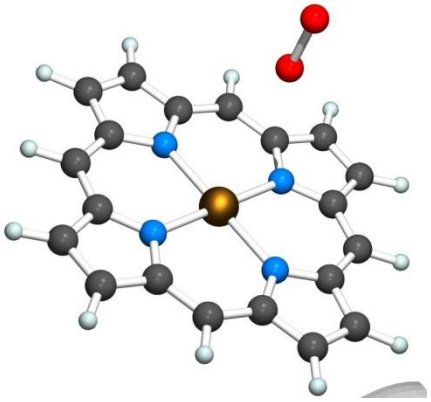
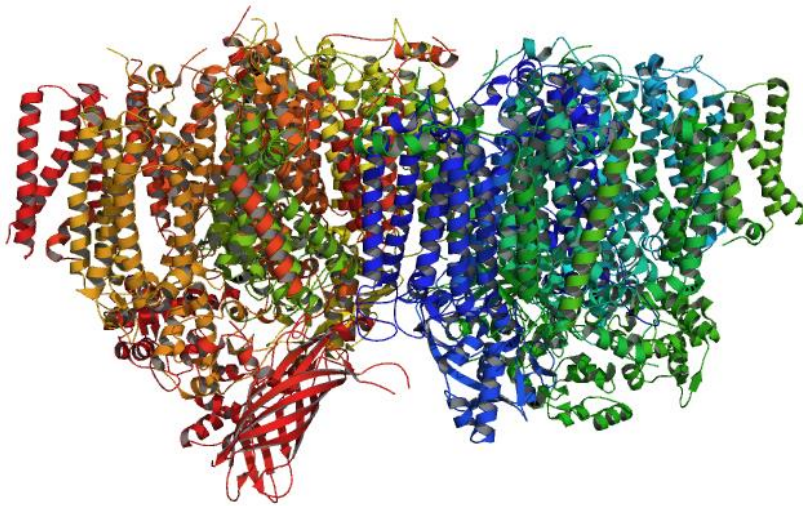
Bioinorganic Chemistry (BIC)

V. Metals in Medical Applications

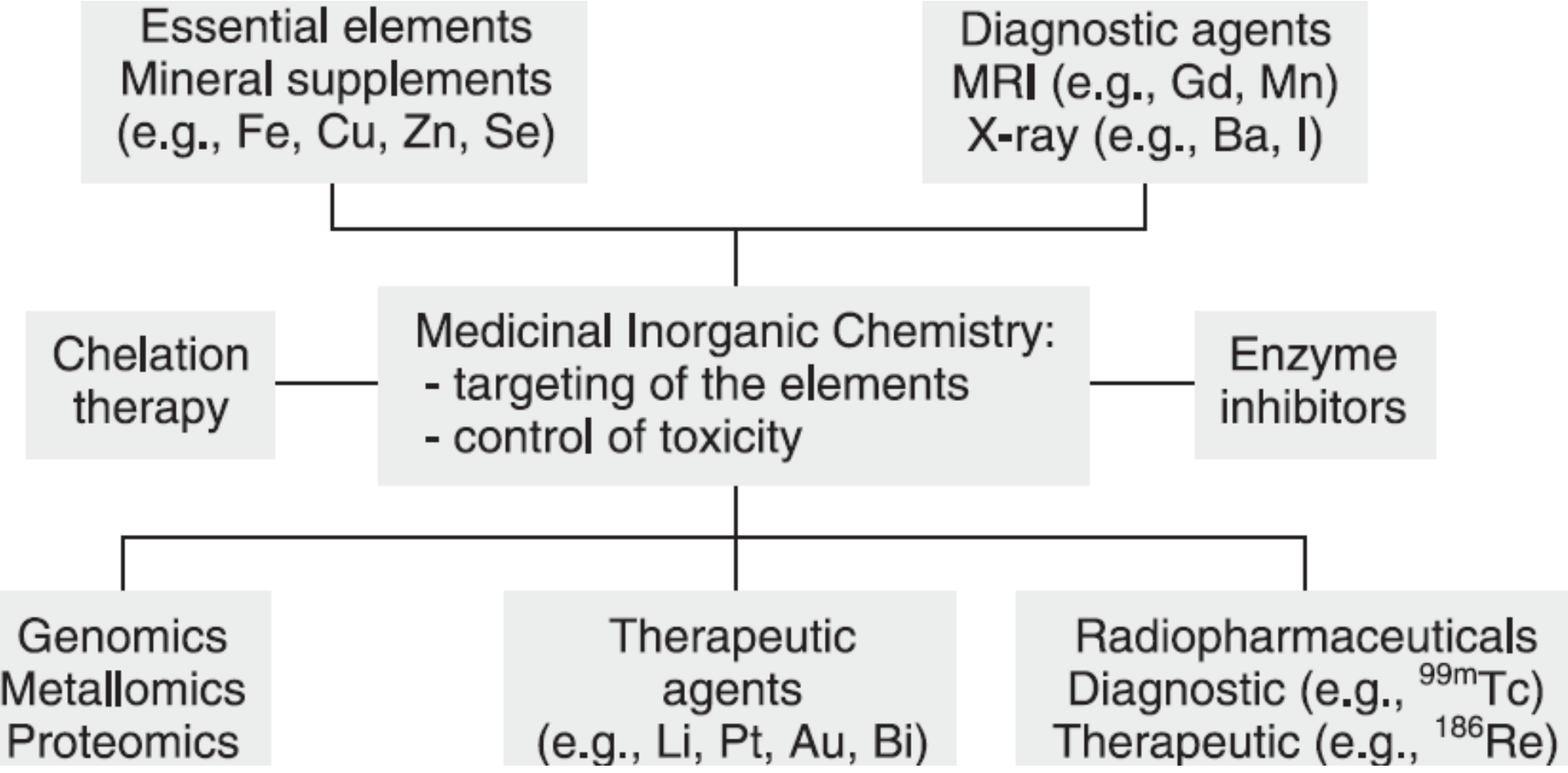




Dr. ($O_6S_4C_4Ar$) Lung Wa CHUNG(钟龙华)
(oscarchung@sustech.edu.cn)
Department of Chemistry

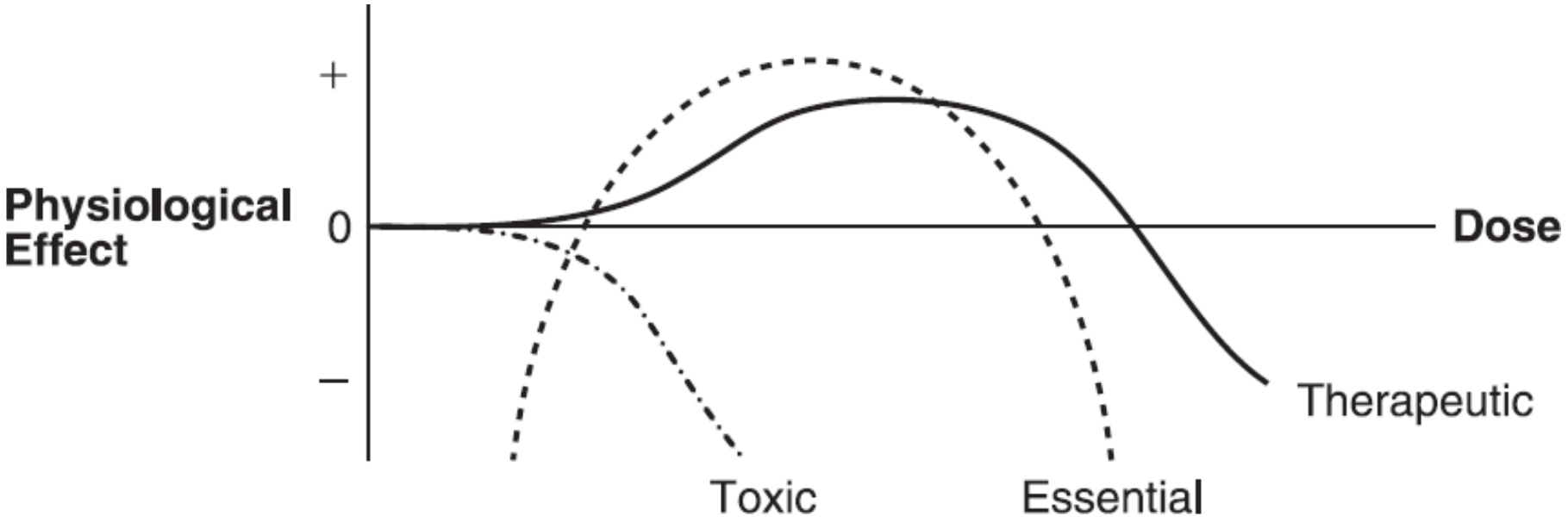
Medicinal Inorganic Chemistry

- Inorganic compounds have long been used in medical (therapeutic & diagnostic) applications.
- Development of better compounds/drugs (*more effective & specific; less/no toxicity/side effect*) are vital!



The Bertrand Diagram

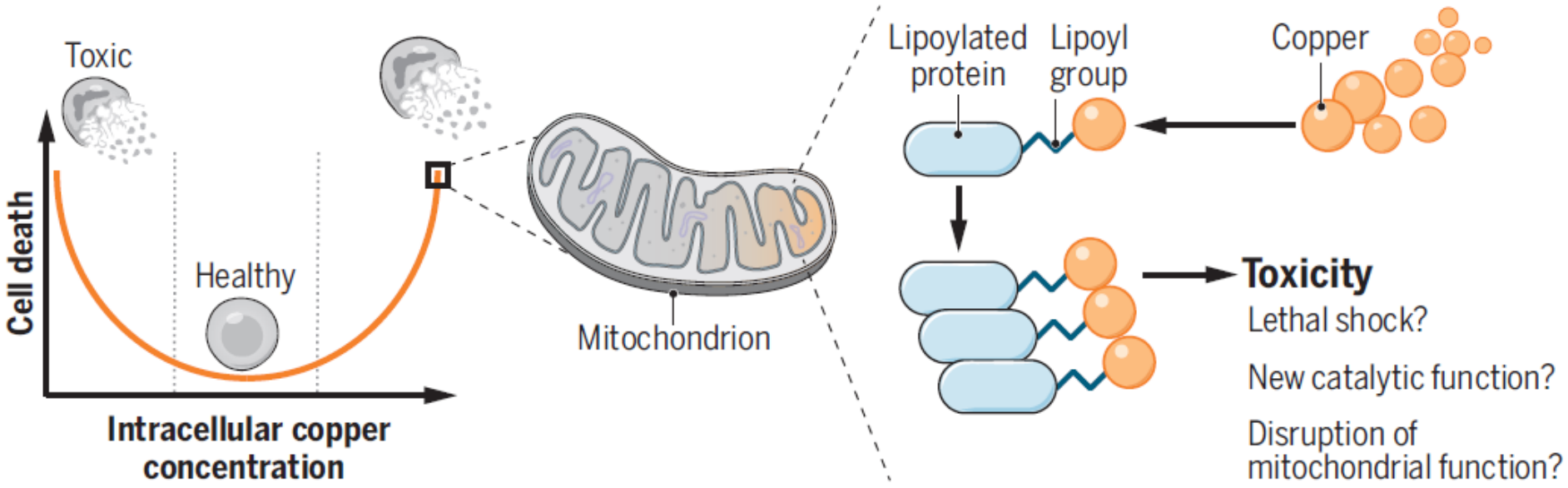
• The toxicity depends on element, its oxidation state, its coordination modes, & dose/mode of administration. Also, the presence of the other elements may affect the effect of an element.



