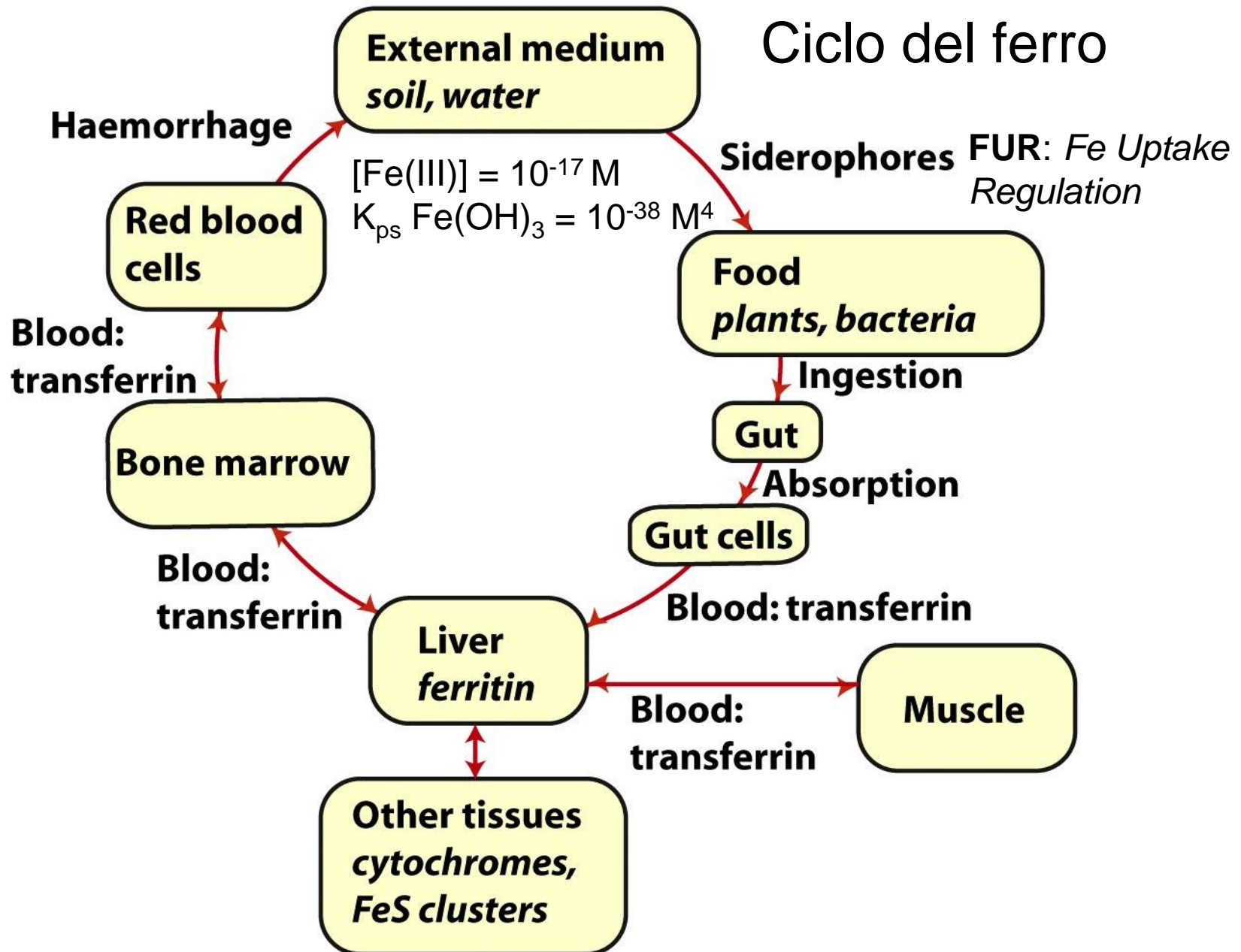


Omeostasi dei *trace elements*:
uptake, trasporto, *storage*....

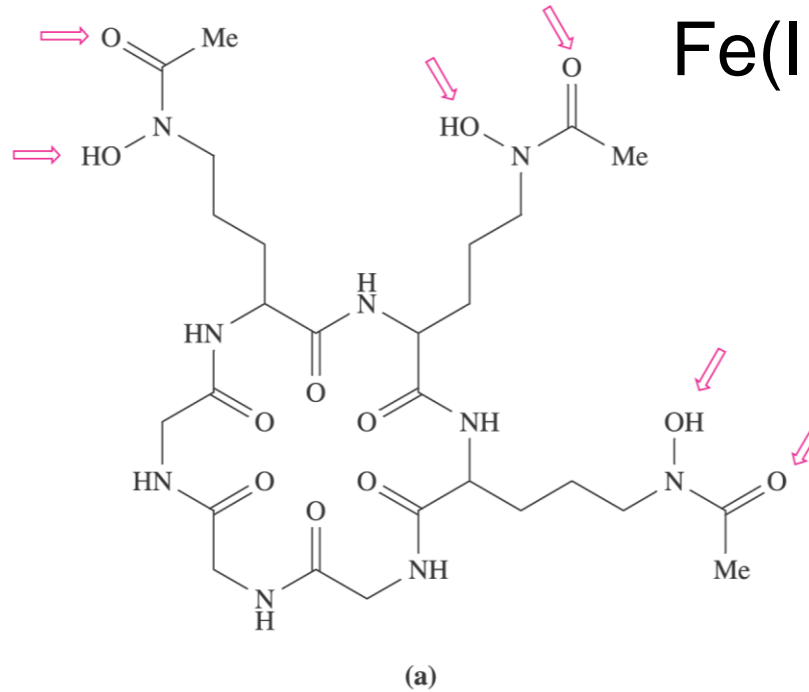
Ciclo del ferro



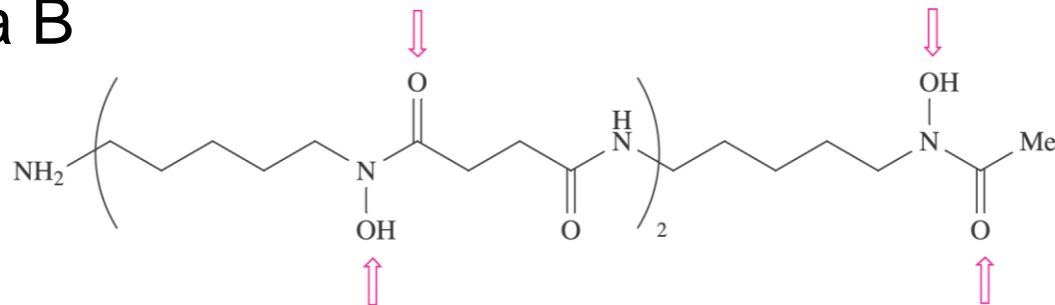
Siderofori idrossammati (funghi, lievito)

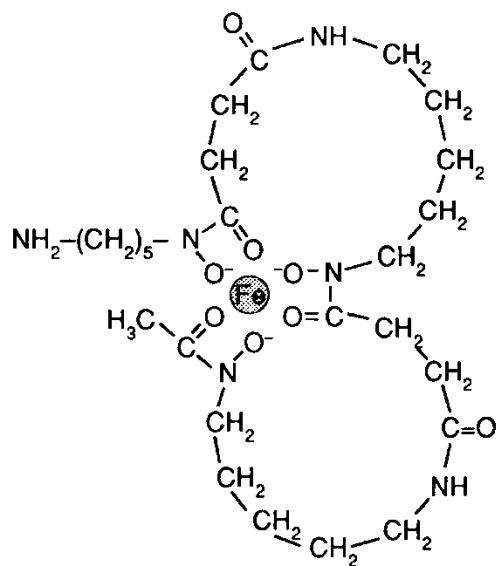
Fe(III) alto spin

desferricromo



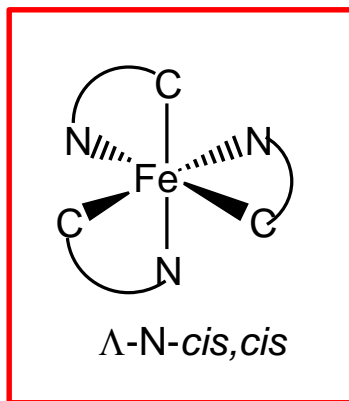
Desferriossamina B



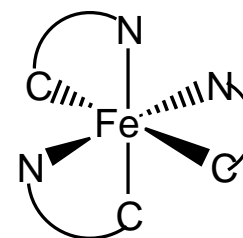


ferrioxamine B

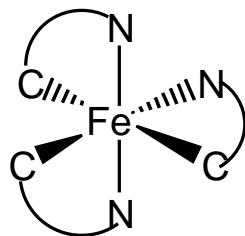
without Fe: deferrioxamine B



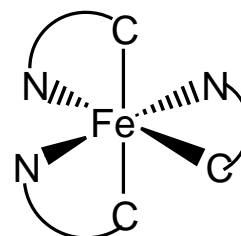
Λ -N-*cis,cis*



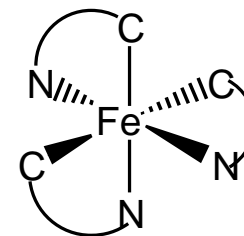
Λ -C-*trans,cis*



Λ -N-*trans,cis*



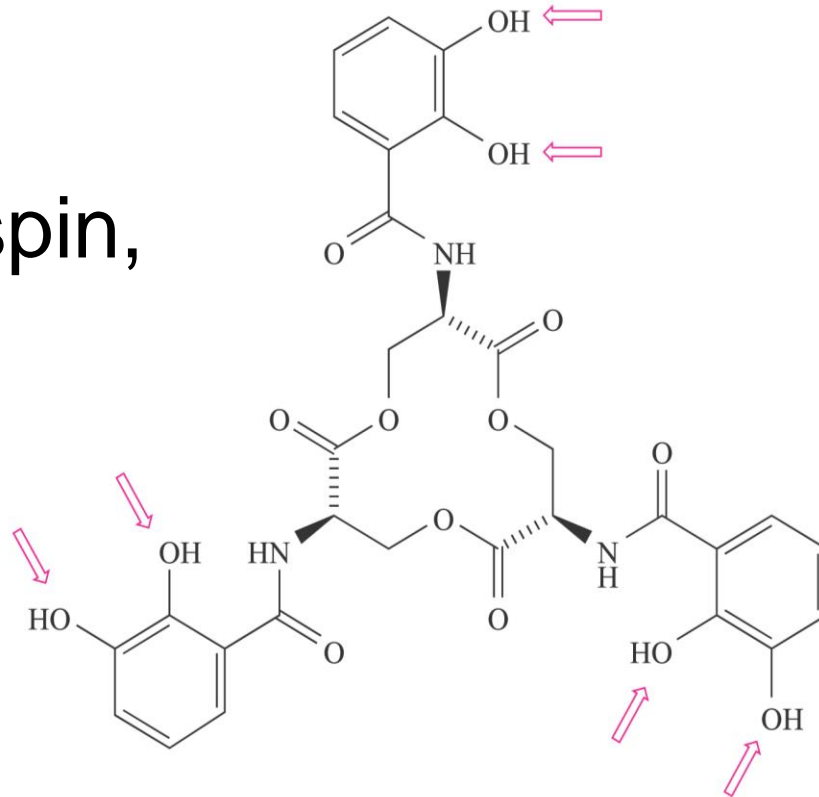
Λ -C-*cis,trans*



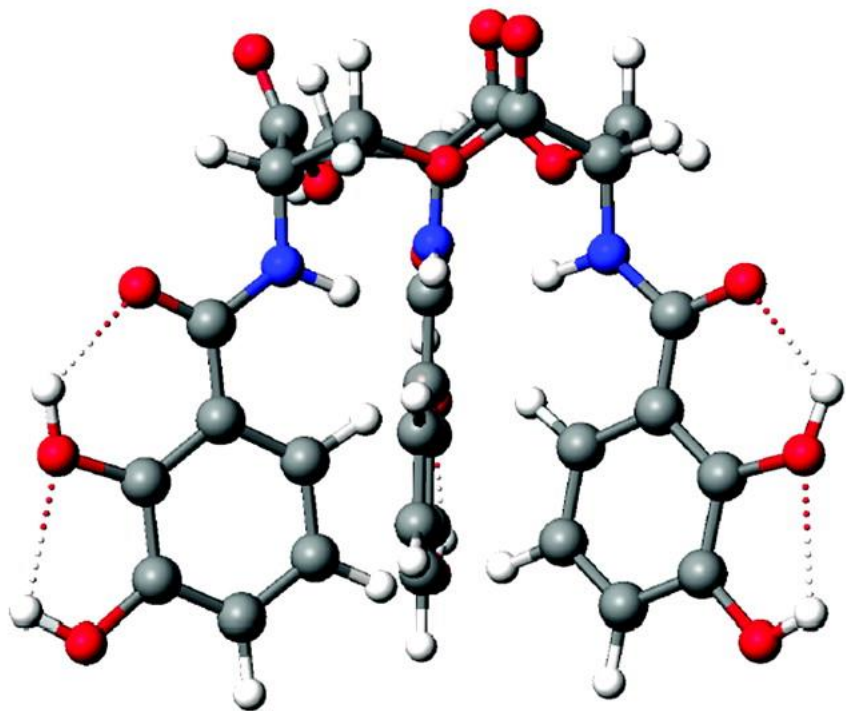
Λ -N-*trans,cis*

Siderofori catecolati (batteri)

