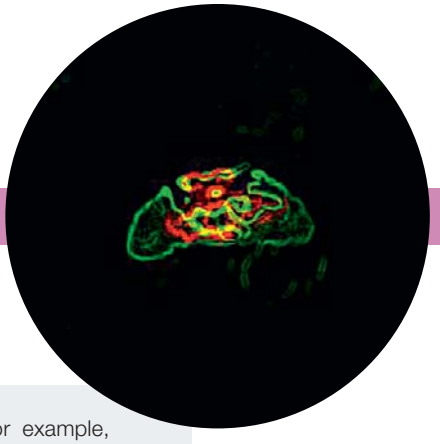
5 Medicines for malaria elimination/eradication



Fluorescent-stained late-stage gametocyte, courtesy of V. Avery Griffith University, Australia

To achieve malaria elimination/eradication, it is necessary to achieve radical cure at the individual level and eliminate the human transmission reservoir at the population level. Medicines are considered most likely to achieve eradication if administered with effective transmission prevention tools.

MMV is uniquely positioned to contribute to the elimination and eventual eradication of malaria by:

- Re-purposing existing malaria medicines for use in short-term elimination efforts.
- Developing a well-tolerated, first-generation SERCaP (single encounter radical cure and prophylaxis) with a combination of drugs that meet stringent target candidate profiles (TCPs) (page 17) for large-scale administration to both symptomatic and asymptomatic infected populations including children and pregnant women.
- Developing the components of a second-generation SERCaP to address the inevitable emergence of drug resistance.

Blocking transmission

To eliminate the reservoir of parasites that continues transmission to the next person we need medicines that target the sexual-stage parasites (which are taken up by the mosquito and continue the parasite's lifecycle). To do so, MMV has a three-pronged strategy addressing short-, medium- and long-term needs.

In the short-term, in line with WHO's recent recommendation for a single low dose of primaquine to be taken alongside ACTs to block transmission,[1] MMV will work in partnership to develop and obtain WHO prequalification for additional peadiatric ACTs. Additionally, as primaquine has been in use for more than 60 years and with its use set to increase, there is a risk its efficacy might start to decline. As a result, MMV is also researching alternatives for the medium-term, such as tafenoquine in partnership with GSK.

To further address medium-term needs, our approach is to look at the candidate molecules we already have in preclinical development, to see how they match primaquine's transmission-blocking activity. For example, the investigational 'single-dose' cures OZ439 and KAE609 have both demonstrated transmission-blocking potential in the laboratory, in addition to their established blood-stage activity.[2,3]

The key now is to investigate this potential further by tracking the development of the parasite between patients and mosquitoes, after treatment with either OZ439 or KAE609. We are also working with scientists in Tanzania to establish an insectary and proof-of-concept (Phase IIa) transmission-blocking model, which can then be used to test and confirm these and other laboratory findings.

In parallel, the hunt continues for novel compounds able to cure and block the transmission of malaria in the long-term. We are working with partners to develop assays[4] capable of screening a high number of compounds at one time. The goal over the coming year is to screen many of the 25,000 blood-stage active molecules that emerged from the extensive malaria screening campaign of more than six million compounds.[5]

1 World Health Organization. *Updated WHO Policy Recommendation (October 2012)*: www.who.int/malaria/diagnosis_treatment/treatment/who_pq_policy_recommendation/en/

2 Delves M *et al*. "The activities of current antimalarial drugs on the life cycle stages of *Plasmodium*: a comparative study with human and rodent parasites." *PLoS Med*. 9(2):e1001169 (2012).

3 van Pelt-Koops JC *et al*. "The spiroindolone drug candidate KAE609 potently inhibits gametocytogenesis and blocks *Plasmodium falciparum* transmission to anopheles mosquito vector." *Antimicrob Agents Chemother*. 56(7):3544-8 (2012).

4 Assay: a laboratory-based platform with which to conduct experiments such as whether a molecule is able to kill the malaria parasite.

5 Collaborations with pharmaceutical companies (including GSK, Sanofi, Novartis, Pfizer, Genzyme and AstraZeneca) as well as academic institutions such as St Jude Children's Research Hospital, led to the screening of more than six million compounds resulting in 25,000 chemical starting points with activity against *P. falciparum*.

