The Malaria Drug Development Catalyst: accelerating R&D for drug combinations

To minimize the risk of drug resistance when developing antimalarial treatments, two compounds with complementary properties are paired up to form a combination therapy. The rationale behind this is that each compound can protect the other and therefore resistance generation is delayed. With 15 candidate compounds currently in preclinical and clinical development, understanding how these different compounds interact in order to select the best combinations for further development is a complex and critical process.

In 2019, MMV launched the Malaria Drug Development Catalyst – a new legal and scientific platform to promote effective collaboration between industry partners and accelerate the development of next-generation drug combinations. The Catalyst is curated by MMV and contains successful single molecules that have entered translational development. Based on the complementary partner characteristics of the drug candidates, the Catalyst helps to identify the best combinations to take forward for clinical testing and to allow a dialogue and exchange of information between MMV’s partners. This enables faster identification and progression of viable combinations.

The Catalyst is open to MMV’s pharmaceutical partners with drugs in translational development, and currently has four members – Zydus Cadila, Novartis, Merck KGaA and MMV – and of the 30 combinations studied so far, 12 have already demonstrated positive results.

Dr Mukul Jain tells us how the Malaria Drug Development Catalyst is helping to find a combination partner for the promising translational candidate MMV253.

Can you tell us about MMV253’s journey so far?

- MMV253 came out of a discovery partnership between MMV and AstraZeneca in 2014, and was acquired by Zydus in 2016 for non-clinical and clinical development. MMV253 has an exciting profile, rapidly clearing parasites from the blood after a single dose and staying in the blood above the concentration needed to kill parasites for >6 days. The compound has an unknown mechanism of action, is active against both Plasmodium falciparum and Plasmodium vivax, and has shown low resistance potential in in vitro studies. It has also shown a good safety profile in both non-clinical toxicology studies in the lab, as well as in Phase I studies in humans, with no indication currently of potential harm for the developing foetus. This suggests it may be suitable for use during pregnancy.

How is the Malaria Drug Development Catalyst assisting Zydus in the search for a combination partner?

- The Catalyst is a great initiative and we are very excited to be a part of it. Given the promising efficacy and safety data we have gathered from studies conducted so far in healthy volunteers, now is the right time to identify a partner for MMV253 and map out a clinical development strategy. By bringing together industry partners of different sizes and backgrounds, and with candidates at similar stages of development, the Catalyst is helping us identify compatible partners for MMV253. Such collaboration is not always common among the private healthcare sector, so this is a really innovative model.

What has it been like working with MMV?

- No other organization in the world has the same depth of knowledge and expertise in malaria drug development as MMV. At Zydus, being able to tap into MMV’s expertise is a great benefit to us and will hopefully ensure that MMV253 can one day become a treatment option for malaria. Zydus recognizes the need to bring forward new and affordable therapies for malaria, especially for use in highly endemic countries such as India, which currently carries the world’s highest burden of P. vivax malaria.¹

¹ According to the WHO World Malaria Report 2019, 47% of the global P. vivax burden is in India: https://www.who.int/publications-detail/world-malaria-report-2019
Discovering new candidate antimalarial drugs

The discovery of new antimalarial drugs is a lengthy and costly process, typically taking 12 to 15 years from early discovery activities to the point when the drug is available to patients. MMV’s Discovery team is small, but through collaboration with centres of excellence around the world, huge progress has been made in delivering high-quality antimalarial candidates. To date, over seven million compounds have been screened against *P. falciparum* – representing one of the single largest screening campaigns against a pathogenic organism in history, and resulting in the delivery of 24 new candidate drugs. Finding out how these compounds work is important, as they can often lead to new molecular targets and mechanisms. MMV is a founding member of the MaLaria Drug Accelerator (MaLDA) – a network of 13 academic and industry partners funded by the Bill & Melinda Gates Foundation, which is focused on unravelling the mechanisms by which these confirmed antimalarial compounds work, and on delivering lead series acting through such mechanisms into the global portfolio.

Countering the ongoing threat of resistance

MMV’s treasure trove of new candidates eligible for clinical development is a key resource for developing new medicines that would be useful if there were widespread failure of the current artemisinin-based combination therapies (ACTs). However, it is important to maximize the chances that these new molecules are not themselves prone to rapid selection of resistance. In 2019, MMV set up a new ‘resistance workflow’, whereby all new candidate molecules moving forward are routinely profiled for their robustness against resistance in standardized assays. The purpose of this is to allow MMV and its partners to prioritize compounds with a low propensity to select for resistance. MMV’s discovery portfolio currently contains 33 distinct chemical series, 21 with a known mechanism of action, and 12 for which the mechanism is unknown. These latter 12 are particularly interesting, as they are fast killing and not cross resistant; three compounds have been unable to identify resistant mutants when the compounds are incubated with a billion parasites for 60 days in the laboratory (e.g. see pp. 36–37) and the same studies are planned to explore the ‘irresistibility’ of the other nine. It’s important to note, however, that historically, compounds such as artesunate, lumefantrine and pyronaridine also successfully cleared this hurdle.

