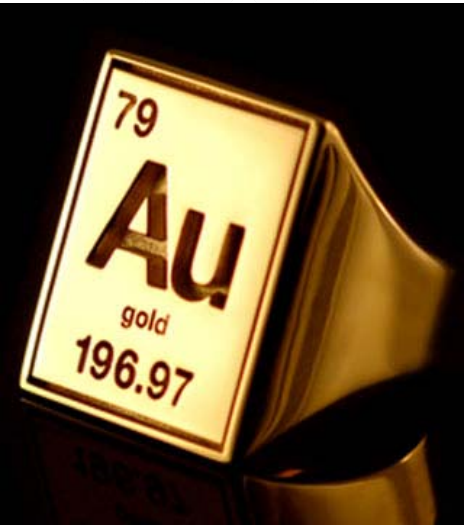
GOLD: MEDICAL APPLICATIONS

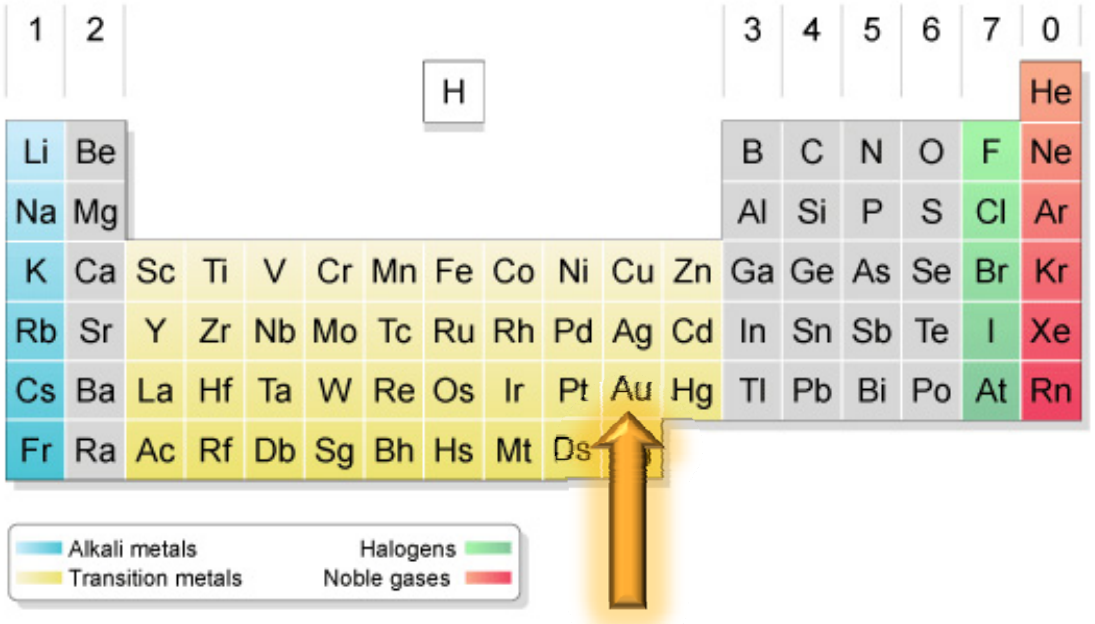
Anti-Arthritis and Anti-Cancer

Bob DeBorde
Matt Ledbetter

PROPERTIES

GOLD





- Au
- Atomic number 79
- Two oxidation states
  - Au^{+}
    - d^{10} electrons
    - Soft acid
    - Linear, trigonal, and tetrahedral geometries
  - Au^{3+}
    - d^{8} electrons
    - Square planar goemetry
    - Harder acid
    - Easily reduced to Au^{+}

HISTORY

EARLY

JEWELRY AND DECORATION

Florentine Codex, Book 9

http://www.mexicolore.co.uk/index.php?one=azt&two=ask&tab=ans&id=16

http://egypttourinfo.com/egyptian-museum_files/BIGking-tut-gold-sarcophagus.jpg

MONEY

http://www.britannica.com/EBchecked/topic-art/288101/117949/Gold-ingots-from-the-Bank-of-Sweden

http://www.goldcoin.net/gold-coin-prices.php

http://www-scf.usc.edu/~ciccone/images/gold%20coin.jpg

DENTAL CARE

http://www.babyboomercaretaker.com/images/Mri-And-Teeth-Gold-Cap.jpg

Gold Fillings were first tried in the 1800's by scientists in France.

Today, highly purified gold is a common material in crowns and fillings.

HISTORY

IN MEDICINE

AURUM POTABILE

•Used as far back as the ancient Egyptians and ancient China as treatment of various illness or disease.

•When gold particles are sufficiently small, they become colloidal (they don't sink). This colloidal solution was a popular drink in many ancient cultures.

•The great alchemist Paracelsus coined the name "Aurum Potabile" for this colloidal gold solution. He believed his purple solution would cure any number of mental, spiritual, and physical ailments.

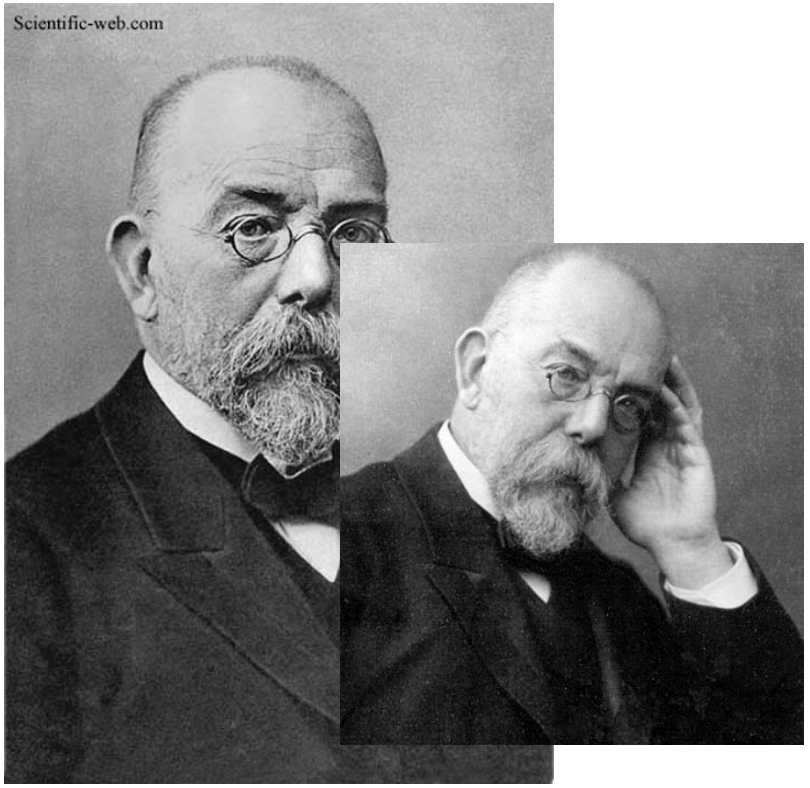
http://www.antimon33.de/assets/images/paracelsius.jpg

134,99 €

http://www.wellango.com/home/

MODERN DAY

- Around the turn of the century, a researcher Robert Koch discovered that gold cyanide killed cultured tuberculosis bacilli.
- This was a HUGE discovery, but subsequent clinical trials proved unsuccessful for treatment of tuberculosis with gold. Koch was given the Nobel Prize for his work.
- The new millennia has brought even more uses for gold as researchers all over the world are finding new ways to use gold in transporting drugs and delivering anti-cancer agents throughout the body.
- Although gold has been successfully tested and used, there has yet to be a perfect method for fighting cancer.



