

Discovery of cisplatin

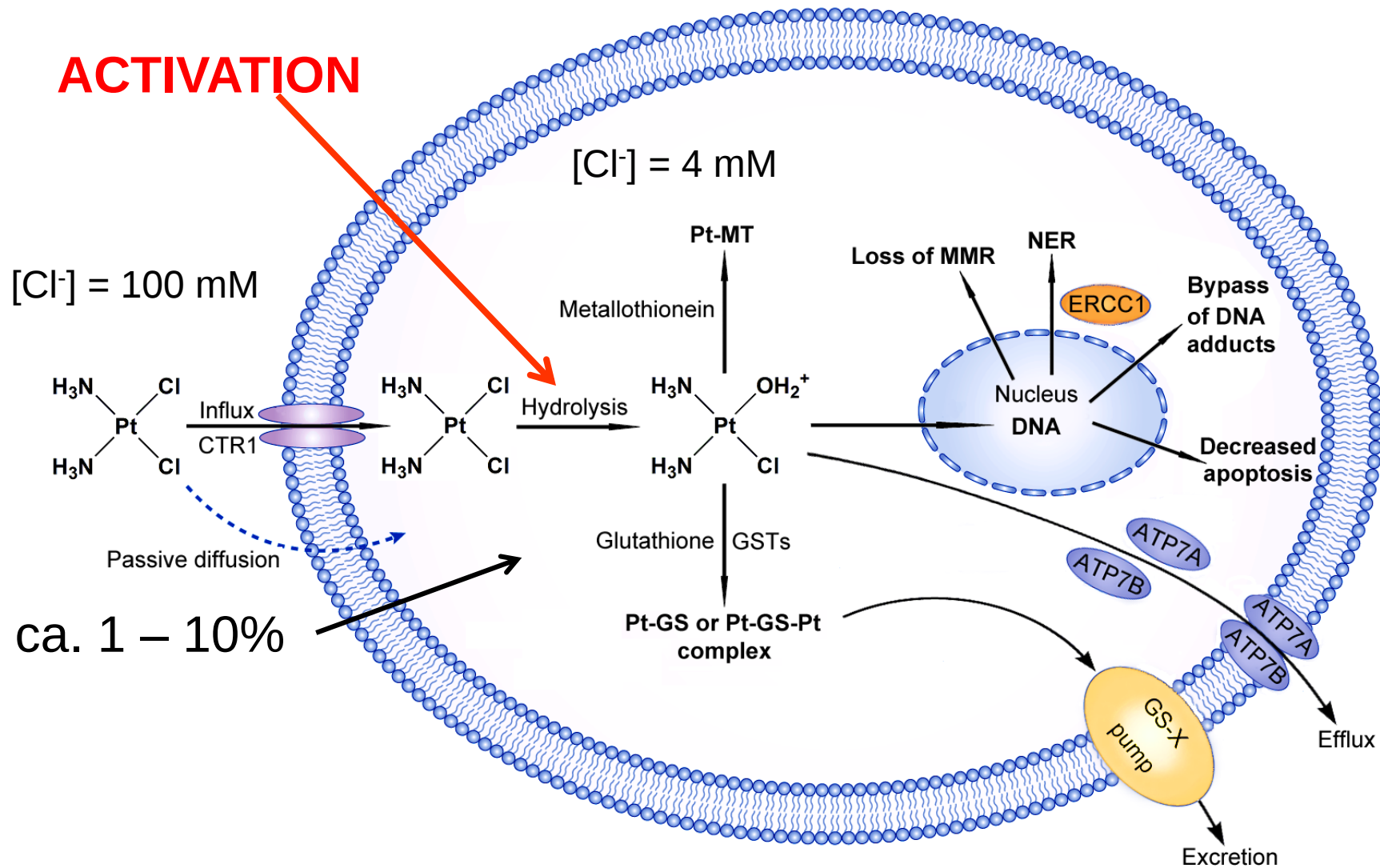
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graph TD; A([Discovery of cisplatin]) --> B[Mechanism of action]; A --> C[Structure – Activity relationships];
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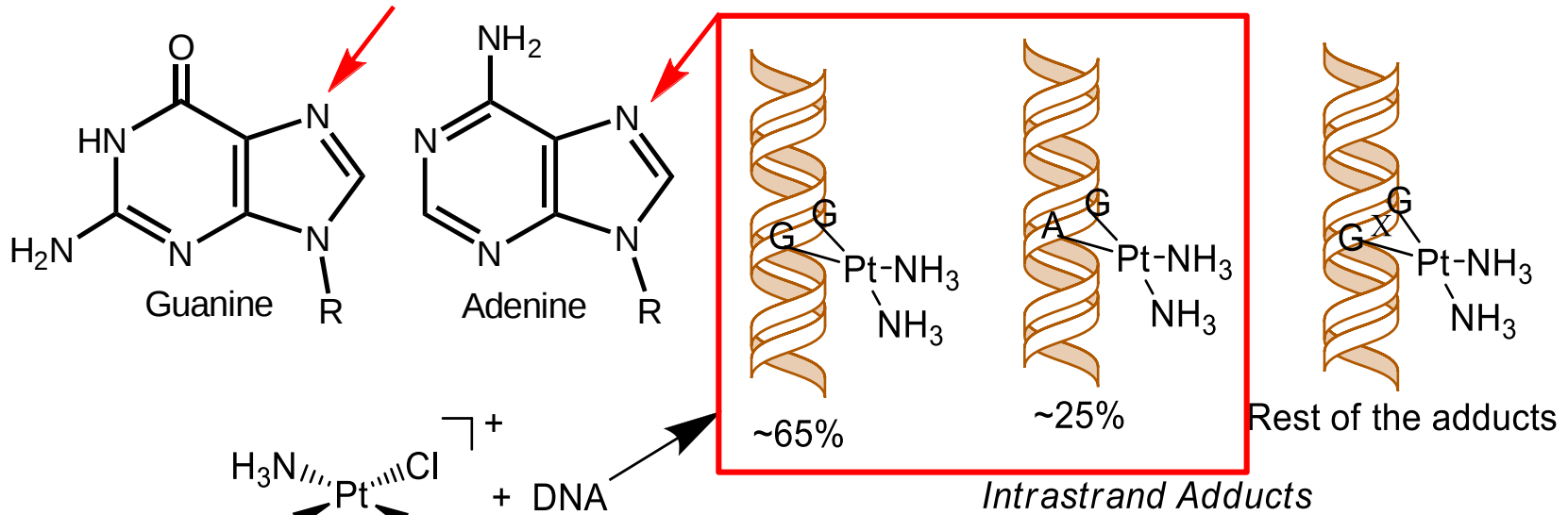
The diagram is a flowchart with a central blue oval at the top containing the text 'Discovery of cisplatin'. Two red arrows originate from the bottom of this oval. One arrow points diagonally down and to the right to a green rounded rectangle containing the text 'Mechanism of action'. The other arrow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