In 2019, three new compounds entered MMV’s portfolio as preclinical candidates, each with its own unique and interesting profile.

**MMV183**

MMV183 (TropIQ) is the first Dutch antimalarial preclinical candidate, arising from a Netherlands-based discovery consortium set up in 2016 by MMV and Lygature (a Dutch public-private life sciences partnership), and funded by the Dutch government. MMV183 is an anti-metabolite, fast-killing compound with potent transmission-blocking activity and a low predicted oral dose in adults. Preclinical studies are currently underway.

**MMV646**

MMV646 (JPC-3210) is a highly potent compound active against both *P. falciparum* and *P. vivax*. It has demonstrated very low resistance potential *in vitro* and exhibited curative activity after a single dose in SCID models. In 2019, an agreement was signed with Jacobus Pharmaceuticals for further development of MMV646, and preclinical dose-range-finding studies were initiated in December of that year.

**INE963**

INE963, developed in collaboration with Novartis and awarded MMV’s Project of the Year 2019 (pp. 36–37), has an unknown, irresistible mechanism of action, and has demonstrated an ability to rapidly clear parasites from the blood. The compound will now undergo GLP safety studies and will be assessed as a potential combination partner.
As countries move towards elimination of malaria, natural immunity to the parasite will decline and there will be an increasing need for new prophylaxis strategies to ensure populations remain malaria free. Furthermore, there is a critical need to protect vulnerable populations such as children in areas of high seasonal malaria transmission (pp. 21–22).

In an effort to develop new strategies for prophylaxis, MMV is exploring the potential of long-acting injectable formulations. P218, currently in Phase I development, is one such compound currently being explored (in collaboration with Janssen) as a potential long-acting, single-administration, injectable prodrug for prophylaxis. P218 inhibits a well-defined, clinically validated enzyme target, dihydrofolate reductase, and is active against both the blood stage and liver stage of the parasite life cycle.

After a mosquito bite, malaria parasites first enter the liver, where they multiply before entering the blood. Killing the parasite at the liver stage of development can therefore prevent a malaria infection from taking hold, effectively blocking disease progression and preventing the emergence of symptoms. In 2019, P218 demonstrated promising activity in the sporozoite VIS model, designed specifically to assess liver-stage prophylactic activity, in Antwerp, Belgium (further studies are ongoing).

In addition, two prodrugs of atovaquone (MMV370 and MMV371), produced by Calibr, USA, underwent preclinical studies in 2019. Both prodrugs have shown high liver-stage activity in laboratory models, remaining in the blood for a long time after a low-dose injection, and will now undergo further formulation and good laboratory practice safety studies.

MMV at the cutting edge of artificial intelligence: machine learning

MMV recognizes the power of machine learning and Big Data in providing quicker, cheaper and more effective drug discovery solutions. By leveraging artificial intelligence to identify patterns from data sets, MMV has developed an in silico model – the first ever in antimalarial drug discovery – to predict which compounds have potential blood-stage activity against malaria. This model will help to identify which compounds to screen, thus expediting the discovery of blood-stage inhibitors. The tool will soon be made publicly available on ChEMBL, a manually curated chemical database of bioactive molecules with drug-like properties. In addition, MMV has initiated a collaboration with AstraZeneca to explore the impact of machine learning on medicinal chemistry within a drug discovery project.

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Optimizing data management to streamline antimalarial research

MMV’s Discovery team is routinely working on more than 25 research projects, supported by 25 technology platforms. These platforms, which are located all over the world, test very large numbers of compounds to evaluate their activity against different stages of the parasite life cycle. Central to the success of this large-scale research effort is a streamlined system of storing, tracking and dispatching compounds to MMV’s partners, which enables rapid delivery of compounds throughout the world to accelerate drug discovery initiatives. The workflow also generates large volumes of data that must be deposited in a standardized format, stored securely and easily accessed by the relevant teams.

Dominique Besson tells us more about the processes that MMV has put in place to manage the huge quantities of data generated by its partners.

Please tell us about your work as Associate Director, Discovery Data at MMV.

- In the context of a virtual R&D organization like MMV, it is important to ensure homogeneity in the way that data is collected, analyzed and reported. In my role, I have two main responsibilities. Firstly, as a compound manager, I ensure that molecules for testing are available at the right time and are of the right quality. Secondly, as a data manager, I check that the data generated by MMV’s various research partners are comparable, by making sure, for example, that all results are reported in the same standardized units.

Day to day, I have certain ‘preventive’ duties, such as formulating rules, processes and guidelines relating to the database, as well as providing appropriate training to both internal and external end-users. In addition, I have ‘corrective’ duties, such as taking actions to correct processes or workflows whenever MMV’s quality control guidelines are not followed properly.

