

# Il lato inorganico della vita

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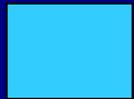


# Elementi di importanza biologica

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	Ln	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	Th	Pa	U												



**Elementi abbondanti**



**Elementi in tracce, importanti per batteri, piante e animali**



**Elementi in tracce, potenzialmente importanti per alcune specie**



**Elementi tossici**



**Elementi benefici**

# Abbondanza e funzione biologica di alcuni metalli nell'uomo

ELEMENT	QUANT. (ppm)	ELEMENT	QUANT. (ppm)	ELEMENT	QUANT. (ppm)
Na	$2.6 \times 10^3$	Ca	$1.4 \times 10^4$	Zn	20-30
K	$2.2 \times 10^3$	Fe	60 - 70	Cu	1.10
Mg	$4.0 \times 10^2$	Mn	0.2 - 0.3	Ni	0.04

Data refers to a healthy human adult of 70 Kg weight

**Na, K**

Charge carrier  
Osmotic balance

**Mg, Ca**

Structural,  
Signalling

**Fe, Zn, Cu, Mn, Ni**

Structural,  
Catalysis & Electron transfer

# Dal ferro al rame

Età della terra:  $4.6 \times 10^9$  anni

Le prime forma di vita comparvero dopo circa  $10^9$  anni

I processi di fotosintesi esistono da  $3.5 \times 10^9$  anni

L'atmosfera riducente esistente inizialmente (e la presenza di  $H_2S$ ) ha favorito la presenza di Cu come  $Cu_2S$ , pochissimo solubile.

L'ossidazione dell'atmosfera trasformò il rame nella sua forma più solubile, Cu(II).



Cu

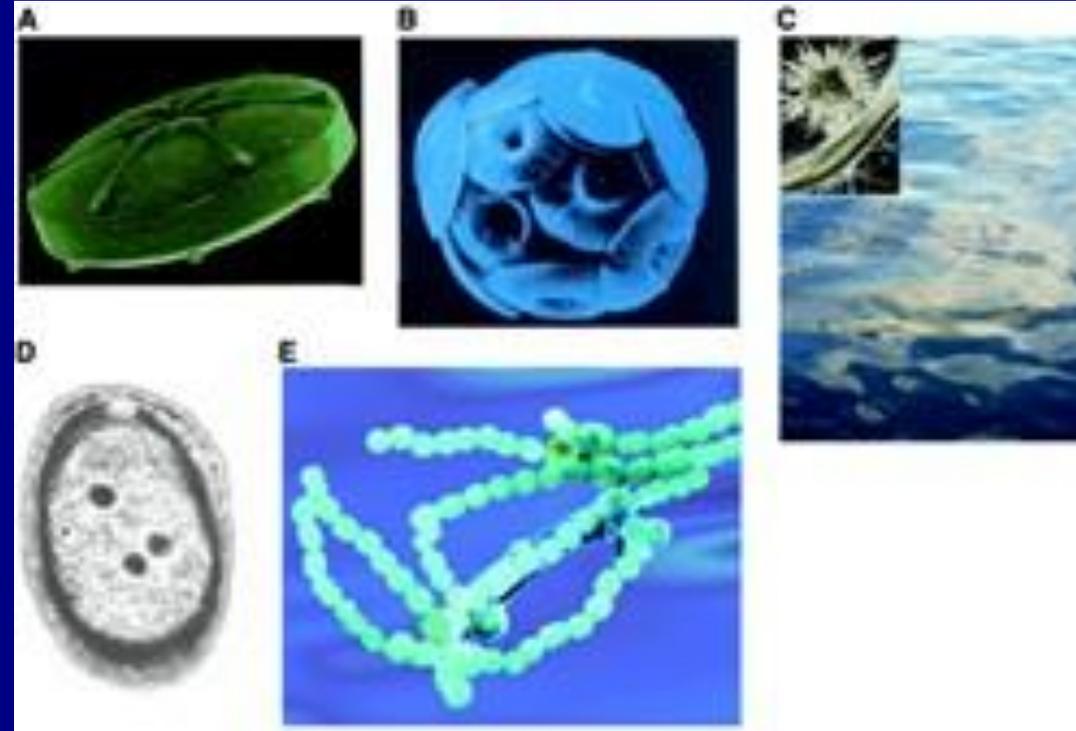
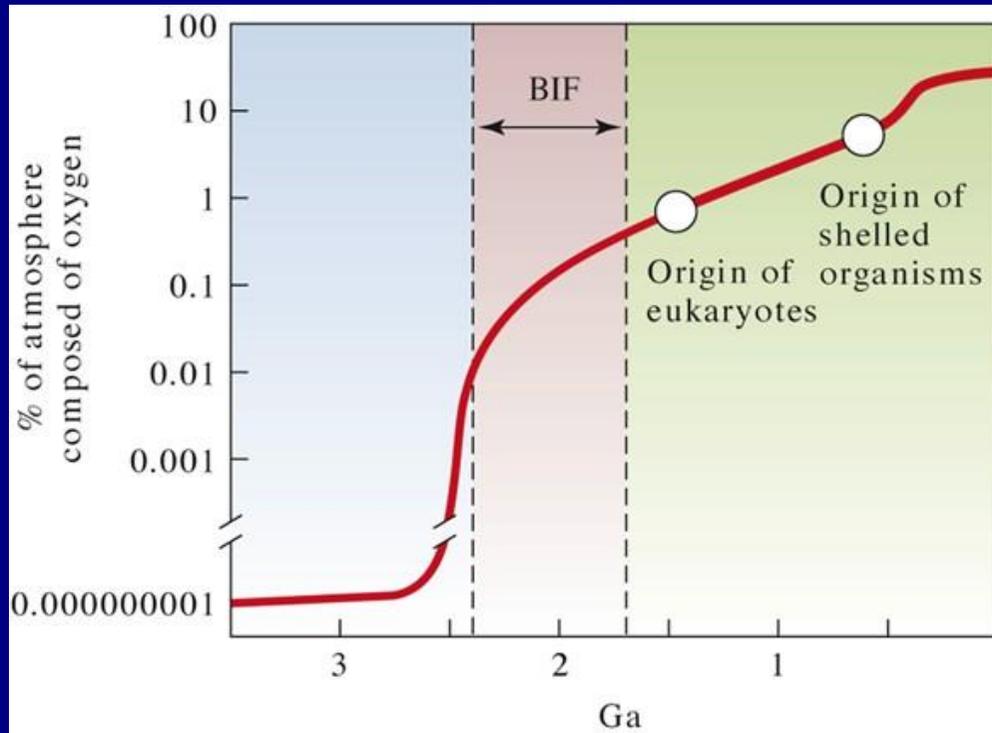


Al contrario l'ossidazione di Fe(II) ad Fe(III) ridusse la biodisponibilità del ferro.

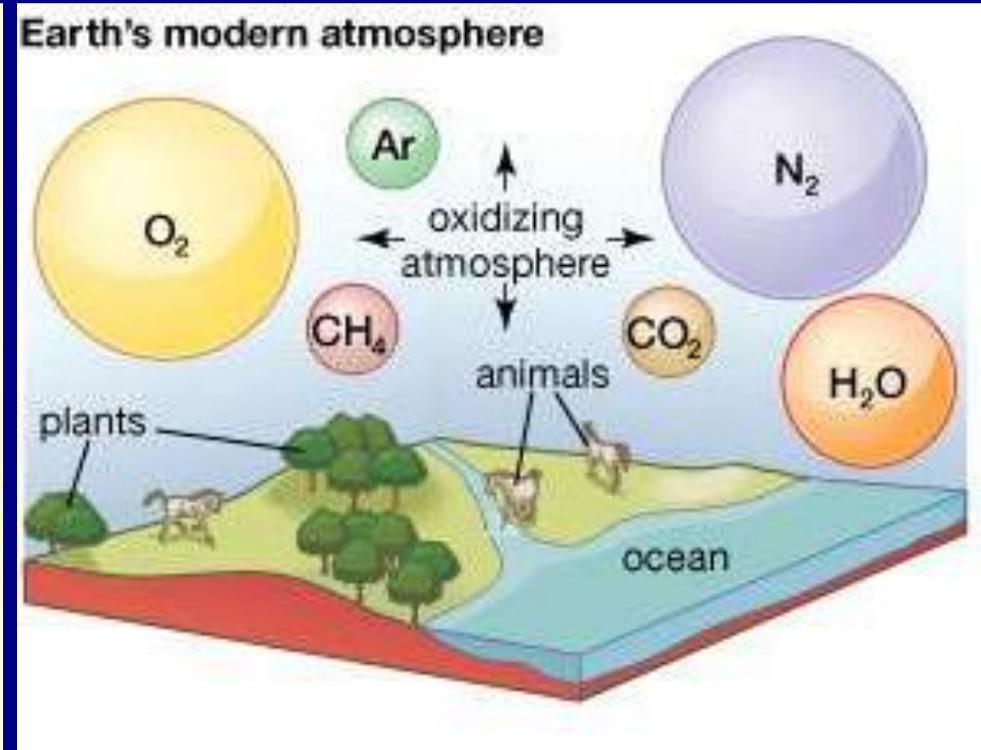
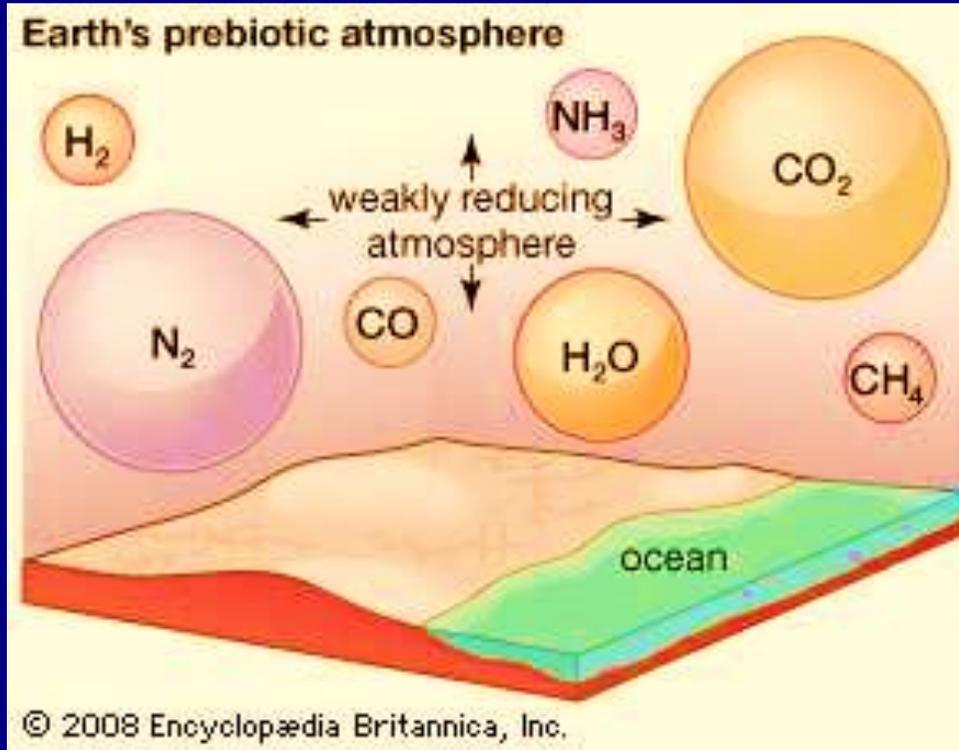
Fe



# Grande evento ossidativo



# Grande evento ossidativo



Fe



Cu

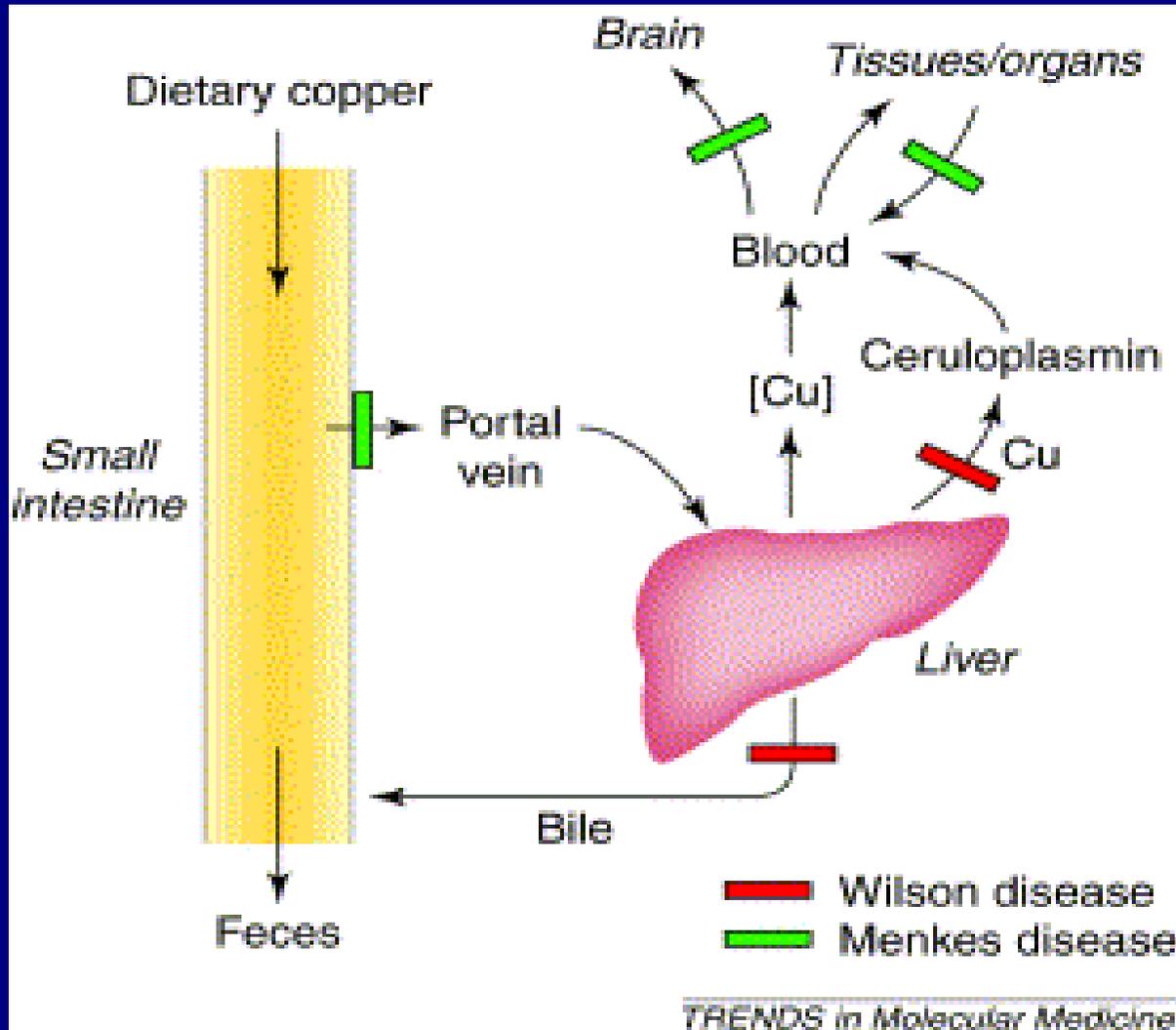
# Dal ferro al rame

**Alcuni aspetti del comportamento biologico del Cu indicano che la sua assunzione negli esseri viventi avvenne dopo la comparsa dell'O<sub>2</sub> atmosferico:**

- non sembrano esistere proteine di Cu negli organismi più primitivi (*archaea*) anaerobici
- in tutte le reazioni catalizzate da enzimi contenenti Cu, l'ossigeno agisce da substrato o come accettore di elettroni
- la tossicità di Cu per alcuni organismi inferiori (alghe e alcuni batteri) e lo stretto intervallo di concentrazione metabolica per molte specie (compreso l'uomo) potrebbe derivare da una incorporazione biochimica tardiva di questo elemento.

