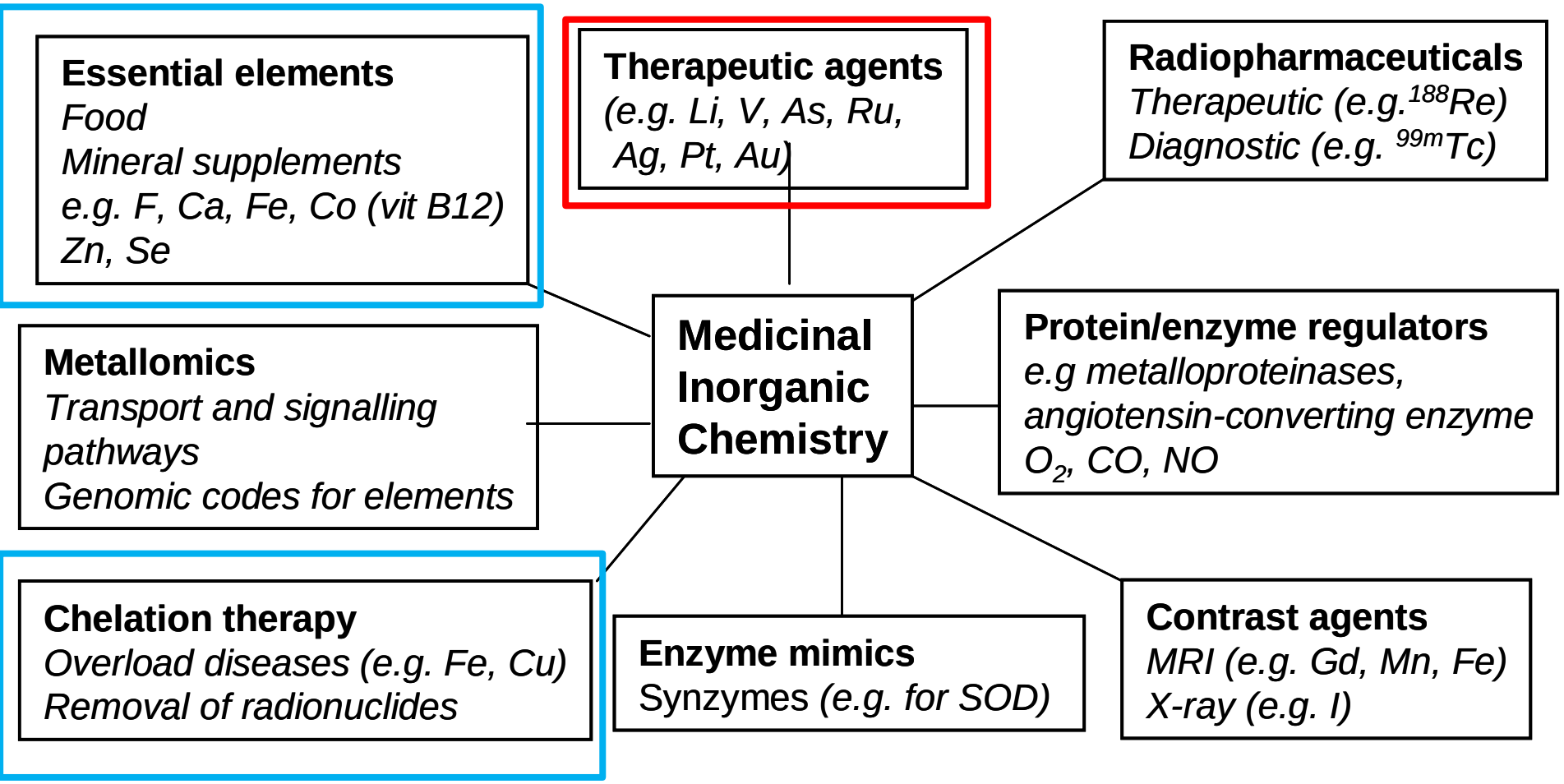
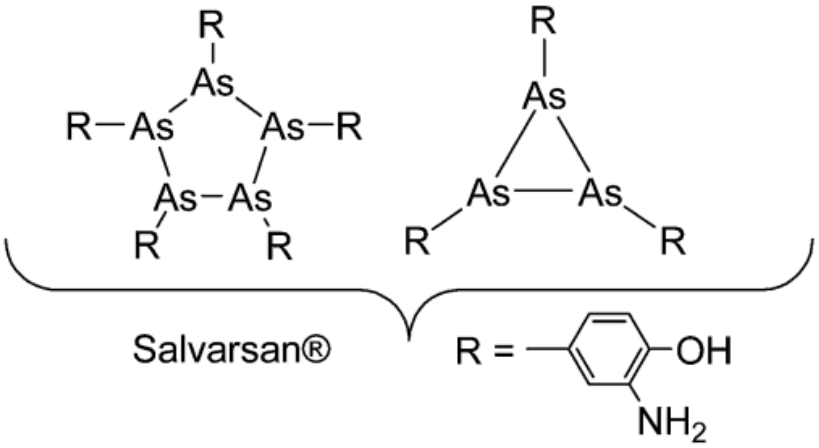
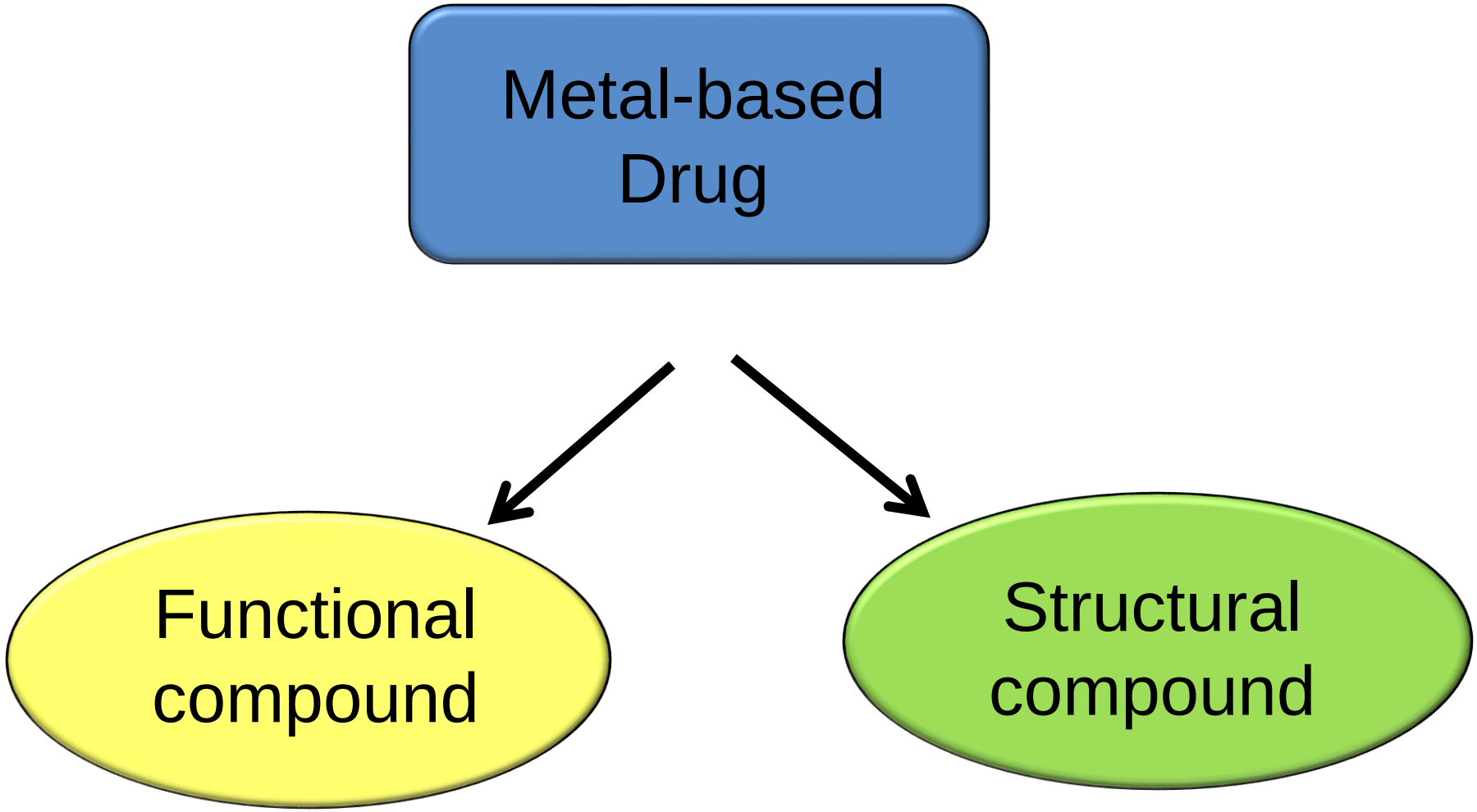

