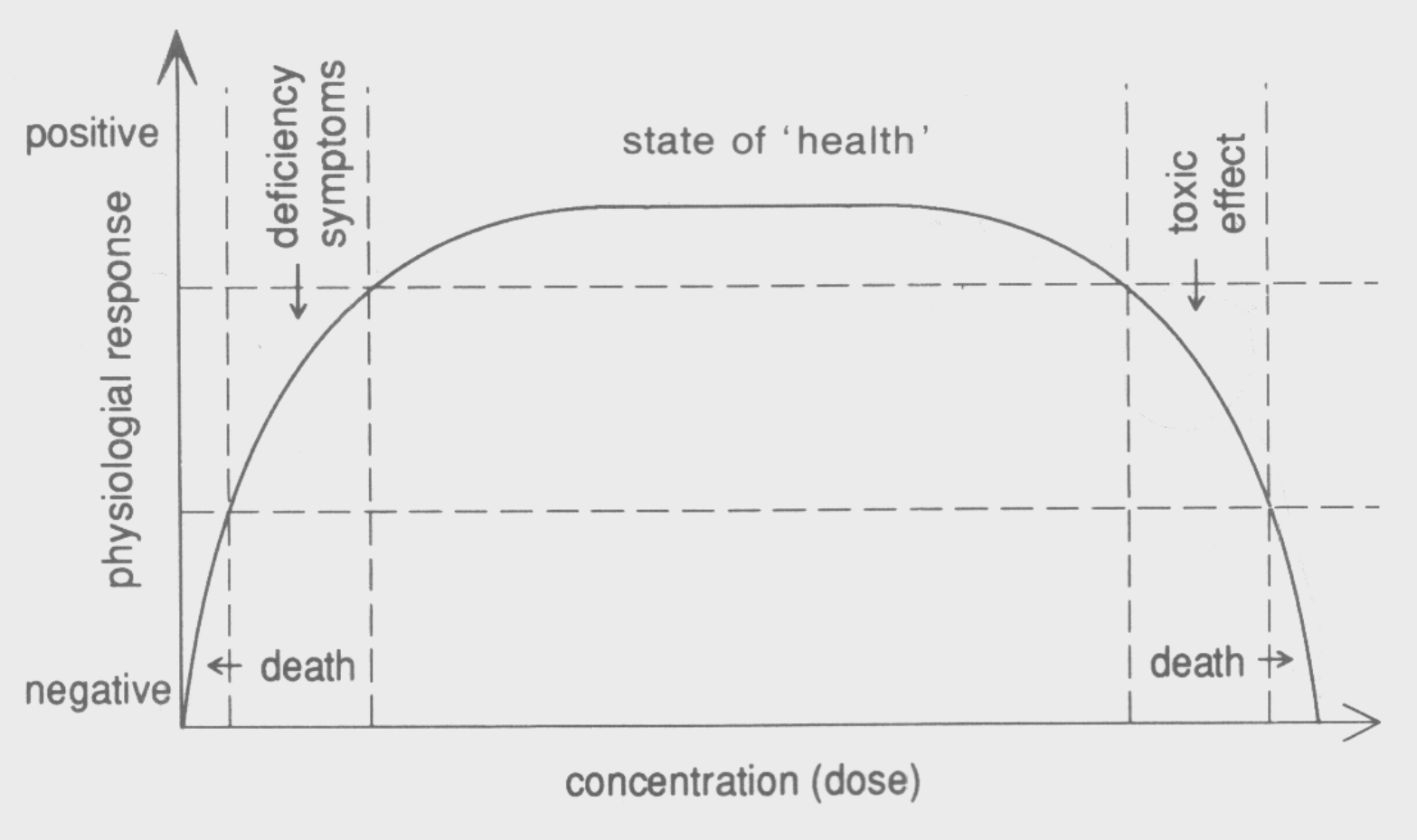
Therapeutic use of coordination compounds

- **Application of therapeutic chelant agents**
- **Chemotherapy and photodynamic therapy**

Schematic dose response diagram for an essential element

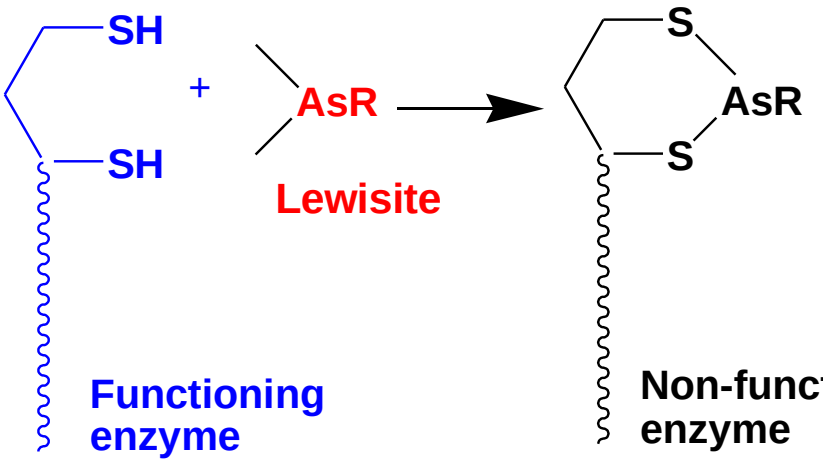


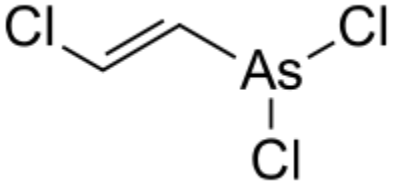
Some characteristic symptoms of chemical element deficiency in humans

