Bacterial Structure and Mechanisms of Antimicrobial Action

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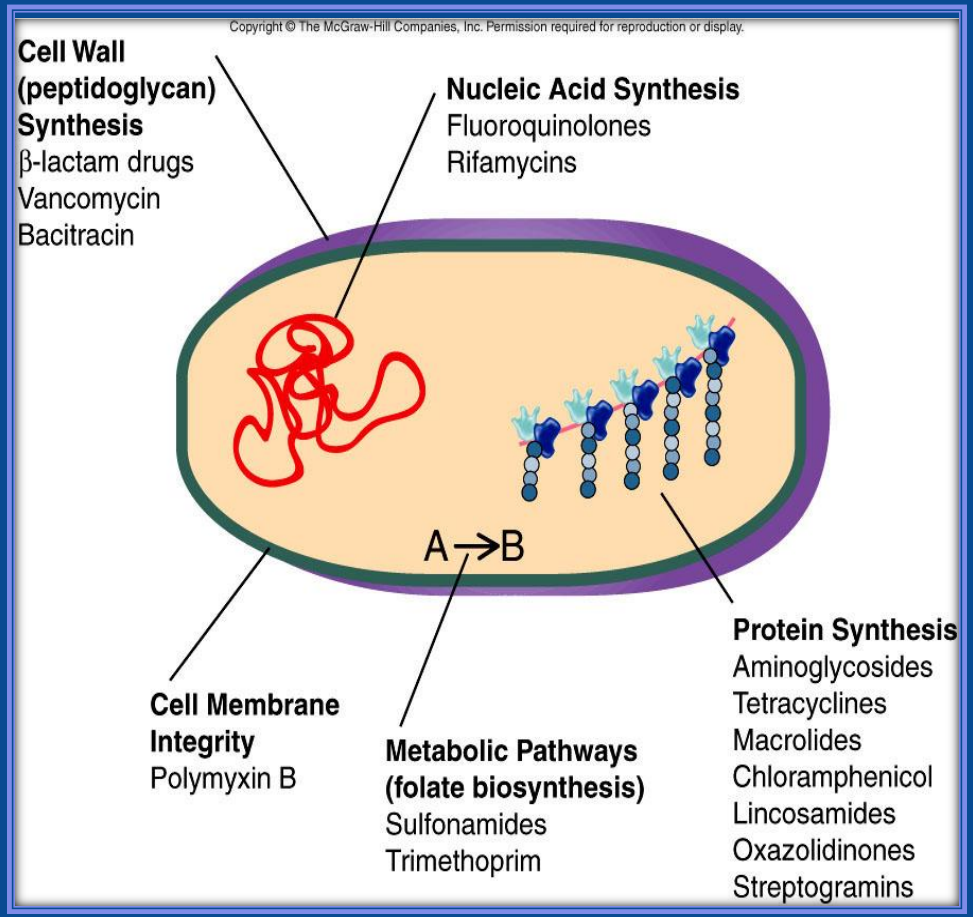
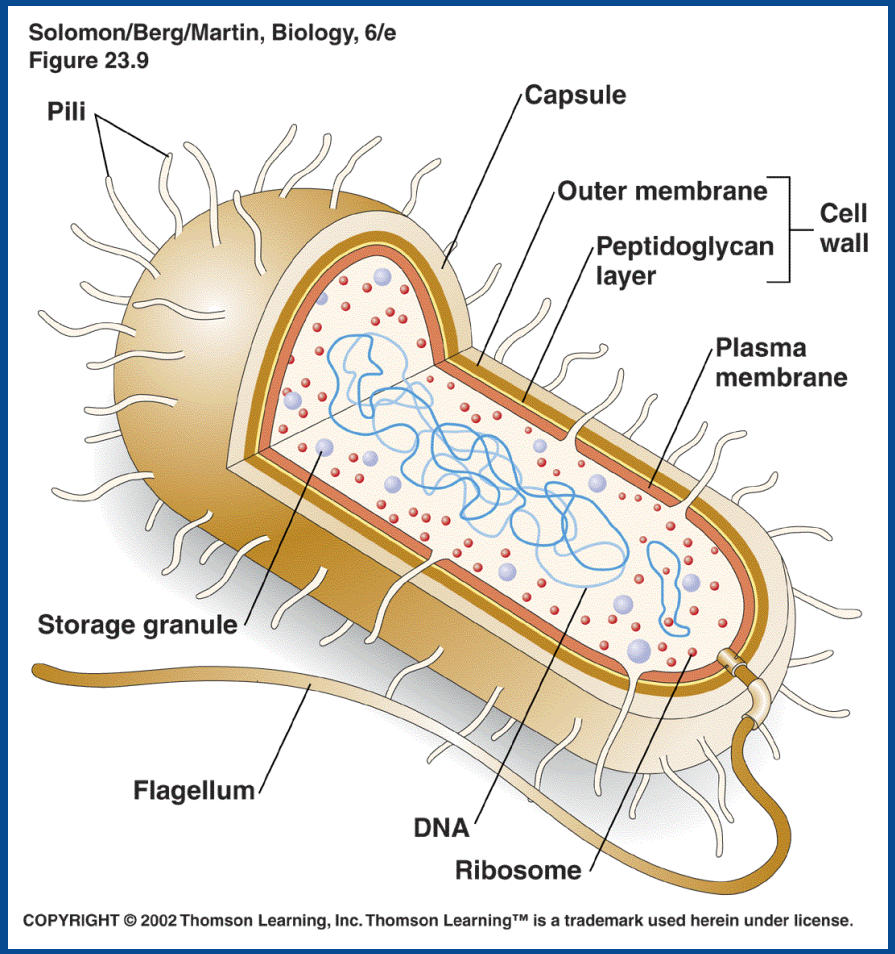
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- Inhibition of cell wall synthesis
- Inhibition of protein synthesis
- Inhibition of nucleic acid synthesis
- Inhibition of metabolic pathways
- Interference with cell membrane integrity

