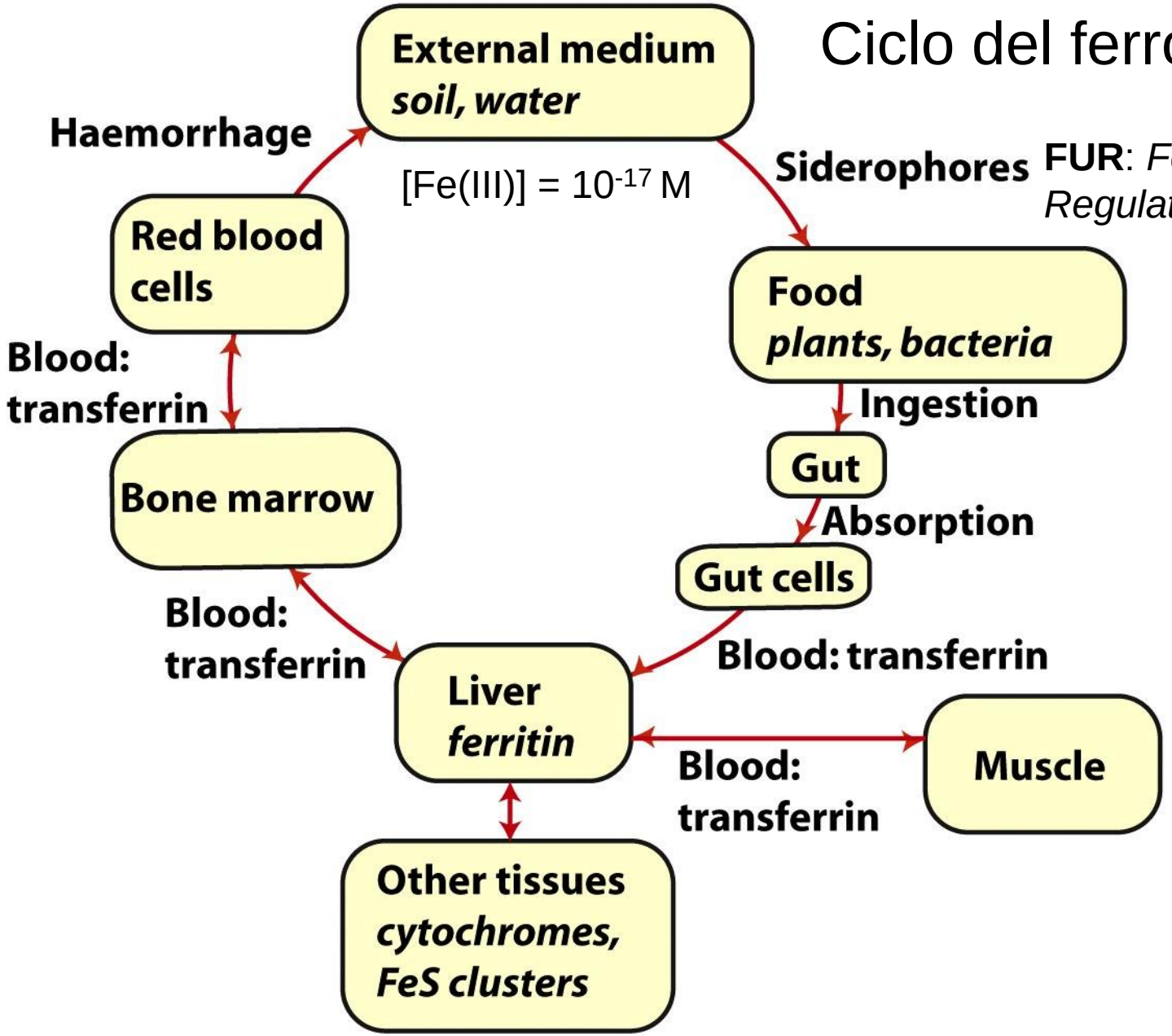
Omeostasi dei *trace elements*: *uptake*, trasporto, *storage*….

Ciclo del ferro

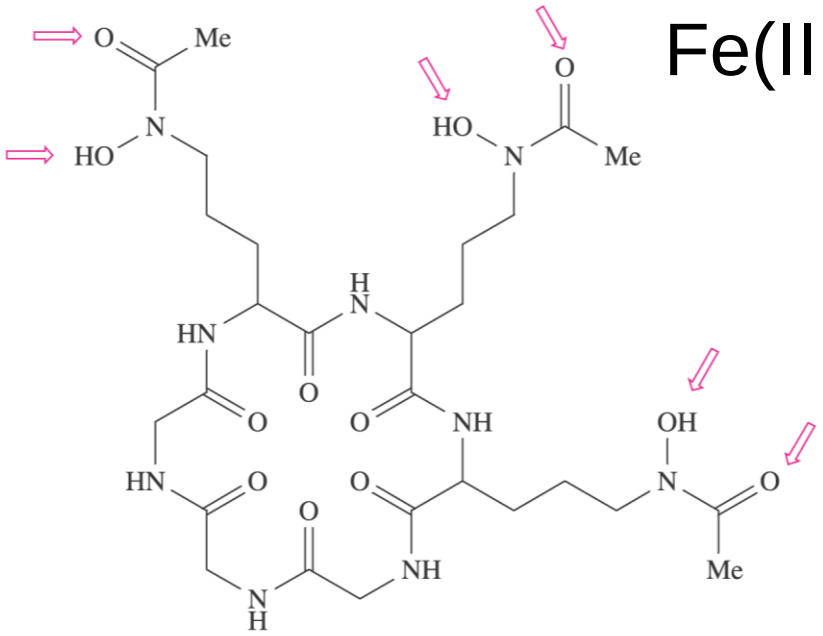


Siderofori idrossammati

(funghi, lievito)

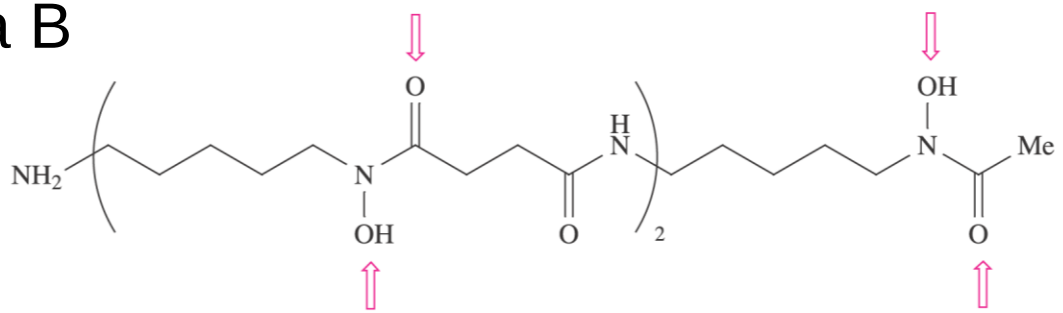
Fe(III) alto spin

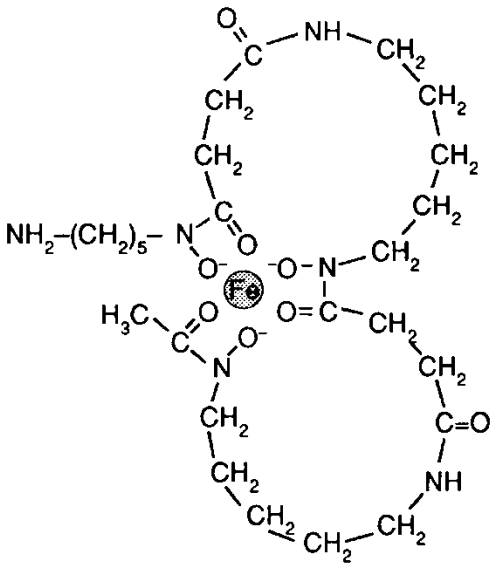
desferricromo



(a)

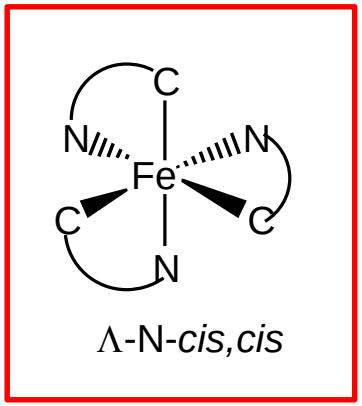
Desferriossamina B



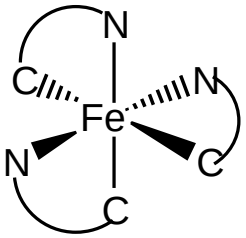


ferrioxamine B

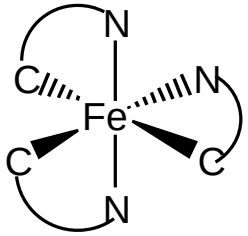
without Fe: deferrioxamine B



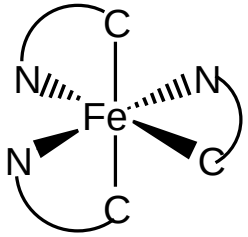
Λ-N-*cis,cis*



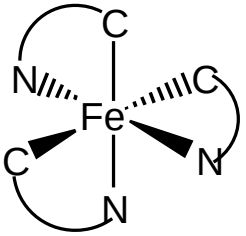
Λ-C-*trans,cis*



Λ-N-*trans,cis*



Λ-C-*cis,trans*

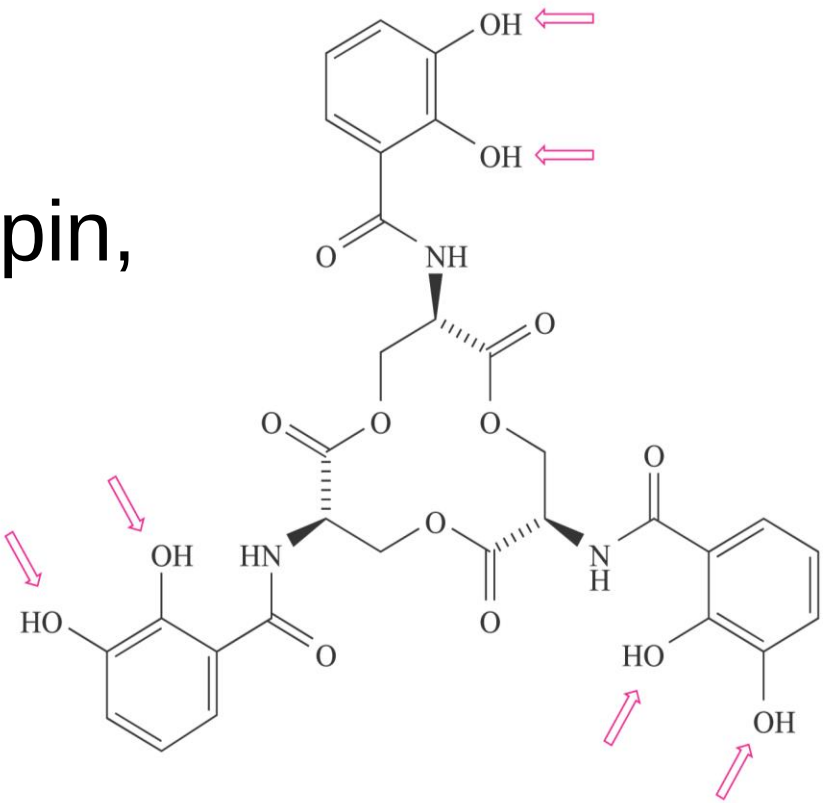


Λ-N-*trans,cis*

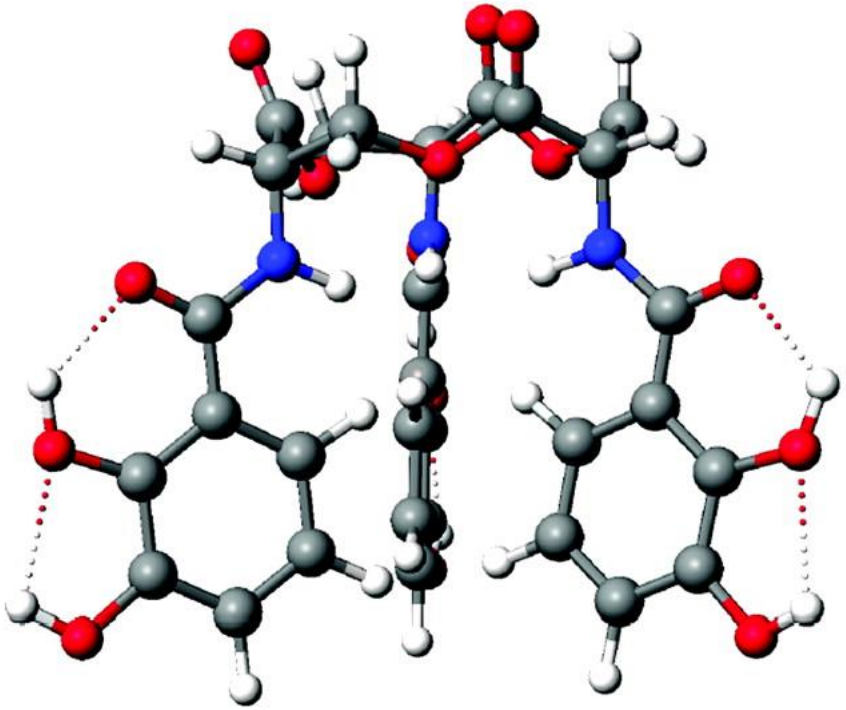
Siderofori catecolati
(batteri)

