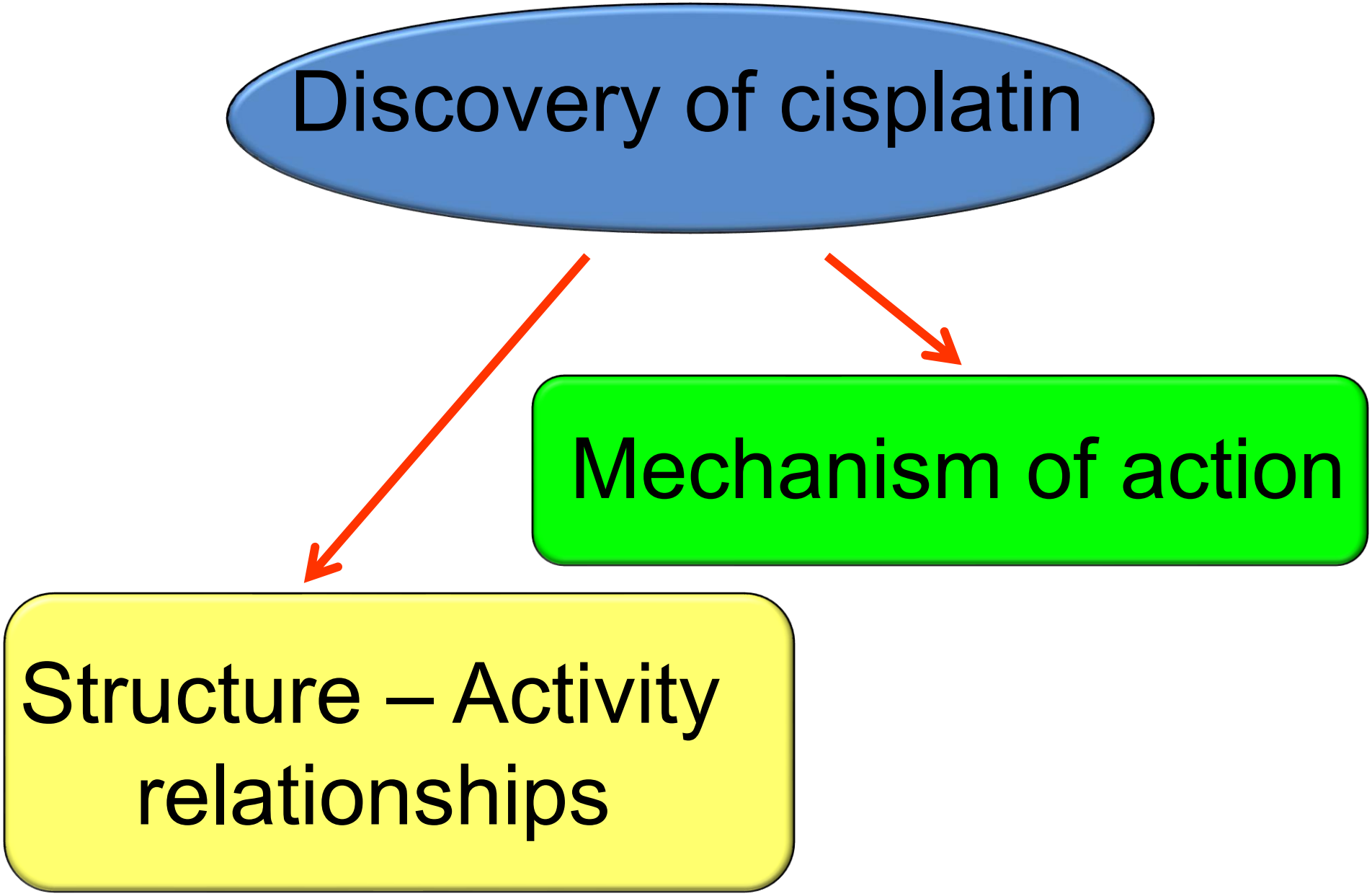
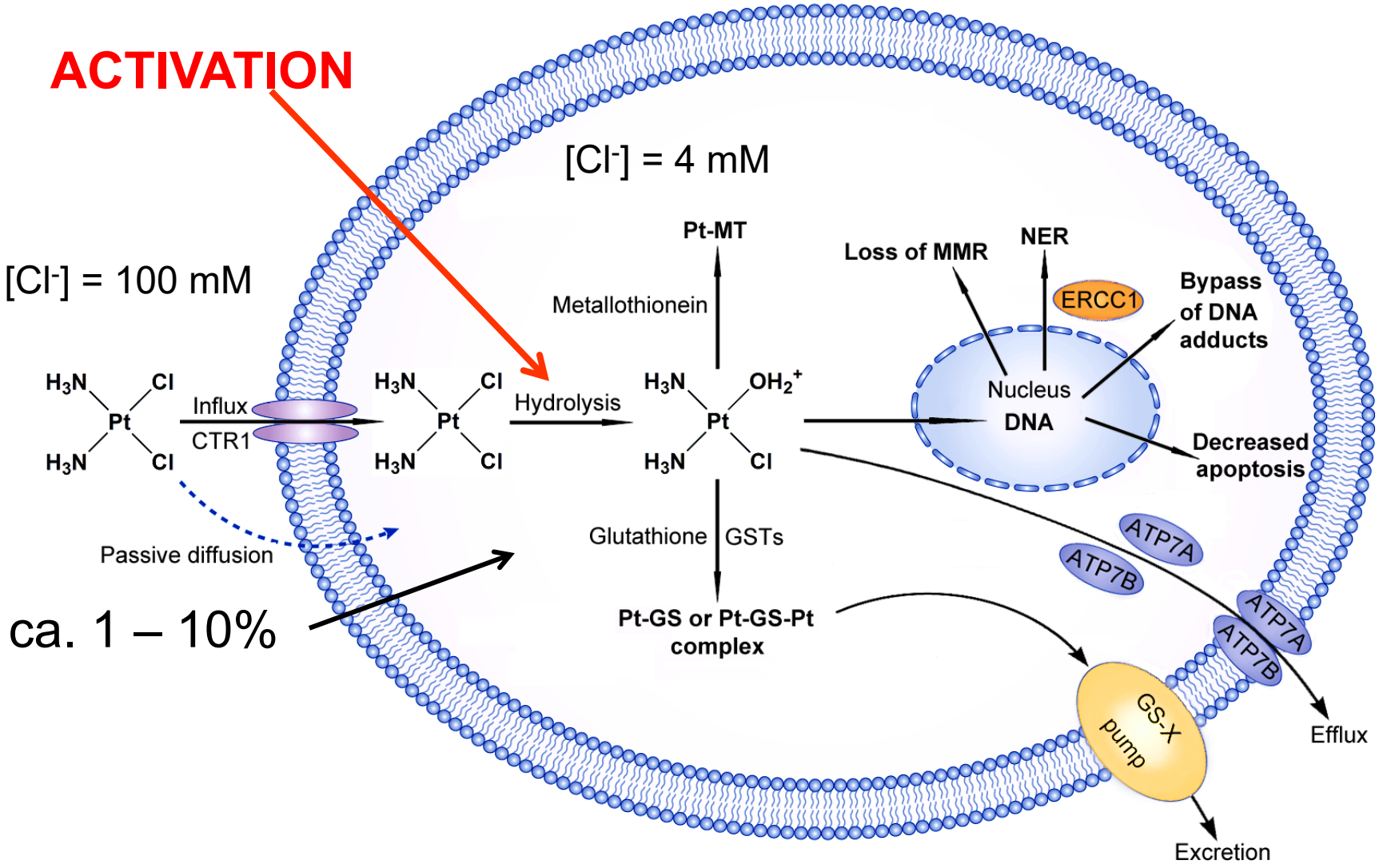
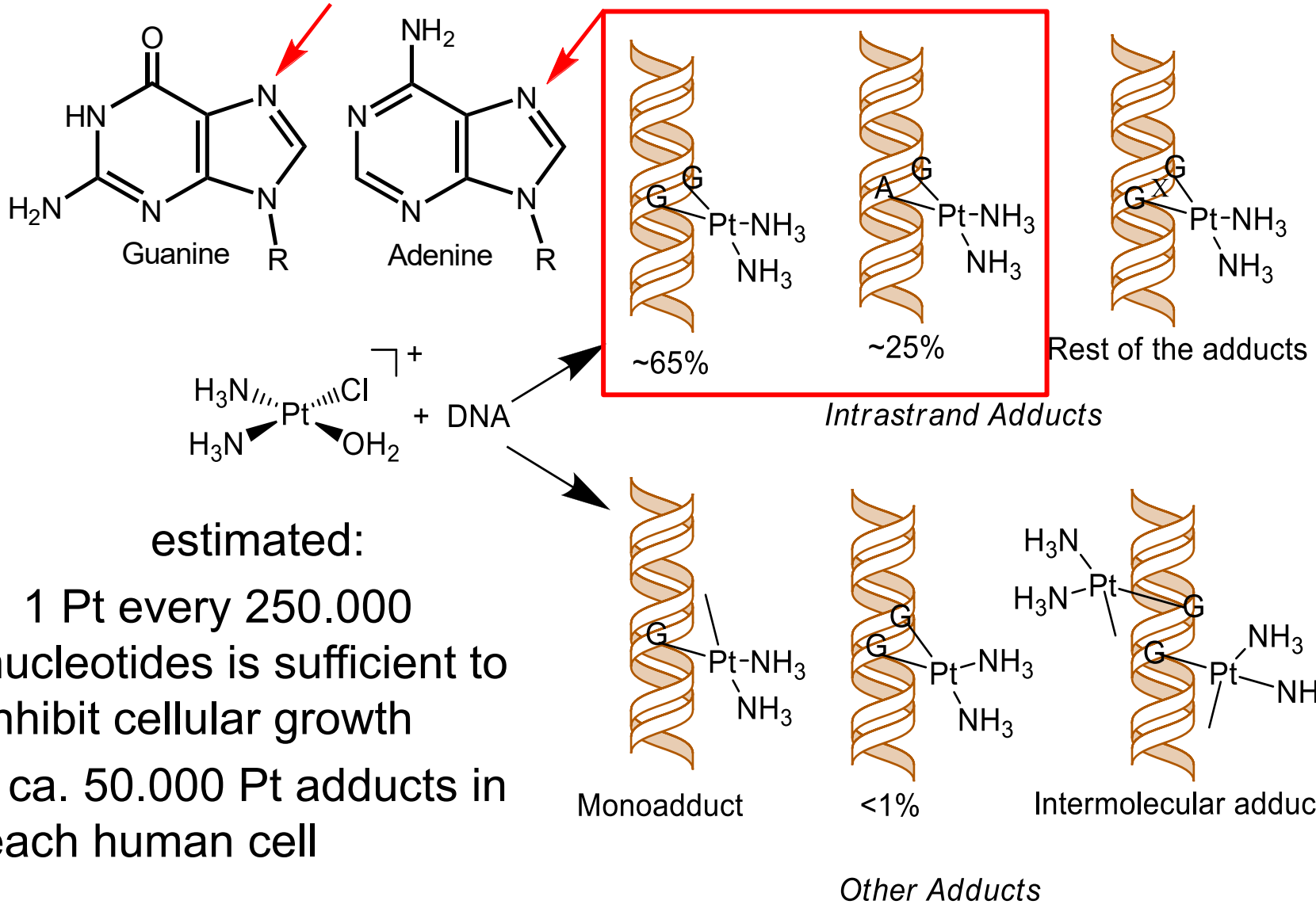

