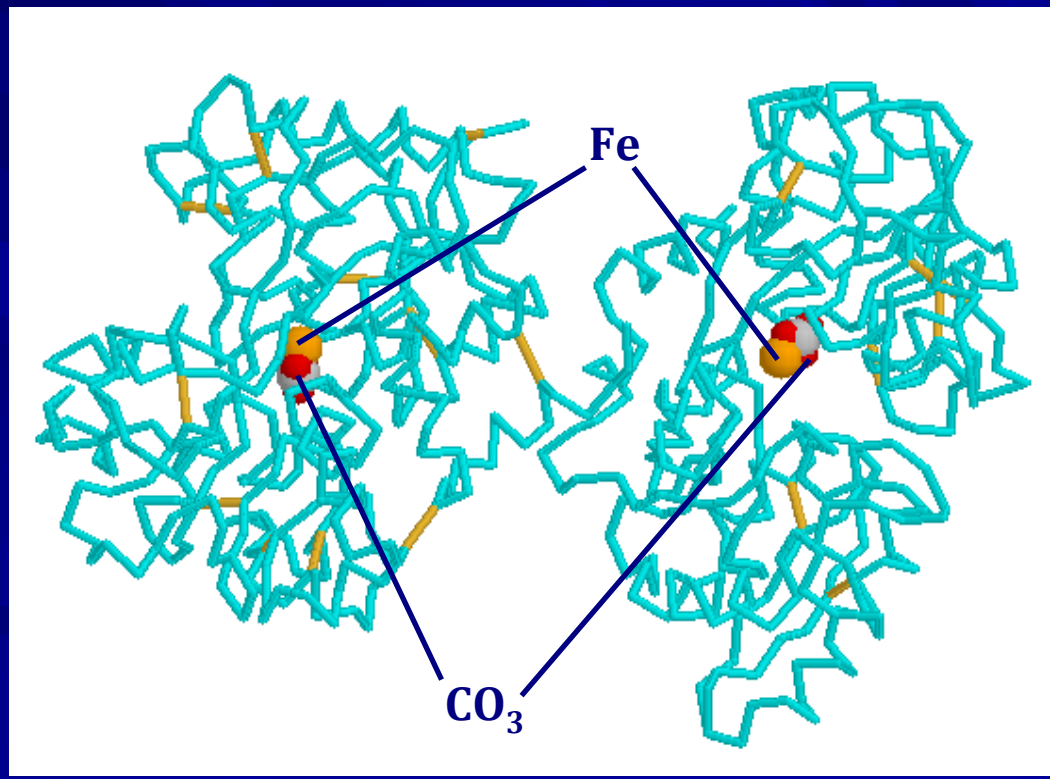
Can we use transferrin to deliver metals to cancer cells that would be lethal to those cells? (ruthenium-imidazolium)

- Tumor cells need more oxygen because they are growing so fast
- Cells have overabundance of receptors on their surface for transferrin, an iron transport protein
- Lauren Benson's Trojan Horse Project

Transferrin

- Transports Fe(III) to many types of cells
  - Two structurally similar lobes
  - Fe(III) binds in each lobe
  - Fe(III) only binds when accompanied by a synergistic anion, typically carbonate

