

Discovery of cisplatin

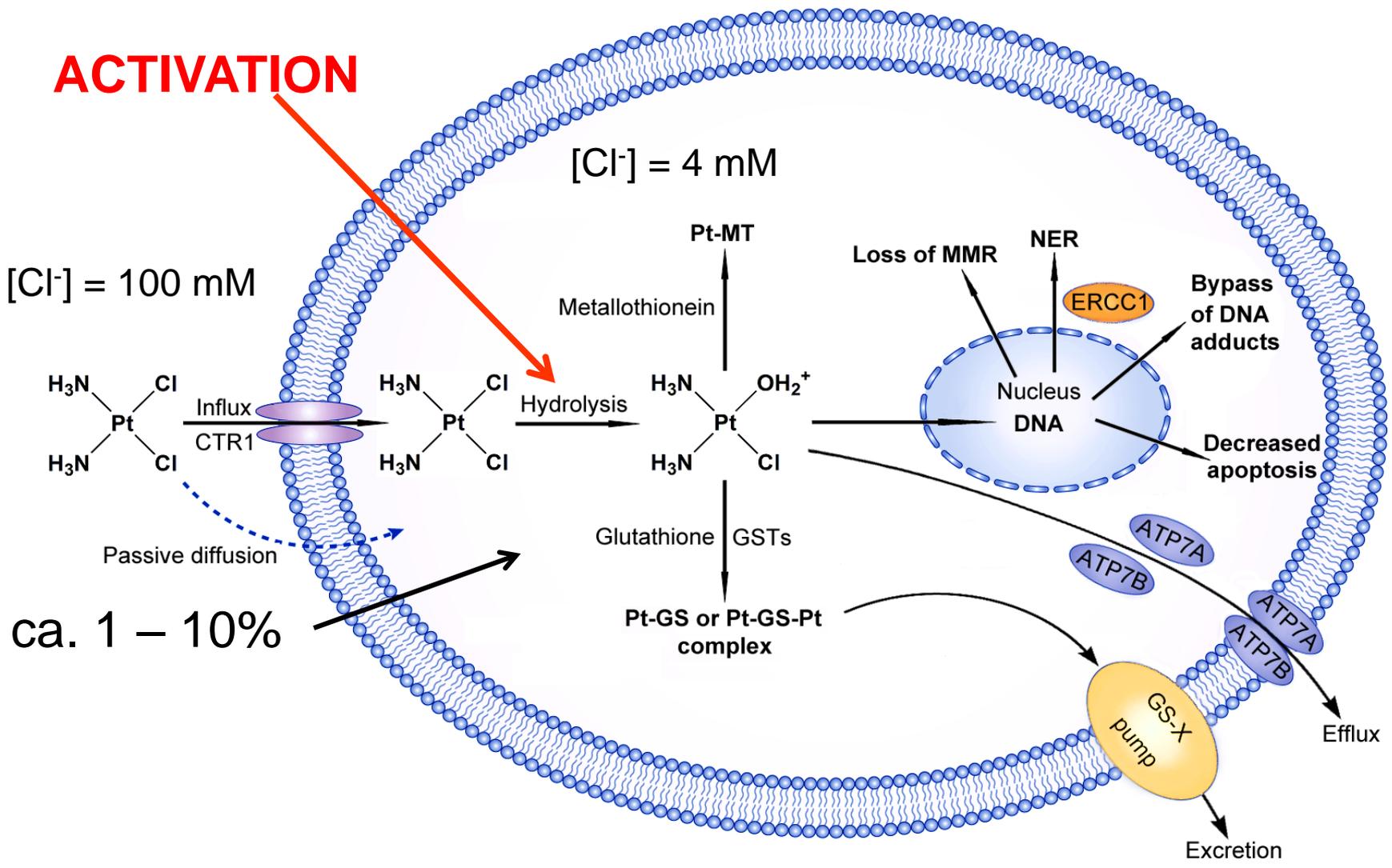
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graph TD; A([Discovery of cisplatin]) --> B[Mechanism of action]; A --> C[Structure – Activity relationships];
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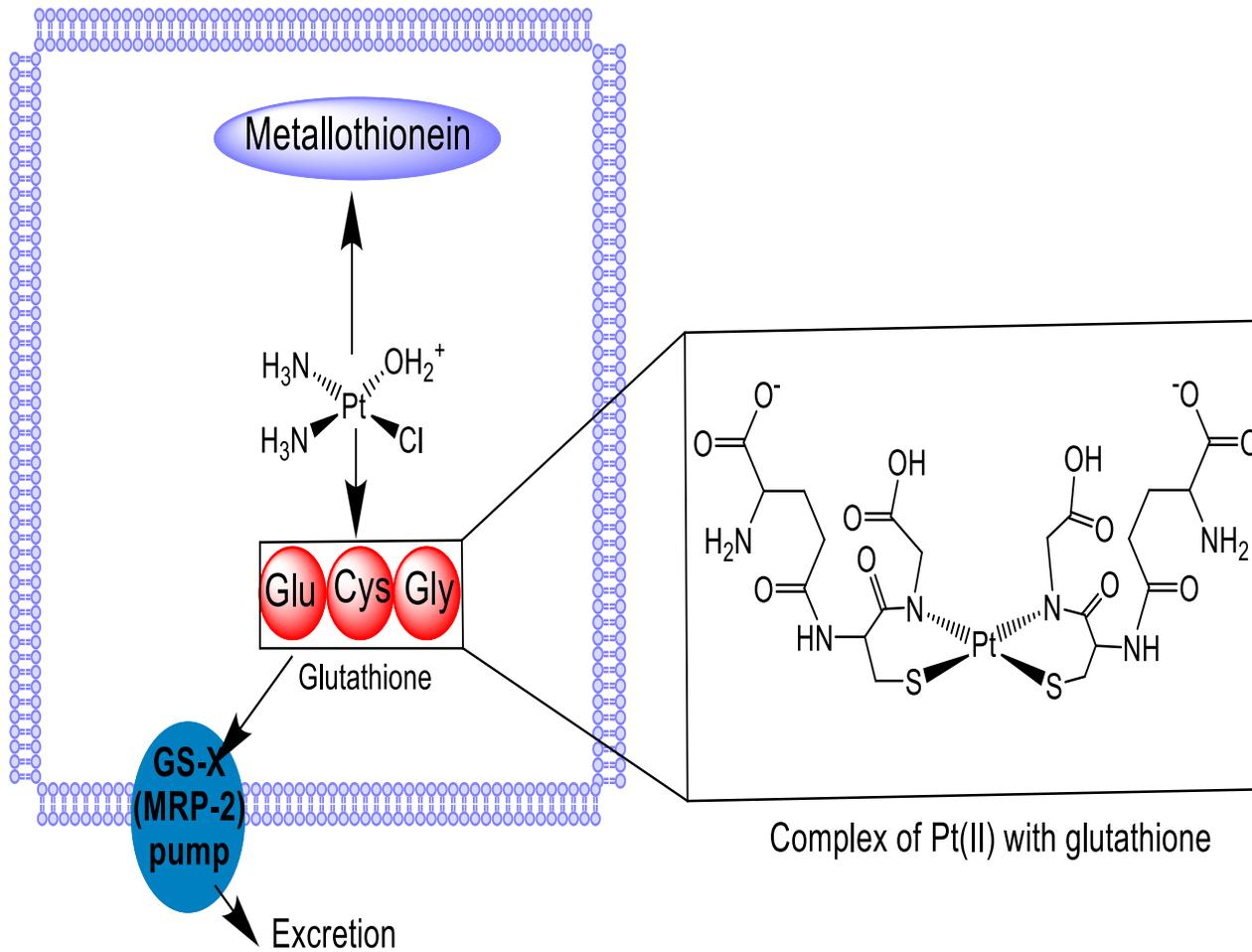
The diagram is a flowchart with three nodes. At the top is a blue oval containing the text 'Discovery of cisplatin'. Two red arrows originate from the bottom of this oval. One arrow points down and to the right to a green rounded rectangle containing the text 'Mechanism of action'. The other arrow points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

