L'ANEMIA DELLO STATO INFIAMMATORIO CRONICO

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Outline

- ✓The “Anemia of Chronic Disease” (ACD): prevalence and importance.
- ✓ACD pathogenesis (role of hepcidin).
- ✓ACD diagnosis (DD with Iron Deficiency Anemia – IDA).
- ✓Treatment (future options).

Anemia of chronic diseases (ACD)

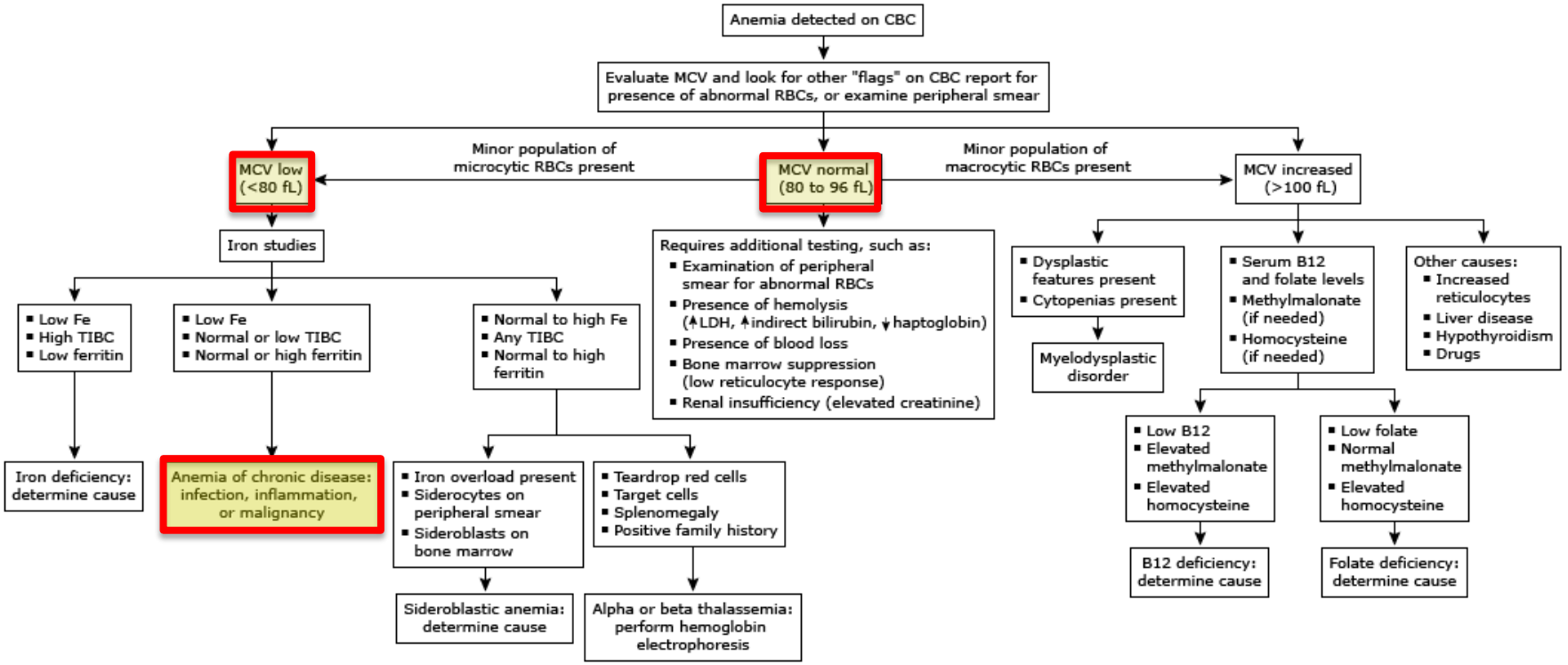
- ✓ Cytokine-driven, multifactorial condition primarily found in patients with diseases involving chronic immune activation (infections, malignancies and auto-immune disorders),
- ✓ **most frequent anemia in hospitalized patients**.
- ✓ Often neglected, aggravated by therapeutic measures (i.e. radiotherapy, chemotherapy)

Table 1. Underlying Causes of Anemia of Chronic Disease.

Associated Diseases	Estimated Prevalence*
	percent
Infections (acute and chronic)	18–95[8-10]
Viral infections, including human immunodeficiency virus infection	
Bacterial	
Parasitic	
Fungal	
Cancer†	30–77[9,12-14]
Hematologic	
Solid tumor	
Autoimmune	8–71[5,9,15,16]
Rheumatoid arthritis	
Systemic lupus erythematosus and connective-tissue diseases	
Vasculitis	
Sarcoidosis	
Inflammatory bowel disease	
Chronic rejection after solid-organ transplantation	8–70[17-19]
Chronic kidney disease and inflammation	23–50[20-22]

Weiss G, N Engl J Med 2005

Evaluation of anemia in the adult according to the mean corpuscular volume

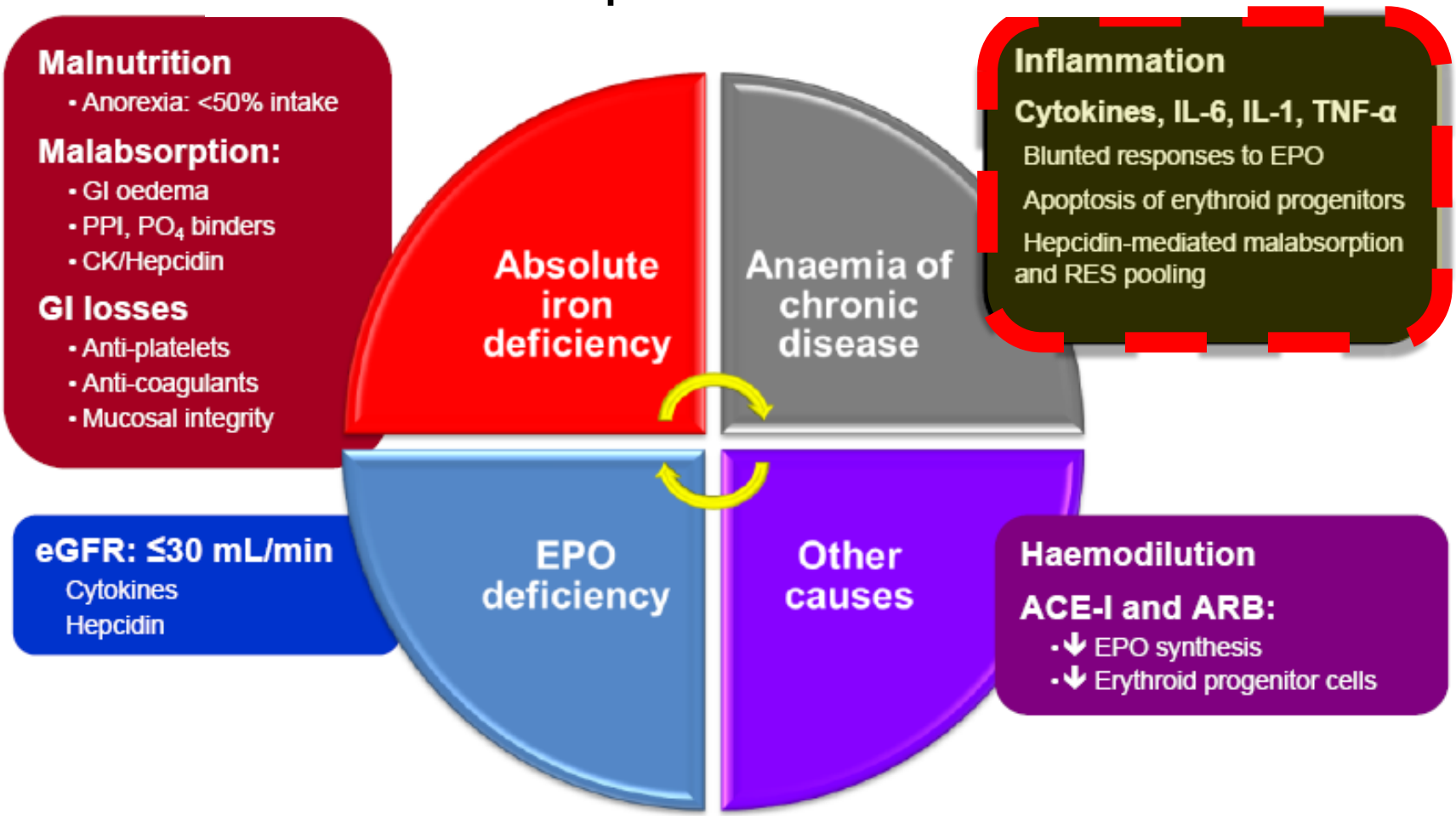


CBC: complete blood count; MCV: mean corpuscular volume; RBCs: red blood cells; Fe: iron; TIBC: total iron-binding capacity (transferrin); LDH: lactate dehydrogenase.

UpToDate®

Relevance of ACD: lesson from cardiology

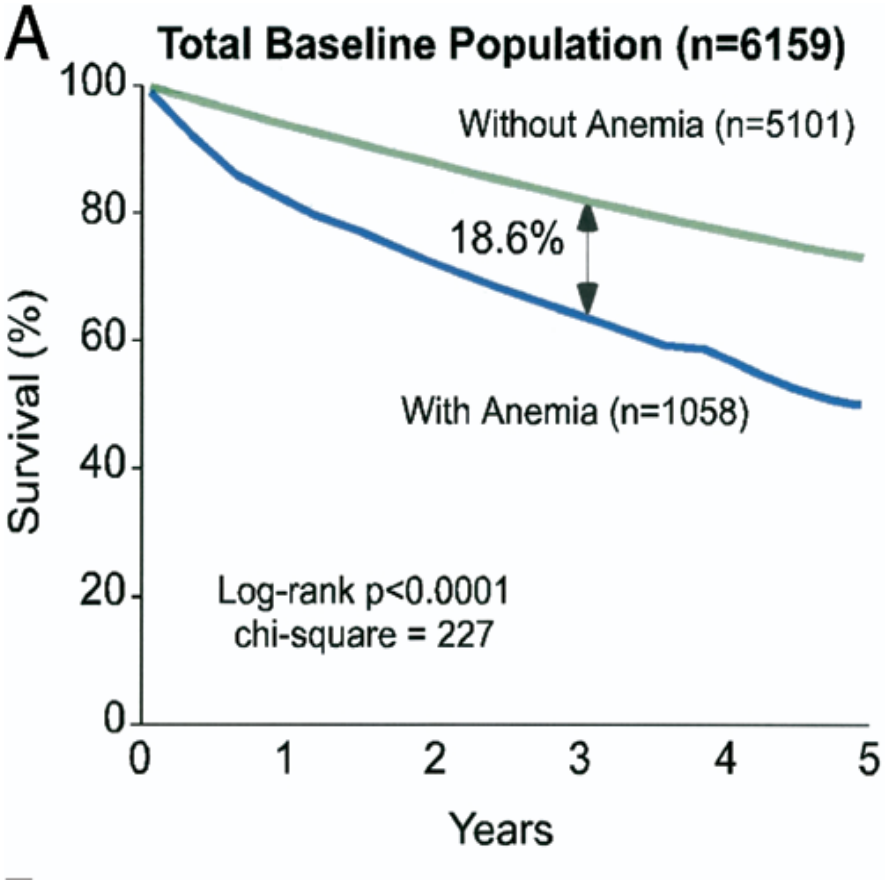
Anemia in HF: multiple concurrent mechanisms

