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2nd year PG

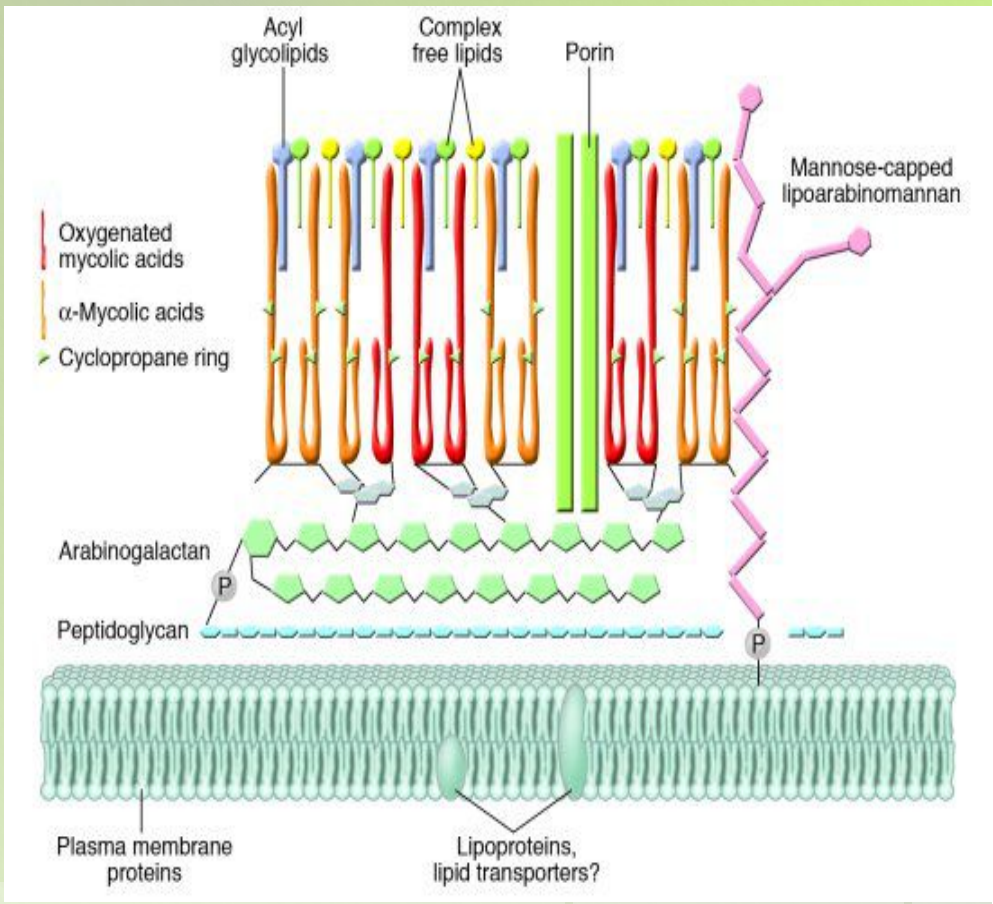
Dept. of Pharmacology

INTRODUCTION

- Tuberculosis is one of the world's most widespread deadly illness.
- It is caused by bacteria *Mycobacterium tuberculosis*
  - ✓ usually affects the lungs, although other organs are involved in up to one-third of cases.
- *Mycobacterium*, from the Greek "mycos," refers to Mycobacteria's waxy appearance,
  - ✓ Due to the composition of their cell walls.

INTRODUCTION

- More than 60% of the cell wall is lipid,
  - ✓Mainly mycolic acids composed of 2-branched, 3-hydroxy fatty acids.
  - ✓This extraordinary shield prevents many pharmacological compounds getting into the bacterial cell membrane or inside the cytosol.



INTRODUCTION

- A second layer of defense
  - ✓abundance of efflux pumps responsible for the resistance of mycobacteria to many standard antibiotics.
  - ✓ Ex: ATP binding cassette
- A third barrier is
  - ✓ability of some of the bacilli to hide inside the patient's cells(intracellular),
  - ✓ an extra barrier that antimicrobial agents must cross to be effective.

INTRODUCTION

- The basic principles of antituberculous treatment are

1. To administer multiple drugs
   - ✓ to which the organisms are susceptible
   - ✓ resistance can be delayed.
2. To add at least two new antituberculous agents to a regimen when treatment failure is suspected.
3. To provide the safest, most effective therapy in the shortest period of time so that patient will become sputum negative.
4. To ensure adherence to therapy.

First line drugs

Isoniazid
Rifampicin
Pyrazinamide
Ethambutol
Streptomycin

Second line drugs

Amikacin
Kanamycin
Capreomycin
Ciprofloxacin
Ofloxacin
Levofloxacin
Moxifloxacin
cycloserine

