Medicines for Malaria Venture is a not-for-profit foundation dedicated to reducing the burden of malaria in disease endemic countries by discovering, developing and delivering new affordable anti-malarials through effective public-private partnerships.
In our report last year we focused on the burden of malaria on the lives of people living in developing countries and on MMV’s vision: a world in which affordable drugs will help eliminate this scourge and protect children, pregnant women, and vulnerable migrant workers. Integral to this vision is the understanding that success in combating a disease as complex and multi-faceted as malaria requires many coordinated public health interventions, in addition to safe and effective drugs.

We are also well aware of the history of over-promise and under-delivery associated with some malaria control programmes in the past. Bearing this history in mind, we are neither tempted to promise more than is possible nor to overstate our achievements. What then have been the achievements in MMV’s first full year of operation?

We have always been passionate advocates of public-private partnerships as a strategy to counter the lack of commercial R&D for new anti-malarial medicines. We also recognise that even where relevant commercial R&D occurs, for example for the modestly sized travellers’ market, little from its output eventually goes to the poor in endemic countries. The reality is that both the R&D value-chain and subsequent so-called “access” issues can be very complex and intimidating. It would be as foolish to pretend that the problem has been fully addressed through public-private partnerships, as it is to point a finger of blame at any one sector.

These caveats notwithstanding, what can be said even after only a short period of MMV’s existence, is that the central partnership concept that sustains MMV’s operations does work better than most expected. Our experience is that we have successfully configured the rather imprecise though widely accepted wisdom, of the benefits of public-private partnerships into a specific template that actually functions to significantly stimulate leading edge drug R&D. This achievement is very clear from...
Critical to this achievement is the fact that we have real pharmaceutical partners - several are at the top of the big Pharma R&D productivity rankings. They are real net contributors to the complex set of human skills and technological resources that need to be marshalled for state of the art pharmaceutical R&D to be possible. The size of the anti-malarial portfolio we now manage is the largest assembled since the Second World War. It is also the first ever specifically targeted at the poor living in the approximately ninety disease endemic countries. MMV’s contractual relationships with our pharmaceutical and academic partners are structured as creative win-win agreements. Although each is unique, MMV always gets free and unfettered access to the key research outputs, including rights to intellectual property within our field of interest.

What is particularly pleasing in reporting these achievements is that they are beginning to be widely recognised. Even erstwhile critics of the partnership concept who imagined that there were irreconcilable differences between our public-health remit and the needs of our pharmaceutical partners are largely conceding that we must be doing something right. Indeed many are now seeking to work with us or to replicate the template we have developed for other neglected diseases. Having established the template, committed to executing it against a detailed business plan and completed the first part of the plan successfully, we are now focusing on fine-tuning and scaling-up the operation. This will involve in the first instance a major updating of the business plan, which is targeted for completion in Q3/Q4 2002.

Many enterprises falter at this crucial “mezzanine” stage of their development. Early success can lead to overconfidence with a subsequent overcommitment of human and financial resources that cannot in the end be sustained. We will be very careful not to do this. Nevertheless, it is clear that we must now begin to scale-up in order to achieve the critical mass and portfolio size that will allow us to deliver our target of registering one new anti-malarial drug every five years. Scaling-up for us involves not only a desire to increase the quantity and quality of the R&D we support; we hope over the next several years to approximately double the size of our portfolio and to apply tried and tested portfolio management techniques to it. It also implies some qualitative changes including a broadening of the malaria indications we hope to target. Additionally our current portfolio, perhaps not surprisingly, originates mainly from developed countries where relevant R&D is largely focused and where most of our partners are located. We now hope, without compromise to quality, to broaden the provenance and scope of this R&D to include programmes from developing and particularly from malaria endemic countries.

Our newly established “International Operations” office in Delhi will thus focus on engaging the science base and the industry of these countries - but only where these resources already exist and can contribute to our vision without the need for priming investments. It is in this context that we recently signed a Memorandum of Understanding with the Indian Council for Scientific and Industrial Research (CSIR), one of the world’s largest R&D organisations with a long history of interest in malaria R&D. We are also particularly delighted that Dr. R A Mashelkar FRS, the Director General of CSIR, has agreed to join MMV’s Board of Directors.

Finally, scaling-up also involves an increased focus over the next several years on efficient financial management and on effective fundraising. As is clear from the financial section of this report, we have in 2001 both managed to increase our R&D spend and portfolio size, decrease the percentage spent on Geneva-based operations and at the same time increase our operational reserves. All of this has been possible with the close involvement and counsel from our donors, stakeholders and professional advisors.

Fundraising is always part of the landscape of not-for-profit organisations like MMV. We believe that for the process to be effective - and it will have to be for us to reach the targets outlined in our business plan - it will require the participation not only of MMV management but of all stakeholders and donors.

In concluding our statement last year we made the point that our primary goal during the next several years was to create an organisation capable of delivering MMV’s vision in a sustainable manner. That strategic goal has not changed but in reviewing the detail of this report we feel that the goal is not only achievable but well on track.

Dame Bridget Ogilvie
Chair
Medicines for Malaria Venture

Dr. Christopher Hentschel
Chief Executive Officer
Medicines for Malaria Venture
The year 2001 ended with global attention becoming increasingly receptive to the problem of neglected diseases in developing countries and culminated in the creation of the Geneva-based Global Fund to fight AIDS, tuberculosis and malaria. The concept for such a fund was initially raised at the G8 Summit in Okinawa in 2000. It was then endorsed at the UN General Assembly Special Session on HIV/AIDS in June 2001 and again at the G8 Summit in Genoa in July 2001.

2001 also saw the relationship between global health and economic growth highlighted in the report of the Commission on Macroeconomics and Health entitled “Macroeconomics and Health: Investing in Health for Economic Development”. The report, authored by a group of eminent economists headed by Harvard’s Professor Jeffrey Sachs, provides detailed analysis and economic arguments as to why it is in the interest of the global community to support health interventions, including R&D that targets the very poor. The Commission argues: “With globalization on trial as never before, the world must succeed in achieving its solemn commitments to reduce poverty and improve health. The resources - human, scientific, and financial - exist to succeed, but must now be mobilized. As the world embarks on a heightened struggle against the evils of terrorism, it is all the more important that the world simultaneously commit itself to sustaining millions of lives through peaceful means as well, using the best of modern science and technology and the enormous wealth of the rich countries. This would be an effort that would inspire and unite peoples all over the world.”

“The Maturation of Medicines for Malaria Within the Global Context”

“Chloroquine, one of the most effective synthetic anti-malarials ever developed, was late to be accepted because it was long considered too toxic. It finally became recognised as an effective treatment when it was adopted as a standard anti-malarial for the United States Army.”

“Malaria research outlays are perhaps $100 million, or $2.20 per DALY (disability-adjusted life years). Thus, the malaria R&D per DALY is around one-twentieth of the global average. It is notable and disturbing that the premier public-private partnership for developing new malaria drugs, the Medicines for Malaria Venture (MMV), currently disburses less than $10 million per year in funding, and is so limited in funding that it currently aims for only $30 million per year by 2004.”

In last year’s annual report, MMV’s first, the scientific section focused on the medical need for anti-malarial drugs, the scientific opportunity that exists for these needs to be met, and the portfolio building process that was under way at MMV to deliver on its mission. At that time, three projects had been initiated and could be described in detail, all of them discovery projects. Eight other projects, many of them at the developmental stage, had been selected for funding, but were not operational. Combining these projects into the portfolio represents a major advance in the level of MMV’s scientific operations and its chances of future success.

The past year has essentially been one of portfolio consolidation, rather than growth and further project selection. MMV has had to work hard to put in place both personnel and procedures to manage what is already perhaps the largest anti-malarial drug development portfolio ever assembled by one organisation.

