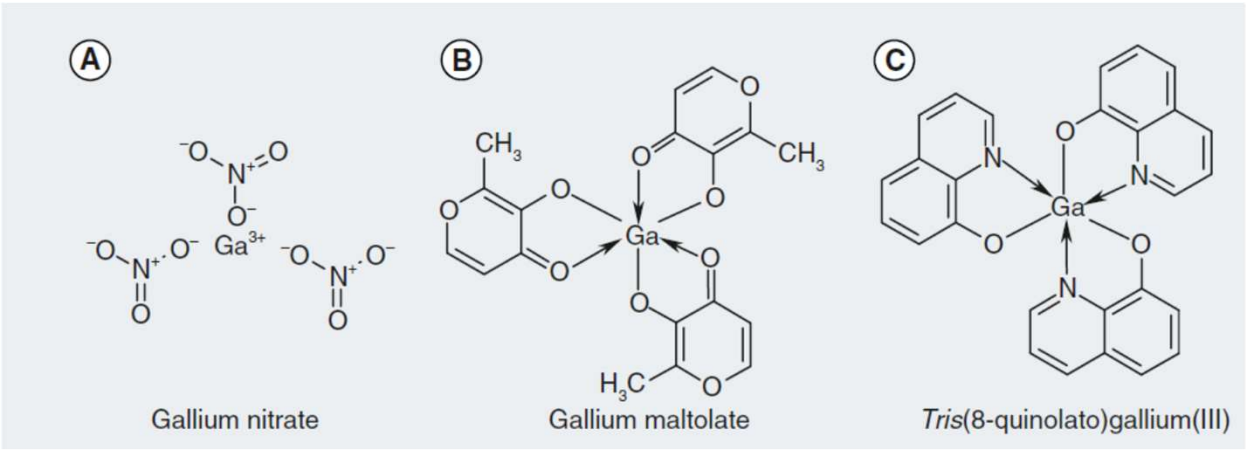
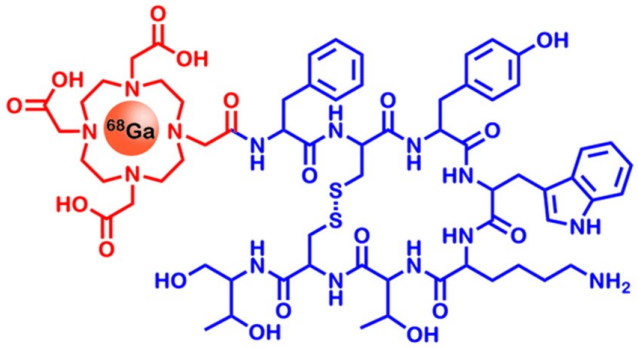
Table 1. Gallium compounds in cancer treatment: advancement from the laboratory to the clinic.

Gallium complex	*In vitro* studies	Animal studies	Human studies
Gallium nitrate	Cytotoxic against a spectrum of malignant cell lines, especially lymphoma and leukemia cells	Antineoplastic activity demonstrated in rodent tumor models Animal toxicity profile established	Human-toxicity profile established in clinical Phase I studies. Antineoplastic activity against bladder cancer and non-Hodgkin's lymphoma demonstrated in numerous Phase II clinical studies. Combination chemotherapy trials conducted
Gallium chloride	Cytotoxic against a variety of malignant cell lines at concentrations similar to gallium nitrate	Intraperitoneal administration inhibited the growth of adenocarcinoma CA755 in mice. Low bioavailability with oral administration. Tissue-distribution studies conducted	Clinical pharmacology studies with oral $GaCl_3$ conducted in lung cancer patients. Partial responses to treatment were seen in patients with ovarian cancer
G4544	Not reported	Pharmacokinetic studies conducted	Clinical pharmacology studies conducted
Gallium maltolate	IC_{50} values lower than gallium nitrate. Inhibits the growth of lymphoma cells resistant to gallium nitrate	Pharmacokinetic studies conducted	Clinical pharmacology studies conducted. Anti-tumor activity demonstrated in a patient with hepatocellular carcinoma
Tris(8-quinolonato)gallium(III) (KP46)	Cytotoxic in melanoma, ovarian, breast, colon and lung cancer cell lines. IC_{50} values lower than that reported for gallium nitrate	Tissue distribution studies conducted in mice. Anti-tumor activity demonstrated *in vivo*	Clinical pharmacology and toxicity studies conducted in clinical Phase I/II trials. Anti-tumor activity noted in renal cancer