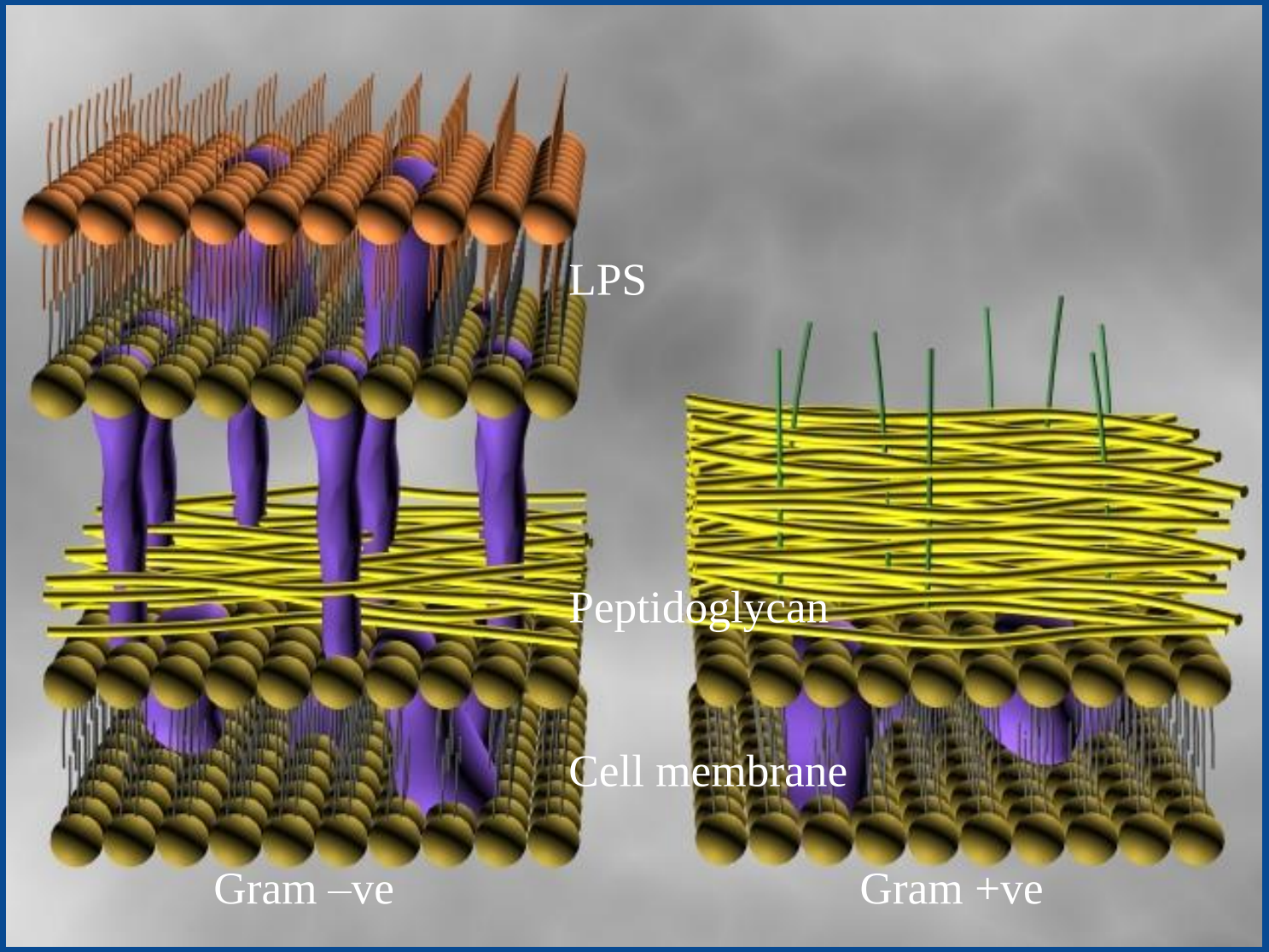


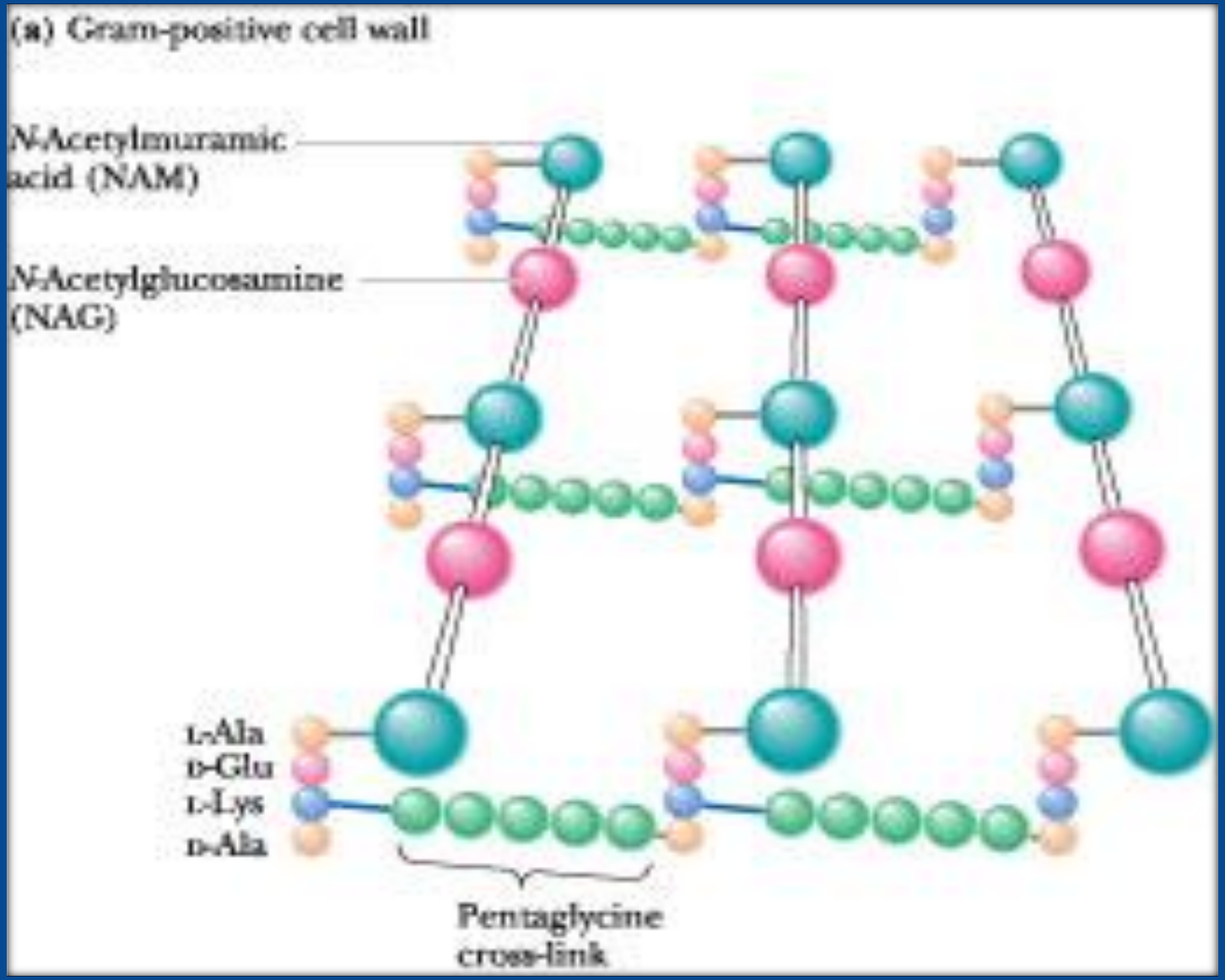
Prokaryotic Organization

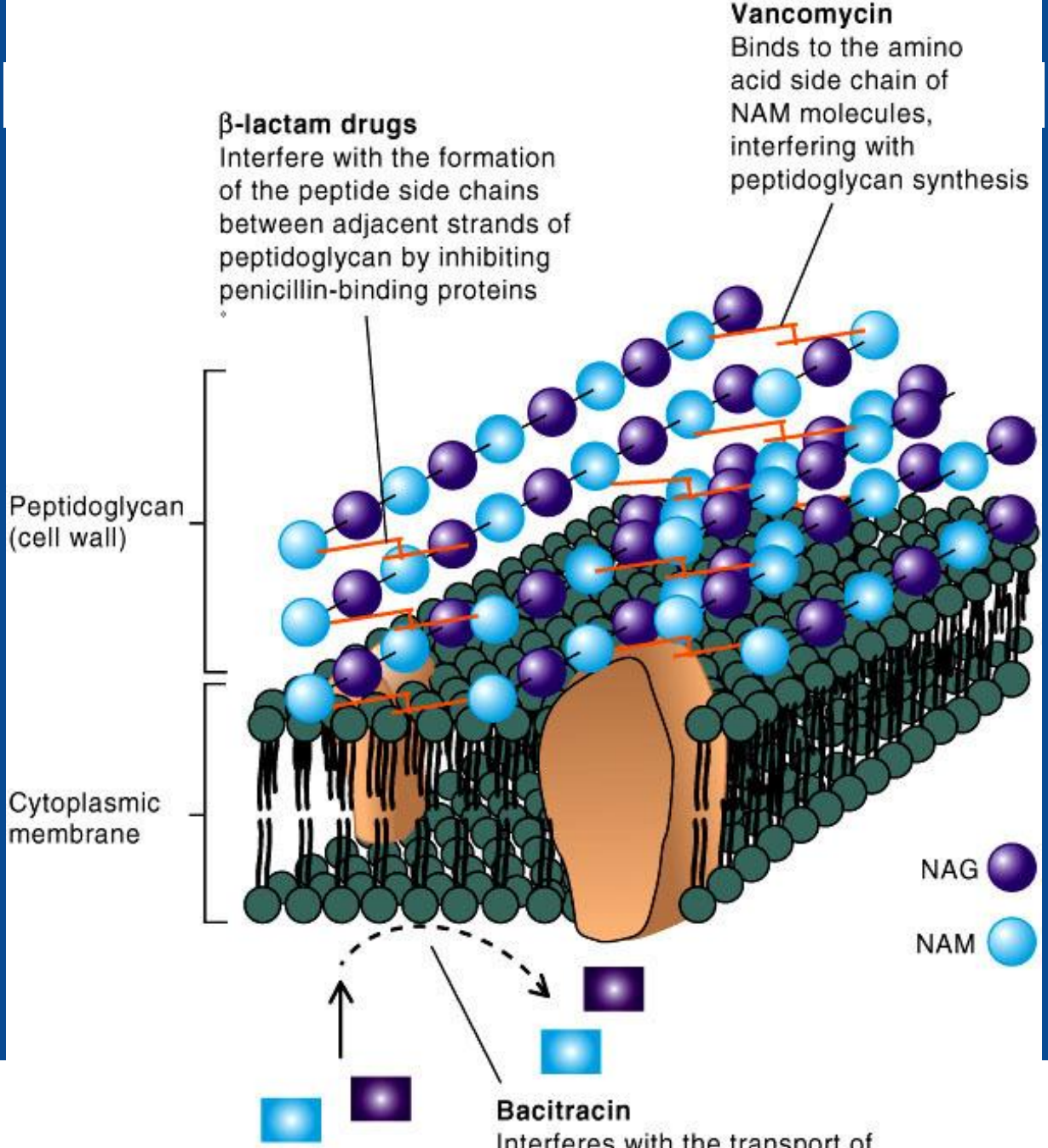
- No nucleus
- DNA held in *nucleoid*
- Cytoplasm dense:
  - Ribosomes
  - Storage granules
  - Limited membranes
- Plasma membrane
- Corkscrew flagellum
- Cell wall is complex
  - Outer membrane
  - Peptidoglycan layer
  - Capsule
  - Pili extend from cytoplasm

