Leveraging data to maximize the global health impact of MMV's assets

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↖ Scientist using computer application

Exploring new approaches to R&D

Changes in the way potential new medicines are identified and optimized have dramatically increased both the number and the diversity of molecules in MMV's early development portfolio.[1] MMV and our partners are exploring new artificial intelligence[2] (AI)-based approaches to better focus our efforts. We are also harnessing open innovation to advance global health priorities by giving scientists free access to data and materials, encouraging them to make results publicly available so they can build on one another's work.

Using AI to streamline optimization of new compounds

Researchers must sift through vast datasets to identify promising new molecules and biological targets (proteins on which a medicine is meant to act), and AI has the potential to greatly facilitate this task.

MMV is partnering with a wide range of AI researchers and companies to design compound libraries for screening against prioritized targets, identify promising starting points (called hits) with the desired activity on their targets, and modify the most promising compounds to improve their drug-like properties[3] (called lead optimization). In each case, the partnership is enabling the company to propose a small number of compounds that MMV can then make and test. This helps to validate the new technology, as well as providing an efficient way to design new compounds.

Using AI to identify patterns from existing chemical and associated biological data, the European Bioinformatics Institute (EBI), in collaboration with MMV and partners, developed an *in silico*[4] model – the first in antimalarial drug discovery – to predict a molecule's potential blood-stage activity against malaria. This model is now publicly available[5] through the malaria inhibitor prediction platform.[6,7]

The AlphaFold database of 3D protein structures from DeepMind and EBI[8] now includes AI-predicted structures for various *Plasmodium* biological targets, a potential game changer already being used in MMV's target-based projects. For phenotypic drug discovery,[9] which is based on cell biology data and does not need an identified target, our partners at Novartis have developed an impressive model,

> AI works best when there are a lot of data, and MMV has a lot of antimalarial data. Our partners know that if their technology finds exciting new molecules, we can talk about the results openly, and that is a real advantage for them.
>
> — **Benoît Laleu**, Associate Director of Drug Discovery, MMV

1. Burrows JN *et al.* "New developments in anti-malarial target candidate and product profiles" *Malar J.* 16(1):26 (2017), doi: 10.1186/s12936-016-1675-x. Erratum in: *Malar J.* 16(1):151 (2017).
2. Artificial intelligence: a branch of computer science encompassing machine learning and deep learning, as well as natural language processing and image recognition.
3. Physical and chemical properties (e.g., solubility, permeability, metabolic stability and transporter effects) suggesting that a compound is likely to have acceptable toxicity and absorption, distribution, metabolism and elimination (ADME) profiles.
4. Conducted or produced by means of computer modelling.
5. Available at https://www.ebi.ac.uk/chembl/maip/
6. Verras A *et al.* "Shared Consensus Machine Learning Models for Predicting Blood Stage Malaria Inhibition" *J Chem Inf Model.* 57(3):445–53 (2017), doi: 10.1021/acs.jcim.6b00572
7. Bosc N *et al.* "MAIP: a web service for predicting blood-stage malaria inhibitors" *J Cheminform.* 13(1):13 (2021), doi: 10.1186/s13321-021-00487-2
8. This database includes more than 200 million 3-dimensional protein structures predicted by AI based on amino acid sequences.
9. Phenotypic screening is a drug discovery strategy for identifying molecules that can alter a cell's observable features (phenotype). See Martin EJ & Jansen JM "Biased Diversity for Effective Virtual Screening" *J. Chem. Inf. Model.* 60(9):4116-19 (2020), doi: 10.1021/acs.jcim.9b01155

called pQSAR,[10] that can predict activity based on data from other compounds in their vast database. We are considering using this and other data-informed models to design our next screening library, which should enrich it with compounds active against malaria.