deficient element	typical deficiency symptoms
Ca	retarded skeletal growth
Mg	muscle cramps
Fe	anemia, disorders of the immune system
Zn	skin damage, stunted growth, retarded sexual maturation
Cu	artery weakness, liver disorders, secondary anemia
Mn	infertility, impaired skeletal growth
Mo	retardation of cellular growth, propensity for caries
Co	pernicious anemia
Ni	growth depression, dermatitis
Cr	diabetes symptoms
Si	disorders of skeletal growth
F	dental caries
I	thyroid disorders, retarded metabolism
Se	muscular weakness, esp. cardiomyopathy
As	impaired growth (in animals)

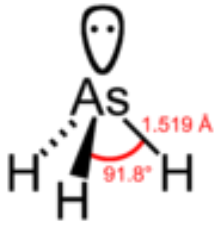
Chelation therapy after metal poisoning

1)

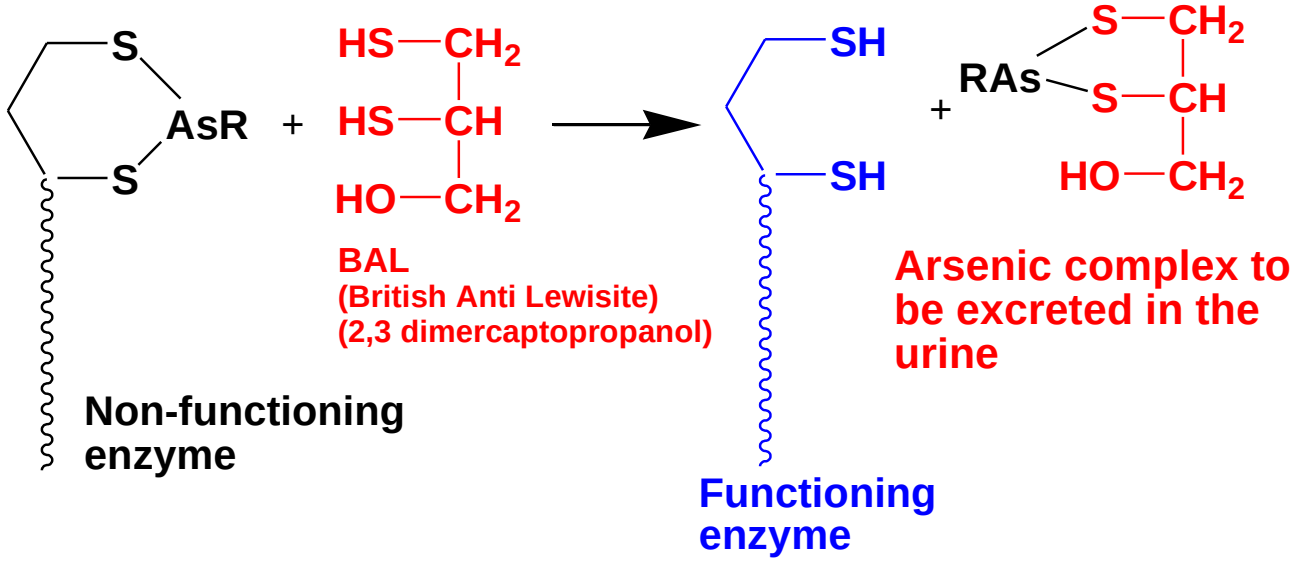




2-chloroethenyldichloroarsine



2)



Schematic representation of chelation therapy: here arsenic is used as the example

Criteri per la scelta dell'agente complessante

- ***Determinazione del sito d'azione dell'elemento in eccesso***

- ***Determinazione del gruppo coordinante responsabile e scelta dello stesso gruppo per il complessante***

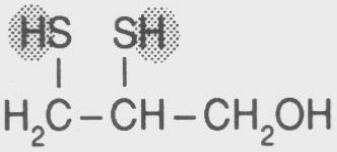
- ***Il complessante non deve essere tossico, ne lo deve essere il complesso formato***

- ***Il complesso deve avere un'alta costante di formazione***

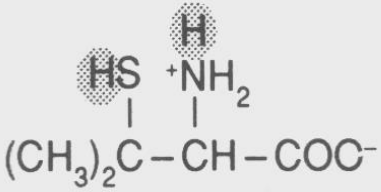
- ***Il complesso deve essere solubile in acqua***

- ***La formazione del complesso deve ripristinare le condizioni che si avevano prima della alterazione dovuta all'elemento in eccesso***

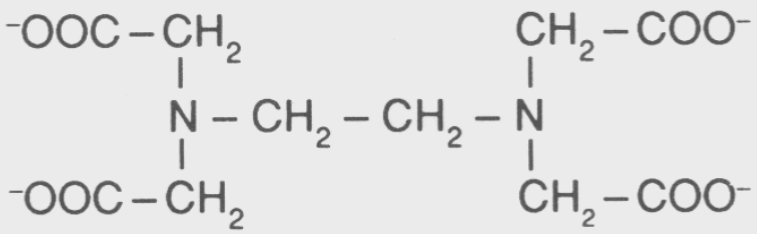
Chelate ligands for detoxification after metal poisoning