Discovery of cisplatin
Mechanism of action
Structure – Activity relationships

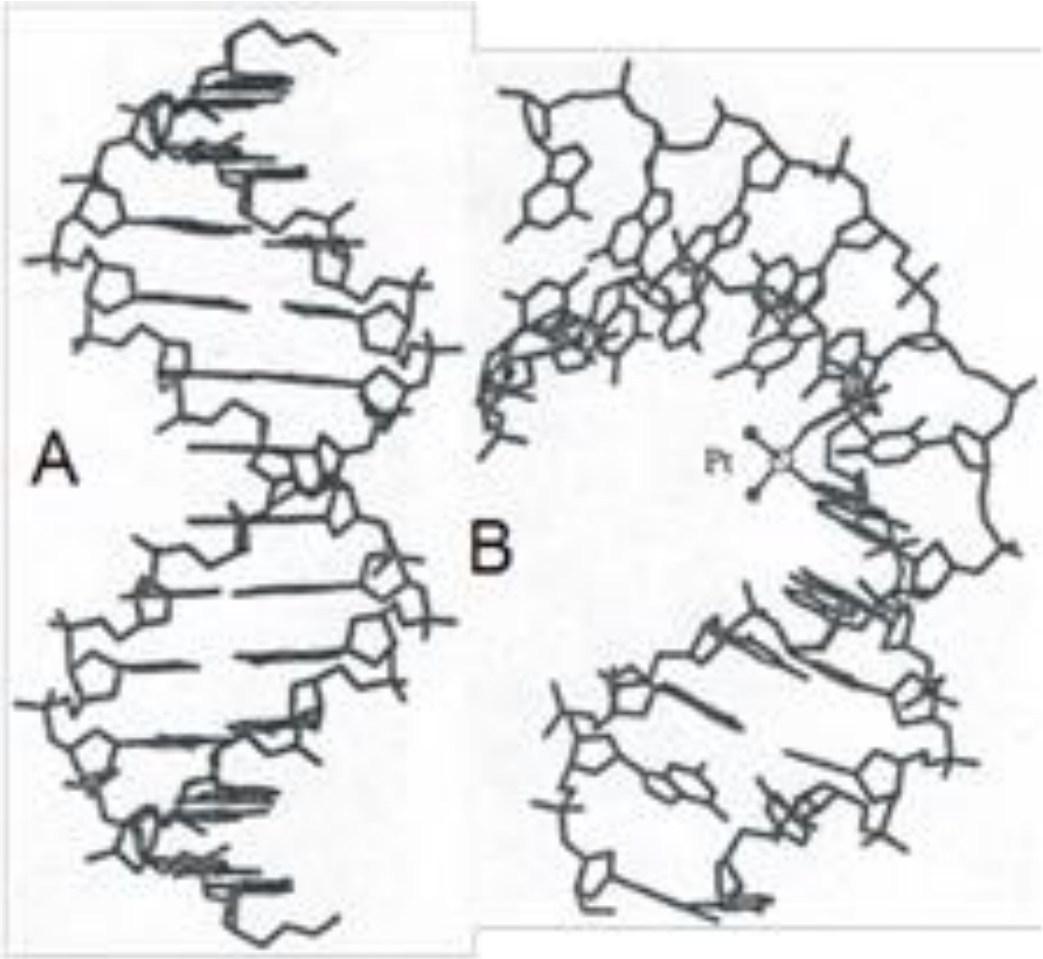

ACTIVATION
[Cl-] = 4 mM
[Cl-] = 100 mM
Pt-MT
Metallothionein
Loss of MMR
NER
ERCC1
Bypass of DNA adducts
Nucleus
DNA
Decreased apoptosis
Influx
CTR1
Hydrolysis
Passive diffusion
ca. 1 – 10%
Glutathione
GSTs
Pt-GS or Pt-GS-Pt complex
ATP7A
ATP7B
ATP7A
ATP7B
GS-X pump
Efflux
Excretion



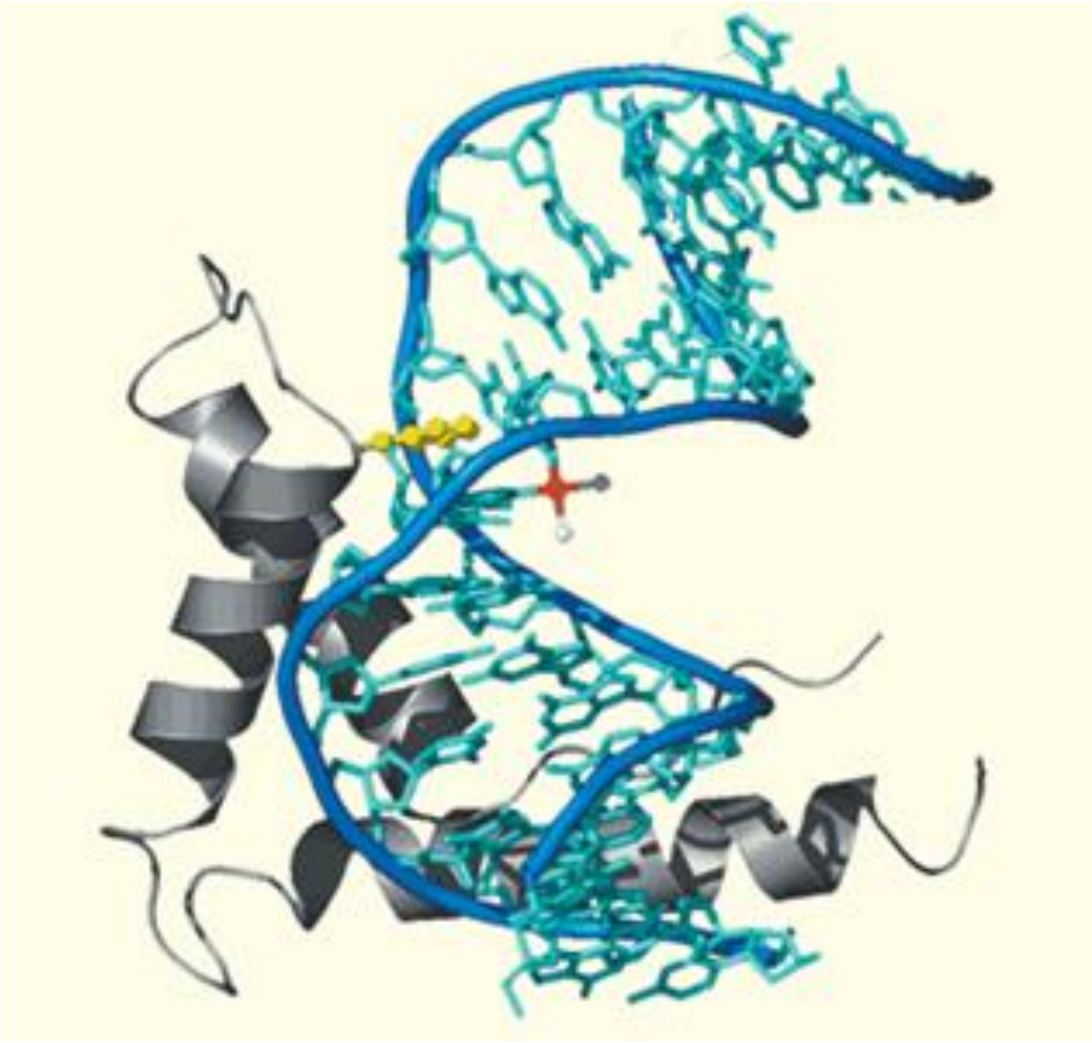
estimated:

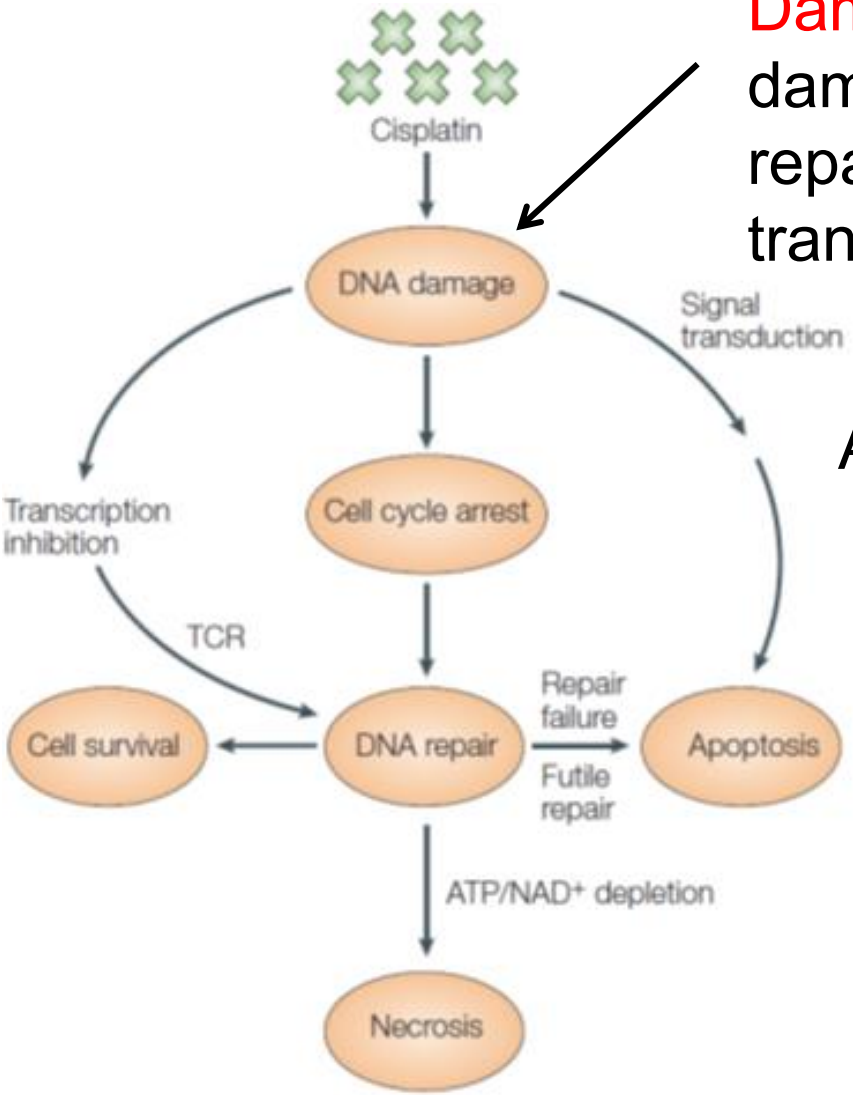
- 1 Pt every 250.000 nucleotides is sufficient to inhibit cellular growth
- ca. 50.000 Pt adducts in each human cell

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

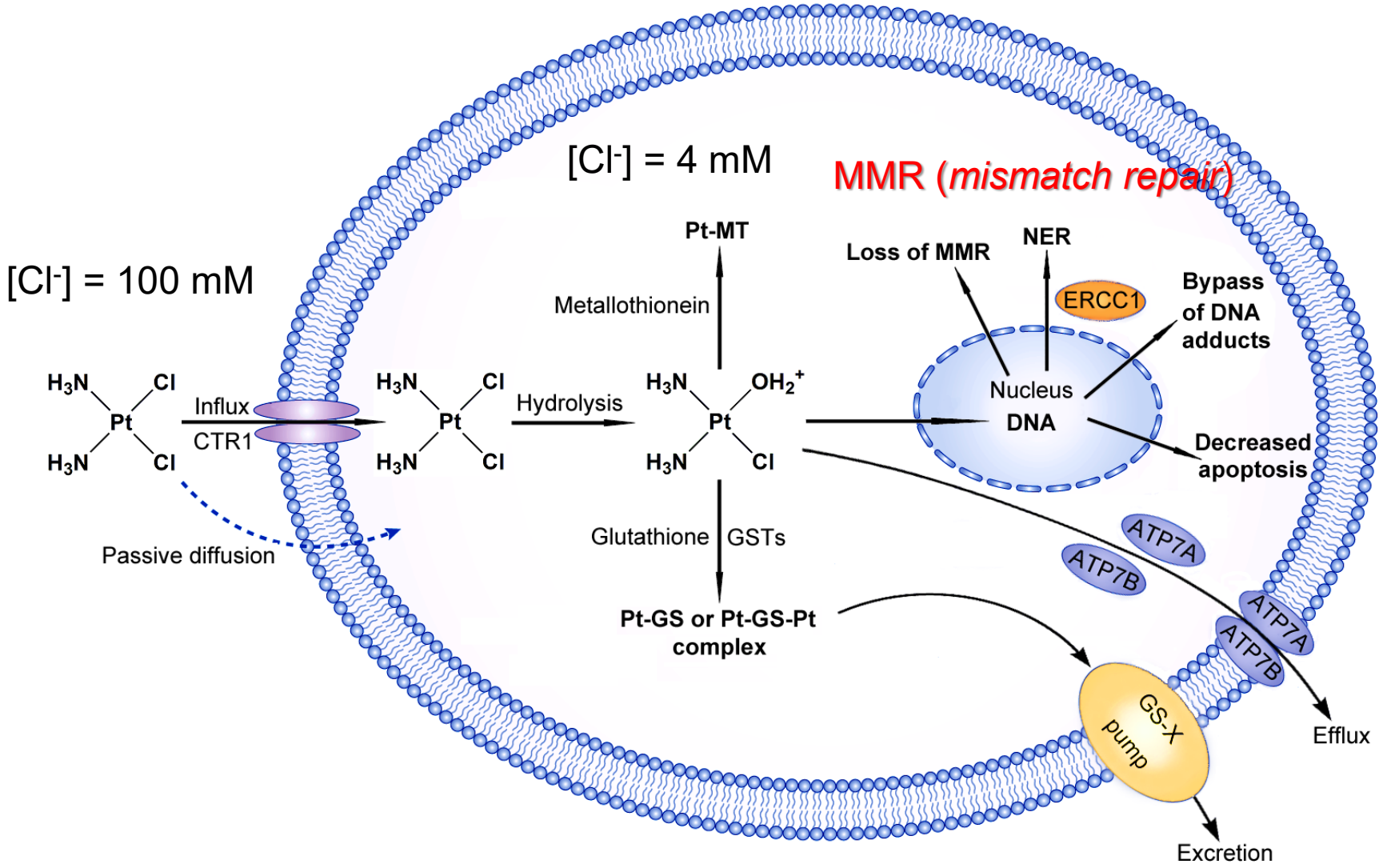
Aspartic proteases

Main mechanisms of resistance

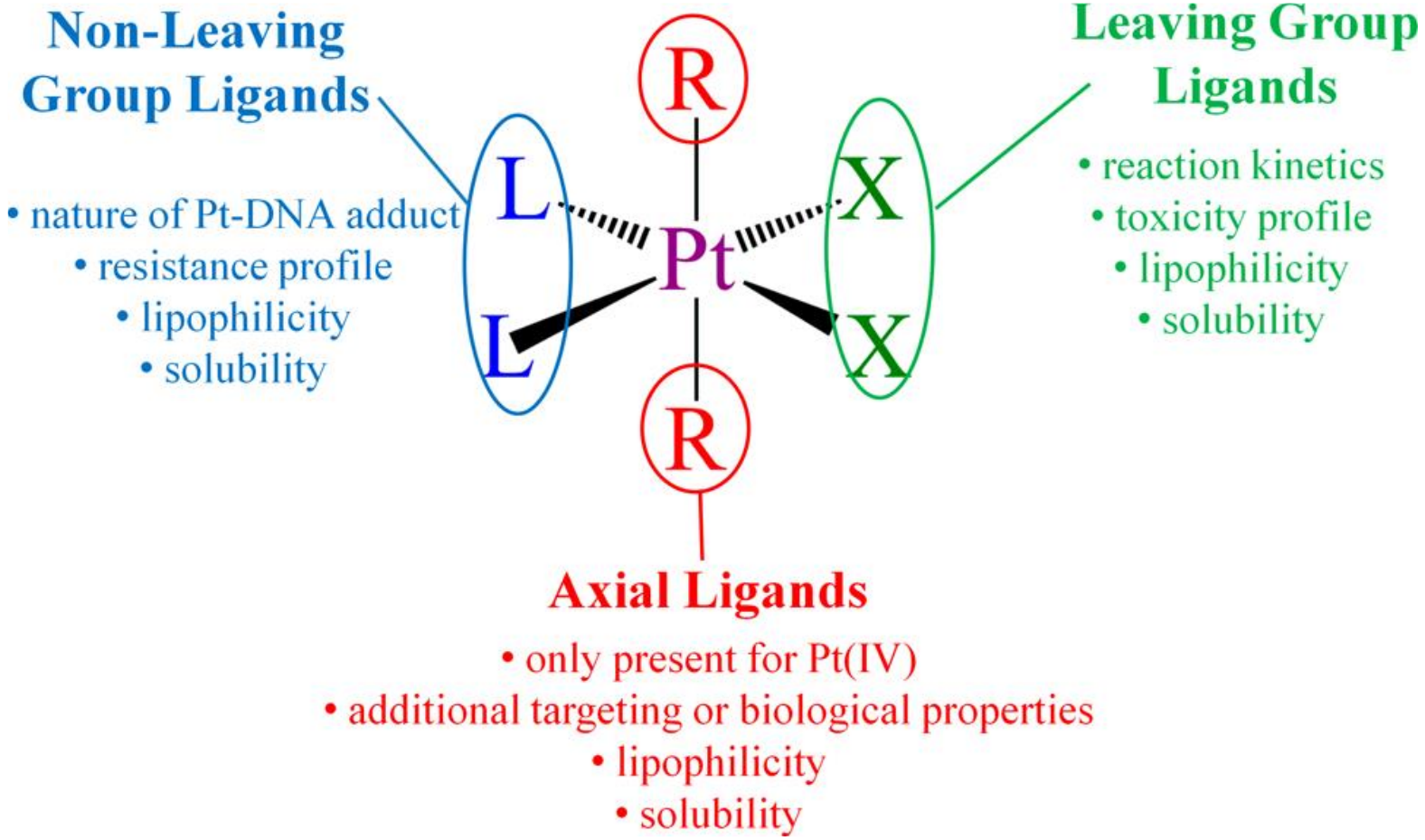
1) decreased level of platinum in the cell;
2) increased level of cellular thiols (glutathione, metallothioneins, and other sulfur-containing molecules);
3) increased DNA repair capacity and/or increased resistance to damage;
4) changes in signal chains leading to cell death (cell-death pathways), or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

