Iron homeostasis – a balancing act

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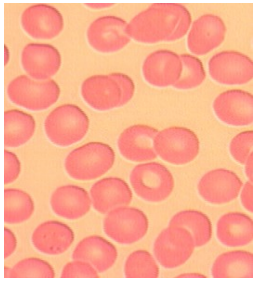
MMPU
Molecular Medicine Partnership Unit

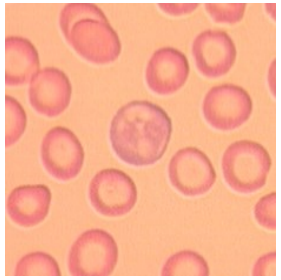
Disturbances in iron homeostasis are common causes of human disease

Iron deficiency

- **Iron deficiency anemia**
  IRIDA (genetic), nutritional deficiency
- **Anemia of chronic disease**
  (chronic infection, inflammation, cancer)



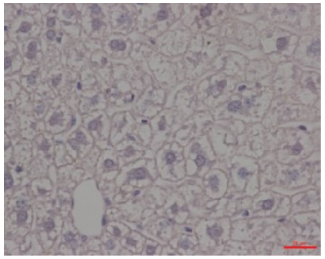
normal

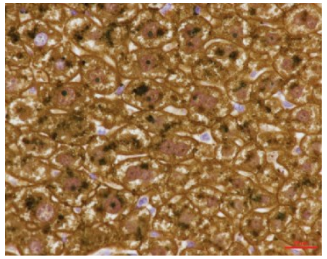


iron-deficient

Iron overload

- **Hereditary Hemochromatosis**
- **ineffective erythropoiesis**
  (e.g. Thalassemias, iron-loading anemia)
- **common acquired diseases**
  (e.g. chronic liver disease, diabetes, Alzheimer, Parkinson)





Hematopoieses

Cell growth

\- ← Fe → +

Damage of cells and tissues

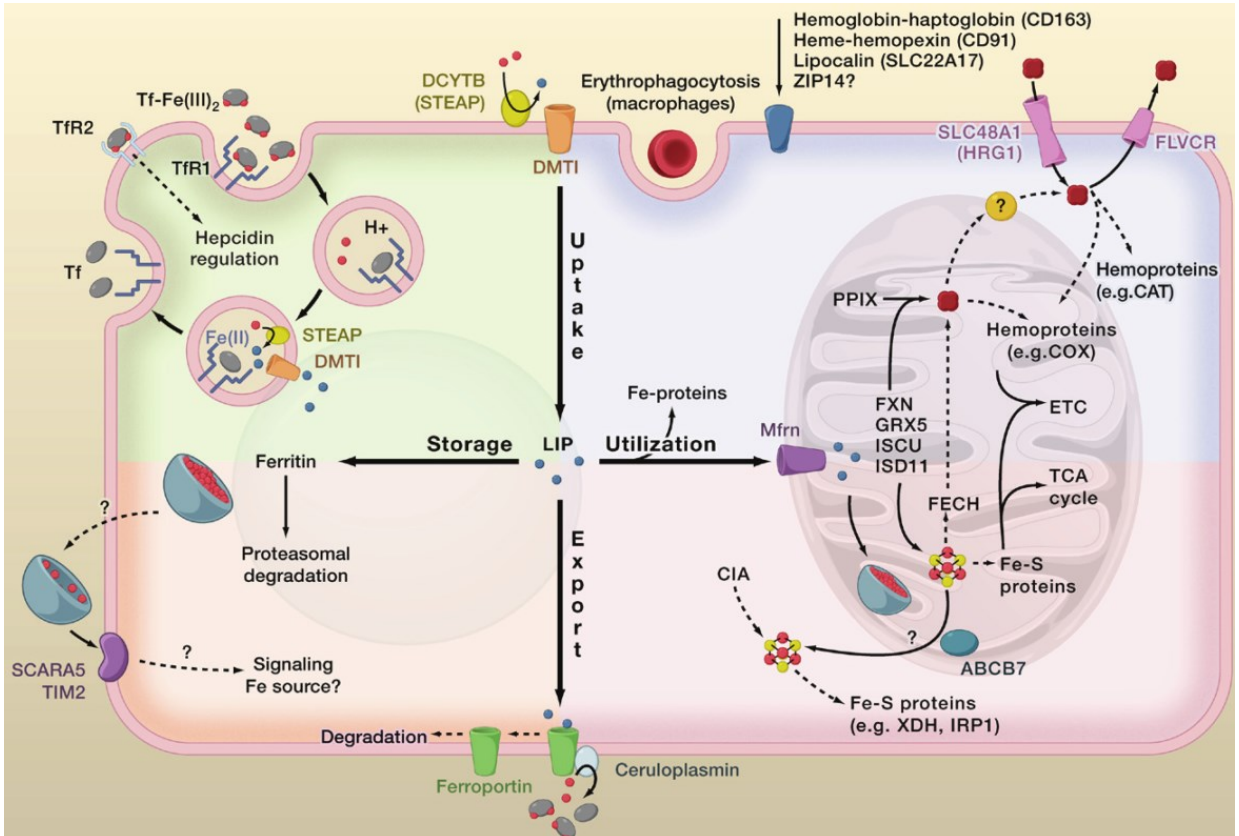
"oxidative stress"
(Fenton-type redox chemistry)

- **Oxygen transport**
- **DNA synthesis**
- **Respiration**

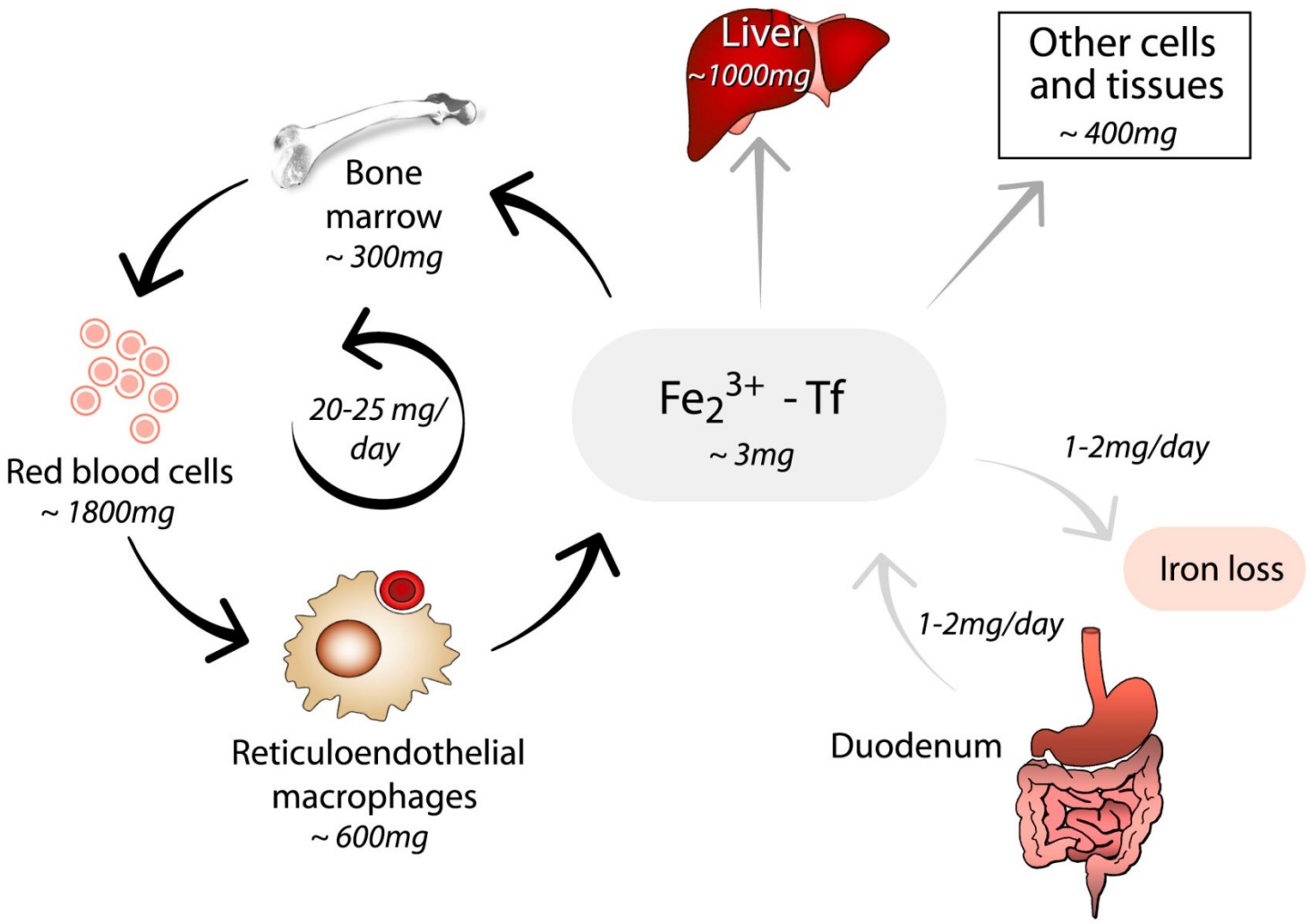
Regulation of iron homeostasis

Systemic: The organism maintains serum iron levels by regulating dietary iron absorption and iron release from storage tissues (e.g. macrophages)

Cellular: Each cell regulates its iron uptake and subcellular distribution in autonomous manner

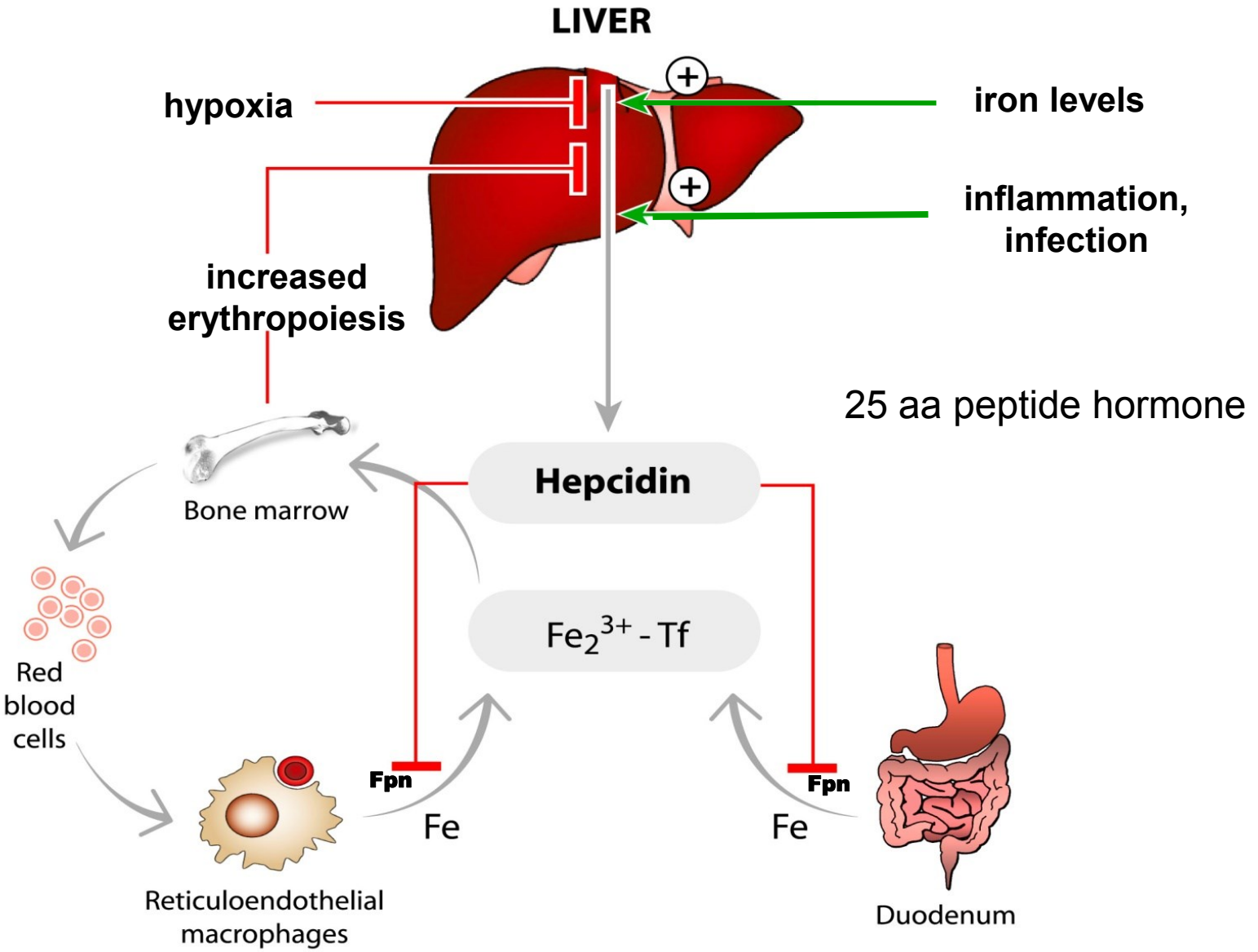


Body iron homeostasis a(n almost) perfect recycling system



Hentze, Muckenthaler and Andrews, Cell (2004)

The Hepcidin/Ferroportin regulatory system controls systemic iron homeostasis

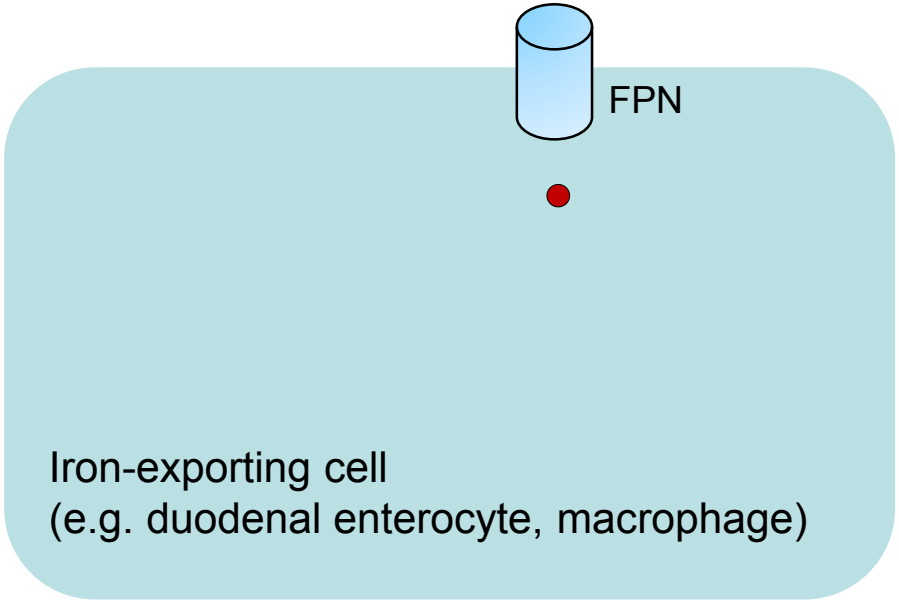


modified from Hentze et .al. Cell. 2004;117:285-97.

