Antimalarial Drug Discovery
CRIMALDDI
Coordination, Rationalisation, Integration

SEVENTH FRAMEWORK PROGRAMME

PROJECT FINAL REPORT

Final Publishable Summary Report

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Executive Summary

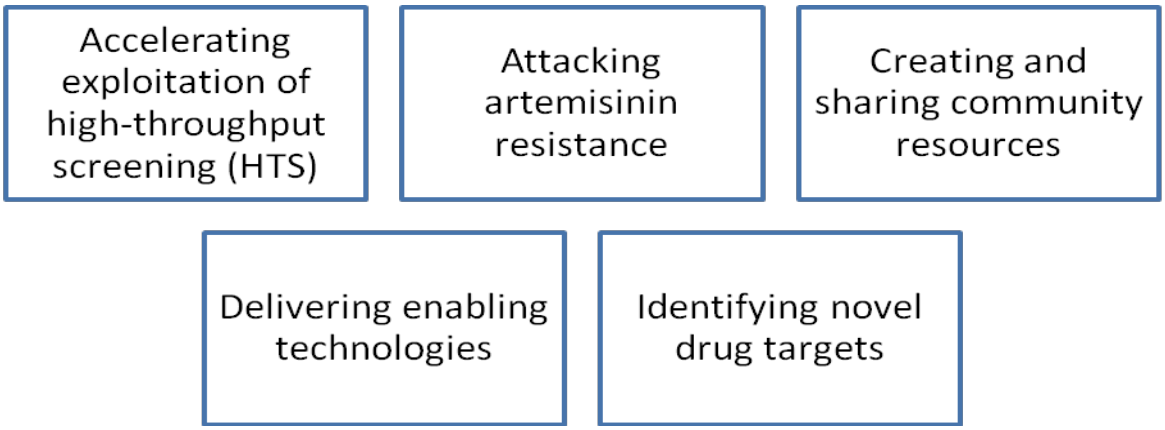
The goal of elimination and eventually eradication of malaria requires a multipronged approach. Since 2007, the Global Malaria Action Plan (GMAP) has guided this ambitious goal. Safe, appropriate, and effective drugs are a critical component. The malERA Initiative has also given guidance on this need.

The CRIMALDDI Consortium began work in February 2009 for a period of 29 months with funding from the EU Commission FP7 Programme. The objective has been to develop and publicise an integrated Five Year Road Map for antimalarial drug discovery to complement GMAP.

The Road Map is published on the CRIMALDDI website (www.crimalddi.eu) and is intended to guide donors, policy makers, and researchers, (both academic and private sector).

The Road Map is the result of a series of facilitated workshops, involving experts from inside and outside the malaria field. The result is a set of clear evidence-based recommendations on drug discovery research priorities. Recommendations include the cost of delivery, the total time needed to deliver, and how long each activity will take before it has an impact on drug delivery.

The recommendations can be grouped into five themes:



Recommendations within each theme reflect the importance and speed at which they could make an impact. The CRIMALDDI team identified recommendations according to the ease and timescale to which they can be implemented. Priority recommendations are listed in four categories:

Quick wins: activities that require only a few resources and can be achieved in a short space of time. (less than one year)

Responses to key roadblocks: identifying ways to overcome major obstacles that are hindering drug discovery programmes.

Speeding up drug discovery: activities that will speed up progress, but which are not considered key blocks to future drug discovery.

Nice to have: activities which will not significantly hold up drug discovery if they were not pursued but which would enhance efforts.

Summary description of the project context and the main objectives

Concept and project objectives

Malaria is one of the three major communicable diseases linked to poverty as identified by the European Commission. About half the world's population (3.3 billion) live in areas with some risk of malaria transmission. About 20% live in high risk areas (1.2 billion). The areas with the highest risk of malaria are Sub-Saharan Africa and South Asia. Malaria is estimated to cause up to 247 million clinical cases and around one million deaths each year.[1] Most deaths are caused by the *P falciparum* parasite and the groups most at risk are children under-five years and pregnant women, Malaria does not just afflict the poor, the impact through childhood mortality and adult disease has a major effect on economic growth of endemic countries. Between 1965 and 1990 economic growth in malaria endemic countries averaged 0.4% per year of GDP/capita compared to 2.3% elsewhere[2]. A major threat to the control of malaria has been the evolution of parasite resistance to the affordable armamentarium of antimalarial drugs and vector control agents.

