20.109 Module 2

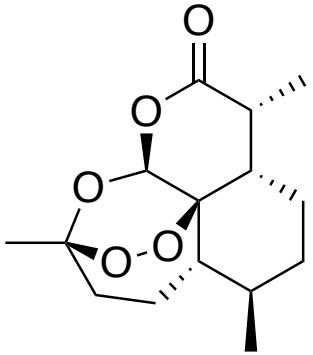
Lecture #2: **Therapeutic target selection**

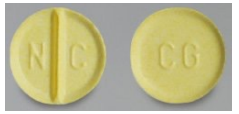
Instructor: Prof. Jacquin C. Niles

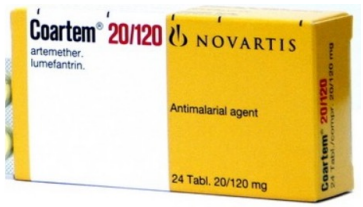
Department of Biological Engineering

Email: jcniles@mit.edu

19 October 2023







Drug discovery framework

Pre-clinical

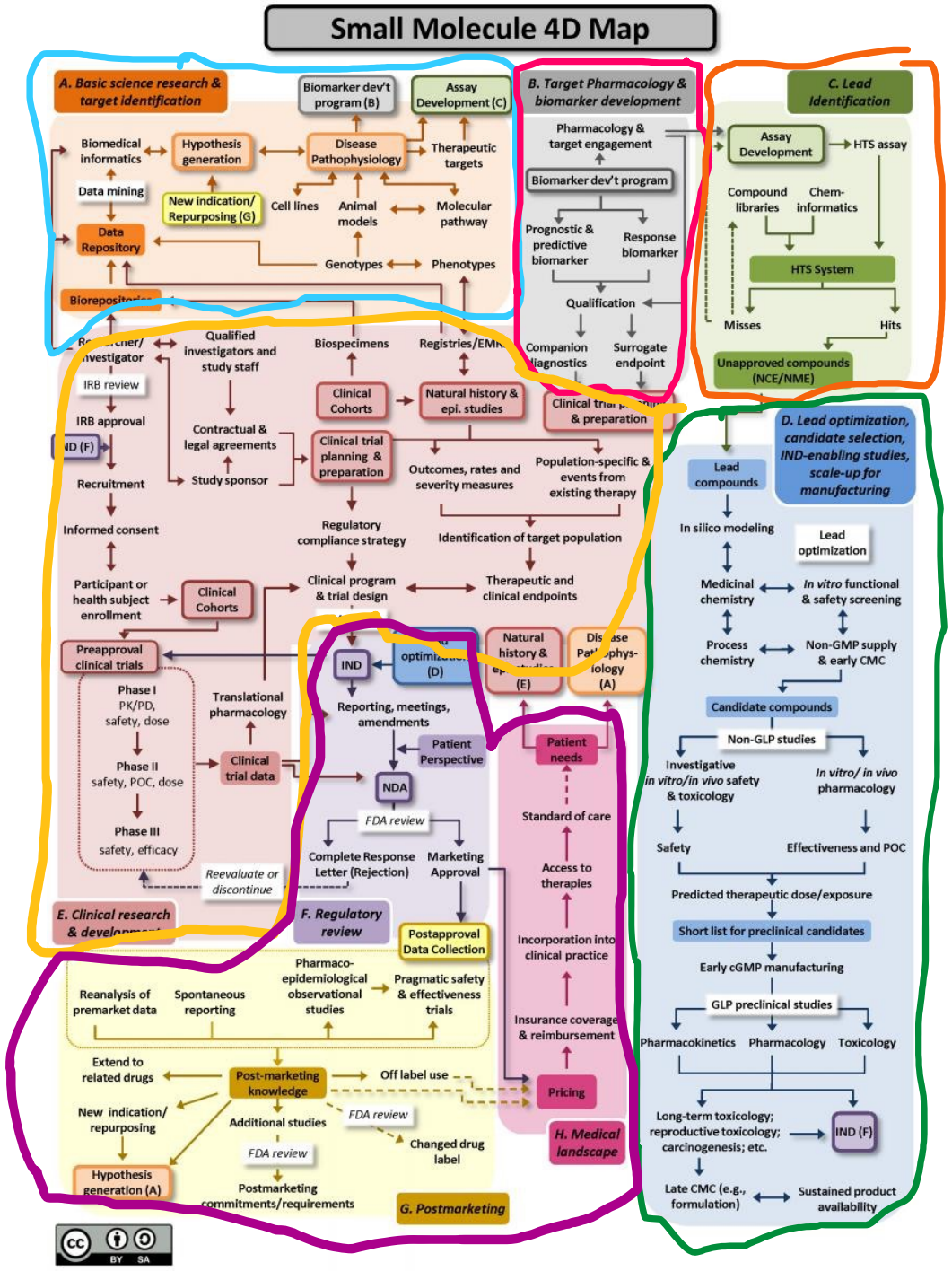
- **A. Basic science research and target identification**
- **B. Target pharmacology and biomarker development**
- **C. Lead identification**
- **D. Lead optimization and candidate selection**
  - Improving pharmacologic, metabolic, safety profiles of lead toward use in humans

