Medicines for Malaria Venture: sustaining antimalarial drug development

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The Medicines for Malaria Venture (MMV) is committed to discovering, developing and delivering new drugs for malaria. Founded in 1999 as a nonprofit organization bringing private sector management methods to bear on a global public health problem, MMV is today recognized as a leader among the public–private partnerships working on diseases for the developing world. Together with its many partners, MMV manages the world’s largest malaria research and development portfolio, covering the innovation spectrum from basic drug discovery to late-stage development.

Introduction to MMV

The Medicines for Malaria Venture (MMV; www.mmv.org) is a not-for-profit Swiss foundation that was created to discover, develop and deliver new affordable antimalarial drugs through effective public–private partnerships (PPPs). After five years of operation, MMV, together with its many partners, manages the world’s largest malaria research and development portfolio from basic drug target discovery and validation projects through to advanced formulations of existing drugs. All MMV development projects are executed to international Good Clinical Practices standards, as defined, for example, by the US Food and Drug Administration or the European Agency for the Evaluation of Medicinal Products. Equally, all drugs are manufactured to quality standards, as promulgated under European Directive 2003/94/EC or equivalent. Several drugs are currently in advanced development and MMV expects to launch several important new antimalarial drugs before 2010.

The extent of the challenge

Malaria kills between one and two million people annually, the majority of those affected being children under five years of age and pregnant women [1]. Each year, 300–500 million new clinical cases of malaria are reported in official statistics. Although preventable through vector control or insecticide-treated bed nets, at present only drugs can be used to cure this life-threatening infection [2]. The true number of clinical cases is not accurately known, and recent estimates suggest that actual numbers might be much larger than the official statistics suggest [3,4]. Between 75% and 90% of malaria cases are currently found in sub-Saharan Africa but global warming and demographic changes could change this. Both warming and increased flooding are conditions that favor the spread of the mosquito species that transmits malaria, thus increasing the possibility that malaria will return to parts of Europe and the USA [5,6].

PPPs have rapidly evolved as the preferred way to ensure that progress can be made in addressing healthcare issues that neither the public nor the private sector can solve on their own. MMV, incorporated as a Swiss foundation and officially launched on 3 November 1999, was among the first PPPs established to tackle the drug innovation gap of a major global neglected disease. The synergistic combination of pharmaceutical industry knowledge and expertise in drug discovery and development, and the public sector with its depth of expertise in basic biology, clinical medicine and malaria control experience, constituted the underlying rationale for its chosen PPP formation.

The organizational structure of MMV (Figure 1) enables flexibility in governance and management, making it possible for objectives to be met efficiently and rapidly. MMV is today governed by a board of up to 12 members chosen for their scientific, medical and public-health expertise in malaria and related fields, their research and management competence, and their experience in business, finance and fundraising. MMV uses an Expert Scientific Advisory Committee (ESAC) to advise on the selection and review of projects for funding by MMV and to provide more general advice and information on appropriate technical strategies for the Foundation to achieve its goals. The members of the ESAC come from both industry and academia and cover the full range of expertise required to assess projects in the extremely complex process of drug research and development. Current and former members of the ESAC also participate in the MMV–ESAC Mentor Program.

The need for continued drug innovation

Although malaria control programs, malaria product research and, indeed, the number of malariologists themselves decreased after the eradication era in the 1950–1960s, resistance to antimalarial drugs and to insecticides has increased [7]. The world’s poorest people in endemic regions do not benefit from drugs developed for...
the specialized travelers' market in wealthy countries because these drugs are expensive and largely designed for prophylaxis rather than therapy. Although the travelers' market in industrialized countries totals, perhaps, some US$300 million per year, this is still well below the amount required to generate commercial research and development from the research-based pharmaceutical industry. Furthermore, the potential market for innovative new antimalarial drugs is hampered by competing counterfeit and substandard drugs, owing to a poor regulatory and enforcement infrastructure in many disease-endemic countries (http://www.cdc.gov/malaria/travel/counterfeit_drugs.htm). The net result has been a lack of innovation and diversity that has led to increasing drug resistance. The old, affordable first-line drug treatments such as chloroquine and sulfadoxine–pyrimethamine are today virtually useless in many parts of Africa and Asia [8,9] (Table 1).

