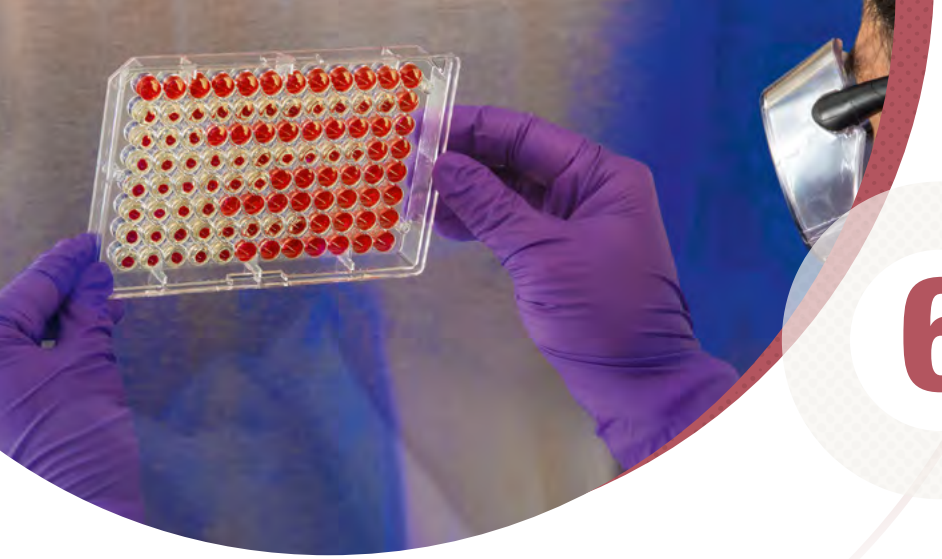

6

New tools for malaria R&D: fast-tracking innovation for case management

Identifying resistance potential and assessing risks early in R&D

For medicines targeting infections, there is a risk that the pathogen will develop resistance, which may lead initially to infections which require a higher dose of medicine to treat, and ultimately the failure of the drug. This is true for many malaria medicines: over the years, the use of chloroquine, mefloquine and amodiaquine monotherapies eventually led to resistance, and their withdrawal in many countries.

Artemisinin combination therapies were designed to reduce the risk of resistance arising to any one drug. However, in 2008, patients with increased parasite clearance times were detected in Western Cambodia.[1] The mutations in the parasite causing this shift were found to be concentrated in the Kelch 13[2] gene. Artemisinin-based combination therapies (ACTs) were shown to be still active, provided there was no partner drug resistance.

New Kelch 13 mutations have now been reported in Africa, some of which are similar to those mutations reported in Asia. There have also been reports of delayed parasite clearance times. On the positive side, ACTs are still reported as being effective in treating malaria patients in Africa, provided there is no resistance to the partner drug.

Fortunately, to date no resistance has been reported in patients or *in vitro* to lumefantrine or pyronaridine. However, to counter this growing resistance risk, it is vital that researchers discover and develop antimalarial compounds with new mechanisms of action and high barriers to resistance. The risk with any compound where resistance can be easily selected is that they will fail early after launch, as illustrated by sulfadoxine-pyrimethamine, which failed as a treatment within a year of launch due to resistance.

Fortunately, as mentioned in chapter 4 (p. 18), MMV has traditionally focused on compounds which showed little propensity for resistance – and we are increasing our focus on this type of molecule. So, the hunt is on to discover and develop 'irresistible' compounds, where resistance cannot be selected either *in vitro* (when tested against a billion parasites) and where no resistance is seen in early clinical studies.

Innovative drug research programmes are carefully designed and strive to progress compounds with promising properties that do not present an unmanageable susceptibility to select for resistance. To identify and prioritize these compounds is a perpetual challenge. A full and early understanding of both a drug candidate's propensity to select for resistance and the possibility that this could translate into the drug's clinical failure down the line is imperative. This assessment of the parasite's genome and a drug's sensitivity (in both cases to a specific compound) immediately gives comprehensive information on whether drug resistance is a significant risk for the future and, thus, which partner drugs would be most suitable within a combination.

1 Evidence of Artemisinin-Resistant Malaria in Western Cambodia: https://www.nejm.org/doi/full/10.1056/nejmc0805011
2 Kelch 13 gene are strongly associated with artemisinin resistance as defined by a ring-stage assay *in vitro* and delayed clearance in patients from southeast Asia.

