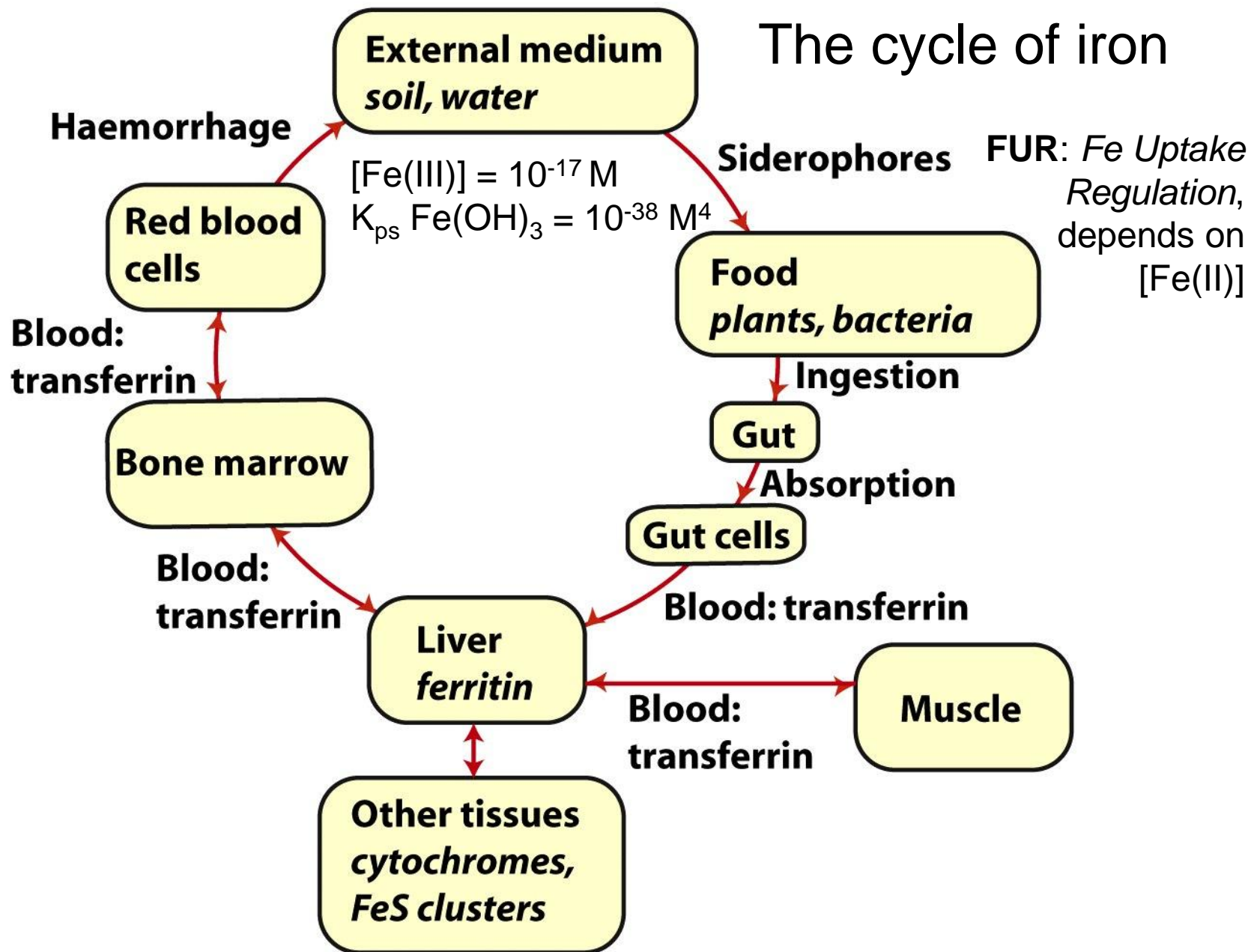


Homeostasis of trace metals:
uptake, transport, delivery and
processing, storage, excretion.

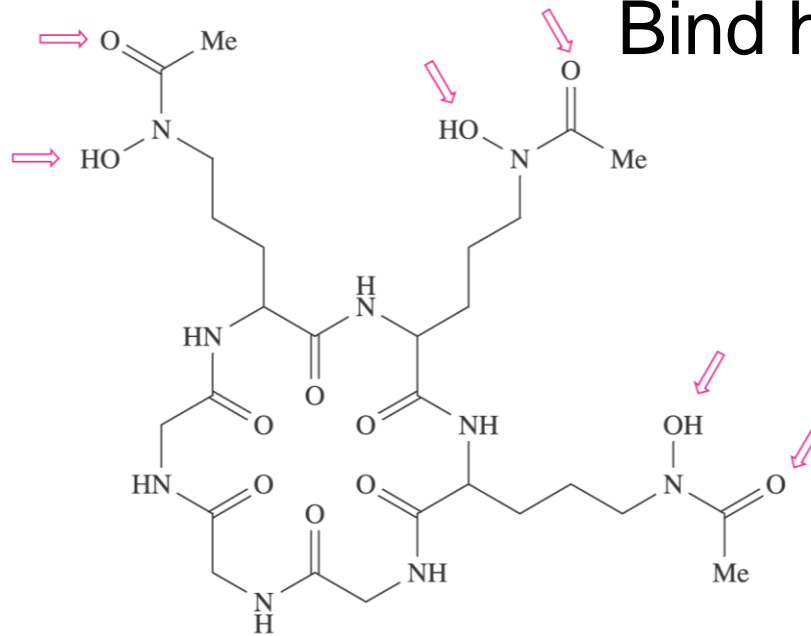
The cycle of iron



Hydroxamate siderophores (fungi, yeast)

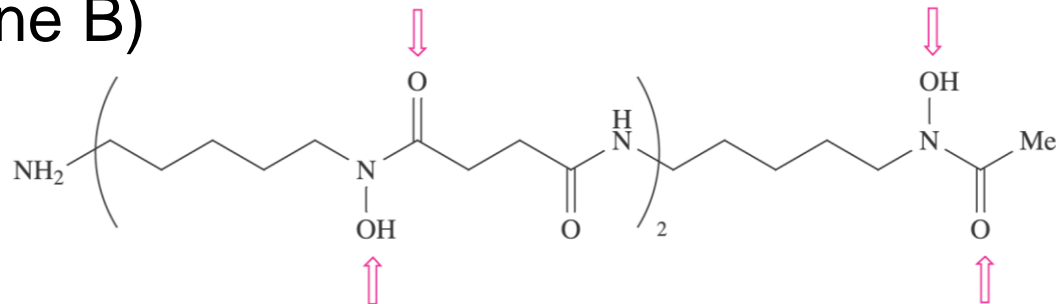
Bind high spin Fe(III)

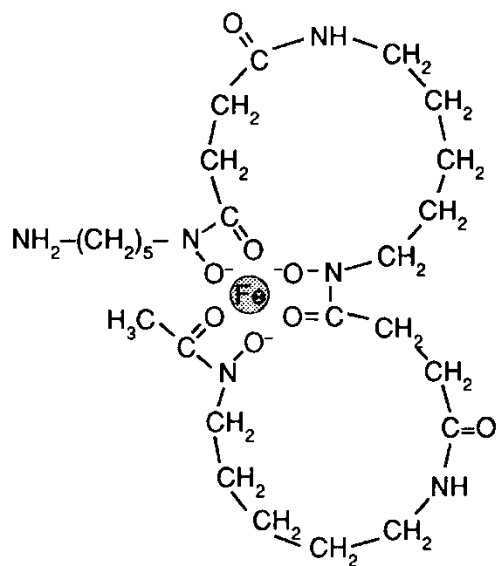
desferrichrome



(a)

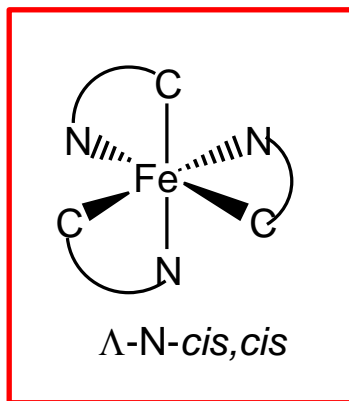
deferoxamine (or
desferrioxamine B)



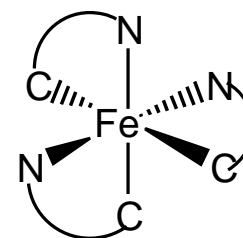


ferrioxamine B

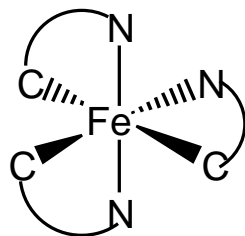
without Fe: deferrioxamine B



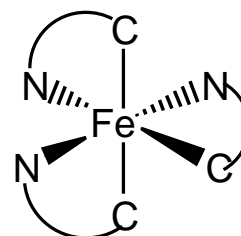
Λ -N-*cis,cis*



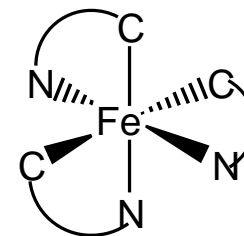
Λ -C-*trans,cis*



Λ -N-*trans,cis*



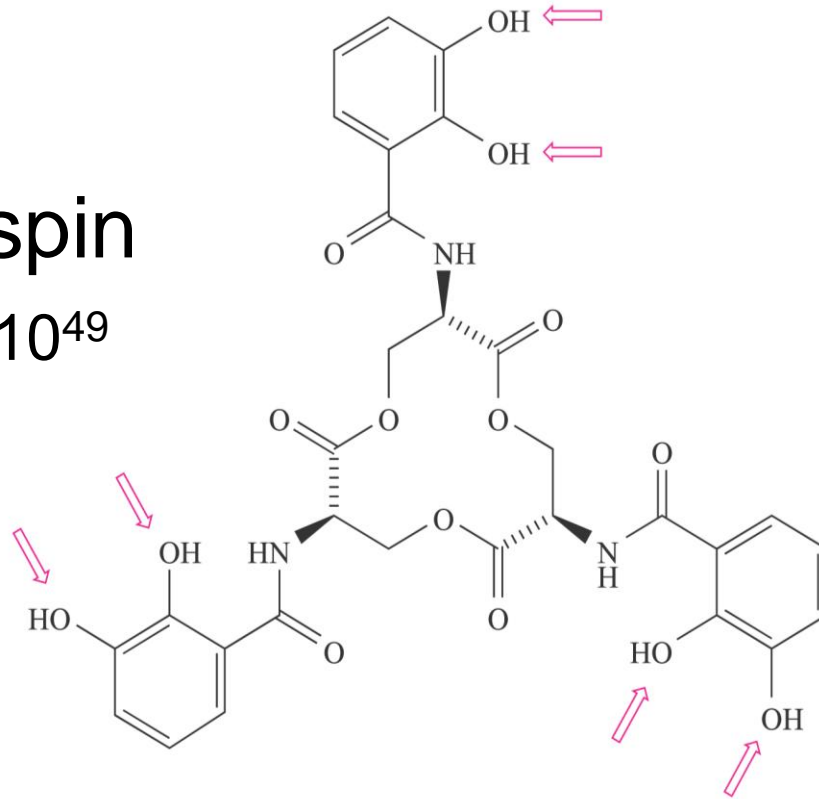
Λ -C-*cis,trans*



Λ -N-*trans,cis*

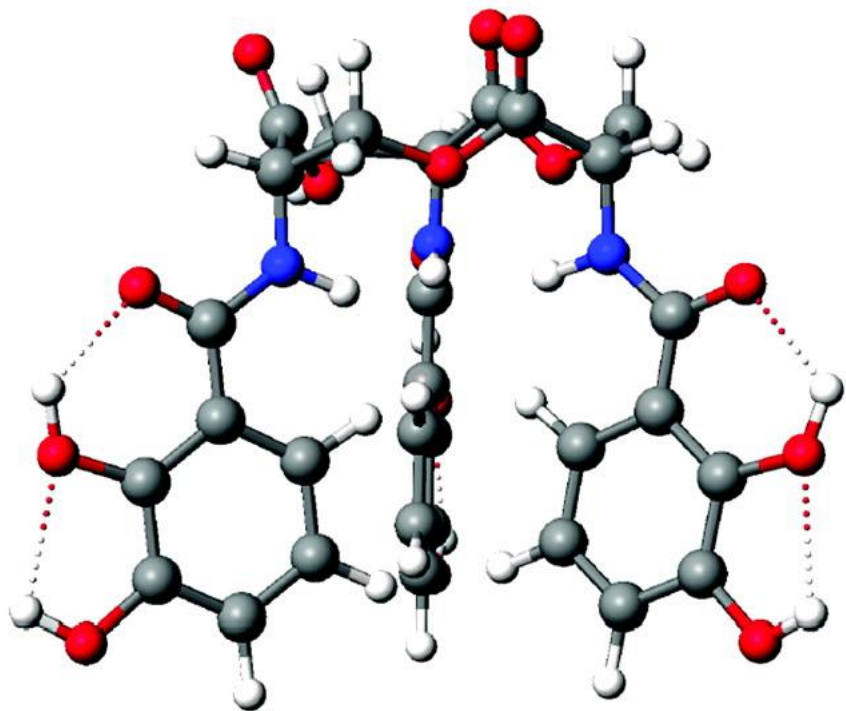
Catecholate siderophores (bacteria)

Binds high spin
 Fe(III) , $K_a = 10^{49}$

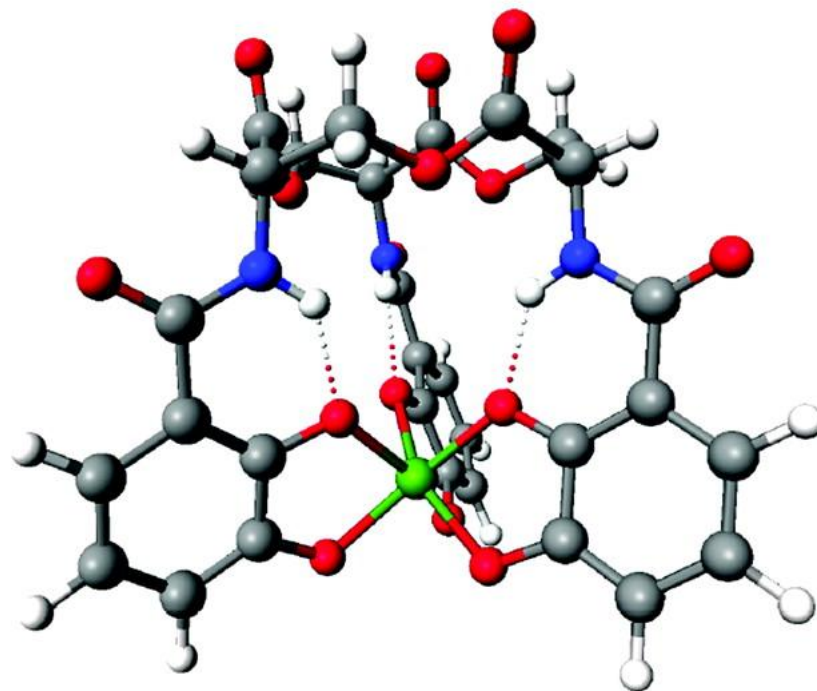


Enterobactin

the highest-affinity iron chelator yet identified in the natural world



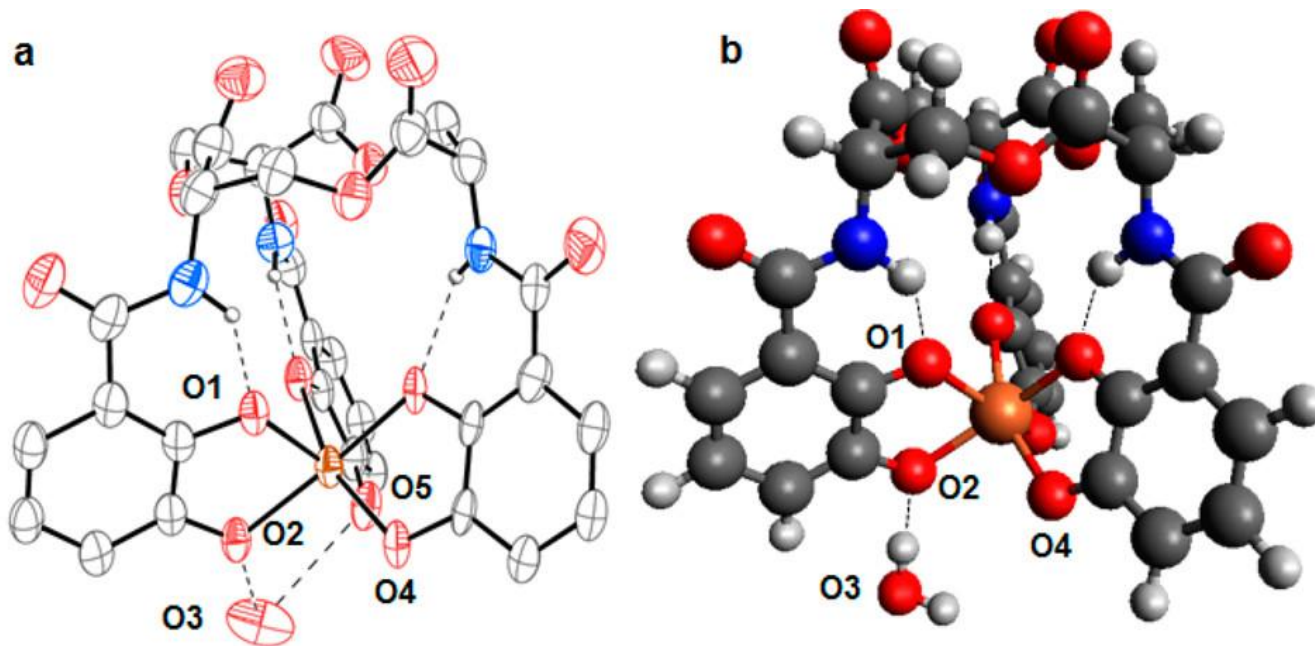
Model for uncoordinated
enterobactin



Structure of V(IV)-enterobactin
complex (1992)