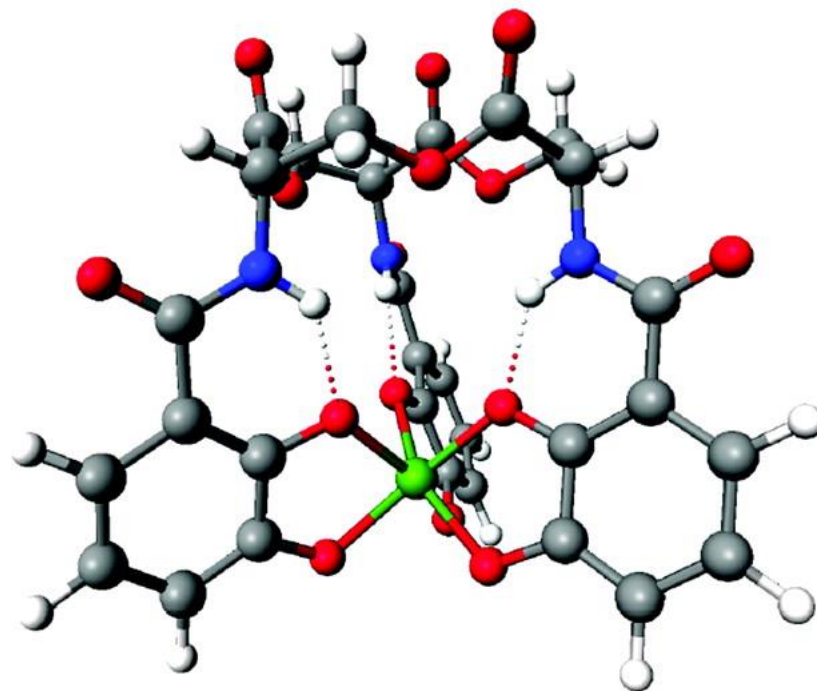
Fe(III) alto spin,
 $K_a = 10^{52}$



Enterobactina

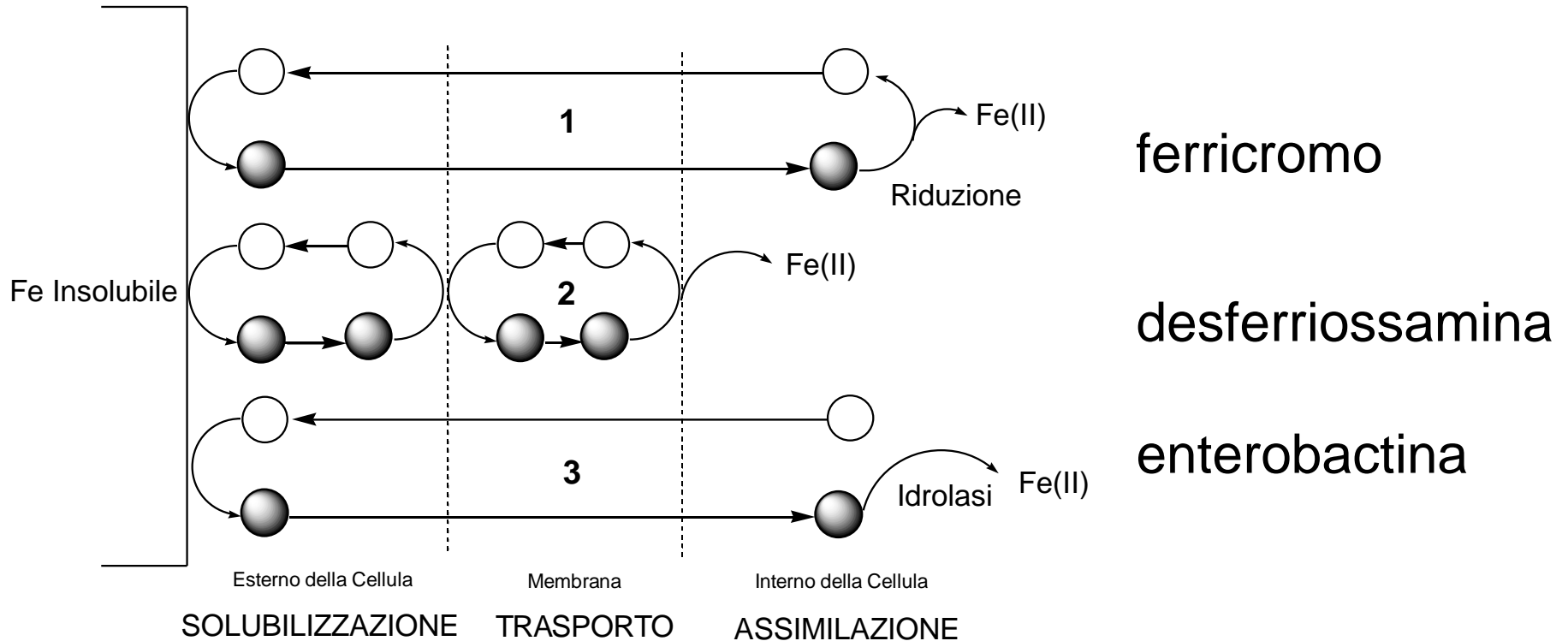


Modello di enterobactina
non coordinata



Complesso V(IV)-enterobactina
 Δ

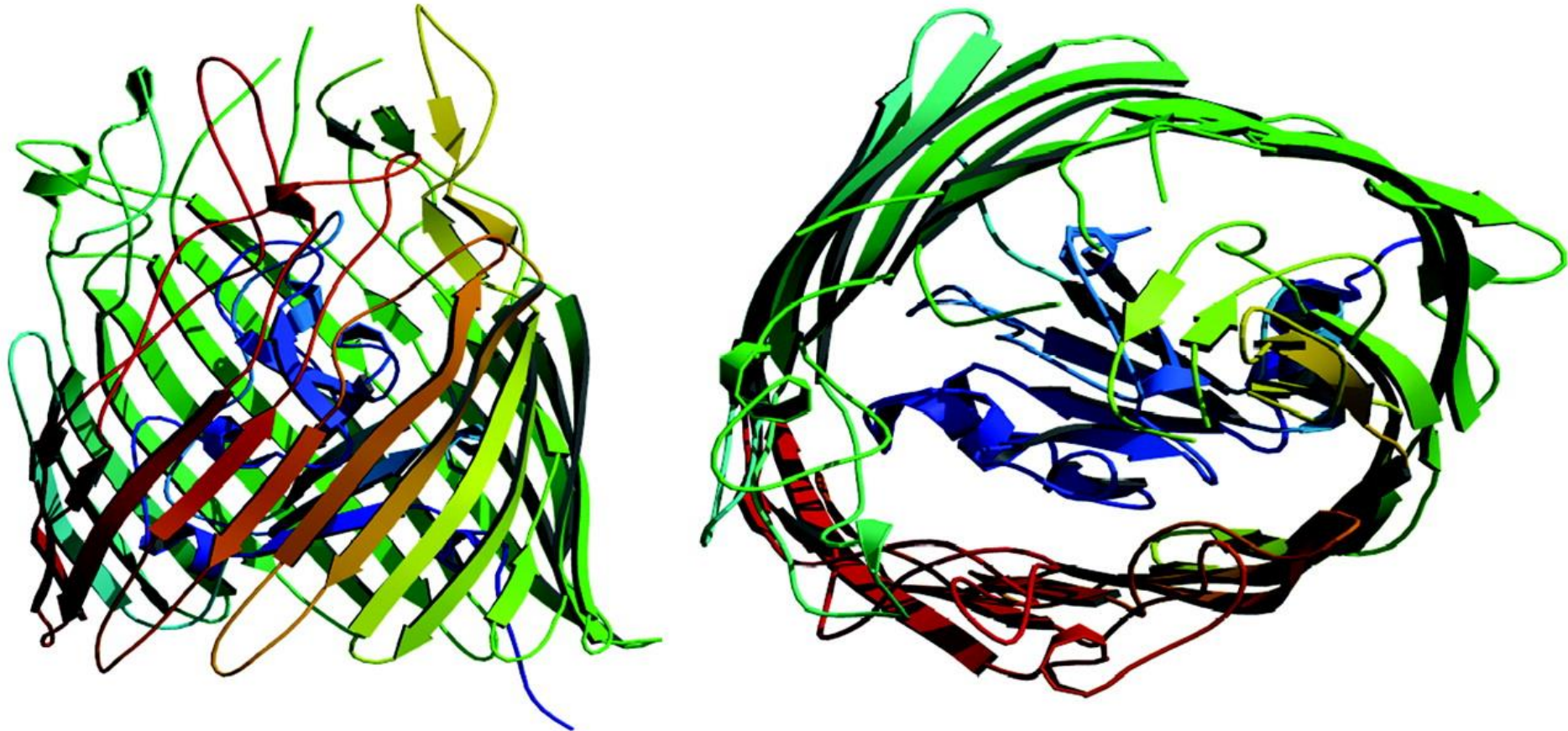
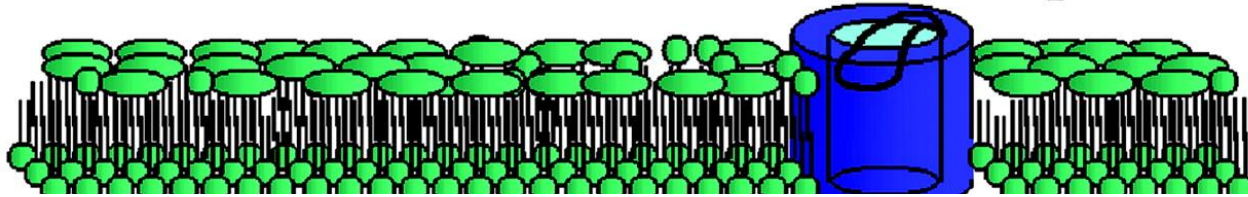
Meccanismi di trasporto trans-membrana



FepA: trasporto trans-membrana di Fe-enterobactina

OM

FepA



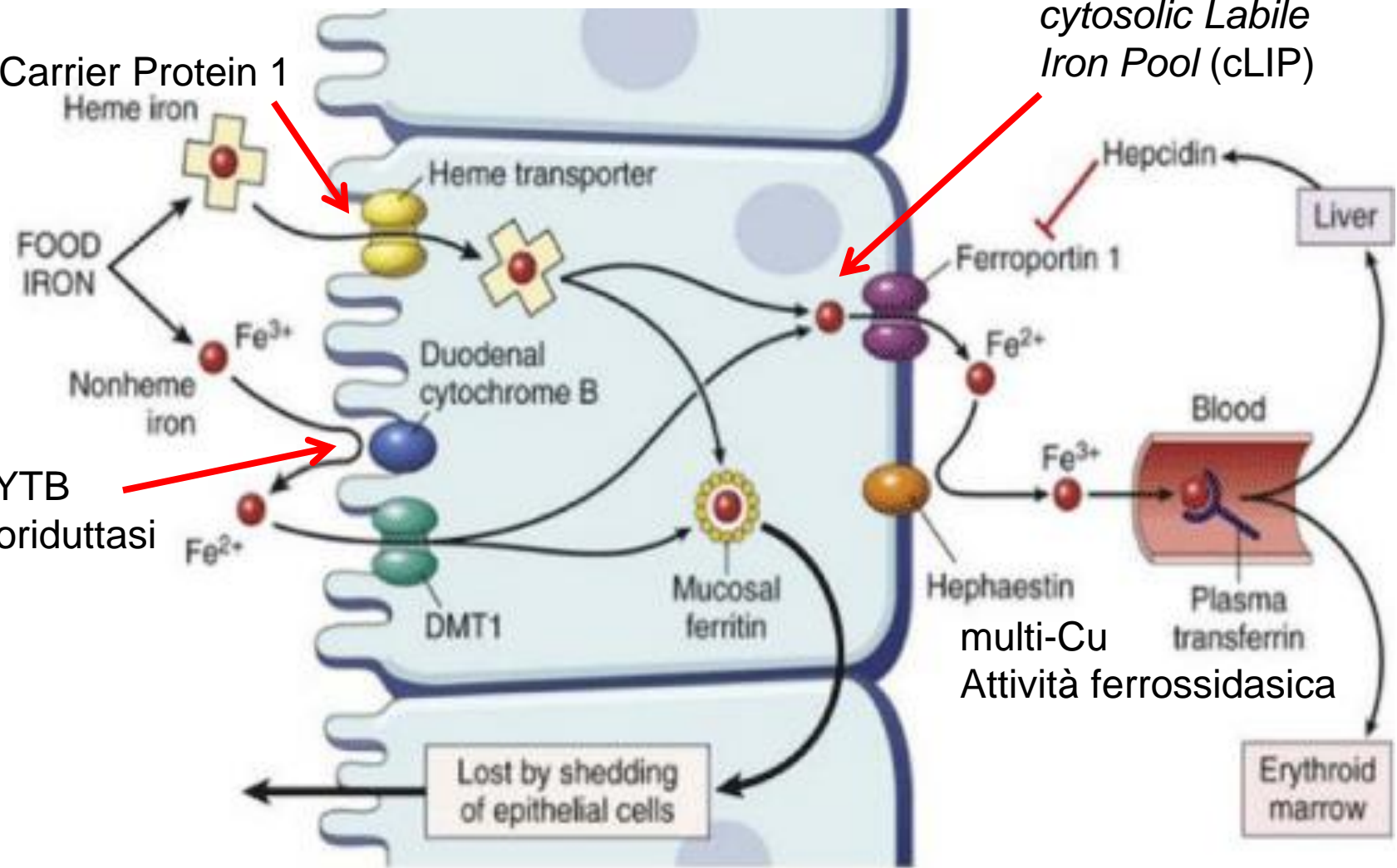
In blu la «gate protein» N-terminale

Assorbimento del ferro nell'intestino e trasporto attraverso gli enterociti del duodeno

HCP-1
Heme Carrier Protein 1

cytosolic Labile Iron Pool (cLIP)

DCYTB
ferroriduttasi



Lost by shedding of epithelial cells

Hephaestin
multi-Cu
Attività ferrossidasica

Erythroid marrow

Liver

Hepcidin

Blood

Plasma transferrin

Hephaestin

multi-Cu

Attività ferrossidasica

Ferroportin 1

Fe²⁺

Hepcidin

Heme transporter

Duodenal cytochrome B

DMT1

Mucosal ferritin

Heme iron

FOOD IRON

Nonheme iron

Fe³⁺

Fe²⁺

Fe²⁺

Fe³⁺

HCP-1

Heme Carrier Protein 1

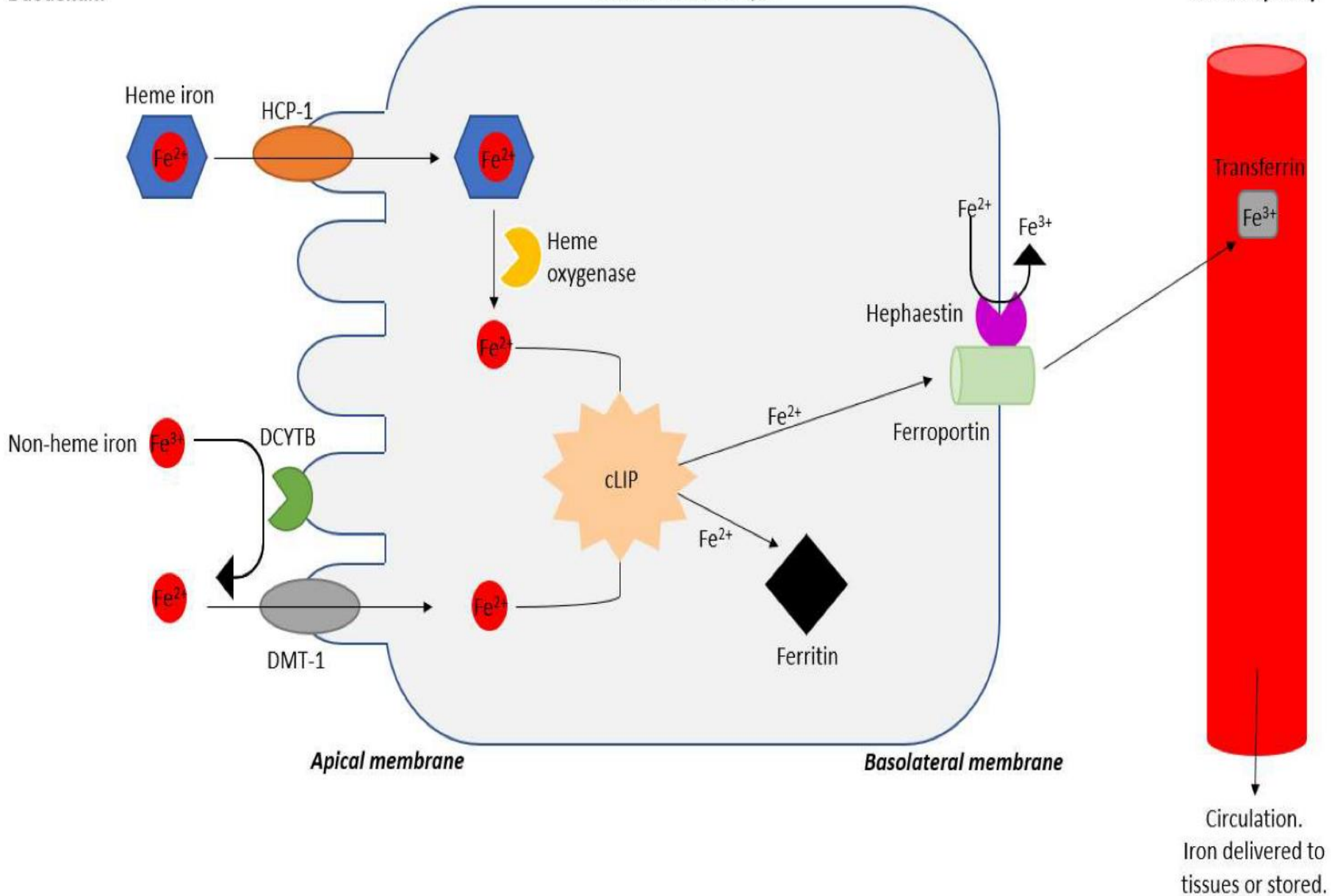
DCYTB
ferroriduttasi

cytosolic Labile Iron Pool (cLIP)