This consolidation has taken several aspects:
- The formal review by MMV’s Expert Scientific Advisory Committee of the three projects already operational
- The establishment of agreed project plans for the newly selected projects
- The hiring of three scientific officers to provide project management support to MMV projects
- The initiation of a third round of project selection, to be completed by early 2003, and the identification of potential new projects for consideration in that process.

The progress within the project portfolio itself is illustrated next page.

Some remarkable advances within individual projects occurred in 2001—particularly noteworthy are:
- The University of Nebraska/Monash University/Swiss Tropical Institute/Roche Synthetic Peroxide project (see page 17)
• The design and identification of compounds with enhanced longer lasting activity than artemisinin derivatives. These compounds could deliver improved drugs with shorter treatment times than those required for the artemisinin derivatives.

• The submission of MMV’s first patent application, with ownership and rights to all anti-malarial applications residing with MMV. A further patent application is likely within the year.

The Bayer Project on Artemisone, a semi-synthetic artemisinin derivative with improved efficacy and reduced neurotoxicity characteristics compared to the artemisinin derivatives (see page 27)

• A full scale pre-clinical programme has been initiated within three months of project selection

• Phase I clinical studies are envisaged in 2003 if all goes well with toxicological assessment.

The GSK/University of Liverpool/WHO project on the chlorproguanil – dapsone – artesunate combination has proceeded very well with pre-clinical safety studies almost complete (see page 32)

• Assuming there are no untoward toxicity results this product should also enter Phase I clinical trials in 2003.

The Korea SP Pharm Inc./WHO project on the pyronaridine – artesunate combination (see page 30)

• Rapid advancement into pre-clinical studies, especially toxicology

• The establishment of appropriate outsourced activities in both South Korea and elsewhere

• Assuming there are no untoward toxicity results this product should also enter Phase I studies by early 2003.

It is perhaps no accident that all the highlighted projects this year involve an artemisinin derivative combination product, or a single agent related to the artemisinins, either as a semi-synthetic, or fully synthetic, compound. This class of agents has received tremendous scientific interest and validation over the last decade and the science was ripe for further exploitation. Increased use of artemisinin derivates to treat malaria, often in poorly financed healthcare systems, has led to an increased and urgent need to better understand and characterise these drugs. In particular it is important to more fully define their safety profile. Improved pharmacovigilance with currently used therapies will help address this issue.

The pre-clinical data currently being obtained in the MMV projects, for example in reproductive toxicology, and the subsequent good clinical practice associated with MMV clinical regulatory studies, will also greatly assist in this process.

Although the artemisinin related projects have been highlighted this year, it should be stressed that MMV is significantly invested in other approaches including entirely novel molecular targets and we envisage that these will start to play a larger role in our portfolio focus in the coming years.

Scientific Opportunities for New Chemotherapeutic Approaches

There has been a quantum increase in our level of understanding of malaria biology in recent years. This is the result of increased investment from many national and regional scientific research agencies and research foundations, such as US National Institutes of Health, Wellcome Trust, Burroughs-Wellcome Fund, and the European Union. Evidence of this is perhaps best illustrated by the revolution in malaria genomics - the completed genome will be published later in 2002. An excellent overview of the current status of malaria research activities can be found in the recent Nature Insight (Nature, February 7th, 2002 issue) which was co-sponsored by MMV and from which the figure next page is taken. Moving in a clockwise direction around the figure, MMV’s projects cover many of the areas highlighted in the figure:

Projects on cytosolic drug targets include: Antifolate inhibition, including inhibitors of dihydrofolate reductase

• Chlorproguanil-dapsone-artesunate development project with GSK: chlorproguanil inhibits dihydrofolate reductase; dapsone inhibits a folate pathway enzyme called dihydropterote synthase (see page 32)

• Dihydrofolate reductase inhibition exploratory project with the National Science and Technology Development Agency, Thailand (see page 25).
Glycolysis inhibition
- Lactate dehydrogenase inhibition discovery project with GSK, University of Bristol and London School of Hygiene and Tropical Medicine (see page 20).

Isoquine is an analogue of chloroquine which interferes with haemazzonin formation (see page 31).

Projects relating to the lysosomal food vacuole include all the artemisinin projects already mentioned including the synthetic peroxides. In addition they include: Interference with hemoglobin degradation and haemazzonin formation
- Isoquine development project with GSK and University of Liverpool.

Projects on mitochondrial related metabolism include:
- Interference in nucleotide biosynthesis
- Dihydroorotate dehydrogenase exploratory project with University of Leeds (see page 26).

Drug discovery and development are many-fold. They include the extensive rise of drug resistance to many of the commonly used anti-malarial drugs, safety issues associated with some drugs and difficulty in ensuring compliance for drugs that have a more complicated dosage regimen.

As stressed in last year’s report, the medical needs driving anti-malarial drug discovery and development are many-fold. They include the extensive rise of drug resistance to many of the commonly used anti-malarial drugs, safety issues associated with some drugs and difficulty in ensuring compliance for drugs that have a more complicated dosage regimen. In addition, the cost of certain drugs greatly risks their inclusion in national policies, especially in Sub-Saharan Africa. The safety issues are of particular significance given the poor infrastructure of many healthcare systems in which malaria is endemic and the resultant lack of supervision of drug use. This is of particular concern for the two most “at risk” groups of patients, namely very young children and pregnant women (see figure above).

It is helpful to divide malaria into several major sub-indications and to acknowledge that a different set of issues exists for each of these.

Projects on apicoplast metabolism include: Inhibition of Type 2 Fatty Acid Biosynthesis
- Enoyl-acyl-carrier protein reductase inhibition discovery project with Texas A & M University, Howard Hughes Medical Institute and Jacobus Pharmaceuticals (see page 19).

Inhibition of protein isoprenylation
- Protein farnesyltransferase inhibition discovery project with University of Washington and Yale University (see page 22).

As stressed in last year’s report, the medical needs driving anti-malarial drug discovery and development are many-fold. They include the extensive rise of drug resistance to many of the commonly used anti-malarial drugs, safety issues associated with some drugs and difficulty in ensuring compliance for drugs that have a more complicated dosage regimen.

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It is helpful to divide malaria into several major sub-indications and to acknowledge that a different set of issues exists for each of these.

Overview of current anti-malarials
Dugs currently in use as anti-malarials have many attributes, but also contain certain liabilities that could be improved upon by further drug discovery and development.

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<tr>
<th>Drug</th>
<th>Main limitations</th>
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<tbody>
<tr>
<td>Chloroquine</td>
<td>Resistance, Compliance, safety, resistance</td>
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<tr>
<td>Quinine</td>
<td>Safety, resistance (cost)</td>
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<td>Atovaquone-proguanil</td>
<td>Resistance potential, cost</td>
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<td>Lumefantrine-artemether</td>
<td>(compliance), resistance potential, (cost)</td>
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<th>Drug</th>
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<td>Artemisinin (artemether, arteether, artemesunate)</td>
<td>Compliance, (safety), (GMP), (cost)</td>
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<tr>
<td>Sulphadoxine-pyrimethamine</td>
<td>Resistance</td>
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<td>Mefloquine</td>
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<td>Halofantrine</td>
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<tr>
<td>Artemisinins</td>
<td>Resistance, compliance, safety, resistance</td>
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Appropriate, stable formulations (intramuscular, intravenous or intra-rectal)

Rapidly acting drugs to bring about rapid recovery from coma.

Plasmodium vivax malaria, for which drugs are needed that are active against both the blood and liver stages of the disease, and where the main issues relate to:

- Overcoming drug resistance for the blood stage of the disease
- Superiority in safety to the only drug currently available to treat the liver stage of the disease, primaquine.

Malaria in pregnancy where the main issues relate to:

- Safety, especially a defined lack of any foetal toxicity
- A profile that facilitates intermittent treatment during pregnancy to prevent women from contracting serious disease.