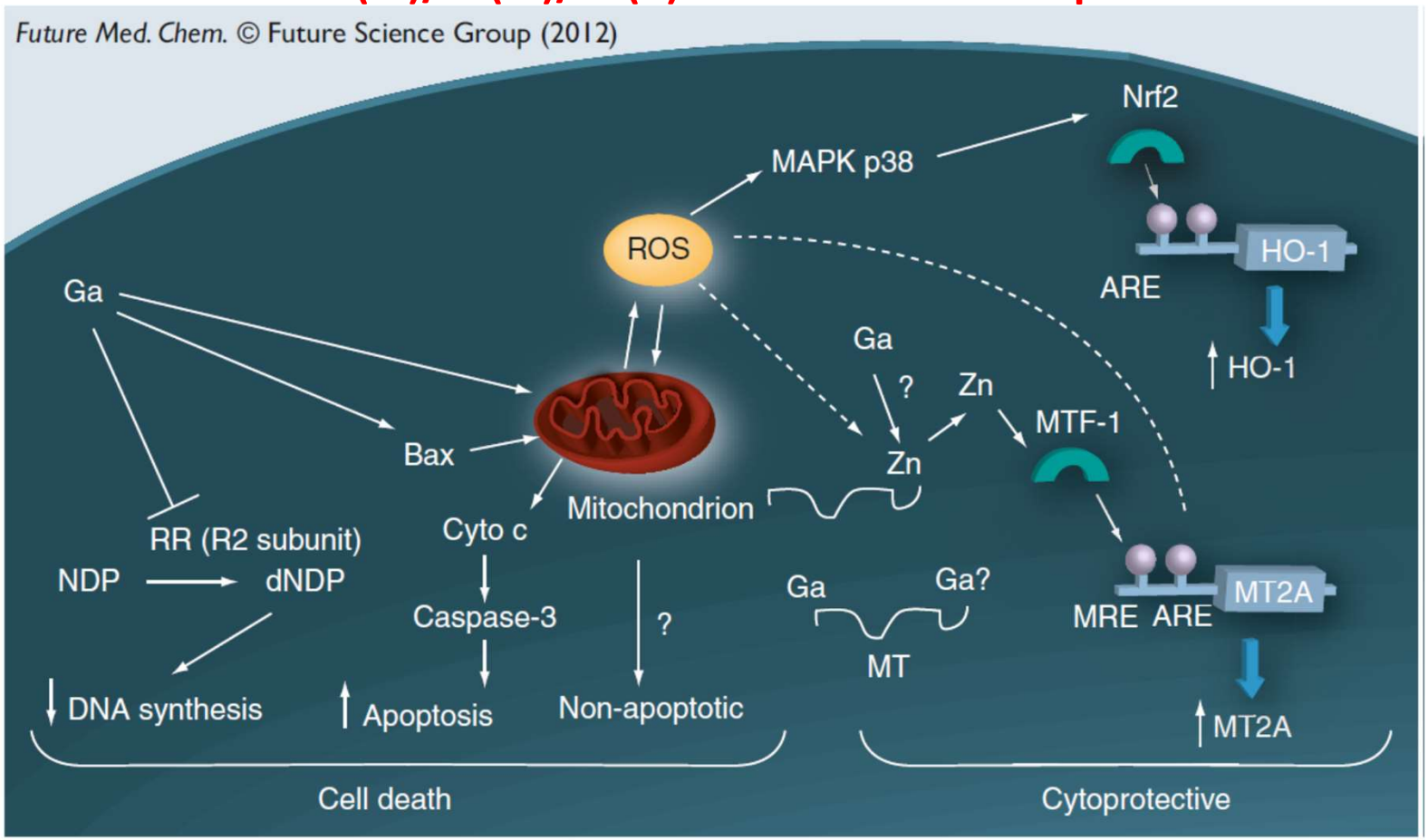




Ga^{68} dotatoc (2019)
(imaging neuroendocrine tumors)

Gallium compounds: known mechanism of action so far

Ga(III)/Fe(III)/Zn(II) ionic radius 70 - 80 pm



increase in intracellular ROS of mitochondrial origin.

Changes in zinc homeostasis along with ROS generation induce the expression of MT2A.

HO-1 gene expression and activation of transcription factor Nrf2.

MT2A and HO-1 are cytoprotective. The iron-dependent R2 subunit of ribonucleotide reductase (RR) is inhibited by Ga(III)

Bax activation → mitochondrial release of Cyt C → caspase-3 activation → Apoptosis

ARE: Antioxidant response element; MRE: Metal-responsive elements; ROS: Reactive oxygen species;

Similarity in structures: promiscuity

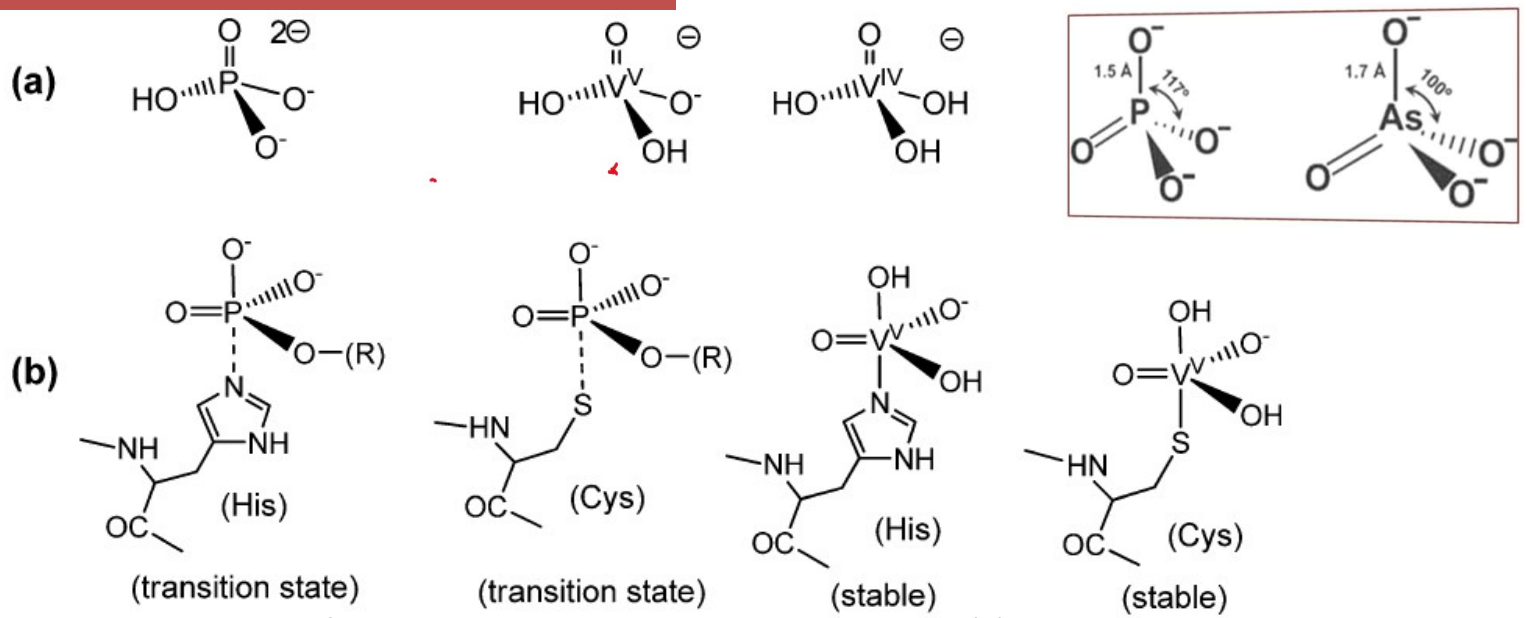


Fig. 1 Analogies and differences between phosphate and vanadates. (a) The predominant protonation states of phosphate and of the vanadates(V) and (IV) at neutral pH. Due to the low solubility of $VO(OH)_2$, dissolved vanadate(IV) H_3VO_4 *(the coordination sphere of V(IV) can be expanded by aqua ligands)* is restricted to the nanomolar concentration range. (b) Penta-coordinate species evolving from the interaction between phosphate (and phosphate esters) or vanadate with peptide–protein residues: phosphate forms labile transition states only, symbolized here by a dashed P…N bond to histidine or a P…S bond to cysteinate (serinate – not shown – is a third alternative), while vanadate ascertains stable complexes. Examples are the binding of vanadate to a histidine residue in vanadate-dependent haloperoxidases and in rat prostate acid phosphatase, and the coordination of vanadate to a cysteinate residue in phosphotyrosyl phosphatase. This coordination mode has also been invoked for the inhibitory effect of vanadate towards intracellular protein tyrosine phosphatase in the context of the insulin enhancing properties of vanadate. The hydroxide in the apical position can be replaced by, for example, tyrosinate.

