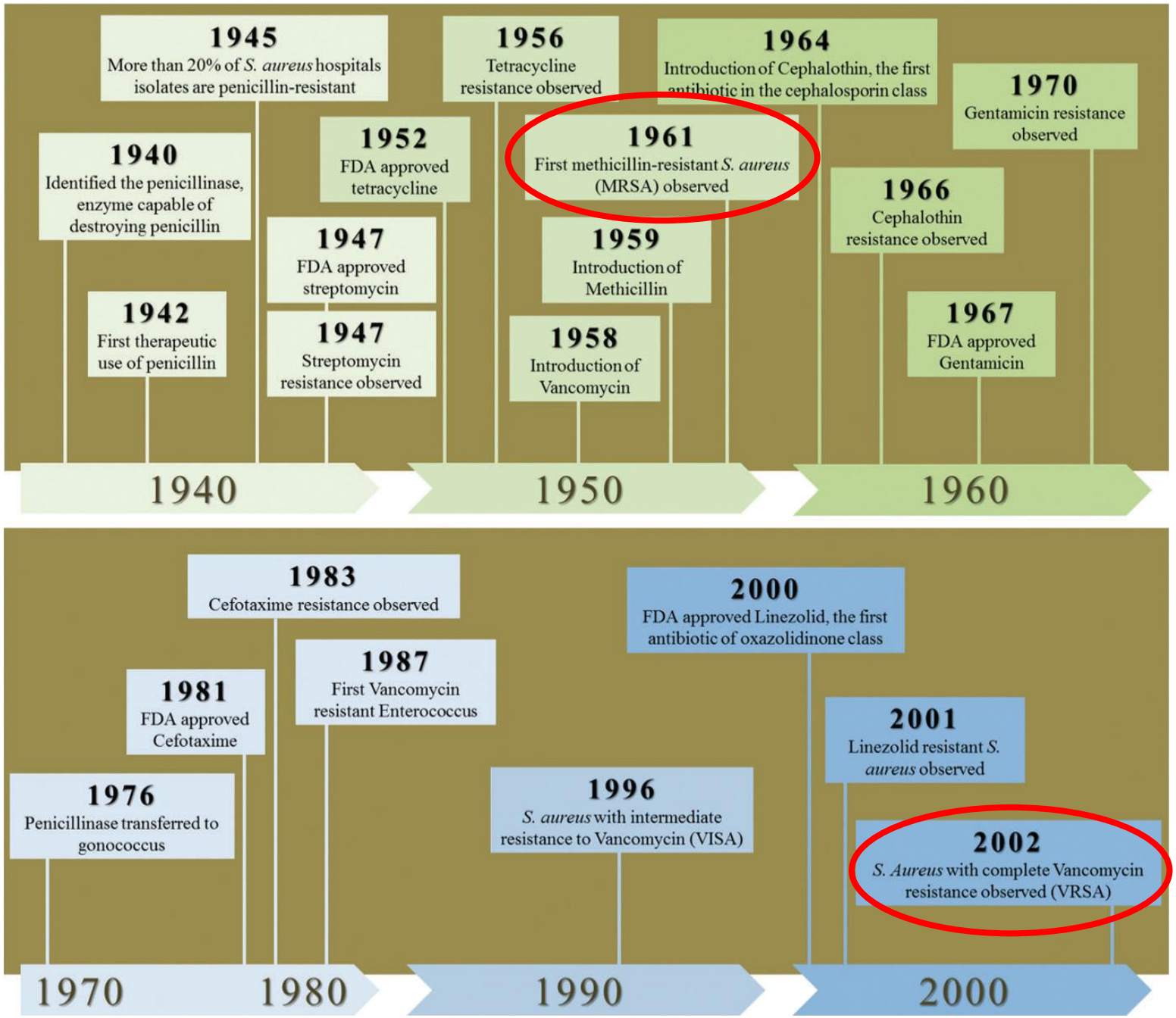
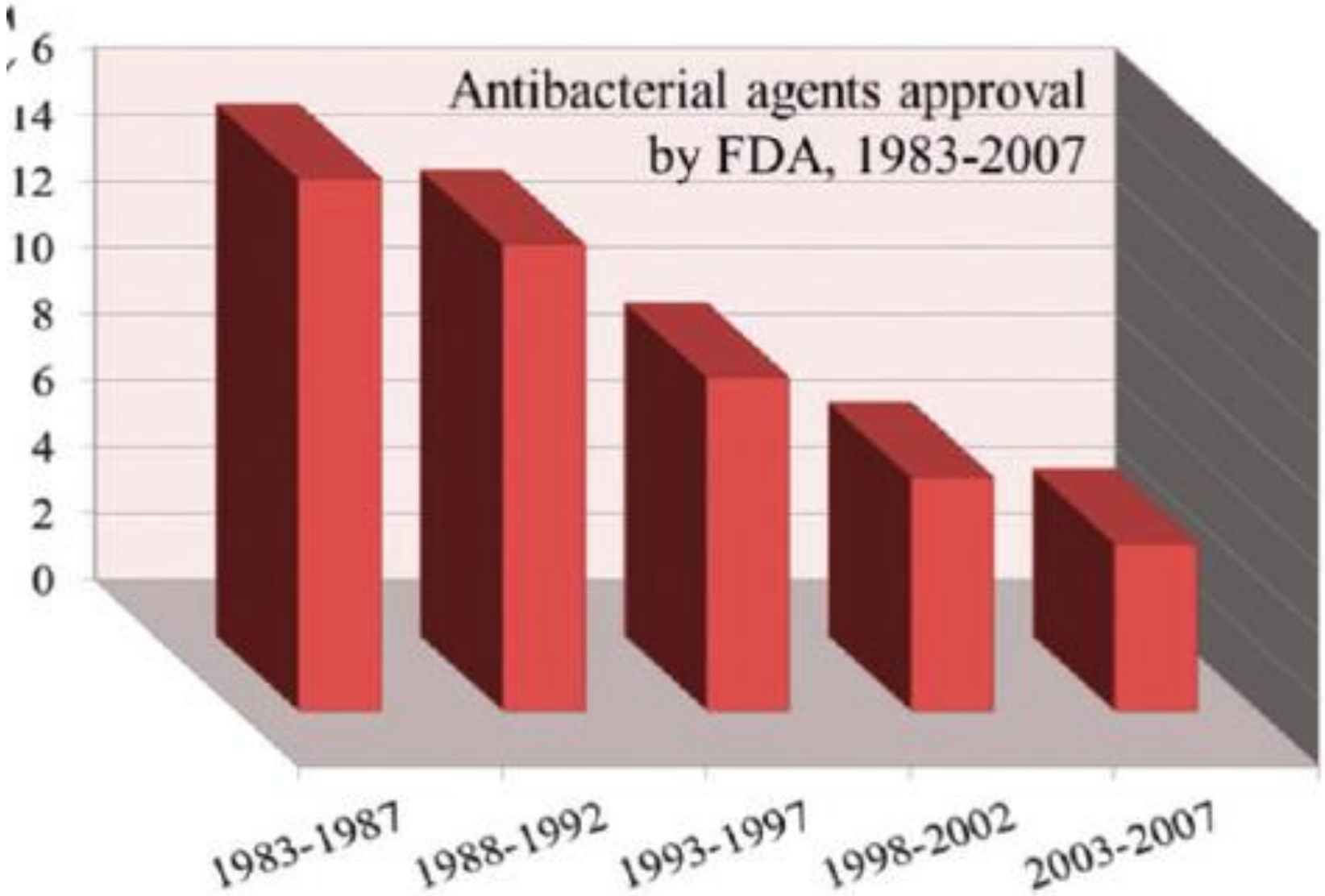
