CARENZA ED ECCESSO DI FERRO: nuove conoscenze ed approccio terapeutico

Ore 9,20- 9,50

Fisiopatologia dei disordini del ferro

E. Angelucci- Genova

ASH 50th anniversary review

Forging a field: the golden age of iron biology

Nancy C. Andrews[1]

BLOOD *The Journal of Hematology*

JANUARY, 1958 VOL. XIII, NO. 1

Absorption of Iron as a Problem in Human Physiology

A Critical Review

By HUGH W. JOSEPHS

Ham-Wasserman Lecture

Iron overload

“All things are poison, and nothing is without poison; only the dose permits something not to be poisonous.“

Or, more commonly:

“The dose makes the poison.“

Paracelsus (1493-1541)

Swiss Renaissance physician, philosopher, astrologer, botanist, alchemist, sometimes called father of toxicology

Iron is essential

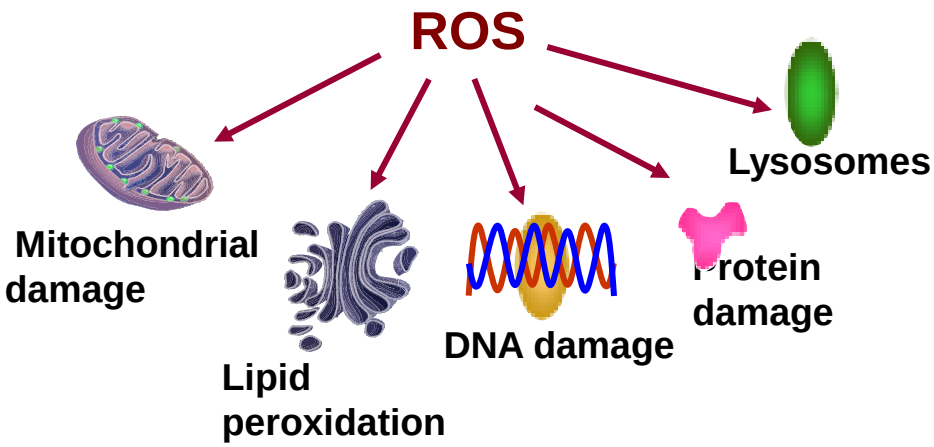
- O_2 transport and exchange
  - haemoglobin and myoglobin
- Respiratory chain
  - complex I and III
- Biosynthetic pathways
  - haem synthesis
  - Fe/S cluster assembly
- DNA synthesis and repair
  - ribonucleotide reductase
  - endonuclease III
- Cell growth and proliferation

Iron is toxic

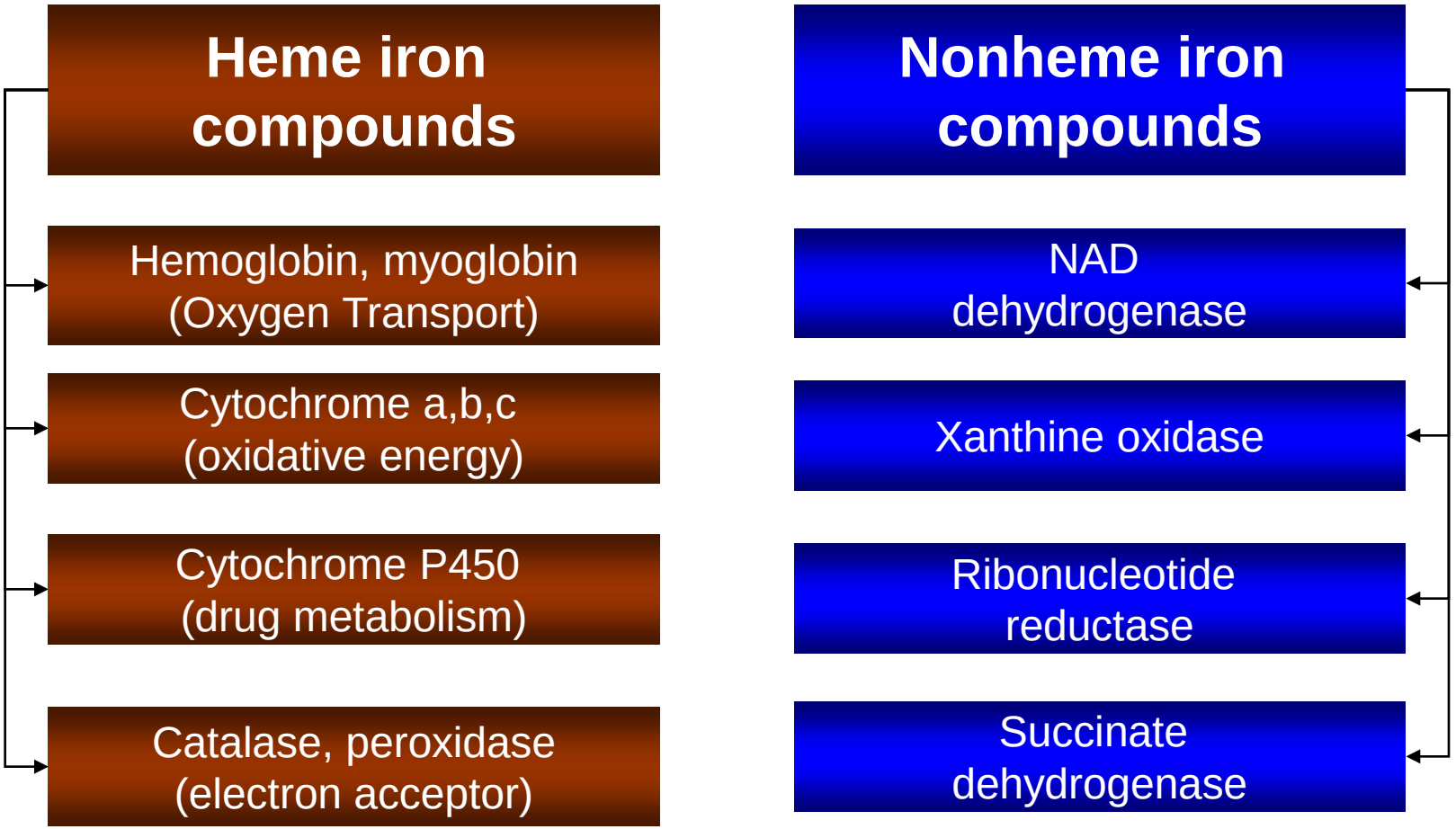
- Ability to transfer electrons
- Production of free O_2 radicals

Fenton reaction:

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH$



Iron plays an essential role in several metabolic processes

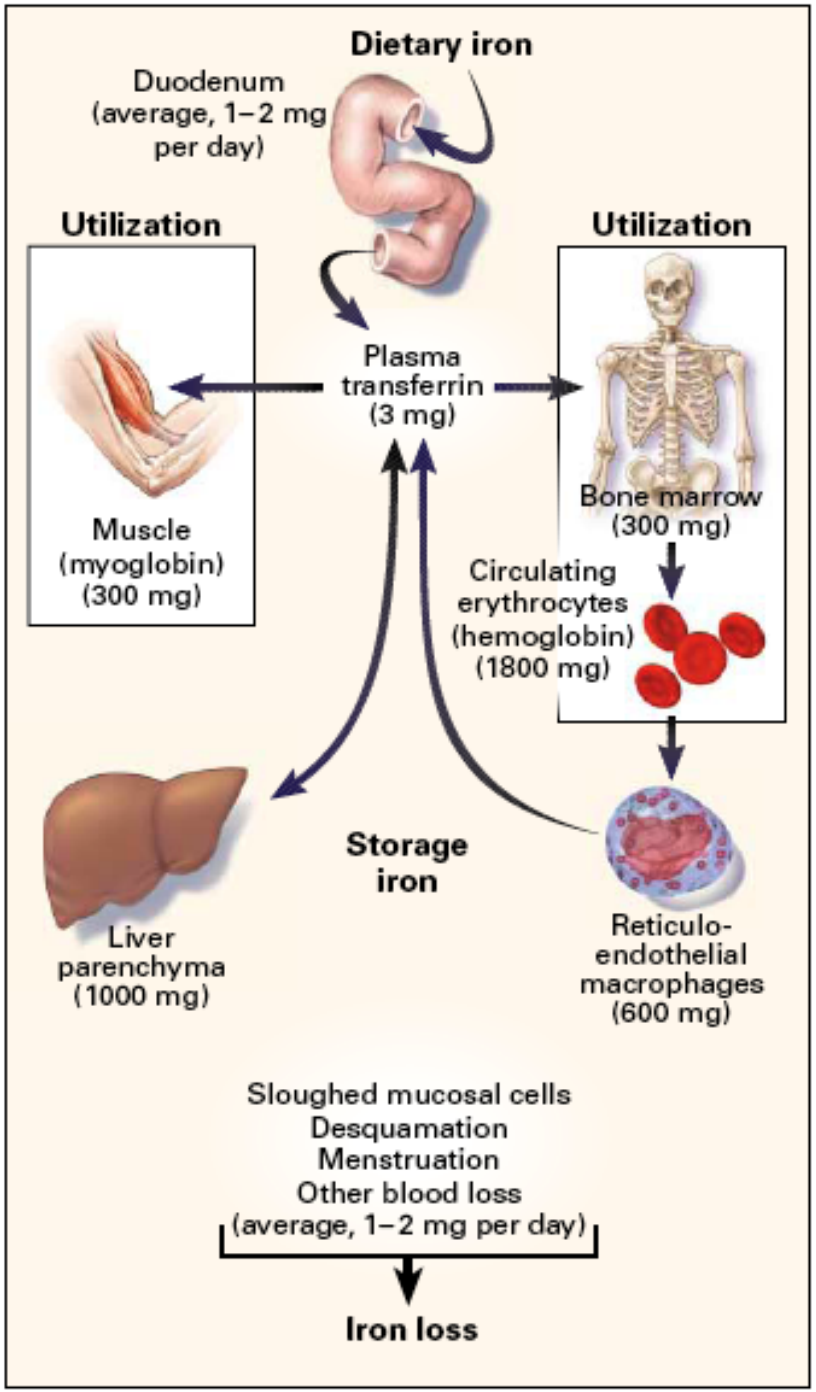


Total body iron

about 4 g

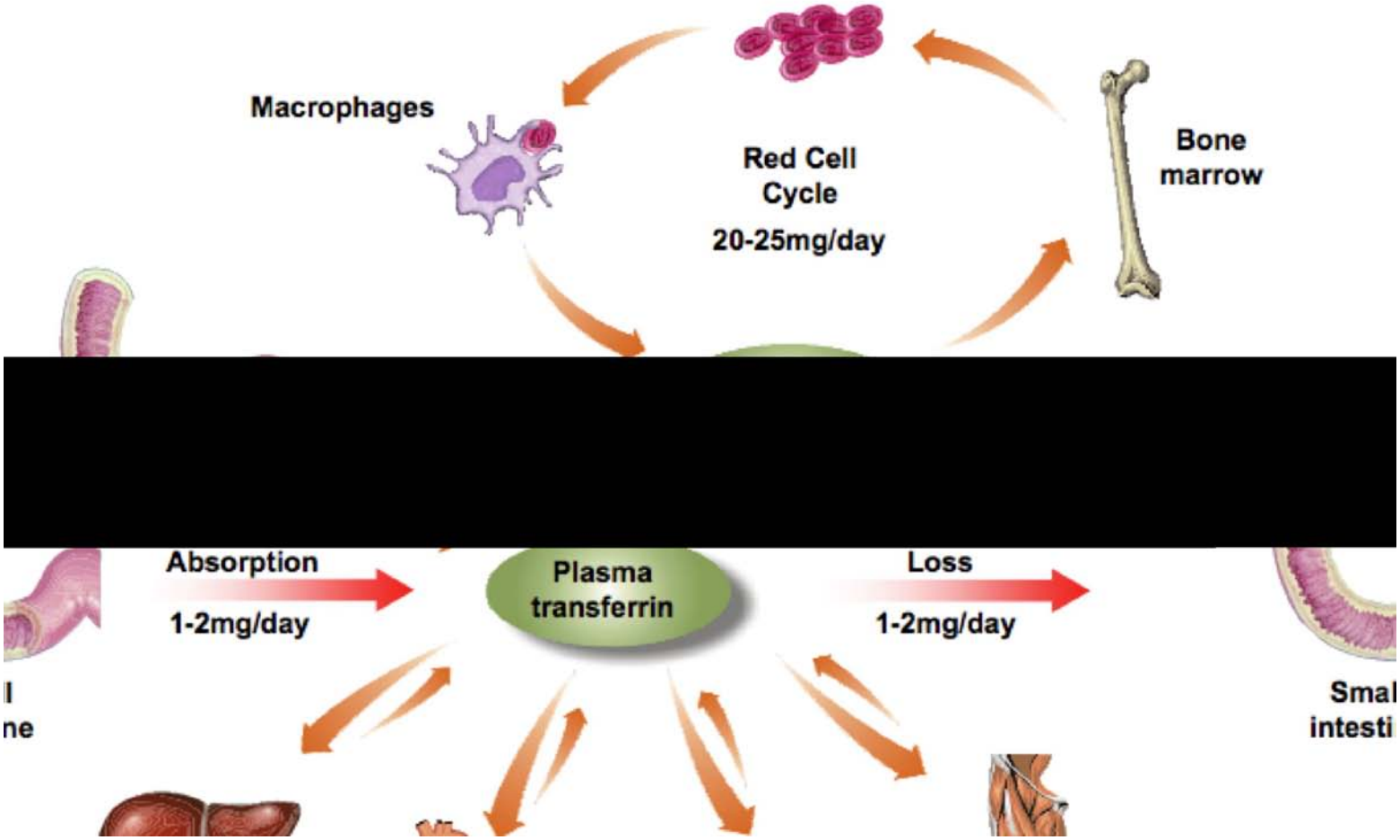
Iron compartments:

