

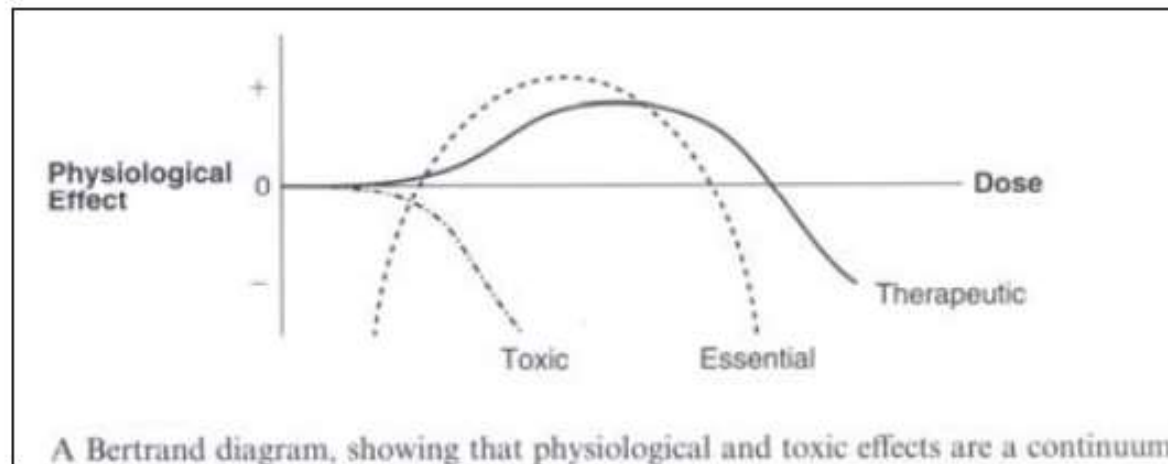
Metals in Medicine

The use of iron and copper can be traced to the ancient Greeks and Hebrews through their writings.

Among metal ions commonly used over the centuries were Hg^{2+} for the treatment of syphilis, Mg^{2+} for intestinal disorders, and Fe^{2+} for anemia.

It is seldom useful to describe elements as "toxic" or "nontoxic". Even so-called toxic compounds can usually be tolerated in low doses, and may exhibit therapeutic effects within narrow concentration ranges, and biochemically essential elements can be toxic at high doses.

The **Bertrand diagram** schematically summarizes this situation:



Chemical Considerations

- **Kinetics**

- Ligand Exchange Rates

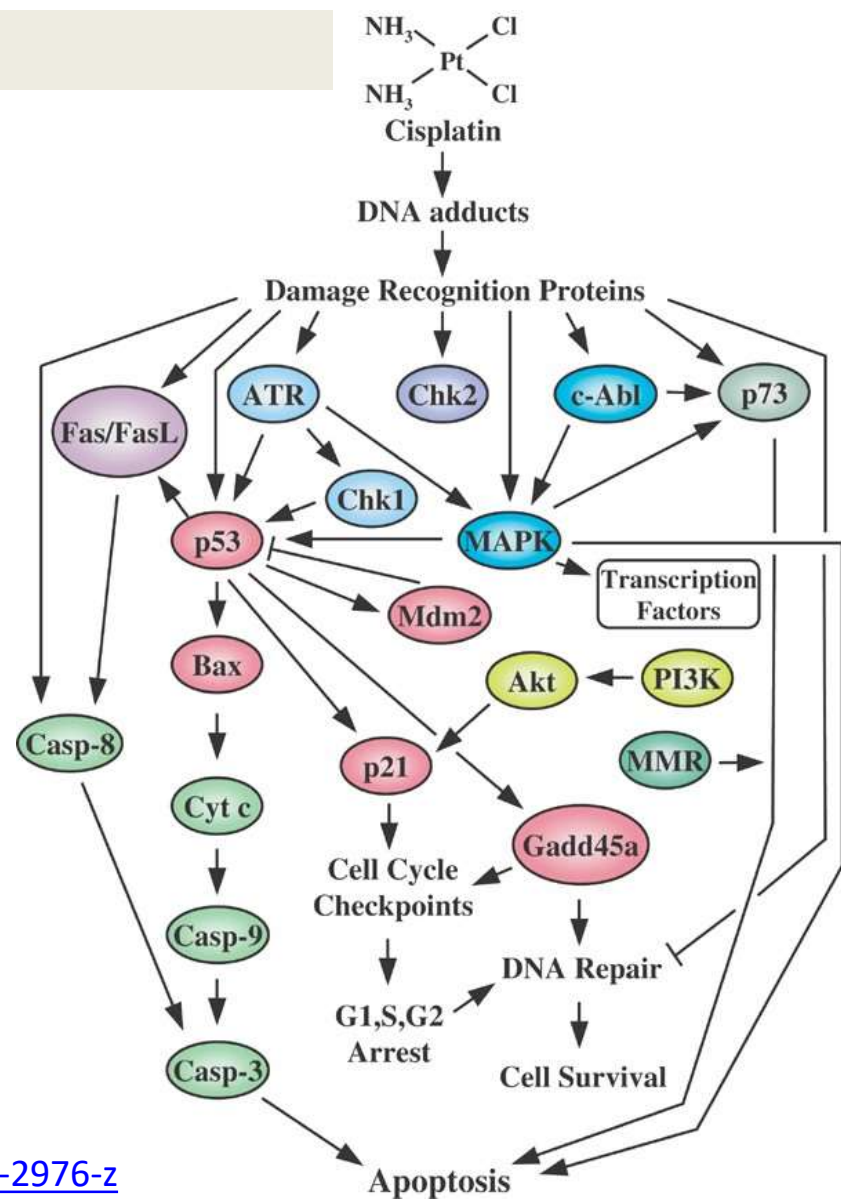
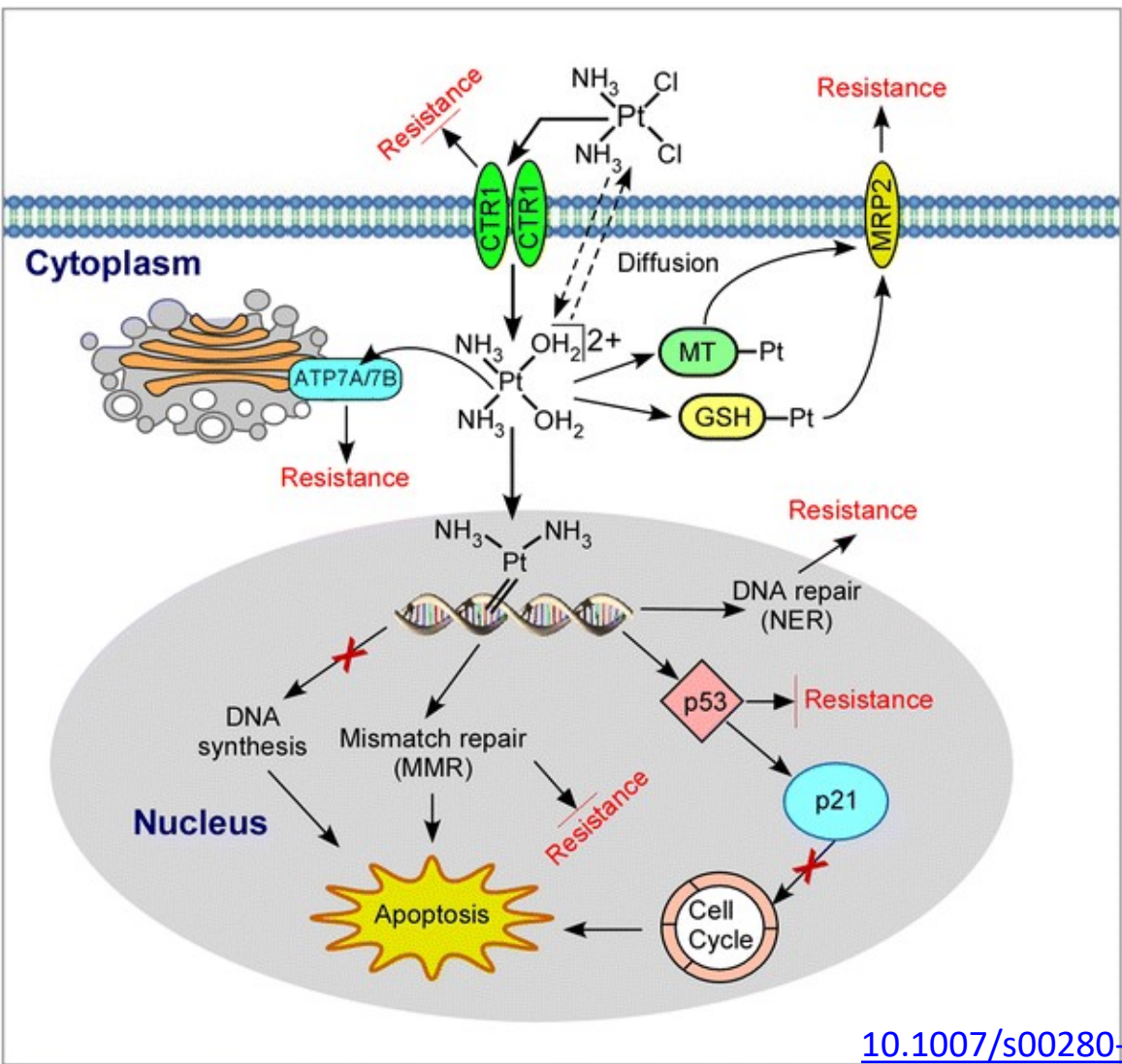
- Determined by:
 - Oxidation state
 - Geometry
 - Electron configuration (e.g. Jahn Teller)
 - Ligand effects