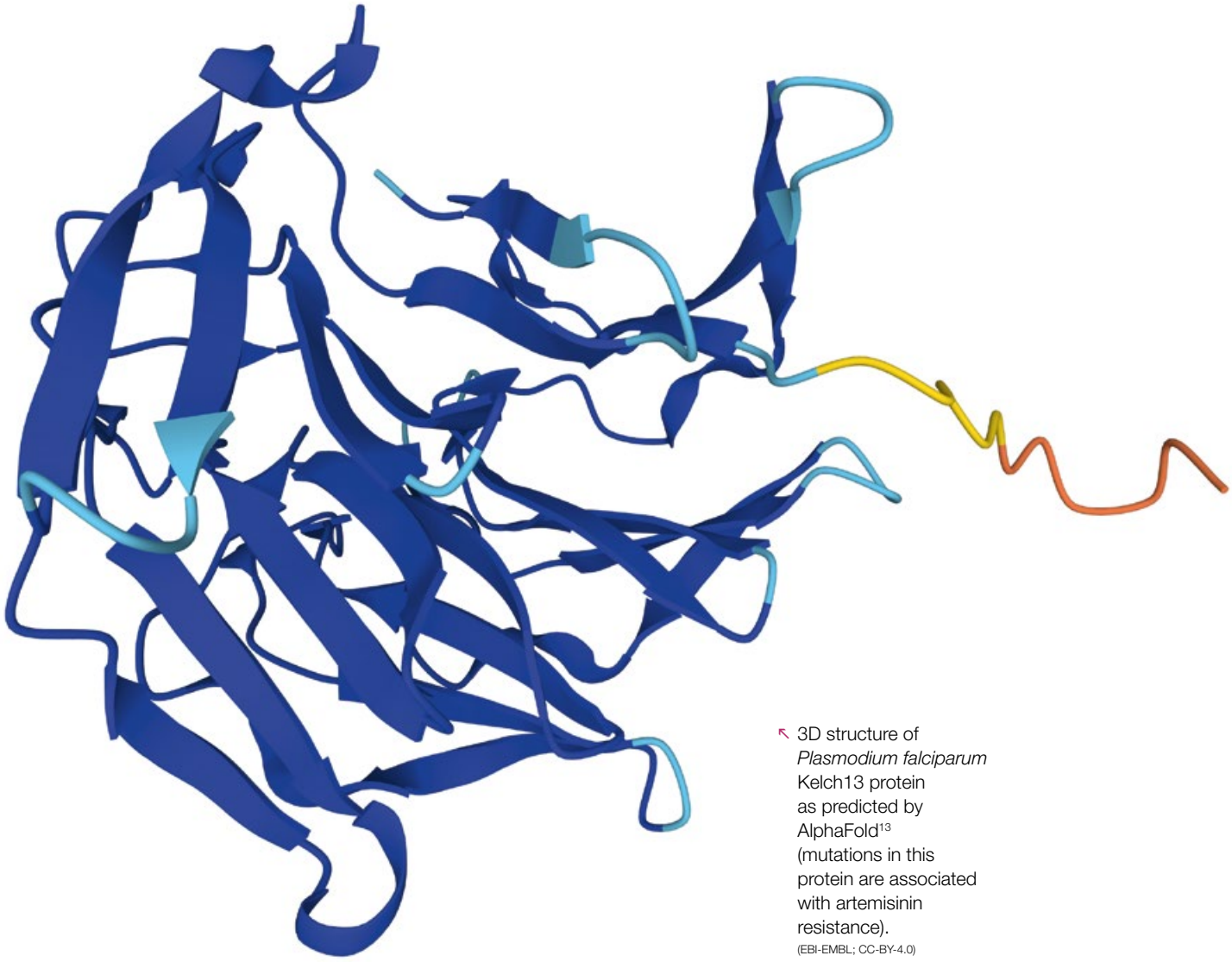
We are partnering with the Bill & Melinda Gates Foundation on two hit identification projects. San Francisco-based Atomwise used neural networks to model five malaria proteins that MMV prioritized as biological targets, then used proprietary algorithms to find the best fits for each amongst some 16 billion compounds: 72 candidates were identified for testing. Exscientia, a company based on technology developed by our partners at Dundee University, is using its algorithms to detect bispecific antimalarials. These compounds act on two distinct molecular targets, reducing the likelihood of selecting a resistant parasite. This is a very challenging but extremely exciting possibility, which would overcome the Achilles' heel of compounds designed for a single target.

MMV has been partnering with Schrödinger, a leader in development of state-of-the-art chemical simulation software, for several years. Their data-informed models allow scaffold-hopping (moving from one chemical series to another based on structural information) to enable new ways of thinking.

In November 2022, MMV and the generative modelling company Iktos announced a partnership to apply their new DockAI technology[11] to deliver novel hit compounds using a molecular target we identified.

In another new collaboration, the Ersilia Open Source Initiative, a tech non-profit organization supporting research in low- and middle-income countries,[12] is using open-source AI to speed up antimalarial drug discovery. This will be our first AI collaboration intended to be led by African scientists – hopefully the first of many.