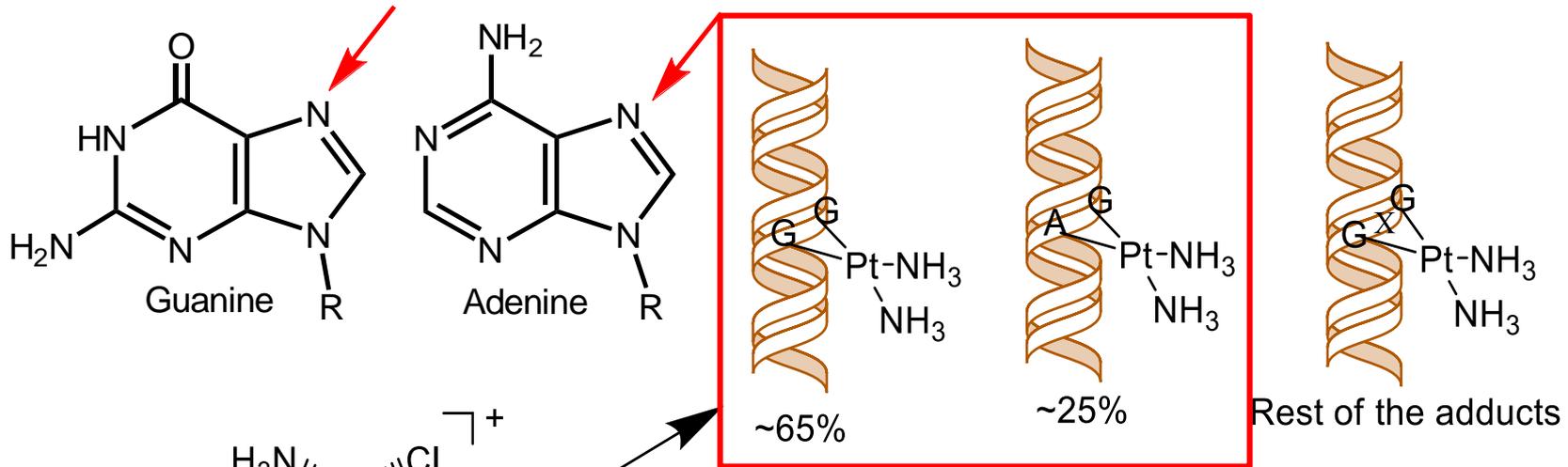
Mechanism of action

Structure – Activity
relationships

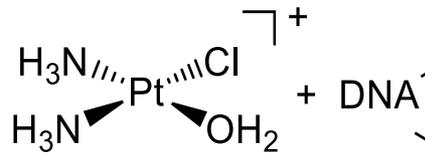
ACTIVATION





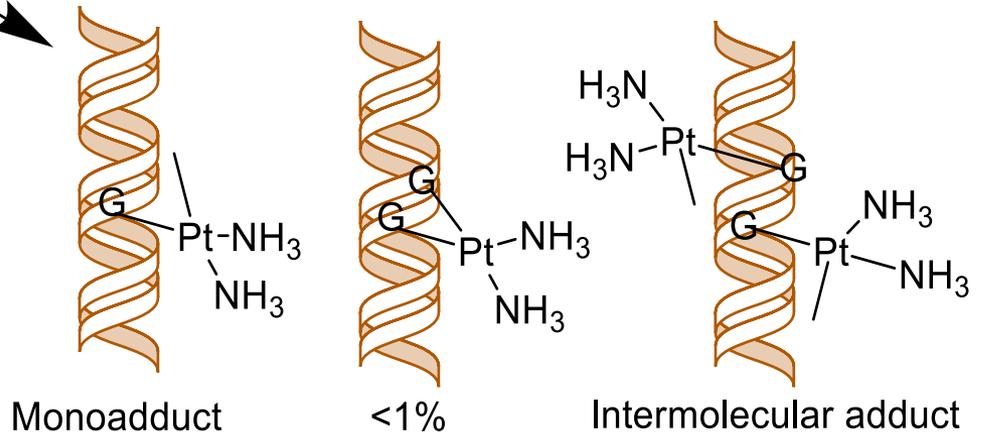


Intrastrand Adducts



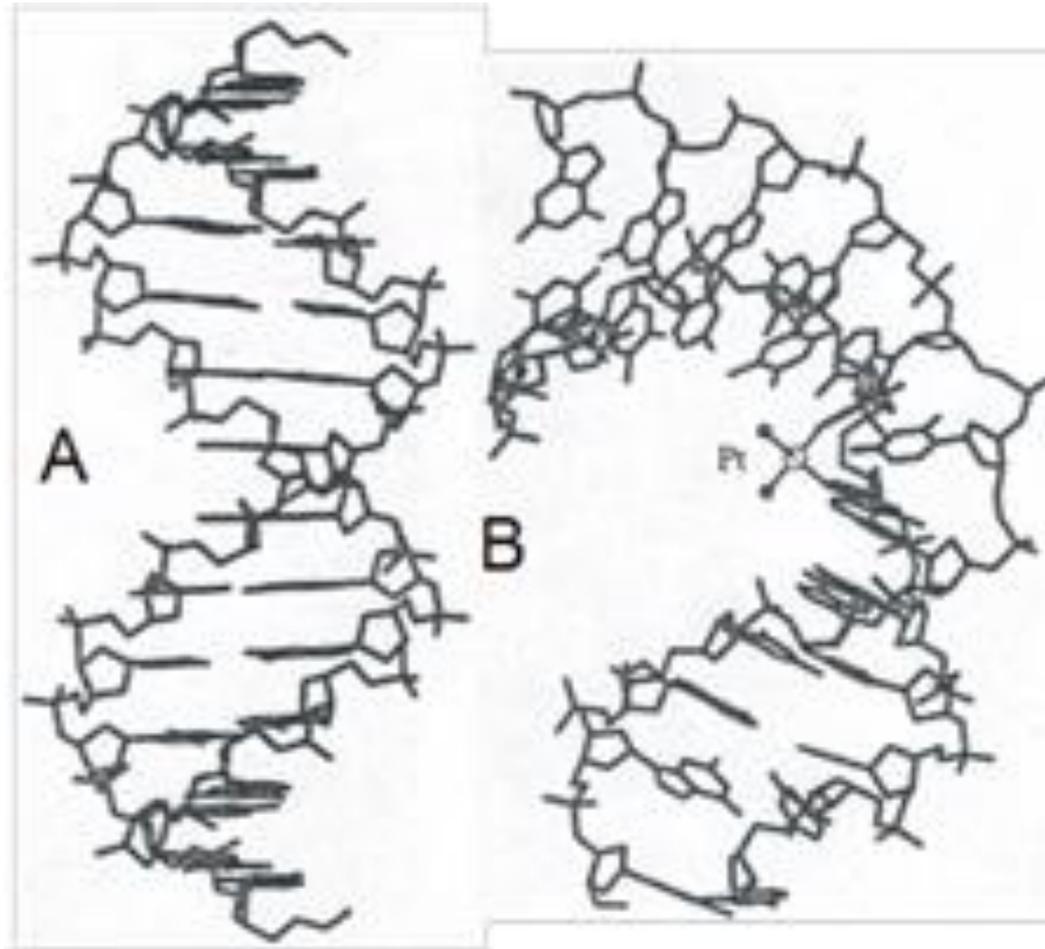
Stima:

- 1 Pt every 250.000 nucleotides is sufficient to inhibit cellular growth
- ca. 50.000 Pt adducts in each human cell



Other Adducts

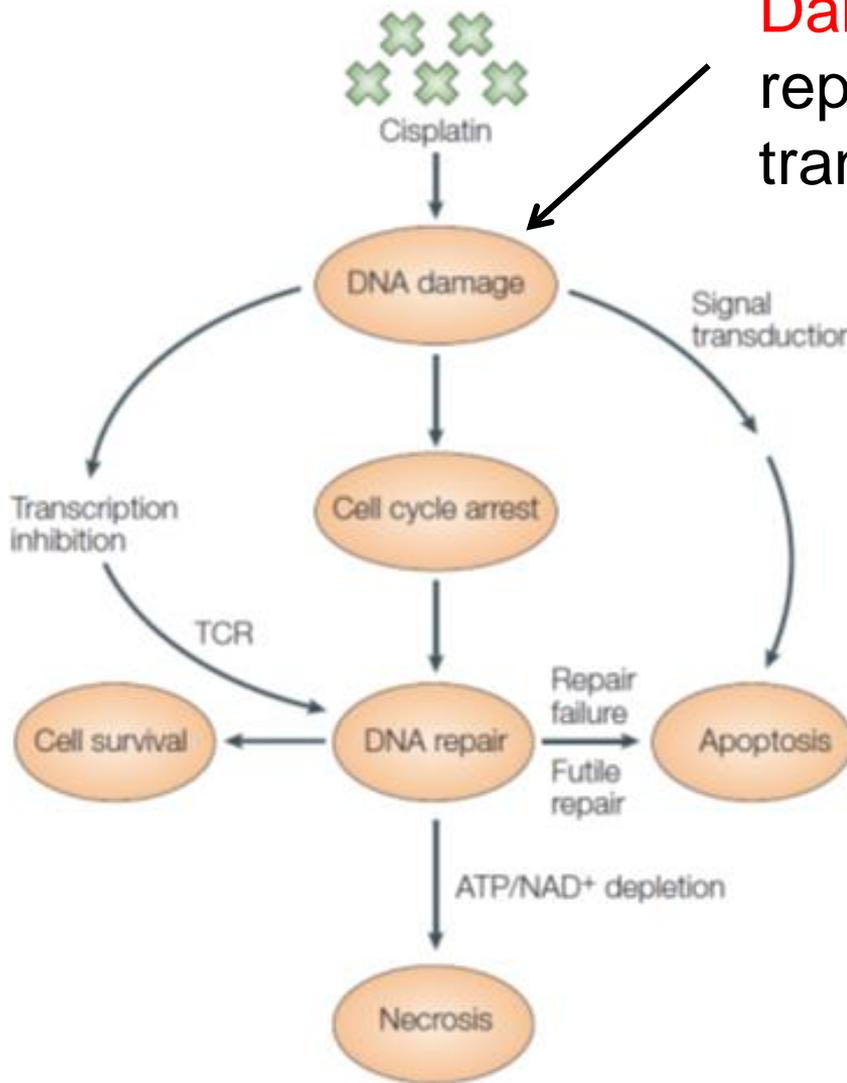
Platination induces a bending (*kink*) towards the major groove and a local unwinding of DNA



