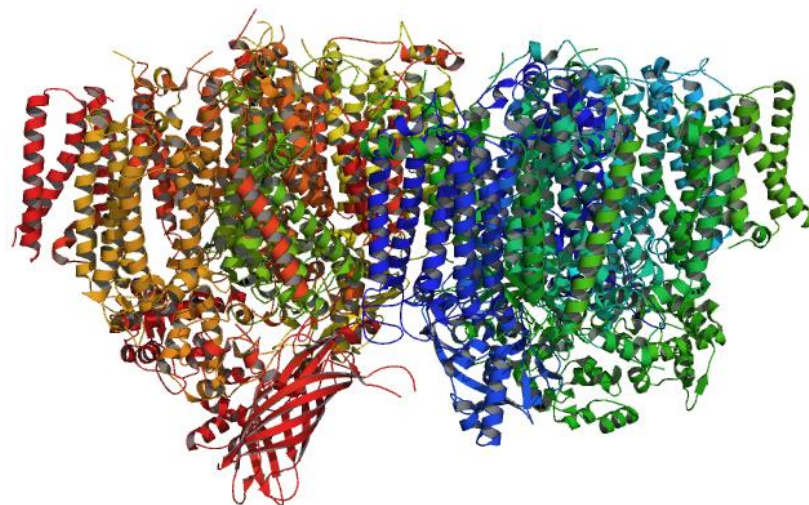
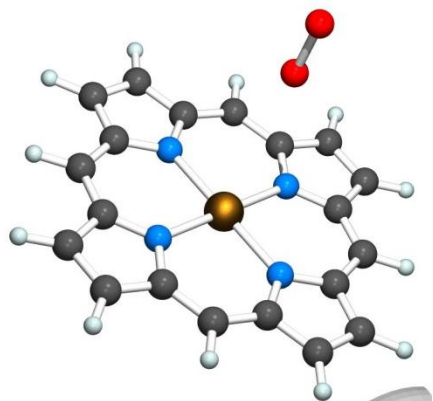
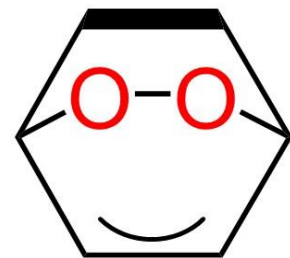


Bioinorganic Chemistry (BIC)

V. Metals in Medical Applications

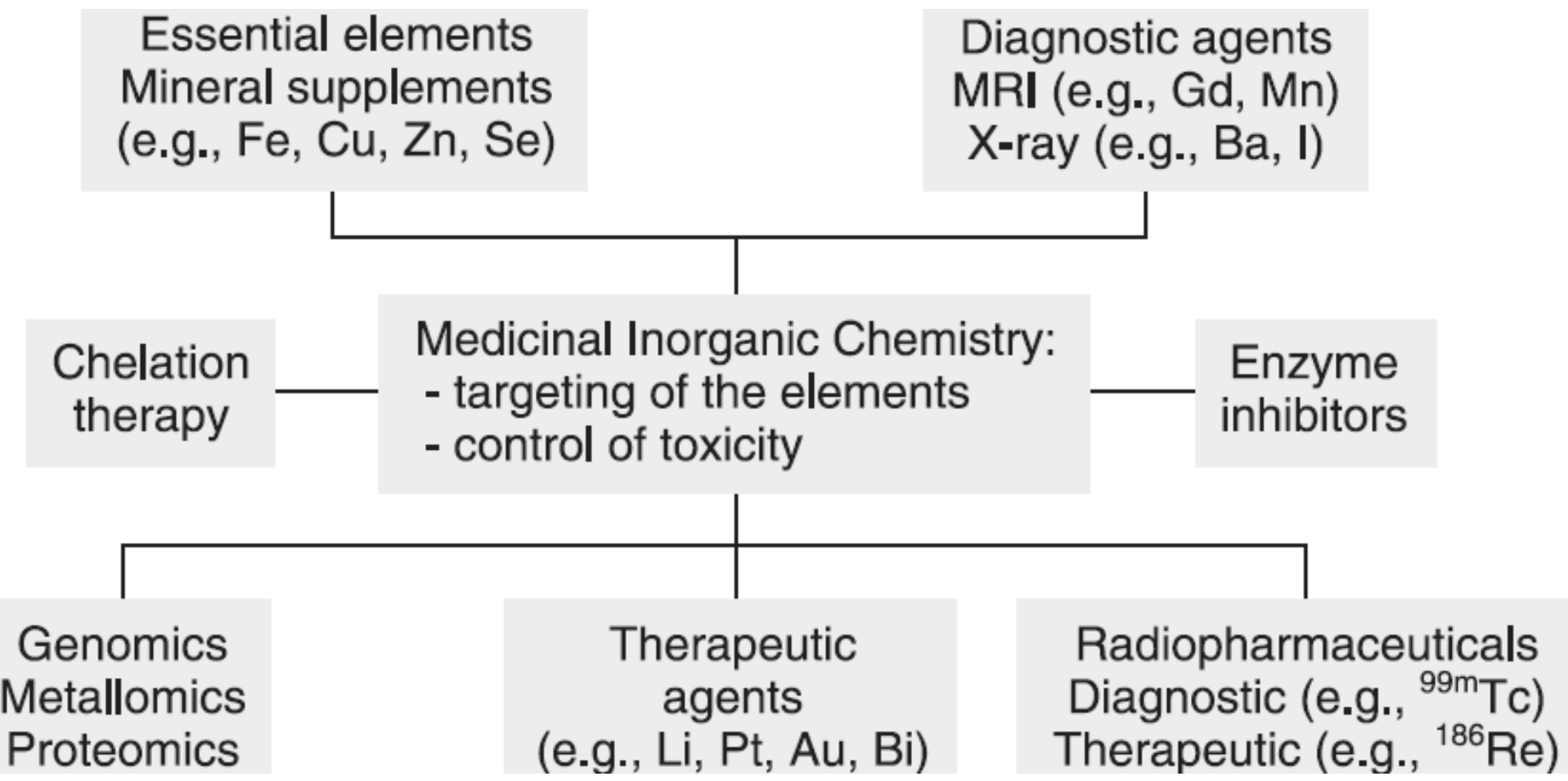


Dr. (O₆S₄C₄Ar) Lung Wa CHUNG (钟龙华)
(oscarchung@sustech.edu.cn)
Department of Chemistry



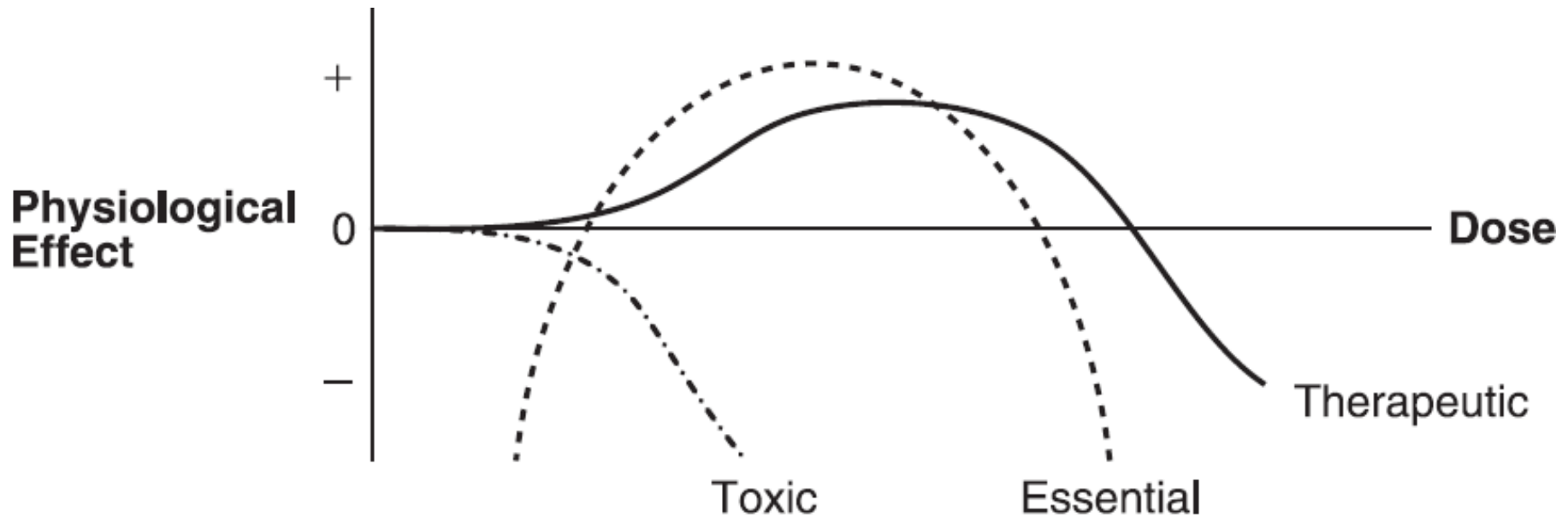
Medicinal Inorganic Chemistry

- 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

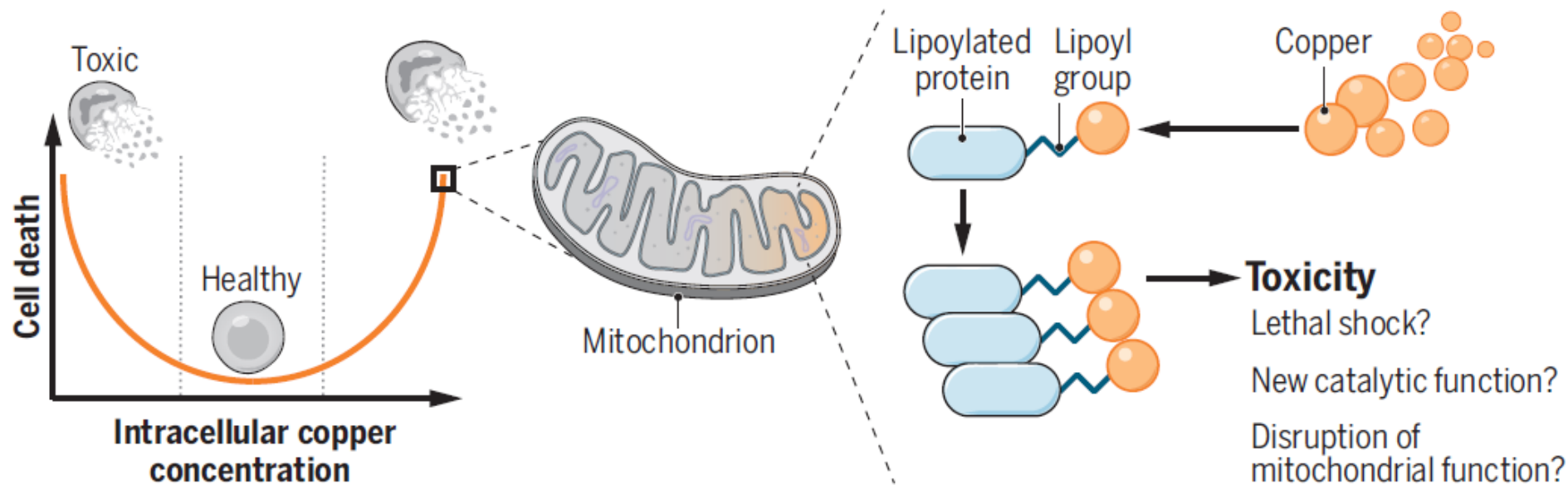
- The toxicity depends on element, its oxidation state, its coordination modes, & dose/mode of administration. Also, the presence of the other elements may affect the effect of an element.



