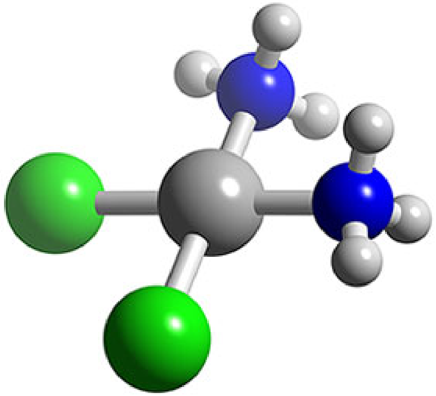
Cisplatin Anti-Cancer Agent

CHEM 489-503

02-16-10

Masato Hirai and Michael Woodie

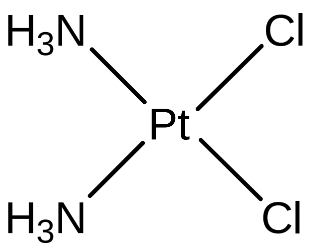
What is Cisplatin?



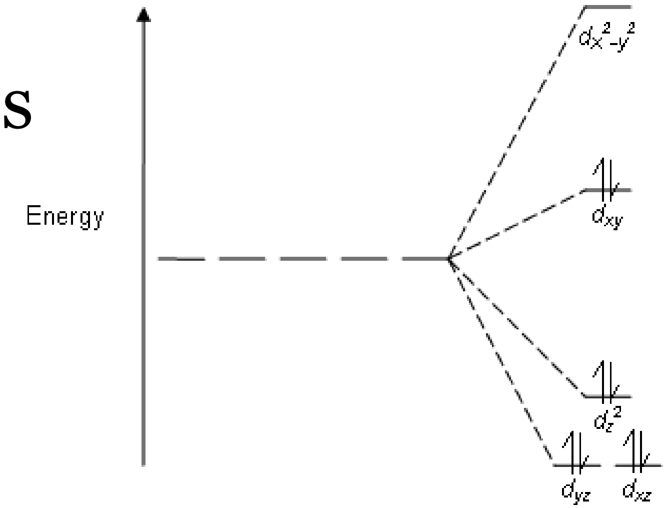
- *Cis*-diamminedichloroplatinum(II)
- Anti-cancer/tumor/leukemia agent
  - Targets fast dividing cells, such as cancer cells, and causes cell death
  - The cure of over 90% of testicular cancer

Alderden, R. A.; *et al. J. Chem. Ed.* **2006**, *83*, 728-734.

Properties of Cisplatin



- Yellow, crystalline “salt”
- Square planar
  - Minimizes repulsive interactions

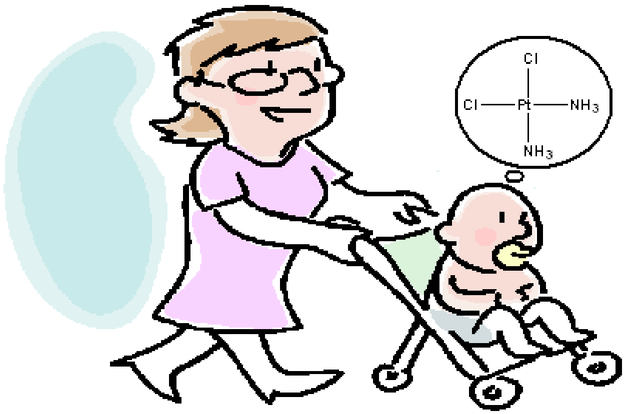


- Platinum (II) is d^8 configuration
  - Low-spin
  - Diamagnetic

- Optimal distance between the two chlorides is approximately 3.4 Å

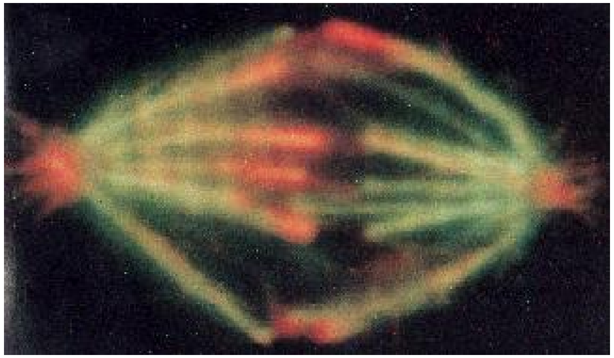
History of Cisplatin

- 1845 - Michel Peyrone first to synthesize cisplatin
- 1913 - Alfred Werner wins Nobel Prize for characterization of coordination compounds
- 1926 – Barnett Rosenberg is born.



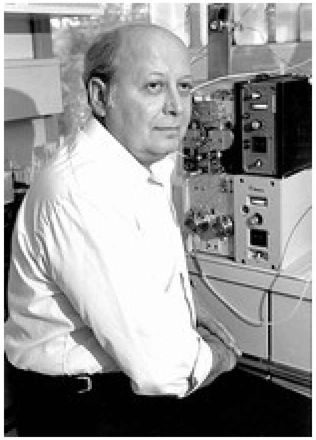
History- Rosenberg's Work

- Mitosis vs electrical field influence on E. coli



http://www.chemcases.com/cisplat/ (Accessed 02/08/10)