Artemisinin combination therapies

The Chinese initiated the development of the fast-acting artemisinin drugs during the Vietnam War (1966–1971) and have continued working on them as combinations with slower-acting partner drugs. Artemisinin combination therapies (ACTs) are by far the best class of antimalarial drugs available today, both in terms of efficacy and prospective longevity. However, ACT drugs are still not ideal in terms of safety, with potential neurotoxicity and neuronal degeneration observed in animals, and cell culture conditions that use artemisinin or artemisinin derivatives at concentrations several times that used to treat malaria [10,11]. They are specifically contraindicated in early pregnancy [12,13]. Moreover, because these agents are extracted from plants, their production time is lengthy and costly. Although usually purchased through global donations for the public sector in developing countries, the underlying cost is still 10–30 times more than the

<table>
<thead>
<tr>
<th>Antimalarial drug</th>
<th>Year introduced</th>
<th>Year resistance found</th>
<th>Other limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine</td>
<td>19th century</td>
<td>1910</td>
<td>Compliance, safety</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>1945</td>
<td>1957</td>
<td>None</td>
</tr>
<tr>
<td>Proguanil</td>
<td>1948</td>
<td>1949</td>
<td>None</td>
</tr>
<tr>
<td>Primaquine</td>
<td>1950</td>
<td>No resistance</td>
<td>Safety</td>
</tr>
<tr>
<td>Sulfadoxine–pyrimethamine</td>
<td>1967</td>
<td>1967</td>
<td>None</td>
</tr>
<tr>
<td>Amodiaquine</td>
<td>1975</td>
<td>No resistance</td>
<td>Safety, possibly resistance</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>1977</td>
<td>1982</td>
<td>Cost, safety</td>
</tr>
<tr>
<td>Artemisinins</td>
<td>1970s</td>
<td>No resistance</td>
<td>Compliance, cost, possibly safety</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>1988</td>
<td>1992</td>
<td>Cost, safety</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>1996</td>
<td>1996</td>
<td>Cost</td>
</tr>
<tr>
<td>Lapdap</td>
<td>2003</td>
<td>No resistance</td>
<td>Resistance potential</td>
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*aSource: MMV, World Health Organization.

*Table reproduced, with permission, from Ref. [27]. © (2005) American Chemical Society.
traditional first-line drug treatments. Scale-up requires a considerable quantity of agricultural land and dedicated extraction plants that can pose environmental risks. Because of the time lag between needs forecasts, procurement and delivery times, which are also affected by lengthy planting and growing seasons, shortages at the point of use of this plant-based drug are common. Furthermore, use of artemisinin-based monotherapy, which threatens much of the rationale of the combination drugs by risking the generation of resistance, continues virtually unabated.

Ideally, the Global Malaria Programme would like to have an effective and affordable first- and second-line drug specifically suited for each country or region. Because no drug will fit the needs of every country, at least three or four good options should ideally be available (the most current World Health Organization treatment guidelines are published elsewhere [9]). MMV and its partners are currently developing several lower-cost ACTs (e.g. chlorproguanil–dapsone–artesunate and Eurartekin™), targeted to be approved within the next three years. However, the longer-term and unique contribution of MMV (Figure 2) to the antimalarial arsenal will be the development of newer antimalarial combination therapies such as the synthetic peroxides, which do not rely on artemisinin as the sole fast-acting drug class (see later).

Developing drugs up close: clinical development projects

*Artokin™ (dihydroartemisinin–piperaquine): Phase I, II and III*
Dihydroartemisinin–piperaquine (Artokin™) is a fixed-ratio drug combination being developed to treat uncomplicated malaria. Artokin™ has been widely used in Southeast Asia but has not yet been developed to international registration or quality standards. The active pharmaceutical ingredients in Eurartekin™ (the new fully international standard drug) were initially manufactured by Sigma-Tau in Italy for the clinical trials, and this expertise is being transferred back to our Chinese partners, Holley Pharmaceuticals. Because of extensive human experience, the nonclinical development plan (toxicology and pharmacokinetics) is being performed concurrently with the clinical development plan, which includes three pharmacokinetic and two confirmatory Phase III studies [14,15].