Clinical

- **E. Clinical research & development**
  - Clinical trials to establish efficacy and safety
- **F. Regulatory review** (FDA approval)

Post-approval

- **G. Post-marketing**
  - **Surveillance (adverse effects)**
  - **Repurposing**
  - **Off-label use**
- **H. Medical landscape**

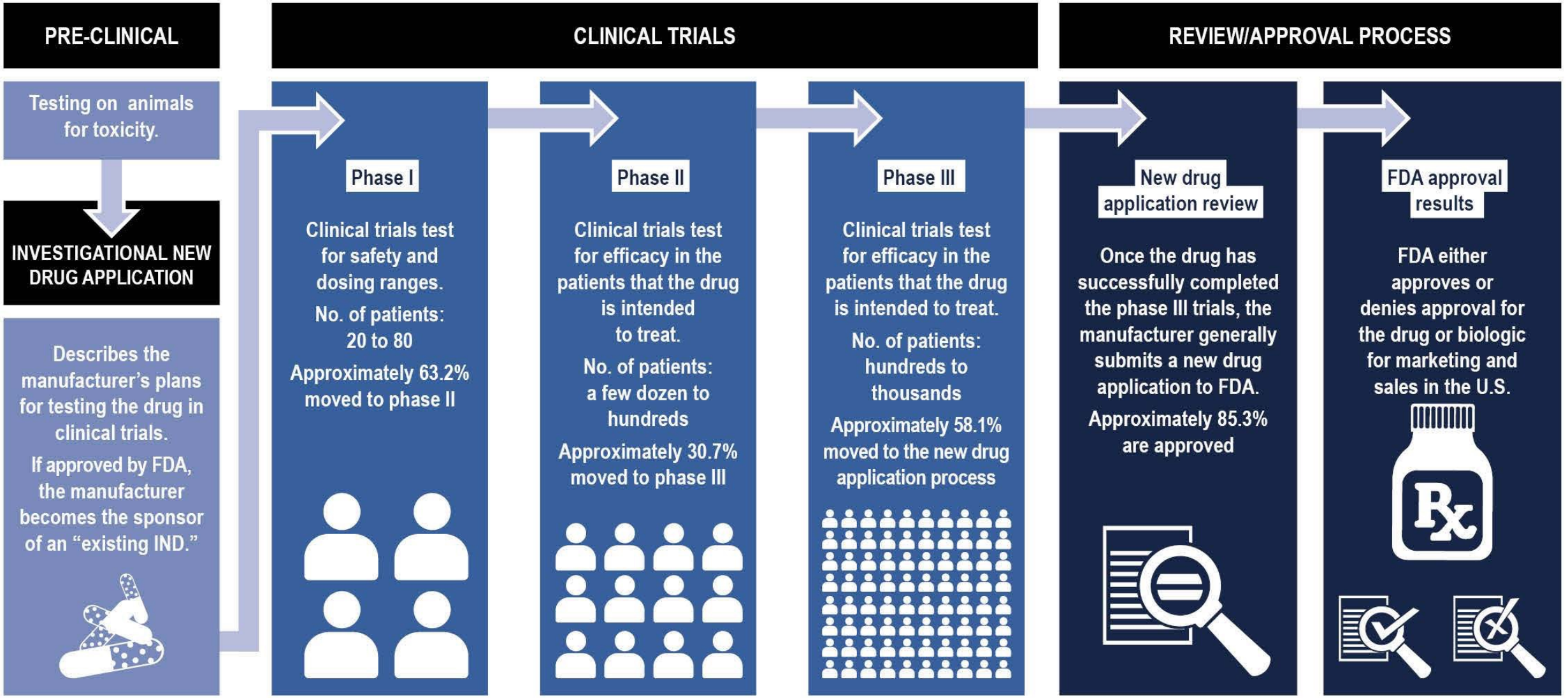


References:

1) Wagner et al; Nature Reviews Drug Discovery; 2018;
2) https://ncats.nih.gov/translation/maps
3) 4D Map (interactive): https://4dmap.ncats.nih.gov/#/

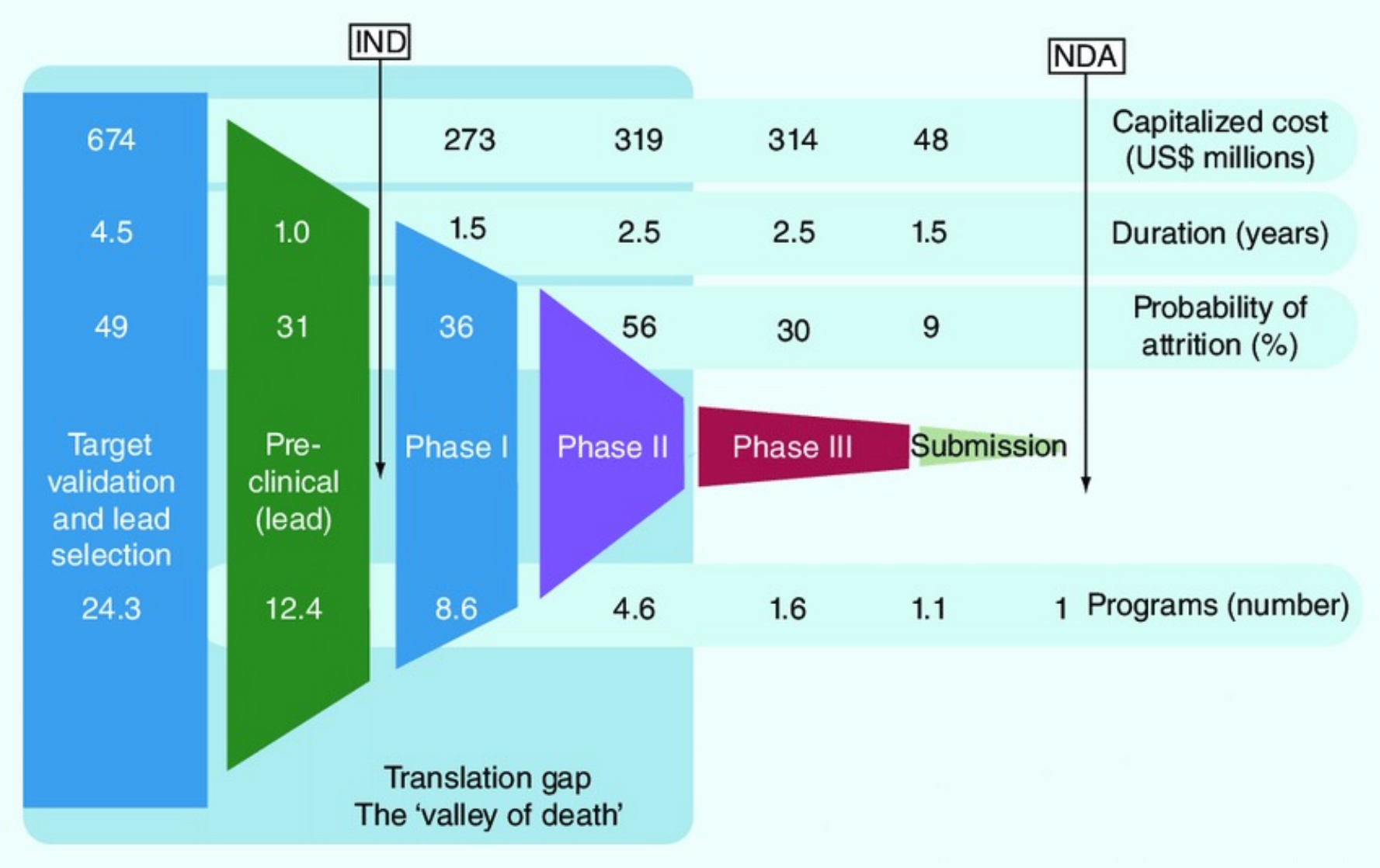
Clinical phase:

Brief overview of clinical research and development



Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion.[a] | GAO-17-564

New drug discovery is expensive, with no guarantee of success …



Between 2009 –2018, the median cost of developing a new drug was $985 million, while the average total was $1.3 billion!

Reference: Jesus Zurdo; Pharm. Bioprocess. (2013) 1(1)
DOI: 10.4155/PBP.13.3

Drug discovery framework

A. Basic science research and target identification

B. Target pharmacology and biomarker development

C. Lead identification

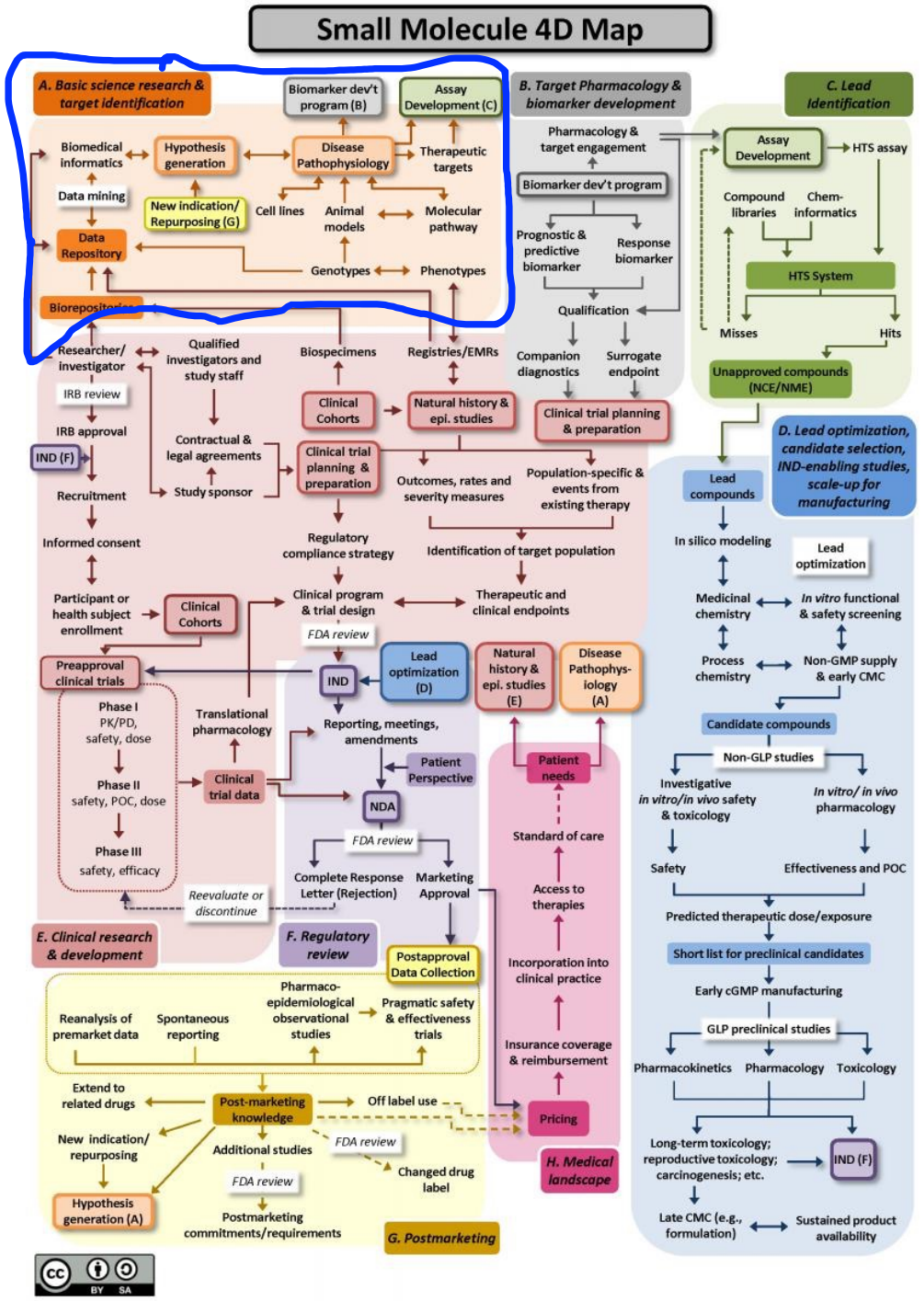
D. Lead optimization and candidate selection
- Improving pharmacologic, metabolic, safety profiles of lead toward use in humans

E. Clinical research & development
- Clinical trials to establish efficacy and safety

F. Regulatory review (FDA approval)

G. Post-marketing
- Surveillance (adverse effects)
- Repurposing
- Off-label use

H. Medical landscape



References:

1) Wagner et al; Nature Reviews Drug Discovery; 2018;
2) https://ncats.nih.gov/translation/maps
3) 4D Map (interactive): https://4dmap.ncats.nih.gov/#/

Learning Objectives

A. Defining the therapeutic intervention:
    A. What is intended goal/ outcome of the intervention?

B. Precisely defining the therapeutic target(s):
    A. What is the biological process(es) to be manipulated?
    B. Choosing an appropriate operational scale
        A. Molecular v. cellular v. tissue/organ v. whole (model) organism level