- **Thermodynamics**

- Complex Stability and Formation Constant

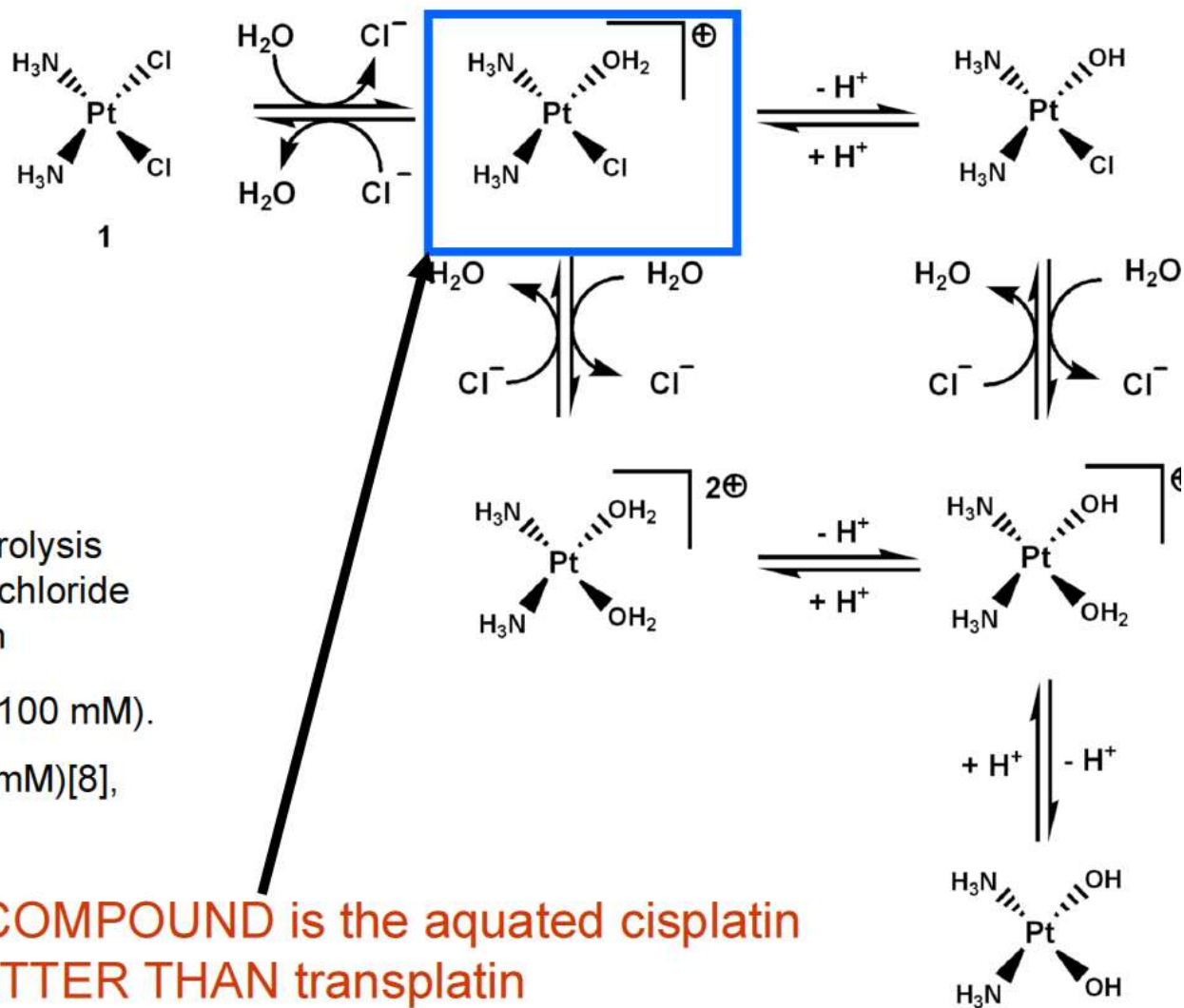
- Determined by
 - Oxidation state
 - HSAB theory
 - Crystal field parameters
 - Ligand field parameters
 - Ligand type / denticity

Cisplatin: Mechanism of action



[10.1007/s00280-016-2976-z](https://doi.org/10.1007/s00280-016-2976-z)

