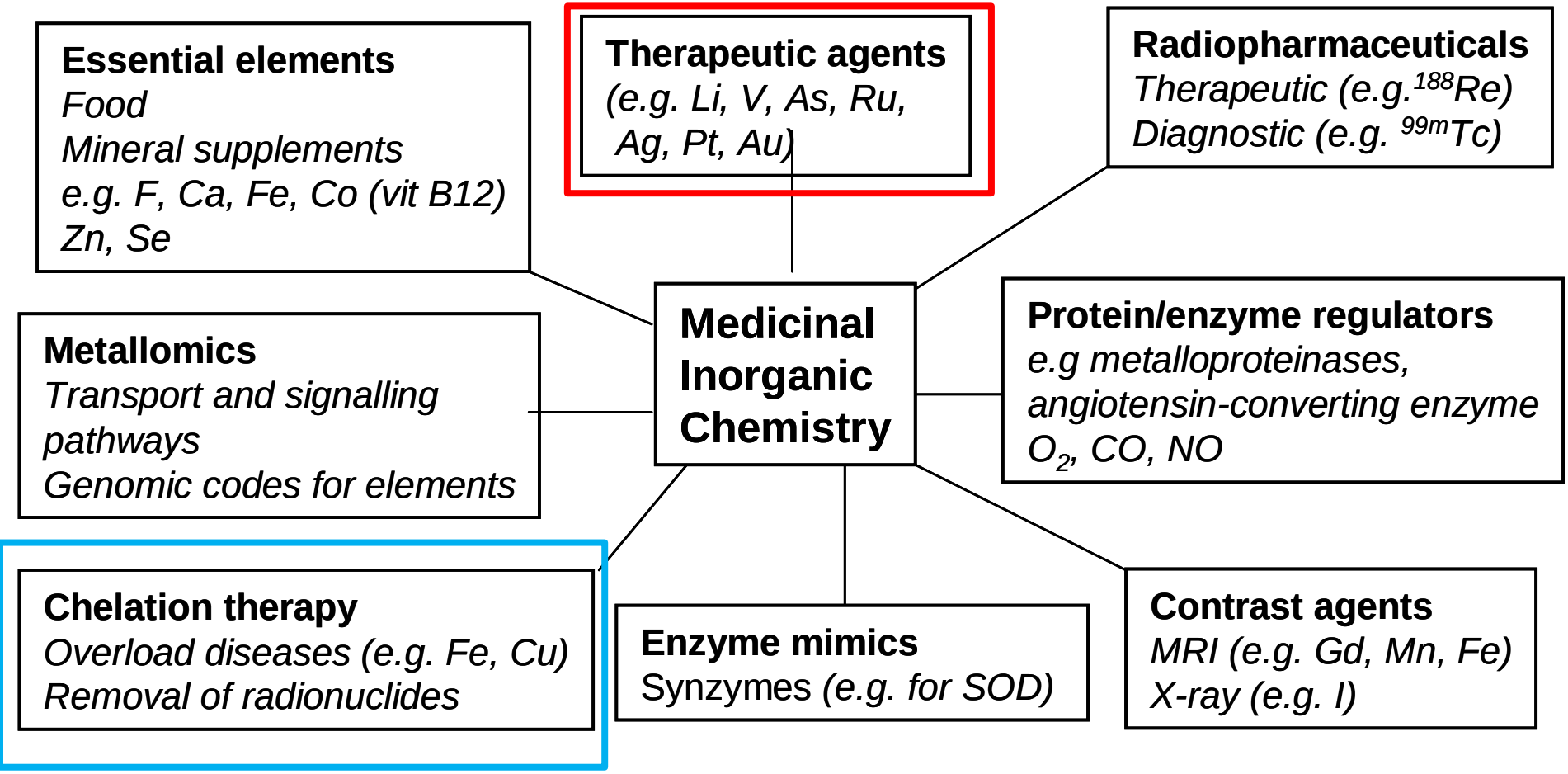
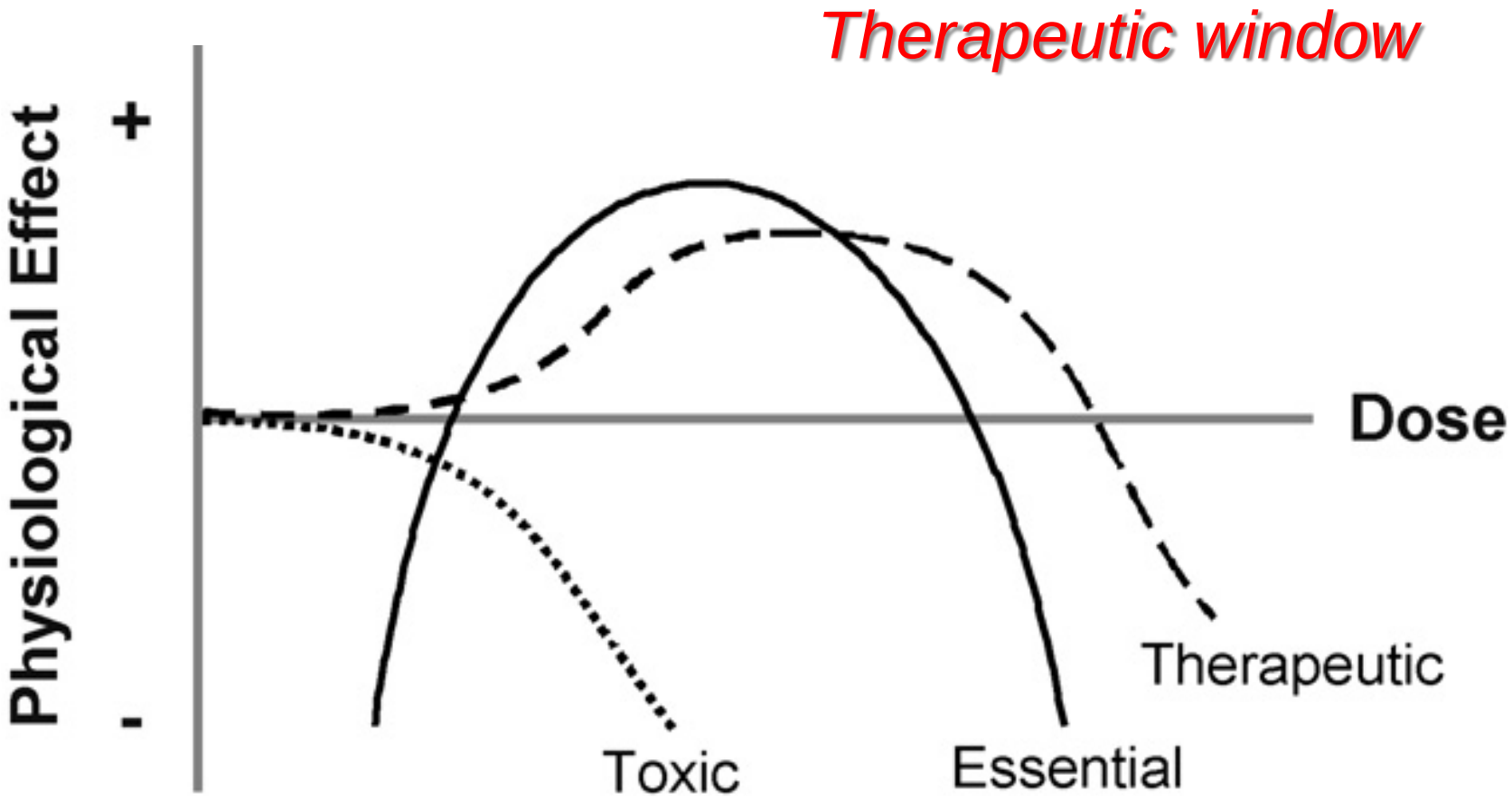
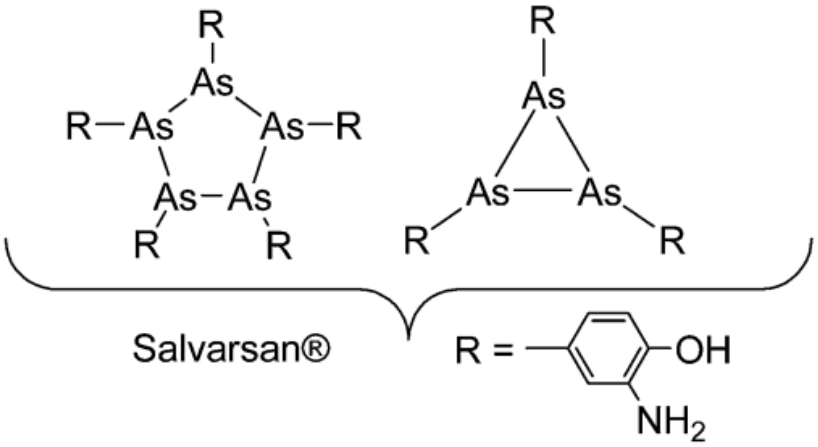