- 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.



1962

First protein X-ray structure: myoglobin with its Fe-centred haem group. Nobel Prize in Chemistry awarded to Perutz and Kendrew

1965

Discovery of the antitumour activity of cisplatin (previously known as Peyrone's chloride) by Rosenberg and co-workers

1973

Nobel Prize in Chemistry awarded jointly to Fischer and Wilkinson for their pioneering work on the chemistry of organometallic compounds

1977

Discovery of the angiotensin-converting-enzyme inhibitor captopril, whose thiol metal-binding group coordinates the active site Zn^{2+} ion

1985

Approval of auranofin as an antirheumatic agent

1995

Carbonic anhydrase inhibitor dorzolamide, developed using structure-based drug design, enters the market

Batimastat is the first synthetic MMP inhibitor to enter clinical studies to treat cancer. Trials were stopped in phase III (REF.¹⁹⁰)

1999

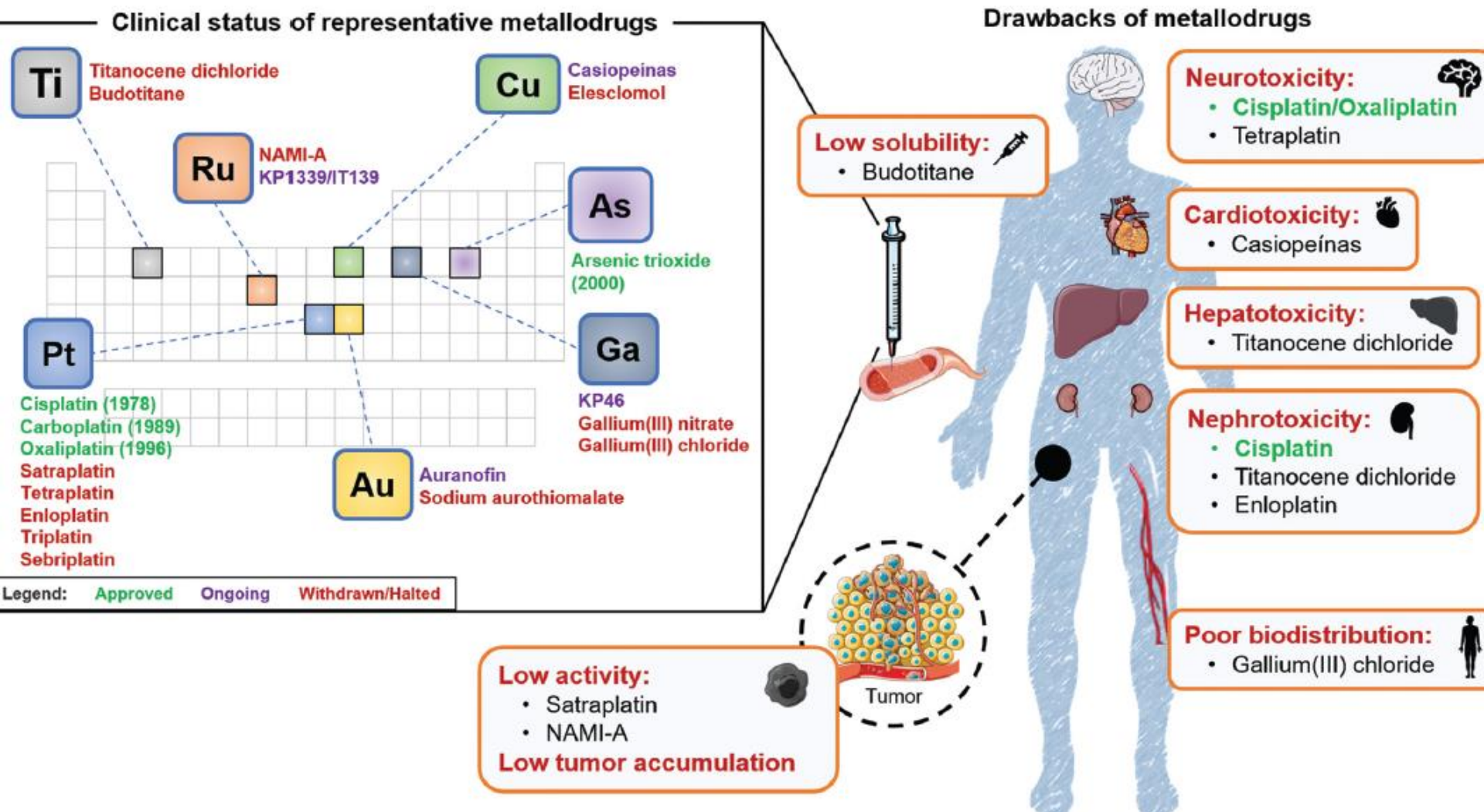
NAMI-A is the first Ru-based compound to enter clinical trials to treat cancer. These organometallic compounds are possible alternatives to Pt derivatives^{191–193}

2006

Zn^{2+} -dependent histone deacetylase inhibitor SAHA approved for clinical use to treat CTCL

2007

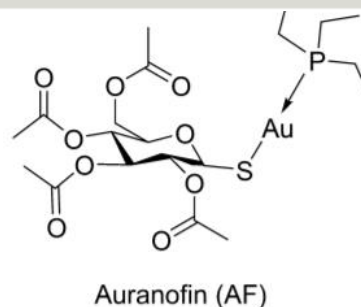
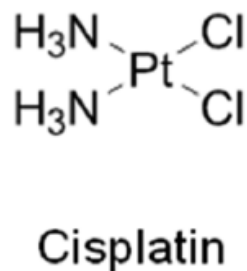
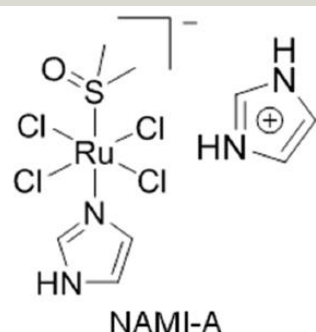
Approval of raltegravir, an HIV integrase inhibitor targeting the Mg^{2+} -aided catalytic site



Compound Example (Brand Name)	Function	Comment
ACTIVE COMPLEXES^a		
<i>cis</i> -[Pt ^{II} Cl ₂ (NH ₃) ₂] (Cisplatin)	Anticancer	Trans isomer is inactive
[Gd ^{III} (DTPA)(H ₂ O)] ²⁻ (Magnevist)	Extracellular MRI ^b contrast agent	Low toxicity
[^{99m} Tc ^I (CNCH ₂ C(CH ₃) ₂ OCH ₃) ₆] ⁺ (Cardiolite)	Myocardial imaging	Positively charged complex taken up by the heart
Vitamin B ₁₂	Coenzyme	Deficiency causes pernicious anemia
ACTIVE METALS		
Li ₂ CO ₃	Prophylaxis bipolar disorders	Li(I) forms weak complexes, labile
Au ^I (thiomalate) (Myocrisin)	Antirheumatoid arthritic	Facile thiol exchange on Au(I)
Ammonium potassium Bi ^{III} citrate (De-Nol)	Antibacterial, antiulcer	Strong binding of Bi(III) to thiols, facile exchange
Na ₂ [Fe ^{II} (CN) ₅ NO]·2H ₂ O (Nipride)	Hypotensive	Releases NO, relaxes vascular muscle
Bleomycin	Anticancer	Requires Fe for DNA ^c attack
<i>p</i> -Xylyl-bicyclam·8HCl (AMD3100)	Anti-HIV ^d	May bind metals <i>in vivo</i>
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	$^{99\text{m}}\text{Tc}$ -pyrophosphate	Bone scanning
Sb	Triostam	NaSb(V) gluconate	Antileishmanial (antiprotozoal)
I		I_2	Antiinfective, disinfectant
Ba	Baridol	BaSO_4	X-ray contrast

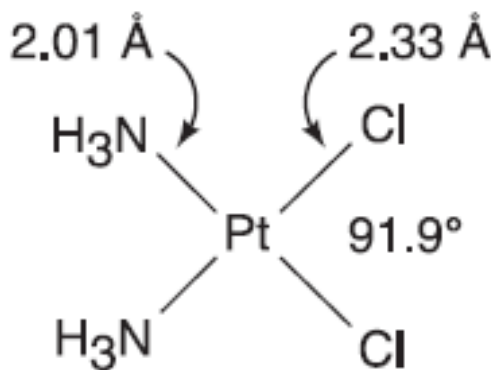
Protein target	Metal	Inhibitor	Type of drug	Application
CAII	Zn	Acetazolamide ^a , benzenesulfonamide	Me-Inhib	Cancer
	Ru	NAMI-A (prodrug)	Me-Drug	Cancer
	Zn (protein)/ Fe (ligand)	Ferrocene-based inhibitor	Me-Inhib/ Me-Drug	Cancer
Cytochrome P450 46A1	Fe	Fluvoxamine ^a	Me-Inhib	Cancer, neurodegenerative 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 <i>Entamoeba histolytica</i>	Au	Auranofin ^a	Me-Drug	Antiparasitic
Methionine aminopeptidase	Co	LAF153	Me-Inhib	Cancer
Urease from <i>Helicobacter pylori</i>	Ni	Acetohydroxamic acid ^a	Me-Inhib	Antibiotic adjuvant



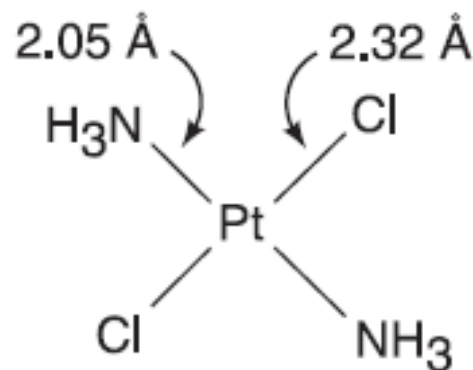
Riccardi et al. *Nat. Rev. Chem.* **2018**, 2, 101.

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.