Prof. Robert Sauerwein

Head of the Division of Medical Parasitology and Centre for Clinical Malaria Studies, Nijmegen Institute, the Netherlands, is adapting assays[4] to identify transmission-blocking molecules. He talks about the assays and what it's like to work with MMV.

Q | How do these assays work?

We incubate gametocytes with the test compounds in microtiter plates and assess at what concentration they kill the gametocytes, if at all. We use a *Plasmodium* lactate dehydrogenase (pLDH) test that can tell us whether the parasites are alive or not at different stages of their development.

We also use a standard membrane-feeding assay, which enables us to investigate what is happening in the mosquito. This is a well-established assay and the closest to reality. We allow mosquitoes to feed on infected blood in the presence or absence of drug and study whether the parasite continues to develop within the mosquito.

We have validated and standardized the assay with test compounds with known activity and are now looking to improve the read-out system. At the moment we use microscopy, which is very labour-intensive. The next step is to move from a 96-well plate to a 384-well plate, which will significantly increase the number of molecules we can screen at once. We hope to be able to screen a few thousand compounds in a year.

Q | What is the added value of working with MMV on this project?

MMV is in a special position as it works across the board, from discovery to characterizing molecules and clinically developing them.

The organization really bridges academic activities and drug development – there are not many that do that. It's the global coordination of these activities that really makes MMV special. As an academic with an interest in translational medicine, for me they are an ideal partner. MMV helps us translate our findings through to clinical development. Our objectives are aligned.

We work well together and have regular reporting back and forth. It's not like an academic project where you send your report to an administrator once a year who checks to see if your report looks nice. No, MMV really has knowledge of the project and co-orchestrates its progress, so it really is a partnership.

Dr Salim Abdulla

Chief Executive Director, Ifakara Health Institute, Tanzania, is working with MMV to establish an insectary and clinical research centre in Bagamoyo. He explains how the work ahead determines the transmission blocking activity of in-development medicines.

Q | How will the research facility be used?

The site will be used to see if different drugs can prevent the transfer of parasites from humans to mosquitoes. There are several ways to do this. Some are already established and others will need to be developed.

The established way is to culture parasites until gametocytes are formed. We then take blood from people who have been treated with different drugs and combine it with the gametocytes to see whether the residual drug in the blood can kill the gametocytes. This is experimental and fast, but most people would argue that they want to see the real thing.

The most realistic approach is to look at patients with malaria that have been treated with potential transmission-blocking drugs, to see how many gametocytes develop and how infectious they are. We do this by watching patients for 7–14 days to see what happens when mosquitoes feed on their blood – either directly or through membrane feeding. We want to know whether or not the gametocytes remain viable and develop in the mosquito. If the medicine administered can block transmission, we will see fewer or no mosquitoes carrying parasites.

Q | Which molecules will you study?

The most promising transmission-blocking molecules are the synthetic peroxides, so we will look at MMV's OZ439 first and then other new compounds coming through with different methods of action, such as KAE609. We will also look at different compounds on the market, such as primaquine artemether-lumefantrine and dihydroartemisinin-piperaquine, to help establish a benchmark for comparison.

Q | How has working with MMV helped to strengthen the research capacity of the Bagamoyo site?

We have been working with MMV since 2005, and the relationship has really increased the knowledge and skill base of the scientists at Bagamoyo. MMV has also contributed to the infrastructure, such as the laboratory and clinical platforms. This is a huge boost to the research capacity here and the site can now also be used for vaccine development.

For me personally, the process of talking to people with a great deal of experience has allowed me to better understand how to be successful in this field. Overall, the work with MMV is very interesting. It has also allowed us to explore new ways of doing things and to look beyond already established models. This is where it really starts to get interesting.