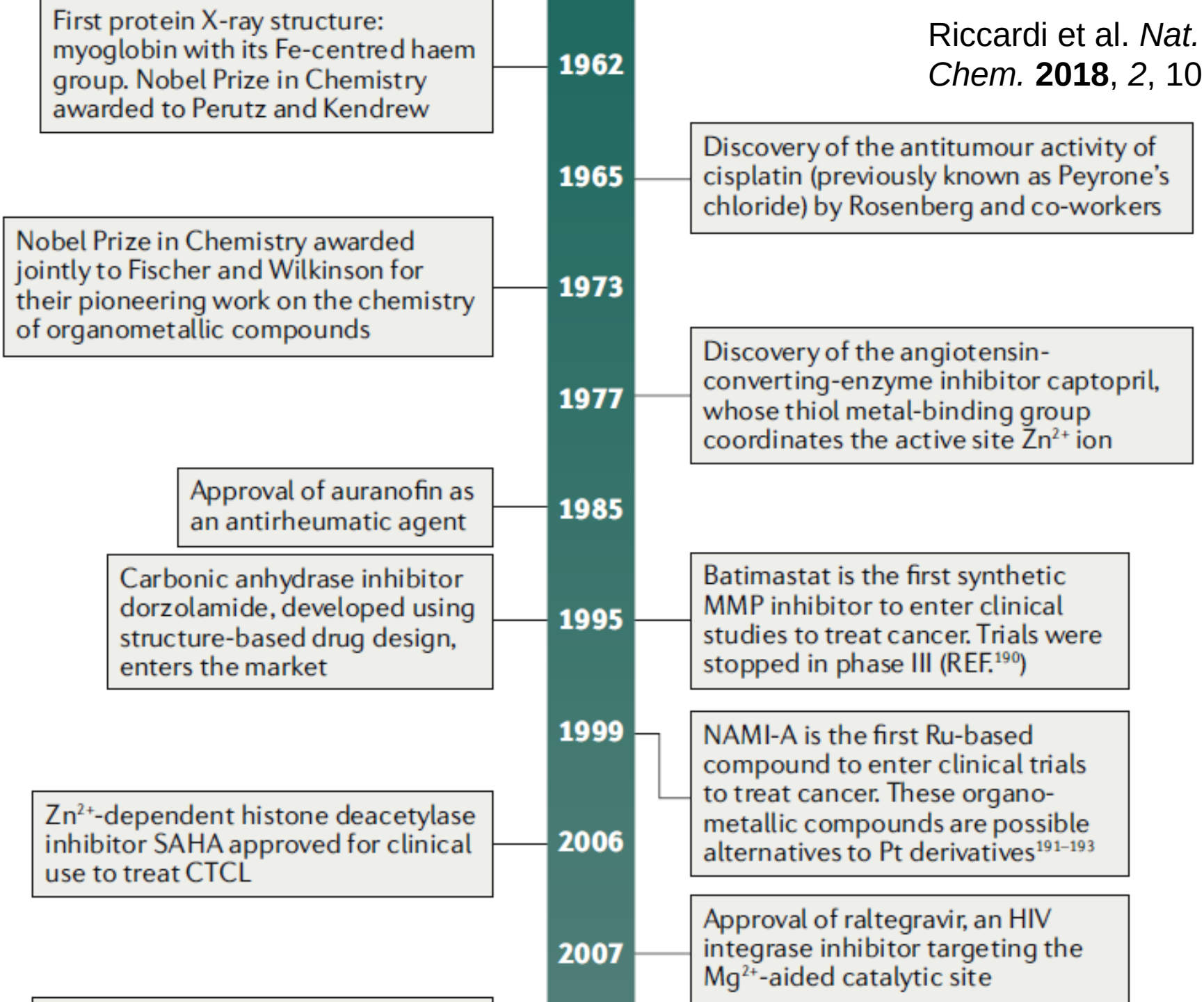
• At least **24 essential elements** for mammal: H, C, N, O, F, Na, Mg, Si, P, S, Cl, K, Ca, V, Mn, Fe, Co, Ni, Cu, Zn, Se, Mo, Sn, & I.

Copper triggers toxic mitochondrial protein aggregation

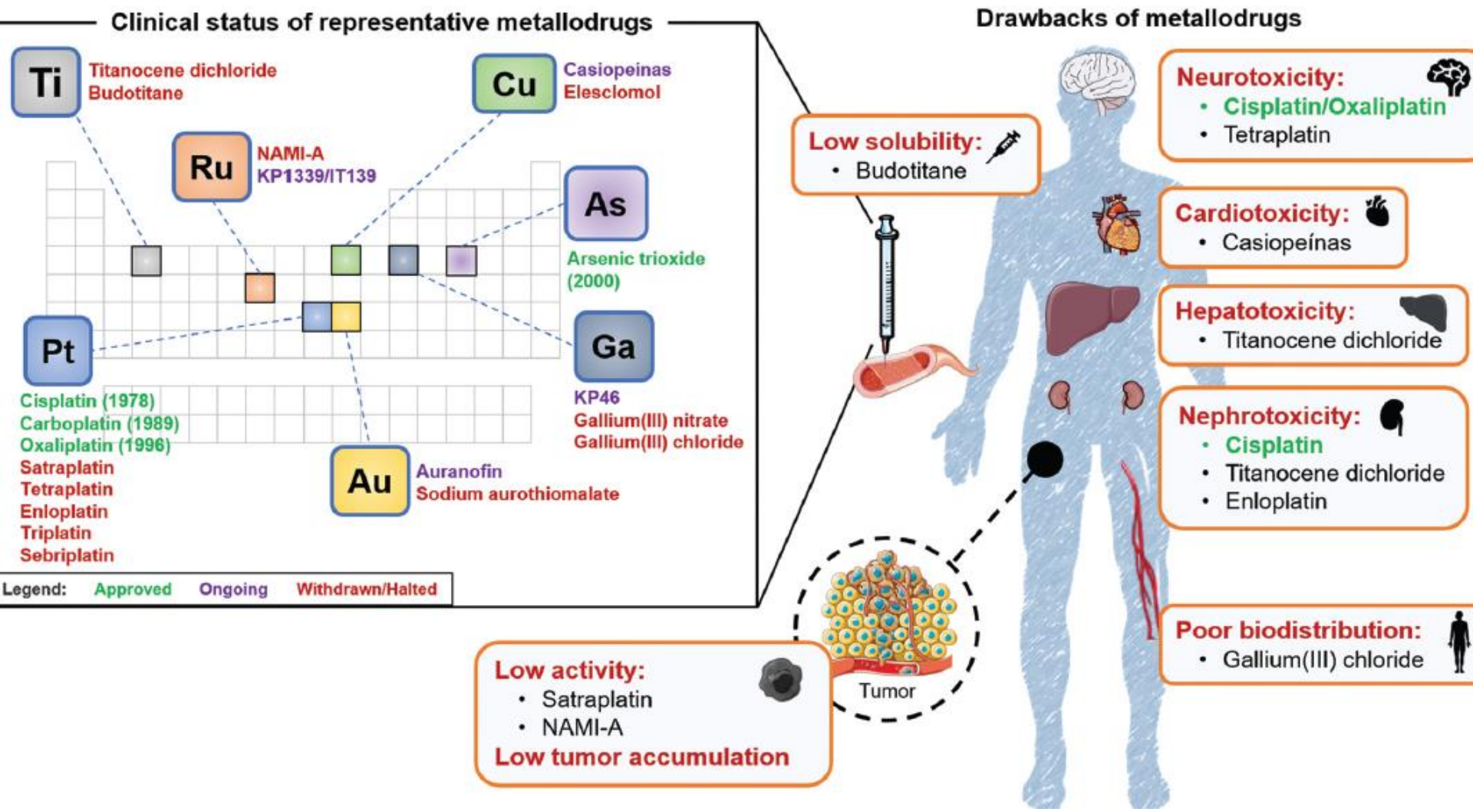
Too little or too much copper is toxic to cells. When there is too much copper, such as through treatment of cells with elesclomol, copper accumulates in the mitochondria. This results in aggregation of lipoylated proteins, including dihydrolipoamide *S*-acetyltransferase (DLAT), leading to cell death.



Science **2022**, 375, 1231 & 1254



Riccardi et al. *Nat. Rev. Chem.* **2018**, *2*, 101.

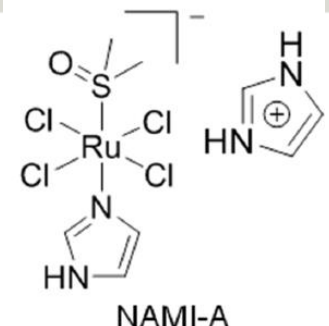


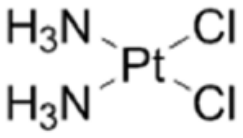
Pena et al. *Chem. Soc. Rev.* **2022**, DOI: 10.1039/d1cs00468a

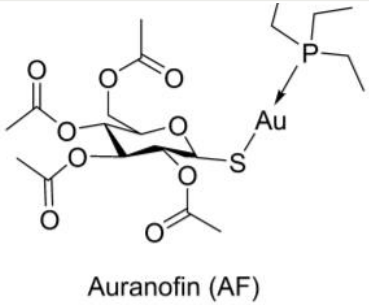
Compound Example (Brand Name)	Function	Comment
ACTIVE COMPLEXES[a]		
cis-$[Pt^{II}Cl_2(NH_3)_2]$ (Cisplatin)	Anticancer	Trans isomer is inactive
$[Gd^{III}(DTPA)(H_2O)]^{2-}$ (Magnevist)	Extracellular MRI[b] contrast agent	Low toxicity
$[^{99m}Tc^{I}(CNCH_2C(CH_3)_2OCH_3)_6]^{+}$ (Cardiolite)	Myocardial imaging	Positively charged complex taken up by the heart
Vitamin B_{12}	Coenzyme	Deficiency causes pernicious anemia
ACTIVE METALS		
Li_2CO_3	Prophylaxis bipolar disorders	Li(I) forms weak complexes, labile
Au^{I}(thiomalate) (Myocrisin)	Antirheumatoid arthritic	Facile thiol exchange on Au(I)
Ammonum potassium Bi^{III} citrate (De-Nol)	Antibacterial, antiulcer	Strong binding of Bi(III) to thiols, facile exchange
$Na_2[Fe^{II}(CN)_5NO]\cdot 2H_2O$ (Nipride)	Hypotensive	Releases NO, relaxes vascular muscle
Bleomycin	Anticancer	Requires Fe for DNA[c] attack
p-Xylyl-bicyclam·8HCl (AMD3100)	Anti-HIV[d]	May bind metals *in vivo*
$CaCO_3$, $Mg(OH)_2$	Antacids	Slow release of alkali
$La_2(CO_3)_3$ (Fosnol)	Chronic renal failure	Reduces phosphate absorption ($LaPO_4$ insol)

Element	Example of a Product Name	Active Compound in the Product	Medicinal Usage
Li	Camcolit	Li_2CO_3	Manic depression
N	Laughing gas	N_2O (nitrous oxide)	Anesthetic
F		SnF_2	Tooth protectant
Mg	Magnesia	MgO	Antacid, laxative
Fe		Fe(II) fumarate, succinate	Dietary iron supplement
Co	Cobaltamin S	Coenzyme vitamin B_{12}	Dietary vitamin supplement
Zn	Calamine	ZnO	Skin ointment
Zn		Zn undecanoate	Antifungal (athlete's foot)
Br		NaBr	Sedative
Tc	TechneScan PYP	^{99m}Tc-pyrophosphate	Bone scanning
Sb	Triostam	NaSb(V) gluconate	Antileishmanial (antiprotozoal)
I		I_2	Antiinfective, disinfectant
Ba	Baridol	$BaSO_4$	X-ray contrast

Protein target	Metal	Inhibitor	Type of drug	Application
CAII	Zn	Acetazolamide[a], benzenesulfonamide	Me-Inhib	Cancer
	Ru	NAMI-A (prodrug)	Me-Drug	Cancer
	Zn (protein)/ Fe (ligand)	Ferrocene-based inhibitor	Me-Inhib/ Me-Drug	Cancer
Cytochrome P450 46A1	Fe	Fluvoxamine[a]	Me-Inhib	Cancer, neurodegenerative disorders
DNA	Pt	Cisplatin[a]	Me-Drug	Cancer
NCP	Ru	RAPTA-T	Me-Drug	Cancer
MTH1	Ru	Ruthenium-based organometallic compound	Me-Drug	Cancer
Glutathione transferase	Ru	(Eta6-benzene)ruthenium	Me-Drug	Multidrug resistance in cancer
PIM2	Ru	Ruthenium-pyridocarbazole-1	Me-Drug	Cancer
PIM1	Os	Pyridocarbazole cyclopentadienyl Os (co-)complex	Me-Drug	Cancer
Thioredoxin reductase from *Entamoeba histolytica*	Au	Auranofin[a]	Me-Drug	Antiparasitic
Methionine aminopeptidase	Co	LAF153	Me-Inhib	Cancer
Urease from *Helicobacter pylori*	Ni	Acetohydroxamic acid[a]	Me-Inhib	Antibiotic adjuvant