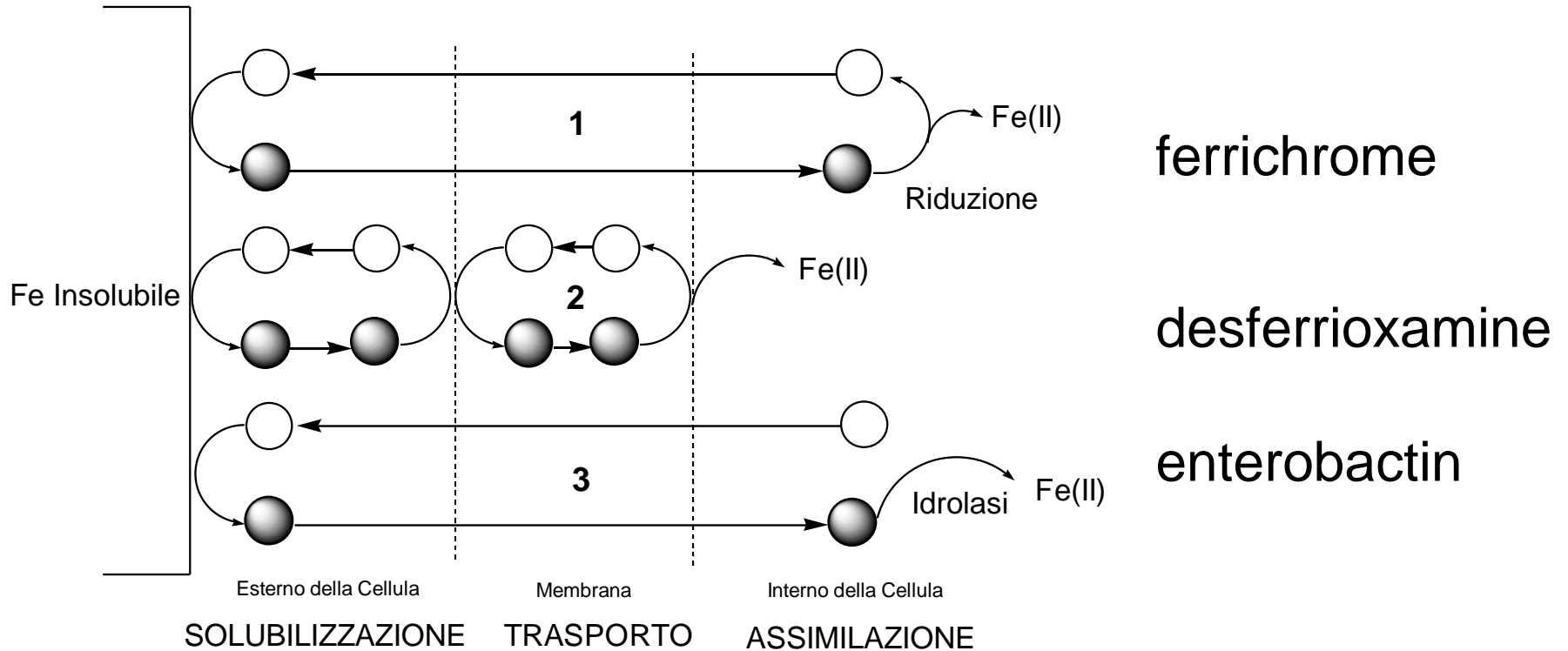
Δ

The recently determined crystal structure affords a definitive Δ assignment to $[\text{Fe}(\text{ent})]^{3-}$



J. Am. Chem. Soc. **2017**, *139*, 15245-15250

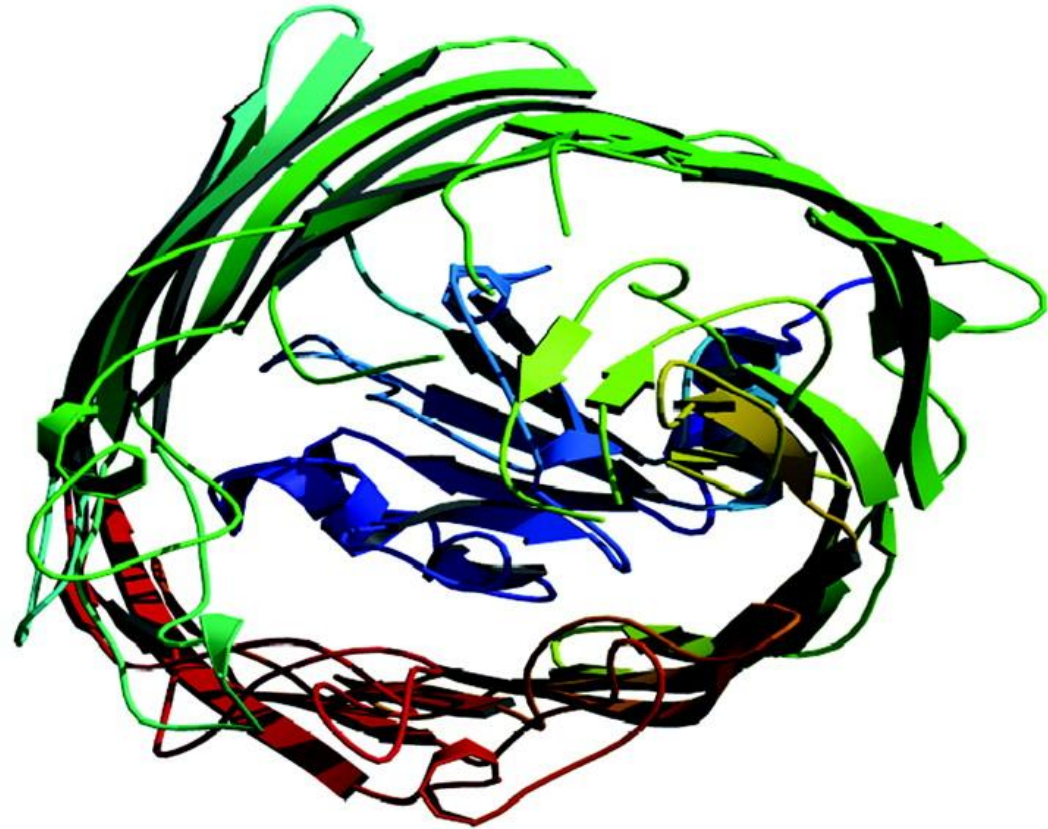
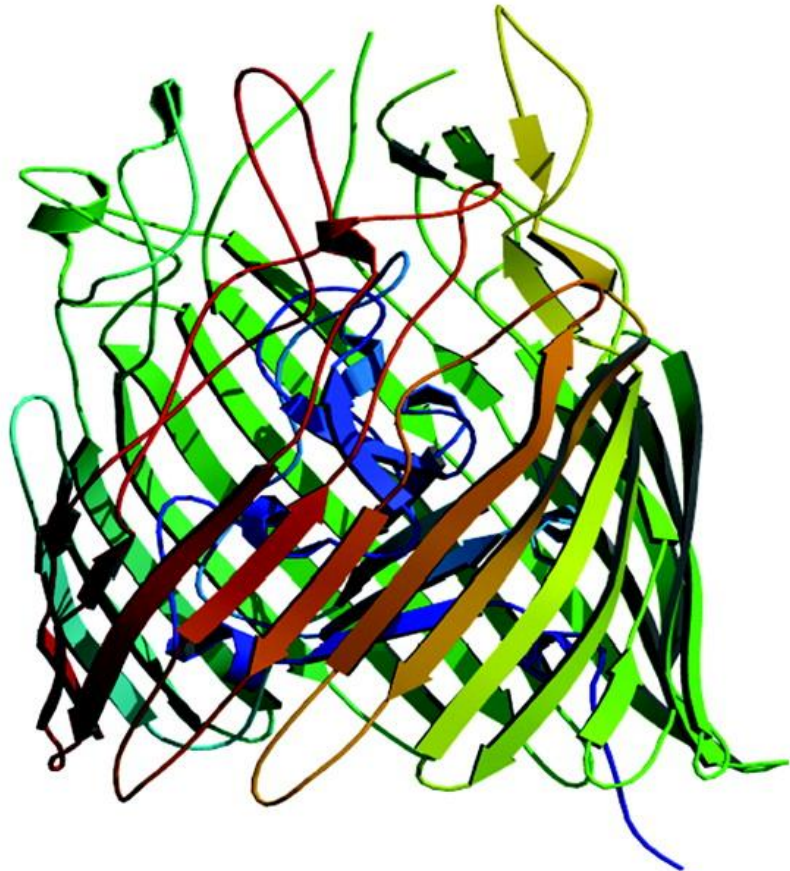
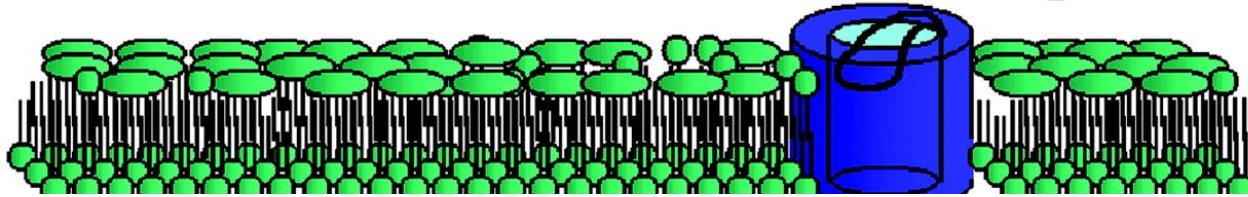
trans-membrane transport mechanisms



FepA: trans-membrane transport of Fe-enterobactin

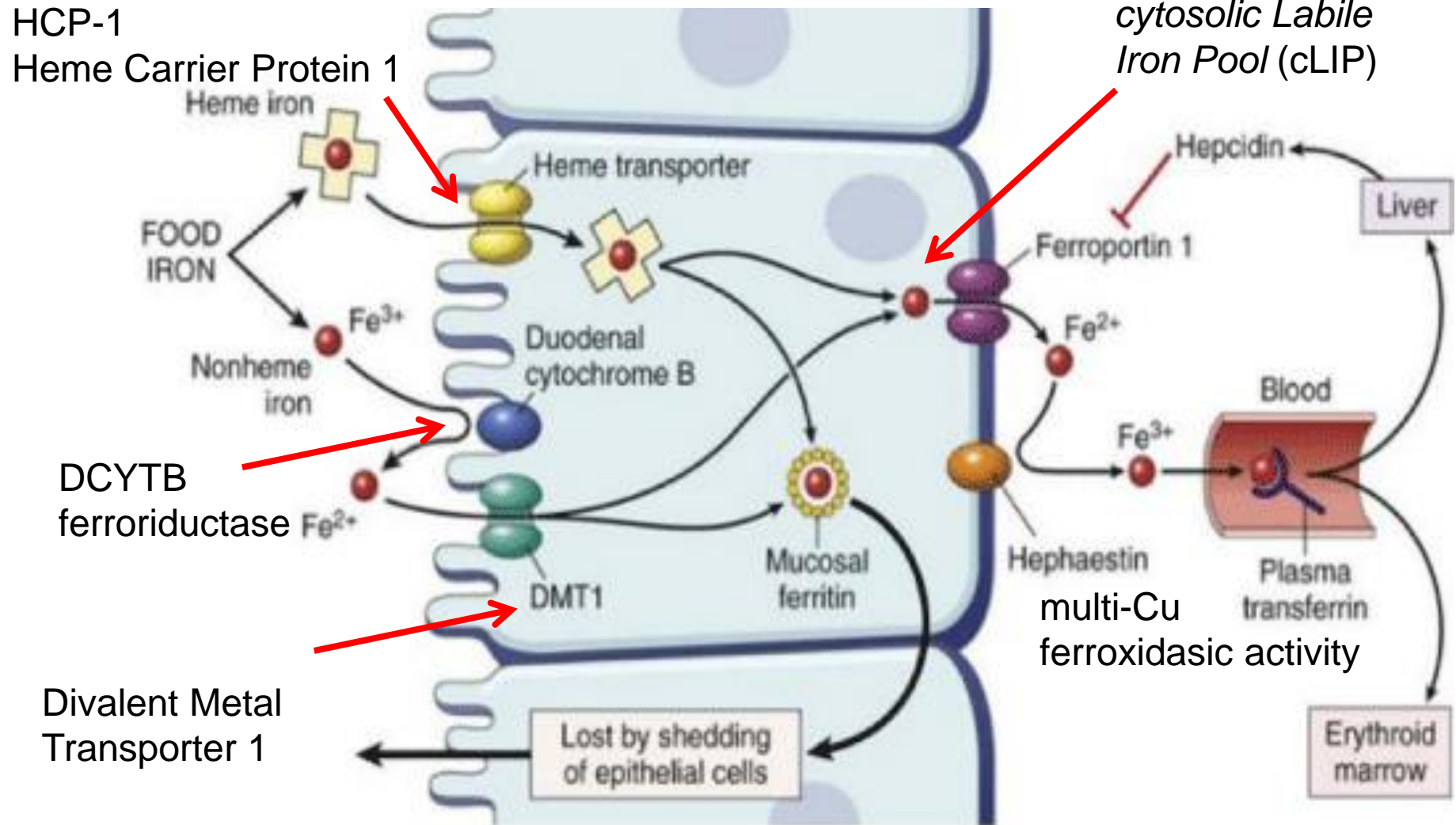
OM

FepA

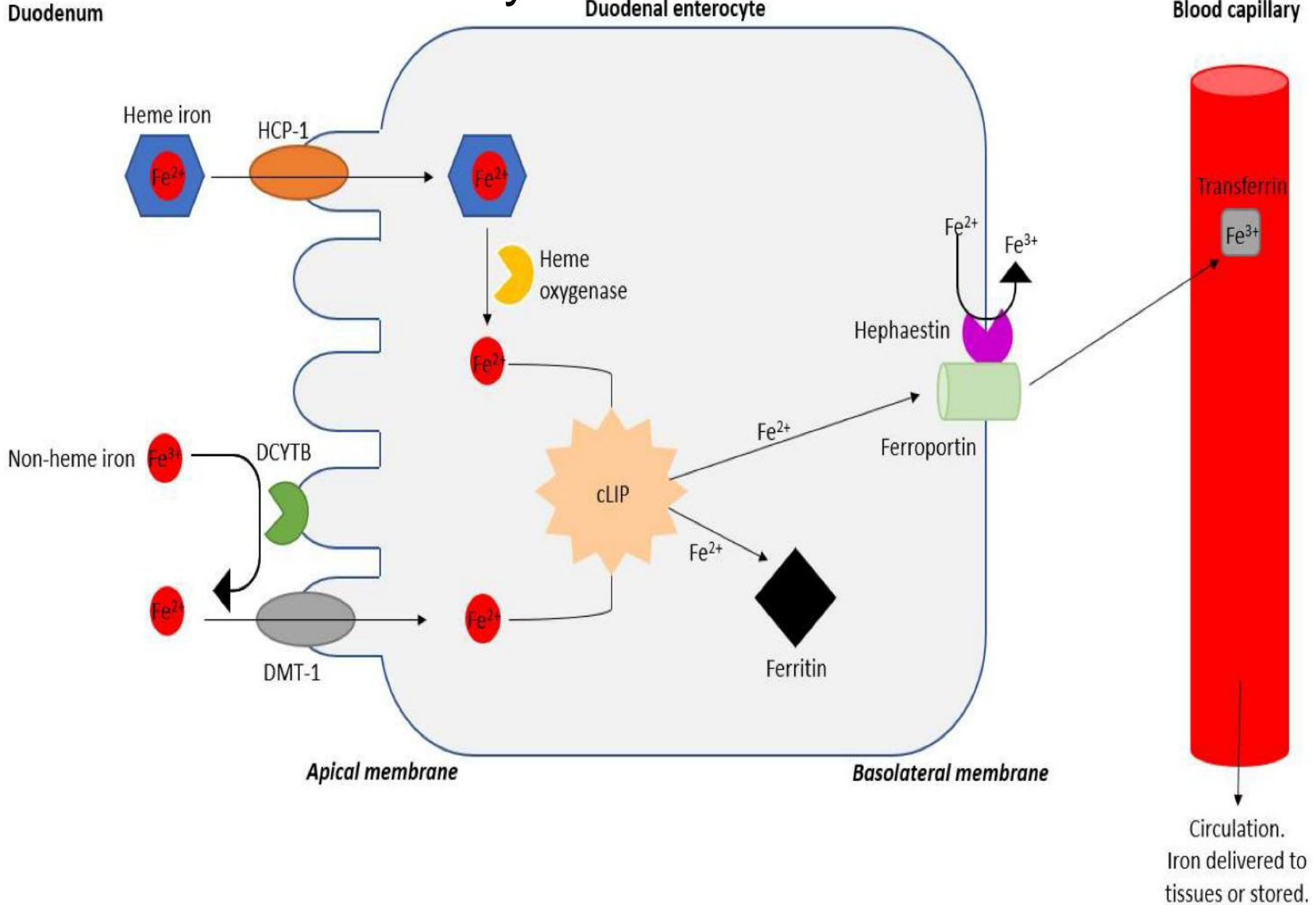


The N-terminal «gate protein» is in blue

Iron absorption in the intestine and transport through enterocytes in the duodenum