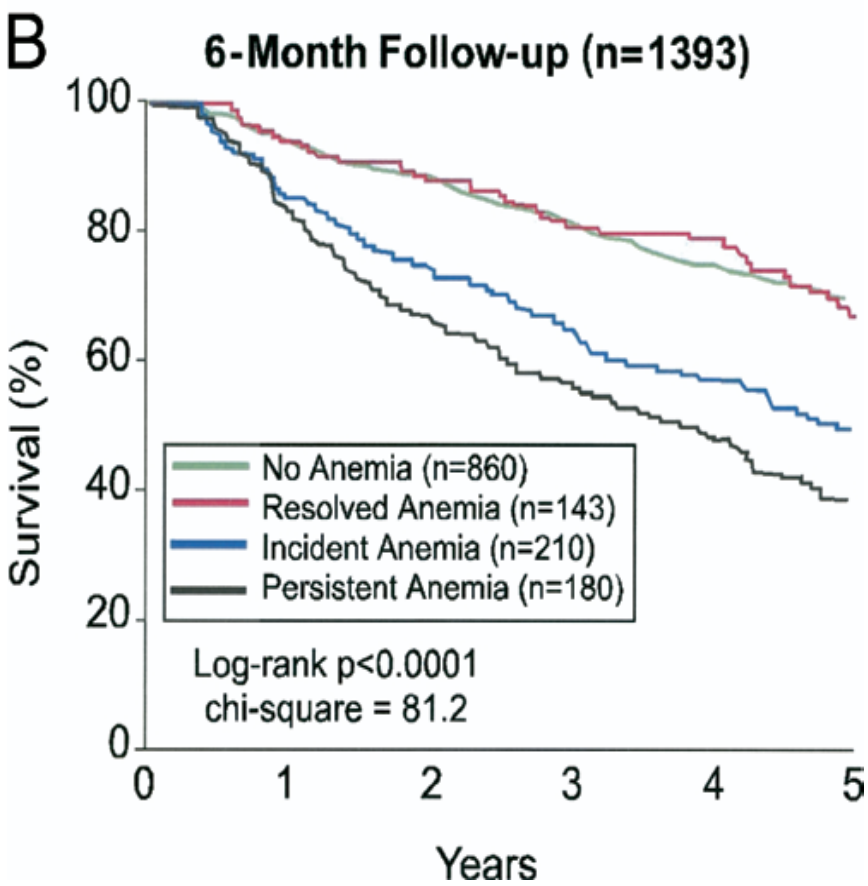


Ble A, et al. Arch Int Med 2005;165:2222–7.

Anemia (whatever the cause) is not an innocent bystander – Data on Pts. with Heart Failure

Kaplan-Meyer survival curves in ambulatory HF patients according to anemia status





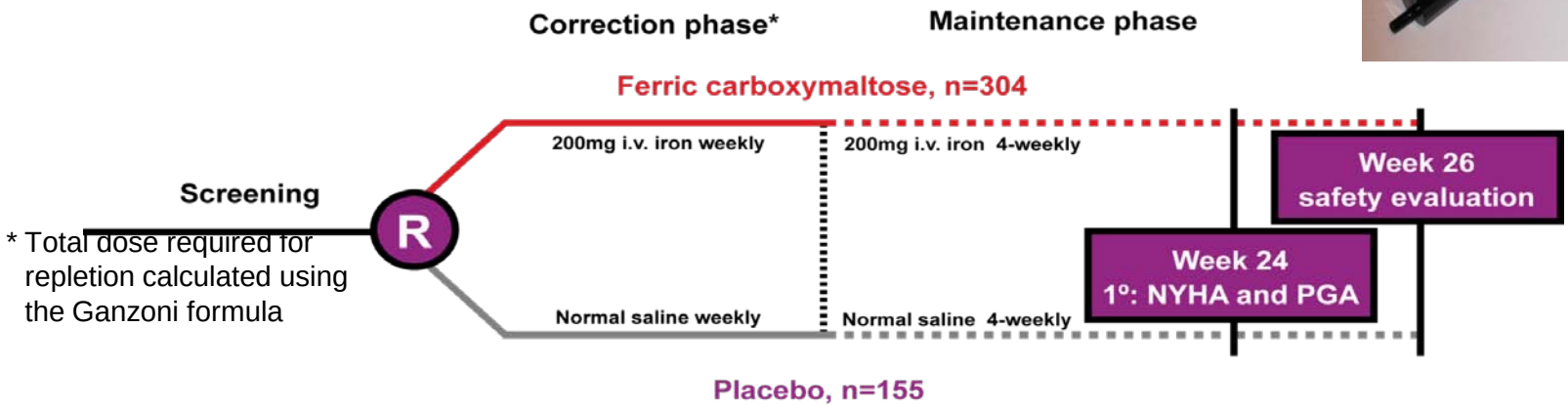
Persistent anemia significantly associated with mortality

Tang WH, J Am Coll Cardiol 2008

FAIR-HF: study design

- **Main inclusion criteria**:
  - NYHA class II/III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb: 95–135 g/L
  - Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT ≤20%

- Blinding:
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections

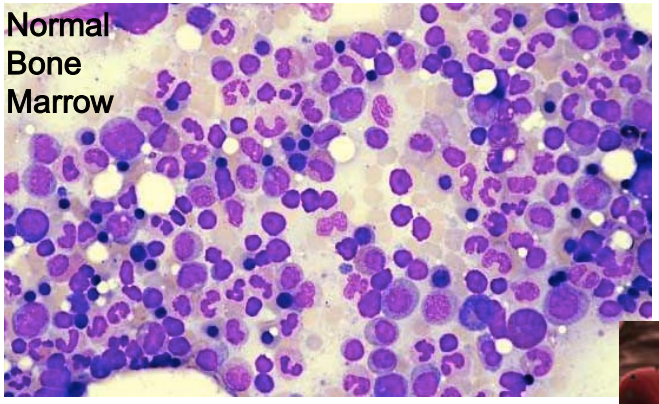


* Total dose required for repletion calculated using the Ganzoni formula

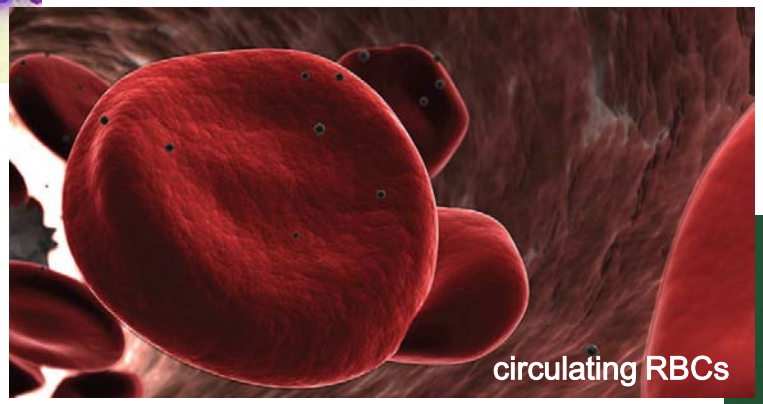
Hb, hemoglobin; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PGA, Patient Global Assessment; TSAT, transferrin saturation.

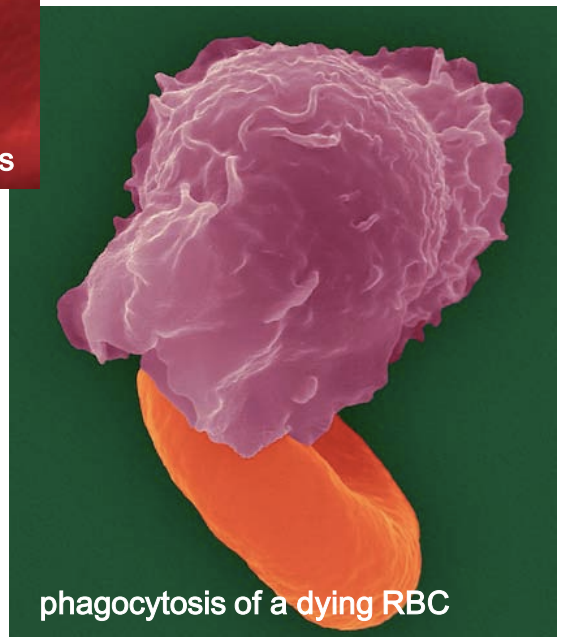
Anker SD, New Engl J Med 2009

RBCs cycle



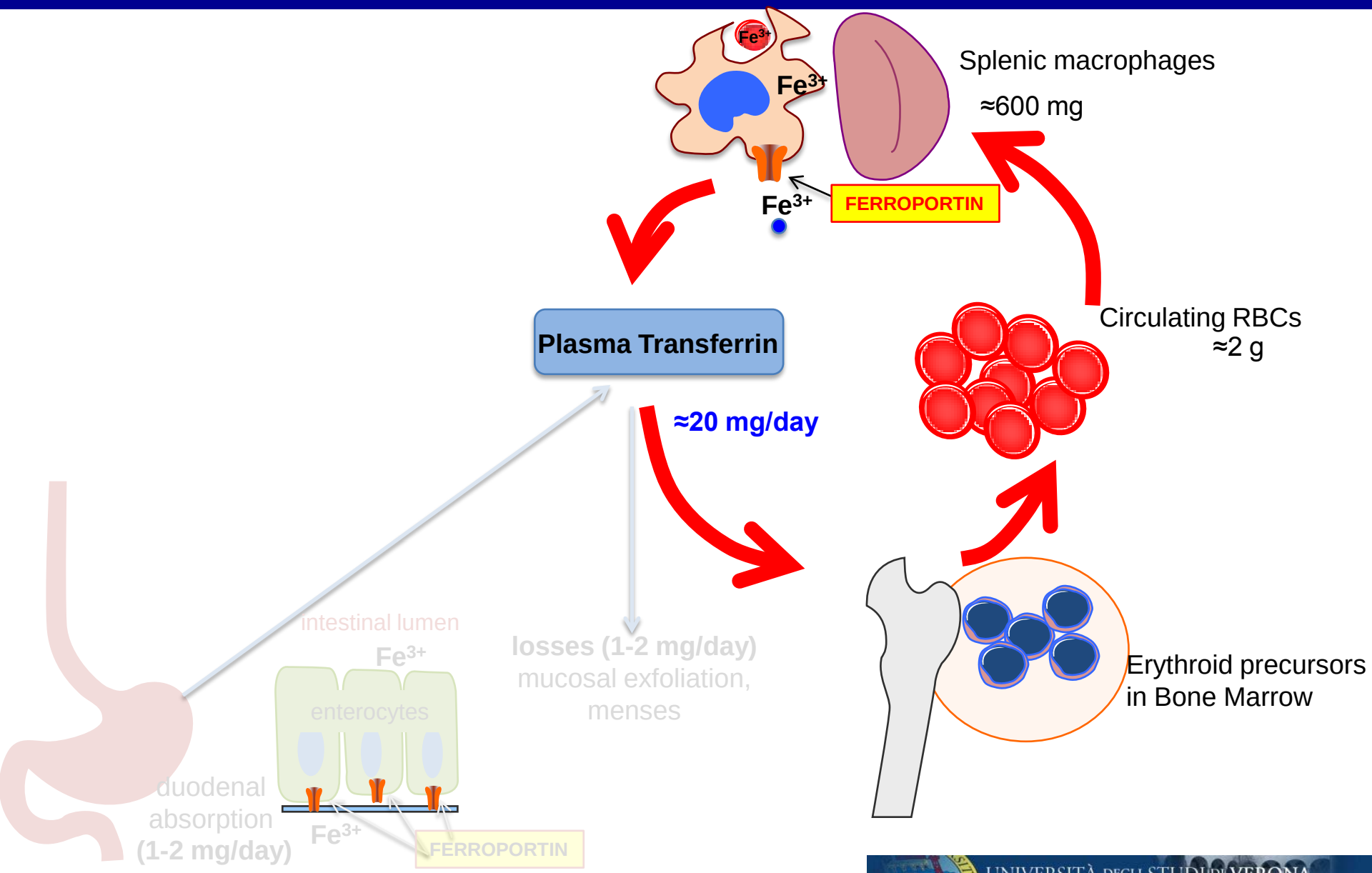
Steady-state erythropoiesis involves the production of **200 billion new RBCs/day** or **2.4 million/second**.