For many of the sub-indications mentioned above, it is very difficult to define how appropriate projects are until they have progressed far into the drug discovery process, or even have entered pre-clinical or clinical development. It is therefore not easy at the moment to state the specific relevance of our projects for these indications. However, as more and more projects are subjected to rigorous toxicological evaluation, their potential will become more apparent.

The MMV portfolio is already quite comprehensive. However, it should be stressed that many projects are reaching the most risky stages of the drug R&D process. That is, they are about to engage in extensive toxicological evaluation and an assessment of their ability to generate useable drug formulations. Several may not survive the rigorous tests ahead and we calculate that we still need to double our project portfolio to deliver on our mission to generate one new anti-malarial every five years.

Nevertheless, progress to date has been far better than we could have predicted. With luck we hope that this portfolio could indeed change the face of anti-malarial drug use in the coming decades.

MMV is making every effort to address the issues of safety in pregnancy early on in development. This is especially important as the current drug of choice for intermittent treatment in pregnancy is sulfadoxine-pyrimethamine against which there is substantial resistance development.

There is an urgent need to address the current lack of effective treatments for this indication.

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The figure on the following page, kindly provided by Tom Sukwa of WHO/AFRO, illustrates the issues facing those charged with malaria control. On the one hand there is a desire to encourage wide distribution of drugs for ease of access. On the other there is a desire to ensure drugs are used only when needed and that they are used appropriately to avoid the generation of drug resistance. The more options there are for malaria treatment, the less acute this dilemma becomes and one can promote widespread use without fear that this will result in no malaria treatment being available downstream.
The objective of this project is to identify an orally active low cost anti-malarial synthetic peroxide more potent than any of the currently available semisynthetic artemisinins with a treatment regimen of no more than three days to ensure good compliance.

The suitability of the compounds for non-oral formulations and their potential for prophylactic use will be important secondary, but not essential, criteria. Our aim is to generate sufficient data by 2003 to allow for selection of a compound to enter development.

Many synthetic anti-malarial peroxides have been prepared, but most suffer from low oral activity, a defect shared in part by the semi-synthetic artemisinins. Therefore, a need exists to identify a new peroxide anti-malarial agent, especially one that is easily synthesised, inexpensive, has high oral activity, and is devoid of neurotoxicity.

At the outset of the project, we began with peroxides that had excellent intrinsic potency against P. falciparum. Thus, our emphasis has been on identification of peroxides with a combination of high oral activity in the P. berghei-infected malaria mouse model and a good pharmacokinetic/metabolic profile. Throughout this process, we have explored structure activity relationship (SAR) in sufficient detail to provide strong patent protection.

There have been a number of key results and achievements to report in 2001:
- Several key synthetic peroxodic intermediates were prepared on a 100 mmol scale and subjected to further transformations that are to obtain target compounds
difficult or, in some cases, impossible to obtain directly by our standard peroxide bond forming reaction.

- A clearer understanding of the structure activity of this class of compounds has been defined.
- Lead optimisation efforts have involved prospective estimation of log P and polar surface area values for compounds, and this has been effective in increasing the previously limiting lipophilicity of the peroxides. Furthermore, rapid metabolism screening of active peroxides using human, rat, and mouse liver microsomes has successfully screened out compounds with high metabolic conversion rates. Those compounds successfully passing the metabolism screen hurdle have been progressed to oral bioavailability studies and intravenous pharmacokinetic studies in rats.
- As shown in the figure below, one peroxide development candidate has, like artemesate, a rapid onset of action, but unlike artemesate, a long lasting anti-malarial effect.
- In an exploratory toxicity study, rats were treated with doses of artemesate and three peroxides up to 300 mg/kg/day for five consecutive days. Clinical laboratory investigations revealed minimal and essentially reversible changes. In summary, at this stage there are no adverse toxicological findings.

**DISCOVERY PROJECT 1**

**Synthetic peroxide**

**Principal Investigators and Affiliations:**
- Prof. Jonathan L. Vennerstrom
  University of Nebraska Medical Center, U.S.A.
- Dr. Yuxiang Dong
  University of Nebraska Medical Center, U.S.A.
- Dr. Reto Brun
  Swiss Tropical Institute, Switzerland
- Dr. Bernard Scornaux
  Swiss Tropical Institute, Switzerland
- Prof. William N. Charman
  Monash University, Australia
- Dr. Susan A. Charman
  Monash University, Australia
- Dr. Hugues Matile
  F. Hoffmann-LaRoche, Switzerland
- Dr. Heinrich Ureyer
  F. Hoffmann-LaRoche, Switzerland

**Funds allocated in 2001:**
$1,079,110

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**DISCOVERY PROJECT 2**

**Anti-malarial drug development focused on inhibition of Plasmodium falciparum fatty acid biosynthesis**

**Project description provided by Dr. Jim Sacchettini**

This project proposes the development of anti-malarial compounds that target P. falciparum enoyl-ACP reductase (ENR), a key enzyme in the Fatty Acid Synthase II system (FAS II).

Three chemical hits against this enzyme have been identified, two of them from a high-throughput combinatorial library screen and the third being triplasone, a known bacterial ENR inhibitor. These chemical structures provide the basis for lead optimisation, with the most effective inhibitors identified through a combination of three screens.

Optimisation has already begun with the synthesis of over twenty triplasone analogs. Synthesised compounds are being screened using assays with purified and active P. falciparum ENR, whole-cell assays against P. falciparum asexual blood stage parasites propagated in vitro, and in vivo assays against P. berghei in mice. The P. berghei screen will employ a recombinant parasite line in which the P. berghei gene encoding ENR is being replaced by the P. falciparum homolog, to establish a rigorous in vitro/in vivo relationship.

Our lead optimisation process benefits from parallel elucidation of the crystal structures of enzyme-inhibitor complexes, which will help develop the structure-activity relationships of the compound series. P. falciparum and Mycobacterium smegmatis will serve to assess whether resistance can be readily selected in vitro.

Optimised leads will be subjected to pharmacokinetic and safety analyses to screen for compounds suitable for pre-clinical and clinical evaluation. The absence of FASII in humans and the identification of specific inhibitors validate this pathway as an outstanding target for the development of new anti-malarial drugs.

In addition to investigating P. falciparum enoyl-ACP reductase, significant progress has also been made on characterising other enzymes in the fatty acid synthase type-II pathway (whose activities lie upstream of that of PFENR, also known as fabI). The genes fabF, fabG and fabH have been subcloned from RT-PCR products and we are now crystalizing recombinant, purified fabF.

The interest in this project is to test whether other enzymes represent valid chemotherapy targets. The project is made feasible by the combination of the...
discovery project 3
inhibitors of plasmodium falciparum lactate dehydrogenase as novel anti-malarials

this coordinated academic and pharmaceutical effort.

an inhibitor that specifically inhibits plasmodia LDH alone. Fortunately, we have obtained crystal structures of both human and Plasmodium falciparum LDH and they demonstrate significant structural differences, implying the development of highly selective inhibitors should be feasible. Initial identification of possible leads has utilised a combined approach incorporating high-throughput screening of over half a million compounds, in silico screening on millions more and structure-based design. From these studies we have identified several classes of compounds that selectively inhibit plasmodial LDH in preference to human forms of the enzyme.

Crystallographic studies are being used to visualise precisely how these compounds bind within the active site of the target enzyme, and hence direct further chemical modifications of these molecules. These studies are, of course, complemented by both in vitro and in vivo studies at the London School of Hygiene and Tropical Medicine using both normal and drug resistant strains of Plasmodia. In order to expand the repertoire of possible inhibitory structures, we are also using computers to interrogate a database containing the three dimensional structures of over nine million drug-like compounds.

