



# Selecting the best combinations: pioneering developments to accelerate R&D

Innovation is critical to achieving Medicines for Malaria Venture's (MMV's) long-term goal of eradicating malaria, and therefore it is our priority to create tools that accelerate the research and development of new antimalarial drugs.

## Malaria Drug Development Catalyst

Successful drug discovery efforts over the last decade mean that MMV and partners now have an increasing portfolio of new drug candidates. To achieve optimal efficacy and reduce the chance of resistance emerging to antimalarial medicines, it is important that they are administered as combination therapies. Ideally, the drugs within these combinations should be complementary in terms of their antimalarial activity and when they are active in the body after administration. Additionally, these drugs should be well tolerated when given together and, preferably, not show signs of generating resistant parasites in laboratory conditions.

At MMV, understanding how different preclinical candidate molecules interact is a crucial, complex and extensive process that allows us to identify the best drug combinations for further development. It is important that all combinations are reviewed through the same lens. In 2019, MMV launched the Malaria Drug Development Catalyst – a scientific platform that helps to provide that lens and promote collaboration between industry partners to accelerate the development of next-generation drug combinations for uncomplicated malaria (Figure 3). The Catalyst is both curated and led by MMV and assesses single molecules that have entered translational development. Through the Catalyst, MMV provides funding and preclinical data (pharmacological assays, pharmacokinetic models and assessments of safety and tolerability), thereby accelerating decision-making

for combination partners. Decisions are based on the complementary characteristics of the drug candidates, irrespective of who owns the compounds. The Catalyst also opens a dialogue between MMV's industry partners, helping to promote the exchange of knowledge and increase the efficiency of drug development. Ultimately, the aim of MMV's Malaria Drug Development Catalyst is to support the identification and progression of the best drug combinations for clinical testing, enabling members to optimize and de-risk their clinical development plans. This helps to get lifesaving medicines to patients whilst making the best use of the resources available.

The Catalyst is open to all of MMV's pharmaceutical partners with drugs within 12 months of entering Phase I studies. In 2019, Merck, Novartis, and Zydus Cadila joined the platform with their respective assets. Shin Poong Pharmaceuticals joined in 2020 and Sanofi is currently an observer. In July of 2020, MMV's Expert Scientific Advisory Committee endorsed a strategy to progress lead combinations, identified from data generated under Catalyst activities, into the clinic. Entry into Phase II is projected for 2022. Future Catalyst research will include more recently approved preclinical candidates, many of which are completely refractory to resistance selection in the laboratory, including compounds from MMV, Novartis and GlaxoSmithKline, along with new candidates approved by MMV's Expert Scientific Advisory Committee in 2020.