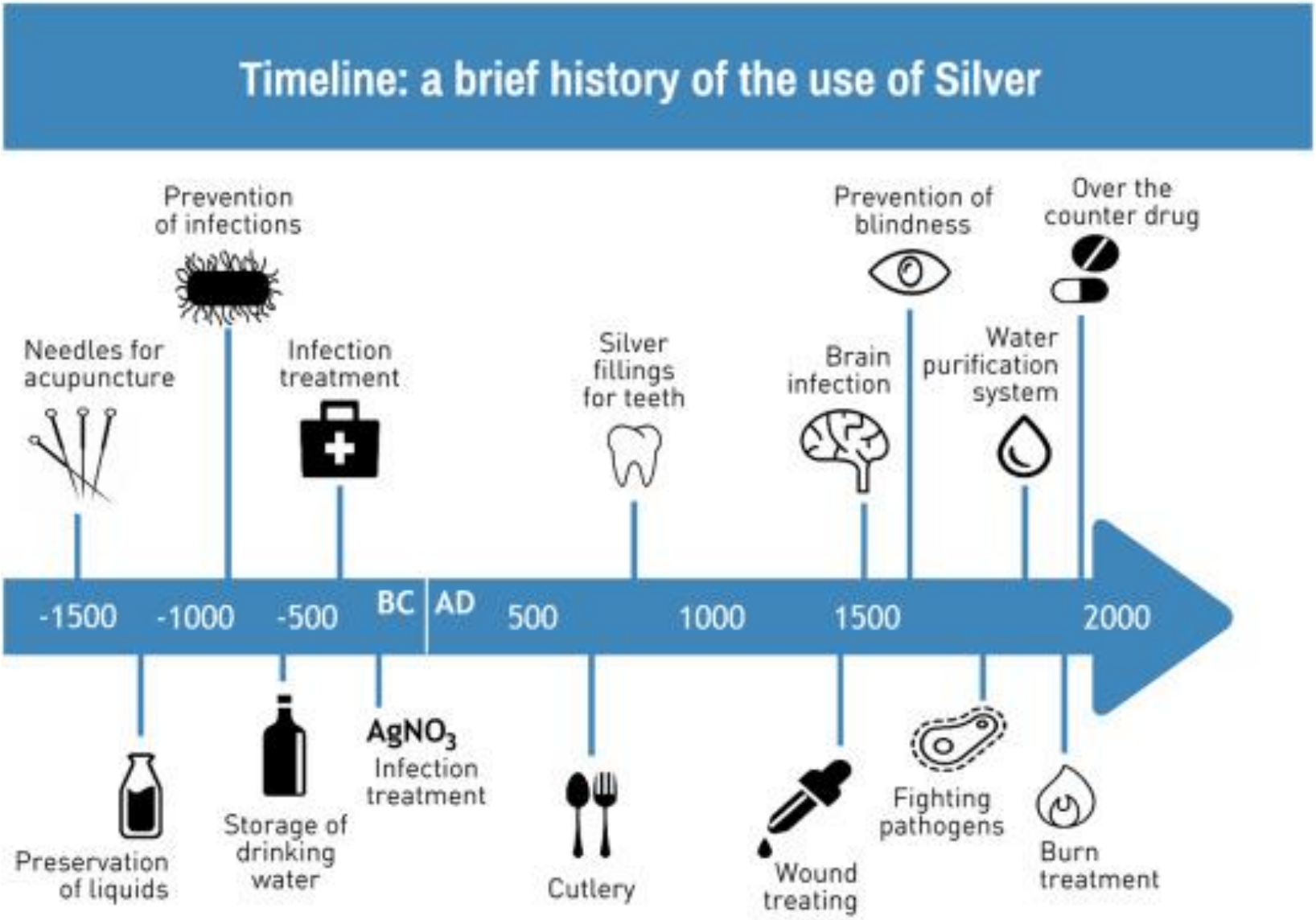
Antibacterials


