# Protein Synthesis Inhibitors

**Largest class of antibiotics**

## THE TARGETS

**Targets**: rRNA of either the **LARGE** or **SMALL** ribosomal subunit

- **LARGE 50S**: polymerizes aa into polypeptides → (–) → interfere with tRNA binding & accuracy of protein synthesis
- **SMALL 30S**: selects tRNA according to mRNA codons → (–) → inhibit peptide bond formation or new peptide chain

- **Location**: interacts with functional center of ribosomal units
- **Resistance is futile**: multiple genes in genome encode for RNAs; therefore, if there’s only a mutation in one gene that confers resistance, all the rest are still susceptible to these antibiotics (but resistance via other mechanisms is possible)

## LARGE TARGETS 50S subunit

### MACROLIDES

- **Structure**: lactone ring (14, 15, or 16 member ring)
- **Generations**
  - 1\(^{st}\): erythromycin (14C)
  - 2\(^{nd}\): clarithromycin, azithromycin (15C)
  - 3\(^{rd}\): ketolides: telithromycin
- **Activity against**: gram positive pathogens
- **Location of action**: nascent peptide tunnel
- **MOA**: binds → obstructs tunnel/closes gate → blocks polypeptide growth (like a plug, but not always tight)
- **Erythromycin**: unstable at low pH → converts into inactive ketal → SE like GI cramping
- **Clarithromycin**: added CH\(_3\) group → no ketal formed, ↑ hydrophobicity to cross membrane, ↑ stability, ↓ SE
- **Azithromycin**: ↑ stability, qd dosing
- **Resistance**: two mechanisms
  - **Site specific modification** of rRNA by Erm methyltransferases
    - Erm enzymes add CH\(_3\) to adenine residue (A2058) → erythromycin cannot bind
    - Horizontally transmit erm gene on plasmids/transposons
    - “MLS\(_B\) resistance”: confers resistance to macrolides, lincosamides, streptogramin B’s
    - Either expressed constitutively (high cost for fitness) or inducible (low cost)
  - **Efflux of drug** by MefA transporters
- **Ketolides**: 3\(^{rd}\) generation
  - Structural modifications improve activity
    - Keto group instead of cladinose sugar ring
    - Carbamate group: ↑ PK and ↑ PD profiles
    - Extended side chain: ↑ ribosome binding
  - Improved activity: poor inducers or erm genes, poor substrates for mef transporters

### LINCOSAMIDES

- **Overlap binding sites with macrolides
- **Drugs**: lincomycin, clindamycin
- **MOA**: inhibition of peptide bond formation
- **Resistance**: target side modification (erm), drug inactivation (lin), or efflux (msr)

### STREPTOGRAMINS

- **Streptogramin A**: dalfopristin
- **Streptogramin B**: quinupristin
- **A+B = synergistic** by inhibiting two consecutive steps
- **Combination Synercid** works even on VRE, MRSA, and penicillin-resistant pneumococci
- **Activity against**: gram positive pathogens
- **A: dalfopristin**: similar to lincosamides: stops formation of peptide chain
• **B: quinupristin**: similar to macrolides: inhibit peptide chain growth
• **Resistance**: methylation of A2058 (erm), just like in macrolides and lincosamides

*Macrolides* stop progression of peptide chain, whereas *lincosamides* prevent them from even starting
*Streptogramins B and A* mirror those, respectively
*Modification of A2058 (erm) affects all three, giving the nickname MLS*$_B$

