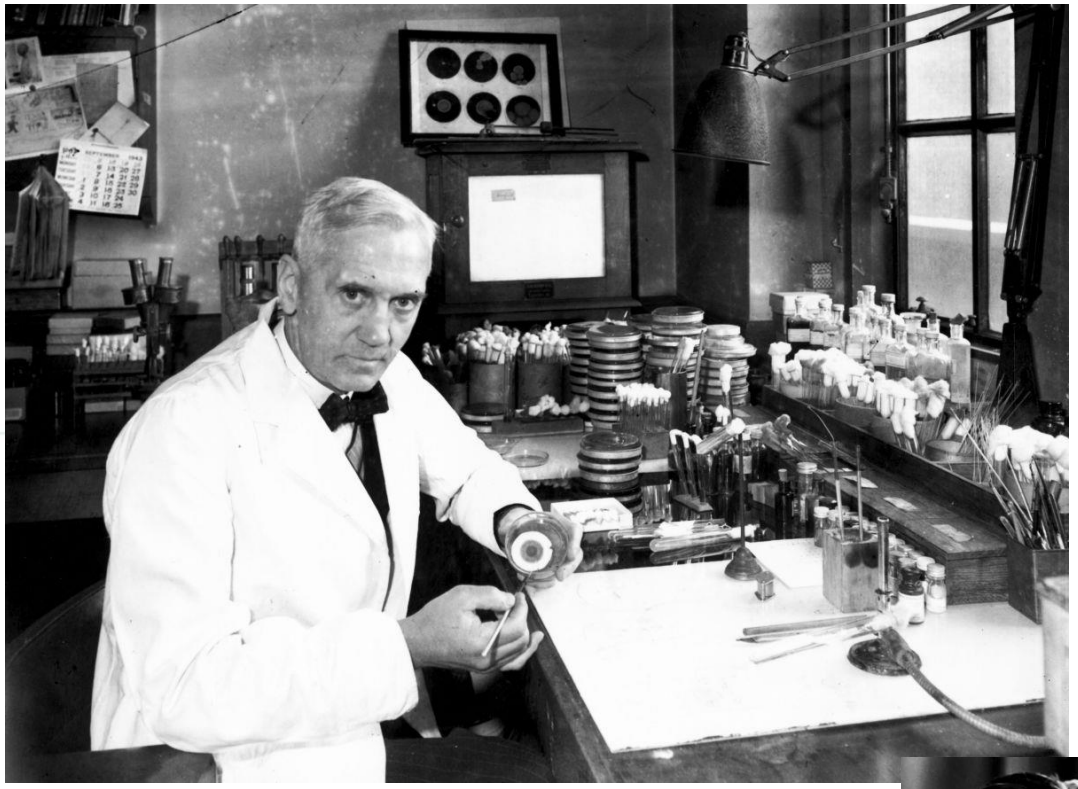
Antibiotics

Division:

- **Antibiotics** = in strict sense antibacterial comp. (products of microorg. + chemotherapeutics)
- **Antifungals** = against fungi
- **Antivirotics** = against viruses
- **Antiparasitics** = against protozoa and worms (+ against ectoparasites)

Alexander Fleming – 28th Sept. 1928

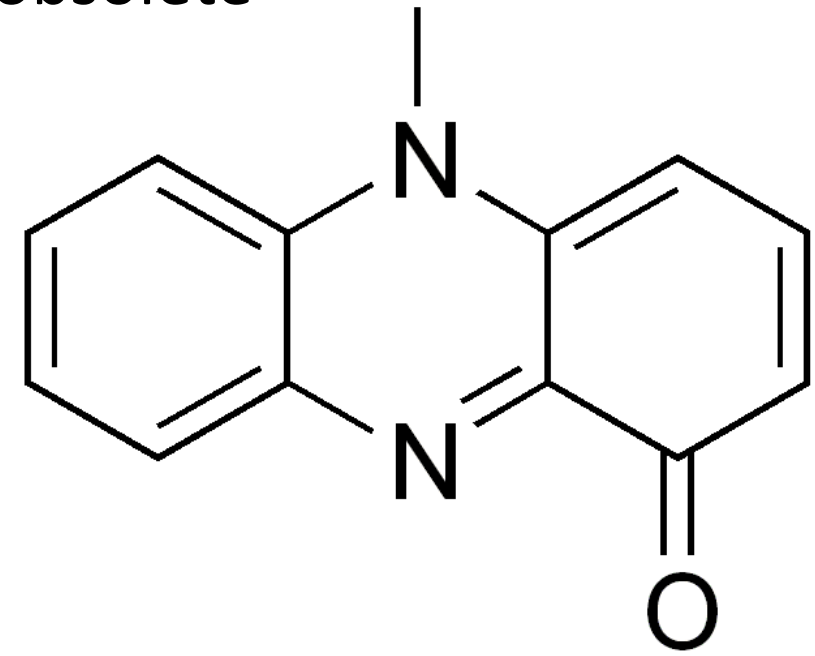


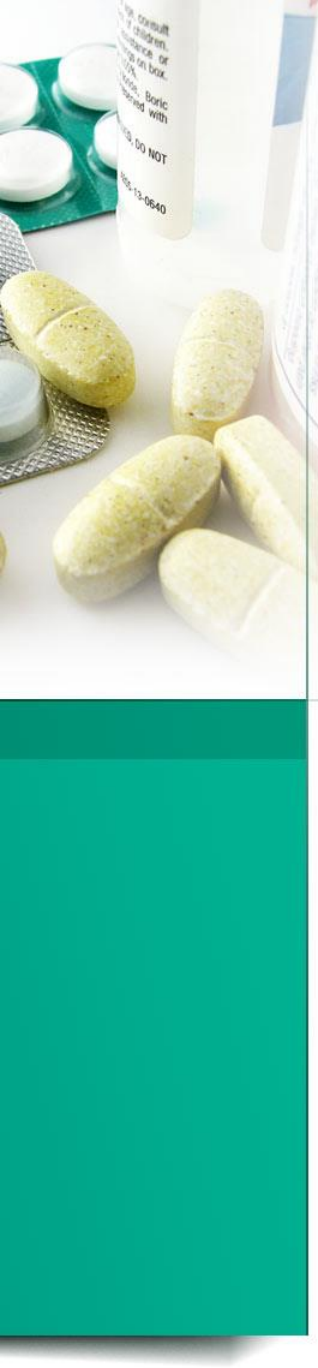
Developing penicillin was a team effort, as these things tend to be. — Howard Florey

1945: NP – Fleming, Florey, Chain

Before penicillin

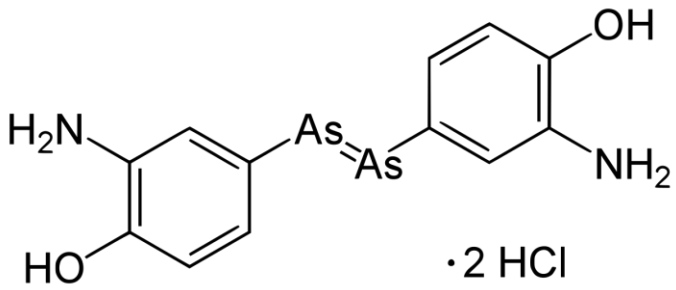
- **pyocyanase**: 1899 Emmerich & Löw (Munich) – discovery of antibiotic effect of *Bacillus pyocyaneus* – extract from „green bandages“ – against cholera, anthrax, etc. – today obsolete

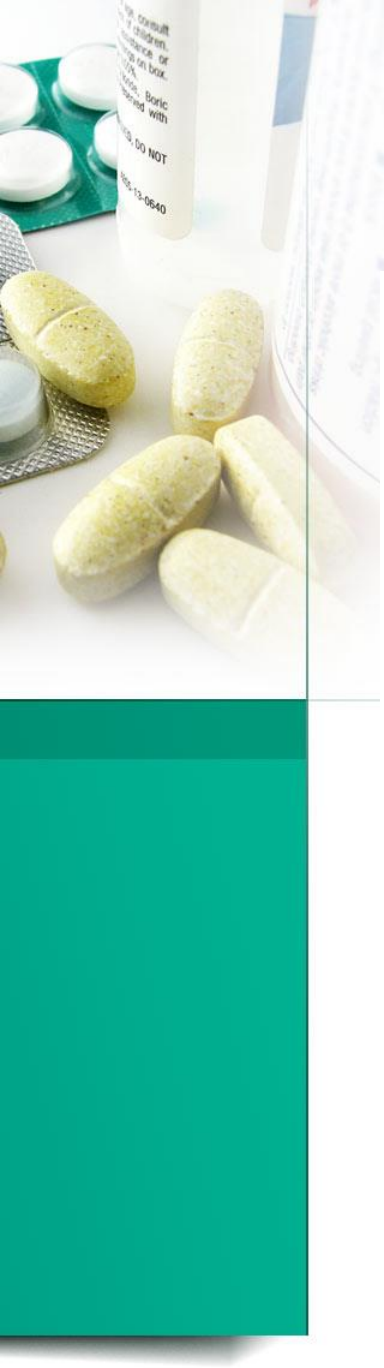




Before penicillin

- **Salvarsan (arsfenamin, compound 606)**: 1907 syntetized in laboratory of P. Ehrlich – 1910 first effective cure for syphilis (*Treponema palidum*) – optimization „magic bullet“
- complicated preparation of solution for injection (without oxygen); AE: rash, liver damage; replaced by PNC in 1940s





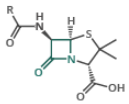
New antibiotics?

DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

Key: COMMONLY ACT AS BACTERIOSTATIC AGENTS, RESTRICTING GROWTH & REPRODUCTION — COMMONLY ACT AS BACTERICIDAL AGENTS, CAUSING BACTERIAL CELL DEATH

β-LACTAMS

MOST WIDELY USED ANTIBIOTICS IN THE NHS



All contain a beta-lactam ring

EXAMPLES

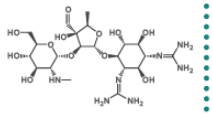
Penicillins (shown) such as amoxicillin and flucloxacillin; *Cephalosporins* such as cefalexin.

MODE OF ACTION

Inhibit bacteria cell wall biosynthesis.

AMINOGLYCOSIDES

FAMILY OF OVER 20 ANTIBIOTICS



All contain aminosugar substructures

EXAMPLES

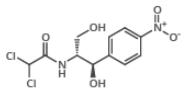
Streptomycin (shown), neomycin, kanamycin, paromomycin.

MODE OF ACTION

Inhibit the synthesis of proteins by bacteria, leading to cell death.

CHLORAMPHENICOL

COMMONLY USED IN LOW INCOME COUNTRIES



Distinct individual compound

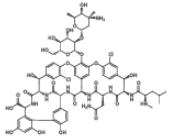
MODE OF ACTION

Inhibits synthesis of proteins, preventing growth.

No longer a first line drug in any developed nation (except for conjunctivitis) due to increased resistance and worries about safety.

GLYCOPEPTIDES

COMMON 'DRUGS OF LAST RESORT'



Consist of carbohydrate linked to a peptide formed of amino acids

EXAMPLES

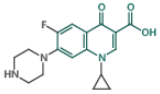
Vancomycin (shown), teicoplanin.

MODE OF ACTION

Inhibit bacteria cell wall biosynthesis.

QUINOLONES

RESISTANCE EVOLVES RAPIDLY



All contain fused aromatic rings with a carboxylic acid group attached

EXAMPLES

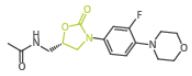
Ciprofloxacin (shown), levofloxacin, trovafloxacin.

MODE OF ACTION

Interfere with bacteria DNA replication and transcription.

OXAZOLIDINONES

POTENT ANTIBIOTICS COMMONLY USED AS 'DRUGS OF LAST RESORT'



All contain 2-oxazolidone somewhere in their structure

EXAMPLES

Linezolid (shown), posizolid, tedizolid, cycloserine.

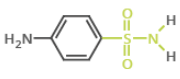
MODE OF ACTION

Inhibit synthesis of proteins by bacteria, preventing growth.

DISCOVERY 1930 1940 1950 1960 1970 1980

SULFONAMIDES

FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES



All contain the sulfonamide group

EXAMPLES

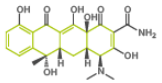
Prontosil, sulfanilamide (shown), sulfadiazine, sulfisoxazole.

MODE OF ACTION

Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.

TETRACYCLINES

BECOMING LESS POPULAR DUE TO DEVELOPMENT OF RESISTANCE



All contain 4 adjacent cyclic hydrocarbon rings

EXAMPLES

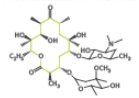
Tetracycline (shown), doxycycline, limecycline, oxytetracycline.

MODE OF ACTION

Inhibit synthesis of proteins by bacteria, preventing growth.

MACROLIDES

SECOND MOST PRESCRIBED ANTIBIOTICS IN THE NHS



All contain a 14-, 15-, or 16-membered macrolide ring

EXAMPLES

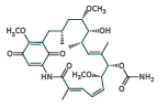
Erythromycin (shown), clarithromycin, azithromycin.

MODE OF ACTION

Inhibit protein synthesis by bacteria, occasionally leading to cell death.

ANSAMYCINS

CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY



All contain an aromatic ring bridged by an aliphatic chain.

EXAMPLES

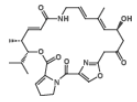
Geldanamycin (shown), rifamycin, naphthomycin.

MODE OF ACTION

Inhibit the synthesis of RNA by bacteria, leading to cell death.

STREPTOGRAMINS

TWO GROUPS OF ANTIBIOTICS THAT ACT SYNERGISTICALLY



Combination of two structurally differing compounds, from groups denoted A & B

EXAMPLES

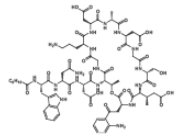
Pristinamycin IIA (shown), Pristinamycin IA.

MODE OF ACTION

Inhibit the synthesis of proteins by bacteria, leading to cell death.

LIPOPEPTIDES

INSTANCES OF RESISTANCE RARE



All contain a lipid bonded to a peptide

EXAMPLES

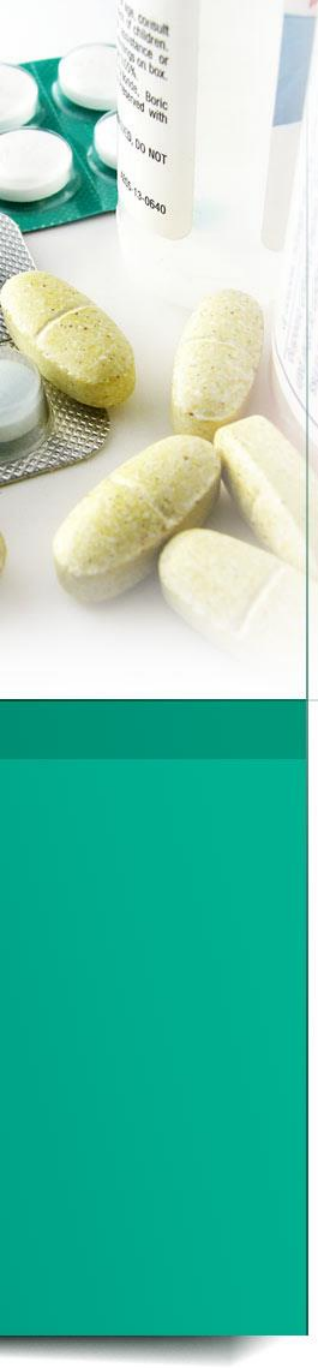
Daptomycin (shown), surfactin.