An HMG protein (High Mobility Group) recognizes the DNA platination site



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

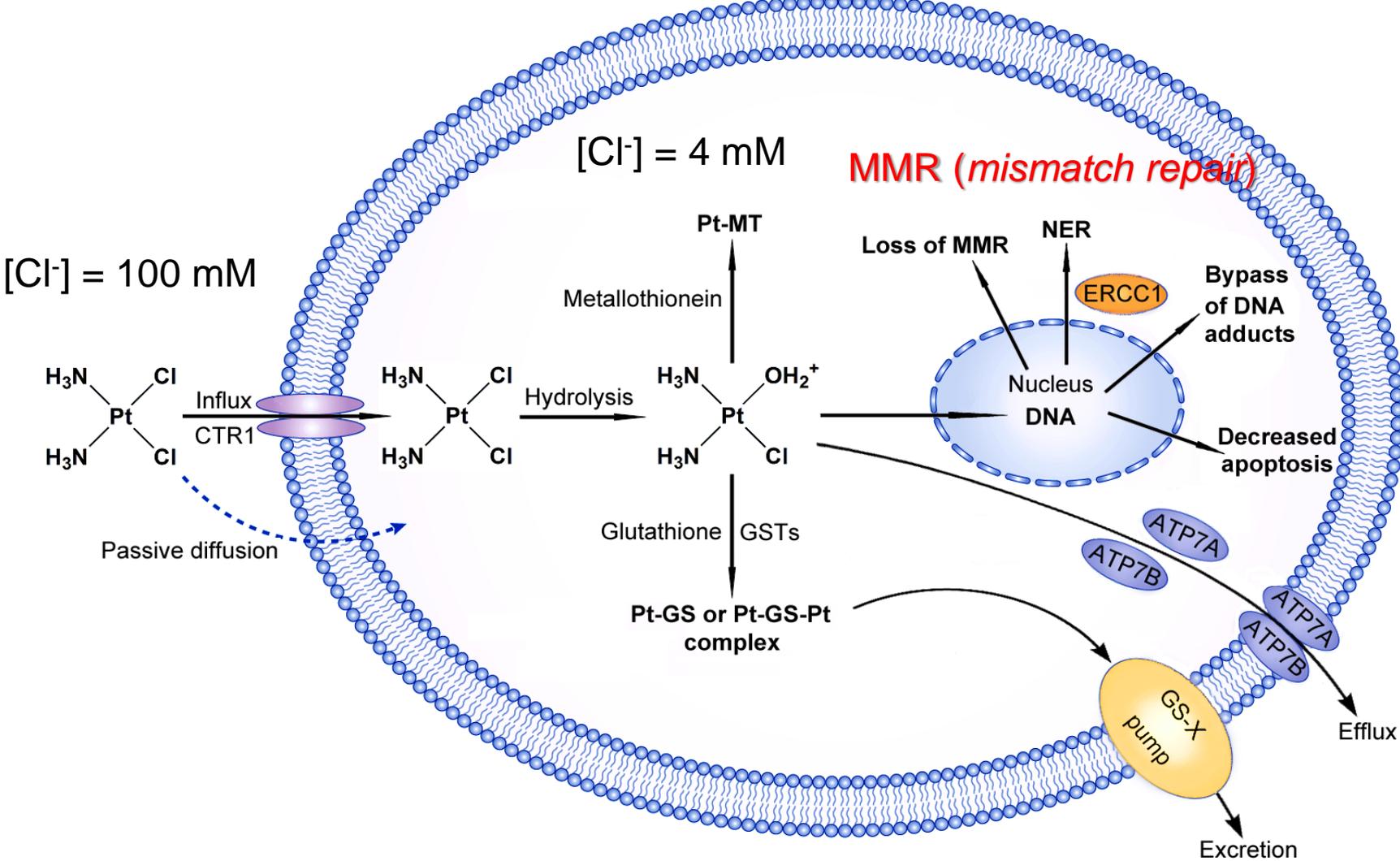


Aspartic proteases

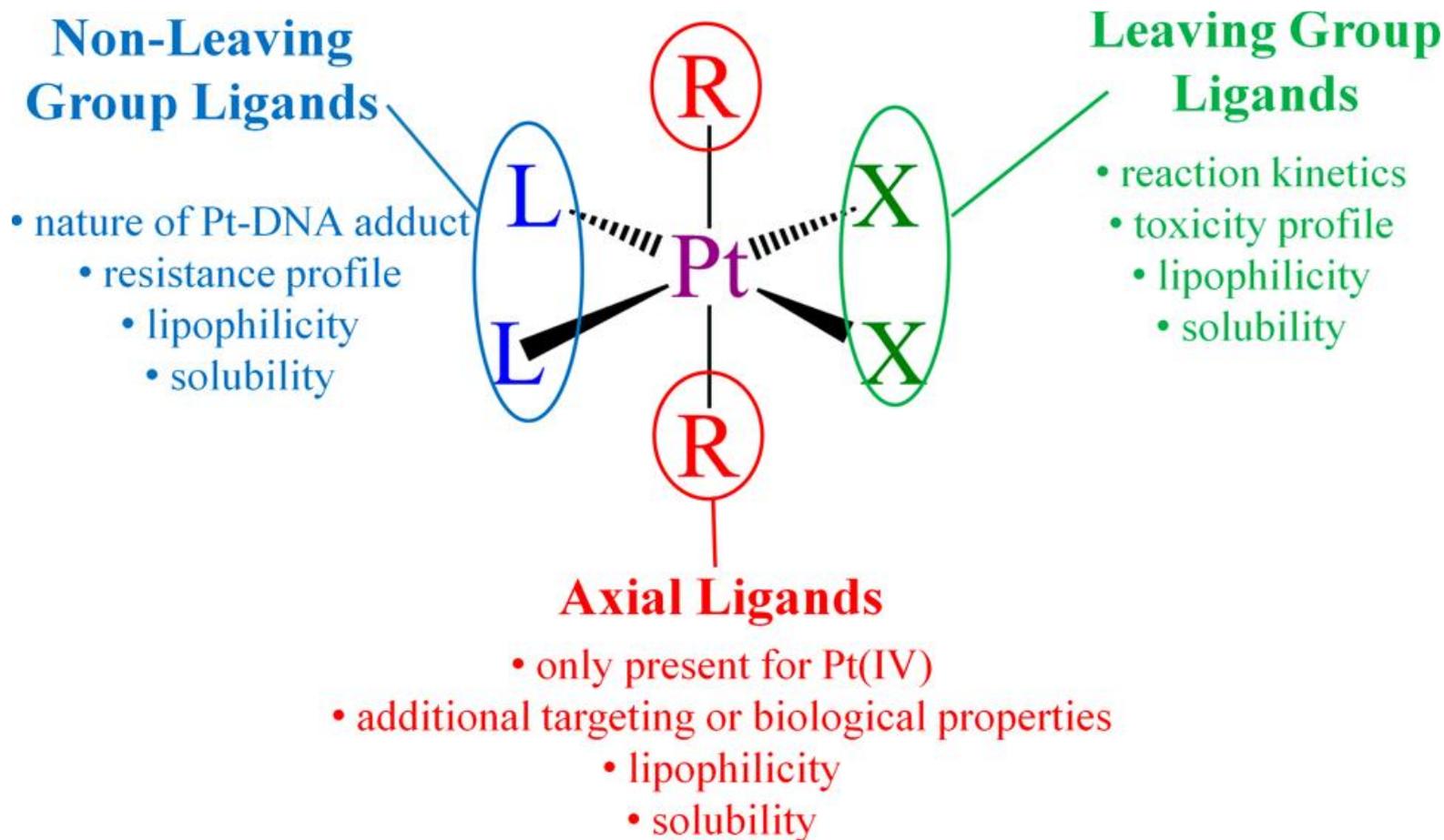
Main mechanisms of resistance

- 1) decreased level of platinum in the cell;
- 2) increased level of cellular thiols (glutathione, metallothioneins, and other sulfur-containing molecules);
- 3) increased DNA repair capacity and/or increased resistance to damage;
- 4) changes in signal chains leading to cell death (cell-death pathways), or its survival. Specifically, reduction of apoptotic response and activation of survival pathways.