Duodenum

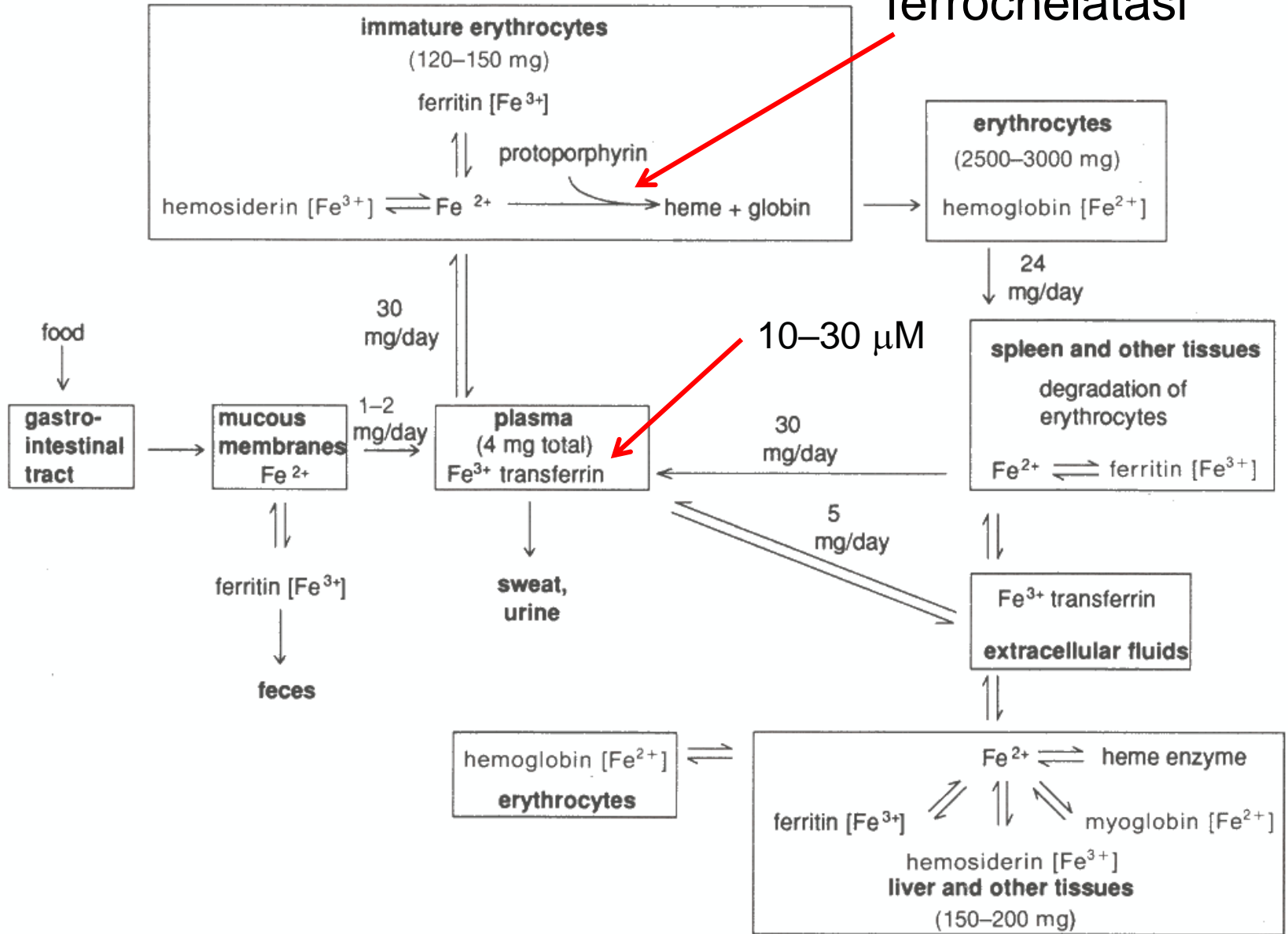
Duodenal enterocyte

Blood capillary



Midollo spinale

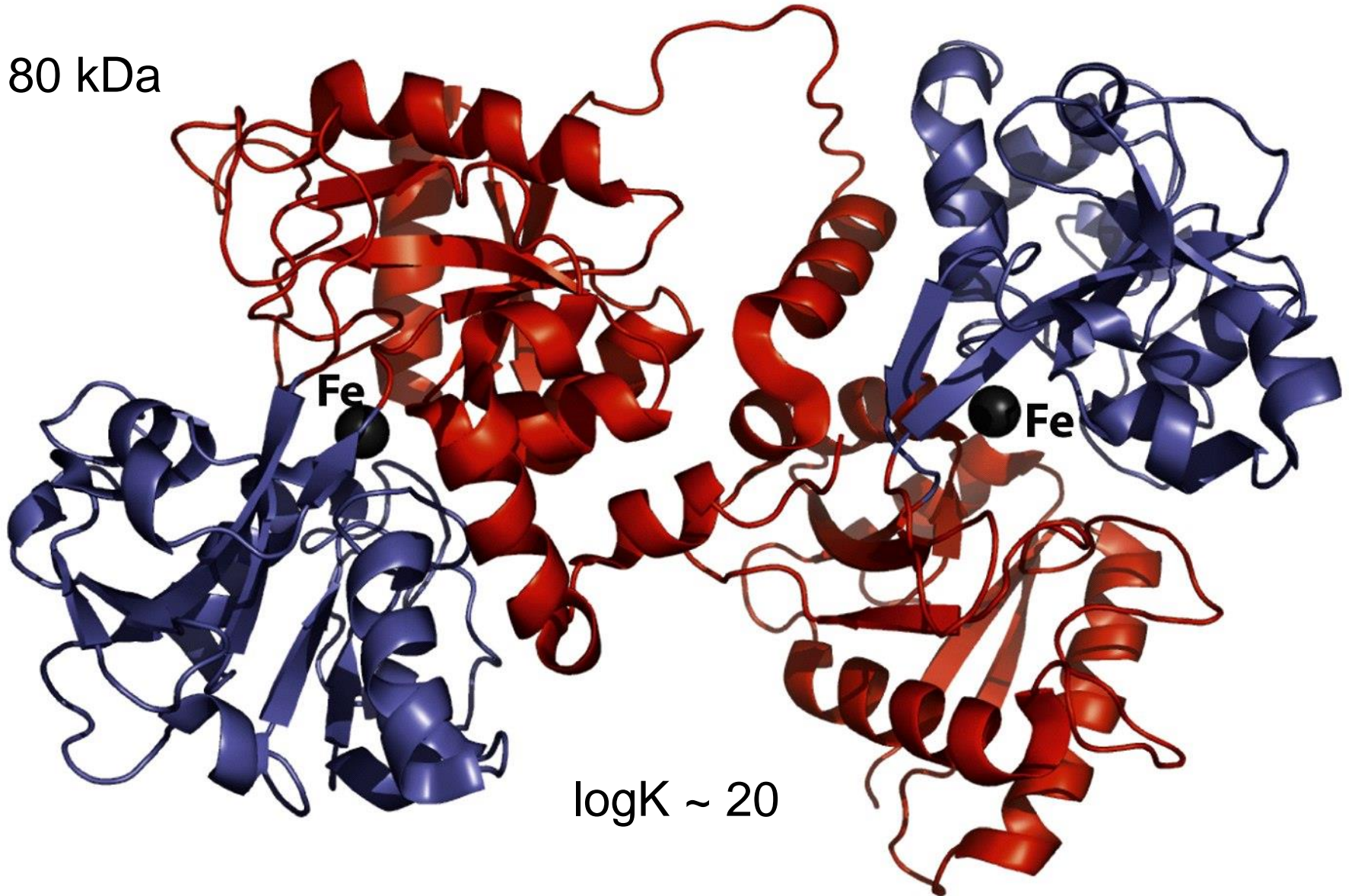
ferrochelatasi



Transferrina

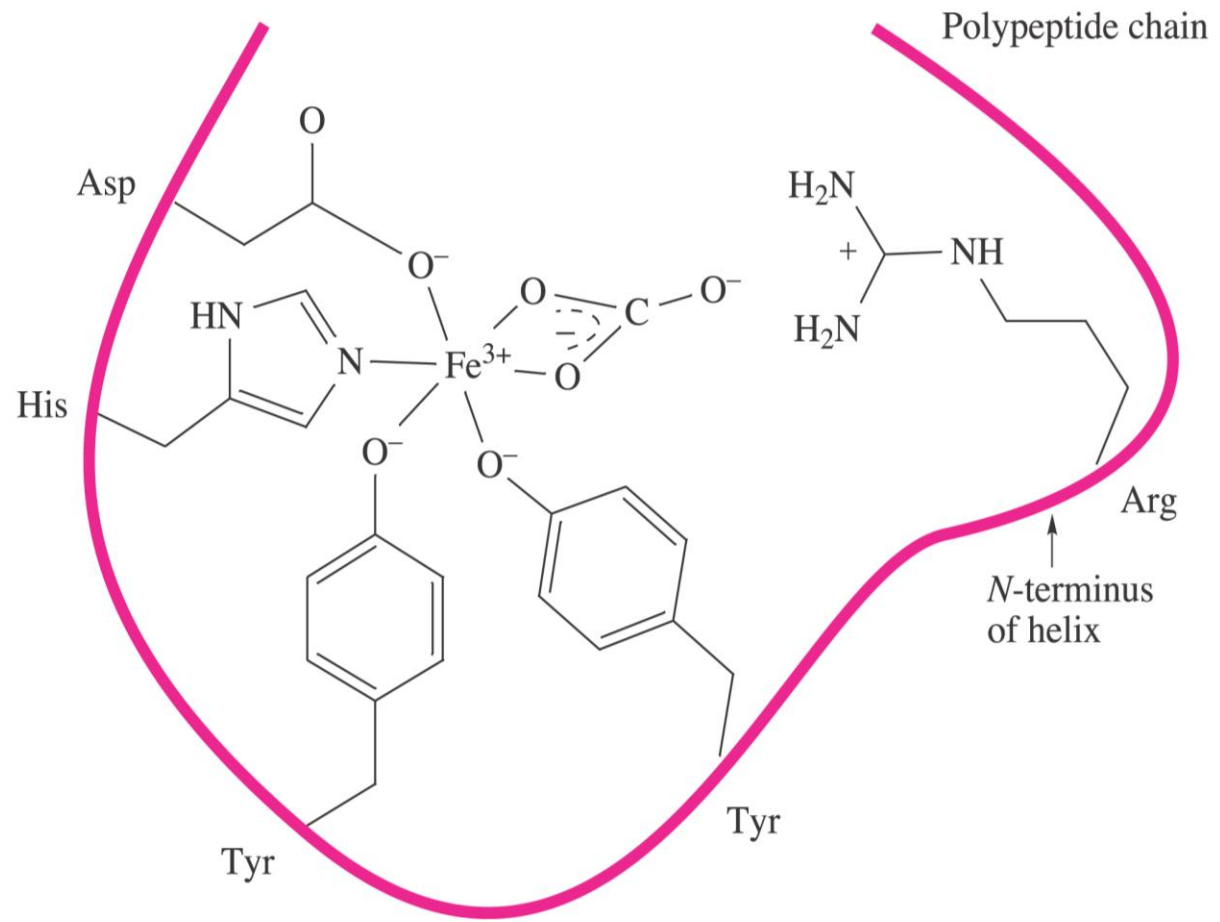
2 lobi, 2 siti di coordinazione del Fe(III)

80 kDa



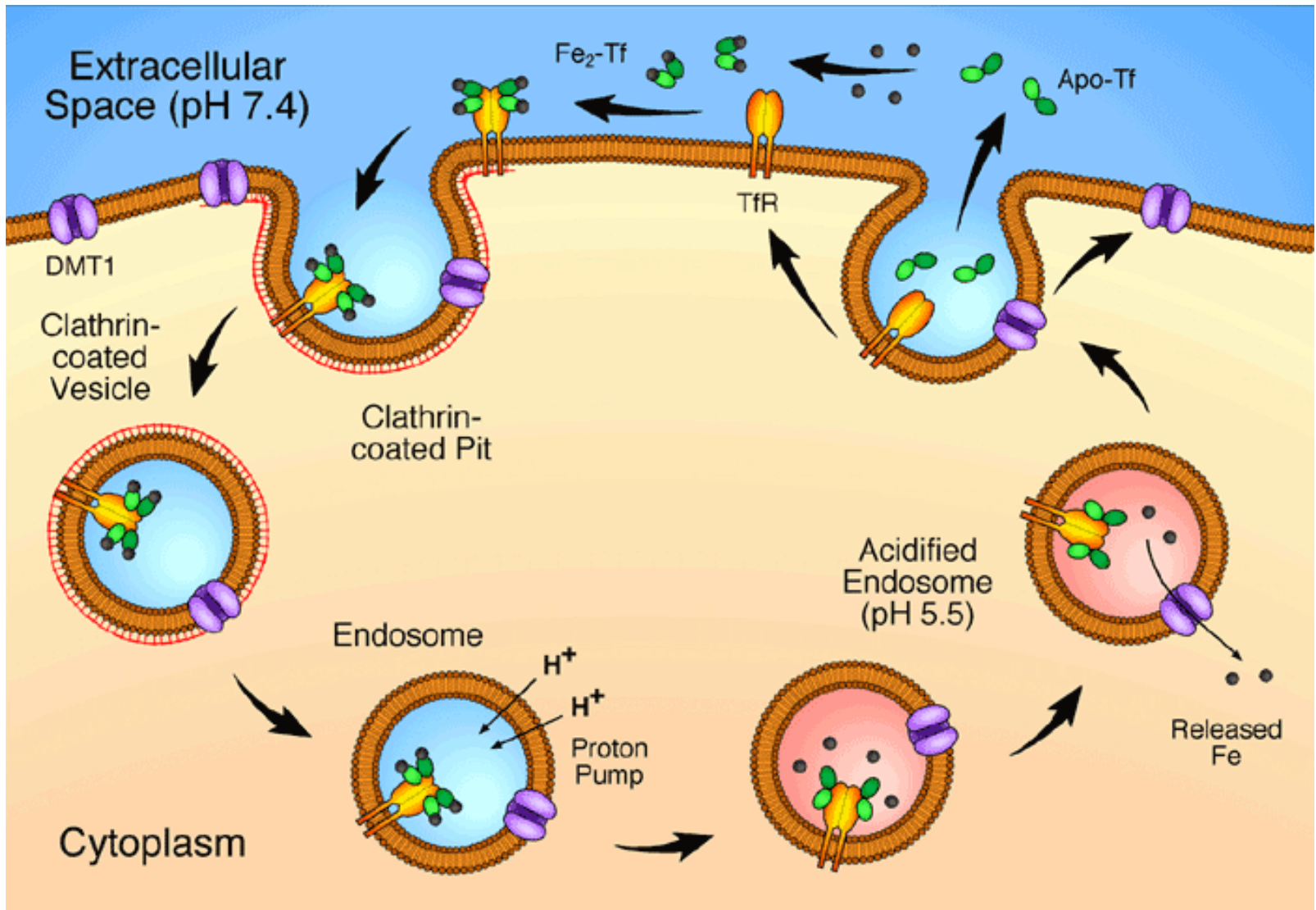
$\log K \sim 20$

Sito di coordinazione del Fe nella transferrina



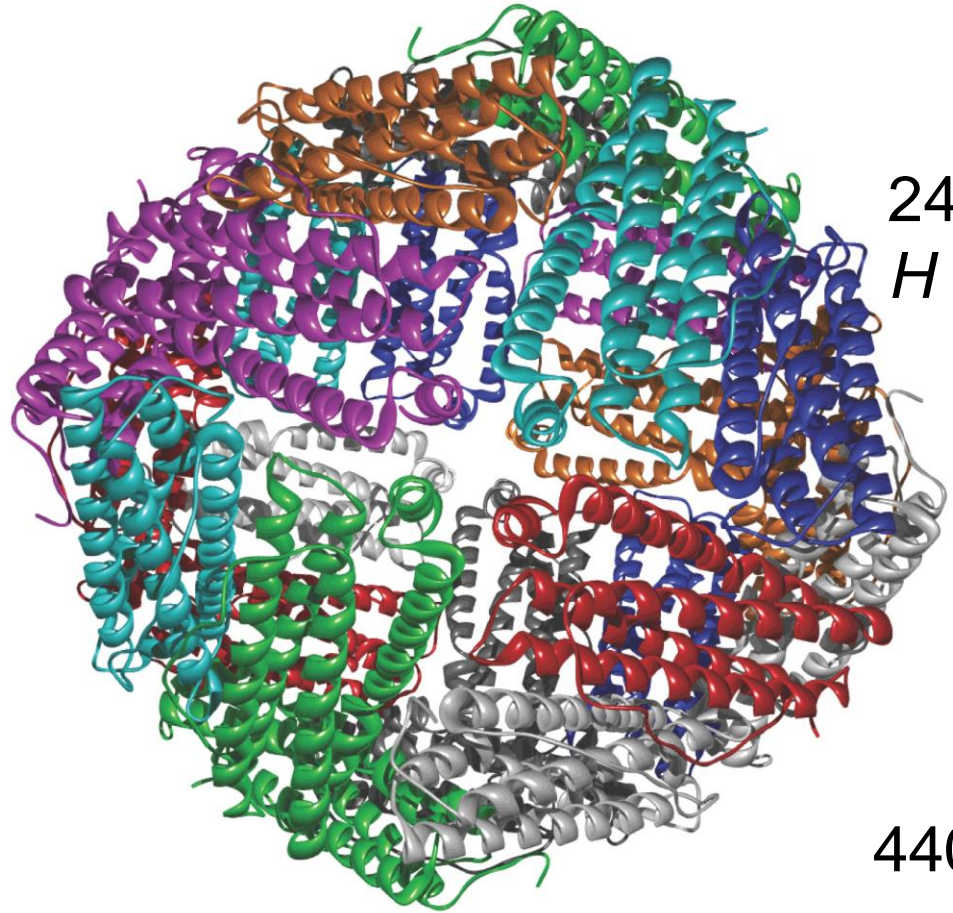
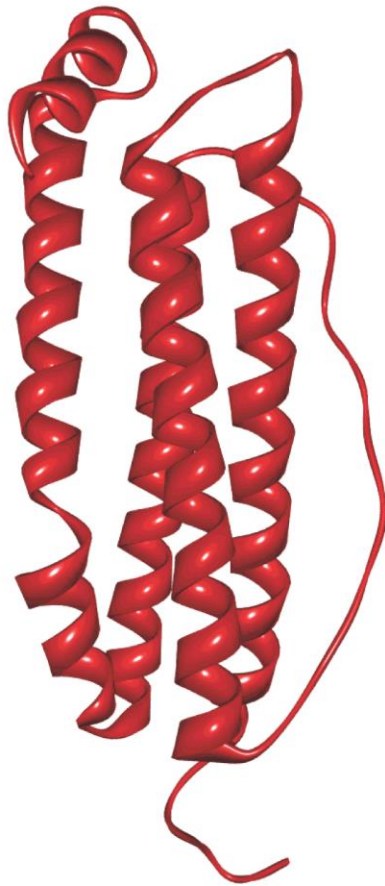
La coordinazione del Fe(III) comporta il rilascio di 3H^+ e una notevole variazione conformazionale della transferrina