MODE OF ACTION

Disrupt multiple cell membrane functions, leading to cell death.

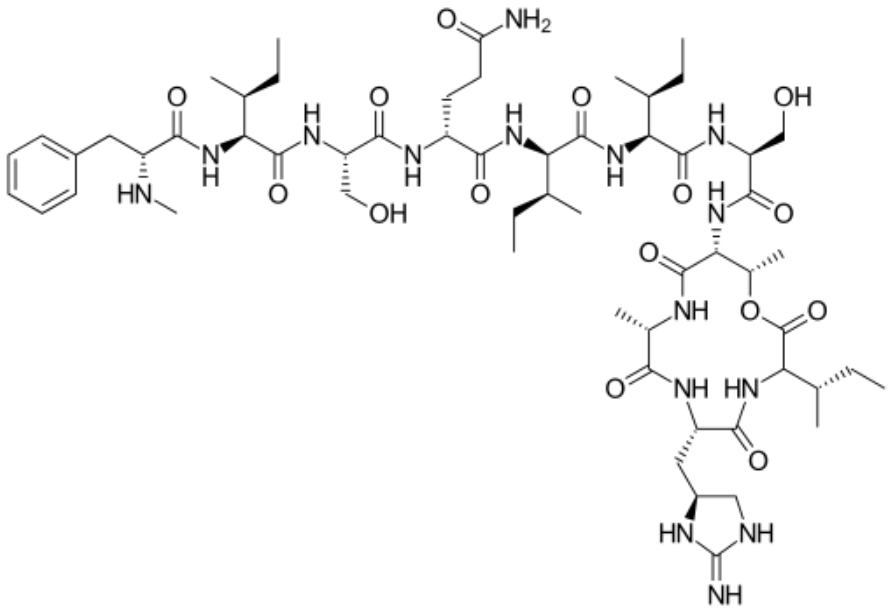
New antibiotics?

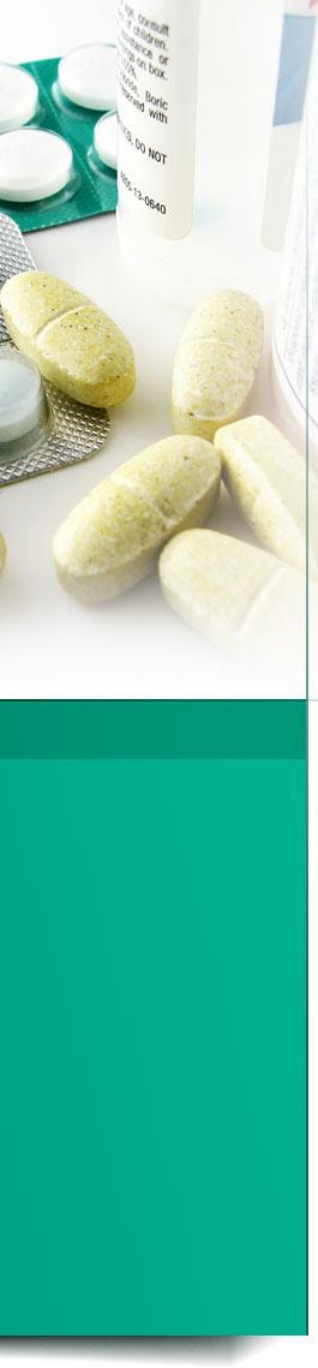
- oxazolidinones (e.g. linezolid, 2000)
- lipoproteins (daptomycin, 2003)
- pleuromutilines (retapamulin, 2007)
- tiacumcines (fidaxomicine, 2010)
- diarylquinolins (bedaquilin, 2012)



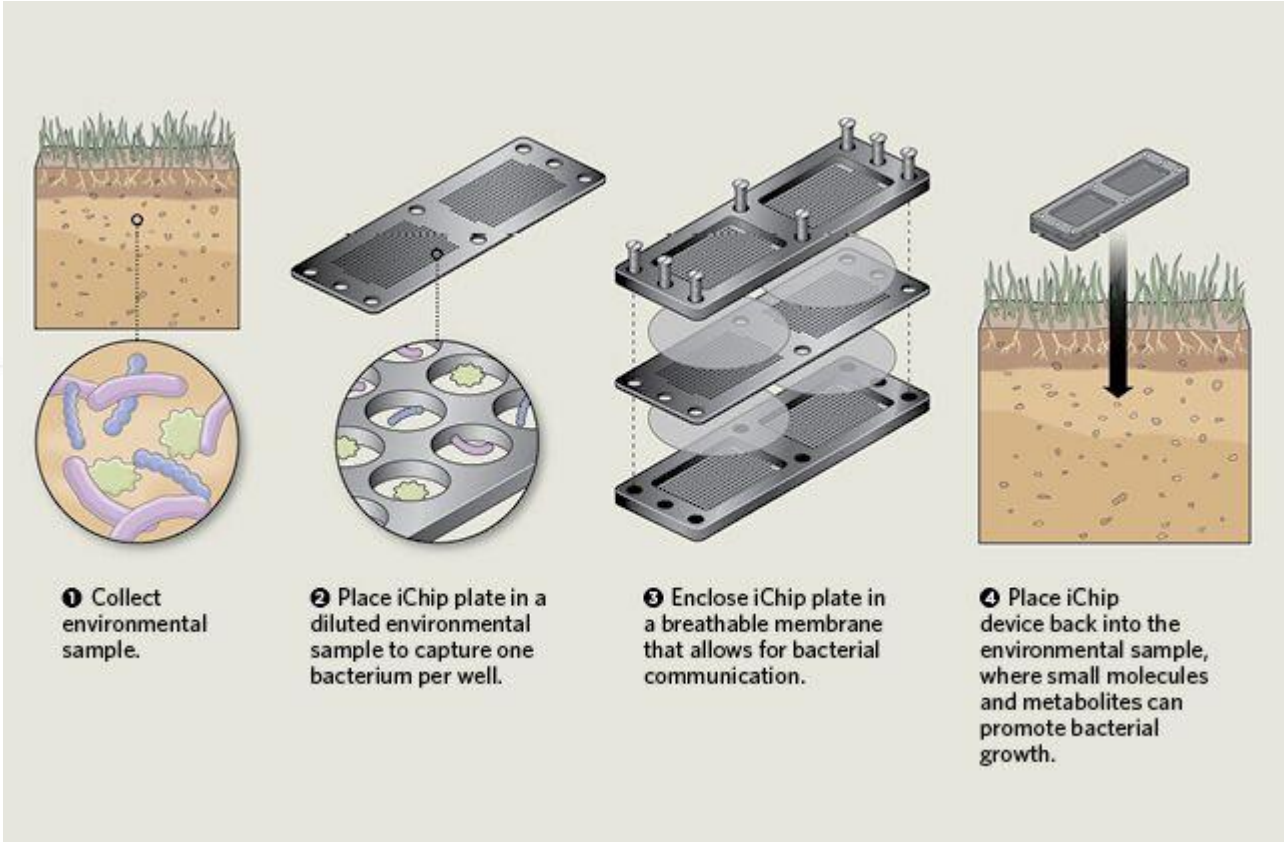
New antibiotics?

- cca 99 % of bac., which are not easy to cultivate (Great Plate Count Anomaly)
- **teixobactin**: product of *Eleftheria terrae*, iChip hethod (isolation chip; 2015); against MRSA

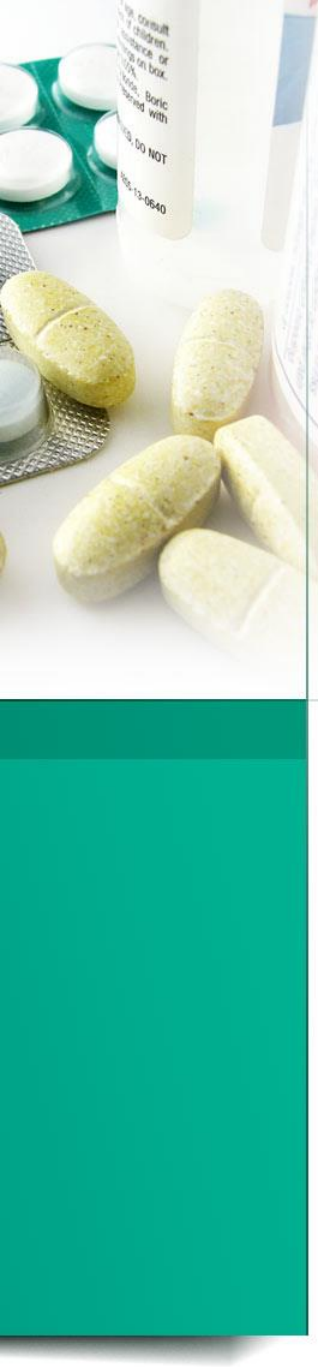




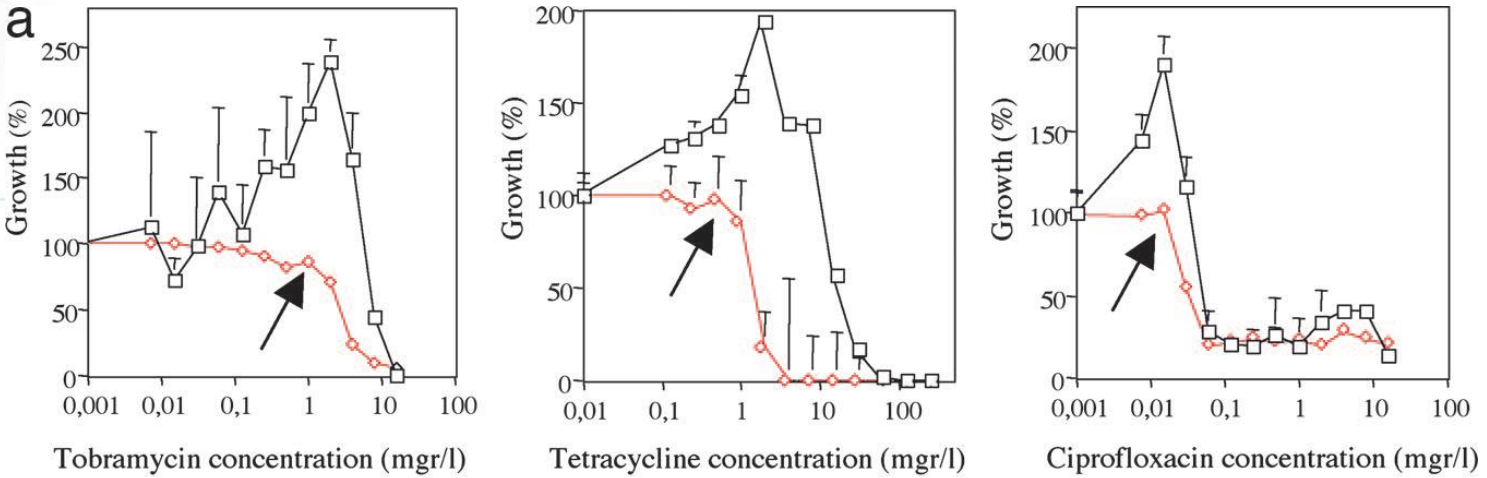
iChip



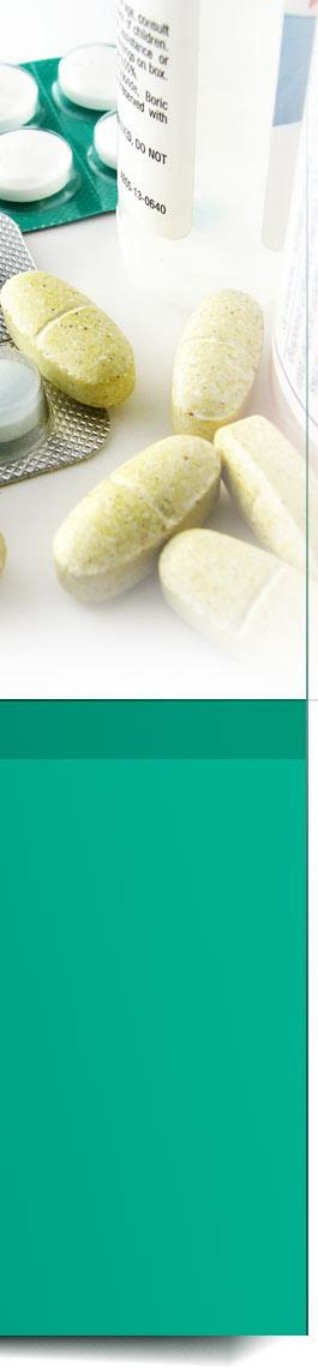
https://www.popsci.com/ichip-new-way-find-antibiotics-and-other-key-drugs#page-2



Antibiotics as intermicrobial signal molecules instead of weapons?