Stopping the relapse

Tafenoquine

Phase IIb

Target indication: Liver stage of *P. vivax* (relapsing malaria)

Advantages:

- Potential for a single-dose cure, and therefore better compliance

Project Leader: Dr JP Kleim, GlaxoSmithKline

Partner: GlaxoSmithKline plc., UK

MMV Project Director: Dr Wiweka Kaszubska

While the parasite, *Plasmodium falciparum*, is responsible for the majority of the annual 610,000–971,000 global malaria deaths,[1] *Plasmodium vivax* results in 70–80 million cases each year.[2] In addition, severe complications are increasingly being associated with *P. vivax* malaria; the long-held perception that this is a benign form of malaria is changing.[3]

The high burden of disease is partly due to *P. vivax*'s ability to lie dormant in the liver and reactivate at any time, leading to intense malaria symptoms in the absence of a new mosquito bite. Known as 'relapsing malaria', the disease is prevalent in south-east Asia, India and South America and parts of Africa, where millions of work and schooldays are lost every year as a result.[2,3] Studies also show that it has adverse effects on children's cognitive ability.[4,5] This tiny parasite traps families and communities in an endless cycle of poverty, hindering social and economic development.

The only approved anti-relapse medicine able to eliminate the dormant liver-stage form (the hypnozoite) is primaquine, which has a 14-day treatment regimen, making compliance difficult to achieve. It is also associated with potentially fatal haemolytic side effects in patients deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD).[6,7] Additionally, it has been in use for approximately 60 years and so the risk of resistance is ever present. Our goal to eradicate malaria cannot be achieved without new anti-relapse medicines.

Tafenoquine, currently in clinical development with MMV and GlaxoSmithKline (GSK), is the lead candidate to provide an alternative option to primaquine. Studies show it could be taken as a single dose – a significant improvement on primaquine's 14-day course. However, tafenoquine is from the same chemical family as primaquine and also likely to be associated with the same side effects in G6PD-deficient patients.

To have a better understanding of the prevalence of G6PD deficiency and the use of primaquine, MMV and GSK conducted market research in India, Indonesia and Brazil. The research revealed widespread use of primaquine without G6PD testing and limited awareness of risk, suggesting the need for a convenient and affordable G6PD deficiency test. MMV plans to work with GSK and PATH to explore the development of a test suitable for field use.

1 World Health Organization. *World Malaria Report 2012*: www.who.int/malaria/publications/world_malaria_report_2012/en/

2 Mendis K *et al*. "The neglected burden of *Plasmodium vivax* malaria." *Am J Trop Med Hyg.* 64(1-2 Suppl):97-106 (2001).

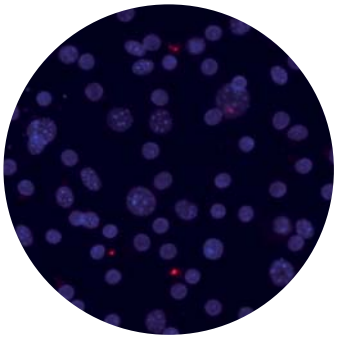
3 Price RN *et al*. "Vivax malaria: neglected and not benign." *Am J Trop Med Hyg* 77:79–87 (2007).

4 Vitor-Silva S *et al*. "Malaria is associated with poor school performance in an endemic area of the Brazilian Amazon." *Malar J*. 8:230 (2009).

5 Fernando SD *et al*. "The 'hidden' burden of malaria: cognitive impairment following infection." *Malar J*. 9:366 (2010).

6 Glucose-6-phosphate dehydrogenase (G6PD) is a key enzyme involved in protecting all human cells from oxidative stress. Deficiency in this enzyme is thought to have co-evolved with malaria as it offers a degree of protection against severe malaria.

7 Wells TN, Burrows JN, Baird JK. "Targeting the hypnozoite reservoir of *Plasmodium vivax*: the hidden obstacle to malaria elimination." *Trends Parasitol*. 2010 26(3):145-51 (2010).



Fluorescent-stained *P. vivax* persistent liver forms (in pink), courtesy of S. March-Riera & S. Bhatia, Massachusetts Institute of Technology, USA

Malaria relapse or completely new infection?

To be able to test the efficacy of new anti-relapse medicines in the real world, we need to know whether a repeat infection is due to relapse or to a new infection from a new mosquito bite. This can be a challenge in malaria-endemic countries. To overcome this, MMV is collaborating with Colonel Bagus Tjahjono, Indonesian Army Health Command and Dr Kevin Baird, Eijkman Oxford Clinical Research Unit, on the development and validation of an innovative clinical model.

