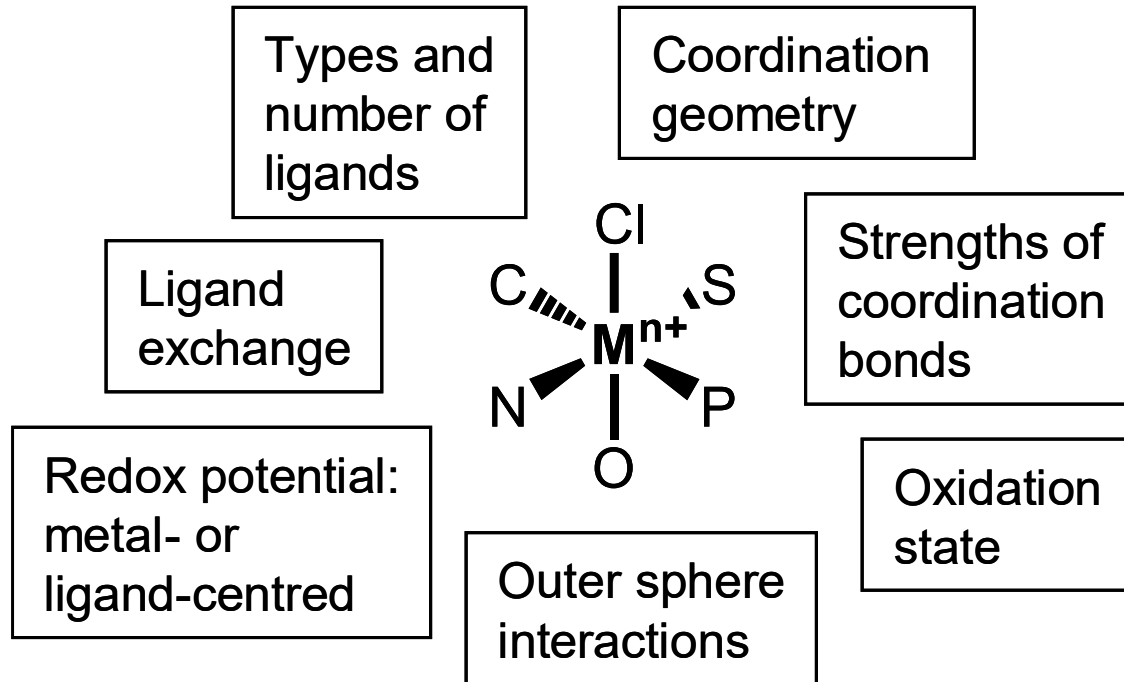


Antimicrobial agent introduced in early 1900 for the treatment of the deadly bacterial infection *Syphilis*. Later replaced by modern antibiotics