Essential elements
Food
Mineral supplements
e.g. F, Ca, Fe, Co (vit B12)
Zn, Se
Therapeutic agents
(e.g. Li, V, As, Ru,
Ag, Pt, Au)
Radiopharmaceuticals
Therapeutic (e.g. 188Re)
Diagnostic (e.g. 99mTc)
Medicinal Inorganic Chemistry
Metallomics
Transport and signalling pathways
Genomic codes for elements
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)



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



Direct binding of the metal to the bio-target (prodrugs = activation, at least one labile ligand)

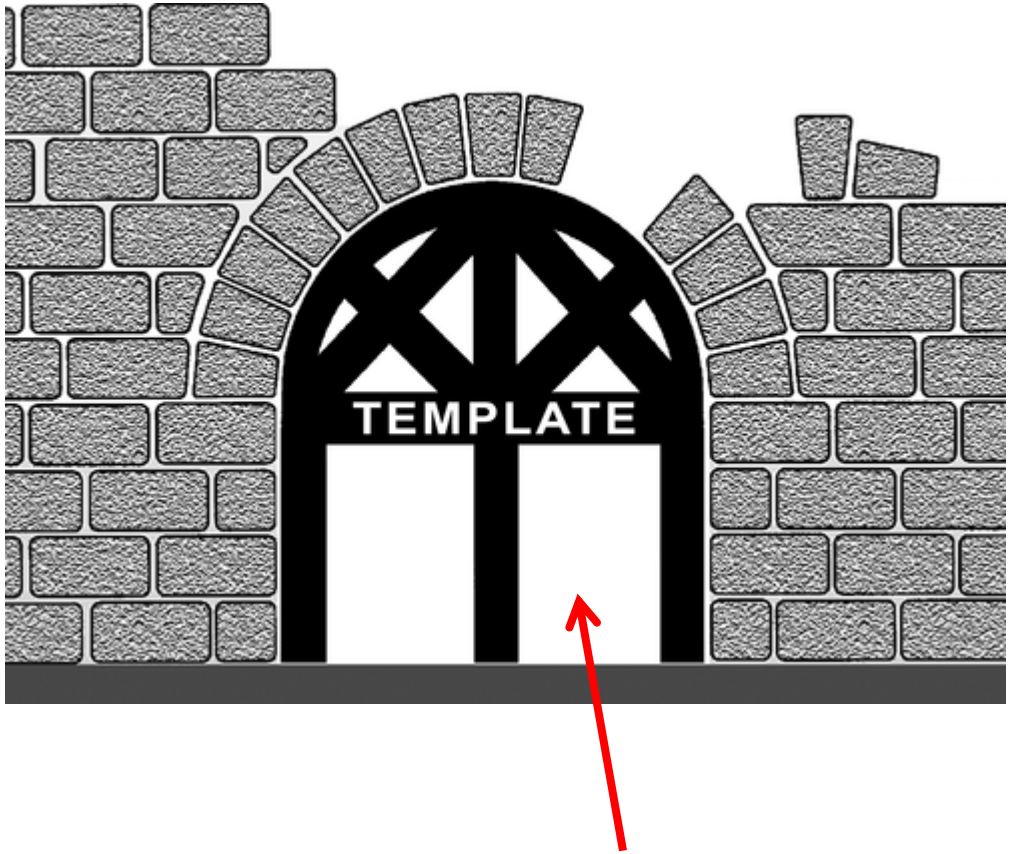
Inert and stable compounds: no direct binding of the metal to the bio-target

Functional compounds: the *multi-stage rocket model*

M (+ inert ligands)