NER (*Nucleotides Excision Repair*)

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

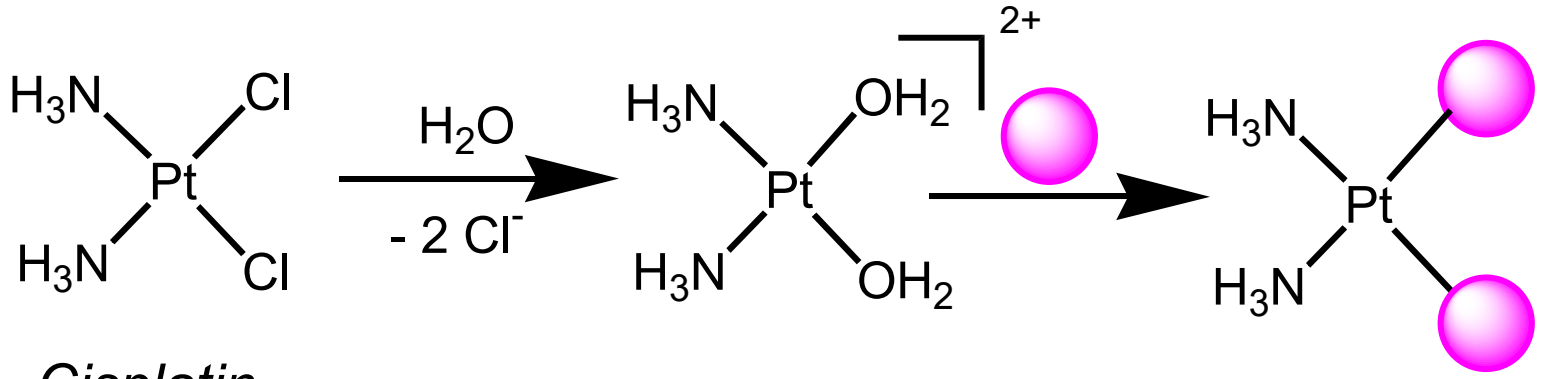


Structure – activity relationships



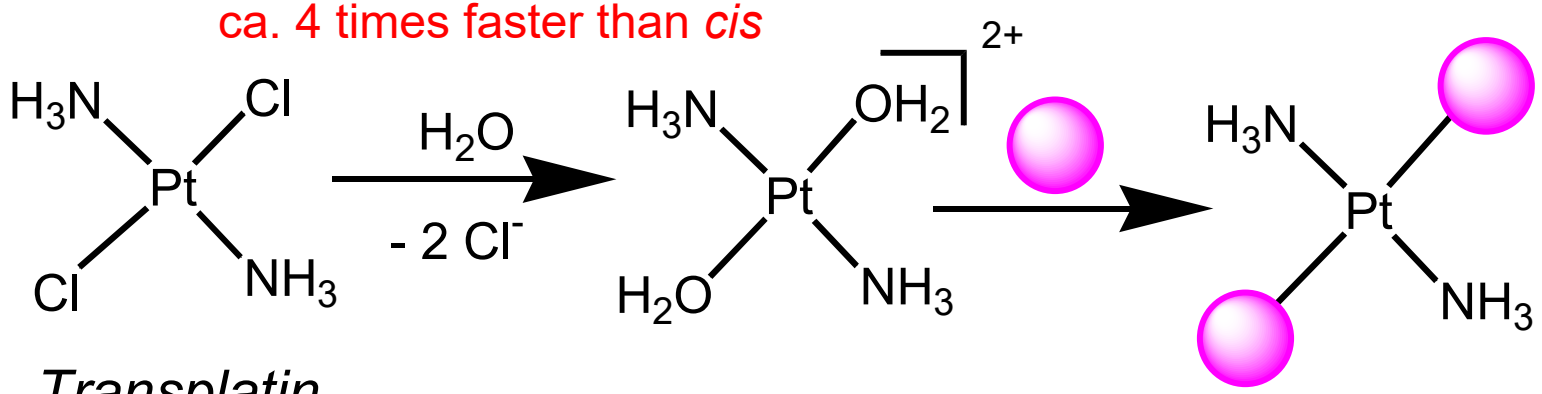
More than 1000 Pt(II) and Pt(IV) compounds screened in vitro for cytotoxic activity