# Diversity



# Metal-based Drug

```
graph TD; A[Metal-based Drug] --> B[Functional compound]; A --> C[Structural compound];
```

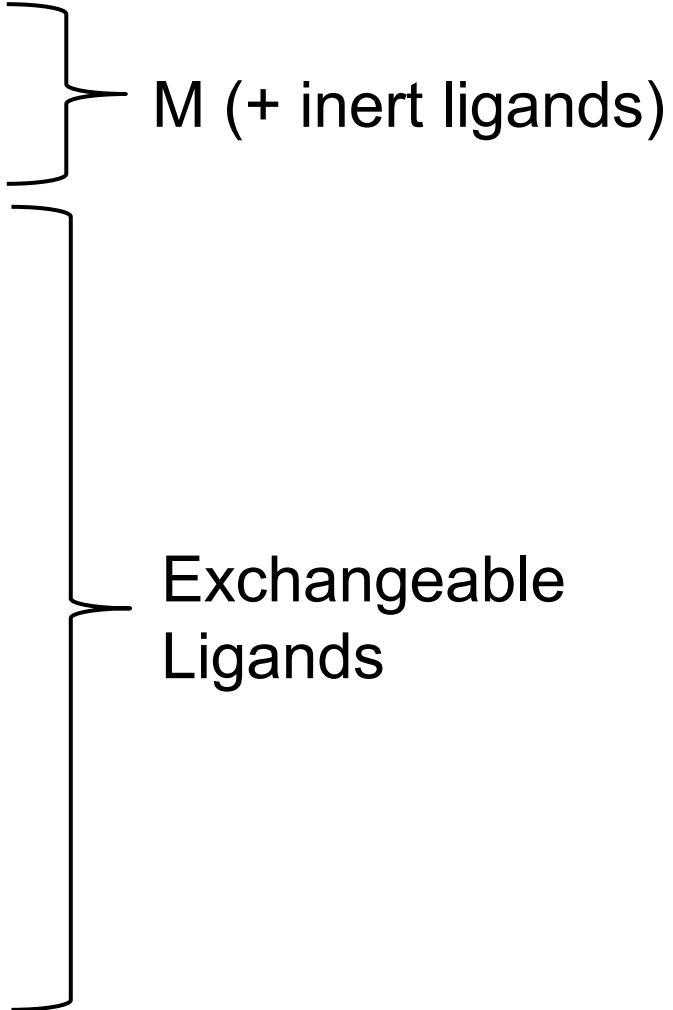
Functional compound

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

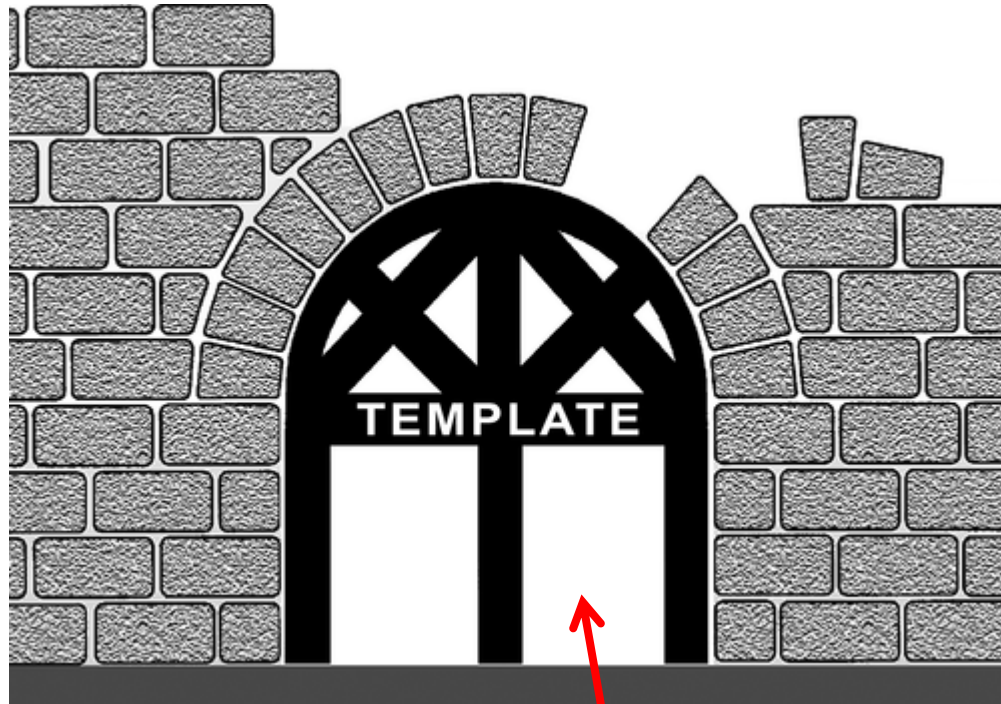
Structural compound

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

# Functional compounds: the *multi-stage rocket model*



# 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)

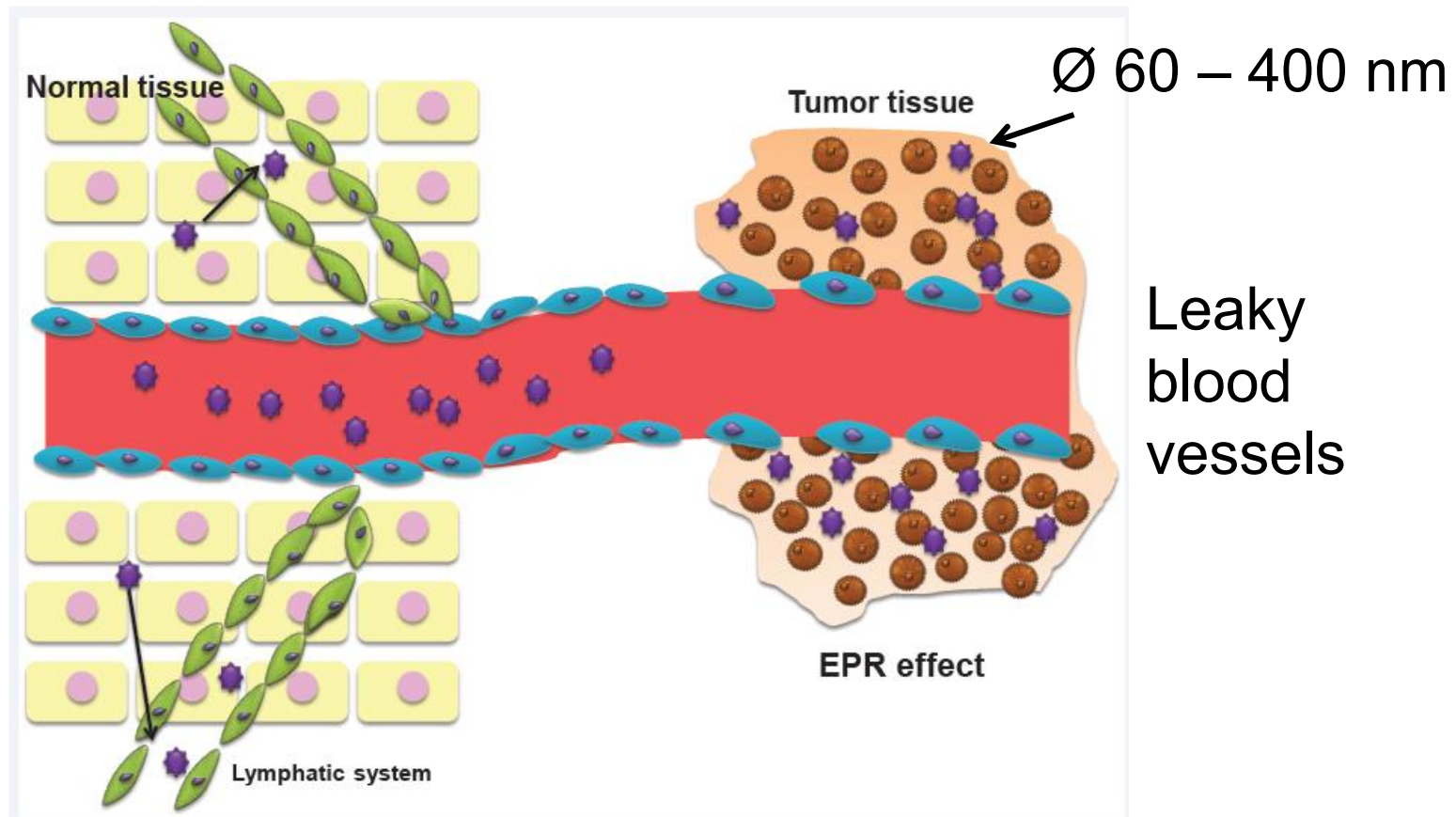
Selectivity

```
graph TD; A[Selectivity] --> B[Selective delivery (targeted therapy)]; A --> C[Selective activation];
```

