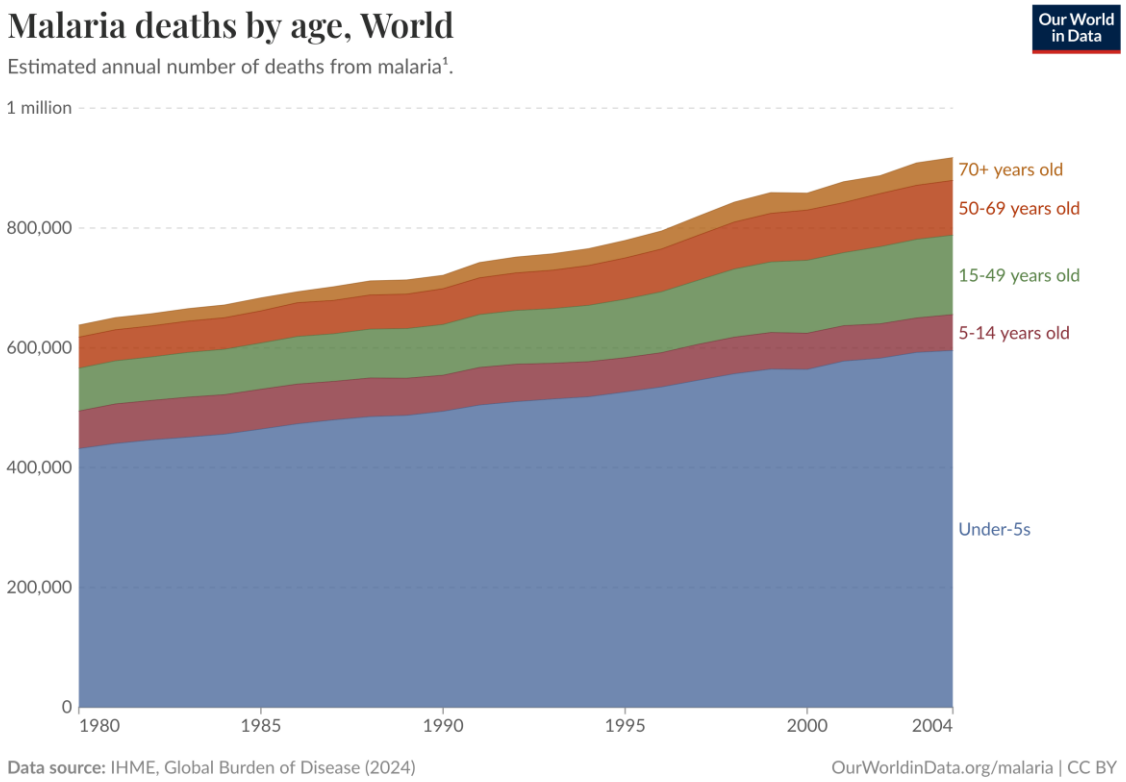
UC San Diego Health

Basic malaria research: the innovation engine for new antimalarial treatments

Elizabeth Winzeler, Professor and Associate Dean for Research and Innovation, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego

Director, Malaria Drug Accelerator

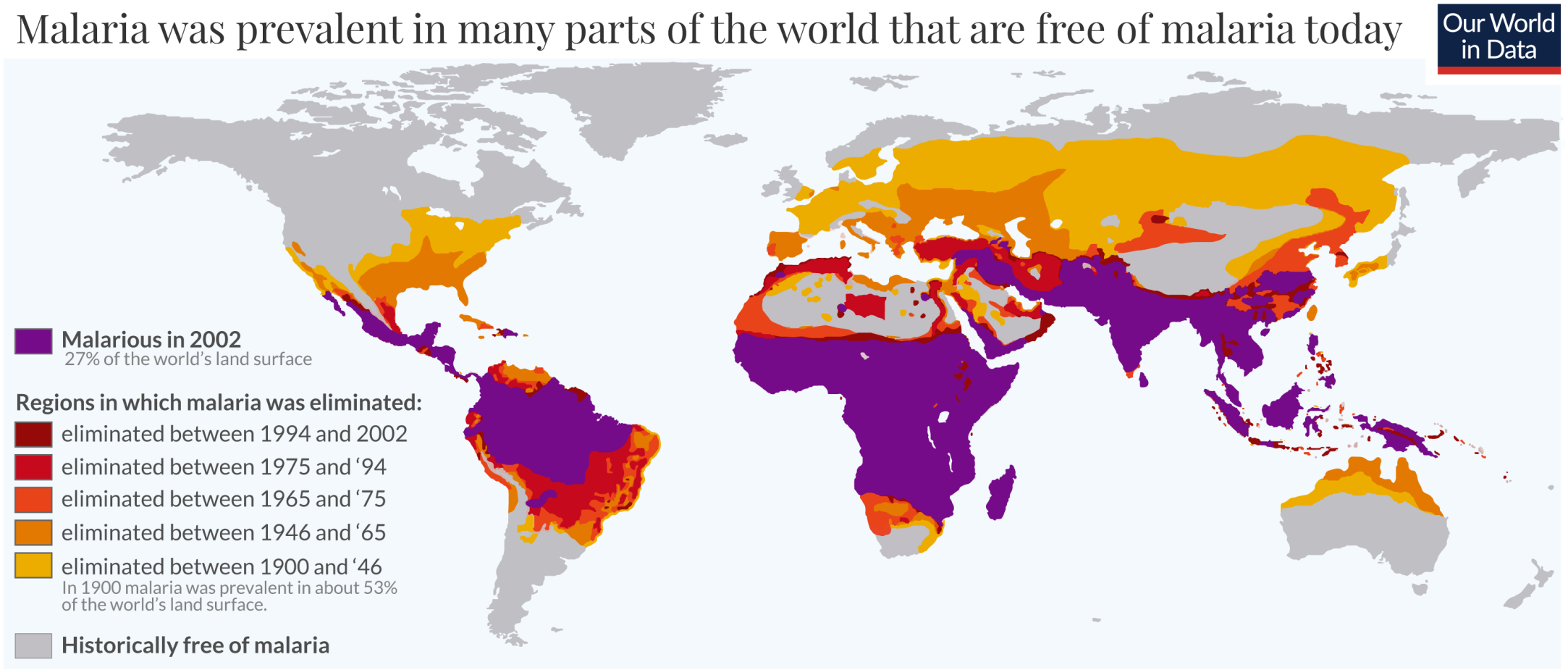
Malaria 20 years ago



1. Malaria: Malaria is a life-threatening disease caused by parasites that are transmitted by female Anopheles mosquitoes. There are five parasite species that cause malaria in humans. Two of these species – P. falciparum and P. vivax – pose the greatest threat. The first symptoms – fever, headache and chills – usually appear 10 to 15 days after the infective mosquito bite and may be mild and difficult to recognize as malaria. Left untreated, P. falciparum malaria can progress to severe illness and death within 24 hours. 📖 Read more on our page on malaria.

- Malaria deaths were high, but exciting new, artemisinin-based combination therapies were coming online. Research was focused on reducing mortality, vaccines, bednet distribution, artemisinin availability and creating replacement medicines for artemisinin