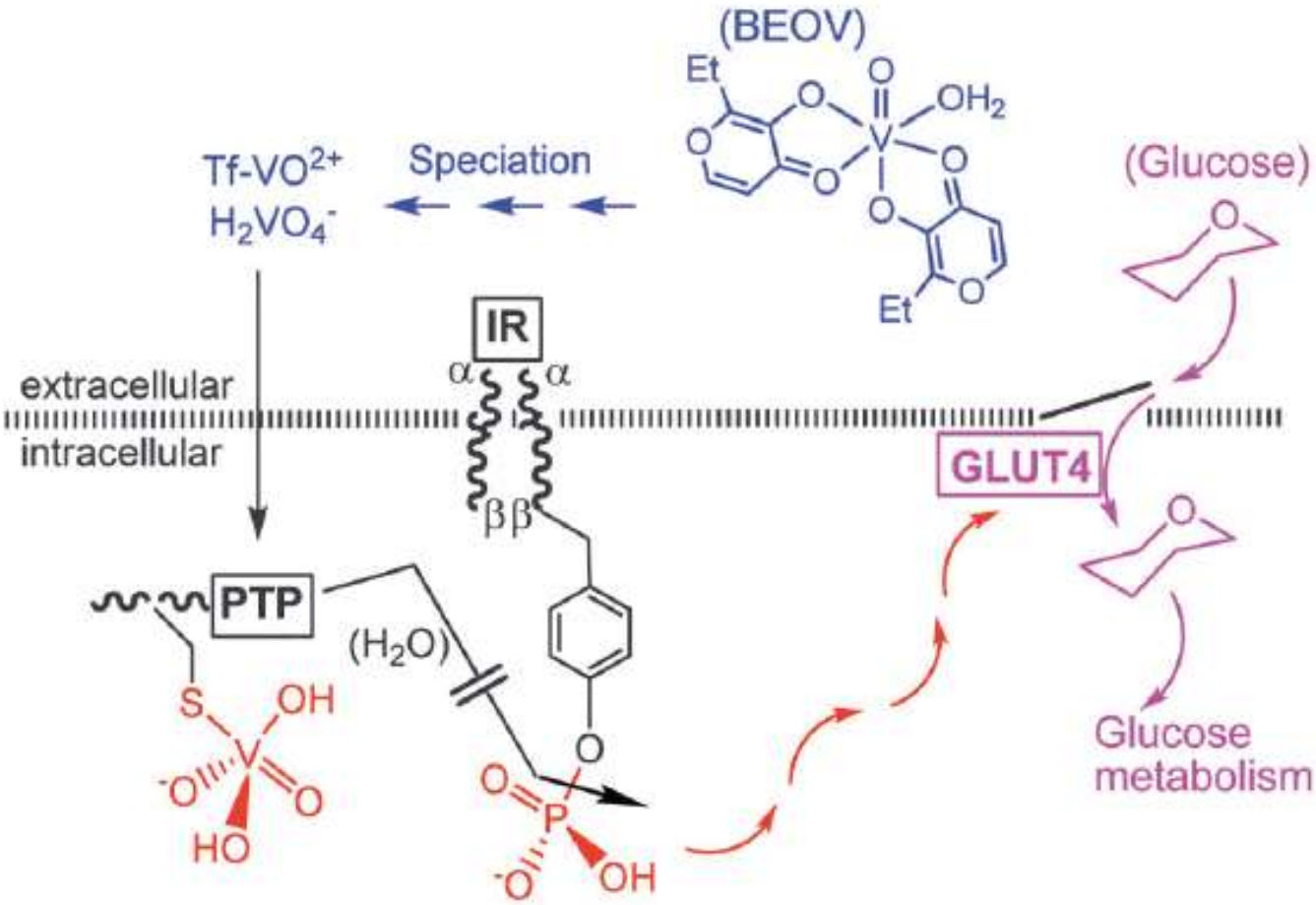
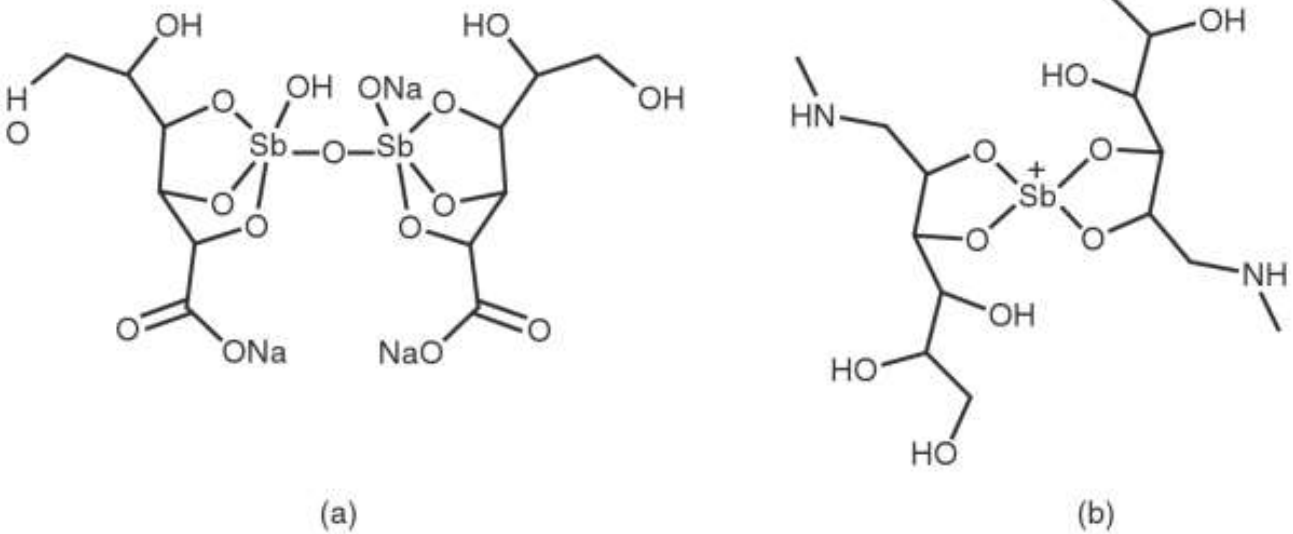