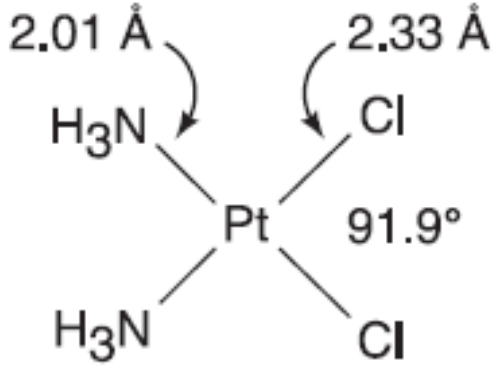




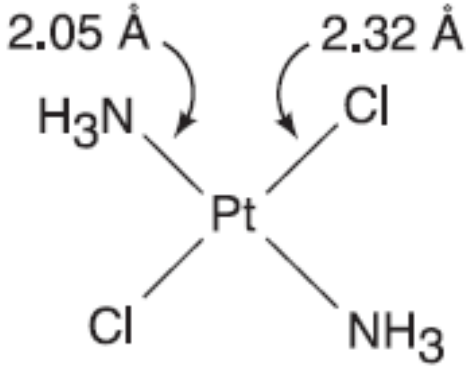
Riccardi et al. *Nat. Rev. Chem*. **2018**, *2*, 101.

Metallotherapeutics: Anti-cancer Agents

• **Pt(II)** complex **cisplatin**: one of the most widely used anticancer drugs, particularly for the treatment of testicular cancer & ovarian carcinoma.



Cisplatin

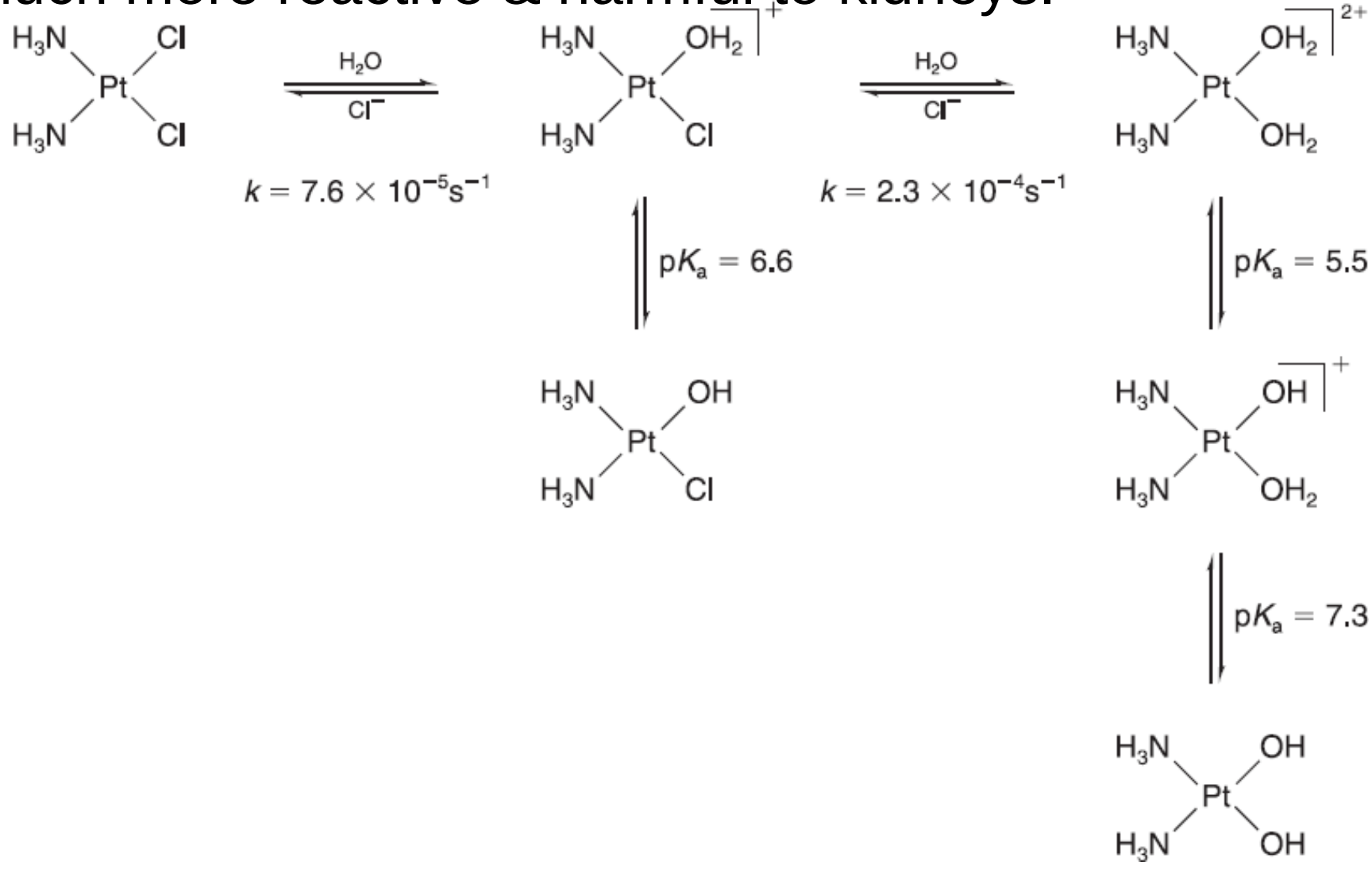


Transplatin

• Only cisplatin could be effective in preventing growth of cancer cells, but **NOT transplatin**.

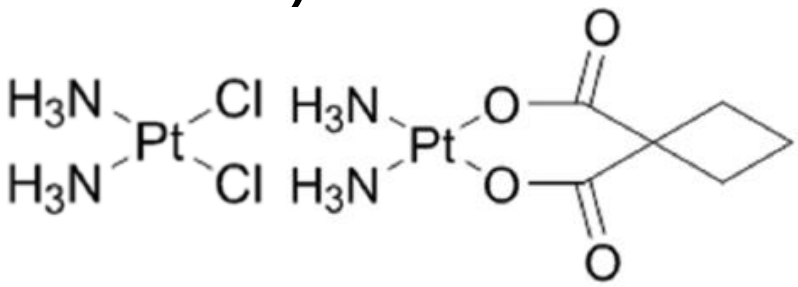
• Generally, μ mol. doses of cisplatin is used to kill cancer cells.

• Cisplatin is not stable in water ($t_{1/2}$: 2.5 hr at 310 K). It is formed in saline (NaCl) solution to administrate to patients to avoid hydrolysis. The aquated species are much more reactive & harmful to kidneys.



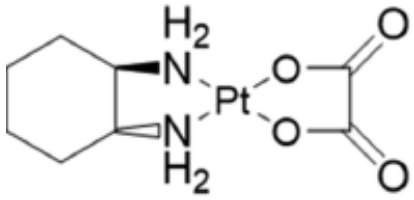
New Generation of Pt Drugs

• **Cisplatin** is *very toxic* & can have severe side effects (e.g. *kidney poisoning*, *loss of high frequency hearing*). Also, after repeated treatment, cancer cells can become resistant to cisplatin. Anti-cancer activity is needed against different cancer types (e.g. lung, breast, & colon cancers).

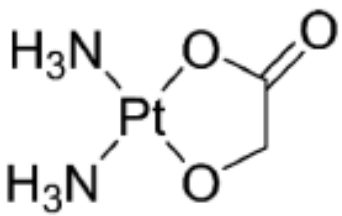


Cisplatin

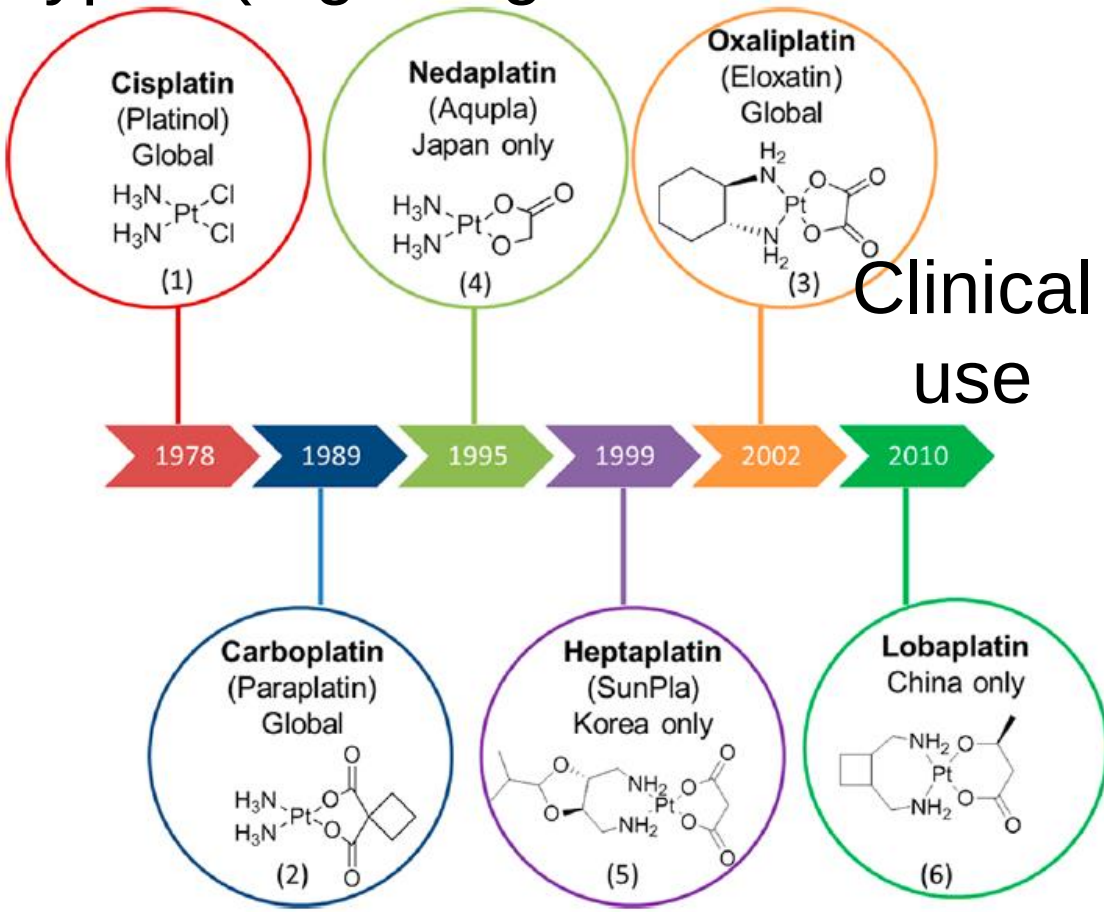
Carboplatin

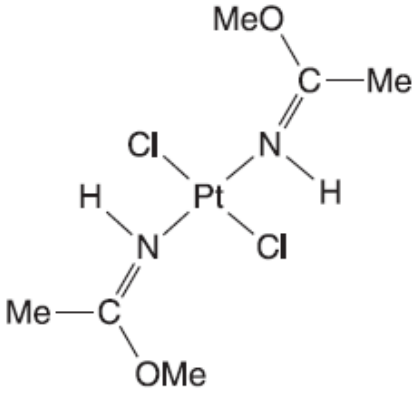


Oxaliplatin

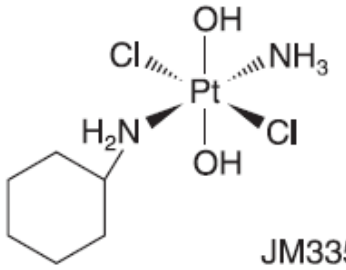


Nedaplatin





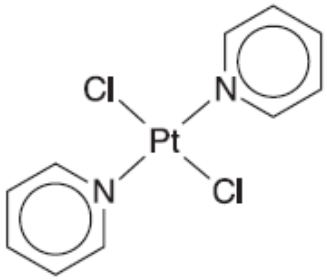
Trans-EE complex with iminoether ligands (more active than *cis* isomer)