Reactions of cisplatin under physiological conditions



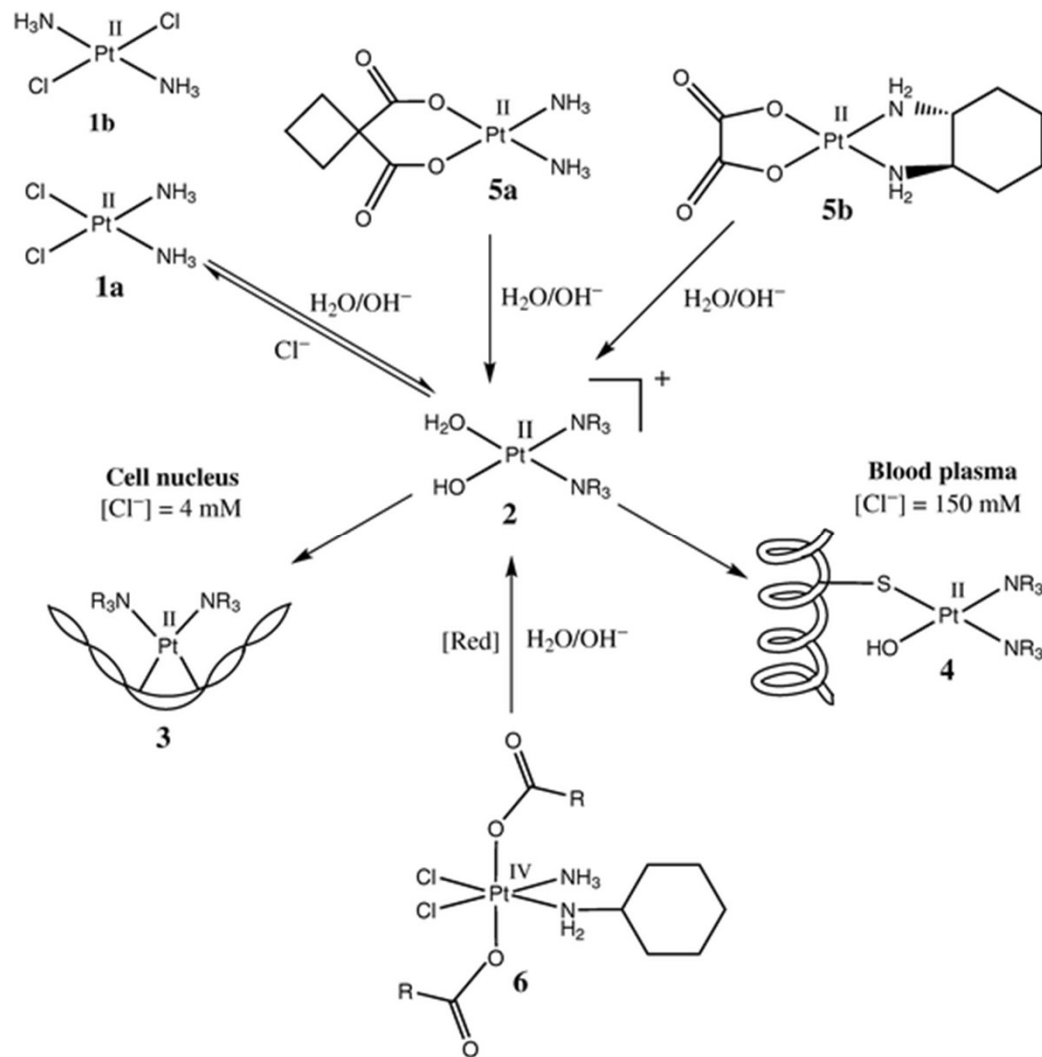
Cisplatin hydrolysis
regulated by chloride
concentration

($[\text{Cl-blood}] = 100 \text{ mM}$).

($[\text{Cl-cell}] = 3 \text{ mM}$)[8],

**Reactive COMPOUND is the aquated cisplatin
MUCH BETTER THAN transplatin**

Platinum drugs: Hydrolysis in cells



DNA binding

- Major adducts of platinum drugs with DNA are the 1,2-GpG and 1,2-ApG **intrastrand crosslinks** – 90%
- Structural studies show that the Pt cross links induce **bending and unwinding** of DNA and cause destacking of the purine bases.
- The B-DNA backbone conformation is significantly altered to accommodate the platinated lesion
- Spectroscopic and calorimetric studies suggest that platination induces a conformational shift from an B-like to an A-like form – may be important in HMG (High Mobility Group protein) recognition.

DNA recognition and repair

- DNA repair system can detect many forms of damage
- Once detected, excision repair removes the damaged DNA to form a gap
- This gap is then filled by DNA polymerase
 - This process is complex, involving around 30 proteins
- DNA repair efficiency order 1,3-d(GTG) crosslink > AG > GG. This implies that 1,2-d(GG) cross-links, as form by cisplatin are toxic.

Cisplatin Resistance: exploitation of Pt(II) by cellular thiols

