METALLI IN MEDICINA

A.A. 2016-2017

PARTE 2

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UNIVERSITÀ
DEGLI STUDI DI TRIESTE

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Medicinal Inorganic Chemistry

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. ^{188}*Re)*
Diagnostic (e.g. ^{99m}*Tc)*

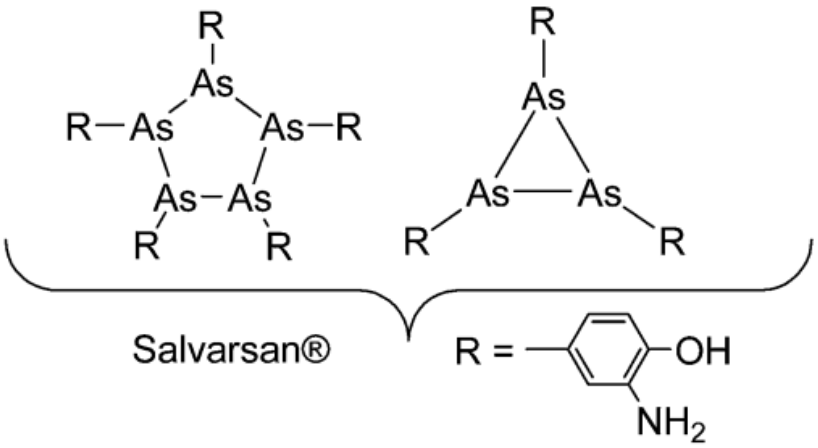
Metallomics
Transport and signalling pathways
Genomic codes for elements

Protein/enzyme regulators
e.g metalloproteinases, angiotensin-converting enzyme
O_2, *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)



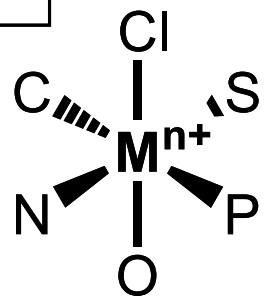
Antimicrobial agent introduced in early 1900 for the treatment of the deadly bacterial infection *Syphilis*. Later replaced by modern antibiotics

Speciation

Types and number of ligands

Coordination geometry

Ligand exchange



Strengths of coordination bonds

Redox potential: metal- or ligand-centred

Outer sphere interactions

Oxidation state

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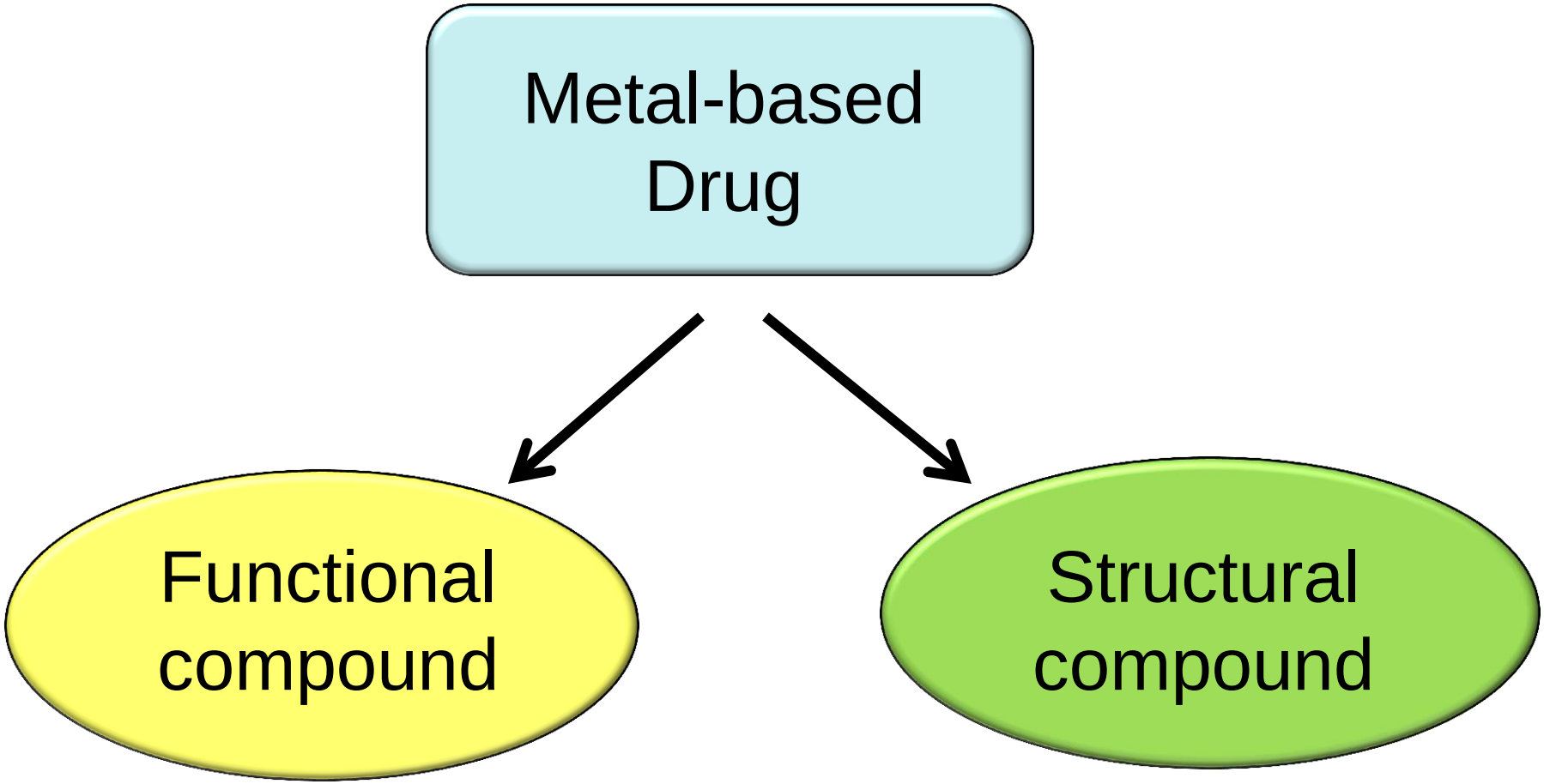
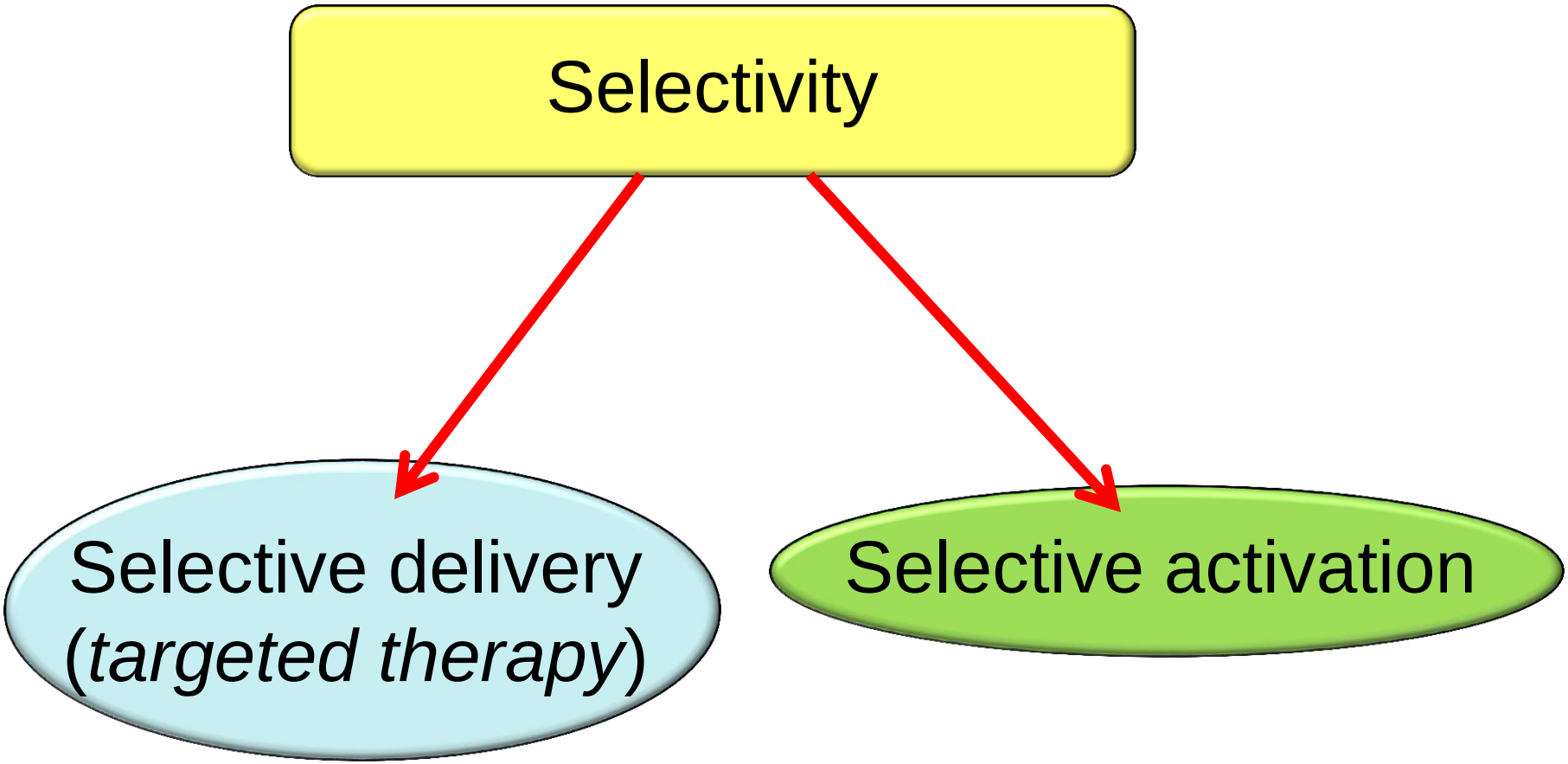
Proprietà	**Commenti (esempi)**
Numero di Coordinazione	Intero intervallo: 2 – 10; tipicamente da 4 a 6 per i metalli di transizione, può essere più variabile per i metalli dei gruppi principali (*e.g.* Bi) e più grande per i lantanidi (*e.g.* 9)
Geometria	Esempi: lineare (Au^{I}), planare-quadrata (Pt^{II}), 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

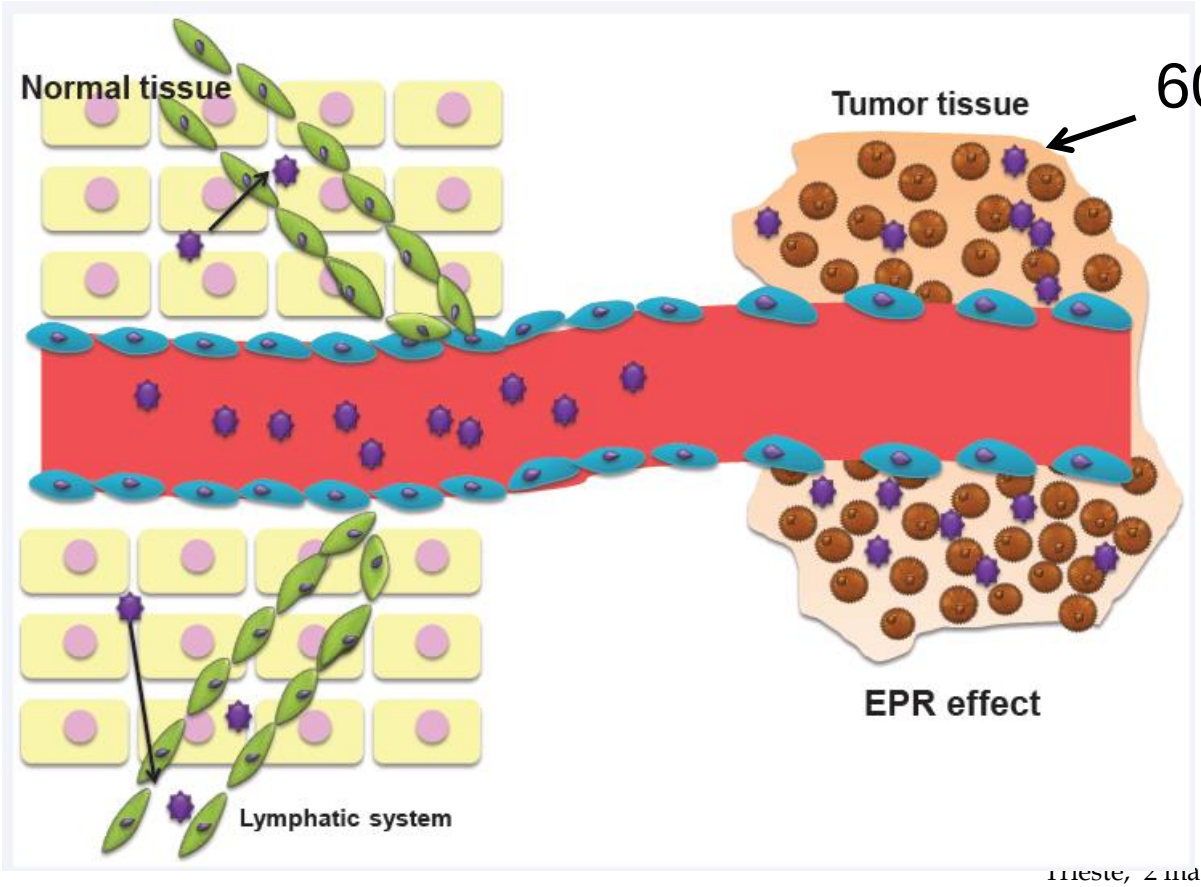
The *multi-stage rocket model*

M (+ inert ligands)

