9° WORKSHOP IN EMATOLOGIA TRASLAZIONALE

DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

Bologna, Aula "G. Prodi" - 19-20 maggio 2025

Come la ricerca ha riscritto il metabolismo e le patologie del ferro

Clara Camaschella
Vita-Salute University & San Raffaele Scientific Institute

Disclosures of Clara Camaschella

Nothing to disclose

The double face of iron

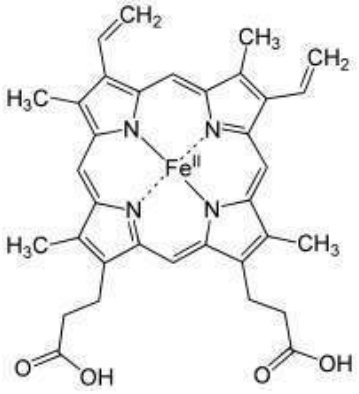
Essential

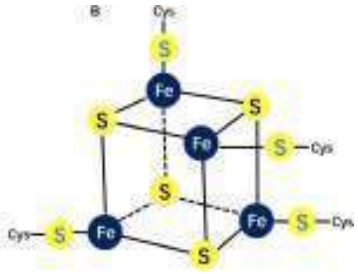
O_2 sensing and transport
Energy production
DNA replication and repair
Catecolamin metabolism
Enzymes