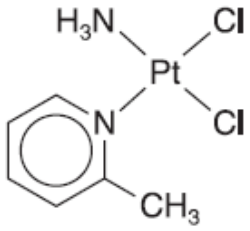
JM3355

The Pt(II) analogue of this Pt(IV) complex, without axial OH^- ligands, is inactive

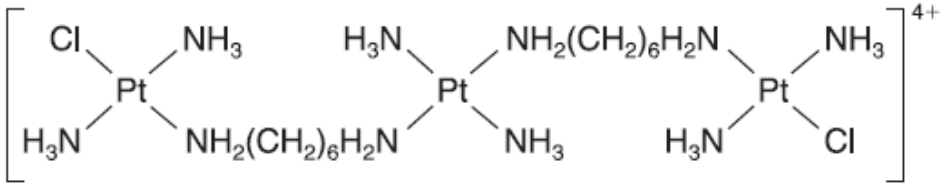
Examples of active Pt complexes based on structure-activity rules



Trans complex with pyridine ligands



Two cis-N ligands, but only one has NH group



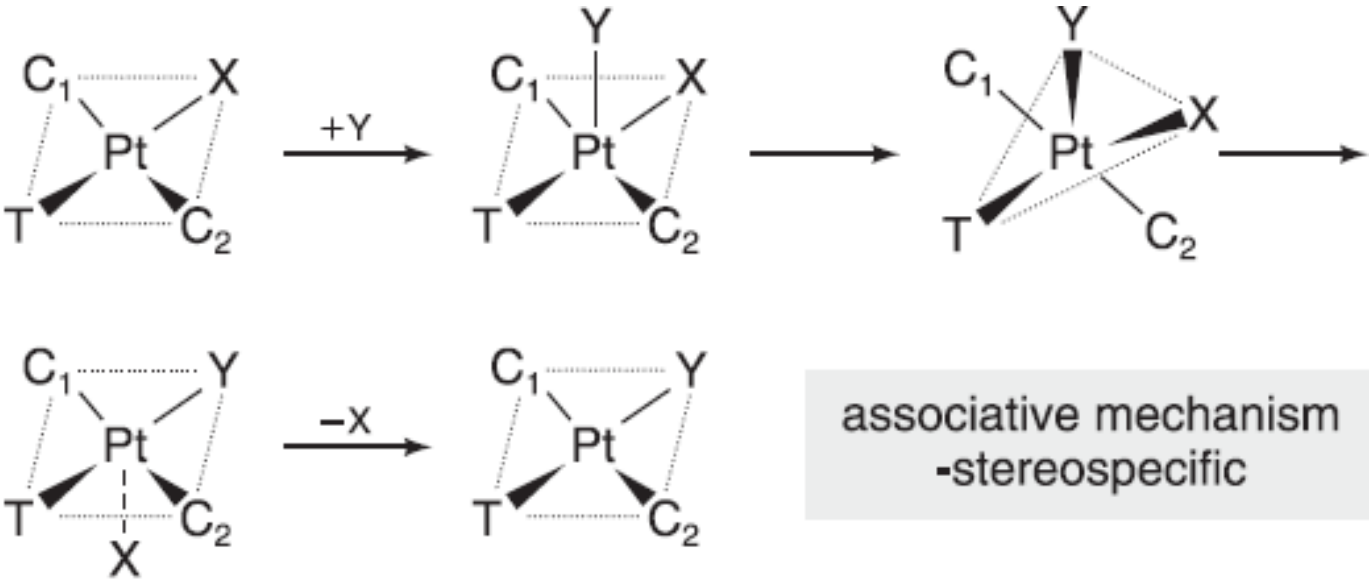
BBR3464

High positive charge, only one leaving group on each terminal Pt

Mechanism of Action of Cisplatin: Ligand Substitution

$$Pt{-}X + Y \rightarrow Pt{-}Y + X$$

- The mechanism of ligand substitution in square-planar Pt(II) complexes: **associative mechanism**.
- The rate depends on ***trans* effect** of a ligand (**T**) *trans* to **X**.



associative mechanism
-stereospecific

$$\text{Rate law} \qquad \frac{-d[\mathrm{PtX}]}{dt} = k_1[\mathrm{PtX}] + k_2[\mathrm{PtX}][\mathrm{Y}]$$

• The order of the ***trans* effect** of different ligands (L):

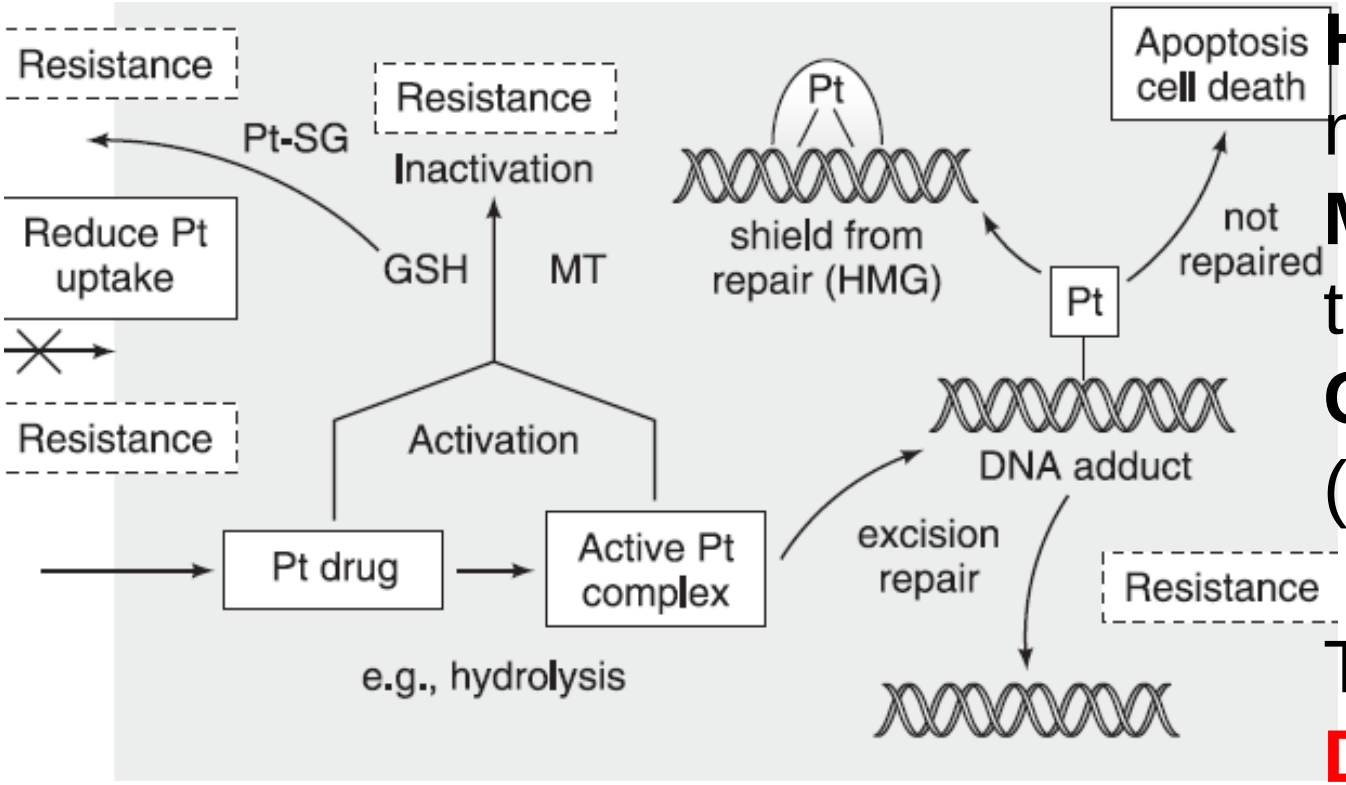
$$CN^-, C_2H_4, CO, NO > R_3P, H^- > SC(NH_2)_2 > CH_3^- > C_6H_5^- > SCN^- > NO_2^- > I^- > Br^- > Cl^- > NH_3 > OH^- > OH_2$$

• ***Trans effect***: a **kinetic** effect to affect the **reaction rate**. The larger ***trans* effect** of a ligand *trans* to **X** ligand, the faster ligand substitution of **X**.

$[PtCl_4]^{2-} + 2\ NH_3$ → ***cis*-$[PtCl_2(NH_3)_2]$** + $2\ Cl^-$

$[Pt(NH_3)_4]^{2+} + 2\ Cl^-$ → ***trans*-$[PtCl_2(NH_3)_2]$** + $2\ NH_3$

• In comparison, ***trans influence*** is a **thermodynamic** effect to affect **ground-state properties** (e.g. **bond strength**, NMR coupling constant & vibrational frequencies) of M-ligand.



HMG: high mobility group

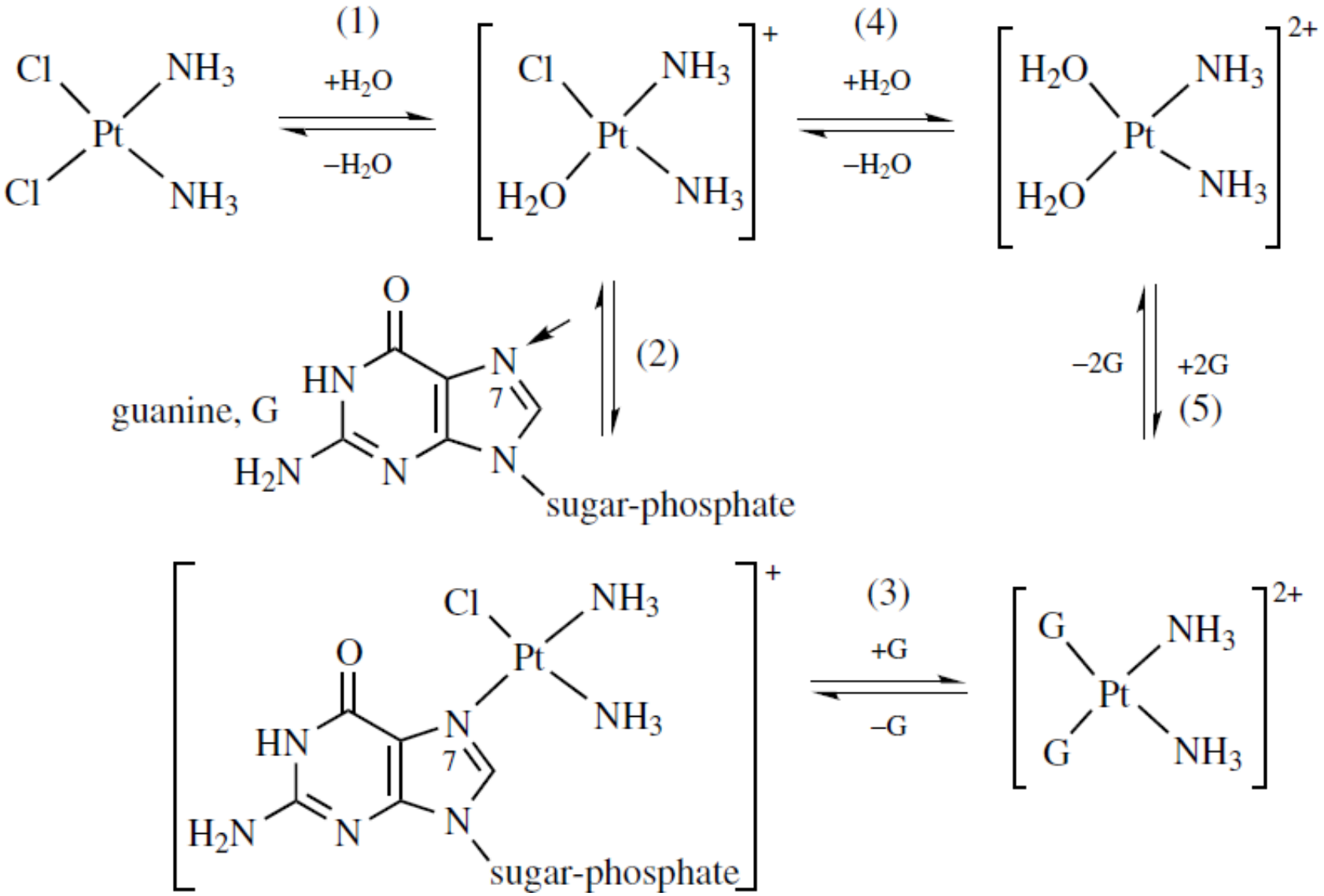
MT: metallo-thionein

GSH: glutathione (strong PtS bond)

