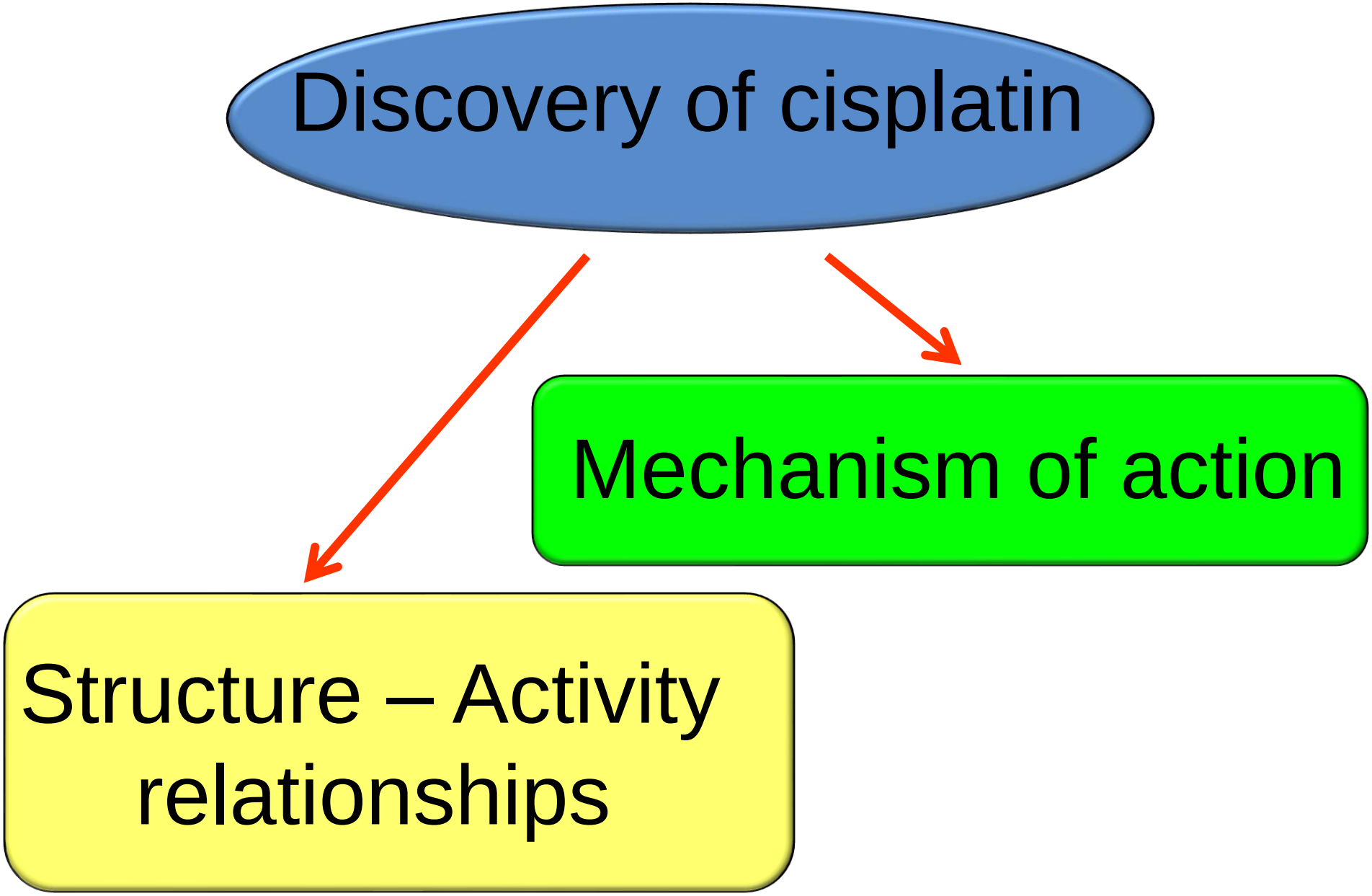
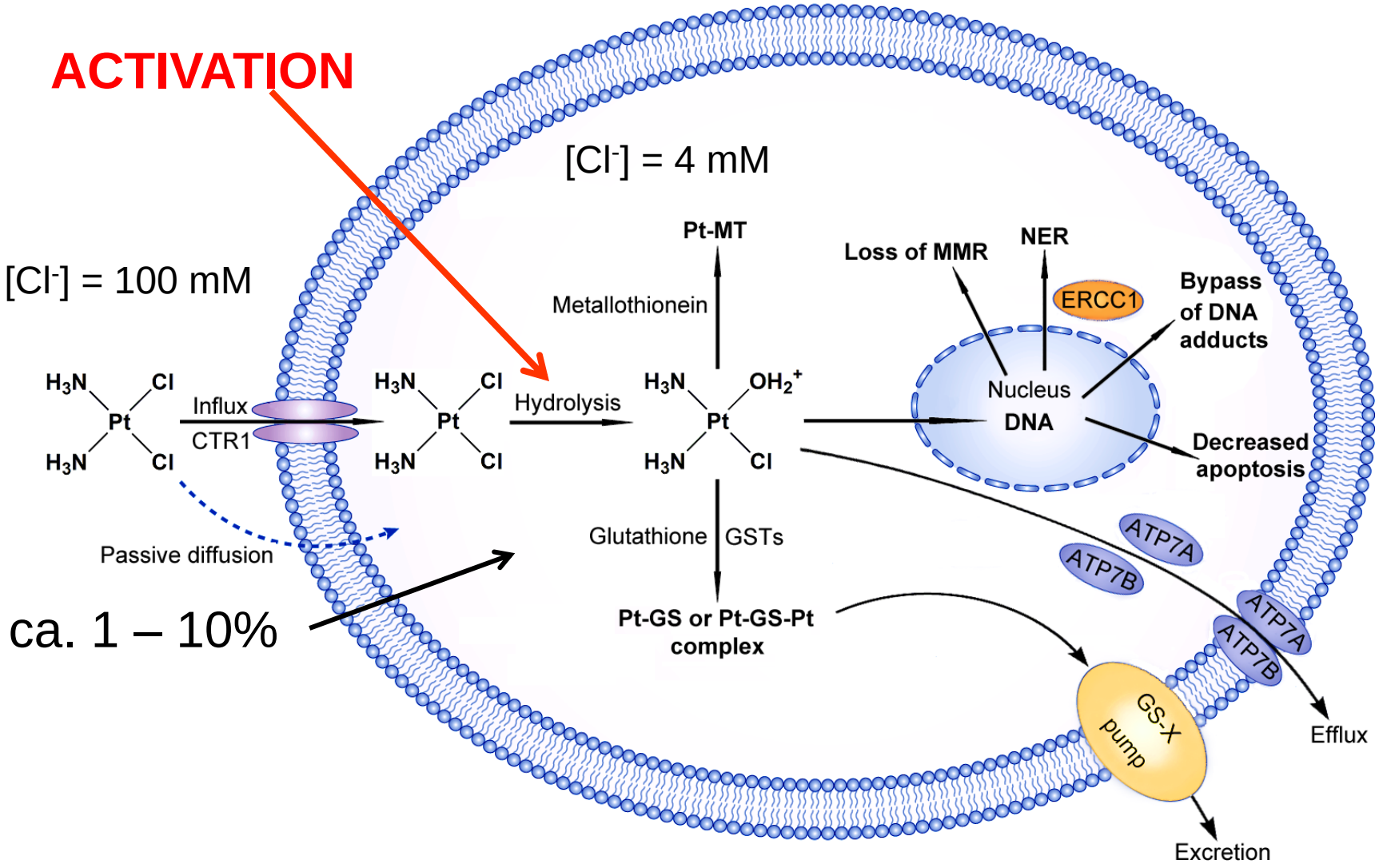
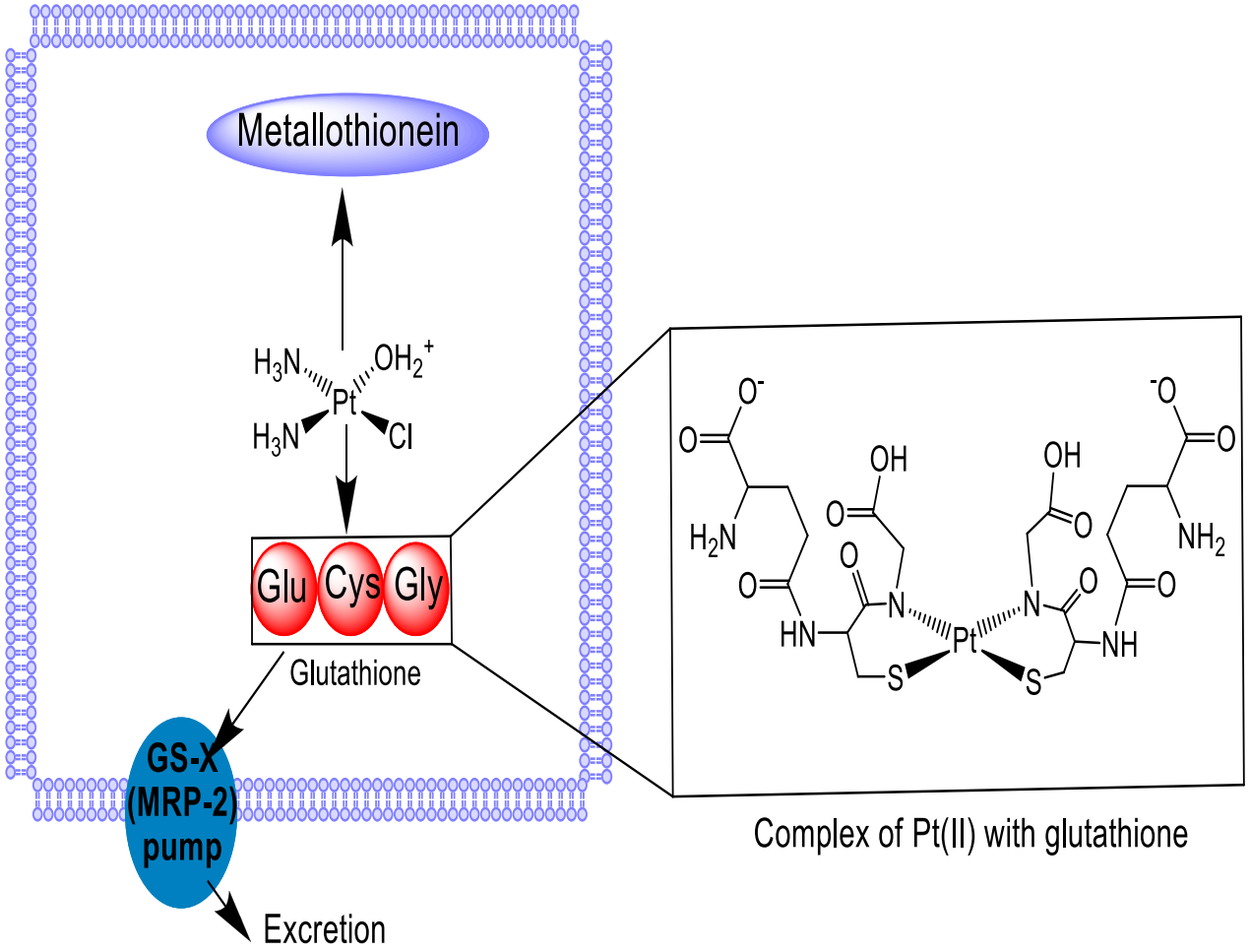
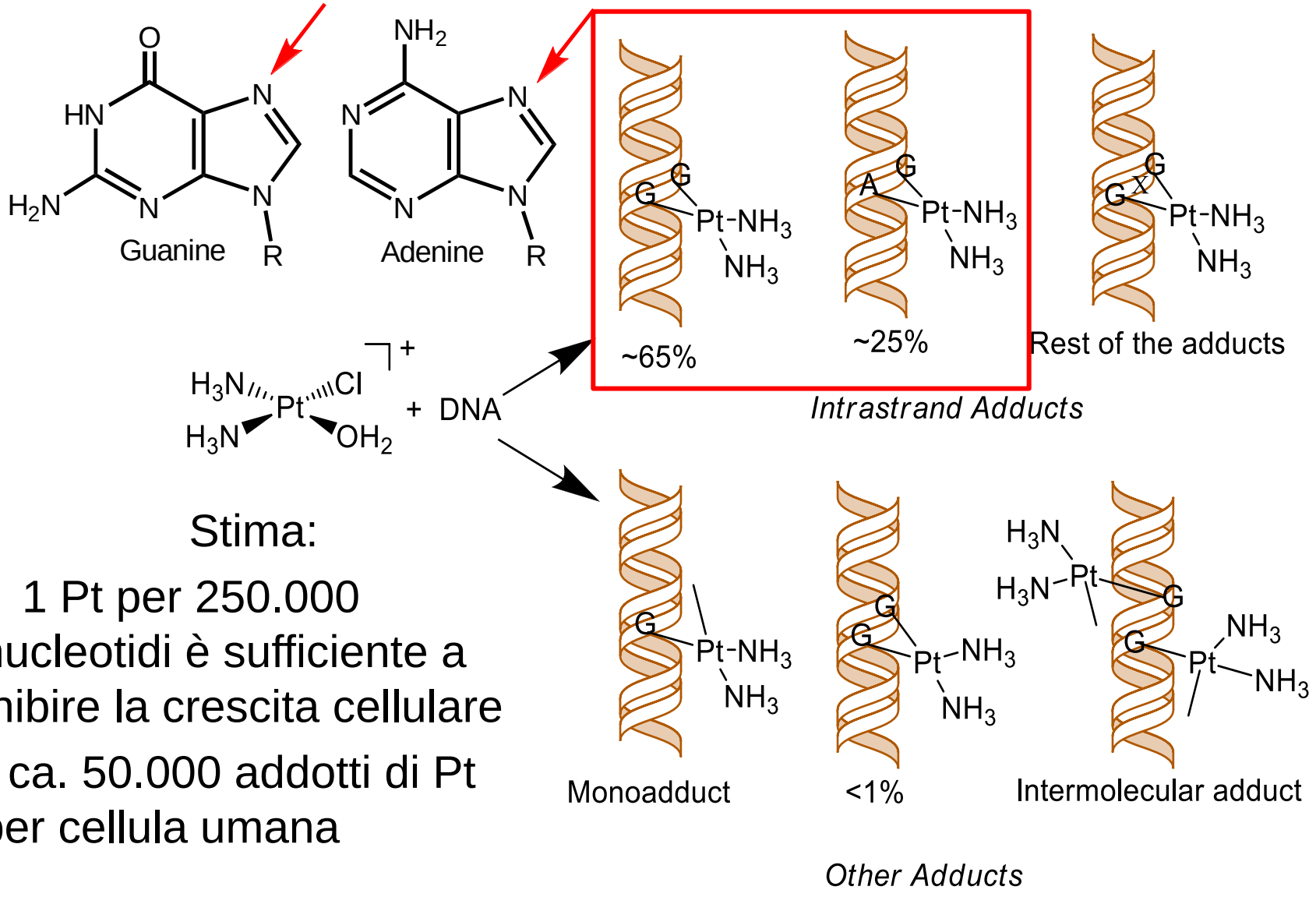

