תלסמיה 2025

ד"ר עידית פזגל

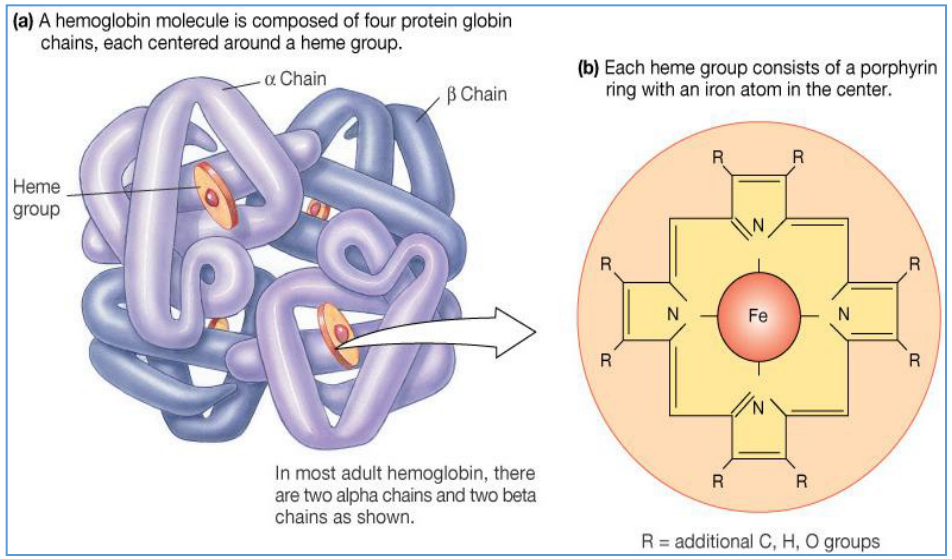
המרכז הכוללני לתלסמיה, המוגלובינופתיות ואנמיות נדירות
ביה"ח בילינסון, מרכז רפואי רבין, פתח תקוה

דצמבר 2025

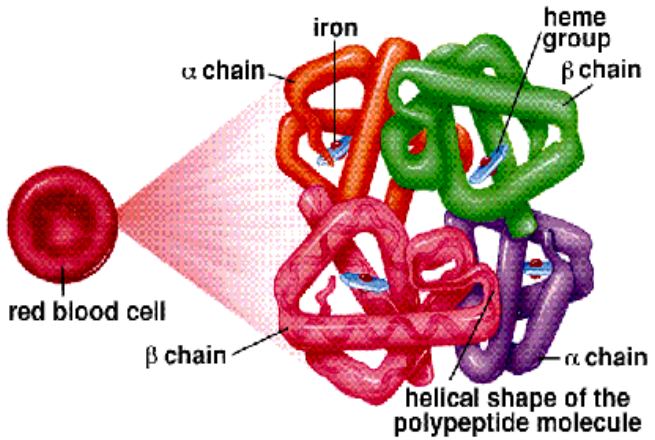
Hemoglobin Review

- 4 globin polypeptide complex:

  2 α & 2 non- α, bound non-covalently
- 4 complexes of heme with iron bound
- 4 O_2 binding sites



- Four subunits
  - two α
  - two β
- Iron
- Heme
- Binds 4 O_2



Genetics

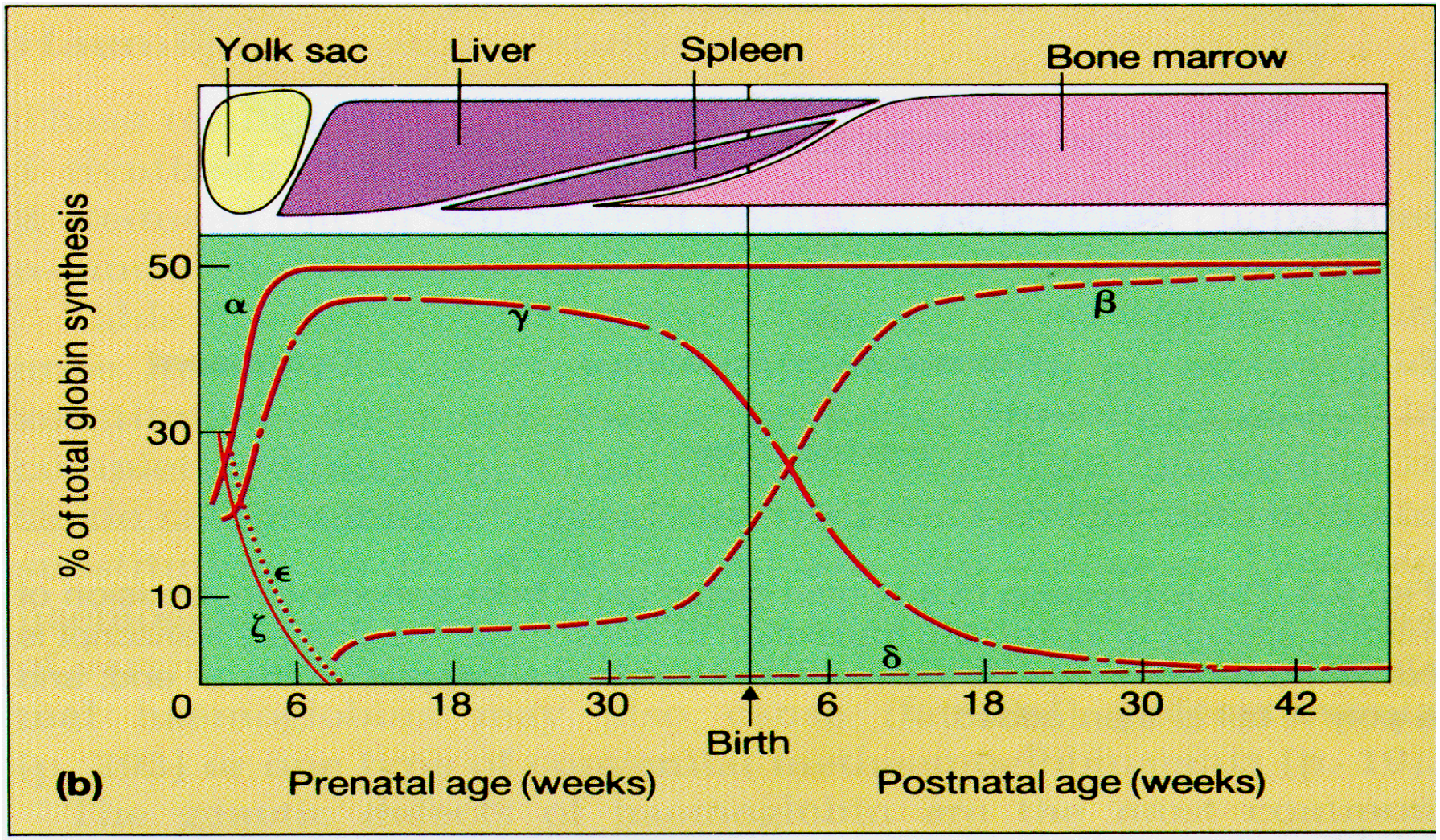
- **Alpha globins are coded on chromosome 16**
  - Two genes on each chromosome
  - Four genes in each diploid cell
  - Gene deletions result in Alpha-Thalassemias
  - Zeta globin genes - Gower's hemoglobin (embryonic) - also on chromosome 16
- **Beta globins are coded on chromosome 11**
  - One gene on each chromosome
  - Two genes in each diploid cell
  - Point mutations result in Beta-Thalassemias
  - Delta (Hgb A2), Gamma (Hgb F) and Epsilon (embryonic) - also on chromosome 11

Hemoglobin Types

Hemoglobin Type	Globin Chains
• Hgb A1..... 94.0-96.0%	$\alpha_2\beta_2$
• Hgb A2 .....3.0-3.5%	$\alpha_2\delta_2$
• Hgb F ..... <1%	$\alpha_2\gamma_2$
• Hgb H	β_4
• Bart's Hgb	γ_4
• Hgb S	$\alpha_2\beta_{26}^{glu\rightarrow val}$
• Hgb C	$\alpha_2\beta_{26}^{glu\rightarrow lys}$

Pre & Postnatal Globin Synthesis

Types & Sites of Production

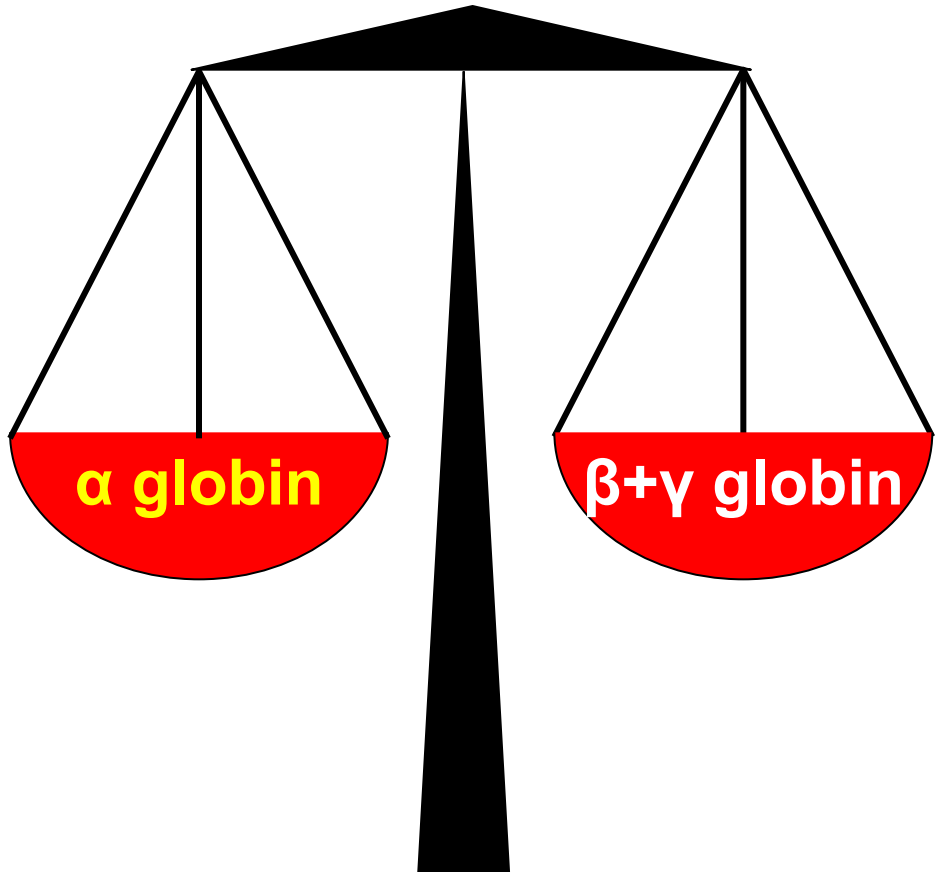


What is Thalassemia?

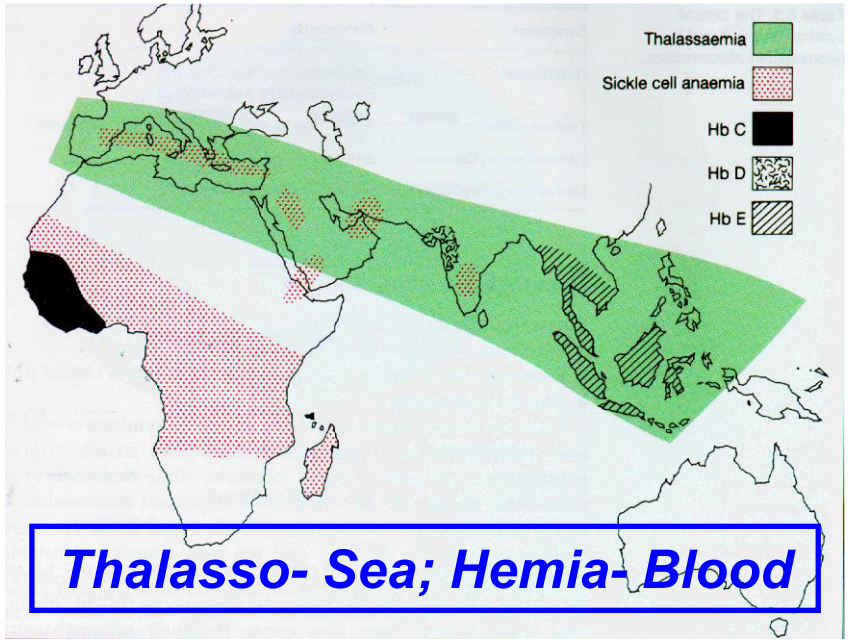
- The two main types,

  α and β thalassemia, caused by imbalance in the number of α and β globin chains.

