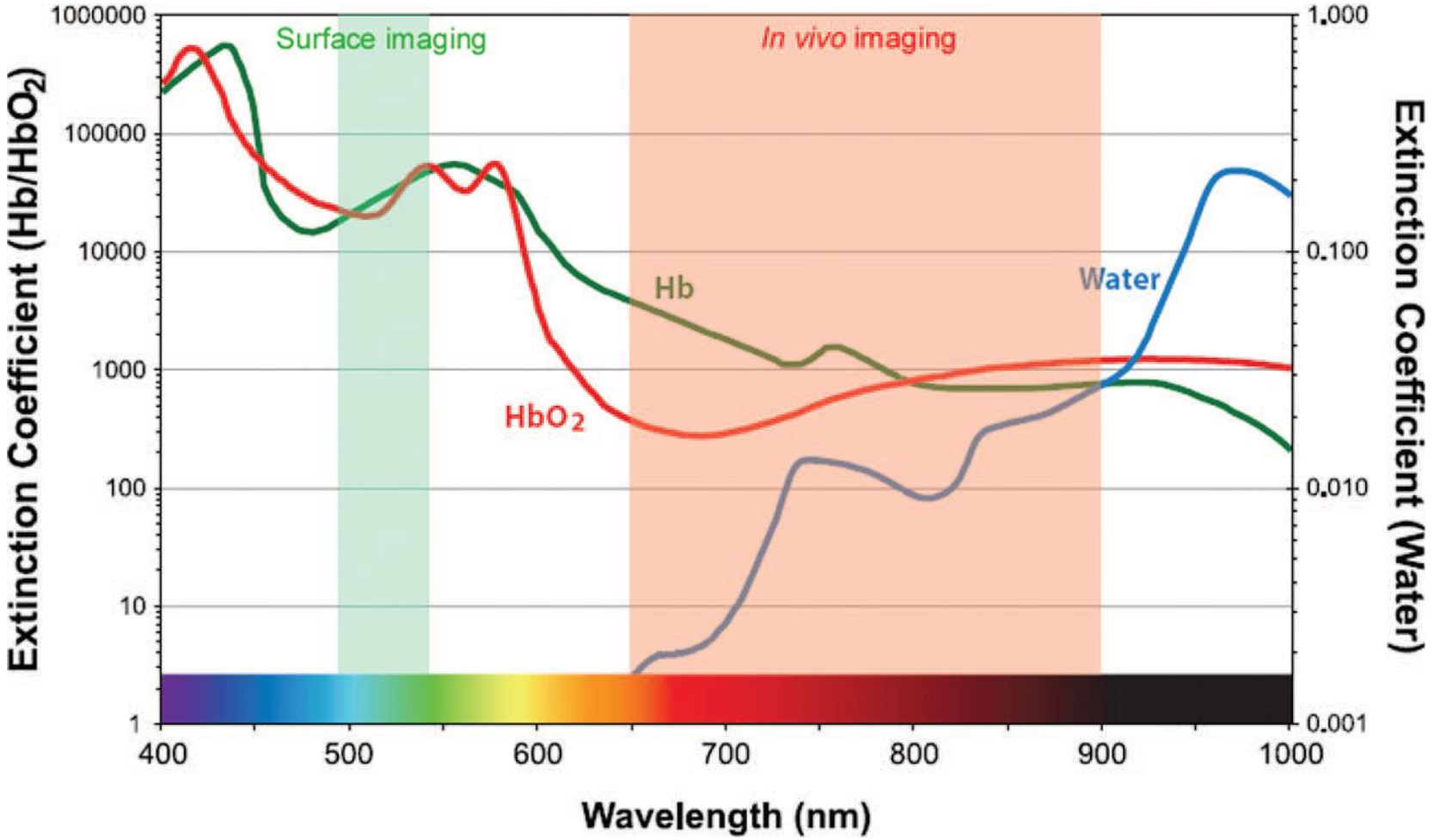
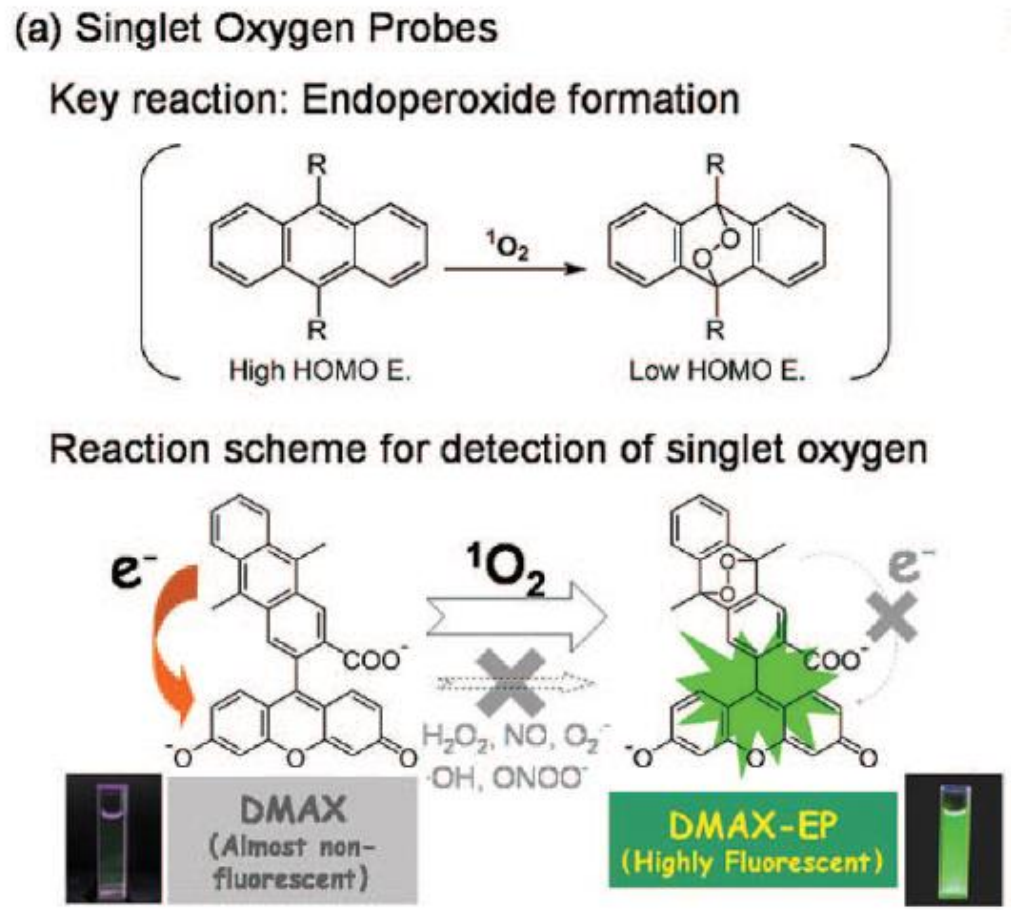
Imaging ottico

- Sensibilità paragonabile a quella di SPECT e PET
- Consente imaging molecolare (*in vitro, ex-vivo*)
- Applicazioni in chirurgia guidata ed endoscopia
- Possibilità di agenti s*witchable* (*responsive*)
- Possibilità di *time-resolved detection* (autofluorescenza di fondo)
- No quantificazione

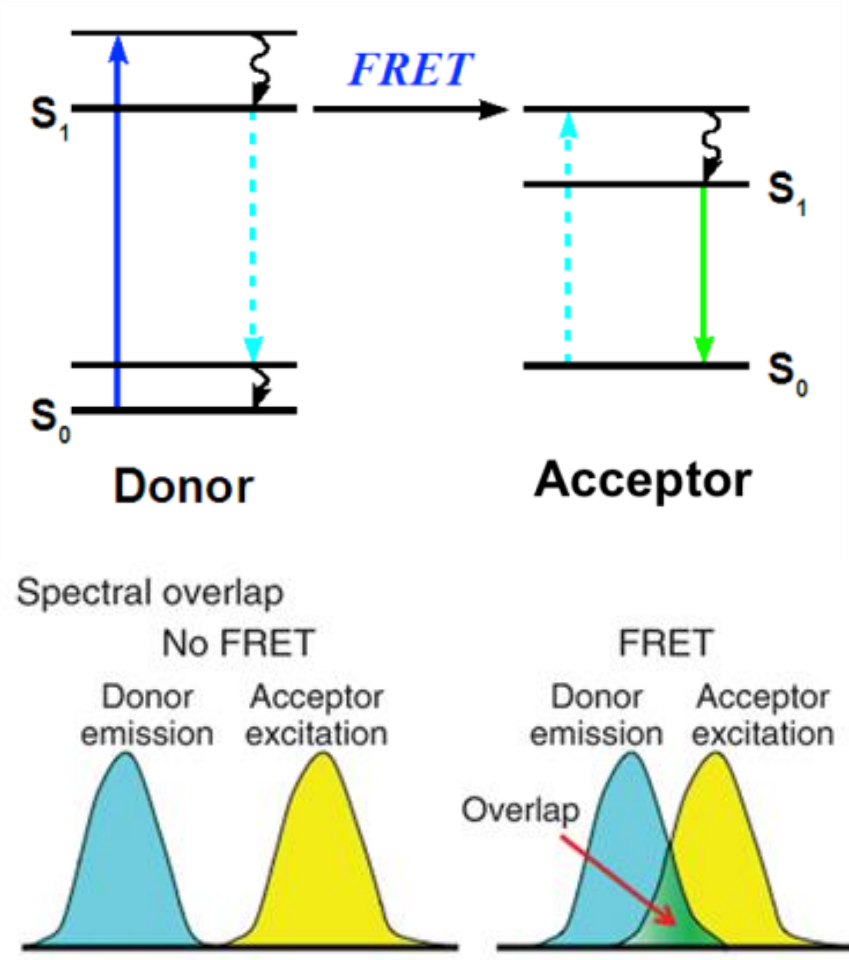
- Window
- Stokes shift
- Brightness
- Stability



