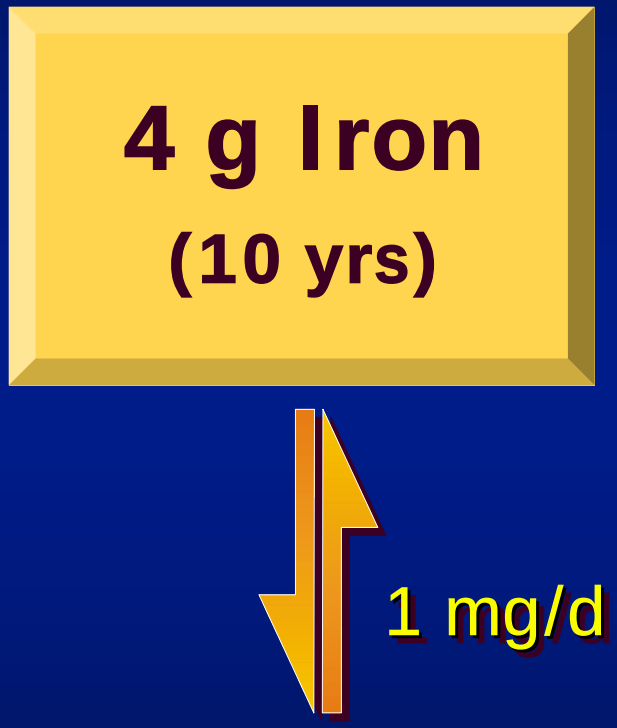
IRON METABOLISM

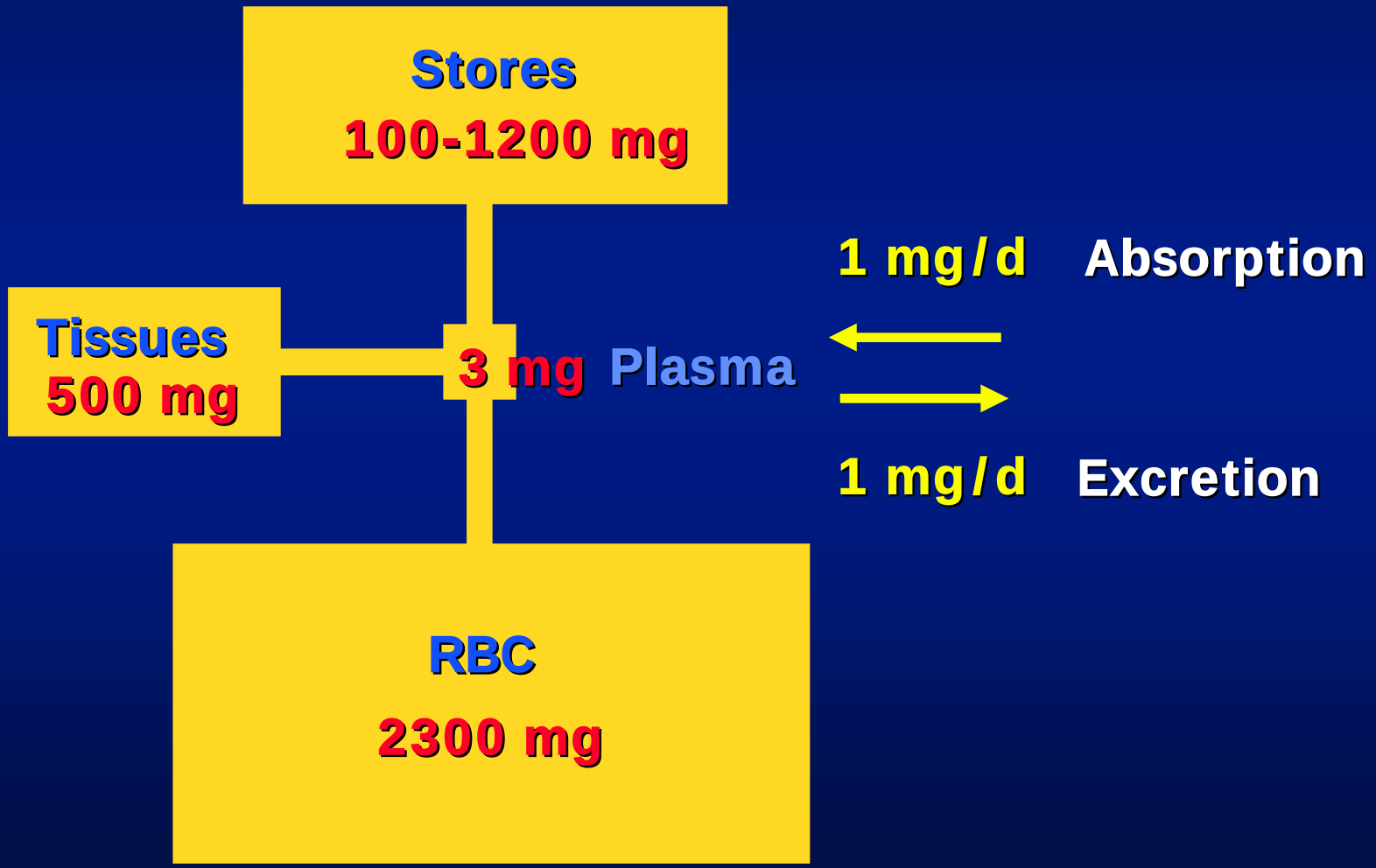
IRON METABOLISM

External iron exchange



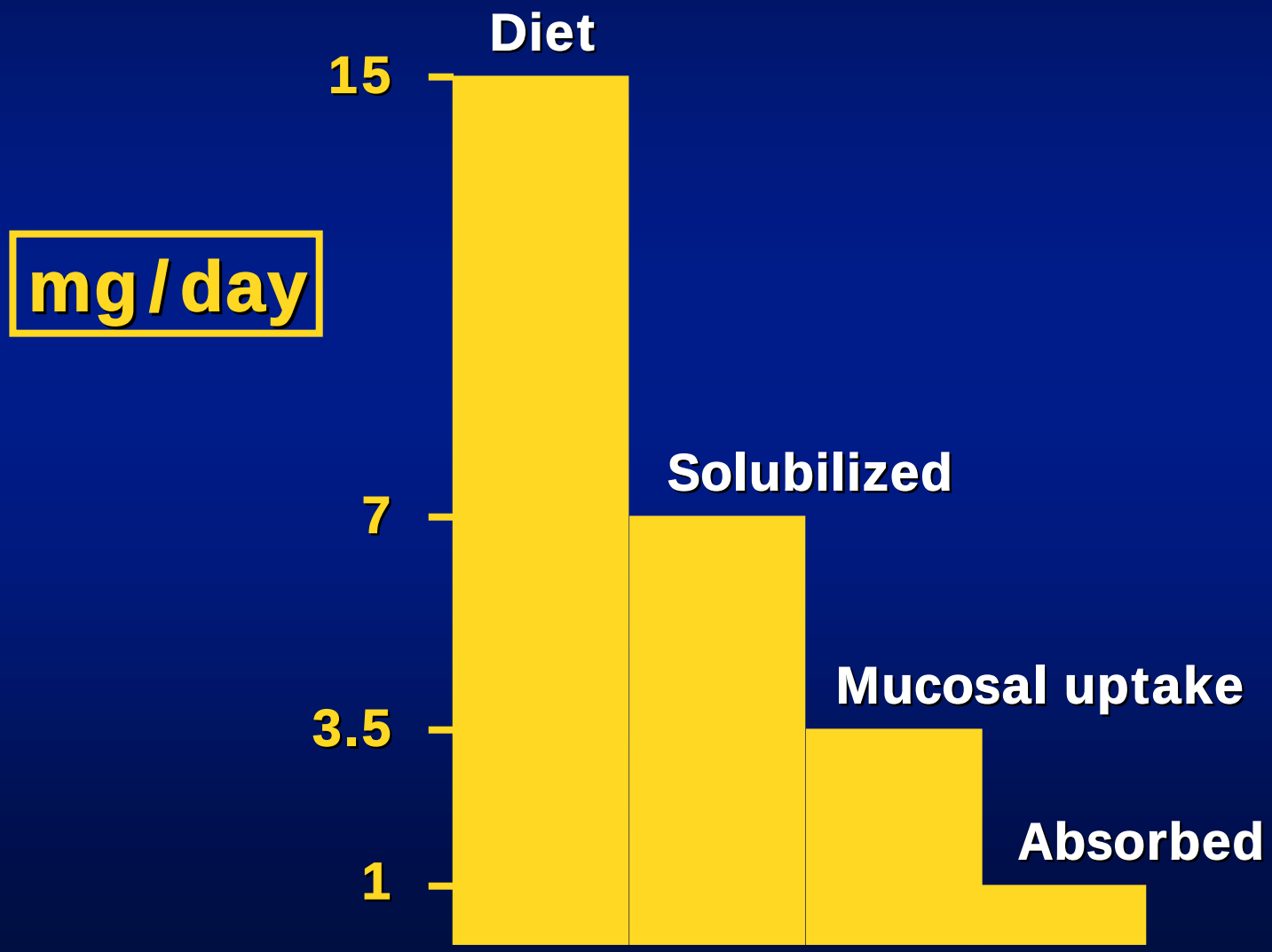
IRON METABOLISM

Iron compartments



IRON METABOLISM

Iron absorption



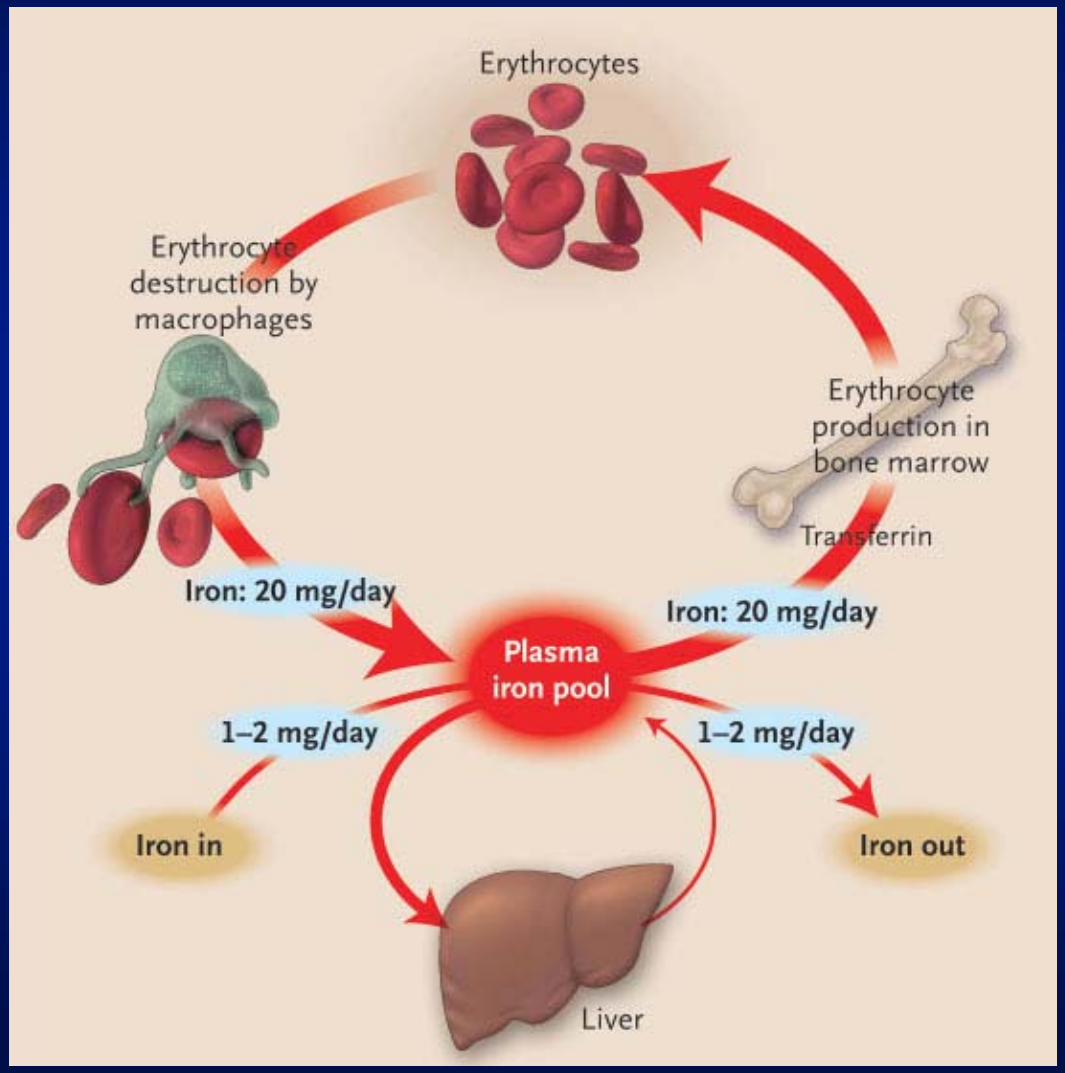
IRON METABOLISM

GI tract

Swinkels et al, Clin.Chem. 52:950, 2006

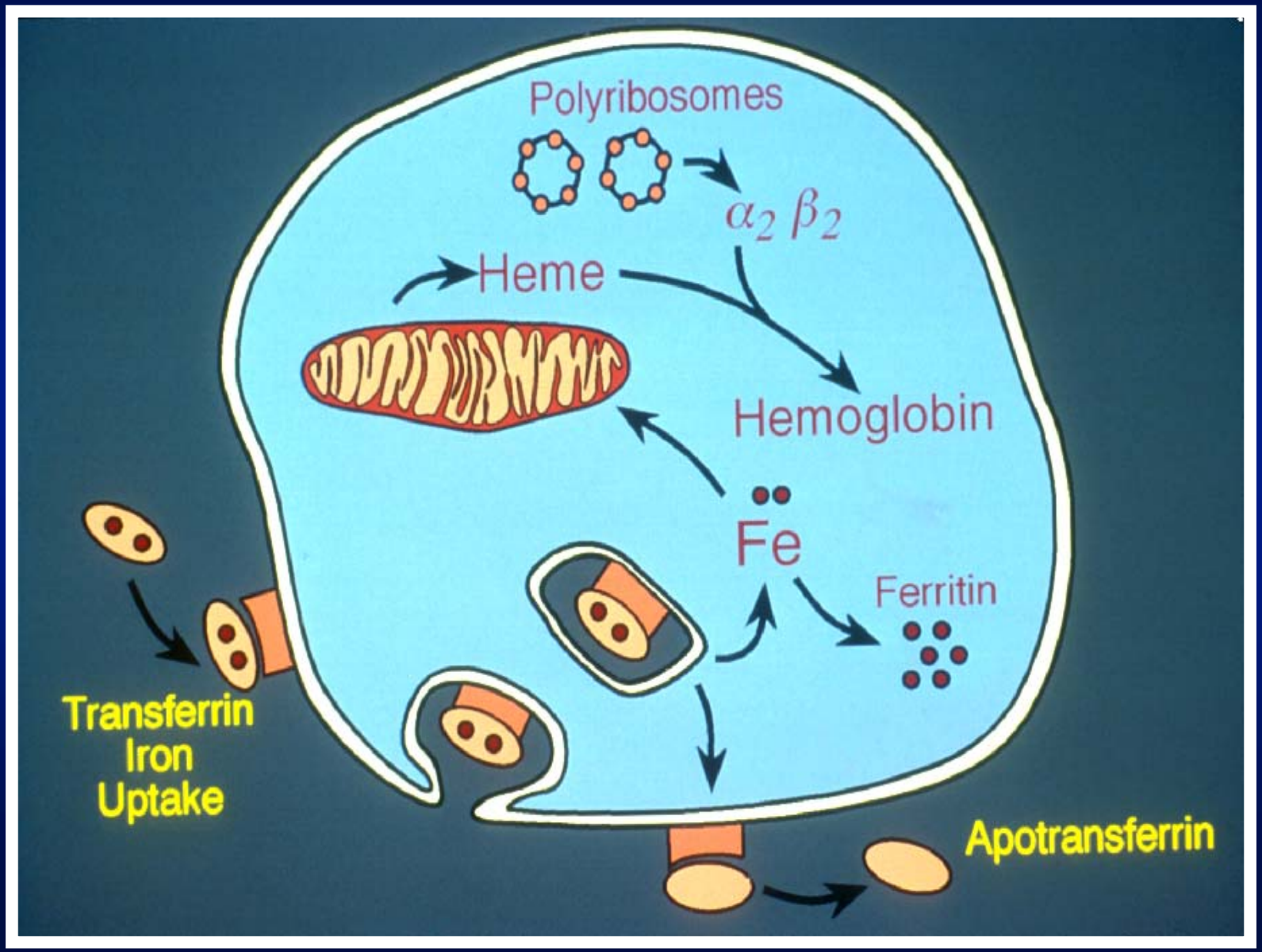
IRON METABOLISM

Internal iron exchanges



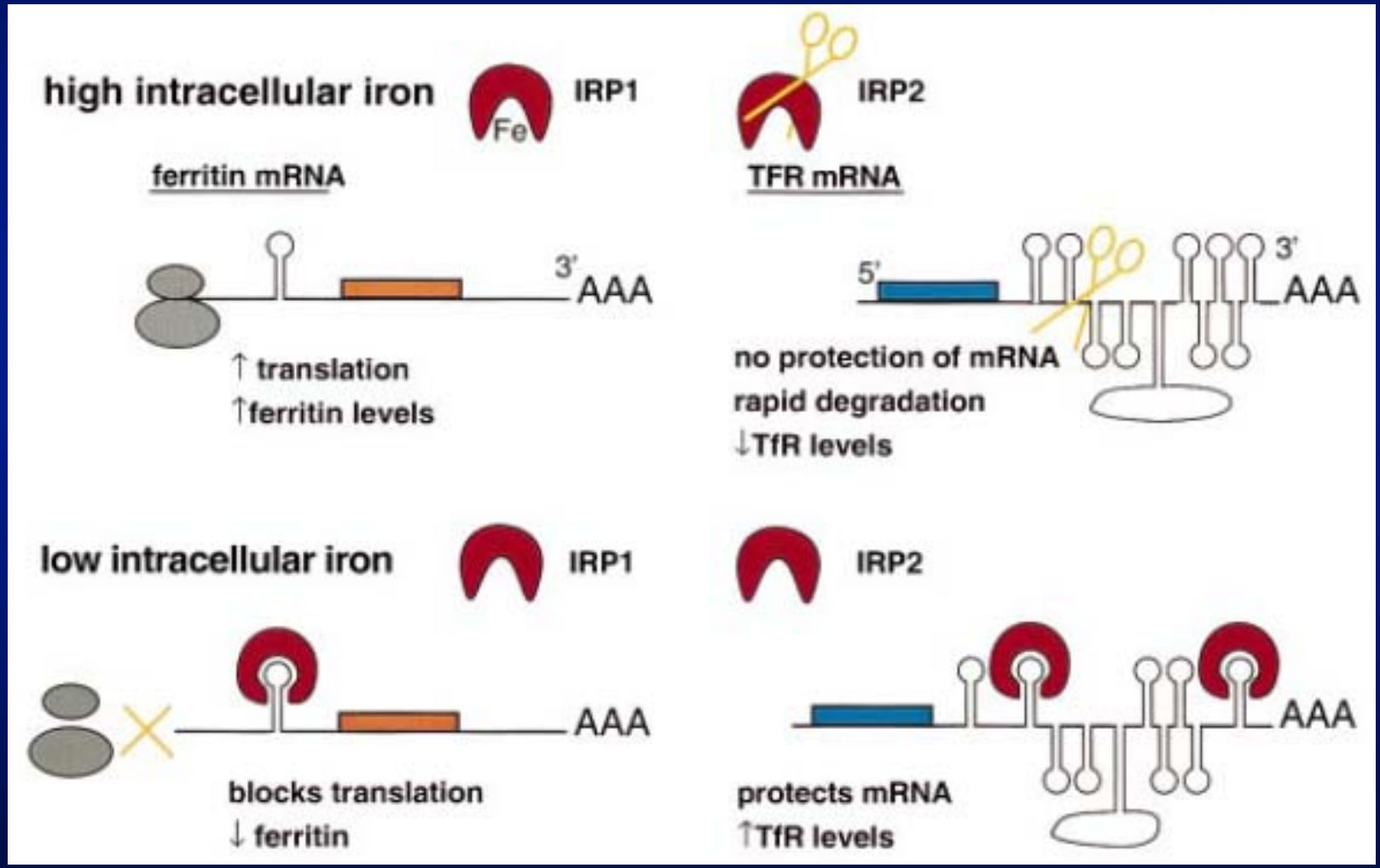
Pietrangelo. N Engl J Med 2004;350:2383–97