Functional
Transport
Storage

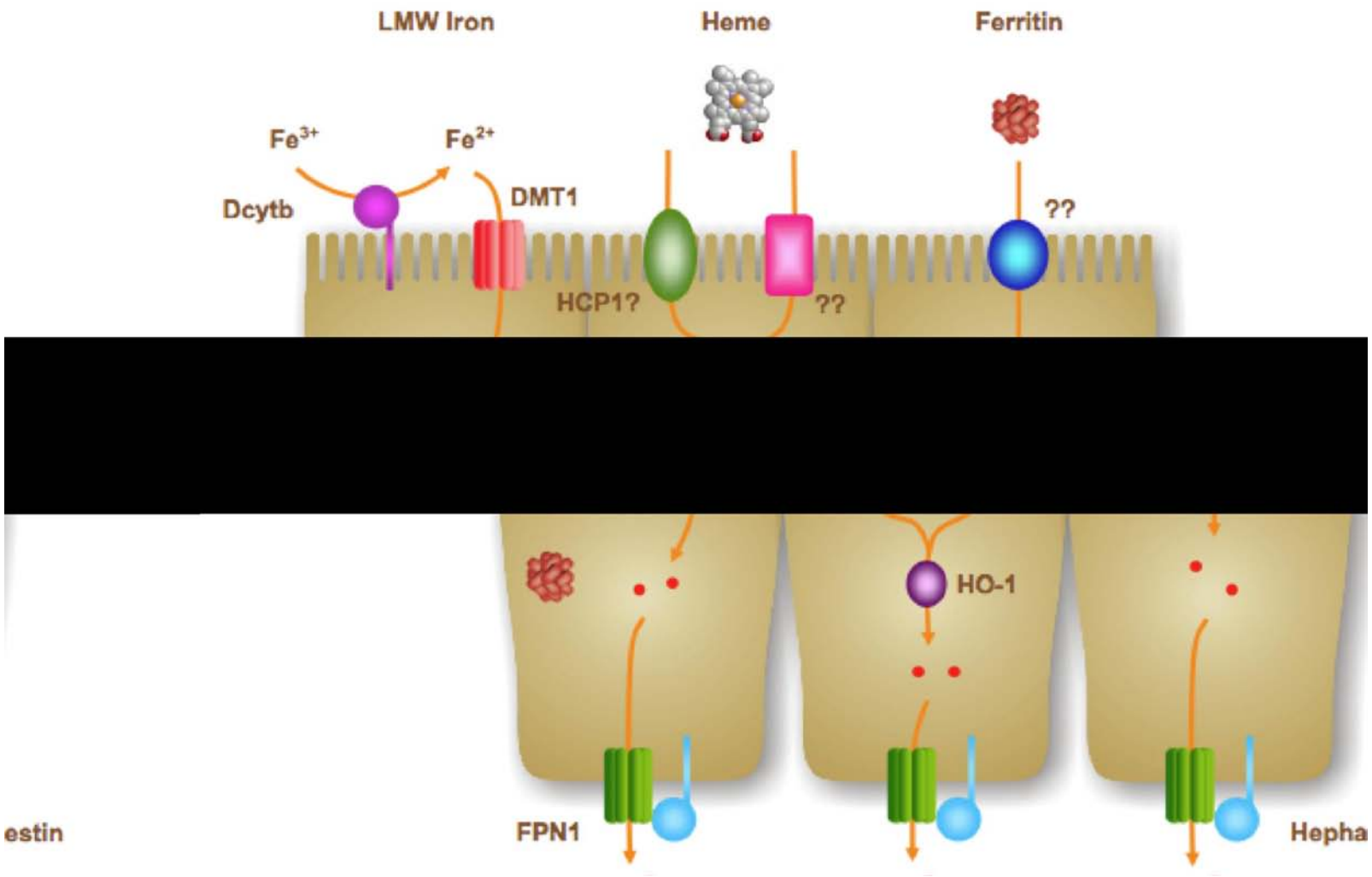


Andrews, NEJM, 1999

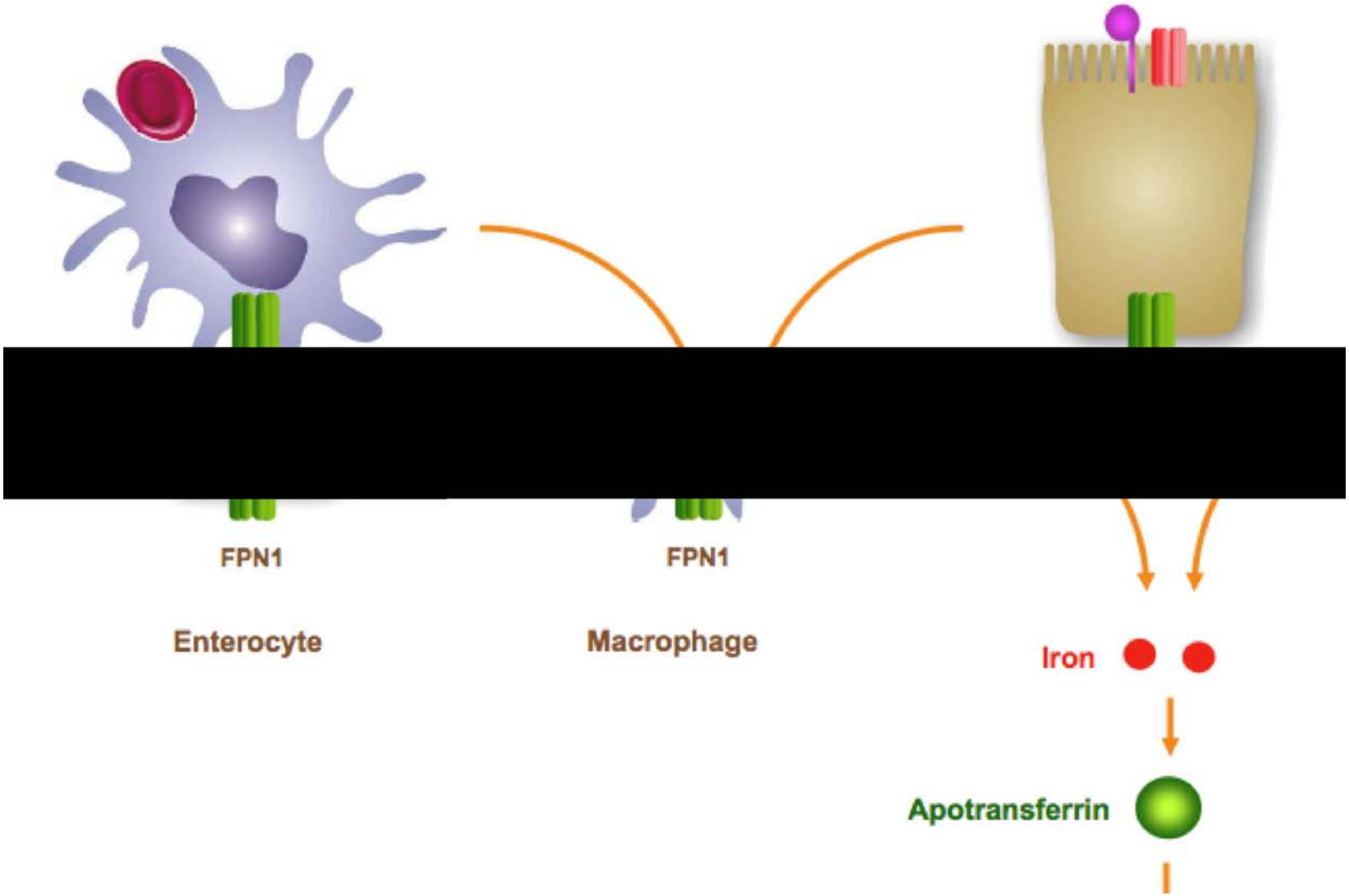
Body iron homeostasis



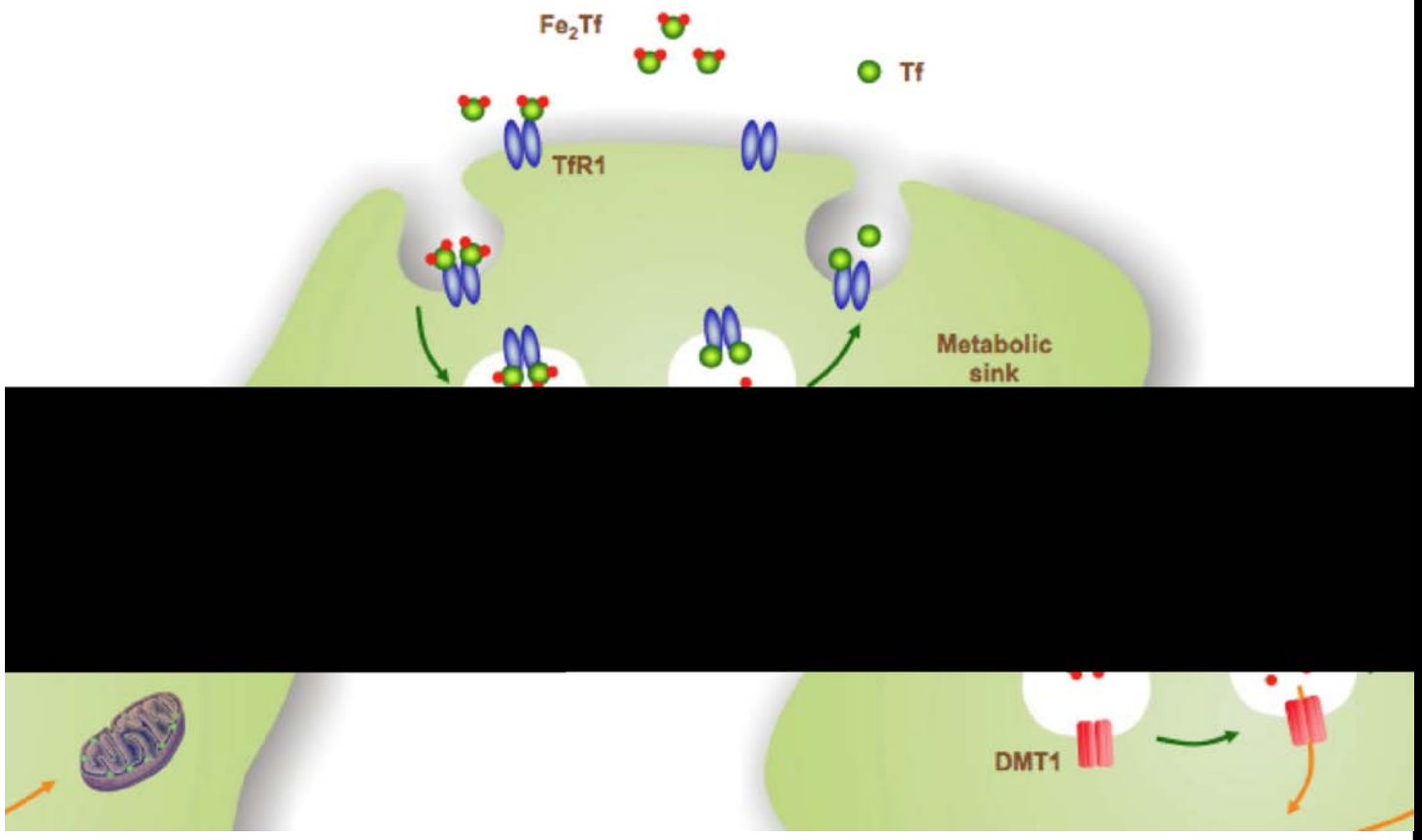
Intestinal iron transport



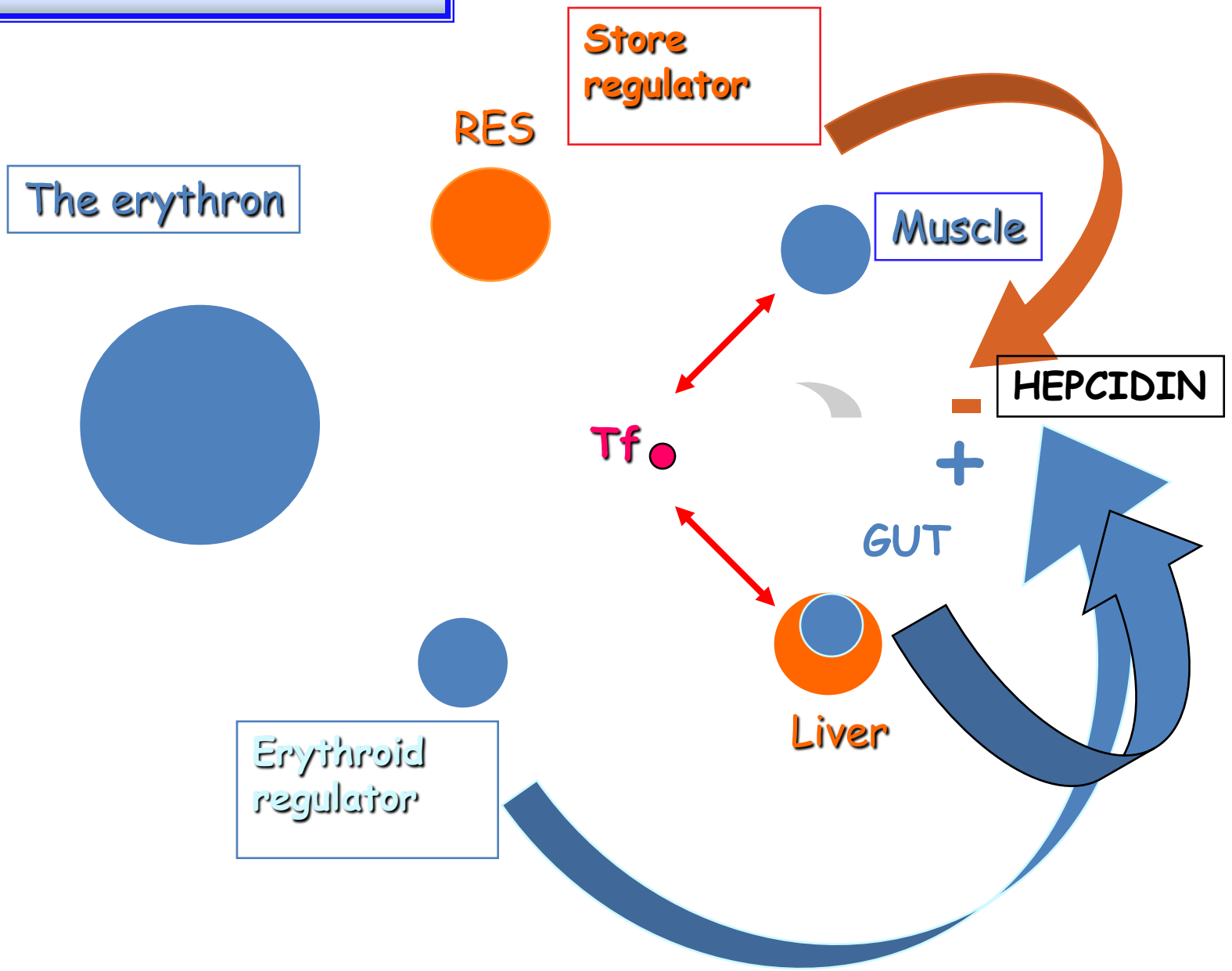
Iron donation to the plasma



Cellular iron transport



Iron cycle control



HEPCIDIN: A KEY IRON REGULATOR

DNA: 2.5 Kb, 3 exons - cDNA: 0,4 Kb

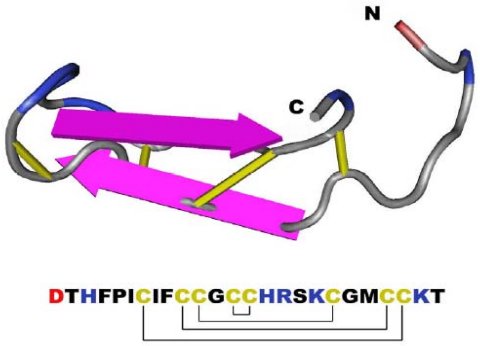
84 aa propeptide -> 20-25aa mature peptide

Liver product

4 S-S bonds

Hairpin structure

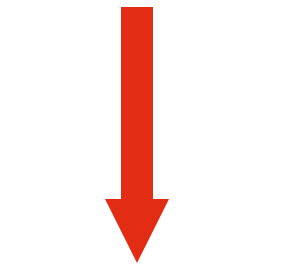
(antimicrobial peptide)



Positive regulation by iron and inflammation

Negative regulation by anemia and hypoxia

Hepcidin: a key iron regulator in mice



Iron overload

(Nicolas et al, PNAS 2001