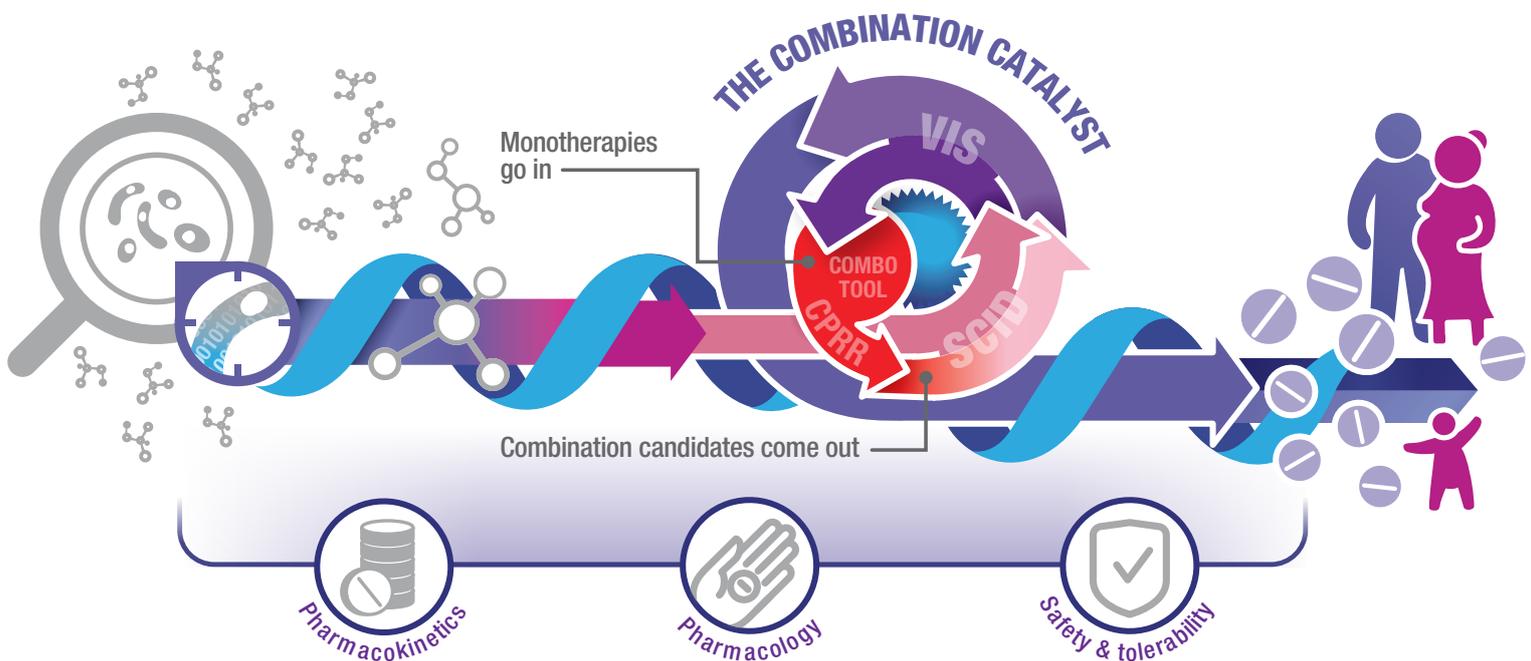
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Figure 3: Malaria Drug Development Catalyst

**1** Hit identification  
 and optimization

**2** Translational science  
 & experimental medicine

**3** Clinical validation



**VIS:** volunteer infection studies / **SCID:** a laboratory model of malaria that provides a prediction of drug response in humans / **CPRR:** *in vitro* checkerboard assays

- 1 The methods and use of models for disease and pharmacological measurement.
- 2 A laboratory process that is not conducted in a living organism.

## ACPR28 modelling for combinations

Antimalarial drugs can be combined to increase efficacy, delay resistance and prolong their clinical utility, but how can we better understand how individual drugs will interact when administered together? The World Health Organization (WHO) and regulatory authorities assess drug combinations by looking at the number of people who achieve an adequate clinical and parasitological response 28 days from the start of treatment (ACPR28). For a drug to be approved,  $\geq 95\%$  of patients must achieve ACPR28. To help MMV decide which drug combinations have such potential, pharmacometric<sup>1</sup> scientists use *in vitro*<sup>2</sup> experiments, laboratory models and clinical trials.

Mathematical models are built from this data to characterize drug combinations and predict the drug dose required. This information helps MMV and partners make decisions driven by data, prioritizing combinations that can feasibly be combined to reach the required target efficacy. These predictive models are becoming an important tool for efficiently identifying new antimalarial drug combinations. For example, in 2020, ACPR28 modelling was successfully used by MMV's Malaria Drug Development Catalyst to analyse and rank six drug combinations. Notably, this helped prioritize four promising combinations, saving resources and time.

INTERVIEW



**Dr Nathalie Gobeau**  
Director of  
Pharmacometrics, MMV

**Dr Nathalie Gobeau discusses the use of ACPR28 modelling in investigating antimalarial drug combinations.**

**Why do we need these new modelling tools? What are their advantages and what challenges do they help us overcome?**

“The new mathematical model we have developed allows us to predict how combinations may behave in patients before clinical trials, which would be much more expensive than establishing and running a model. These models enable us to incorporate all the knowledge available on compounds from different sources and predict the clinical outcome. Based on simulations for six combinations, four are being progressed to clinical trials. We hope that these tools will help select the most promising combinations for further development.

**Who did MMV partner with to develop them?**

“We worked with the mathematical modelling company IntiQuan based in Basel, Switzerland, to develop our algorithm, with additional support from Daniel Lill, a student from the University of Freiburg, Germany. We built our pharmacokinetic/pharmacodynamic models in collaboration with Prof. Sebastian Wicha from the University of Hamburg. To obtain information on the pharmacological interaction, Claudia Demarta-Gatsi from the MMV team worked closely with the Swiss Tropical and Public Health Institute to set up *in vitro* assays, and with The Art of Discovery in Spain to set up laboratory experiments.