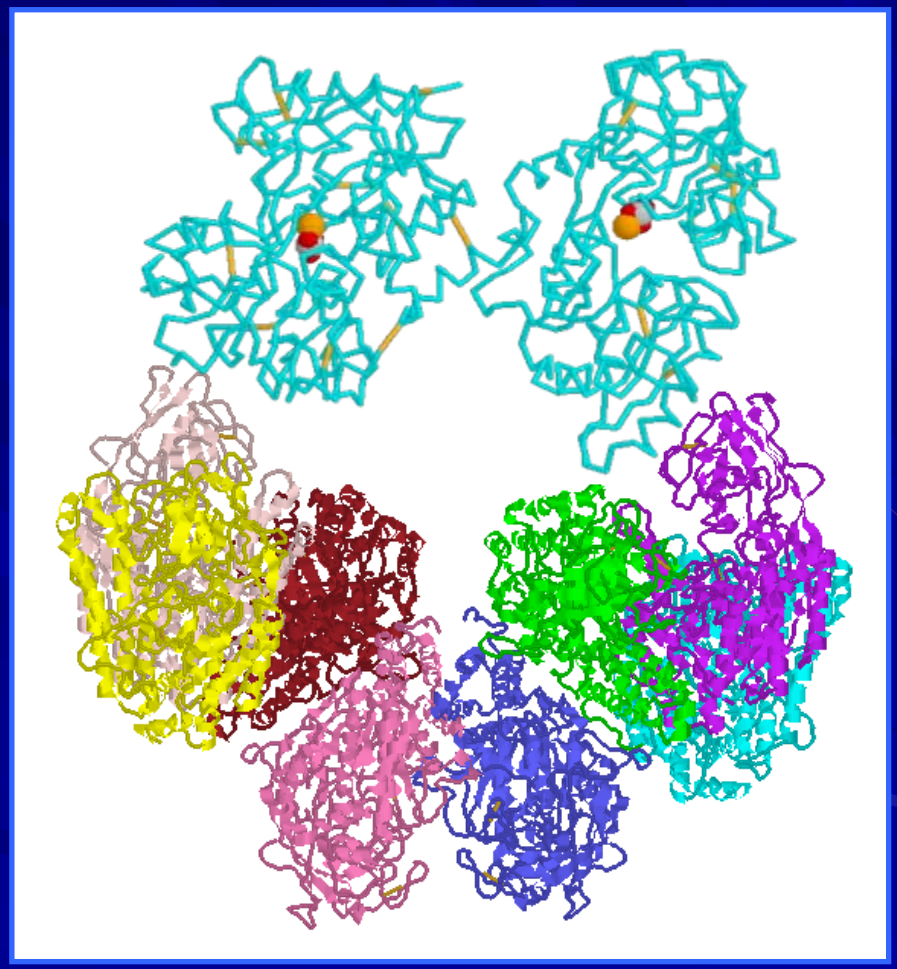


Transferrin

Berners-Price, 1996

Cellular uptake of transferrin

- Diferric transferrin binds to receptor proteins on the cell surface
- Enters the cell in a vesicle with low pH (~5.5)
- Fe(III) is released
- Apoprotein and receptor are transported back to cell surface, where they dissociate at extracellular pH (~7.4)

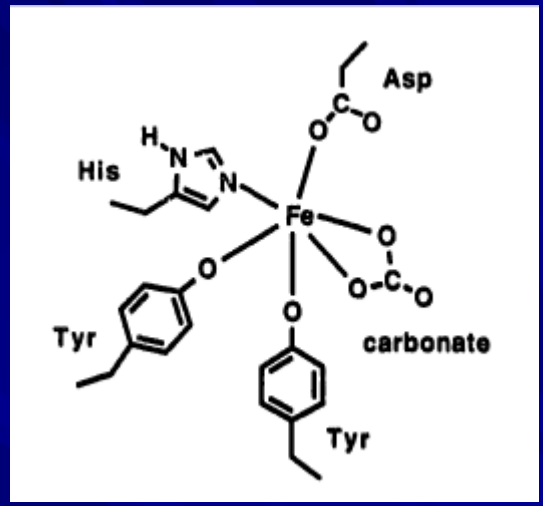


Transferrin and its receptor

Berners-Price, 1996

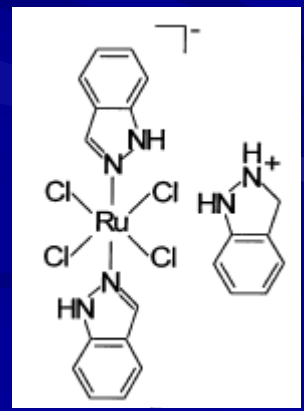
Ruthenium binds to transferrin

- Using X-ray crystallography it has been shown that ruthenium binds to the imidazole ring of the His residue in the metal-binding site
- This binding is facilitated by the loss of a chloride ligand
- $[RuInd_2Cl_4]^-$ retains its activity against colon cancer cells when bound to transferrin