- At least 1000 distinct mutations. Varying degrees of severity.

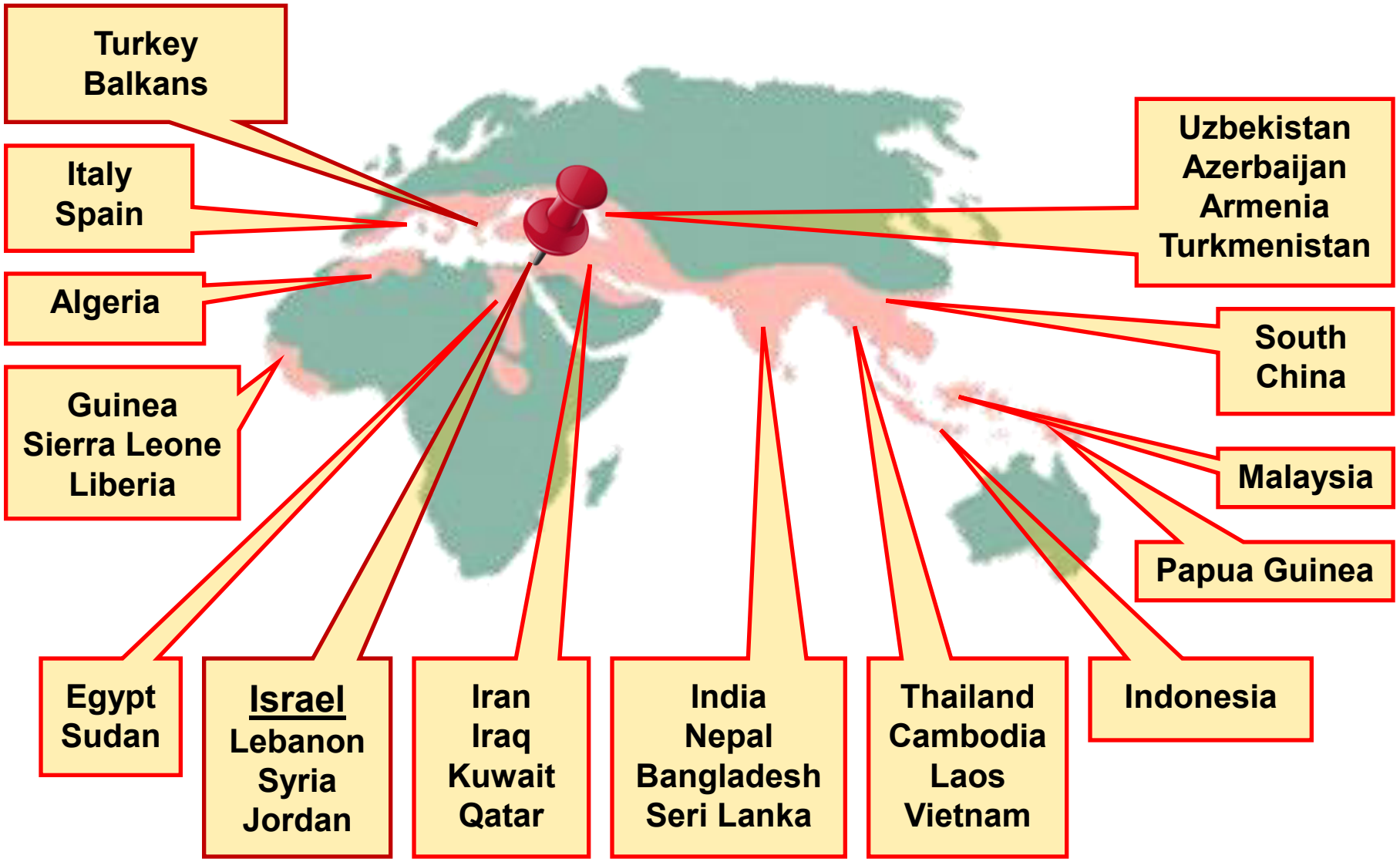


Epidemiology of β Thalassemia

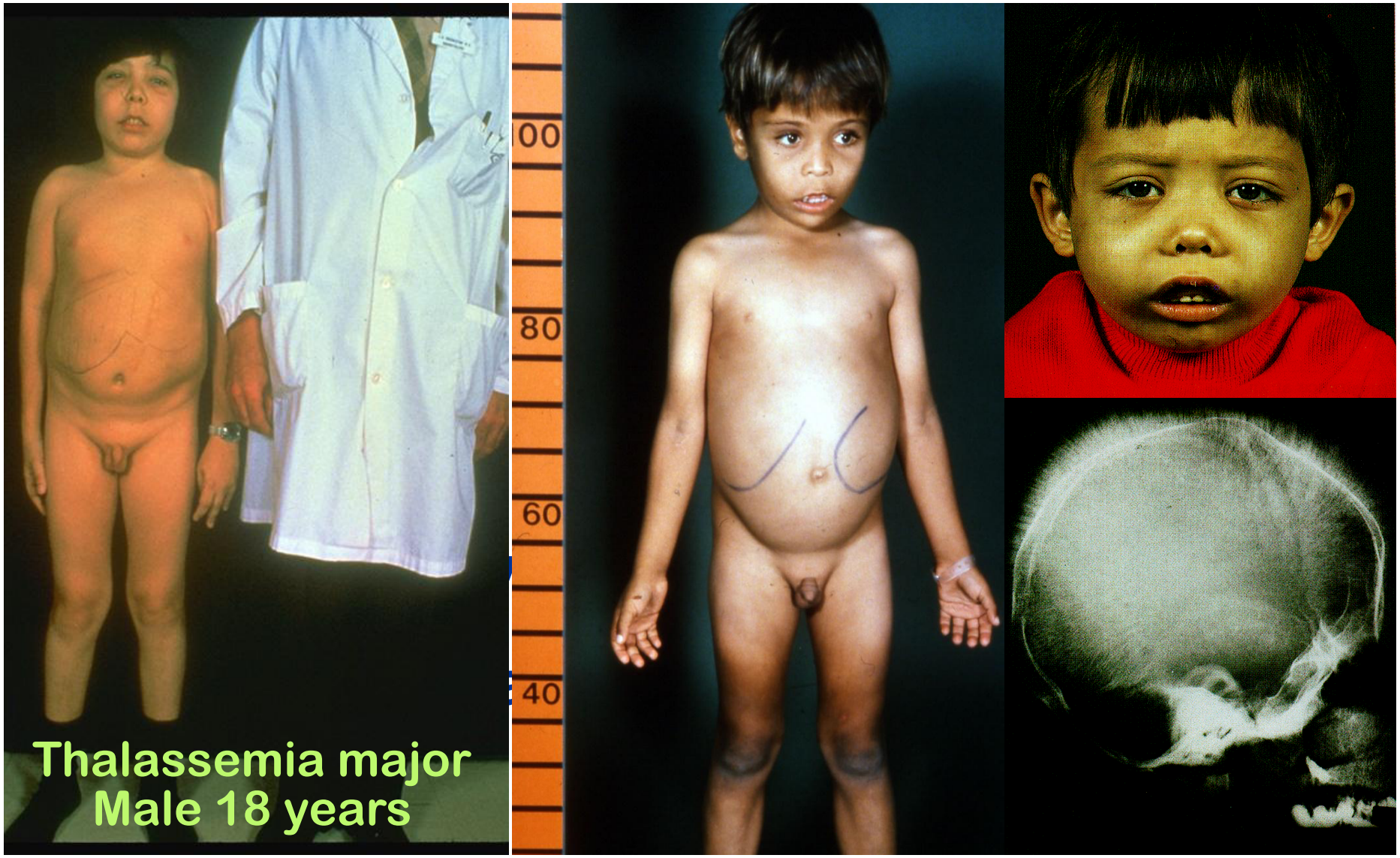


- The 'thalassemia belt' extends along the shores of the Mediterranean, throughout the Arabian peninsula, Turkey, Iran, India and SE Asia, including Thailand, Cambodia, southern China.
- In Mediterranean area ~15-25 million of healthy carriers

Thalassemia: Epidemiology



Clinical Manifestations of Thalassemia



Clinical Classification and Management of Thalassemia

Thalassemia major

- Homozygous disorder
- Significant imbalance of α / β globin chains
- Severe anemia presenting early in life
- Requires lifelong RBC transfusions
- If untreated, leads to death usually in first decade

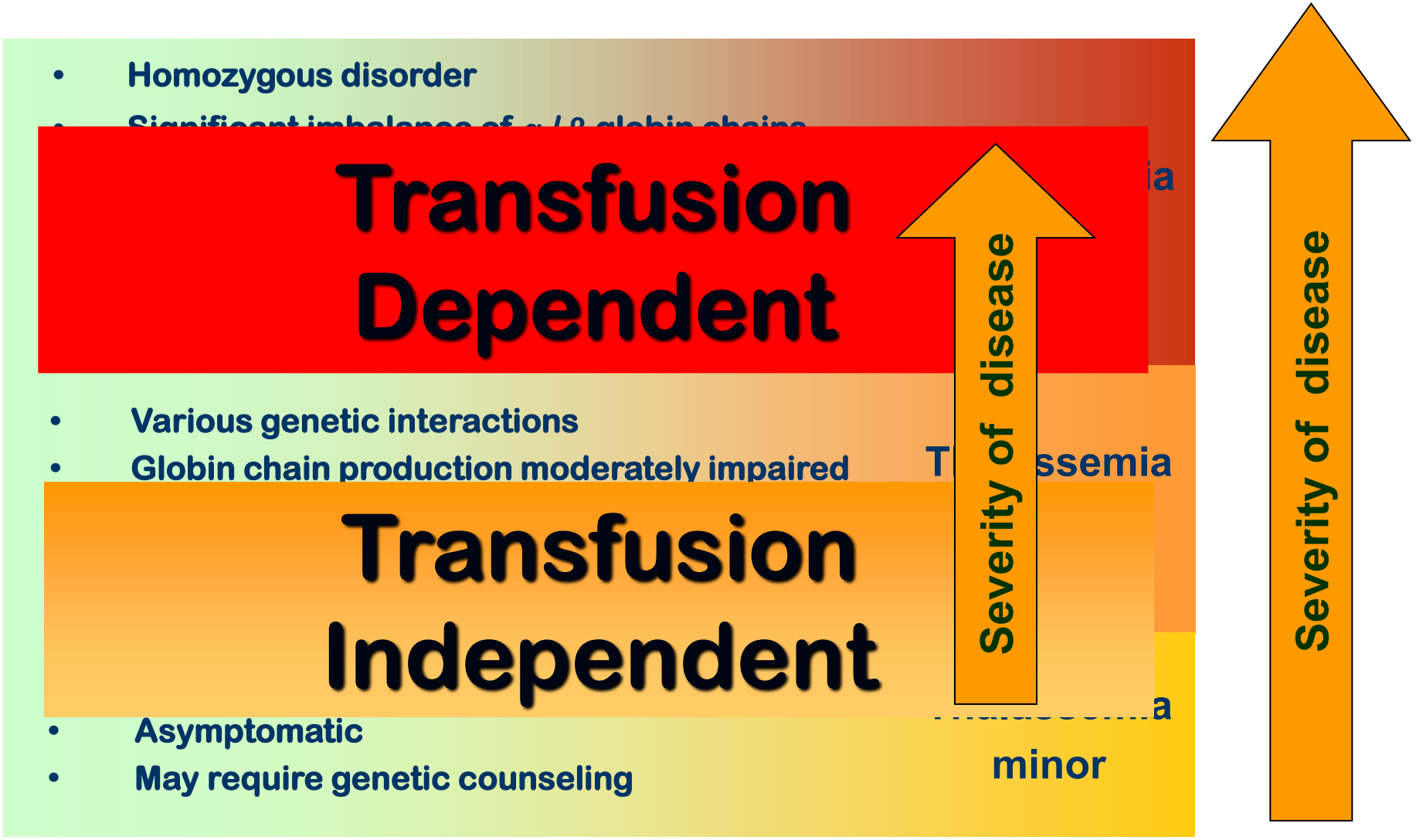
Thalassemia intermedia

- Various genetic interactions
- Globin chain production moderately impaired
- Mild anemia, diagnosed usually in late childhood
- Occasional blood transfusions may be required