Lesbordes-Brion et al, Blood 2006)

Iron deficiency

(Nicolas et al, PNAS 2002)

Hepcidin: a key iron regulator in humans

Mutant antimicrobial peptide hepcidin is associated with severe juvenile hemochromatosis

Published online 9 December 2002; doi:10.1038/ng1053

Animal models indicate that the antimicrobial peptide hepcidin (HAMP; OMIM 606464) is probably a key regulator of iron absorption in mammals. Here we report the identification of two mutations (93delG and 166C→T) in *HAMP* on 19q13 in two families with a new type of juvenile hemochromatosis.

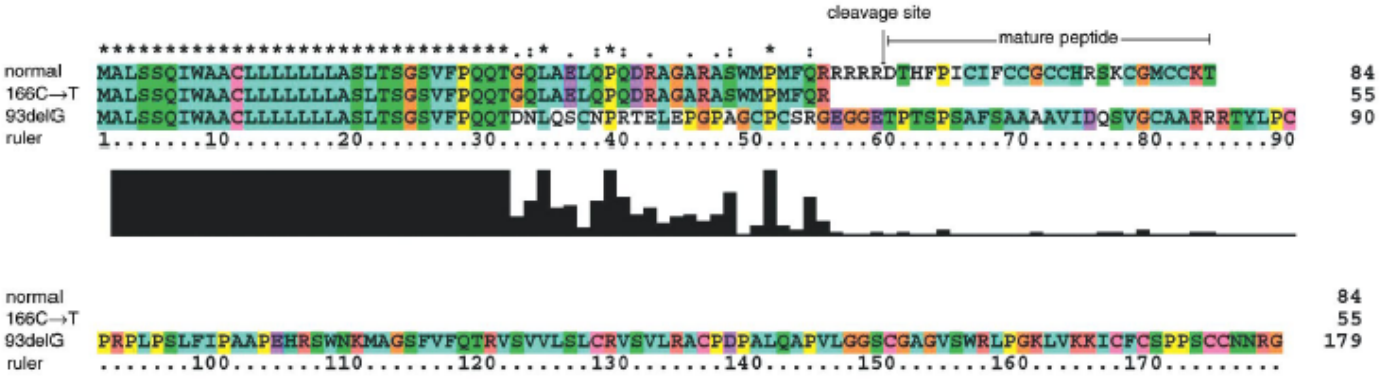
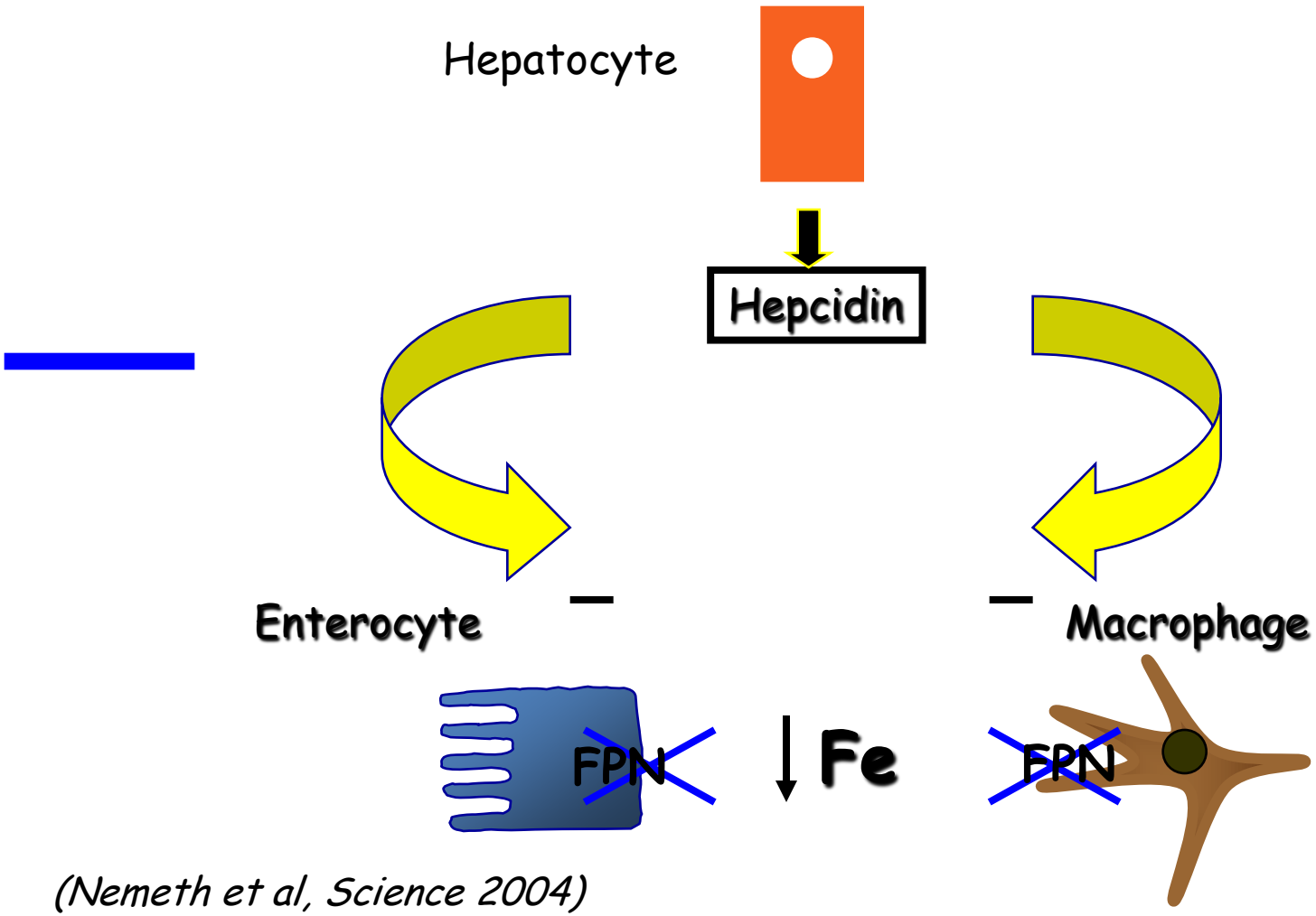


Fig. 2 Comparison of the predicted mutant peptides resulting from the 93delG and 166C→T mutations with normal pro-hepcidin.

