

Discovery of cisplatin

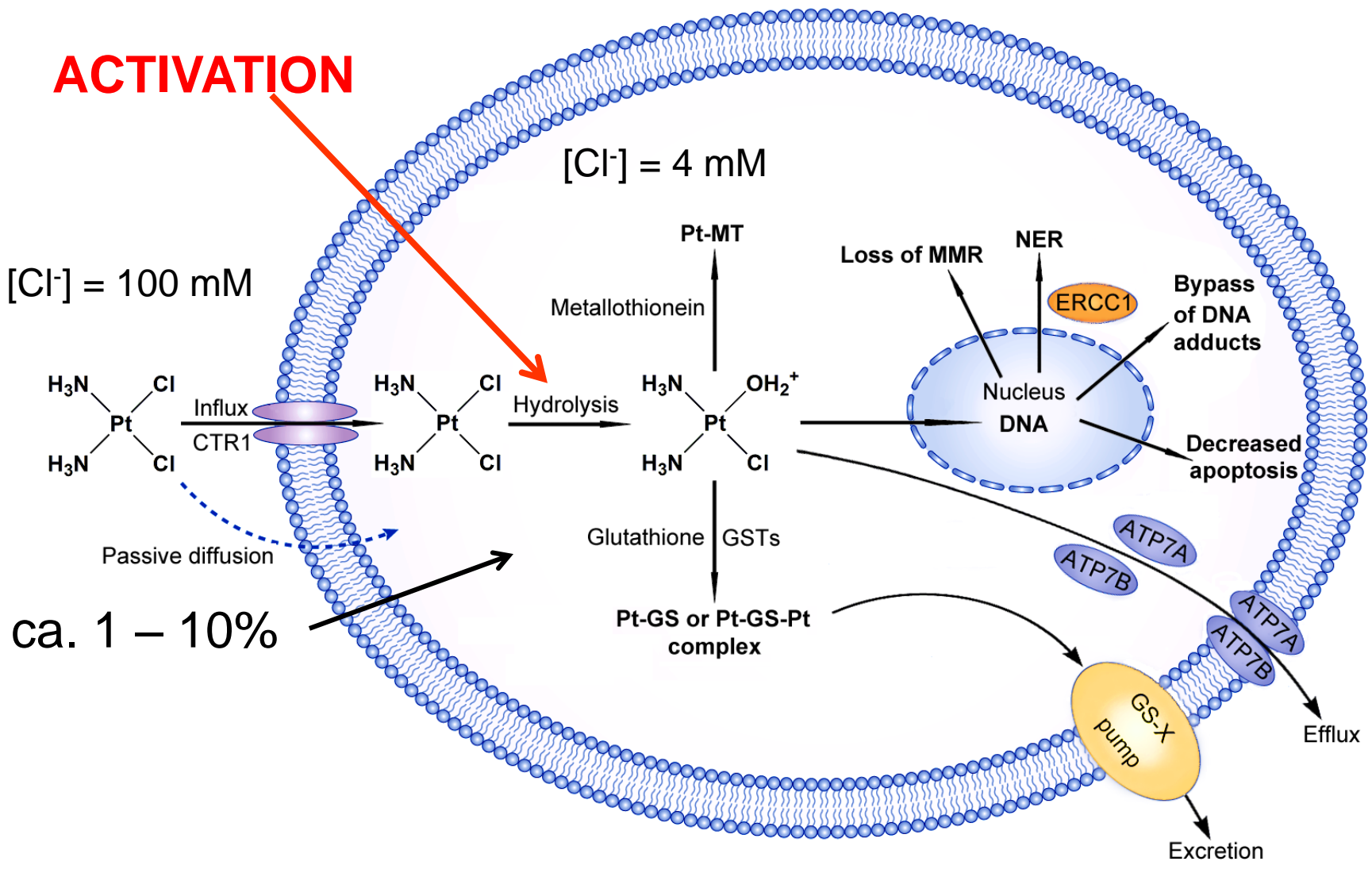
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graph TD; A([Discovery of cisplatin]) --> B[Mechanism of action]; A --> C[Structure – Activity relationships];
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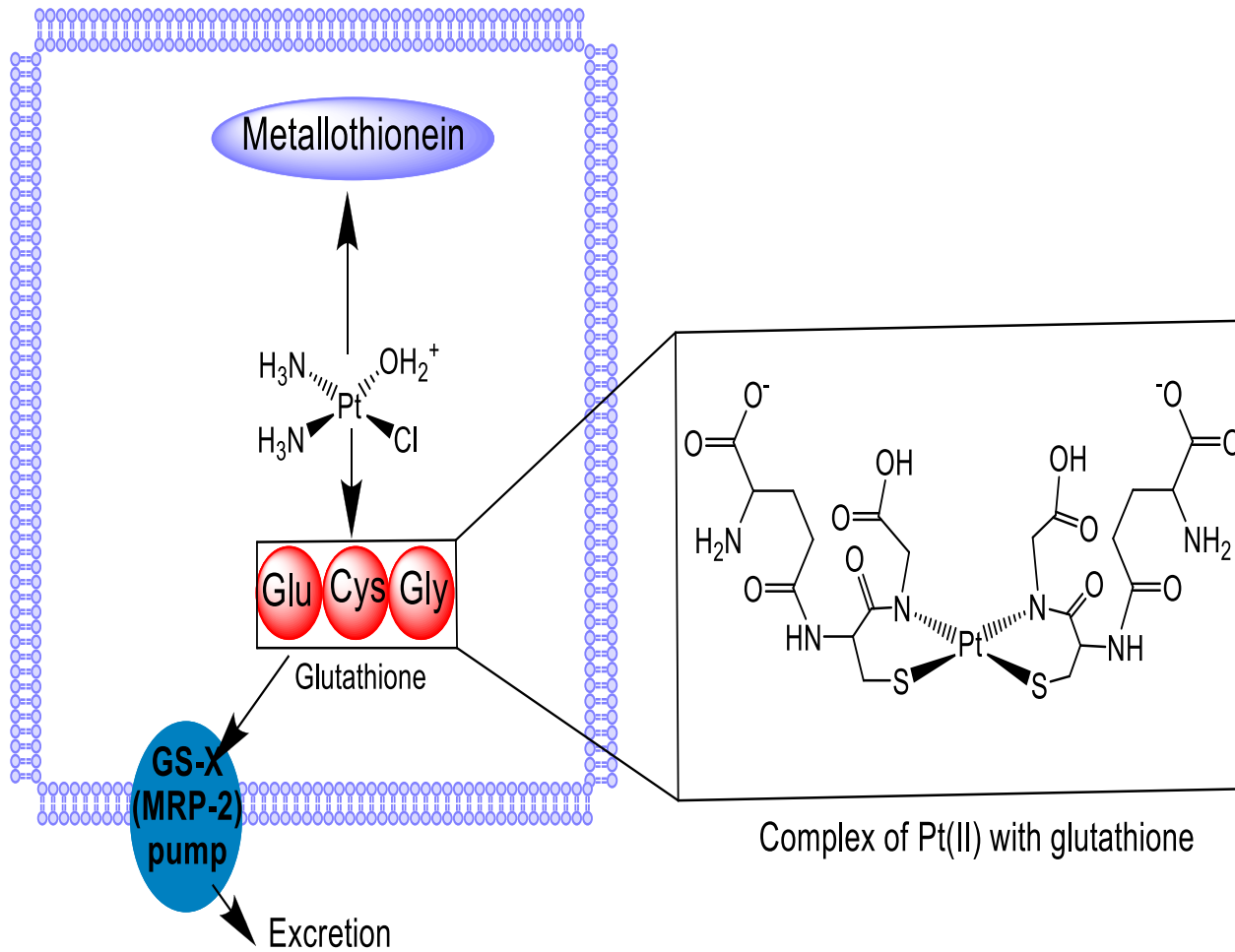
The diagram is a flowchart with three nodes. The top node is a blue oval containing the text 'Discovery of cisplatin'. Two red arrows originate from the bottom of this oval. One arrow points diagonally down and to the left to a yellow rounded rectangle containing the text 'Structure – Activity relationships'. The other arrow points diagonally down and to the right to a green rounded rectangle containing the text 'Mechanism of action'.