Ciclo della transferrina



endocitosi

Storage del ferro: Ferritina

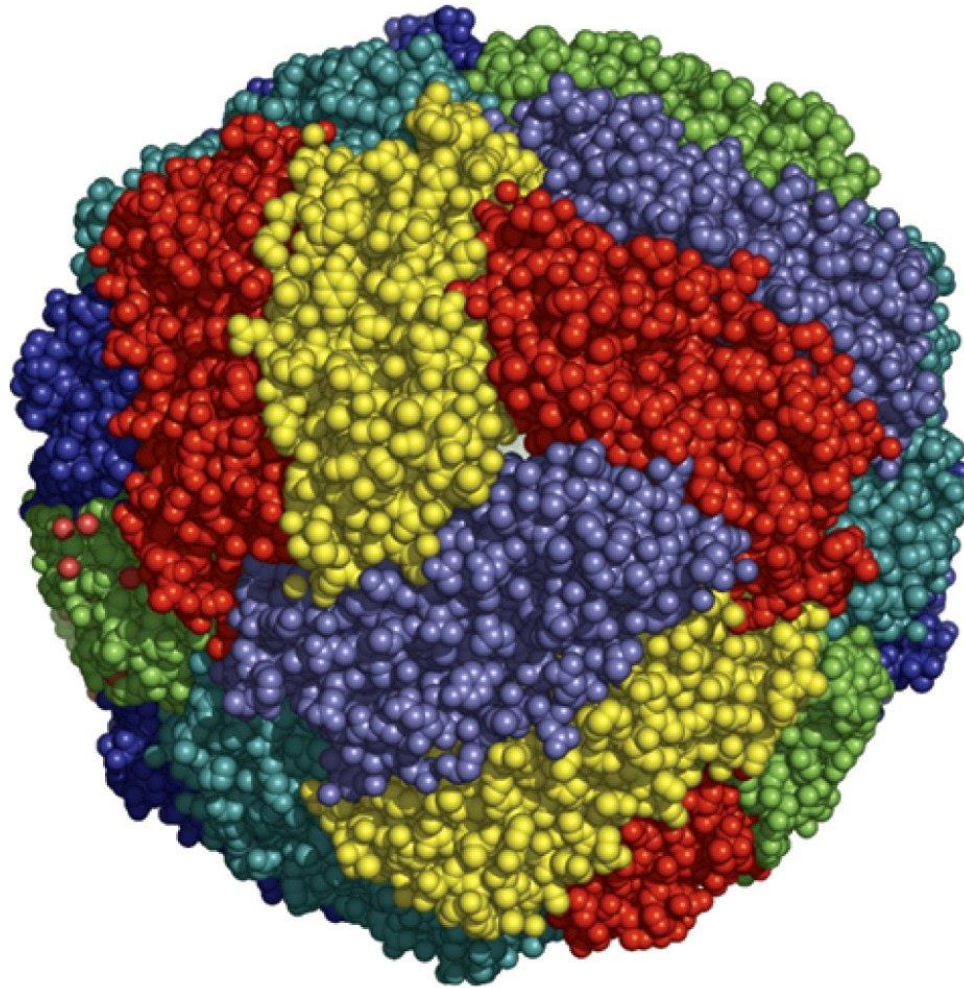


24 unità,
H e L

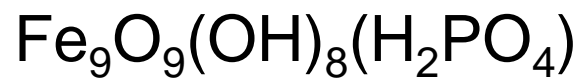
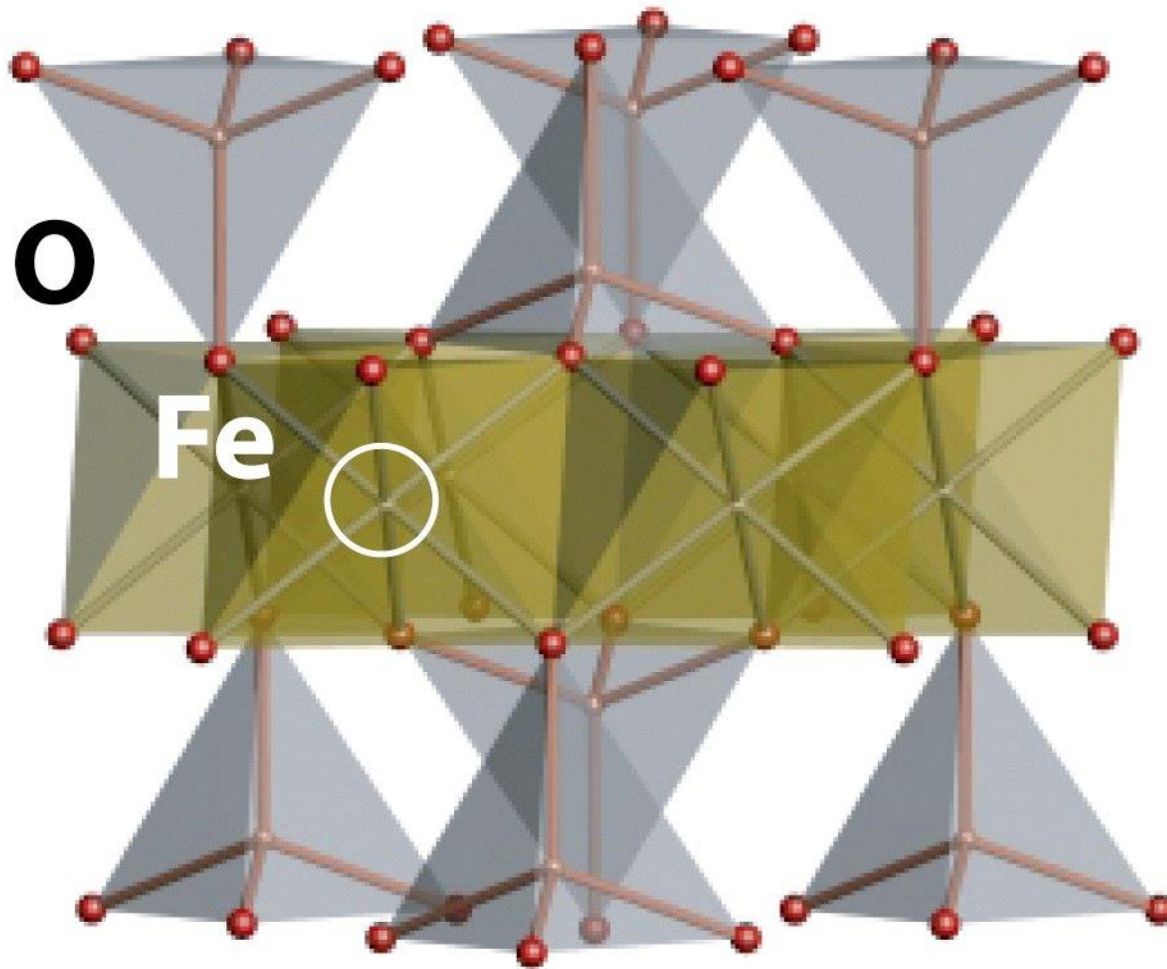
440 kDa

La *Heavy-chain ferritin (H)* ha attività ferrossidasica
8 pori idrofilici con simmetria ternaria (*Fe in*)
6 pori idrofobici con simmetria quaternaria (*Fe out*)

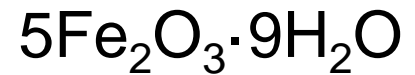
In, 7.5nm



Out, 12 nm

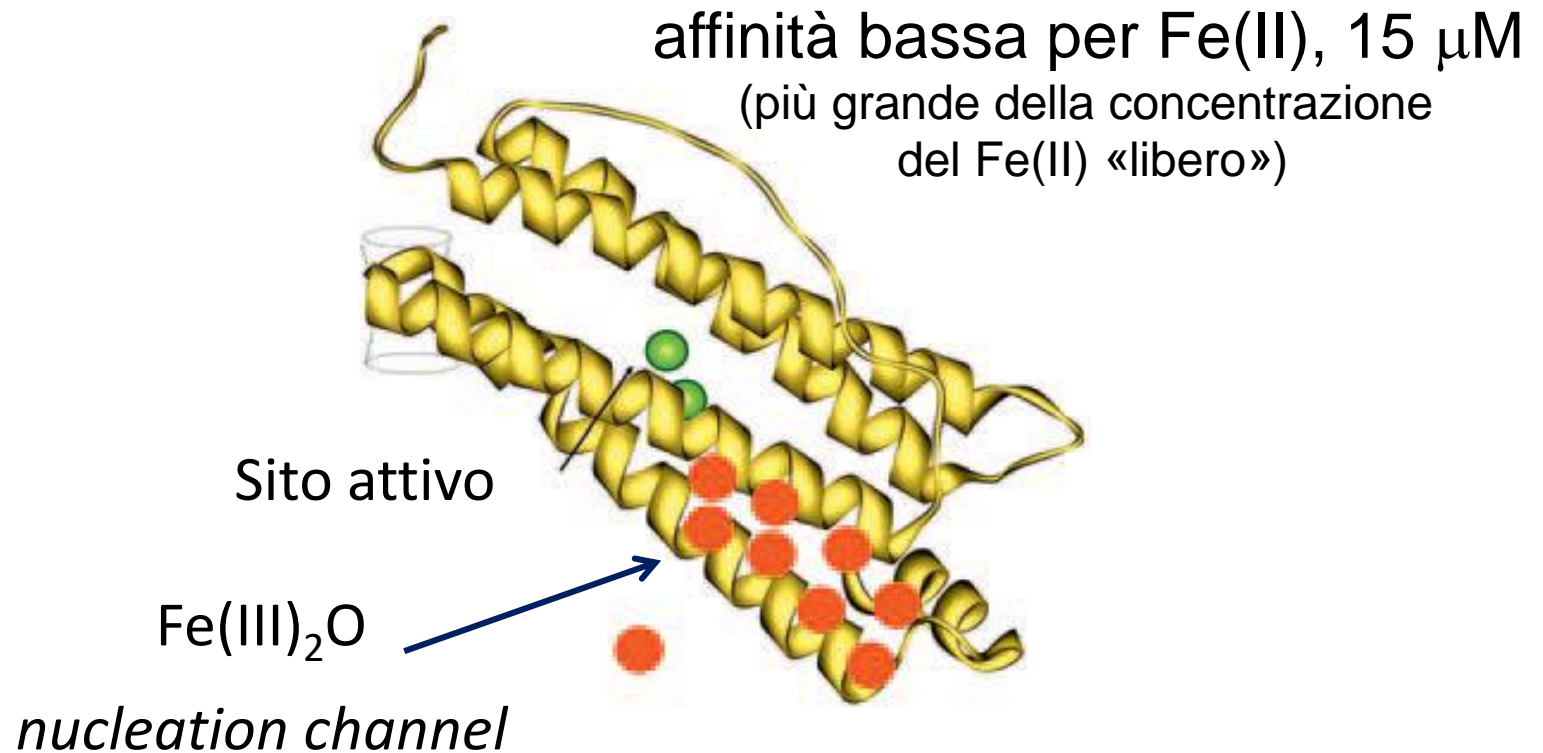


Ferrihydrite



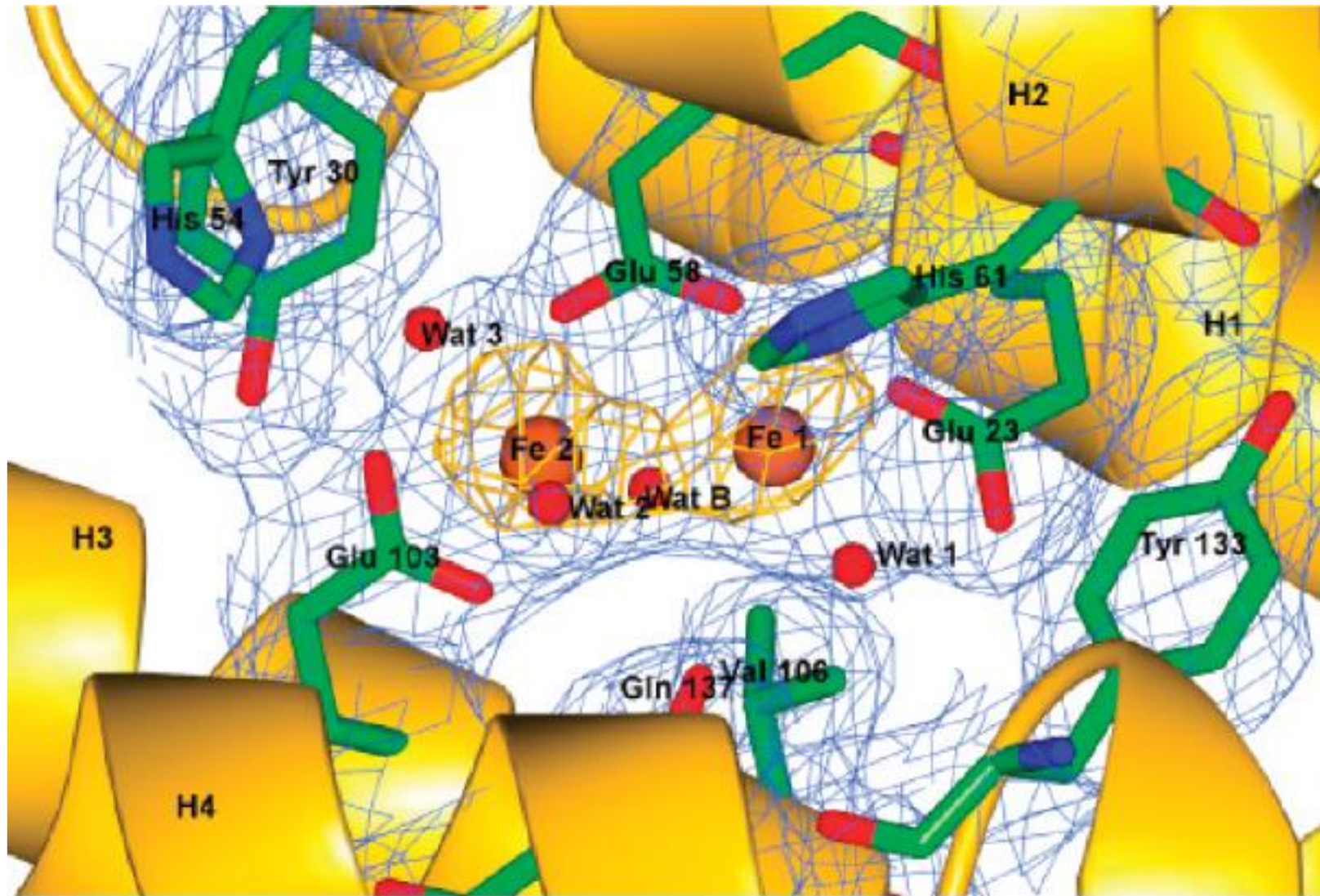
Fino a 4500 atomi di Fe, mediamente 1200

