

Mechanism of Anthelmintic Resistance

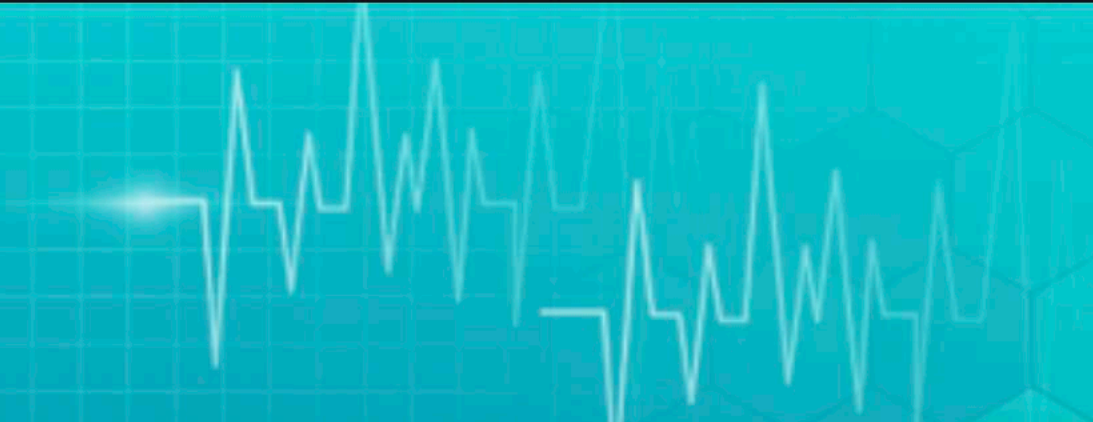
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Learning Objectives

- ▶ **Factors that affect Anthelmintic Activity**
- ▶ **Mechanism of Anthelmintic Resistance**
- ▶ **Resistance to Benzimidazole**
- ▶ **Resistance to Macrocyclic lactones**
- ▶ **Resistance to Imidazothiazoles and Tetrahydropyrimidines**
- ▶ **Factors affect the speed of development of anthelmintic resistance**



Anthelmintic Activity

Anthelmintic activity
Depends on...

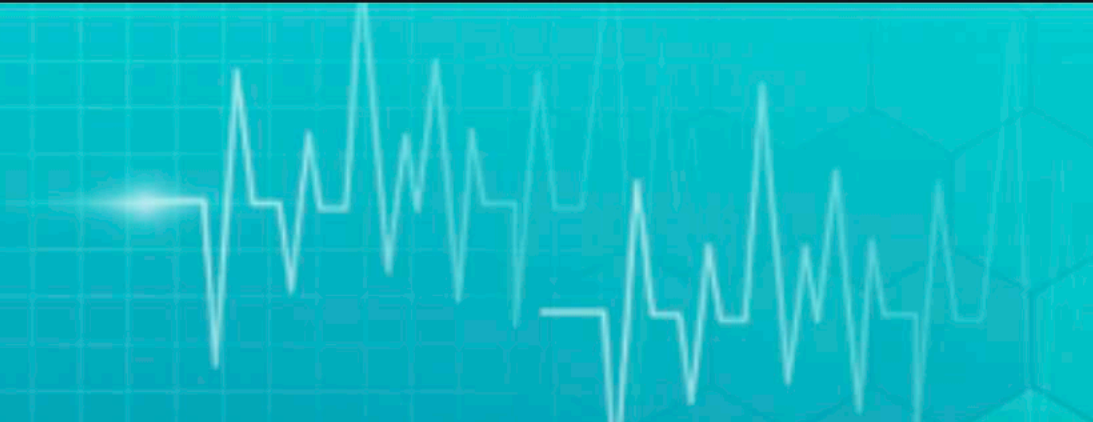
- ▶ Drug concentrations at the site of parasite location
- ▶ Time of parasite exposure
- ▶ Mechanisms of drug acquisition by target parasites
- ▶ The fate of the drug/metabolites within the target parasites (influx–efflux balance)