Mechanism of action

Structure – Activity
relationships

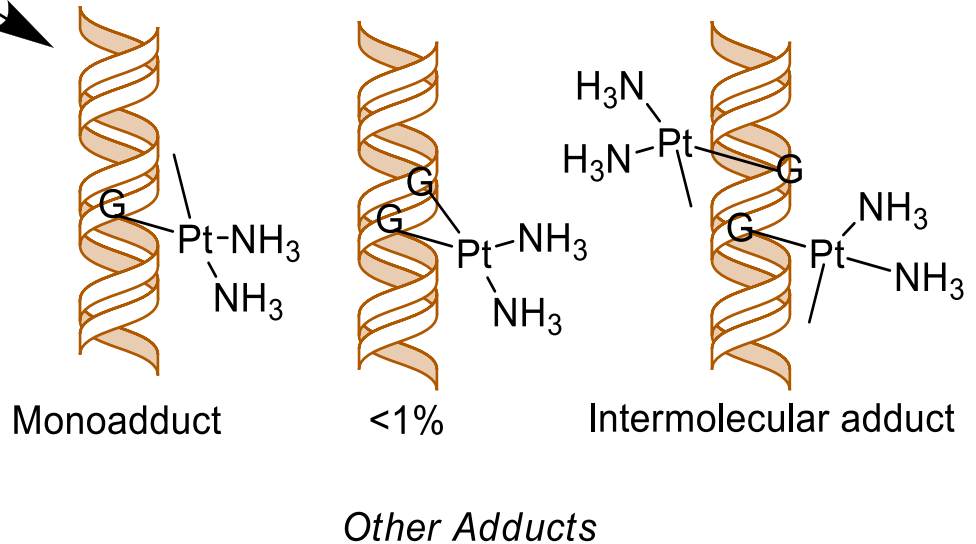
ACTIVATION



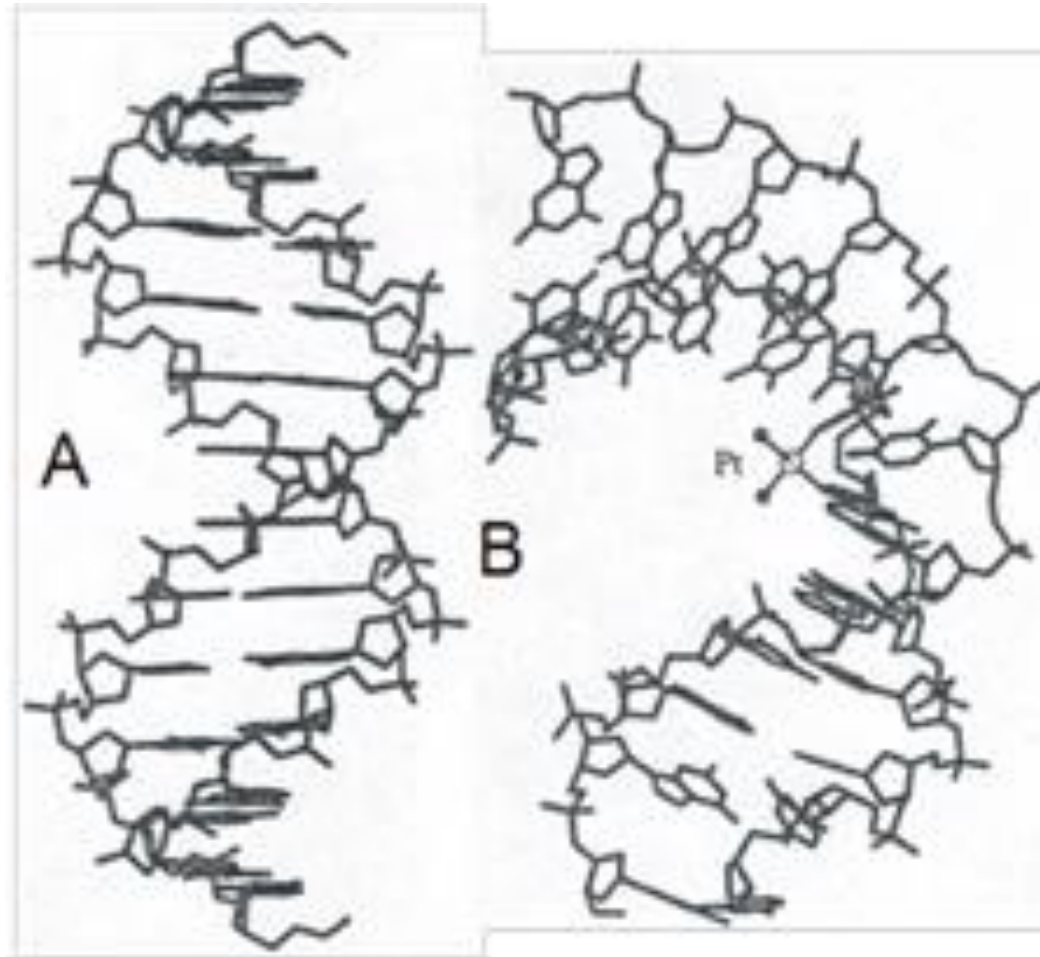


Stima:

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



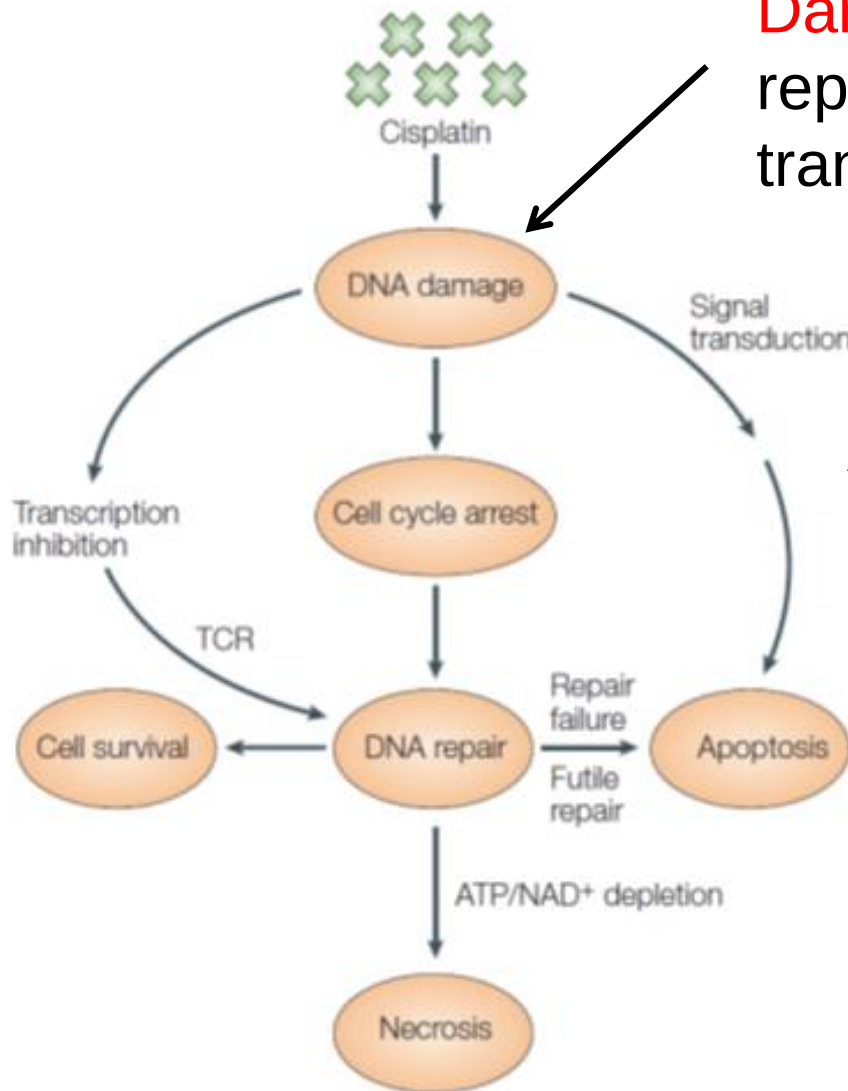
La platinazione induce un piegamento (*kink*) e uno svolgimento (*unwinding*) locale del DNA



Riconoscimento del sito di platinazione del DNA da parte di una proteina HMG

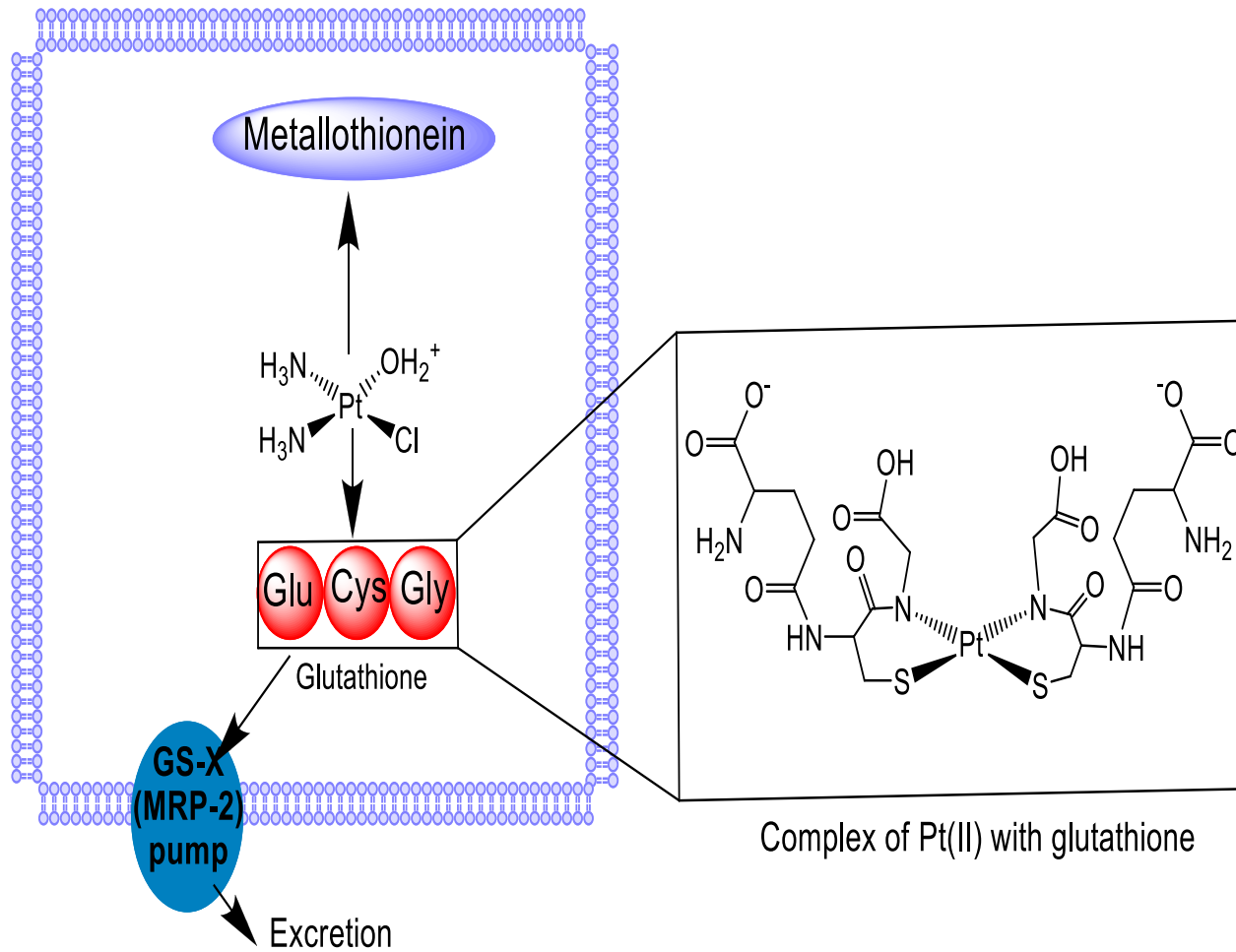


Damage-response proteins: DNA repair system, HMG proteins, transcription factors...