Fig. 8 A simplified illustration of the action of vanadate as an insulin-mimetic/enhancing agent (red and mauve traces). BEOV is bis(ethylmaltolato)oxidovanadium(IV); Tf = transferrin, IR = insulin receptor, PTP = protein tyrosine phosphatase. GLUT4 is a glucose transporter. For additional details, see

Simplified mechanistic pathway

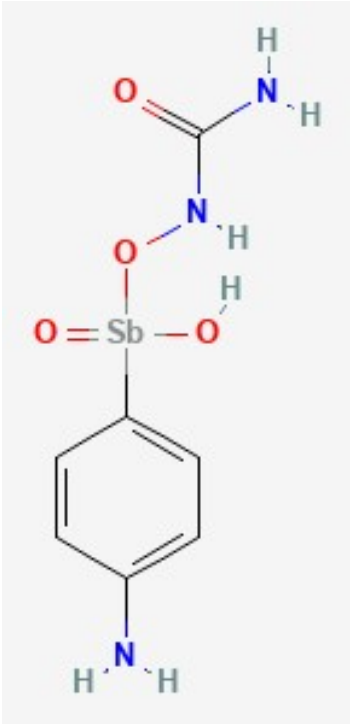
- BMOV undergoes (partial) speciation in blood serum. The speciation includes removal of the maltolato ligand, coordination of the VO^{2+}moiety to Tf, and/or oxidation to vanadate.
- Both the Tf complex and vanadate can enter the intracellular space via endocytosis and through phosphate channels, respectively.
- The insulin receptor (IR) is a trans-membrane receptor having at its disposal tyrosine residues linked to the intracellular subunits. Docking of insulin to the extracellular subunit promotes phosphorylation of the tyrosines.
- In the absence of insulin (type I diabetes) or in the case of insufficient insulin there is poor response of the receptor (common type II diabetes) -- a protein tyrosine phosphatase PTP counteracts the phosphorylation of IR-β and thus the signaling path (red arrows) responsible for the cellular uptake of glucose (mauve arrows) by the glucose transporter GLUT4.
- **This is the point where vanadate comes in:** vanadate strongly coordinates to a cysteine residue of the PTP, thus preventing dephosphorylation of the IR-β subunits and restoring the signaling path.

Antimony: Anti-Leishmania Drugs

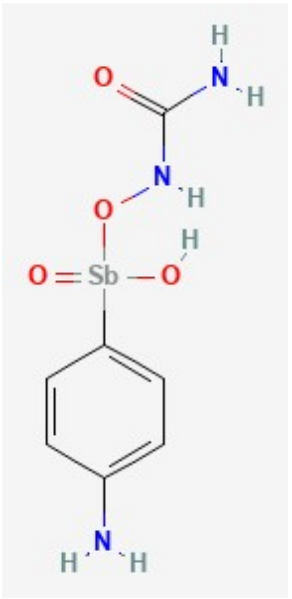


(a) (b)

Figure 23.2 Proposed structures of clinically used Sb^{V} drugs: (a) Pentosam and (b) Glucantime



