webinar

HEALTH PROFESSIONALS

Thursdays Webinars

Pathophysiology and recent advances in inherited forms of Iron Loading Anemias

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Milano, Italy

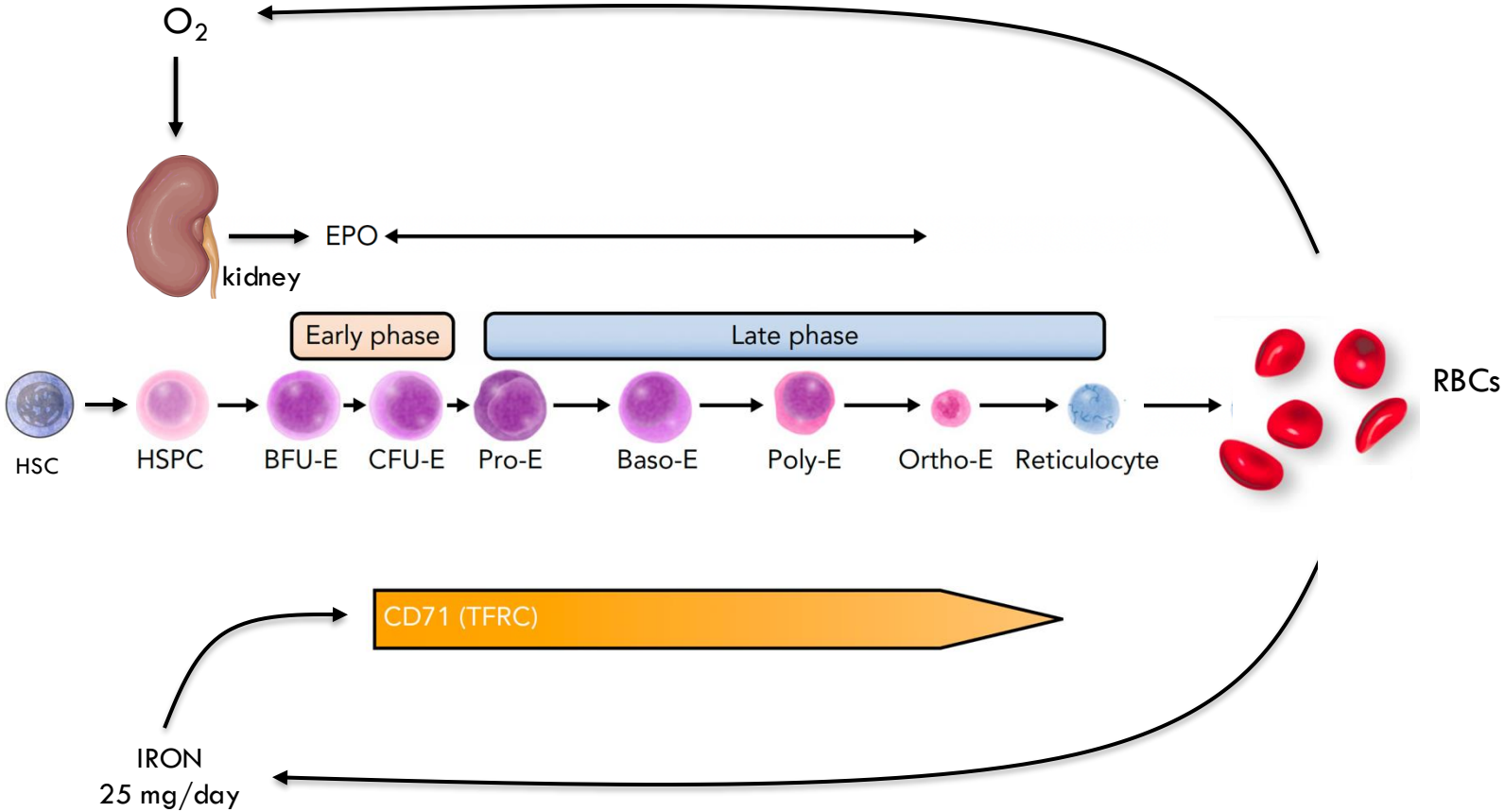
10 April 2025

ebn
ERN | EuroBloodNet

Outline

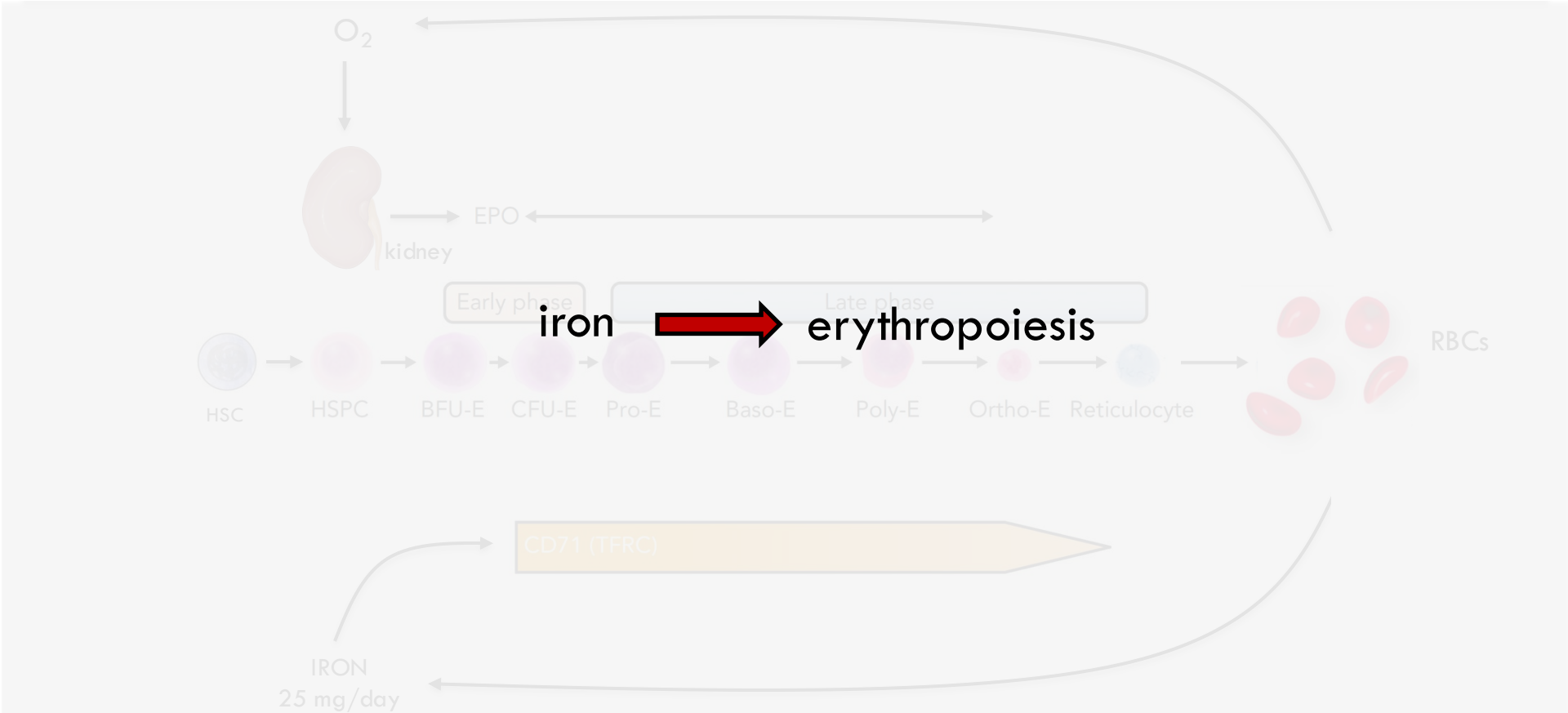
- Functional (and reciprocal) crosstalk between iron and erythropoiesis
- Iron loading anemias: definition and mechanisms
- *New therapeutic approaches*

Erythropoiesis



Modified from Caulier and Sankaran, Blood 2022

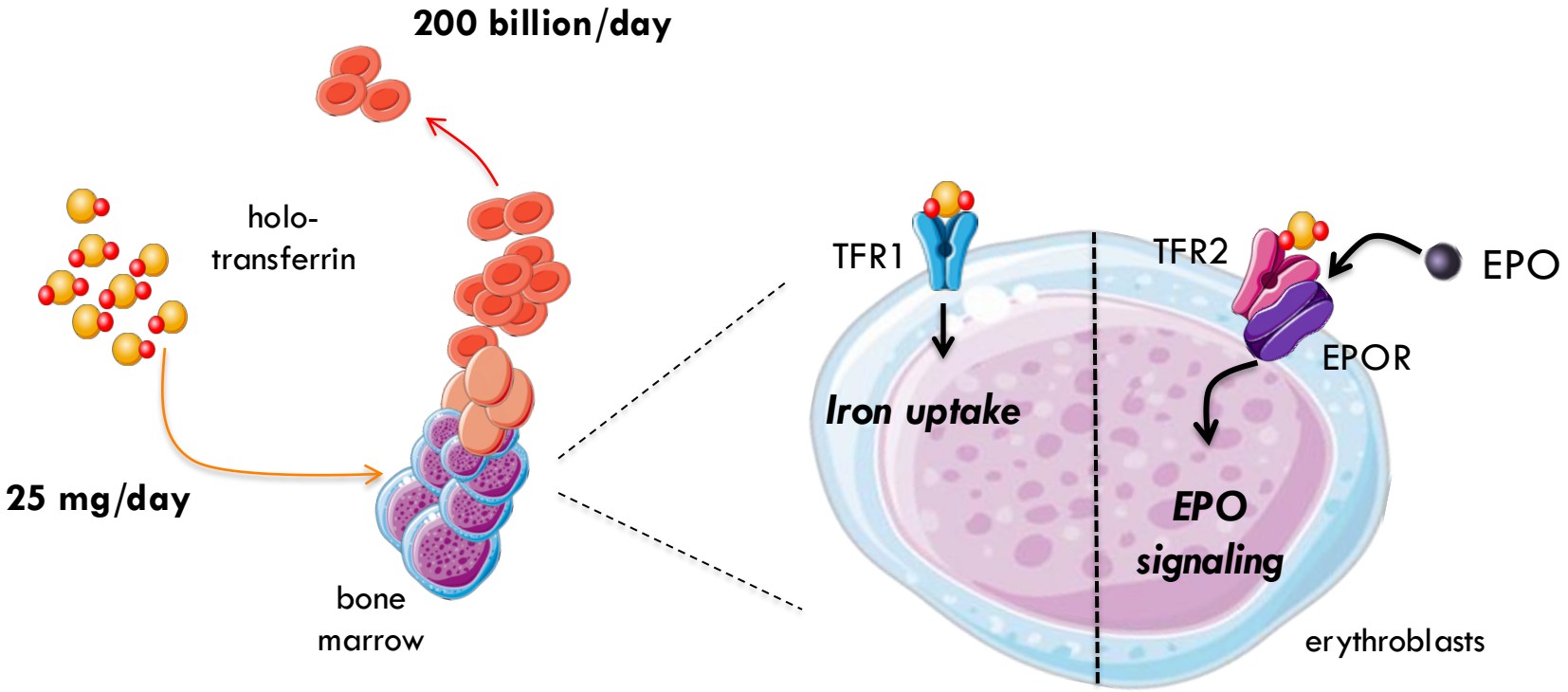
Erythropoiesis



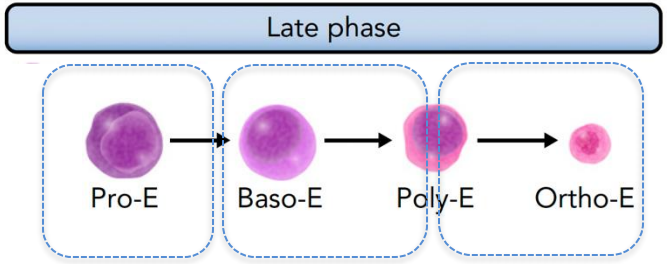
iron ➡ erythropoiesis

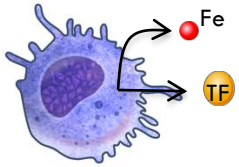
Modified from Caulier and Sankaran, Blood 2022

Iron availability regulates erythropoiesis

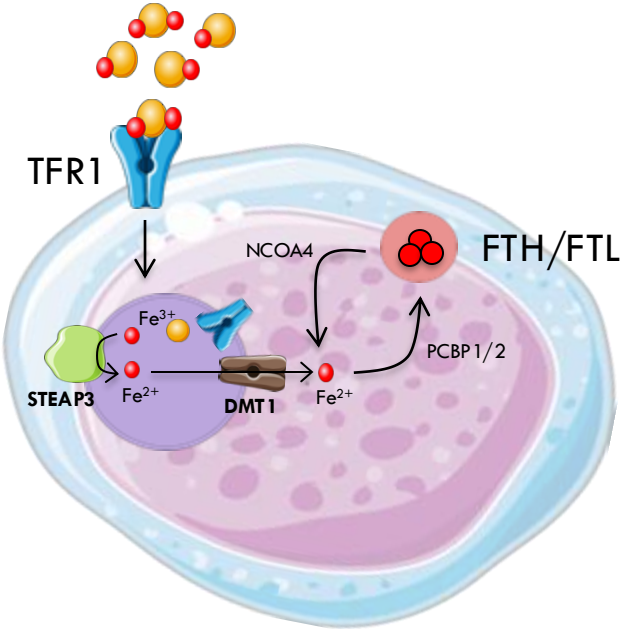


Iron plays a crucial role in terminal erythropoiesis





nurse
macrophages



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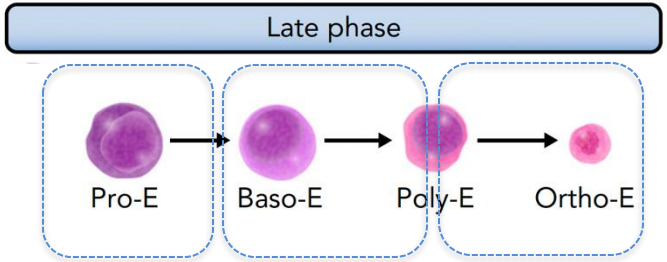

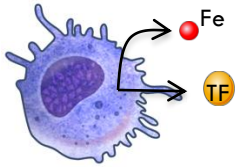

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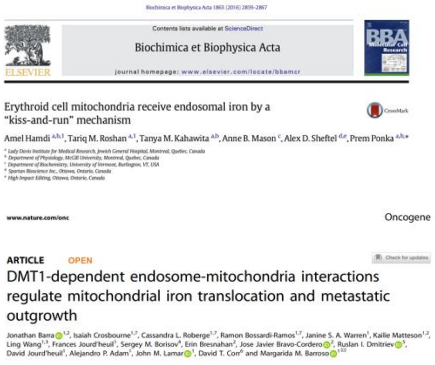