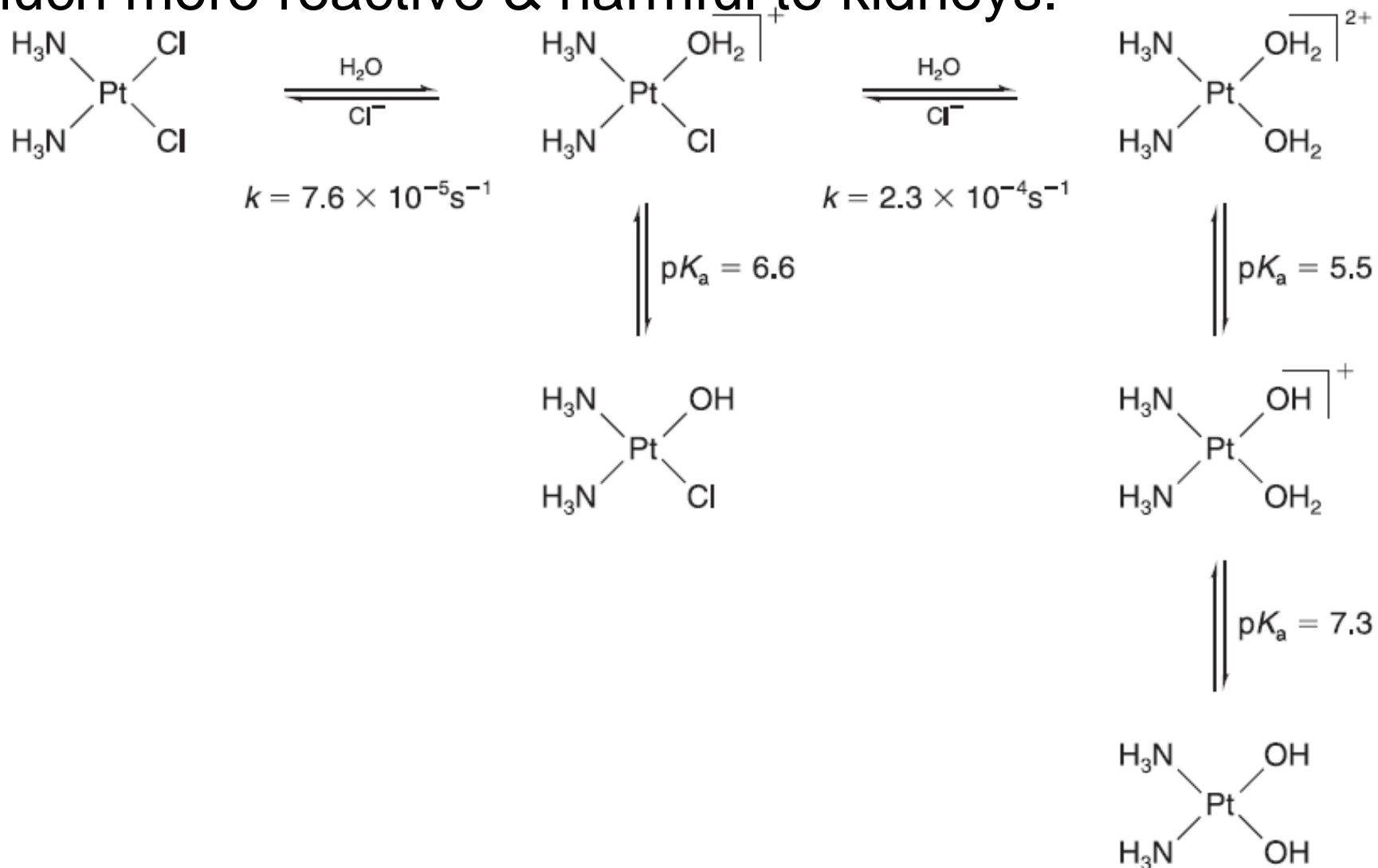
Cisplatin



Transplatin

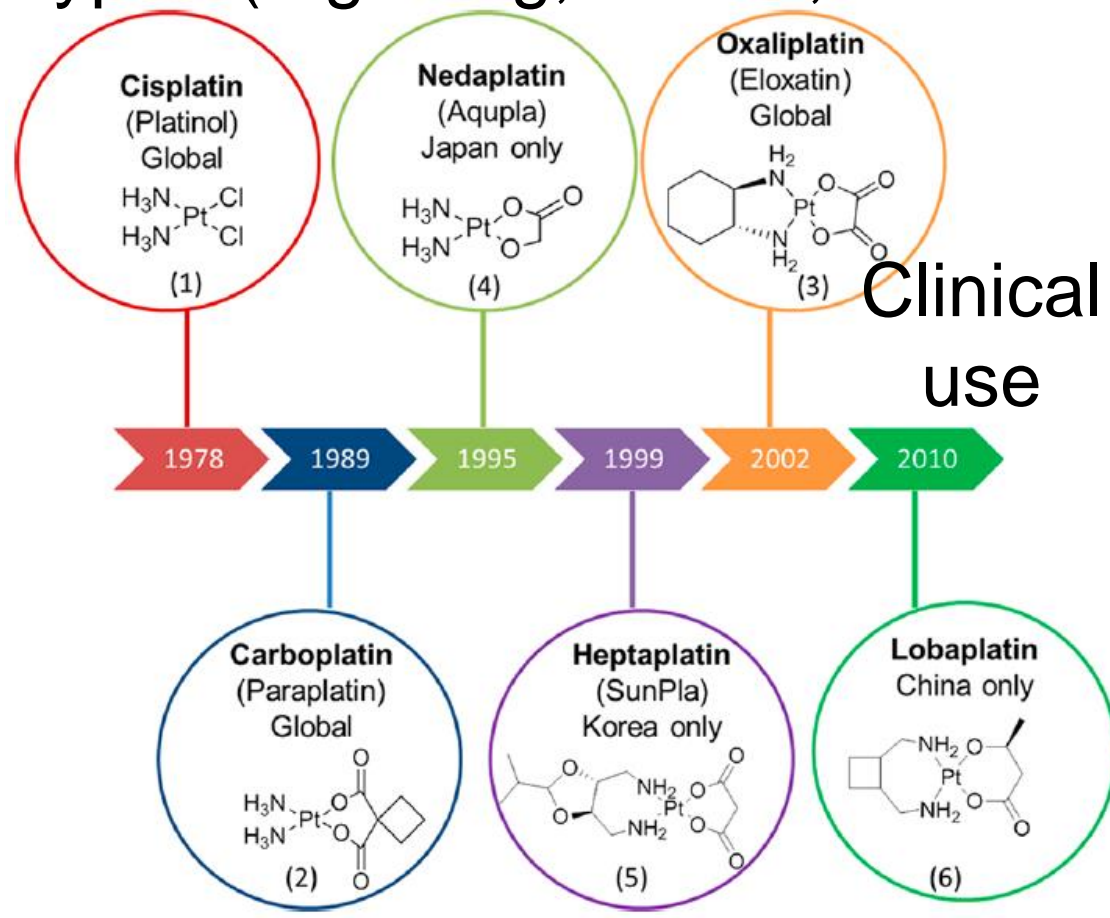
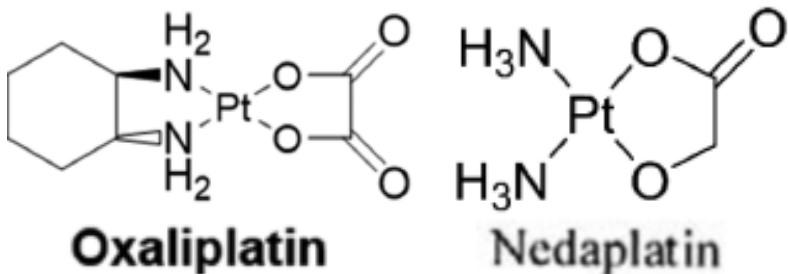
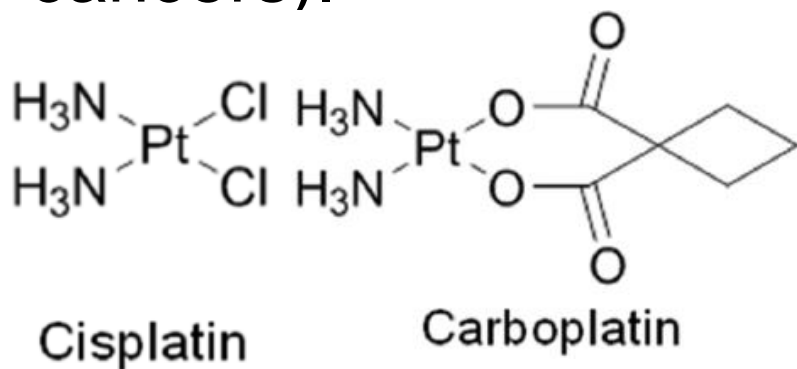
- Only cisplatin could be effective in preventing growth of cancer cells, but **NOT transplatin**.
- Generally, μ mol. doses of cisplatin is used to kill cancer cells.

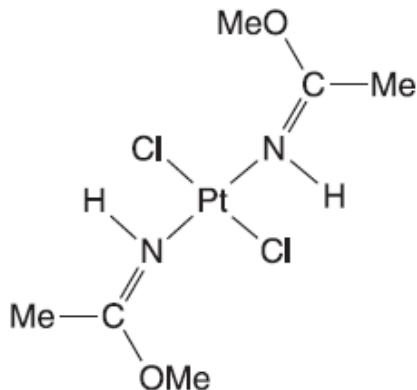
- Cisplatin is not stable in water ($t_{1/2}$: 2.5 hr at 310 K). It is formed in saline (NaCl) solution to administer to patients to avoid hydrolysis. The aquated species are much more reactive & harmful to kidneys.



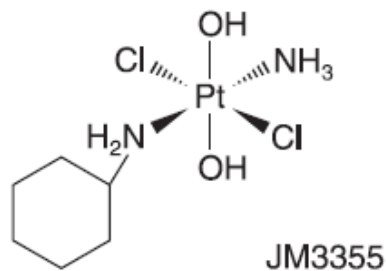
New Generation of Pt Drugs

- **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).



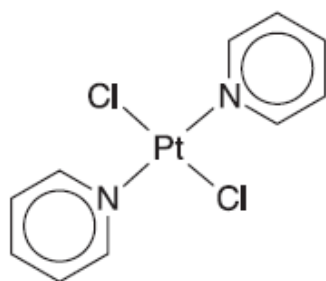


Trans-EE complex with iminoether ligands (more active than *cis* isomer)

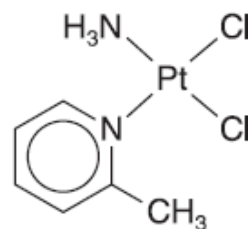


The Pt(II) analogue of this Pt(IV) complex, without axial OH⁻ ligands, is inactive

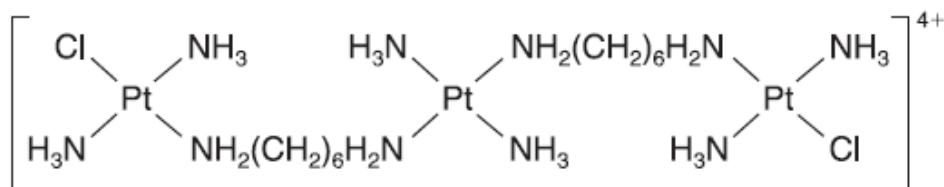
Examples of active Pt complexes based on structure-activity rules