http://www.scientific-web.com/en/Medicine/Biographies/images/RobertKoch01.jpg

USES

ANTI-ARTHRITIS

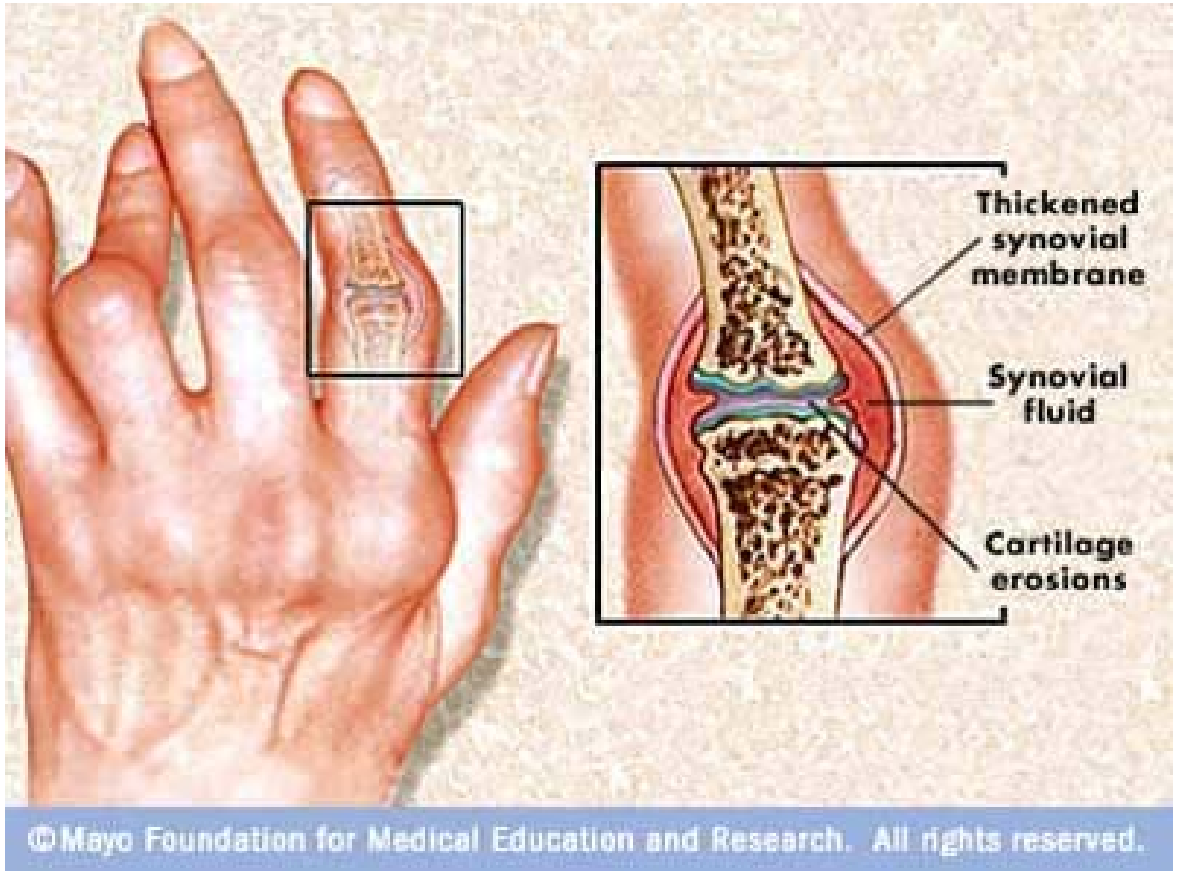
RHEUMATOID ARTHRITIS

- Autoimmune disorder
- Chronic inflammation
- Affects the small joints
- Two to three times more common in women

http://www.usnews.com/listings/fitness-excuses/have-arthritis

RHEUMATOID ARTHRITIS(CONT.)

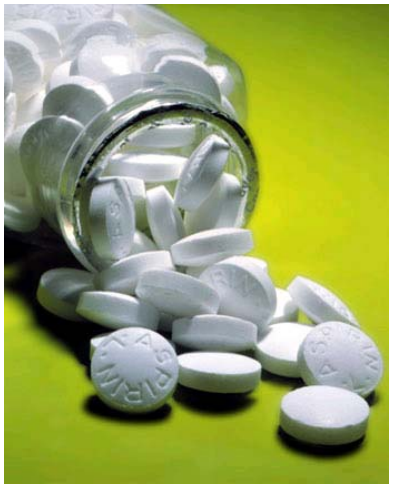
- Rheumatoid arthritis can cause pain, swelling and deformity



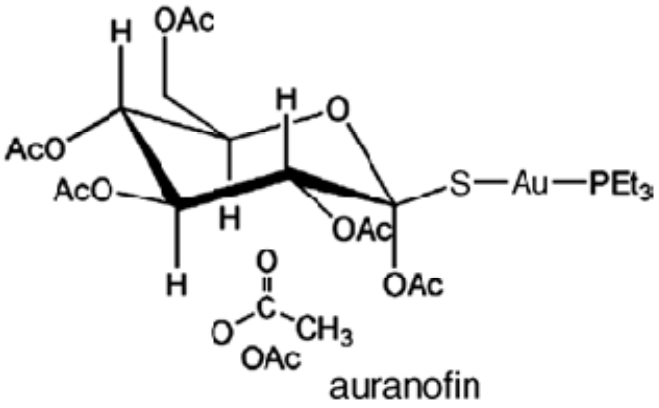
http://www.bing.com/health/article/mayo-116976/Rheumatoid-arthritis?q=rheumatoid+arthritis

TREATMENT

- Two types of drugs:
  - Relieve symptoms
    - Aspirin
  - Control the progression
    - DMARDs



http://paddyk.files.wordpress.com/2009/11/5-aspirin.jpg



auranofin

Ridaura
(auranofin)

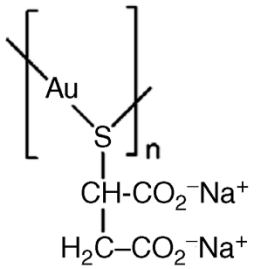
TREATMENT(CONT.)

- Dr. Jacques Forestier
  - French physician
  - Chrysotherapy
    - 1920s
    - Injectable gold salts
    - Assumed rheumatoid arthritis(RA) was caused by microorganisms
    - Improved the outcome for certain RA patients

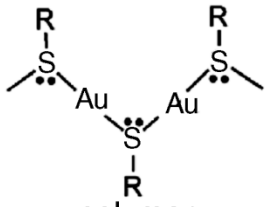
http://www.leplaisirdesdieux.fr/LePlaisirDesDieux/AAIHP/InternatDeParis/idp22forestier.htm

TREATMENT(CONT.)