Esempio di *switchable fluorescent probe* sensore di $^1O_2$

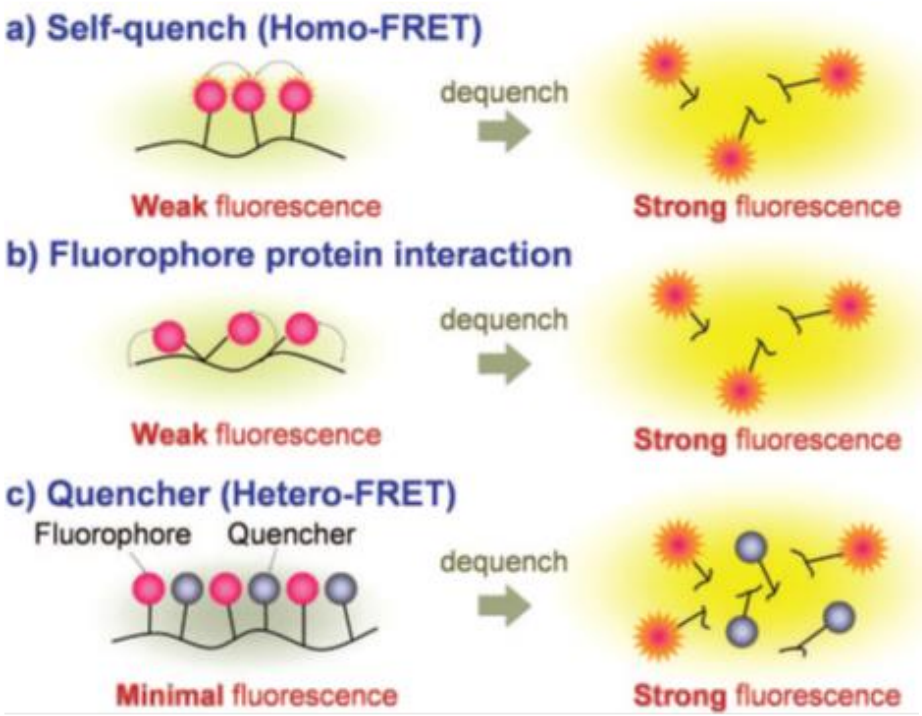


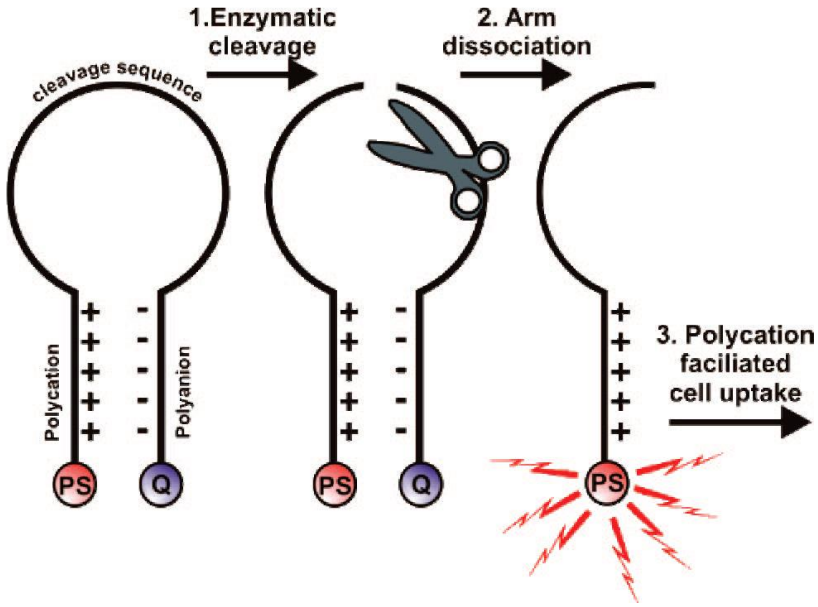
FRET *fluorescence – resonance energy transfer*

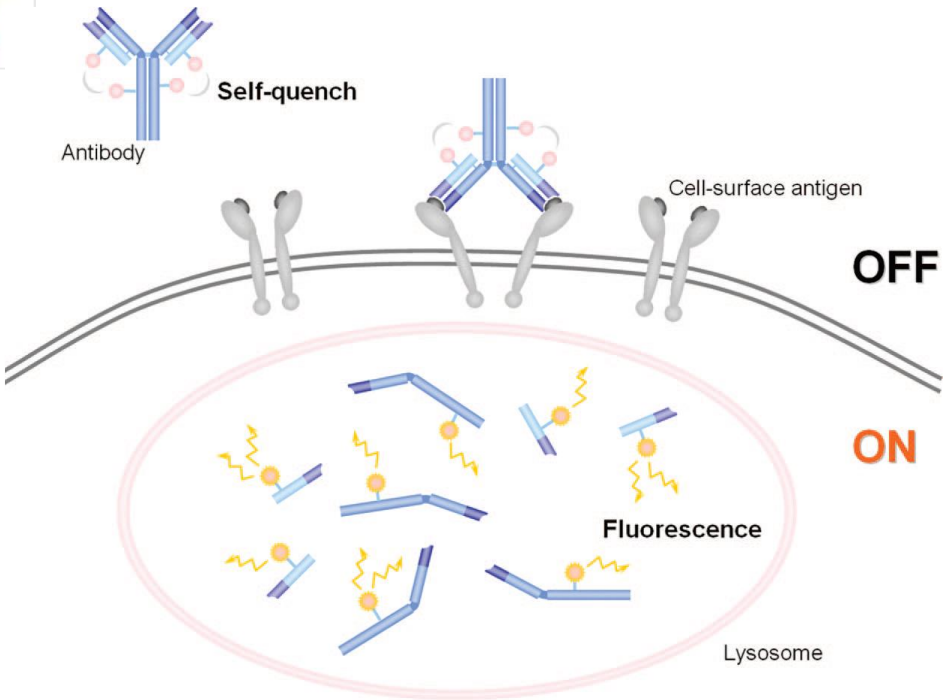


$1/r^6$

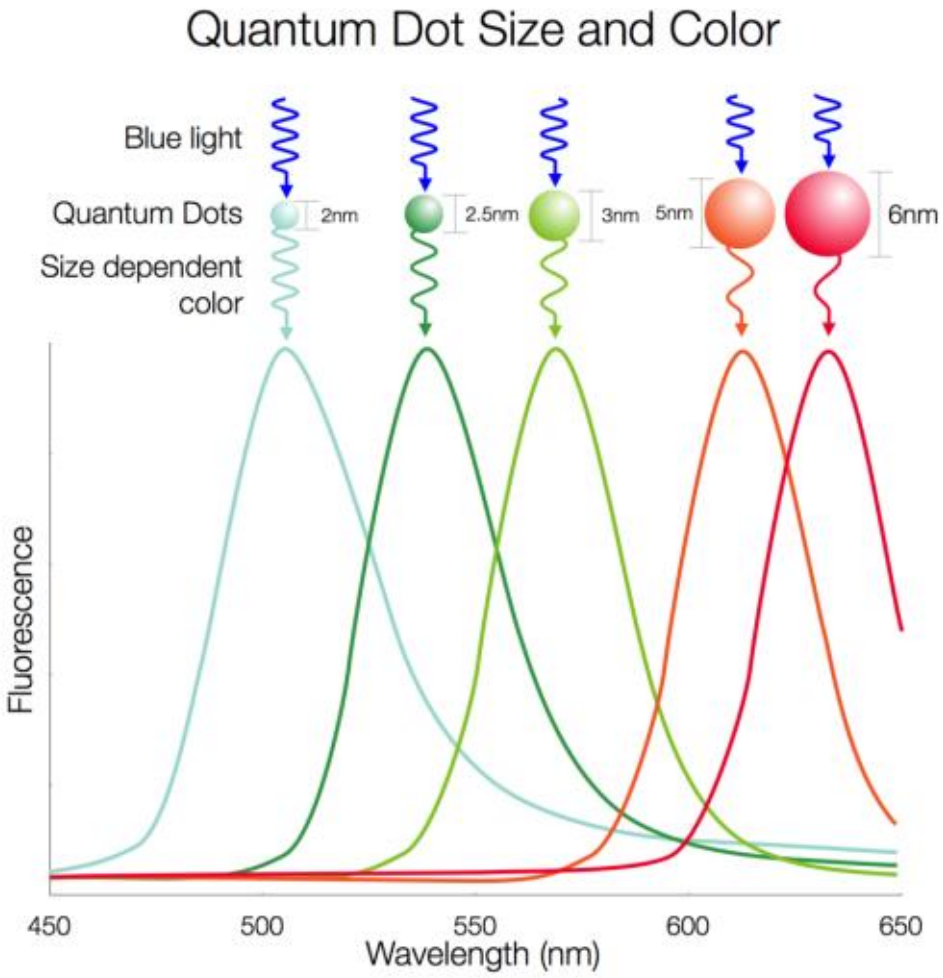
Il FRET è attivo solo quando i due cromofori distano fra loro pochi nanometri (<10 nm) e hanno la giusta orientazione reciproca.


a) Self-quench (Homo-FRET)
dequench
Weak fluorescence
Strong fluorescence
b) Fluorophore protein interaction
dequench
Weak fluorescence
Strong fluorescence
c) Quencher (Hetero-FRET)
Fluorophore
Quencher
dequench
Minimal fluorescence
Strong fluorescence


1.Enzymatic cleavage
2. Arm dissociation
cleavage sequence
Polycation
Polyanion
PS
Q
3. Polycation faciliated cell uptake


Antibody
Self-quench
Cell-surface antigen
OFF
ON
Fluorescence
Lysosome

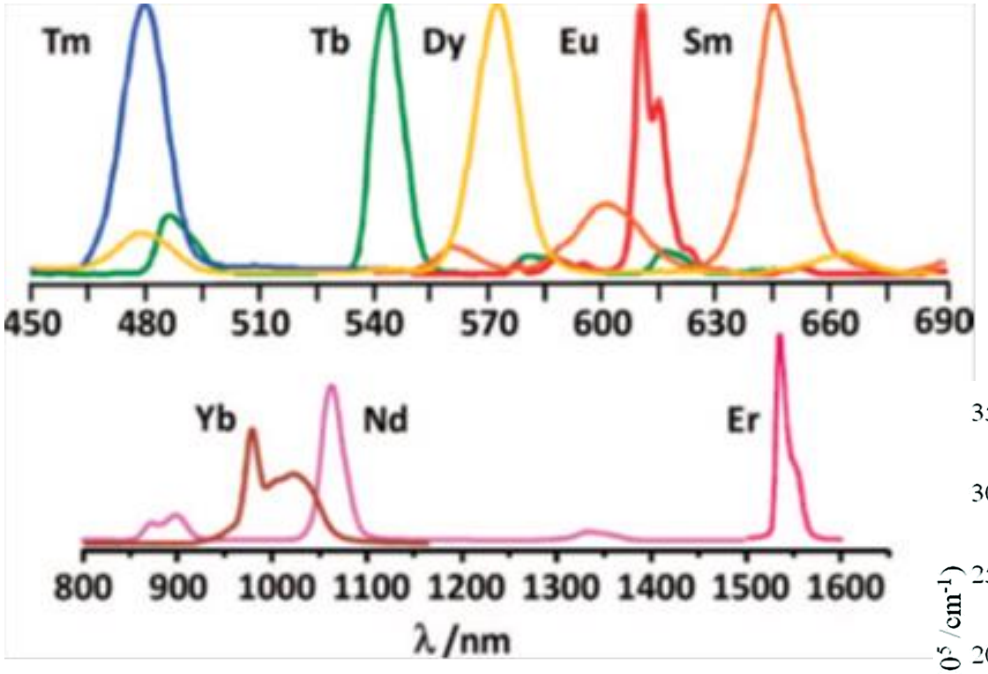
quantum dots (QD)
nano-cristalli di semiconduttori (e.g. CdSe)



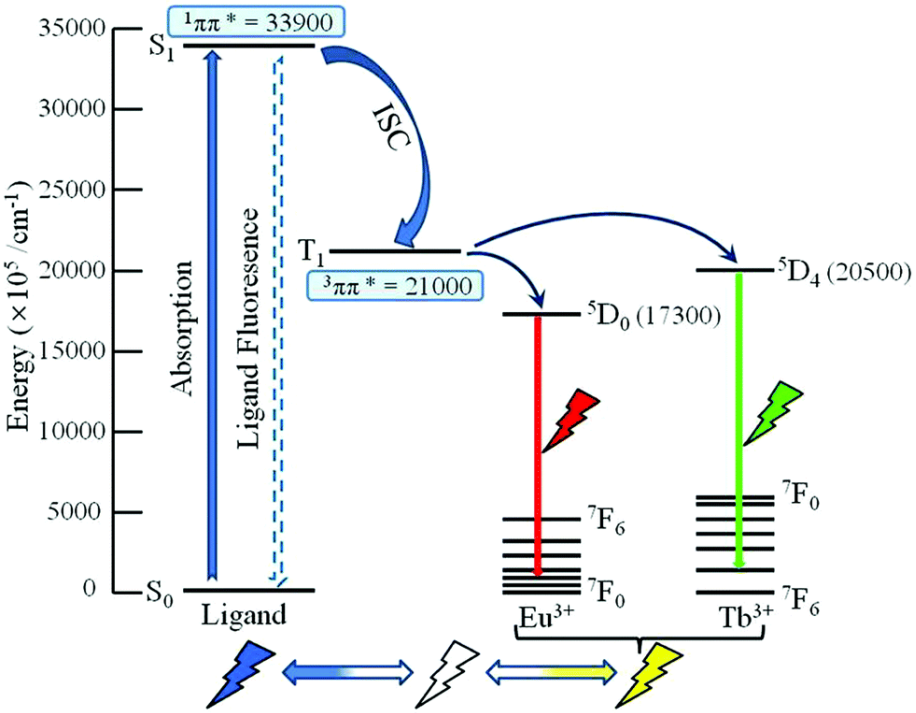
Ø 2 – 10 nm

Ampio intervallo di frequenze di eccitazione, banda di emissione stretta, molto intensa e modulabile con le dimensioni del QD