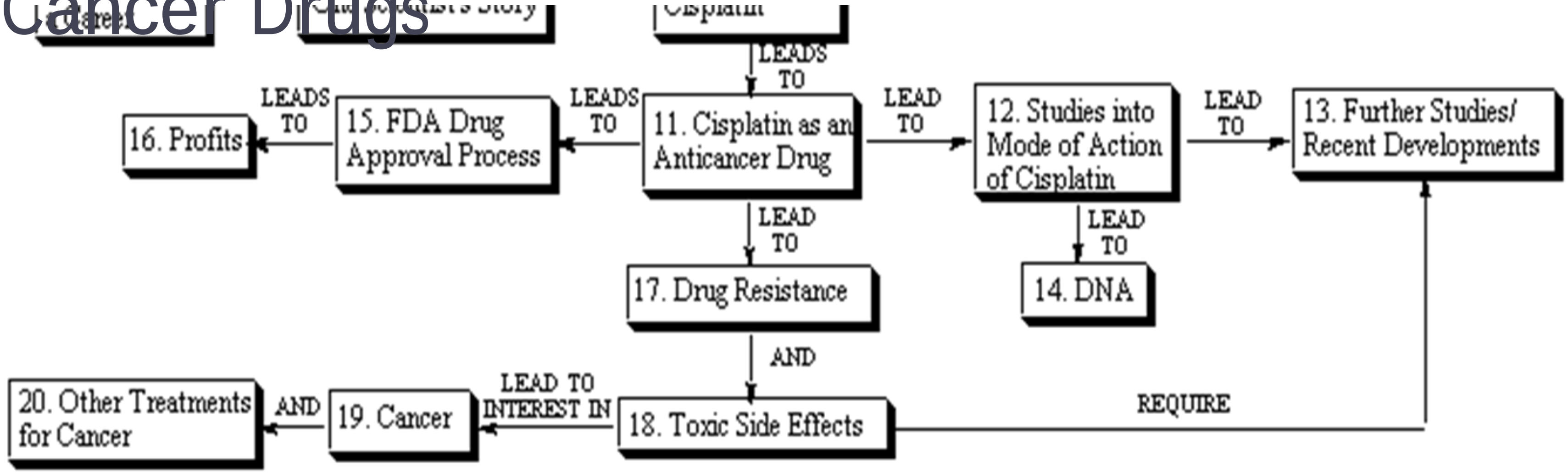
- Inhibits cell division, but induced filamentous cell growth

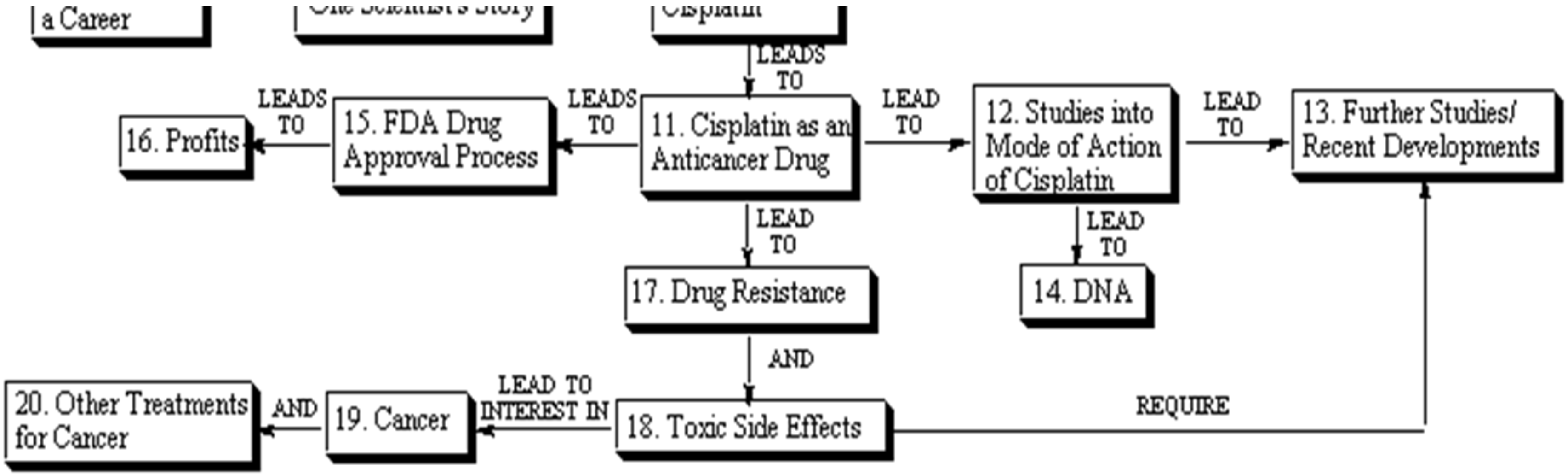


http://news.msu.edu/staff-faculty/story/6673/ (Accessed 2/8/10)

Rosenberg, B. *Platinum Metals Rev.* **1971,** *15*, 42-51

Historical Development of Cisplatin and Anti-Cancer Drugs





Chemcases.com http://www.chemcases.com/cisplat/index.htm (Accessed 02/15/10)

Control Experiments

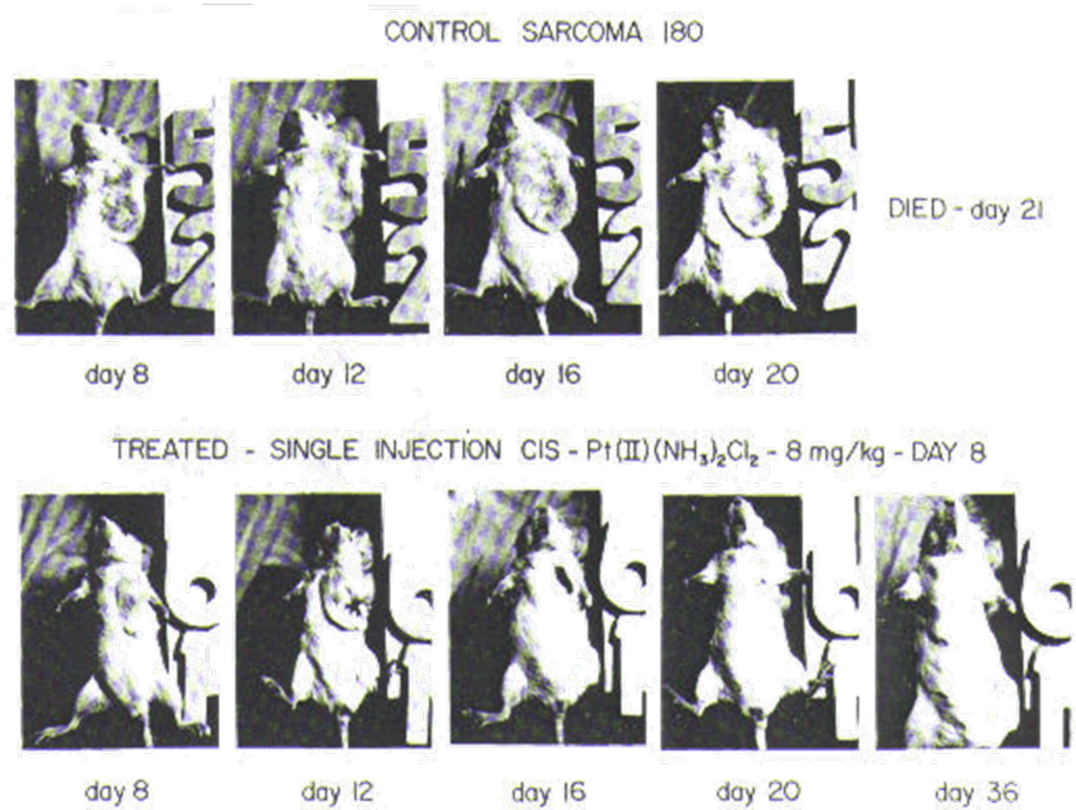
- Changing one parameter at a time
  - Dyes such as methlyene blue and penicillin, osmotic pressure change, UV, Mg deficiency, etc.