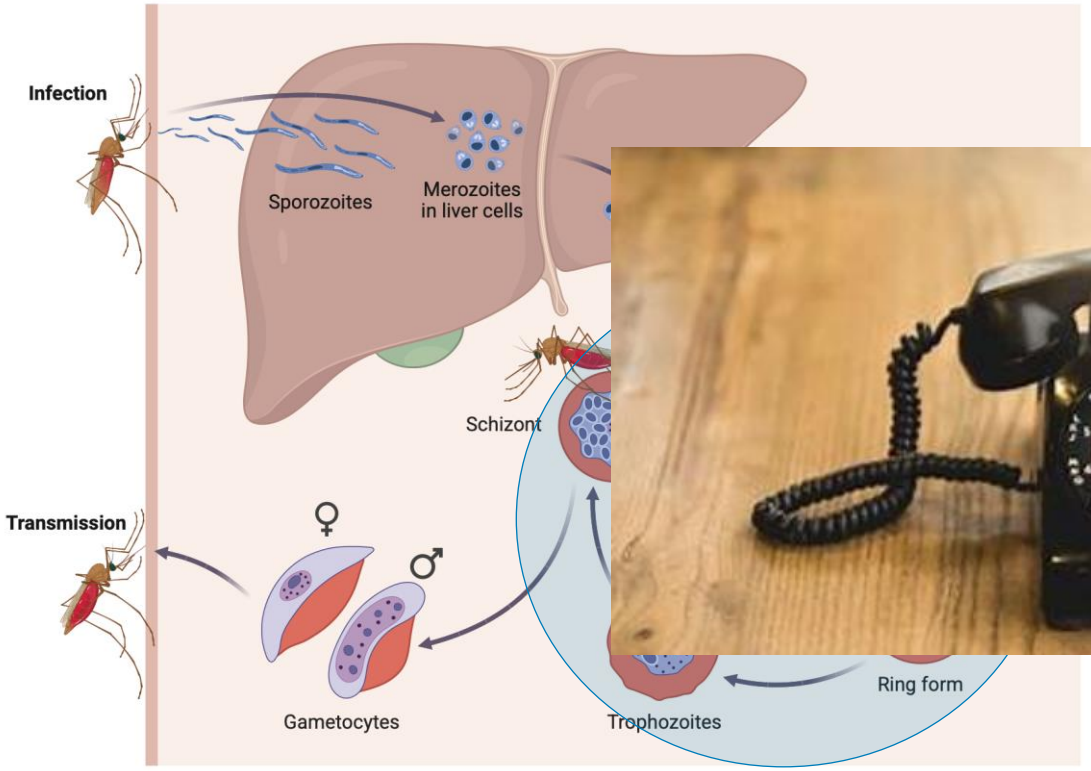
In addition, but we were beginning to imagine a world without malaria.



Source: Hay et al. (2004) – The global distribution and population at risk of malaria: past, present, and future. In The Lancet Infectious Diseases. Redrawn by Our World in Data.
OurWorldinData.org – Research and data to make progress against the world's largest problems.

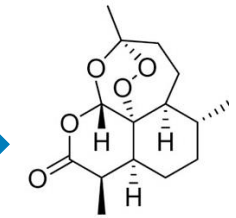
And this might involve new approaches

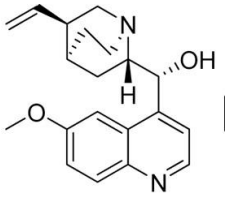
Artemisinin and quinoline-based drugs (both derived from natural products) might not be the best choice for long term malaria control and elimination



Artemesia annua

Artemisinin





Quinine

Cinchona officinalis

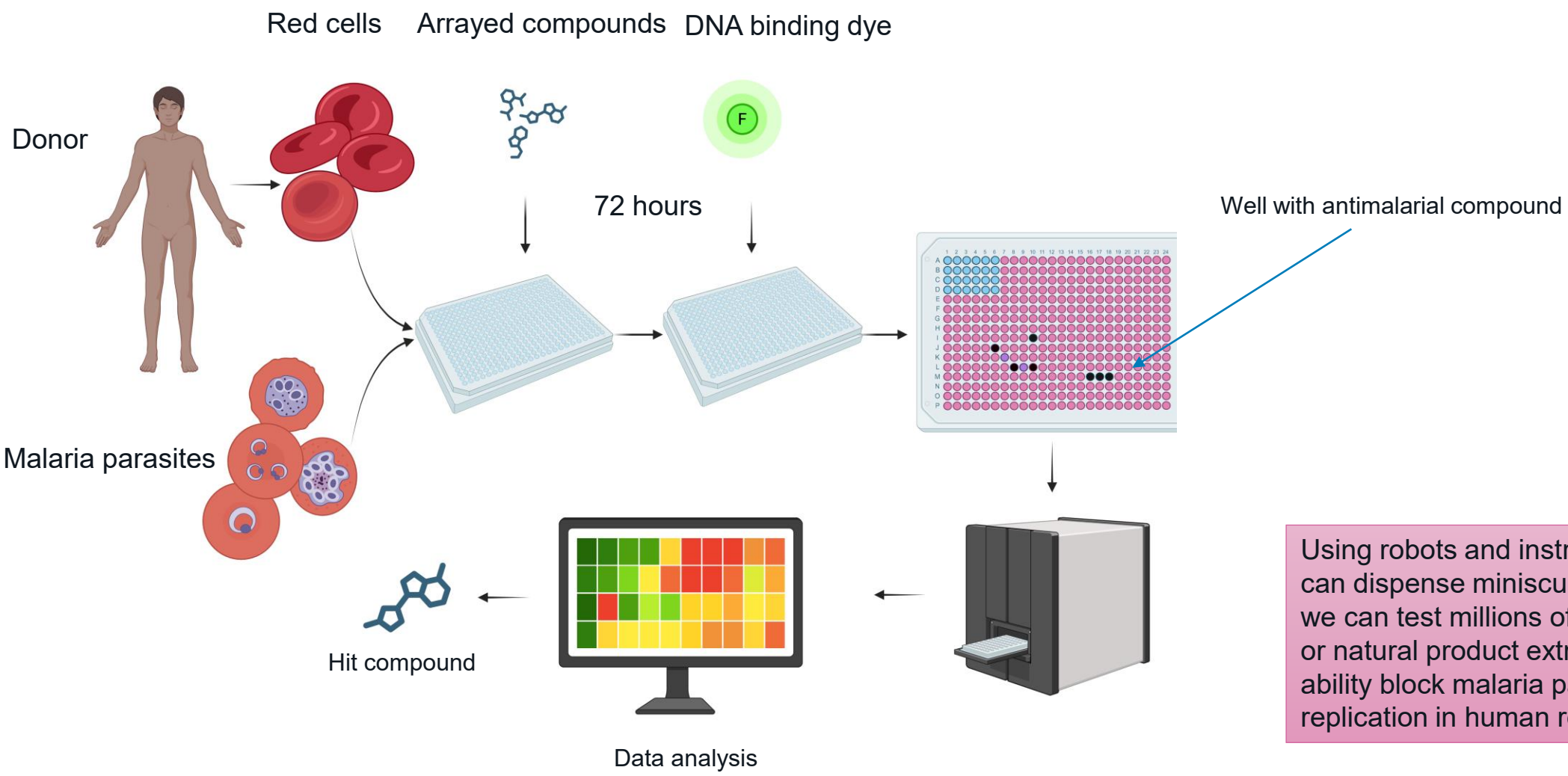
Artemisinin and quinoline-based drugs need frequent dosing, don't really impact transmission stages or prevent malaria. For quinolines and antifolates, multidrug resistance mechanisms can impact the entire class

Making new versions of old compounds would not improve problems

The ideal new antimalarial therapy

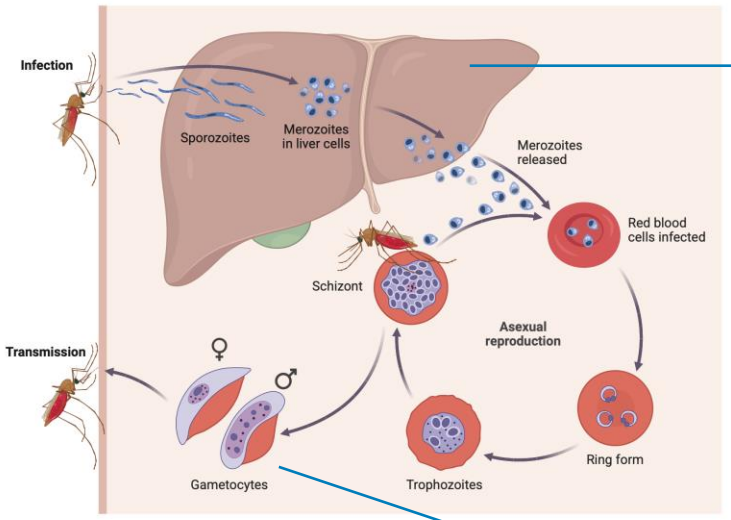
- Easy to take and no side effects
- Infrequent dosing—could even protect for an entire season
- Stops transmission to other households
- Few concerns about existing drug resistance
- Difficult for parasites to acquire resistance
- Inexpensive to manufacture
- Improves symptoms rapidly
- Active against *P. malaria, ovale, vivax* as well as *P. falciparum*
- Potentially suitable for an elimination agenda

1. To look for the next new magic bullet start with millions of candidates using automation and miniaturization

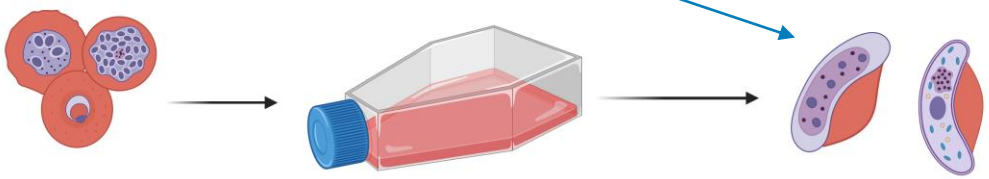


Using robots and instruments that can dispense miniscule droplets, we can test millions of compounds or natural product extracts for their ability block malaria parasite replication in human red cells