These calculations use the known structures of lead compounds that have been co-crystallised in the active site of LDH to identify contact sites and generate a pharmacophore - a generalised representation of the compound based on one-dimensional (physical and biological), two-dimensional (substructures) and three-dimensional (charged groups, hydrophobic groups, hydrogen bond acceptors and donors) properties. Once the pharmacophore has been assembled, compounds in the database with similar properties can be identified. This state of the art technique uses many weeks of computer time, but has enabled the project team to identify compounds that not only bind to the enzyme, but also inhibit the growth of the parasite. Once lead compounds have been identified, the complementary range of skills that are available across the three sites are brought into play to fully characterise the molecules: the activity against the parasite is determined by the parasitologists at LSHTM while the crystallographers at Bristol attempt to obtain the structure of the inhibitory complex formed with the target enzyme. This information is then used by the bio-molecular modellers to direct the design of new compounds that are synthesised by the chemists at GSK. Central to these studies is the availability of structural data describing the intimate interactions of inhibitors with the target enzyme. The combination of complementary skills across the project team has enabled us to make good progress within a relatively short period of time.
Malaria parasites reside within red blood cells during the portion of their life cycle that is responsible for clinical malaria. While inhabiting red cells, the parasites take up and degrade human hemoglobin as a key source of amino acids. A number of proteases participate in hemoglobin degradation, including cysteine-class proteases known as falcipains. Inhibitors of cysteine proteases blocked hemoglobin degradation and development by cultured malaria parasites. In addition, peptide cysteine protease inhibitors cured mice of otherwise lethal malaria infections. Thus, the falcipains offer a validated drug target.

An important current goal is the identification of safe and effective falcipain inhibitors for rigorous testing as potential new anti-malarial drugs.

Important progress since our original application has included the following:

**DISCOVERY PROJECT 5**

**Development of falcipain inhibitors as anti-malarial drugs**

Project description provided by Dr. Philip J. Rosenthal

Malaria parasites reside within red blood cells during the portion of their life cycle that is responsible for clinical malaria. While inhabiting red cells, the parasites take up and degrade human hemoglobin as a key source of amino acids. A number of proteases participate in hemoglobin degradation, including cysteine-class proteases known as falcipains. Inhibitors of cysteine proteases blocked hemoglobin degradation and development by cultured malaria parasites. In addition, peptide cysteine protease inhibitors cured mice of otherwise lethal malaria infections. Thus, the falcipains offer a validated drug target.

An important current goal is the identification of safe and effective falcipain inhibitors for rigorous testing as potential new anti-malarial drugs.

Important progress since our original application has included the following:

**DISCOVERY PROJECT 4**

**P. falciparum** Protein Farnesyltransferase Inhibitors as Drugs Against Malaria

Project description provided by Prof. Wesley C. Van Voorhis

The long-term objective of this research is to develop inhibitors of **P. falciparum** protein farnesyltransferase (PIFFT) as drugs against malaria.

PIFFT is an excellent candidate drug target for a number of reasons:
- **Inhibition of PFT is predicted to be lethal to** **P. falciparum** because **P. falciparum** probably lacks an enzyme called PGGT-1 that rescues PFT-inhibited mammalian cells. Consistent with this hypothesis, preliminary evidence demonstrates that PFT inhibitors kill **P. falciparum** rather than being cytostatic.
- The genes for PIFFT have been identified.
- PIFFT is transcribed in erythrocytic forms of **P. falciparum**, and is thus likely synthesised in the life cycle stage that is the target of therapy.
- There is a good correlation with some inhibitors of PIFFT between enzyme inhibition and **P. falciparum** growth inhibition.
- It is likely that selective inhibitors of PIFFT can be found, and selective PIFFT inhibitors may increase the therapeutic window of PFT inhibitors for malaria therapy.

Our goals for the first 2 years are:
- To express recombinant PIFFT for screening potential inhibitors and for structure determination. PFT is a heterodimeric protein with α and β subunits. We have found that the native PIFFT α and β genes would not express in either E. coli or in insect cells using baculovirus constructs, probably because of the high AT nature of plasmodium DNA and the resulting codon bias. We have constructed completely synthetic PIFFT α and β genes with optimal codon usage for baculovirus and are in the midst of constructing baculoviruses for expression of these synthetic genes.
- Discovery of lead PIFFT inhibitors by screening compounds prepared by medicinal chemists at Bristol-Myers Squibb and Schering Plough Research Institute as part of their efforts to develop mammalian PFT inhibitors as anticancer drugs. We will also test compounds prepared in the labs of Prof. Andrew Hamilton (Yale University) and Michael Gelb (University of Washington). Some of these compounds show activity against **P. falciparum** infected red blood cells with an IC50 of <100 nM. Some of these compounds have a >20-fold selectivity in growth inhibition of **P. falciparum** compared with mammalian cells.
- Optimisation of lead compounds using computer-assisted structure-based drug design with the assistance of Christophe Verinde and Wim Hoi (University of Washington) combined with parallel organic synthesis for rapid preparation of lead compound derivatives in the Gelb and Hamilton laboratories with attention to optimization of pharmacokinetic properties of lead compounds measured in the laboratory of S. Sebti (University of South Florida).
- We hope to screen at least 500 promising compounds. Enzyme inhibition studies will be complemented by evaluation of compound activities in the erythrocyte-based culture assay and the P. berghei malaria model in mice. If appropriate, follow-up studies in a primate **P. falciparum** model (laboratories of Wesley Van Voorhis and Fred Bruckner) and toxicology studies will be initiated.

**Protein Prenylation**

Proteins containing a C-terminal CaaX are first prenylated on the cysteine group. This is followed by endoproteolytic removal of aaX tripeptide and methylation of -carboxyl group of the prenylated cysteine. Shown on the left is the cysteine-attached 15-carbon farnesyl group. Some proteins contain the 20-carbon geranylgeranyl group (right).

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Contract under negotiation
Three falcipains and multiple orthologs from other species were identified, enabling us to better plan our activities for drug discovery against cysteine proteases would be more complex than initially anticipated.

The key *P. falciparum* targets falcipain-2 and falcipain-3 were expressed in a heterologous system, purified, and extensively characterised.

High yield expression of falcipain-2 and production of crystals of this enzyme were achieved.

Falcipain-2 orthologs from *P. vinckei* and *P. berghei* were expressed, purified, and biochemically characterised, and key differences between these enzymes and falcipain-2 were identified.

Partial screening of the GSK cysteine protease inhibitor collection against falcipain-2 has resulted in the identification of potent and selective inhibitors, some of which have demonstrated potent in vitro anti-malarial activity against chloroquine sensitive and resistant *P. falciparum* strains.

The overall plan of the project is to prepare recombinant *P. falciparum* dihydrofolate reductase (DHFR), both in wild-type and mutant forms responsible for drug resistance, to crystalize and obtain the structure of the enzyme through X-ray diffraction and to design and screen compounds likely to be effective inhibitors for further development as anti-malarials. We have achieved the expression and purification of the wild-type, single (S108N), double (S108N+C59R and A16V+S108T), triple (N51I+C59R+S108N and C59R+S108N+I164L) and quadruple (N51I+C59R+S108N+I164L) mutant forms of *P. falciparum* DHFR through the use of both natural and our synthetic genes.

Major project objectives for the coming year include:

- Optimisation of expression, purification, and characterisation of falcipains and orthologs from other plasmodial species.
- Complete screening of the GSK cysteine protease inhibitor collection against falcipain-2 has resulted in the identification of potent and selective inhibitors, some of which have demonstrated potent in vitro anti-malarial activity against chloroquine sensitive and resistant *P. falciparum* strains.
- The *P. falciparum* cysteine protease inhibitor collection was extensively enlarged, and available biochemical and biological data for components was expanded.
- A major effort has gone into reorganising chemistry efforts to incorporate the Tres Cantos site, which in 2001 was dedicated entirely to research targeted at developing world diseases. Currently, a high throughput screen is evaluating the activity of the entire GSK cysteine protease inhibitor collection against recombinant falcipain-2, falcipain-3, and vinkepap-2. The full screen will be completed and data from it analysed in the near future. At that point, effective compounds will be identified and collected, and they will then be evaluated for in vitro anti-malarial activity and for pharmacokinetic properties.