Hepcidin-mediated control of iron export

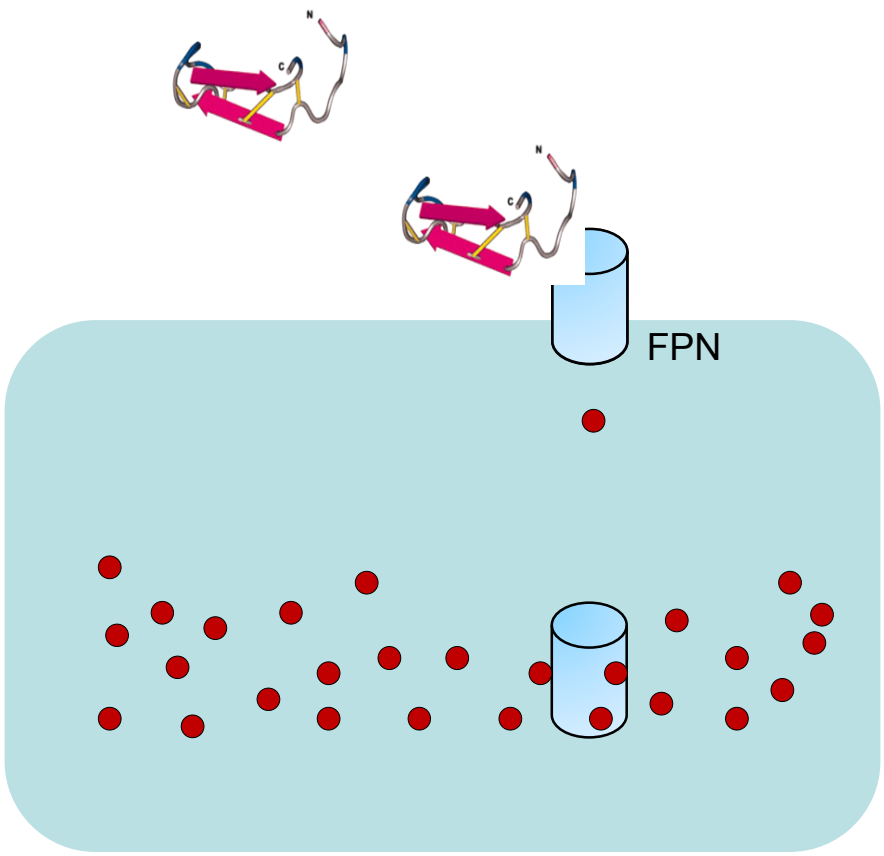
HEPCIDIN ↓

Iron export into the plasma

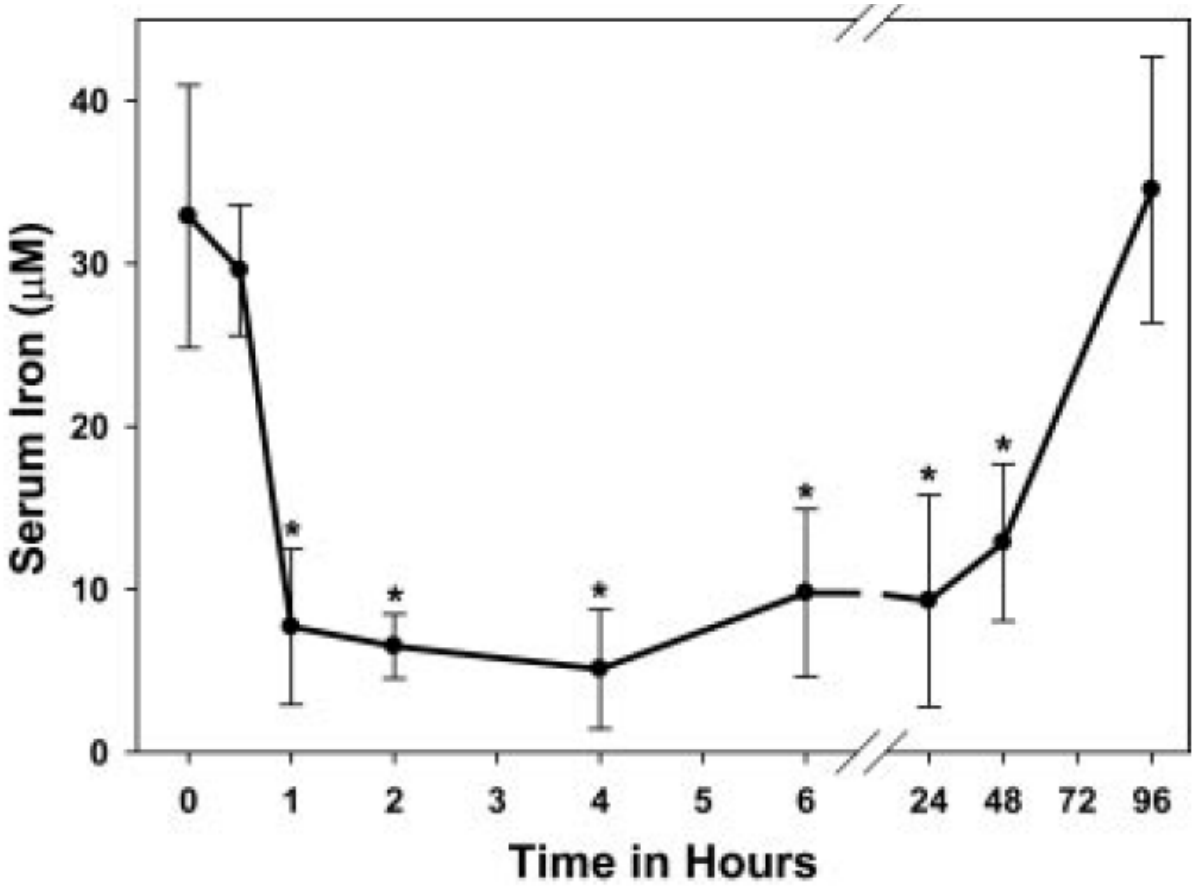


HEPCIDIN ↑

Cellular iron retention due to FPN internalization and degradation



Hepcidin injection rapidly reduces serum iron levels



50μg hepcidin
i.p. injection

Hepcidin reduces serum iron by 80% within 60 minutes

Rivera et al
Blood 2005

How is hepcidin synthesis regulated?

- **iron levels**
  e.g. Hereditary Hemochromatosis
- **hypoxia and increased erythropoiesis**
  e.g. secondary Hemochromatosis (iron-loading anemias)
- **inflammation and infection**
  e.g. anemia of inflammation

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Hereditary Hemochromatosis

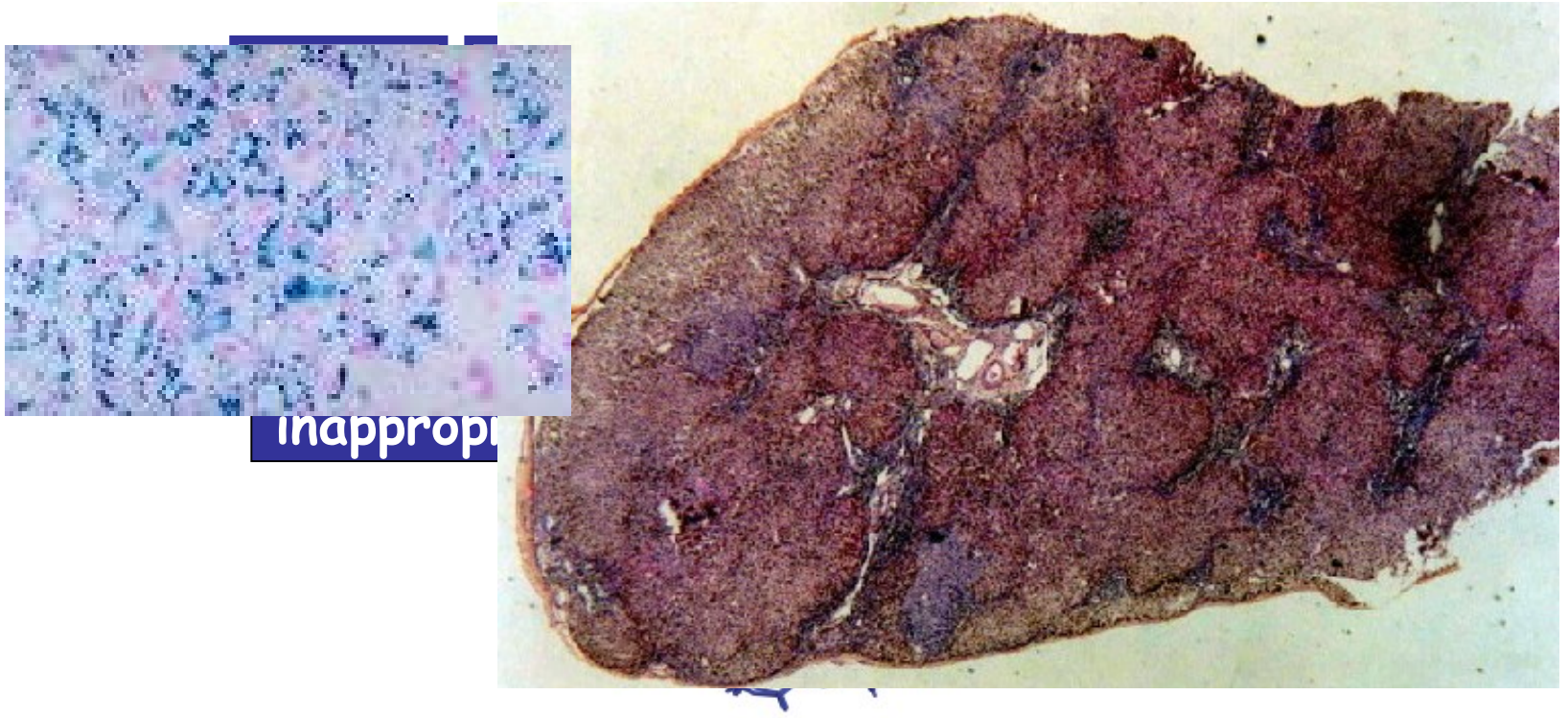
… he observed

- tiredness und petulance
- stomach pain
- pain in the joints
- susceptibility for infections
- impotence
- heart failure
- diabetes
- bronze colouring of the skin

‚von Recklinghausen'
Versammlung deutscher Naturforscher und Ärzte (1889)

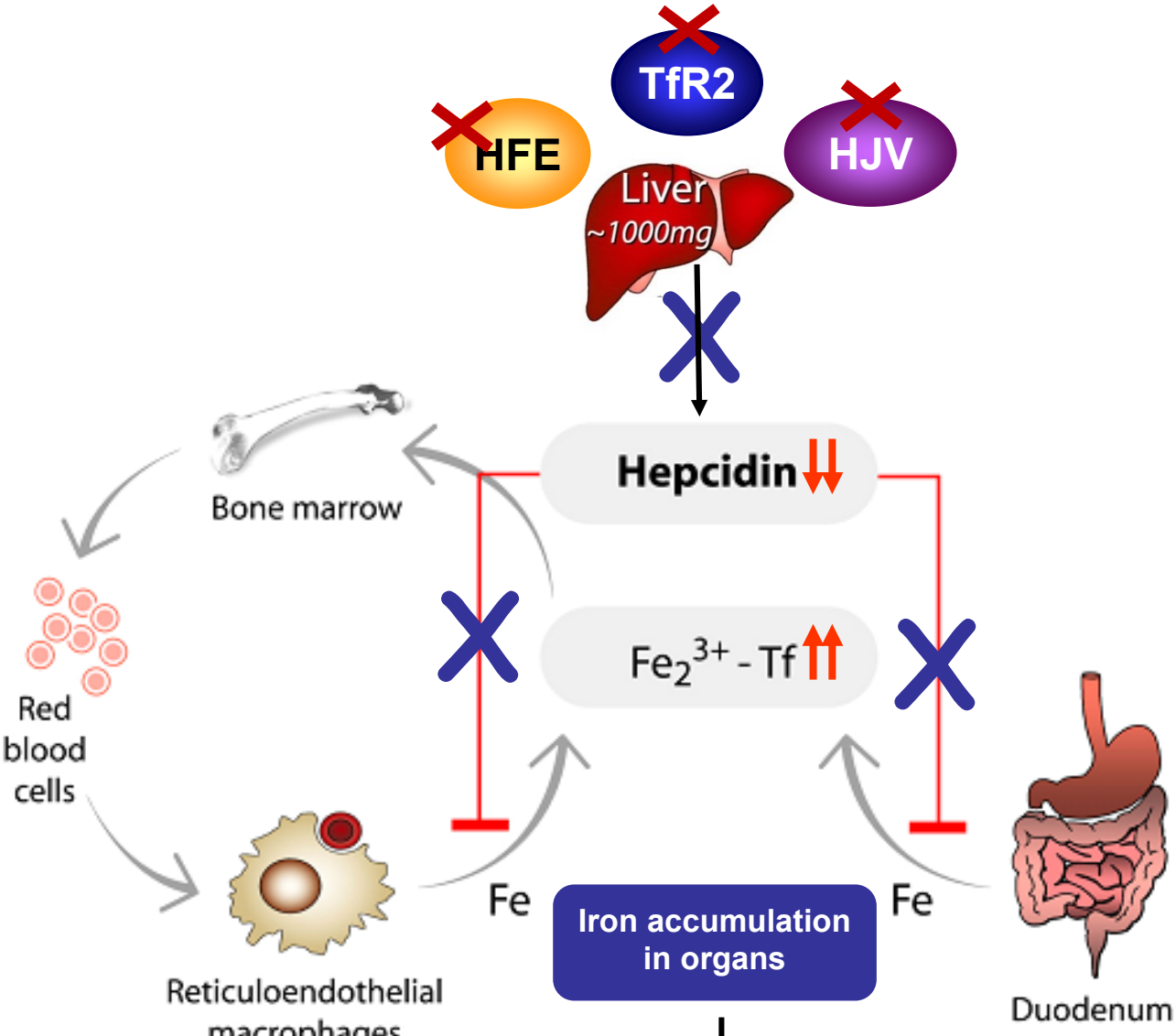
Hereditary Hemochromatosis

- frequent iron overload disorder (carrier frequency 1:8)
- increased iron absorption
- and iron deposition in the liver, heart and endocrine organs
- complications: liver cirrhosis and cancer, heart failure, endocrinopathy