1940
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
1947
FDA approved streptomycin
1947
Streptomycin resistance observed
1950
1952
FDA approved tetracycline
1956
Tetracycline resistance observed
1958
Introduction of Vancomycin
1959
Introduction of Methicillin
1961
First methicillin-resistant S. aureus (MRSA) observed
1960
1964
Introduction of Cephalothin, the first antibiotic in the cephalosporin class
1966
Cephalothin resistance observed
1967
FDA approved Gentamicin
1970
Gentamicin resistance observed
1970
1976
Penicillinase transferred to gonococcus
1980
1981
FDA approved Cefotaxime
1983
Cefotaxime resistance observed
1987
First Vancomycin resistant Enterococcus
1990
1996
S. aureus with intermediate resistance to Vancomycin (VISA)
2000
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)

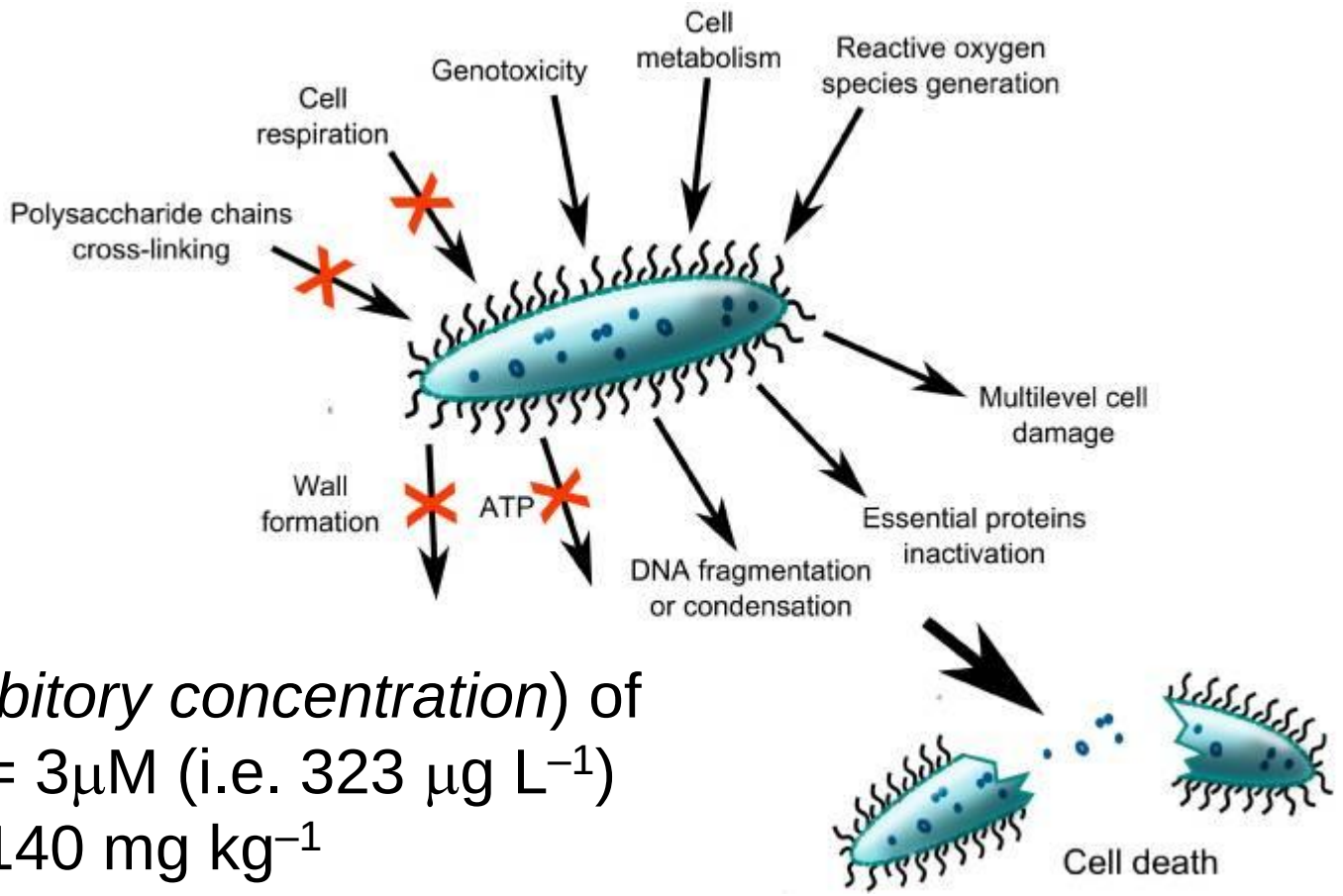

Antibacterial agents approval
by FDA, 1983-2007
16
14
12
10
8
6
4
2
0
1983-1987
1988-1992
1993-1997
1998-2002
2003-2007

Si stima che nel 2050 a livello mondiale le morti da infezione batterica – dovute soltanto a ceppi di batteri resistenti – arriveranno a 50 milioni all'anno (vs 8.8 milioni dovute al cancro).



Metallo massivo – Nanoparticelle – Sali (Ag+)

Multiple mechanism of action of Ag^+ ions

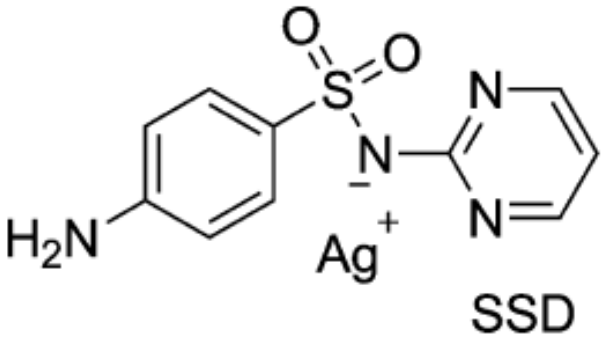


MIC (*minimal inhibitory concentration*) of $AgNO_3$ to *E. coli* = 3μM (i.e. 323 μg L^{-1})

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

WHY CHOOSE SILVER PLATING FOR MEDICAL DEVICES?

Silver salts



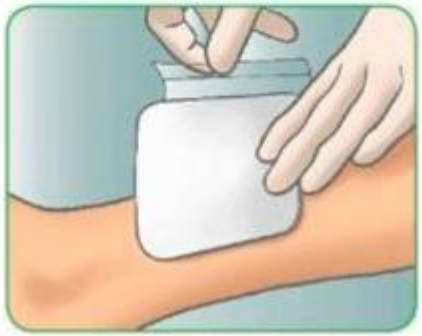
SSD

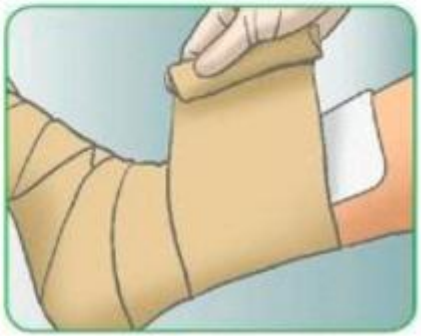
silver sulfadiazine

Silver nanoparticles (AgNPs)