Geometry matters



Cisplatin

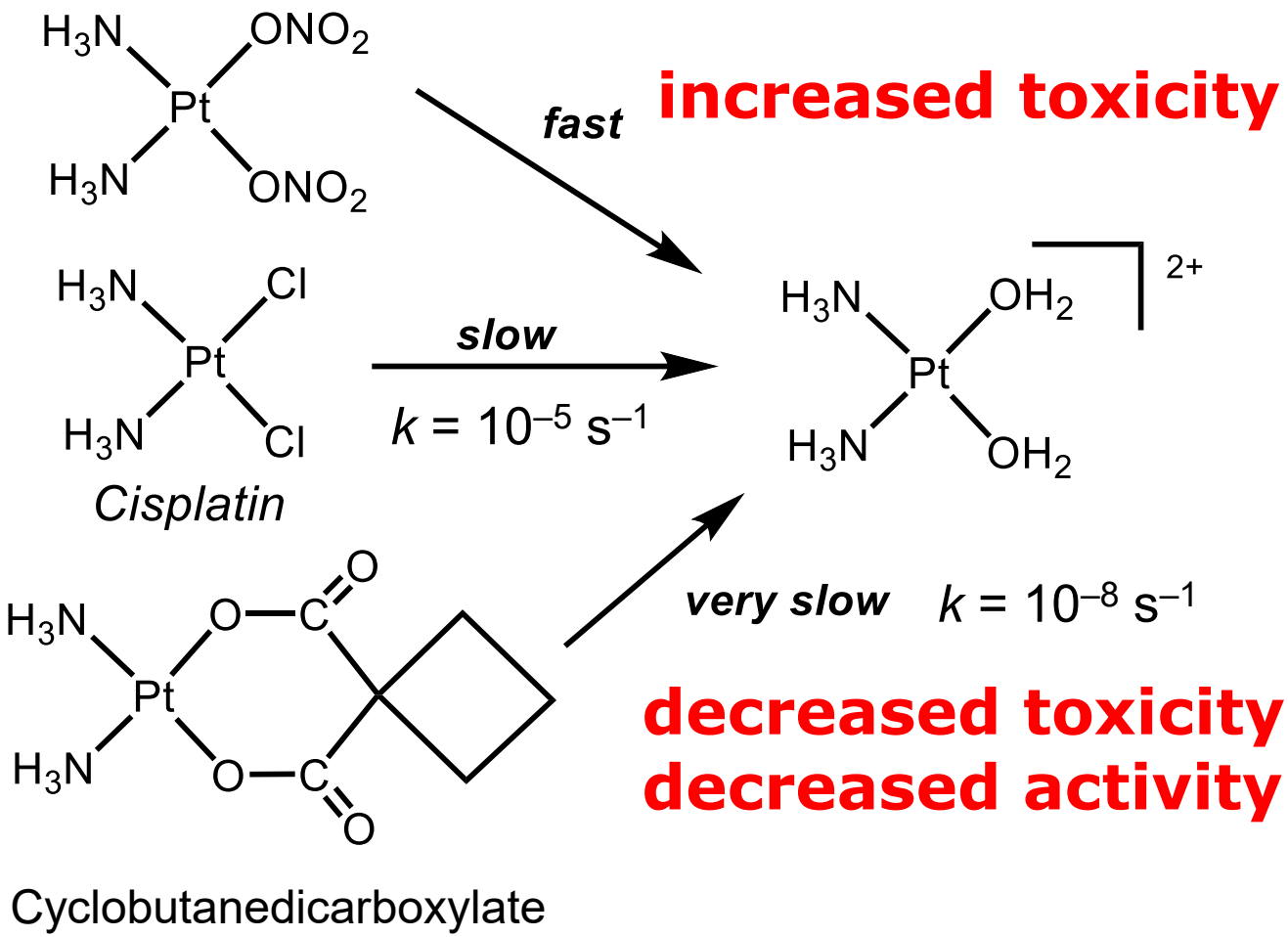
ca. 4 times faster than *cis*



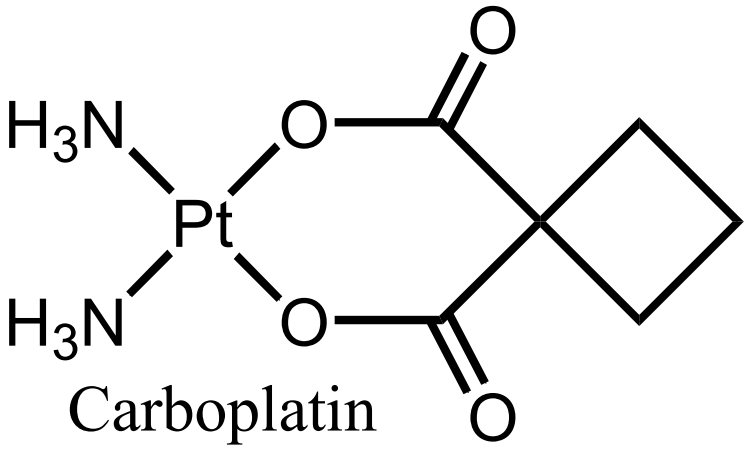
Transplatin

Toxic, but not anticancer active

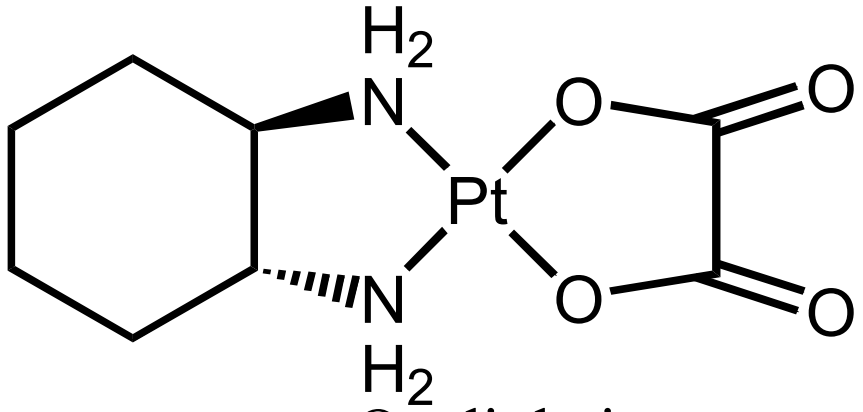
Kinetics matters



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



Carboplatin



Oxaliplatin

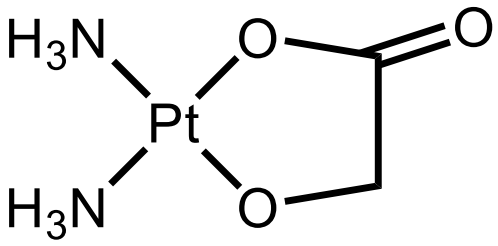
1,1-cyclobutanedicarboxylate

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

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

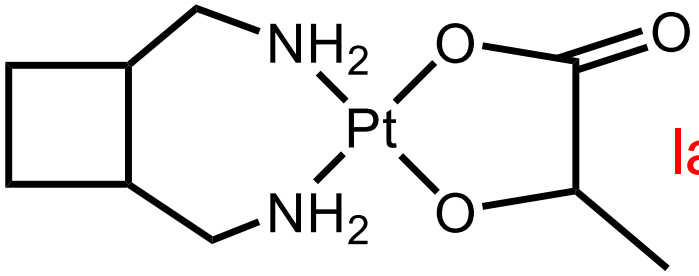
300–450 mg/m^2 vs 20–120 mg/m^2 of cisplatin

2-hydroxyacetate



Nedaplatin (Japan)

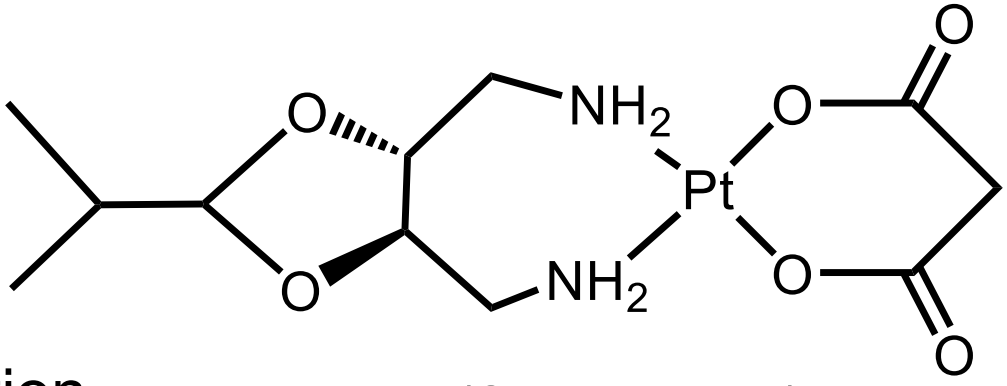
II generation



lactate

Lobaplatin (China)

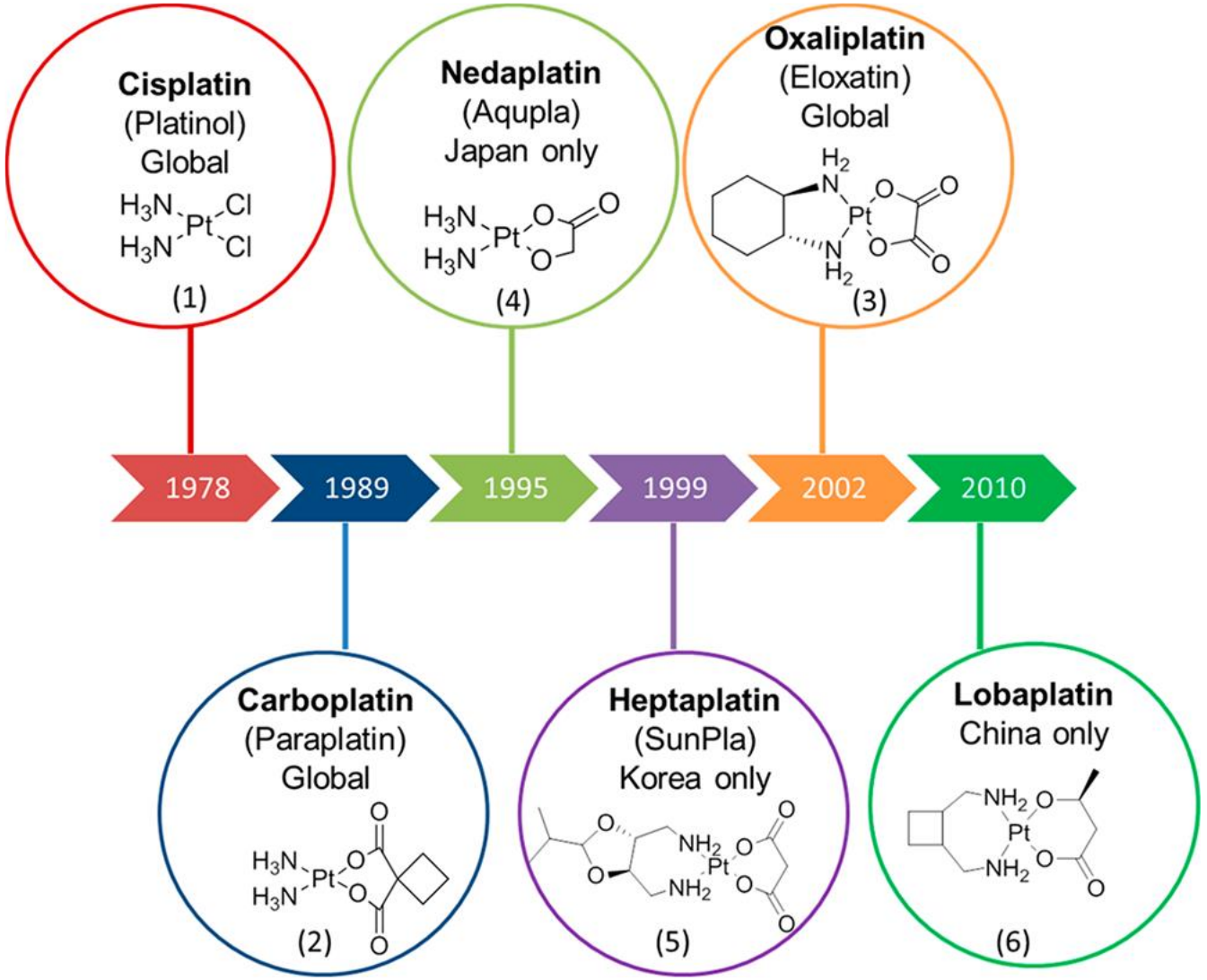
III generation



malonate

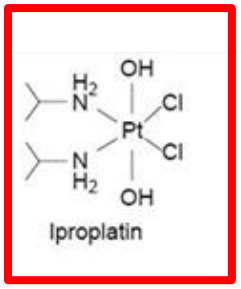
III generation

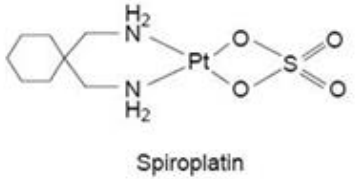
Heptaplatin (South Korea)

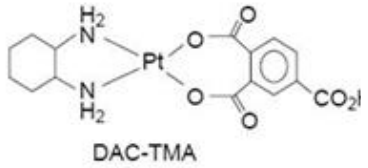

Cisplatin
(Platinol)
Global
(1)
Nedaplatin
(Aqupla)
Japan only
(4)
Oxaliplatin
(Eloxatin)
Global
(3)
1978
1989
1995
1999
2002
2010
Carboplatin
(Paraplatin)
Global
(2)
Heptaplatin
(SunPla)
Korea only
(5)
Lobaplatin
China only
(6)

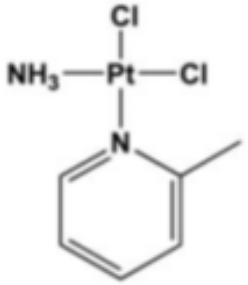
Some of the 23 Pt compounds tested in clinical phase