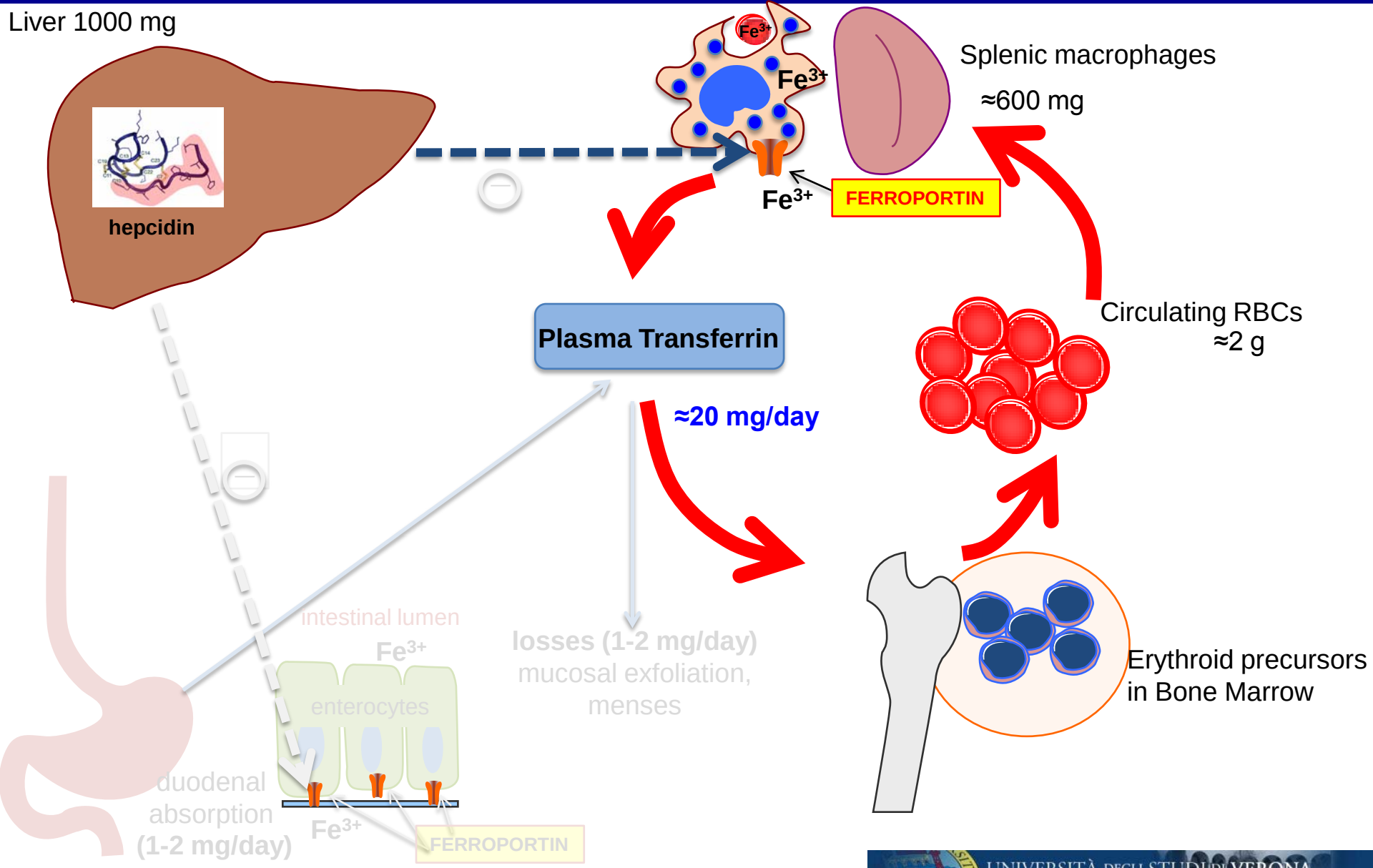


It needs **20-25 mg iron/day** in the form of holotransferrin, that derives from recycling of senescent RBCs by macrophages (**erythrophagocytosis**).

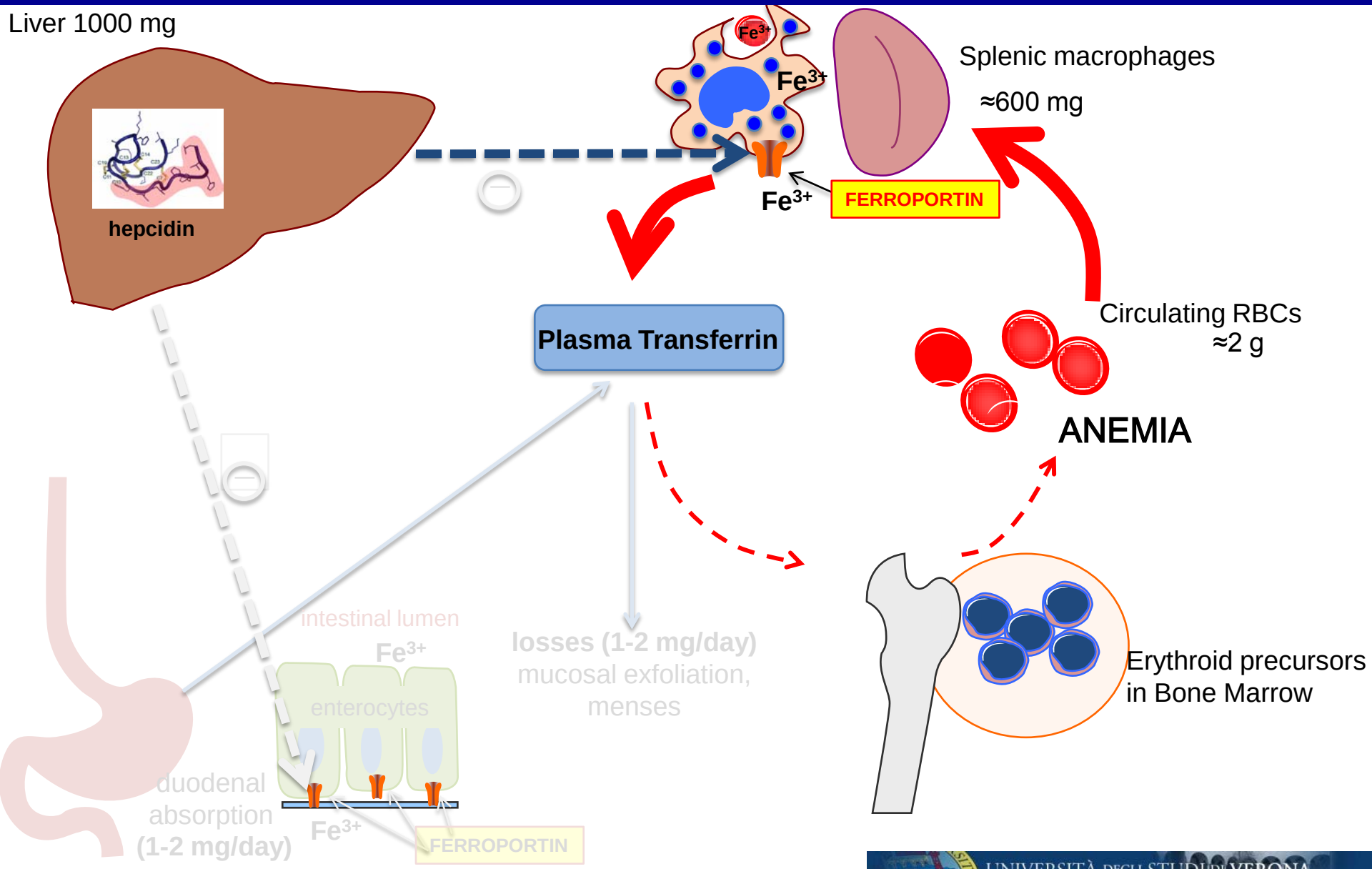
IRON "ECOLOGY"



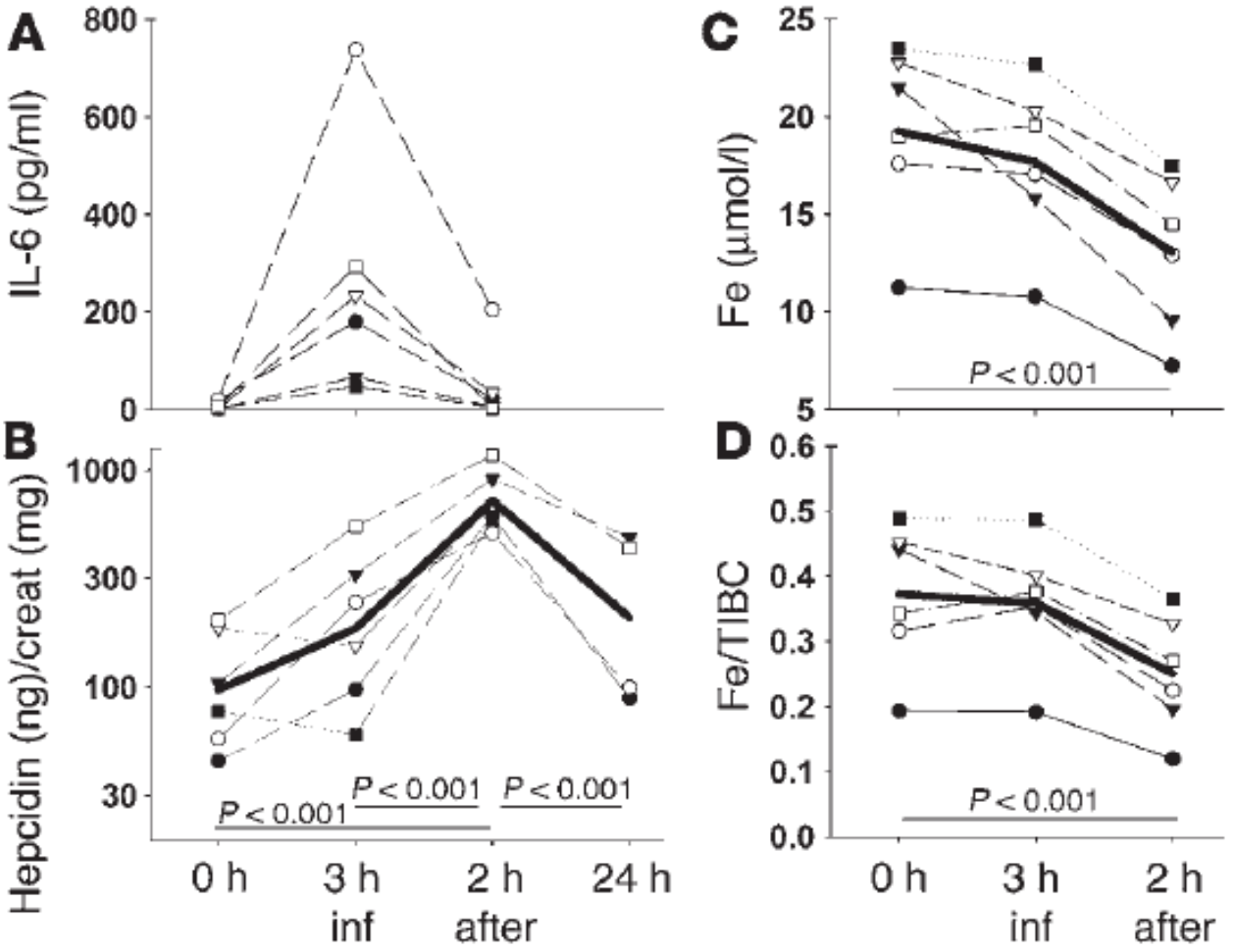
ACD pathogenesis (cytokine-driven ↑ hepcidin) - 1