What tools does MMV use to manage its data?

- MMV’s data repository is called ScienceCloud, which, as its name suggests, is a cloud-based solution developed commercially that stores all data generated by MMV’s research partners. A second tool, the Logistics Management Tool, was developed in-house to help manage compound logistics. Developed initially for tracking compounds internally, the tool will be further modified to grant access to external users to facilitate communication. Both databases are integrated with one another to provide MMV’s discovery and translational teams with up-to-date information on particular compounds or assays.

How do you guarantee the quality of the data you receive?

- MMV’s Discovery team ensures the quality of the data it collects and stores in its database by applying basic rules – defined by the acronym QUARTZ. This internal checklist allows us to confirm that data are:

1) of the expected Quality
2) Useful to the projects
3) Accessible to the end-user
4) Relevant for decision-making
5) Traceable to their origin
6) standardized according to MMV’s guidelines.

If data adhere to these six principles, we can be confident that the data are of an acceptable quality.

What is the importance of databases in research?

- Data are the currency of drug discovery, and MMV’s database is the bank where we save these data. The importance of MMV’s database is that it stores, as well as connects, all chemical and biological information in a single place. When information is well connected, it is possible for a scientist to better understand how modifying the structure of a particular chemical compound is likely to impact its biological activity.

The information kept in a database effectively forms a kind of ‘roadmap’, which explains how and why a particular project reached a particular decision point. It is critical for this information to be easily extractable – and in a format that is useful for specific users. For example, we have developed a specific method of extracting preclinical data from the database, in a format that helps the translational team to predict the human dose of a particular compound. Insights like these are invaluable to the progress of the portfolio.
In the modern era of increased air travel and densely concentrated, interconnected populations, the world is more vulnerable to pandemic diseases than ever before, as seen by the recent and ongoing outbreaks of COVID-19, Ebola, Zika, chikungunya, dengue fever, Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS) and influenza. Now more than ever, new and innovative approaches are urgently needed to mobilize the potential for discovering new drugs to fight global health emergencies.

Under its ethos of ‘openness’, MMV has pioneered several drug discovery initiatives to support R&D efforts in malaria and other neglected tropical diseases. Open-access libraries, such as the Malaria Box, Pathogen Box, Stasis Box, Pandemic Response Box and larger compound collections have catalysed drug discovery research across the globe. These libraries contain drug-like compounds that researchers can use to screen against neglected or pandemic diseases. So far, around 700 of these open-access libraries have been distributed worldwide free of charge, and findings from them have led to over 110 publications, adding significantly to the global scientific knowledge base.

Prof. Lyn-Marie Birkholtz tells us more about her research experience with the Pandemic Response Box.

What made you want to request the Pandemic Response Box?

The Pandemic Response Box is a really exciting tool for a researcher, as it contains compounds with antiviral, antibacterial and antifungal properties. This allows us to identify entirely new targets that we might not otherwise identify from screening only antimalarial compound libraries, with the aim of repurposing these new targets against malaria.

Have you had any success in identifying hits so far?

We have identified a number of hits. Some of them target all stages of the parasite life cycle (we call these ‘pan-reactive hits’), while others appear to target one or more specific stages. We are particularly excited about the stage-specific hits as we have found activity against both the asexual and sexual (gametocyte) blood stages of the life cycle. Targeting gametocytes, the reproductive form of the malaria parasite, would allow us to prevent transmission of parasites back into the mosquito during its next blood meal, effectively breaking the parasite’s life cycle and preventing another cycle of reinfection.

How are you collaborating with the MaLaria Drug Accelerator (MaLDA)?

As part of our testing, we are trying to profile the mechanisms of action of the hits we have identified from the Pandemic Response Box. Some of these compounds already have very well characterized mechanisms of action in other diseases, which certainly helps to focus our research; but other compounds don’t. MaLDA, a network of academic and industry partners, gives us access to drug discovery techniques and resistance screening tools that enable us to profile these compounds much quicker.

In the wider context of malaria eradication, how important is drug discovery in terms of identifying and bringing forward next-generation antimalarial compounds?

We have learnt from the past that we cannot rely on a single approach to achieve eradication. Continued efforts are needed to develop next-generation drugs that not only treat symptomatic patients but can also eliminate the parasite reservoir of asymptomatic patients. We must remain innovative and explore new chemical and biological targets, as well as develop tools to assess and predict the efficacy of compounds as early as possible in the development process.

What has it been like working with MMV?

It has been extraordinary. With MMV’s support, we have been able to accelerate the progress of our discovery initiatives. In South Africa, we have a proud record in antimalarial drug discovery, having brought forward MMV048 with another of MMV’s partners, Prof. Kelly Chibale at the University of Cape Town. It is collaborations like these that have allowed us to come so far, so quickly, in antimalarial drug discovery.