

# Au complexes with Anti-arthritic, Anti-tumour and Anti-HIV activity...

## Chrysotherapy

For thousands of years gold has been considered to be of medical, therapeutic value. Even in the 19<sup>th</sup> century gold was considered to be a “cure-all” for diseases. The alchemists knew that metallic gold dissolves in aqua regia and can be reduced back to **metallic gold** in the form of a stable **colloid** (gold sol), the colour of which depends on the size of the particles and ranges from blue (large particles) to dark purple (small particles; “Purple of Cassius” first prepared by Andreas Cassius in 1685). Neutralised solutions (“aurum potabile”, drinkable gold) were widely used in therapy during the Middle Ages but their true value is in doubt.

The rational use of gold in medicine began in the early 20<sup>th</sup> Century when the bacteriologist Koch discovered that  $\text{K}[\text{Au}(\text{CN})_2]$  could kill the bacteria which cause tuberculosis. In common with many  $\text{Au}^{\text{I}}$  complexes,  $[\text{Au}^{\text{I}}(\text{CN})_2]^-$  contains **linear, two-coordinate  $\text{Au}^{\text{I}}$**  with carbon-bound cyanide:  $[\text{NC} - \text{Au} - \text{CN}]^-$ . Three coordinate  $\text{Au}^{\text{I}}$  and four-coordinate tetrahedral  $\text{Au}^{\text{I}}$  complexes are known but are less common.

**Very painfully administered as  
intramuscular injections...ouch!**

The greatest user of gold in medical history is said to have been **Leslie Keeley** who treated thousands of patients in the Chicago area of the USA with gold preparations in the late 19<sup>th</sup> century.

**“ Gold cure for opium habit \$10  
Gold cure for drunkenness \$9  
Gold cure for neurasthenia \$8  
Remedies sold only in pairs”**

The patients seemed to be pleased with their treatment and formed the “*Bichloride of Gold Club*” (but note that  $[\text{Au}^{\text{I}}\text{Cl}_2]^-$  is not very stable!). The chemical nature of Keeley’s gold preparations is uncertain.

27 Co	28 Ni	29 Cu	30 Zn
45 Rh	46 Pd	47 Ag	48 Cd
77 Ir	78 Pt	79 Au	80 Hg
109 Uue	110 Uun		

- 1)  $\text{Au}^{1+}$  “Soft” metal atom...prefers  $\text{P} > \text{N}$  and  $\text{S} > \text{O}$ ...(likes heavier atom ligands)
- 2) In biological systems it binds to Cys sulfur, S.
- 3) Weak  $\text{Au}^{\text{I}}\text{-Au}^{\text{I}}$  interactions “aurophilicity”
- 4) Doesn't like  $2+$  oxidation state

It is common to find weak  $\text{Au}^{\text{I}}\text{-Au}^{\text{I}}$  interactions in the X-ray structures of  $\text{Au}^{\text{I}}$  complexes. This “*aurophilicity*” is often ascribed to the strong influence of relativistic effects on gold chemistry (inner shell electrons moving with velocities approaching the speed of light – heavy electrons – shell contractions)



In contrast to Cu, which is also in group 11, **gold in oxidation state +2, Au<sup>II</sup>, is very unstable.** Square-planar Au<sup>III</sup> complexes are readily prepared but tend to be reduced in biological media (to Au<sup>I</sup> and Au<sup>0</sup>).

During the early 20th Century, gold treatment for tuberculosis switched from  $K[Au(CN)_2]$  to the less toxic AuI thiolate complexes. In the early 1930's the French physician **Jacques Forestier** was the first to use these thiolate complexes to treat rheumatoid arthritis, a condition which he believed to be related to tuberculosis. The use of gold for the treatment of rheumatoid arthritis has continued ever since.