Biochimica et Biophysica Acta

Erythroid cell mitochondria receive endosomal iron by a "kiss-and-run" mechanism

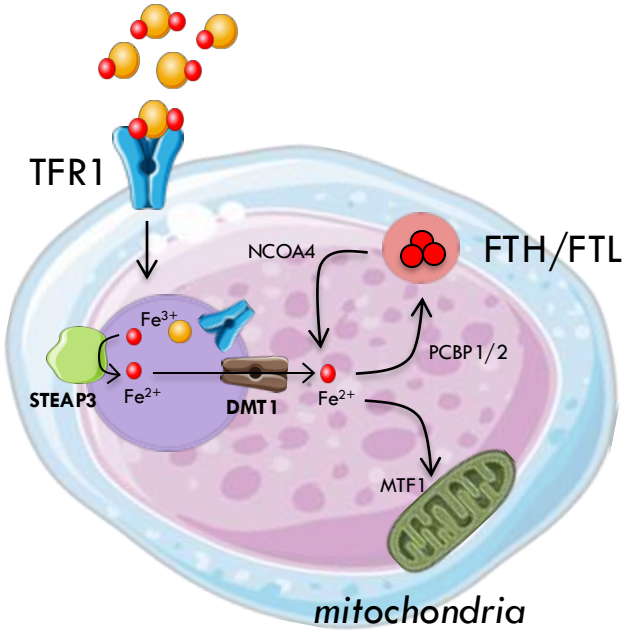
Amel Hamdi, Tariq M. Roshan, Tanya M. Kahawita, Anne B. Mason, Alex D. Sheftel, Prem Ponka

Oncogene

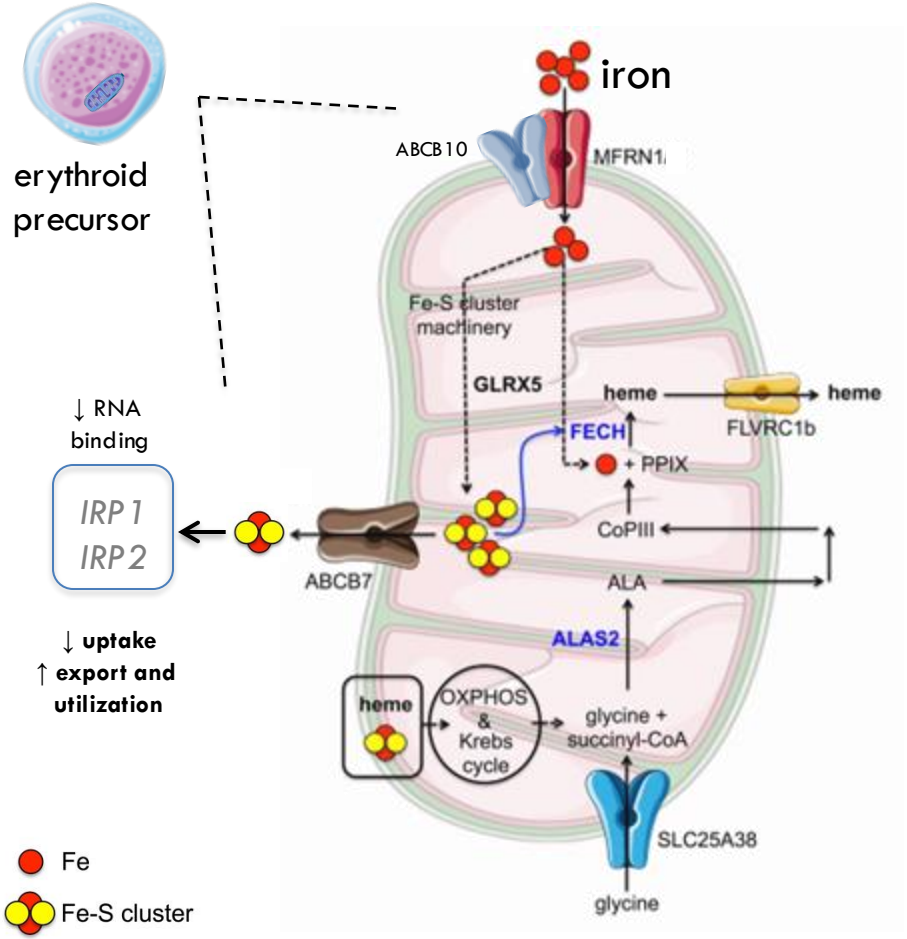
ARTICLE OPEN

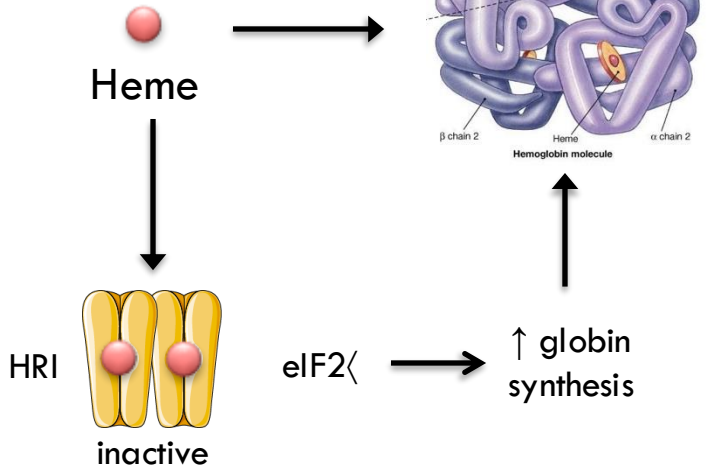
DMT1-dependent endosome-mitochondria interactions regulate mitochondrial iron translocation and metastatic outgrowth

Jonathan Barra, Isaiah Crosbourne, Cassandra L. Roberge, Ramon Bossardi-Ramos, Janine S. A. Warren, Kallie Matteson, Ling Wang, Frances Jourdheuil, Sergey M. Borisov, Erin Bresnahan, Jose Javier Bravo-Cordero, Ruslan I. Dmitriev, David Jourdheuil, Alejandro P. Adam, John M. Lamar, David T. Corr and Margarida M. Barroso



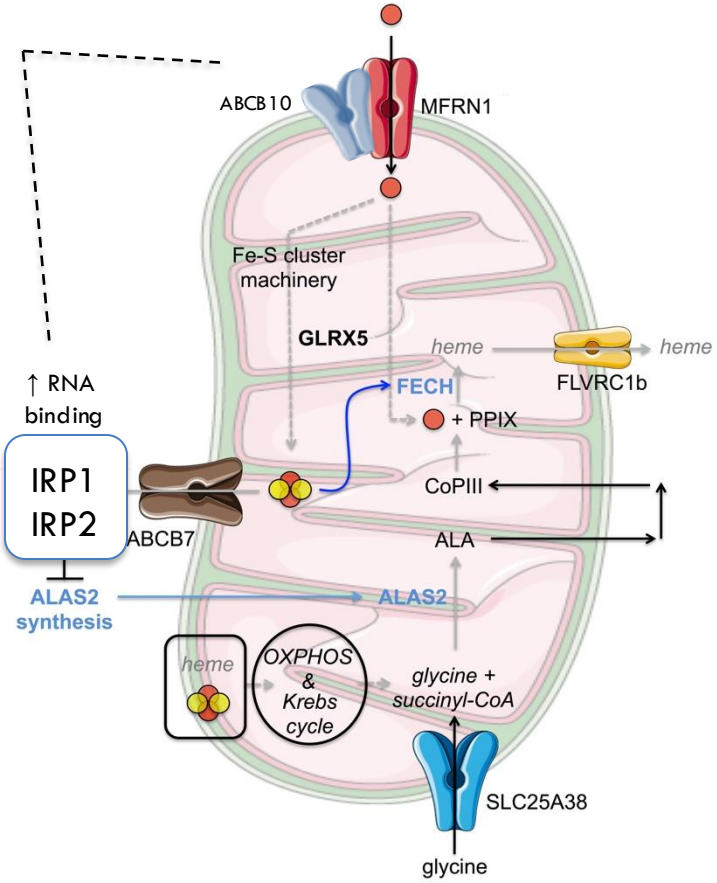
Hemoglobin synthesis in iron replete conditions



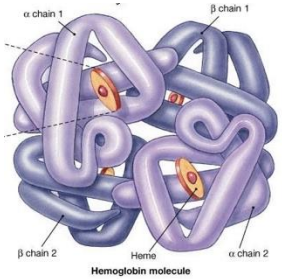


Hemoglobin synthesis in iron deficient conditions

erythroid precursor



↓ Heme



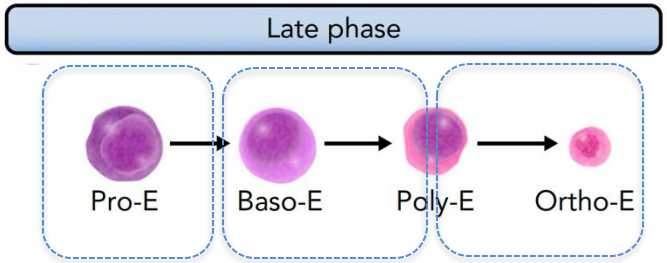
HRI → PeIF2⟨ ⊣ ↓ globin synthesis

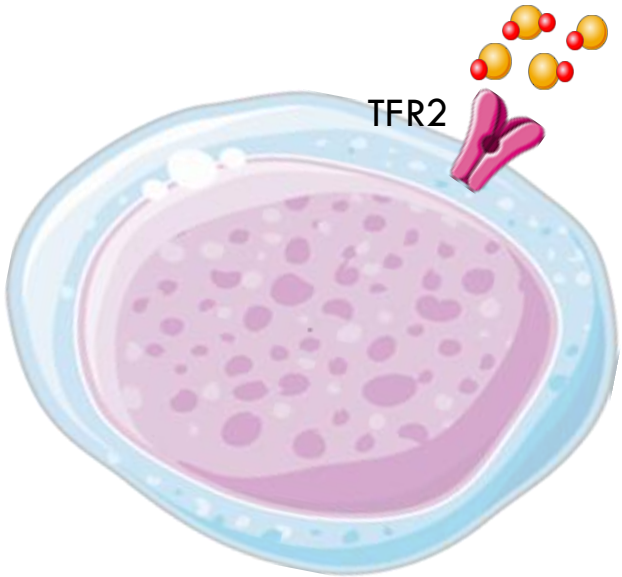
active

Fe

Fe-S clus

The second TFR links iron sensing to EPO-EPOR signaling





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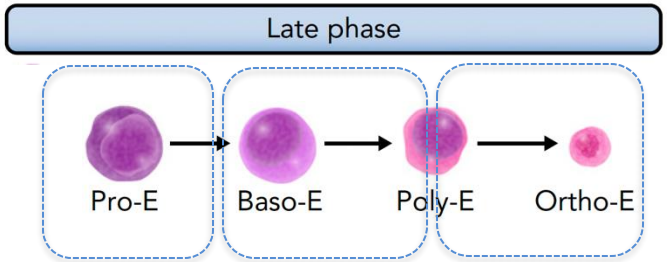

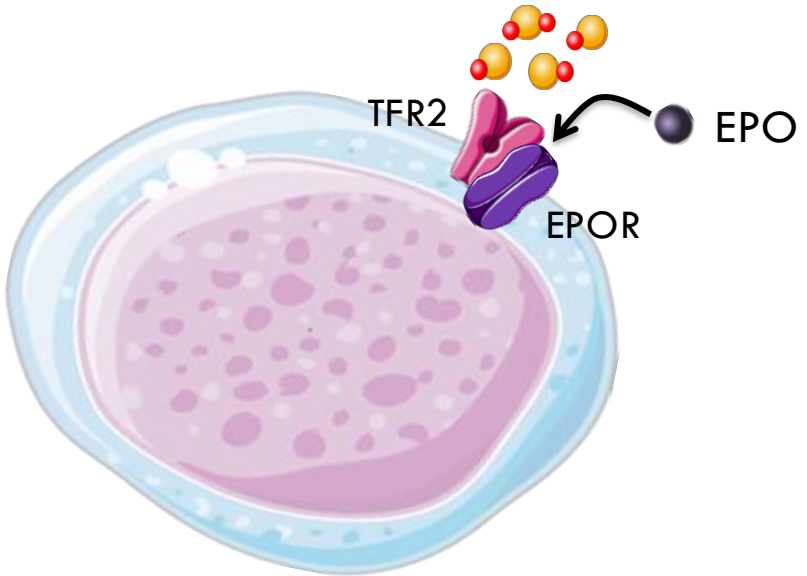

Nai et al., Blood 2015

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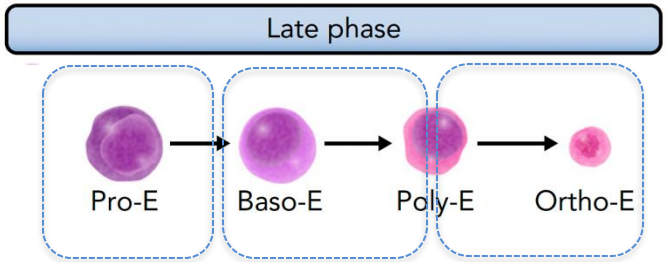
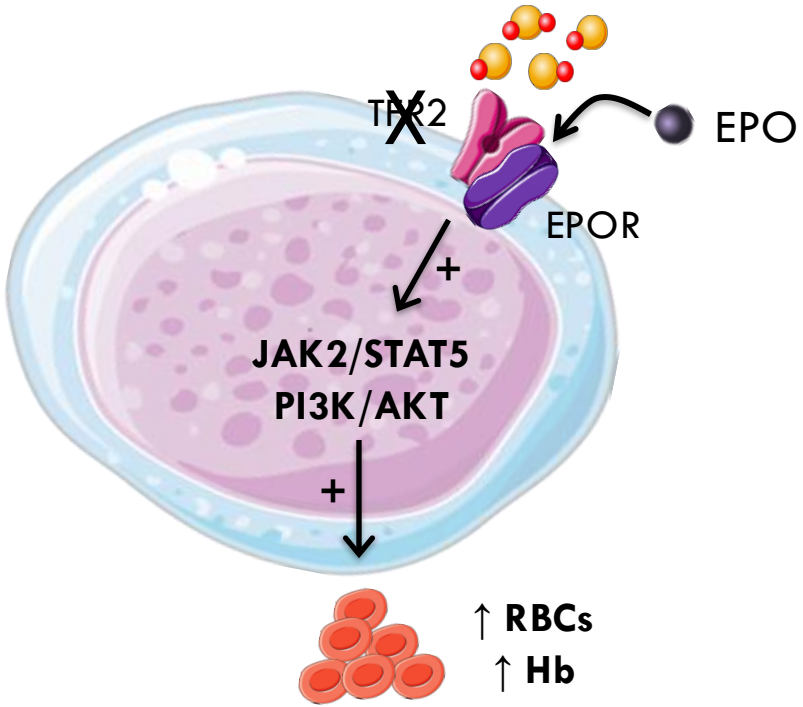
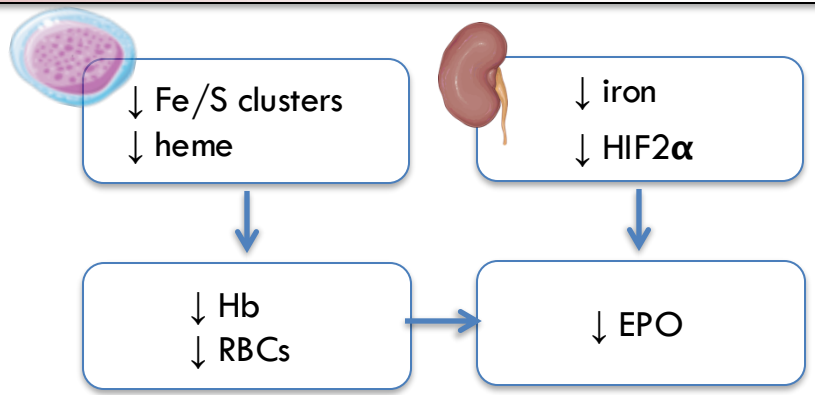




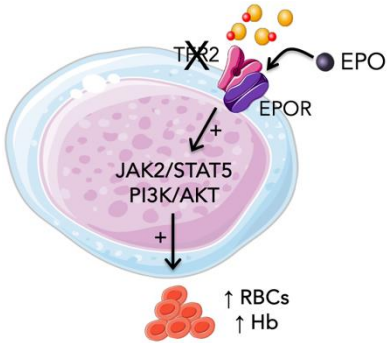
Forejtnikovà et al., Blood 2010
Nai et al., Blood 2015

How does the erythroblast adapt its function according to iron availability?