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

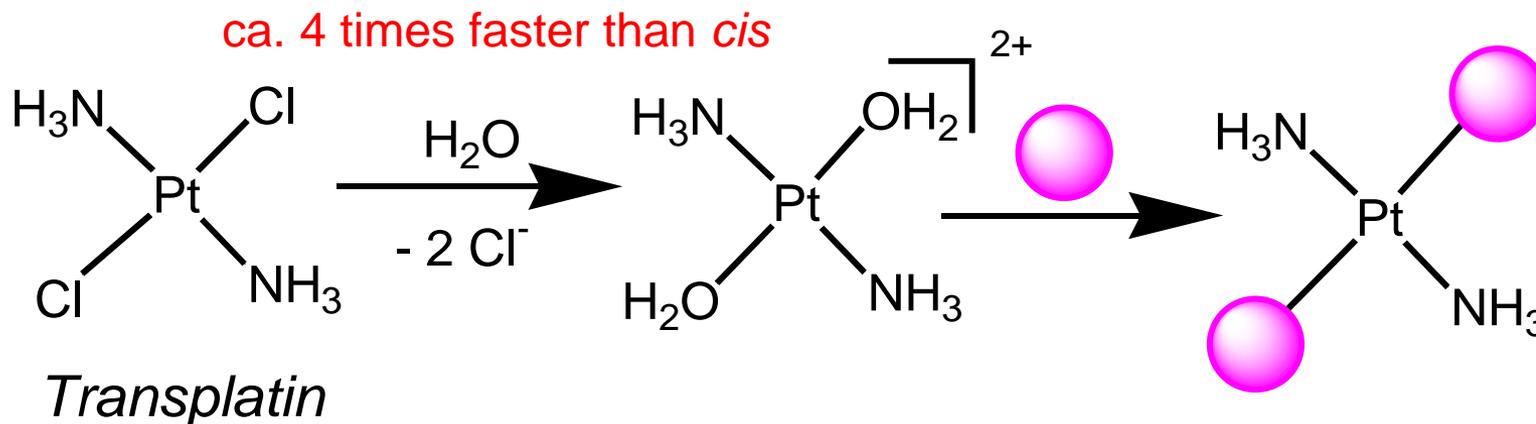
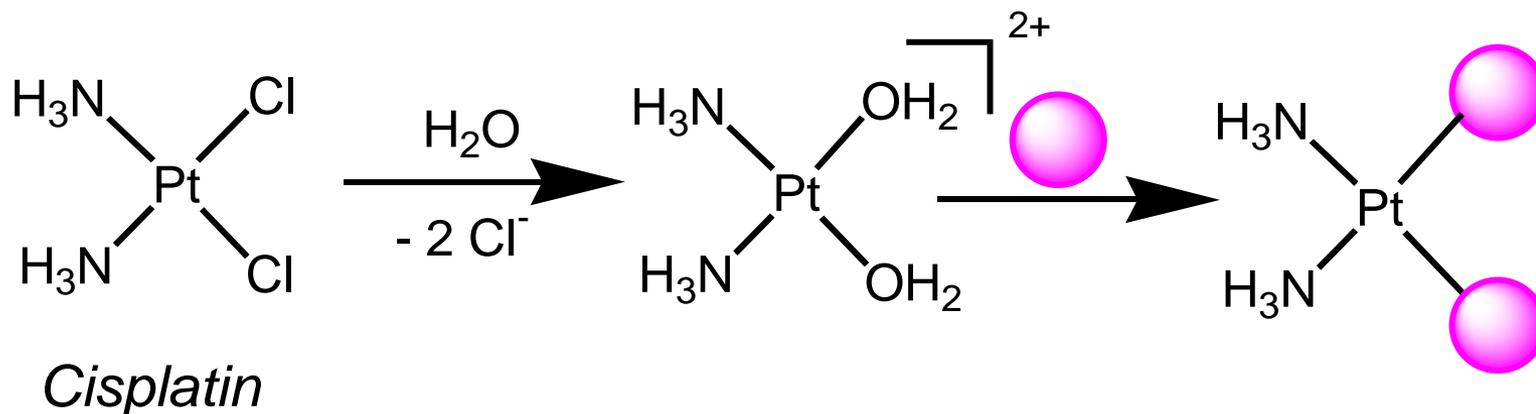


Structure – activity relationships



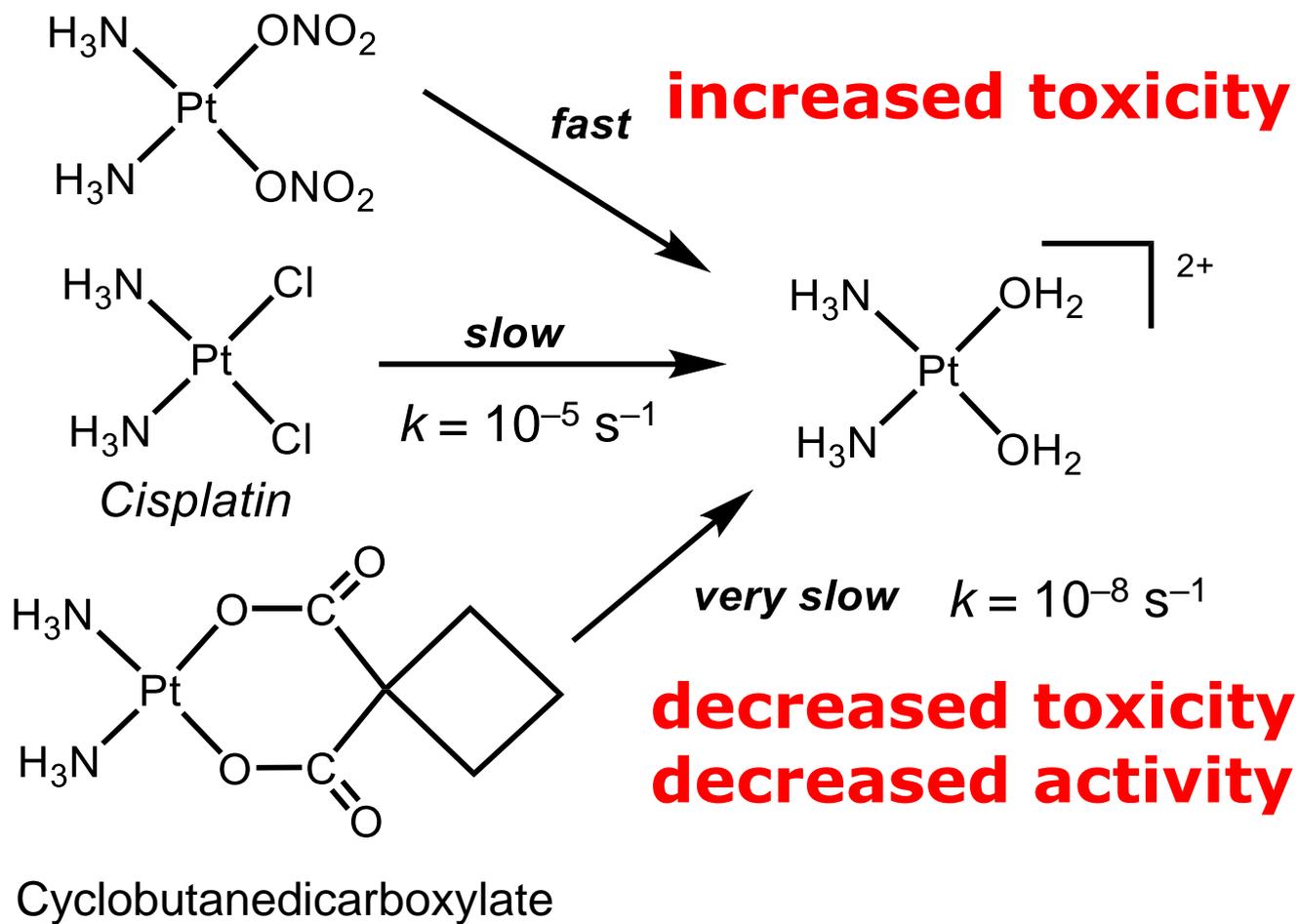
More than 1000 Pt(II) and Pt(IV) compounds screened in vitro for cytotoxic activity