ACD pathogenesis (cytokine-driven ↑ hepcidin) - 2



IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin

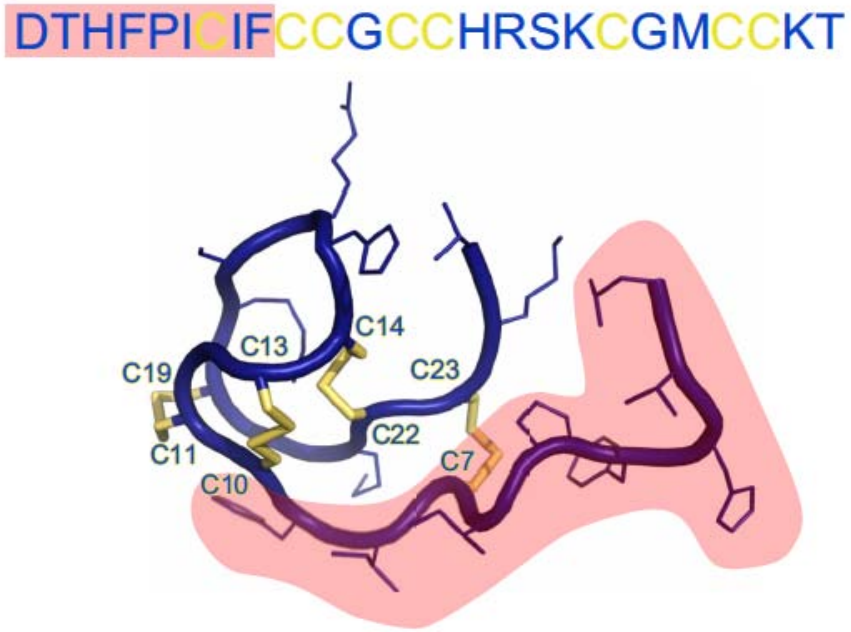


Nemeth E, J Clin Invest 2003

HEP-(atic) CIDIN (antimicrobial)

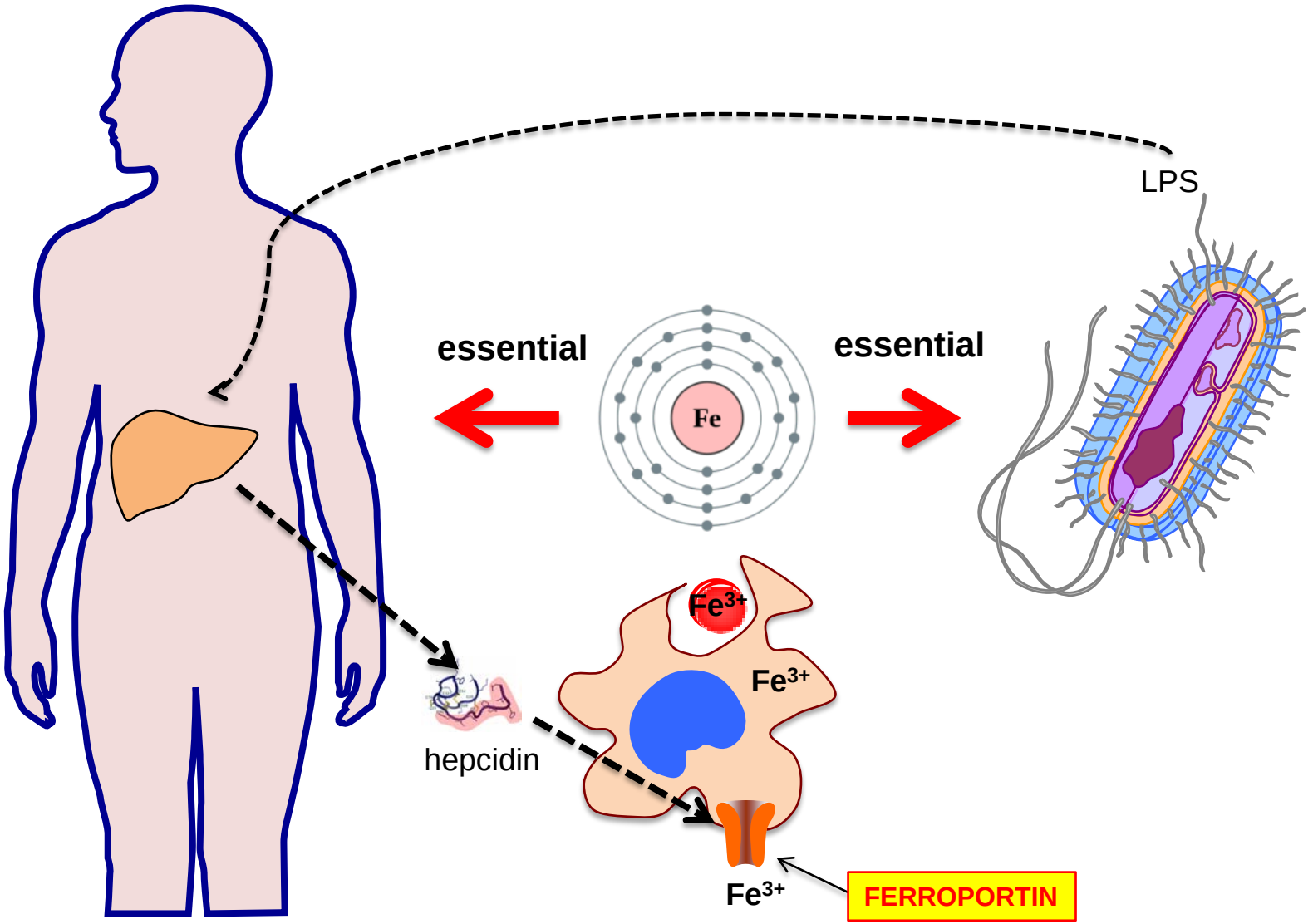
- **small (25 aa) peptide**

- **defensin-like (innate immunity-related peptides with natural antimicrobial acitvity)**

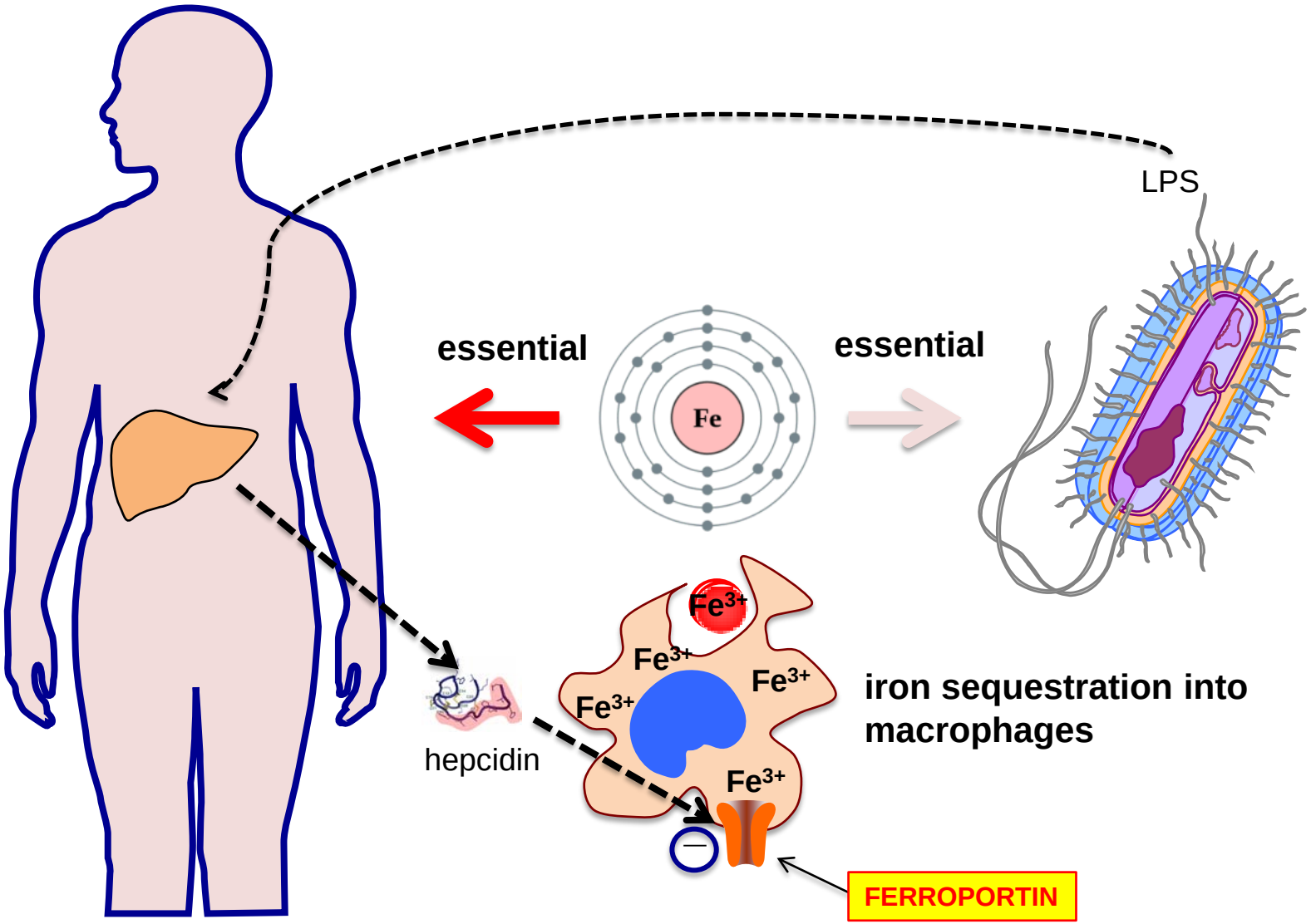


Ganz T, Physiol Rev 2013

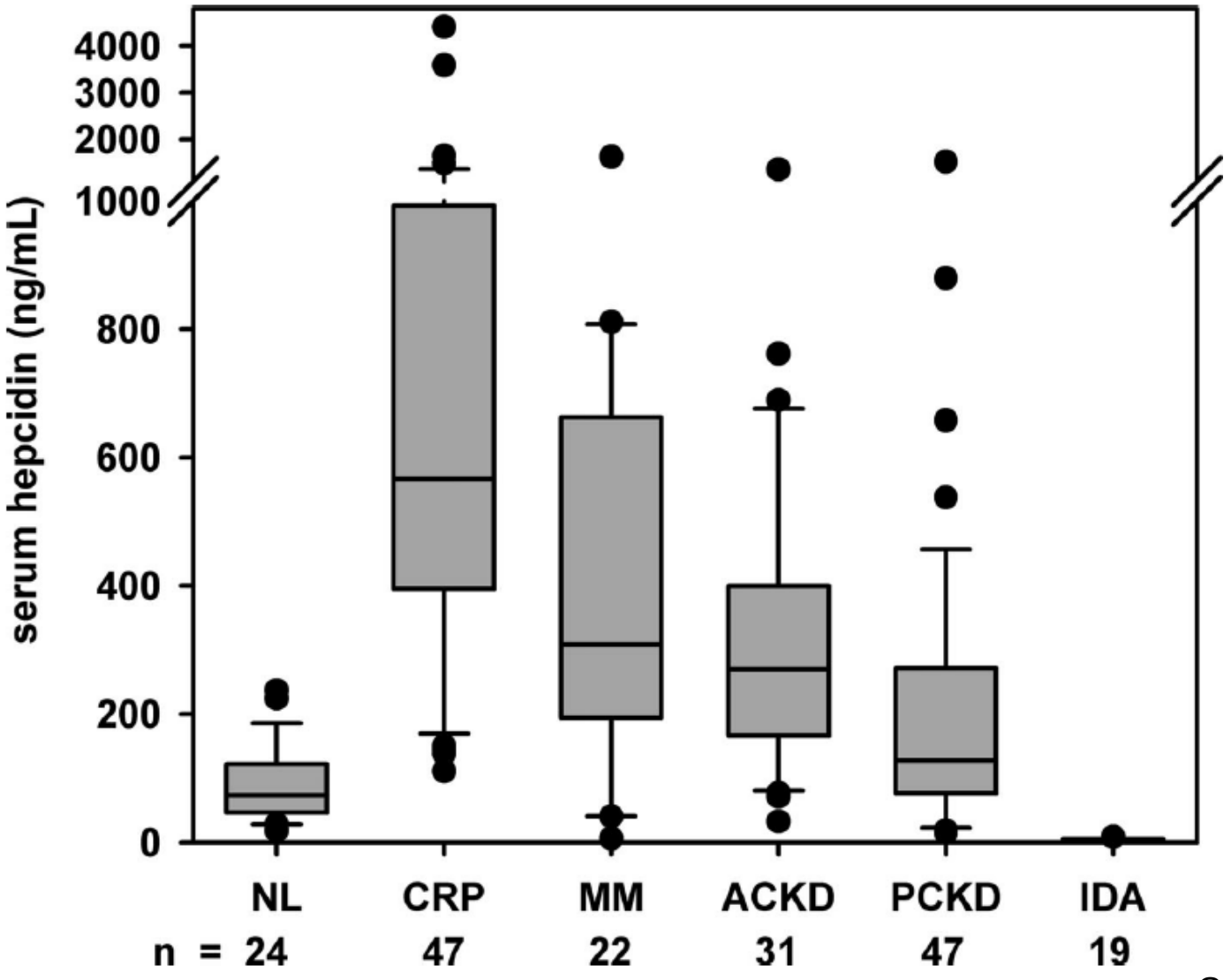
Hepcidin indirect antimicrobial activity by reducing iron availability to invading pathogens