- No influence by mutation

- Electrical current was not responsible for cell growth but formed chemical species that affected it
  - Pt electrode oxidized to form platinum hexachloride

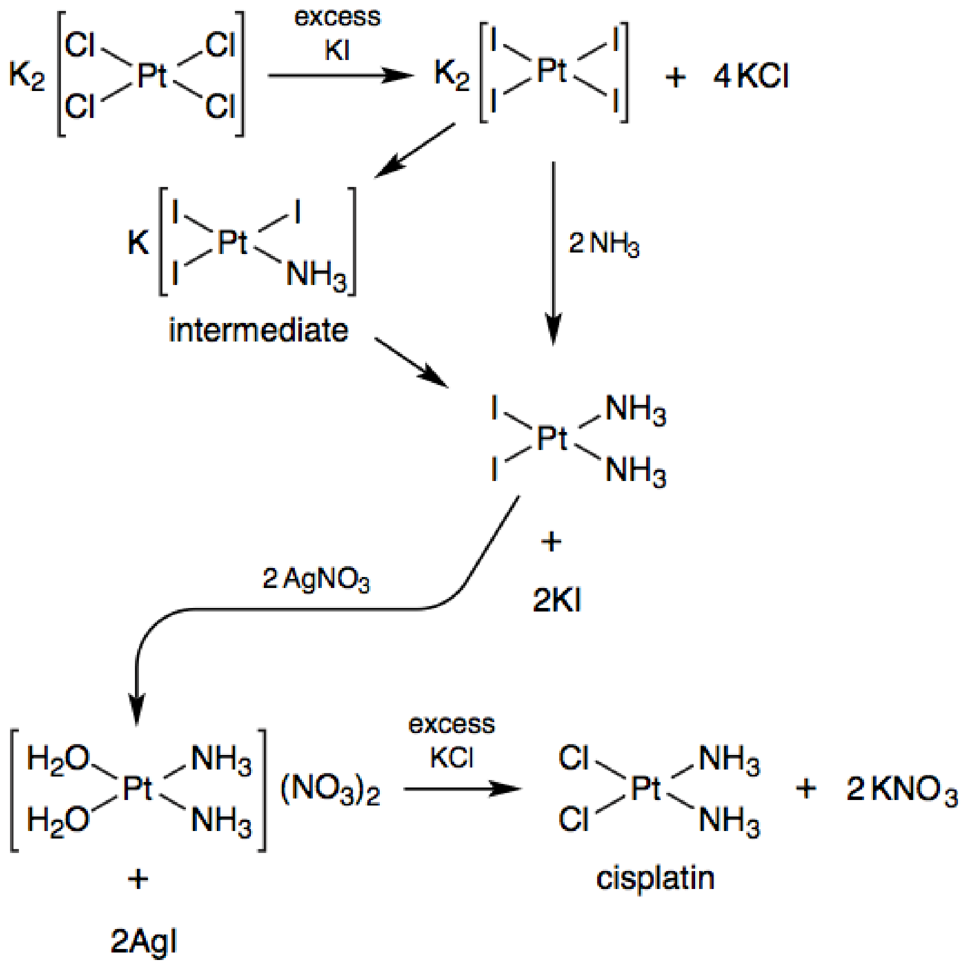
Chemcases.com http://www.chemcases.com/cisplat/cisplat02.htm (Accessed 02/15/10)

Rosenberg's Rat Experiment



Rosenberg, B. *Platinum Metals Rev.* **1971,** *15*, 42-51

Dhara Synthesis of Cisplatin



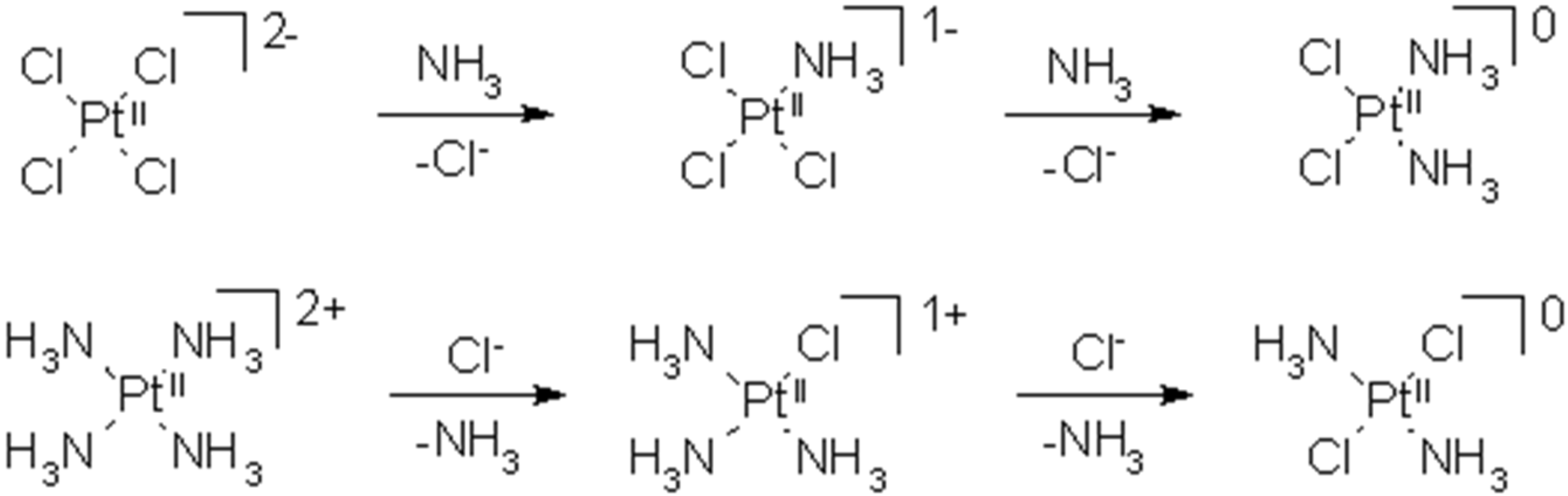
Alderden, R. A.; Hall, M. D.; Hambley, T. W. *J. Chem. Ed.* **2006,** *83*, 728-734.