Thalassemia minor

- Heterozygous condition
- Asymptomatic
- May require genetic counseling

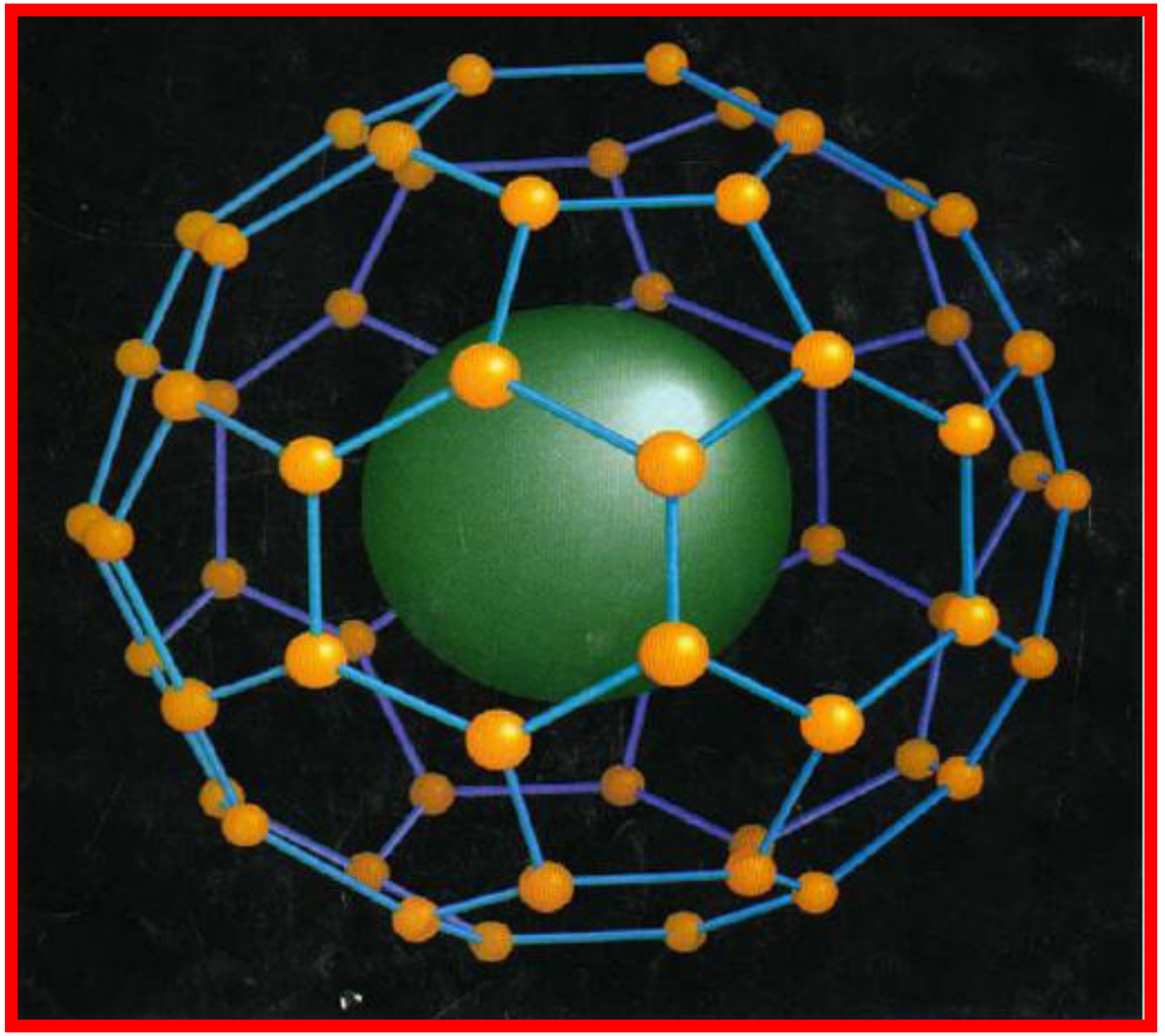
Clinical Classification and Management of Thalassemia



Iron Homeostasis
&
Iron Overload

Ferritin protein consisting
of 24 subunits

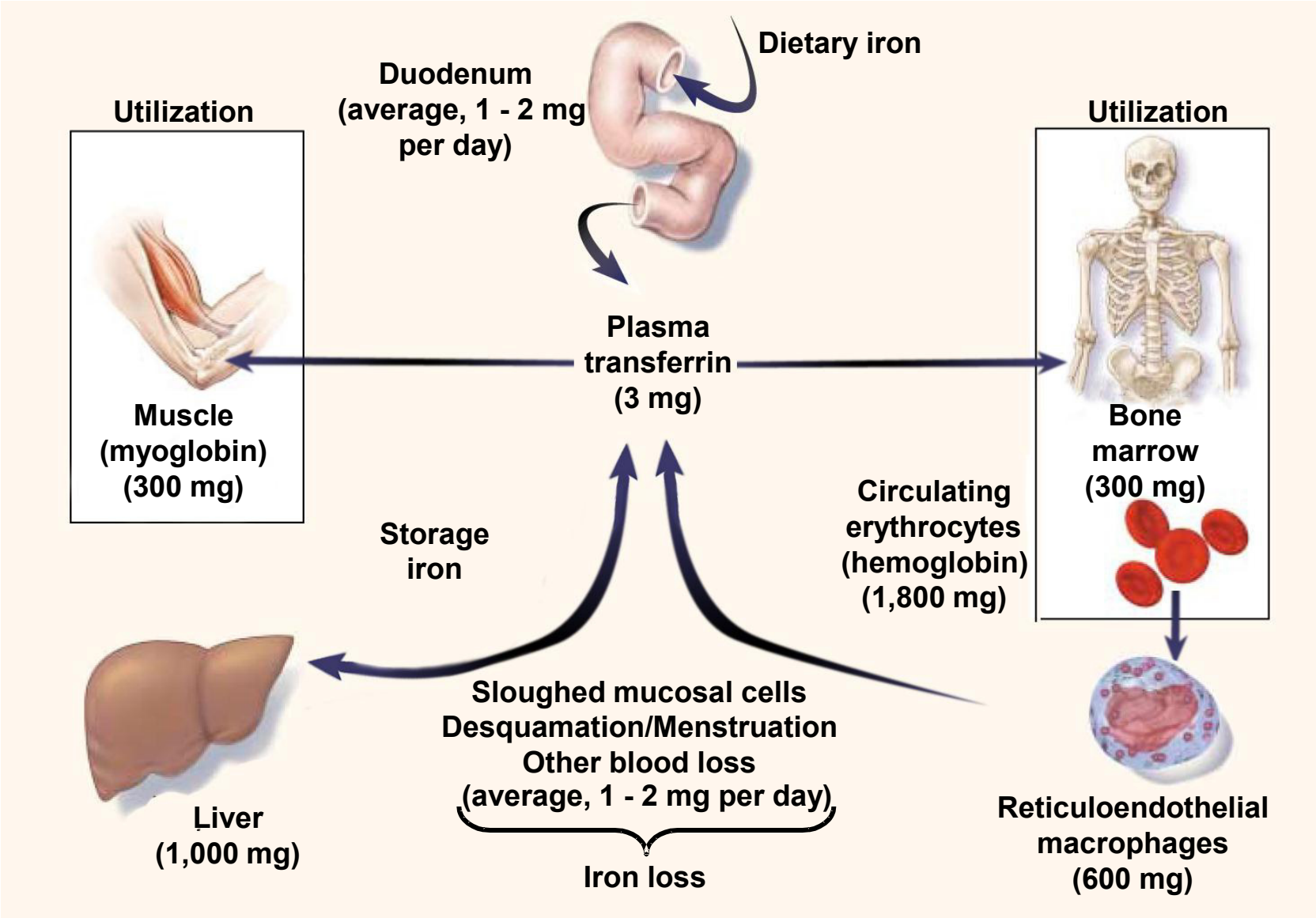
Iron: The name of the game



The iron economy is well-balanced

מאזן הברזל בגוף
בשיווי משקל עדין ומדויק

Body Iron Distribution and Storage



Blood transfusion overwhelms the iron balance

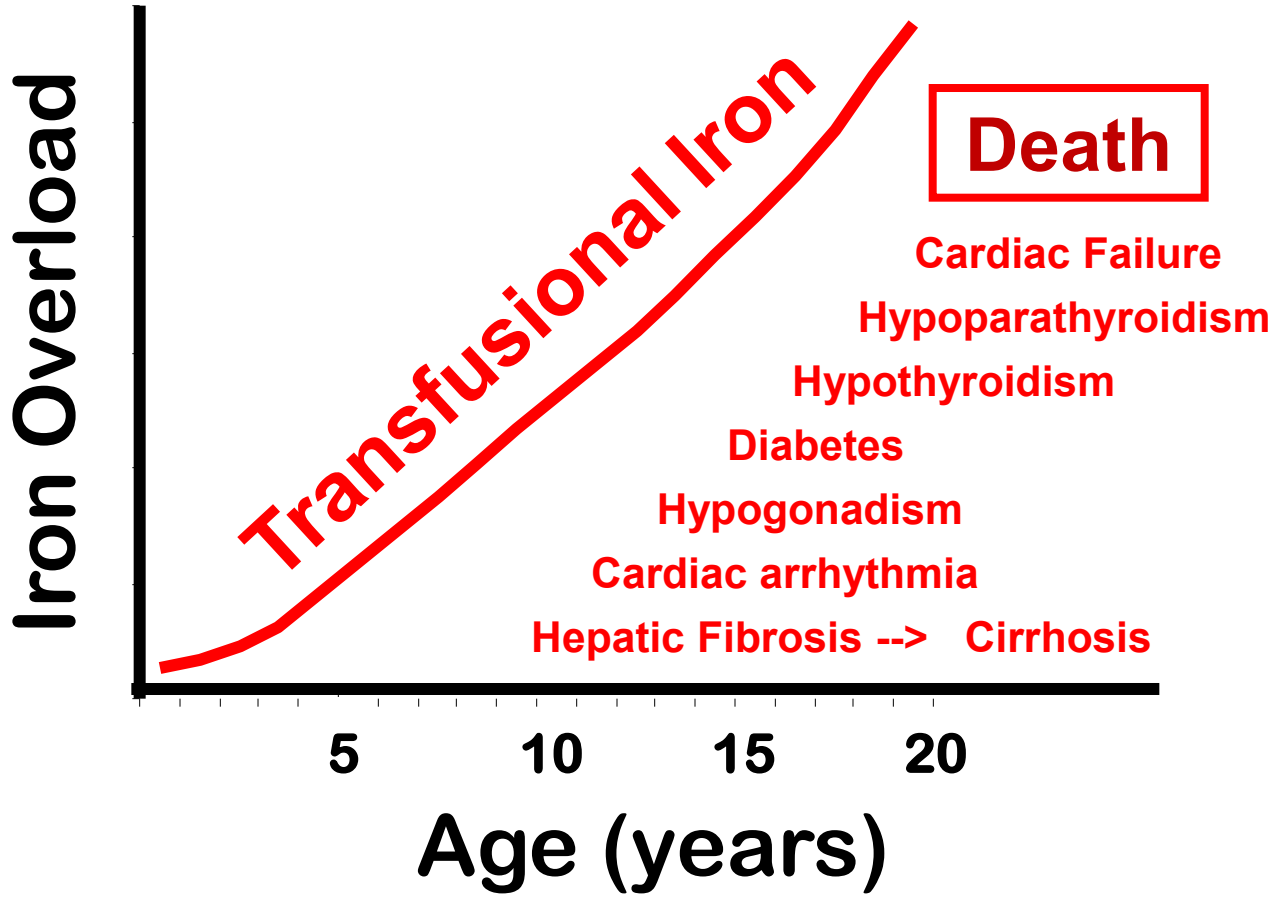
- Normal daily iron flux: 1-2 mg
- Each unit of PRBC: 200-250 mg
- Normally: total body iron ~3-4 g

- Chronic transfusion-dependent patients:

  iron excess of 0.3-0.7 mg/kg/day, equivalent to 4–10 g of iron per year
- Iron accumulation via repeated blood transfusions

