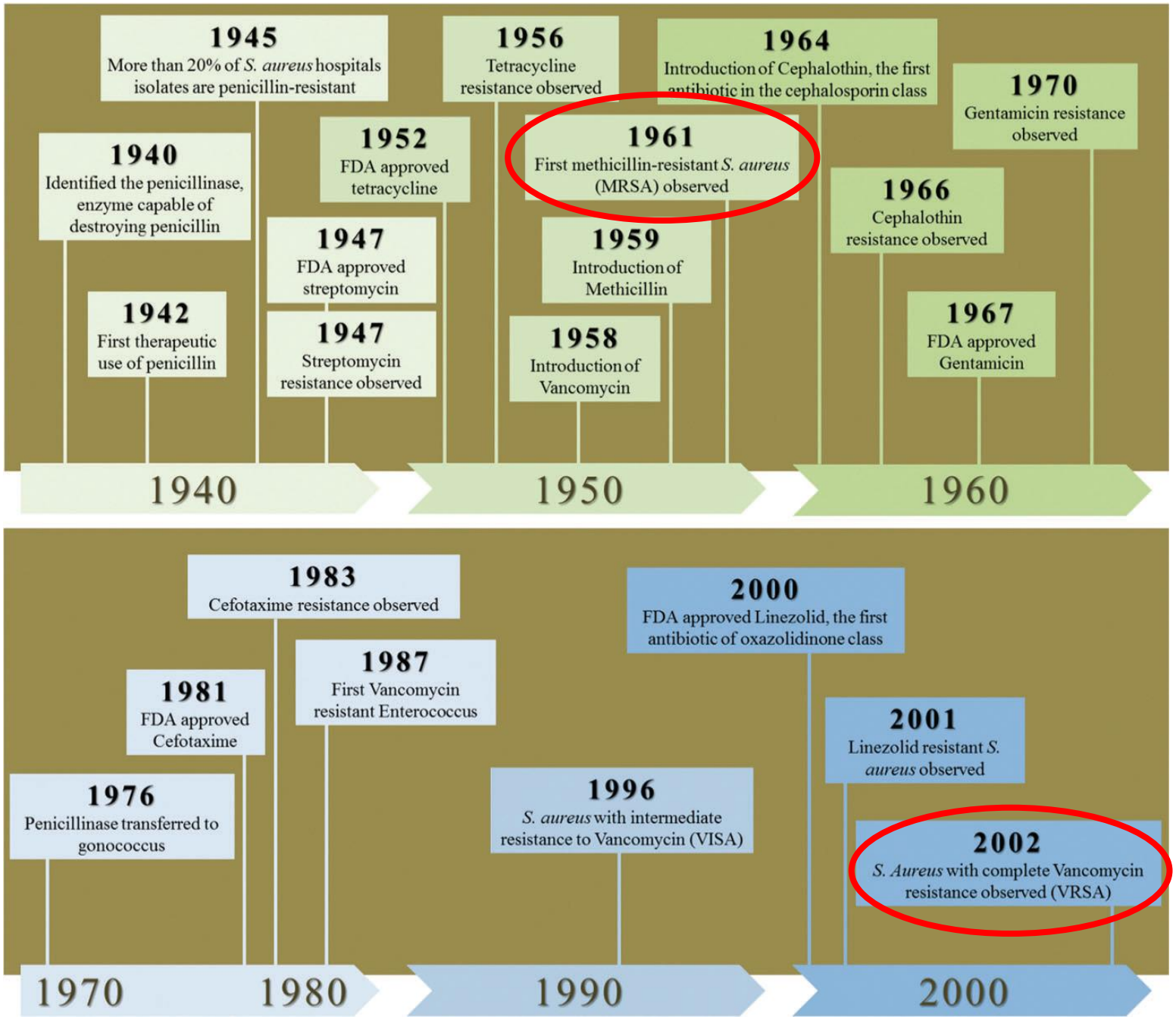
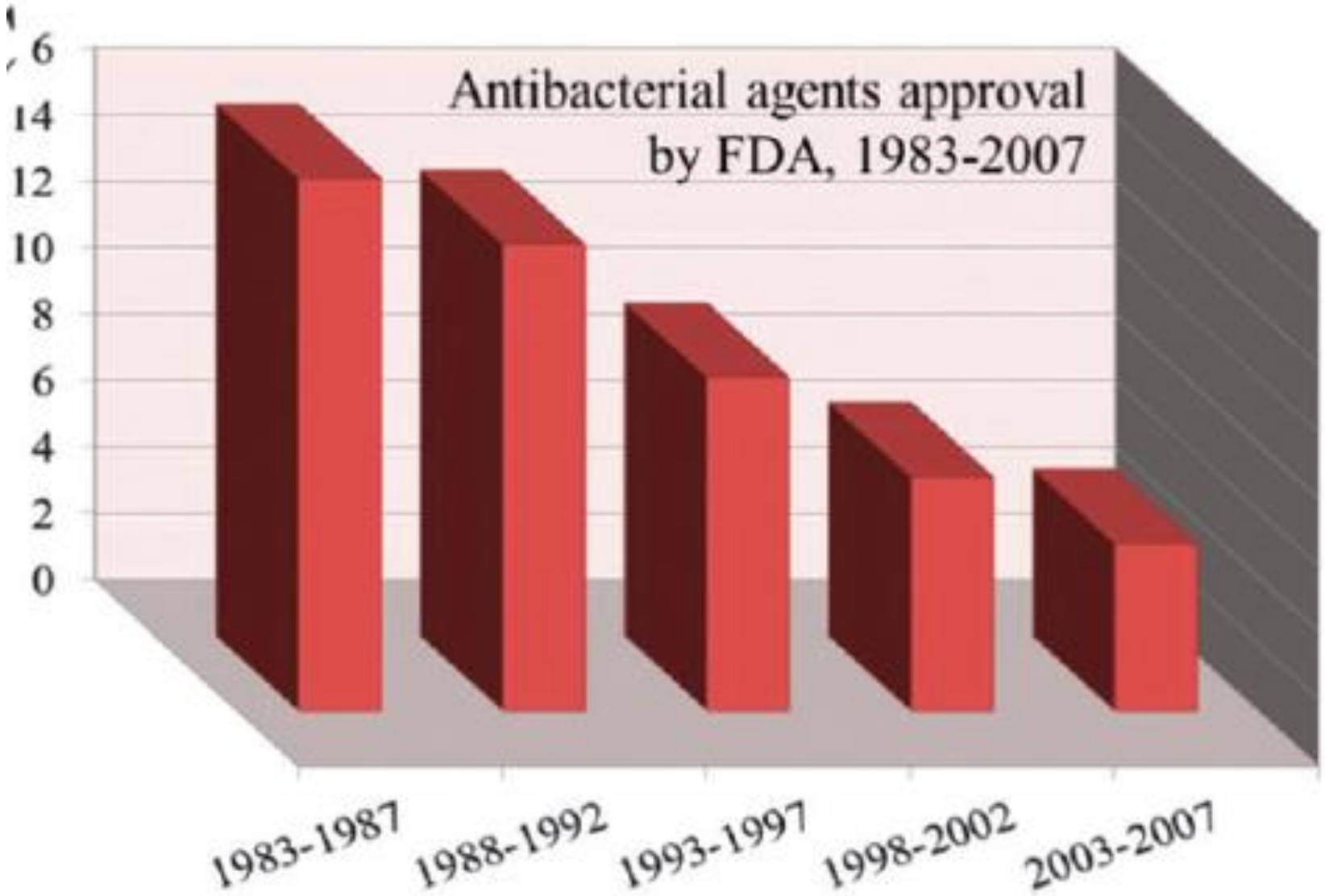