✓ Decrease in cytosolic iron



✓ Decrease in serum iron



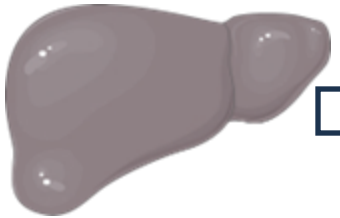
How does the erythropoiesis regulate body iron metabolism?

liver

Hepcidin

iron ⟵ erythropoiesis

Hepcidin is the master regulator of iron metabolism



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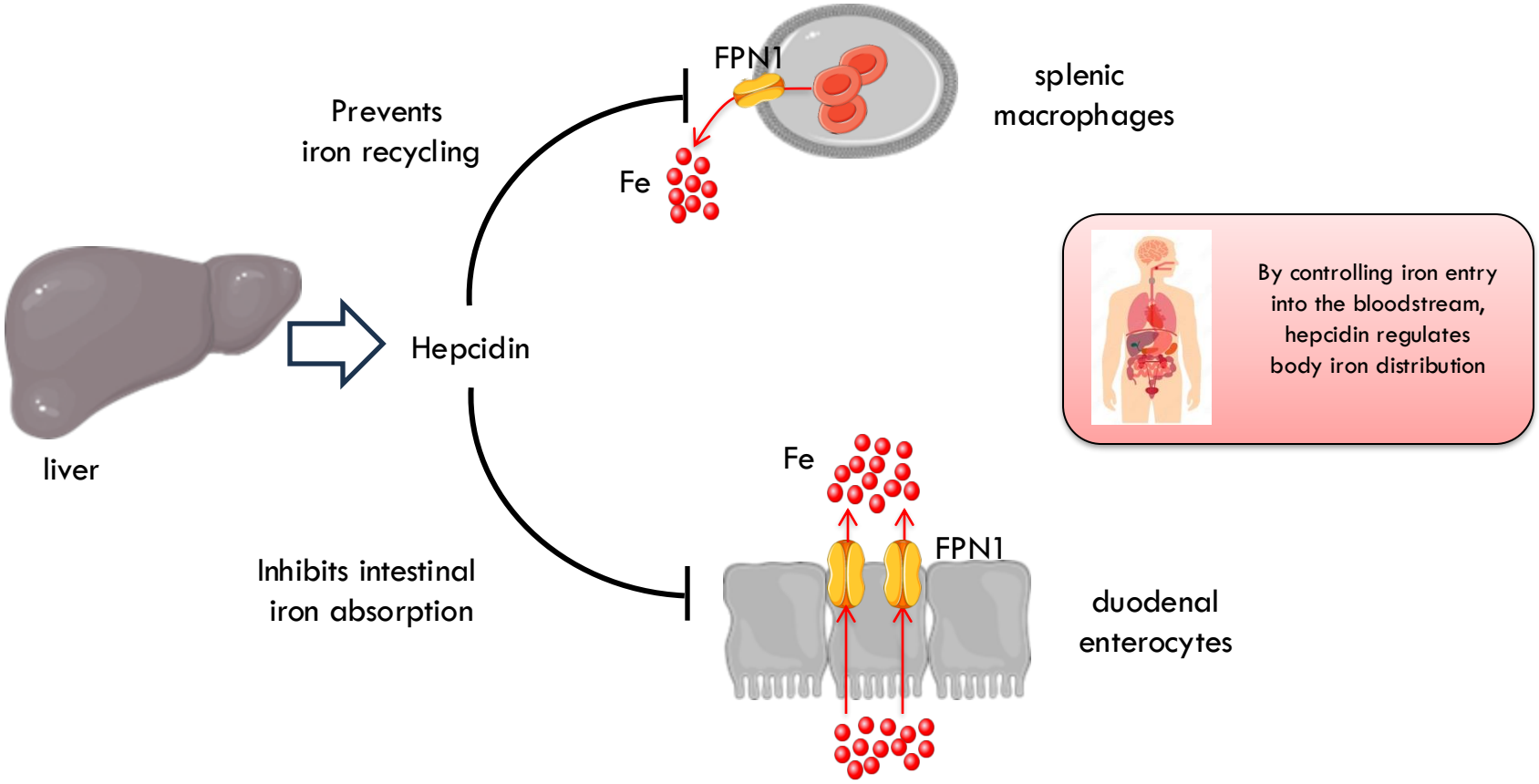
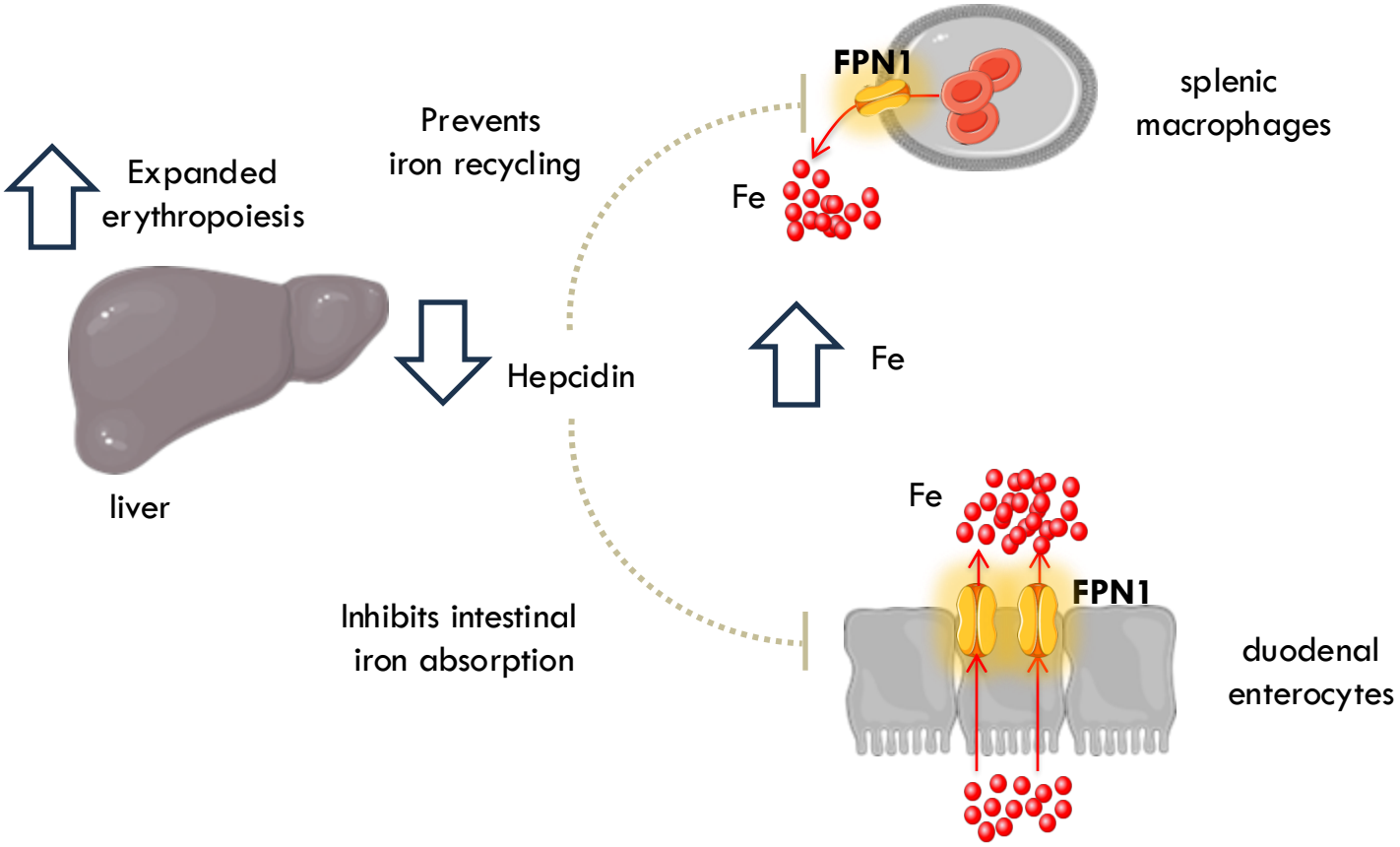
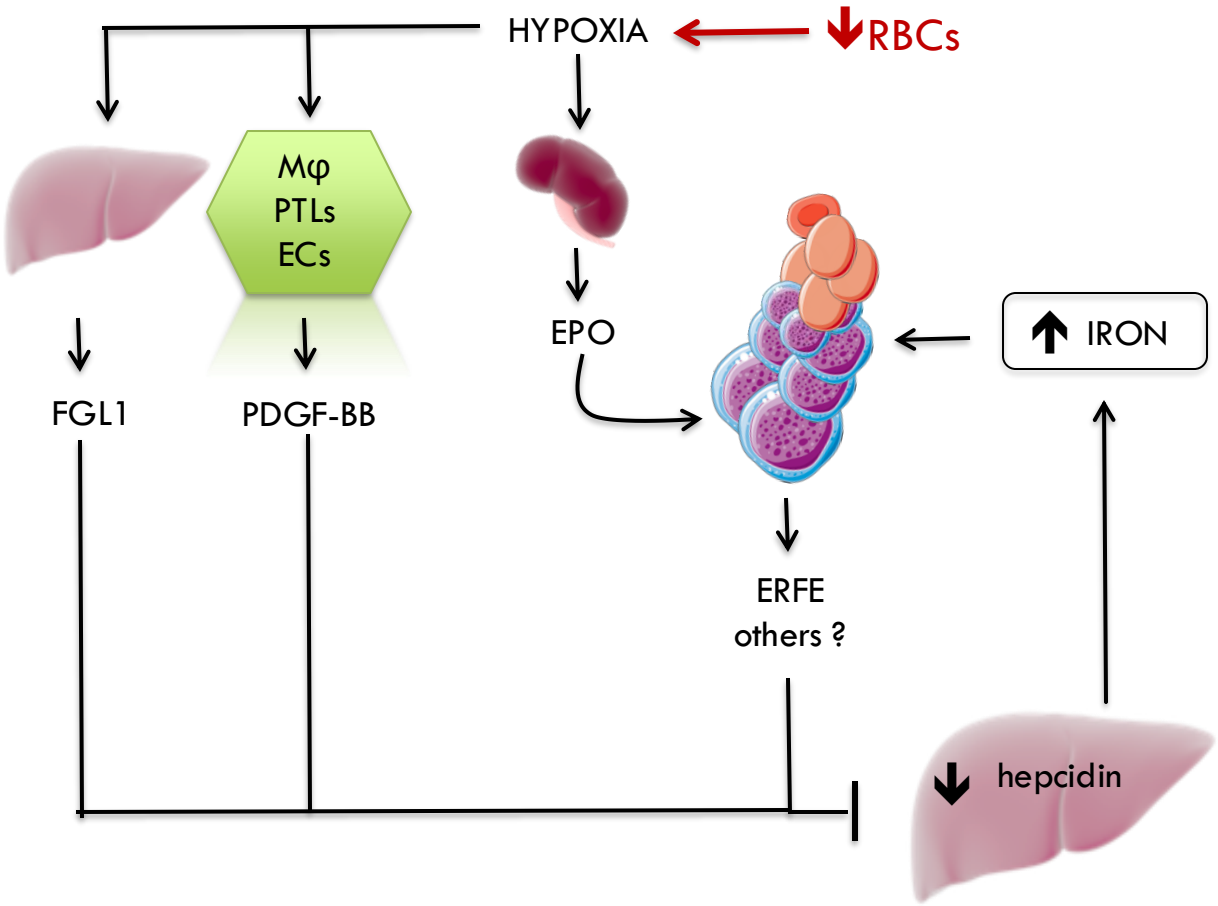


Hepcidin regulation under physiological conditions



Erythropoietic activity regulates iron metabolism



Kautz et al., 2014;
Sonnweber et al., 2014
Sardo et al., bioRxiv 2023

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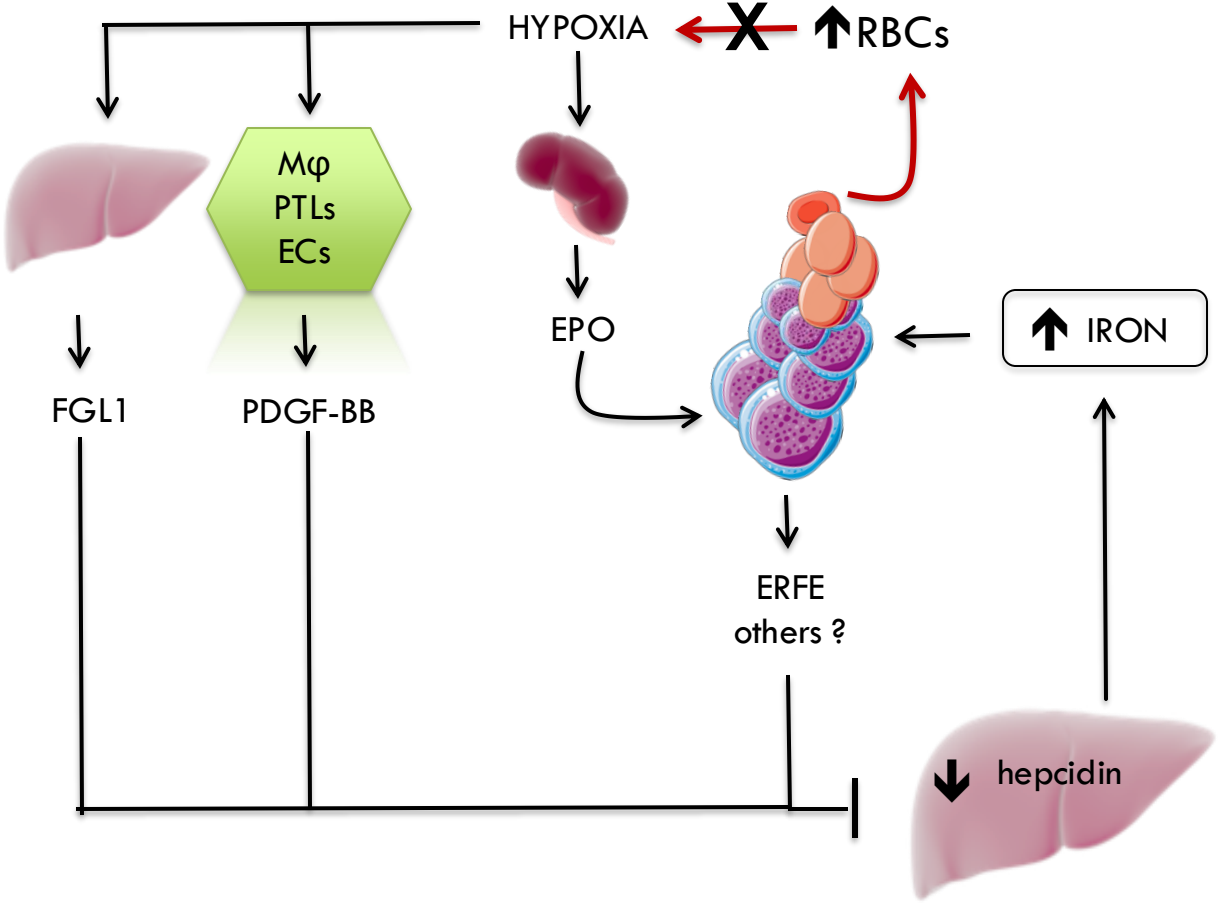