Essential elements
Food
Mineral supplements
e.g. F, Ca, Fe, Co (vit B12)
Zn, Se
Therapeutic agents
(e.g. Li, V, As, Ru,
Ag, Pt, Au)
Radiopharmaceuticals
Therapeutic (e.g. 188Re)
Diagnostic (e.g. 99mTc)
Medicinal Inorganic Chemistry
Metallomics
Transport and signalling pathways
Genomic codes for elements
Protein/enzyme regulators
e.g metalloproteinases, angiotensin-converting enzyme
O2, CO, NO
Chelation therapy
Overload diseases (e.g. Fe, Cu)
Removal of radionuclides
Enzyme mimics
Synzymes (e.g. for SOD)
Contrast agents
MRI (e.g. Gd, Mn, Fe)
X-ray (e.g. I)

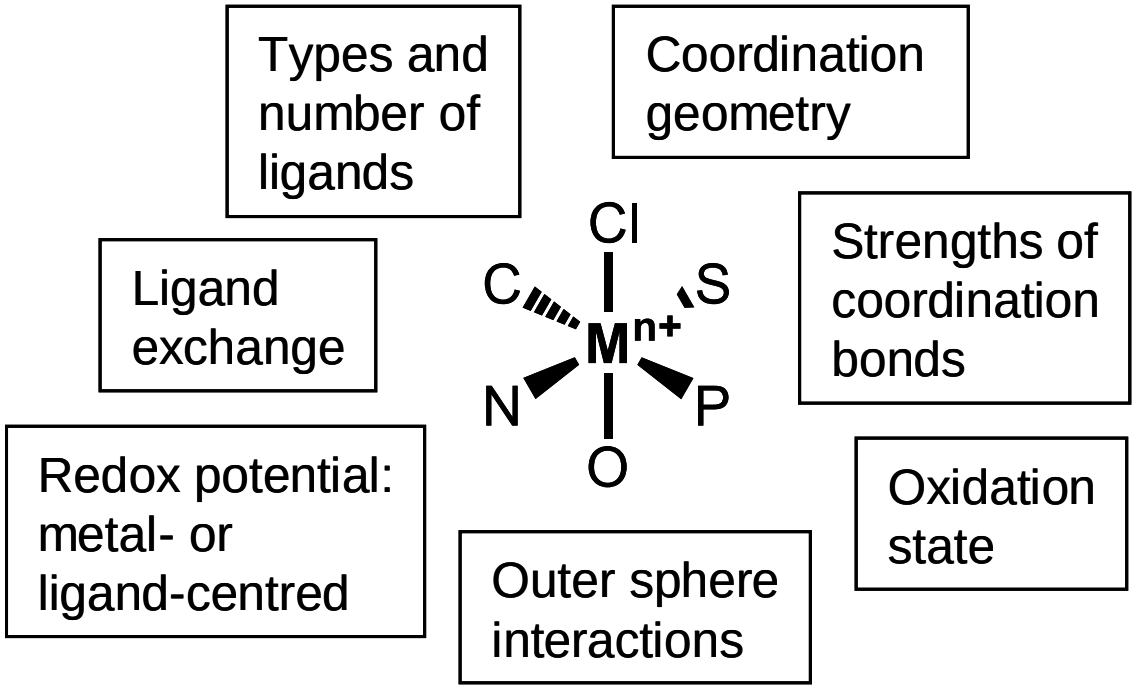
Diagramma di Bertrand



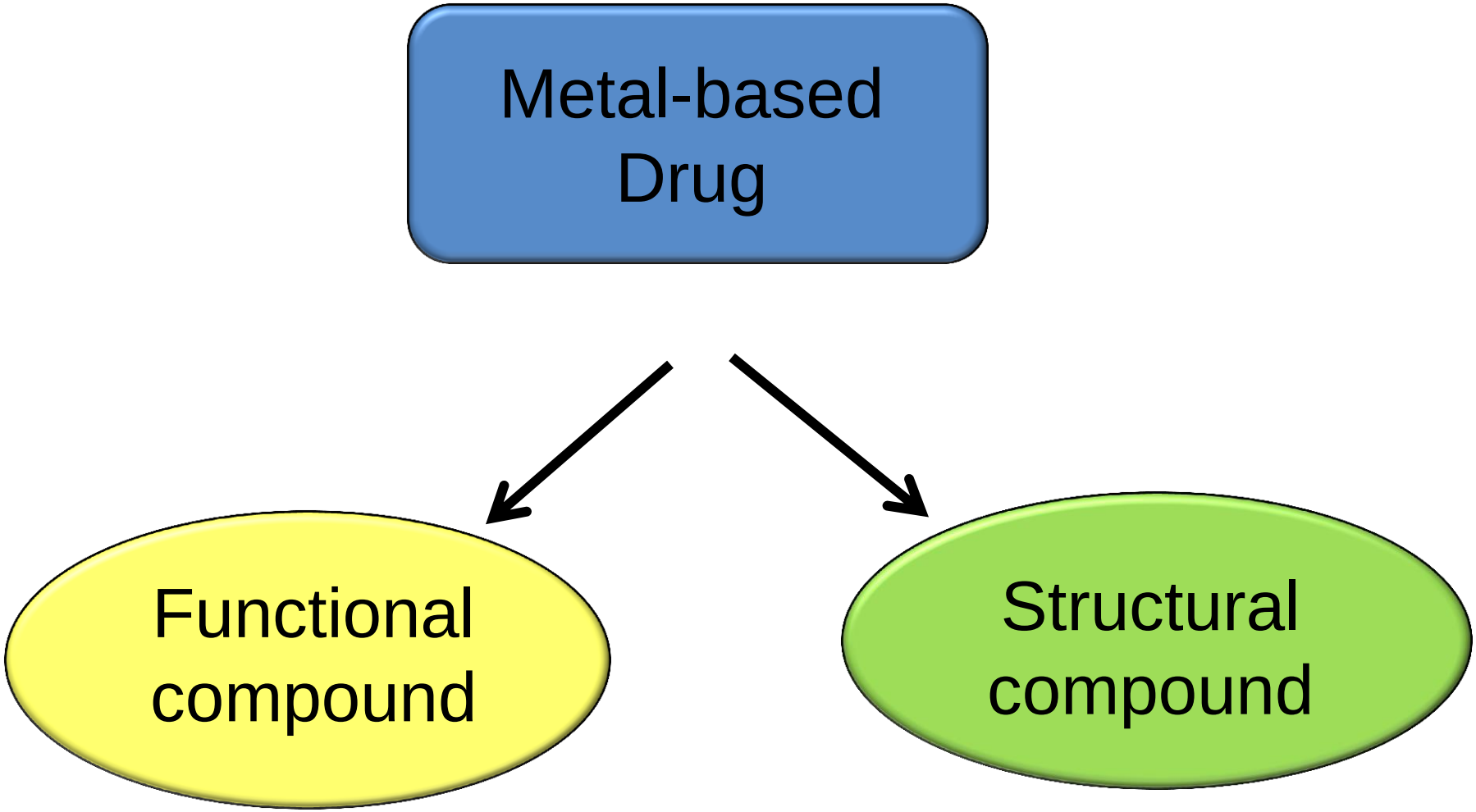


Antimicrobial agent introduced in early 1900 for the treatment of the deadly bacterial infection *Syphilis*. Later replaced by modern antibiotics

Speciazione



Proprietà	**Commenti (esempi)**
Numero di Coordinazione	Intero intervallo: 2 – 10; tipicamente da 4 a 6 per i metalli di transizione, può essere più variabile per i metalli dei gruppi principali (*e.g.* Bi) e più grande per i lantanidi (*e.g.* 9)
Geometria	Esempi: lineare (Au^{I}), planare-quadrata (Pt^{II}), tetraedrica (*e.g.* complessi 'piano-stool' Ru^{II}), bipiramidale trigonale, ottaedrica (Ti^{IV}, Ru^{III}, Pt^{IV}), possibile chiralità centrata sul metallo (Co^{III}, Rh^{III})
Stato di Ossidazione	Ampio intervallo (tipicamente 0 – 7 in ambiente biologico); i diversi stati di ossidazione favoriscono diversi numeri di coordinazione e velocità di scambio dei leganti (*e.g.* Pt^{IV} *vs* Pt^{II})
Tipo di Legante	Ampio numero di atomi donatori *e.g.* C, N, O, alogenuri, P, S, Se. Leganti chelanti; denticità *e.g.* (κ^2) 1,2-diamminoetano, (κ^6) EDTA; apticità *e.g.* legami di tipo η^6 e η^4 per il benzene
Stabilità Termodinamica	Ampio intervallo di forza del legame M–L (tipicamente 50-150 $kJ \cdot mol^{-1}$), molto più debole rispetto al tipico legame covalente, *e.g.* legame singolo C–C (250 – 500 $kJ \cdot mol^{-1}$)
Stabilità Cinetica	Il tempo di vita dei legami M–L copre un intervallo molto ampio (ns – anni). Dipende molto dallo stato di ossidazione del metallo e dagli altri leganti; può essere stereospecifico, *e.g.* effetto *trans* nel Pt^{II}.
Proprietà dei Leganti	Interazioni relative alla sfera esterna dei leganti, *e.g.* legame a idrogeno, interazioni idrofobiche (< 50 $kJ \cdot mol^{-1}$), possono servire al riconoscimento recettoriale (chiralità inclusa); possono subire trasformazioni *in vivo e.g.* di tipo redox, idrolisi, reazioni enzimatiche (*e.g.* ad opera del P450 nel fegato).
Stabilità Nucleare	Nuclei radioattivi possono essere usati per seguire il metabolismo dei composti *e.g.* ^{195m}Pt ($t_{½}$ = 4 d) e ^{99m}Tc ($t_{½}$ = 6 h). A seconda del nuclide variano il tipo di decadimento (α, β, γ) e il tempo di semi-vita.