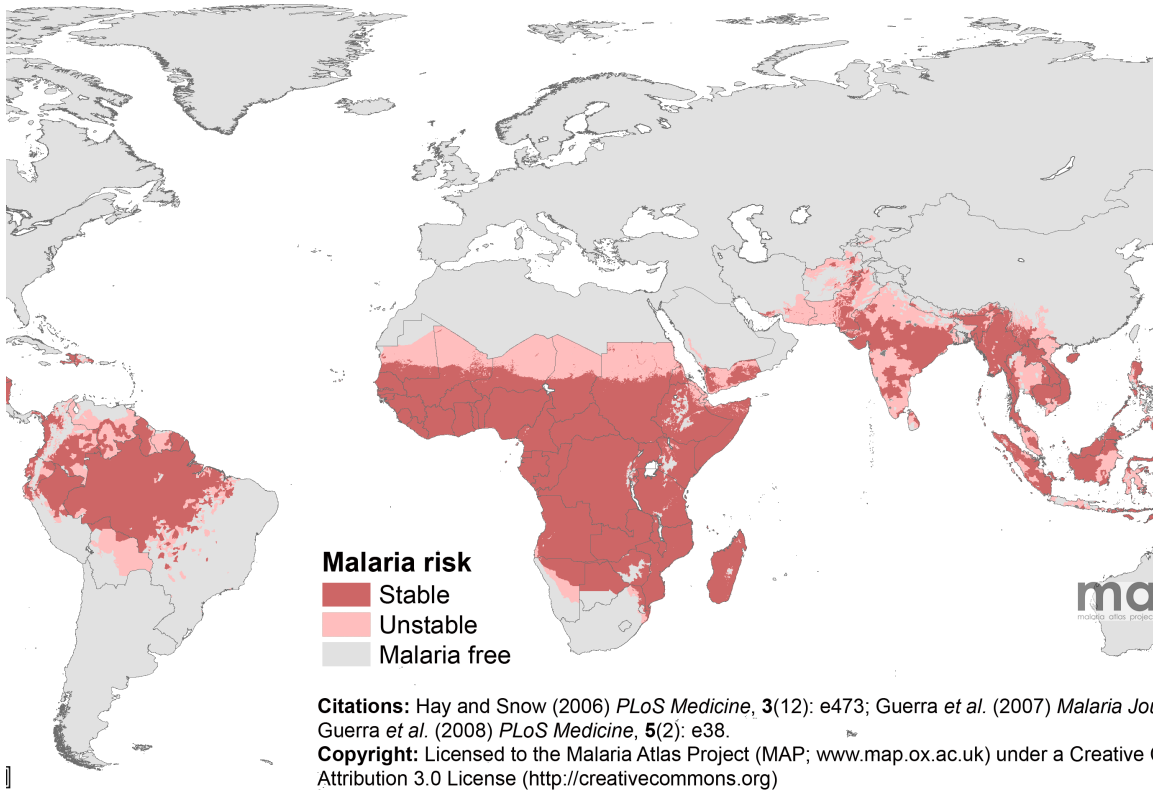
C. Validating the therapeutic potential of selected target(s):
    A. What evidence do you need to establish the suitability of a therapeutic target?

Case Study: Defining potential therapeutic interventions for malaria

Disease background: Malaria is a major threat to global human health

- Estimated **247 million cases in 2021**
  - 85% in African Region
  - 10% South-East Asia Region

- **619,000 deaths in 2021**
  - 89% in African Region
  - 5% in South-East Asia Region
  - Children < 5 years old account for the majority of deaths



– Human malaria caused by 5 protozoan (eukaryotic) parasite species
  – *Plasmodium falciparum*
  – *Plasmodium vivax*
  – *Plasmodium knowlesi*
  – *Plasmodium malariae*
  – *Plasmodium ovale*