Chemotherapy has been and will remain the central strategy for malaria treatment. The emergence of resistance, particularly to the first and second line treatments (chloroquine and sulphadoxime/pyrimethamine (SP) respectively), coupled with a dearth of new anti-malarial drugs under development, has compromised our ability to deal with this major human pathogen. Recently new hope has been the introduction into malaria control policy of artemisinin containing treatments (ACTs), notably lumefantrine/artemether and amodiaquine/artesunate. Several other ACTs are in late stage development. However there remains an urgent need for new drugs. In the last 12 months a reduced efficacy of artemisinins has been noted in SE Asia which may put all ACTs at risk. This is not a trivial issue that can be addressed as part of short term funding initiatives. It illustrates the need for ongoing efforts to discover and develop new antimalarials to protect against the parasite's ability to find resistance pathways eventually to all antimalarials it is exposed to. Drug discovery, from identification and evaluation to pre-clinical and clinical development, is characterised by a high casualty rate as compounds that do not achieve the desired anti-malarial, pharmacokinetic or clinical properties are dropped. It is estimated that only 1 in 25 compounds that enter pre-clinical development reach the clinic and only 1 in 10 of those that reach Phase I clinical trials are finally marketed. Although the European pharmaceutical industry has an international status and plays a major role in the European economy it has largely abandoned research and development of drugs for the treatment of diseases of poverty, like malaria, as the small financial return makes it difficult to even cover the costs of development. The current cost of bringing a drug to market is estimated at 500M Euros. Of 1,223 new chemical entities registered between 1975 and1996, less than 1% (11) was specifically indicated for tropical diseases. This problem is amplified when we consider drug affordability, where anti-malarial treatment costing more than $1.00 is beyond the budget of most populations at risk.

However a number of recent events have made antimalarial drug development a more attractive proposition. The recent success in characterising genomes of *Plasmodium sp.* malaria parasites and their hosts has provided the information base and associated technology platforms to aid the rational development of novel chemotherapeutics. In addition increased public awareness, political and financial support, and the recognition by industry of a need to become involved in diseases of poverty has facilitated the establishment of Product Development Partnerships (PDPs) with a remit to fill the shortfall in affordable, safe and effective antiparasitic drugs. Successful examples of such PDPs have relied heavily on academia. Indeed it is only by harnessing the specific domain expertise available in academia and using this to provide a proof of concept that these PDPs can operate as an economically viable model solution.

[1] World Malaria Report 2008.
[2] Sachs J, Maleney P. The Economic and Social Burden of Malaria. Nature. 2002: 415 (6872); 680-685

Currently there are a number of European and international initiatives that are committed to antimalarial drug discovery, development and deployment. In Europe these include WHO/TDR[3], The Medicines for Malaria Venture (MMV), AntiMal (an EU funded FP6 Integrated Project), EDCTP[4], DFID, the Wellcome Trust, and many academic groups and pharmaceutical companies such as GlaxoSmithKline (GSK), Novartis and sanofi-aventis. There is also an increasing interest from pharma companies based in malaria endemic countries (*e.g.* Ranbaxy – India, Shin Poong – S Korea, Holley – China). Within the global community the Bill and Melinda Gates Foundation and the National Institutes of Health in the USA are central to initiatives in antimalarial drug development with other agencies focusing on global financing of drugs and deployment.

These various initiatives remain fragmented and uncoordinated with little formalised linkages between programmes. There is an urgent need for coordination, rationalisation and integration between initiatives to ensure that research priorities are identified in a systematic and transparent way and that programmes conform to standardised and internationally acceptable methods without excessive duplication. Engagement with small and large industrial partners and endemic country scientists, all of whom could contribute significantly to these initiatives is weak, as are dissemination efforts. This coordination effort (**HEALTH-2007- 2.3.2-13: Coordination of European research activities with global initiatives, including Public Private Partnerships)** aims to address these deficiencies and maximise the potential effectiveness of existing activities and gain synergies through this coordination. This initiative has the potential to shape the antimalarial drug discovery and development agenda for the next decade and put Europe at the centre of such activities.