Linares et al., PNAS 2006, 103, 19484-19489

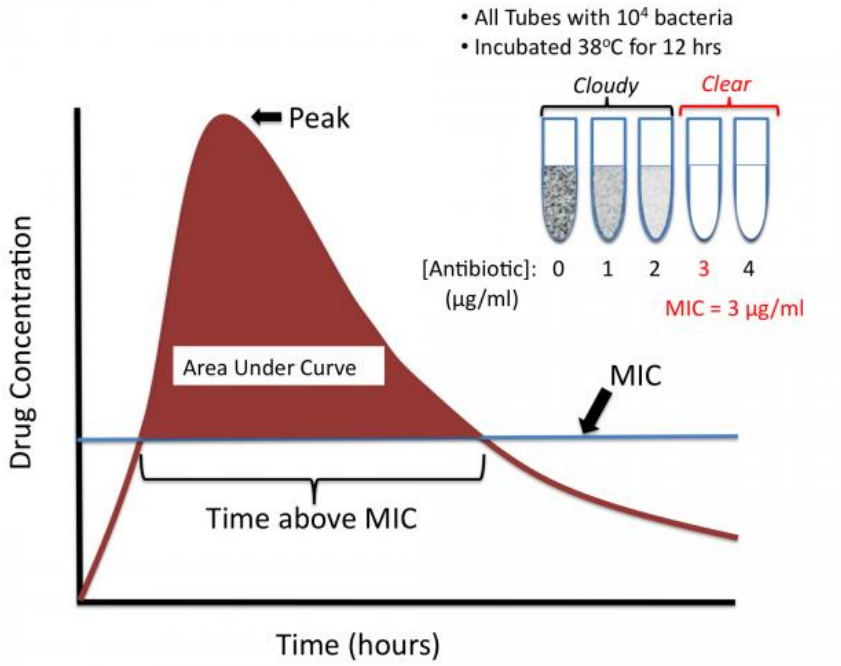


Important concepts:

- **Sensitivity** = receptivity of certain MO to ATB
- Opposite is **resistance** (natural or acquired)

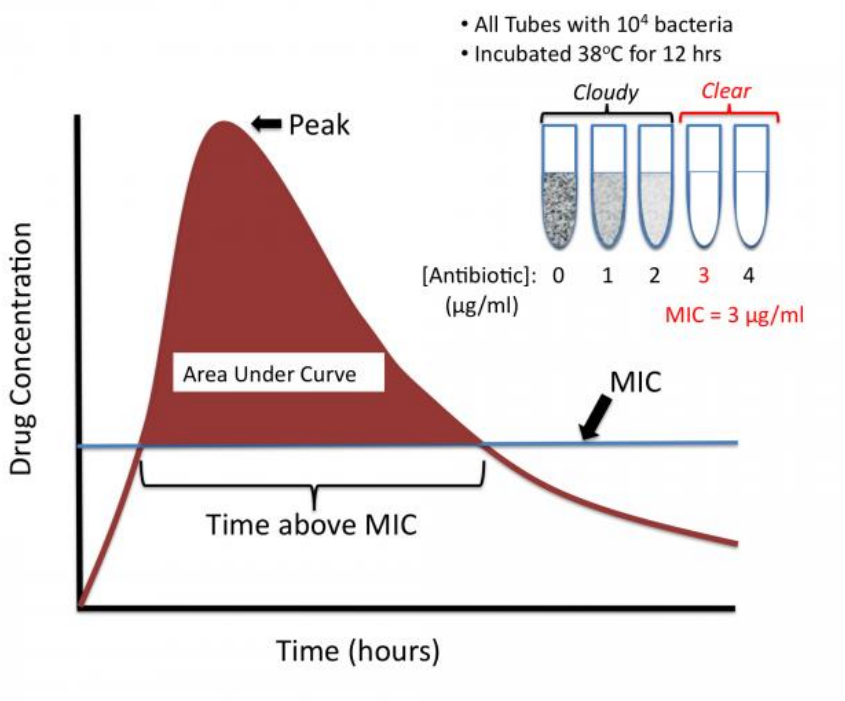
Important concepts:

- Minimal inhibition concentration (MIC) = lowest concentration of ATB still able to inhibit visible growth of MO



Important concepts:

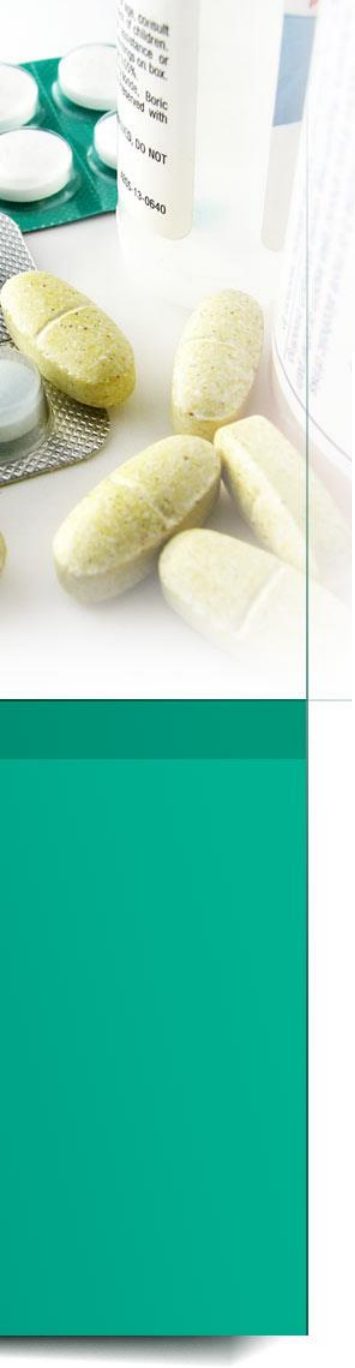
- Postantibiotic effect = time (in hours), when bacteria do not grow, even though the antibiotic is not detectable in patient
- Aminoglycosides, quinolones



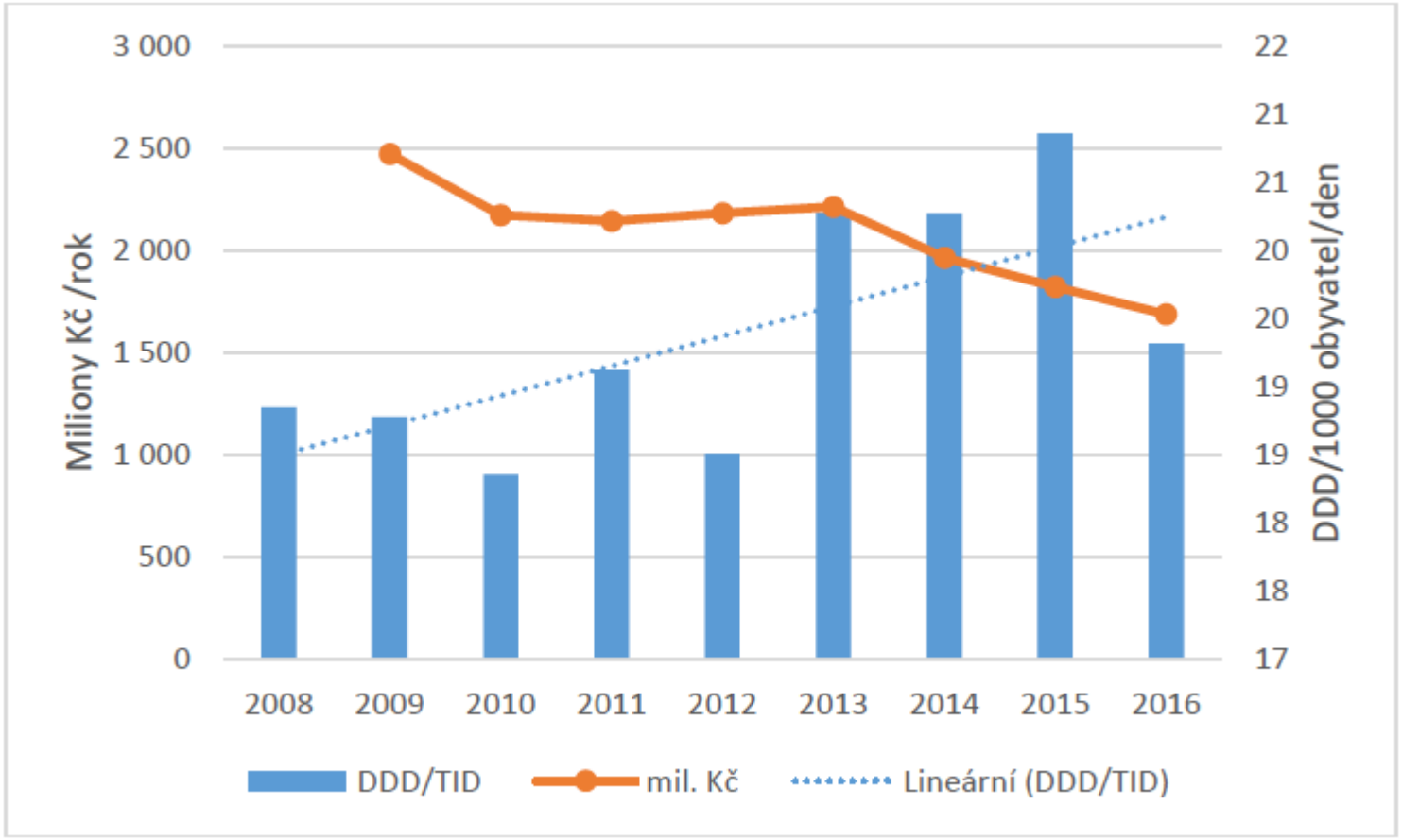
Important concepts:

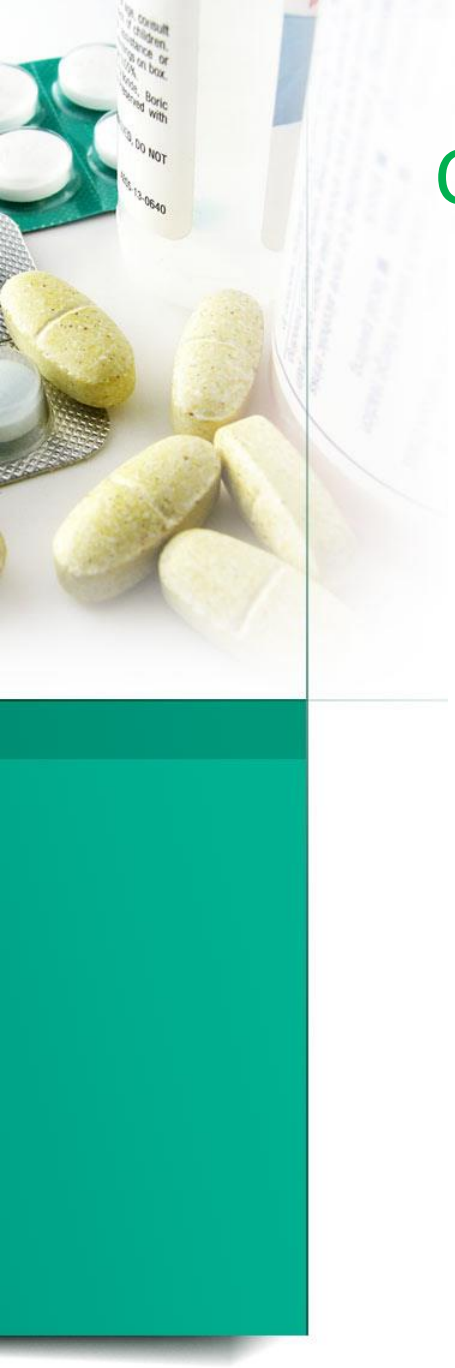
Minimal bactericidal concentration (MBC):

- amount of ATB in mg/l able to kill bacterial colony under given circumstances
- values of MBC are for highly bactericidal ATB close to MIC, max. 2 - 4x higher
- for bacteriostatic ATB are values of MBC 16 – 64times higher than MIC