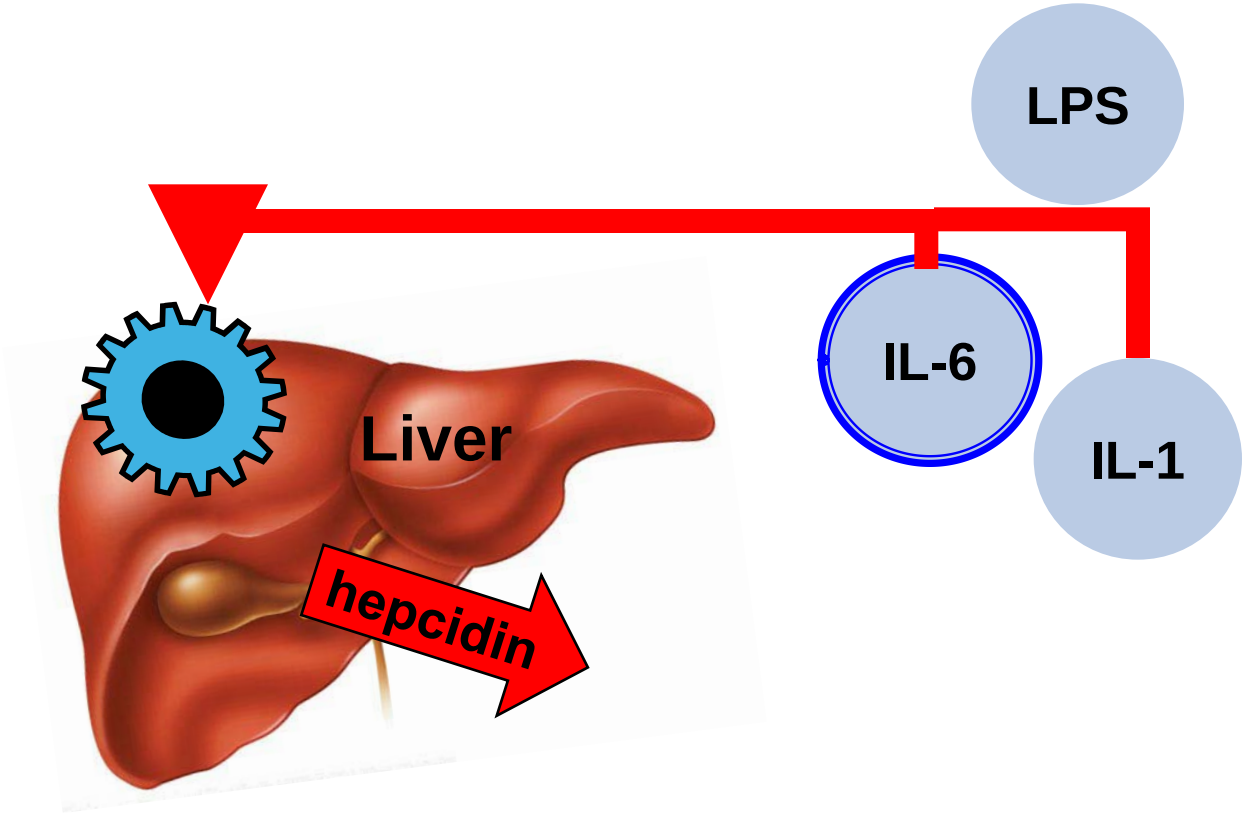
Roetto et al Nat Genet 2003

Hepcidin: a key iron regulator

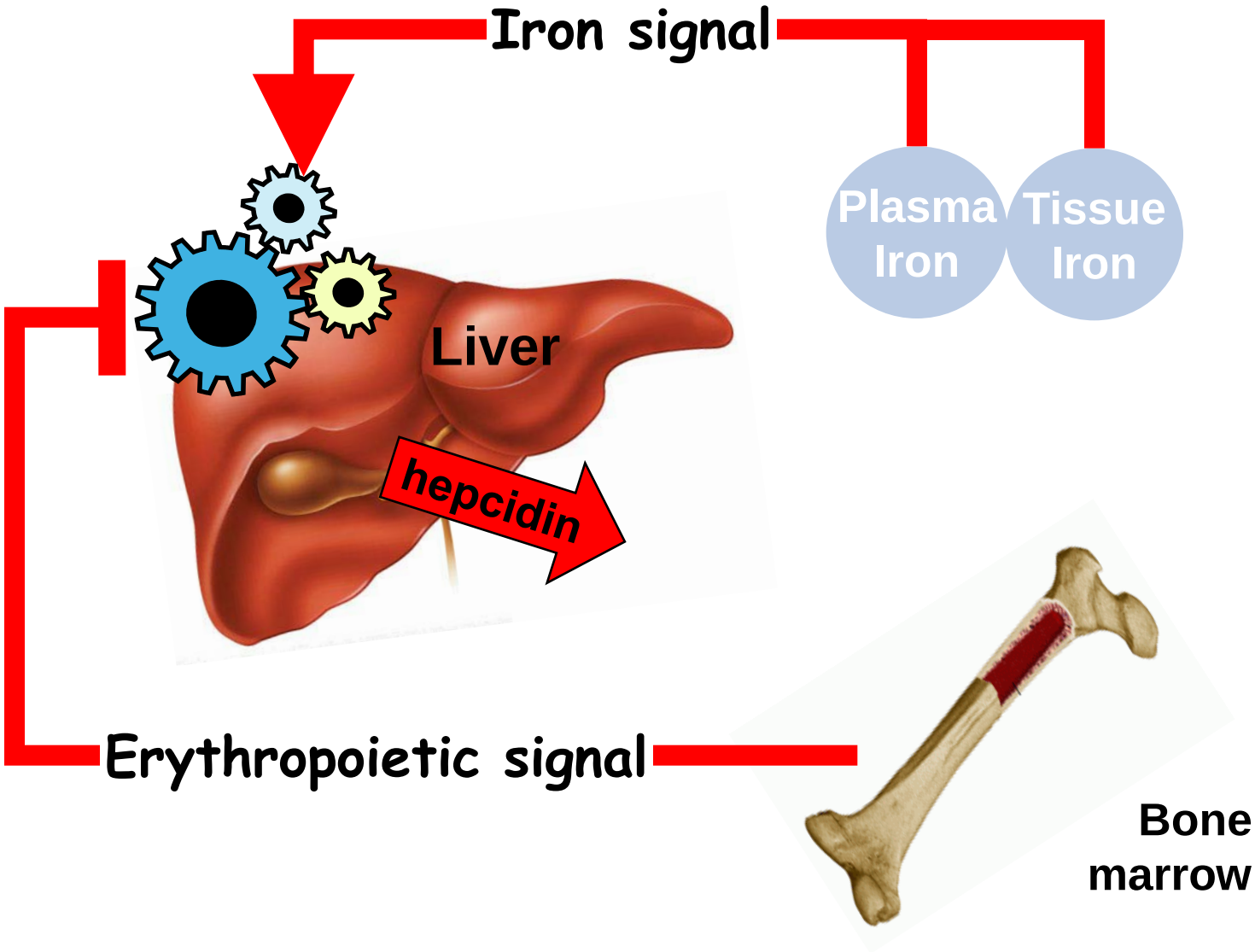


(Nemeth et al, Science 2004)

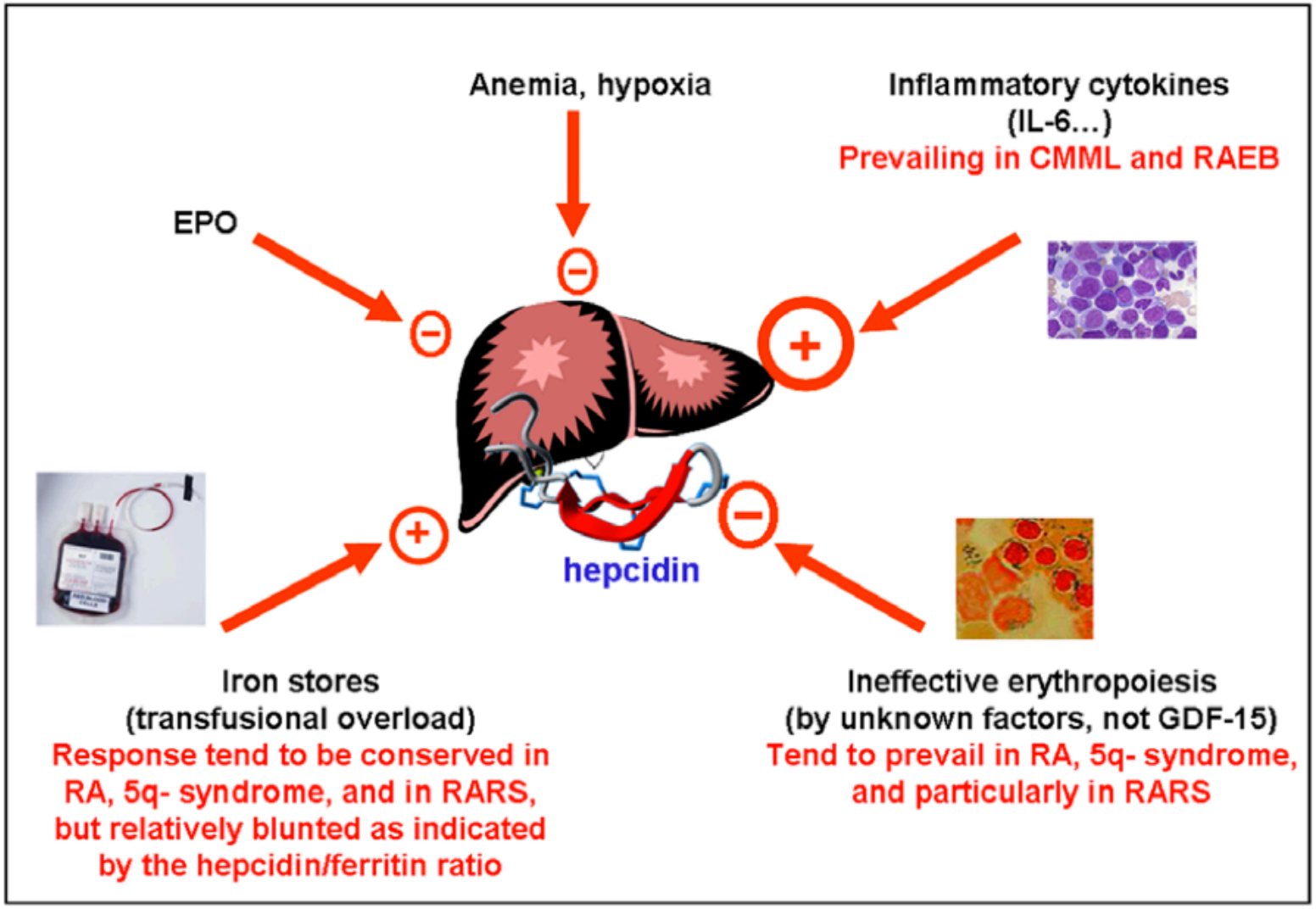
HEPCIDIN REGULATION BY INFLAMMATION



HEPCIDIN REGULATION BY ANEMIA



Proposed mechanisms controlling hepcidin production in different MDS types



Santini et al. (2011) PLoS ONE 6(8): e23109. doi:10.1371

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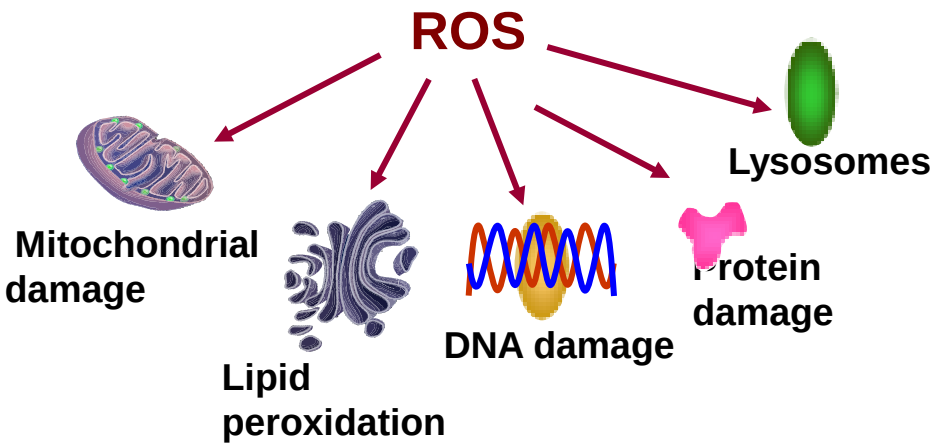