ERYTHROBLAST IRON METABOLISM



IRE AND IRP

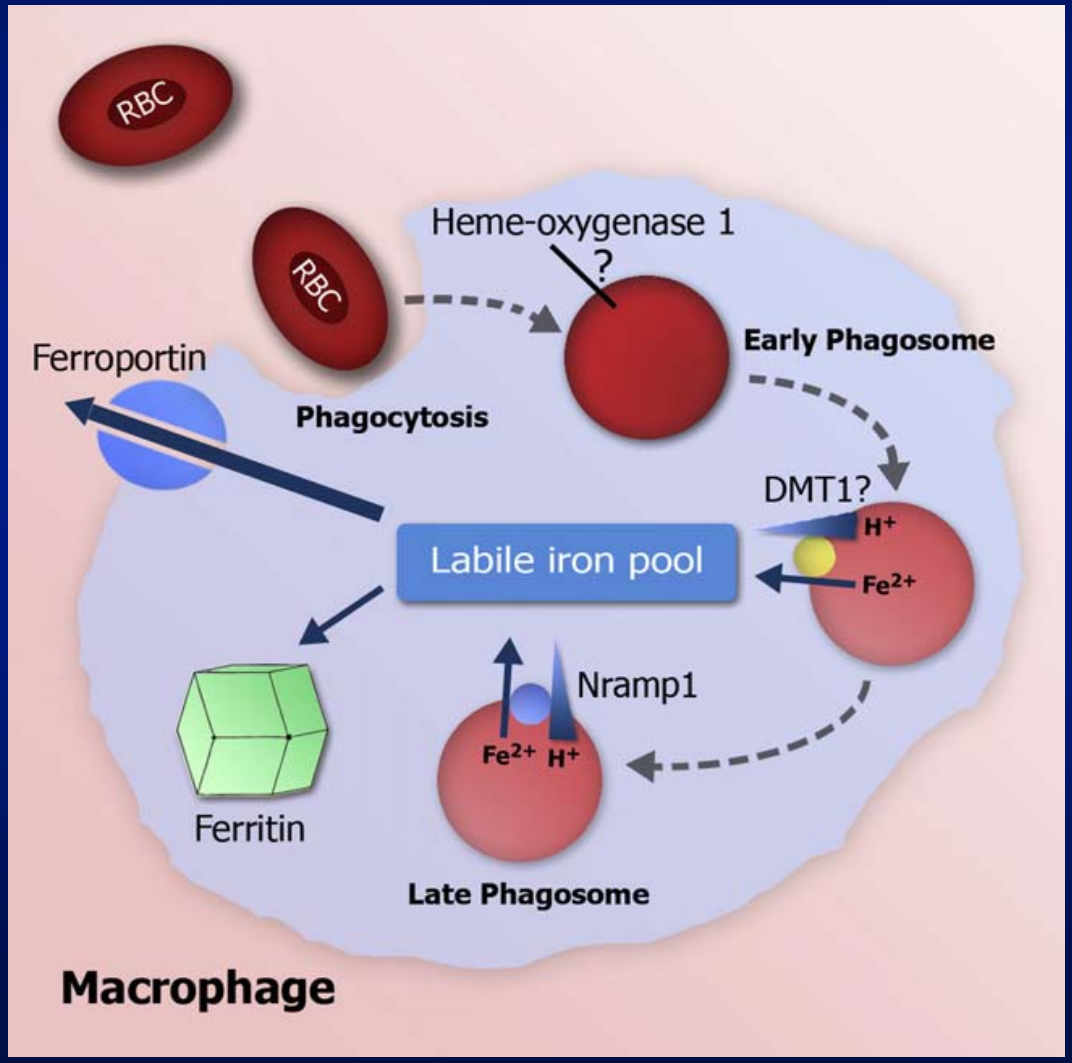
Regulation of ferritin and TfR



Enns, Traffic 2:167, 2001

IRON METABOLISM

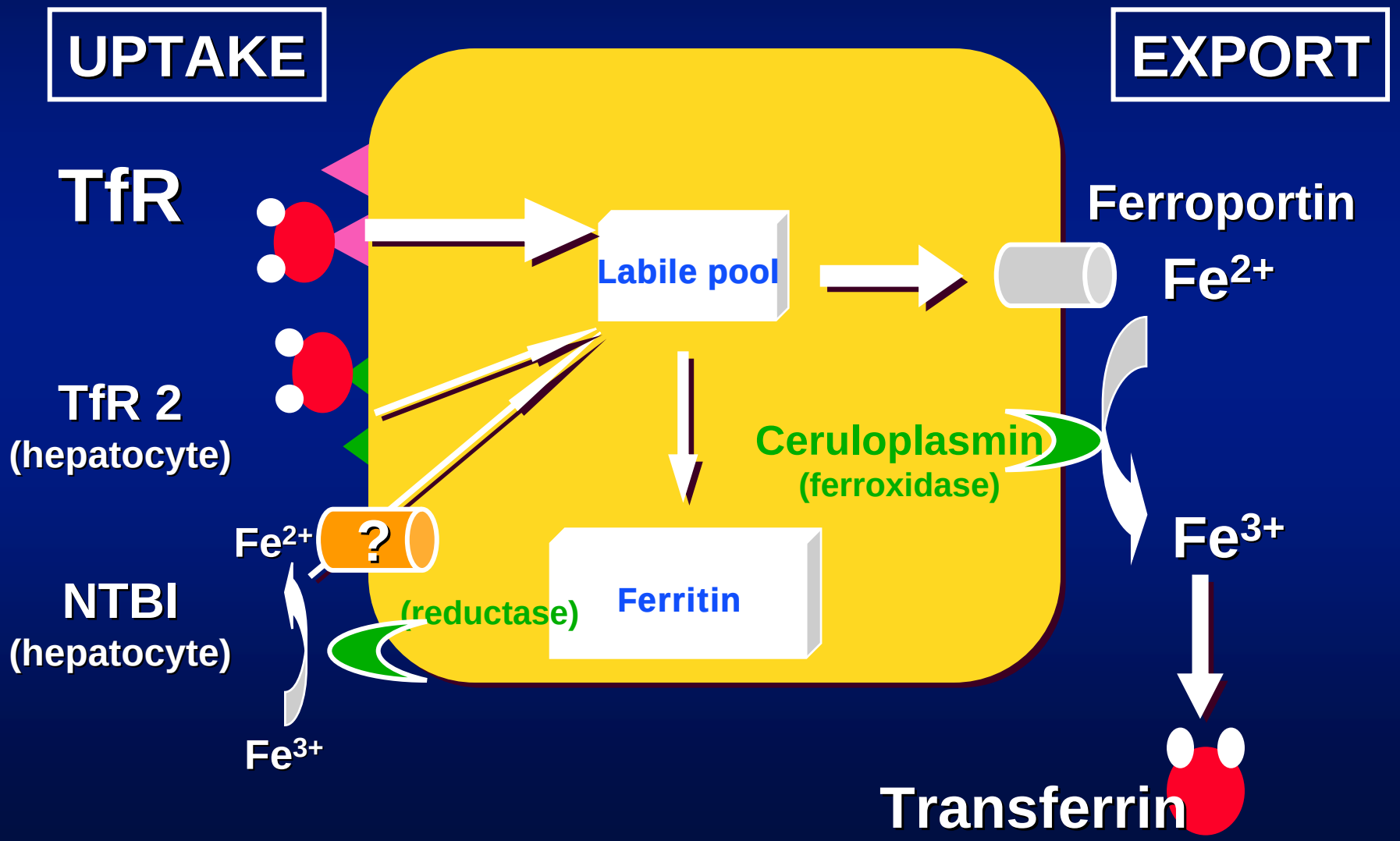
Macrophages



Soe-Lin et al,
Exp Hematol
36:929, 2008

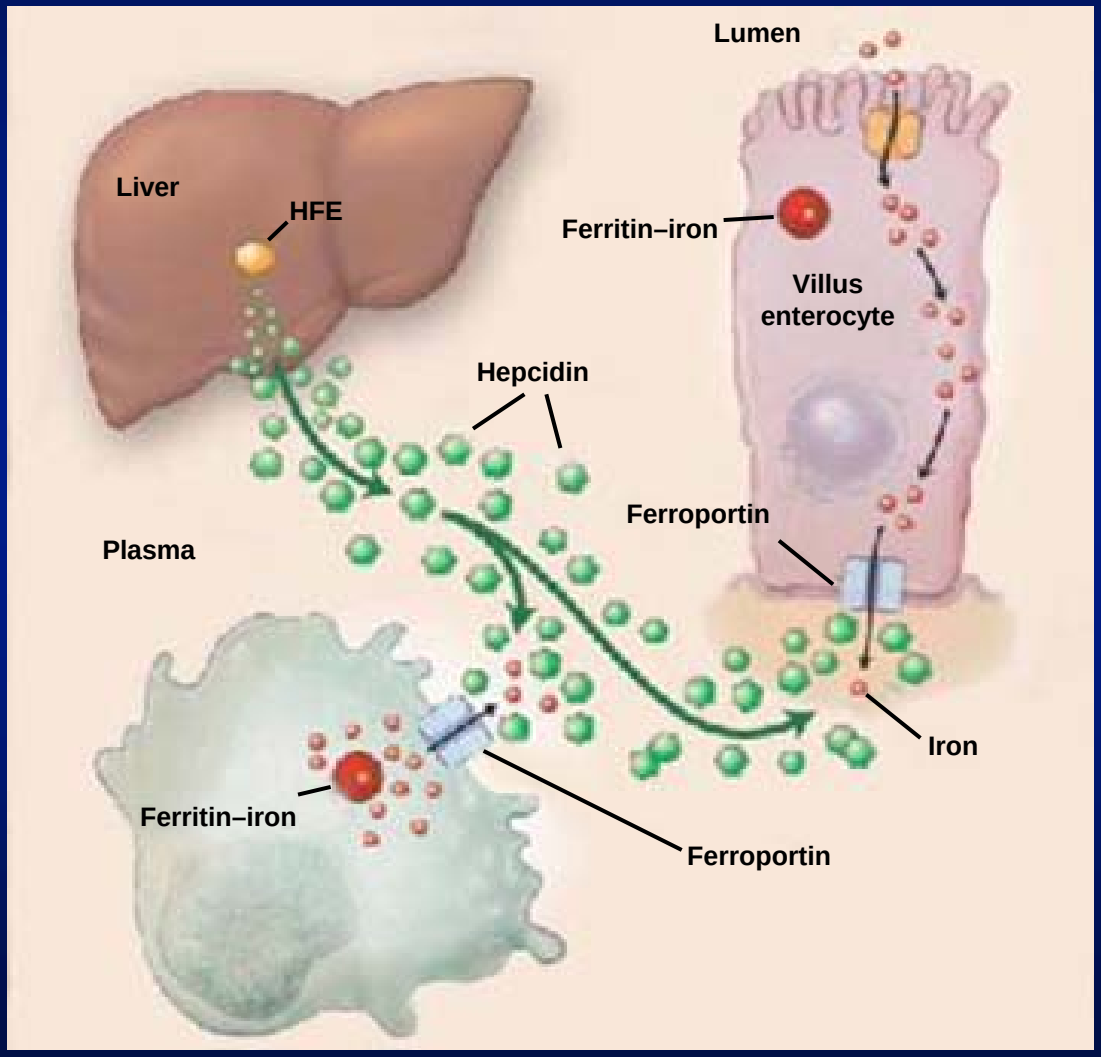
IRON METABOLISM

Iron uptake and export



IRON METABOLISM

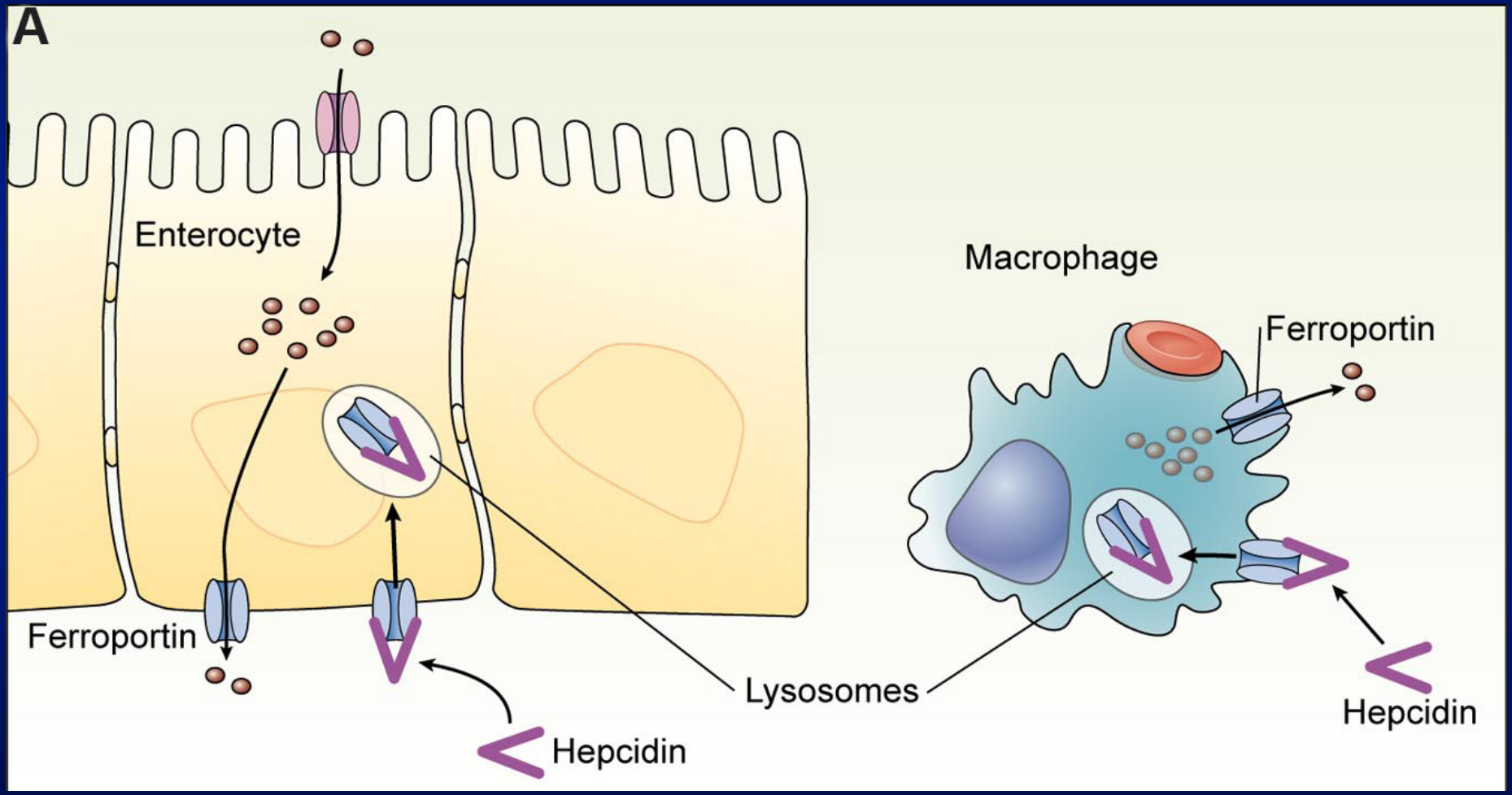
Hepcidin



Ganz. Best Pract Res Clin Haematol 2005;18:171–82

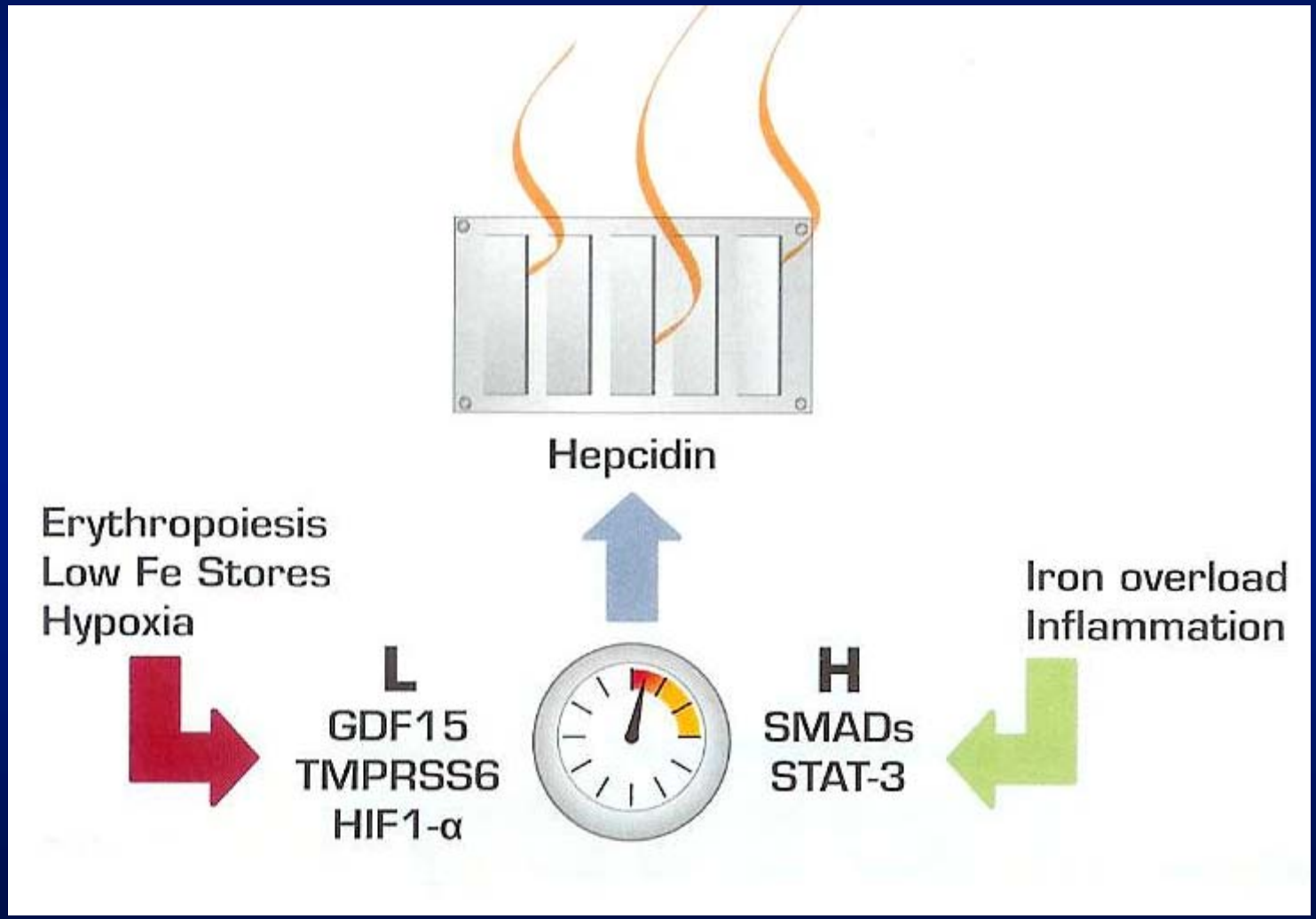
IRON METABOLISM

Hepcidin



Andrews, Blood 112:219, 2008

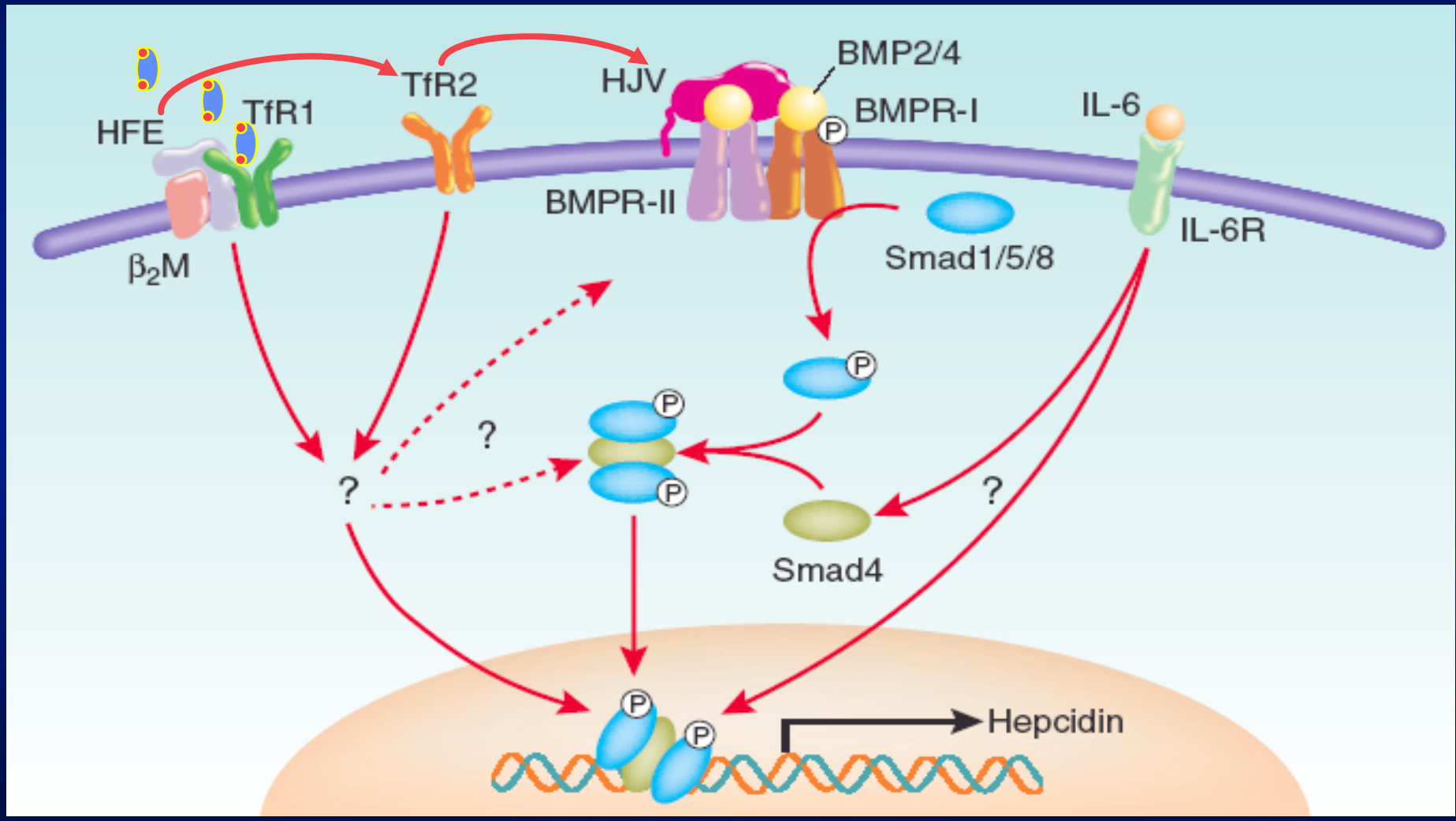
IRON METABOLISM
Regulation of hepcidin synthesis



Ajioka et al, The Hematologist 2008

IRON METABOLISM

Regulation of hepcidin synthesis

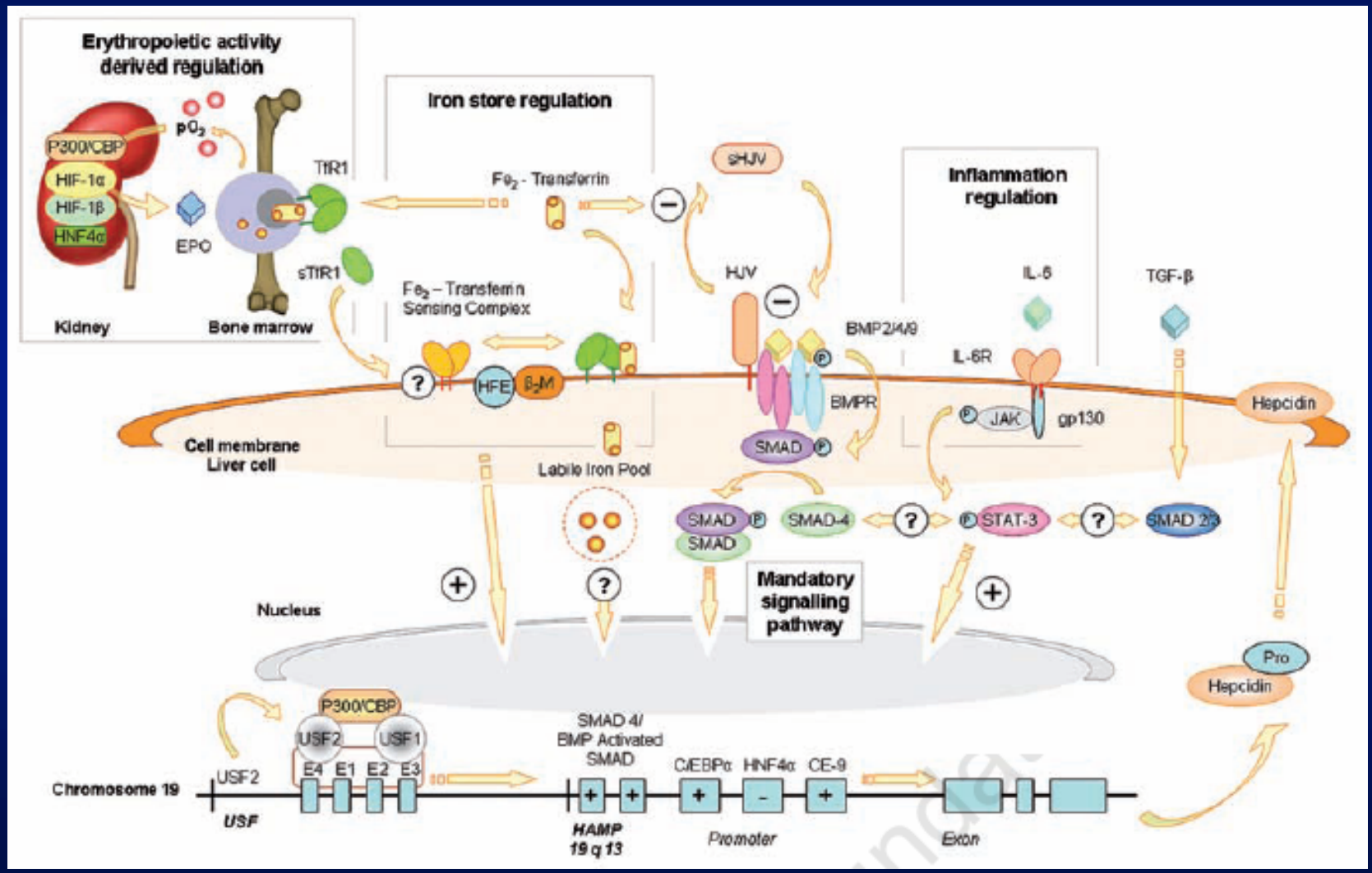


Anderson et al, Nature Genetics 5:503, 2006

Adapted from: Goswami T, Andrews NC. J Biol Chem. 2006;281: 28494-8

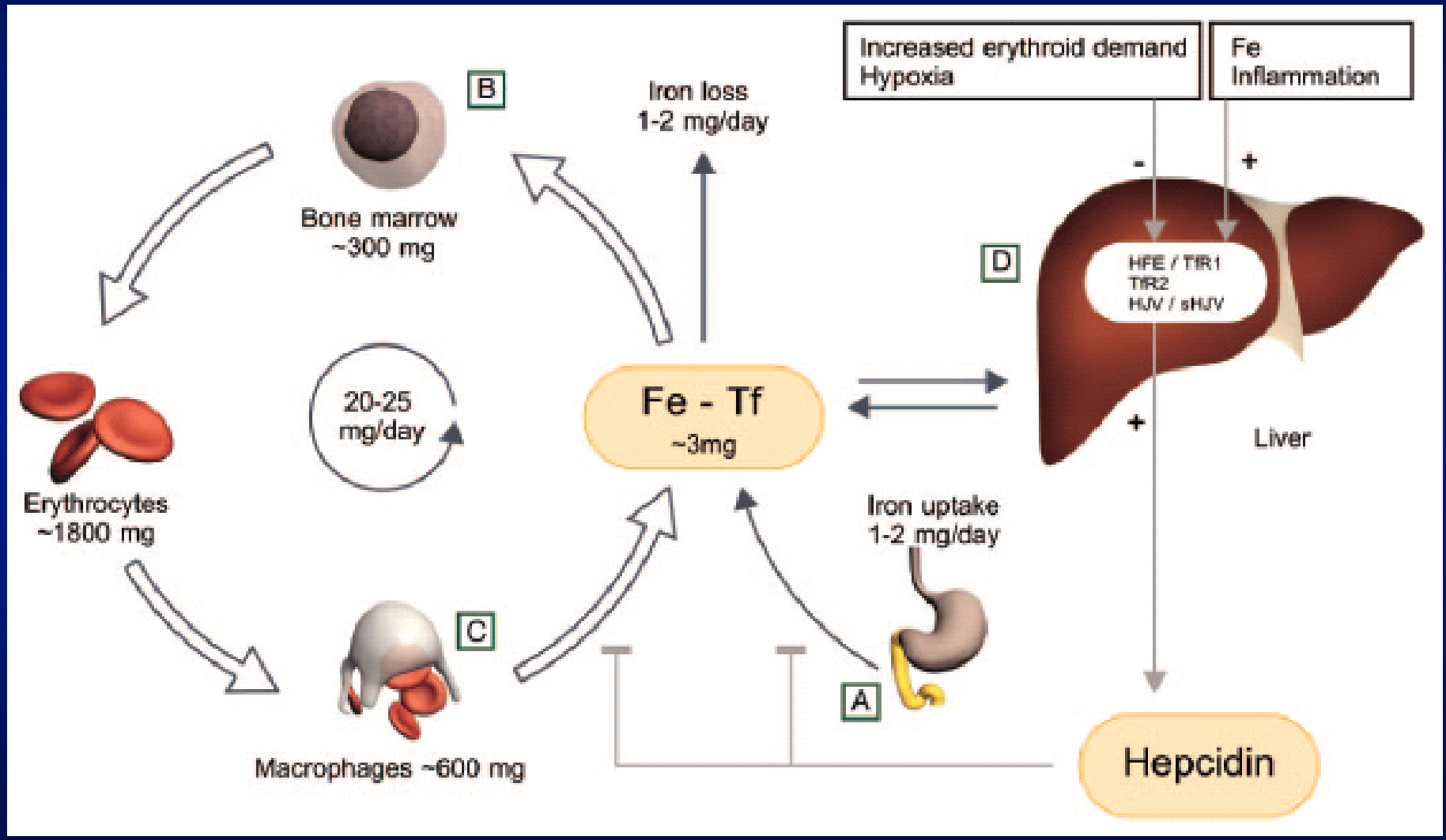
IRON METABOLISM

Regulation of hepcidin synthesis



Kemna et al, Haematologica 2008

IRON METABOLISM



Swinkels et al, Clin.Chem. 52:950, 2006

IRON PARAMETERS

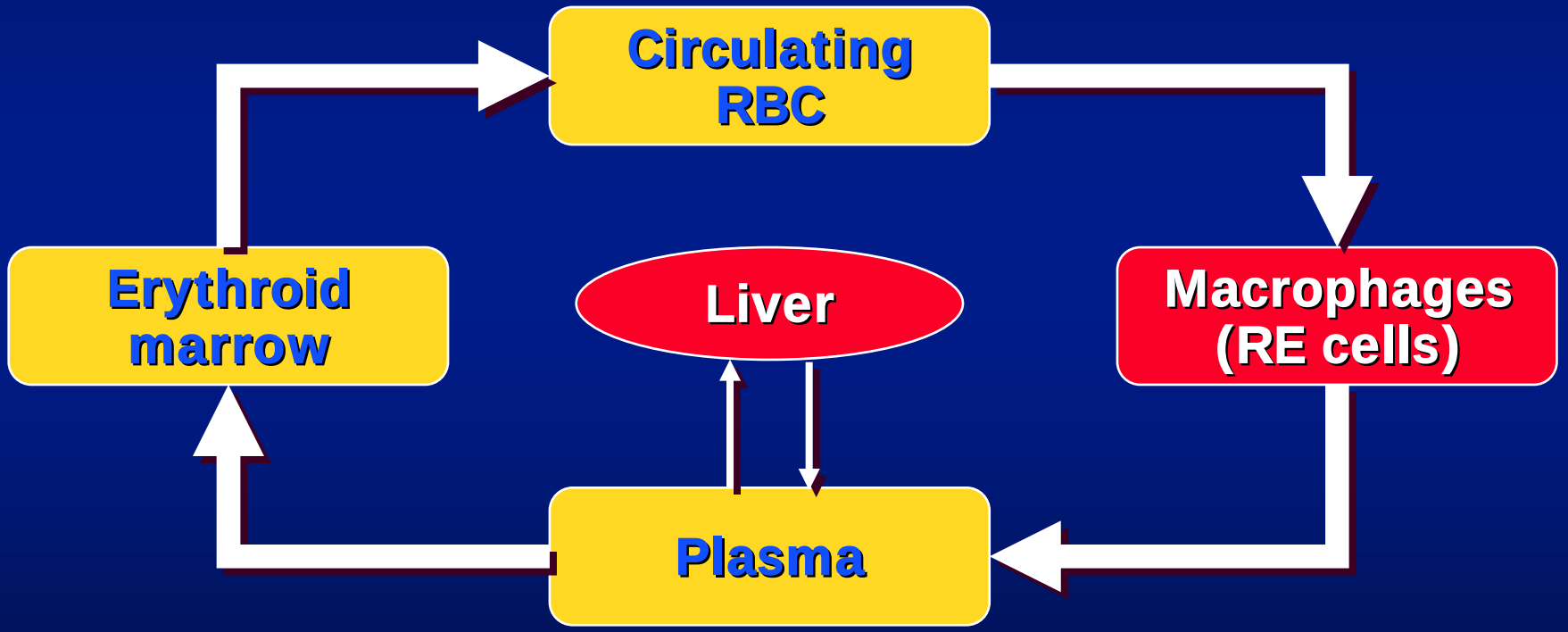
IRON METABOLISM
Biological markers

- Ferritin
- Transferrin saturation
- sTfR
- Red cell indices (HYPO, CHr)
- Hepcidin

FERRITIN