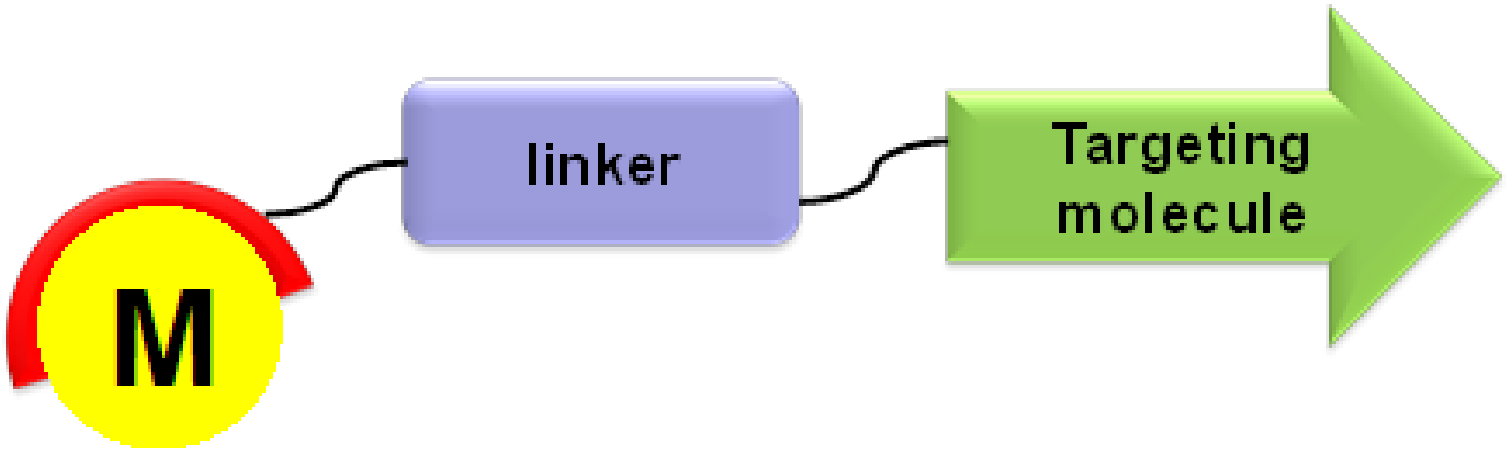
Exchangeable Ligands

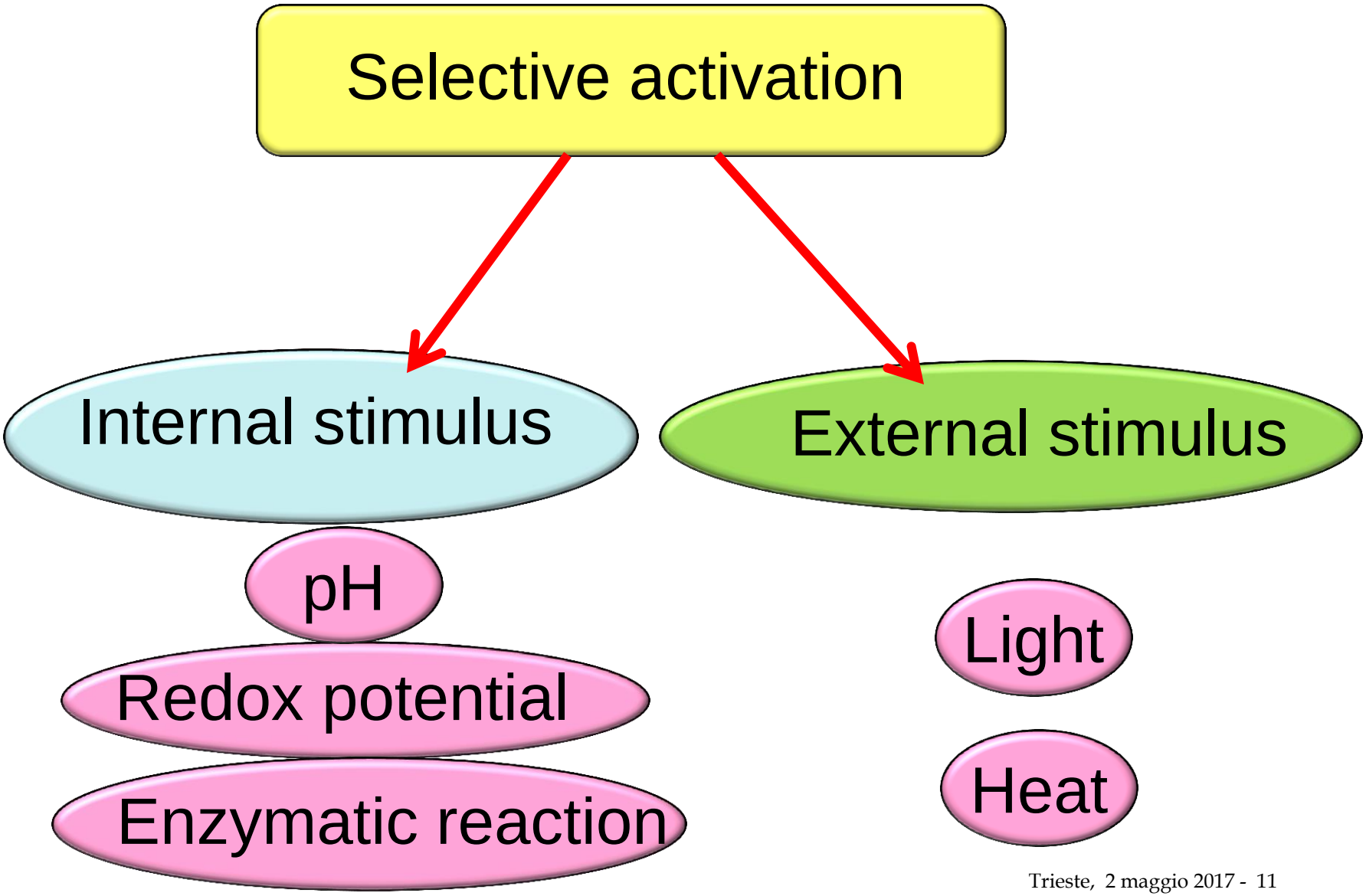

Selectivity
Selective delivery
(*targeted therapy*)
Selective activation

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

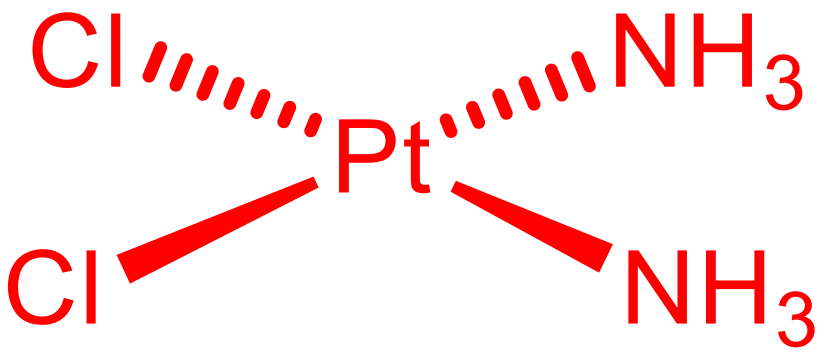
Platinum anticancer compounds

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.

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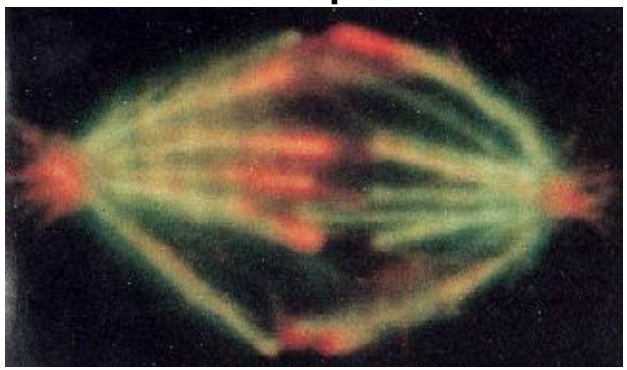
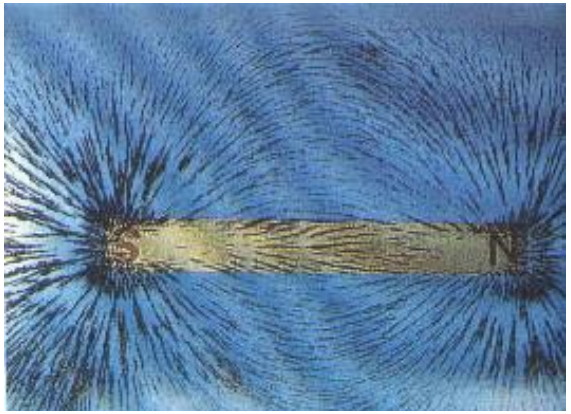
Barnett Rosemberg
1927 - 2009

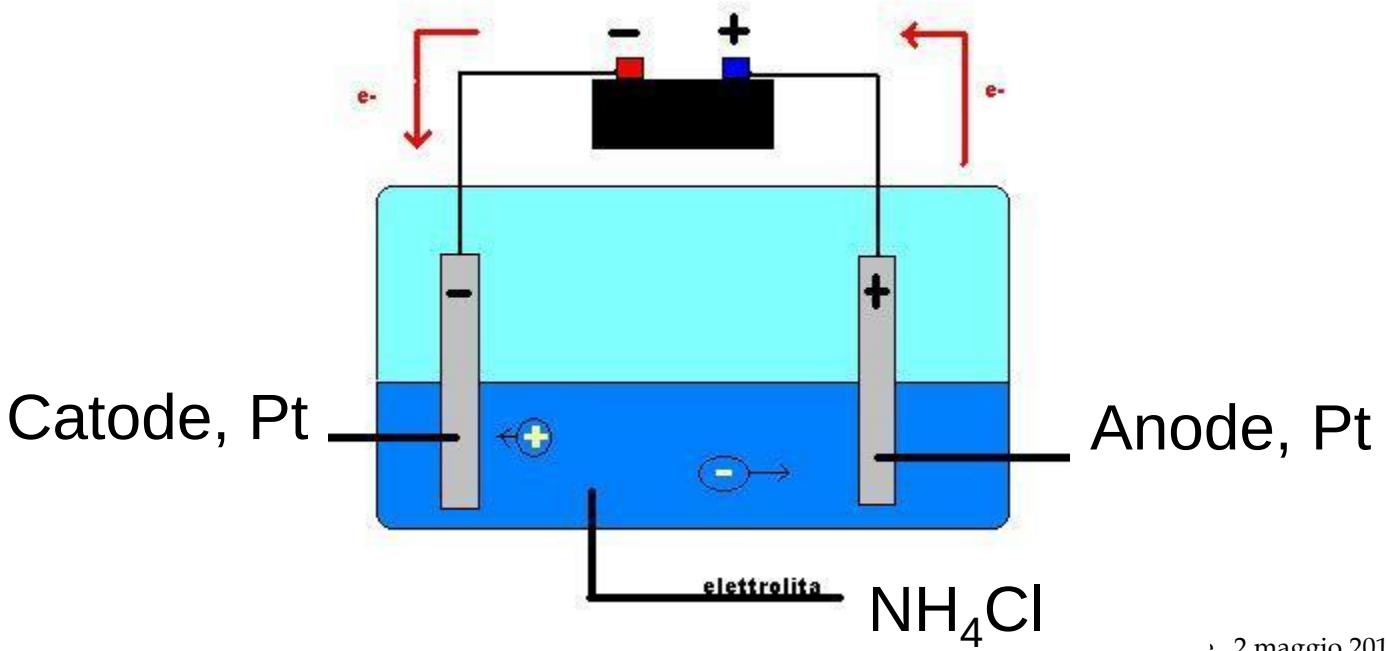
1961: Rosemberg joins the Biophysics Department at Michigan State University

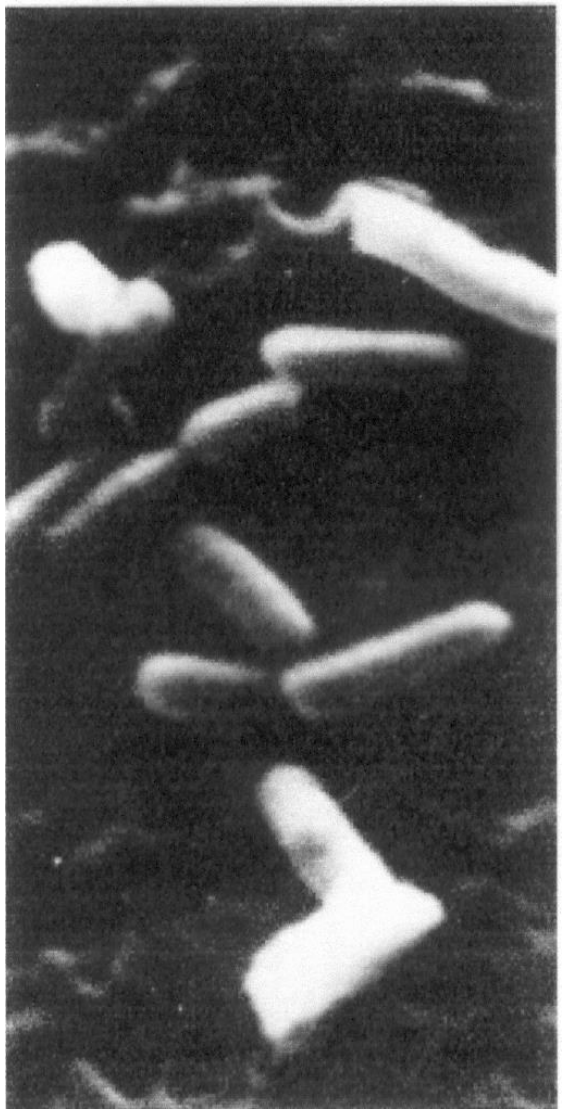
***Serendipity**: when you discover something unexpected and unsought for, while searching for something else.*

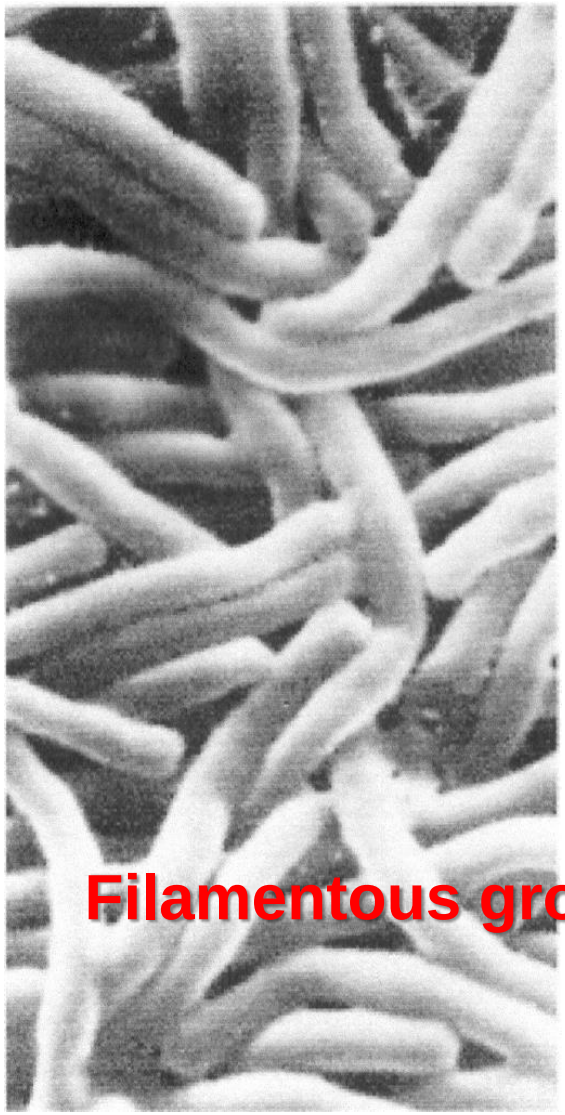
mitotic spindles









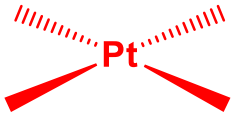


1963 - 1964

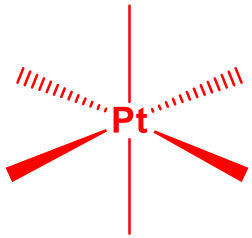
Filamentous growth in *E. coli*

Platinum has two positive oxidation states:

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



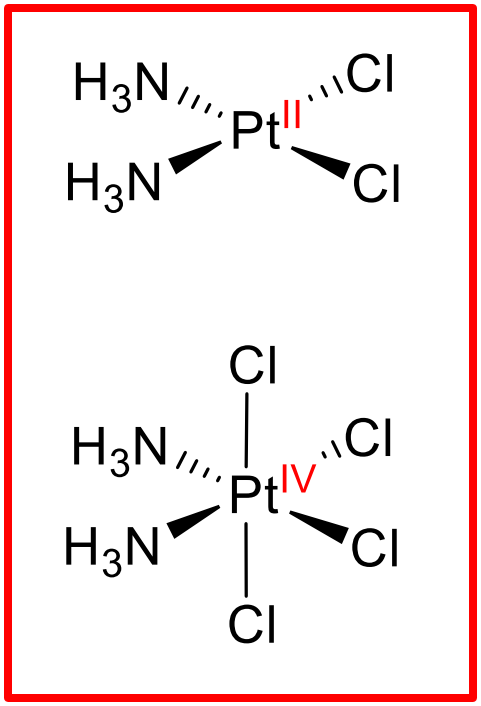
Pt(IV), d^6, diamagnetic, octahedral

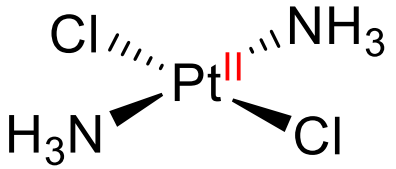


In both oxidation states platinum behaves as a *soft* Lewis acid (high affinity for sulfur ligands), makes stable compounds (strong coordination bonds) and is very inert.

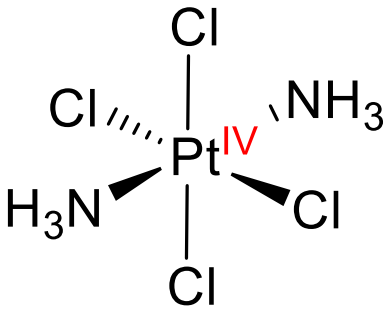
Anionic complexes, e.g. $[PtCl_4]^{2-}$, are quite toxic at low concentrations, but induce no filamentous growth

cis

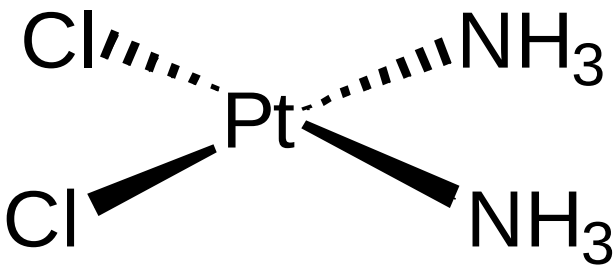




trans



The *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

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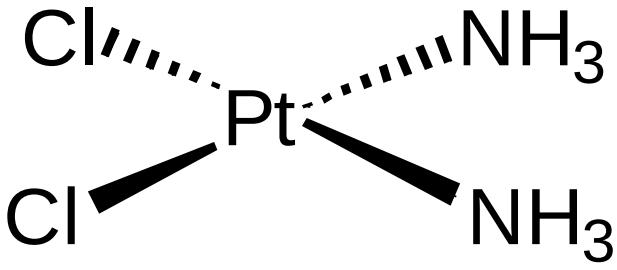
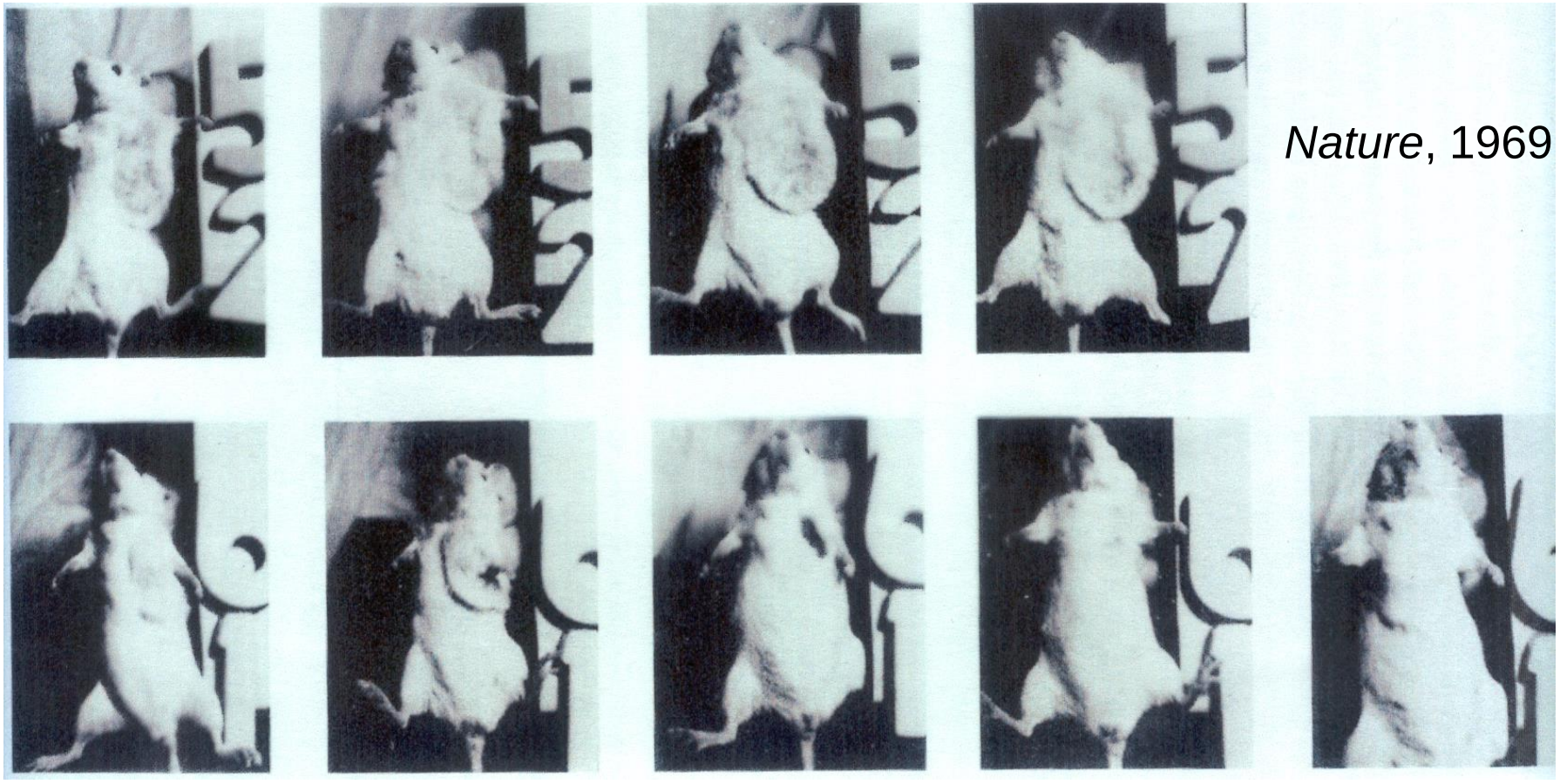
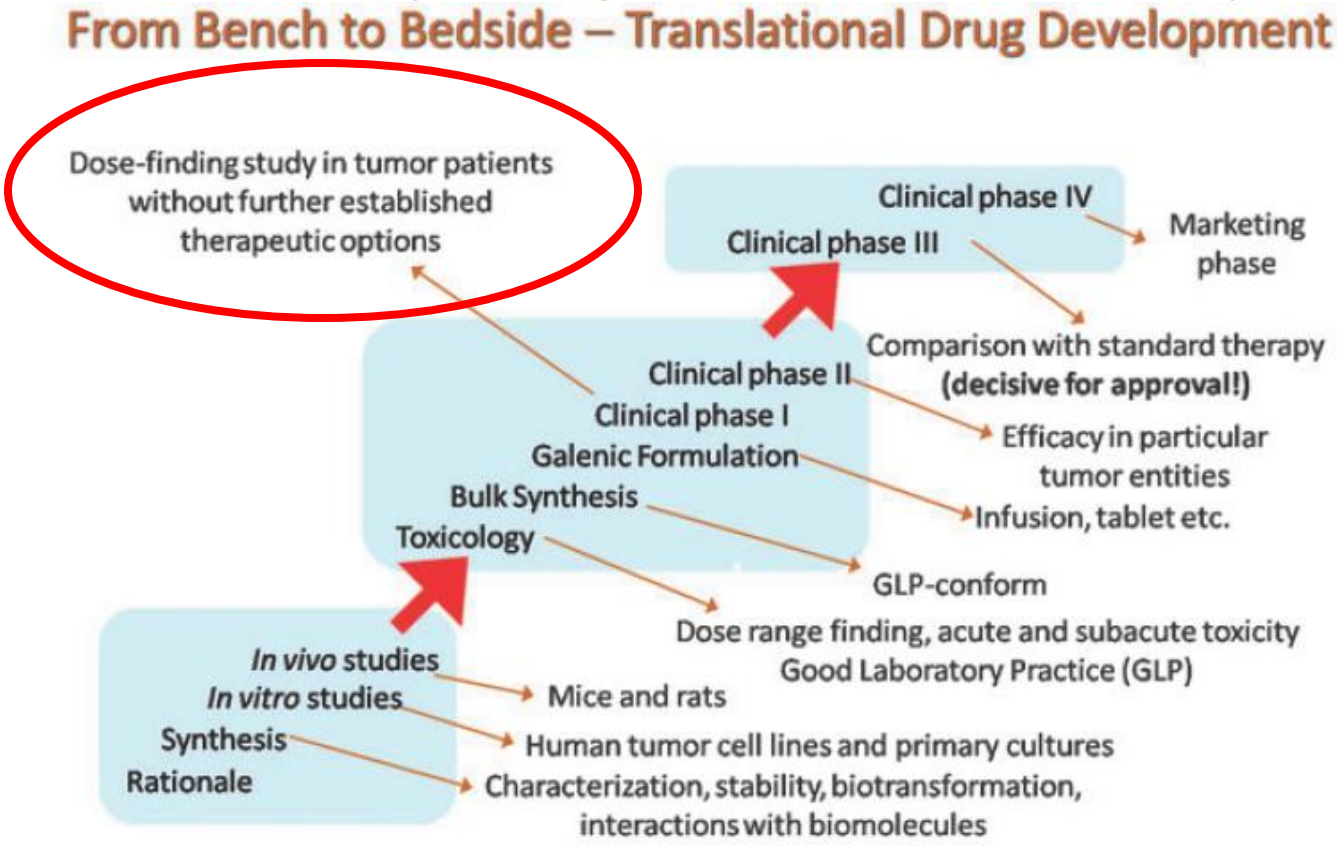


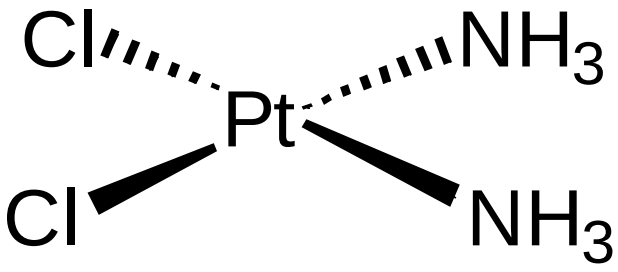
Sarcoma 180
Cisplatin injection on day 8

