FACULTÉ DE PHARMACIE

université PARIS-SACLAY

Mechanisms of action of antiparasitic drugs

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International Master

TU N° 02, Infectiology

2025

Parasites

Definition:

Eukaryotic organism depending from another organism, the host, during a part of its life or the total lifetime

Diversity:

Endoparasites

→ living inside their host

- Protozoa → unicellular eukaryotic organisms non producing photosynthesis
- Metazoa → pluricellular organisms → Helminths (= worms)
  - Cestodes (segmented flat worms): Tenias
  - Trematodes (non-segmented flat worms): Flukes
  - Nematodes (cylindrical worms): Ex: pinworms

} Cosmopolitan diseases more frequent in tropical areas

Ectoparasites

→ living on the host surface

- Arthropods
  - Insects
  - Mites

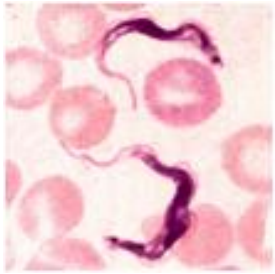
Diversity of parasites:

Taxonomic position:

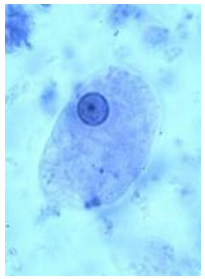
→ Domain Eukaryota:

→ Protozoa (non photosynthetic unicellular Eukaryota)

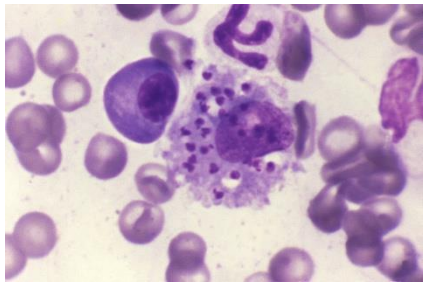
Plasmodium sp.



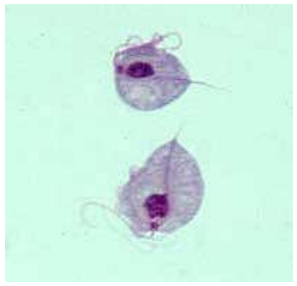
Trypanosoma brucei gambiense



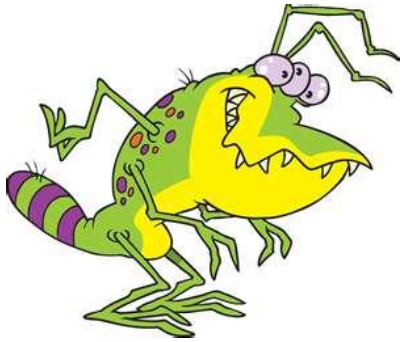
Entamoeba histolytica



Leishmania infantum



Trichomonas vaginalis



Diversity of parasites:

Taxonomic position:

→ Domaine Eukaryota:

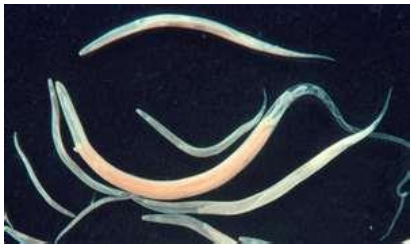
→ Helminths (pluricellular Eukaryota → vorms)

*Fasciola hepatica (*fluke)

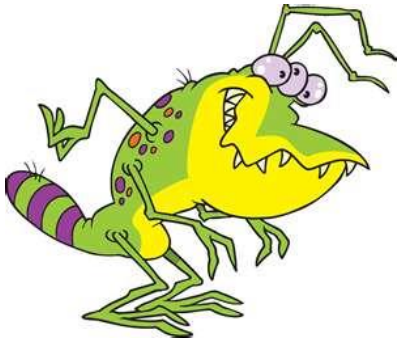
Schistosoma mansoni

Taenia saginata

Ascaris lumbricoides



Enterobius vermicularis



Parasite genus

Protozoa

Plasmodium

Entamoeba

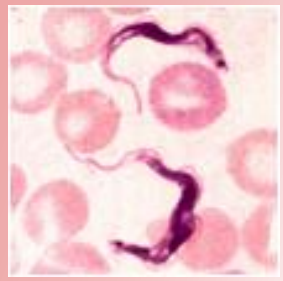
Giardia

Trichomonas

Trypanosoma

Leishmania

…



Helminths

Nematodes
(round worms)

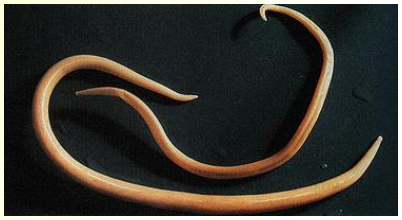
Ascaris

Ankylostoma

Strongyloides

Enterobius

…



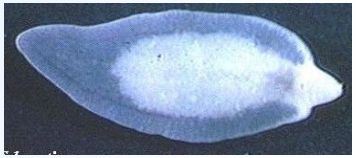
Plathelminths
(flat worms)

Trematodes
(non segmented)

Fasciola

Schistosoma

…



Cestodes
(segmented)

Taenia

Echinococcus

…

Antiparasitic drugs

Definition

Synthetic or natural compound

→ active against one or several parasite stages → biocide or biostatic actitivities

→ well tolerated by the host → requires selective activity and low toxicity

Setting up a treatment

- After diagnosis on the +/- symptomatic host: what kind of parasite ?

  → Requires a precise identification of the parasite species

- Then, choosing the treatment targeting the diagnosed parasite

Conditions for the efficacy of an antiparasitic treatment :

- Patient compliance (duration, dosage)
  - → Getting the healing
  - → Preventing drug resistance emergence

- Avoiding personal and social behaviours favouring new contamination

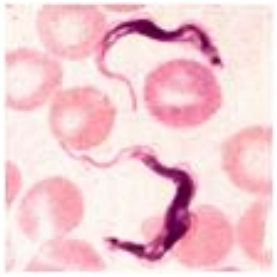
  → Following sanitary recommendations

Antiprotozoal drugs

→ should concentrate where the parasite dwells to prevent toxicity

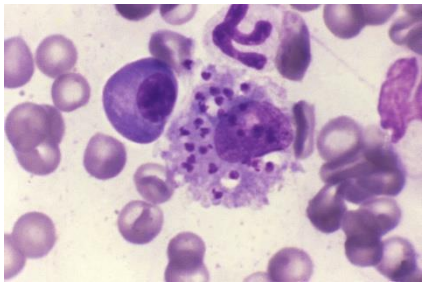
→ within blood

Plasmodium sp.



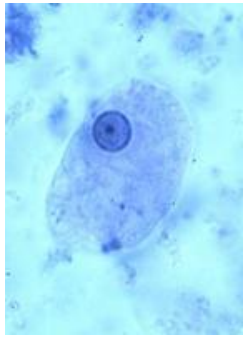
Trypanosoma brucei

→ within tissues

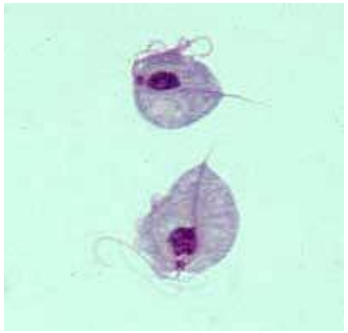


Leishmania infantum

→ within cavities



Intestine → *Entamoeba histolytica*



Uro-genital tractus → *Trichomonas vaginalis*

Main biological targets of antiprotozoal drugs

- **Inhibition of heme biomineralisation**
  → Toxicity for the parasite

- **Inhibition of oxidative phosphorylation**
  → Impairment of parasite respiration

- **Inhibition of trypanothione-reductase**
  → Impairment of detoxification

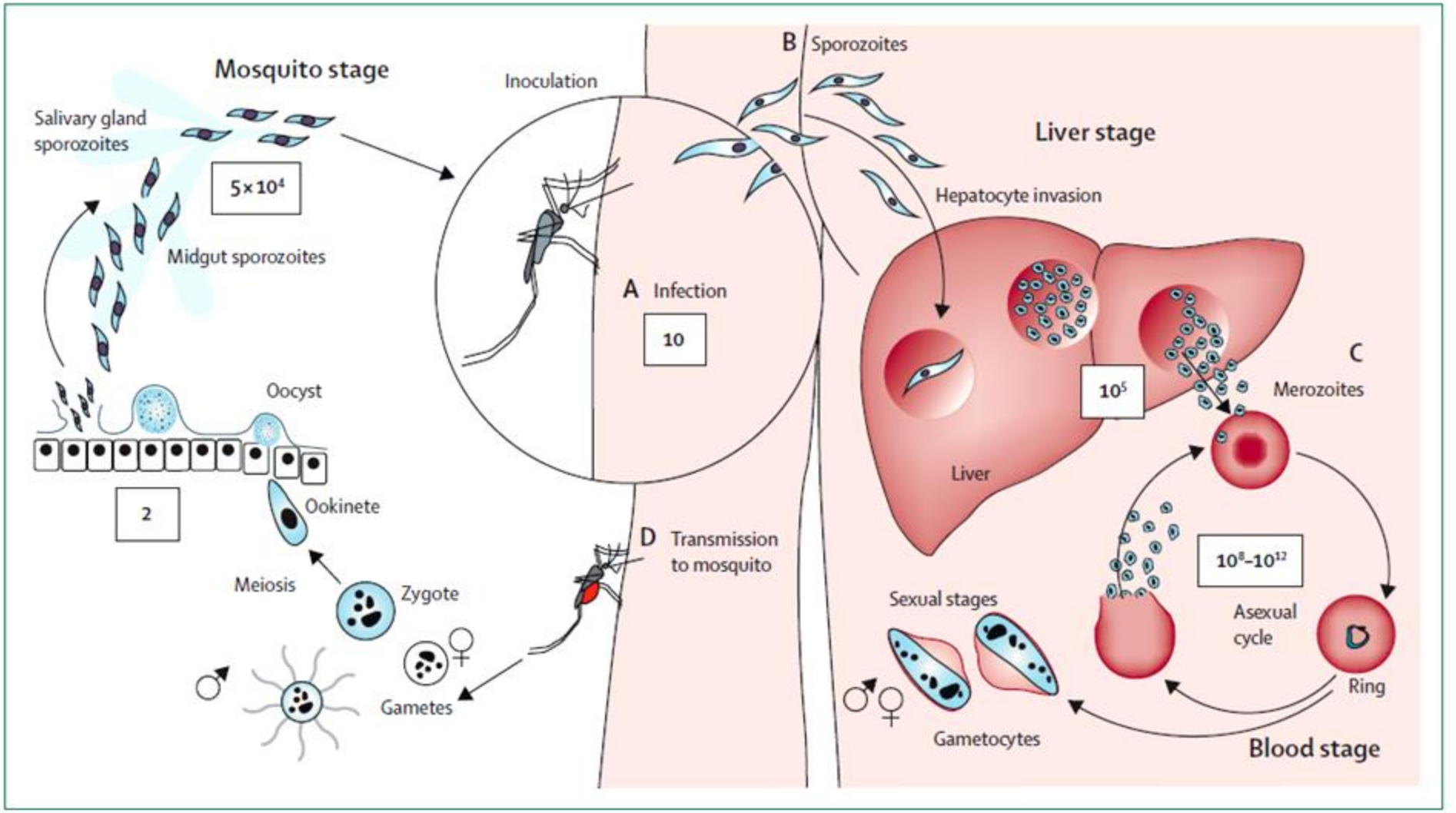
- **Inhibition of polyamine metabolism**
  → Impairment in cell functions

- **Damages to membranes**
  → Loss of membrane integrity
  → Impairment in the biosynthesis of membrane lipids