Fe(III) alto spin,

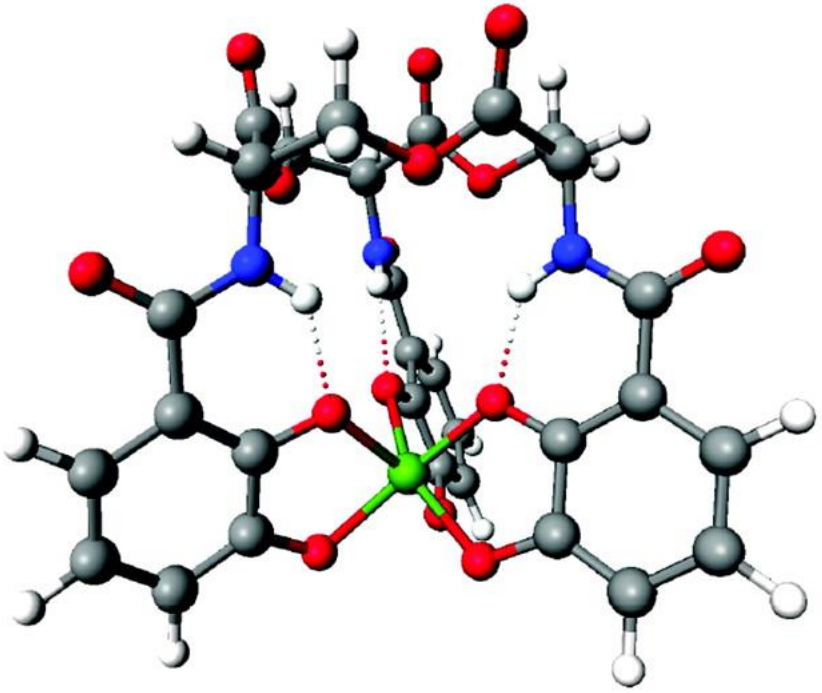
$K_a = 10^{52}$



Enterobactina

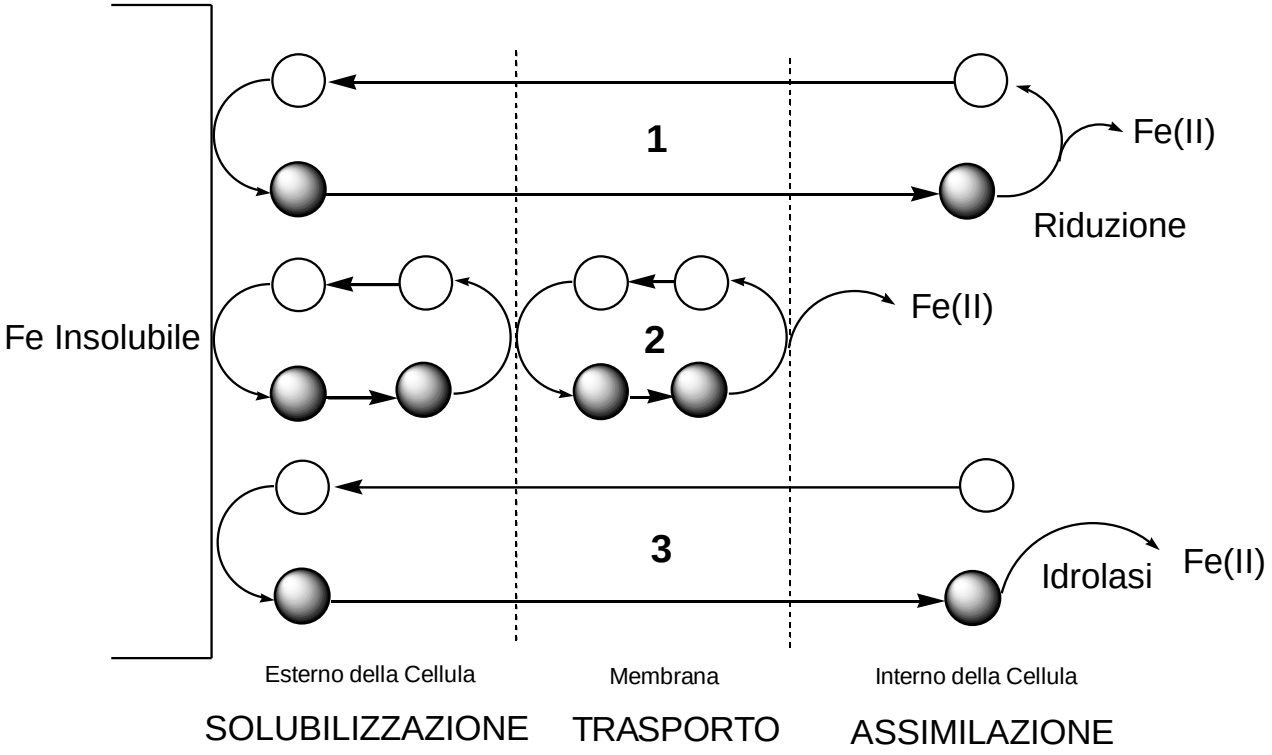


Modello di enterobactina non coordinata



Complesso V(IV)-enterobactina Δ

Meccanismi di trasporto trans-membrana

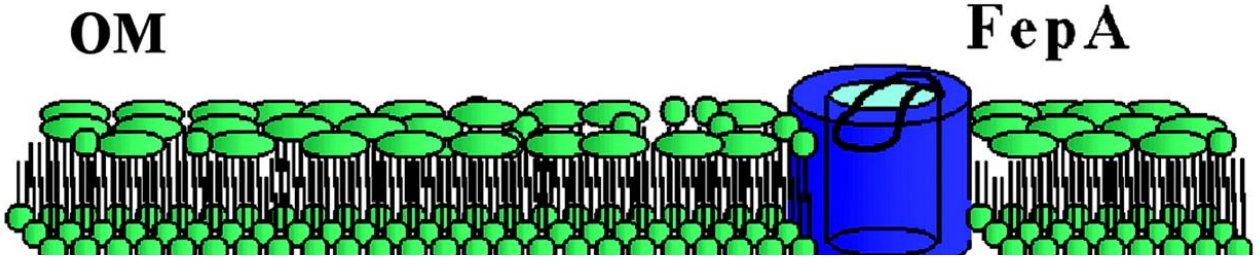


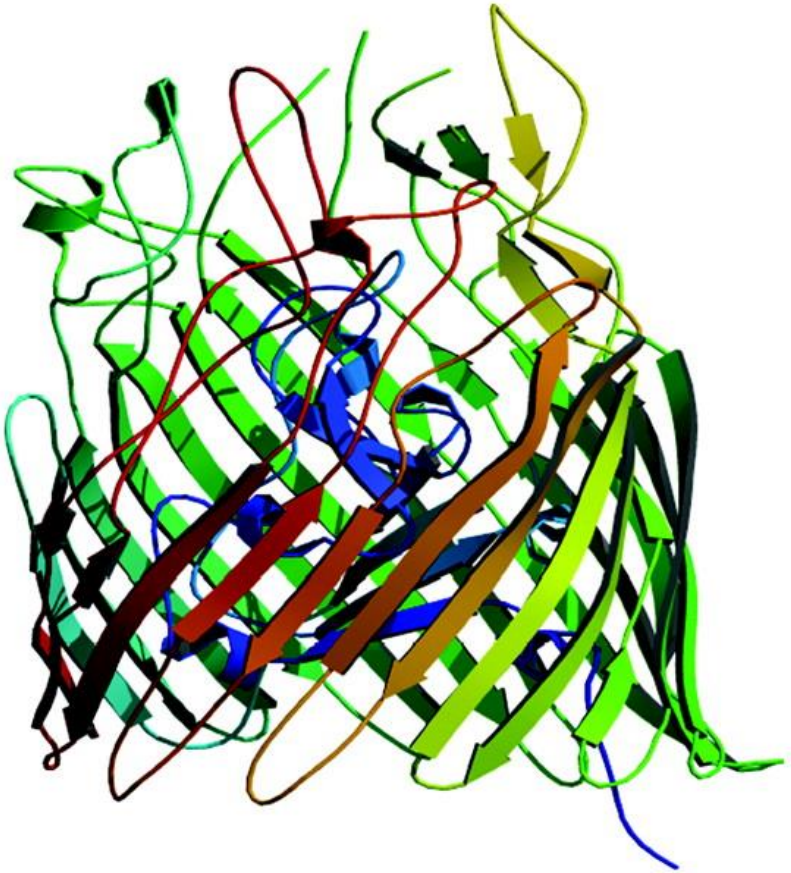
ferricromo

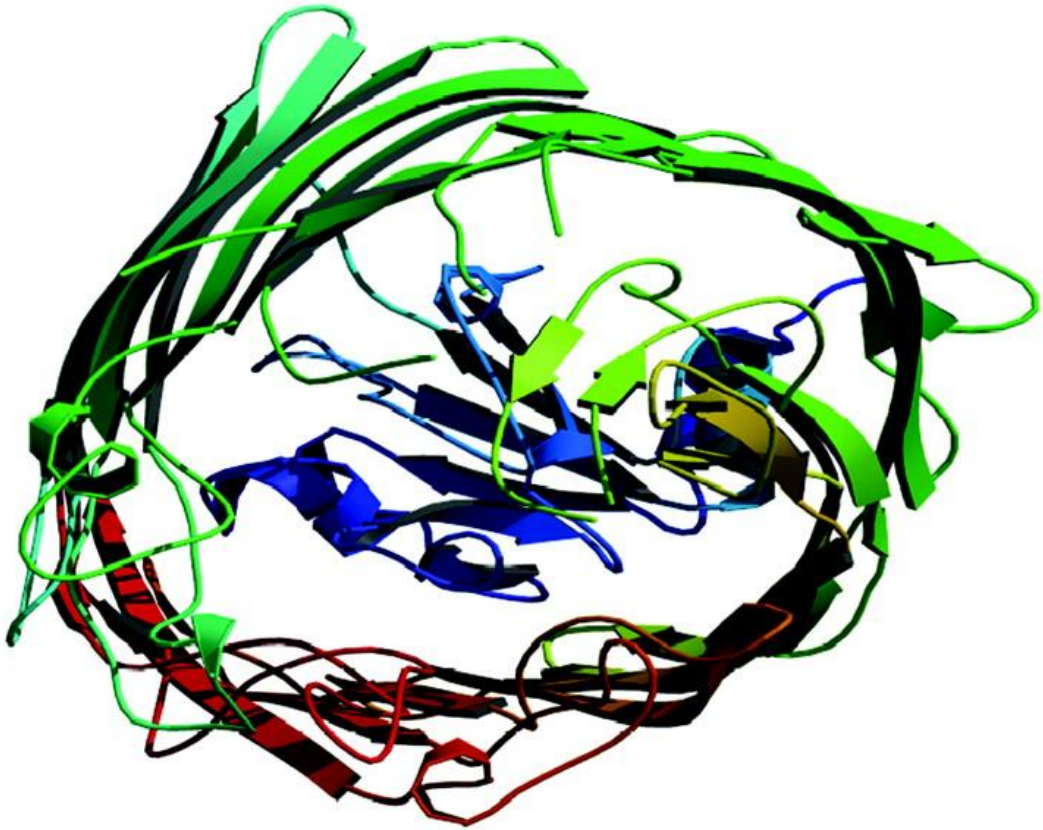
desferriossamina

enterobactina

FepA: trasporto trans-membrana di Fe-enterobactina





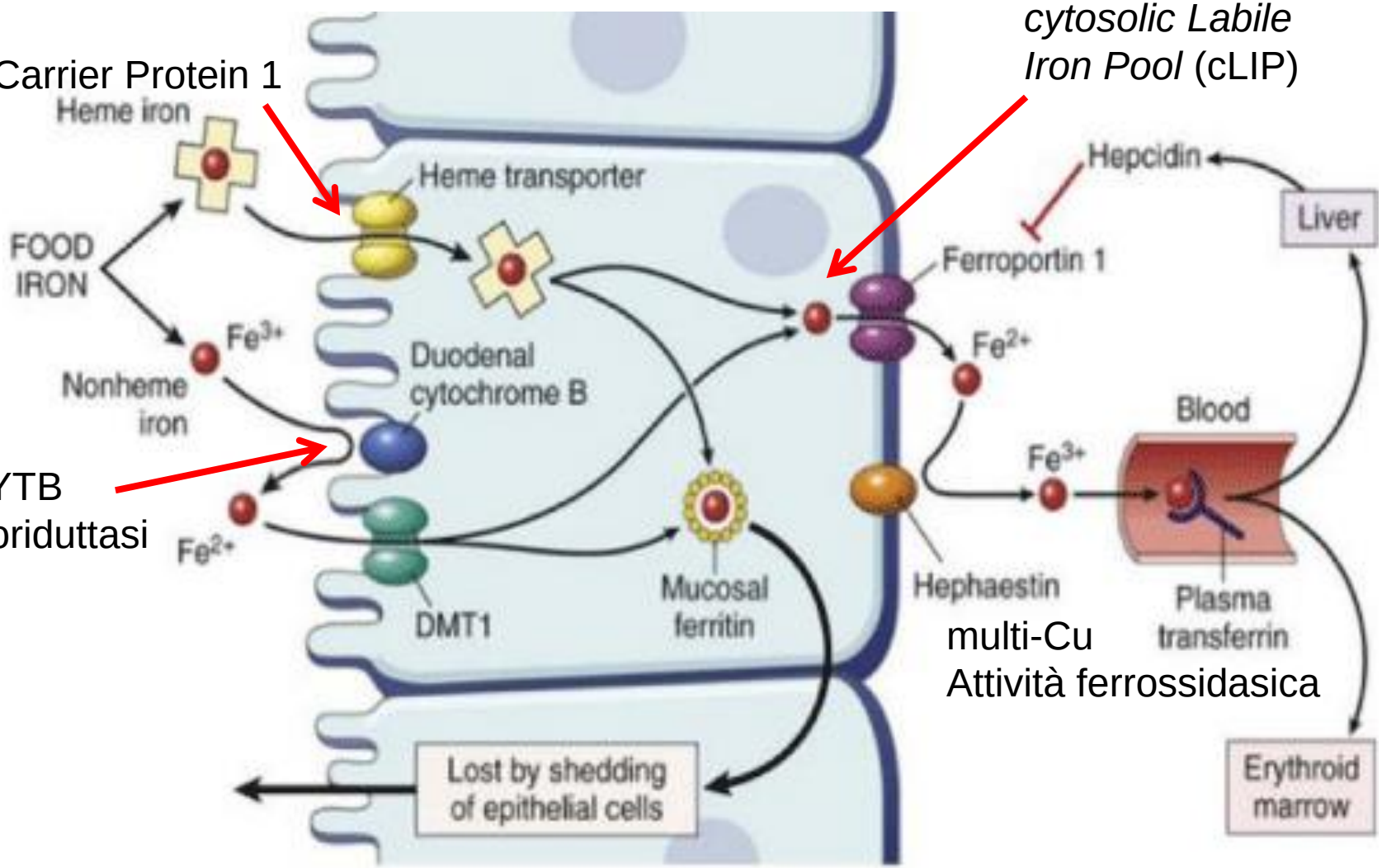


In blu la «gate protein» N-terminale

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

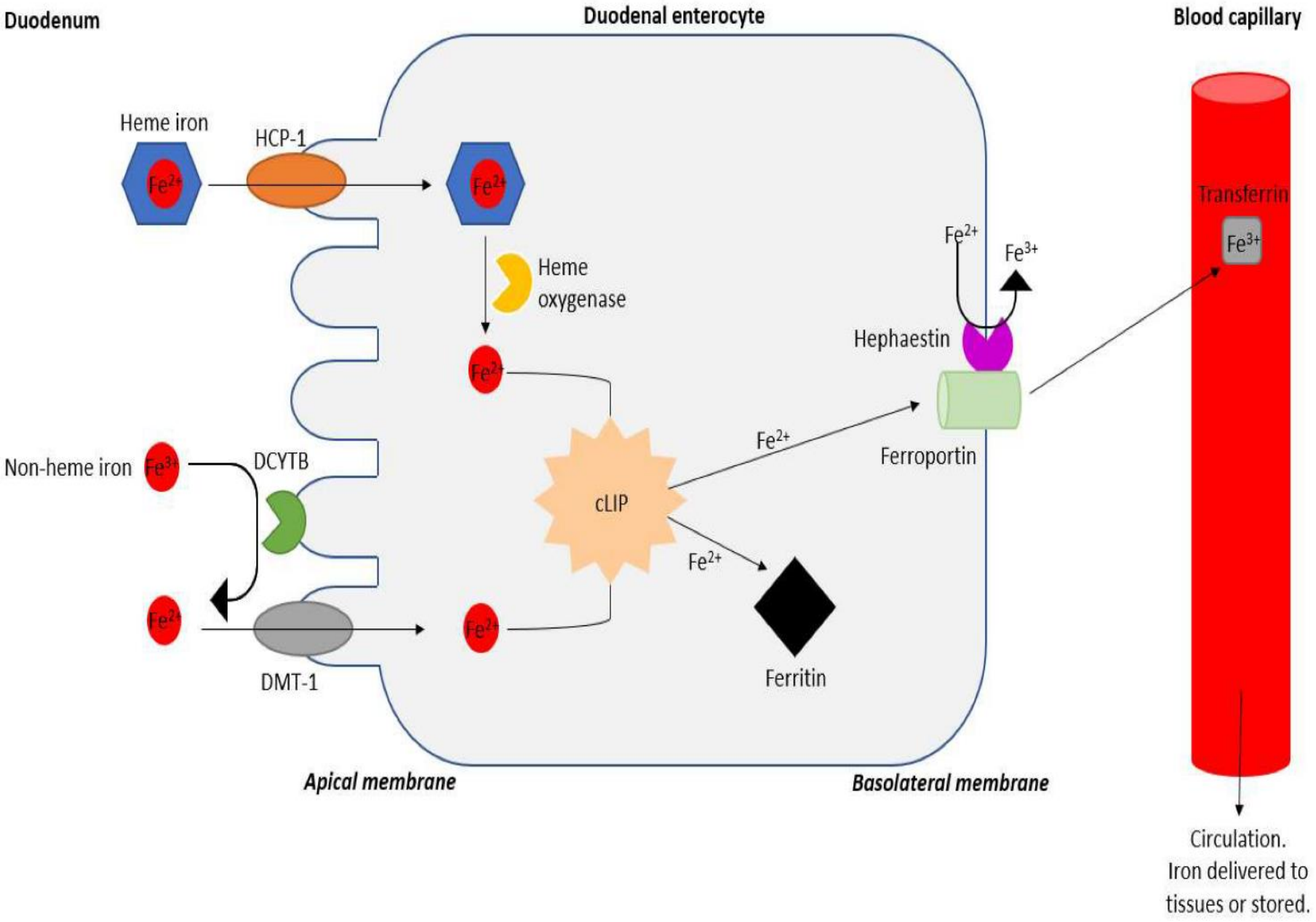
HCP-1
Heme Carrier Protein 1

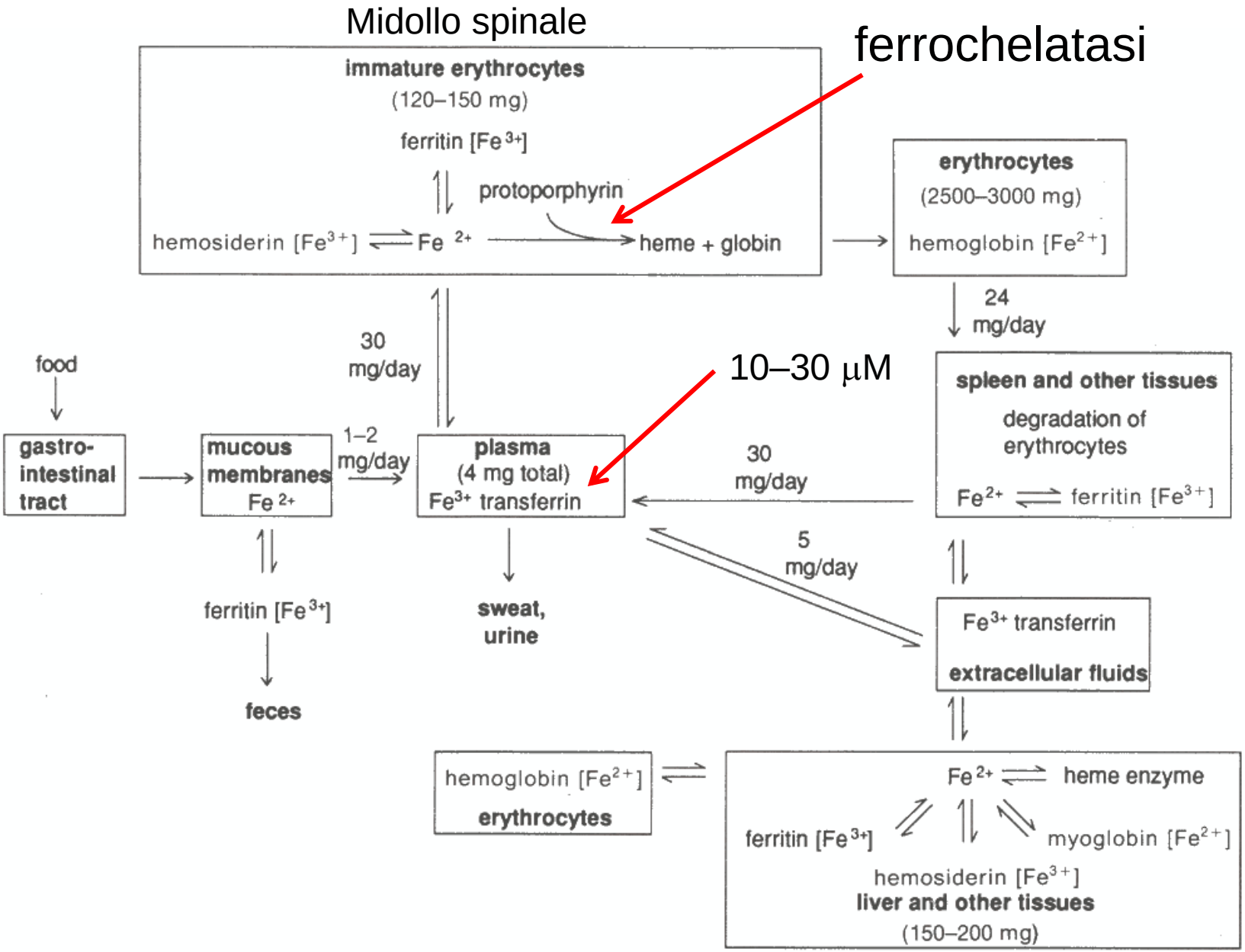
cytosolic Labile Iron Pool (cLIP)



DCYTB
ferroriduttasi

multi-Cu
Attività ferrossidasica

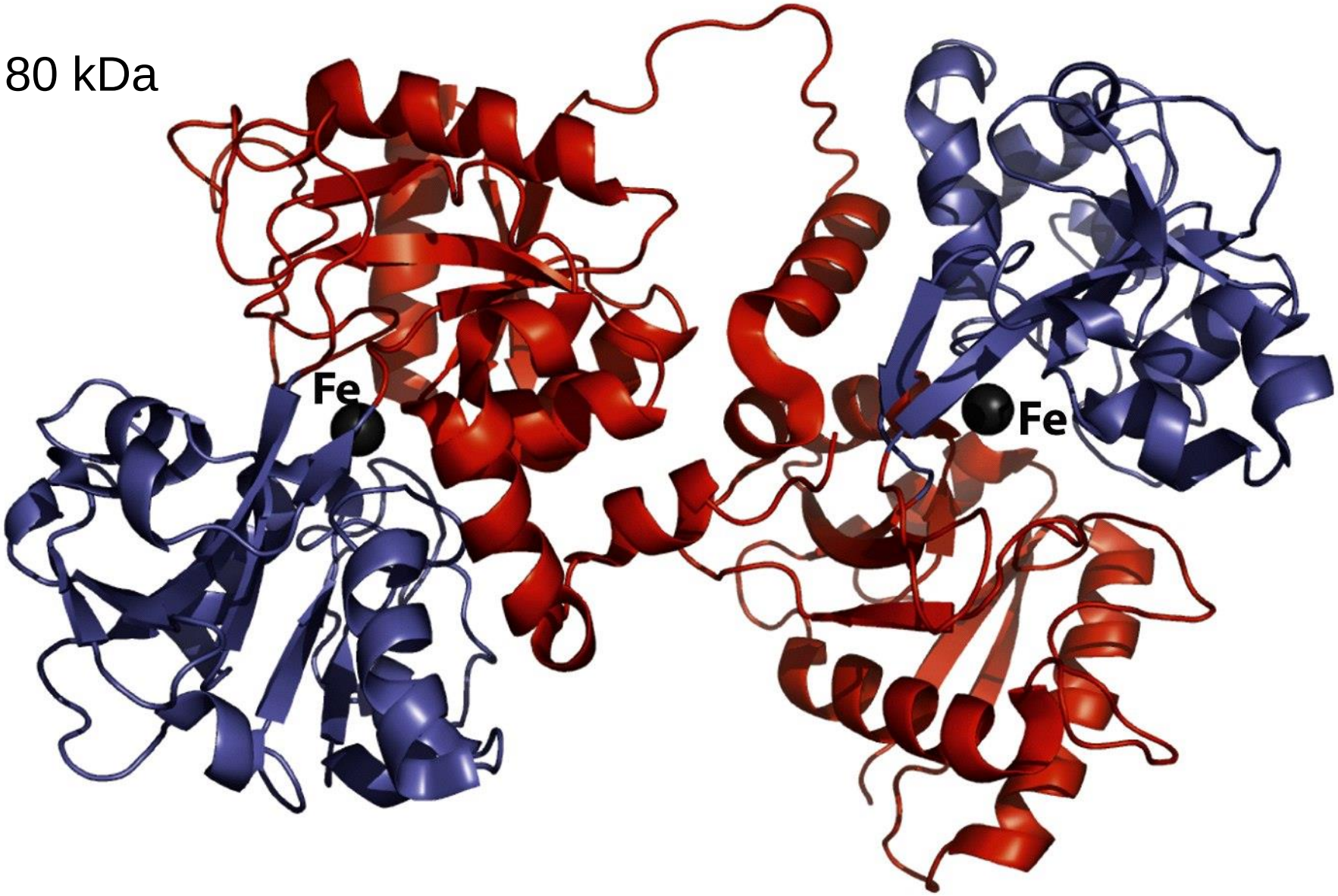

Duodenum
Duodenal enterocyte
Blood capillary
Heme iron
HCP-1
Fe2+
Heme oxygenase
Fe2+
Fe2+
Fe3+
Hephaestin
Transferrin
Fe3+
Non-heme iron
Fe3+
DCYTB
cLIP
Fe2+
Ferroportin
Fe2+
Fe2+
Ferritin
DMT-1
Apical membrane