The dark side of iron

ROS, oxidative stress

NTBI, LPI

Iron overload

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Or, more commonly:

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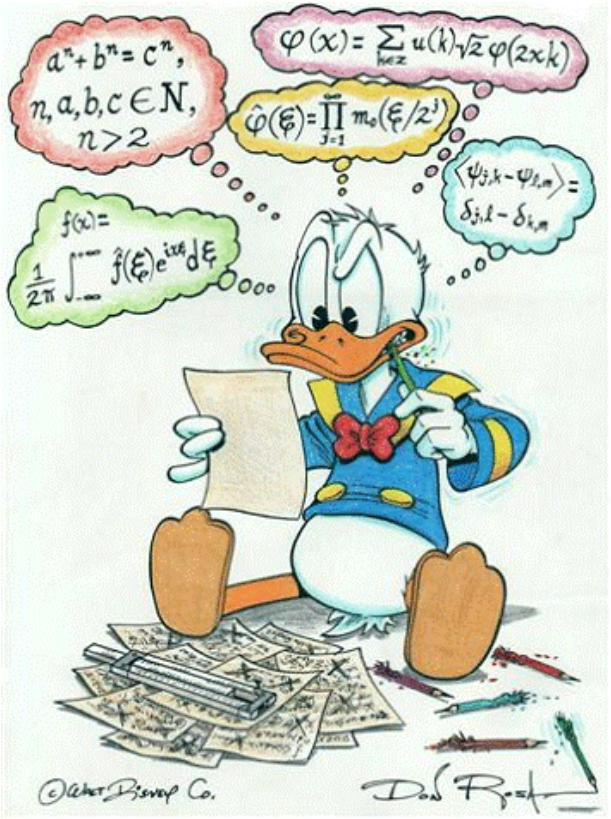
Iron toxicity depends on many factors in addition to the level of iron per se

Coates TD. Free Radic Biol Med 2014

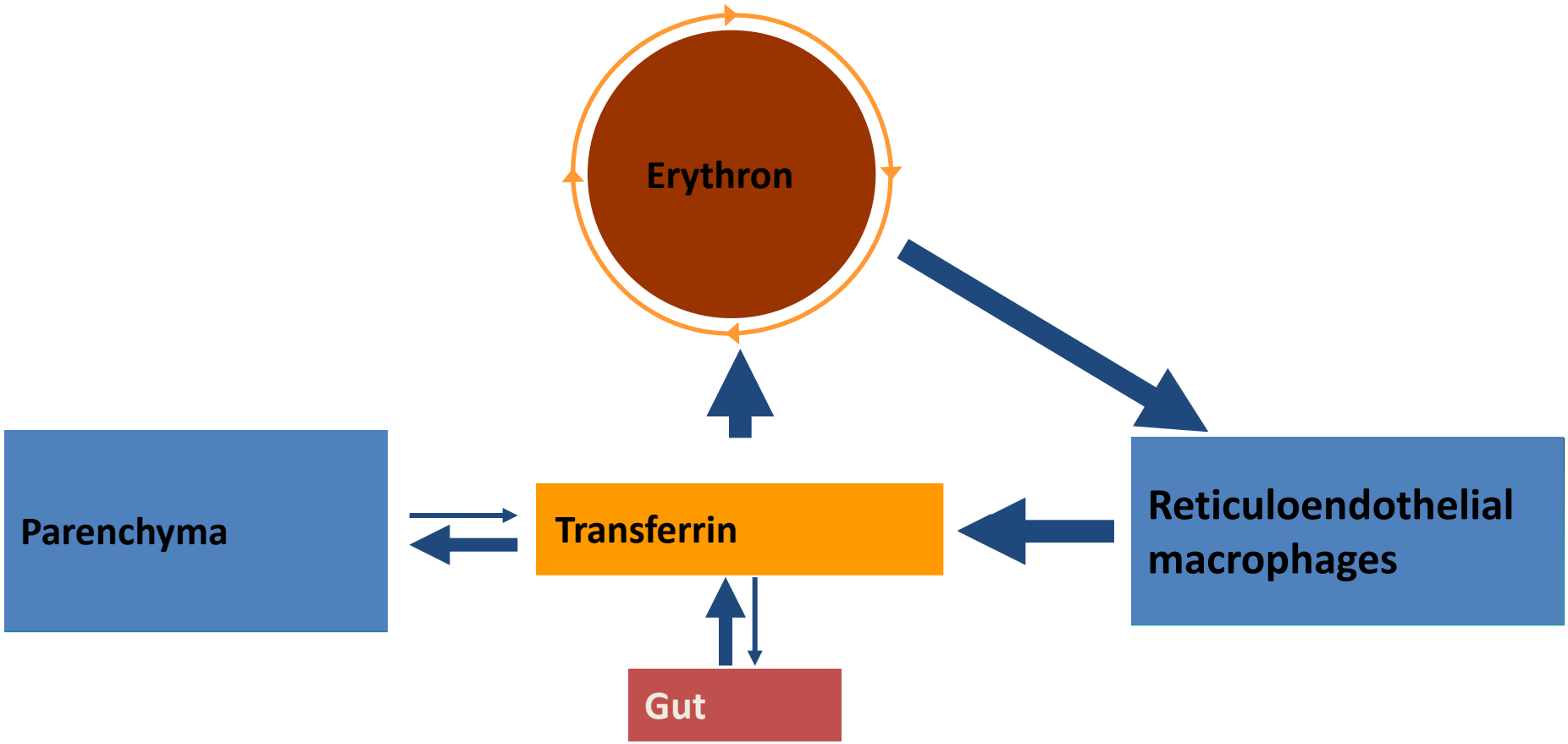


Fe Toxicity tissue =

Σ Tissue Reactive Iron **x** Genetics **x** Environmental Factors **x** Time

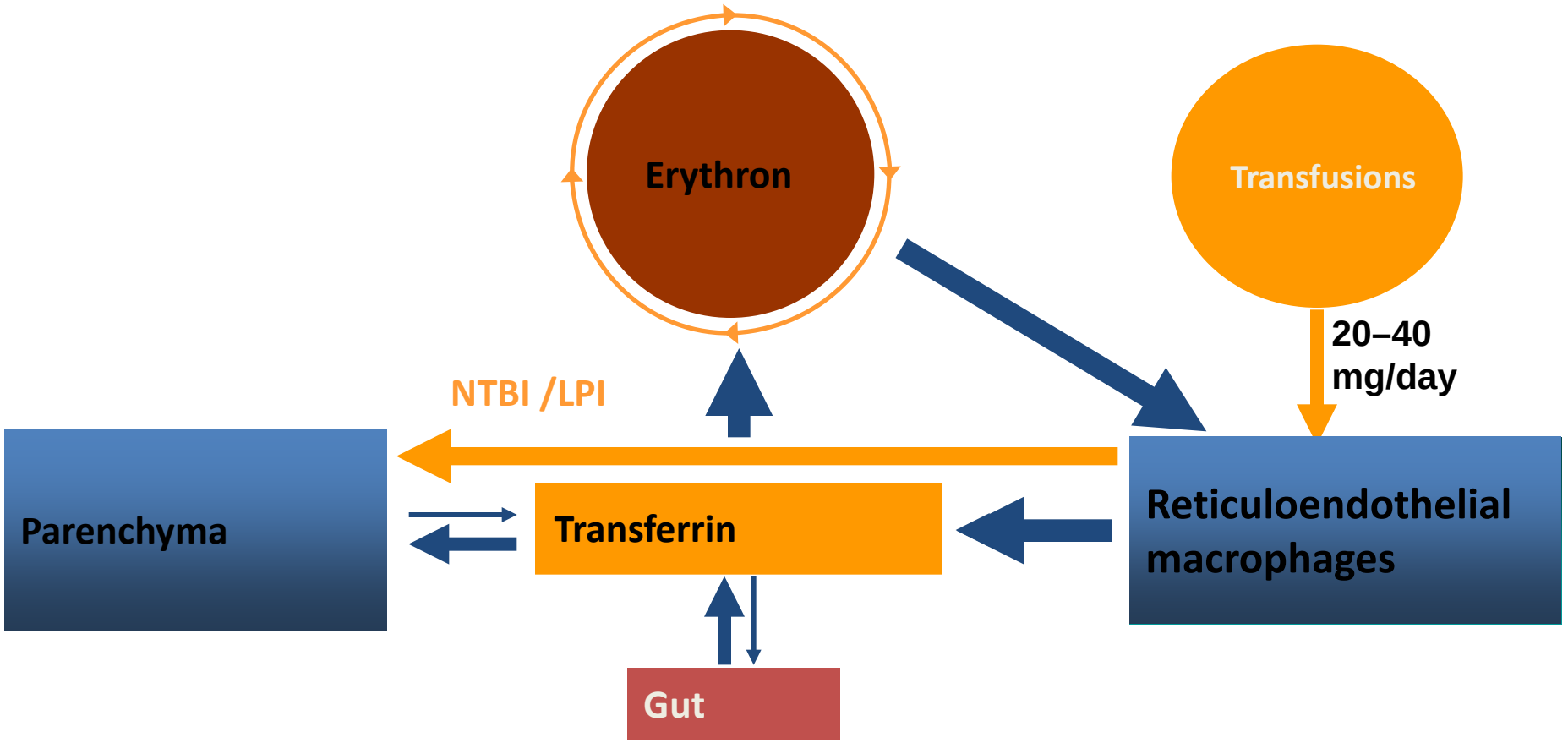
Coates TD. Free Radic Biol Med 2014

Iron Distribution and Turnover



Hershko C, et al. *Ann NY Acad Sci*. 1998;850:191-201.

Imbalance of Distribution and Turnover of Body Iron With Transfusion Therapy



Iron balance is disturbed by blood transfusion because the body cannot remove the excess iron

NTBI=non–transferrin-bound iron.

Hershko C, et al. *Ann NY Acad Sci*. 1998;850:191-201.

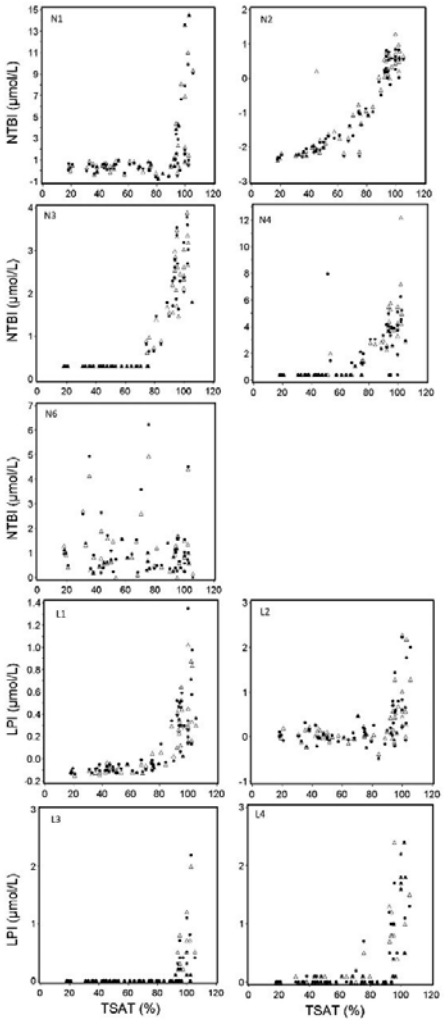
Relationship between the assay concentrations and transferrin saturation (TSAT).