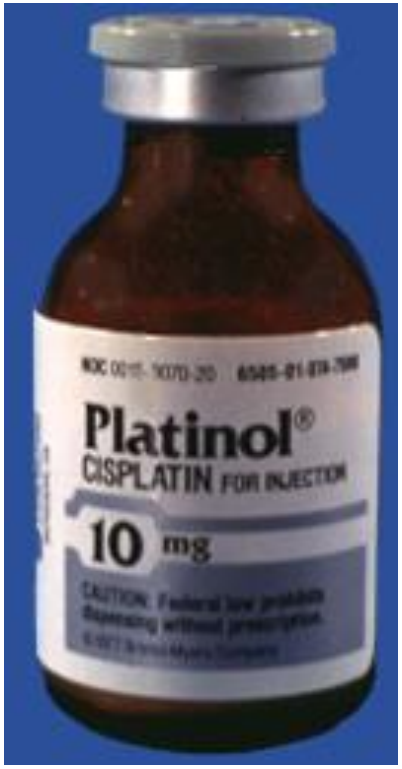


Nature, 1969

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







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**

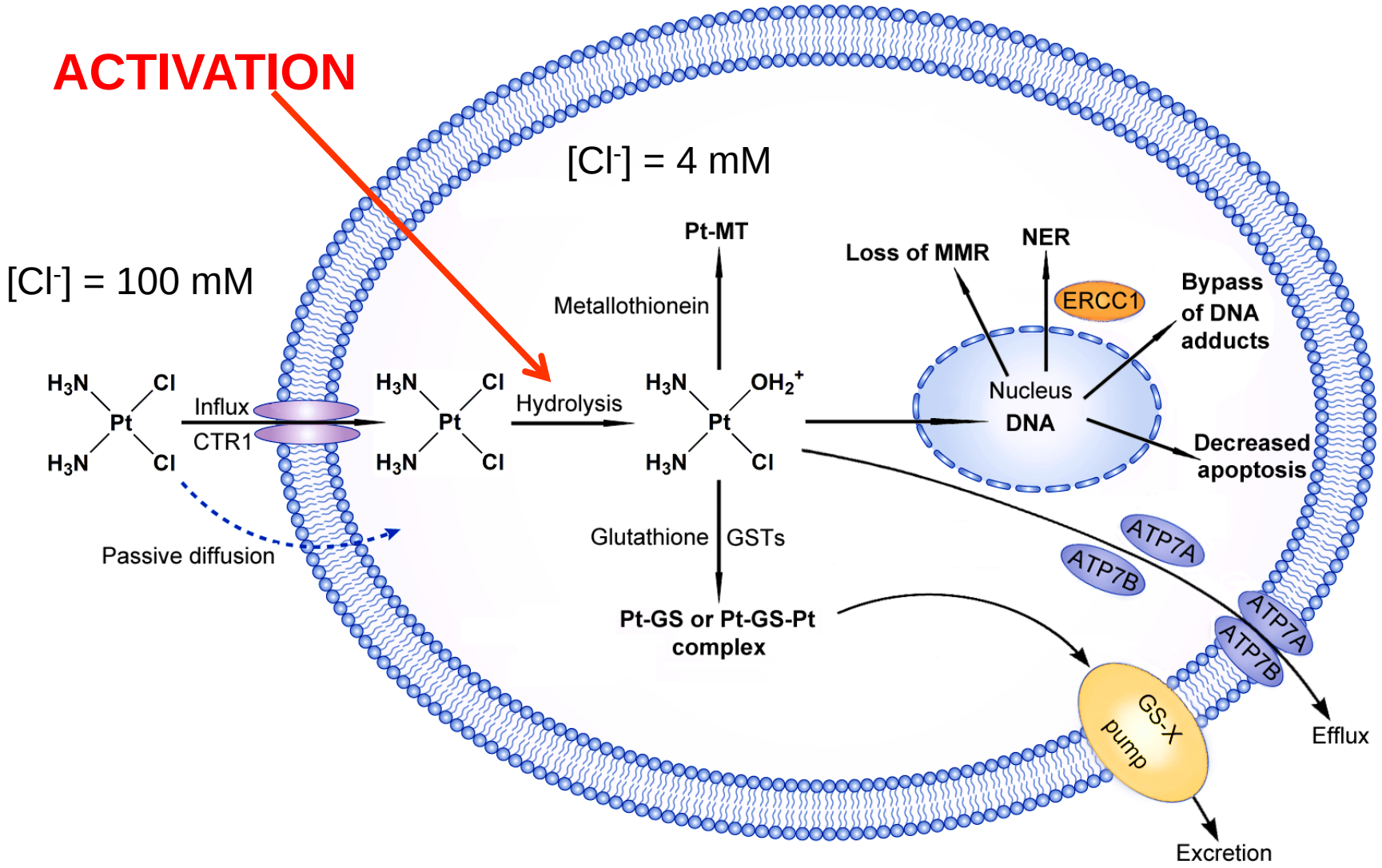
  Nausea, vomiting, neurotoxicity (*dose-limiting toxicity*), kidney and ear damage.
- **Resistance**

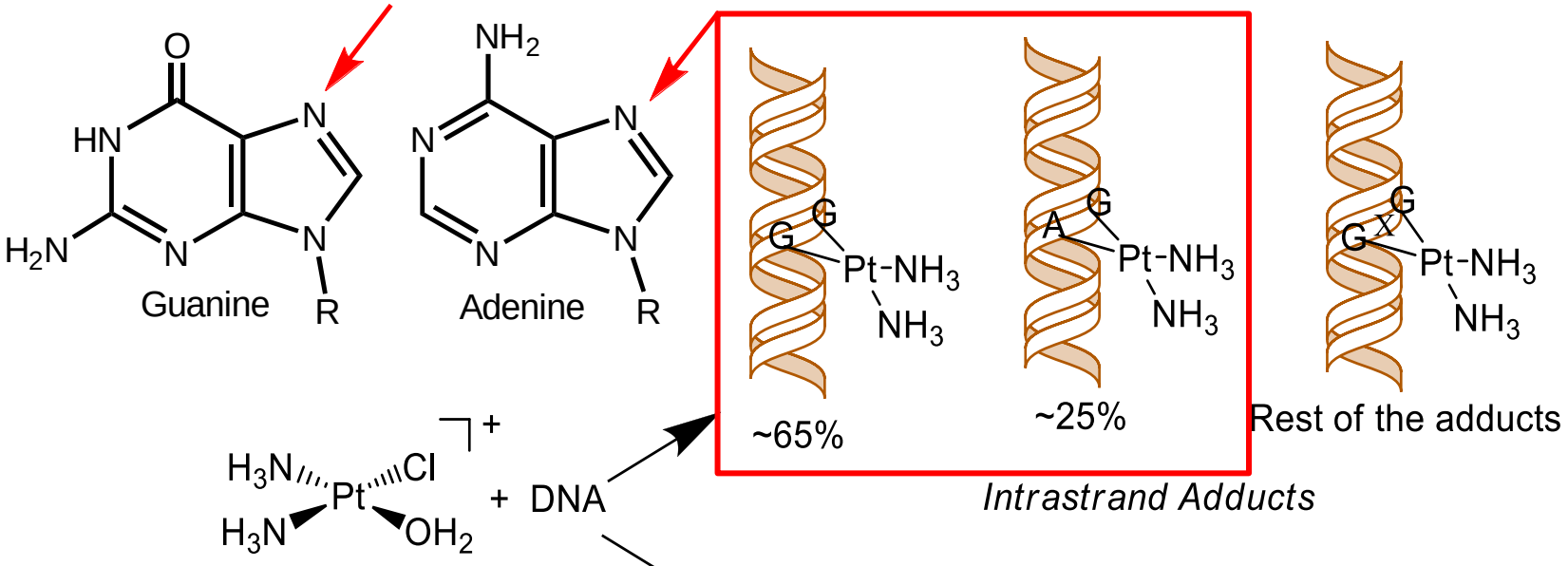
  Spontaneous or acquired.

Discovery of cisplatin

Mechanism of action

Structure – Activity relationships

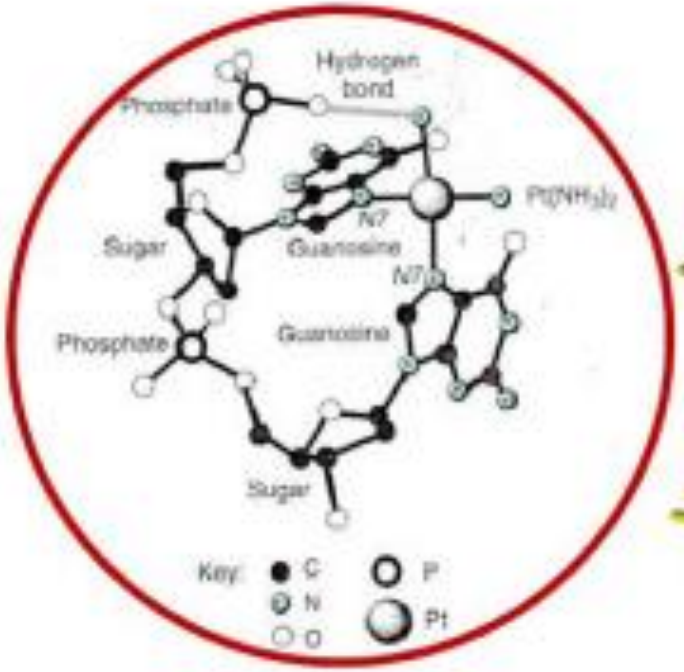

ACTIVATION
[Cl-] = 4 mM
[Cl-] = 100 mM
Pt-MT
Metallothionein
Loss of MMR
NER
ERCC1
Bypass of DNA adducts
Nucleus
DNA
Decreased apoptosis
Influx
CTR1
Hydrolysis
Passive diffusion
Glutathione
GSTs
Pt-GS or Pt-GS-Pt complex
ATP7A
ATP7B
ATP7A
ATP7B
GS-X pump
Efflux
Excretion

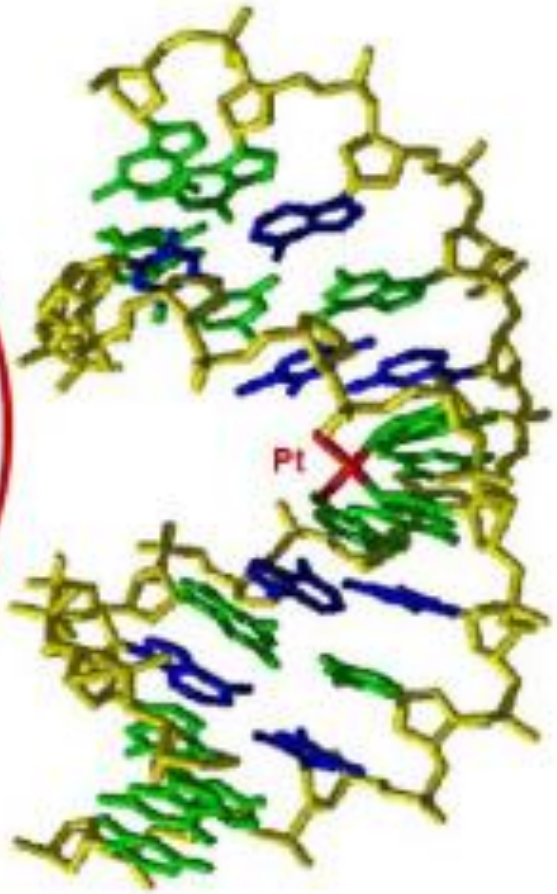


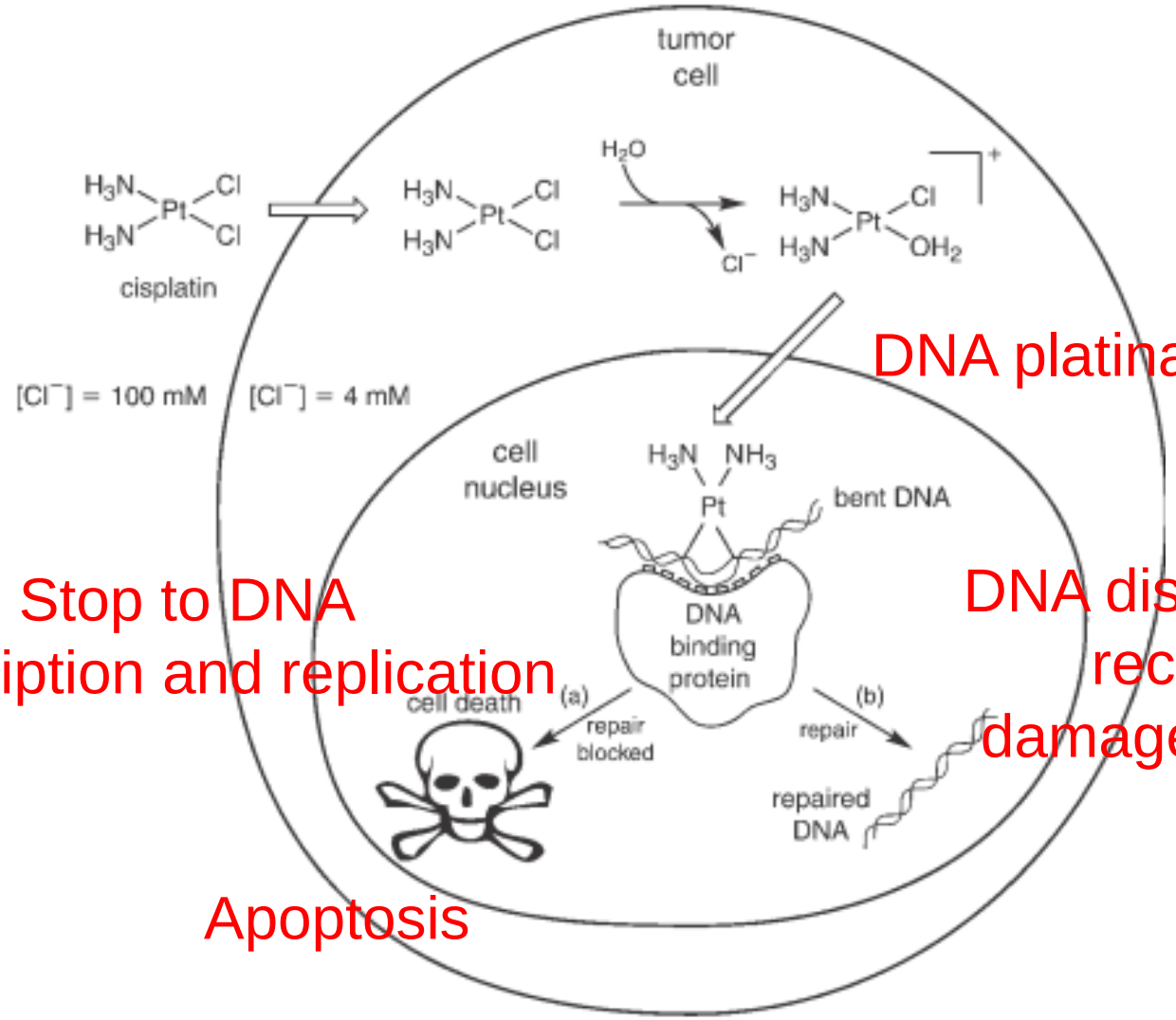
Estimation:

- 1 Pt per 250.000 nucleotides sufficient to inhibit cell growth
- ca. 50.000 Pt adducts per mammalian cell