Discovery of cisplatin
Mechanism of action
Structure – Activity relationships


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

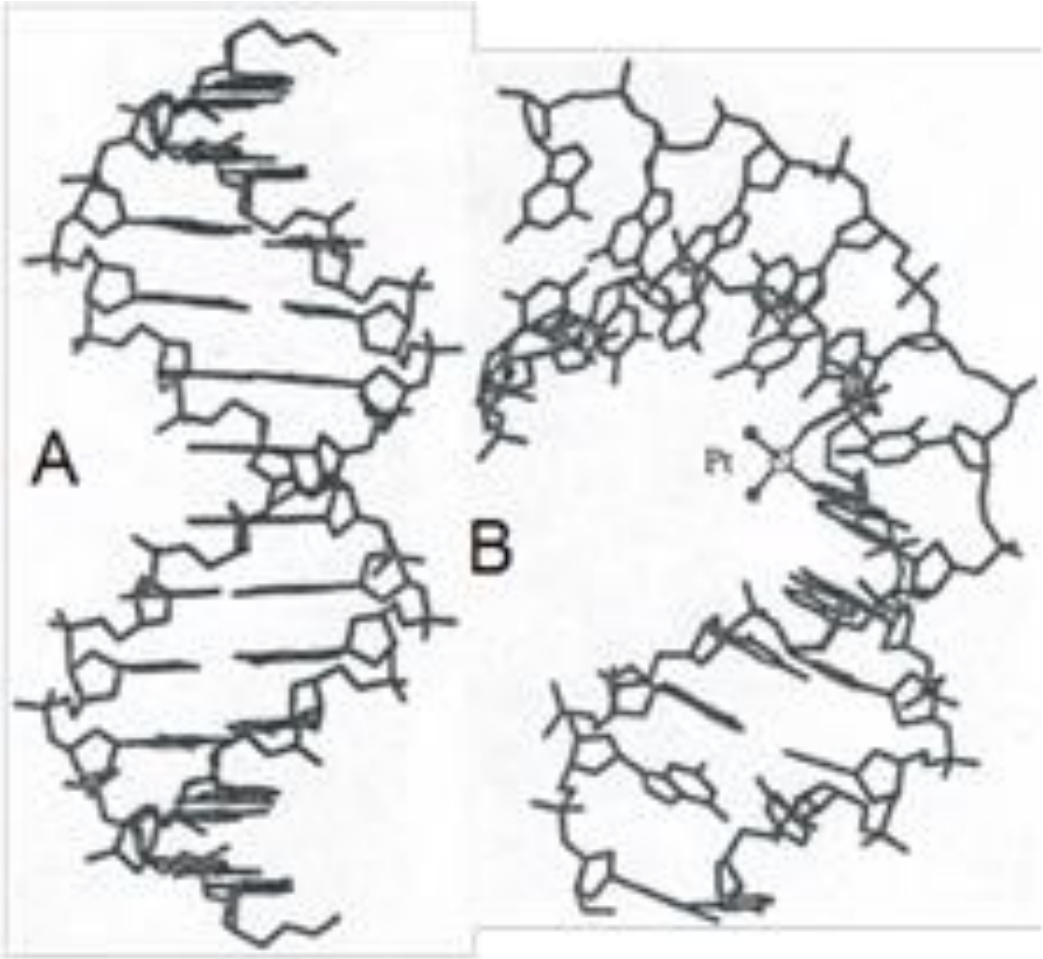

Metallothionein
H3N
OH2+
Pt
H3N
Cl
Glu
Cys
Gly
Glutathione
GS-X
(MRP-2)
pump
Excretion
O-
O
H2N
O
HN
OH
O
O
N
Pt
S
N
OH
O
O
S
O
NH
-O
O
NH2
O
Complex of Pt(II) with glutathione