Cell and systemic iron regulation

Toxic

Proteins
Lipids
DNA
Mitochondria

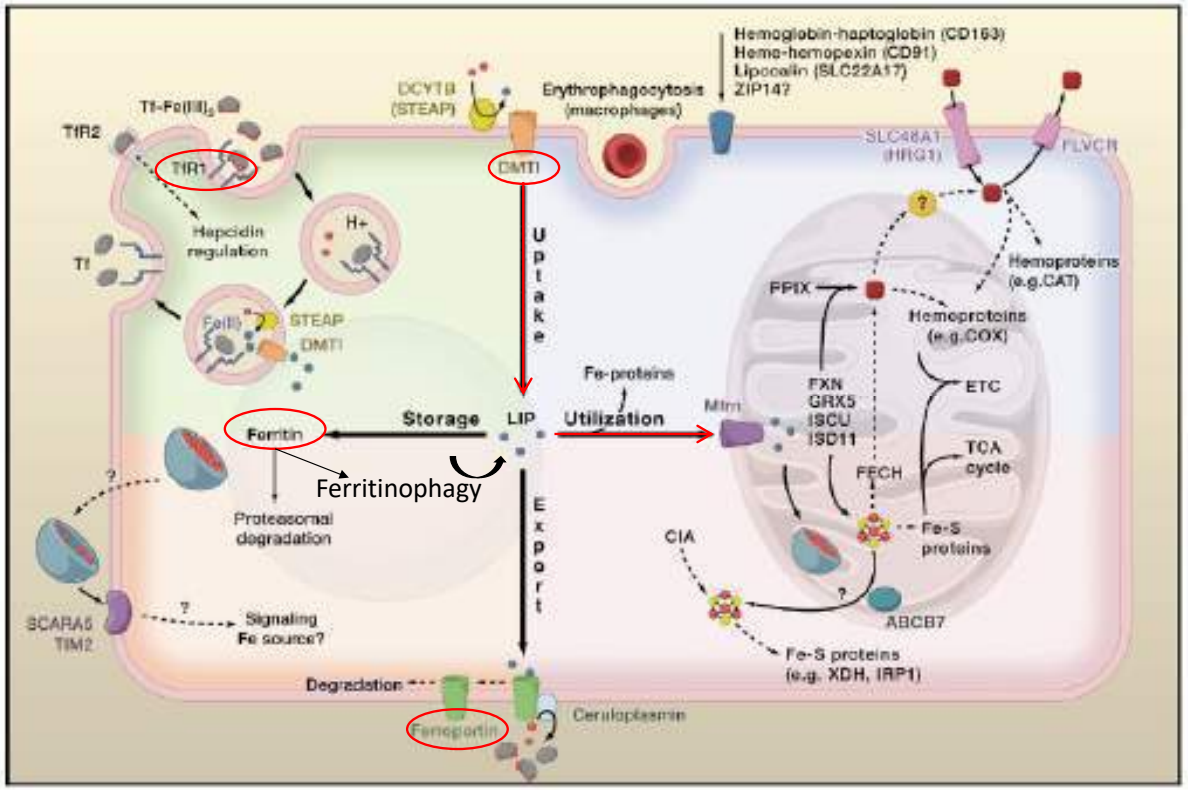




Fe^{2+} + H_2O_2 → Fe^{3+} + HO• + HO^-

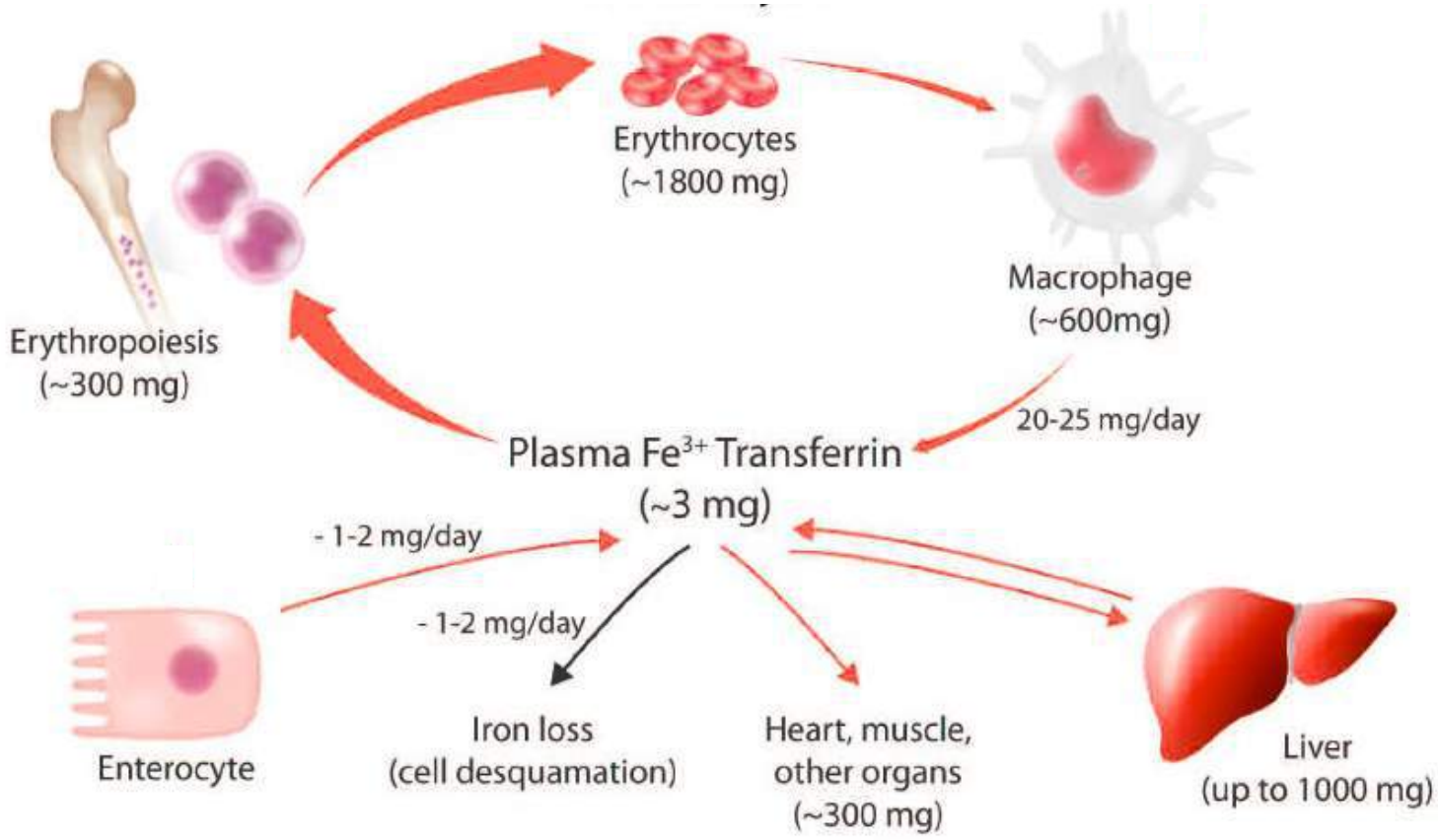
Fe^{3+} + H_2O_2 → Fe^{2+} + HOO• + H^+

Cellular iron regulation



Adapter from Hentze, Galy, Muckenthaler & Camaschella, Cell 2010

Body iron cycle



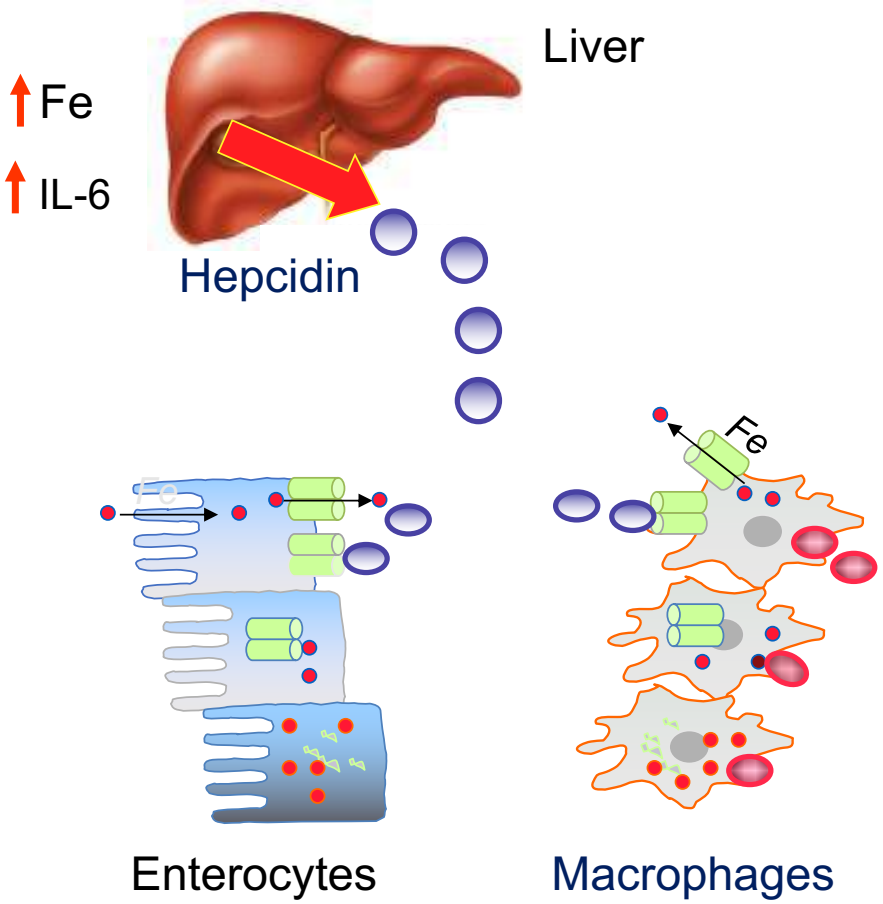
Ferritin

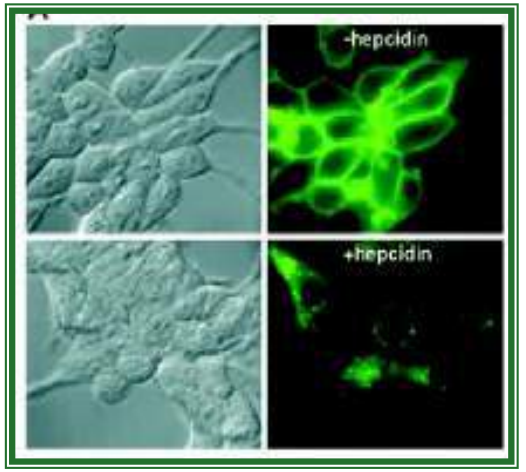
Tsat

LIC

Camaschella et al, Haematologica 2020

Hepcidin: the master iron regulator



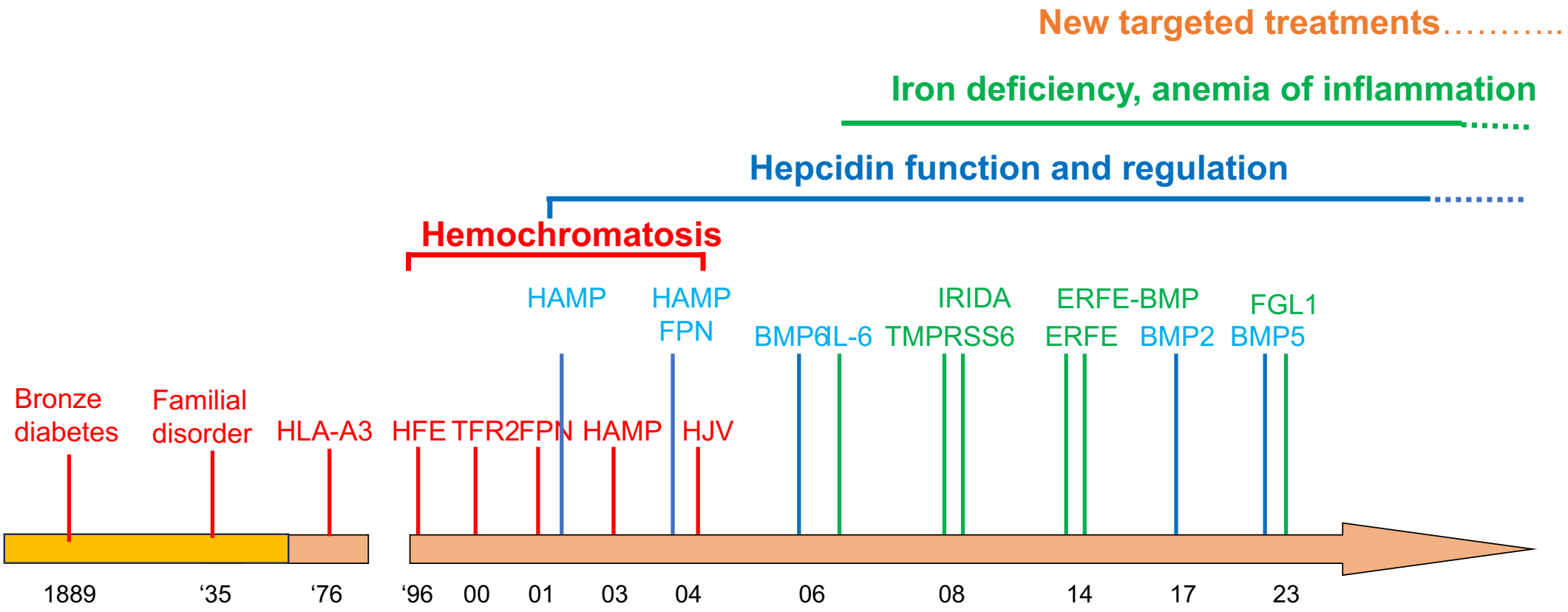


Nemeth et al, Science 2004

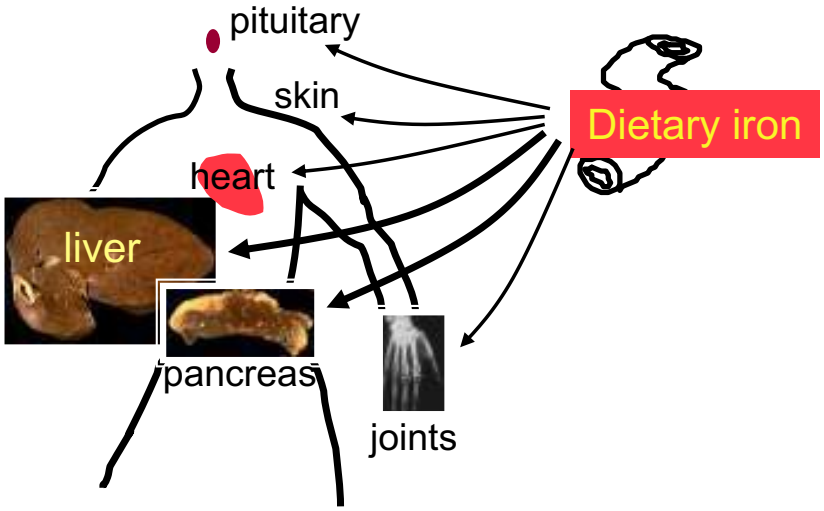
Ferroportin occlusion mechanism

Aschemeyer et al, Blood 2018

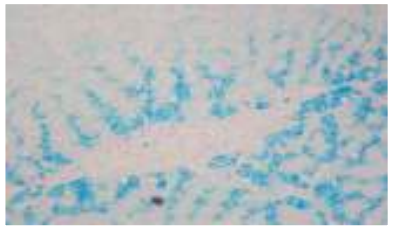
Hemochromatosis and the golden age of iron research



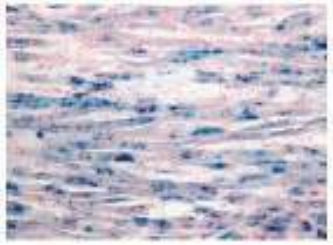
Hemochromatosis: pathophysiology



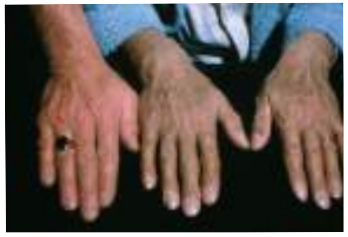
Liver: fibrosis, cirrhosis, HCC



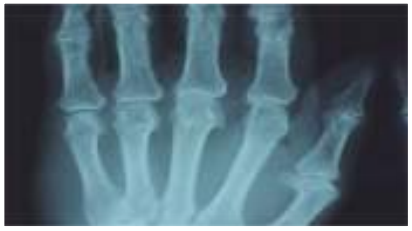
Cardiomyopathy



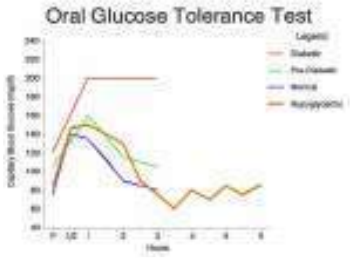
Skin pigmentation



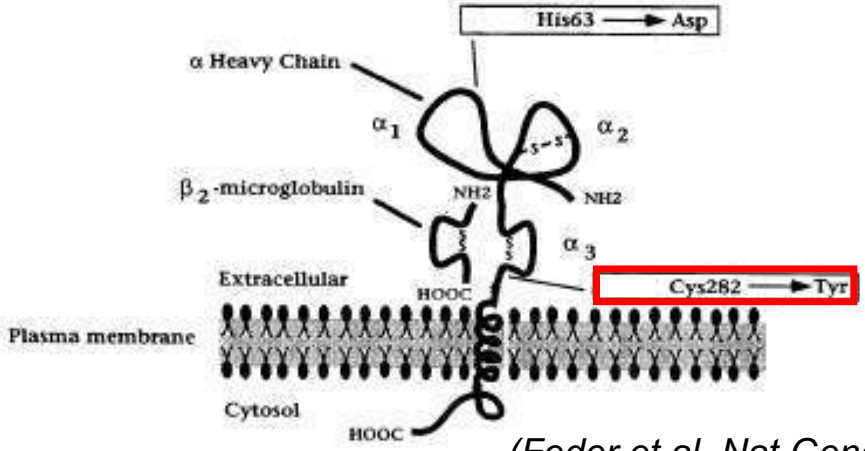
Joint disease



Endocrine damage



HFE, the first Hemochromatosis gene



(Feder et al, Nat Genet 1996)

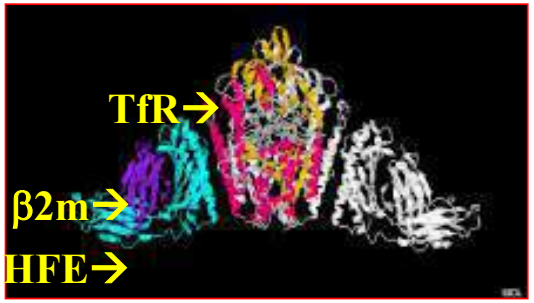
Genetic test for diagnosis

C282Y/C282Y > 90 % of cases in Northern Europe

C282Y/H63D < 5 % of cases + cofactors

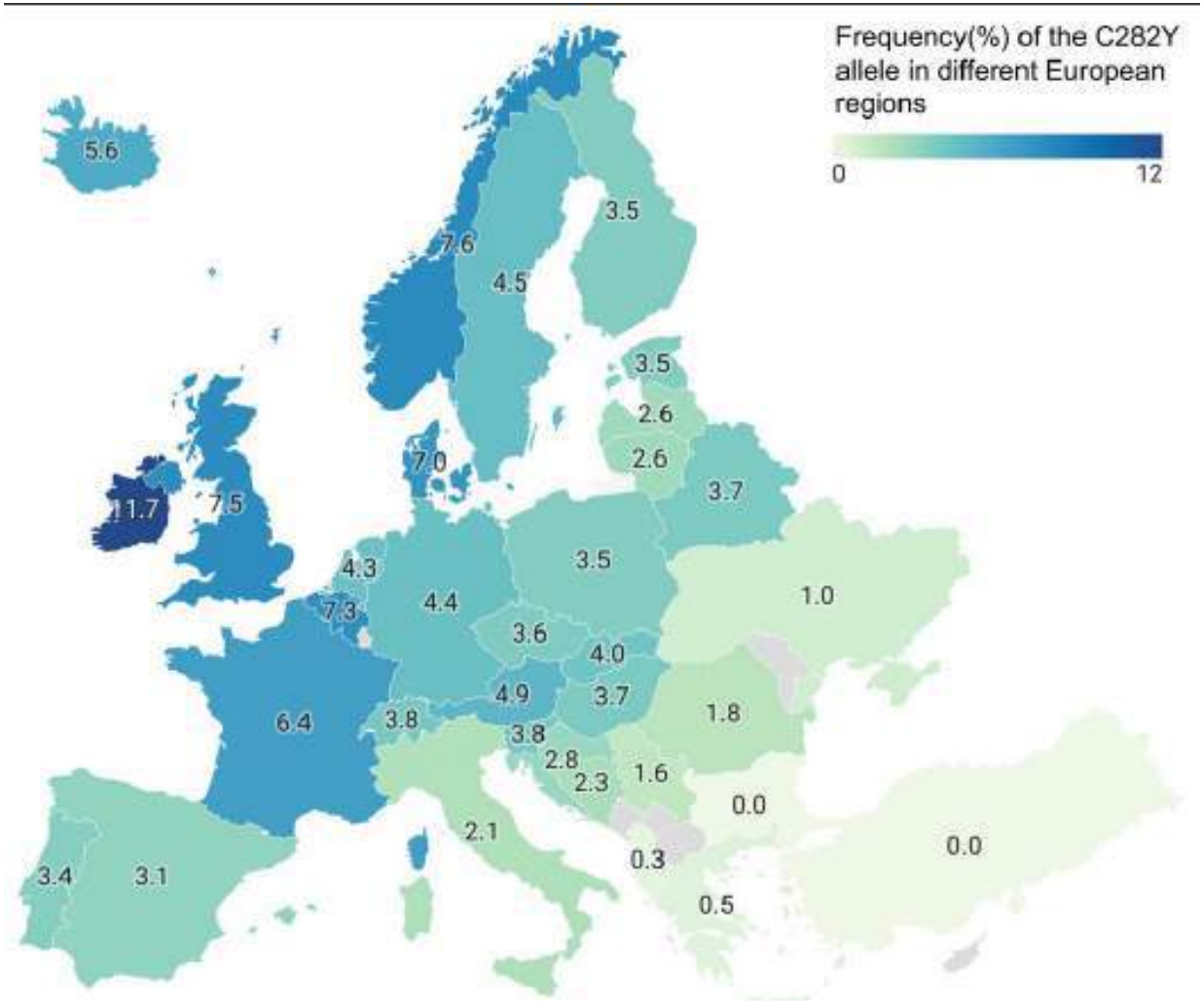
Which role in iron homeostasis?