BAL — *Hg(II), As(III), Sb(III), Ni(II)*

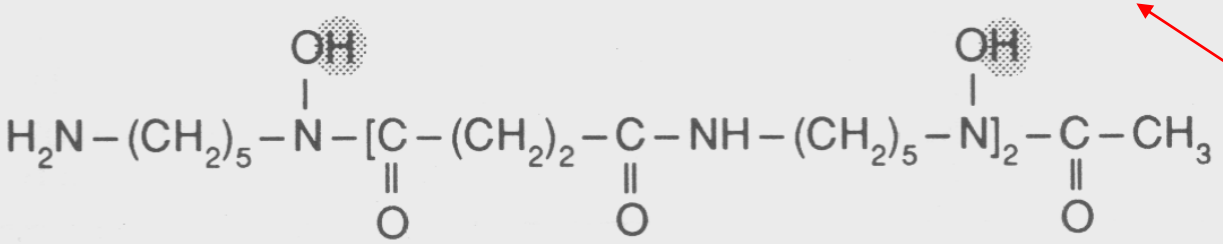


Penicillamine — *Cu(II), Hg(II)*



EDTA — *Ca(II), Pb(II)*

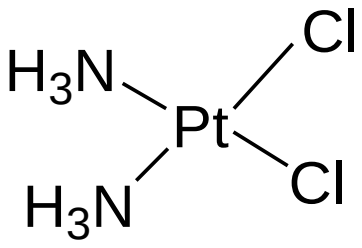
Desferal — *Fe(III), Al(III)*



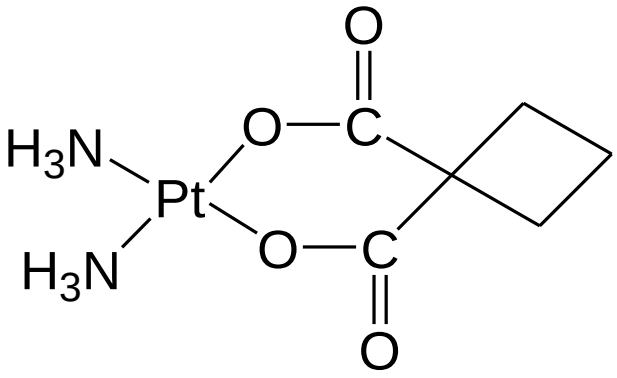
Deferoxamine (DFOA)