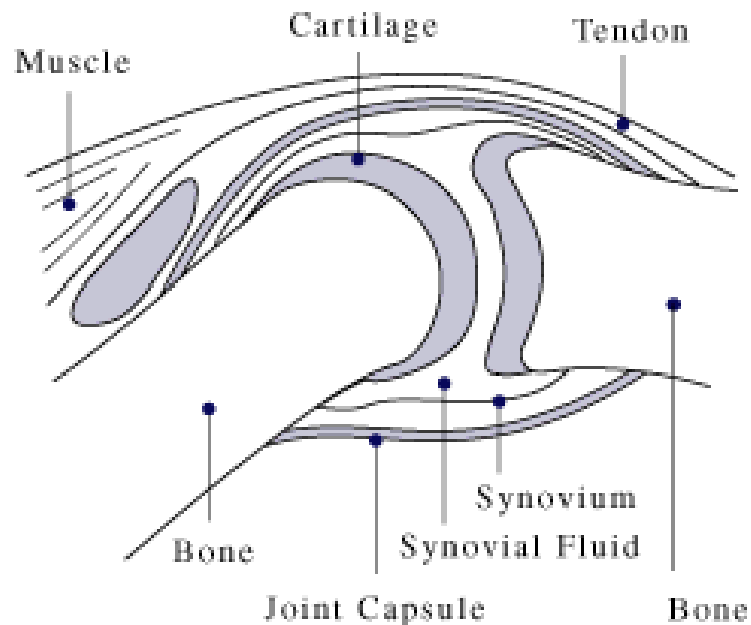


DR. JACQUES FORESTIER

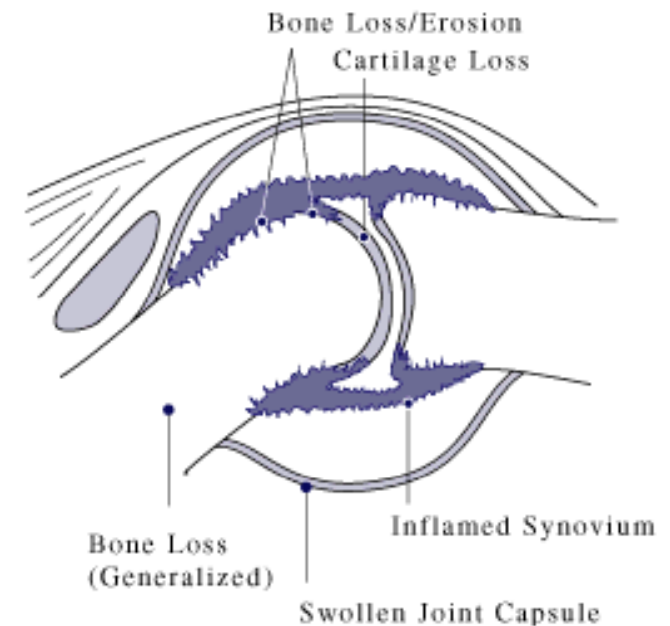
# Rheumatoid arthritis (RA)

...An inflammatory condition that leads to progressive erosion of the articular cartilage lining the interfaces of bones in joints.' If the attack, which shows many characteristics of an autoimmune disease, is not checked, the bones will eventually fuse after complete loss of the cartilage. The initial inflammation occurs in the synovial membrane, which surrounds the joints, and then moves into the synovial cavity between the bones

**Normal Joint**



**Joint Affected by Rheumatoid Arthritis**





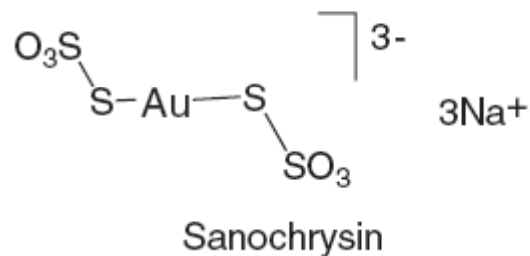
About **1% of the world's population** is afflicted by rheumatoid arthritis, **women three times more often than men**. Onset is most frequent **in 40 to 50 years**, but no age is immune. It can be a **disabling and painful condition**, which can lead to **substantial loss of functioning and mobility**. It is diagnosed chiefly on symptoms and signs, but also with **blood tests** (especially a test called **rheumatoid factor**) and **X-rays**.  
Diagnosis and long-term management are typically performed by a **rheumatologist**, an expert in the diseases of joints and connective tissues