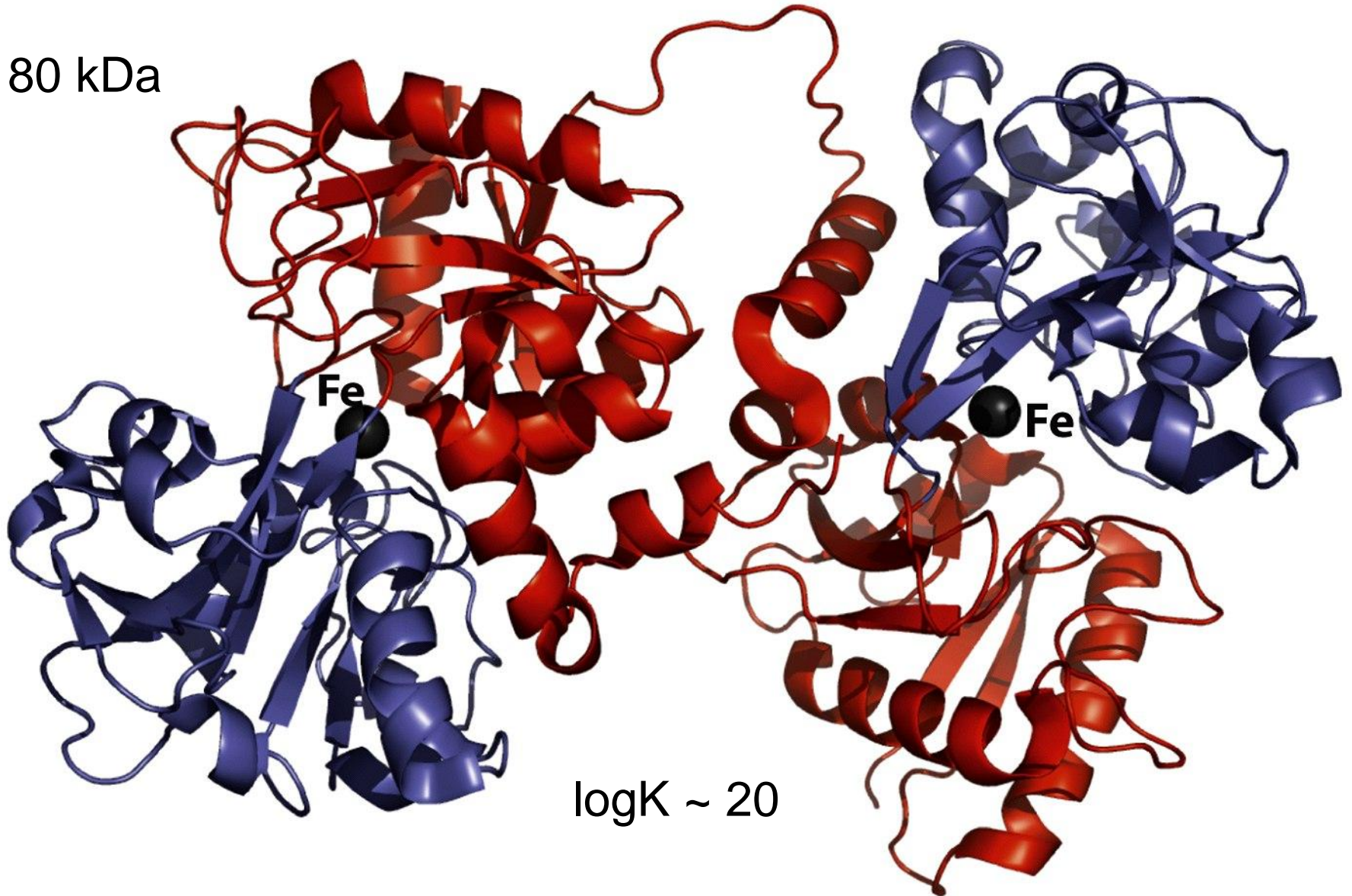
Iron absorption in the intestine and transport through enterocytes in the duodenum



Transferrin

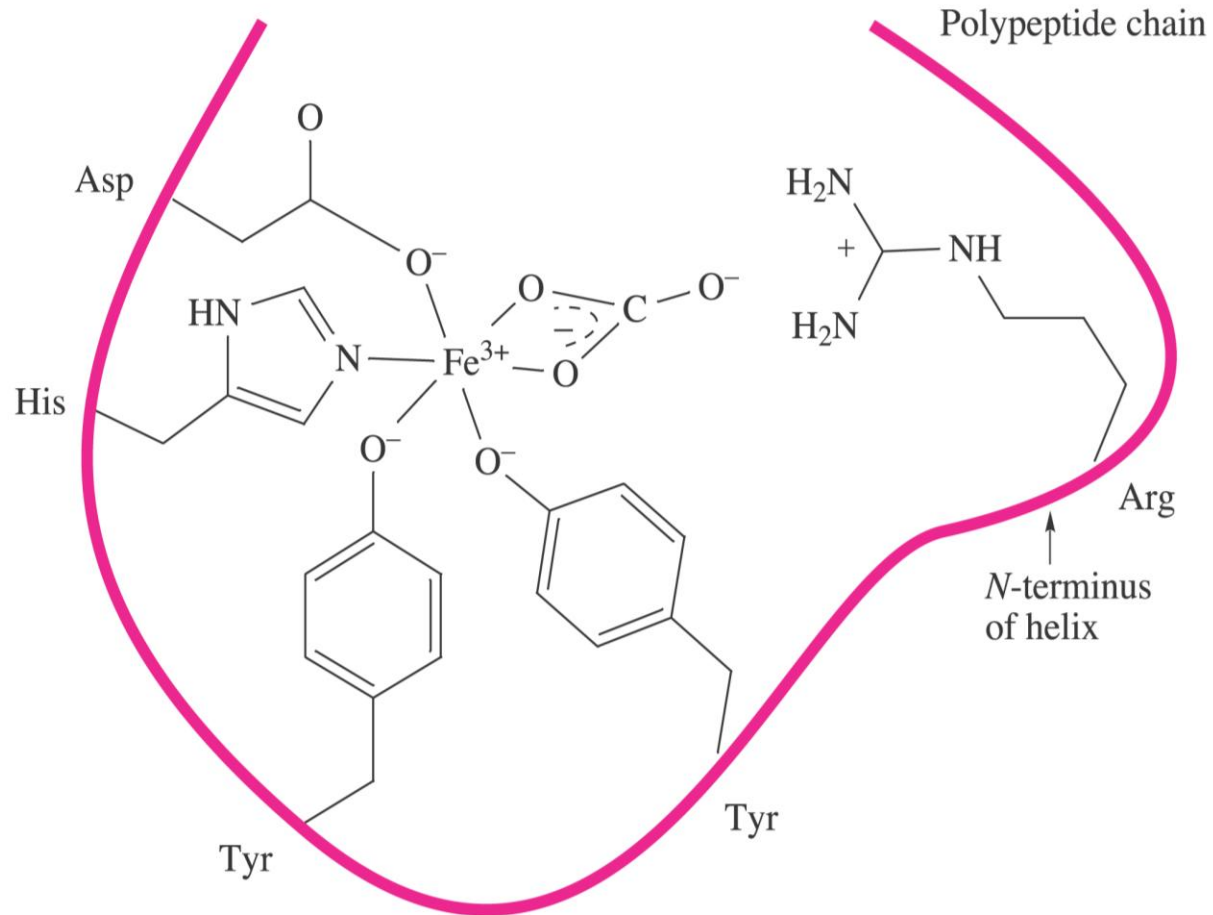
2 lobes, 2 Fe(III) coordination sites

80 kDa



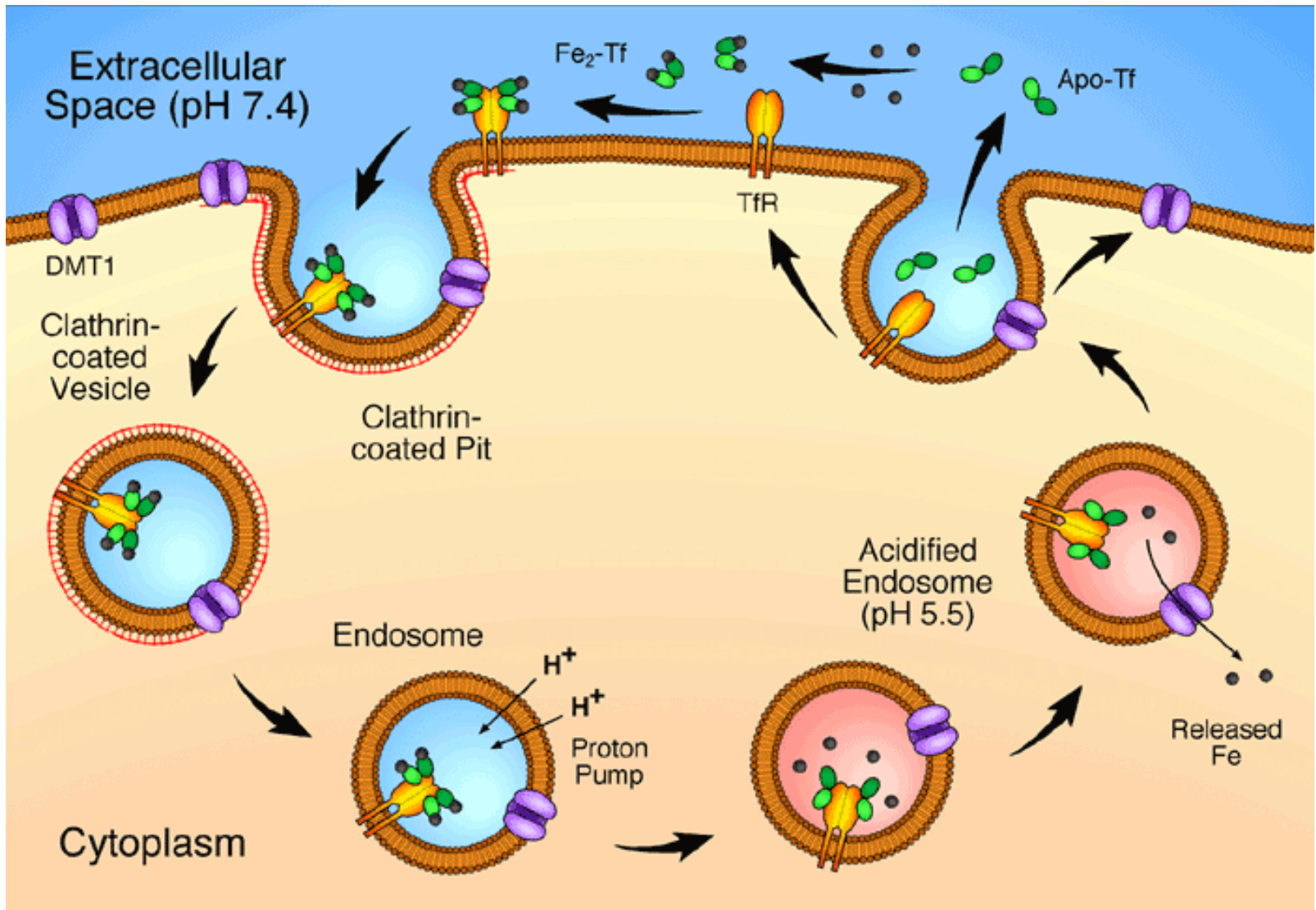
$\log K \sim 20$

Fe(III) coordination site in transferrin

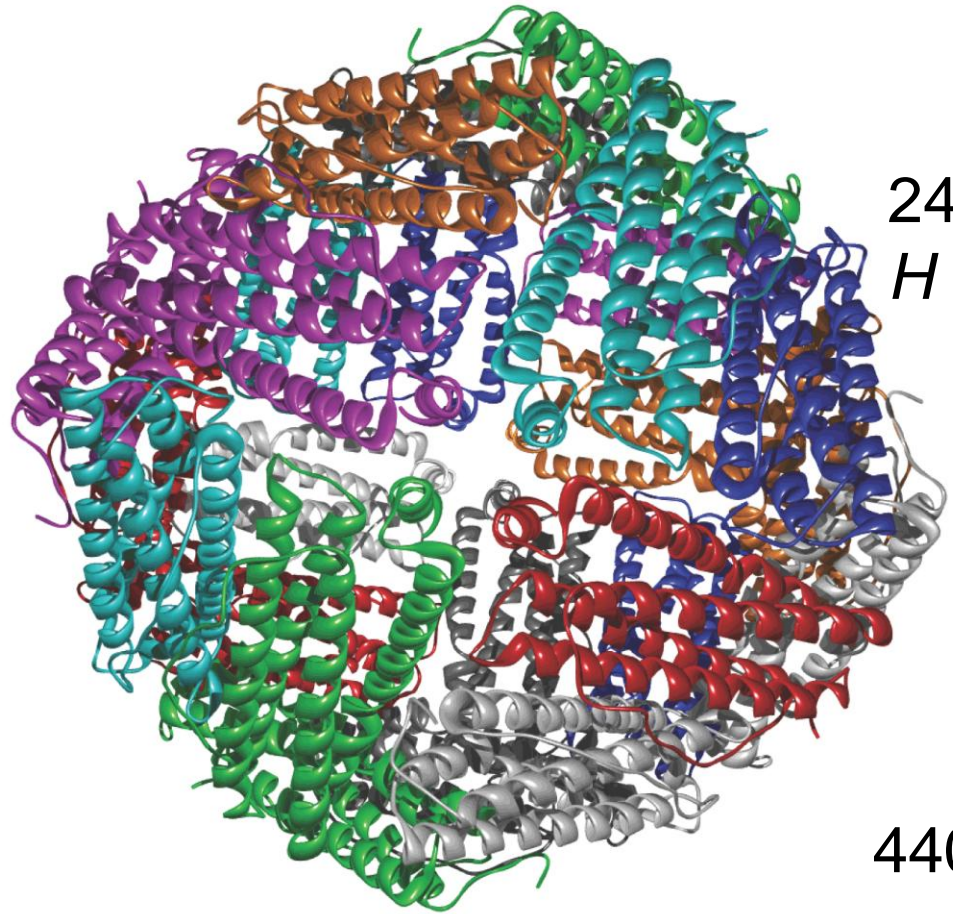
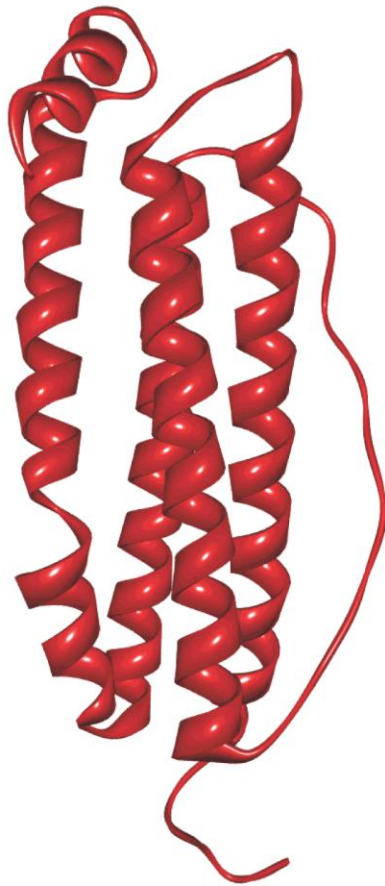


The coordination of Fe(III) involves the release of 3H⁺ and a remarkable **conformational change** of transferrin

