411-9

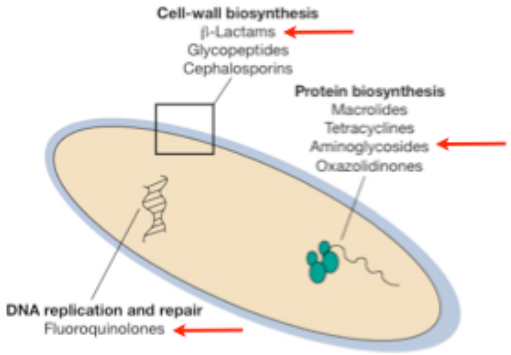
Antibiotics and resistance

I. Fluoroquinolones
II. beta-lactams
III. aminoglycosides

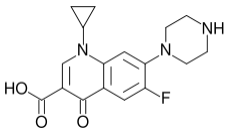
Model Loses Hands, Feet to Severe Infection

Friday , January 23, 2009

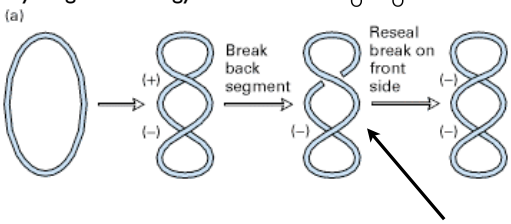
Proven targets for antibiotics



Action of fluoroquinolones (e.g., ciprofloxacin)



Primary target= DNA gyrase



fluorquinolones stabilize cleaved DNA intermediate
=> leads to chromosome fragmentation and induction of the SOS response

Secondary target = Topoisomerase IV (chromosome partitioning)

Fluoroquinolone resistance

Target site mutations:

Missense changes at a limited number of sites render gyrase and/or Topoisomerase IV resistant to inhibition

Fluoroquinolone resistance

Damage tolerance (homeostasis):

Fluoroquinolone inhibition of gyrase, topoisomerase IV

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DNA damage

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SOS induction

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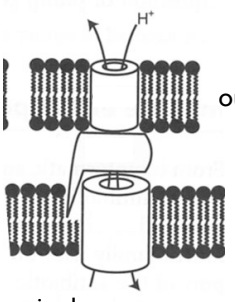
Repair of DNA damage

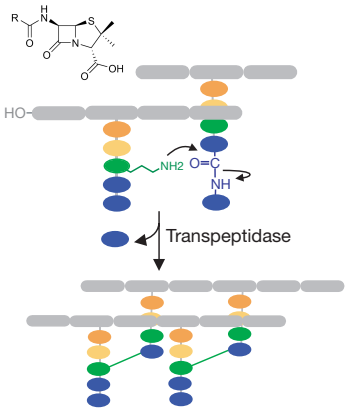
Important consequence: Increased mutation rate due to error-prone replication

Fluoroquinolone resistance

Antibiotic efflux:



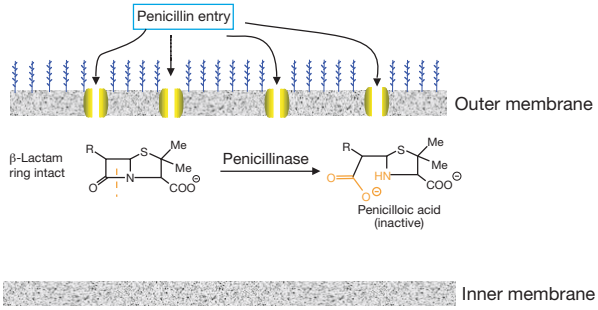
Action of beta-lactams
(e.g., penicillin)



Peptidoglycan biosynthesis: peptide cross-linking step

beta-lactam resistance:

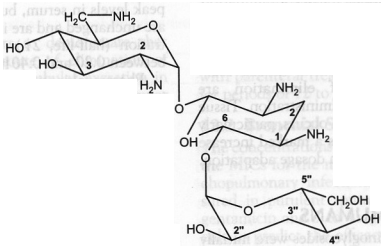
Antibiotic inactivation



beta-lactam resistance:

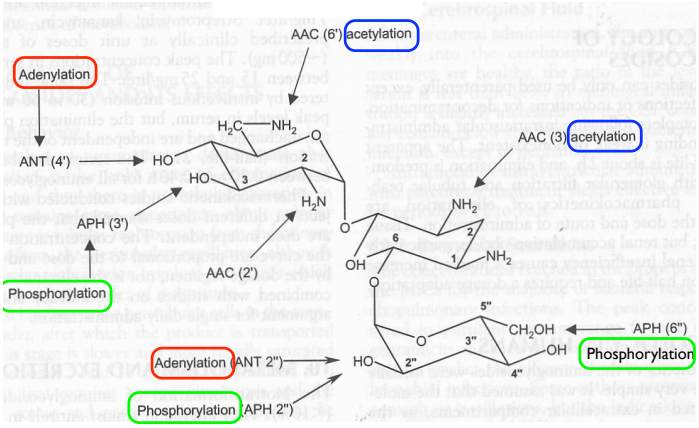
Damage tolerance

Action of aminoglycosides
(e.g., kanamycin)



Aminoglycoside resistance

antibiotic modification



Aminoglycoside resistance

target modification

aminoglycoside sensitive

16S ribosomal RNA

specific methylase

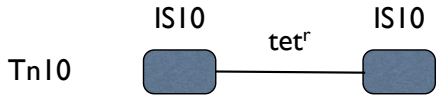
methyl-16S ribosomal RNA

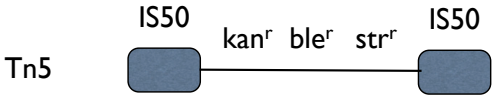
aminoglycoside resistant

Genetic elements associated with resistance

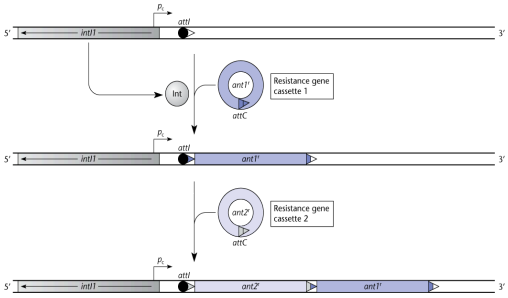
I. Transposons
II. Integrons
III. Plasmids
IV. Integrative conjugative elements

I. Transposons- examples

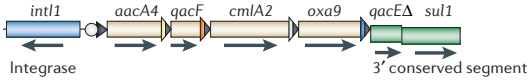




II. Integrons- elements of bacterial evolution

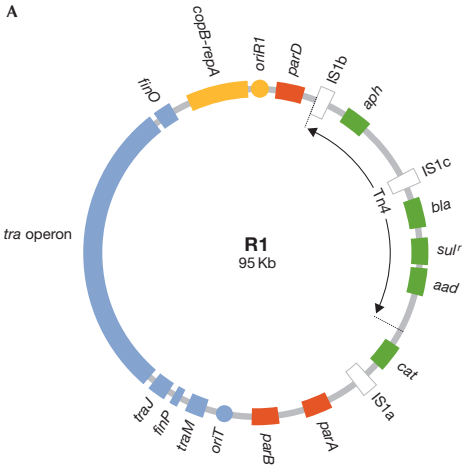


II. Integrons- example



III. Plasmid- example

Conjugal plasmid RI



IV. Integrative conjugative elements