Basolateral membrane
Circulation.
Iron delivered to
tissues or stored.


Midollo spinale
ferrochelatasi
immature erythrocytes
(120–150 mg)
ferritin [Fe 3+]
protoporphyrin
hemosiderin [Fe3+] Fe 2+ heme + globin
erythrocytes
(2500–3000 mg)
hemoglobin [Fe2+]
24
mg/day
30
mg/day
10–30 μM
food
gastro-
intestinal
tract
mucous
membranes
Fe 2+
1–2
mg/day
plasma
(4 mg total)
Fe3+ transferrin
30
mg/day
spleen and other tissues
degradation of
erythrocytes
Fe2+ ferritin [Fe3+]
5
mg/day
ferritin [Fe3+]
feces
sweat,
urine
Fe3+ transferrin
extracellular fluids
hemoglobin [Fe2+]
erythrocytes
Fe 2+ heme enzyme
ferritin [Fe3+]
myoglobin [Fe2+]
hemosiderin [Fe3+]
liver and other tissues
(150–200 mg)

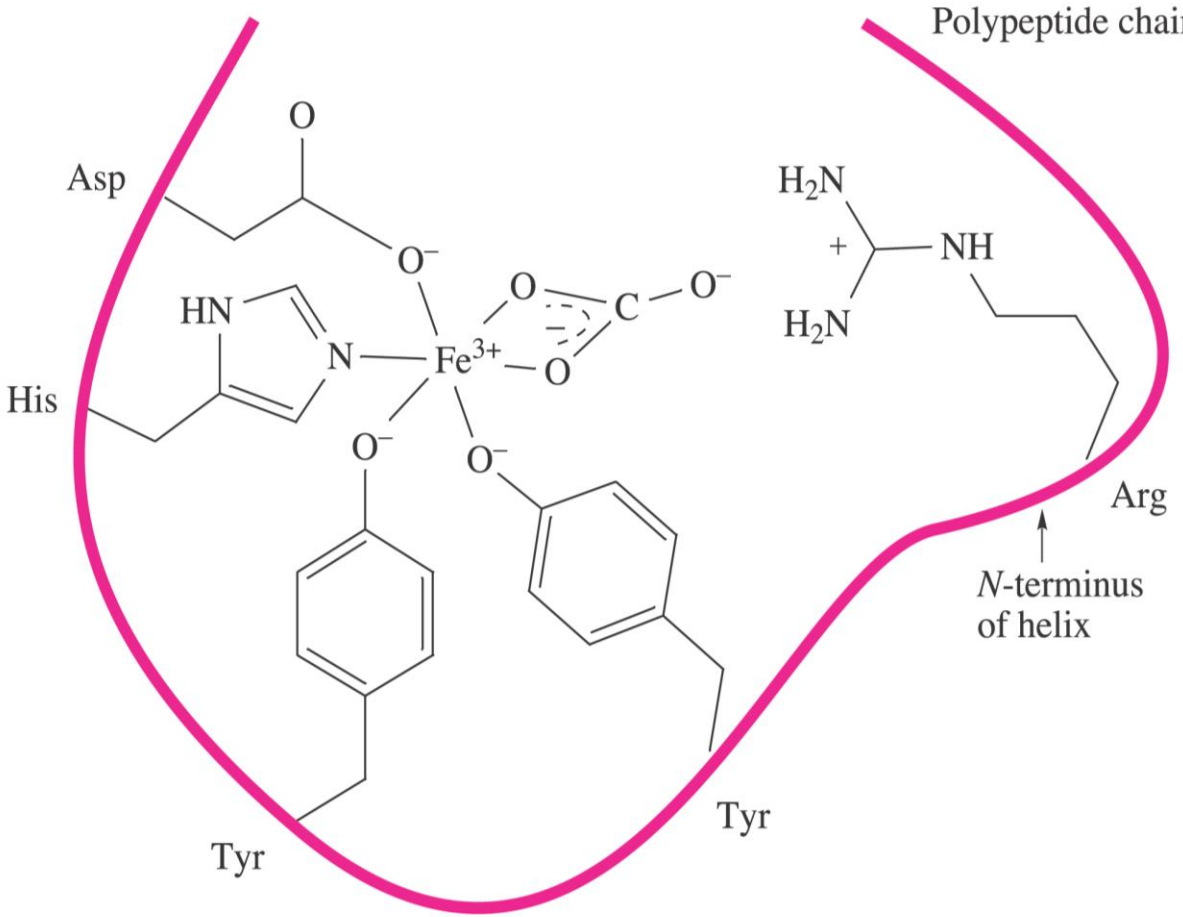
Transferrina

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

80 kDa



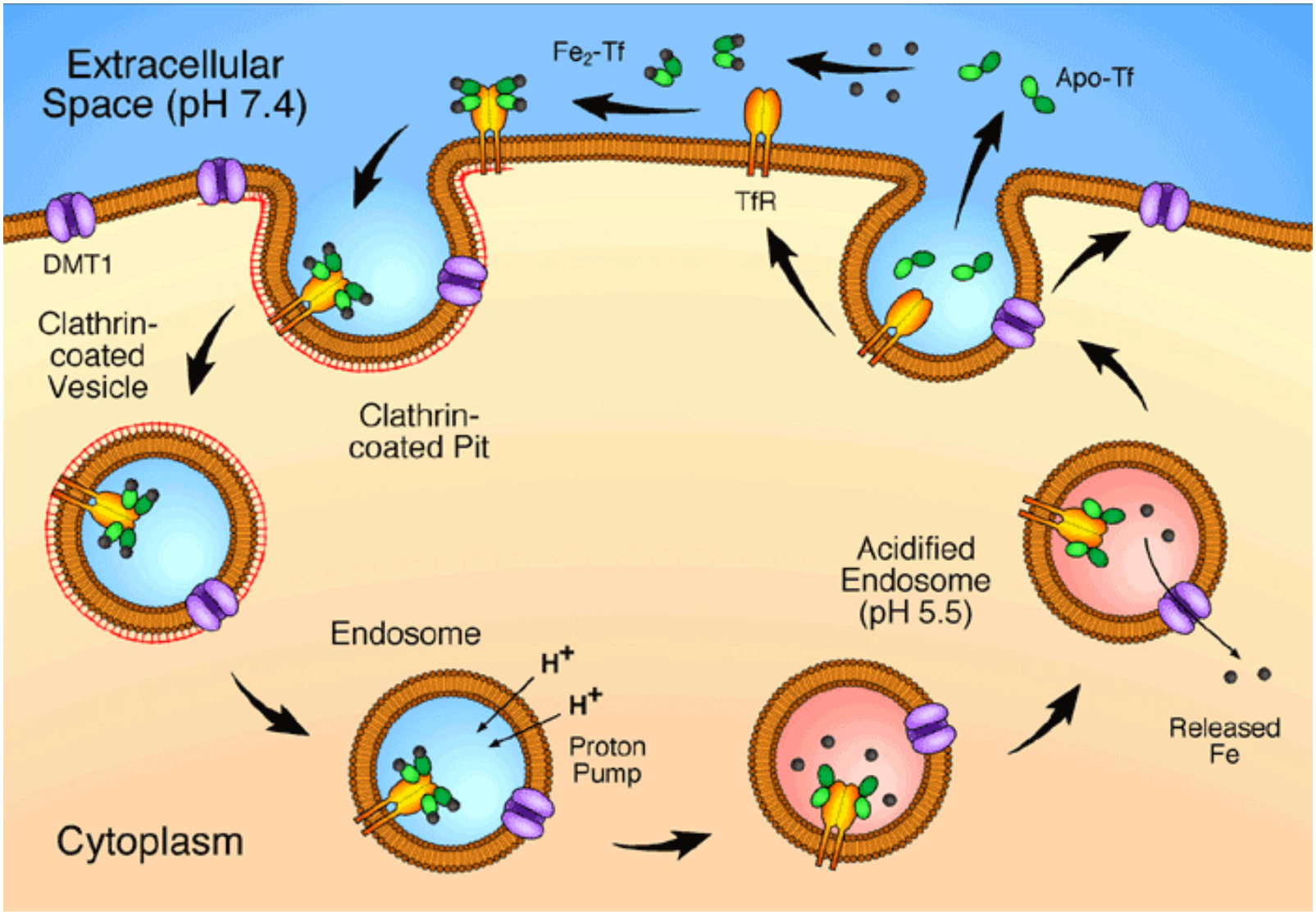
Sito di coordinazione del Fe nella transferrina



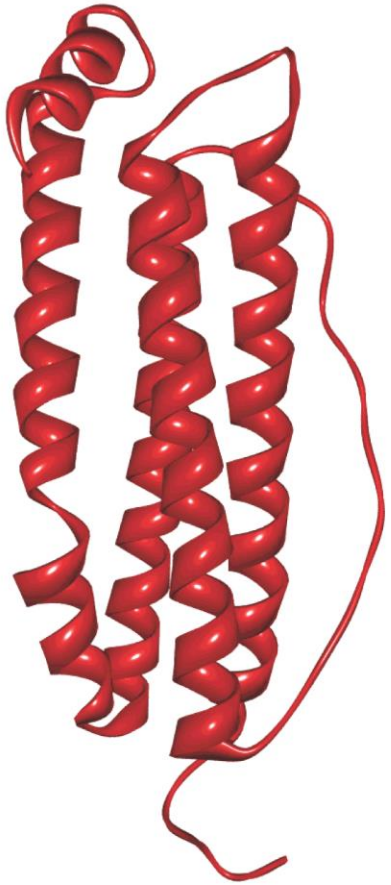
La coordinazione del Fe(III) comporta il rilascio di $3H^+$
e una notevole variazione conformazionale della transferrina