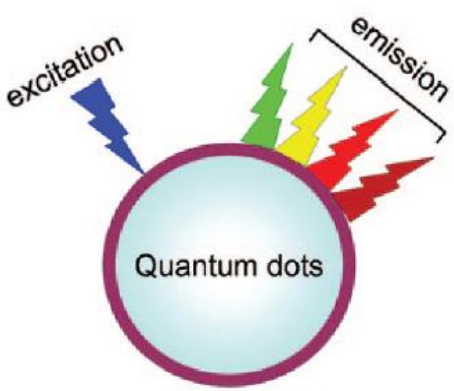
Complessi dei lantanidi

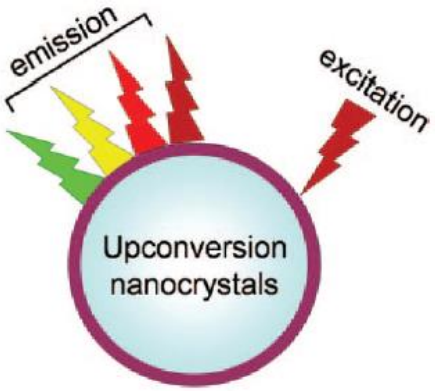


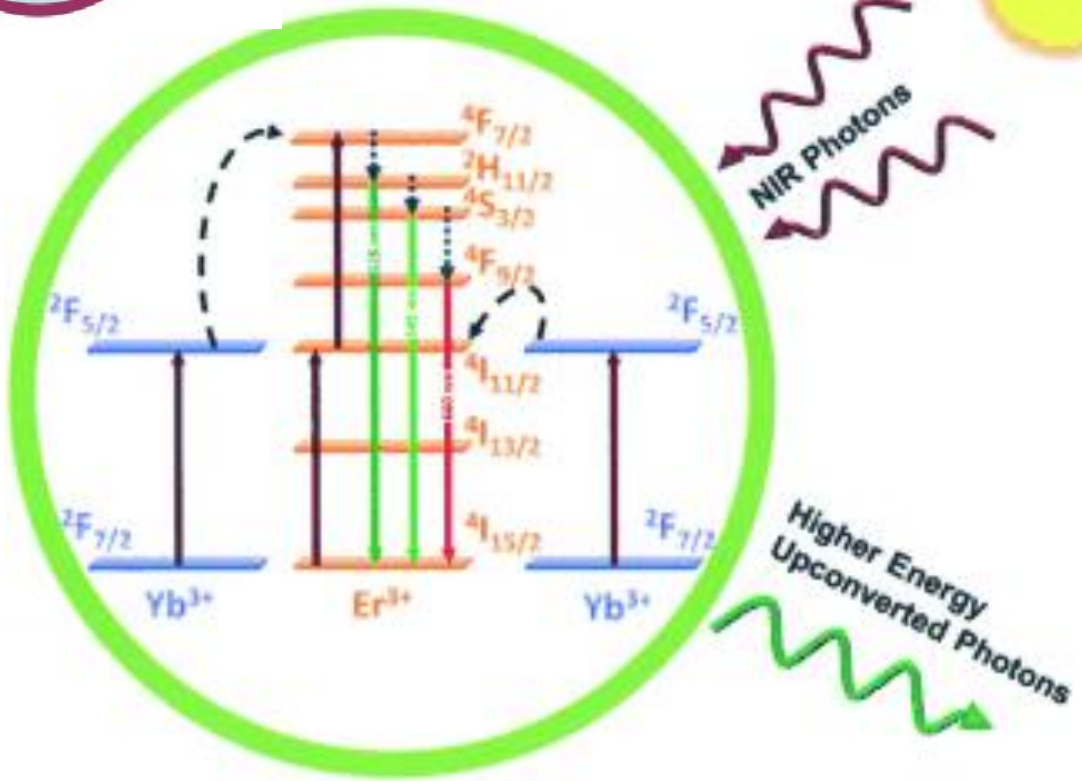
Effetto antenna dei leganti



Upconverting QDs e LnNPs

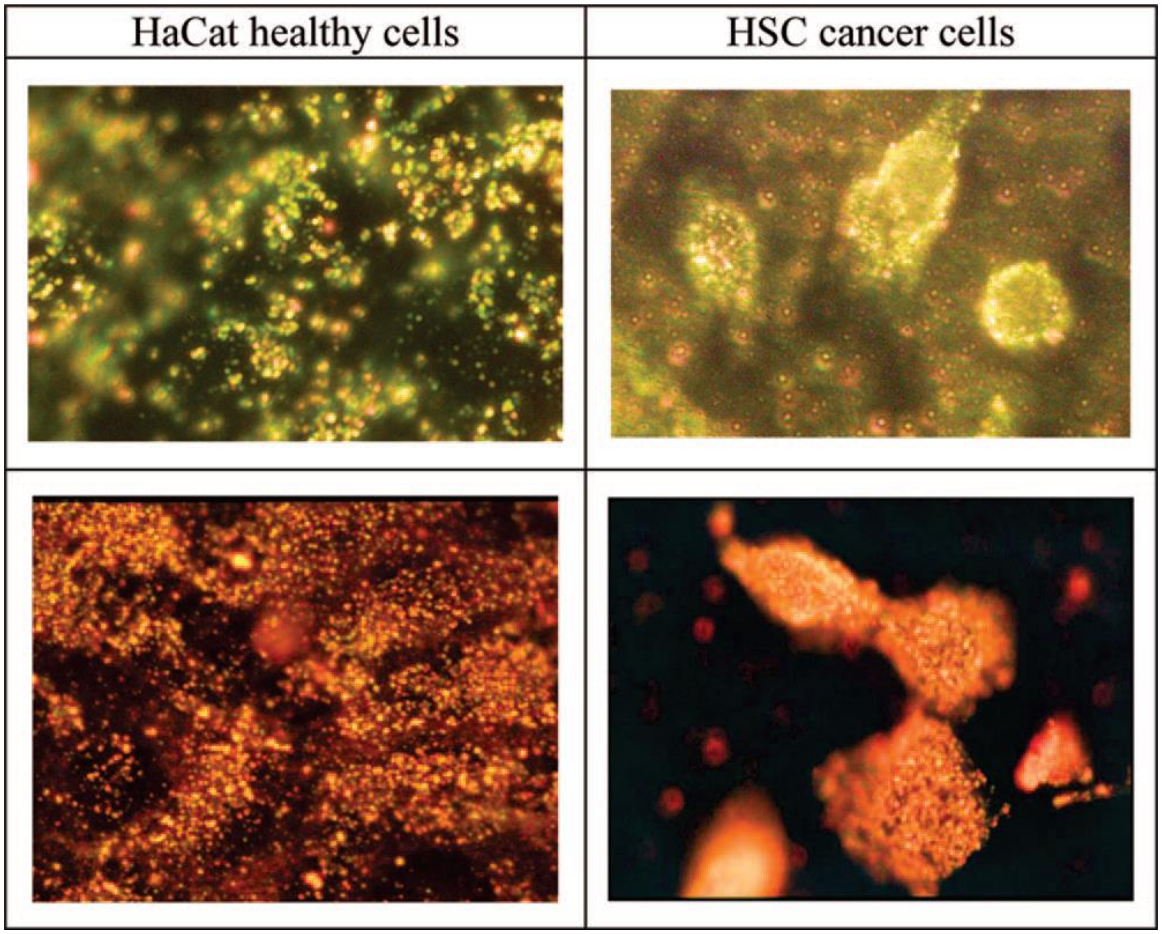






Dark-field fluorescence imaging con AuNP

scattered light



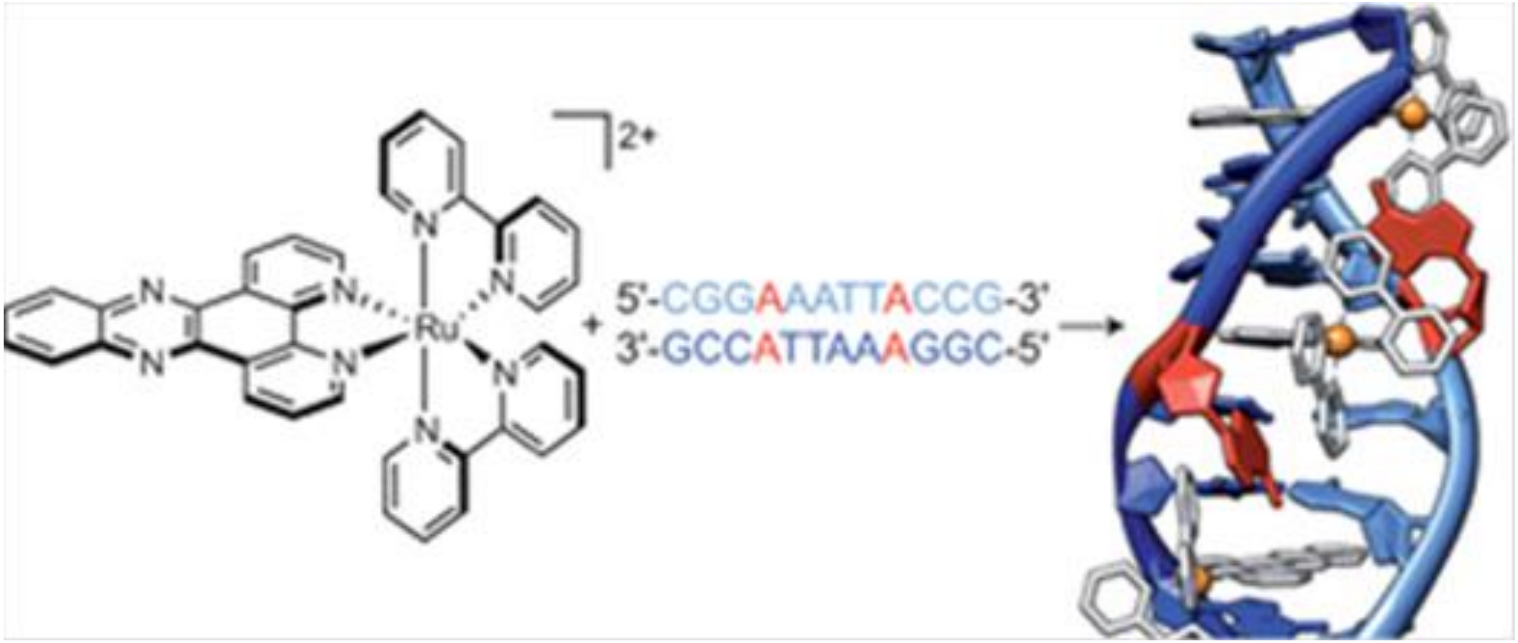
Au nanospheres

Au nanorods

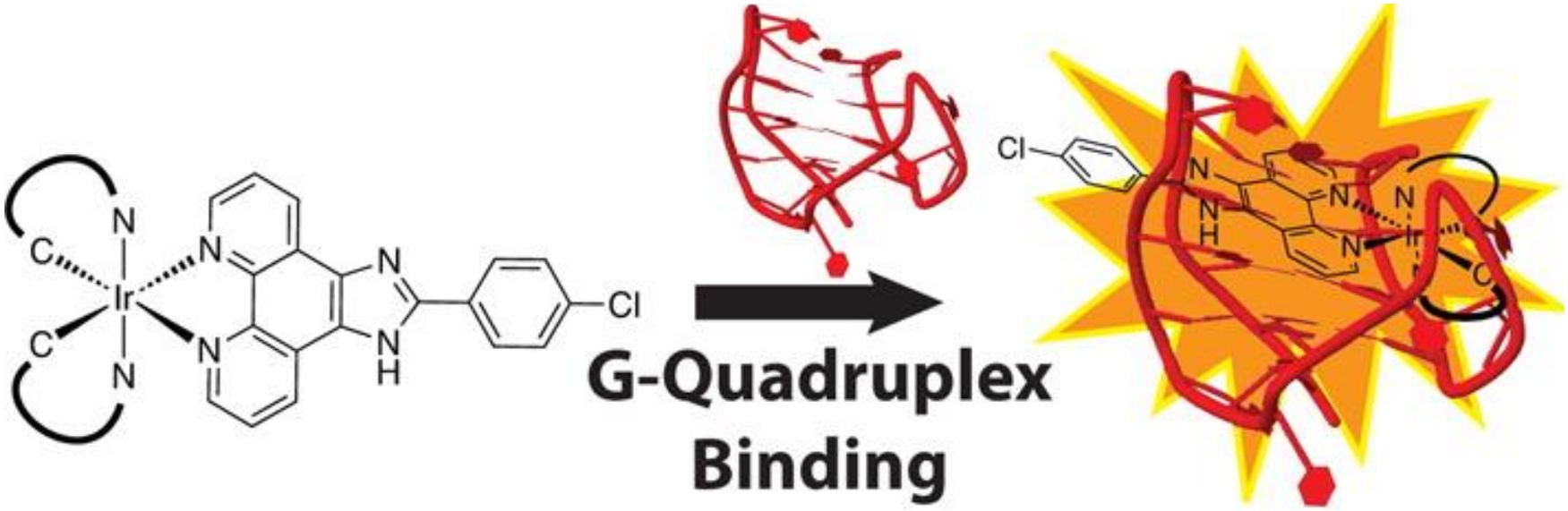
AuNP coniugate a anticorpi anti-EGFR