- Gold compounds currently in use:

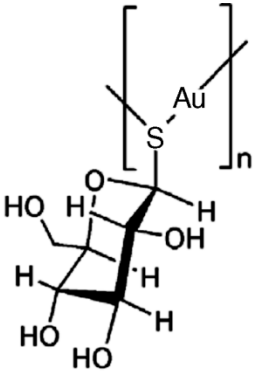


sodium aurothiomalate (myochrysine)

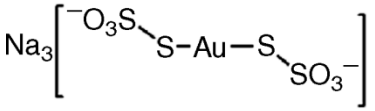


polymer connectivity

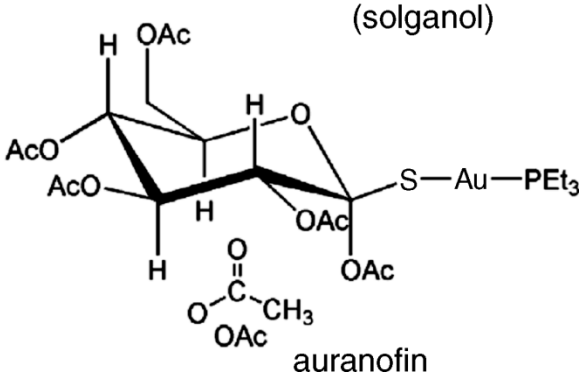
- We will focus on auranofin



aurothioglucose (solganol)

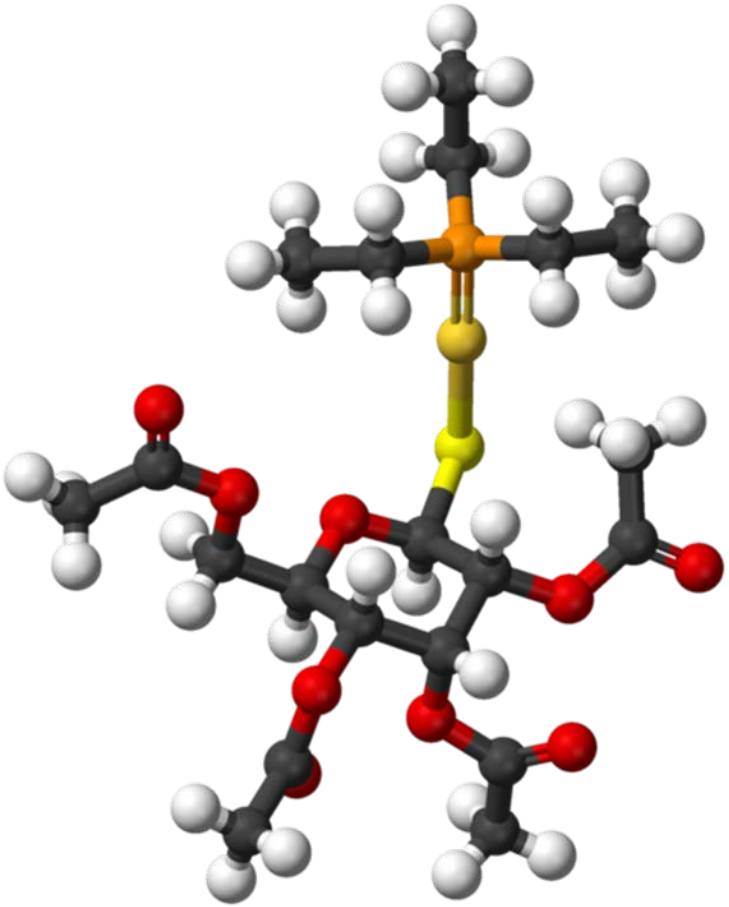


aurothiosulfate (sanochrysine)