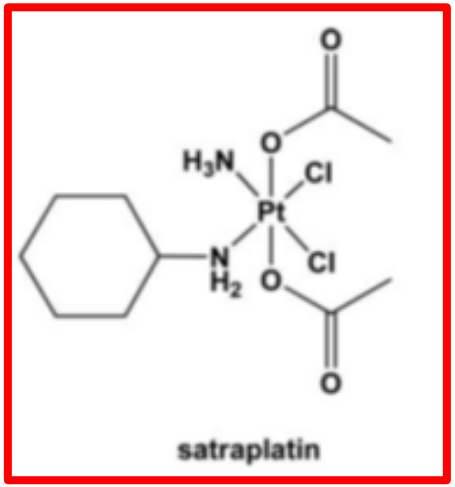
5 phase 1 studies, 22 phase 2 studies, 1 phase 3 study , > 1000 patients

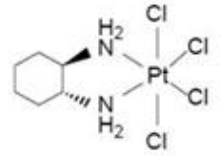


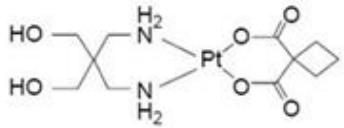


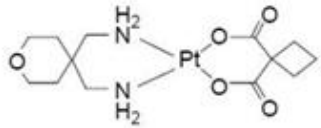


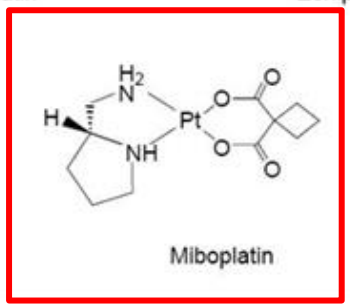


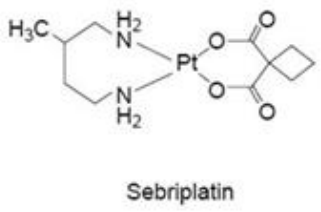








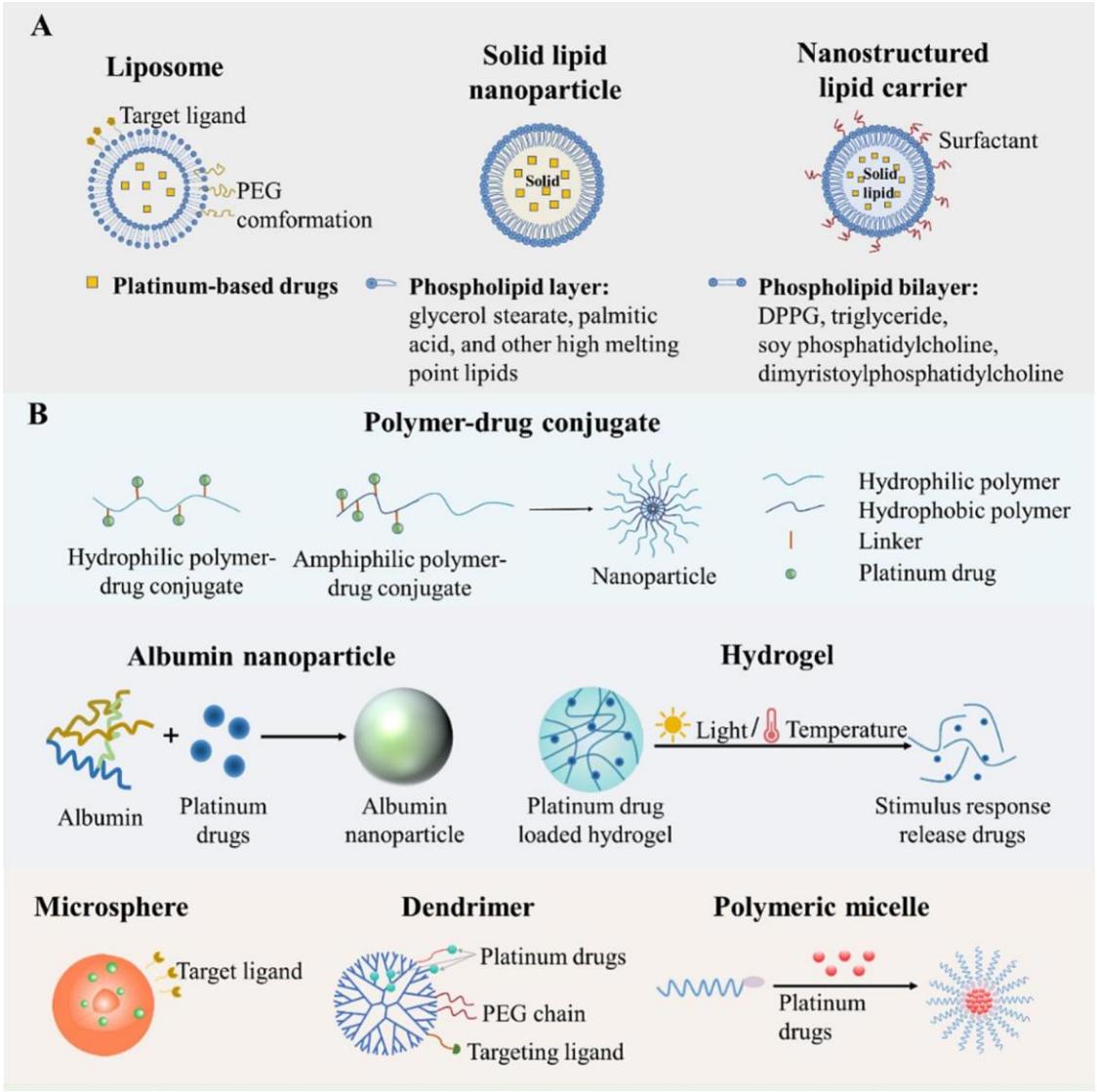




Potentially available for oral administration

= phase 3

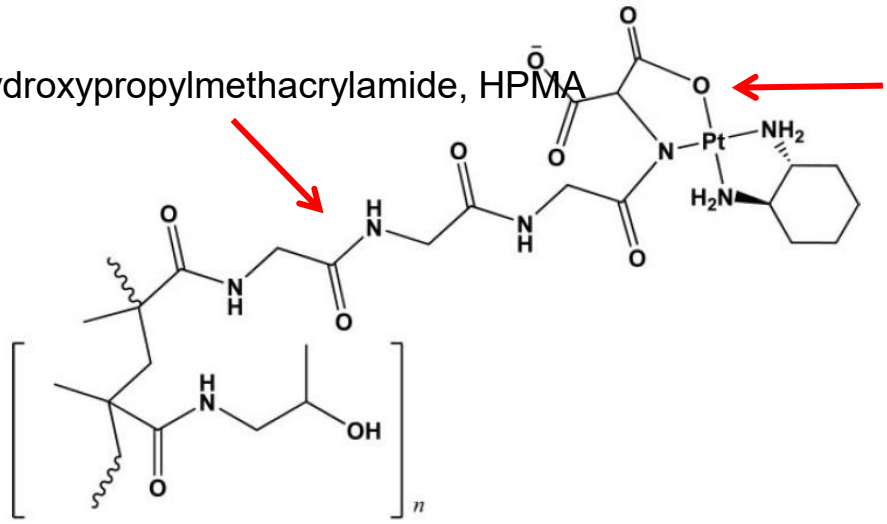
Drug delivery systems for Pt drugs based on lipids or polymers

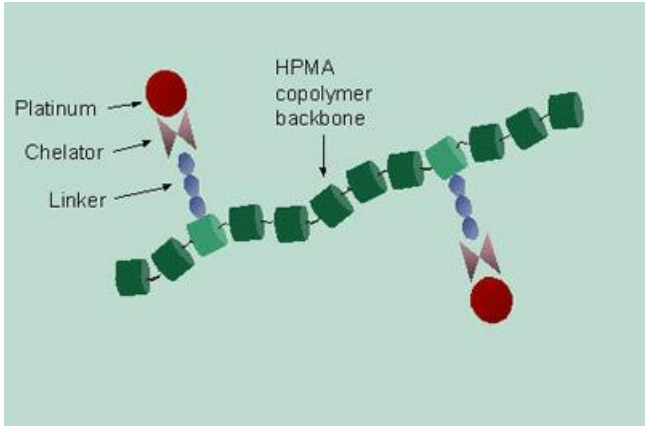


Some Pt formulations in clinical phase: the **nano-carriers** ProLindac™ and Lipoplatin™

hydroxypropylmethacrylamide, HPMA

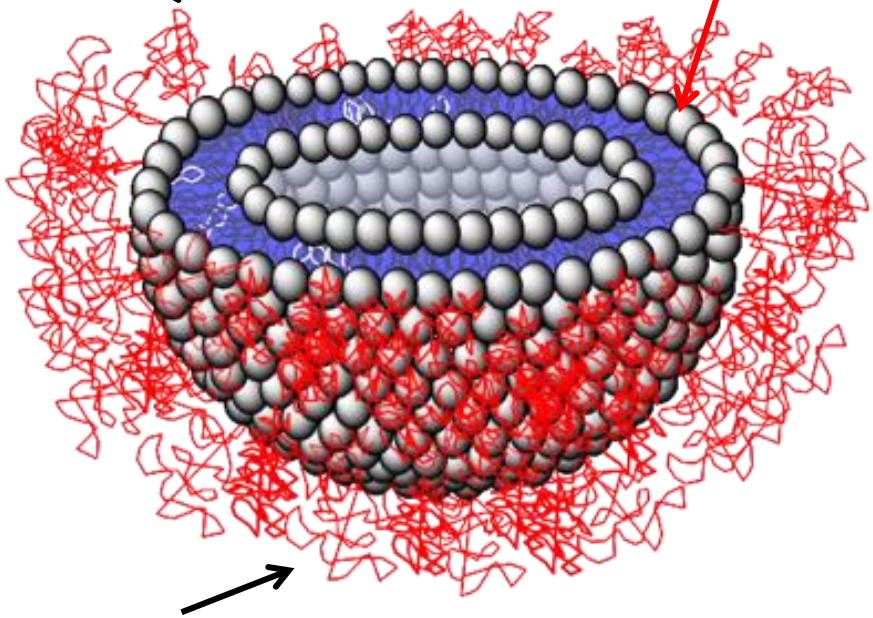
amidomalonate





Lipid double layer:
glycerophospholipids, e.g. dipalmitoyl phosphatidyl glycerol (DPPG)

90 – 130 nm



PEG

inverse micelle

Table 3
Platinum-based DDSs in clinical trials.