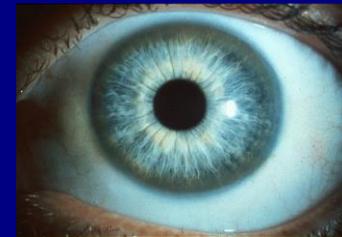
# Assorbimento e distribuzione del rame

## Sindrome di Menkes



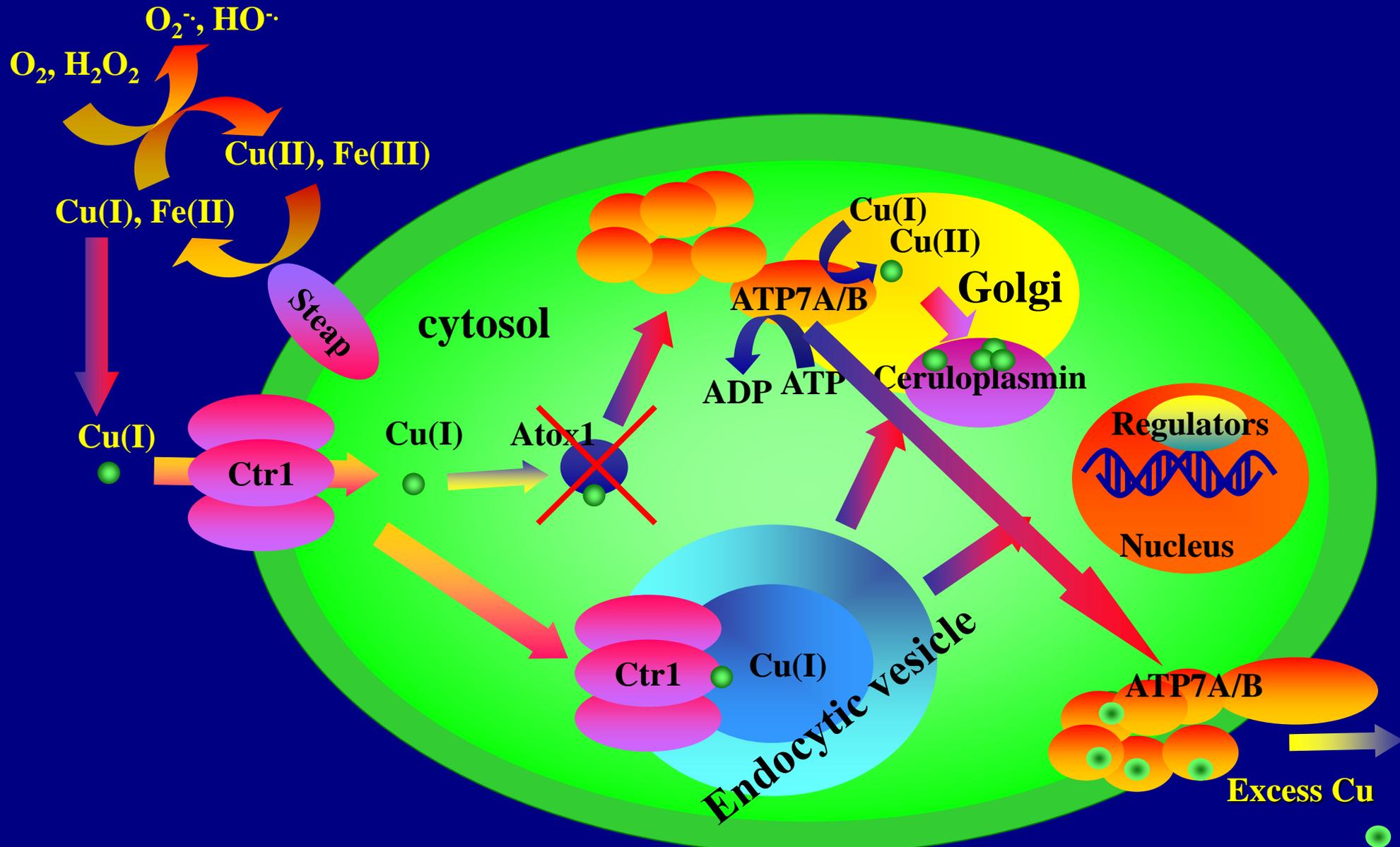
**Kinky hair**

## Malattia di Wilson



**Kayser-Fleischer ring**

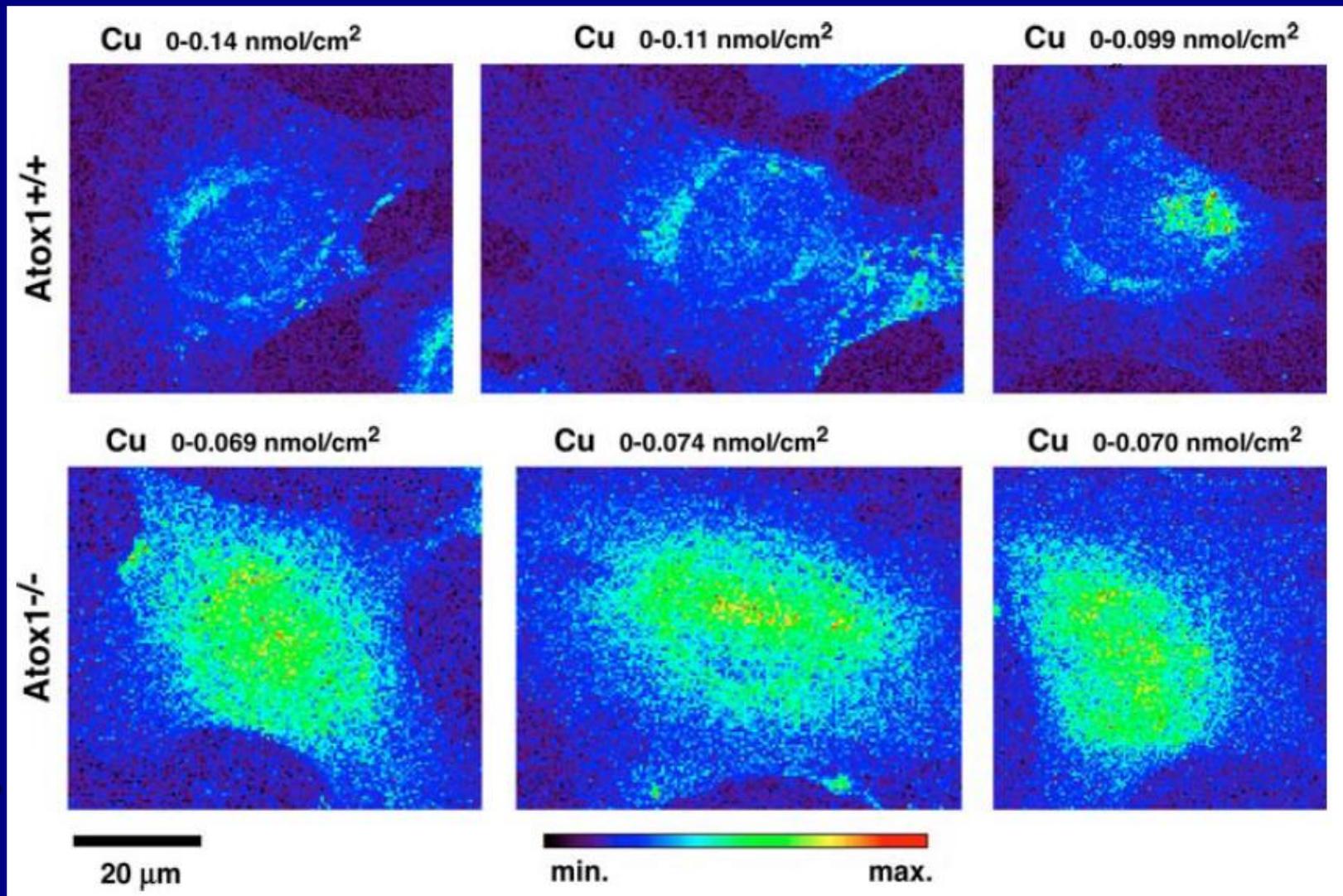
# Trasporto del rame in una cellula umana



# Distribuzione del rame in assenza di Atox1

**Wild-type  
(perinuclear  
localization)**

**Atox1-  
deficient  
(no compart-  
mentalization,  
no efflux)**



# La necessità di un *chaperone* del rame

**TOTAL [Cu]**                      **70 X 10<sup>-6</sup> M in yeast**

**FREE [Cu]**                      **less than 10<sup>-18</sup> M in an unstressed cell.**  
**For comparison one free copper ion**  
**corresponds to a [Cu]<sub>free</sub> of 10<sup>-10</sup> M**

**There is less than one free copper atom per cell!**

ATPase Atox1

ATPase Atox1

90°

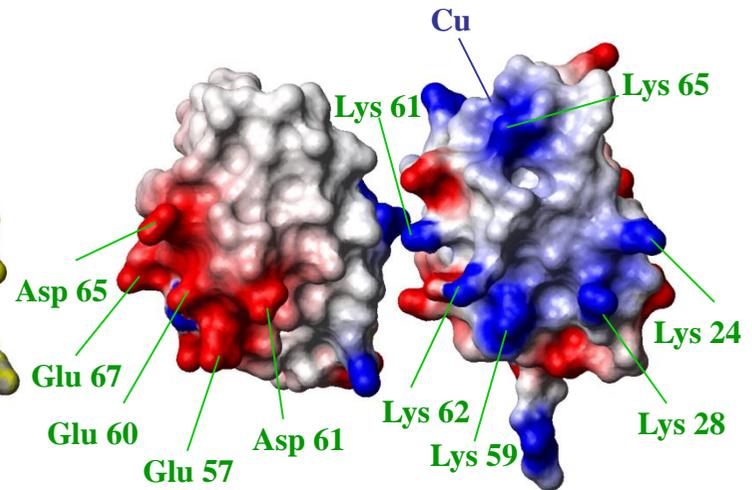
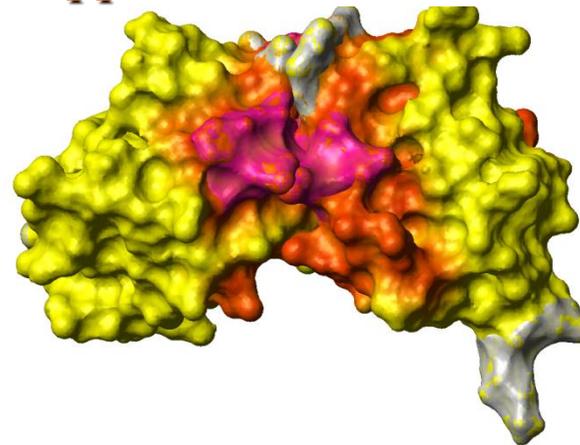
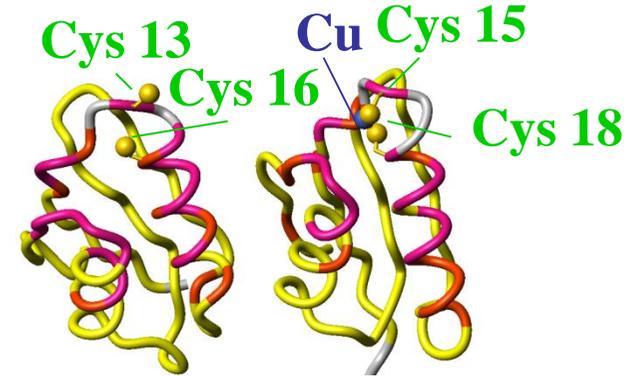
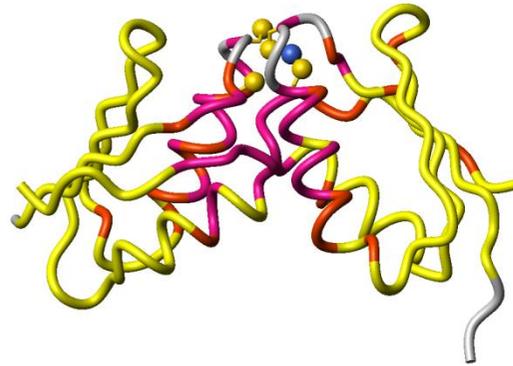
90°

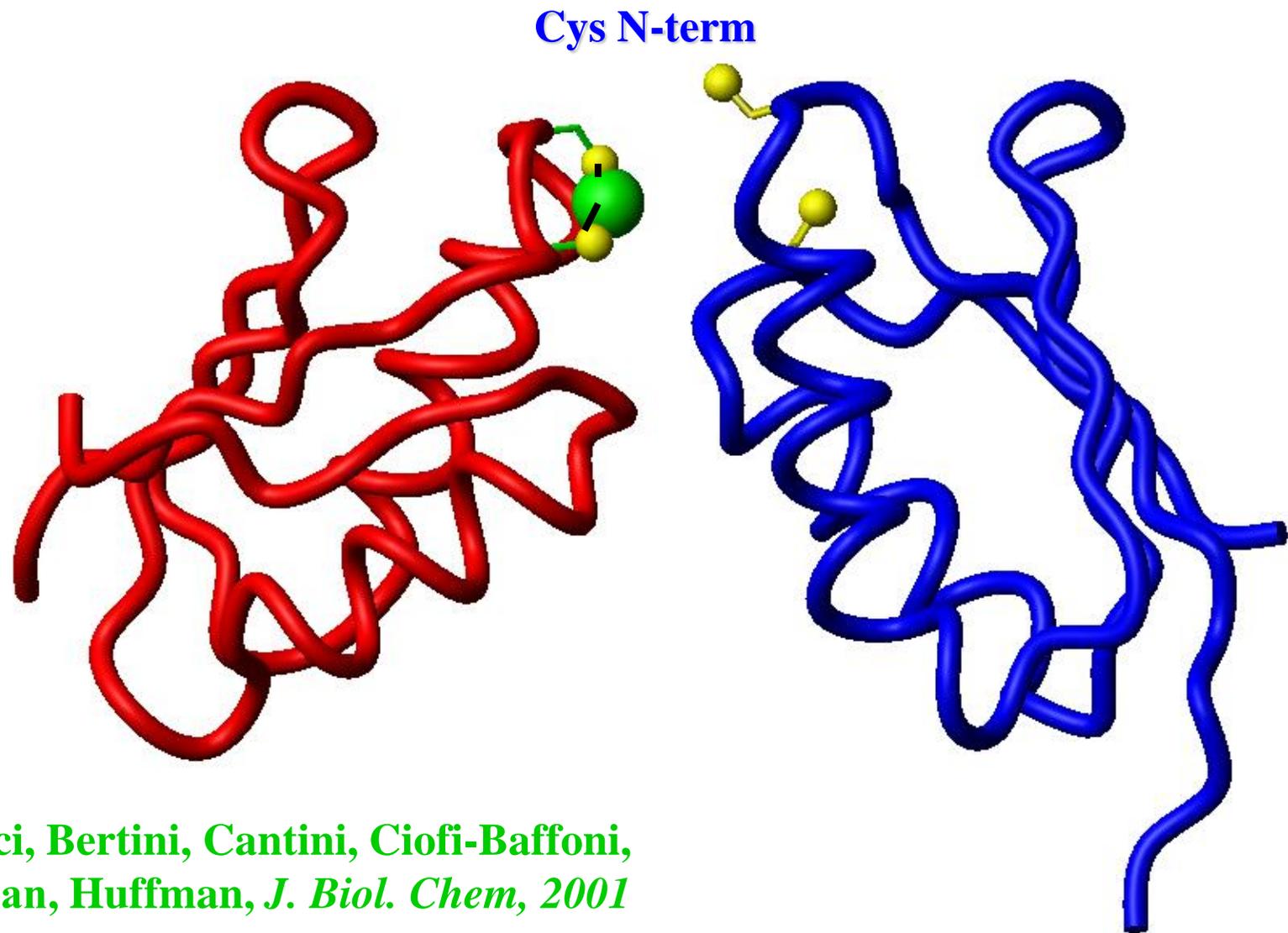
$\Delta_{\text{avg}}(\text{HN}) > 0.1 \text{ ppm}$

