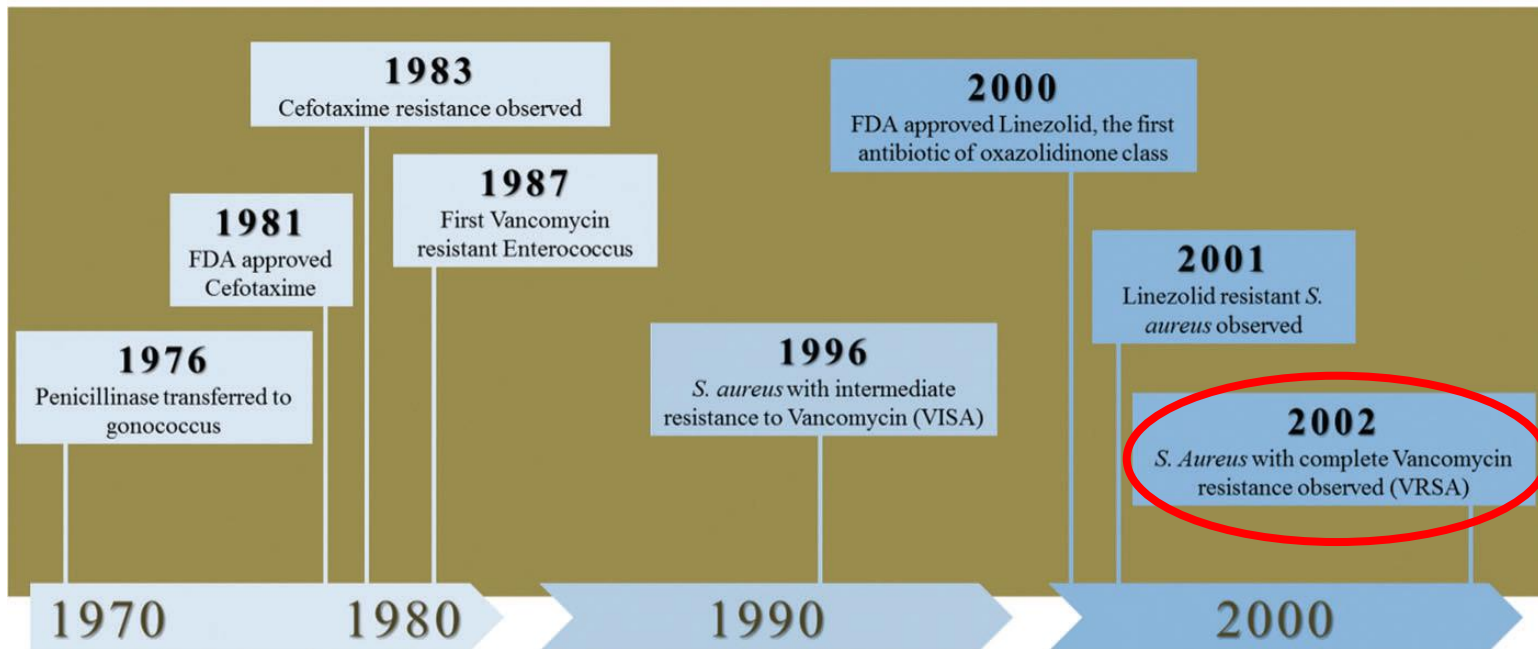
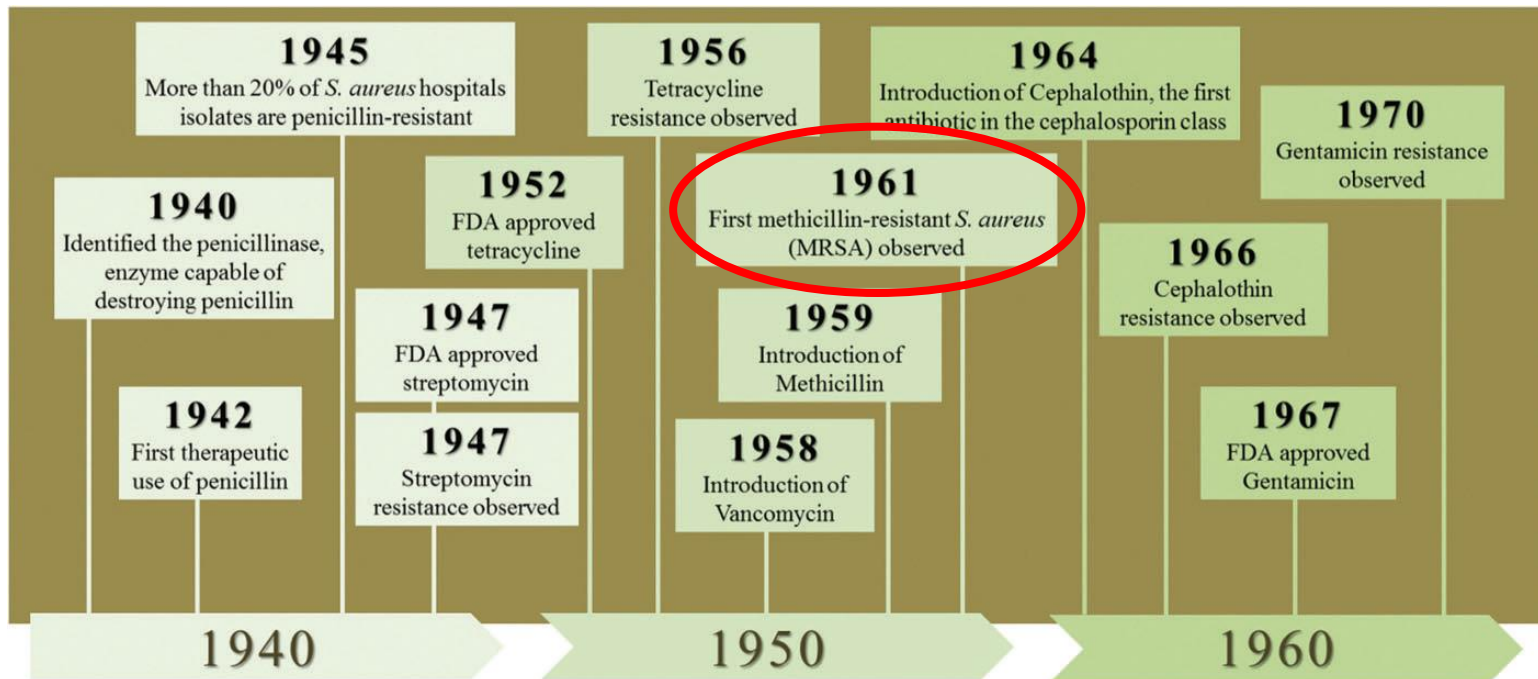
