

# Overview on drug discovery for tropical diseases

Field et al. *Nature Reviews*, 2017; Rycker et al. *Nature*, 2018

# Tropical Diseases

WHO Definition-

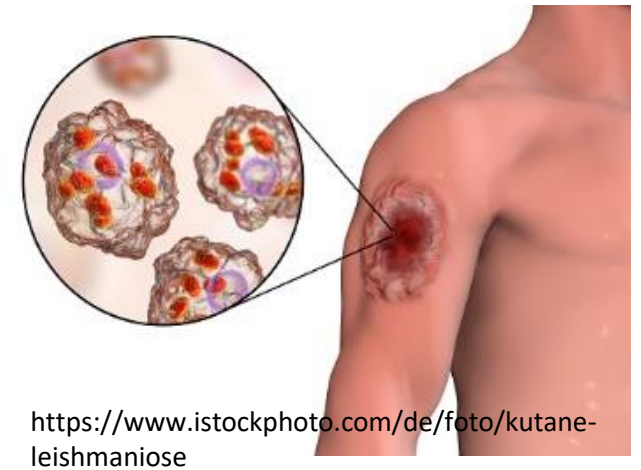
- Diseases that **occur** principally in the **tropics**
- Infectious **diseases** that **thrive in hot, humid** conditions



**Malaria**



**Human African Trypanosomiasis (HAT)**



**Leishmaniasis**

**Figure 1. Examples of tropical diseases**

# Consequence of tropical diseases

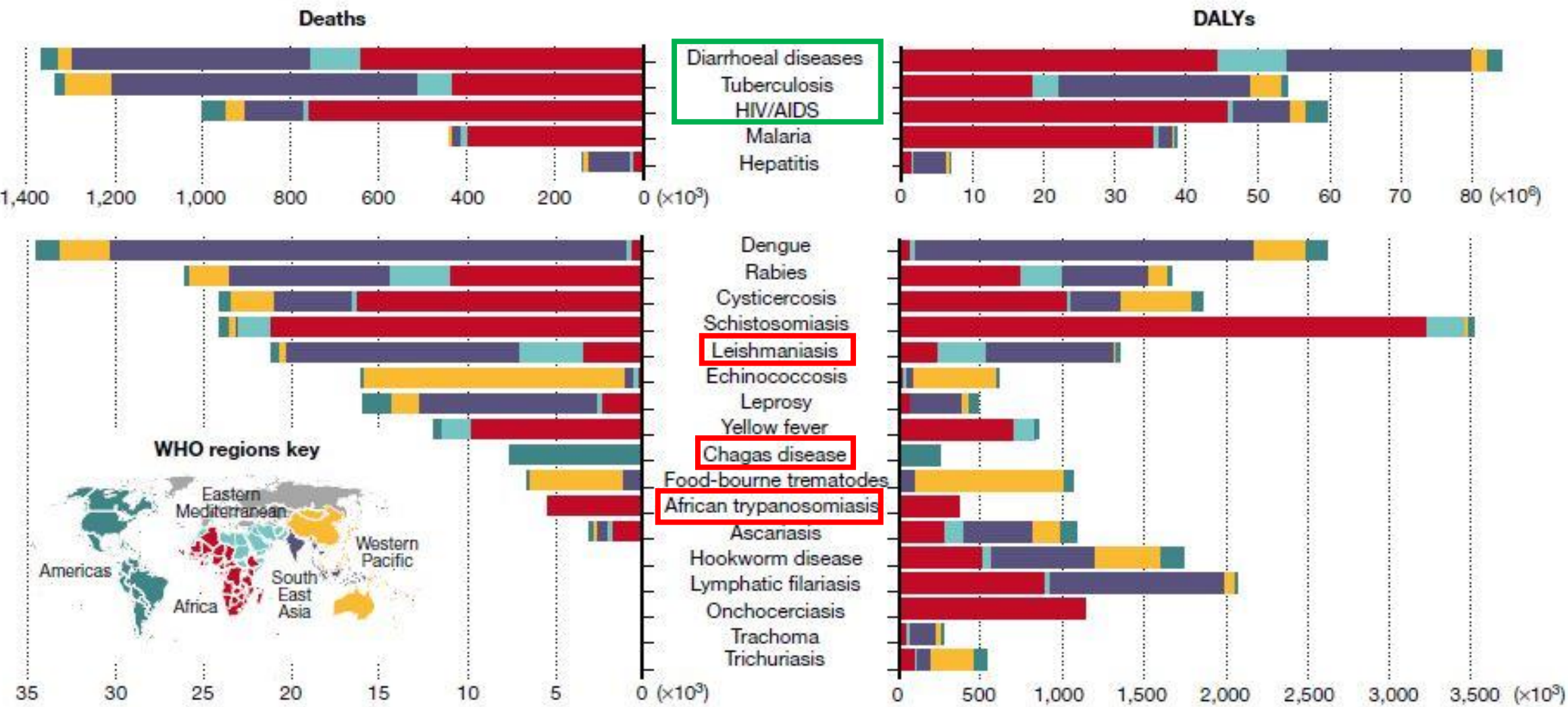


Figure 2. Deaths and disability-adjusted life years (DALYS) due to tropical diseases (Rycker et al. *Nature*, 2018).