$0.04 \text{ ppm} < \Delta_{\text{avg}}(\text{HN}) < 0.1 \text{ ppm}$

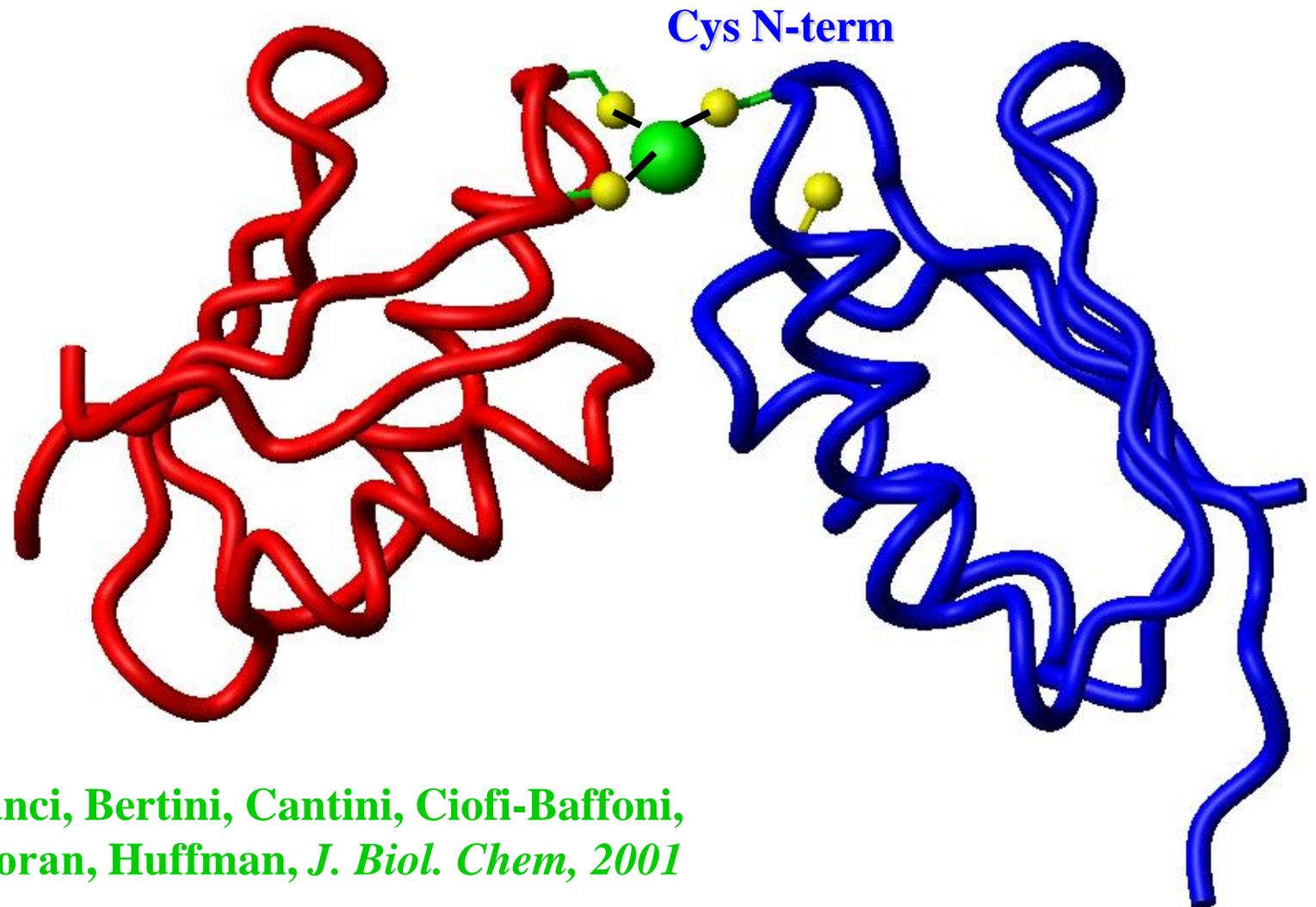
$\Delta_{\text{avg}}(\text{HN}) < 0.04 \text{ ppm}$

Not observed

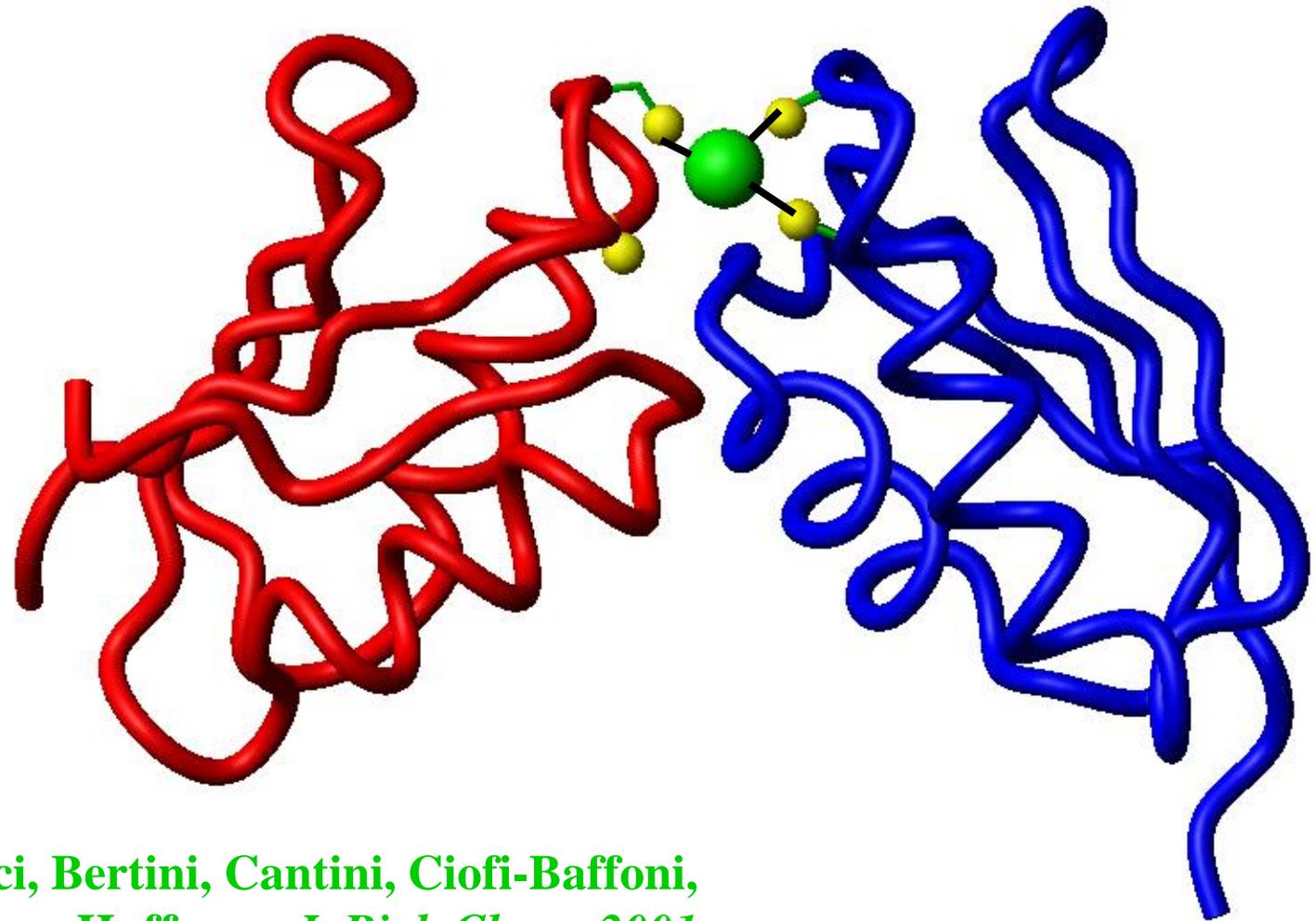




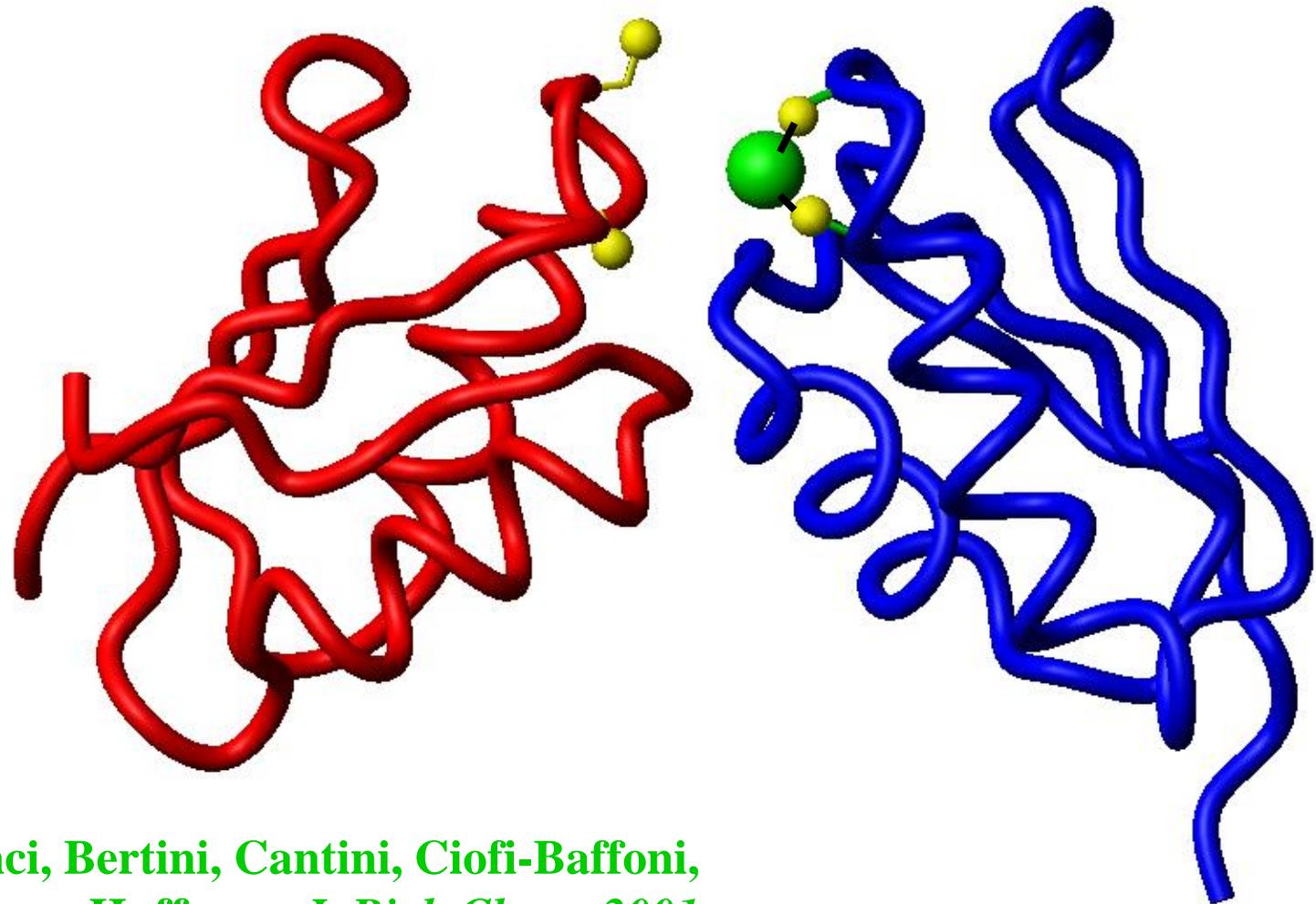
Arnesano, Banci, Bertini, Cantini, Ciofi-Baffoni,  
O'Halloran, Huffman, *J. Biol. Chem.*, 2001



Arnesano, Banci, Bertini, Cantini, Ciofi-Baffoni,  
O'Halloran, Huffman, *J. Biol. Chem.*, 2001