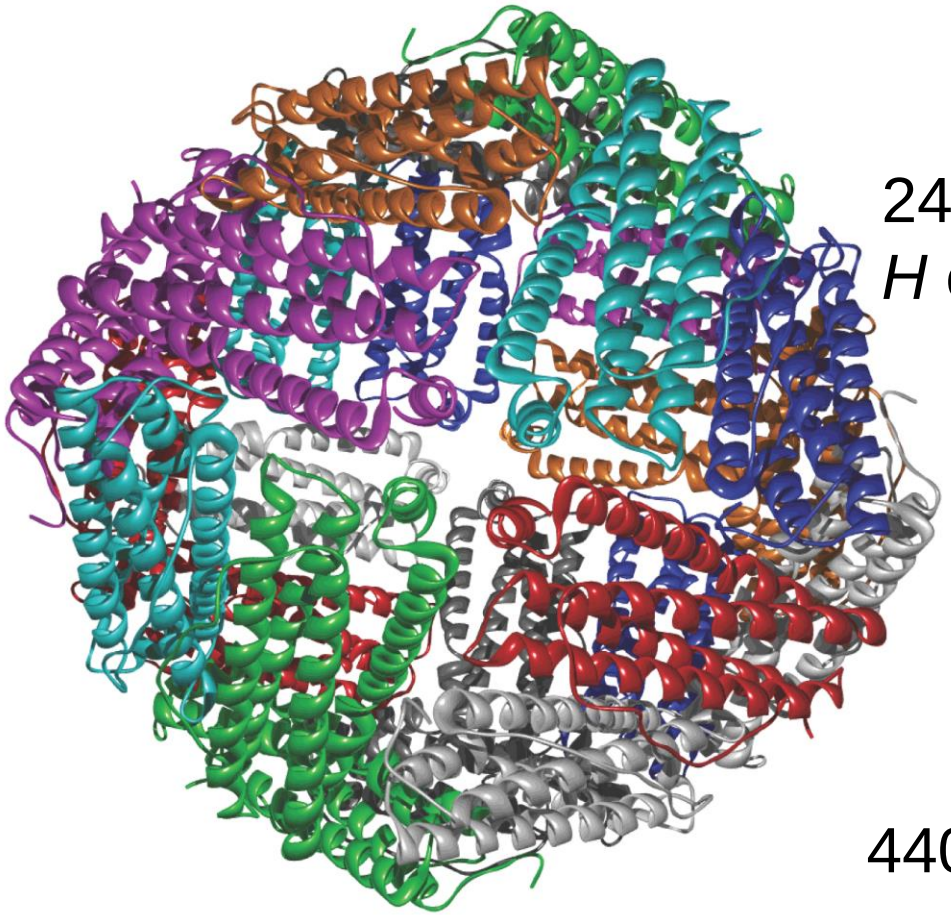
Ciclo della transferrina

endocitosi



Ferritina



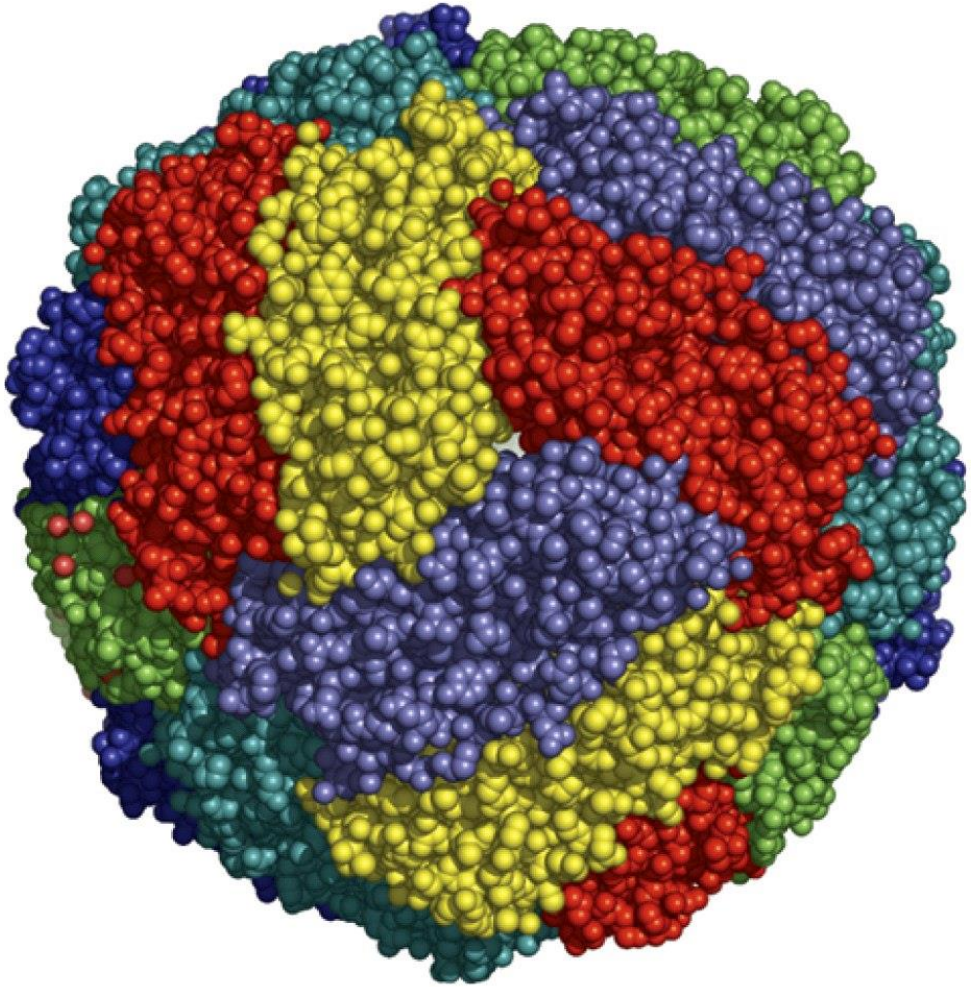


24 unità,
H e *L*

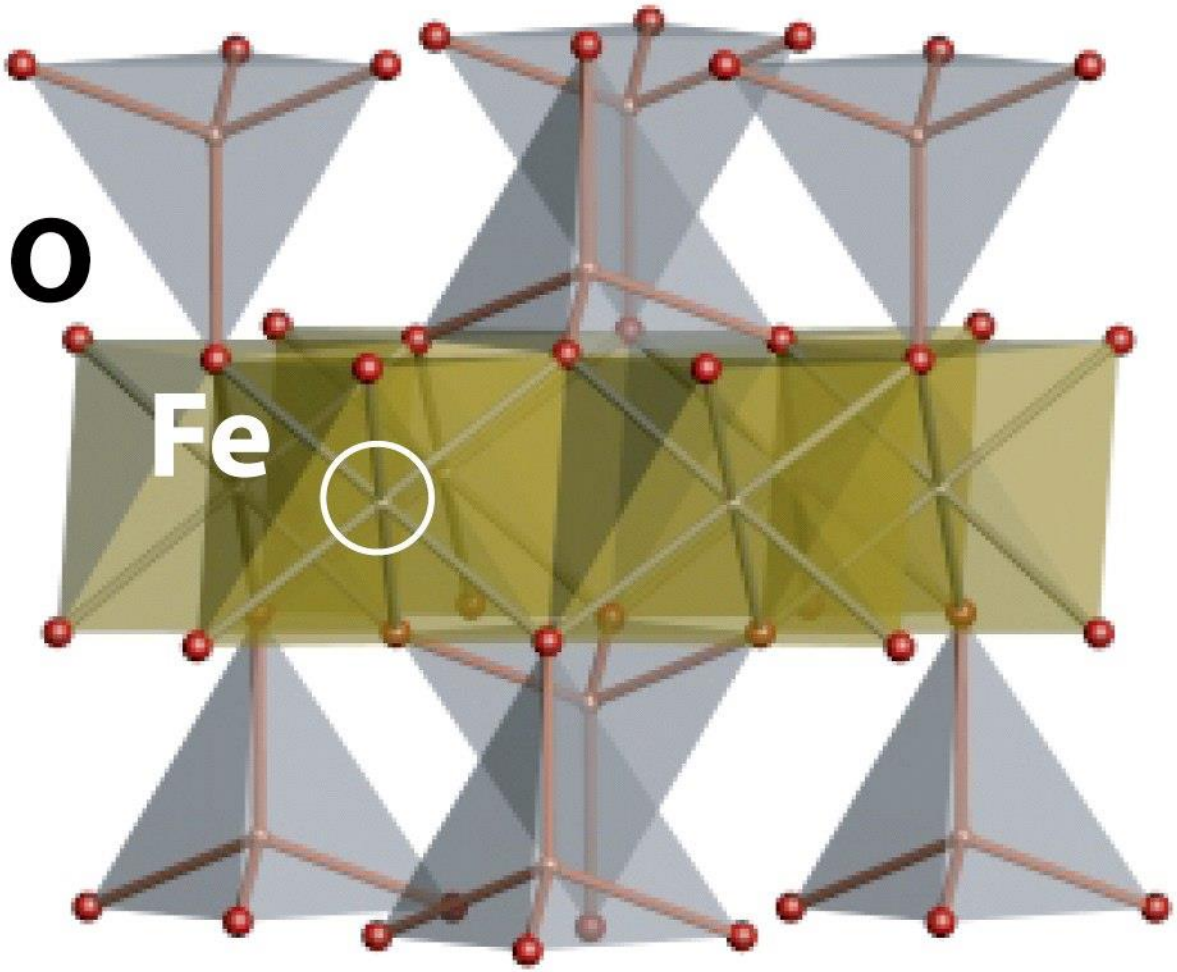
440 kDa

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



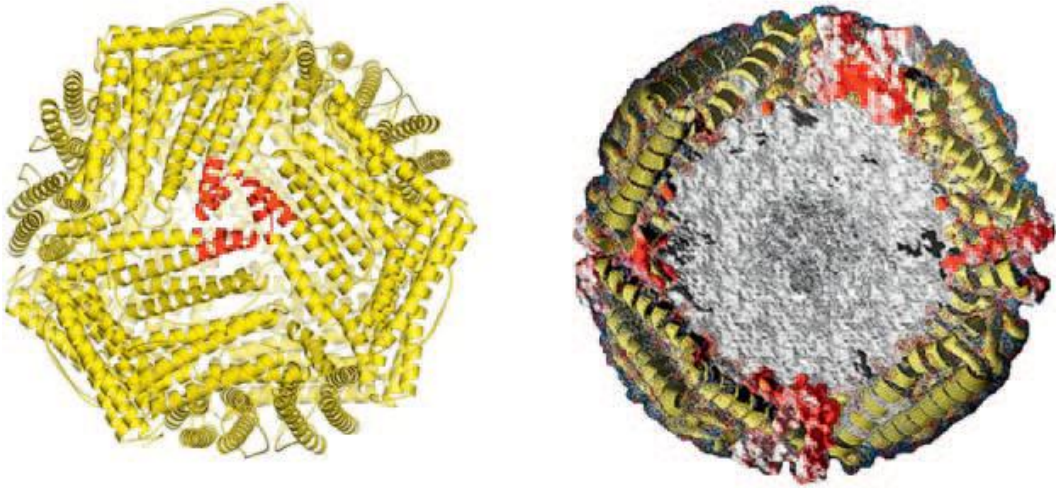
Out, 12 nm

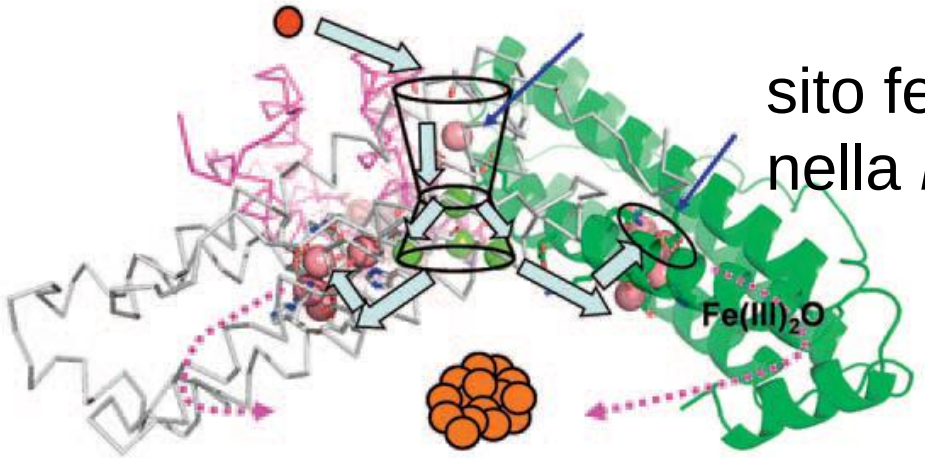


$Fe_9O_9(OH)_8(H_2PO_4)$

Ferrihydrite $5Fe_2O_3 \cdot 9H_2O$

Fino a 4500 atomi di Fe, mediamente 1200

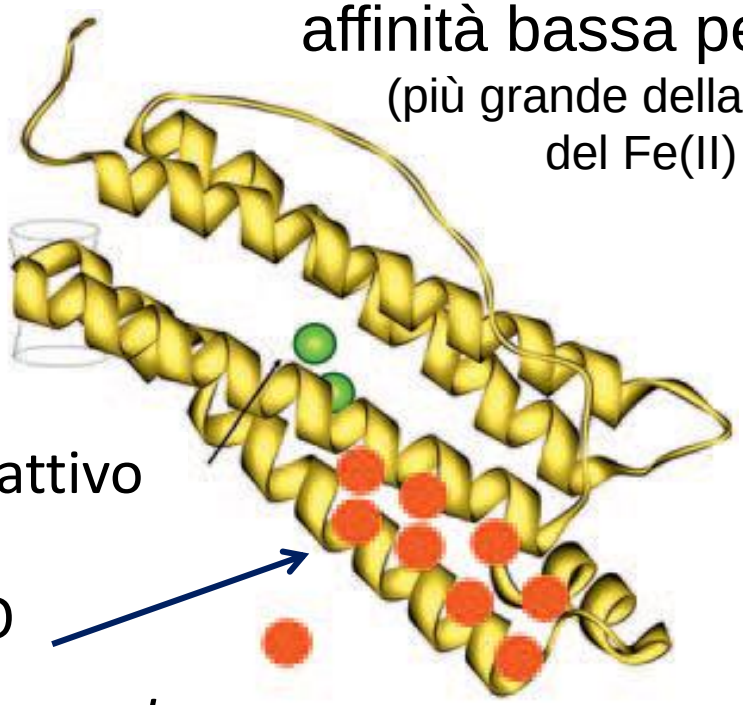




sito ferrossidasico
nella *H*-ferritina

sito ferrossidasico

affinità bassa per Fe(II), 15 μM
(più grande della concentrazione
del Fe(II) «libero»)