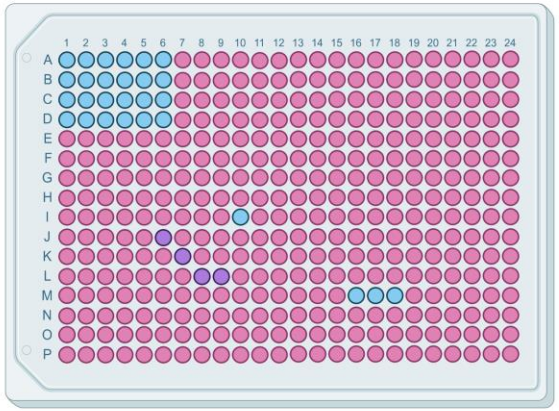
2. Look for starting points that prevent malaria and block transmission

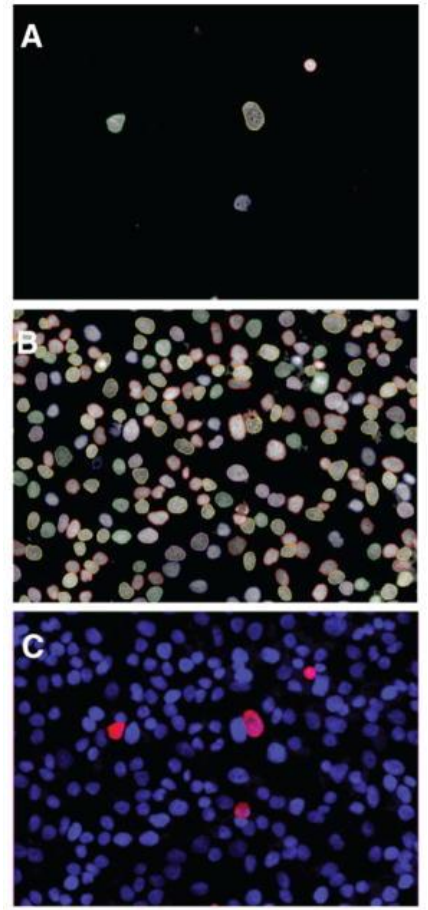


Sporozoites



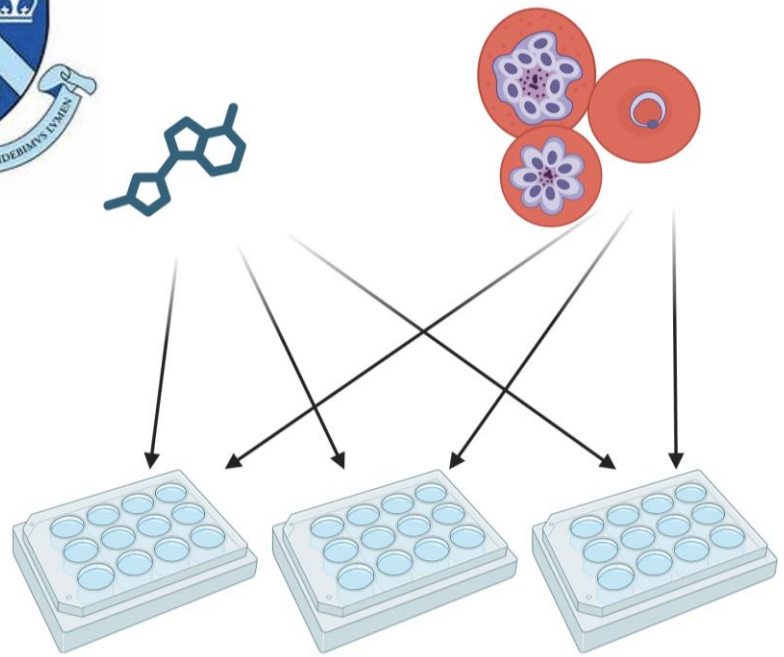
gametocytes



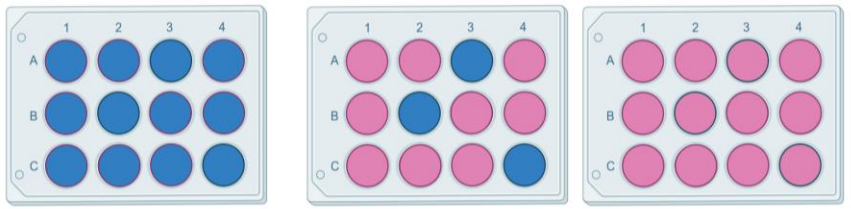


Assays have been developed that measure a drug candidate's activity against different stages of the lifecycle