MMV's new predictive strategy to identify potential resistance risks

In May 2021, MMV published[3] a new strategy illustrating a cost-effective approach for identifying and quantifying the risk of resistance in malaria drug discovery and drug development. This approach, with tests standardized across all projects, helps to characterize the resistance risk of candidate drugs and identify the optimum combination strategy to further reduce the potential of drug resistance to develop in the clinic.

"The guiding principle was to develop an assessment tool that could integrate data from across different parasitology platforms and studies to help predict the intrinsic risk of resistance emerging in patients, if not properly managed, and most importantly, its potential impact on clinical efficacy."

Lead author of the publication, **Dr Didier Leroy**, Senior Director Drug Discovery, MMV.

This predictive tool was the outcome of a discovery project, led by Prof. David Fidock at Columbia University, USA, that focused on profiling potential new antimalarials in the laboratory to determine their propensity to select for resistance and characterizing such resistance to ascertain their suitability for further R&D. The project was awarded MMV's Project of the Year 2020.

The impact of this project on MMV's portfolio has been significant. This approach, including the use of genetic and genomic studies, has enhanced the understanding of resistance mechanisms and this information has, in turn, helped elucidate drug modes of action. As a consequence, over the past 11 years, the team has profiled over 215 compounds from MMV and partners and contributed to the discovery of over 20 new modes of action and resistance.

Guided by the 'triangle of resistance'

The predictive tool relies on three pillars: the clinical outcome of resistance to the drug (successful treatment vs therapeutic failure), the genotyping of the recrudescing parasites, and the *in vitro* study of their sensitivity to the drug. This helps to build an understanding of the factors leading to clinical failure and, specifically, whether such failure is due to resistance or other factors, such as insufficient drug exposure. Verification of this triangle is vital before concluding that a clinical trial failure is due to resistance.

Advantages of a predictive tool

An early understanding of how candidate compounds lose efficacy as parasites evolve resistance will help the prioritization of candidate drugs and future drug targets, inform the necessary combination strategy, improve resistance detection in the field, and potentially help future drug design. If the analysis shows a significant and unacceptable risk of resistance this will allow early decisions to stop or deprioritize a compound/series.

The tool also presents a major advantage in terms of optimizing resources and accelerating research, with a focus on prioritizing the development of compounds that demonstrate a low risk of resistance generation and spread.

3 Assessing risks of *Plasmodium falciparum* resistance to select next-generation antimalarials: https://www.cell.com/trends/parasitology/fulltext/S1471-4922(21)00086-6

Malaria *Libre*: open collaborative science to accelerate drug discovery

With the launch of MMV Open with our partners in 2010, MMV initiated a further evolution in malaria research through sharing data in the public domain. Over 200 groups benefited from the first iteration of MMV Open through the receipt of the Malaria Box that provided access to a set of compounds that drove the development of new medicines for malaria and other infectious diseases, resulting in new drug discovery projects and ideas. By opening the door to global research collaboration, MMV is making access to compounds and research tools more equitable, and transforming innovation.

Malaria *Libre*, a more recent project under the umbrella of MMV Open's collaborative drug discovery, enables participants to share the structures of any molecules being made, as well as the results in biological assays. Anyone can contribute their ideas, time and resources, resulting in virtual team building for drug discovery projects. Malaria *Libre* can be compared to open-source software development, but for drug discovery.

Malaria *Libre*'s scientific activities take place in the participants' laboratories, and results are shared in open forum discussions and meetings. The in-kind and intellectual contributions of researchers from around the globe include synthesizing compounds or running biological assays to discover preclinical candidates for malaria treatment and prevention.[4] An open repository of chemical structures and corresponding data is available on MMV's website for researchers to view, build on and share their own data. The repository is updated regularly as the project advances.

Based in India, where malaria is endemic, Malaria *Libre* is a prime example of how excellent research groups working in different geographies without any legally binding agreement are able to contribute to real-time collaborative research, with the goal of identifying the first-ever preclinical candidate for malaria from an open-source project. The programme not only engages participants in a live global drug discovery project but also provides a platform to contribute ideas and share analyses in transparent discussions led by MMV scientists under the guidance of MMV's Expert Scientific Committee. This project also provides opportunities for development and mentoring, especially for next-generation drug discovery scientists in malaria-endemic countries.