The model looks at soldiers in Indonesia who are at risk of contracting malaria during their tour of duty in north-eastern Papua. When they return to base in East Java, where there is no malaria transmission, they are tested for the disease. If positive, they are treated with an ACT. If the symptoms of malaria reappear after treatment, we can be sure they are due to a relapse and not a new infection.

So far, the model has been used to explore the efficacy of primaquine given 28 days after a treatment of the blood-stage parasites with the ACT dihydroartemisinin-piperaquine. The next step is to investigate the efficacy of primaquine given together with dihydroartemisinin-piperaquine and other ACTs, and then next-generation anti-relapse medicines like tafenoquine.

Dr Brice Campo

Associate Director of Drug Discovery, MMV, explains the research challenges presented by *P. vivax* and MMV's discovery strategy to stop the relapse.

Q | Why have so few medicines been discovered and developed to treat relapsing malaria?

For a long time, the species *P. vivax* was considered benign and so focus was placed on the more lethal *P. falciparum*. We now know *P. vivax* is far from benign and so it is starting to get the attention it deserves.

Up until 5 years ago, there were a lack of suitable assays in which to test potential molecules: there was no cell assay[8] and the only biological assay[9] relied on a substitute primate model of infection. Significant progress has been made; we now also have a substitute rodent cell assay that can be used to prioritize testing. However, we are not yet using human parasites, so some molecules active solely against *P. vivax* could be missed.

Q | What is MMV's discovery strategy to identify anti-relapse molecules?

To be pragmatic and until we have a *P. vivax* cell assay, we plan to use currently available cell assays to screen each of the blood-stage active series in our portfolio.

In parallel, MMV and the Bill & Melinda Gates Foundation are working with different groups to develop the optimal assay: a cost-effective *P. vivax* cell assay able to screen large numbers of compounds at the same time. One of the biggest challenges is gaining access to sporozoites (which are used to infect liver cells and generate hypnozoites).

We are working with partners in disease-endemic countries such as India, Peru and Thailand, which have laboratory facilities to dissect sporozoites from mosquitoes that have fed on infected blood. In addition, we have partners in the USA who are working to culture *P. vivax* parasites in the lab, which simplifies the sporozoite supply issue.

Because this is such a challenging area of research it's important to integrate our activities and share knowledge between the groups. MMV is taking a key role in this integration process.

All being well, in the next 5 years we plan to screen as many compounds as possible for activity against the hypnozoite of *P. vivax*.[10] It's an ambitious goal, as no one has been able to do this in a low- let alone a high-throughput fashion before. If we are successful with these approaches we will have made a huge advance towards identifying the next-generation of anti-relapse medicines.

Q | What progress has been made so far?

We've found that some of our compounds already in development have activity against the hypnozoite as well as the blood stages. One promising chemical series has recently transitioned from discovery to preclinical development, and several others show some signs of activity.

As for the assays, the cell assay based on rodent parasites has been improved and is now ready to be used for the screening of a large library of 500,000 compounds. This will help us pre-screen to see which compounds really can work in liver tissue. We will then progress interesting liver-stage hits into a specific hypnozoite assay.

The *P. vivax* cell assays are also progressing well. With the support of the Gates Foundation, Prof. Sangeeta Bhatia of Massachusetts Institute of Technology has developed a new culture system that may provide the assay we need to identify the next-generation anti-relapse medicine.[11] We hope to be able to demonstrate feasibility of such an assay and begin high-throughput screening in the coming years.

8 Cell or *in vitro* assay: using components of an organism isolated from their usual biological surroundings to test, in this case, the efficacy of molecules to kill the dormant liver stage of *P. vivax* malaria; also known as a 'test tube model'.

9 Biological *in vivo* assay: using a living organism, in this case to test the efficacy of a molecule to kill the dormant liver stage of malaria; also known as an 'animal model'.

10 Between 2008–2012, MMV and partners screened more than six million molecules for activity against the blood stage of malaria, leading to the identification of 25,000 chemical compounds. Given the priority and unmet medical need for *P. vivax* malaria, we would plan a similar screening campaign against this parasite.

11 Khetani SR, Bhatia SN. "Microscale culture of human liver cells for drug development." *Nat Biotechnol.* (1):120-6 (2008).