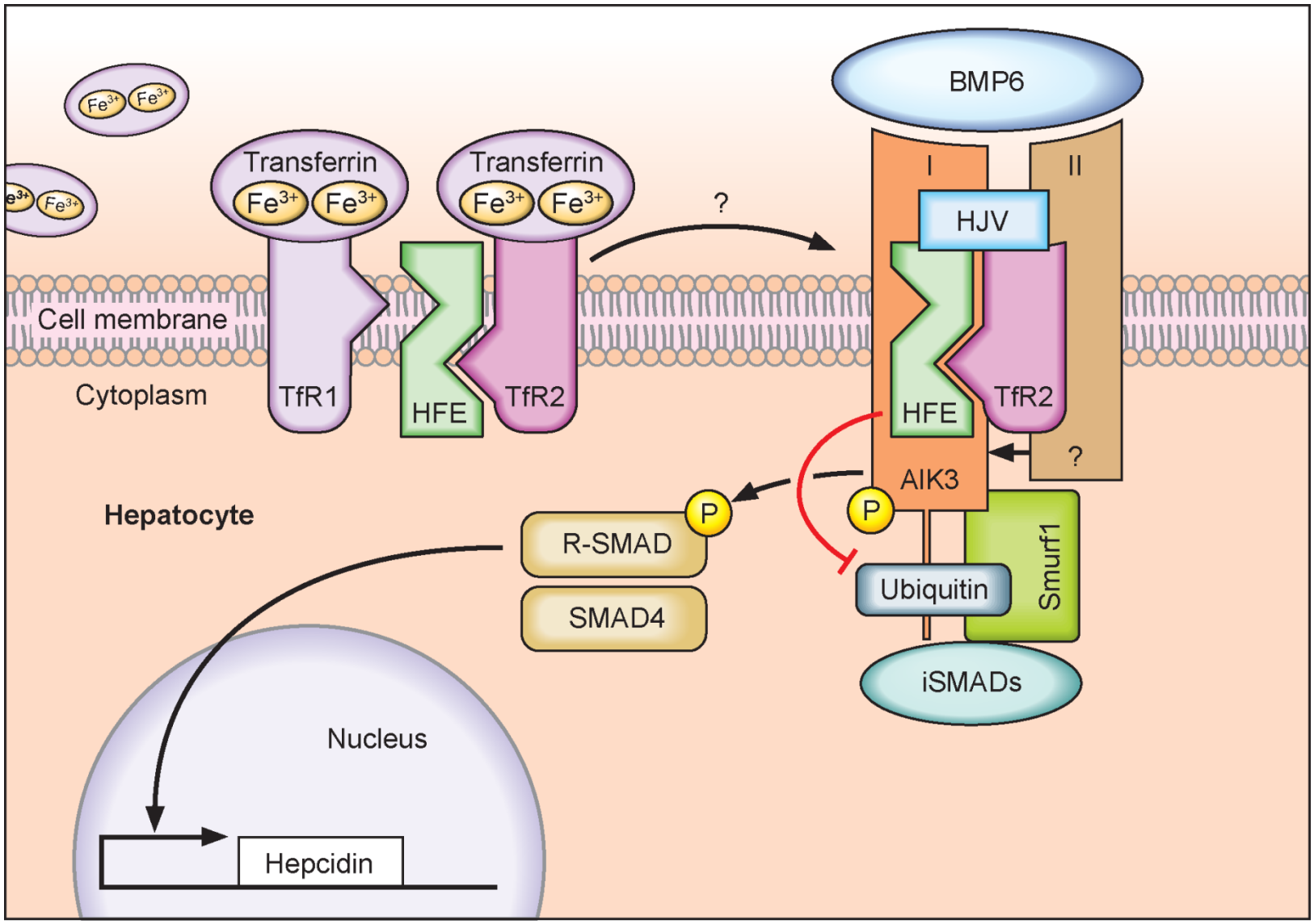
Jordan et al., 2009

Hereditary Hemochromatosis



Muckenthaler M, et al. Nat Genet. 2003;34:102-7.
Bridle KR, et al. Lancet. 2003;361:669-73.
Nemeth E, et al. Blood. 2005;105:1803-6.
Papanikolaou G, et al., Nat Genet. 2004;36:77-82.

HFE, TfR2, HJV sense systemic iron levels and control Hepcidin expression via the BMP/SMAD signalling pathway



Muckenthaler, Blood 2014

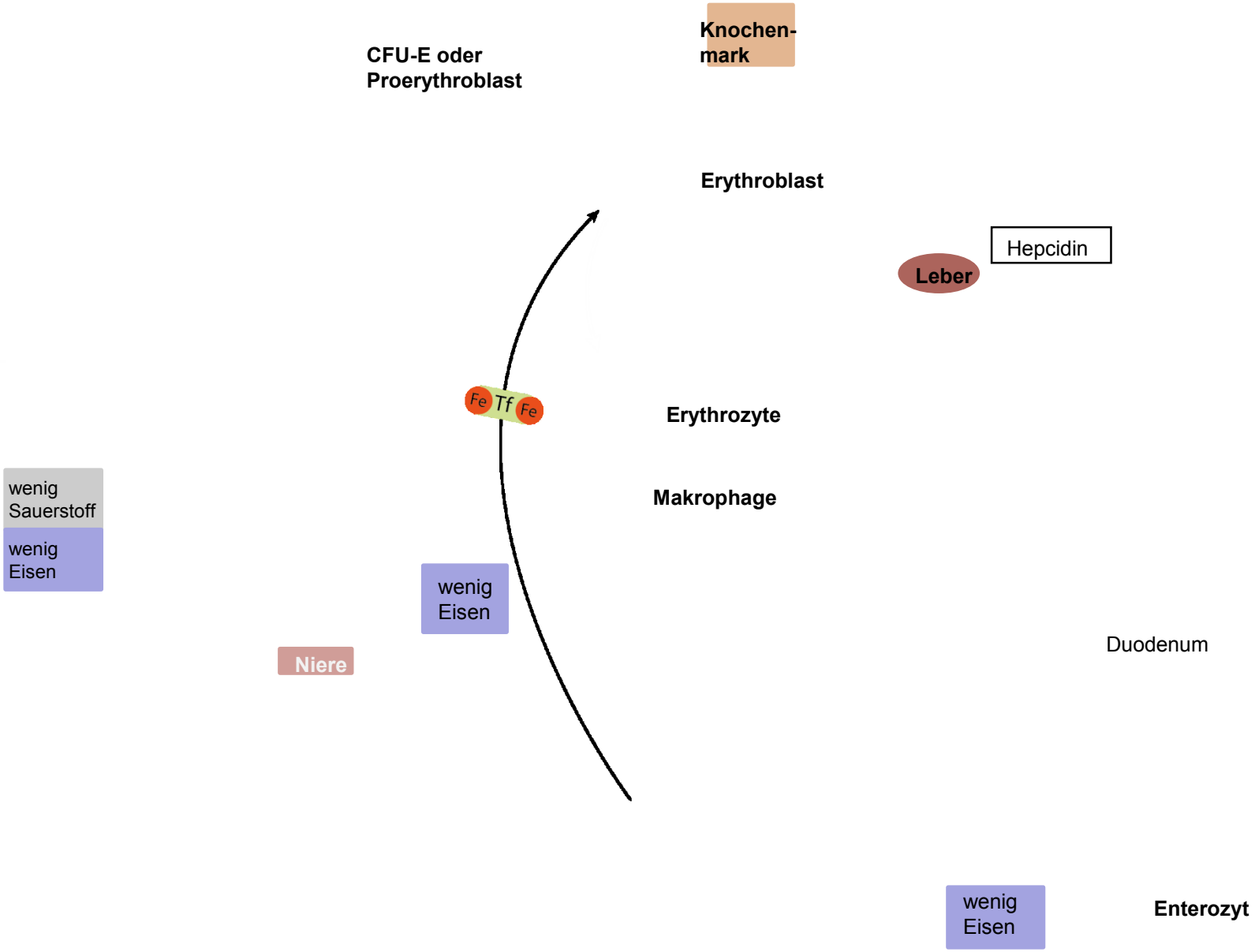
Mutations in HFE, HJV and TfR2 (proteins mutated in HH) disrupt the formation of a hepatic iron-sensing complex that regulates BMP/SMAD signalling and hepcidin levels to maintain iron homeostasis

Vujic-Spacic et al., Cell Metabolism 2008
Vujic-Spacic et al., BBA 2012
D'Allessio et al. J Hepatology 2012
Corradini et al. 2009
Kautz et al., Blood 2009

Hereditary Hemochromatosis is a wide-spread disorder in the caucasian population...

How is hepcidin synthesis regulated?

- iron levels
  e.g. Hereditary Hemochromatosis
- **hypoxia and increased erythropoiesis**
  e.g. disorders with ineffective erythropoiesis (iron-loading anemias)
- inflammation and infection
  e.g. anemia of inflammation



CFU-E = colony-forming unit erythroid (Erythrozyten-Vorläuferzellen der myeloischen Hämatopoese).

Disorders of ineffective or dysplastic erythropoiesis

Haemoglobinopathies (e.g. thalassaemic syndromes)

- Common causes of ineffective erythropoiesis→ *thalassaemia major and intermedia*
- Imbalances of α, β-globin chains→ *increased apoptosis during erythroblast maturation*
- iron overload is a well-recognized complication

Sideroblastic anaemias

- erythropoiesis characterized by mitochondrial iron accumulation in a ring around the nucleus
- caused by mutations in genes controlling mitochondrial iron metabolism

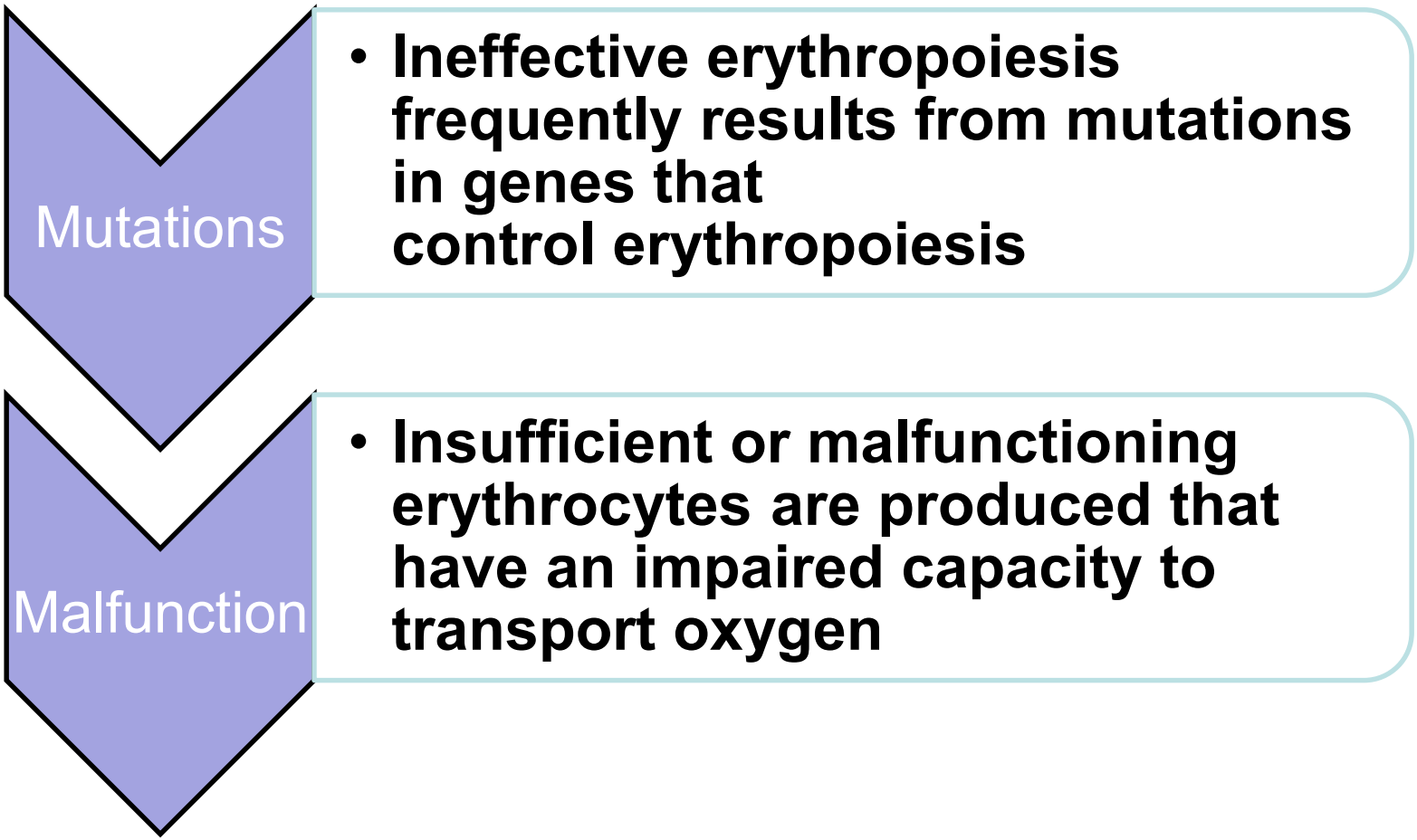
Dyserythropoietic anaemias (e.g. pyruvate kinase deficiency)

- defective glycolysis results in erythroblast apoptosis and peripheral blood haemolysis

Myeolodysplastic syndrome (MDS)