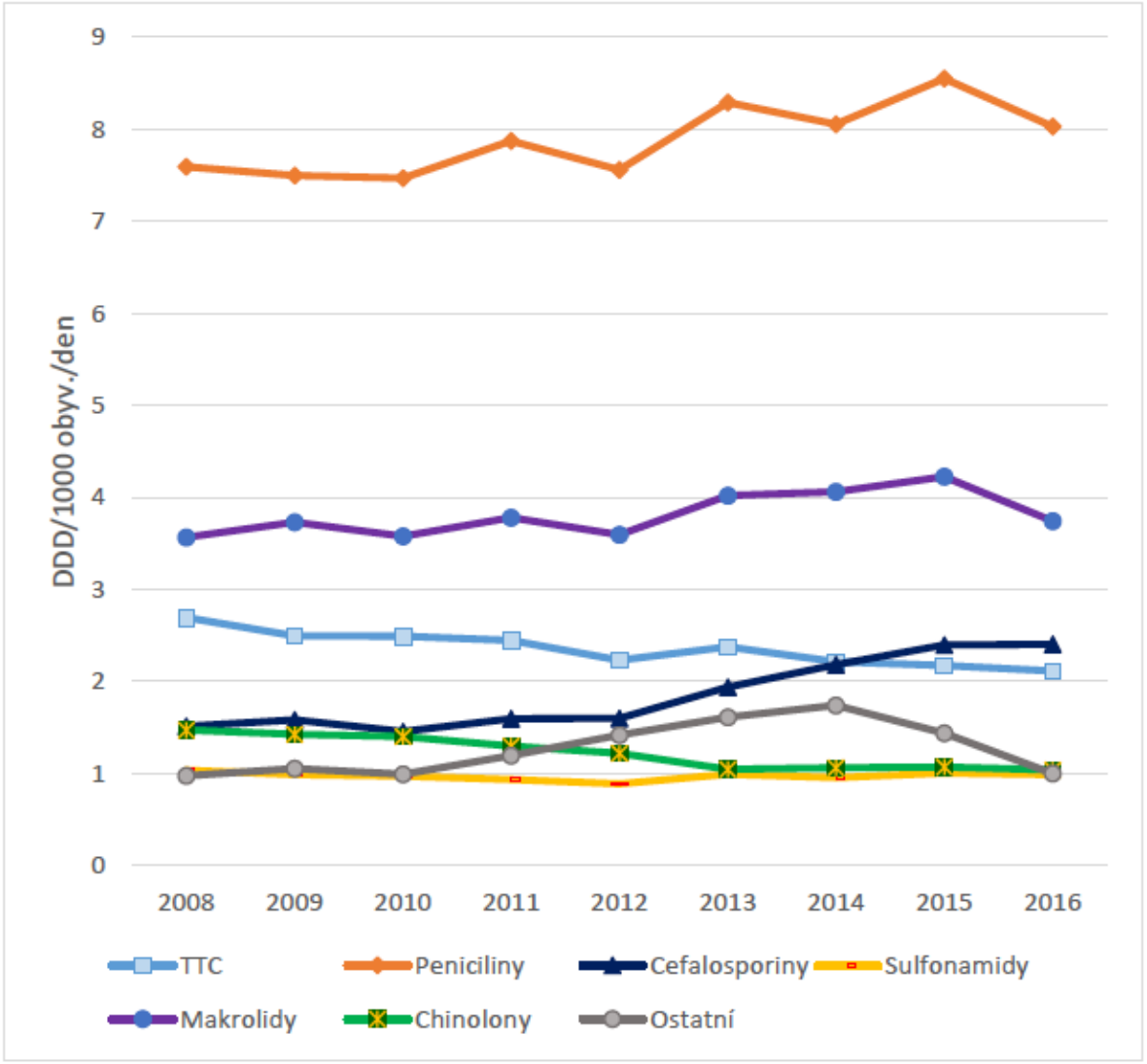


Consumption of ATBs in CZ

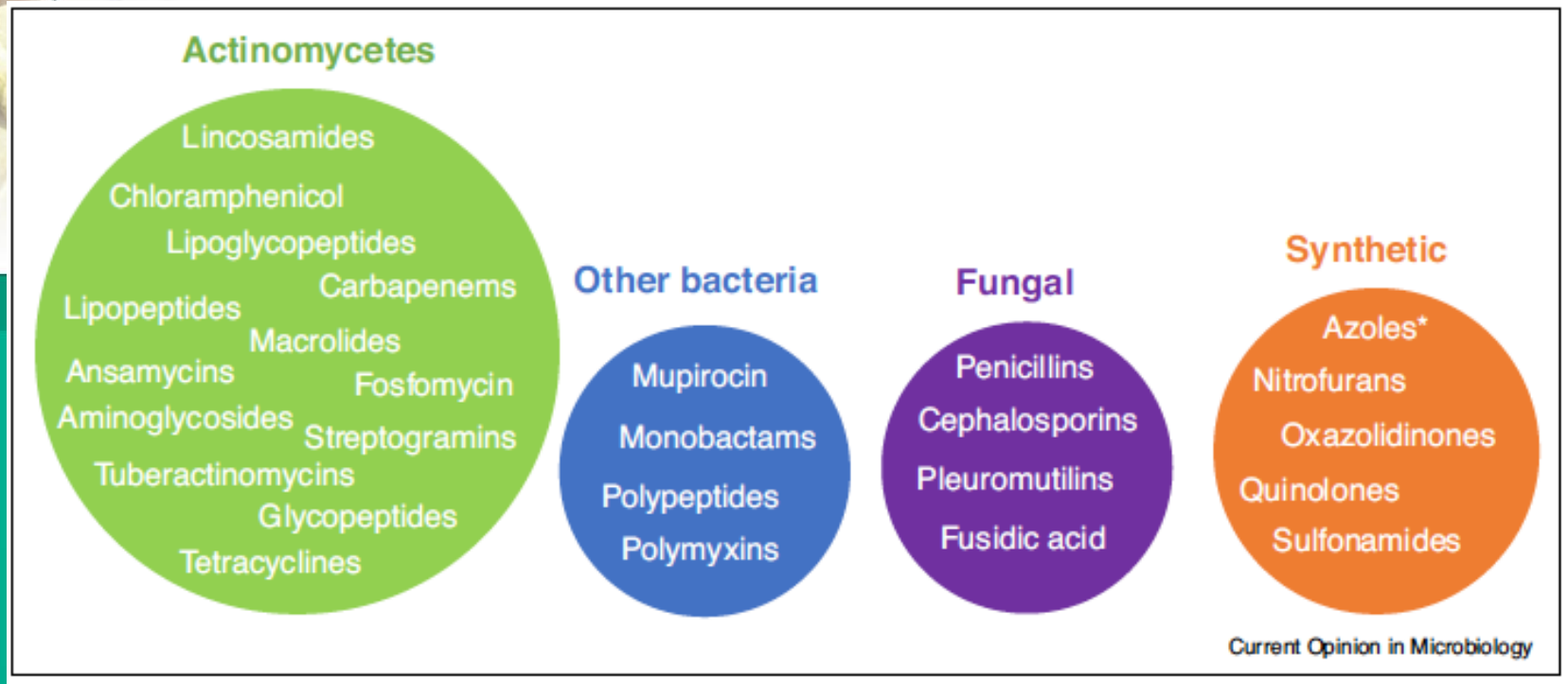




Consumption of ATBs in CZ



ATB = secondary metabolites



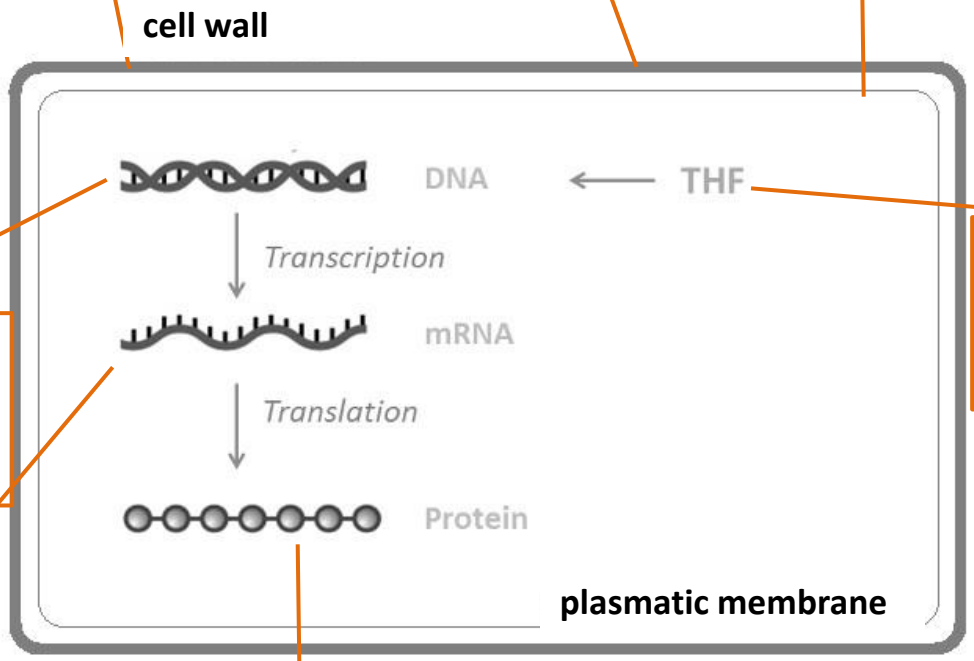
Hutchins et al. Curr Op Microbiol 2019

Antibacterial compounds

penicillins
cephalosporins

bacitracin
vancomycin

polymyxins
daptomycin

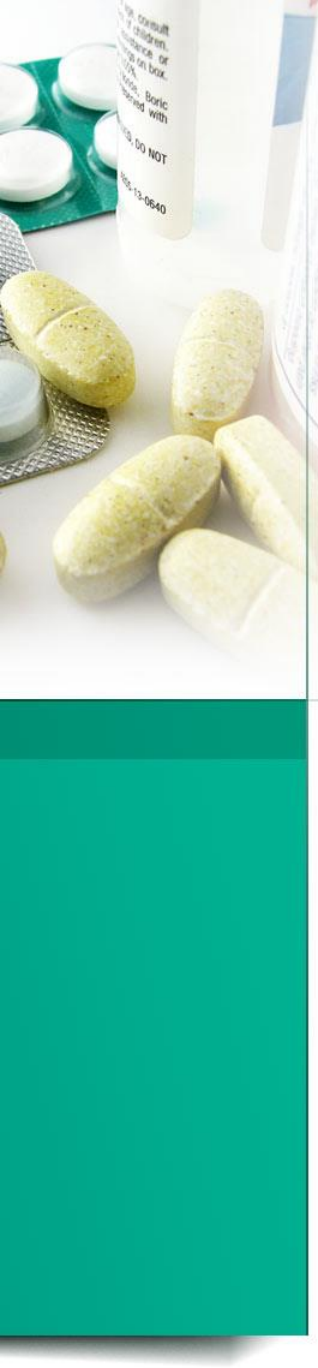


quinolones
nitroimidazols

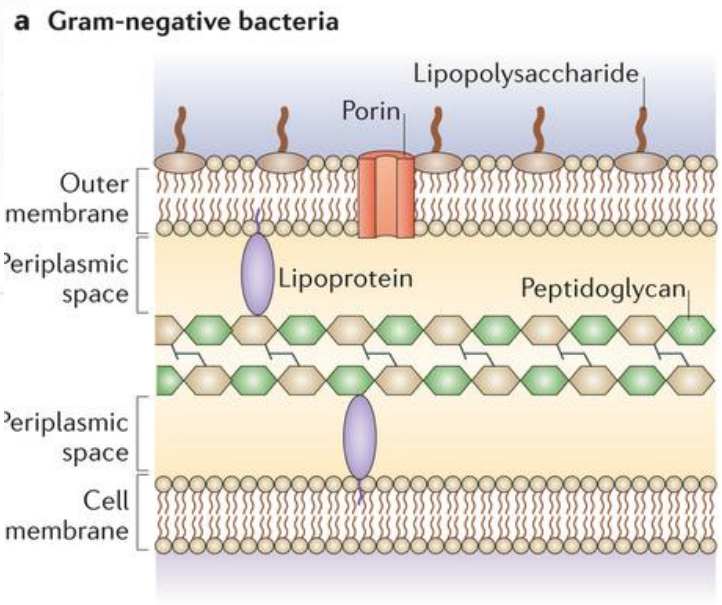
sulfonamides
trimethoprim

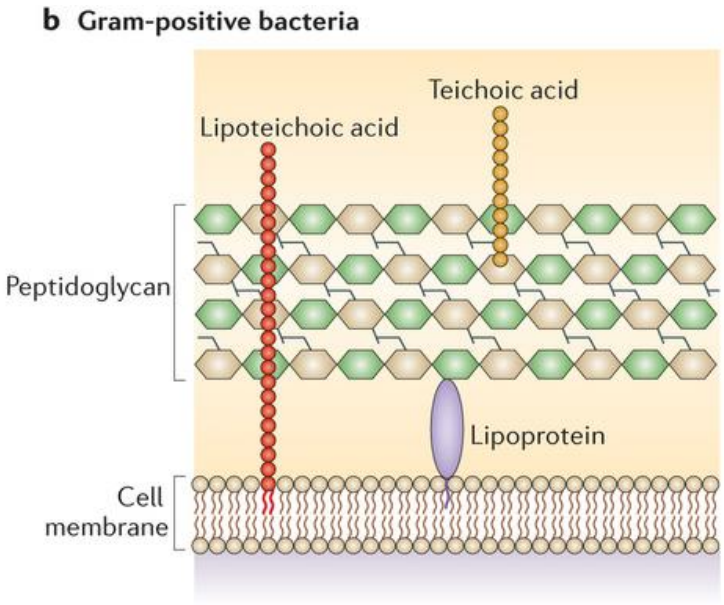
rifampicin

tetracyklines
macrolides
chloramphenicol
aminoglycosides



Inhibitors of cell wall synthesis





N-acetylglukosamid + N-acetylmuranic acid

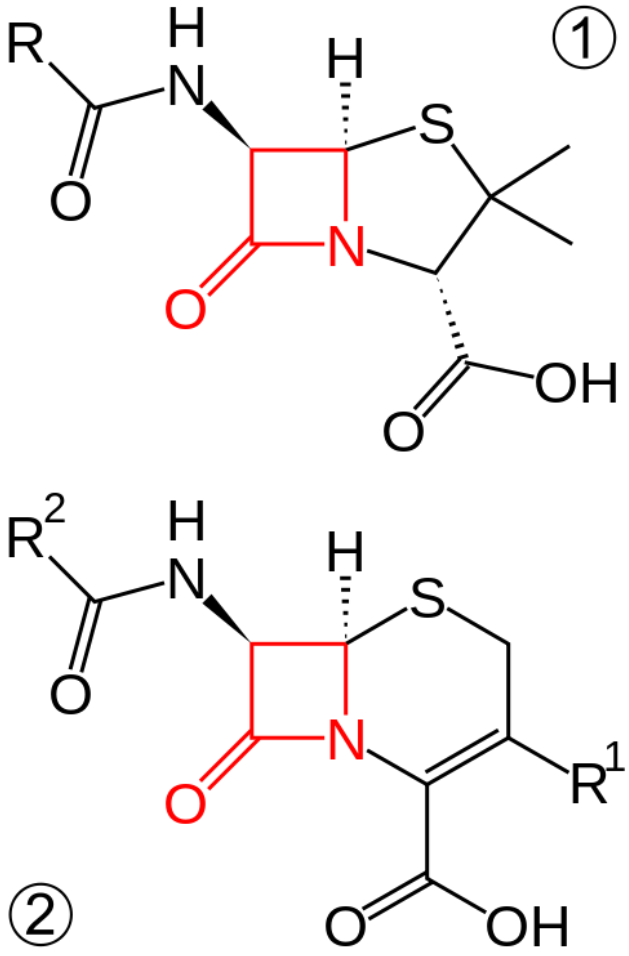
Nature Reviews Microbiology 13, 620–630 (2015) doi:10.1038/nrmicro3480

Inhibitors of cell wall synthesis

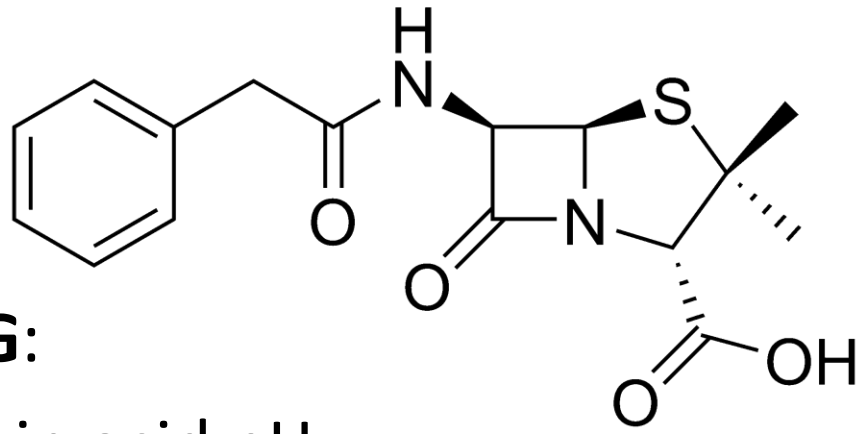
- **β-lactams**: inhibition of peptidyltransferase – cell wall assembly stops – hyperosmotic bacteria ruptures (bactericidal)
- **glycopeptides**: only G+ (do not get through CPM); interferes with last phase of synthesis, binds to D-ala-D-ala part of pentapeptide
- **bacitracin**: inhib. dephosphorylation of undecaprenylphosphate, which transports molecules to be incorporated into cell wall

β – lactam antibiotics

1. penicillins
2. cephalosporins
3. carbapenems (S > C)
4. monobactams (without 2nd ring)



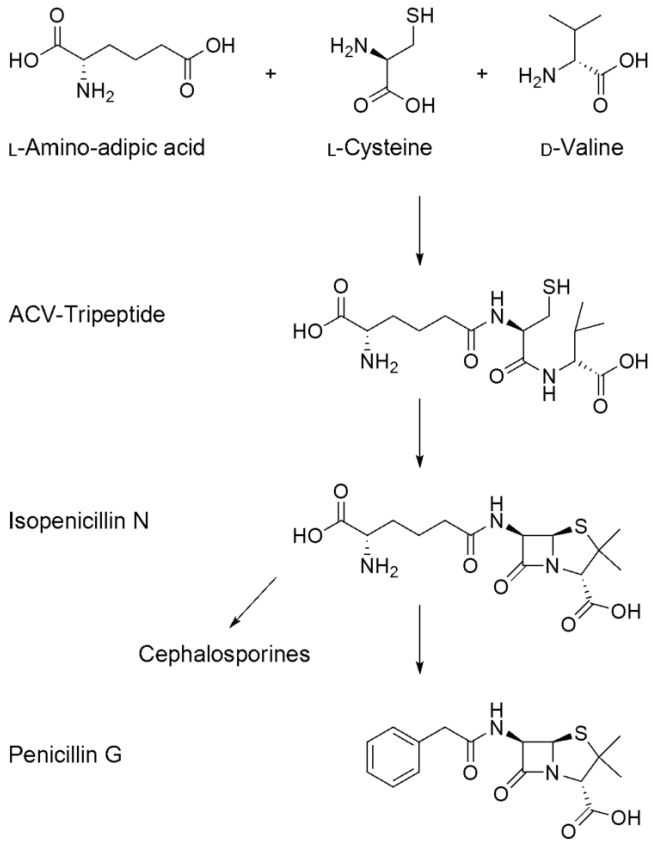
Penicillins



first was **penicillin G**:

- inj., inactivation in acid pH (fenoxymethylderivative, pen. V stable -> p.o. administration)
- sensitive to penicillinase (β-lactamase)
- spectrum mainly G+ (some G- cocci)
- AE: allergies, high doses are neurotoxic

Penicillin G - biosynthesis



δ-(L-α-aminoadipyl)-L-cysteine-D-valine synthetase (ACVS)

isopenicillin N synthase (IPNS)

isopenicillin N N-acyltransferase

CC: Cacycle

Penicillins

Semisynt. derivatives – isoxazolylpenicillins:

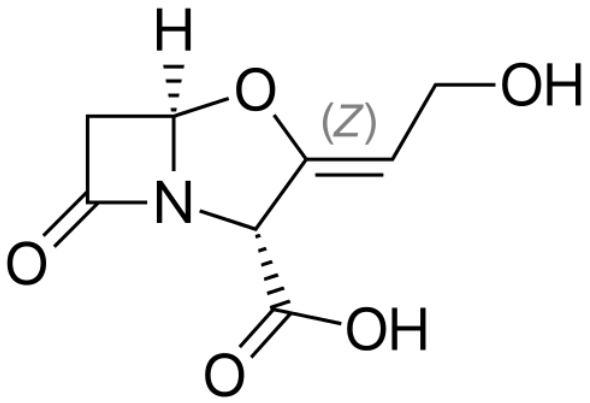
- resistant to penicillases – suitable for p.o. therapy of *Staphylococci* inf.
- e.g.: **oxacillin**, **dicloxacillin**

Derivatives with broader spectrum – against G- (*E. coli, S. typhi*) and *Pseudomonas*:

- aminopenicillins (**amoxicillin**)
- carboxypenicillins (**tikarcillin**)

Penicillins + inhibitors of β-lactamases

- **clavulanate**; **sulbactam**, tazobactam
- weak antibiotic effect
- mechanism: suicide
  (covalent and irreversibile bond to the enzyme – displacement of ATB)



Cephalosporins

- structure of 7-aminocephalosporanic acid
- acidoresistant, but bad resorption (mainly p.e.) – e.g. **cephalexin** can be administered p.o.
- broad spectrum – **cefotaxime**, **ceftriaxone** (also for multiresitant inf.)
- well tolerated, can induce allergies

Other inhibitors of cell wall synthesis

Bacitracin:

- mixture of polypetides; neurotoxic, used locally

Vancomycin:

- glycopeptide
- therapy of pseudomembranose colitis (*C. difficile*) – not absorbed

Inhibition of CPM function

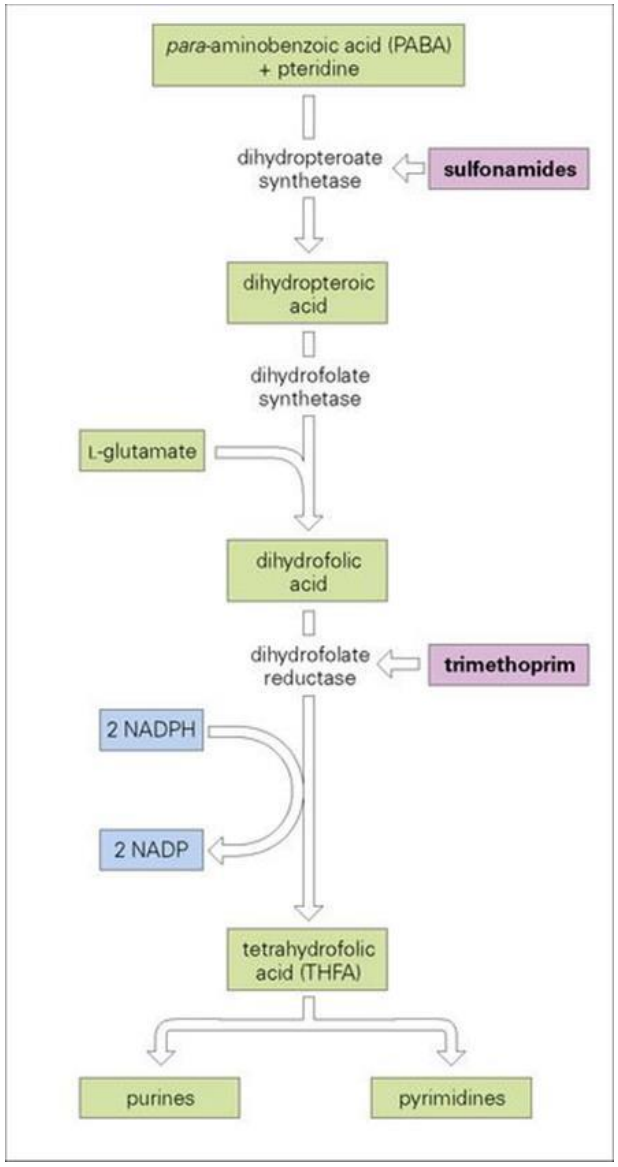
cyclic polypeptides:

- **polymyxines** and **colistine**
- neuro- and nephrotoxic – ATB of last resort
- acts as detergent on CPM

lipopeptides:

- **daptomycin** (reg. in 2003) : aggregates in CPM and forms pores

Metabolism of folic acid



Sulfonamides

- 1st chemoterapeutics – 1932 – IG Farben
- false substrates; similar with PABA
- broad spectrum, bacteriostatic
- often resistance – gradually squeezed out of practice
- urinary inf. treatment; comb. with trimethoprim
- AE: skin allergies
- **sulfathiazole** (local); **sulfametoxazole**

Trimethoprim

- inhibition of bacterial DHF-reductase
- human enzyme is much less sensitive – bone marrow depression is rare
- bacteriostatic
- Mainly in combinaton with sulfametoxazole as **co-trimoxazole** (synergism)

Inhibition of DNA function - quinolones

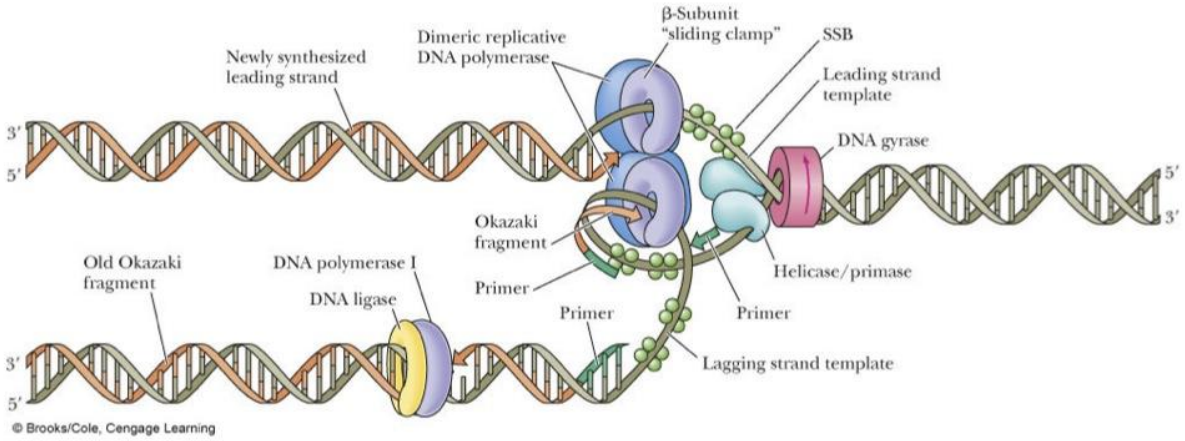
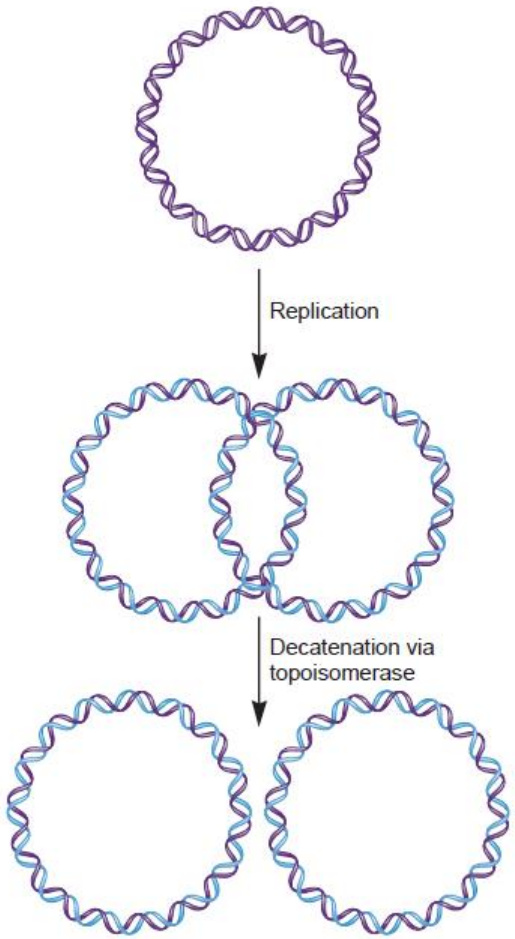


Fig. 10-9, p. 271



DNA gyrase

Topoisomerase IV

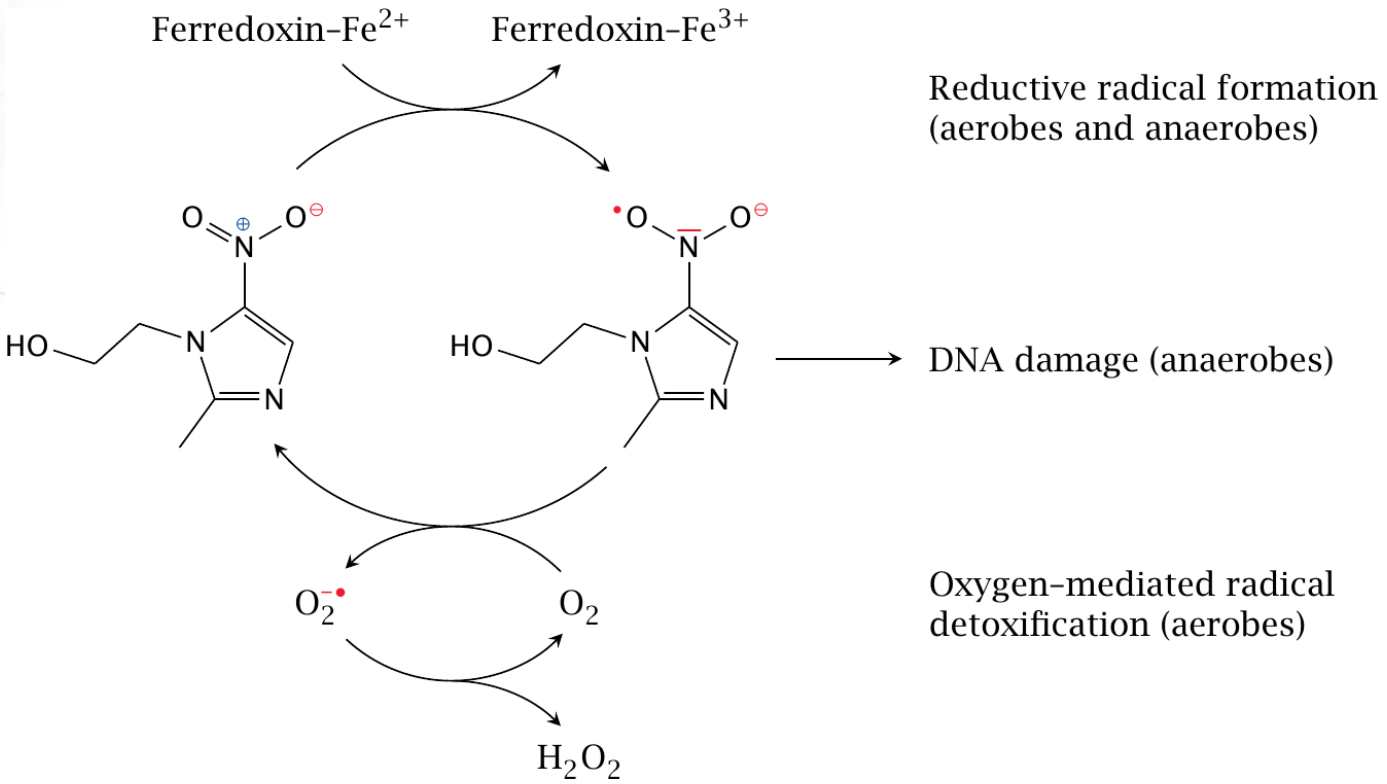
Quinolones (4-quinolon-3-carboxylic acid)

- block reconnection of strands = bactericidal
- AE: allergy, indigestion, confusion,..
- CI: children below 16 yrs – damage to cartilaginous parts of bones
- **nalidixic acid**: narrower spectrum, urinary infections only
- next gen. – fluorinated derivatives (**norfloxacin**, **ciprofloxacin**) – broad spectrum

Derivatives of nitroimidazole

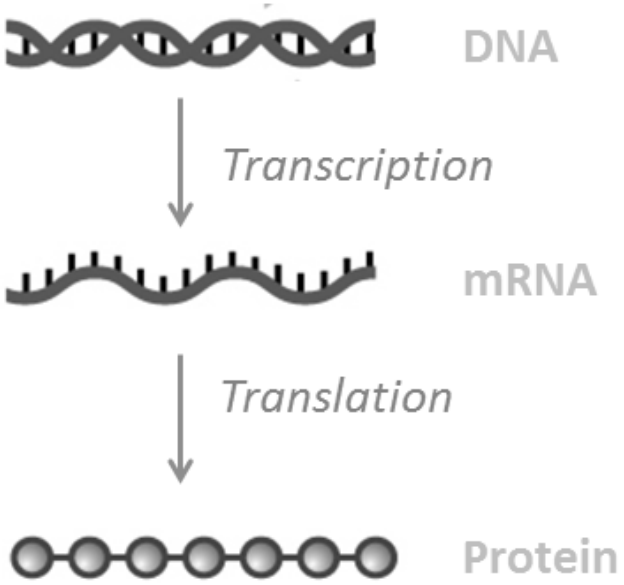
- damage to DNA by forming complexes and strand breaks (reactive metabolites)
- bactericidal (usual anerobes) + protozoa *(Trichomonas vaginalis*; *Entamoeba histolytica)*
- **metronidazole**: p.o., vag. tbl.
- CI: pregnant, breastfeeding women