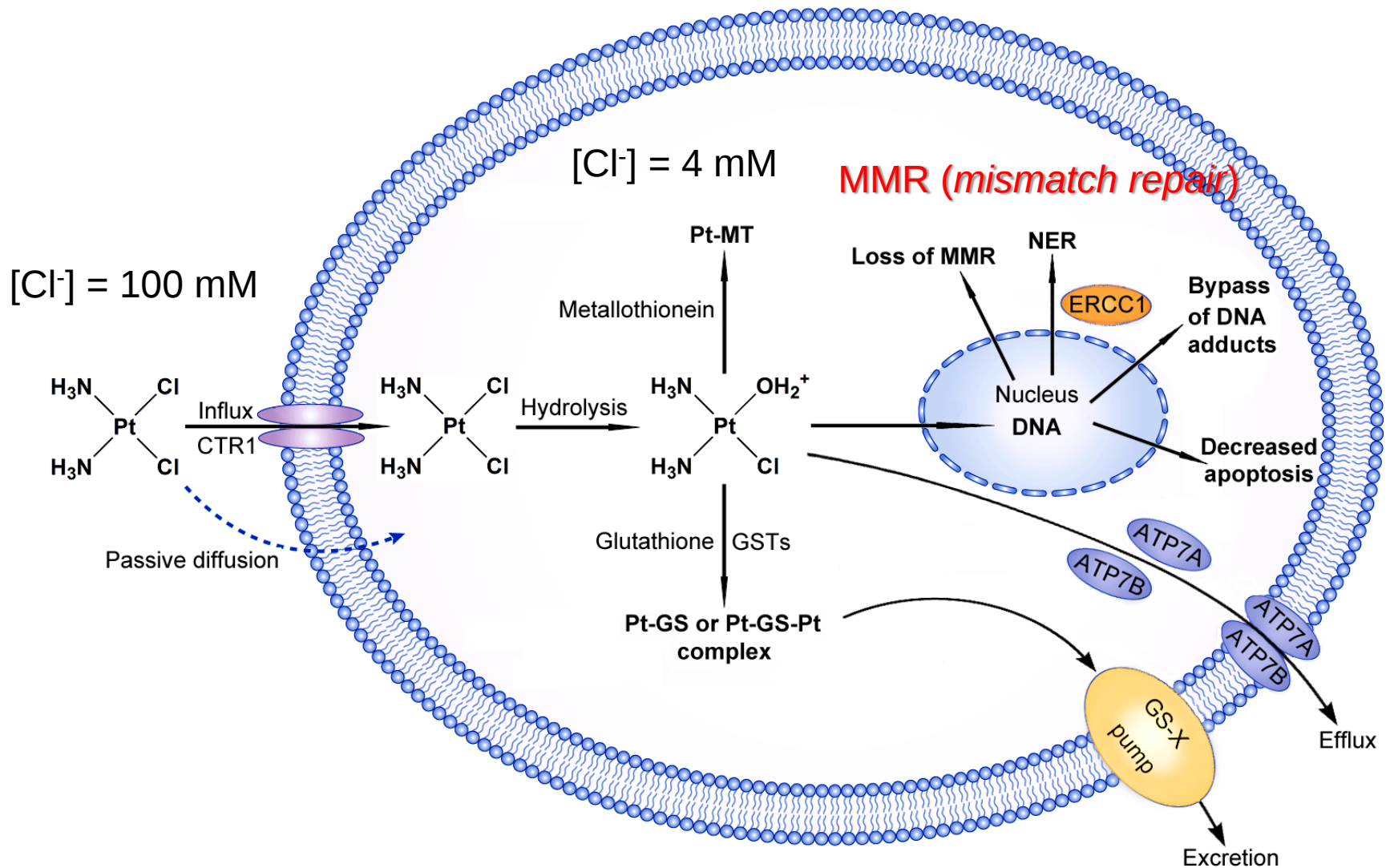


Principali meccanismi di resistenza

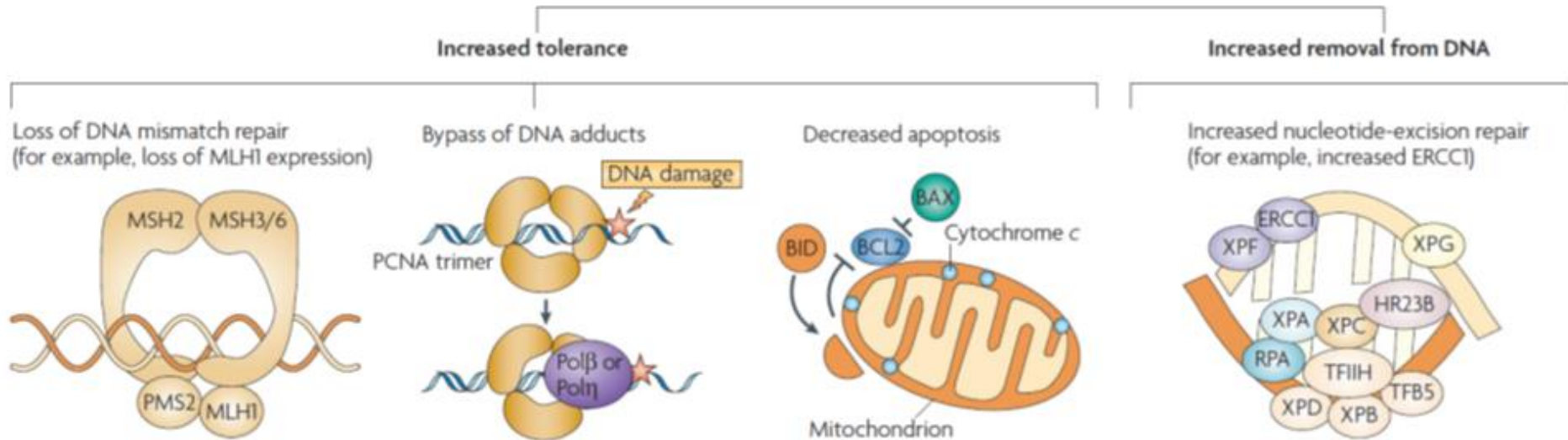
- 1) diminuzione del livello di platino nella cellula;
- 2) aumento del livello di tioli cellulari (glutathione, metallothioneine e altre molecole contenenti zolfo);
- 3) aumento della capacità di riparo del DNA e/o aumento della resistenza al danno;
- 4) cambiamenti nelle catene di segnali che portano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