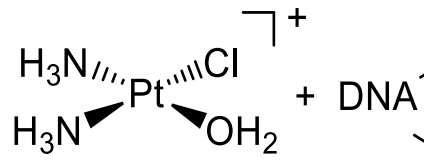
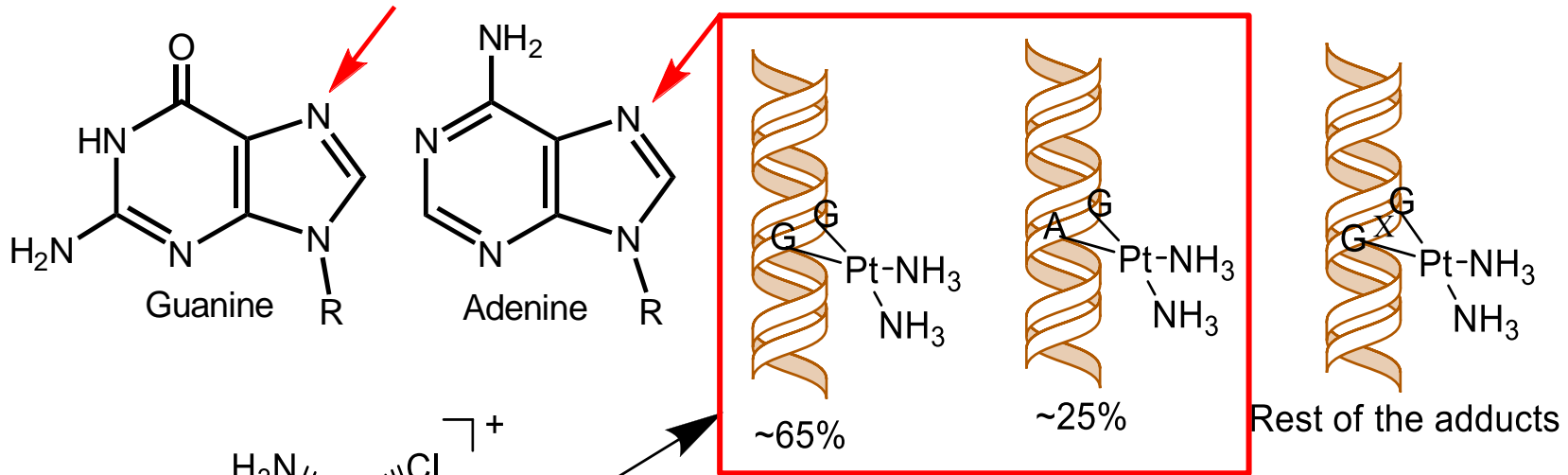
Mechanism of action

Structure – Activity
relationships

ACTIVATION



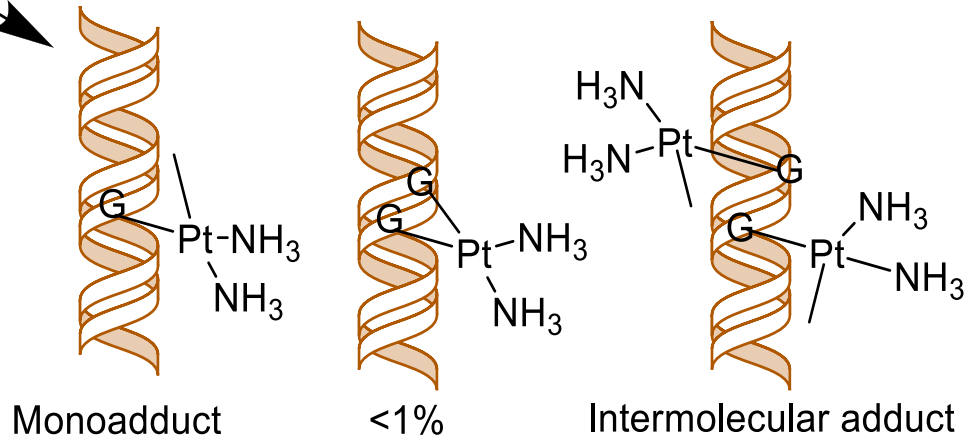




Intrastrand Adducts

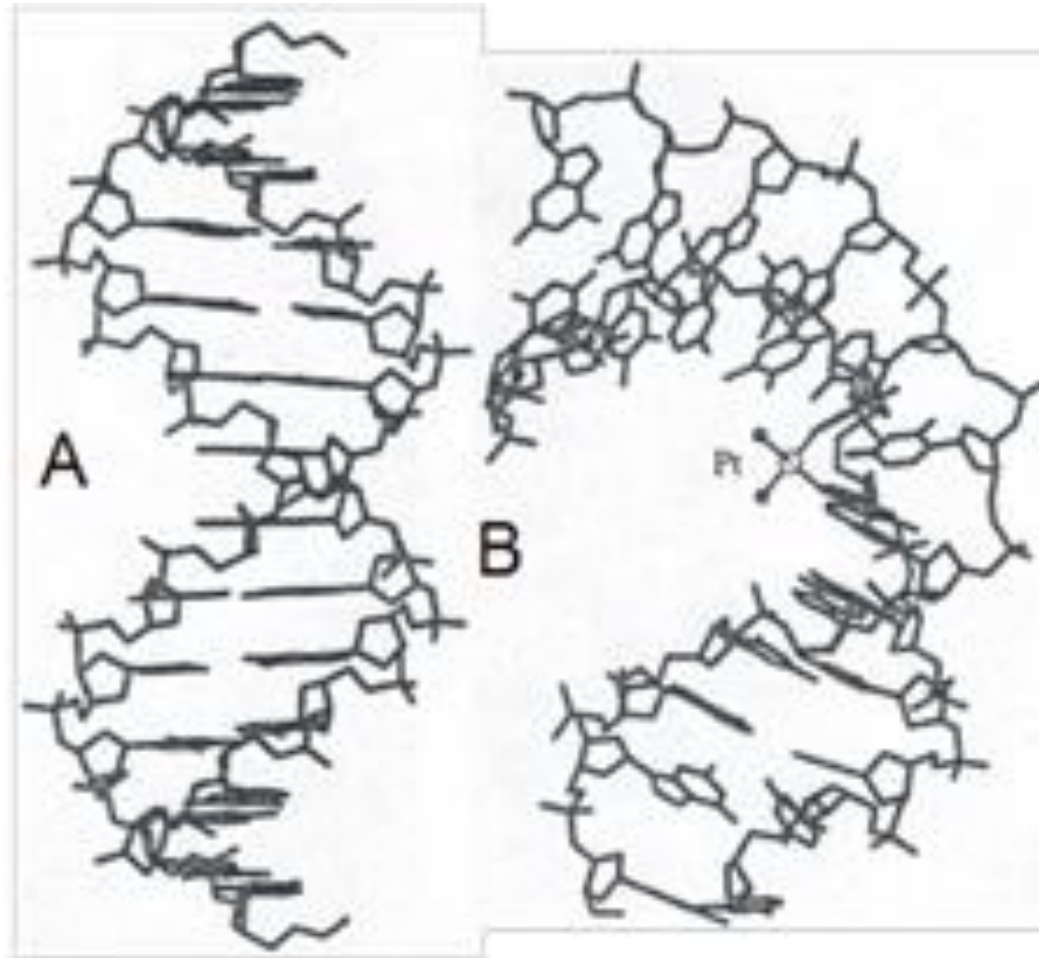
Stima:

- 1 Pt per 250.000 nucleotidi è sufficiente a inibire la crescita cellulare
- ca. 50.000 addotti di Pt per cellula umana

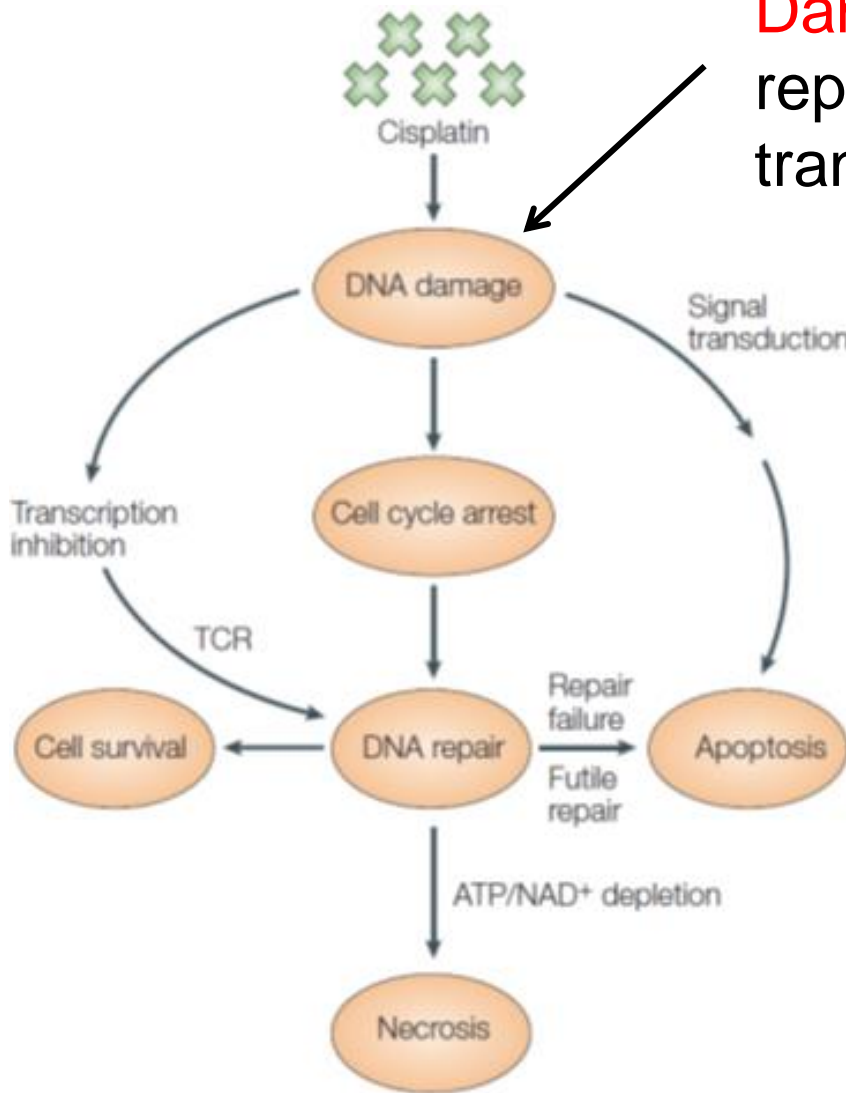


Other Adducts

La platinazione induce un piegamento (*kink*) verso il *major groove* e uno svolgimento (*unwinding*) locale del DNA