Trans Effect

- Introduced by Ilya Ilich Chernyaev in 1926
- Labelization of ligands
  - Some ligands can direct the incoming ligands into the trans position
- $H_2O < NH_3 < py < Cl^- < Br^- < I^-$ as it increases in trans effect strength

Coe, B. J.; Glenwright, S. J. *Coordin. Chem. Rev.* **2000**, *203*, 5-80.

Priorities in Tran Effect



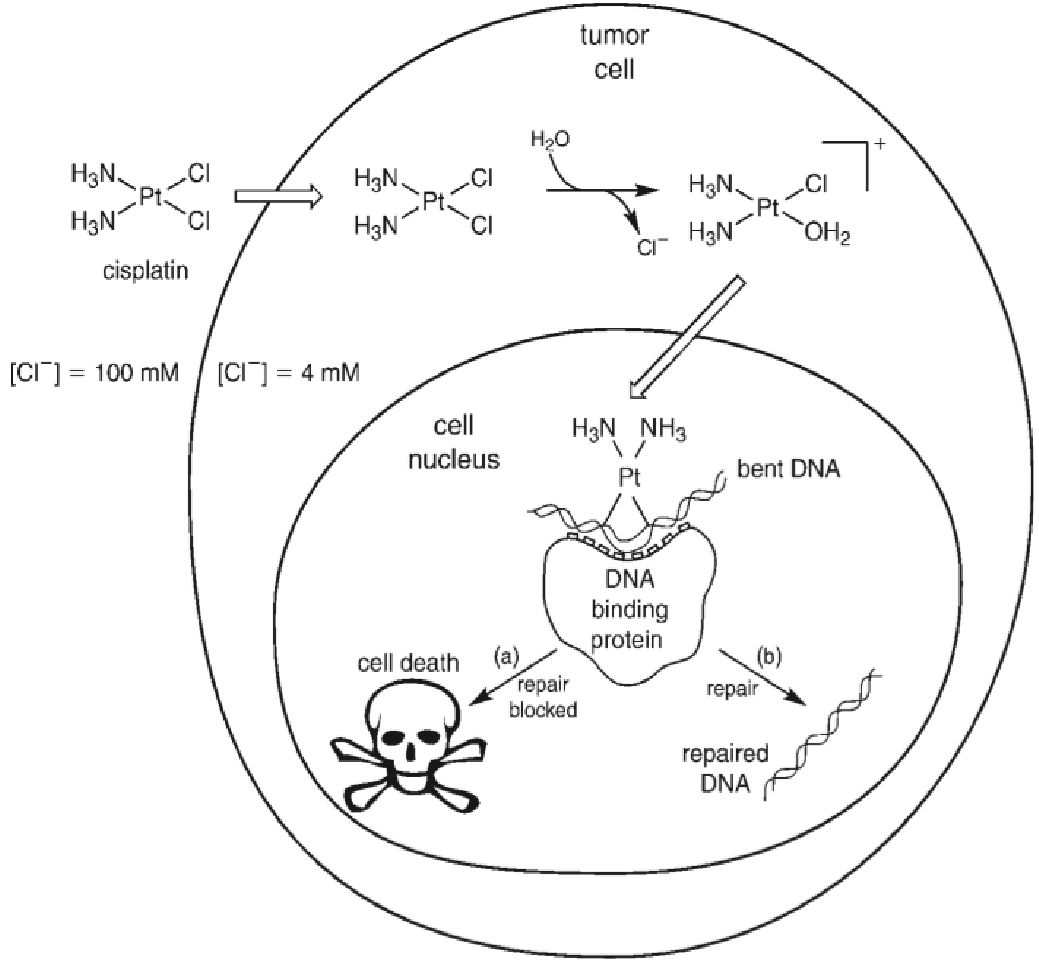
$$H_2O < NH_3 < py < Cl^- < Br^- < I^-$$

http://en.wikipedia.org/wiki/Trans_effect (Accessed 02/02/10)

Coe, B. J.; Glenwright, S. J. *Coordin. Chem. Rev.* **2000**, *203*, 5-80.