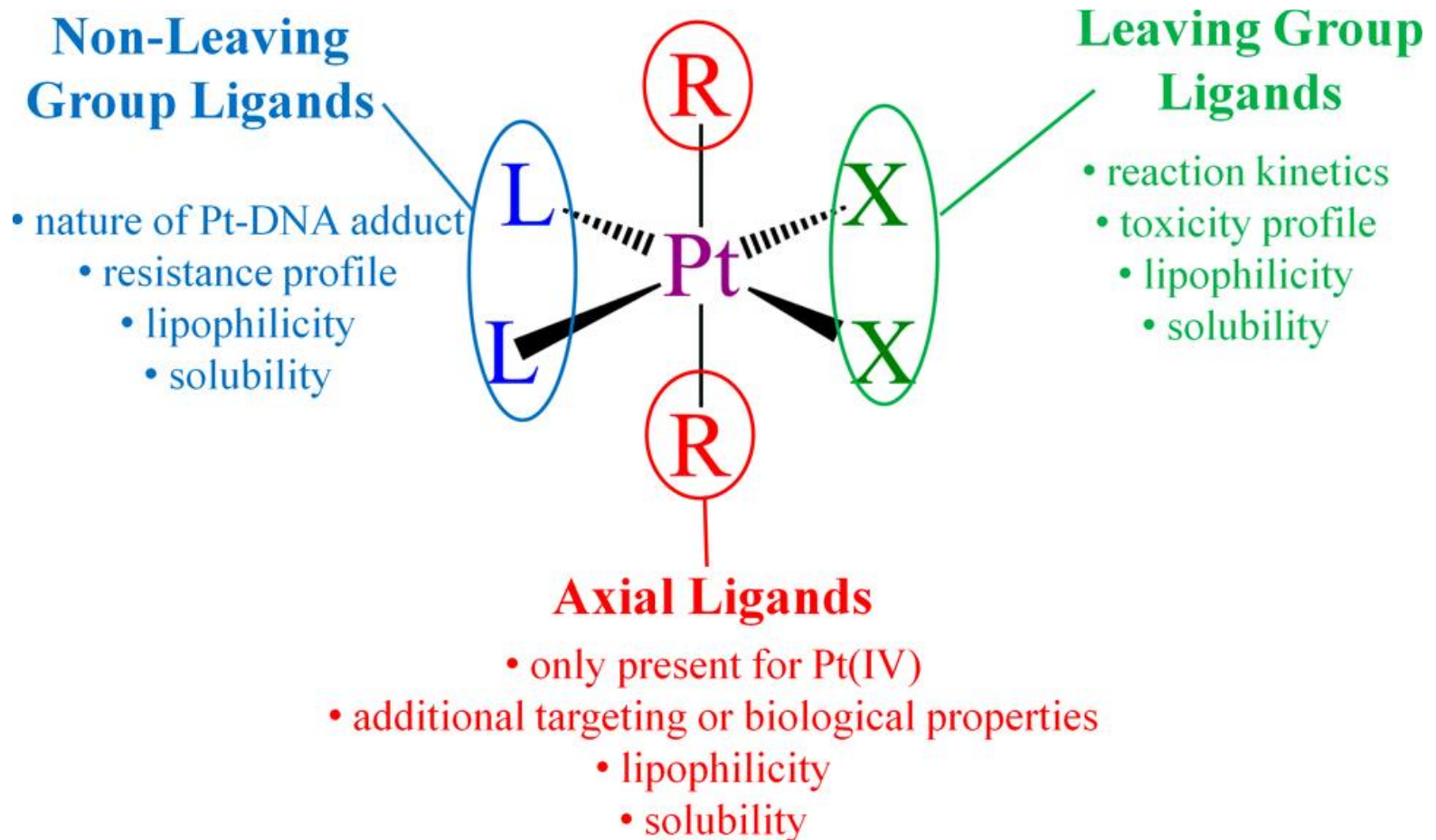
NER (Nucleotides Excision Repair)
ERCC1 (excision repair cross-complementing-1)



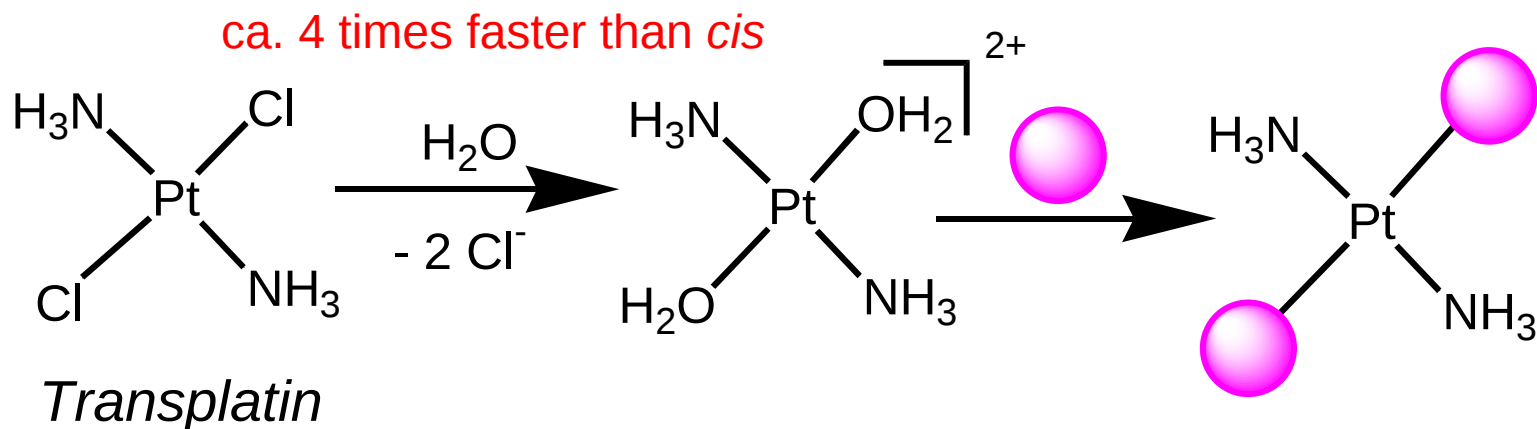
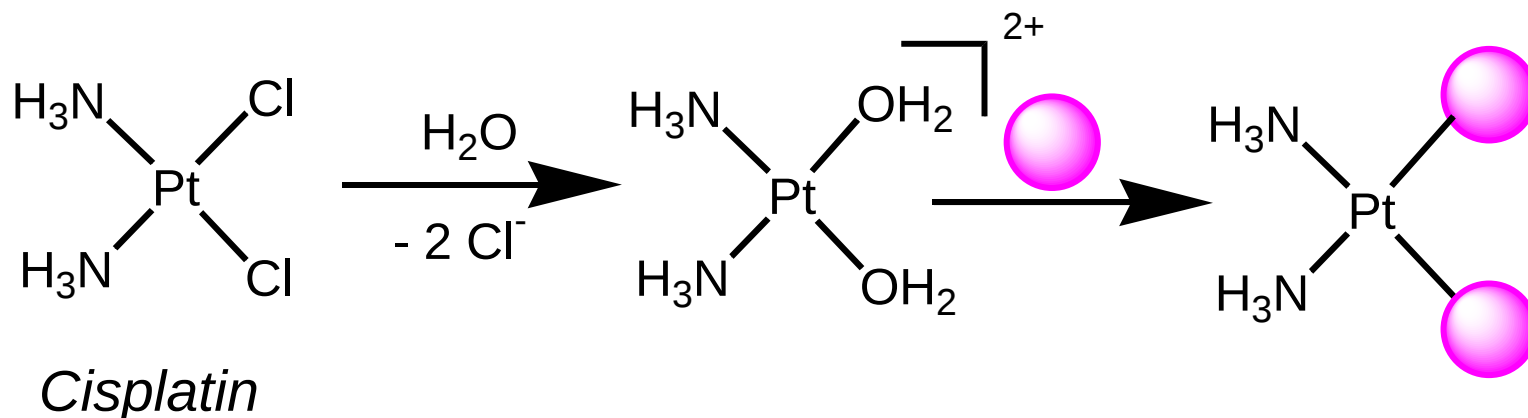
Meccanismi di resistenza