Trans complex with pyridine ligands



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



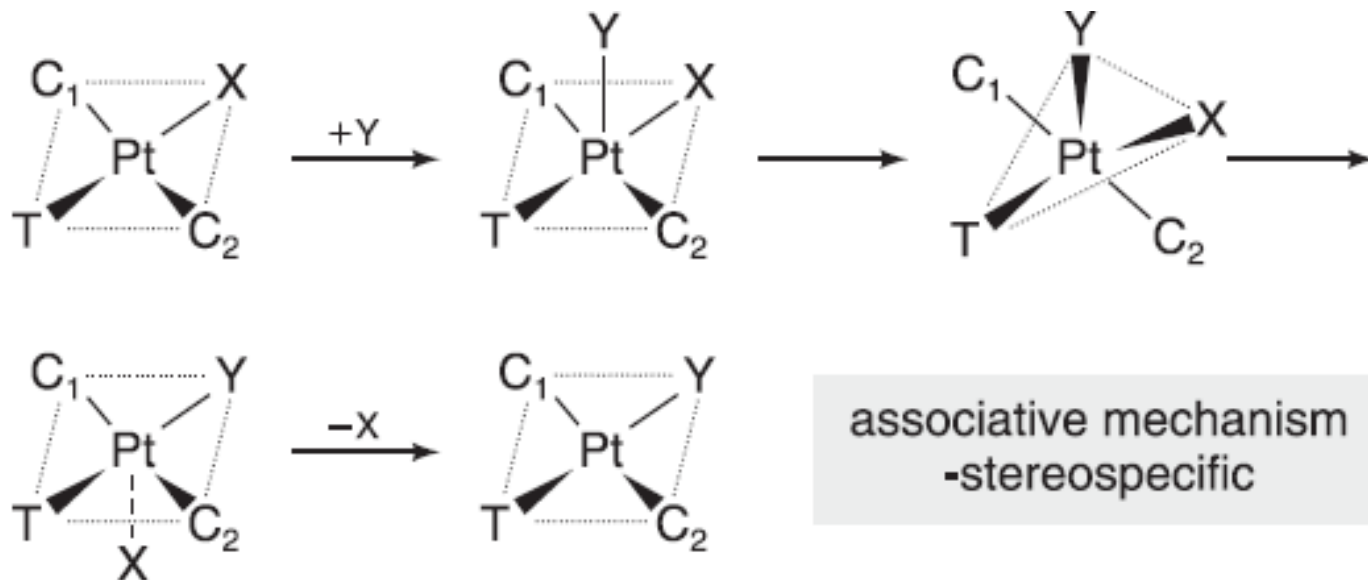
BBR3464

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

Mechanism of Action of Cisplatin: Ligand Substitution



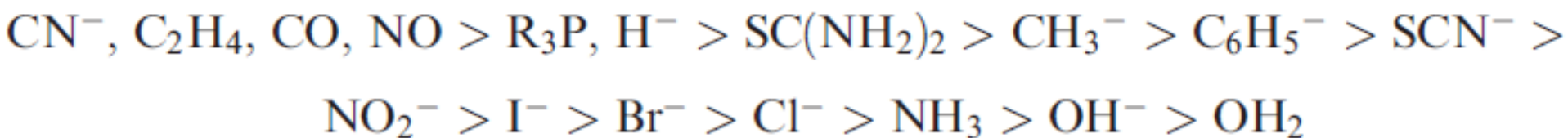
- The mechanism of ligand substitution in square-planar Pt(II) complexes: **associative mechanism**.
- The rate depends on **trans effect** of a ligand (**T**) *trans* to **X**.



Rate law

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

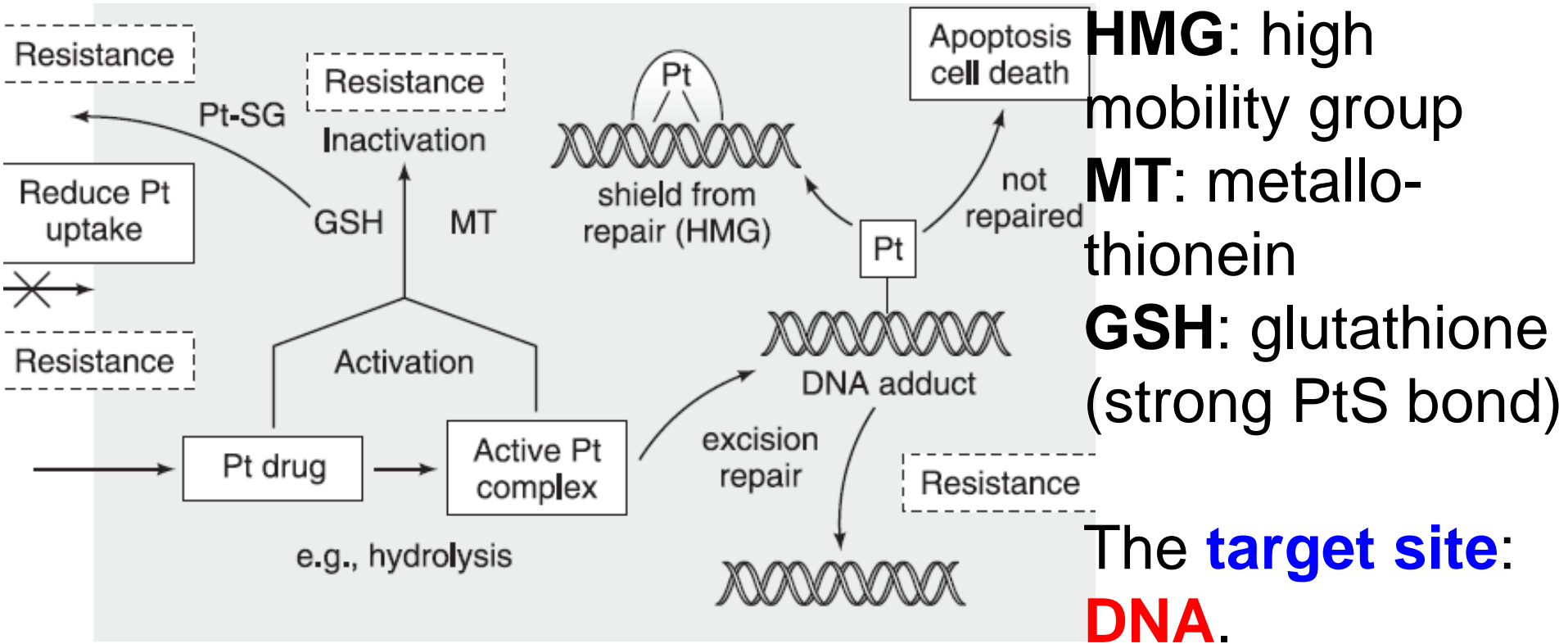
- The order of the **trans effect** of different ligands (L):



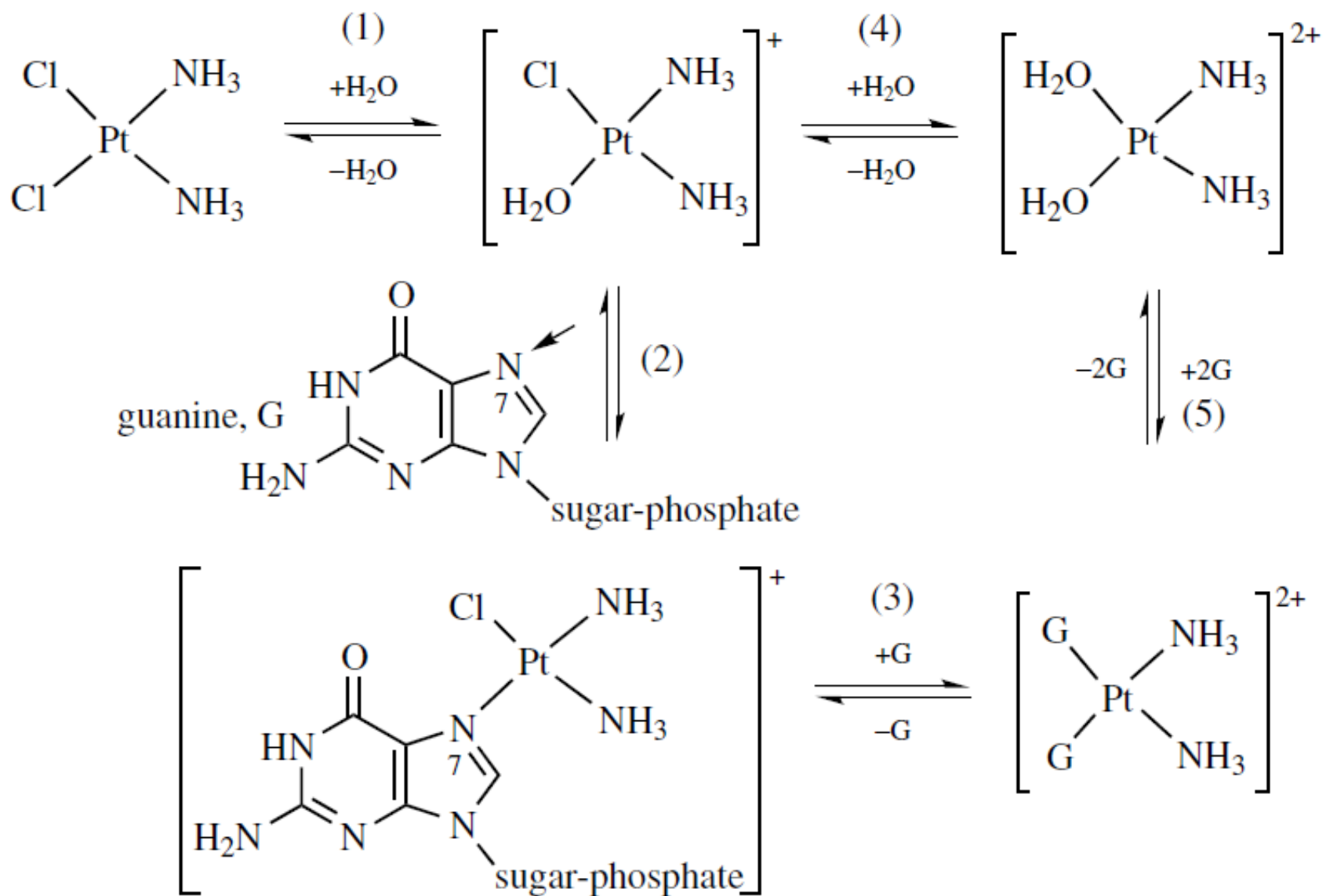
- Trans effect**: a **kinetic** effect to affect the **reaction rate**. The larger **trans effect** of a ligand *trans* to **X** ligand, the faster ligand substitution of **X**.



