Advancing malaria drug discovery

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MMV, H3D, UCSD, Gates Foundation & CDD

CDD Vault Webinar – 26 June 2025

Ending malaria, rewriting the future

Speaker Introductions

Advancements in Antimalarial Drug Discovery and Development

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H3D
PIONEERING WORLD-CLASS DRUG DISCOVERY IN AFRICA

MMV
Medicines for Malaria Venture

25 YEARS

Malaria: a pressing challenge

Despite much progress against the disease, malaria remains an unresolved and urgent global health issue. Long-standing inequities in healthcare leave **millions of people unprotected and untreated,** while **drug resistance, climate change** and **fragile health systems** threaten to undo hard-won gains.

IN 2022[1]:

249 million cases | **608,000 deaths**

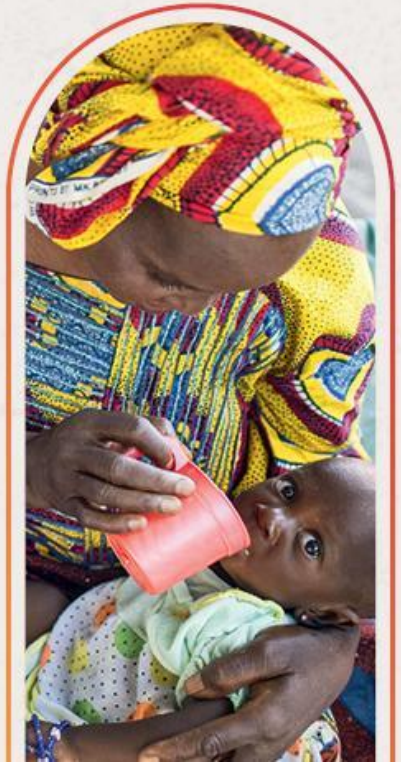
Endemic in
85 countries

94% of cases
occur in Africa

Children under five and pregnant women are most at risk

76% of deaths
occur in children under five

>35 million
at-risk pregnancies



[1]WHO World Malaria Report 2023

Introducing MMV

Established in 1999, MMV was born out of one of the world's greatest health inequities – a lack of high-quality, low-cost malaria medicines, coupled with chronic limitations in access.

By bringing public and private partners together, we work to deliver a global portfolio of accessible and affordable medicines with the power to treat, prevent and eliminate malaria.

Cumulatively to 2023:

15 new medicines

15.4 million lives saved*

*In absolute terms (in the absence of any treatment).

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MMV Medicines for Malaria Venture

25 YEARS

The challenges we are facing today

Emerging resistance

- Artemisinin resistance
- Decreased susceptibility of *Pf* to lumefantrine
- SP resistance (IPTp; SMC)

Malaria prevention

- Limited choice of interventions
- Vaccines protecting infants and children < 5 years old
- Duration of protection

Pregnant and lactating women

- Very limited options for pregnant and lactating women
- Unmet medical need in chemoprevention space

Prevention of relapse

- Current single-dose treatment cannot be used globally (G6PD liability and blood stage limited to CQ)

Transmission blocking

- Effectiveness & acceptance of low-dose PQ
- Unmet need in medium to high transmission areas

Global malaria drug portfolio aimed to mitigate resistance

Artemisinin resistance

2024–26

- Multiple first line therapies
- Triple ACTs (artemether-lumefantrine-amodiaquine, ALAQ)
- Single low-dose primaquine added to ACT
- Ganaplacide-lumefantrine (GAN-LUM)

Lumefantrine resistance

2026–30

- Ganaplacide-lumefantrine-cipargamin
- Cabamiquine+pyronaridine
- ZY19489+ferroquine
- Cipargamin+X (severe malaria)

Single-dose cure (SDC) combination pool

2030+

Potential molecules to add-on or for novel combinations:

- MMV533
- GSK701
- INE963
- GSK484
- IWY357

The missing tools: advancing transformative interventions for malaria elimination

Target Product Profiles (TPPs), and Target Compound Profile (TCPs): **The bar is getting higher and higher**

Long-acting chemoprevention medicines:
"Complementing vaccines to protect the most vulnerable"

Targeted to all ages, reducing the disease burden in elimination efforts

- *Long duration of action*
- *Low risk of resistance (alone or in combination)*
- *Injectables and Oral dosing*
- *Clearing parasites*
- *Non-teratogenic profile*
- *Transmission blocking activity*