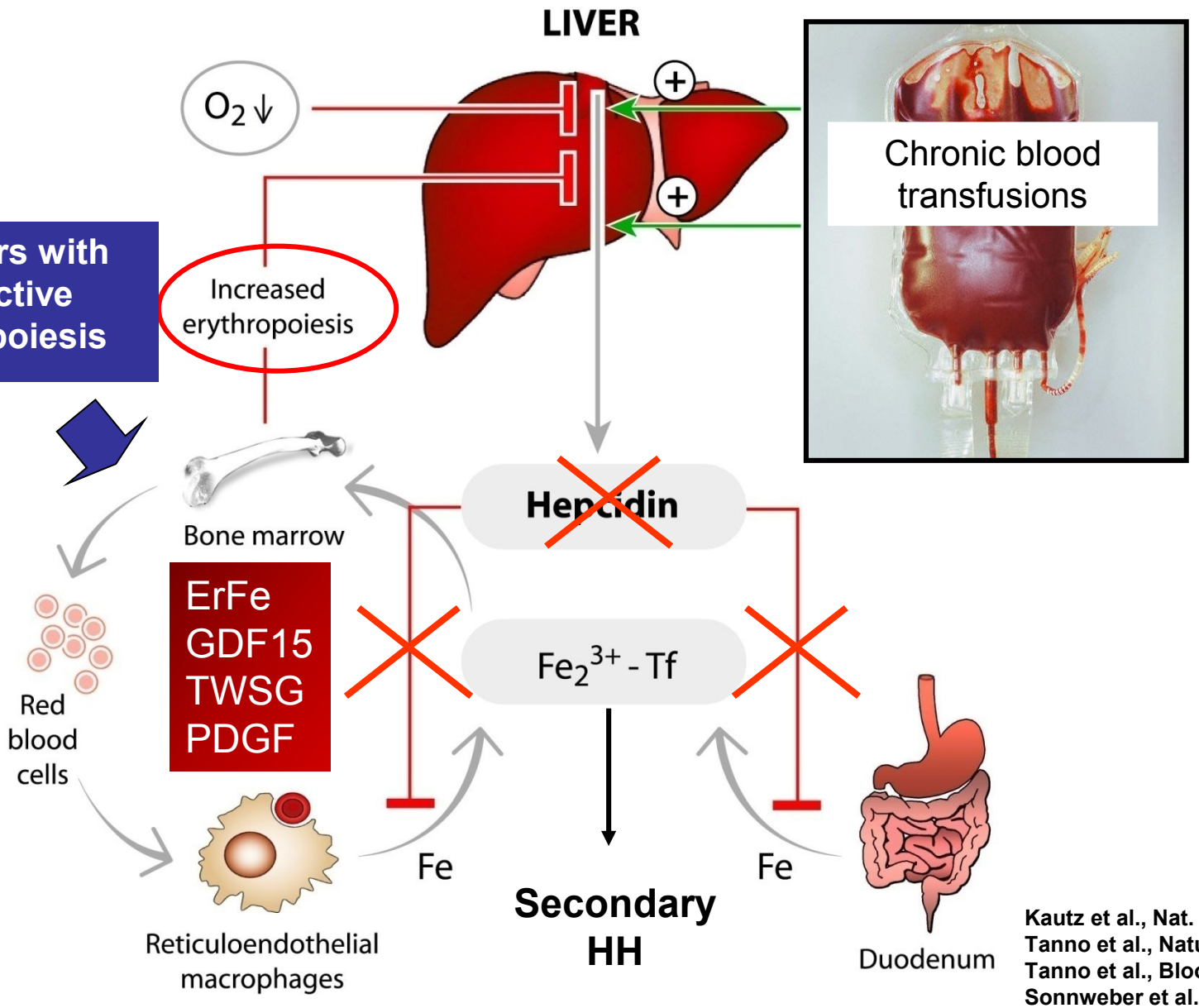
- BM failure, peripheral blood cytopenias, iron overload, reduced survival
- Expansion or evolution of the abnormal clone to AML can occur

Ineffective erythropoiesis



Disorders with ineffective erythropoiesis are hallmarked by iron overload

Disorders with ineffective erythropoiesis



Kautz et al., Nat. Genet. (2014)
Tanno et al., Nature Medicine (2007)
Tanno et al., Blood (2009)
Sonnweber et al., Gut 2014

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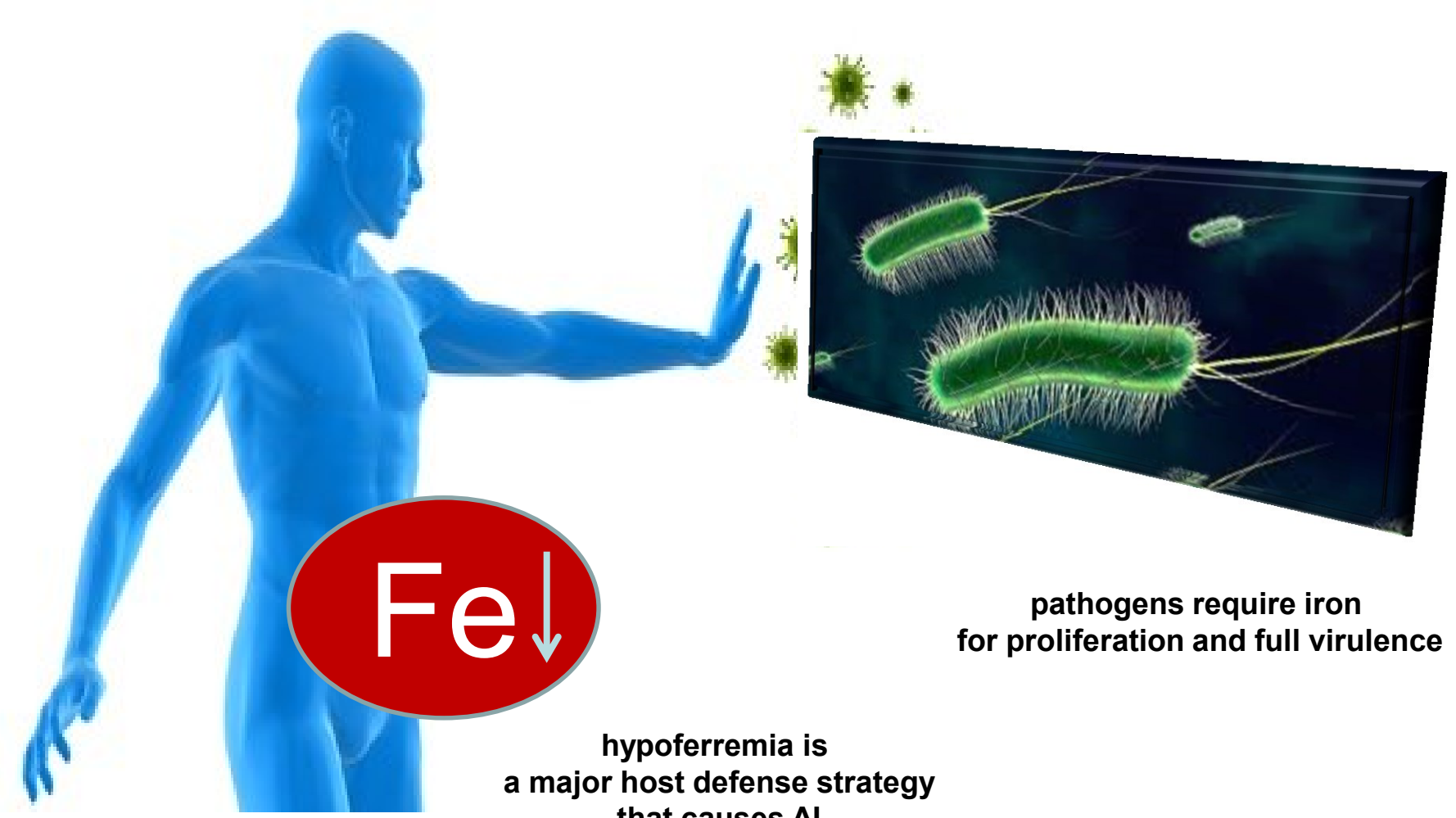
Iron plays a central role in host-pathogen interactions

innate immune system
fights infection
by iron sequestration



pathogens require iron
for proliferation and full virulence

hypoferremia is
a major host defense strategy
that causes AI

Accidental reactivation of Tb by iron

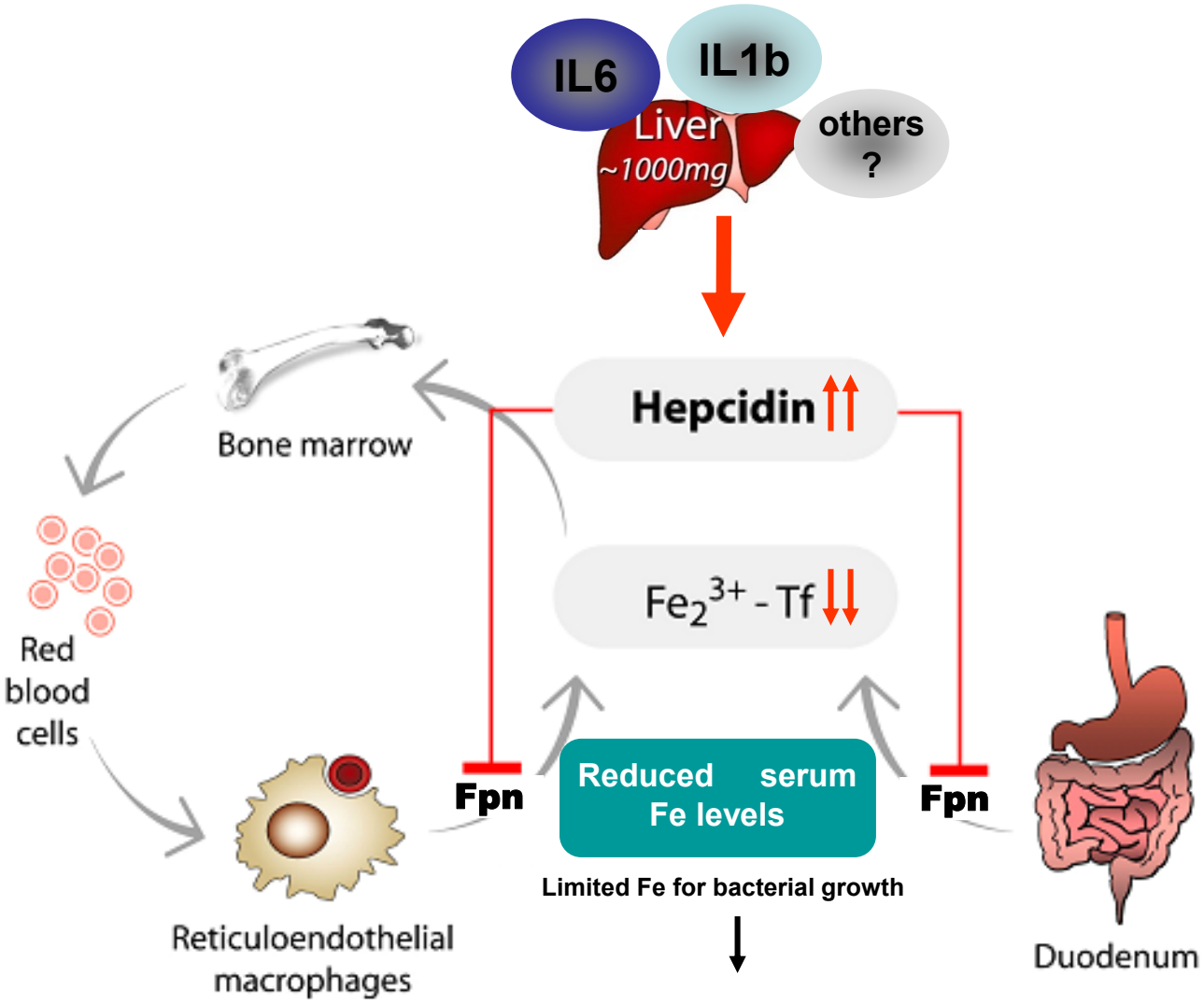
True and False Chlorosis, Lectures in Clinical Medicine
Armand Trousseau, Paris 1872

"When a very young physician, I was called to see the wife of an architect, a pale woman, presenting every appearance of chlorosis: I prescribed large doses of iron. There was a complete change: the young woman acquired a ravenous appetite, and an unwonted vivacity: but her gratitude and my delight did not last long. The restored colour of the cheek became every evening after dinner more ardent than it had been when she was in good health. A short cough supervened; and in less than a month there appeared signs of phthisis which nothing could impede."

"The first case of galloping consumption which I had to deplore occurred under nearly similar circumstances. A girl of fifteen fell into a state of anaemia which I considered chlorosis. I administered ferruginous remedies, which rapidly restored her to florid health: and although there was nothing in the family history to lead me to fear the coming calamity, she was simultaneously seized with hemoptysis and menorrhagia, and died two months afterwards"

"Gentlemen, I am constrained to impute to iron some of the evil consequences which I had to deplore"

Chronic infections and inflammation cause hypoferremia



ANAEMIA

associated with chronic infections, autoimmune disorders and malignancies

Interaction network of putative hepcidin regulators

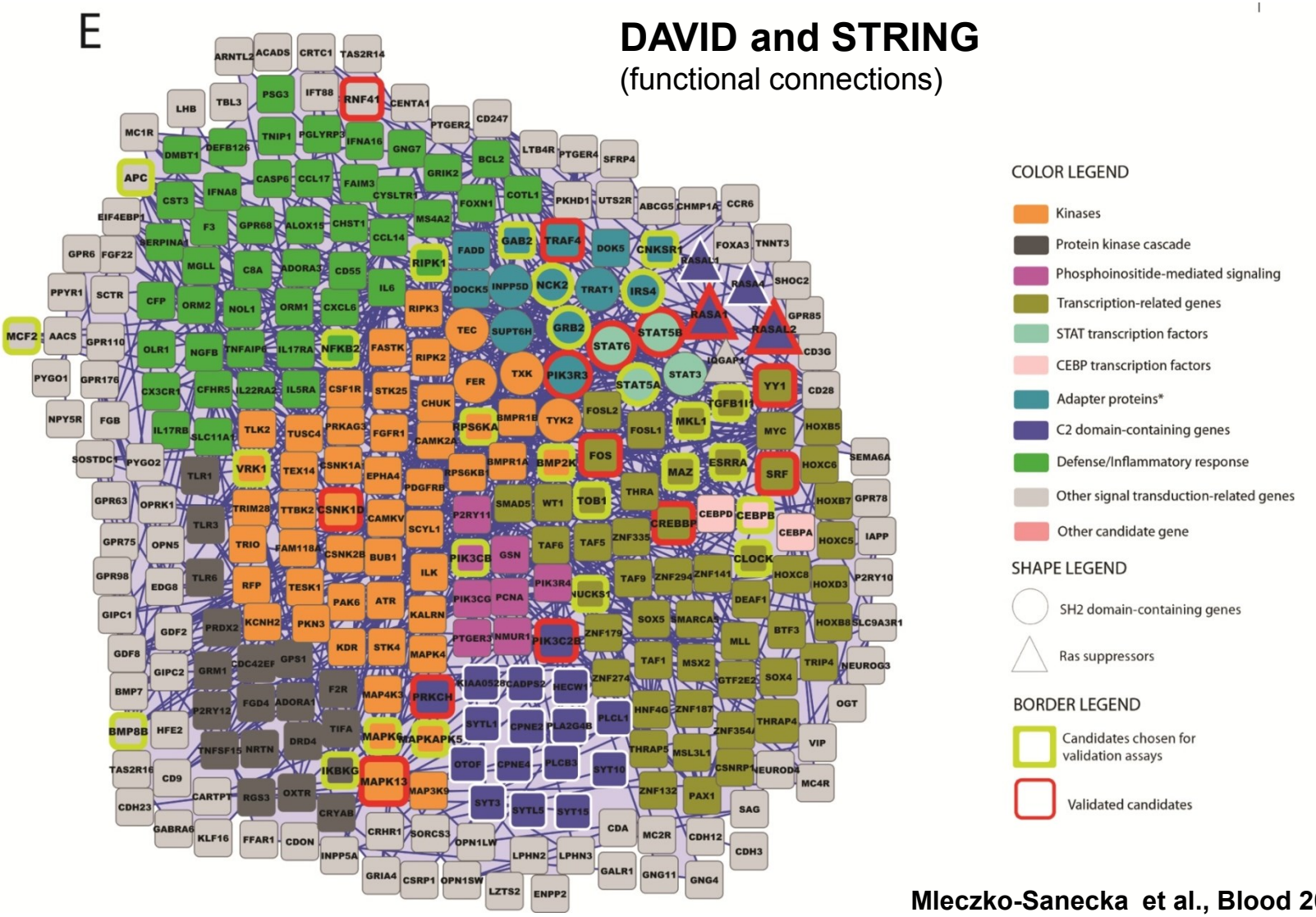
DAVID analysis

(90 enriched, nonredundant functional terms)