Correlazione struttura – attività

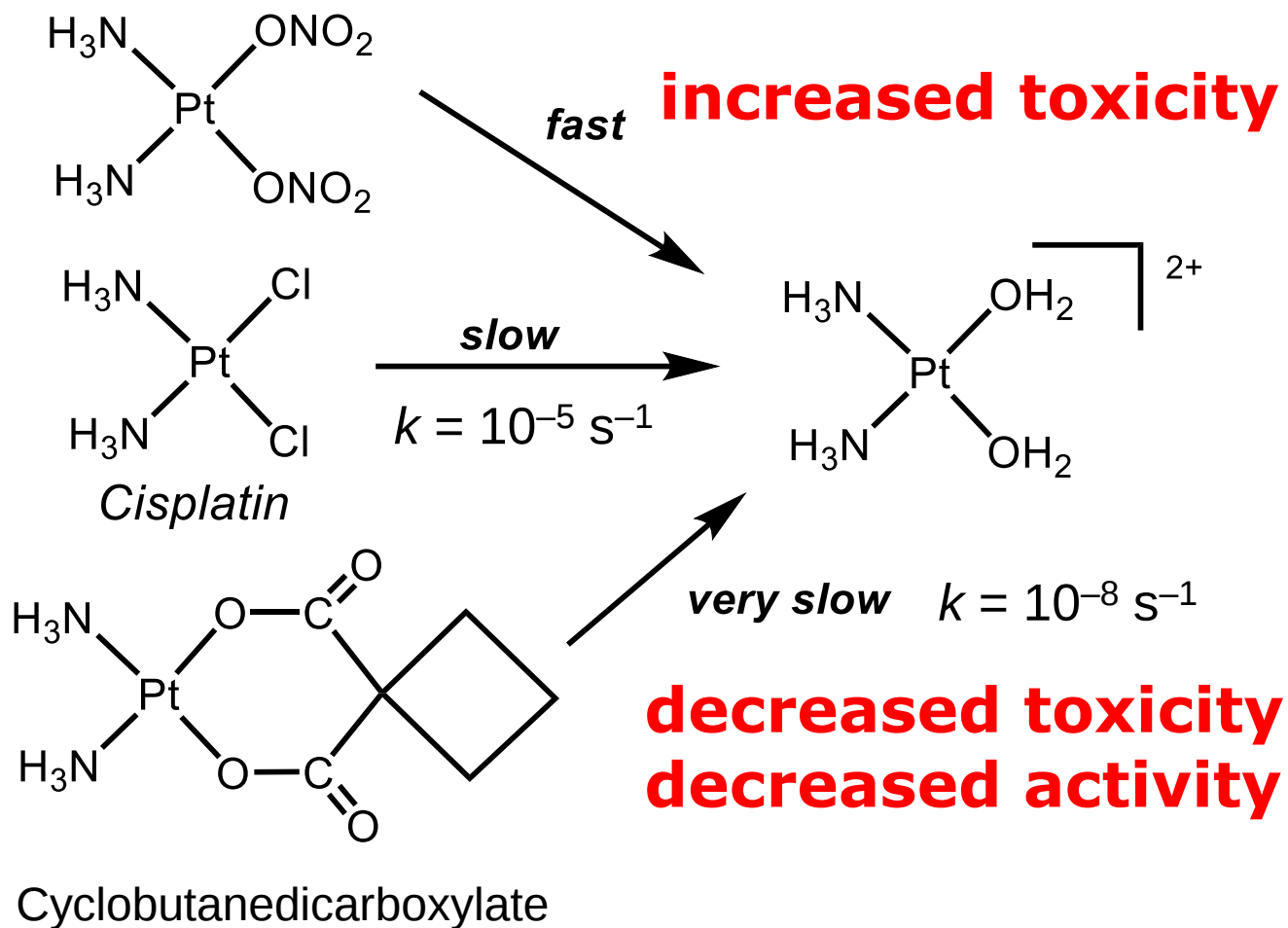


La geometria conta!

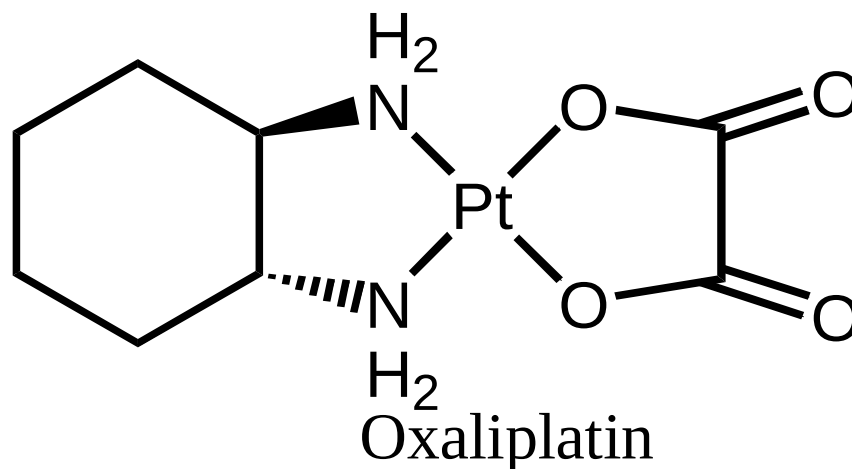
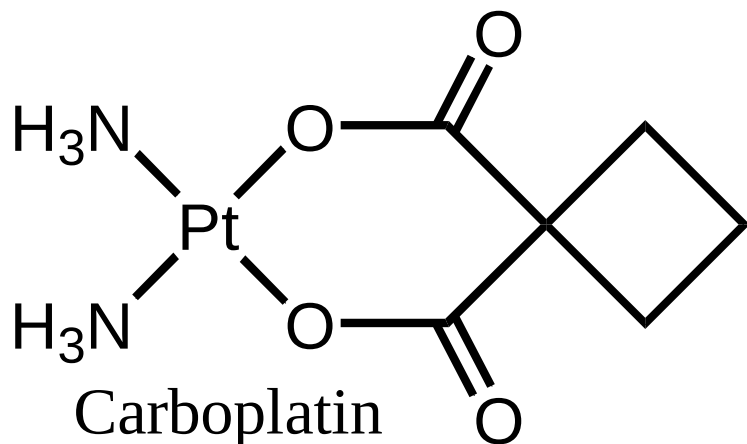


Toxic, but not anticancer active

La cinetica conta!



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



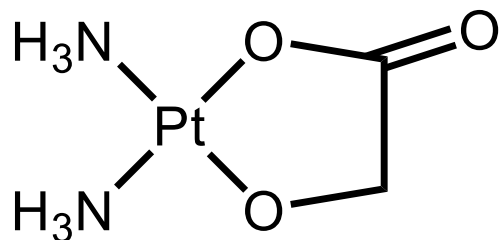
1,1-cyclobutanedicarboxylate

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

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

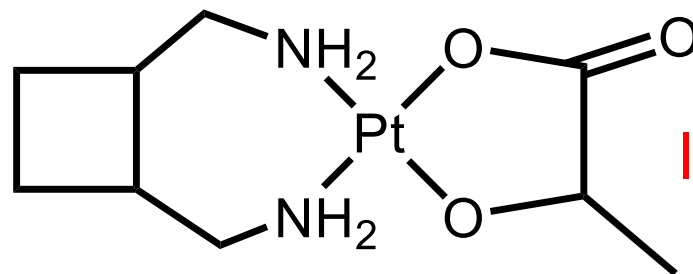
trans-(1*R*,2*R*)-1,2-diaminecyclohexane

2-hydroxyacetate



Nedaplatin (Japan)

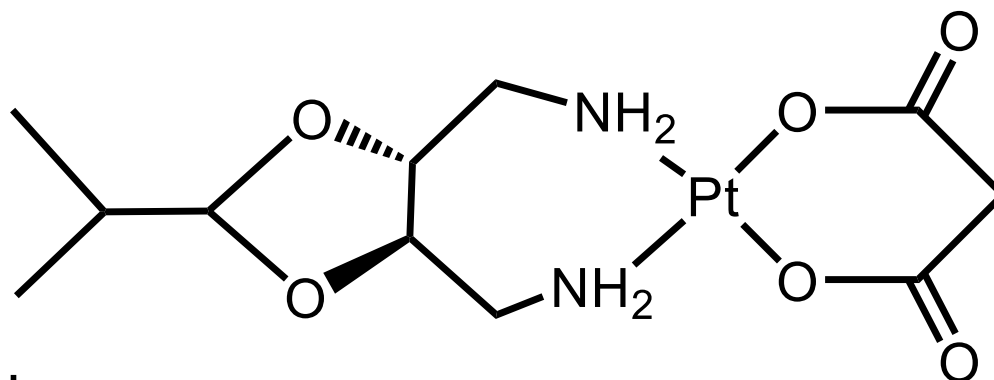
II generation



lactate

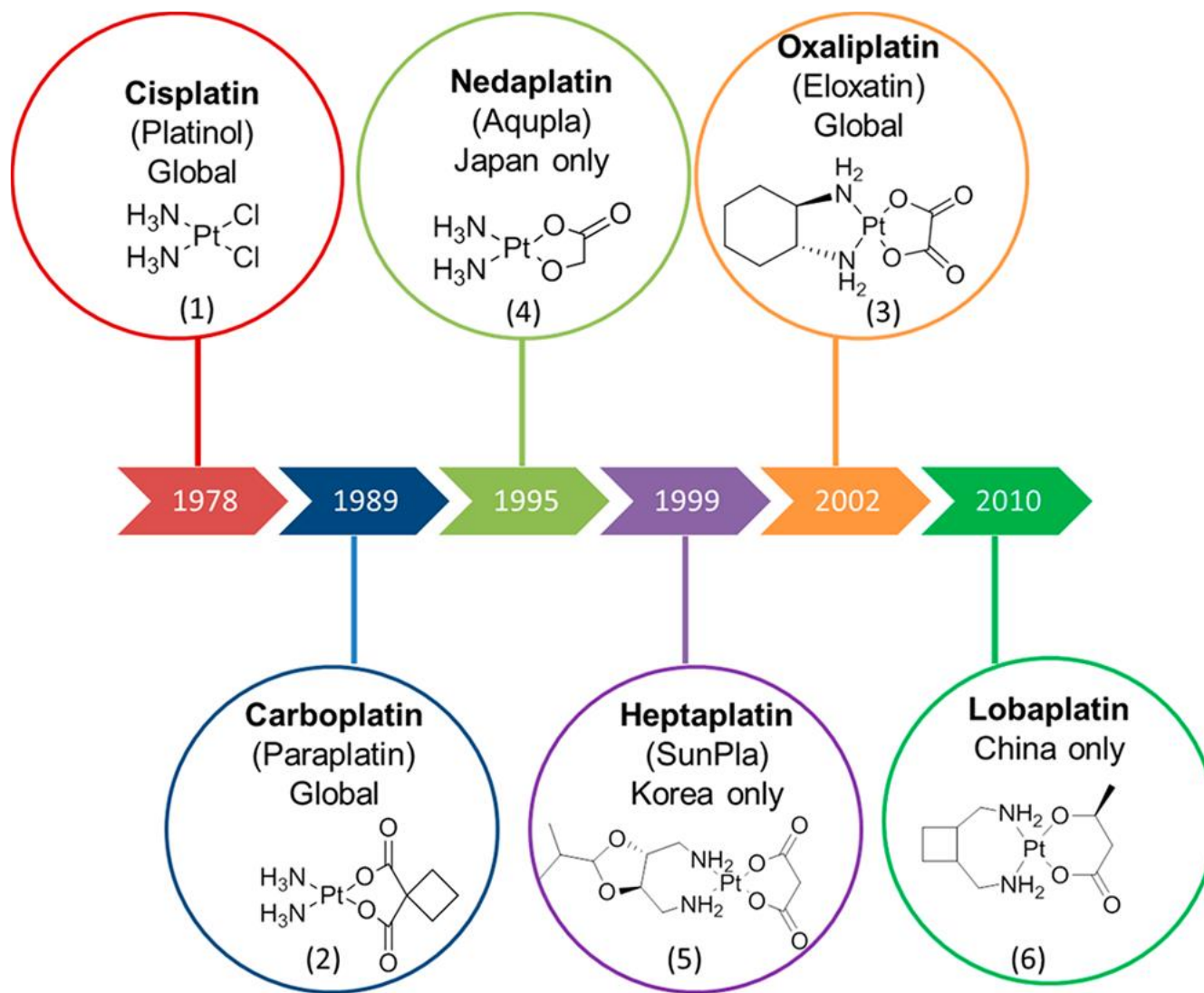
Lobaplatin (China)