HFE/TfR interaction



(Bennett et al, Nature 2000)

HFE ^{C82Y} allele distribution in Europe

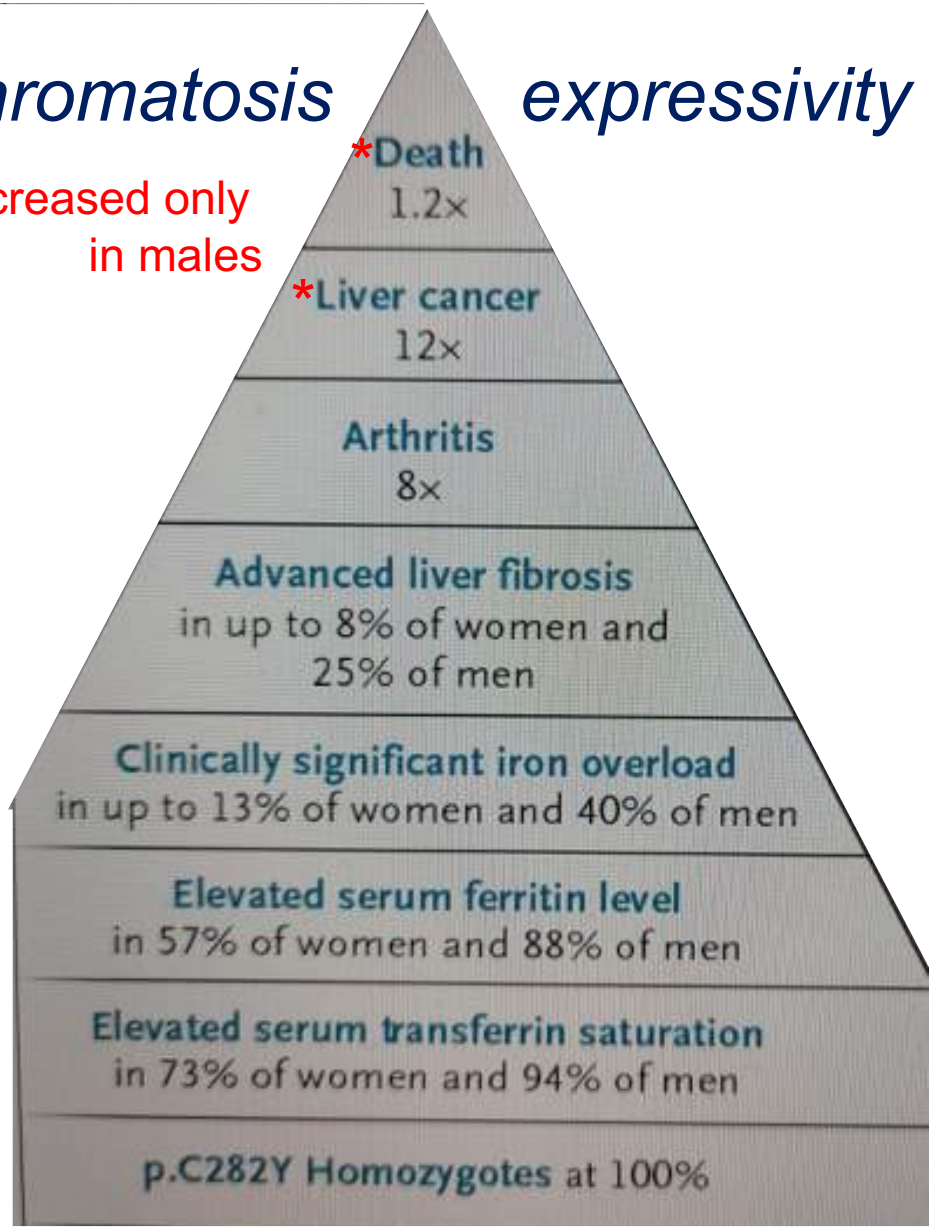


"The founder"

EASL, J Hepatol 2022

HFE Hemochromatosis expressivity

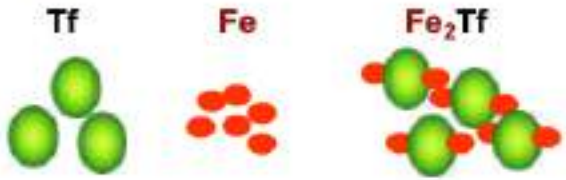
* Increased only in males



Liver disease prevalent

Olynk et al, N Engl J Med 2022

The iron toxicity of non-transferrin bound iron (NTBI)



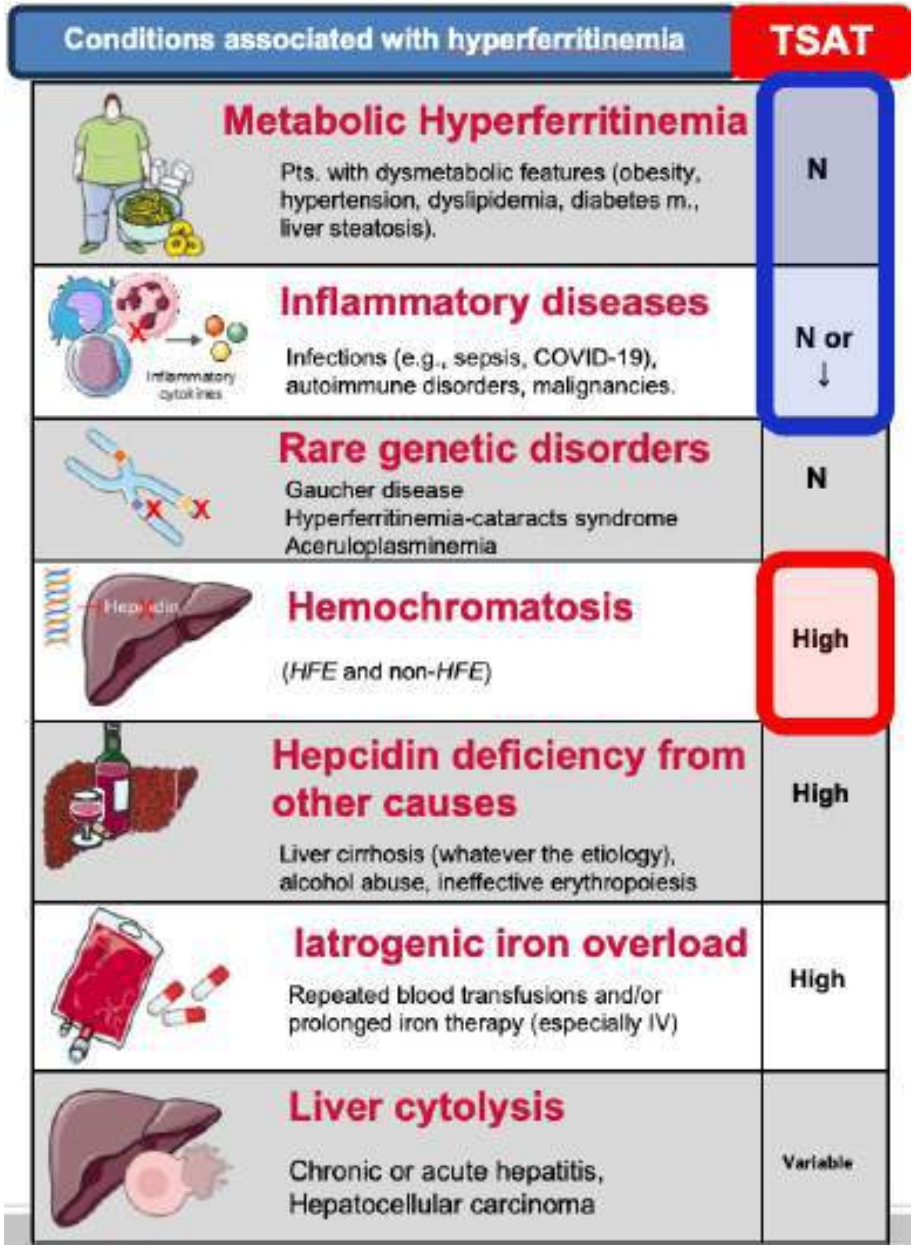
NTBI appears at Tf sat > 60-70%. NTBI (LIP) is uptaken by

and it is toxic to cells

when antioxidant defence system is overtaken → oxidation of polyunsaturated fatty acids → membrane rupture

Ferroptosis

Differential diagnosis



All these conditions may contribute/worsen the C282Y/C282Y phenotype

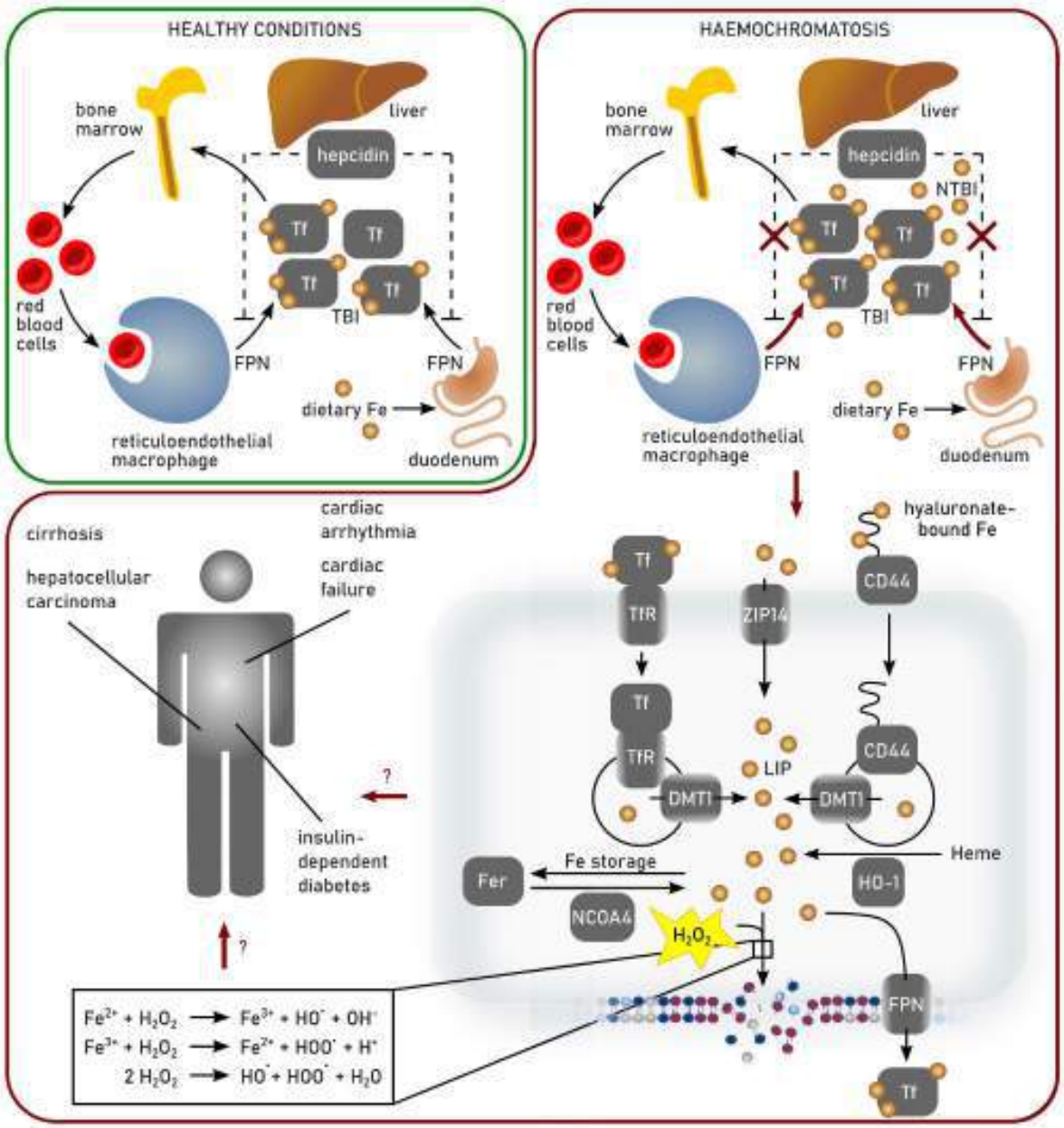
Ferroptosis in iron overload disorders

A form of cell death driven by iron-dependent damage to membrane lipids

Oxidation of polyunsaturated fatty acids is usually counteracted by cellular repair mechanisms, as glutathione peroxidase 4 (GPX4).