# Why?



**Unsatisfactory**



**Few or no  
treatment**



**Lack of efficacious  
treatments**



**High cost  
treatment**



**No efficient  
vaccine**



**Very few new  
drugs**

# Vector mediated transmission of trypanosomatids

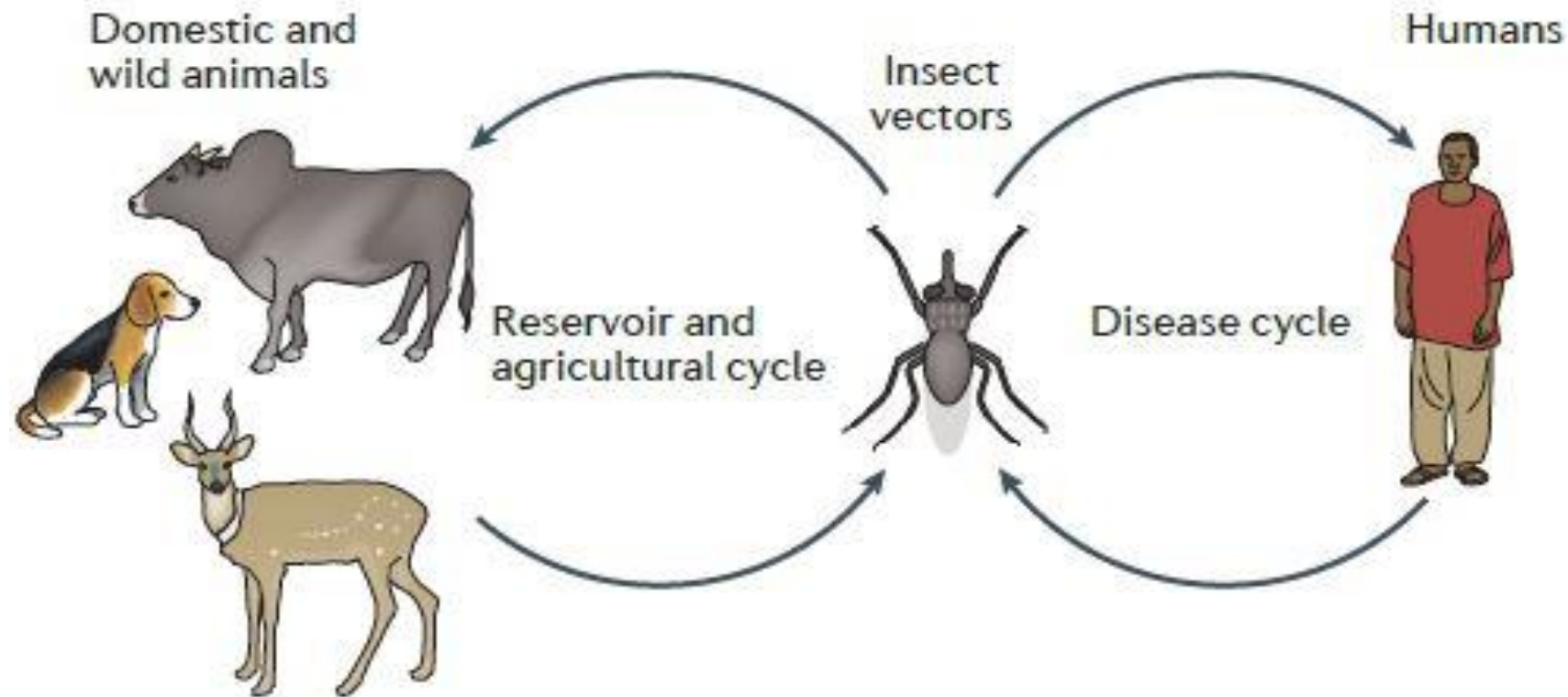
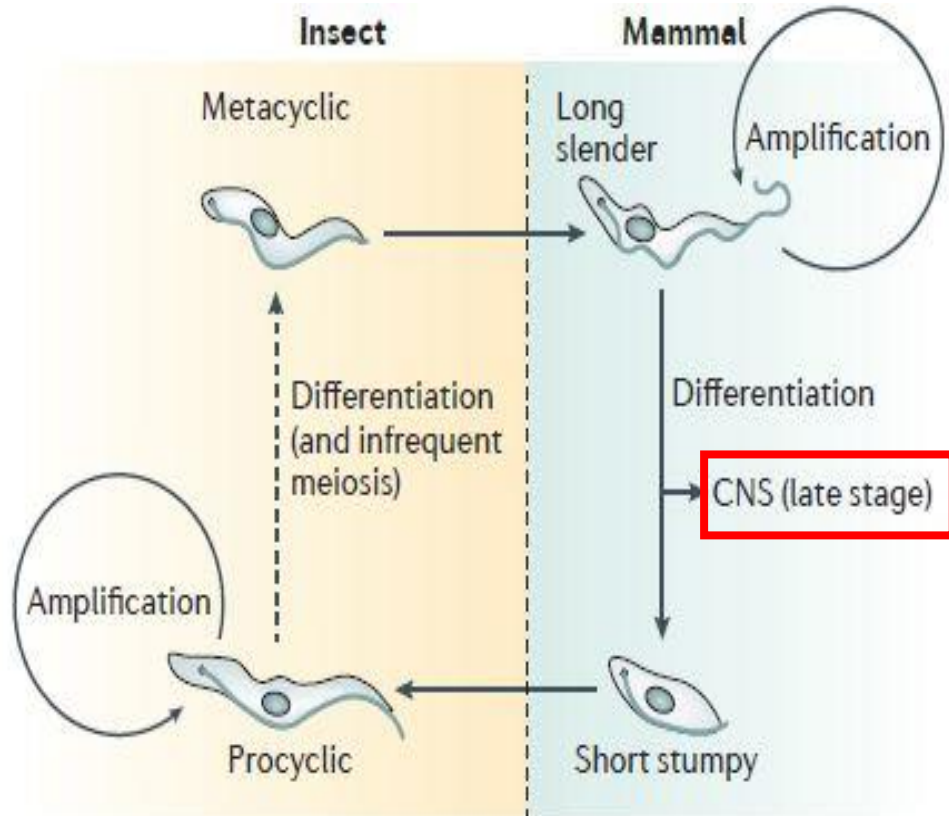


Figure 3. Vector mediated transmission of trypanosomatids (Field et al. *Nature Reviews*, 2017)

# Life cycle of trypanosomatids

## *Trypanosoma brucei*



## *Leishmania* spp.

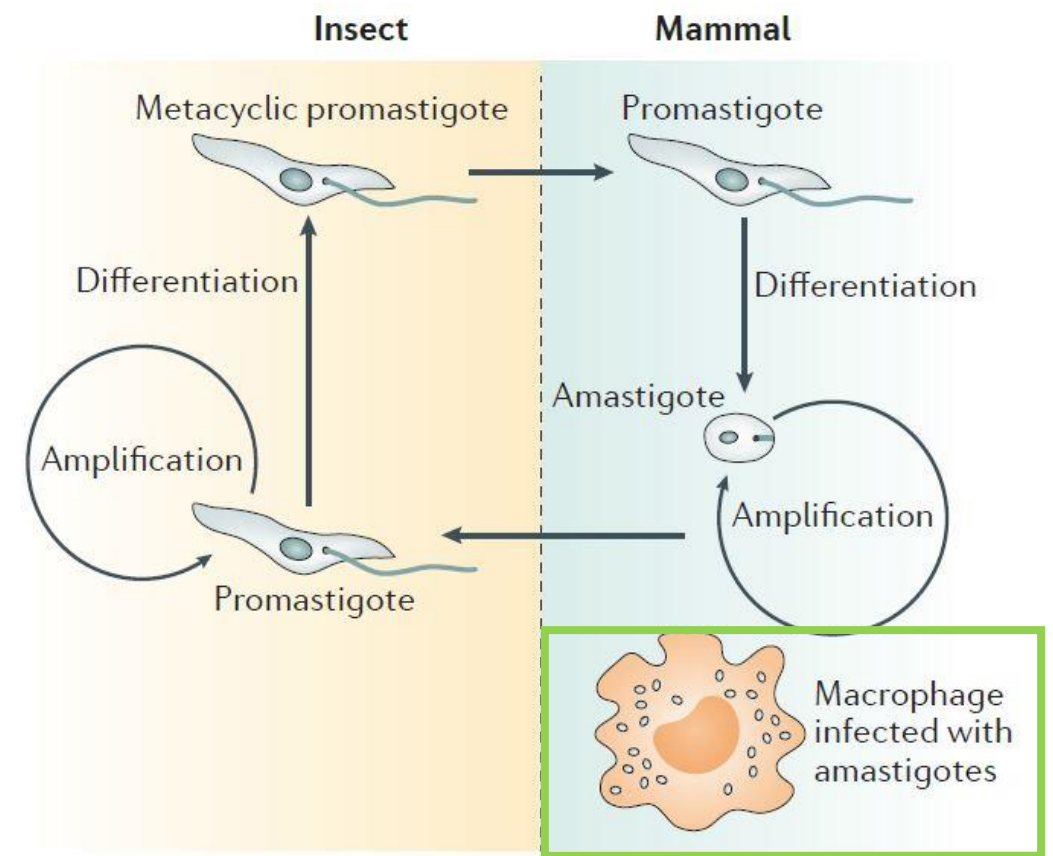
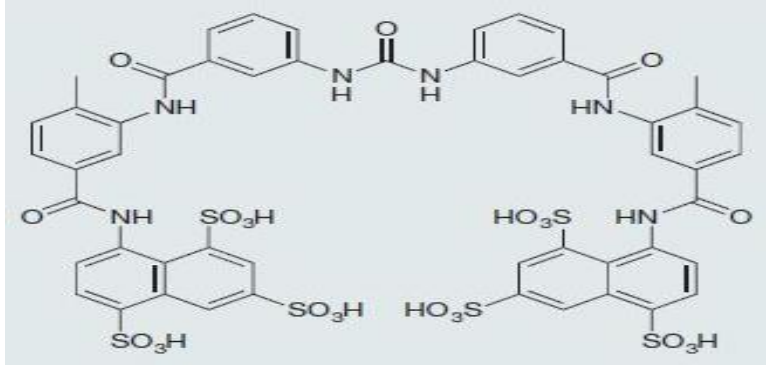