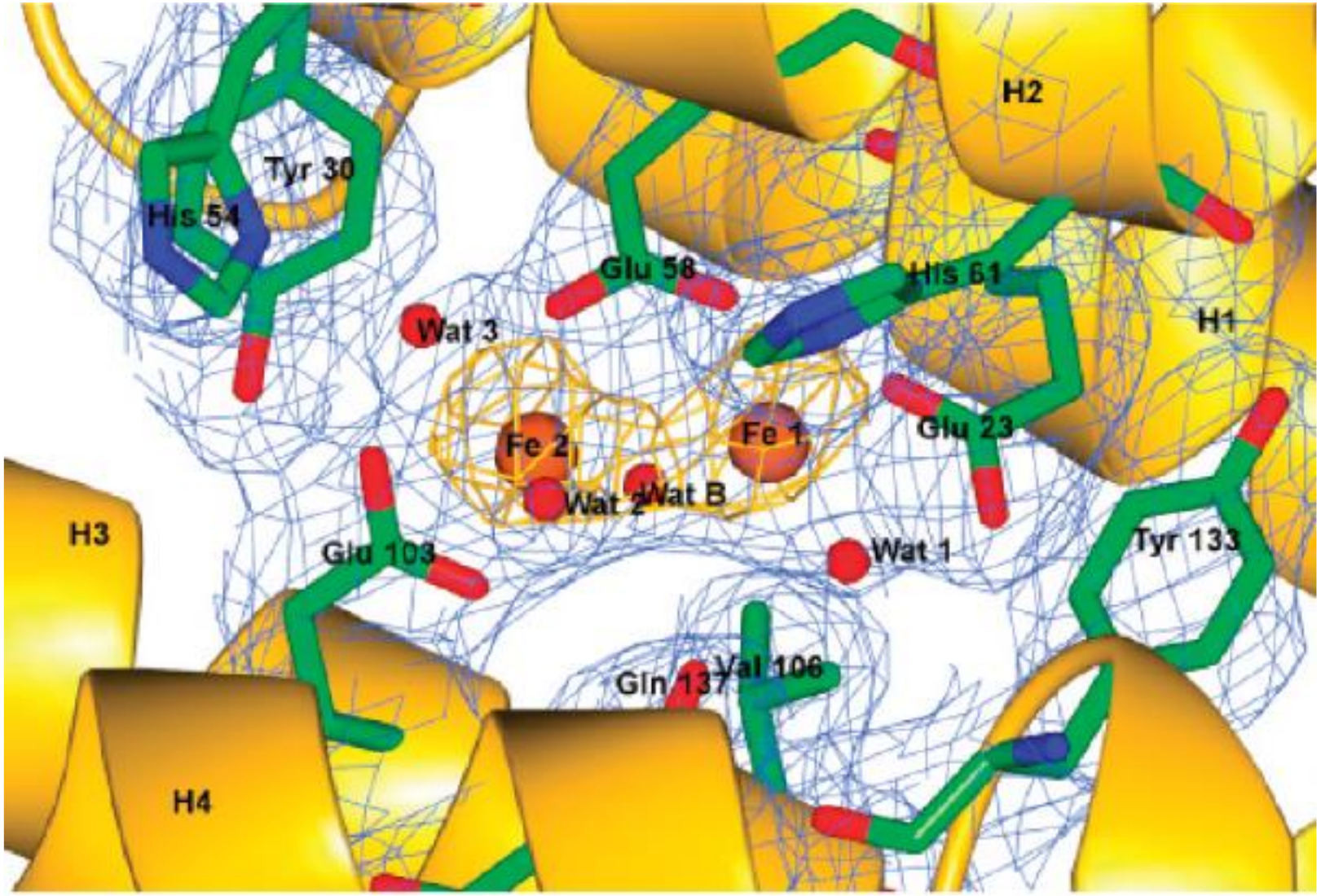
Sito attivo

$Fe(III)_2O$

nucleation channel

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

Struttura ai raggi X di un sito ferrossidasico



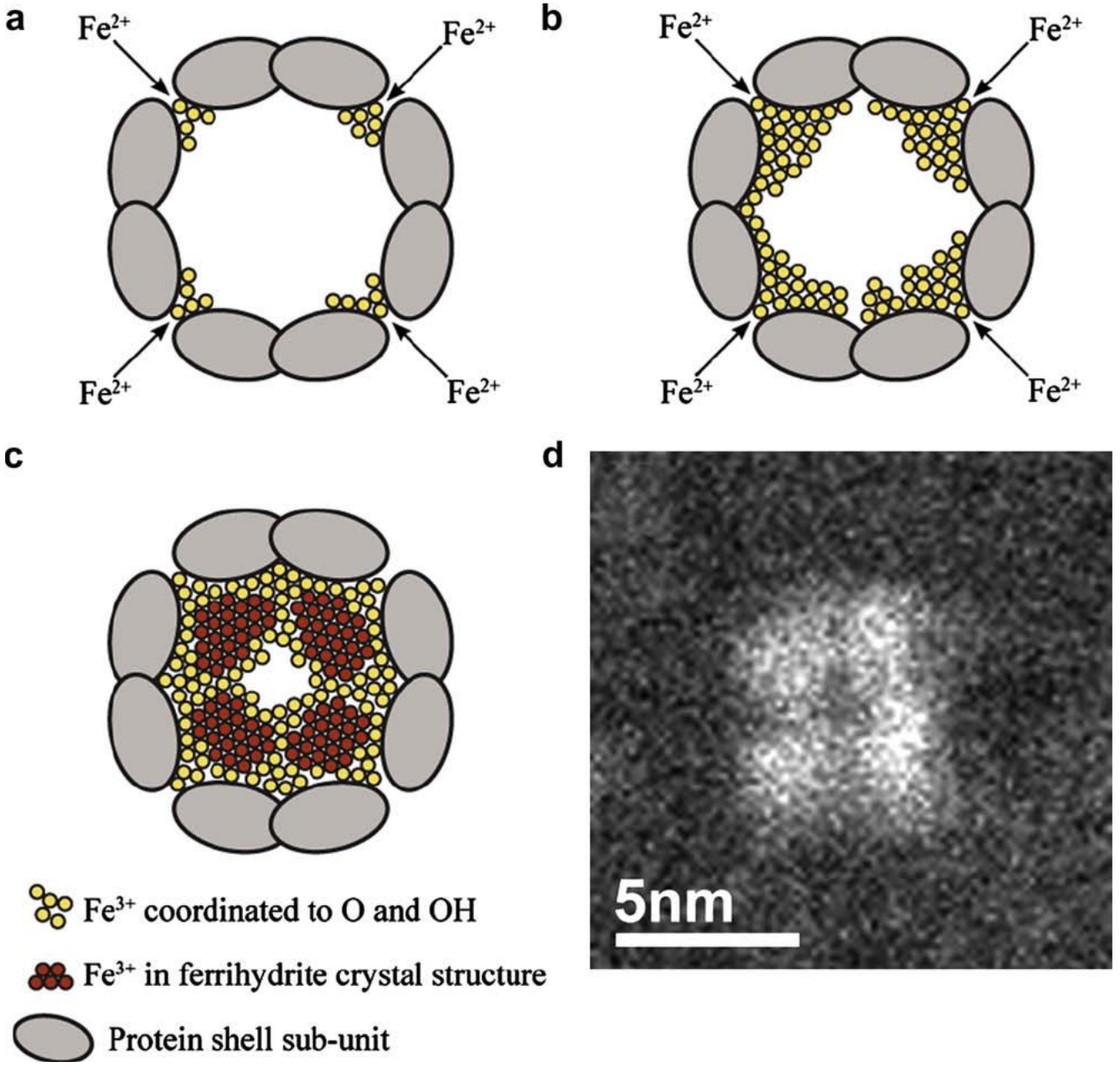
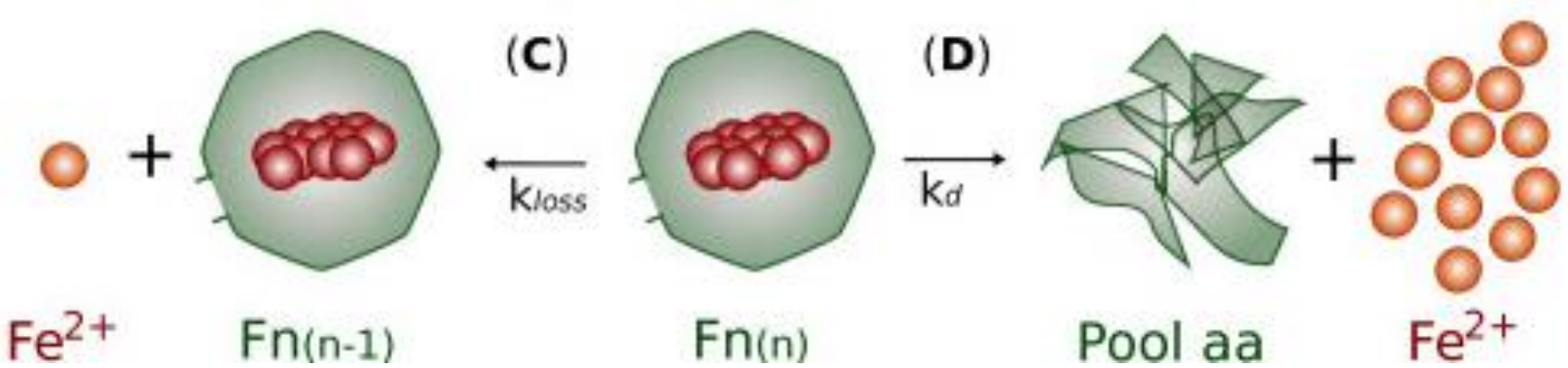
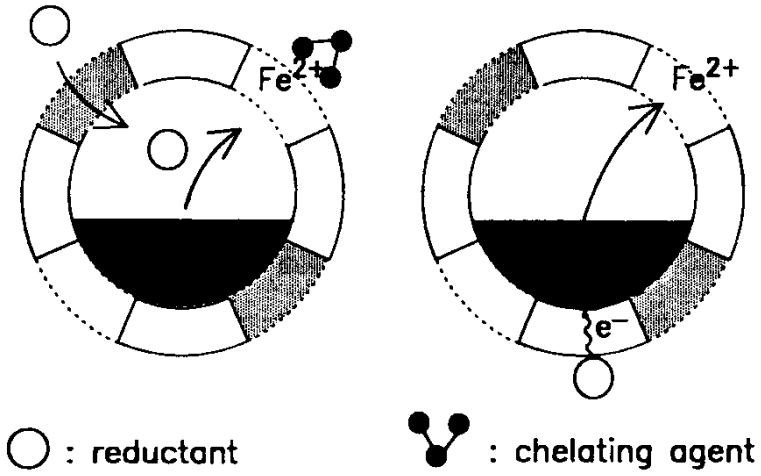


Immagine TEM

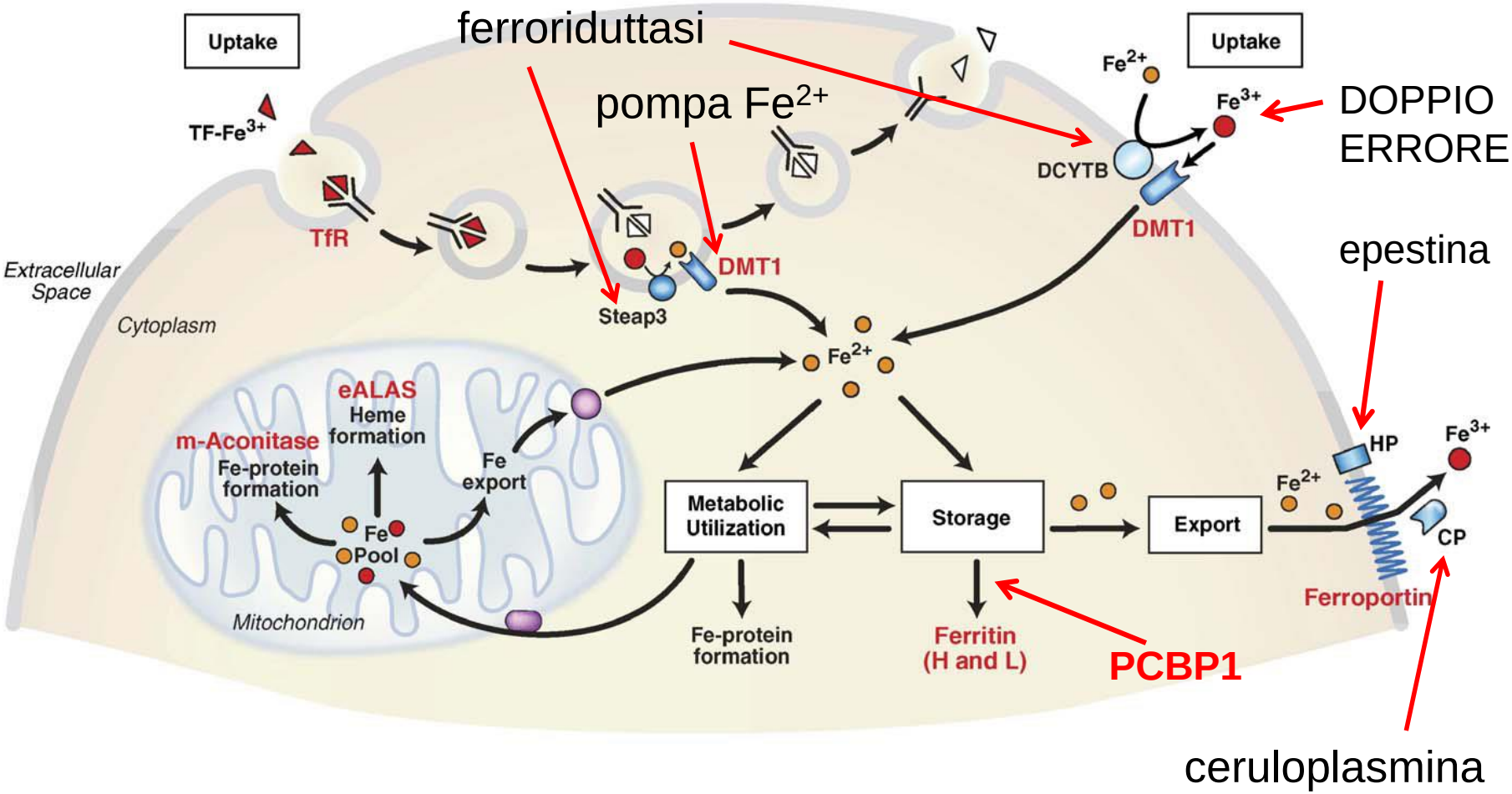
Rilascio del ferro



degradazione della proteina nei lisosomi?