Chemotherapy with compounds of nonessential elements

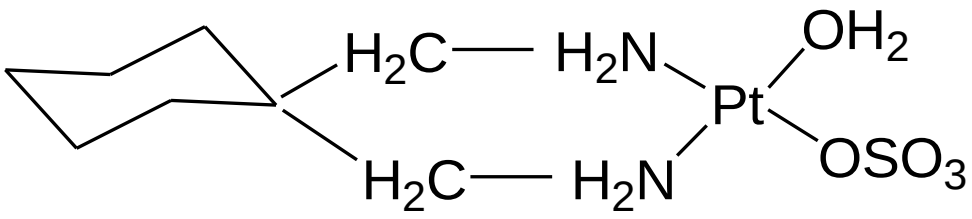
Platinum complexes in cancer therapy



Cis-platin

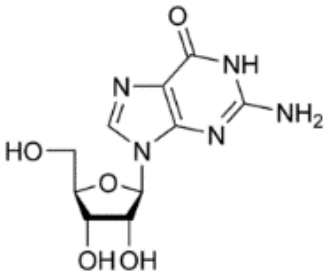


Carboplatin

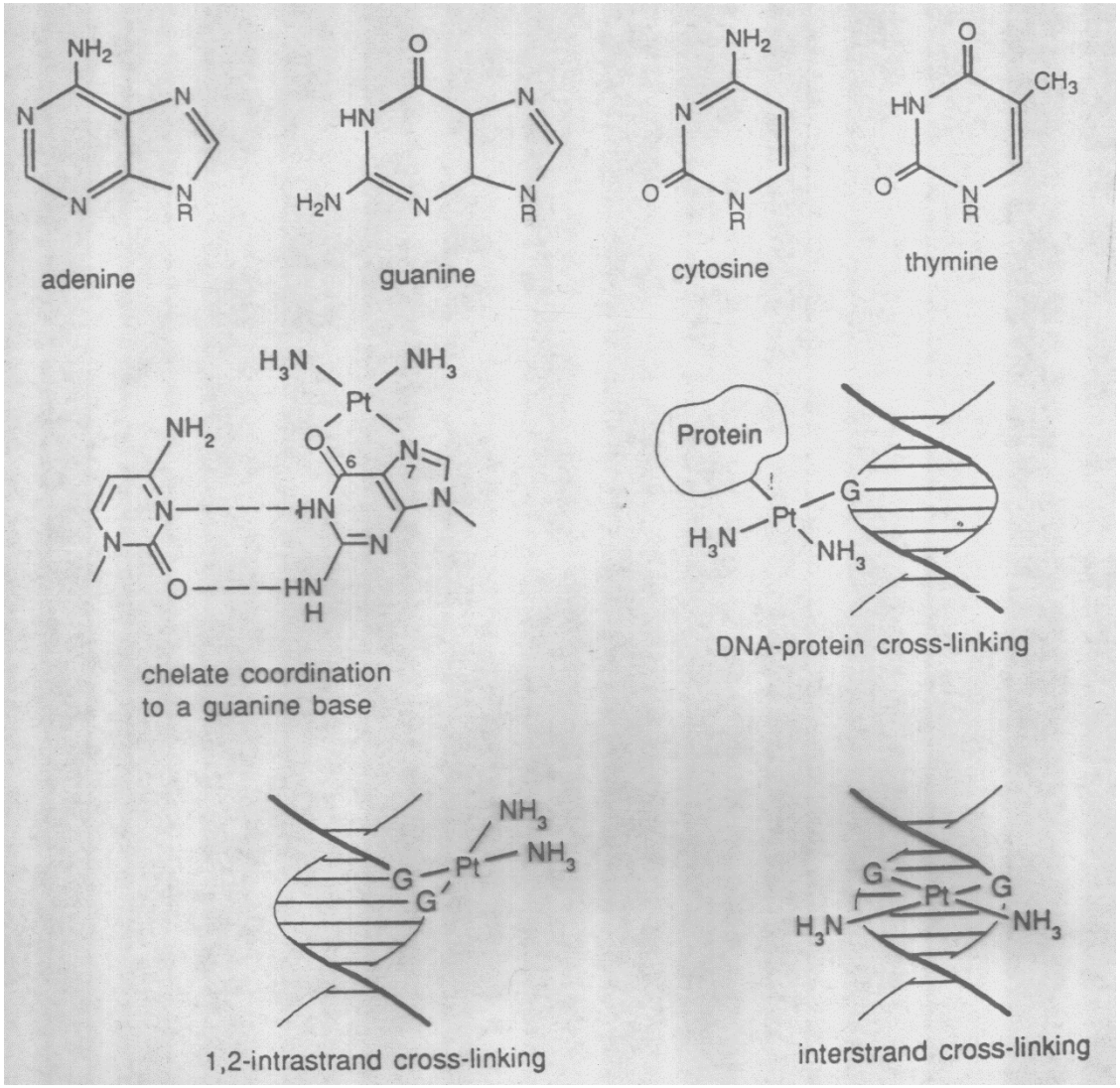


Spiroplatin