EGFR = *epidermal growth factor receptor*, marcatore tumorale

Complessi polipiridilici di Ru(II) come *DNA light switch*

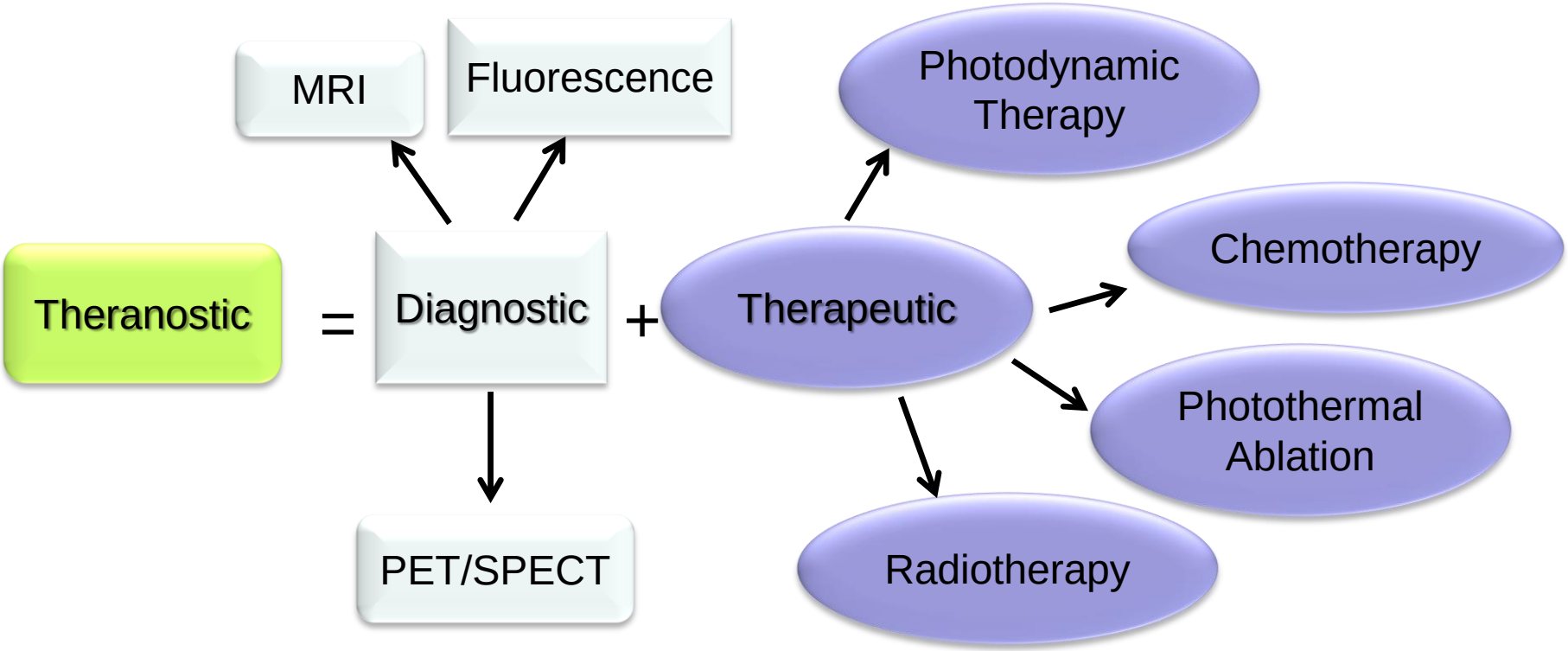


G-quadruplex sensing

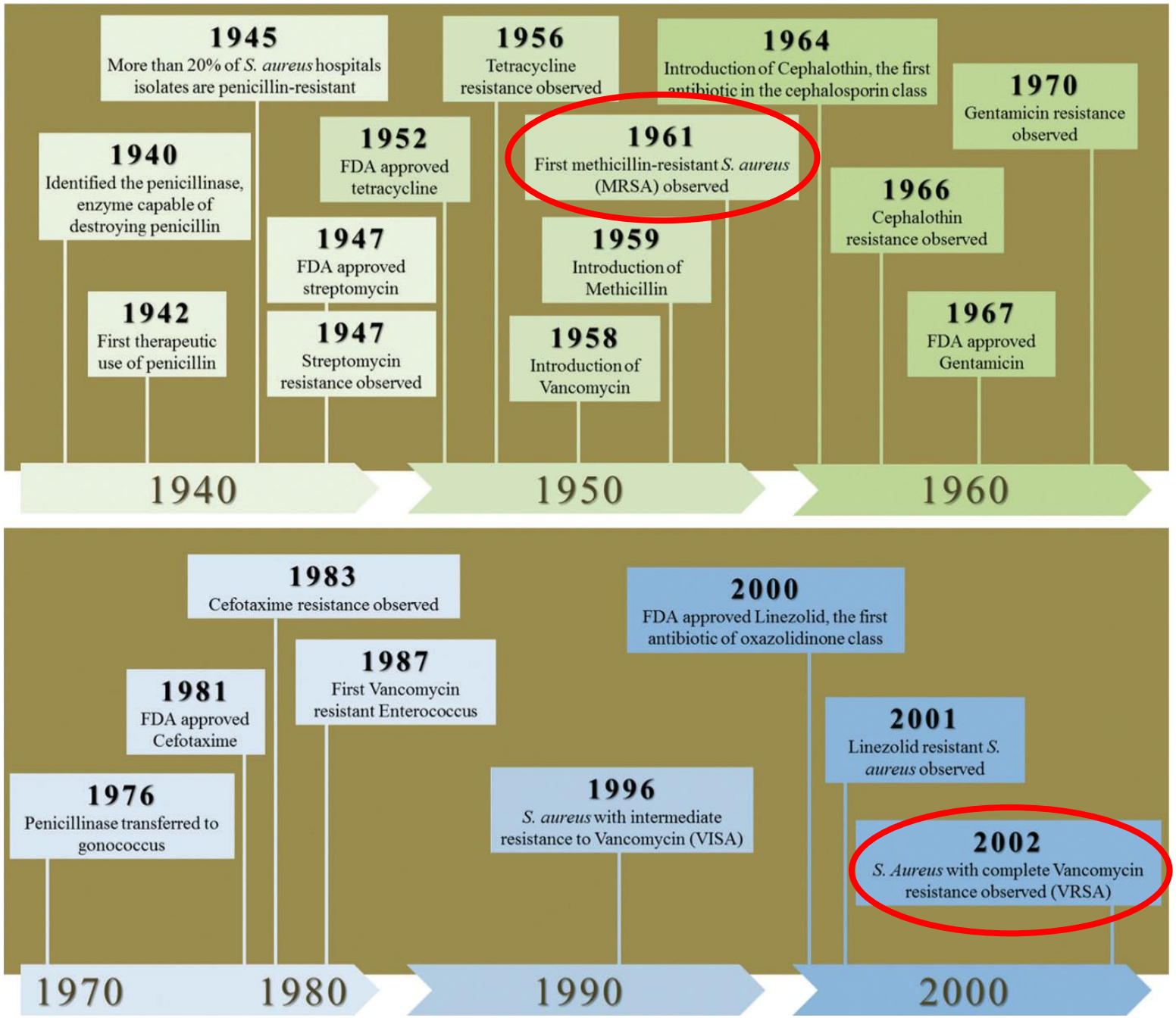


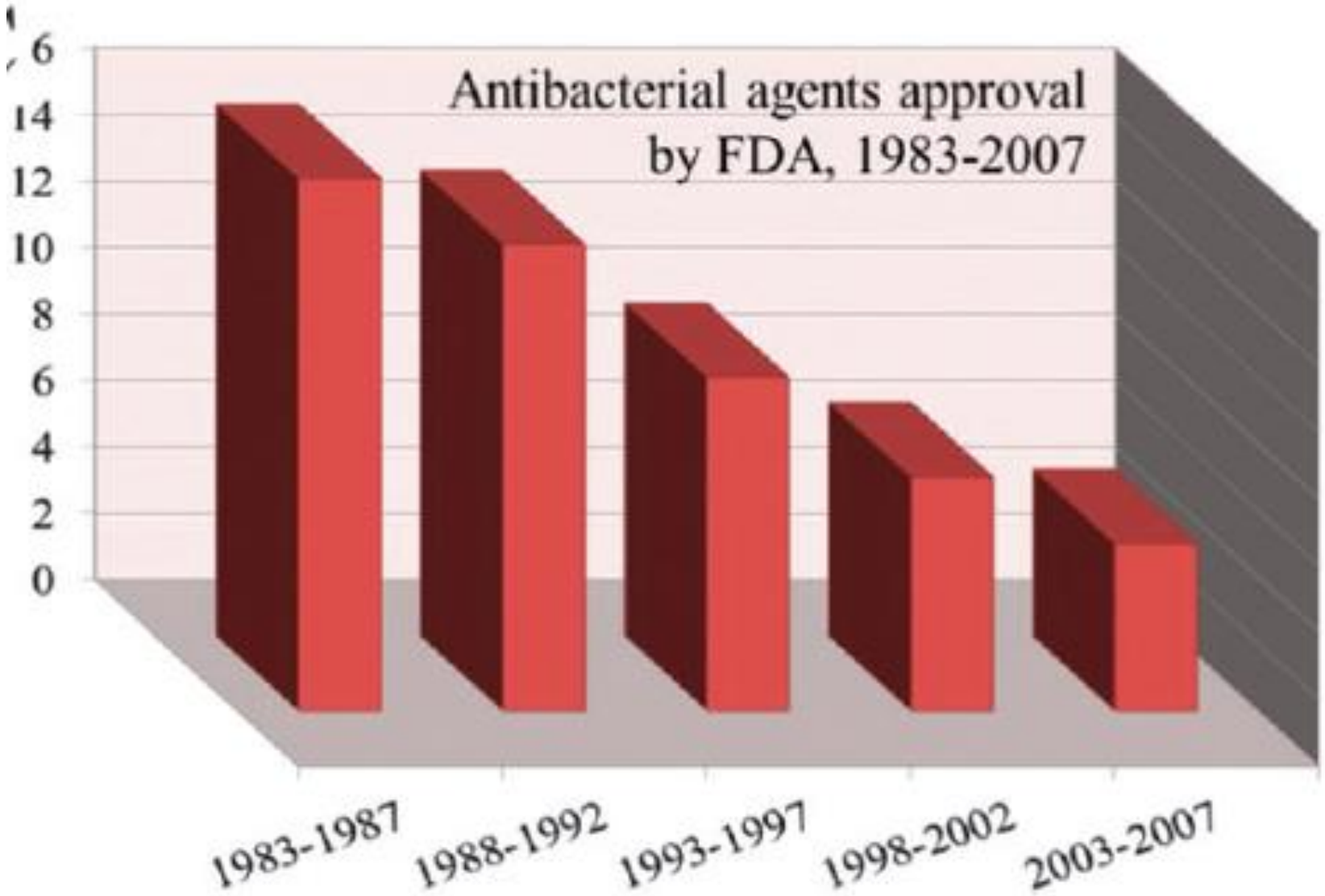
Sviluppi futuri

Multimodal imaging agents and theranostics

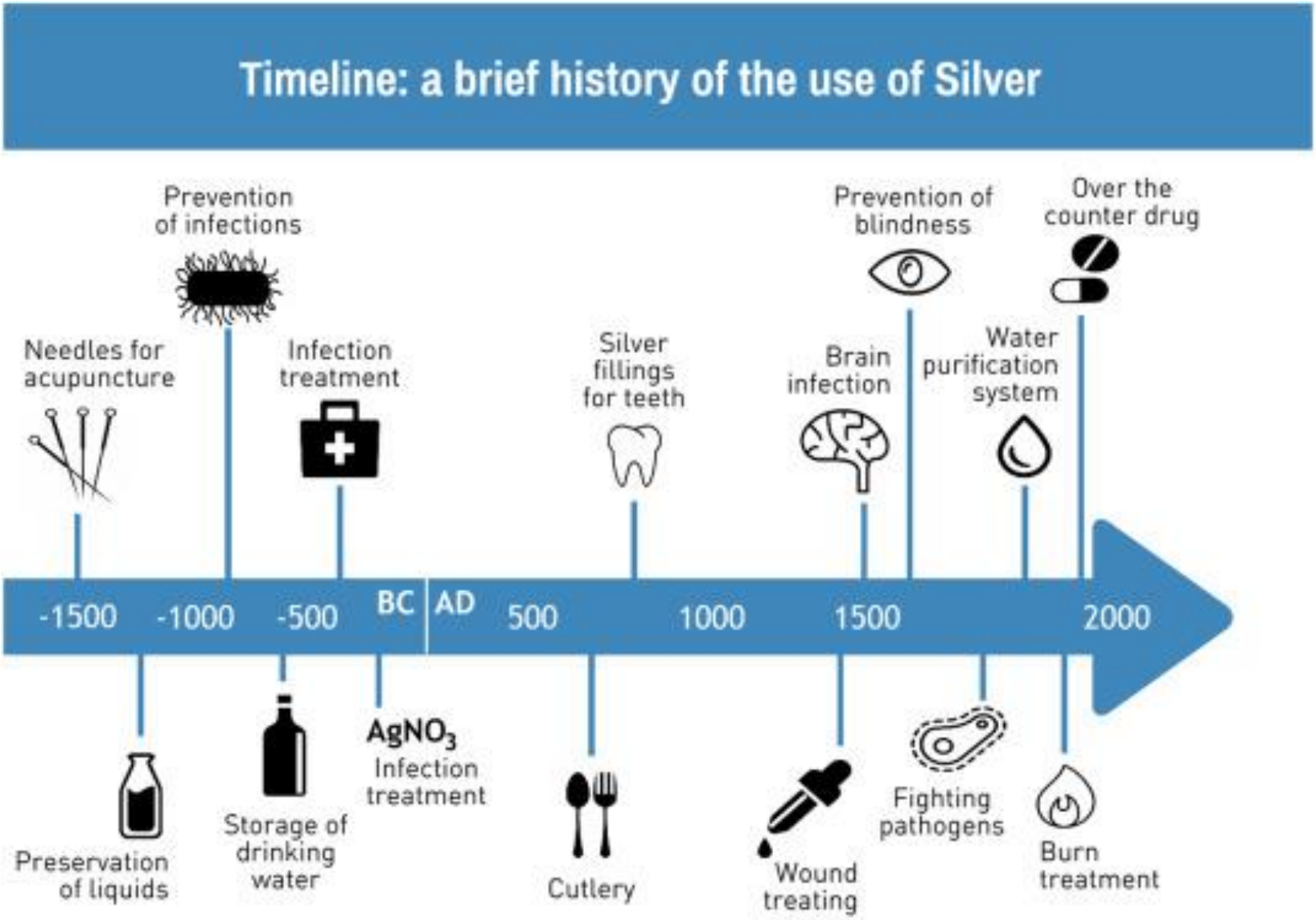


Antibacterials


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)