Derivatives of nitroimidazole



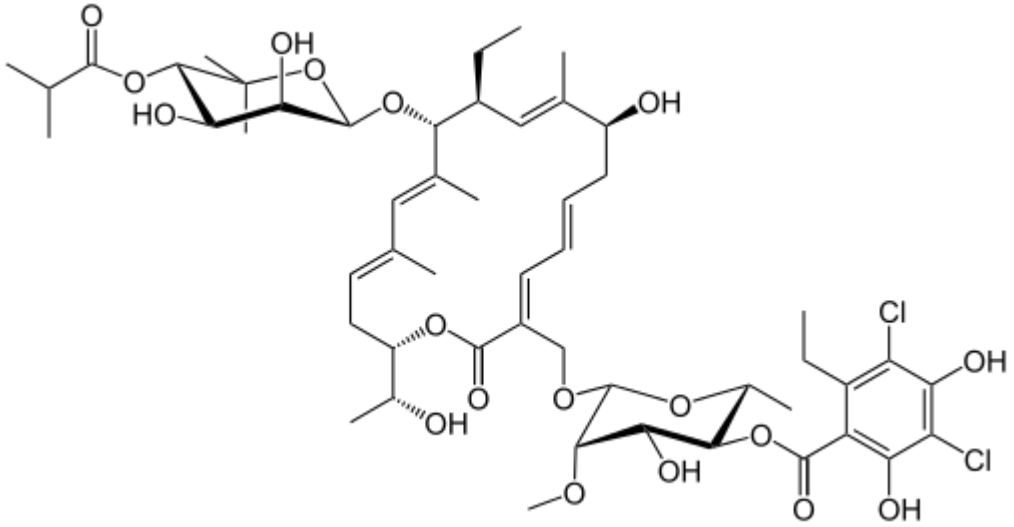
Rifampicin

- inhibits bacterial DNA-dependent RNA polymerase – inh. of transkription (-cidal)
- I: mainly TBC and leprosy

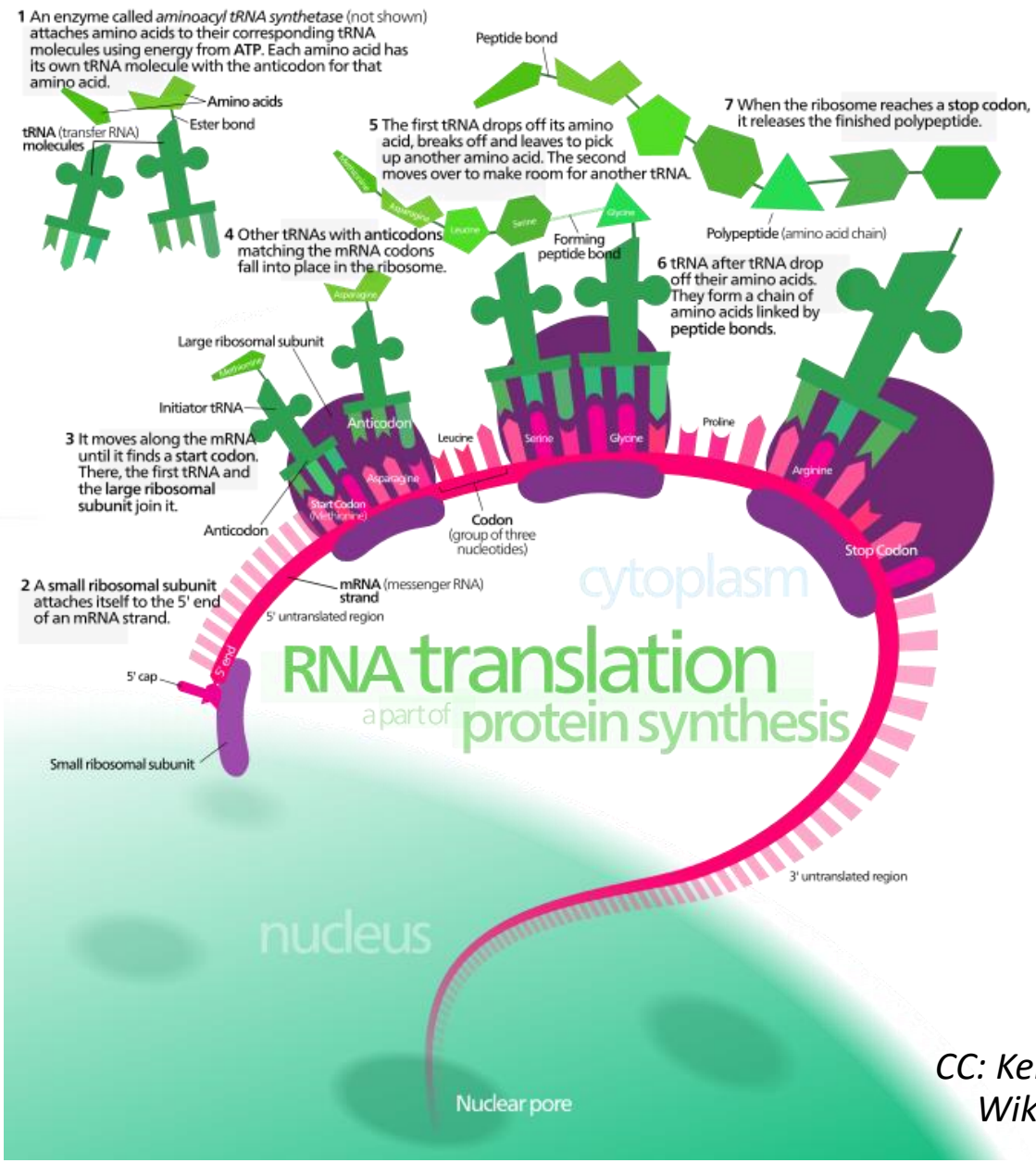


Fidaxomicin (tiacumcins)

- also inhibiting transcription (-cidal)
- approv. in 2011; macrocyklic ATB from actinomyces *Dactylosporangium aurant.*
- I: intestinal inf. caused by *Clostridium difficile*

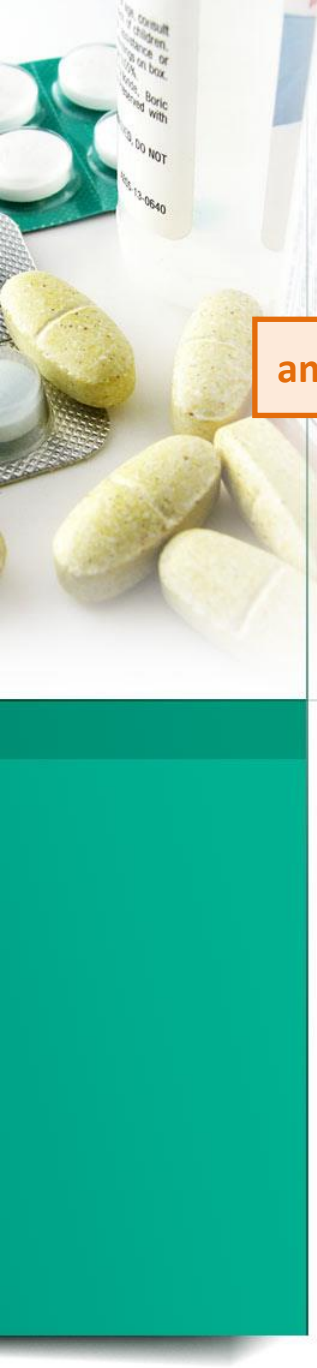


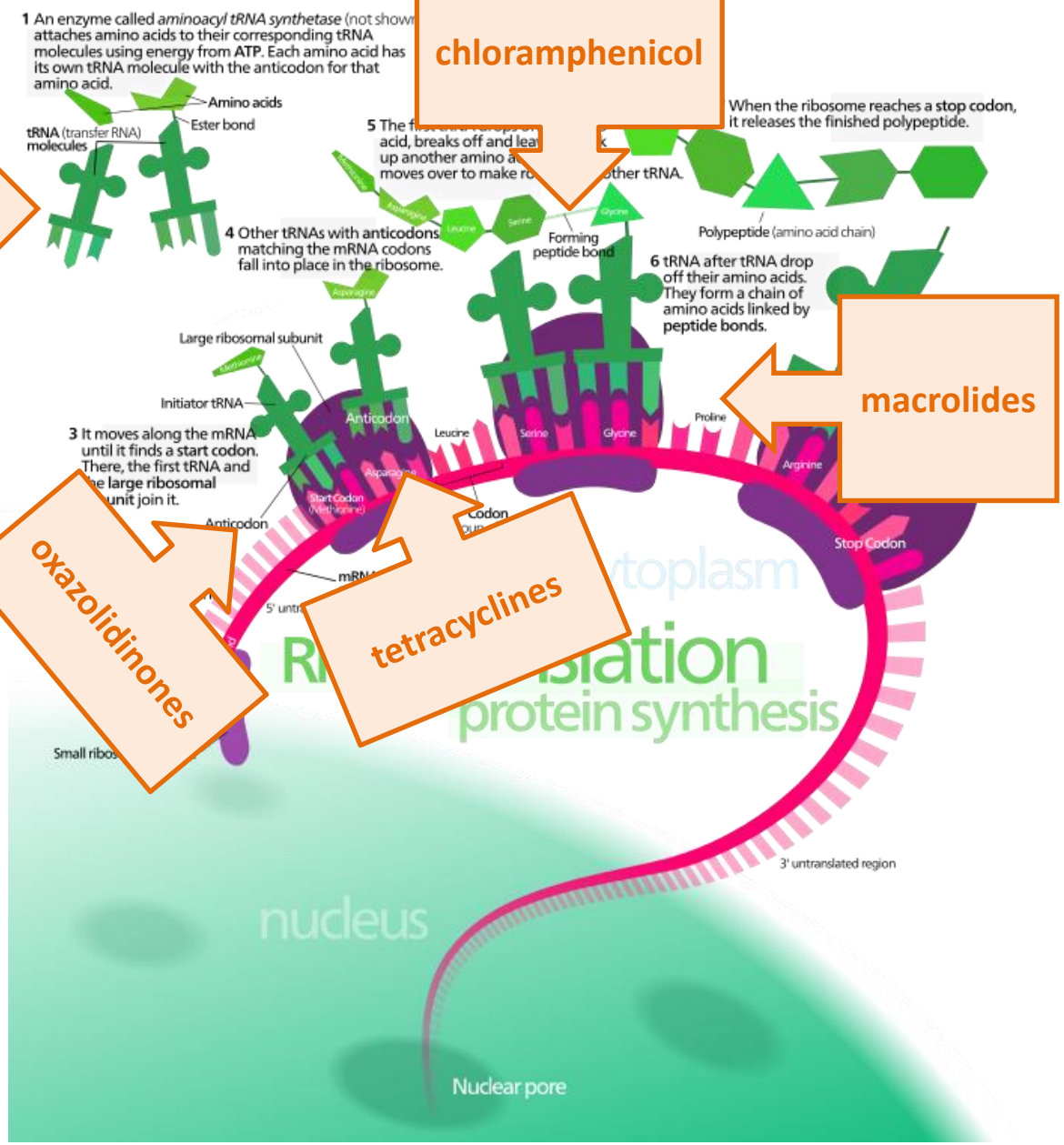
Proteosynthesis



CC: Kelvinsong; Wikipedia

Inhibitors of proteosynthesis





aminoglycosides

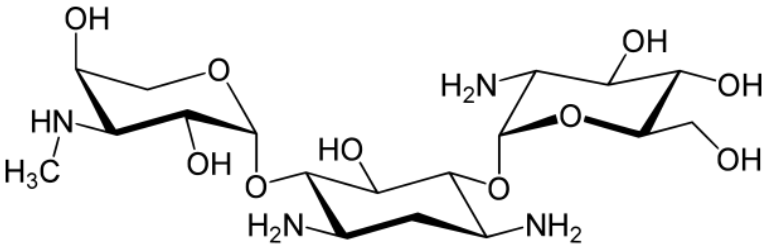
chloramphenicol

macrolides

oxazolidinones

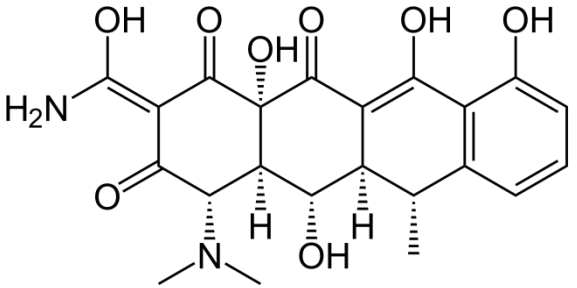
tetracyclines

Aminoglycosides



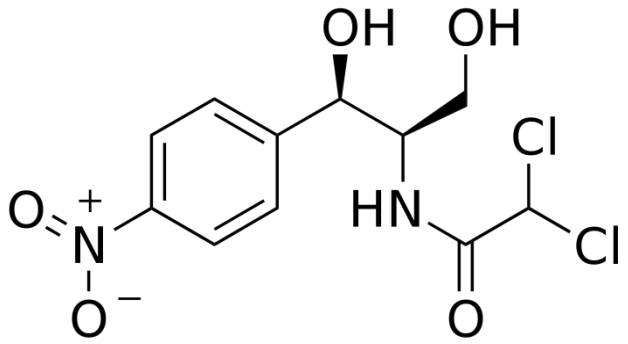
- synthesis of wrong tRNA+AMK (-cidal)
- aminosugars connected via glycosidic bond (many OH- groups => bad resorption)
- **neomycin**: p.o. before surgery (X intestinal bacteria)
- inj. at severe infections G- bac.: **gentamicin**
- **streptomycin**: therapy of TBC
- AE: nephrotoxicity, vestibular and cochlear ototoxicity

Tetracyclines



- bacteriostatical broad sprectrum effect
- **tetracycline**, newer generation: **doxycykline**
- AE: indigestion (broad spectrum)
- do not administer with milk/diary products/antacids/minerals – insoluble complexes, loss of effect
- storage in bones, colouration of teeth (CI: from 3rd month of pregnancy – 8th year)