Too much iron is a bad thing

Morbidity and Mortality from Transfusional Iron Overload

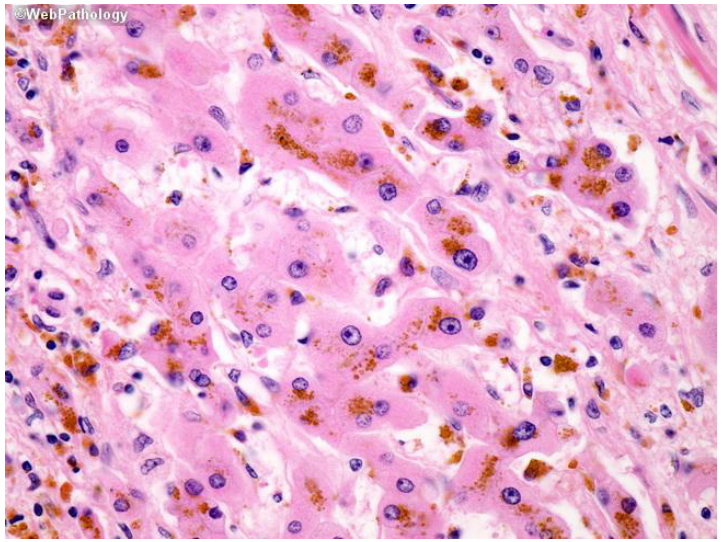


Thalassemia, Iron Overload & the Liver

- Iron accumulation in hepatocytes
- Impaired LFT
  - 2nd to iron overload
  - 2nd to iron chelation drugs
- Hepatic Fibrosis
- Hepatic Cirrhosis

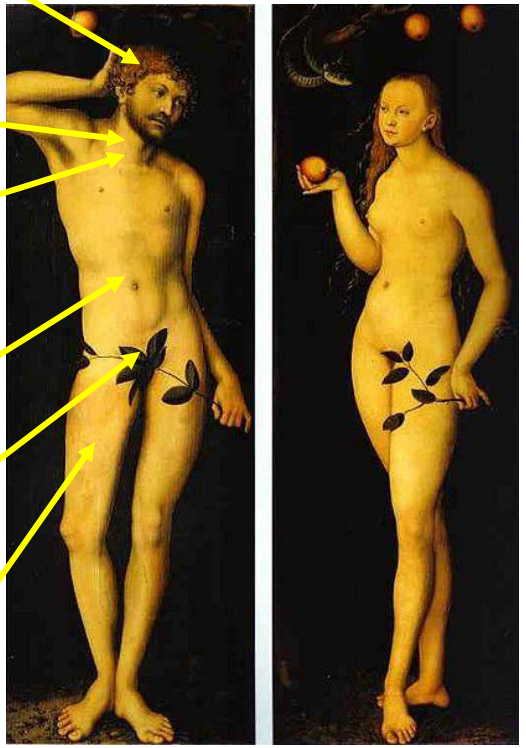
- HCV infection

- HCC (late complication)



הפרעות אנדוקריניות בתלסמיה

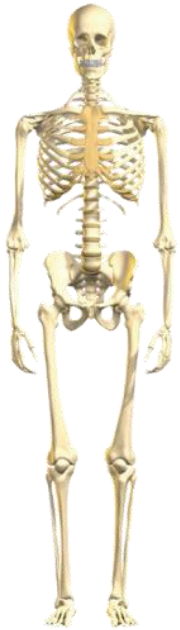
- תת פעילות היפותלמית היפופיזרית ..... 80% - 90%
- תת פעילות התירואיד ..... 3% - 5%
- תת / יתר פעילות פאראתירואיד ..... 5% - 10%
- סכרת ..... 5% - 15%
- אי ספיקה גונדאלית ראשונית ..... 1% - 2%
- אוסטיאופורוזיס אוסטיאופניאה ..... 70% - 80%

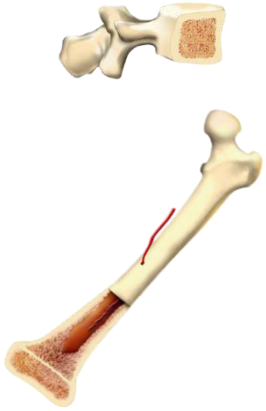


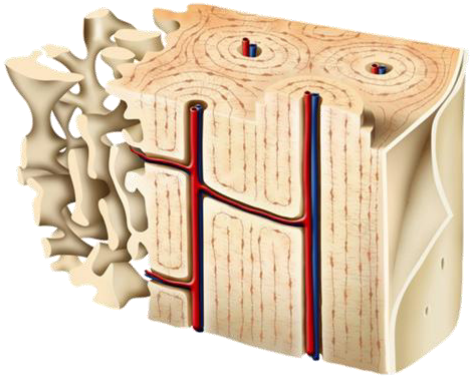
Osteopenia & Osteoporosis in the adult thalassemia patient

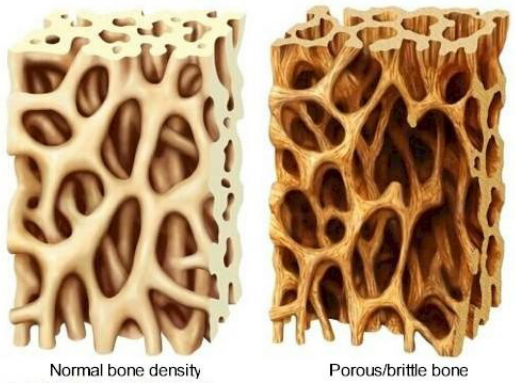
Frequency in TM patients up to 90%
Pathogenesis complex & multifactorial:

- **Hypogonadism**
- **Bone marrow expansion**
- **Direct iron toxicity on osteoblasts**
- **Chelating therapy**
- **GH deficiency**









Cardiac complications in the adult thalassemia patient

Iron overload complications

1. Reversible oxidative damage induced myocyte failure
2. Arrhythmia, heart block, often life threatening
3. Arterial changes - loss of vascular compliance

Non-iron overload complications

1. Pulmonary hypertension
2. Arrhythmia – particularly AF > 40 years old
3. Myocardial Infarction, CHF
4. Cardiac function changes

CARDIAC COMPLICATIONS IN THALASSEMIA MAJOR. M Walker, J Wood, A Taher.
TIF Guidelines for the Management of TDT. 3rd edition, 2014.

High Incidence of Silent Cerebral Infarcts in Adult Patients with Beta Thalassemia Major

I Pazgal, E Inbar, M Cohen, O Shpilberg, P Stark

Thrombosis Research 144 (2016) 119–122

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

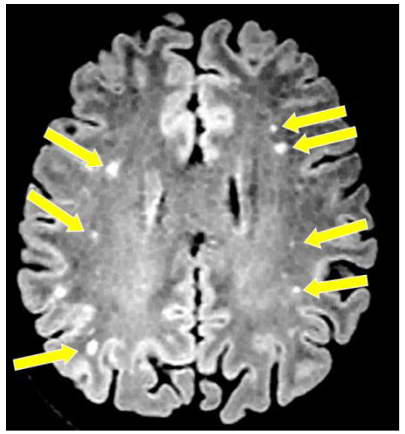
Full Length Article

High incidence of silent cerebral infarcts in adult patients with beta thalassemia major

Idit Pazgal [a,c], Edna Inbar [b,c], Maya Cohen [b,c], Ofer Shpilberg [a,c], Pinhas Stark [a,c,*]

- **Brain MRI studies in 28 adult TDTM patients**
- **Focal bright foci in the cerebral white matter in 17 (60.7%) patients; most of them had multiple lesions**
- **Significant association with elevated serum ferritin (p<0.031)**

- **Effective continuous ICT,**
- **preventive low dose aspirin, & routine periodical brain MRI are recommended**



Treatment of Thalassemia:

RBC transfusions

Annals of Hematology
https://doi.org/10.1007/s00277-020-04104-4

ORIGINAL ARTICLE

Alloimmunization and autoimmunization in adult transfusion-dependent thalassemia patients: a report from a comprehensive center in Israel

Idit Pazgal[1,2] · Vered Yahalom[3] · Bruria Shalev[3] · Pia Raanani[1,2] · Pinhas Stark[1,2]

Received: 8 October 2019 / Accepted: 27 May 2020

- This study is the first report from Israel showing a substantially high rate (42.5%) of alloimmunization among 48 adult TD TM patients.
- Alloimmunization rate was higher in patients who started transfusion later in life and had been splenectomized.
- Early initiation of RBC transfusions, avoidance of splenectomy and extended Rh and K antigen matching, can reduce the incidence of alloimmunization in TD TM patients.

Beta Thalassemia Major: Life Expectancy

Without regular transfusion:

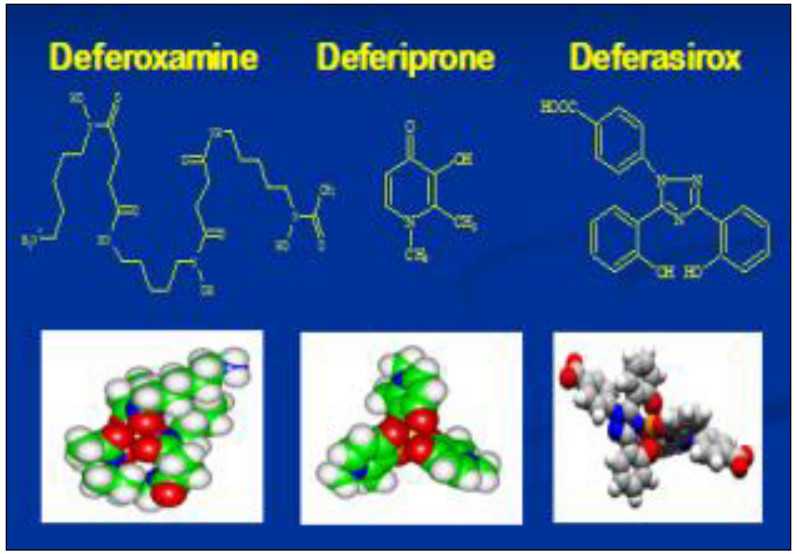
Less than 10 years

With regular transfusion:

Less than 20 years

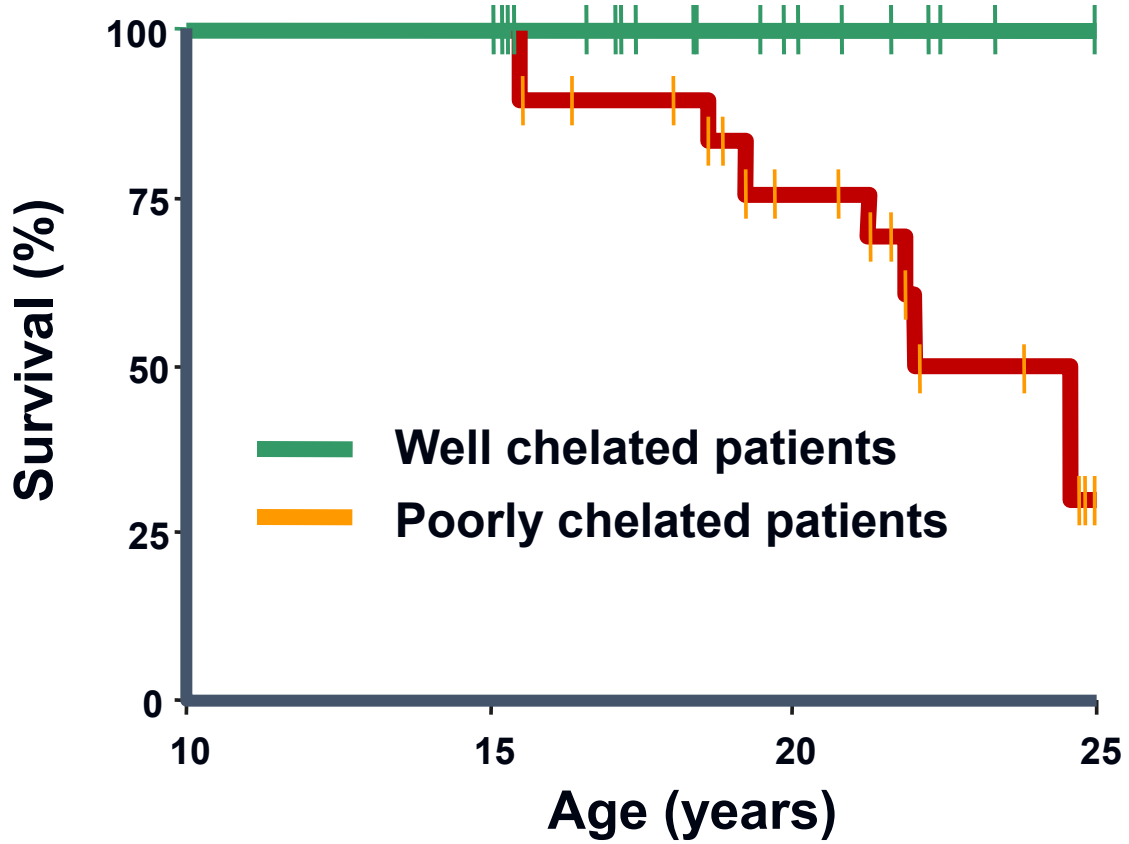
Treatment of Thalassemia:

Iron chelation therapy



Chelation Therapy and Survival

Brittenham GM et al. *N Engl J Med* 1994;331:567–573



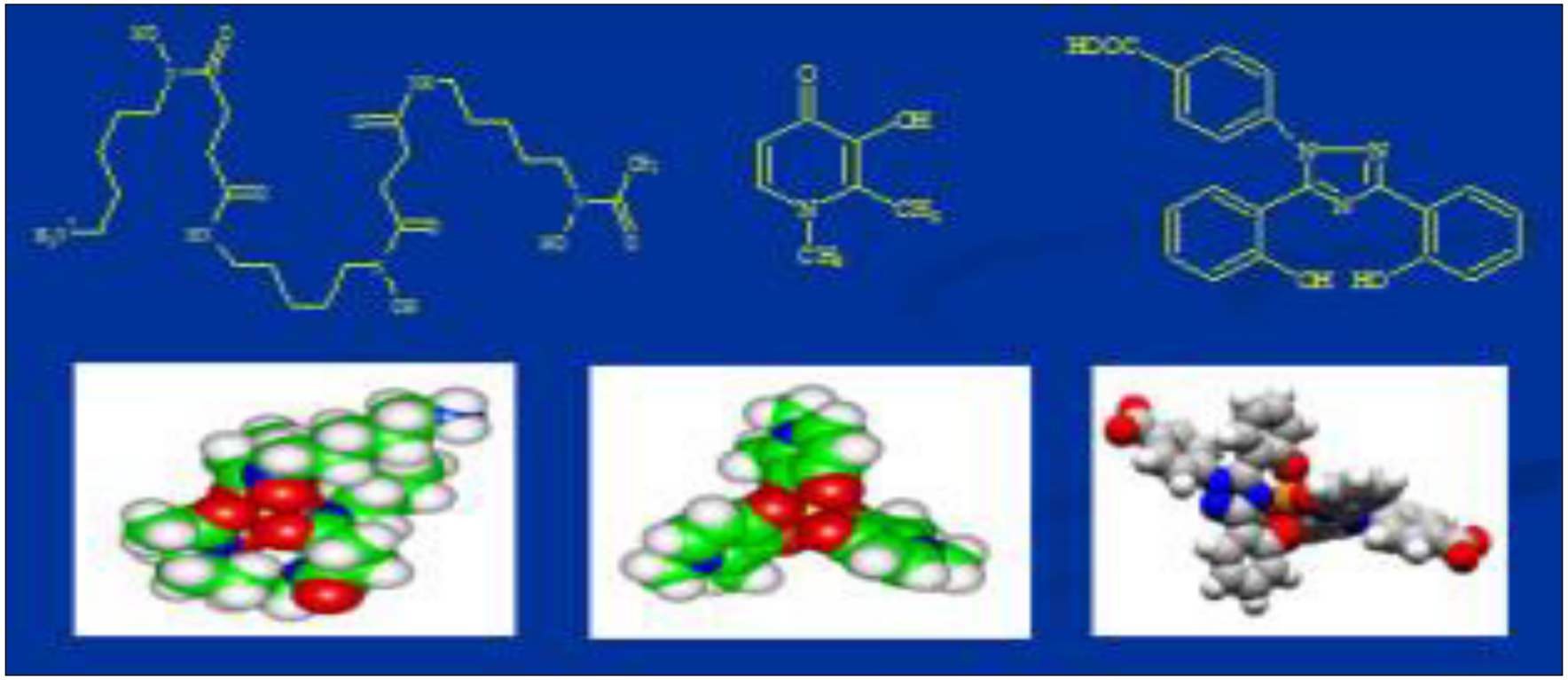
Probability of survival to at least 25 years of age in poorly chelated patients was just <u>one-third</u> that of patients whose iron levels were well managed

Currently Marketed Iron Chelators

DFO
Deferoxamine

DFP
Deferiprone

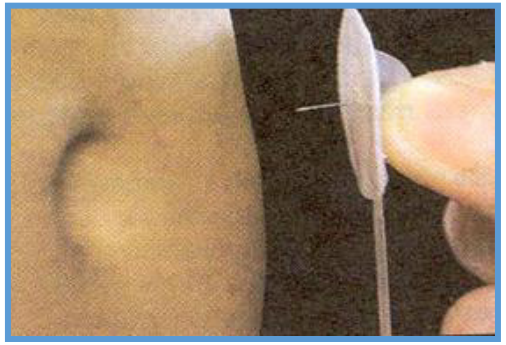
DFX
Deferasirox



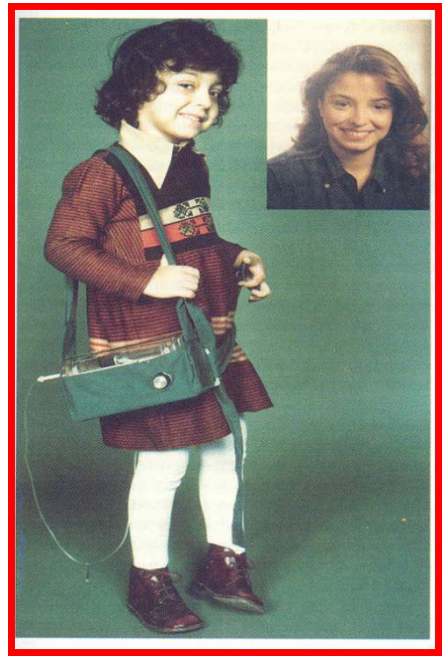
Desferrioxamine, Desferal

- FDA Approval: 1968
- EU Approval: 1973 (UK first)

- Short half-life (20 minutes), must be given by continuous infusion
  - 8 to 12 hours/day
  - 5 to 7 days/week



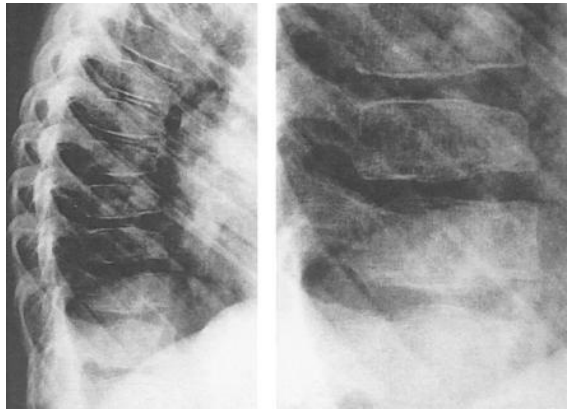
Then…

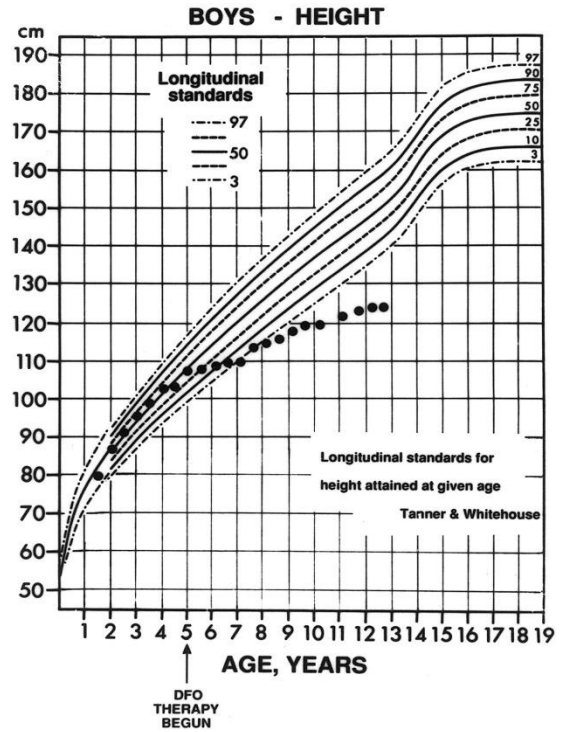


& now

Desferrioxamine: Important AEs

- Failure of linear skeletal growth & dysplasia due to DFO toxicity
- Sensorineural hearing loss
- Retinal toxicity
- Yersinia infection
- ?Osteoporosis

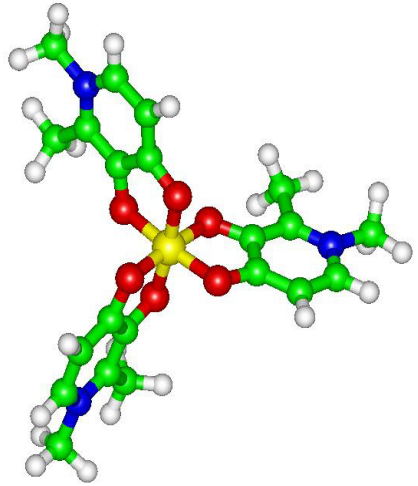




Deferiprone, Ferriprox, L1

- EU Approval: 1999
- FDA Approval: 2011

- Molecular Weight: 139 g/mol
- MW Chelator-Iron Complex: 470 g/mol
- Charge: Neutral
- Volume of Distribution: Large



- Route: Oral
- Oral Absorption: 45 minutes
- $T_{1/2}$: 53 – 166 minutes
- Iron Excretion: Pred. Urine

Deferiprone, Ferriprox

- First orally active iron chelator
- Relatively small molecule, easily penetrating cells, esp. cardiac cells, easily getting out of cells w iron
- No growth alteration reported in pediatric patients
- Needs ANC regular monitoring due to risk of agranulocytosis
- Effective in lowering serum ferritin & LIC & Cardiac iron

Ferriprox™
deferiprone

Deferiprone Adverse Effects

- Neutropenia & agranulocytosis
  - Probably an idiosyncratic response, not dose dependent
  - Frequency: 0.5–1%
  - Usually in the 1st year of treatment
  - Reversible after cessation of therapy
  - G-CSF treatment may be warranted
  - May recur upon re challenge
  - Requires close surveillance (CBC q 7–10 days)
- GI disturbance
- Arthropathy
- Zinc deficiency

Deferasirox, Exjade®

- ✓ FDA Approval: 2005
- ✓ EU Approval: 2006

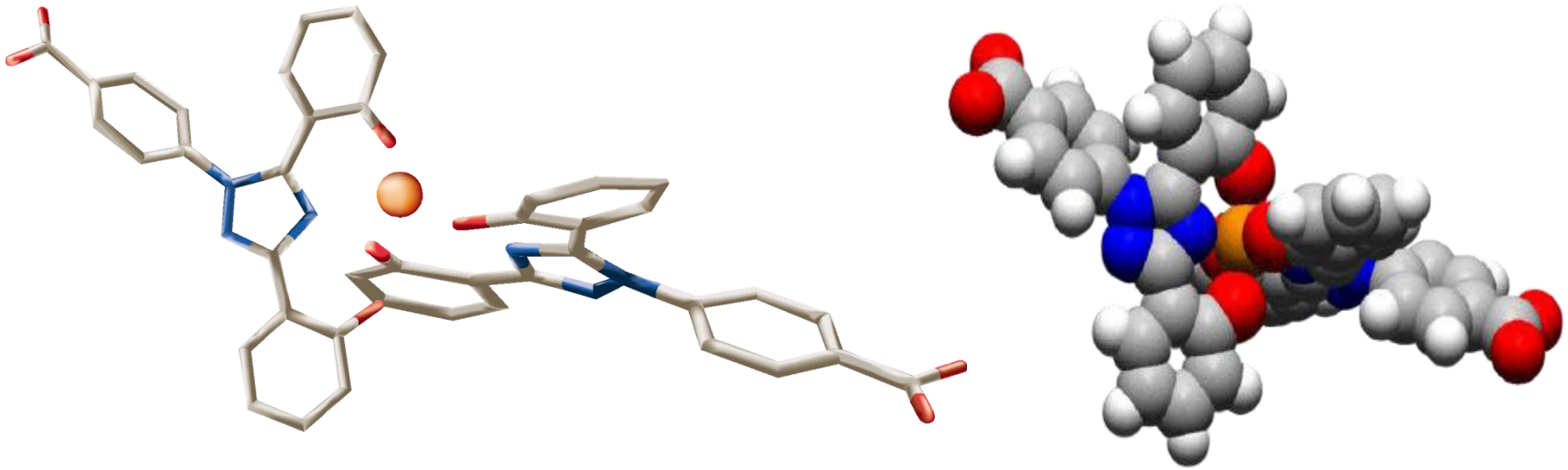
- Selected from more than 700 compounds tested
- Tridentate* iron chelator
  - An oral, dispersible tablet
  - Administered once daily
  - Highly specific for iron
- Chelated iron excreted mainly in feces (<10% in urine)