Ferroptosis is regulated by multiple processes, as iron accumulation, ROS, lipid metabolism, and antioxidant defence systems.
Implicated in several disorders, as neurodegeneration, cancer, and organ injury

Berndt et al, Redox Biology, 2024



Unraveling the Hemochromatosis genetic heterogeneity

nature genetics

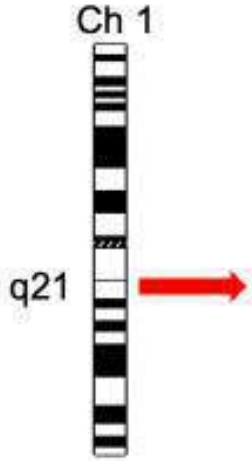
Clara Camaschella[1], Antonella Roetto[1], Angelita Cali[1], Marco De Gobbi[1], Giovanni Garozzo[2], Massimo Carella[3], Nunzia Majorano[3], Angela Totaro[3] & Paolo Gasparini[3]

The gene *TFR2* is mutated in a new type of haemochromatosis mapping to 7q22

nature genetics

Antonella Roetto[1]*, George Papanikolaou[2]*, Marianna Politou[2], Federica Alberti[1], Domenico Girelli[3], John Christakis[4], Dimitris Loukopoulos[2] & Clara Camaschella[1]

Mutant antimicrobial peptide hepcidin is associated with severe juvenile hemochromatosis



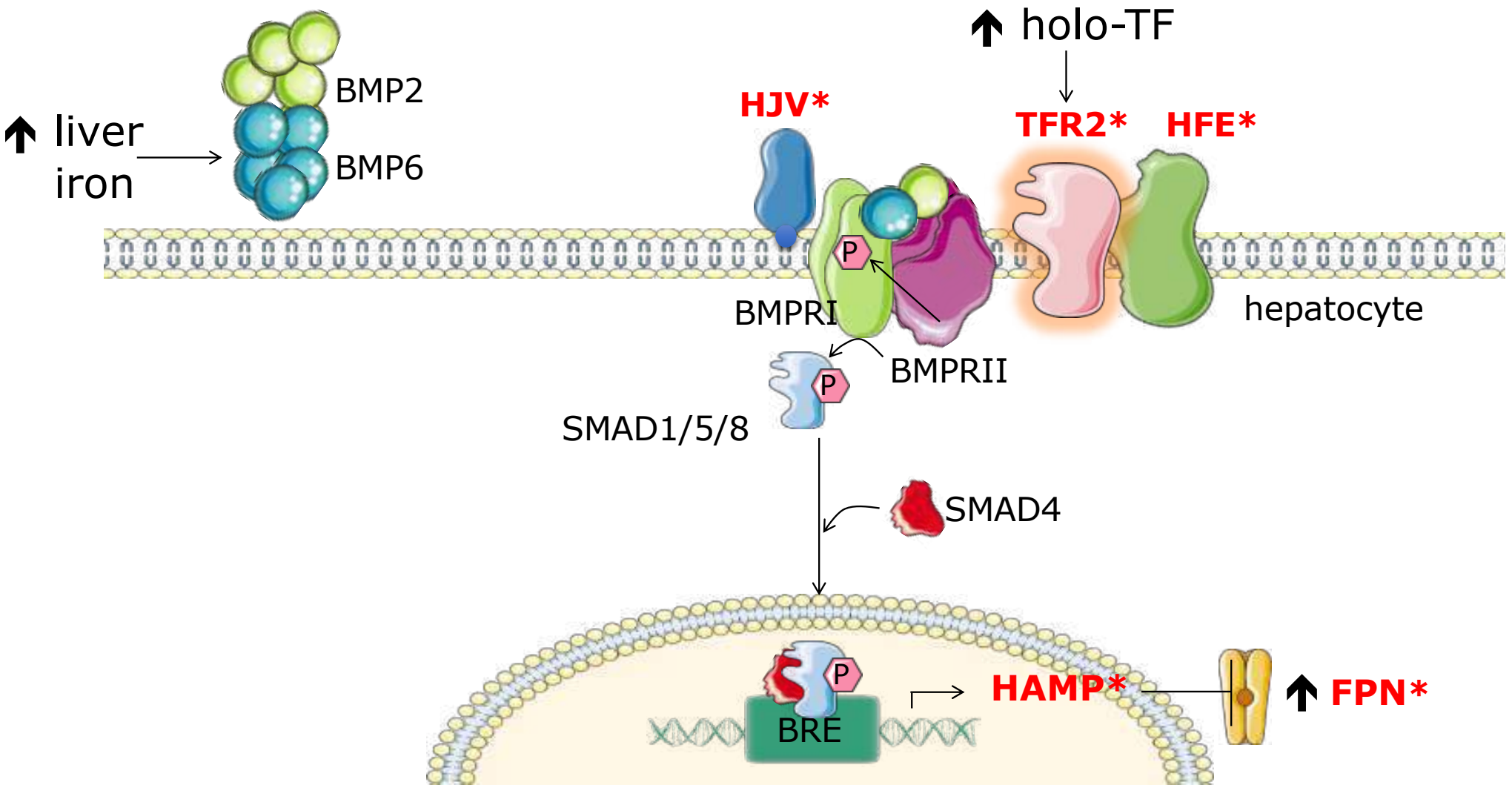
Mutations in *HFE2* cause iron overload in chromosome 1q–linked juvenile hemochromatosis

George Papanikolaou[1], Mark E Samuels[2], Erwin H Ludwig[2], Marcia L E MacDonald[2], Patrick L Franchini[2], Marie-Pierre Dubé[3], Lisa Andres[2], Julie MacFarlane[2], Nikos Sakellaropoulos[1], Marianna Politou[1], Elizabeta Nemeth[4], Jay Thompson[2], Jenni K Risler[2], Catherine Zaborowska[2], Ryan Babakaiff[2], Christopher C Radomski[2], Terry D Pape[2], Owen Davidas[2], John Christakis[5], Pierre Brissot[6], Gillian Lockitch[7], Tomas Ganz[4], Michael R Hayden[2,8] & Y Paul Goldberg[2,8]

Roetto, Am J Hum Genet 1999

Papanikolaou, Nat Genet 2004

BMP-SMAD signaling and Hemochromatosis proteins



FPN-disease and *FPN*-Hemochromatosis

Type-4A: Ferroportin disease

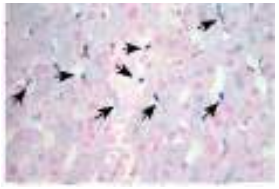
Loss of function mutations

Transmembrane domain mutations

↓

Reduced iron export or
FPN surface localization
N Tsat - High Ft

Macrophage iron overload



Type-4B: *FPN*-Hemochromatosis

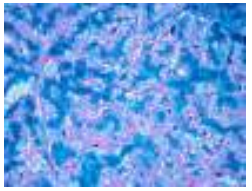
Gain of function mutations

C326Y, C326S

↓

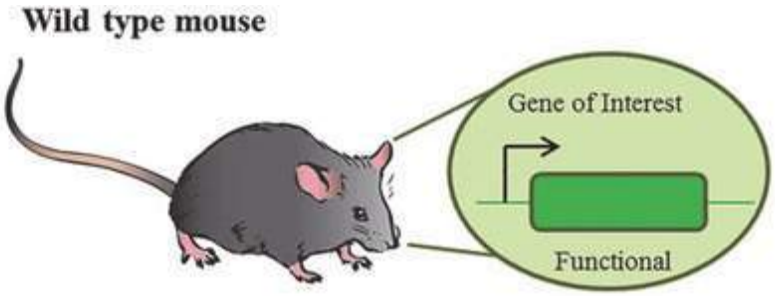
FPN hepcidin resistant
High Tsat – High Ft

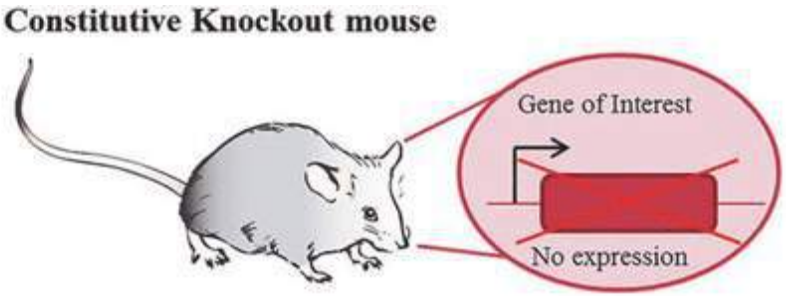
Hepatocyte iron overload



Pietrangelo A. Haematologica 2017

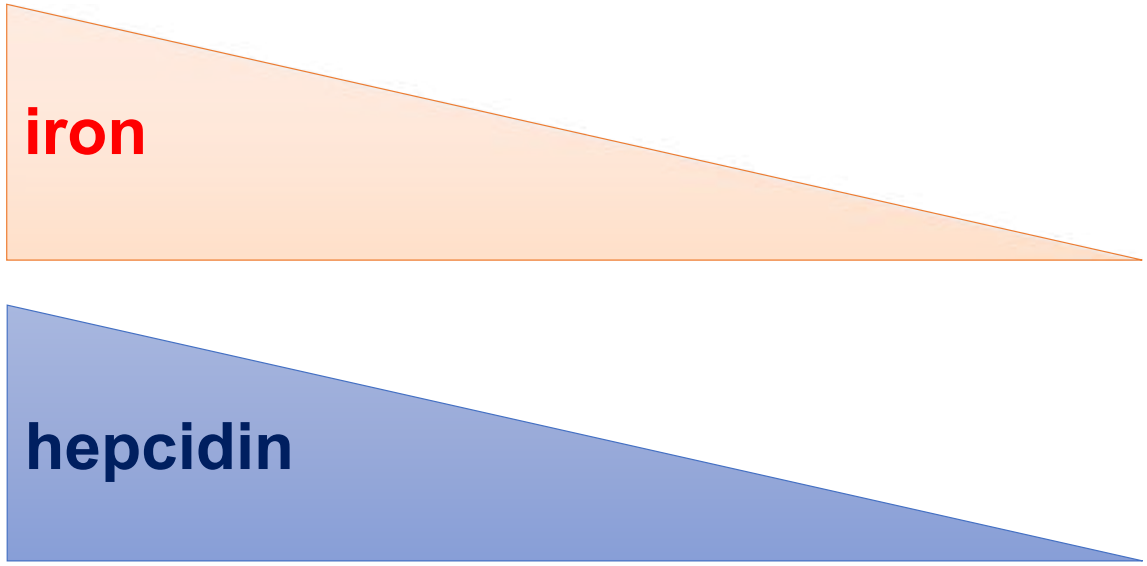
Animal models for preclinical studies





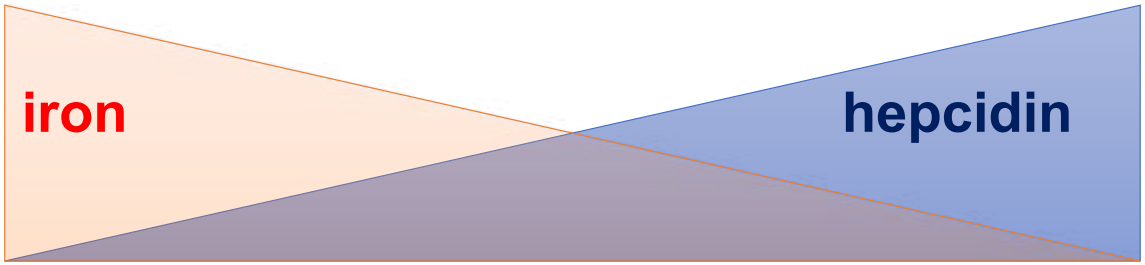
Hfe$^{-/-}$	Moderate, late iron overload
Hjv$^{-/-}$	Severe, early iron overload
Hamp$^{-/-}$	Severe, early iron overload
Tfr2$^{-/-}$	Iron overload
Bmp6$^{-/-}$	Iron overload
Bmpr Alk2$^{-/-}$	Moderate iron overload
Bmpr Alk3$^{-/-}$	Severe iron overload
Tmprss6$^{-/-}$	Iron deficiency