Exchangeable
Ligands

Structural compounds

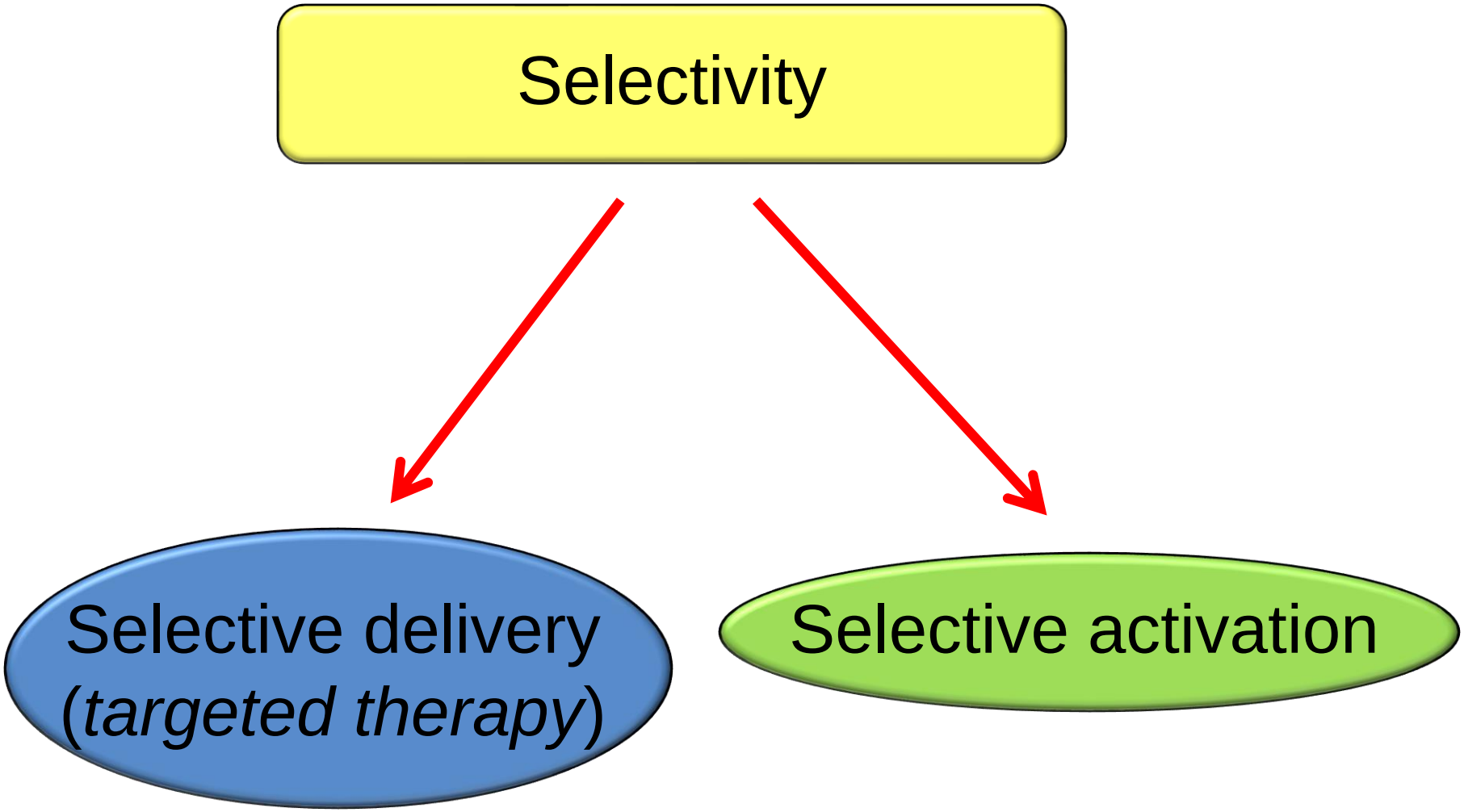


Metal: great structural diversity

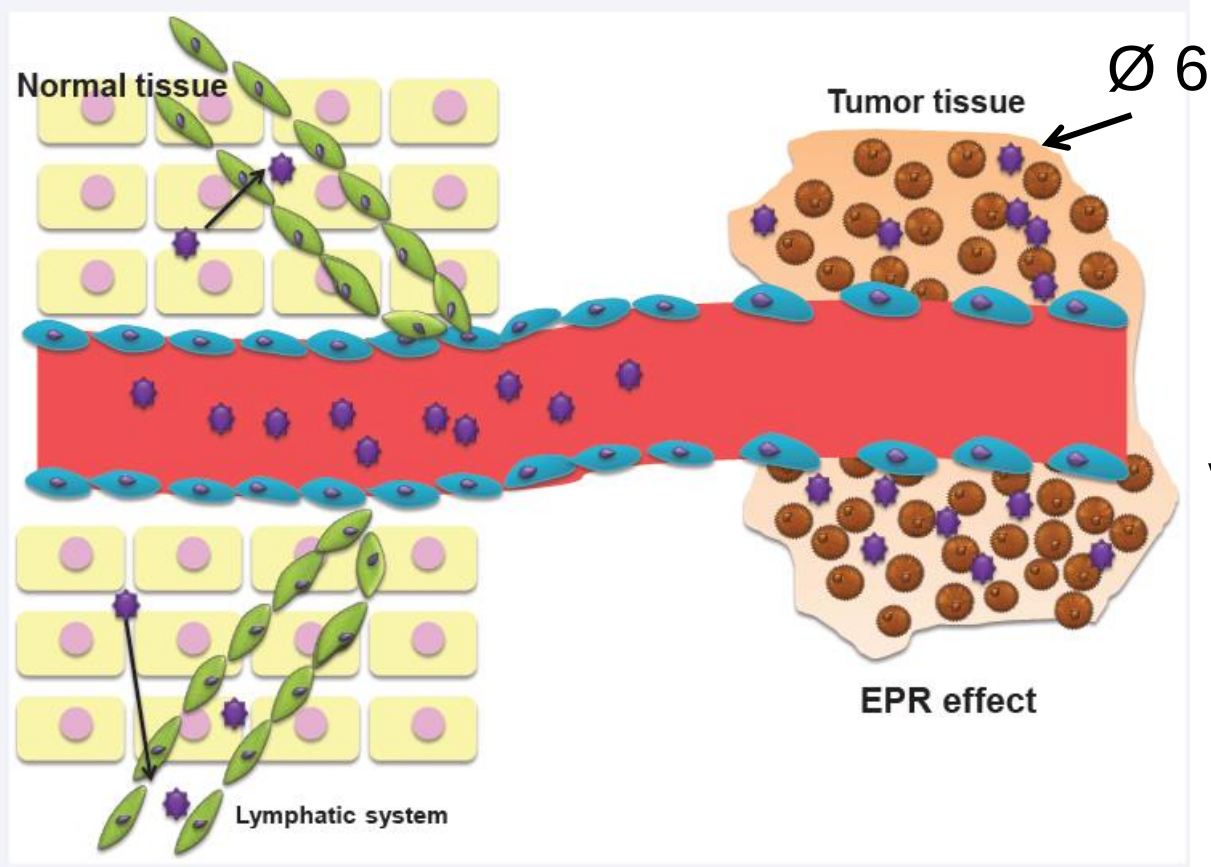
Structural compounds

Physical properties of the metal that are exploited:

- Radioactive emissions (radiopharmaceuticals)
- Relaxivity (MRI contrast agents)
- Absorption and photoreactivity (PDT, PTT, imaging)

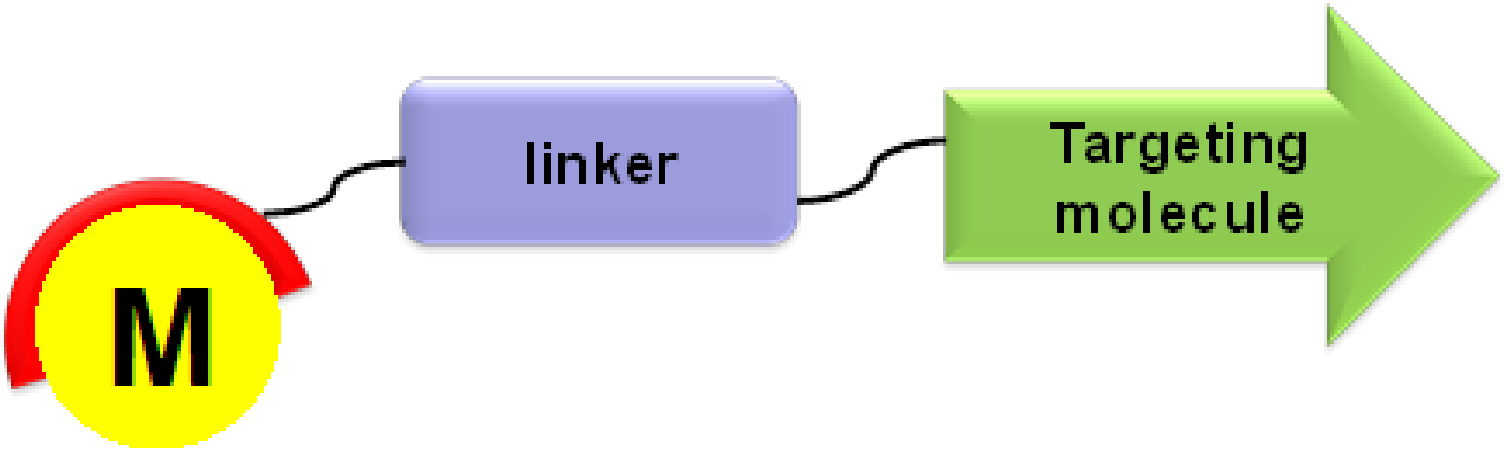

Selectivity
Selective delivery
(*targeted therapy*)
Selective activation

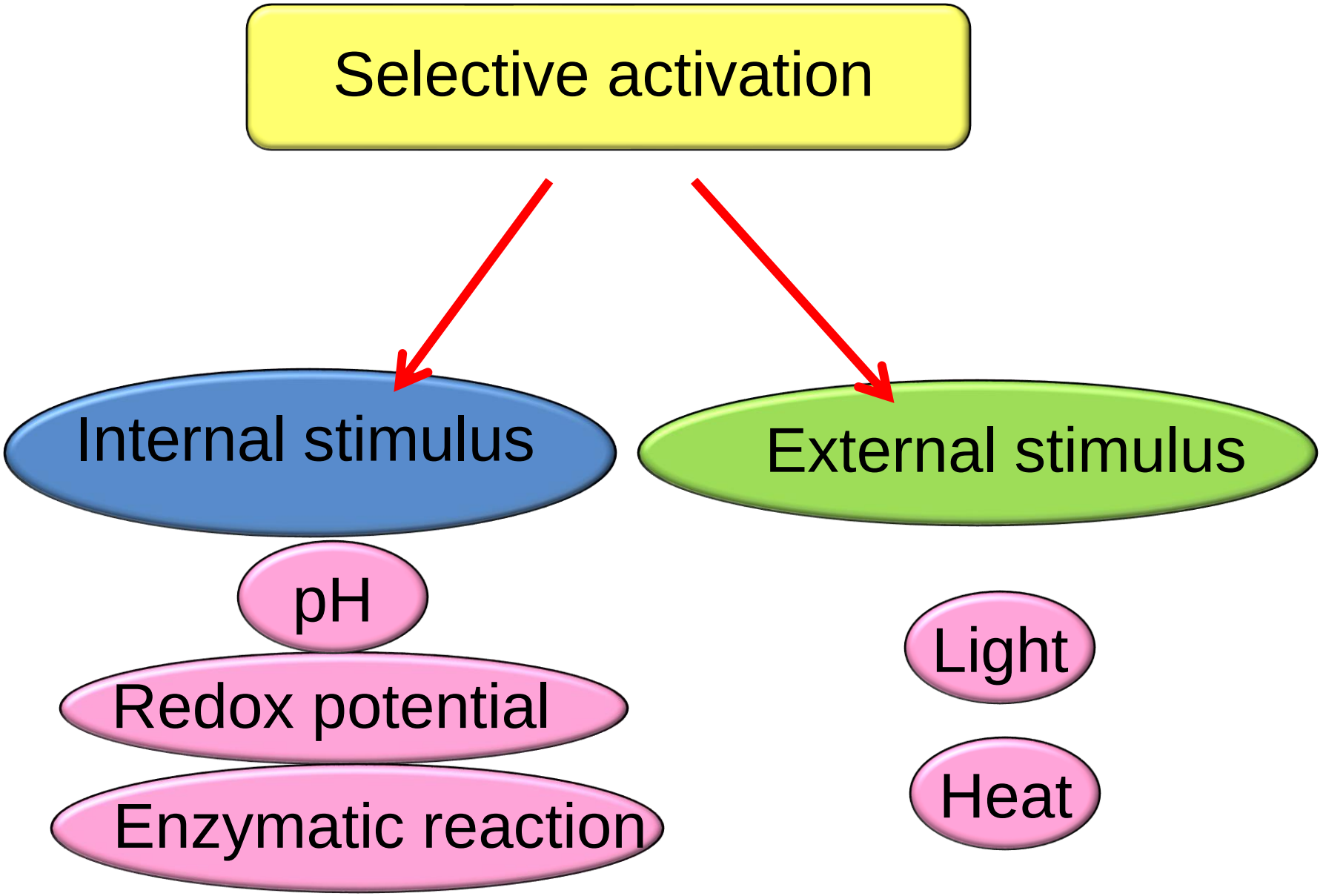
Passive selectivity: EPR effect (*Enhanced Permeability and Retention*)