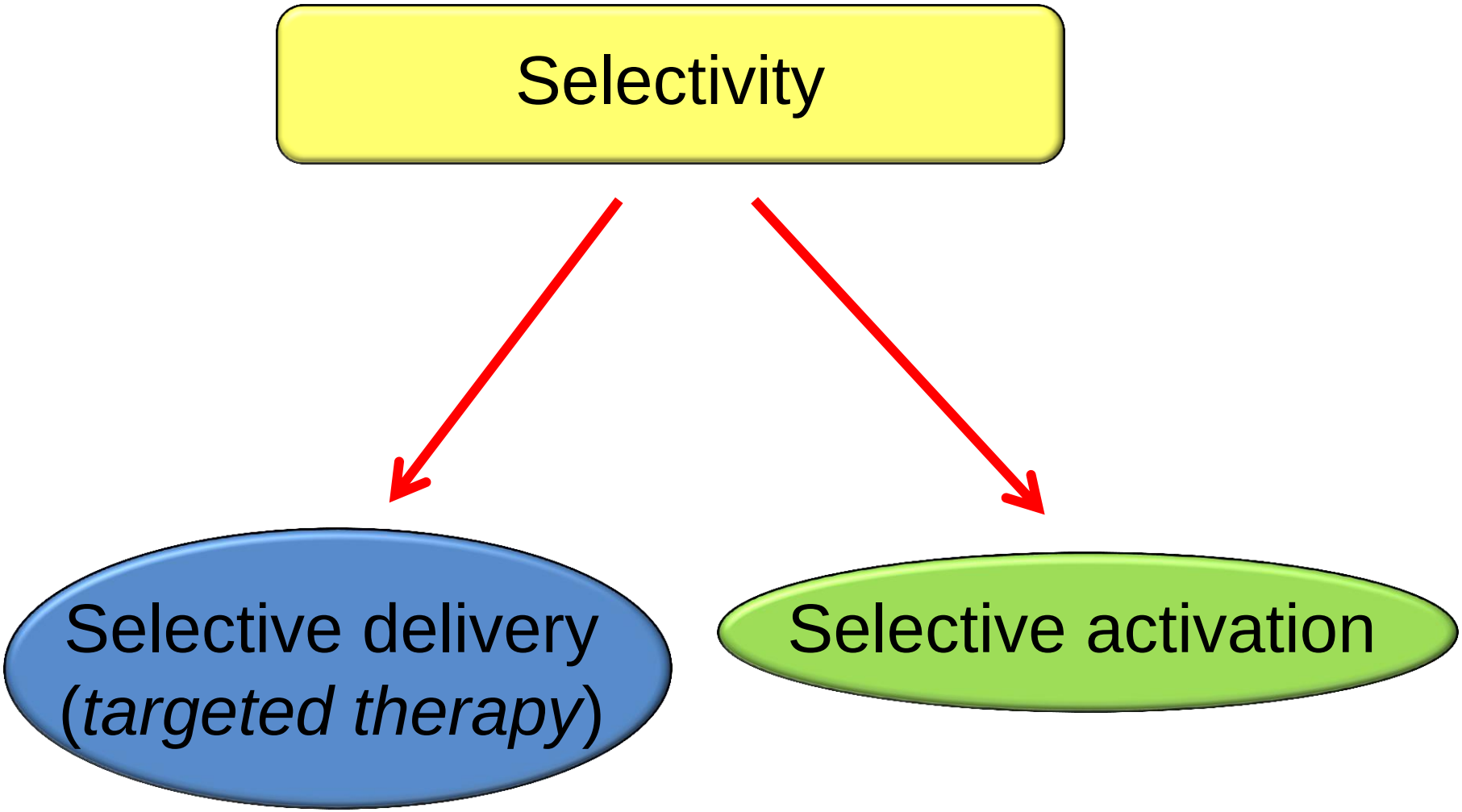

Metal-based
Drug
Functional
compound
Structural
compound

profarmaci

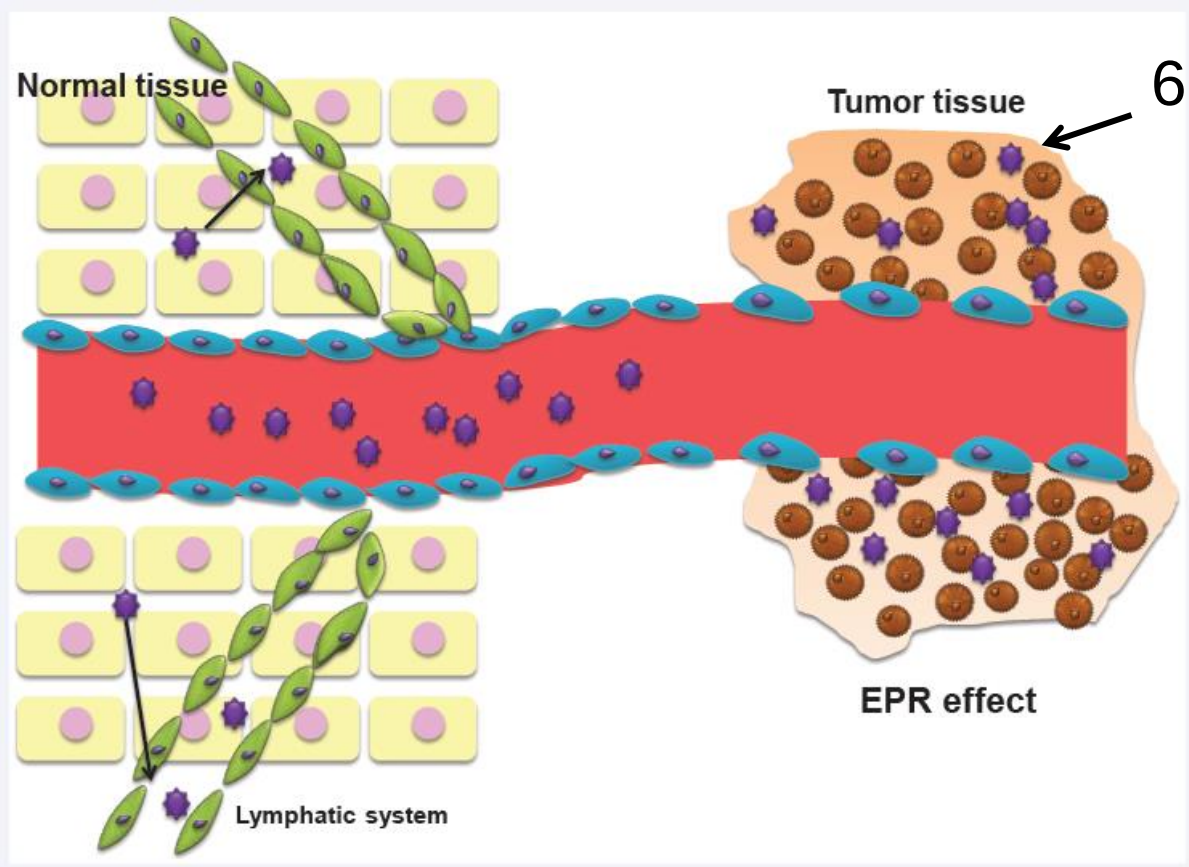
The *multi-stage rocket model*

M (+ inert ligands)