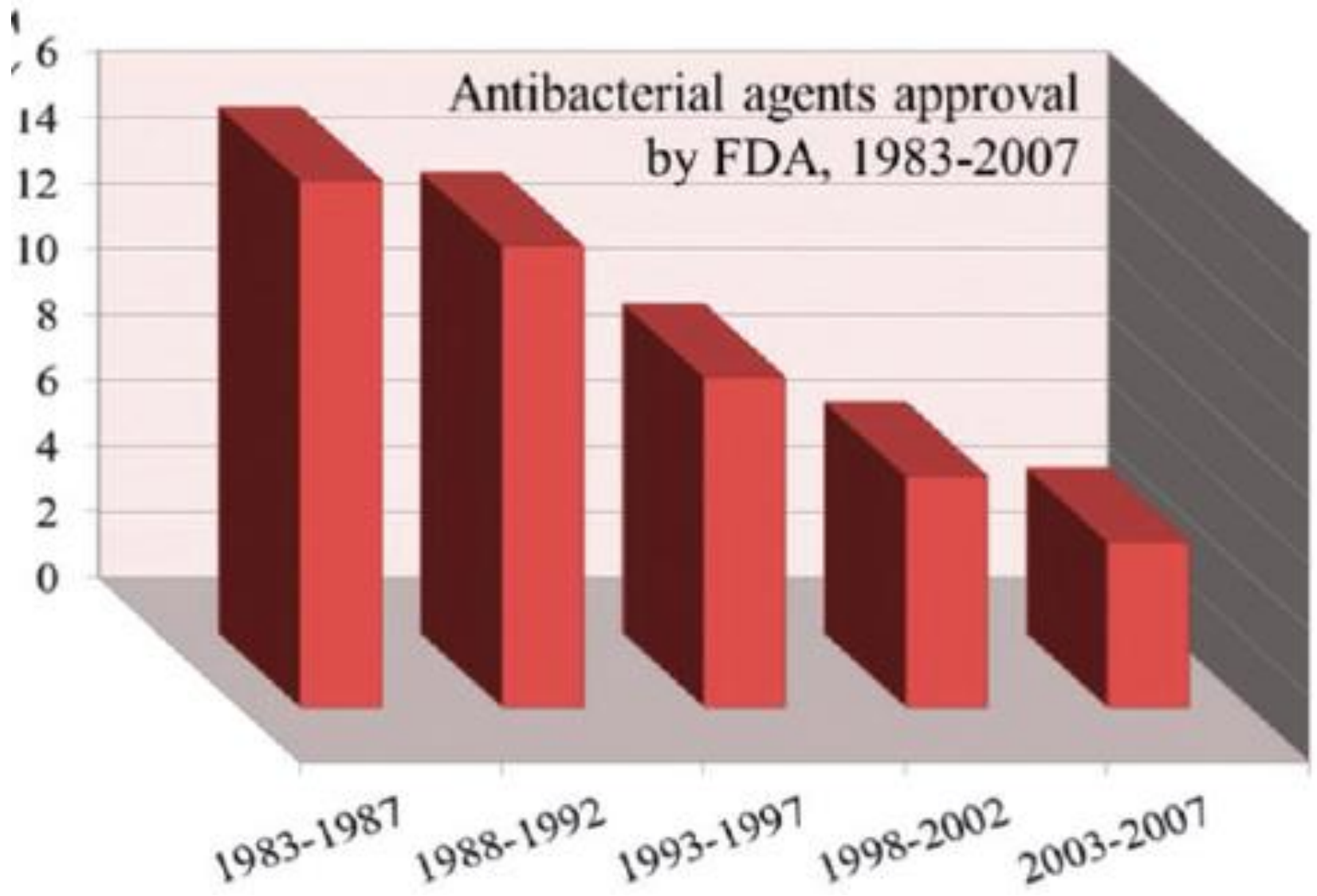