The transferrin cycle



Iron storage: Ferritin

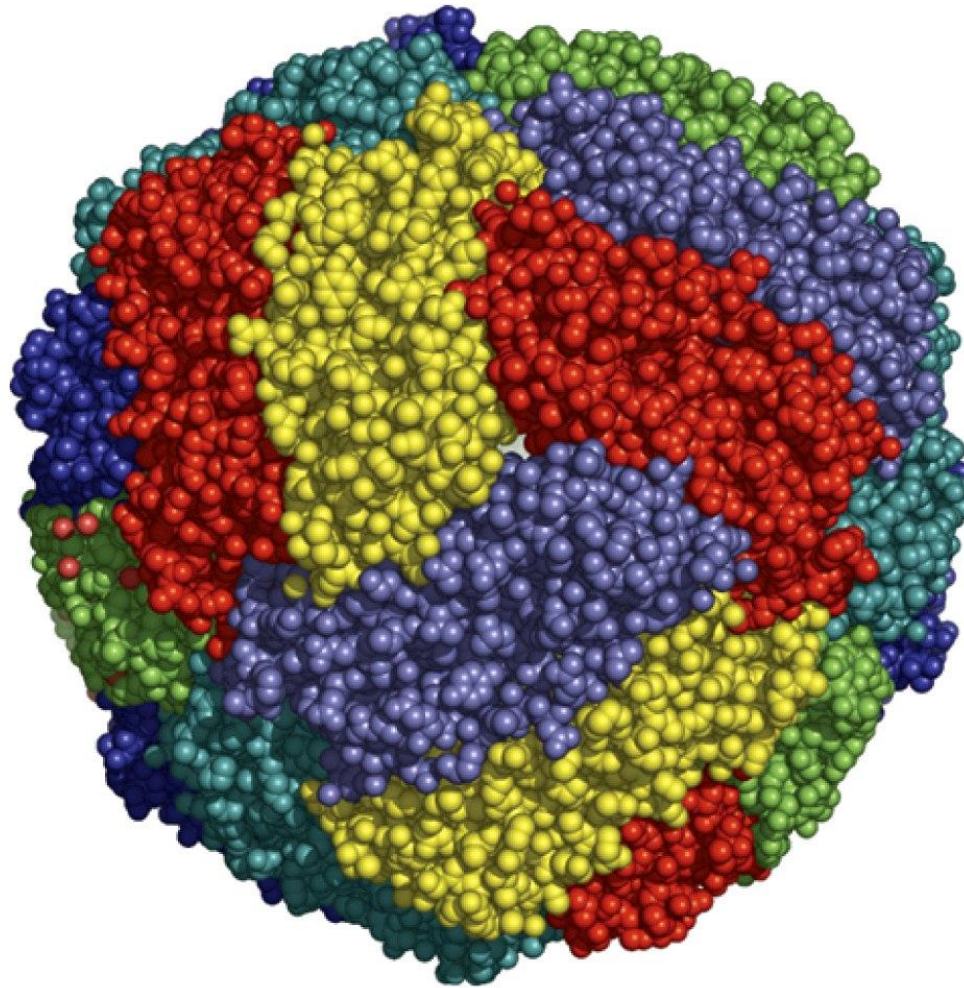


24 units,
H e L

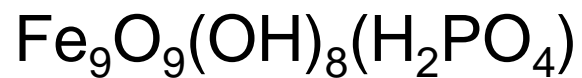
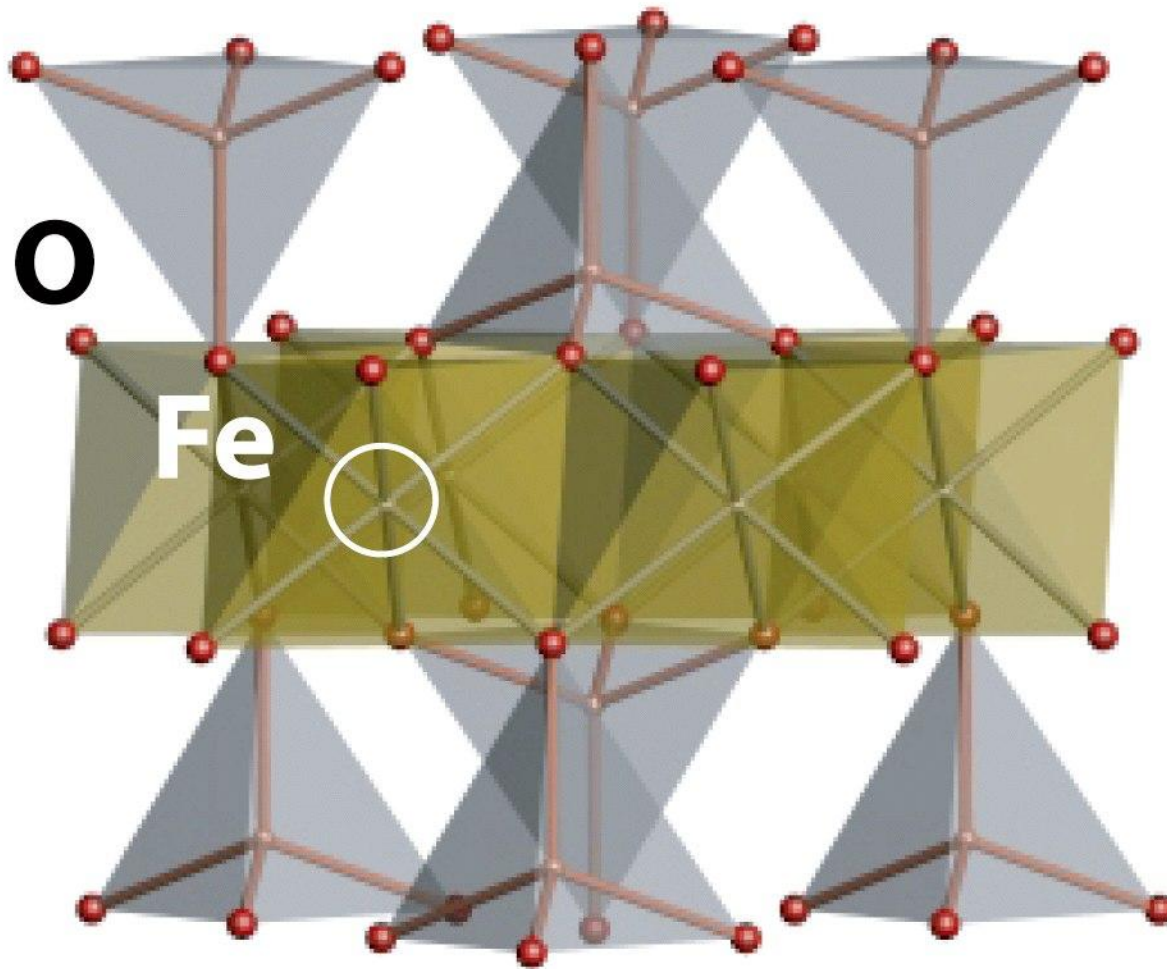
440 kDa

The *Heavy-chain ferritin (H)* has ferroxidasic activity
8 hydrophilic pores with ternary symmetry (*Fe in*)
6 hydrophobic pores with quaternary symmetry (*Fe out*)

In, 7.5nm

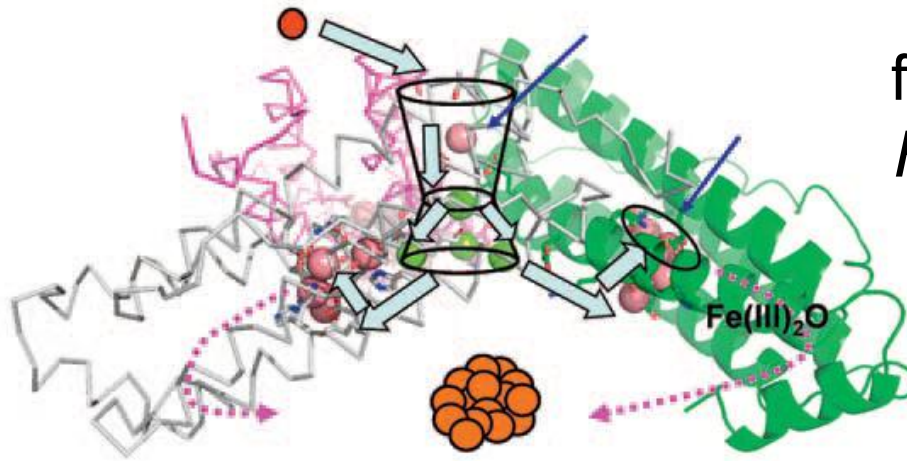
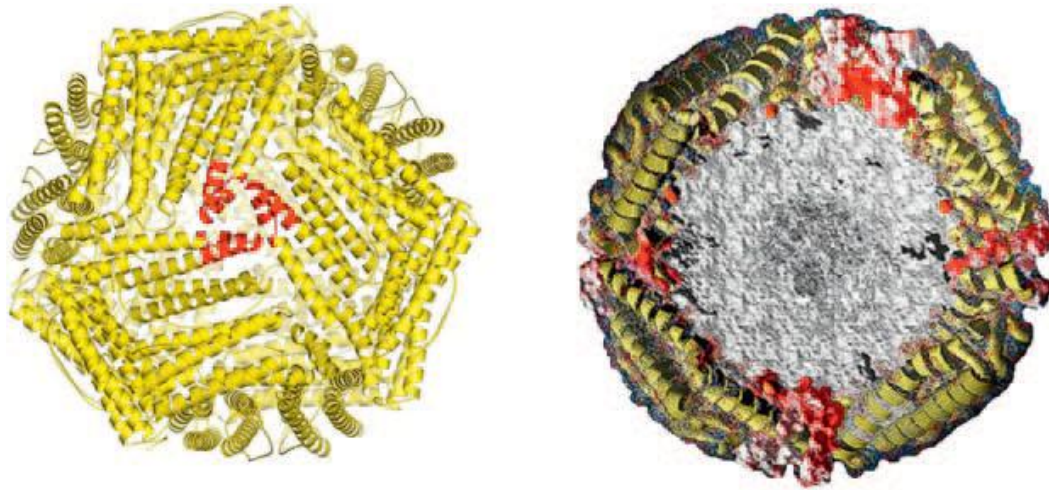


Out, 12 nm



Ferrihydrite $5\text{Fe}_2\text{O}_3 \cdot 9\text{H}_2\text{O}$

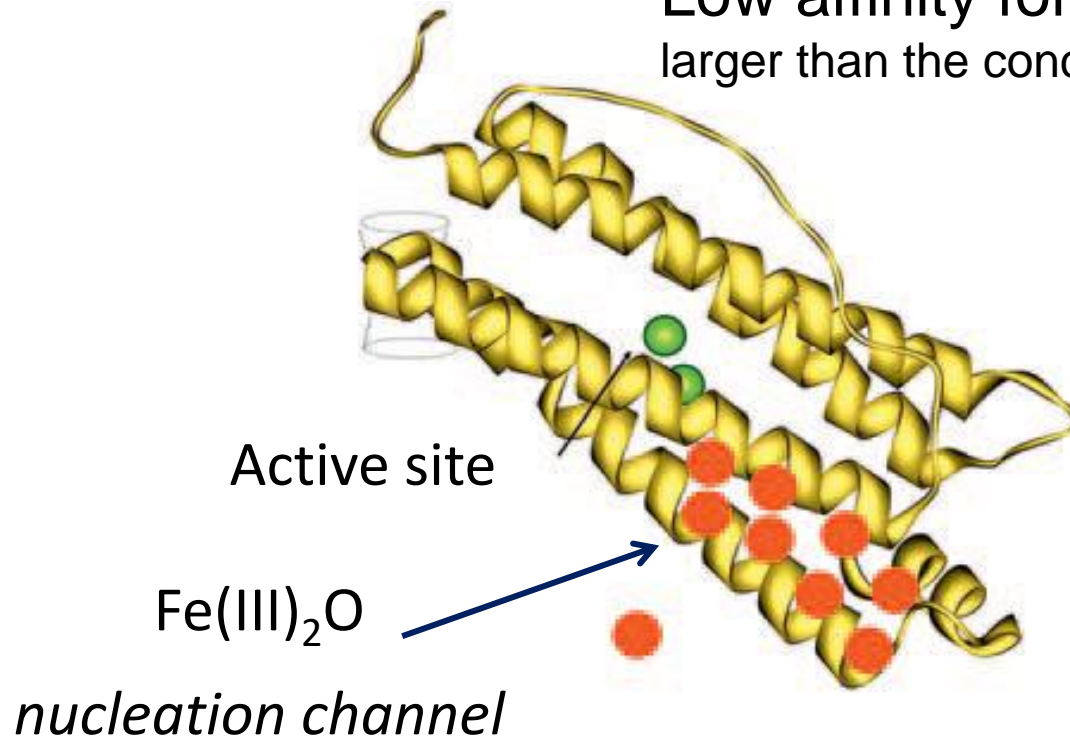
Up to 4500 Fe atoms Fe, 1200 on average



ferroxidase site in
H-ferritin

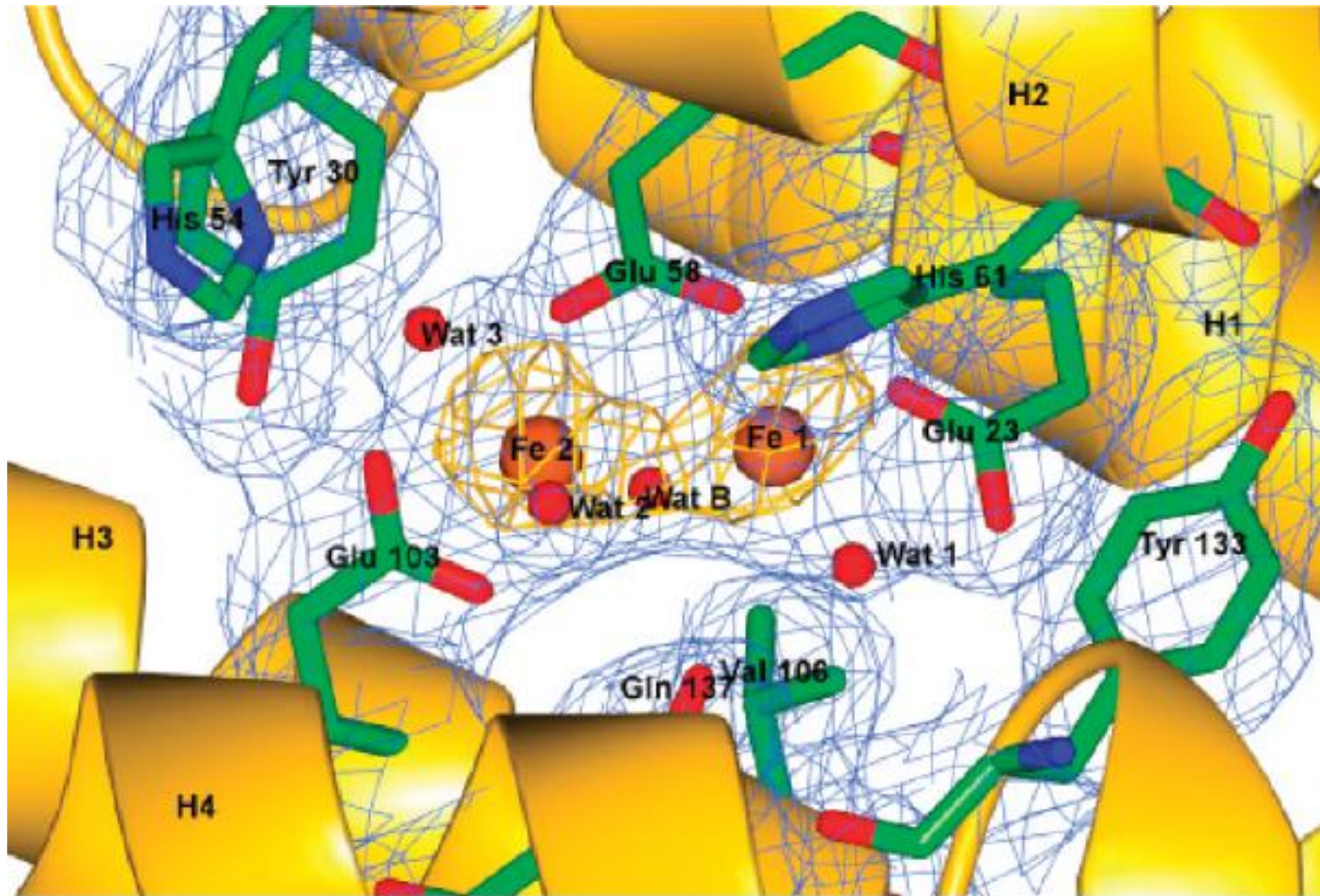
ferroxidasic site

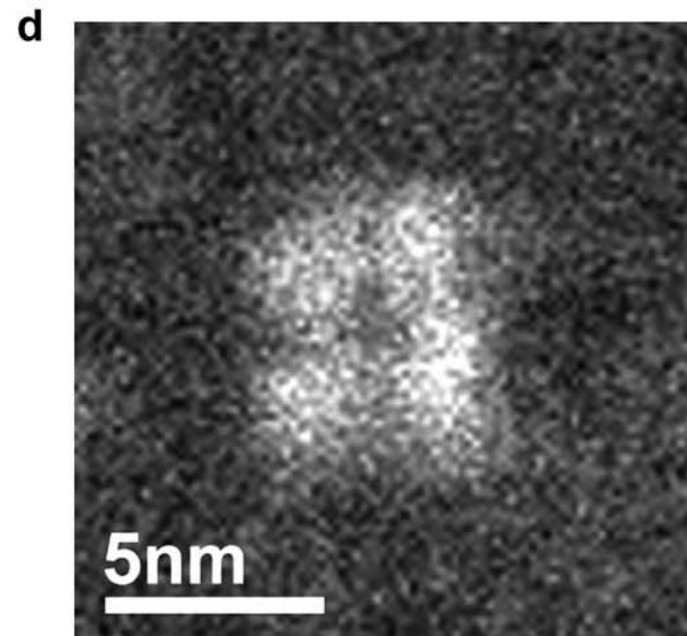
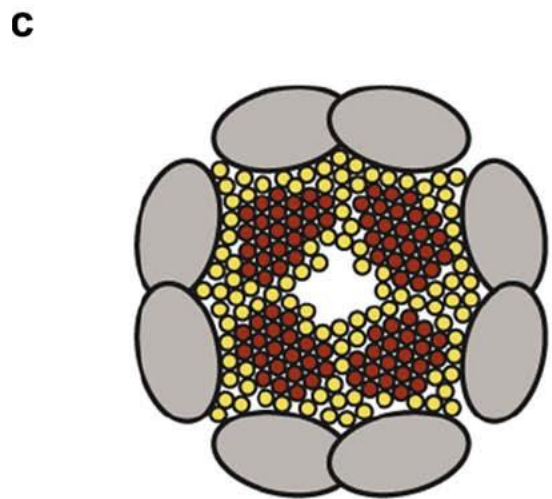
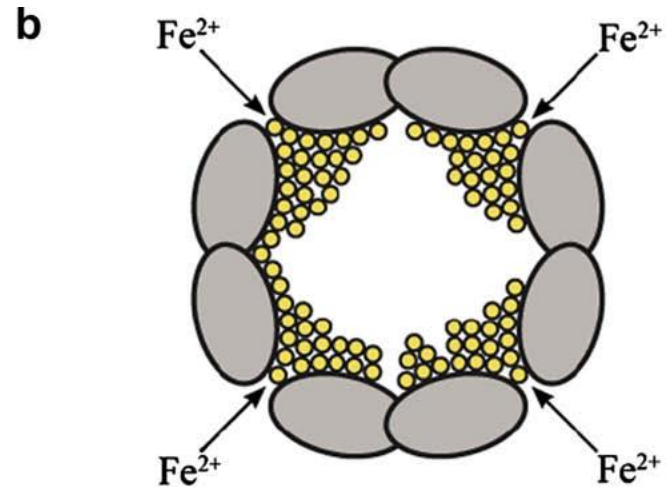
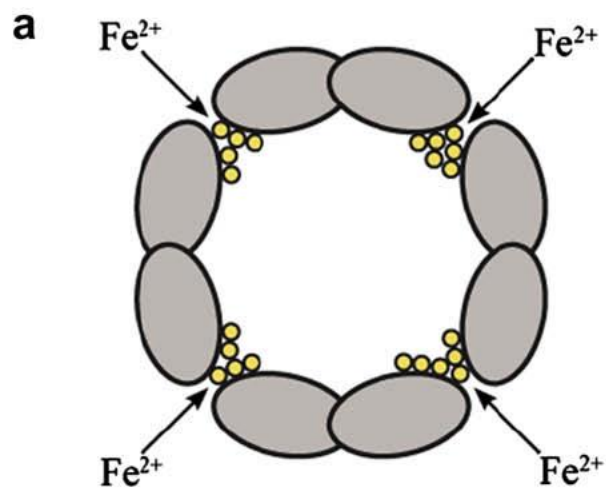
Low affinity for Fe(II), 15 μM
larger than the concentration of «free» Fe(II)