Kautz et al., 2014;
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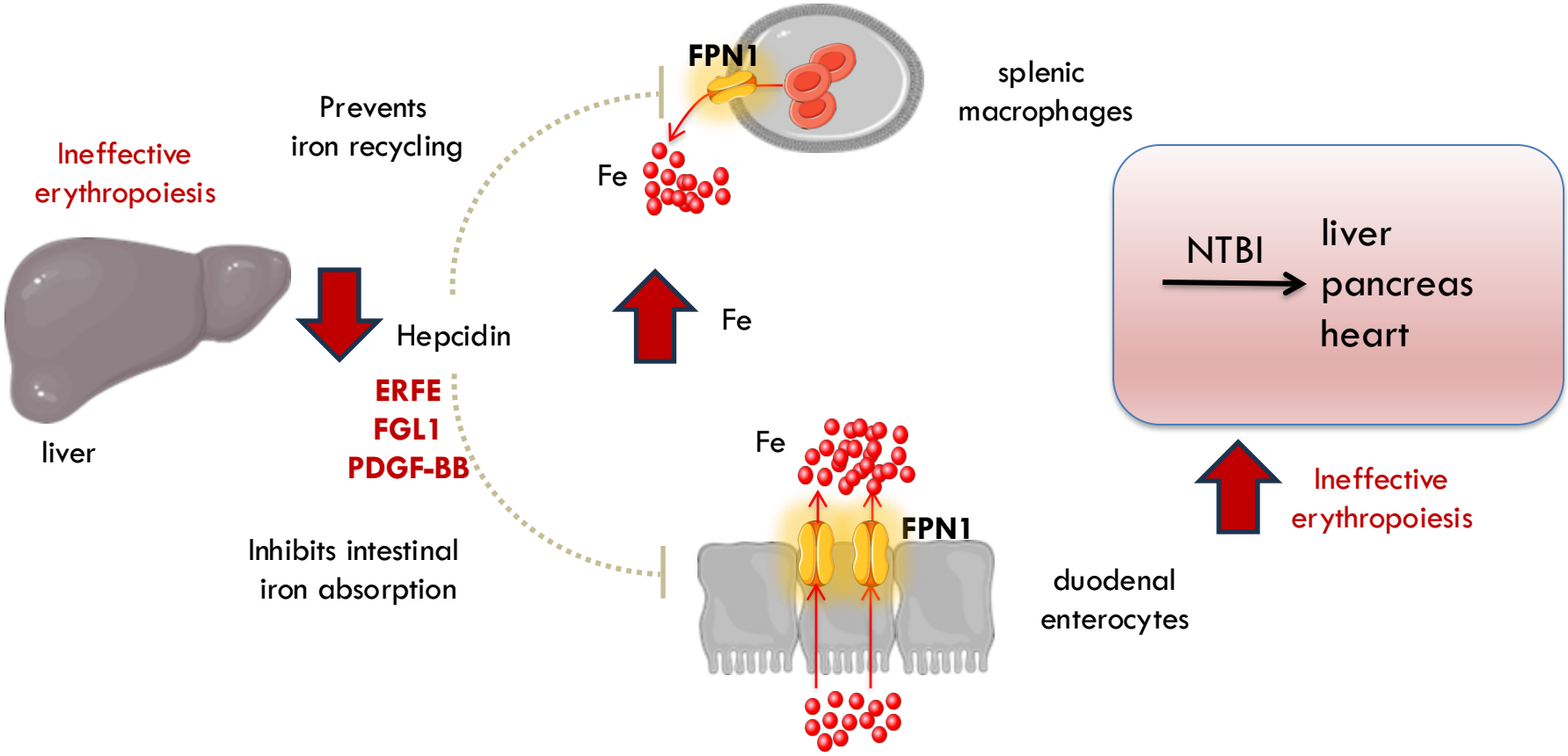
Sardo et al., bioRxiv 2023

Hepcidin regulation under pathological conditions



Definition of Iron Loading Anemias

A group of *inherited* or *acquired* anemias characterized by:

- ineffective erythropoiesis
  - low hepcidin levels
- excessive iron absorption
- secondary iron overload

Camaschella and Nai, BJH 2015; Cazzola, Blood 2022

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inherited

- sideroblastic anemias
- β-thalassemia
- congenital dyserythropoietic anemias (CDAs)

acquired

- some forms of myelodysplastic syndromes (MDS-RS)

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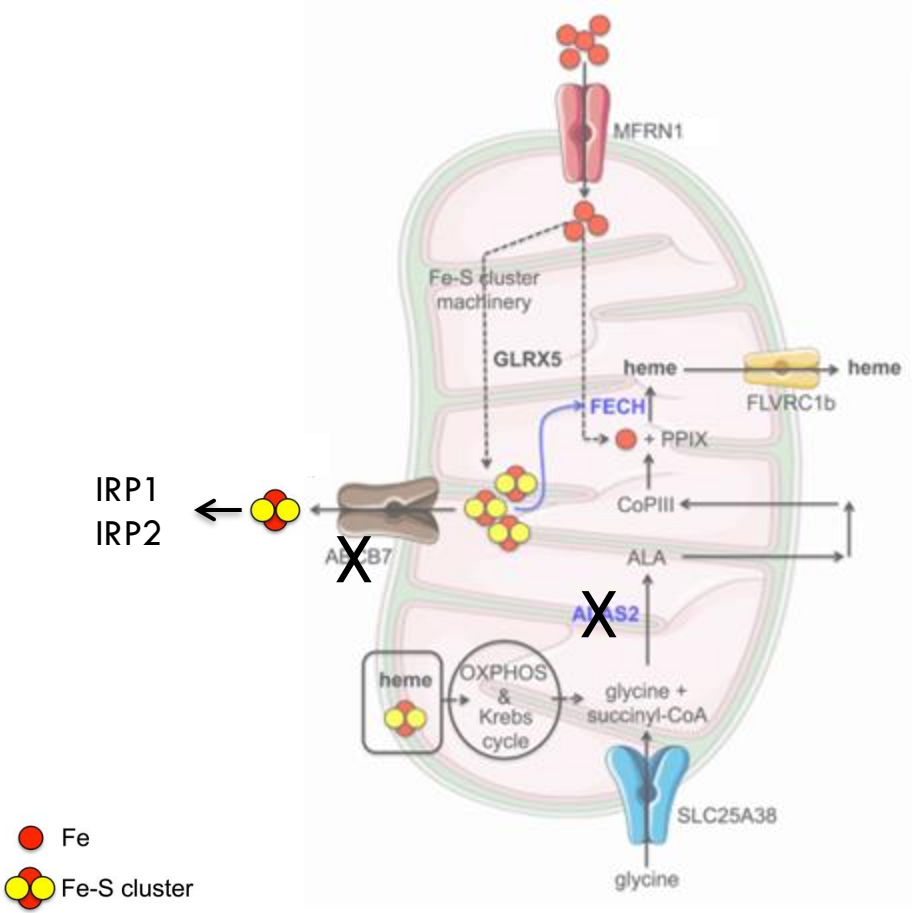
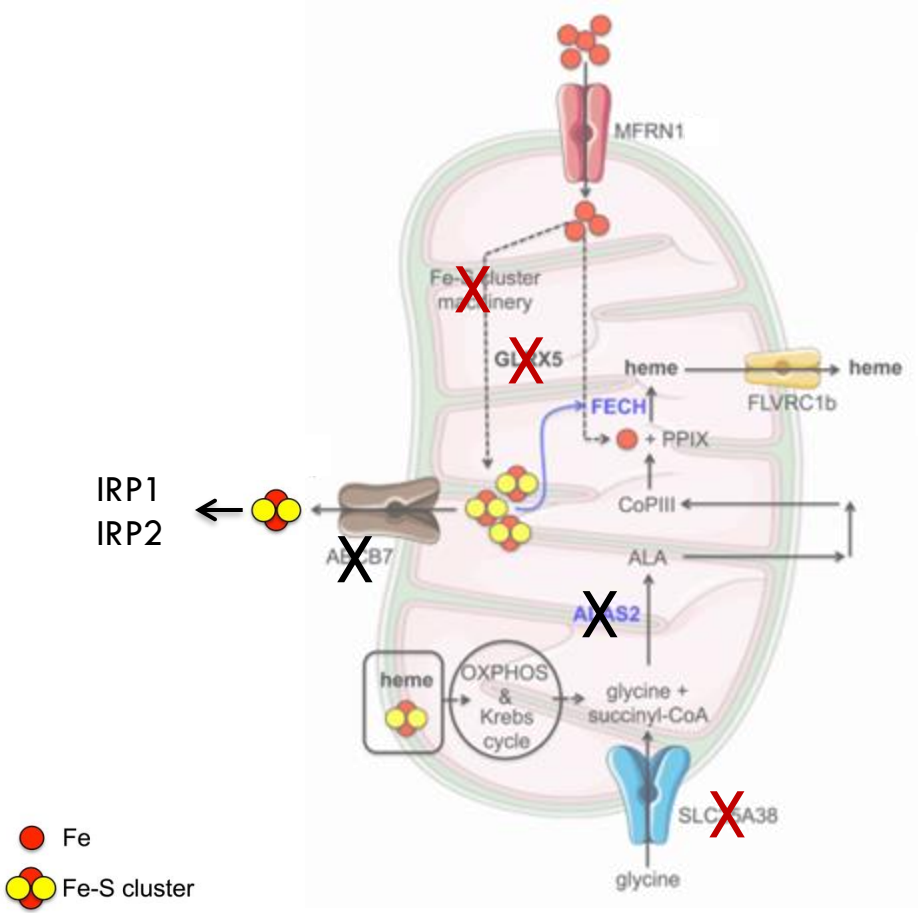
Sideroblastic Anemia

- X-linked sideroblastic anemia

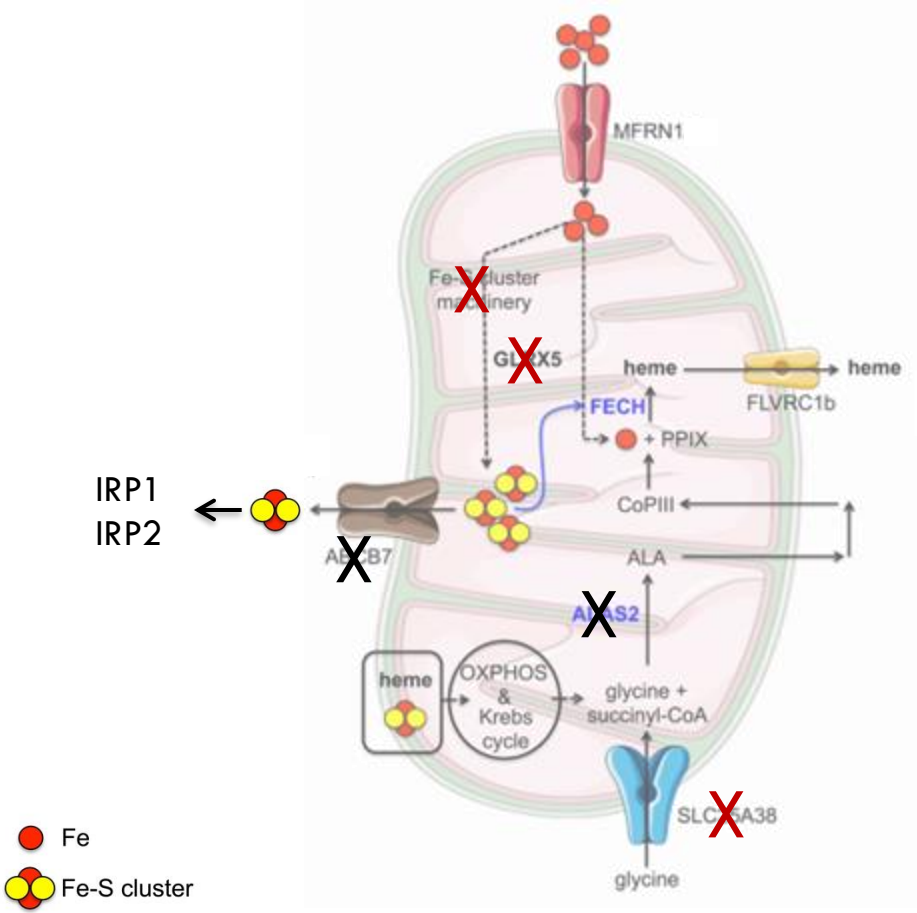


Sideroblastic Anemia



- X-linked sideroblastic anemia
- AR sideroblastic anemia (*SLC25A38*, *GLRX5*, *HSPA9*, *HSCB*)

Sideroblastic Anemia



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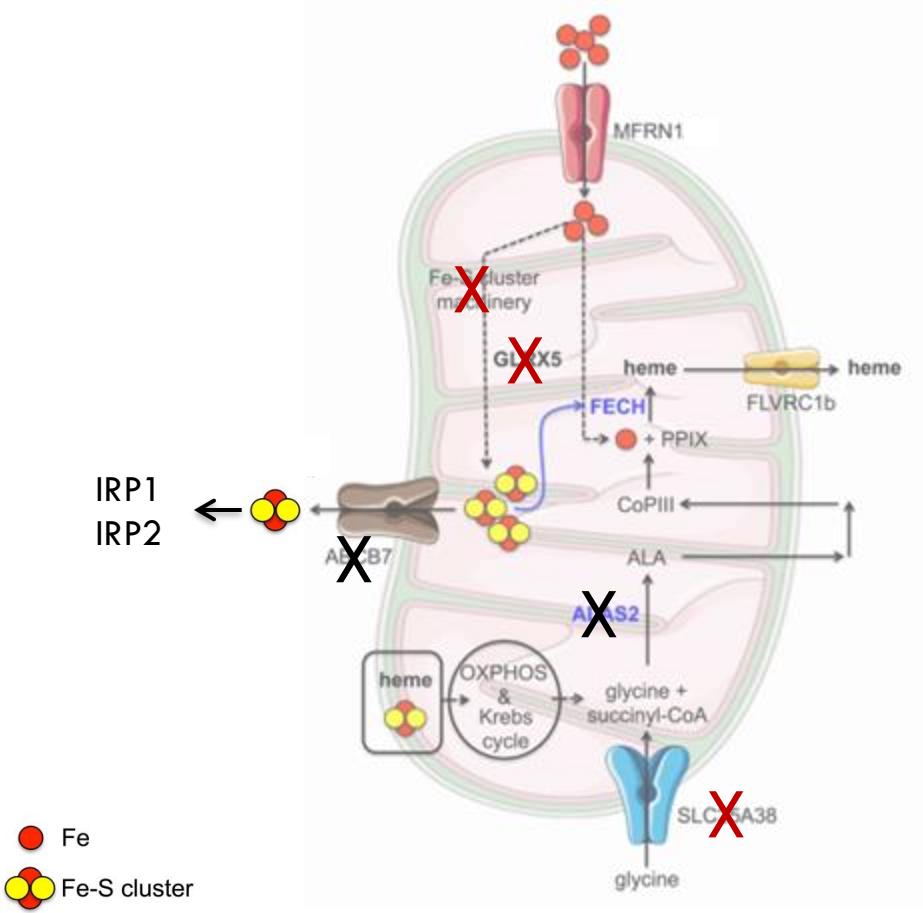