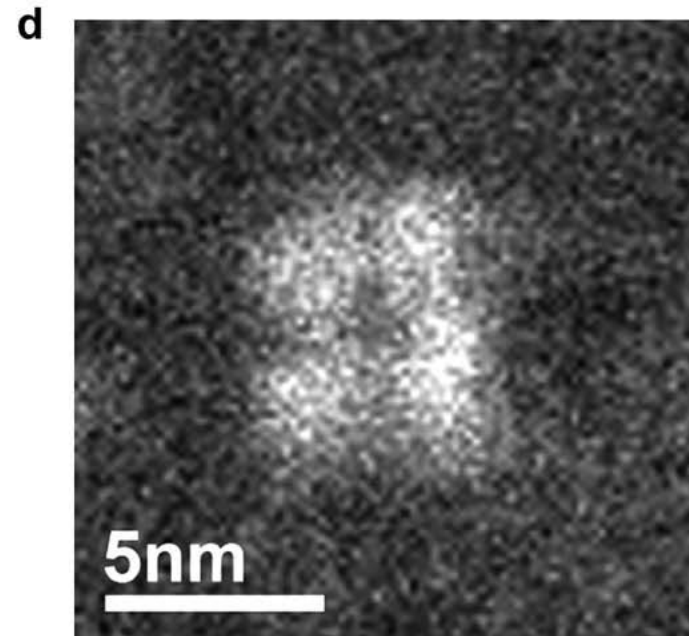
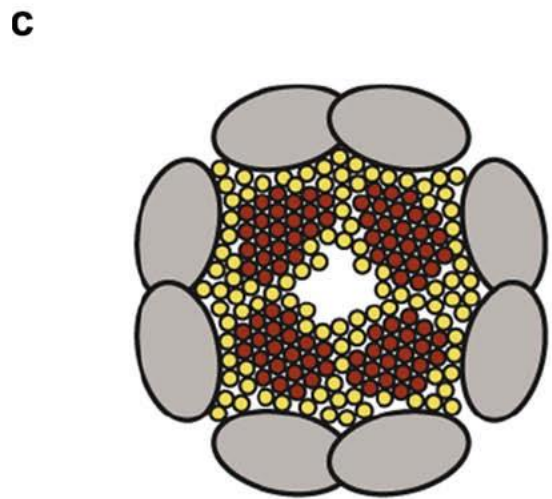
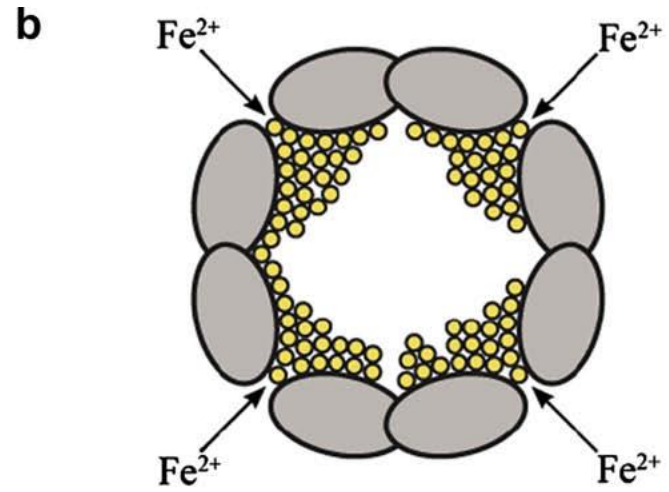
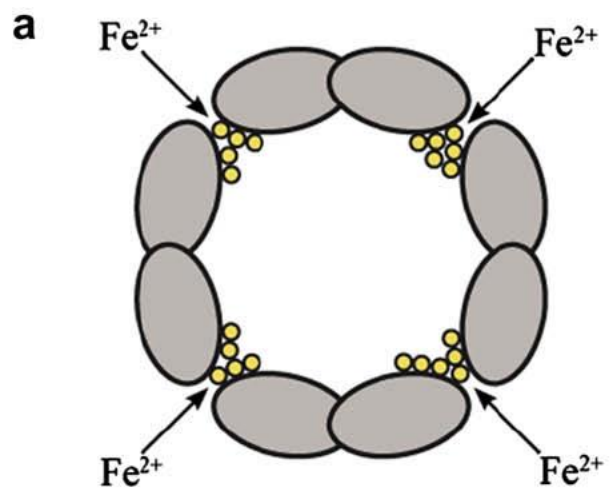
sito ferrossidasico






Ipotesi di proteine *chaperone* per il Fe(II) (e.g. PCPB1)

Struttura ai raggi X di un sito ferrossidasico

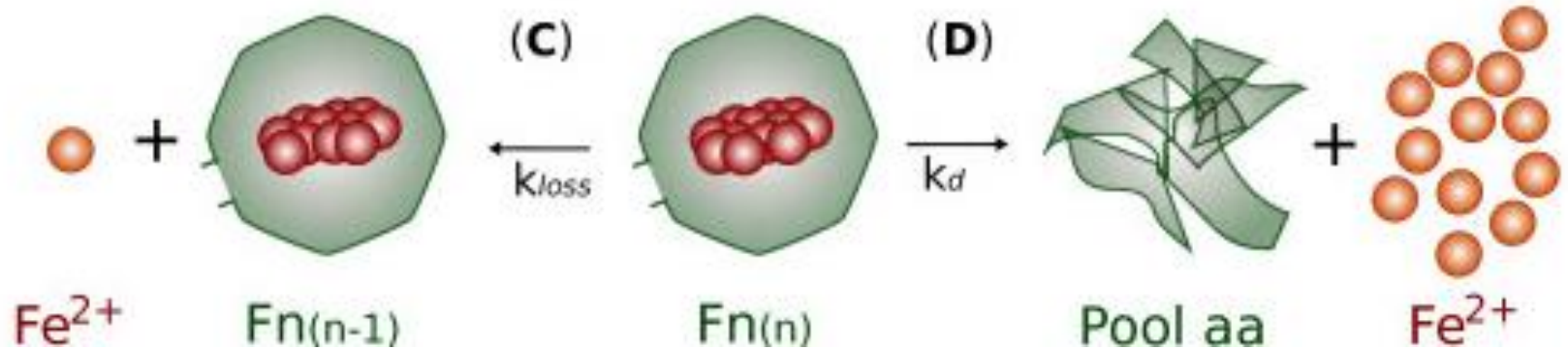




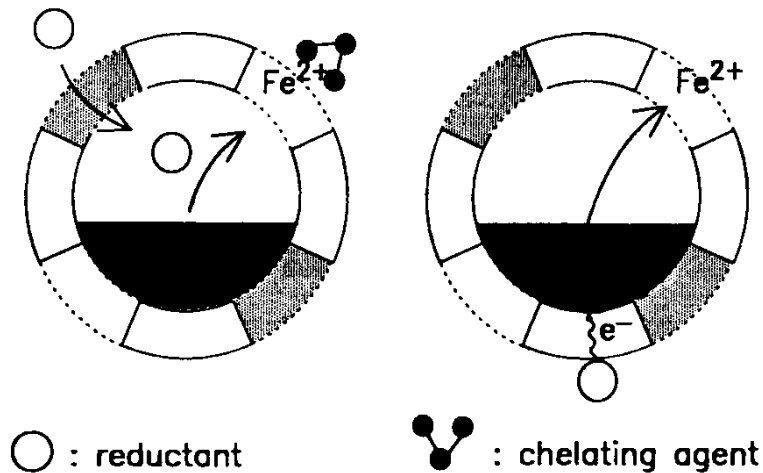
Imagine
TEM

-  Fe^{3+} coordinated to O and OH
-  Fe^{3+} in ferrihydrite crystal structure
-  Protein shell sub-unit

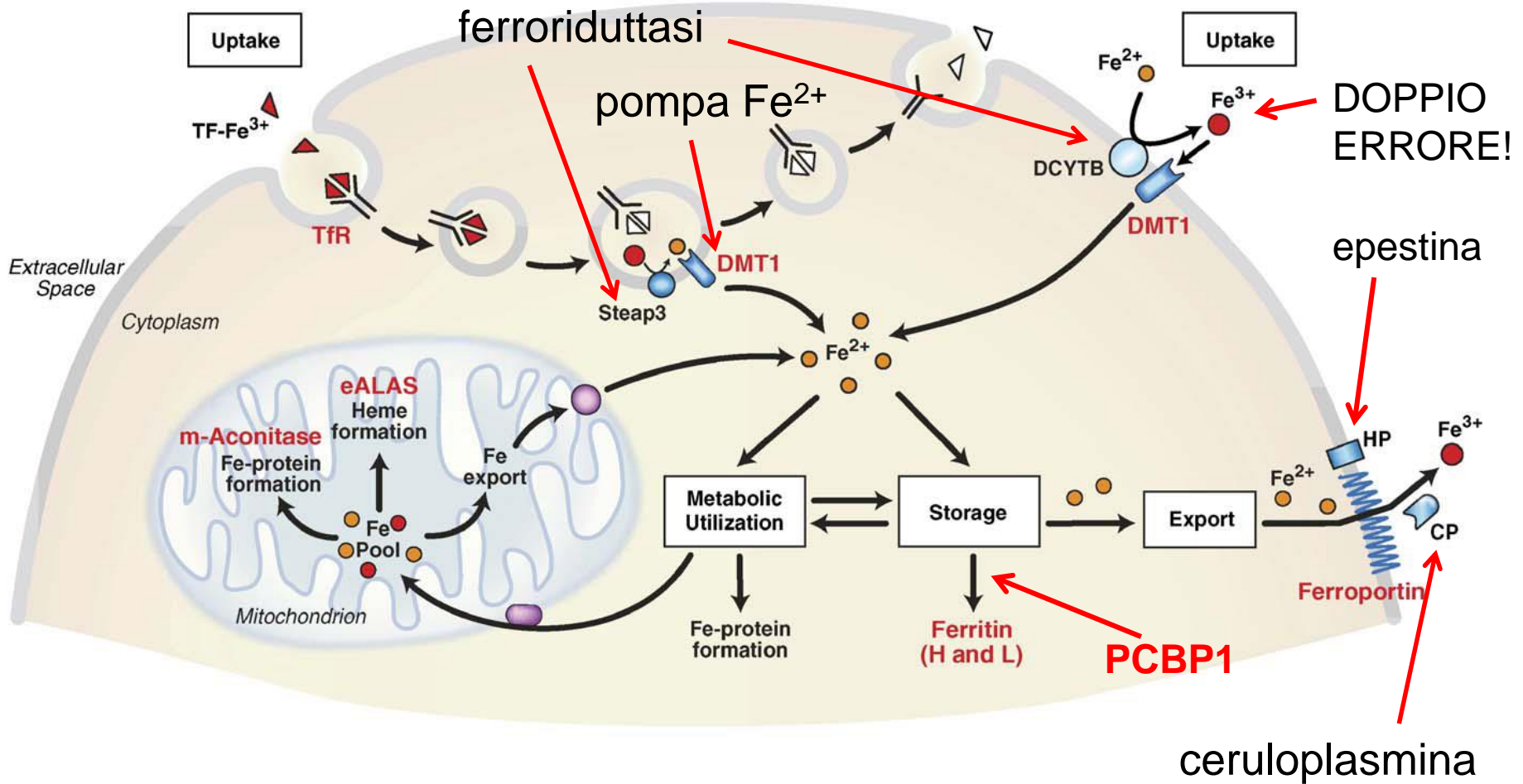
Rilascio del ferro



degradazione della proteina nei lisosomi?



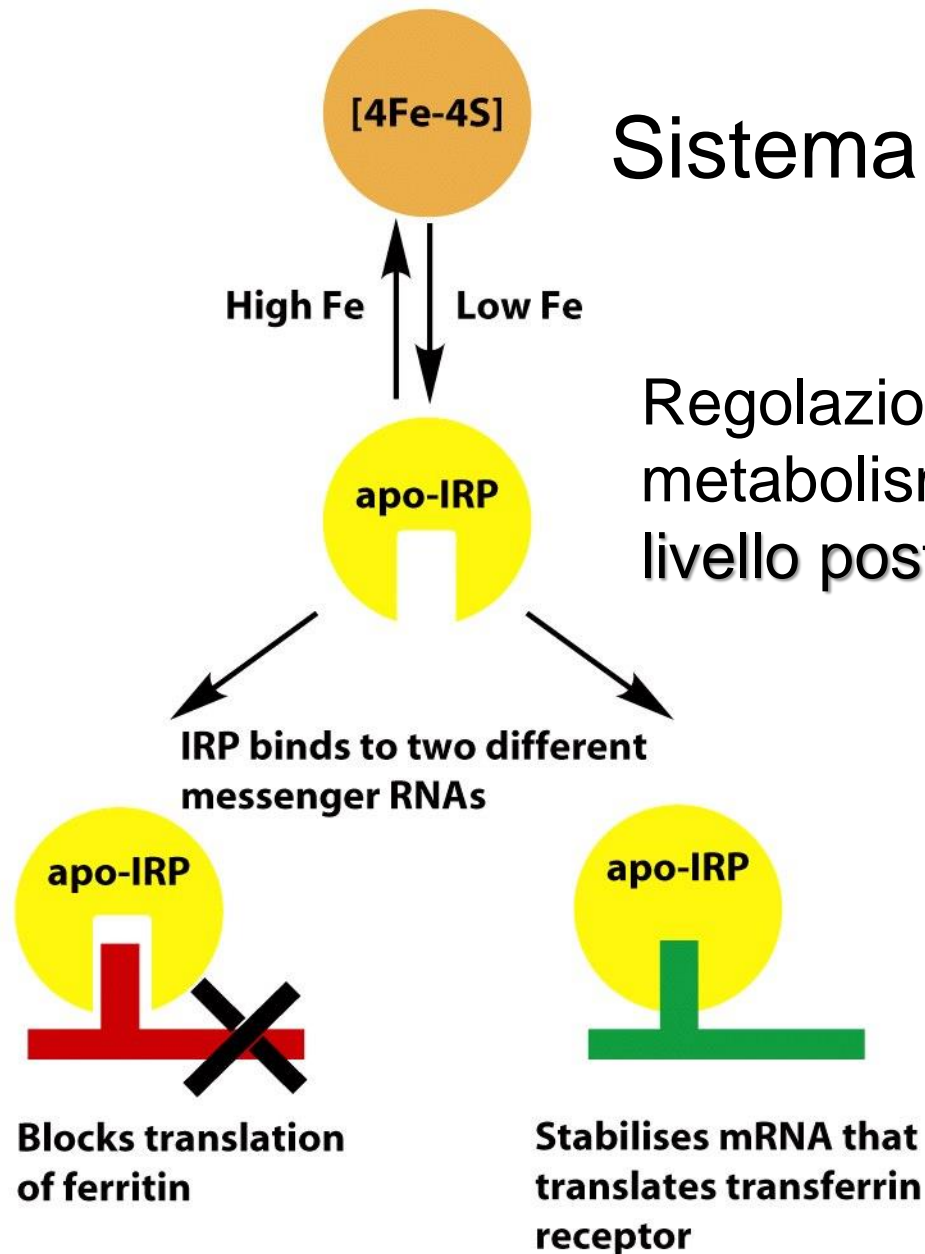
Omeostasi del ferro – Sistema IRP/IRE



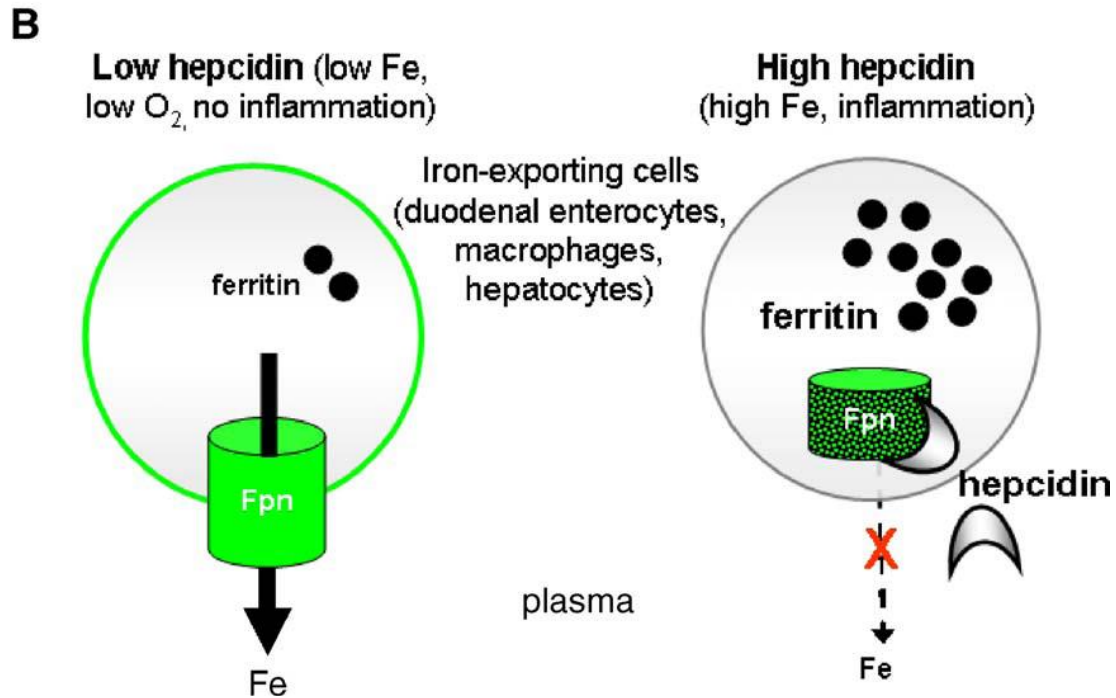
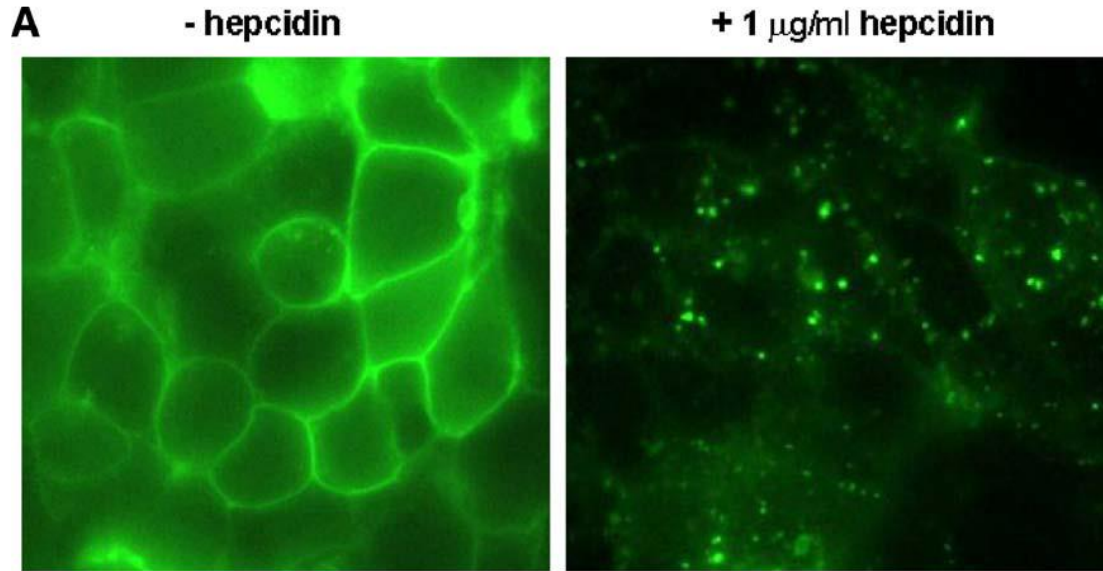
IRP: Iron Regulatory Proteins