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



Aspartic proteases

Riconoscimento del sito di platinazione del DNA da parte di una proteina HMG (High Mobility Group)

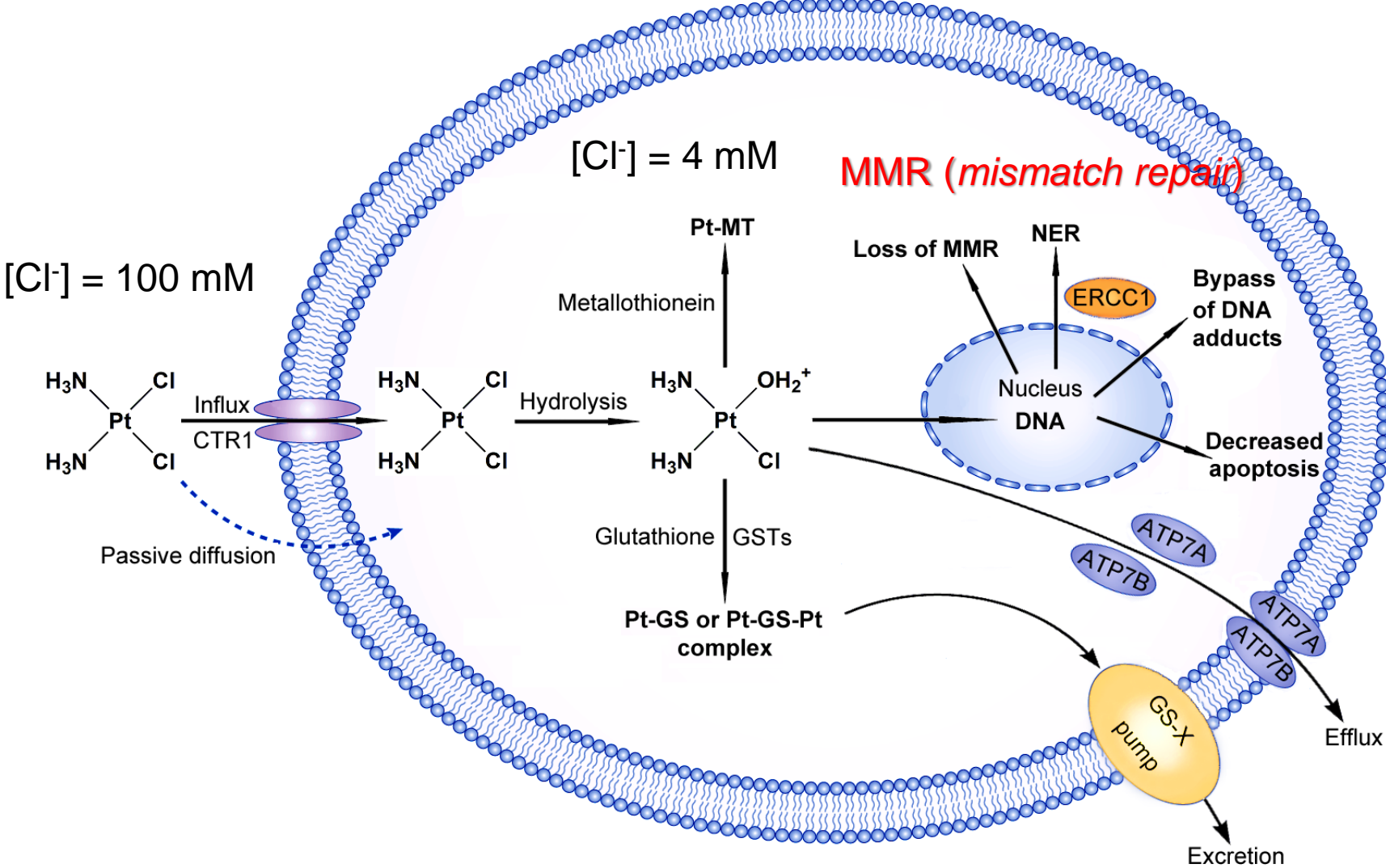


Principali meccanismi di resistenza

- 1) diminuzione del livello di platino nella cellula;
- 2) aumento del livello di tioli cellulari (glutathione, metallothioneine 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)

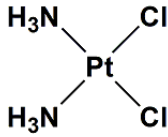
ERCC1 (excision repair cross-complementing-1)



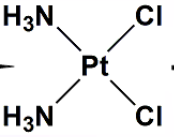
[Cl⁻] = 100 mM

[Cl⁻] = 4 mM

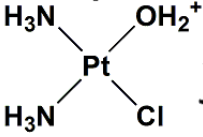
MMR (mismatch repair)