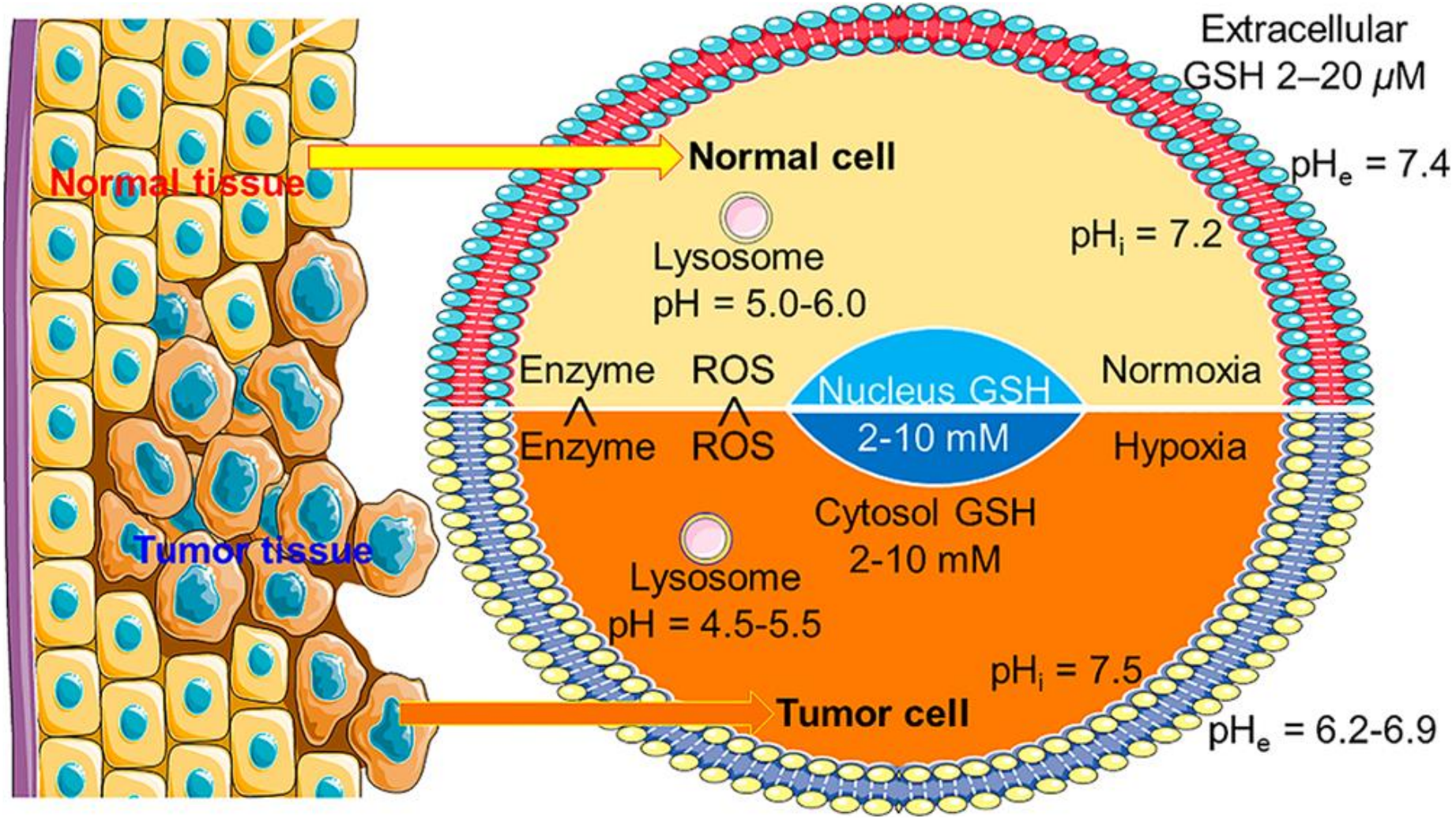


for solid tumors

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

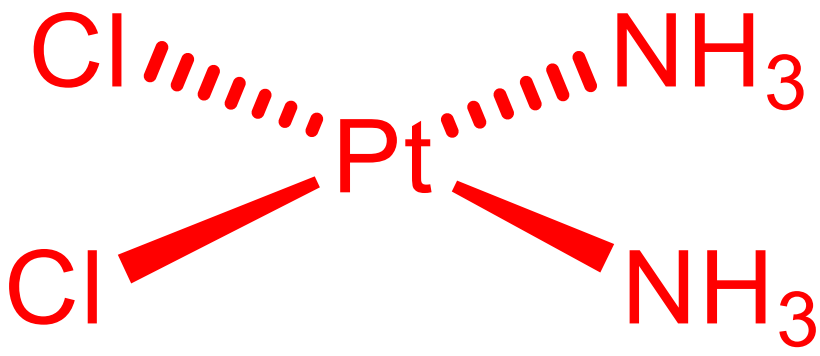
Platinum anticancer compounds

Worldwide most widely used anticancer compounds

Sales for billions of $

Lifesaver compounds

The story of cisplatin



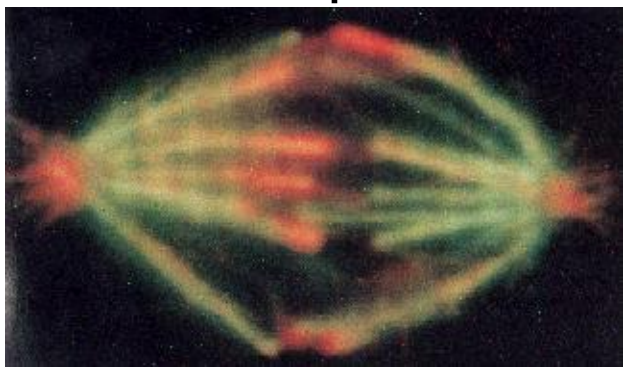
Cisplatin and few other platinum coordination complexes (i.e. without Pt–C bonds) are included in approximately 50–70% of therapeutic schemes used to treat cancer patients.