Platination induces a kink and local unwinding in DNA





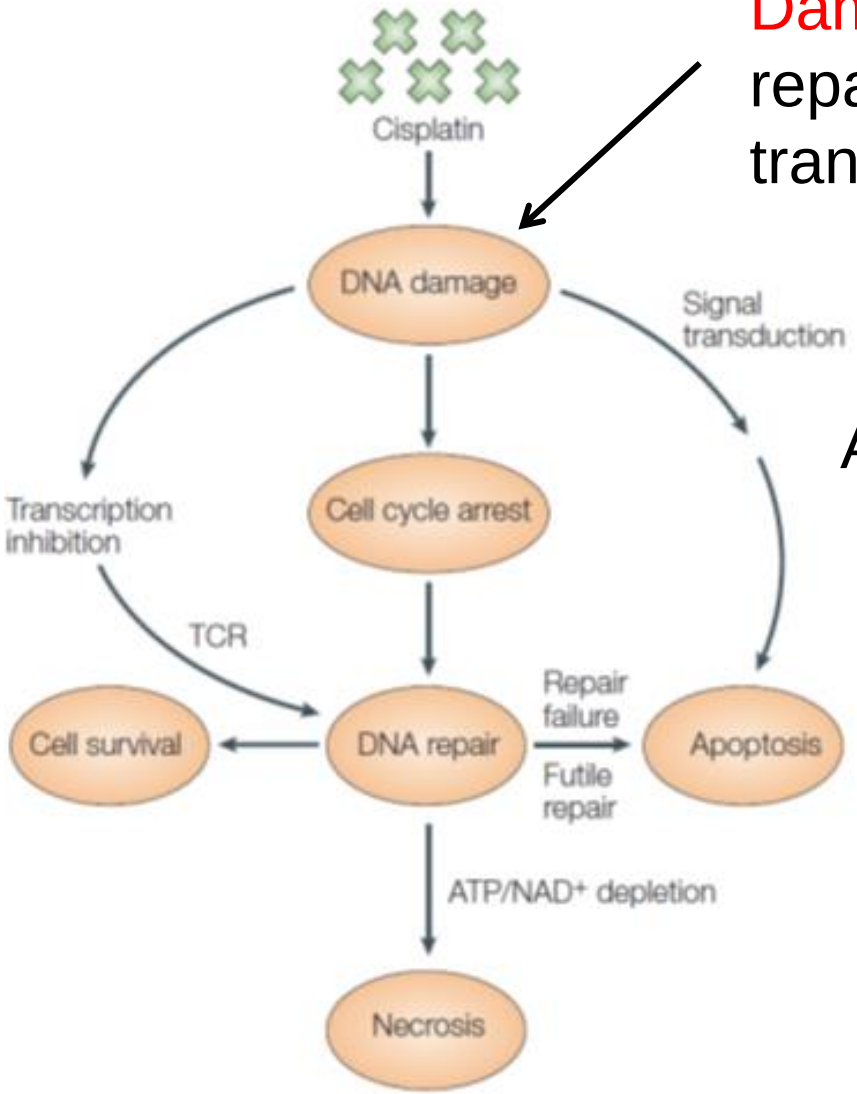


DNA platination

Stop to DNA transcription and replication

DNA distortion and recognition by damage-response proteins

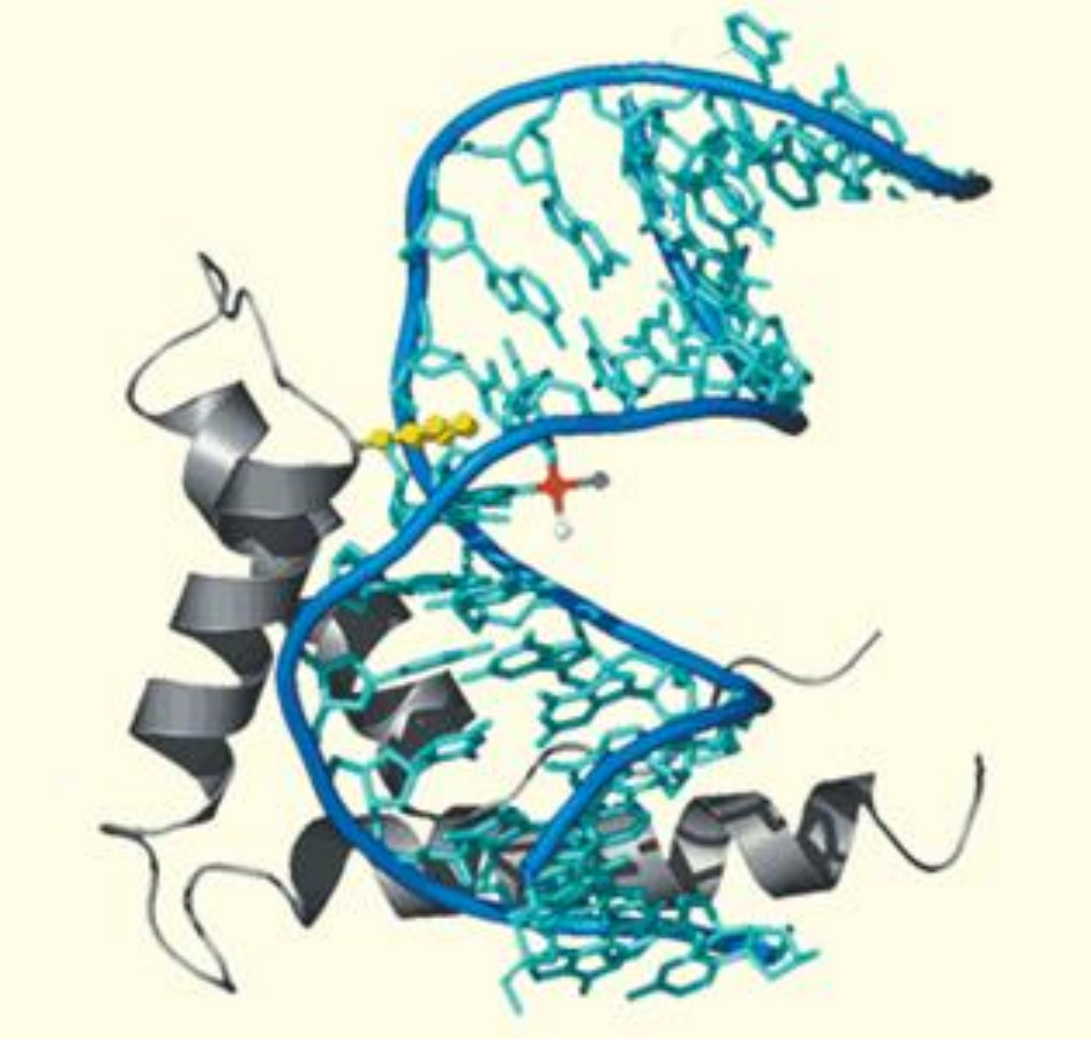
Apoptosis



Damage-response proteins: DNA repair system, HMG proteins, transcription factors…

Aspartic proteases

Recognition of platinated DNA by a HMG protein

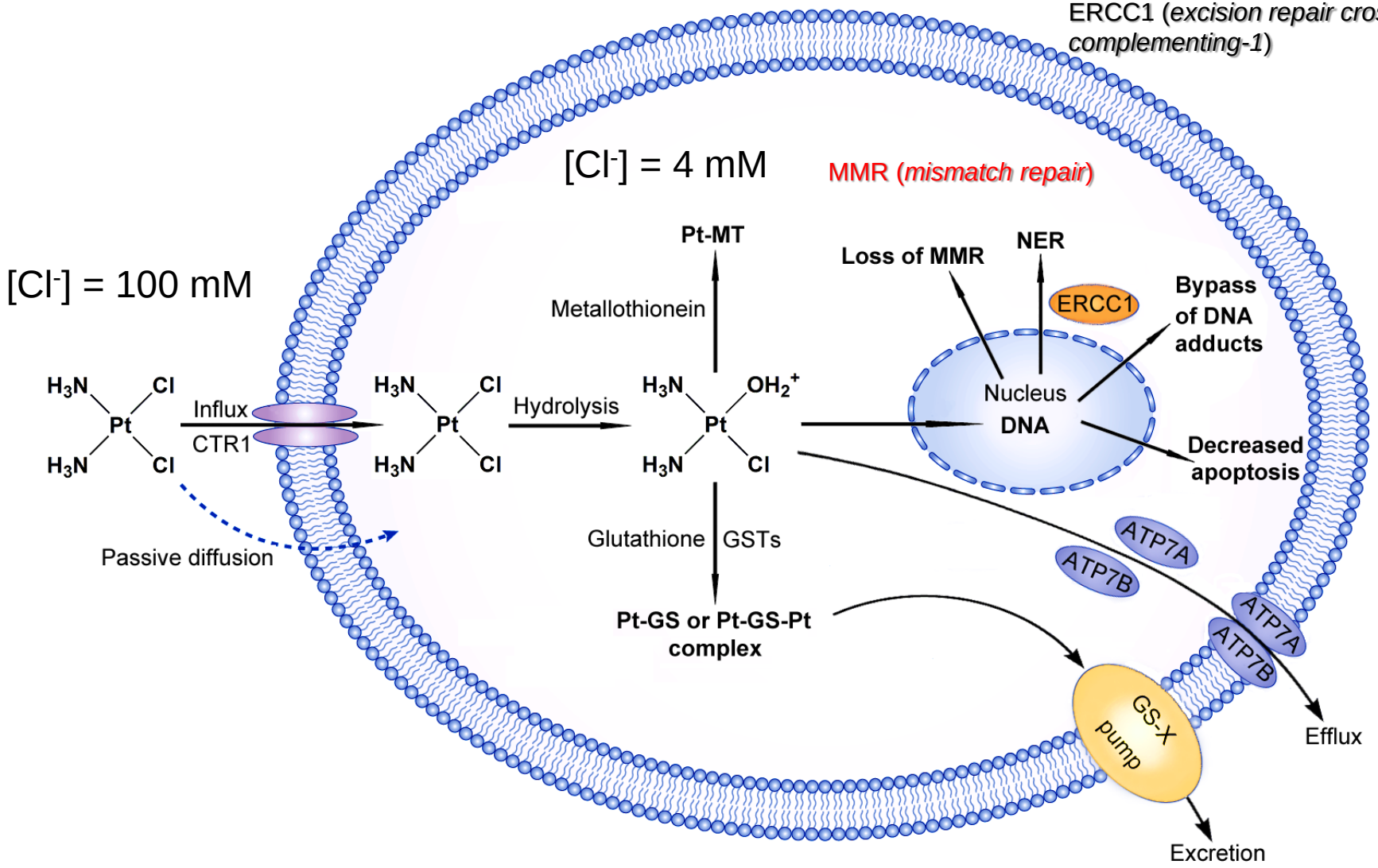


Main resistance mechanisms

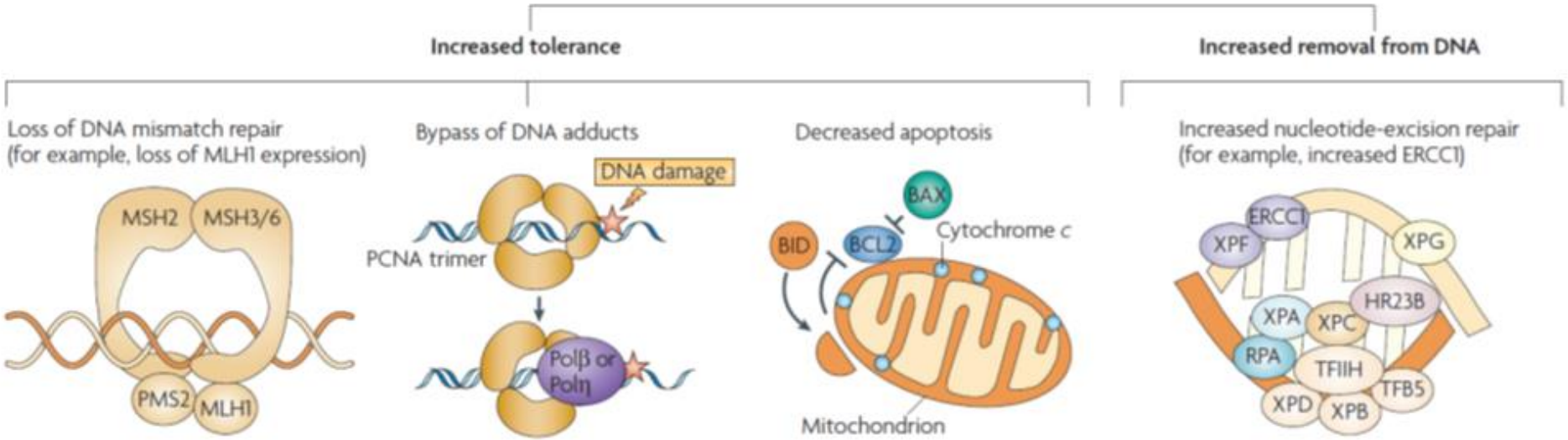
1) diminuzione del livello di platino nella cellula;
2) aumento del livello di tioli cellulari (glutatione, metallotioneine e altre molecole contenenti zolfo);
3) aumento della capacità di riparo del DNA e/o aumento della resistenza al danno;
4) cambiamenti nelle catene di segnali che portano alla morte cellulare (*cell-death pathways*), o alla sua sopravvivenza. In particolare, riduzione della risposta apoptotica e attivazione di *survival pathways*.

NER (*Nucleotides Excision Repair*)

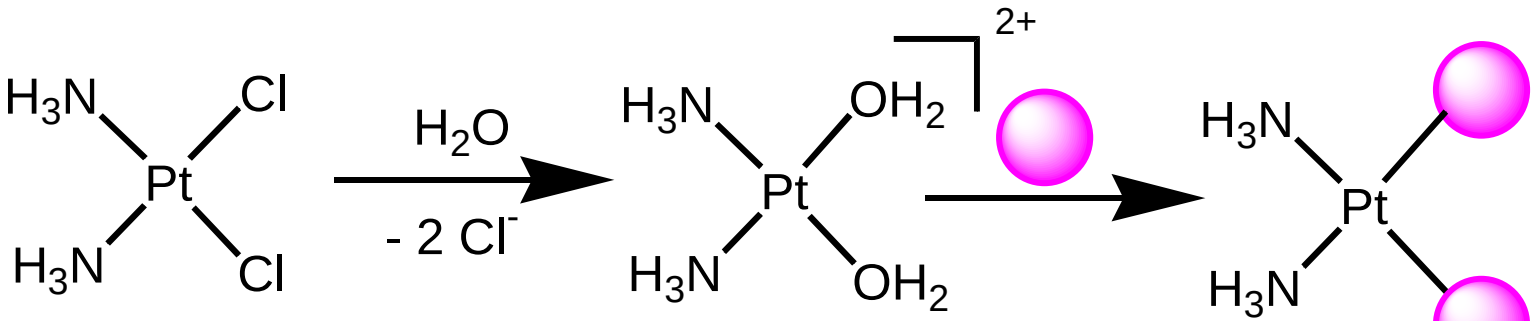
ERCC1 (*excision repair cross-complementing-1*)



Resistance mechanisms

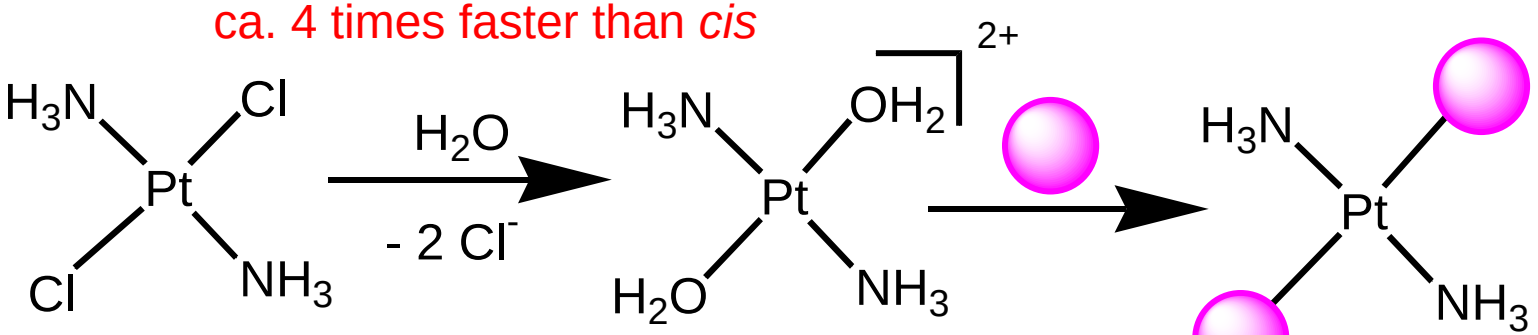


Geometry matters!