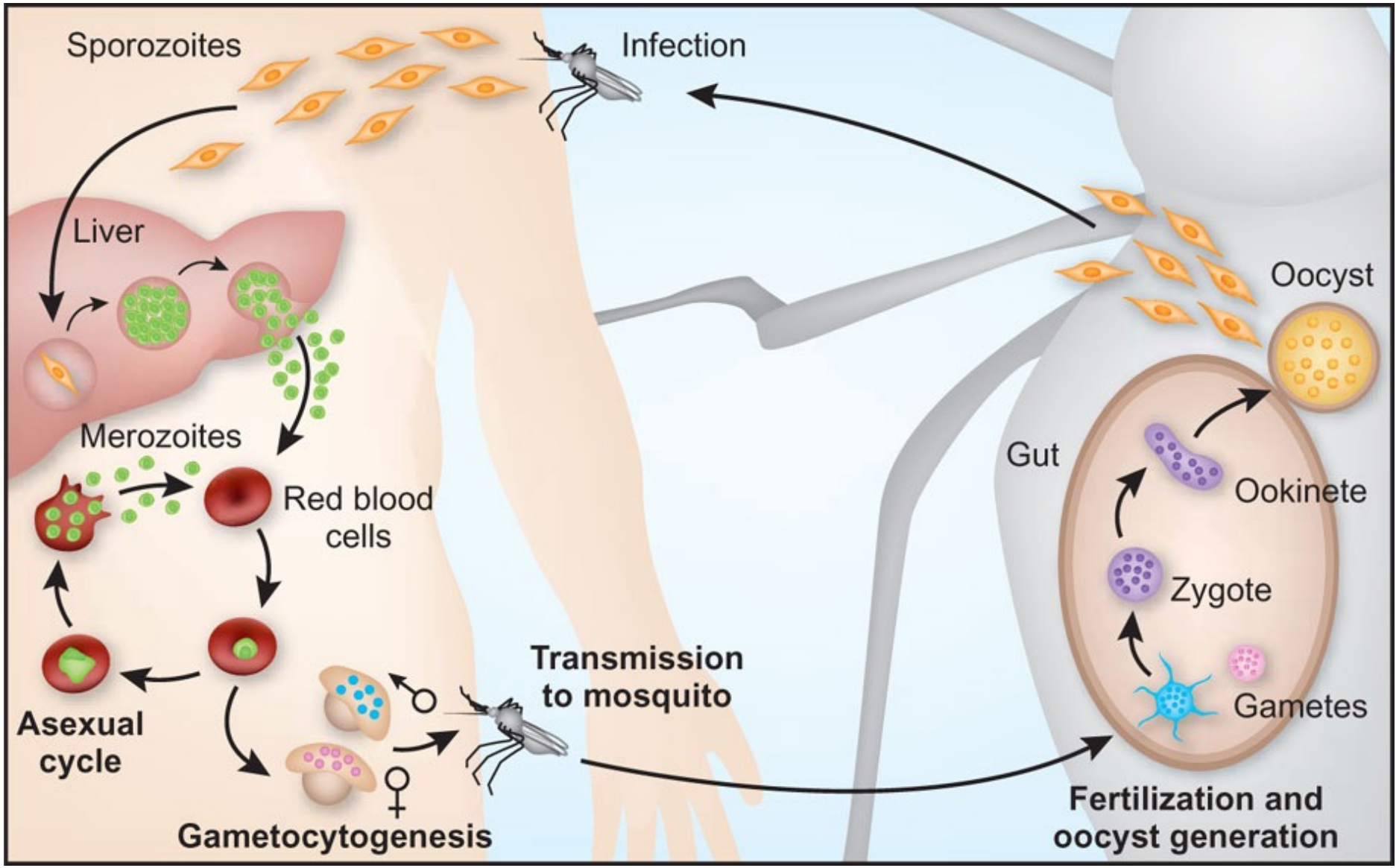
1. High-level ideas on your intervention strategy?