Launesse et al., 2018

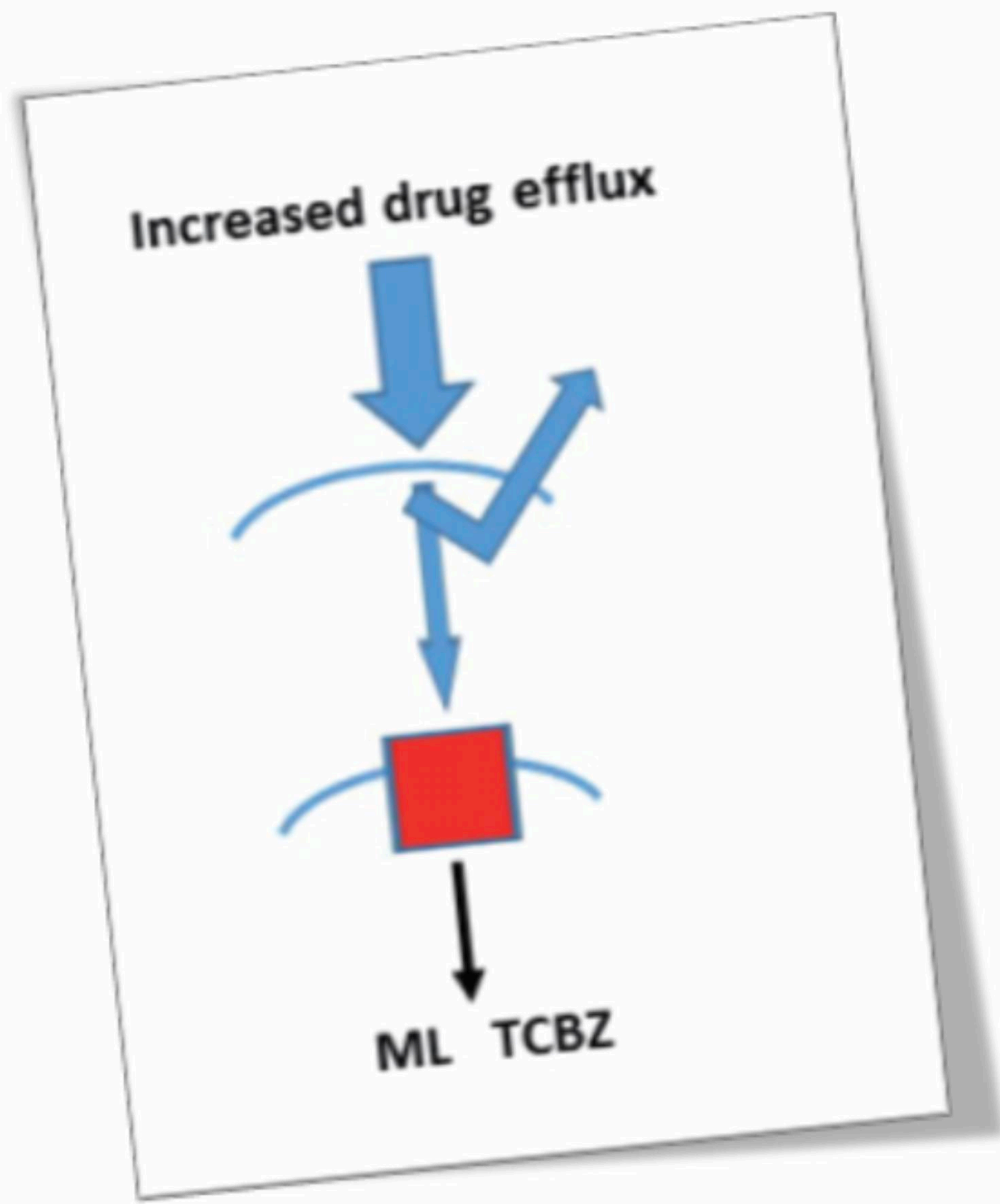


Mechanism of Anthelmintic Resistance

- **There are four major mechanisms**
- ▶ **Up-regulation of cellular efflux mechanism**
- ▶ **Increased drug metabolism**
- ▶ **Mutations in the drug receptor sites that reduces the drug binding**
- ▶ **Decrease in the drug receptors abundance through reduced expression within the parasites**