IRON PARAMETERS

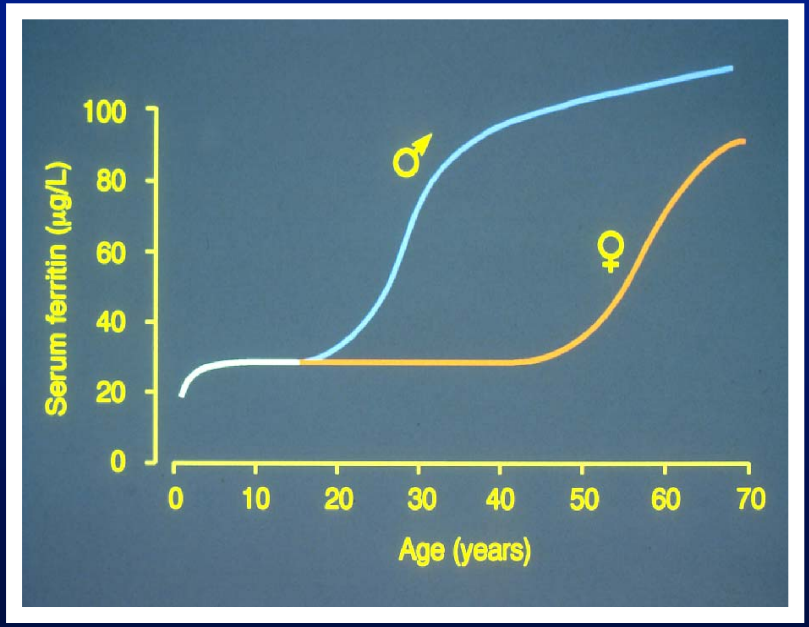
Storage iron : serum ferritin



FERRITIN

Serum ferritin

- Represents iron stores (macrophages and hepatocytes) 1 µg/L = 120 µg/kg storage iron
- Low ferritin (< 12 to 25 mg/L according to assay) 100% specific for iron deficiency
- Normal range varies with age and sex



FERRITIN

Serum ferritin

- **Falsely elevated serum ferritin**
  - **Inflammation : lower limit 40-120 µg/L**
  - **Renal failure : lower limit 40-100 µg/L**
  - **Liver damage**
  - **Hyperthyroidism**
  - **Some forms of cancer**
  - **Poorly controlled diabetes mellitus (ferritin glycosylation)**
  - **Hyperferritin-cataract syndrome**
  - **Benign hyperferritinemia**

FERRITIN
Hyperferritin-cataract syndrome

- Moderately increased SF
- Normal TS
- No tissue IO (LIC, MRI)
- Early-onset cataract

- Autosomal dominant
- Mutation in L-ferritin IRE

FERRITIN
Benign hyperferritinemia

- Moderately increased SF
  (SF > 90% glycosylated)
- Normal TS
- No tissue IO (LIC, MRI)
- No clinical symptom

- Autosomal dominant
- No mutation in L-ferritin IRE
- C89T mutation (gene), T30I mutation (protein) L-ferritin
  - 50% of family cases
  - Some sporadic cases

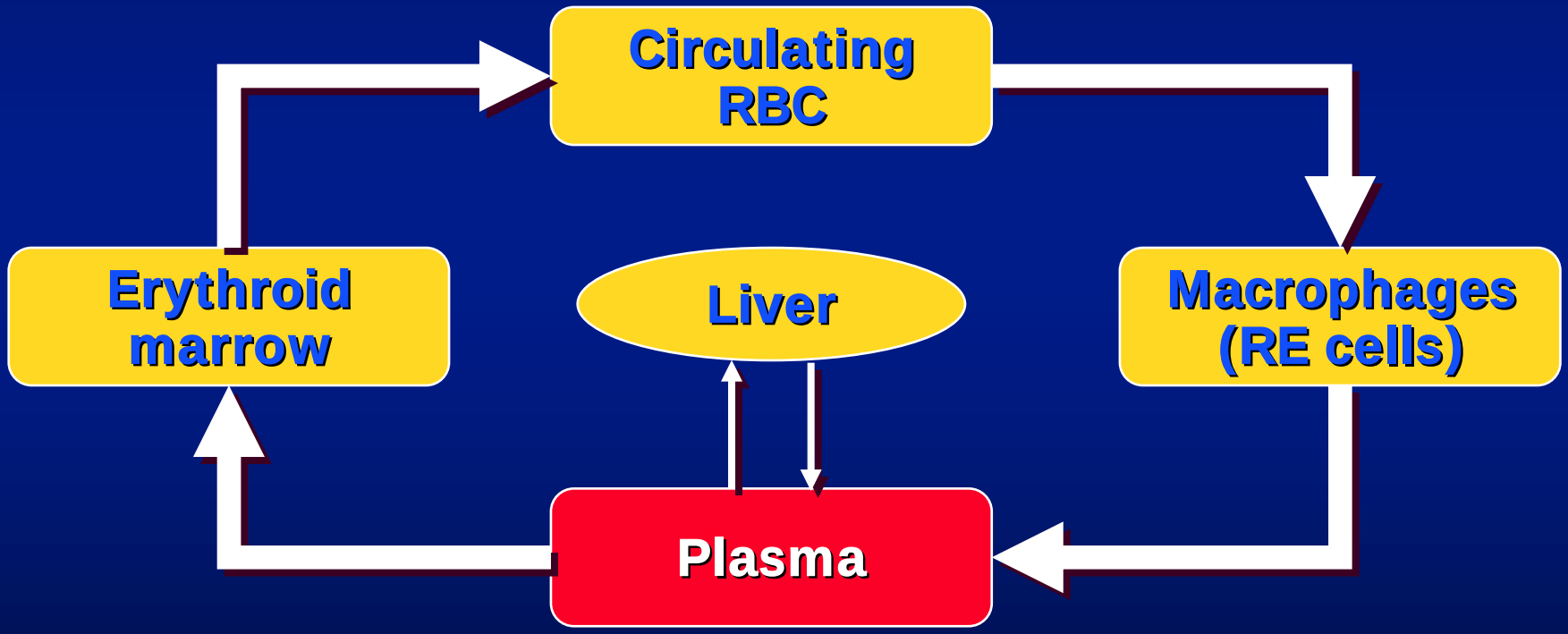
Kannengiesser et al, Haematologica 94:335, 2009