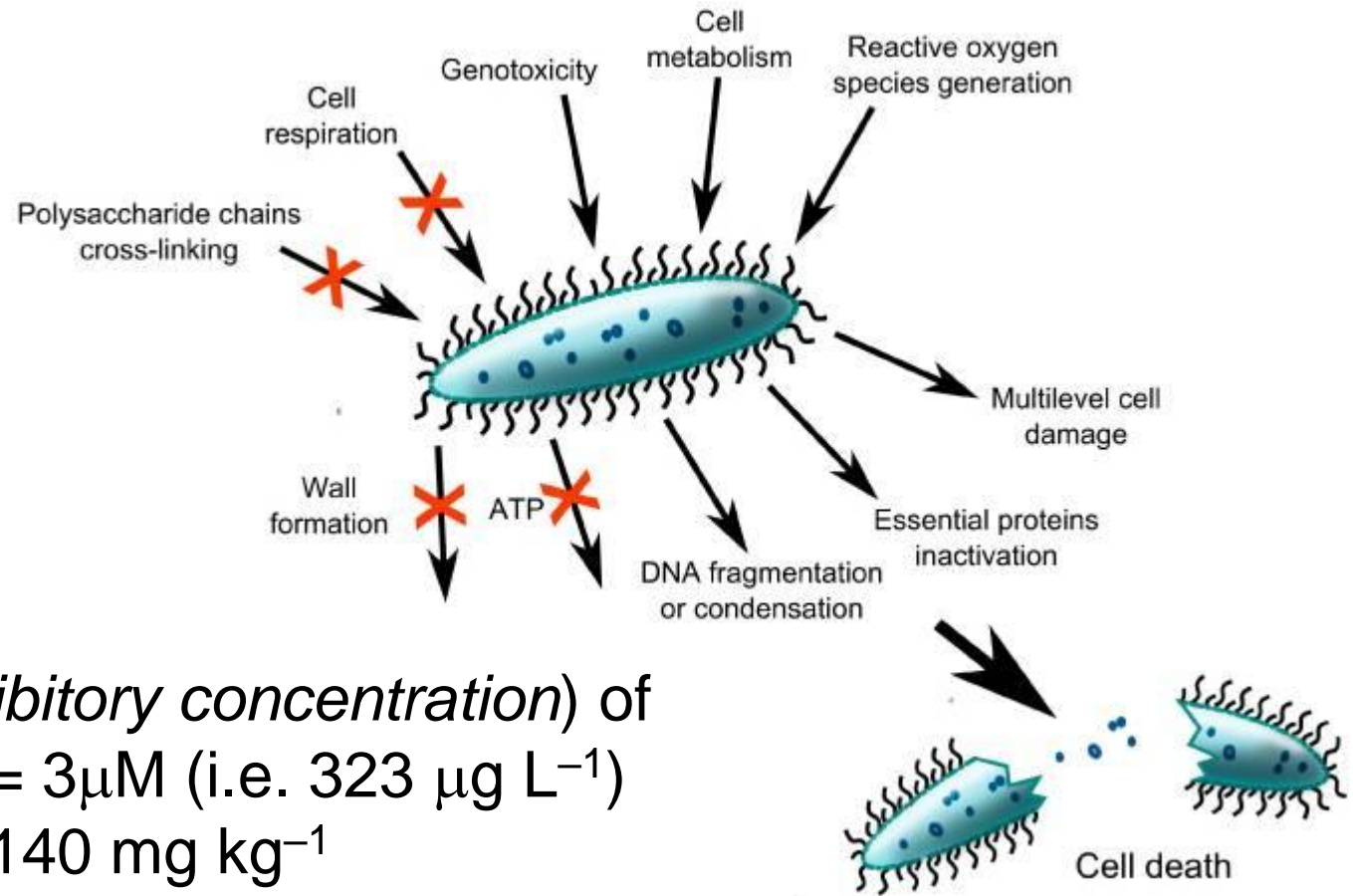


**Antibacterials**

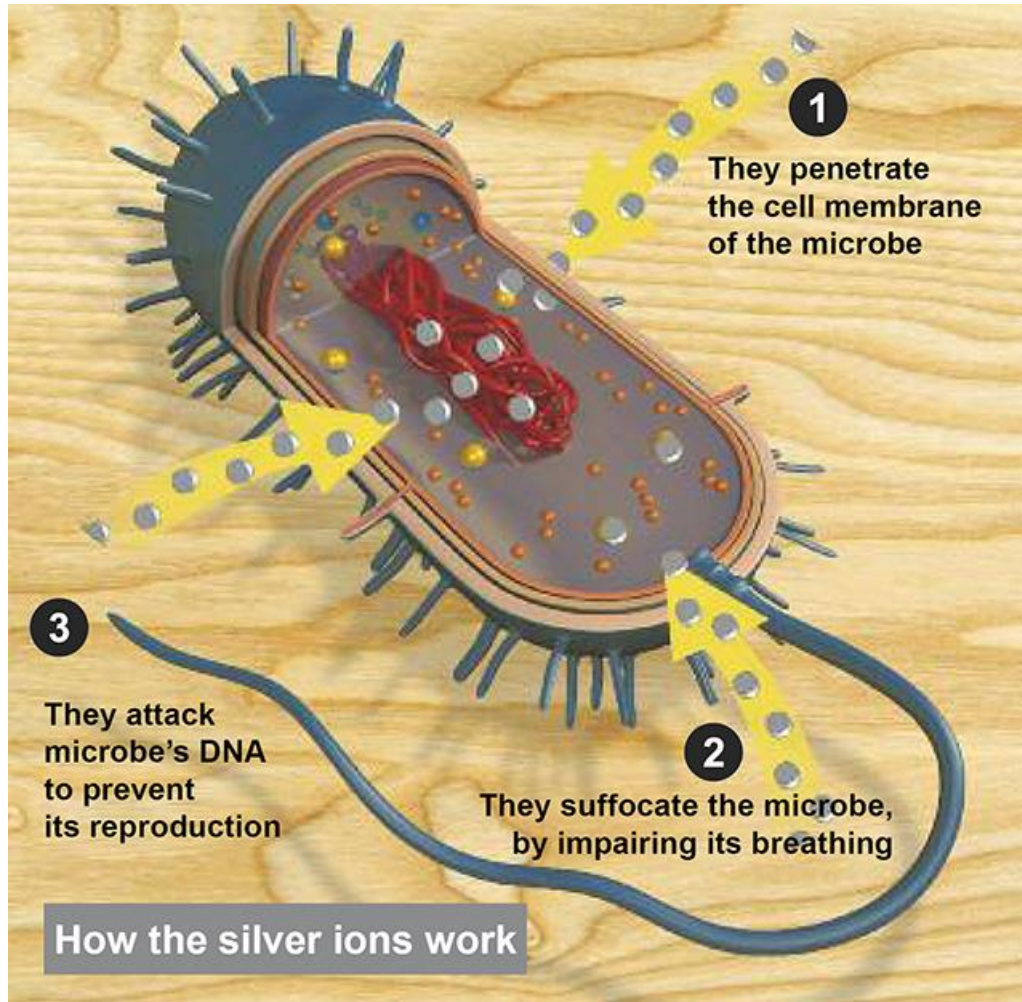




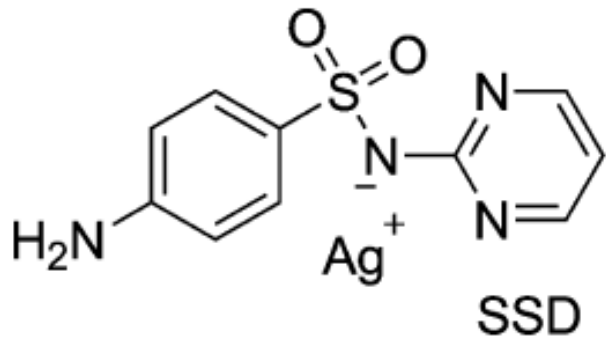
# Multiple mechanism of action of Ag<sup>+</sup> ions