Estimated 2014 production of commercial AgNPs: 320 t

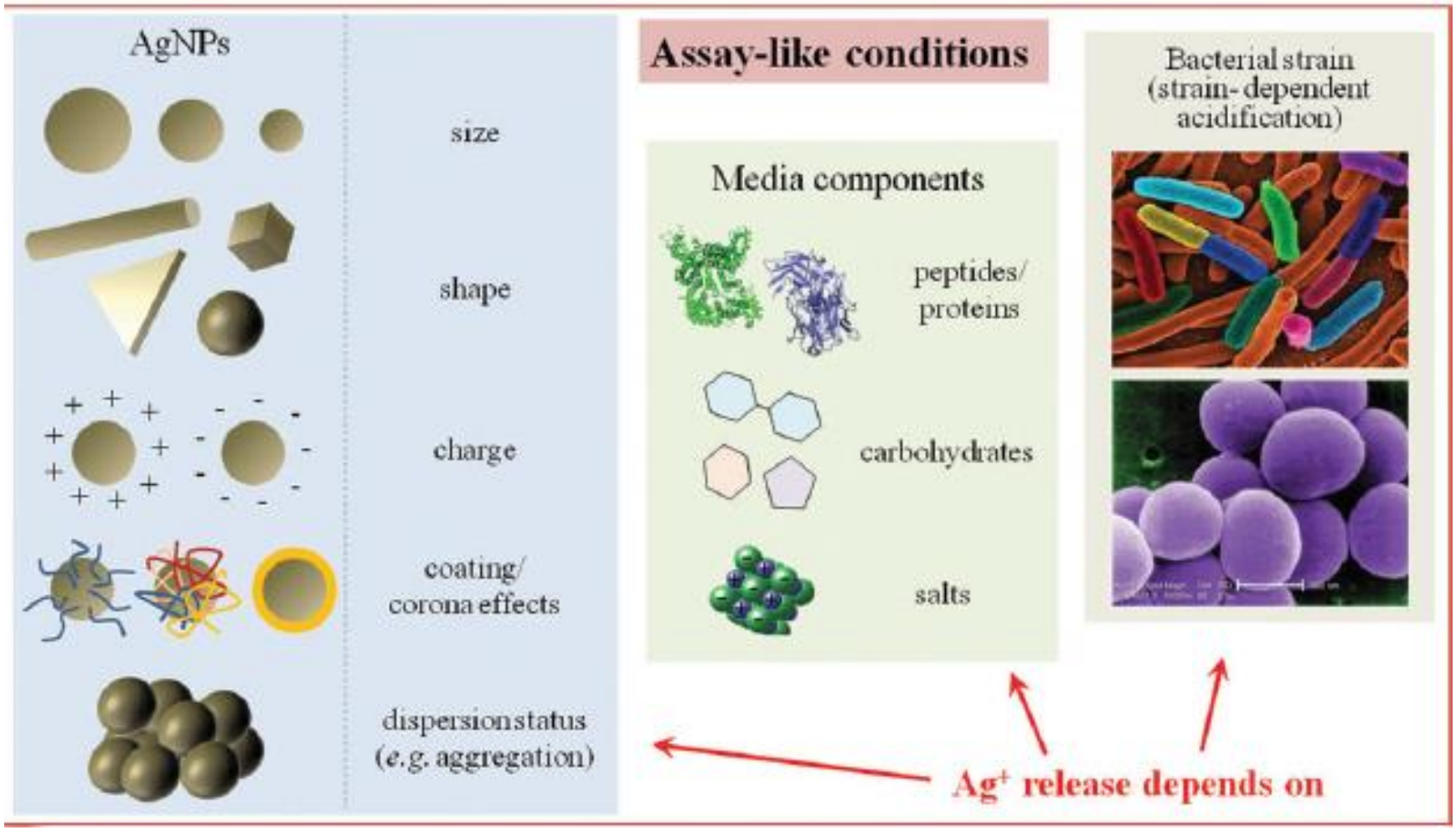

Mepilex® Ag
Mepilex® Ag
10 x 10 cm/4 x 4 in
Safetac
Safetac
TECHNOLOGY



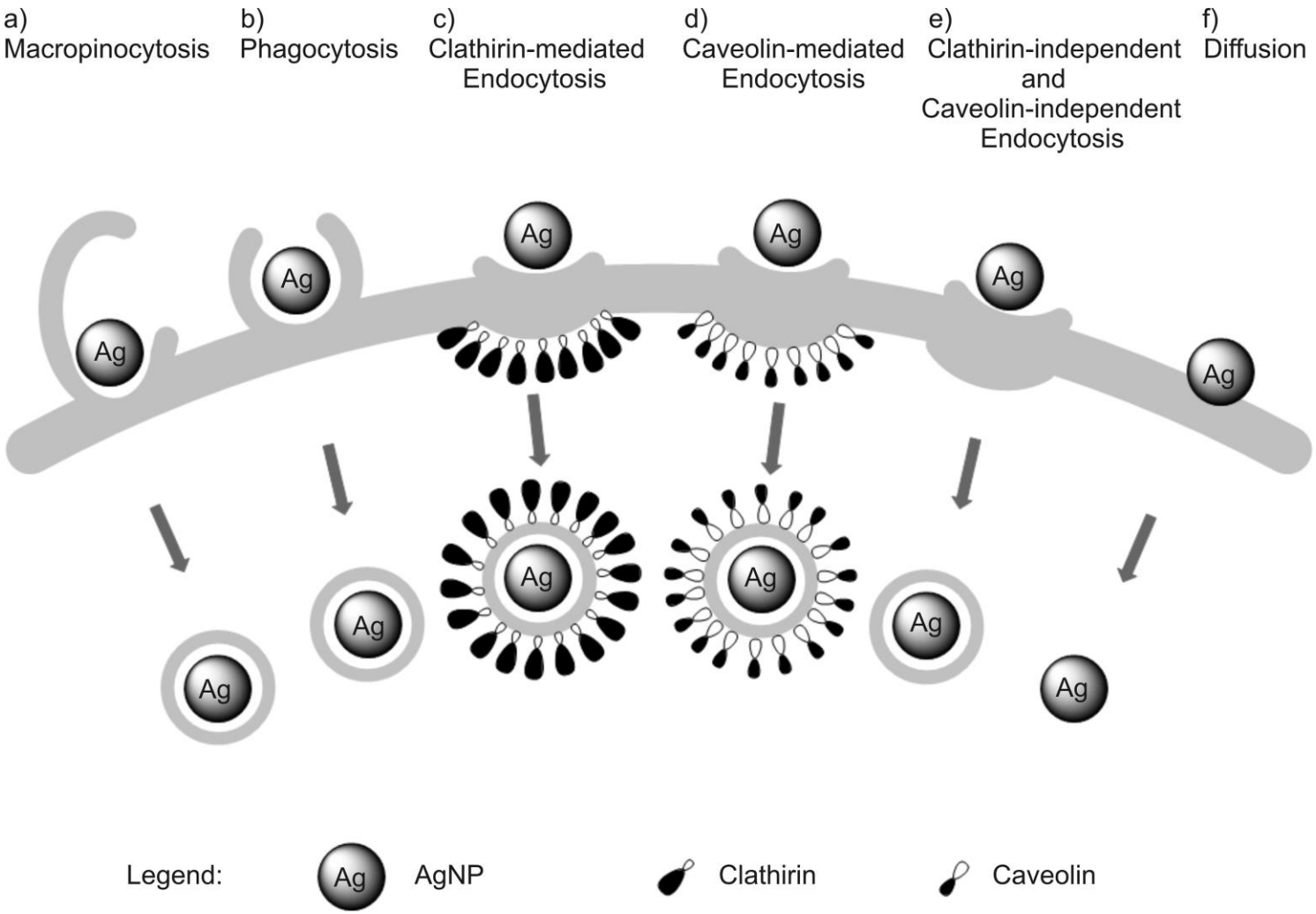



Elastoplast
ANTIBACTERIAL
FABRIC
REDUCES THE RISK OF INFECTION
Extra flexible
20 Plasters
antibacterial
SILVER
NIVEA MEN
SILVER PROTECT
SHOWER GEL
BODY, FACE & HAIR
NIVEA MEN
48h
SILVER PROTECT
DYNAMIC POWER
NIVEA MEN
48h
SILVER PROTECT