TRANSFERRIN SATURATION

Tsat

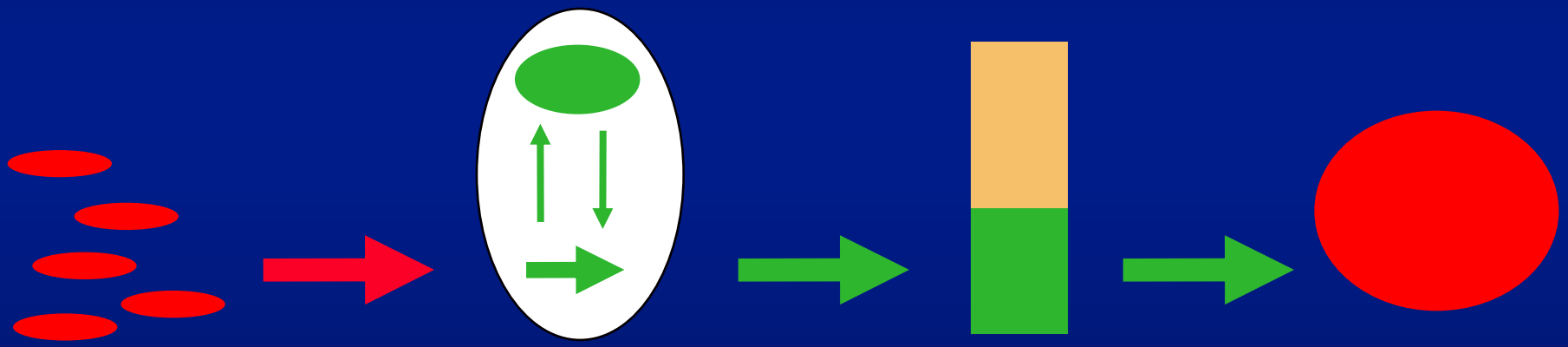
IRON PARAMETERS

Plasma iron : transferrin saturation



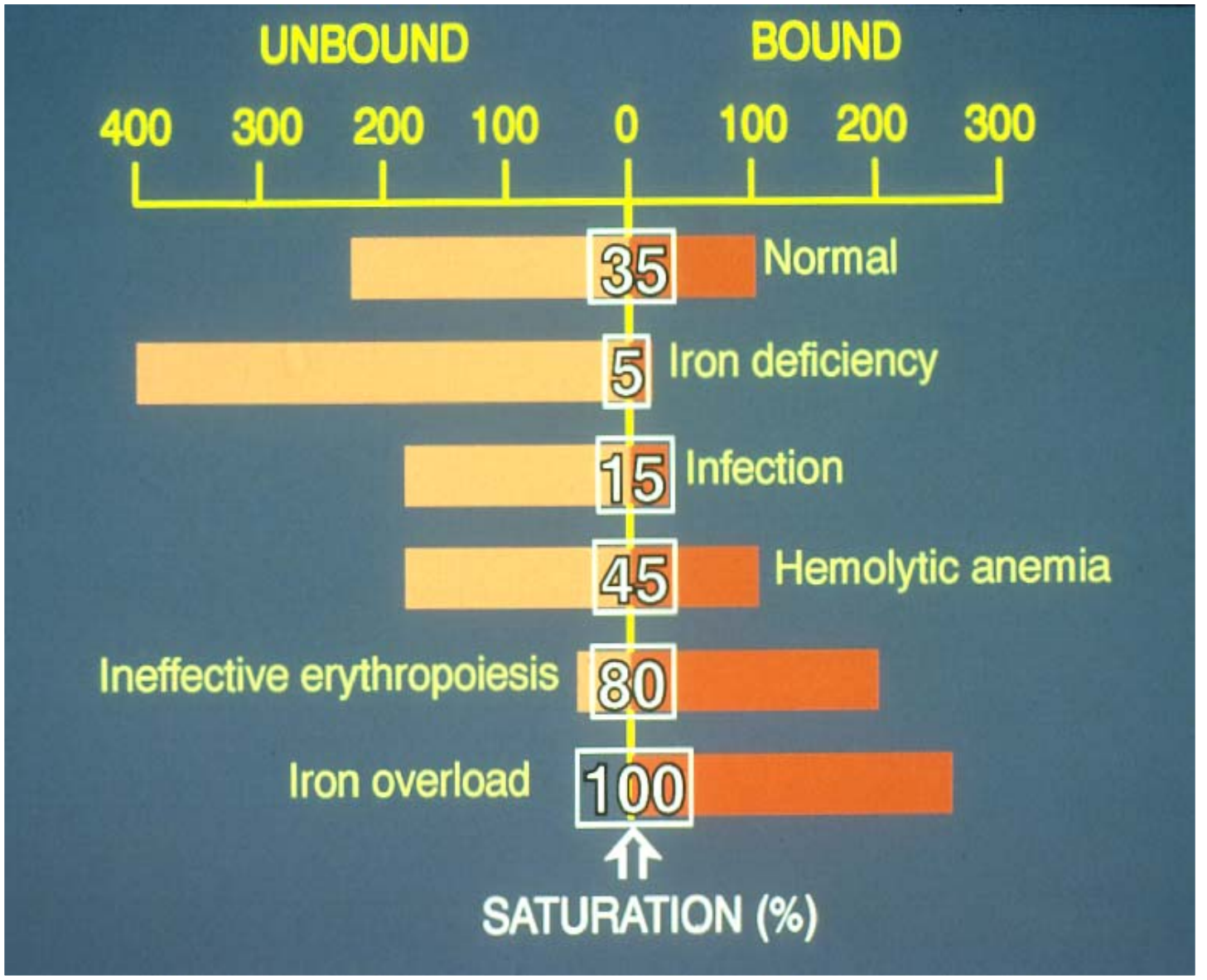
TRANSFERRIN SATURATION

Normal



Macrophages Plasma Marrow

TRANSFERRIN SATURATION

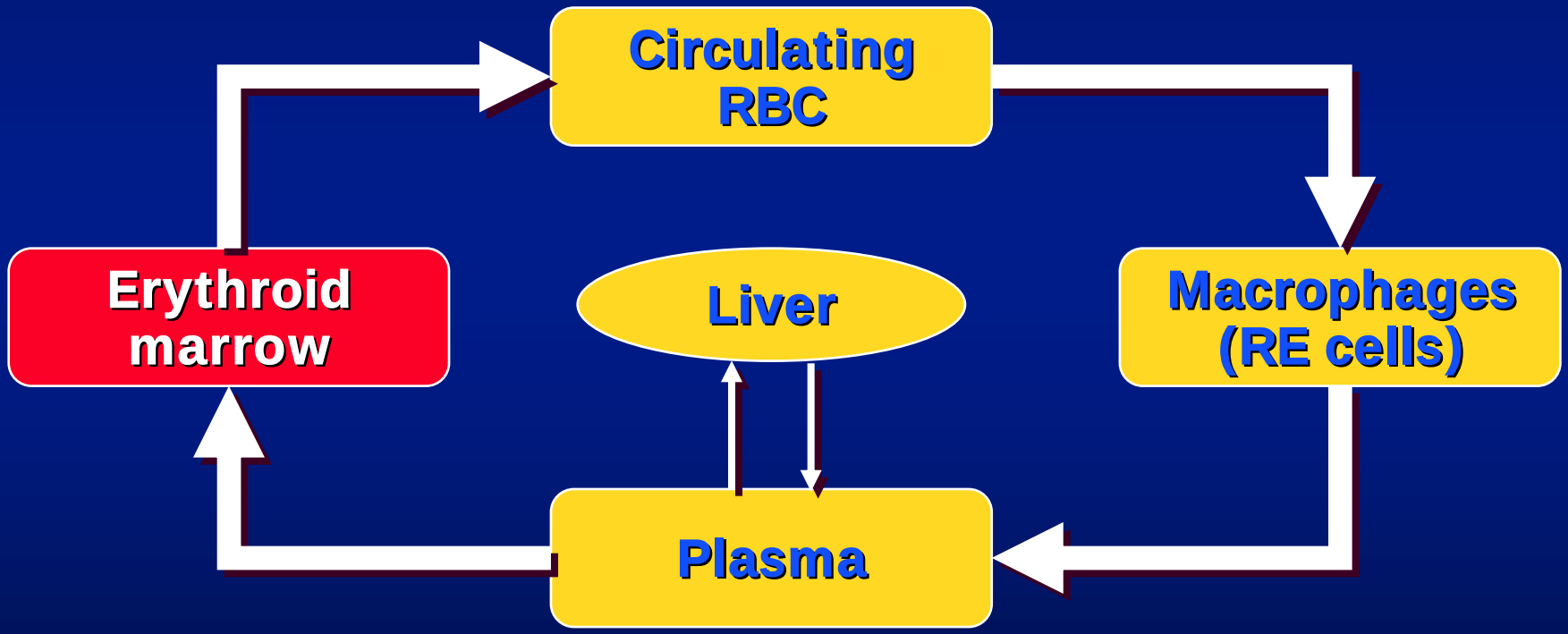


SOLUBLE TRANSFERRIN RECEPTOR

sTfR

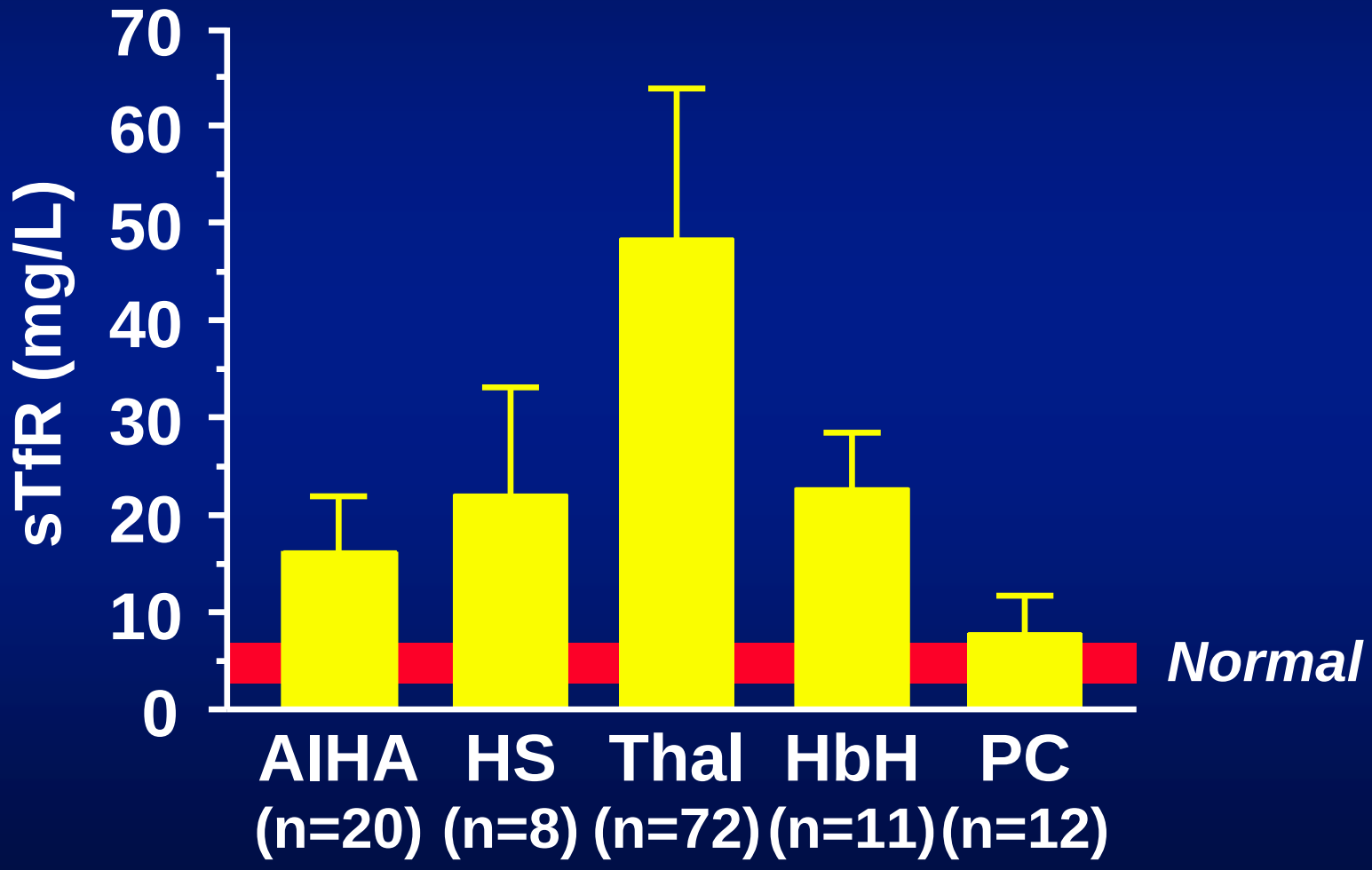
IRON PARAMETERS

Erythroid marrow : sTfR



SOLUBLE TRANSFERRIN RECEPTOR

Hyperplastic erythropoiesis

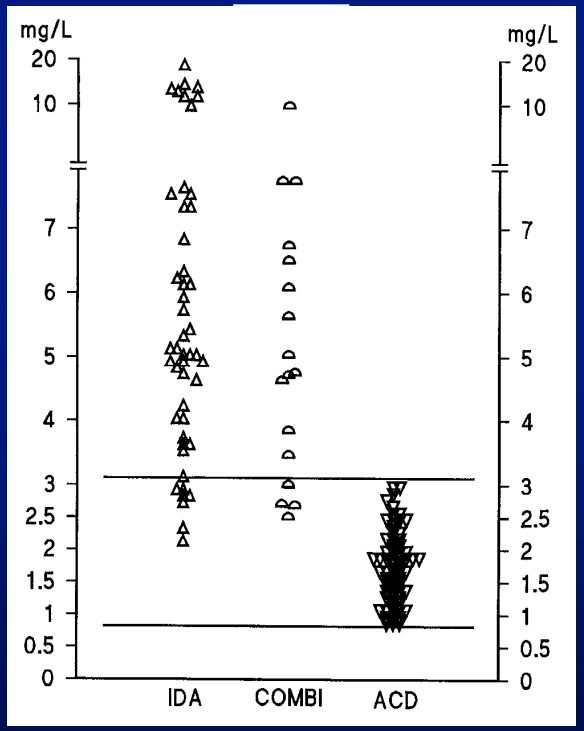


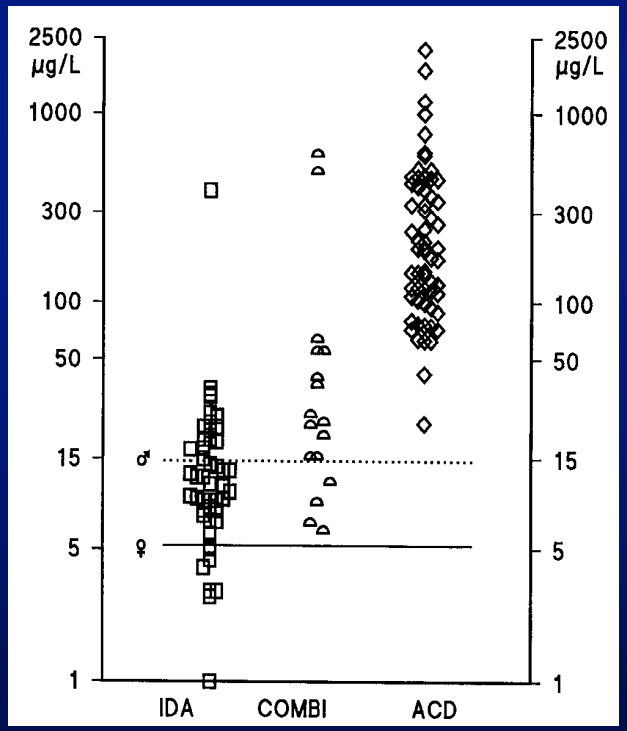
Hubers et al. *Blood* 1990;75:102

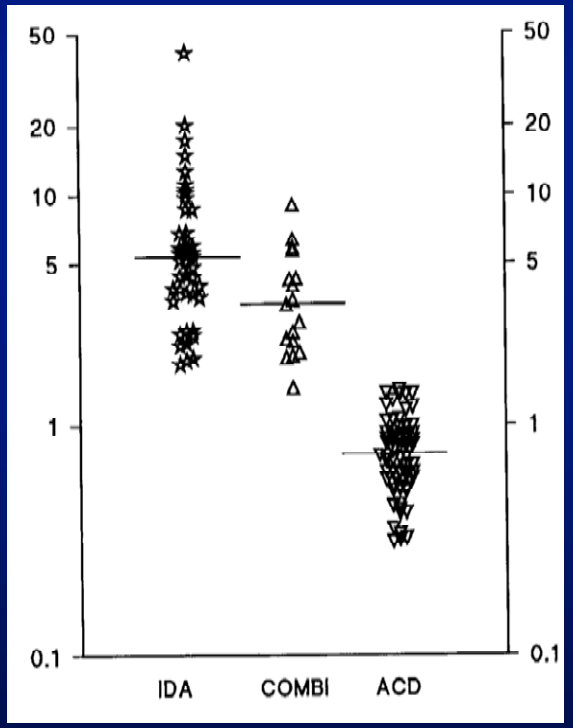
SOLUBLE TRANSFERRIN RECEPTOR

IDA *vs* ACD *vs* combined ACD+ID

sTfR | **Ferritin** | **sTfR/log ferritin**







Marrow iron

Punnonen *et al*., Blood 1997, 89:1052

RBC INDICES

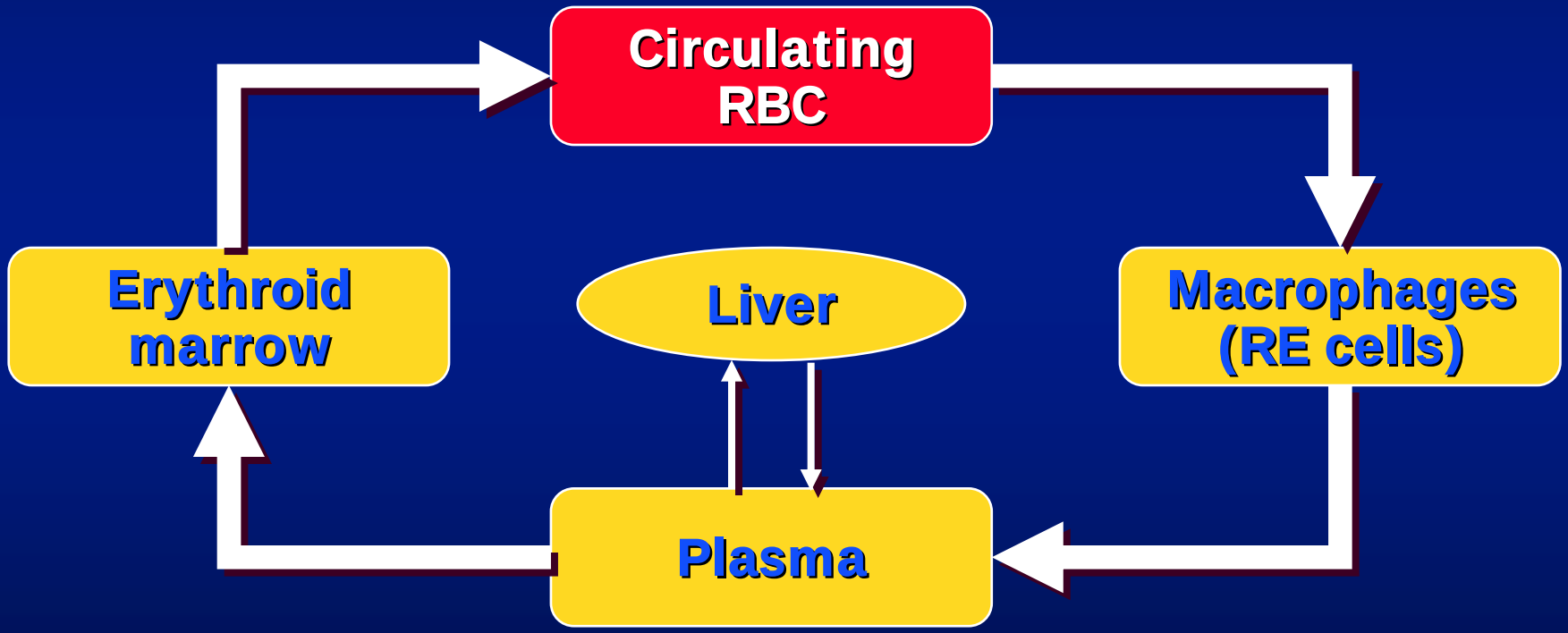
HYPO

&

CHr

IRON PARAMETERS

RBC iron : CHr and HYPO

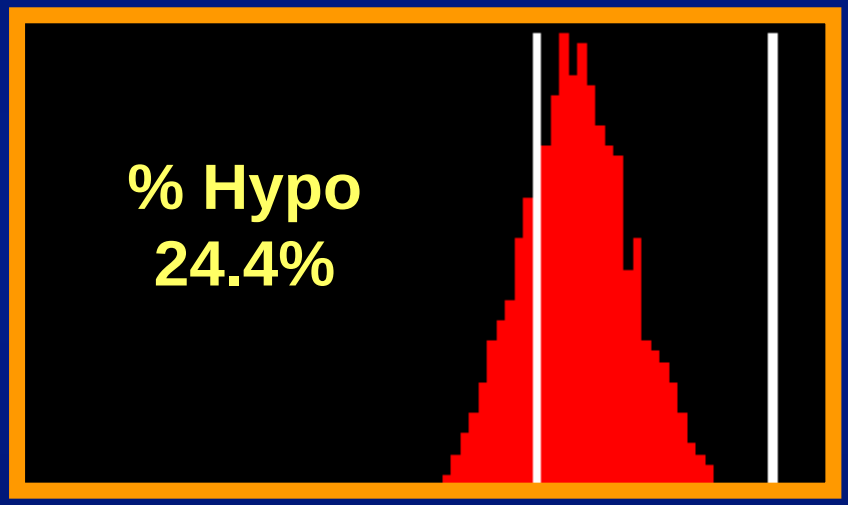


RBC INDICES

Hypochromic erythrocytes : HYPO

- **Normal < 5%**
- **Increased % HYPO (>5-10 %) indicative of iron deficient erythropoiesis**

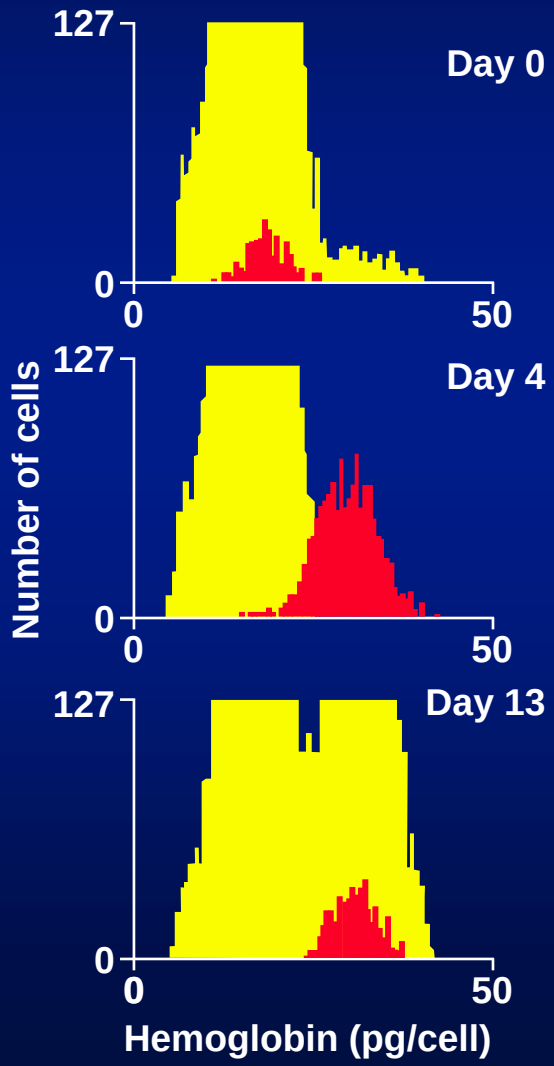
  (long-term)



RBC INDICES

Hb content of reticulocytes : CHr

ID anemia
Treatment with IV iron



Yellow : MCH
Red : CHr

- **Normal 26–30 pg**