Hartinger, 2005

Metal-binding site



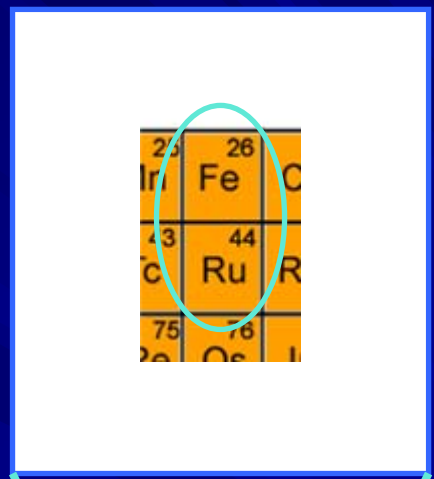
Brabec, 2006

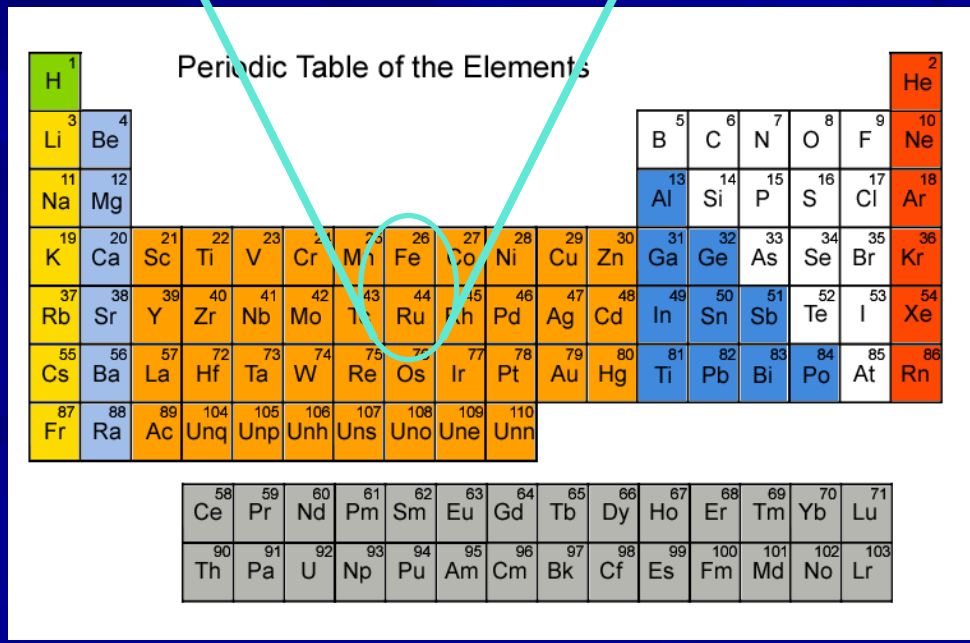
$[RuInd_2Cl_4]^-$

Berners-Price, 1996

Ruthenium binds to transferrin

- In blood, transferrin is only about 30% saturated with iron
- Other metals can bind to transferrin
- Ruthenium is similar to iron (group VIII of the transition metals)
- Ruthenium can be transported to tissues as a ruthenium-transferrin complex





Berners-Price, 1996; Sava, 1990

Preferential distribution to tumor cells

- Tumor cells have a higher requirement for iron
  - There are more transferrin receptors on tumor cells than normal cells
- Ruthenium is distributed in tumor tissue in levels higher than normal tissue
  - e.g. 5-fold that of muscle
- Ruthenium bound to transferrin is preferentially distributed in cancer cells

