

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. ^{99m}Tc)

Metallomics

Transport and signalling
pathways
Genomic codes for elements

**Medicinal
Inorganic
Chemistry**

Protein/enzyme regulators

e.g metalloproteinases,
angiotensin-converting enzyme
O₂, CO, NO

Chelation therapy

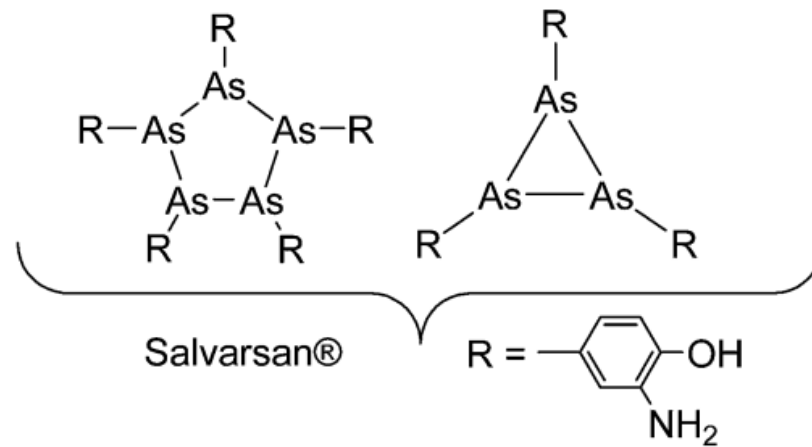
Overload diseases (e.g. Fe, Cu)
Removal of radionuclides

Enzyme mimics

Synzymes (e.g. for SOD)

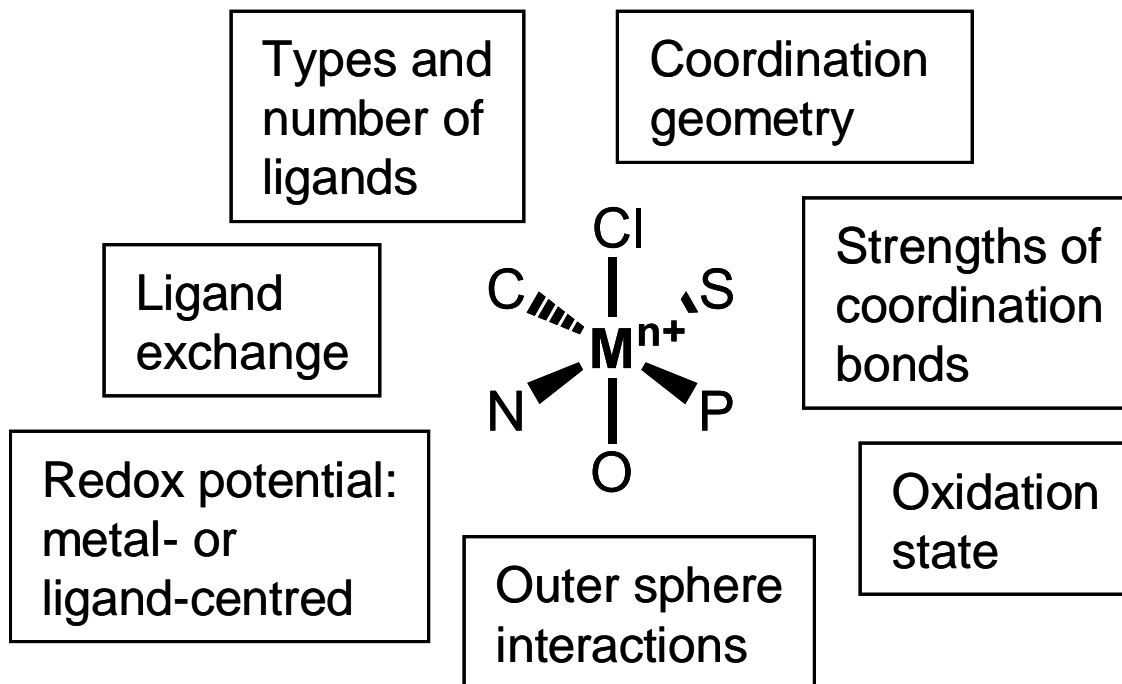
Contrast agents

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

Speciation



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 (<i>e.g.</i> Bi) e più grande per i lantanidi (<i>e.g.</i> 9)
Geometria	Esempi: lineare (Au^{I}), planare-quadrata (Pt^{II}), tetraedrica (<i>e.g.</i> 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 (<i>e.g.</i> Pt^{IV} vs Pt^{II})
Tipo di Legante	Ampio numero di atomi donatori <i>e.g.</i> C, N, O, alogenuri, P, S, Se. Leganti chelanti; denticità <i>e.g.</i> (κ^2) 1,2-diamminoetano, (κ^6) EDTA; apticità <i>e.g.</i> legami di tipo η^6 e η^4 per il benzene
Stabilità Termodinamica	Ampio intervallo di forza del legame M–L (tipicamente 50–150 $\text{kJ}\cdot\text{mol}^{-1}$), molto più debole rispetto al tipico legame covalente, <i>e.g.</i> legame singolo C–C (250 – 500 $\text{kJ}\cdot\text{mol}^{-1}$)
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, <i>e.g.</i> effetto <i>trans</i> nel Pt^{II} .
Proprietà dei Leganti	Interazioni relative alla sfera esterna dei leganti, <i>e.g.</i> legame a idrogeno, interazioni idrofobiche (< 50 $\text{kJ}\cdot\text{mol}^{-1}$), possono servire al riconoscimento recettoriale (chiralità inclusa); possono subire trasformazioni <i>in vivo e.g.</i> di tipo redox, idrolisi, reazioni enzimatiche (<i>e.g.</i> ad opera del P450 nel fegato).
Stabilità Nucleare	Nuclei radioattivi possono essere usati per seguire il metabolismo dei composti <i>e.g.</i> $^{195\text{m}}\text{Pt}$ ($t_{1/2} = 4$ d) e $^{99\text{m}}\text{Tc}$ ($t_{1/2} = 6$ h). A seconda del nuclide variano il tipo di decadimento (α , β , γ) e il tempo di semi-vita.