Coordination objectives

Through a logical series of meetings, conferences, workshops and dissemination strategies:

- To establish the CRIMALDDI consortium including a dedicated member of staff employed at LSTM (but working closely with all stakeholders, especially the WHO) and an expert advisory group
- To gather information on the current antimalarial drug development initiatives worldwide
- To interview funders, experts in the field and industry representatives to gather information on the current needs and future research and funding plans
- To identify research gaps, areas of duplication and funding opportunities and present findings to the community and funding bodies
- To produce a coordinated action plan for future research programmes and funding opportunities
- To prepare the European antimalarial research agenda for the next decade by implementation of aspects of the action plan

Contribution to the coordination of high quality research

There is a substantial amount of high quality research in the area of malaria currently in progress. Some of this activity is part of larger consortia such as AntiMal but much of the research is undertaken by small groups of scientists, funded through a variety of initiatives, but without any formal mechanism for communication and coordination outside the normal venues of the scientific literature and scientific meetings. This is inadequate for translational science such as that involved in drug discovery and development. This proposal sets out a series of linked activities that will overcome these limitations and bring much needed transparency to efforts in drug development and discovery internationally. By seeking to bring together all relevant stakeholders and activities from the European and the Global community, we will be able to identify all current research programmes of relevance, identify areas of duplication and overlap and areas that are currently neglected. We will be able to develop agreed and harmonised approaches to this area of science

[3] WHO/WB/UNICEF/UNDP Special Programme for Research & Training in Tropical Disease
[4] European & Developing Countries Clinical Trials Partnership

and create the research agenda in this area for many years to come. The central involvement of European scientists that also participate in the FP6 malaria drugs Integrated Project AntiMal will certainly contribute to coordination of activities in Europe but should also help to enhance the quality of our activities based on stakeholder driven demand for our science.

Quality and effectiveness of the coordination mechanisms and associated work plan

A team of internationally recognised scientists and organisations with complementary expertise has been assembled in order to ensure the success of this coordination action. The primary objective of the project was to bring together all major groups involved in antimalarial drug development and discovery and to establish an international Expert Advisory Group (EAG) which is chaired by Simon Croft from the London School of Hygiene and Tropical Medicine. Through meetings, conferences and related supporting actions we will contribute to the development of the research agenda in this area, rationalise ongoing activities, look for potential synergies between programmes and ensure dissemination of information.
The implementation plan comprises 5 coordination WPs managed under a single management WP. Day to day management of each WP will be the responsibility the specific WP leader. The overall coordination action will be managed by a management committee with a representative nominated from each collaborating institution. This management team will communicate regularly in person in face to face meetings held as described in the WPs. Wherever possible, decisions will be reached by consensus. The collaborative project will be managed in line with the predefined deliverables and milestones. Internal review will be established initially at the level of WPs and conducted by WP leaders and subsequently at the annual face to face Management Committee reviews. External evaluation will be performed by the independent EAG and through the Commission's annual review process.

Overall strategy and general description

The overall objective of this coordination project is to correct the current fragmentation that exists in the antimalarial drug discovery and development area both in Europe and Globally. To achieve this overall objective five specific but interlinked coordinating activities will be pursued through individual WPs. This proposal forms a cohesive intellectual and technical framework, which together with effective project management and integration are designed to deliver the overall project objective. The goal of each of these Coordination WPs is described as follows:

Establishment of the CRIMALDDI consortium structure and Expert Advisory Group (EAG) (WP1): The CRIMALDDI consortium comprises the PIs of the consortium, a dedicated project coordinator – Ian Boulton who is working closely with all stakeholders and the management support team at LSTM. The CRIMALDDI consortium will identify and engage key stakeholders and contribute to the completion and implementation of the coordinated action plan. Representatives from these primary key stakeholders who are willing to commit to a long-term vision in antimalarial drug discovery and development were asked to establish the EAG and define the remit and governance of this group. The members of the EAG were appointed by MMV, WHO/TDR, the EU FP6 malaria drugs IP AntiMal, the European Commission and include representation from DND, the Bill and Melinda Gates Foundation and Sanofi Aventis.

Malaria community engagement (WP2):
The CRIMALDDI consortium in liaison with the EAG will engage all stakeholder groups including European players, endemic country scientists and policy makers, other International groups and the pharma industry to provide a situation analysis of the current funding and research position. The current and projected future issues will be identified together with plans for future research and funding initiatives. Areas of overlap, current research gaps, funding gaps and priorities will be identified. We will undertake a number of targeted workshops with appropriate membership specifically challenged to identify mechanisms and structures that will accelerate the discovery and

development process. These workshops will identify technologies, support systems and partnerships that need to be established or improved.

Completion of a coordinated action plan (WP3): The findings from WP2 will be integrated into a consensus document of research priorities. The CRIMALDDI consortium and the EAG will meet to develop a coordinated action plan aimed at addressing these priorities over the next decade. Potential funding routes, collaborations and the way forward will be developed.