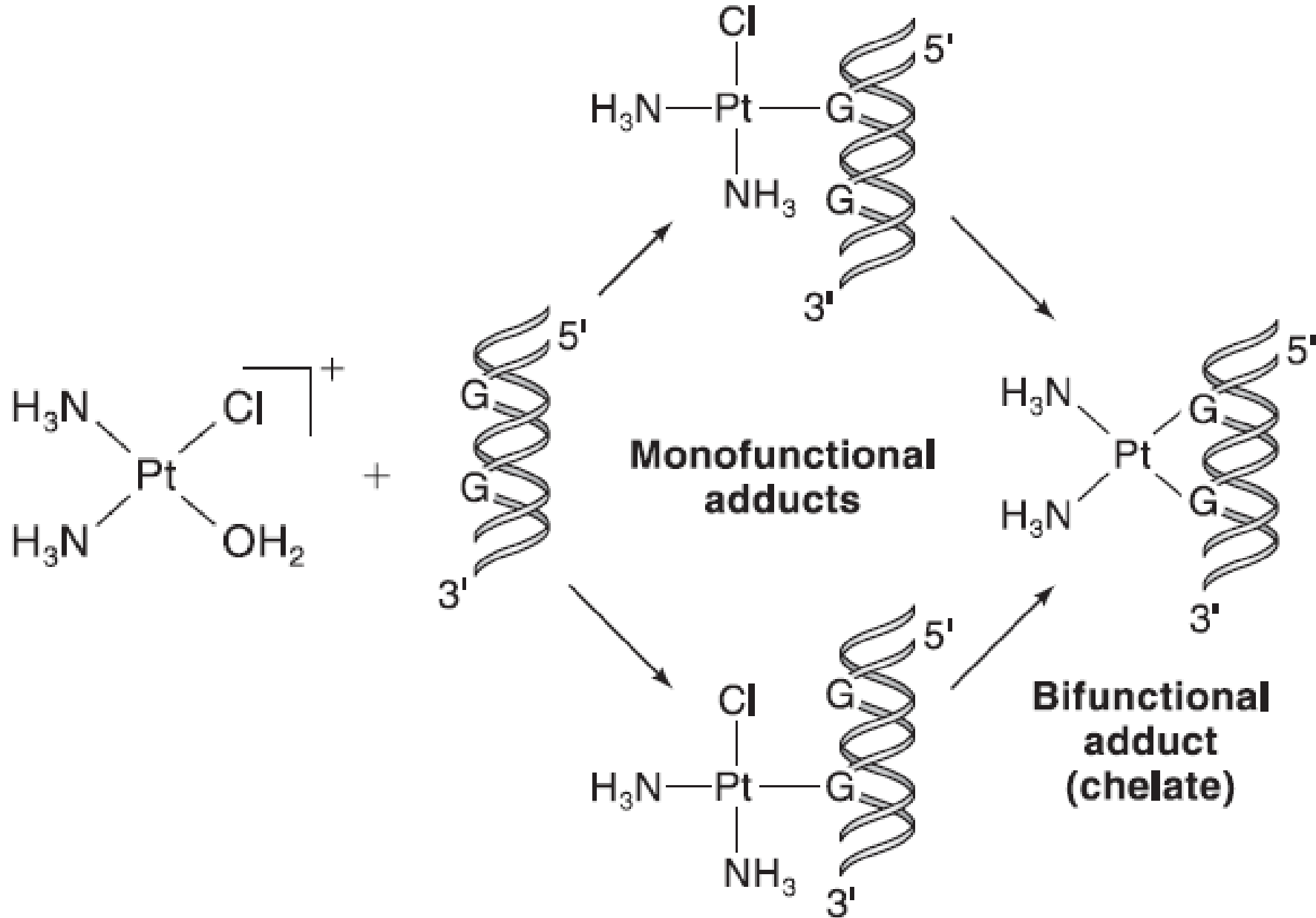
- In comparison, **trans influence** is a **thermodynamic** effect to affect **ground-state properties** (e.g. **bond strength**, NMR coupling constant & vibrational frequencies) of M-ligand.



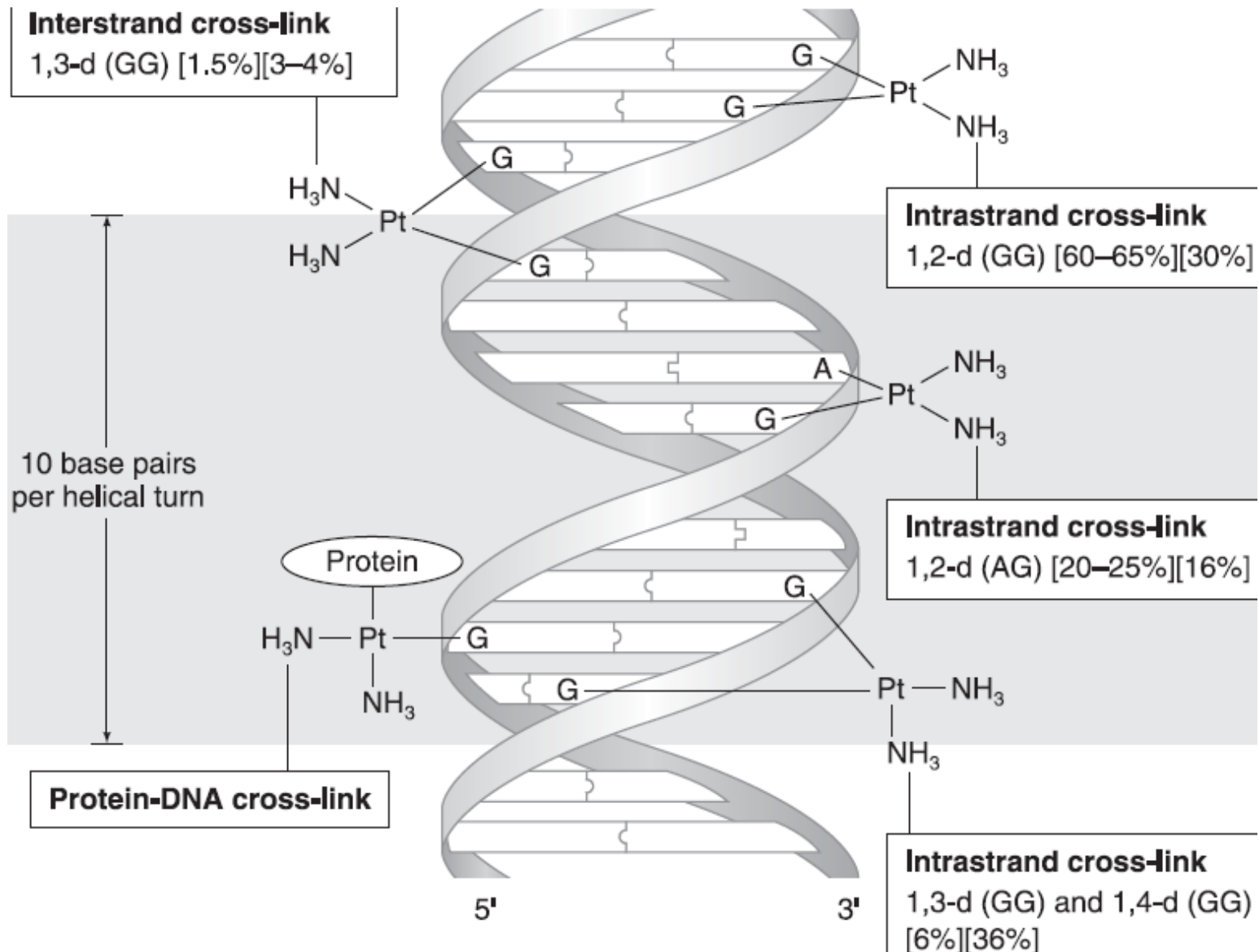
- The **major** binding site is **N7** of (most e-rich) **guanine**.
- The bent platinated B-DNA is recognized by HMG proteins. The platinated DNA adducts which are **not repaired** in cells trigger **apoptosis** (programmed cell death), instead of normal function as transcription factors. Then, DNA 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 $\sim 35\text{-}40^\circ$.



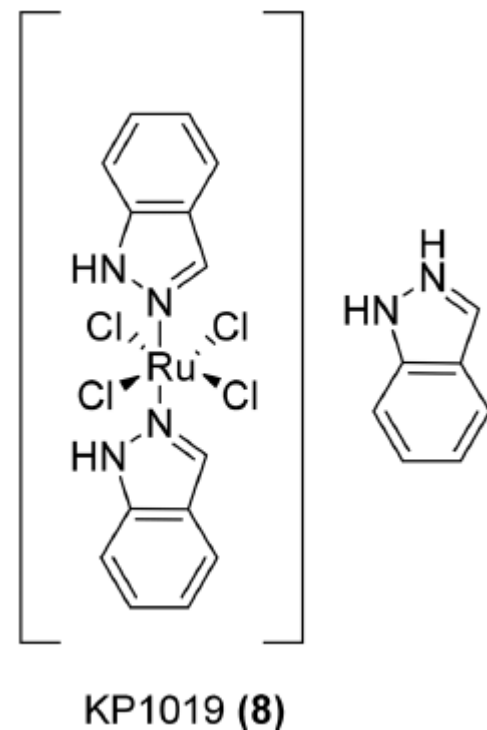
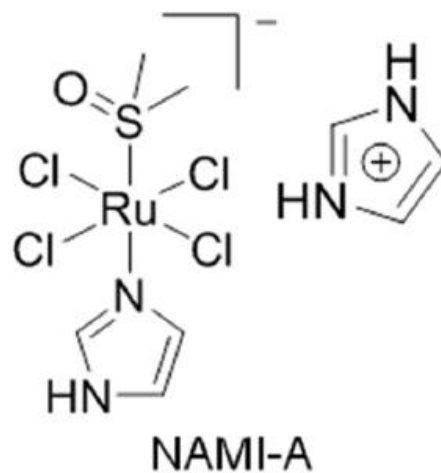
- **Major adduct: 1,2 intrastrand** cross-links with G-G & sometimes G-A.
- Other binding sites: N7 of adenine & N3 of cytosine.

Other Metal Compounds

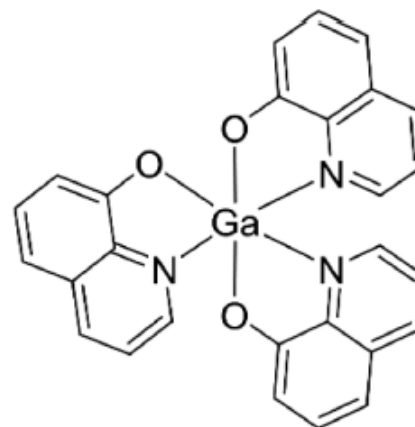
- **Pd** complexes: much more reactive than Pt(II) (by $\sim 10^4$ - 10^5). Pd(II) complexes tend to have side reactions before accessing the DNA target.