**Chlorproguanil–dapsone (Lapdap™)–artesunate: Phase III**
Chlorproguanil–dapsone–artesunate is a fixed-ratio three-drug combination (Lapdap™ with artesunate) that is being developed to treat uncomplicated *Plasmodium falciparum* malaria. The Phase II dose-ranging study in adults and children with uncomplicated malaria has been completed and the optimum ratio of artesunate to the fixed combination of chlorproguanil and dapsone has been established. A Phase III clinical development program will involve multiple sites in Central, East and West Africa.

**Pediatric Coartem™**
Based on the data obtained with various trial pediatric formulations, a user-friendly pediatric dispersible tablet is in development. The efficacy and safety of the Coartem™ dispersible tablet will be compared with the conventional crushed Coartem™ tablet in an investigator-blinded, multicenter Phase III study in infants and children (in

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**Figure 2.** The project portfolio of MMV. Projects in the MMV pipeline are categorized according to stages from exploratory to clinical trials and then towards product registration. Abbreviation: PSAC, plasmodial surface anion channel.
the weight range 5–35 kg) suffering from malaria. Six centers in Africa were selected for this study and the trial began in early 2006.

**Pyronaridine–artesunate: Phase II**
A fixed combination of pyronaridine and artesunate is being assessed as a once-daily oral treatment in both adults and children suffering from acute uncomplicated *P. falciparum* and *Plasmodium vivax* malaria. A multi-objective Phase I study was completed in 2005 and a study to assess the tolerability, safety and pharmacokinetics in children is being initiated in Gabon in 2006. Following this study, the Phase III program is planned to be conducted in 2006 both in Africa and Southeast Asia, in child and adult patients.

**Synthetic peroxide RBx11160/OZ 277: Phase II and partner drug selection**
RBx11160/OZ 277 [16] completed Phase I clinical trials in 2004. A Phase I–II pharmacodynamic study in adult patients in Thailand completed enrolment in 2005 and trial data are currently being analyzed. Additional Phase I studies and a Phase II dose-ranging study are to be started in 2006. Development of both a pediatric formulation and an intravenous formulation are underway, together with piperazine as the first partner. Preclinical studies are ongoing with the combination and a Phase I clinical trial is planned for 2006.

**Preclinical development projects**

*Isoquine (an improved aminoquinoline)*
Isoquine is being developed in partnership with GlaxoSmithKline and the University of Liverpool, where it was discovered. It is a second-generation aminoquinoline, which retains the ease of synthesis of amodiaquine and promises a new generation of affordable, well-tolerated and effective antimalarial drugs that are devoid of any cross-resistance to the chemically related chloroquine and amodiaquine. In 2005, the N-tert-butyl form passed candidate selection criteria and, with the preclinical phase completed, is scheduled to be first tested in humans in 2006.

**Discovery projects – lead optimization**

*4(1H)-pyridones*
In 2004, the 4(1H)-pyridone derivative GW844520 progressed from discovery to development. The preclinical program revealed problems that made it unlikely for this specific molecule to progress further. A pyridone back-up lead optimization program was then initiated and several promising drug candidates have now been generated with increased solubility and enhanced oral bioavailability. After an exploratory animal toxicology program, a new candidate with improved properties was selected in early 2006. The rapid success in the back-up program is a part of the strategic portfolio approach built into the Glaxo-SmithKline and MMV collaboration.

*New dicationic molecules*
Pentamidine, a dicationic molecule, has been used to treat *Pneumocystis carinii* pneumonia, antimony-resistant leishmaniasis and early-stage African trypanosomiasis (sleeping sickness), and has also been tested in a Phase II proof-of-concept study to treat malaria. Its low toxicity and demonstrated activity in humans is an encouraging proof of concept for improved-activity dicationic molecules. These molecules concentrate selectively in *P. falciparum*-infected red blood cells, where they enter and kill the parasites. The exact mechanism of action of these compounds is not understood but, along with DNA intercalation [17], they are also believed to interfere with the heme degradation pathway. Recent work has demonstrated that superior compounds with excellent selective activity against malaria can be designed, and these compounds are currently being evaluated in the Aotus monkey model of *P. falciparum* to select the best candidate.