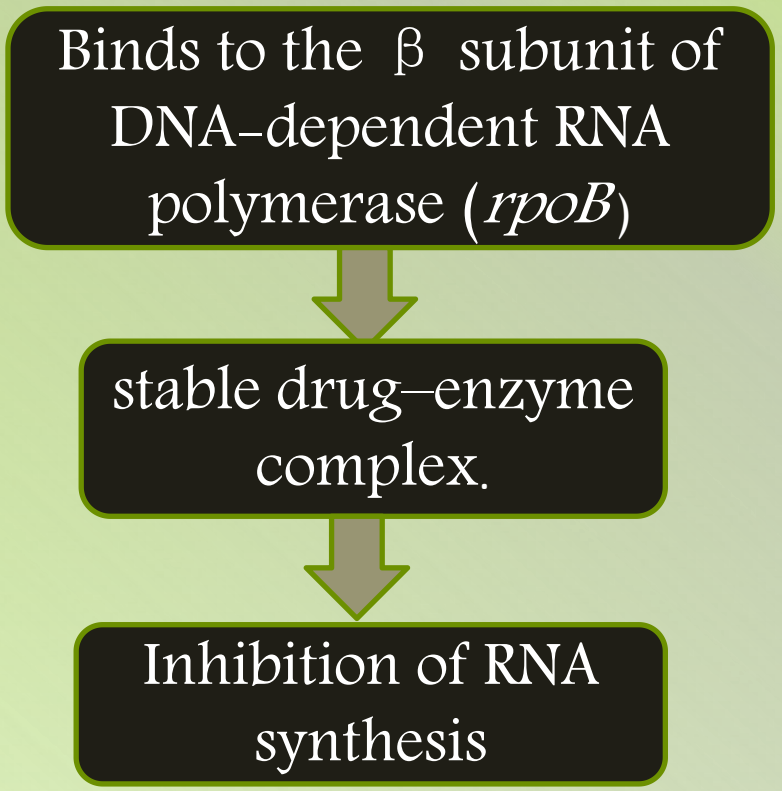
FIRST LINE DRUGS

- Agents are recommended on the basis of their
  - Bactericidal activity:
    - ✓ i.e., their ability to rapidly reduce the number of viable organisms and render patients noninfectious
  - Sterilizing activity:
    - ✓ i.e., their ability to kill all bacilli and thus sterilize the affected tissues, measured in terms of the ability to prevent relapses
  - Low rate of induction of drug resistance.
  - To be effective against both intracellular and extracellular growing bacilli.

RIFAMPICIN

- It is a derivative of rifamycin B, isolated from streptomyces mediteranei.
- It is bactericidal and acts against intracellular and extracellular organisms
- The only drug that acts on persisters.

MECHANISM OF ACTION



RIFAMPICIN

- ***Bacterial Resistance***

  Due to mutations at codons 526 and 531 of the *rpoB* gene

- ***Pharmacokinetics :***

  - ✓ Food interferes with its absorption.
  - ✓ It penetrates all membranes including blood brain and placental barrier.
  - ✓ Metabolized in liver, undergoes enterohepatic circulation ; secreted in bile and saliva.
  - ✓ It is eliminated mainly in feces so can be used safely in renal dysfunction.

RIFAMPICIN

- ***Dose:*** 10mg/kg

  Max:600mg/dose

- ***Adverse effects:***
  - ✓ Hepatitis, fever, rash
  - ✓ orange-colour discoloration of skin, urine, feces, saliva, tears.
  - ✓ Flu-like syndrome:
    - Fever, chills, myalgia.
    - Eosinophilia, interstitial nephritis, acute tubular necrosis, thrombocytopenia, hemolytic anemia, and shock
  - ✓ Gastrointestinal upset

RIFAMPICIN

- ***Drug interactions :***

✓ Rifampin potently induces CYPs 1A2, 2C9, 2C19 and 3A4.

✓ Leads to therapeutic failure of these agents

- Oral contraceptives, corticosteroids, warfarin, oral hypoglycemics, protease inhibitors and nonnucleoside reverse transcriptase inhibitors.

- Aminosalicylic acid may interfere with absorption of rifampin.

PYRAZINAMIDE

- Is the synthetic pyrazine analog of nicotinamide
- Pyrazinamide is "activated" by acidic conditions.
- ***Mechanism of Action***: Three mechanisms have been proposed

1. Inhibition of fatty acid synthase type I leading to interference with mycolic acid synthesis
2. Reduction of intracellular pH
3. Disruption of membrane transport by HPOA

PYRAZINAMIDE

- ***Mechanism of resistance:***
  - Pyrazinamide-resistant *M. tuberculosis* have pyrazinamidase with reduced affinity for pyrazinamide
  - Single point mutations in the *pncA* gene.
- ***Pharmacokinetics :***
  - oral bioavailability is >90%
  - The drug is concentrated 20-fold in lung epithelial lining fluid (Conte et al., 2000)

PYRAZINAMIDE

- Metabolized by microsomal deamidase to POA.
- Excreted by kidneys.