Name	Drug	DDSs	Clinical phase	Study Start	Indications	Ref.
Lipoplatin	CDDP	Liposome	Phase III	2009	NSCLC, breast cancer, gastric cancer	[105]
L-NDDP	NDDP	Liposome	Phase II	1998	malignant pleural mesothelioma, colorectal cancer	[86]
SPI-77	CDDP	Liposome	Phase II	1999	NSCLC, ovarian cancer	[106]
LiPlaCis	CDDP	Liposome	Phase I	2005	Advanced Breast Cancer	[100]
Lipoxal	Oxaliplatin	Liposome	Phase I	2003	gastrointestinal cancer	[107]
MBP-426	Oxaliplatin	Liposome	Phase II	2009	gastroesophageal, Gastric, esophageal adenocarcinomas	[108]
NC-4016	DACHPT	Micelle	Phase I	2013	Various solid tumors	[105]
NC-6004	CDDP	Micelle	Phase III	2014	pancreatic cancer	[71]
AP5346	DACHPT	HPMA-Pt conjugate	Phase II	2006	Advanced ovarian cancer	[109]
AP5280	CDDP	HPMA-Pt conjugate	Ended at Phase II	2002	Various solid tumors	[110]

2025 review

Summary

- 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:

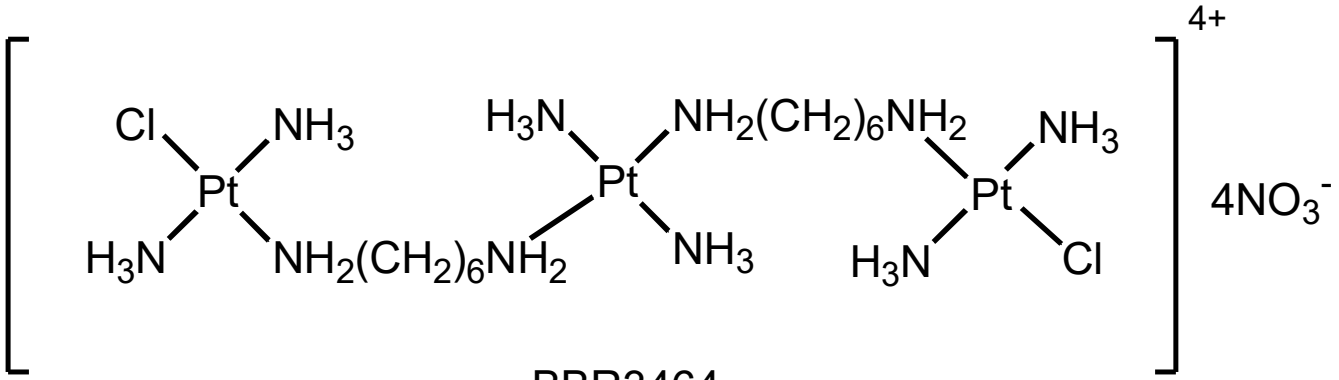
1. on the nature of the metal center (*thermodynamic and kinetic parameters, hard-soft nature, oxidation state*)
2. on the nature of the non-leaving ligands (*lipophylicity, charge, solubility, non-covalent interactions*…);
3. on the kinetics of activation (*e.g. aquation rate*)

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)



BBR3464

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.

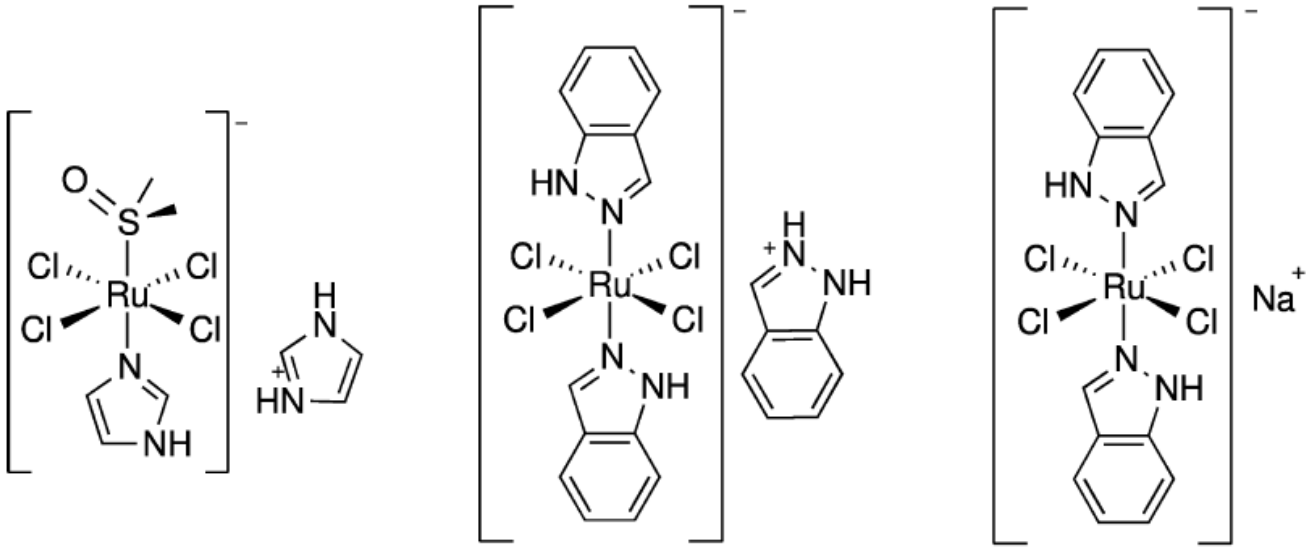
2. to show a lower (or at least different) toxicity compared to Pt drugs.

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

Trieste, 1999 (phase I) and 2008 (phase II)

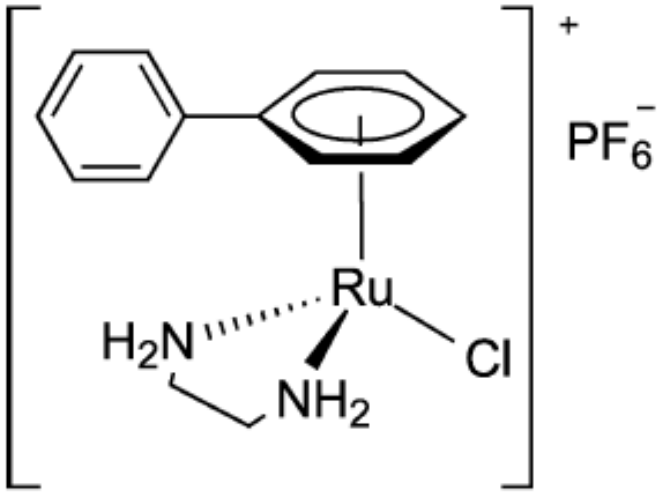
KP1019

Wien, 2001 and 2012 (phase I)