Influx
CTR1



Hydrolysis

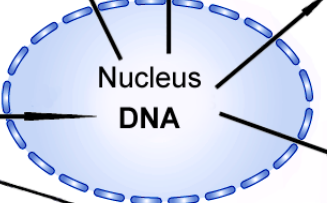


Pt-MT

Metallothionein

Glutathione GSTs

Pt-GS or Pt-GS-Pt complex



Loss of MMR

NER

ERCC1

Bypass of DNA adducts

Decreased apoptosis

ATP7A

ATP7B

ATP7A

ATP7B

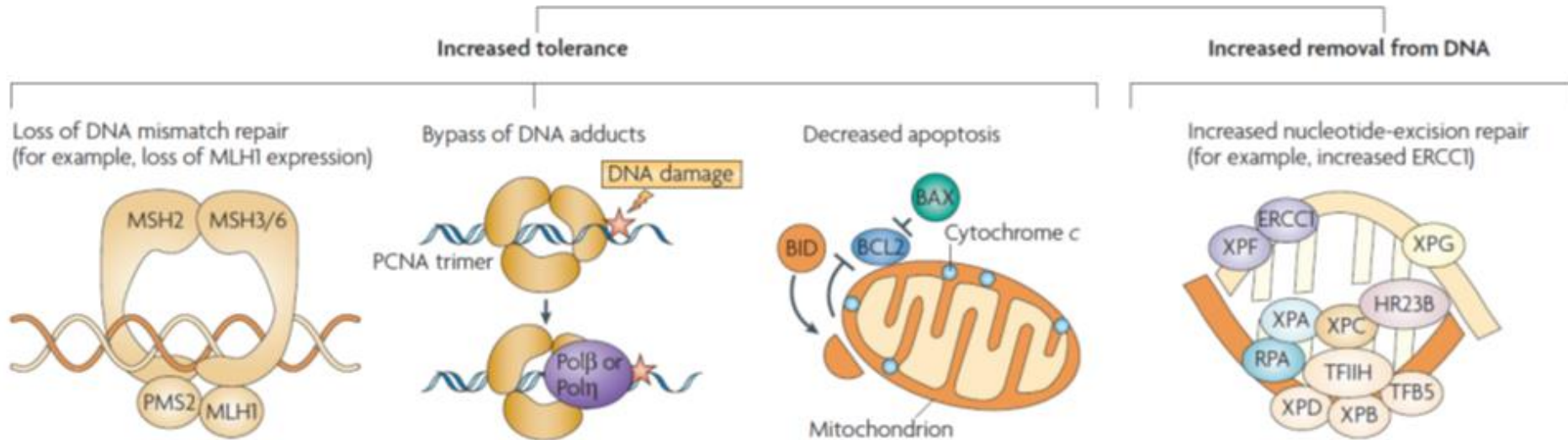


Efflux

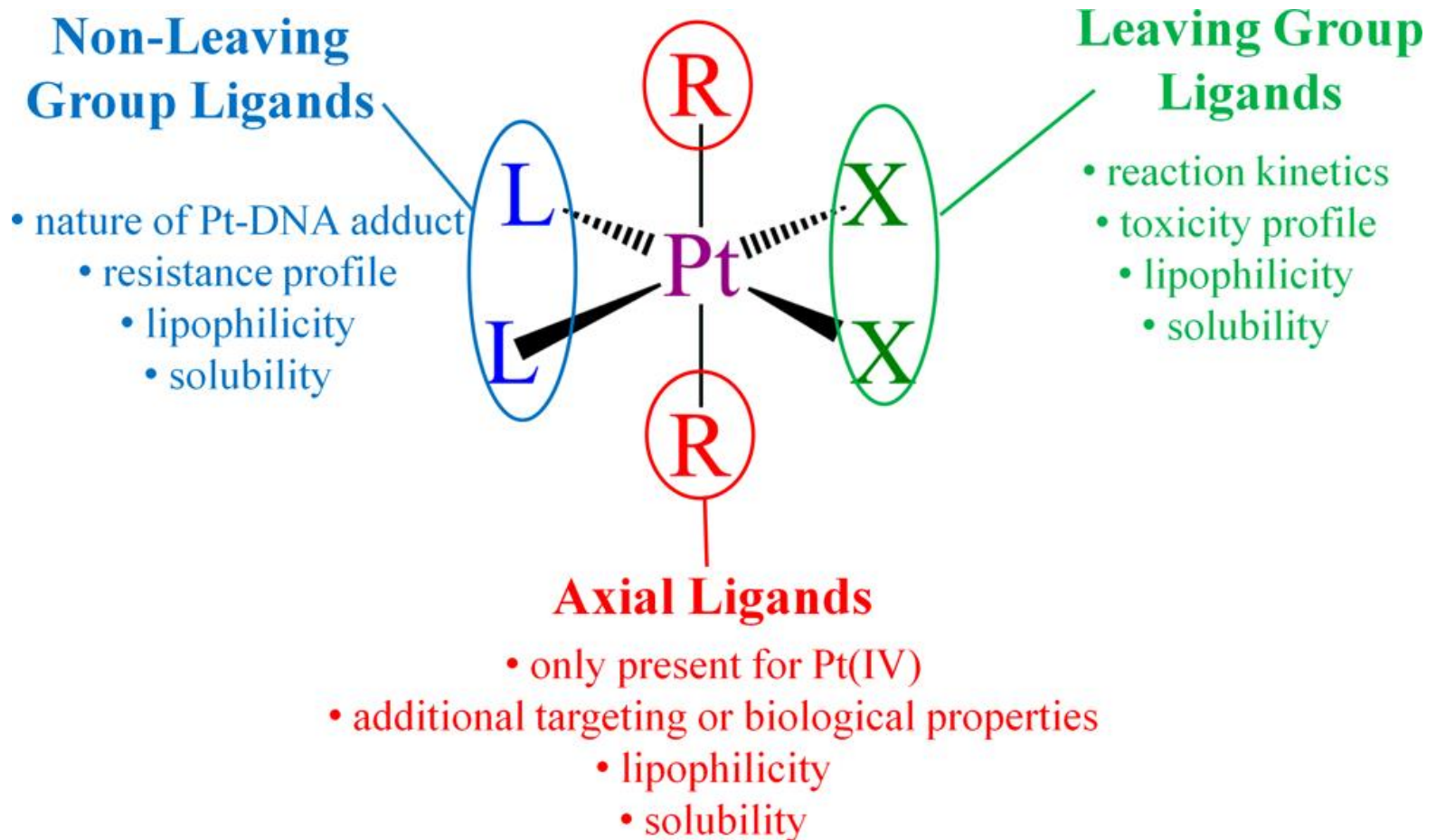
Excretion

Passive diffusion

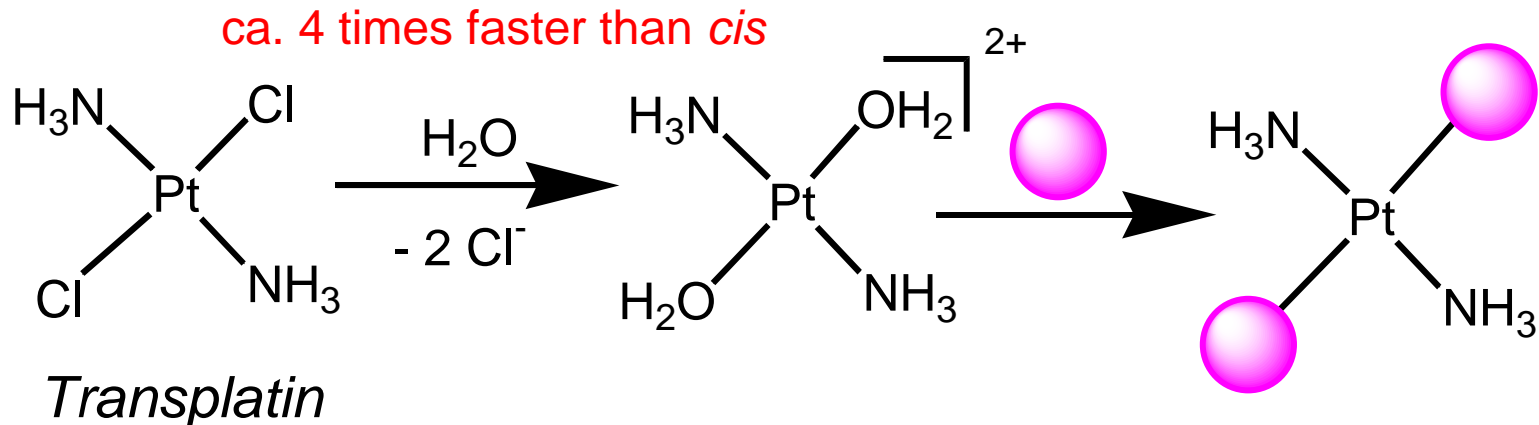
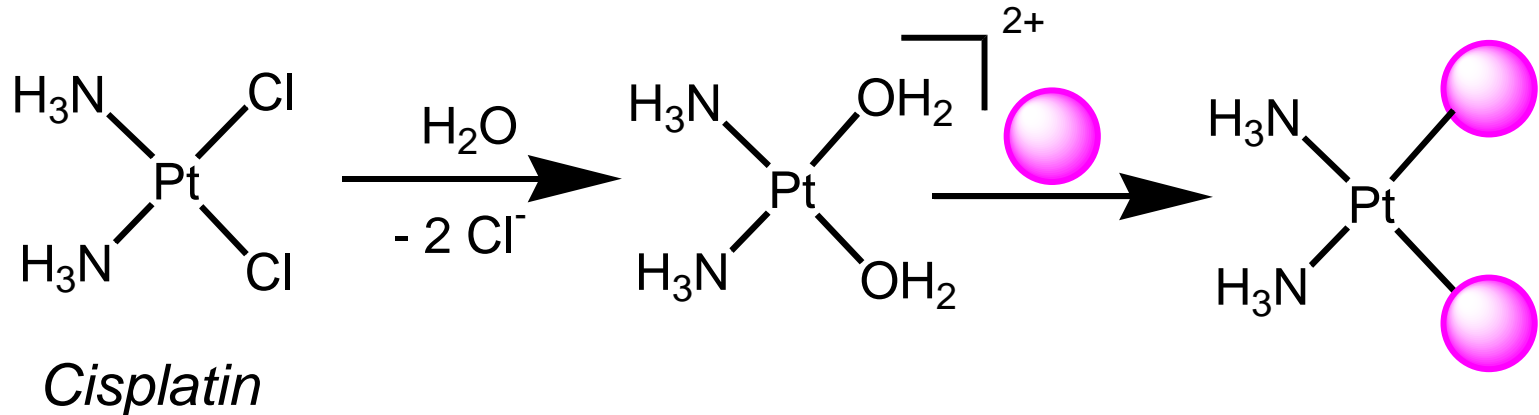
Meccanismi di resistenza