Physiologic homeostatic regulation of hepcidin



Deregulation of hepcidin in iron and other disorders

Impairment of the hepcidin-ferroportin axis



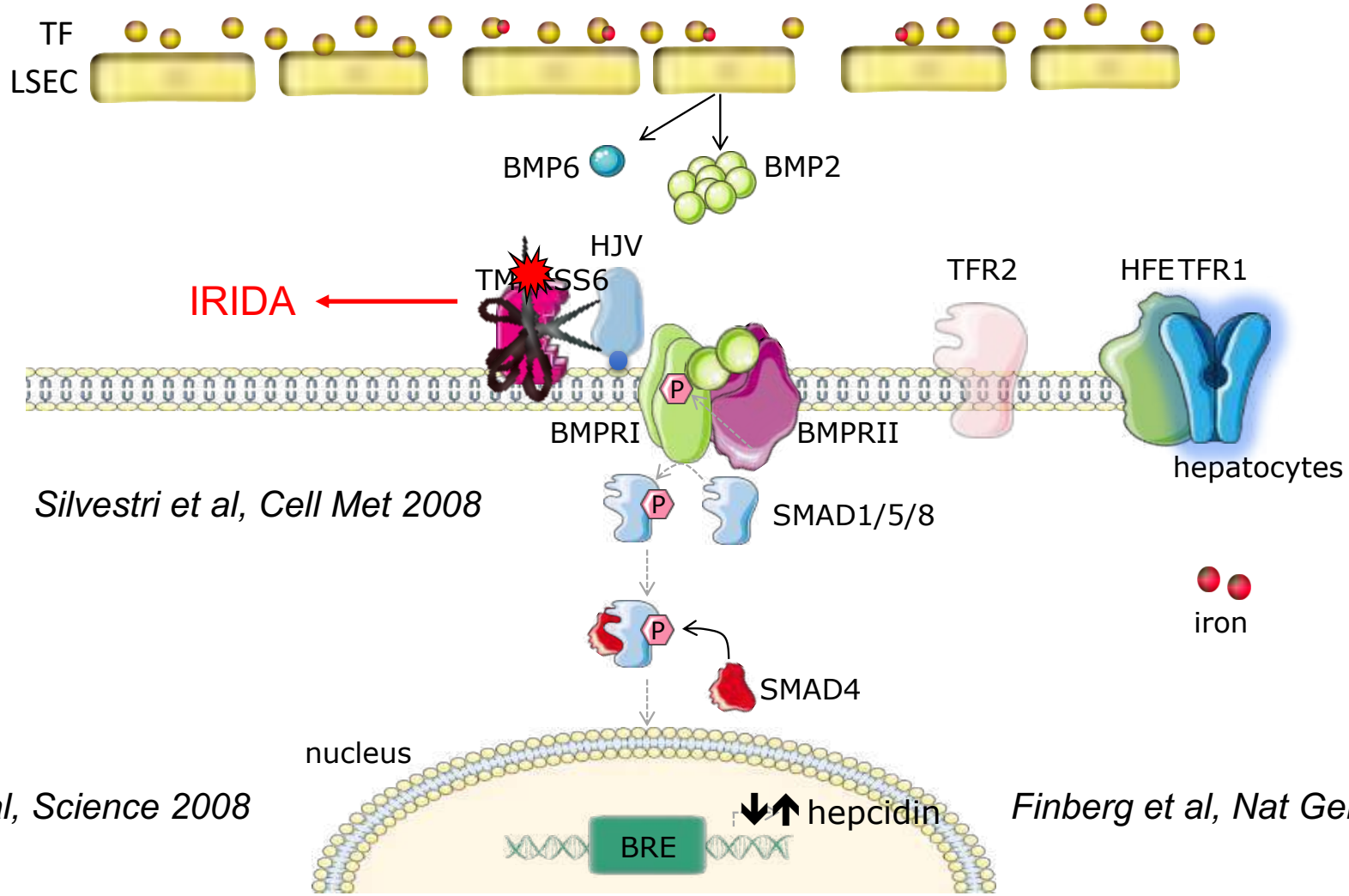
Hemochromatosis

IRIDA

Iron loading anemias

Anemia of inflammation

TMPRSS6 is essential in iron deficiency



Iron refractory iron deficiency anemia
(IRIDA - OMIM #206200)

Rare recessive disorder due to *TMPRSS6* mutations

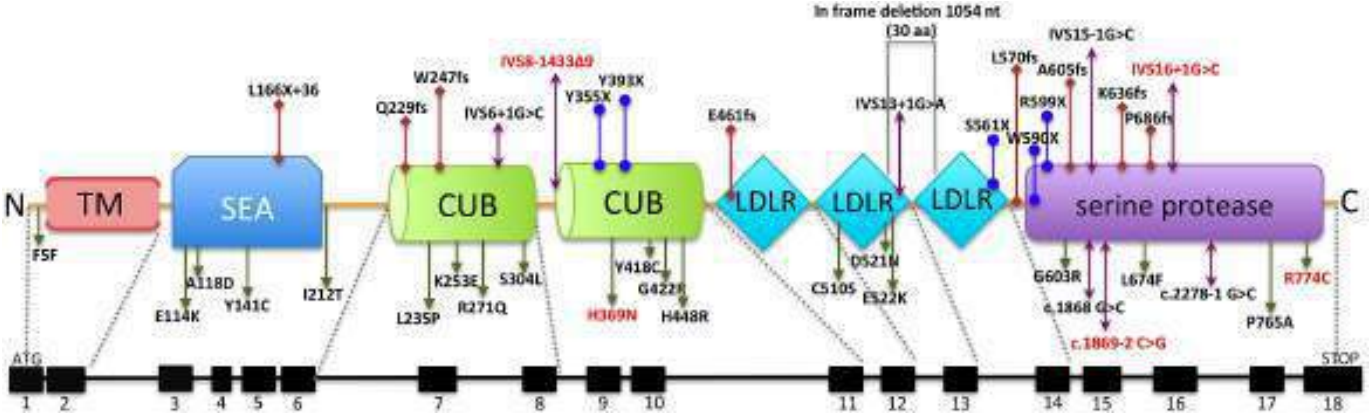
Iron deficiency anemia – normal/high hepcidin

Moderate anemia (childhood)

Low MCV and Tsat. Normal/high serum ferritin

Refractory to oral and partially refractory to iv iron

(Finberg et al, Nat Genet 2008)



Lessons from IRIDA

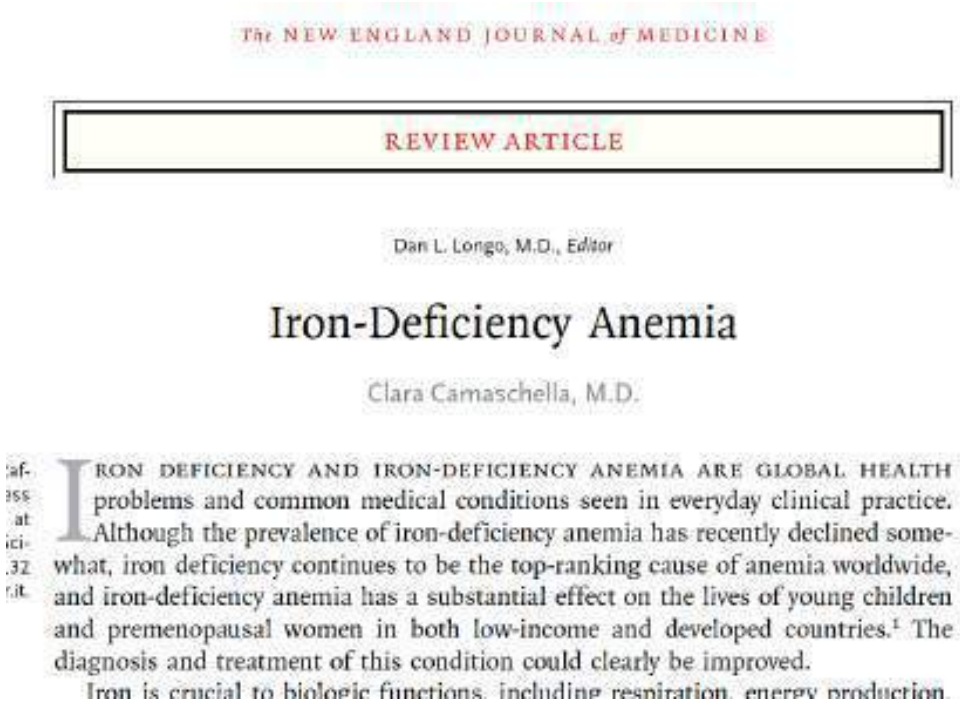
- ✓ High hepcidin levels → oral iron refractoriness
  e.g. in inflammation → i.v. iron needed

- ✓ Genetic susceptibility to iron deficiency
  Differences in different populations (GWAS)
  Data in blood donors according to *TMPRSS6* SNPs
  Sørensen E, Transfusion 2016; Mast, Transfusion 2020

- ✓ Oral iron effective on alternate days

  Moretti, Blood 2014; Stoffel, Lancet Hematol 2017;von Siebenthal, Am J Hematol 2023

From hemochromatosis to iron deficiency and …… anemia of inflammation



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., Editor

Iron-Deficiency Anemia

Clara Camaschella, M.D.

IRON DEFICIENCY AND IRON-DEFICIENCY ANEMIA ARE GLOBAL HEALTH problems and common medical conditions seen in everyday clinical practice. Although the prevalence of iron-deficiency anemia has recently declined somewhat, iron deficiency continues to be the top-ranking cause of anemia worldwide, and iron-deficiency anemia has a substantial effect on the lives of young children and premenopausal women in both low-income and developed countries.[1] The diagnosis and treatment of this condition could clearly be improved.