- **Inhibition of DNA biosynthesis**
  → Impairment of parasite reproduction

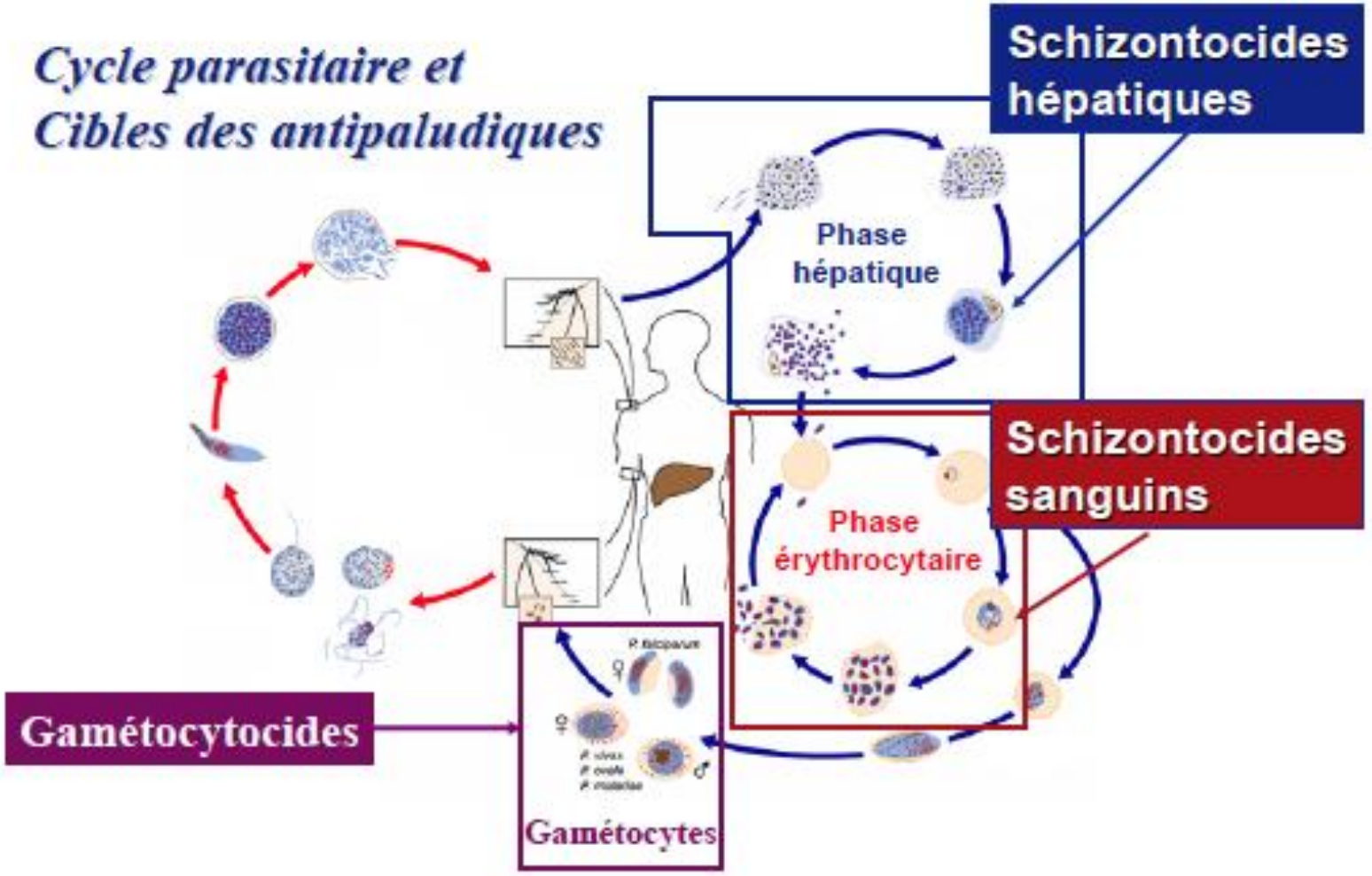
Antimalarial drugs

Life cycle of *Plasmodium sp.* → Malaria

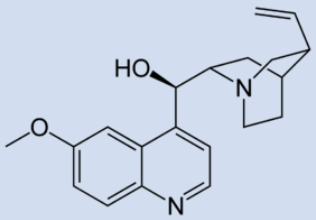
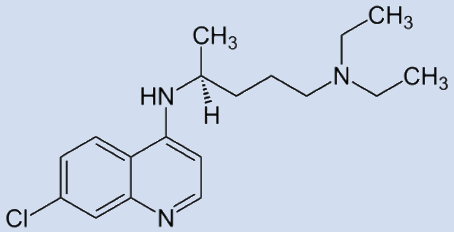
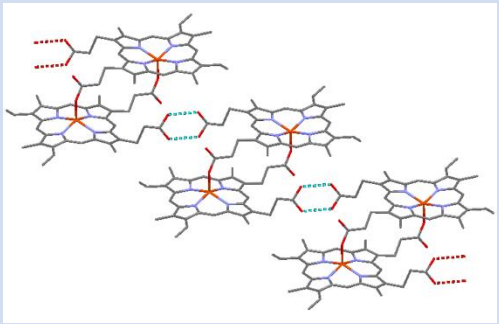
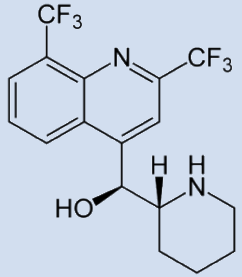
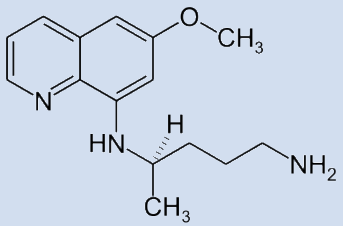
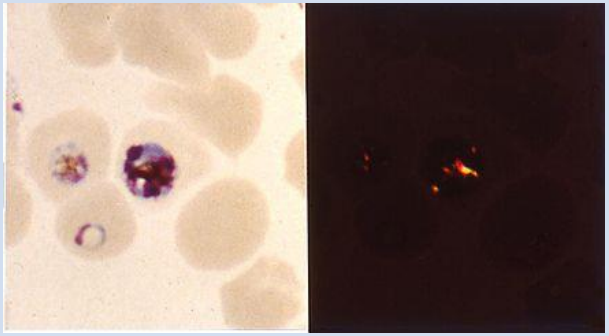


Antimalarial drugs

→ **The main sites of action of antimalarial drugs**



Mechanism of action of antimalarials

Antiparasitic drugs	Mechanism of action
Quinolines	
- Quinine 	→ Weak bases → Lysosomotropic substances → Accumulate into parasite digestive vacuole → Inhibition of heme polymerization
- Chloroquine (not marketed anymore) 	
- Mefloquine 	
- Primaquine 	

Schizonticide

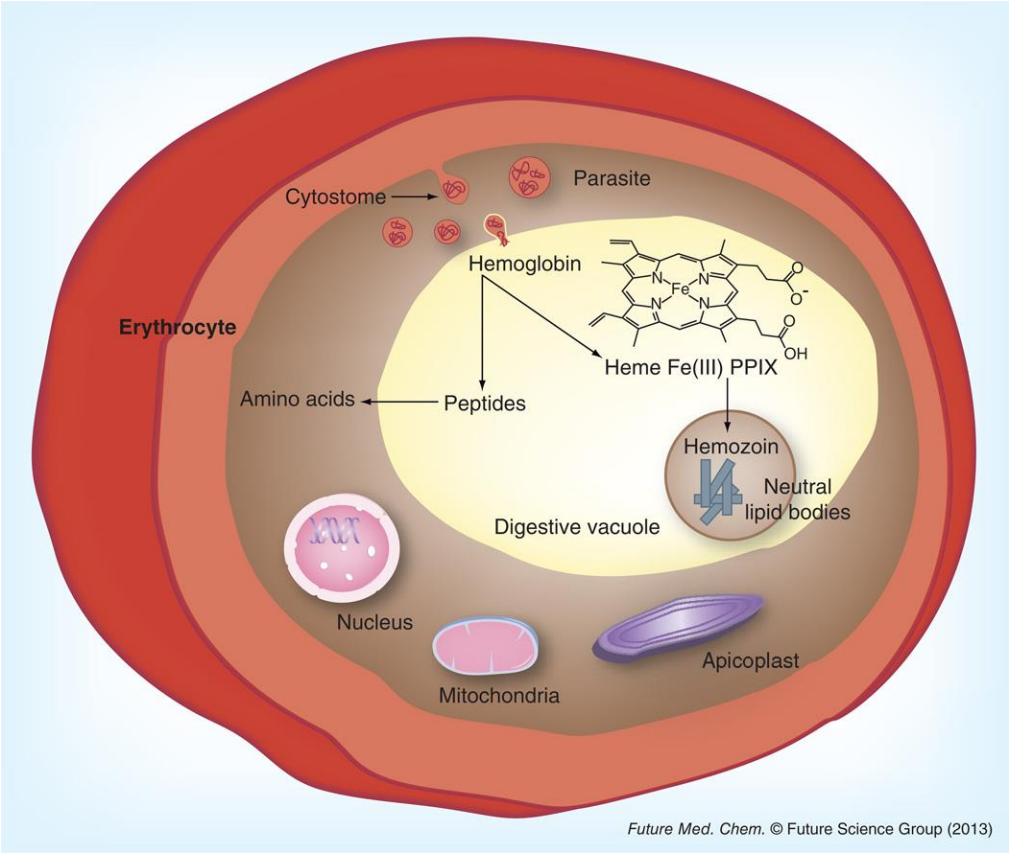
Gametocytocide

Main mechanism of action of quinolines

→ Inhibitors of heme biomineralisation

→ Formation and accumulation of a cytotoxic complex with protoporphyrin IX produced from the hemoglobin degradation within the digestive vacuole, normally transformed into hemozoin

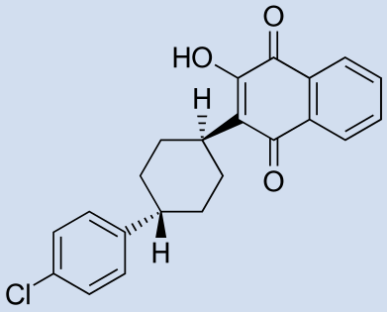
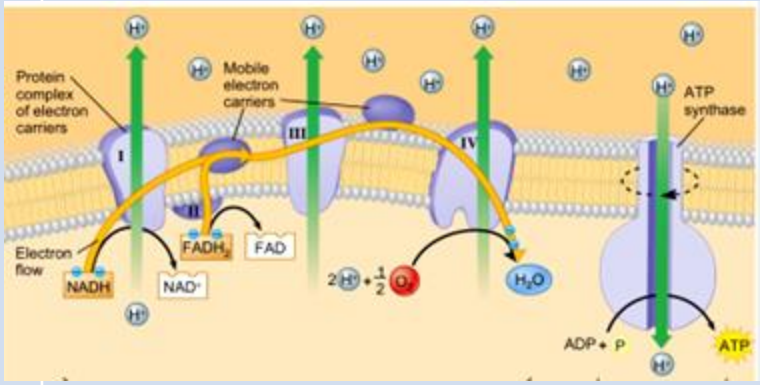
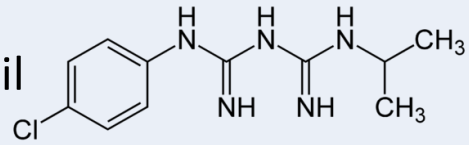
(= non toxic malaria pigment)



Mechanisme of action of antimalarial drugs

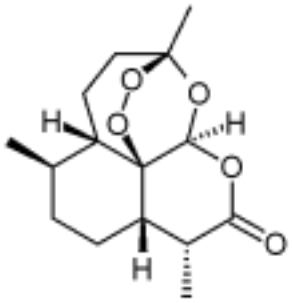
Drug combination

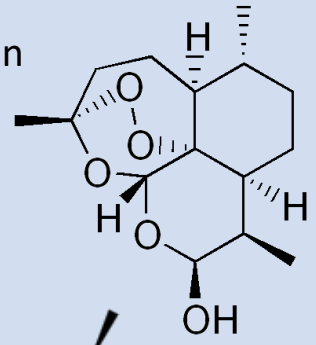
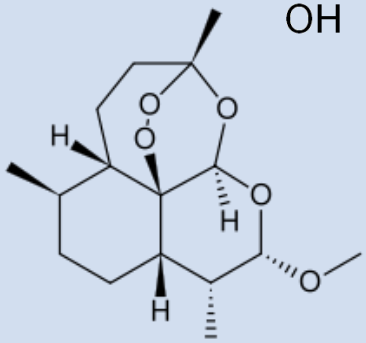
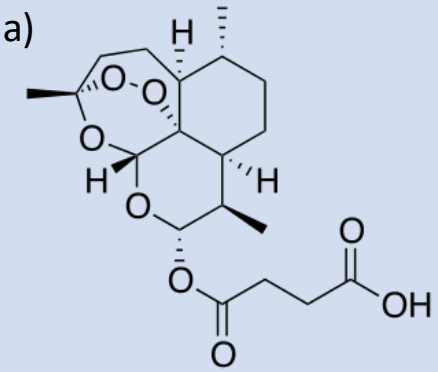
Atovaquone + Proguanil

Antiparasitic drugs	Mechanism of action
Naphtoquinone - Atovaquone  	→ Antimetabolite → Analogue of Coenzyme Q → Inhibition of oxydative phosphorylations (complex II or bc1) 
Biguanide - Proguanil  	→ Active form: cycloguanil (metabolite) → Inhibitor of DHFR (DiHydroFolate Reductase)

Mechanism of action of antimalarial drugs:

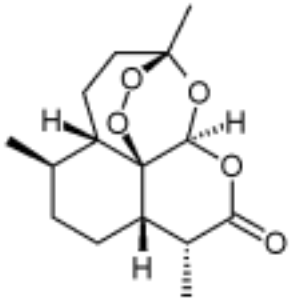
Artemisinin derivatives



Antiparasitic drugs	Mechanism of action
Sesquiterpene lactones - Dihydroartemisinin  - Artemether  - Artesunate (severe malaria) 	→ Opening the endoperoxide bridge → Production of free radicals → Oxidative activity → Cell functional impairments → Damages on nuclear, endoplasmic reticulum and mitochondrial membranes → Ribosome aggregation → Reduction of protein biosynthesis

Mechanism of action of antimalarial drugs:

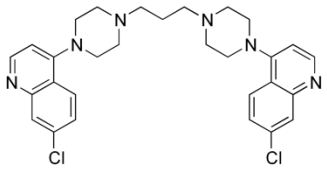
Artemisinin derivatives



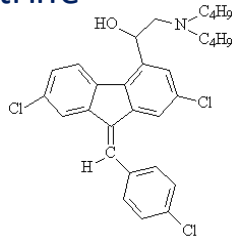
ACT: Artemisinin Combination Therapy

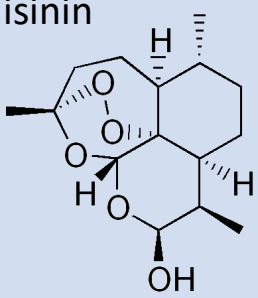
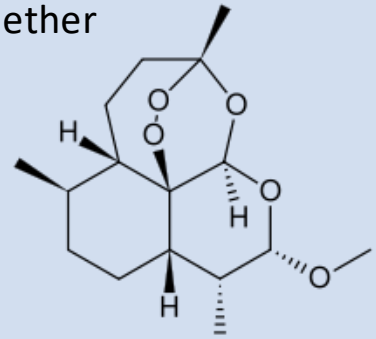
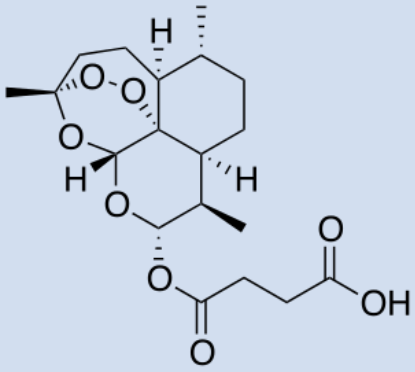
Combined with:

Piperaquine

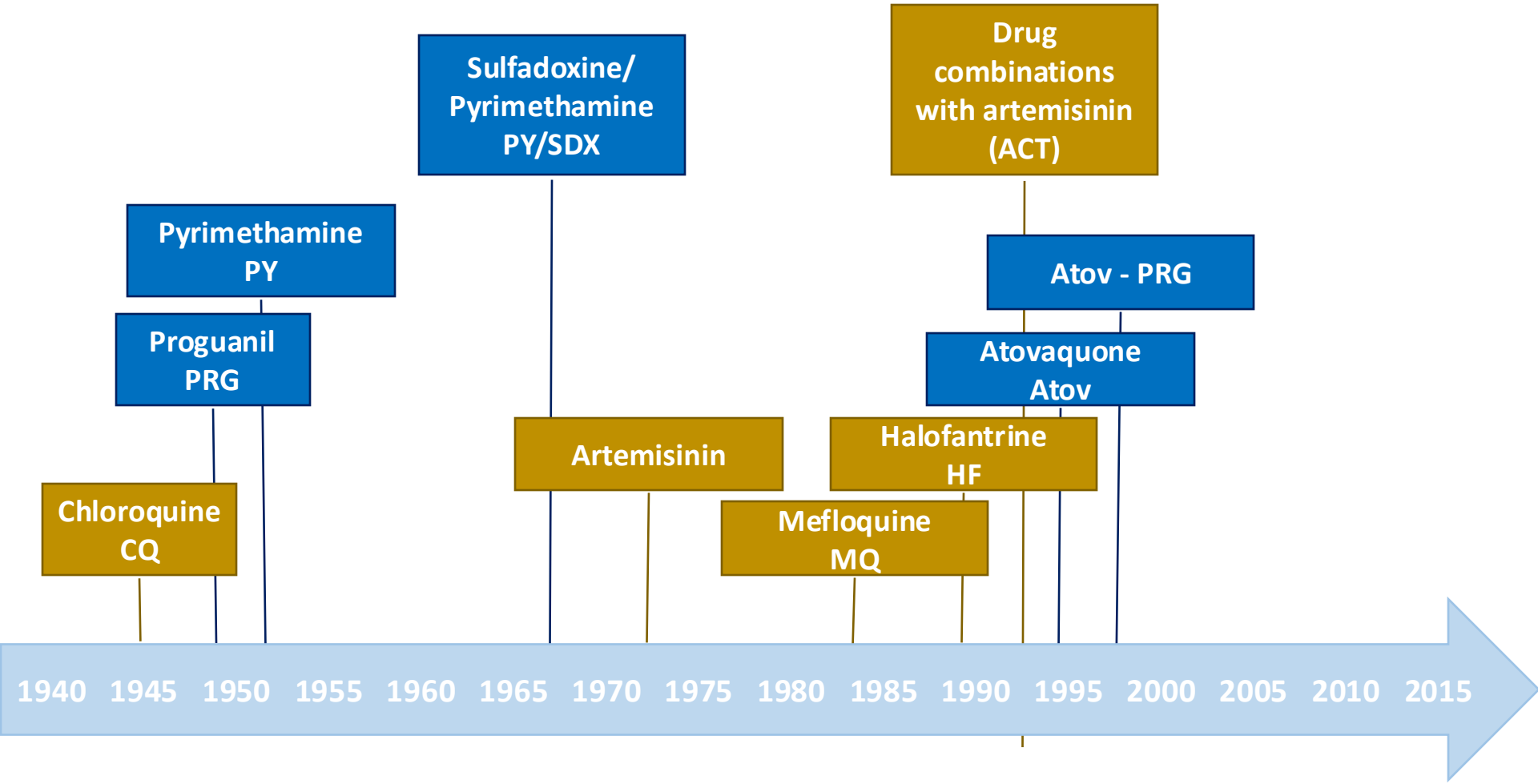


Lumefantrine



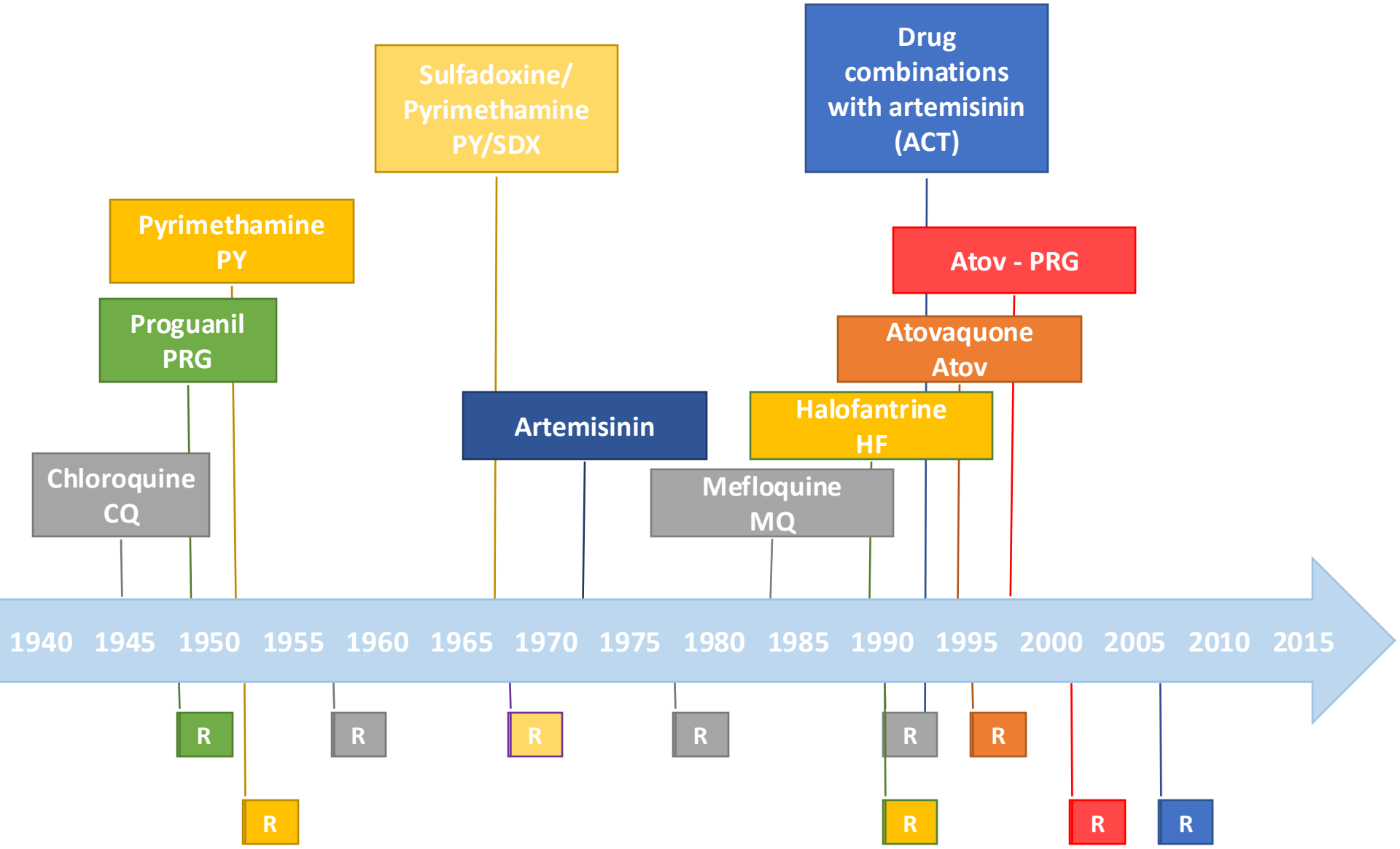
Antiparasitic drugs	Mechanism of action
Sesquiterpene lactones - Dihydroartemisinin  - Artemether  - Artesunate (severe malaria) 	→ Opening the endoperoxide bridge → Production of free radicals → Oxidative activity → Cell functional impairments → Damages on nuclear, endoplasmic reticulum and mitochondrial membranes → Ribosome aggregation → Reduction of protein biosynthesis

History of antimalarial chemotherapy



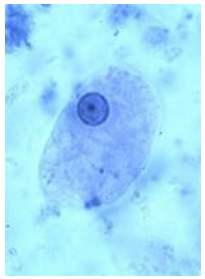
Adapteed from Pradines, 2010

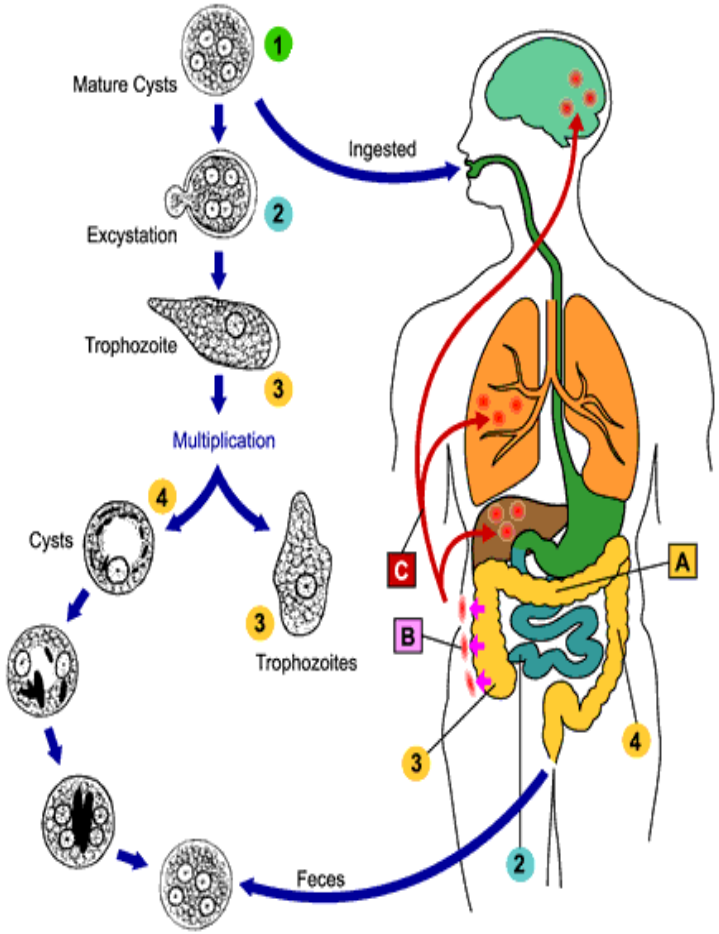
History of drug resistance emergence

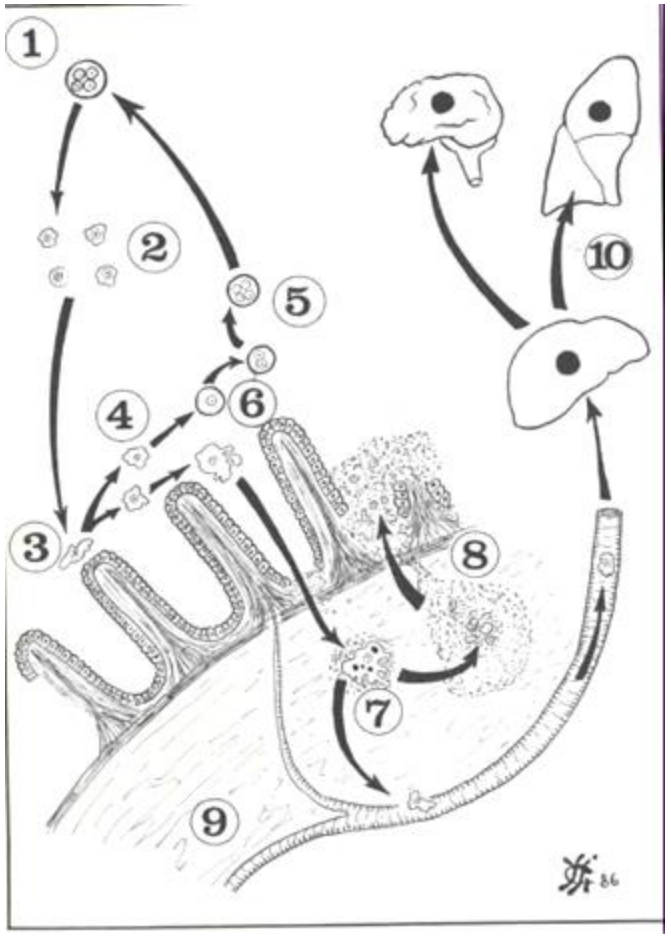


Life cycle of *Entamoeba histolytica* → Amoebiasis

- **Monoxenic direct life cycle**

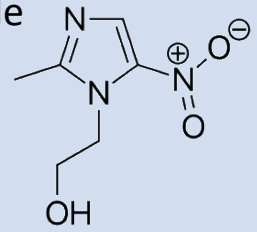
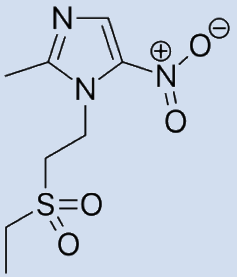
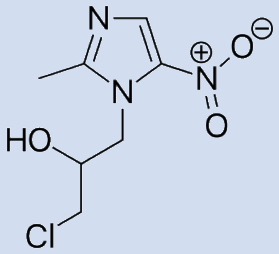
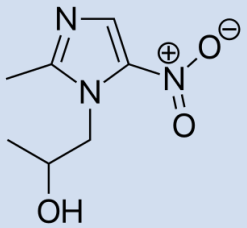






Mechanism of action of antiamoebic drugs:

Diffusible antiamoebic drugs

Antiparasitic drugs	Mechanism of action
Nitro-5-imidazole	
- Metronidazole 	→ Act as a prodrug → NO_2 reduction by pyruvate ferredoxine oxydoreductase (PFOR)
- Tinidazole 	→ Nitro-radical anion: R-NO_2^- → Increase of nitro-5-imidazole uptake through diffusion gradient → Production of ROS: superoxide anion
- Ornidazole 	→ DNA fragmentation → Inhibition of nucleic acid biosynthesis
- Secnidazole 	No drug resistance observed in the field

Mechanism of action of nitro-5-imidazoles

Interaction with pyruvate-ferredoxine oxydo-reductase (PFOR) = specific pathway in anaerobic bacteria and some protozoa (equivalent to pyruvate dehydrogenase of aerobic organisms)

→ Neutralization of radicals in host cell by oxygen that is toxic for the parasite
→ SOD absent from the parasite (anaerobic)

In parasite cells

Reduction by PFOR

$R\text{-}NO_2 \xrightarrow{1e^-} R\text{-}NO_2^{-\bullet} \xrightarrow{ROS}$ **Death of parasites**

In host cells

$R\text{-}NO_2^{-\bullet} + O_2 \rightarrow R\text{-}NO_2 + O_2^{-\bullet}$

$2H^+ \rightarrow$ **SOD (SuperOxide Dismutase)**

H_2O_2

Catalase

$H_2O + ½\ O_2$ → **Protection of host cells**

Nitro-5-imidazoles

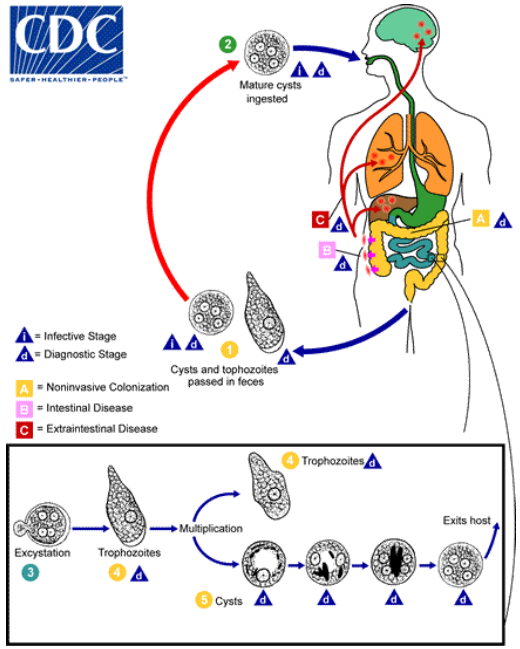
Comparative pharmacokinetics:

	Metronidazole	Ornidazole	Tinidazole	Secnidazole
Bioavailability	100% (not reduced by meals)			
Distribution	Excellent distribution within all tissues and biological liquids			
Biotransformation	Hepatic → Cyt P3A4 → Oxidized metabolites			
Plasmatic peak	1-3h	2-4h	2h	2-3h
Half-life	8-10h	12-14h	12-14h	25h
Elimination	Urinary (70%) and fecal	Urinary	Urinary and fecal	Urinary (slow)
Trade name	Flagyl®	Tiberal®	Fasigyne®	Secnol®

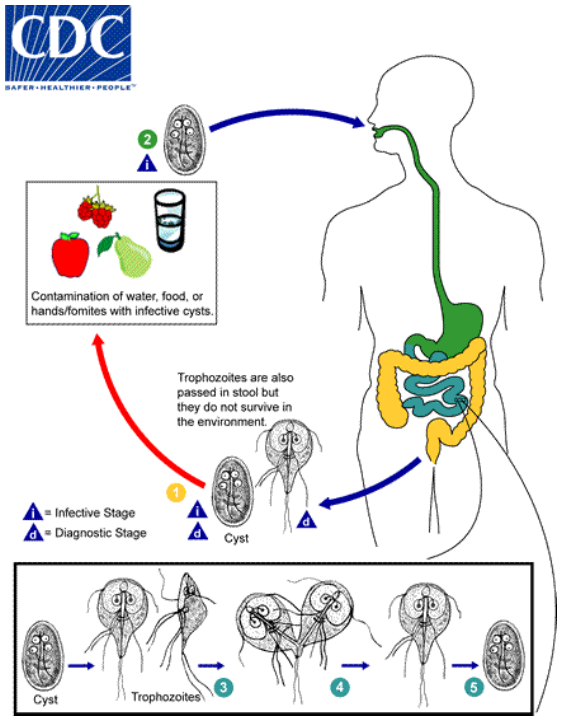
Spectrum of activity of nitro-5-imidazoles

Some protozoa

→ *Entamoeba histolytica*



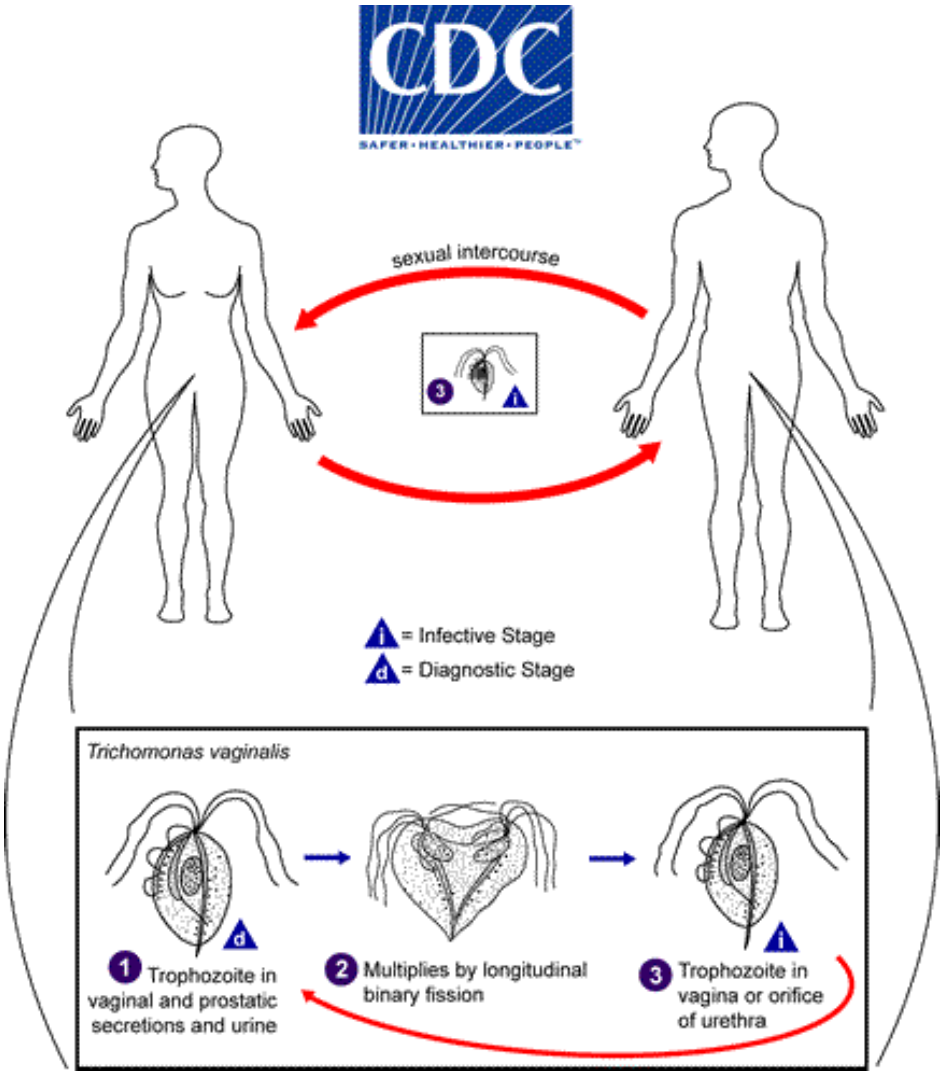
→ *Giardia intestinalis*



Spectrum of activity of nitro-5-imidazoles

Some protozoa

→ *Trichomonas vaginalis*

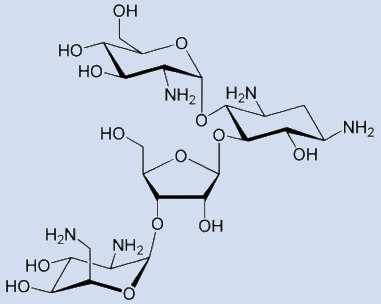
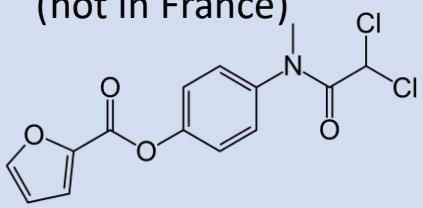


Some anaerobic bacteria

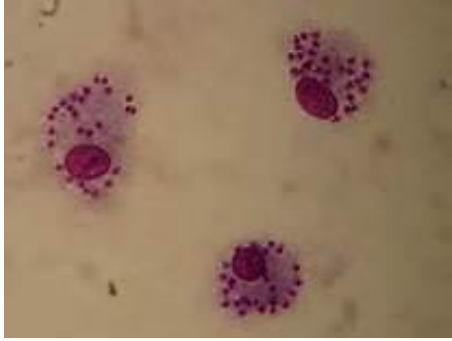
→ *Clostridium difficile*

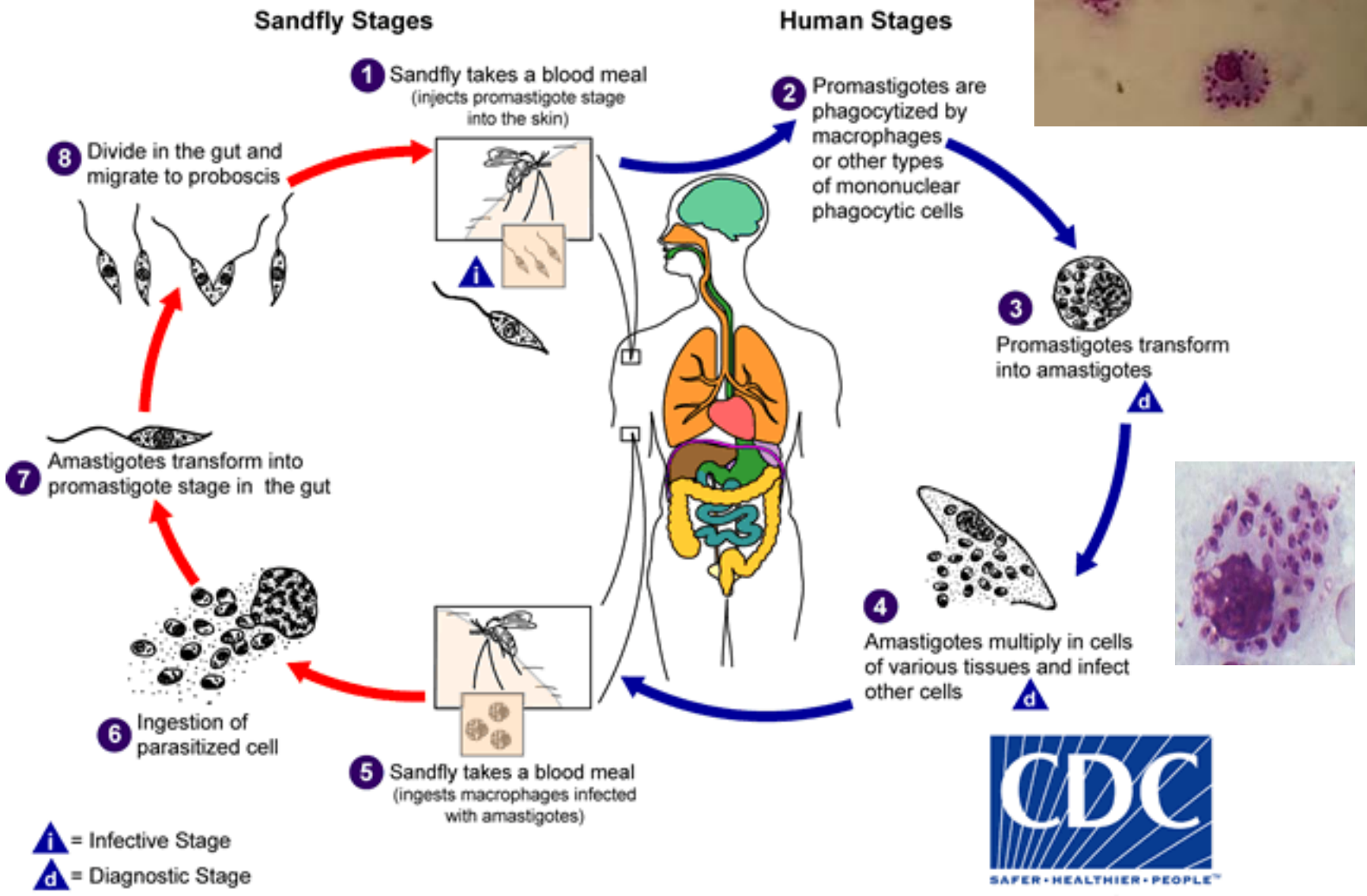
Mechanism of action of antiamoebic drugs:

Antiamoebic drugs having intraluminal action only

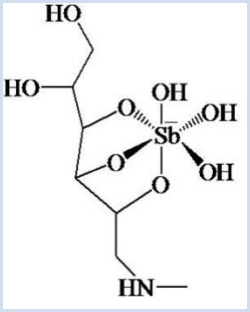
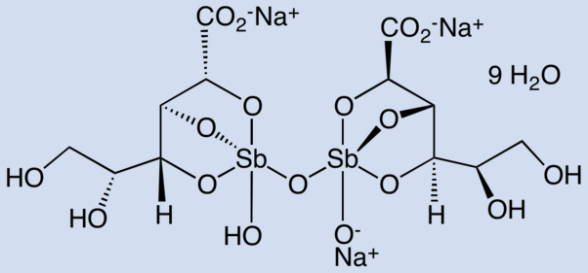
Antiparasitic drugs	Mechanism of action
	→ Poorly absorbed by oral route → Intraluminal action
Aminoside (or aminoglycoside) - Paromomycin (Humatin®) 	→ Binding to rRNA 16S → Accumulation of aberrant proteins → Inhibition of protein biosynthesis
Dichloracetamide - Diloxanide (Entamide®, Furamide®)) (not in France) 	→ Disrupting ribosomes ?