Clinical trial formulation

*3 polar interaction sites in the binding pocket
Nick H, *Curr Med Chem.* 2003;10:1065–1076

Deferasirox, Exjade
A Once-Daily Oral Iron Chelator

- **Tridentate iron chelator with high specificity for iron**
- **Pharmacokinetics indicate its stability for once daily dose**
- **Two Exjade Molecules Chelate One Iron Atom**



Deferasirox: Important AEs

- GI problems
- Skin rash
- Increase in serum creatinine
- Increase in ALT
- Neurosensory deafness
- Cataract

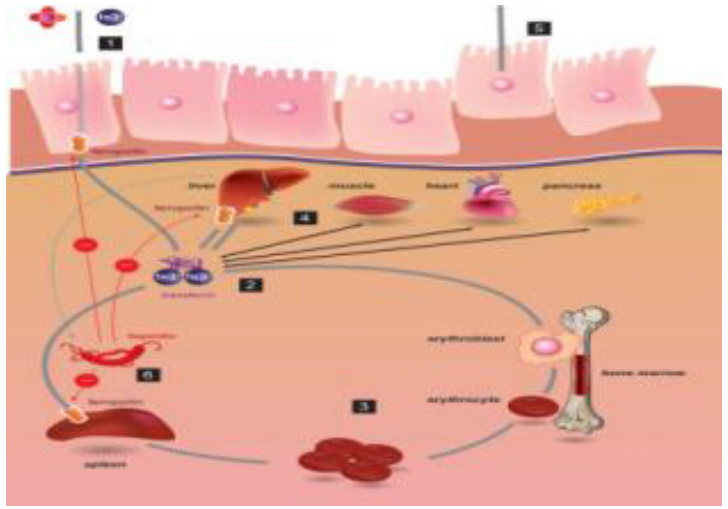
JADENU™ Film-Coated Tablets:
Strength-Adjusted Formulation of EXJADE®

- ✓ FDA Approval: 2015, improved versions- 2016, 2017
- ✓ EU Approval: 2016
- ✓ Generic versions: 2019-2020

- A once daily oral iron chelation therapy
- Same active ingredient as EXJADE® (deferasirox)
- Tablets are swallowed whole, with liquid
- No need to dissolve
- Film-coated tablets can be taken w or w/o light meal
- Does not contain sodium lauryl sulfate or lactose as does EXJADE® (deferasirox)

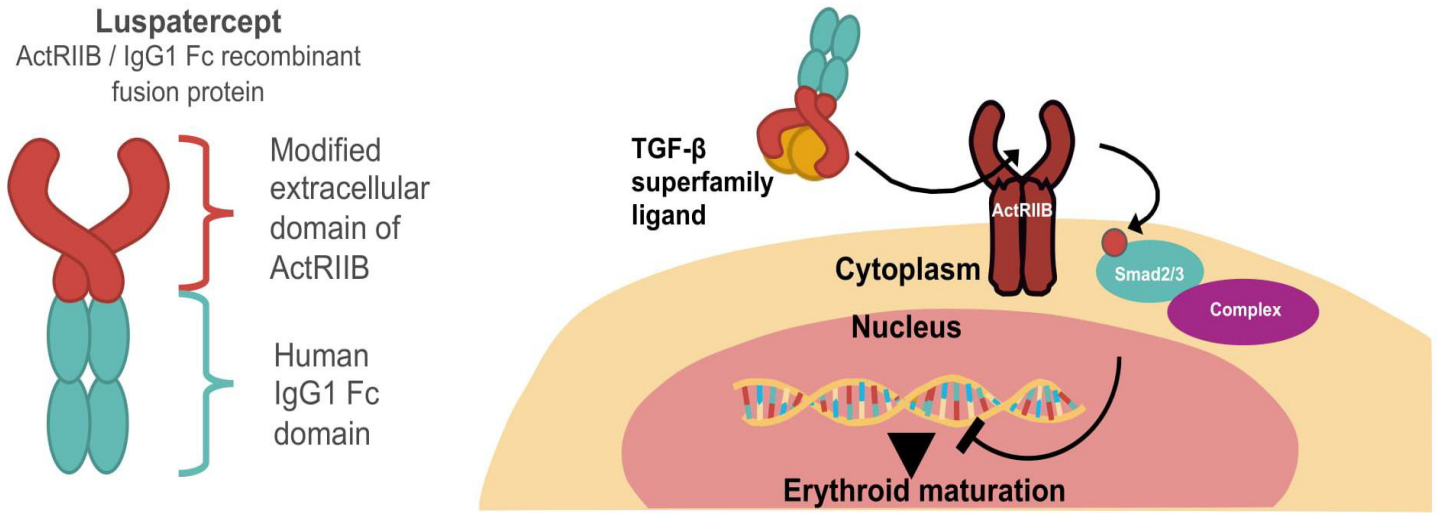
Treatment of Thalassemia:

Modulators of erythropoiesis



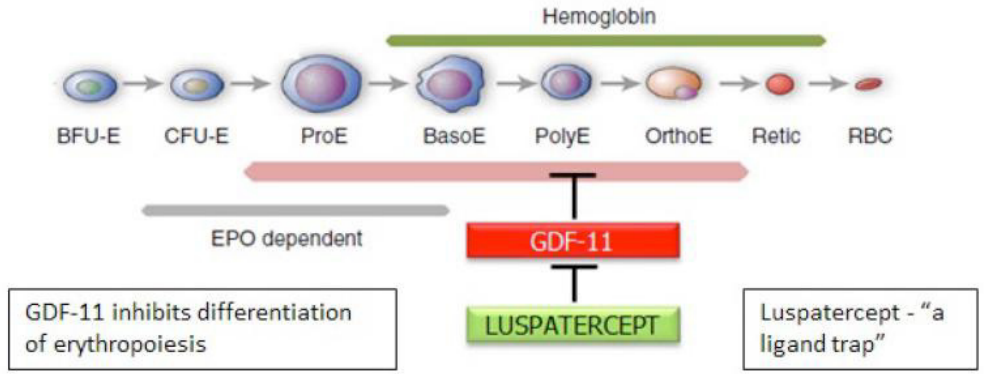
Luspatercept

- Luspatercept is an investigational first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis[1,2]



ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; TGF-β, transforming growth factor beta.
The BELIEVE Trial studied adult patients.

1. Attie KM, et al. Am J Hematol. 2014;89:766-770.
2. Suragani RN, et al. Nat Med. 2014;20:408-414.



The BELIEVE Trial

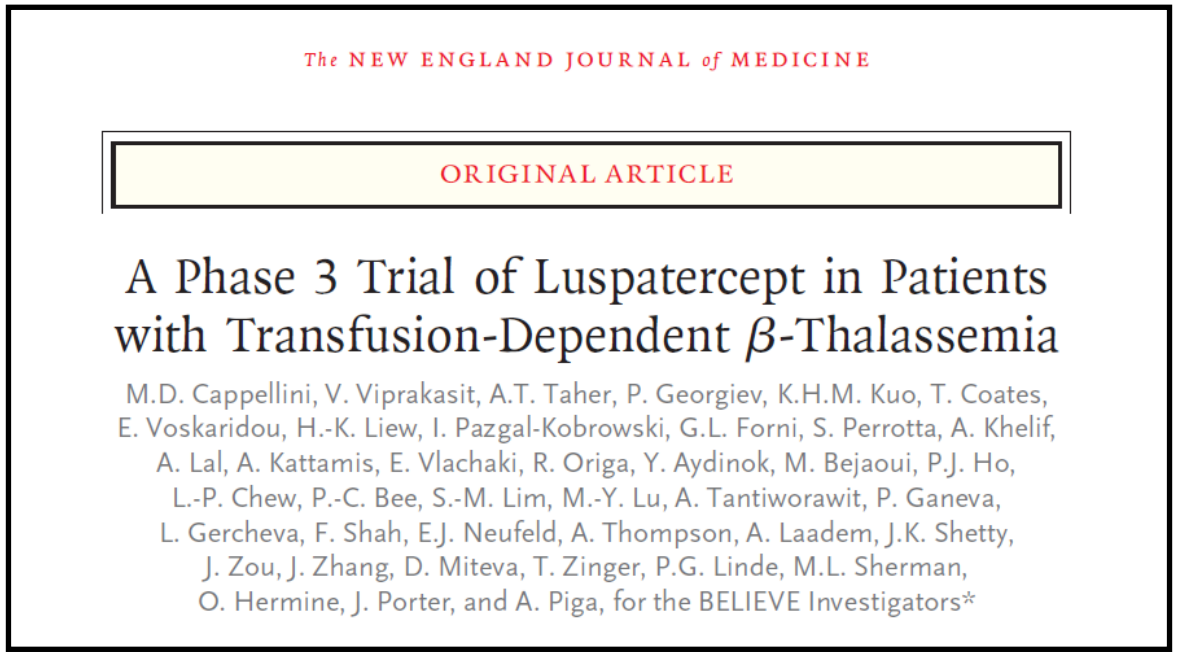
Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept in Adult Beta-Thalassemia Patients Who Require Regular Red Blood Cell (RBC) Transfusions

MD Cappellini, V Viprakasit, A Taher, P Georgiev, KHM Kuo, T Coates, E Voskaridou, HK Liew, I Pazgal-Kobrowski, G Forni, S Perrotta, A Khelif, A Lal, A Kattamis, E Vlachaki, R Origa, Y Aydınok, M Bejaoui, PJ Ho, LP Chew, PC Bee, SM Lim, MY Lu, A Tantiworawit, P Ganeva, L Gercheva, F Shah, EJ Neufeld, A Laadem, JK Shetty, J Zou, D Miteva, T Zinger, PG Linde, ML Sherman, O Hermine, J Porter, A Piga

Presented at the 60th Annual Meeting of the American Society of Hematology (ASH)
December 1–4, 2018; San Diego, CA, USA

The BELIEVE Trial - Conclusions

- Luspatercept showed a statistically significant improvement in the primary endpoint of ≥ 33% reduction in transfusion burden compared with placebo
- Statistical significance was also demonstrated with luspatercept versus placebo for all key secondary endpoints, including ≥ 33% and ≥ 50% reductions in transfusion burden
- Luspatercept showed a statistically significant and clinically meaningful reduction in transfusion burden compared with placebo during any 12 or 24 weeks in the study period
- Luspatercept was generally well tolerated in this patient population



CONCLUSIONS

- Luspatercept showed a statistically significant improvement in the primary endpoint of ≥ 33% reduction in transfusion burden compared with placebo
- Statistical significance was also demonstrated with luspatercept versus placebo for all key secondary endpoints, including ≥ 33% and ≥ 50% reductions in transfusion burden
- Luspatercept showed a statistically significant and clinically meaningful reduction in transfusion burden compared with placebo during any 12 or 24 weeks in the study period
- Luspatercept was generally well tolerated in this patient population
- Luspatercept is a potential new treatment for adult patients with β-thalassemia who require regular RBC transfusions

The BELIEVE Trial studied adult patients.

Luspatercept: real-world and extended data – 2025

- Luspatercept produces significant and sustained reductions in transfusion burden, with some patients achieving ≥50% reduction and improved iron parameters over long-term follow-up.

- New work emphasized alternative response definitions that capture patients whose main benefit is raising pre-transfusion Hb to guideline-recommended thresholds (e.g., ≥9.5 g/dL), which is particularly relevant where baseline pre-transfusion Hb is low.

LUSPATERCEPT Approval History

FDA -

- ✓ 2019: Adults with TDT.
- ✓ 2020: Low-risk TD MDS.
- ✓ 2023: Low-risk MDS who may require transfusions and are ESA-naïve.