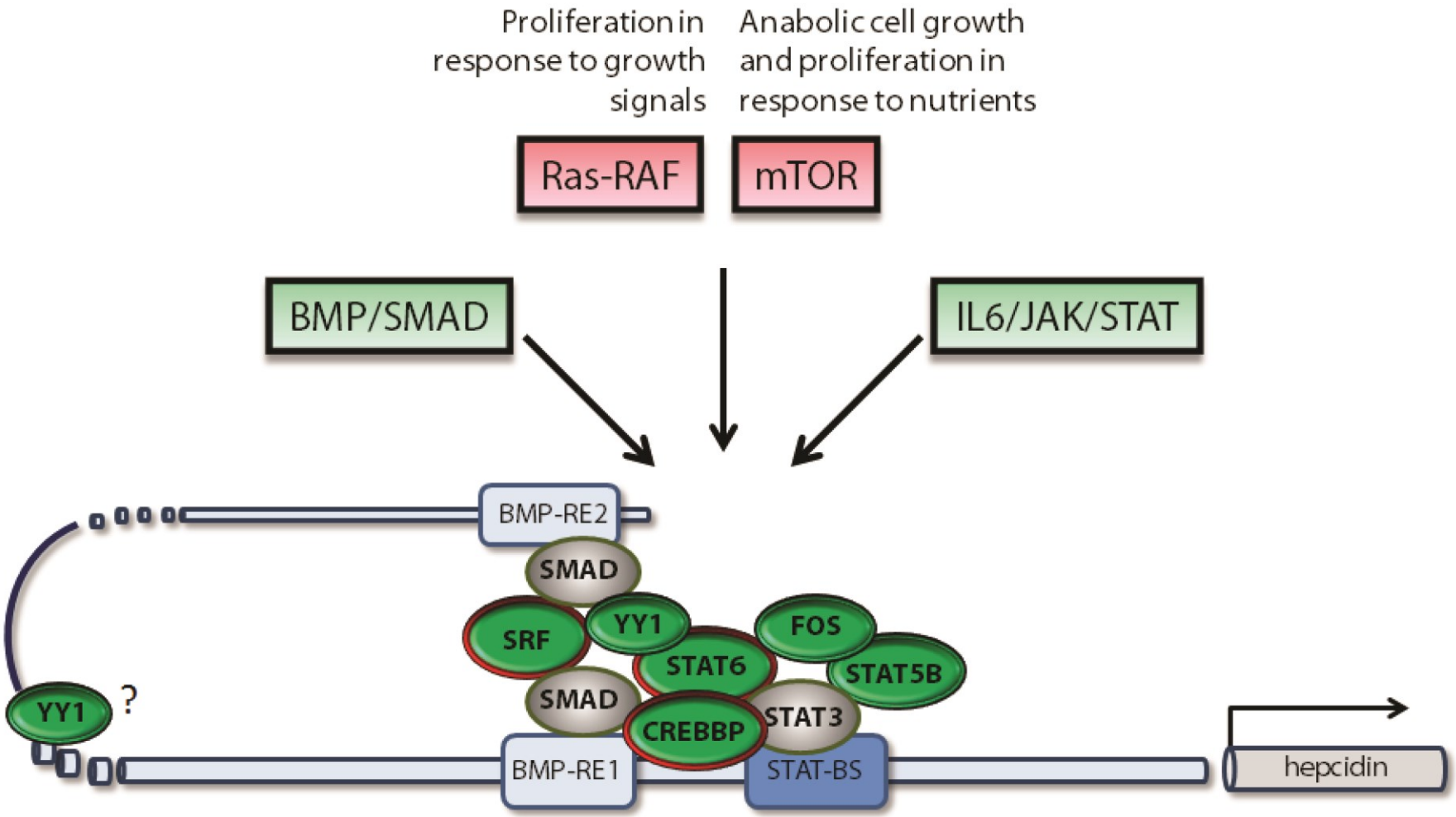
-> screen coherance and high quality

DAVID and STRING

(functional connections)



Mleczko-Sanecka et al., Blood 2014



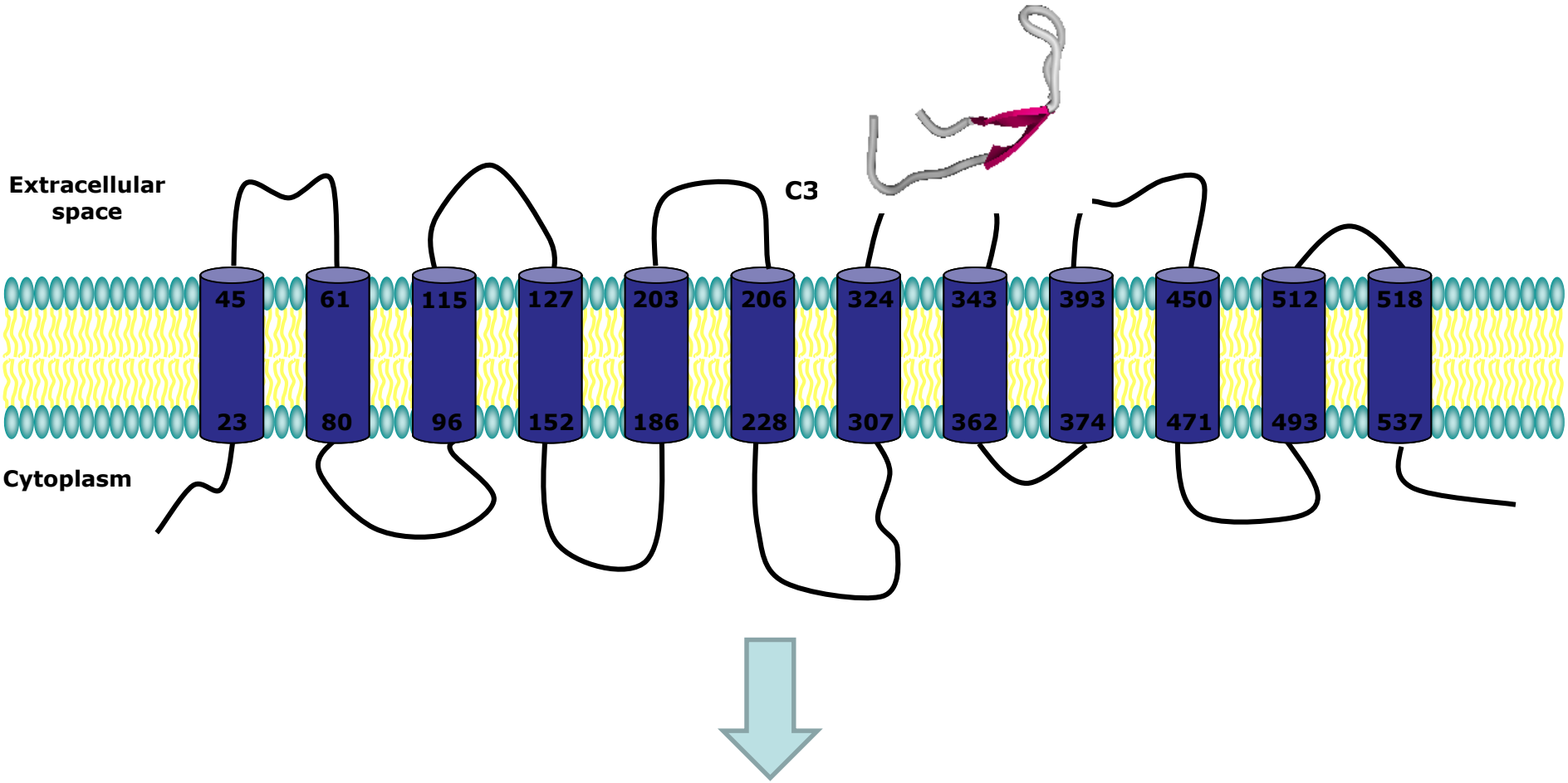
- **Regulation of hepcidin expression is integrated into signaling pathways that respond to growth-stimulating and nutrient-rich conditions**

- **Important clinical implications for liver stress conditions, including liver regeneration, viral and alcohol hepatitis, HCC and diabetes that involve the activation of the Ras/MAPK and mTOR pathways**

Failure of the Hepcidin-Ferroportin axis causes fatal iron overload in mice

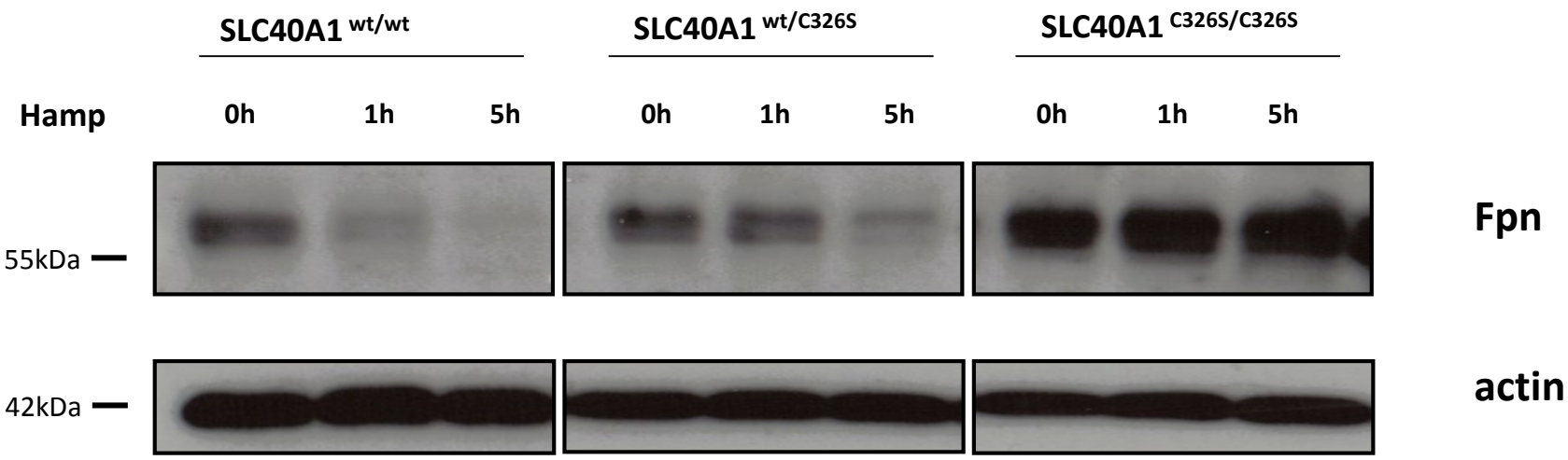
Sandro Altamura

Mutations in ferroportin cause disease



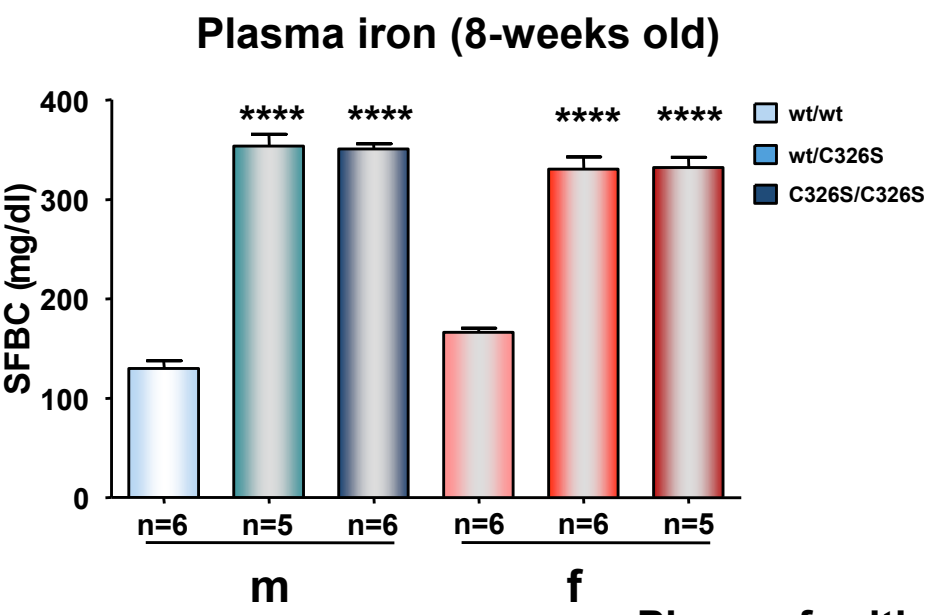
Internalization and degradation

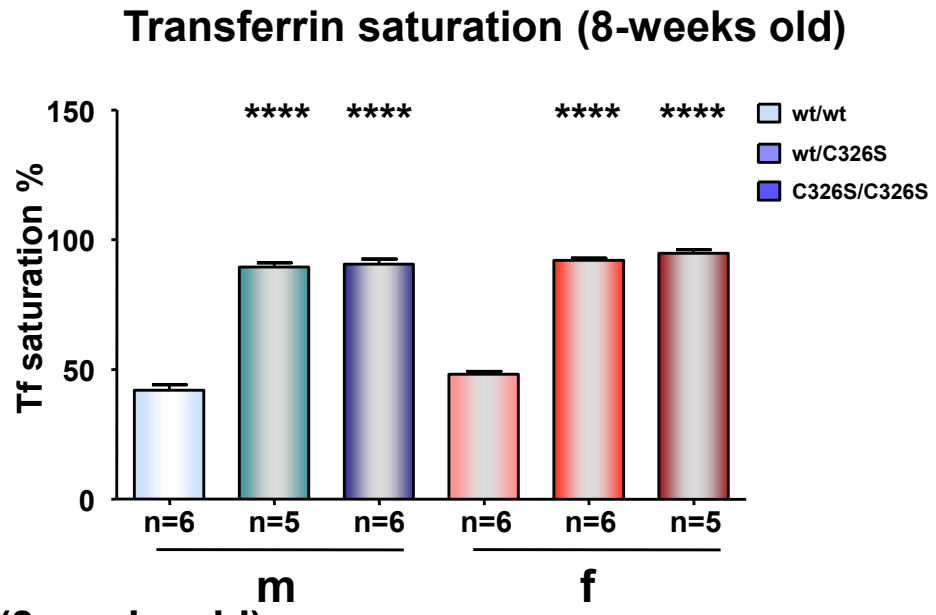
BMDM from the FPNC326S mice are hepcidin resistant