Iron is crucial to biologic functions, including respiration, energy production

blood Review Series

IRON METABOLISM AND ITS DISORDERS

Iron deficiency

Clara Camaschella

Division of Genetics and Cell Biology, San Raffaele Scientific Institute, Milan, Italy

Iron deficiency anemia affects >1.2 billion individuals worldwide, and iron deficiency in the absence of anemia is even more frequent. Total-body (absolute) iron deficiency is caused by physiologically increased iron requirements in children, adolescents, young and pregnant women, by reduced iron intake, or by pathological defective absorption or chronic blood loss. Adaptation to iron deficiency at the tissue level is controlled by iron regulatory proteins to increase iron uptake and retention; at the systemic level, suppression of the iron hormone hepcidin increases iron release to plasma by absorptive enterocytes and recycling macrophages. The diagnosis of absolute iron deficiency is easy unless the condition is masked by inflammatory conditions. All cases of iron deficiency should be assessed for treatment and underlying cause. Special attention is needed in areas endemic for malaria and other infections to avoid worsening of infection by iron treatment. Ongoing efforts aim at optimizing iron salts–based therapy by protocols of administration based on the physiology of hepcidin control and reducing the common adverse effects of oral iron. IV iron, especially last-generation compounds administered at high doses in single infusions, is becoming an effective alternative in an increasing number of conditions because of a more rapid and persistent hematological response and acceptable safety profile. Risks/benefits of the different treatments should be weighed in a personalized therapeutic approach to iron deficiency. (Blood. 2019;133(1):30-39)

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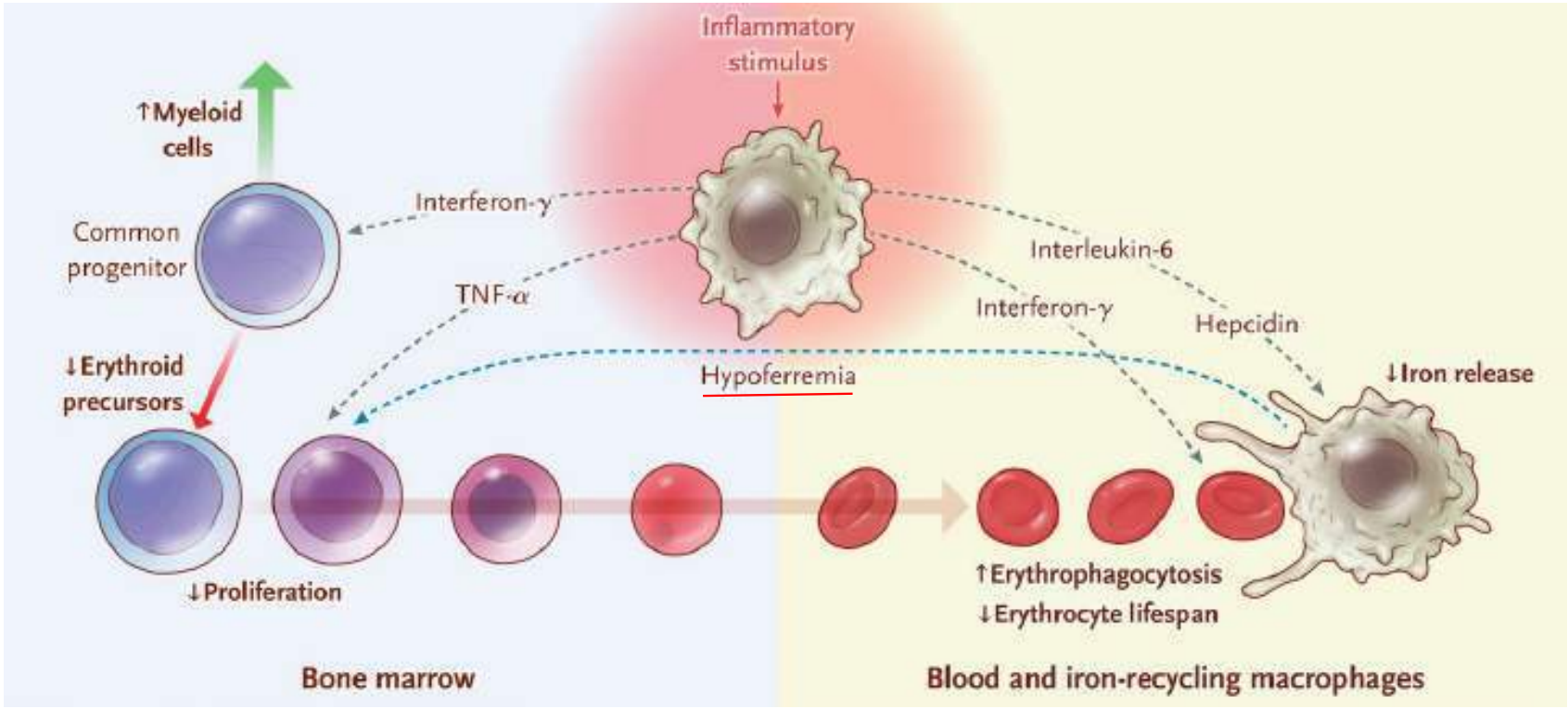
The changing landscape of iron deficiency

Clara Camaschella[a,*], Domenico Girelli[b]

Systemic inflammation and anemia

Cytokine overproduction

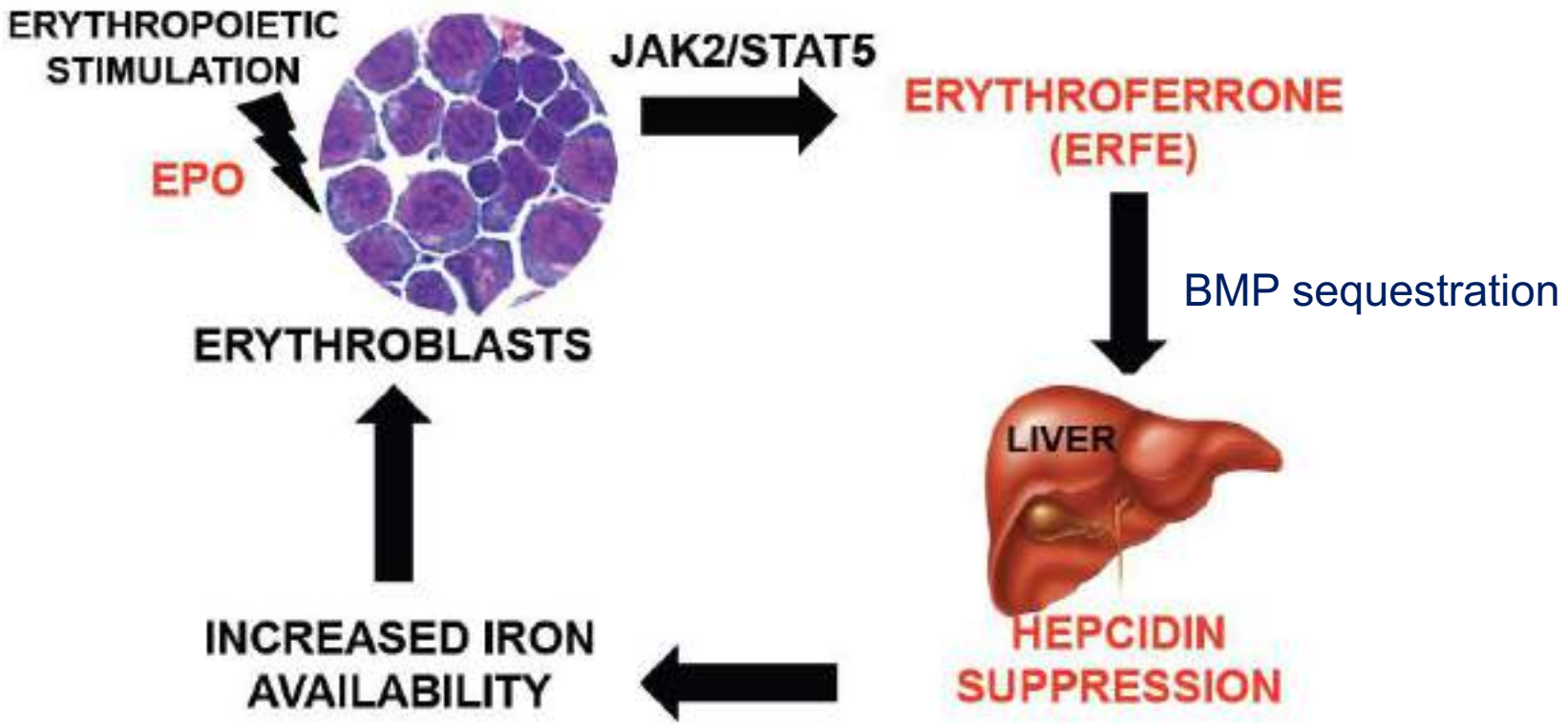


Decreased EPO and erythropoiesis

High hepcidin
Decreased iron recycling

Adapted from Ganz T, NEJM 2019

Crosstalk of iron and erythropoiesis: erythroferrone



(Kautz et al, Nat Genet 2014)

Iron loading anemia

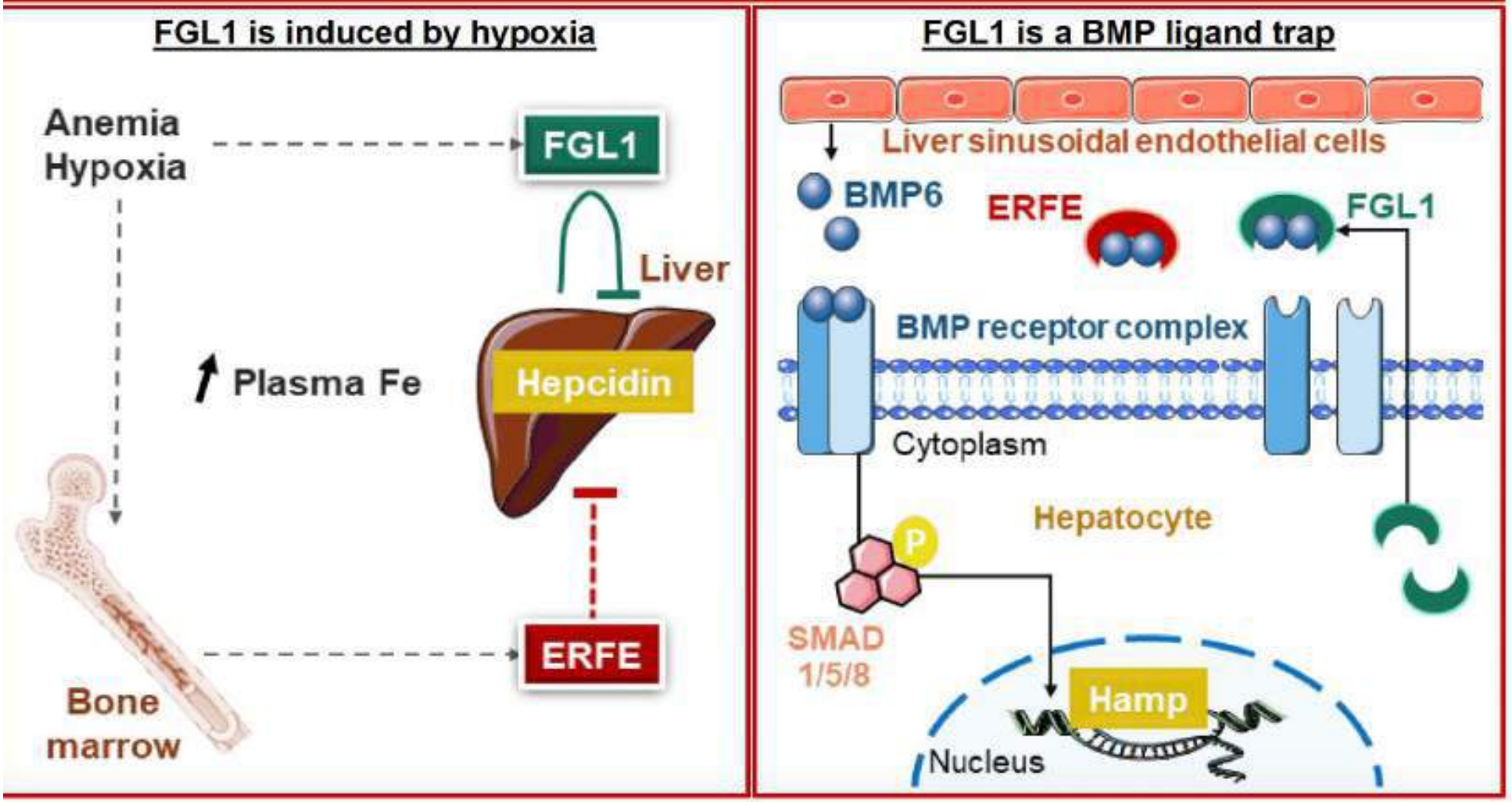
Anemia characterized by ineffective erythropoiesis and transfusion-independent iron overload

NTD β-thalassemia (thalassemia intermedia)

Congenital dyserythropoietic anemia
Sideroblastic anemia
Selected enzyme and membrane defects:
(PK deficiency, stomatocytosis)