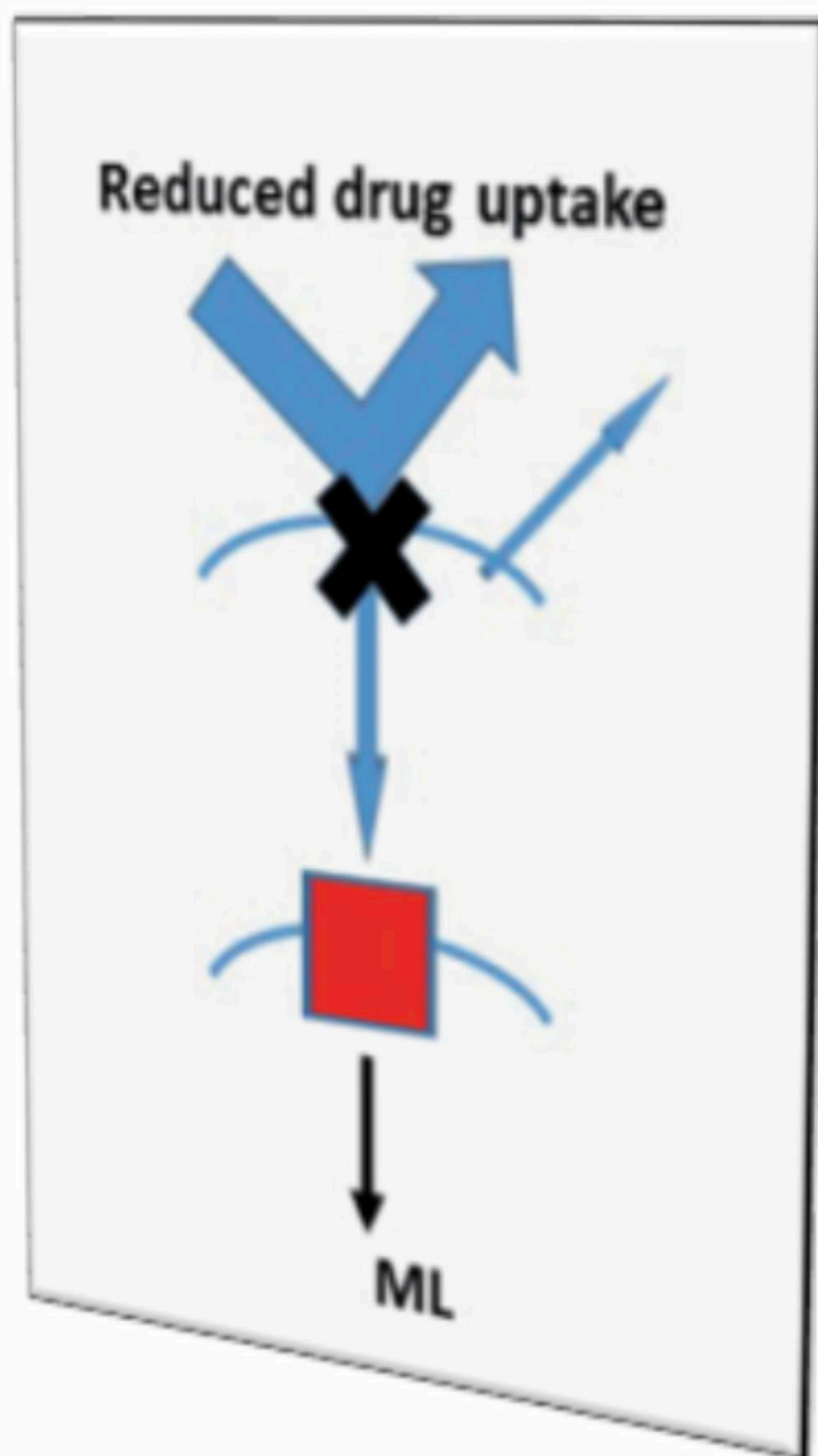
Up-regulation of cellular efflux mechanism