Geometry matters

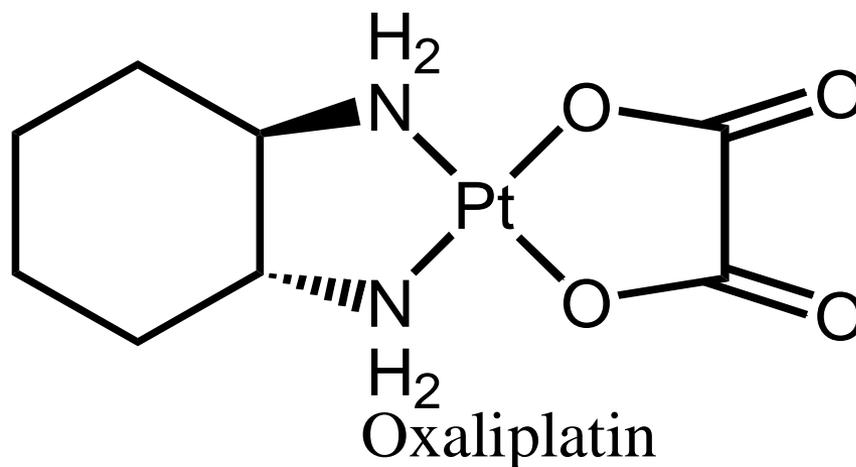
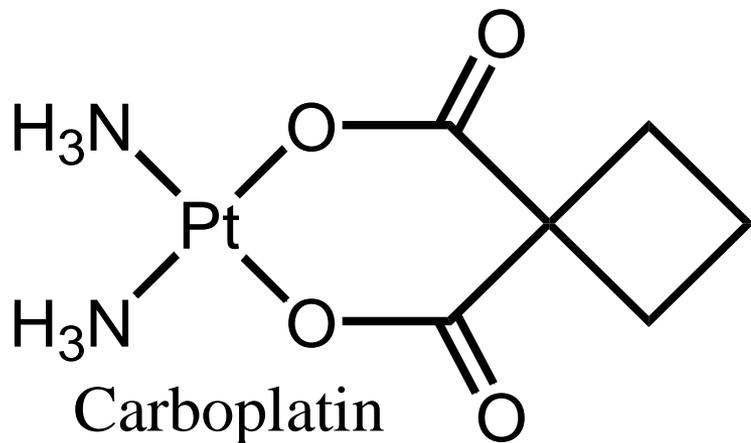


Toxic, but not anticancer active

Kinetics matters



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



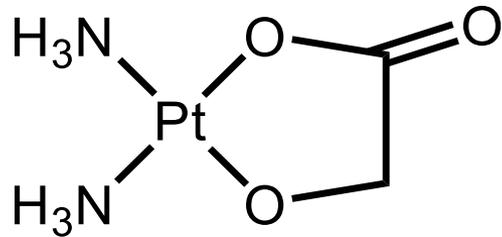
1,1-cyclobutanedicarboxylate

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

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

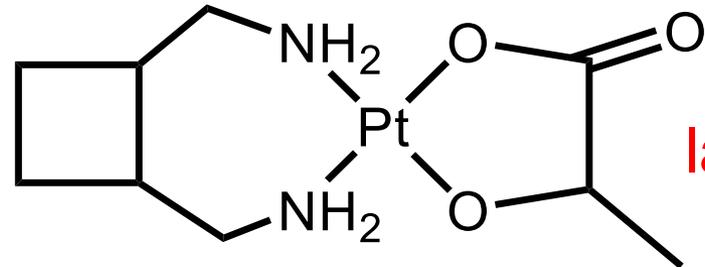
trans-(1*R*,2*R*)-1,2-diaminecyclohexane

2-hydroxyacetate



Nedaplatin (Japan)

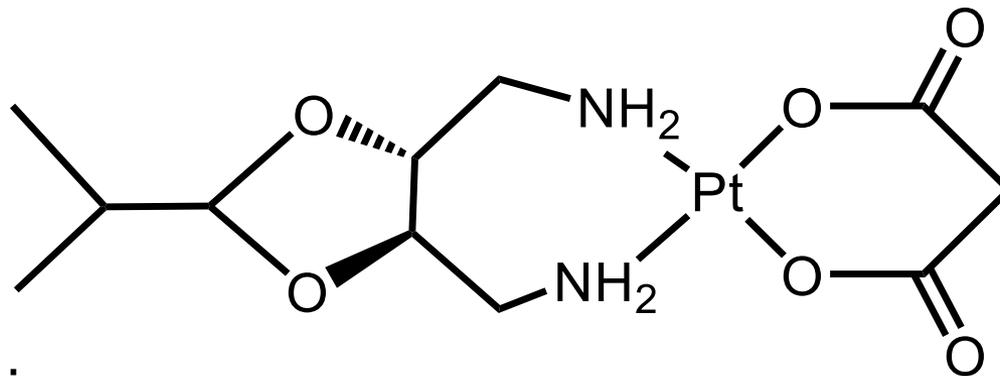
II generation



lactate

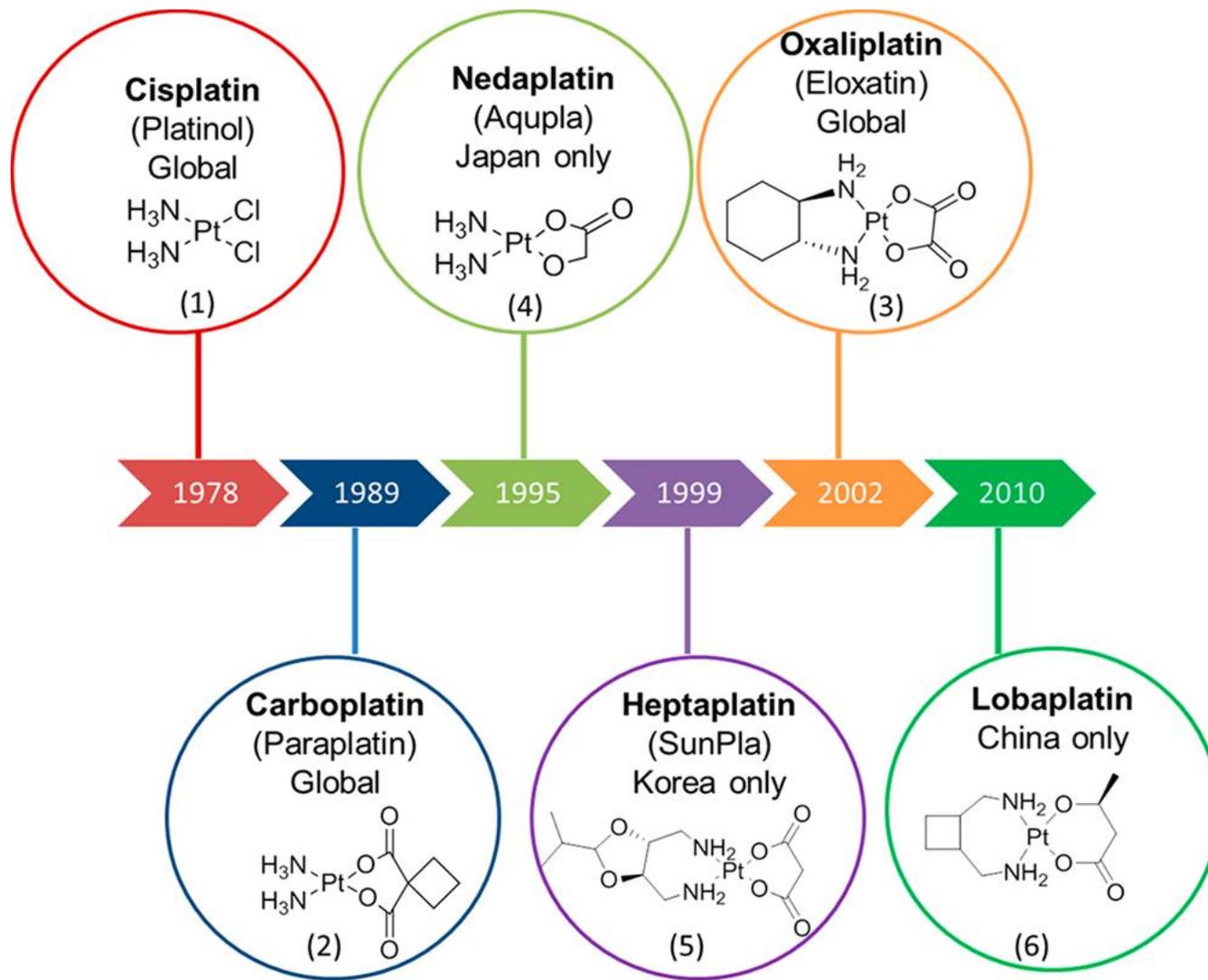
Lobaplatin (China)