Correlazione struttura – attività

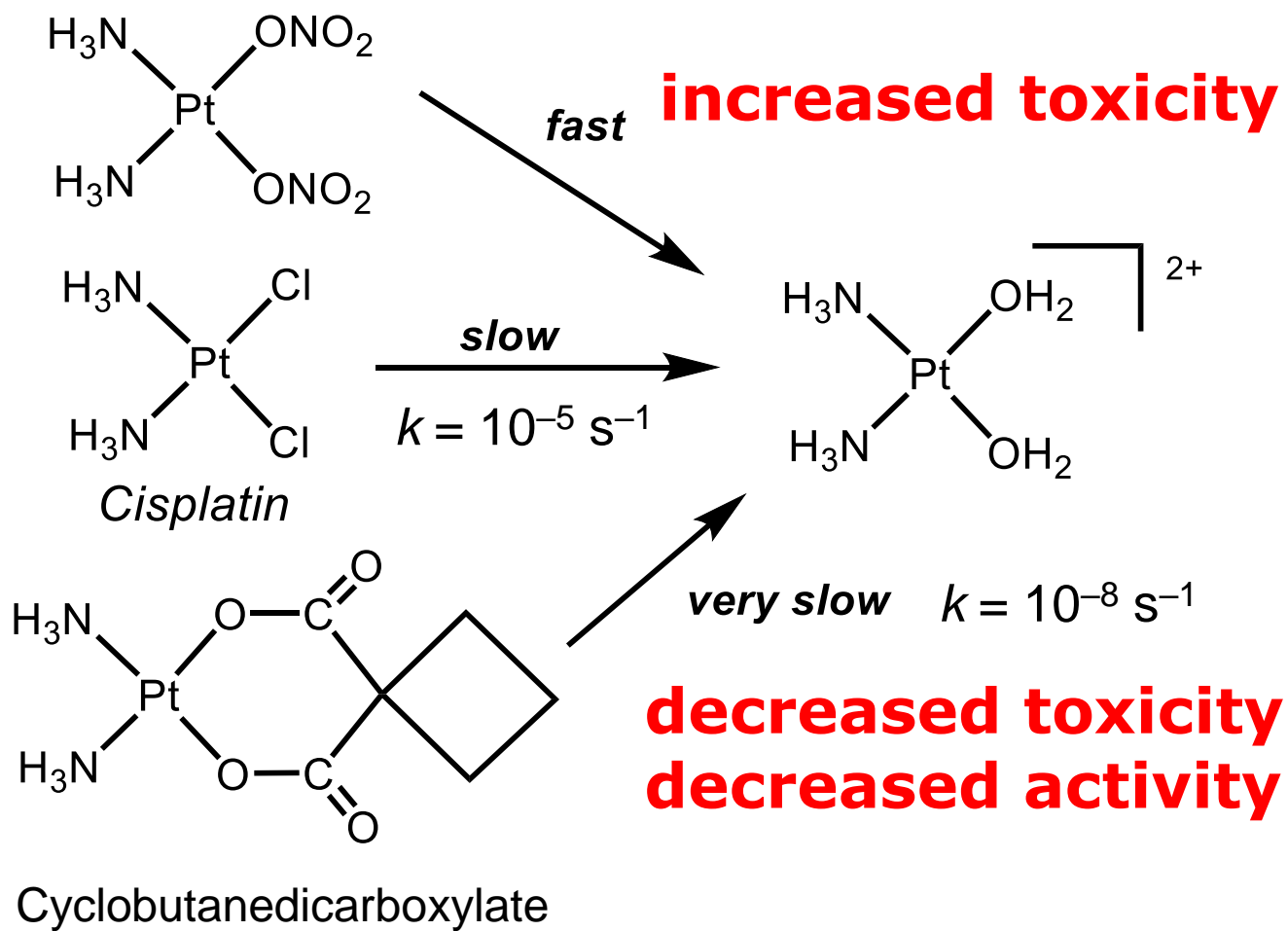


La geometria conta!

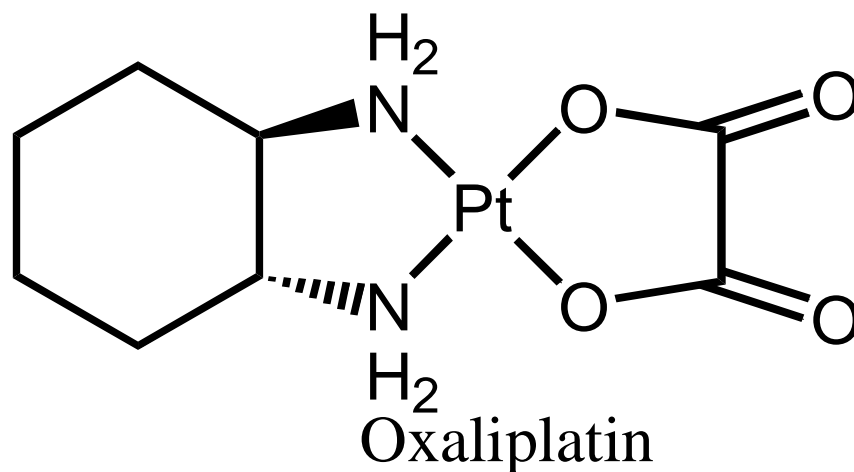
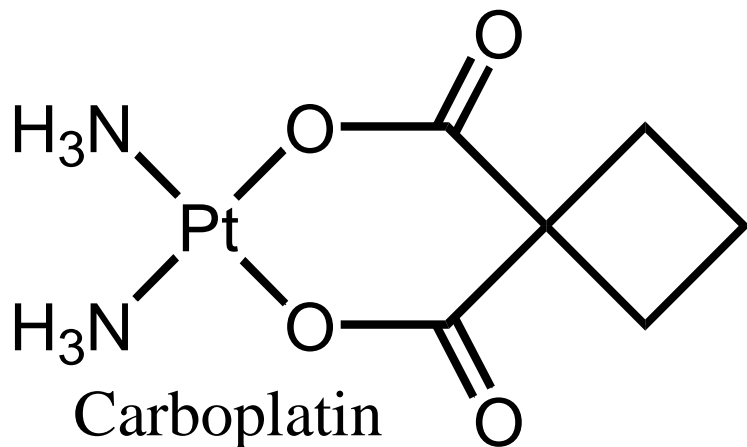


Toxic, but not anticancer active

La cinetica conta!



2nd and 3rd generation Pt(II) drugs: Carboplatin and Oxaliplatin



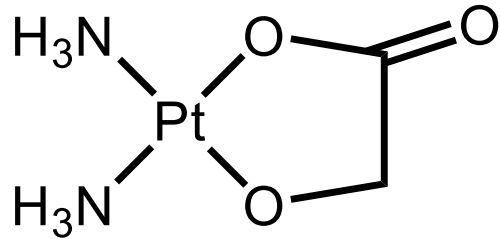
1,1-cyclobutanedicarboxylate

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

300–450 mg/m² vs 20–120 mg/m² of cisplatin

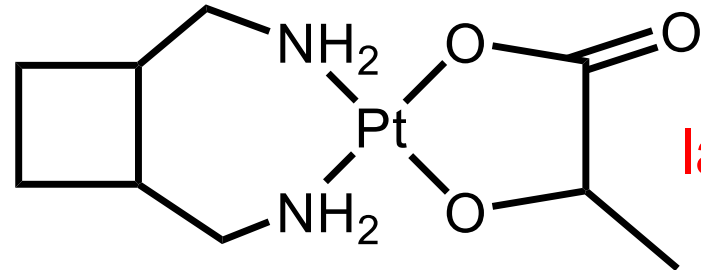
trans-(1*R*,2*R*)-1,2-diaminecyclohexane

2-hydroxyacetate



Nedaplatin (Japan)

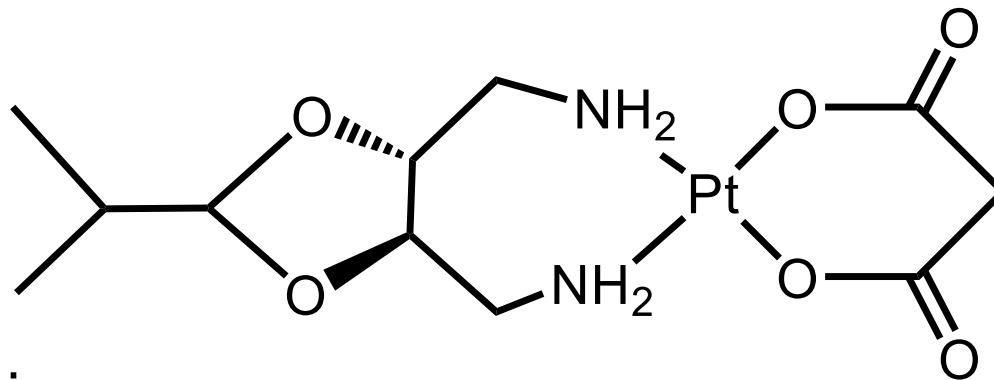
II generation



lactate

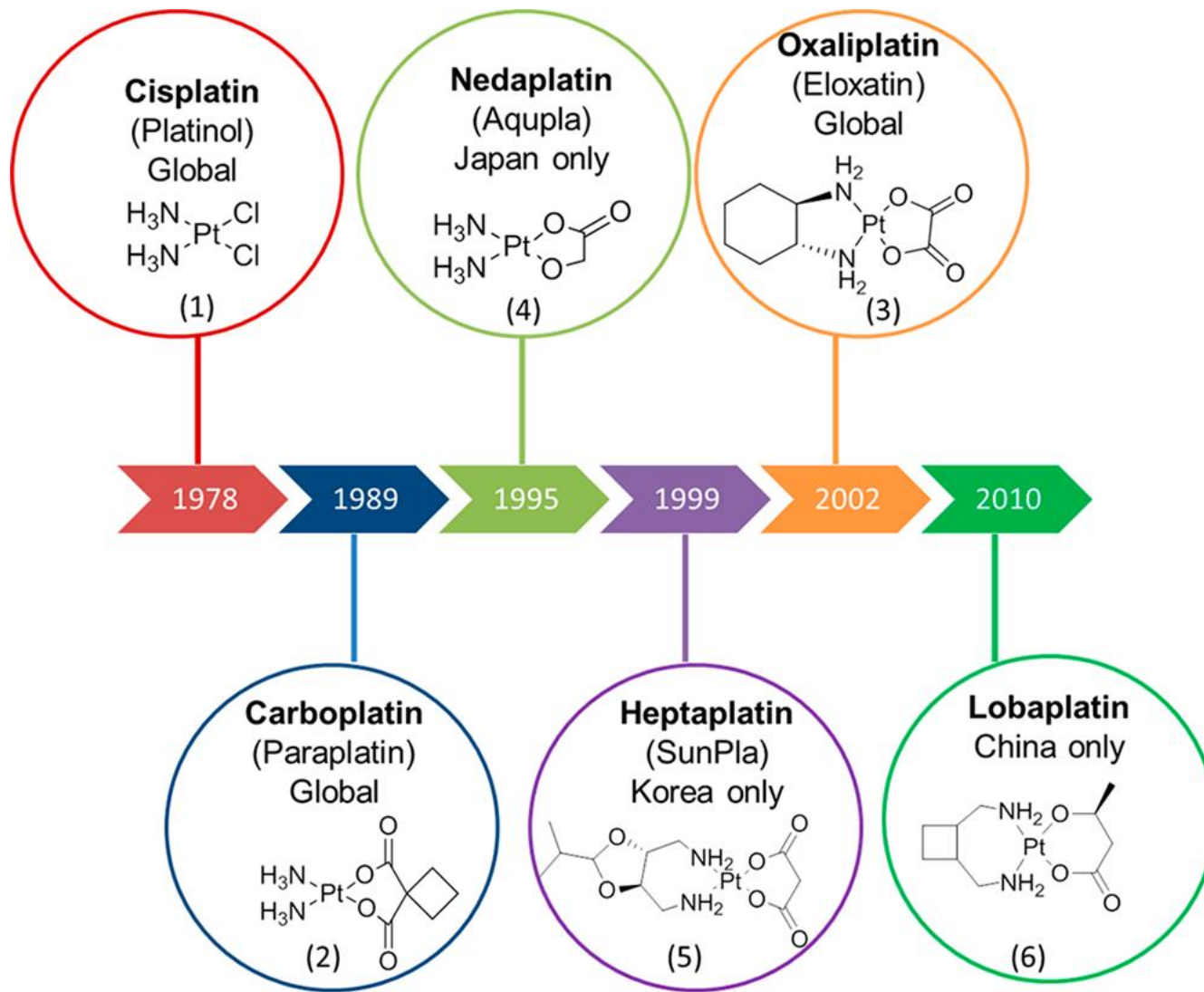
Lobaplatin (China)