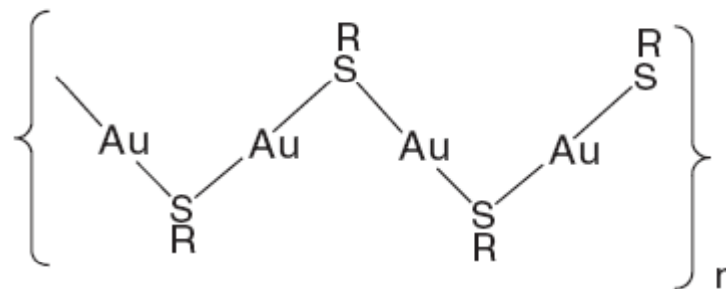
**Inflammation:** the complex biological response of tissues to harmful stimuli, such as [pathogens](#), damaged cells, or irritants. It is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue. **Inflammation is not a synonym for infection.** Even in cases where inflammation is caused by infection, the two are not synonymous: **infection is caused by an exogenous pathogen, while inflammation is the response of the organism to the pathogen.**

In the absence of inflammation, wounds and infections would never heal and progressive destruction of the tissue would compromise the survival of the organism. However, an inflammation that runs unchecked can also lead to a host of diseases, such as [atherosclerosis](#), and [rheumatoid arthritis](#)

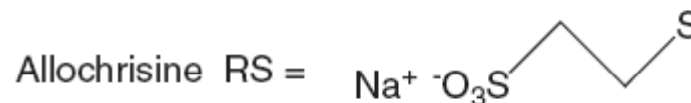
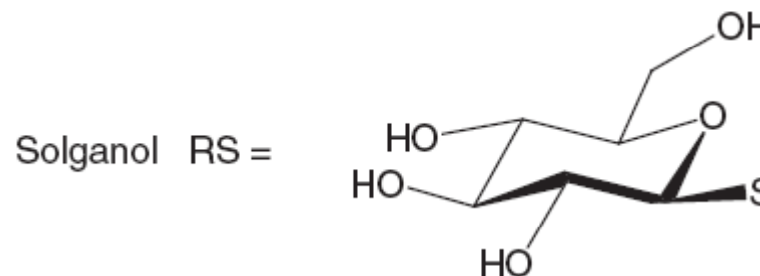
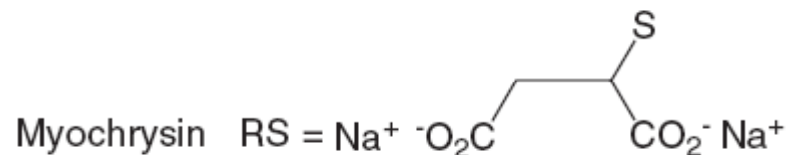




### Injected Drugs (AuSR)<sub>n</sub> Oligomers



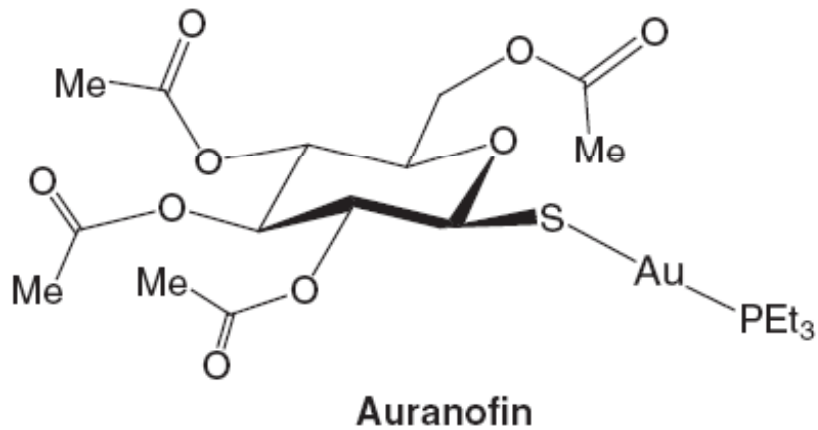
The **major injectable** antiarthritic gold drugs are the **water-soluble** complexes aurothiomalate (Myochrysin), aurothioglucose (Solganol), sodium bis(thiosulfate) gold(I) and sodium thiopropanolsulfonate-S-gold(I). **The thiolate complexes are formulated as approximate 1:1 complexes but their structures in solution are complicated. Au<sup>I</sup> must be at least two-coordinate and thiolate sulfur acts as a bridge between Au<sup>I</sup> ions: -S-Au-S-Au-S-Au-**