EUROPEAN HEMATOLOGY ASSOCIATION
Ferrata Storti Foundation

Haematologica 2016
Volume 101(1):38-45

Second international round robin for the quantification of serum non-transferrin-bound iron and labile plasma iron in patients with iron-overload disorders

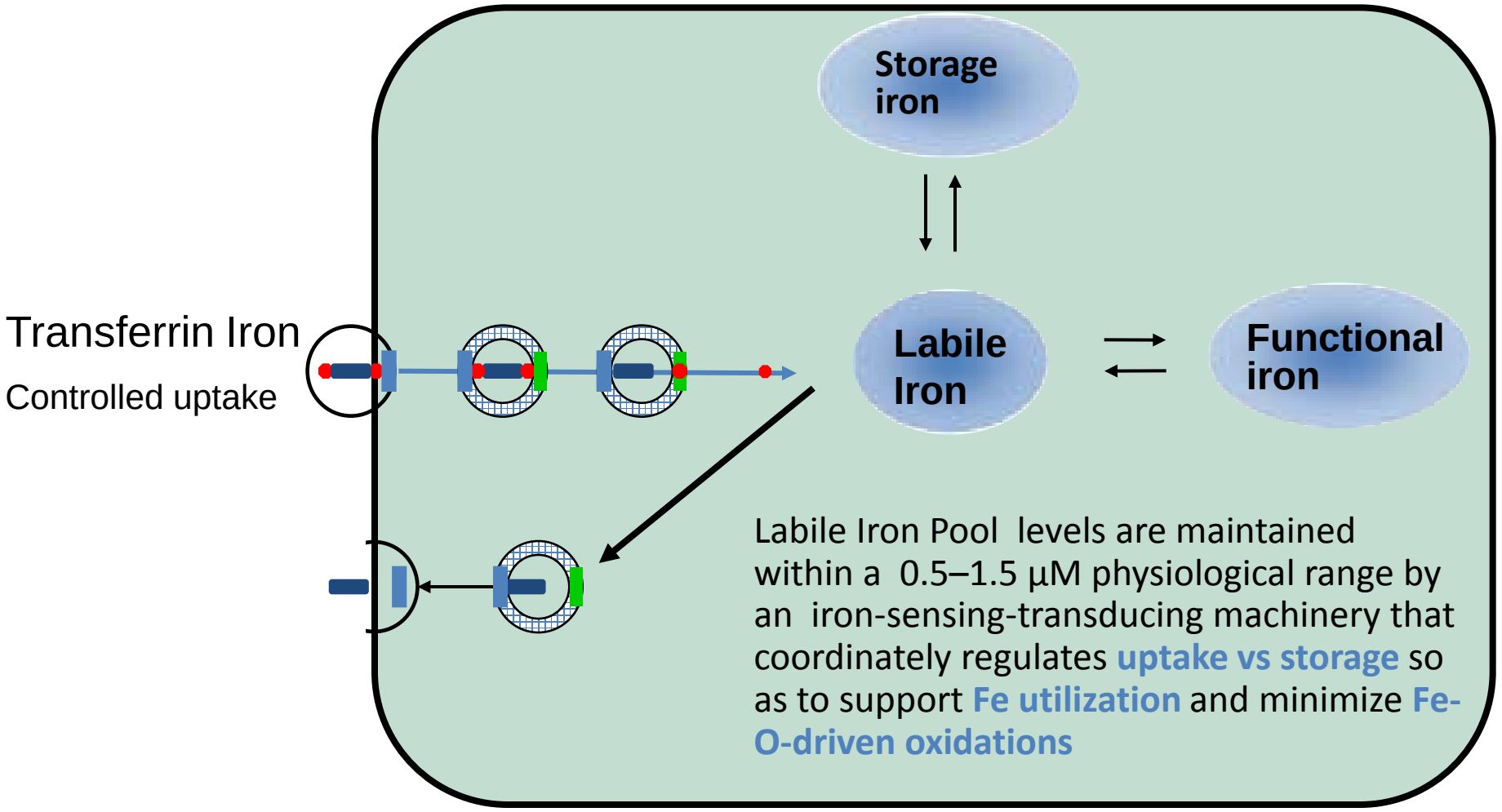
Louise de Swart,[1] Jan C.M. Hendriks,[2] Lisa N. van der Vorm,[3] Z. Ioav Cabantchik,[4] Patricia J. Evans,[5] Eldad A. Hod,[6] Gary M. Brittenham,[7] Yael Furman,[8] Boguslaw Wojczyk,[6] Mirian C.H. Janssen,[9] John B. Porter,[5] Vera E.J.M. Mattijssen,[10] Bart J. Biemond,[11] Marius A. MacKenzie,[1] Raffaella Origa,[12] Renzo Galanello,[12*] Robert C. Hider,[13] and Dorine W. Swinkels[3]



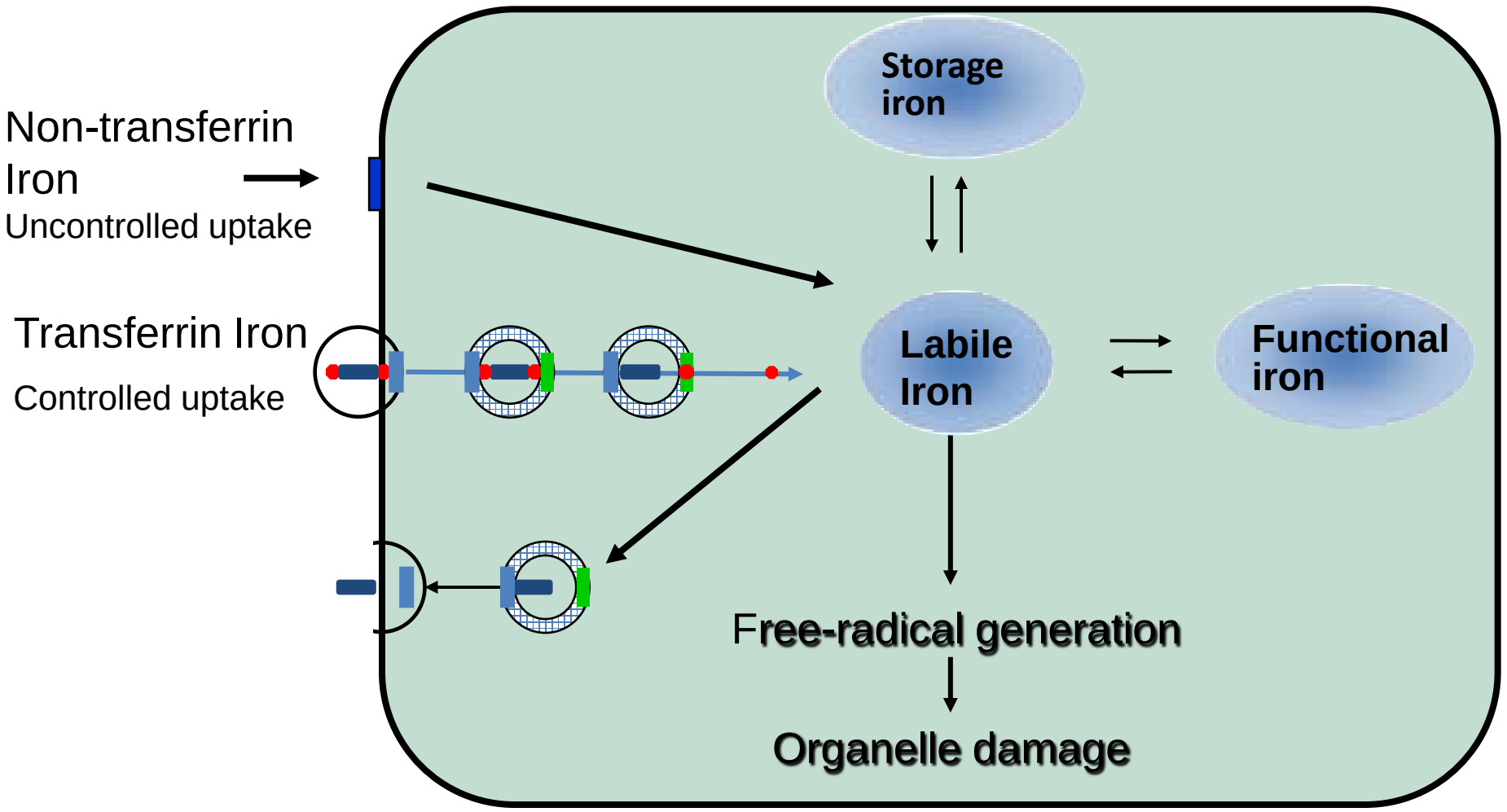
Louise de Swart et al. Haematologica 2016;101:38-45

haematologica
the hematology journal

Uncontrolled Uptake of Labile Iron Leads to Cell and Organ



Uncontrolled Uptake of Labile Iron Leads to Cell and Organ



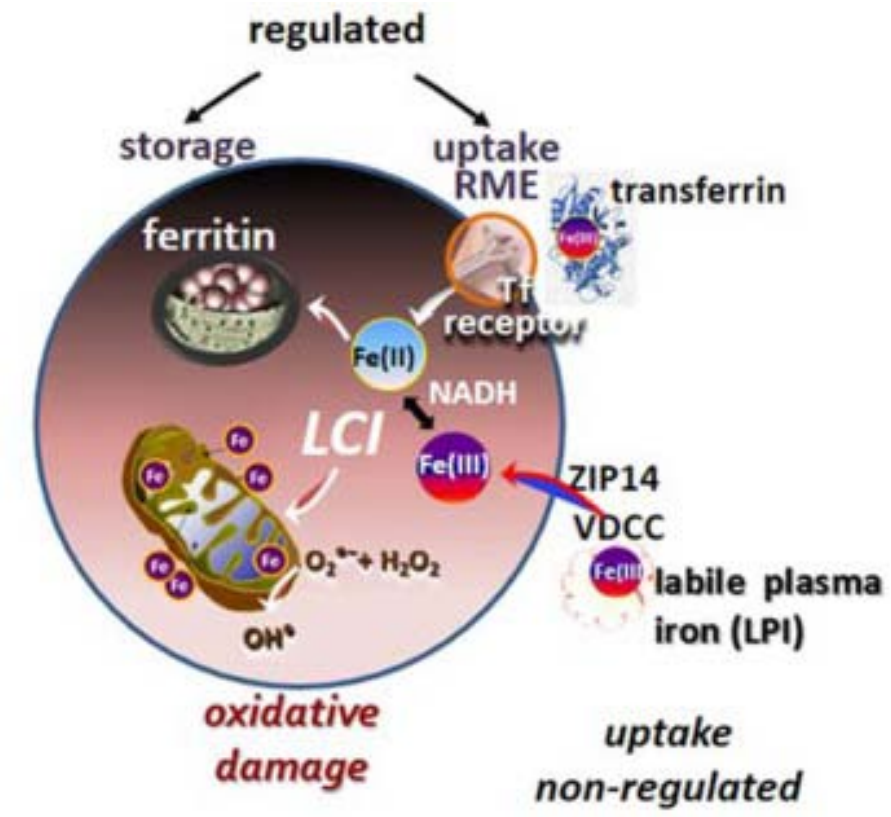
Uncontrolled Uptake of Labile Iron Leads to Cell and Organ

LIP rises following prolonged exposure of cells to **labile plasma iron (LPI)** or when faulty cell iron-utilizing machineries lead to maldistribution of the metal (e.g. excessive iron accumulation in mitochondria)

An excessive rise in LIP can promote the generation of reactive-O species (ROS) by reacting with respiratory O intermediates and thereby override the cellular antioxidant defences and chemically damage cell components and associated functions