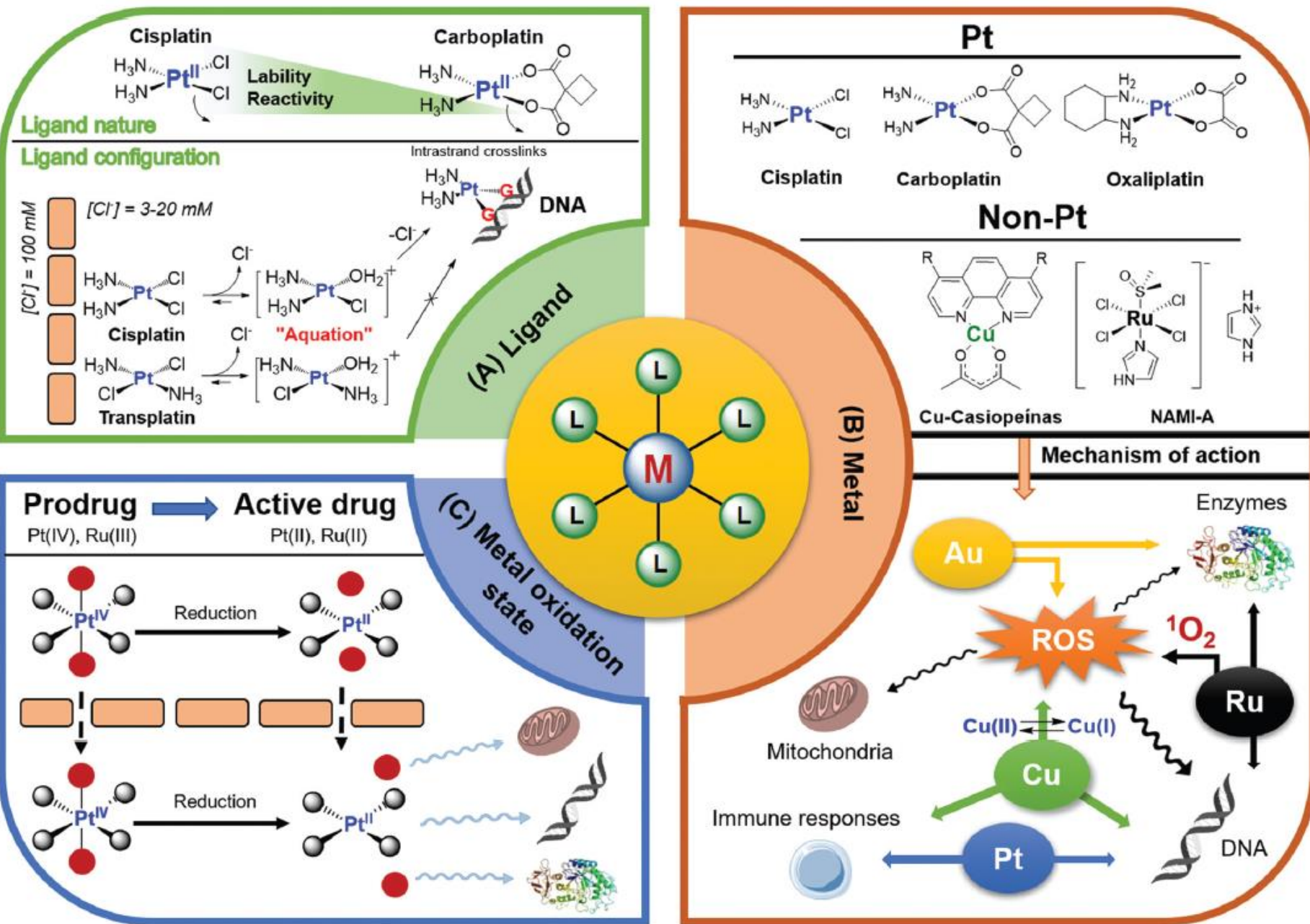
- **Ru** complexes:

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



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

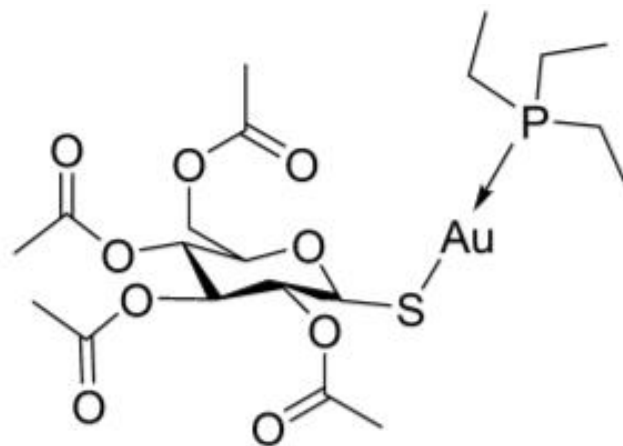
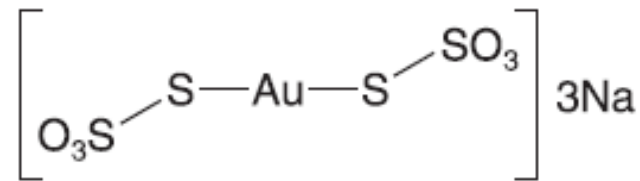
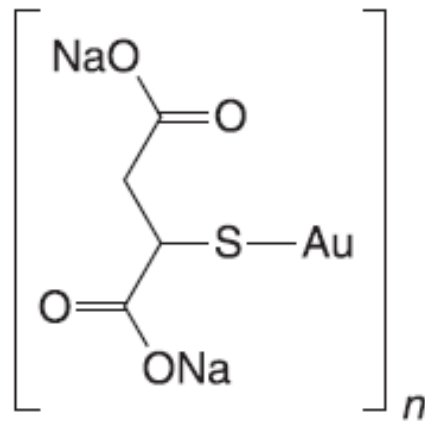
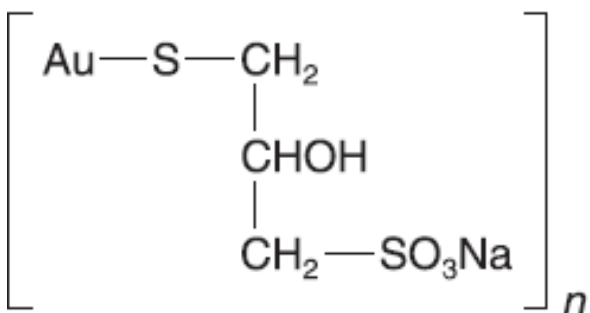




- **As** complexes are often toxic.
- **As₂O₃** (砒霜): a therapeutic agent for treating acute promyelocytic leukemia (前骨髓球性白血病) in China.
- Arsenic trioxide (Trisenox) was approved as a chemotherapeutic agent by US FDA.
- Arsenic trioxide induces cancer cells to occur apoptosis.



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



Auranofin (AF)

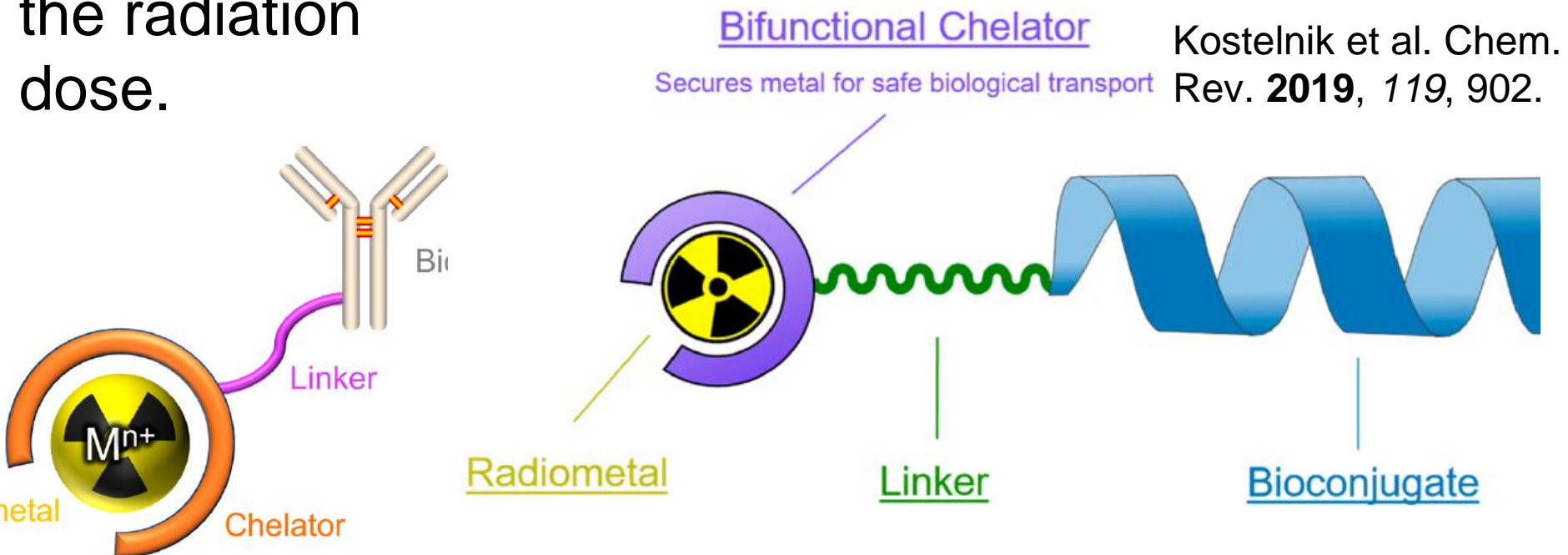


- **Li** drug (Li_2CO_3) treats bipolar affective disorders (情感表达障碍症), e.g. manic depression (狂躁忧郁症).






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)
 $^{117\text{m}}\text{Sn}$ (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)