Possibility for *chaperone* proteins for Fe(II) (e.g. PCPB1)

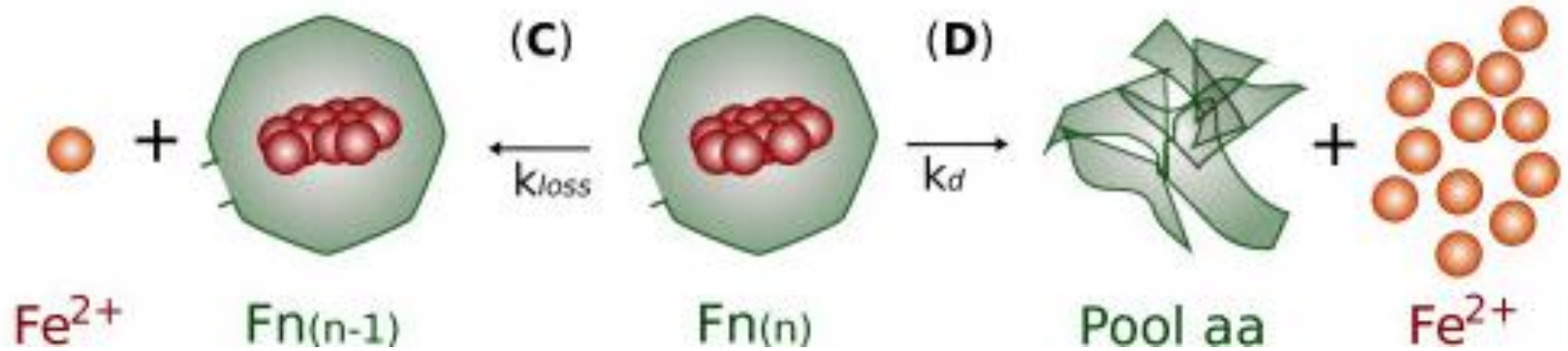
X ray structure of a ferroxidasic site



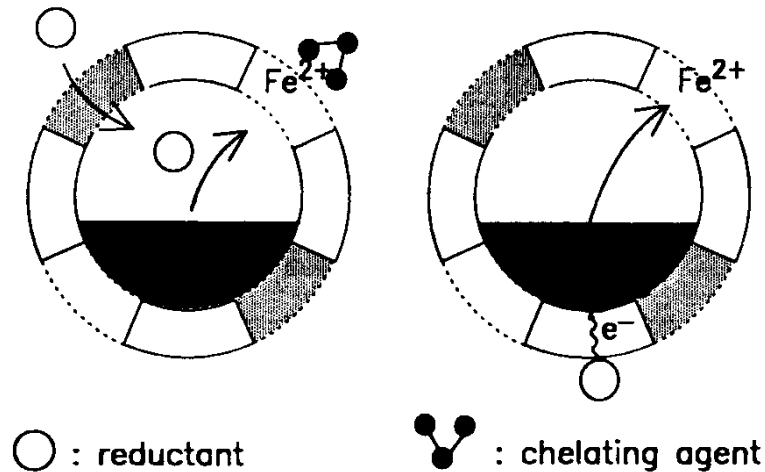


-  Fe^{3+} coordinated to O and OH
-  Fe^{3+} in ferrihydrite crystal structure
-  Protein shell sub-unit

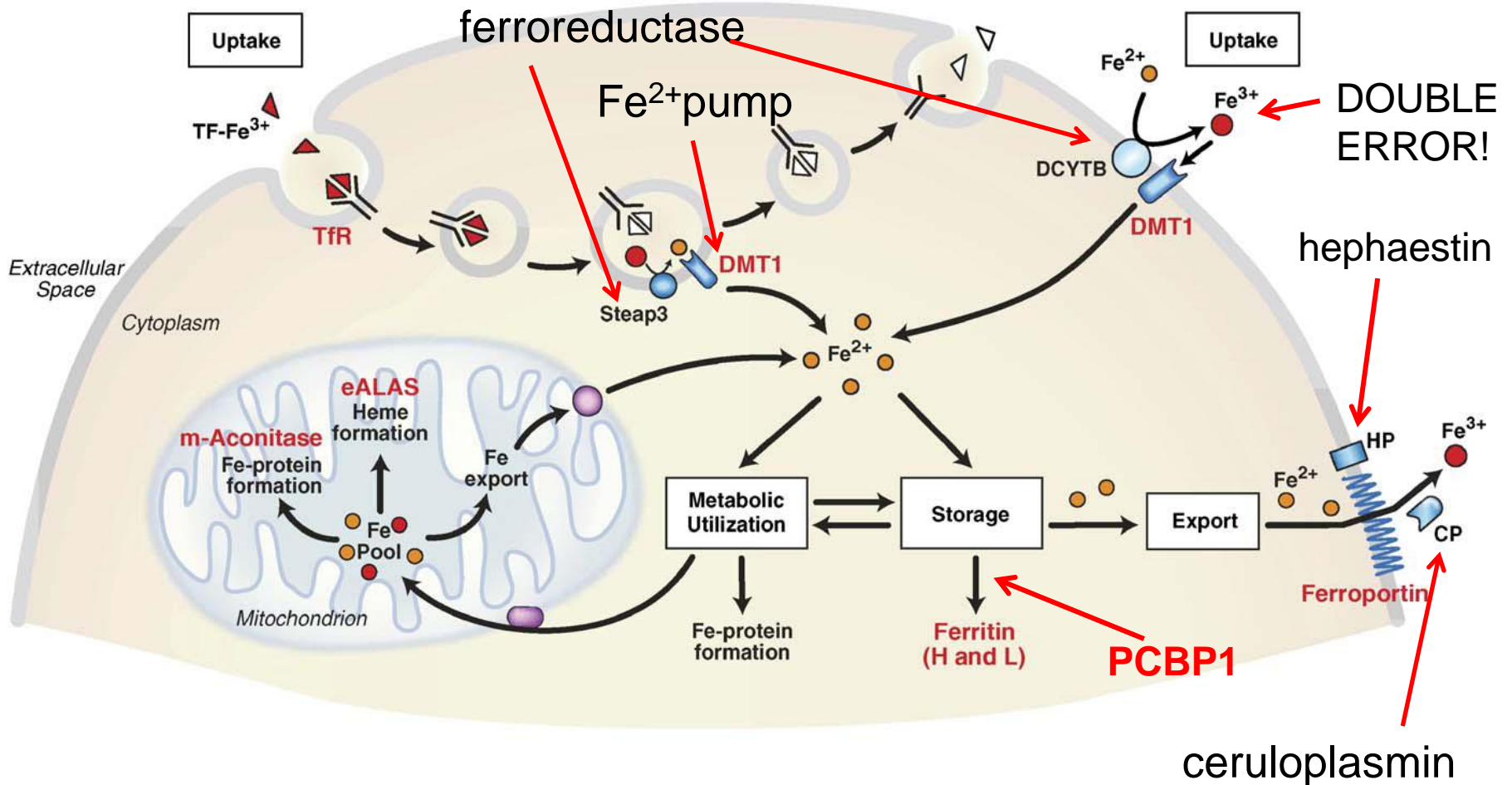
Iron release



protein degradation in lysosomes?



Iron homeostasis – IRP/IRE system

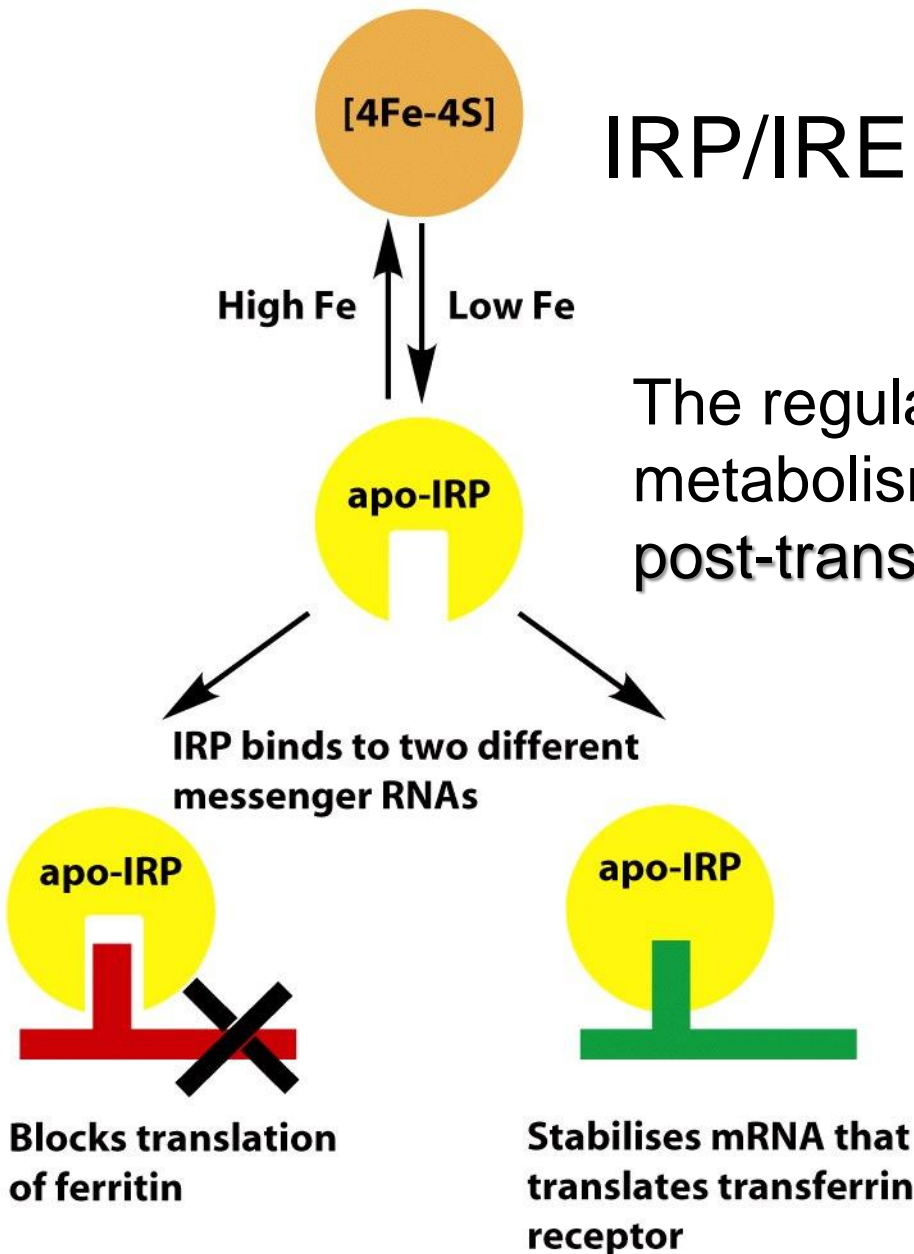


IRP: Iron Regulatory Proteins

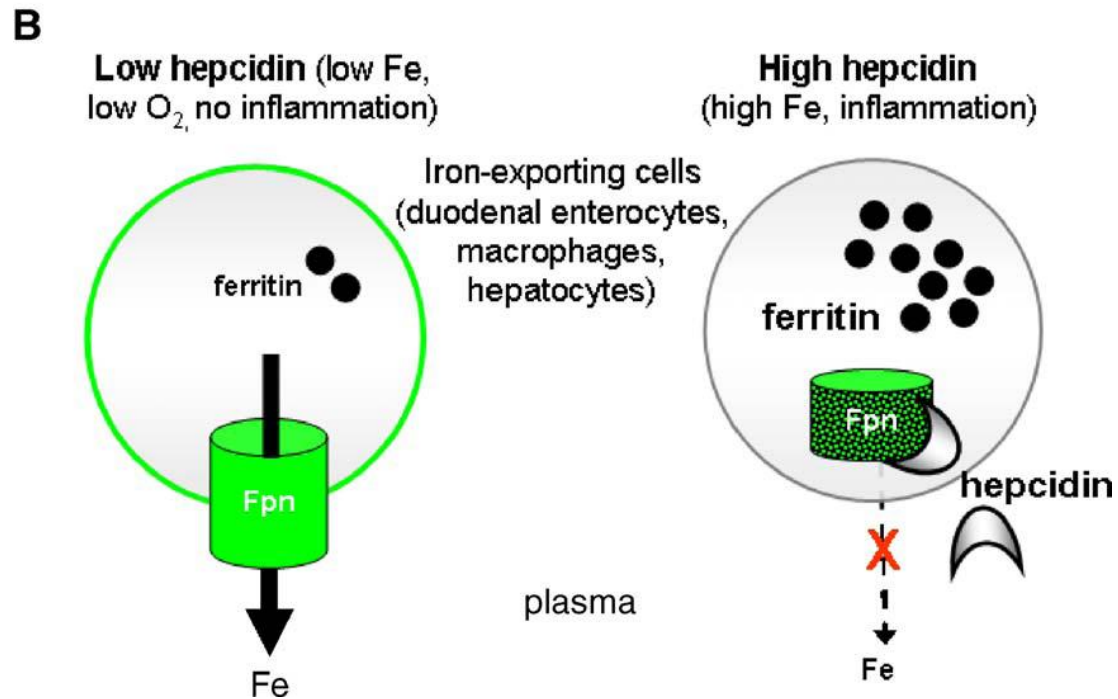
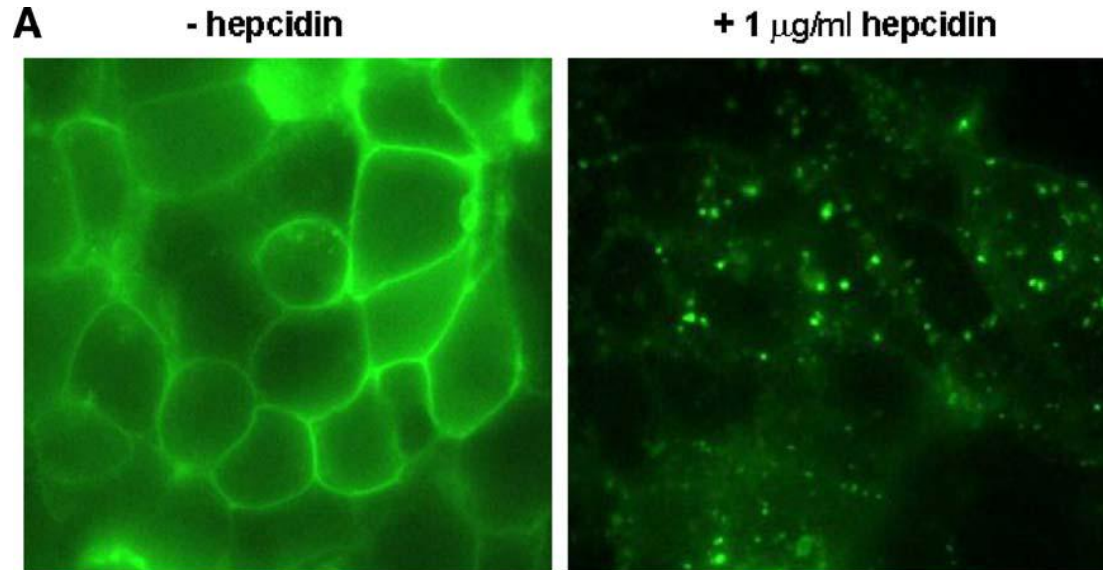
IRE: Iron Responsive Elements (mRNA)