Hepcidin indirect antimicrobial activity by reducing iron availability to invading pathogens



Serum hepcidin levels in different chronic disorders

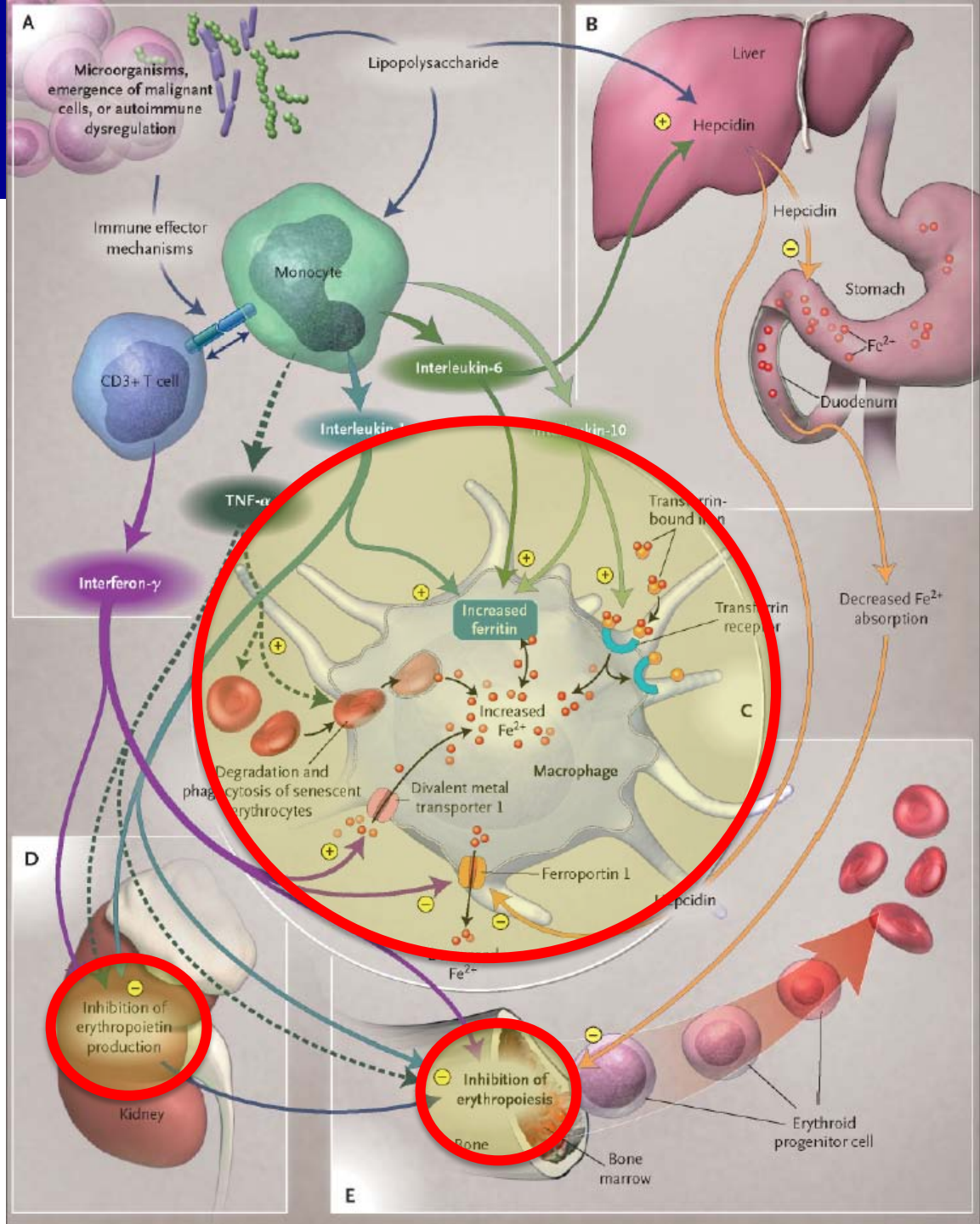


Ganz T, Blood 2008

ACD pathogenesis

hepcidin-induced “macrophage block” → iron-restricted erythropoiesis → major contributing factor

(+ cytokine-driven ↓ EPO activity and ↓ proliferative capacity of RBC precursors)

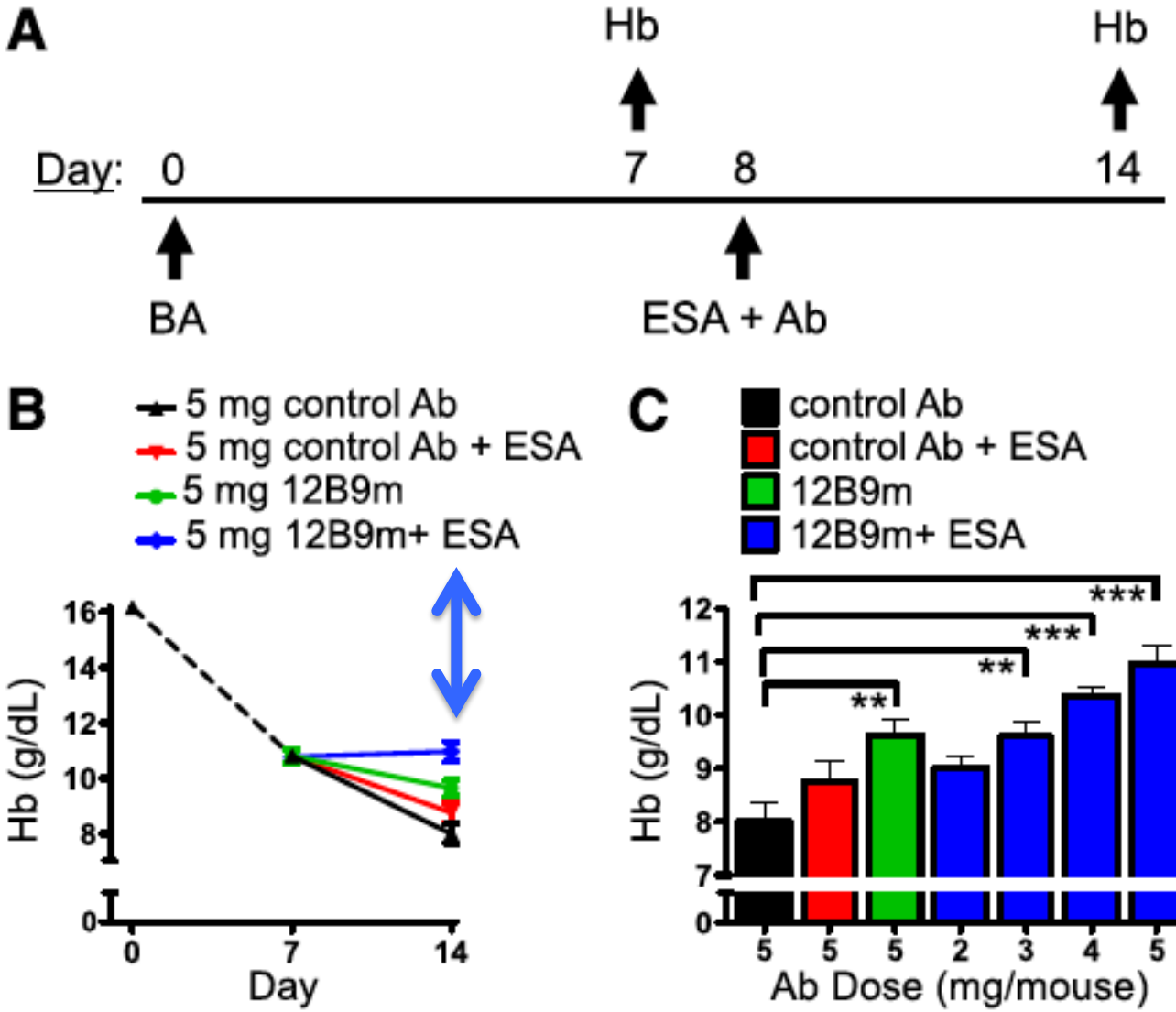


Weiss G, N Engl J Med 2005
Weiss G, Semin Hematol 2015

A fully human anti-hepcidin antibody modulates iron metabolism in both mice and nonhuman primates

Key Points

- Fully human anti-hepcidin Abs have been generated for use as a potential therapeutic to treat AI.
- The mechanism of action was shown to be due to an increase in available serum iron leading to enhanced red cell hemoglobinization.



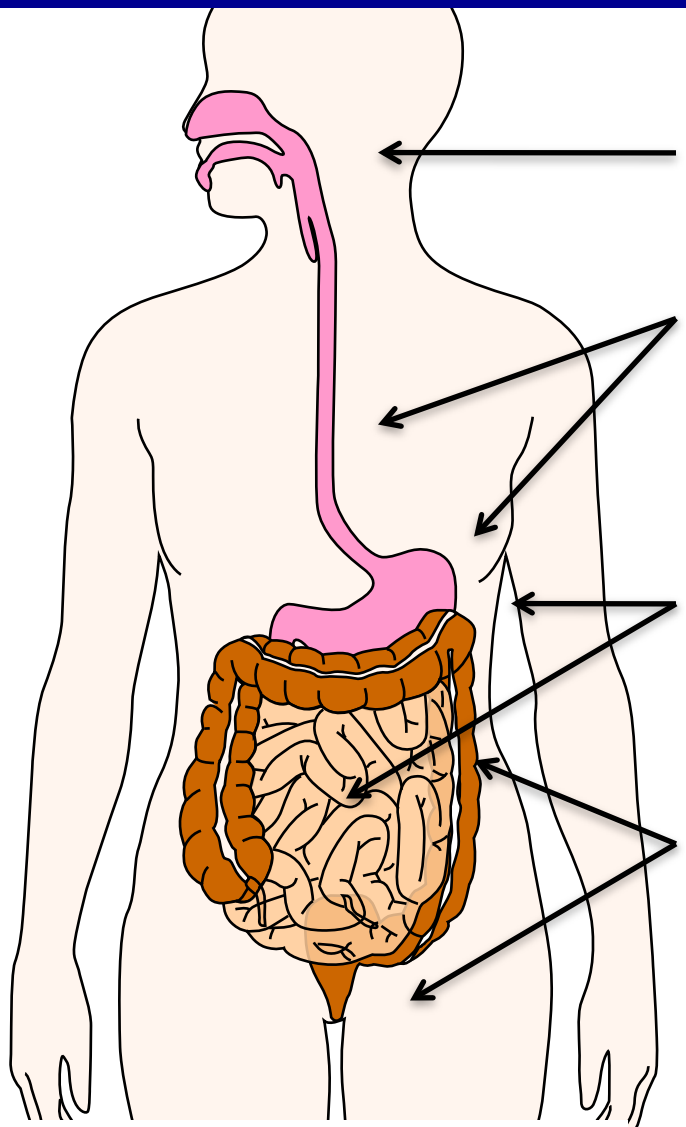
Cooke KS, Blood 2013

ACD diagnosis

- ✓**Anemia AND clinical/biochemical evidence of inflammation.**
- ✓**<u>Key problem</u>: exclude other causes of anemia, especially concomitant Iron Deficiency Anemia (IDA), as:**

  a) **The association is frequent**
  b) **Treatment is different**

Patients with ACD (i.e RA or IBD) often also have iron deficiency (correctable)



