Pharmacology of Bacterial Protein Synthesis Inhibitors (part I)

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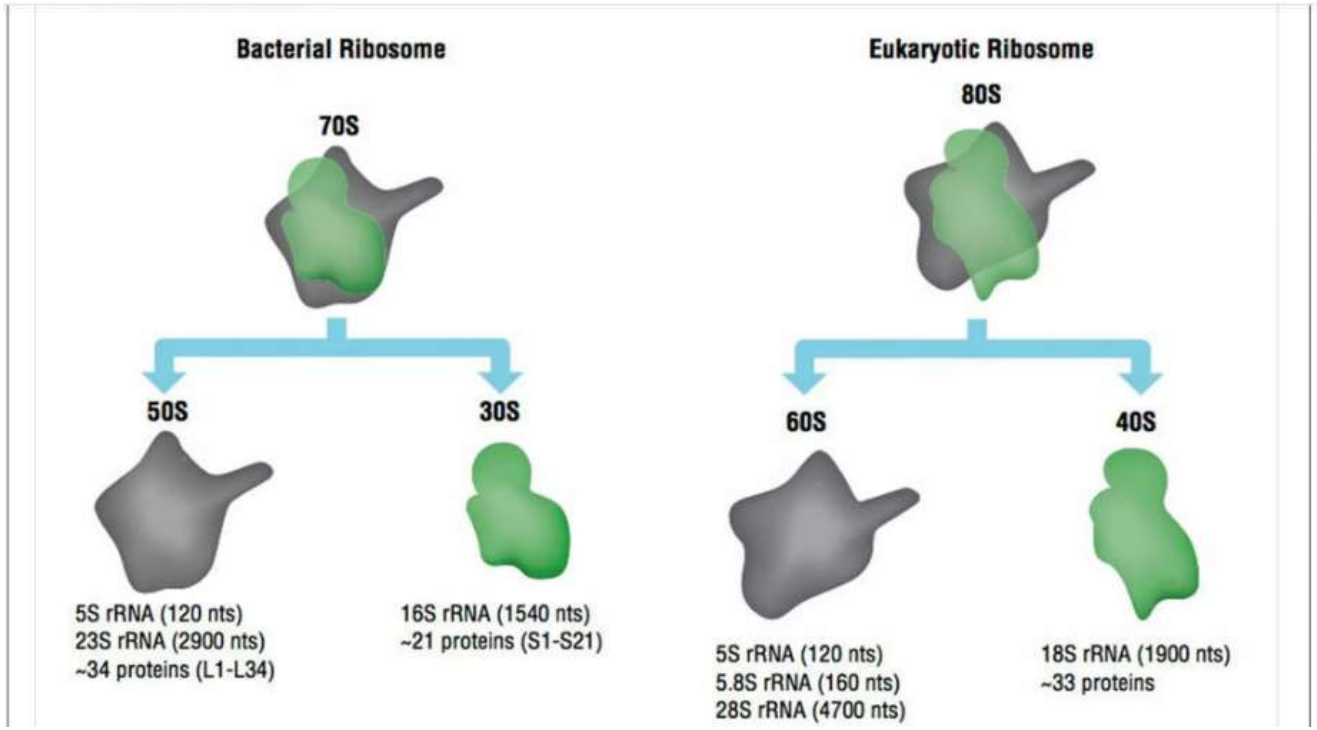
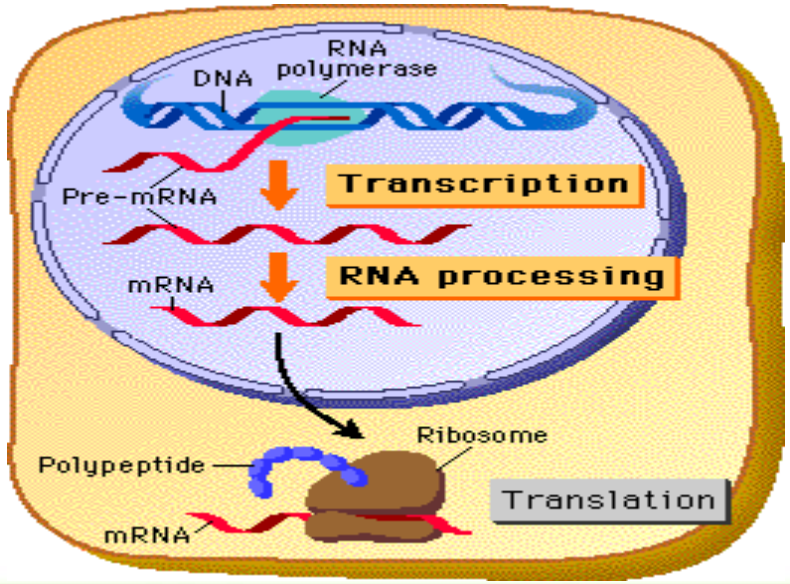
Objectives