Life cycle of *Leishmania sp.*→ Leishmaniases





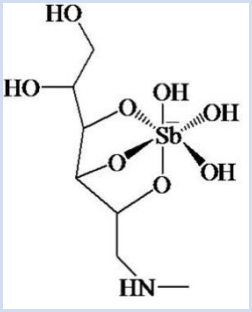
Mechanism of action of antileishmanial drugs: Antimony derivatives

Antiparasitic drugs	Mechanism of action
Pentavalent antimonials	
- Meglumine antimoniate (Glucantime®) 	- Inhibition of trypanothione-reductase - Impairment of glycosomal activity (Glycosomes = organites where glycolysis occurs in Kinetoplastidae)
- Sodium stibogluconate (Pentostam®) 	

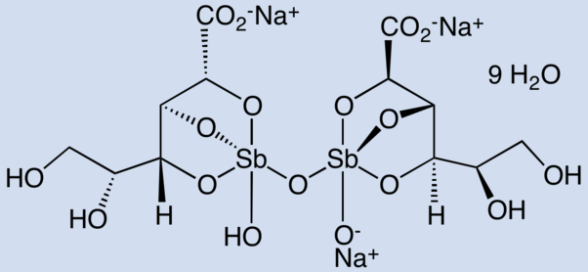
Antiparasitic drugs

Pentavalent antimonials

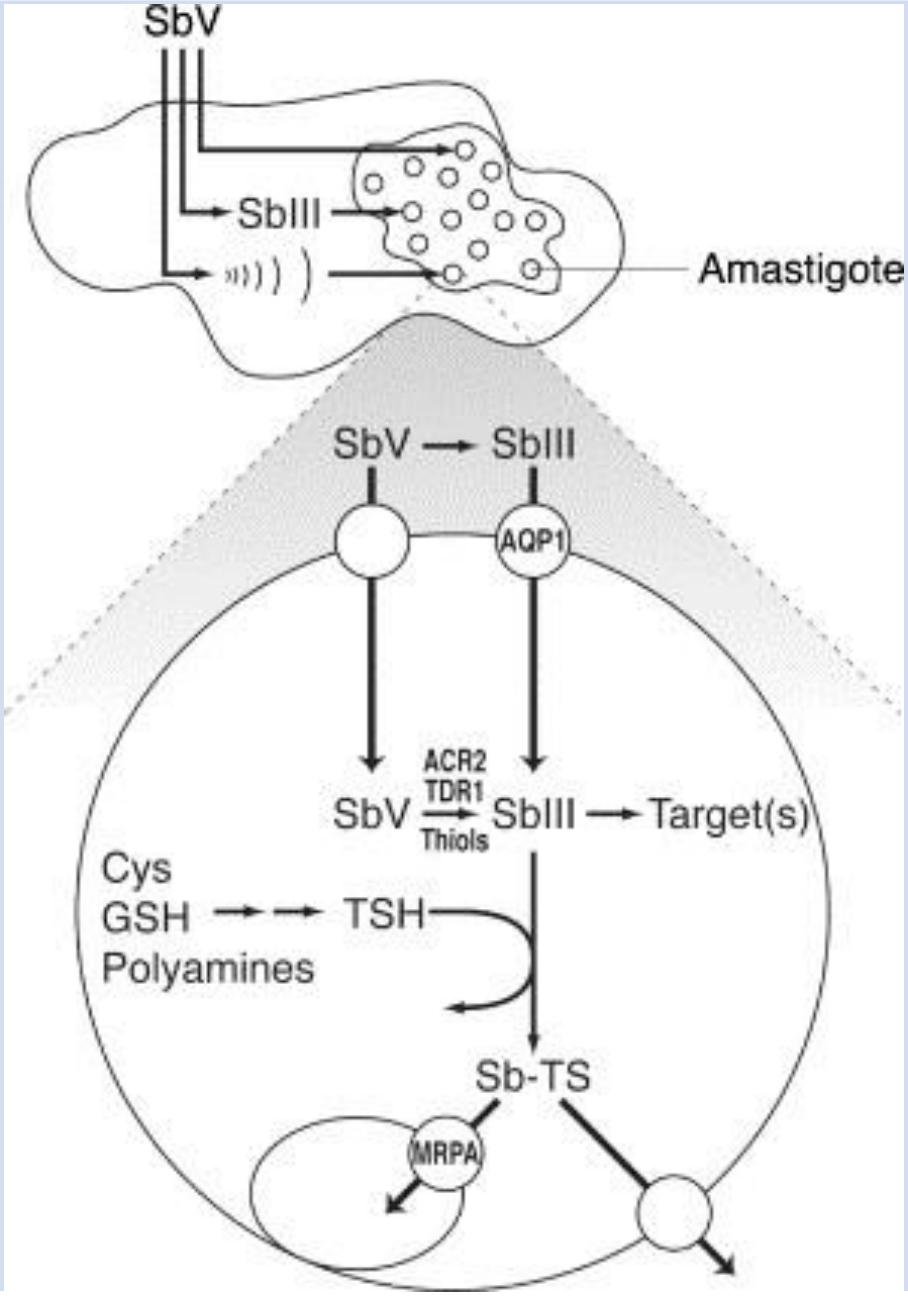
Meglumine antimoniate (Glucantime®)



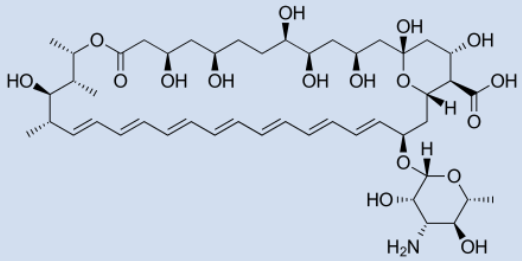
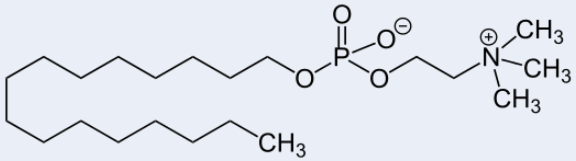
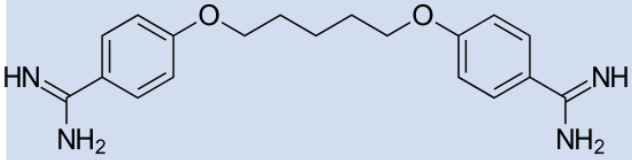
Sodium stibogluconate (Pentostam®)



Mechanism of drug resistance



Mechanism of action of antileishmanial drugs

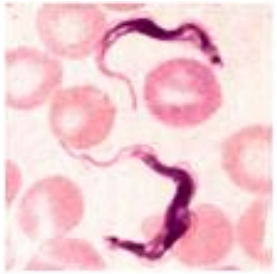
Antiparasitic drugs	Mechanism of action
Polyene macrolide - Amphotericin B (Fungizone®, now used under the liposomal form: AmBisome®) 	→ Formation of pores → K+ leakage → Decrease membrane fluidity → Stimulation of INF-γ production by macrophages → Biosynthesis of TNFα and IL1 → Production of nitric oxide (NO) → Increase of oxidative burst → Apoptosis
Alkylphospholipide - Miltefosine 	- Impairment of the membrane lipid biosynthesis - Inhibition of cytochrome c oxidase - Apoptosis
Aromatic diamidine - Pentamidine 	- Inhibition of DNA biosynthesis (rich in AT bases in these parasites) = inhibition of thymidine synthetase - Fixation to tRNA - Impairment of the mitochondrial activity

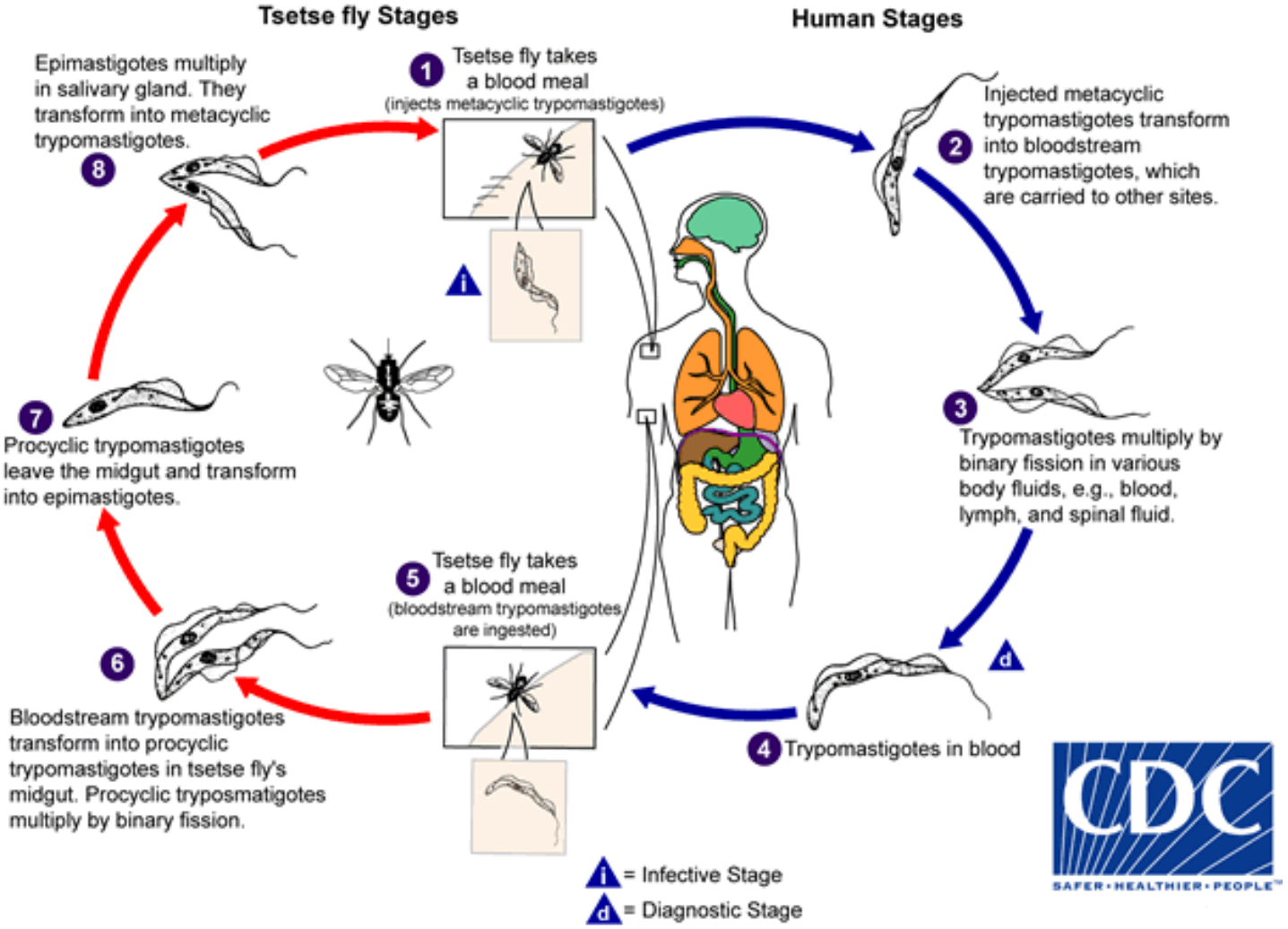
Life cycle of *Trypanosoma brucei* → Human African Trypanosomiasis

→ **2 phases of the disease: haemolymphatic and meningoencephalitic**

→ **2 *Trypanosoma* species:**

- → ***T. brucei gambiense*** **(West Africa)**
- → ***T. brucei rhodesiense*** **(East and South Africa)**

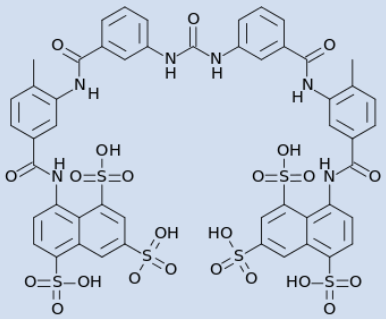
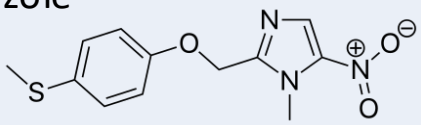
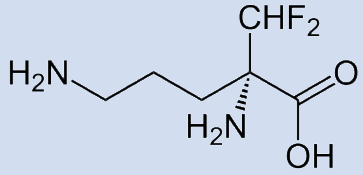
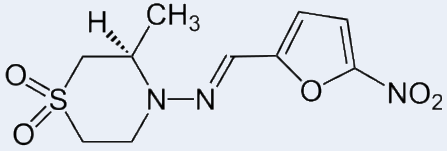




Mechanism of action of trypanocidal drugs

NECT: Nifurtimox-Eflornithine Combination Therapy

→ **Active on the meningo-encephalitis** phase provoked by *T. b. gambiense* (West Africa)

Antiparasitic drugs	Mechanism of action
Naphtalene derivative - Suramine (Moranyl®, Germanin®) 	- **Active on the haemolymphatic phase of *T. b. rhodesiense*** - Inactive on the late phase (meningo-encephalitis)
- **Nitro-5-imidazole** - Fexinidazole 	- Sulfoxide and sulfone metabolites - **Active on hemolymphatic and meningoencephalitic stages (*T. b. gambiense*)**
- Eflornithine (Ornidyl®) 	- Competitive and suicide inhibitor of ornithine decarboxylase (ODC) - High affinity for parasitic ODC - ODC turn-over → slower in parasite than in host
Nitrofurane - Nifurtimox 	- Formation of an anionic metabolite reacting with DNA - Reduction of nifurtimox → ROS