EMA -

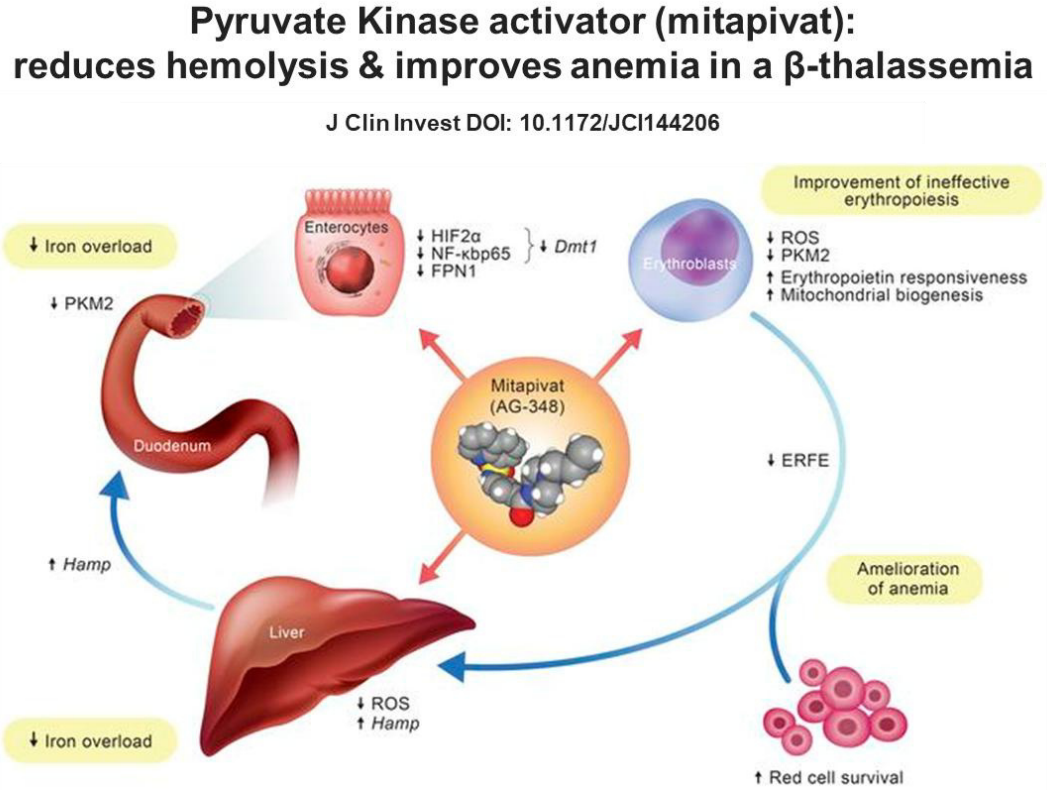
- ✓ 2020: TDT and very low-, low-, or intermediate-risk MDS.
- ✓ 2023: NTD beta-thalassemia.
- ✓ 2024: First-line in TD low-risk MDS.

Mitapivat (Energize-T)

- An oral medication that serves as a first-in-class activator of the enzyme pyruvate kinase (PK).
- By increasing the activity of the enzyme, it boosts energy production (ATP) in RBCs, helping them live longer and reducing chronic anemia.

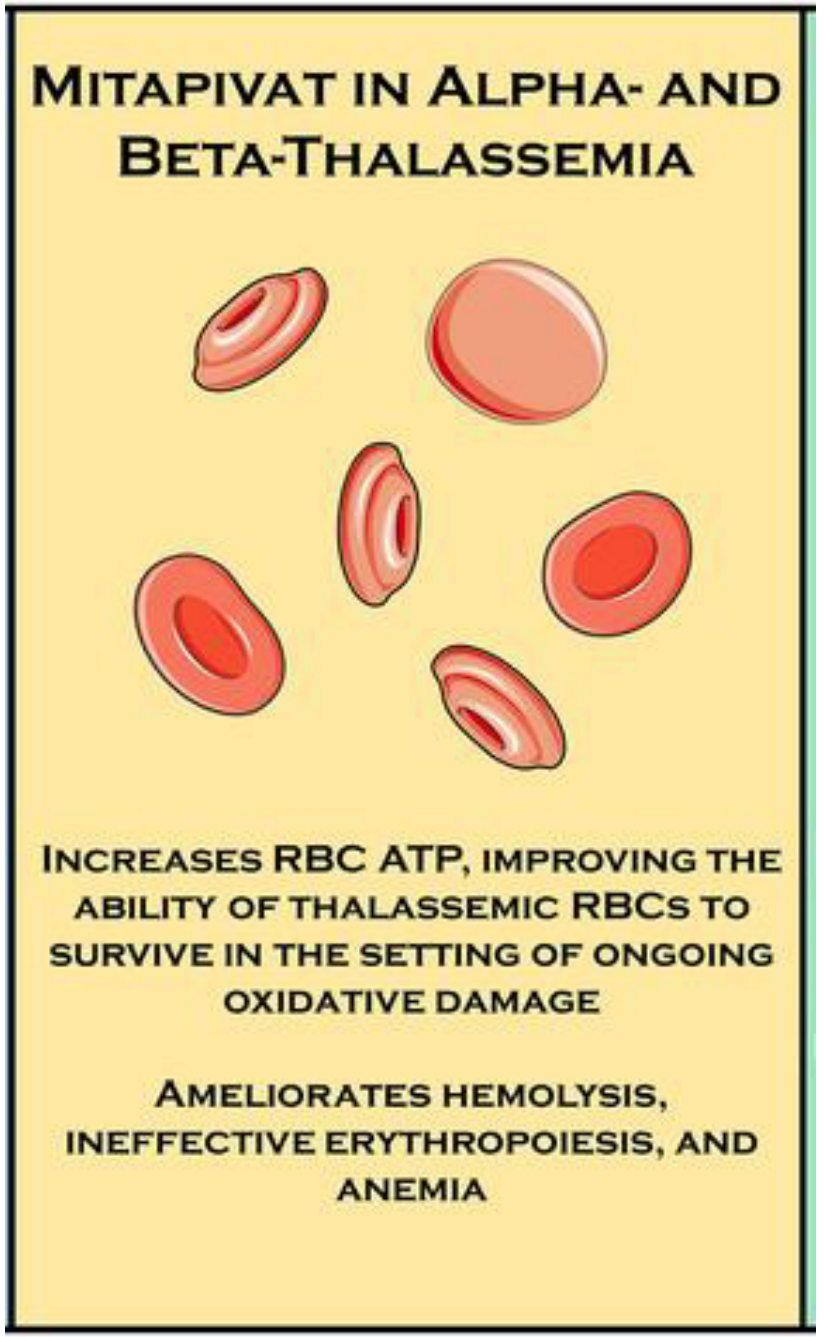
How It Works

- Energy Production: Allosterically binds to the PK enzyme, increasing the production of ATP, which is essential for RBC survival.
- Oxygen Affinity: Reduces levels of 2,3-DPG, a metabolite that influences how hemoglobin releases oxygen. This reduction is particularly helpful in sickle cell disease to prevent cells from "sickling"



Mitapivat (ENERGIZE-T)

- At ASH 2025, Prof. Cappellini presented the phase III ENERGIZE-T trial in TDT, evaluating mitapivat as add-on therapy.
- The update reported clinically meaningful reductions in transfusion requirements in a subset of patients and a safety profile consistent with earlier studies.
- By addressing different aspects of ineffective erythropoiesis and RBC health, the combination with Luspatercept aims to provide a more comprehensive treatment strategy for inherited anemias.



MITAPIVAT (ENERGIZE-T) Approval History

FDA -

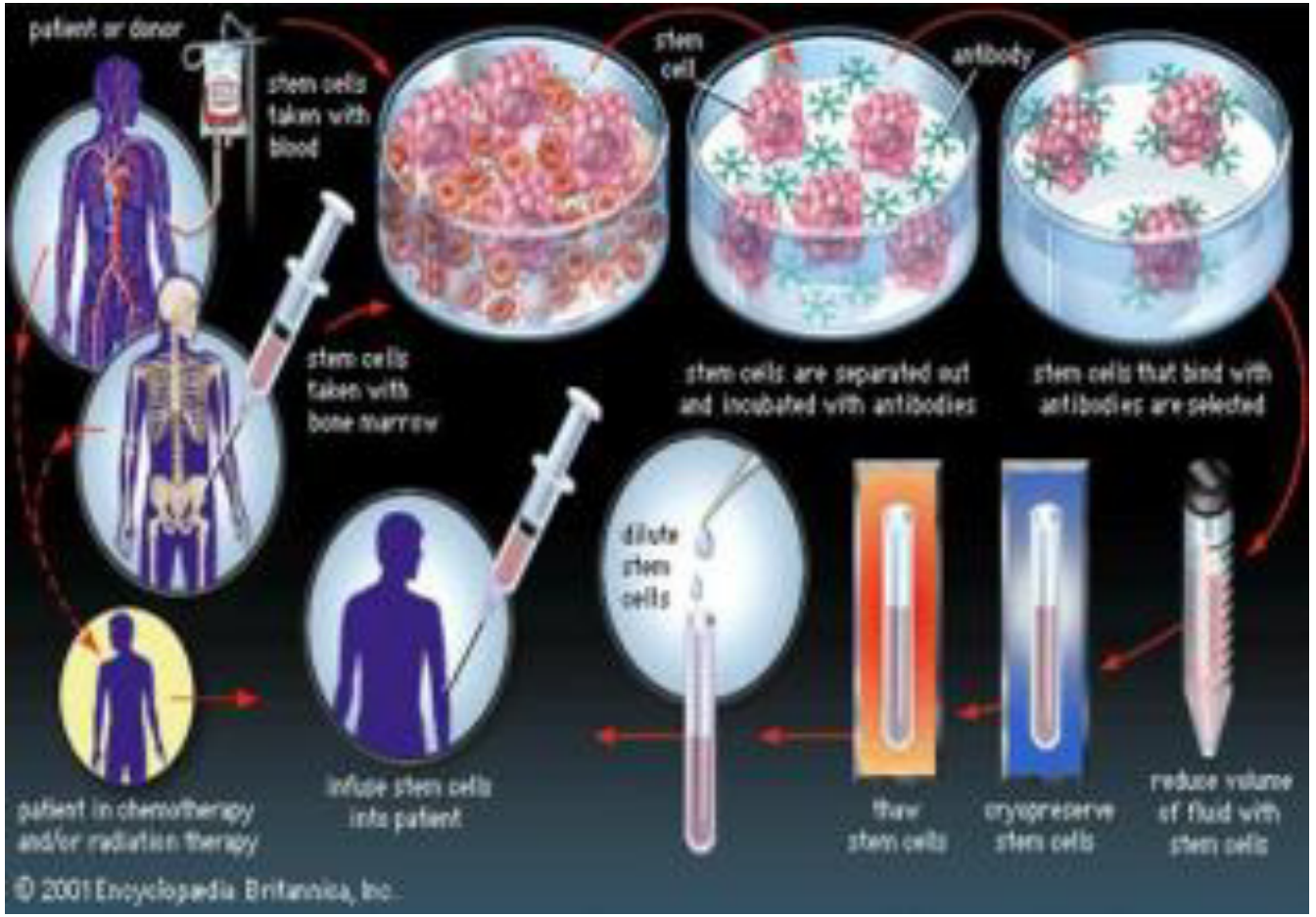
- ✓ 2022: PK Deficiency anemia.
- ✓ 2025: thalassemia anemia (alpha- & beta-).

EMA-

- ✓ 2022: PK Deficiency anemia.