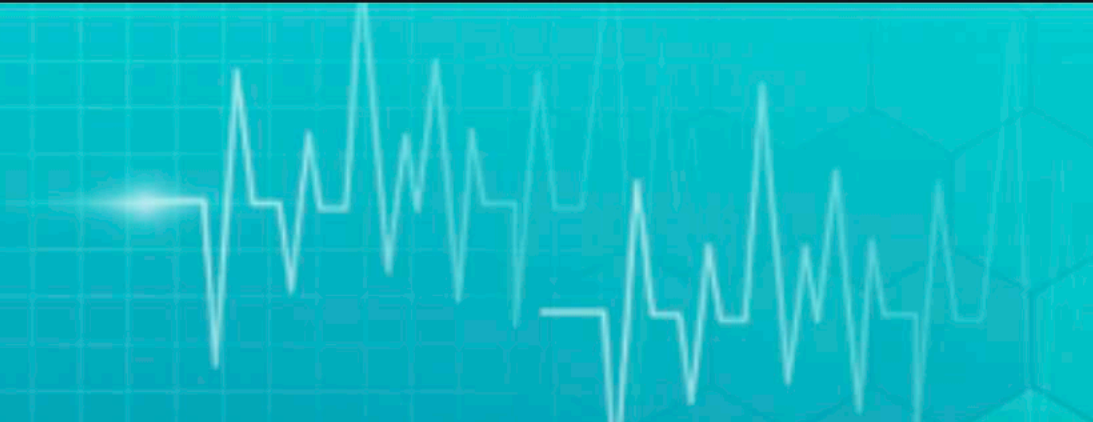
(Mphahlele et al, 2019)



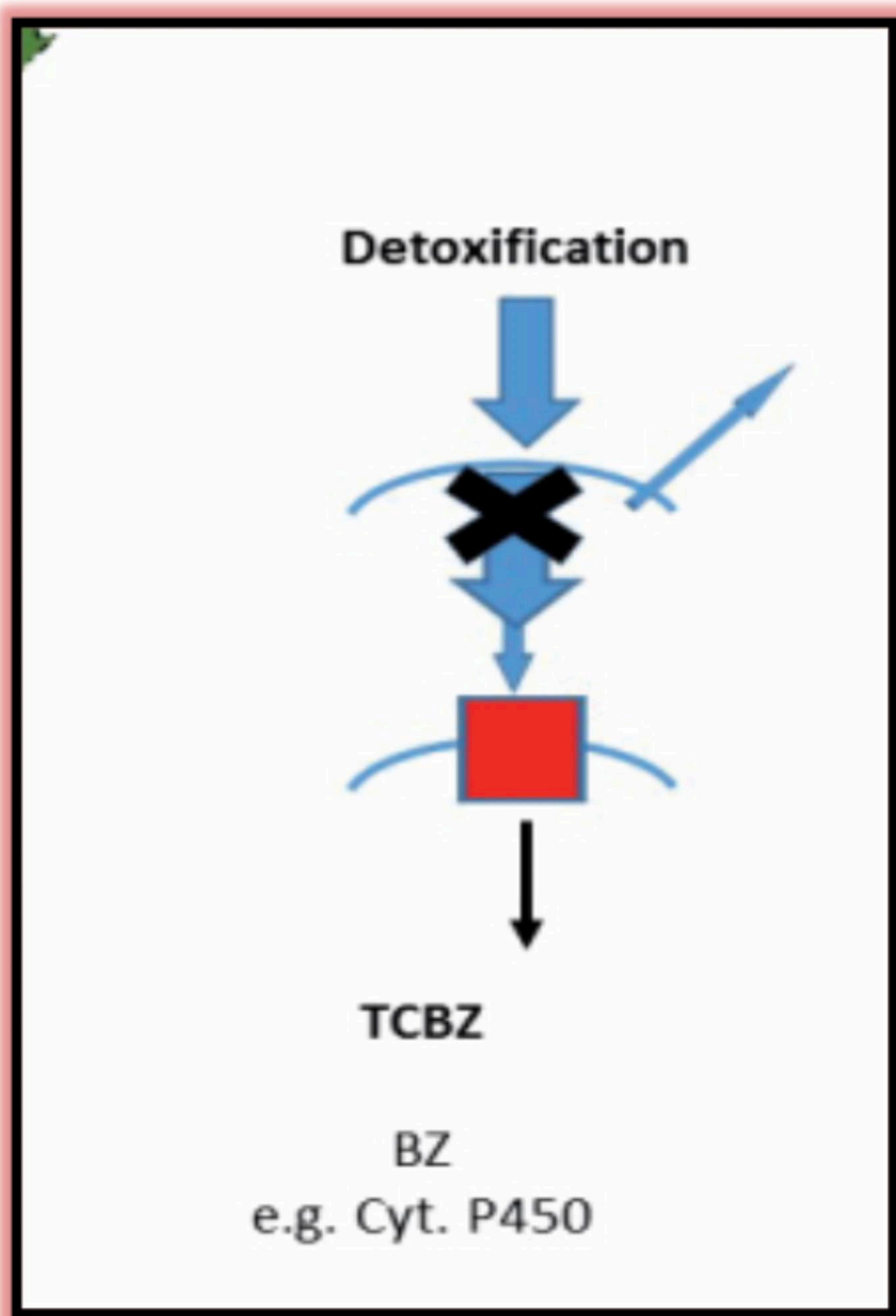
Mutations in the drug receptor sites that reduces the drug binding