Cellular Uptake

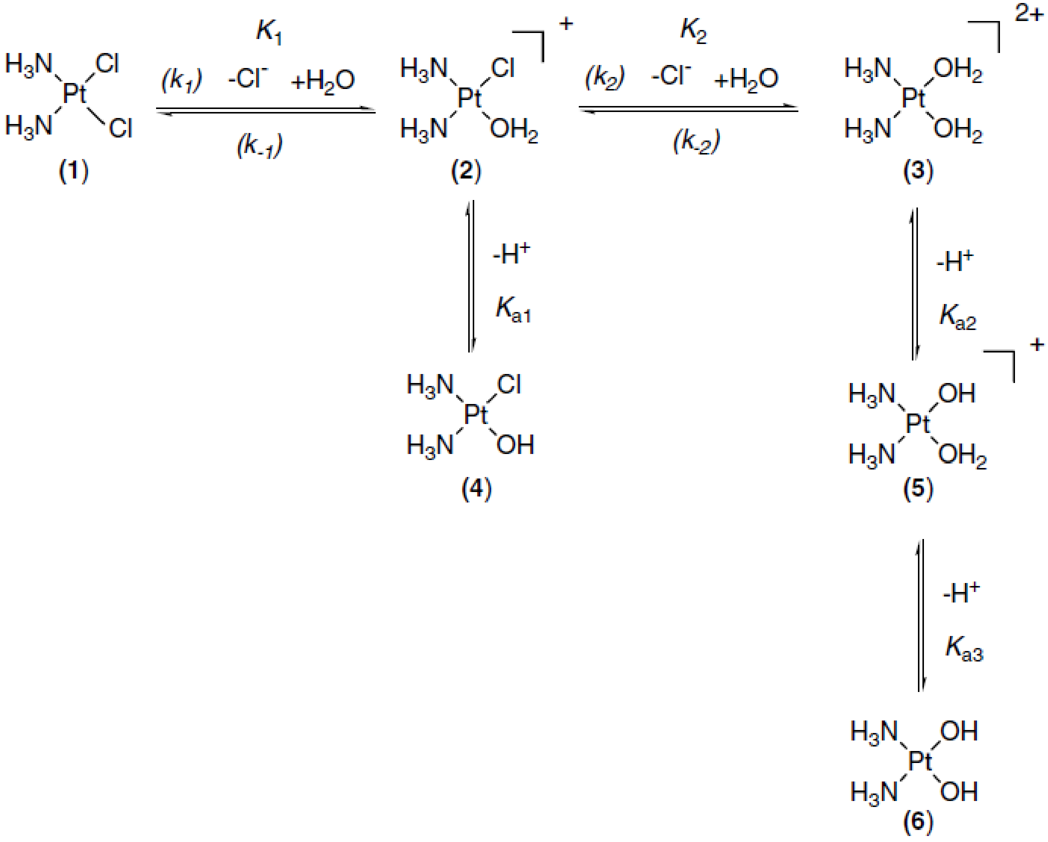
- Enters by passive diffusion or active uptake (Cu-transporting protein)
- Activated due to low concentration of chloride (Chloride is replaced with water)
- 98% binds to the nucleus



Alderden, R. A.; Hall, M. D.; Hambley, T. W. *J. Chem. Ed.* **2006,** *83*, 728-734.

Rate and Equilibrium Constants in Water

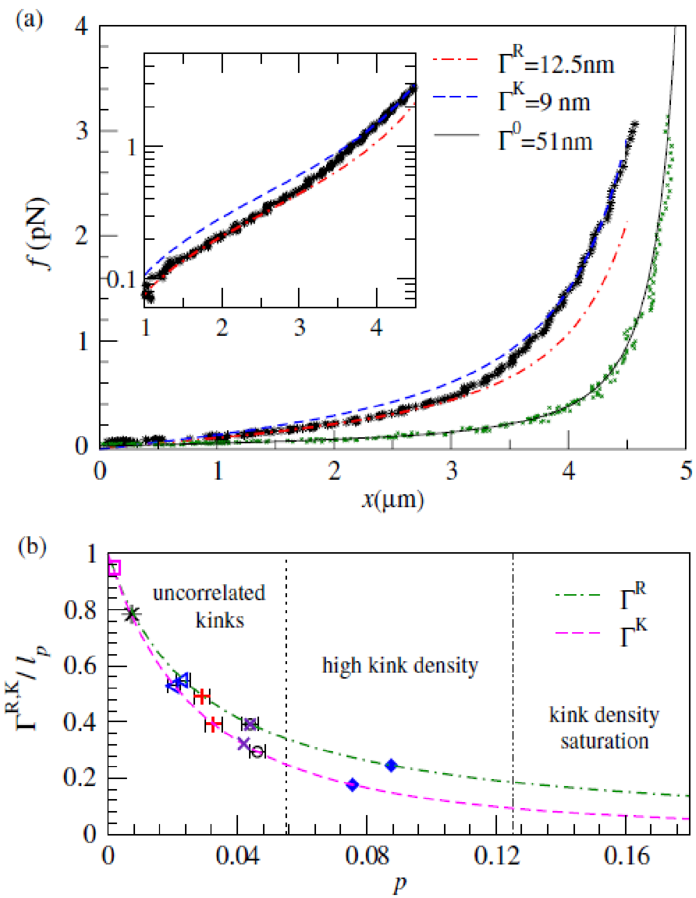
Parameter	Value	Temp (°C)
k_1	$5.18\times10^{-5}\ s^{-1}$	25
k_1	$1.84\times10^{-4}\ s^{-1}$	35.5
k_{-1}	$7.68\times10^{-3}\ M^{-1}\ s^{-1}$	25
pK_1	2.17	25
	2.07	37
k_2	$2.75\times10^{-5}\ s^{-1}$	25
k_{-2}	$9.27\times10^{-2}\ M^{-1}\ s^{-1}$	25
pK_2	3.53	25
pK_{a1}	6.41	27
pK_{a2}	5.37	27
pK_{a3}	7.21	27



Berners-Price, S. J.; Ronconi, L.; Sadler, P. J. *Prog. Nucl. Mag. Res. Sp.* **2006,** *49*, 65-98.