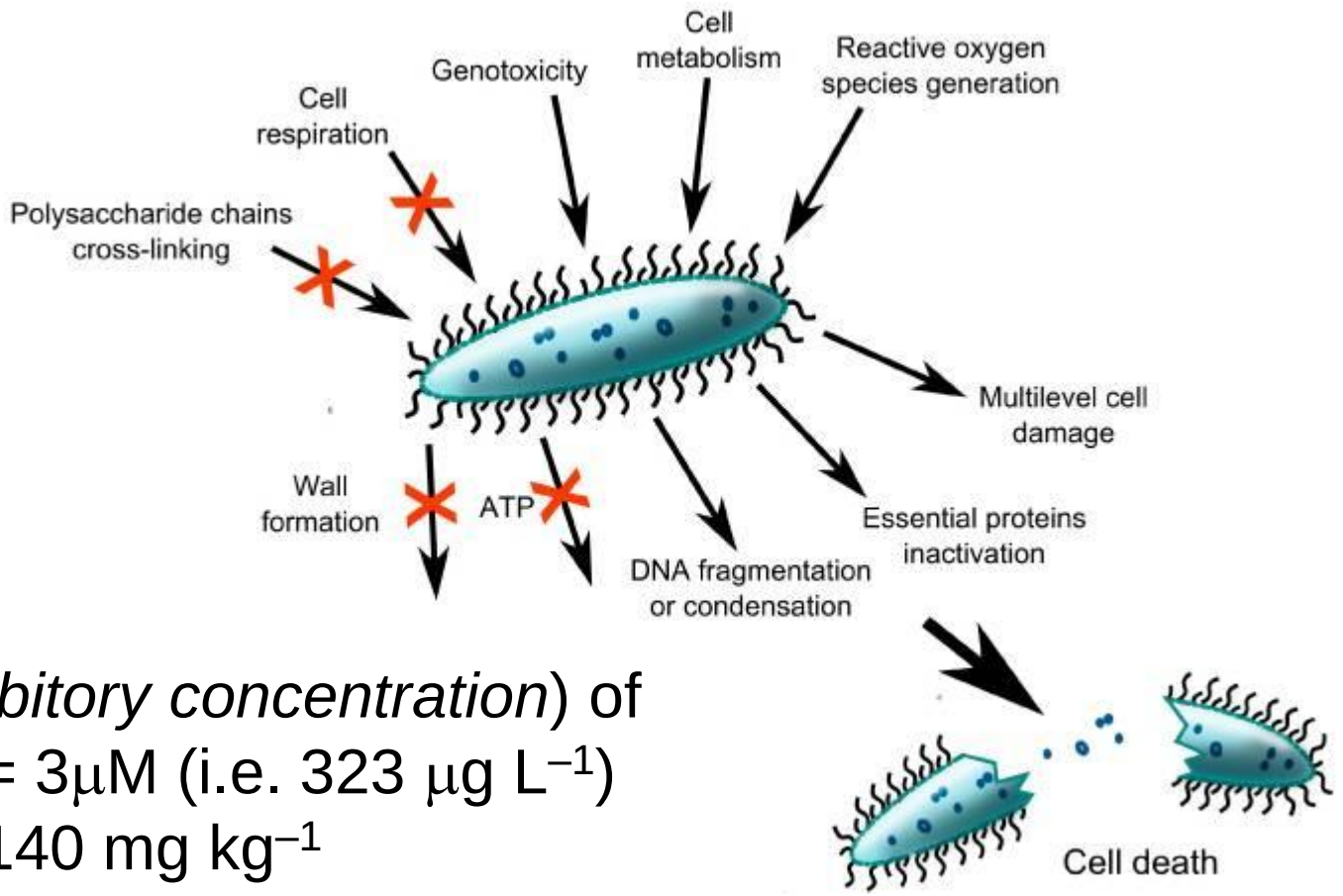
Antibacterials