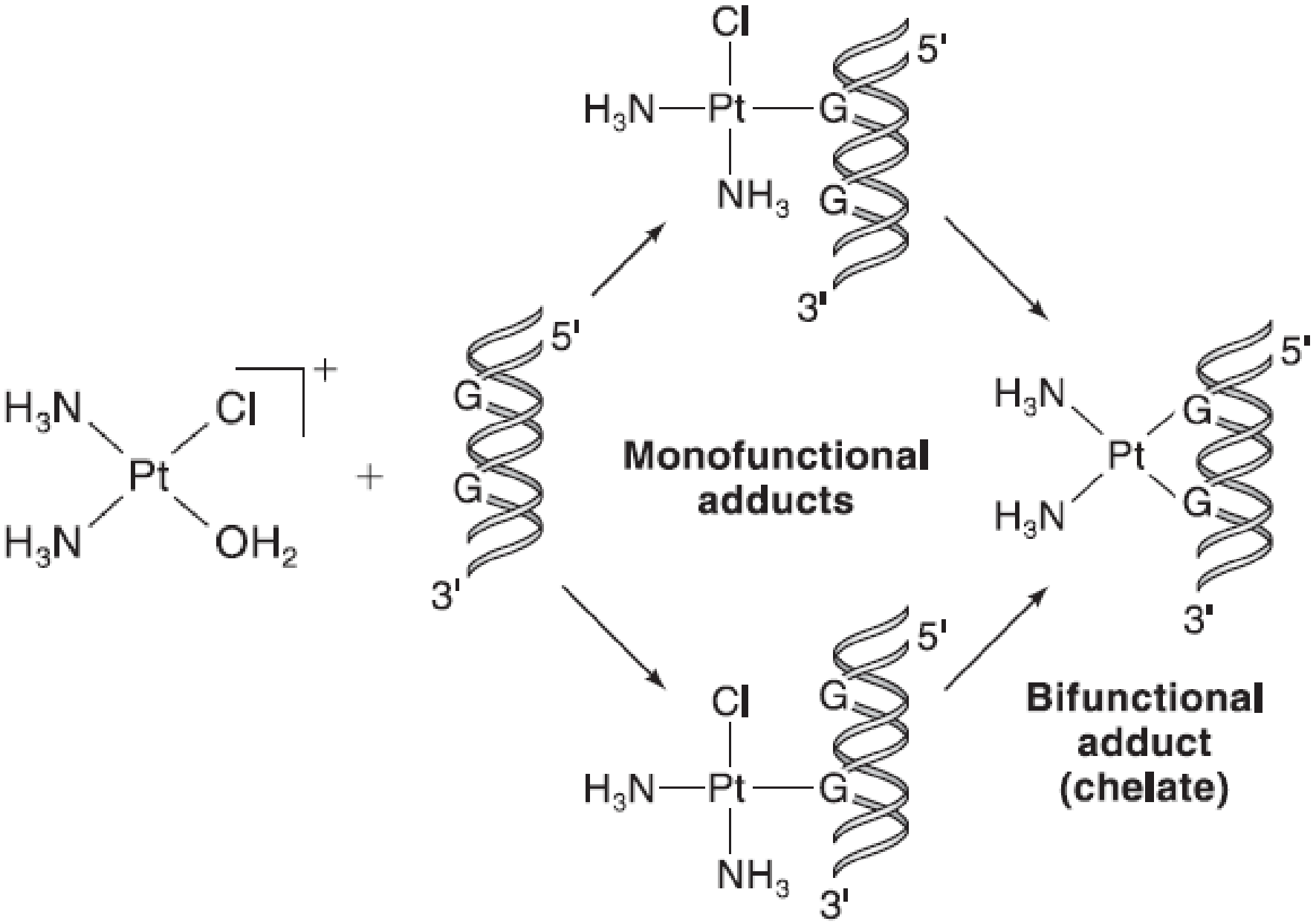
The **target site**: **DNA**.

- The **major** binding site is **N7** of (most e^--rich) **guanine**.

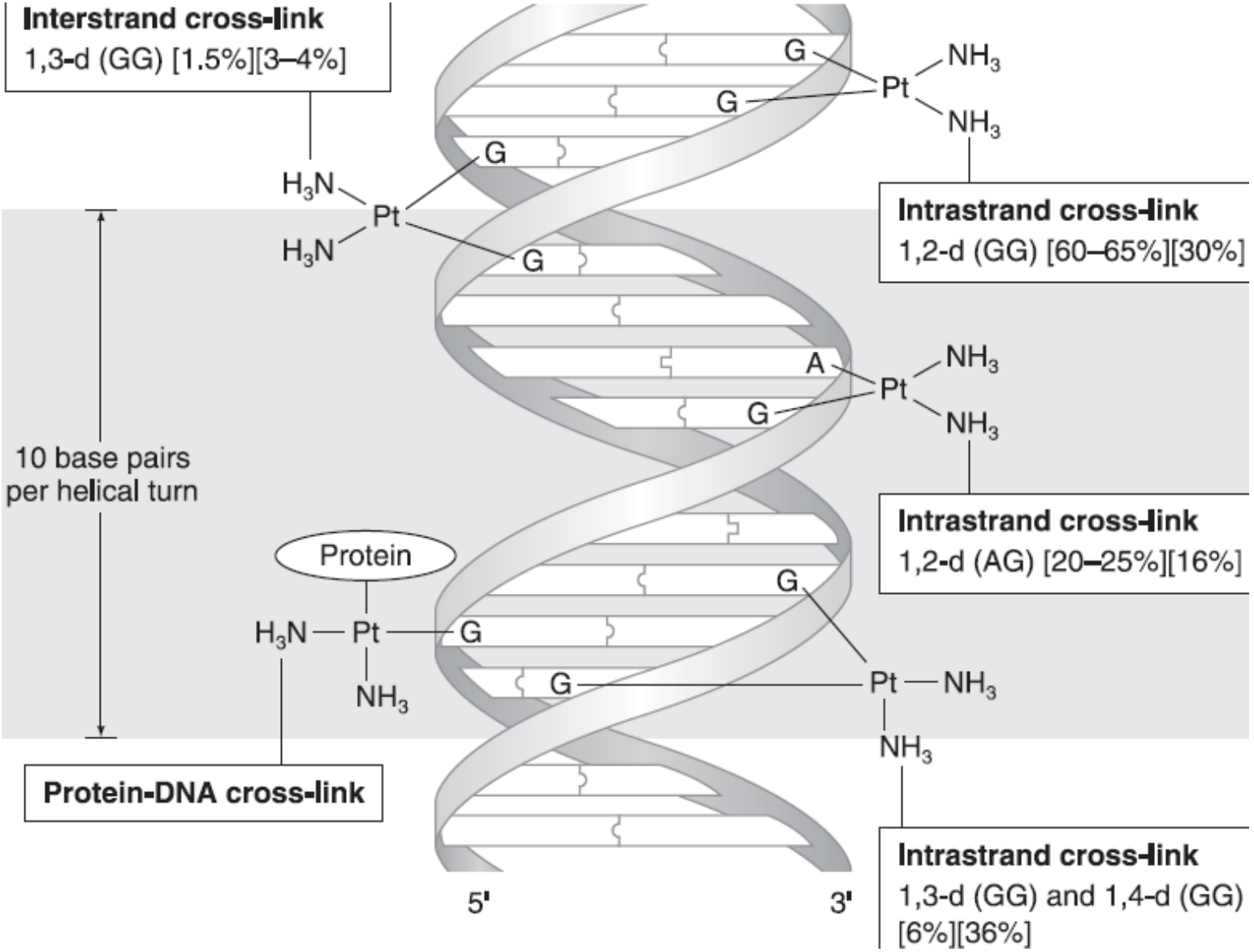
- The bent platinated B-DNA is recognized by HMG proteins. The platinated DNA adducts which are not repaired in cells trigger **apoptosis** (programmed cell death), instead of normal function as transcription factors. Then, DNA is digested by endonucleases.



- Hydrolysis is followed the Pt-N chelation.
- H-bond between Pt-NH & phosphate or C6 carbonyl groups can stabilize such adduct.



• The G-G platination (chelate) causes B-DNA to bend by ~35-40º.



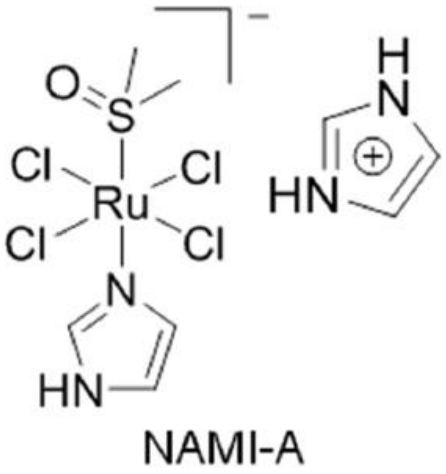
- **Major adduct: 1,2 intrastrand** cross-links with G-G & sometimes G-A.
- Other binding sites: N7 of adenine & N3 of cytosine.

Other Metal Compounds

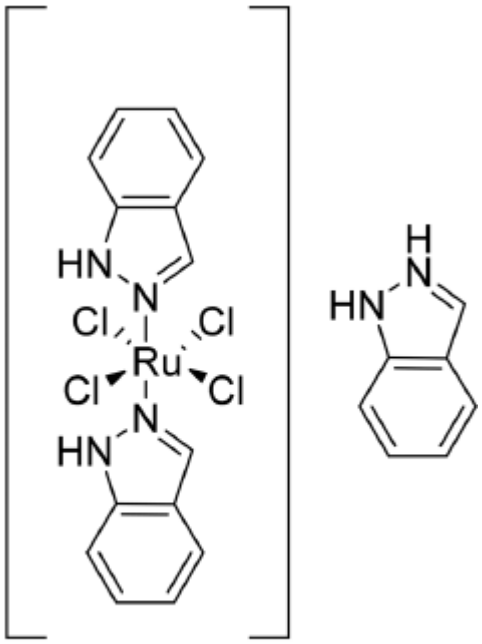
• **Pd** complexes: much more reactive than Pt(II) (by ~10^4-10^5). Pd(II) complexes tend to have side reactions before accessing the DNA target.

• **Ru** complexes:

NAMI-A (the 1st Ru complex to enter the clinic trials); **KP1019** (the 2nd Ru complex to enter the clinical trials).