III generation

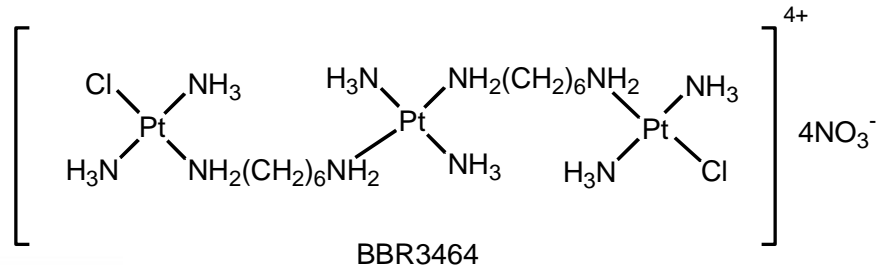
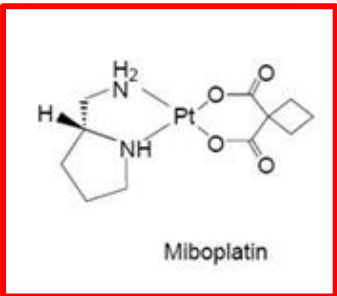
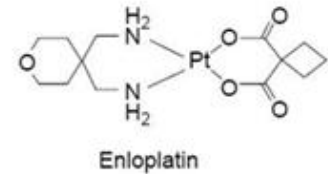
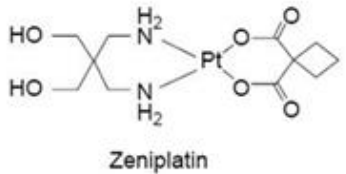
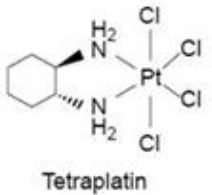
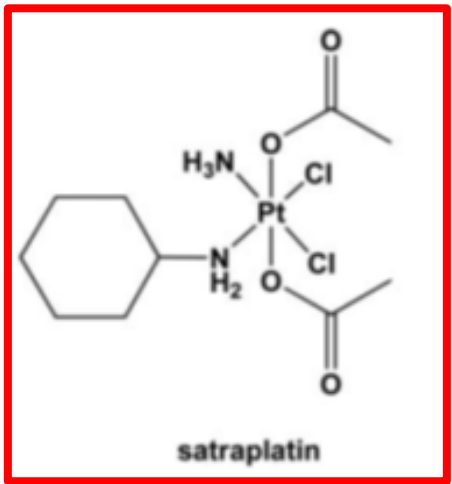
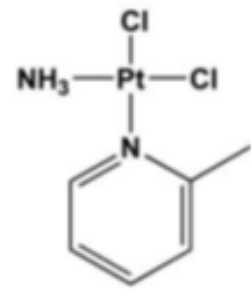
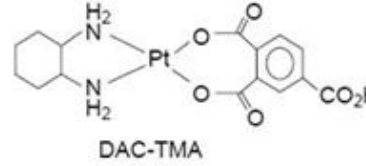
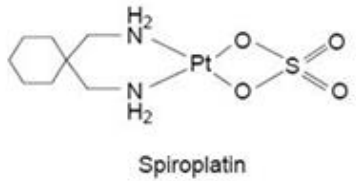
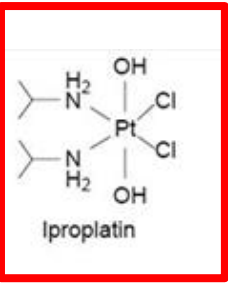



malonate

III generation Heptaplatin (South Korea)

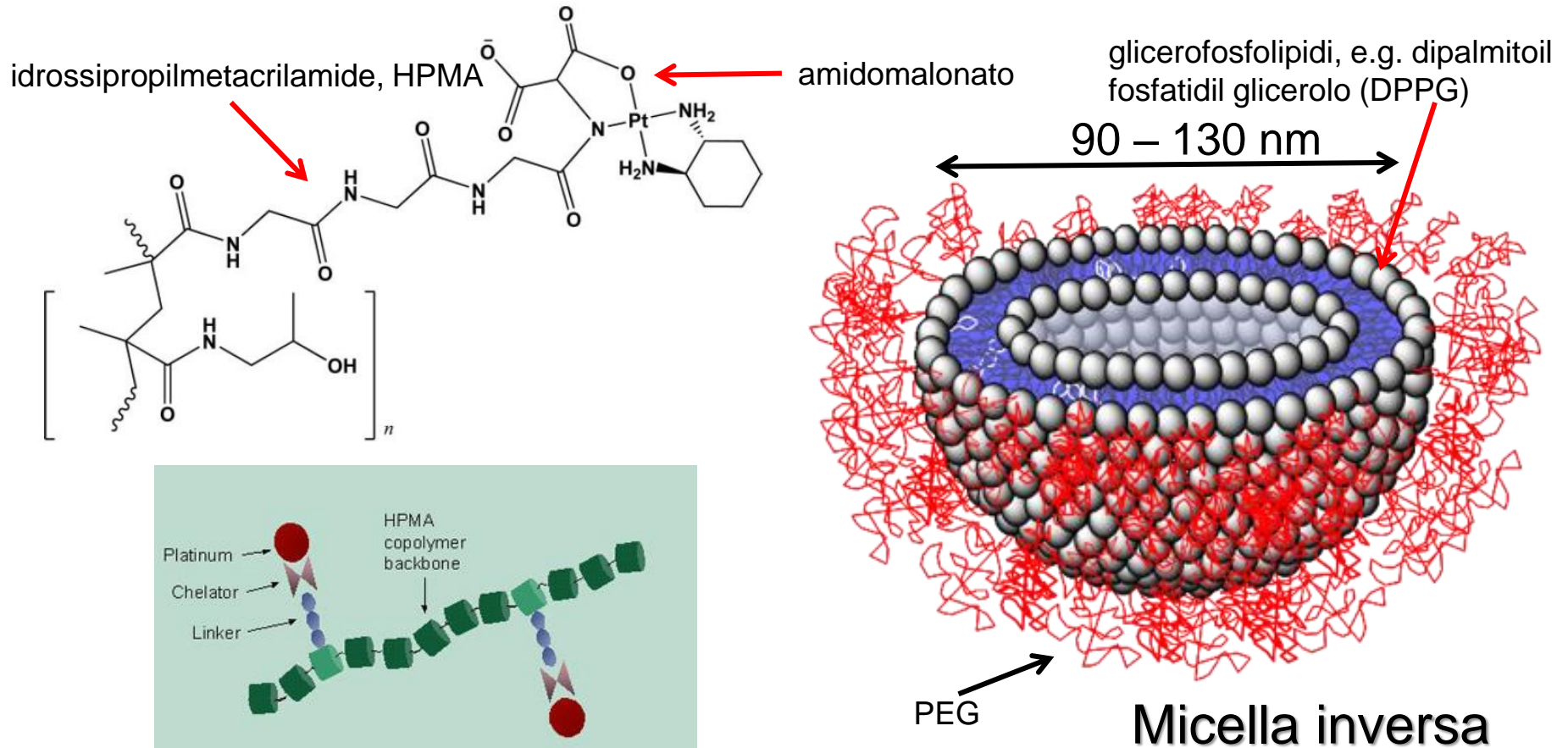


Alcuni dei 23 composti di Pt testati in fase clinica



 = fase 3

Alcune formulazioni di Pt in fase clinica: i nano-carrier ProLindac™ e Lipoplatin™



- 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:

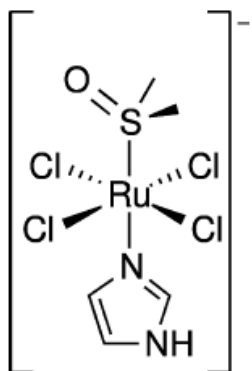
1. to be active against those human malignancies that are resistant, or have acquired resistance, to Pt drugs.
2. to show a lower (or at least different) toxicity compared to Pt drugs.