Selective delivery  
*(targeted therapy)*

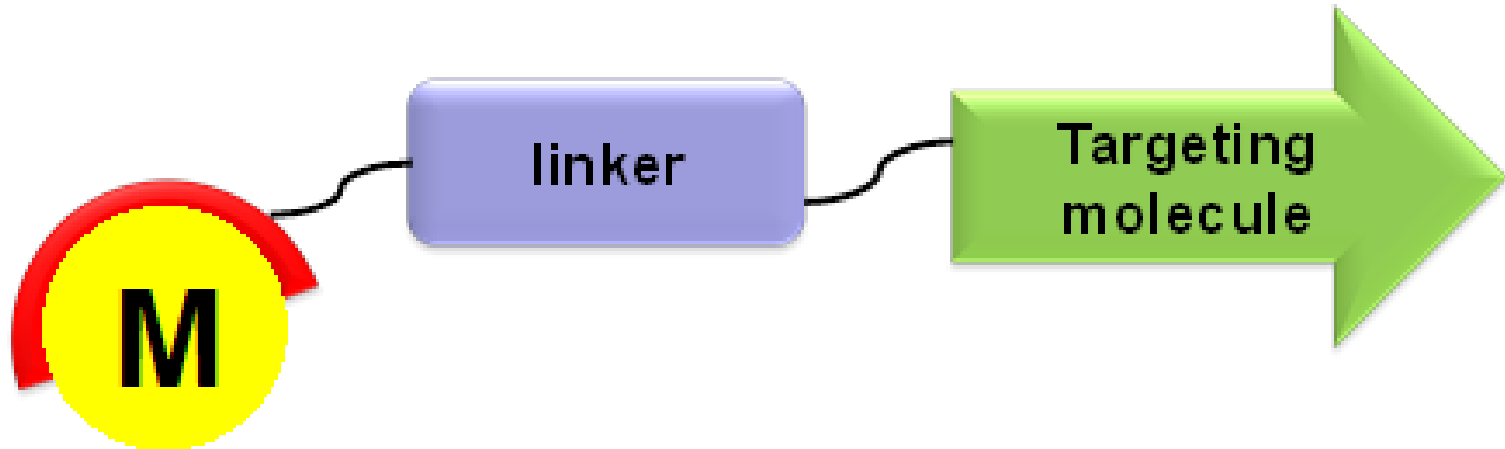
Selective activation

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

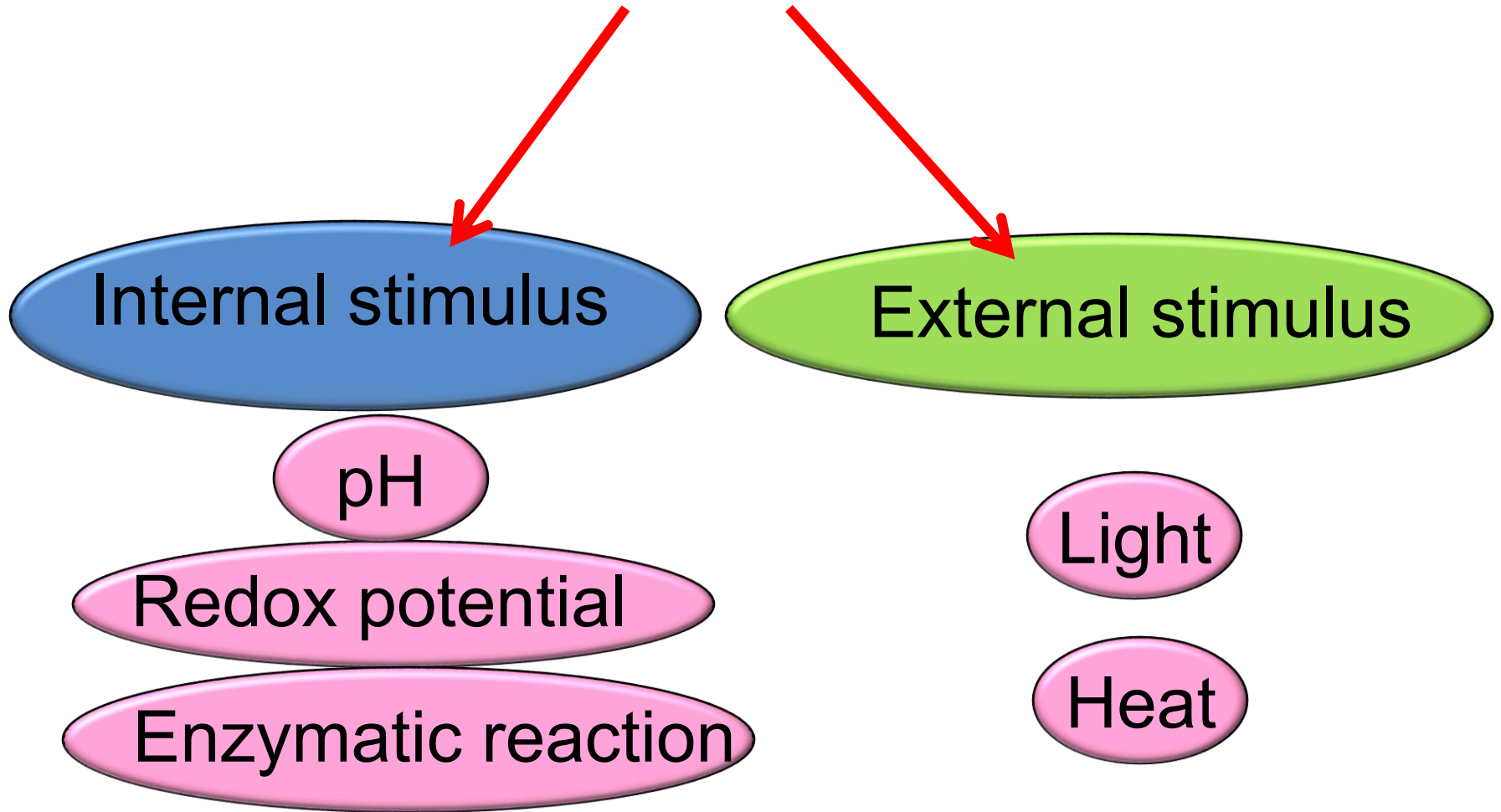