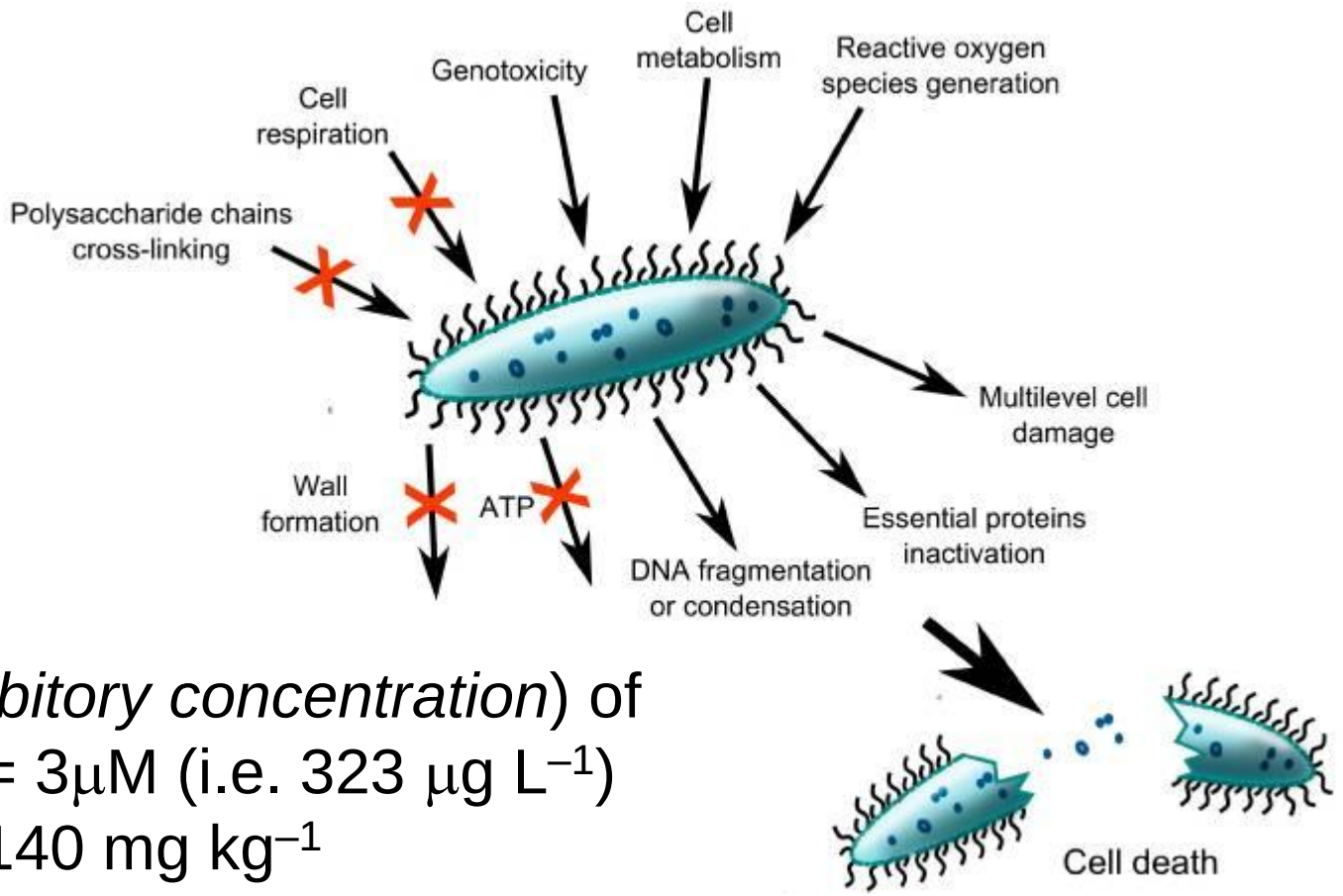

Antibacterial agents approval
by FDA, 1983-2007
16
14
12
10
8
6
4
2
0
1983-1987
1988-1992
1993-1997
1998-2002
2003-2007

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

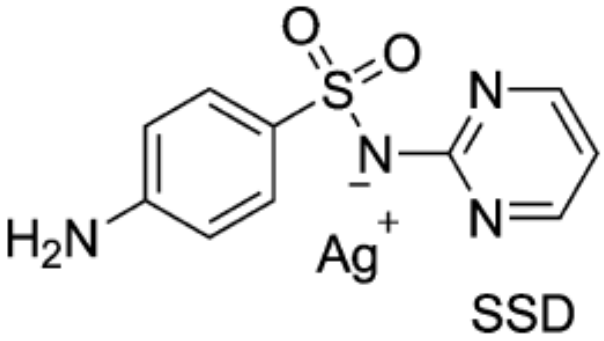


MIC (*minimal inhibitory concentration*) of $AgNO_3$ to *E. coli* = 3μM (i.e. 323 μg L^{-1})

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

WHY CHOOSE SILVER PLATING FOR MEDICAL DEVICES?