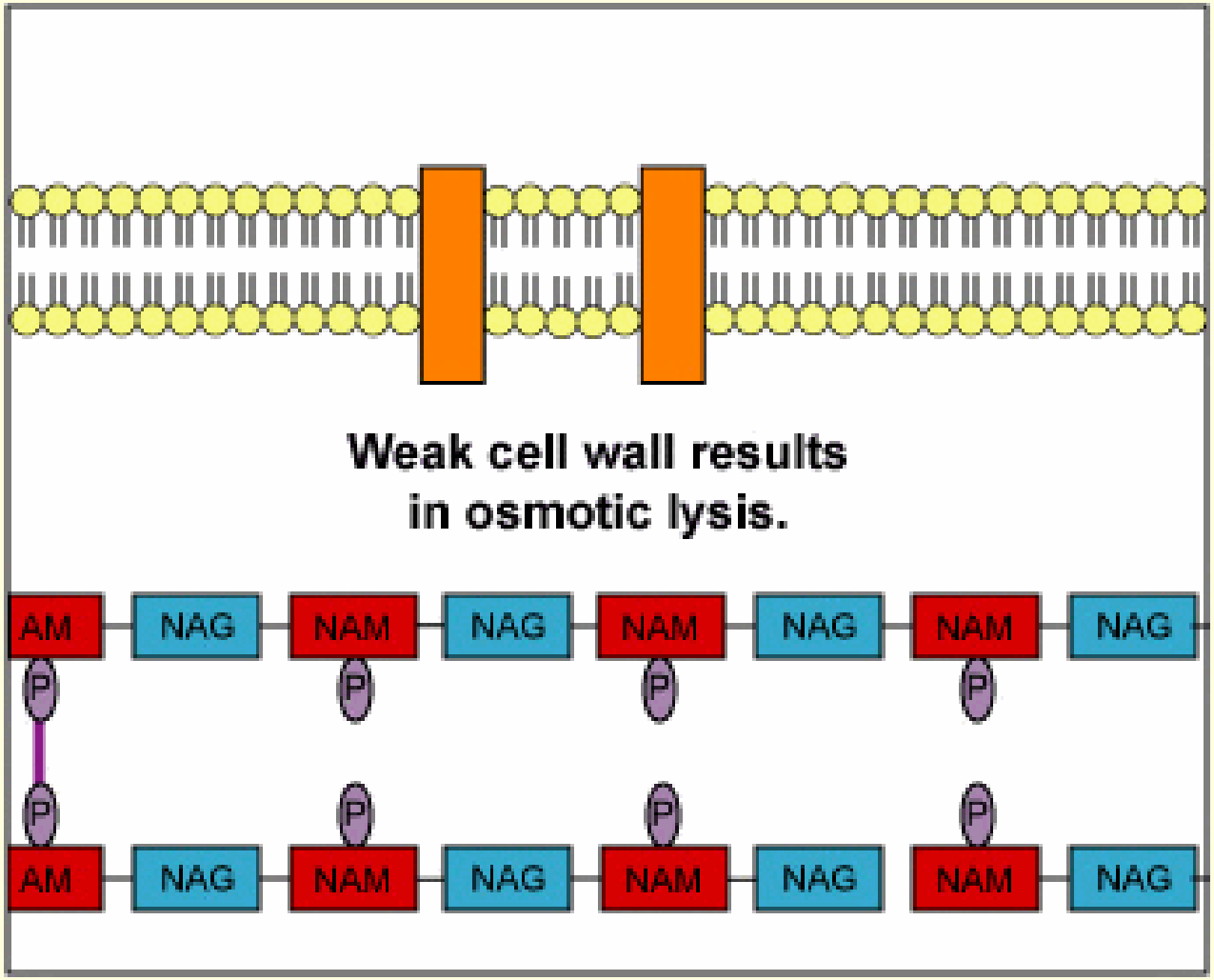


INHIBITION OF CELL WALL SYNTHESIS

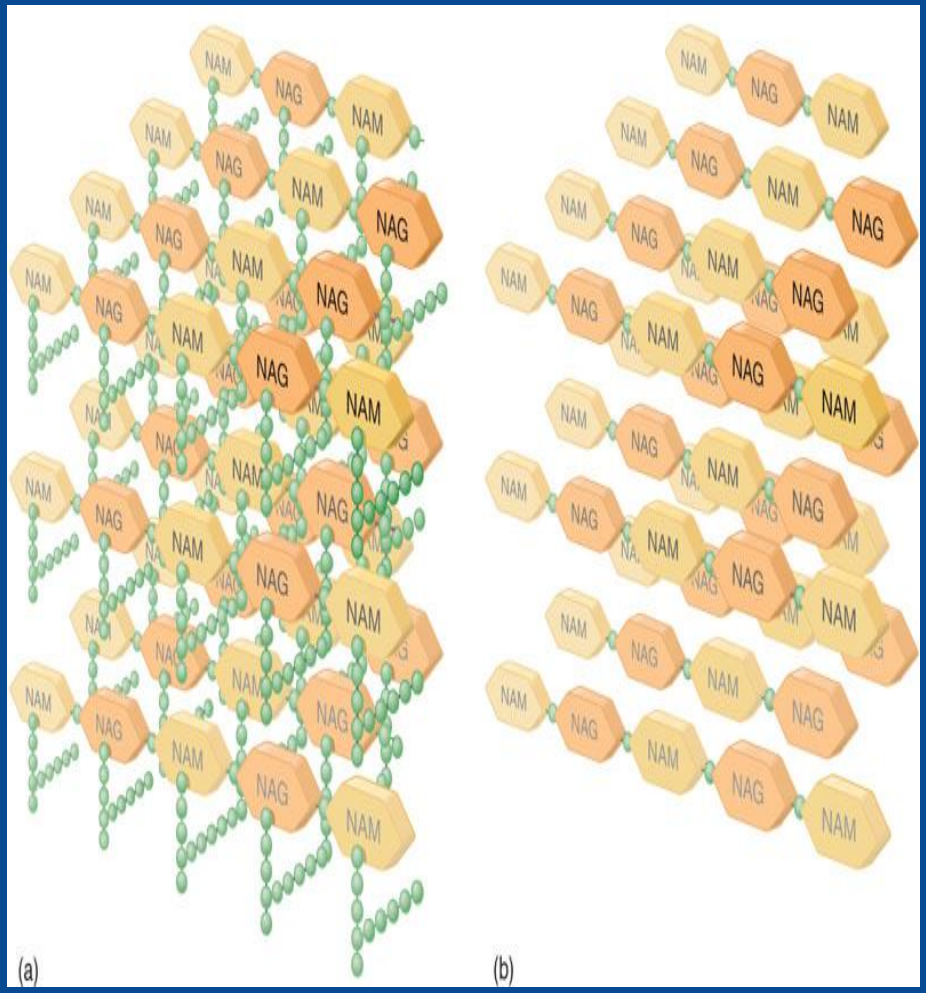

LPS
Peptidoglycan
Cell membrane
Gram –ve
Gram +ve


(a) Gram-positive cell wall
N-Acetylmuramic acid (NAM)
N-Acetylglucosamine (NAG)
L-Ala
D-Glu
L-Lys
D-Ala
Pentaglycine cross-link


Vancomycin
Binds to the amino acid side chain of NAM molecules, interfering with peptidoglycan synthesis
β-lactam drugs
Interfere with the formation of the peptide side chains between adjacent strands of peptidoglycan by inhibiting penicillin-binding proteins
Peptidoglycan (cell wall)
Cytoplasmic membrane
NAG
NAM
Bacitracin
Interferes with the transport of peptidoglycan precursors across the cytoplasmic membrane

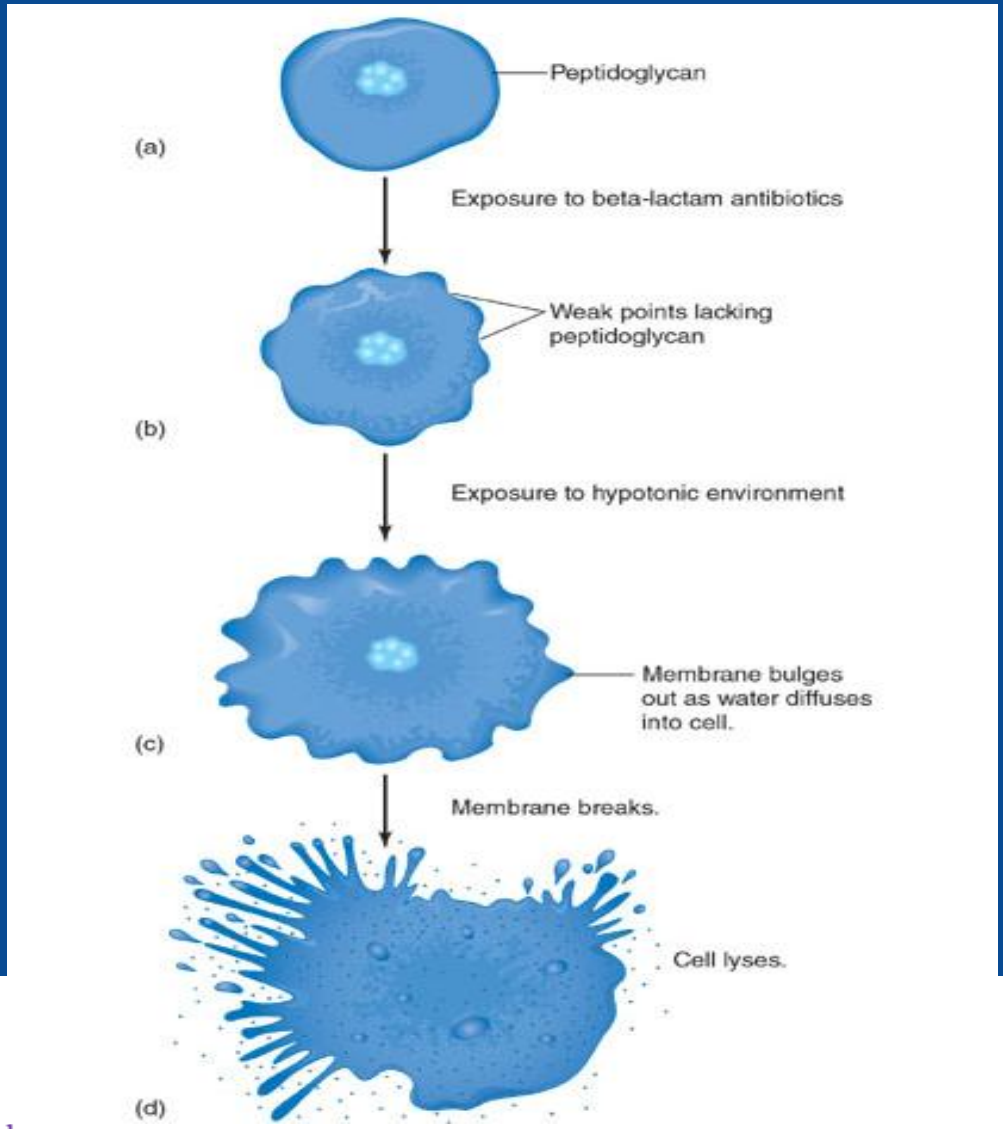

Weak cell wall results
in osmotic lysis.
AM
NAG
NAM
NAG
NAM
NAG
NAM
NAG
P
P
P
P
P
P
P
P
AM
NAG
NAM
NAG
NAM
NAG
NAM
NAG

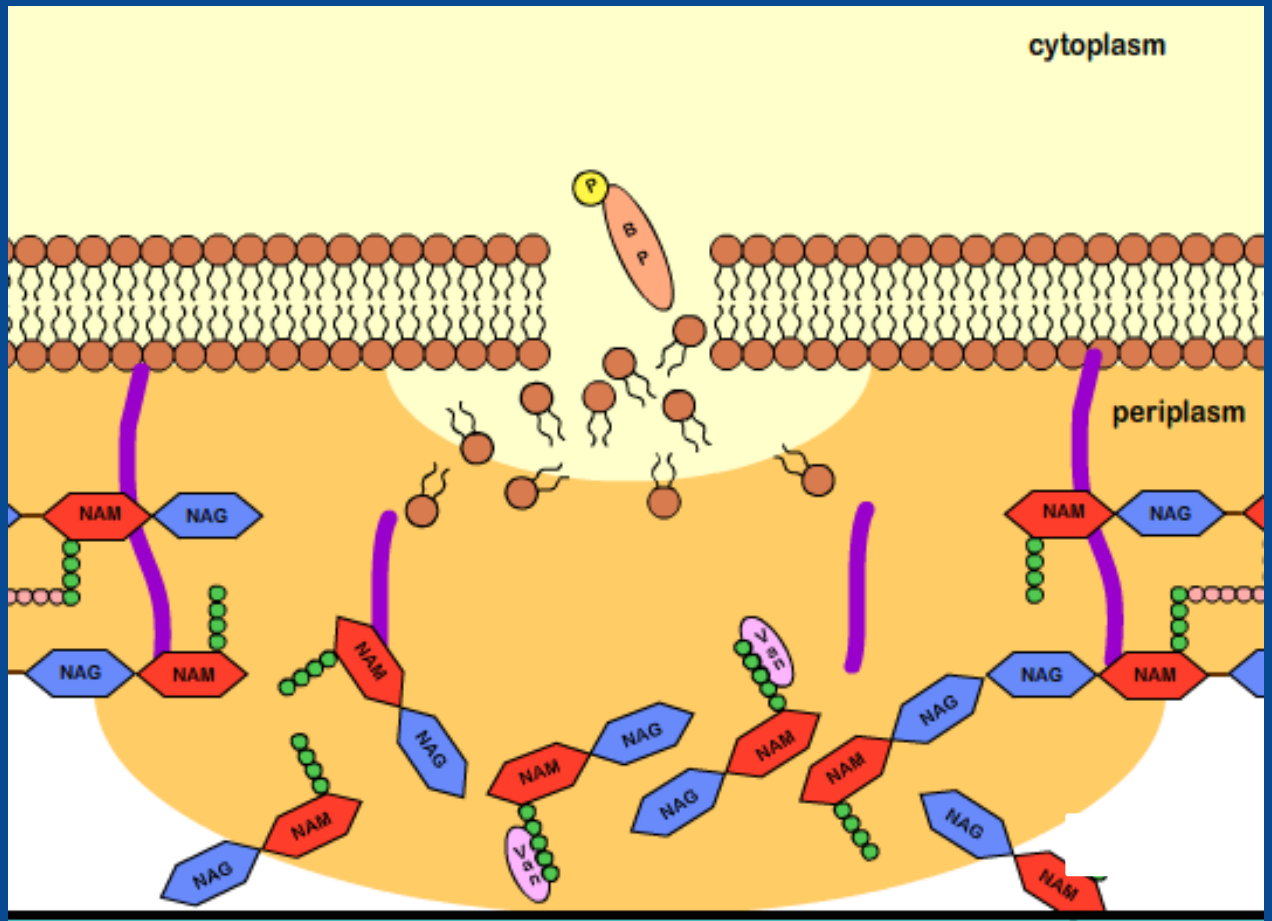
Competitively inhibits function of penicillin-binding proteins