Metal-based
Drug

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

profarmaci

Structural
compound

The *multi-stage rocket model*



M (+ inert ligands)

Exchangeable
Ligands

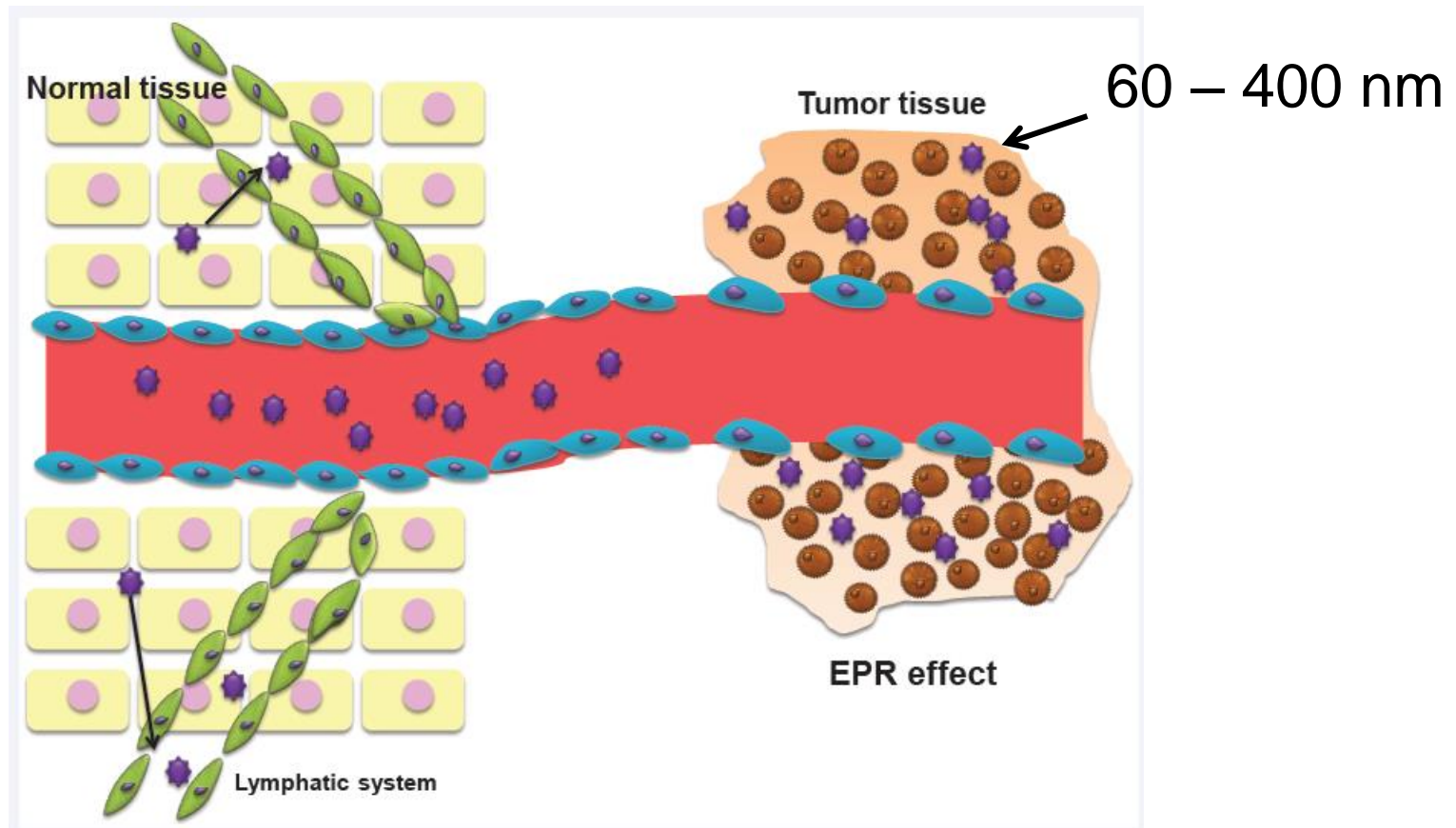
Selectivity