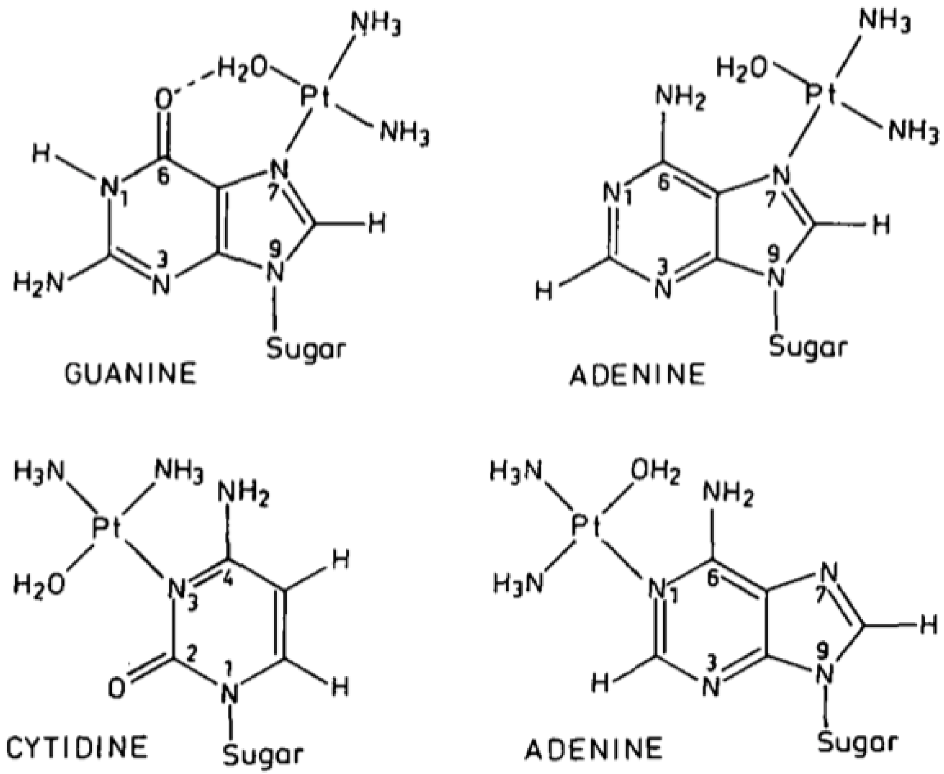
Importance of Saline

- Stabilize chlorine ligands
- Makes binding to DNA more effective at ~10-20mM
- Increases elasticity of bond



Lee, N. K.; *et. al. Phys. Rev. Lett.* **2008,** *101*, 248101-1-4

Binding of Nucleotide Bases



- Binding with N^7 in guanine is the most kinetically favored composition

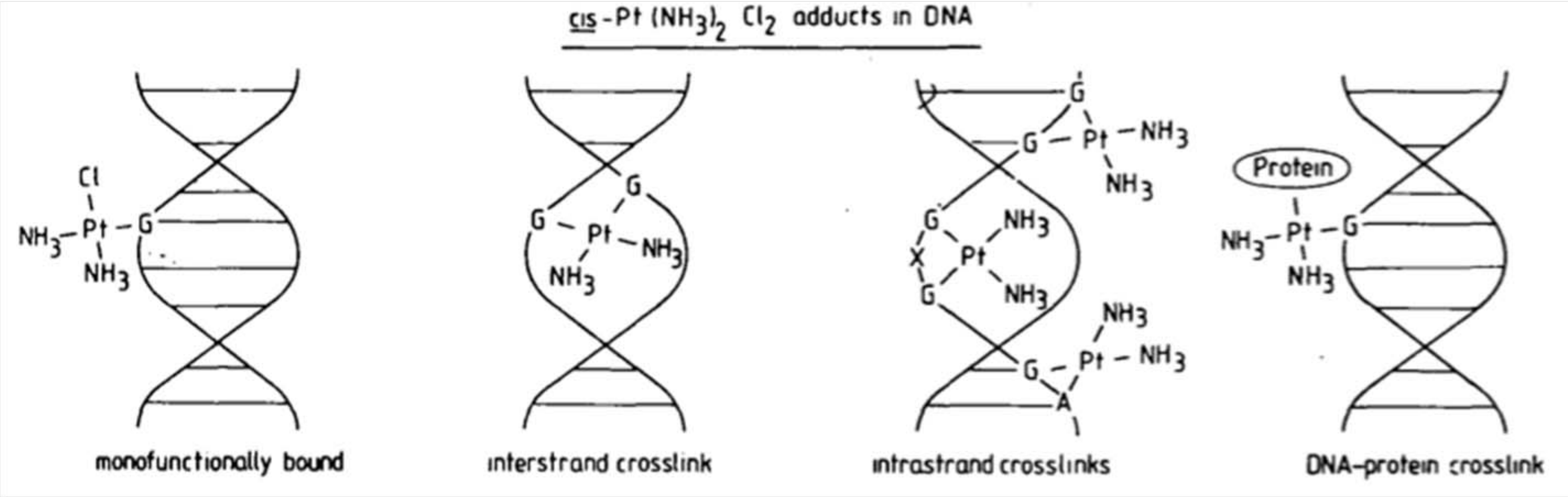
Reedijk, J.; Lohman, P. H. M. *Pharm. Weekblad.* **1985,** *7*, 173-180.

Binding of RNA

- Can also bind to RNA in a similar fashion as DNA
- Not as harmful as DNA since RNA can be replaced
- Does not affect RNA synthesis (But it affects DNA synthesis)
- Only 1 – 10% of RNA is damaged at lethal dosage

Pil, P.; Lippard, S. J. In Encyclopedia of Cancer, J. R. Bertino, Ed. Academic Press: San Diego, CA**, 1997**, *1*, 392-410.