III generation



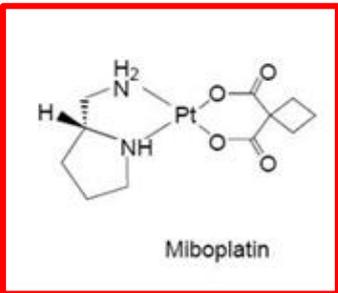
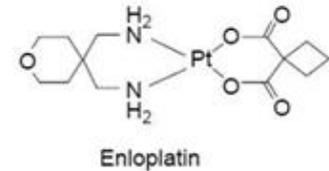
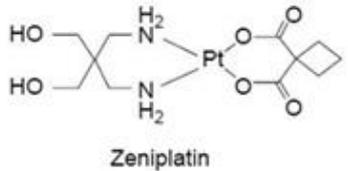
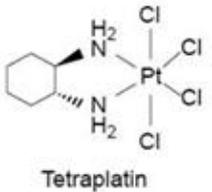
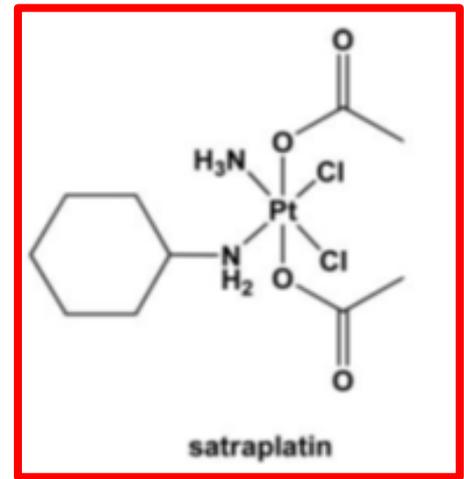
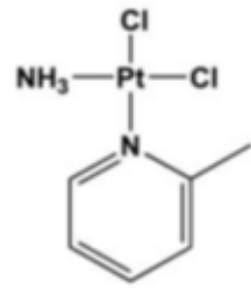
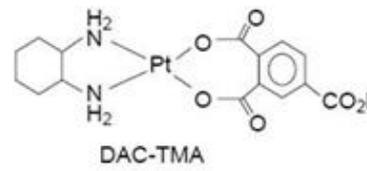
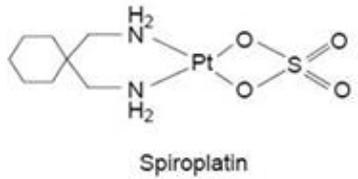
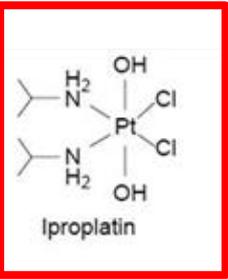
malonate

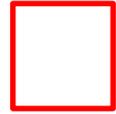
III generation Heptaplatin (South Korea)



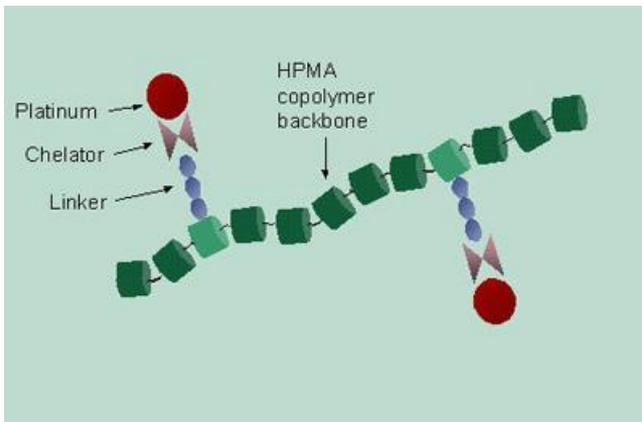
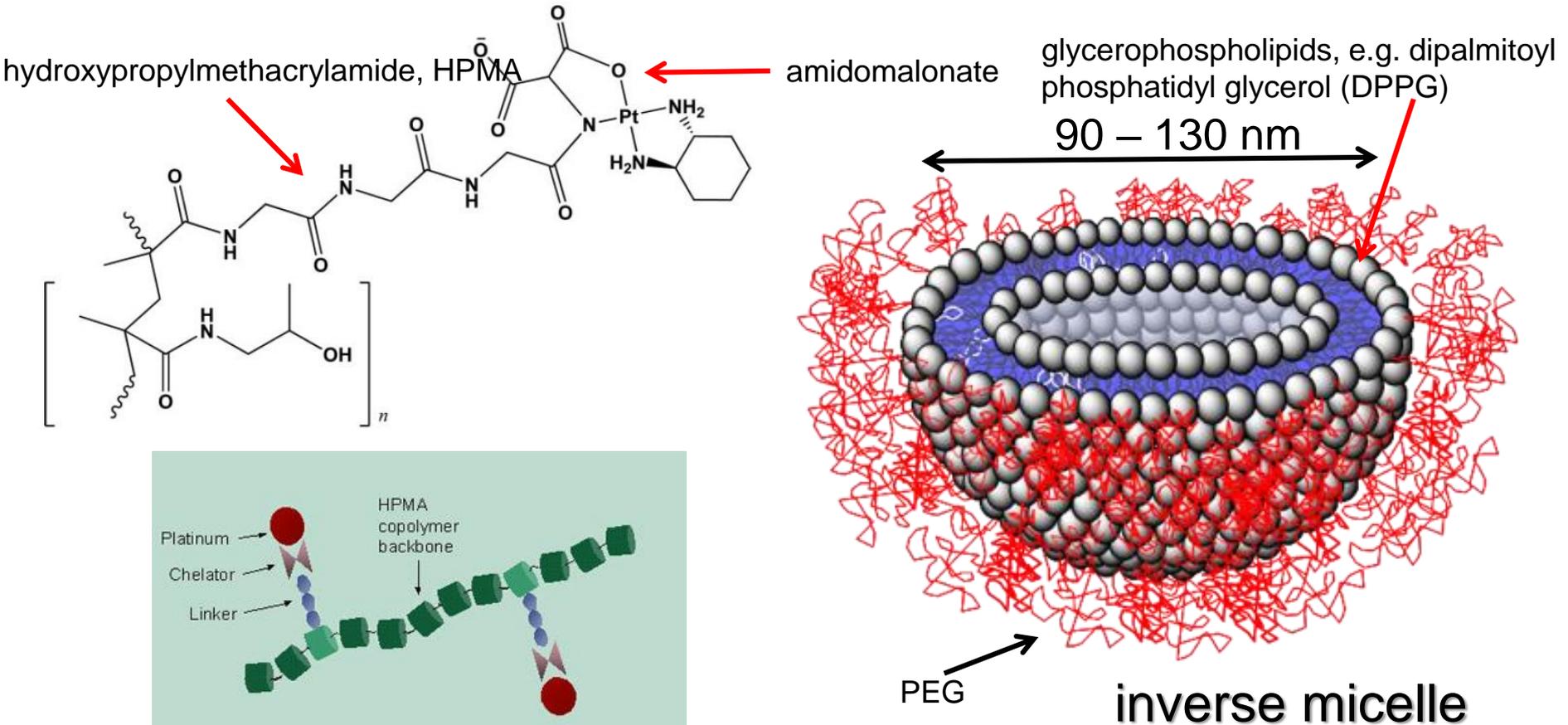
Some of the 23 Pt compounds tested in clinical phase

5 phase 1 studies, 22 phase 2 studies, 1 phase 3 study , > 1000 patients



 = phase 3

Some Pt formulations in clinical phase: the **nano-carriers** ProLindac™ and 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:

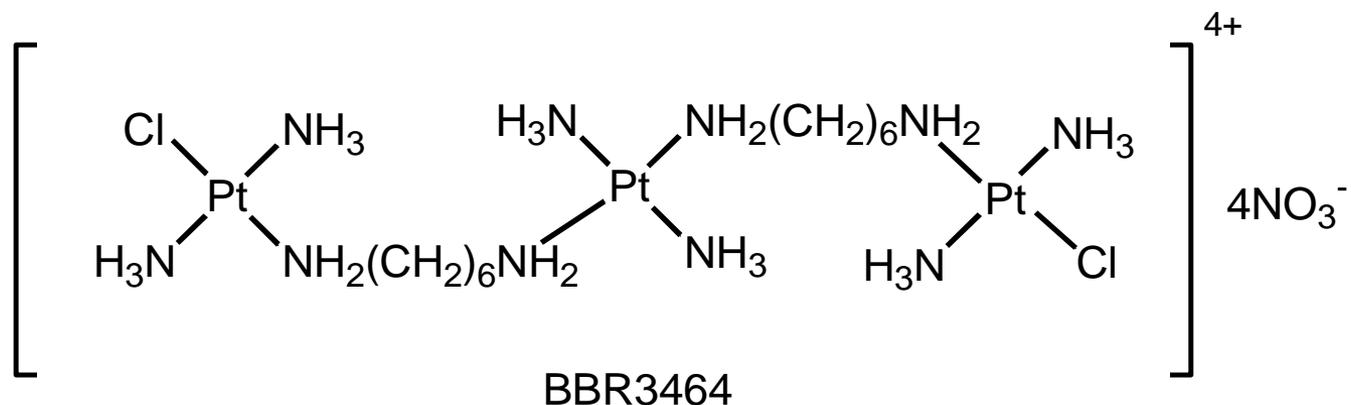
1. on the nature of the metal center (*thermodynamic and kinetic parameters, hard-soft nature, oxidation state*)
2. on the nature of the non-leaving ligands (*lipophylicity, charge, solubility, non-covalent interactions...*);
3. on the kinetics of activation (*e.g. aquation rate*)

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.