- **Low CHr (< 26 pg) indicative of iron deficient erythropoiesis**

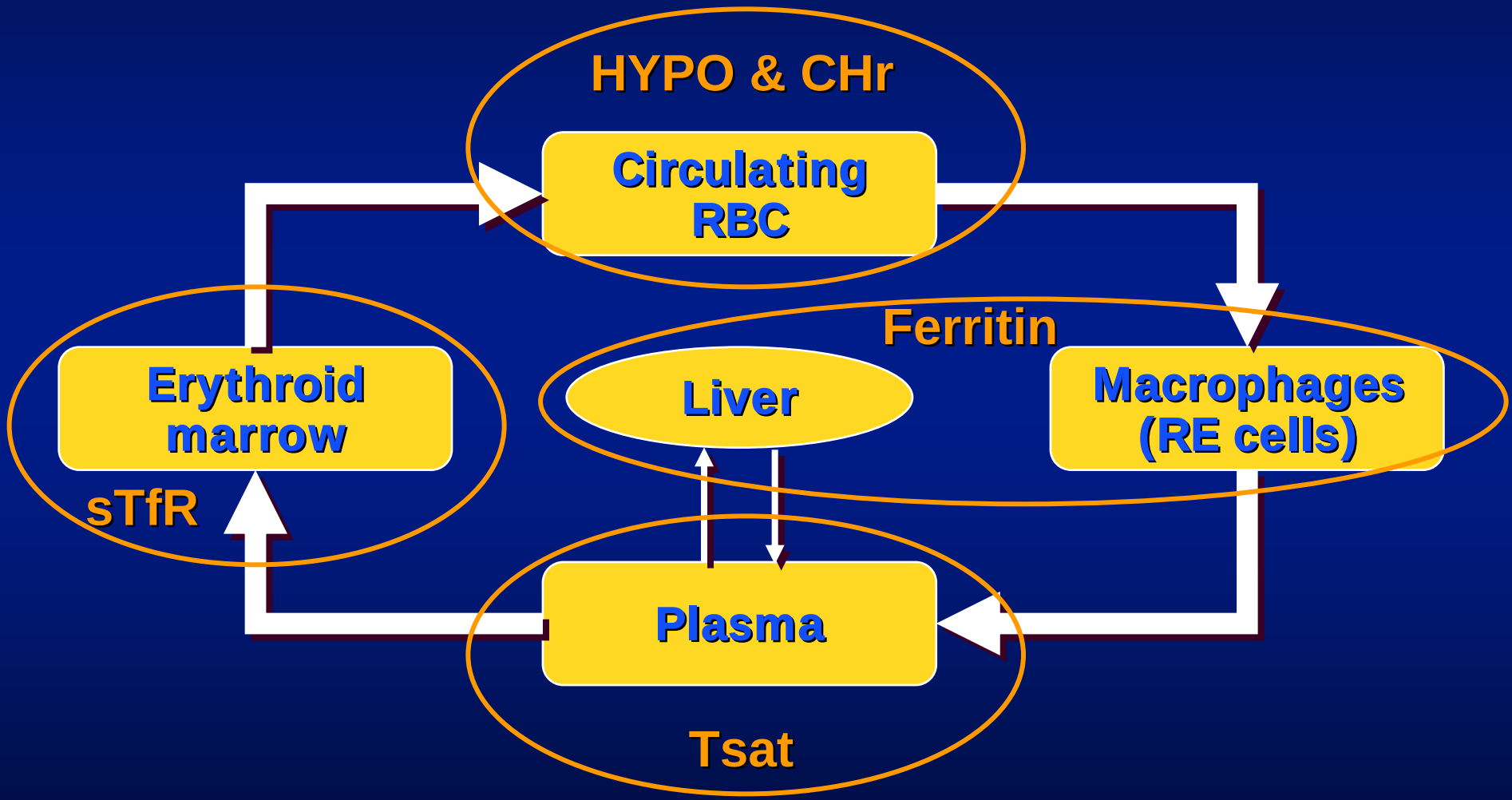
(short-term)

Brugnara et al.
Blood 1994;83:3100

IRON PARAMETERS
SUMMARY

IRON METABOLISM

Iron compartments



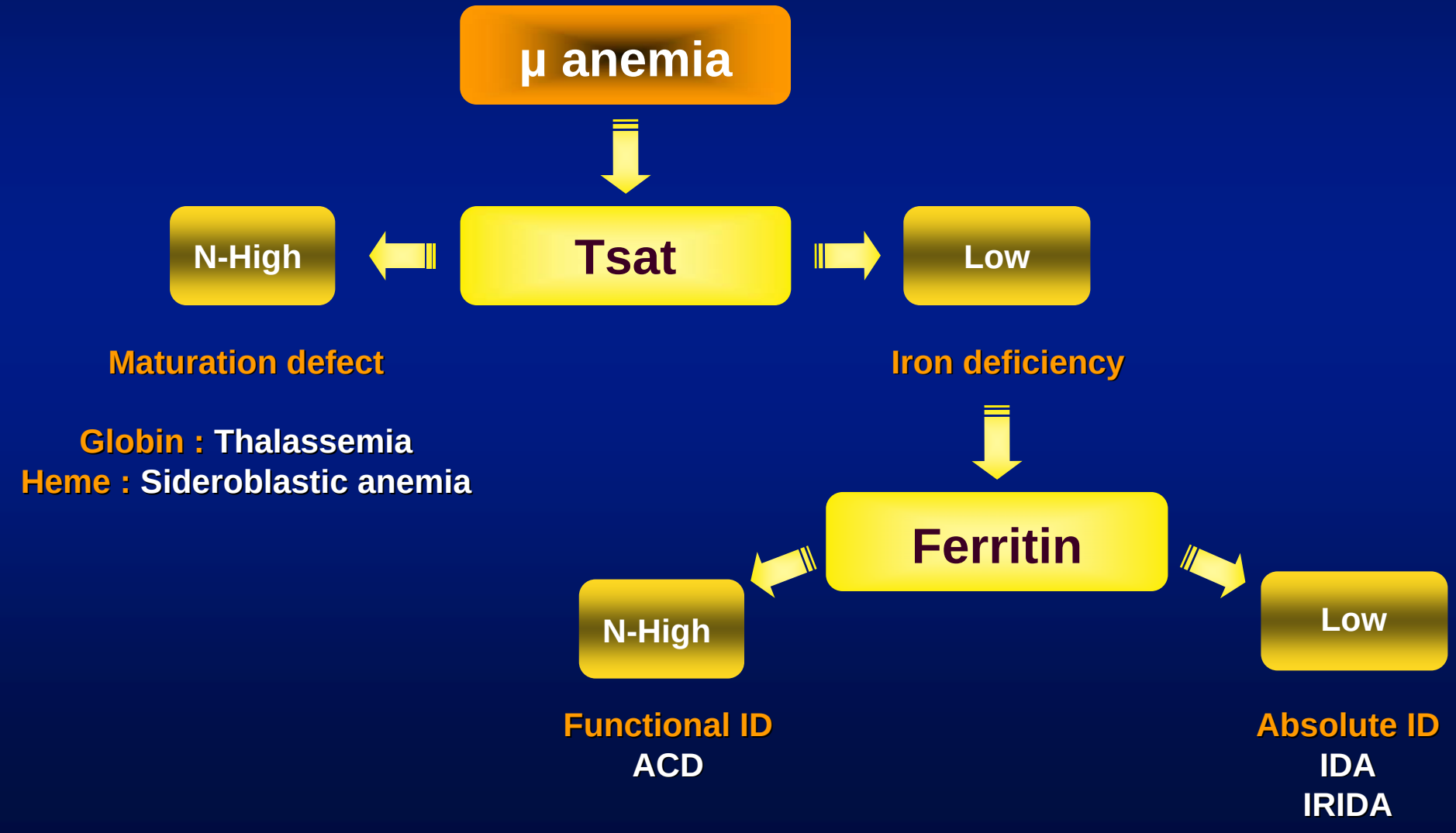
IRON DEFICIENCY

IRON DEFICIENCY
Disorders

- Iron deficiency anemia (IDA)
- Functional iron deficiency
  - Inflammation
  - EPO therapy
- IRIDA

MICROCYTIC ANEMIA

Differential diagnosis



IRON DEFICIENCY

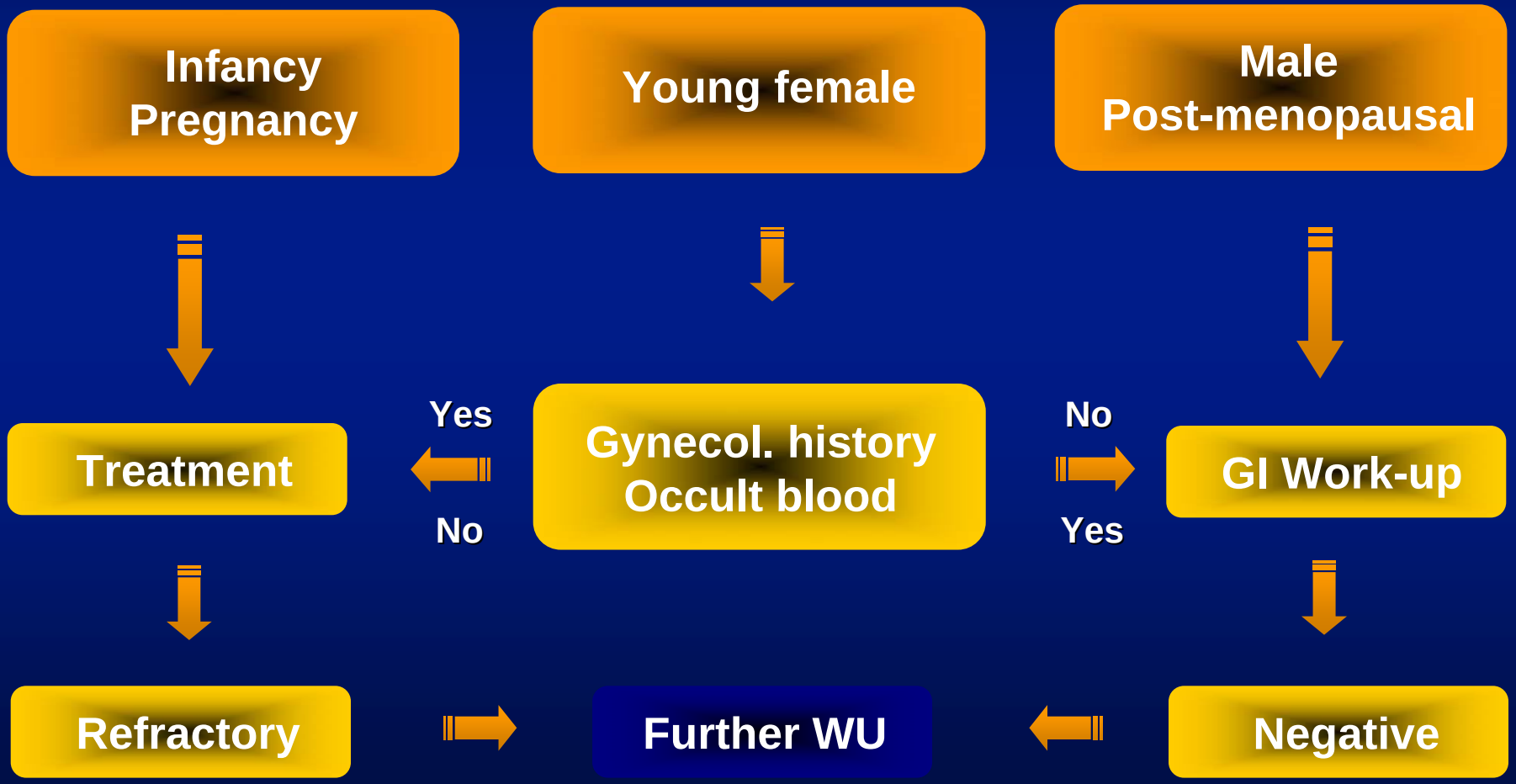
IDA

IRON DEFICIENCY ANEMIA

Etiology

IRON DEFICIENCY ANEMIA

Work-up



IRON DEFICIENCY ANEMIA
Additional work-up

- Celiac disease
  - Endomysial antibodies
  - Gliadin antibodies
- Autoimmune atrophic gastritis
  - Elevated gastrin
  - Parietal cell antibodies
- H. Pylori chronic gastritis
  - H. Pylori antibodies
  - Urea breath test

IRON DEFICIENCY ANEMIA

Stages (1)

- **Stage 1 : depletion of iron stores**
  - **Serum ferritin : ↓ to < 12 µg/L**
- **Stage 2 : iron-deficient erythropoiesis**
  - **Serum iron : ↓ < 60 µg%**
  - **Tf saturation ↓ < 15 %**
  - **% hypochromic RBC ↑ > 5 %**
  - **CHr ↓ < 26 pg**
  - **Soluble TfR ↑ > 7 mg/L**
  - **RBC protoporphyrin ↑ > 70 µg%**
- **Stage 3 : iron-deficiency anemia**

IRON DEFICIENCY ANEMIA

Stages (2)