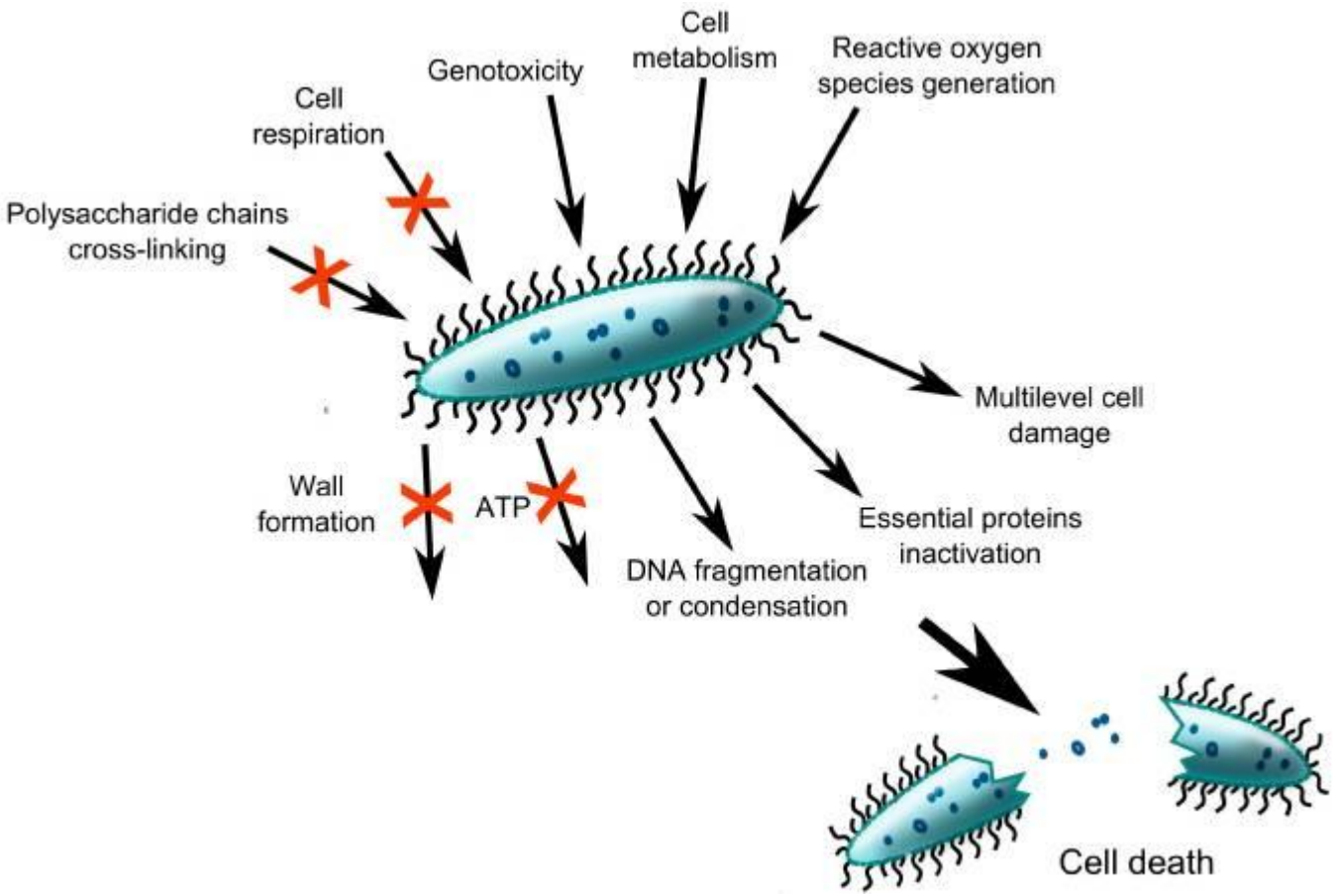
Ag^+ release from AgNPs

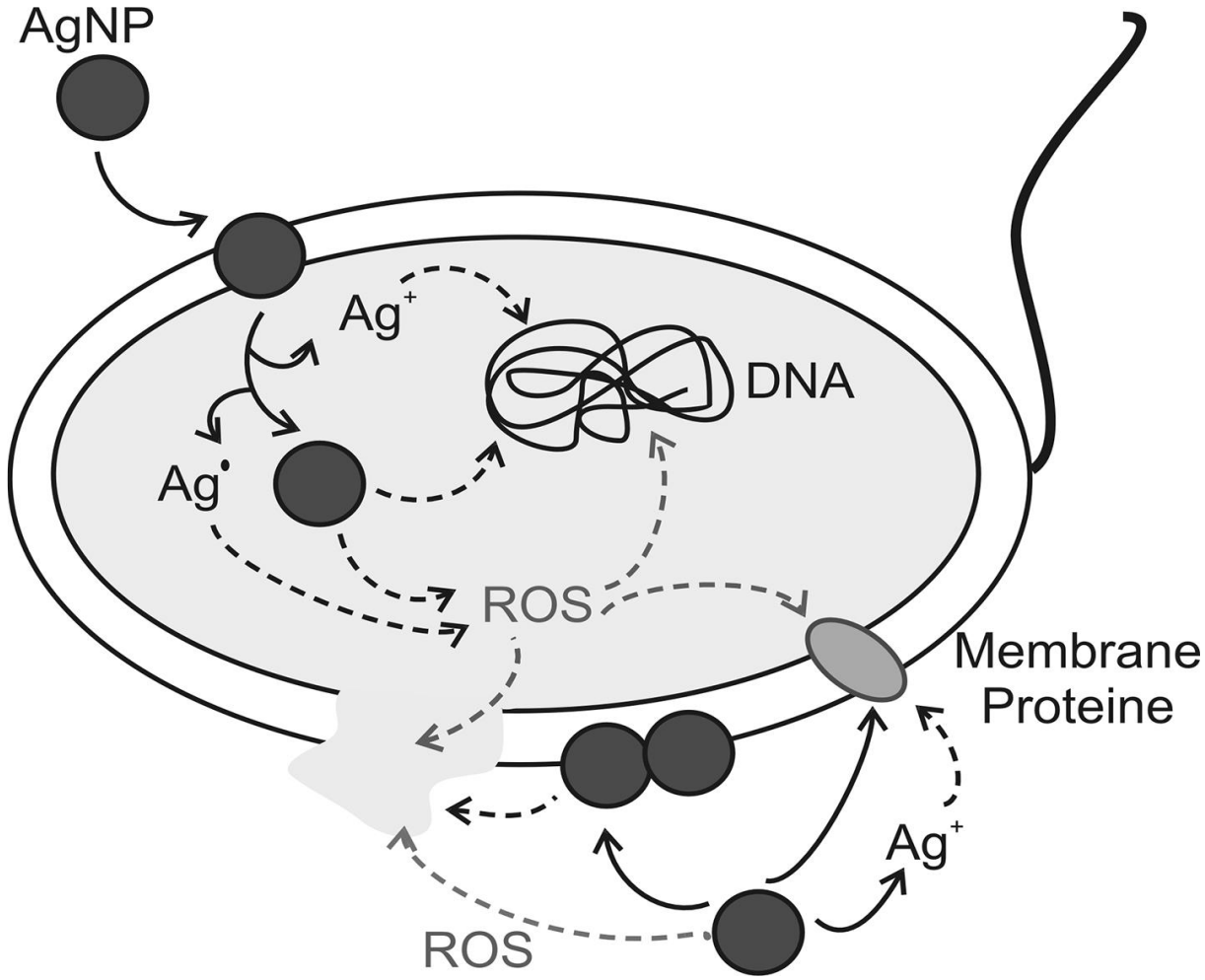


Uptake of AgNPs

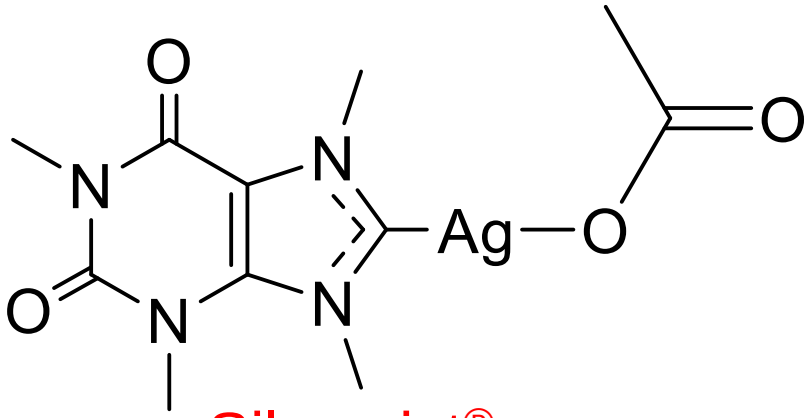


Multiple mechanism of action of Ag^+ ions



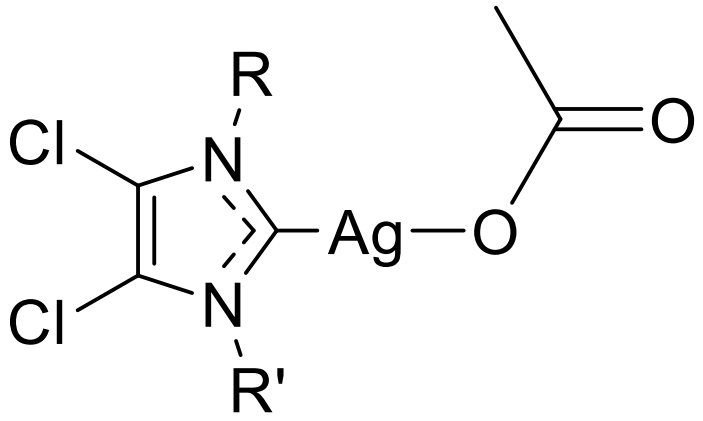

AgNP
Ag+
DNA
Ag•
ROS
Membrane
Proteine
Ag+
ROS

Antibacterial Ag-NHC compounds



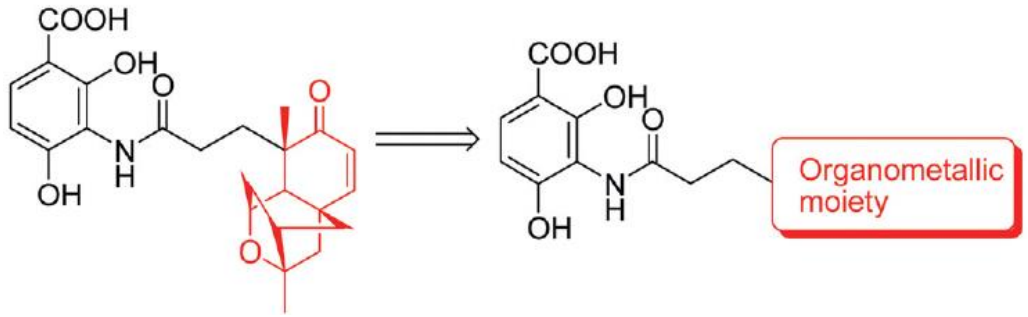