3. Look for starting points that will provide rapid relief and do not give resistance quickly

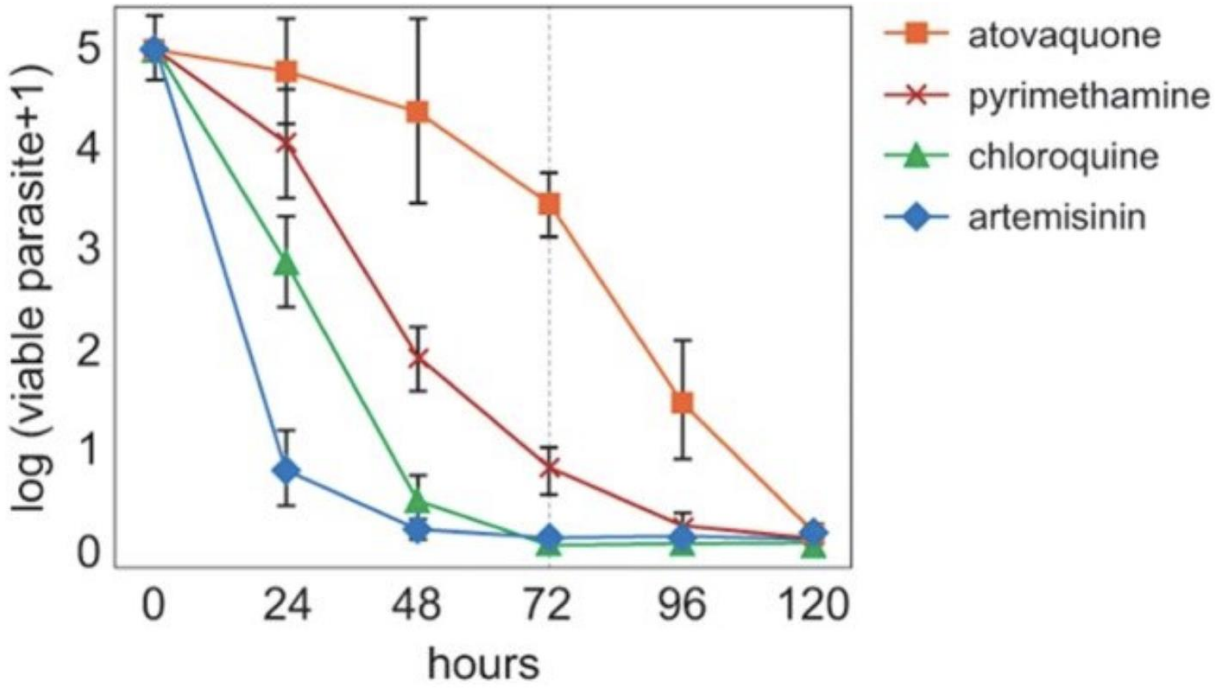


10,000 parasites 1000,000 parasites 1,000,000 parasites



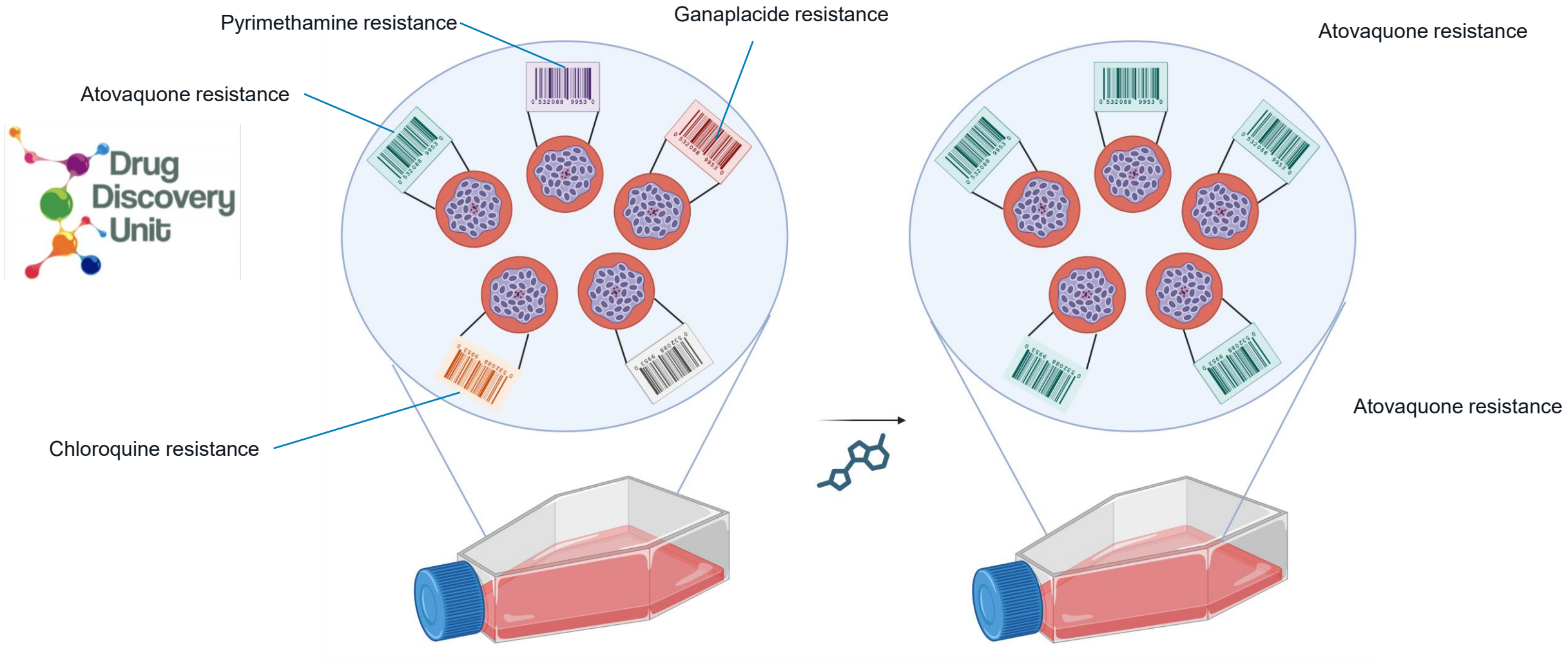
60 days incubation

Parasite Reduction Ratio

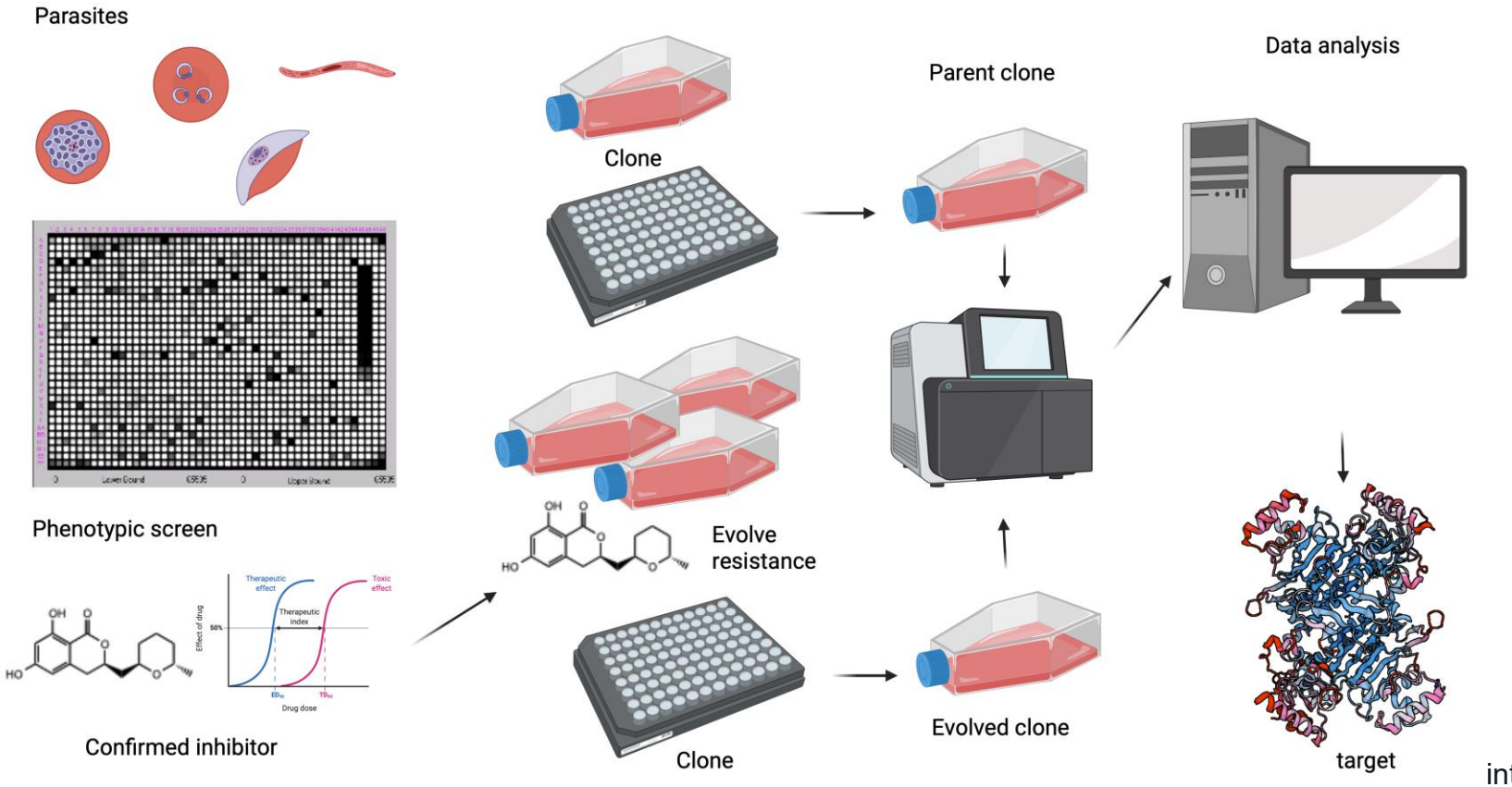


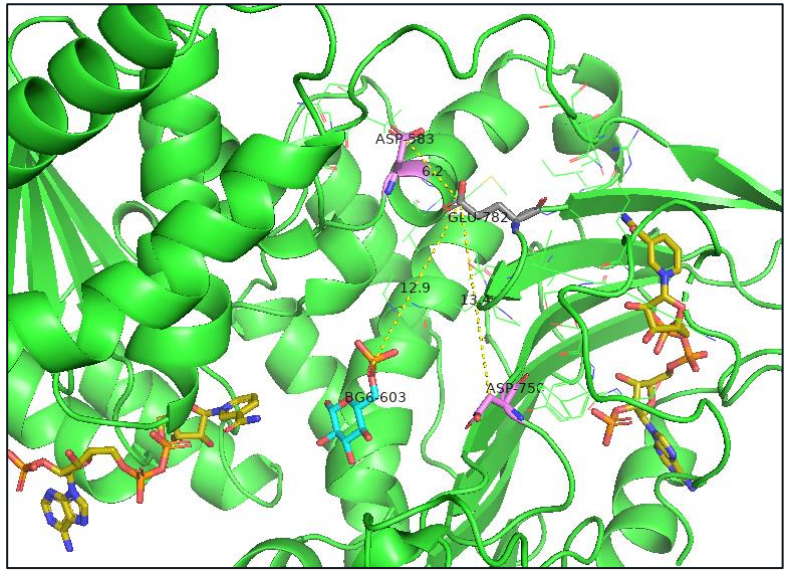
PlosONE 7(2) e30949. Sanz et al. doi:10.1371/journal.pone.0030949

4. Make sure starting points won't have same resistance liabilities



5. Use genetics to discover how the compound might be working. Focus on targets that are conserved across parasite species.