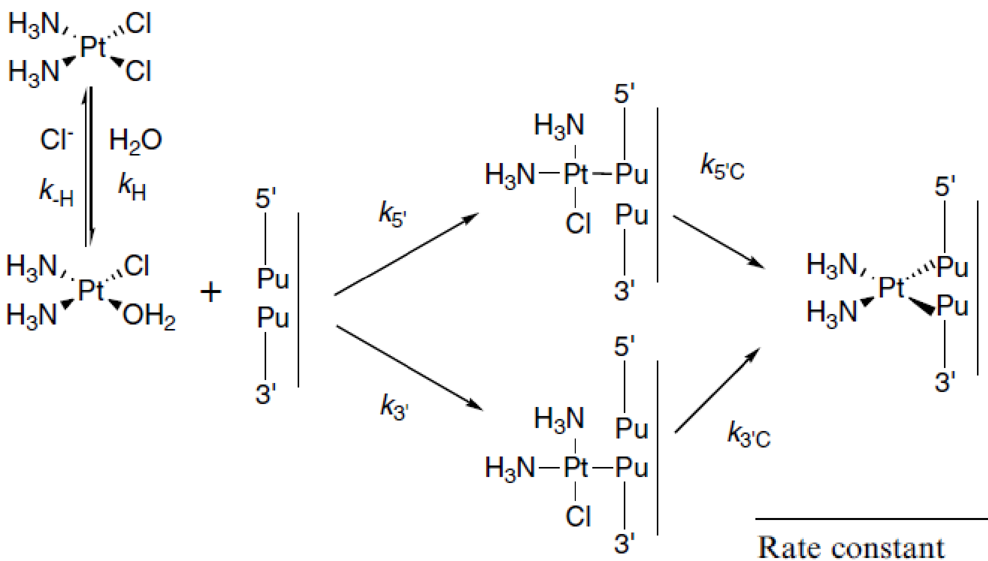
Binding of DNA



- DNA contains high amount of lone paired electrons for metals to bind
- Activated due to low concentration of chloride
- 1,2-intrastrand creates the largest bent to structure

Reedijk, J.; Lohman, P. H. M. *Pharm. Weekblad.* **1985,** *7*, 173-180.

The kinetics of Binding to Purine



- Obtained by 2D [^1H,^{15}N] NMR spectra

Rate constant	-GG-[a]	-AG-[a]	-GA-[a]
k_H (10^{-5} s^{-1})[b]	1.62 ± 0.02	1.57 ± 0.02	1.23 ± 0.02
$k_{3'}$ (M^{-1} s^{-1})	0.48 ± 0.19	0.37 ± 0.02	0.018 ± 0.002
$k_{5'}$ (M^{-1} s^{-1})	0.16 ± 0.06	0.061 ± 0.007	0.046 ± 0.003
$k_{3'c}$ (10^{-5} s^{-1})	2.55 ± 0.07	1.46 ± 0.05	2.5 ± 0.5
$k_{5'c}$ (10^{-5} s^{-1})	0.171 ± 0.011	0.29 ± 0.09	0.07 ± 0.02

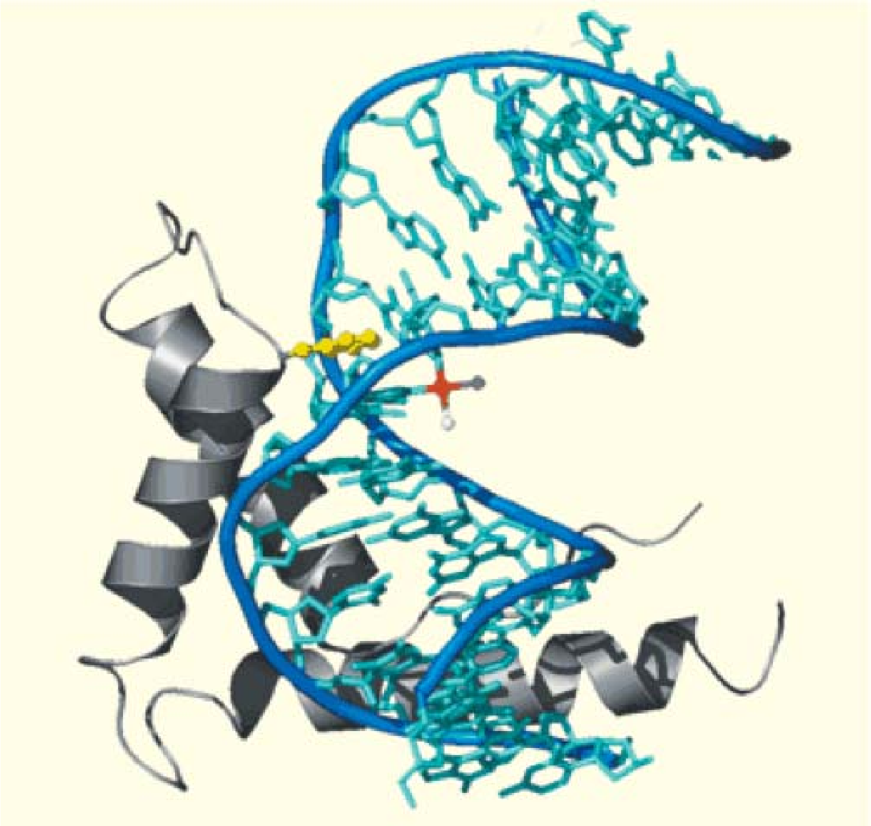
[a] Sequences are -GG- 5′-d(AATTGGTACTACTAATT)-3′, -AG- 5′-d(AATTAGTACTACTAATT)-3′ and -GA- 5′-d(AATTGATACT ACTAATT)-3′.

[b] k_H values are the aquation rate constants with the anation rate constant fixed at 4.6×10^{-3} (M^{-1} s^{-1})

Tornaghi, E. *et. al. Chem. Phys. Lett.* **1995,** *246*, 469-474.

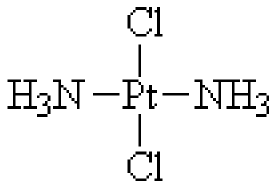
High Mobility Group (HMG) Domain Protein

- HMG – Chromosomal protein that helps transcription, replication, recombination and DNA repair
- HMG tightly binds to the complex, destacks nucleotide bases, and induces a kink
- Protection from DNA repair protein



McCormick. M. *Chem. and Eng. News.* **1999**, 77, 3-7.
http://pubs.acs.org/cen/coverstory/83/8325/8325cisplatin.html (Accessed 02/08/10)

Transplatin



- Greater reactivity than cisplatin – aquates 4 times faster, reacts with ammonia ~30 times faster, and reacts with 70% of the glutathione
  - Trans effect
- Cannot form 1,2-adduct (Only 1,3-adduct, which is inactive)
- Rapid conversion between intrastrand binding and interstrand binding
- Low recognition by HMG

Colvin, C. B.; *et. al. Inorg. Chim. Acta* **1968,** *2*, 487-489.
Berners-Price, S. J.; Kuchel, P. W. *J. Inorg. Biochem.* **1990,** *38*, 327-345.