Figure 4. Life cycle of *Trypanosoma brucei* and *Leishmania* spp. (Field et al. *Nature Reviews*, 2017)

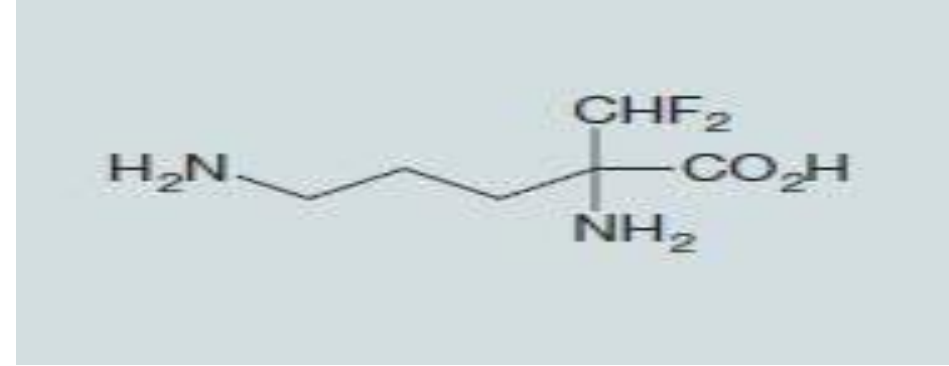
# Current drugs for trypanosomatid diseases

## Human African trypanosomiasis



**Suramin**

- Only suitable for first stage infection *T. brucei*
- Associated with toxicity
- Given intravenously

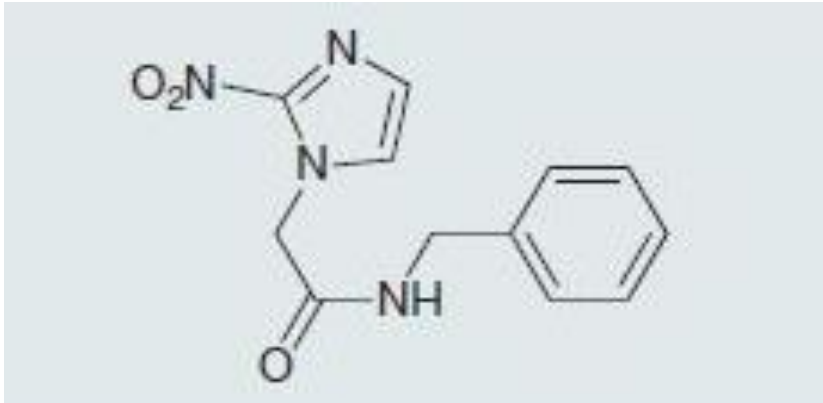


**Eflorenithine**

- Suitable for second stage infection
- High cost
- Given by slow intravenous infusion
- Septicaemia is the major adverse effect
- Not effective against *T. b. rhodesiense*

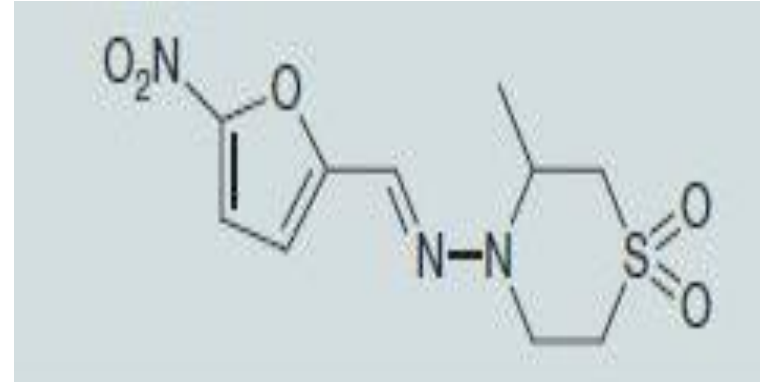
# Current drugs for trypanosomatid diseases

## Chagas Disease



**Benznidazole**

- Effective against acute form
- Problem with tolerability and compliance
- No effect after heart failure in Chronic condition

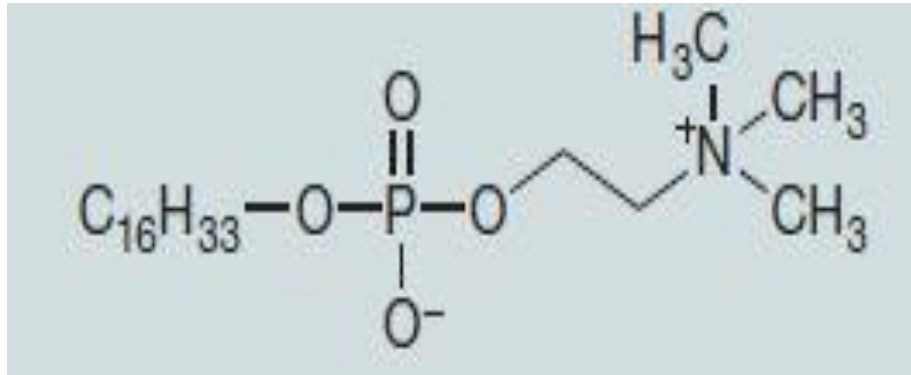


**Nifurtimox**

- Effective against acute form
- Problem with tolerability and compliance

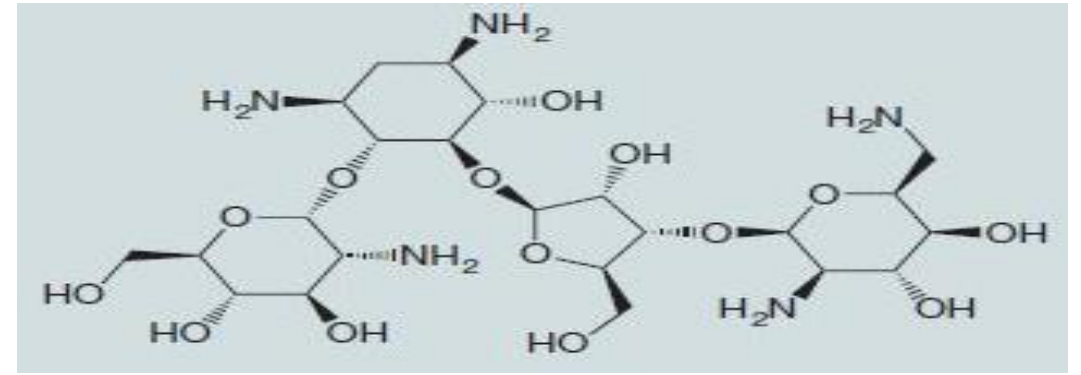
# Current drugs for trypanosomatid diseases