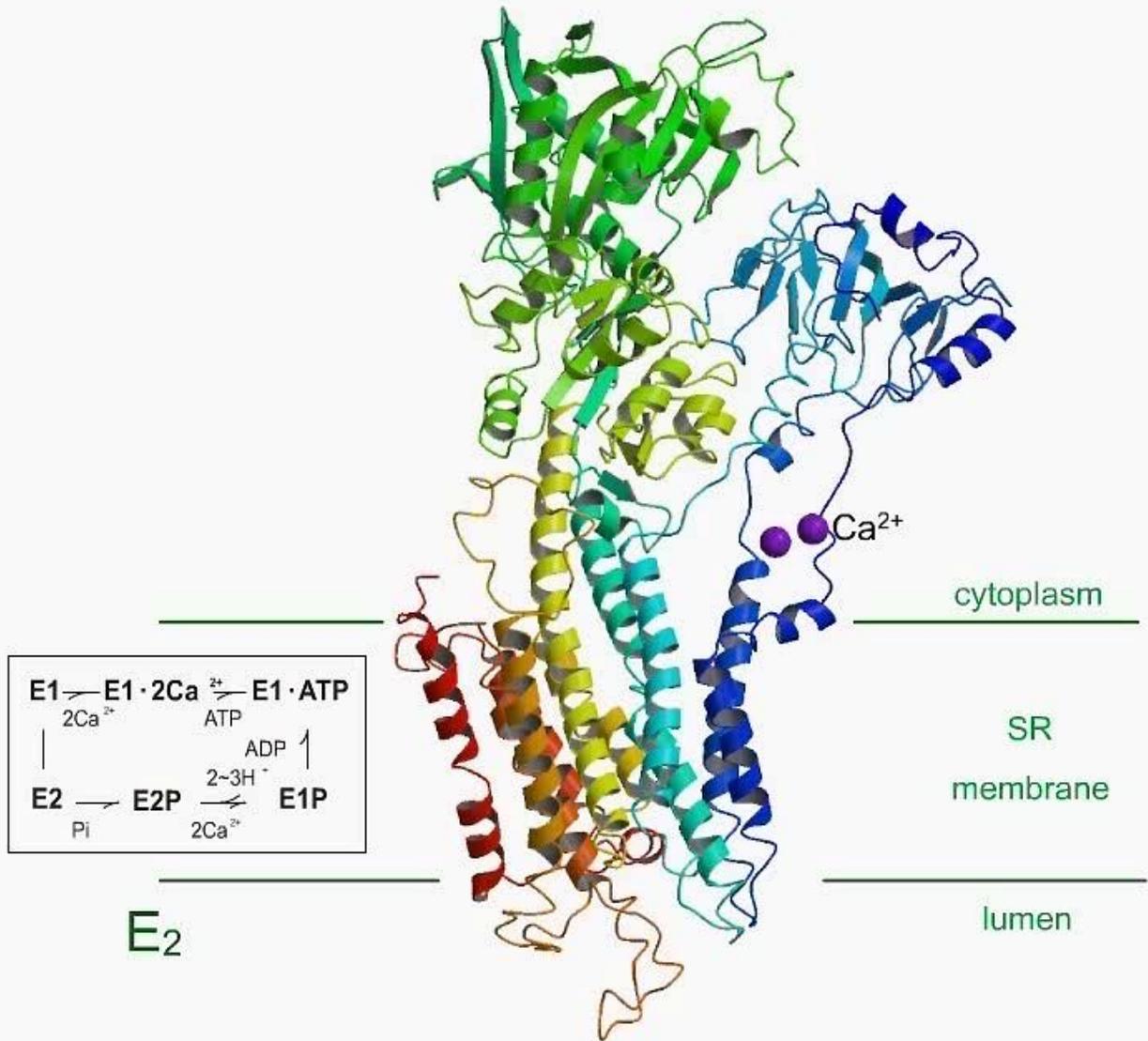


**Arnesano, Banci, Bertini, Cantini, Ciofi-Baffoni,  
O'Halloran, Huffman, *J. Biol. Chem.*, 2001**

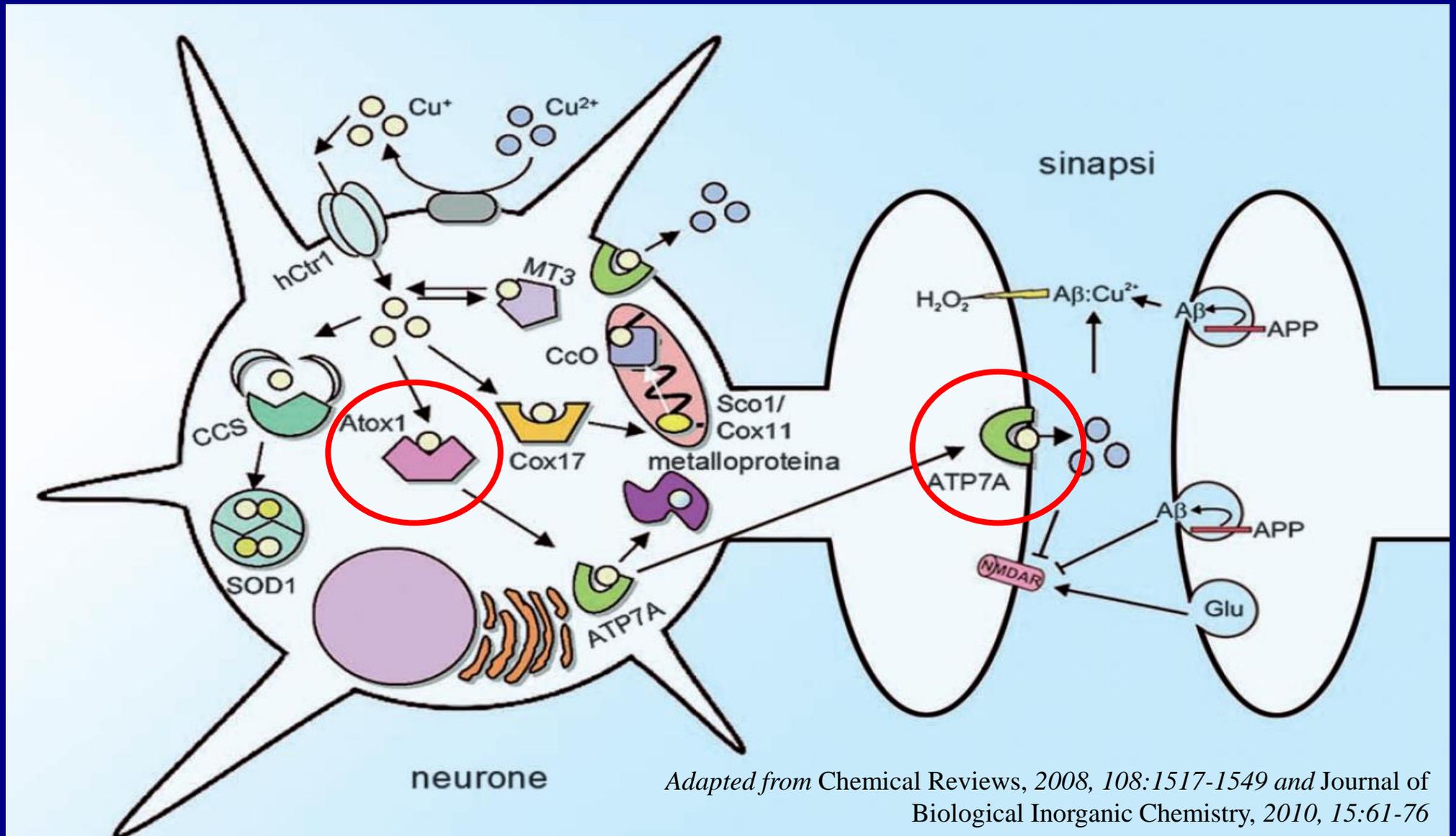


Arnesano, Banci, Bertini, Cantini, Ciofi-Baffoni,  
O'Halloran, Huffman, *J. Biol. Chem.*, 2001

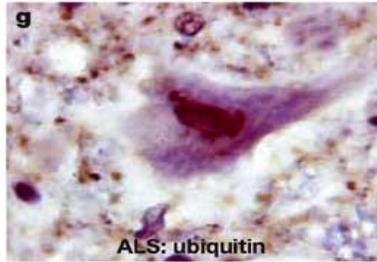




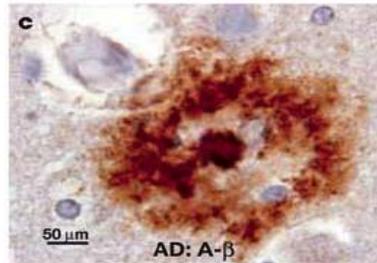
# Omeostasi del rame nei neuroni



# Neurodegenerazione



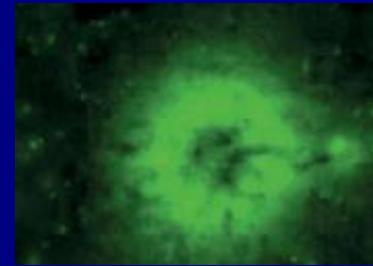
Sclerosi Laterale  
Amiotrofica



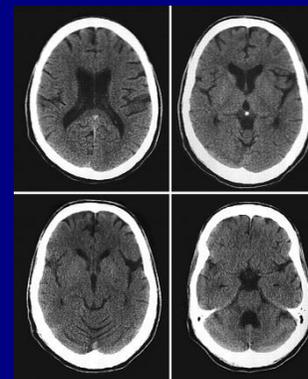
Alzheimer



Parkinson



Lo zinco è  
presente nelle  
placche amiloidi  
dell'Alzheimer



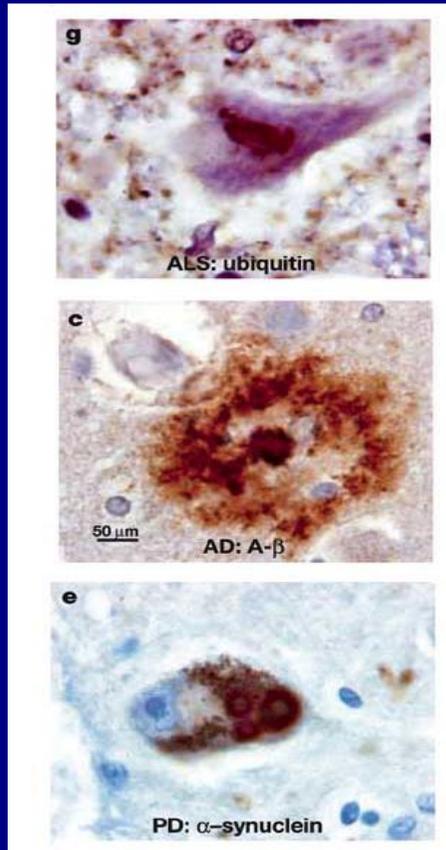
Il manganese  
causa una  
sindrome simile  
al Parkinson

Ross and Poirier, *Nature Med.* 2004

Frederickson, Koh, Bush, *Nat. Rev. Neurosci.* 2005

Lindquist et al., *Nat. Genet.* 2009

# Neurodegenerazione



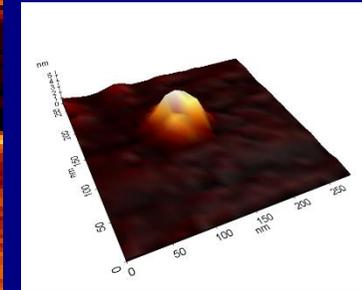
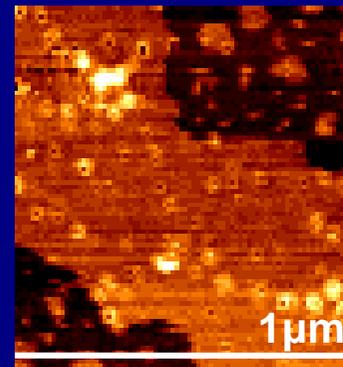
Sclerosi Laterale  
Amiotrofica

Alzheimer

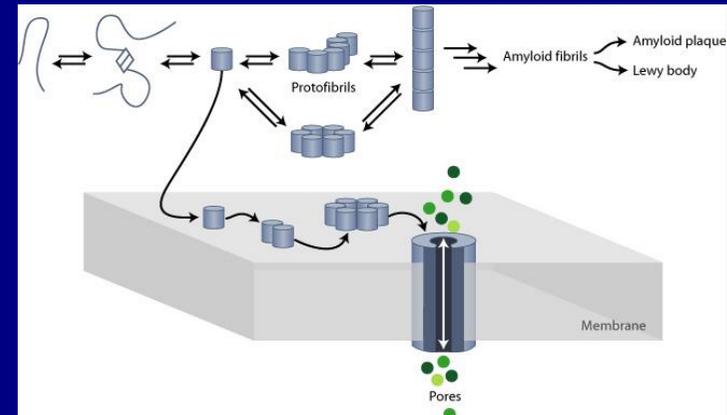
Parkinson

Ross and Poirier, *Nature Med.* 2004

## Fibrille amiloidi

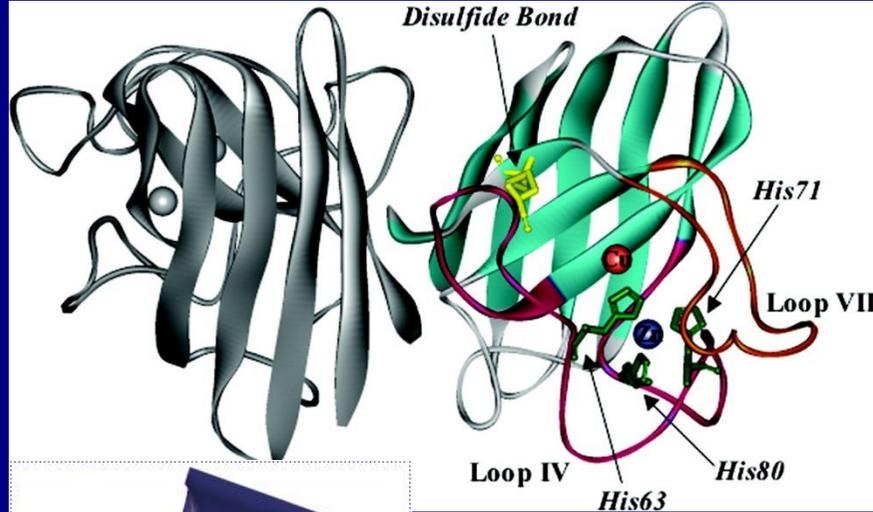


## Pori amiloidi

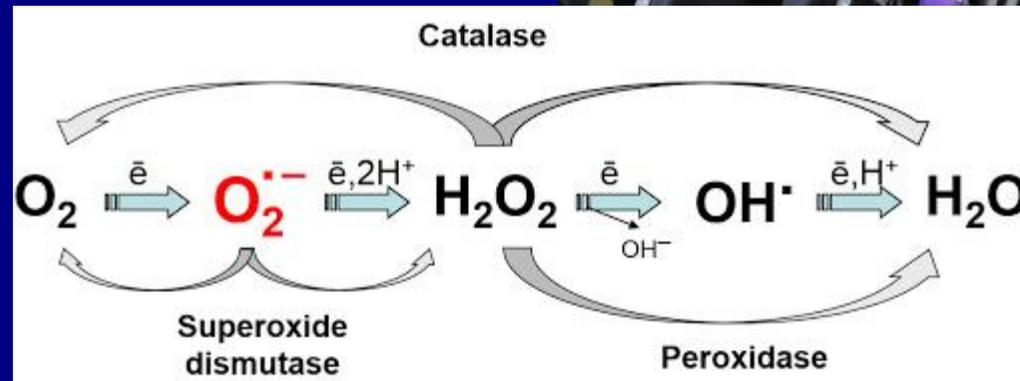


# Neurodegenerazione

Cu, Zn superossido dismutasi

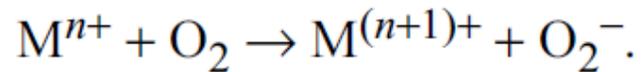


Sclerosi Laterale Amiotrofica

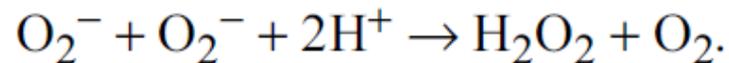


# Ioni metallici e stress ossidativo

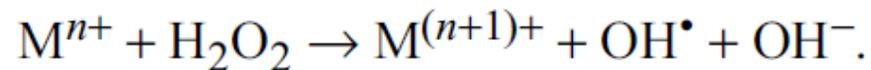
Reduced Fe(II)/Cu(I) reacts with molecular oxygen ( $O_2$ ) to generate the superoxide anion ( $O_2^-$ ):



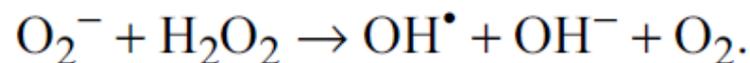
The  $O_2^-$  generated undergoes dismutation to  $H_2O_2$  and  $O_2$  either catalyzed by SOD or spontaneously:



The reaction of reduced metals with  $H_2O_2$  generates the highly reactive  $OH^\bullet$  by the Fenton reaction. Cu(I) catalyzes this reaction at a rate constant magnitude higher than that for Fe(II).<sup>3</sup>



Additionally, the Haber-Weiss reaction can form  $OH^\bullet$  in a reaction catalyzed by  $M^{(n+1)+}/M^{n+}$ :