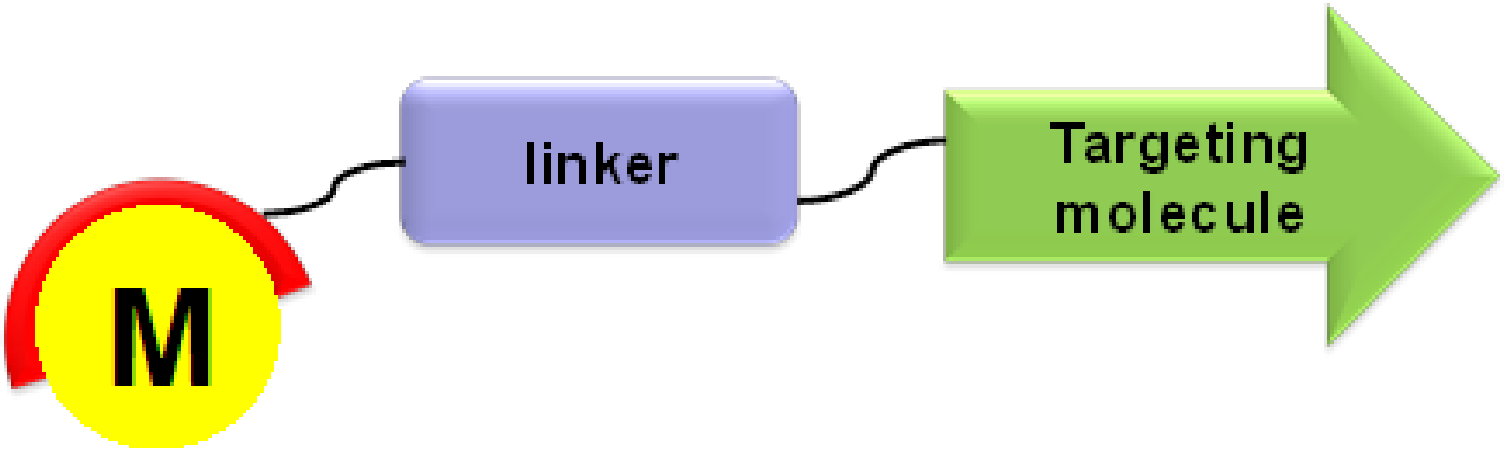
Exchangeable Ligands

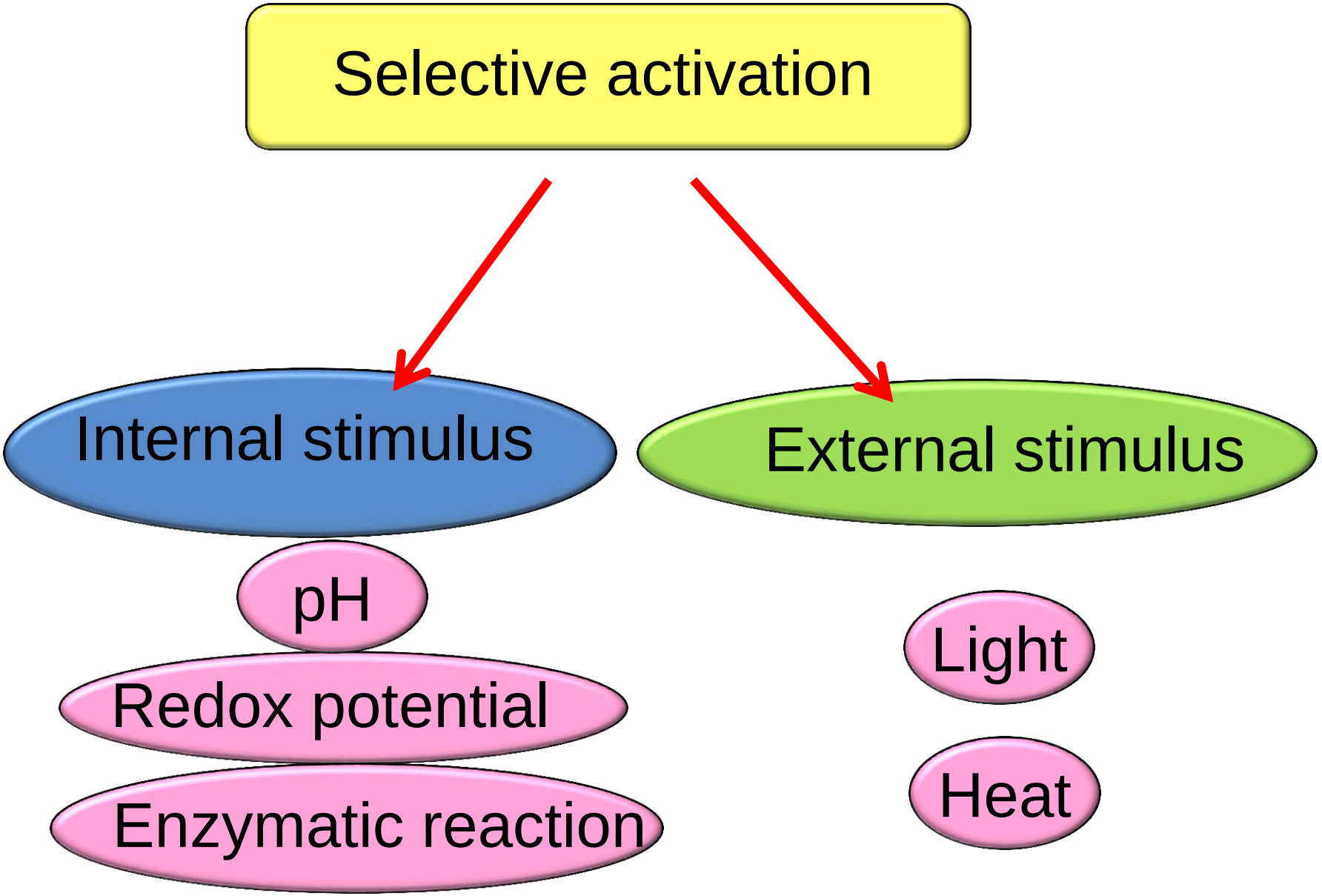

Selectivity
Selective delivery
(*targeted therapy*)
Selective activation

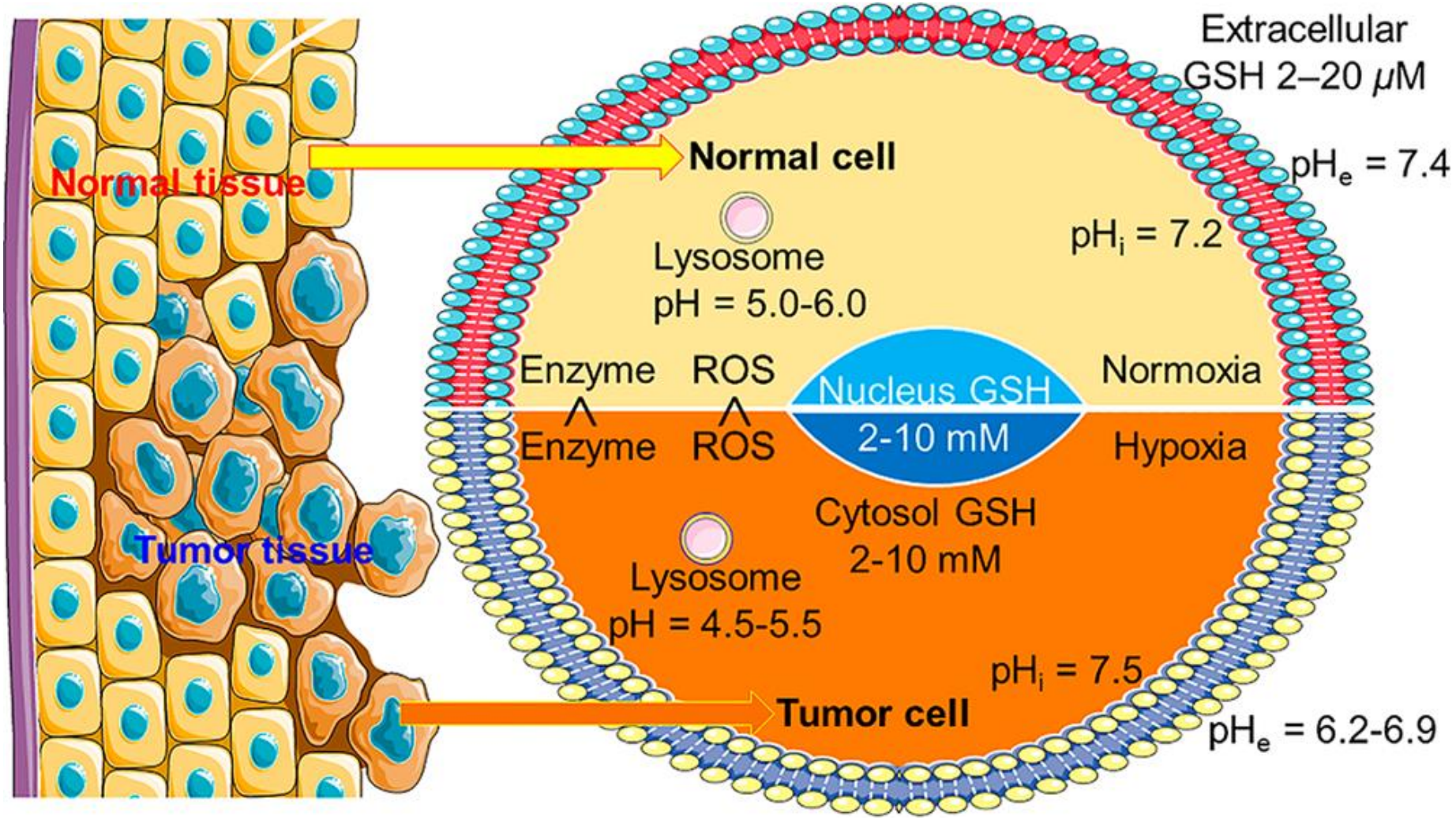
Passive selectivity: EPR (*Enhanced Permeability and Retention*) effect



Active selectivity: targeted approach




Selective activation
Internal stimulus
External stimulus
pH
Redox potential
Enzymatic reaction
Light
Heat


Extracellular
GSH 2–20 μM
Normal tissue
Normal cell
pHe = 7.4
pHi = 7.2
Lysosome
pH = 5.0-6.0
Enzyme
ROS
Enzyme
ROS
Nucleus GSH
2-10 mM
Normoxia
Hypoxia
Cytosol GSH
2-10 mM
Tumor tissue
Lysosome
pH = 4.5-5.5
pHi = 7.5
Tumor cell
pHe = 6.2-6.9