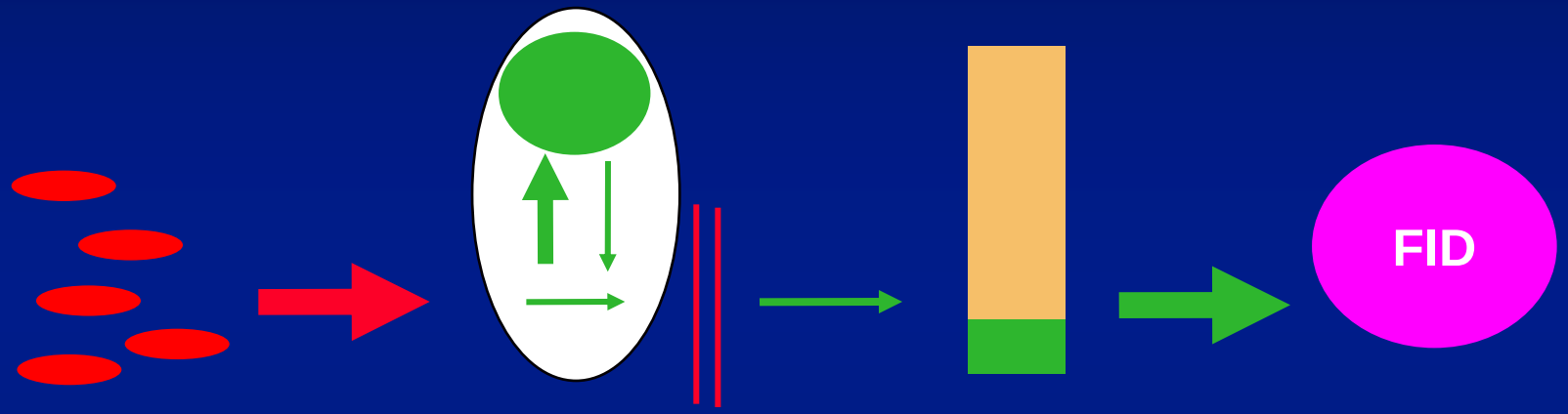
- Stage 1 : depletion of iron stores
- Stage 2 : iron-deficient erythropoiesis
- Stage 3 : iron-deficiency anemia
  - Hemoglobin : ↓ < 12 gr/dl (F) 13.5 gr/dl (M)
  - Hematocrit : ↓ < 36 % (F) or 41 % (M)
  - RBC : N then ↓
  - MCV : ↓ < 80 fl (microcytosis)
  - MCH : ↓ < 28 pg (hypochromia)

IRON DEFICIENCY

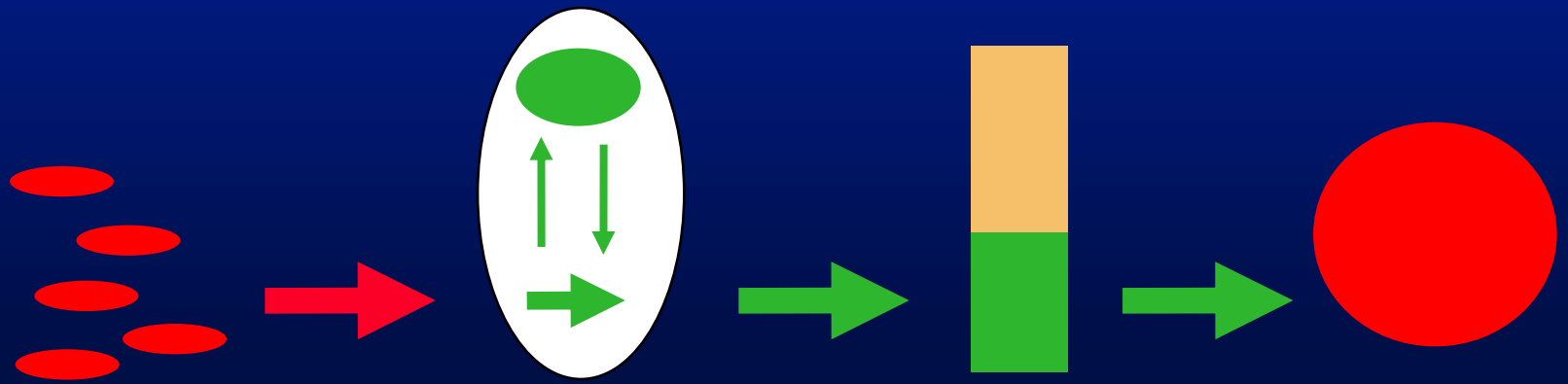
Functional ID

FUNCTIONAL IRON DEFICIENCY

Inflammation

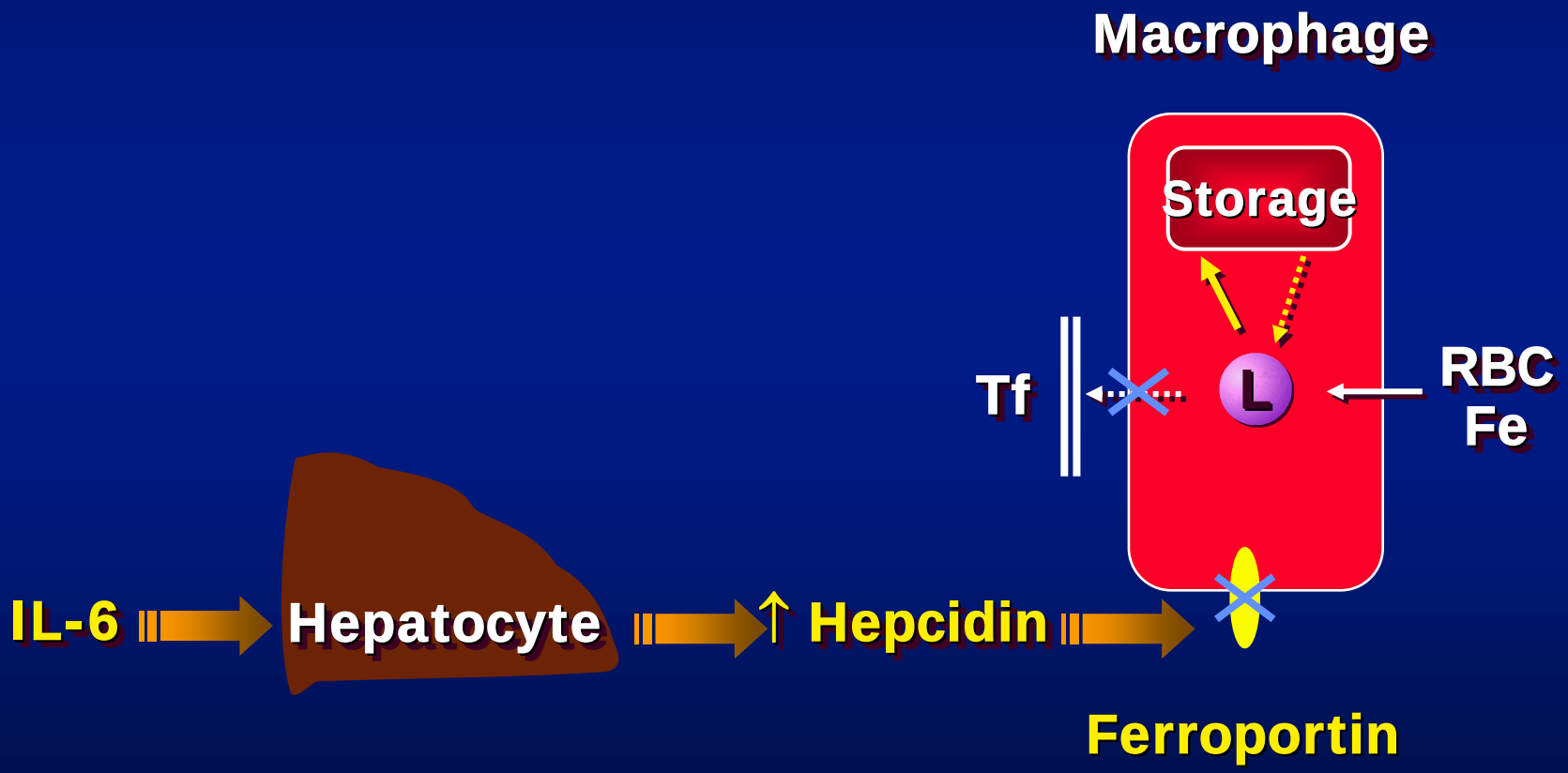


Macrophages Plasma Marrow



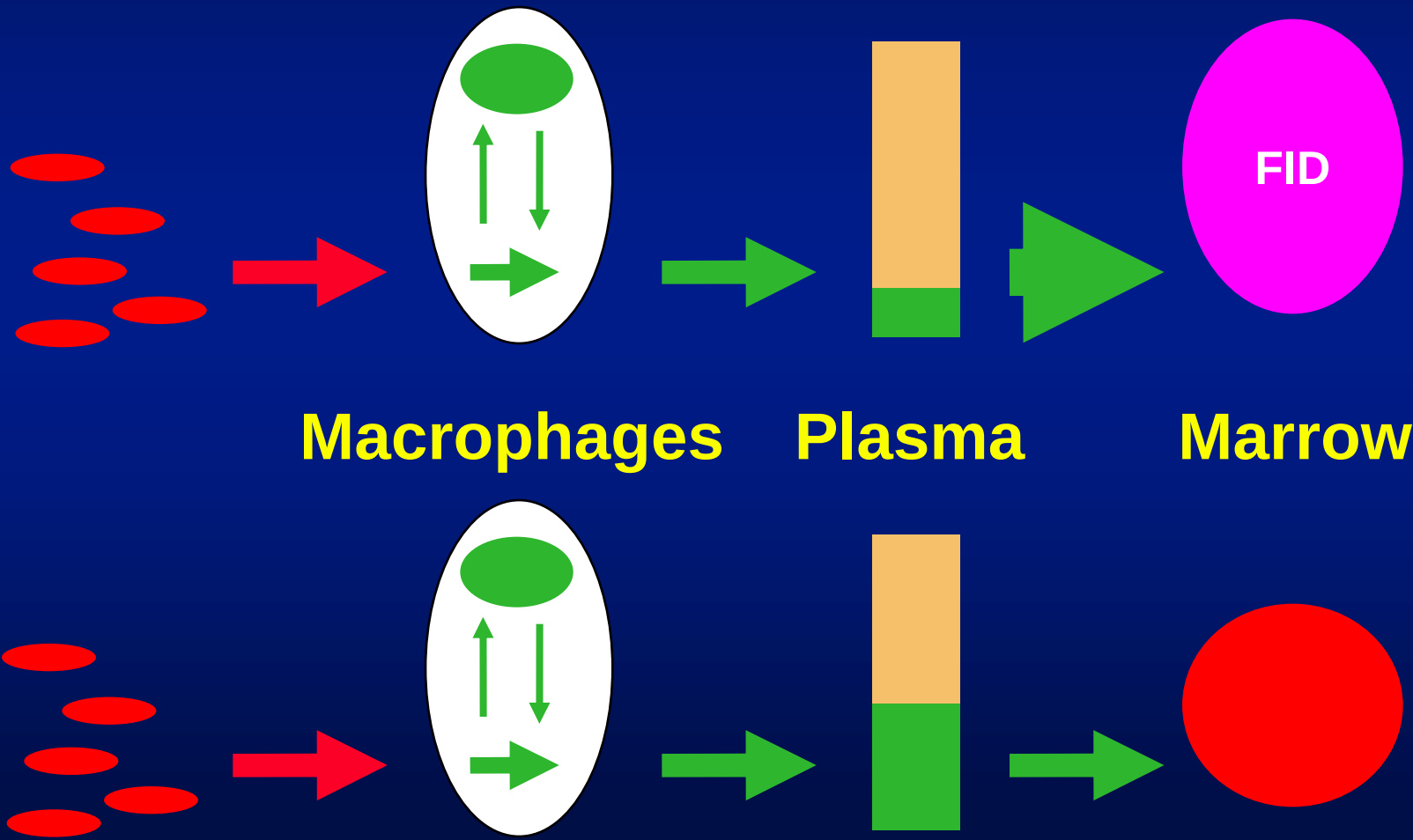
HEPCIDIN

Mediator of inflammation ?