Next-generation elimination tool:
"Single-dose cure as the backbone of population-wide malaria elimination strategies"

Shorter and more convenient regimen that could revolutionize mass drug administration and accelerate elimination efforts

- *Low dose*
- *Long duration of action*
- *Low risk of resistance (alone or in combination)*
- *Non-teratogenic profile*
- *Transmission-blocking activity*
- *Radical cure (an upside)*

MMV's current pipeline aims to deliver on big bets, yet a strong early-stage portfolio is essential to mitigate risk

Need to ensure future impact and next-generation solutions if existing platforms do not deliver

Deliver a **first generation of non-ART treatment** combinations (GAN-LUM)

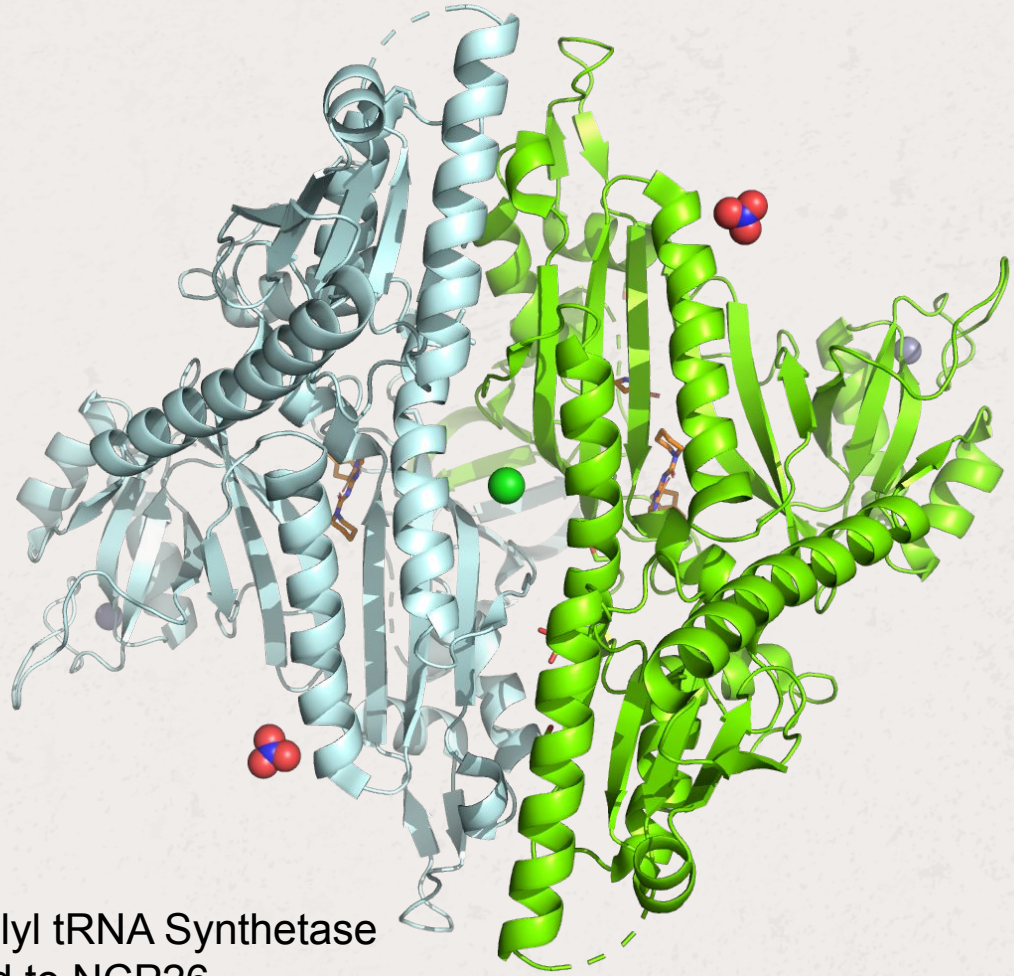
Deliver the **first generation single-dose cure**, non-ART, non-LUM (e.g., GAN-LUM-X)

Deliver **a long-acting injectable for chemoprevention** (MMV371 + MMV055)

Deliver a **PoC for severe malaria** (MMV183)