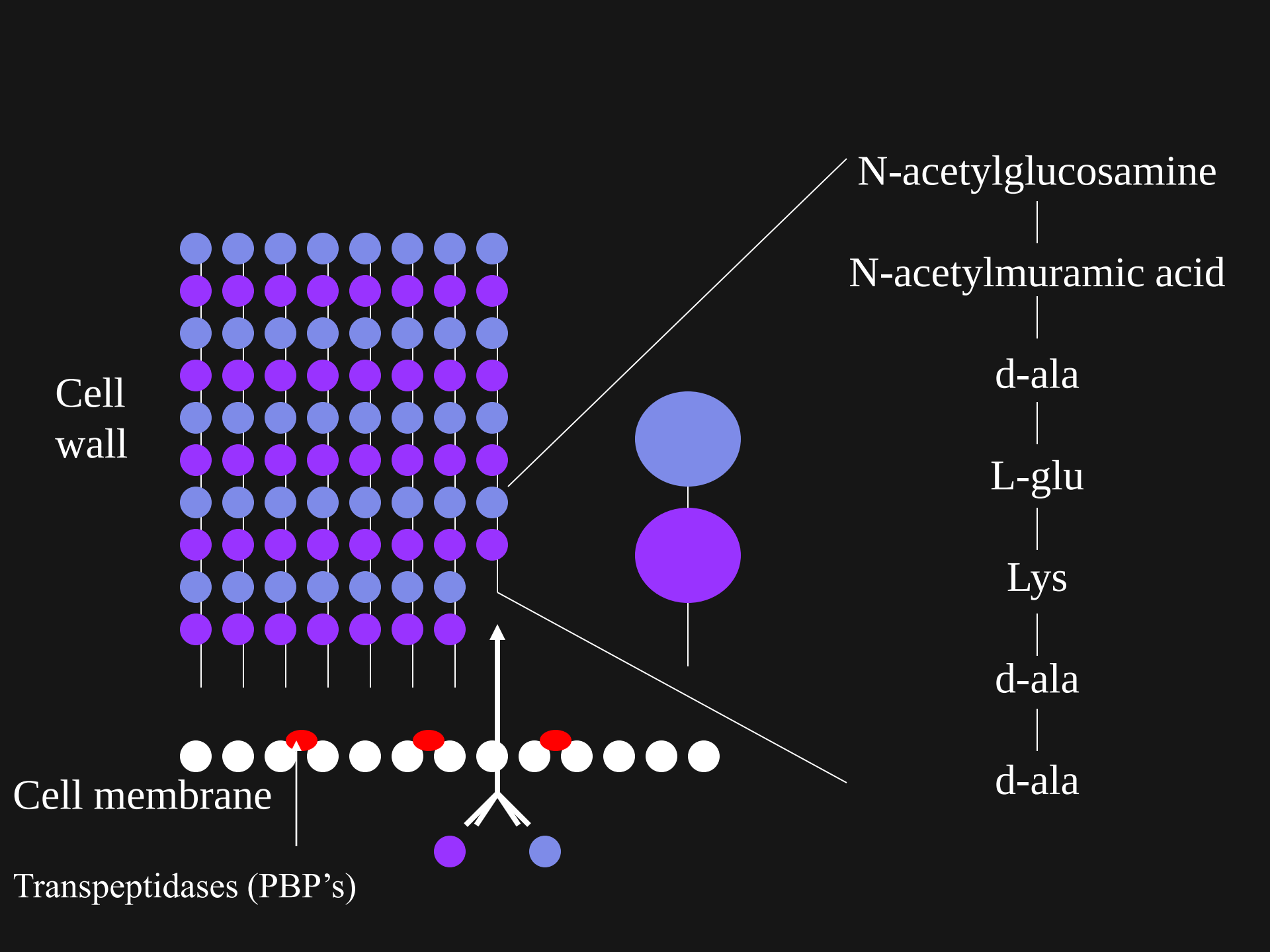
Inhibits peptide bridge formation between

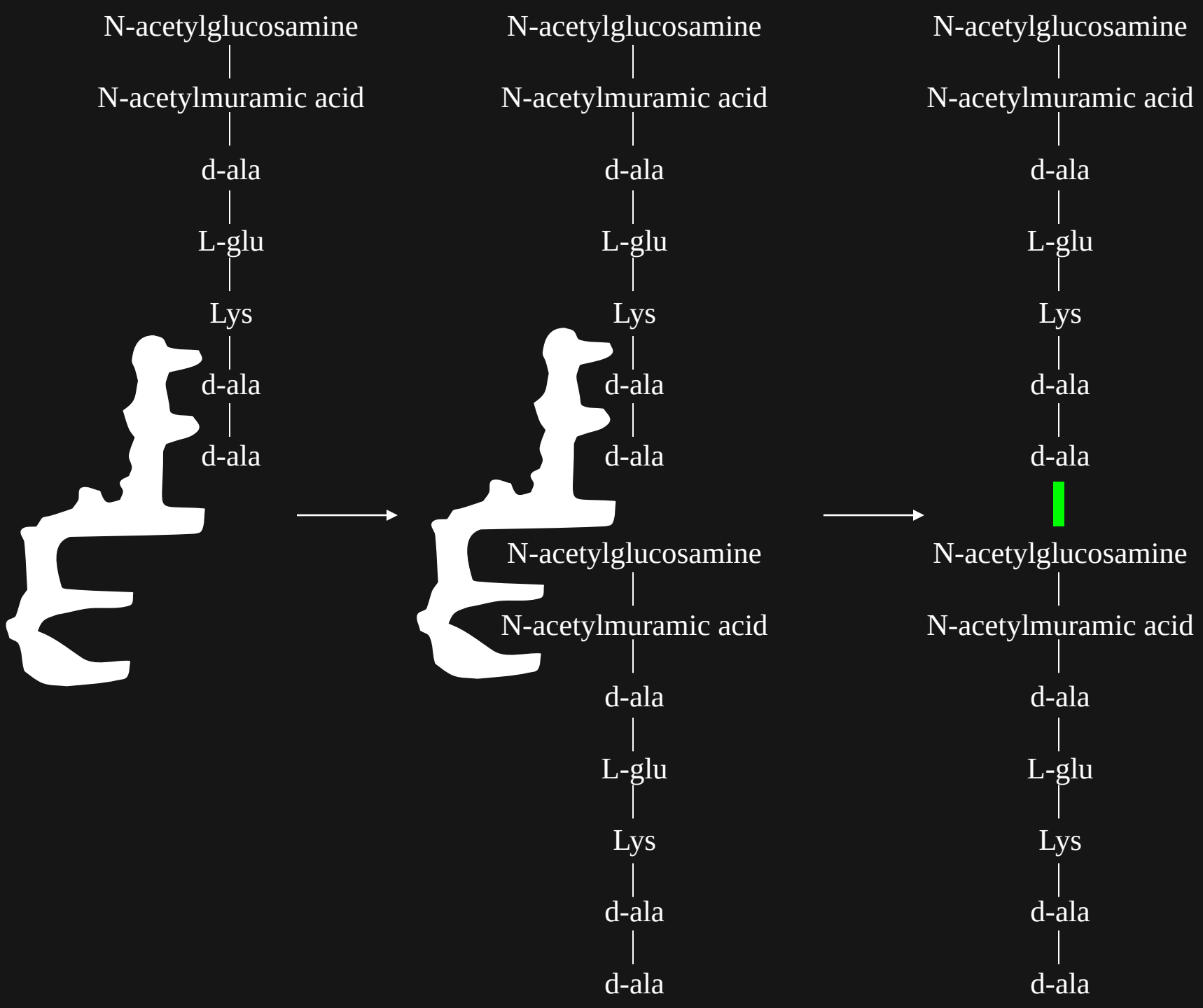
The weakness in the cell wall causes the cell to lyze





As the autolysins continue to break the peptide cross-links and new cross-links fail to form, the bacterium bursts from osmotic lysis.


N-acetylglucosamine
N-acetylmuramic acid
d-ala
L-glu
Lys
d-ala
d-ala
Cell wall
Cell membrane
Transpeptidases (PBP's)


N-acetylglucosamine
N-acetylmuramic acid
d-ala
L-glu
Lys
d-ala
d-ala
N-acetylglucosamine
N-acetylmuramic acid
d-ala
L-glu
Lys
d-ala
d-ala
N-acetylglucosamine
N-acetylmuramic acid
d-ala
L-glu
Lys
d-ala
d-ala
N-acetylglucosamine
N-acetylmuramic acid
d-ala
L-glu
Lys
d-ala
d-ala
N-acetylglucosamine
N-acetylmuramic acid
d-ala
L-glu
Lys
d-ala
d-ala

Mechanism of action of Vancomycin

Vancomycin blocks cell wall synthesis
By binding to the d-alanyl-d-alanine site
on the growing peptidoglycan chain