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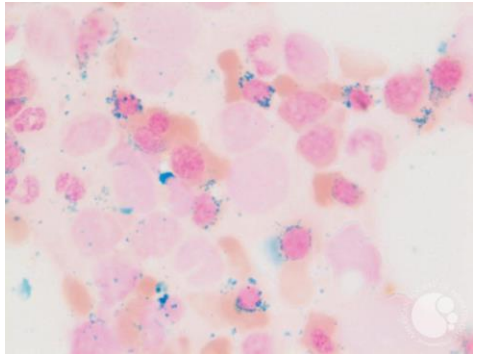
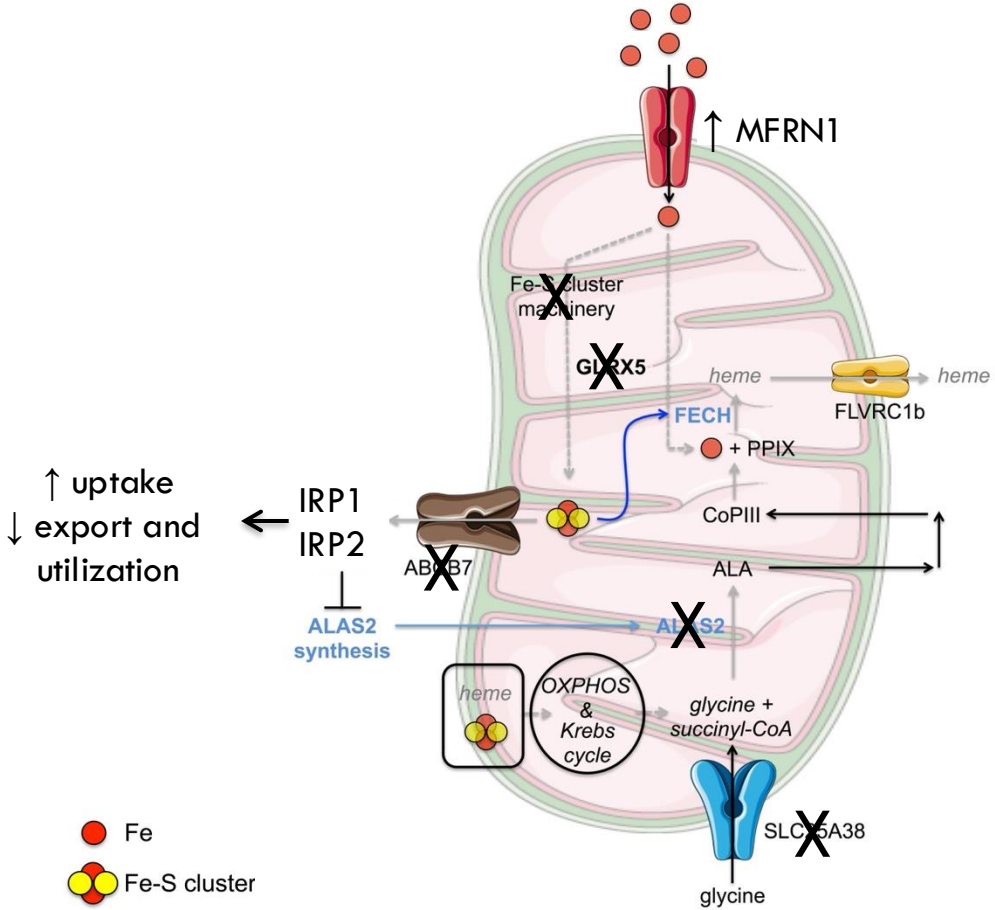
- maternal inheritance (large mtDNA deletion)



Ring sideroblasts

ASH image bank

Sideroblastic Anemia



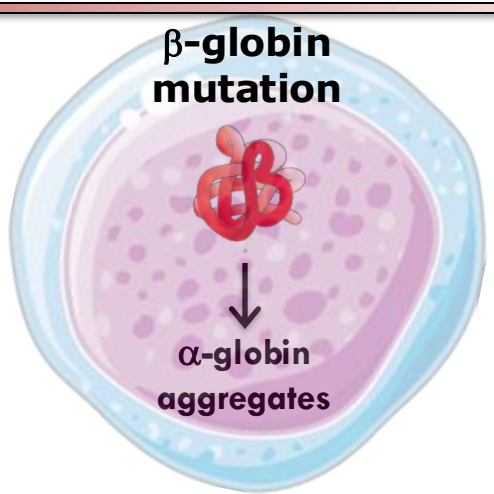
↓ **Fe-S clusters**

- *False* signal of iron deficiency
- Mitochondrial iron overload
- Increased ROS production
- Impaired mitochondrial f(x)
- Reduced heme synthesis