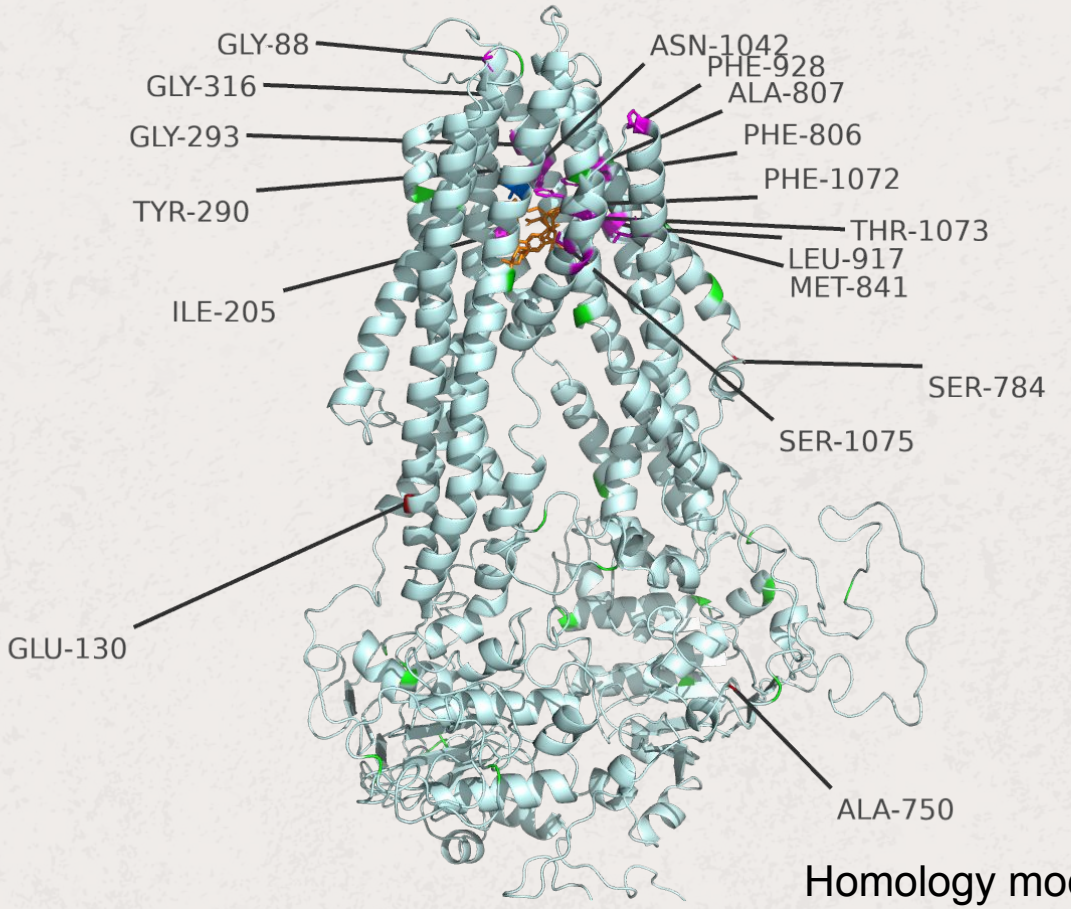
Deliver an **endectocide for elimination** campaigns (Lotilaner)

New biological targets and resistance



PfProlyl tRNA Synthetase bound to NCP26

PDB DOI: https://doi.org/10.2210/pdb7BBU/pdb



Homology model of PfMDR1

Science . 2024 Nov 29;386(6725):eadk9893. doi: 10.1126/science.adk9893. Epub 2024 Nov 29.