N-acetylglucosamine

N-acetylmuramic acid

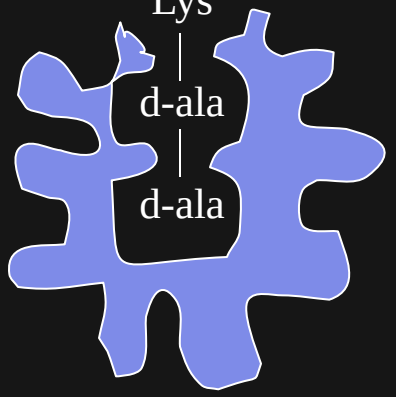
d-ala

L-glu

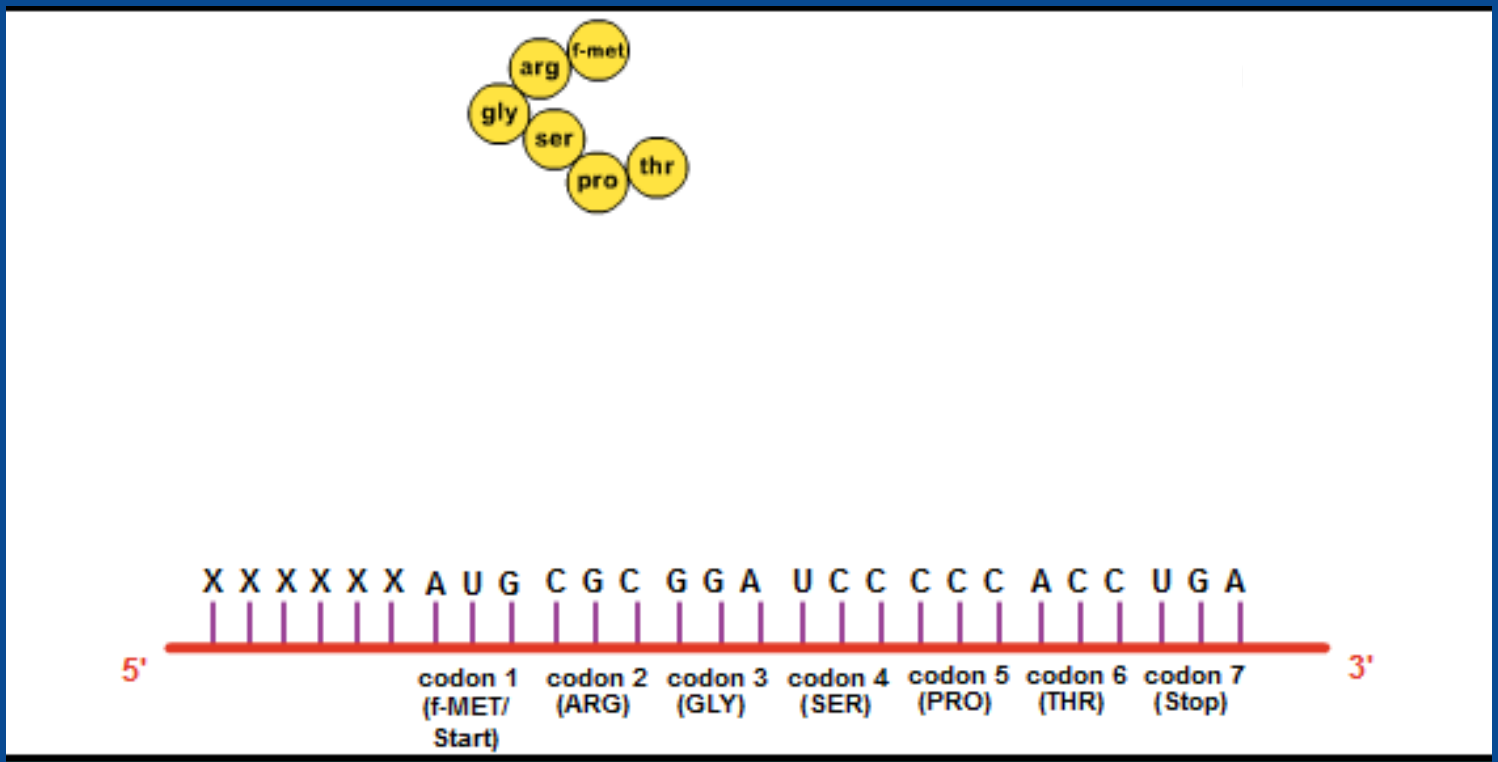
Lys

d-ala

d-ala

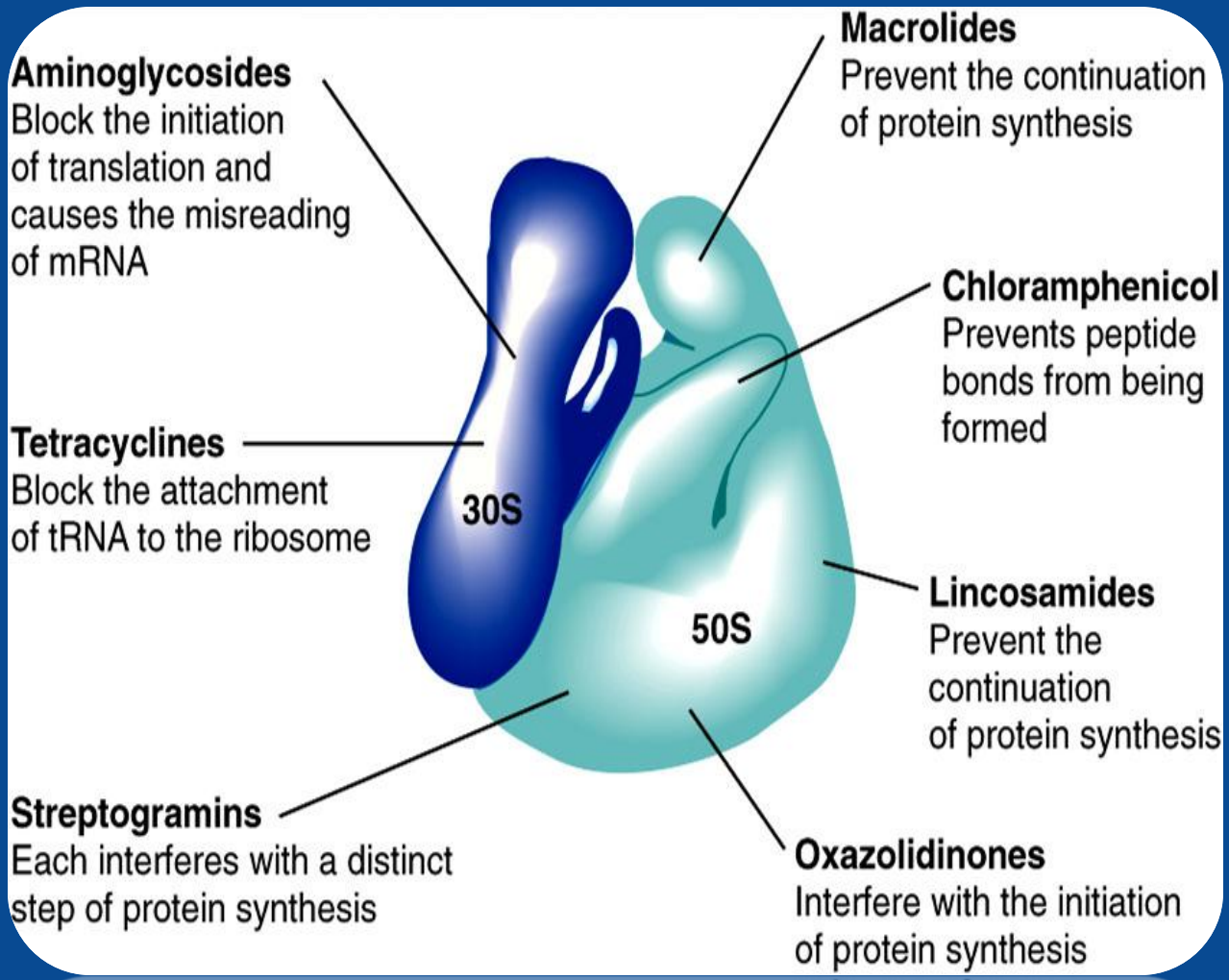


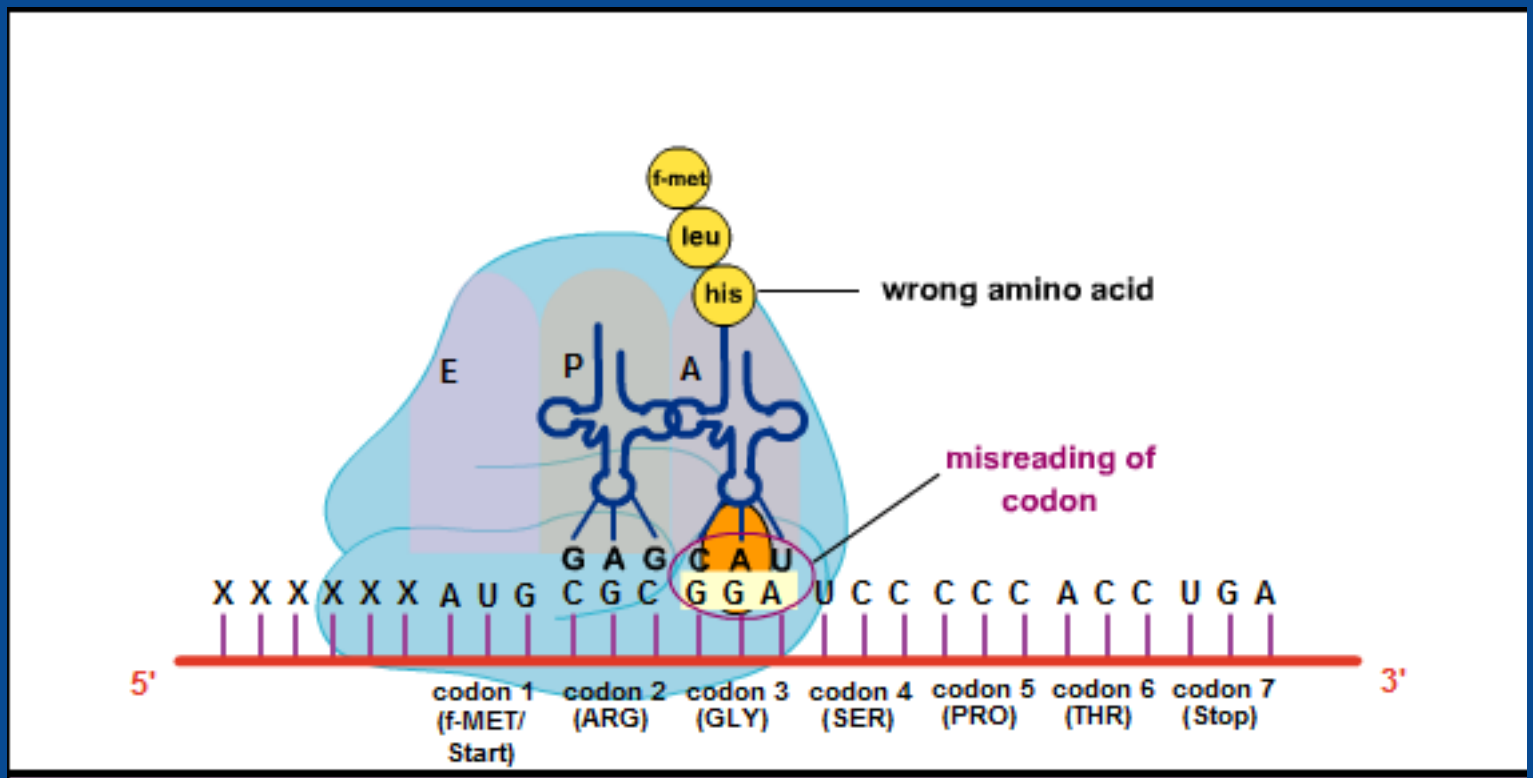
INHIBITION OF PROTEIN SYNTHESIS



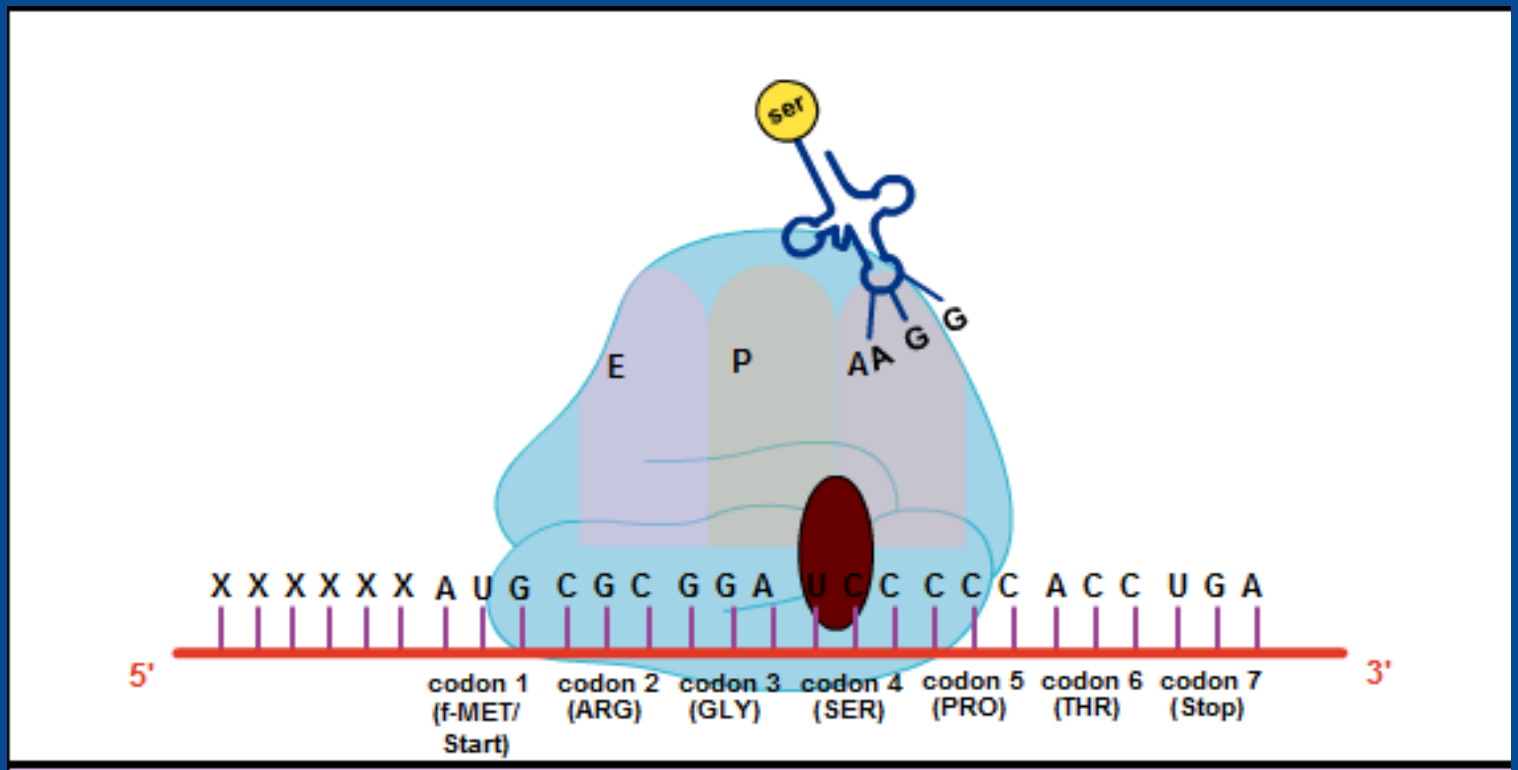
There is no corresponding tRNA for a stop codon - UGA in this case. The completed protein is released from the last tRNA and the ribosomal subunits separate.

Inhibition of Protein Synthesis

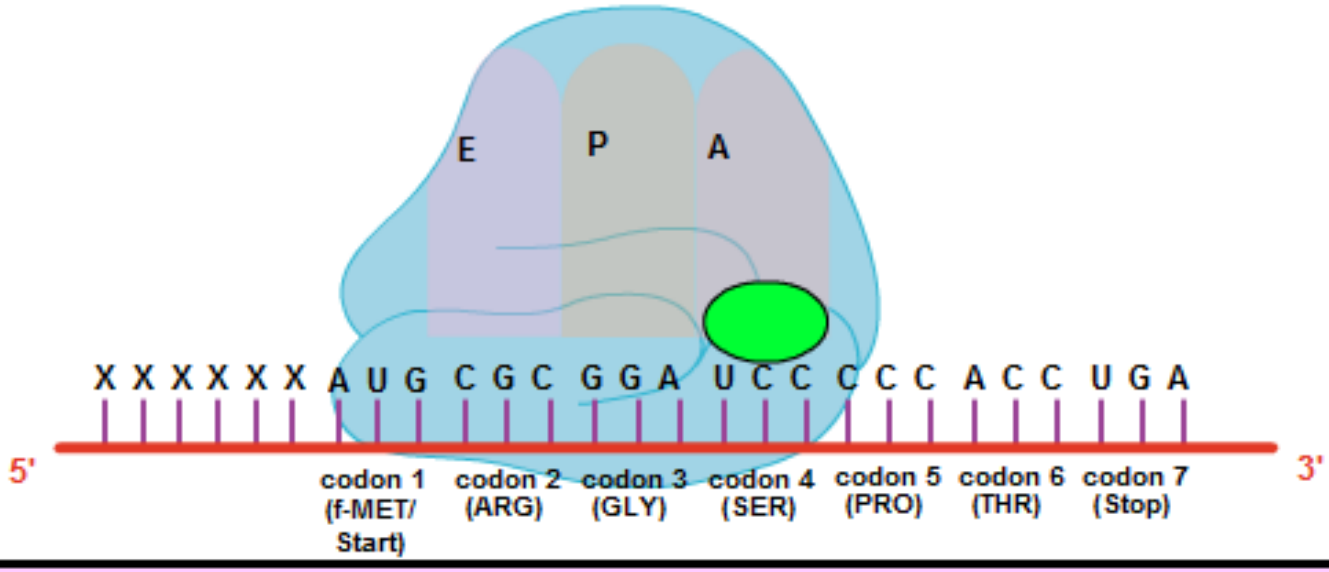




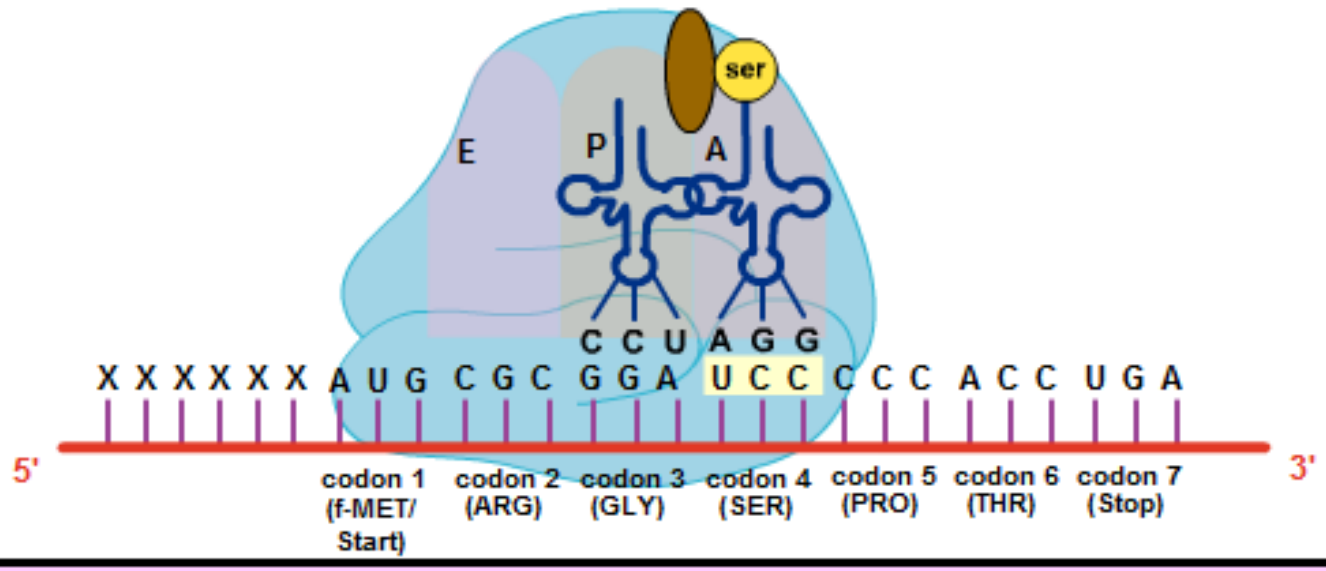