1945
More than 20% of S. aureus hospitals isolates are penicillin-resistant
1940
Identified the penicillinase, enzyme capable of destroying penicillin
1942
First therapeutic use of penicillin
1952
FDA approved tetracycline
1947
FDA approved streptomycin
1947
Streptomycin resistance observed
1956
Tetracycline resistance observed
1961
First methicillin-resistant S. aureus (MRSA) observed
1959
Introduction of Methicillin
1958
Introduction of Vancomycin
1964
Introduction of Cephalothin, the first antibiotic in the cephalosporin class
1966
Cephalothin resistance observed
1970
Gentamicin resistance observed
1967
FDA approved Gentamicin
1940
1950
1960
1983
Cefotaxime resistance observed
1981
FDA approved Cefotaxime
1976
Penicillinase transferred to gonococcus
1987
First Vancomycin resistant Enterococcus
1996
S. aureus with intermediate resistance to Vancomycin (VISA)
2000
FDA approved Linezolid, the first antibiotic of oxazolidinone class
2001
Linezolid resistant S. aureus observed
2002
S. Aureus with complete Vancomycin resistance observed (VRSA)
1970
1980
1990
2000

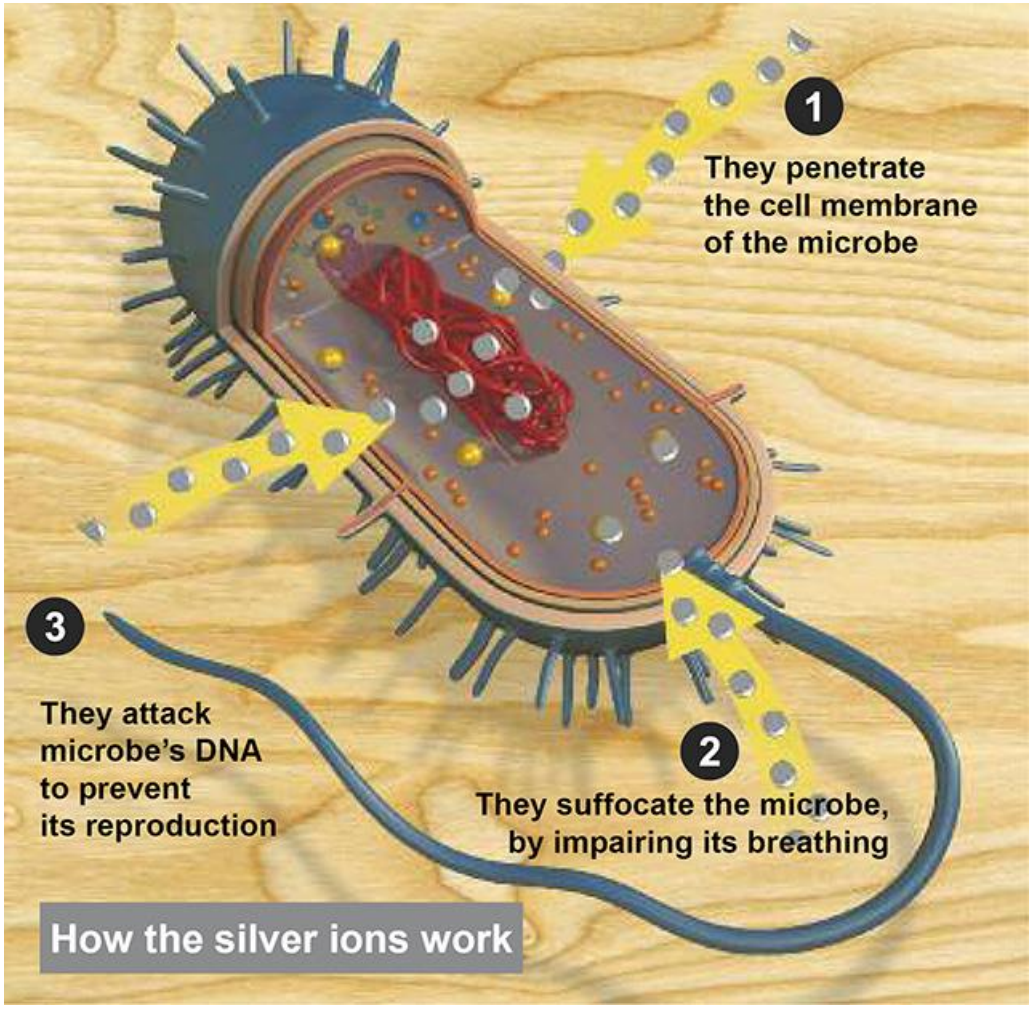

Antibacterial agents approval
by FDA, 1983-2007
16
14
12
10
8
6
4
2
0
1983-1987
1988-1992
1993-1997
1998-2002
2003-2007

Multiple mechanism of action of Ag^+ ions

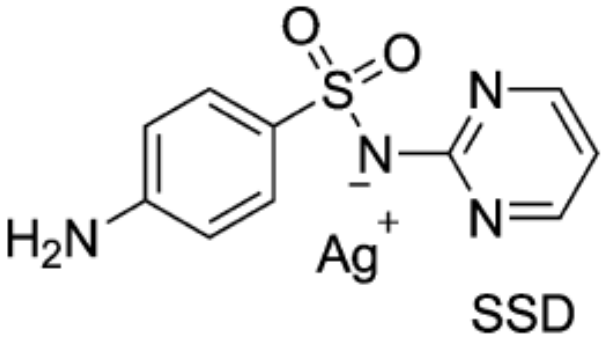


MIC (*minimal inhibitory concentration*) of $AgNO_3$ to *E. coli* = 3μM (i.e. 323 μg L^{-1})

LD_{50} in humans: 140 mg kg^{-1}


1
They penetrate
the cell membrane
of the microbe
2
They suffocate the microbe,
by impairing its breathing
3
They attack
microbe's DNA
to prevent
its reproduction
How the silver ions work