FUNCTIONAL IRON DEFICIENCY

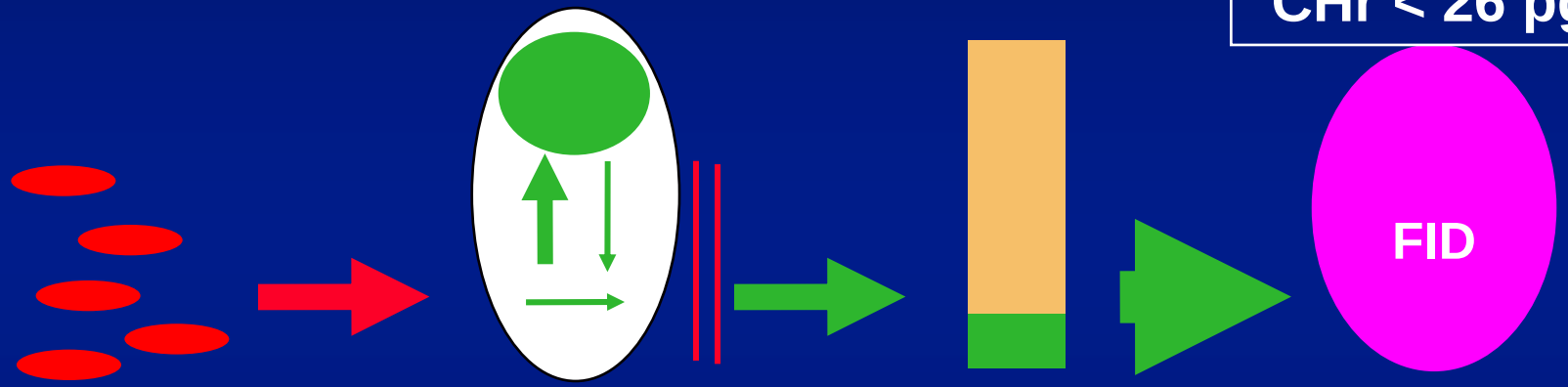
EPO therapy



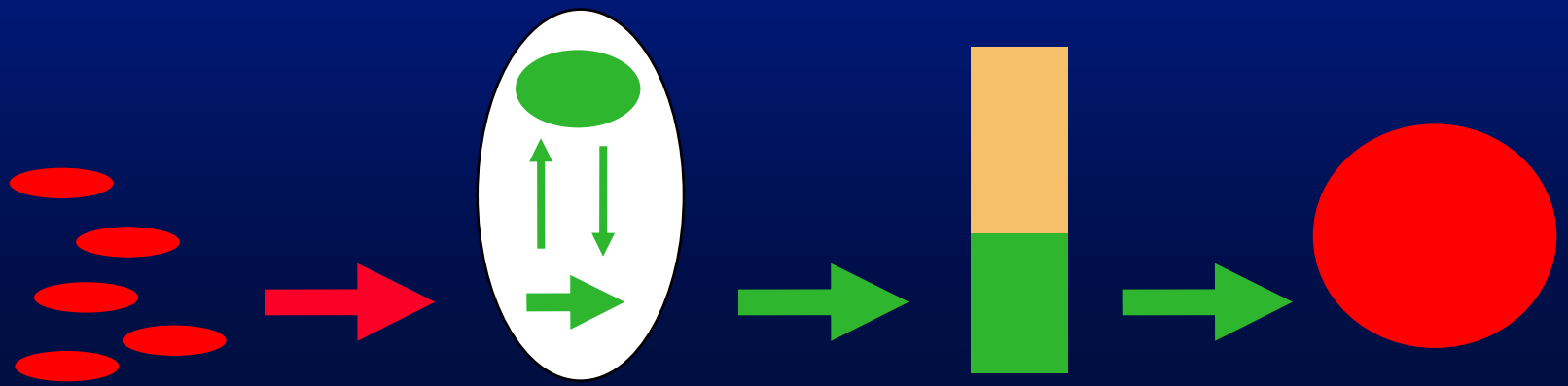
FUNCTIONAL IRON DEFICIENCY

EPO therapy in cancer

TSat < 20%
%HYPO > 5%
CHr < 26 pg

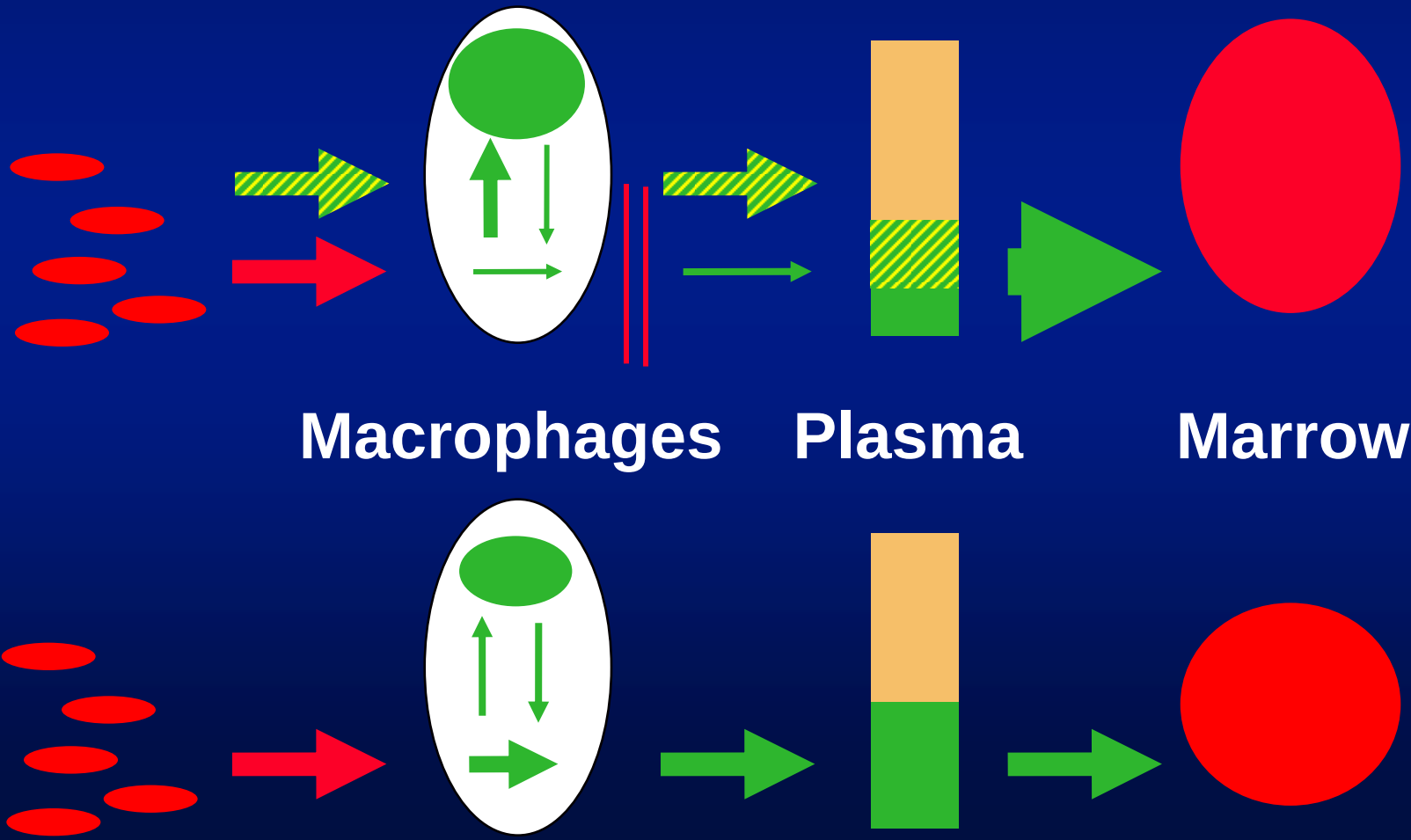


Macrophages Plasma Marrow



FUNCTIONAL IRON DEFICIENCY

ACD + EPO therapy : IV iron

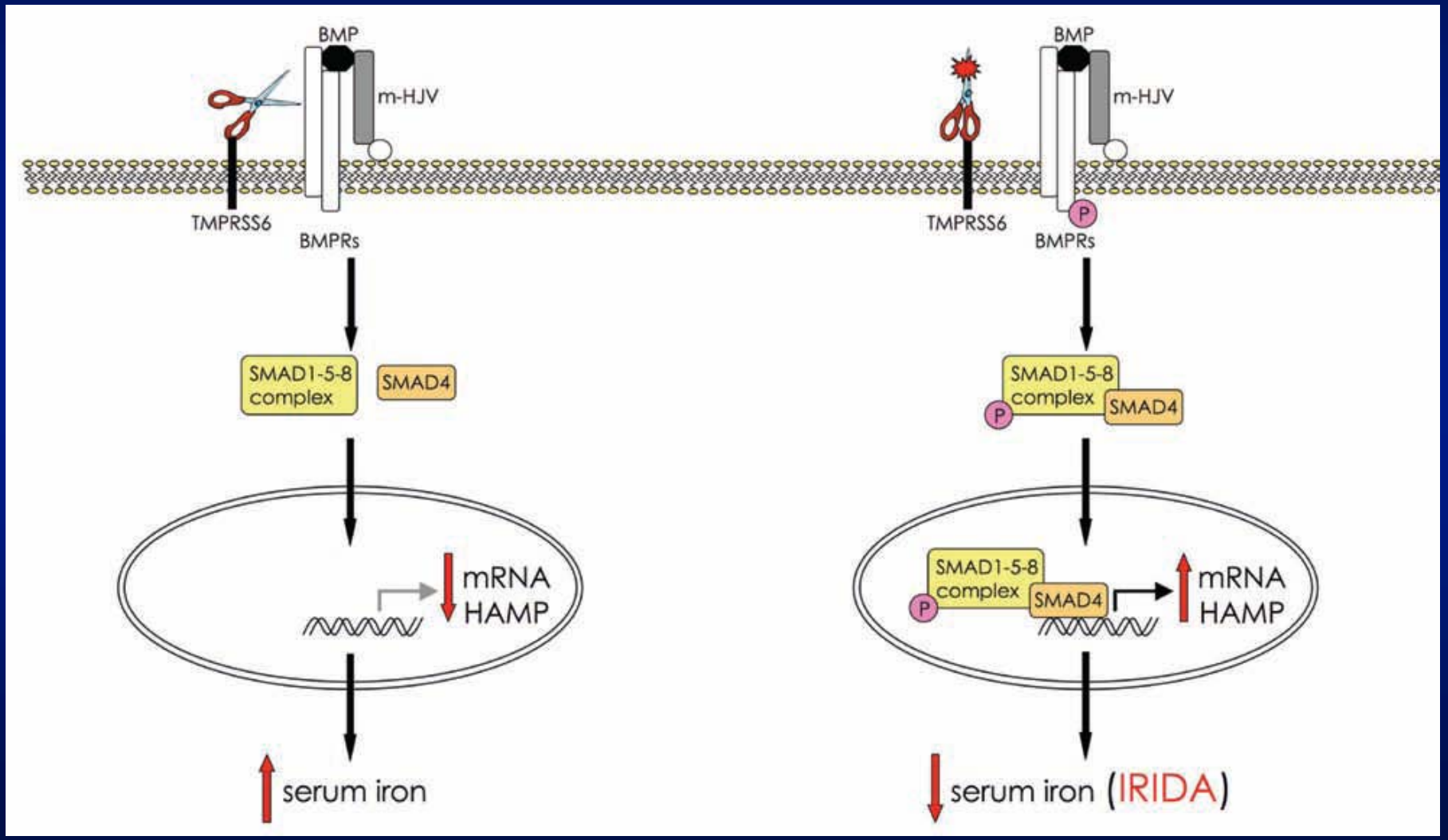


IRON DEFICIENCY

IRIDA

IRON DEFICIENCY ANEMIA

IRIDA



Camaschella, Haematologica 93:1441, 2008

IRON OVERLOAD

IRON OVERLOAD
Disorders

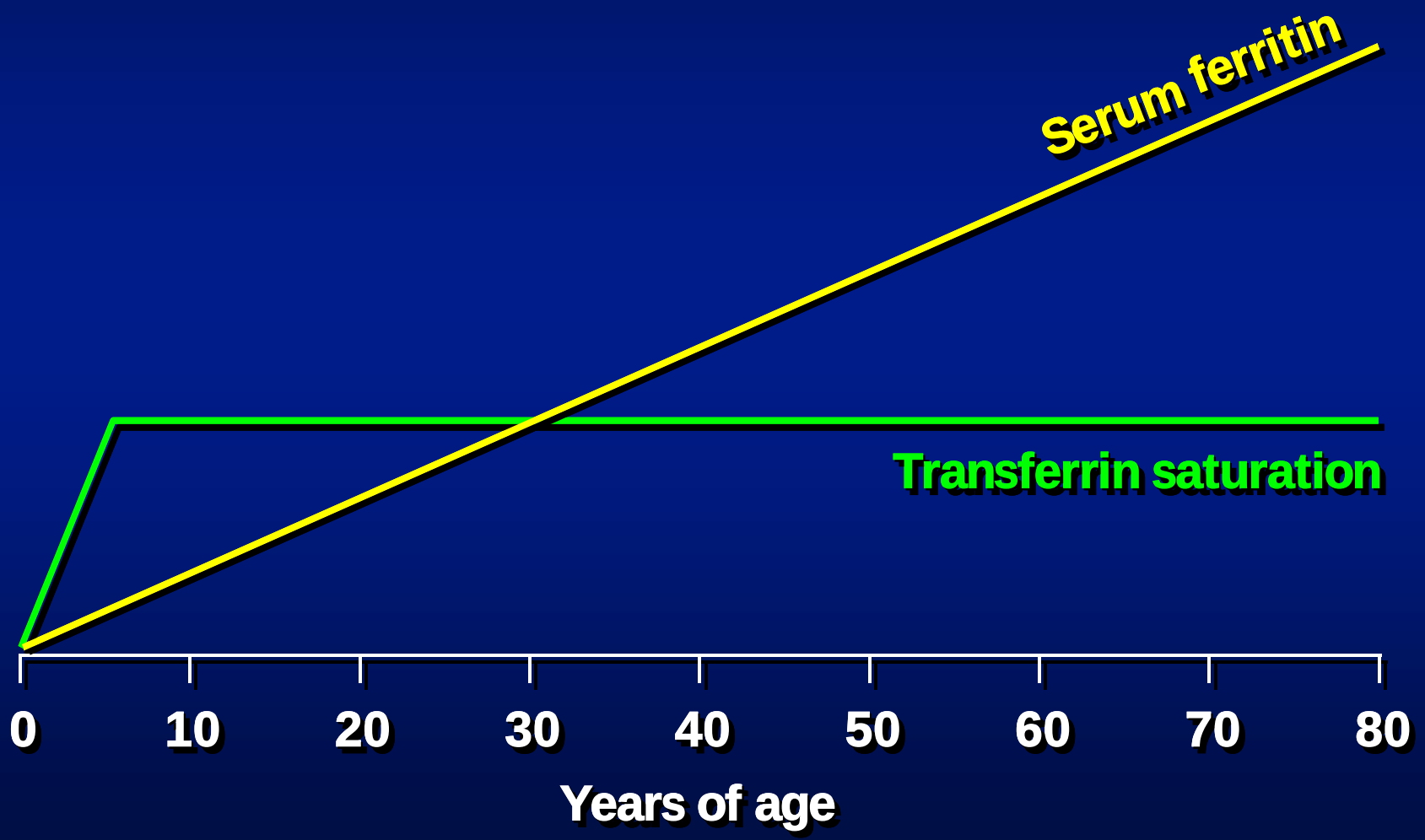
- Genetic hemochromatosis
- Ferroportin disease
- Metabolic syndrome
- Secondary IO

IRON OVERLOAD

Genetic hemochromatosis

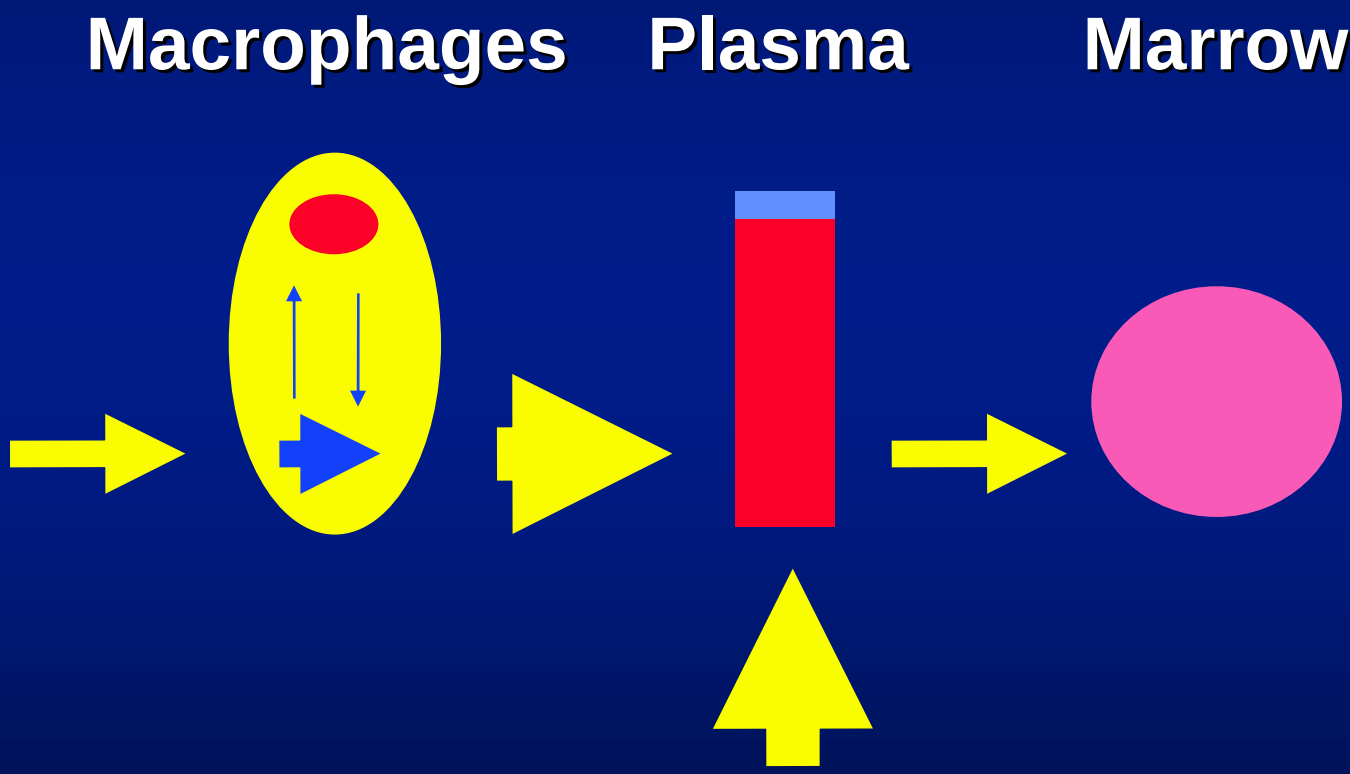
HEREDITARY HEMOCHROMATOSIS

Iron parameters



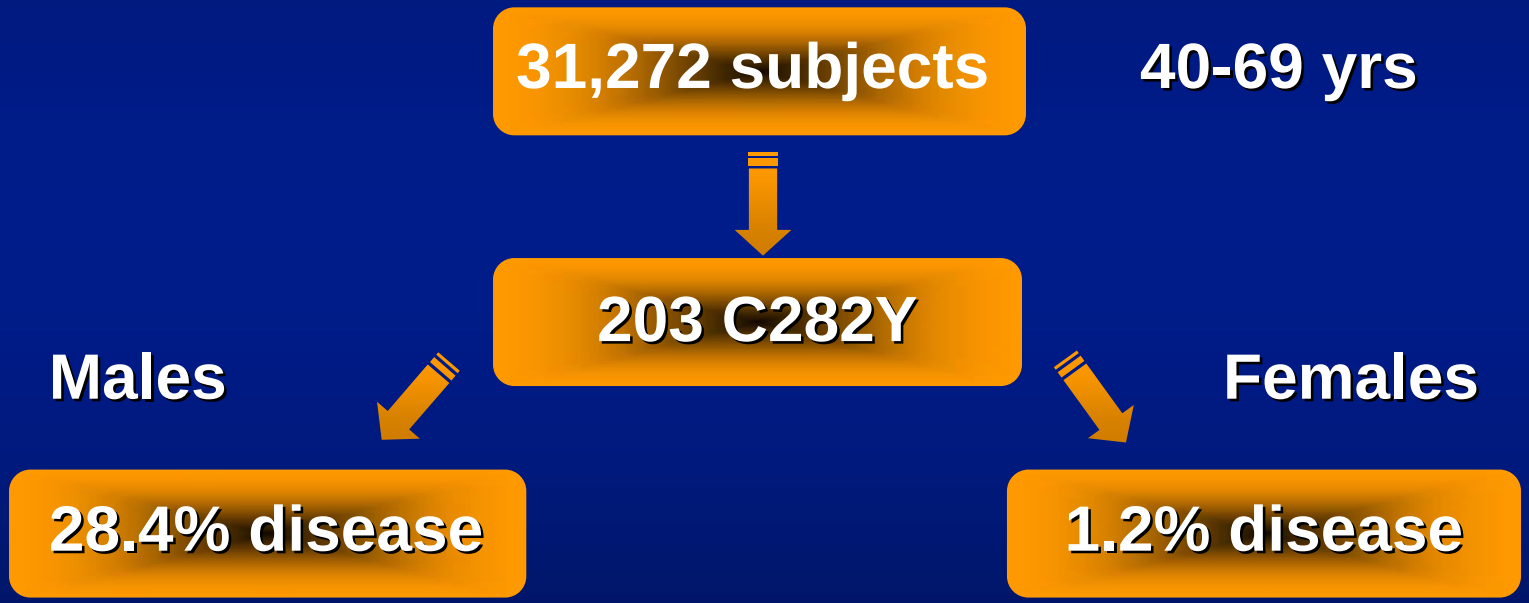
IRON KINETICS

Classical hemochromatosis



HEREDITARY HEMOCHROMATOSIS

Phenotypic expression



IO-related disease/symptoms

Allen et al, NEJM 358:221, 2008

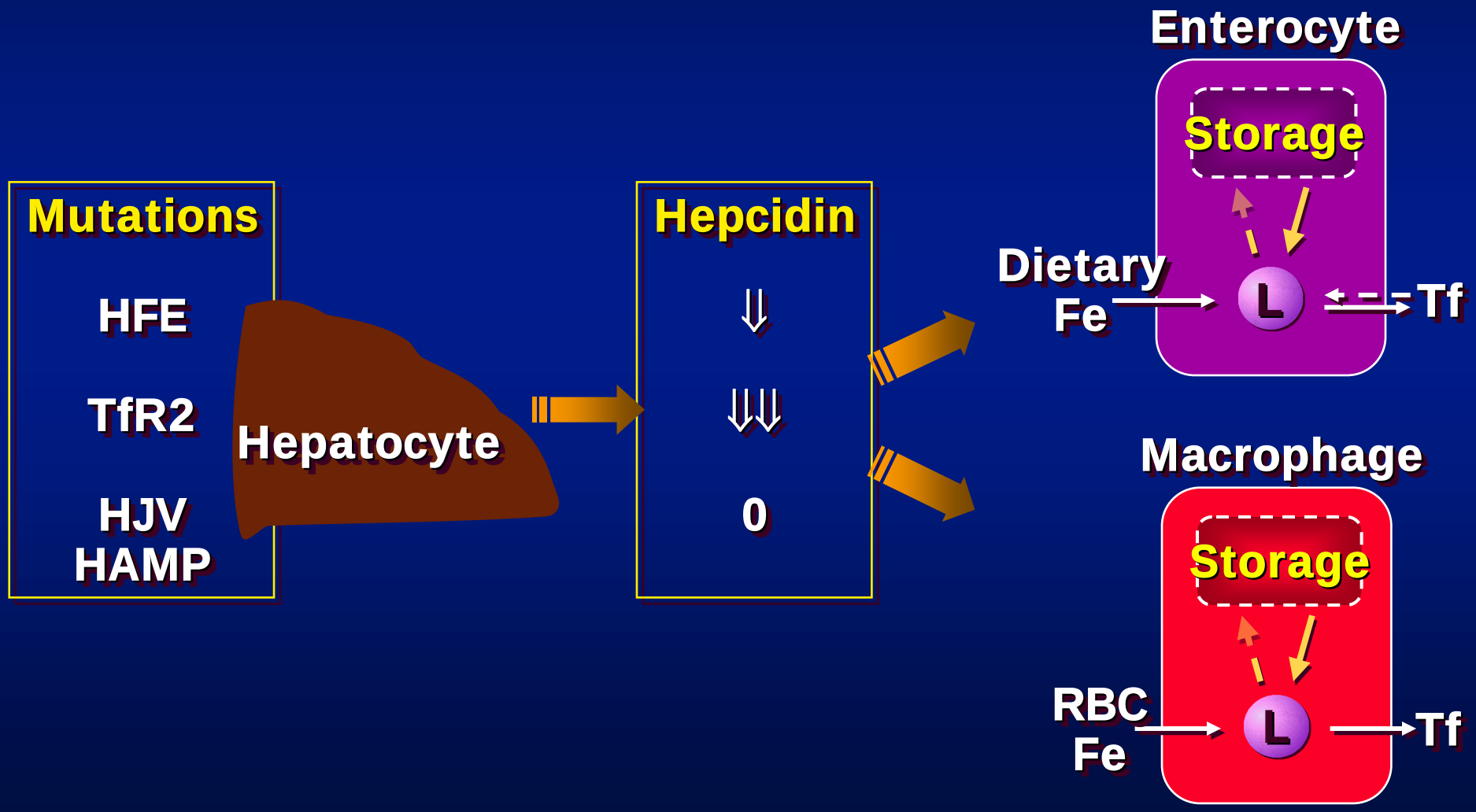
HEREDITARY HEMOCHROMATOSIS

Genetic classification

Disease	Gene	Chromosome	Inheritance	Phenotype
Type 1	HFE	6p	Recessive	Classic
Type 2 A	Hemojuvelin	1q	Recessive	Juvenile
Type 2 B	Hepcidin	19q	Recessive	Juvenile
Type 3	TfR 2	7q	Recessive	Intermediate
Type 4	Ferroportin	2q	Dominant	Atypical

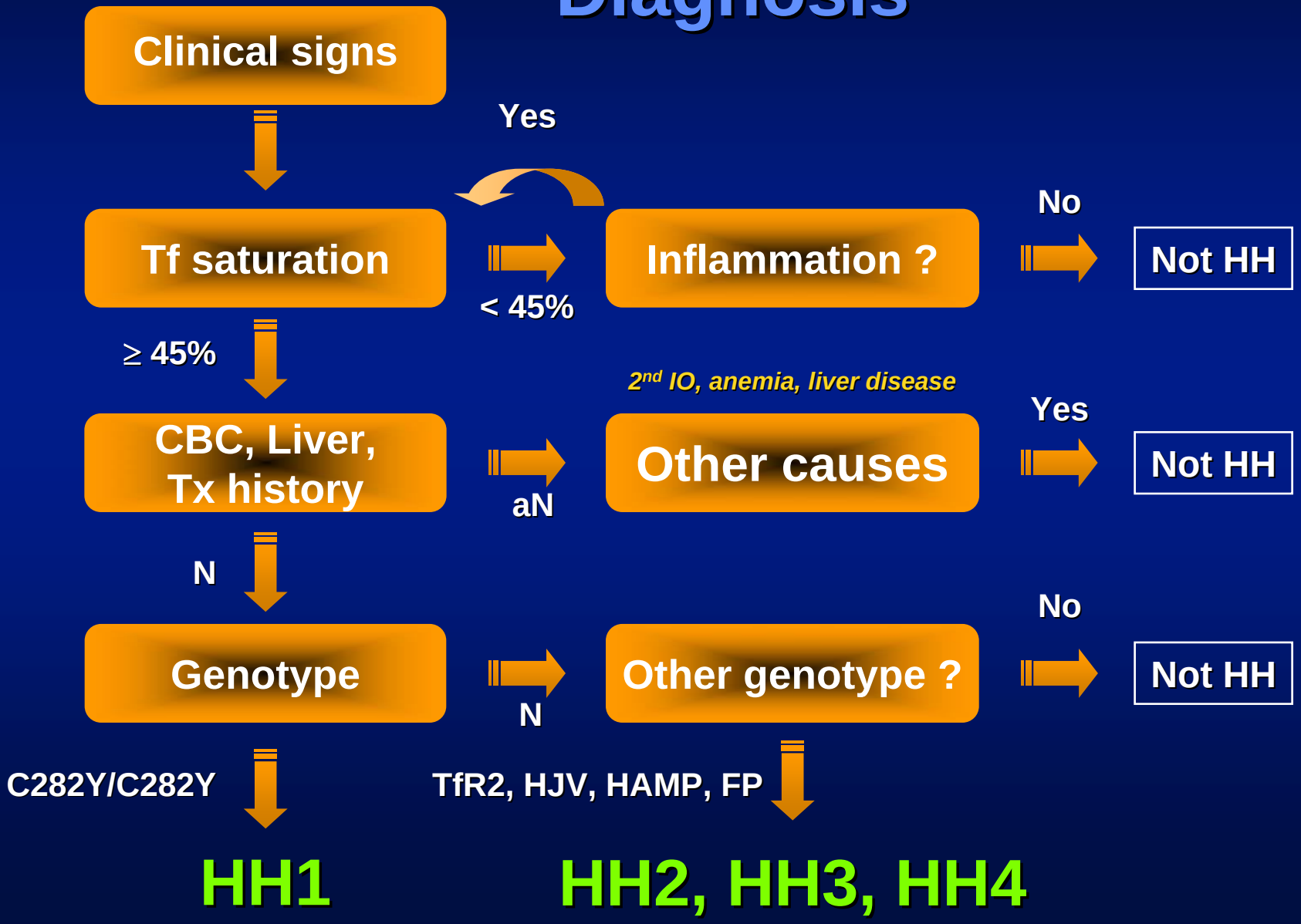
HEPCIDIN

Mediator of hemochromatosis ?