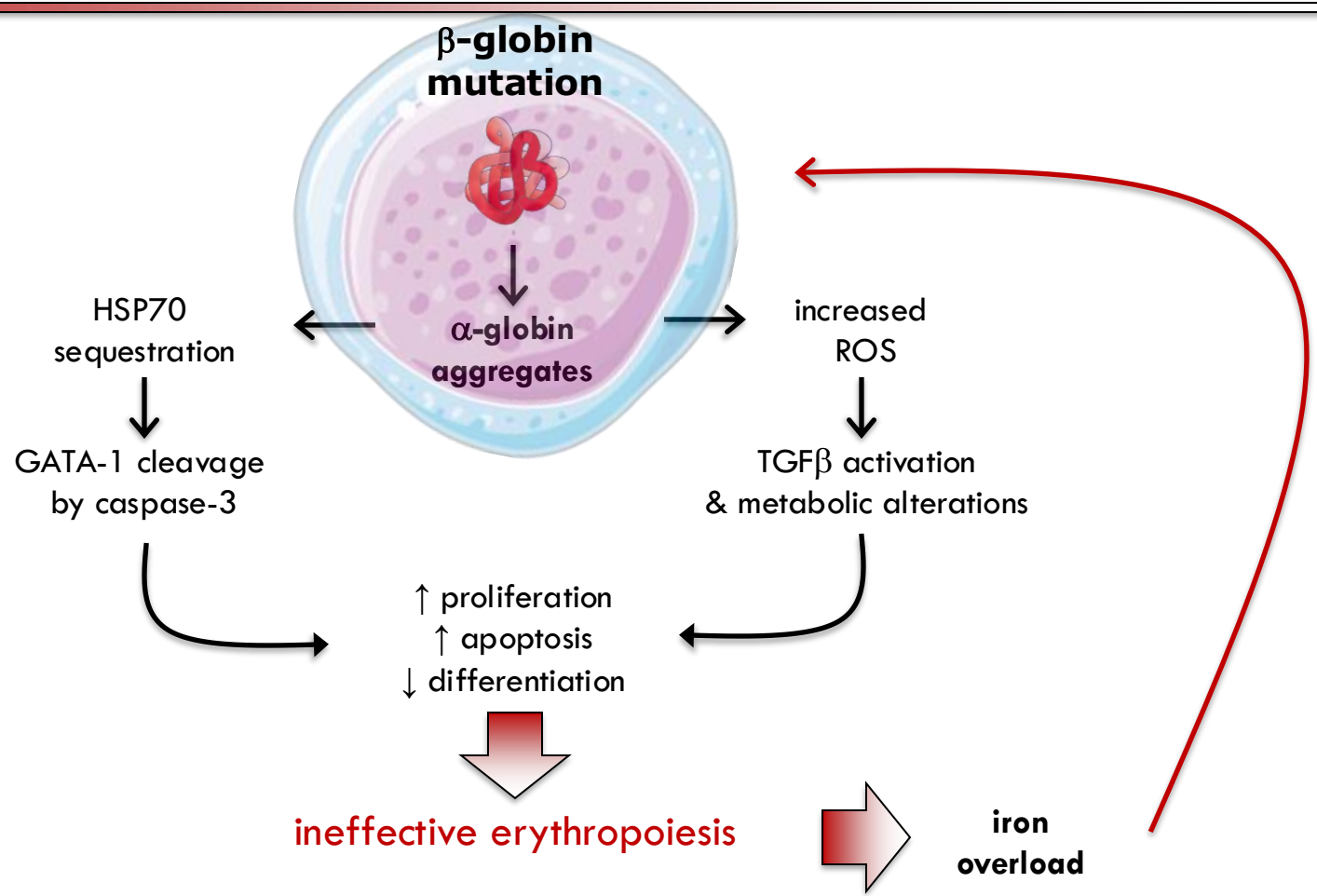
↓ **heme**

HRI (active) → P-eIF2α → ↓ globin synthesis

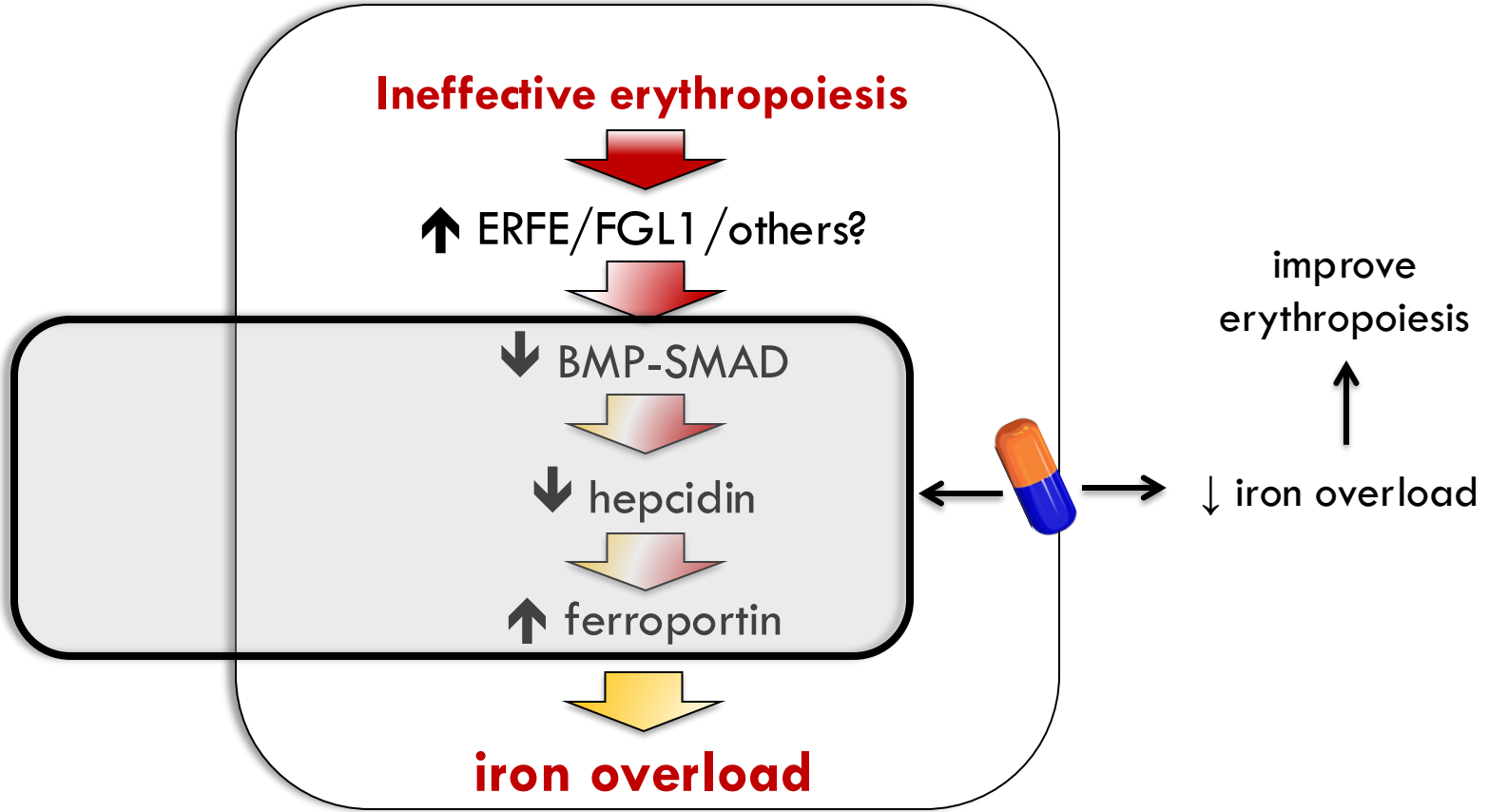
β-thalassemia



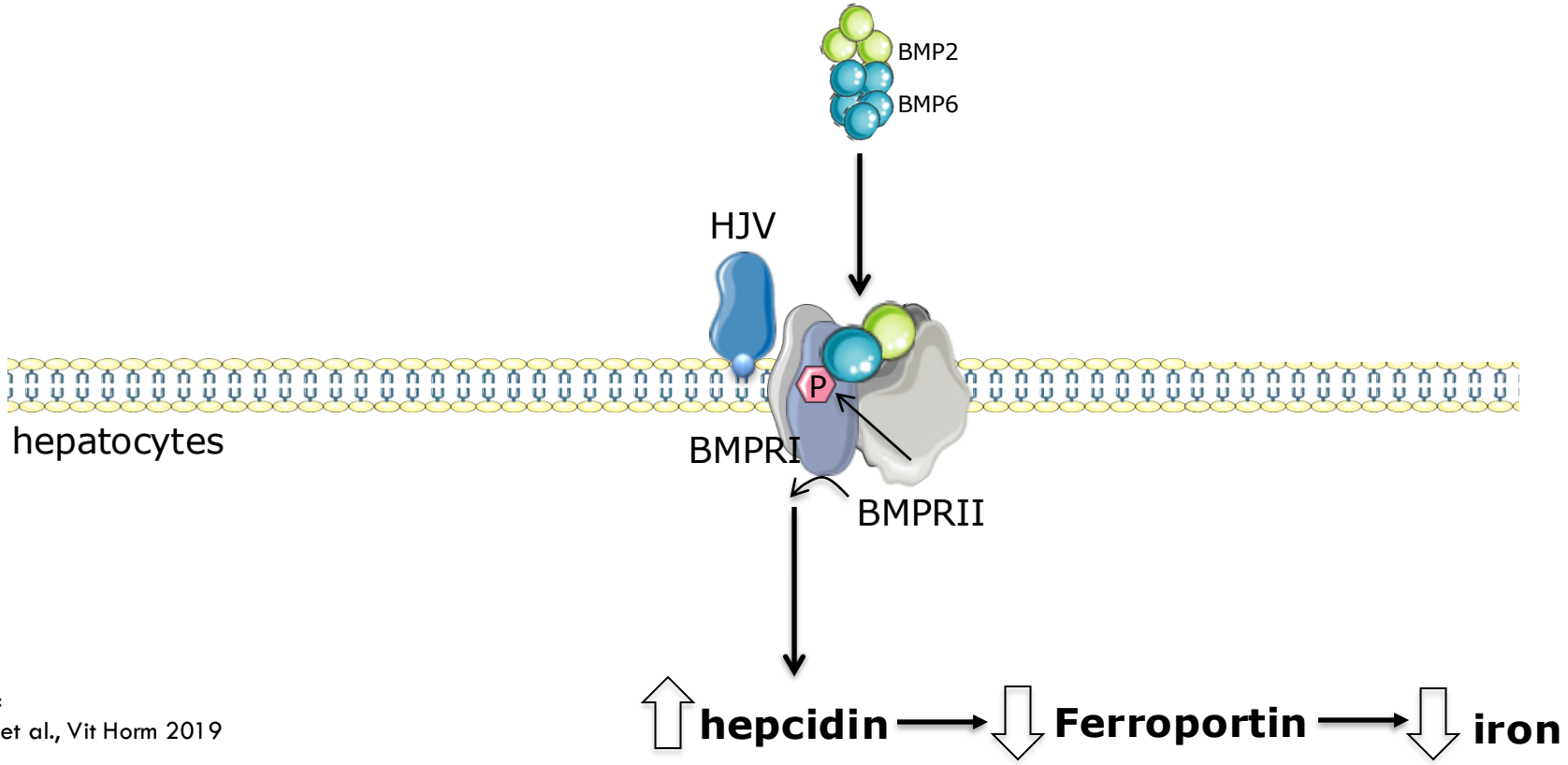
β-thalassemia



Targeting iron overload in iron loading anemias



Hepcidin expression is regulated by the BMP-SMAD pathway



Reviews:
Silvestri et al., Vit Horm 2019

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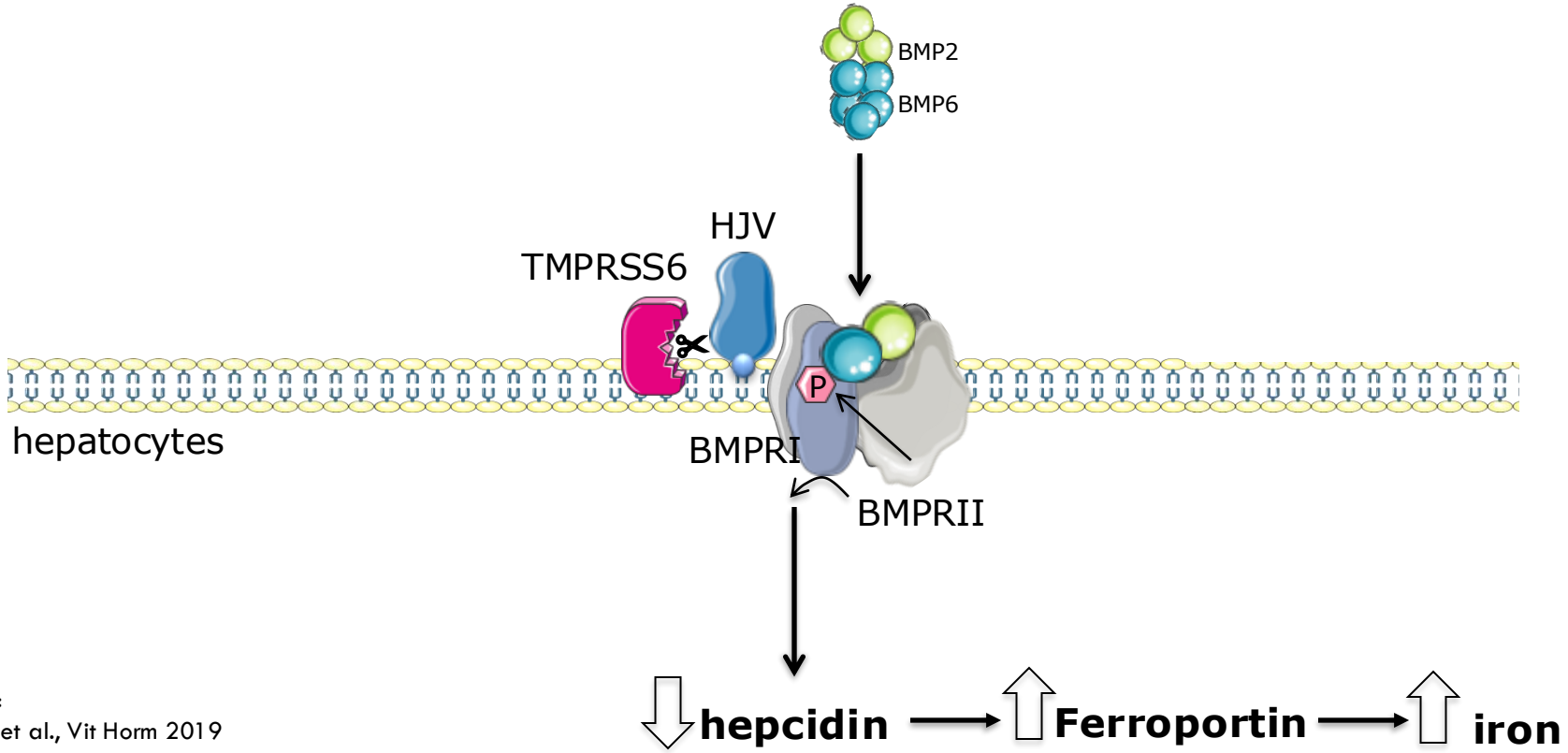
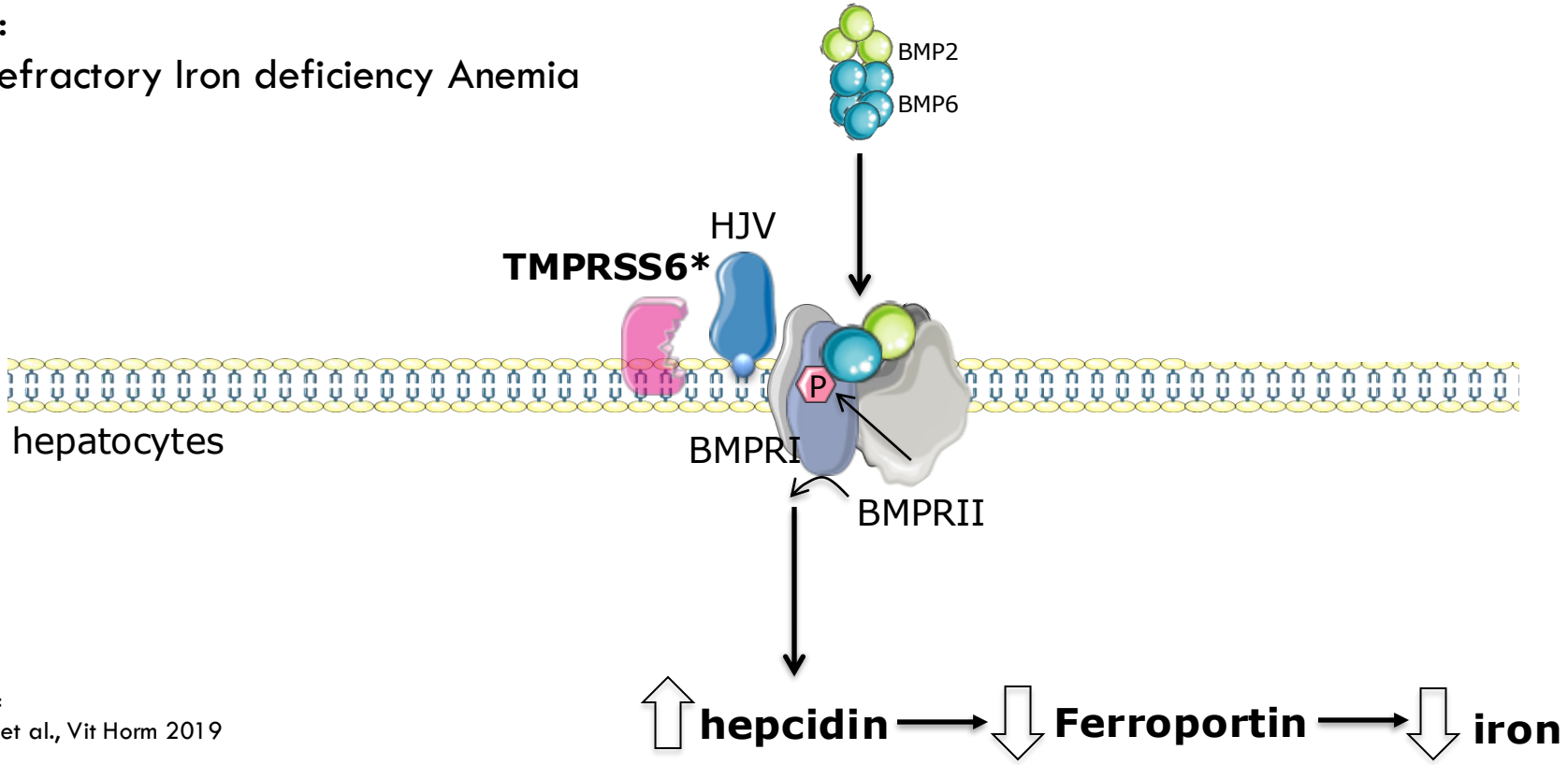


Reviews:
Silvestri et al., Vit Horm 2019

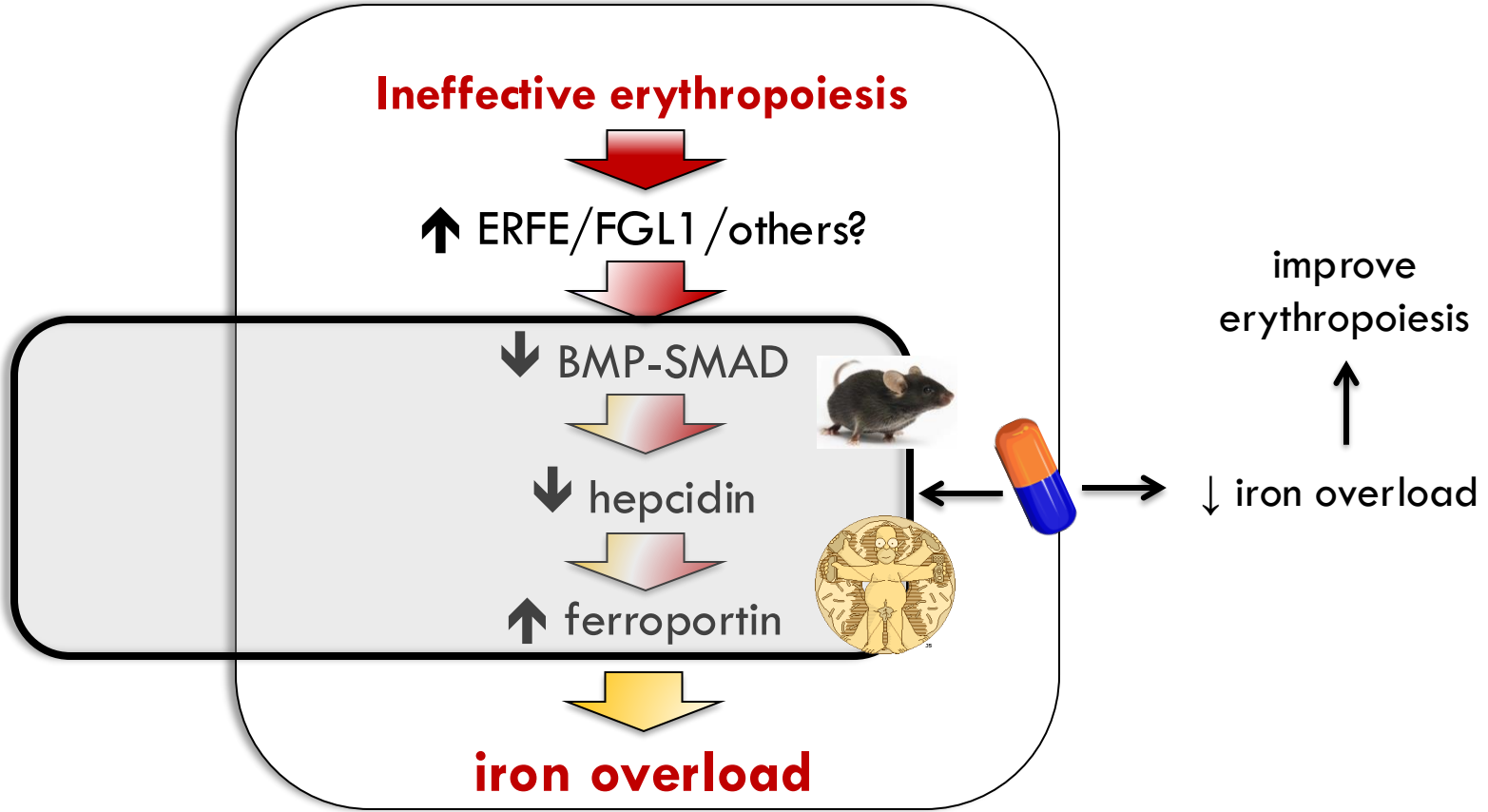
TMPRSS6 mutations leave hepcidin constitutively high

IRIDA:
Iron refractory Iron deficiency Anemia



Reviews:
Silvestri et al., Vit Horm 2019

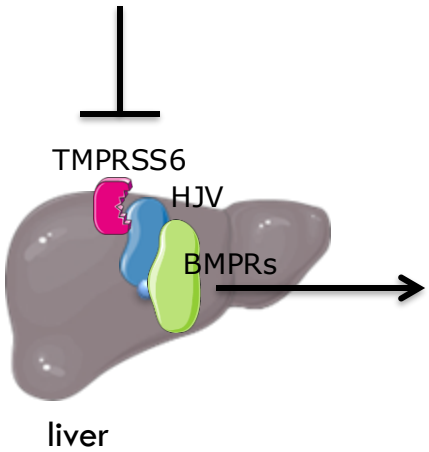
Therapeutic targets to reduce iron overload



Targeting the hepatic BMP-SMAD pathway

ê BMP-SMAD
ê hepcidin
é ferroportin
iron overload

Anti-TMPRSS6 agents (ASO, siRNA, mAb)