III generation

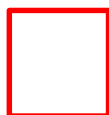
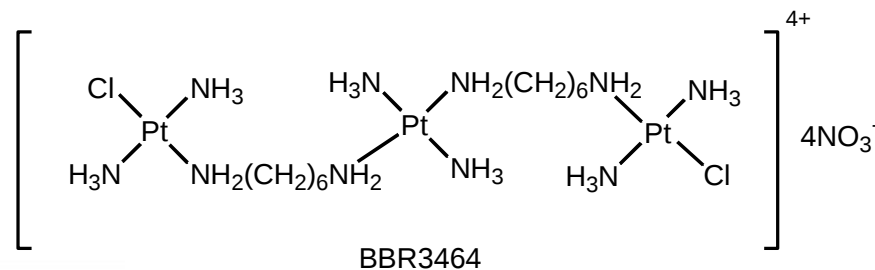
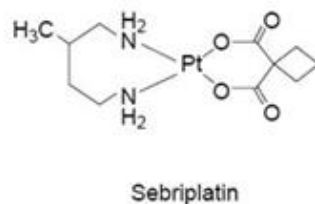
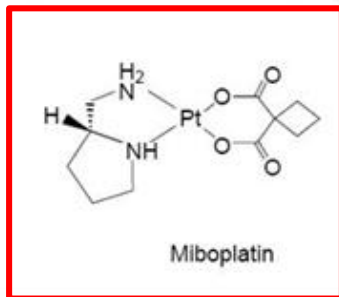
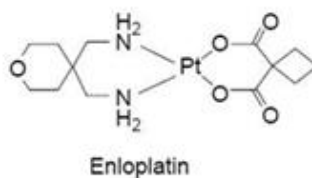
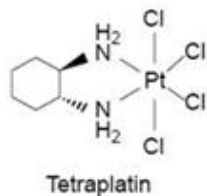
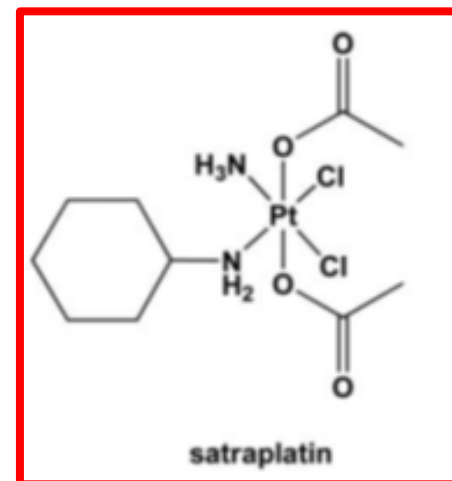
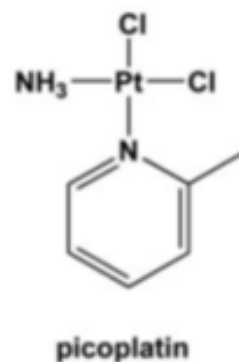
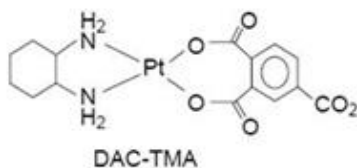
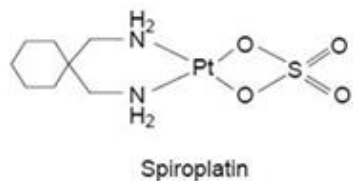
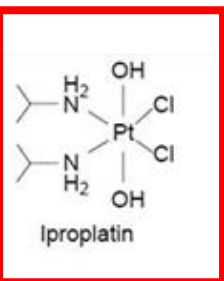


malonate

III generation Heptaplatin (South Korea)

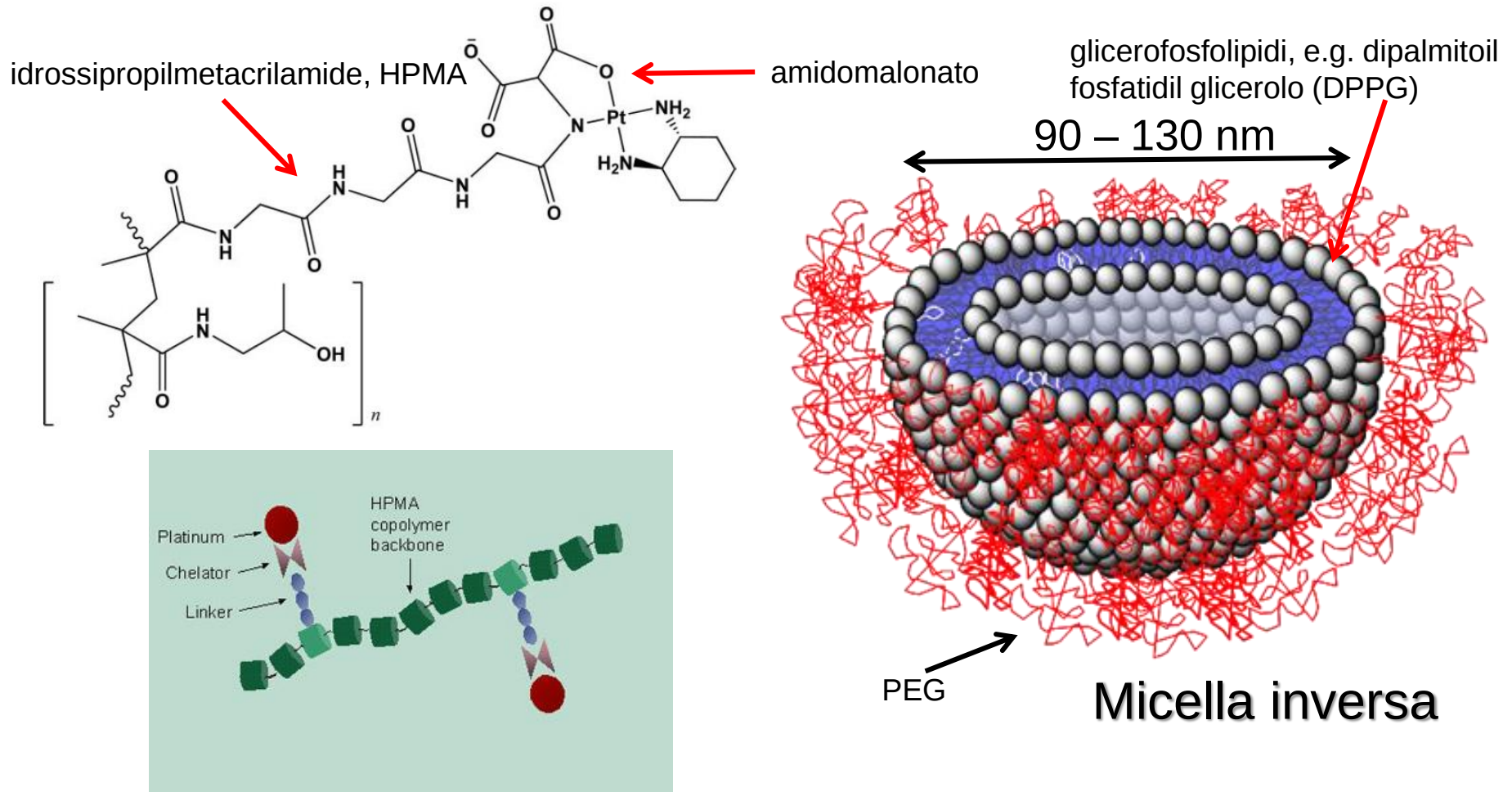


Alcuni dei 23 composti di Pt testati in fase clinica



= 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:

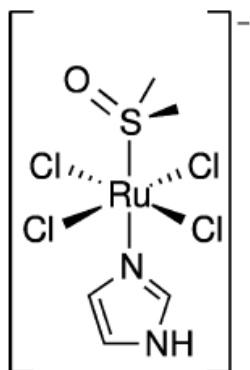
1. to be active against those human malignancies that are resistant, or have acquired resistance, to Pt drugs.
2. to show a lower (or at least different) toxicity compared to Pt drugs.