**Now that you and your team have developed these tools, what are the next projects in the pipeline?**

“In the future, we aim to look at combinations of three or more compounds using similar models. This would allow us to explore the combination of additional characteristics in one medicine, such as transmission-blocking and parasite clearance. We would also like to extend the model to look at chemoprophylaxis.



- 3 <https://www.mmvsola.org/>
- 4 Duration of activity of the drug in the body.
- 5 The biochemical and physiological effects of drugs in the body.

## MMVSola: the science of predicting compound power

In 2020, MMV developed the innovative, free, user-friendly application 'MMVSola'.<sup>3</sup> MMVSola combines information on the chemical, physical and biological properties of a compound to predict the human dosage required to clear all malaria parasites from a patient. It uses state-of-the-art mathematical modelling to consolidate data from different preclinical experiments, seamlessly translating the results into predictions on the clinical activity of different drug candidates in humans. This means that, for the first time, an accessible application can be used to predict dosing

and treatment durations for potential antimalarial candidates as early as the discovery phase. This helps identify the best possible candidates, and design better and more informative clinical trials. It also removes the need for animal efficacy studies, saving crucial resources, reducing animal usage and expediting drug development timelines. MMVSola will also help standardize malaria drug discovery data, so that laboratories can collaborate more effectively. MMVSola is a powerful and innovative tool, which can be used to select drug candidates and transform early drug development.

INTERVIEW



**Dr Stephen Brand**  
Associate Director of Drug Discovery, MMV

**Dr Stephen Brand discusses the MMVSola project.**

### Could you briefly introduce us to MMVSola?

“MMVSola is a free, web-based tool based on a well-established methodology developed by MMV and launched in 2020. It performs human exposure and dose predictions for antimalarial compounds using preclinical data. We have specific dose and parasite-reduction criteria for our clinical candidates – aiming for a single-dose combination treatment of less than a gram to cure a typical adult. MMVSola allows teams to confirm compounds are in line with these criteria from the early discovery stages and, if not, identifies which of the compound properties are best to focus optimization on. Beyond malaria drug discovery, MMVSola’s human pharmacokinetic prediction capability can be freely used for drug discovery in any other therapeutic area.

### What are the main advantages of MMVSola?

“The tool allows researchers to take early (and limited) data and perform a preliminary estimation of the efficacious dose in humans by the discovery teams without the need for an expert. As predictions are made using *in vitro* and limited animal data, MMVSola can be used early, before investing in expensive and time-consuming experiments. It also identifies key compound properties for further development during the lead optimization phase, including potency, metabolism and protein binding. By using this tool for all our discovery projects, we also aim to standardize the comparison of compounds across projects.

### Where does the name MMVSola come from and who did you partner with to develop it?

“MMVSola was named to commemorate Suresh Solapure, who tragically passed away recently and was an early champion of using pharmacokinetic<sup>4</sup>/pharmacodynamic<sup>5</sup> modelling to predict dosage at MMV. He also contributed to the discovery and development of one of our key candidates (ZY19489 – Zydus Cadila, p. 16). For the pharmacokinetic aspects of the tool, we partnered with Peter Webborn (an independent pharmacokinetic consultant) to develop our predictions of human exposure using well-established and robust methodology. For pharmacodynamic modelling and tool construction, we worked with Ghaith Aljayoussi (Liverpool School of Tropical Medicine, UK), who also developed the *in vitro* methodology, which replaces animal efficacy studies. Key members of the MMV modelling team were Nathalie Gobeau, Aline Fuchs and Mohammed Cherkaoui, who supported Ghaith and validated the methodology.

### Now that you and your team have developed this tool, what are the next projects in the pipeline?

“We will now focus on further developing the tool and creating new capabilities. We are aiming to use real-world pharmacokinetic/pharmacodynamic population data to enable predictions for ACPR28 and, importantly, to predict a dose in children and a dose for prophylaxis. We are also providing continuous support to users of the tool and working towards publishing this work.