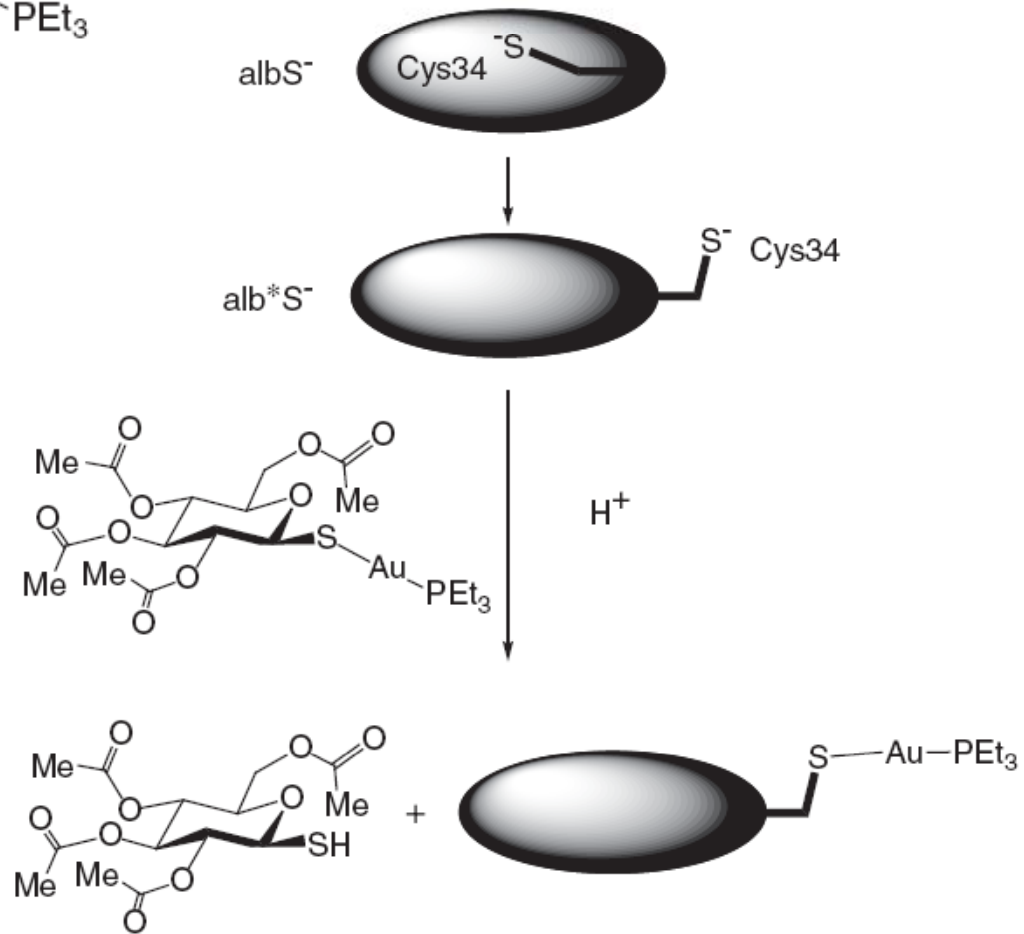
*...Chains and cyclic structures are also possible...*

Chrysotherapy is effective for about 70% of the patients taking the treatment. Others do not benefit from gold, or suffer side effects that require cessation of treatment. Most side effects are mild, and some are only cosmetic (e.g. skin rashes). Only occasionally are there life-threatening consequences (*ca.* 1 : 10,000 patients): usually inhibition of white or red blood cell formation in the bone marrow.