Data from in vitro and pharmacokinetic analyses will guide SAR determinations and optimisation of the inhibitors for activity against falcipains and cultured *P. falciparum* parasites, and for pharmacokinetic properties.

Major project objectives for the coming year include:

- Optimisation of expression, purification, and characterisation of falcipains and orthologs from other plasmodial species.
- Complete screening of the GSK cysteine protease inhibitor collection against recombinant falcipains.
- Screening of active GSK inhibitors against cultured *P. falciparum* parasites.
- Pharmacokinetic analysis of lead GSK inhibitors in rodents.
- Crystalisation and initial structure determination for falcipains.
- Synthesis of new candidate falcipain inhibitors based on results of initial screens and SAR determinations.

A major achievement in obtaining crystals of the enzyme, both in the wild-type and double mutant (C59R+S108N) forms are available of sufficient size and quality for X-ray diffraction studies. As for active-site inhibitors, we have designed and screened a number of compounds against the two types of mutants: one is the A16V+S108T and another comprises mutants containing S108N, single, double (C59R+S108N or C59R+S108N+I164L) or quadruple (N51I+C59R+S108N+I164L).

The enzymes, expressed both as DHFR domain only and as DHFR-TS, constitute the most important mutants responsible for antifolate resistance, are now routinely prepared and purified for both screening and crystallization purposes. This represents the first time that *P. falciparum* DHFR crystal structures have been available to assist in drug discovery efforts.
DISCOVERY PROJECT 7
Dihydroorotate dehydrogenase inhibition
Project description provided by Dr. Glen McConkey

This year this project has advanced greatly with the discovery of new compounds that inhibit the targeted enzyme dihydroorotate dehydrogenase. The targeted enzyme catalyzes an intermediate step in synthesis of pyrimidines, building blocks of the genetic material RNA and DNA.

Unlike animals, malaria parasites must derive their pyrimidines from synthesis and cannot salvage pyrimidines. Related studies this year have demonstrated that this enzyme is essential for growth of Plasmodium falciparum. This validates our rationale for targeting this enzyme. In the first year of the study, we developed an in vitro assay for testing compounds based on expression of recombinant enzyme from malaria parasites and humans.

This year we have adapted the assay for screening series of compounds. Several “hits” identified from the screening have been tested and found to inhibit parasite growth.

Over 60 compounds based on prototype dihydroorotate dehydrogenase inhibitors were synthesised at the University of Hull (A. Boa). The most potent inhibitors were tested in parasite assays and found to inhibit growth at low concentrations.

Current efforts are characterising the mechanism of inhibition. Understanding how the compounds inhibit the enzyme will guide the synthesis of a second generation of compounds to search for more potent inhibitors. The kinetics of inhibition and X-ray crystallography with co-crystals of the enzyme and inhibitor will elucidate the interactions. Based on these findings libraries of derivatives will be synthesised in a full drug discovery program.

Bayer AG, Germany, has a successful history in developing drugs against tropical infectious diseases. As far back as 1934, Bayer discovered chloroquine (Resochin®) which in subsequent decades was developed to become the most effective medicine for prevention and therapy of malaria. In 1995, in the context of growing chloroquine resistance, Bayer Central Research department started collaboration with Professor Richard K. Haynes of the Hong Kong University of Science and Technology (HKUST), an internationally renowned authority on the study of Artemisinins.

The goal of the “Bayer-HKUST Anti-malarial Project” was to discover and develop improved artemisinin derivatives for the treatment of uncomplicated, non-severe malaria via oral and suppository formulations. Design features would also seek to ensure suitability for intravenous treatment of severe malaria, for which the only current therapy is intravenous quinine.

The existing artemisinin class of drugs thus had to be improved regarding efficacy, neurotoxicity, stability and pharmacokinetic behaviour. From the beginning of the cooperation, parasicidal efficacy and the establishment of reliable safety parameters were of equal importance. In particular, Dr. Gabrielle Schmuck at Bayer developed novel in vitro assays to test for neurotoxic potential. This proved extremely valuable in the selection of compounds to take forward as potential development candidates.

By the end of the year 2000 several C-10 aminoalkylartemisinin derivatives had been identified, that met the selected criteria for entry into development; high activity in rodent malaria, lack of neurotoxicity both in vitro and in vivo, as well as easy chemical access and scalability. The final development selection was done in cooperation with the Australian Army Malaria Institute in Brisbane. Plasmodium falciparum naive Aotus trivirgatus monkeys were infected with a multi-drug-resistant Plasmodium strain. Parasitemia developed over 6-9 days after inoculation up to a level of 10%. The best compound, later given the proposed name “Artesinone”, when applied as a single dose of 10 mg/kg p.o. reduced parasite density to zero within 1 day, whereas artesunate achieved clearance from parasites after 4 days under the same conditions. Artemisone is in fact 10-30 fold more active than artesunate based on preliminary pharmacokinetic and efficacy data in monkeys.

In 2001, MMV decided to support the accelerated development of
Artemisone as a new drug candidate against non-severe and severe malaria. Pre-clinical development is being done by Bayer Central Research under the leadership of Dr. B. Fugmann. Clinical development is managed by Bayer Pharma division in cooperation with MMV staff.

The pre-clinical development of Artemisone in 2001 has focused on the development of a competitive multi-kg scale synthesis as well as GLP process development and analytical method for toxicology and pharmacokinetics. Additional milestones have been the elaboration of a detailed pre-clinical and clinical development plan and conclusion of the chemical backup program. In 2002, the pre-clinical development will continue with a safety package, further biological testing with exploratory dose finding and combination experiments, GMP synthesis optimisation and formulation development. Clinical phase I with healthy human volunteers is scheduled to start in 2003.

The management of severe malaria requires good medical care and the use of chemotherapy to decrease parasitemia to a non life-threatening level. At present this is accomplished primarily by administering quinine intravenously. However, this treatment is unsatisfactory as the mortality rate reported in the late 1990’s was up to 27% in South East Asia and up to 20% in Africa. Additionally, adverse effects such as cinchonism, hyperinsulinemic hypoglycemia, and often fatal cardiotoxicity have been attributed to quinine. Artemisinins are now being used in an attempt to improve upon quinine’s efficacy and toxicity. As illustrated in the figure, oil soluble artesiminins, artemether and artether, have a methyl and ethyl group respectively, with ether links to oxygen. In contrast the water soluble artesiminins, artelnic acid (AL: figure left) and artesunic acid (AS: figure right) have a polar group attached to the oxygen. Oil-soluble artesiminins and artesunate have been developed as intra-muscular and rectal formulation for severe malaria. However, absorption from the intramuscular site is slow and absorption from the rectum is highly variable. Our rationale is that a better approach which would improve cure rates would be an intravenous formulation of artesiminins that can achieve reproducible peak plasma concentrations. Our plan is first to compare AL to a current formulation of AS, with respect to chemistry and manufacturing, pharmacology, toxicology (including neurotoxicity), pharmacokinetics and metabolism. The better of the two compounds would then be synthesised under Good Manufacturing Practices (GMP) conditions and evaluated in GLP animal studies to meet regulatory Investigational New Drug (IND) requirements. Assuming that there are no safety concerns, a clinical development program will be designed to meet current international regulatory and ethical requirements.

The project status and achievements can be summarised as follows:

Chemistry, Manufacturing, Control (CMC): AL has been formulated in a soluble salt with purity greater than 99%. The AL salt is dissolved prior use to form a stable solution suitable for i.v. injection. The dissolved salt decays over time (10% in two months). Other formulations with improved stability are being studied. AS dissolves in bicarbonate but decays at a 10% rate in hours. In rat, a single dose study showed that only 1% of AL is cleaved to dehydroartesiminin (DHA), indicating that efficacy and toxicology findings may be attributed to the parent compound rather than the metabolite. In contrast, 80% and 38% of a single dose of AS is converted to DHA in man and rat, respectively. It has been shown that human liver microsomes in vitro metabolise AL into 2-hydroxy artelinate. Because microsomes of rhesus monkey, but not dog, also produce 2-hydroxy artelinate, rhesus monkey have been selected as non-rodent animal model for pre-clinical studies.