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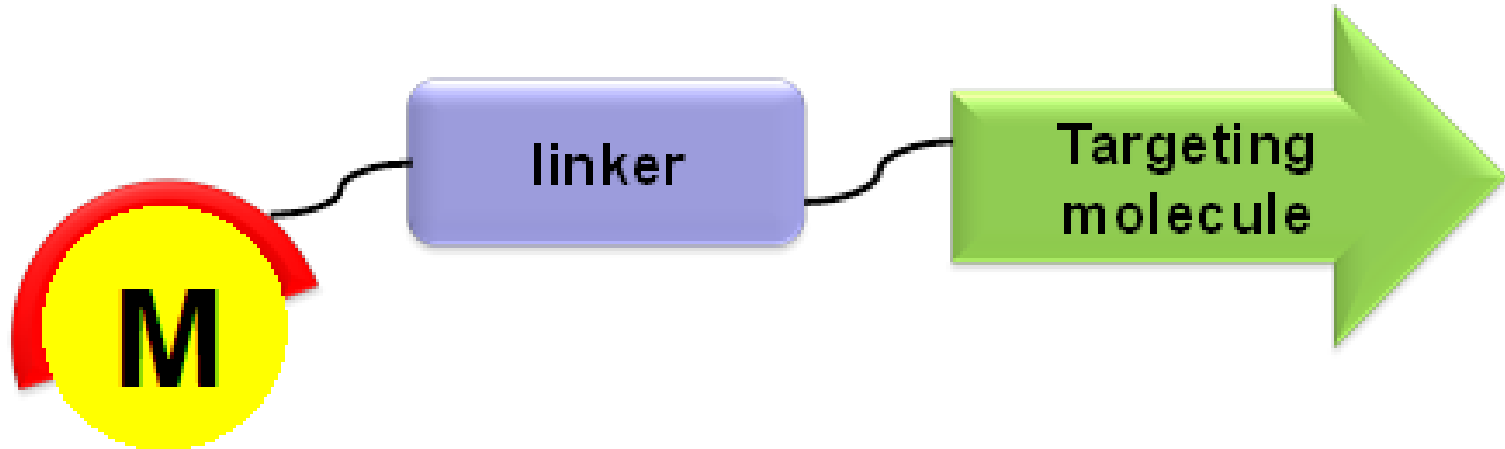
Selective delivery
(targeted therapy)

Selective activation

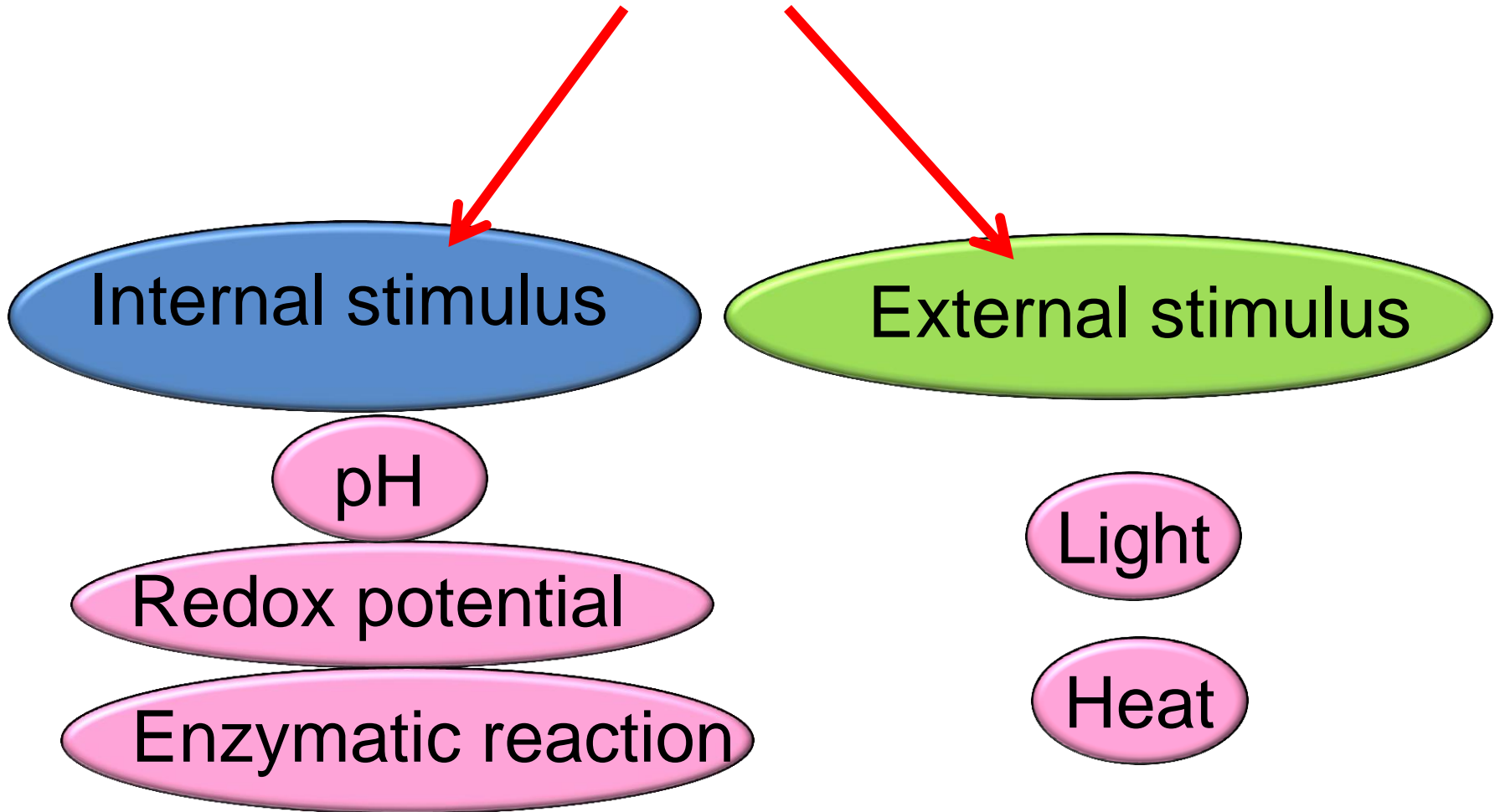
Passive selectivity: EPR (*Enhanced Permeability and Retention*) effect