The dark side of iron – NTBI and LPI

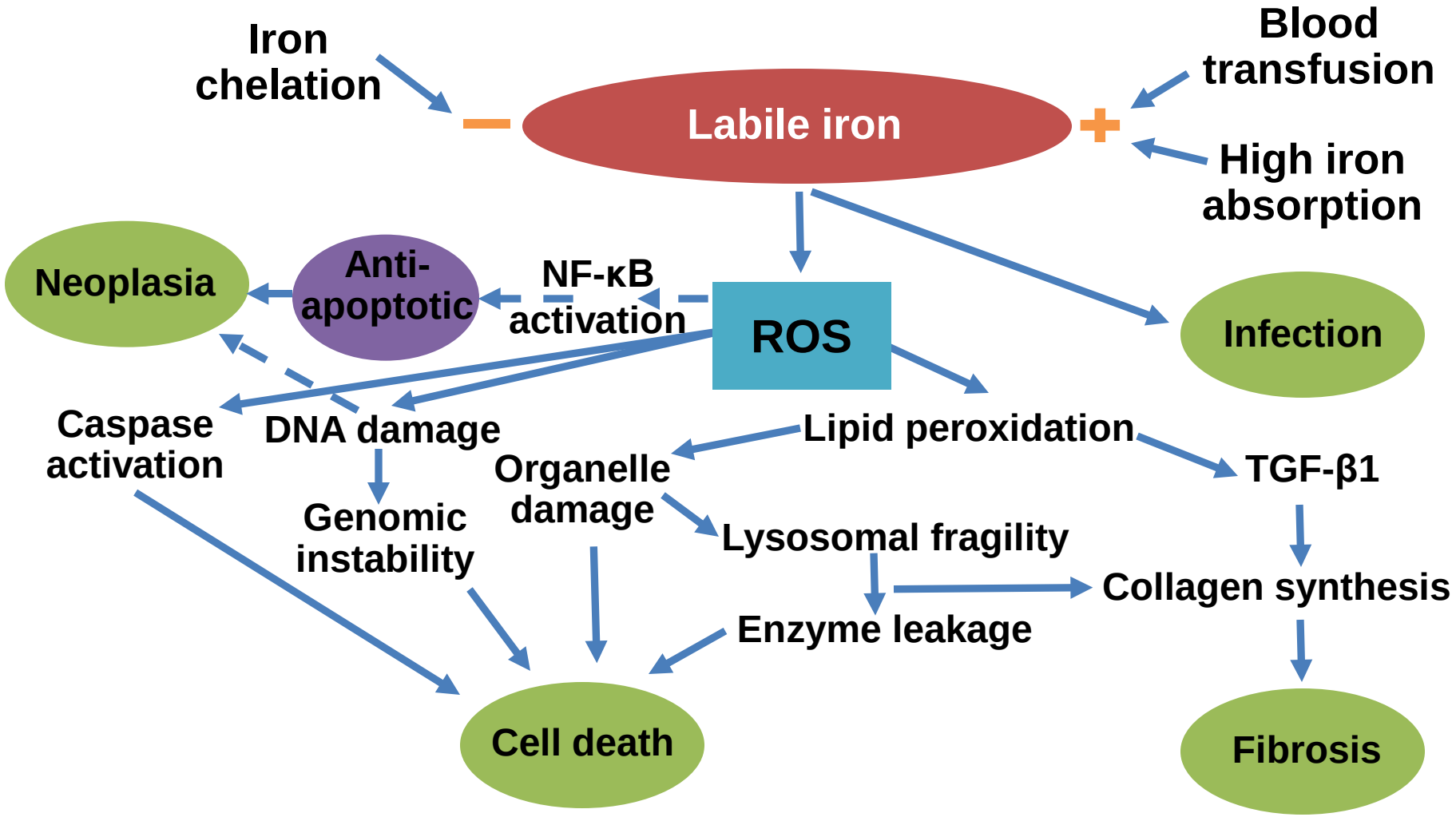
- The labile iron pool (LIP, LCI) - redox active, exchangeable and chelatable
- LIP levels are maintained within a 0.5–1.5 µM physiological range by an iron-sensing-transducing machinery that coordinately regulates **uptake vs storage** so as to support **Fe utilization** and minimize **Fe-O-driven oxidations**
- LIP rises following prolonged exposure of cells to **labile plasma iron (LPI)** or when faulty cell iron-utilizing machineries lead to maldistribution of the metal (e.g. excessive iron accumulation in mitochondria)
- An excessive rise in LIP can promote the generation of reactive-O species (ROS) by reacting with respiratory O intermediates and thereby override the cellular antioxidant defences and chemically damage cell components and associated functions



LIP, labile iron pool.

Cabantchik ZI. Front Pharmacol. 2014;5:45.

Pathological mechanisms and consequences of iron overload

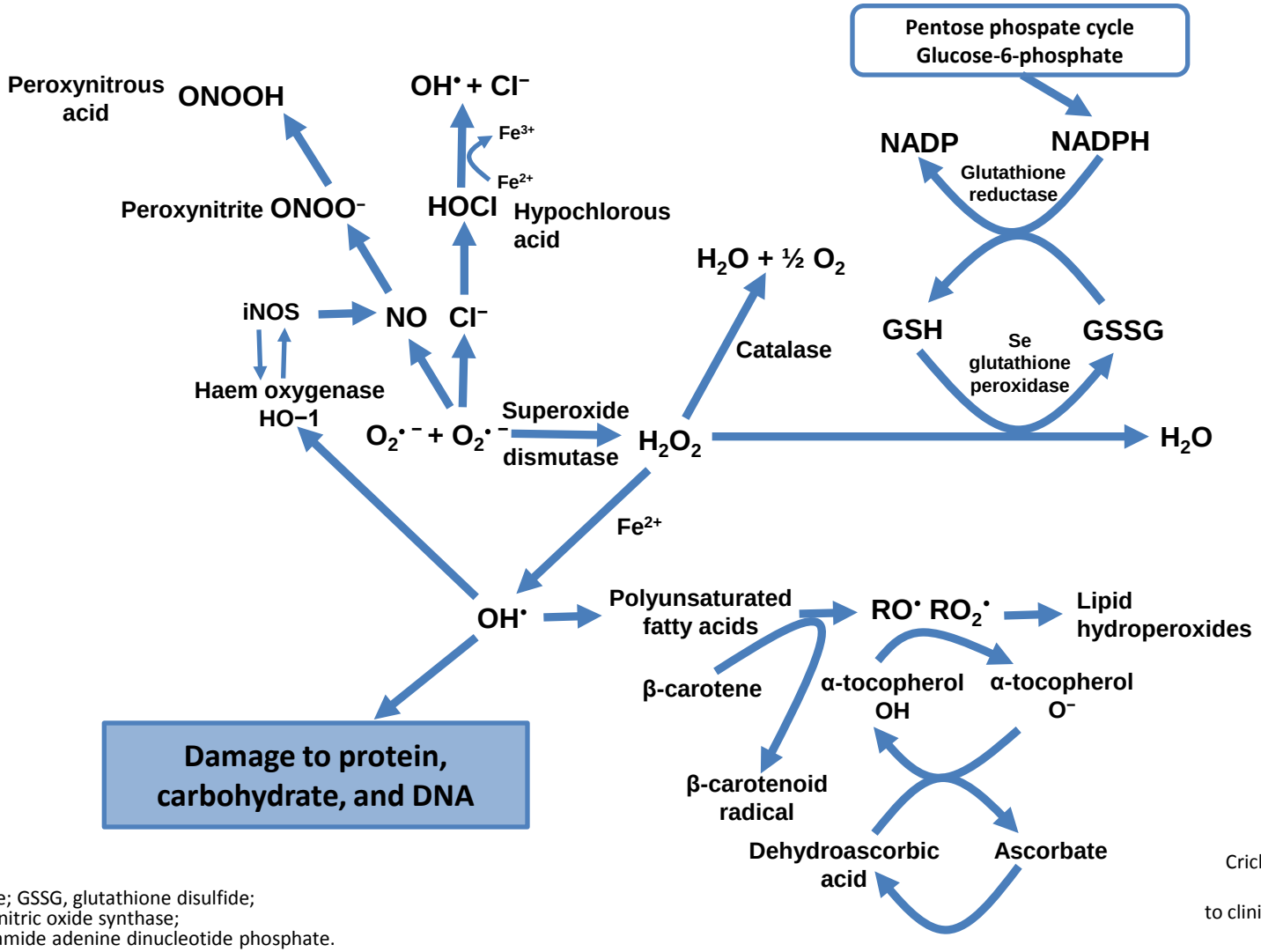


NF-κB, nuclear factor-κB;
TGF, transforming growth factor.

Porter JB, Garbowski M. Hematol Oncol Clin North Am. 2014;28:683-701.

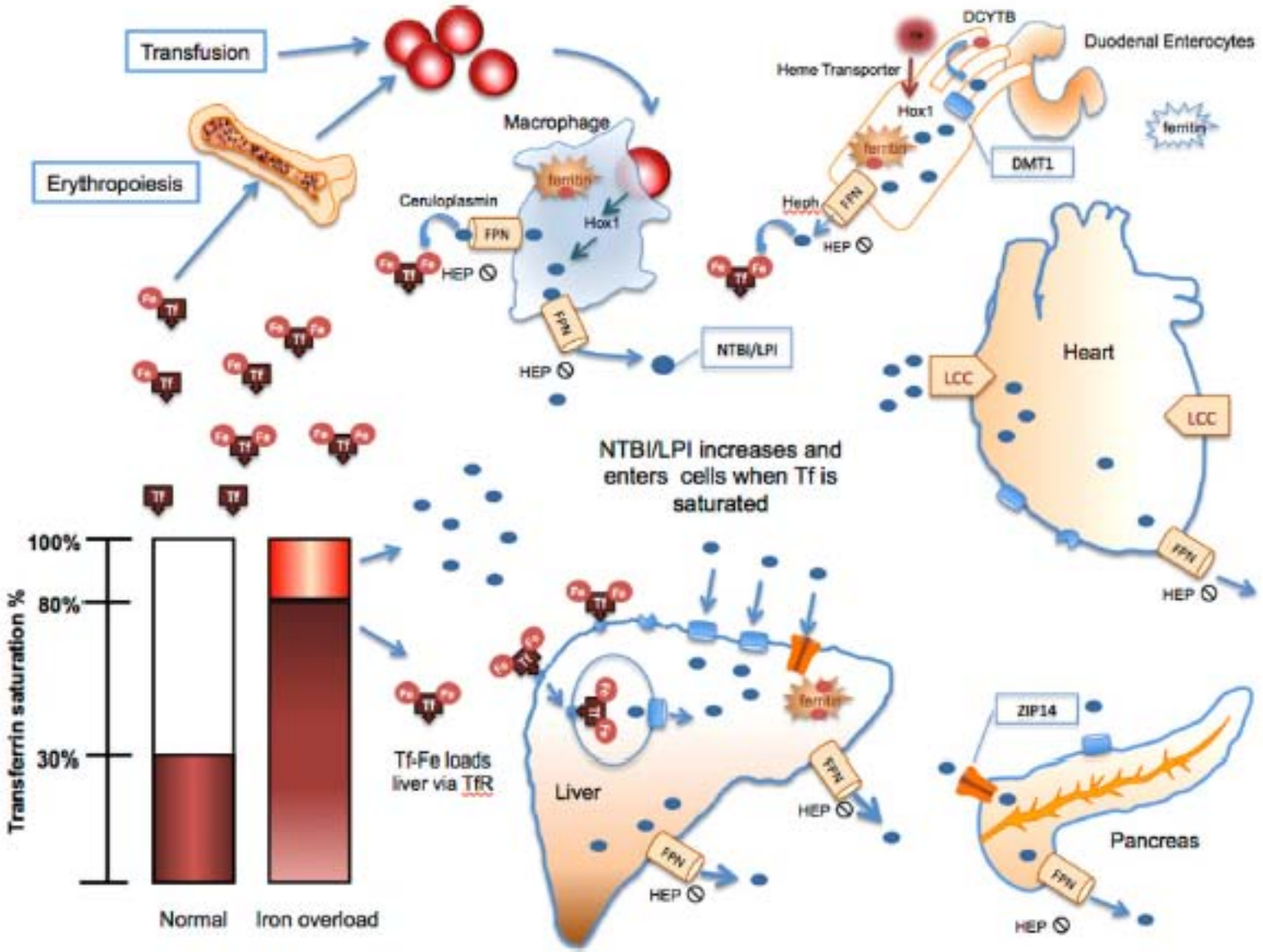
The dark side of iron: ROS and oxidative stress

The battlefield of oxidative stress



GSH, glutathione; GSSG, glutathione disulfide;
iNOS, inducible nitric oxide synthase;
NADPH, nicotinamide adenine dinucleotide phosphate.