Silvamist®

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

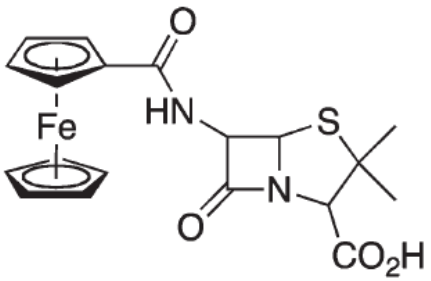


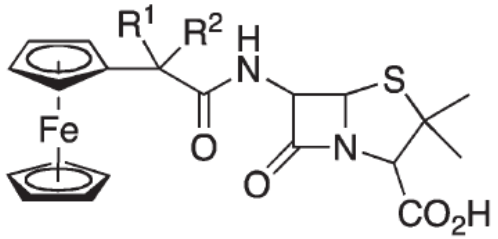
Improved stability to hydrolysis due to the electron-withdrawing Cl substituents that pull electron density from the carbene

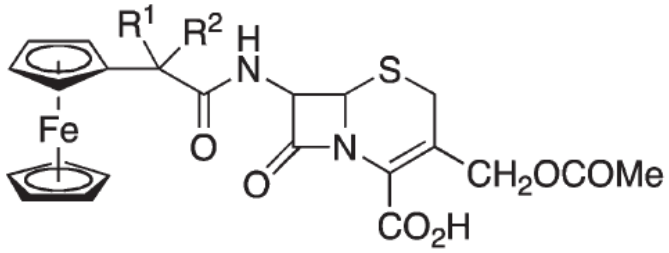
Other strategies: metal modification of known antibiotics