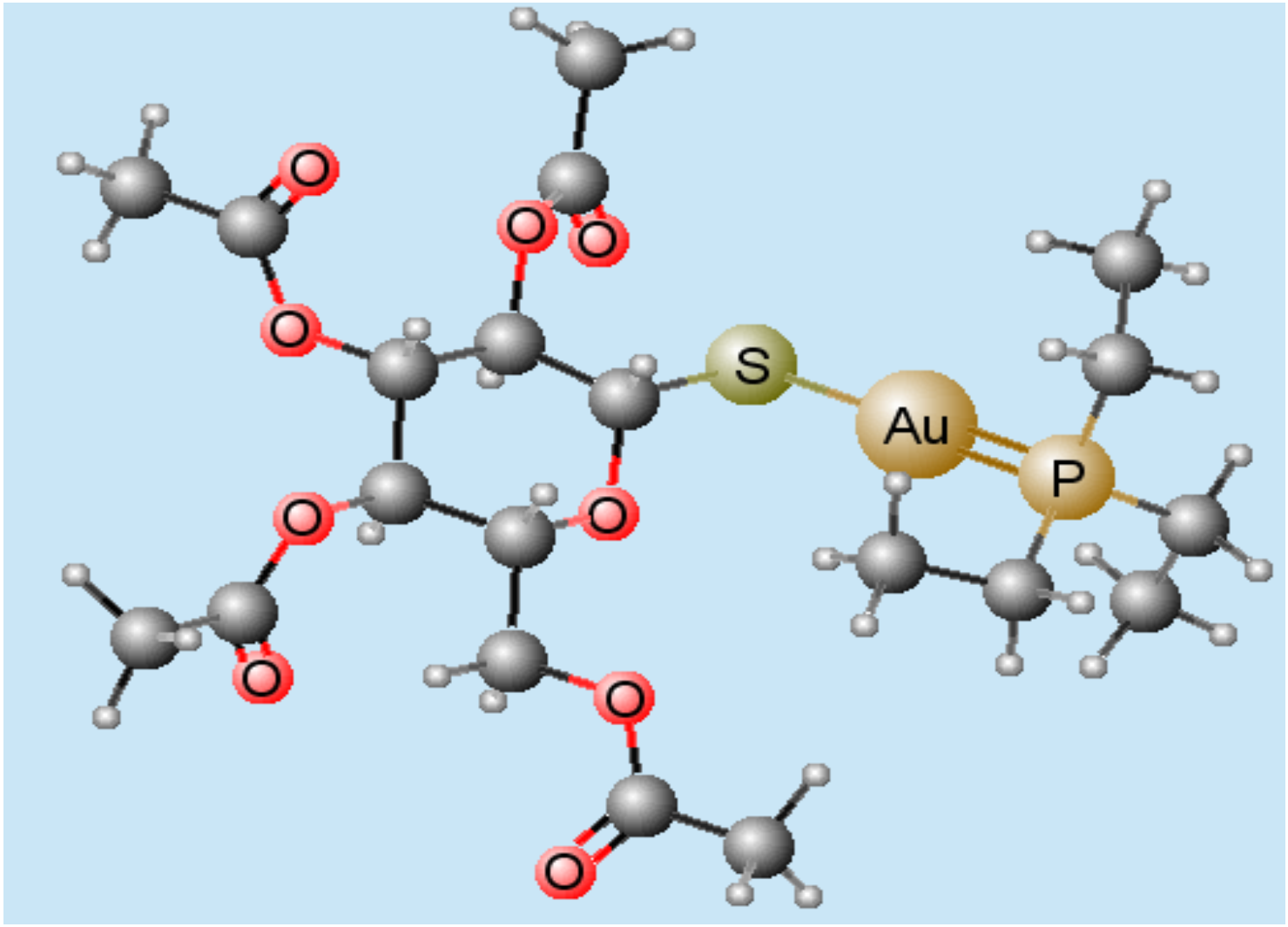
auranofin

AURANOFIN



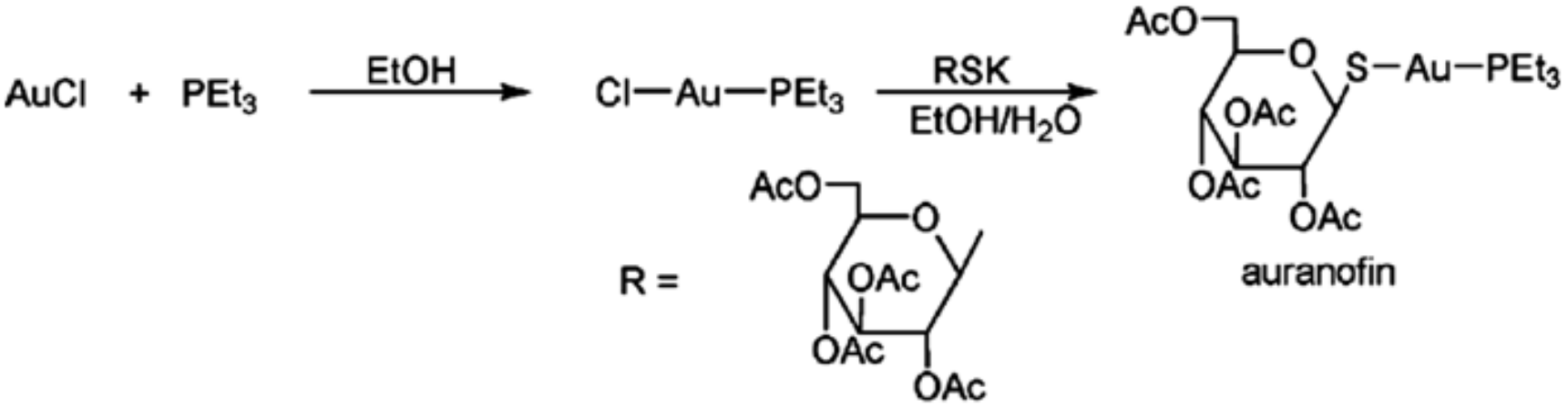
- "What is in a name…"
  - 2,3,4,6-tetra-O-acetyl-1-thio-b-D-glucopyranosato-S
  - Triethylphosphine gold(I)
  - Ridaura
- Not water soluble

AURANOFIN(CONT.)



SYNTHESIS OF AURANOFIN

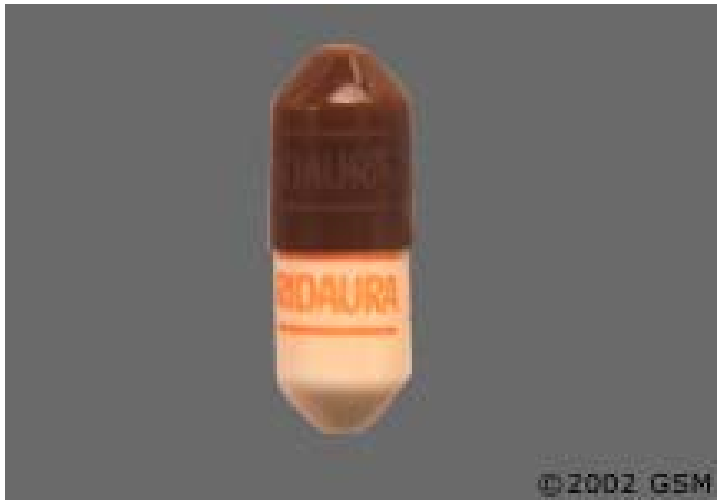
- One side of the gold complex is “blocked” by a strongly-binding triethylphosphine ligand
  - The RSK can only occupy one of the coordination sites



ADMINISTRATION OF AURANOFIN

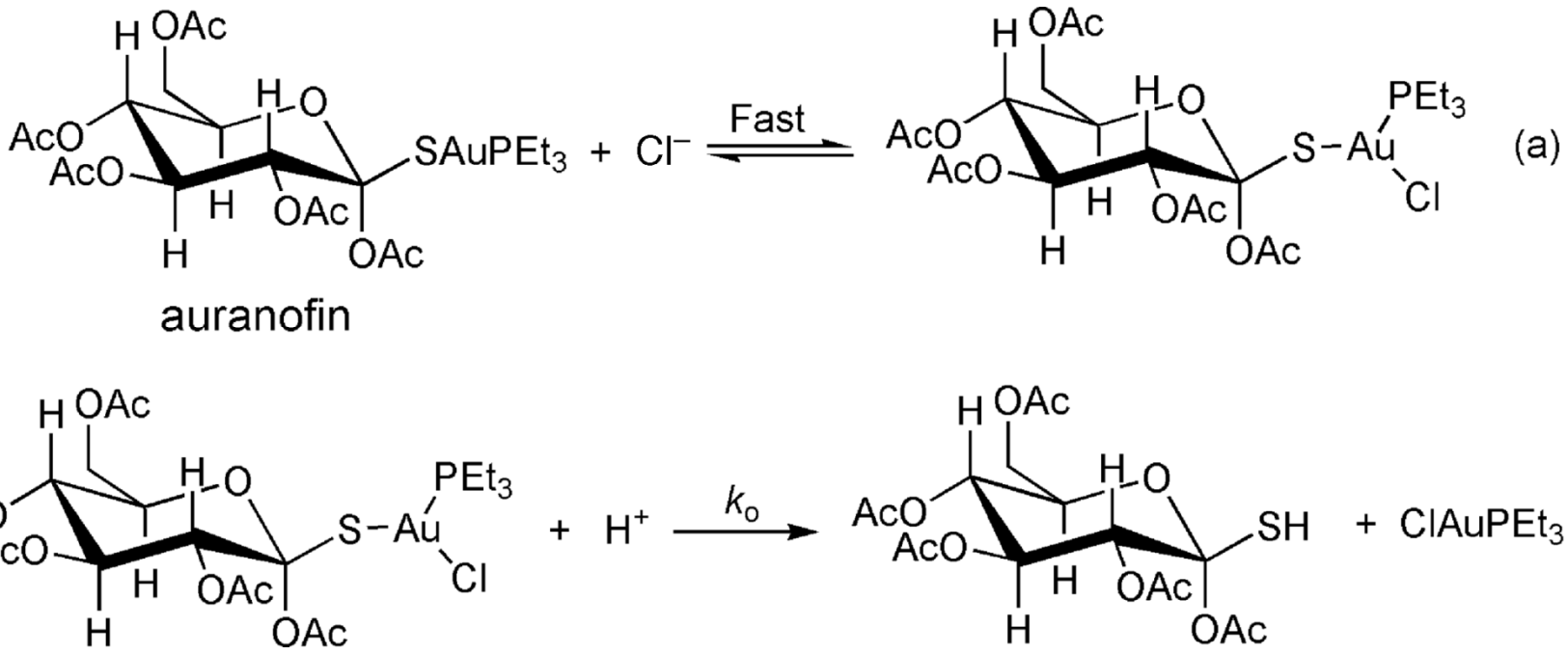
- Orally
- ~6 mg/day
  - Patient monitored
  - Effects are slow to become apparent
- Treatment is carried out over an extended period of time
- Eventually all parts of the body accumulate small amounts of gold

Ridaura
(auranofin)