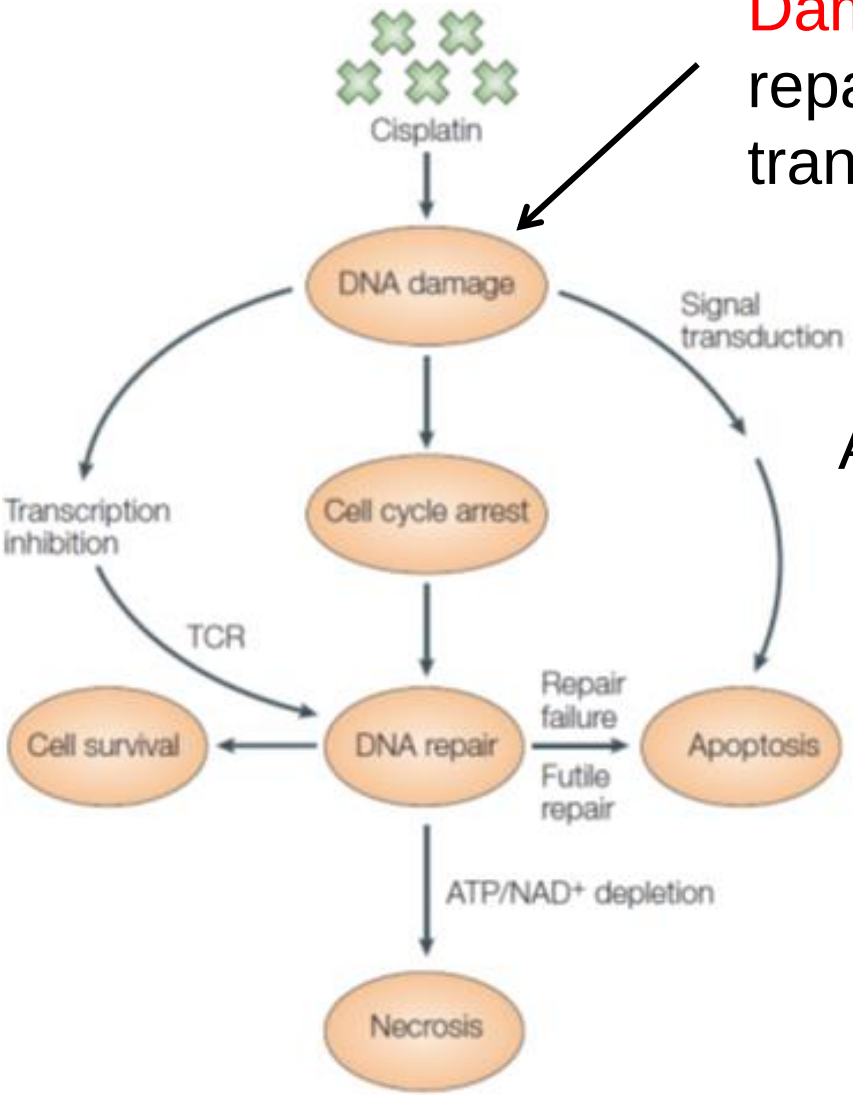


Stima:

- 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*) verso il *major groove* e uno svolgimento (*unwinding*) locale del DNA

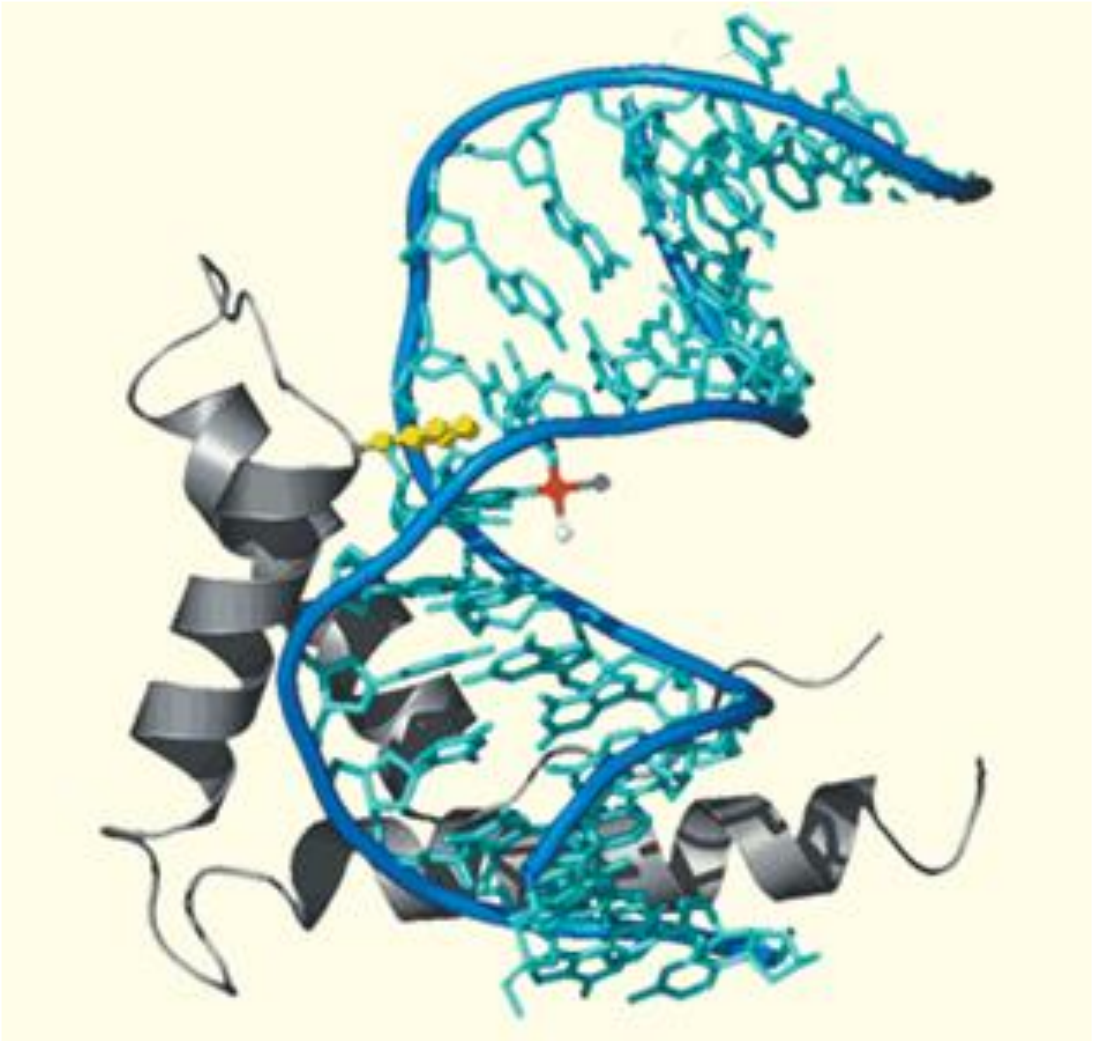




Damage-response proteins: DNA repair system, HMG proteins, transcription factors…