WRAIR has developed a rat model for severe malaria. Using an i.v. dose of 40mg/kg/day for three days, both AL and AS cleared parasite Plasmodium berghei from rat. Efficacy has also been studied in Aotus monkey infected with Plasmodium falciparum, a commonly used animal model. Our data indicate that AL clears parasite at 8mg/kg/day for three days and AS clears parasites at 2mg/kg for three days. Definite efficacy studies in Rhesus monkey model are now underway.

Rat and Rhesus have proven to be good models to study toxicity and toxicokinetics (drug levels in blood associated with toxicity). These studies will allow the determination of the non-toxic levels and the appropriate therapeutic dose.
DEVELOPMENT PROJECT 3
Pyronaridine Artesunate
Project description provided by Dr. Tom Kanyok

Pyronaridine, an acridine-type Mannich-base, is a water soluble blood schizontocide first synthesised in China in 1970. Data indicate that it is effective against chloroquine resistant parasites and is well tolerated. Artesunate is a water-soluble semi-synthetic derivative of artemisinin. Artesunate has been developed in various forms by several pharmaceutical companies and is registered for clinical use in many countries.

A pyronaridine-artesunate fixed dose combination should provide the following advantages over non-artemisinin-containing drugs already marketed:

- Rapid onset of action translating into rapid fever and parasite clearance time.
- Possible decrease in the rate of development of resistance when compared to standard single agent anti-malarial regimens.
- Possible decrease in transmission of malaria due to the ability of artemisinin derivative to prevent the development of gametocytes.

In addition this fixed combination should present the following advantages over other artemisinin containing drugs:

- Once daily regimen for three days will improve compliance and ease control program in Asian and African setting, compared to the other artemisinin fixed dose combination currently marketed which needs to be administered twice a day for three days.
- Possibility of broader geographic use since widespread development of resistance to pyronaridine has not yet been reported.
- The long-half-life of pyronaridine (60-190 hrs) may increase the interval between new infections in some high transmission settings.

A Product Development team is in place to manage the development programme and has representation from Iowa University, WHO-TDR, MMV, Korea SP Pharm Inc., and other consultants from academic or governmental institutions.

Under the leadership of Korea SP Pharm Inc., the pharmaceutical development is well advanced with a major achievement realised in the form of a simplified route to the synthesis and evaluation of some two hundred novel 4-aminoquinolines with improved pharmacological profiles. We developed two parallel lines of investigation: using chloroquine as the lead molecule we focused on understanding the chemical basis for resistance and using amodiaquine as our lead we tried to separate anti-malarial activity from the liability of this drug to produce potentially life threatening idiosyncratic adverse drug reactions, a feature which has blighted the widespread use of the drug. Clearly there are many areas of overlap between these two research programmes.

Isoquine is the most promising lead compound to have emerged from these research programmes after the synthesis and evaluation of some two hundred novel molecules. Isoquine is an isomeric derivative of amodiaquine under patent to the University of Liverpool. This molecule has been re-designed to remove the metabolic alert for reactive metabolite formation, a feature that is central to the toxicity of the molecule. This manipulation has been achieved without any loss of anti-malarial activity. In fact the drug shows improved activity both in vivo against P. falciparum and in vitro against a rodent model of malaria after oral drug administration compared to amodiaquine or the therapeutically relevant de-ethylated metabolite of amodiaquine. The chemical modification introduced into isoquine also shifts the overall metabolic pattern of the drug in a way that could have therapeutic benefit. Importantly this new drug of 2003. Parallel registration with the European Agency for Evaluation of Medicinal Products is envisaged.

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DEVELOPMENT PROJECT 4
Development of a novel and superior 4-aminoquinoline – Isoquine
Project description provided by Prof. Steve Ward

The 4-aminoquinoline class of anti-malarial, as exemplified by chloroquine and amodiaquine, have been the most successful class of anti-malarial drugs to date. The success of the class is partly based on their ability to exploit features of the haemoglobin degradation pathway, a unique malarial parasite pathway. In addition to this selective mode of action these drugs are affordable, easy to use and prior to the emergence of chloroquine resistance the drugs were highly effective.

For the past fifteen years the Tropical Pharmacology Group in Liverpool has attempted to establish the pharmacological basis of drug action, resistance and toxicity to this class of drugs. Our ambition was to use this information in the rational re-design of novel 4-aminoquinolines with improved pharmacological profiles. We developed two parallel lines of investigation: using chloroquine as the lead molecule we focused on understanding the chemical basis for resistance and using amodiaquine as our lead we tried to separate anti-malarial activity from the liability of this drug to produce potentially life threatening idiosyncratic adverse drug reactions, a feature which has blighted the widespread use of the drug. Clearly there are many areas of overlap between these two research programmes.

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can be synthesised in three simple steps from readily available chemical intermediates. As such the drug should be affordable to our target population.

In order to develop this drug quickly we have developed a public-private partnership between the University of Liverpool, the Liverpool School of Tropical Medicine and GSK pharmaceuticals. The product development team is made up of academic and industry expertise that covers all aspects of the drug development process. The core members of this development team have already successfully managed the development to UK registration of another new anti-malarial agent, chlorproguanil-dapsone. The pre-clinical pharmacology study plans have just been completed and mutagenicity testing should begin within the next four months following the scaled up synthesis of drug. The development of our programme is structured so as to allow a first into man decision within two years with a product registration within five years.

**DEVELOPMENT PROJECT 5**

**Chlorproguanil-dapsone-artesunate**

Project description provided by Prof. Peter Winstanley

Chlorproguanil-dapsone (Lapdap; CPG-DDS), is the partner component of this artemisinin combination. It is a rapidly-eliminated antifolate drug currently submitted for regulatory approval for the treatment of uncomplicated malaria. It has been shown:

- To select less readily for resistant parasites than sulfadoxine-pyrimethamine (SP).
- To be safe and well tolerated.
- To have clinical utility in patients whose prior treatment with SP had failed. It is also available at a price that is affordable in the context of malaria in Sub-Saharan Africa.

Further development of the product with the addition of artesunate, an artemisinin compound (CDA), is now being undertaken for the following reasons:

- Artemisinin combination therapy (ACT) has been shown to reduce the rate at which resistance to mefloquine is evolving in Thailand.
- A large body of scientific opinion believes that ACT has the potential to reduce the rate at which drug resistance will evolve in Africa - where approximately 90% of the deaths due to malaria occur.

A Product Development Team (PDT) has been formed to manage the CDA project. Its membership includes academics, an MMV Officer, and personnel from WHO and GSK. A full pre-clinical programme has been commissioned and is well advanced. Pharmaceutical development of CDA is progressing within GSK.

The ratio of CPG and DDS is fixed but the ratio of these components and artesunate is not determined. Pharmaceutical development will proceed with a number of ratios until the optimal ratio has been finally determined by clinical trial.

A stop/go decision point to initiate Phase-I studies will be made shortly. The main aim of the first Phase-I study will be pharmacokinetic interaction between CPG-DDS and artesunate.

Following the Phase-I programme, a dose-finding Phase-II study will be performed to determine the optimal artesunate dose in patients with uncomplicated malaria. Lapdap will be co-administered with artesunate at various ratios for a preliminary assessment of efficacy and safety.

As immunity can be expected to influence the efficacy results of the above Phase-II study, CDA will also be studied in less-immune children populations. A clinical development plan will be prepared in accordance with current ICH guidelines and discussed with partners and appropriate regulatory authorities prior to implementation.