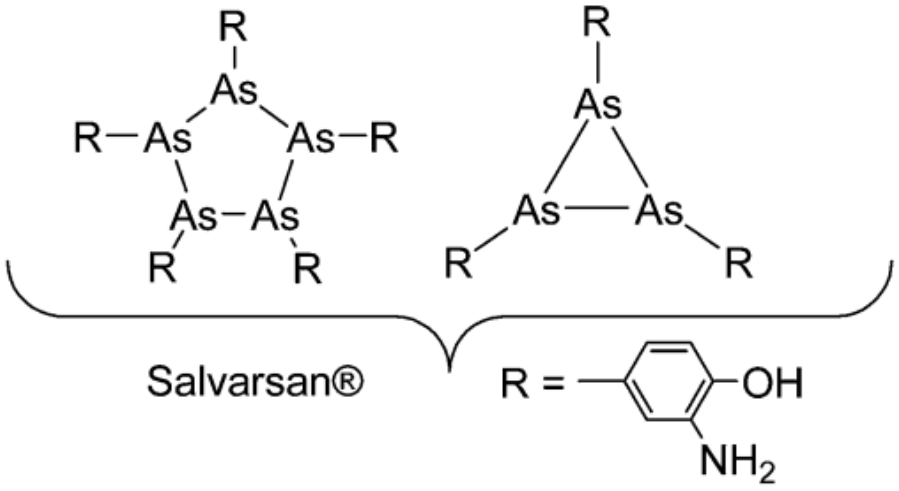
Platensimycin mimics





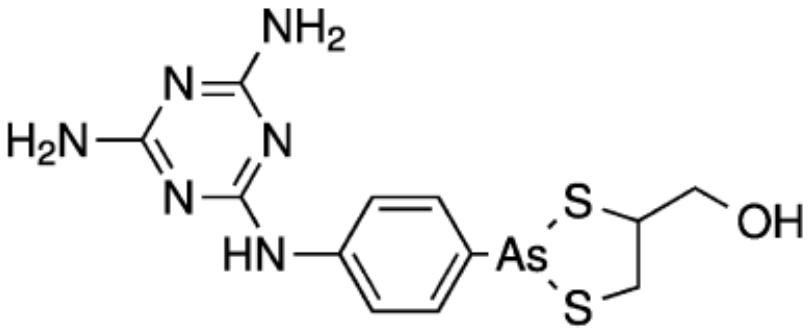


Other metals: As, Sb, Bi, Hg



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

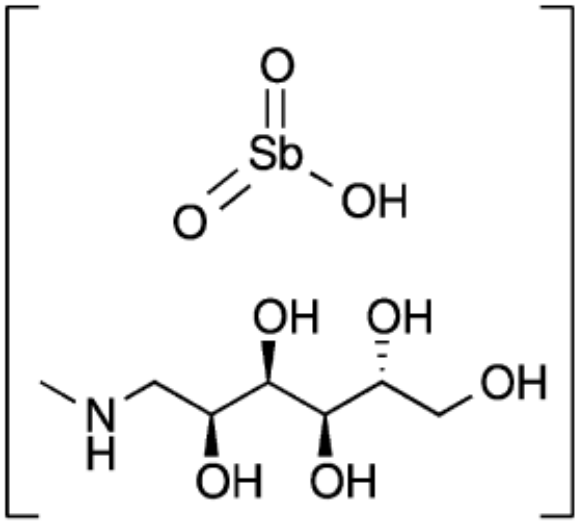
Antiparasitic compounds



melarsoprol

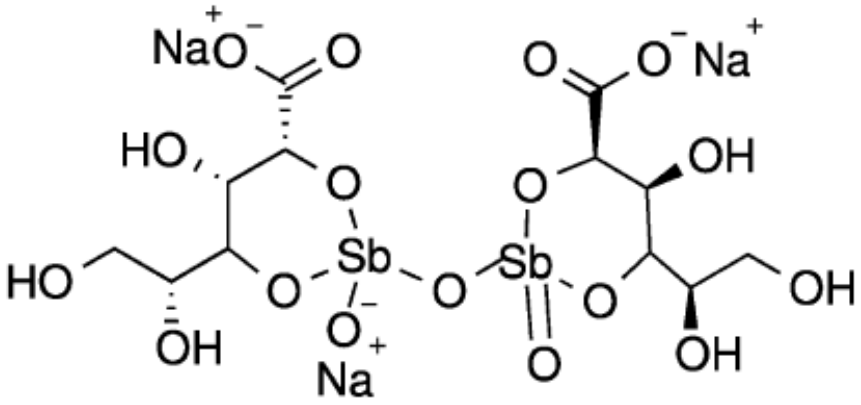
treatment of sleeping sickness (*African trypanosomiasis*)

Anti-leishmaniasis compounds



meglumine antimoniate

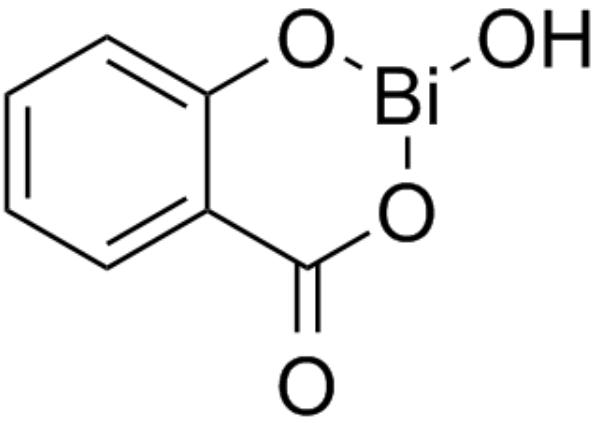
Veterinary use



sodium stibugluconate

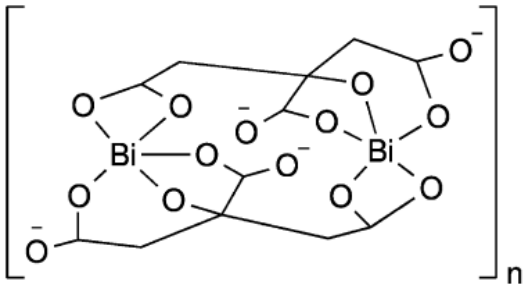
Sb, reduced to Sb(III), inhibits *trypanothione reductase*, an essential enzyme of the parasite

Infezioni da *Helicobacter pylori*

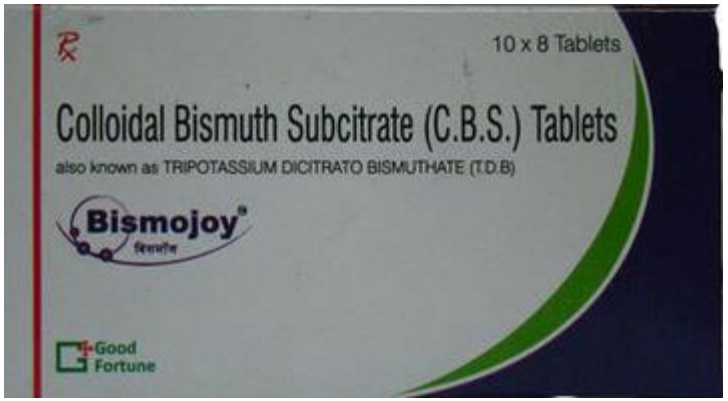


bismuth subsalicylate

The pink stuff (introduced 1901)