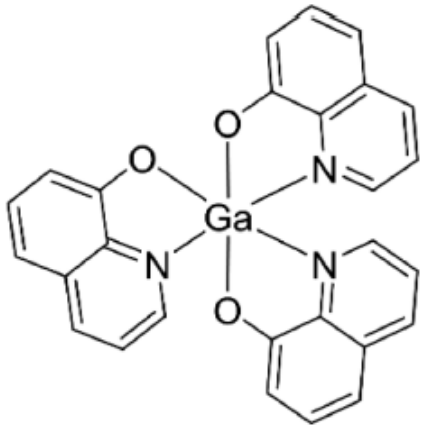


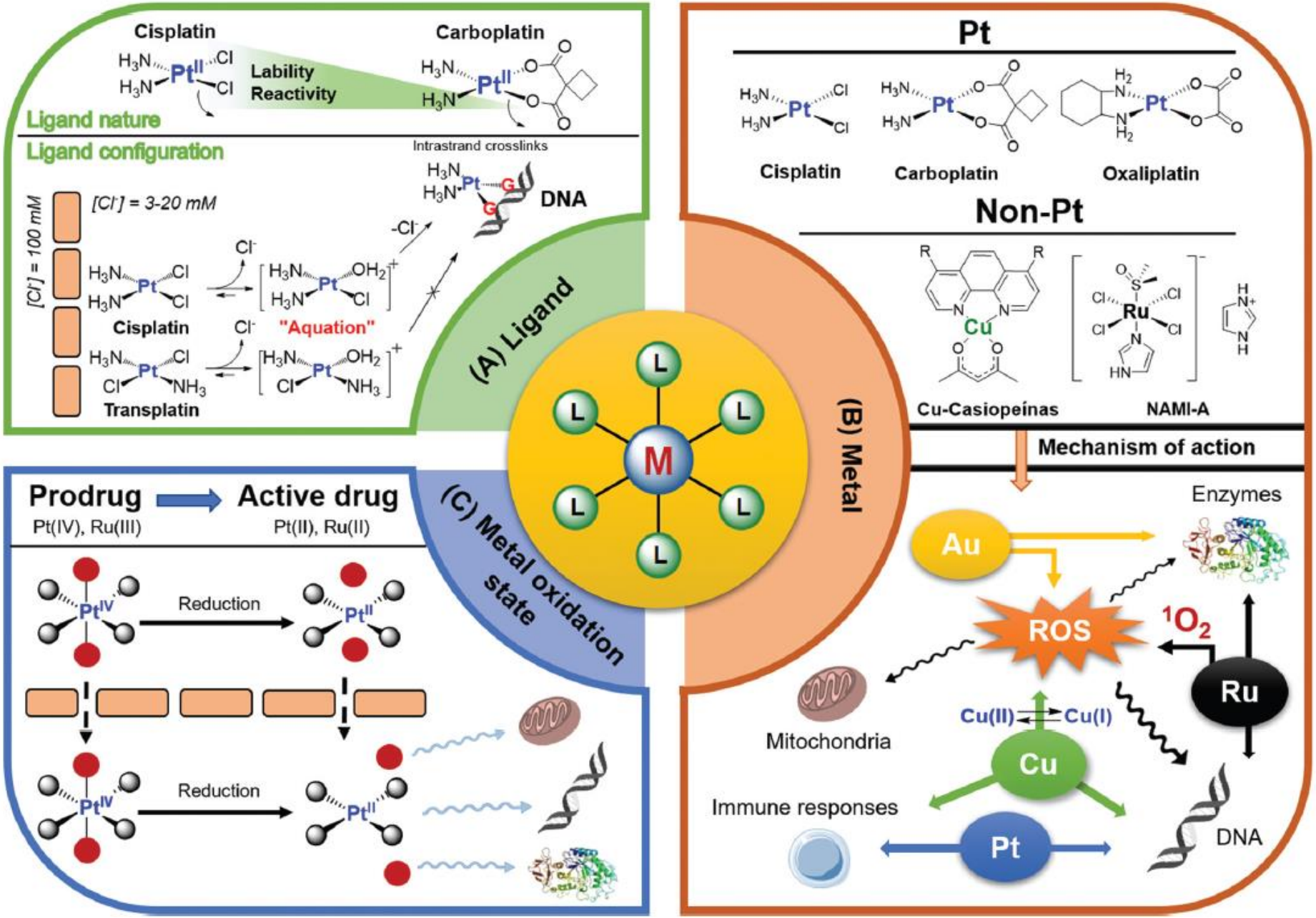
NAMI-A



KP1019 **(8)**

• **Ga** complex (**KP48**): clinical trial as an oral anticancer drug.





Pena et al. *Chem. Soc. Rev.* **2022**, DOI: 10.1039/d1cs00468a

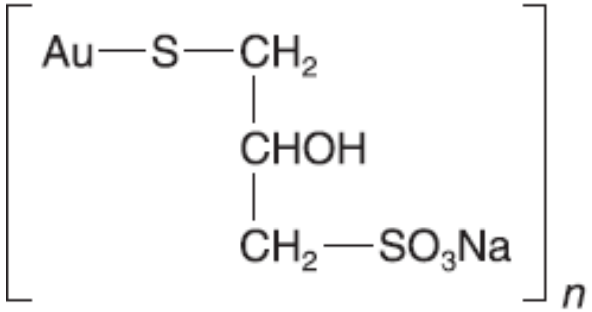
• **As** complexes are often toxic.

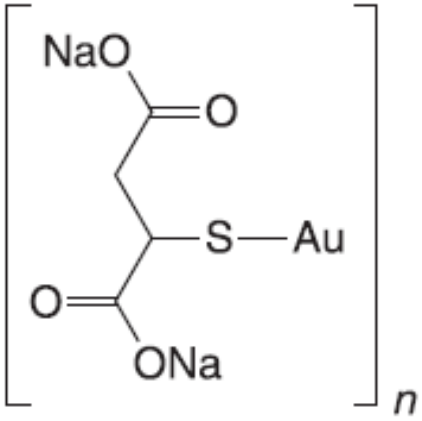
• **As_2O_3** (砒霜): a therapeutic agent for treating acute promyelocytic leukemia (前骨髓球性白血病) in China.

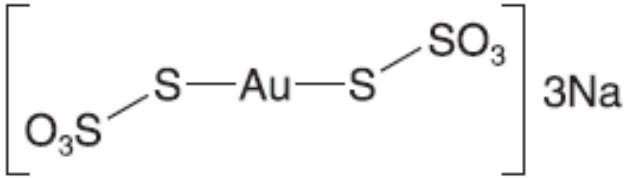
• Arsenic trioxide (Trisenox) was approved as a chemo-therapeutic agent by US FDA.

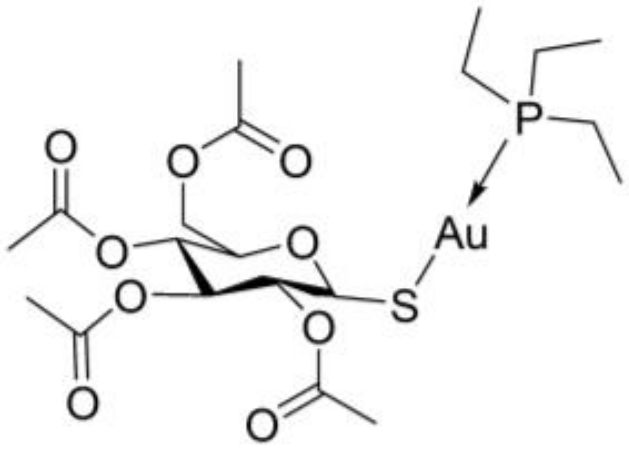
• Arsenic trioxide induces cancer cells to occur apoptosis.

- **Au** antiarthritic (抗关节炎) Drugs (Au-S bonds).









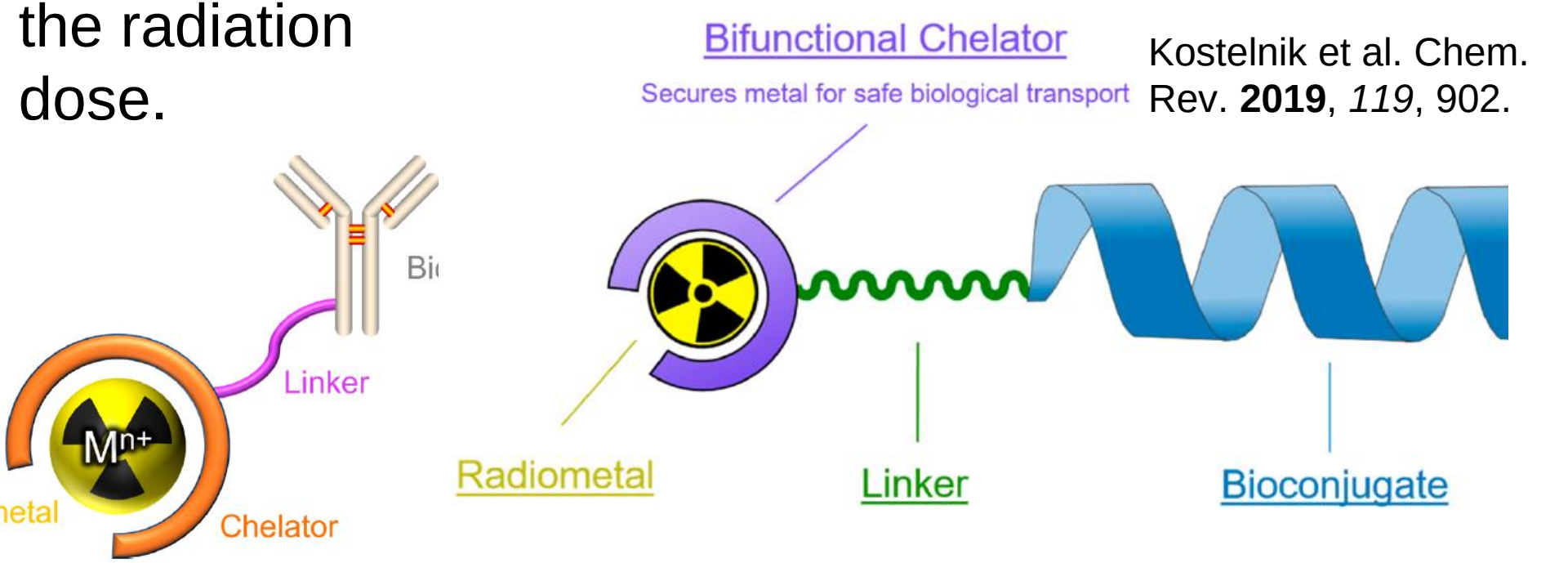
Auranofin (AF)

- **Li** drug (Li_2CO_3) treats bipolar affective disorders (情感表达障碍症), e.g. manic depression (狂躁忧郁症).