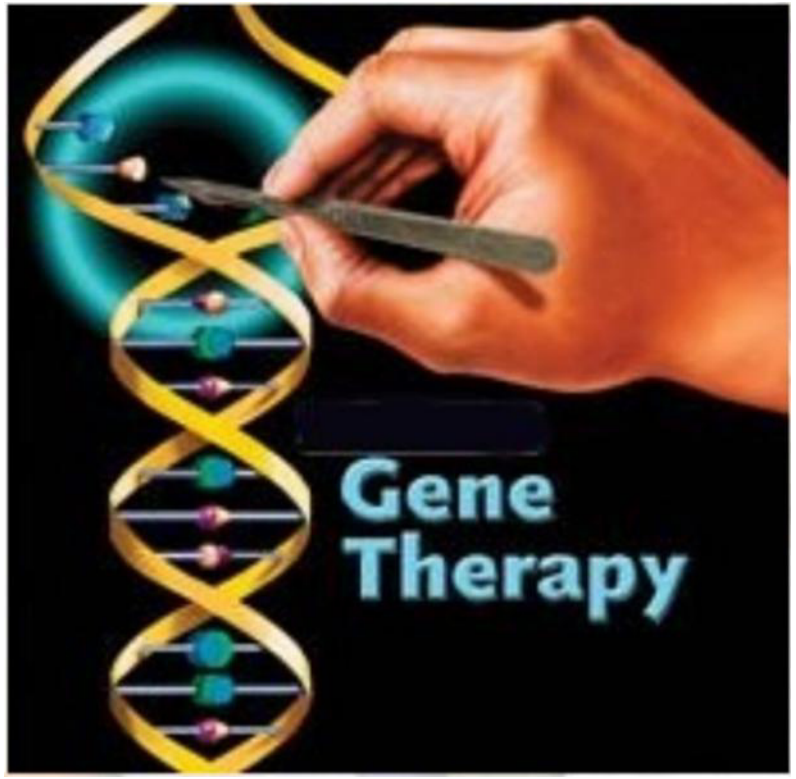
Treatment of Thalassemia:

Gene therapy



Gene therapy – Molecular Surgery

Gene therapy can be broadly defined as the transfer of genetic material into a cell to transiently or permanently alter the cellular phenotype



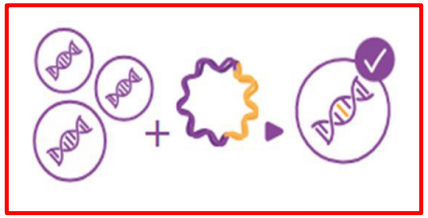
Gene Therapy for Inherited Diseases

- Severe Combined Immunodeficiency Disease
- Ornithine transcarbamylase (OTC) deficiency
- Familial Hypercholesterolemia
- Cystic Fibrosis
- Thalassemia
- Lesch-Nyhan syndrome
- Hunter’s syndrome
- Sickle cell Disease

Risks of Gene Therapy

- Conditioning toxicity
  - Mouth sores (mucositis)
  - Hair Loss
  - Liver problems (rare, highly unlikely)
  - Lung scarring (rare, highly unlikely)
- Graft Failure
  - Depends on number of cells given
  - Conditioning important in heavily transfused patients
- Cancer (insertional oncogenesis)
- Viral infection
- Sterility

Gene Therapies for TDT



Stepwise procedure of gene therapy

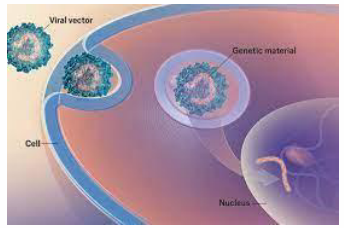
Autologous transplantation after myeloablative chemotherapy

Gene modified CD34+ stem cells

Patient with TDT

Selection of CD34+ stem cells (bone marrow or peripheral blood)

Quality control procedures



one-time treatment

Gene Editing

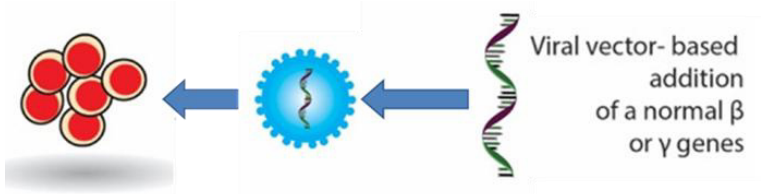
Gene editing to correct the β-globin mutation or disrupt the BCL11A gene to increase fetal hemoglobin

CRISPR/Cas9 or ZFN

Gene Addition

Viral vector- based addition of a normal β or γ genes

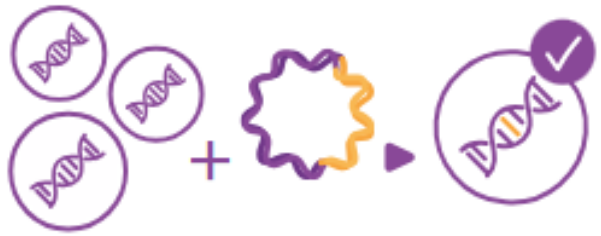
bluebirdbio™

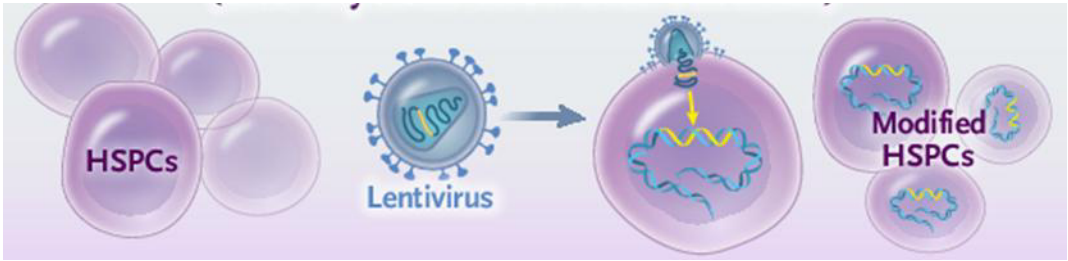


Betibeglogene Autotemcel, Zynteglo

Gene Insertion (Addition) by Bluebird Bio

- Insertion of lentiviral vector containing whole regulatory machinery and β-globin or γ-globin producing genes into autologous HSCs “ex-vivo”, then infusing these modified HSCs back to patient after myeloablative conditioning.
- Viral vector insertions into the genome of stem cells remain largely an uncontrolled and random process. There is an unknown risk that some insertions into human stem cells can occur near proto-oncogenes, stimulating clonal proliferation leading to AL/MDS.
- With new optimized lentiviral vectors, insertions occur at preferential sites in the transcription units of human genome.





Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 19, 2018 VOL. 378 NO. 16

Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

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ESTABLISHED IN 1812 APRIL 19, 2018 VOL. 378 NO. 16

Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

- **mobilized autologous CD34+ cells were obtained from:**
  - **22 patients**
  - **12 - 35 years of age**
  - **transfusion-dependent β-thalassemia**
- **cells were transduced ex vivo with LentiGlobin BB305 vector, which encodes adult hemoglobin (HbA) with a T87Q amino acid substitution (HbAT87Q)**
- **cells were then reinfused after patients undergone myeloablative busulfan conditioning.**
- **without SAE related to the drug product**

The NEW ENGLAND JOURNAL of MEDICINE

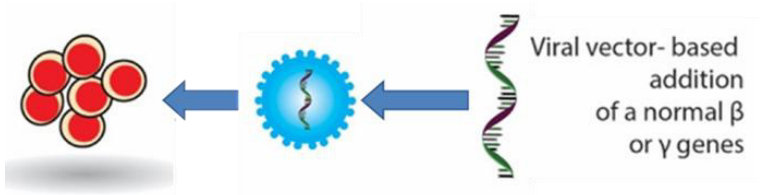
ESTABLISHED IN 1812 APRIL 19, 2018 VOL. 378 NO. 16

Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

At a median of 26 m (range 15 - 42) after infusion of the gene-modified cells:

- **13 patients w non–β0/β0 genotype**
  - **all but 1 had stopped receiving RBC transfusions**
  - **HbAT87Q level range 3.4 - 10.0 g/dL**
  - **total hemoglobin level range 8.2 - 13.7 g/dL**
- **9 patients w β0/β0 genotype or IVS1-110 mutation homozygote**
  - **73% decrease in median annualized transfusion volume**
  - **red-cell transfusions discontinued in 3 patients.**

bluebirdbio™



Betibeglogene Autotemcel, Zynteglo

- The first gene therapy for TDT, approved by FDA in August 2022.
- Patient's stem cells are transduced ex vivo with a BB305 lentiviral vector that carries a modified beta-globin gene ($\beta^{A\text{-}T87Q}$-globin).
- After infusion, transduced $CD34^+$ cells engraft in the bone marrow and differentiate to produce RBCs containing $\beta^{A\text{-}T87Q}$-globin, which then pairs with alpha-globin and produces a modified functional HbA (HbA^{T87Q}).
- ICER calculation: lifetime cost for regular transfusions 6.4 million USD.
- One time treatment.
- Cost per patient in USA 2.8 million USD

ZYNTEGLO™ (gene therapy)

Clinical Update

Product Information

Scientific name: beti-cel (betibeglogene autotemcel)

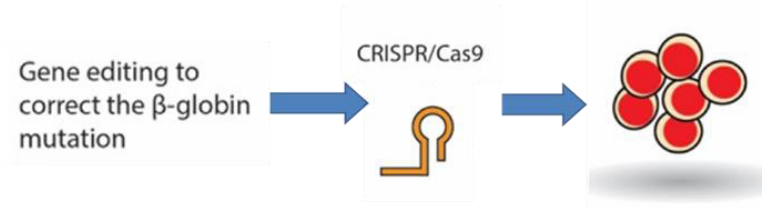
Brand name: ZYNTEGLO™

RESPONSIBLE: bluebird bio Inc.

Regulatory Information

Status: Authorized

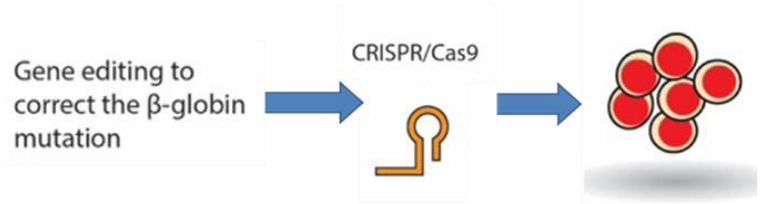
- EMA: Conditional authorization for patients >12 y old with TDT who do not have a β0/β0 genotype (2019). Marketing authorization withdrawn at request of marketing authorization holder (bluebird bio) (2022)
- FDA: Approved to treat beta-thalassemia TDT patients (2022)
- MHRA (UK): Not approved (2021)



Exagamglogene Autotemcel, Casgevy (Exa-Cel, CTX-001)

Gene Editing by Vertex – Crisper

- CRISPER- Clustered Regularly Interspaced Short Palindromic Repeats- technology precisely & efficiently modifies genome sequence to induce insertions, deletions, or base substitutions in the genome.
- Ideal for treating diseases by permanently correcting deleterious base mutations or disrupting disease causing genes.
- Vertex-CRISPR therapy for TDT uses CRISPR to turn off the HbF suppression, thus increases amount of healthy HbF RBCs.



Exagamglogene Autotemcel, Casgevy (Exa-Cel, CTX-001)

Gene Editing by Vertex – Crisper

- Cell-based gene therapy for TDT approved by FDA in January 2024.
- Gene editing via CRISPR/Cas9 technology.
- Genomic DNA modified to inactivate erythroid-specific enhancer of *BCL11A* gene, resulting in an increase in gamma-globin expression.
- In TDT patients, gamma-globin production improves imbalance of alpha-globin to non-alpha-globin, leading to improved erythropoiesis & increased total Hb levels.
- ICER calculation: lifetime cost for regular transfusions 6.4 million USD.
- One time treatment. Cost per patient in USA 2.2 million USD.

THALASSAEMIA INTERNATIONAL FEDERATION

CASGEVY™ (gene editing)

Clinical update

Product Information

Scientific name: exa-cel (exagamglogene autotemcel)

Brand name: CASGEVY™

RESPONSIBLE: Vertex Pharmaceuticals & CRISPR Therapeutics collaboration

Regulatory Information

Status: Authorized

- EMA: Orphan Drug Designation (2019), marketing authorization for SCD & TDT patients >12 y (Feb 2024)
- FDA: Fast Track Designation (2019), Orphan Drug Designation (2020), Approved for TDT patients >12 y old (Jan 2024)
- MHRA (UK): Granted Innovation Passport (2023), Conditional approval for SCD & TDT in patients >12 y old (Nov 2023)

Gene Therapies for TDT
How far have we gone?

Cumulative total number of protocols & number patients treated as of mid 2024

Gene Addition – Zynteglo: 14 studies in TDT, 7 studies in SCD patients.

- 86-91% achieved TI > 12 months.

Gene Editing – Casgevy: 12 studies in TDT patients, 9 studies in SCD patients.

- 91% achieved TI of > 12 months.

TDT protocols: Total – 229 patients, of them - 145 completed study.

SCD protocols: Total – 314 patients, of them - 66 completed study.

TDT/SCD combined protocols: Total – 238 patients, of them – 52 completed study.

Total numbers of patients – 781, of them – 263 completed study.

Where are we now, end of 2025, with gene therapy in TDT?

- A total of ~150 patients worldwide have now received autologous gene therapy in trials and early real-world use, with most evaluable patients achieving durable transfusion independence:
  - ✓ sustained Hb ≥9 g/dL
  - ✓ marked reduction in transfusion/iron burden
  - ✓ toxicity dominated by busulfan conditioning rather than vector or editing per se
- Increasing platform diversity (CRISPR/Cas9, base editing, optimized lentiviral vectors), with similar clinical efficacy but varying manufacturing complexity and potential cost implications.
- while disease-modifying agents like luspatercept and mitapivat improve transfusion burden and quality of life, curative options (HSCT, gene therapy) are increasingly central in discussions for eligible TDT patients.

ASH 2025 consolidated gene therapy as a realistic curative strategy for TDT, including early pediatric exa-cel data, but also highlighted conditioning-related mortality as the key safety concern in young children.

תודה עבור
תשומת הלב
Thanks for your attention