Cisplatin

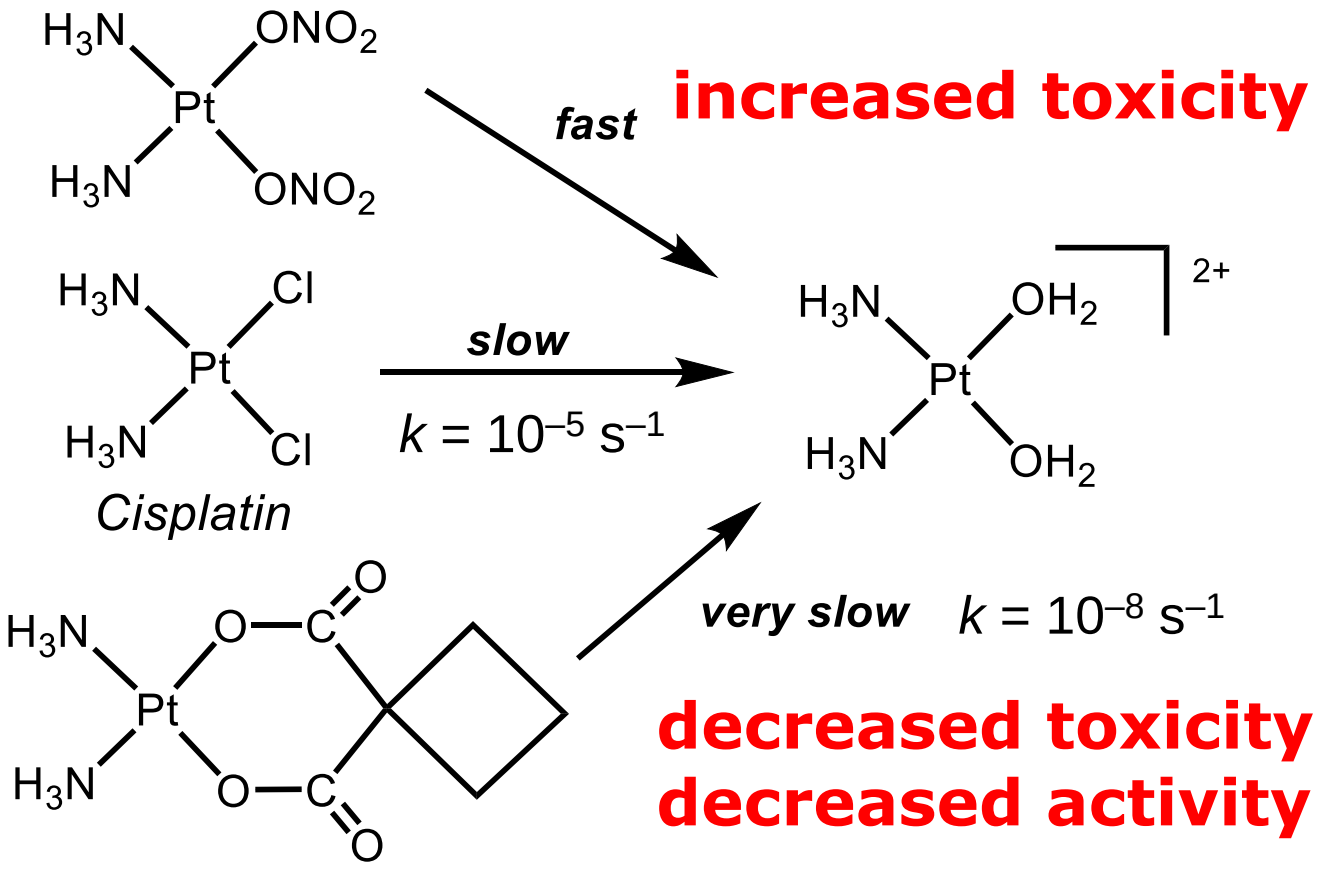
ca. 4 times faster than *cis*

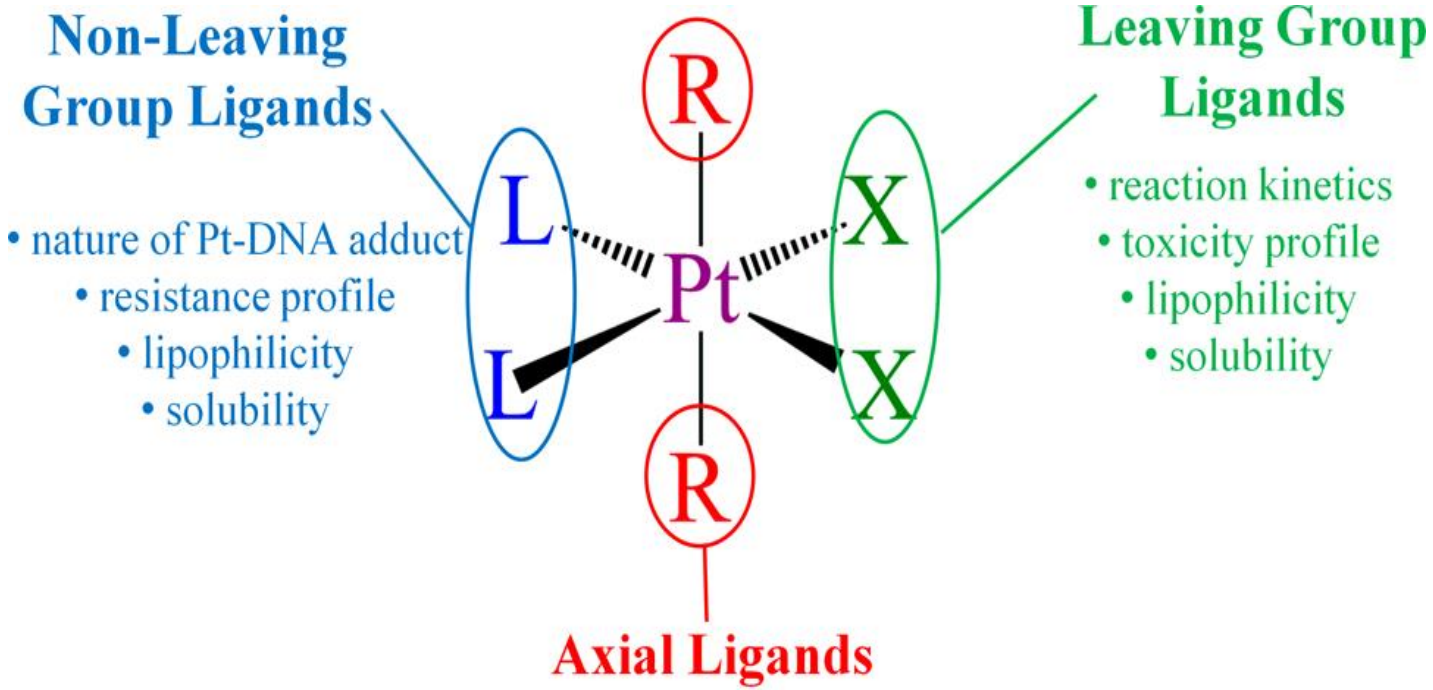


Transplatin

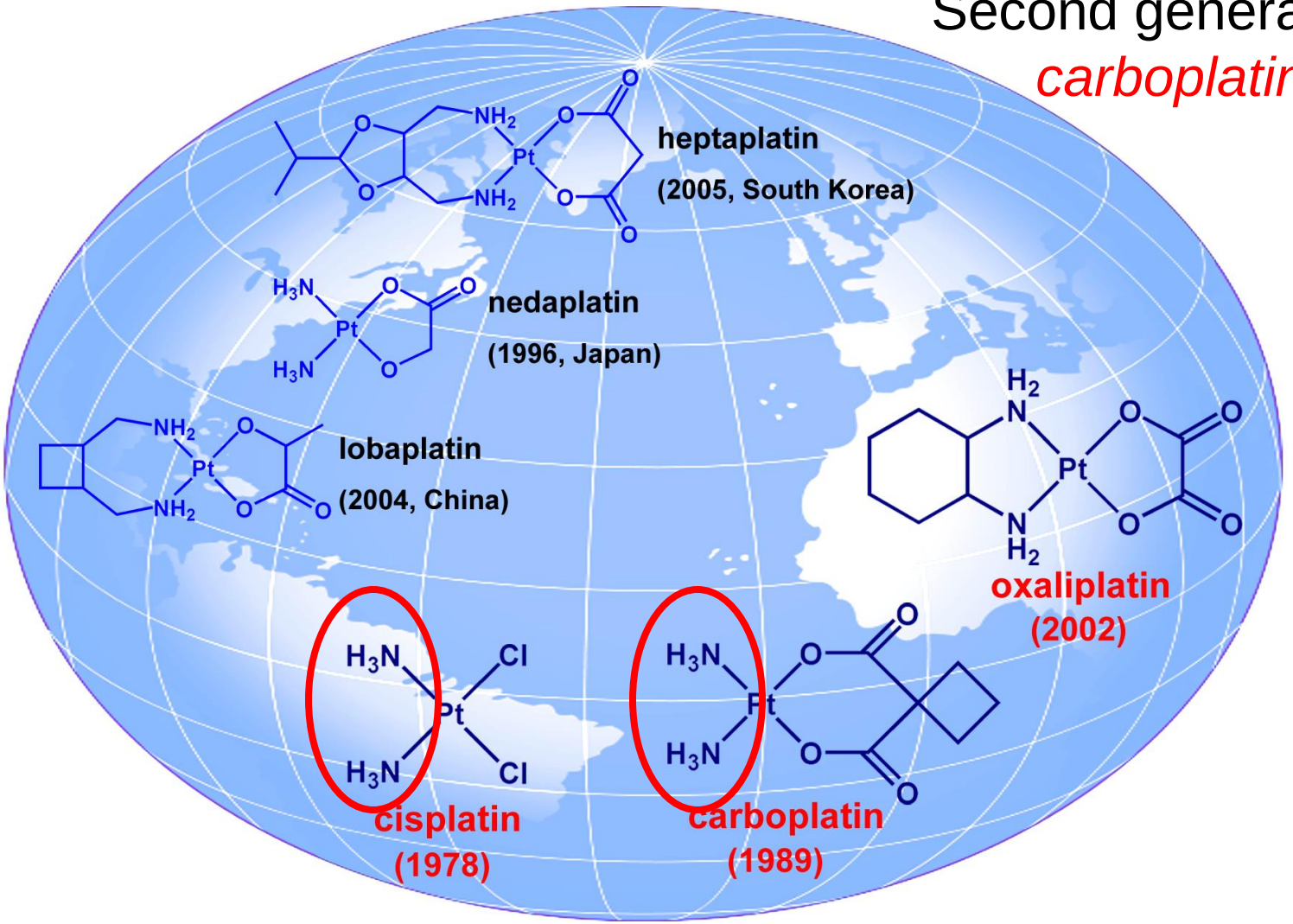
Toxic, but not anticancer active

Kinetics matter!

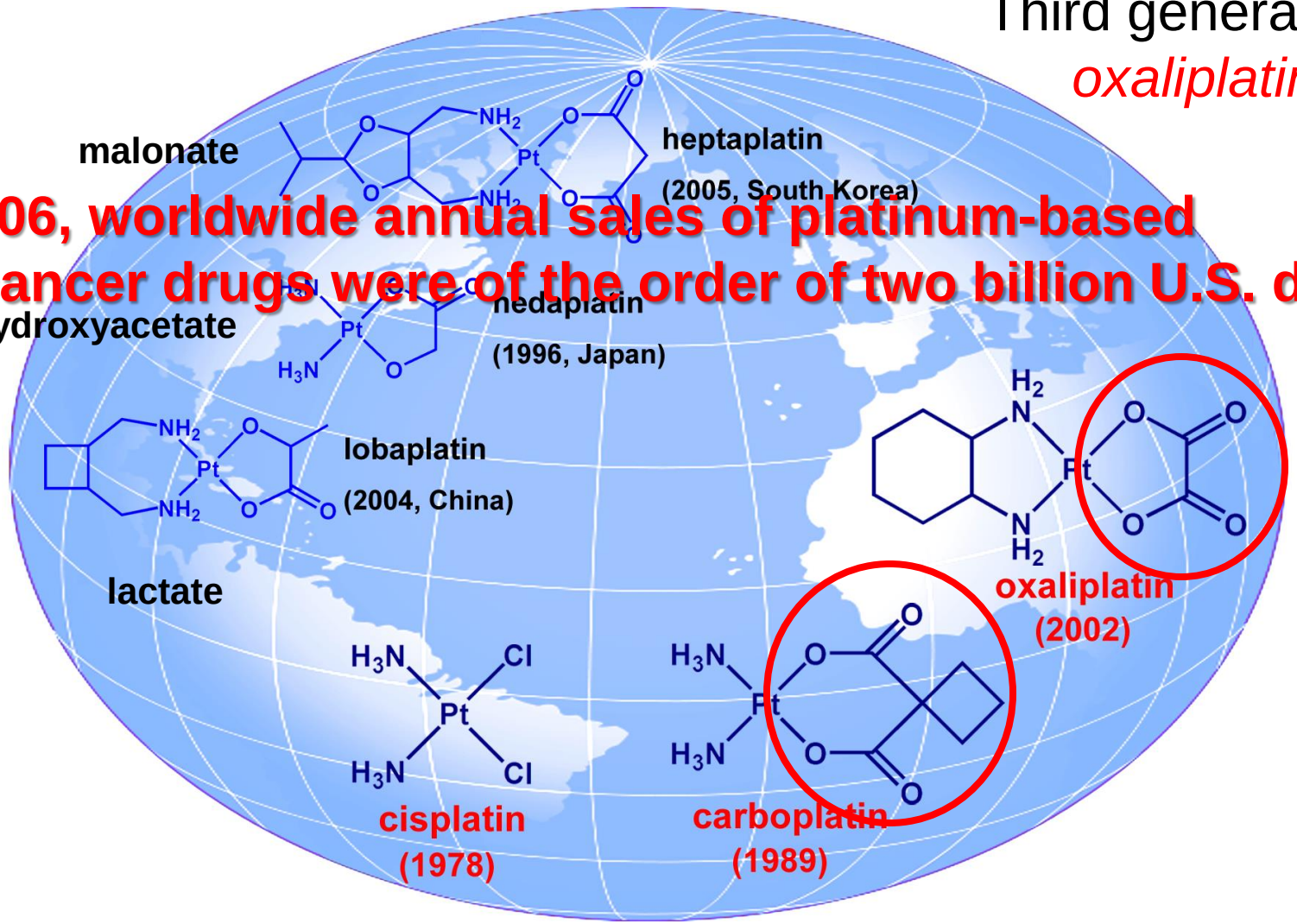



Non-Leaving Group Ligands
• nature of Pt-DNA adduct
• resistance profile
• lipophilicity
• solubility
R
L
L
Pt
X
X
R
Leaving Group Ligands
• reaction kinetics
• toxicity profile
• lipophilicity
• solubility
Axial Ligands
• only present for Pt(IV)
• additional targeting or biological properties
• lipophilicity
• solubility