## Visceral leishmaniasis



**Miltefosine**

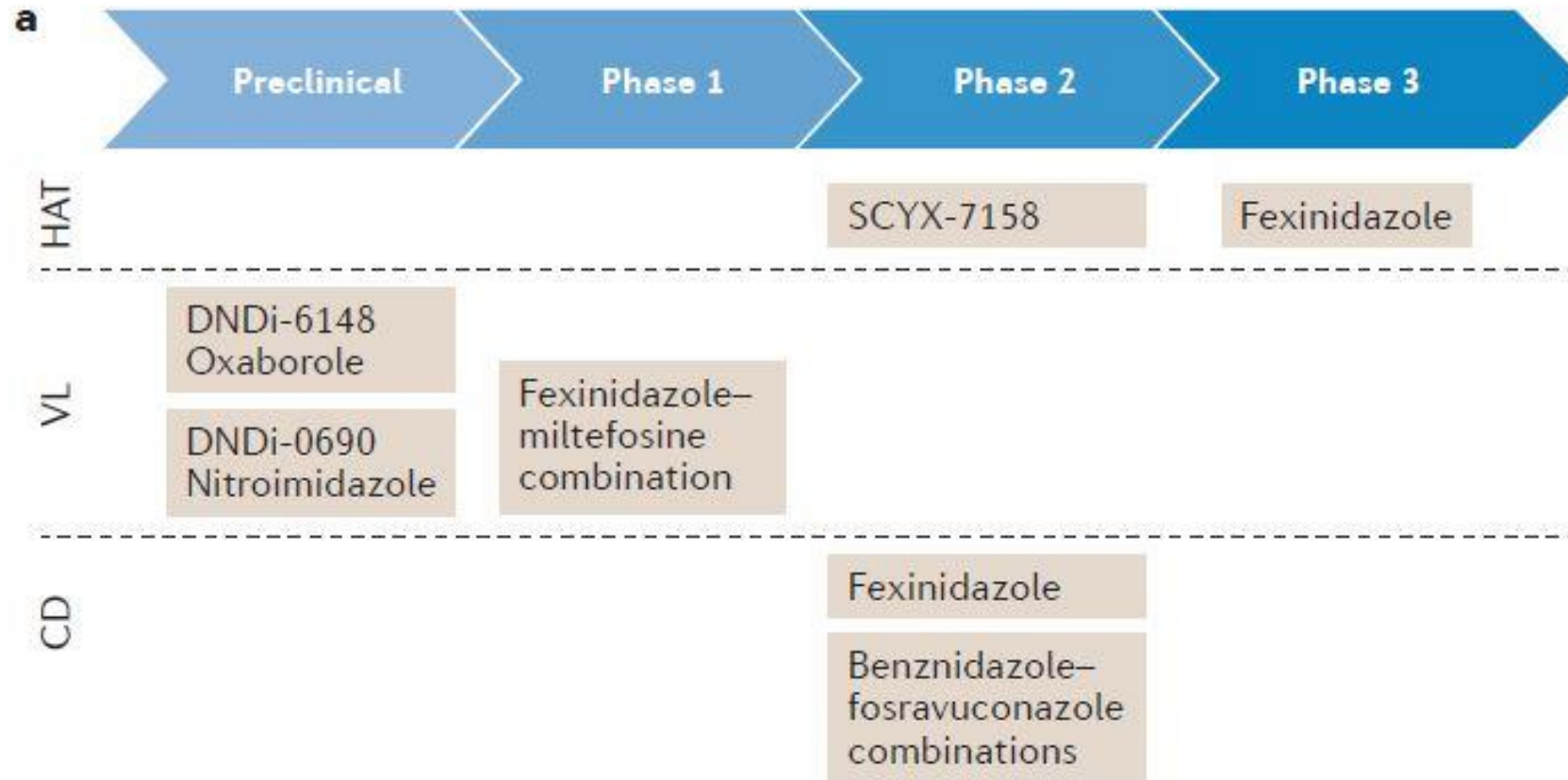
- Only oral treatment
- Teratogenic
- Reports on treatment failures



**Paromomycin**

- Very toxic
- Effective in India but less in East Africa
- Given Intravenously
- 21-day treatment
- Ototoxicity

# Drugs in the pipeline



**HAT:** Human African Trypanosomiasis  
**VL:** Visceral leishmaniasis  
**CD:** Chagas disease

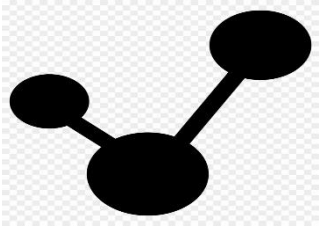
Figure 5. Current drugs in the pipeline (Field et al. *Nature Reviews*, 2017)



# Drug discovery

- Disease or clinical **condition without** suitable **medical products** available
- Research in **academia** generates **data**
- Develop a **hypothesis of therapeutic effect**
- **Complex** process
- Takes **12–15** years
- **Cost** in excess of **\$1 billion**