The last Pt compound to reach clinical phase (1999)



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:

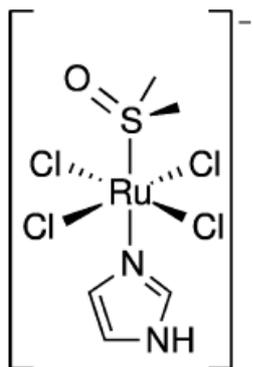
1. to be active against those human malignancies that are resistant, or have acquired resistance, to Pt drugs.
2. to show a lower (or at least different) toxicity compared to Pt drugs.

General features of ruthenium compounds

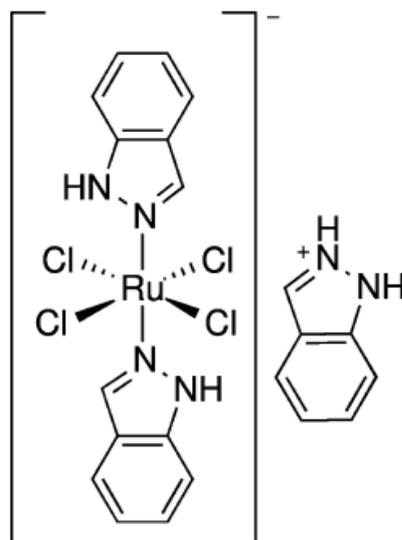
- Six-coordinate, octahedral geometry
- High affinity for nitrogen and sulfur ligands
- Two readily accessible oxidation states in aqueous solution: Ru(III) (d^5 , paramagnetic) and Ru(II) (d^6 , diamagnetic)
- Ru(III) complexes are usually more inert than the corresponding Ru(II) species
- The kinetics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

Clinically tested anticancer Ru(III) compounds

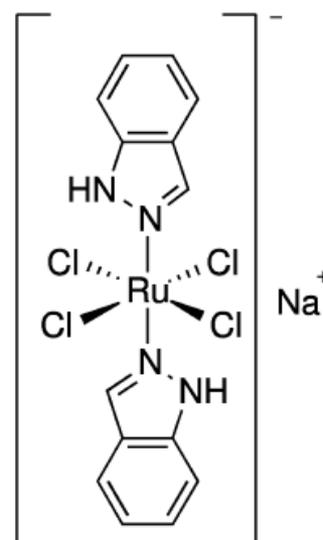
Deceptively similar



NAMI-A



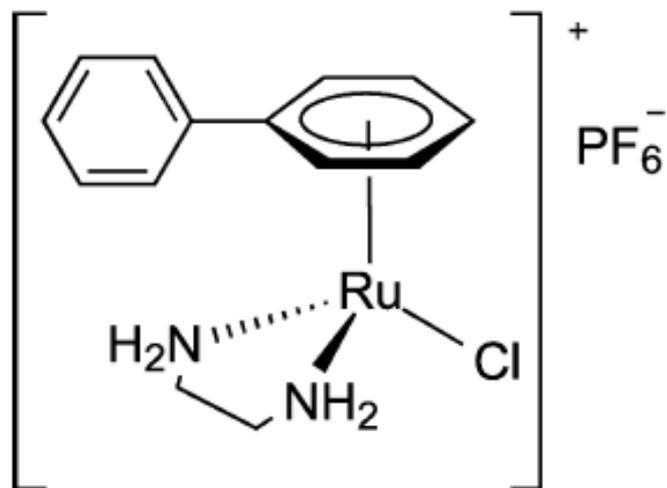
KP1019



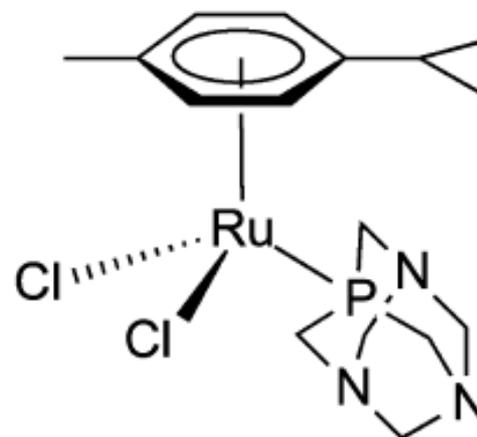
(N)KP1339

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

Anticancer organometallic Ru(II) compounds



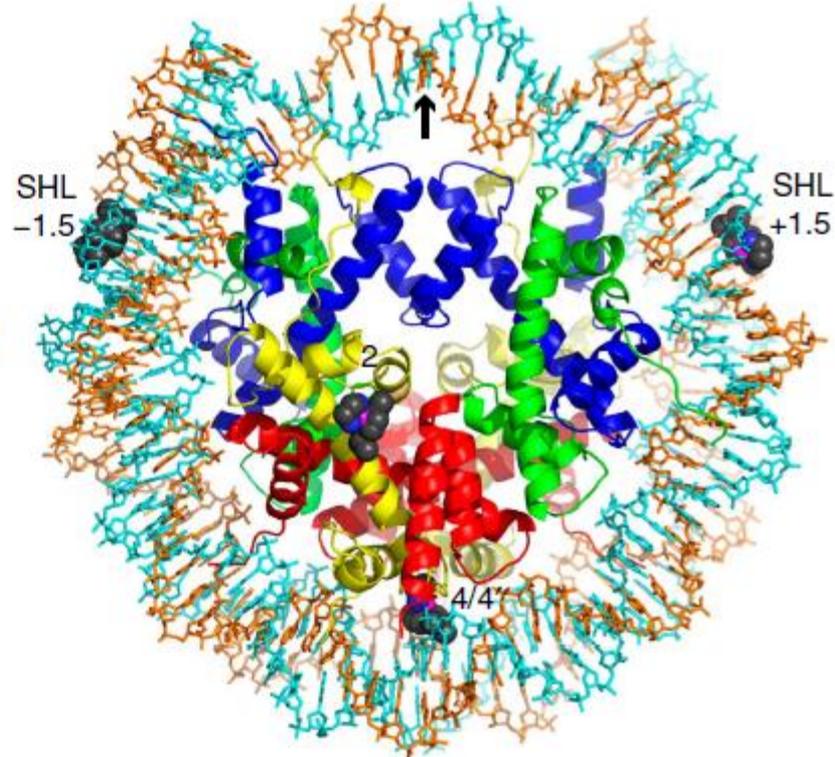
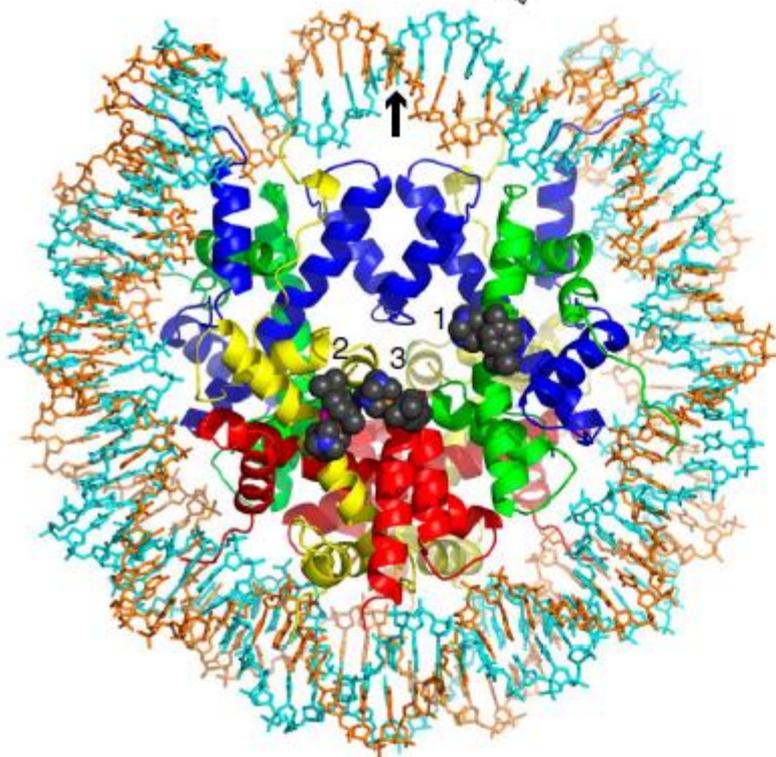
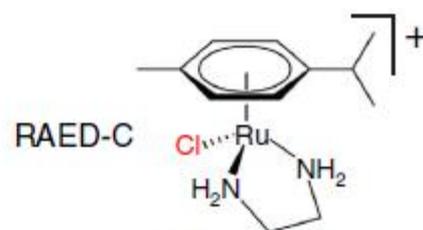
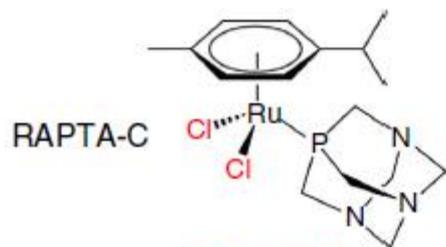
RM175