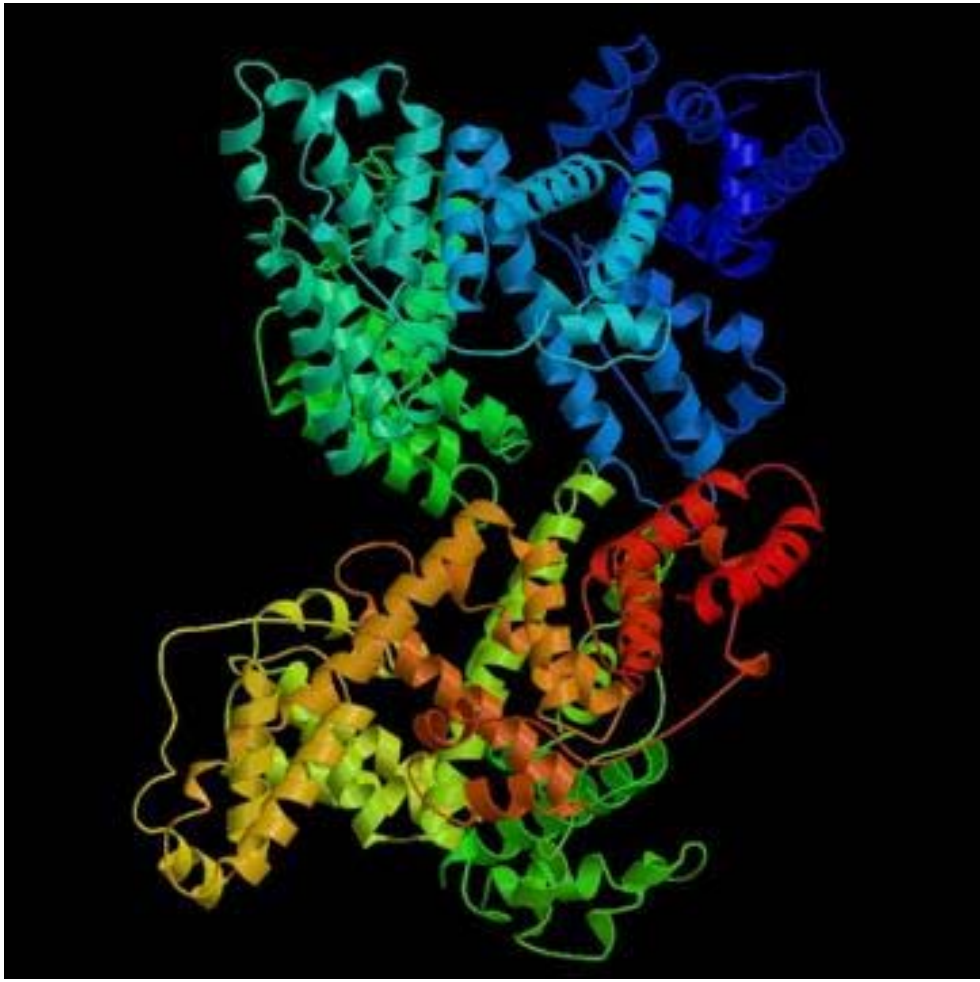
ISSUES

- Stability with pH
  - pH of stomach: 1-3
  - Degradation depends on the $[H^+]$and $[Cl^-]$



ALBUMIN

- Most abundant protein in blood
- ~600 μ*M*
- MW: 66kDa
- 585 amino acids
- One free cysteine residue
  - Ideal binding site for a gold ion
    - Might be means by which gold ion could be distributed throughout the body



INTERACTIONS WITH CELLULAR TARGETS

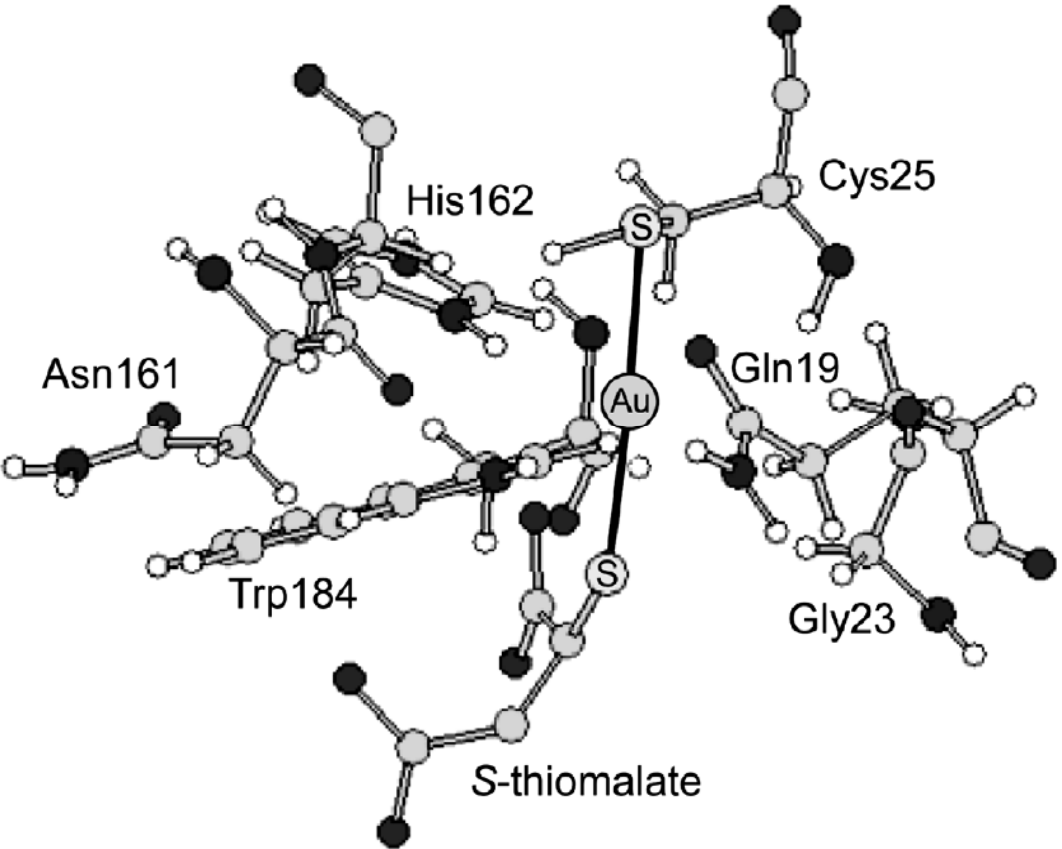
- Gold compounds have their chemical compositions rapidly modified soon after entering the biological system
  - Can cause possible changes in oxidation state
    - No clear mechanistic picture
- The most likely targets for Au^{+} containing drugs in the cell are proteins and other small molecules that have thiol or thioether functional groups

CATHEPSINS

- Group of cysteine proteases
  - Believed to play an important role in the degrading of bone in RA
- Found inside lysomes in osteoclast cells
  - Where gold from chrysotherapy is known to accumulate

CATHEPSIN K

- The thiomalate-Au fragment binds to the Cys_{25} of the protein



- Auranofin inhibits the catalytic function of cathepsin K inside the synovial fibroblasts by binding directly to the thiolate ion of Cys_{25}
  - Blocking protein degradation