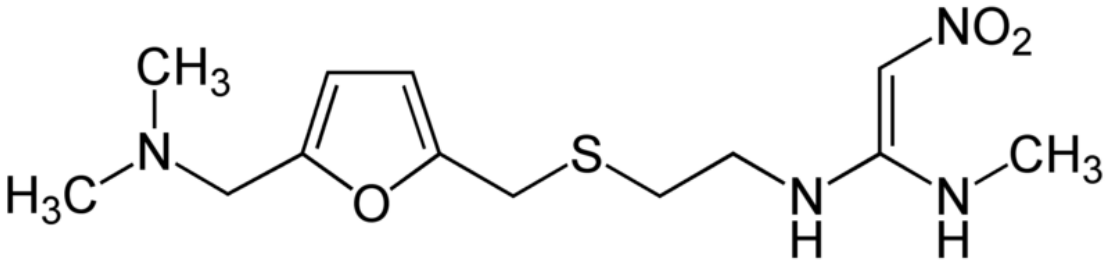


CBS



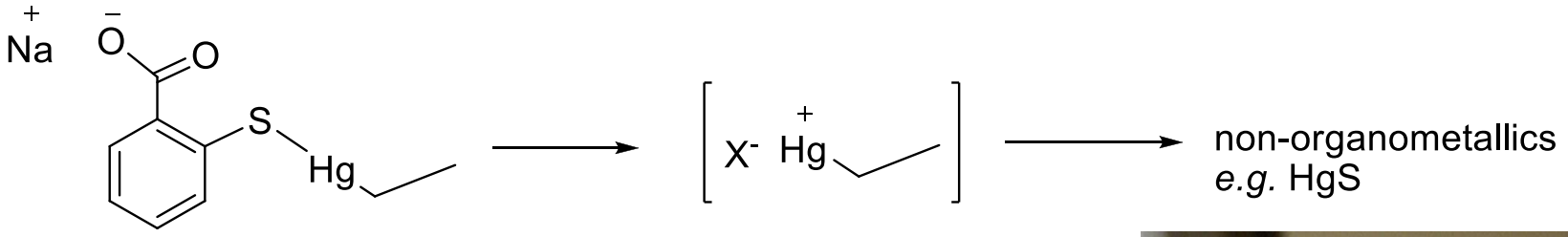
bismuto subcitrato colloidale

Infezioni da *Helicobacter pylori*



ranitidine bismuth citrate

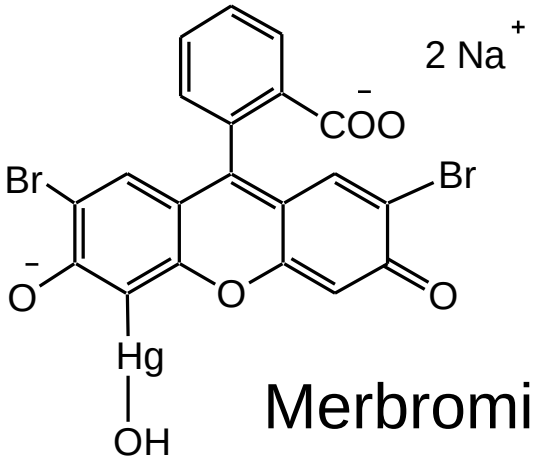
Antibacterial mercury compounds



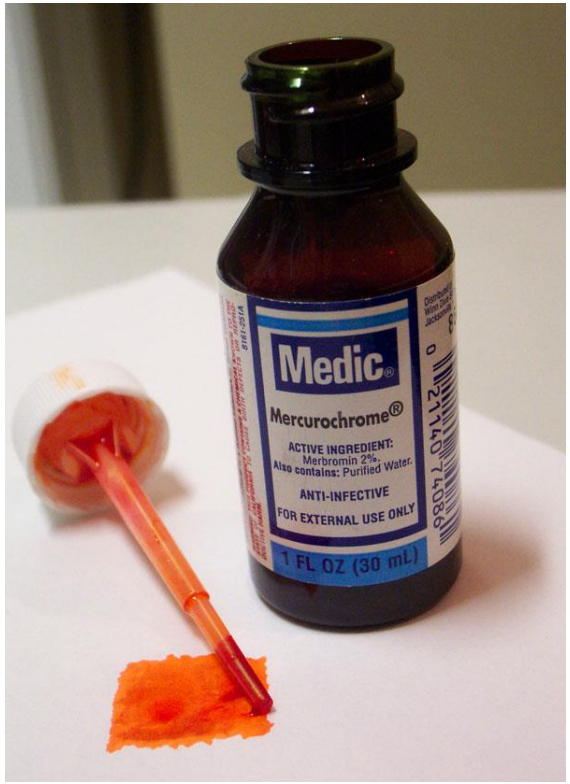
Thiomersal

ethyl mercury

vaccine adjuvant



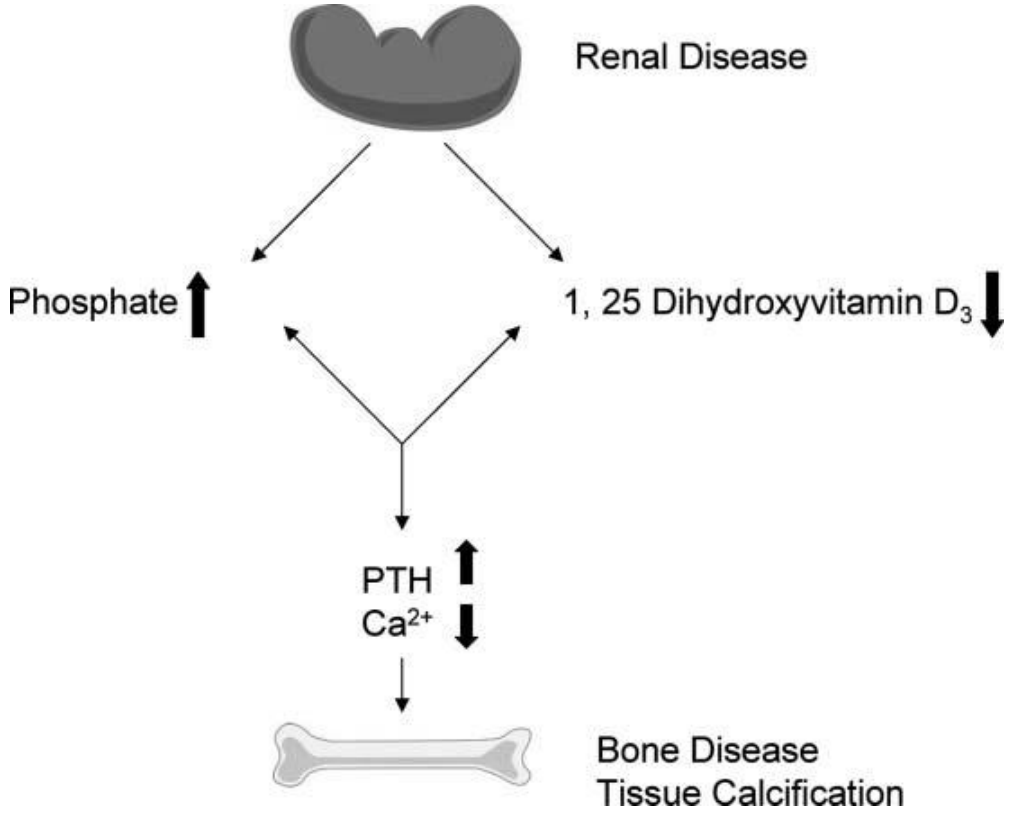
Merbromin (mercurochrome)



Fosrenol^{TM}: $La_2(CO_3)_3 \cdot 4H_2O$ 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.