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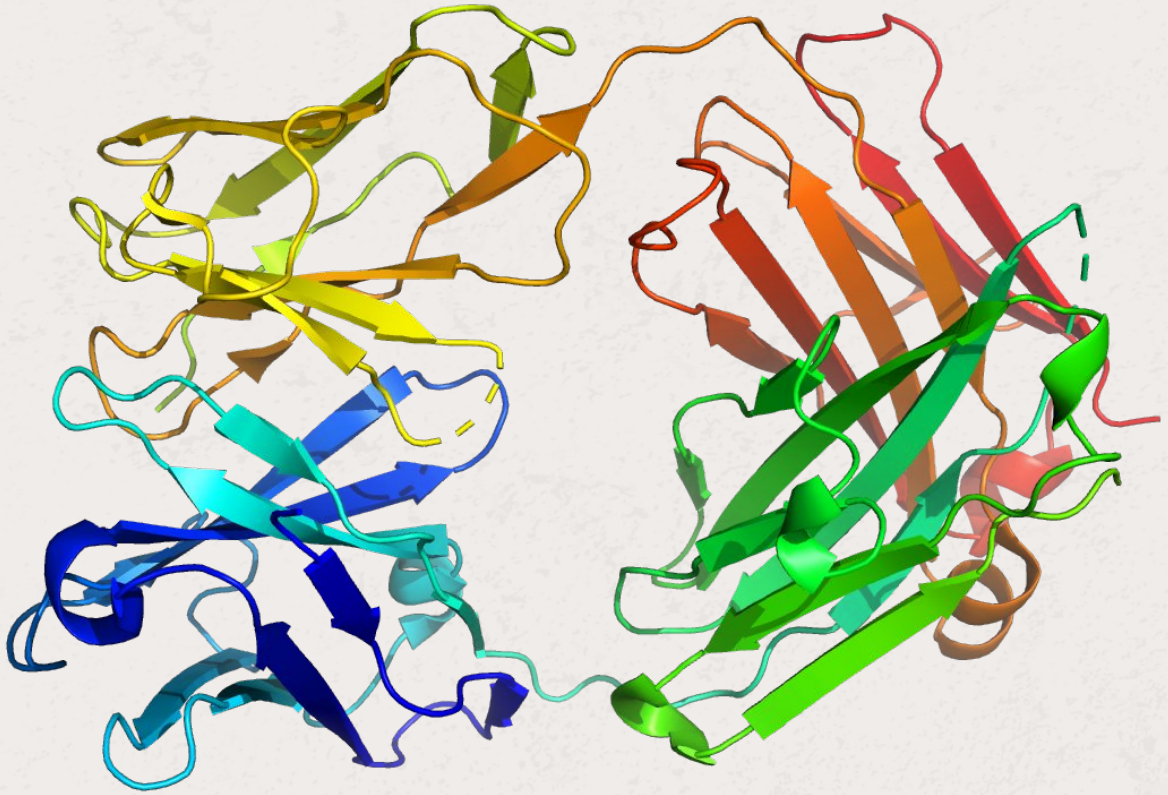
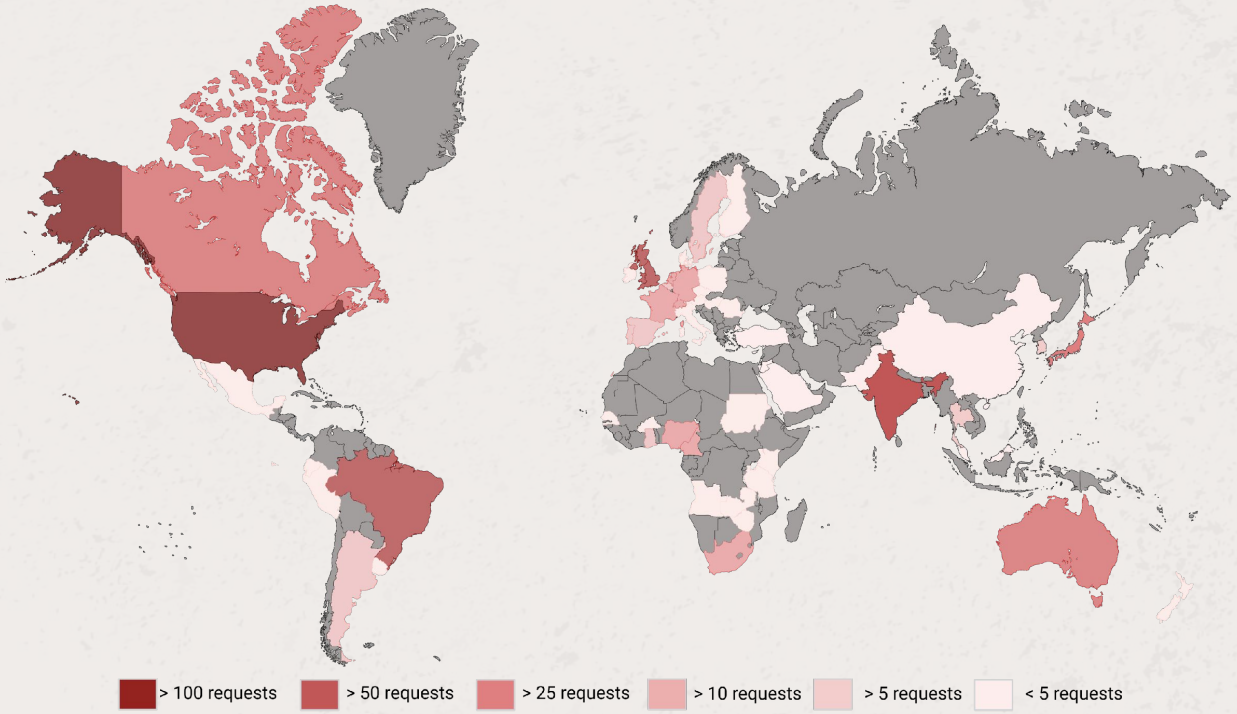
New biological modalities