Dissemination (WP4): It will be essential that the consensus views that develop as a result of WP's 1-3 reach as many stakeholders, interested organisations and individuals as possible. WHO and LSTM have extensive experience in this area. This specific WP will adopt a range of initiatives to ensure exposure of the outputs of this action to as broad an audience as possible including representation at the American Society of Tropical Medicine and Hygiene meeting.

Implementation of the coordinated action plan (WP5): The CRIMALDDI consortium and the EAG will establish a five year review timetable (rolling) with defined quantitative endpoints that map directly to the action plan. EAG will work towards securing funding to enable the five year review and update timetable to be followed (this will be coordinated through WHO/TDR).

Sustainability of the initiative (WP6): The CRIMALDDI consortium and the EAG will source funding to continue aspects of the CRIMALDDI programme after month 29. Possibilities include the coordination of a COST action or the formation of a European Economic Interest Grouping (EEIG) that could become a focal funding target for a coordinated malaria drugs development effort. Sustainability will depend on our ability to shape the EU funding agenda over the next decade and thereby develop the critical mass in relevant scientific expertise within Europe.

Description of the main results

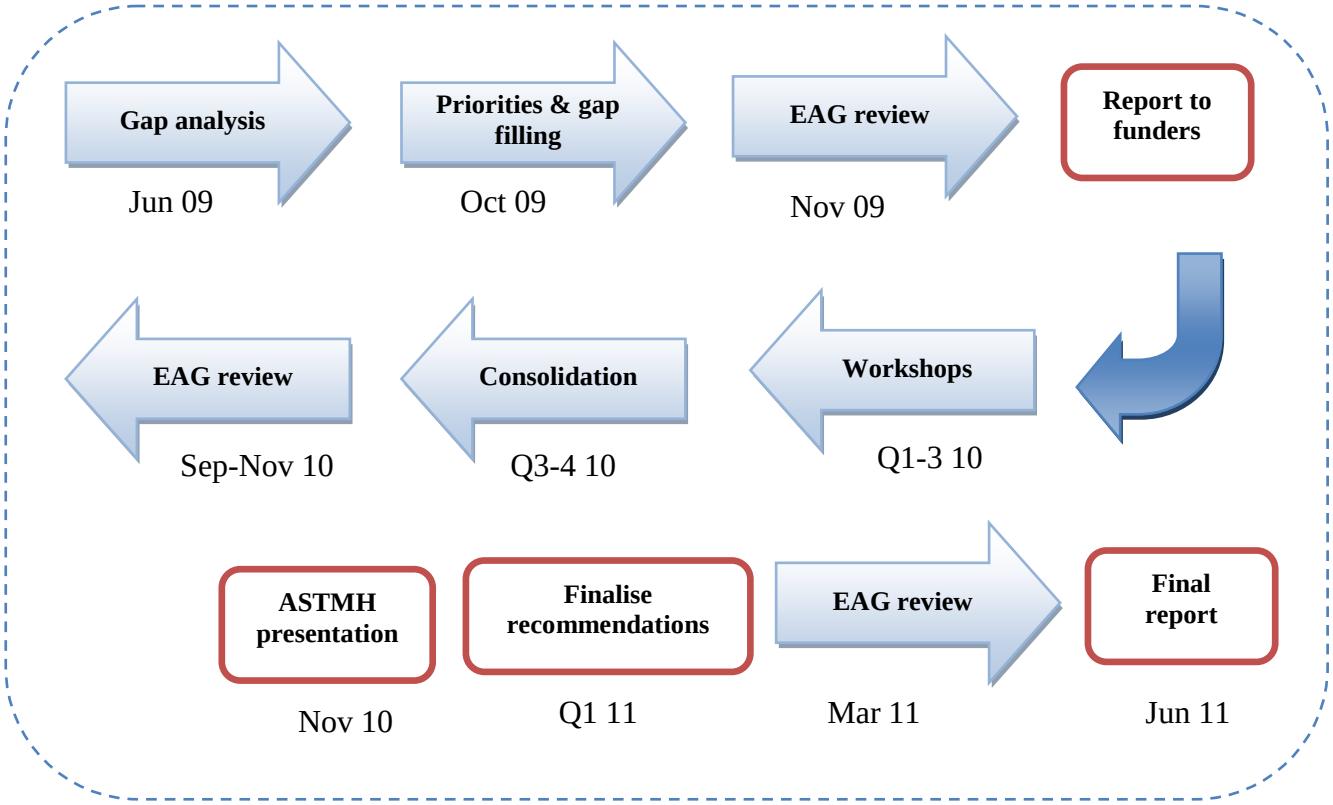
The consortium was set up on the 1st February 2009 with a total of 7 beneficiaries. The consortium was expanded to include two new African beneficiaries – the University of Cape Town in South Africa and the University of Buea in Cameroon. These two Institutions joined the consortium on the 1st September 2009.