- ***Dose :*** 15–30 mg/kg

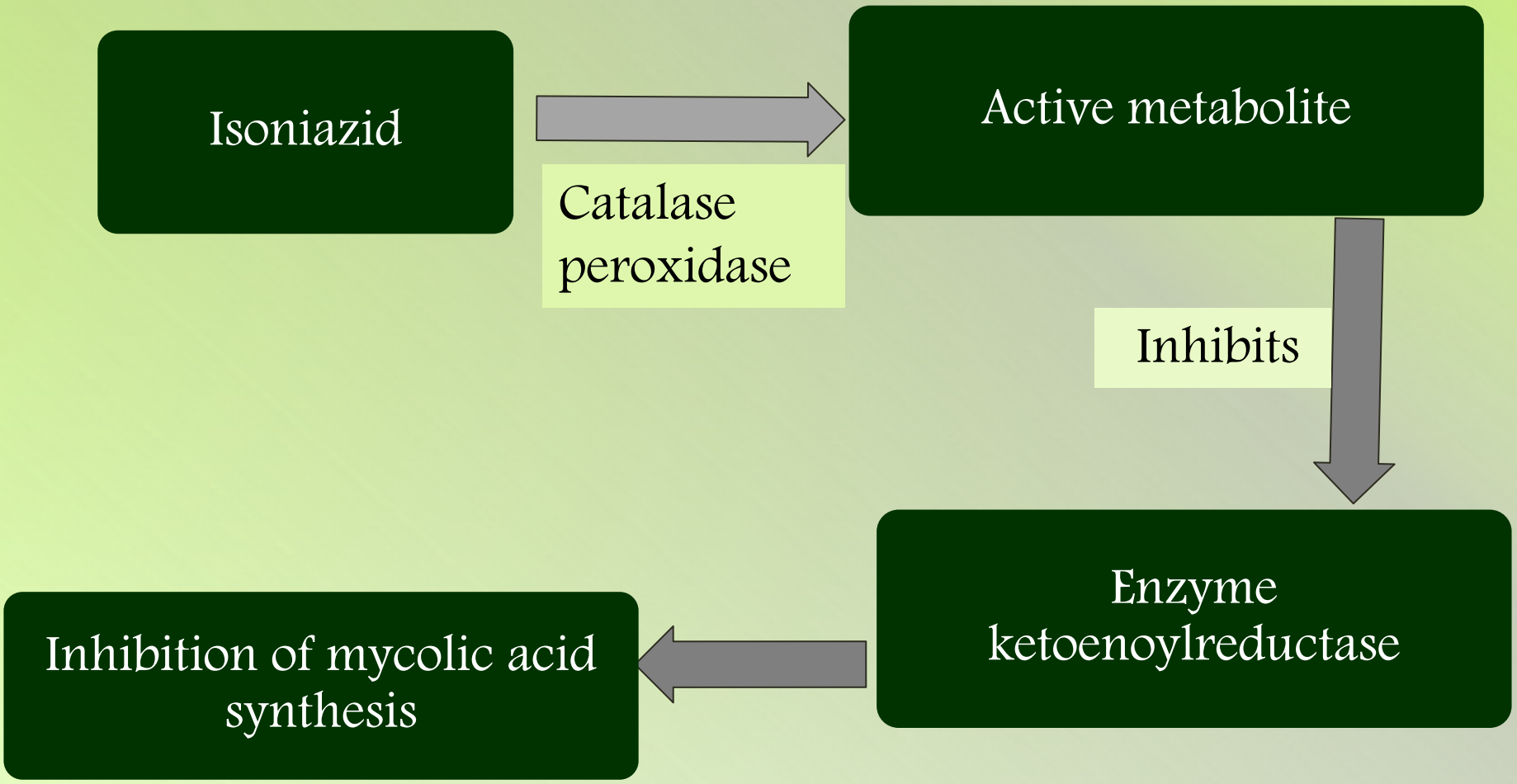
  Max: 2 g/dose

- ***Adverse effects:***
  - Hyperuricemia, hepatotoxicity
  - Rash, gastrointestinal upset
  - Joint aches.

ISONIAZID

- It is an prodrug.
- It is
  - Bacteriostatic– resting bacteria
  - Bactericidal– rapidly multiplying organisms
- It is effective against intracellular and extracellular mycobacteria.

Mechanism of action



ISONIAZID

- ***Mechanisms of Resistance:***
- It occurs due to mutation in KatG (gene for catalase peroxidase) or inhA.
- Mutations in *katG* is responsible for high level of resistance.
- Mutation in inhA gene confers cross resistance to ethionamide.

ISONIAZID

- ***Pharmacokinetics:***
  - oral bioavailability ~100%
  - Widely distributed in body including CSF
  - Metabolized by ACETYLATION which is genetically controlled.
  - ✓ Fast acetylators require high dose
  - ✓ Slow acetylators are predisposed to toxicity(peripheral neuritis)
- Dose: 5 mg/kg

  Max: 300 mg/dose

Adverse effects

- Hepatotoxicity
- Peripheral neuritis
- Hemolysis in G-6-PD deficiency
- Inhibits MAO-A (cheese reaction)
- "shoulder-hand syndrome"- back pain; bilateral proximal interphalangeal joint involvement; arthralgia of the knees, elbows and wrists.
- Neurological toxicities :
  - ✓ convulsions in patients with seizure disorders,
  - ✓ optic neuritis and atrophy, muscle twitching, dizziness, ataxia, paresthesias, stupor, and toxic encephalopathy

ETHAMBUTOL

- It is a BACTERIOSTATIC agent for mycobacterium.
- ***Mechanism of action:***
  - Inhibition of synthesis of arabinogalactan (component of cell wall) due to inhibition of arabinosyl transferase III.
- **Mycobacterial resistance:**
  - Mutations in the *embB* gene.

ETHAMBUTOL

- ***Pharmacokinetics:***
  - It is distributed throughout the body except CSF.
  - Ethambutol elimination is biexponential, with a
    - $t_{1/2}$ of 3 hours in the first 12 hours, and
    - $t_{1/2}$ of 9 hours between 12 and 24 hours, due to redistribution of drug.
  - Excreted by kidneys, so in renal failure ethambutol should be dosed at 15–25 mg/kg, three times a week instead of daily, even in patients receiving hemodialysis.