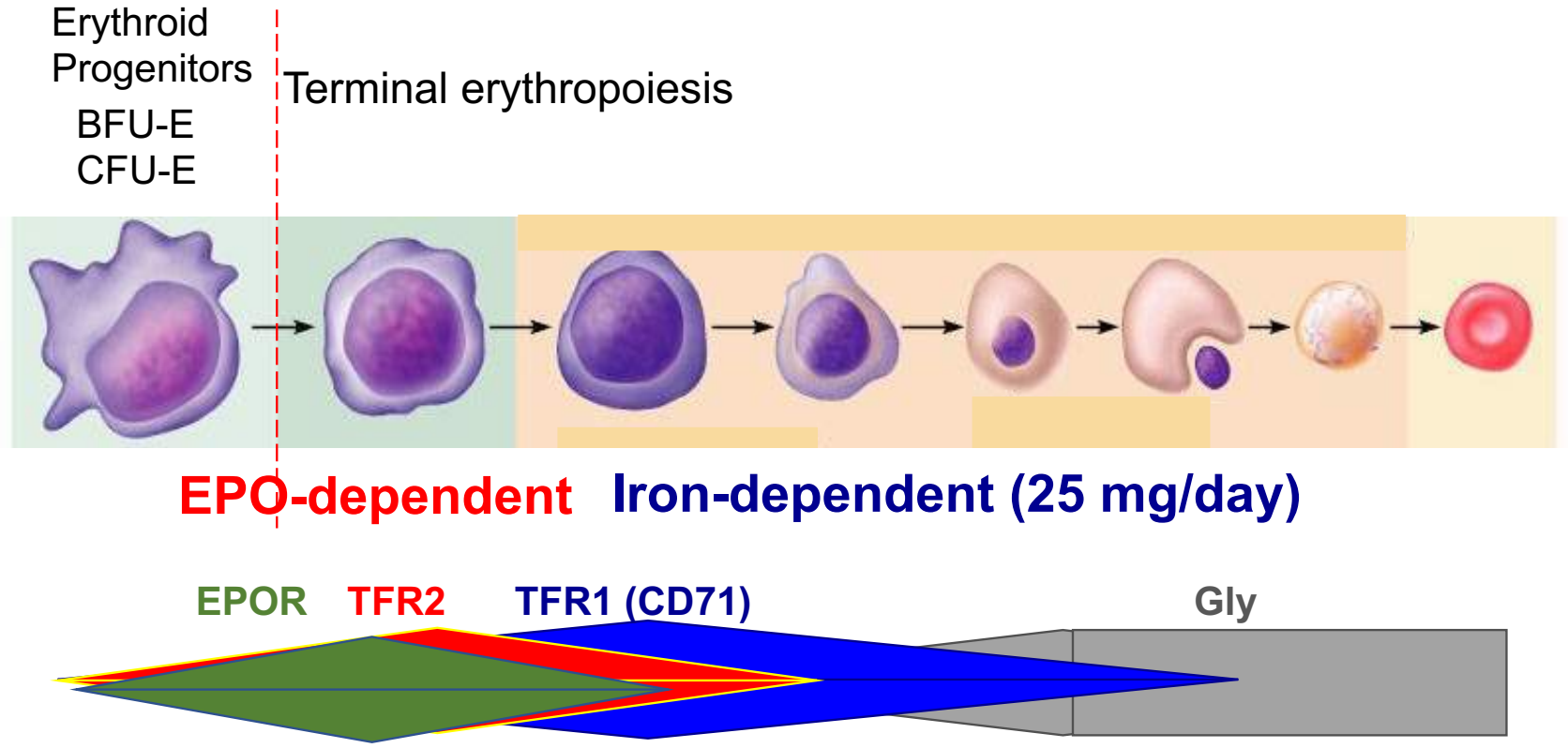
Low-risk MDS (*SF3B1* mutations)

Role of the Hepatokine FGL1 in the Regulation of Hepcidin and Iron Metabolism During the Recovery From Anemia in Mice



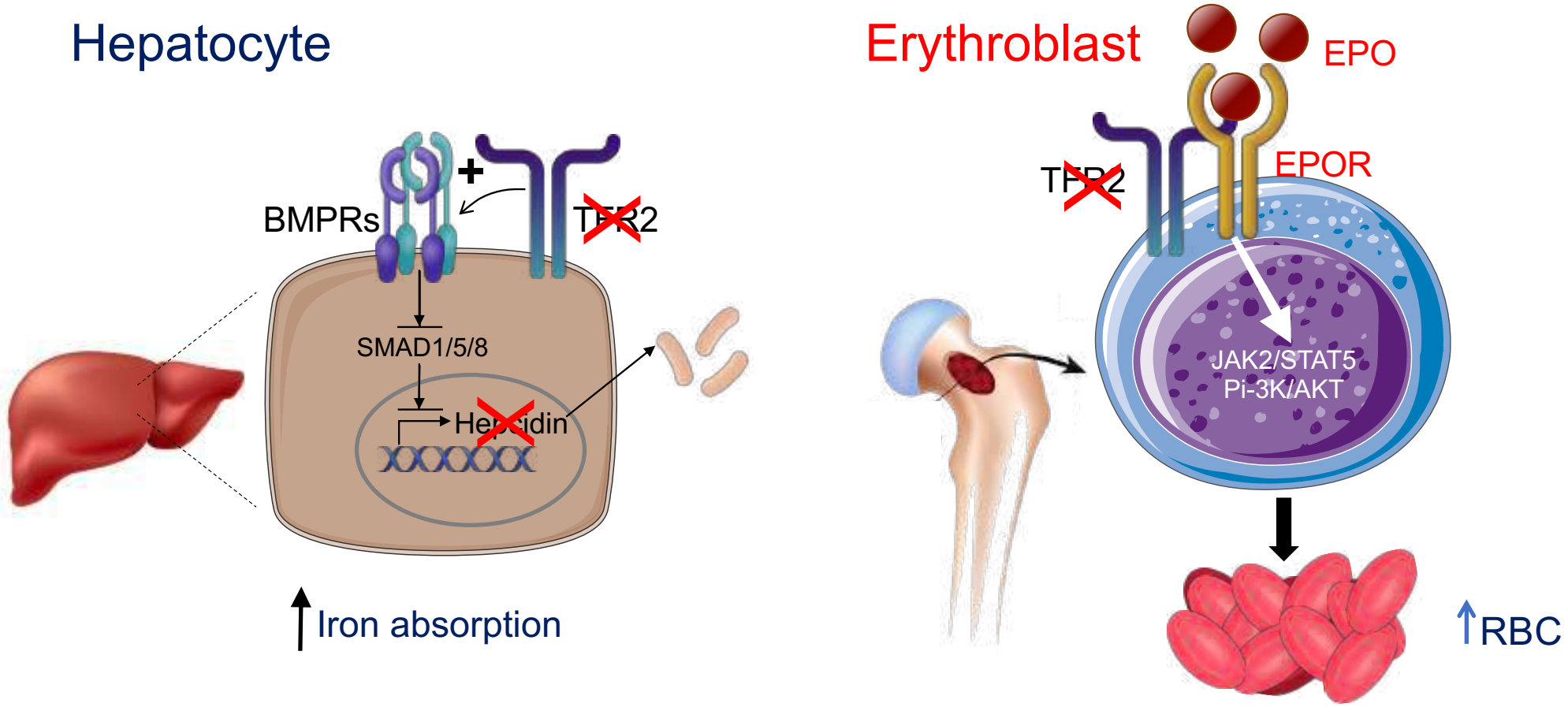
Sardo et al. Blood 2023

Crosstalk of iron and erythropoiesis:TFR2



Forejtnikova et al, Blood 2010

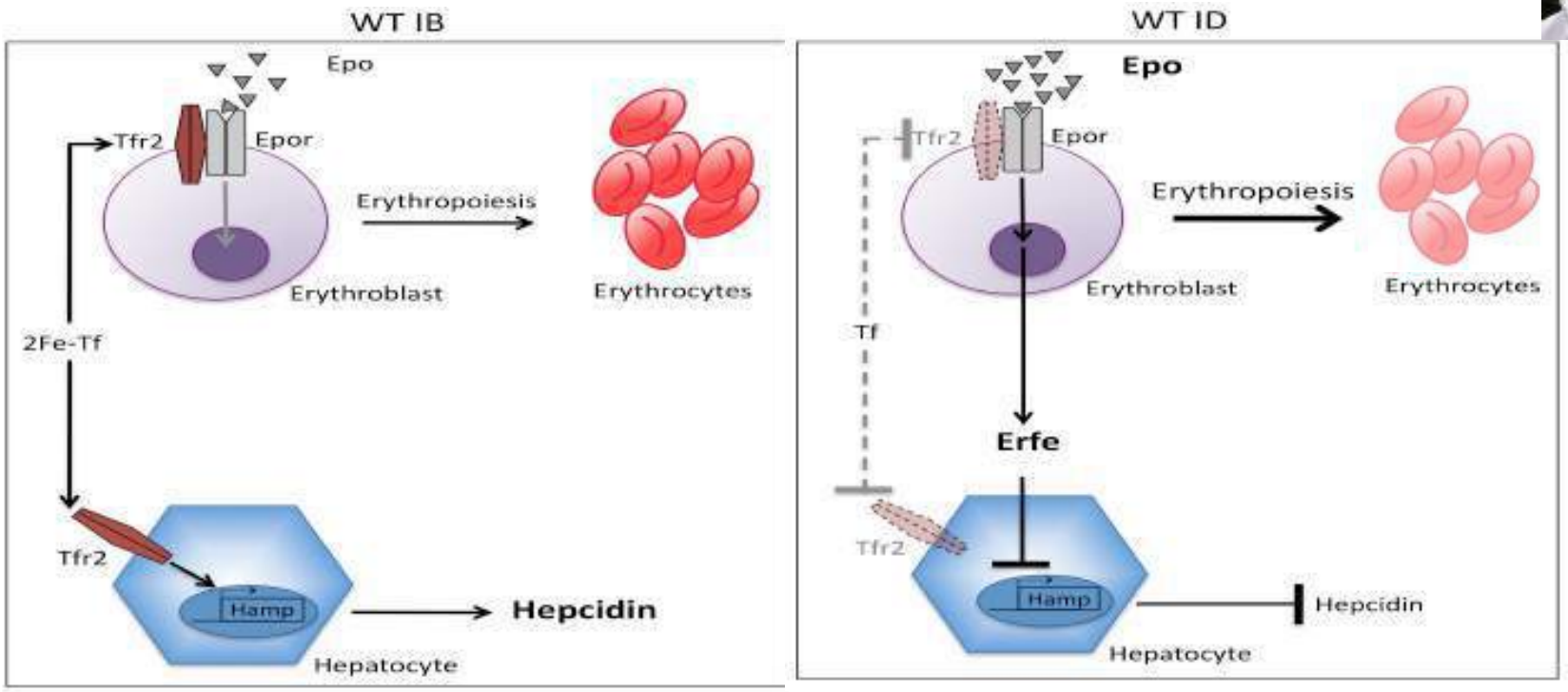
TFR2 a link between hepcidin and erythropoiesis