CLASSIC DOUBLE FEATURE

# DR. JEKYLL AND MR. HYDE

FREDRIC MARCH  
MIRIAM HOPKINS  
ROSE HOBART

SPENCER TRACY  
INGRID BERGMAN  
LANA TURNER



1932 VERSION

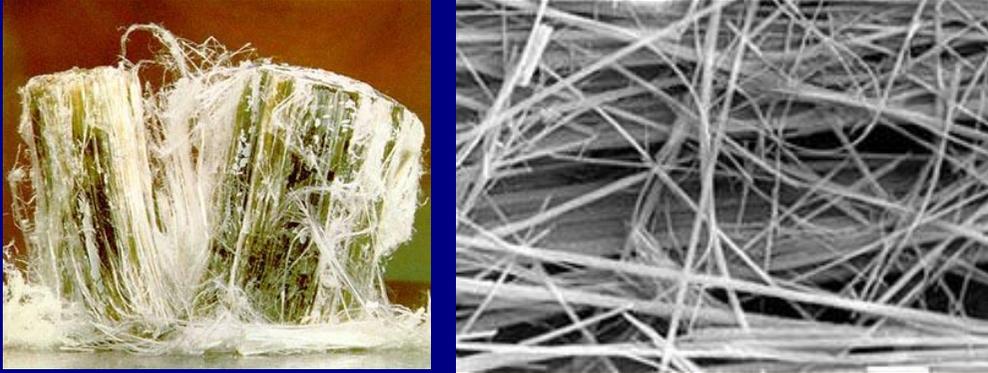


1941 VERSION

DVD  
VIDEO

TWO FEATURE FILMS ON ONE DISC

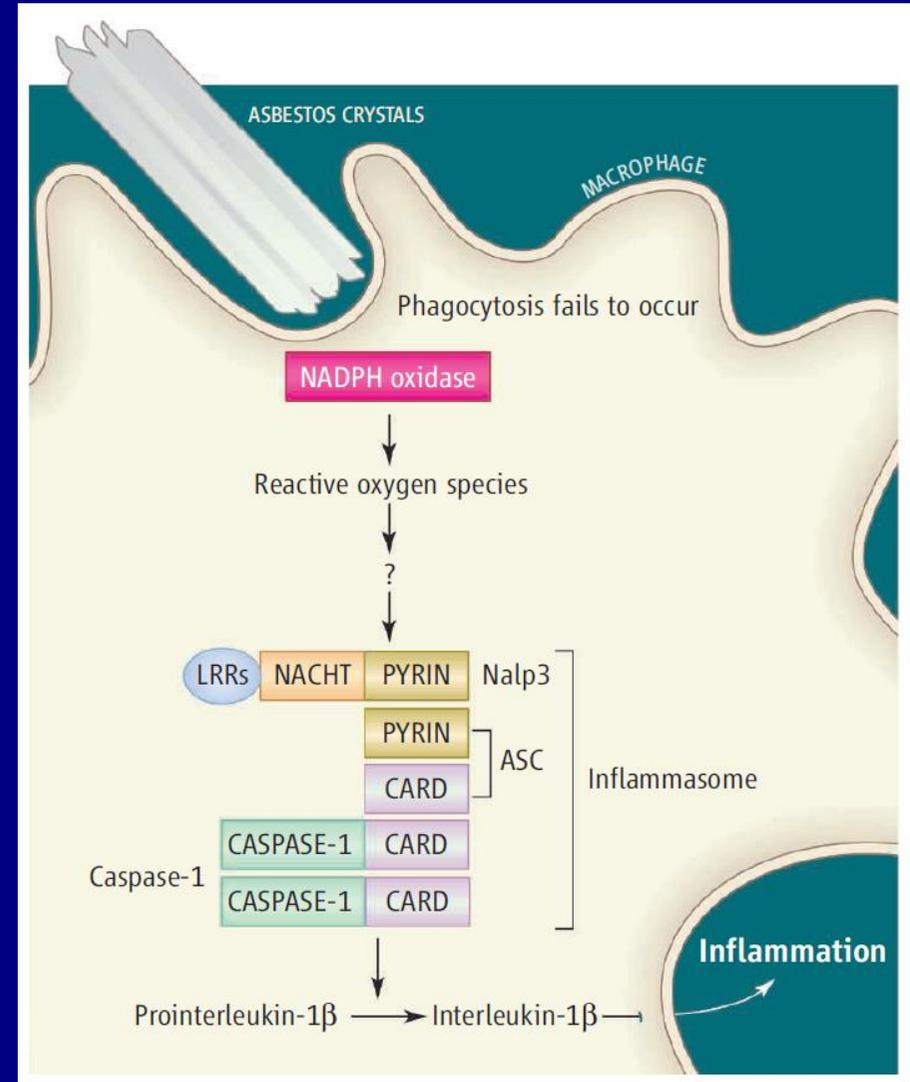
# L'amianto



Le dimensioni e la natura chimica delle fibre di amianto ne impediscono l'eliminazione da parte di cellule fagocitarie

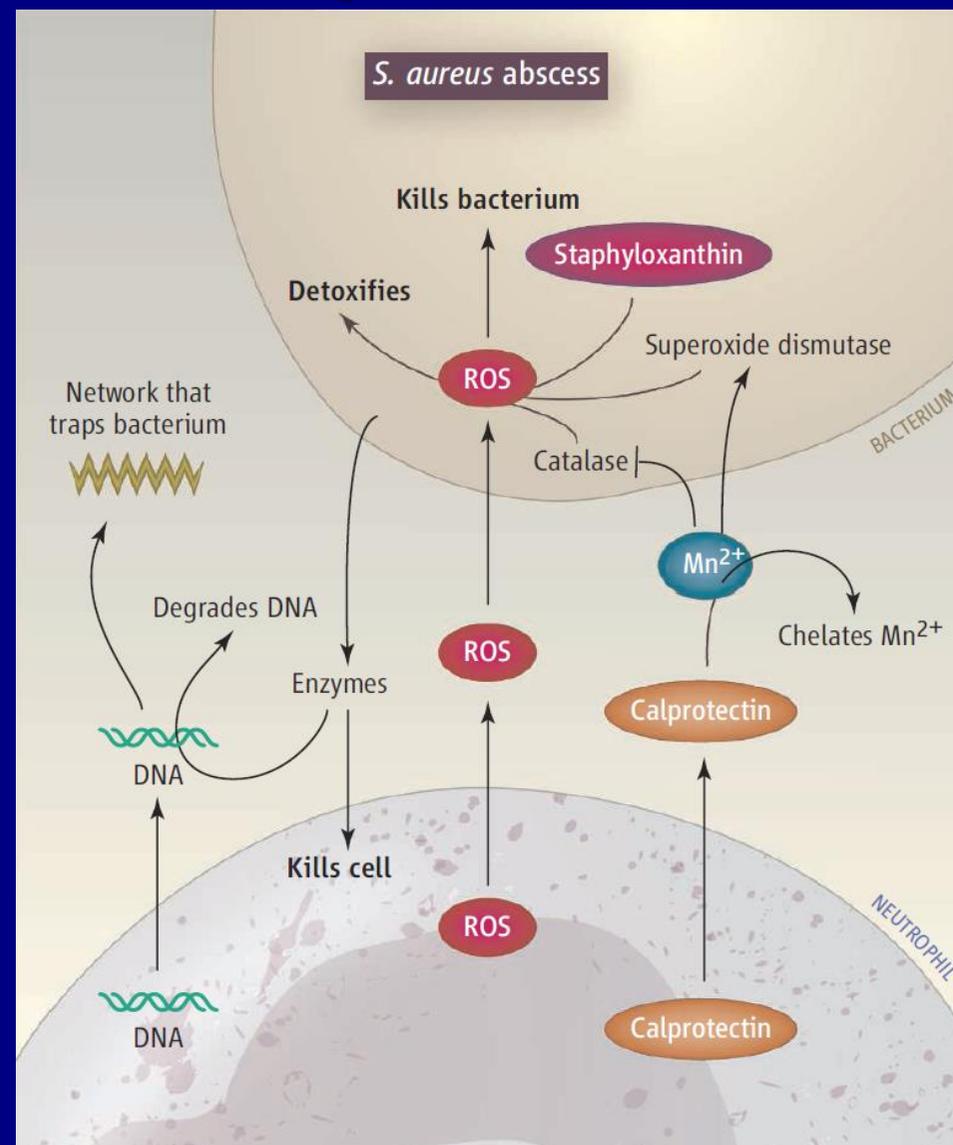
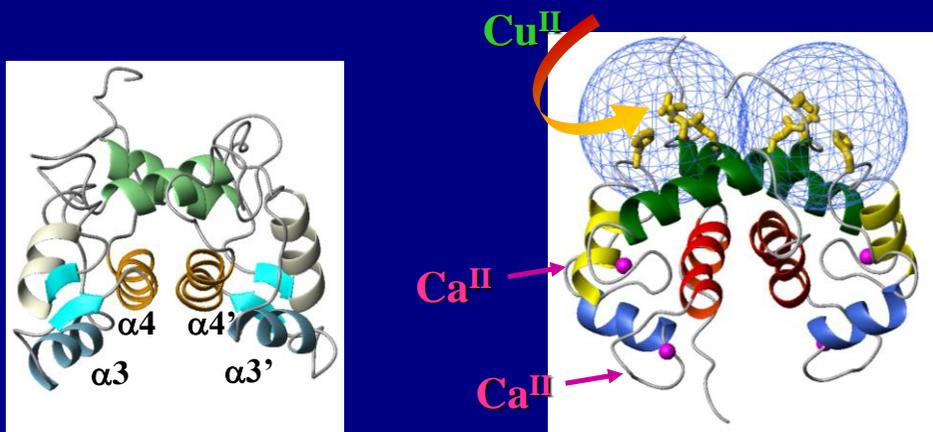
Gli ioni metallici sulla superficie delle fibre stimolano la produzione di specie radicaliche molto reattive che aumentano la tossicità dell'amianto

Antiossidanti e chelanti del ferro attenuano la tossicità di questo ed altri materiali inorganici nanostrutturati



# Sequestro dei metalli come terapia antimicrobica

Le infezioni da batteri patogeni resistenti agli antibiotici possono essere trattate con molecole chelanti sintetiche o di origine naturale

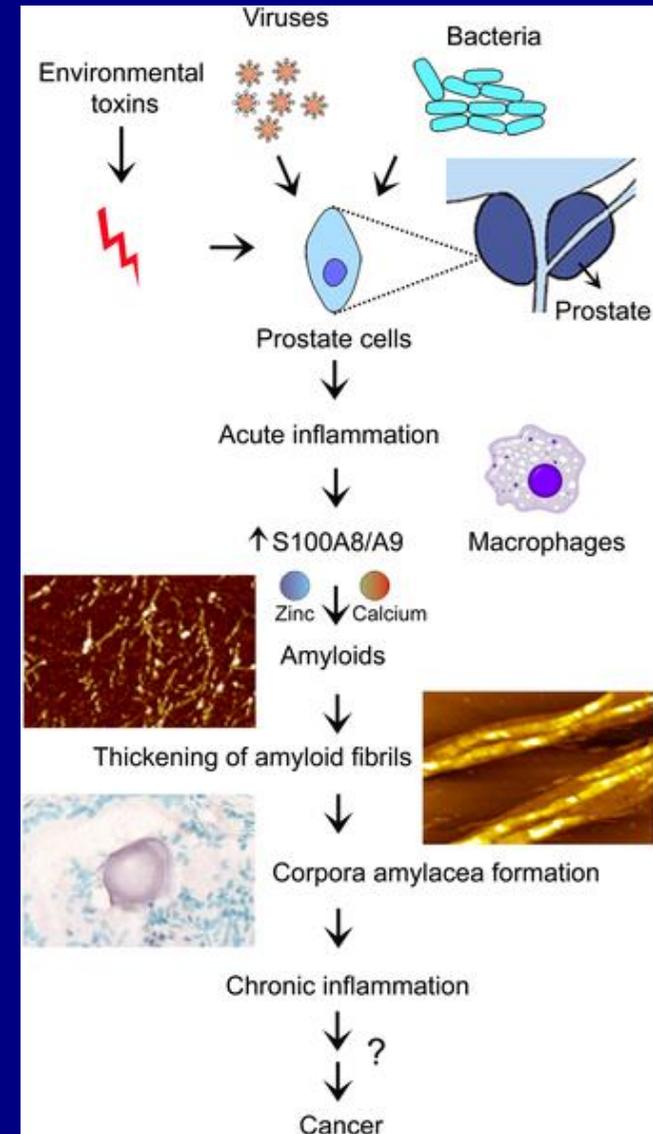


# Sequestro dei metalli come terapia antimicrobica

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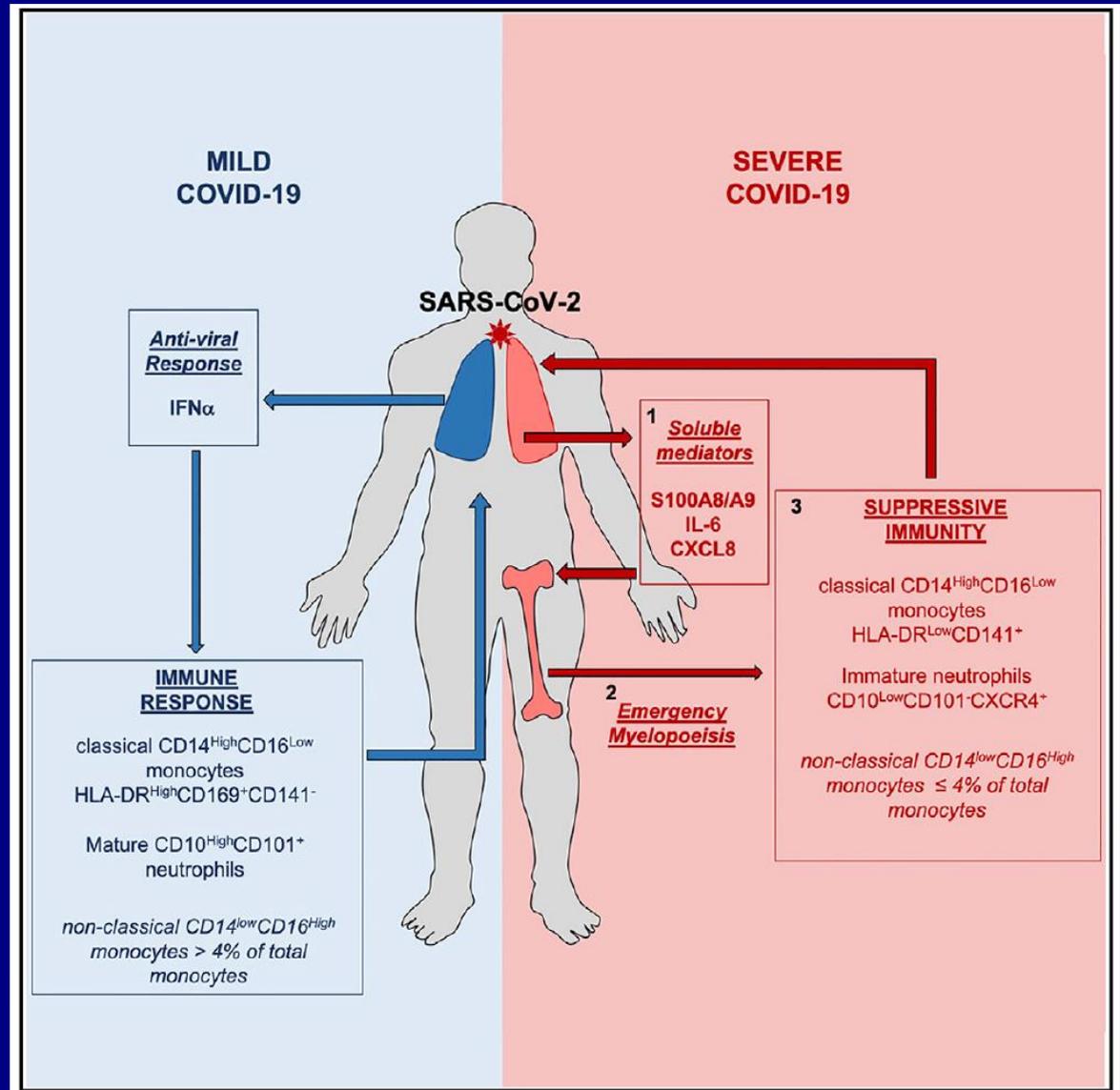
Arnesano et al., *Angew. Chem. Int. Ed. Engl.*, 2005



Morozova-Roche et al., *PLoS One* 2009

# Sequestro dei metalli come terapia antimicrobica

I livelli di calprotectina (S100A8/A9) in pazienti COVID-19 sono correlati alla gravità della malattia.