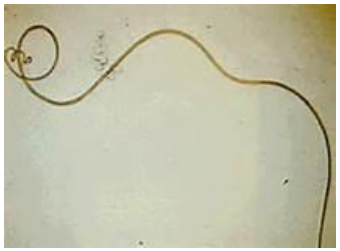
Anthelminthic drugs

→ should concentrate where the parasite dwells to prevent toxicity

→ Intraveinous

Schistosoma mansoni (schistosome)

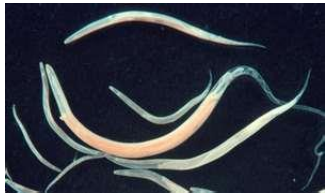
→ Intra-lymphatic



Wuchereria bancrofti (filaria)

→ Intestinal

Taenia saginata (tapeworm)



Enterobius vermicularis (pinworm)

Ascaris lumbricoides (roundworm)

→ Biliary duct

Fasciola hepatica (fluke)

Main biological targets of anthelminthic drugs

- **Cuticle and/or plasma membrane**

- **Tubulin polymerization and microtubule biosynthesis**

- **Carbohydrate absorption and metabolism**

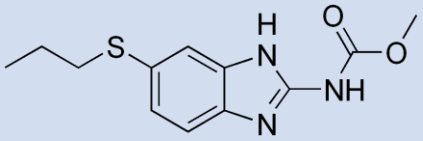
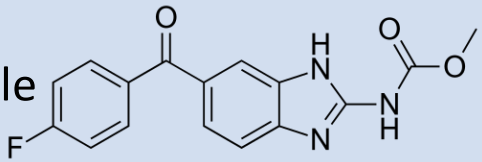
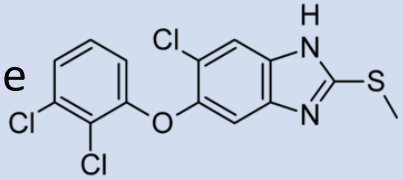
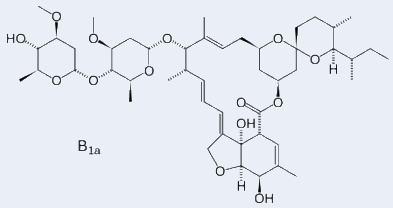
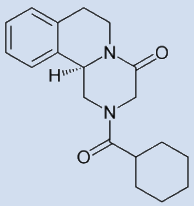
- **Protein biosynthesis**

- **Nucleic acid biosynthesis**

- **Nervous system: neurotoxicity**

    - Action on cholinergic synapses (cholinomimetic)
    - Action on GABAergic synapses
    - Action on adrenergic receptors
    - Action on nerve impulse transmission

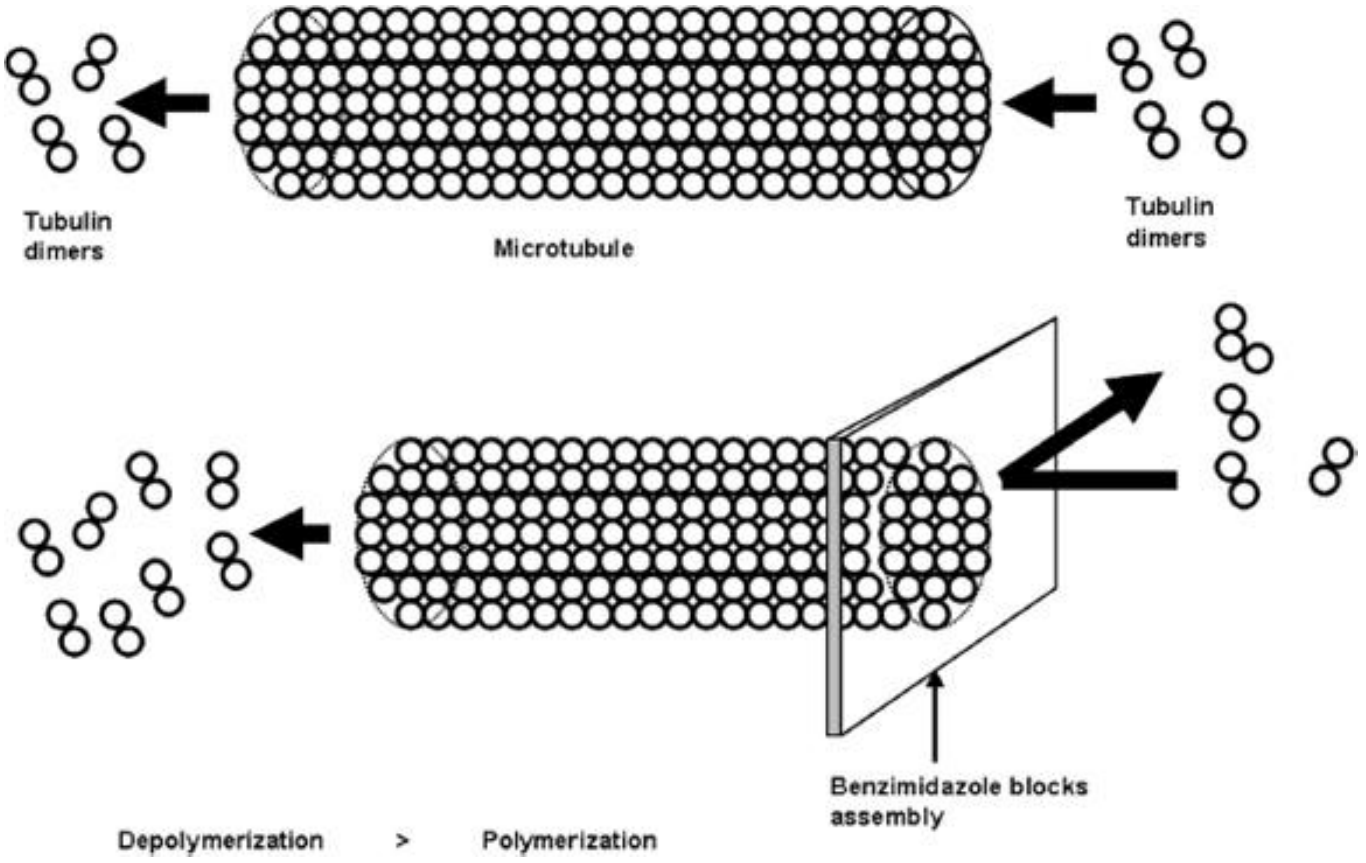
Main anthelminthic drugs

Antiparasitic drugs	Mechanism of action
Benzimidazoles - Albendazole  - Flubendazole  - Triclabendazole 	Beta-tubuline → Inhibition of microtubule polymerization
Avermectines - Ivermectine 	Inhibition of nerve impulse
Pyrazino-isoquinoline - Praziquantel 	Impairment of membrane permeability

Mechanism of action of benzimidazoles

Fixation of benzimidazoles to β-tubulin dimers → Inhibition of microtubule polymerisation

→ Mitosis inhibition and impairment of cell activity
→ Inhibition of absorption of nutrients (glucose, etc…)
→ Decrease of glycogen stock
→ Impairment of energetic metabolism (reduction of ATP production)
→ Paralysis leading to parasite death → expulsion



Comparative action of the main benzimidazoles

Caracteristics	Flubendazole	Albendazole	Triclabendazole
Bioavailability	Low intestinal absorption (5-10%)	Low intestinal absorption (5-10%)	Increases with fat-laden meal → Absorption > 80%
Biotransformation		Hepatic	Hepatic
Active compound outside digestive tract		Albendazole sulfoxyde	Triclabendazole sulfoxyde
Elimination half-life		8h30	11h
Elimination route	Feces (during 3 days)	Biliary (90%) → Feces	Biliary (90%) → Feces
Trade name	Fluvermal®	Zentel® Eskazole®	Egaten®

Spectrum of benzimidazoles activity in medicine

→ Extended to Cestodes (+/- Trematodes)
→ Adulticidal and/or larvicidal

Flubendazole

→ Intestinal nematode infections except strongyloidiasis (= anguillulosis)

Albendazole

→ Intestinal nematode infections: ascaridiosis, ancylostomiasis, pinworm infection, whipworm infection (*T. trichiura*), anguillulosis and trichinellosis

→ Larval cestode infections such as echinococcosis (*Echinococcus granulosus* and *E. multilocularis)*, cysticercosis (*Taenia solium*)
  → High dose and long duration treatment
→ Protozoan diseases: giardiasis and microsporidiosis (*Enterocytozoon bieneusi)*

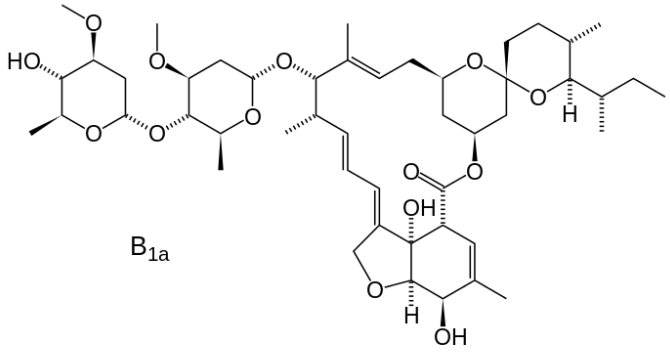
Triclabendazole

→ Distomatosis due to *Fasciola hepatica*

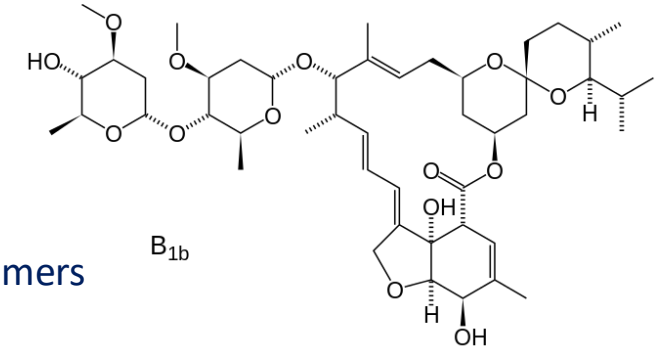
Avermectins

→ Chemical family: macrocyclic lactone

→ Isolated from *Streptomyces avermitilis* fermentation



B_{1a}



B_{1b}

→ Ivermectin

Semi-synthetic mixture of two isomers

→ Nobel Prize in Medicine and Physiology on 2015:

→ William Campbell (Irlande) and Satoshi Omura (Japan)

→ for their discovery of ivermectin, whose the derivatives have significantly reduced the prevalence of river blindness and those of lymphatic filariasis

The same year, the Chinese researcher, Youyou Tu, shared this Nobel Prize for her treatment of malaria with artemisinin

Mechanism of action of ivermectin

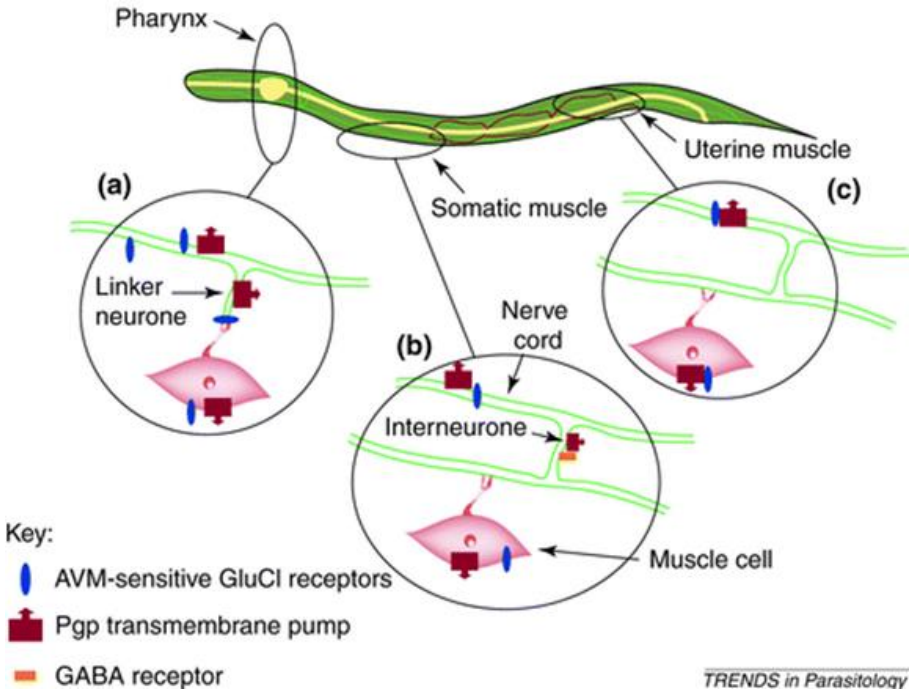
→ Parasite paralysis as the consequence of neurotransmission inhibition (GABA-mimetic effect)

→ Fixation with high affinity on calcium channels chloride-glutamate dependent of invertebrate nervous and muscular cells