OSDD powering the pipeline and changing the paradigm

In 2011, MMV launched the Open Source Drug Discovery (OSDD) programme working with scientists initially in Australia and then in India. With many compounds to investigate, following the identification of more than 25,000 active molecules, we need as many of the world's best scientific minds as possible working together.

OSDD differs from traditional drug discovery, which is commercially driven and typically conducted behind closed doors with limited information released into the public domain until patents are published. Given the minimal commercial value of new medicines against malaria and neglected diseases, we have an opportunity to explore how this paradigm can be changed.

Since 2011, MMV has been collaborating with Dr Mat Todd at the University of Sydney, Australia, to discover new molecules active against malaria. Mat posts all the details of his research onto a website, The Synaptic Leap,[1] using a kind of 'electronic lab book'. As posts are added, alerts go out via social media. Scientists from around the world can then input their expertise and contribute to the project's progress. Some laboratories have even contributed by synthesizing and screening compounds. With many people working in parallel, problems can be solved quickly. This initiative is the first to show the approach can work for drug discovery and has thus paved the way for other open source projects.

MMV is now also working closely with India's OSDD malaria programme[2] to investigate the most promising compound series, initially for blood-stage malaria. However, given the burden of relapsing malaria in India, the ultimate objective is to identify molecules capable of targeting the liver stage to stop the relapse. The MMV/OSDD partnership also has the scope and potential to progress molecules through preclinical and clinical development.

1 The Synaptic Leap: www.thesynapticleap.org
2 Open Source Drug Discovery India: www.osdd.net/home
3 National Center for Biotechnology Information PubChem: pubchem.ncbi.nlm.nih.gov
4 ChEMBL database: www.ebi.ac.uk/chembl/malaria/

Dr Tanjore Balganesh

Project Head at India's OSDD Initiative, explains how open source research is taking off in India.

Q | What are the objectives of India's OSDD model?

The ultimate objective is to provide affordable health care to patients. To that end, OSDD consolidates research for new therapies for neglected diseases (malaria, tuberculosis and leishmaniasis). The idea is that the products developed will be licenced to India's Council of Scientific & Industrial Research (CSIR), and then to the generics industry without royalties, which will help keep the cost of the medicine low and increase patient access.

Q | How can scientists participate in OSDD?

We employ a crowdsourcing model: CSIR-funded scientists working to discover promising molecules, share their results and problems via an online platform. Researchers from around the world, from product development partnerships, small and large pharma – basically anyone with an interest in the research – offer their advice via the platform.

Q | What are the advantages of the model?

The major advantage is increased scientific capability as it brings more minds together. Also, because the model uses public funds the final products will be affordable. We hope that the platform will encourage the formation of new research collaborations.

Q | How do you encourage scientists to join the platform?

We offer scientists the opportunity to screen their molecules free of charge. We have built speciality centres where they can get specific information on their compounds. We hope to do the same for malaria in the next 6 months. We also offer opportunities to collaborate with other scientists: consultants and experts who can help expedite their work. We simply request that if they use the facilities they share their data.

Q | What will success look like?

The first success we are hoping for in 2013 is to set up facilities in India where scientists can conduct clinical research studies for TB, malaria and neglected diseases. Today, in India, there are limited public or private institutions where you can do so. I strongly believe that once these platforms have been set up it will encourage further research and incentivize biotech and pharma companies to re-evaluate molecules previously deemed low-priority, as it will cost little. This will be the first step to establishing drug research excellence in India.

Q | What's the advantage of working with MMV?

MMV offers us access to high-quality expertise via its global networks. MMV has the best experience in progressing molecules in malaria. OSDD would like to tap into that experience and learn from it. I think our success is very much dependent on MMV's contribution. If you take MMV off the OSDD radar it's a recipe for failure.

I've worked with MMV for many years, and the key thing it offers is the culture of collaboration. The people are really great to work with. I have worked with Tim Wells and Jeremy Burrows on MMV's science team and know I can pick up the phone and say, "Jeremy, I have a problem" and he will help. Otherwise, it just wouldn't work.