# Inattivazione del *Coronavirus* su una superficie di rame

*Human coronavirus 229E on copper*

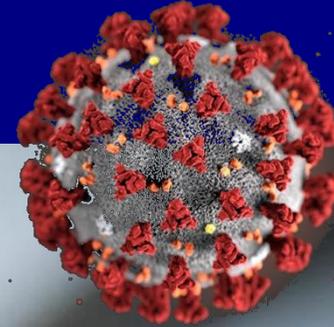
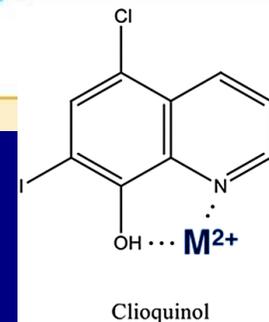
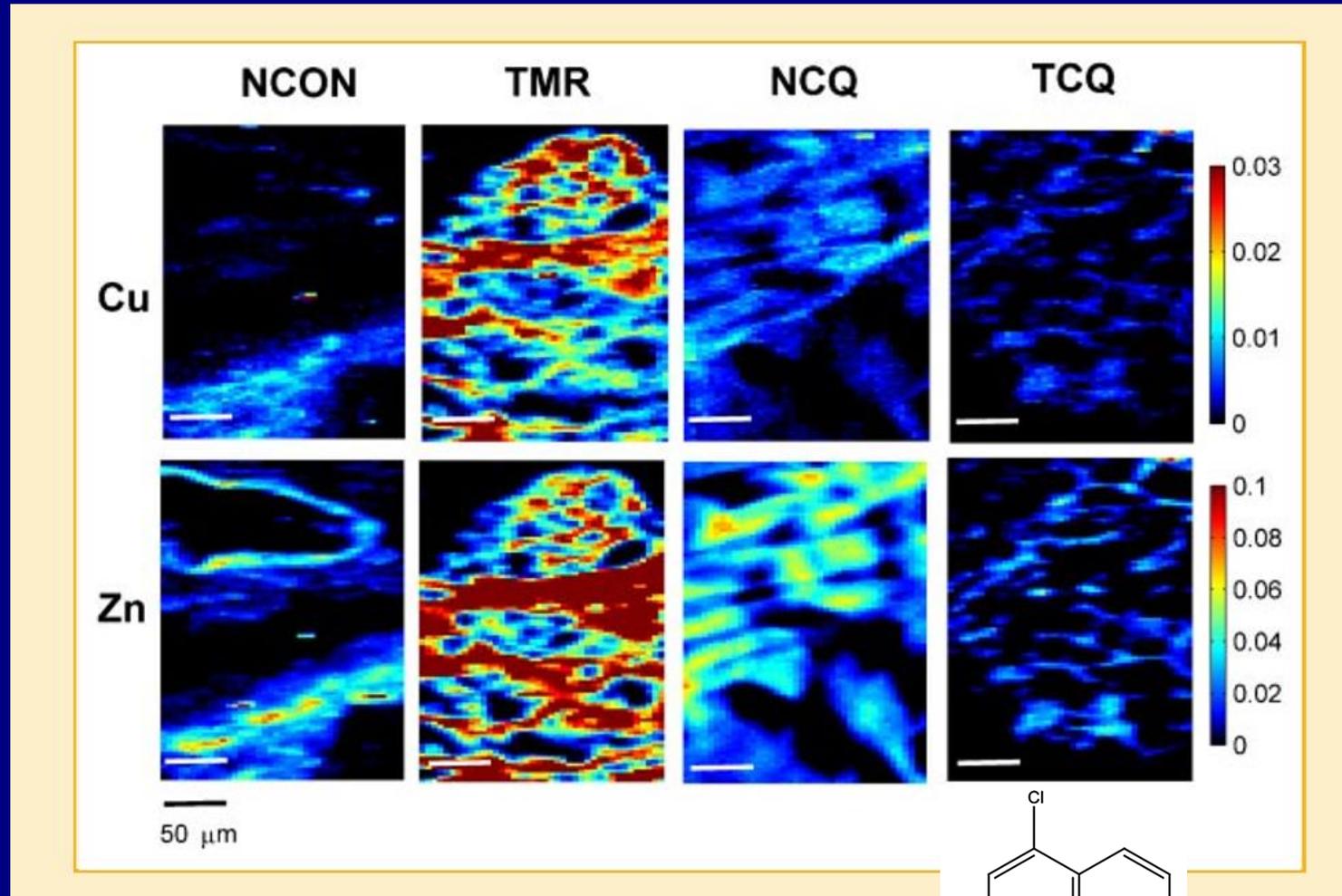
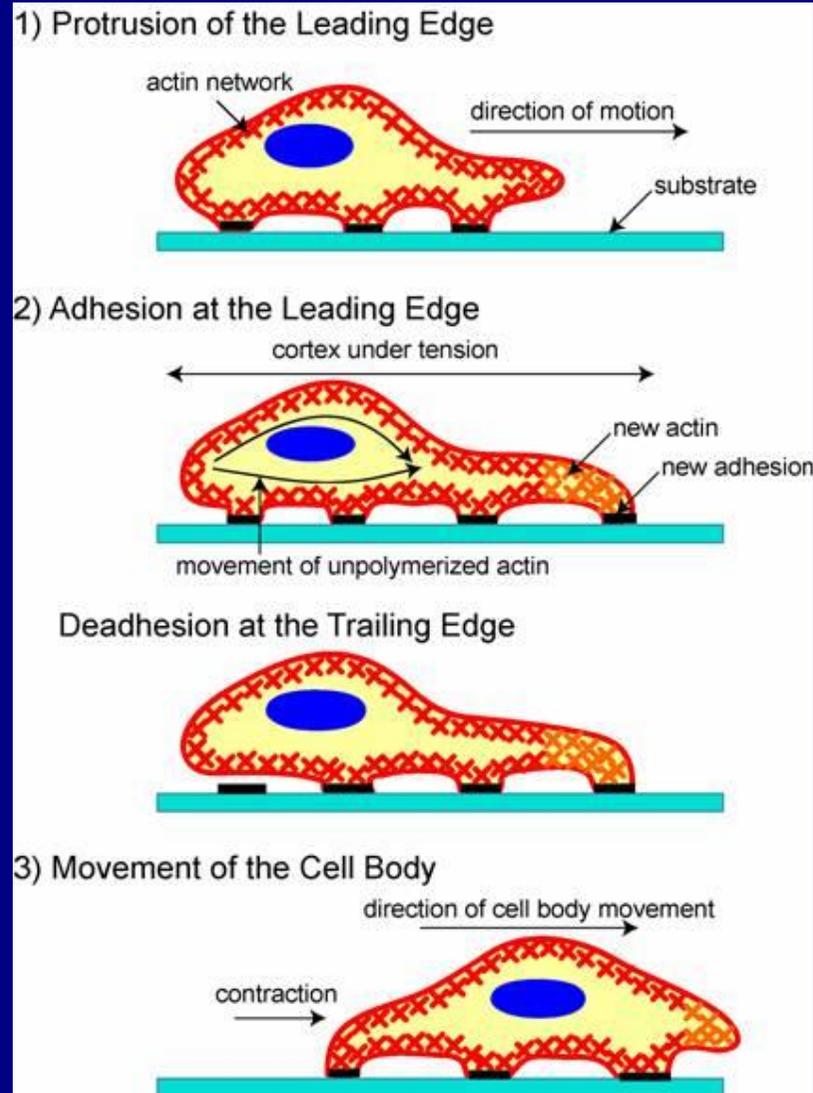


Photo by University of Southampton  
CDC / Alissa Eckert, MS; Dan Higgins, MAM

# Il rame si accumula nei tessuti tumorali



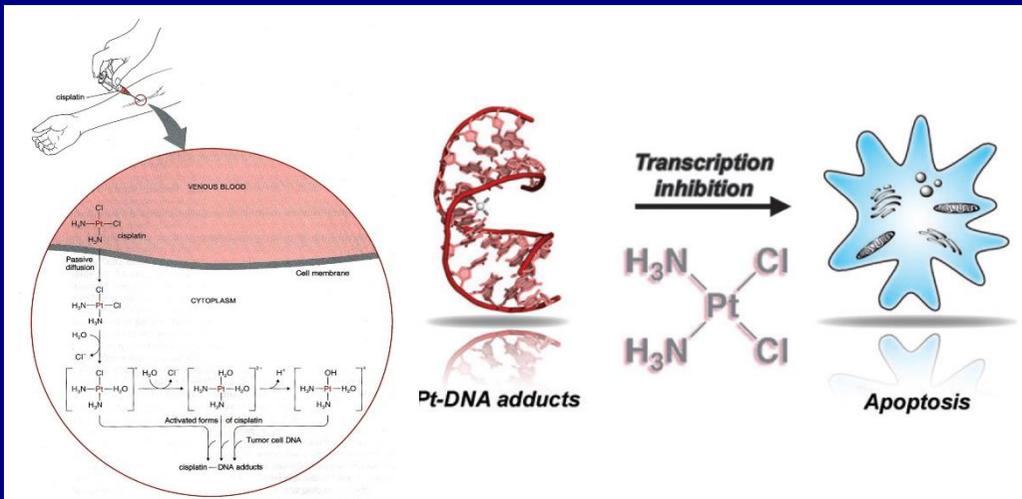
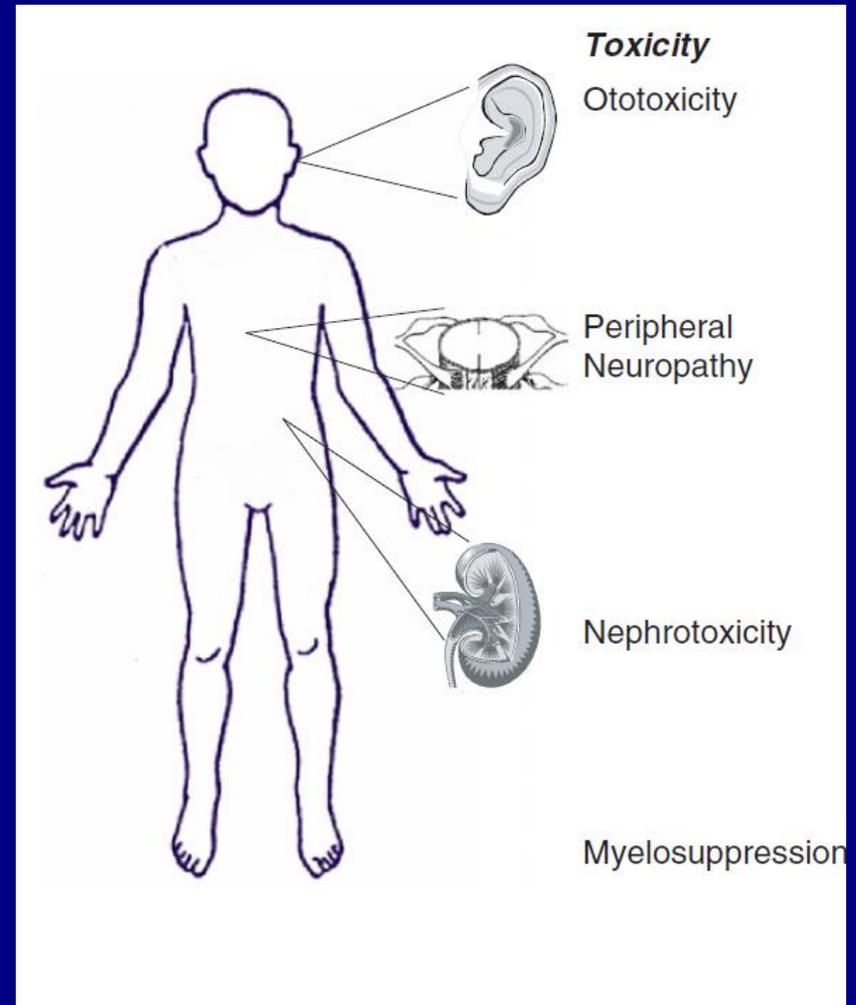
# Ruolo del rame nella migrazione di cellule cancerose



# Chemioterapia con farmaci a base di platino



Platinum-based drugs are used in the treatment of various types of cancers; cisplatin is particularly effective against testicular cancer (cure rate 95%)

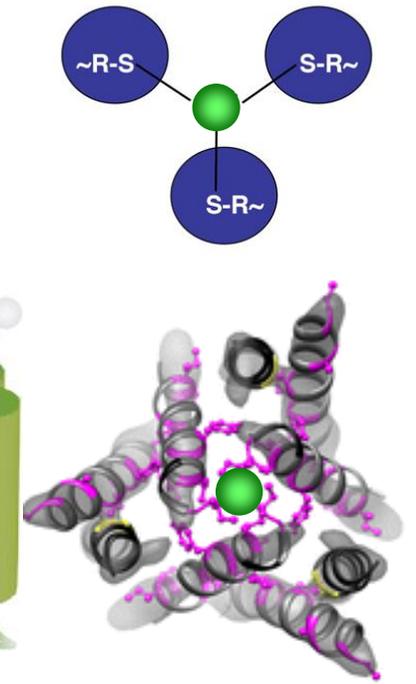
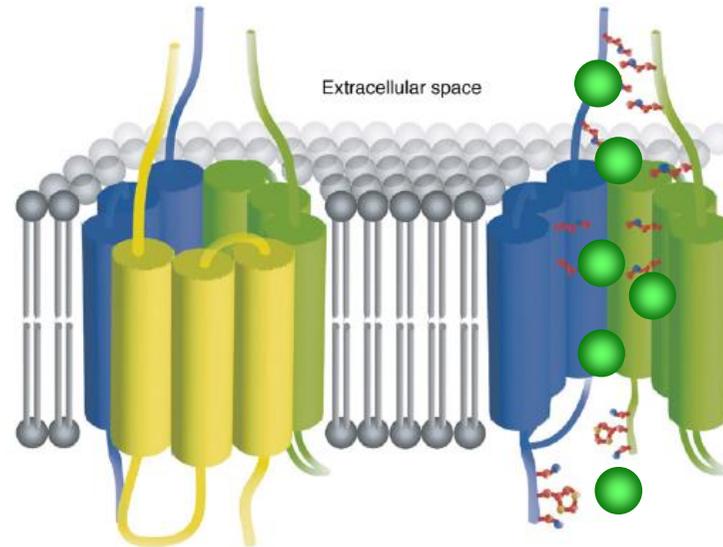
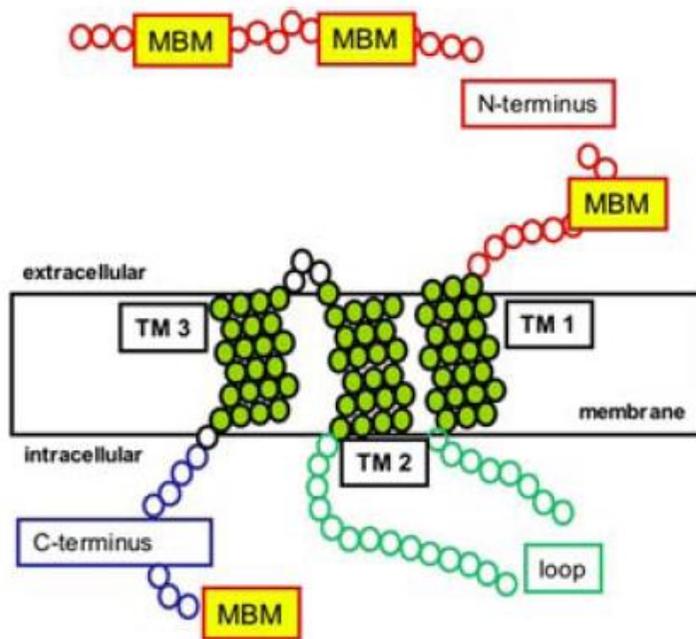


Rabik and Dolan, *Cancer Treatment Reviews*, 2007

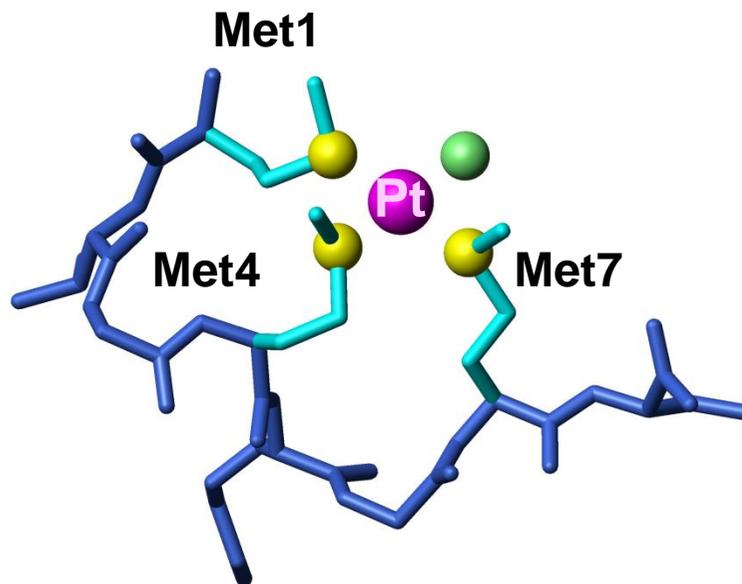
Possible mechanism of anticancer action of cisplatin