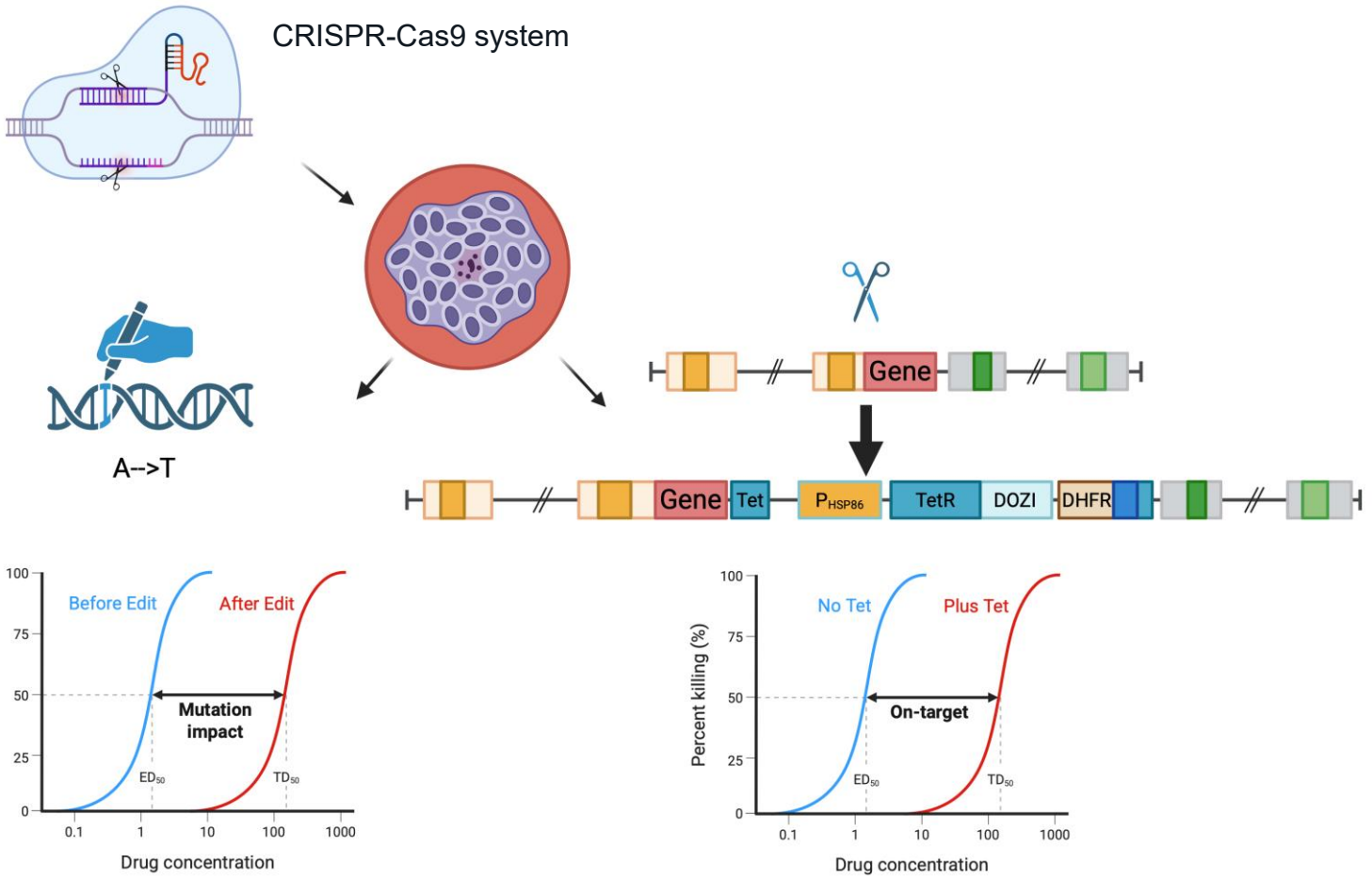
intelligence allow rapid new interpretation of data

The use of Alphafold and other computationally intensive research has greatly facilitated our research