Silver salts



SSD

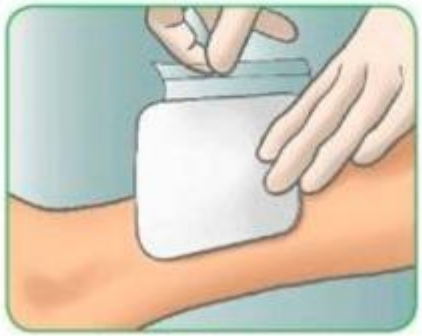
silver sulfadiazine

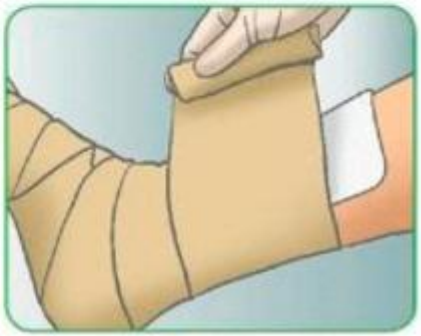

Soluzione salina spray
con Argento Cloruro e Aloe Vera
Saline solution spray
with Silver Chloride and Aloe Vera
VULNOMED
per la Detersione, l'Irrigazione
e l'Idratazione della cute
è un prodotto
eurofarm

Silver nanoparticles (AgNPs)

Estimated 2014 production of commercial AgNPs: 320 t

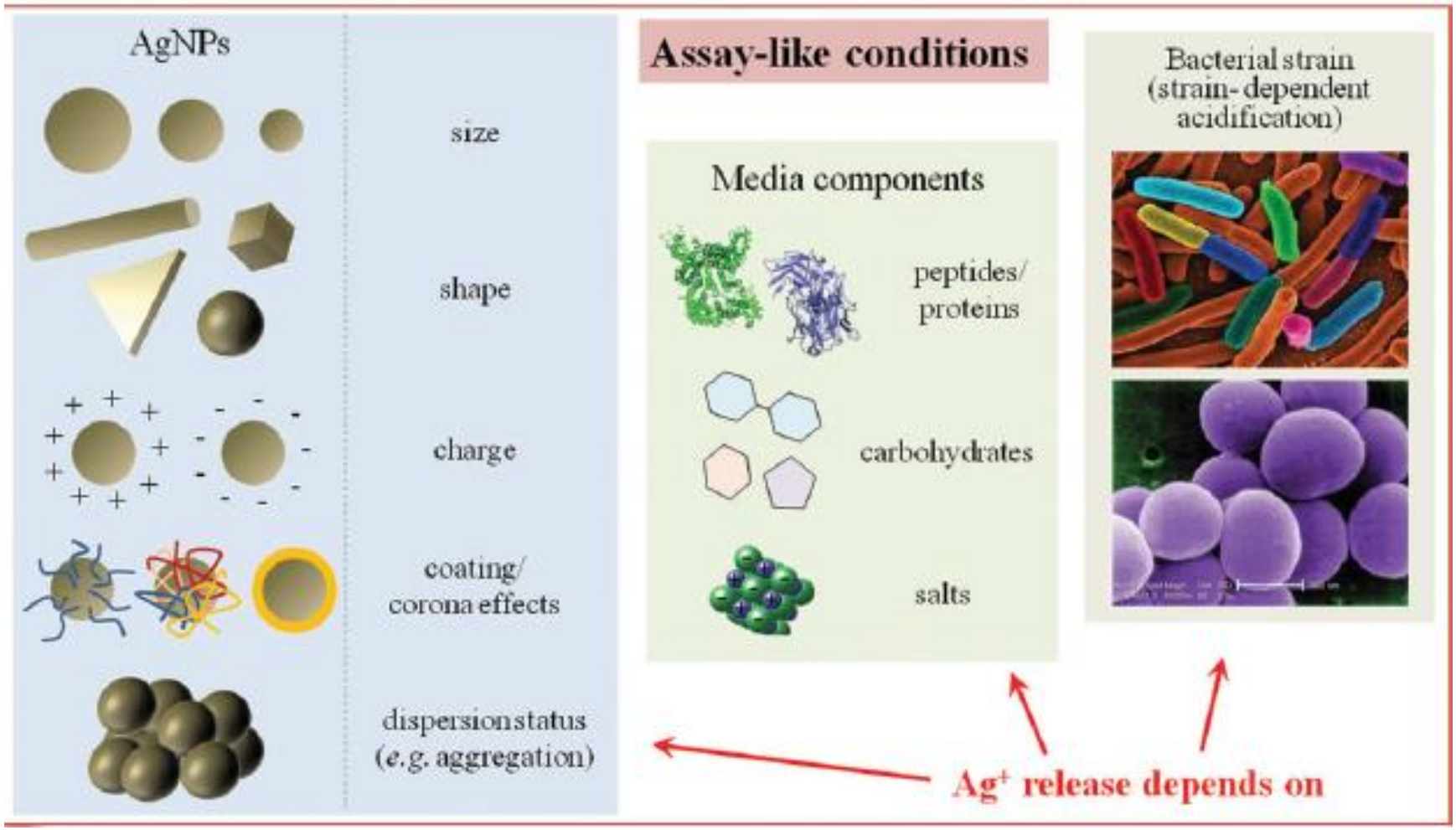

Mepilex® Ag
Mepilex® Ag
10 x 10 cm/4 x 4 in
Safetac
Safetac
TECHNOLOGY



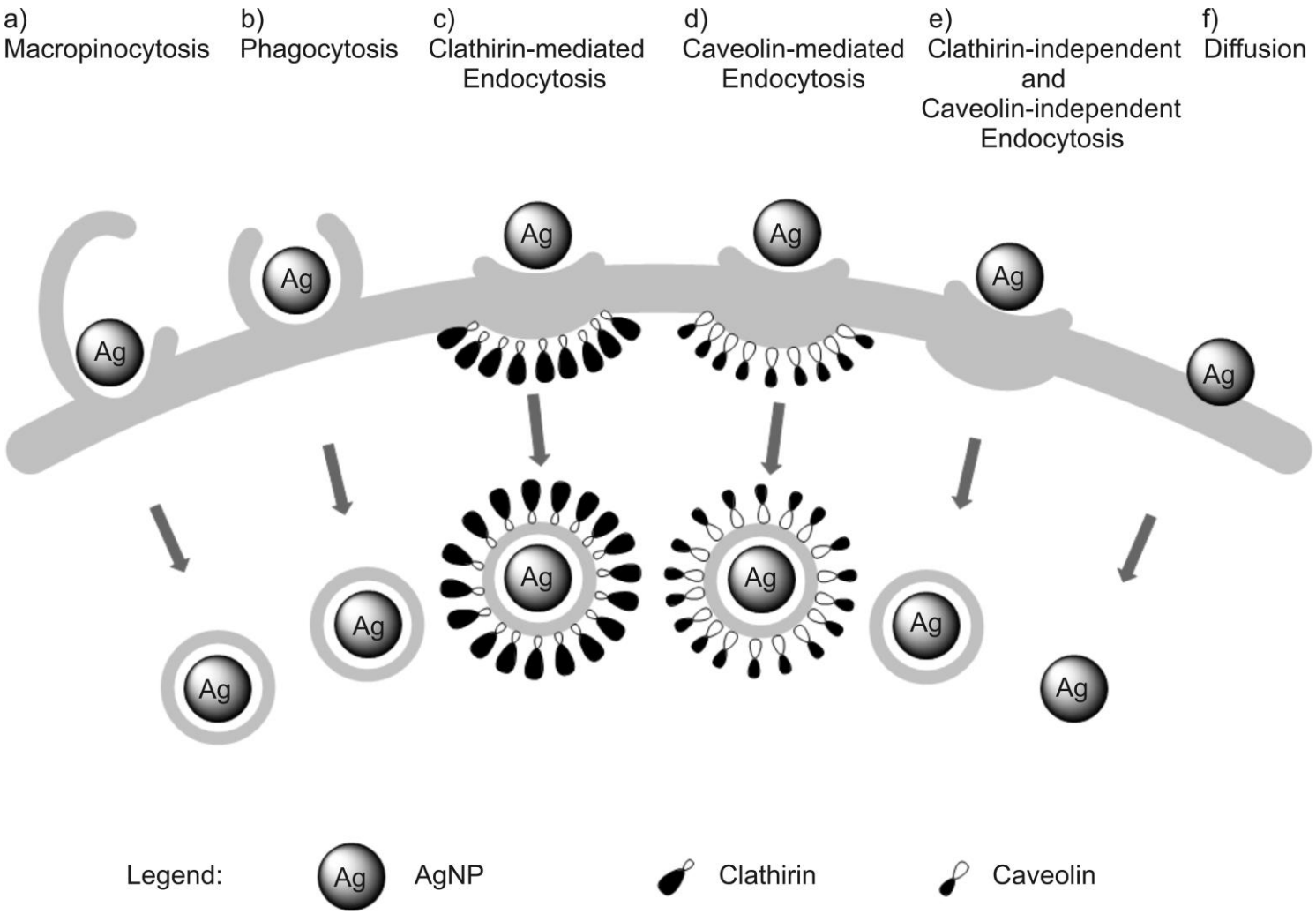



Elastoplast
ANTIBACTERIAL
FABRIC
REDUCES THE RISK OF INFECTION
Extra flexible
20 Plasters
antibacterial
SILVER
NIVEA MEN
SILVER PROTECT
SHOWER GEL
BODY, FACE & HAIR
NIVEA MEN
48h
SILVER PROTECT
DYNAMIC POWER
NIVEA MEN
48h
SILVER PROTECT