IRP/IRE system

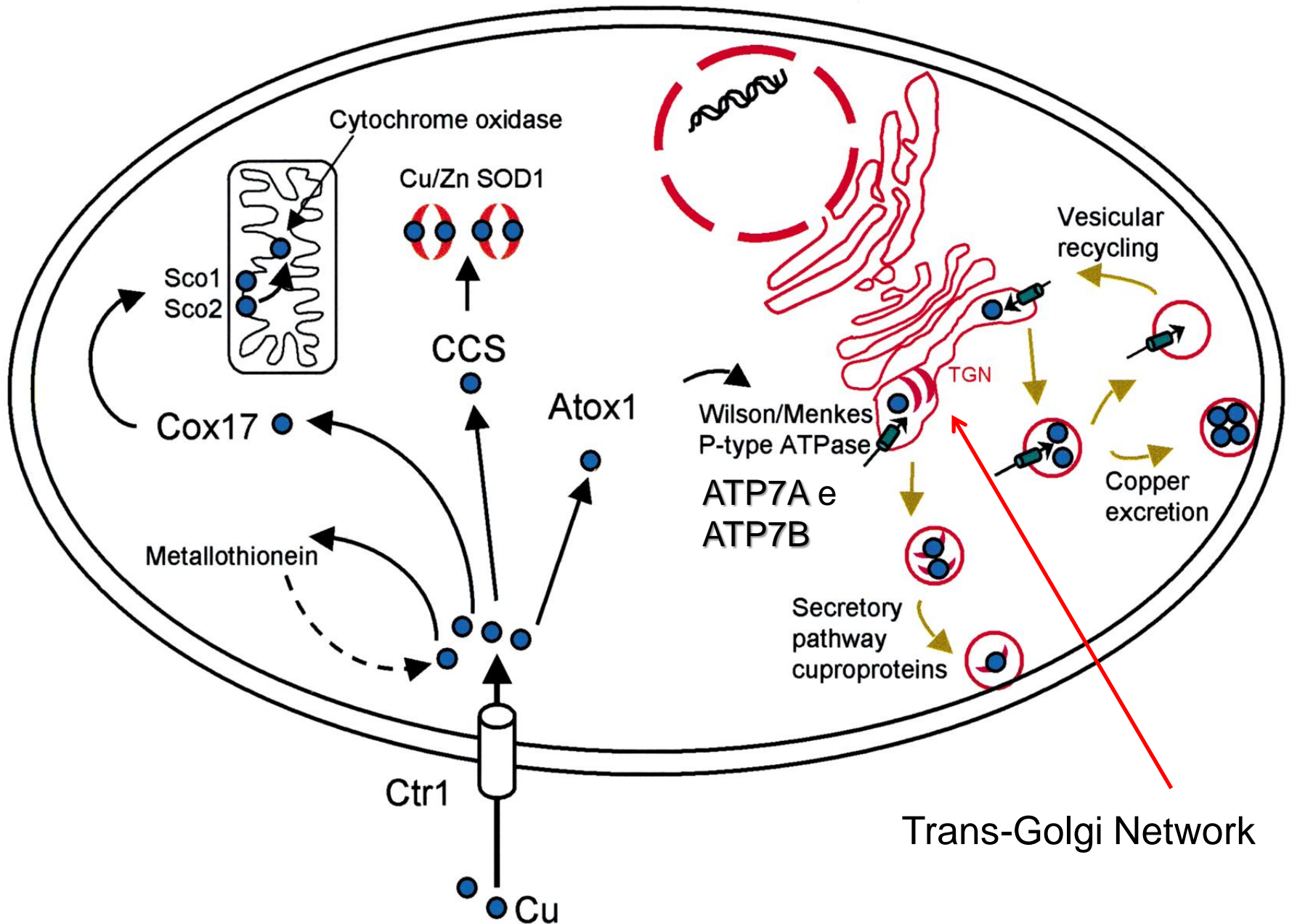
The regulation of iron metabolism occurs at the post-transcriptional level

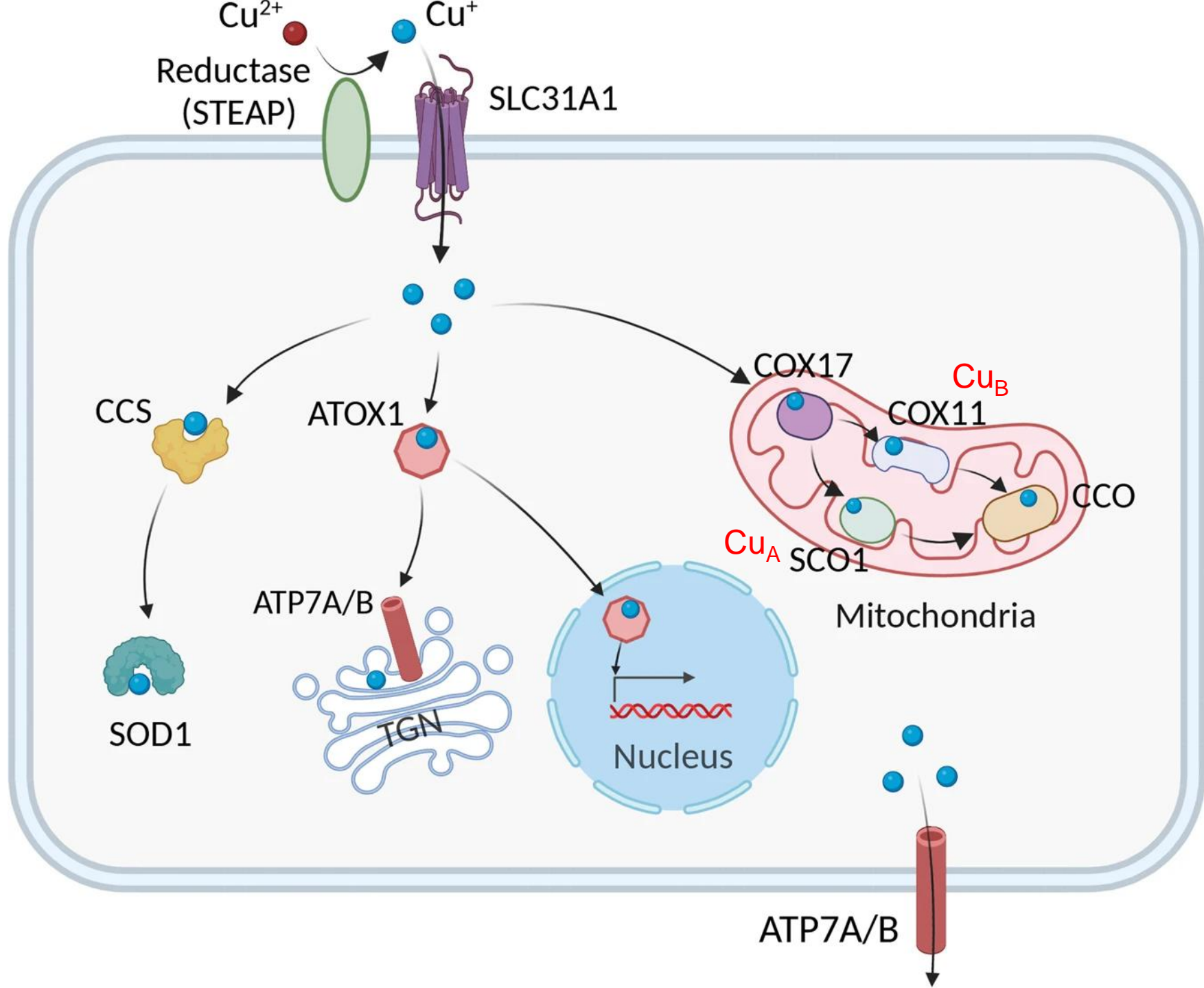


hepcidin-regulated iron export in plasma



Copper homeostasis



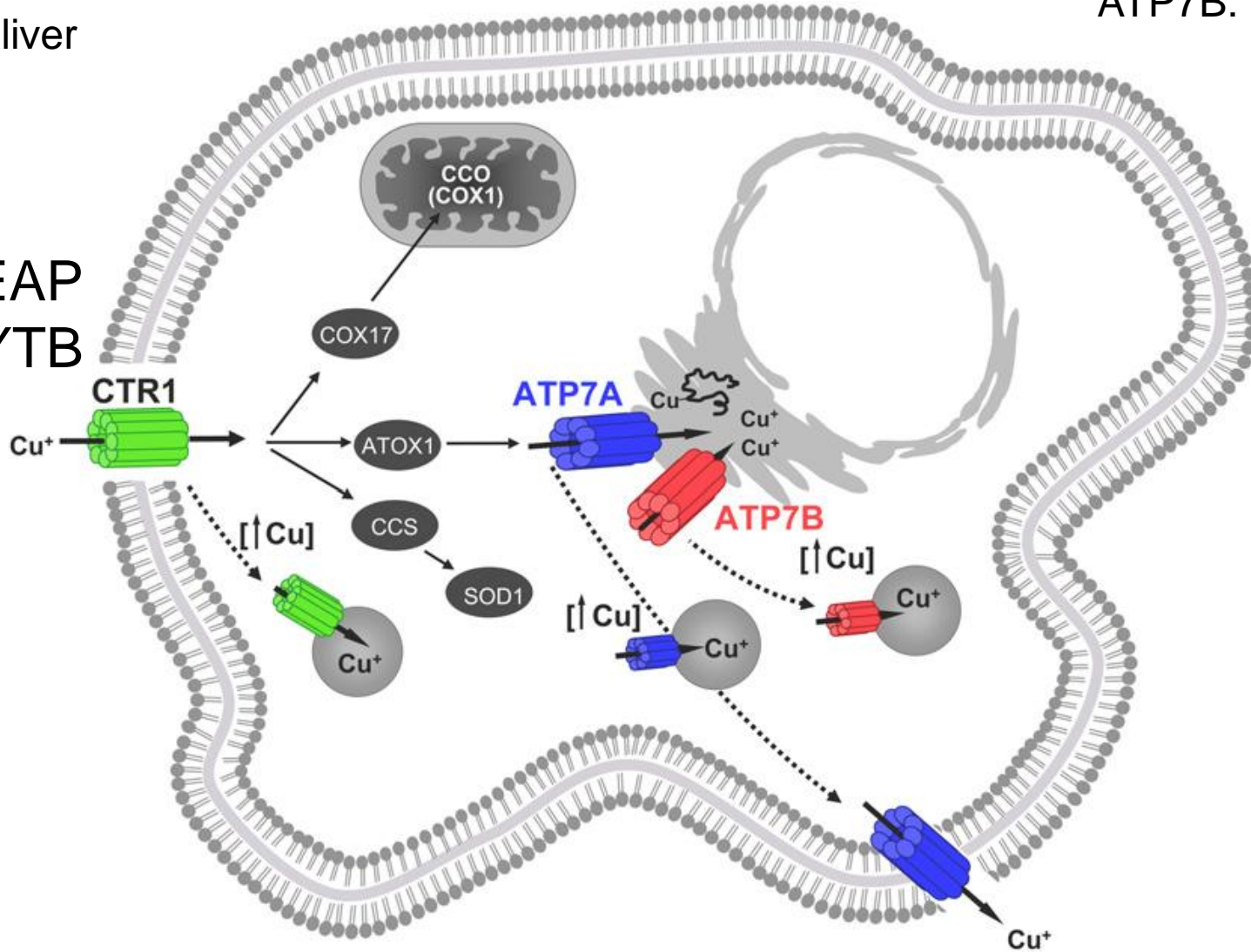


Copper homeostasis

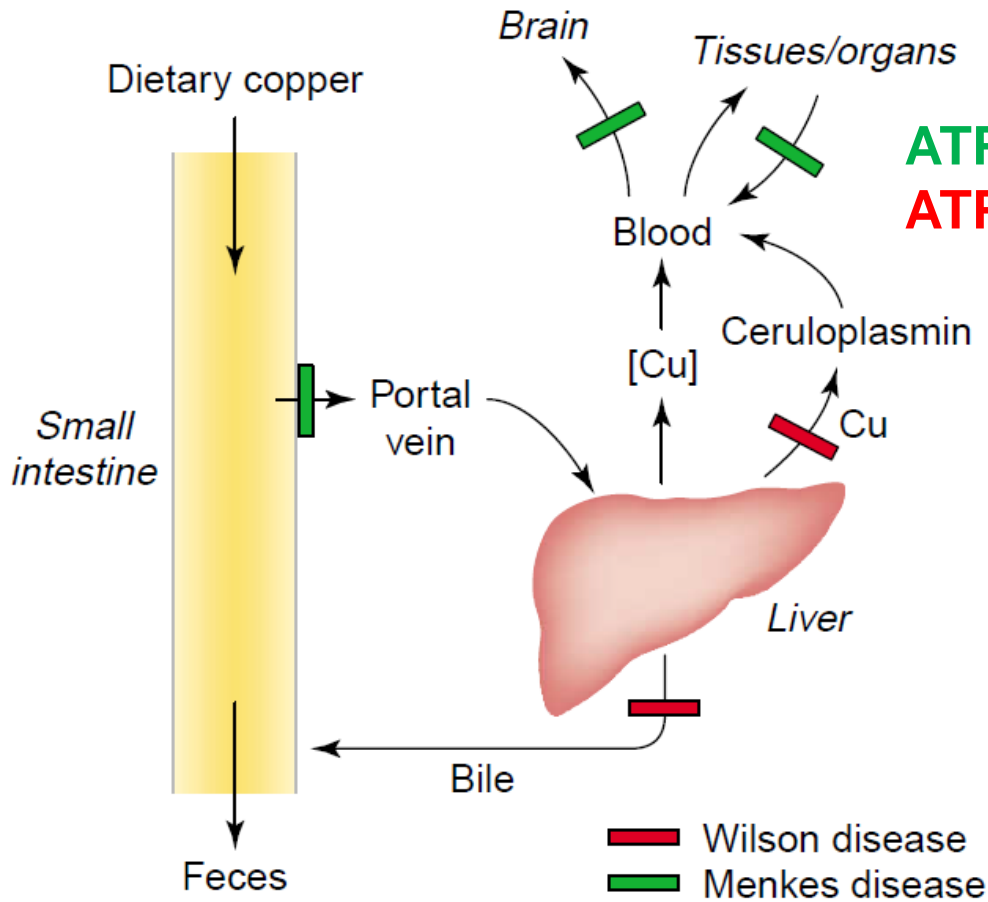
ATP7A: all tissues
except liver

ATP7B: mainly liver

STEAP
DCYTB



Cu^{2+} : albumin, ceruloplasmin, macroglobulins, ...



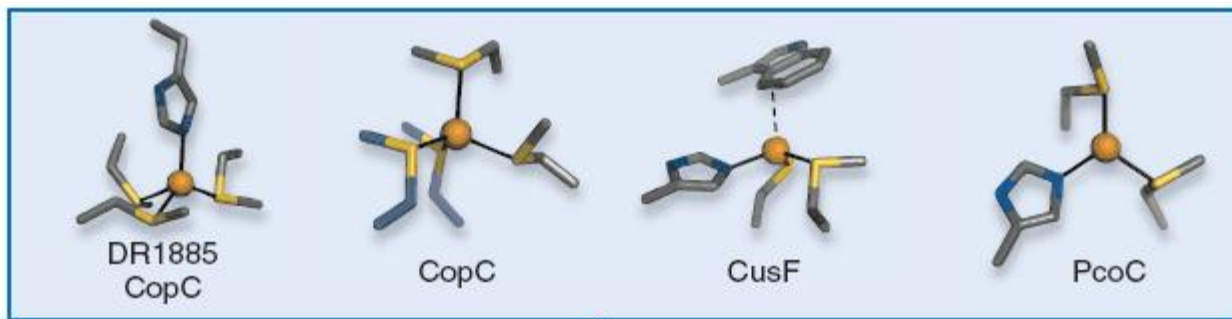
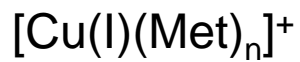
ATP7A: Menkes disease, Cu deficiency

ATP7B: Wilson's disease, Cu overload

ATP7A is expressed in most tissues/organs, with the exception of the liver.

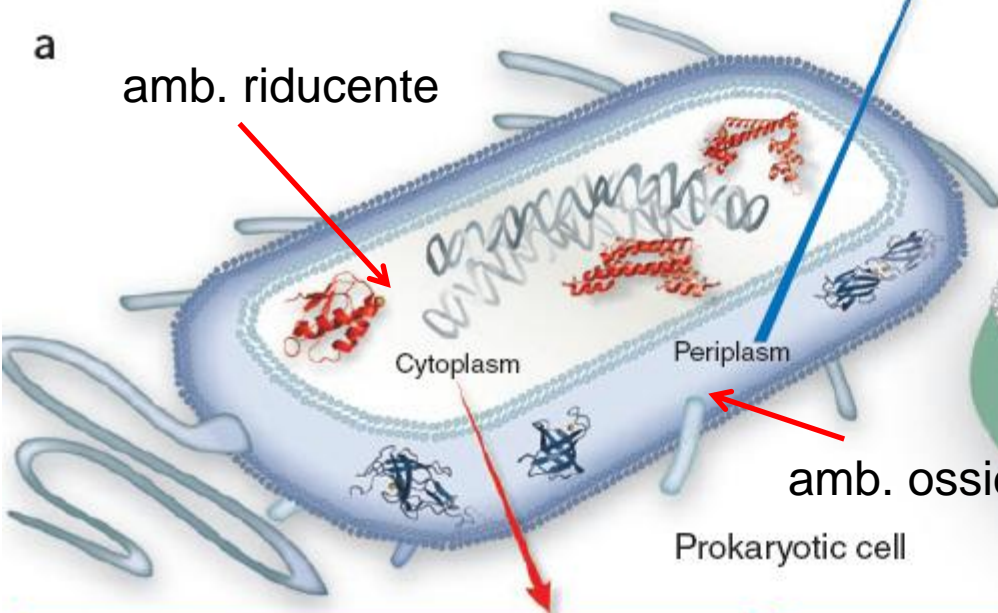
ATP7B is found to be predominantly expressed in the liver