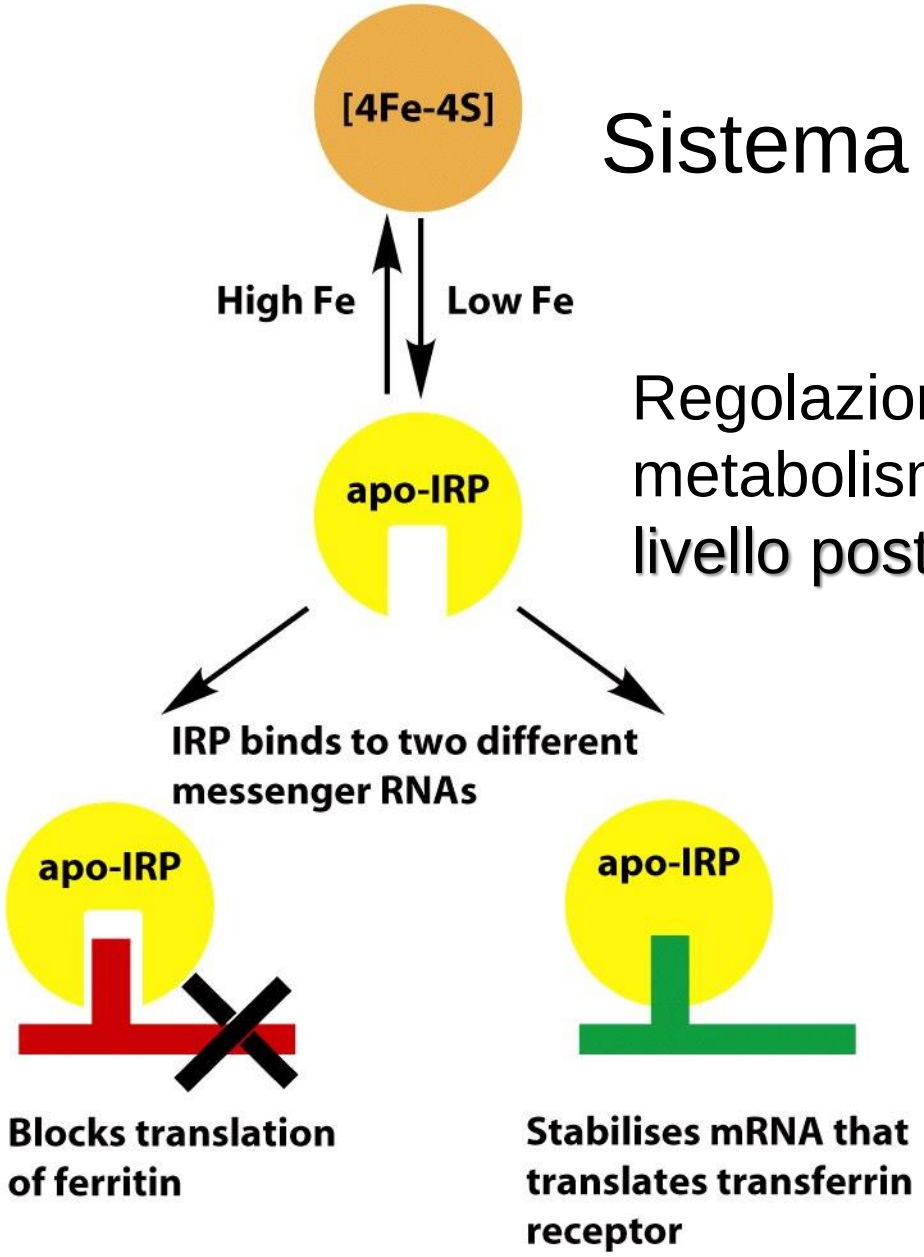
Omeostasi del ferro – Sistema IRP/IRE



IRP: Iron Regulatory Proteins

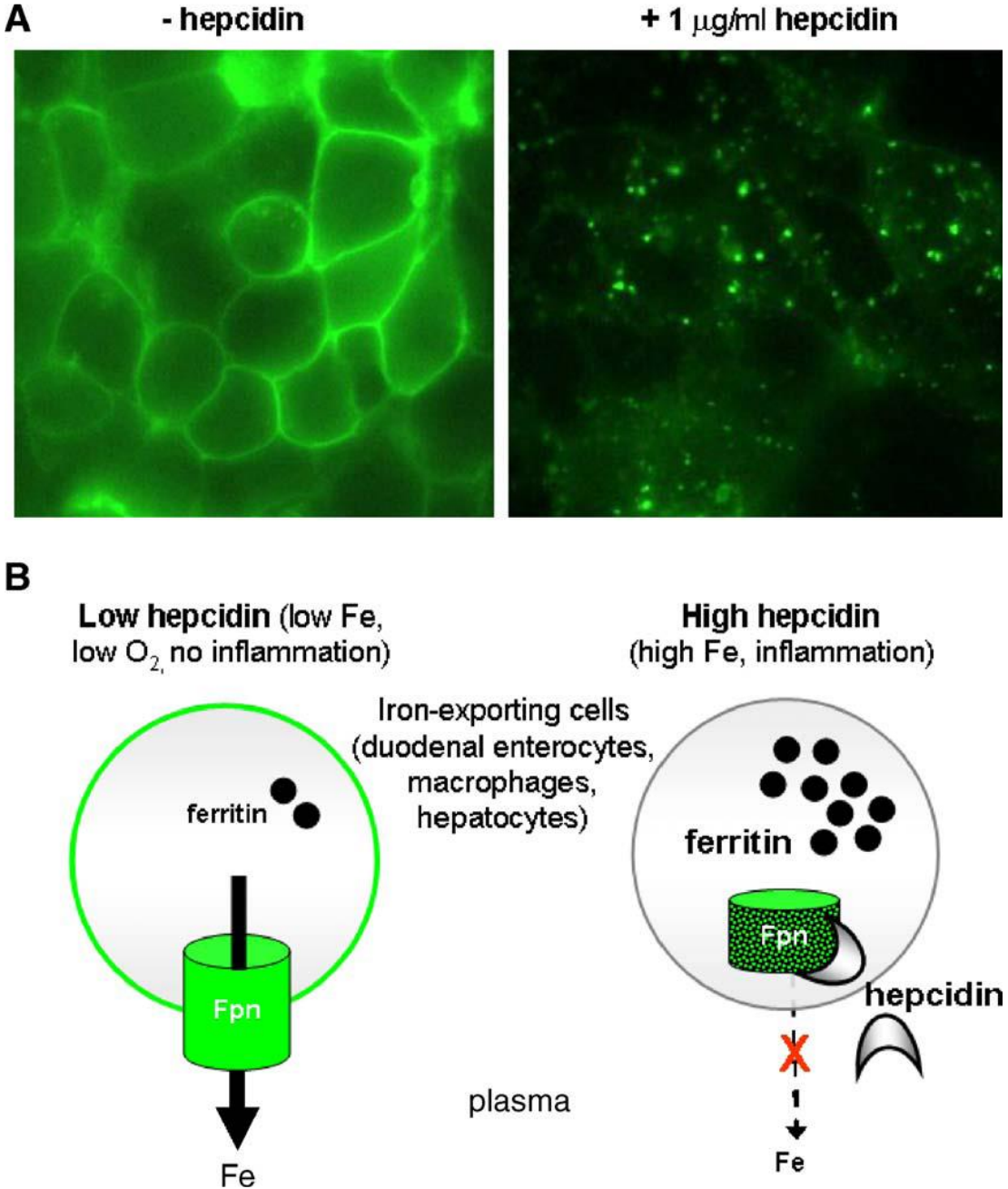
IRE: Iron Responsive Elements (mRNA)

Sistema IRP/IRE

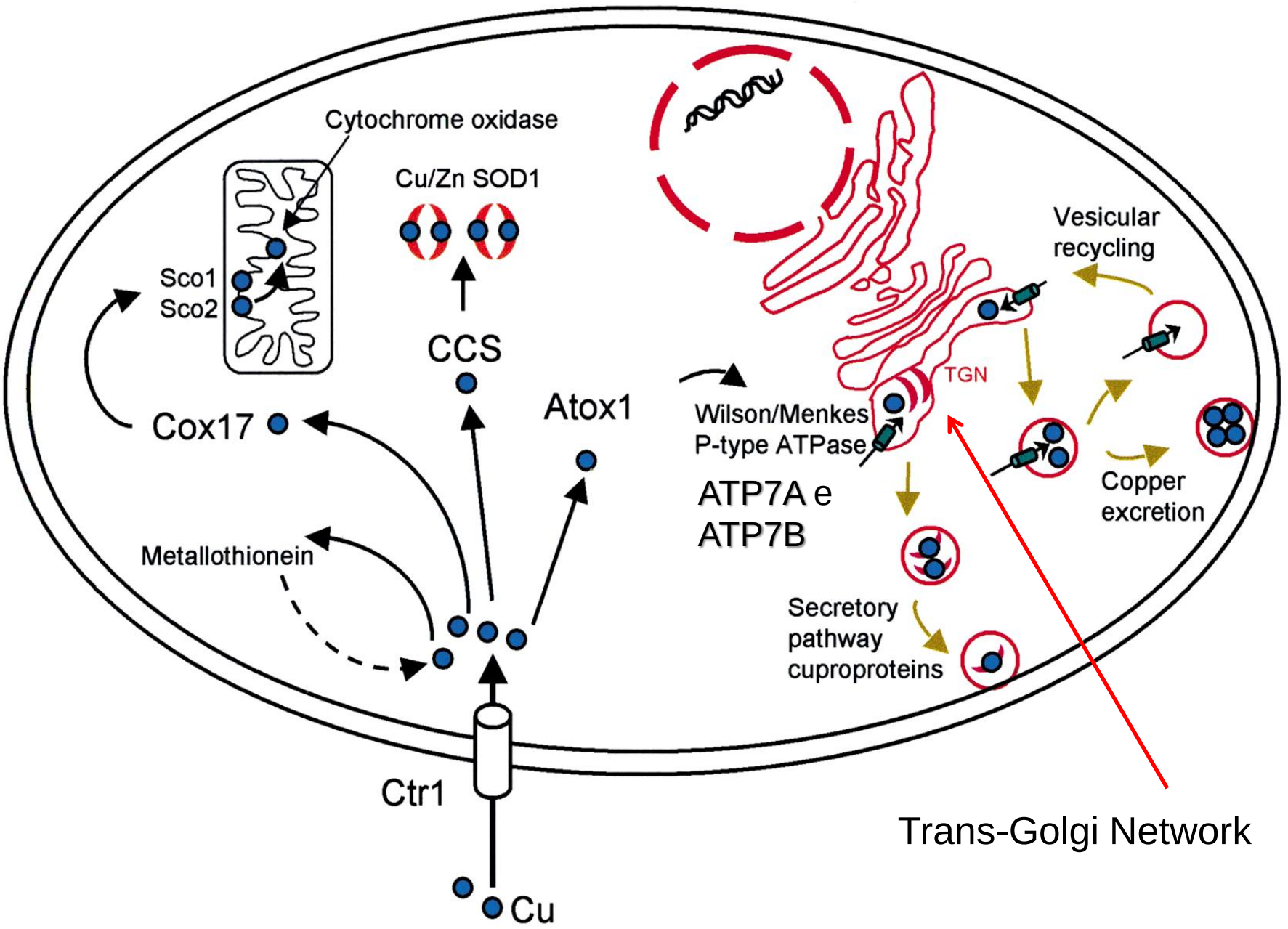


Regolazione del metabolismo del ferro a livello post-trascrizionale

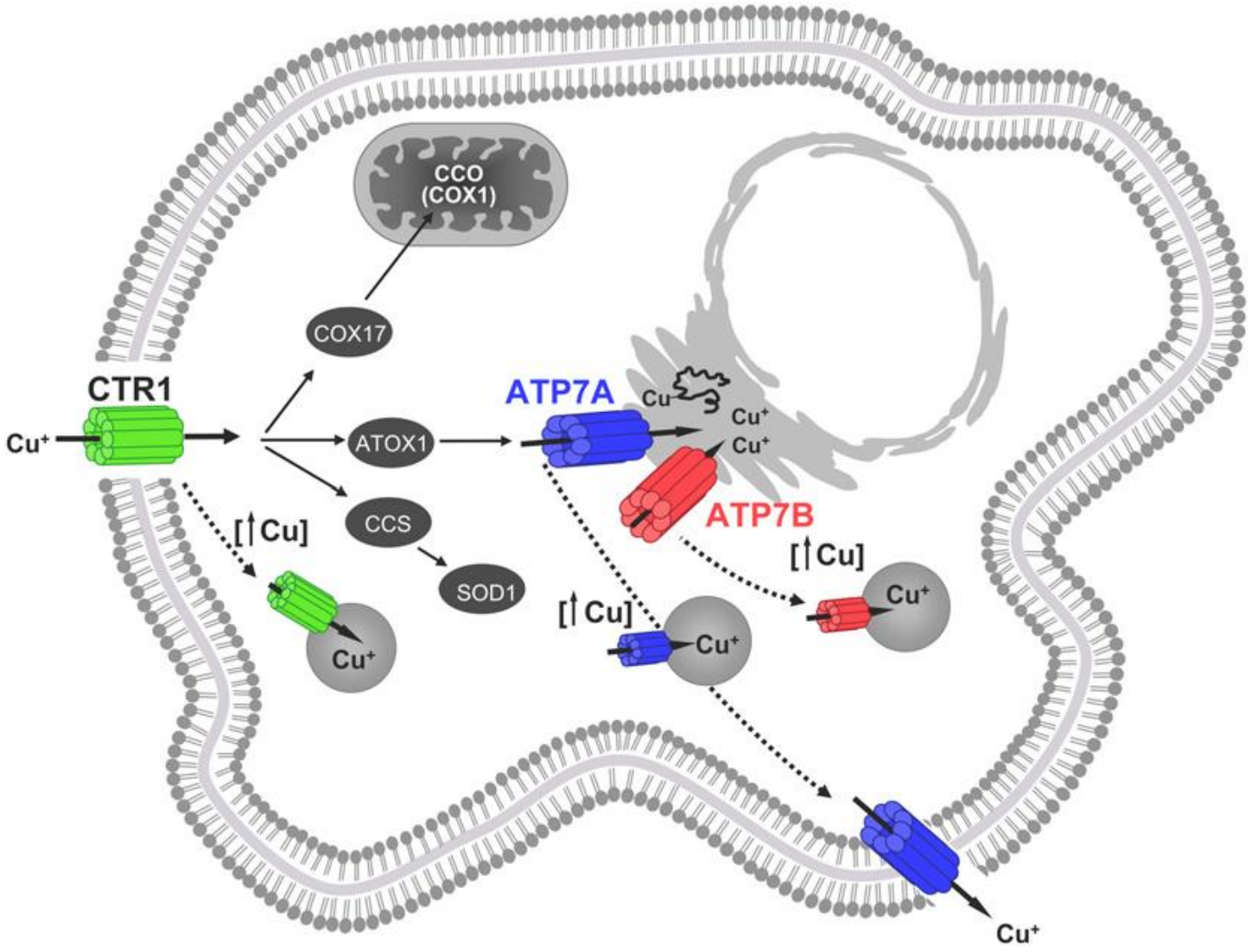
Export del ferro nel plasma regolato da epcidina