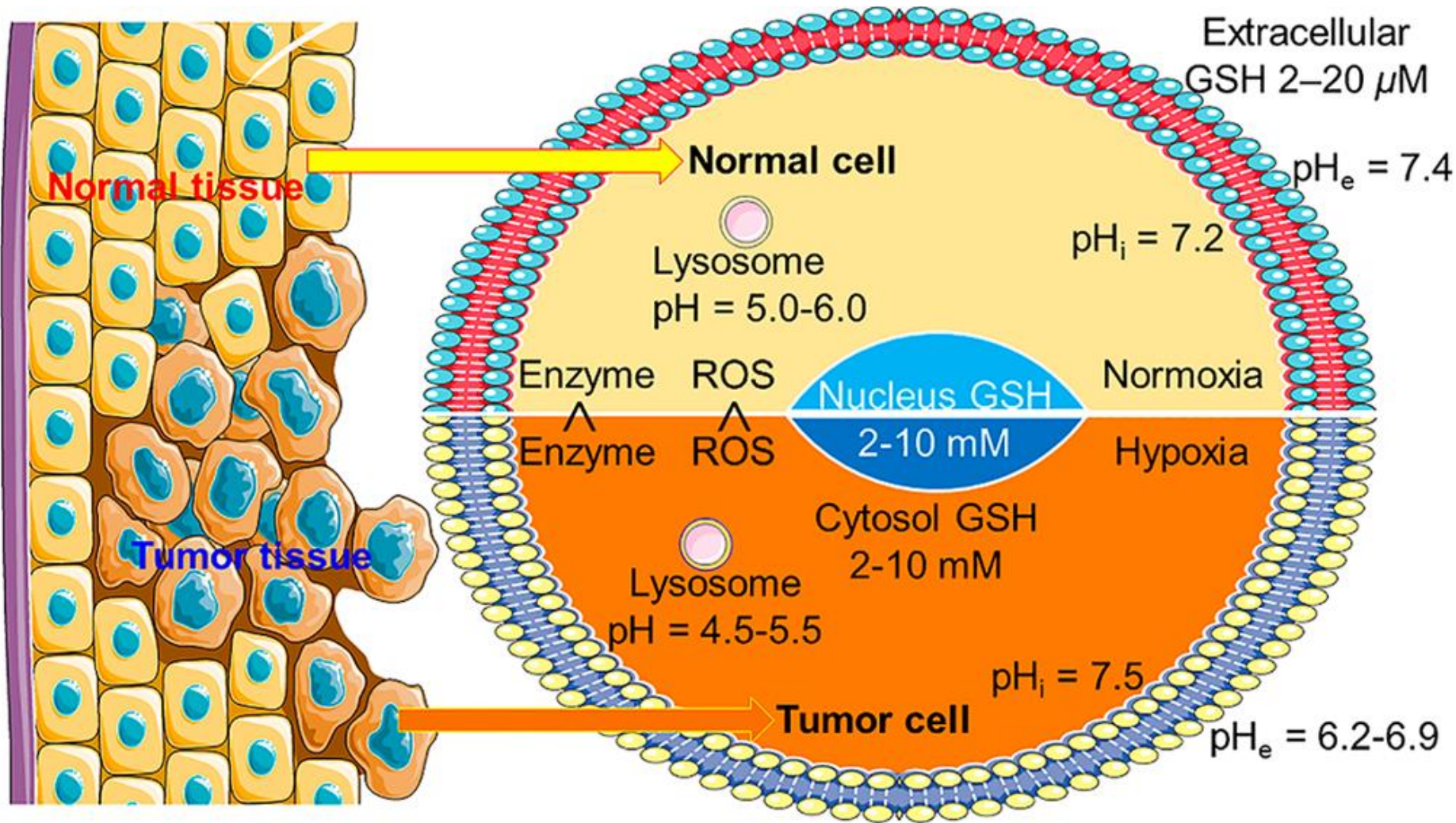
*for solid tumors*

# Active selectivity: targeted approach



# Selective activation





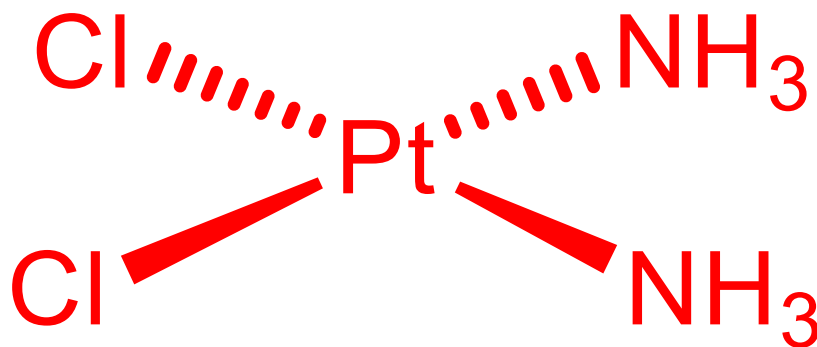
Platinum  
anticancer  
compounds