cis-platin mechanisms of action



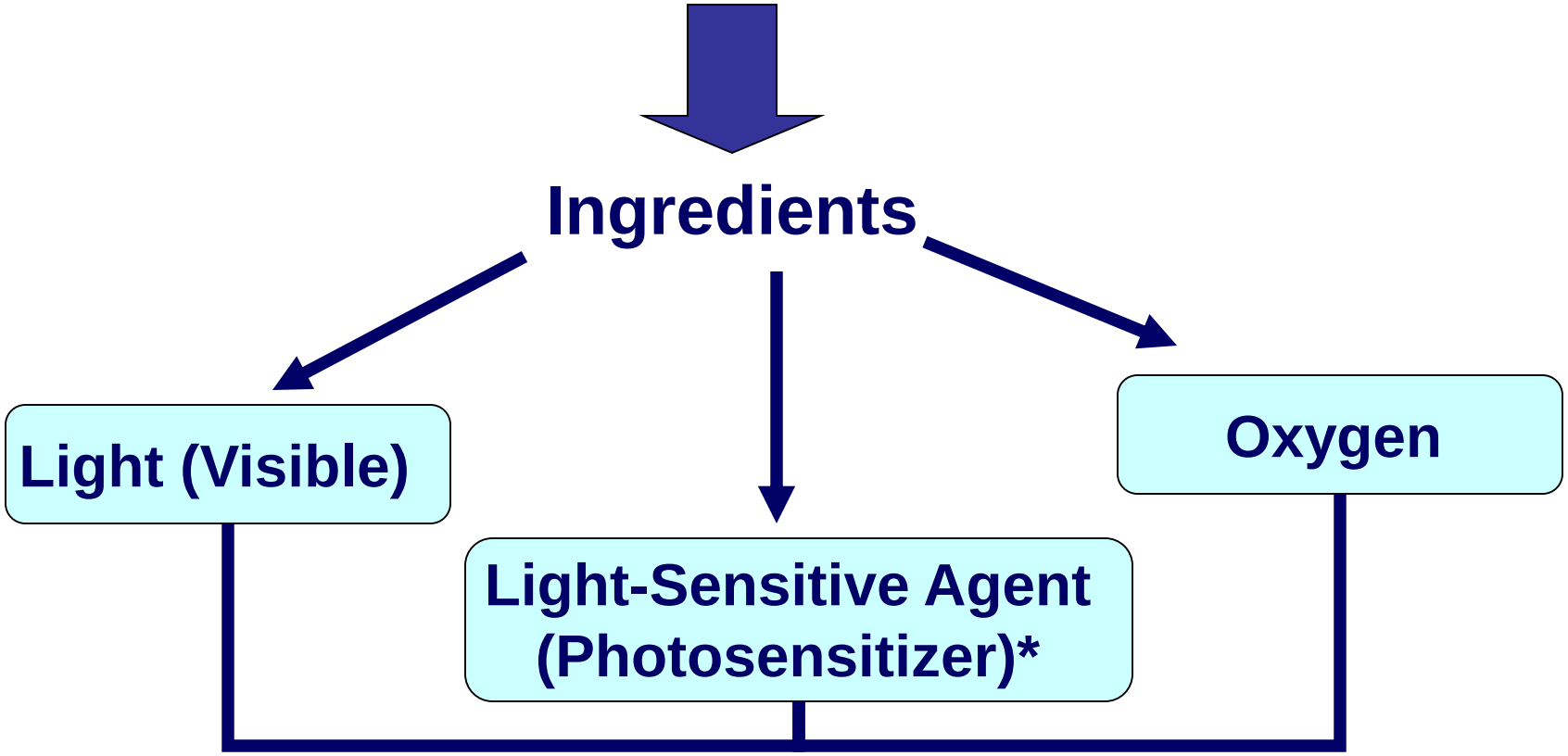
guanosine



Possible kinds of bonding between cis-platin and guanosine (G) in double-stranded DNA

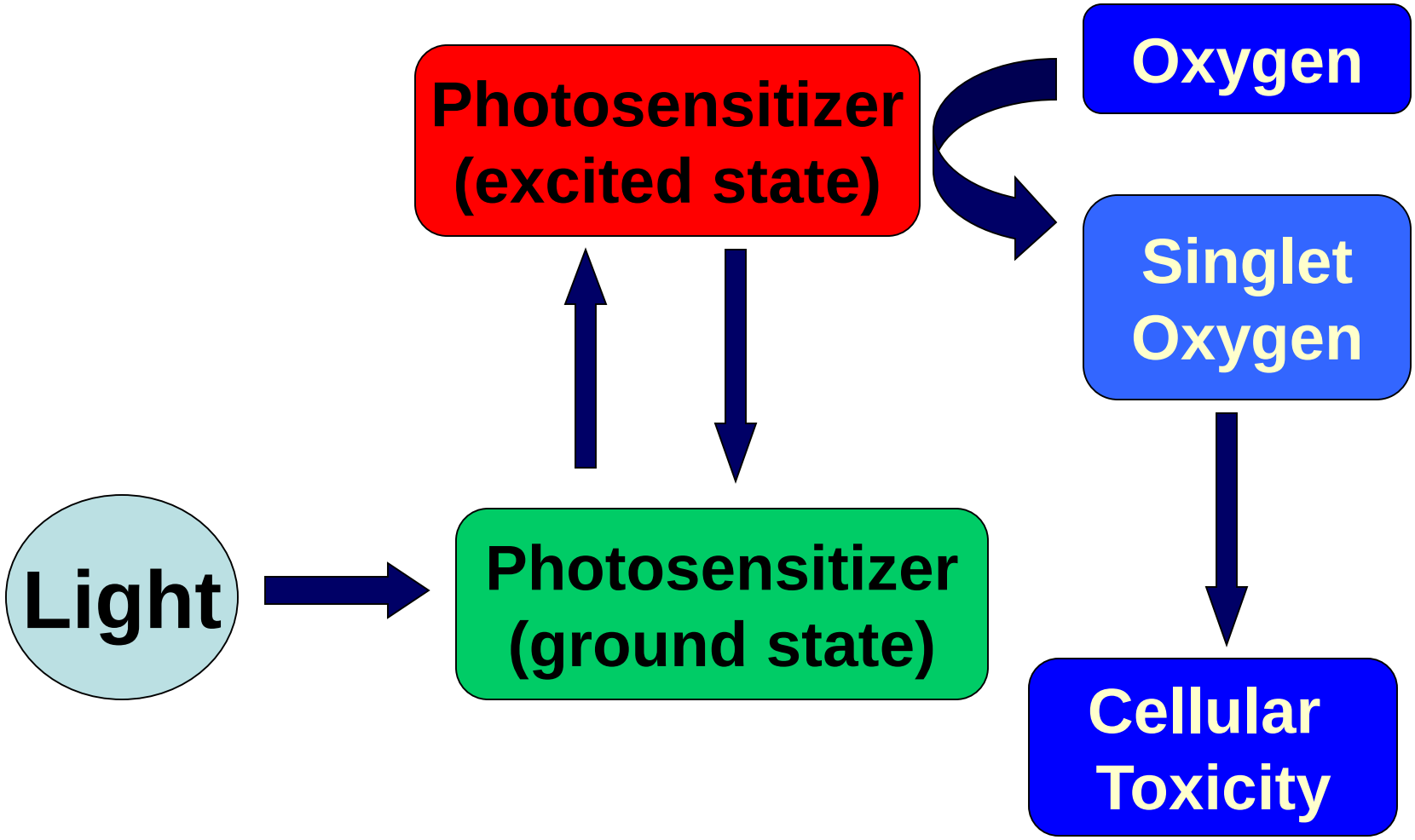
The Photodymamic Therapy:

“ *Killing Cancer with Light* ”