ETHAMBUTOL

- ***Dose:*** 5–25 mg/kg

  Max: 2.5 g/dose

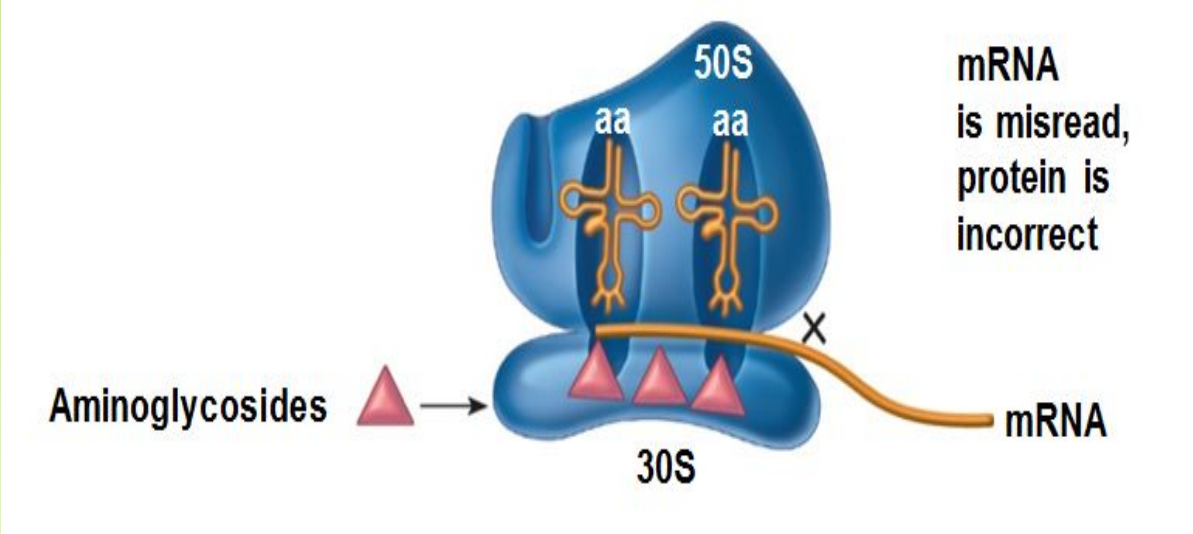
- ***Adverse effects:***
  - optic neuritis
    - Resulting in decreased visual acuity
    - Loss of ability to differentiate red from green.
    - May be due to effect on amacrine and bipolar cells of retina.
  - Hyperuricemia and peripheral neuritis
  - Pruritus, joint pain, GI upset, abdominal pain, malaise, headache, dizziness, mental confusion, disorientation, hallucinations.

AMINOGLYCOSIDES

- Streptomycin, Amikacin, Kanamycin, capreomycin
- Aminoglycosides are bactericidal– inhibitors of protein synthesis.
- Bacterial killing – concentration dependent.
- *MECHANISM OF ACTION:* Binds to the 30S ribosomal subunit,
  - ✓ interferes with initiation of protein synthesis by fixing the 30S–50S ribosomal complex at the start codon (AUG) of mRNA.

AMINOGLYCOSIDES

- Binding to the 30S subunit causes
  - ✓ Misreading of mRNA
  - ✓ Leading to premature termination of translation
- Incorporation of incorrect amino acids, resulting in
  - ✓ production of abnormal or nonfunctional proteins.