Imaging & Diagnosis

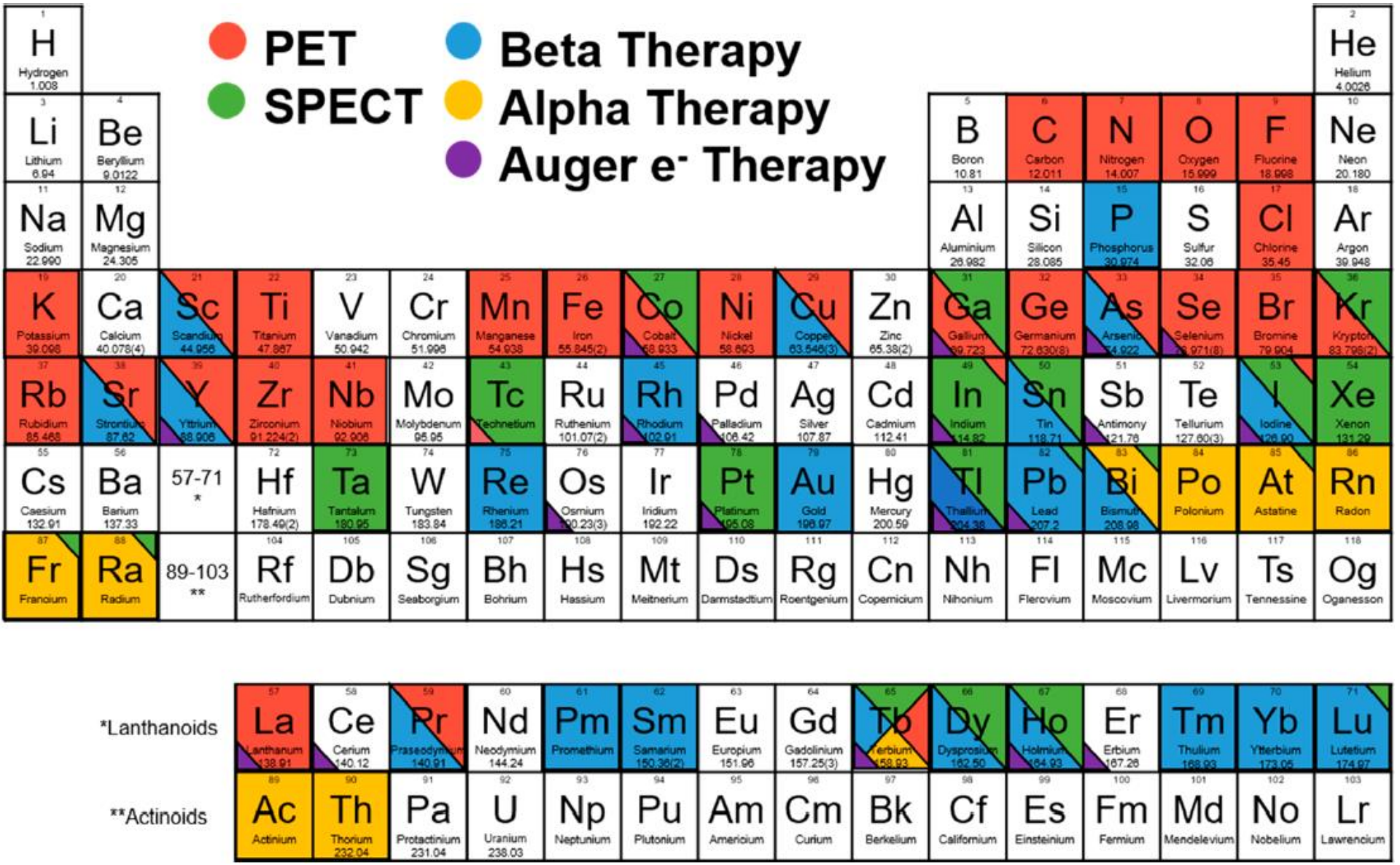
• **Radionuclides** can be used for imaging & therapy. Their half-life should be long enough for diagnostic imaging, but short enough to minimize the radiation dose.

^{32}P (14.3 day), ^{47}Sc (3.3 day), ^{64}Cu (0.5 day), ^{67}Cu (2.6 day)
^{89}Sr (50.5 day), ^{90}Y (2.7 day), ^{105}Rh (1.5 day), ^{111}Ag (7.5 day)
^{117m}Sn (13.6 h), ^{131}I (8.0 day), ^{149}Pm (2.2 day), ^{153}Sm (1.9 day)
^{166}Ho (1.1 day), ^{177}Lu (6.8 day), ^{186}Re (3.8 day), ^{188}Re (0.7 day)

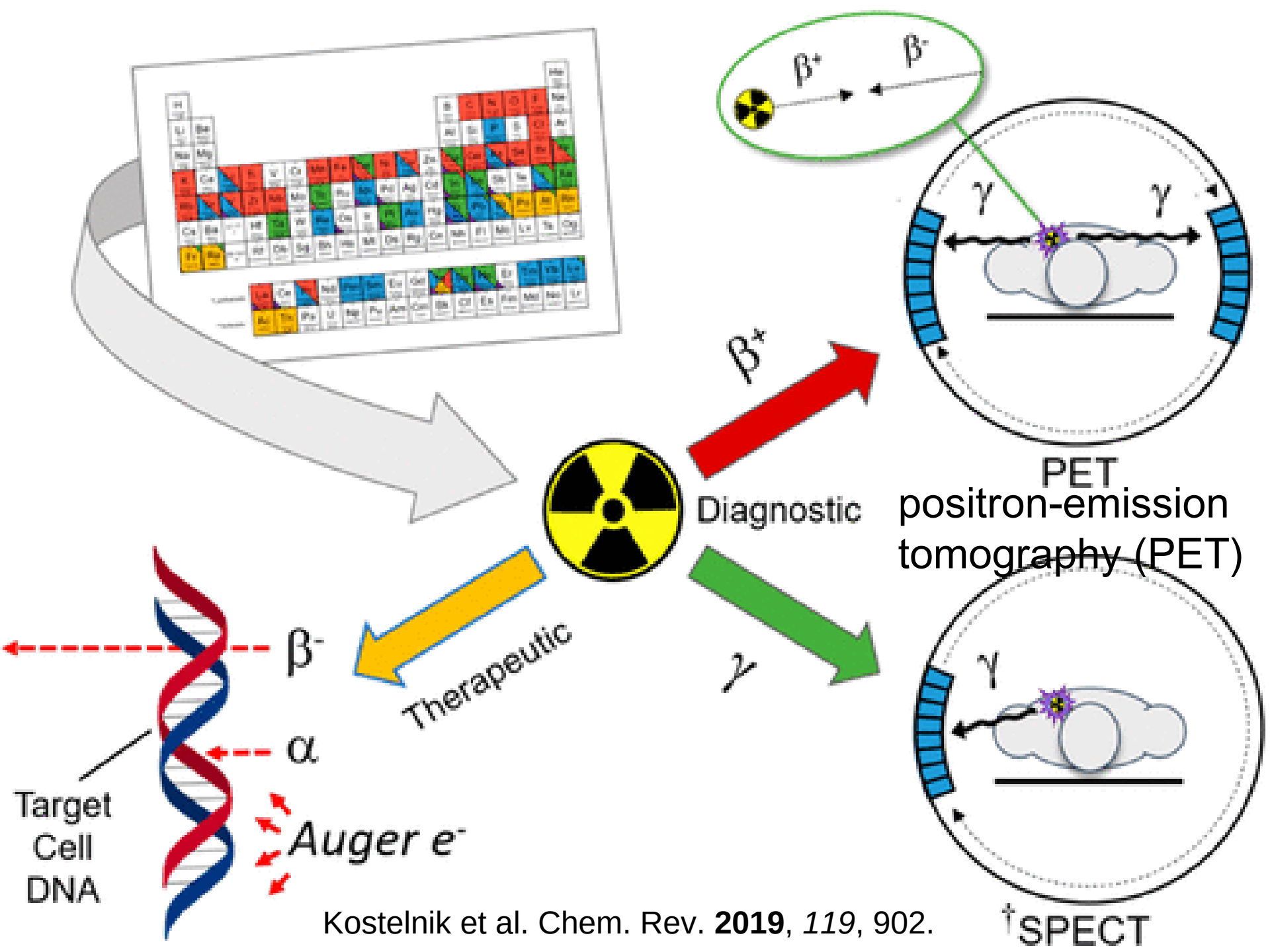


Kostelnik et al. Chem. Rev. **2019**, *119*, 902.

Current or potential applications of each element in diagnostic and/or therapeutic radiopharmaceuticals



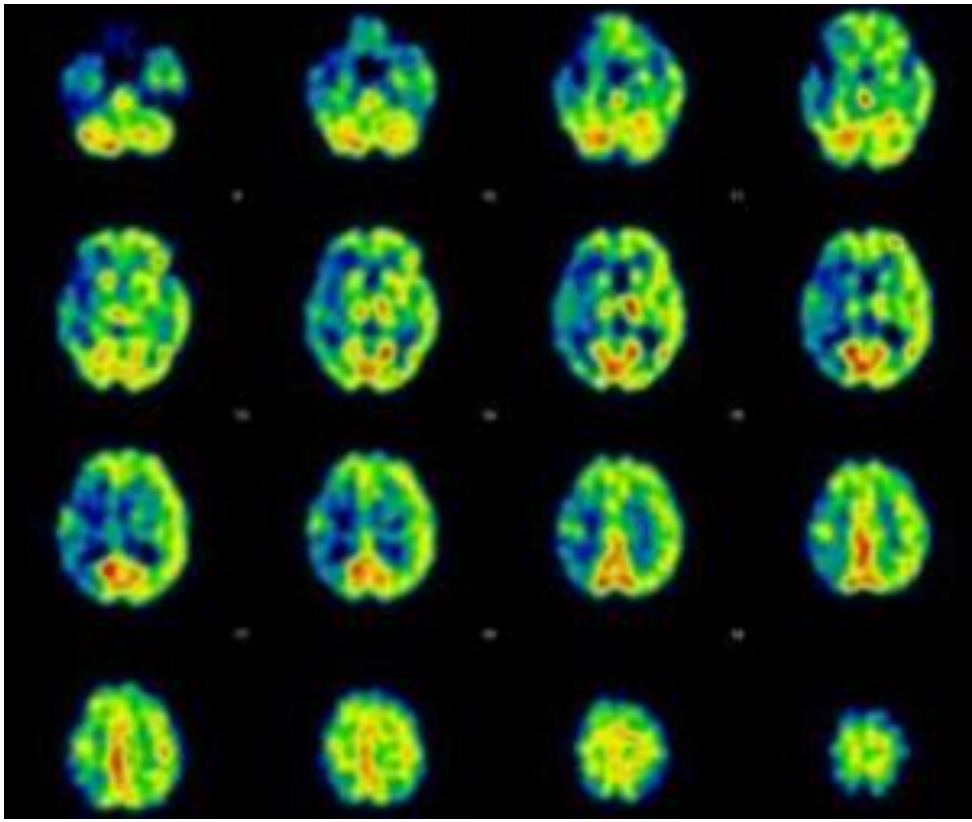
Kostelnik et al. Chem. Rev. **2019**, *119*, 902.



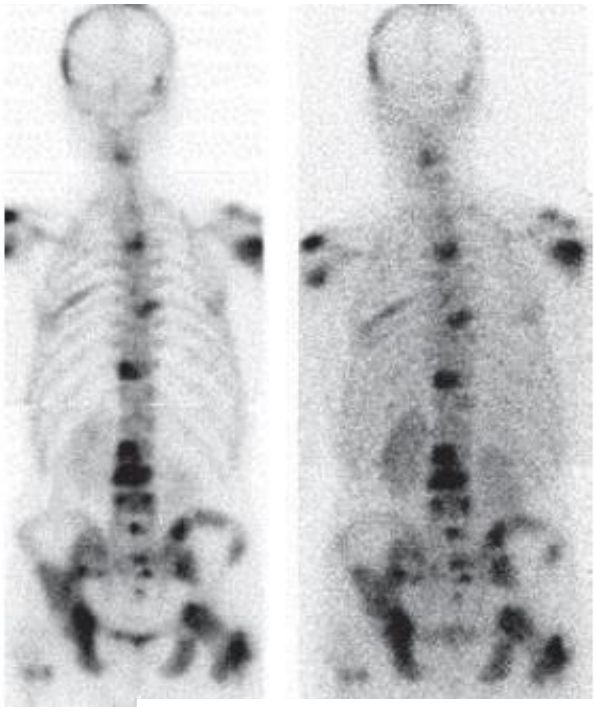
Kostelnik et al. Chem. Rev. **2019**, *119*, 902.

• Single-photon emission computed tomography (SPECT, 单光子发射计算机断层成像) requires a γ-emitting radionuclide. ^{99m}Tc is widely used of all diagnostic scans.

^{67}Ga (3.3 day), ^{111}In (2.8 day), ^{99m}Tc (6.0 h), ^{201}Tl (3.0 day)

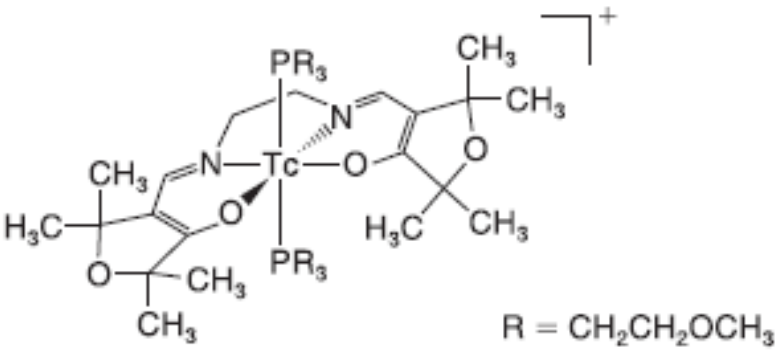


- ^{131}I is used for effective treatment of hyperthyroidism (甲状腺功能亢进) & thyroid cancer (甲状腺癌).