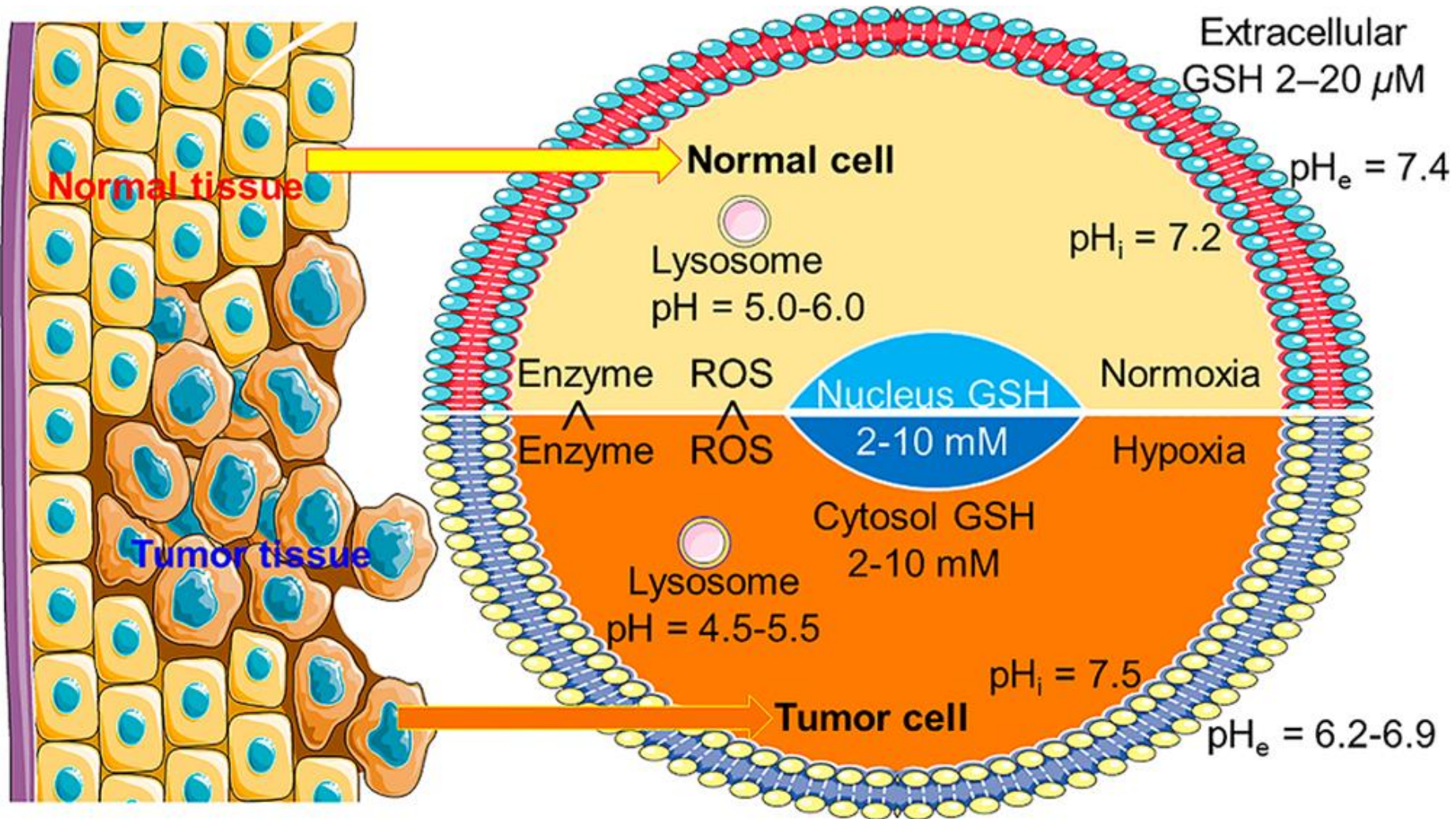


Active selectivity: targeted approach



Selective activation





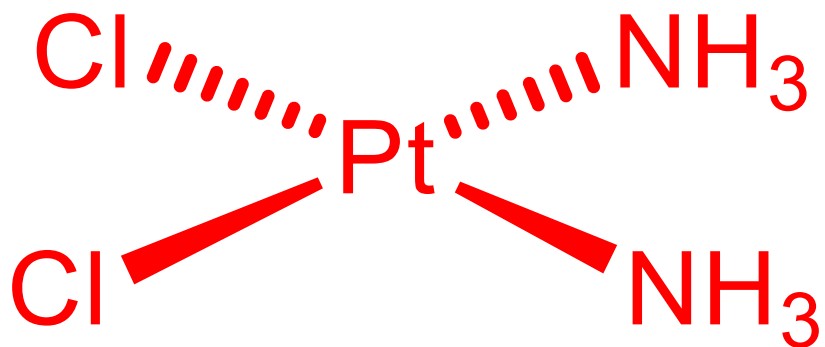
Platinum
anticancer
compounds

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.