Beneficiary Number	Beneficiary name	PI	Beneficiary short name	Country	Project entry date
1 (Coordinator)	Liverpool School of Tropical Medicine	Professor Steve Ward	LSTM	UK	Month 1
2	WHO/TDR	Dr Solomon Nwaka	WHO	Switzerland	Month 1
3	Medicines for Malaria Venture	Ian Bathurst	MMV	Switzerland	Month 1
4	University of Heidelberg	Professor Michael Lanzer	UKL-HD	Germany	Month 1
5	University of Milan	Professor Donatella Taramelli	UMIL	Italy	Month 1
6	CNRS	Dr Henri Vial	CNRS	France	Month 1
7	Institut National de la Sante et de la Recherche Medicale	Professor Christian Doerig	INSERM	France	Month 1
8	University of Buea	Professor Simon Efange	UB	Cameroon	Month 8
9	University of Cape Town	Professor Kelly Chibale	UCT	South Africa	Month 8

Since 2007, the global malaria community has refocused on the ambitious goal of eliminating and ultimately eradicating malaria, rather than merely trying to control this devastating disease. The Global Malaria Action Plan (GMAP) co-ordinates this effort[1]. It recognises that elimination (and ultimately eradication) cannot be achieved with the currently available tools. It must be backed up with a robust research & development programme to develop these tools, including new drugs. The malERA Initiative [2] was set up to define such an agenda. However its drug component has deliberately focused on research goals that will be achieved in the longer term.

CRIMALDDI was set up with funding from the European Commission in response to the need to develop new anti-malarial drugs. Its main objective has been to develop a co-ordinated and prioritised Road Map for antimalarial drug research to guide Europe researchers and donors over the next five years and beyond.

Funding for antimalarial drug discovery and development globally has been strong in recent years. Yet there is evidence this support may not be maintained. A recent G-Finder report [3] found that support may be shifting from drug development to basic research. This is a concern for those who recognise the importance and urgency of drug discovery and development as a critical component to eliminate and eradicate malaria.



CRIMALDDI used a structured approach, focusing on work streams that needed to begin in the next five years, either to address immediate challenges or to lay foundations to develop new tools.

1. Gather and review all ongoing drug discovery research and enabling technology development.

2. Brainstorm work needed to drive forward drug discovery in line with the needs of GMAP.

3. Compare the work required and the work actually underway and carry out a GMAP analysis. Gaps identified informed the priorities to be invesitigated in more detail through a series of interactive workshops.

4. Convene five workshops to explore the key gaps and to develop recommendations. Workshops involved leaders in the malaria field as well as experts from other field who might bring new perspectives. The workshops were designed to be interative and focused on developing recommendations rather than merely reviewing the field and identify challenges. Workshop attendees can be found in appendix 3

5. Bring the recommendations together, remove duplications, and identify common themes. The recommendations were prioritised to give guidance on their relative urgency and importance.

6. Develop estimates of time and resources needed to deliver each recommendation and idetify the dependancies between recommendations.

Full reports of the workshops and their detailed recommendations can be found on the CRIMALDDI website www.crimalddi.eu.

An Expert Advisory Group (EAG) supported and reviewed the work of the Consortium. Membership of the EAG is shown in Appendix One. The EAG reviewed the work of the Consortium against three standards:

1. Progress of the project against the objective
2. Co-ordination of the project with other related initiatives
3. Maintaining relevance of the recommendations to the drug discovery process

Key themes and priorities

5 key themes emerged during the process

- **Attacking artemisinin resistance**
  ACTs are fundamental in malaria control. In Southeast Asia emerging intolerance to artemisinins threatens all our control efforts. It is crucial to the future of antimalarial design that we understand the mechanisms of restistance and how to kill parasites in a similar way to artemisinins. Current research efforts into analogues of artemisinin derivatives is fundamental to the design of future antimalarials.

- **Accelerating high-throughput screening**
  The structures of about 15,000 compunds that have given positive hits in High-Throughput Screening (HTS) are now publicly available. We need to be able to filter this unparalleled quantity of information quickly and efficiently to identify the most promising leads and move them into drug development.