Malnutrition

Anorexia
Inadequate dietary intake

Upper GI blood losses

NSAIDs
Antithrombotic drugs
IBD (by itself)

Malabsorption

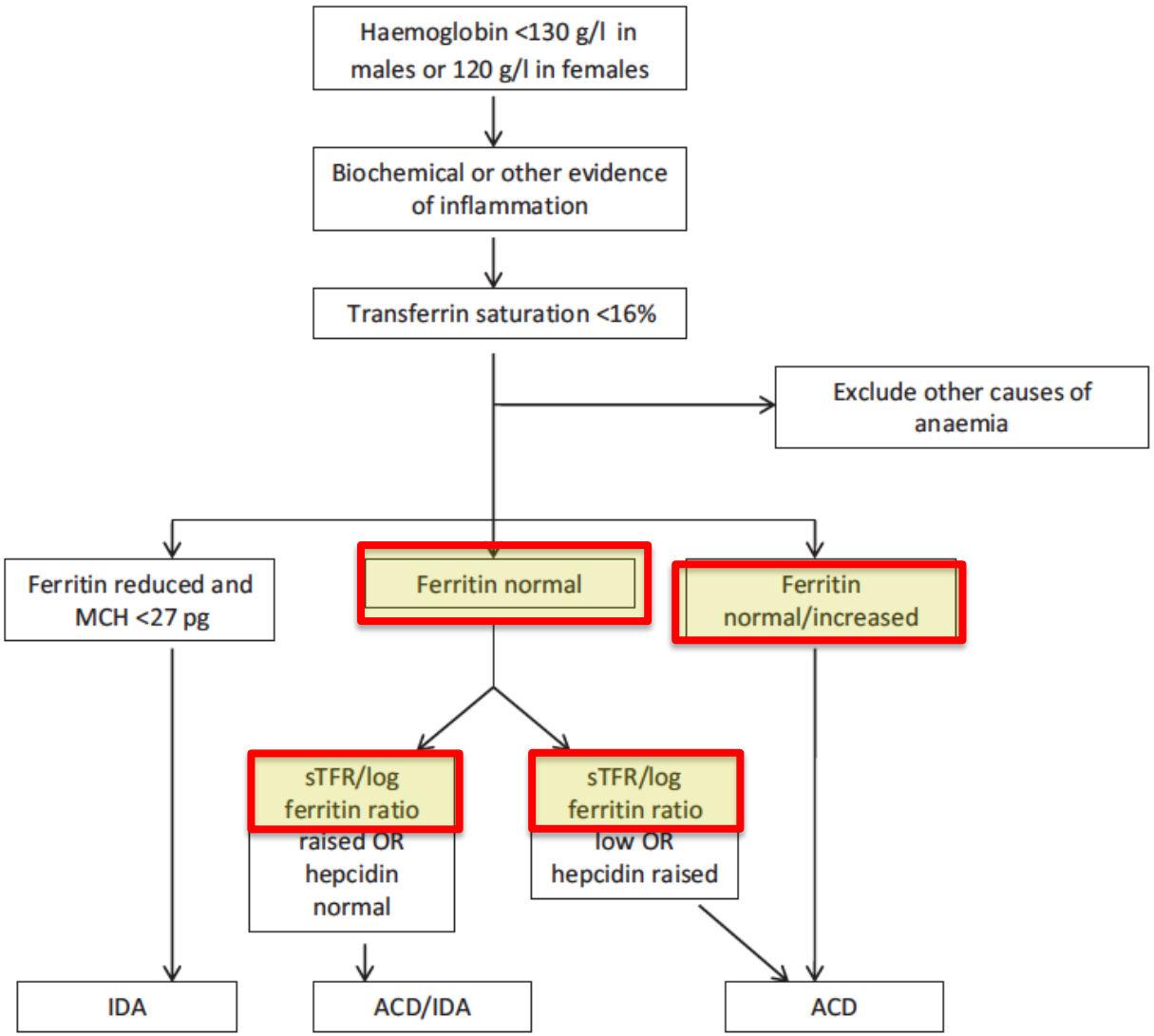
PPI

Lower GI blood losses

Antithrombotic drugs
IBD (by itself)

Busti F, Front Pharmacol 2014 (adapted)

(Complex) algorithm for differential diagnosis of IDA, ACD/IDA, or "pure" ACD



Ferritin, classical IDA biomarker = (acute phase reactant)

Controversy on the cut-off value defining "increased" ferritin (i.e. iron not beneficial)

- 100 μg/L ? (Weiss G, NEJM 2005)
- Pts. with HF or cancer respond to i.v. iron also with ferritin up to 300 (HF)-800 (cancer) μg/L

Algorithm requires serum Transferrin receptor (sTFR, not universally available)

Cullis JO, Brit J Haematol 2011
Anker SD, New Engl J Med 2009
NCCN guidelines (2015)

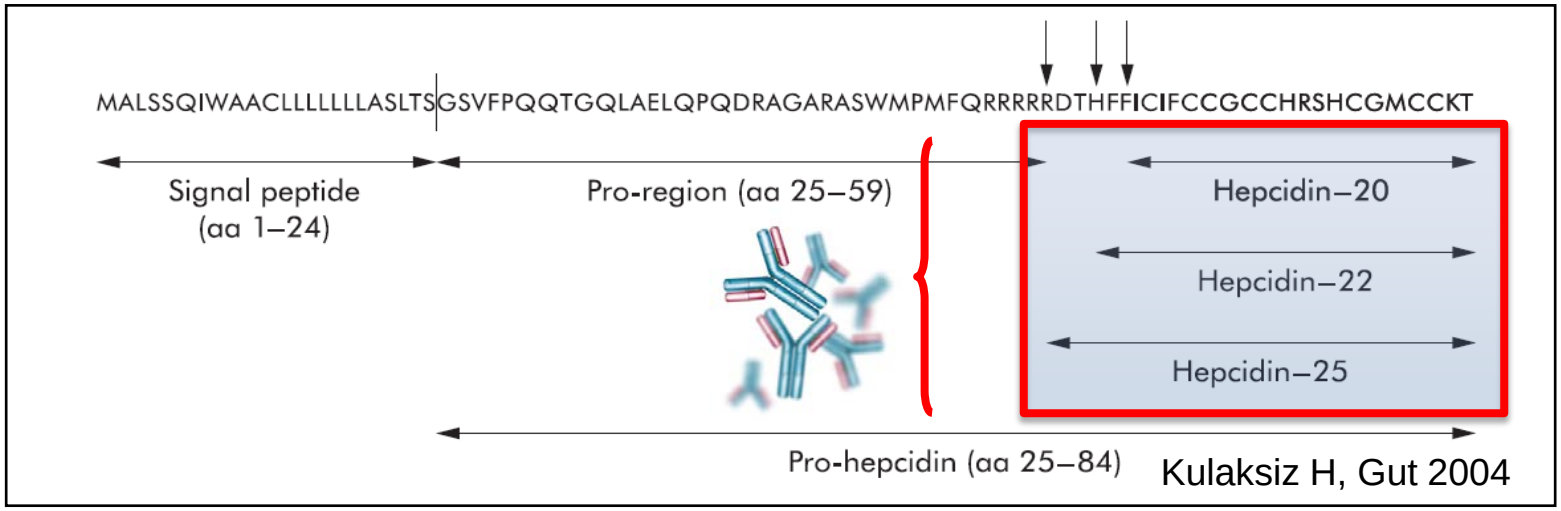
Hepcidin measurement in clinical practice. A decalogue for the hematologists

A) Checklist before ordering the assay			
		Comments	References
1.	Ensure local availability of a validated assay	See text and Supplementary Table 1	(19)
2.	Ensure control of pre-analytical conditions (including diurnal rhythm)	See text	(8, 25, 26)
3.	Refer to age- and sex-specific ranges	Significant differences between males and females, particularly during fertile period.	(22, 23)
4.	Interpret hepcidin value into a minimum laboratory context (CBC, ferritin, transferrin saturation, CRP, serum creatinine, liver function tests).	See Figure 1	-
5.	Be aware of many potential confounders/comorbidities in the individual patient	See Figure 1	

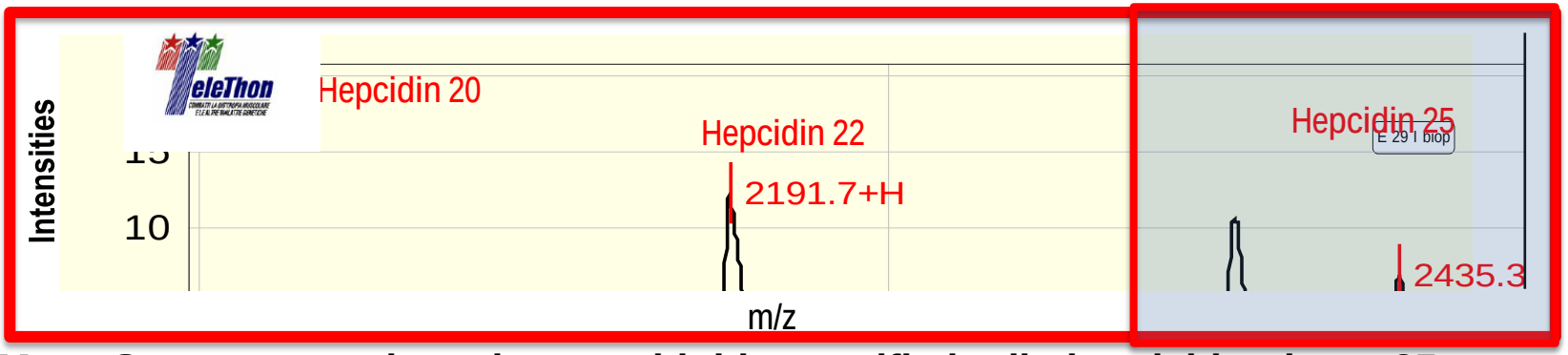
B) Most promising applications			
6.	Evaluation of suspected IRIDA	Virtually diagnostic in an appropriate clinical context	(41, 42)
7.	Evaluation of iron overload disorders	e.g.: ferroportin disease due to hepcidin resistant mutations (see text)	(34, 37, 45, 46, 48, 49)
8.	Diagnosis of concomitant iron deficiency in patients with anemia of chronic disease	Promising reports in rheumatoid arthritis, inflammatory bowel disease, and African children	(53, 62, 66, 67)
9.	Guide for iron therapy	e.g.: selection of patients for direct I.V. supplementation; oral administration in children from developing countries with high prevalence of infectious diseases (see text)	(6, 50, 52-54, 62)
10.	Monitoring of treatments targeting the hepcidin/ferroportin axis	To be confirmed by further studies	(69)