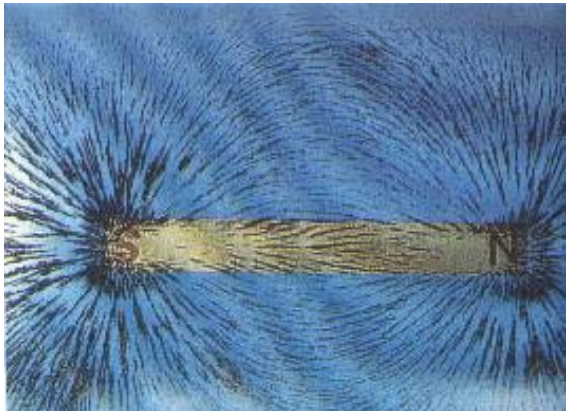
Barnett Rosenberg
1927 - 2009

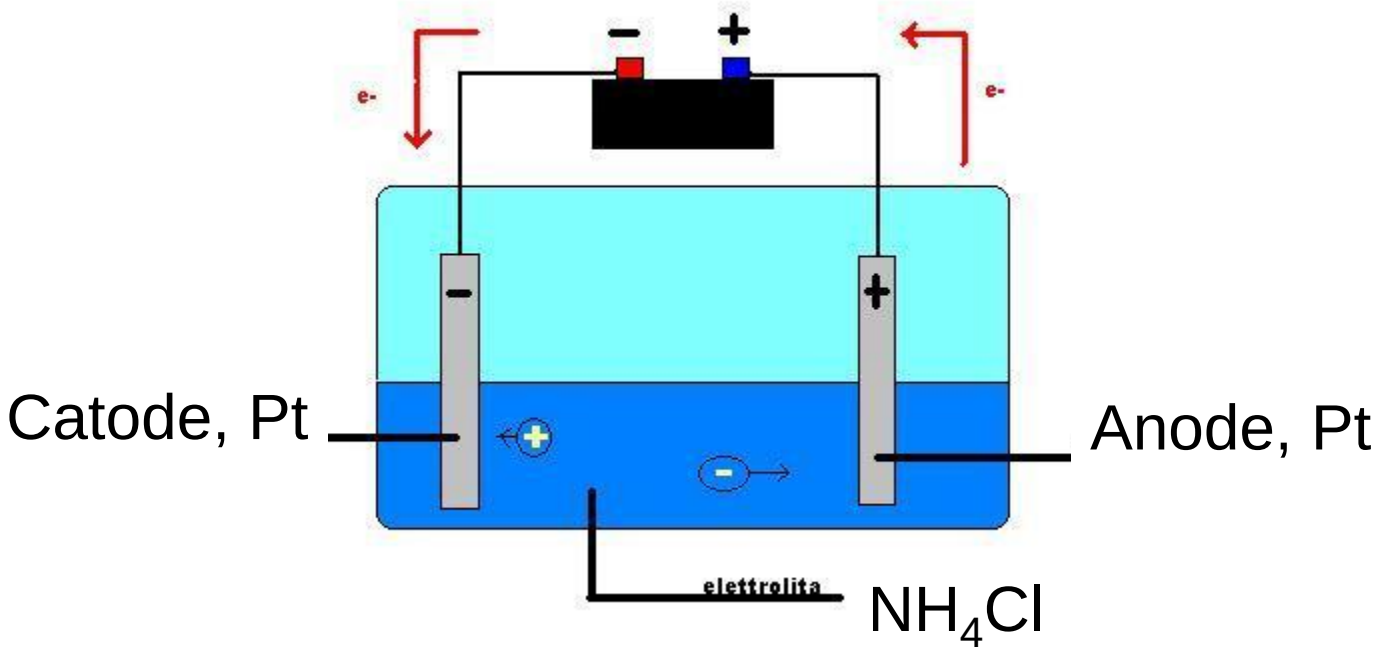
1961: Rosenberg joins the Biophysics Department at Michigan State University

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

mitotic spindles



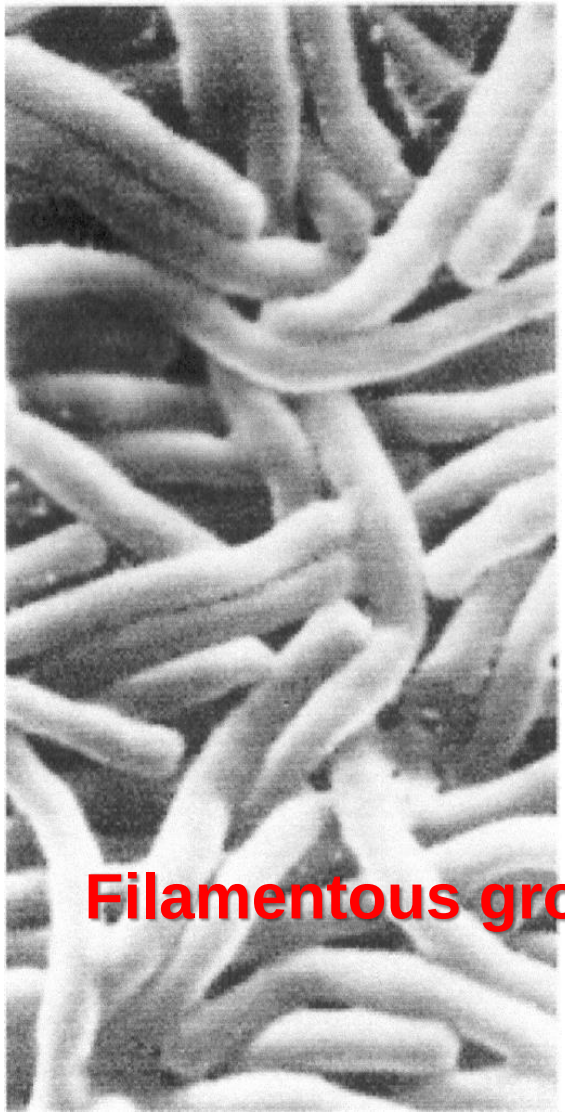




Catode, Pt

Anode, Pt

NH_4Cl



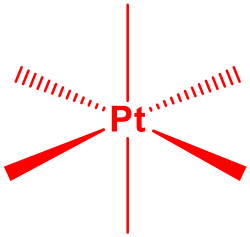
1963 - 1964

Filamentous growth in *E. coli*

Platinum has two positive oxidation states:

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

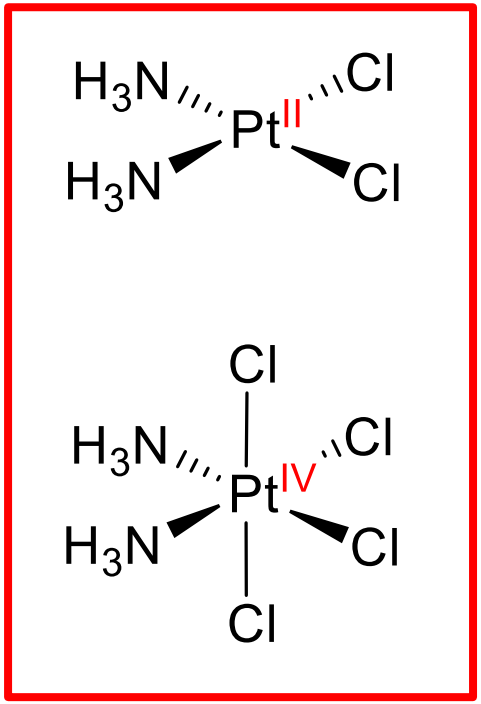
Pt(IV), d^6, diamagnetic, octahedral

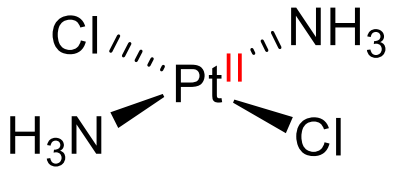


In both oxidation states platinum behaves as a *soft* Lewis acid (high affinity for sulfur ligands), makes stable compounds (strong coordination bonds) and is very inert.

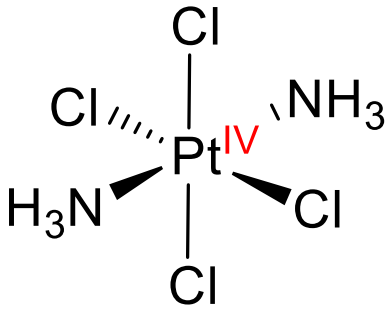
Anionic complexes, e.g. $[PtCl_4]^{2-}$, are quite toxic at low concentrations, but induce no filamentous growth

cis



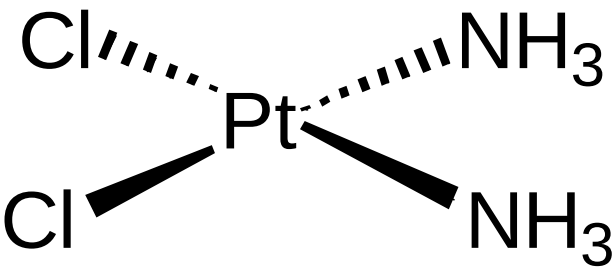


trans



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.



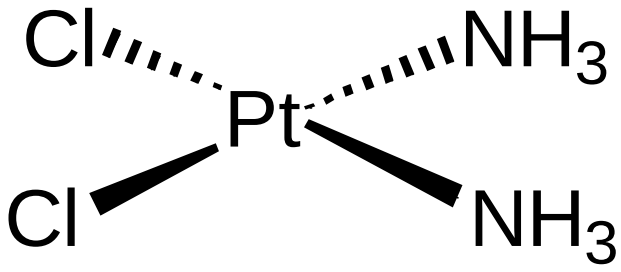
cis-dichloridodiamminoplatinum(II)
(*cisplatin*, cisDDP, *platinol*,…)

Peyrone's chloride, 1844

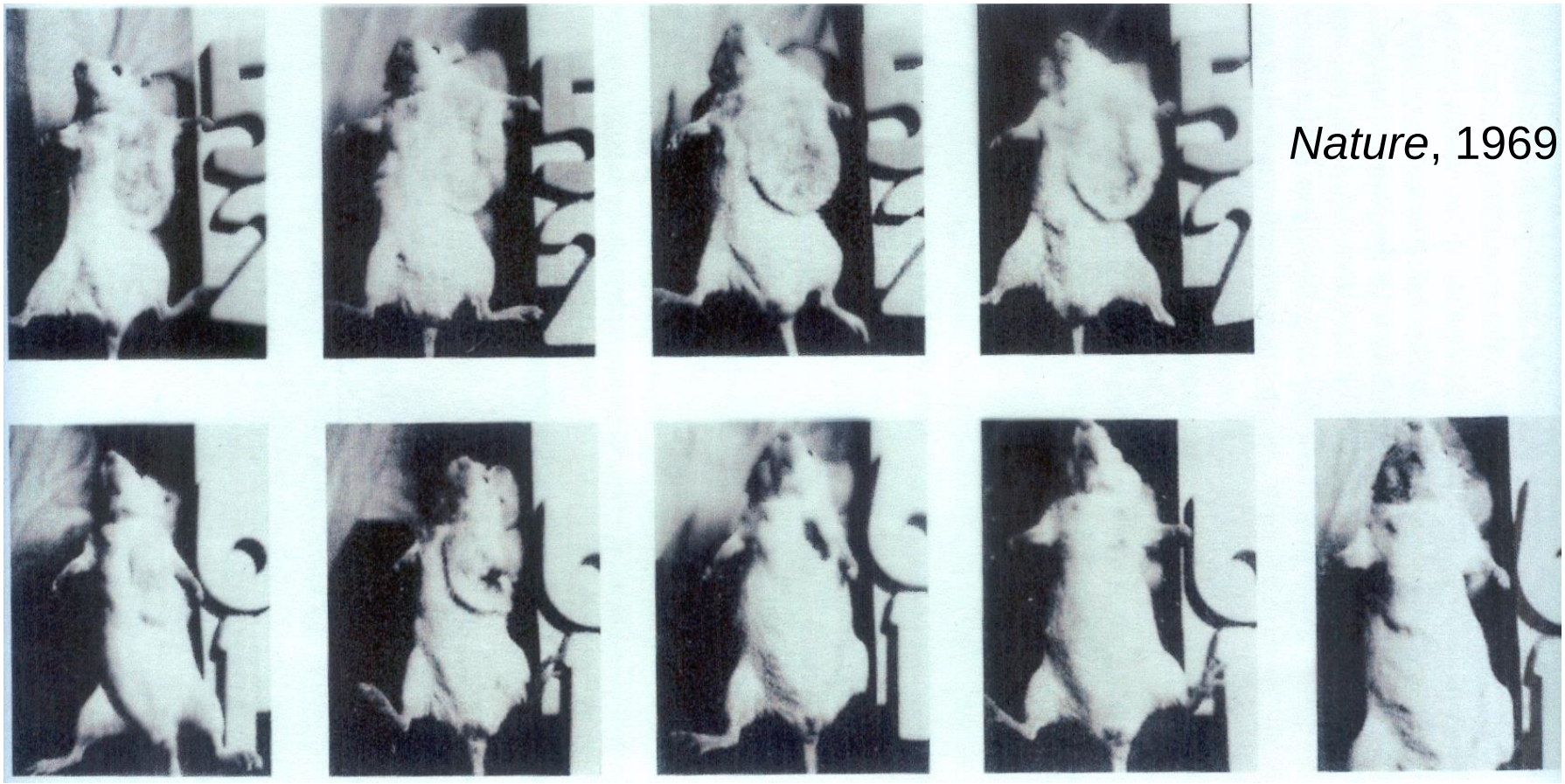
Michele Peyrone (1813–1883)