Sava, 1990

Preferential distribution to tumor cells

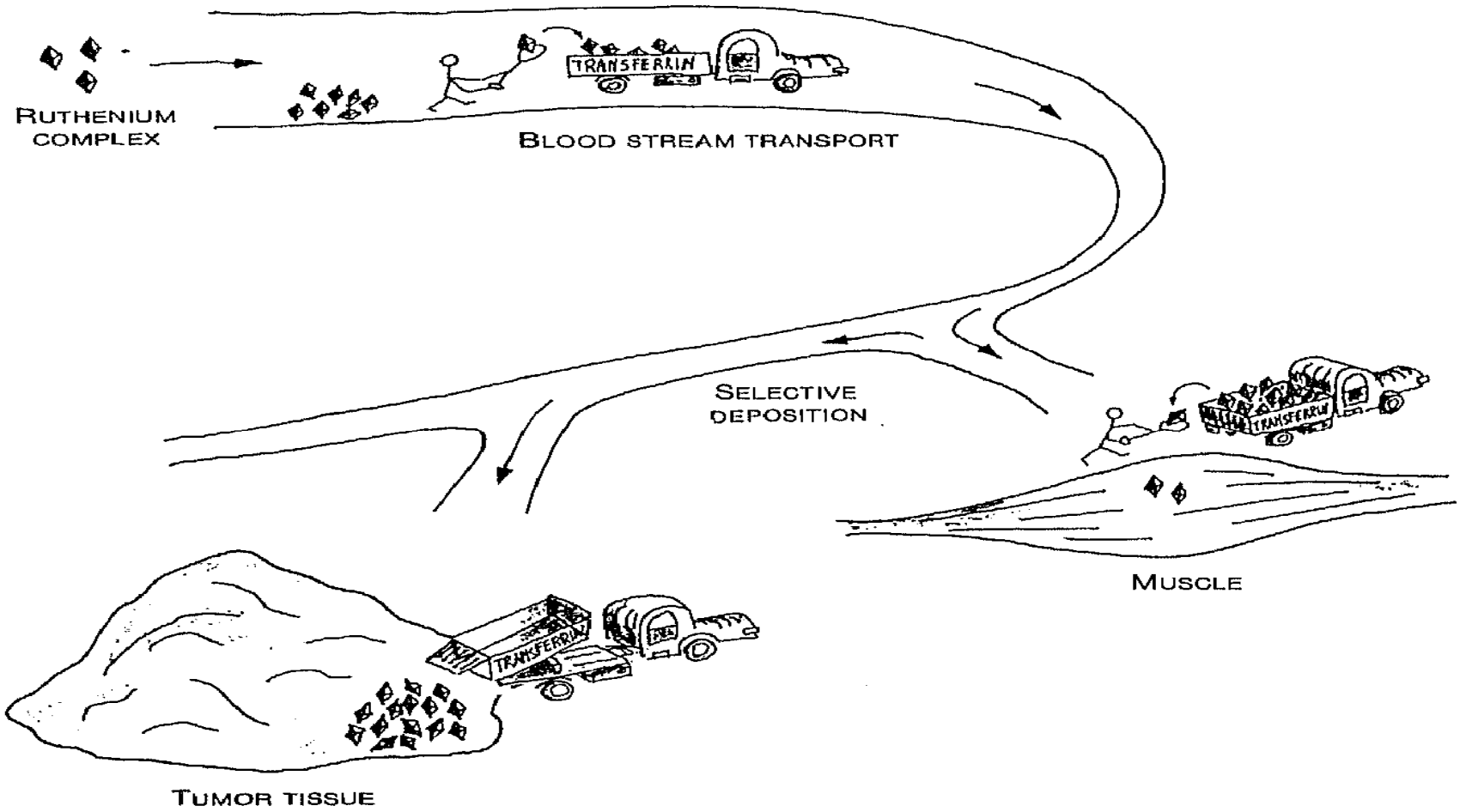


Figure 1. Preferential selective deposition of ruthenium ions by transferrin transport.

Sava, 1990

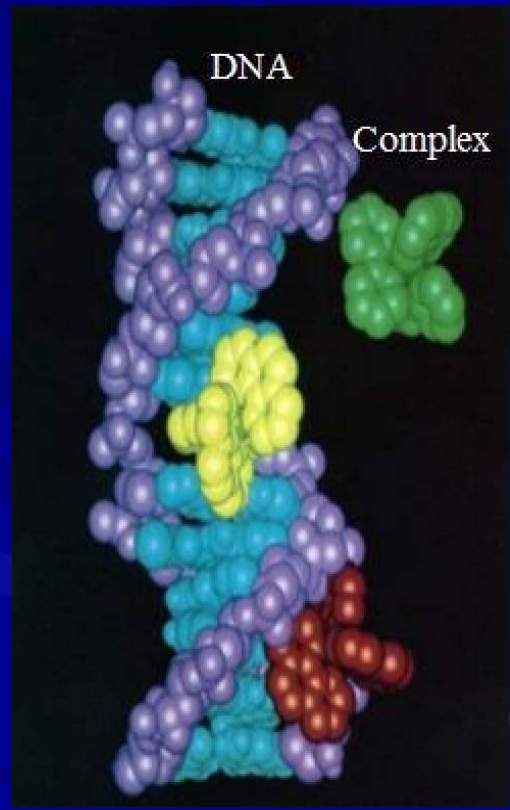
Activation by reduction hypothesis

- Tumor cells rapidly use oxygen and other nutrients
  - Low levels of oxygen in tumor cells
- Tumor cells rely on glycolysis; generate lactic acid
  - Low pH in tumor cells
- The relative electrochemical potential inside tumors is lower than the surrounding normal tissue
- Reduction of Ru(III) to Ru(II) is favored in tumors
- Ru(III) complexes serve as prodrugs
  - Administered in an inactive or less active form {Ru(III)} and metabolized *in vivo* into the active form {Ru(II)}