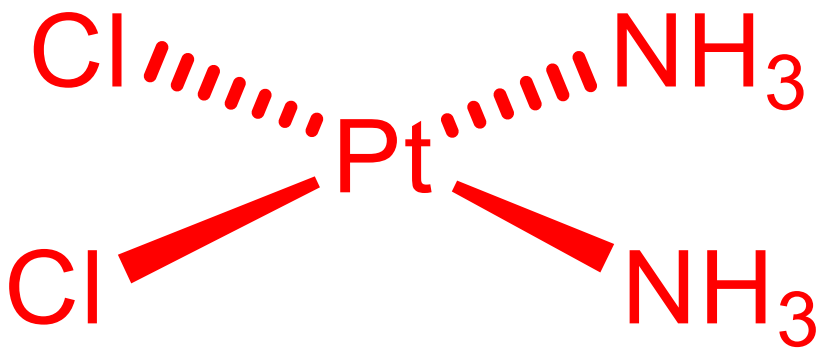
Platinum anticancer compounds

Worldwide most widely used anticancer compounds

Sales for billions of $

Lifesaver compounds

The story of cisplatin



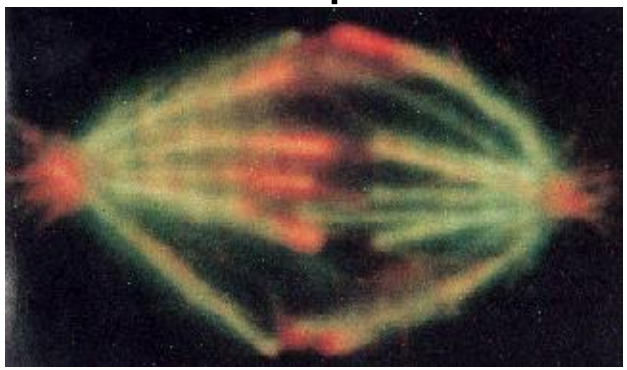
Cisplatin and few other platinum coordination complexes (i.e. without Pt–C bonds) are included in approximately 50–70% of therapeutic schemes used to treat cancer patients.

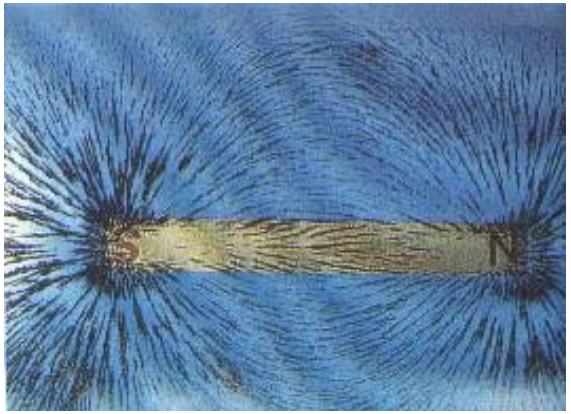
Barnett Rosemberg
1927 - 2009

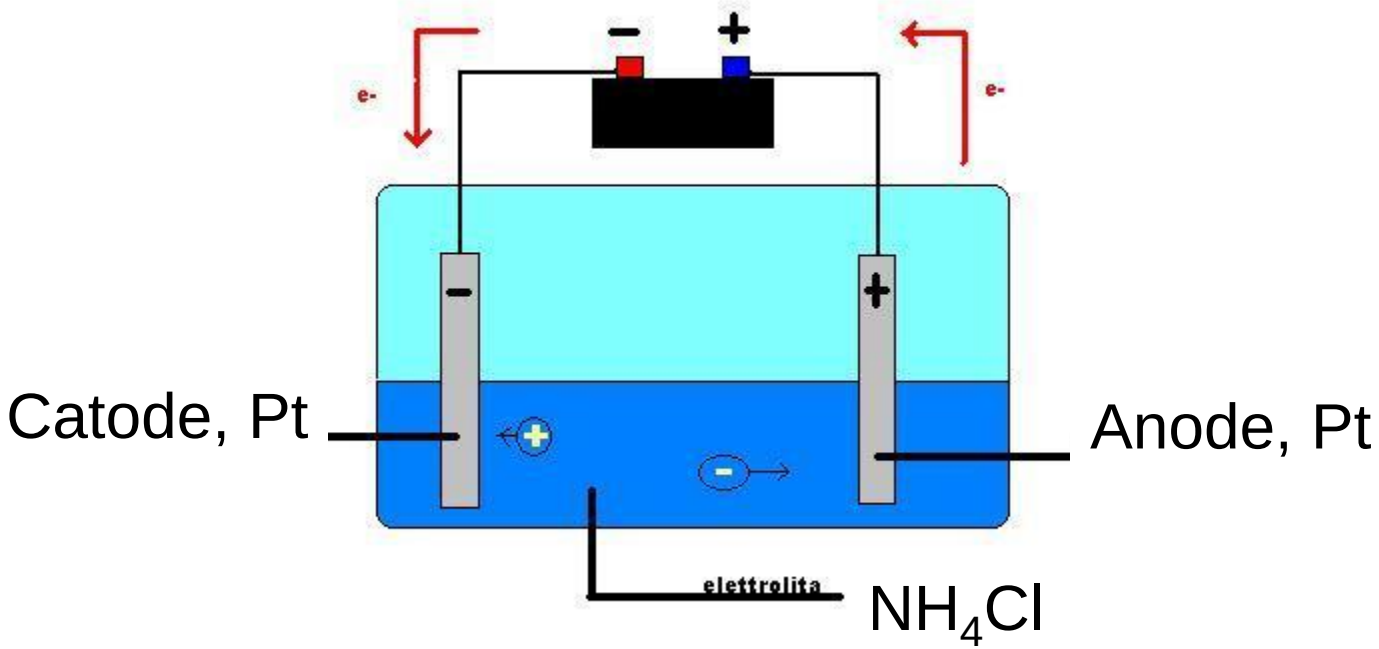
1961: Rosemberg joins the Biophysics Department at Michigan State University

***Serendipity**: when you discover something unexpected and unsought for, while searching for something else.*

mitotic spindles



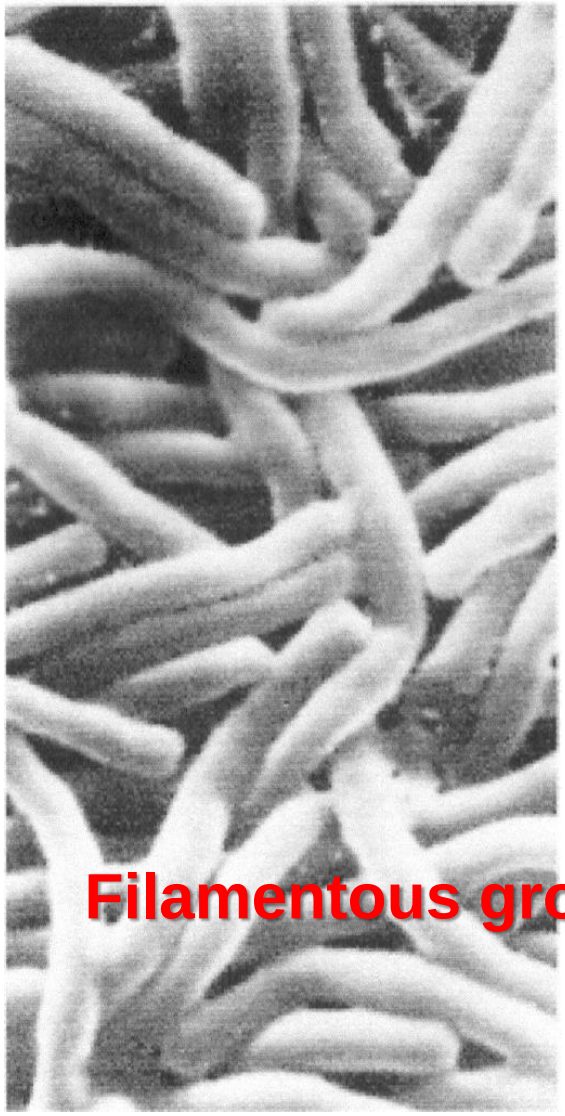




Catode, Pt

Anode, Pt

NH_4Cl



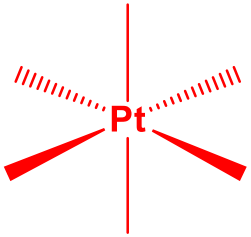
1963 - 1964

Filamentous growth in *E. coli*

Platinum has two positive oxidation states:

Pt(II), d^8, diamagnetic, square planar

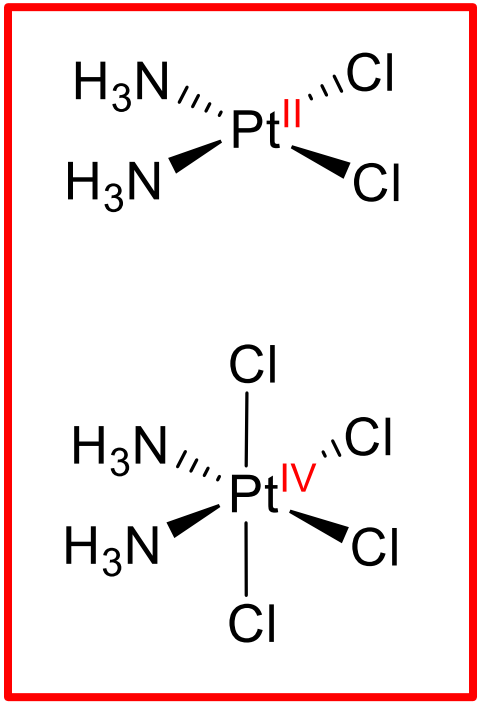
Pt(IV), d^6, diamagnetic, octahedral



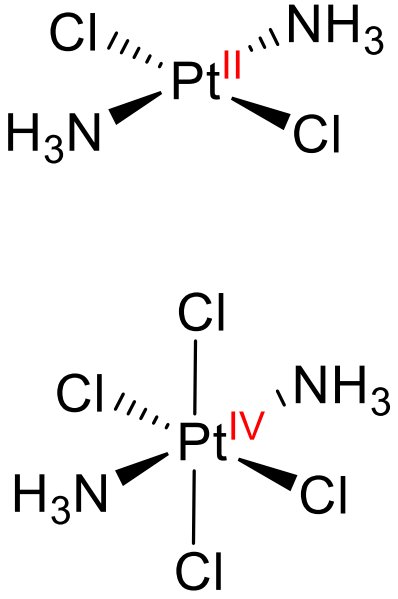
In both oxidation states platinum behaves as a *soft* Lewis acid (high affinity for sulfur ligands), makes stable compounds (strong coordination bonds) and is very inert.

Anionic complexes, e.g. $[PtCl_4]^{2-}$, are quite toxic at low concentrations, but induce no filamentous growth

cis

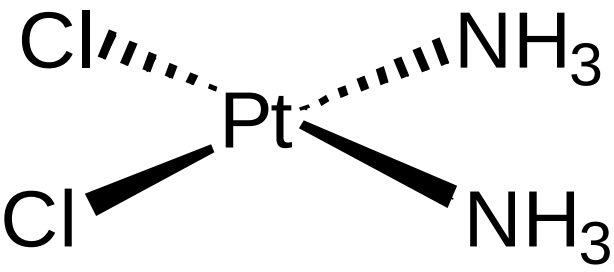


trans



The *cis* neutral species are active at sub-toxic concentrations

The *trans* neutral species are inactive at low concentrations (ppm), become toxic at higher concentrations.



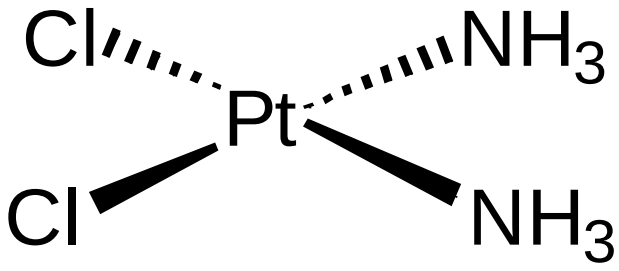
cis-dichloridodiamminoplatinum(II)
(*cisplatin*, cisDDP, *platinol*,…)

Peyrone's chloride, 1844

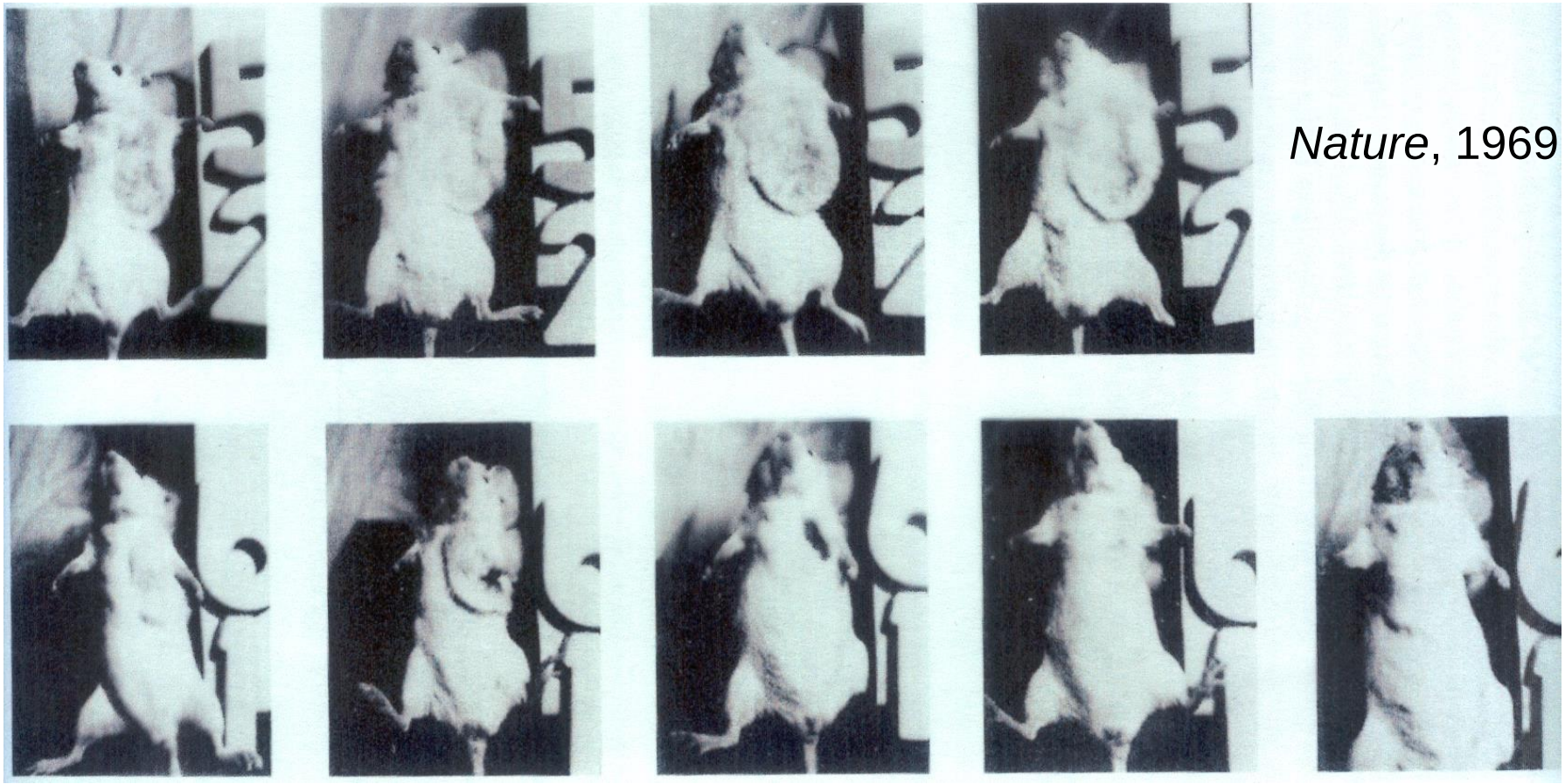
Michele Peyrone (1813–1883)