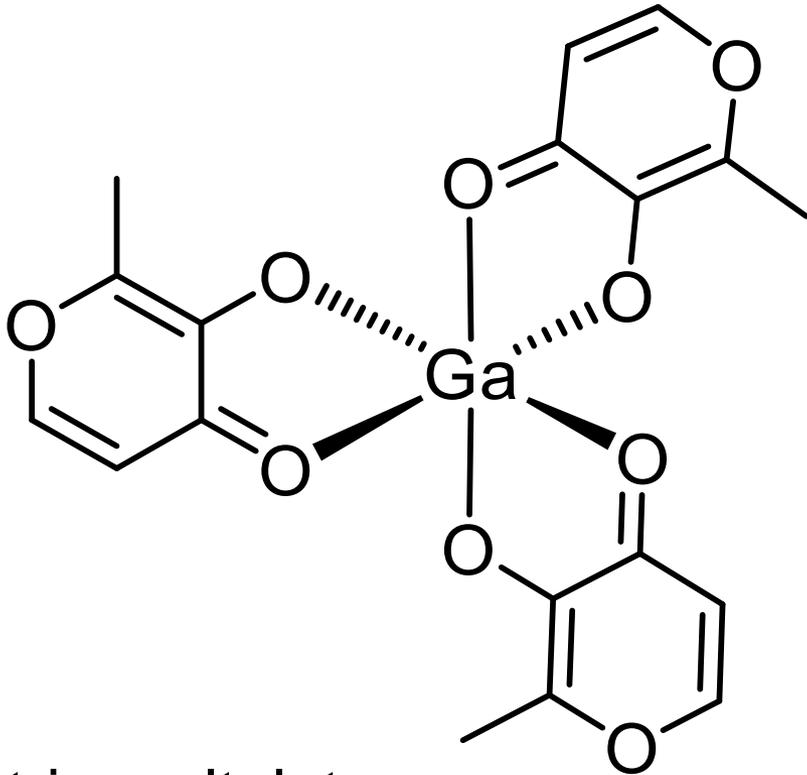
RAPTA-C

Different interactions of half-sandwich Ru(II) compounds with chromatin

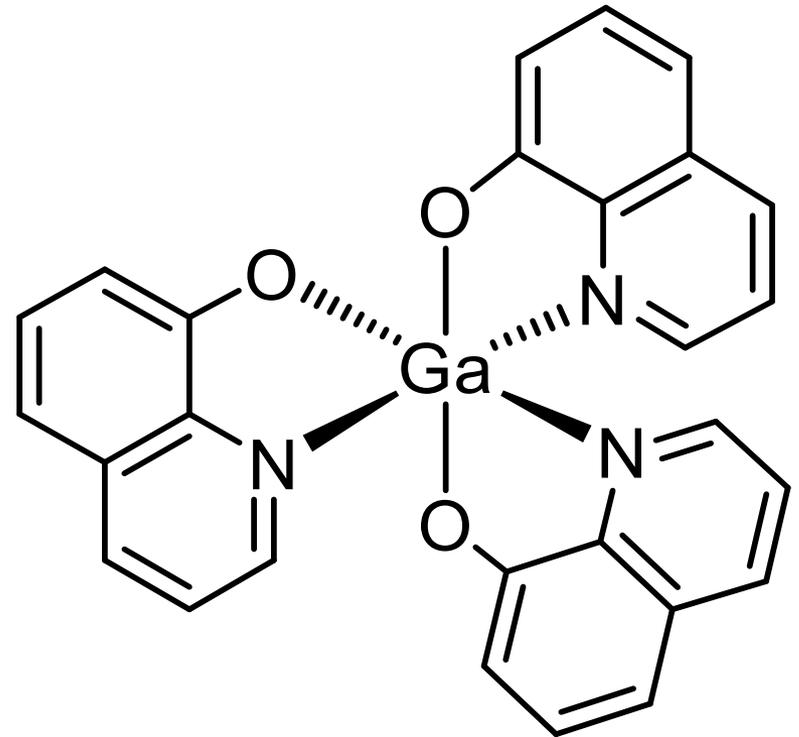
a



Gallium anticancer compounds



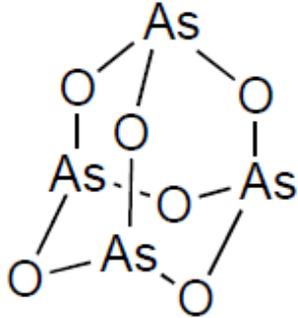
tris-maltolate



tris(8-hydroxyquinolate)

Ga^{3+} is similar to Fe^{3+} but inhibits ribonucleotide reductase

Arsenic anticancer compounds



ATO

0.15 mg/kg

FDA 2000

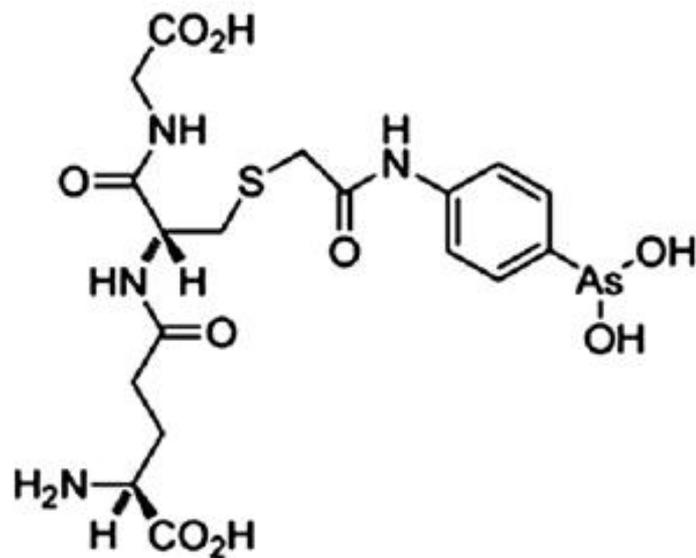
acute promyelocytic leukemia

ATO/ATRA therapy

(ATRA = all-trans retinoic acid)

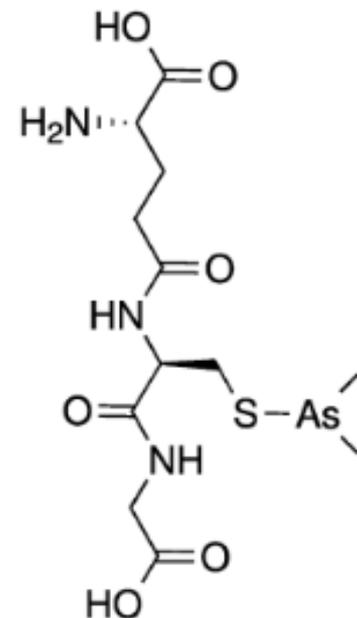
- Degradation of mutant protein PML-RAR α that blocks myeloid differentiation
- Inhibition of anti-ROS S/Se-enzymes (glutathione reductase, glutathione peroxidase (Se), thioredoxin reductase (Se), and thioredoxin peroxidase)

Potential organo-arsenic anticancer compounds



GSAO

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



Darinaparsin

S-dimethylarsinoglutathione