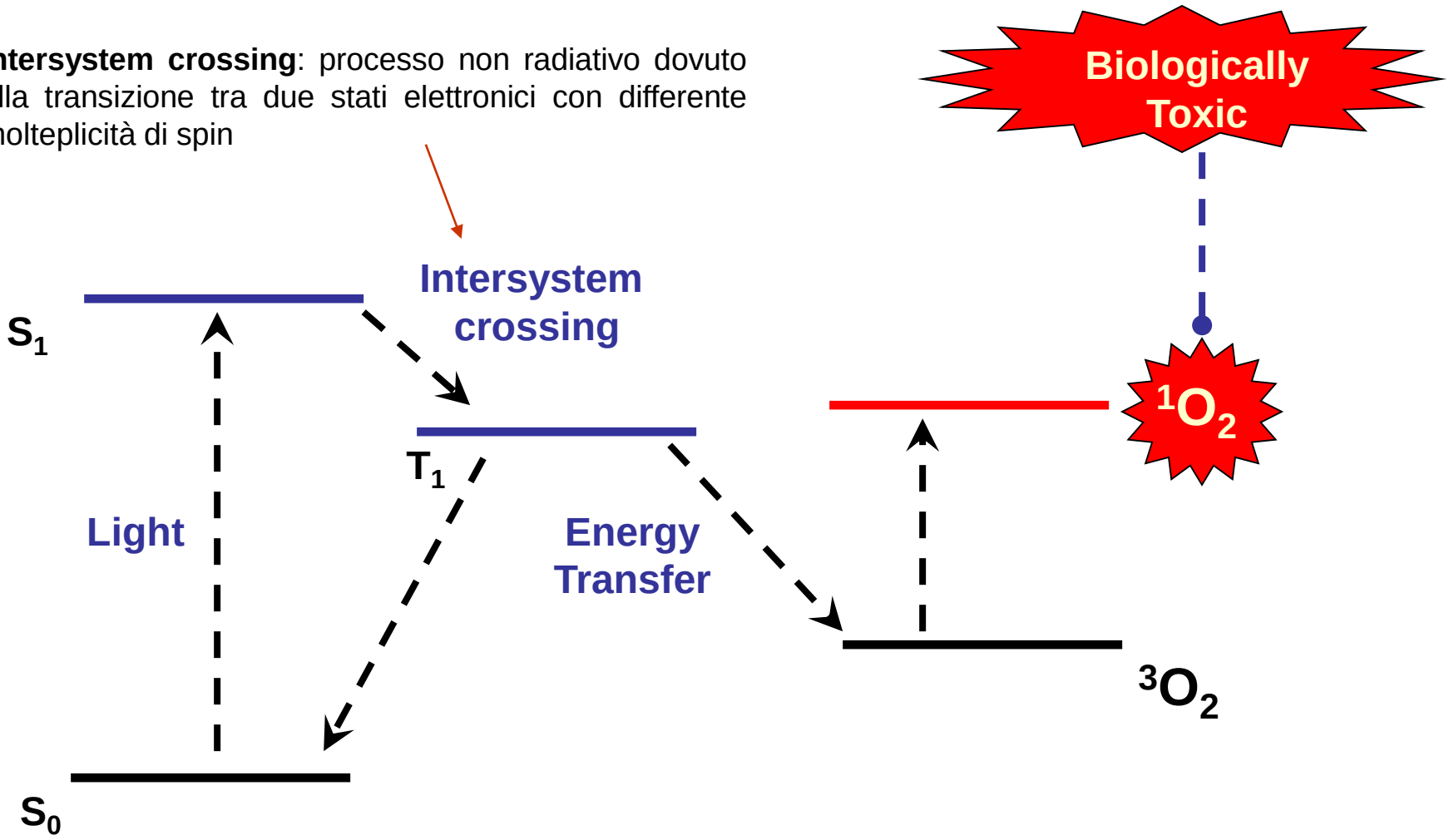
* (fotosensibilizzatore) : a molecule that produces a chemical change in another molecule in a photochemical process

Combination of the 3 ingredients leads to Formation of "*Singlet Oxygen*"