*Enantioselective 8-aminoquinolines*
Over the past few years, there has been increasing concern that morbidities resulting from *P. vivax* malaria have been underestimated and that chloroquine resistance is spreading [18,19]. The need for a new, safe, efficacious and affordable treatment for both the acute and relapse phases of *P. vivax* malaria is pressing. To date, 8-aminoquinolines are the only compounds that have been shown to be efficacious as anti-relapse therapy; NPC1161B is the (−) enantiomer of 8-aminoquinoline. Although it retains potent pharmacological activities both *in vivo* and *in vitro*, it was shown to be significantly less toxic than the (+) enantiomer or the racemic mixture in the models tested so far.

**Discovery projects – exploratory and lead identification**

*P. falciparum* enoyl-acyl carrier protein reductase (*Fab I*)
Fab I is the only known enoyl-acyl carrier protein reductase in *P. falciparum*. Phylogenetically, this enzyme is in the same group as the plant and bacterial enoyl reductases, and is different from the FAS I system present in animals. In bacteria, Fab I has been shown to be essential for fatty acid synthesis and is the molecular target for several antimicrobial drugs, including isoniazid and triclosan. *P. falciparum* (*Pf*) is sensitive to triclosan, and *Pf* Fab I has been validated pharmacologically with triclosan. The *Pf* Fab I enzyme assay and enzyme 3D structure are being used to guide hit-to-lead chemistry to progress current inhibitors to the lead declaration decision point.

*Second-generation ozonide (synthetic peroxide)*
This project was conceived to identify a second-generation ozonide that will provide single-dose oral cures for patients with uncomplicated *P. falciparum* malaria. The screening and selection strategy has focused on optimizing the pharmacokinetic–pharmacodynamic relationship of these ozonides to provide single-dose cures with outstanding prophylactic potential, optimized bioavailability and low cost of goods. Specifically, current studies are focused on identifying compounds with an increased half-life after oral administration to enable extended exposure following a single dose. The lead ozonide has a 100% cure rate when administered as a single dose at 30 mg per kg
body weight in a murine malaria model, and is as effective as mefloquine as a prophylactic agent, with a faster mode of action. It has an extended half-life in rats relative to the original OZ 277 and has high oral bioavailability.

**Dihydrofolate reductase**

Drugs that inhibit the folate pathway have been widely used for the treatment of malaria but their use is declining owing to the emergence of drug resistance developed through mutations in the dihydrofolate reductase (DHFR) enzyme. However, the folate pathway remains a good target for chemotherapy because the enzyme is limited in its mutational capability. The availability of the crystal structures of wild and mutant DHFR, both individually and complexed with inhibitors, has meant that it has been possible to design and synthesize compounds that inhibit the mutant enzymes. These new DHFR inhibitors are inexpensive, active against multidrug-resistant strains and cure malaria within three days. The chemistry program, guided by the enzyme structure, pharmacokinetics, metabolism and in vitro and in vivo activity studies, is aimed at overcoming the issue of oral bioavailability.

**Falcipain (cysteine protease)**

Inhibitors of cysteine proteases block hemoglobin degradation and parasite development in malaria parasites *in vitro* [20]. A proof-of-concept study using azepanone compounds in a severe combined immunodeficiency mouse model of *P. falciparum* was successful. The lead compound has demonstrated potent activity against falcipains and against cultured malaria parasites, with good pharmacokinetic and metabolic properties and low potential cost of goods, and can eradicate malaria infections in *P. falciparum*-infected mice. Future plans include the selection of an orally active lead candidate for preclinical studies by the end of 2006, resolution of the structures of falcipains with candidate inhibitors, and continued synthesis and study of related compounds as back-up falcipain inhibitors.