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.*

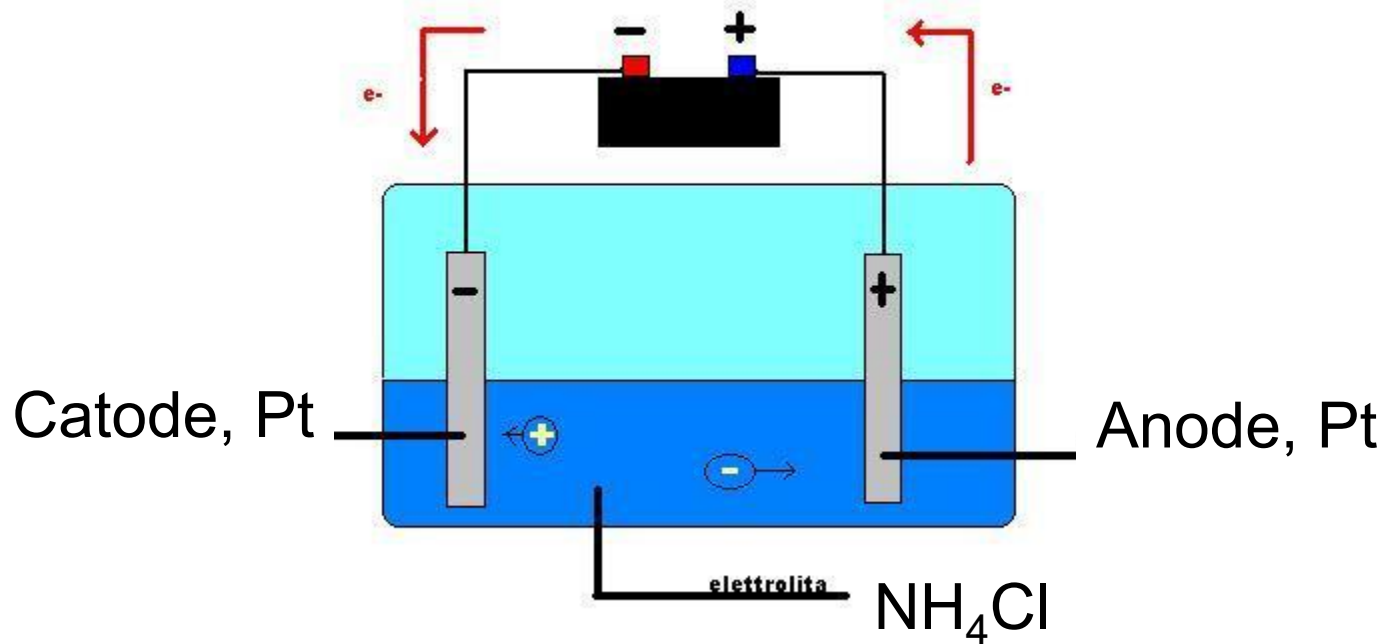
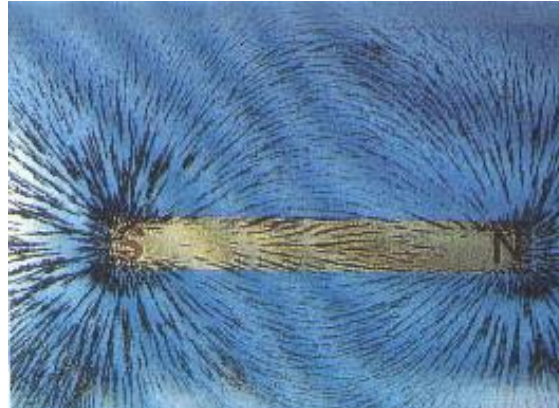
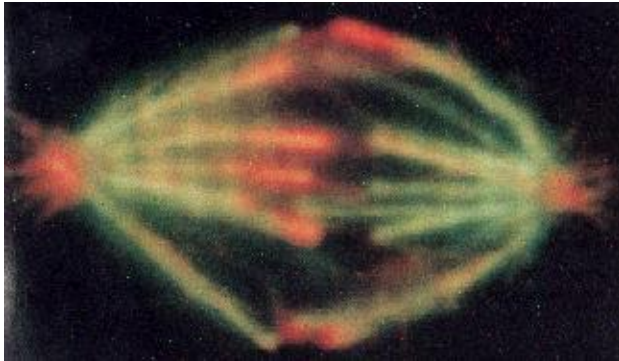
Barnett Rosenberg  
1927 - 2009