Aspartic proteases

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

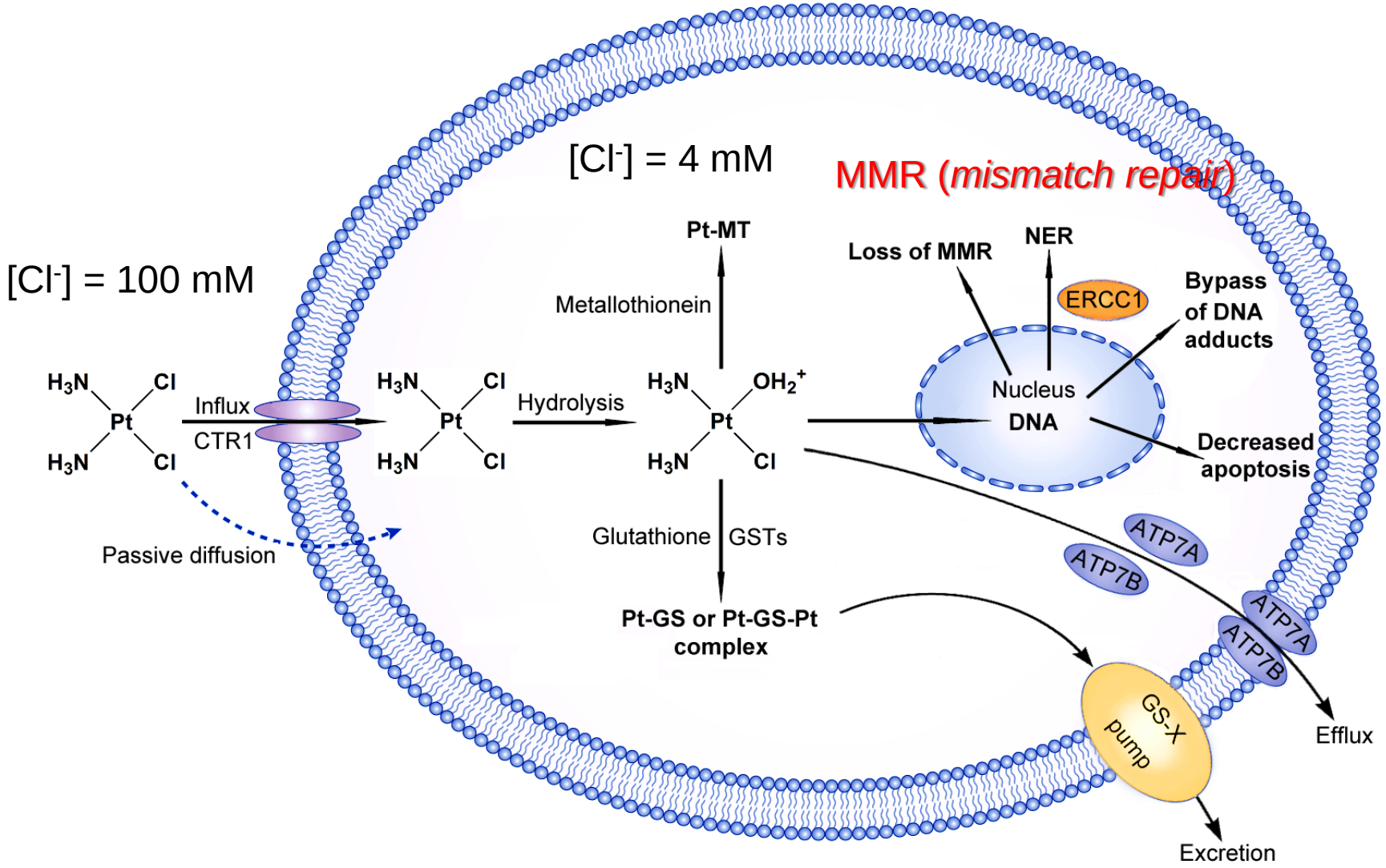


Principali meccanismi di resistenza

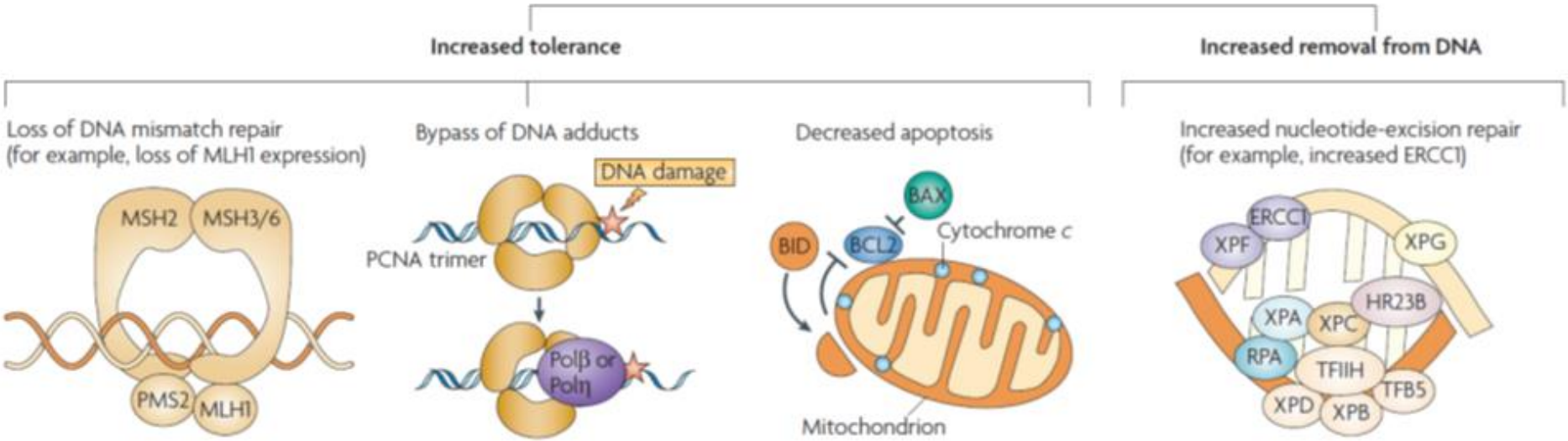
1) diminuzione del livello di platino nella cellula;
2) aumento del livello di tioli cellulari (glutatione, metallotioneine e altre molecole contenenti zolfo);
3) aumento della capacità di riparo del DNA e/o aumento della resistenza al danno;
4) cambiamenti nelle catene di segnali che portano alla morte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

NER (*Nucleotides Excision Repair*)

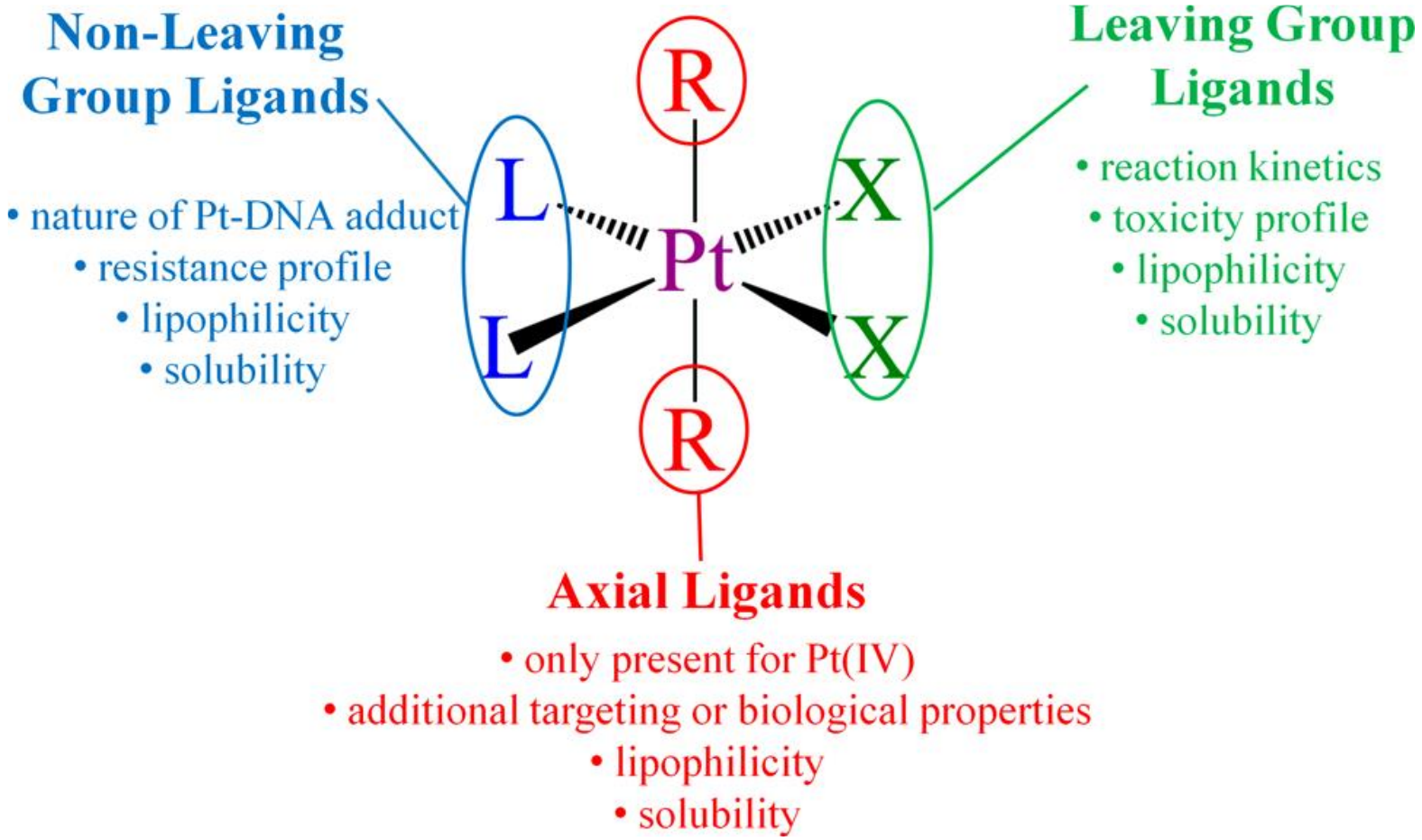
ERCC1 (*excision repair cross-complementing-1*)