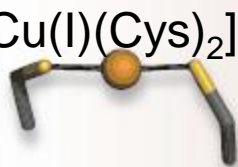
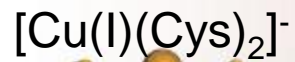
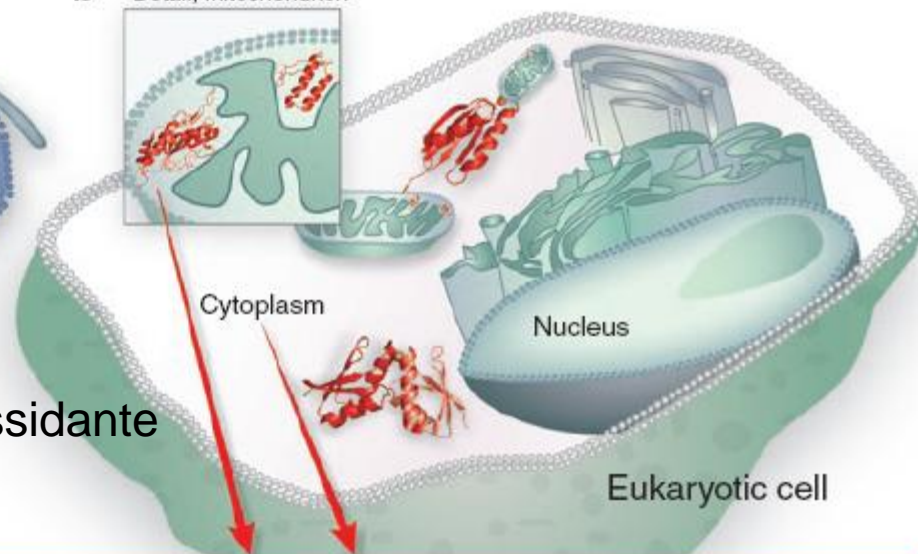
a