**Chlorproguanil-dapsone-artesunate.**

Principal Investigators and Affiliations:

- Prof. Peter Winstanley University of Liverpool, U.K.
- Dr. John Horton GlaxoSmithKline, U.K.
- Dr. Tom Kanyok WHO/TDR, Switzerland

Co-sponsors:

- WHO/TDR United Kingdom Department for International Development (DFID).

Contract under negotiation

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MMV gratefully recognizes, that all partner institutions have contributed to the projects through writing off overhead costs and through the provision of other services and gifts in kind.
The Chair of the Board is Dame Bridget Ogilvie, a former head of the Wellcome Trust, with a distinguished career in pharmaceutical research. Dame Bridget is now on the faculty of University College London.

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Dr. Simon Efange
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Prof. Gilbert Kokwaro
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Clinician with experience in malaria, Dean of Faculty of Tropical Medicine, University of Mahidol, Thailand.

Dr. Yves Ribeill
Chemist with experience in malaria through earlier work as Head of Anti-infective Chemistry Research with Rhône-Poulenc Rorer France, now President and CEO, Scynexis Chemistry and Automation Inc. USA.

Dr. David Roos
Professor of Biology and Director, University of Pennsylvania Genomics Institute. Expertise in the cell biology of apicomplexan parasites and joint coordinator of the Plasmodium genome database, USA.

Dr. Dennis Schmatz
Biolologist with expertise in parasitology, including malaria. Executive Director, Human and Animal Infectious Disease Research, Merck Research Laboratories, USA.

Dr. Thomas E. Wellems
Biologist with expertise in cell and molecular biology of malaria and mechanisms of drug resistance. National Institutes of Health, USA.

Dr. David Wesche
Clinical Pharmacologist with expertise in malaria from previous position with Walter Reed Army Institute of Research, currently with Pfizer Global Research and Development, Ann Arbor, USA.

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John Sudduth
IT consultant
This second financial year has been one of innovation and consolidation. The MMV Financial Regulations, Investment Guidelines and Financial & Accounting Rules and Procedures were drafted and ratified. Internal compliance procedures and controls were formalised and a new in-house multi-currency, multi-lingual accounting system was installed and is fully operational. We continue to use PricewaterhouseCoopers Ltd. as external international auditors and UBS, a major Swiss bank, for our global banking services such as current accounts, investments and cash-management facilities. The on-line bank-to-customer link already in use was extended to include electronic payment facilities. The year was characterised by a number of exceptional factors. The capital fund which, was largely under the custodianship of WHO in 2000, is now almost fully subscribed, considerable additional donations and pledges were received, liabilities increased as new staff took up their posts and more were recruited and, most important of all, expenditure on malaria drug research & development increased dramatically.

Research & Development Expenditure
Project-related expenditure in 2001 was virtually 3 times the figure for the year 2000, with USD 6'709'653 as against USD 2'280'748 (note 4).

Foundation Capital
The legally stipulated foundation capital of USD 4'000'000 was, for historic reasons, under the custodianship of the World Health Organisation. At 31 December 2000 USD 1'976'619 had been received. During 2001 a further USD 2'309'741 originating from the Netherlands Minister for Development Cooperation was transferred. At 31 December 2001 the amount still outstanding amounted to USD 492'640 (note 2g/6).

Donations & Pledges
Donations received at bank amounted
Financial Tables

The detailed financial tables that follow - Balance Sheet, Statement of Income & Expenditure, Cash Flow and Notes - represent MMV in its second full year of operation in which all the fundamental compliance and financial components of the organisation have been consolidated.

Staff & General Administration

The senior management team was completed with the arrival of the Chief Scientific Officer and Chief Financial Officer. There were 8 new appointments in 2001 and MMV also financed the start-up costs of its permanent headquarters offices, including furniture, IT and communications. In spite of this significant investment in infrastructure, general administration (non R&D) spending is on a downward trend as a percentage of total expenditure (note 5b/c).

The financial year ahead to December 2002

Great consideration is given to efficient financial management at MMV, which operates in a complex multi-currency environment. The bulk of donations are received in US dollars, although other currencies are sometimes involved. Outflows for projects are mostly in USD as per the various agreements signed with project partners. Other operational expenses, however, are normally in Swiss Francs. The resulting exposure or exchange risk is hedged at budget time to provide a realistic fixed USD/CHF budget rate for the year. The accounts are kept in US dollars. A sophisticated treasury management and accounting approach is therefore required, matching inflows to outflows by currency, and taking timely multi-currency investment and foreign exchange decisions.

Our financial management is one of prudent, conservative control, including appropriate return on interim treasury investments. We also seek to forecast various long-term funding and income scenarios so as to manage MMV’s growing R&D portfolio more efficiently and to enable us to fundraise proactively. The figure “the funding-gap scenario” illustrates one such scenario and shows why effective fundraising...

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## Medicines for Malaria Venture - MMV Statement of Cashflow at 31st December 2001

### Income

<table>
<thead>
<tr>
<th>Notes</th>
<th>2001 USD</th>
<th>2000 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donations received</td>
<td>5'386'290</td>
<td>4'390'477</td>
</tr>
<tr>
<td>Financial Income</td>
<td>377'441</td>
<td>78'162</td>
</tr>
<tr>
<td>Exchange Difference</td>
<td>10'385</td>
<td>0</td>
</tr>
<tr>
<td>Other Income</td>
<td>39'540</td>
<td>(49'735)</td>
</tr>
<tr>
<td>Total Income</td>
<td>13'559'677</td>
<td>7'606'949</td>
</tr>
</tbody>
</table>

### Expenditure

#### Research & Development Expenditure

<table>
<thead>
<tr>
<th>Notes</th>
<th>2001 USD</th>
<th>2000 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project-Related Variable Expenditure</td>
<td>6'633'542</td>
<td>2'241'373</td>
</tr>
<tr>
<td>Expert Scientific Advisory Committee Expenses</td>
<td>76'111</td>
<td>39'375</td>
</tr>
<tr>
<td>Research &amp; Development Expenditure</td>
<td>6'709'653</td>
<td>2'280'748</td>
</tr>
</tbody>
</table>

#### General Administration Expenses

<table>
<thead>
<tr>
<th>Notes</th>
<th>2001 USD</th>
<th>2000 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staff-Related Benefits/Compensation</td>
<td>82'247</td>
<td>117'598</td>
</tr>
<tr>
<td>Recruitment/Retracement</td>
<td>12'488</td>
<td>117'598</td>
</tr>
<tr>
<td>Office Rental</td>
<td>16'975</td>
<td>46'074</td>
</tr>
<tr>
<td>General Insurance</td>
<td>15'851</td>
<td>1'987</td>
</tr>
<tr>
<td>State Emoluments</td>
<td>10'024</td>
<td>0</td>
</tr>
<tr>
<td>Supplies</td>
<td>29'447</td>
<td>1'903</td>
</tr>
<tr>
<td>Travel, Internet &amp; Postal Charges</td>
<td>16'072</td>
<td>2'737</td>
</tr>
<tr>
<td>Training, Education &amp; Journals</td>
<td>97'849</td>
<td>46'074</td>
</tr>
<tr>
<td>I.T. Expenses</td>
<td>3'402</td>
<td>1'062</td>
</tr>
<tr>
<td>Web Site &amp; Advertisements</td>
<td>47'953</td>
<td>0</td>
</tr>
<tr>
<td>Printing &amp; Brochures</td>
<td>47'230</td>
<td>2'447</td>
</tr>
<tr>
<td>Public Relations</td>
<td>47'953</td>
<td>80'268</td>
</tr>
<tr>
<td>Communications Consultancy</td>
<td>2'013</td>
<td>300'430</td>
</tr>
<tr>
<td>Financial Charges</td>
<td>3'402</td>
<td>7'062</td>
</tr>
<tr>
<td>Exchange difference (loss)</td>
<td>126</td>
<td>0</td>
</tr>
<tr>
<td>Depreciation on Fixed Assets</td>
<td>40'008</td>
<td>0</td>
</tr>
<tr>
<td>General Administration Expenses</td>
<td>1'525'267</td>
<td>90'479</td>
</tr>
</tbody>
</table>

### Total Expenditure

<table>
<thead>
<tr>
<th>Notes</th>
<th>2001 USD</th>
<th>2000 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancillary Activity Income</td>
<td>100'761</td>
<td>0</td>
</tr>
<tr>
<td>Transfer to Operations reserve</td>
<td>5'386'290</td>
<td>4'390'477</td>
</tr>
<tr>
<td>Result</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Notes to financial statements for the year ending 31 December 2001

1a. Introduction
Medicines for Malaria Venture is a Swiss Foundation, established as a non-profit legal entity, registered in Geneva under statutes dated 15 November 1999. It is managed by a foundation council, a chief executive officer and 3 senior managers.