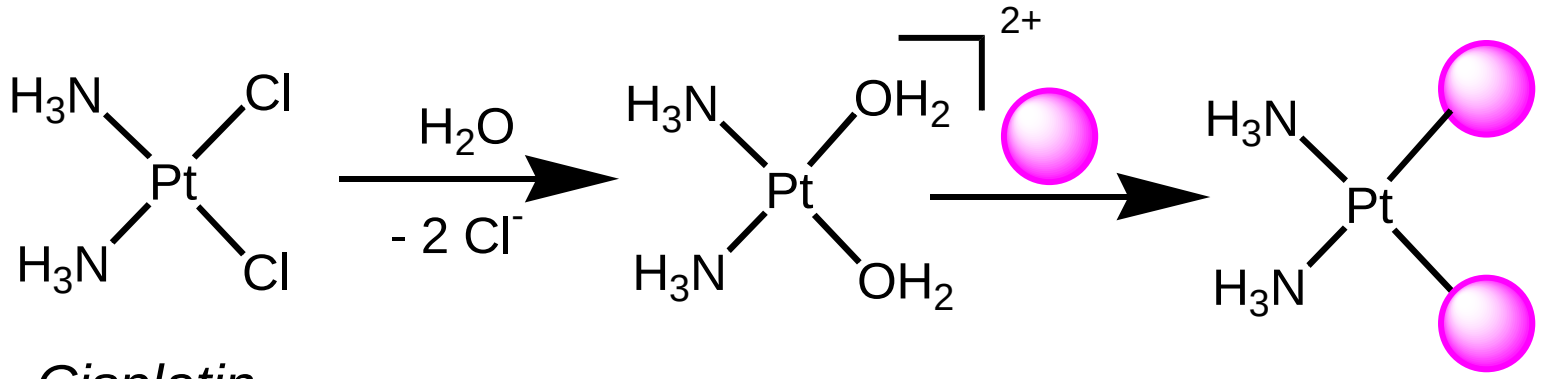
Meccanismi di resistenza



Correlazione struttura – attività

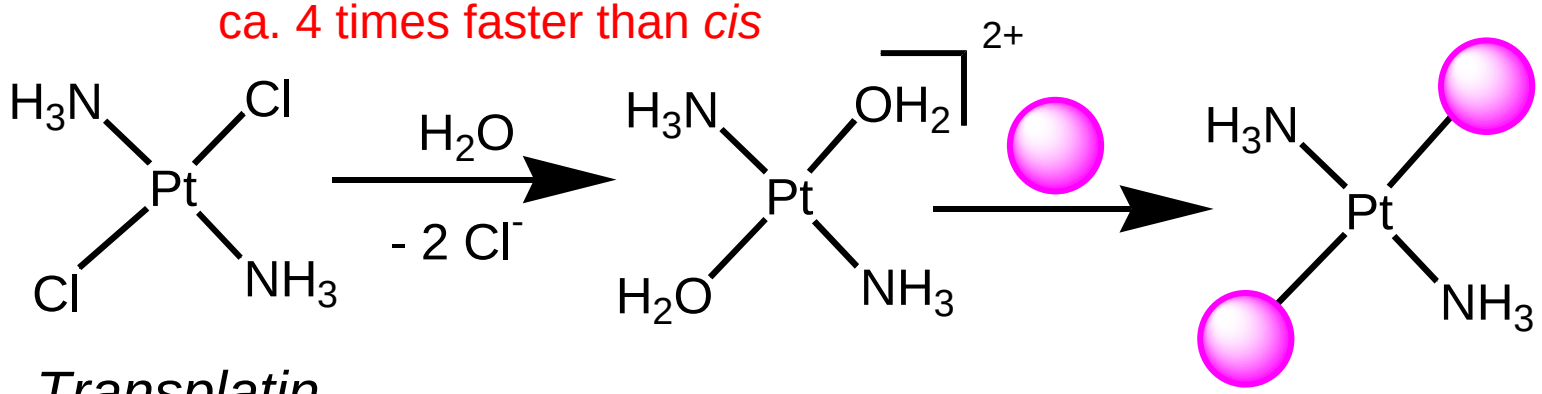


La geometria conta!



Cisplatin

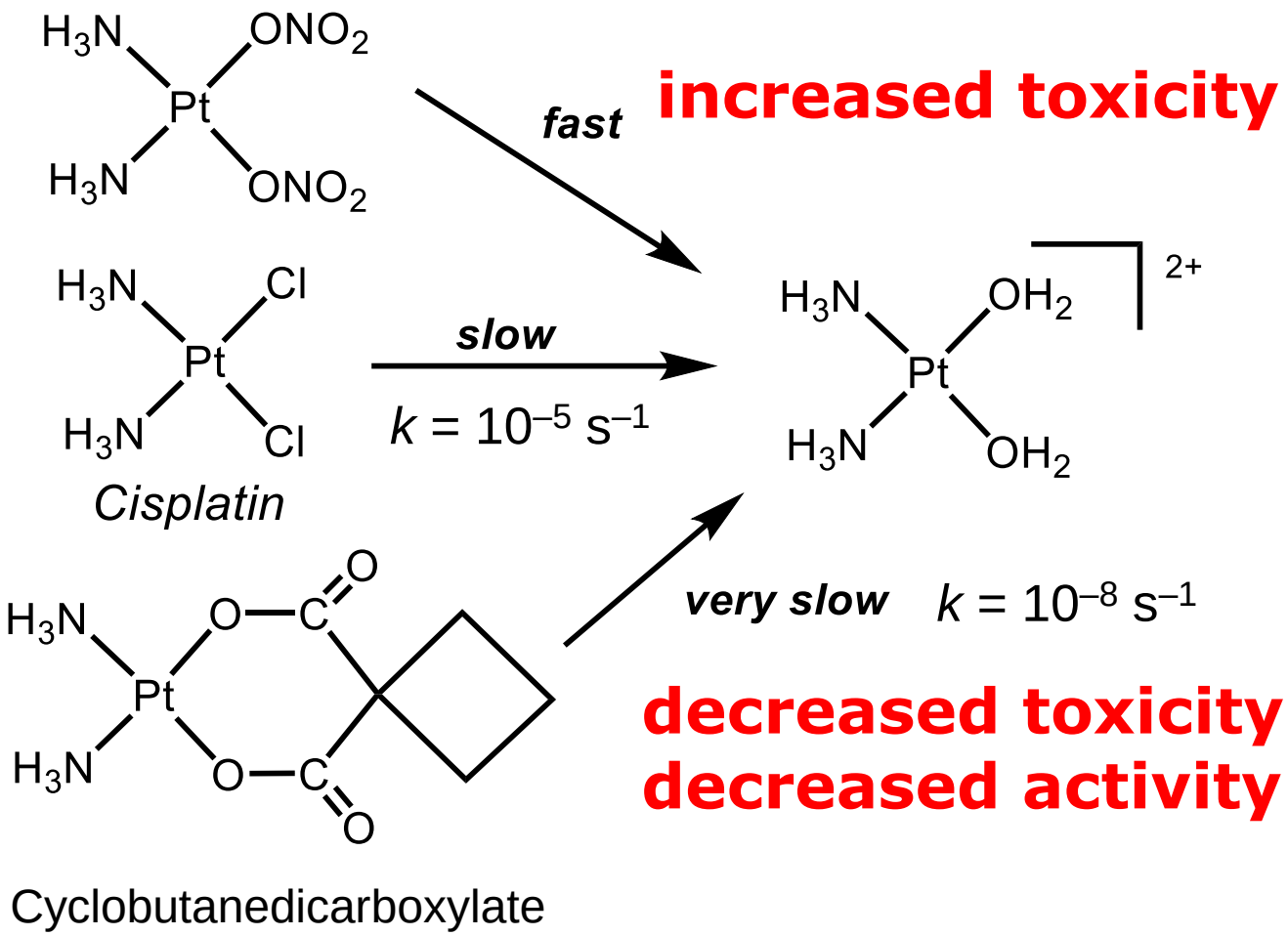
ca. 4 times faster than *cis*



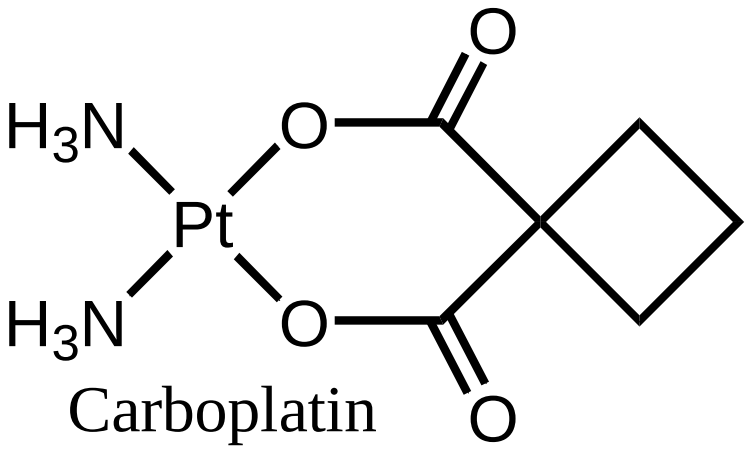
Transplatin

Toxic, but not anticancer active

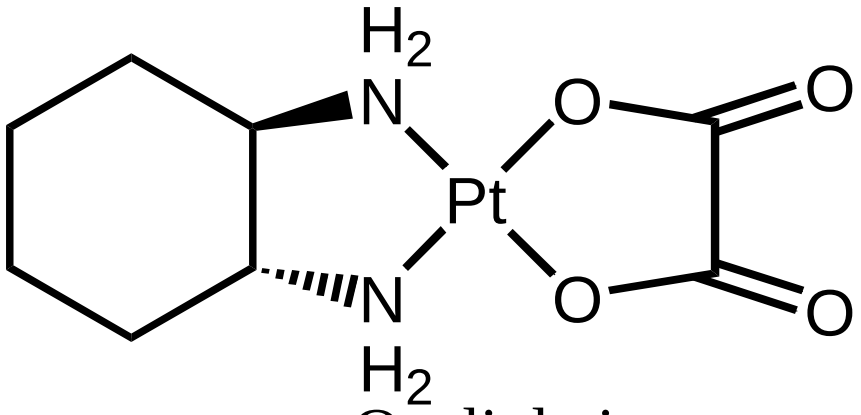
La cinetica conta!



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



Carboplatin



Oxaliplatin

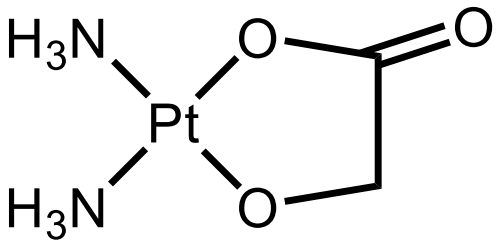
1,1-cyclobutanedicarboxylate

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

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

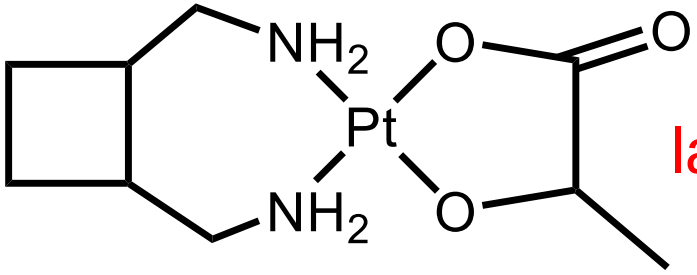
300–450 mg/m^2 vs 20–120 mg/m^2 of cisplatin

2-hydroxyacetate



Nedaplatin (Japan)