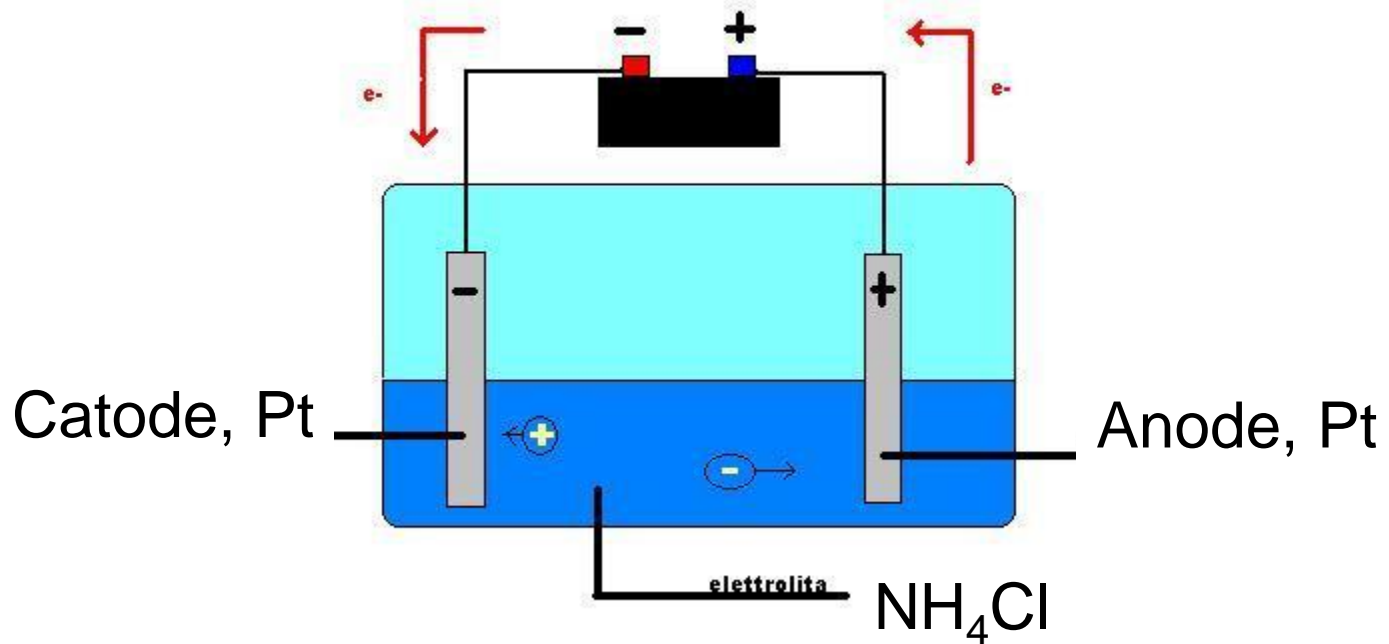
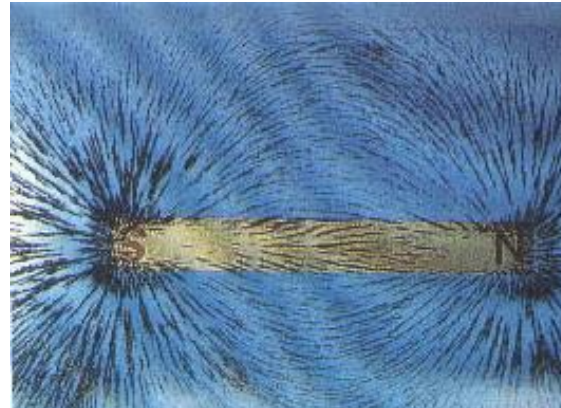
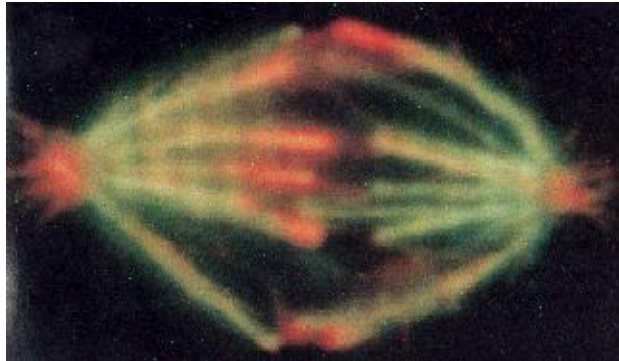
Barnett Rosenberg
1927 - 2009