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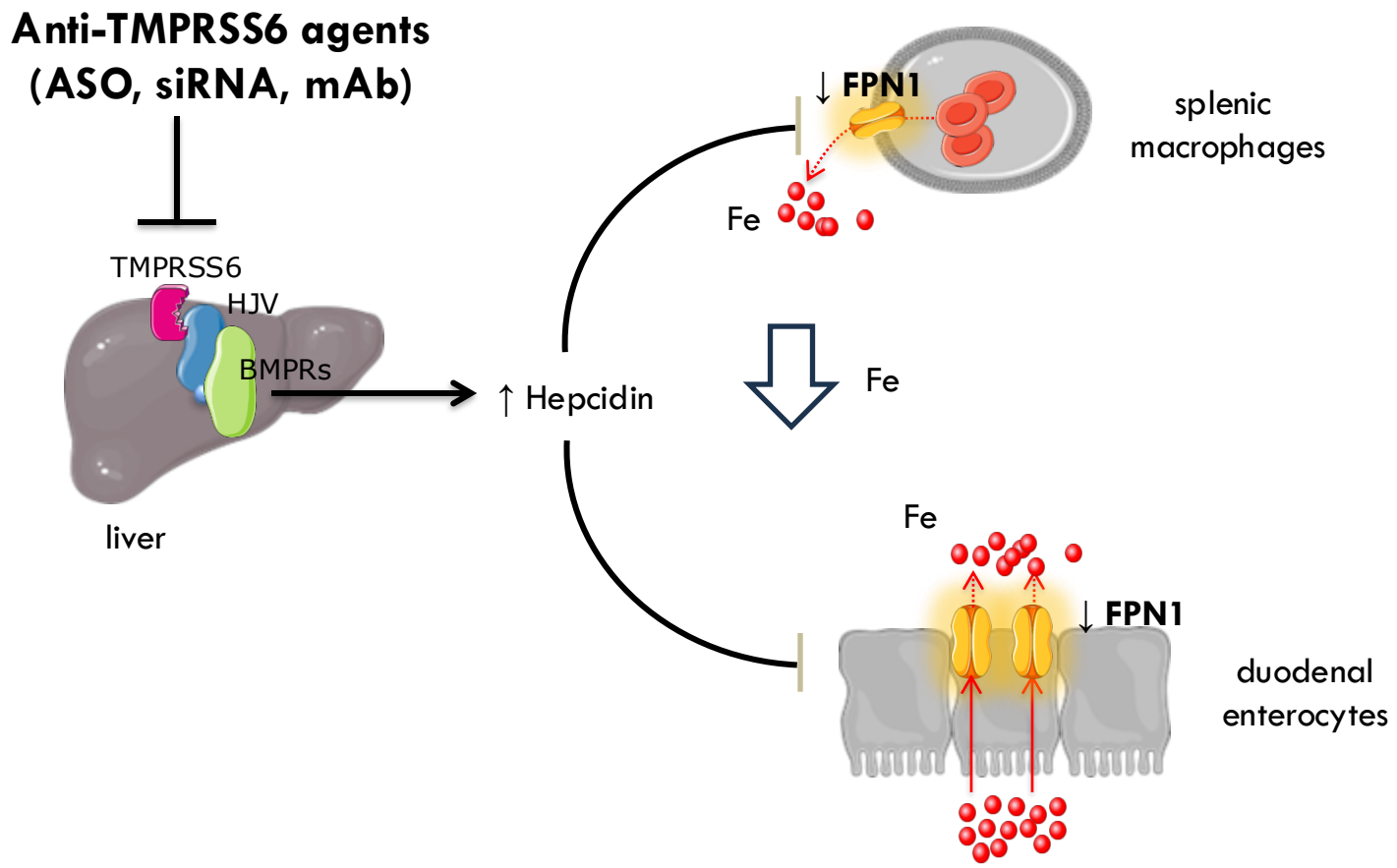

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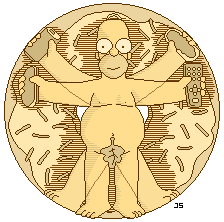

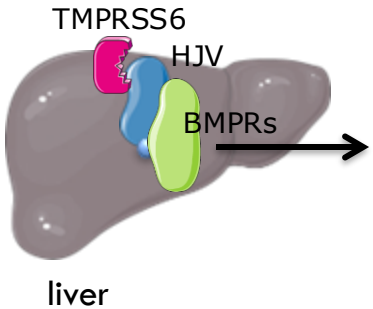

liver

- ✓ ***TMPRSS6*-ASO** (sapablursen, IONIS):
  - *Healthy (phase 1, completed, NCT03165864)*
  - Beta thal (phase 2, terminated, NCT04059406)
- ✓ ***TMPRSS6*-siRNA** (SLN127, Silence Therapeutics):
  - *Healthy (early phase 1, completed, NCT04559971)*
  - Thalassemia+MDS (phase 1, completed, NCT04718844)
- ✓ ***mAb anti-TMPRSS6*** (REGN7999, Regeneron):
  - *Healthy (phase 1, completed, NCT05481333)*
  - Beta thal (phase 2, not yet recruiting, NCT06421636)

clinicaltrial.gov

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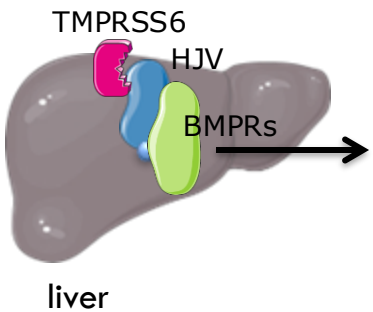
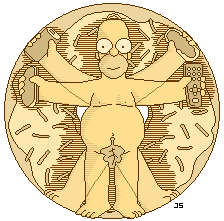
Anti-TMPRSS6 agents (ASO, siRNA, mAb)





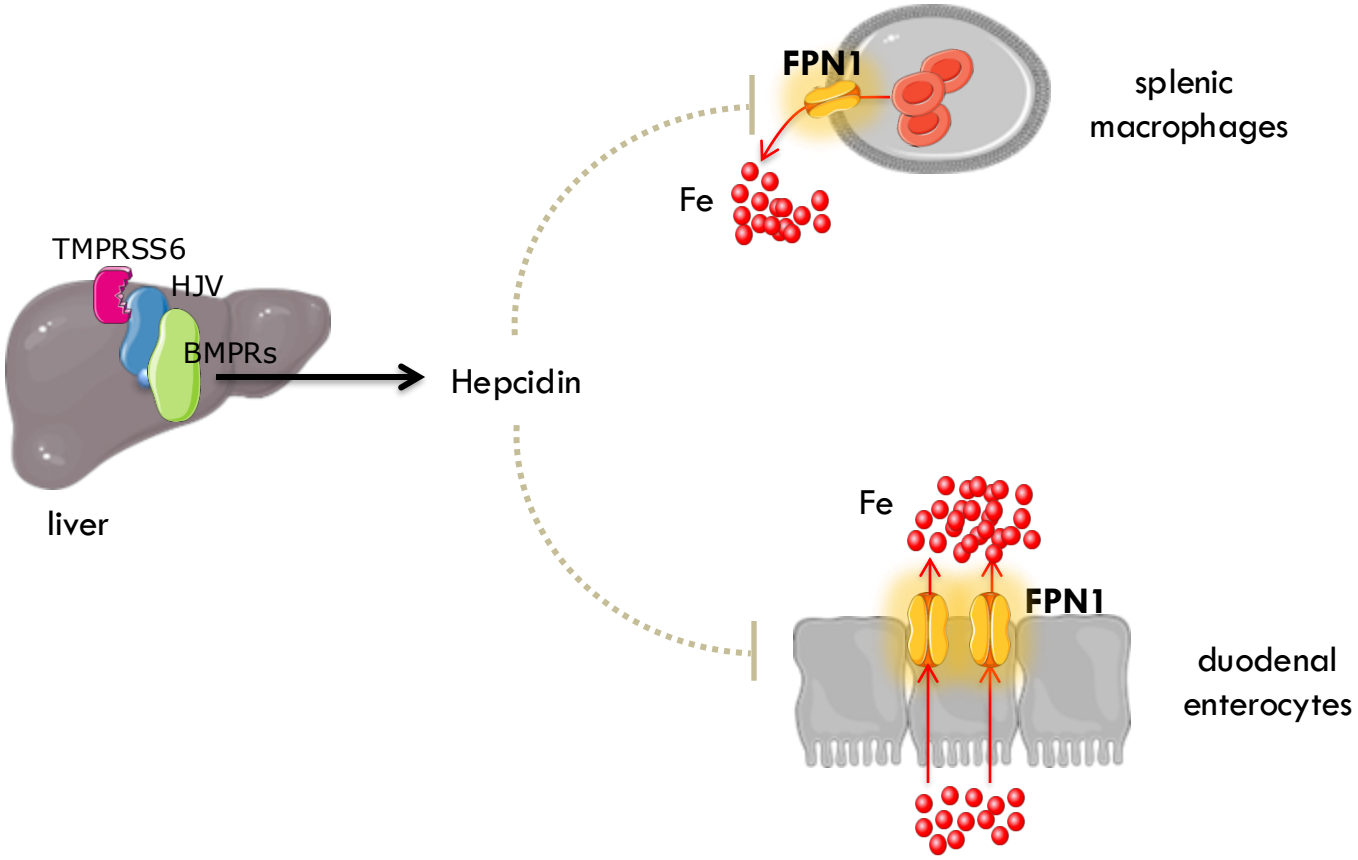
- ✓ ***TMPRSS6*-ASO** (sapablursen, IONIS):
  - Healthy (phase 1, completed, NCT03165864)
  - **Beta thal** (phase 2, terminated, NCT04059406)

The study was terminated for lack of efficacy (https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-003505-96/results)

clinicaltrial.gov

Targeting hepcidin

ê BMP-SMAD
ê hepcidin
é ferroportin
iron overload



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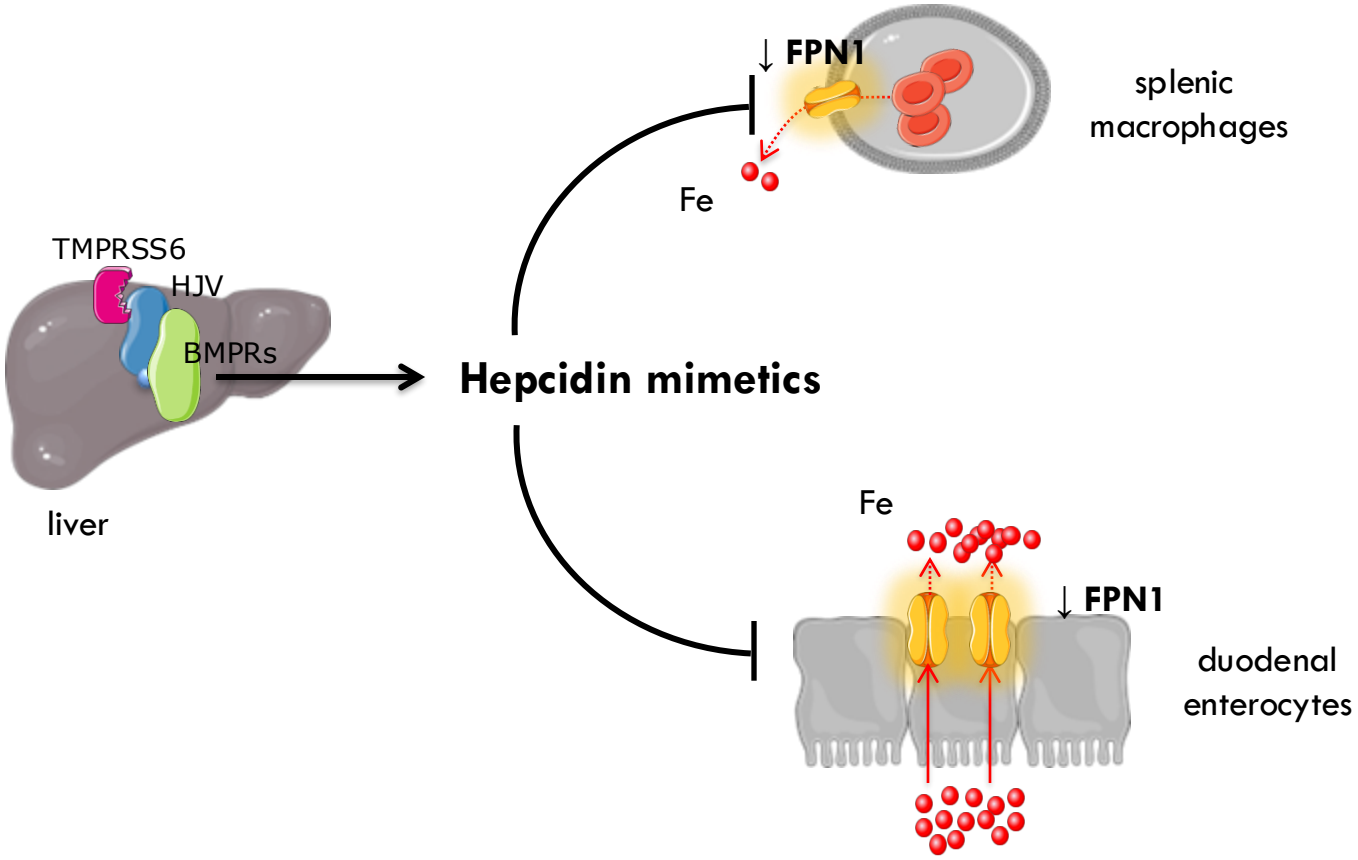

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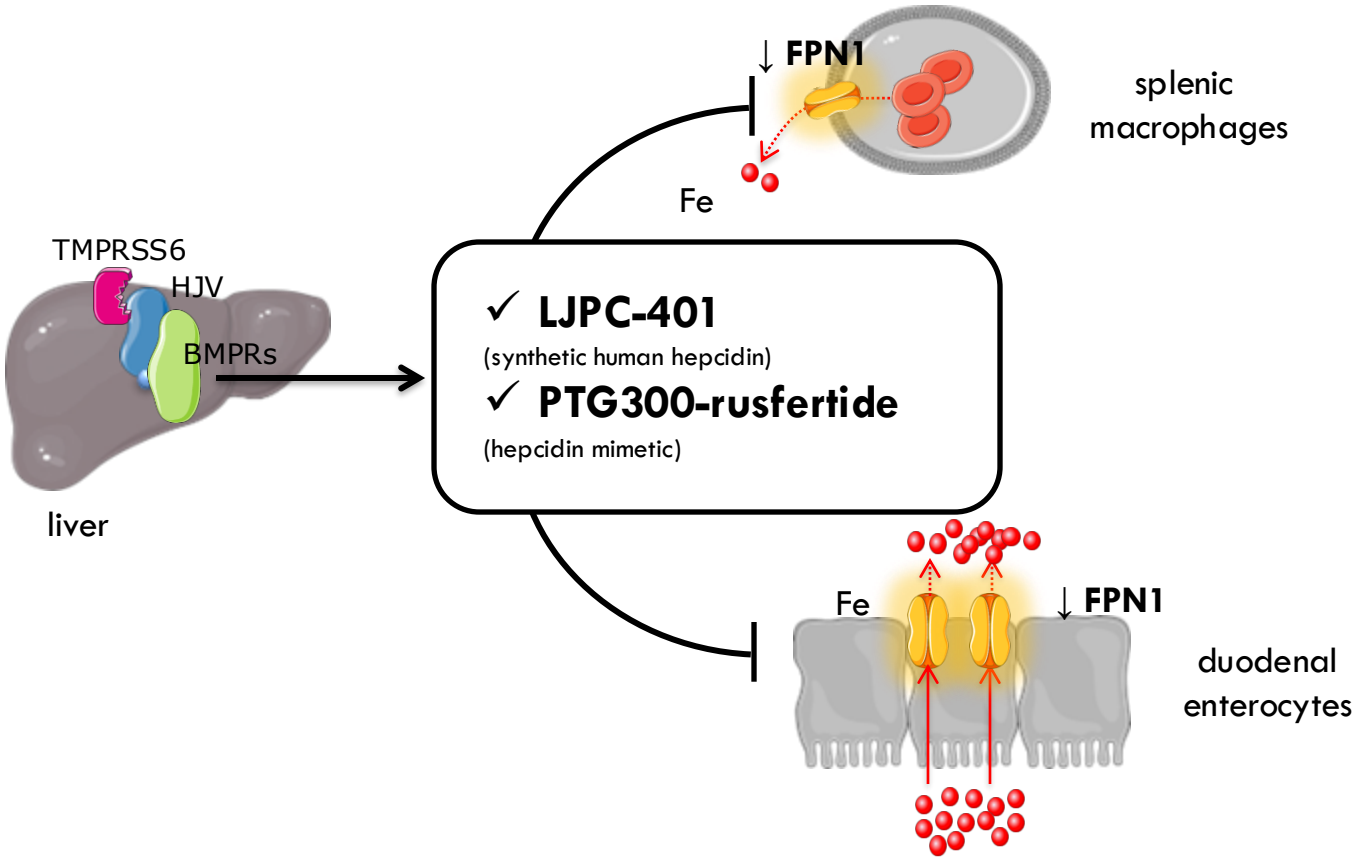