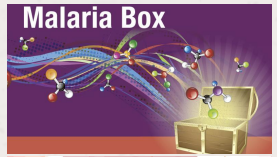


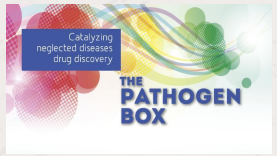
Cryo-EM structure of an essential Plasmodium vivax invasion complex
Gruszczyk J, Huang RK, Chan LJ, Menant S, Hong C, Murphy JM, Mok YF, Griffin MDW, Pearson RD, Wong W, Cowman AF, Yu Z, Tham WH. *Nature* (2018) **559** p.135-139

6BPB: Plasmodium vivax invasion blocking monoclonal antibody 4F7

MMV Open Access Strategy







Hit Generation Libraries

HGL1, 2, 3, 4...

MMVoi open innovation

MMV OPEN

Research

Discovery

Early development

Malaria inhibitor prediction EMBL

dd4gh deepmirror

MMVFree

MMVSola

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CDD Vault African Program

Training & support provided:

- Ensures adoption and long-term sustainability

Focus diseases:

- Malaria, TB, leishmaniasis, and other regionally relevant threats

Objectives:

- Improves data management and **collaboration**
- Modernizes data management of African research labs
- Secure, private, hosted, R&D digital platform: CDD Vault
- Enables data-driven decision-making
- **Data is AI ready AI module available**

25+ groups involved: Growing network of empowered, connected researchers

Join the program at:

https://info.collaborativedrug.com/Africa-access

MMV Medicines for Malaria Venture

AI and pharmacometrics computational pipeline

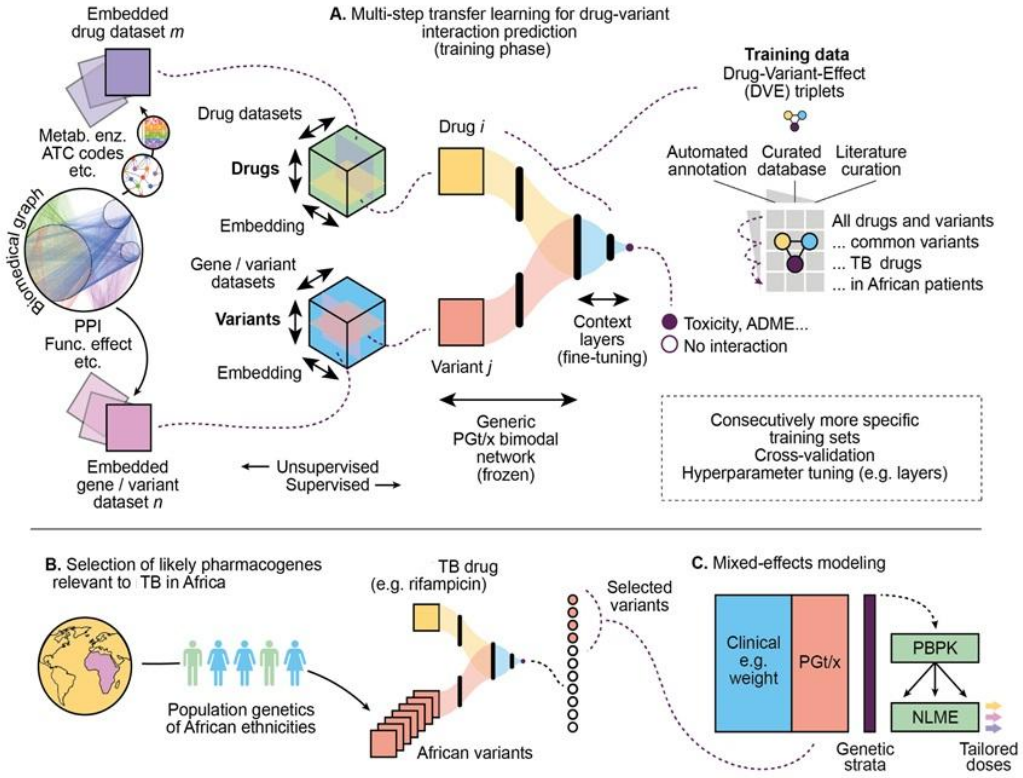
Data harmonization (Knowledge Graph)