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

 **PET**  **Beta Therapy**
 **SPECT**  **Alpha Therapy**
 **Auger e⁻ Therapy**

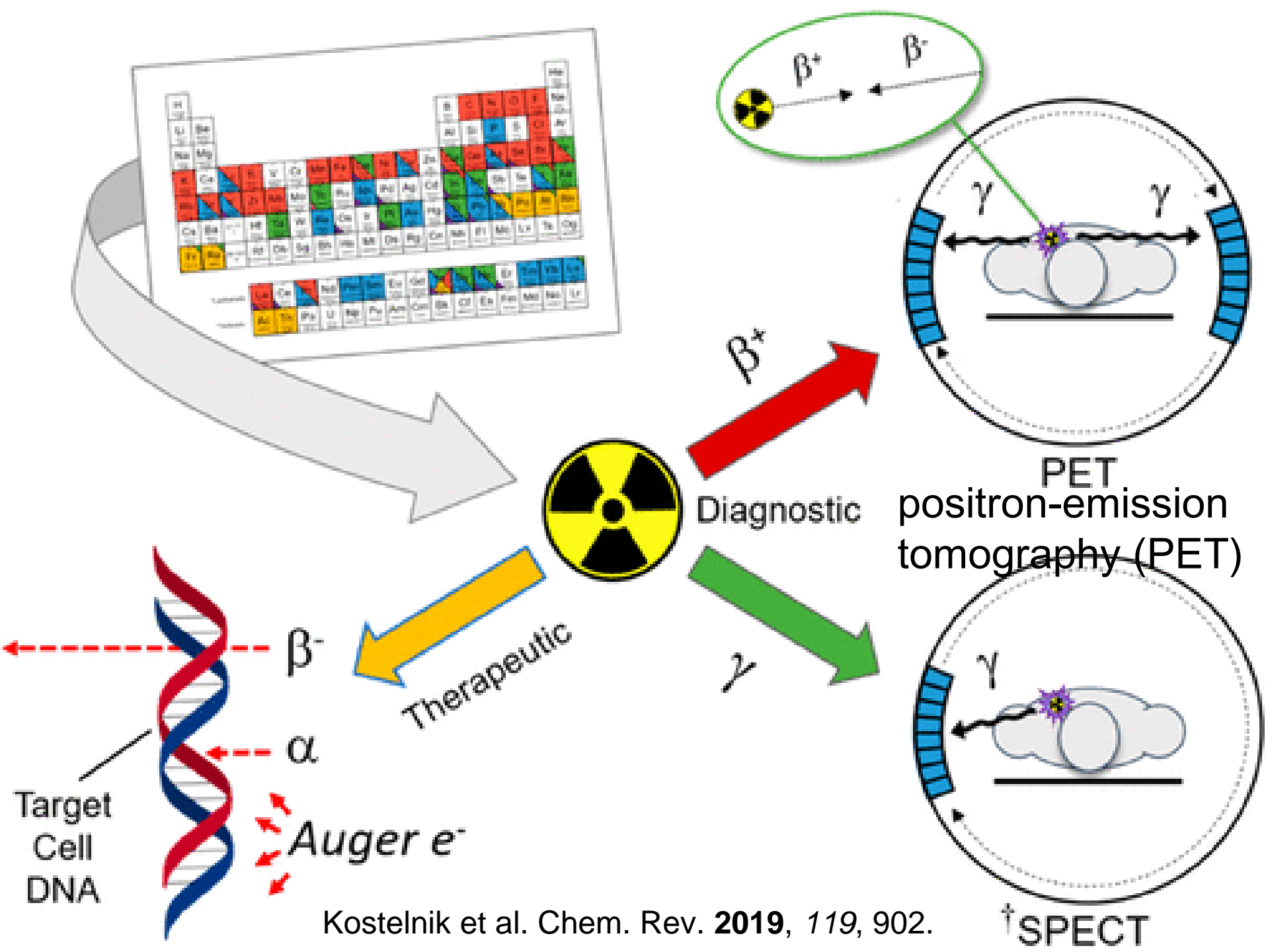
1 H Hydrogen 1.008																	2 He Helium 4.0026	
3 Li Lithium 6.94	4 Be Beryllium 9.0122																	10 Ne Neon 20.180
11 Na Sodium 22.990	12 Mg Magnesium 24.305																	18 Ar Argon 39.948
19 K Potassium 39.098	20 Ca Calcium 40.078(4)	21 Sc Scandium 44.956	22 Ti Titanium 47.887	23 V Vanadium 50.942	24 Cr Chromium 51.996	25 Mn Manganese 54.938	26 Fe Iron 55.845(2)	27 Co Cobalt 58.933	28 Ni Nickel 58.693	29 Cu Copper 63.546(3)	30 Zn Zinc 65.38(2)	31 Ga Gallium 69.723	32 Ge Germanium 72.630(8)	33 As Arsenic 74.922	34 Se Selenium 78.971(8)	35 Br Bromine 79.904	36 Kr Krypton 83.796(2)	
37 Rb Rubidium 85.468	38 Sr Strontium 87.62	39 Y Yttrium 88.906	40 Zr Zirconium 91.224(2)	41 Nb Niobium 92.906	42 Mo Molybdenum 95.95	43 Tc Technetium	44 Ru Ruthenium 101.07(2)	45 Rh Rhodium 102.91	46 Pd Palladium 106.42	47 Ag Silver 107.87	48 Cd Cadmium 112.41	49 In Indium 114.82	50 Sn Tin 118.71	51 Sb Antimony 121.76	52 Te Tellurium 127.60(3)	53 I Iodine 126.90	54 Xe Xenon 131.29	
55 Cs Caesium 132.91	56 Ba Barium 137.33	57-71 *	72 Hf Hafnium 178.49(2)	73 Ta Tantalum 180.95	74 W Tungsten 183.84	75 Re Rhenium 186.21	76 Os Osmium 190.23(3)	77 Ir Iridium 192.22	78 Pt Platinum 195.08	79 Au Gold 196.97	80 Hg Mercury 200.59	81 Tl Thallium 204.38	82 Pb Lead 207.2	83 Bi Bismuth 208.98	84 Po Polonium	85 At Astatine	86 Rn Radon	
87 Fr Francium	88 Ra Radium	89-103 **	104 Rf Rutherfordium	105 Db Dubnium	106 Sg Seaborgium	107 Bh Bohrium	108 Hs Hassium	109 Mt Meitnerium	110 Ds Darmstadtium	111 Rg Roentgenium	112 Cn Copernicium	113 Nh Nihonium	114 Fl Flerovium	115 Mc Moscovium	116 Lv Livermorium	117 Ts Tennessine	118 Og Oganesson	

*Lanthanoids

57 La Lanthanum 138.91	58 Ce Cerium 140.12	59 Pr Praseodymium 140.91	60 Nd Neodymium 144.24	61 Pm Promethium	62 Sm Samarium 150.36(2)	63 Eu Europium 151.96	64 Gd Gadolinium 157.25(3)	65 Tb Terbium 158.93	66 Dy Dysprosium 162.50	67 Ho Holmium 164.93	68 Er Erbium 167.26	69 Tm Thulium 168.93	70 Yb Ytterbium 173.05	71 Lu Lutetium 174.97
---------------------------------	------------------------------	------------------------------------	---------------------------------	------------------------	-----------------------------------	--------------------------------	-------------------------------------	-------------------------------	----------------------------------	-------------------------------	------------------------------	-------------------------------	---------------------------------	--------------------------------

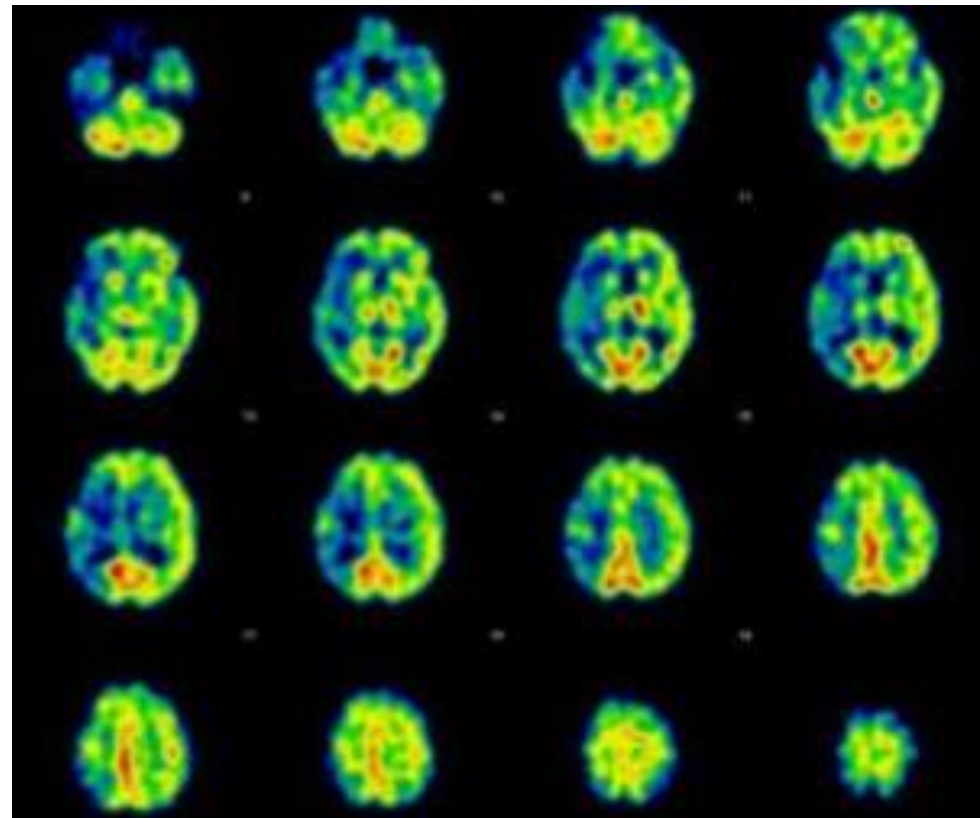
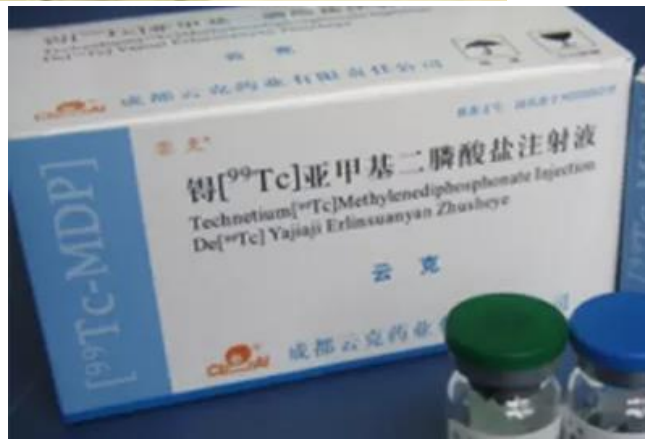
**Actinoids

89 Ac Actinium	90 Th Thorium 232.04	91 Pa Protactinium 231.04	92 U Uranium 238.03	93 Np Neptunium	94 Pu Plutonium	95 Am Americium	96 Cm Curium	97 Bk Berkelium	98 Cf Californium	99 Es Einsteinium	100 Fm Fermium	101 Md Mendelevium	102 No Nobelium	103 Lr Lawrencium
----------------------	-------------------------------	------------------------------------	------------------------------	-----------------------	-----------------------	-----------------------	--------------------	-----------------------	-------------------------	-------------------------	----------------------	--------------------------	-----------------------	-------------------------



• 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.

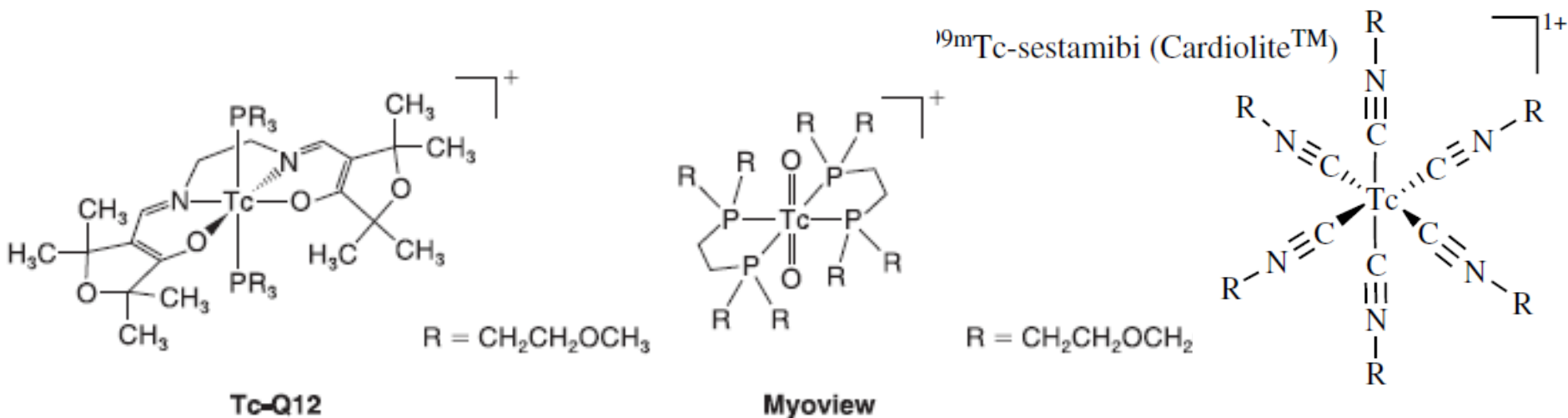
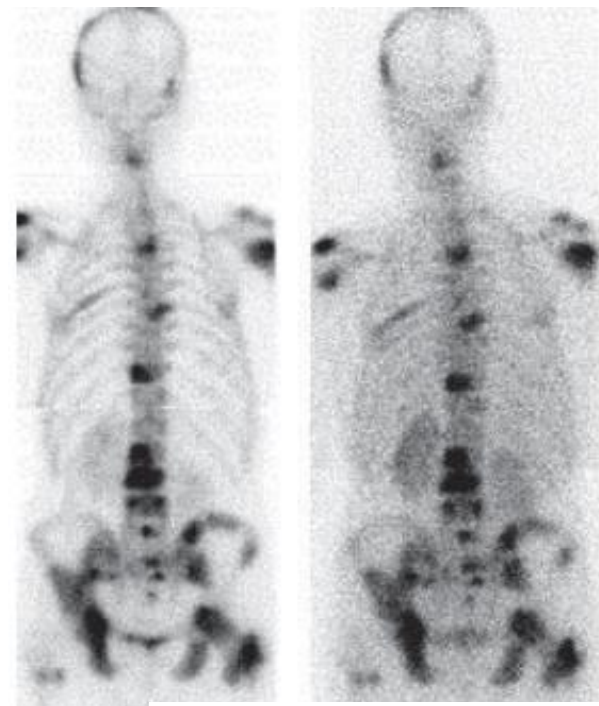
^{67}Ga (3.3 day), ^{111}In (2.8 day), ^{99m}Tc (6.0 h), ^{201}Tl (3.0 day)