Malaria Box

Some 20,000 structures active against malaria have been released into the public domain[3] as a result of the screening efforts at St Jude Children's Research Hospital, Tennessee (USA), Novartis and GlaxoSmithKline. Yet, researchers need physical access to the compounds to be able to work with them. In response to this need, MMV set up the Malaria Box project. The Malaria Box is a treasure trove of 400 diverse compounds selected from these original active hits. Compounds were clustered into chemical families, and members chosen based on their structures and availability.

In 2012, MMV and the Bill & Melinda Gates Foundation each offered 12 grants for scientists working on Malaria Box compounds, with projects seeking to establish mechanisms of action, resistance profiles as well as activity on other related parasites.

To continue the virtuous cycle of research, Malaria Box recipients are requested to place all data generated on the compounds into the public domain via the ChEMBL database.[4] Hosted by the European Molecular Biology Laboratory-European Bioinformatics Institute (EMBL-EBI), the database provides a one-stop shop for all publicly available malaria drug research in one easy-to-search format.

By the end of 2012, 103 copies of MMV's Open Access Malaria Box had been dispatched to 26 countries to catalyze malaria and neglected diseases' drug research.

To date, the Drugs for Neglected Diseases *initiative* (DNDi), has identified several chemical series with activity against sleeping sickness and leishmaniasis from the Malaria Box compounds. The results have since been shared with the community via ChEMBL.

Top 10 MMV publications of 2012

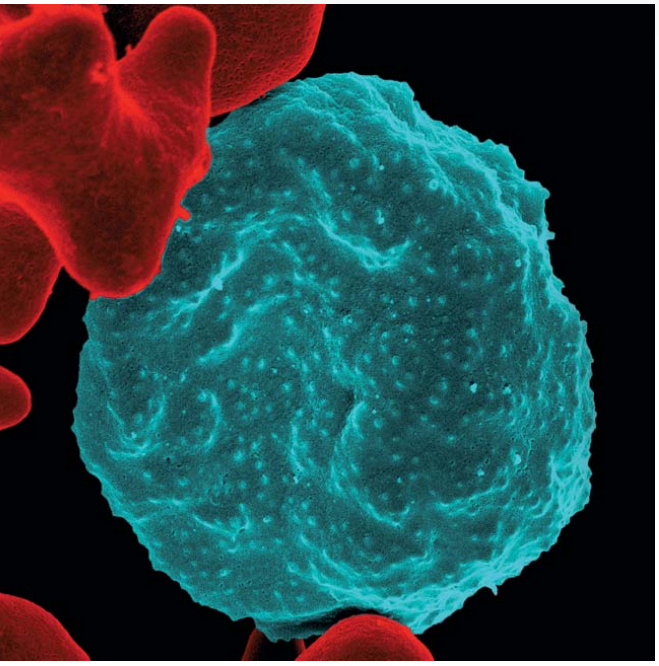
Malaria Journal	Kayentao K *et al.* **"Pyronaridine-artesunate granules versus artemether-lumefantrine crushed tablets in children with *Plasmodium falciparum* malaria: a randomized controlled trial."** *Malar J.* 11:364 (2012).	→ Pivotal Phase II study demonstrating pyronaridine-artesunate paediatric formulation is efficacious and non-inferior to the current gold standard paediatric formulation.
PLoS Medicine	Delves M *et al.* **"The activities of current antimalarial drugs on the life cycle stages of *Plasmodium*: a comparative study with human and rodent parasites."** *PLoS Med.* 9(2):e1001169 (2012).	→ Details the activity of marketed and in-development medicines at each stage in the parasite's lifecycle, providing invaluable insight into which drugs to combine for next-generation antimalarials.
Journal of Medicinal Chemistry	Younis Y *et al.* **"3,5-Diaryl-2-aminopyridines as a novel class of orally active antimalarials demonstrating single dose cure in mice and clinical candidate potential."** *J Med Chem.* 55(7):3479-87 (2012).	→ Demonstrates the potent antimalarial potential of the aminopyridine compound, MMV390048 – selected as MMV's Project of the Year 2012.
Malaria Journal	Ding XC *et al.* **"A framework for assessing the risk of resistance for anti-malarials in development."** *Malar J.* 11:292 (2012).	→ Details a methodology to assess the susceptibility of new antimalarial compounds to the development of drug resistance – a critical tool in prioritization of new compounds.
BJCP British Journal of Clinical Pharmacology	Moehrle J *et al.* **"First-in-man safety and pharmacokinetics of synthetic ozonide OZ439 demonstrates an improved exposure profile relative to other peroxide antimalarials."** *Br J Clin Pharmacol.* 75(2):524-37 (2013).	→ Demonstrates the safety and pharmacokinetic profile of OZ439, enabling progression of the compound to malaria patients.
Malaria Journal	Anthony MP *et al.* **"The global pipeline of new medicines for the control and elimination of malaria."** *Malar J.* 11:316 (2012).	→ Key paper summarizing the current status of the global pipeline of antimalarial medicines and the challenges ahead if malaria elimination is to be achieved.
New England Journal of Medicine	Rueangweerayut R *et al.* **"Pyronaridine-artesunate versus mefloquine plus artesunate for malaria."** *N Engl J Med.* 366(14):1298-309 (2012).	→ Pivotal Phase III study demonstrating the safety and efficacy of pyronaridine-artesunate.
Malaria Journal	Talisuna AO *et al.* **"Closing the access barrier for effective anti-malarials in the private sector in rural Uganda: consortium for ACT private sector subsidy (CAPSS) pilot study."** *Malar J.* 11:356 (2012).	→ Pilot study demonstrating that subsidizing the cost of quality ACTs along with targeted communications can significantly increase their uptake and use in the private sector.
PLoS one	Sanz LM *et al.* **"*P. falciparum* in vitro killing rates allow to discriminate between different antimalarial mode-of-action."** *PLoS One.* 7(2):e30949 (2012).	→ High-priority paper as it represents a paradigm shift in assessing the killing rate of antimalarial compounds.
American Society for Microbiology	van Pelt-Koops JC *et al.* **"The spiroindolone drug candidate NITD609 potently inhibits gametocytogenesis and blocks *Plasmodium falciparum* transmission to anopheles mosquito vector."** *Antimicrob Agents Chemother.* 56(7):3544-8 (2012).	→ Details transmission-blocking potential of the first novel-acting antimalarial compound to enter Phase II in 20 years.