6. Avoid mistakes/extra costs by testing hypotheses.

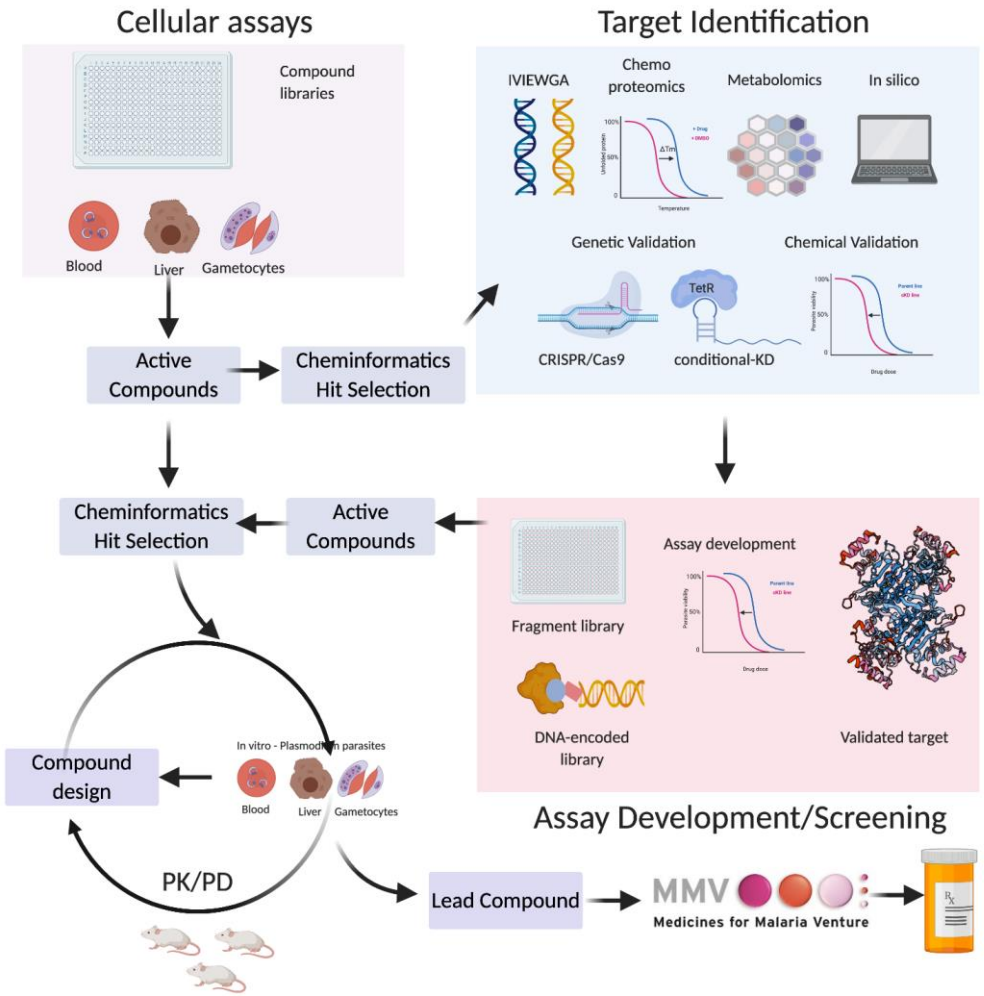
Drug Discovery Unit

Massachusetts Institute of Technology



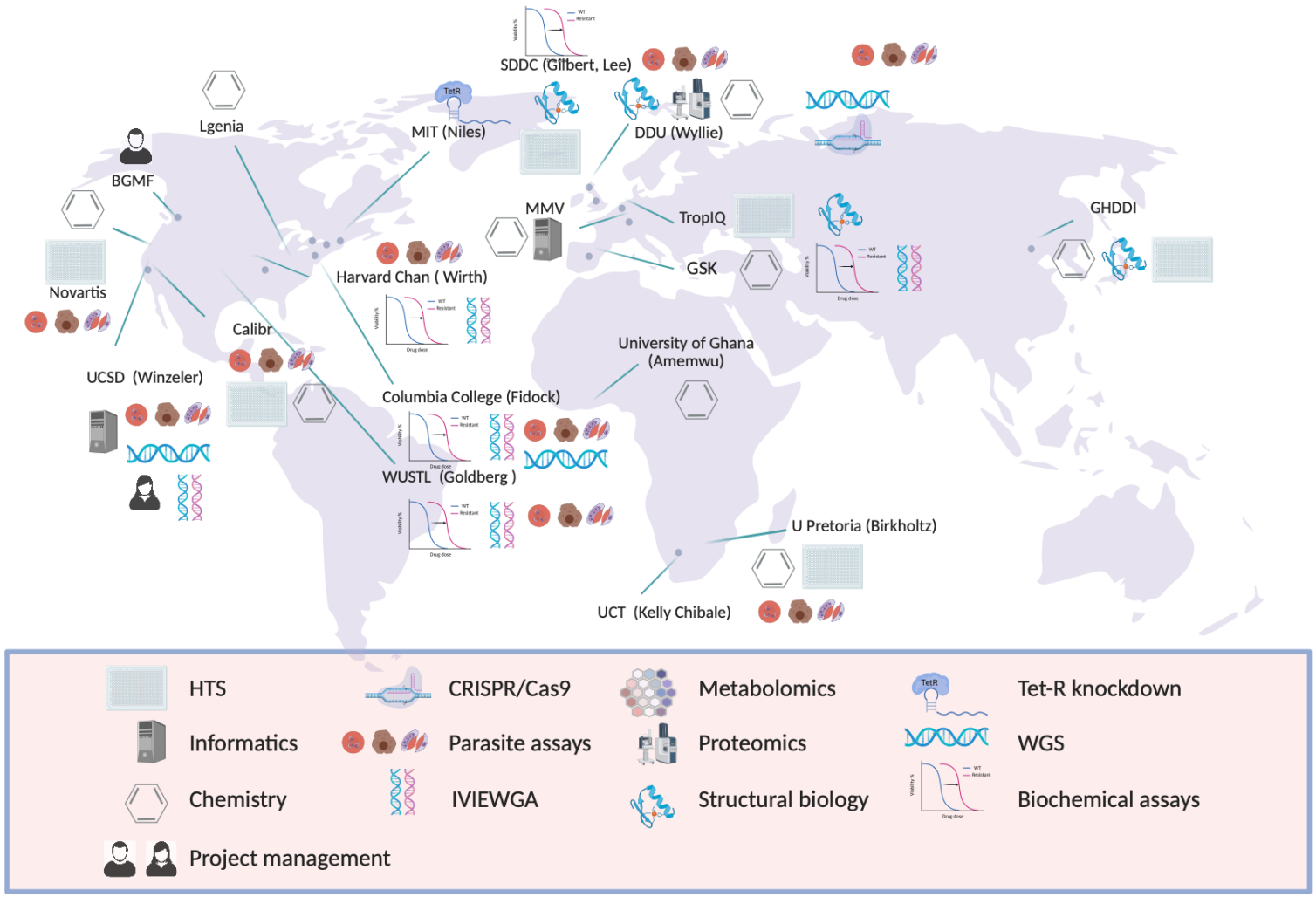
Work makes use of prize-winning new molecular methods for changing the genomes of parasites

Malaria Drug Accelerator (MalDA), a model for drug discovery for neglected disease

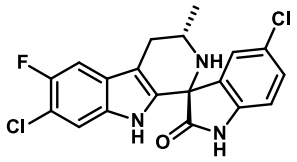


The MALDA Consortium is an innovative target-guided discovery platform and collaboration between 18 international groups that seeks to prime the drug development pipeline

Collaboration and capacity building: a virtual discovery department

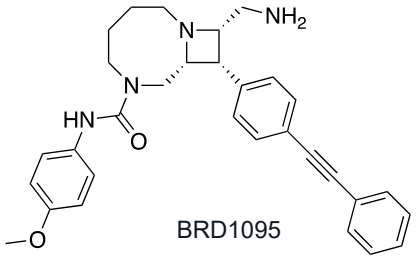


Dozens of critical parasite vulnerabilities have been identified, and many have given rise to new drug development programs including ones around Acetyl coA synthetase



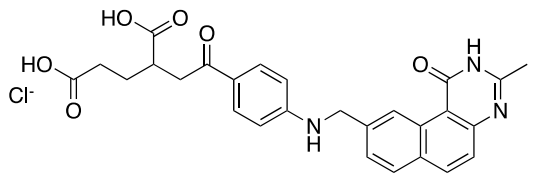
NITD609 (KAE609)
Currently in Phase Iib for treatment of symptomatic malaria

PfATP4 (P-type ATPase involved in sodium/hydrogen homeostasis



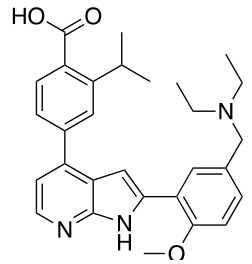
BRD1095

Phenylalanine tRNA synthetase



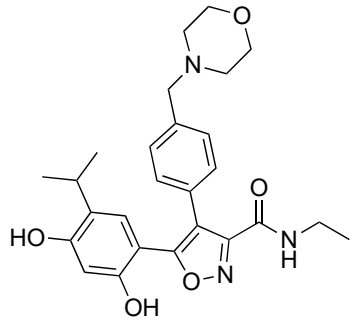
MMV027634

Thymidylate Synthase



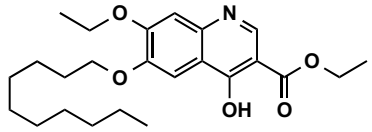
TCMDC-135051

CLK3



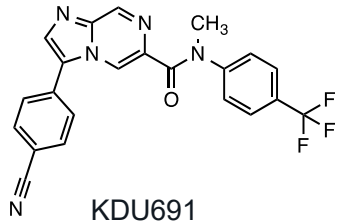
AUY-922

HSP90



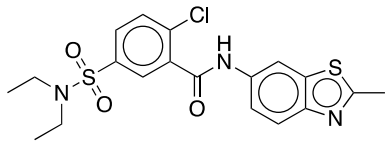
Decoquinate
Possible antimalarial and approved coccidostat

Cytochrome bc1



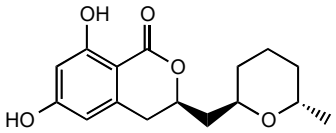
KDU691

PfPI4K



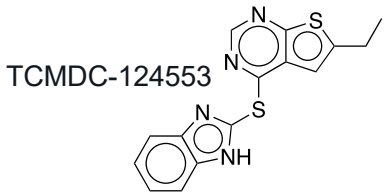
MMV019721

Acetyl-CoA Synthetase



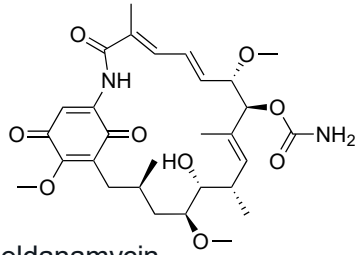
Cladosporin
Potent antiplasmodial activity