Silver salts



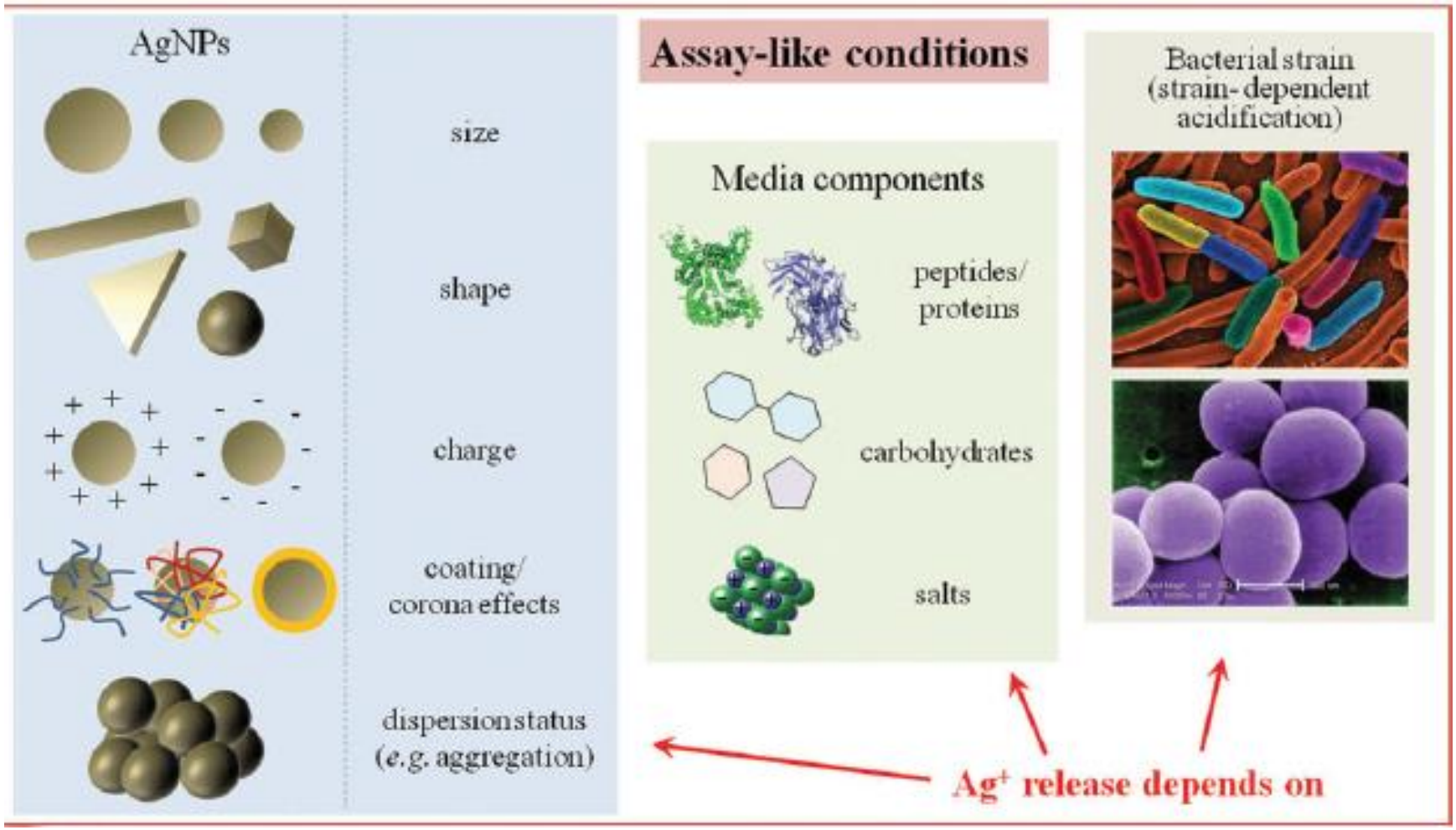
SSD

silver sulfadiazine

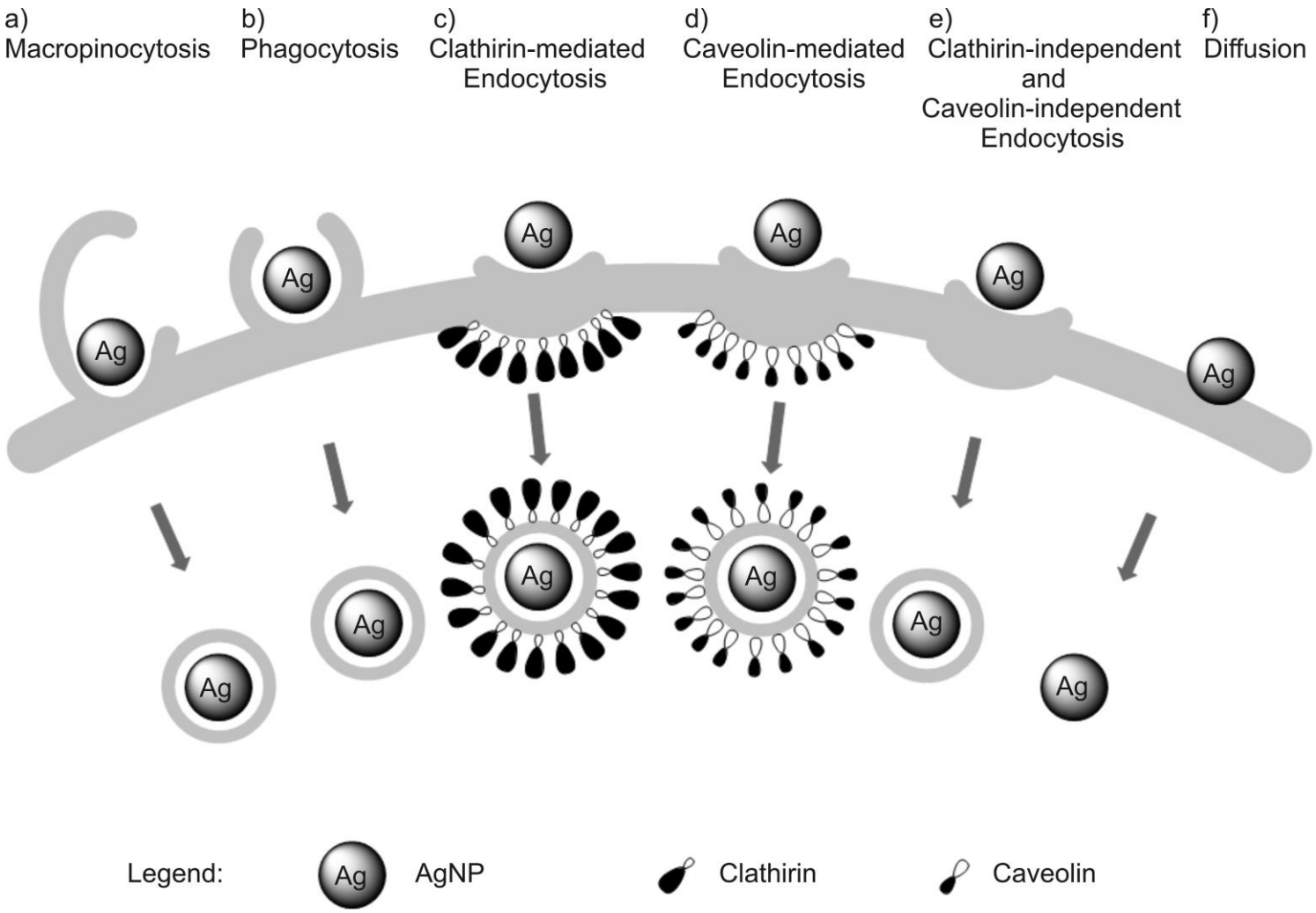
Silver nanoparticles (AgNPs)