(Mphahlele et al, 2019)

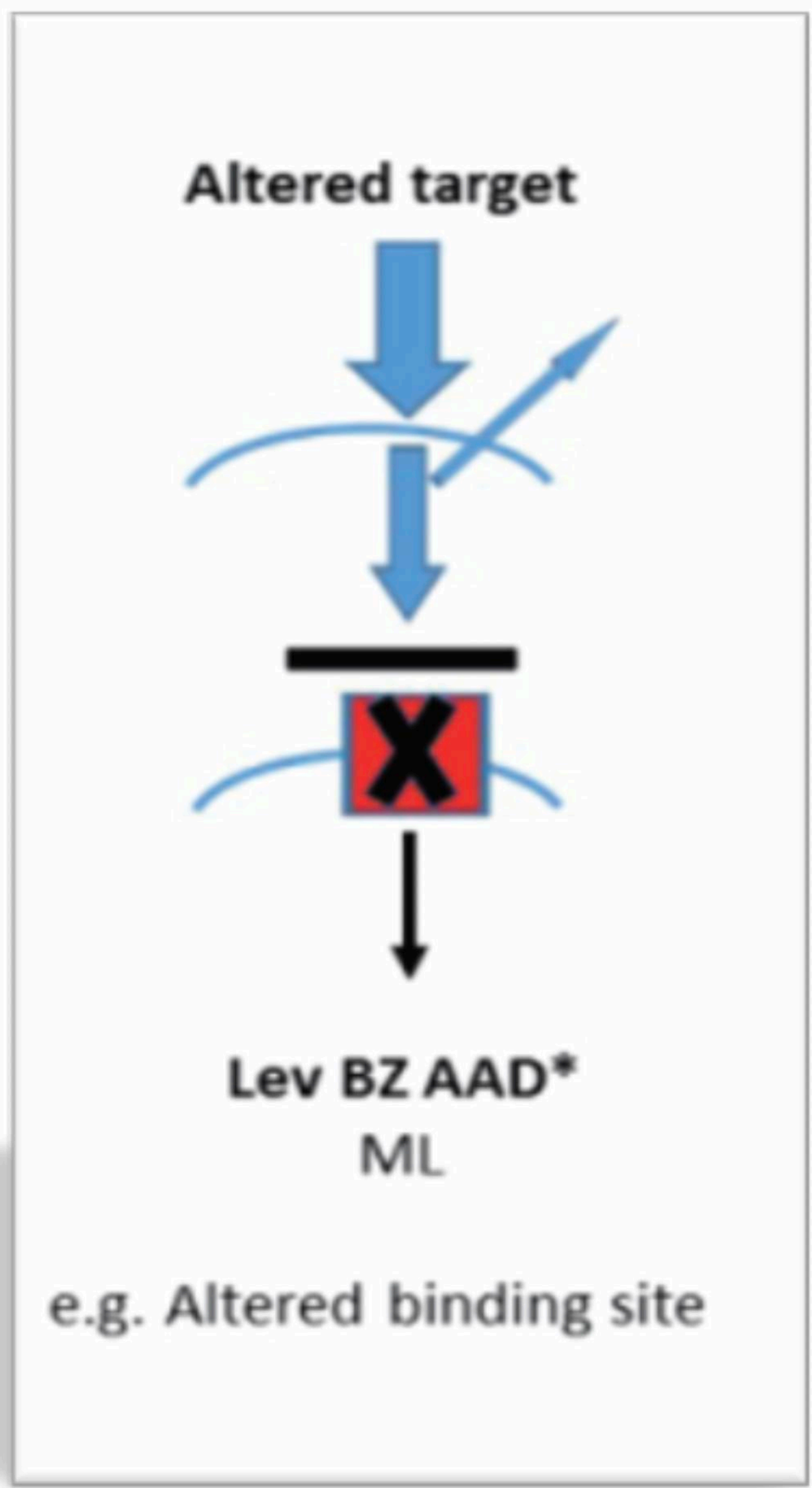


Increased drug metabolism

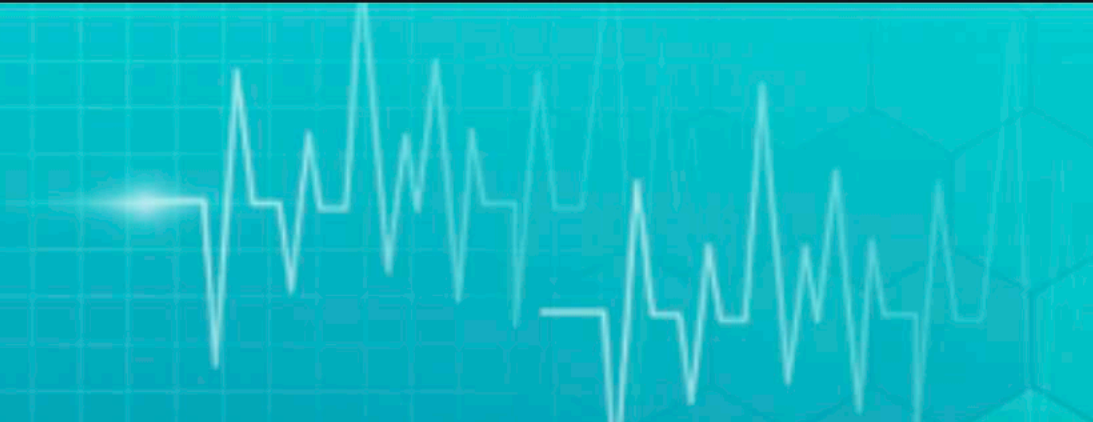