HEREDITARY HEMOCHROMATOSIS

Diagnosis



HEREDITARY HEMOCHROMATOSIS
Transferrin saturation

- **If < 45% :**
  - **Excludes HH (except if inflammation)**
  - **Does not exlude IO :**
    - **Metabolic syndrome**
    - **Aceruloplasminemia**
    - **Ferroportin disease**
- **If ≥ 45% : not specific**
  - **IO**
  - **Anemias (hemolysis, ineffective erythrop., aplasia)**
  - **Liver disease (hepatitis, alcohol)**

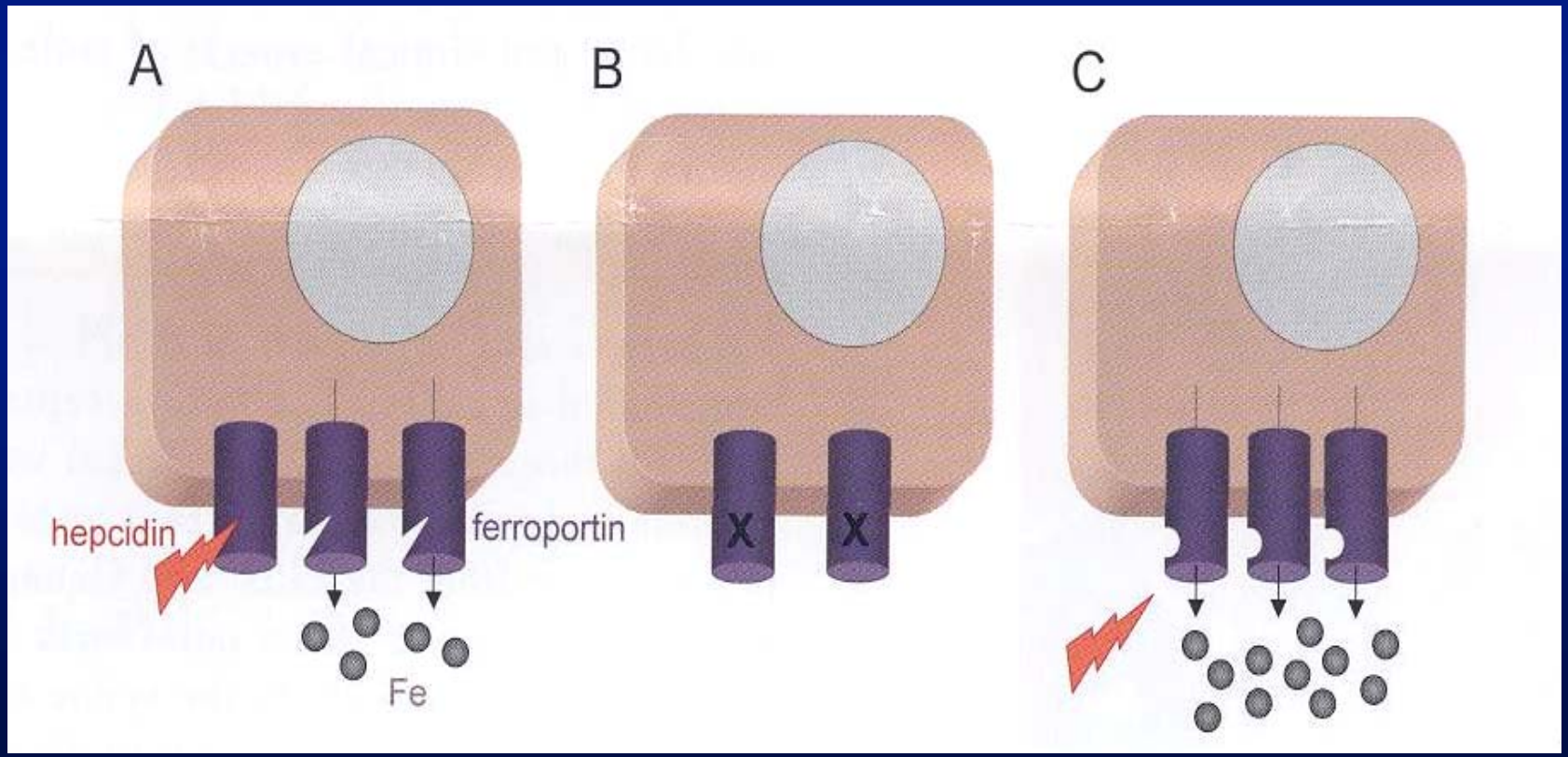
IRON OVERLOAD

Ferroportin disease

HEREDITARY HEMOCHROMATOSIS

Ferroportin

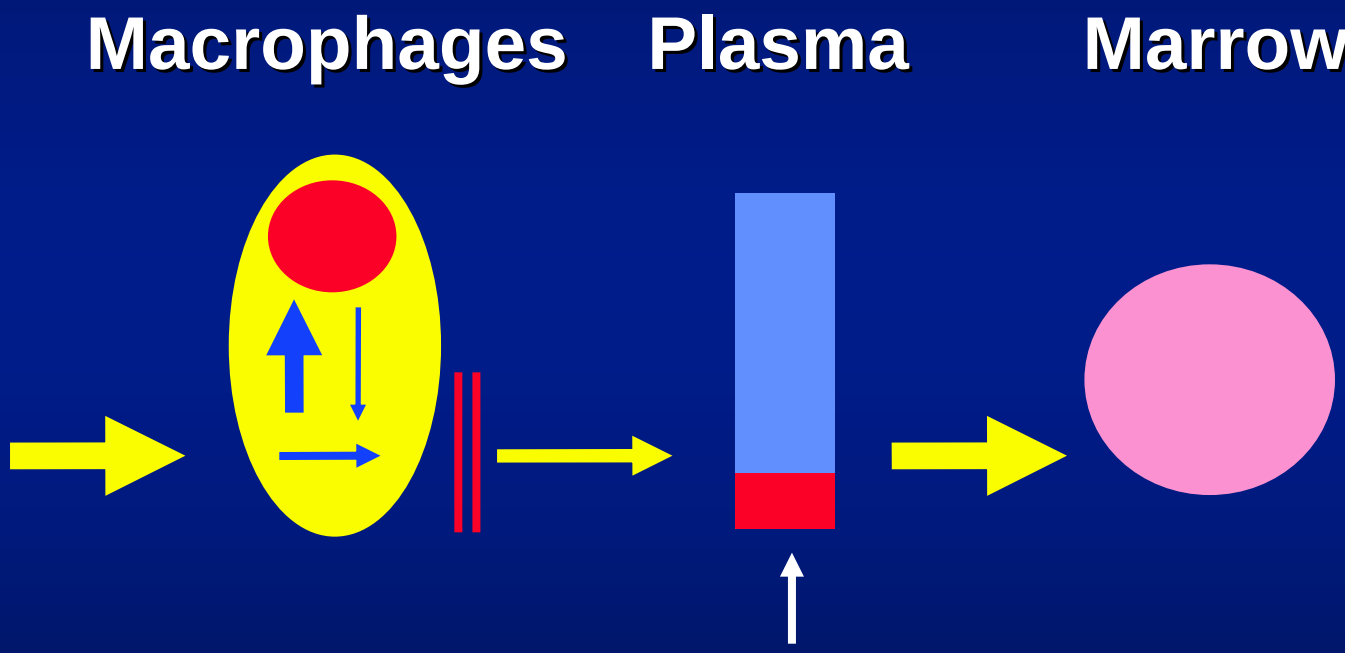
Normal	Class 1 mutation Loss of function FP disease	Class 2 mutation Gain of function HH4



Andrews, The Hematologist 2005

IRON KINETICS

Ferroportin disease



- Only some have IO
- Phlebotomy → anemia

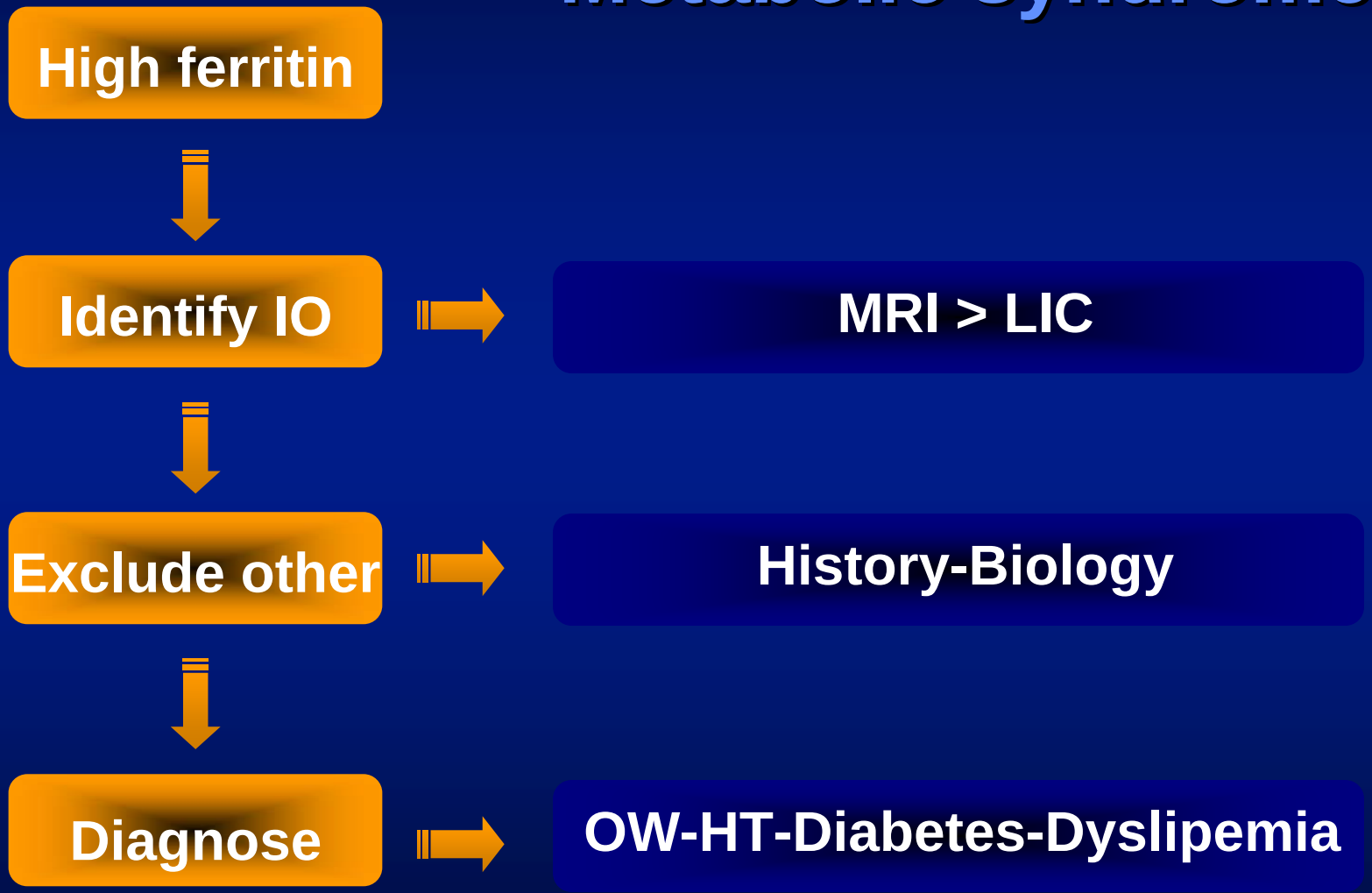
IRON OVERLOAD

Dysmetabolic syndrome

IRON OVERLOAD
Dysmetabolic hepatosiderosis

- **Iron overload (Kupffer > hepatocytes) :**
  - ↑ ferritin (up to 1000-1500)
  - Normal Tsat
- **Multiple dysmetabolic disorders**
  - Obesity
  - Dyslipemia
  - Liver steatosis
  - Hypertension
  - Glucose intolerance / diabetes

IRON OVERLOAD
Metabolic syndrome



IRON OVERLOAD

Secondary IO

TRANSFUSIONAL IRON OVERLOAD

Iron loading : transfusions

- 1 blood unit = 200 mg iron
- 2 units / month
  = 24 units / year
  = 100 units / 4 years
  = 5 g iron / year
- Normal body iron = 3-4 g
  Iron overload after 10–20 U
  100 units = 20 g

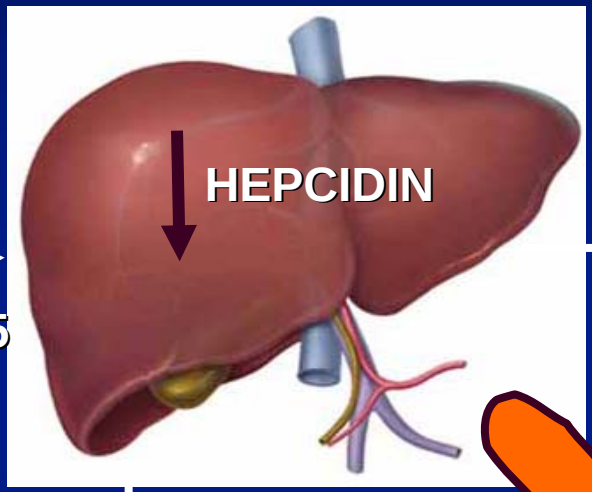
TRANSFUSIONAL IRON OVERLOAD

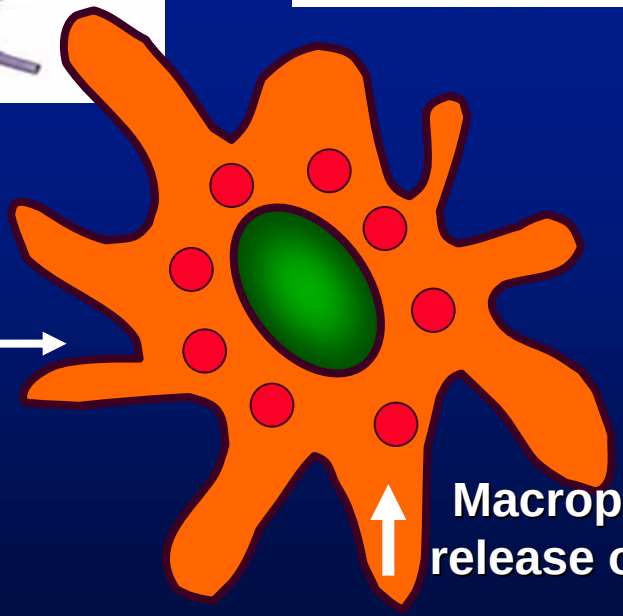
Iron loading : ineffective erythropoiesis

Ineffective erythropoiesis

↑ sTfR

↑ GDF15

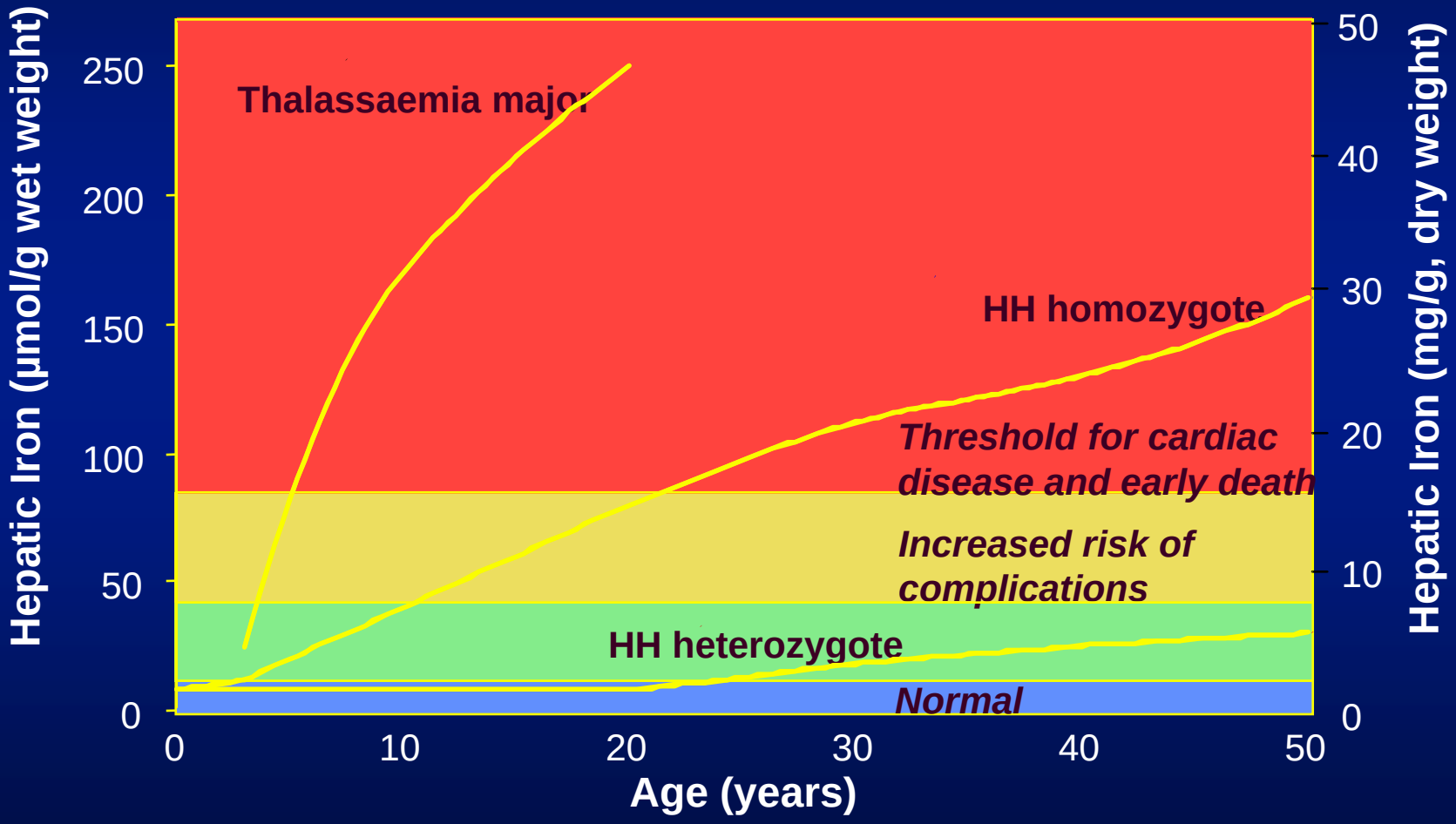




Malcovati L, et al. Blood. 2008;112:[abstract 2676].
Dreyfus F. Blood Rev. 2008;22 Suppl 2:S29-34.

TRANSFUSIONAL IRON OVERLOAD

Hepatic iron



Olivieri et al, *Blood* 1997;89:739