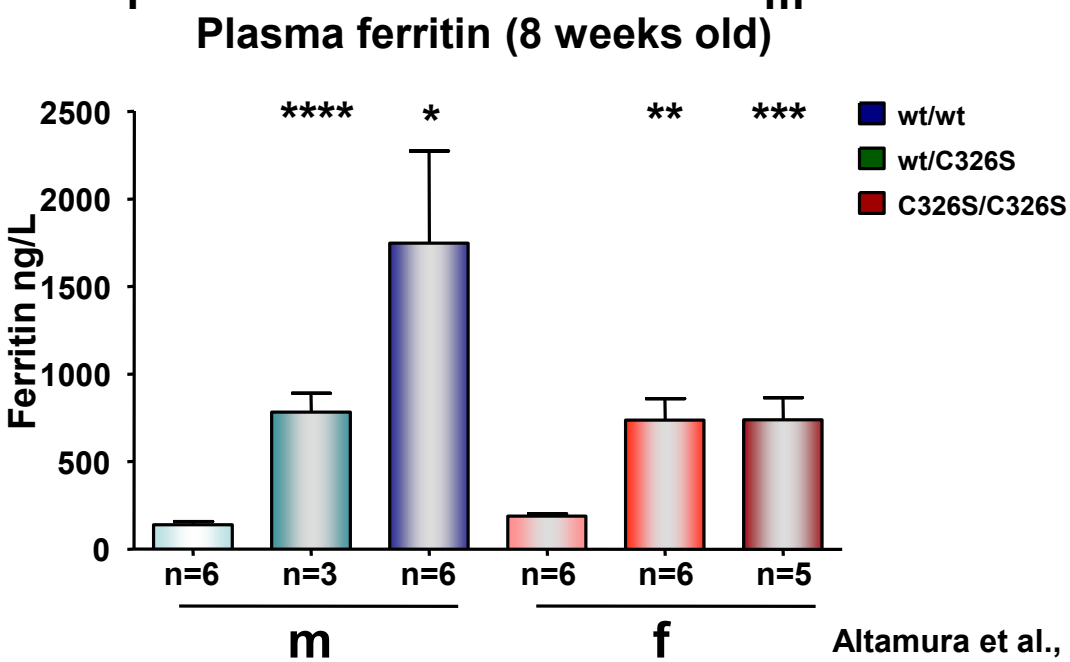


Altamura et al., Cell Metabolism (2014)

Increased serum iron levels hallmark FPN(C326S) mice



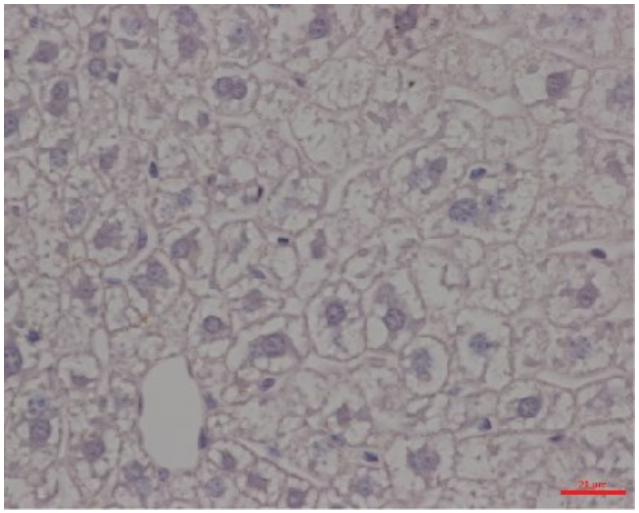




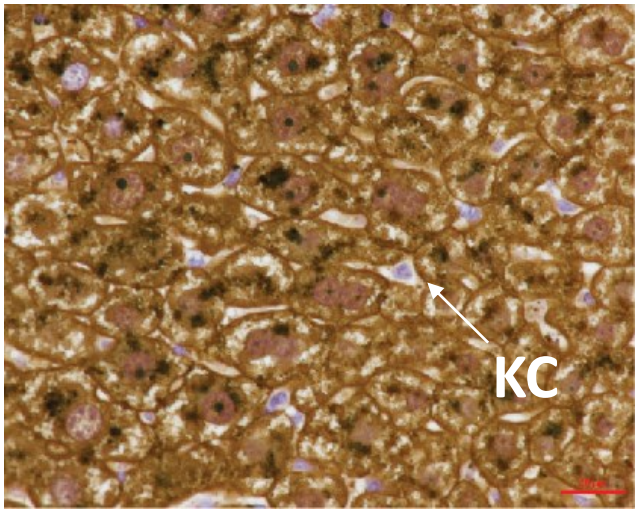
Altamura et al., Cell Metabolism (2014)

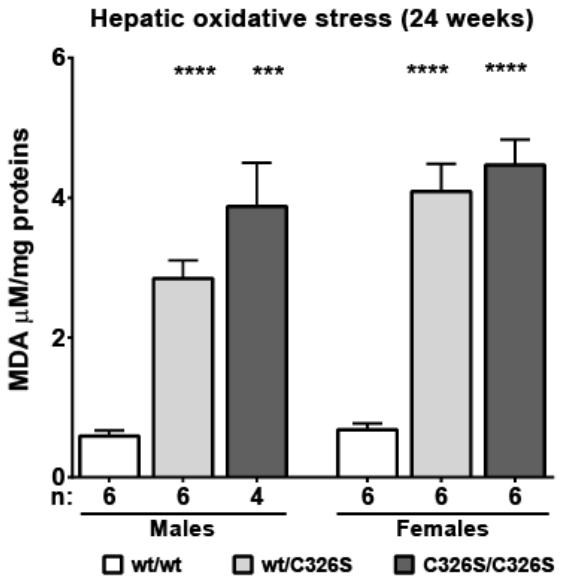
Hepatic iron overload in FPNC326S mice

SLC40A1(wt/wt)



SLC40A1(C326S/C326S)

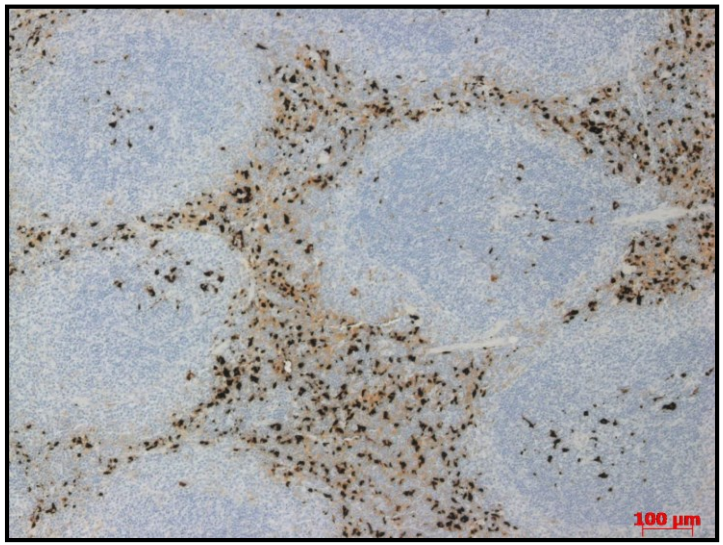




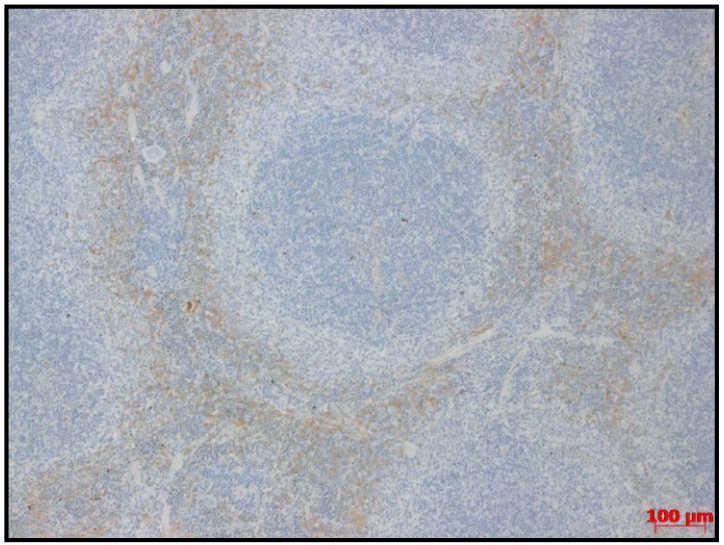
Altamura et al., Cell Metabolism (2014)

Splenic macrophages are iron-deficient in FPNC326S mice

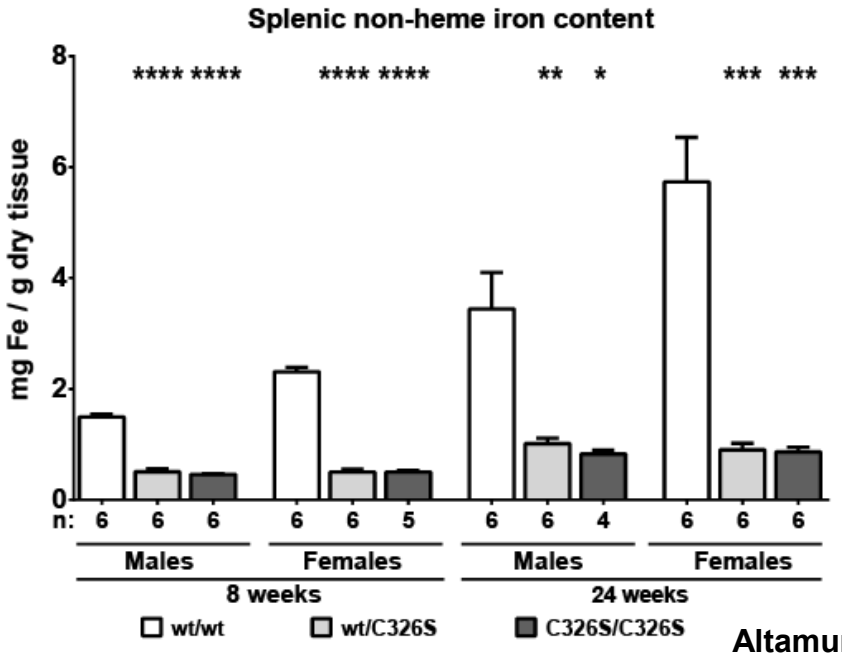
SLC40A1(wt/wt)



SLC40A1(C326S/C326S)



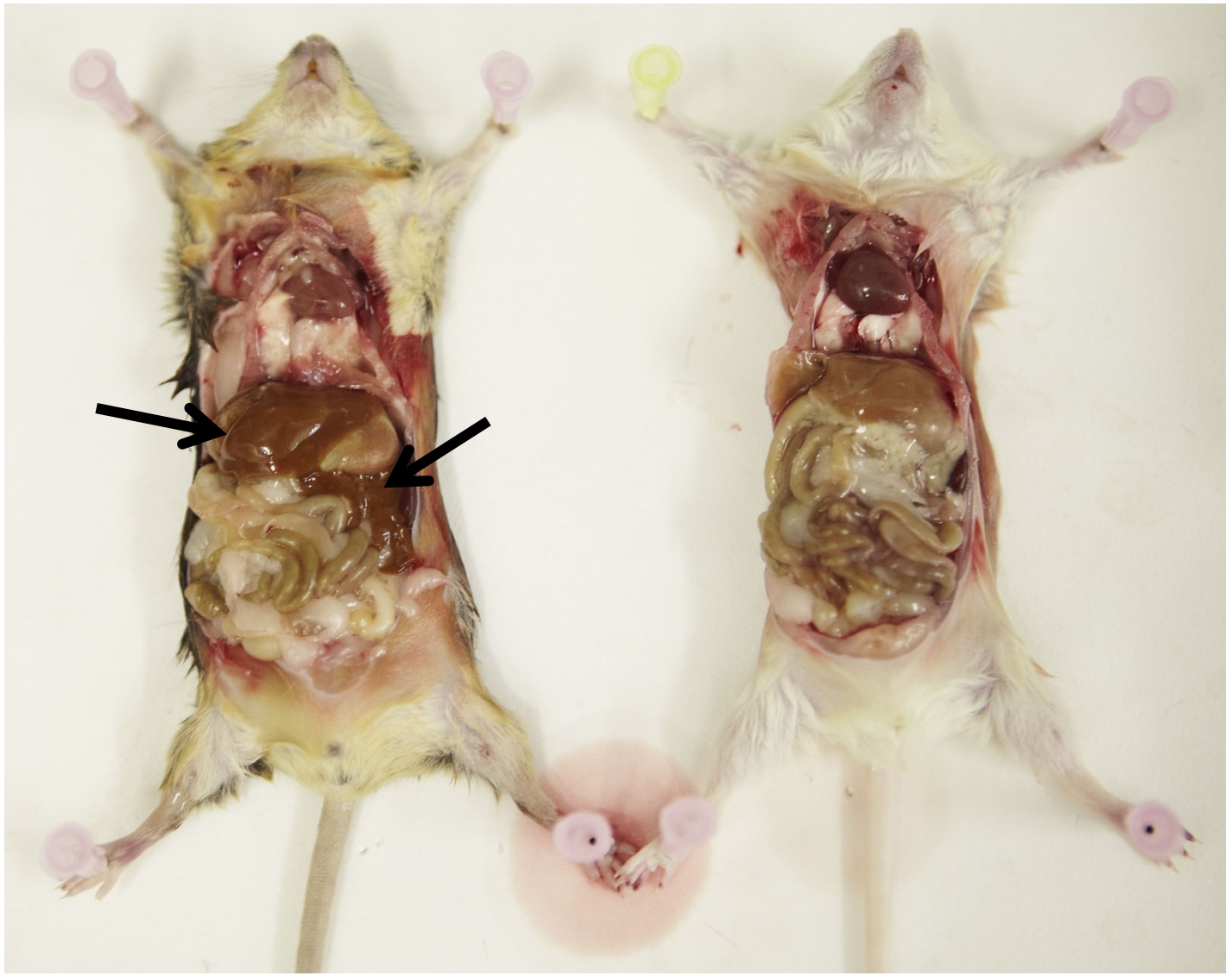
Perls stain



Altamura et al., Cell Metabolism (2014)