Indian Anti-leishmanial drug
by
Sir Upendranath Brahmachari

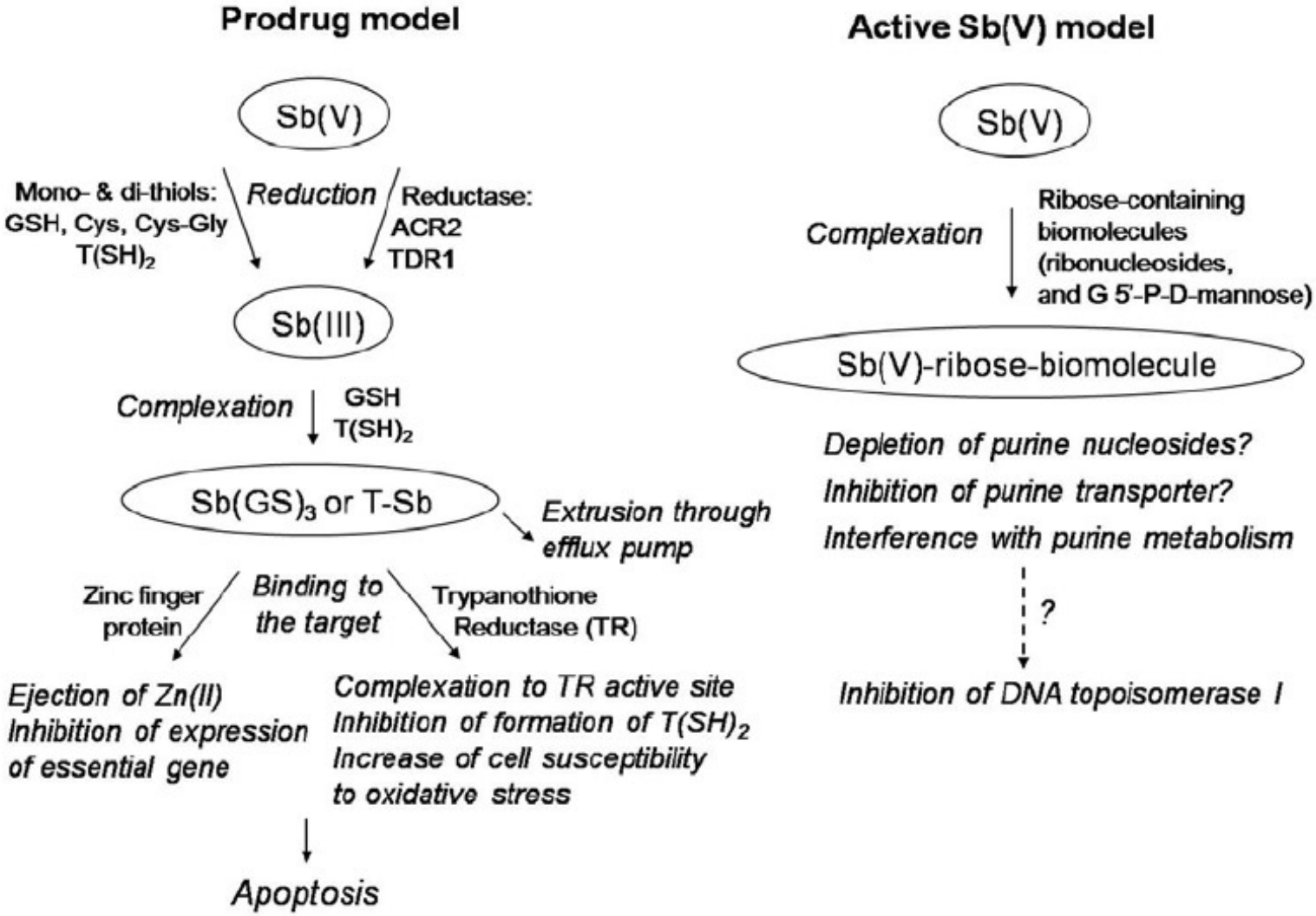


At the Campbell Hospital he was able to synthesize a new potent compound against Kala-azar named urea stibamine – the urea salt of para-amino phenyl stibnic acid in 1920. Using urea stibamine, Kala-azar mortality rate could be brought down to 10% by 1925 and it had a cure rate of 95%. This drug was used for the treatment of Kala-azar not only in India but also in Greece, France, and China for many years.

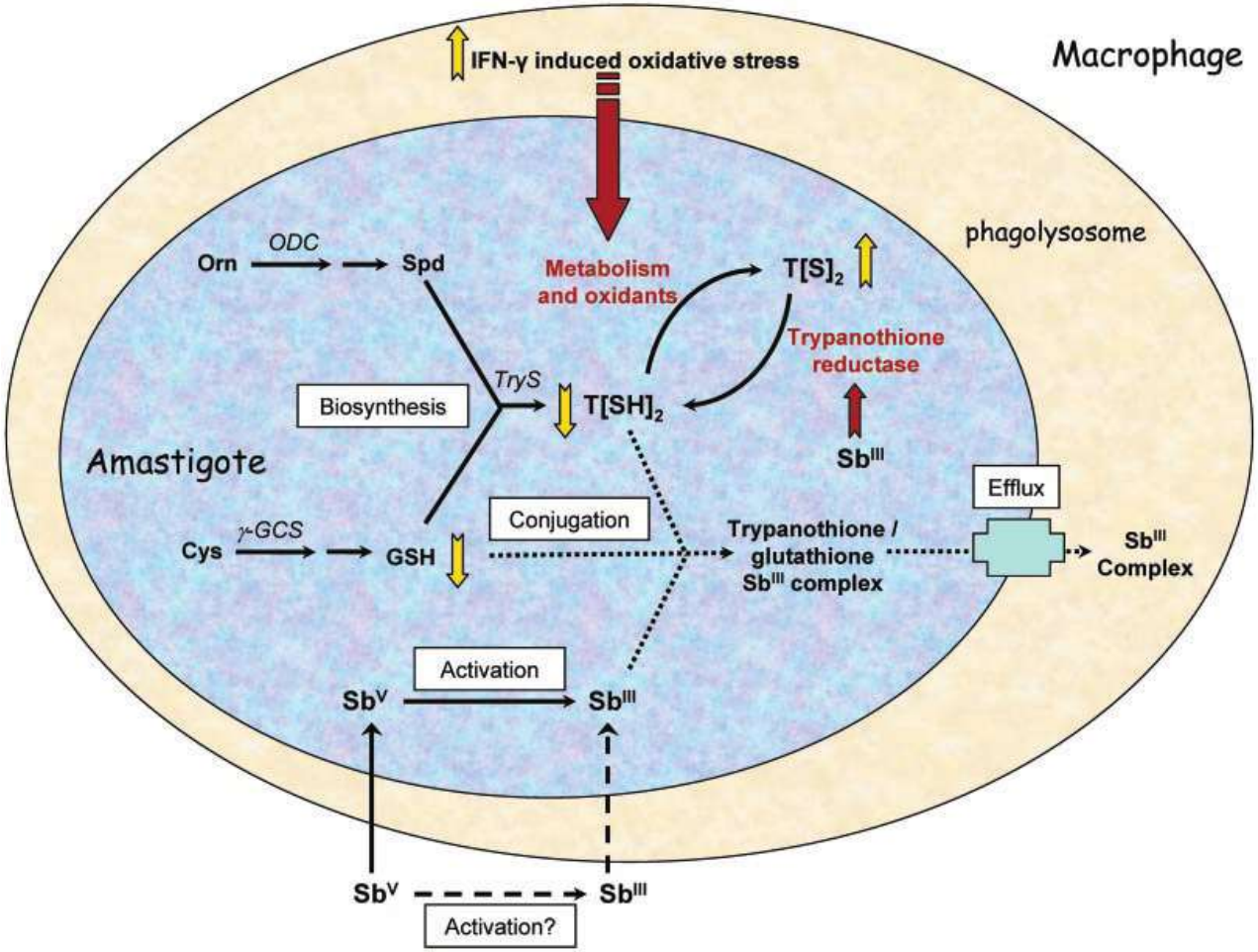
Dr. Brahmachari was nominated for the Nobel Prize in Medicine in 1929 and 1942. Unfortunately, he did not receive the Nobel Prize.

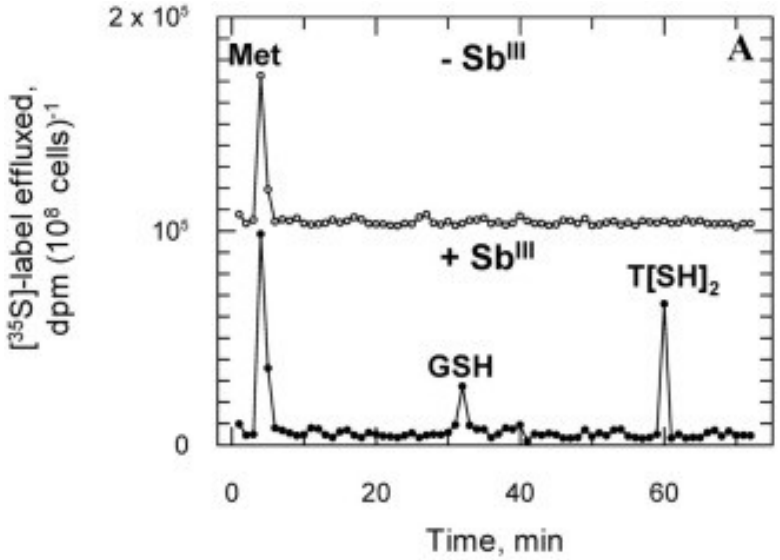
He also established India's first blood bank at the Calcutta School of Tropical Medicine in 1935.