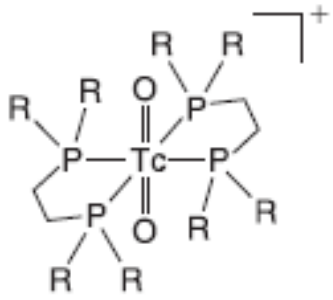
- **^{99m}Tc Imaging Agents**:

A patient with prostatic (前列腺) cancer. (left) After adding ^{99m}Tc-hydroxymethylenediphosphonate & (right) after adding ^{186}Re-hydroxyethylidene-1,1-diphosphonate (therapy).



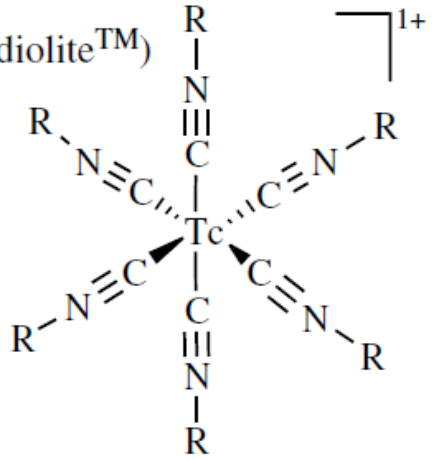
Tc-Q12

R = $CH_2CH_2OCH_3$



Myoview

^{99m}Tc-sestamibi (Cardiolite™)



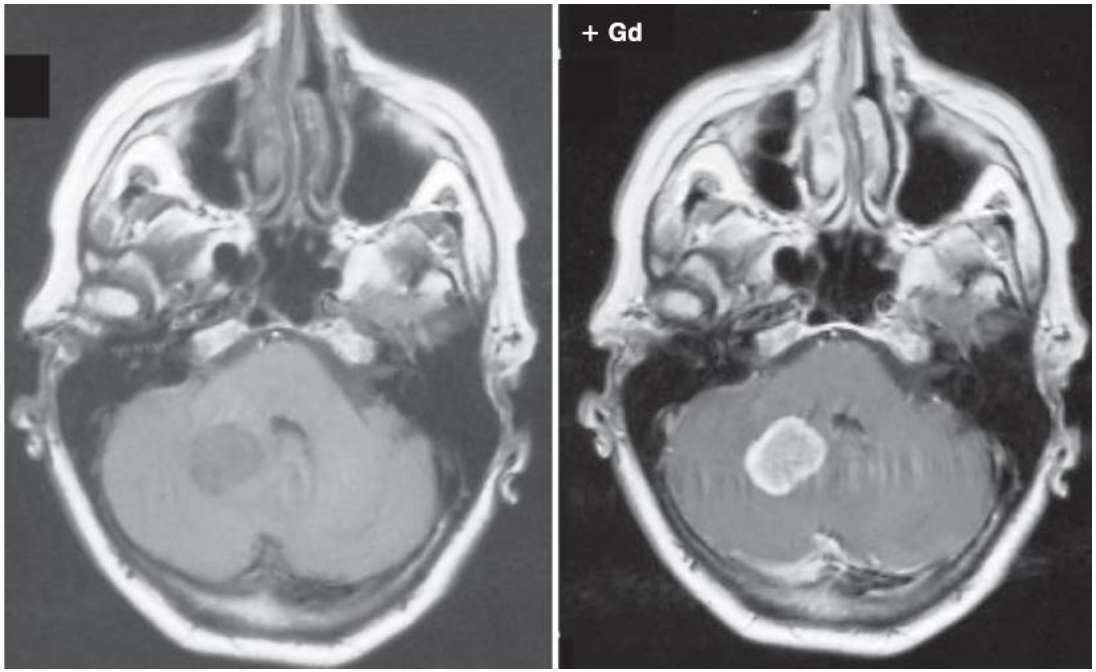
R = $CH_2CH_2OCH_3$

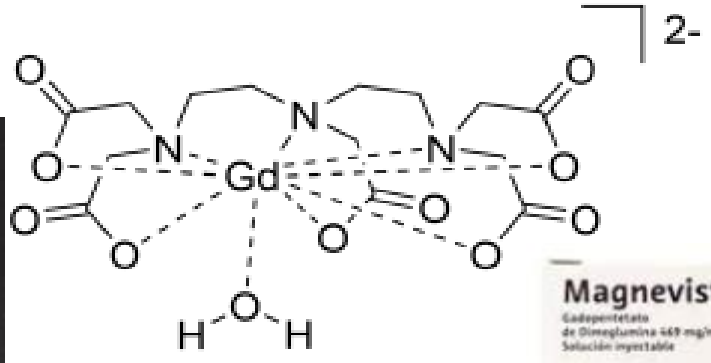
• **Magnetic Resonance Imaging (MRI) Contrast Agents**

• Spatial distribution of protons (mostly from H_2O) is detected in slices of the body by **MRI** (= NMR imaging).

• The harmless magnetic field & non-invasive.

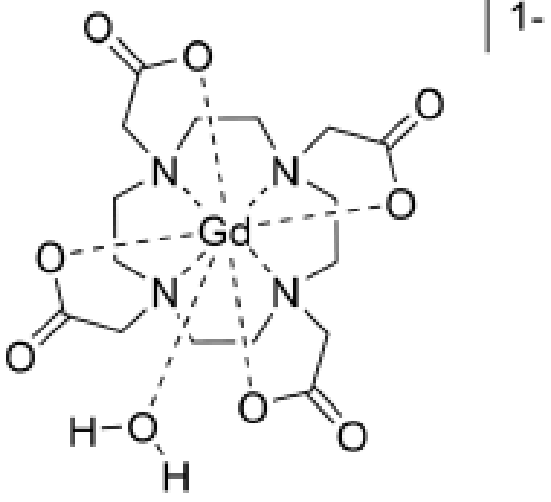
• The 1st MRI contrast agent: **Gd(III)** complex **$[Gd^{III}(DTPA)(H_2O)]^{2-}$**. Gd(III) ($[Xe]4f^7$) contrast agents are widely used in MRI.



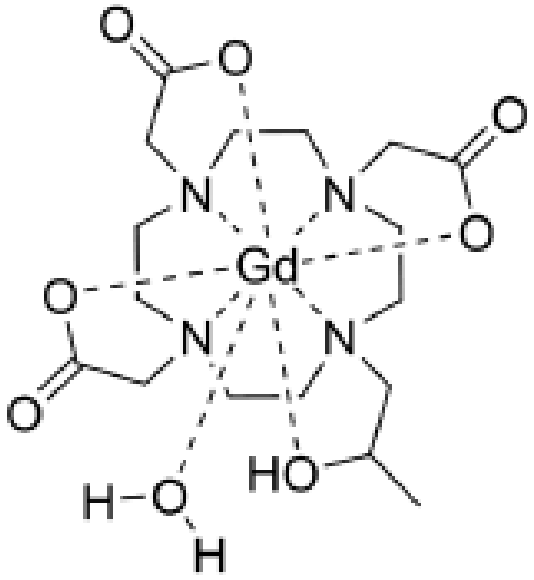


Gd-DTPA

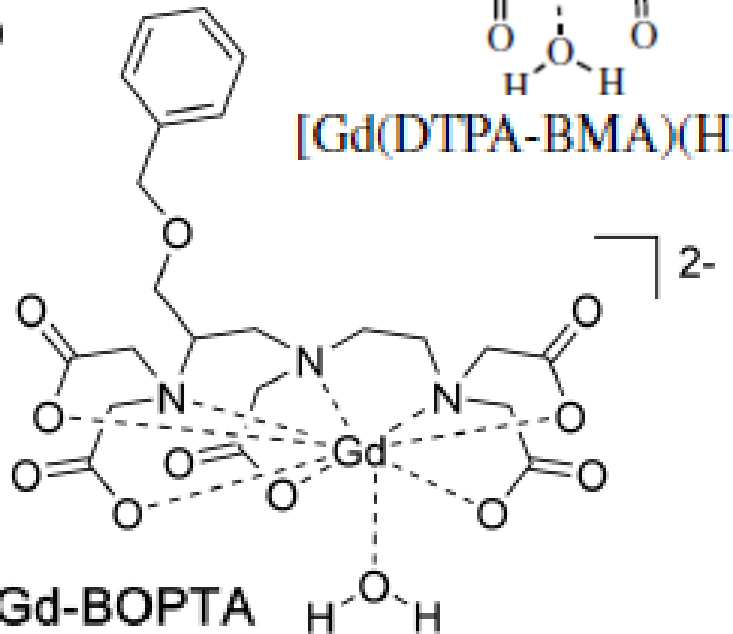
Complex[a]	Brand Name	log K^b	log K^{*c}
$[Gd(DTPA)(H_2O)]^{2-}$	Magnevist	22.5	17.7
$[Gd(DOTA)(H_2O)]^{-}$	Dotarem	25.3	18.3
$[Gd(DTPA\text{-}BMA)(H_2O)]$	Omniscan	16.8	14.9
$[Gd(HP\text{-}DO3A)(H_2O)]$	ProHance	23.8	17.2
$[Gd(bopta)(H_2O)]^{2-}$	MultiHance	22.5	
$[Gd(DO3A\text{-}butrol)(H_2O)]$	Gadovist		



Gd-DOTA

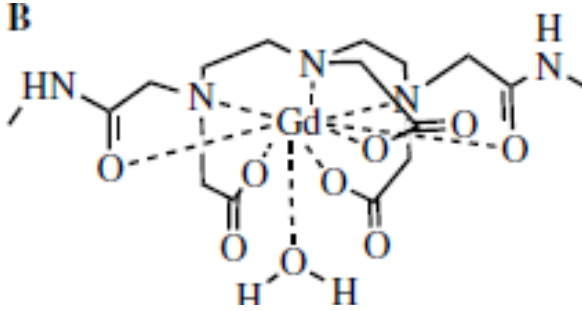


Gd-HP-DO3A



Gd-BOPTA

B



$[Gd(DTPA\text{-}BMA)(H_2O)]$

Mineral Supplements

- *~24 essential elements* are required for our bodies.
- **Fe** deficiency leads to anemia (贫血). Fe(II) compounds (e.g., Fe(II) succinate), not Fe(III) compounds, are used as oral Fe supplements.
- **Zn** deficiency induces growth retardation (many zinc-binding proteins associated with steroid hormones).
- Excess **Ca** intake interferes with Fe absorption & hardens arteries (动脉).

Metal	Recommended Daily Dose (U.S.)	Result of Deficiency	Toxic Level	Toxic Effects
Ca	1 g	Bone deterioration	$>2.5\,g\,day^{-1}$	Magnesium deficiency
Cr	5–200 μg	May regulate insulin levels	>70 mg [Cr(III)]	Irregular heartbeat
Fe	10–15 mg	Anemia	$>60\,mg\,kg^{-1}$	Liver cirrhosis, vascular congestion
Cu	~2 mg	Brain disease, anemia, heart disease	7.5 g (death)	Hemolytic anemia
Zn	15 mg	Growth retardation, skin changes	$>500\,mg\,day^{-1}$	Heavy vomiting

Key Summary

• Various inorganic compounds have long been used in therapeutic & diagnostic applications.

• **Cisplatin** which coordinates to (usually **2 G bases** of) **DNA** is a common anticancer drugs. It can induce the cancer cells to undergo **apoptosis**.

• **As_2O_3** is a drug developed in China.
• **^{99m}Tc agents** are widely used in **diagnostic** imaging.
• **Gd(III)** contrast agents are widely used in **MRI**.

• *~24 elements* are *essential* for our bodies. Insufficient or excess amount of these elements can affect various biological functions & diseases.

Thank You for Your Attention!
Any Questions?