AMINOGLYCOSIDES

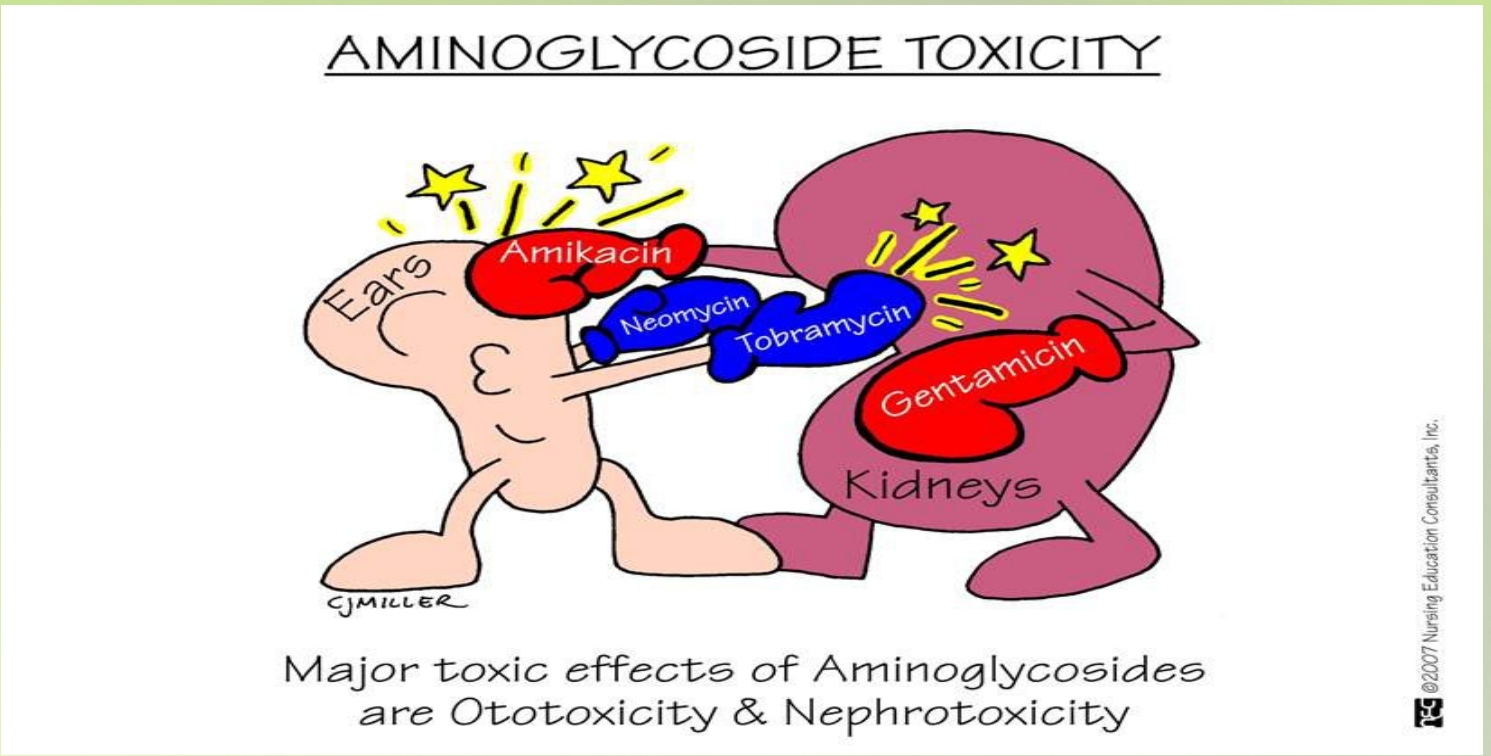
- ***Mechanism of resistance :***
  - Mutations in *rpsL* and *rrs* are associated with high-level resistance.
  - *GidB* mutations lead to high-level streptomycin resistant mutants
- ***Pharmacokinetics :***
  - Absorbed rapidly from intramuscular sites of injection
  - Distributed poorly into adipose tissue, must be considered when using weight-based dosing regimens in obese patients. .

AMINOGLYCOSIDES

- High concentrations are found
  - Renal cortex
  - Endolymph and perilymph of the inner ear
- Streptomycin can cause hearing loss in children born to women who receive the drug during pregnancy.
- Excreted by glomerular filtration

AMINOGLYCOSIDES

- *Adverse effects :*



AMINOGLYCOSIDES

Dosage:

- Amikacin: 15 mg/kg/day
- Streptomycin: 15 mg/kg/day, IM , for 2-3 months and then two or three times a week thereafter.
- Kanamycin:15 mg/kg/day

  max-1.5 g/day

CYCLOSERINE

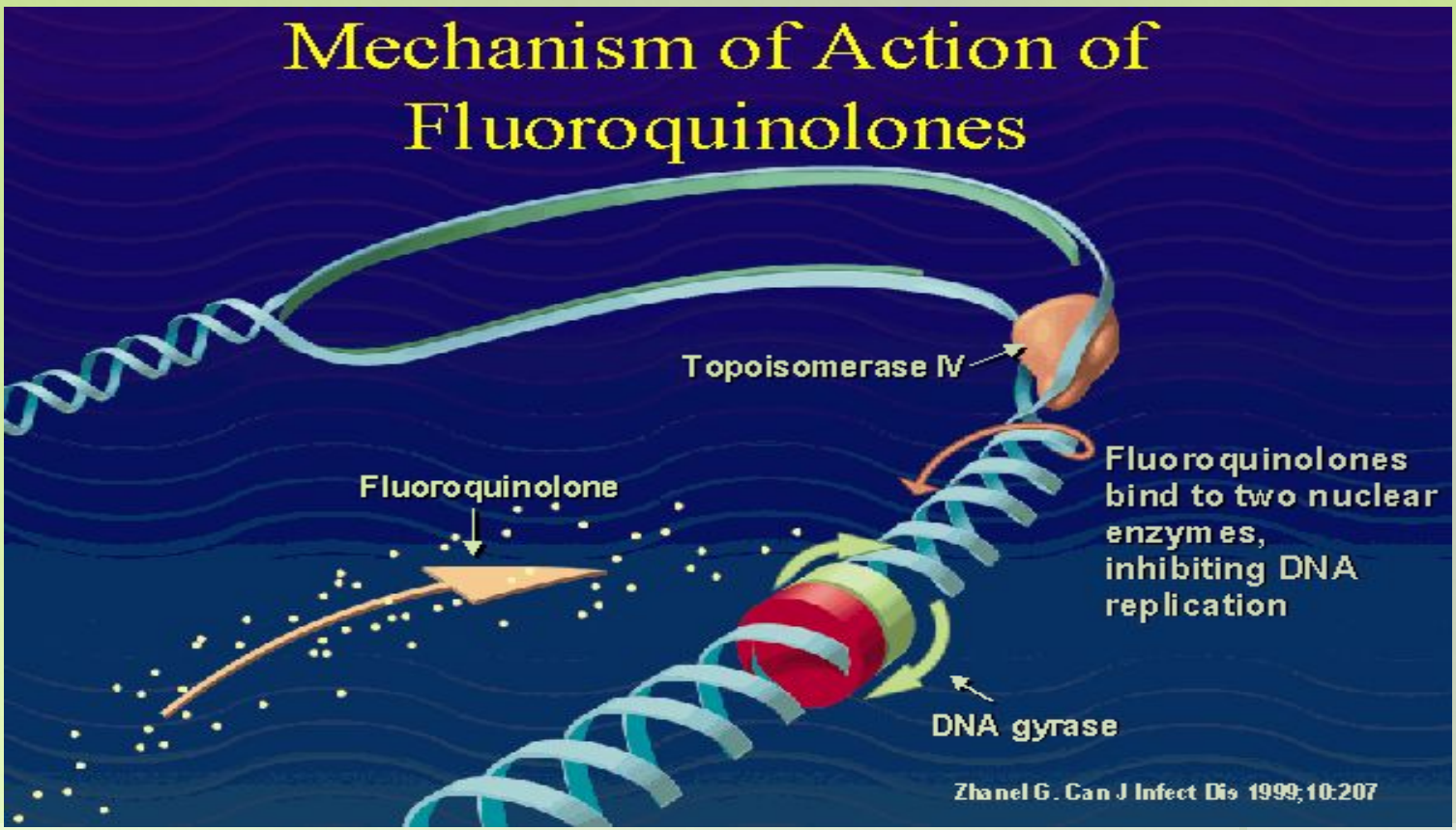
- It is a broad-spectrum antibiotic produced by *Streptococcus orchidaceous.*
- ***Mechanism of action :***
  - Cycloserine and d-alanine are structural analogs
  - Thus cycloserine inhibits alanine racemase which converts L-alanine to d-alanine stopping reactions in which d-alanine is incorporated into bacterial cell-wall synthesis .
- ***Pharmacokinetics:***
  - Oral cycloserine is almost completely absorbed
  - $t_{1/2}$ is 9 hours ; well distributed throughout body.
  - Excreted by kidneys