2. Who is at risk , and how does that impact conceptualization of your intervention?

Disease transmission

P. vivax – a dormant form (hypnozoite) persists in the liver

All malaria symptoms associated with red blood cell infection

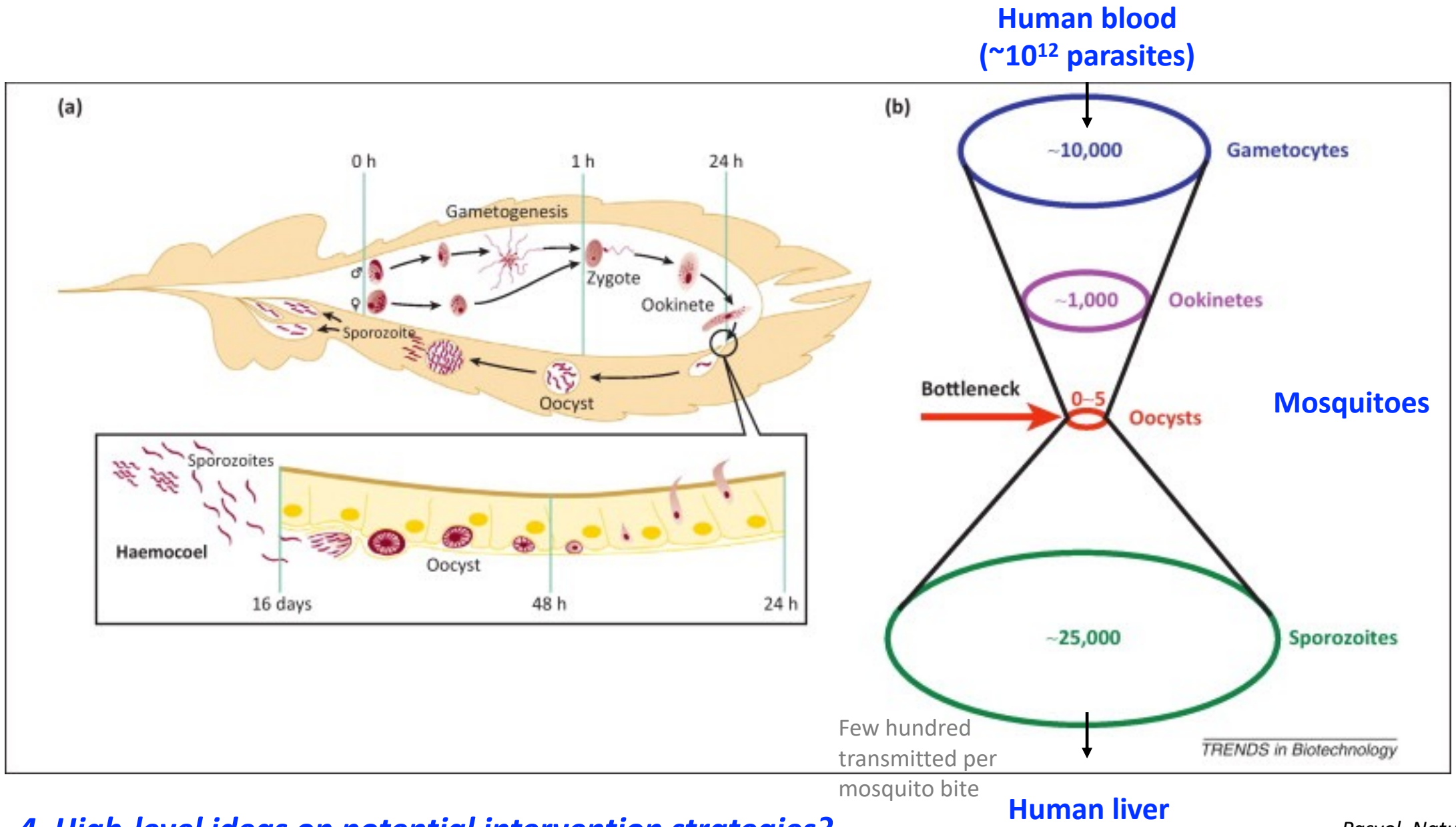


3. High-level ideas on your intervention strategy?

Pasvol, Nature Genetics (2010)

Mosquito Nets:
Inexpensive, but effective intervention

Transmission bottlenecks: Parasite life cycle by the numbers



4. High-level ideas on potential intervention strategies?

Pasvol, Nature Genetics (2010)

Summary

A. Drug discovery is expensive
   A. Need to carefully choose intervention strategy and target

B. Precisely define the desired outcomes of treatment / intervention
   A. Target candidate profiles (TCPs)
   B. Target product profiles (TPP)

C. Translating the desired outcome from macroscopic observables into targetable molecular processes to guide therapeutics development