Estimated 2014 production of commercial AgNPs: 320 t

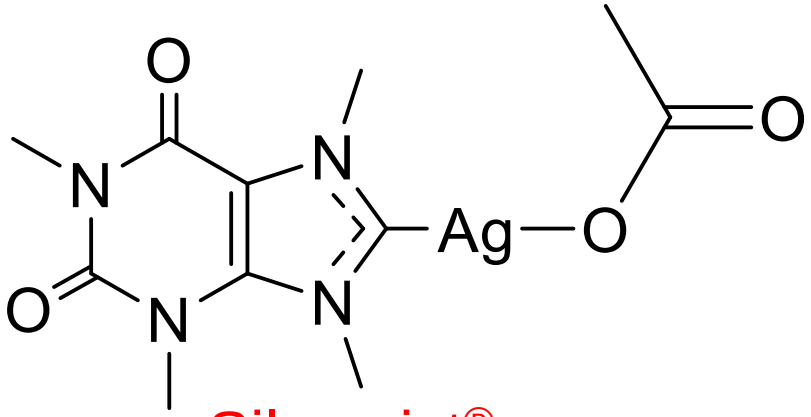
Ag^+ release from AgNPs



Uptake of AgNPs

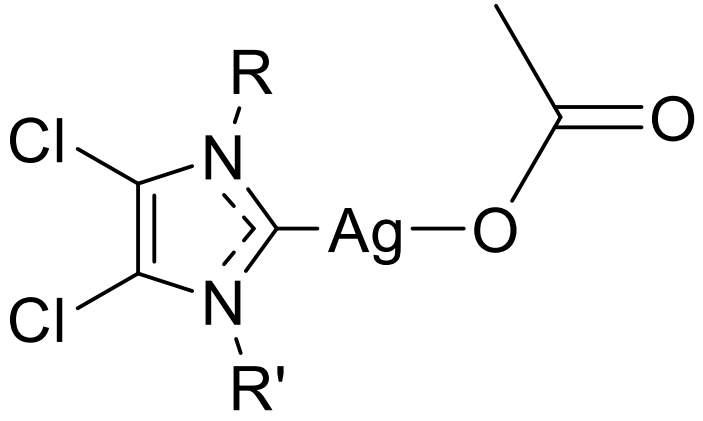


Antibacterial Ag-NHC compounds



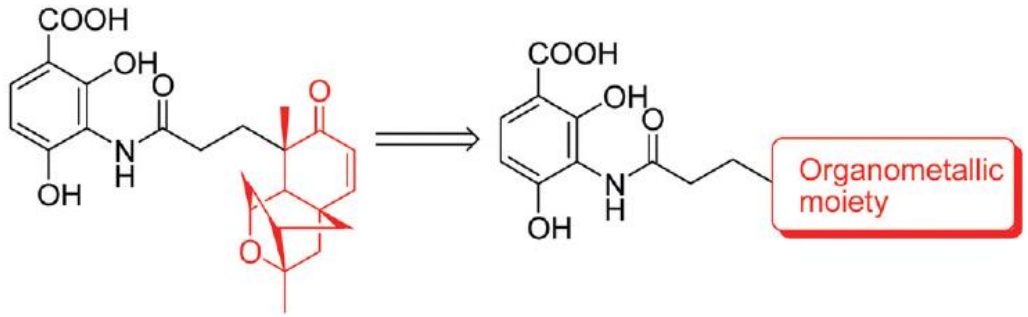
Silvamist®

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

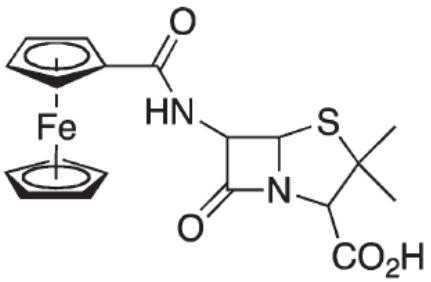


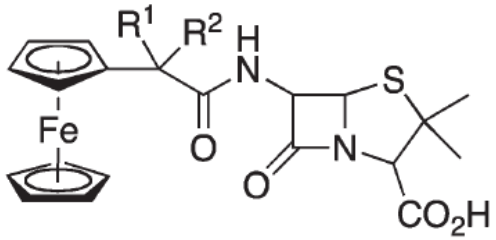
Improved stability to hydrolysis due to the electron-withdrawing Cl substituents that pull electron density from the carbene

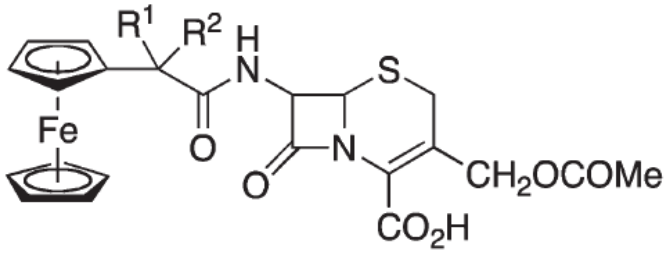
Other strategies: metal modification of known antibiotics