# Target Deconvolution



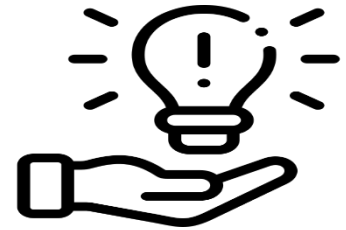
**Molecular targets  
identification**



**Essential for  
target based  
screening**

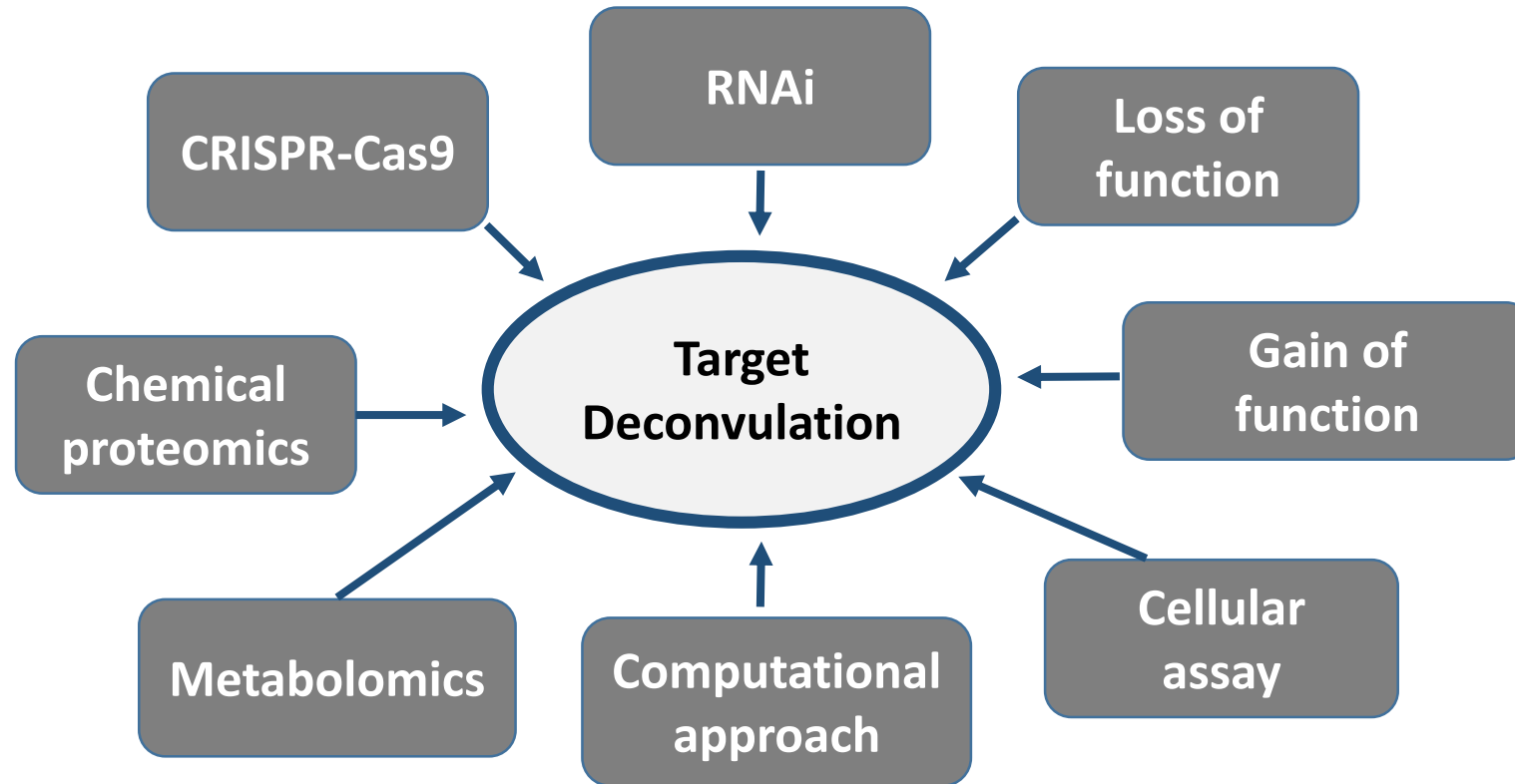


**Overcoming  
pharmacokinetic  
issues, insufficient  
potency or off-  
target toxicity**



**Examples: Malaria,  
Trypanosomatid  
Proteosome**

# Target Deconvolution: Approaches



# Molecular targets in trypanosomatids

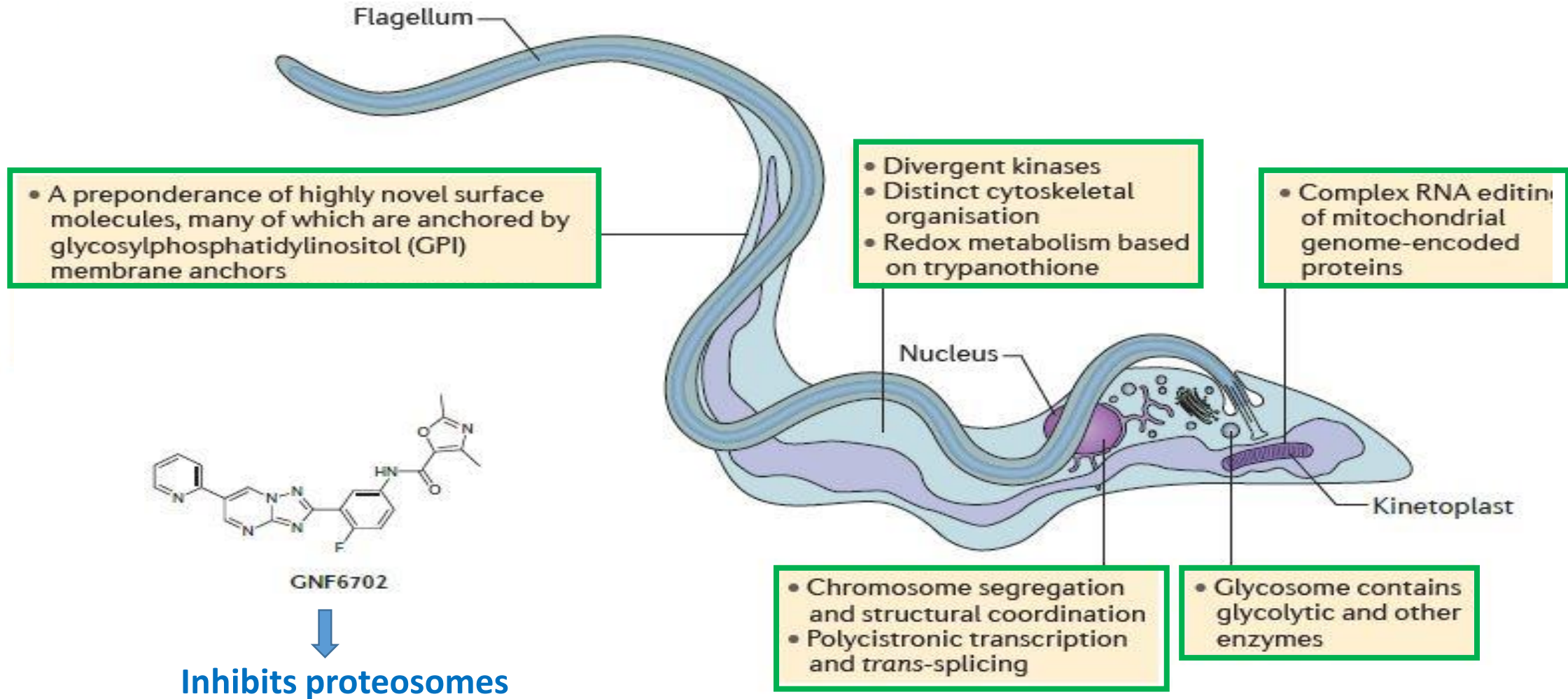


Figure 6. Possible molecular targets in trypanosomatids (Field et al. *Nature Reviews*, 2017)