Lysyl tRNA synthetase



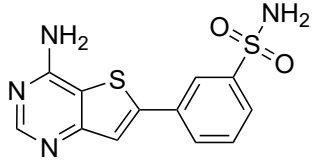
TCMDC-124553

Isoleucyl tRNA synthetase



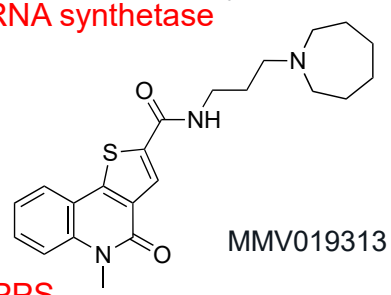
Geldanamycin

HSP90



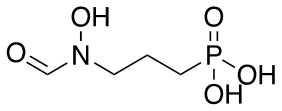
OSM-106

Asparagine tRNA synthetase



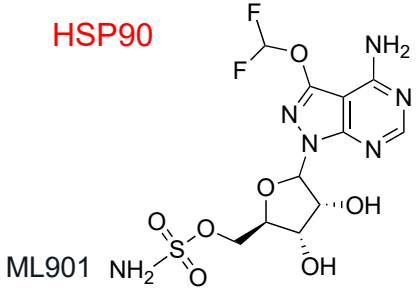
MMV019313

GGPPS



Fosmidomycin

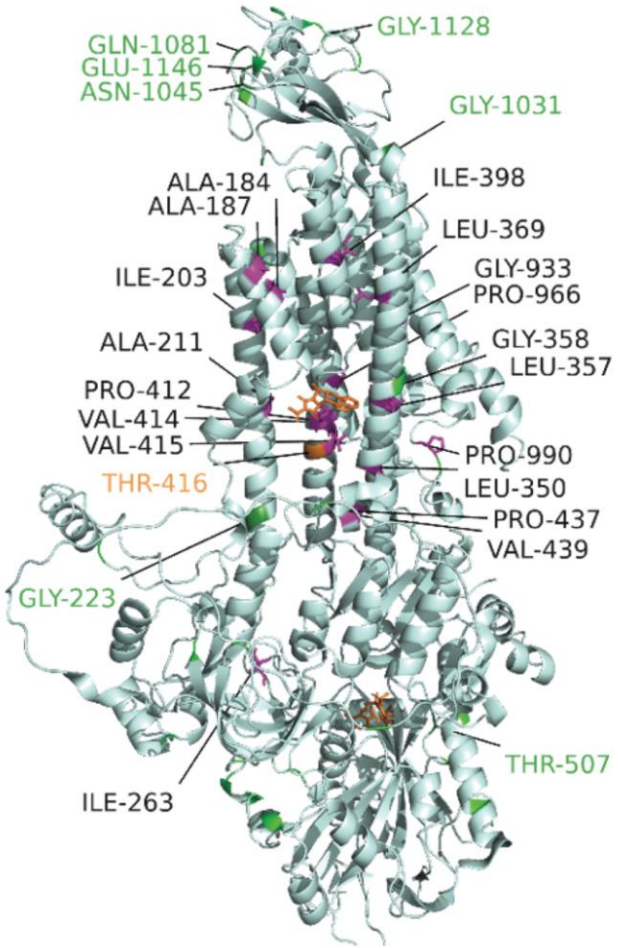
1-deoxy-D-xylulose 5-phosphate reductoisomerase

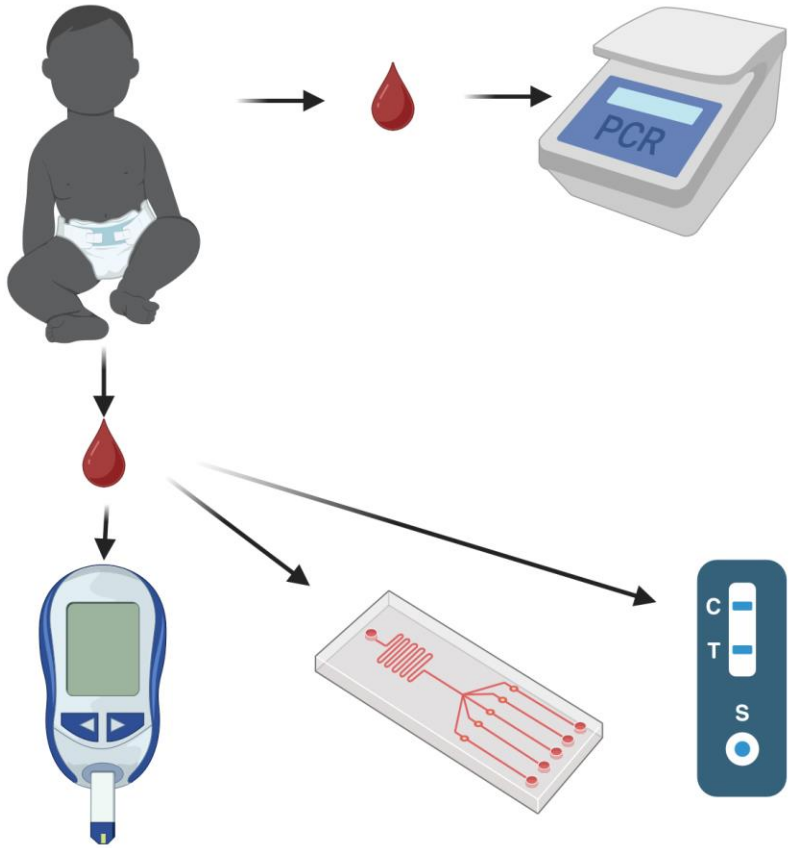


ML901

Tyrosine tRNA synthetase

Dozens of new antimalarial resistance genes as well as specific mutations have been discovered as well. These will inform field-based efficacy studies could allow drug resistance to be monitored using inexpensive, molecular methods

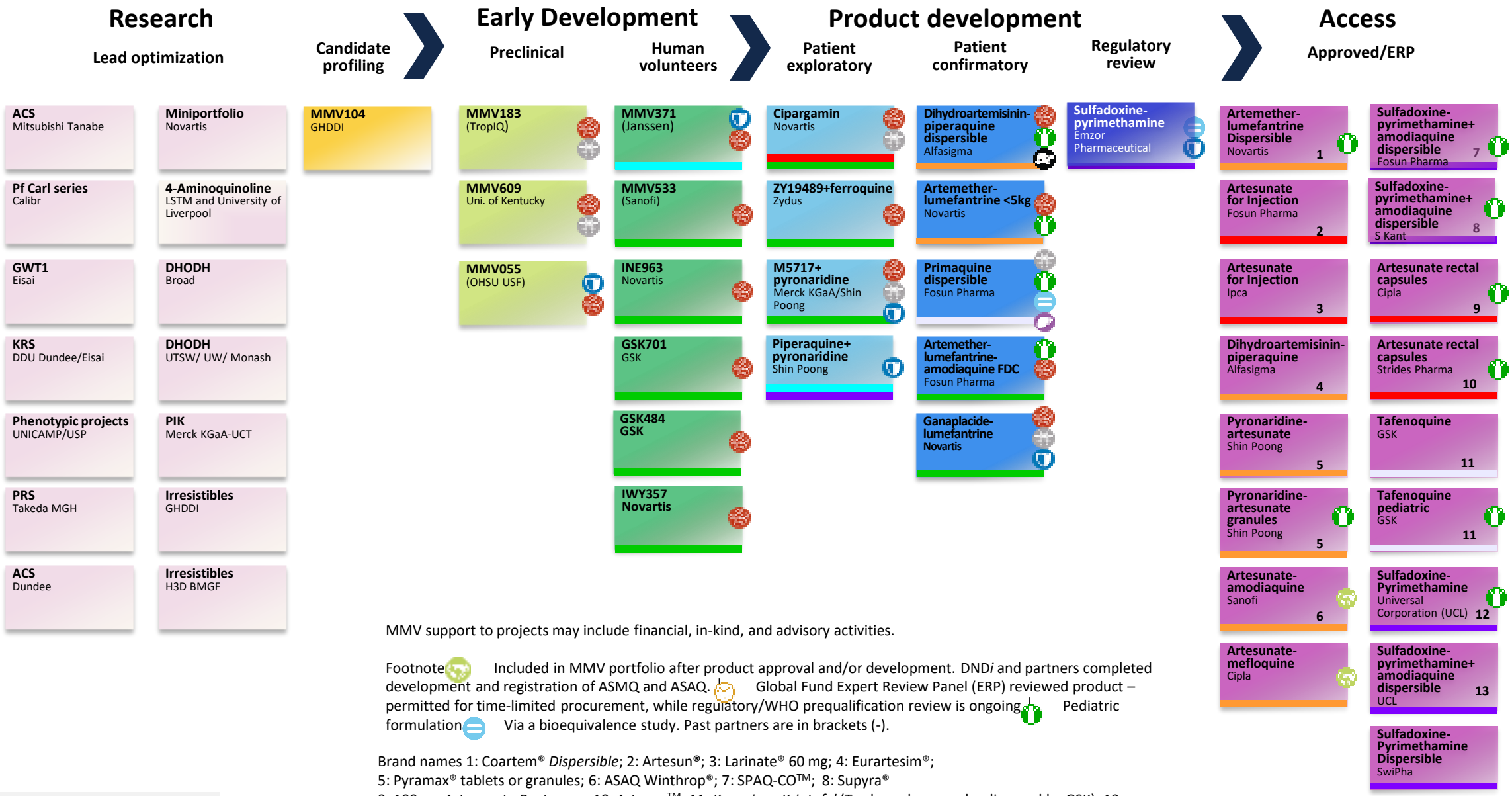




Careful data curation from MalDA projects allows machine learning and AI approaches to be applied

Plasmodium falciparum multidrug resistance gene

These biological innovations have laid the foundation for the MMV pipeline



MMV support to projects may include financial, in-kind, and advisory activities.

Footnote Included in MMV portfolio after product approval and/or development. DND*i* and partners completed development and registration of ASMQ and ASAQ. Global Fund Expert Review Panel (ERP) reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing. Pediatric formulation Via a bioequivalence study. Past partners are in brackets (-).