..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

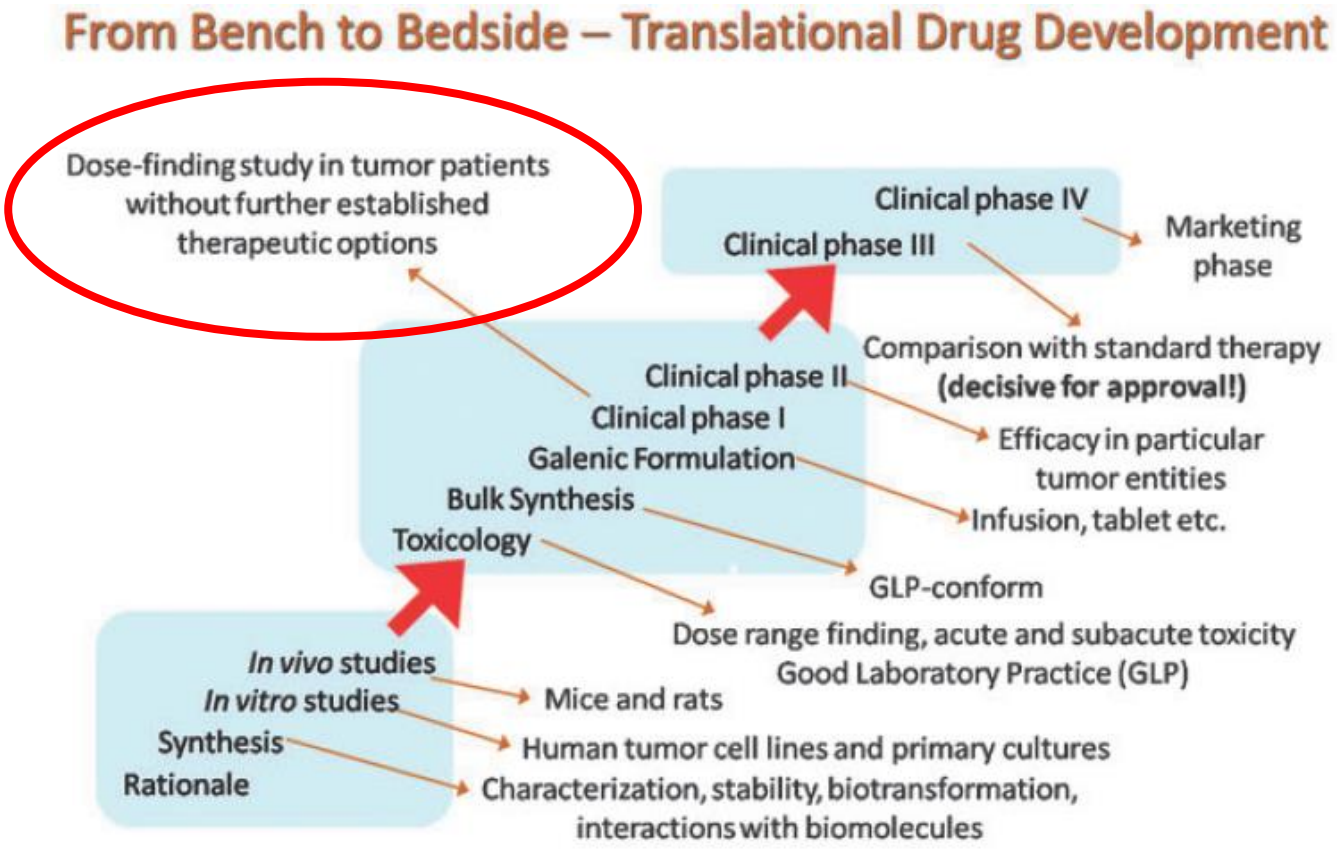


Sarcoma 180
Cisplatin injection on day 8

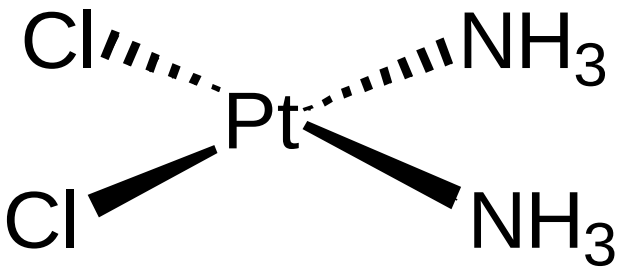


Nature, 1969

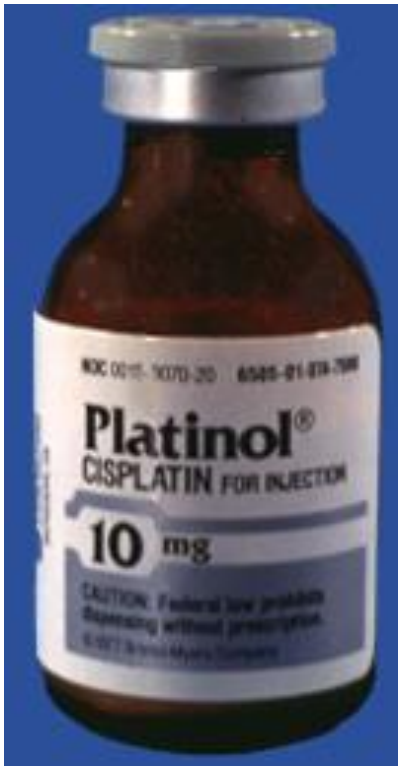
In 1971 a phase I study of cisplatin, which included 11 patients with refractory testicular cancer was performed: 9 of 11 responded to cisplatin, including several CRs, an unprecedented finding for a phase I trial even today



Lance Armstrong



Shotgun Drug



1978
FDA approval

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.