# Validated molecular targets in *Trypanosoma*

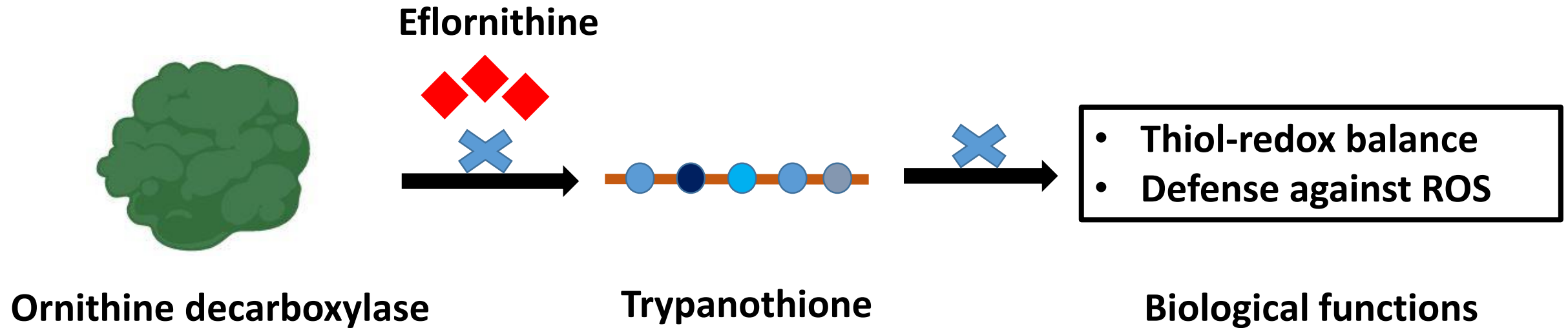


Figure 7. Role of ornithine decarboxylase in *Trypanosoma*

# cAMP independent PKA in *Trypanosoma*

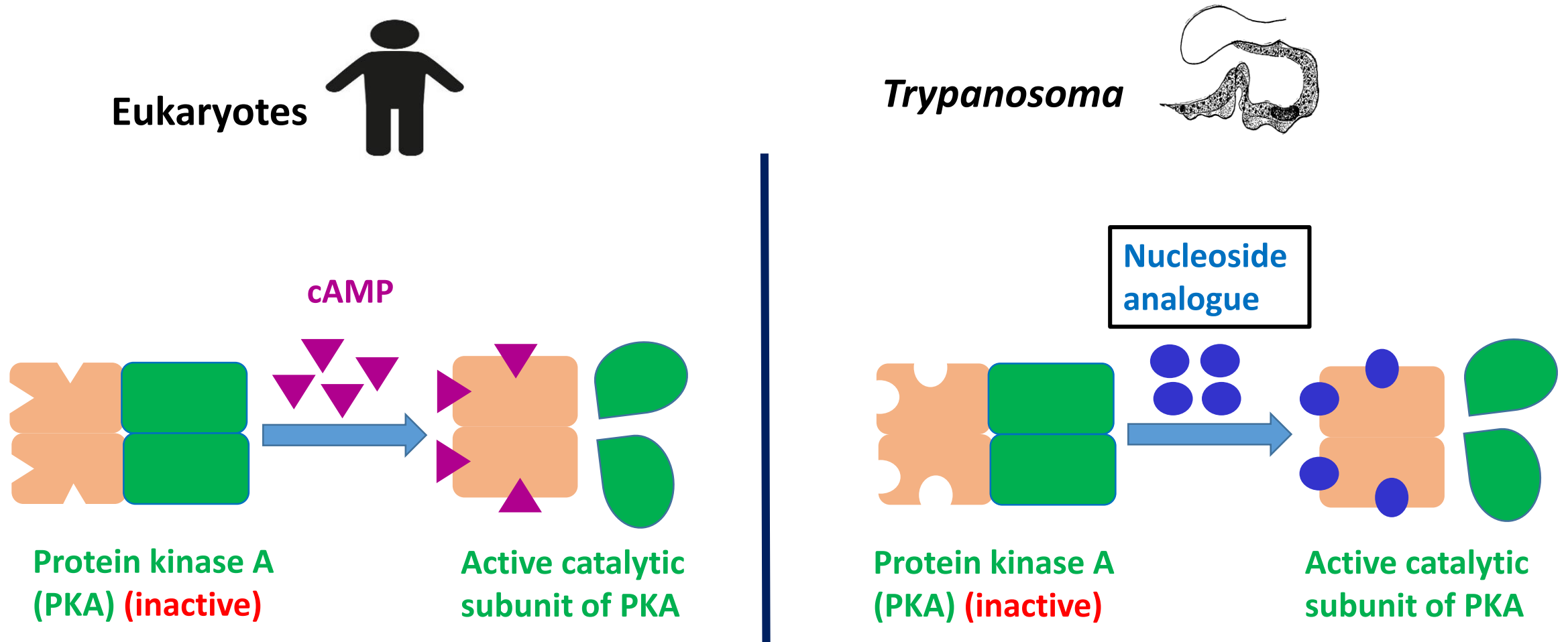
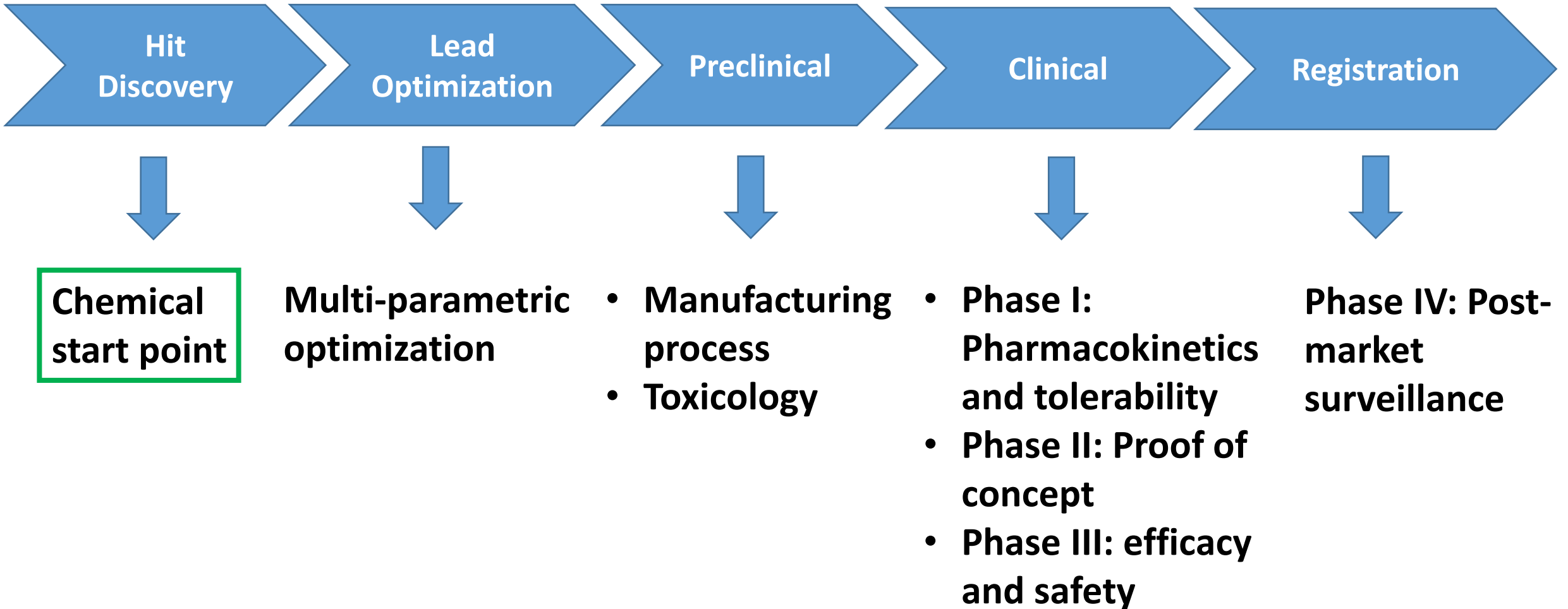
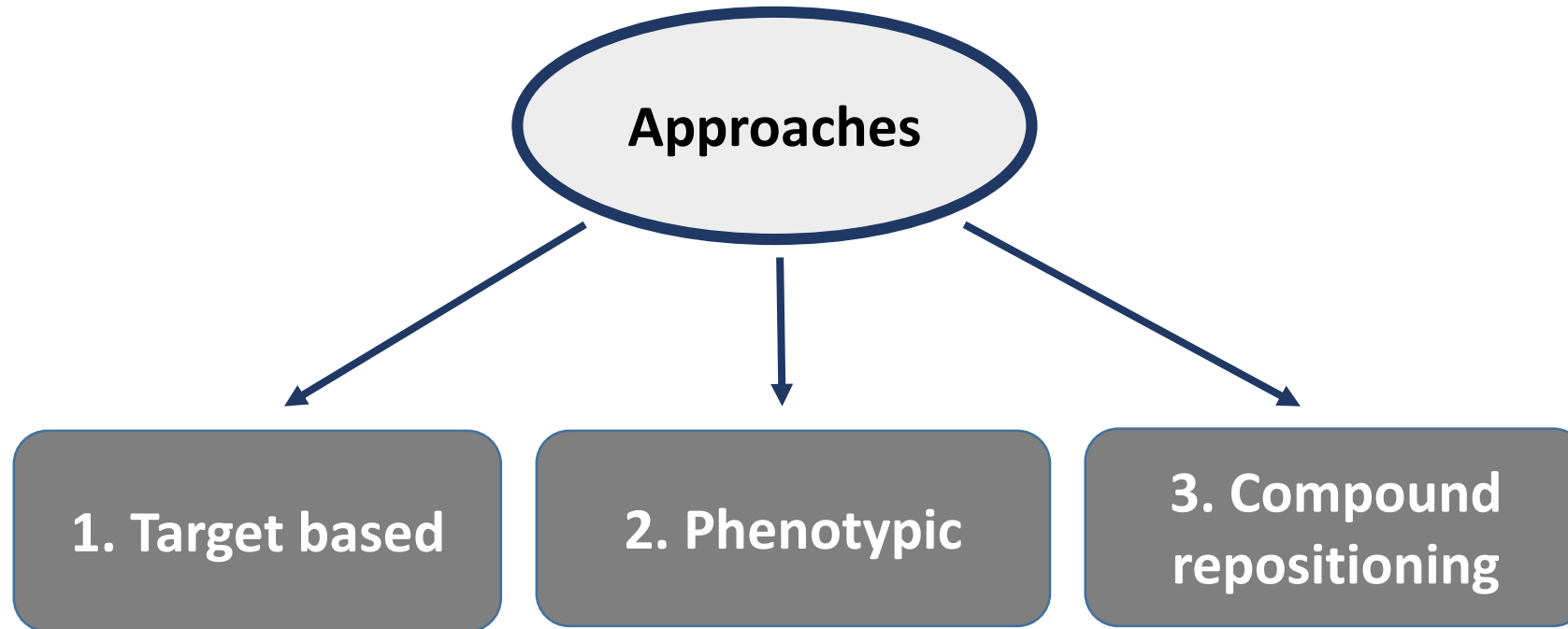