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

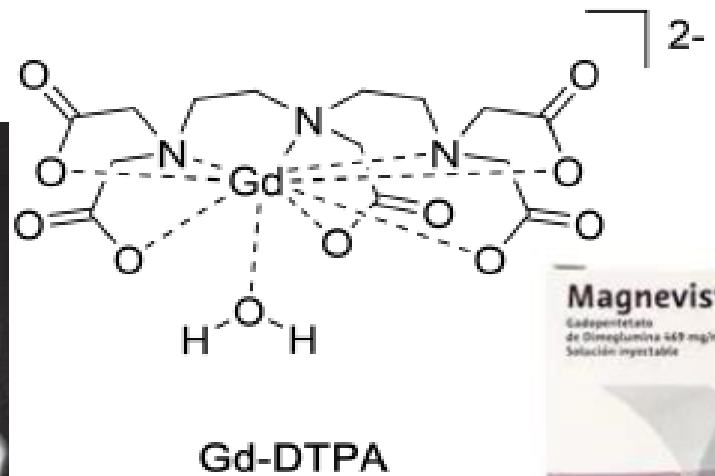
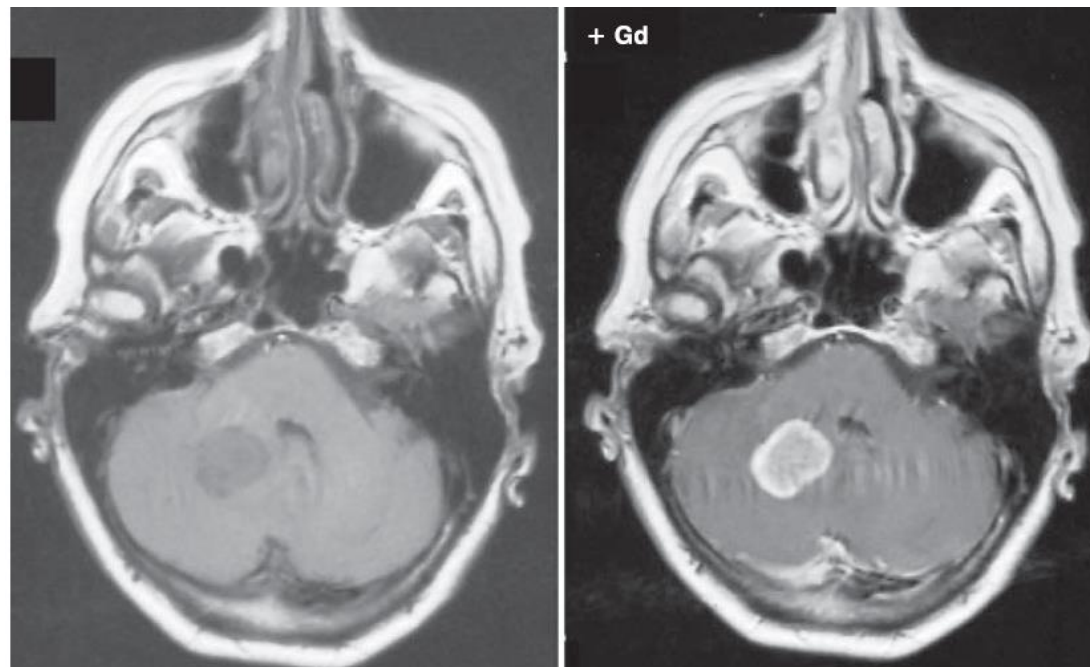
- **$^{99\text{m}}\text{Tc}$ Imaging Agents:**

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

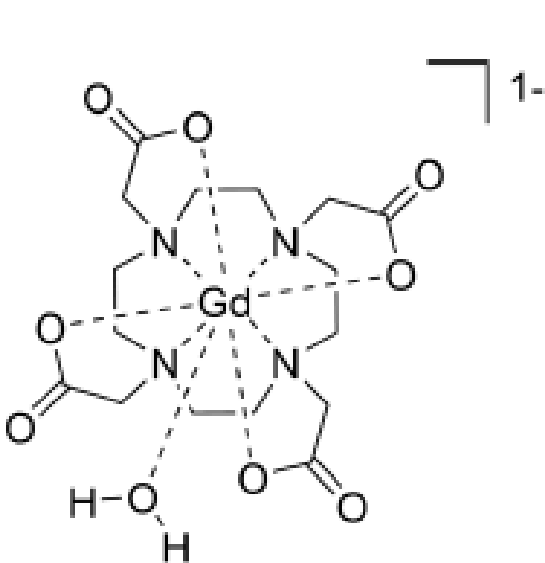


• Magnetic Resonance Imaging (MRI) Contrast Agents

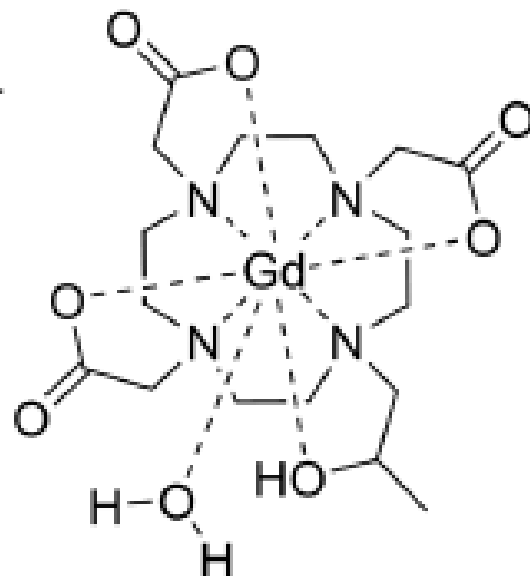
- Spatial distribution of **protons** (mostly from H_2O) is detected in slices of the body by **MRI** (= NMR imaging).
- The harmless magnetic field & non-invasive.
- The 1st MRI contrast agent: **Gd(III)** complex **$[\text{Gd}^{\text{III}}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$** . Gd(III) ($[\text{Xe}]4f^7$) contrast agents are widely used in MRI.



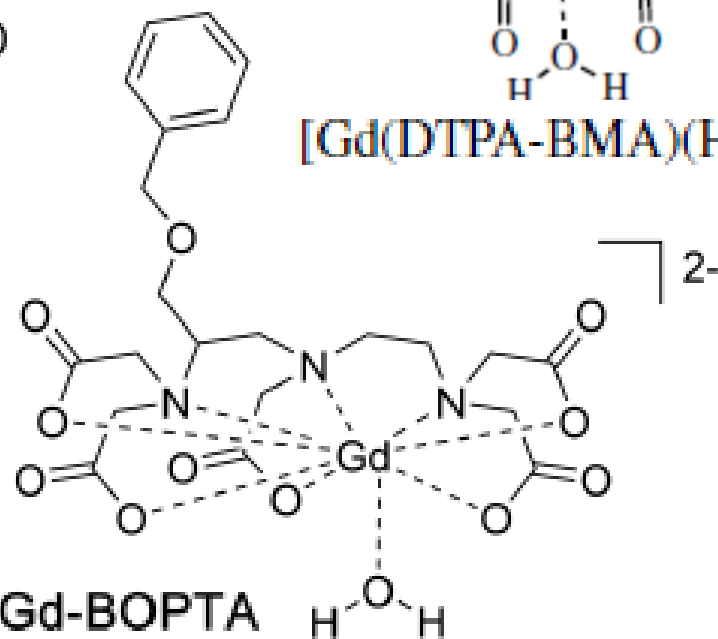
Complex ^a	Brand Name	log <i>K</i> ^b	log <i>K</i> ^{*c}
[Gd(DTPA)(H ₂ O)] ²⁻	Magnevist	22.5	17.7
[Gd(DOTA)(H ₂ O)] ⁻	Dotarem	25.3	18.3
[Gd(DTPA-BMA)(H ₂ O)]	Omniscan	16.8	14.9
[Gd(HP-DO3A)(H ₂ O)]	ProHance	23.8	17.2
[Gd(bopta)(H ₂ O)] ²⁻	MultiHance	22.5	
[Gd(DO3A-butrol)(H ₂ O)]	Gadovist		



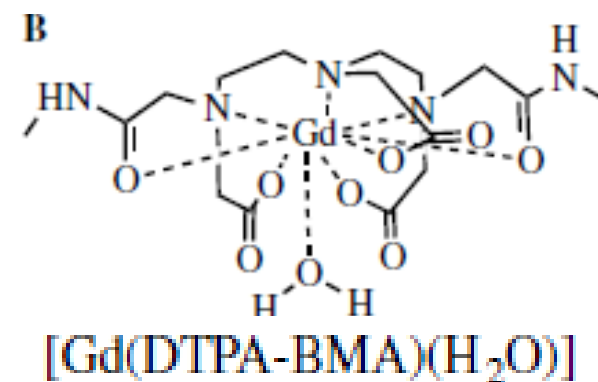
Gd-DOTA



Gd-HP-DO3A



Gd-BOPTA



[Gd(DTPA-BMA)(H₂O)]

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	$> 2.5 \text{ g day}^{-1}$	Magnesium deficiency
Cr	5–200 μg	May regulate insulin levels	$> 70 \text{ mg [Cr(III)]}$	Irregular heartbeat
Fe	10–15 mg	Anemia	$> 60 \text{ mg kg}^{-1}$	Liver cirrhosis, vascular congestion
Cu	$\sim 2 \text{ mg}$	Brain disease, anemia, heart disease	7.5 g (death)	Hemolytic anemia
Zn	15 mg	Growth retardation, skin changes	$> 500 \text{ mg day}^{-1}$	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**.
- **As₂O₃** 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?**