OTHER RESEARCH

(Staff photo Jon Chase/Harvard News Office)

http://www.jleukbio.org/cgi/content/full/83/1/39/F1

- Disrupting MHC-peptide interactions
  - Dr. Brian DeDecker

or

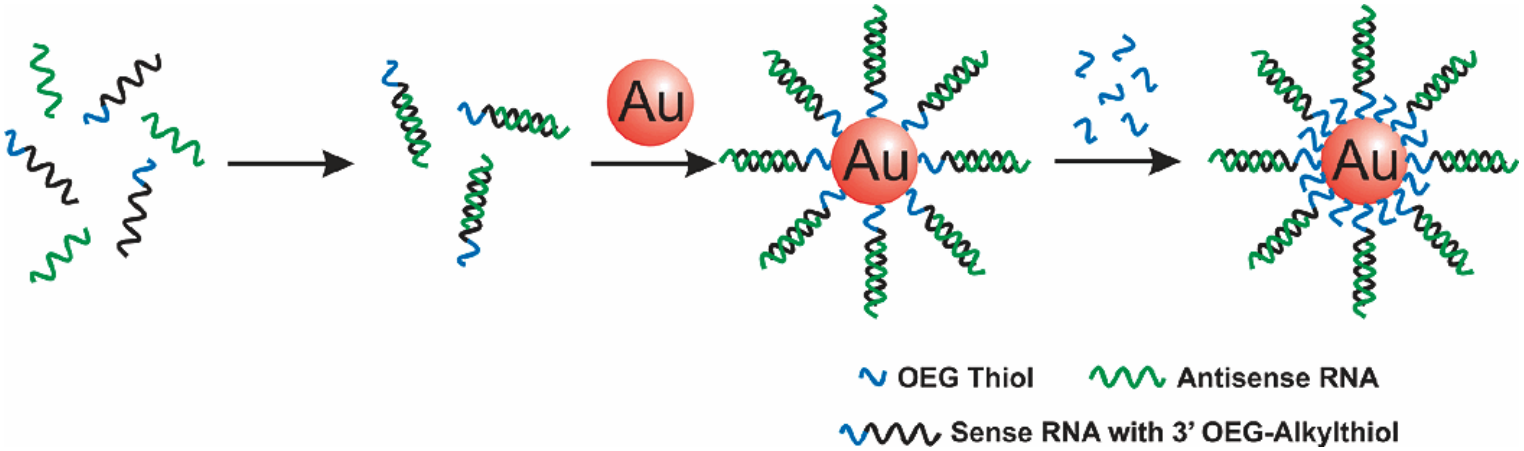
- Inhibit nuclear translocation of the intracellular cytokine HMGB1
  - Dr. Ulf Andersson

USES

Anti-Cancer

CURRENT RESEARCH

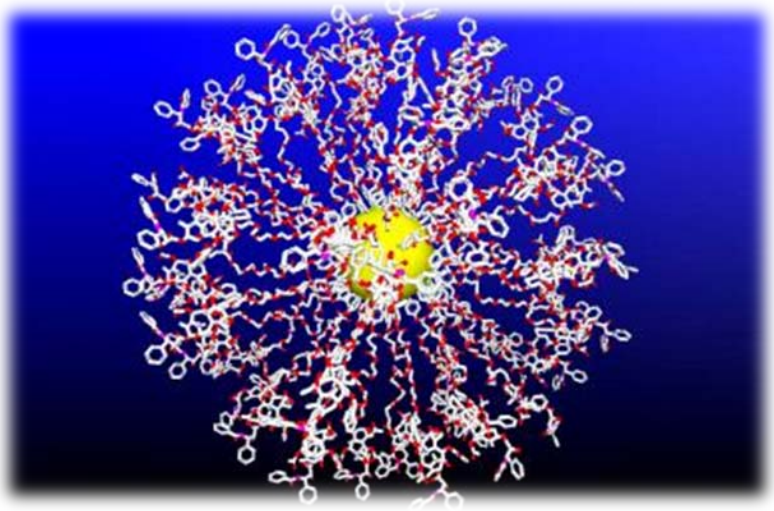
- One of the properties of gold that makes it a valid transport agent, is that it is a very inert metal.
- It is very un-reactive and in the human body therefore it can travel through the blood without problems of degrading or reactive with normal cells.
- Researchers have found that sulfur will bond to gold nanoparticles and that we can attach anti-cancer drugs to the gold using thiol groups.



http://pubs.acs.org/JACSbeta/mobile/select5.html

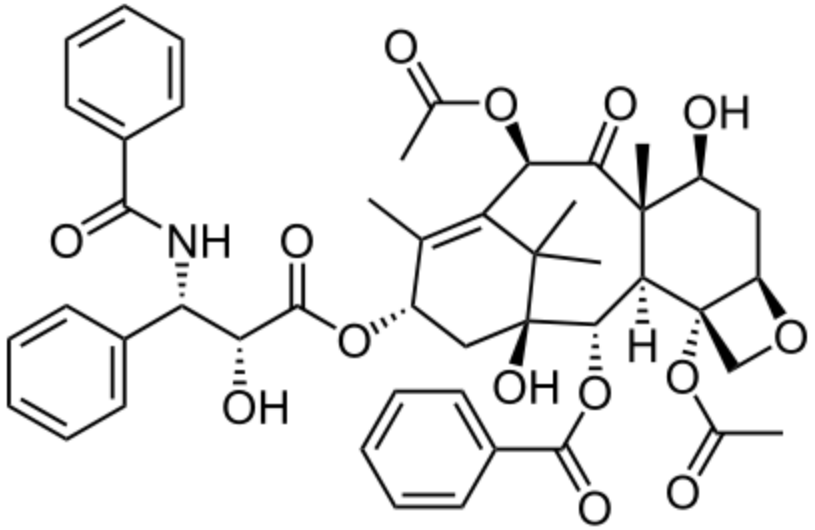
MECHANISM (CONT)

- In 2007, researchers at Rice University have discovered a way to attach dozens of the cancer clogging drug “Taxol” or paclitaxel to gold nanoparticles.
- The gold particles will deliver the drug to the cancer cells and then Taxol will keep the cells from dividing by “jamming their inner works”.
- One major problem was attaching the drug to the particles in a uniform manner, with the effective side pointing outwards so the drug could interact with the cancerous matter.

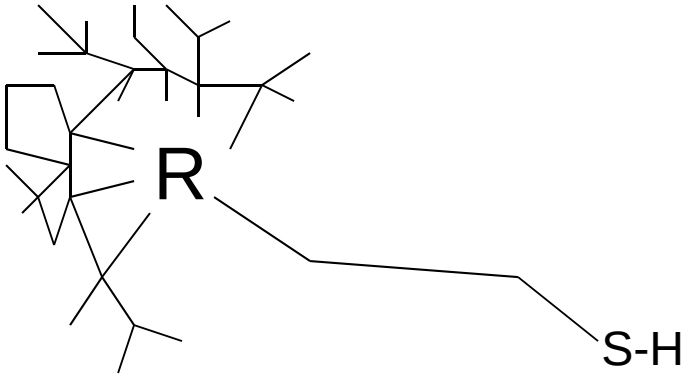


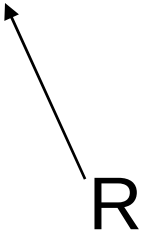
MECHANISM (CONT)

- The way that the Rice University researchers attached Taxol® is by using a “wrapper and key method”.
- Its is easy to understand this method, even if the actual chemistry is out of our league.