Figure 8. Different ligand dependent activation of PKA in eukaryotes and *Trypanosoma* (Sabine et al. *Nature Communications*, 2019)

# Process of drug discovery



# Approaches used for Drug discovery





# 1. Target based approach

- **Selection** of the most promising **molecular targets**
- **Screening** for **inhibitors** against a **purified protein**
- **Optimized** to show **efficacy** in a **cellular model**

## Cons

- Very **limited success** (no drugs for trypanosomatids)
- **Different behavior** in **Animal disease model**

## 2. Phenotypic approaches

- **Screening** for growth **inhibitors** directly against an **intact parasite**
- **Widely used** for neglected **tropical** disease

### Success

- New developable series
- Examples:
  1. HAT- fexinidazole
  2. Oxaborole SCYX-7158

### Challenges

- **Specificity** to **laboratory strains**
- Interpretation of **compound potency**

# 3. Compound reposition approach

‘the most fruitful basis for the discovery of a new drug is to start with an old drug’-Sir James Black

- **Repurposing** or repositioning drugs
- Many drugs **currently used** are **repositioned** drugs (anticancer, antibacterial, antifungal and anti-helminthic)
- **Examples:** For Visceral leishmaniasis
  1. Amphotericin B (antifungal)
  2. Miltefosine (anticancer)
  3. Paromomycin (antibiotic)

### 3. Compound reposition: Drawbacks

- **Optimized** for a **different** human disease
- Initial **therapeutic activity** may has **undesirable side effect**
- Does **not fit the TPP** for neglected diseases
- High cost
- **Lack** of oral **bioavailability**

# Target product profiles (TPP)

- **Physiochemical properties**
- **Route of administration**
- **Dosing**
- **Course of treatment**
- **Safety**
- **Tolerability**
- **Cost and shelf-life**