IRE: Iron Responsive Elements (mRNA)

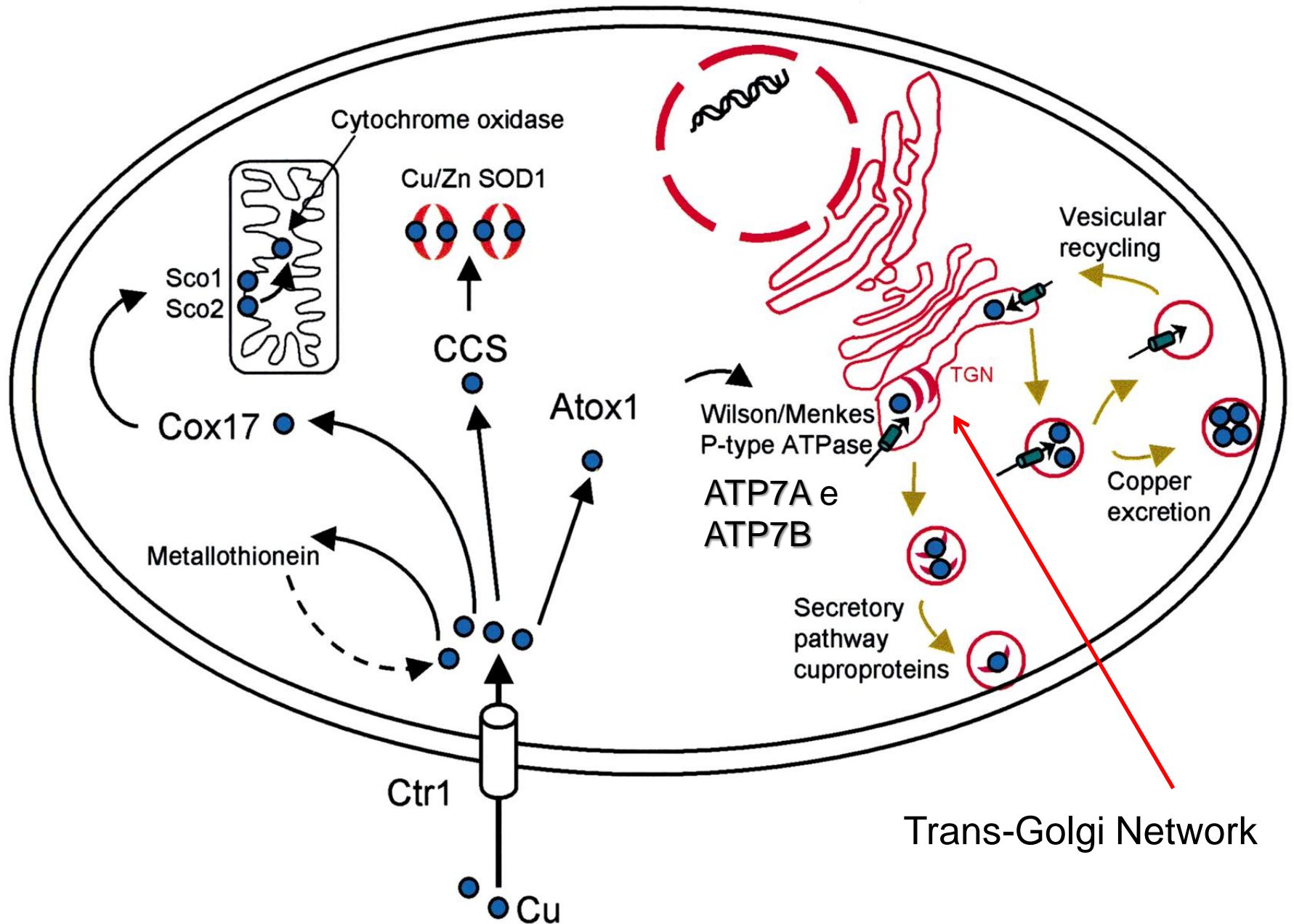
Sistema IRP/IRE



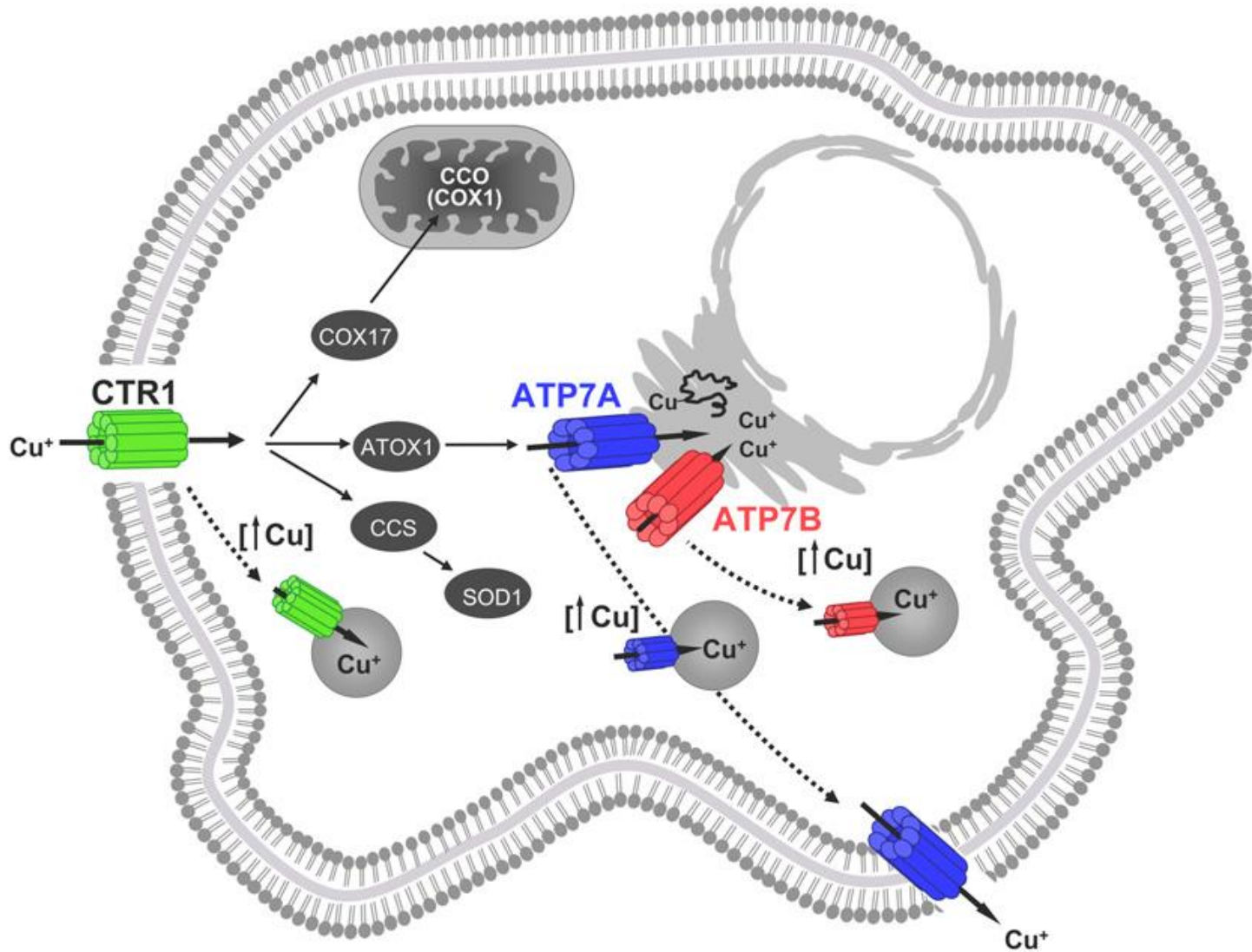
Export del ferro nel plasma regolato da epcidina

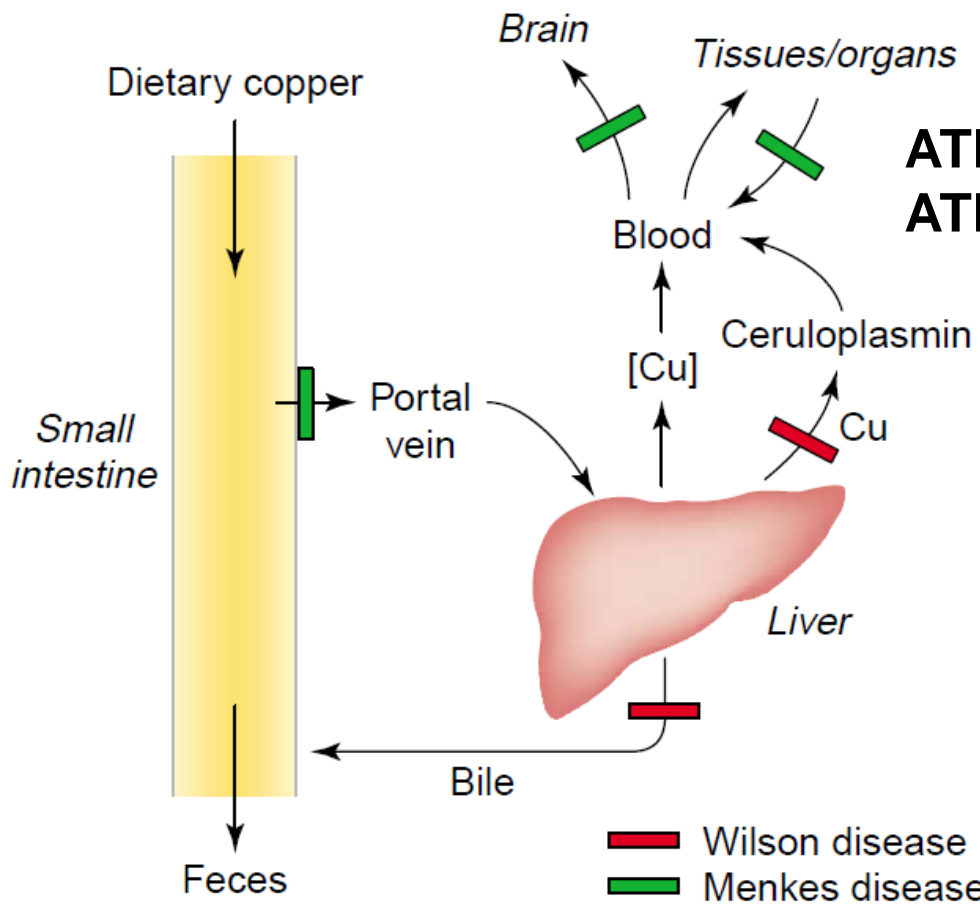


Omeostasi del rame

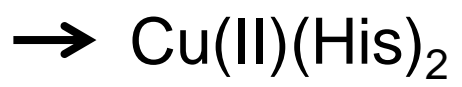


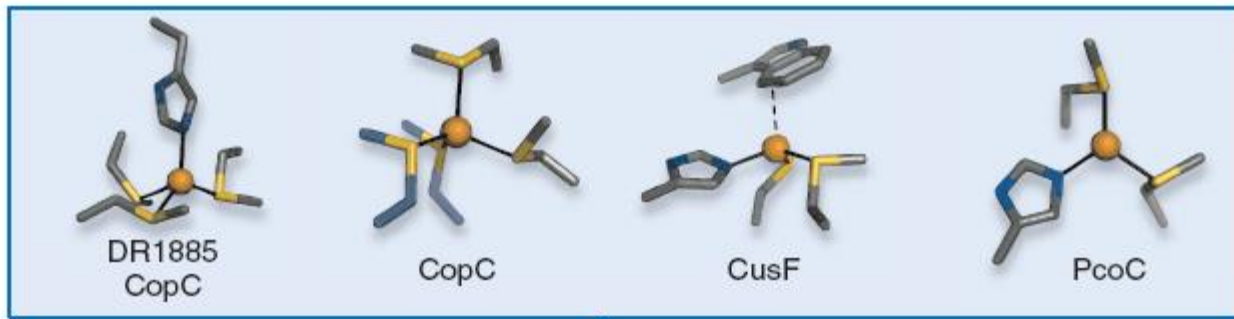
Omeostasi del rame





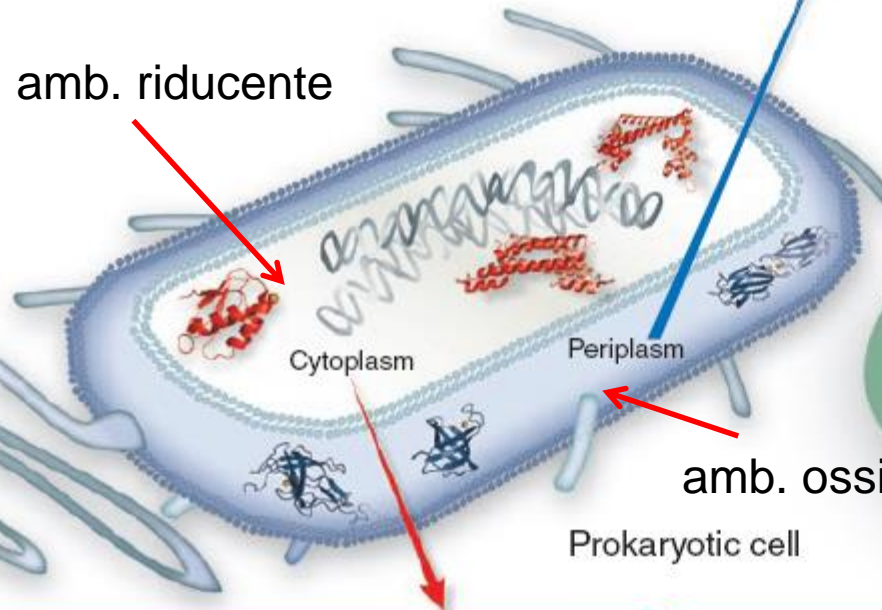
ATP7A: Menkes disease, Cu deficiency
ATP7B: Wilson's disease, Cu overload