MMV Project of the Year 2012

MMV390048 – boosting African research

MMV Project Directors:
Drs David Waterson and Cristina Donini
Partners: University of Cape Town, South Africa; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Monash University, Australia

A novel antimalarial compound from the aminopyridine class, MMV390048, becomes the first researched in Africa to enter preclinical development. In recognition of the potential of this exciting compound, the University of Cape Town (UCT) team has been awarded MMV Project of the Year 2012.



Malaria-infected red blood cell courtesy of National Institute of Allergy and Infectious Diseases, USA

Prof. Kelly Chibale

Founder and Director of the University of Cape Town's Drug Discovery and Development Centre (H3-D), was the Project Leader of the UCT team that delivered MMV390048 as a preclinical candidate.

Q What is special about the collaboration that identified the compound?

The project was not conducted using the traditional pharmaceutical industry model but the product development partnership model of MMV. We worked with partners from across the world: Griffith University and Monash University, both in Australia, Swiss TPH, and Syngene in India. That's what makes it special. Academic institutions worked together under the mentorship of experienced scientists from pharma, specifically Mike Witty of MMV's Expert Scientific Advisory Committee (ESAC) and David Waterson (MMV Project Director), with some key assays carried out by GlaxoSmithKline (GSK). Without MMV's network the project would simply not have got this far.

Q How did you coordinate the input of different partners from all over the world?

From the outset, MMV set clear progression criteria and a need to integrate all activities. This meant regular meetings. We held biweekly chemistry meetings and monthly project meetings, with all partners. But nothing beats face-to-face, so we also had two meetings each year where everyone came together under one roof to discuss all the data and the next steps. The project management provided by MMV was a critical ingredient.

Q Are there any other advantages of working with MMV on this kind of project?

MMV gave us a head start by providing access to a good project and the starting points selected from a library of drug-like molecules. As Tim Wells (MMV's Chief Scientific Officer) once said, by working from such a library "we start in year 4 instead of year 1". Also, by working with MMV, we knew that our project was globally aligned, and the work would not be duplicated elsewhere.