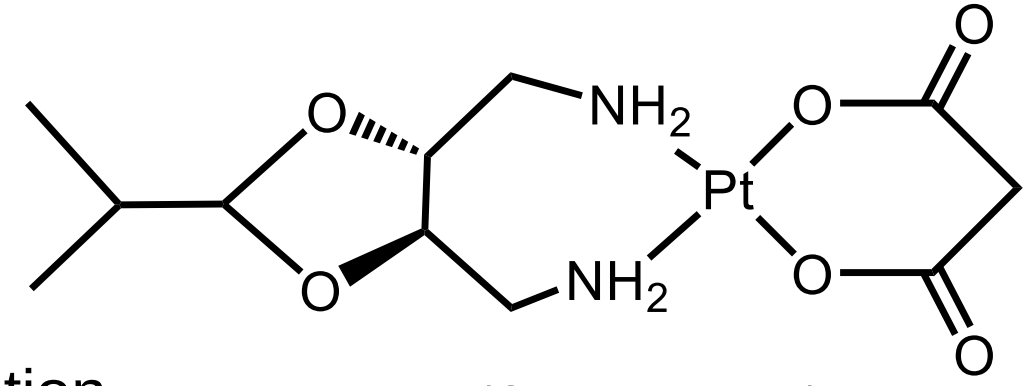
II generation



lactate

Lobaplatin (China)

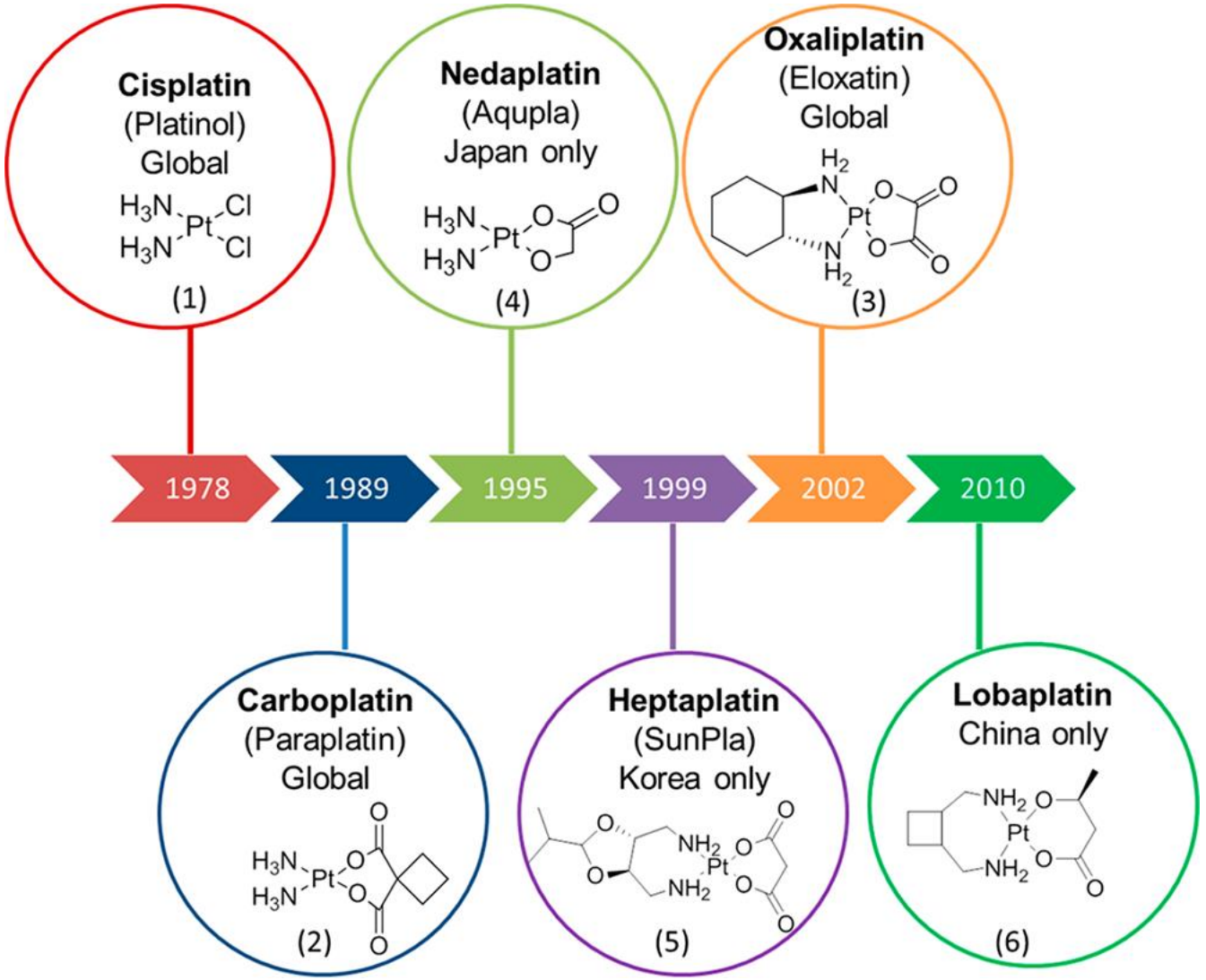
III generation



malonate

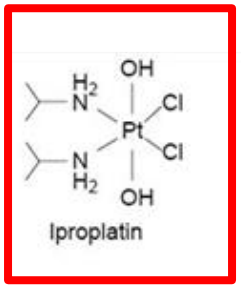
III generation

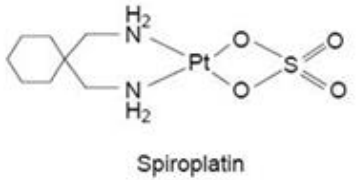
Heptaplatin (South Korea)

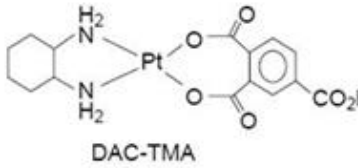

Cisplatin
(Platinol)
Global
(1)
Nedaplatin
(Aqupla)
Japan only
(4)
Oxaliplatin
(Eloxatin)
Global
(3)
1978
1989
1995
1999
2002
2010
Carboplatin
(Paraplatin)
Global
(2)
Heptaplatin
(SunPla)
Korea only
(5)
Lobaplatin
China only
(6)

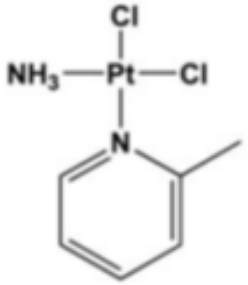
Alcuni dei 23 composti di Pt testati in fase clinica

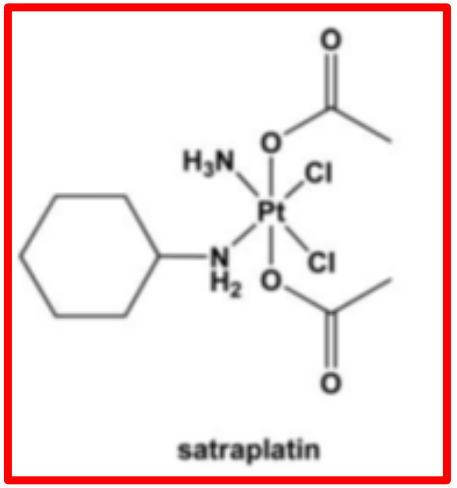
cinque studi di fase 1, ventidue di fase 2, uno di fase 3, > 1000 pazienti