Brand names 1: Coartem® *Dispersible*; 2: Artesun®; 3: Larinate® 60 mg; 4: Eurartesim®;
5: Pyramax® tablets or granules; 6: ASAQ Winthrop®; 7: SPAQ-CO™; 8: Supyra®
9: 100 mg Artesunate Rectocaps; 10: Artecap™; 11: *Kozenis or Krintafel* (Trademarks owned or licensed by GSK); 12: Wiwal®

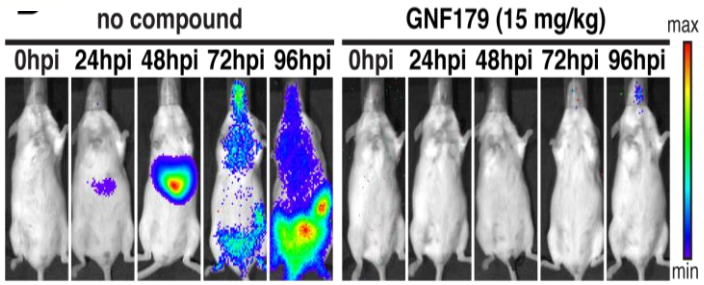
Sept 2024

Imidazopiperazines (e.g. Ganaplacide,GNF179) are the first new medicine designed with the new feature wish list in mind, but others are coming (cabamaquine, others).

Provides better outcome than gold standards in curing asexual blood stage infection

	Dose mg/kg p.o.	Animals tested	Parasitemia reduction (%)	Survival (days)
Untreated	n/a	10	0	6.5
GNF179	1 x 100	3	99.5	19.0
GNF179	3 x 30	3	99.8	16.3
Artesunate	1 x 100	>10	97	6.7
Artesunate	3 x 30	10	98	7.2
Chloroquine	1 x 100	>10	>99.9	12
Chloroquine	3 x 30	10	98.6	18.8

In vivo antimalarial activity in groups of 5 mice intravenously infected on day zero with $2x10^7$ erythrocytes parasitized with *P. berghei* GFP ANKA

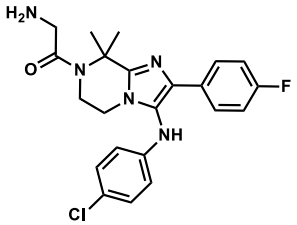


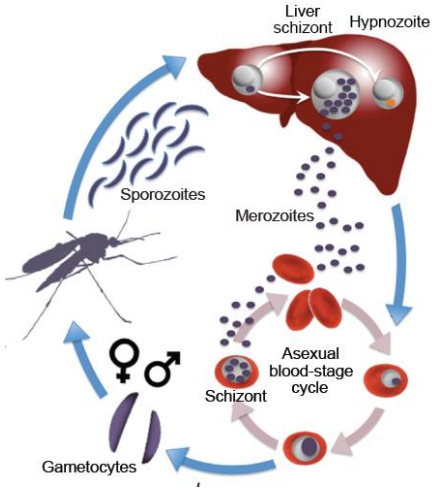
Complete prophylactic protection at a single oral 15 mg/kg dose

Malaria protection

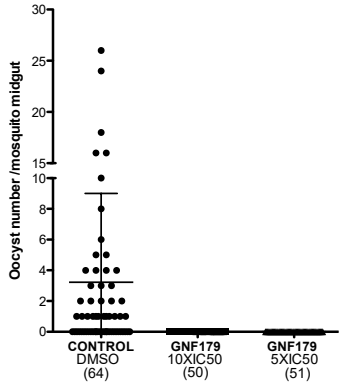
Good Pharmacokinetics, orally bioavailable

- *Pf* W2 (EC_{50}): 6 nM
- Py EEF (EC50) 4.51±3.82
- hERG (binding) IC_{50} = 7.2 µM
- CL = 21.92 mL/min/kg; V_{ss} = 11.8 L/kg
- Oral T½ = 8.4 h
- PO C_{max} (D.N.) = 60.5 nM / (mg/kg)
- PO AUC_{inf} (D.N.) = 1035 hr*nM (mg/kg)
- F (%) = 58





Mosquitoes are not infected if bloodmeal is treated with GNF179



Transmission-blocking

Novartis and Medicines for Malaria Venture report positive results for Phase IIb study of novel ganaplacide/lumefantrine combination in children with malaria

The positive Phase IIb results for the next generation antimalarial therapy support continued development of the combination

29 Sep 2021

Likely licensing in 2025/2026

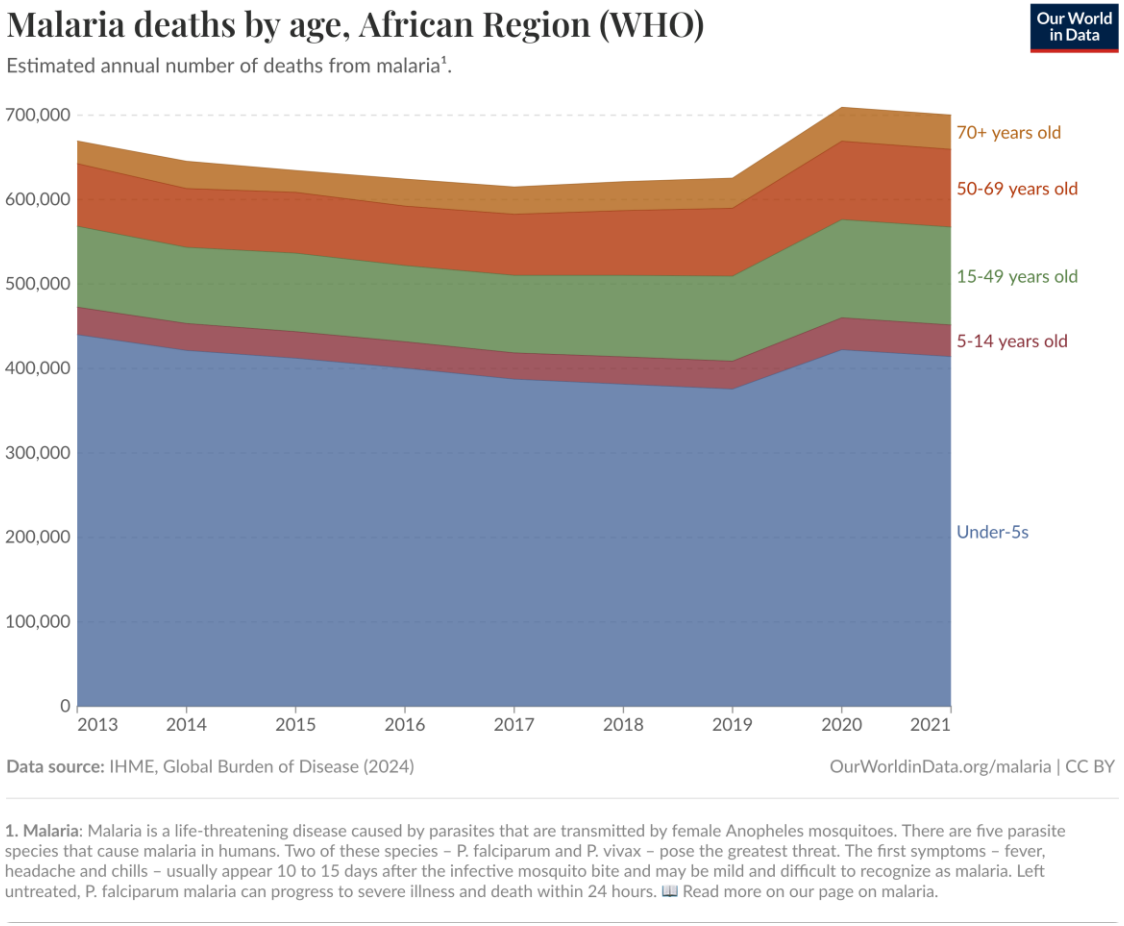
Completely novel mechanism of action

The starting point for ganaplacide was discovered almost 20 years ago and elimination progress has stalled.

New drugs may help, but we may yet reach another plateau with existing tools

- What could lead to more radical changes?
  - Advances in biologics, including using artificial intelligence to design proteins and compounds.
  - New delivery methods that target drugs to specific organs (e.g. the liver).
  - Discovery of critical new vulnerabilities, especially targets that are specific to parasites
  - New biological innovations (e.g. CRISPR and gene drive)

Should we stop now?




3:06
Freehold
83°
Partly Cloudy
H:83° L:52°
Weather
SATURDAY
10
No events today
Calendar
FaceTime
SAT
10
Calendar
Photos
Camera
Mail
Notes
Reminders
Clock
News
TV
Podcasts
App Store
Maps
Health
Wallet
Settings
Search

Thanks to all collaborators, funders and others