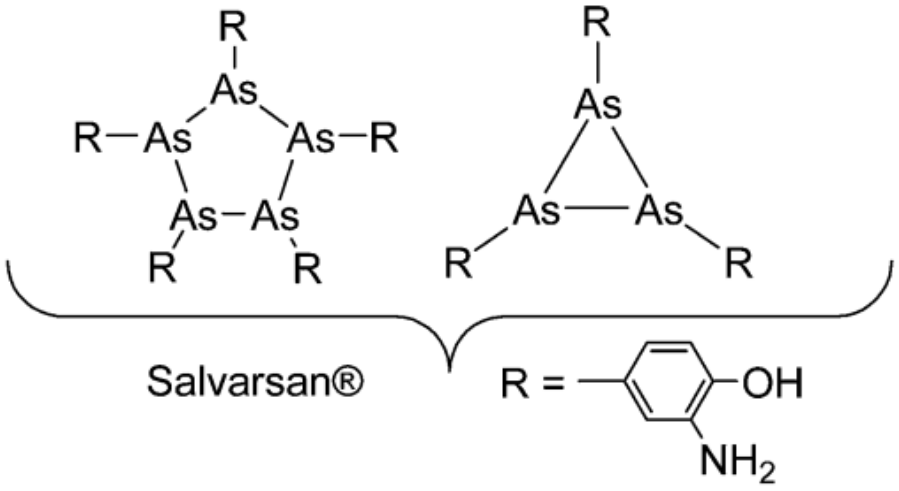
Platensimycin mimics





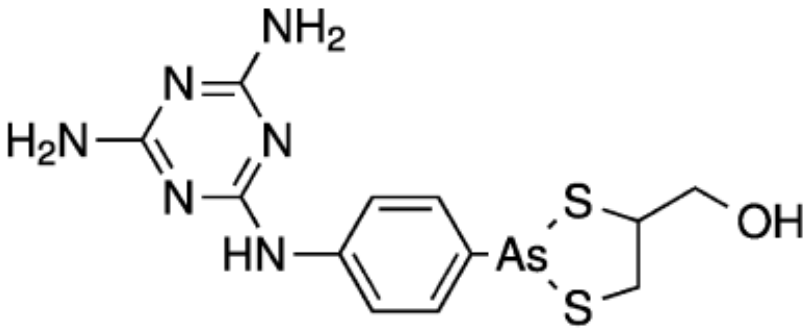


Other metals: As, Sb, Bi, Hg



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

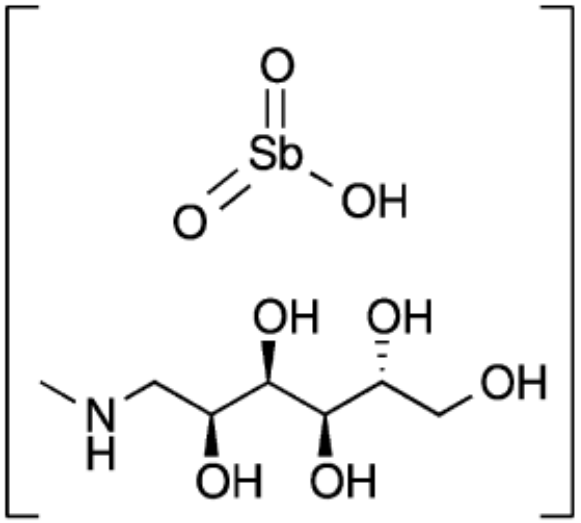
Antiparasitic compounds



melarsoprol

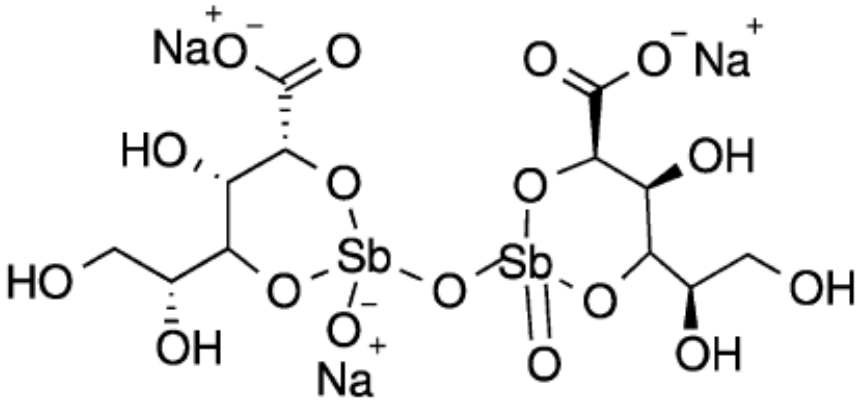
treatment of sleeping sickness (*African trypanosomiasis*)

Anti-leishmaniasis compounds



meglumine antimoniate

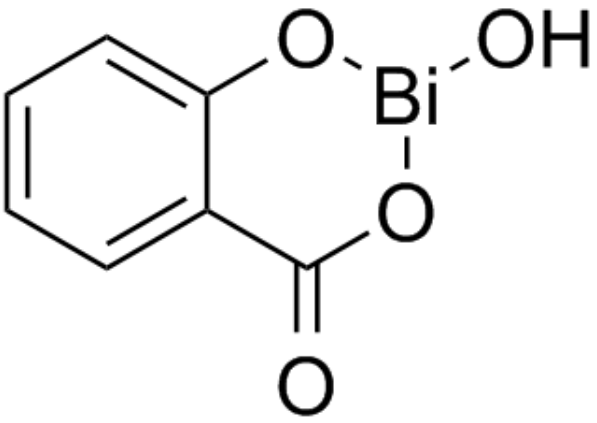
Veterinary use



sodium stibugluconate

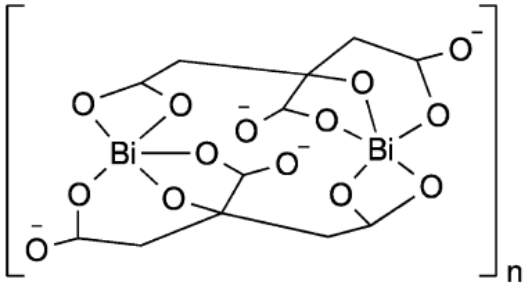
Sb, reduced to Sb(III), inhibits *trypanothione reductase*, an essential enzyme of the parasite