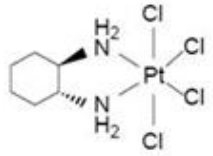


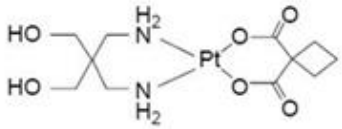


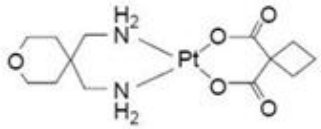


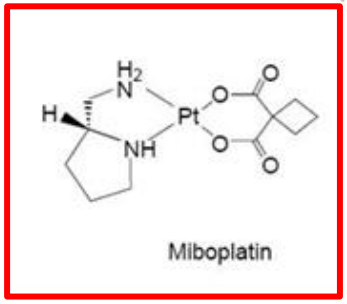


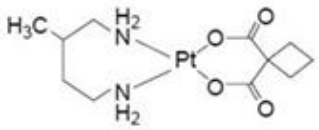


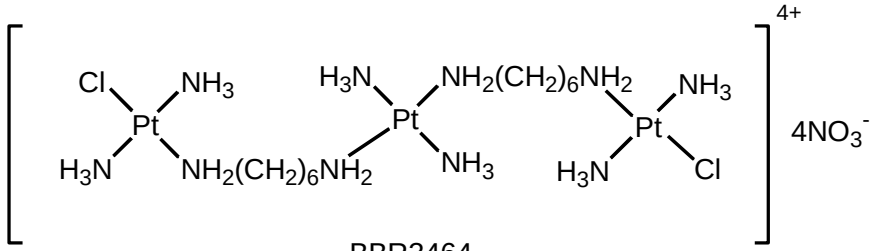










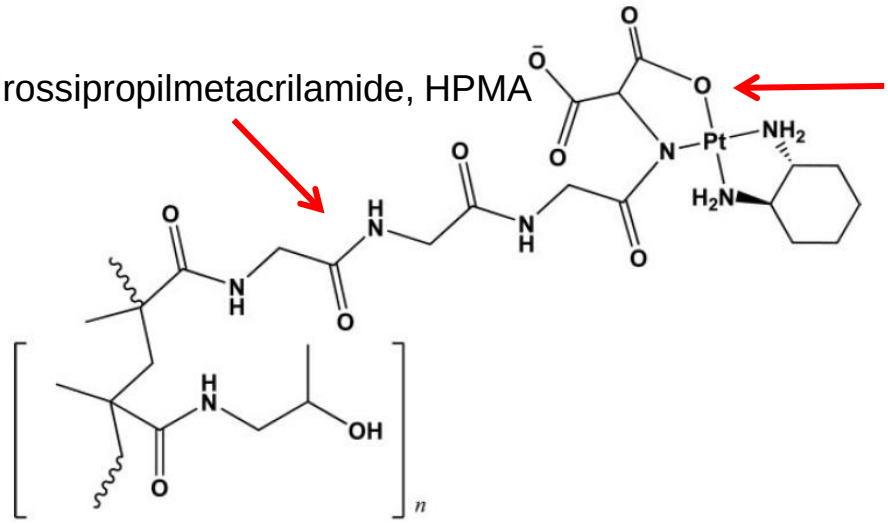


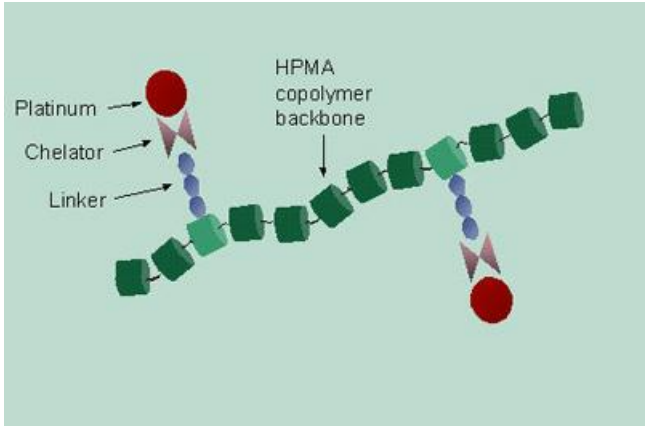
= fase 3

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

idrossipropilmetacrilamide, HPMA

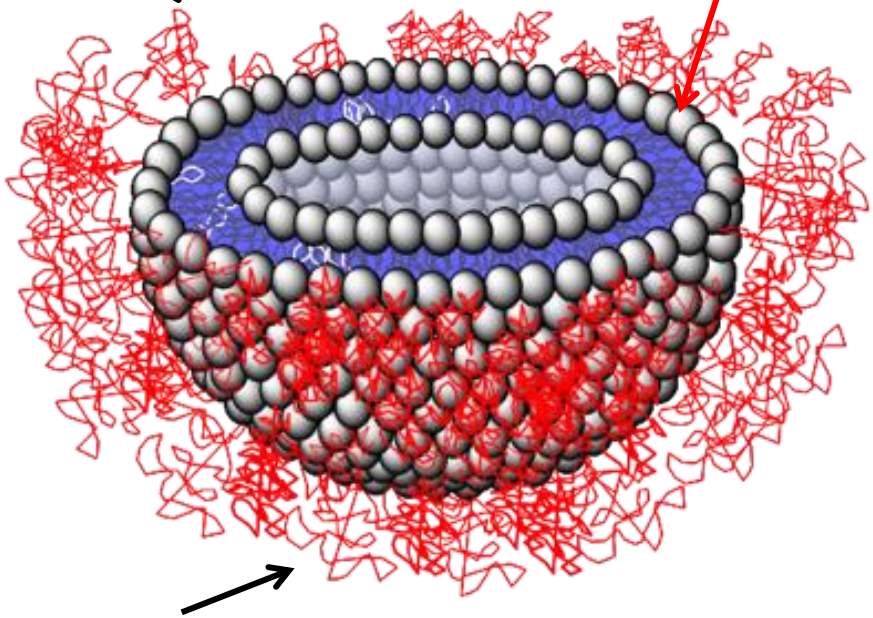
amidomalonato





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.

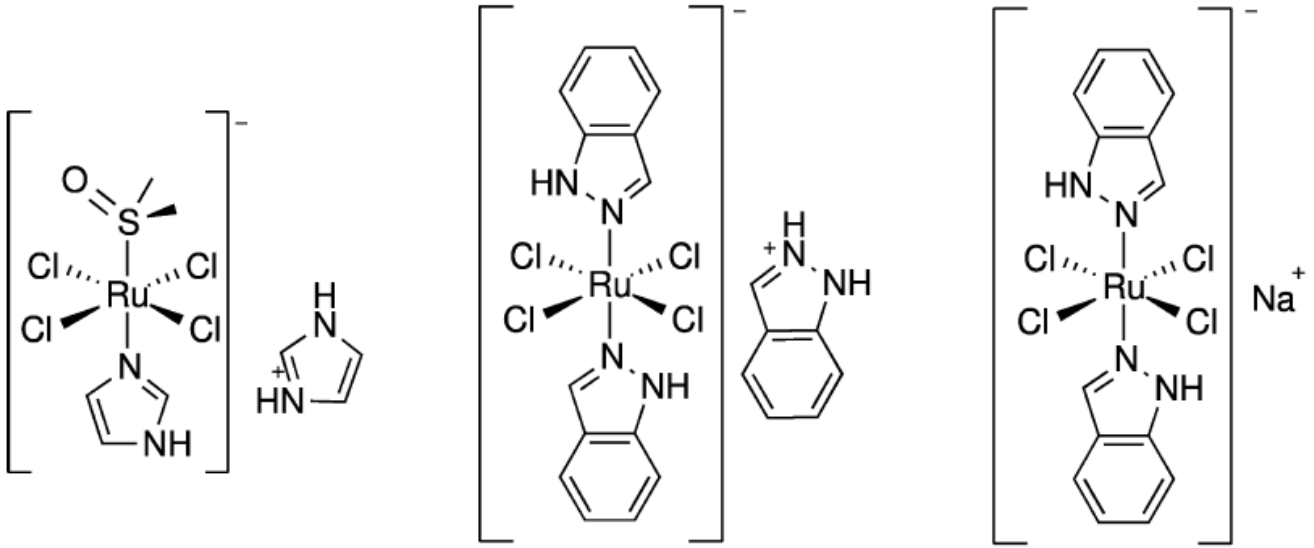
2. to show a lower (or at least different) toxicity compared to Pt drugs.

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)

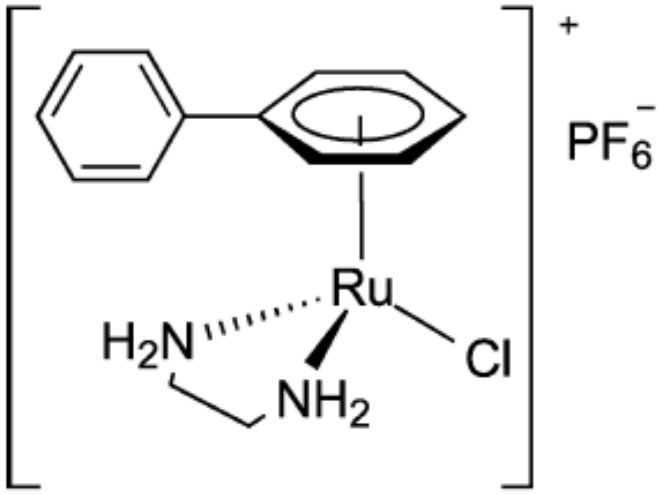
Clinically tested anticancer Ru(III) compounds

Deceptively similar

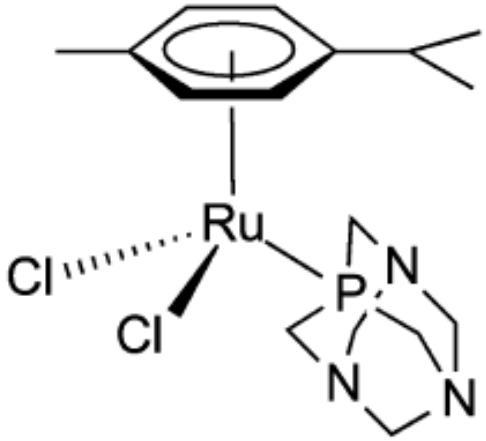


Both NAMI-A and KP1019 are prodrugs; they are activated through hydrolysis, possibly after reduction to Ru(II).