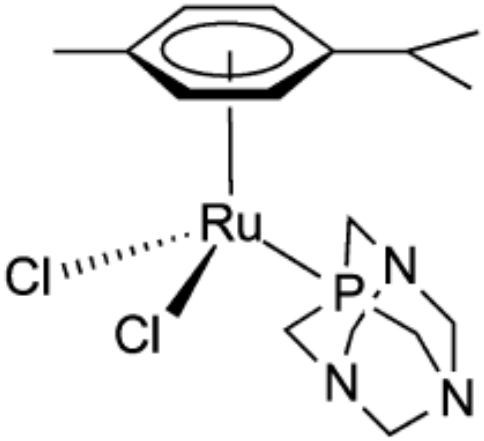
(N)KP1339

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

Anticancer organometallic Ru(II) compounds

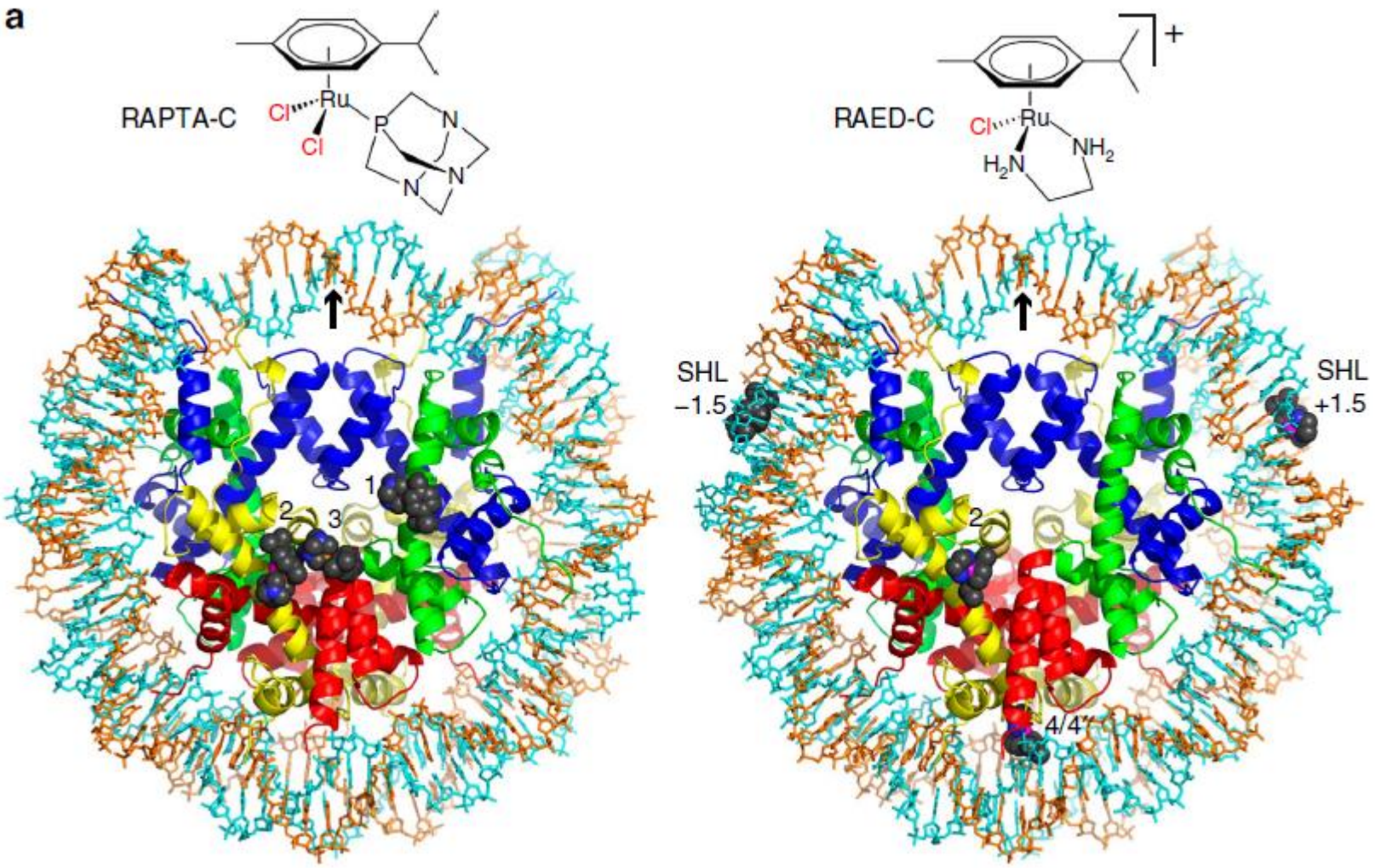


RM175

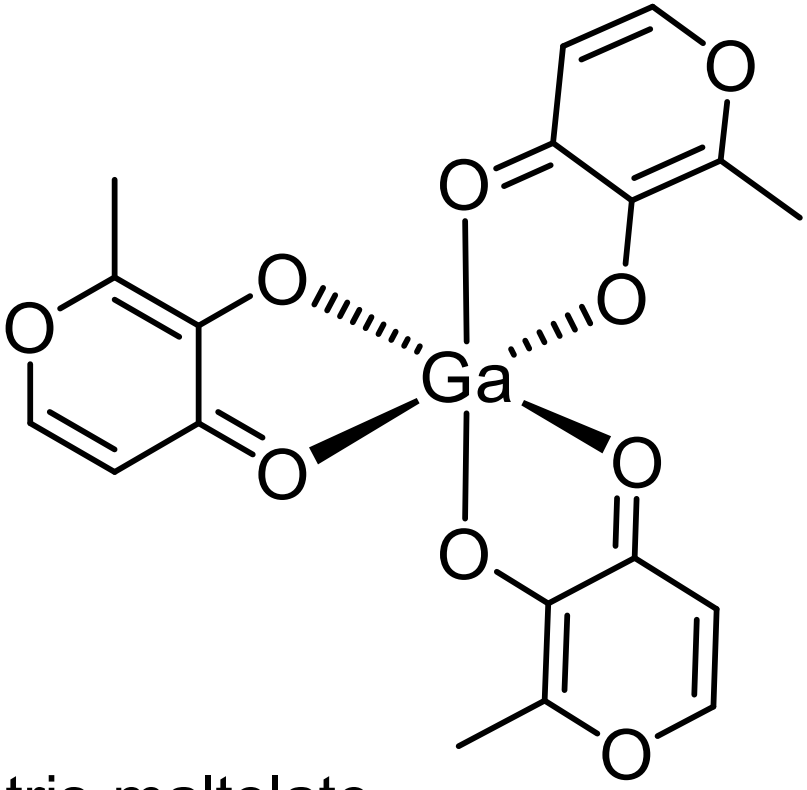


RAPTA-C

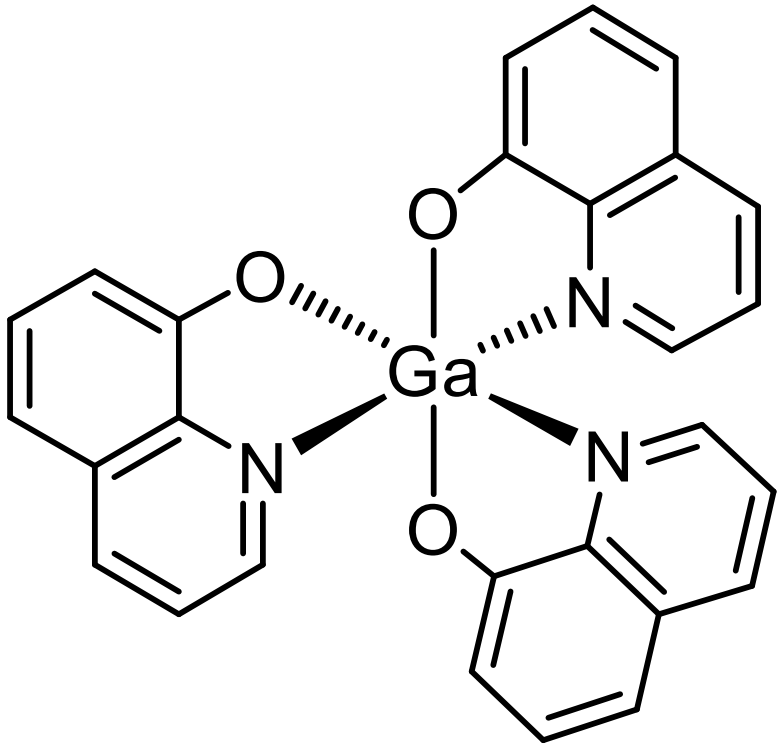
Different interactions of half-sandwich Ru(II) compounds with chromatin



Gallium anticancer compounds



tris-maltolate

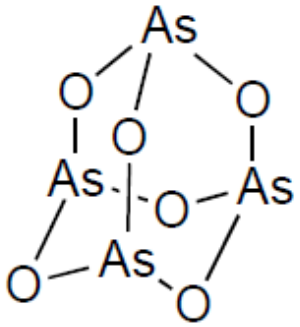


tris(8-hydroxyquinolinate)

oral administration, 2009 (phase I)

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

Arsenic anticancer compounds



ATO

0.15 mg/kg

LD_{50} = 50 mg/kg

FDA approval in 2000

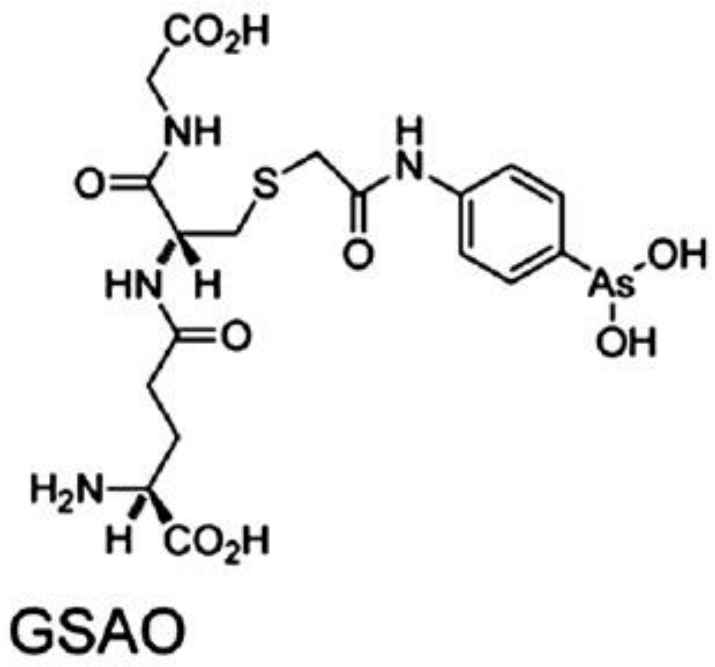
acute promyelocytic leukemia

ATO/ATRA therapy

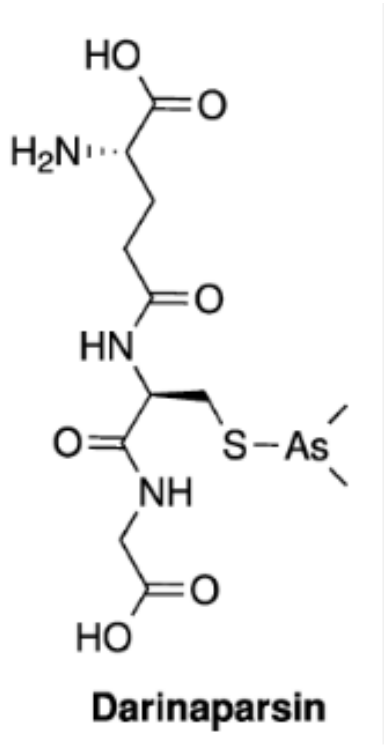
(ATRA = all-trans retinoic acid)

- Degradation of mutant protein PML-RARα that blocks myeloid differentiation
- Inhibition of anti-ROS S/Se-enzymes (glutathione reductase, glutathione peroxidase (Se), thioredoxin reductase (Se), and thioredoxin peroxidase)
- Inhibits histone methylation and thus signal transduction (epigenetic activity)

Potential organo-arsenic anticancer compounds



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



S-dimethylarsinoglutathione