→ Depolarization blockage through intake flux of Cl^-

→ Hyperpolarization of nervous and muscular cells

→ Neuromuscular paralysis of nematodes → Parasite death



Ivermectin characteristics

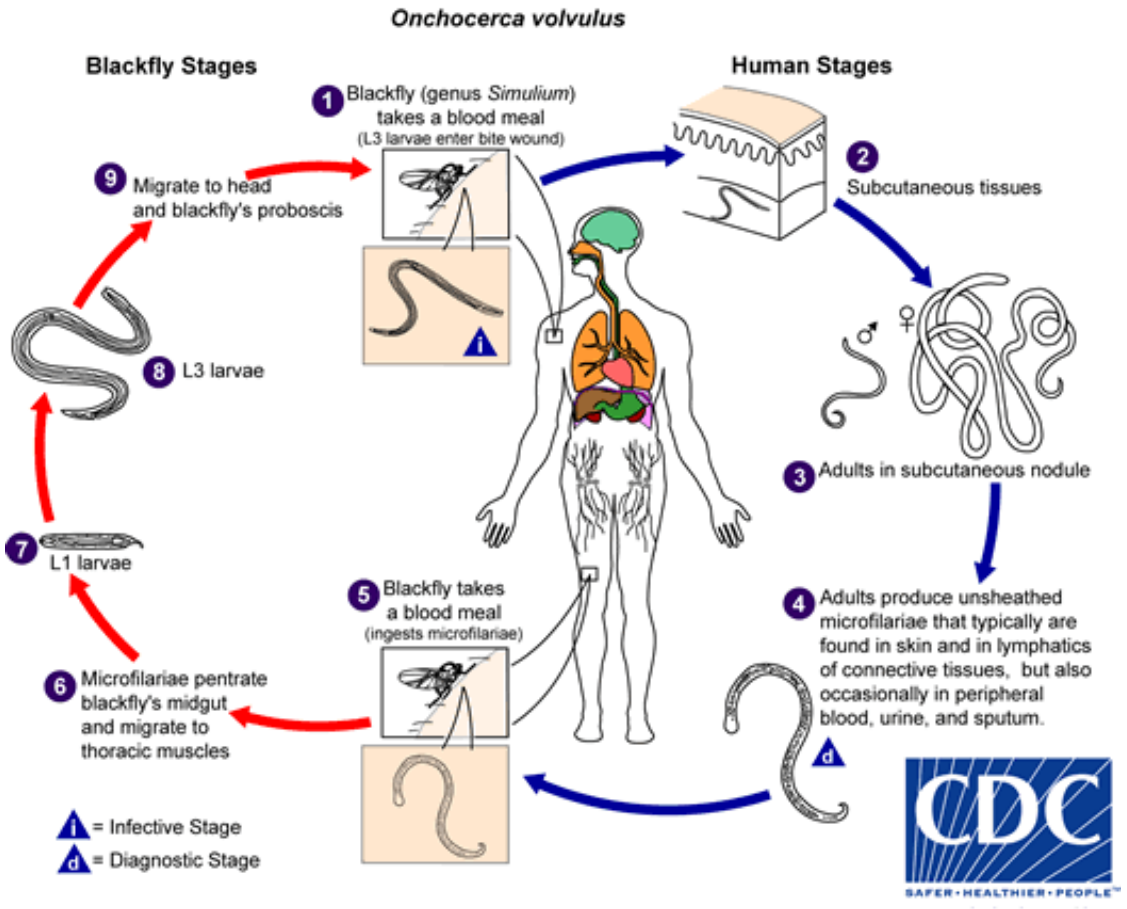
Characteristics	Data
Bioavailability	Administration on an empty stomach with 2 h-fasting before and after treament Good tissue distribution, even within the eye Low diffusion in cerebrospinal fluid
Plasma peak and half-life	4h/12h No brain barrier crossing
Biotransformation	Hepatic (Cyt P450)
Elimination	Feces (<1% eliminated in urine)
Secondary effects	Reaction to microfilariae lysis: prurit, skin rash, œdema…
Trade name	Stromectol® Mectizan® (OMS)

Spectrum of ivermectin activity

Nematode infections

Onchocerciasis = River blindness (*Onchocerca volvulus*)

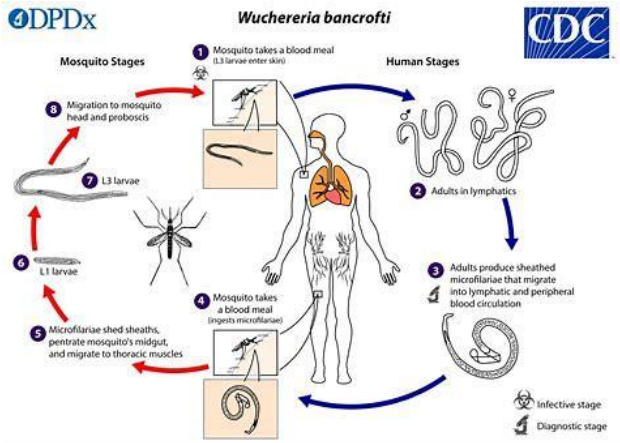
Mectizan®
→ Larvicidal on *Onchocerca volvulus* microfilariae living in sub-cutaneous tissue
→ No adulticidal activity
→ Progressive paralysis
Intense infammatory reactions occuring when parasites suddenly die



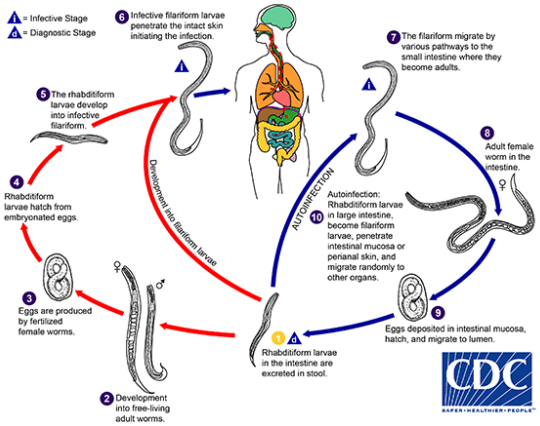
Adult worms can continue producing microfilariae
→ Ivermectin treament should be given once a year for as long as there is evidence of continued infection in order to stop transmission

Spectrum of ivermectin activity

Bancroftian filariasis (*Wuchereria bancrofti*)
(Mectizan®)



Anguillulosis = strongyloidosis
(Stromectol®)



Ectoparasitic disease

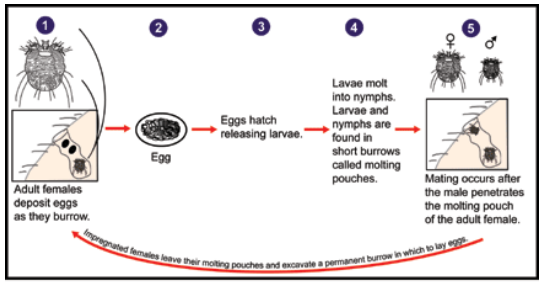
→ Sarcoptic mange (*Sarcoptes scabiei)*

→ Provoked by a mite (and not an helminth)

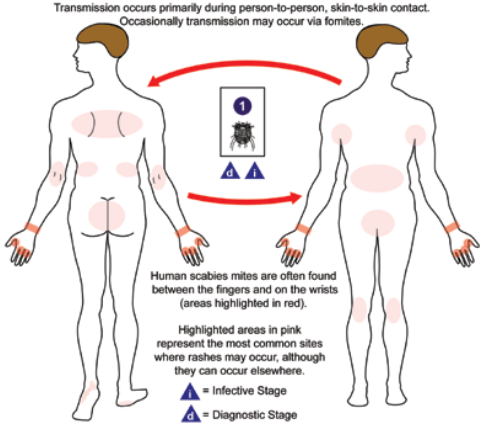
→ If high parasite burden

→ 2nd treatment dose and/or association with a topical treatment

→ necessary within the 8 to 15 days in order to get healing

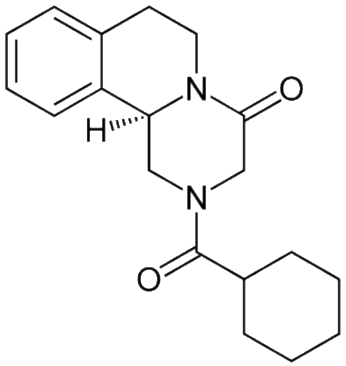


Transmission occurs primarily during person-to-person, skin-to-skin contact. Occasionally transmission may occur via fomites.



Pyrazino-isoquinoline

Praziquantel



Mechanism of action

Praziquantel antagonizes voltage-gated calcium channels

→ Increase of tegument/muscles membrane permeability to Ca^{2+}

→ Muscle tetany and paralysis

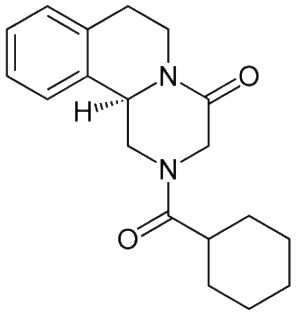
→ Vacuolization of teguments

→ Greater impact on adult worms than on immature forms

ADME characteristics of praziquantel

Characteristics	Data
Bioavailability	Good digestive absorption
Plasma peak	0.8 to 1.5 h (4 to 5 h for metabolites)
Biotransformation	Hepatic (Cyt P450) → hydroxylated metabolites with first pass effect → Inter-individual variations of plasma concentrations
Elimination	Renal for 80% praziquantel (>70% of the dose under metabolite forms within 24h)
Trade name	Biltricide®

Spectrum of praziquantel activity



Action against all the parasite stages (adults and larvae):

Trematode diseases

→ Schistosomiases provoked by *Schistosoma haematobium, S. mansoni, S. intercalatum, S. japonicum*

→ Distomatoses provoked by *Clonorchis sinensis, Opistorchis viverrini, Paragonimus westermani*

Cestode diseases

→ Hydatid cyst provoked by the tapeworm: *Echinococcus granulosus*

→ Alveolar echinococcosis provoked by the tapeworm *Echinococcus multilocularis*

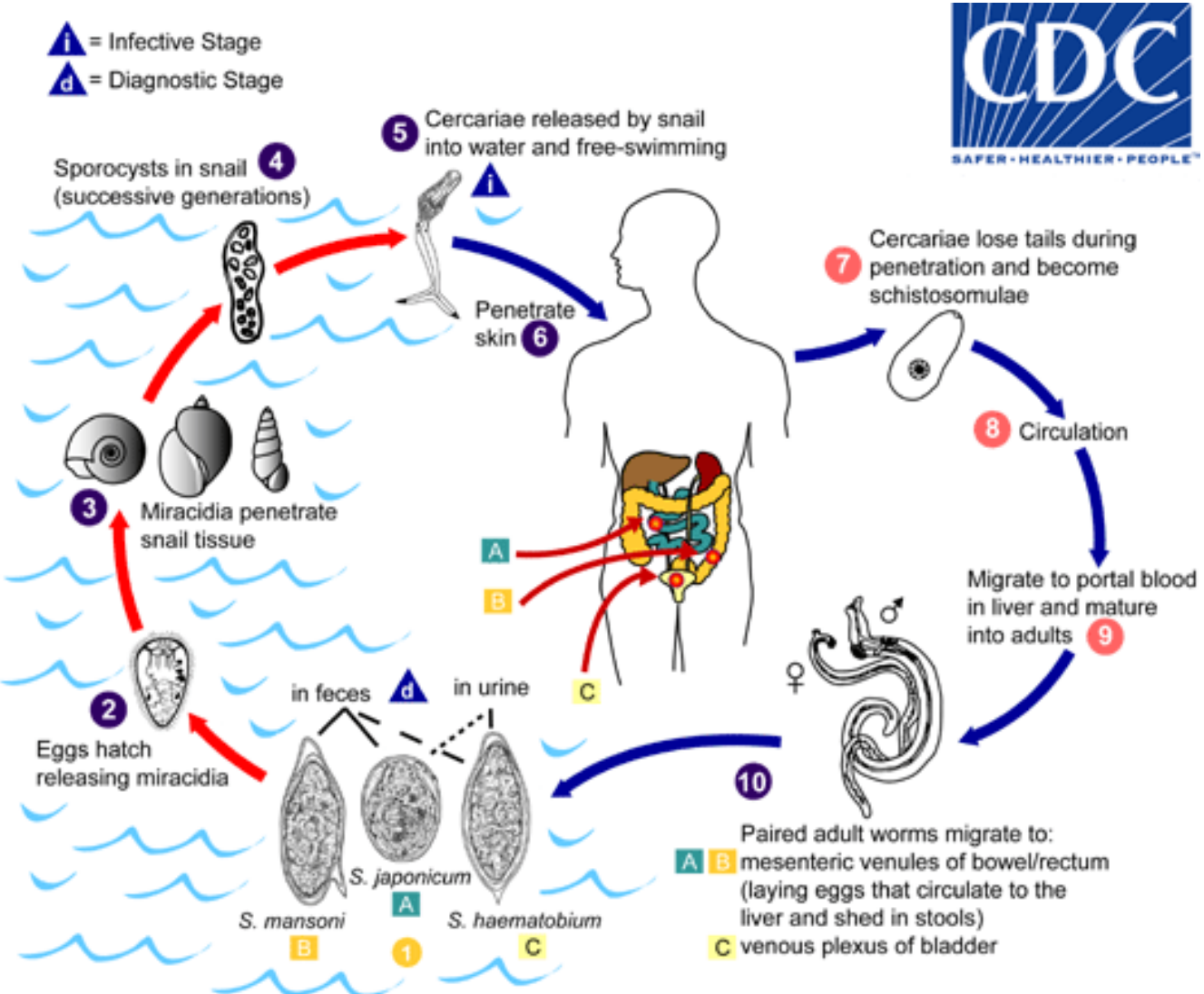
→ Cysticercosis provoked by *Taenia solium*