Chloramphenicol

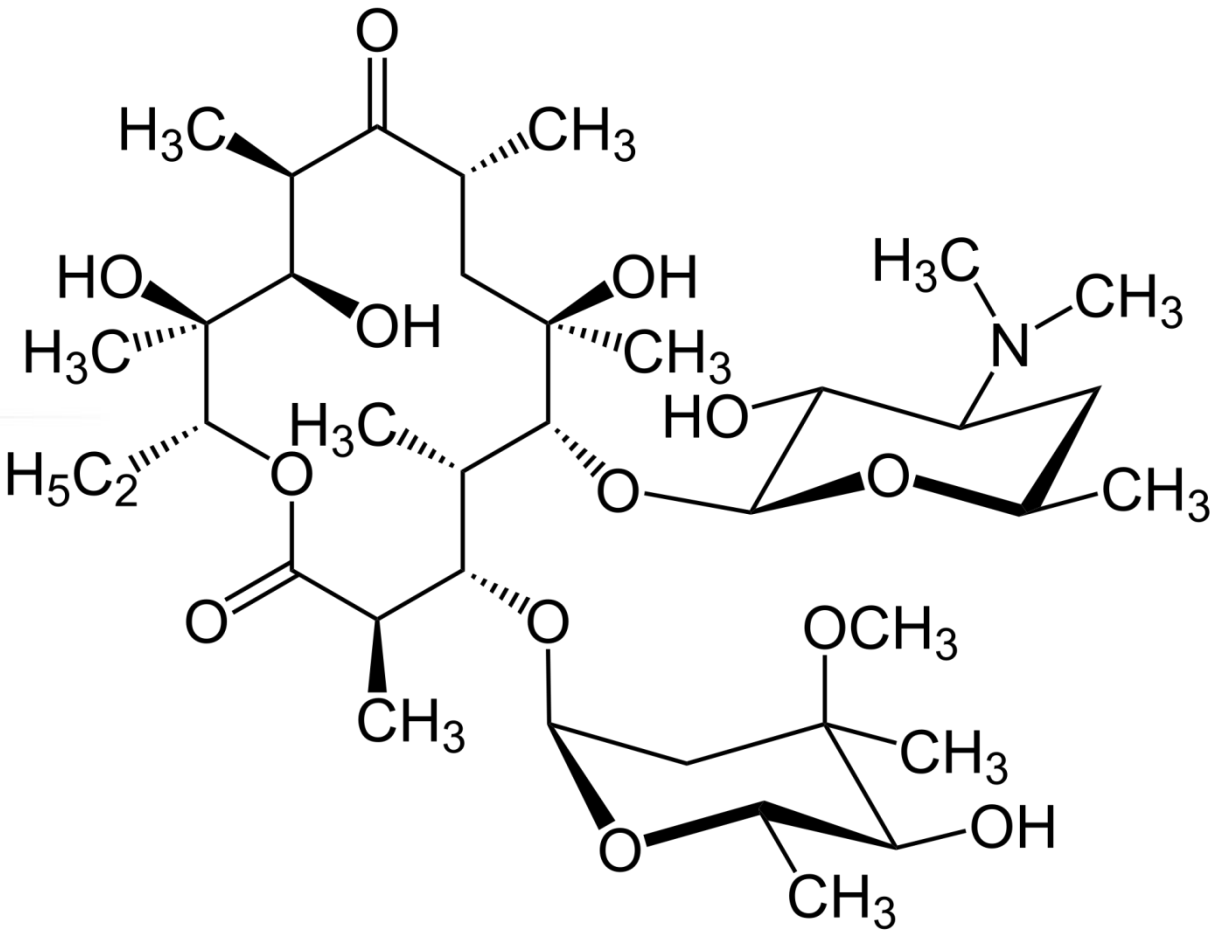


- inhibition of peptidyltransferase – bacteriostatical, broad spectrum
- indicated rarely, e.g. for severe CNS inf.
- AE: bone marrow depression (either instantly during therapy – reversibile; or later after, often deadly)

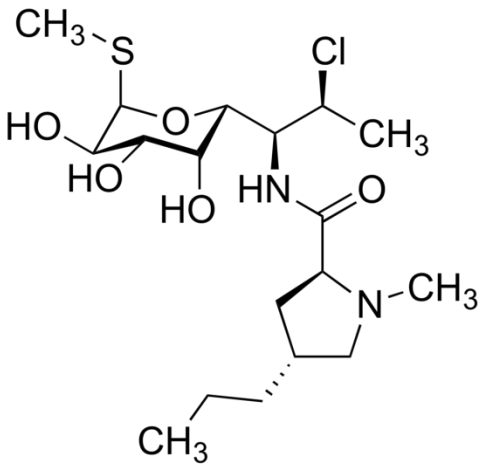
Macrolides

- interfere with movement of mRNA on ribosome (bacteriostatical on G+, chlamydia and mycoplasmata)
- **erythromycin**: subtitute when resistance for PNC
- **clarithromycin**, **azithromycin**,…
- AE: indigestion, inhibition of CYP3A4 (interaction)

Erythromycin

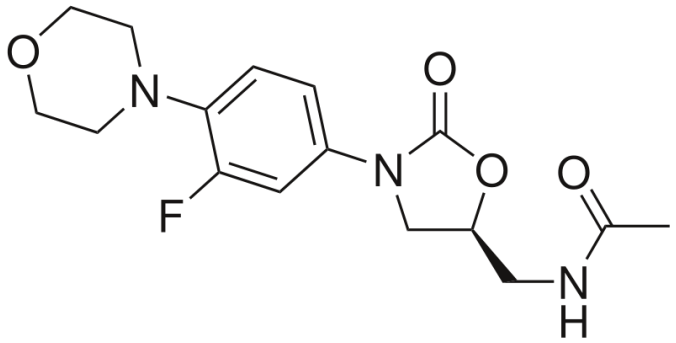


Lincosamides

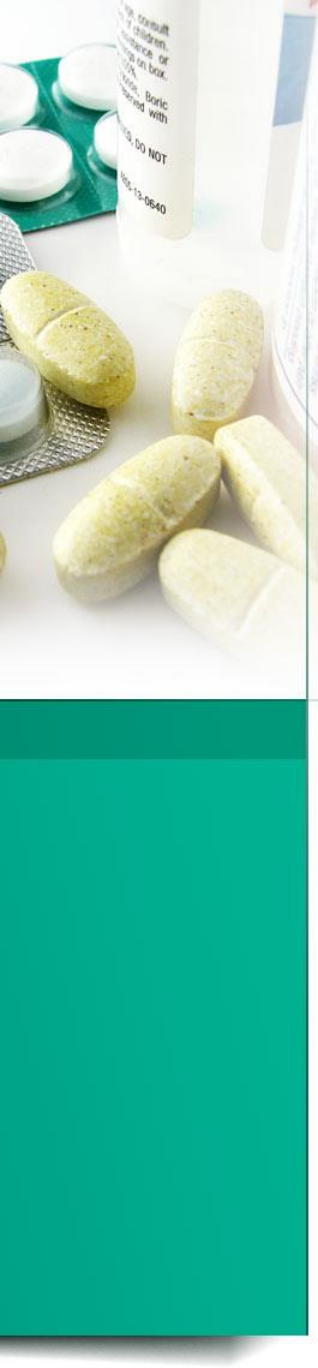


- similar effect as macrolides
- bacteriostatical mainly on G+ aerobes and anaerobes
- **lincomycin**, **clindamycin**
- good bone penetration => th. *Staphylococci* osteomyelitis

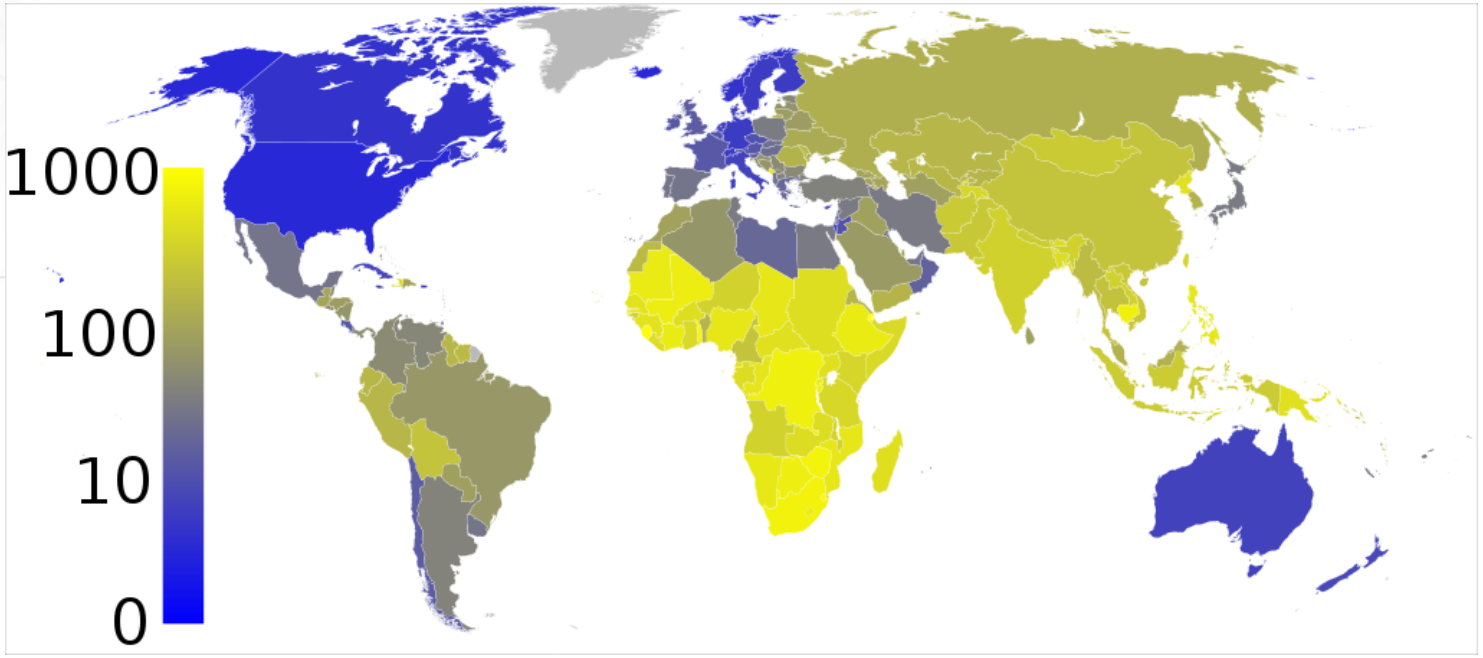
Oxazolidinones



- inhibition of proteosynthesis initiation (complex: ribosomes, mRNA, tRNA+AMK)
- bacteriostatical on G+ bacteria, also MRSA and VRE
- AE: bone marrow depression
- spare, backup antibiotics
- **linezolid**



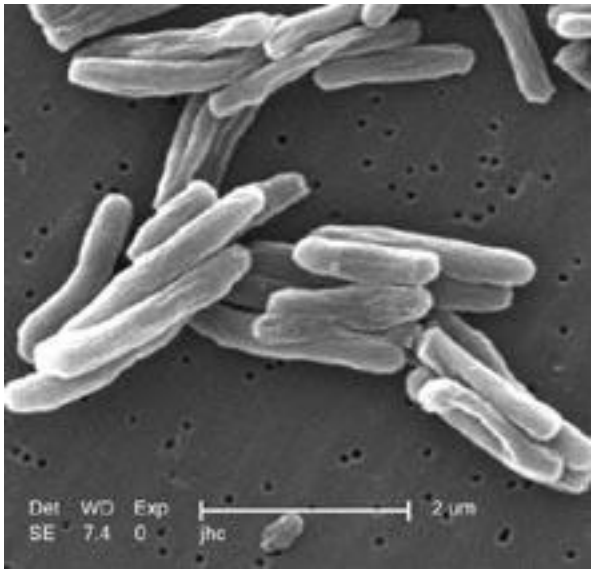
Therapy of tuberculosis



prevalence, 2007 (cases/100 000 inhabitants)

Therapy of tuberculosis

- therapy is long-term (6 – 12 month) and combined (resistance)
- cause: *Mycobacterium tuberculosis*



Therapy of tuberculosis – 1st line

- **izoniazid**: -cidal on growing mycobateria
  - in the mycobacteria converted to isonicotinic acid, which accumulates
  - AE: damage of peripheral nerves and CNS (prevention: vitamin B_6) and of liver
- **rifampicin**
- **streptomycin**

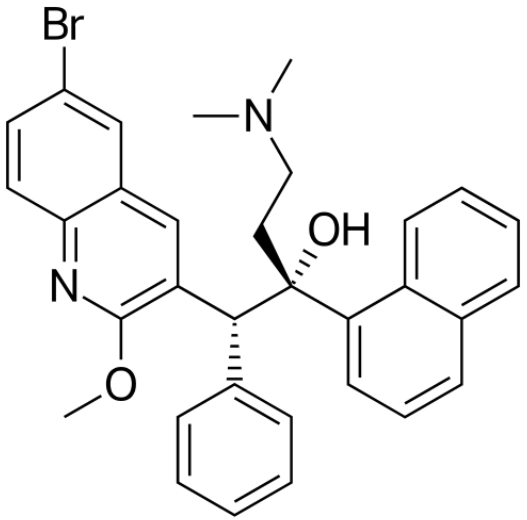
Therapy of tuberculosis – 1st line

- **pyrazinamide:** MoA not clear
  - damage of liver
- **ethambutol**: MoA not clear
  - AE: reversible visual disturbance with colourblindness and scotoms

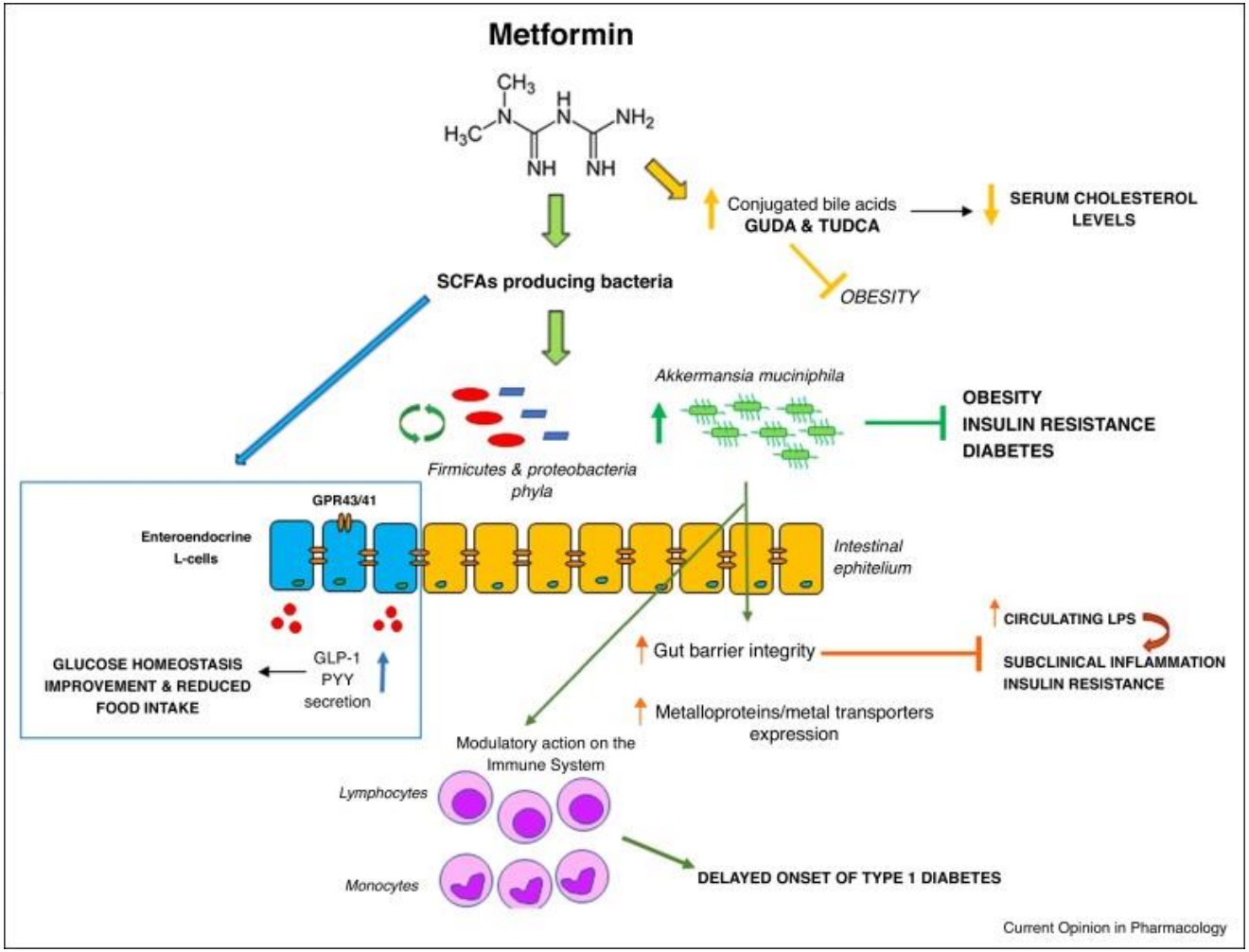
- 2nd line: *p*-aminosalicylic acid, kanamycin, cycloserine, etc.

