Identifying optimal drug combinations

Developing new antimalarial medicines that can successfully treat the disease and combat drug resistance requires the use of at least two drugs in combination, each with a different mechanism of action and resistance profile. With 15 compounds currently in preclinical and early translational development, understanding how different candidate compounds interact in order to select the best combinations for clinical development is a highly complex process.

Human volunteer infection studies and SCID models

To accelerate the selection of next-generation drug combinations, MMV and its partners are using two pioneering technologies in the field of translational science and experimental medicine: the SCID mouse model and human volunteer infection studies (VIS).

The SCID model is a laboratory model of human malaria, which allows scientists to predict the activity of candidate compounds and generate data to inform the design of clinical studies in humans. SCID testing in 2018 occurred at the Swiss Tropical and Public Health Institute (Swiss TPH), as well as at two sites in Spain: one in Tres Cantos (GSK) and the other in Bilbao (The Art of Discovery [TAD]).

In 2018, 15 new combinations of MMV compounds were evaluated in SCID models to inform the choice of partner drugs. The SCID model is now also starting to provide insights into how standard antimalarial drugs are affected by resistance. This is achieved by comparing the activity of a given drug in a model with malaria parasites that are sensitive to key antimalarial drugs (the *Plasmodium falciparum* 3D7 strain), versus its activity in a model using artemisinin-resistant parasites.

Data from the SCID studies allow MMV to model the pharmacokinetic and pharmacodynamic properties of new drug combinations, which enable the best combinations to be selected for human VIS. The VIS were first developed to assess the blood-stage activity of single candidate compounds, but recent technological developments have allowed researchers to gain insights into the prophylactic and anti-gametocyte activity of candidates, as well as the activity of different compounds in combination and more recently, against resistant strains of parasites (Figure 3).

Humanized FRG model

Until recently, it was only possible to study the complete liver stage (both for anti-relapse and prophylaxis) of parasite development using non-human species of malaria in rodents or primates. However, an exciting new tool, originally developed by Prof. Stefan Kappe and his team at the Center for Infectious Disease research in Seattle (and which now is being established at TAD, in collaboration with TropIQ and MMV), has changed what is possible. The FRG mouse model, makes it possible to study how the malaria parasites that infect humans develop first in the liver and then enter the blood to cause a clinical infection. In short, the model allows researchers to mimic more of the human parasite lifecycle than ever before – all in a non-human host.

As is being shown by the Kappe lab and others, the FRG model could prove particularly useful in the study of *P. vivax* malaria, shining a light on its complex liver stage of development. For the first time, assuming access to *Plasmodium vivax* sporozoites, it will be possible to see whether a given compound can kill hypnozoites in vivo in a rodent model. As such, the data obtained from the model will be more physiologically relevant than data from in vitro studies, generating important insights about a compound before human testing. The FRG model is currently being established and validated for *P. falciparum* malaria, and the first full study on a new compound will be run in 2019.
The volunteer infection study platform is a valuable tool for accelerating the evaluation of promising new drugs. In a tightly controlled environment, volunteers receive a low number of drug-sensitive or drug-resistant malaria parasites (sporozoites) and the level of parasitaemia in their blood is monitored closely. Around 7 days later, the volunteers receive the experimental drug candidate, while parasitaemia continues to be monitored. In this way, these studies enable us to understand quickly whether a compound will be efficacious against malaria and/or known resistant strains of malaria and guide dose selection for subsequent clinical studies.

In the same study, we can also explore the activity of experimental drugs against the sexual (gametocyte) stages of the malaria parasite to assess transmission-blocking activity. The simplest way is to monitor the development of gametocytes at the same time as blood-stage parasitaemia. In addition, we can feed mosquitoes with the test subject’s blood containing gametocytes to see if the drug can prevent transmission.
Evolution of drug discovery

How have MMV’s discovery activities evolved over the past year?

In 2018, we continued to focus our discovery efforts on delivering a steady stream of new preclinical candidates. However, through the use of novel platforms — such as Plasmodium liver and gametocyte in vitro assays, in vivo SCID and FRG models, and the human VIS — we are now developing a much deeper understanding of the potential of new series and targets. This has allowed us to identify new compound series active beyond the blood stage of the parasite lifecycle and optimize them for clinical development. As such, the range of profiles displayed by preclinical candidates is evolving.

Can you tell us about new screening collaborations?