## Possible mode of action...

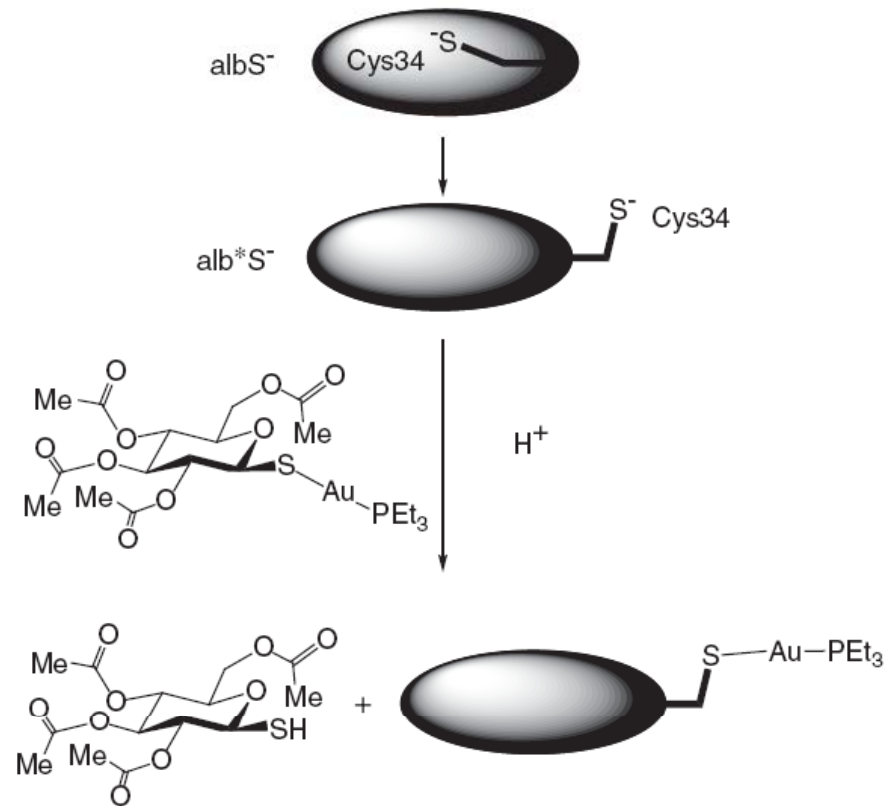


The **oral** drug **auranofin** is a monomer and contains linear 2-coordinate Au<sup>I</sup>. It is a stable white crystalline complex, sparingly soluble in water but soluble in organic solvents....first example of the use of a **phosphine** in a drug. **Phosphine ligands alone are often associated with high reactivity...**



*A schematic view of the binding of Au<sup>+</sup> to an externalised thiolate group on albumin*

In the structure of the principle form of albumin, mercaptoalbumin (albS), a cysteine residue is present at position **34 (Cys34)** which carries an **acidic thiol group**. This is normally deprotonated at physiological pH and offers a potential binding site for Au<sup>I</sup>. However, kinetic and spectroscopic studies of the interaction between mercaptoalbumin and Auranofin indicate that a rearrangement of the albumin structure to an active form, **alb\*S**, is required before the Au<sup>I</sup> ion is bound. This involves the **relocation** of the Cys34 thiolate group within the protein **to the protein surface**.

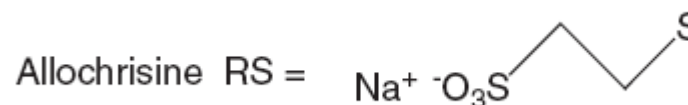
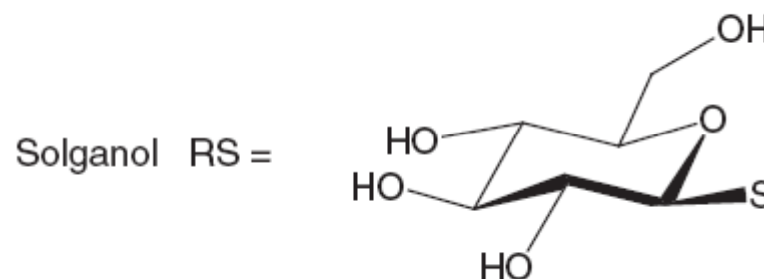
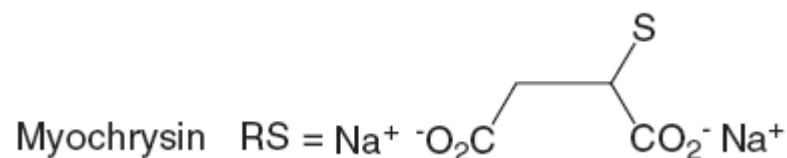
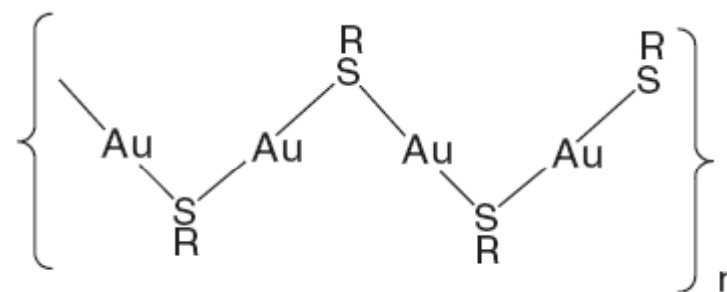