..the complex stopped cell division in bacteria at concentrations without marked toxicity.
Perhaps then it would stop cell division in tumors which grow rapidly, without unacceptable toxicity to the host animal.

B. Rosemberg

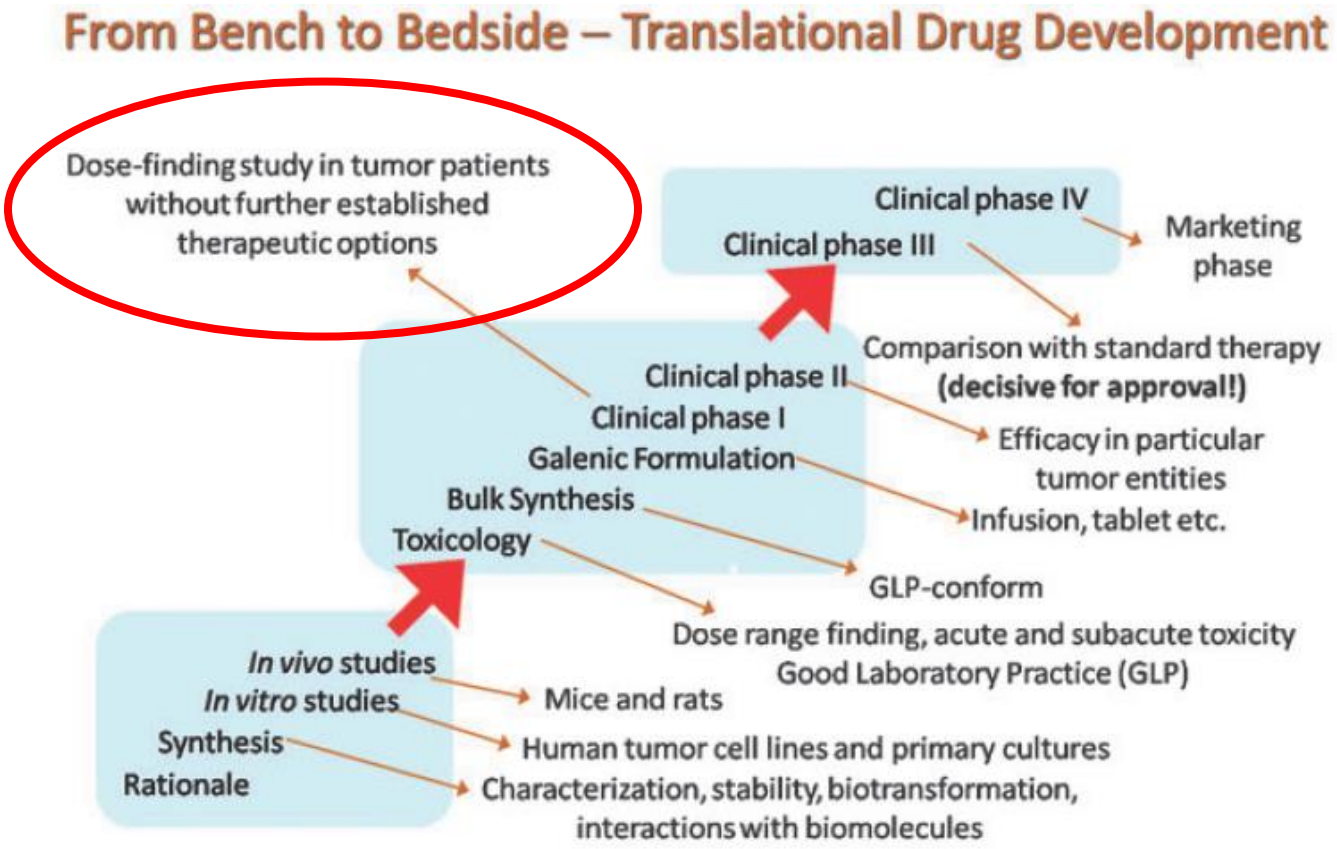


Sarcoma 180
Cisplatin injection on day 8

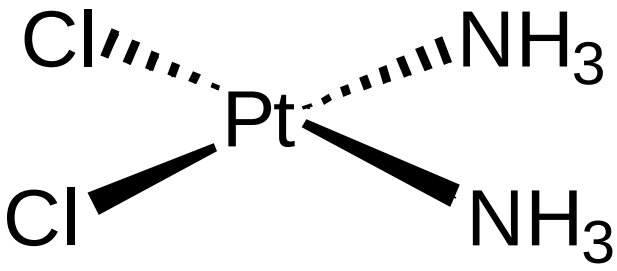


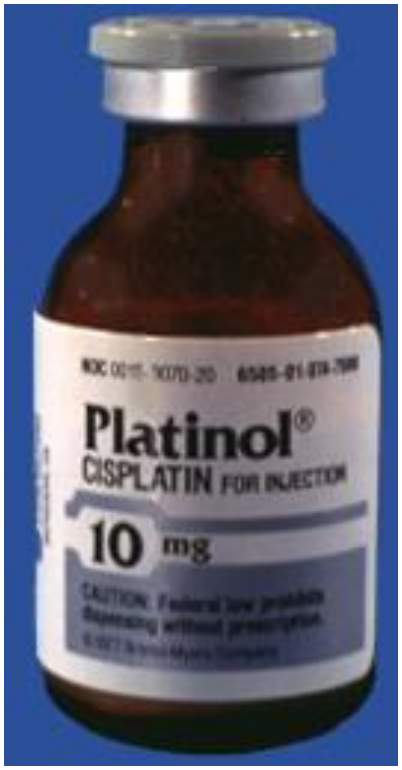
Nature, 1969

In 1971 a phase I study of cisplatin, which included 11 patients with refractory testicular cancer was performed: 9 of 11 responded to cisplatin, including several CRs, an unprecedented finding for a phase I trial even today



Lance
Armstrong





1978
FDA approval

Shotgun Drug

Cisplatin

- **High Anticancer Activity**

  Testicular and ovarian cancer, cervical, bladder, head/neck tumors.
- **Minor Anticancer Activity**

  Breast cancer, lung, colon and rectum adenocarcinomas.
- **Toxic Side Effects**

  Nausea, vomiting, neurotoxicity (*dose-limiting toxicity*), kidney and ear damage.
- **Resistance**

  Spontaneous or acquired.