CYCLOSERINE

- ***Dose*** : Adults :250-500 mg twice daily
- ***Adverse effects:***
- Neuropsychiatric symptoms (psychserine.“): headache and somnolence to severe psychosis, seizures, and suicidal ideas

FLUOROQUINOLONES

- They are DNA gyrase inhibitors



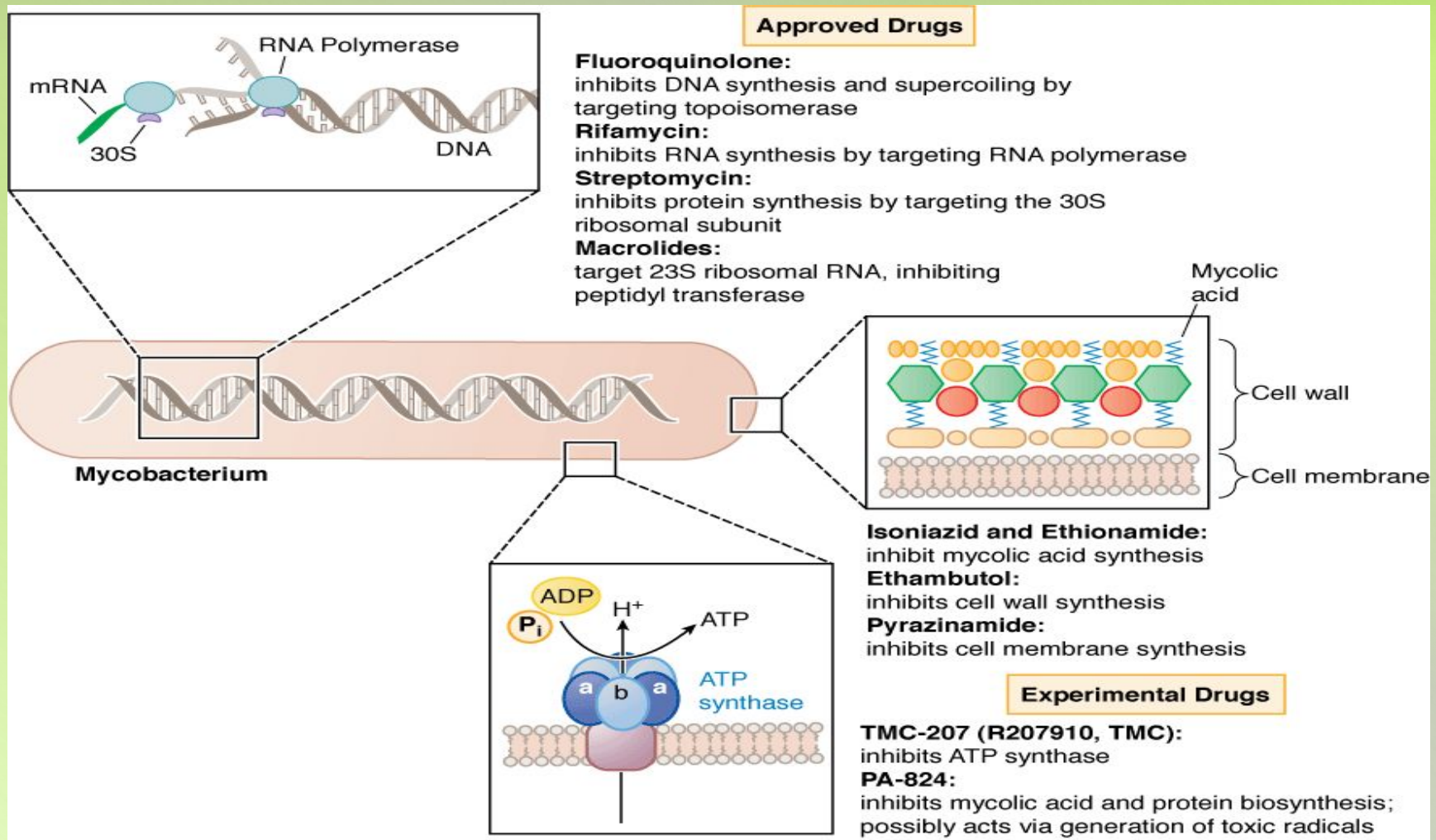
FLUOROQUINOLONES

- Drugs such as ofloxacin and ciprofloxacin have been second-line anti-TB agents for many years, but they are limited by the rapid development of resistance.
- Adding C8 halogen and C8 methoxy groups markedly reduces the propensity for drug resistance.
- Of the C8 methoxy quinolones, moxifloxacin is being studied to replace either isoniazid or ethambutol.

FLUOROQUINOLONES

- Moxifloxacin (400 mg/day) has bactericidal effects similar to that of standard doses of isoniazid (Johnson et al., 2006).
- 400 mg/day of moxifloxacin produces faster sputum conversion at 4 weeks than ethambutol (Burman et al., 2006b)