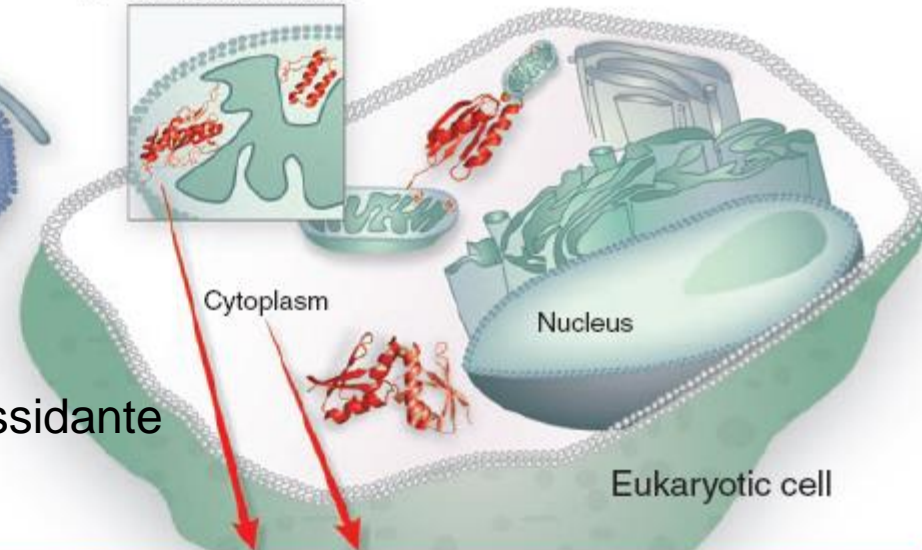
a

amb. riducente



b

Detail, mitochondrion



CopZ
CueR



CsoR



Atx1, Hah1
Ccc2, Mnk, Wnd
Cox17

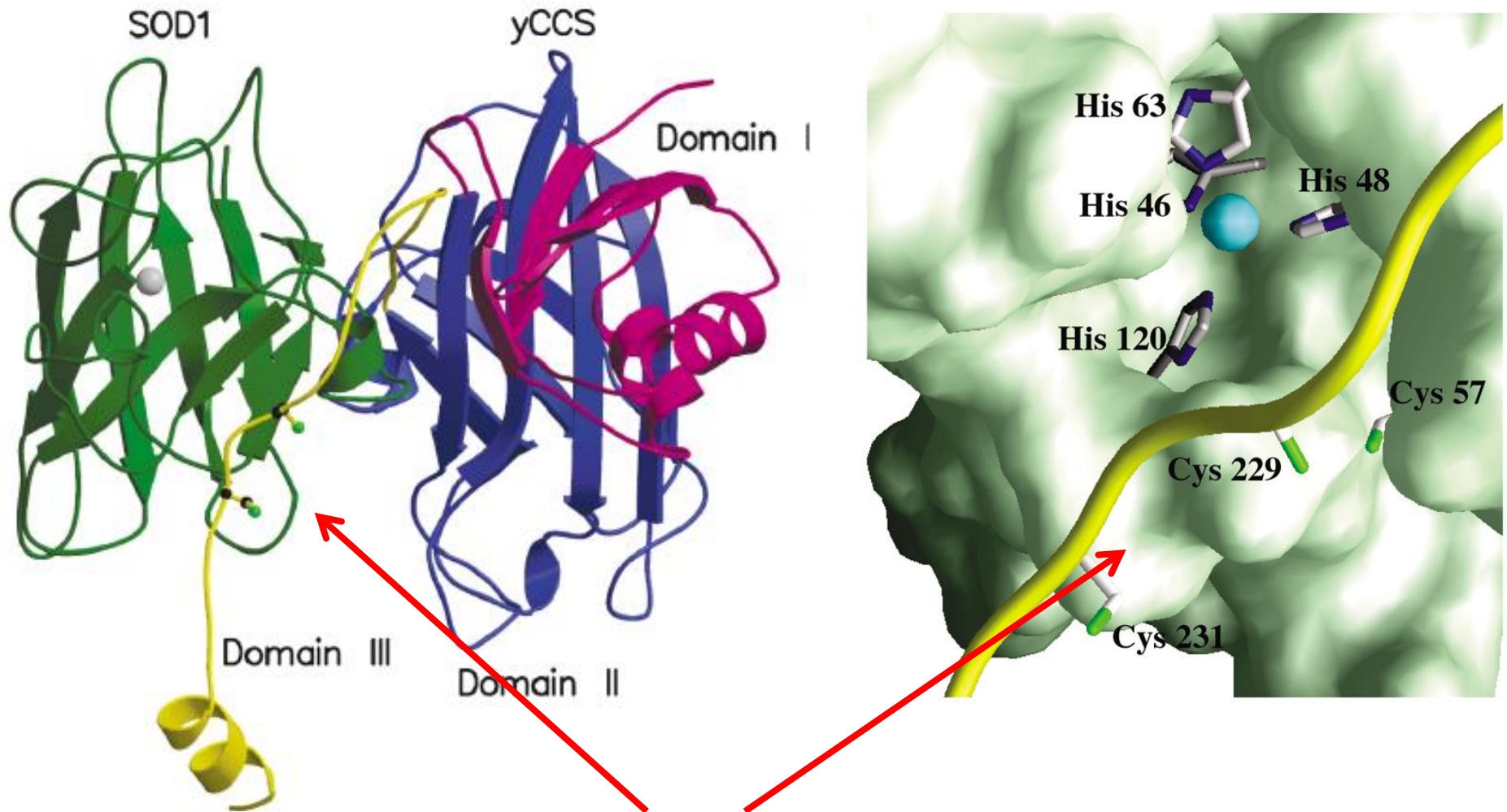


Hah1



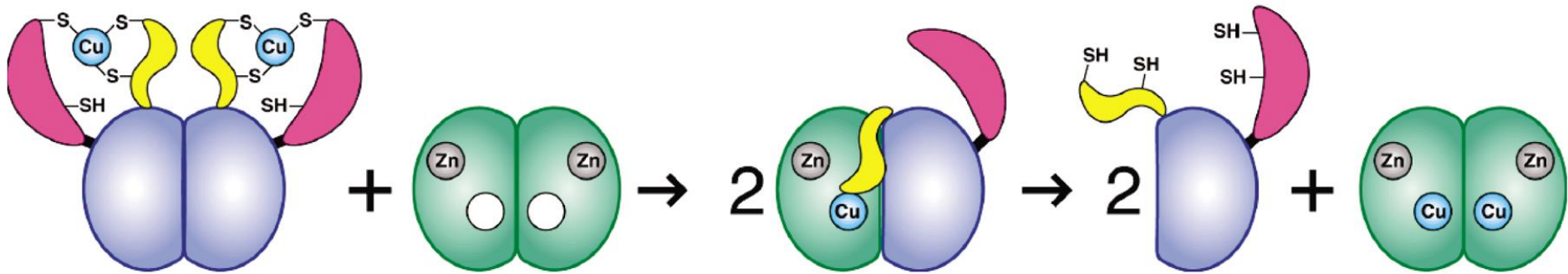
Sco1

yCCS/Zn-SOD



Sito di binding del Cu(I)