KG embedding

AI/ML training

African population genetics virtual screening

PBPK / NLME modeling



- AI-predicted African specific or abundant gene variants involved in metabolism of malaria & tuberculosis drugs.
- To facilitate for building of physiologically based pharmacokinetic (PBPK) models incorporating effects of gene variants

https://www.medrxiv.org/content/10.1101/2024.11.07.24316884v1

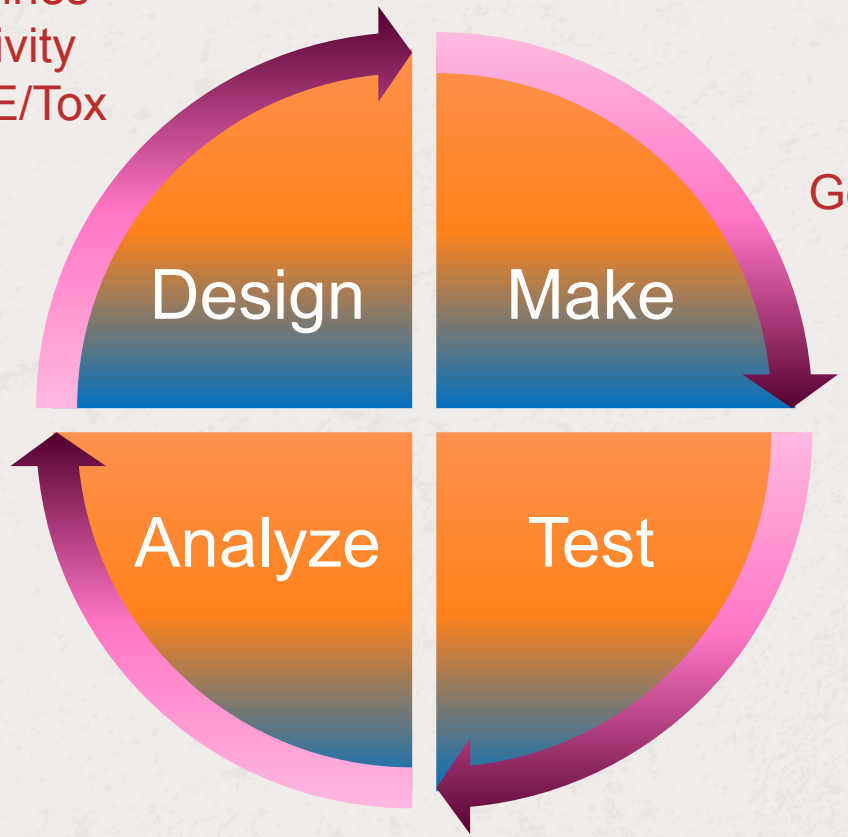
AI Impact

Design *with strategy*

Ideas generation is where AI shines
Virtual Docking to evaluate activity
Predict properties such as ADME/Tox

Make *useful priorities*

Prioritize compounds that matter
not just those that are easy
Assess synthetic feasibility
Generate compounds that bring light



Analyze *to learn*

Confirm hypothesis & predictions
Uncover insights hidden in complex
Multi-modal data
Improve modeling

Test *for relevance*

Evaluate key parameters
Optimize assays cascade
Identify patterns of secondary impacts
Reduce noise

AI has the potential to accelerate the full DMTA cycle

Pharmacogenomics

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AI Initiatives

Malaria inhibitor prediction

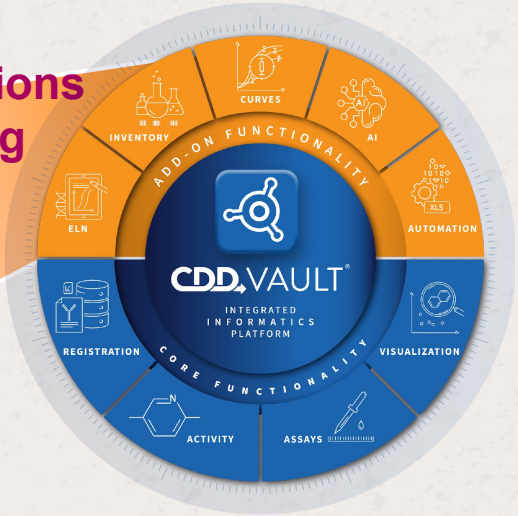
EMBL

dd4gh

deepmirror

AI: Malaria Activity prediction
AI/ML: Modelling data
AI/ML: Drug design
AI/ML: Active learning