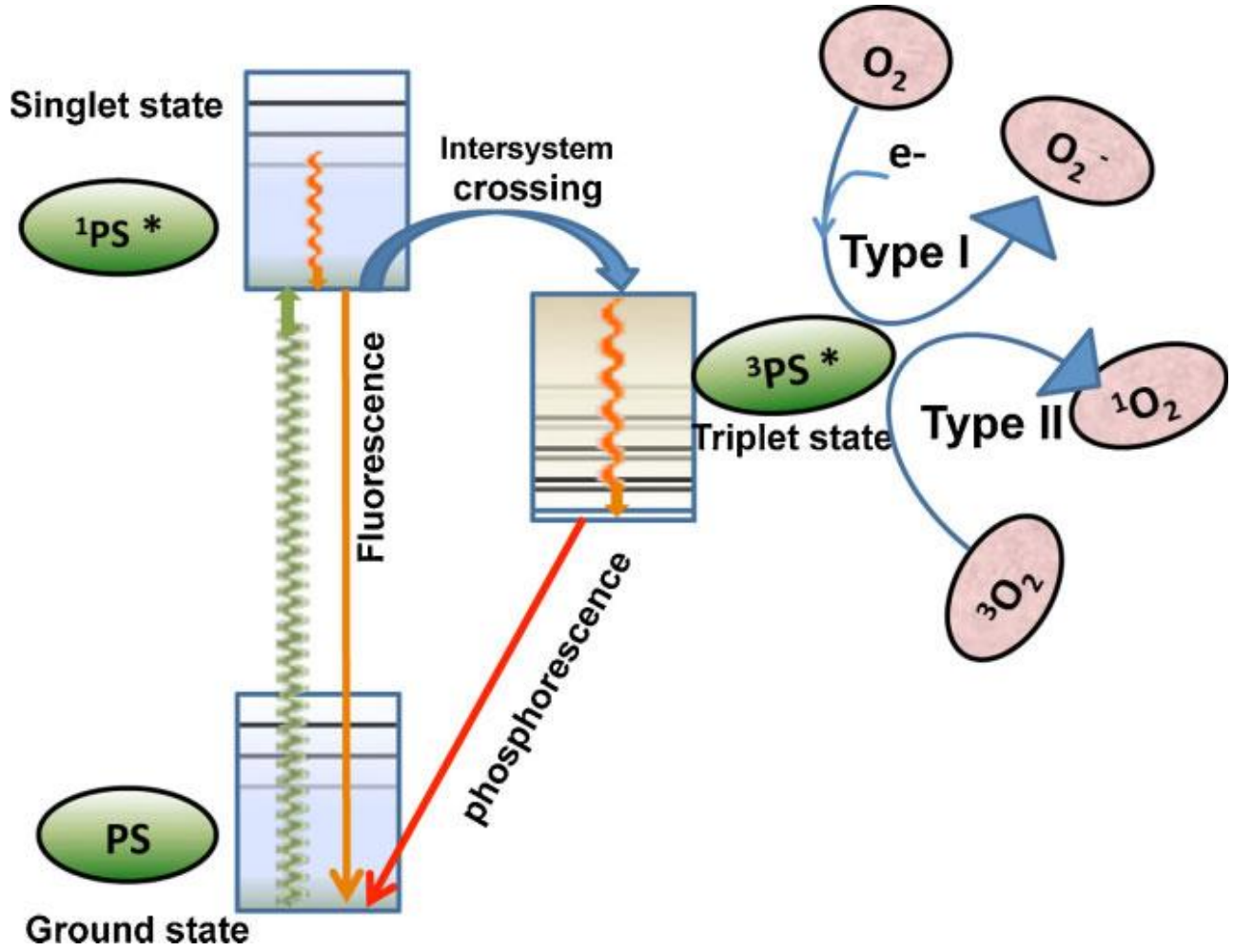


Mechanism of photogeration of "*Singlet Oxygen*"

intersystem crossing: processo non radiativo dovuto alla transizione tra due stati elettronici con differente molteplicità di spin



The triplet state lives enough time to transfer its energy to molecular oxygen


Singlet state
^1PS *
Intersystem crossing
Fluorescence
^3PS *
Triplet state
phosphorescence
PS
Ground state
O_2
e-
O_2^-
Type I
Type II
$^1O_2$
$^3O_2$

How does the photosensitizer kill the tumor?

- **The drug transfers its energy to an oxygen molecule, which in turn produces a reactive oxygen species (ROS). This ROS usually is "singlet oxygen".**

- **The so generated ROS initiates lipid peroxidation in the endothelial cells of small blood vessels that supply oxygen to the tumor cells, which kills the tumor.**

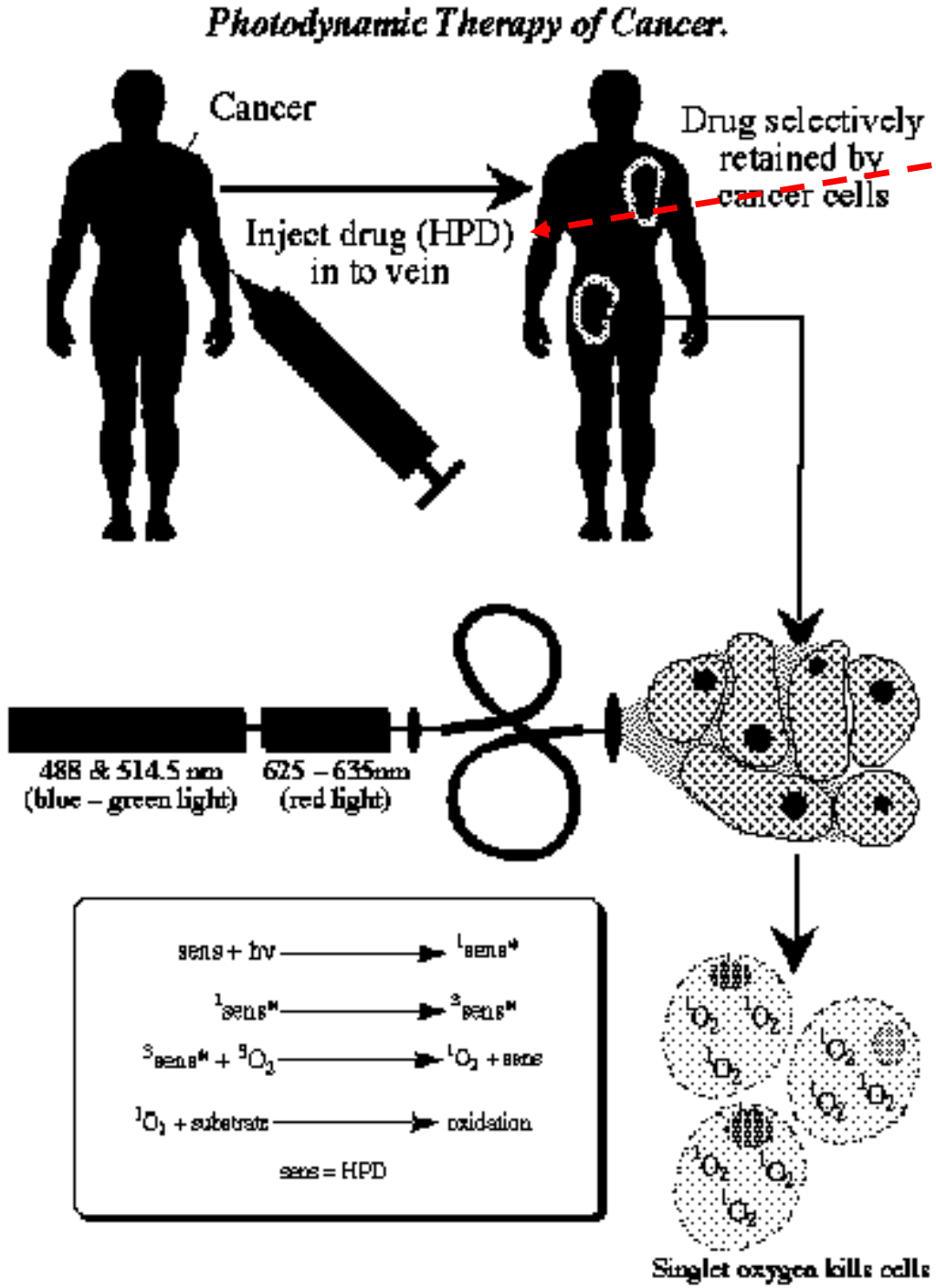
Steps leading to photogeration of "*Singlet Oxygen*"