*A schematic view of the binding of Au<sup>+</sup> to an externalised thiolate group on albumin*



It turns out that the gold compounds should really be thought of as **prodrugs** in that they do not represent biologically active species but **rather they provide a source of biologically available gold**. Thus the primary function of the ligands used in the gold drugs is **to provide a soluble gold complex suitable for administration to the patient and sufficiently stable for transportation and storage prior to clinical use**. Improved aqueous solubility is conferred by the **carboxylate groups in Myochrysin**, the **hydroxyl groups in Solganol** and the **sulfonate group in Allochrysin**.

Injected Drugs (AuSR)<sub>n</sub> Oligomers



Gold drugs are “*pro-drugs*” because *ligand substitution reactions are relatively facile on Au<sup>I</sup>. They have low activation energies and proceed via 3-coordinate intermediates. Thiol exchange reactions are important in vivo. The initial ligands on the gold drugs are displaced (substitution of thiols, displacement and oxidation of PEt<sub>3</sub> to OPEt<sub>3</sub>). In the blood most of the Au<sup>I</sup> is carried by the thiol of cysteine-34 of albumin.*

Half-time for Au-excretion: 5 – 31 days...but it can stay for years

Patients-Smokers contain MUCH higher Au-conc. in their blood...

Why?...remember  $[\text{Au}(\text{CN})_2]^-$ ?



# Anti-tumour activity

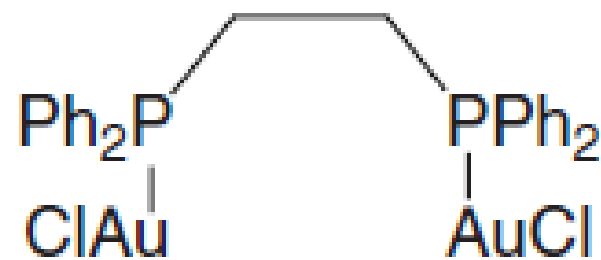
Interest over the last several decades in the potential anti-tumour activity of gold complexes has been driven by three common rationales:

(1) analogy to the immunomodulatory properties underlying the benefit from Au(I) complexes in treating rheumatoid arthritis,

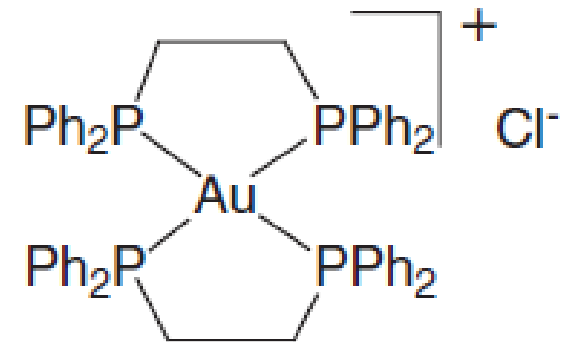
(2) the structural analogy of square-planar Au(III) to Pt(II) complexes, which are potent anti-tumour agents, and

(3) Complexation of Au(I) or Au(III) with other active anti-tumour agents in order to enhance the activity and/or alter the biological distribution of the latter.

Unfortunately, promising in vitro results did not translate into significant **in vivo** results. Au(+1) complexes with the ligand bisdiphenylphosphinoethane (dppe)  $[(\text{AuCl})_2(\mu\text{-dppe})]$ , showed significant activity against a variety of tumor cell lines, sometimes greater than that of dppe, itself a known antitumor agent



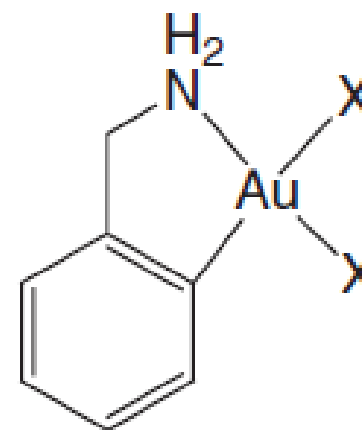
The **complex**  $[\text{Au}(\text{dppe})_2]\text{Cl}$ , was similarly **active against P388 leukaemia** but only if applied directly to the tumor, intravenous, subcutaneous or intraperitoneal administration were ineffective. The complex, **inhibits protein synthesis more than DNA or RNA synthesis, forms DNA-protein crosslinks and causes DNA strand breaks**. Unfortunately the cardiovascular toxicity of this class of compound has precluded clinical trials.