4 Participants include CSIR-Central Drug Research Institute, the Special Centre for Molecular Medicine at Jawaharlal Nehru University, and TCG Lifesciences in India, as well as research organizations from Australia, Brazil, South Africa, Uruguay and USA. Monash University, University of São Paulo, University of Stellenbosch, Universidad de la Republica | Montevideo, Massachusetts College of Pharmacy and Health Sciences, and Drexel University that have contributed with lab work.

INTERVIEW

Dr Kirandeep Samby, MMV Open project leader, MMV, discusses MMV's open drug discovery initiatives in India.

Why are MMV Open and Malaria *Libre* considered pioneering approaches to drug discovery?

"Open collaboration in research, especially drug discovery, is relatively rare. The advantages are many: researchers collaborating from diverse fields can bring in skills, expertise and facilities, adding immense value to the project. It saves us from reinventing the wheel – for example, it is quite possible that an issue faced in the project has already been addressed and solved by other researchers and their learning can be immediately shared and implemented, thus saving time and resources.

What is your role within MMV Open/Malaria *Libre*?

"I am a PhD medicinal chemist with over 20 years of experience, and joined MMV in 2018 to work on MMV Open. I am responsible for building research networks for malaria, particularly in the context of testing MMV compounds such as Open Access Boxes on non-malaria pathogens for other infectious diseases. I am currently leading the Malaria *Libre* project, helping to build both the scientific body of knowledge on malaria drug discovery as well as a strong open science community.

How does the open science of Malaria *Libre* fulfil its aim?

"The primary aim is to identify a preclinical candidate. In parallel, we are working to build a strong community of next-generation drug discovery scientists committed to collaboration and open sharing of ideas and data. This open approach helps save time and resources. For example, based on the mode of action of a frontrunner compound confirmed by groups at Monash University, Drexel University and Jawaharlal Nehru University (JNU), the team decided to defer medicinal chemistry work on a series until more parasitology data was generated, especially on the propensity to generate resistance that would enable a decision to stop or go ahead with the series.

What has Malaria *Libre* achieved so far and when could it deliver a preclinical candidate to advance into antimalarial research?

"Malaria *Libre* is still at an early hit-to-lead stage, where the hits identified from phenotypic screening are being optimized to identify promising lead compounds. So far, we have been able to build a network of collaborators who have proactively contributed to the project, despite a huge shift towards COVID-19 research. We hope to be able to deliver on our primary goal of a preclinical candidate by 2025, if all goes according to plan, but this is an experiment in a new way of working, so that's quite an ambitious goal.

Malaria *Libre* is operating out of India and working with several partners across the world – what do they contribute to the project?

"India is an important geography for drug research – its drug discovery work boasts a highly competent research community, robust infrastructure and skilled human resources. In India, Malaria *Libre* launched with the participation of researchers from three institutions: CSIR-Central Drug Research Institute to help synthesize compounds, the Special Centre for Molecular Medicine at JNU to conduct parasitology tests, and TCG Lifesciences to conduct the majority of compound screening, primary assays and syntheses. TCG is also engaged in chemistry work for other MMV projects. Other groups at Monash, Drexel and University of São Paulo have contributed to target deconvolution of the hits that are worked upon and other groups have supported medicinal chemistry. These have been made as in-kind contributions. The project team also has access to all the assay platforms that support the project progression.

Does MMV have experience in empowering drug discovery research in other disease areas?

"The compound licensed out to Merck from Salvensis[5] for preclinical development against schistosomiasis had its origin in one of the MMV Open libraries. In addition, hit compounds identified through screening of open-access compound collections are taken through iterative 'make-test-analyse' cycles that design drug candidates for other neglected diseases, like tuberculosis and Chagas.

What's next for MMV Open?

"We are anticipating the launch of the Global Health Priority Box (GHPB) in the second half of 2022 in collaboration with the Innovative Vector Control Consortium and Bristol Myers Squibb. Like the previous Open Access Boxes, the GHPB will comprise compounds that have shown promise against malaria or other neglected diseases or for vector control. It will be available free of charge to researchers with the only stipulation that their research is posted in the public domain. Meanwhile, we remain focused on identifying a high-quality preclinical candidate by 2025.

5 A not-for-profit, small molecule drug discovery company with a focus on rare and neglected diseases.

"We hope to be able to deliver on our primary goal of a preclinical candidate by 2025."