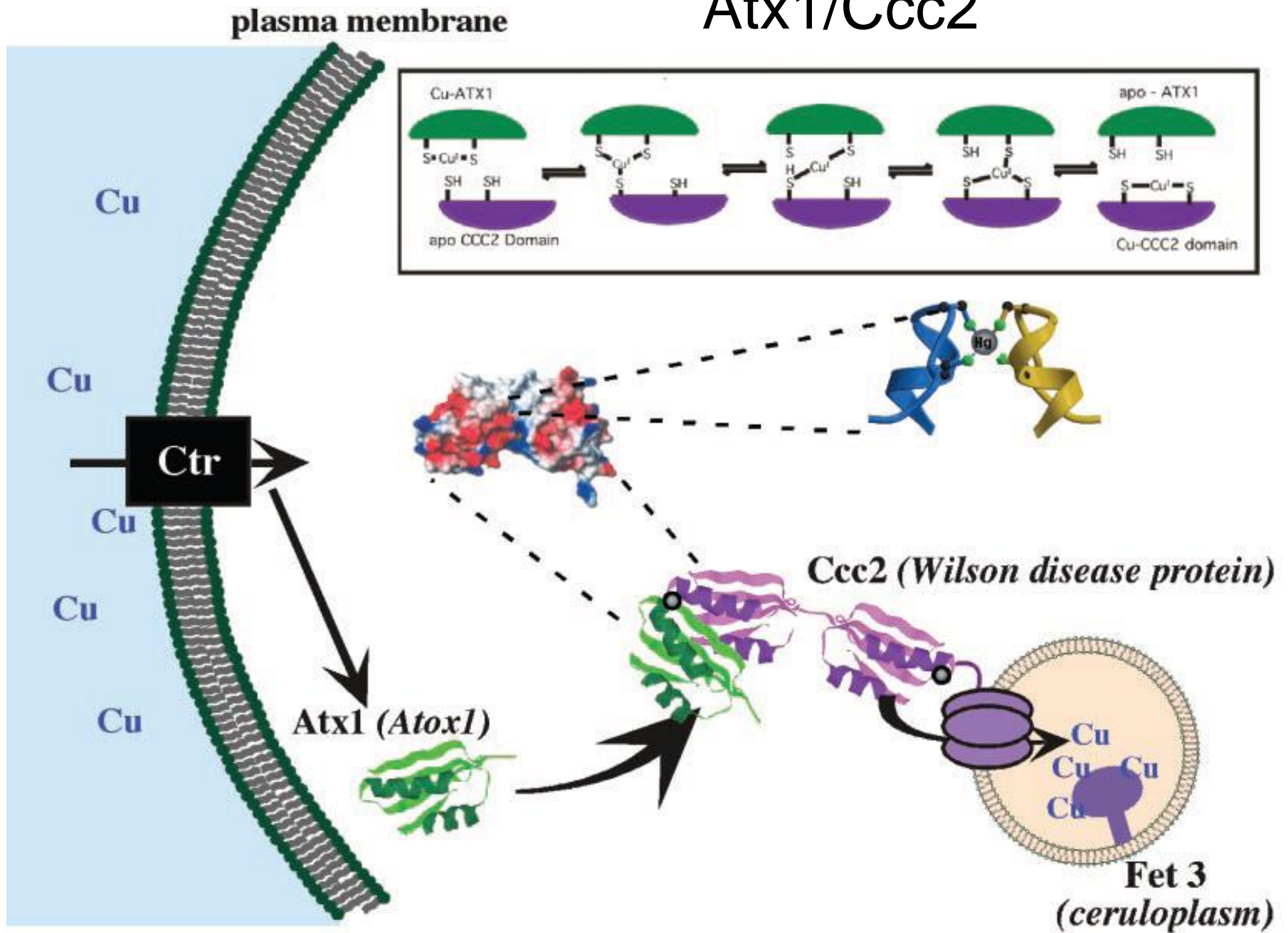
CCS/Zn-SOD



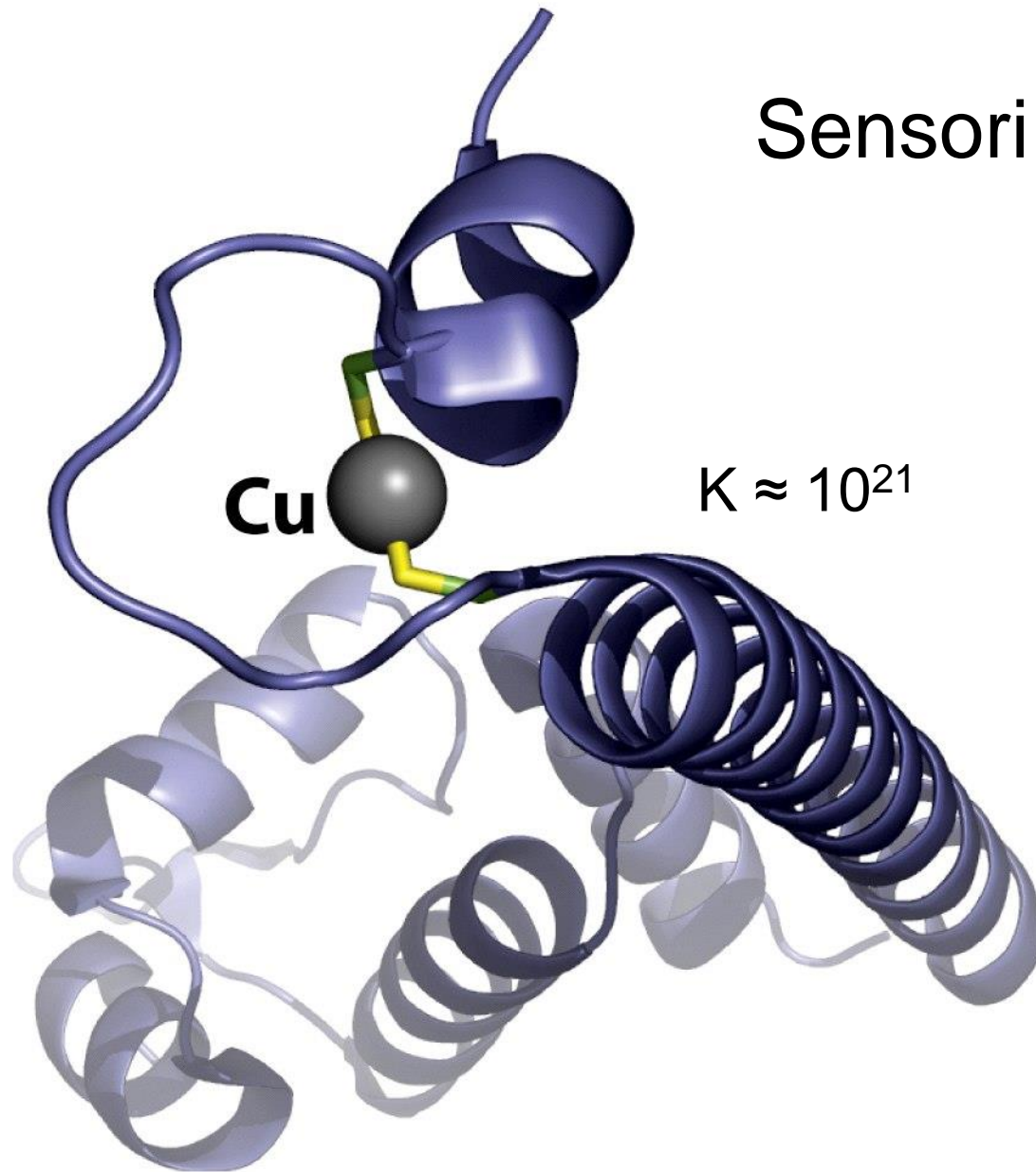
omodimeri

eterodimero

Atx1/Ccc2

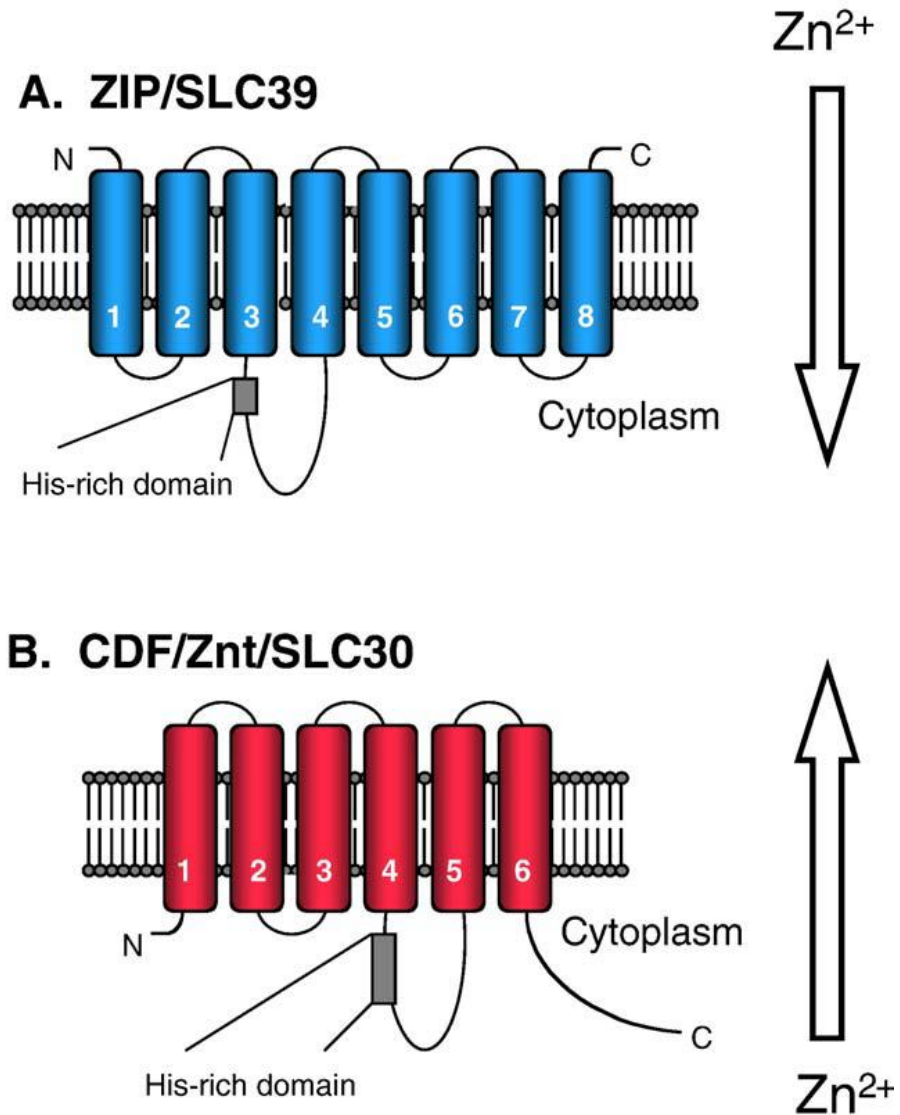


Sensori del Cu



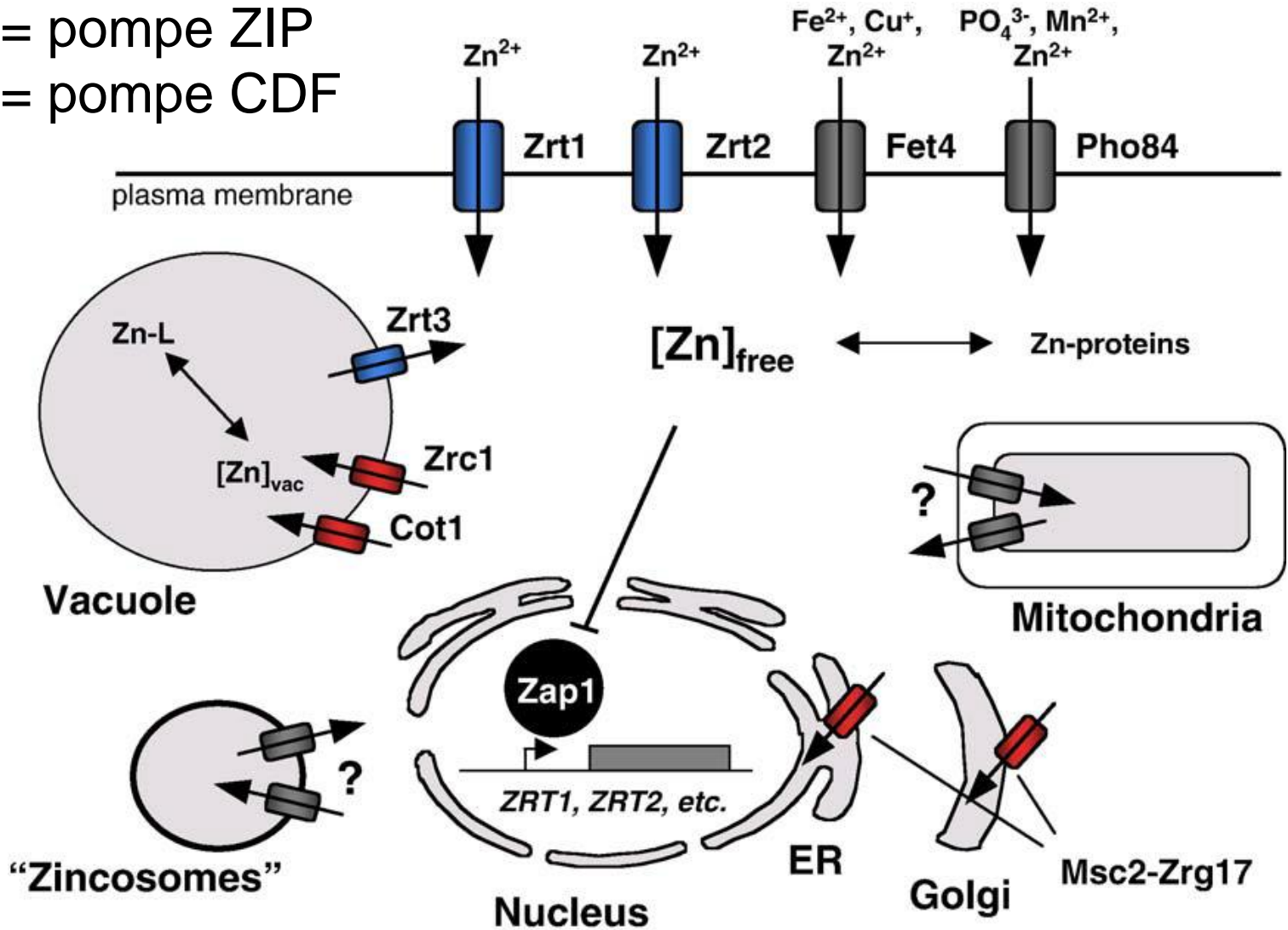
Fattore di trascrizione CueR (da *E. Coli*)

Omeostasi dello zinco in cellule eucariote

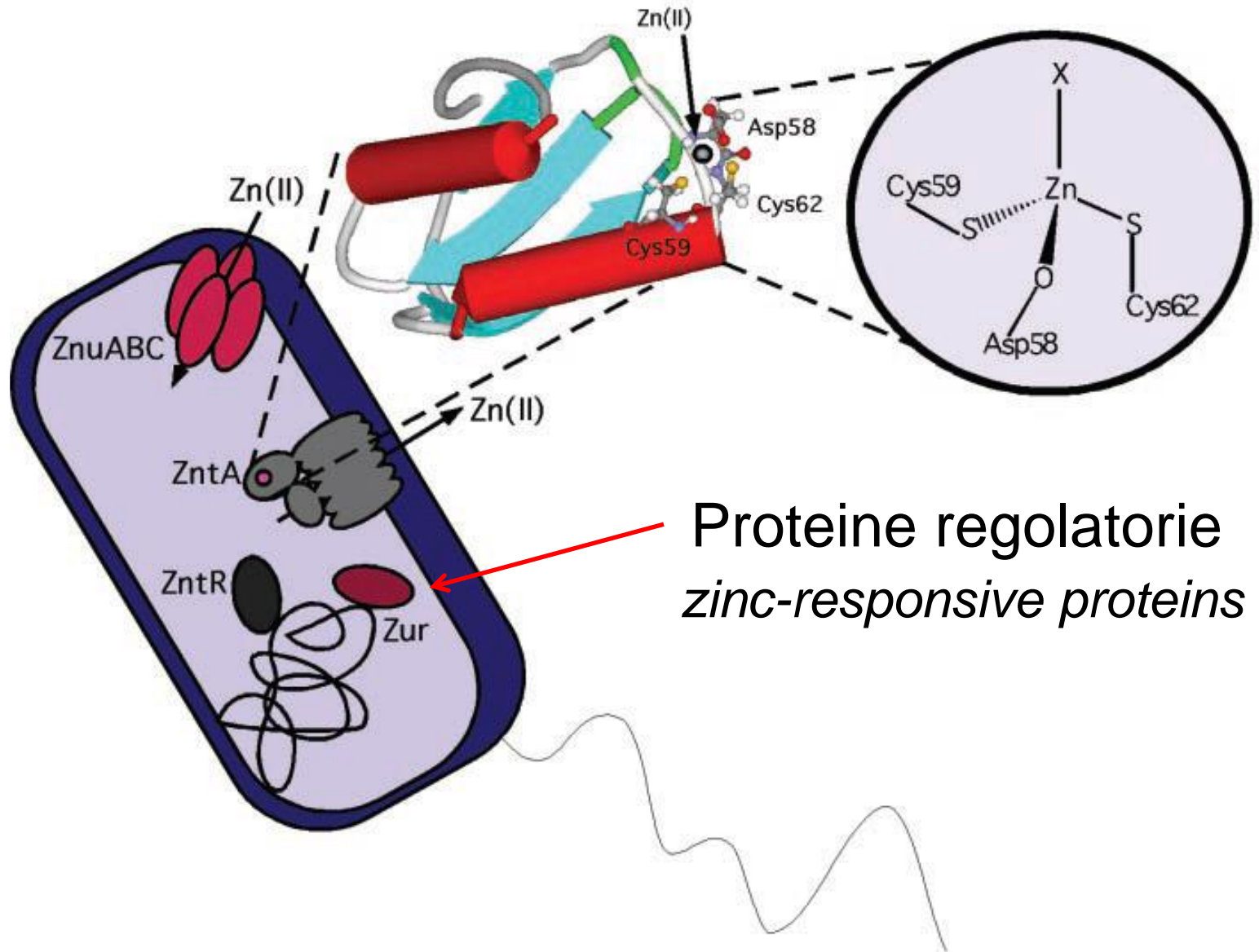


Omeostasi dello zinco in cellule eucariote

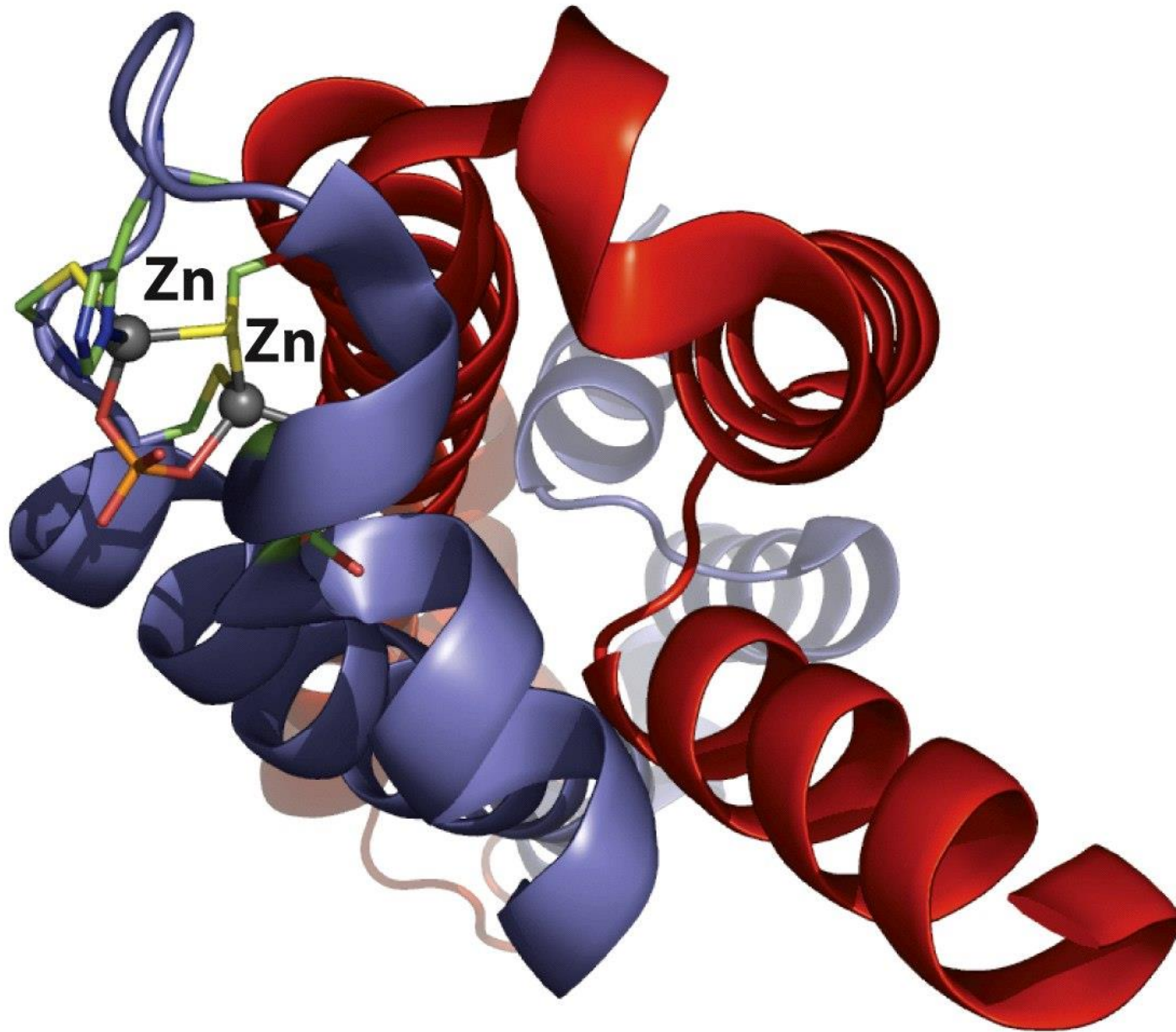
- = pompe ZIP
- = pompe CDF



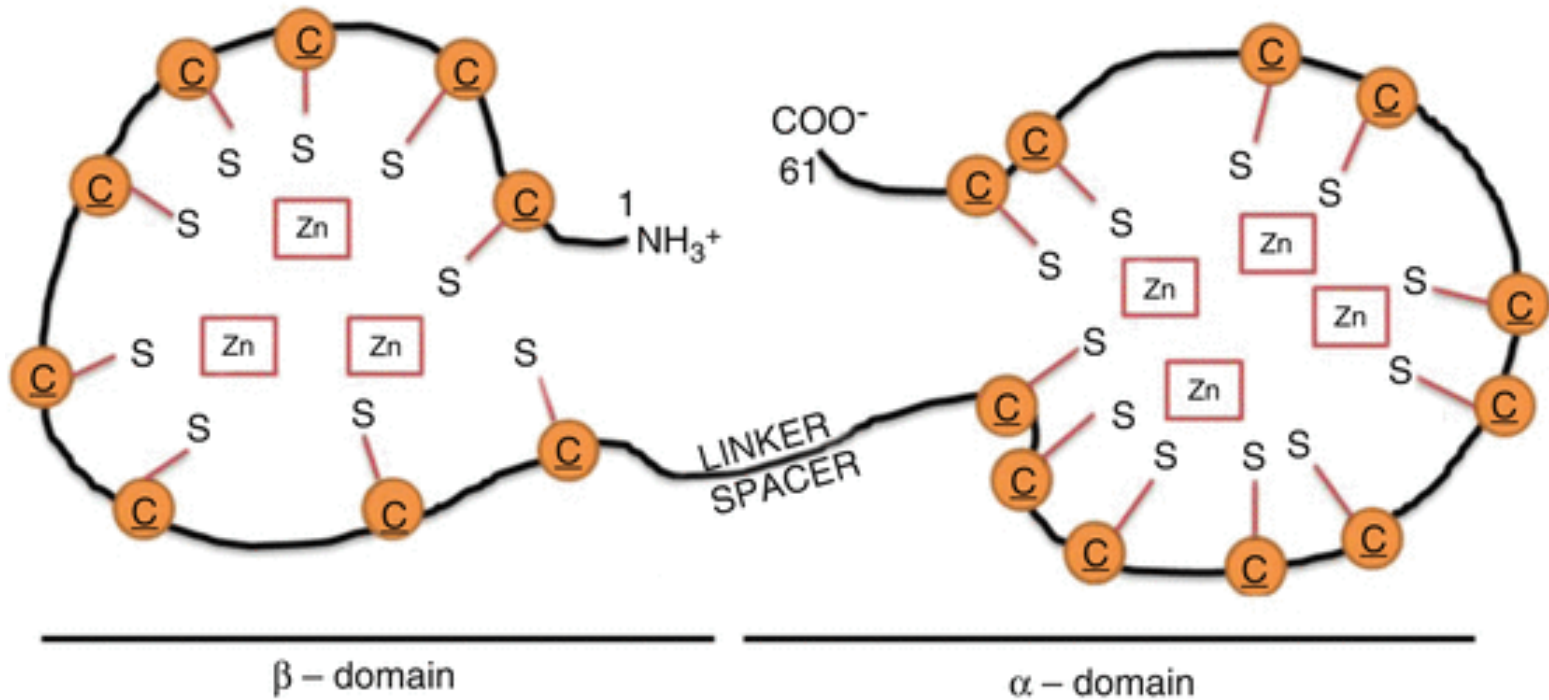
Omeostasi dello zinco nei batteri



Fattore di trascrizione ZntR

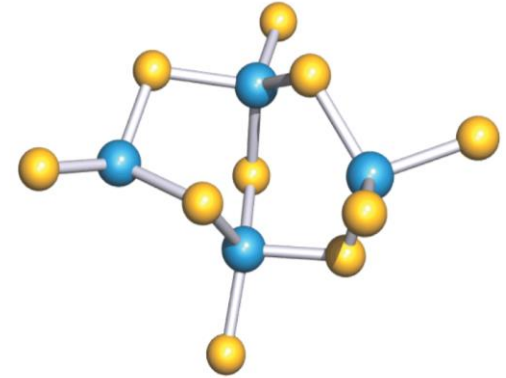
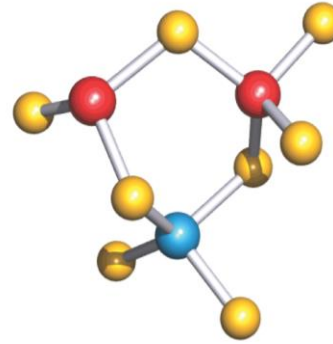
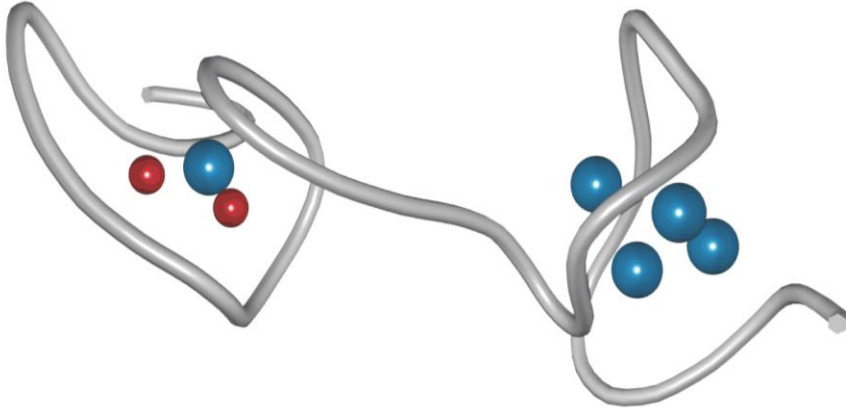


Metallotioneine



6 kDa,
ca. 60 a.a.
fino 30% cys

Metallotioneine



Proteine multifunzionali (?):

- Detossificazione/protezione dai metalli xenobiotici (Cd, Hg)
- *Storage* temporaneo di Zn e Cu
- *Chaperones*
- Ruolo protettivo verso i ROS