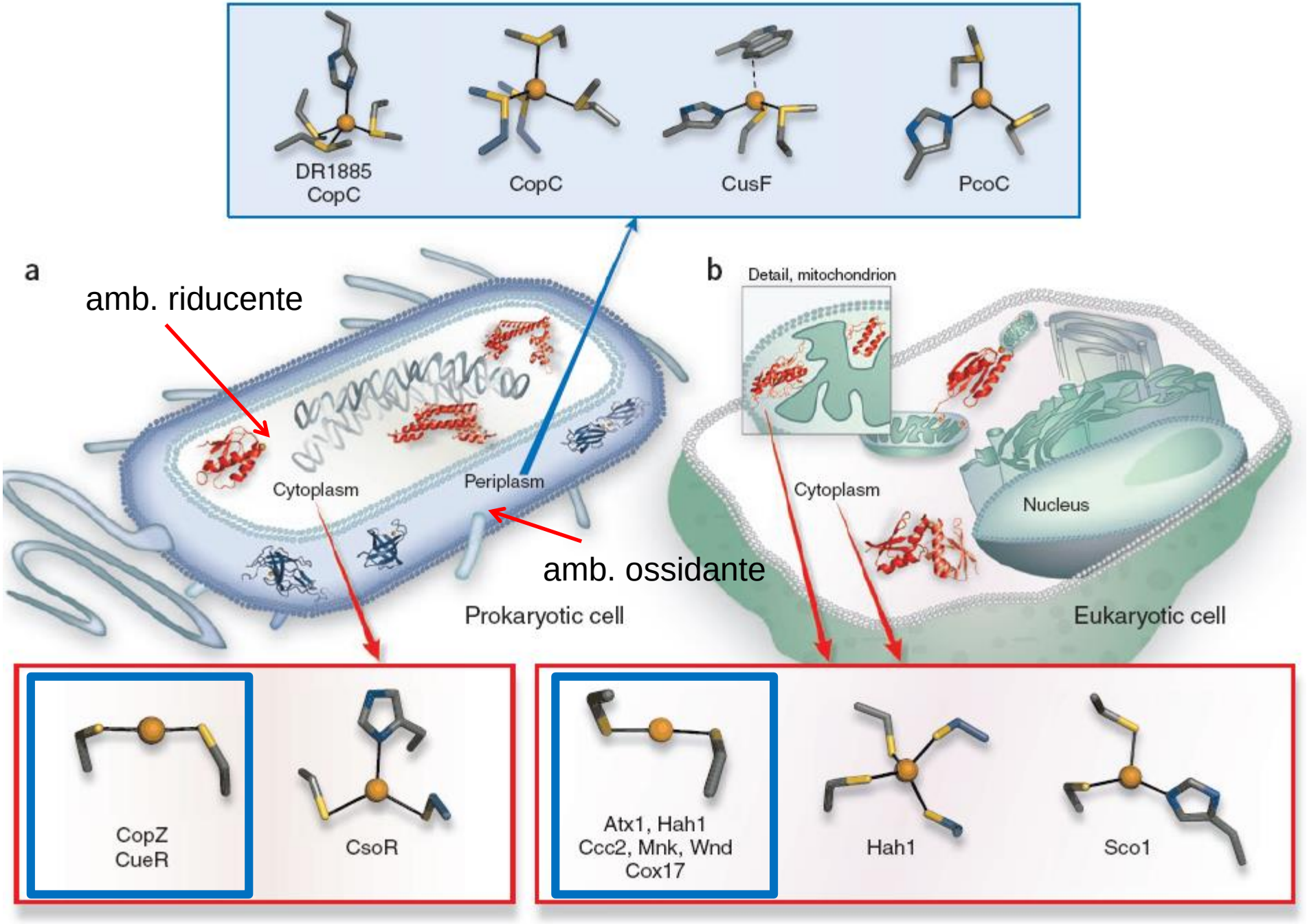


Omeostasi del rame

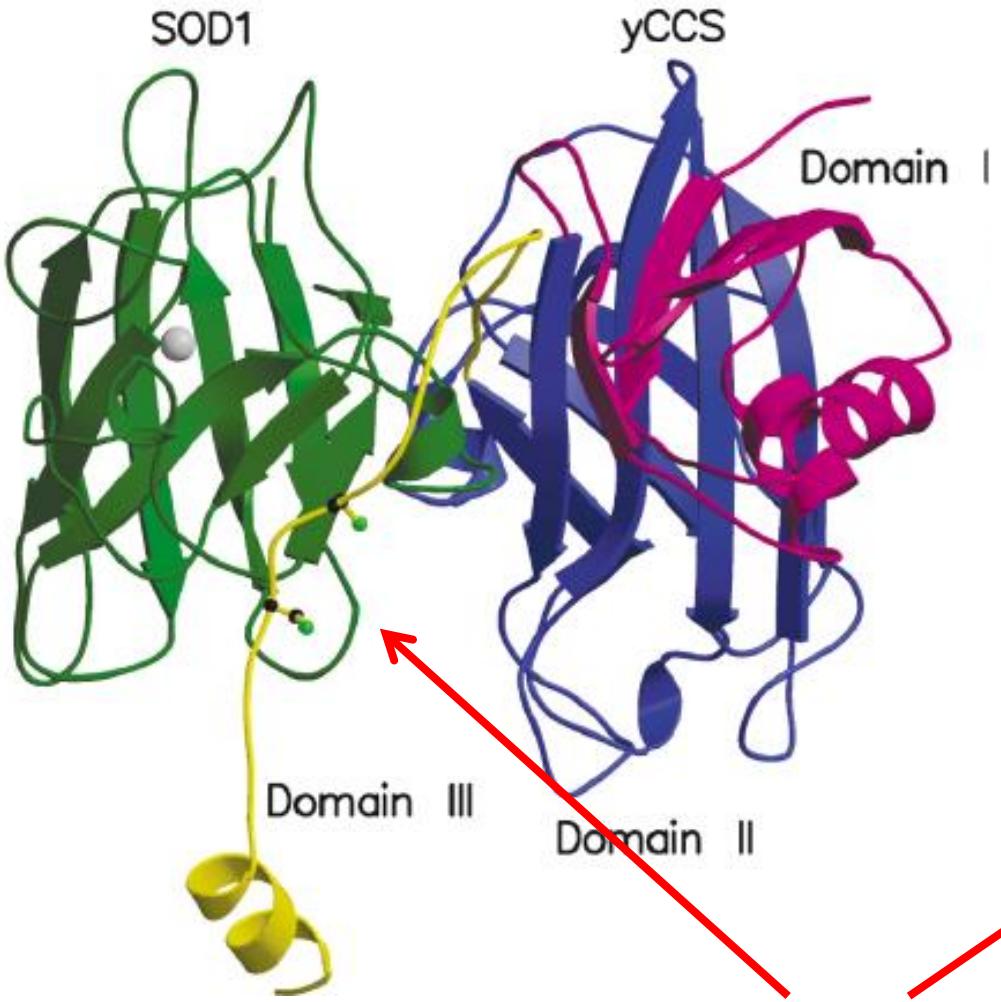


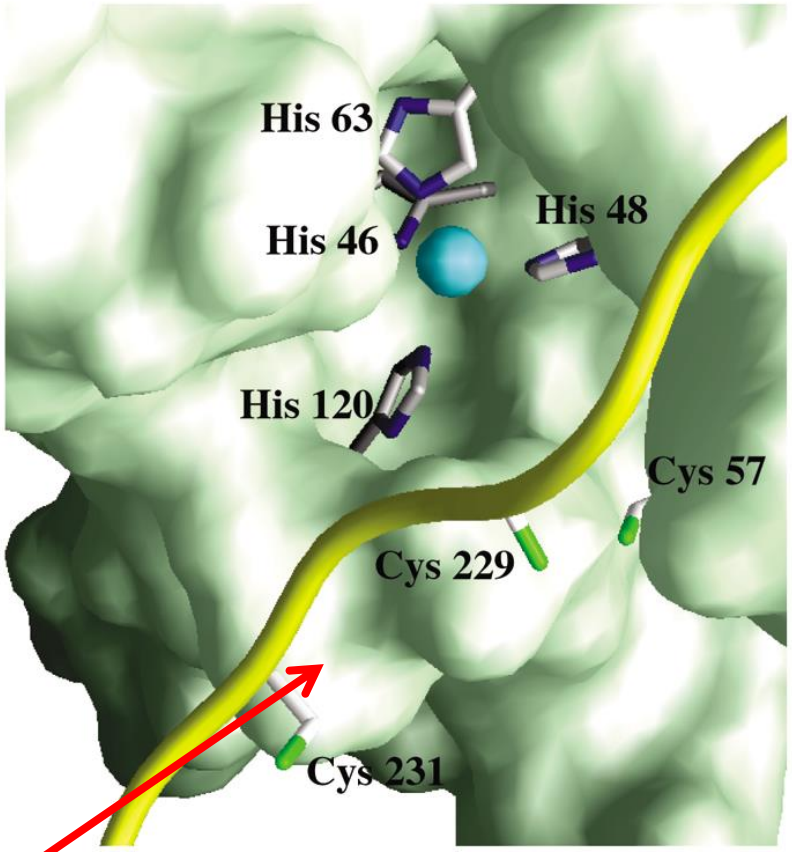
Omeostasi del rame




DR1885
CopC
CopC
CusF
PcoC
a
amb. riducente
Cytoplasm
Periplasm
amb. ossidante
Prokaryotic cell
b
Detail, mitochondrion
Cytoplasm
Nucleus
Eukaryotic cell
CopZ
CueR
CsoR
Atx1, Hah1
Ccc2, Mnk, Wnd
Cox17
Hah1
Sco1

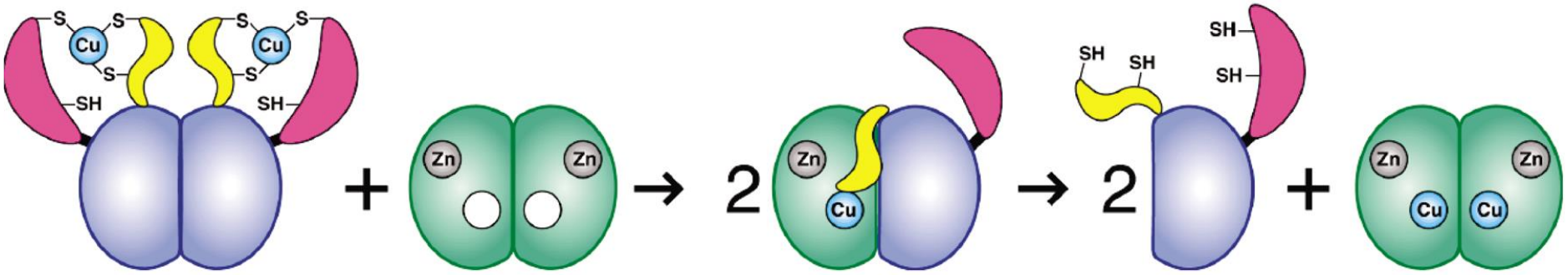
yCCS/Zn-SOD





Sito di binding del Cu(I)

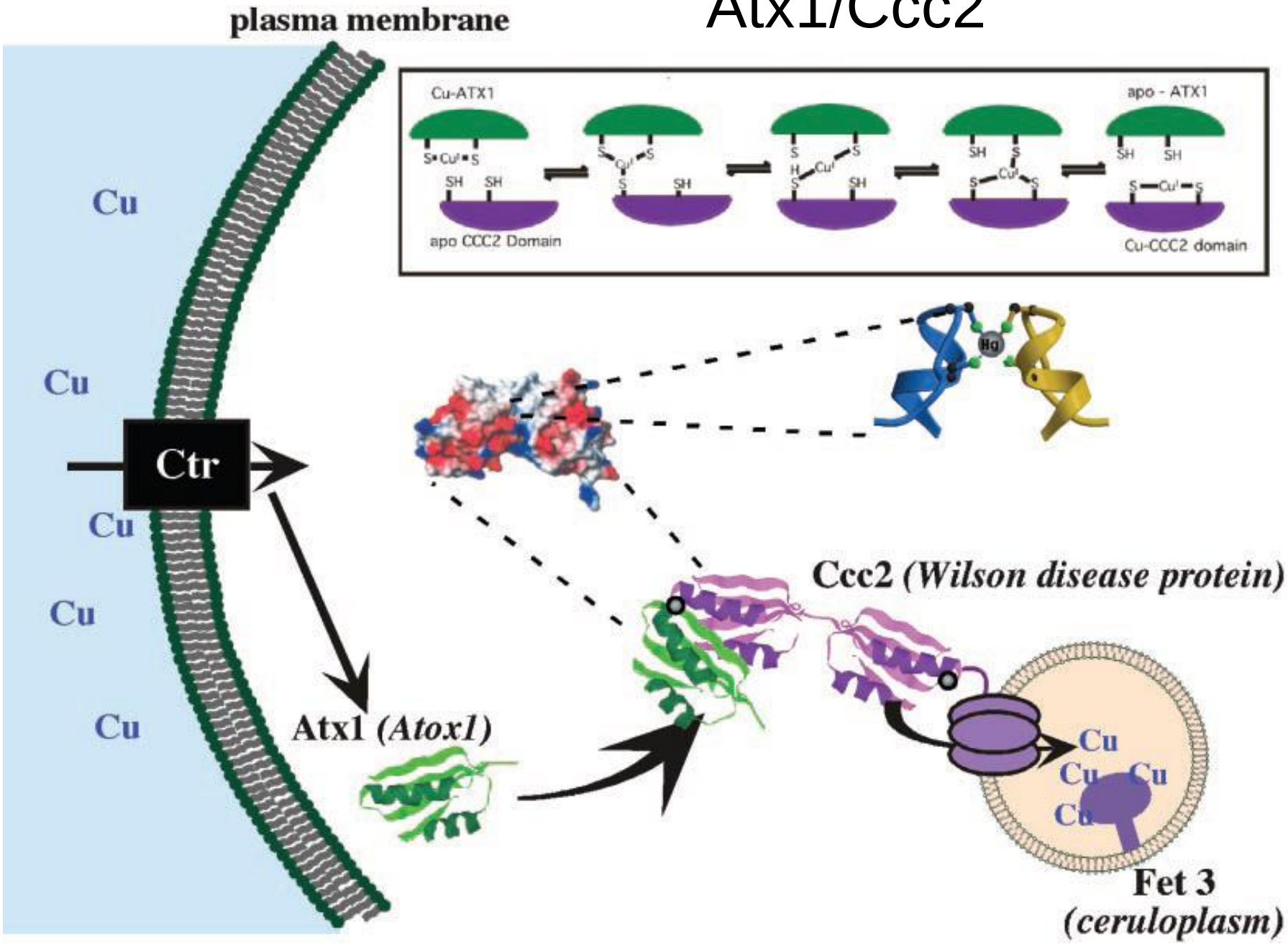
CCS/Zn-SOD



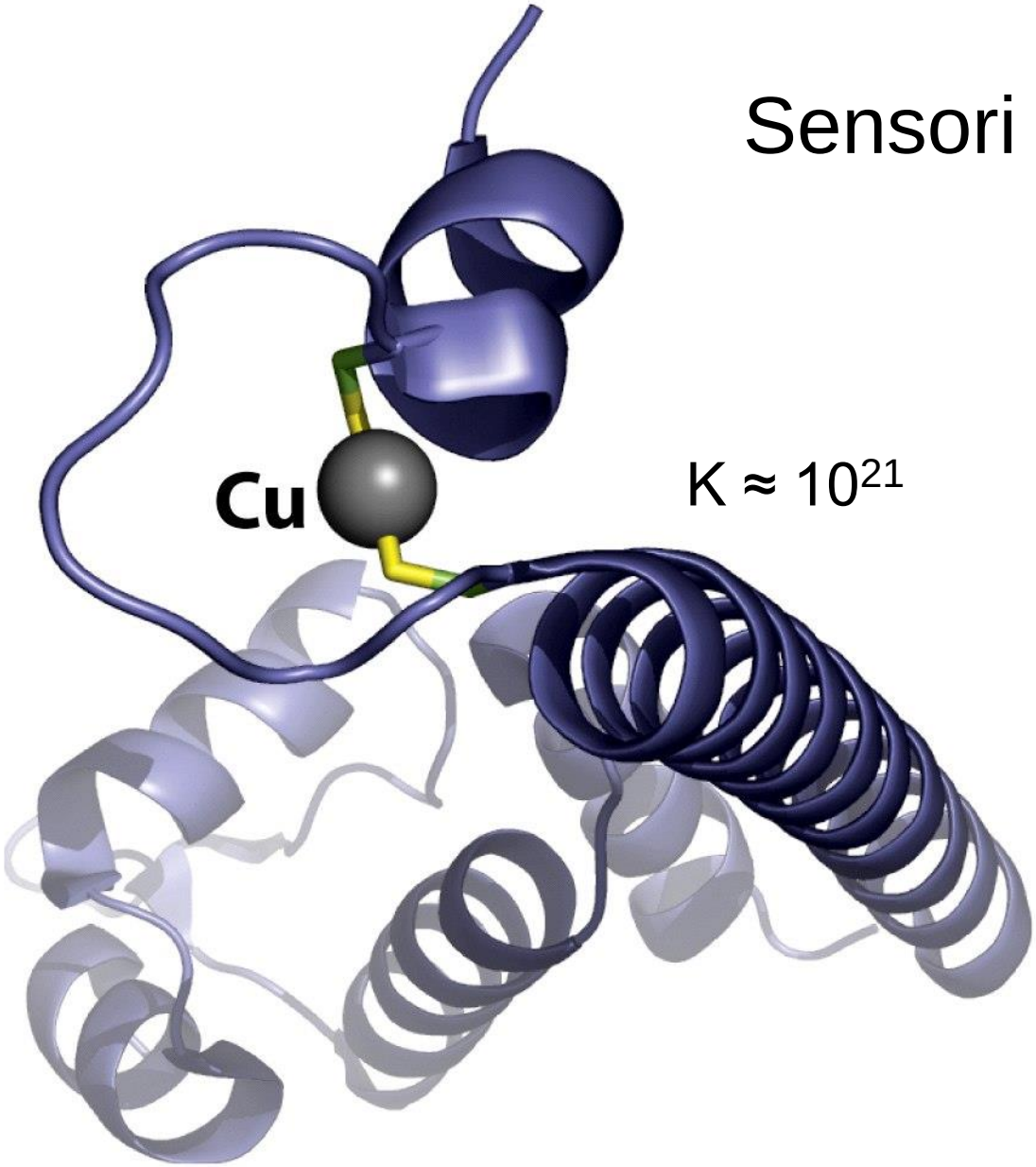
omodimeri

eterodimero

Atx1/Ccc2


plasma membrane
Cu-ATX1
apo - ATX1
apo CCC2 Domain
Cu-CCC2 domain
Cu
Cu
Cu
Cu
Cu
Ctr
Atx1 (Atox1)
Ccc2 (Wilson disease protein)
Cu
Cu
Cu
Cu
Fet 3
(ceruloplasm)