With its head-office in Geneva, the aim of MMV is to bring public and private sector partners together to fund, and provide managerial and logistical support for the discovery and development of new medicines for the treatment and prevention of malaria. The products should be affordable and appropriate for use by populations in developing countries.

b. Accounting Standards
The accounting standards followed are those of the Swiss Code of Obligations, articles 957 to 964.

c. Fixed assets
Fixed assets are stated at cost less depreciation in three classes. The foundation applies the straight-line method for the depreciation of these assets, using rates of 20% p.a. for office furniture and 33% p.a. for both fixtures and installations and computers and equipment.

d. Guarantees
Guarantees concern office rental only and are recoverable on vacating the premises subject to the prevailing contracts.

e. Grants committed for projects
The grants allocated are recorded on a contract or letter of understanding basis, the expense being accounted for by MMV at the moment of allocation and initial payment. In the case of any portion remaining unpaid at the year-end, it is included under current liabilities.

f. Short-term provisions
These provisions represent estimated costs for certain performance-related staff payments and for audit services.

g. Capital
The founding capital referenced in the statutes amounted to USD 4'000'000 from WHO – Roll Back Malaria & UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR). The TDR funds represent earmarked funding from the U.K. Department for International Development, the World Bank and the Netherlands Minister for Development Cooperation prior to the foundation of MMV. At 31 December 2000 the amount of USD 2'802'381 was still to be transferred from the World Health Organisation. At 31 December 2001, the remaining balance for transfer was USD 492'640 (see also Note 6).

h. Operations reserve
This represents the excess of income over expenditure for the period and accrued. This amount is ascribed to the Operations Reserve utilised for future operation and project funding costs by MMV as its rapidly evolving research and development project pipeline dictates.

3. Donations received at bank in addition to Foundation Capital received (see also Note 6)
During 2001 the following donations were received:

<table>
<thead>
<tr>
<th>Organization</th>
<th>AmountUSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rockefeller Foundation (received in 2000 for 2001)</td>
<td>1'000'000</td>
</tr>
<tr>
<td>Bill &amp; Melinda Gates Foundation</td>
<td>5'000'000</td>
</tr>
<tr>
<td>U.K. DFID</td>
<td>2'827'850</td>
</tr>
<tr>
<td>W.H.O. Roll Back Malaria</td>
<td>2'500'000</td>
</tr>
<tr>
<td>World Bank via Global Forum</td>
<td>750'000</td>
</tr>
<tr>
<td>Exxon Mobil</td>
<td>100'000</td>
</tr>
</tbody>
</table>

Total received at bank USD 12'177'850

*An additional amount of USD 1'000'000 expected from W.H.O. Roll Back Malaria after presentation of the Financial Statements and Annual Report for 2001 has been taken as income for 2001 as it relates to an agreement up to 31 December 2001. This explains total Donations Received of USD 13'177'850 as taken to Income & Expenditure.
4. a) Project-related variable expenditure: Grants committed

During 2001, the foundation awarded grants to the following projects:

<table>
<thead>
<tr>
<th>Project</th>
<th>Partners</th>
<th>Award</th>
<th>Paid</th>
<th>Prepayment</th>
<th>Accrued</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Discovery Projects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Discovery Project 990006</td>
<td>GSK1</td>
<td>290'825</td>
<td>290'825</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lactate dehydrogenase inhibition</td>
<td>U. Bristol1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LSHTM3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Discovery Project 990086</td>
<td>Roche4</td>
<td>1'079'110*</td>
<td>1'020'110</td>
<td>59'000* (from 2000)</td>
<td>0</td>
</tr>
<tr>
<td>Synthetic endoperoxide</td>
<td>U. Nebraska4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>STI7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>U. Monash1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Discovery Project 990069</td>
<td>Roche4</td>
<td>1'458'694</td>
<td>1'458'694</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cysteine protease inhibition</td>
<td>GSK8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UCSF9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Discovery Project 001007</td>
<td>Bayer10</td>
<td>2'442'000</td>
<td>2'442'000</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Artemisone</td>
<td>H.K.U.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Discovery Project 001010</td>
<td>Korea SP Pharm Inc.12</td>
<td>643'000</td>
<td>643'000</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyronaridine artesunate</td>
<td>WHO/TDR13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Exploratory Projects**

<table>
<thead>
<tr>
<th>Exploratory Project 990016</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exploratory Project 990050</td>
<td>118'038</td>
<td>118'038</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Exploratory Project 990099</td>
<td>50'000</td>
<td>50'000</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total USD: 6'081'667, 6'022'667, 59'000

4. a) Grants committed mainly covered the effective period from June 2001 to June 2002

**5. Expenses**

a) Governing Board and ESAC expenses represent travel and a per diem.

b) Internal capacity building advanced efficiently in 2001 with 8 staff appointments and effective operations in new, dedicated office premises.

c) Ancillary activity income refers to office space and infrastructure sub-let income, which can be offset against total rental, telecom and related operational expenses.

6. Foundation Capital pending

Foundation Capital still pending at 31 December 2001 to be transferred from the books of the World Health Organisation originates from the following agencies:

- UK Department for International Development
- World Bank
- UNDP/World Bank/WHO Special Program for Research & Training in Tropical Diseases (TDR), World Health Organisation, Geneva, Switzerland
- Rockefeller Foundation
- Swiss Agency for Development Cooperation
- United Kingdom Department for International Development
- World Bank
- World Health Organization
- Roll Back Malaria
- TDR

Medicines for Malaria Venture has received funding and support from the following organisations:

- Bill and Melinda Gates Foundation
- ExxonMobil Corporation
- Global Forum For Health Research
- International Federation of Pharmaceutical Manufacturers Associations
- Netherlands Minister for Development Cooperation
- Rockefeller Foundation
- Swiss Agency for Development Cooperation
- United Kingdom Department for International Development
- World Bank
- World Health Organization
- Roll Back Malaria
- TDR
To the Governing Board of
Meditines for Malaria Venture
Geneva

As auditors, we have audited the accounting records and the financial statements (balance sheet, income statement, cash flow and notes) of the Medicines for Malaria Venture (MMV) for the year ended December 31, 2001.

These financial statements are the responsibility of the Foundation's management. Our responsibility is to express an opinion on these financial statements based on our audit. We confirm that we meet the legal requirements concerning professional qualification and independence.

Our audit was conducted in accordance with auditing standards promulgated by the profession in Switzerland, which require that an audit be planned and performed to obtain reasonable assurance about whether the financial statements are free from material misstatement. We have examined on a test basis evidence supporting the amounts and disclosures in the financial statements. We have also assessed the accounting principles used, significant estimates made and the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the accounting records and financial statements comply with the Financial Regulations of the Foundation and the accounting principles as described in the Appendix 4 of the financial statements.

We recommend that the financial statements submitted to you be approved.

PricewaterhouseCoopers SA

J.-P. Gallay  J.-A.-Ducrest

Geneva, March 8th, 2002

Appendix
Financial statements (balance sheet, income statement, cash flow and notes)