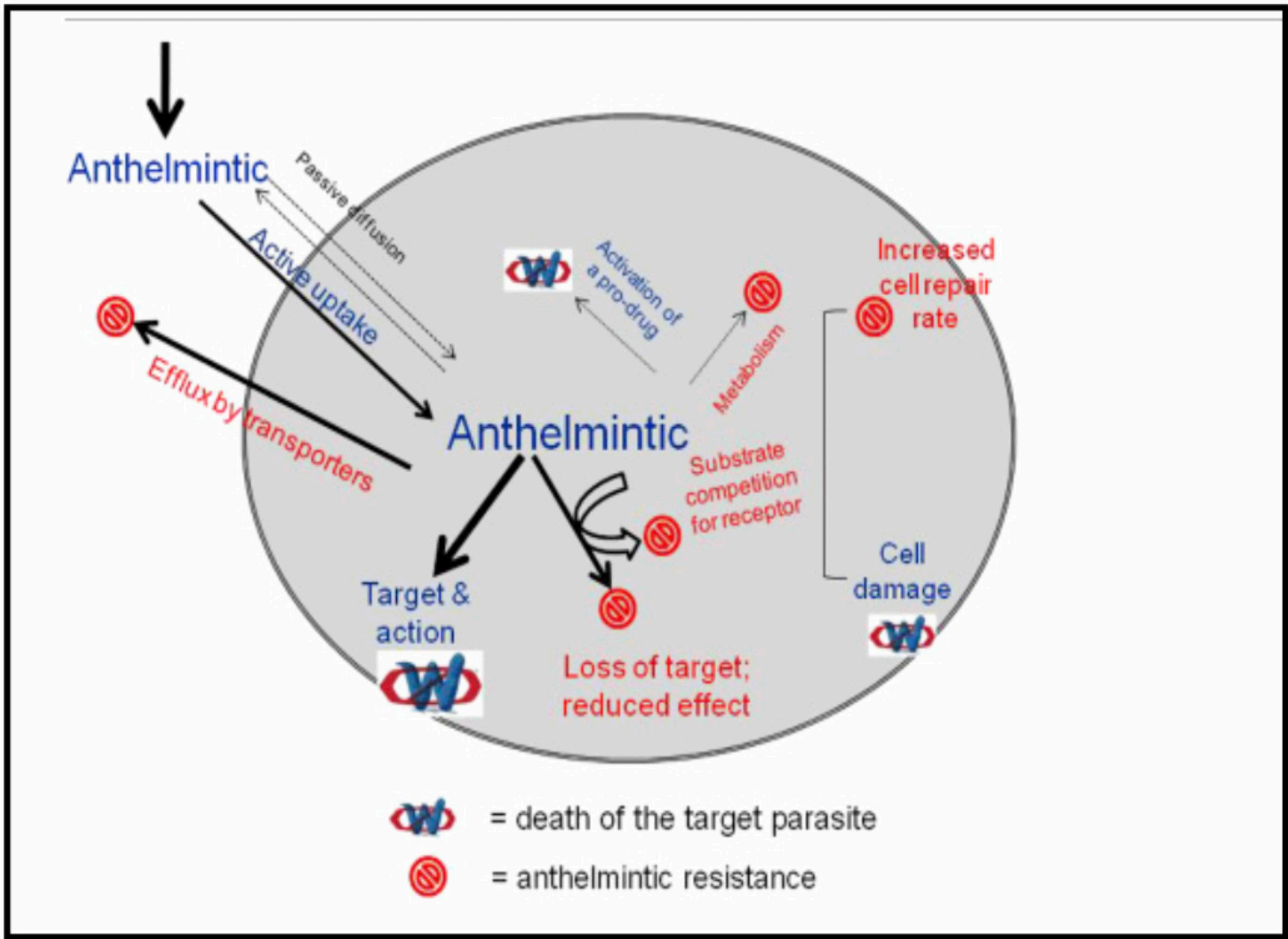
Decrease in the drug receptors abundance through reduced expression within the parasites