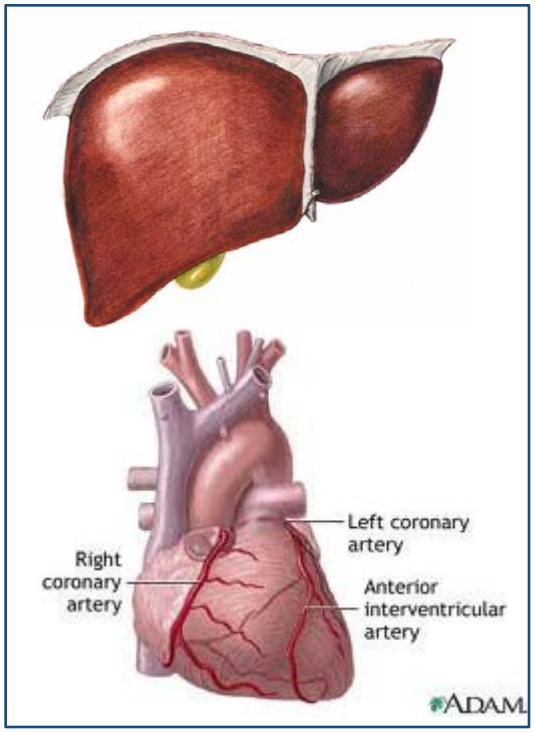
Crichton R. Iron metabolism: from molecular mechanisms to clinical consequences. Chichester: Wiley; 2009.


Transfusion
Erythropoiesis
Macrophage
ferritin
Hox1
Ceruloplasmin
FPN
HEP
NTBI/LPI
DCYTB
Duodenal Enterocytes
Heme Transporter
DMT1
Heph
Heart
LCC
NTBI/LPI increases and enters cells when Tf is saturated
Transferrin saturation %
100%
80%
30%
Normal
Iron overload
Tf-Fe loads liver via TfR
Liver
ZIP14
Pancreas

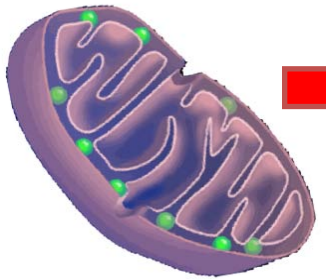
- ...pituitary, pancreatic and cardiac iron detected by MRI reflects **time-averaged exposure to toxic reactive iron** since loading of these organs essentially only occurs when NTBI/LPI enters through ion channels and transporters.

Coates, Carson Wood & Berdoukas. Management of Iron Overload in Hemoglobinopathies: What is the 1 Appropriate Target 2 Iron Level?. Annals of the New York Academy of Sciences 2016

Why does iron toxicity mainly affect heart and liver?



High levels of mitochondrial activity



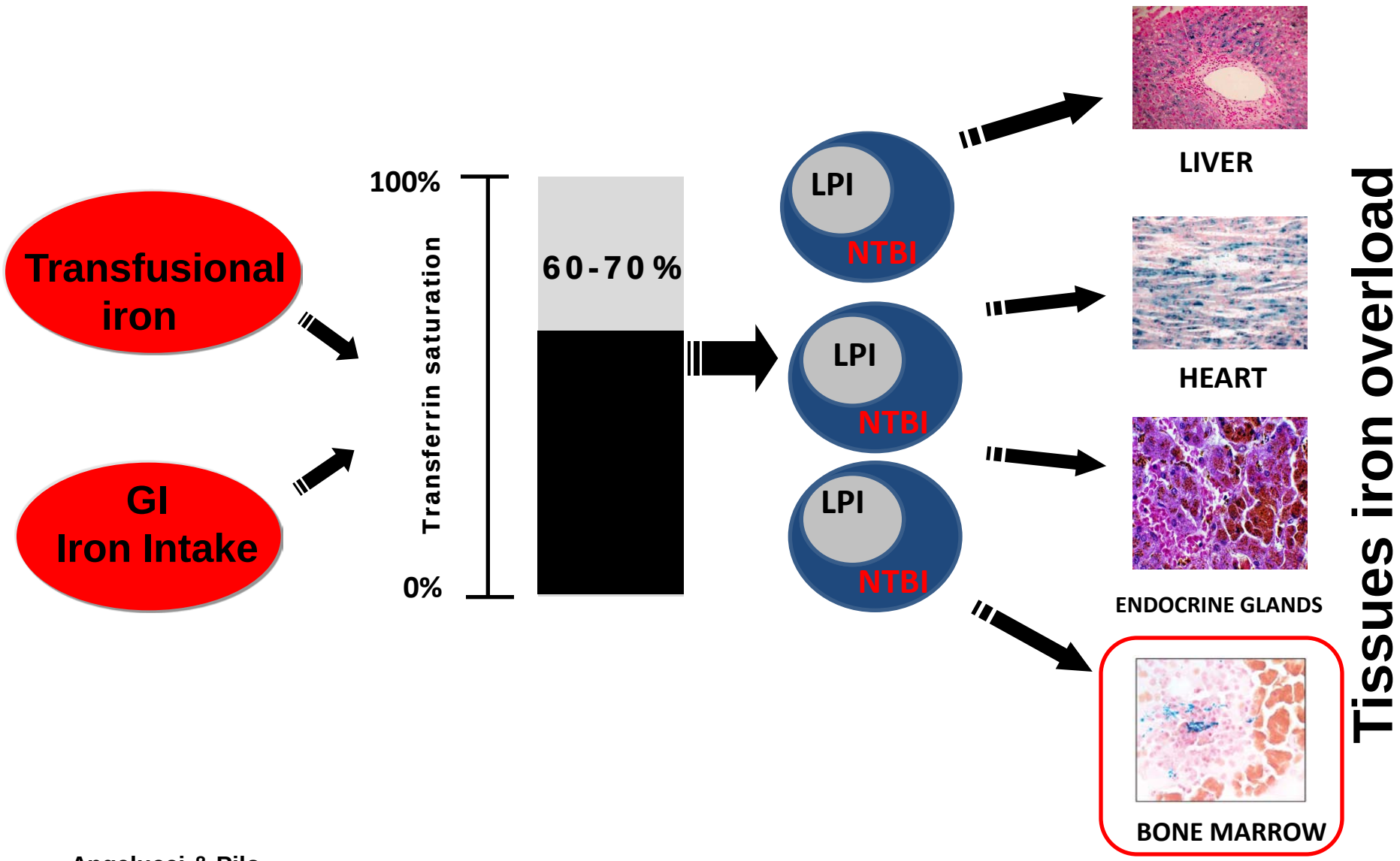
ROS production

Tissue damage

Fe Toxicity tissue =

$$\sum \text{Tissue Reactive Iron} \times \text{Genetics} \times \text{Environmental Factors} \times \text{Time}$$

Coates TD. Free Radic Biol Med 2014



Angelucci & Pilo
Ann N Y Acad Sci. 2016 Mar;1368(1):115-21

Research Article

Uptake of Non-Transferrin Iron by Erythroid Cells

Eugenia Prus and Eitan Fibach

Department of Hematology, Hadassah-Hebrew University Medical Center, Ein-Kerem, P.O. Box 12000, Jerusalem 91120, Israel

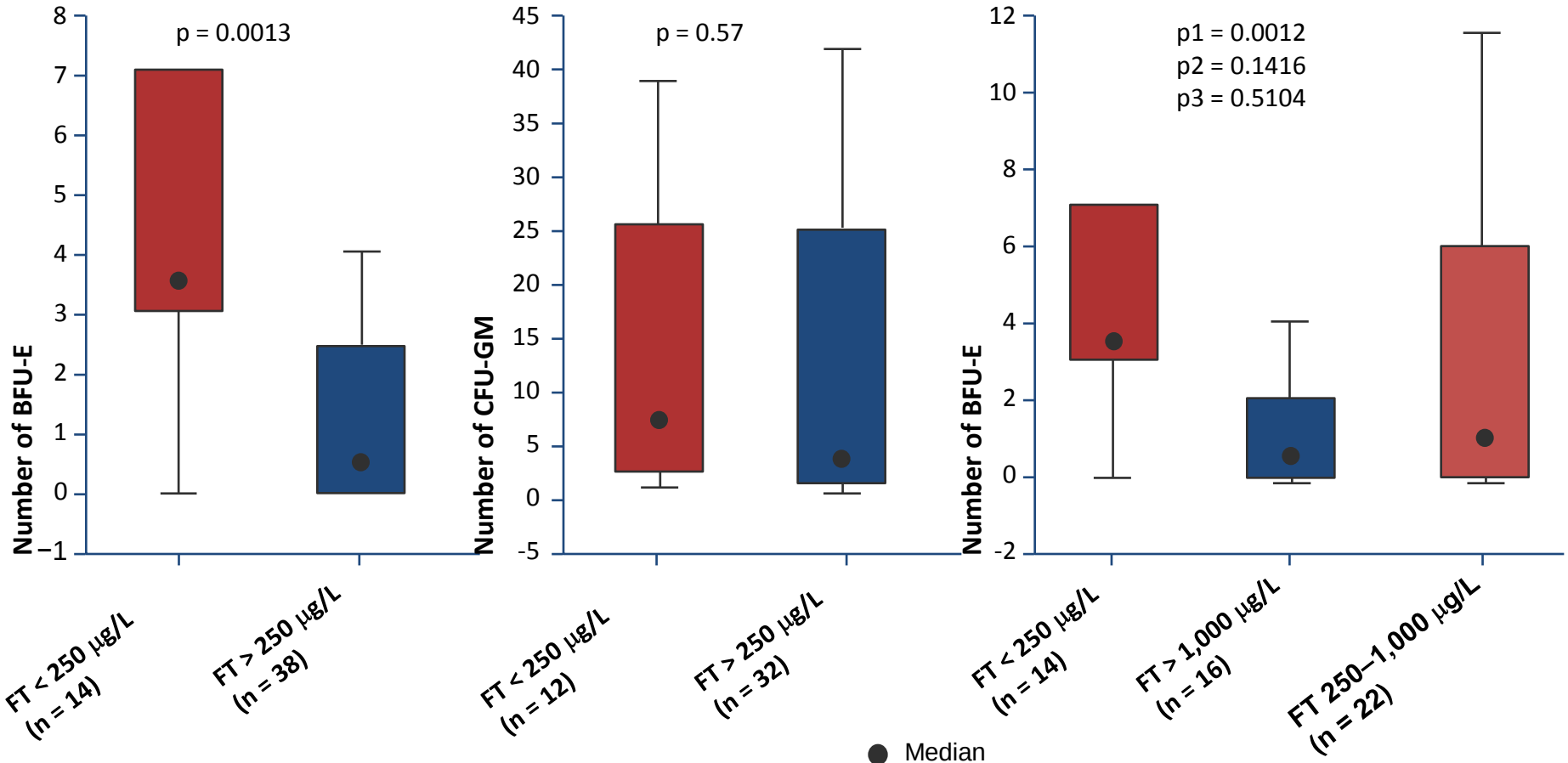
Correspondence should be addressed to Eitan Fibach, fibach@yahoo.com

Received 20 September 2010; Accepted 7 November 2010

- RBCs, retics, and developing erythroid precursors take up iron through a Tf-independent pathway.
- This pathway is operative under pathological iron-overload situation in the presence of non-Tf iron in the serum.
- The incoming non-Tf iron does not participate in haem synthesis and Hb production, but induces ROS generation, which results in cytotoxicity and a decrease in the erythroid cell yield.

Prus E, Fibach E. Anemia. 2011;2011:945289.

Proliferation of BFU-E in patients with normal and elevated serum ferritin



BFU-E, burst-forming units-erythroid; CFU-GM, colony-forming units granulocyte-macrophage; FT, ferritin.

Hartmann J, et al. Leuk Res. 2013;37:327-32.

Thank you for your very kind attention