General features of ruthenium compounds

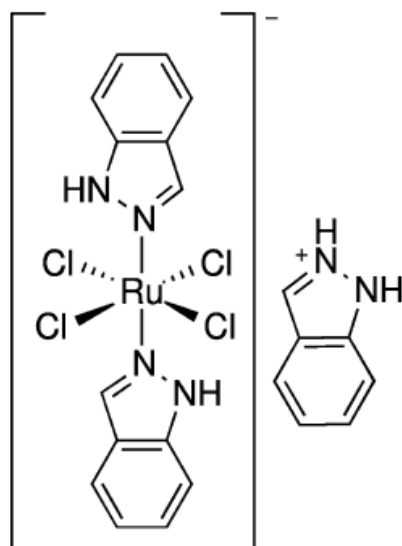
- Six-coordinate, octahedral geometry
- High affinity for nitrogen and sulfur ligands
- Two readily accessible oxidation states in aqueous solution: Ru(III) (d^5 , paramagnetic) and Ru(II) (d^6 , diamagnetic)
- Ru(III) complexes are usually more inert than the corresponding Ru(II) species
- The kinetics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

Clinically tested anticancer Ru(III) compounds

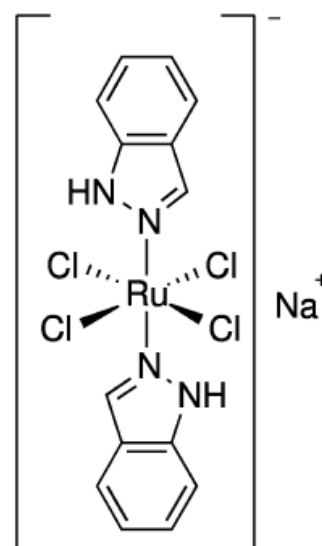
Deceptively similar



NAMI-A



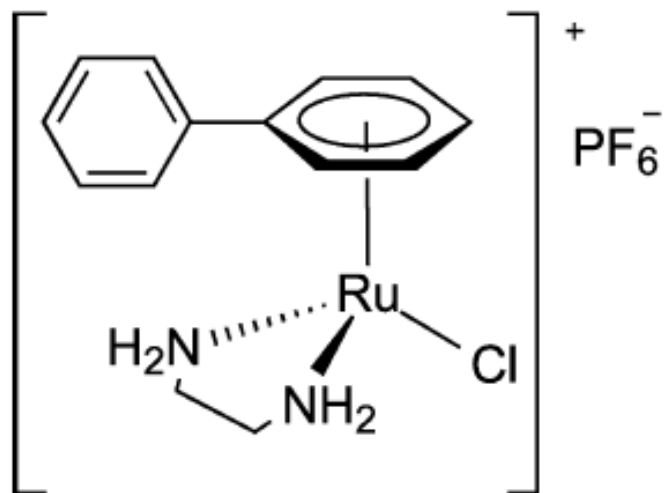
KP1019



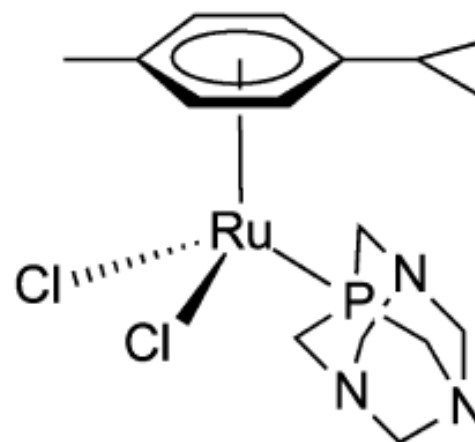
(N)KP1339

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

Anticancer organometallic Ru(II) compounds

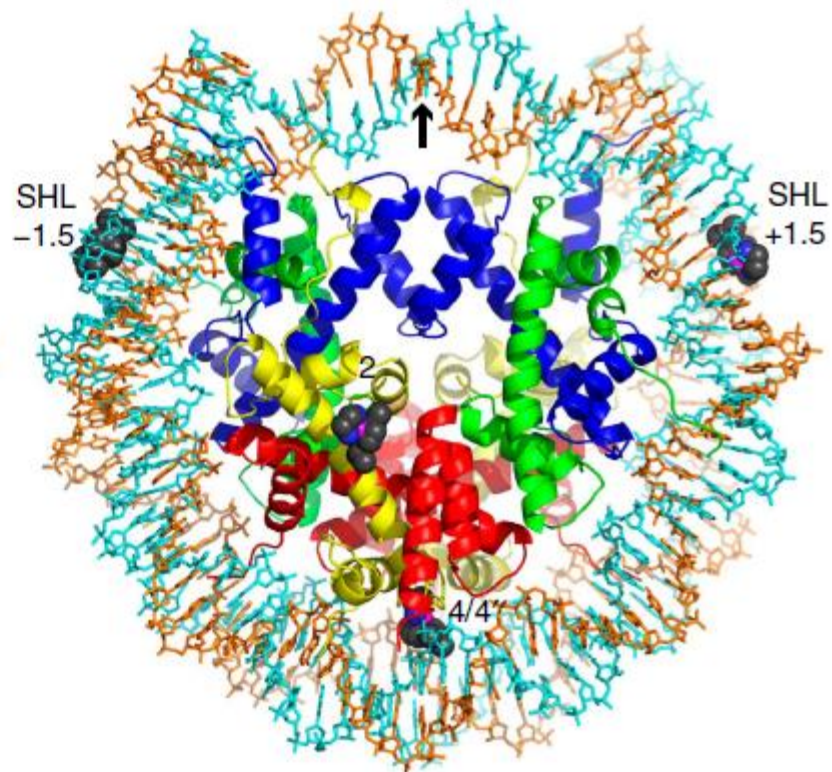
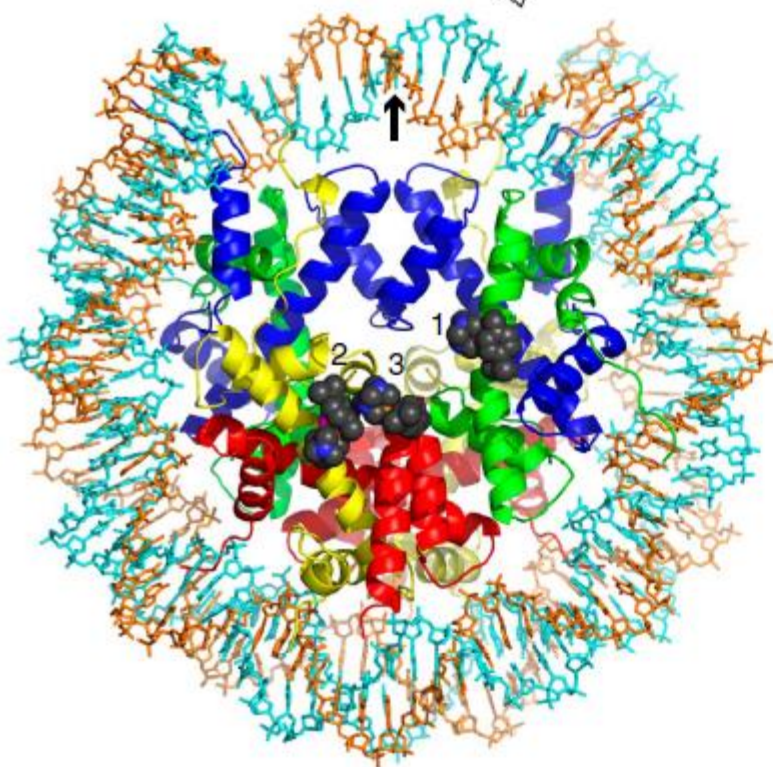
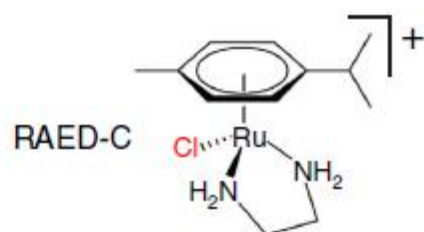
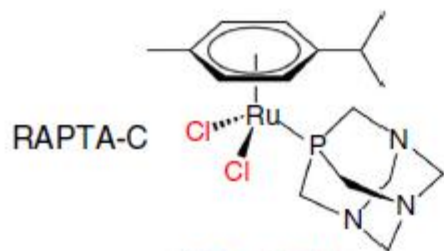