**MIC** (*minimal inhibitory concentration*) of AgNO<sub>3</sub> to *E. coli* = 3 μM (i.e. 323 μg L<sup>-1</sup>)  
LD<sub>50</sub> in humans: 140 mg kg<sup>-1</sup>



# Silver salts



silver sulfadiazine



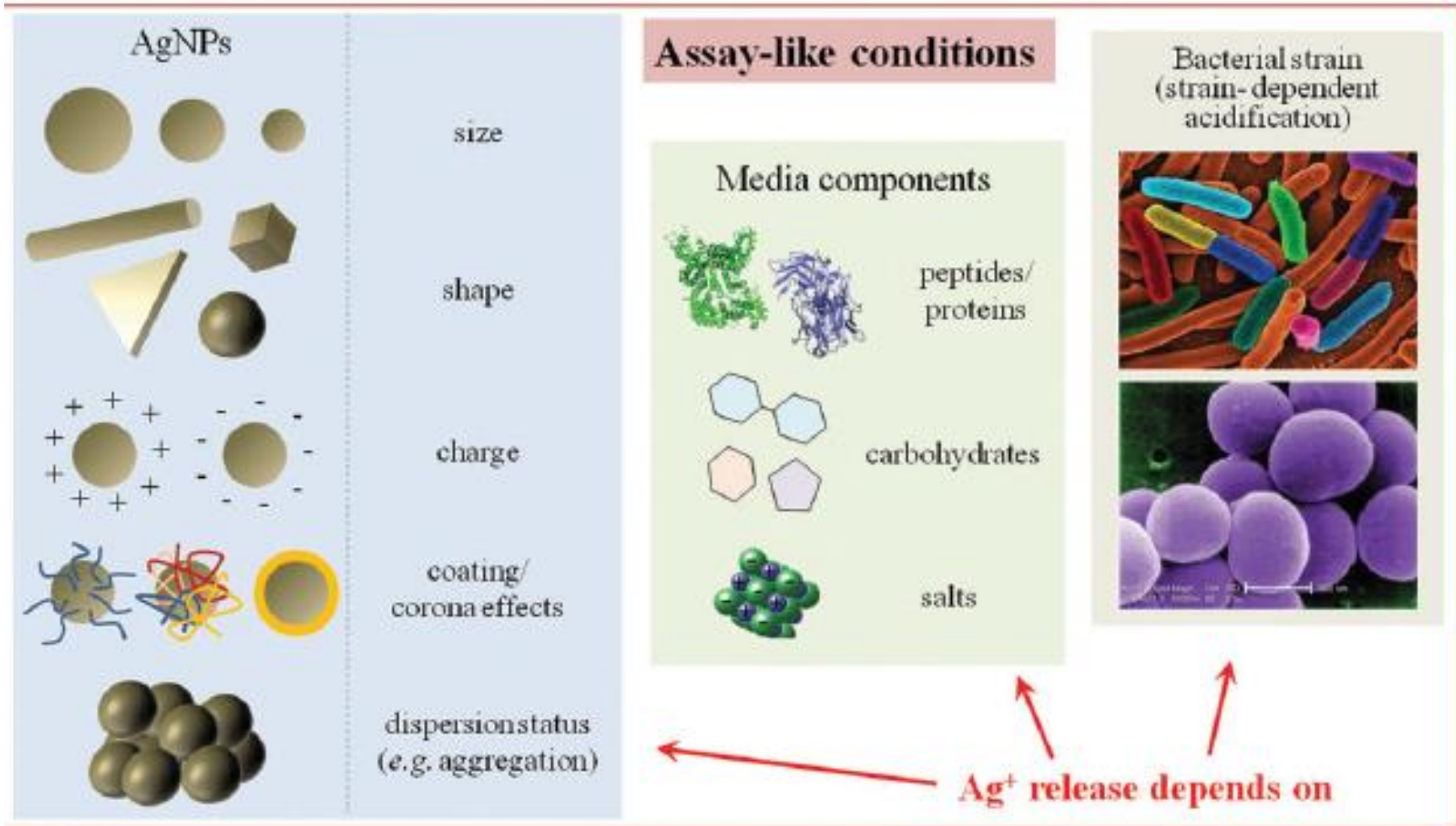


# Silver nanoparticles (AgNPs)



Estimated 2014 production of commercial AgNPs: 320 t

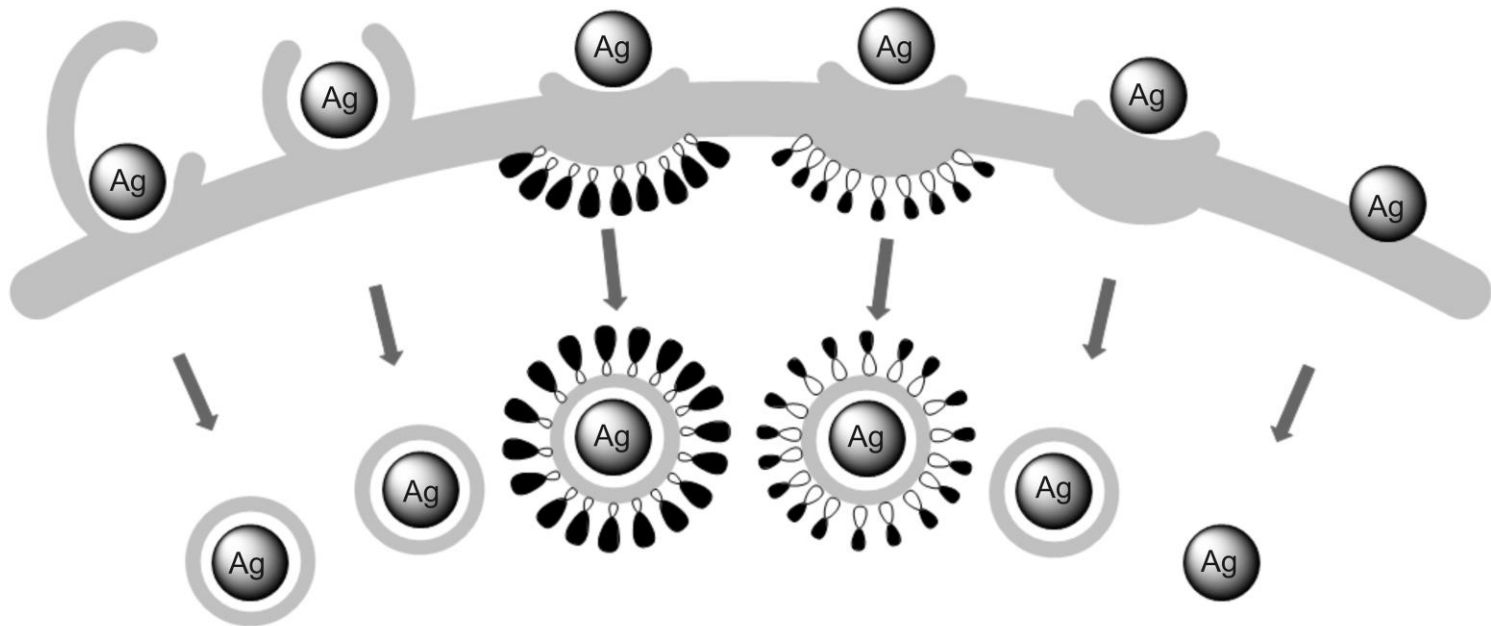
# Ag<sup>+</sup> release from AgNPs





# Uptake of AgNPs

- a) Macropinocytosis
- b) Phagocytosis