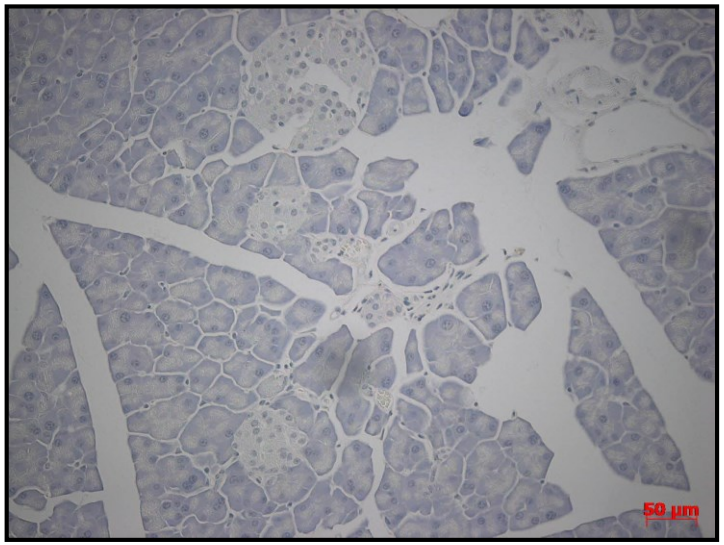
SLC40A1(C326S/C326S)

SLC40A1(wt/wt)



FPNC326S mice show pancreatic iron overload

SLC40A1(wt/wt)



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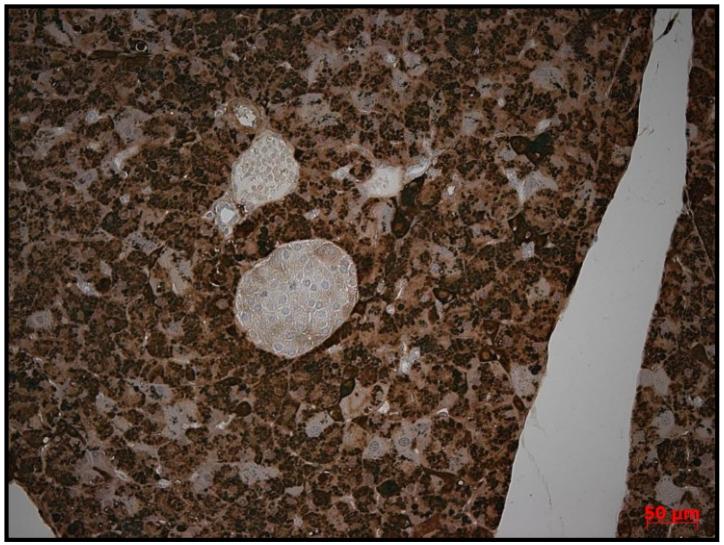
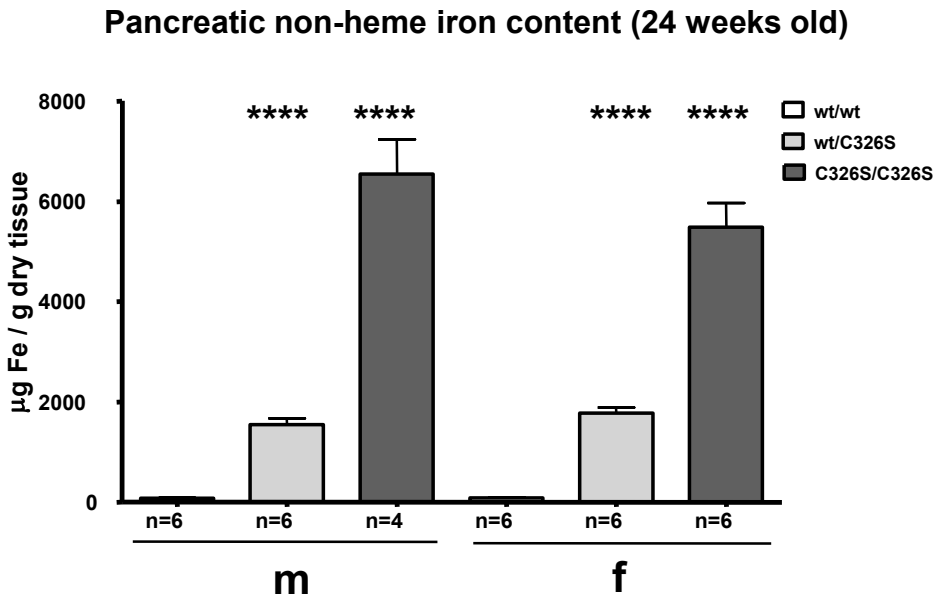
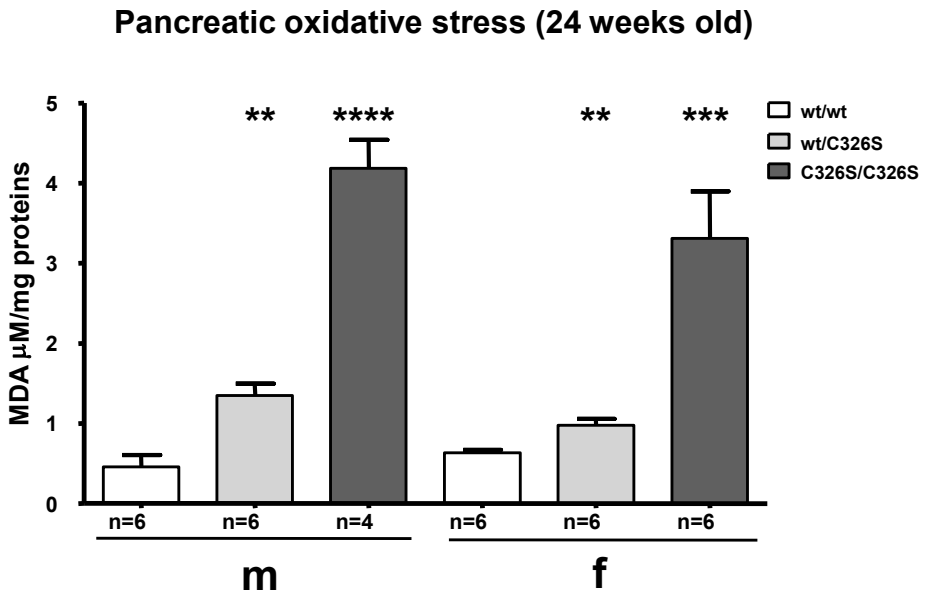


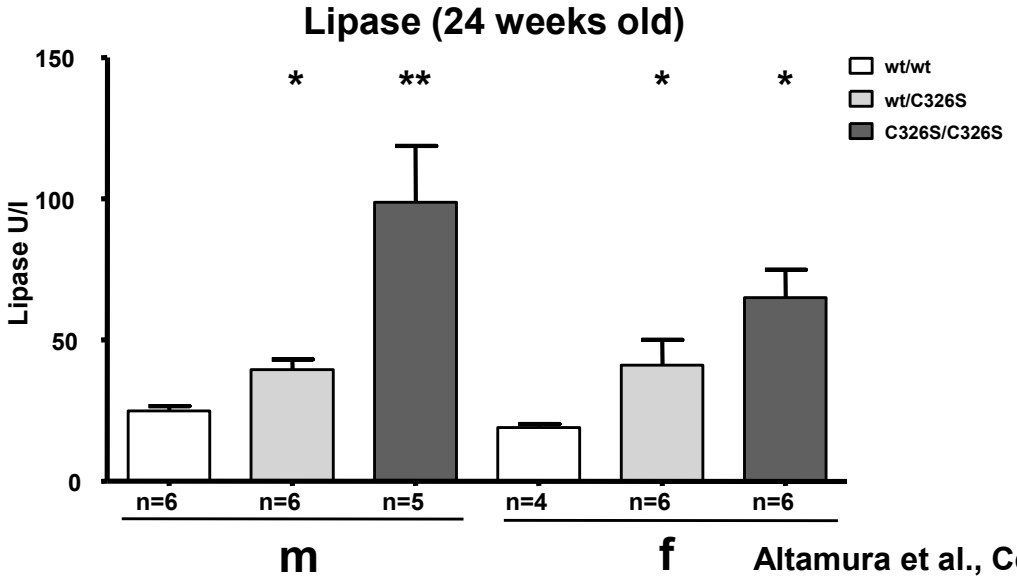
Perls staining

Altamura et al., Cell Metabolism (2014)

Pancreatic iron overload is associated with oxidative stress and elevated plasma lipase levels



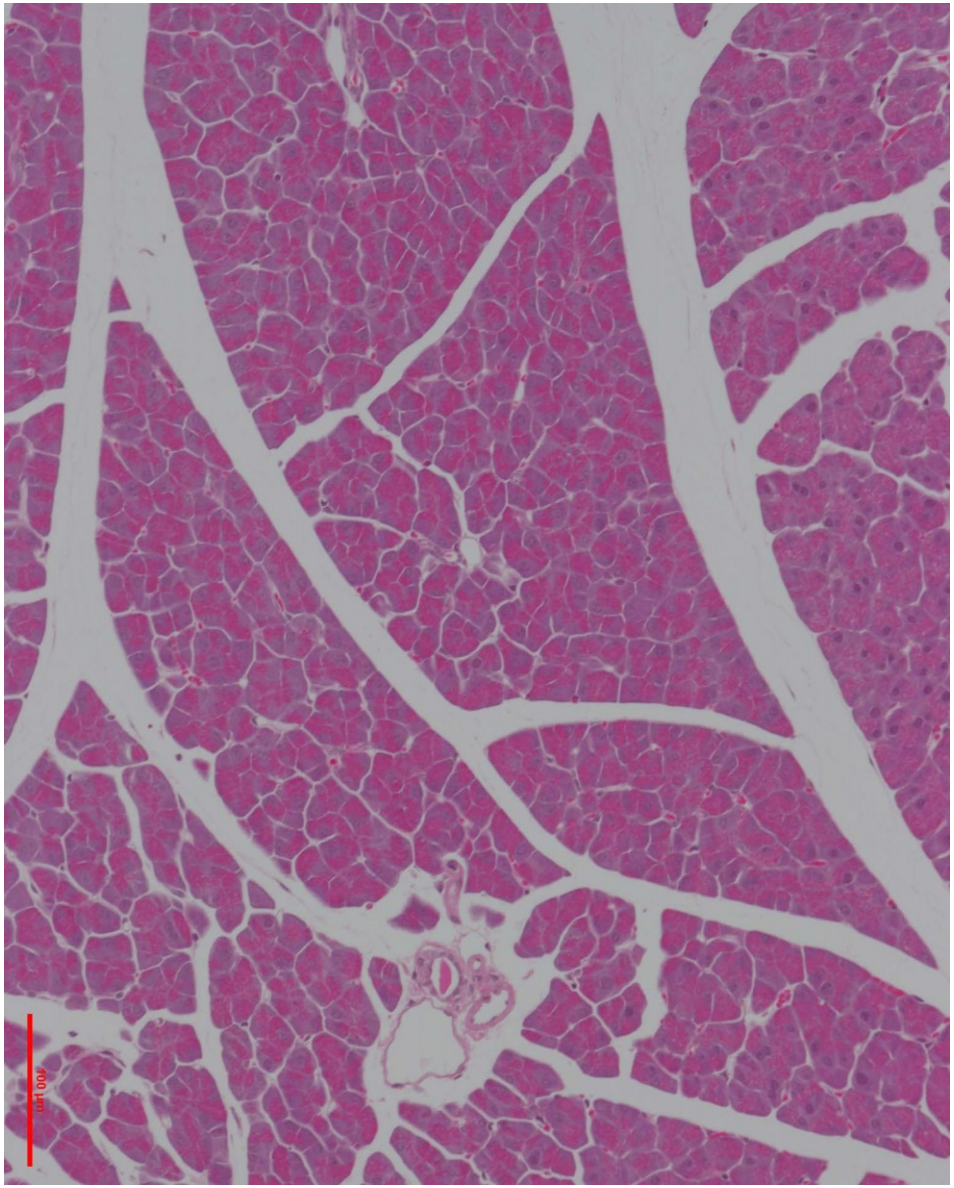




Altamura et al., Cell Metabolism (2014)

Degenerated pancreatic tissue in FPNC326S mice

SLC40A1(wt/wt)