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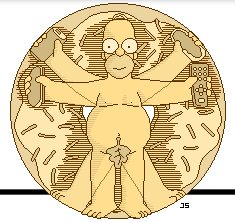
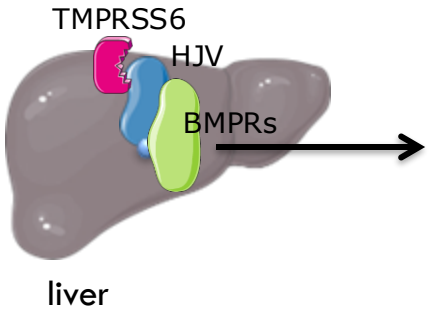


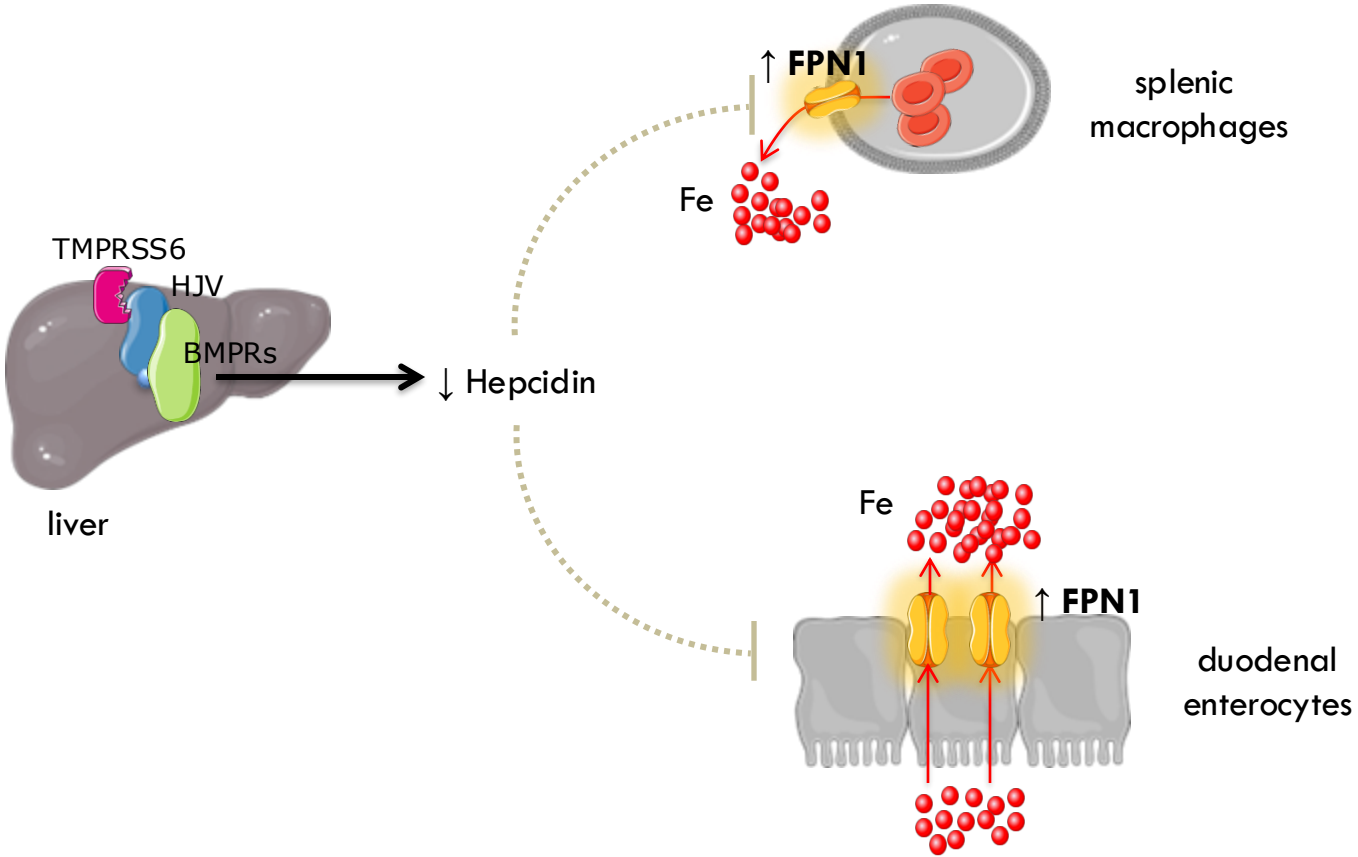


- ✓ **LJPC-401** (La Jolla Pharmaceutical):
  - *Hemochromatosis (phase 2, completed, NCT03395704)*
  - TD beta thal (phase 2, terminated, NCT03381833)
- ✓ **PTG300** (rusfertide, Protagonist):
  - *Healthy (phase 1, completed, NCT04516382)*
  - *Hemochromatosis (phase 2, completed, NCT04202965)*
  - NTD and TD beta thal (phase 2, completed, NCT03802201)

clinicaltrial.gov

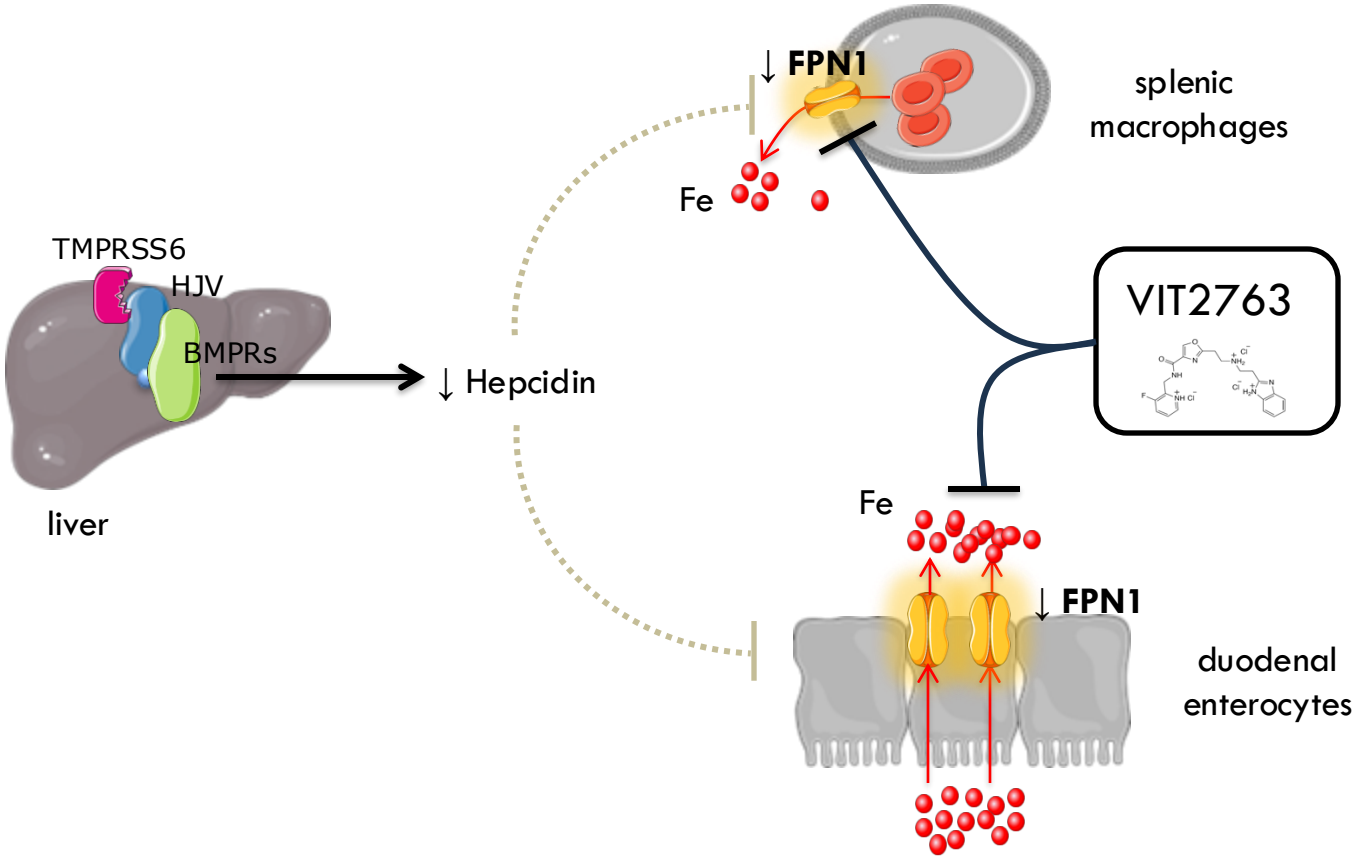
Targeting ferroportin function

ê BMP-SMAD
ê hepcidin
é ferroportin
iron overload



Targeting ferroportin

ê BMP-SMAD
ê hepcidin
é ferroportin
iron overload



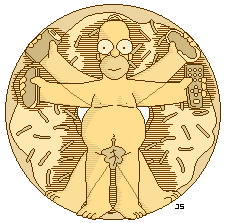
Targeting ferroportin

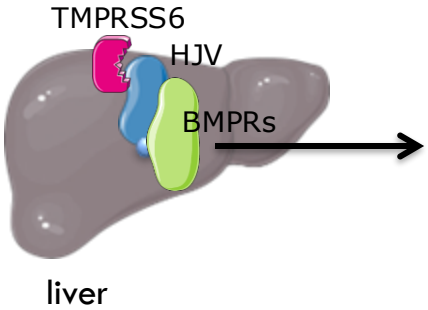
ê BMP-SMAD

ê hepcidin

é ferroportin

iron overload





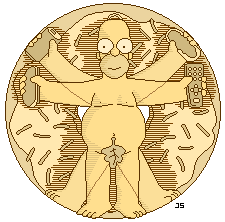
liver

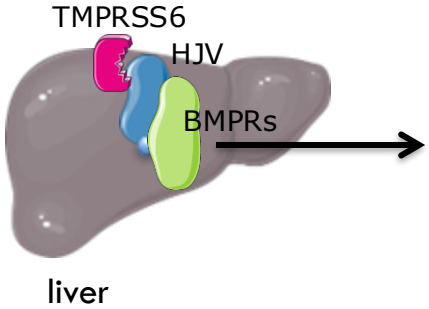
- ✓ **VIT2763** (vamifeport, Vifor Pharma):
  - beta thal (phase 2, completed, NCT04364269)
  - Sicke cell disease (phase 2, completed, NCT04817670)

clinicaltrial.gov

Targeting ferroportin

ê BMP-SMAD
ê hepcidin
é ferroportin
iron overload





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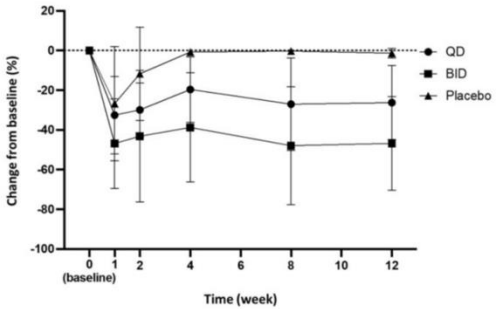
S272: **SAFETY AND PRELIMINARY PHARMACODYNAMIC EFFECTS OF THE FERROPORTIN INHIBITOR VAMIFEPORT (VIT-2763) IN PATIENTS WITH NON-TRANSFUSION-DEPENDENT BETA THALASSEMIA (NTDT): RESULTS FROM A PHASE 2A STUDY**

Taher et al., HemaSphere 2022

clinicaltrial.gov



Take home message

⌘ Balanced coordination of iron metabolism with erythropoietic activity is a protective mechanism against iron overload and anemia.

⌘ Deregulation of the hepcidin-ferroportin axix is the main cause of iron overload in anemias characterized by ineffective erythropoiesis.

⌘ Erythroid precursors regulate iron homeostasis by secreting the hepcidin inhibitor ERFE under conditions of expanded erythropoiesis. However, other organs and tissues may also contribute to hepcidin suppression in hypoxia, as shown by the identification of PDGF-BB and FGL1.

⌘ The common pathogenetic mechanisms of iron loading anemias allow the identification of several therapeutic targets worth testing as single or combined therapies.

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Acknowledgments

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I.R.C.C.S. Ospedale San Raffaele

Rusfertide decreases the phlebotomy rate in hemochromatosis…

Rusfertide for the treatment of iron overload in HFE-related haemochromatosis: an open-label, multicentre, proof-of-concept phase 2 trial

Kris V Kowdley, Nishit B Modi, Kevork Peltekian, John M Vierling, Christopher Ferris, Frank H Valone, Suneel Gupta

Lancet Gastroenterol Hepatol 2023

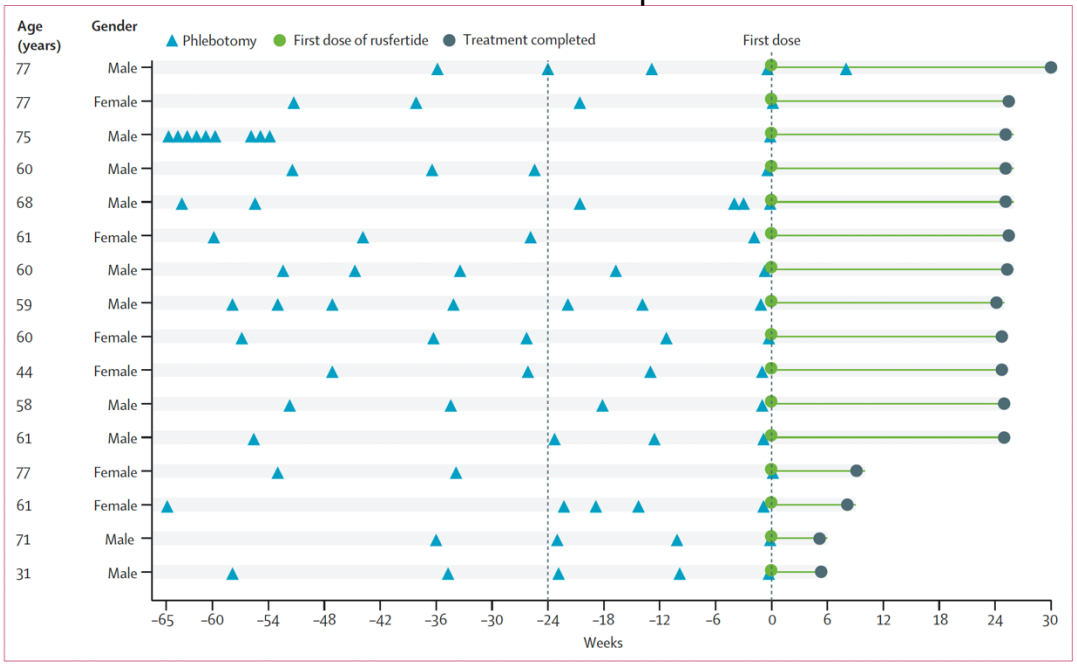

Figure 1: Effect of rusfertide on phlebotomy rate

…and in PV patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rusfertide, a Hepcidin Mimetic, for Control of Erythrocytosis in Polycythemia Vera

M. Kremyanskaya, A.T. Kuykendall, N. Pemmaraju, E.K. Ritchie, J. Gotlib, A. Gerds, J. Palmer, K. Pettit, U.K. Nath, A. Yacoub, A. Molina, S.R. Saks, N.B. Modi, F.H. Valone, S. Khanna, S. Gupta, S. Verstovsek, Y.Z. Ginzburg, and R. Hoffman, for the REVIVE Trial Investigators

NEJM 2024