General features of ruthenium compounds

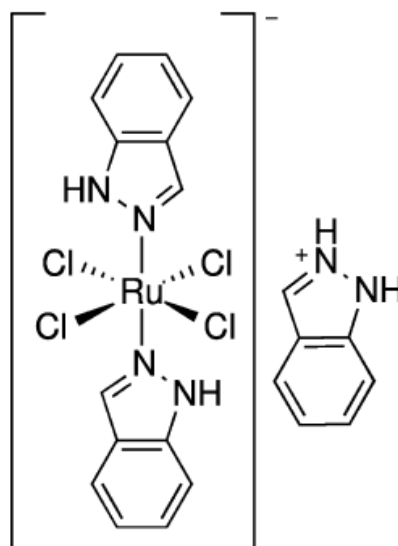
- Six-coordinate, octahedral geometry
- High affinity for nitrogen and sulfur ligands
- Two readily accessible oxidation states in aqueous solution: Ru(III) (d^5 , paramagnetic) and Ru(II) (d^6 , diamagnetic)
- Ru(III) complexes are usually more inert than the corresponding Ru(II) species
- The kinetics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

Clinically tested anticancer Ru(III) compounds

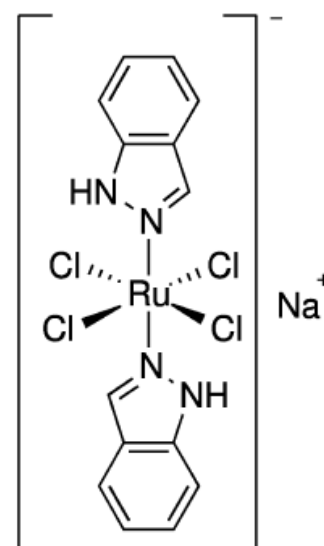
Deceptively similar



NAMI-A



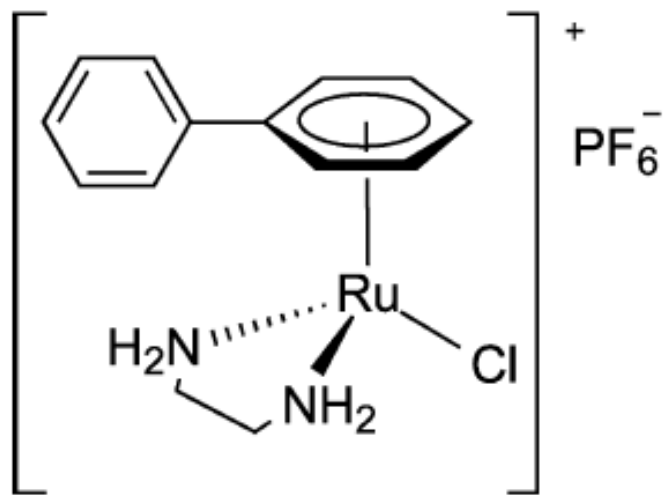
KP1019



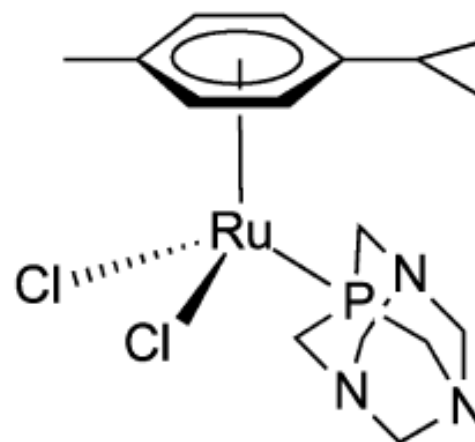
(N)KP1339

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

Anticancer organometallic Ru(II) compounds

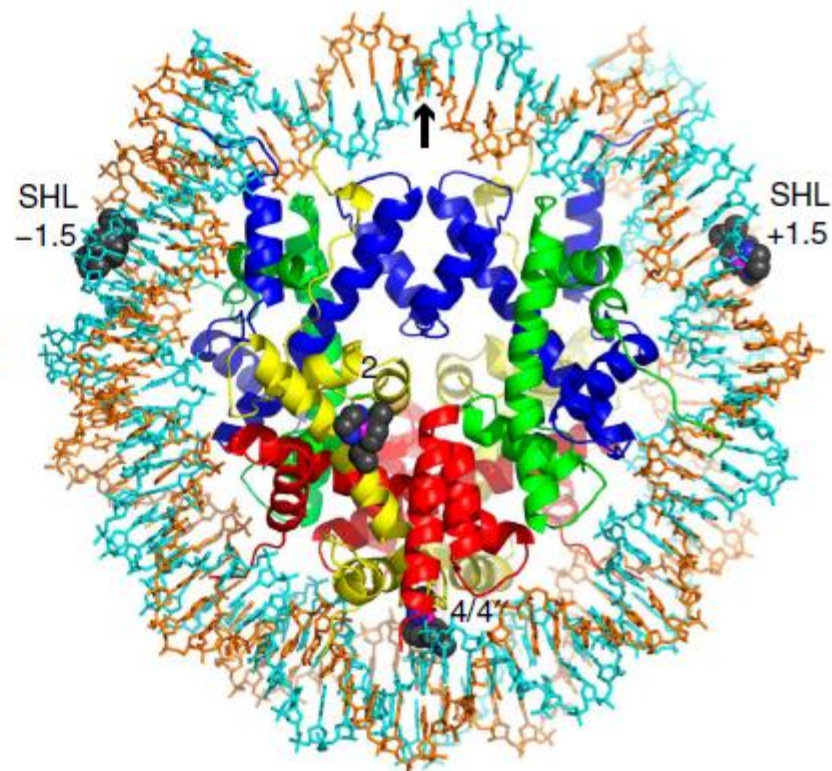
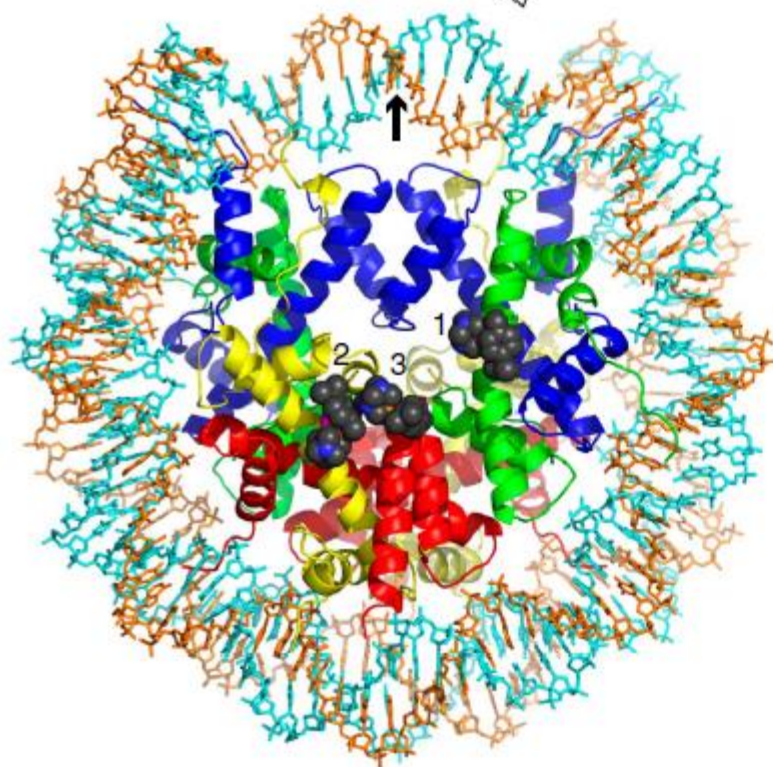
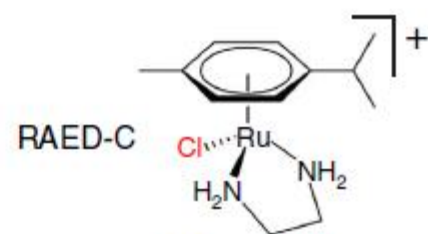
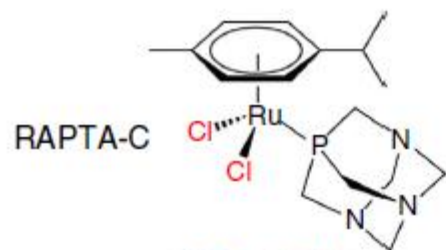