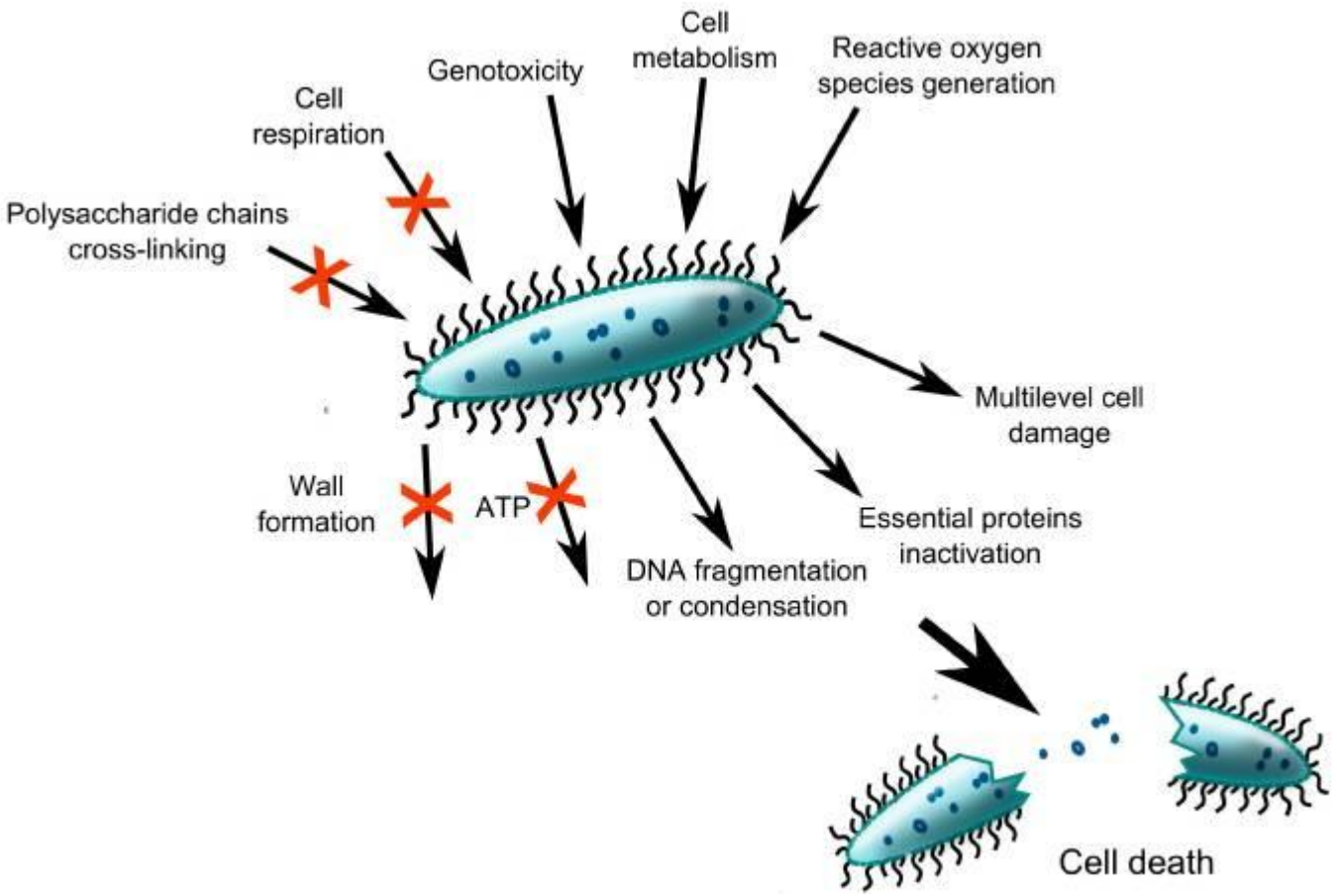
Ag^+ release from AgNPs



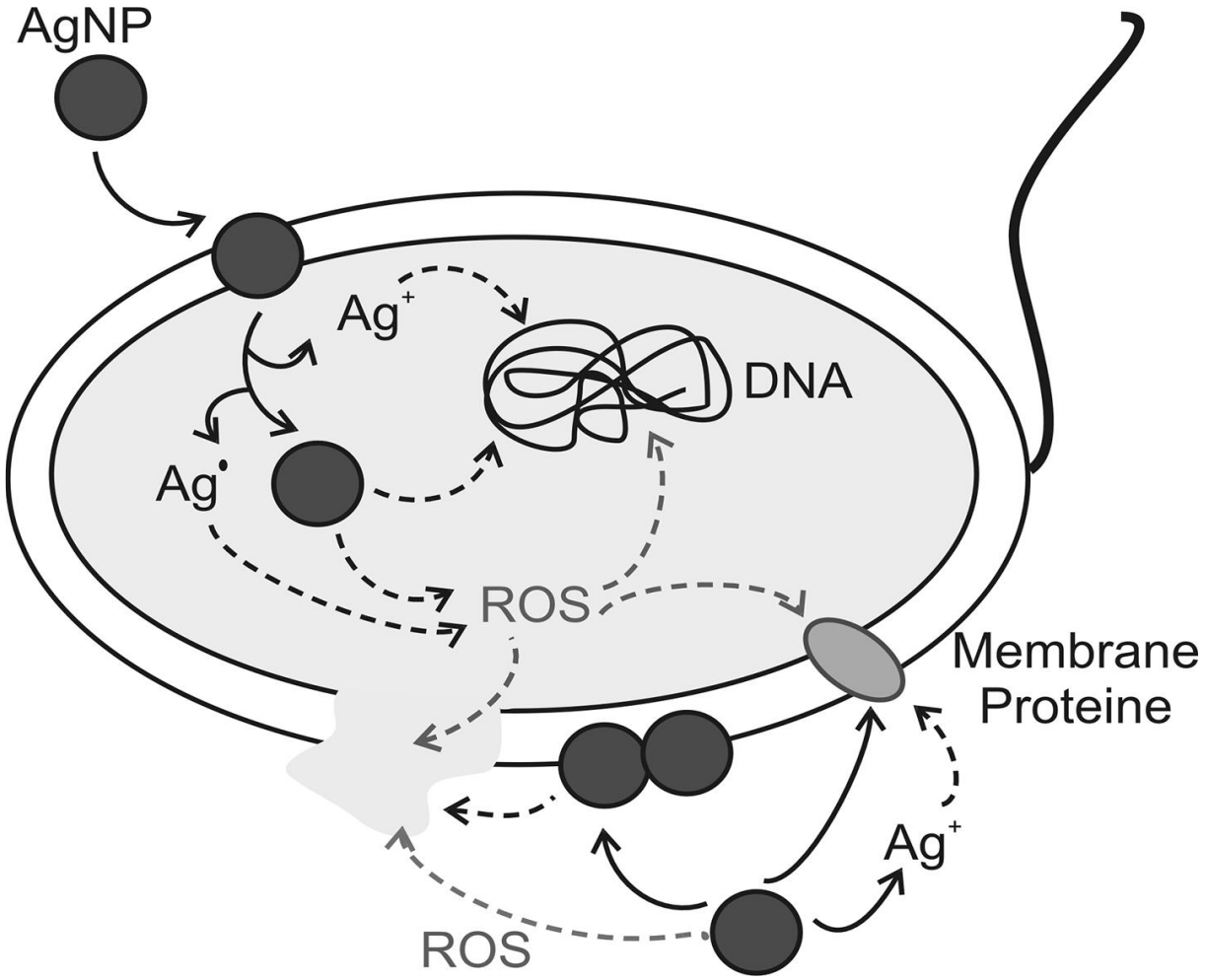
Uptake of AgNPs



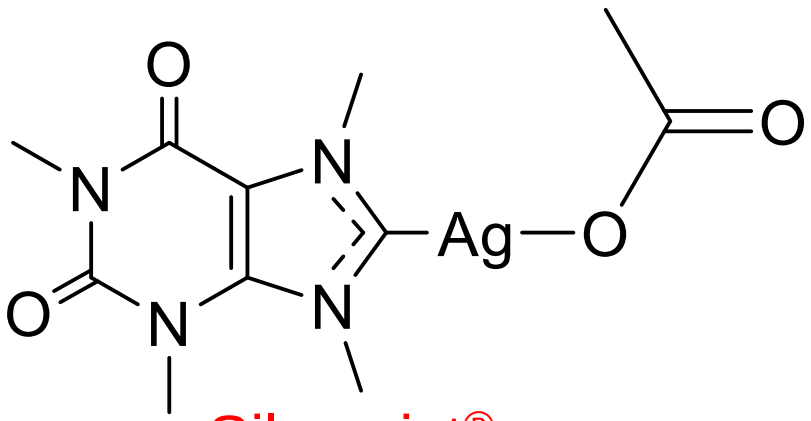
Multiple mechanism of action of Ag^+ ions



Multiple mechanism of action of AgNP's

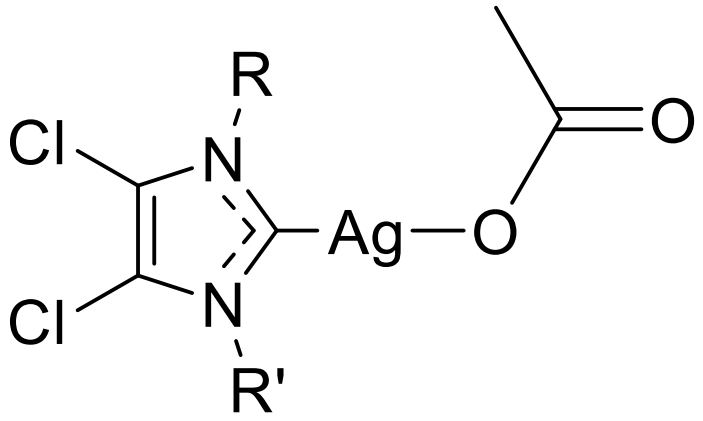


Antibacterial Ag-NHC compounds



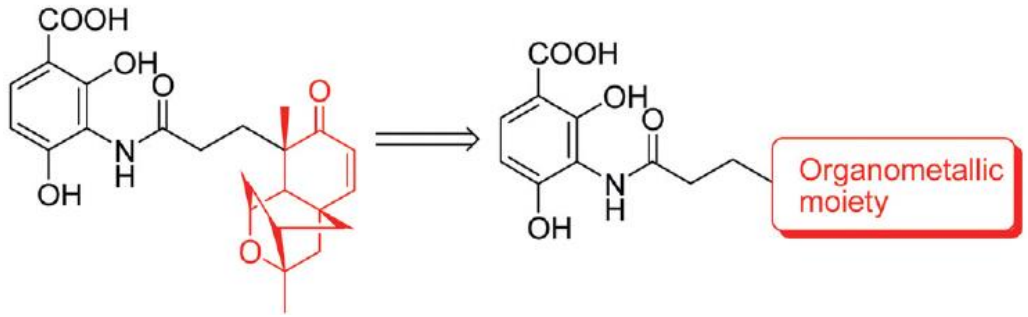
Silvamist®

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

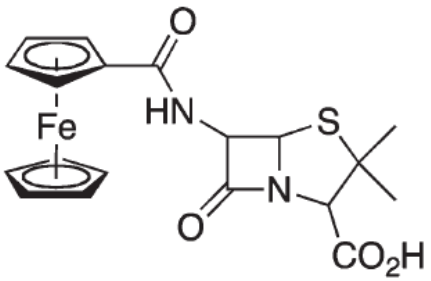


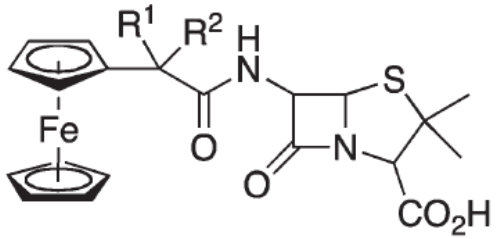
Improved stability to hydrolysis due to the electron-withdrawing Cl substituents that pull electron density from the carbene

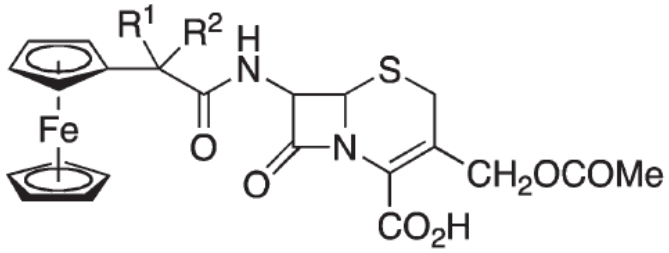
Other strategies: metal modification of known antibiotics



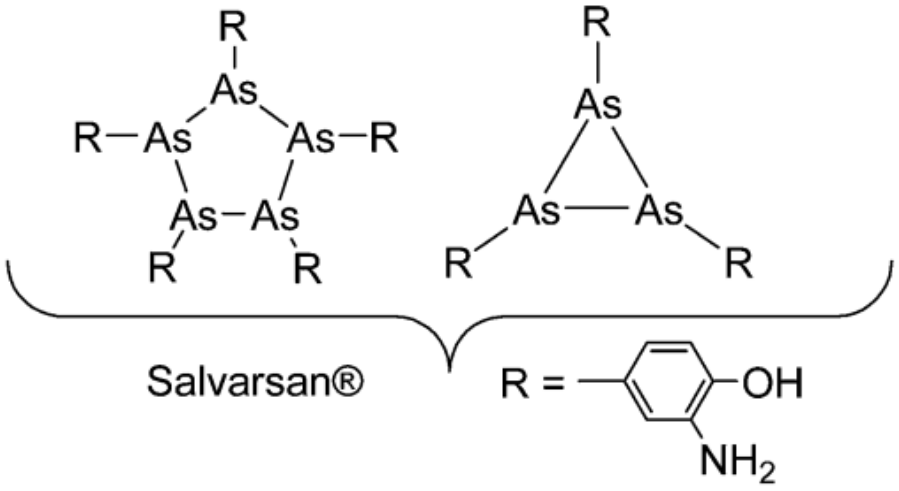
Platensimycin mimics





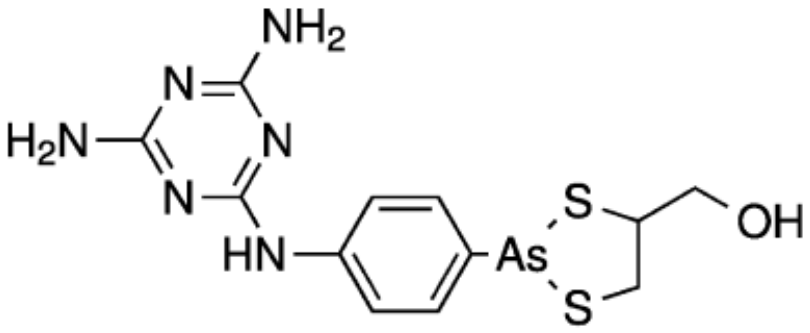


Other metals: As, Sb, Bi, Hg



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

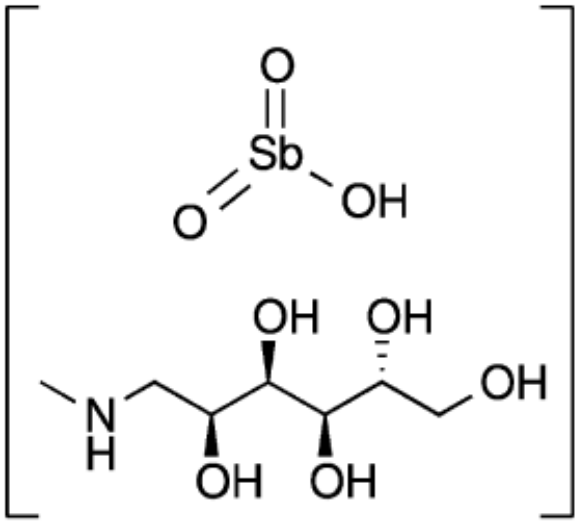
Antiparasitic compounds



melarsoprol

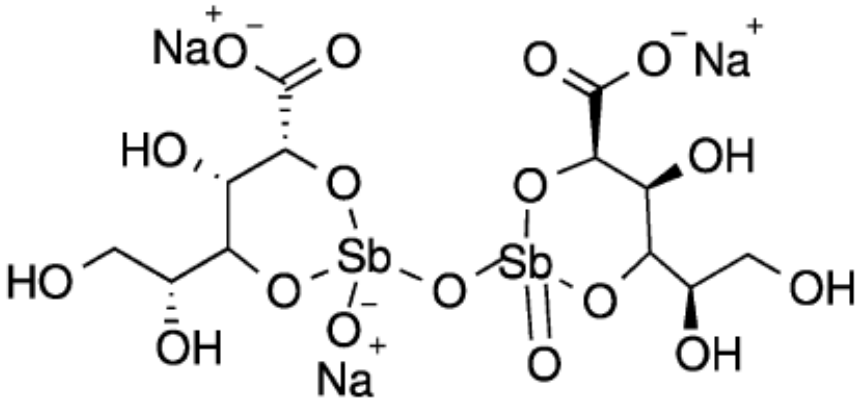
treatment of sleeping sickness (*African trypanosomiasis*)