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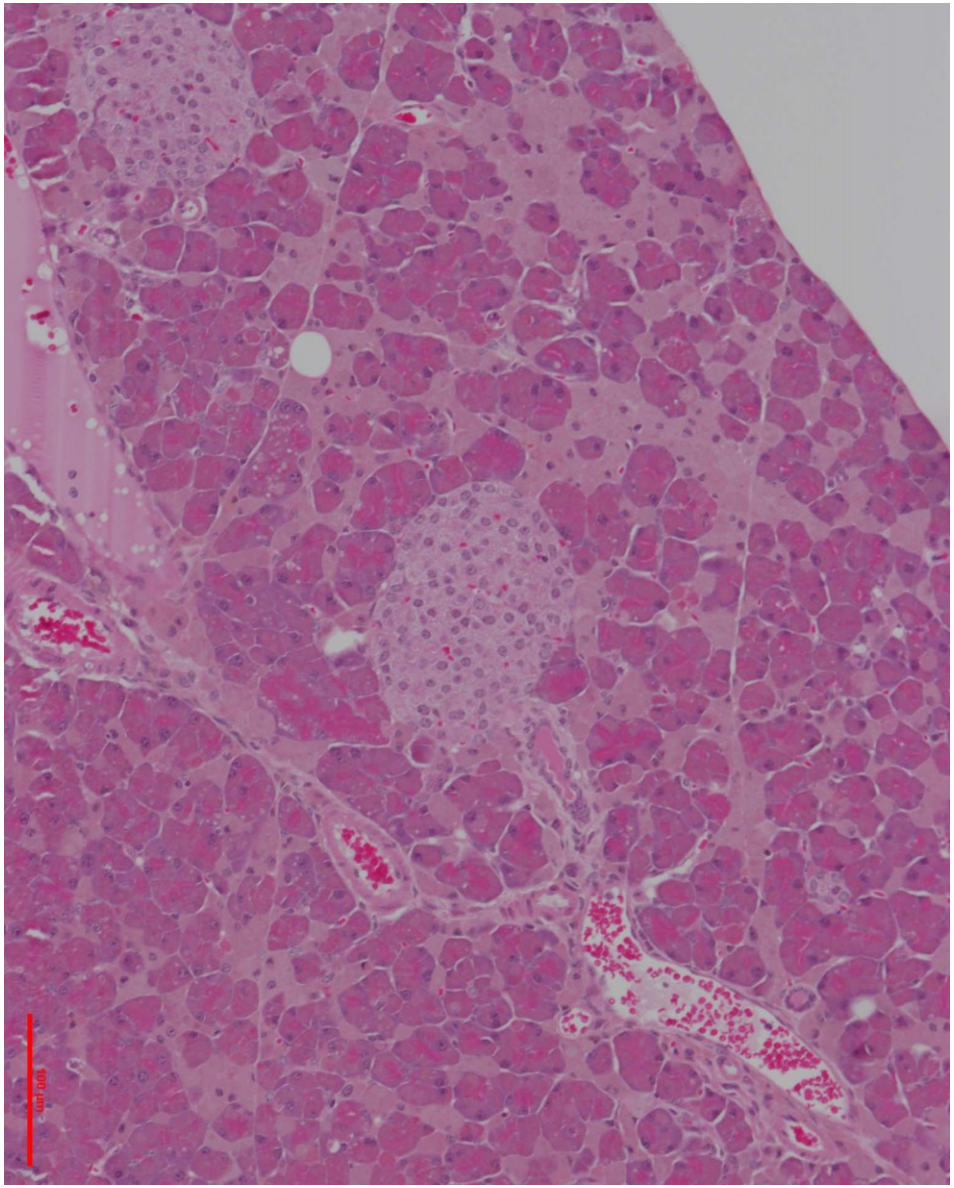
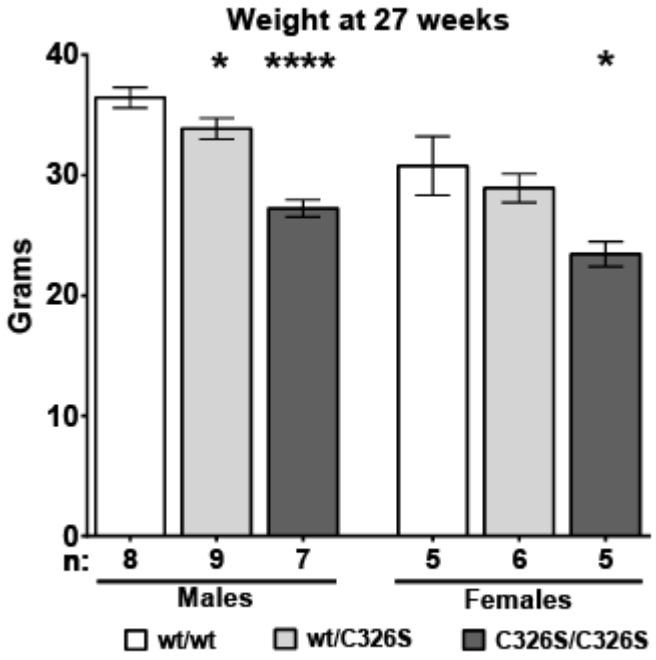
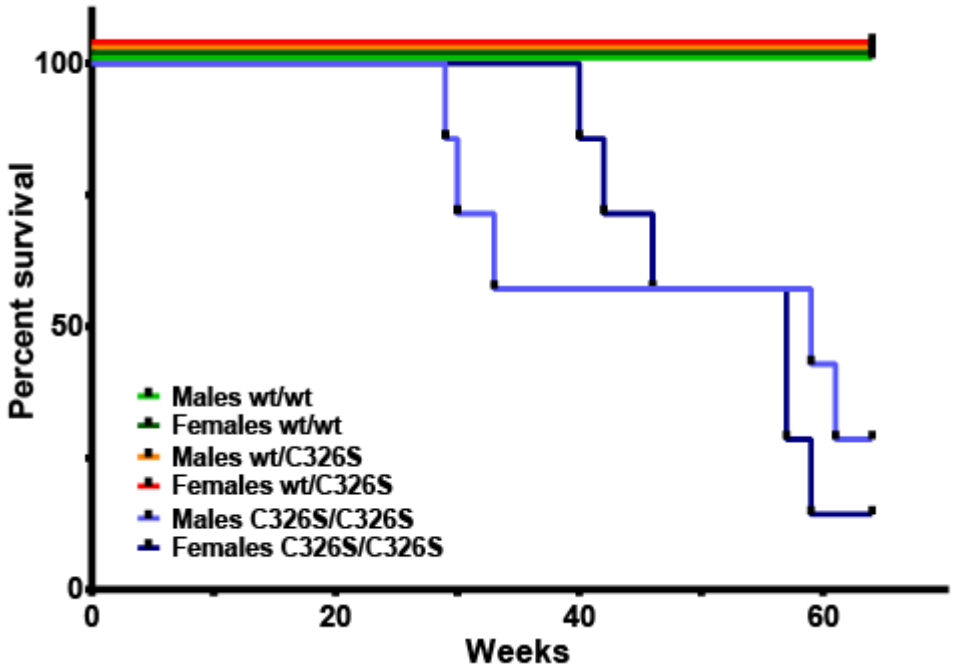


FPNC326S mice die around 35 weeks of age



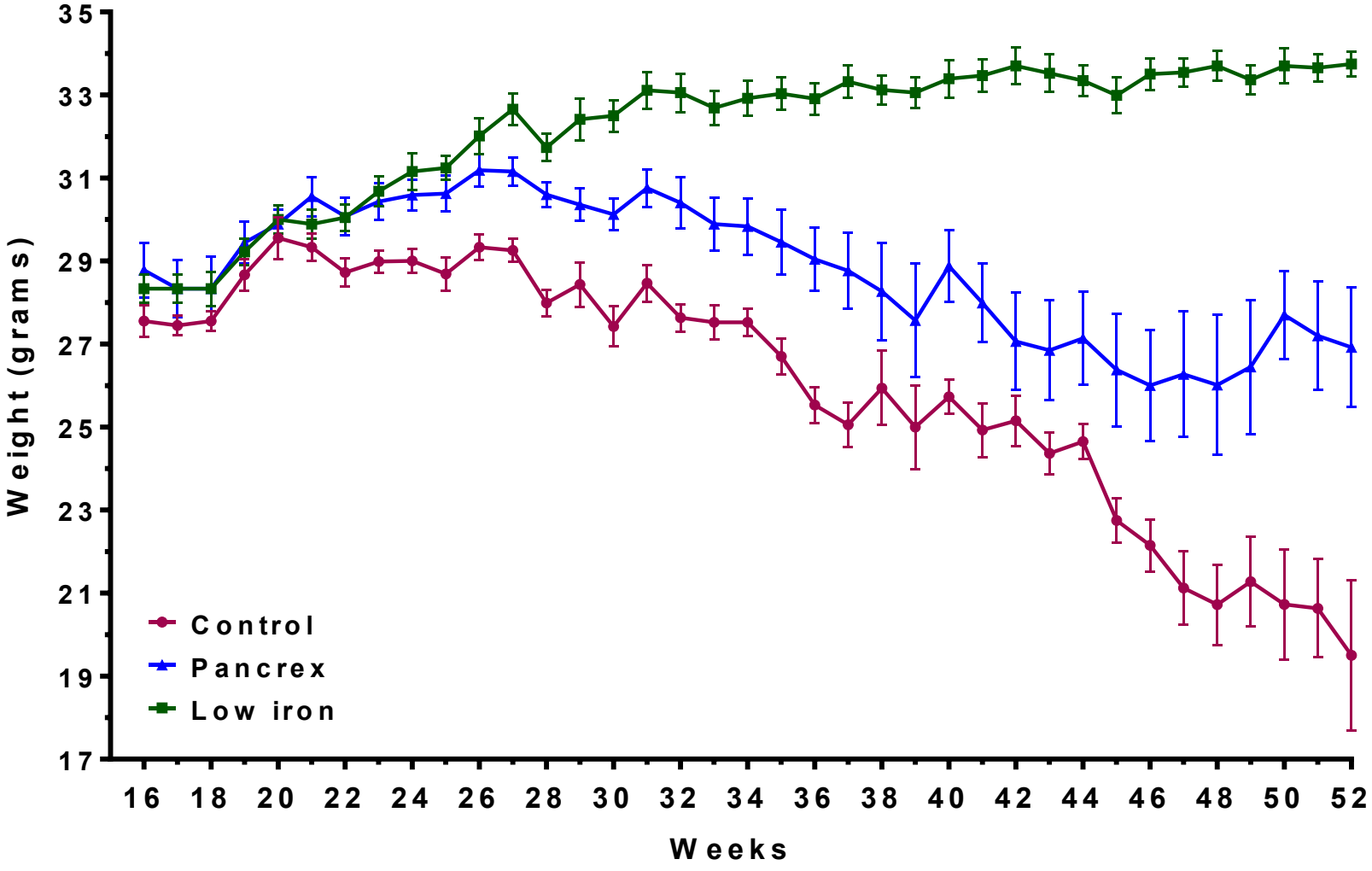


Altamura et al., Cell Metabolism (2014)

Is death of the SLC40A1(C326S/C326S) mice related to the iron overload?

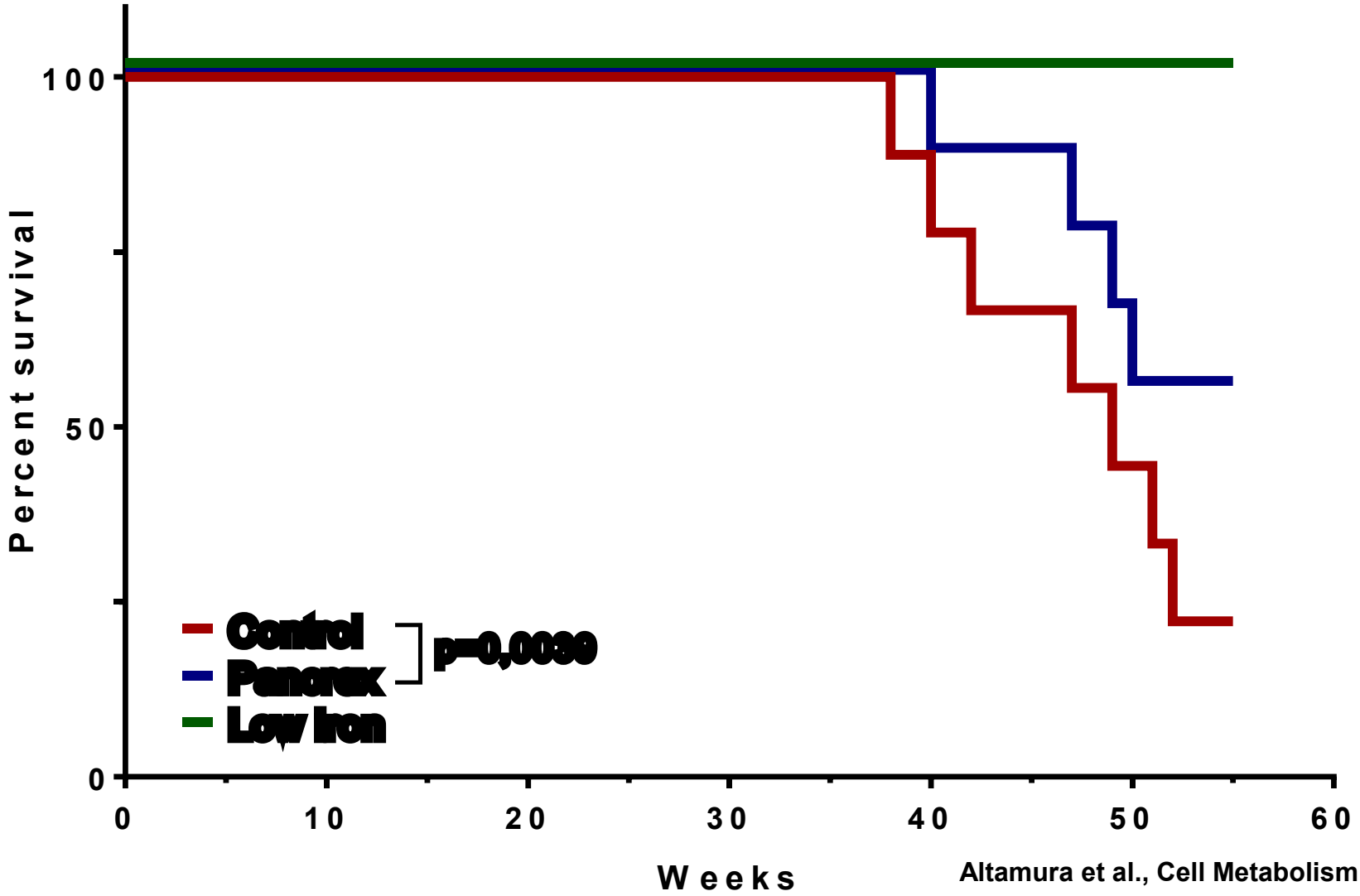
Is pancreatic failure the cause of death?

Weight loss can be rescued by a low iron diet and pancreatic enzyme replacement



Altamura et al., Cell Metabolism (2014)

Death of the FPNC326S mice is prevented by a low iron diet



Altamura et al., Cell Metabolism (2014)

Disruption of the hepcidin/ferroportin axis causes …

- **Severe iron overload in vital organs**
- **Failure of the exocrine pancreas, wasting and eventual death**
- **This represents the first mouse model of fatal dietary iron overload.**

Outlook:

Work is in progress to investigate pathologies related to iron overload and/or iron deficiency in various tissues e.g. lung, vasculature and kidney

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