Infezioni da *Helicobacter pylori*

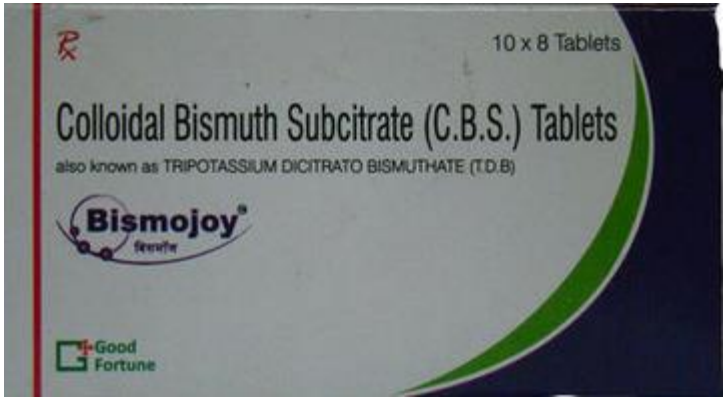


bismuth subsalicylate

The pink stuff (introduced 1901)

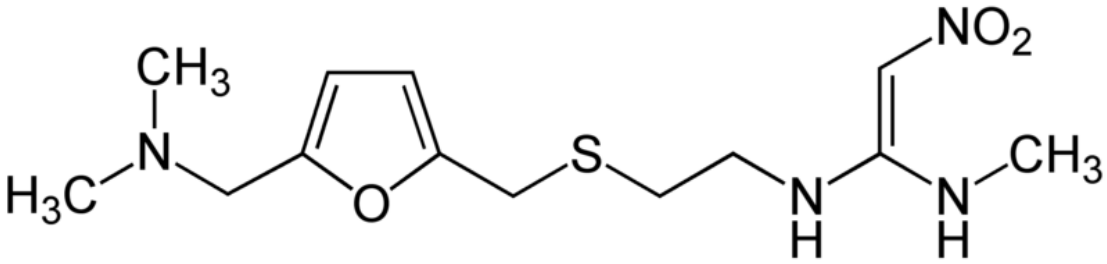


CBS



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

$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

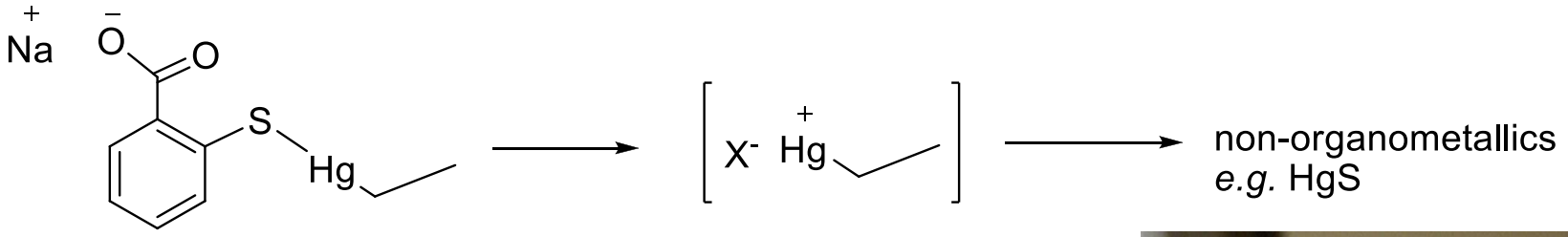
Debate at Penn: Have We Lost the Spirit of Compromise in America?

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: Reawakening the Spirit of Compromise in American Politics* will address how we can best avoid