- c) Clathrin-mediated Endocytosis
- d) Caveolin-mediated Endocytosis
- e) Clathrin-independent and Caveolin-independent Endocytosis
- f) Diffusion



Legend:



AgNP

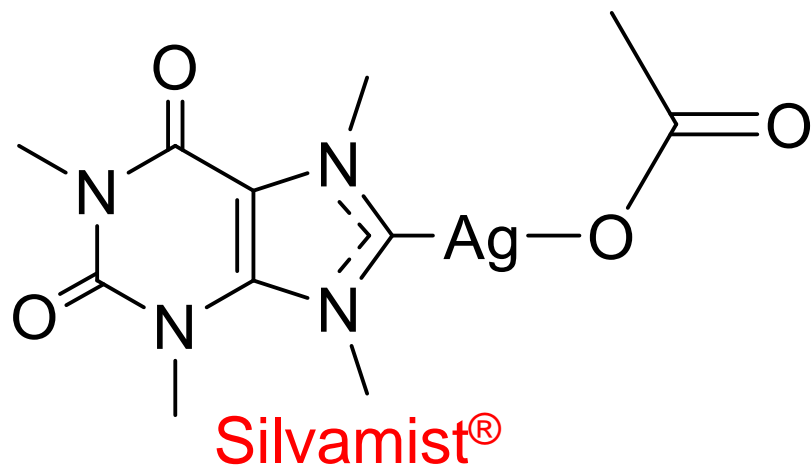


Clathrin

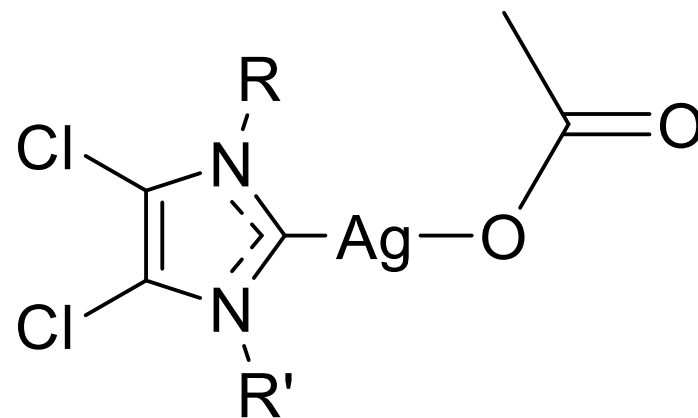


Caveolin

## Antibacterial Ag-NHC compounds

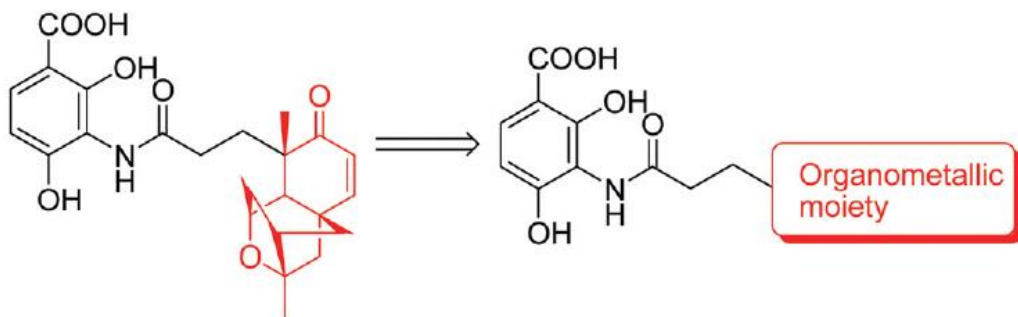


Drug candidate: high activity against tobramycin-resistant pathogenic bacteria *in vitro* as well as *in vivo*.