Anti-Leishmania Drugs



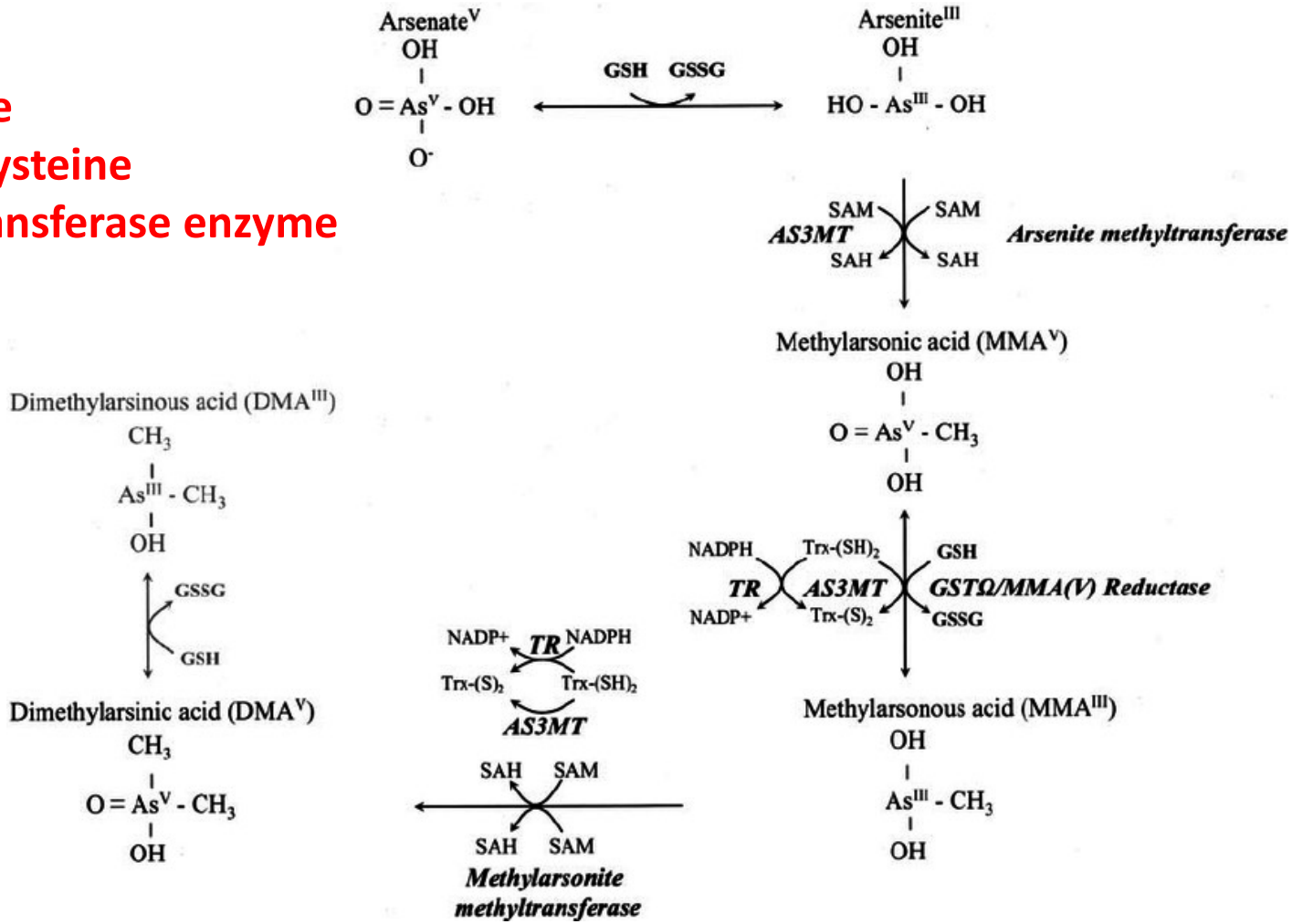
Anti-Leishmania Drugs





Fate of Trisenox® (Arsenic pentaoxide): metabolism

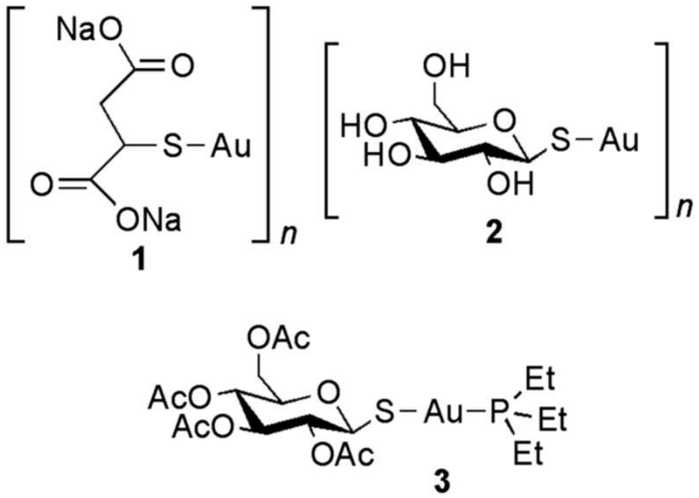
SAM: S-Adenosylmethione
SAH: S-adenosyl-L-homocysteine
AS3MT : arsenic methyltransferase enzyme



American Journal of Clinical Nutrition 2006, 4(5):1093-101

Gold in Rheumatoid arthritis/Tuberculosis and cancer

- Gold in medicine as far back as 2500 BC in china
- Modern interest: Discovery in 1890 by Robert Koch, that gold cyanide inhibits the growth of of Tubercle bacillus
- "Gold decade'' (1925–1935) followed: intravenous Au(I) thiolate salts to treat tuberculosis → lack of experimental evidence for any anti-tubercular benefits
- Gold therapy was found to significantly reduce joint pain → French physician Jacques Forestier investigated the use of gold compounds for treatment of rheumatoid arthritis (1960) → double-bind trial concluded that gold drugs have a beneficial effect
- Some gold(I) thiolate drugs (Scheme 1), first introduced in the 1920s, are still in clinic