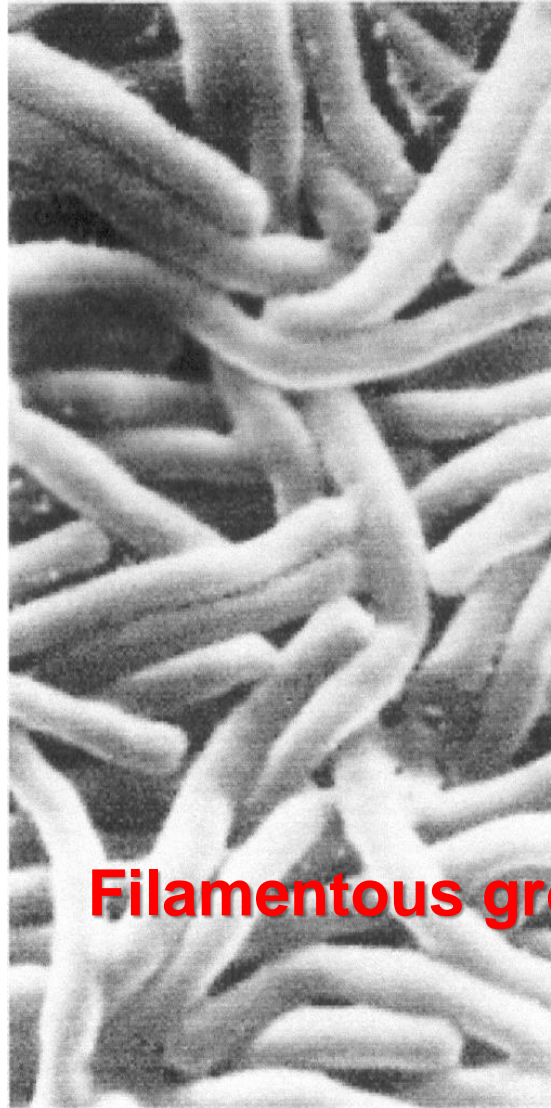


1961: Rosenberg joins the Biophysics Department at Michigan State University

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

mitotic spindles





1963 - 1964

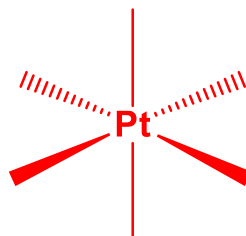
Filamentous growth in *E. coli*

Platinum has two positive oxidation states:

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

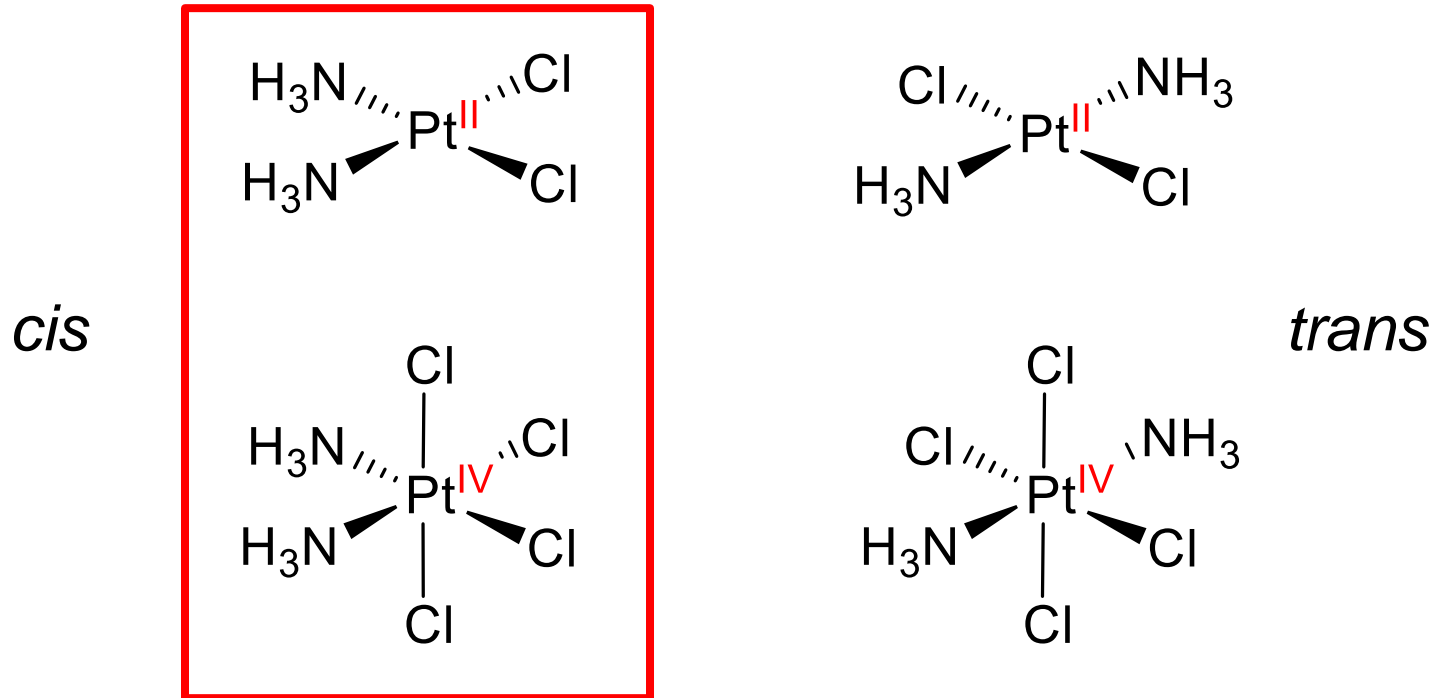


Pt(IV), d^6 , diamagnetic, octahedral



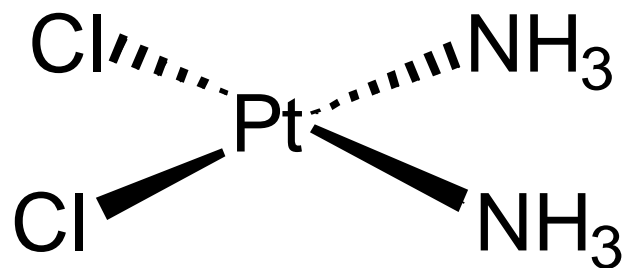
In both oxidation states platinum behaves as a *soft* Lewis acid (high affinity for sulfur ligands), makes stable compounds (strong coordination bonds) and is *very inert*.