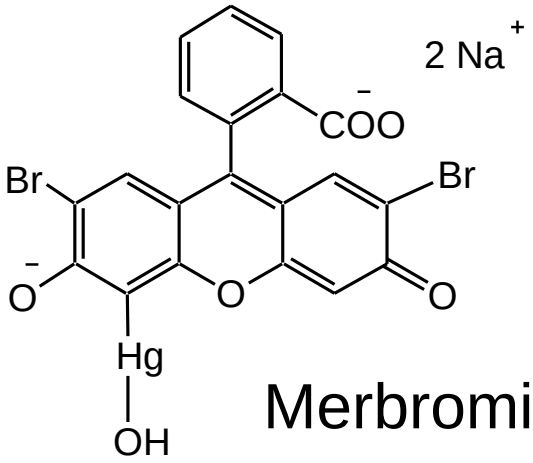
Antibacterial mercury compounds



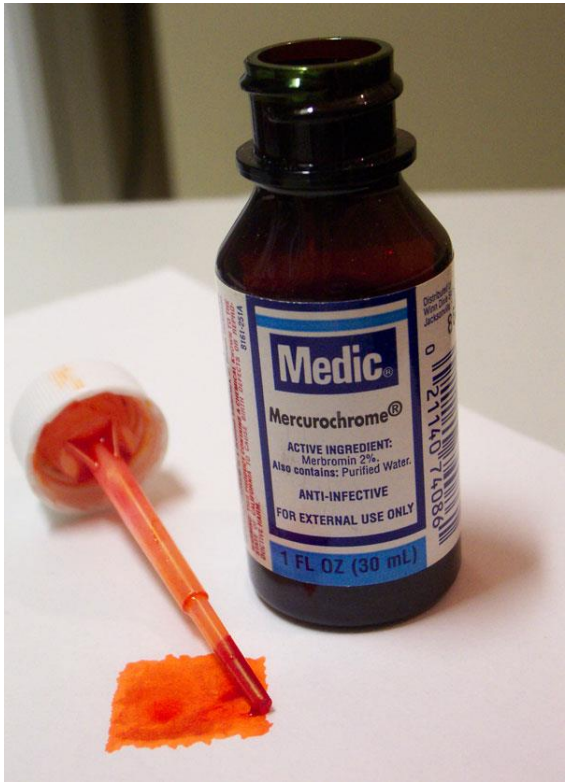
Thiomersal

ethyl mercury

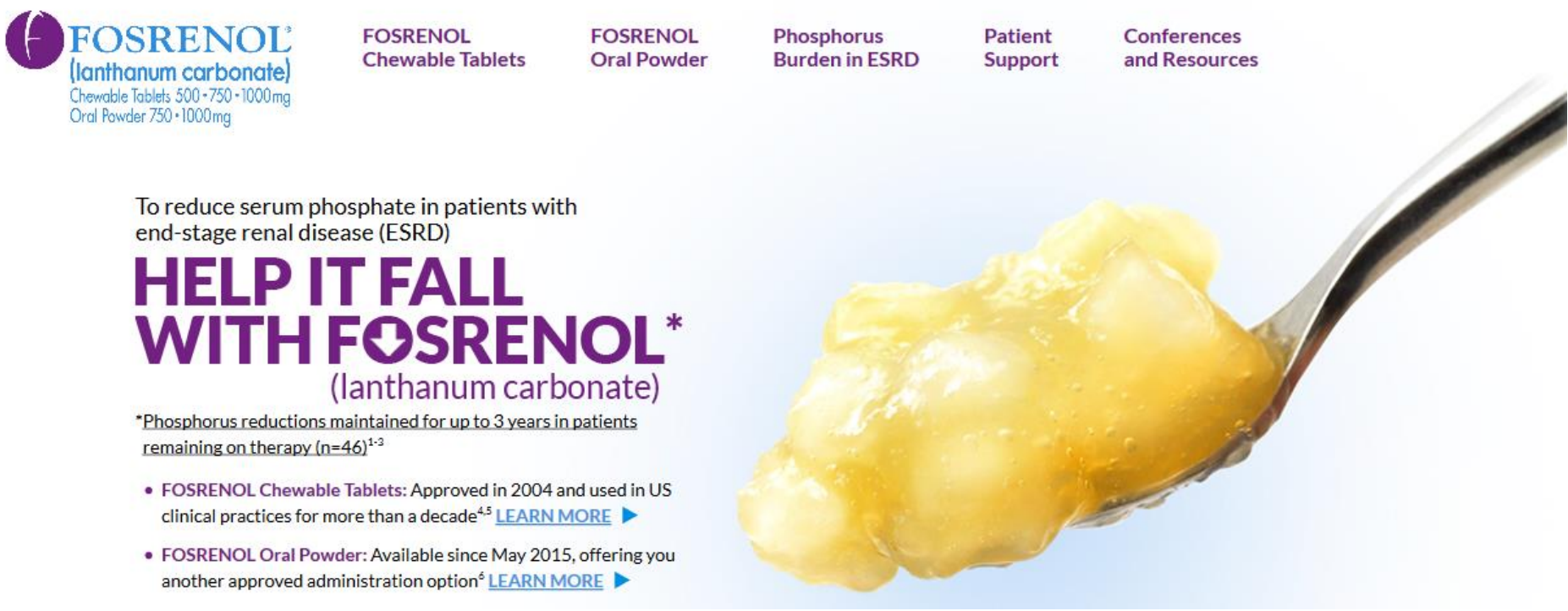
vaccine adjuvant



Merbromin (mercurochrome)

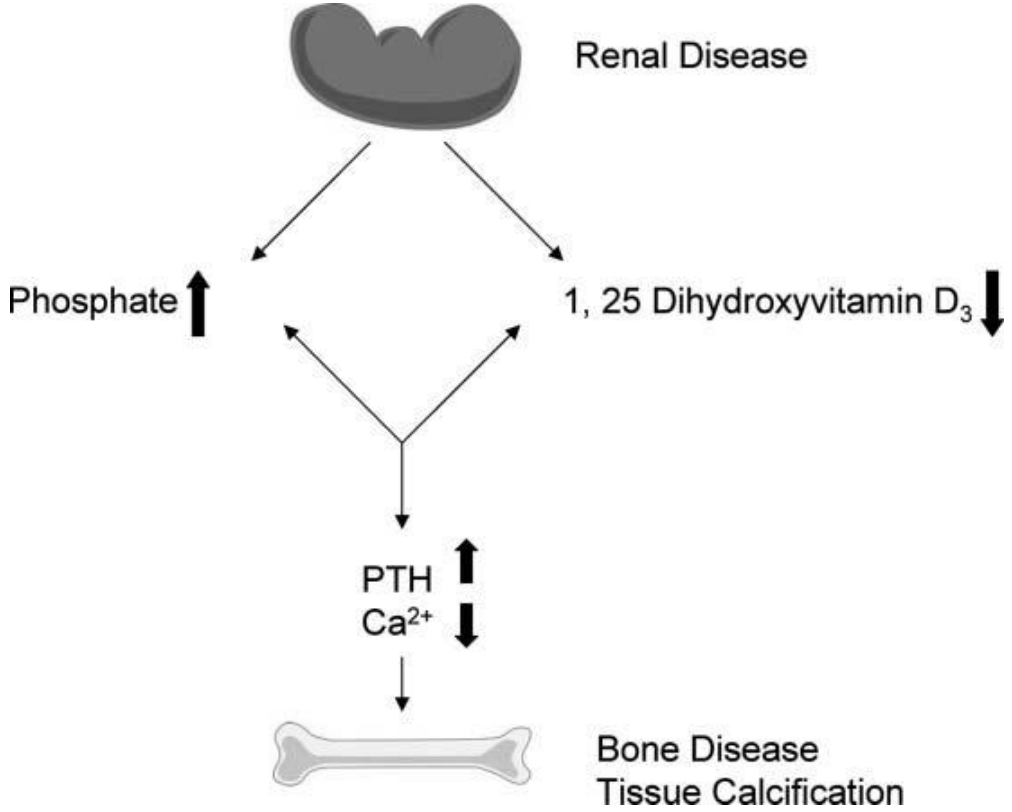


Fosrenol™: a success story



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, $La_2(CO_3)_3 \cdot 4H_2O$ 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 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.