Camaschella, Nat Genet 2000

Nai, Blood 2015

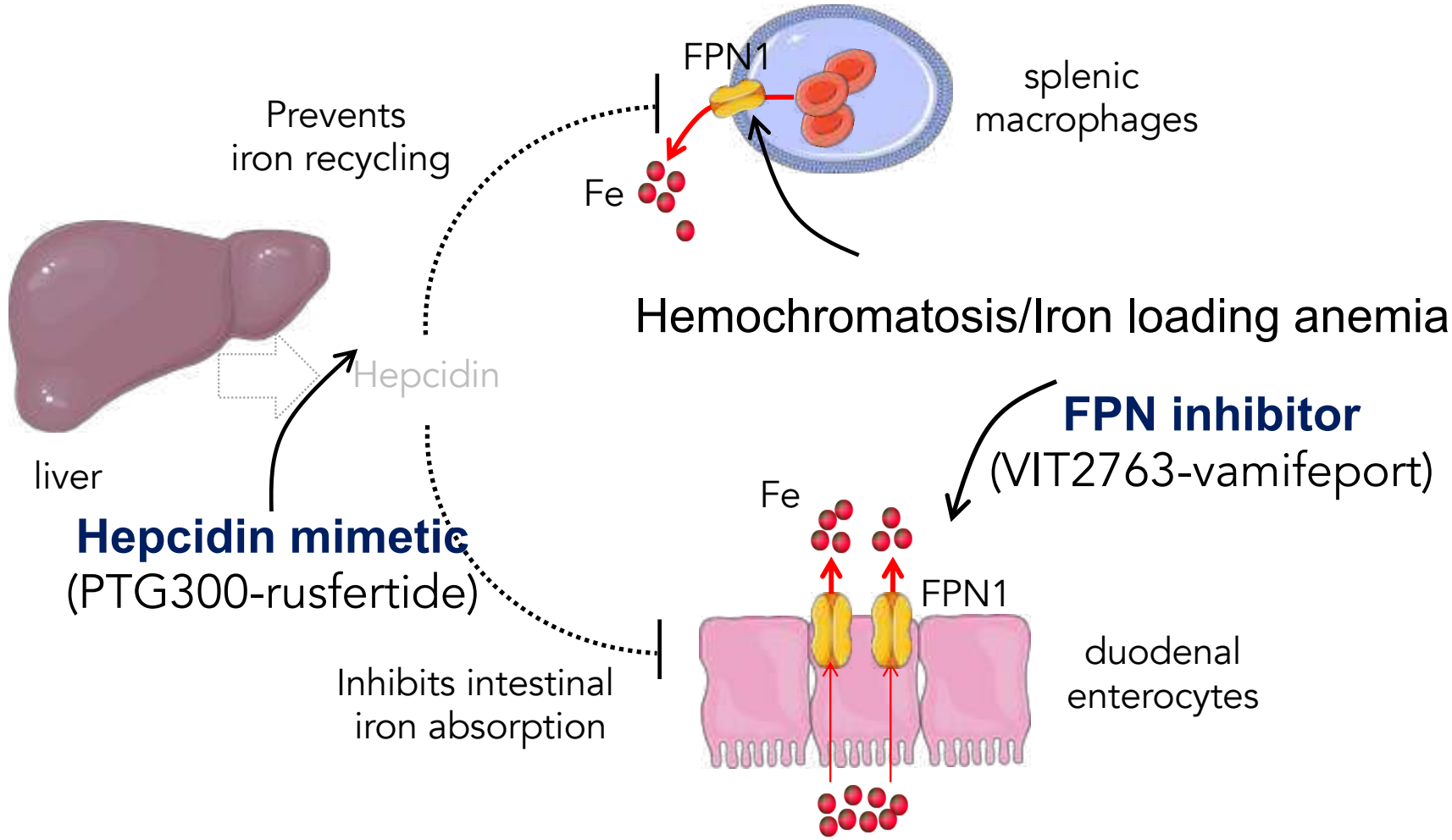
TFR2 modulates the erythroblast Epo sensitivity…



... and hepcidin expression according to available iron

Nai, Blood 2015; Artuso, Blood 2018; Casu, Blood 2020
Di Modica, Am J Hematol 2023; Olivari, Kidney Int 2023…

New therapeutic strategies for iron disorders?



Other compounds and targetable disorders

Hepcidin agonists: Inhibitor inhibitors: anti-TMPRSS6 (ASO, siRNA, MoAb)

Targeting the TF-TFreceptor (TFR1-TFR2) and combo therapy

Hemochromatosis: maintenance phase (?)

Thalassemia: complex patophysiology (Combo therapy?)

Ph negative MPN. PV: Rusfertide phase 3 trial *(Kremyanskaia. NEJM 2024)*

Hepcidin antagonists: anti-Hamp, anti-BMP pathway, anti-HJV Mo Ab…

Anemia of chronic disease, anemia of inflammation (CKD)

Ph negative MPN. Myelofibrosis: Momelotinib (anti-JAK1/2 & anti-ALK2)

Iron and other hematopoietic cells

Lymphocytes

A recurrent Y20H mutation in *TFRC* → **combined immunodeficiency** with marginal anemia. Iron is **essential in B and T lymphocytes** *(Jabara, Nat Genet 2016; Aljohani, J Clin Immunol 2020)*

Iron deficiency, adaptive immunity and Vaccine Efficacy *(Stoffel & Drakesmith, Adv Nutr. 2024)*

Granulocytes

Iron homeostasis in mice is critical for **neutrophil development and differentiation.** Hypoferremia reduces granulocytes number, inhibits granulopoiesis and **alters neutrophil functions** (*Bonadonna Sci Adv 2022; 8(40) eabq4469 and eabq5384)*.

Iron and other hematopoietic cells. Platelets

Iron is a modifier of the phenotypes of *JAK2*-mutant myeloproliferative neoplasms

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JAK2 mutant mice……..

V617P (Ki)

PV, ET, (Myelofibrosis)

Exon 12

Pure PV

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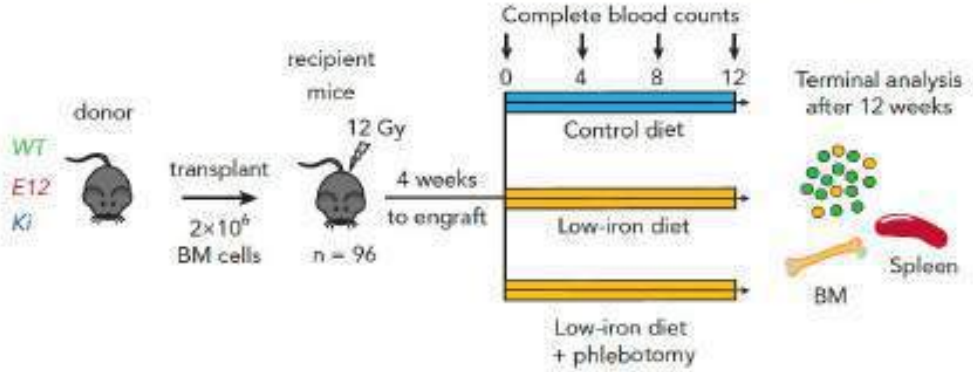
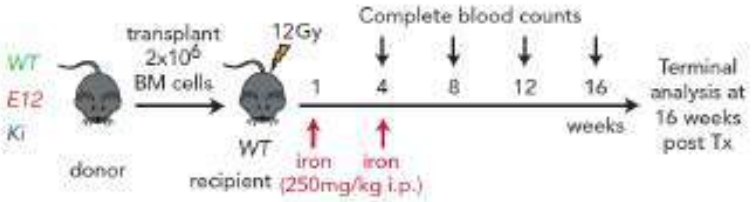
Iron deficiency



Iron overload



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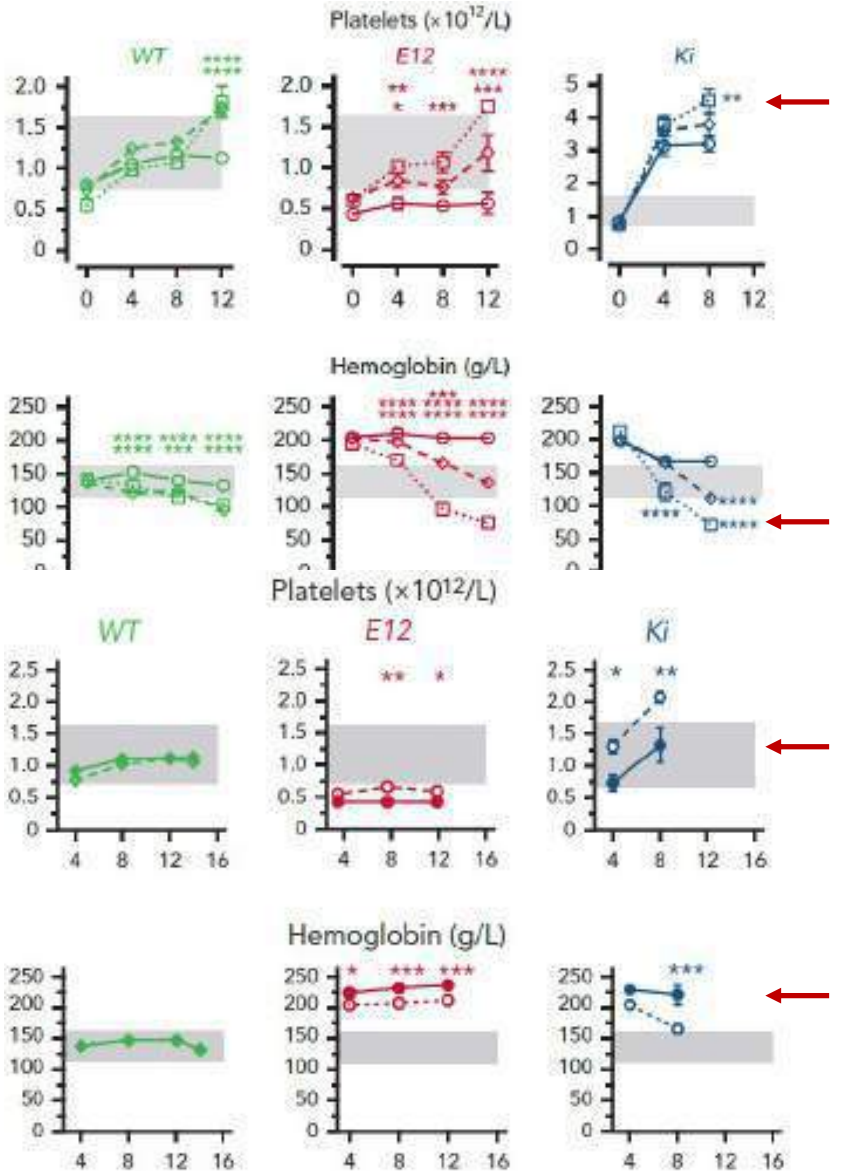
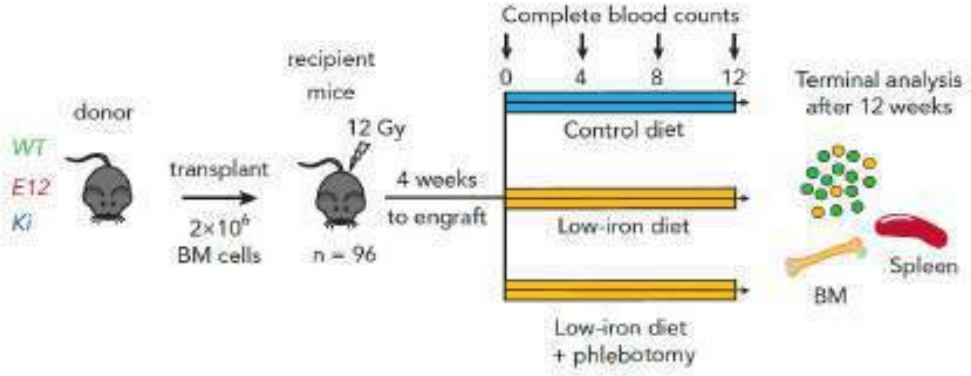


Iron deficiency

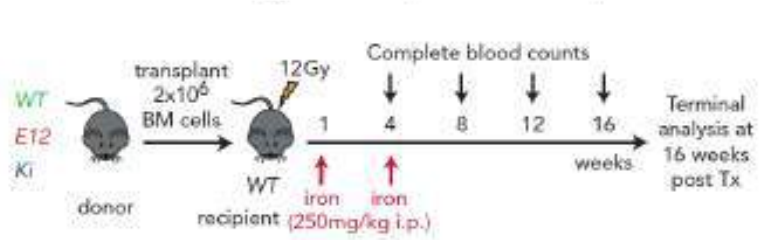


Flow cytometry of bone marrow and spleen

↓ terminal erythropoiesis
↑ megakaryocyte/erythroid progenitors (preMeg-E)

in all models both JAK2 mutant and WT

Iron overload



↑ terminal erythropoiesis
↓ megakaryopoiesis (↓ preMeg-E)

in JAK2 mutant models, not in WT

The iron-sensitive cell is the common erythroid-megakaryocyte progenitor

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Iron beyond Hematology

- Iron and chronic liver disease
- Iron and neurodegenerative disorders
- Iron and cancer
- Cardiac iron and hepcidin
- Iron and immunity

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