- Moxifloxacin is currently being studied in a phase 3 trial that may eventually lead to 4-month duration of anti-TB therapy compared to the current 6 months.

Mechanism of action



Approved Drugs

Fluoroquinolone:
inhibits DNA synthesis and supercoiling by targeting topoisomerase

Rifamycin:
inhibits RNA synthesis by targeting RNA polymerase

Streptomycin:
inhibits protein synthesis by targeting the 30S ribosomal subunit

Macrolides:
target 23S ribosomal RNA, inhibiting peptidyl transferase

Isoniazid and Ethionamide:
inhibit mycolic acid synthesis

Ethambutol:
inhibits cell wall synthesis

Pyrazinamide:
inhibits cell membrane synthesis

Experimental Drugs

TMC-207 (R207910, TMC):
inhibits ATP synthase

PA-824:
inhibits mycolic acid and protein biosynthesis; possibly acts via generation of toxic radicals

Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com
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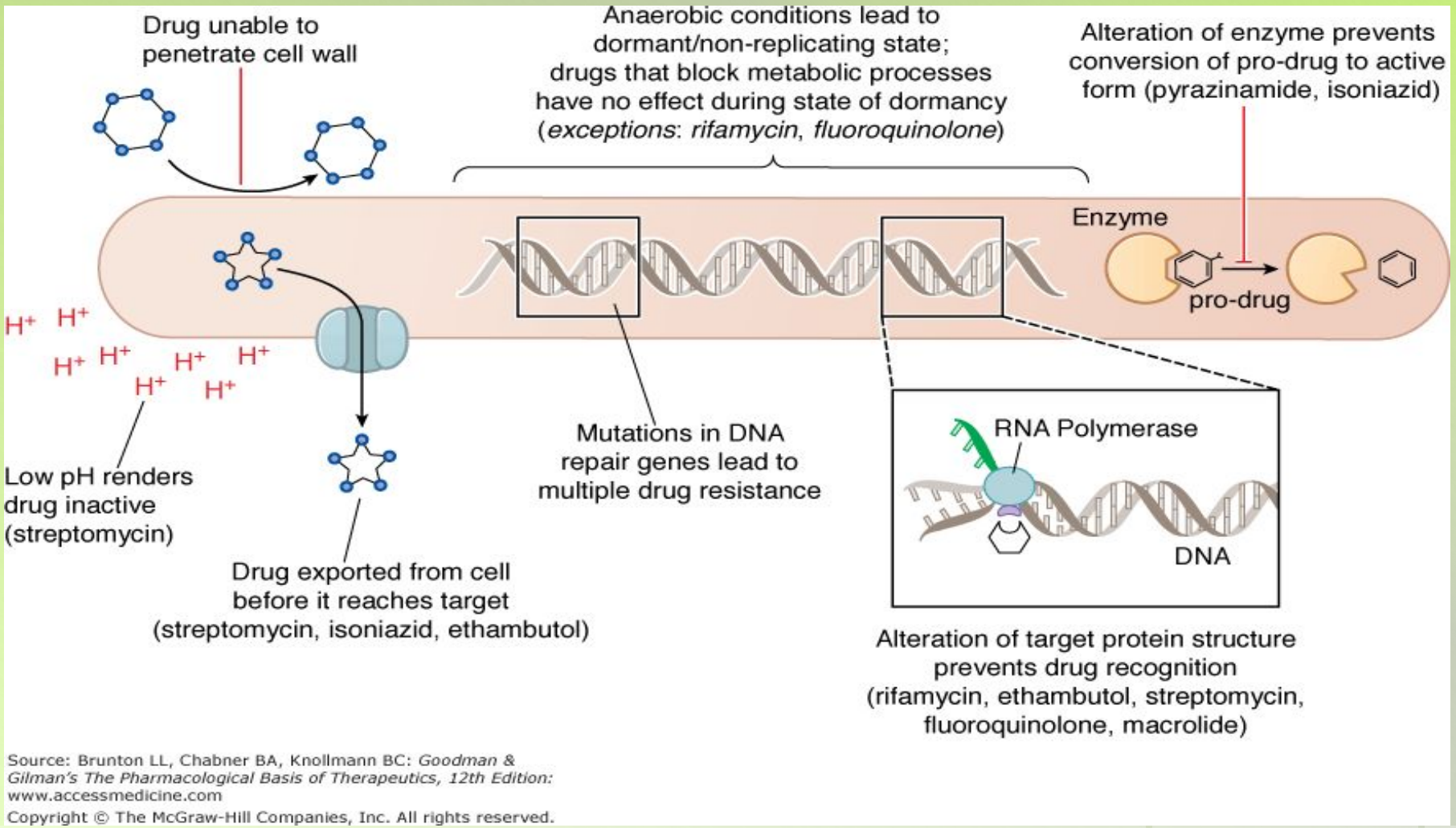
Mechanism of resistance