$$^{0}\text{Sensitizer} + h\nu \longrightarrow {}^{1}\text{Sensitizer}$$

$$^{1}\text{Sensitizer} \longrightarrow {}^{3}\text{Sensitizer}$$

$$^{3}\text{Sensitizer} + {}^{3}O_2 \longrightarrow {}^{0}\text{Sensitizer} + {}^{1}O_2$$

$$^{1}O_2 + \text{Tissue} \longrightarrow \text{Necrosis}$$

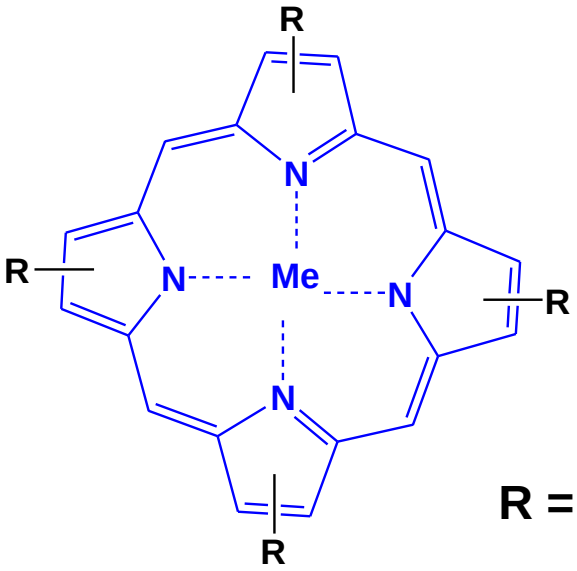


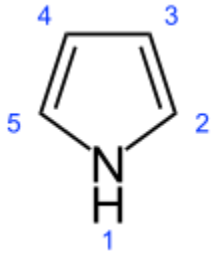
HematoPorphyrin Derivative (HPD)

What are Photodynamic Therapy Advantages?

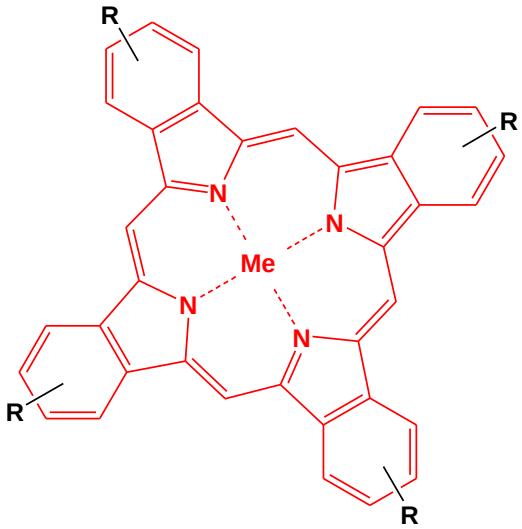
- ***Much less invasive, than normal surgery.***
- ***Less side effects, than other types of treatment.***
- ***Highly unique; can initiate therapy when light is introduced. Therefore some control.***
- ***Can be used to treat dermatological, oncological, ophthalmic, and cardiovascular diseases.***

Photosensitizers





pyrrole



R = suitable substituents

Porphyrins

Phthalocyanines

The photosensitizer is designed to:

→ **Be biologically inert**
→ **Localize in tumor**
→ **Absorb red light**
→ **Generate singlet oxygen**

The BIG Problem of Photosensitizers: most are poorly water soluble

Aqueous systems = must have carrier delivery systems to disperse the photosensitizer.