In this example, the codon GGA codes for the amino acid glycine. As a result of misreading, a near-match tRNA with the anticodon CAU pairs with the GGA codon. This tRNA, however, carries the amino acid histidine not glycine.



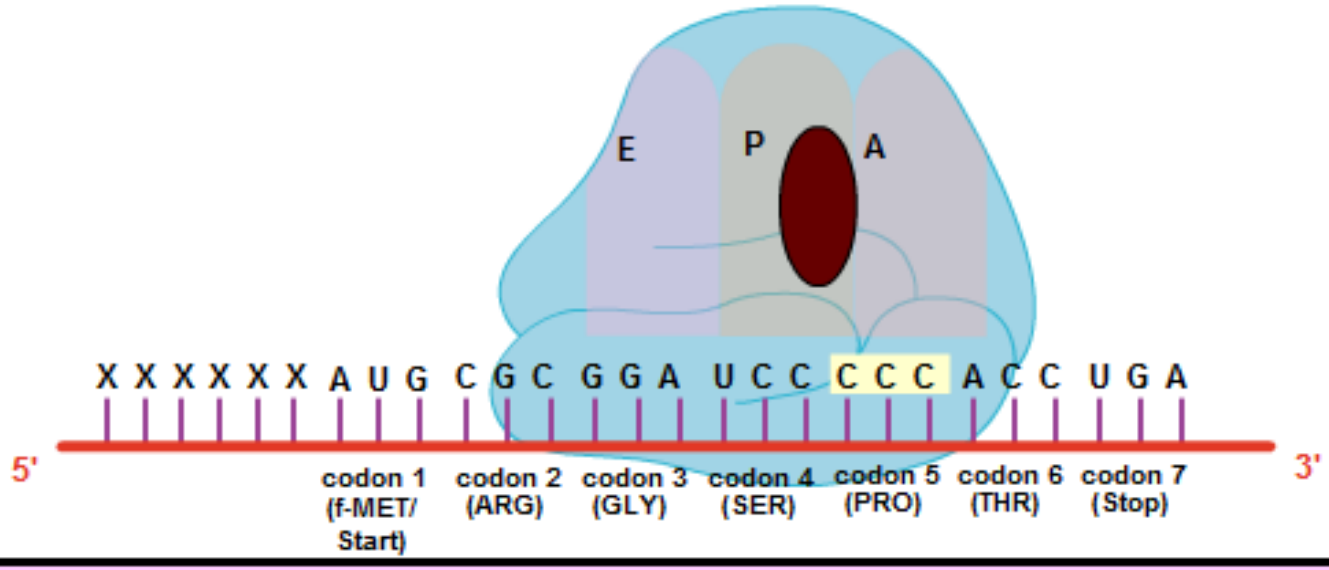
The aminoglycosides bind irreversibly to the 30S subunit of bacterial ribosomes. In addition to interfering with the proofreading process as described in mechanism 1, there is evidence that aminoglycosides also prevent the transfer of the peptidyl tRNA from the A-site to the P-site, thus preventing the elongation of the polypeptide chain.