MMV provided us with an outstanding mentor, Mike Witty. His and David's input have been invaluable for me and all the postdocs[1] here. Between David, Mike, and now Leslie Street, who joined H3-D in April 2012 as Head of Medicinal Chemistry, we benefit from 80 years' worth of combined pharma industry experience!

MMV also provides sustained funding, which does not always happen for academic projects. This enables us to build and maintain the talent needed to progress the project. Of course, it all depends on us meeting project goals and milestones and all going well at the ESAC annual review.

MMV's contribution to the future of drug discovery in Africa is immeasurable – it has set in motion a virtuous circle of capacity building at UCT that can now not only be used for malaria but also for other diseases, like TB. It means that African scientists have a chance to develop their careers at home rather than abroad.

Plus the project is helping to counter Afro-pessimism. It's the first time a drug researched on African soil has progressed this far. Once you have shown you can do something never done before it sets a precedent.

1 Post-doctoral researchers.

Back row (left to right): Kelly Chibale, Sergio Wittlin, Susan Charman, Yassir Younis, Karen White, David Waterson, Michael Witty & Aloysius Nchinda
Front row (left to right): Diego Gonzalez Cabrera, Frederic Douelle & Claire Le Manach

Dr Michael Witty

Member of MMV's ESAC and project mentor for MMV390048, Mike has more than 30 years of pharmaceutical research experience. Since retiring in 2008, he provides support mostly to not-for-profit research organizations, like MMV.

Q | What was your role as project mentor?

My role was three-fold – strategic, tactical and personal. First, to assist the development of the project I brought my own creativity, knowledge and experience of the malaria field. Second, I helped to provide a link between the team and ESAC to ensure alignment with MMV's Target Product Profiles and Progression Criteria. Third, I helped where I could in terms of team and project management.

Q | Why is this project important to you?

I have contributed to a number of successful drug and vaccine R&D projects over a long career but this one has the potential to relieve suffering for millions of people.

I have been involved in this project since its outset, initially prioritizing and optimizing the hits from screening of the Biofocus libraries at the Eskitis Institute and now overseeing the work to move the compound into man. I have invested a lot of myself in the work, as have Kelly and his team.

The project is very important to the UCT team, as it has the potential to deliver the first antimalarial drug researched in Africa.

Q | Why has this project been successful?

Traditionally, academic groups are slower than industry teams in progressing hits into development, owing to other demands on their time, such as teaching, and grant and article writing. From the outset, Kelly has been willing to embrace the industry approach in an academic setting. His team has been focused on selecting and progressing the best compound for clinical development. Creating H3-D[2], Africa's first integrated drug discovery and development centre, demonstrates this commitment.

Kelly has also been very proactive in seeking funding for equipment and bringing in expertise. Through the MMV network, we have been able to access the expertise of world-class talent such as Drs Sue Charman (Monash University) and Sergio Wittlin (Swiss TPH) among others.

Q | What has the experience taught you?

The lessons are not new but worth repeating:

- Commitment, focus and collaboration are critical to team success.
- Visions can be achieved by hard-working, enthusiastic and committed leaders.
- MMV's partnership model can achieve success where the individual pharmaceutical companies have fallen short.
- There is as much satisfaction in helping others to succeed as succeeding oneself.
- Retirement can be even more satisfying, productive and fun than working full-time!

Dr Cristina Donini

Associate Director, Translational Medicine, MMV, took over as Project Director in July 2012, when MMV390048 was selected as a candidate.

Q | What is exciting about MMV390048?

MMV390048 is potent against the blood stage of malaria – it can completely cure animal models of malaria in a single dose. This result is outstanding and noteworthy since drugs such as the artemisinins and chloroquine do not achieve this. It suggests MMV390048 could become part of a single-dose cure in humans.

Moreover, the compound also has activity against other stages of the lifecycle and all known resistant strains of the parasite, suggesting a role in malaria control, transmission blocking and eradication.

Q | What are the next steps in developing the molecule?

The preclinical work is underway. This includes manufacturing more compounds, assessing the stability of the solid drug and regulatory safety studies. So far, MMV390048 appears well tolerated and promises real clinical benefit, although more definitive data is required. Planning for success, the next step will be a Phase I trial in healthy volunteers expected to start in 2014 in South Africa.

2 University of Cape Town Drug Discovery and Development Centre: www.h3d.co.za