# Il trasportatore di rame Ctr1

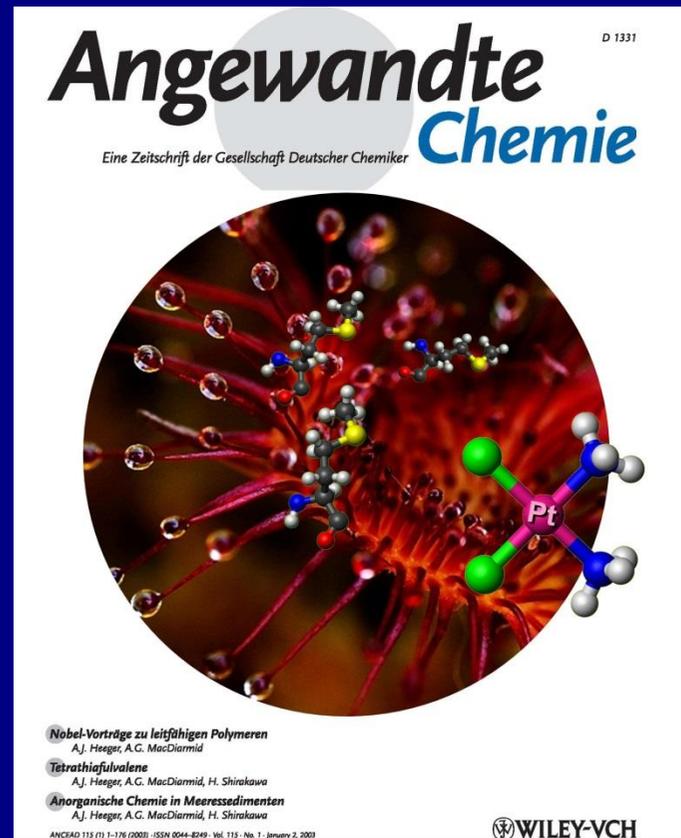
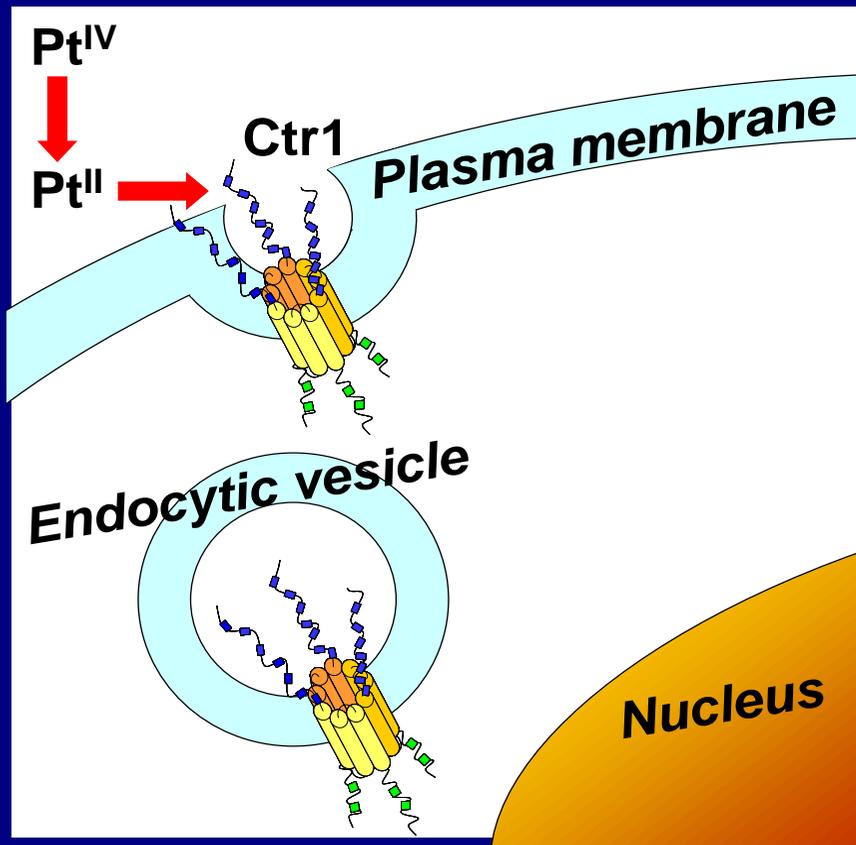
$M_{xx}M_{xx}M$



# Il trasportatore di rame Ctr1 lega il cisplatino



Arnesano, Scintilla, Natile, *Angew. Chem. Int. Ed.*, 2007  
Nguyen, Arnesano, Scintilla, Rossetti, Ippoliti, Carloni, Natile,  
*J. Chem. Theory Comput.*, 2012

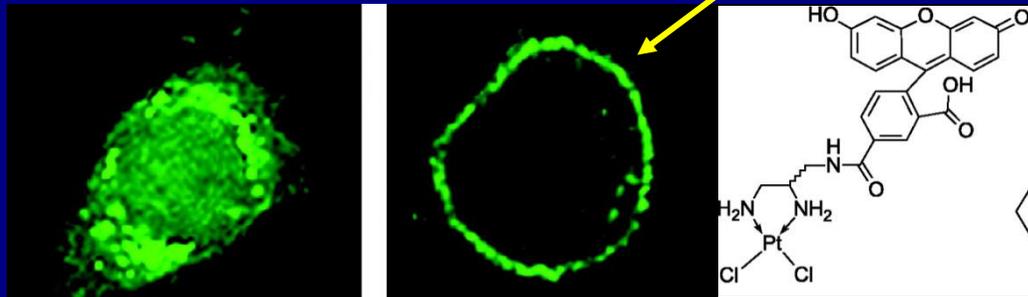


**2008 Ovarian carcinoma cells**

Sensitive

Resistant

FDDP



**Arnesano, Scintilla, Natile,  
 Angew. Chem. Int. Ed. Engl., 2007**

0 0 3 0 7 3 4 2 2 2 8 3 0 0 0 4 3 3 8 4 7 4 2 4 4 5 6 6 0 2 6 1  
4 8 0 3 8 6 1 3 3 4 5 0 3 3 3 3 3 4 1 4 3 8 5 4 3 5 3  
4 1 2 6 0 3 1 3 3 4 5 0 3 3 3 3 3 4 1 4 3 8 5 4 3 5 3  
6 5 7 6 0 3 1 3 3 4 5 0 3 3 3 3 3 4 1 4 3 8 5 4 3 5 3  
8 1 3 3 1 9 0 3 1 3 3 4 5 0 3 3 3 3 3 4 1 4 3 8 5 4 3 5 3  
7 2 1 3 2 9 4 1 3 3 4 5 0 3 3 3 3 3 4 1 4 3 8 5 4 3 5 3  
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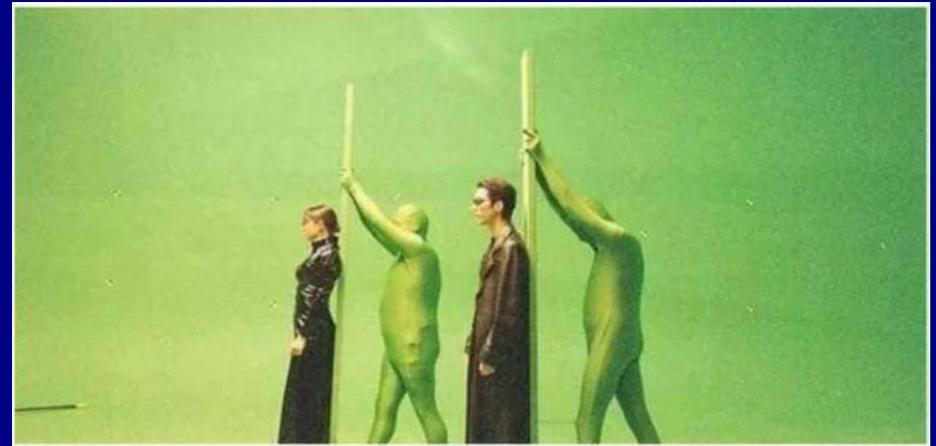
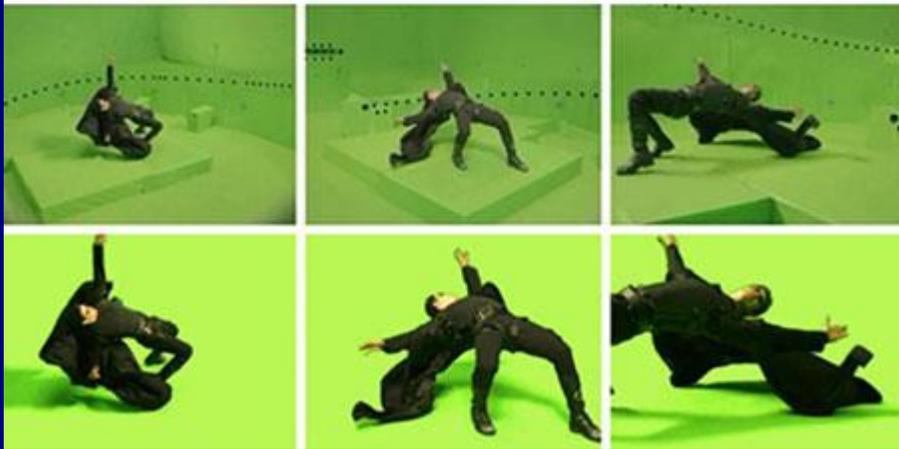
# MATRIX

# Bullet-time effect

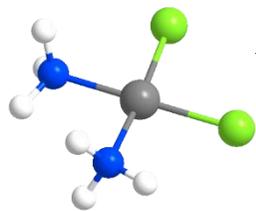


# MATRIX

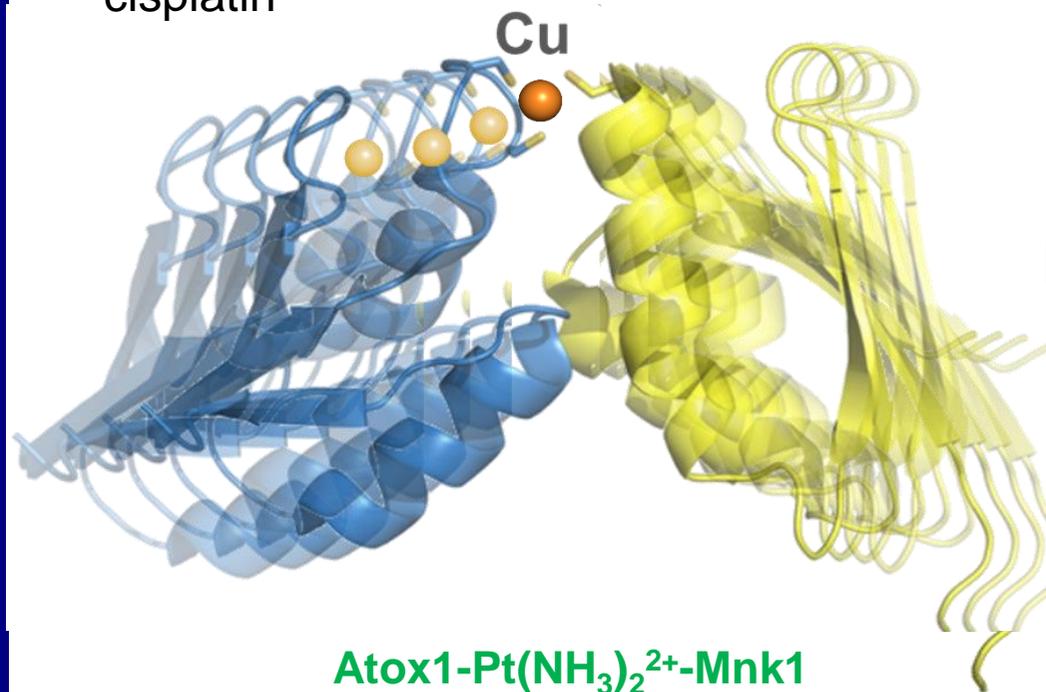
## Bullet-time effect



# Copper release induced by platinum binding



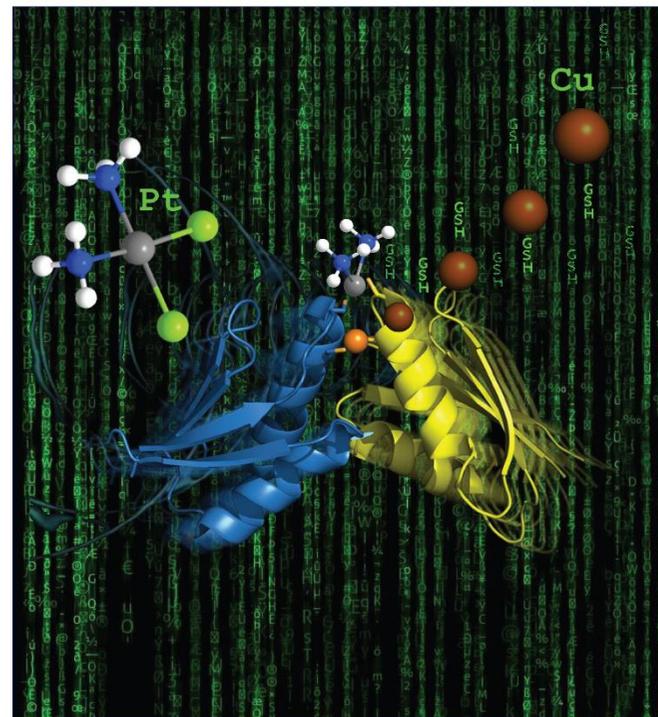
cisplatin



Atox1-Pt(NH<sub>3</sub>)<sub>2</sub><sup>2+</sup>-Mnk1

August 21, 2019  
Volume 141  
Number 33  
pubs.acs.org/JACS

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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