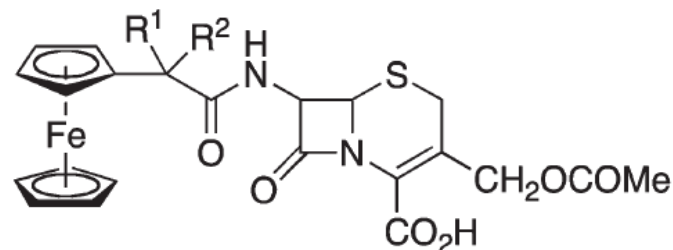
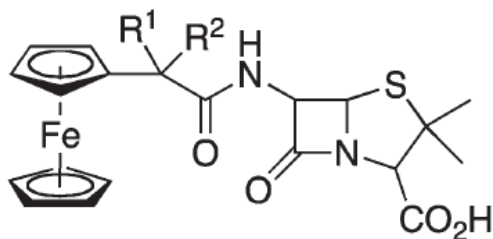
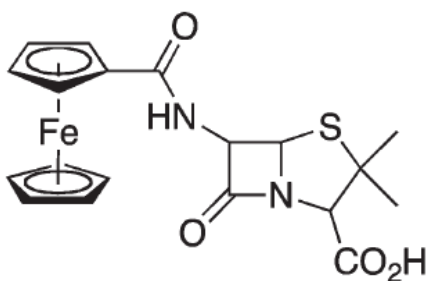


Improved stability to hydrolysis due to the electron-withdrawing Cl substituents that pull electron density from the carbene

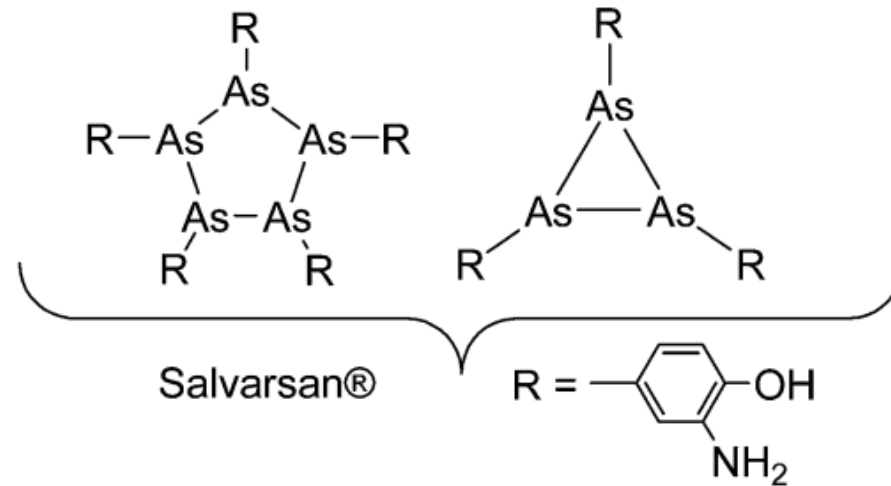
# Other strategies: metal modification of known antibiotics



Platensimycin mimics



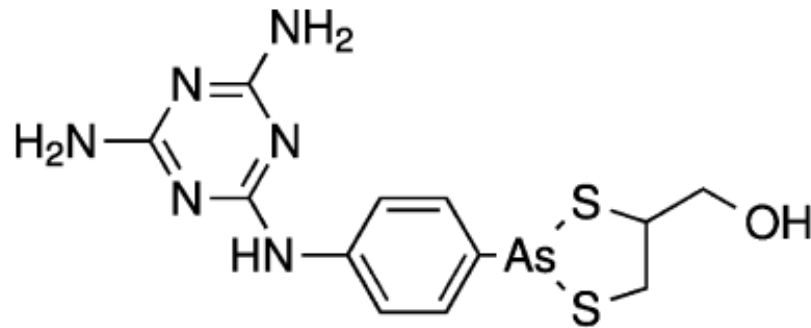
Other metals: As, Sb, Bi, Hg



Antimicrobial agent introduced in early 1900 for the treatment of the deadly bacterial infection *Syphilis*. Later replaced by modern antibiotics



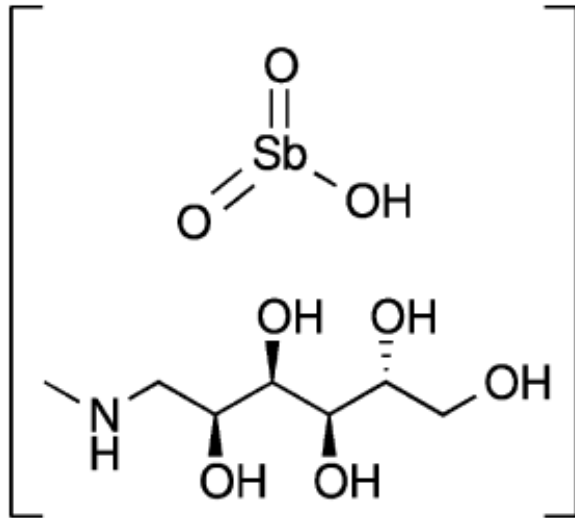
# Antiparasitic compounds



**melarsoprol**

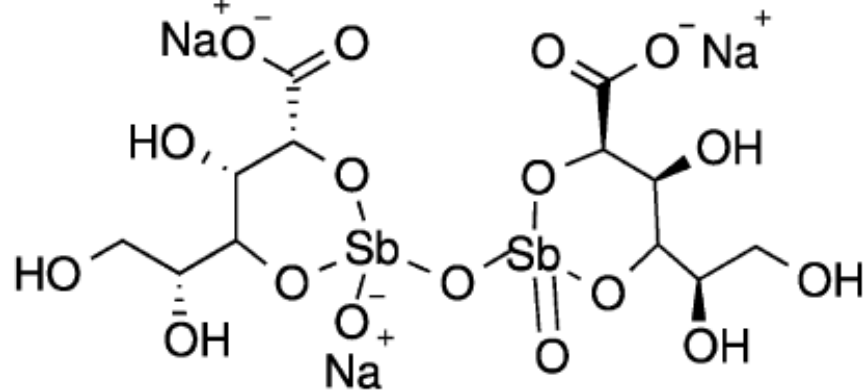
treatment of sleeping sickness (*African trypanosomiasis*)

# Anti-leishmaniasis compounds



**meglumine antimoniate**

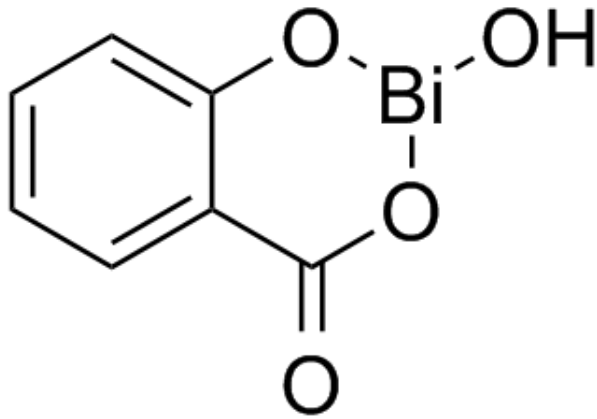
*Veterinary use*



**sodium stibogluconate**

Sb, reduced to Sb(III), inhibits *trypanothione reductase*, an essential enzyme of the parasite