The electronic similarity between  $d^8$   $\text{Au}(3+)$  and  $d^8$   $\text{Pt}^{2+}$  leads to them both adopting square planar coordination geometries and suggests the use of  $\text{Au}^{3+}$  compounds as possible anticancer agents by analogy with cisplatin. Complexes of the form  **$[\text{AuLCl}_3]$**  (LQN-methylimidazole, methylbenzoxazole or dimethylbenzoxazole) **show reasonable cytotoxicities and antitumor activity in vivo.**

However, **in vivo reduction of  $\text{Au}^{3+}$  to  $d^{10}$   $\text{Au}^{1+}$**  presents a significant problem in the application of  $\text{Au}^{3+}$  complexes and the choice of suitable ligands is important in controlling the chemistry of the system.

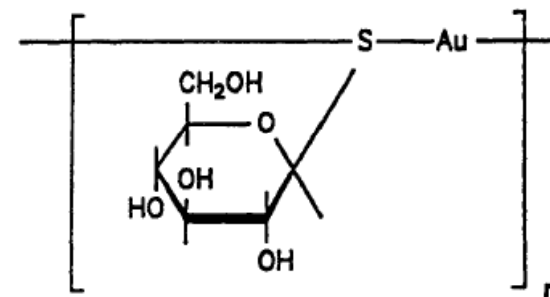
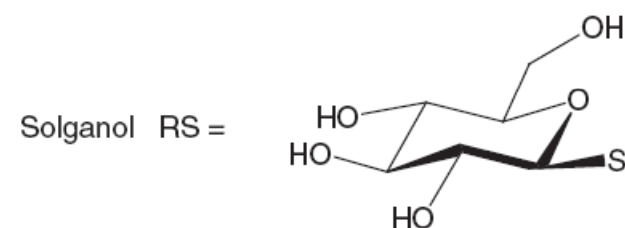
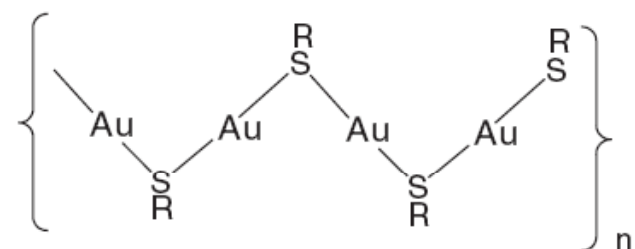
The presence of the orthometallated benzylamine ligand (damp) in  $[\text{Au}(\text{damp})\text{X}_2]$  ( $\text{X}=\text{Cl}, \text{O}_2\text{CCH}_3, \text{SCN}; \text{X}_2=\text{C}_2\text{O}_4, \text{CO}_2\text{CH}_2\text{CO}_2$ ) prevents reduction of the  $\text{Au}^{3+}$  centre by thiols and these compounds **are active against a panel of tumor cell lines. The acetate and malonate complexes show activity similar to cisplatin against the HT1376 xenograft in vivo.** Their mechanism of action is different from that of cisplatin raising the possibility that such compounds might be of potential use against cisplatin resistant tumors.



# Anti-HIV activity

Investigations of the anti-HIV activity of gold complexes were stimulated by reports that **AuSTg inhibits reverse transcriptase (RTase), an enzyme that converts viral RNA into DNA in the host cell.** AuSTg is indeed active in the cell-free extracts where it was studied, but it is unable to enter the cells where RTase acts. A different mechanism of action has been proposed for  $\text{Au}(\text{STg})_2^-$ , which can be generated *in situ* from AuSTg and TgSH.  **$\text{Au}(\text{STg})_2^-$  inhibits the infection of MT-4 cells by HIV strain HL4-3 without inhibiting the RTase activity in the intact virions.** The critical target site has been tentatively identified as a thiol group, cys-532 on gp160, which is a glycoprotein of the viral envelope...

Injected Drugs  $(\text{AuSR})_n$  Oligomers



AuSTg = gold(I)  $\beta$ -D-thioglucose  
(solganol)