→ Diphyllobothriasis caused by *Diphyllobothrium latum*

No action against nematodes

Spectrum of praziquantel activity

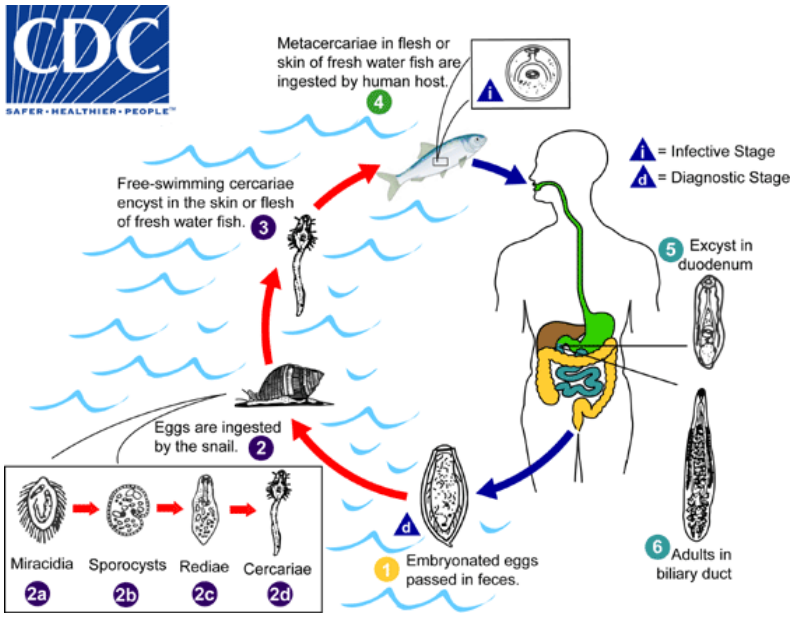
→ Schistosomiases caused by *Schistosoma haematobium, S. mansoni, S. intercalatum, S. japonicum*



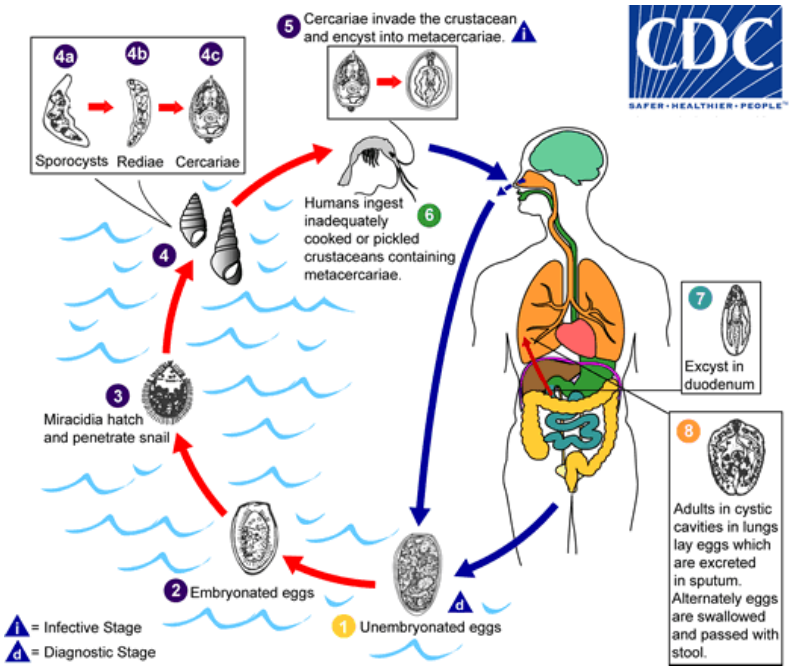
Spectrum of praziquantel activity

→ Distomes

Clonorchis sinensis, Opistorchis viverrini,



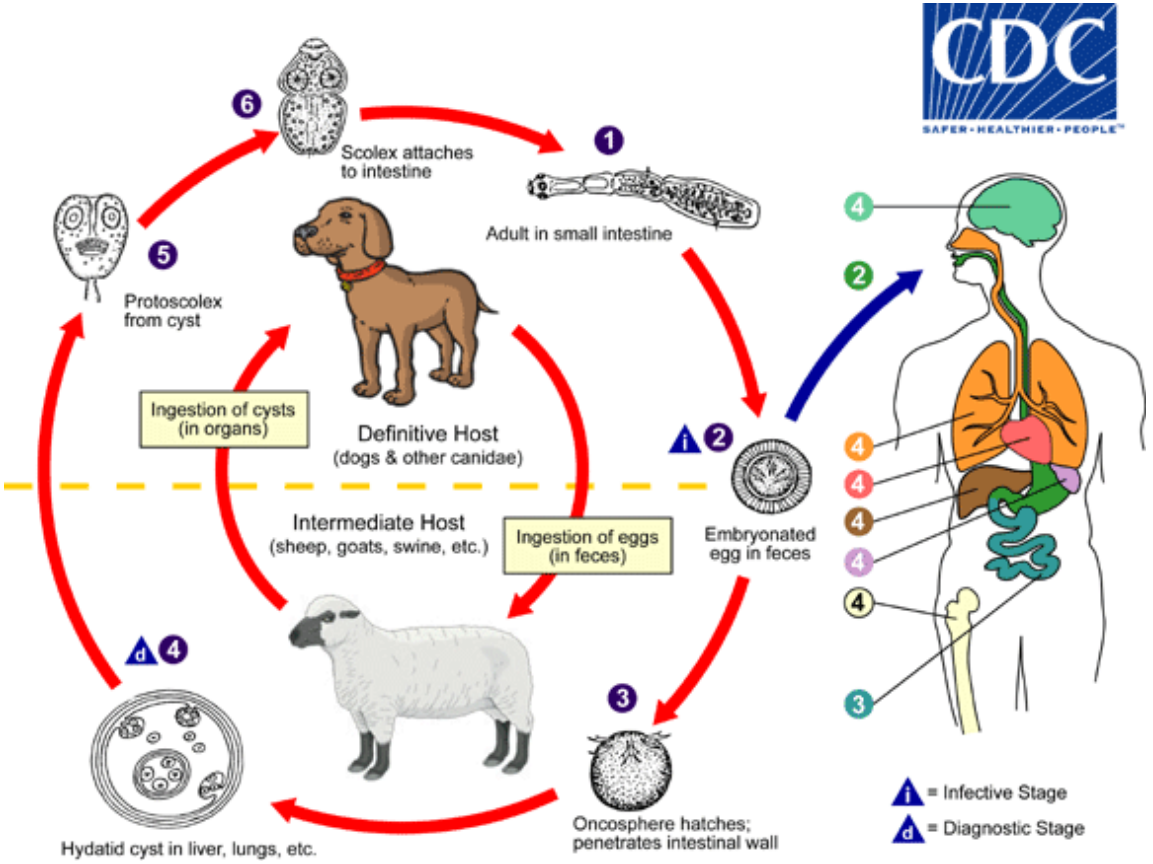
Paragonimus westermani



Spectrum of praziquantel activity

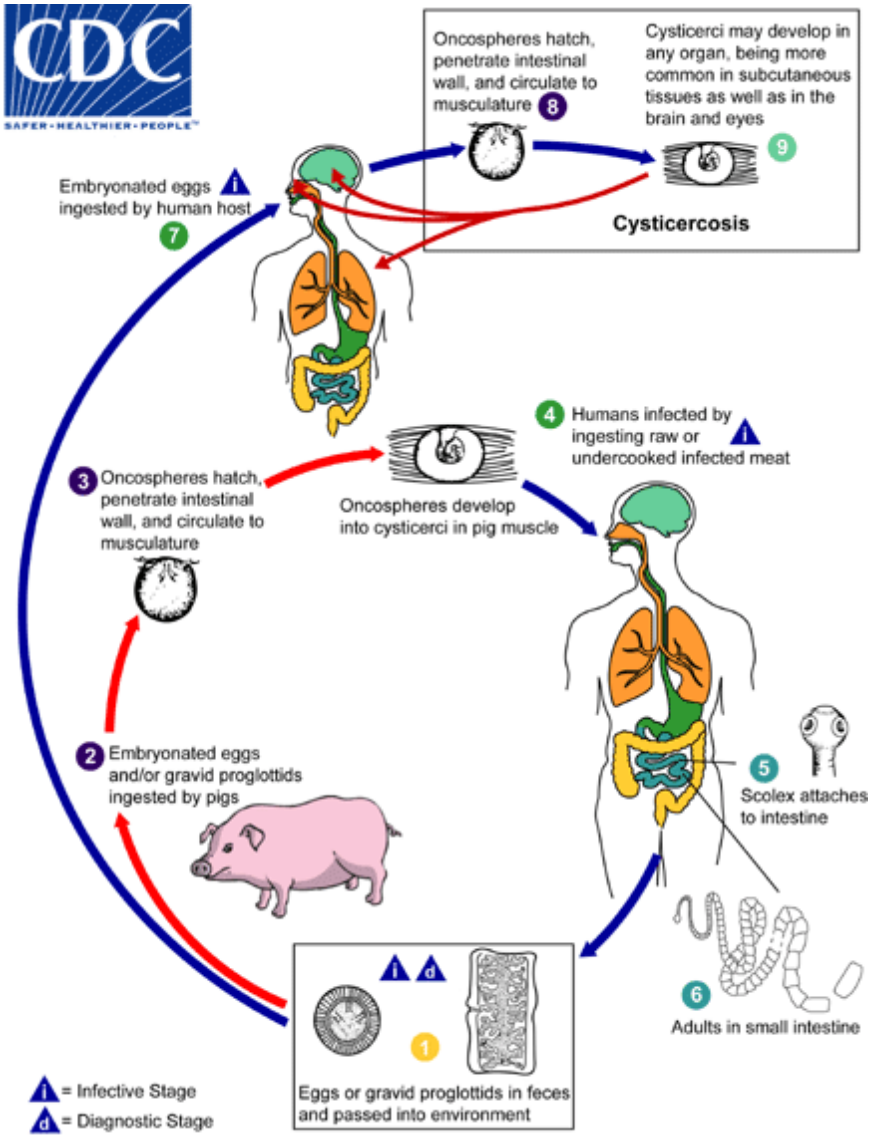
→ Hydatid tapeworm
(*Echinococcus granulosus*)

→ Alveolar hydatid tapeworm
(*Echinococcus multilocularis*)



Spectrum of praziquantel activity

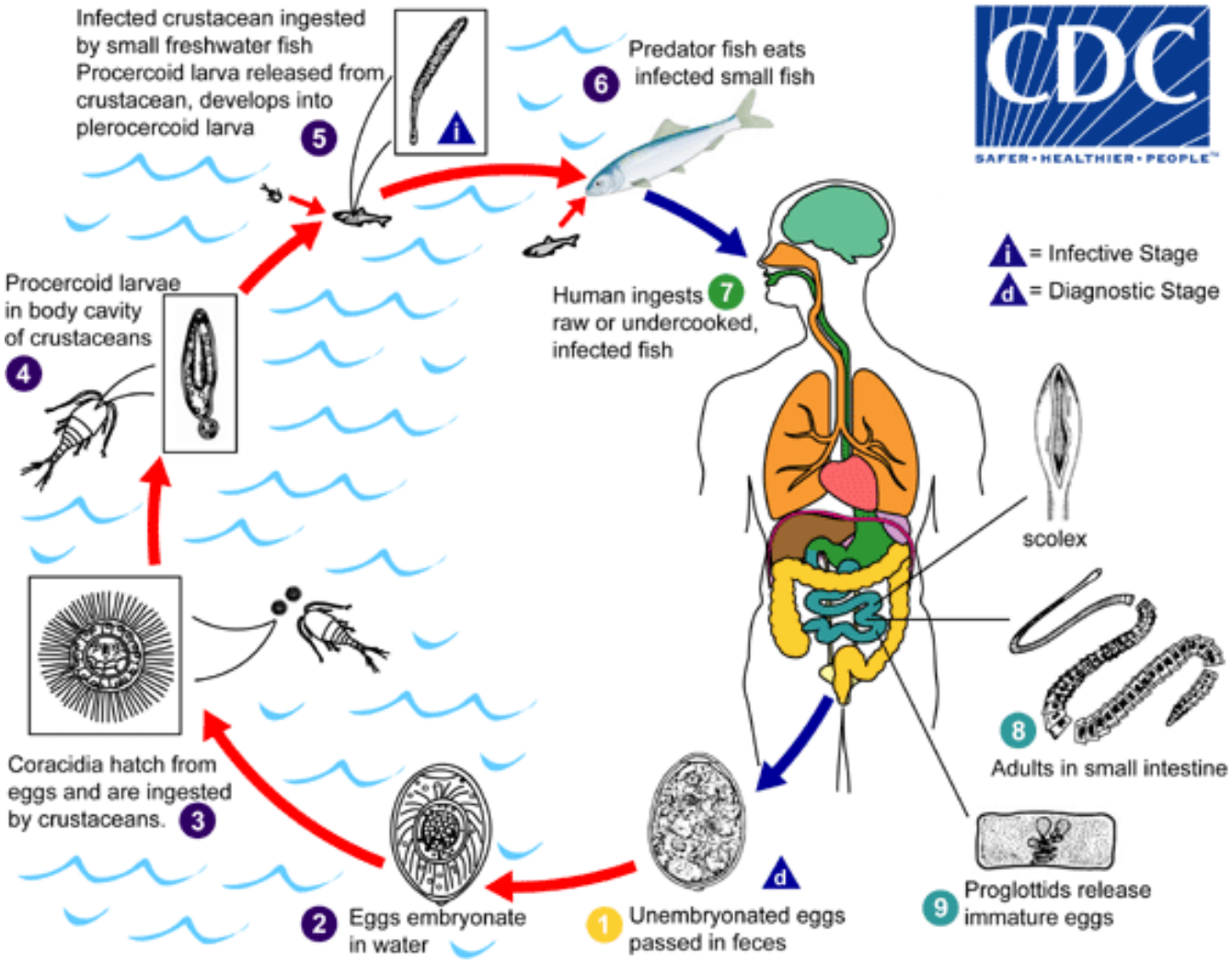
→ Cysticercosis
(*Taenia solium*)



Spectrum of praziquantel activity

→ Diphyllobothriasis

(*Diphyllobothrium latum)*



Conclusion

→ Few human vaccines against parasites

→ Antiparasite chemotherapy
  → Necessary despite
    → Problems of toxicity
    → Problems of drug resistance
      → Protozoa → ++
      → Helminths → +/-

→ Need of:
  → Identification of new therapeutic targets
    → New drugs
  → Drug targeting approaches
    → Reducing toxicity

  → Drug combination
    → Reducing toxicity
    → Reducing drug resistance