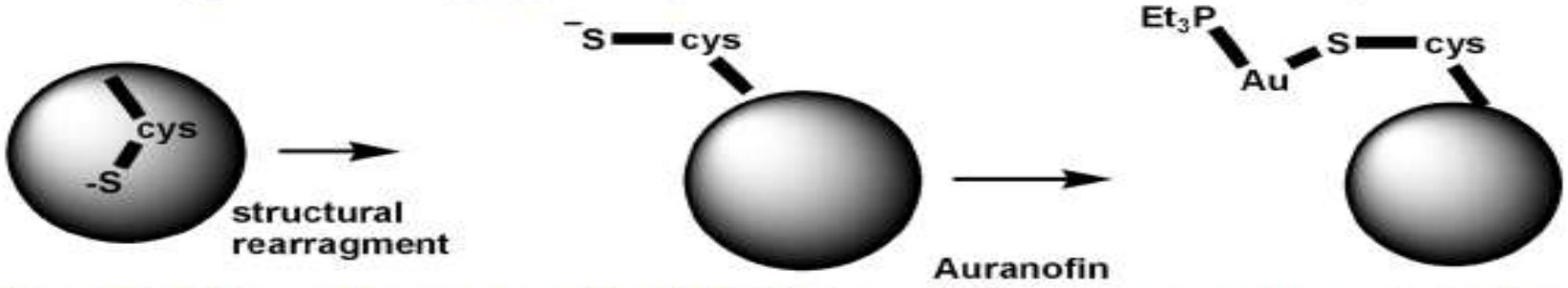


Scheme 1 Examples of gold(I) drugs used for the treatment of rheumatoid arthritis (**1**) sodium aurothiomalate (Myocrisin), (**2**) aurothioglucose (Solganol), (**3**) tetraacetyl-β-D-thioglucose gold(I) triethylphosphine (auranofin). The 1 : 1 Au–S drugs (**1** and **2**) are polymers.

AU(I) Thiolates: Disease-modifying antirheumatic drugs (DMARDs), slow the progression of the disease.

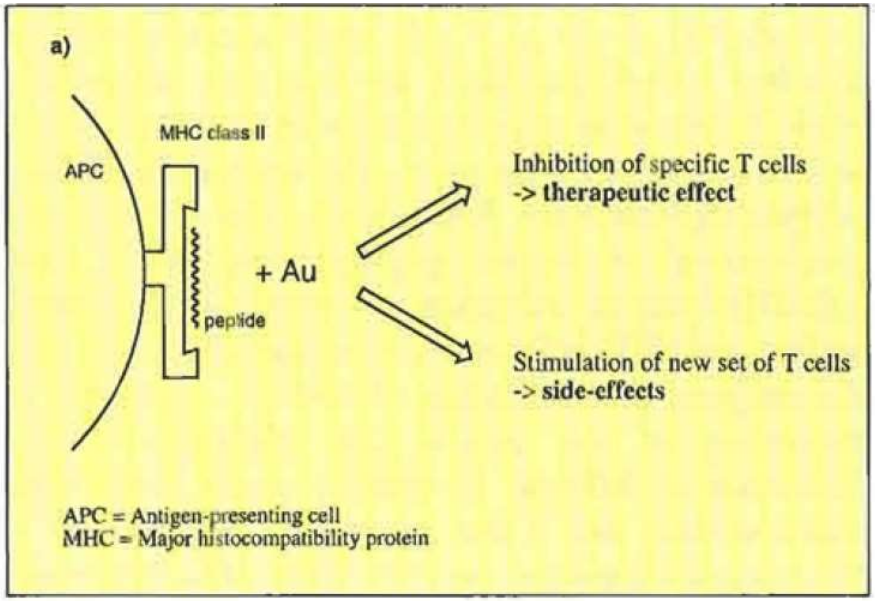
Rheumatoid Arthritis: Chrysotherapy

- Crysotherapy is the use of gold compounds in medicine
  - Gold compounds are particularly effective in the treatment of Rheumatoid Arthritis
  - Injected (i.e – water soluble) drugs are more active than Oral drugs (auranofin)
  - Gold drugs show anti-inflammatory effects and inhibition of tissue degradation
  - Mechanism of action is uncertain, the compounds used are pro-drugs undergoing ligand-exchange with serum proteins
  - Trialkyl phosphine is more strongly bound to Au(I) than thiolate
  - Drugs can transfer Au^+ to cysteine-S^- in serum albumin after a structural rearrangement bringing the cysteine-S^- to the surface of the protein



$[Au(CN)_2]^{2-}$ can form from Au(I) thiolates which are common metabolites

Gold in Rheumatoid arthritis:



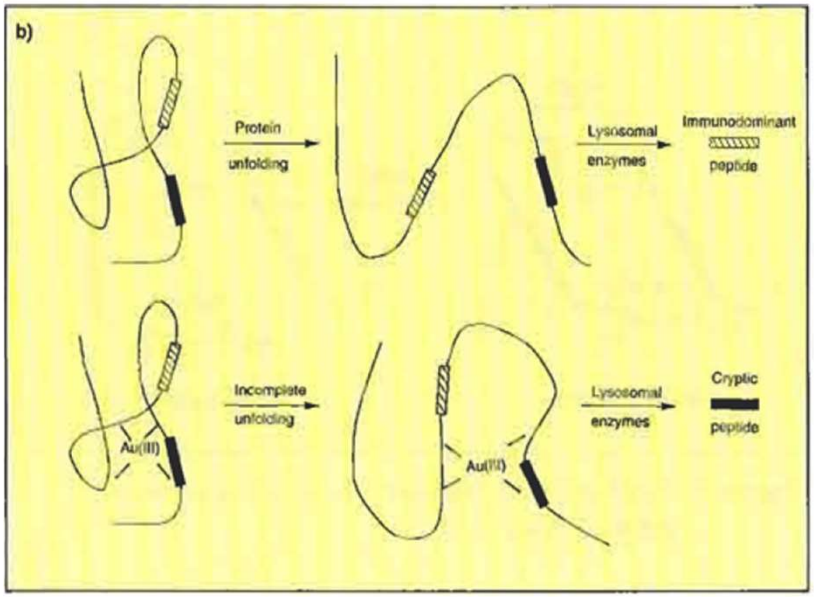


Figure 2a Proposed *MHC class II - peptide - gold - T cell*

Altering Peptide Presentation (MHC Class II): Au(I) compounds like **auranofin** and **sodium aurothiomalate** can bind directly to MHC class II proteins on antigen-presenting cells (APCs). This binding can strip peptides from the MHC binding pocket or prevent their proper loading, essentially blocking the formation of a functional MHC-peptide complex that can be recognized by T helper (CD4+) cells. This mechanism helps explain the therapeutic anti-inflammatory effects of gold in autoimmune diseases by suppressing the T cell-mediated immune response.