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

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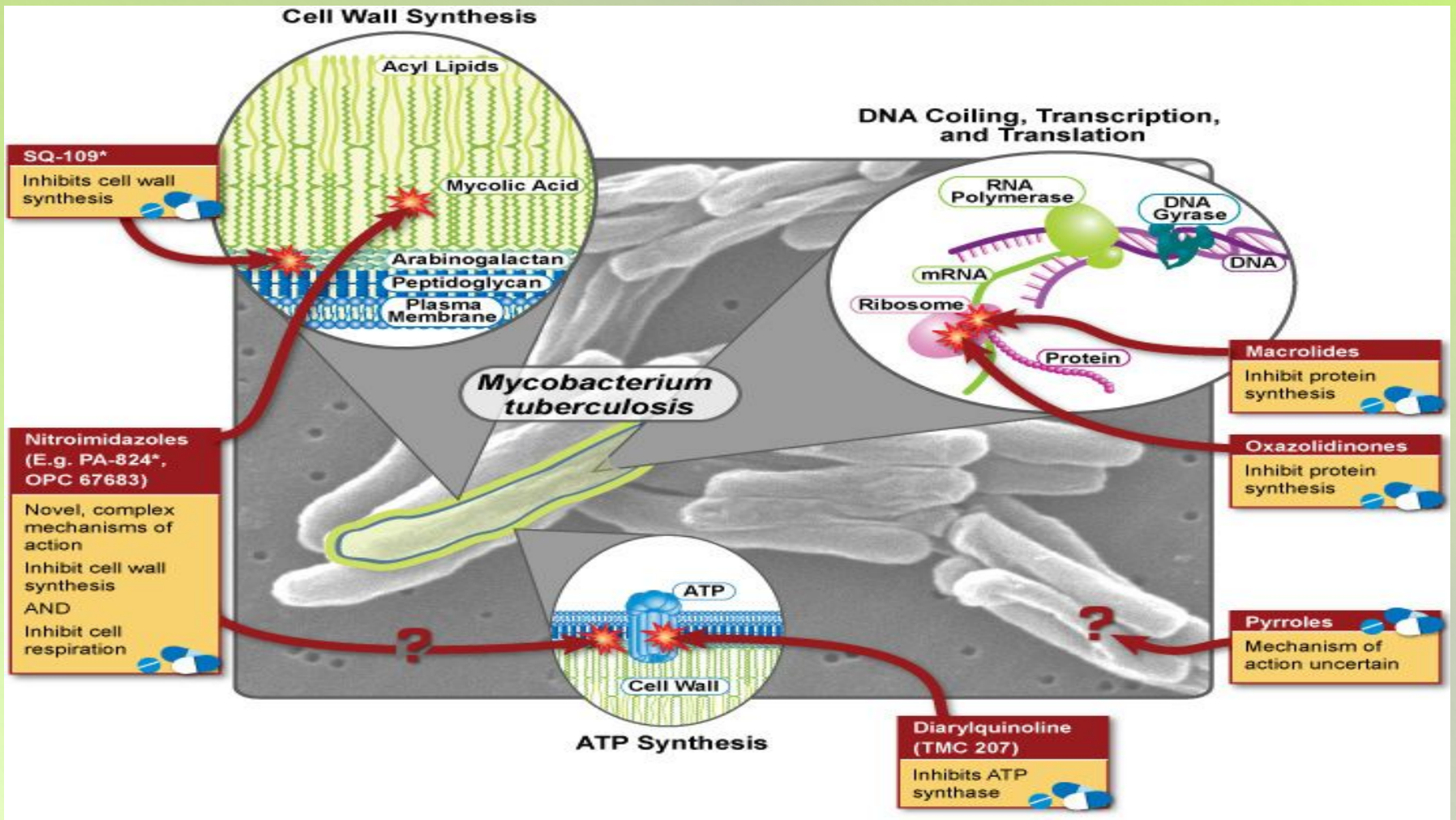
NEWER DRUGS

- **BEDAQUILINE** (TMC207)
  - A novel drug to combat multiple drug-resistant tuberculosis
  - Is the first compound from the new class diarylquinolines
  - Acts by inhibiting bacterial adenosine triphosphate (ATP) synthetase enzyme, a novel mode of action (Andries *et al.*)

TARGETS OF NEWER DRUGS



NEWER DRUGS

- **DELAMANID**
  - Newer drug for drug resistant tuberculosis.
  - Is a dihydro-nitroimidazooxazole derivative.
  - It acts by inhibiting
    - ✓ synthesis of mycobacterial cell wall components
    - ✓ Methoxy mycolic acid and ketomycolic acid.


THANK
YOU