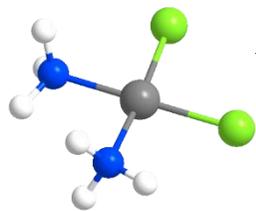


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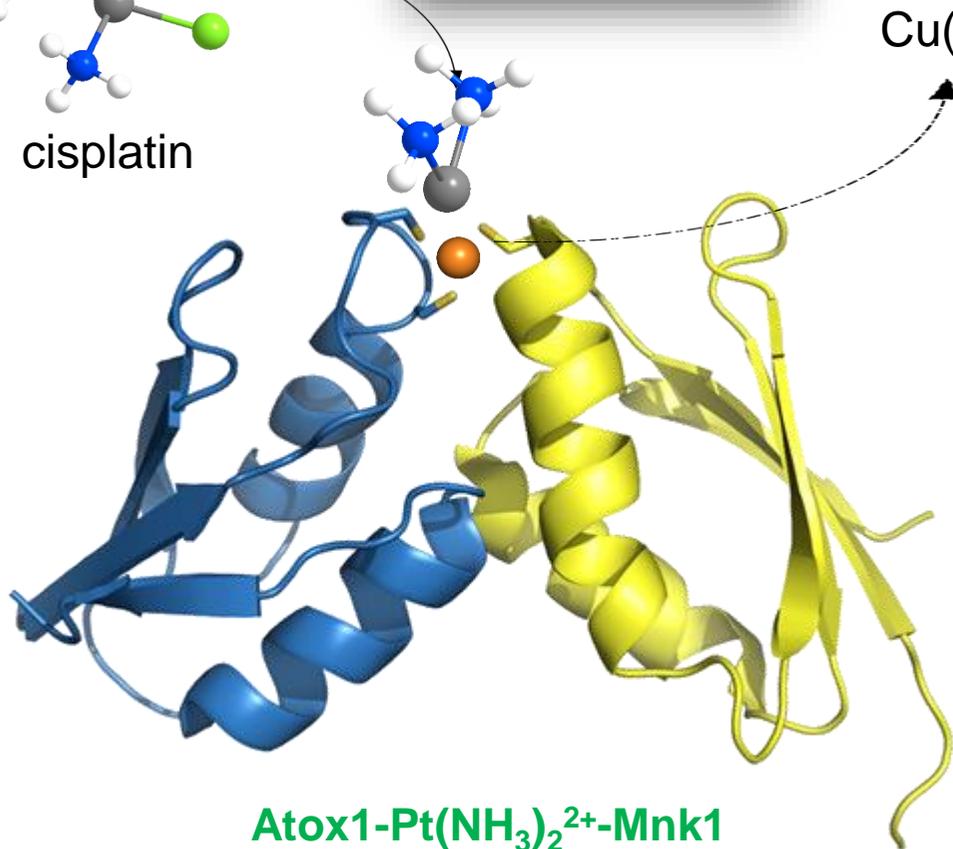
Lasorsa, Nardella, Rosato, Mirabelli, Caliandro, Natile, Arnesano, JACS 2019

# Copper release induced by platinum binding



cisplatin

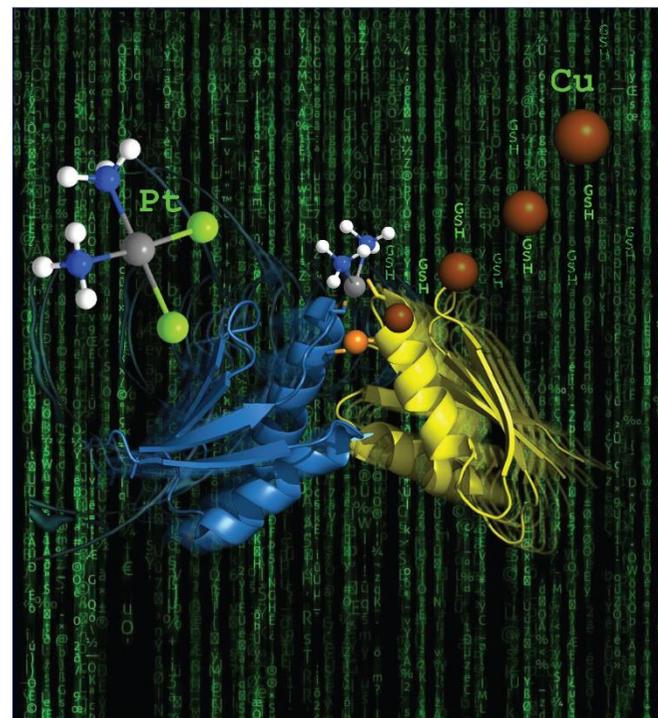
Cu(I)



Atox1-Pt(NH<sub>3</sub>)<sub>2</sub><sup>2+</sup>-Mnk1

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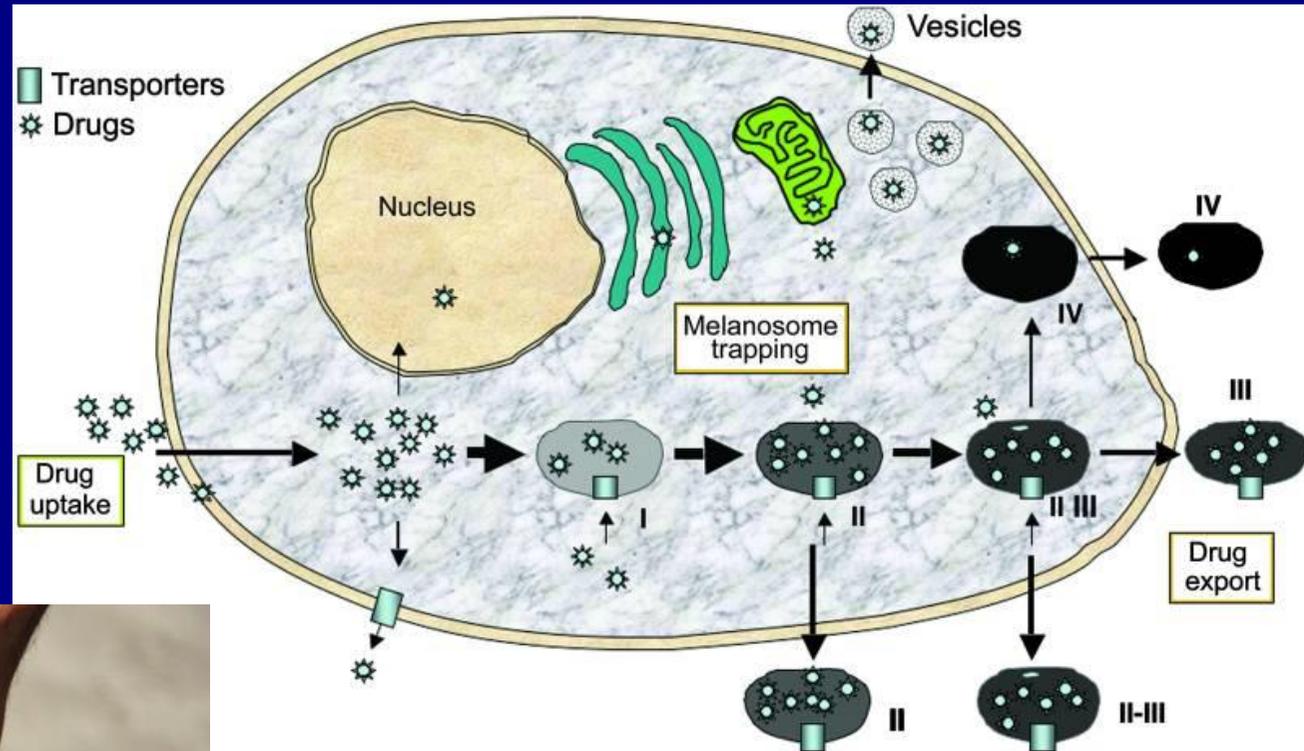
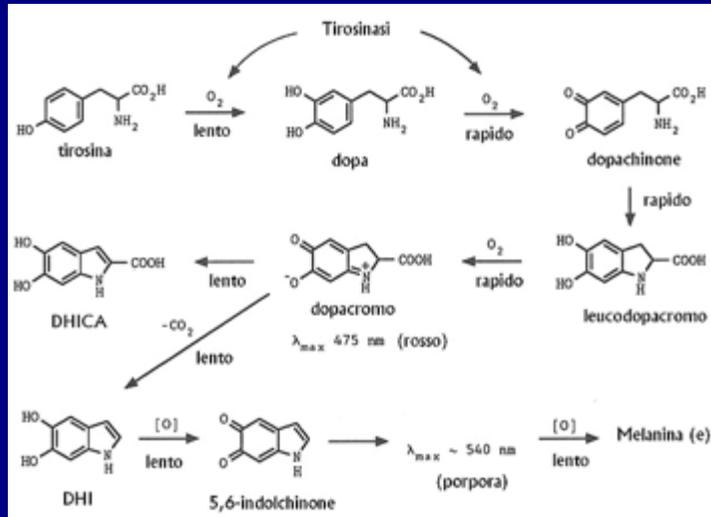


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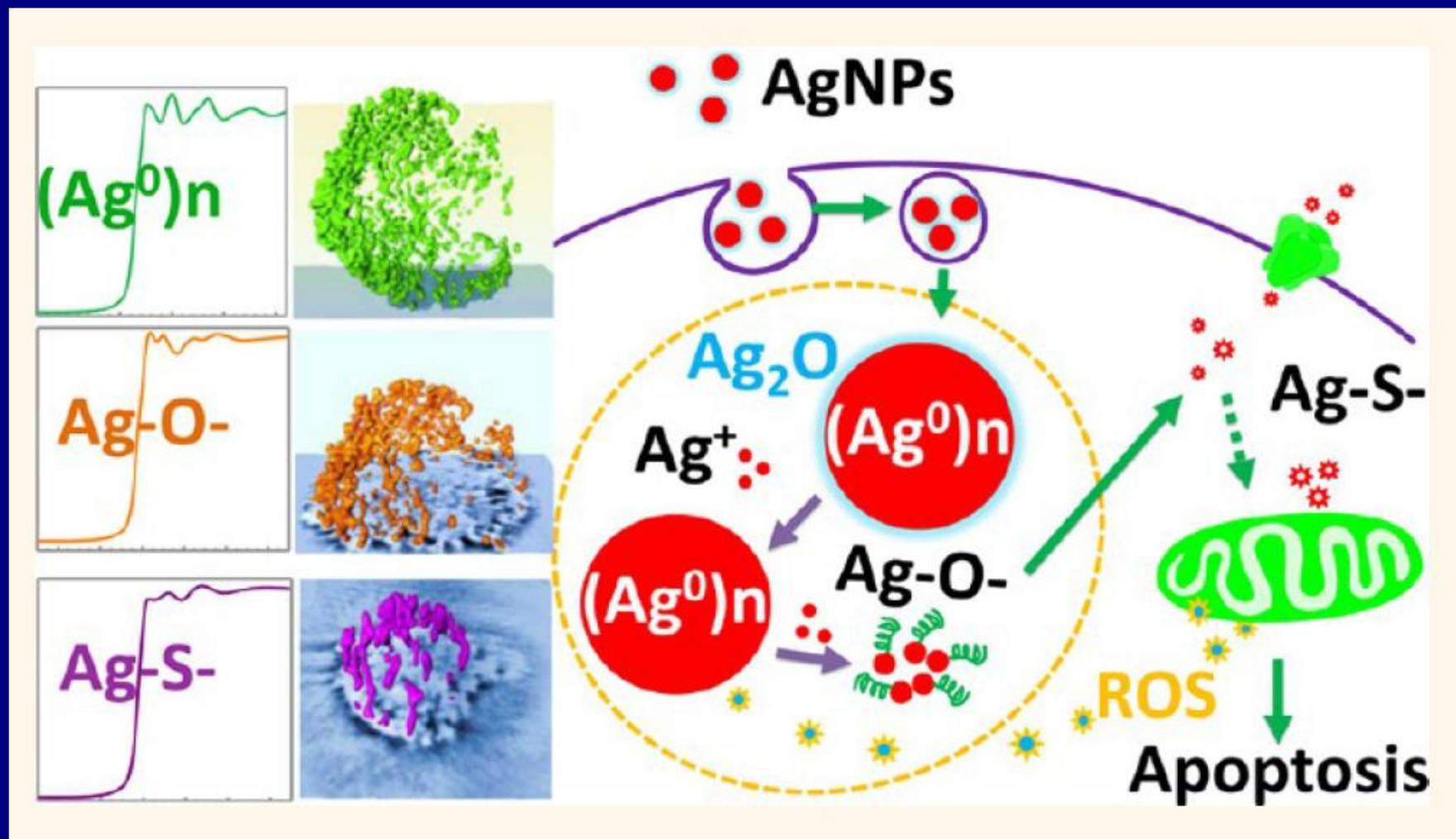
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Lasorsa, Nardella, Rosato, Mirabelli, Caliandro, Natile, Arnesano, JACS 2019

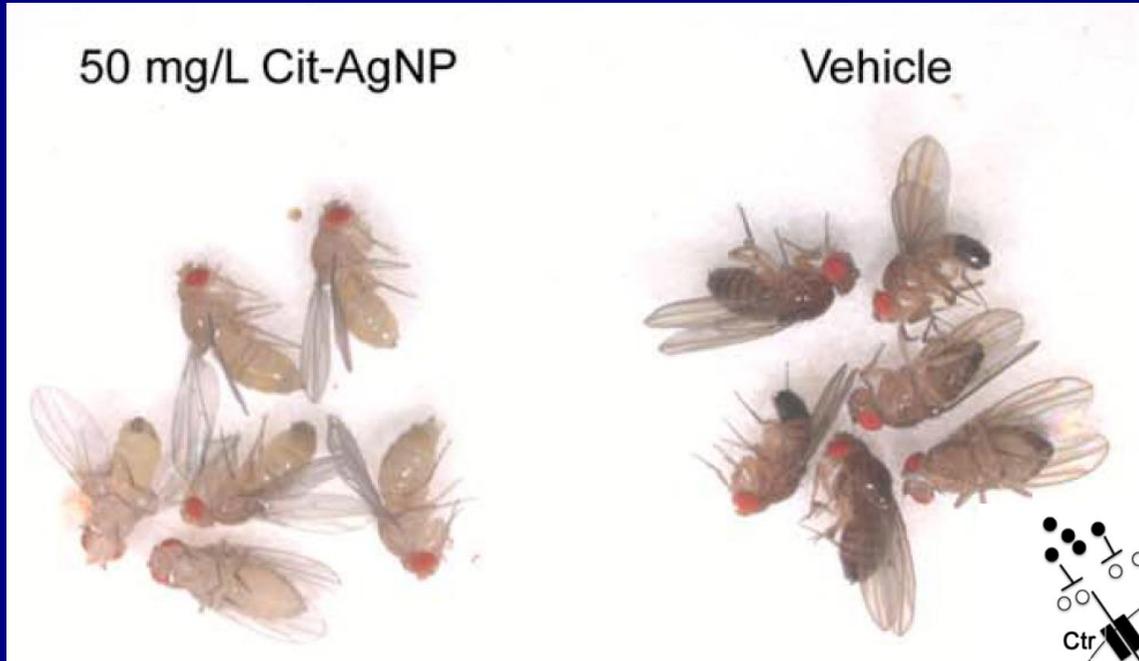
# I melanosomi sono responsabili del colore della pelle



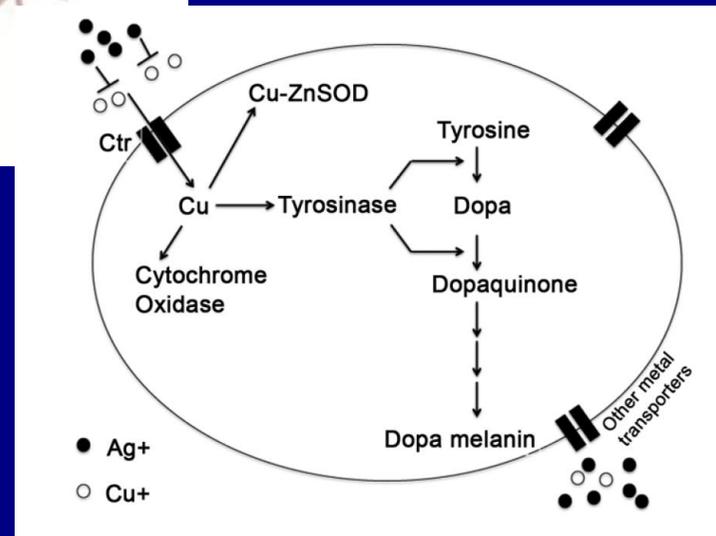
# Distribuzione cellulare delle nanoparticelle d'argento



# Effetto delle nanoparticelle d'argento sulla pigmentazione



**Exposure of *Drosophila* to 50 mg/L AgNP effectively eliminates all melanin pigments from their body.**





European  
Commission

# Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)

nanoAg



Is it safe to use cosmetics containing  
silica in nanoform?



nanoSiO<sub>2</sub>

Are silver nanoparticles safe?

nanoZnO



Nano-form  
zinc oxide  
in sunscreens