(Mphahlele et al, 2019)



Mechanism of Anthelmintic Resistance





Resistance to Benzimidazoles

- ▶ Target site of BZ is β -tubulin gene

- ▶ Mechanism of AR to BZ
 1. Alterations in β -tubulin: replacement of phenylalanine²⁰⁰ by tyrosine
Eg. Many species of Gastro-intestinal nematodes of ruminants

 2. Single Nucleotide Polymorphism (SNP) in β -tubulin protein at three sites
 - a. Position 167 and 200: Phenylalanine to tyrosine substitution
 - b. Position 198: Glutamic acid to alanine substitution



Resistance to Benzimidazoles

- ▶ β -Tubulin coding sequence in **Haemonchus contortus**, showing single nucleotide polymorphic (SNP) sites which can cause resistance.

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5'ATAACGTATTAGACGTTGTCCGCAAAGAAGCTGAAGGTTGTGATTGCCTTCAGGGCTTCCA
ATTGACGCATTCACCTGGAGGAGGCACTGGATCTGGAATGGAAATTCGTGAAGAGTACCCT
      167
GATAGAATTATGGCTTCGTTCTCCGTTGTTCCATCACCCAAGGTATCCGACACTGTCGTAGA
      TAC
ACCCTACAATGCTACCCTTTAGAACACCGATGAAACATTCTGTATTGACAACGAAGCTCT
      198 200
      GCA  TAC
GTATGATATCTGCTTCCGCACTTTGAACTCACAAATCCAACCTATGGAGA 3'
    
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Resistance to Macrocyclic Lactones

▶ Action is by potentiating Glutamate mediated chloride (GluCl) channel present in oropharynx of the nematodes and ecto-parasites

Mechanisms of AR for ML are

1. Mutations in the GluClRs genes - Eg. *H. contortus*
2. Lowering efflux of protein transporter, P-glycoprotein (Pgps) thus lowering drug entry into intracellular space
3. Increased expression of drug metabolizing enzymes eg. Cytochrome-P (CYP34/35)

Eg. Multidrug resistant *H. contortus*



Resistance to Imidazothiazoles and Tetrahydropyrimidines

Mechanism of AR

- ▶ Action is by activation of L- nicotinic acetylcholine receptors which causes neuromuscular depolarization and spastic paralysis.
- ▶ Reduced expression of genes coding for L-nAChRs
- ▶ *Eg. Haemonchus contortus, Ancylostoma caninum*



Factors affect the speed of resistance

SCOPS PRINCIPLE

(Sustainable Control of Parasites in Sheep)

- 1. Proportion of resistant worms on a farm**
 - 2. Frequency of anthelmintic use**
 - 3. Efficacy of each treatment**
 - 4. Proportion of the total worm population in the animal at the time of treatment**
 - 5. Dilution of any worms that survive treatment with unselected worms**
- [\(https://www.scops.org.uk/ \)](https://www.scops.org.uk/)



Thank you