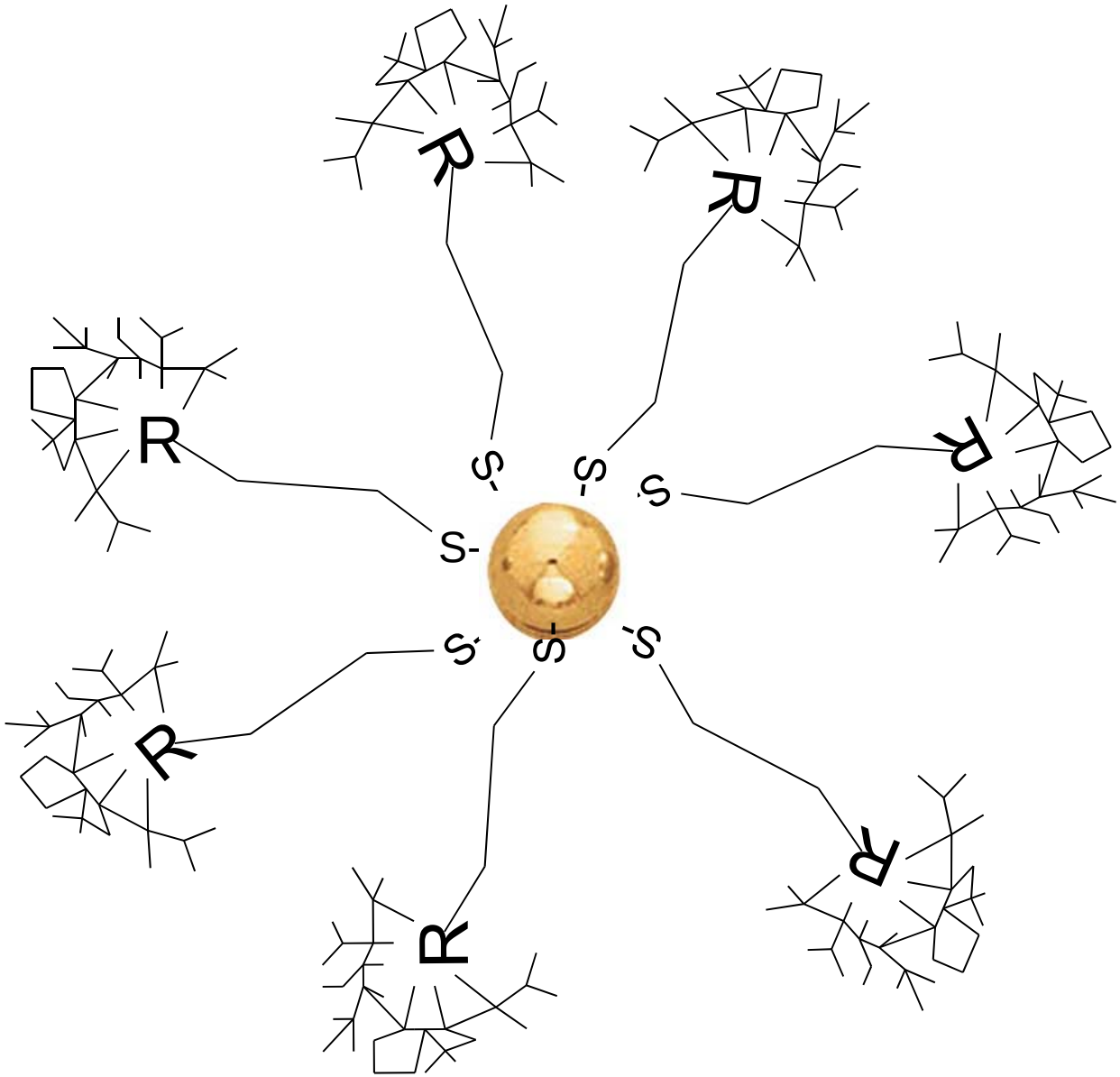
“Wrapper”





http://upload.wikimedia.org/wikipedia/commons/5/59/Taxol.svg

http://www.argos.co.uk/wcsstore/argos/images/6-2108917A70UC503201M.jpg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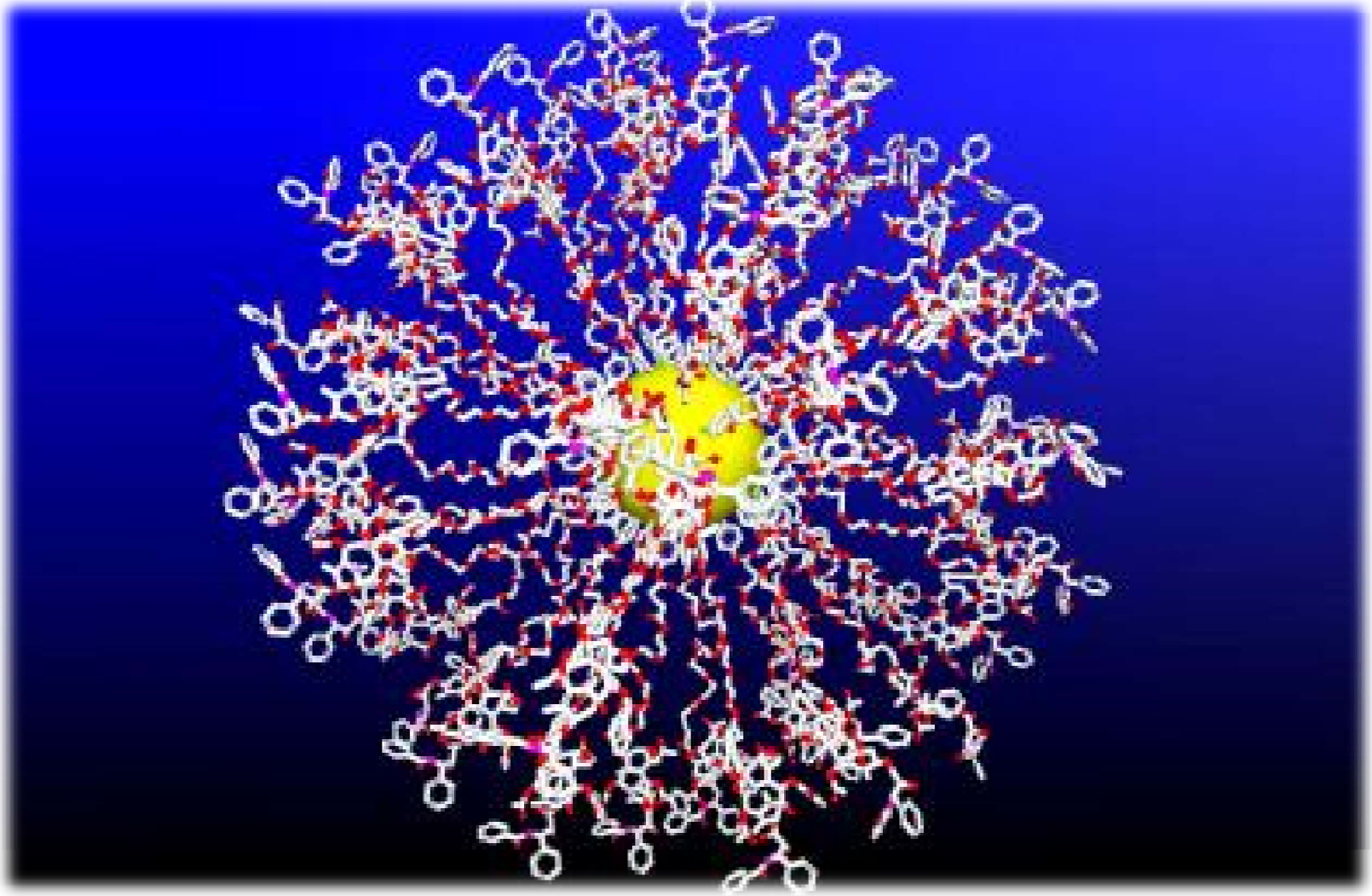
MECHANISM (CONT)