amb. riducente



b

Detail, mitochondrion



CopZ
CueR



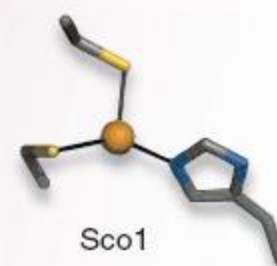
CsoR



Atx1, Hah1
Ccc2, Mnk, Wnd
Cox17

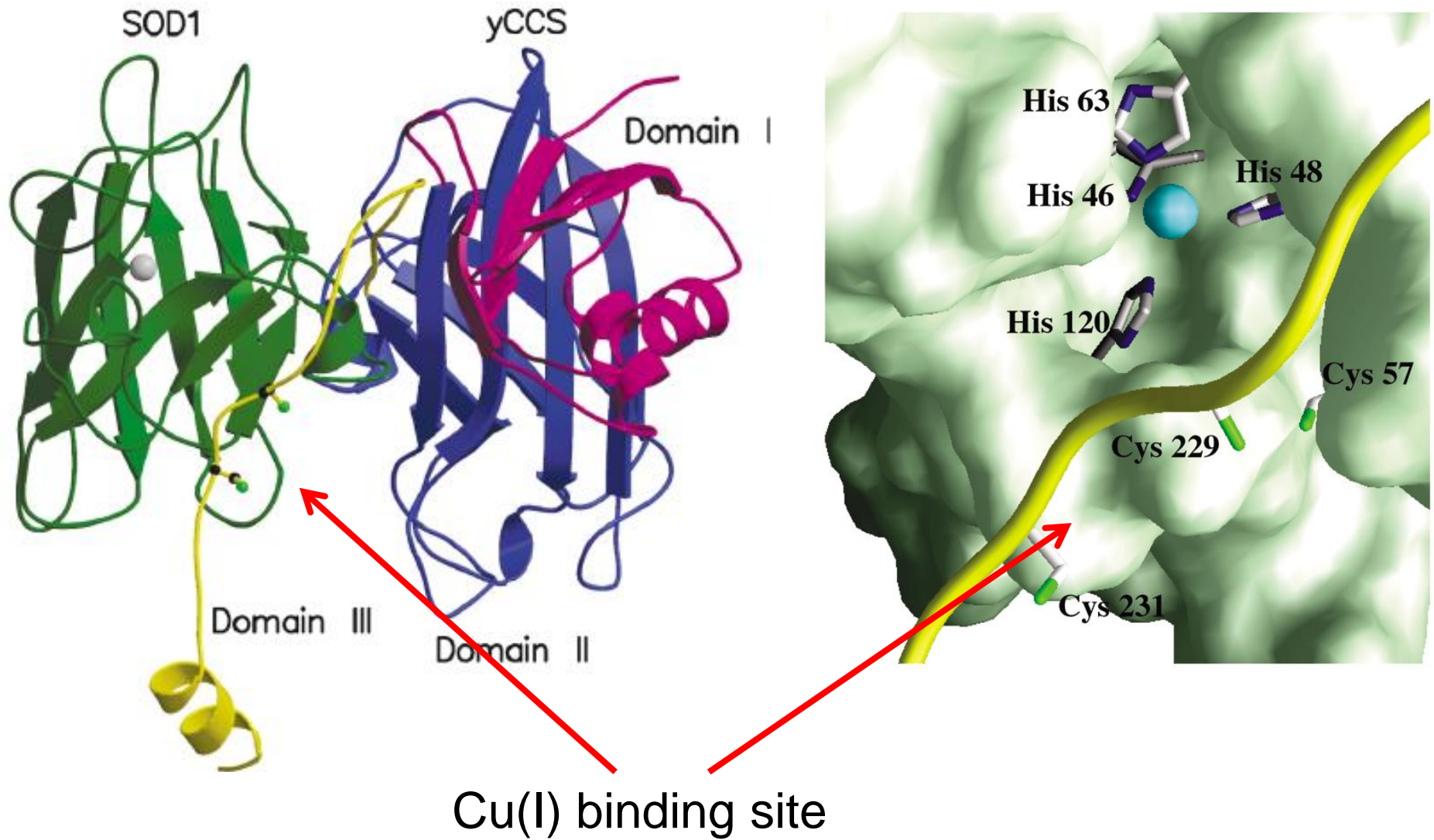


Hah1

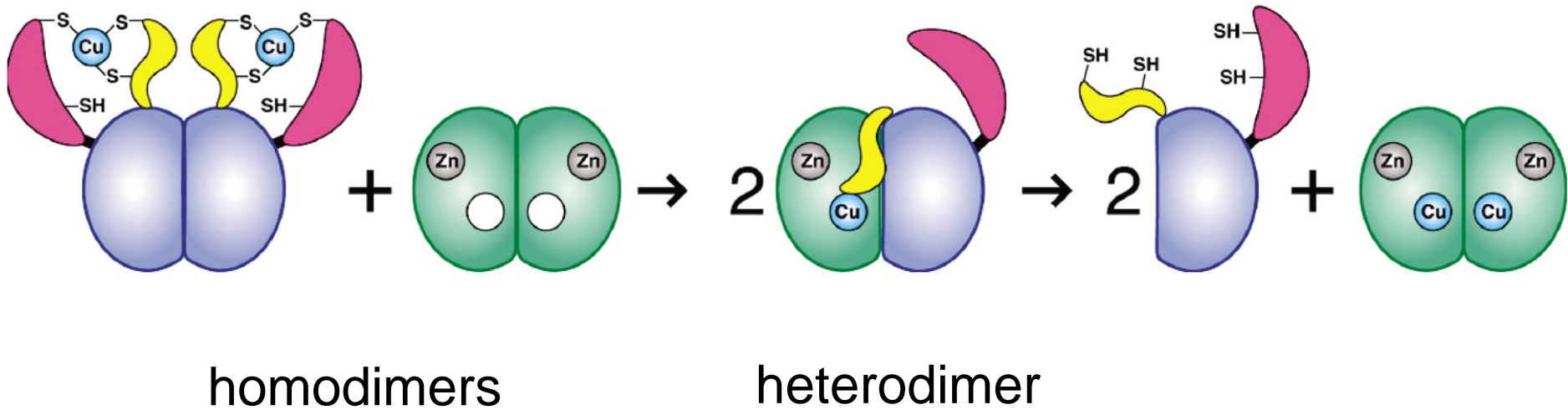


Sco1

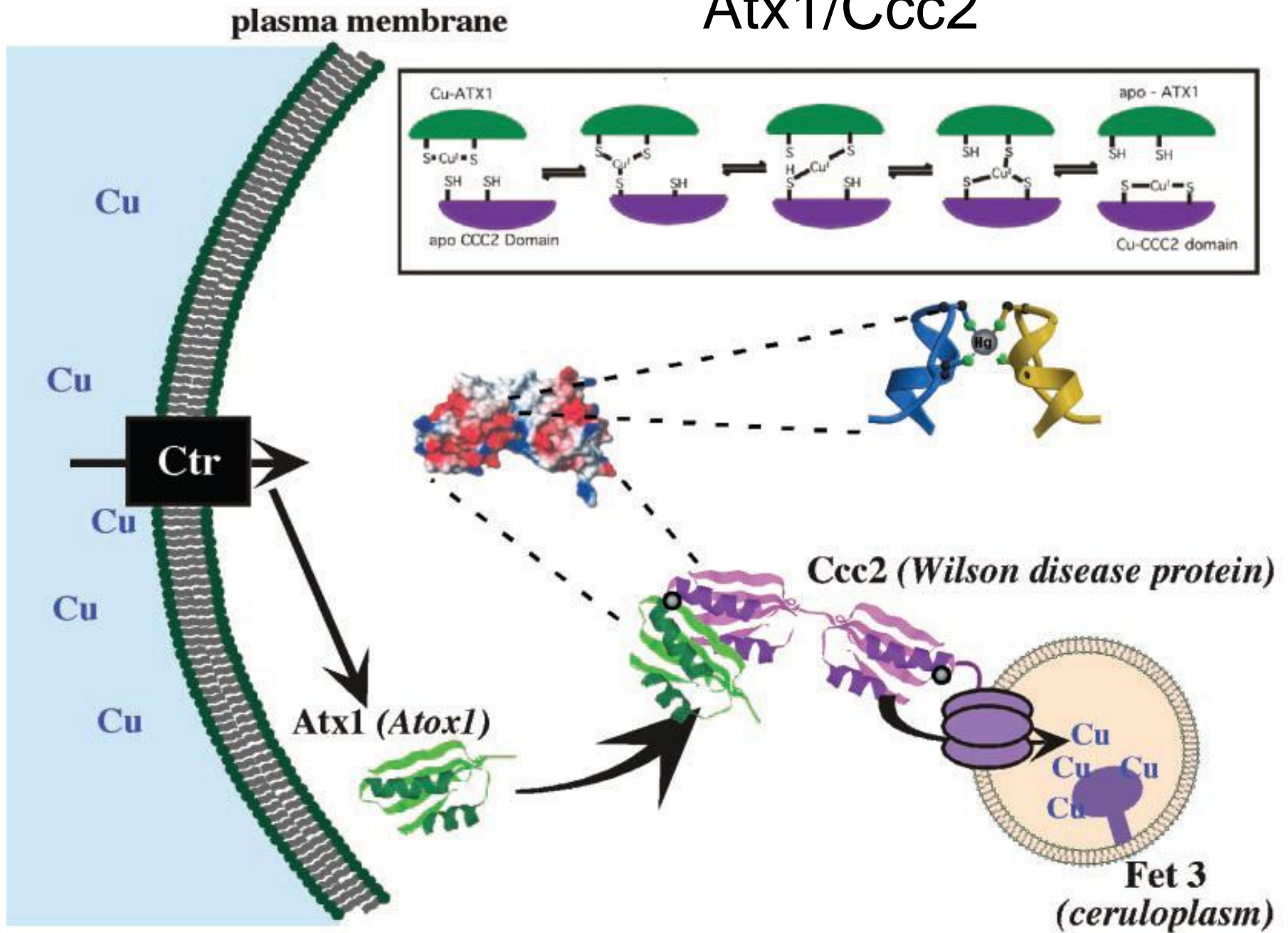
yCCS/Zn-SOD



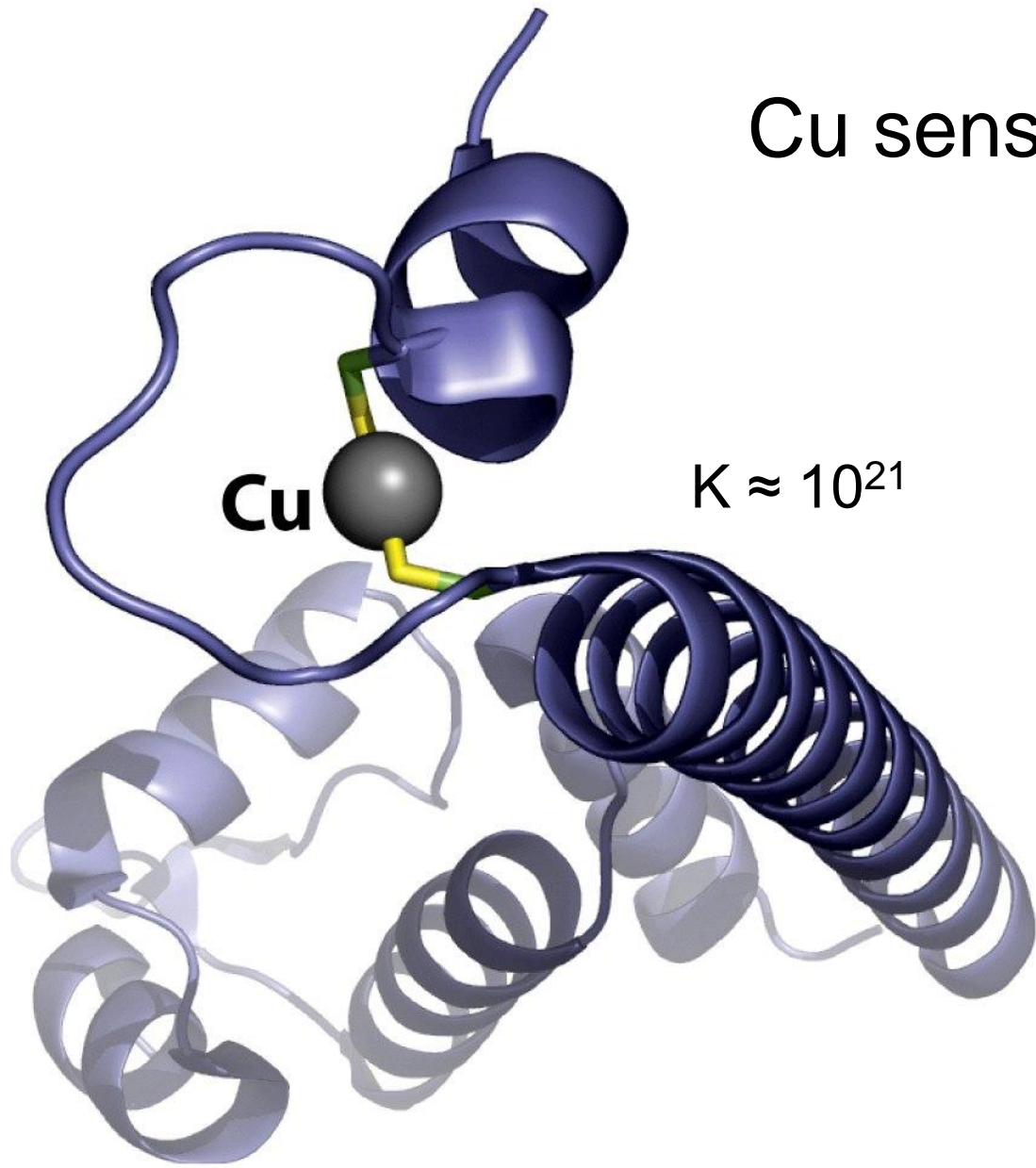
CCS/Zn-SOD



Atx1/Ccc2

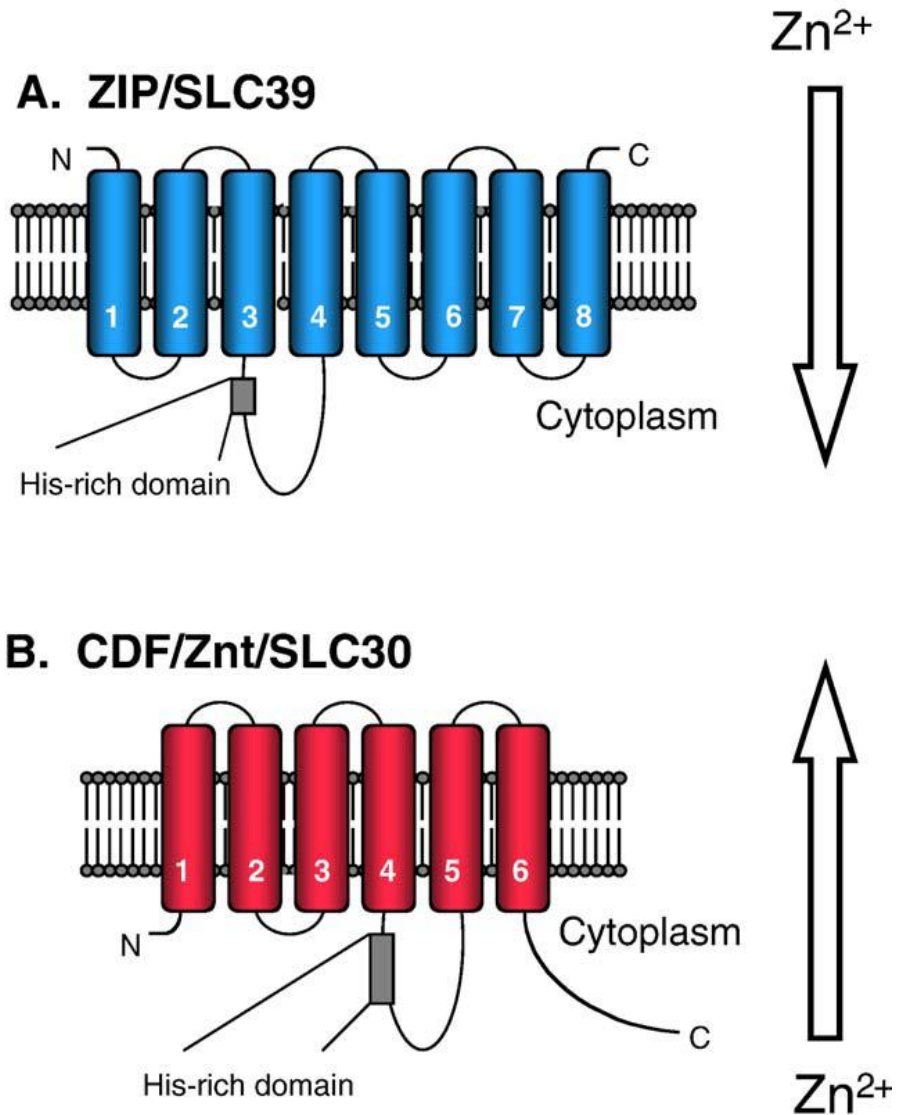


Cu sensors



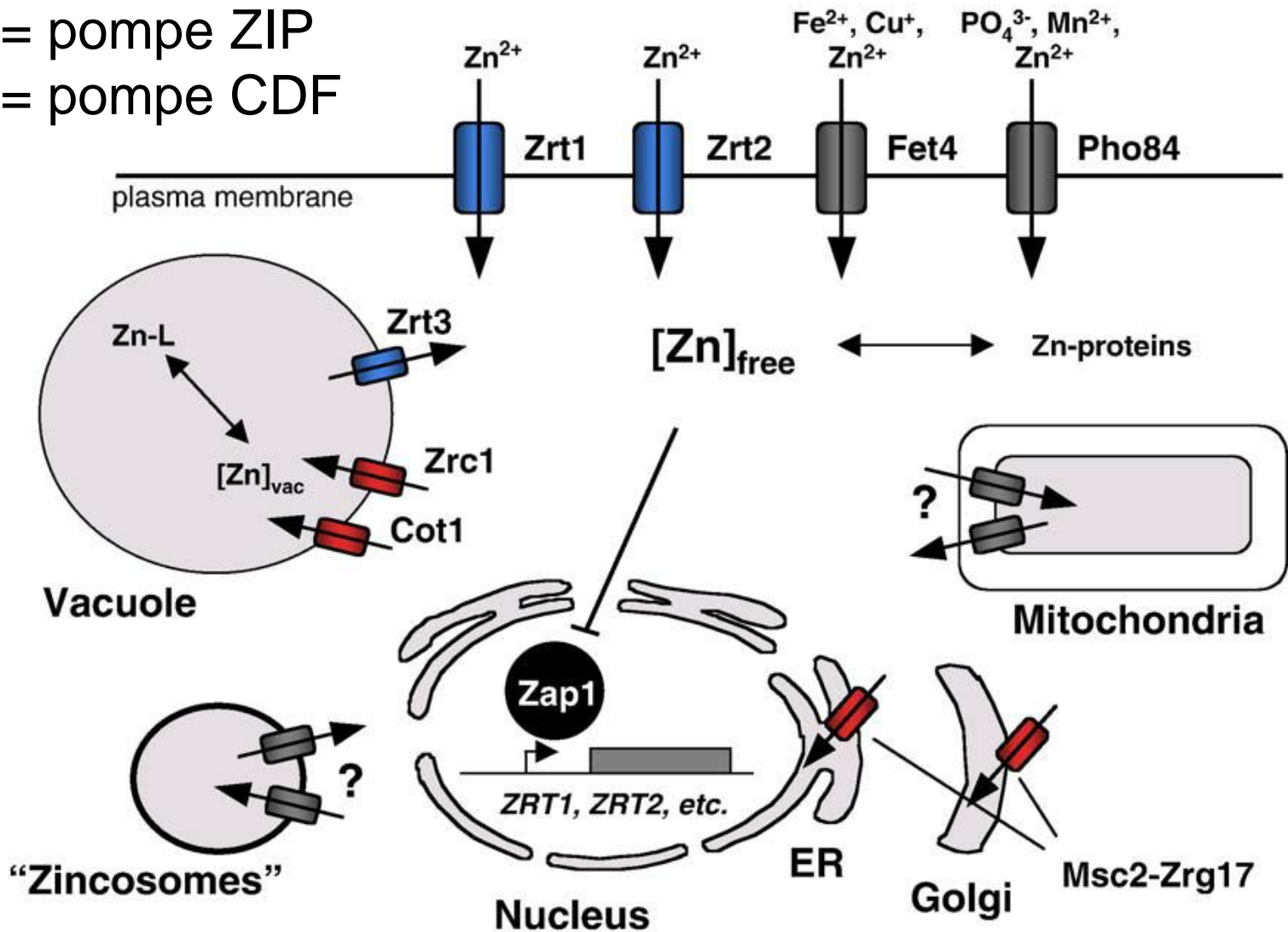
CueR transcription factor (from *E. Coli*)

zinc homeostasis in eukariotic cells

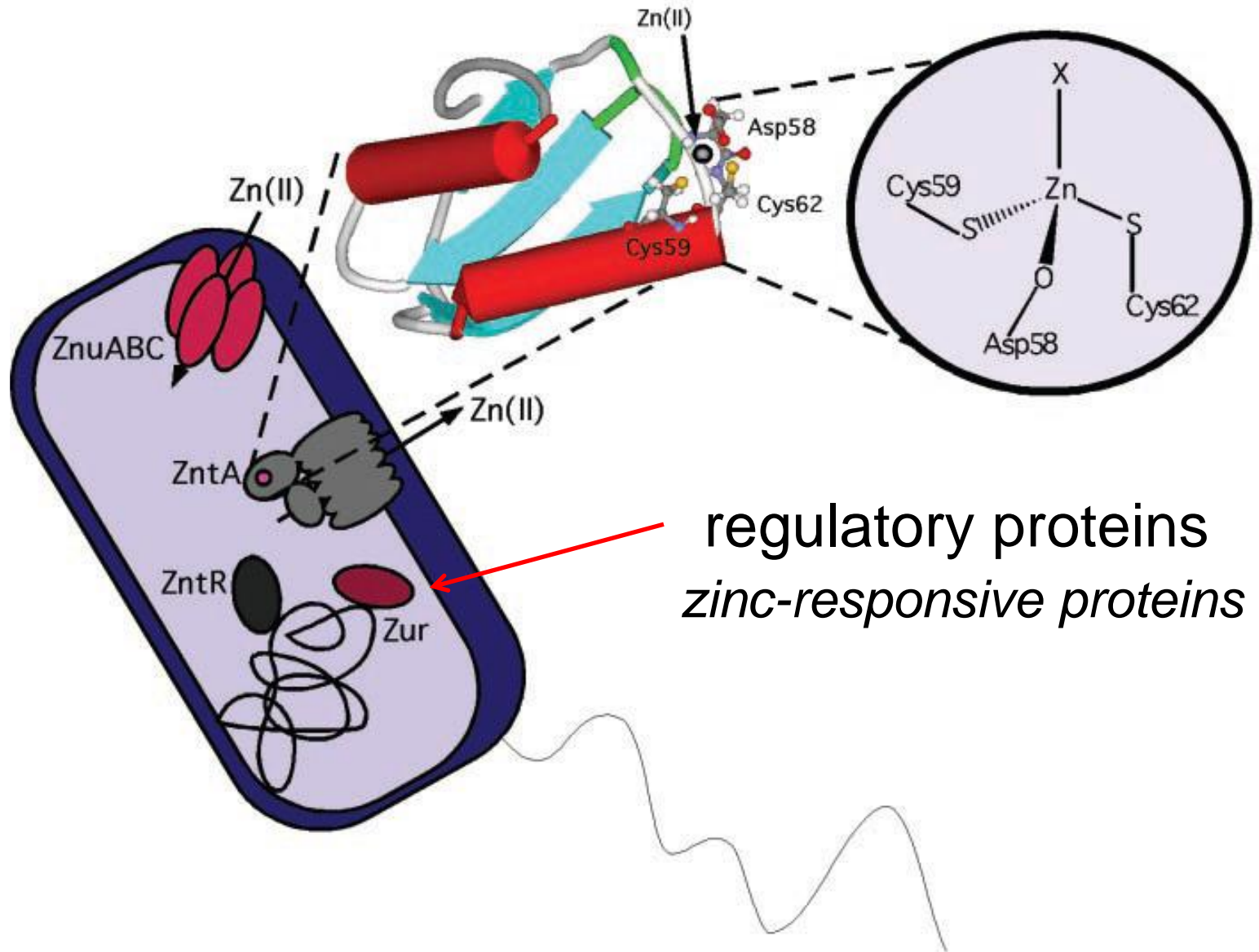


zinc homeostasis in eukaryotic cells

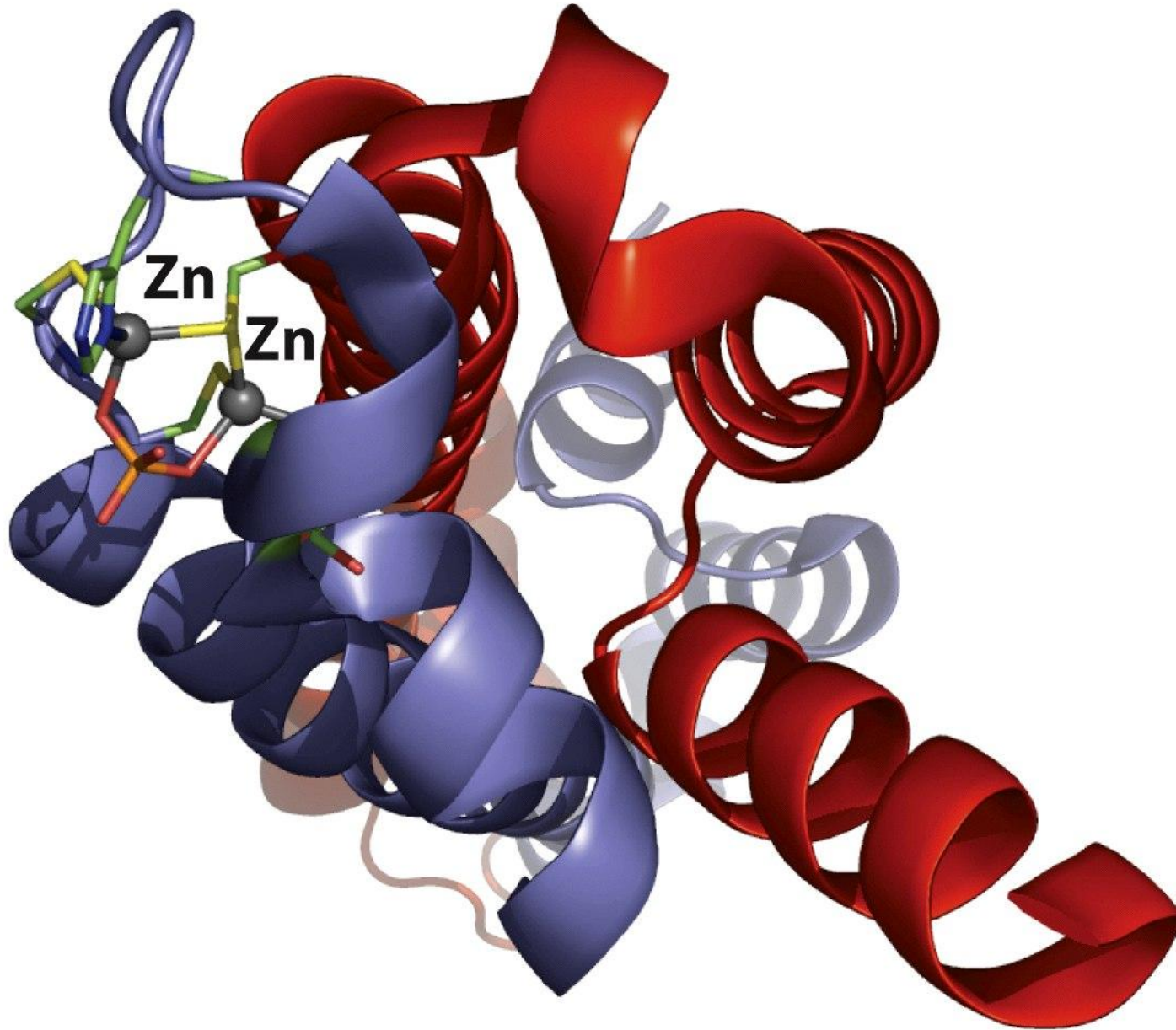
- = pompe ZIP
- = pompe CDF



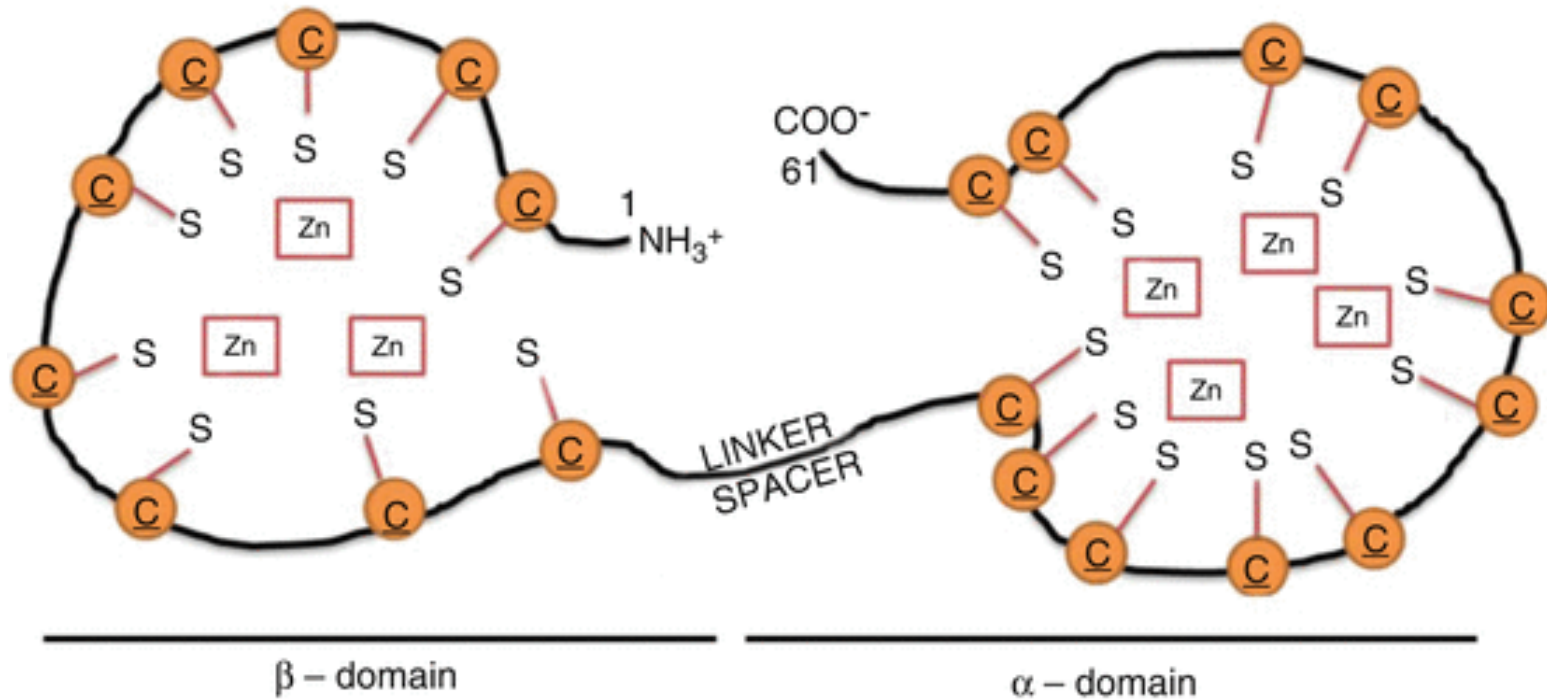
zinc homeostasis in bacteria



ZntR transcription factor

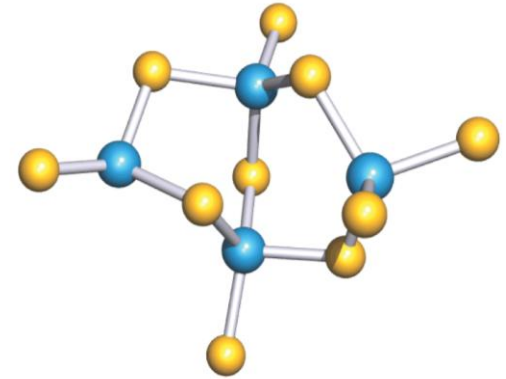
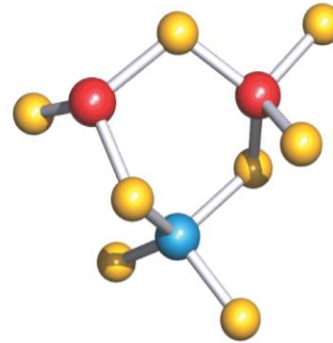
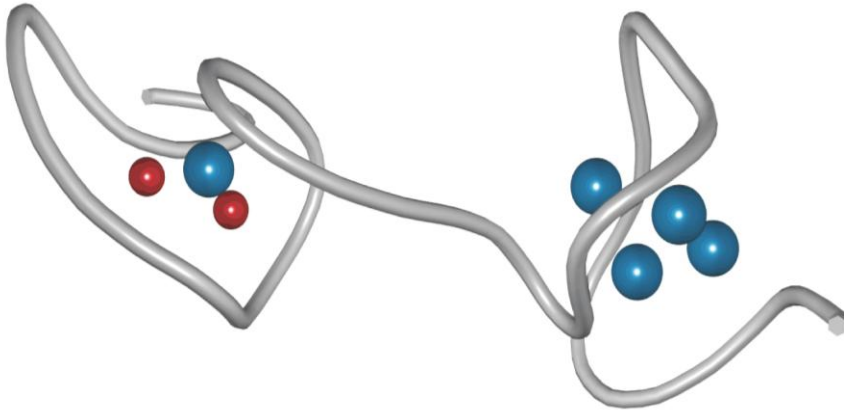


Metallothioneins



6 kDa,
ca. 60 a.a.
up to 30% cys
large homology among species
evolutionary well conserved

Metallothioneins



What is the evolutionary function of metallothioneins?

multifunctional proteins (?):

- Detoxification/protection from xenobiotic metals (Cd, Hg)?
- Temporary storage of Zn and Cu?
- *Chaperones*?
- Protective role towards ROS?