RM175

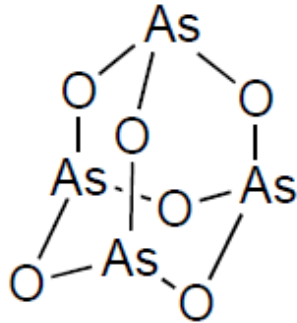


RAPTA-C

a



Composti antitumorali di arsenico



ATO

0.15 mg/kg

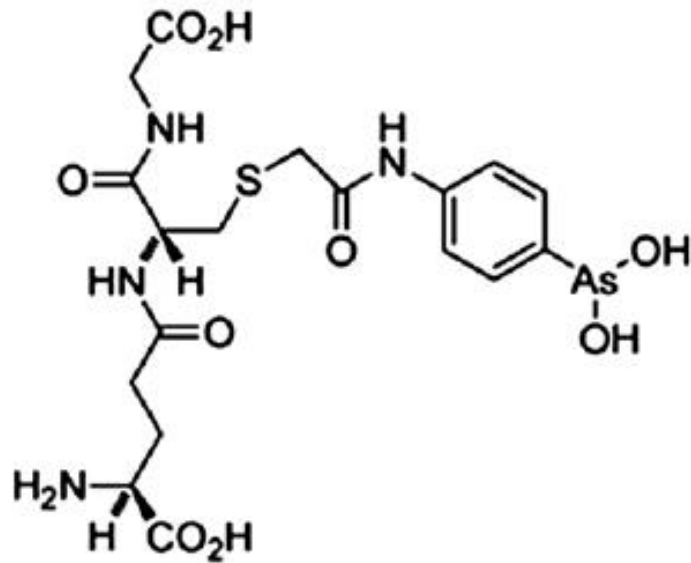
FDA 2000

acute promyelocytic leukemia

ATO/ATRA therapy

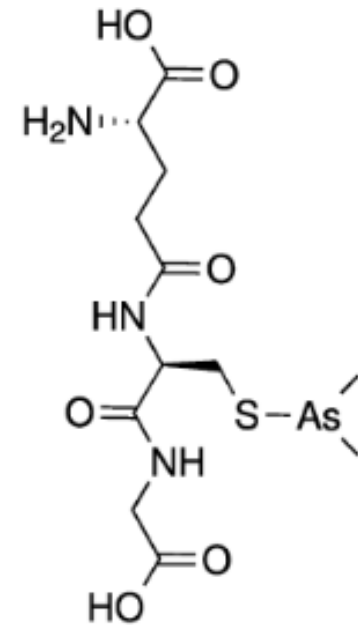
- Degradazione della proteina mutante PML-RAR α che blocca la differenziazione mieloide
- Inibizione di enzimi anti-ROS (glutathione reduttasi, glutathione perossidasi, tioredossina reduttasi e tioredossina perossidasi)

Potenziali composti antitumorali di organo-arsenico



GSAO

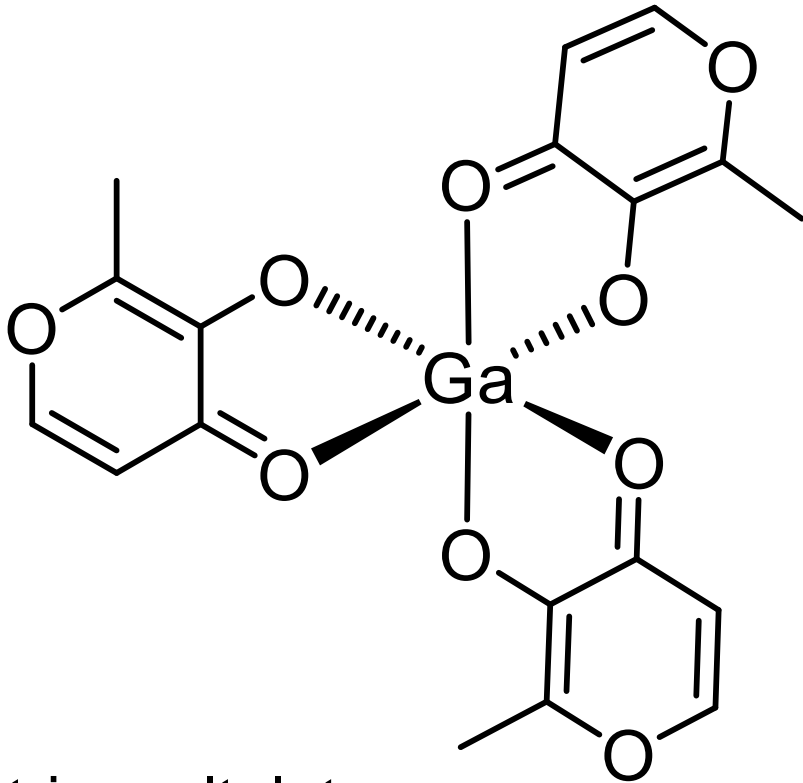
4-(N-(S-glutathionylacetyl)amino)phenylarsonous acid



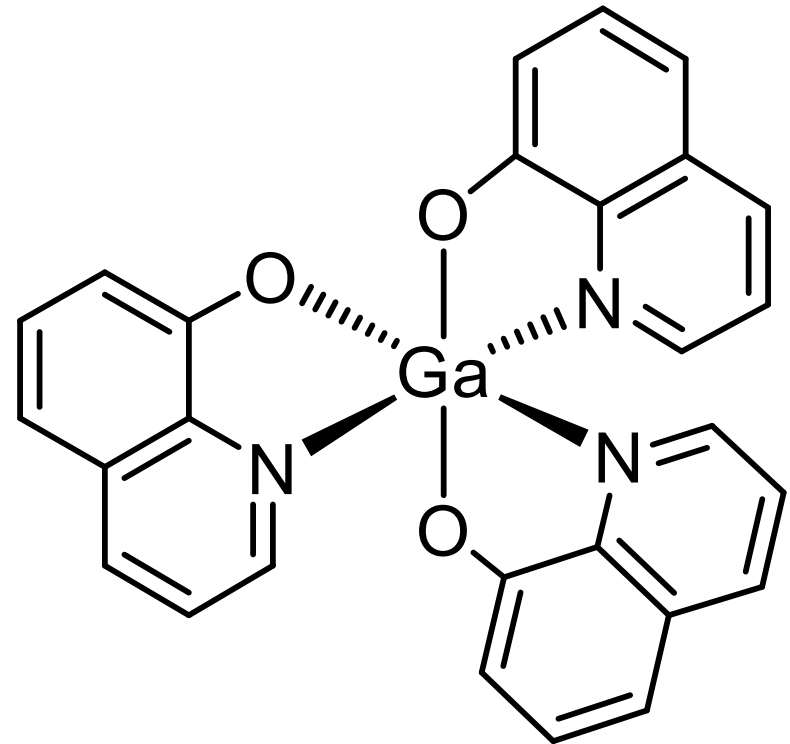
Darinaparsin

S-dimetilarsinoglutathione

Potenziali composti antitumorali di gallio



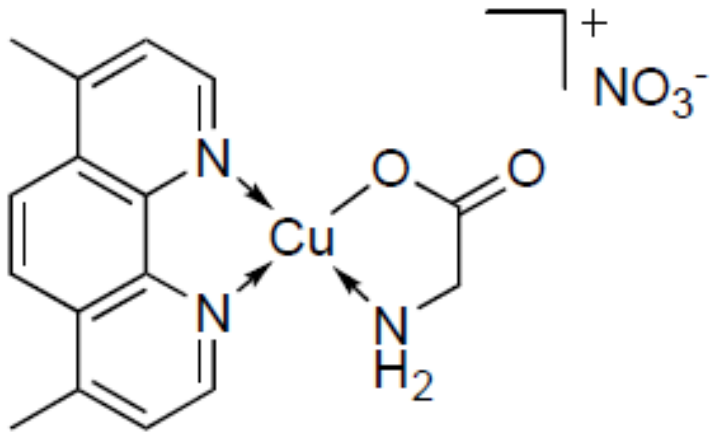
tris-maltolato



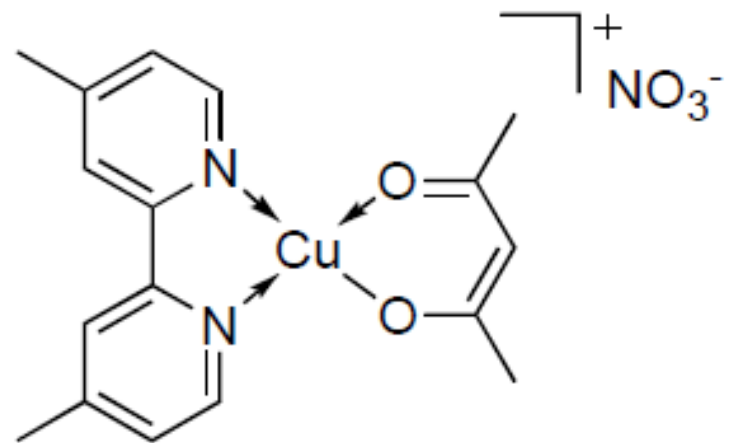
tris(8-idrossichinolinato)

Ga^{3+} è simile a Fe^{3+} ma inibisce la ribonucleotide reductasi

Potenziati composti antitumorali di rame (*Casiopeine*)



Cas II-gly



Cas III-ia

Intercalazione nel DNA + generazione di ROS