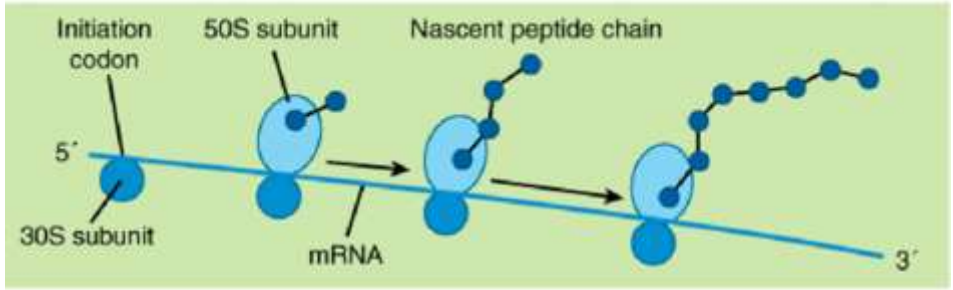
- 1- Protein synthesis in bacterial ribosomes
- 2- Mechanism of action of protein synthesis inhibitors antibiotics
- 3- Classification of protein synthesis inhibitors
- 4- Aminoglycosides
- 5- Macrolides
- 6- Tetracyclines
- 7- Chloramphenicol
- 8- Clindamycin

Ribosomes: site of protein synthesis

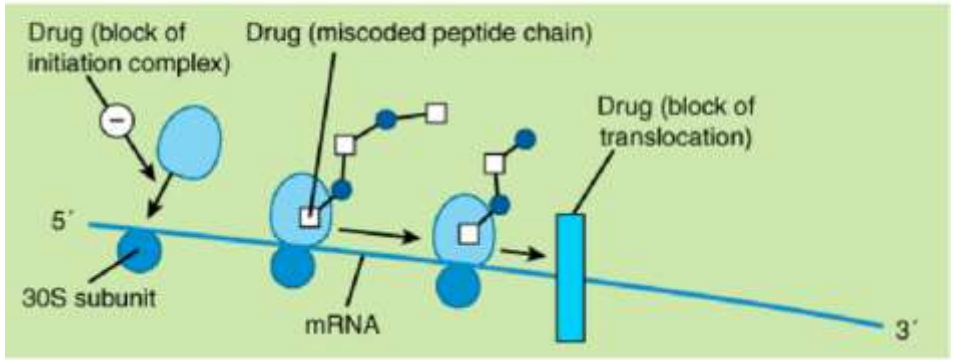
- **Prokaryotic ribosomes are 70S**:
- Large subunit: 50 S
    - 33 polypeptides
- Small subunit: 30 S
    - 21 polypeptides
- **Eukaryotic are 80S**
- **Selective toxicity:**
- **acting at the ribosomal level taking the advantage of major differences prokaryotic and eukaryotic ribosome structure**