AI: Ideas generation
AI: Bioisosteric suggestions
AI+: Predictive Folding
AI+ Ligand Docking

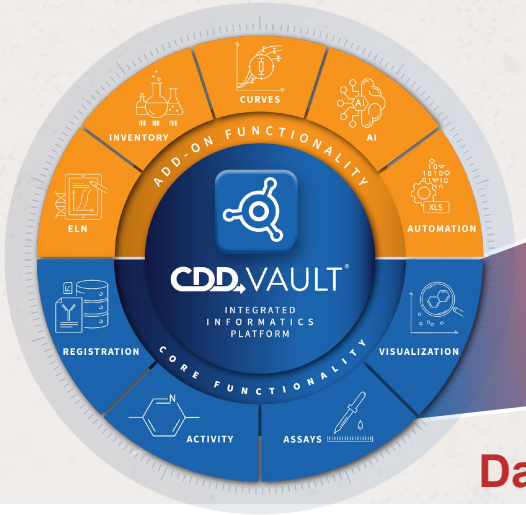


Design

Make

Test

Analyze



Assay classification
Data analysis
Pattern recognition
Data structure & storage

AI: Dose to man prediction
AI: Early dose simulation – unbound potency

MMVSola

MMVFree

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Importance of R&D in Africa

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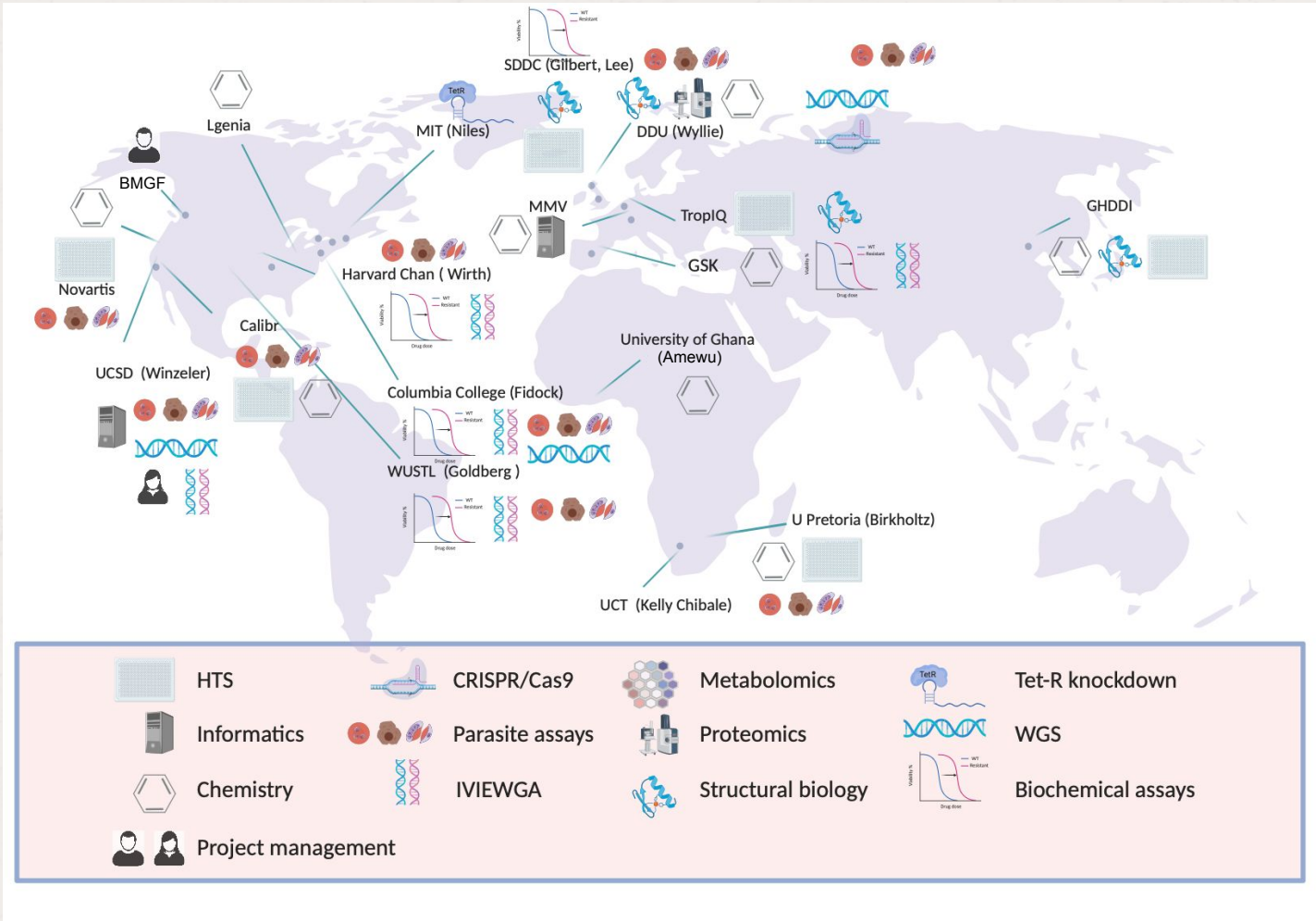
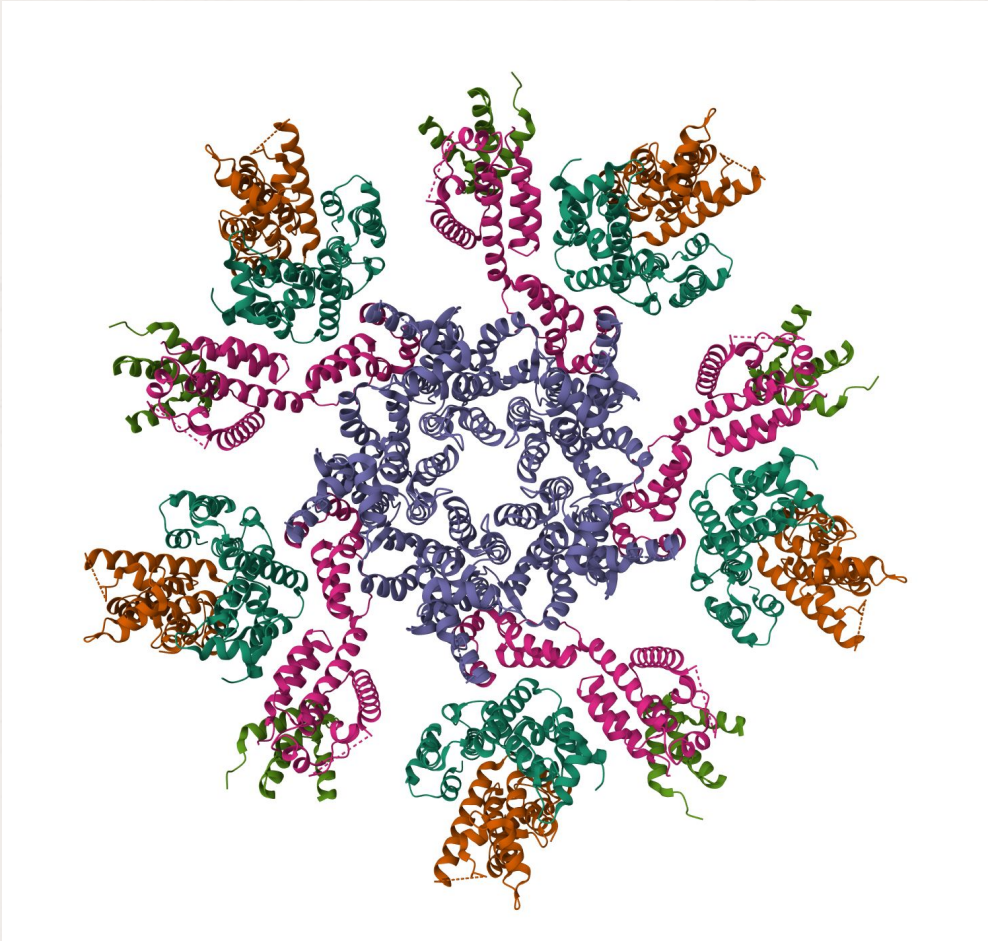
Collaboration



Members of the Malaria Drug Accelerator Consortium (MalDA)

Future directions



(2022) mBio **13**: e0180422-e0180422. Lencapavir bound to HIV capsid

Photographer: Natalia Szczygielska