**OXAZOLIDINONES**

• **Drug**: linezolid
• **Pharmacophore**: oxazolidinone ring (stereochemistry important)
• **Activity against**: gram pos cocci (*S. aureus, E. faecium, E. faecalis, Strep pneumoniae, etc. and even VRE & MRSA*)
• **Treats**: complicated SSSI, diabetic foot infections, nosocomial pneumonia, bacteremia
• **MOA**: binds inside tunnel of large subunit at the peptidyl transferase (catalytic center) → competes with N-terminus of tRNA for binding → inhibits catalysis of peptide bond formation
• **Resistance**: mutations in 23S rRNA at drug target site (mutation G2576U)
  - Gram pos streptococci carry multiple copies of rRNA genes
  - Spontaneous mutation in one rRNA gene: not a big deal
  - Via recombination, mutation spread to the other rRNA genes: big deal
• **SE**: myelosuppression, anemia, thrombocytopenia (all related to new RBC generation)
  - Due to linezolid’s inhibition of mitochondrial protein synthesis (as descendants of bacteria)

*Resistance to ALL antibiotics that target the large ribosomal subunit*

• Resistance to some macrolides, lincosamides, streptogramins A, oxazolidinones, chloramphenicol, muiltins
• All antibiotics that act upon the peptidyl transferase center
• The villain: *cfr* gene
• *cfr* and *erm* genes are neighboring genes that are expressed together as the *mlr* operon
• *cfr* codes for a methyltransferase that modifies A2503 → protection against large subunit antibiotics

**SMALL TARGETS 30S subunit**

**AMINOGLYCOSIDES**

• **Structure**: a bunch of flexible sugar rings connected together
• **Pharmacophore**: substituted 2-deoxystreptamine group (either 4,5 or 4,6 substituted)
  - 4,5: neomycin, paromomycin
  - 4,6: gentamicin, kanamycin
• **Target**: 16S rRNA segment, the decoding center (responsible for correct codon-anticodon pairing)
• **MOA**: cause synthesis errors & miscoding
  - Binding to small subunit → induce “flipped-out” conformation of decoding center → decoding center keeps sending out a “green light” signal even when the codon and anticodon don’t match well → results in bad proteins with erroneous amino acids
• **Selectivity**: in the nucleotide sequence, bacteria have A (adenine) where humans have G (guanine)
• **SE**: ototoxicity
  - Due to the drugs acting on mitochondrial ribosomes
  - Familial mitochondrial mutations in the decoding center of mitochondrial ribosomes genetically predispose a patient to ototoxic effects from aminoglycosides
• Positively charged → binds to rRNA site, but also can bind to different cellular rRNAs (promiscuous)
• Active against both gram pos and neg, but usually used for gram neg infections due to toxicity issues
• Poor absorption from GI tract → primarily act on GI infections
• **Resistance**
  - Methylase enzymes methylating rRNA residues
  - N-acetylation, O-phosphorylation, O-adenylation of specific functional side groups in aminoglycosides which disrupts H-bonding needed for the drug to bind to rRNA and causes steric hindrance
• Kanamycins
  o Kanamycin
  o Amikacin
  o Tobramycin
  o Gentamicin

• Streptomycin
  o Pharmacophore: streptamine (has two very basic guanidine groups)
  o Greater activity against *Mycobacterium tuberculosis*
  o Used in combination with other drugs to prevent resistance
  o Different mechanism, same outcome: acts at site different from other aminoglycosides, but still kills bacteria by inducing miscoding

• Tetracycline
  o Broad spectrum; bacteriostatic
  o **Structure**: napthacene ring system; basic + acid functions
  o **Polar**: achieves easy access through outer membrane porin channels of gram neg bacteria allowing accumulation in periplasmic space
  o **MOA**: blocks any tRNA from binding to ribosomal A-site
  o **Resistance**: two mechanisms
    - Gram positives: ribosome cleans itself: proteins Tet(M) or Tet(O) bind to ribosome → promote release of tetracycline
    - Gram negatives: acquire genes coding for efflux pumps Tet(A,B,etc.)
    - Pathogens may carry several different pumps or even a combination of pump and Tet cleaners
    - Macrolide resistance helps maintain tetracycline resistance
  o **Newest tetracyclines**: glycylcyclines
    - Tigecycline
    - Can withstand tetracycline resistance mechanisms
  o **SE**: irreversible discoloration of teeth
    - Tetracyclines chelate polyvalent metal ions like Ca^{2+}