> Ersilia is leveraging MMV's data on new antimalarial candidates to build AI models, and is fostering innovation and AI development from within the African continent by partnering with research institutions like the Holistic Drug Discovery and Development (H3D) Centre in Cape Town, which is training local scientists in the use of AI tools. H3D now has a local AI expert, whom we trained, who takes care of the use, implementation and development of new models.
>
> — **Dr Gemma Turon**, CEO, Ersilia Open Source Initiative



↖ 3D structure of *Plasmodium falciparum* Kelch13 protein as predicted by AlphaFold[13] (mutations in this protein are associated with artemisinin resistance).
(EBI-EMBL; CC-BY-4.0)

10. Martin EJ *et al.* "All-Assay-Max2 pQSAR: Activity Predictions as Accurate as Four-Concentration IC_{50}s for 8558 Novartis Assays" *J Chem Inf Model.* 59(10):4450-59 (2019), doi: 10.1021/acs.jcim.9b00375
11. For ultra-large-scale combined with cloud-based high-performance computing (HPC).
12. See https://www.ersilia.io/
13. Jumper J *et al.* "Highly accurate protein structure prediction with AlphaFold" *Nature* 596:583-89 (2021), doi: 10.1038/s41586-021-03819-2
    Varadi M *et al.* "AlphaFold Protein Structure Database: massively expanding the structural coverage of protein-sequence space with high-accuracy models" *Nucleic Acids Research* 50(D1):D439-44 (2021), doi: 10.1093/mar/kgab1061

↘ Family on the road in Zambia

Launch of the Global Health Priority Box

14. Transmitted from animals to humans.
15. Dr Mary Mader rejoined the ESAC in 2023 after a pause in 2021–2022.

One of the most successful MMV programmes has been the assembly and distribution of standardized high-quality, open-access compound collections, starting with the Malaria Box in 2011. Since then, over 500 boxes have been distributed, resulting in many new drug discovery collaborations and over 200 publications.

On 20 August 2022 (World Mosquito Day), MMV and the Innovative Vector Control Consortium (IVCC) launched the Global Health Priority Box, providing scientists with free access to a collection of 240 compounds with confirmed activity against pathogens and vectors of global concern. The structurally diverse collection contains three sets of 80 compounds in various stages of development:

- Compounds active against drug-resistant malaria, selected by MMV.
- Compounds for screening against neglected and zoonotic[14] diseases and diseases at risk of drug resistance, from a compound library donated by Bristol Myers Squibb.
- Compounds active against vector species, selected with input from IVCC.

The box provides confirmed starting points for the development of tools to combat antimicrobial resistance and communicable diseases, two priorities defined by the World Health Organization in late 2021.

MMV's open source work is highly cost-effective, and has led to the identification of promising compounds to treat cryptosporidiosis, leishmaniasis, toxoplasmosis, trypanosomiasis and drug-resistant candidiasis as well as malaria. ●

> MMV's Open Access collections provide invaluable access to pre-plated sets of compounds together with annotations of their activity, with the aim of facilitating hypothesis testing in target identification and validation. The demand for the prior offerings, including the Malaria Box and Pandemic Response Box, has been very strong, and we are looking forward to seeing the impact of the newest box, the Global Health Priority Box.
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> — **Dr Mary Mader**, Vice-President of Molecular Innovation, Indiana Biosciences Research Institute, and Co-Chair (Discovery), MMV Expert Scientific Advisory Committee[15]

INTERVIEW

Larry Norton, Senior Project Manager, IVCC (UK) and **Dominique Besson**, Associate Director, Discovery Data Research & Development, MMV (Switzerland) discuss the vision and aspirations behind the Global Health Priority Box.

Could you briefly describe the objective of the Global Health Priority Box?

DB: Like other MMVOpen boxes, the Global Health Priority Box is intended to stimulate research on diseases affecting vulnerable populations by granting any scientist in the world free-of-charge access to samples and information to support their research. It's specifically targeting research on vector control, and drug research for malaria and other neglected or zoonotic diseases with a high risk of drug resistance.

What is the vision behind this project?

LN: The goal is to improve collaboration among public and private organizations in developing new tools to combat public health threats, and to improve communication among scientists to speed up research. Emerging resistance to current mosquito and malaria interventions has increased the urgency of finding effective alternatives. A major objective is to spark interest in developing interventions for managing current and future public health threats. The key drivers here are novelty, structure-guided diversity and, for the malaria set, staying away from resistance. This new box was developed not only to stimulate research, but to provide meaningful starting points that could lead to drug discovery programmes to fight diseases that affect the poorest people.

What has it been like to work with MMV?

LN: The Product Development Partnership model that IVCC and MMV share has led to a strong working relationship over the past two decades. By understanding this mutual way of working, we're better able to share relevant knowledge and expertise for addressing the threats of drug and insecticide resistance. Working with MMV on the Global Health Priority Box has been an opportunity to widen and deepen our partnership, and to stimulate innovation among a more diverse group of stakeholders to achieve our common goal of eradicating malaria.

What do you hope this project will achieve?

DB: Our ambition is to stimulate the scientific community's interest and involvement in global health. The box provides an opportunity to reach researchers who might not have been targeted or impacted by our previous MMVOpen boxes. Similarly, we hope that Bristol Myers Squibb's donation might inspire other pharmaceutical partners to propose compound libraries or submit discovery projects to fuel our pipeline. Overall, we believe that this collection will help us identify new partners who can propose novel, interesting ideas or research strategies.