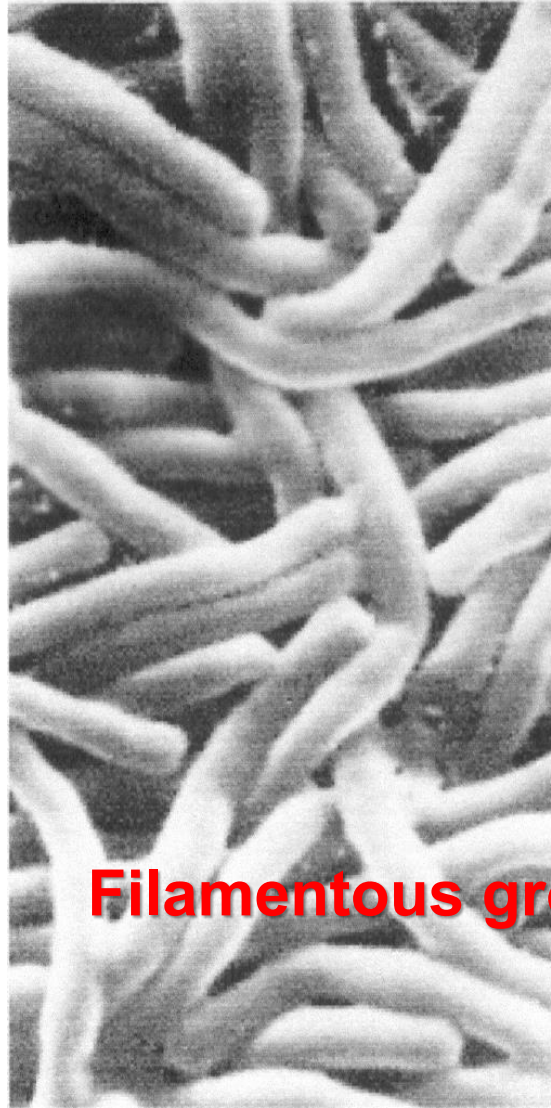


1961: Rosenberg joins the Biophysics Department at Michigan State University

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

mitotic spindles





1963 - 1964

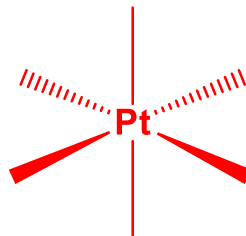
**Filamentous growth in *E. coli***

Platinum has two positive oxidation states:

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

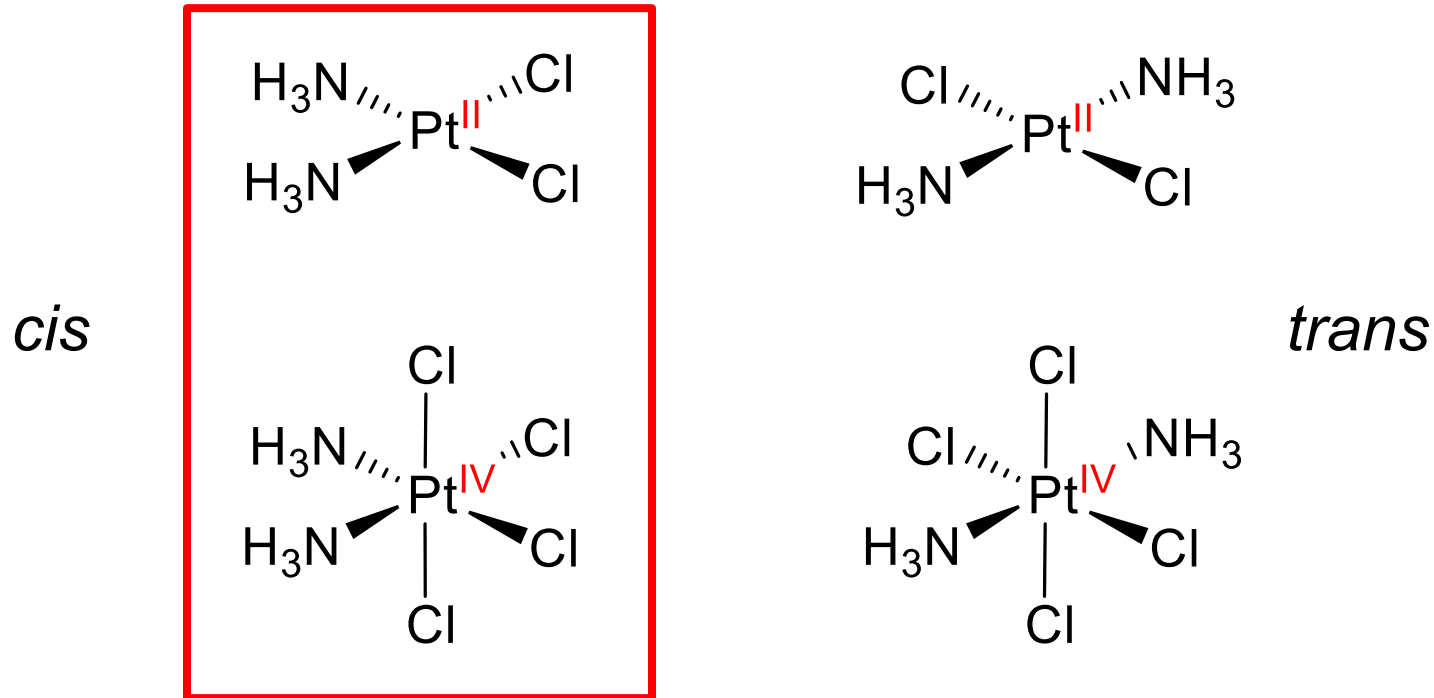


Pt(IV),  $d^6$ , diamagnetic, octahedral



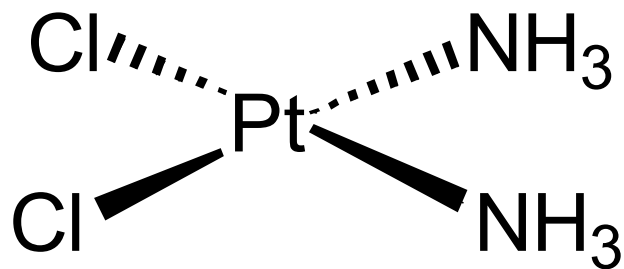
In both oxidation states platinum behaves as a *soft* Lewis acid (high affinity for sulfur ligands), makes stable compounds (strong coordination bonds) and is *very inert*.

Anionic complexes, e.g.  $[\text{PtCl}_4]^{2-}$ , are quite toxic at low concentrations, but induce no filamentous growth

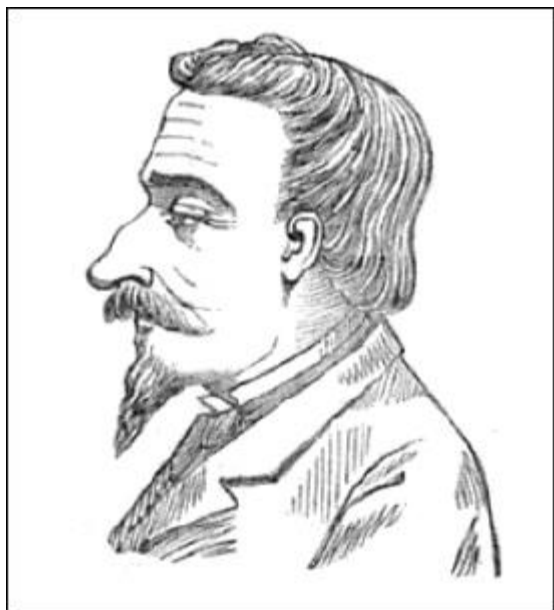


The *cis* neutral species are active at sub-toxic concentrations

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



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



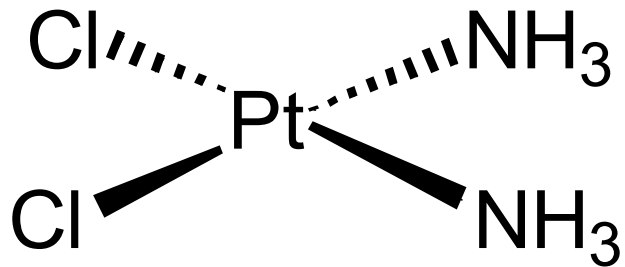
Peyrone's chloride, 1844

*Michele Peyrone (1813–1883)*

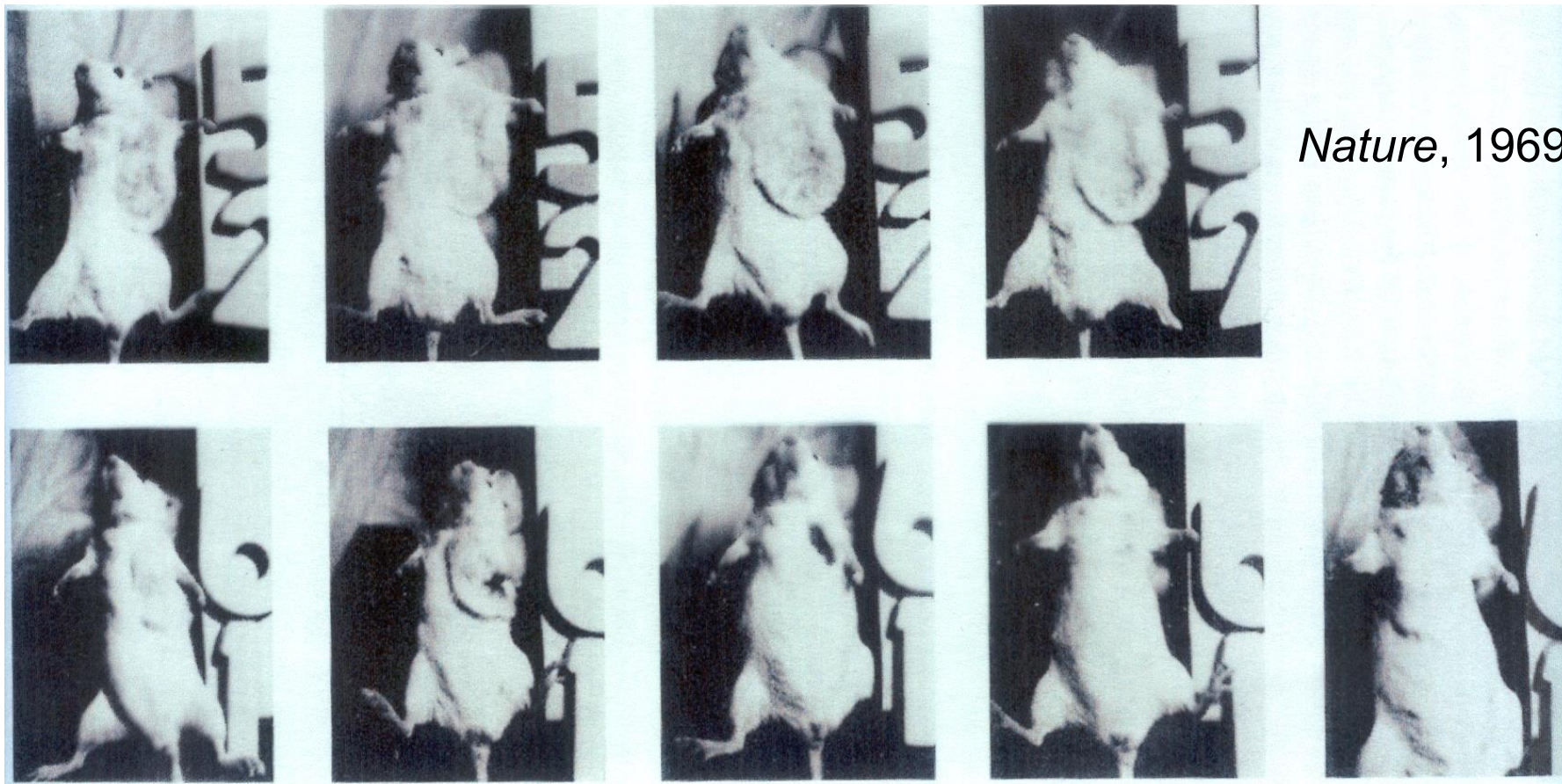
*..the complex stopped cell division in bacteria at concentrations without marked toxicity.*