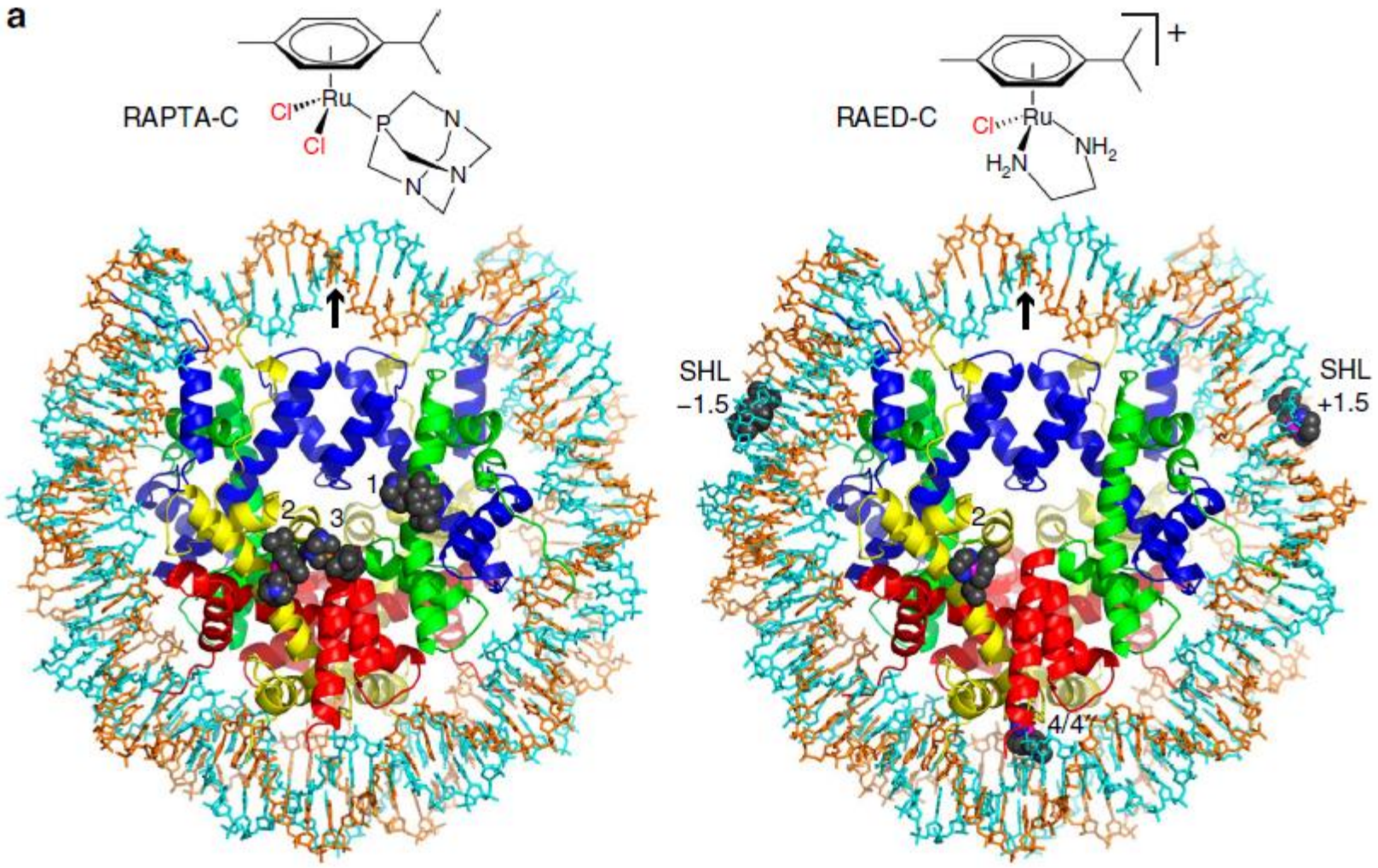
Anticancer organometallic Ru(II) compounds



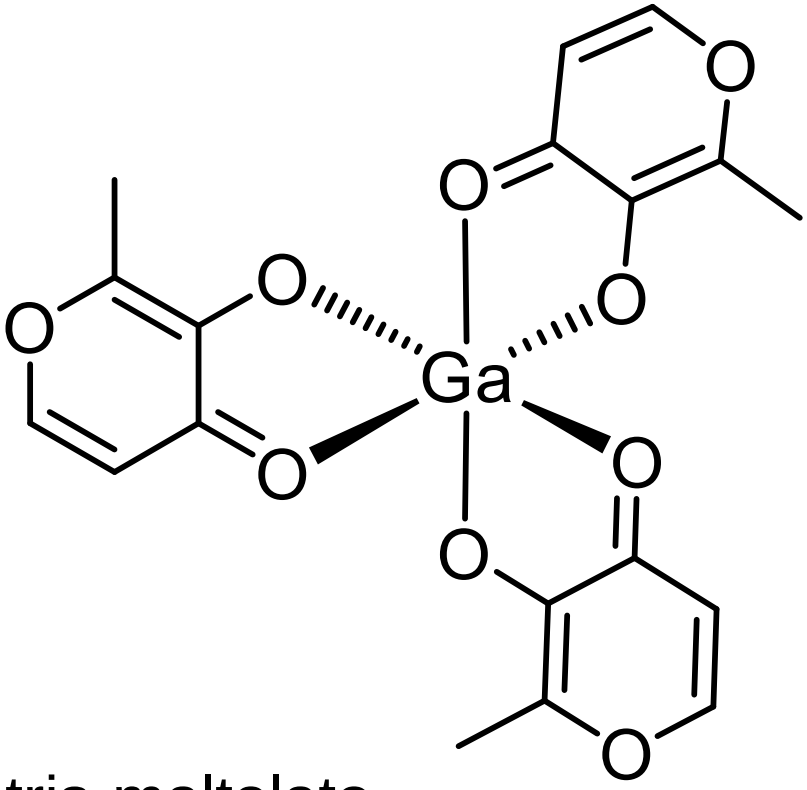
RM175



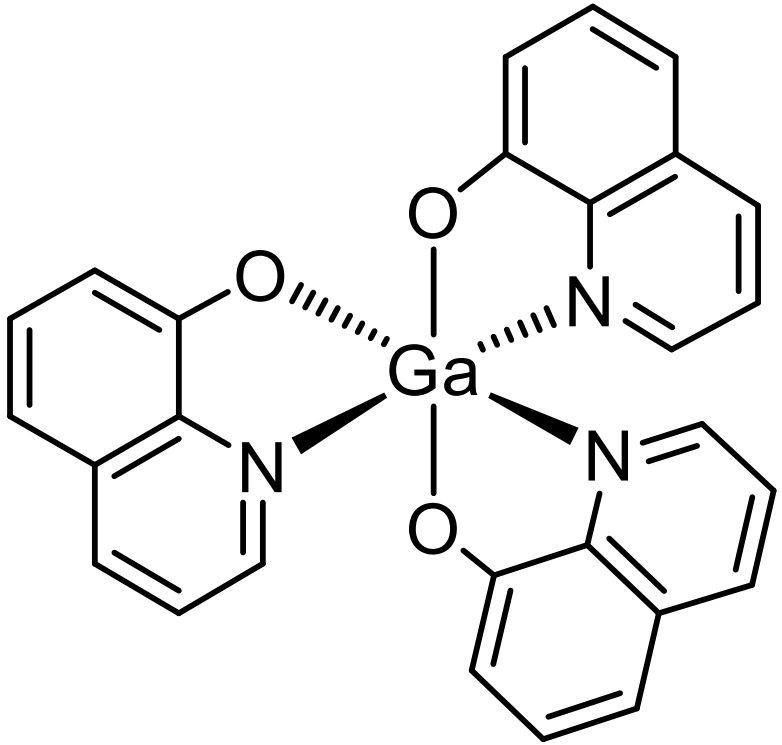
RAPTA-C


a
RAPTA-C
Cl
Ru
Cl
P
N
N
N
RAED-C
Cl
Ru
NH2
H2N
+
SHL
−1.5
SHL
+1.5
1
2
3
1
2
4/4′

Potenziali composti antitumorali di gallio



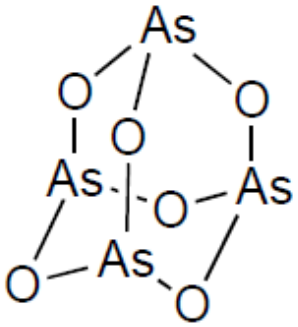
tris-maltolato



tris(8-idrossichinolinato)

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

Composti antitumorali di arsenico



ATO

0.15 mg/kg

FDA 2000

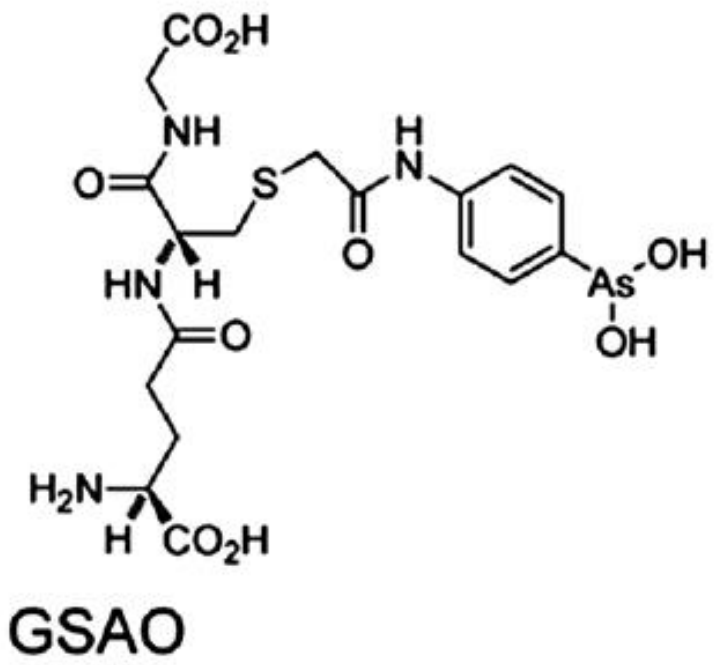
acute promyelocytic leukemia

ATO/ATRA therapy

(ATRA = all-trans retinoic acid)

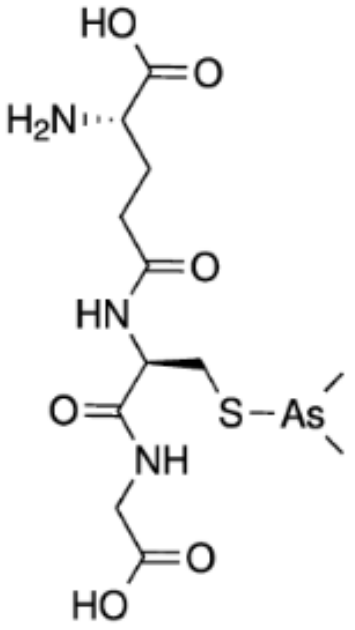
- Degradazione della proteina mutante PML-RARα che blocca la differenziazione mieloide
- Inibizione di enzimi anti-ROS (glutatione reduttasi, glutatione perossidasi, tioredossina reduttasi e tioredossina perossidasi)

Potenziali composti antitumorali di organo-arsenico



GSAO

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



Darinaparsin

S-dimetilarsinoglutatione