Second generation: *carboplatin*

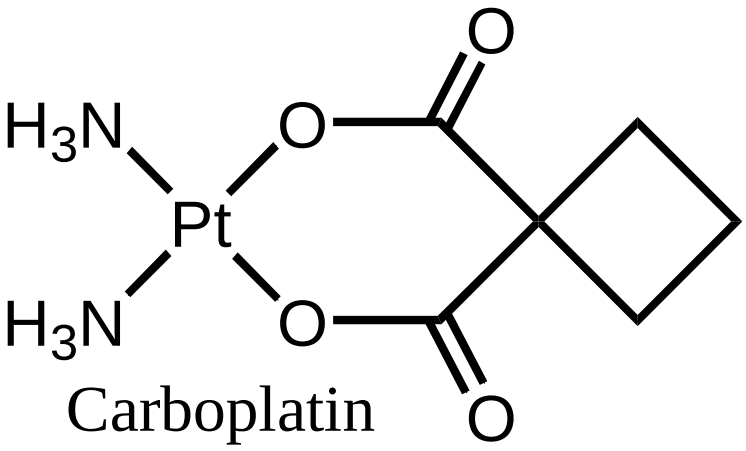


Third generation:
oxaliplatin

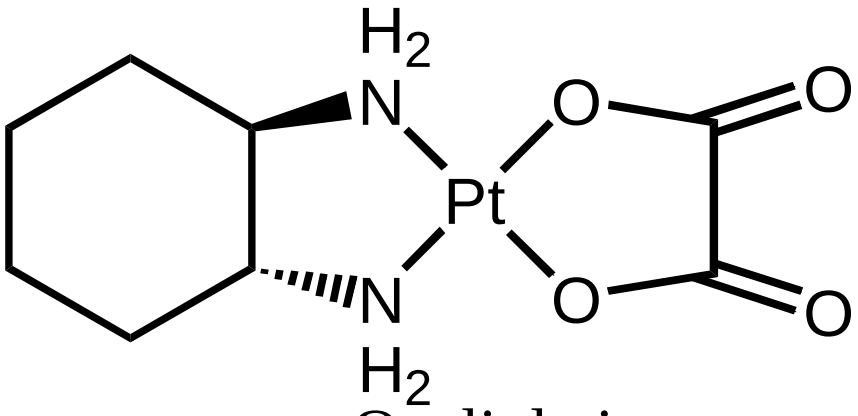


In 2006, worldwide annual sales of platinum-based anticancer drugs were of the order of two billion U.S. dollars

Carboplatin and Oxaliplatin



Carboplatin



Oxaliplatin

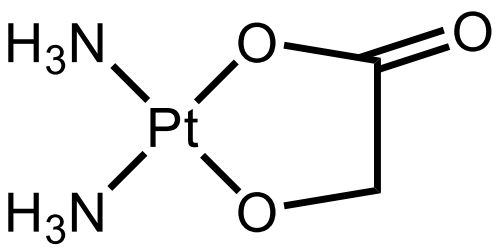
1,1-cyclobutanedicarboxylate

trans-(1*R*,2*R*)-1,2-diaminecyclohexane

$t_{1/2}$ aquation = 268h vs 2.4h of cisplatin

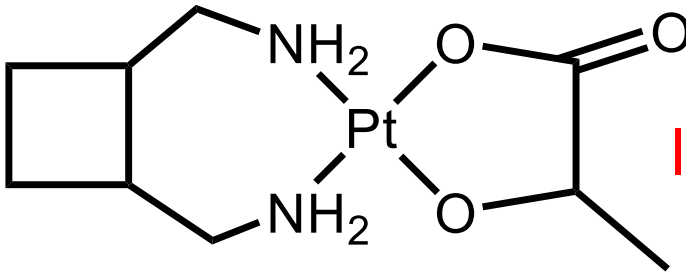
300–450 mg/m^2 vs 20–120 mg/m^2 of cisplatin

2-hydroxyacetate



Nedaplatin (Japan)

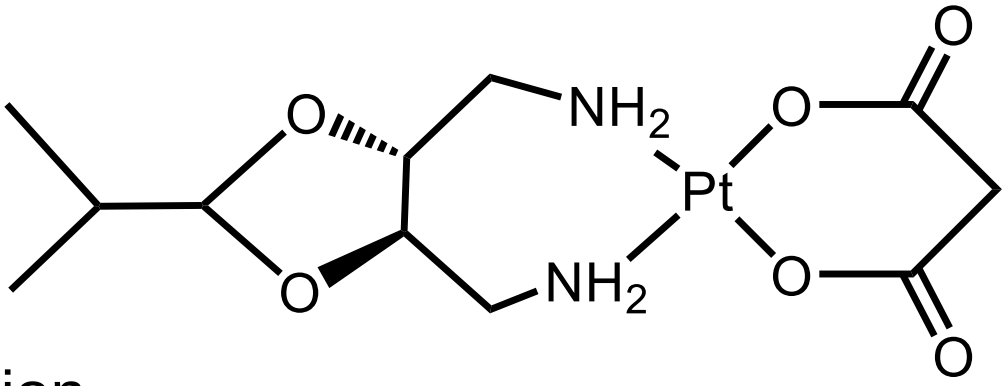
II generation



lactate

Lobaplatin (China)

III generation

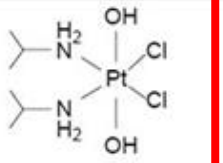


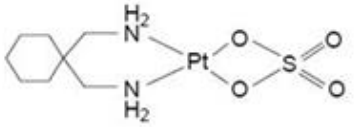
malonate

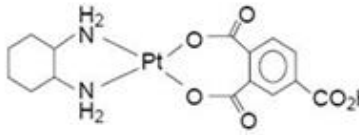
III generation

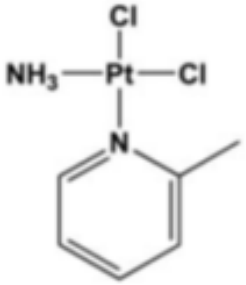
Heptaplatin (South Korea)

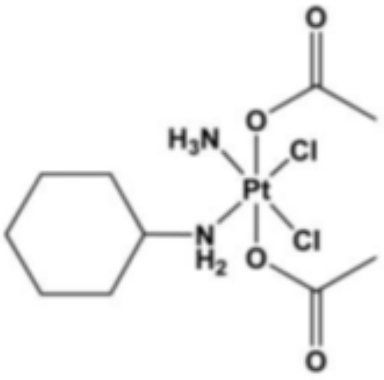
Some Pt compounds (23) tested in clinical phase

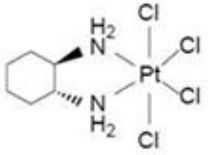

Iproplatin

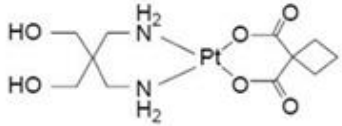

Spiroplatin

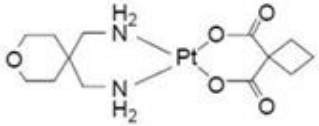

DAC-TMA

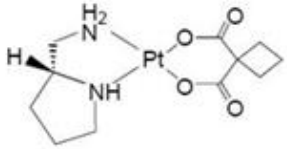

picoplatin

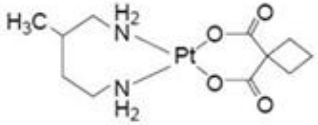

satraplatin

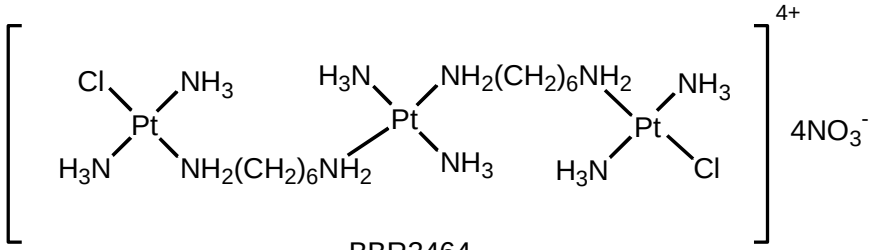

Tetraplatin


Zeniplatin


Enloplatin


Miboplatin

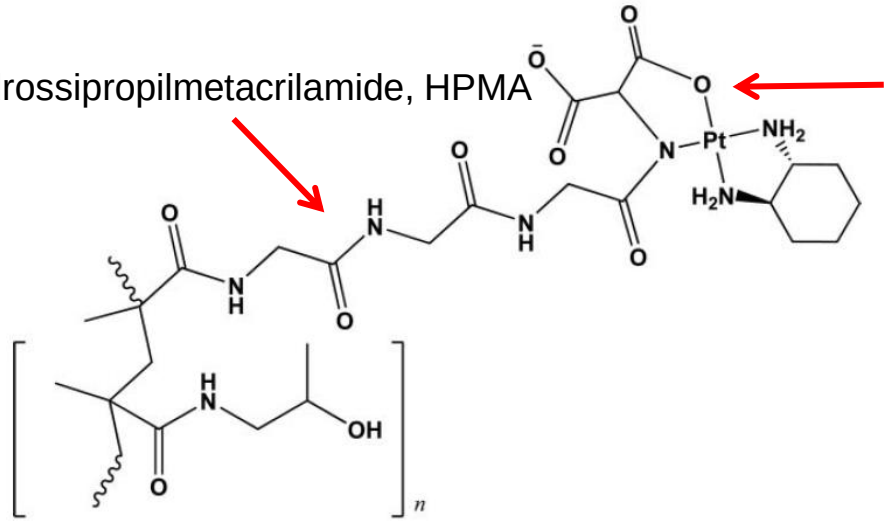

Sebriplatin

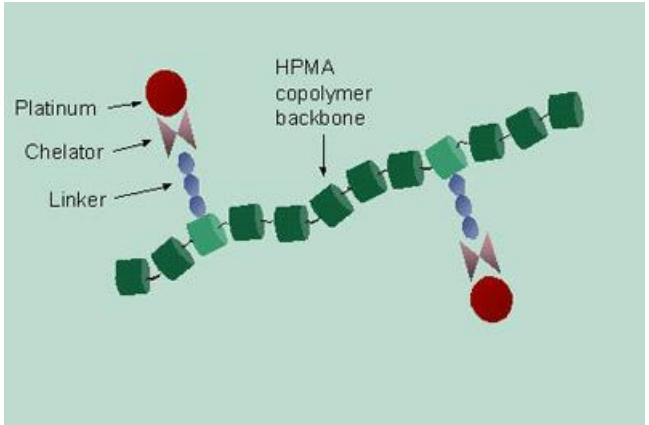

BBR3464

Some Pt formulations in clinical phase: ProLindac™ and Lipoplatin™

idrossipropilmetacrilamide, HPMA

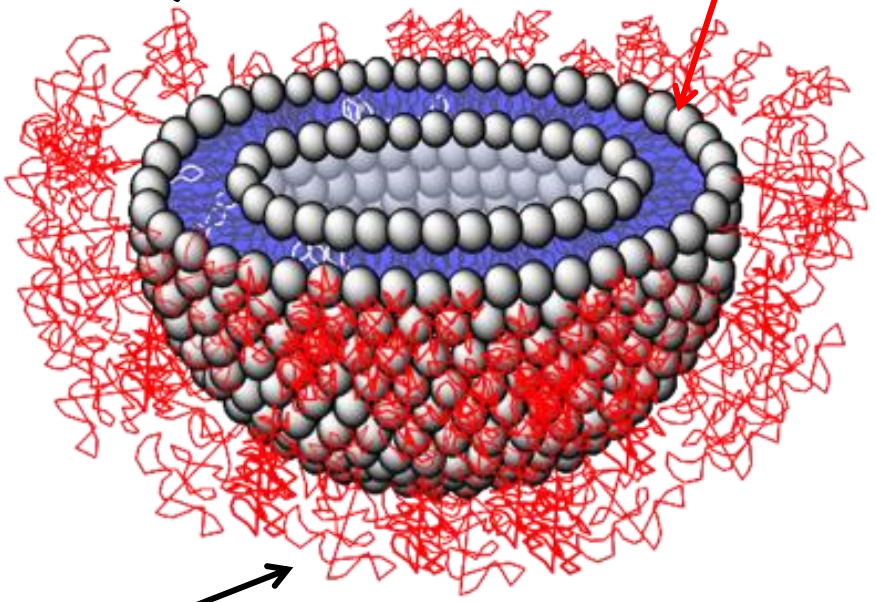
amidomalonato





glicerofosfolipidi, e.g. dipalmitoil fosfatidil glicerolo (DPPG)

90 – 130 nm



PEG

Micella inversa

- Pt drugs are actually prodrugs (or *functional compounds*) and need an activation step.
- For functional compounds activation occurs typically by hydrolysis, possibly preceded by reduction/oxidation.
- The coordination of the metal to the bio-target is the main interaction responsible for the activity. Additional, less energetic, interactions may be also important.

Functional Compounds

The anticancer activity (e.g. cytotoxicity) of functional compounds will depend on many parameters, very often strictly interconnected:

1. on the nature of the metal center (*thermodynamic and kinetic parameters, hard-soft nature, oxidation state*)
2. on the nature of the non-leaving ligands (*lipophylicity, charge, solubility, non-covalent interactions*…);
3. on the kinetics of activation (*e.g. aquation rate*)

Not surprisingly, the few metal anticancer drugs that are in clinical use – all of them functional – were found serendipitously or by rational design from a lead compound (cisplatin → carboplatin → oxaliplatin).