MMV is a founder member of MaLDA – the malaria drug accelerator, a network of academic and industry labs funded by the Bill & Melinda Gates Foundation, and led by Prof. Elizabeth Winzeler at University of California, San Diego. Through research involving resistance selection, genomic analysis and editing, metabolomics, proteomics, conditional gene knockdowns and full malaria lifecycle fingerprinting, MaLDA is helping us to identify new drug targets and mechanisms of action for confirmed antimalarial compounds identified from screening. In 2018, we worked very closely with MaLDA, supplying compounds, prioritizing biological targets and discussing key MMV portfolio projects. Ultimately, we hope that collaborations with MaLDA and MMV’s partners will bring about a renaissance in target-based drug discovery. This would be significant, as knowing what the biological targets are gives us a real advantage for compound optimization, as per MMV’s Project of the Year 2018 (pp. 10–11).

What are the key lessons learned from 2018?

We continue to learn from the successes and failures of different projects. As more and more candidates are delivered, we develop a greater understanding of the potential risks and liabilities of different compound series. One recent example is SJ733, a compound that in 2018 was found to have lower concentrations in humans than expected. Although no longer in MMV’s portfolio, our experience with SJ733 has informed the development of a back-up series by a project team led by Prof. Kip Guy at the University of Kentucky, which, crucially, aims to circumvent the liability identified in SJ733. As such, the “failure” of SJ733, viewed from a different perspective, will hopefully catalyse the success of a back-up.
Since the turn of the 21st century, the world has battled multiple epidemics – both old and new, viral and bacterial. Some of these have reached pandemic proportions. The Zika virus outbreak across the Americas in 2015–2016, for example, demonstrated how quickly a relatively unknown mosquito-borne disease can become a global health emergency.

Drug-resistant pathogens have the potential to increase the frequency and gravity of pandemics, posing a major threat to the world’s population. Alarmingly, current estimates suggest that the number of deaths associated with antimicrobial drug resistance could increase to 10 million per year by 2050.8

New and innovative approaches to drug discovery are needed to foster new research into treatments for neglected and potentially pandemic diseases. One such approach – “open innovation” – has the power to do just this. Since 2015, MMV has pioneered several drug discovery initiatives to support R&D efforts in malaria and other disease areas – all under the ethos of open innovation.

The first open-source library made available by MMV was the Malaria Box, a collection of 400 diverse compounds with antimalarial activity, distributed free of charge to 30 countries between 2011 and 2015. Over this period, more than 250 boxes were provided to research groups around the world, resulting in 56 publications. In 2015, a second library, the Pathogen Box, was made available. Containing 400 diverse, drug-like molecules active against neglected tropical diseases of interest, 319 copies of the Pathogen Box had been shipped to 42 countries, generating 32 publications, by the end of 2018.

The latest open-source library to be made available is the Pandemic Response Box, launched by MMV and the Drugs for Neglected Disease initiative in January 2019. We spoke to Kirandeep Samby, a medicinal chemist and MMV consultant working on MMV Open activities, to find out more about this latest initiative.

What is the Pandemic Response Box?

The Pandemic Response Box is a new library of 400 diverse compounds with antibacterial, antiviral or antifungal activity. It is freely available to members of the scientific community upon request. In return, researchers are required to publish any findings in an open-access journal within 2 years of data generation.

What types of compounds are included? How were these selected?

Anti-infective compounds included in the box are in various phases of discovery or development. Initially, we took around 20,000 compounds that were reported in the public domain and had relevant biological activity. These were triaged using computational techniques to provide a selection of compounds with a range of molecular properties, chemical scaffolds, target pathogens and biological mechanisms of action. Around 2,300 compounds were then shortlisted from this triage. Lastly, a group of external disease experts assessed each of the 2,300 compounds individually and selected the final set of 201 antibacterial, 153 antiviral and 46 antifungal compounds.

What is the value of open-source libraries such as the Pandemic Response Box?

In the field of neglected tropical diseases, initiatives like the Pandemic Response Box are vital. Such libraries give scientists the tools to explore and validate new targets, which in turn leads to new scientific discoveries and new drug discovery projects. The overarching goal of the project is to help shorten the time between a new pandemic emerging and new drugs becoming available to treat it, because as we know from experience, saving time saves lives.

How many orders do you expect to receive?

Based on our experience with the Malaria Box and Pathogen Box to date, we expect to receive orders for around 200–300 boxes. However, it will probably take 2–3 years to reach this number.

What has it been like working with MMV?

It’s been a wonderful experience. MMV is a very open organization to work with and is always receptive to feedback from its partners. I believe the work they do is extremely important in safeguarding our society from future threats to global health.