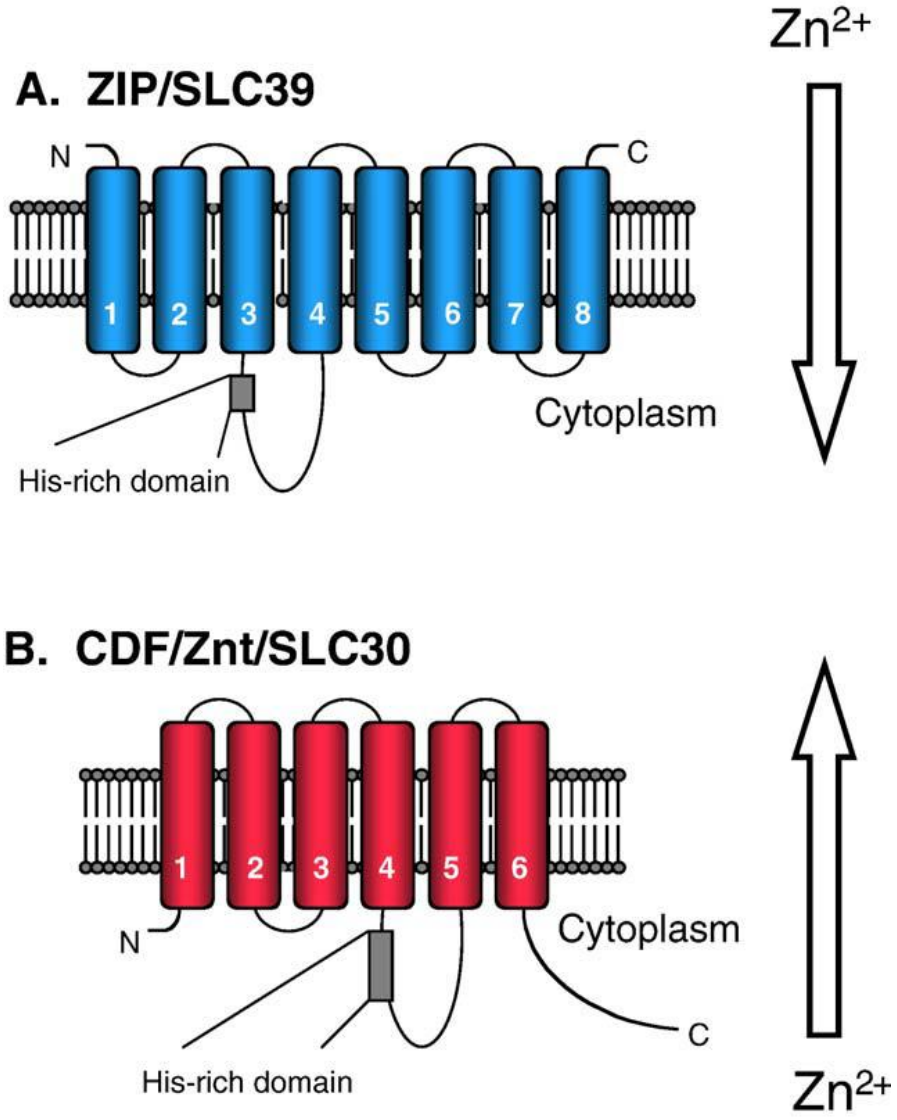
Sensori del Cu



$K \approx 10^{21}$

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

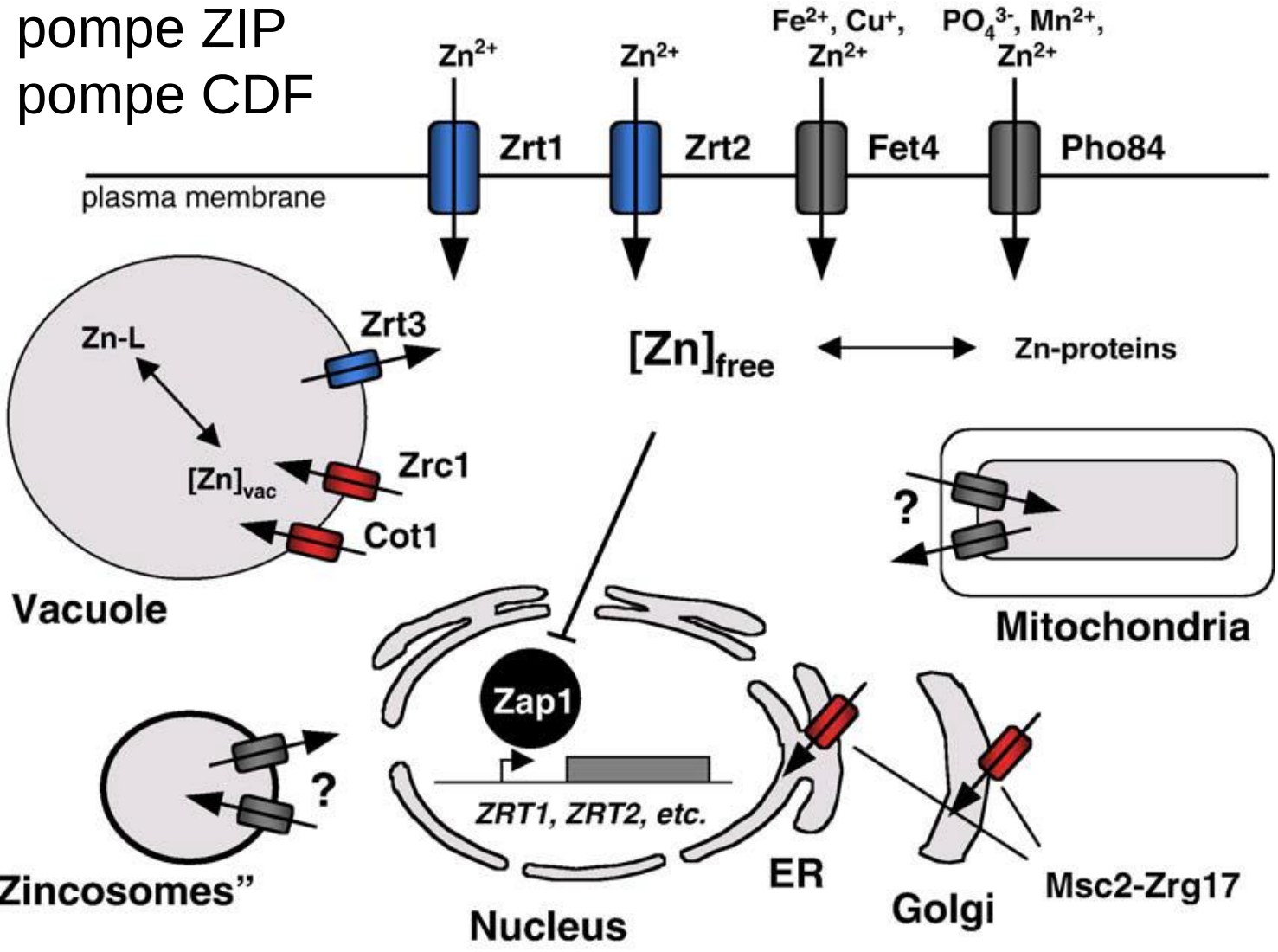
Omeostasi dello zinco in cellule eucariote



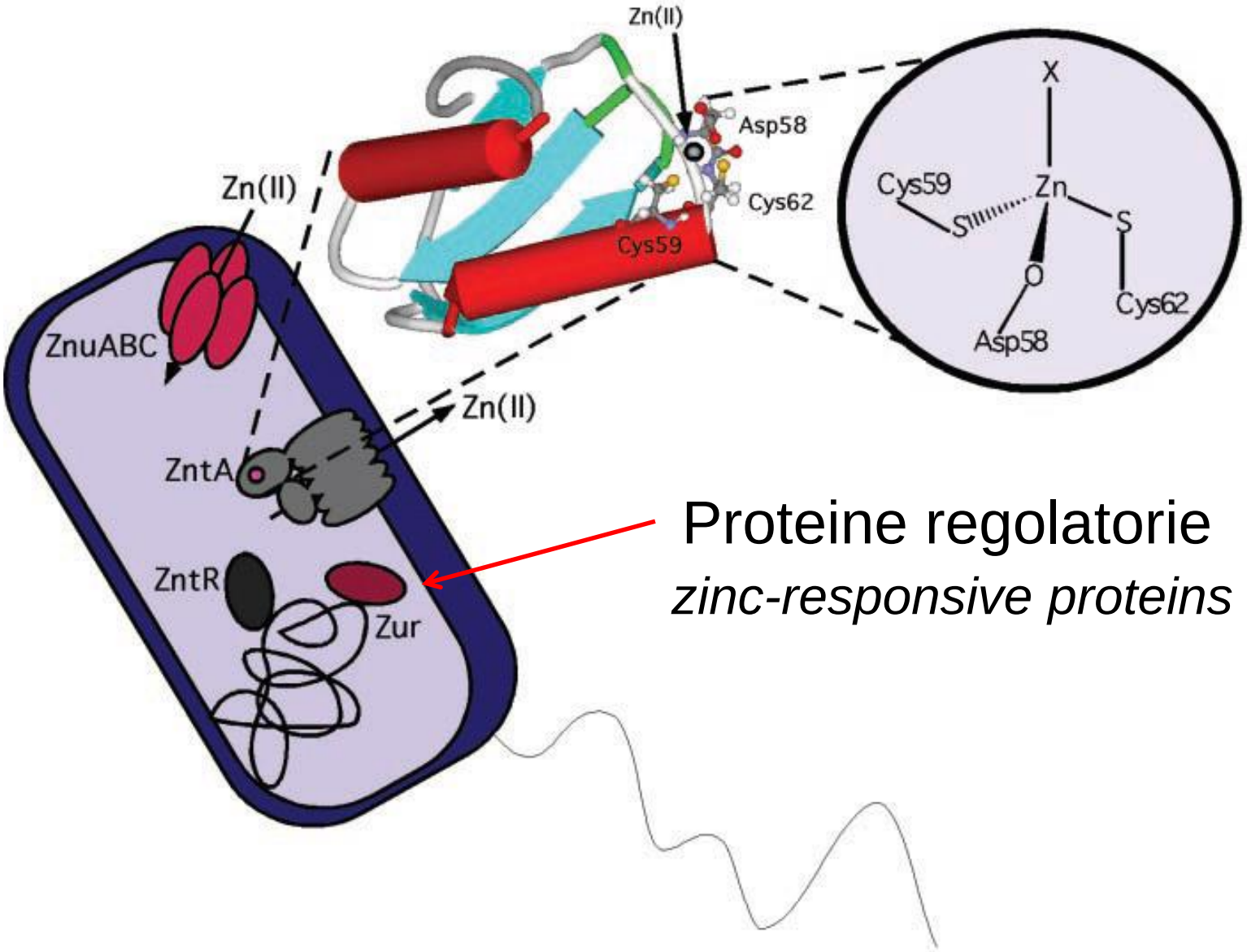
Omeostasi dello zinco in cellule eucariote

= pompe ZIP

= pompe CDF



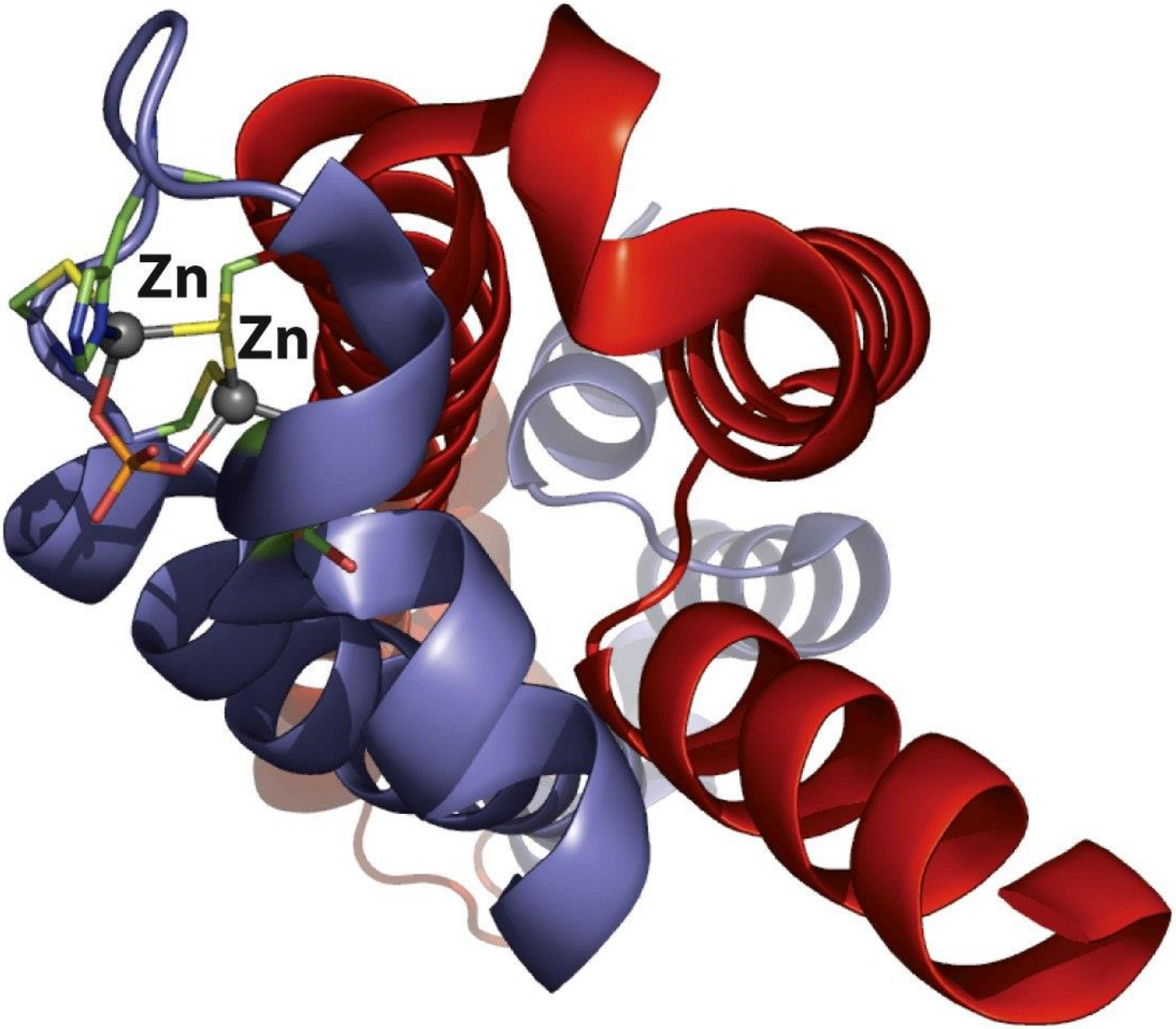
Omeostasi dello zinco nei batteri



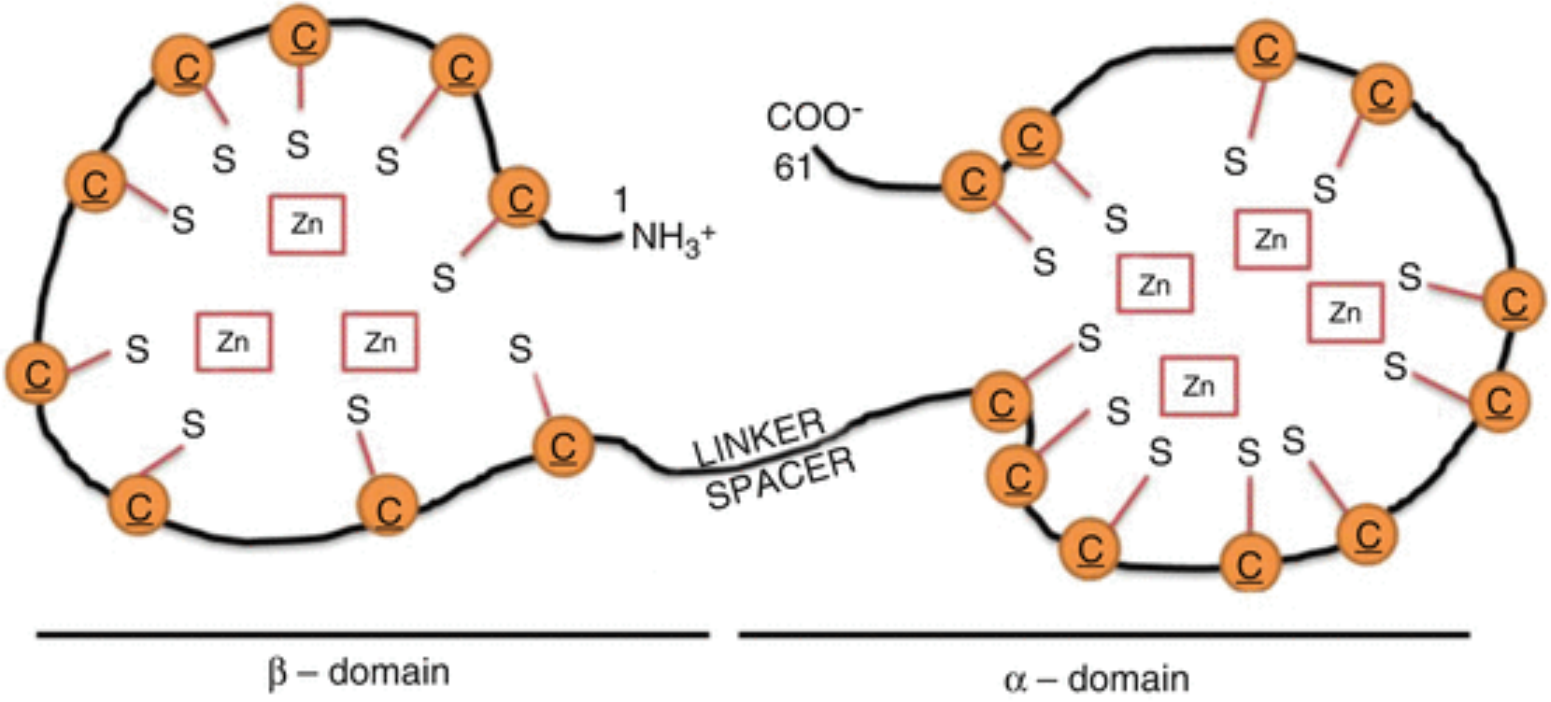
Proteine regolatorie

zinc-responsive proteins

Fattore di trascrizione ZntR

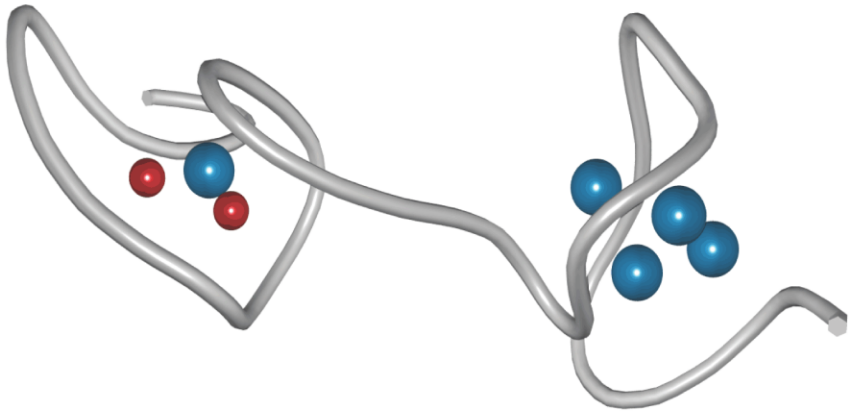


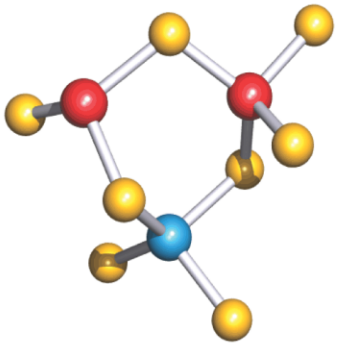
Metallotioneine



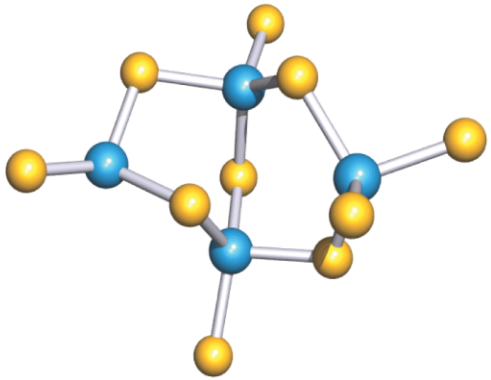
6 kDa,
ca. 60 a.a.
fino 30% cys

Metallotioneine





$CdZn_2S_8$



Cd_4S_{10}