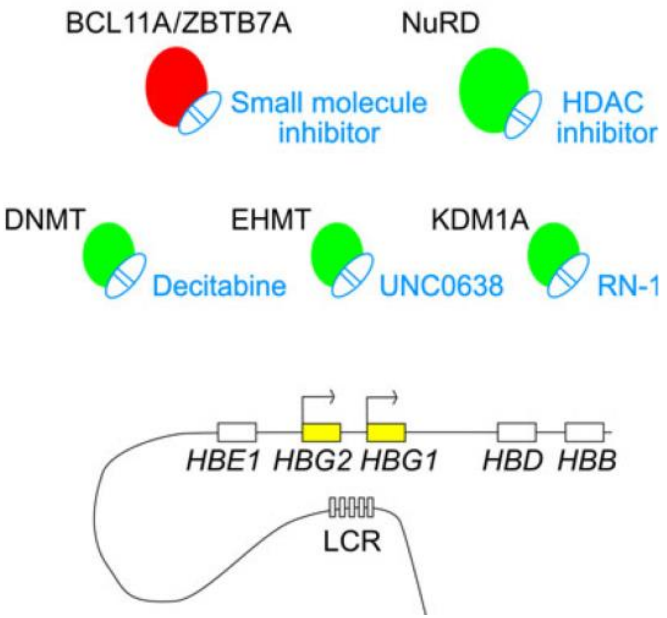


Human Molecular Genetics, 2016, Vol. 25, No. R2

HBF Switch - komplexe Interaktion diverser Mechanismen

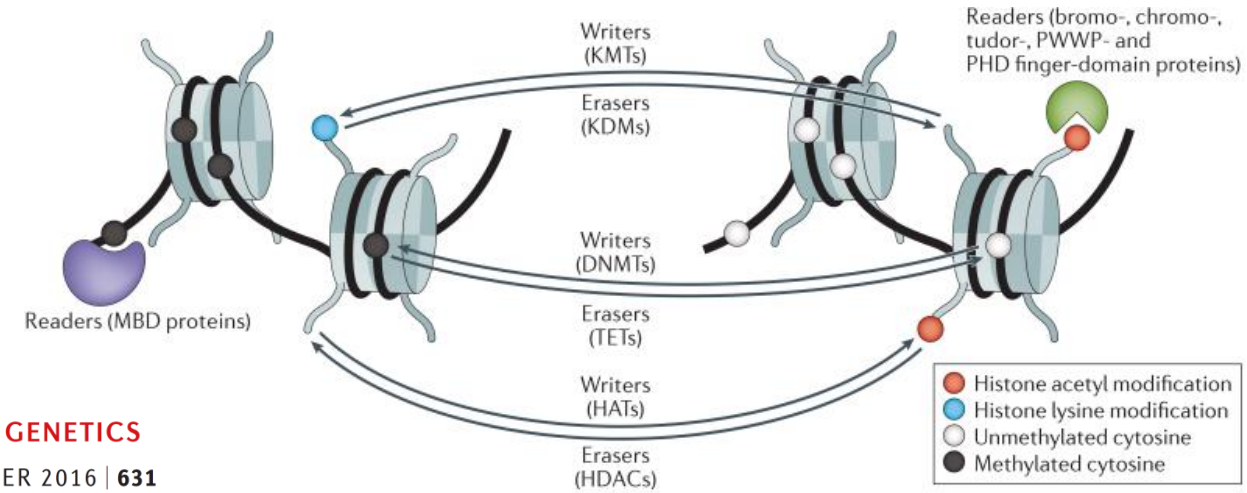


Therapeutische Zielstrukturen



British Journal of Haematology, 2018, **180,** 630–643

Epigenetische Modifikationen - Epidrugs

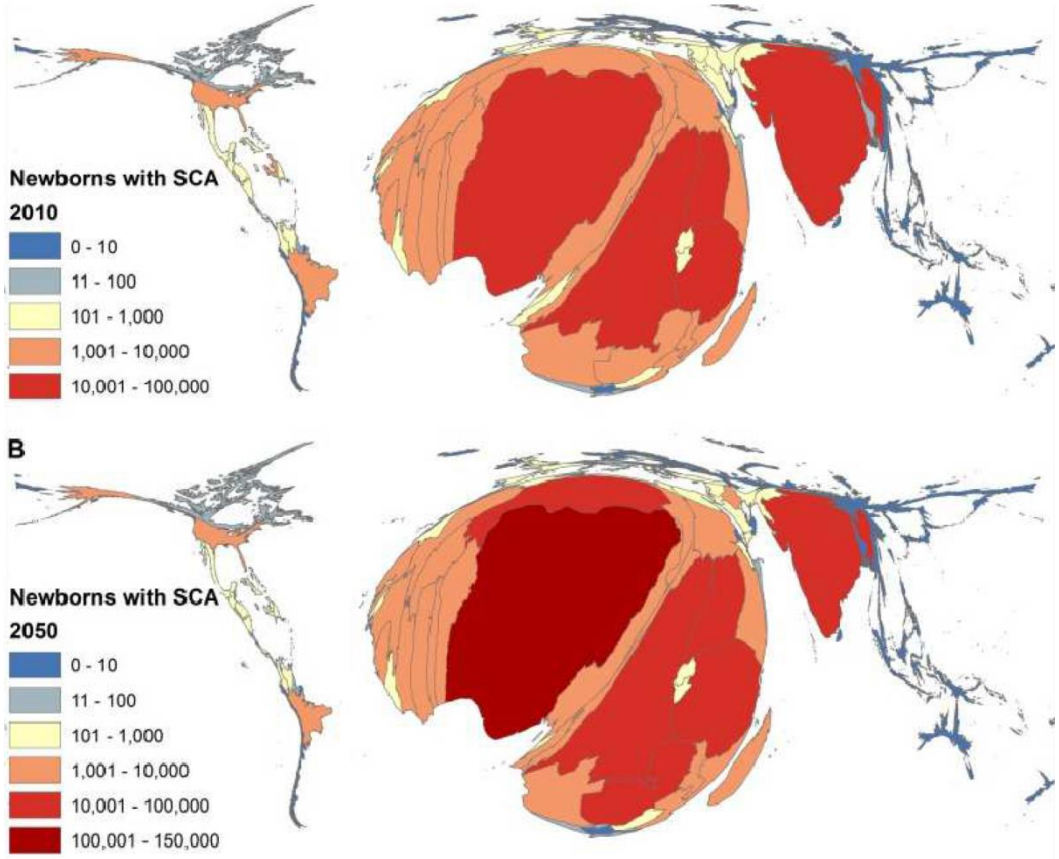


NATURE REVIEWS | GENETICS
VOLUME 17 | OCTOBER 2016 | 631

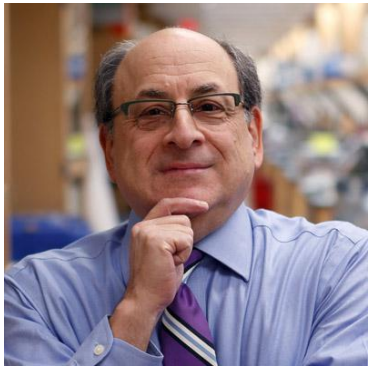
Trial	NCT identifier	Status	Reported results
Study of decitabine and THU in patients with SCD	NCT01685515	Active, not recruiting	N/A
Gum arabic as a HbF agent in SCA	NCT02467257	Completed	None
Hydroxyurea and erythropoietin to treat SCA	NCT00270478	Completed	None
Study to determine the maximum tolerated dose, safety and effectiveness of pomalidomide for patients with SCD	NCT01522547	Completed	None
Effects of HQK-1001 in patients with SCD	NCT01601340	Completed	None
Decitabine for high-risk SCD	NCT01375608	Completed	4·8% average HbF increase
Effectiveness of arginine as a treatment for SCA	NCT00513617	Completed	None for HbF induction
Fetal haemoglobin induction treatment with metformin	NCT02981329	Recruiting	N/A
Gene transfer for patients with SCD	NCT02186418	Recruiting	N/A
Study of panobinostat in patients with SCD	NCT01245179	Recruiting	N/A
A study to evaluate safety, pharmacokinetic, and biological activity of INCB059872	NCT03132324	Recruiting	N/A
Efficacy of vorinostat to induce HbF in SCD	NCT01000155	Terminated	None; closed for slow accrual

VOLUME 17 | OCTOBER 2016 | 631

British Journal of Haematology, 2018, **180,** 189–200



Piel et al, PLOS Medicine, 2013



‚...There are moonshots for cancer, but there are no moonshots for SCD, which has comparable impact globally...' [Stuart Orkin]

https://www.hhmi.org/scientists/stuart-h-orkin