There are apparently two ways for overcoming the limitations of Pt anticancer drugs:

1. Find novel, non-conventional Pt drugs, i.e. Pt compounds that do not follow the established SAR rules;
2. Find new anticancer drugs based on different metals.

Non-platinum active compounds are likely to have thermodynamic and kinetic parameters different from those of Pt drugs and, as a consequence, also different

- mechanism of action
- biodistribution
- toxicity

Among the several metals that are currently being investigated for their anticancer activity, ruthenium (among others) occupies a prominent position.

Expectations

Ruthenium drugs are expected:

1. to be active against those human malignancies that are resistant, or have acquired resistance, to Pt drugs.

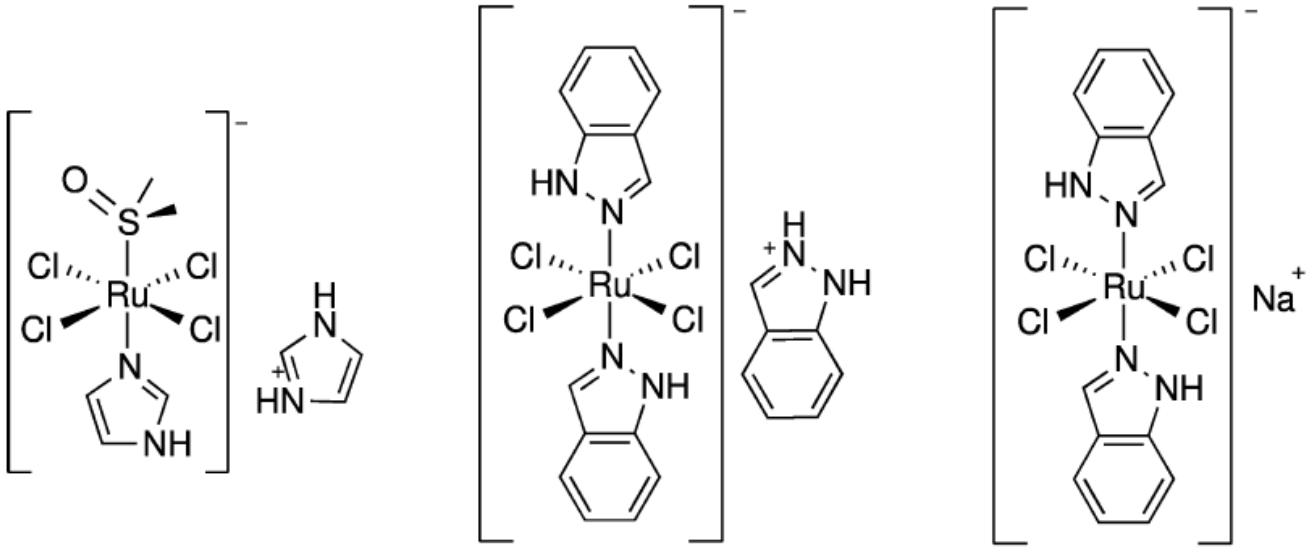
2. to show a lower (or at least different) toxicity compared to Pt drugs.

General features of ruthenium compounds

- Six-coordinate, octahedral geometry
- High affinity for nitrogen and sulfur ligands
- Two readily accessible oxidation states in aqueous solution: Ru(III) (d^5, paramagnetic) and Ru(II) (d^6, diamagnetic)
- Ru(III) complexes are usually more inert than the corresponding Ru(II) species
- The kinetics of ligand dissociation of Ru compounds are similar to those of Pt compounds (with remarkable exceptions)

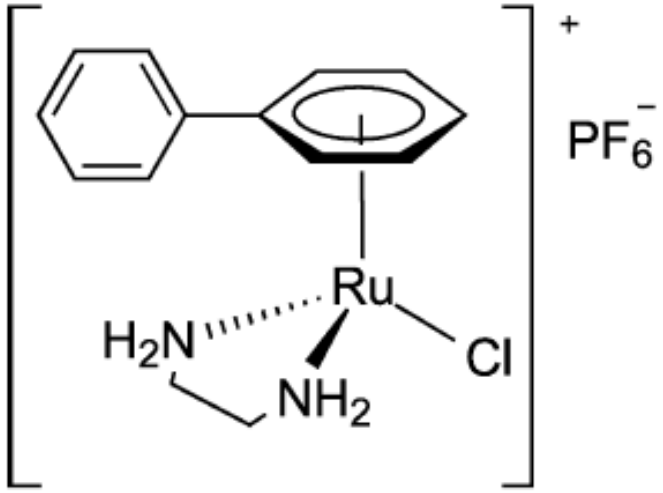
Clinically tested anticancer Ru(III) compounds

Deceptively similar

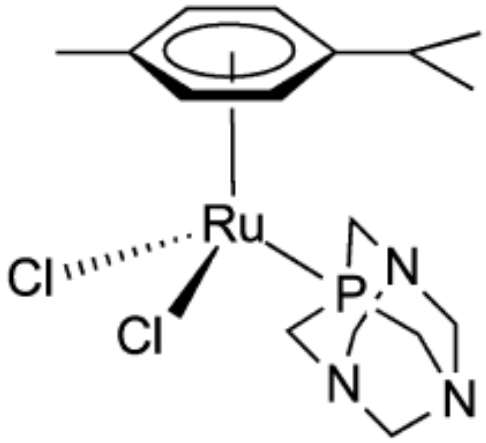


Both NAMI-A and KP1019 are prodrugs; they are activated through hydrolysis, possibly after reduction to Ru(II).

Anticancer organometallic Ru(II) compounds



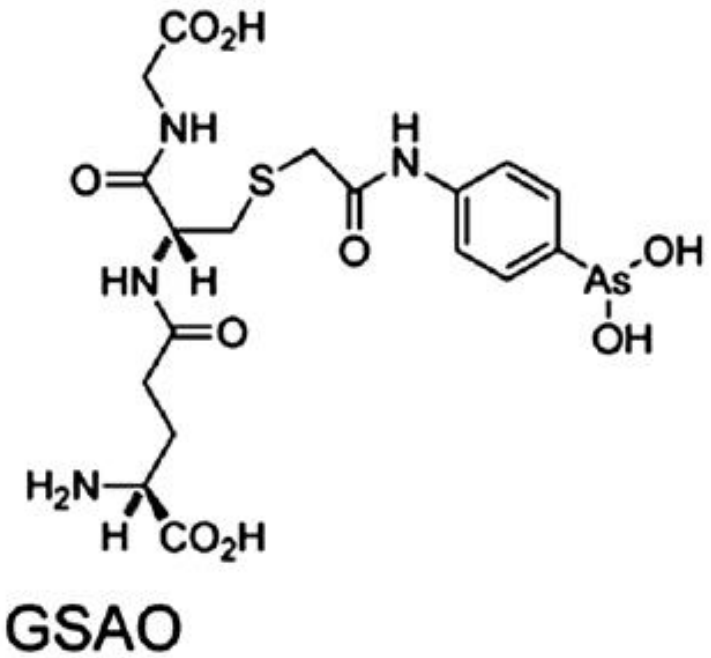
RM175



RAPTA-C

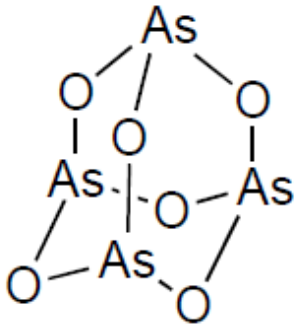
Arsenic anticancer compounds

(*acute promyelocytic leukemia*)



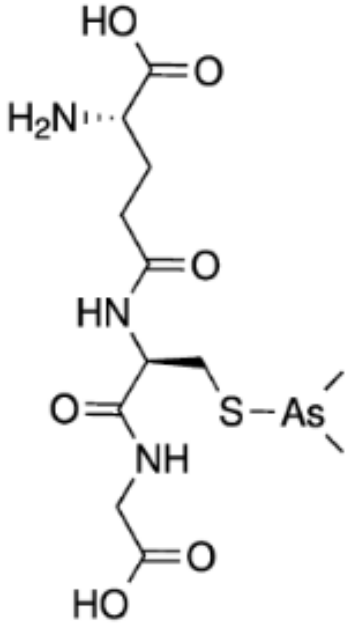
GSAO

4-(N-(S-glutathionylacetyl)amino)phenylarsonous acid



ATO

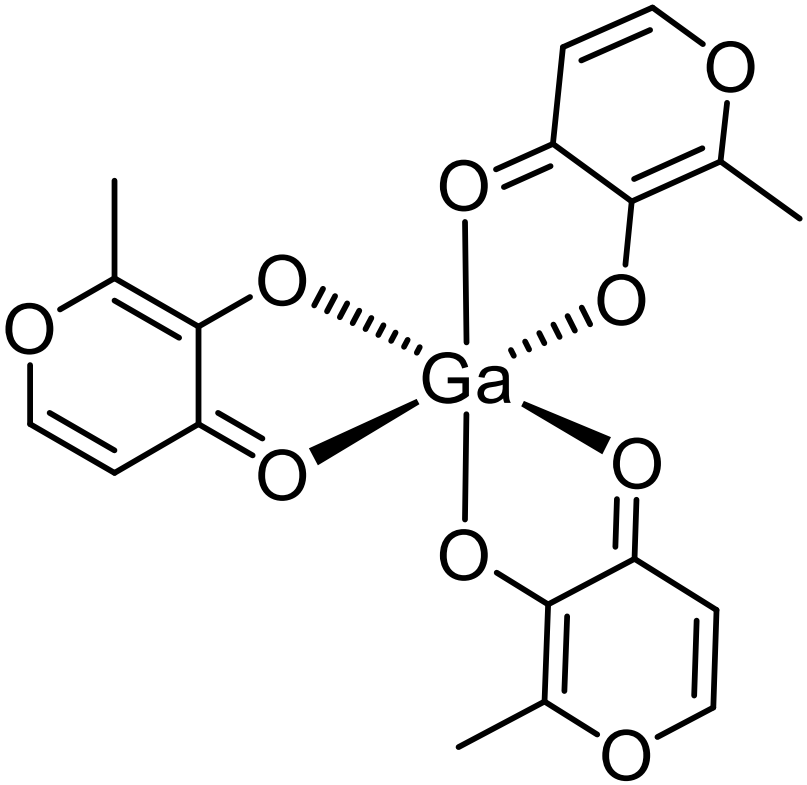
0.15 mg/kg

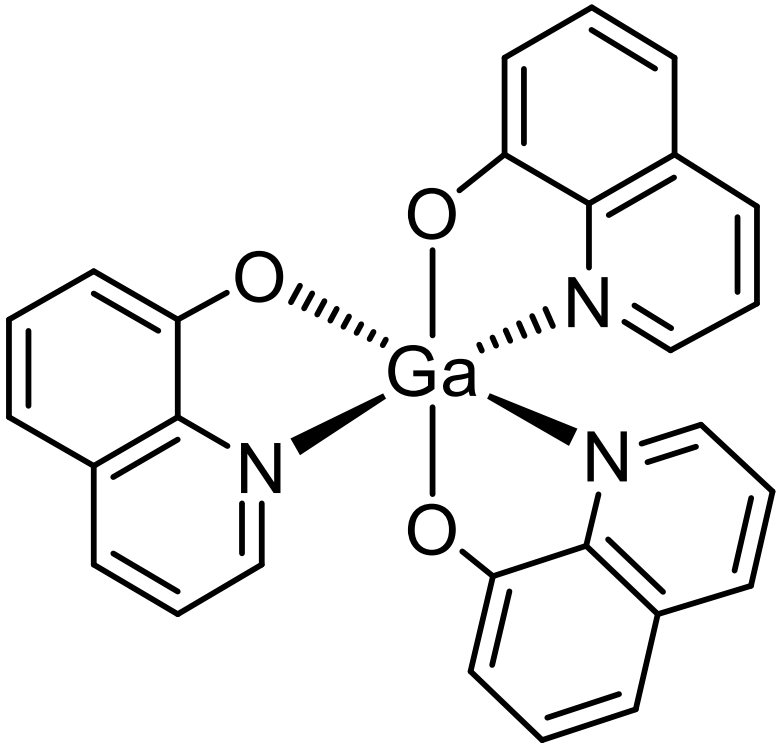


Darinaparsin

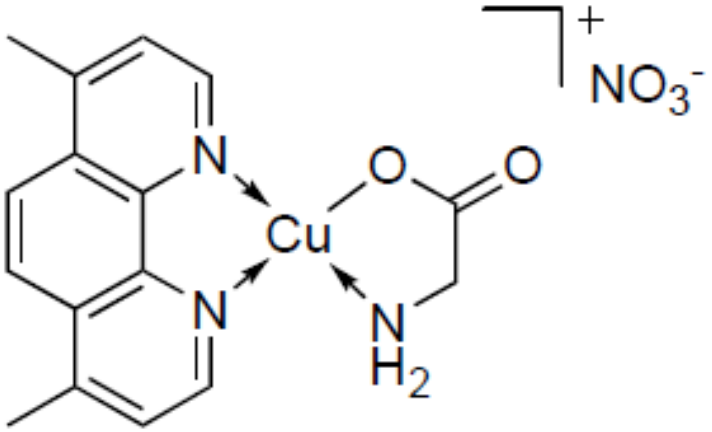
S-dimetilarsinoglutatione

Gallium anticancer compounds

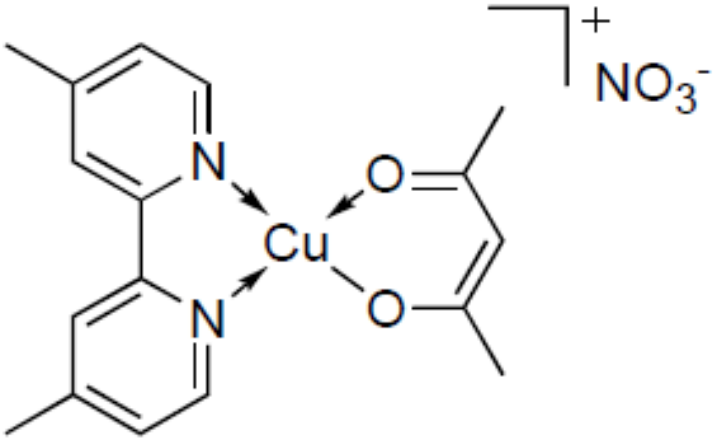




Copper anticancer compounds (*Casiopeine*)



Cas II-gly



Cas III-ia