RM175

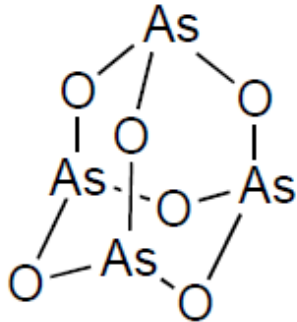


RAPTA-C

a



Composti antitumorali di arsenico



ATO

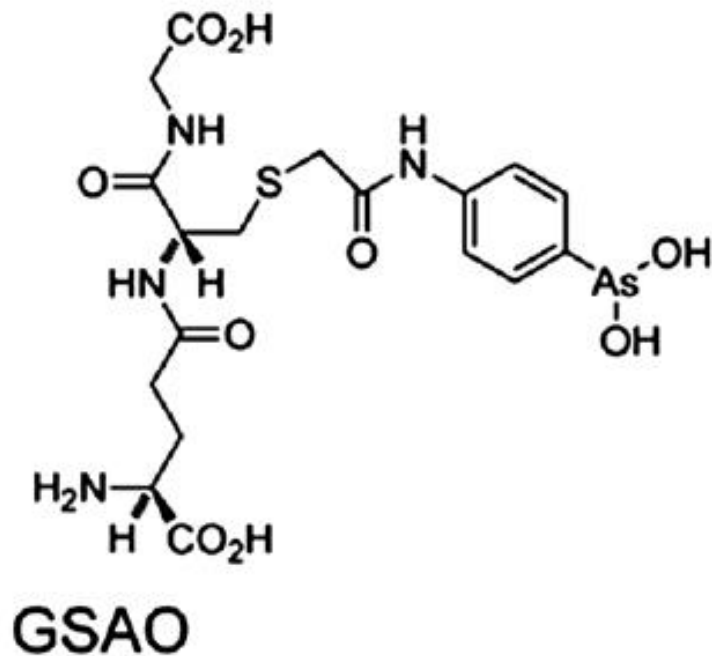
0.15 mg/kg

FDA 2000

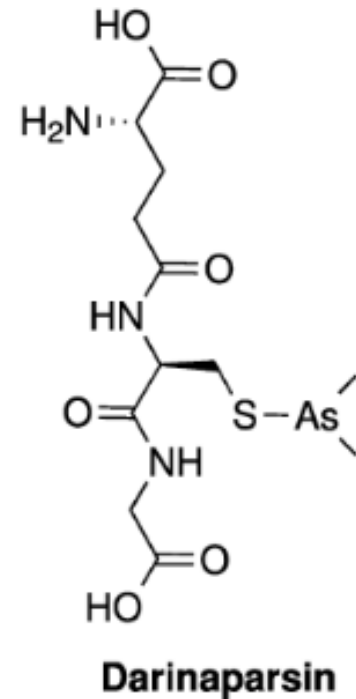
acute promyelocytic leukemia

- 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

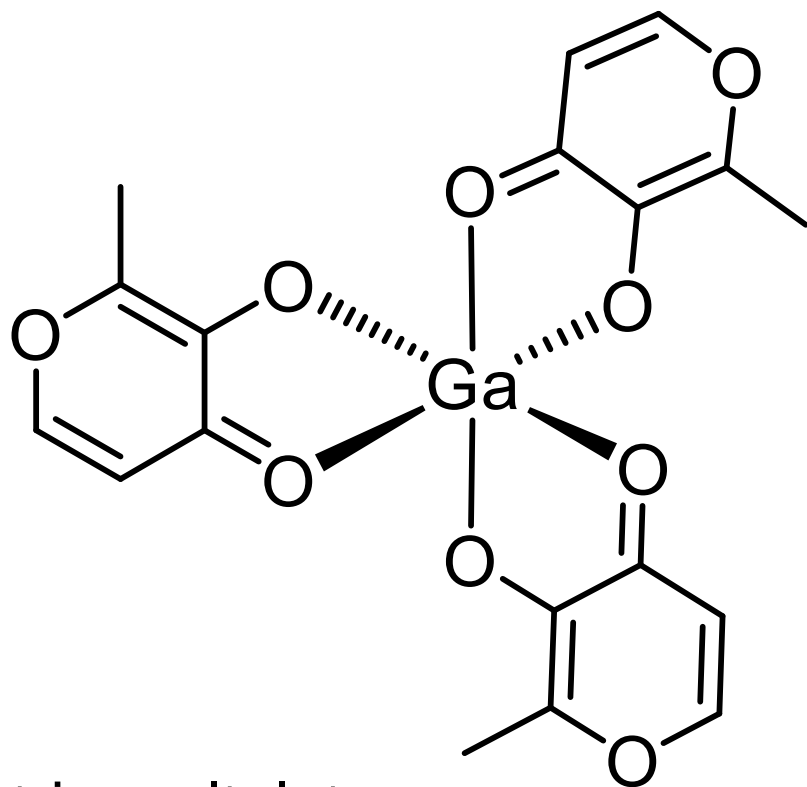


4-(N-(S-glutathionylacetyl)amino)phenylarsonous acid

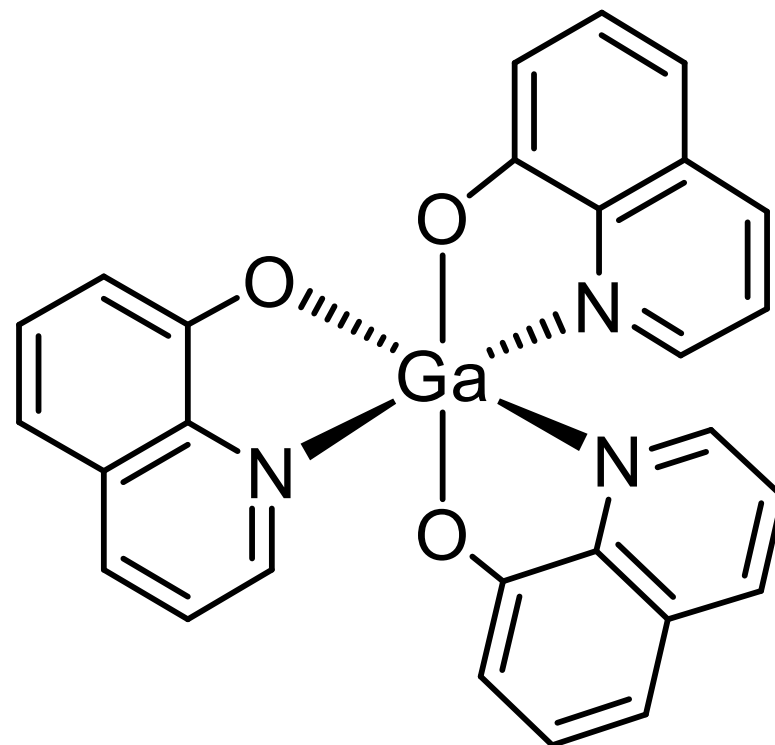


S-dimetilarsinoglutatione

Potenziali composti antitumorali di gallio



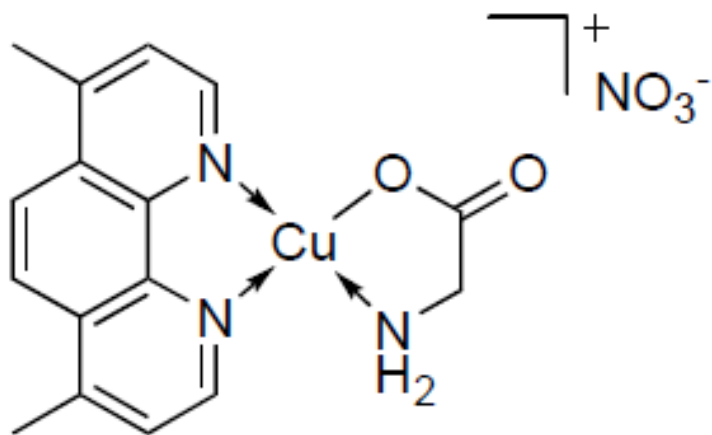
tris-maltolato



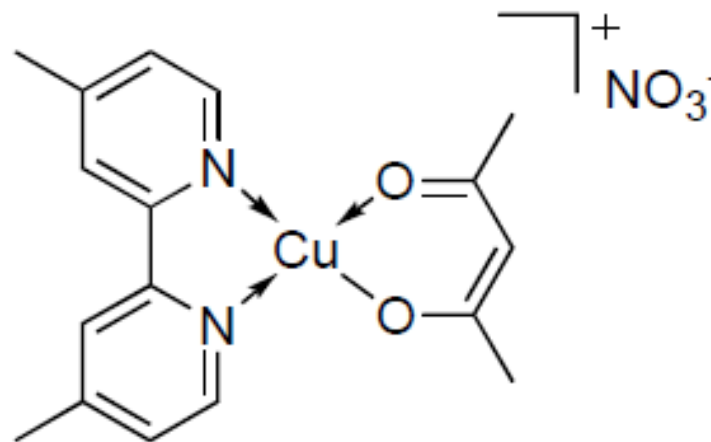
tris(8-idrossichinolinato)

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

Potenziali composti antitumorali di rame (*Casiopeine*)



Cas II-gly



Cas III-ia

Intercalazione nel DNA + generazione di ROS