Girelli D, Blood 2016

Hepcidin-25 (only iron-active isoform) assays



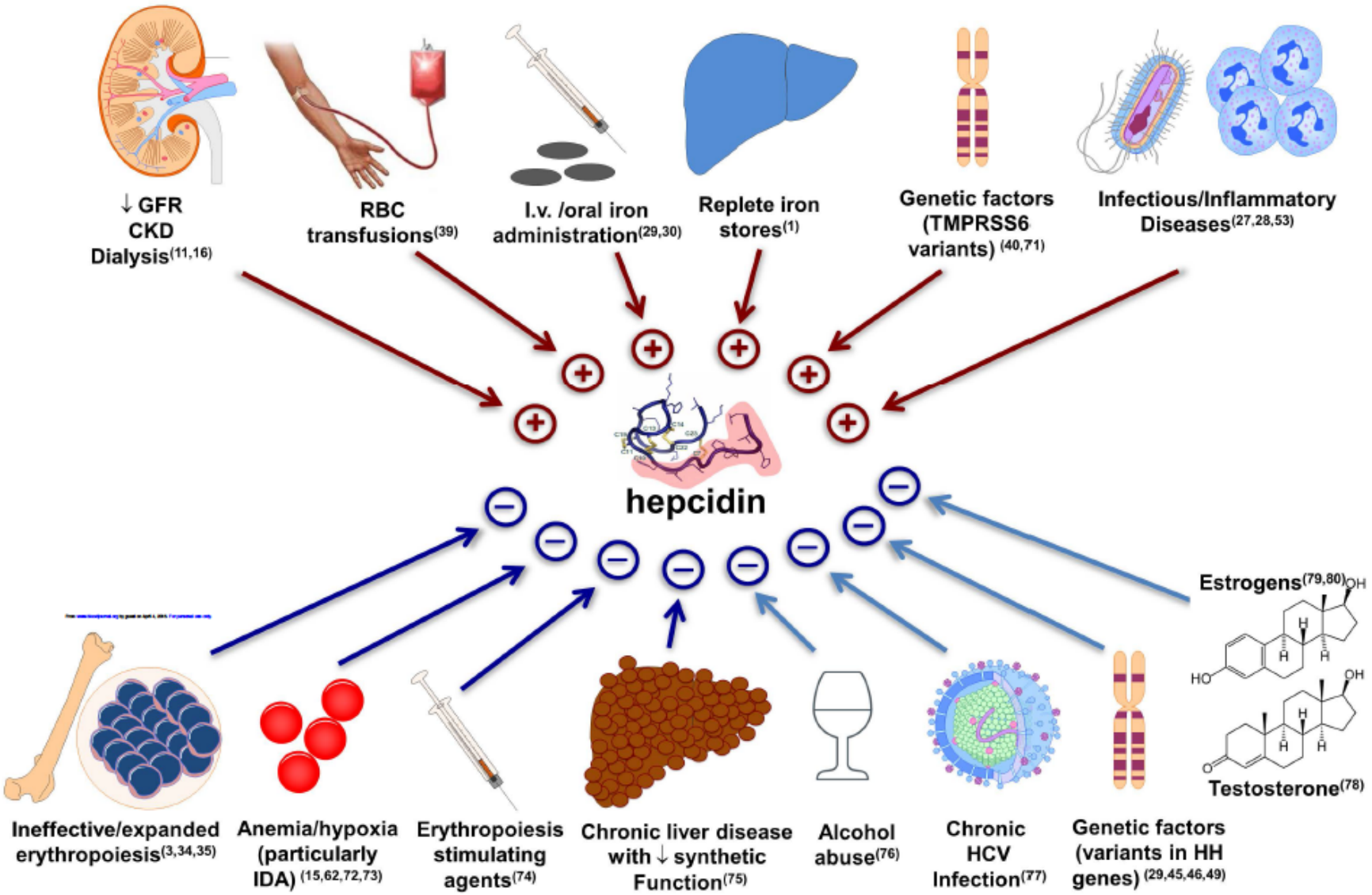
ELISA: Ab cross-reacting with smaller inactive isoforms (total hepcidin measured)



Mass-Spectrometry based assay: highly specific in distinguishing hepc-25

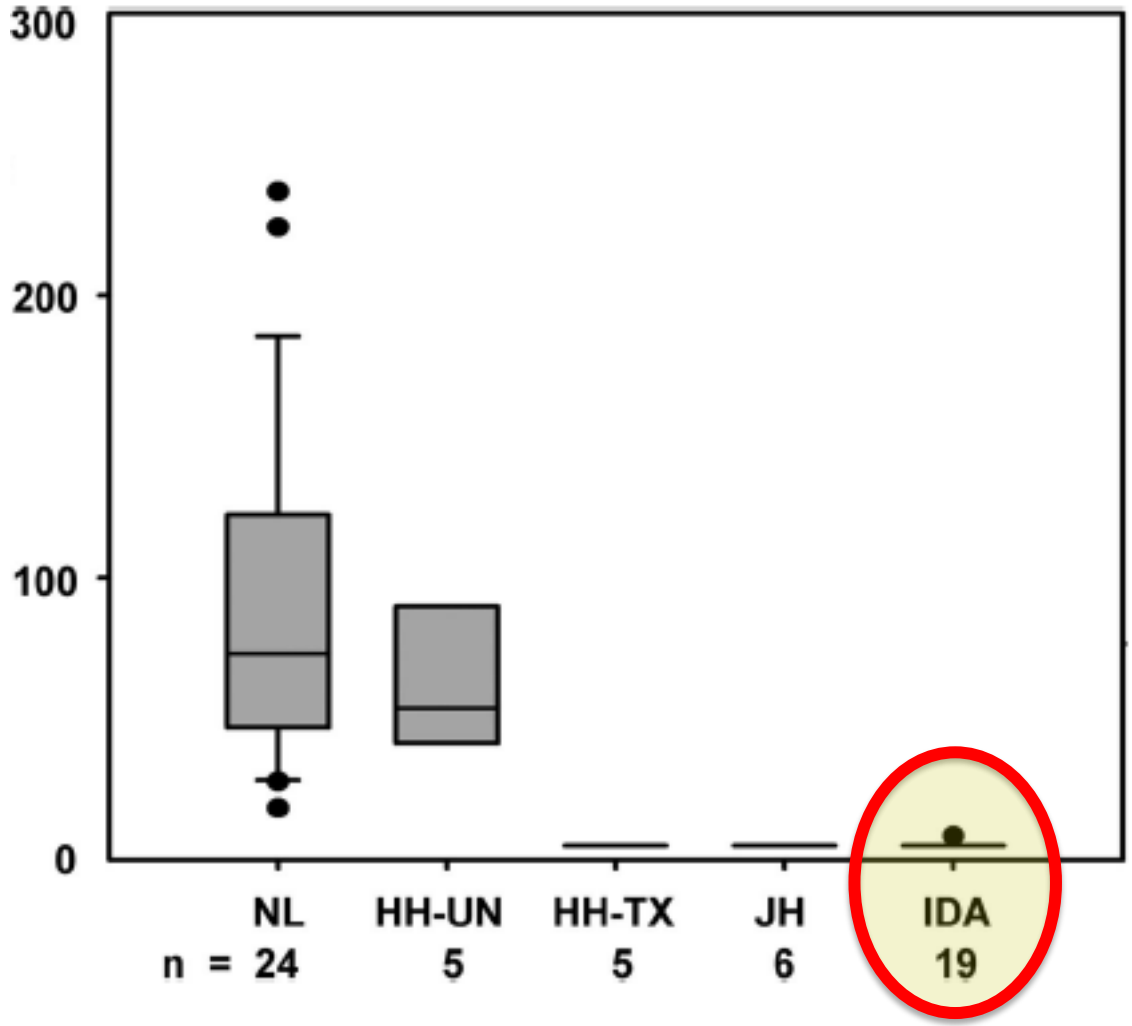
Castagna A, J Proteom 2010

Clinical conditions influencing circulating hepcidin levels



Girelli D, Blood 2016

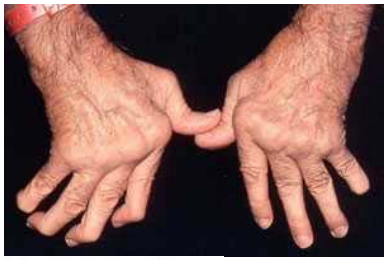
Serum Hepcidin levels are suppressed in IDA

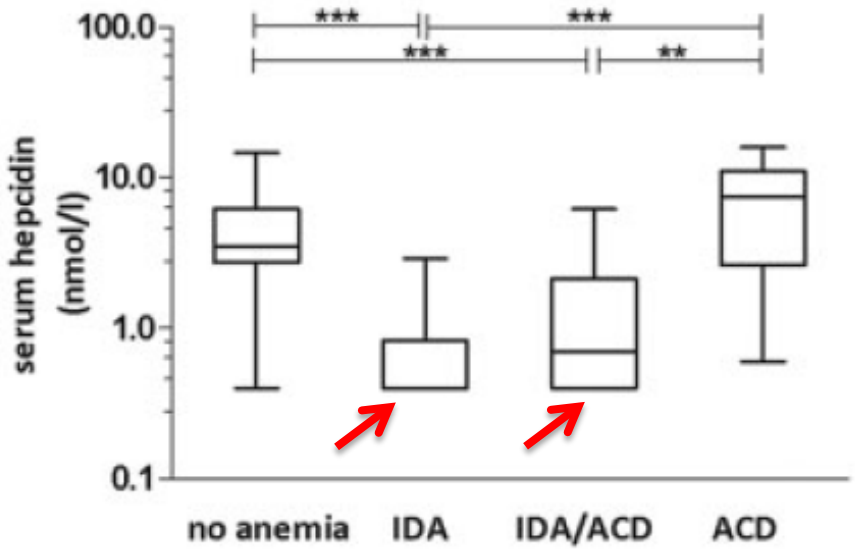


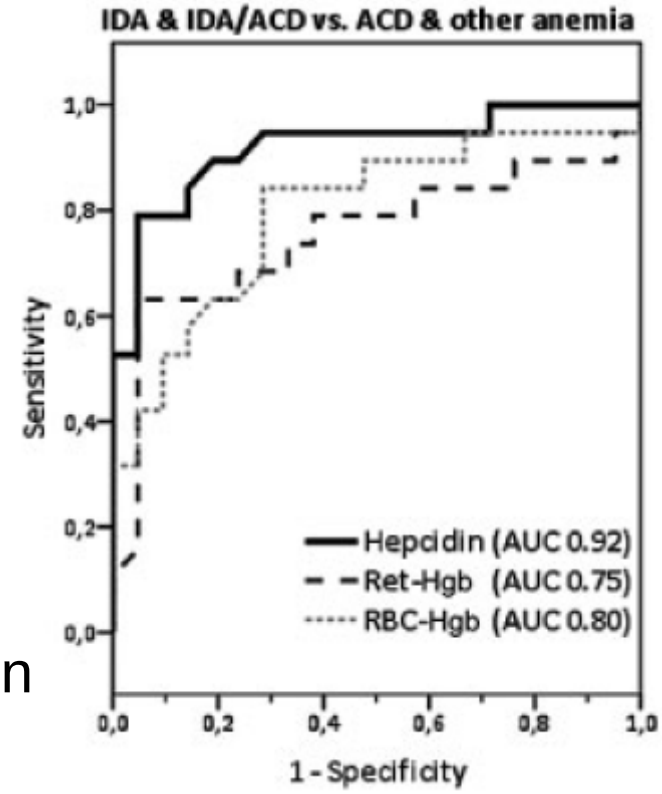
Less influenced by concurrent inflammation as compared to ferritin (suppression tends to prevail)

Ganz T, Olbina G, Girelli D et al. Blood 2008

Low hepcidin levels allow detection of concurrent iron deficiency in anemic patients with Rheumatoid Arthritis







↓ hepcidin pts. may benefit from iron

van Santen S, Arthritis & Rheumatism 2011

Low hepcidin levels allow detection of concurrent iron deficiency in anemic patients with IBD

Serum Hepcidin in Inflammatory Bowel Diseases: Biological and Clinical Significance

Gaetano Bergamaschi, MD, Antonio Di Sabatino, MD,* Riccardo Albertini, MD,† Filippo Costanzo, MD,* Marco Guerci, MD,* Michela Masotti, MD,* Alessandra Pasini, PhD,* Alessandro Massari, MD,* Natascia Campostrini, MD,‡ Michela Corbella, MD,‡ Domenico Girelli, MD,‡ and Gino Roberto Corazza, MD**