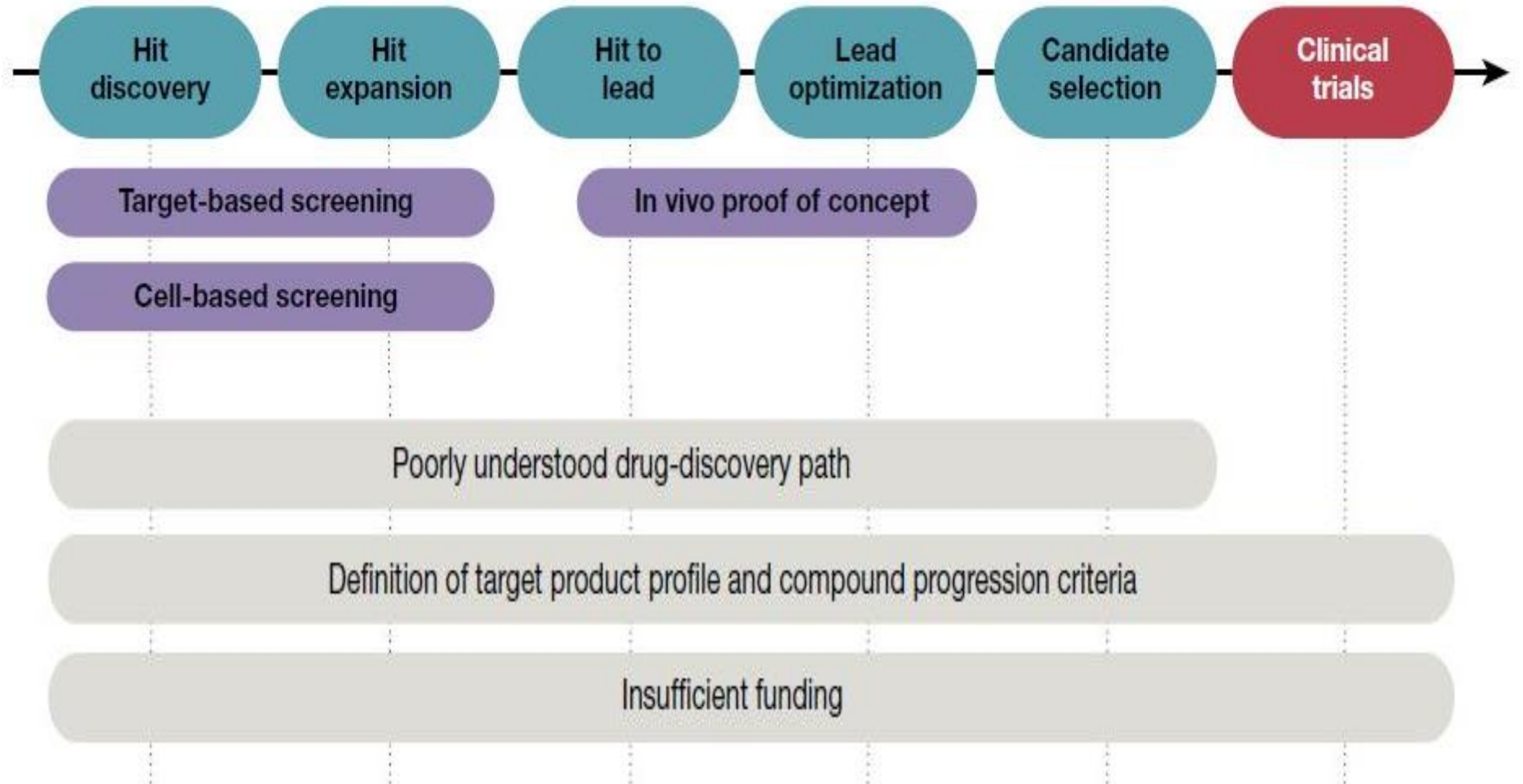


# Drug Discovery: Overall Challenges

- **Hit discovery:** Chemical point identification
- **Biological Challenges:** Well validated targets
- **Quiescence and dormancy:** Reduced metabolism, less susceptible to drug
- **Chemistry:** Physiological properties
- **Pathogen localization:** Intra or extracellular, Blood brain barrier
- **Resistance:** Poor management of treatment, combination therapy

# Summary

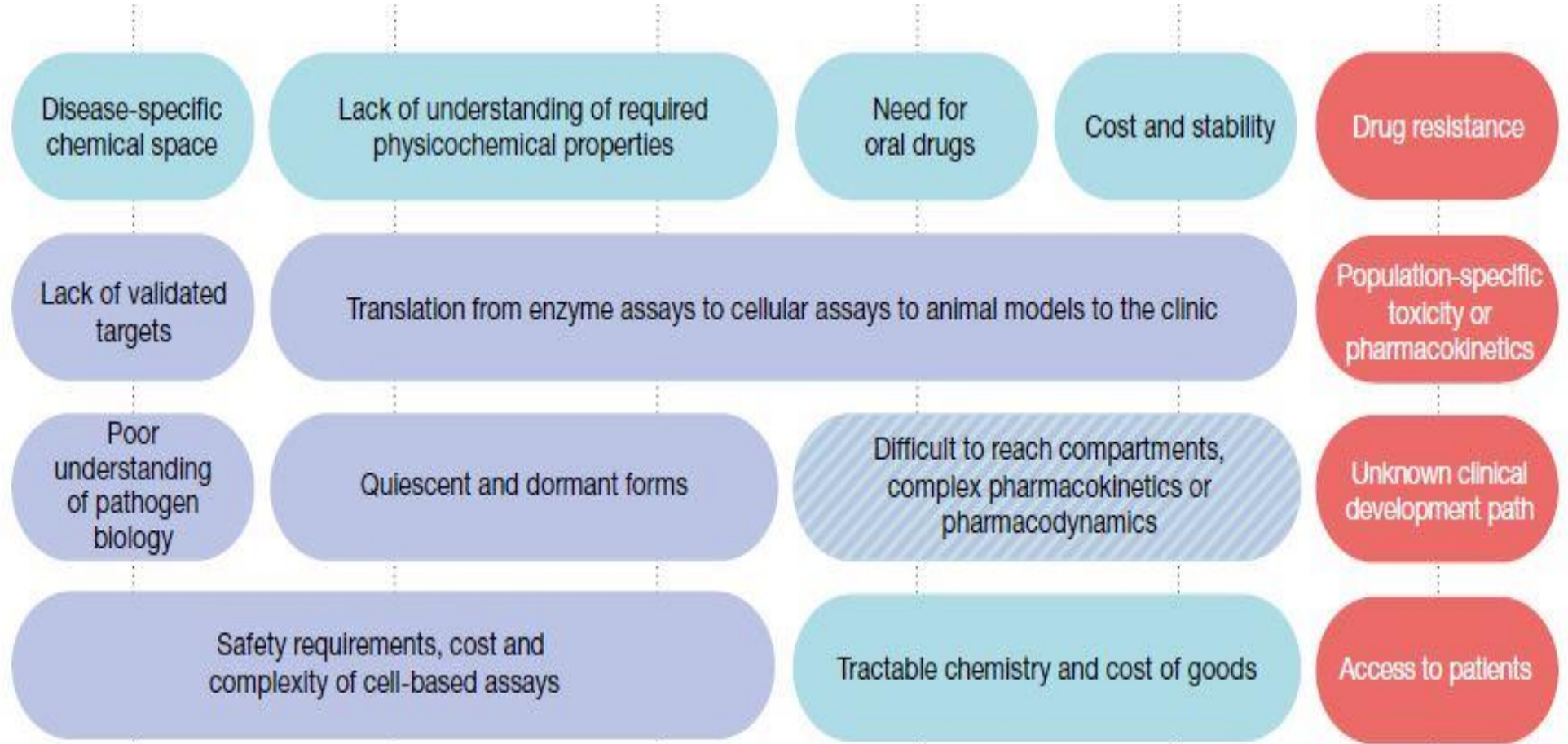
## Drug discovery pipeline



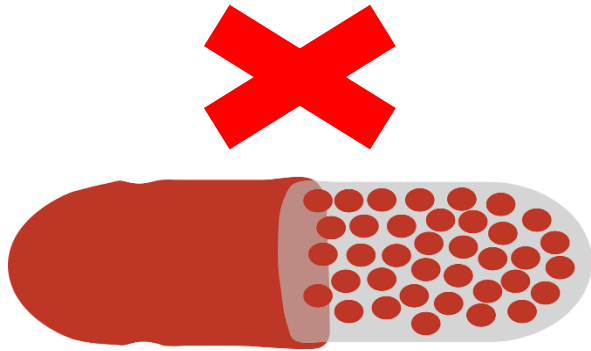
## Generic Issues

# Summary

## Challenges



# Take home message



**Available drugs are not satisfactory**



**Suitable new drugs for the rural systems**

*THANK YOU*