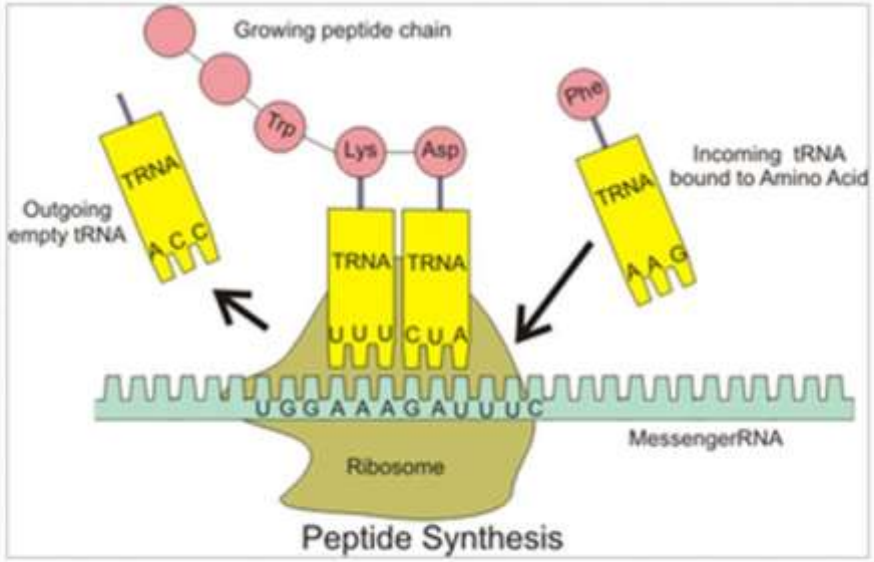




Aminoglycoside-treated bacterial cell



Bacteria protein synthesis



Classification

TETRACYCLINES 1

Demeclocycline DECLOMYCIN
Doxycycline VIBRAMYCIN
Minocycline MINOCIN
Tetracycline SUMYCIN

GLYCYLCYCLINES 2

Tigecycline TYGACIL

AMINOGLYCOSIDES 3

Amikacin AMIKIN, OTHERS
Gentamicin GARAMYCIN
Neomycin NEO-FRADIN
Streptomycin STREPTOMYCIN

MACROLIDES/KETOLIDES 4

Azithromycin ZITHROMAX
Clarithromycin BIAXIN
Erythromycin E-MYCIN
Telithromycin KETEK

OTHERS 5

Chloramphenicol CHLOROMYCETIN
Clindamycin CLEOCIN
Linezolid ZYVOX
Quinupristin/Dalfopristin SYNERCID

	Aminoglycosides (cidal)	Macrolides (static) Moderate spectrum	Chloramenihecol (Static- broad spectrum)	Clindamycin (static)	Tetracyclines (static-broad spectrum)
PDs	Irreversible binding to 30S subunit: misreading of mRNA	Binding of 50S subunit: (weak reversible binding) Increasing concentration turns the drug into cidal MW>500	Binding (weak) to 50S subunit MW<500, only 2 –OH groups, 2 Cl atoms Not used nowadays except topical for eye infections	Binding to 50 S subunit (as erythromycin) at the same binding site MW <500	Reversible (weak) binding to 30S subunit MW<500 except tigecycline (parentral) Containing –OH groups, least in minocycline
PKs	• Not absorbed orally • Parentral • Not pass BBB • Can pass placenta and breast milk • Not metabolized • Excreted unchanged in urine: active in alkaline urine • N.B. **Synergy** - The aminoglycosides synergize with β-lactam antibiotics. The β-lactams inhibit cell wall synthesis and thereby increase the permeability of the aminoglycosides.	• Poor oral absorption, affected by food (on empty stomach) • Not pass BBB • Pass placenta but not teratogenic**: safe in pregnancy: erythromycin, zithromycin** • Pass to most body fluids in good concentration (prostate) • **Concentrated in macrophages and polymorphs (long biological half life)** • Metabolism: liver • Excretion: bile, enterohepatic circulation • **Membres:** **erythromycin**, clarithromycin, azithromycin, spiramycin	• Well-absorbed, not affected by food • Pass BBB: **2nd choice in meningitis** • Widely distributed: high Vd • Pass placenta, in breast milk • Metabolized by glucorunidation in liver: glucoronyl transferase phase II • Excreted in urine: inactive metabolites	• Rapid complete oral absorption • pass BBB in small amounts **enough to treat meningitis** • Penetrates bone, tissue fluids including prostate • Pass placenta: **not teratogenic** • Metabolism: liver • Excretion: bile	• Partially absorbed • Absorption decreased with: food, milk, antacid, iron (binds to heavy metals) • Incomplete passage to BBB • Concentrated in bone, teeth • Pass placenta (teratogenic) and breast milk **(high affinity to Ca) ≠ pregnancy, lactation, children<8 y** • Metabolism: extensive in liver • Excreted in urine 80% (inactive) more than in bile (enterohepatic circulation) • N.B. doxycycline and minocycline : nearly complete oral absorption, 50% renal excretion, 50% in bile: can be used in renal impairment

To be continued.....