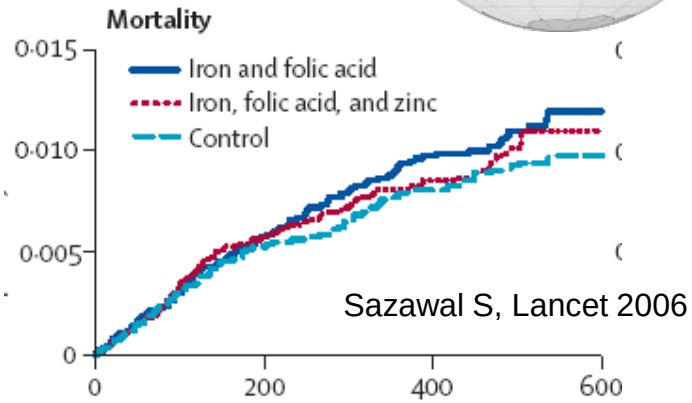
TABLE 2. Serum Hepcidin-25 Concentrations in Different Groups of IBD Patients and Controls

Study Population (N)	Serum Hepcidin, nM	*P*
CD (22)	2.43 (1.38–4.29)	NS
UC (32)	1.33 (0.85–2.06)	—
IBD, quiescent disease (28)	1.58 (1.05–2.40)	NS
IBD, active disease (26)	2.35 (1.28–4.29)	—
Nonanemic IBD (28)	1.70 (1.10–2.63)	NS
IBD with anemia (26)	1.86 (1.05–3.31)	0.006[a]
IDA (9)	0.21 (0.19–0.23)	
IDA + AI (4)	1.06 (0.01–4.61)	
AI (7)	7.61 (2.15–23.94)	

Bergamaschi G, Inflamm Bowel Dis 2013

The MOST promising application of hepcidin assay
(from a global health perspective)

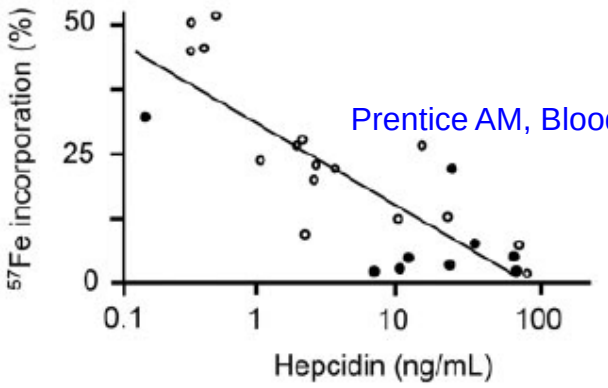
- I.D. major health problem in children from low-incoming countries.
- The "Pemba" trial: "routine" iron supplementation is not the solution, but rather can ↑ mortality due to infections.



Sazawal S, Lancet 2006

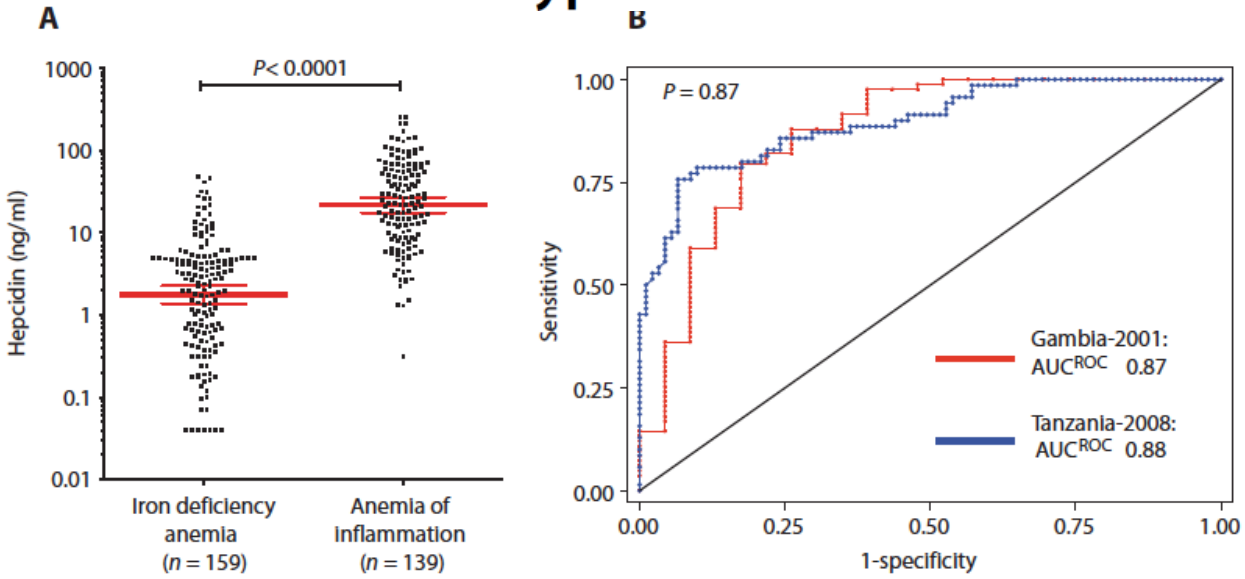
- Hepcidin is the major predictor of RBC iron incorporation in anemic African (Gambia) children, indicating iron utilization for children's growth rather than for the growth of infectious agents.

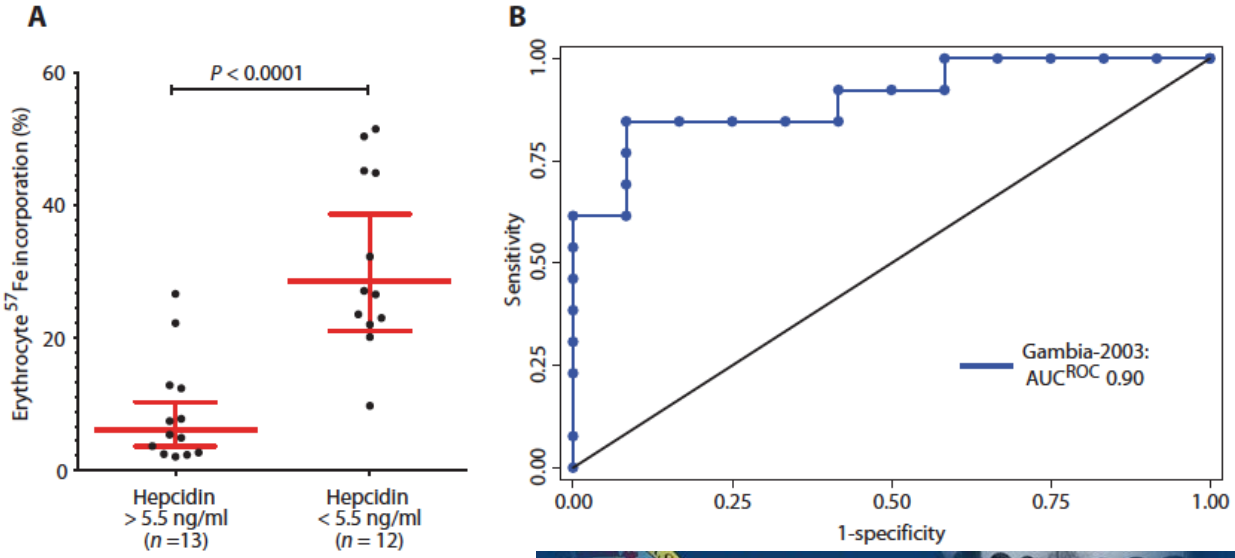
Hepcidin as a point-of-care index guiding "safe" and effective iron therapy



Prentice AM, Blood 2012

Expression of the Iron Hormone Hepcidin Distinguishes Different Types of Anemia in African Children





Pasricha SR, Sci Transl Med 2014

ACD- therapeutic options

- “pure” ACD: treat the underlying disease
- Concomitant IDA: correct with iron supplementation
- Anti-hepcidin strategies

Pharmacology of hepcidin

Review

Cell PRESS

The pathophysiology and pharmacology of hepcidin

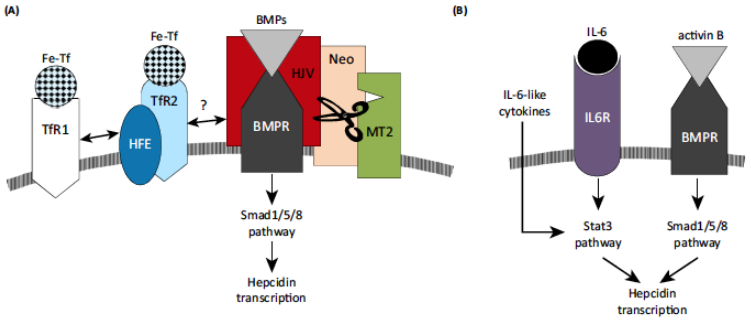


Table 1. Principles of hepcidin-targeting therapeutic approaches

Therapeutic approach	Targeted disease	Mode of action	Agents
Hepcidin agonists	Iron overload (hereditary hemochromatosis and iron-loading anemias)	Hepcidin mimics	Minihepcidins [47]
		Stimulators of hepcidin production	Gene silencing of TMPRSS6 [50,51]
			BMP pathway agonists [52]
Hepcidin antagonists	Iron-restricted anemias (anemia of inflammation, anemia of chronic kidney disease, anemia of cancer, IRIDA)	Suppressors of hepcidin production	BMP pathway inhibitors [54,56,74]
			Anti-inflammatory agents [60–62]
			Erythropoiesis-stimulating agents [65]
			Gene silencing of hepcidin and its regulators [66][a]
		Hepcidin peptide neutralizing binders	Anti-hepcidin antibodies [67][b]
			Anticalins [68]
			Spiegelmers [69]
		Agents interfering with hepcidin–ferroportin interaction	Anti-ferroportin antibodies [71]
			Thiol modifiers [72]

[a] http://ir.isispharm.com/phoenix.zhtml?c=222170&p=irol-newsArticle&ID=1828284&highlight=

[b] http://www.clinicaltrials.gov/ct2/show/NCT01340976

Ruchala P & Nemeth E, Trends Pharmacol Sci 2014

Oral abstracts at ASH 2015

ASH | 57th Annual Meeting & Exposition
Orlando, FL · December 5-8, 2015

537 Phase 1 Study of a Hepcidin Antagonist, LY2787106, in Cancer-Associated Anemia

273 ALK2 Inhibition Via TP-0184 Abrogates Inflammation-Induced Hepcidin Expression and Is a Potential Therapeutic for Anemia of Chronic Disease

536 A Phase I Study Investigating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Activity of the Hepcidin Antagonist PRS-080#022. Results from a Randomized, Placebo Controlled, Double-Blind Study Following Single Administration to Healthy Subjects[a]

Conclusions/Take-home messages

- ✓**Hepcidin, which stands at the crossroad between iron metabolism and the immune system, plays an important role in ACD.**
- ✓**Hepcidin measurement is a promising tool for distinguishing concomitant iron deficiency (possibly correctable) in anemic patients with chronic inflammatory disorders.**
- ✓**In a near future, hepcidin antagonists may help in increasing Hb levels in ACD patients.**

The Verona Interdisciplinary group on Iron Disorders

GIMFer
AOUI VERONA
GRUPPO INTERDISCIPLINARE MALATTIE DEL FERRO

http://www.gimferverona.org

Participants Units

1. Internal Medicine
2. Clinical Chemistry & Molecular Biology
3. Blood Bank / Transfusional Service
4. Radiology
5. Pathology
6. Gastroenterology

Paolo Bozzini, Fabiana Busti, Paola Capelli, Annalisa Castagna, Michela Corbella, Massimo Delledonne, Giorgio Gandini, Alejandro Giorgetti, Giacomo Marchi, Oliviero Olivieri, Roberto Pozzi-Mucelli, Monica Rizzi, Alice Vianello, Luciano Xumerle.

Telethon

Ministero della Salute

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REGIONE DEL VENETO

MINISTERO DELL'ISTRUZIONE, DELL'UNIVERSITÀ E DELLA RICERCA

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