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

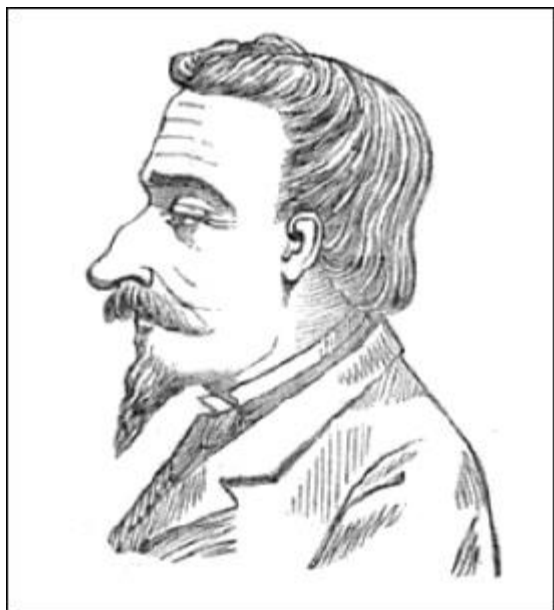


The *cis* neutral species are active at sub-toxic concentrations

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



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



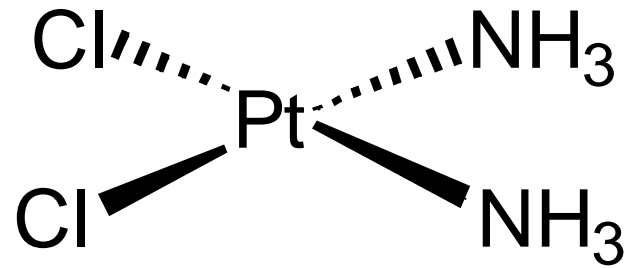
Peyrone's chloride, 1844

Michele Peyrone (1813–1883)

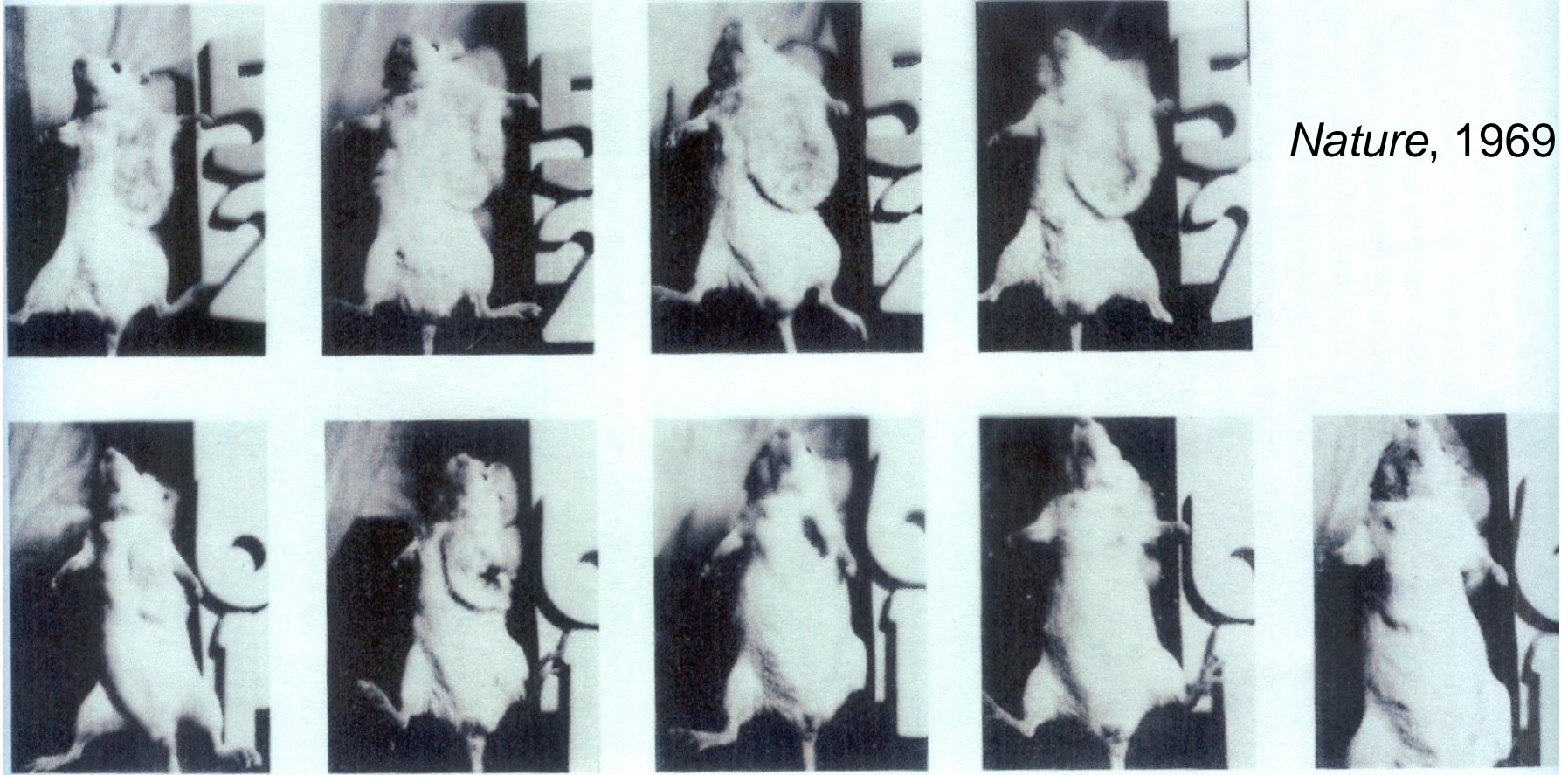
..the complex stopped cell division in bacteria at concentrations without marked toxicity.