*Perhaps then it would stop cell division in tumors which grow rapidly, without unacceptable toxicity to the host animal.*

B. Rosemberg

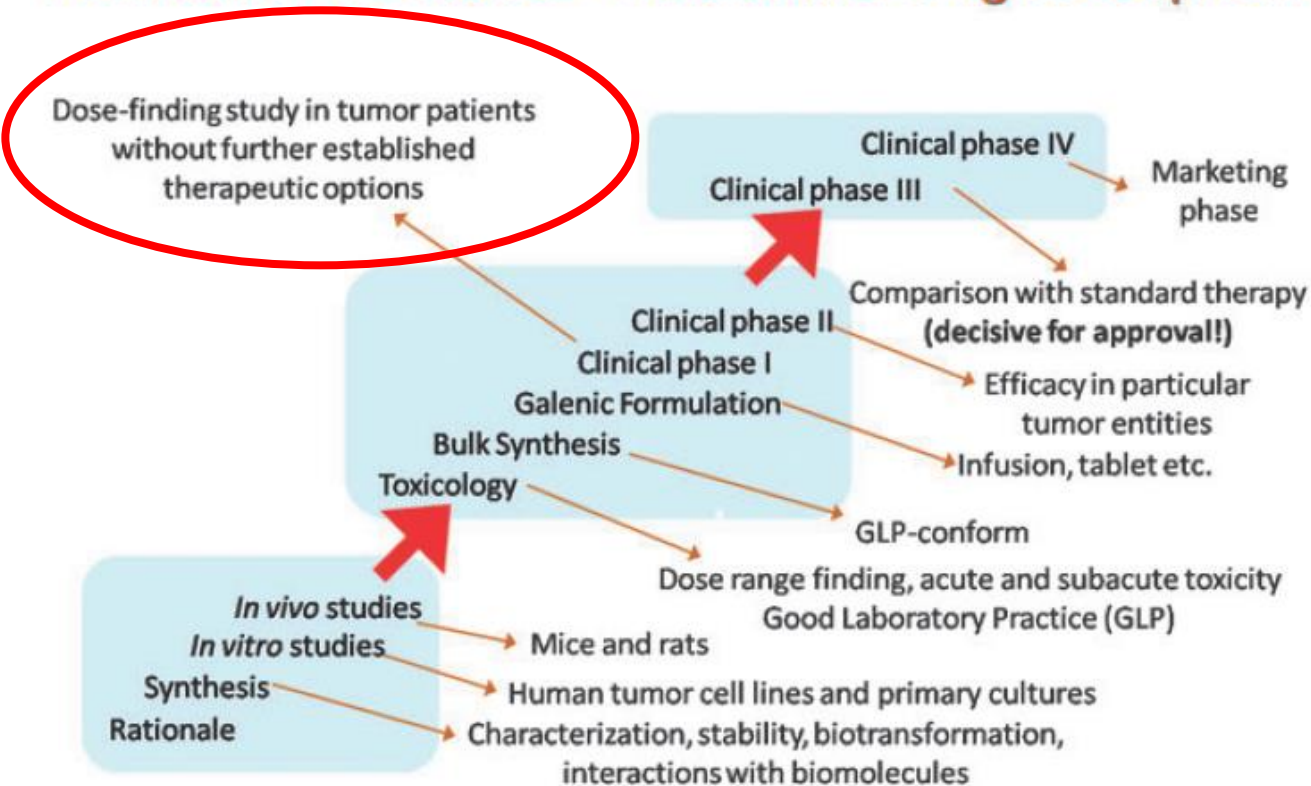


Sarcoma 180  
Cisplatin injection on  
day 8



*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*

## From Bench to Bedside – Translational Drug Development



1978  
FDA approval

Lance  
Armstrong



Winner of seven consecutive editions of the Tour de France (1999 – 2005), after surviving – thanks to cisplatin – an advanced testicular cancer diagnosed in 1996.

# 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.