Gold(I) Compounds
(e.g., Auranofin, Gold Sodium Thiomalate)

↓

Interaction with Cellular Thiol Groups (Cys Residues)
Inhibition of Thioredoxin Reductase (TrxR)
Disruption of Redox Homeostasis |

↓

Oxidative Stress and ER Stress
Misfolding of MHC Class I/II Molecules
Impaired Peptide Loading in ER

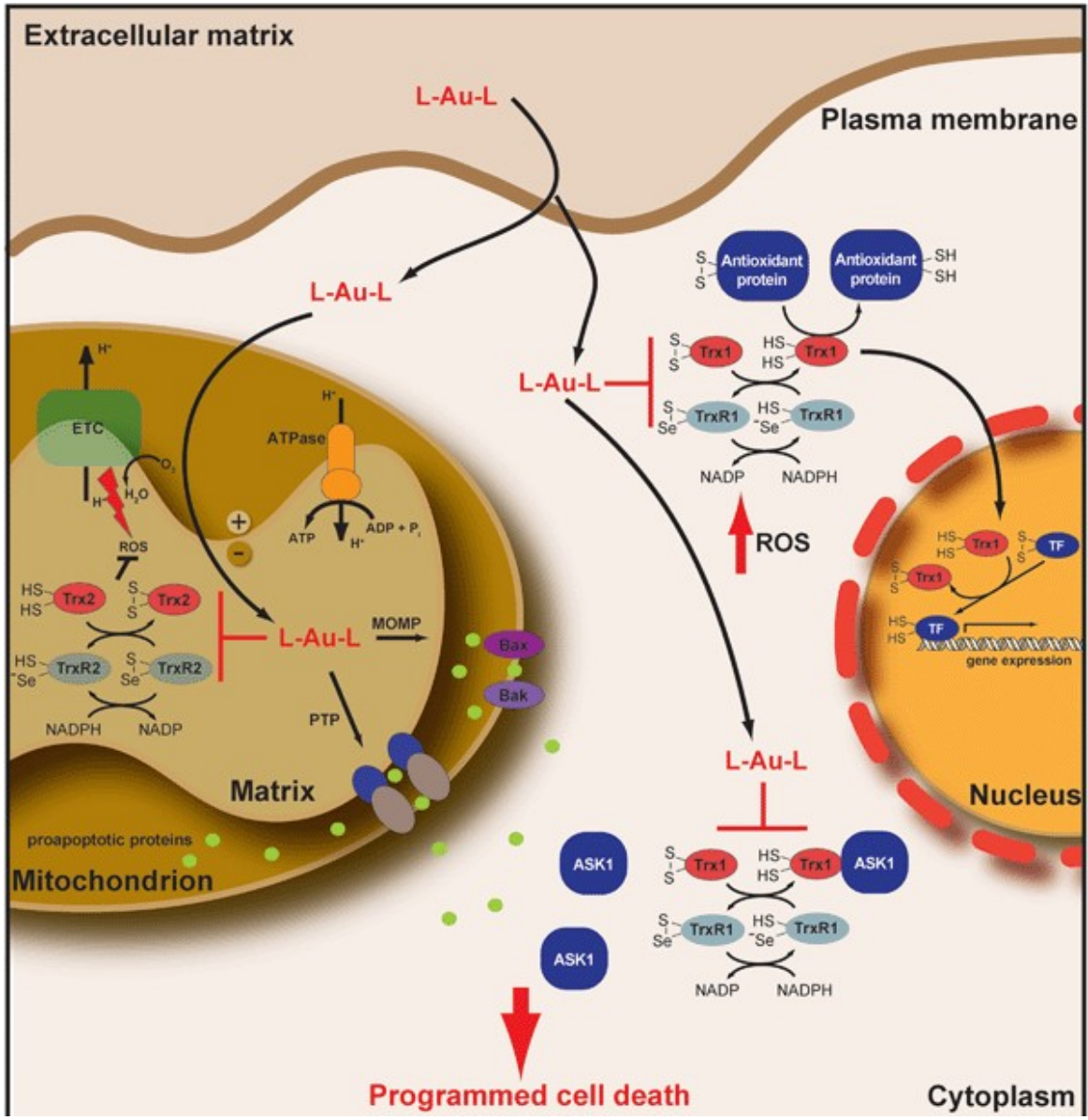
↓

Inhibition of Antigen Processing Pathway
Reduced TAP Transporter Activity
Decreased Peptide-MHC Complex Formation

↓

Impaired MHC Surface Expression
Reduced Antigen Presentation to T Cells
Suppressed Immune Activation

MHC = Major Histocompatibility complex
Trx = thioredoxin protein
PTP = Protein tyrosine phosphatase



Au(I) compounds Mechanism of action → for reading

1.Gold(I) Compound Entry

Gold(I) complexes such as auranofin enter immune cells and bind to cysteine-rich proteins due to their high affinity for thiol groups.

2.Inhibition of Thioredoxin Reductase (TrxR)

Gold(I) compounds irreversibly inhibit TrxR, a key enzyme maintaining cellular redox balance. This leads to accumulation of reactive oxygen species (ROS).

3.Endoplasmic Reticulum (ER) Stress

Elevated ROS levels cause ER stress, impairing the folding and assembly of MHC class I and II molecules.

4.Disruption of Antigen Processing

Gold(I) compounds interfere with the transporter associated with antigen processing (TAP) and peptide loading complex, reducing the supply of peptides to MHC molecules.

5.Reduced MHC Expression and Immune Response

The combined effects lead to decreased MHC surface expression, limiting antigen presentation to T cells and dampening immune activation.