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

B. Rosemberg

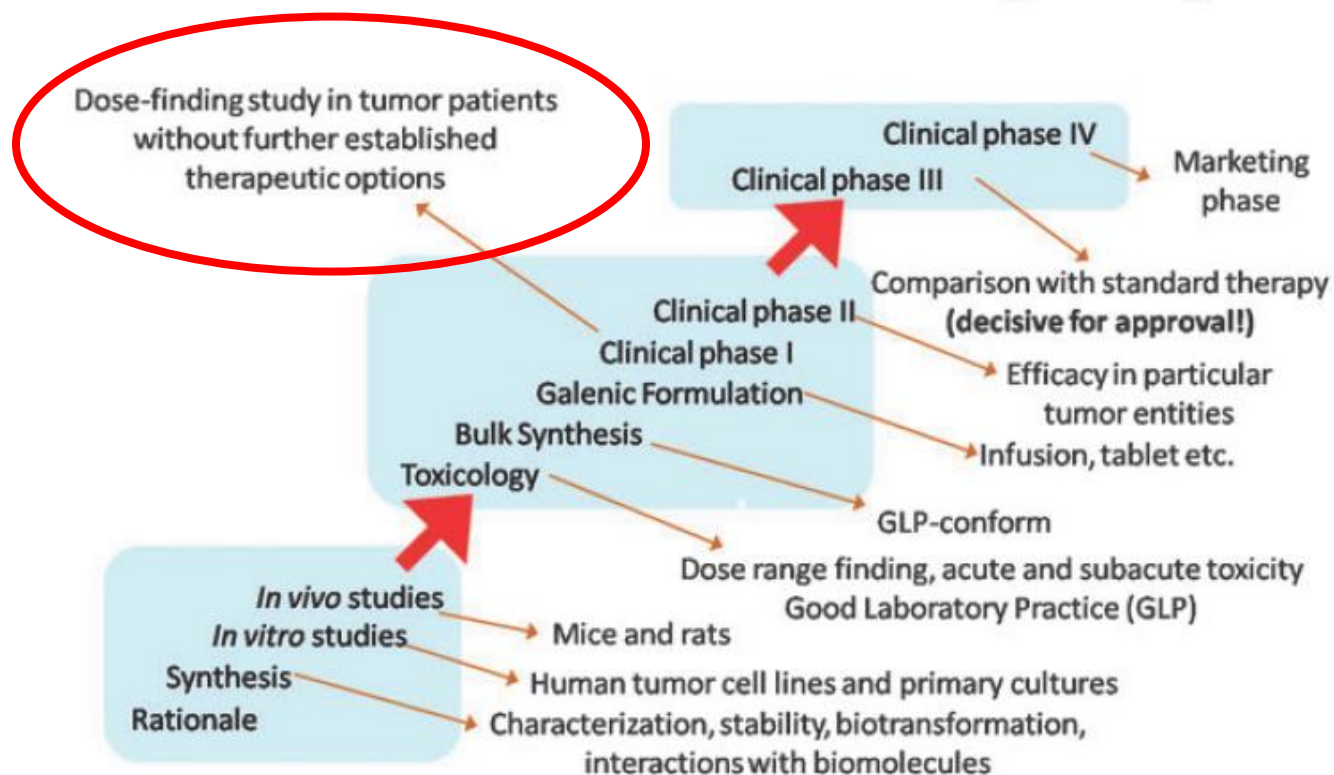


Sarcoma 180
Cisplatin injection on
day 8



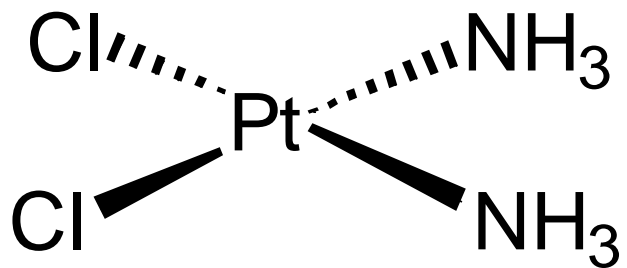
In 1971 a phase I study of cisplatin, which included 11 patients with refractory testicular cancer was performed: 9 of 11 responded to cisplatin, including several CRs, an unprecedented finding for a phase I trial even today

From Bench to Bedside – Translational Drug Development



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.