The tetracyclines block bacterial translation by binding reversibly to the 30S ribosomal subunit. This prevents the binding of the aminoacyl tRNAs (charged tRNAs) to the A-site of the ribosome.



Macrolides bind reversibly to the 50S subunit of bacterial ribosomes. Macrolides are thought to inhibit elongation of the protein by preventing the enzyme peptidyltransferase from forming peptide bonds between the amino acids.



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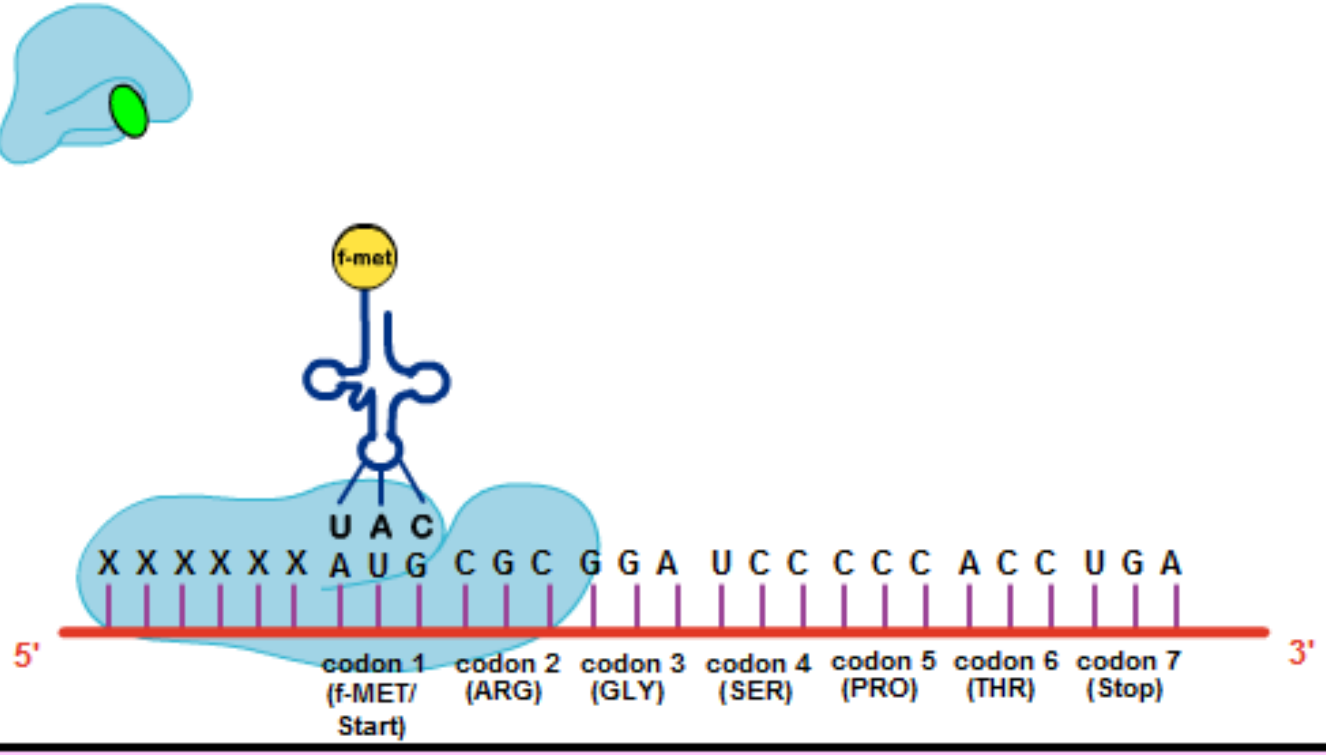
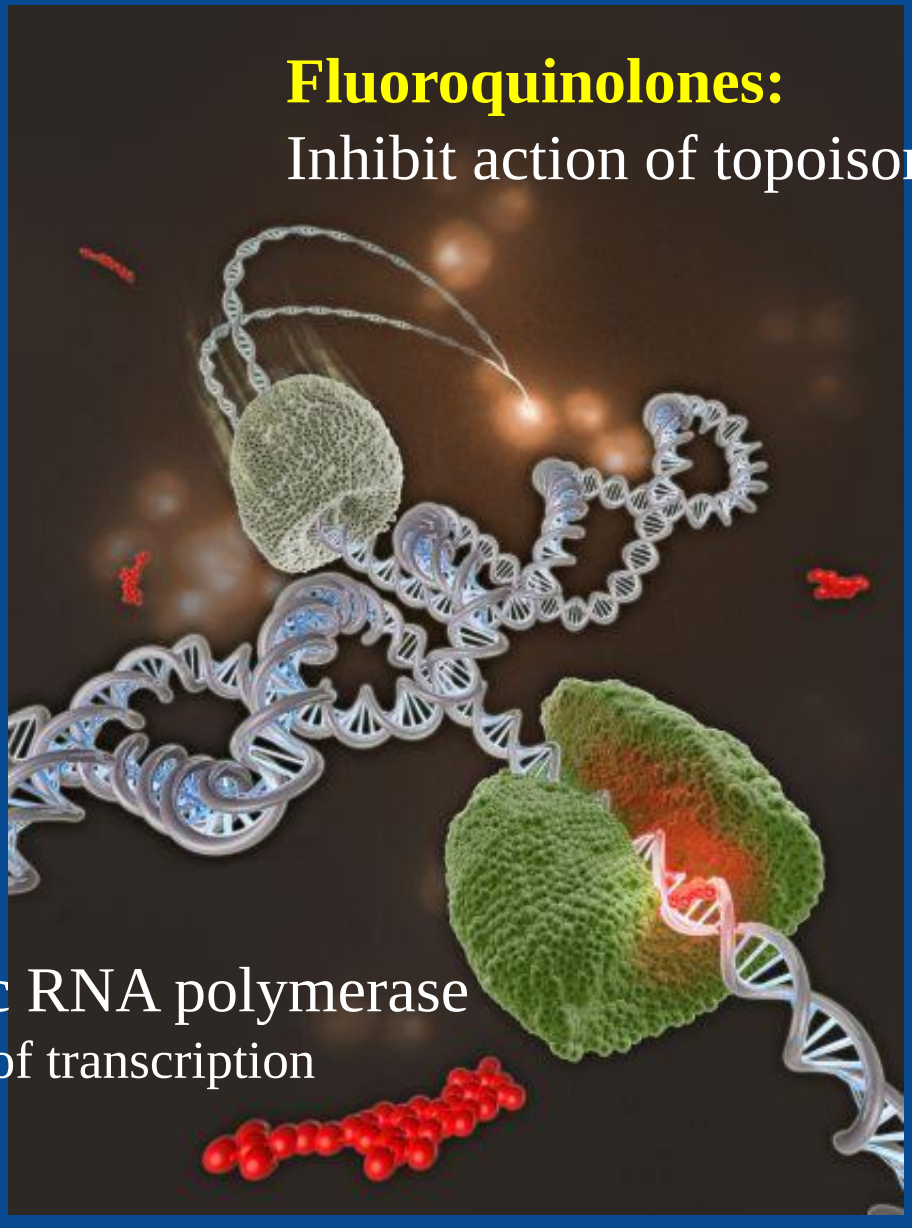


The oxazolidinones bind to the 50S ribosomal subunit and interfere with formation of the complex that associates the mRNA, the *f-met*-tRNA, and the 50S ribosomal subunit.

Inhibition of Nucleic Acid Synthesis

Fluoroquinolones:

Inhibit action of topoisomerase DNA gyrase

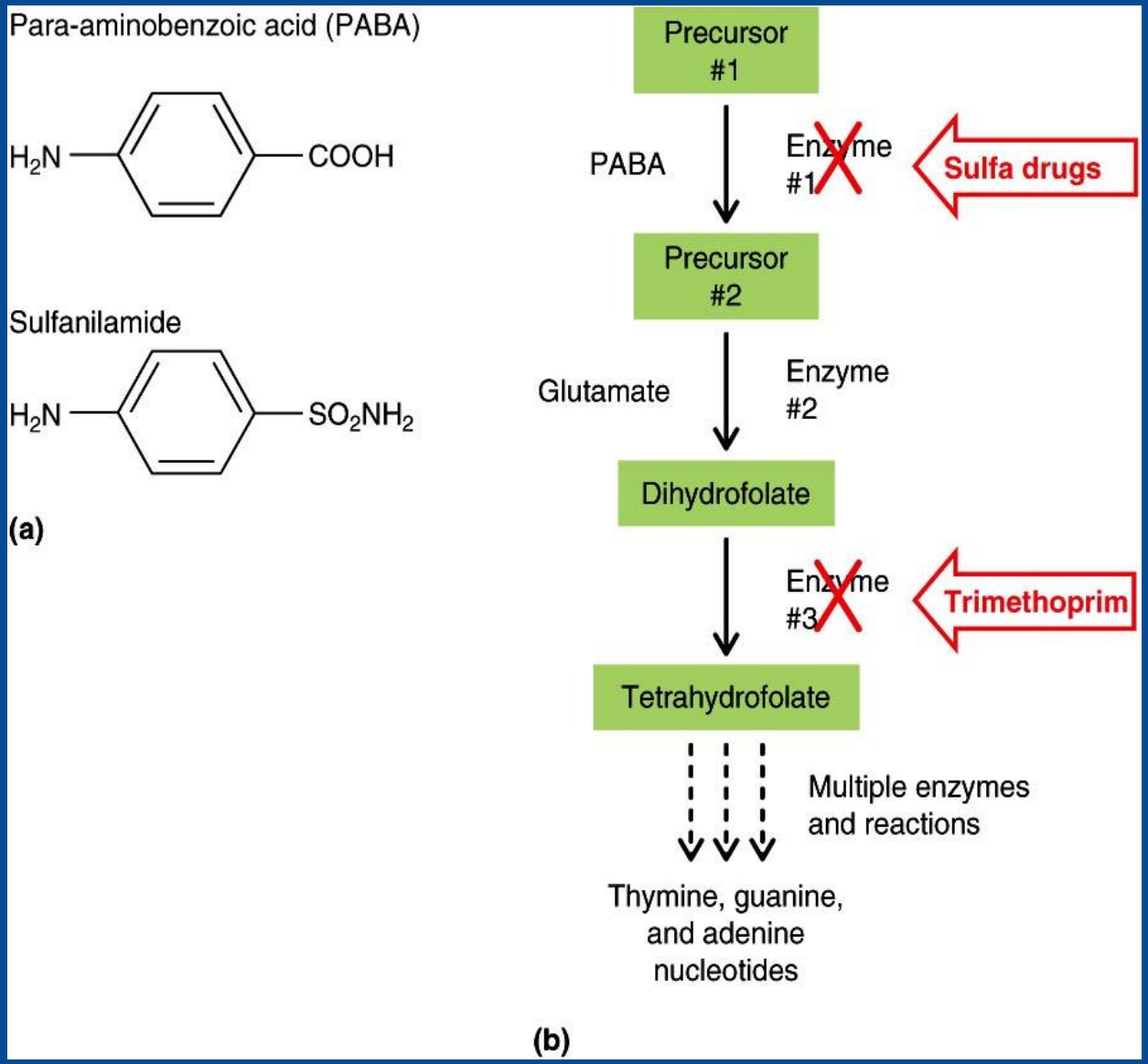


Rifamycins:

Block prokaryotic RNA polymerase

Block initiation of transcription

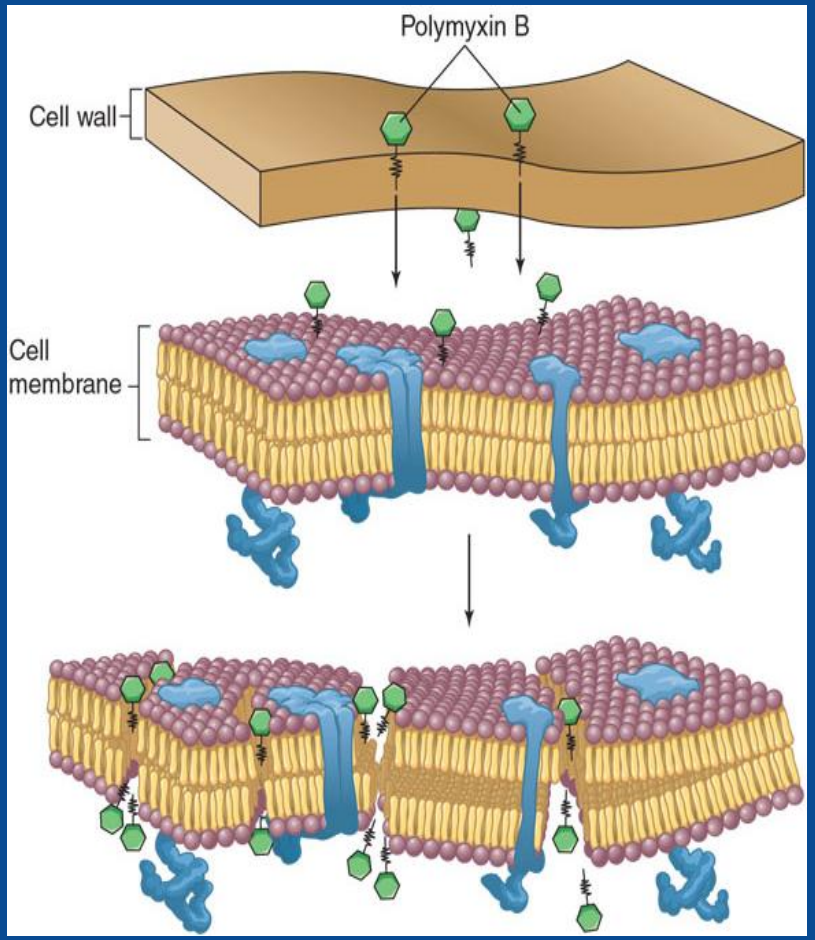
Inhibition of Metabolic Pathways


Para-aminobenzoic acid (PABA)
H_2N
COOH
Sulfanilamide
H_2N
SO_2NH_2
(a)
Precursor #1
PABA
Enzyme #1
Sulfa drugs
Precursor #2
Glutamate
Enzyme #2
Dihydrofolate
Enzyme #3
Trimethoprim
Tetrahydrofolate
Multiple enzymes and reactions
Thymine, guanine, and adenine nucleotides
(b)

Interference with Cell Membrane Integrity

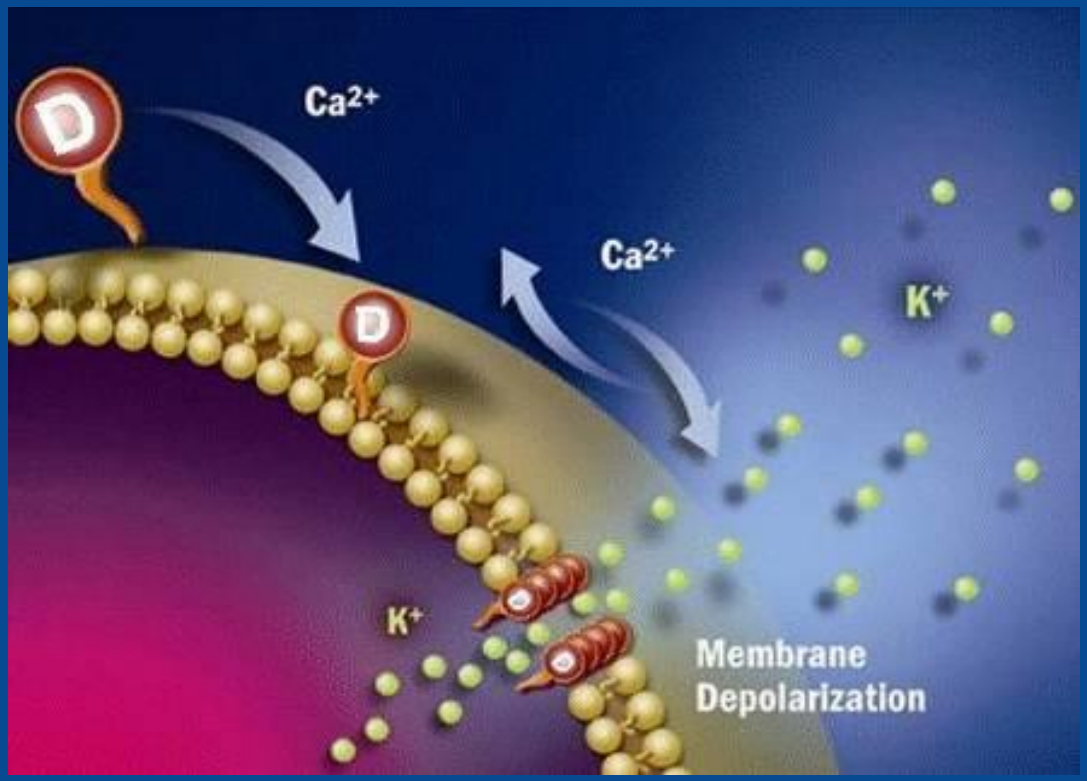
Interference with cell membrane integrity

- Polymixn B most common
- Binds membrane of Gram - cells
  - Alters permeability
    - Leads to leakage of cell and cell death
  - Also bind eukaryotic cells but to lesser extent



Daptomycin's Mechanism of Action

- Irreversibly binds to cell membrane of Gram-positive bacteria
  - Calcium-dependent membrane insertion of molecule
- Rapidly depolarizes the cell membrane
  - Efflux of potassium
  - Destroys ion-concentration gradient



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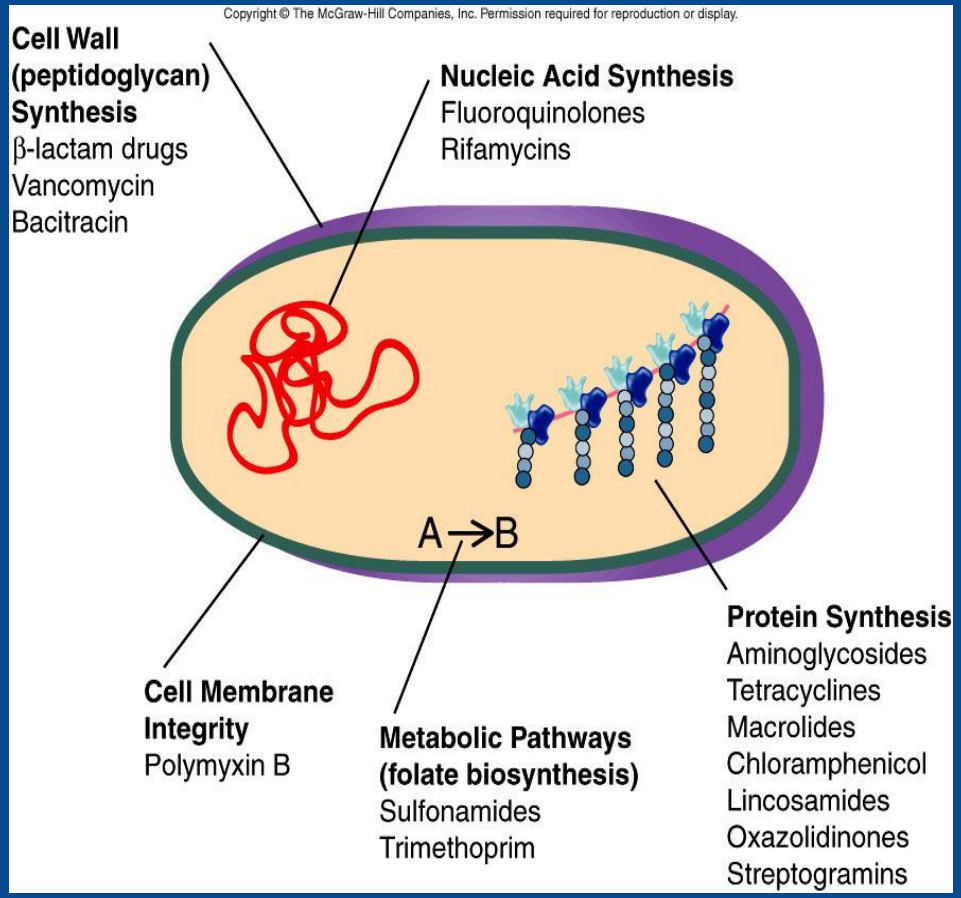


Thank You