**P. falciparum protein farnesyltransferase**

In 2000, the project team showed that farnesyltransferase inhibitors display potent anti-*P. falciparum* properties *in vitro* [21]. This led to the possibility of 'piggy-backing' on farnesyltransferase inhibitors being developed by several pharmaceutical companies. Protein farnesyltransferase was validated as the target for *P. falciparum* growth inhibition with the tetrahydroquinoline class of inhibitors from Bristol-Myers Squibb. The evidence suggested that *P. falciparum* protein farnesyltransferase is a viable target for antimalarial drug development [22]. Several tetrahydroquinoline molecules have good activity against the target and the parasite but the challenge still remains to turn these into compounds that can be developed as drugs.

**Looking to the future**

The projects of MMV are evaluated continuously by the project management teams against set milestones. Once a year, the entire portfolio is assessed by the ESAC. Their insights and contributions to the success of the MMV pipeline are invaluable. Finally, our rapid advances are made possible by the partners of MMV in academic research institutes and industry, of which there are nearly 40 in total. Currently, there are ~300 scientists and clinicians around the world working on antimalarial projects supported by MMV (Figure 3).

During the past five years, MMV has focused on developing drugs that would be used primarily to treat uncomplicated *P. falciparum* malaria but there are other malaria indications that need new drugs. Intermittent preventive treatment in pregnancy is one such indication [23]. Developing drugs for pregnant women is difficult in that the drugs must be safe and effective for the mother without causing damage to the developing fetus. Artemisinin-based drugs have clear early embryo toxicity in animal studies, although accidental human exposure shed little light on the potential safety in humans.

Intermittent preventive treatment in early infancy is also needed because the majority of victims of malaria are African children less than five years of age. During the first months after birth, the child gradually loses maternal protection and is susceptible to severe malaria. Intermittent preventive treatment in early infancy has been found to be successful in preventing severe malaria and decreasing the morbidity and mortality rates in young children, even when apparently less-effective drugs have been used. This suggests that intermittent preventive treatment can help to protect children from malaria while they develop immunity [24].

A malaria epidemic can have disastrous consequences for a population with low or no natural immunity. In emergency situations, such as natural disasters and in refugee camps where health infrastructure is poor and the potential for an epidemic is high, a single-dose antimalarial cure would be particularly relevant.

Although *P. vivax* does not normally cause death, it is still a significant health problem in many parts of the world. Treatment of acute blood-stage *P. vivax* malaria can still be achieved with chloroquine followed by a 14-day course of primaquine but relapses often occur because of failure to complete the full course of treatment [25]. A new, effective, radical cure that is significantly more easily tolerated is urgently needed. The MMV enantioselective 8-aminooquinoline project is working towards this goal.

Ultimately, severe cerebral malaria due to *P. falciparum* is the main cause of malaria-related death. Prompt treatment of uncomplicated malaria at an early stage should prevent most patients from progressing to severe malaria. However, patients often present after the disease has already progressed to a stage where they cannot take oral drugs and need to be treated with intravenous or intramuscular drugs. Intravenous forms of pyronaridine–artesunate and the synthetic peroxide are the two drugs in the portfolio that are being developed to treat severe malaria.

An ideal antimalarial drug will kill not only the parasite but also the gametocytes, thus blocking transmission as well as treating the infection. Artemisinins and synthetic peroxides seem to be transmission-blocking...
agents but new partner drugs should also be developed with this activity.

Although most of the 11 discovery projects in the MMV portfolio have had successes in achieving their goals, others are struggling to meet their milestones, as might be expected based on standard pharmaceutical attrition rates. To achieve the longer-term goals of MMV – to provide new, improved drugs that can replace the older ones – the number of discovery projects is less than optimal; MMV therefore plans to increase the number of discovery projects in 2006. This will be done by: (i) adding more projects to the portfolio, achieved through a focused Call for Proposals; and (ii) by seeking to build more portfolio-based partnerships with industry.

The potential of malaria drug research, both within and outside of the MMV pipeline, is promising. There are no technical reasons why research cannot deliver more than the ACT drugs that are today’s standard of care. A balance between continuous innovation and evidence-based use of malaria control and treatment measures provides the only rational way forward to achieving the vision of MMV. It is now crucial that the well-documented mistakes of the failed eradication era in the 1950–1960s are not repeated by thinking that all that is needed is already at hand [26].

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