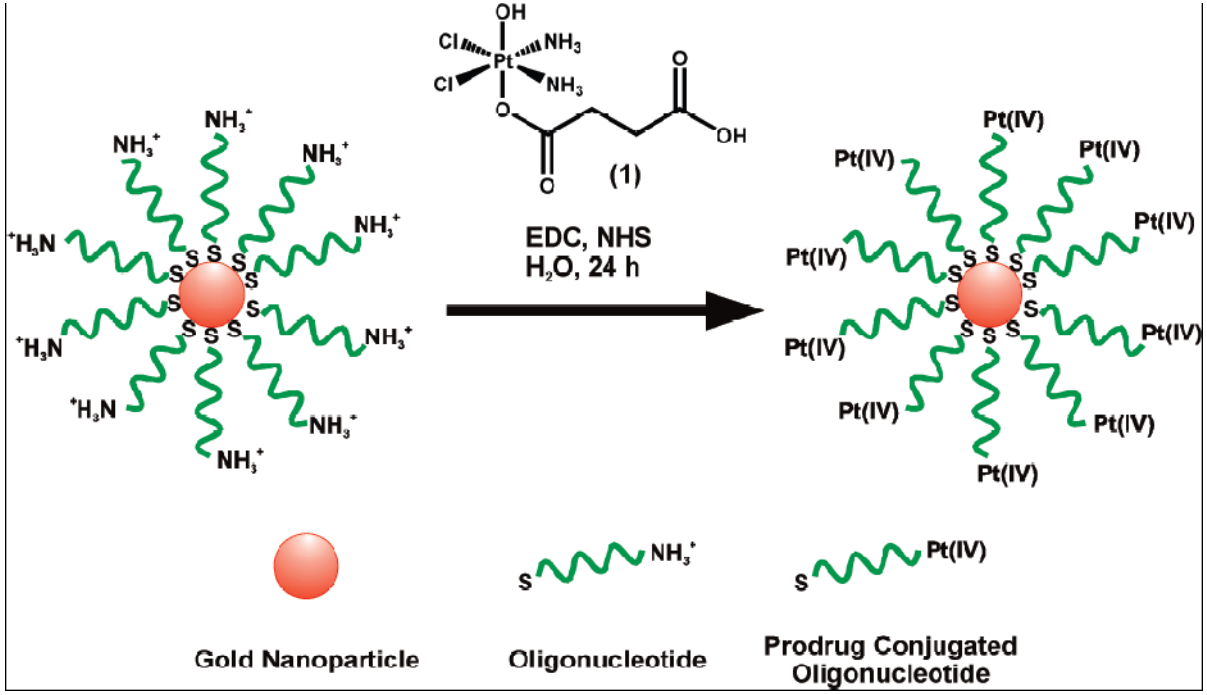


MECHANISM (CONT)

- For specific anti-cancer drugs, the Lippard group at MIT have developed a reliable way to attach cisplatin to gold nanoparticles.

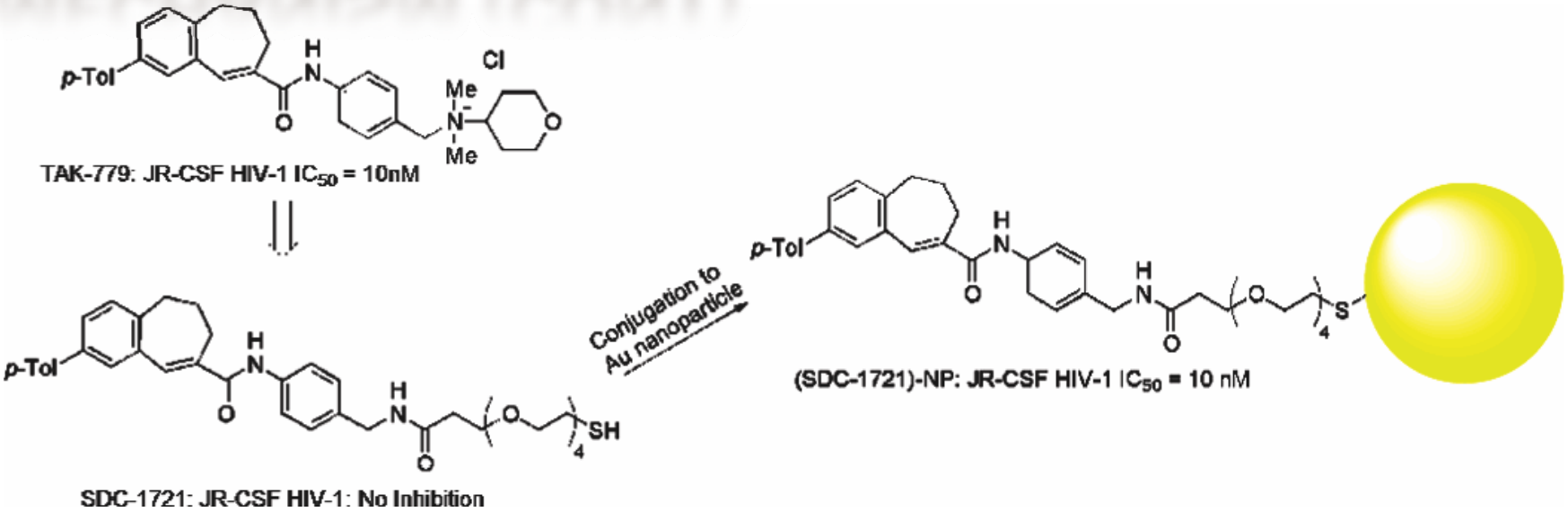
- They first attached oligonucleotides, which are just short nucleic acid chains.

- Then they utilized the NH_3^+ to bind conjugated cisplatin to the short chains.



http://pubs.acs.org/doi/pdf/10.1021/ja9071282?cookieSet=1

MECHANISM (CONT)



- Researchers at the University of North Carolina studied how gold can help transport HIV inhibiting drugs.
- The mechanism they used is similar to anti-cancer methods, they just use a different drug.
- As you can see, the researchers dcveloped a derivative of TAK-779 called SDC-1721. This new drug is very inactive in its free state, but they found that if they attach it to 2nm sized gold particles that the drug would arrive at its destination and inhibit HIV interaction with T-cells.
- The size of gold nano-particles is relative to that of proteins that the cells uses to perform vital growth functions. By delivering a drug that can disrupt these functions one can stop cell growth.

http://pubs.acs.org/doi/pdf/10.1021/ja710321g