Deactivation of Drugs

- Protein bound
- Sulfur-containing species such as gluthathione and metallothionein
  - Strong coordination of soft sulfur donor to soft platinum (II)
  - Prefers over hard ligands such as amine nitrogen donors
  - Hard-Soft Acid-Base Theory

Ivanov, A. I.; *et. Al. J. Biol. Chem*. **1998**, *273*, 14721–14730.
Guo, Z.; Sadler, P. J. *Adv. Inorg. Chem*. **2000**, *49*, 183–306.

Hard-Soft Acid-Base (HSAB) Theory

- Hard – small, high charge, and weakly polarizable

  Soft – large, low charge, and strongly polarizable
- Qualitatively predicts the complexation preferences of metal ions and ligands
  - Hard acids react with hard bases, and soft acids bases react with soft bases

Common Side Effects of Cisplatin

- 65 – 98% of the platinum in blood plasma is protein bound
  - Can lead to severe side effects such as blood clotting
  - Deactivates the drug
- Thinned or brittle hair, loss of appetite or weight, diarrhea, nausea and vomiting, changes in taste, neurotoxicity, *etc*.

Ivanov, A. I.; *et. Al. J. Biol. Chem*. **1998**, *273*, 14721–14730.

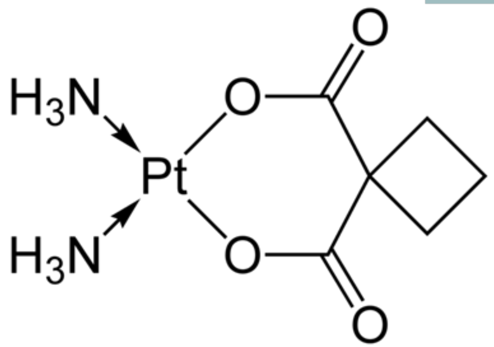
Other disadvantages

- Only works on few kinds of tumor cells
  - Colon and non-small-cell lung cancer are resistant
  - Decrease in cellular drug accumulation

- Can build resistance
  - Cancer cells are believed to somehow reject cisplatin out of the system
  - Acceleration of removal of cisplatin

- Target is unselective

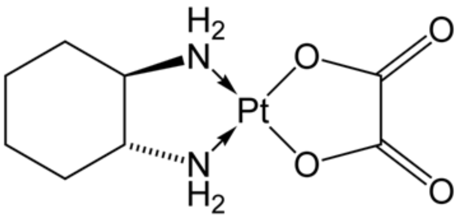
Carboplatin



- Developed at the Institute of Cancer Research
  - Replacing chlorides of cisplatin with cyclobutan dicarboxylate group
- Bidentate leaving group ligand – dicarboxylate is more kinetically inert
- Pt-N bond – from 2.07 Å to 2.06 Å
- Works on ovarian carcinoma, lung, head and neck cancer
- Less nephrotoxic

Tornaghi, E.; *et. al. Chem. Phys. Lett.* **1995,** *246*, 469-474.

Oxaliplatin

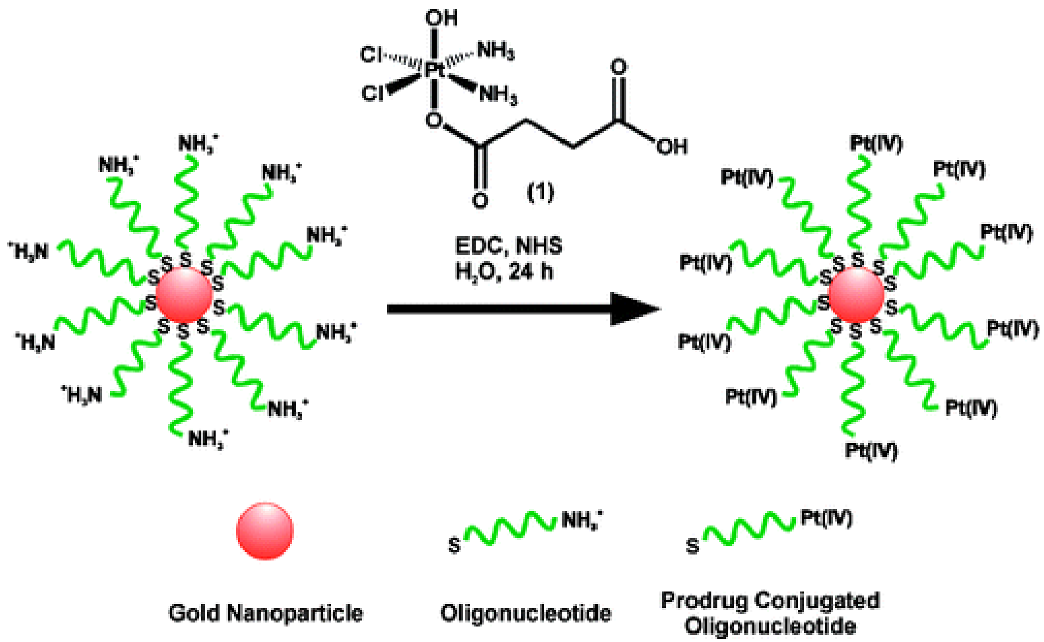


- Discovered in 1976 by Yoshinori Kidani
- Enhanced activity by addition of fluorouracil and leucovorin (FOLFOX)
  - Effective on colorectal cancer
- Can bind to cisplatin-resistive DNA
- Milder side effects

Los, G.; *et. al. Cancer Lett.* , **1990,** *51*, 109 - 117.
Extra, J. M.; *et. al. Cancer Chemoth Pharm.* , **1990,** *25*, 299-303

Future Works

- Gold nanoparticles with Platinum (IV) Drugs
  - Reduces from Pt(IV) to Pt(II) after entering cell membrane



Dhar, S.; *et. al., J. Am. Chem. Soc.*, **2009**, *131*, 14652–14653