Clarke, 2003

Ruthenium anticancer mechanisms

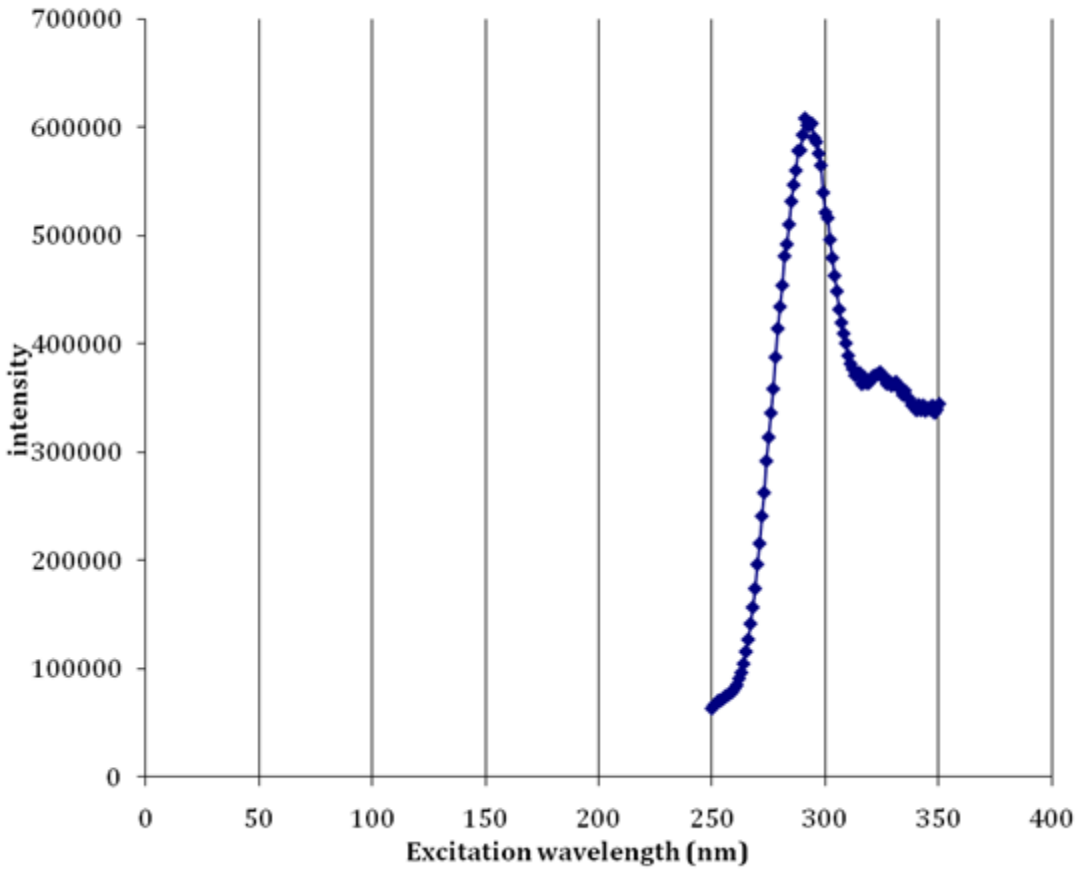
- Ruthenium complexes function differently from platinum (II) compounds, hence altered activity in tumor cells
- It is generally accepted that their cytotoxicity is related to their ability to bind DNA
- Binding may not affect DNA conformation
  - Ruthenium atom is coordinately bound to DNA while ligands are cross-linked to topoisomerase II

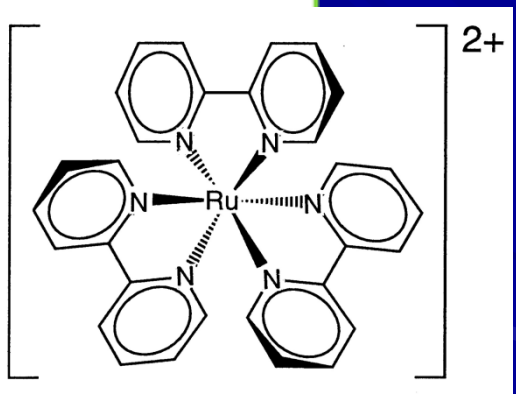


http://it.stlawu.edu/~chem/faculty/Sam-research1.htm

Brabec, 2006

Excitation of Ru(bpy)2+





Damrauer, 1997

R. Ampiah-Bonney