Anti-leishmaniasis compounds



meglumine antimoniate

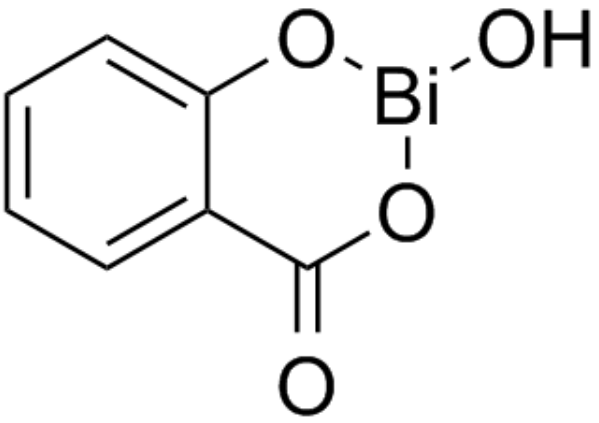
Veterinary use



sodium stibugluconate

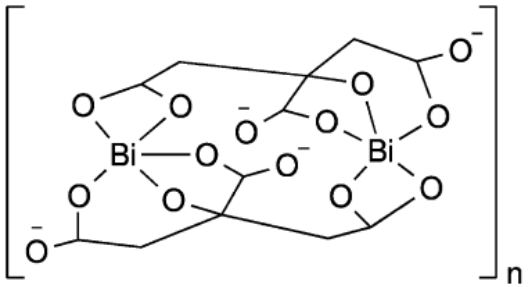
Sb, reduced to Sb(III), inhibits *trypanothione reductase*, an essential enzyme of the parasite

Infezioni da *Helicobacter pylori*

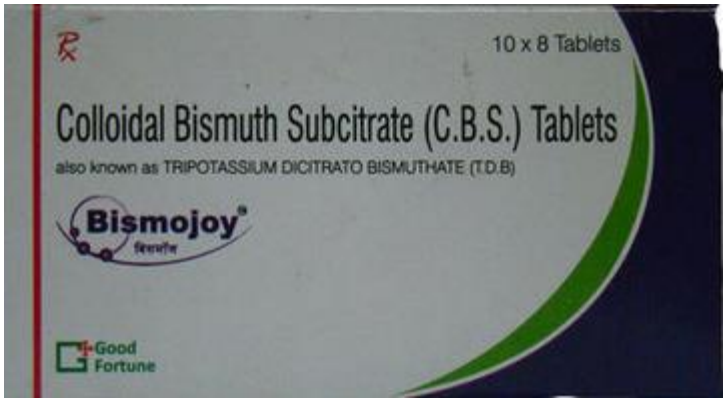


bismuth subsalicylate

The pink stuff (introduced 1901)

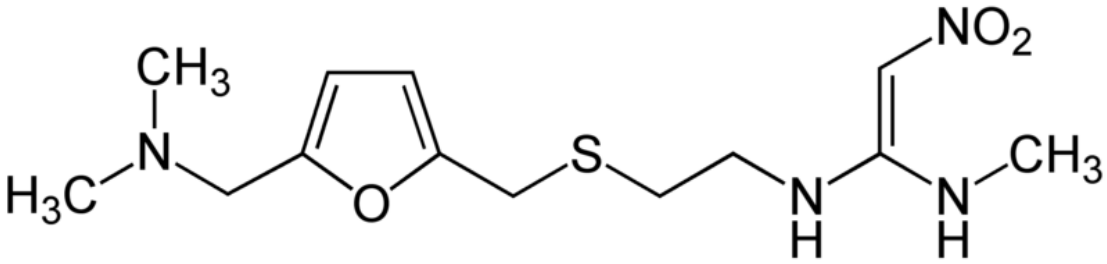


CBS



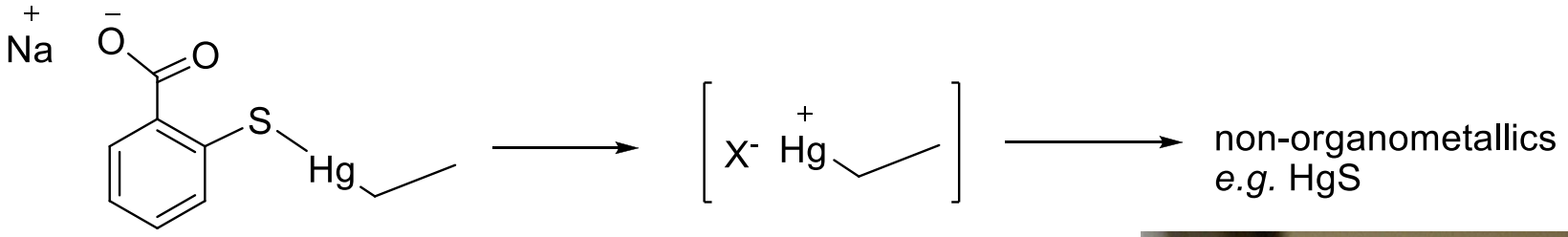
bismuto subcitrato colloidale

Infezioni da *Helicobacter pylori*



ranitidine bismuth citrate

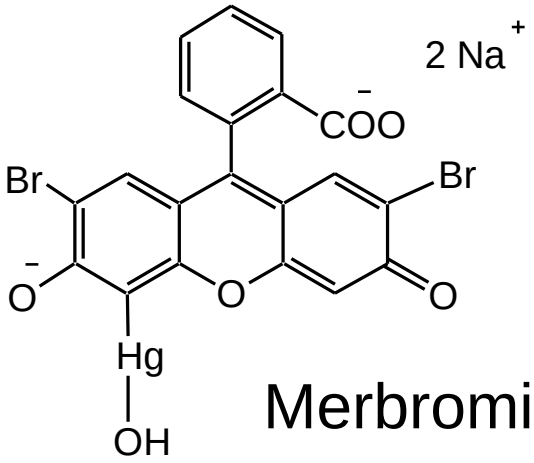
Antibacterial mercury compounds



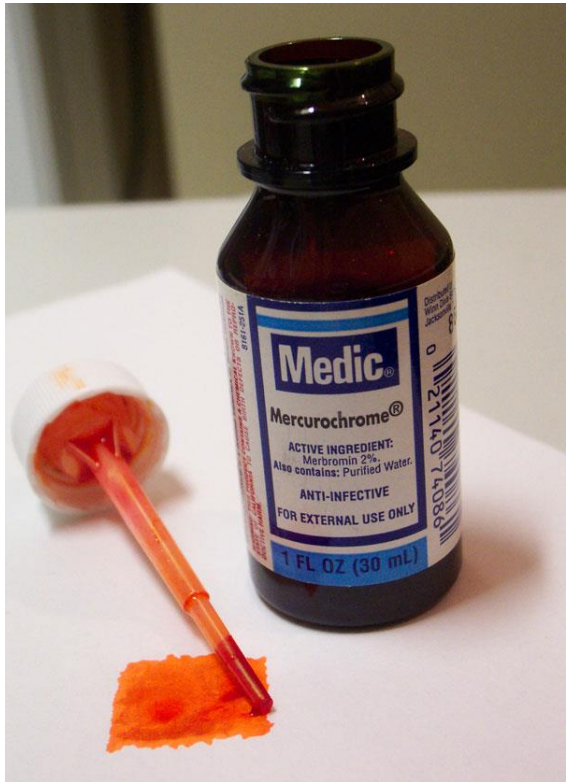
Thiomersal

ethyl mercury

vaccine adjuvant



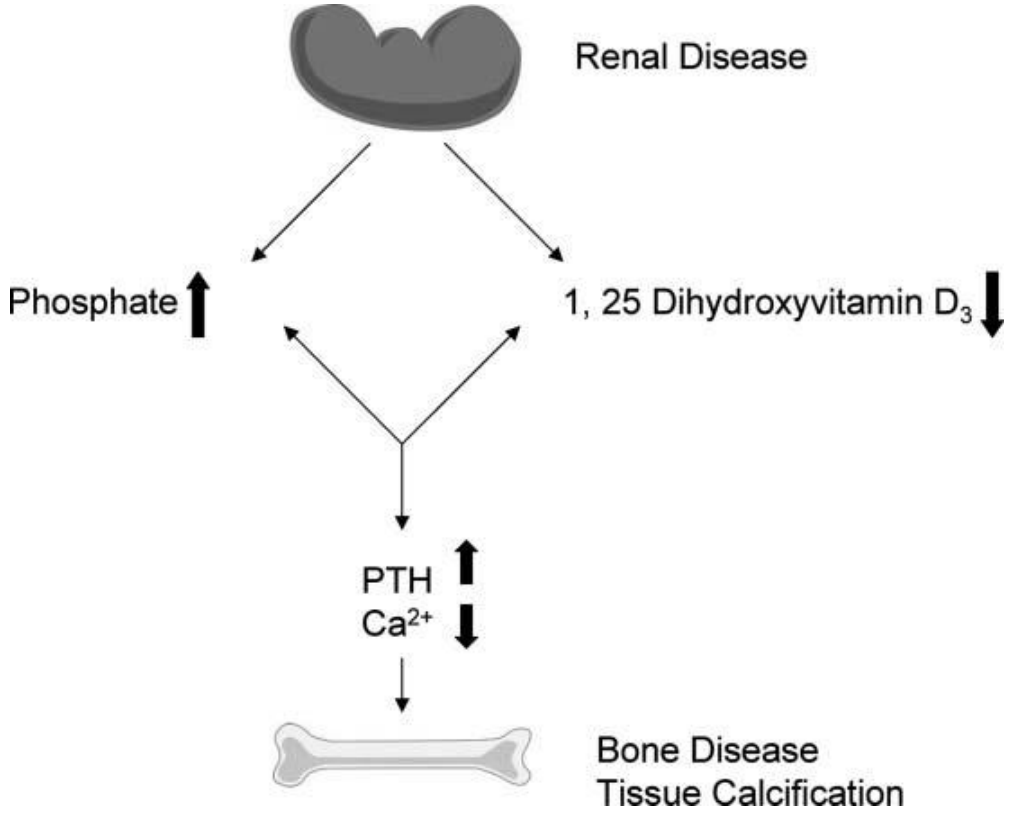
Merbromin (mercurochrome)



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

Calcium phosphate binders (e.g. calcium carbonate or calcium acetate) 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 salt 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.