Therapy of tuberculosis – novel drug

- **bedaquilin**: approv. 2012
  - new class of diarylquinolins; combin. th.
  - I: lung multiresistant TBC
  - MA: inh. mycobacterial ATP-syntase; without energy; -cidal



Microbiome + drugs

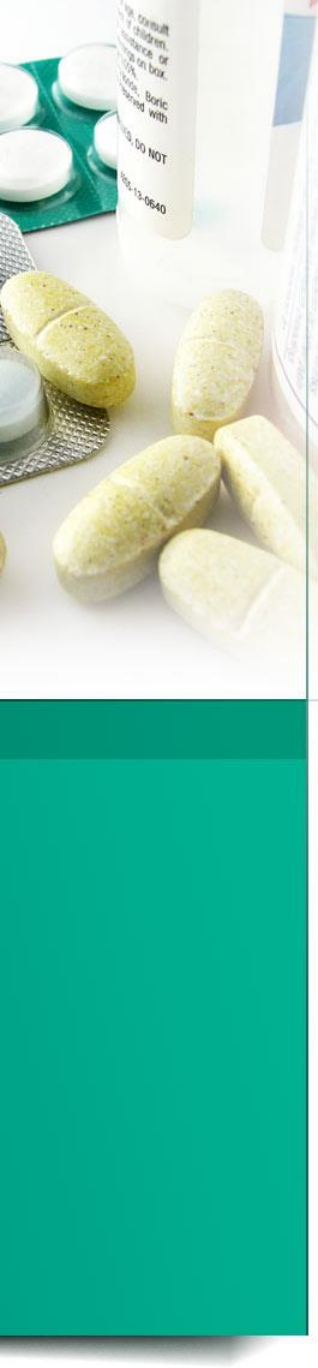


Pascale et al. Curr Op Pharmacol 2019

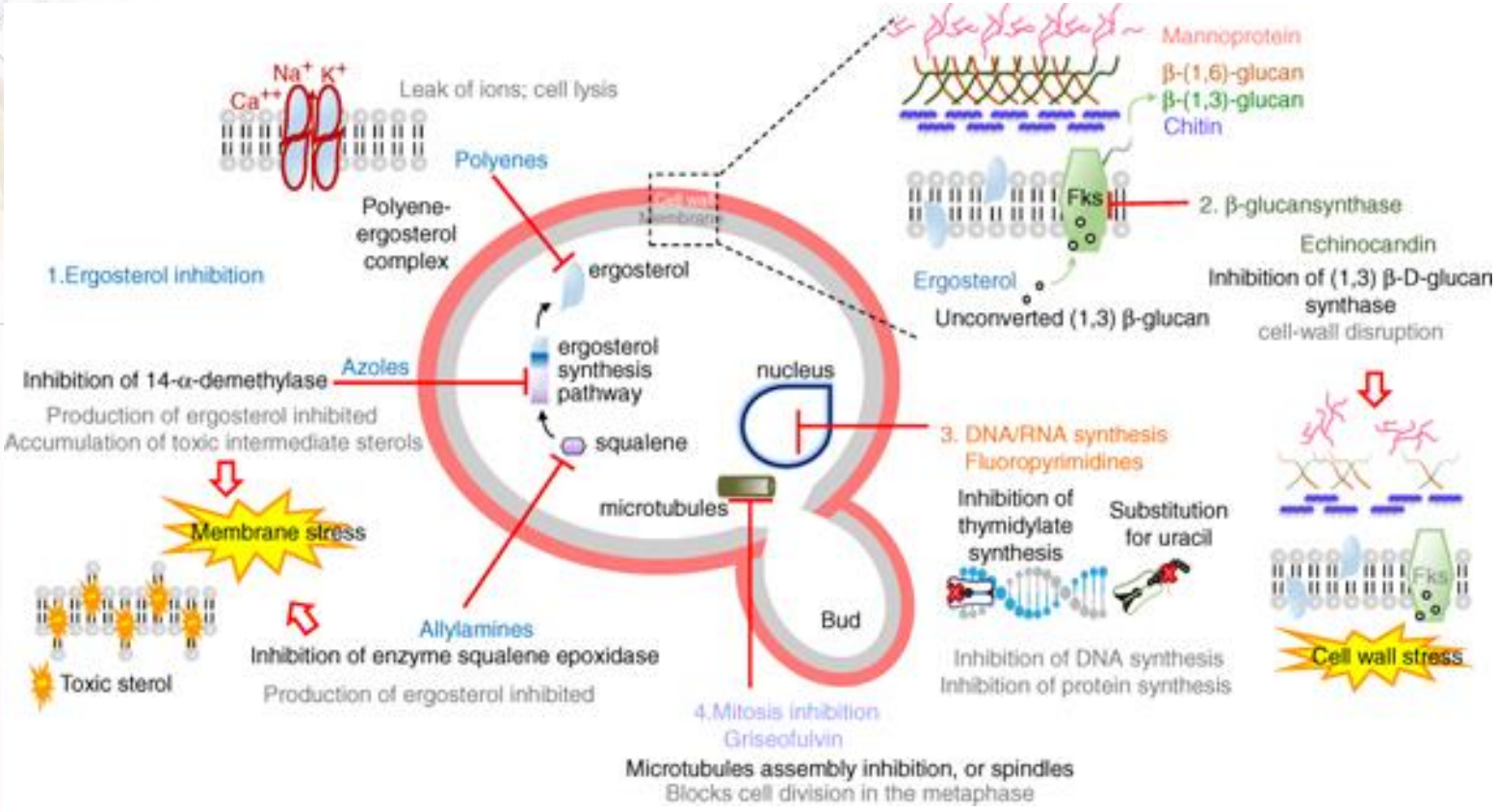
Antifungals

Mycosis

- usually on skin and mucosa – **local** administration – cremes
- rarely, during imunne deficiency also infection of internal organs – **systemic** administration
- most usually caused by: dermatophytes, *Candida albicans* (yeast)



Antifungals

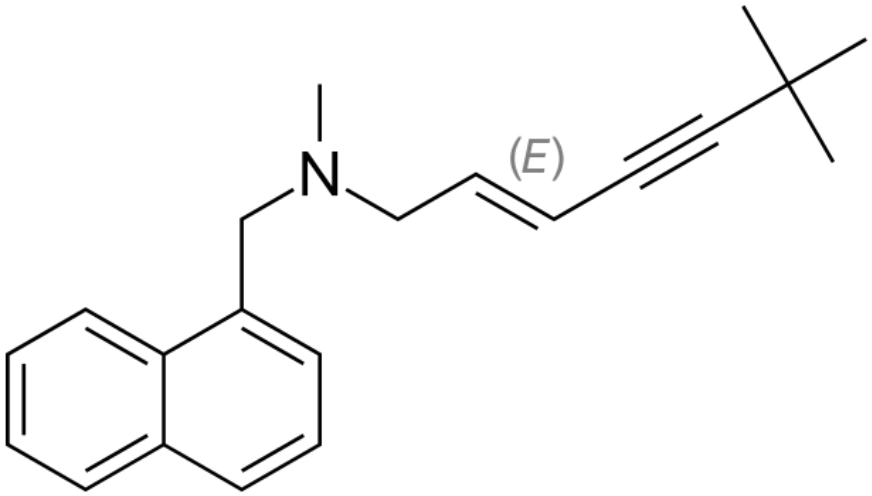


http://www.cellmoloto.net/index.php/acmo/article/view/23955#CIT0004_23955

Antifungals – inhibition of ergosterol

Allylamines - **terbinafine**:

- broad spectrum, low toxicity; suitable p.o. and locally (onychomycosis)
- -statical, sometimes -cidal
- interference with squalenepoxidase

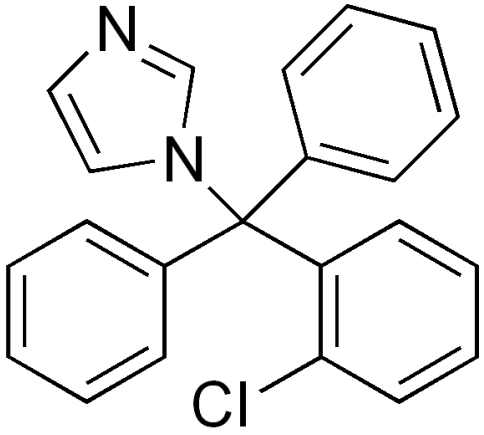


Antifungals – inhibition of ergosterol

Azole antifungals:

Imidazoles:

- –statical, sometimes –cidal
- bad resorption, mainly local admin.
- **clotrimazole**, **econazole**, etc.

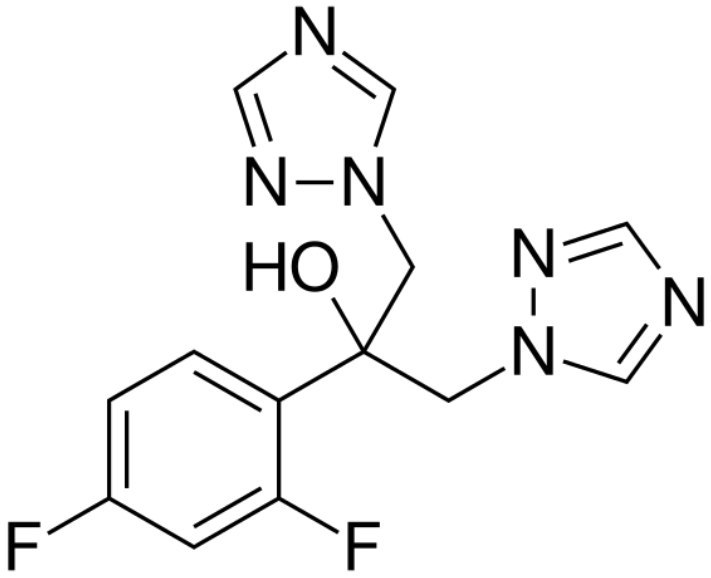


Antifungals – inhibition of ergosterol

Azole antifungals:

Triazoles:

- good resorption and solubility – so p.o. or inj. - systemic
- **fluconazole, itraconazole**



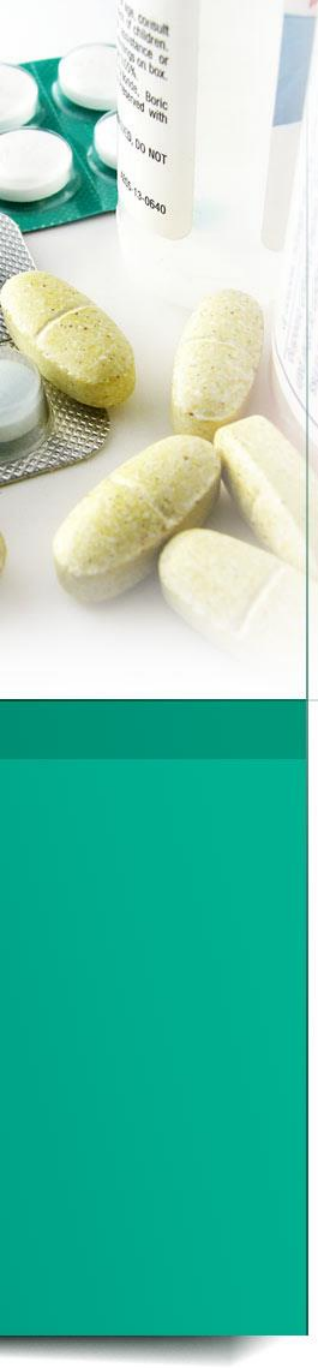
Antifungals – inhibition of ergosterol

Polyene antibiotics:

- form pores in membrane, cell dies
- **amphotericin B**: treatment of systemic infections; bad resorption, so infusions onto blood; AE: chills, fever, CNS disorders
- **nystatin**: only locally against candidosis

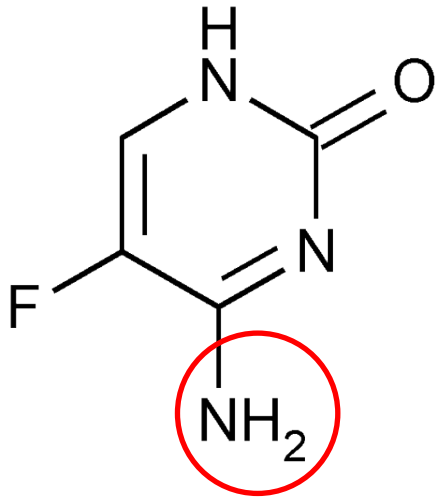
Antifungals – echinocandins

- new group of antifungals
- cyclic polypeptides – inhibition of cell wall, specifically inhibition of synthesis of (1,3)β-glucan – lysis of the cell
- e.g. **capsofungin**



Antifungals – synthesis of DNA/RNA

- **flucytosine**: by cytosinedeaminase specific for *Candida* yeasts converted to 5-fluorouracil
- antimetabolite – damages NA, –cidal
- narrow spectrum, in combination with amphotericin B



Antifungals – inhibition of mitosis

- **griseofulvin**: procust of mold *P. griseofulvum*
- acts only against dermatophytes; mitotic spidle toxin - fungistatical
- although acts locally, must be administred systemically (stores in ceratin – which is then not a good broth for fungi) – used for dermatomycosis, incl. onychomycosis