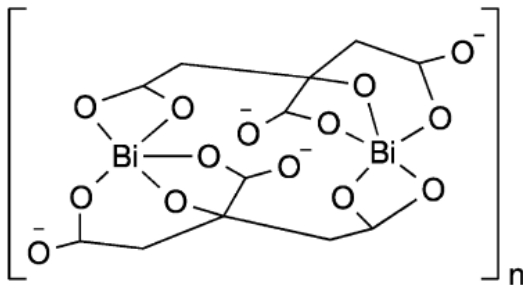
# Infezioni da *Helicobacter pylori*



bismuth subsalicylate

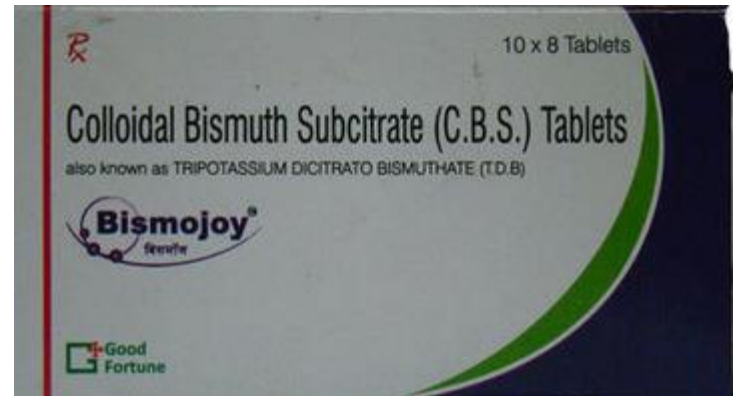


*The pink stuff* (introduced 1901)

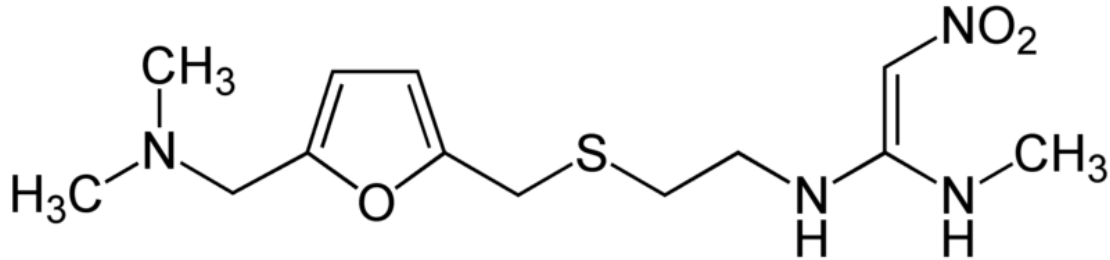


CBS

bismuto subcitrato colloidale



# Infezioni da *Helicobacter pylori*



ranitidine bismuth citrate



# Bismuth-ethanedithiol (BisEDT)

UNIVERSITY OF PENNSYLVANIA

# Almanac

Tuesday

November 13, 2012

Volume 59 Number 12

[www.upenn.edu/almanac](http://www.upenn.edu/almanac)

## \$2.5 Million Grant for Penn Researchers to Investigate Anti-Infection Drug

A team of researchers led by Dr. Samir Mehta, chief of the Orthopaedic Trauma & Fracture Service at the Perelman School of Medicine at the University of Pennsylvania, has received a \$2.5 million grant from the Congressionally Directed Medical Research Program (CDMRP), provided through the US Department of Defense (DoD), to begin Phase 2 human trials of a study that examines the effective treatment of post-surgical orthopedic infections using Microbion Corporation's topical BisEDT drug. The University of Pennsylvania will work with a team of researchers from Microbion and the University of California, San Francisco, on the trial, set to begin pending FDA approval.

"We're honored to be given this award from



Samir Mehta

forms of surgery (2.8 percent) as a result of the high-energy nature of the injury. With approximately 2.6 million orthopaedic devices implanted annually in the United States, approximately 4.3 percent of patients (112,000) will suffer from a post-operative infection.

Orthopaedic extremity injuries also constitute the majority

## Debate at Penn: Have We Lost the Spirit of Compromise in America?

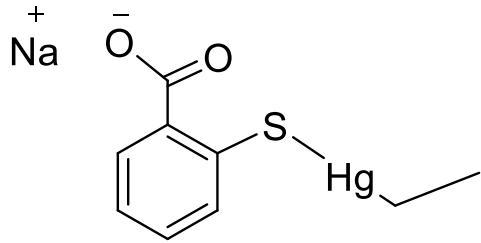
Will a hard-fought US election, replete with record spending and ever more divisive rhetoric, really change anything in Washington?

A panel including University of Pennsylvania President Amy Gutmann and moderated by Michael X. Delli Carpini, dean of Penn's Annenberg School for Communication, will debate these questions and more today at Penn. The event is sponsored by Penn's Annenberg School for Communication, the department of political science and the philosophy, politics & economics program.

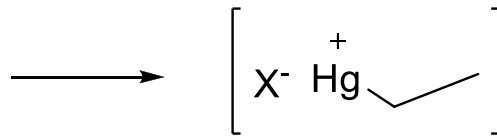
Panelists participating in *Time to Deal: Re-awakening the Spirit of Compromise in American Politics* will address how we can best avoid



# Antibacterial mercury compounds



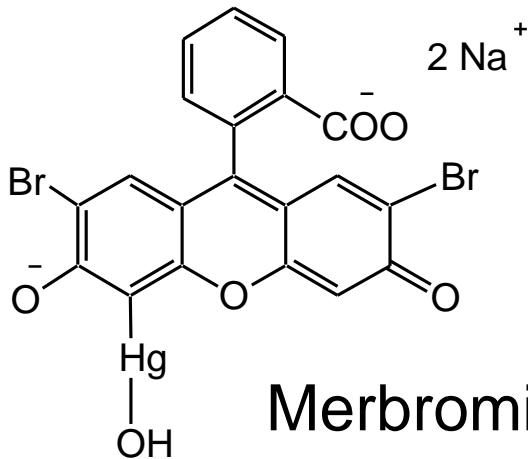
Thiomersal



ethyl mercury

*vaccine adjuvant*

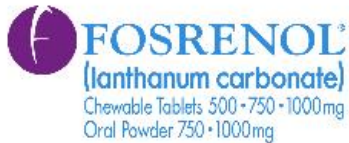
non-organometallics  
e.g. HgS



Merbromin (mercurochrome)



# Fosrenol™: a success story



FOSRENOL  
Chewable Tablets

FOSRENOL  
Oral Powder

Phosphorus  
Burden in ESRD

Patient  
Support

Conferences  
and Resources

To reduce serum phosphate in patients with  
end-stage renal disease (ESRD)

**HELP IT FALL  
WITH FOSRENOL\***  
(lanthanum carbonate)

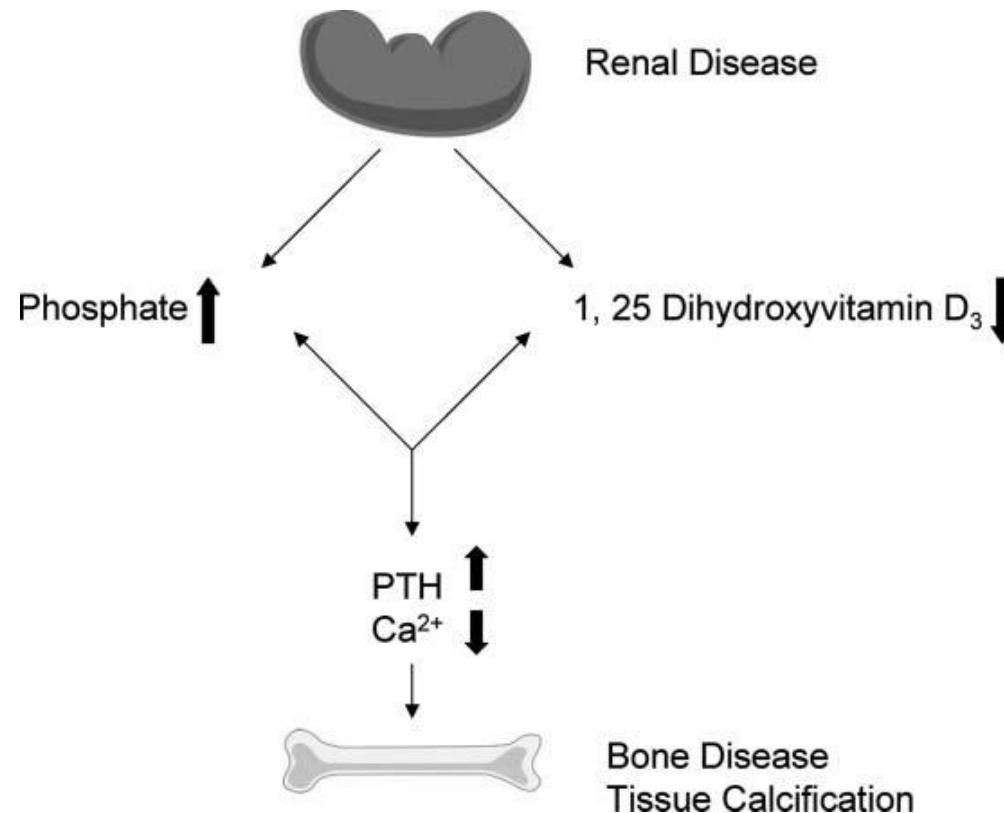
\*Phosphorus reductions maintained for up to 3 years in patients  
remaining on therapy (n=46)<sup>1-3</sup>

- **FOSRENOL Chewable Tablets:** Approved in 2004 and used in US clinical practices for more than a decade<sup>4,5</sup> [LEARN MORE](#) ▶
- **FOSRENOL Oral Powder:** Available since May 2015, offering you another approved administration option<sup>5</sup> [LEARN MORE](#) ▶



Approved by FDA in 2004 for the treatment of hyperphosphatemia (increased phosphate levels in serum) in patients with end stage renal disease.

Phosphate metabolism is intimately linked with calcium metabolism, and is regulated by parathyroid hormone (PTH) and vitamin D



Pathological consequences of hyperphosphatemia: cardiac and vascular tissue calcification, bone malformations in the joints

The **ideal phosphate binder** should:

- have a high affinity for phosphate and
- be able to bind dietary phosphate rapidly in the guts
- have low solubility and
- little or no systemic absorption.
- be non-toxic,
- be available as a palatable oral dosage form, with a low pill burden.

*Calcium phosphate binders are effective....however, calcium can be absorbed, resulting in hypercalcemia and increased risk of cardiovascular calcification.*

# Fosrenol™: a success story

Among the many lanthanide salts screened,  $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$  possessed the best phosphate binding properties:

- Optimal binding at pH 3–5, but retains binding activity in the full pH range of 1–7
- It is very insoluble and the  $\text{La}^{3+}$  cation does not cross biological membranes (when given by the oral route, >90% excreted in the feces, and <0.001% absorbed)
- No toxicity observed in animal studies, in particular no direct effects on calcium, vitamin D, or PTH metabolism



*Fosrenol™ represents a significant improvement in treatment options for patients with end-stage renal disease.*

- in the acidic environment of the stomach lanthanum carbonate dissociates sufficiently to allow formation of a highly insoluble phosphate.
- It has the required pharmacokinetic properties, it is poorly absorbed, with both the parent molecule and the phosphate product being eliminated in the feces.
- Because of the lack of absorption it has no systemic toxicity, it has no detrimental effect on calcium, vitamin D or PTH metabolism, and is safe and well tolerated.
- Its effectiveness as a phosphate binder results in a lower pill burden for patients, an advantage over competing medications.