- **Creating and sharing community resources**
  Improved sharing of information about all aspects of antimalarial drug discovery will help speed up drug development. Ways of achieving this need to be developed.

- **Delivering enabling technologies**
  Antimalarial drug discovery is being held up, especially to treat *P vivax* infections because we do not have certain technologies in place. Developing these technologies is key to discovering novel drugs needed to achieve global malaria control, elimination, and ultimately eradication.

- **Identifying novel drug targets**
  Research remains too focused on a few well characterised drug targets, nearly all in asexual blood stages of *P falciparum* infections. We are currently constrained in our search for new drug targets by our poor understanding of the underlying biology of the parasites lifecycle in humans. New targets need to be identified and validated.

Within each theme the consortium identified recommendations

Quick wins: activities that require only a few resources and can be achieved in a short space of time (less than one year).

Quick wins	Recommendations
Attacking artemisinin resistance	Establish a clear definition of 'artemisinin resistance'.
	Make resistant parasites more widely available to the malaria research community.
Identifying novel targets	Define what constitutes target validation to ensure that putative targets are real and practical.

Responses to key roadblocks: identifying ways to overcome major obstacles that are hindering drug discovery programmes.

Responses to key roadblocks	Recommendations
Accelerating exploitation of High-Throughput Screening	Establish a single repository for all 20,000 compounds identified as positive hits, including the synthesis of compound 'powders' and ongoing replenishment of the holdings.
Attacking artemisinin resistance	Define the molecular and cellular basis of artemisinin resistance / induced dormancy and develop easier- to- measure markers.
	Identify discriminatory phenotypes by systematic re-evaluation all of the *in vitro* assays available.
Creating and sharing community resources	Develop, roll-out, and maintain a single antimalarial drug discovery reference database.
Delivering enabling technologies	Develop *in vitro* and *in vivo* culture methods, models and assays to study *P. vivax* across all stages of its lifecycle.
	Elucidate the causes/biology of hypnozoite dormancy in *P. vivax* infections and so develop markers to differentiate hypnozoites from active infected hepatocytes.

Speeding up drug discovery: activities that will speed up progress, but which are not considered key blocks

Speeding up drug discovery	Recommendation
Accelerating exploitation of High-Throughput Screening	Continue routine screening of compound libraries and prioritisation of positive hits in secondary screening.
	Emphasise early use of ADME and toxicology screens to filter positive HTS hits.
	Utilise information relationship between chemical structure and parasite resistance to probe underlying biological processes.
	Evaluate speed of action and stage specificity of current HTS hits to identify new chemotypes with similar PD to artemisinins.
Attacking artemisinin resistance	Establish stable resistant parasite lines to improve access and broaden the number of groups able to study resistance mechanisms. Identify and evaluate an appropriate range of 'omic' approaches to search for discriminatory tools and markers of artemisinin resistance.
Delivering enabling technologies	Develop robust, transferable, cheap, simple and quick standardised assay and culture systems to study key stages of the plasmodium lifecycle. • Disseminate existing tools to all interested parties • Ring stages (especially the first 12 hours) • Gametocytes • Sporozoites • Active infected hepatocytes
Identifying novel targets	Focus on looking for novelty in first and last 12 hours of the erythrocytic ring stages.
	Phenotype parasite strains to identify differential chemotype activity and identify novel targets.
	Phenotyping • Identify novel targets from phenotyping information. • Develop mathematical tools from other biological fields to be used in malaria.
	Focus on increasing understanding of activity of current antimalarial in high priority areas

Key Theme: accelerating exploitation of high-throughput screening

The recent publication of the structures of about 15,000 compounds showing anti-parasite activity in whole cell *P. falciparum* blood stage screens has given us access to an unparalleled wealth of structural information [6, 7]. This unique asset gives us an opportunity to explore a wide range of chemical space for novel antimalarials. We need to rapidly screen and filter the compounds to several hundred promising candidates that can then be pushed through to human clinical trials.

The development of the proper array of assays and screens to achieve this has been addressed in the section on 'Delivering Enabling Technologies'. However there is a pressing need for research groups to be able to access the actual chemical compounds to enable this filtering. We need a single repository containing compounds of high purity that can be accessed by research groups. While there is some work being done on this (*e.g.* by MMV) it is still at too small a scale to allow all the positive hits to be accessible. The scale of this work needs to be increased quickly. It entails increasing the amount of medicinal chemistry support to synthesise those compounds that are not commercially available. Commercial confidentiality issues need to be resolved as well as ensuring the requests from groups are reasonable and will not unnecessarily deplete the repository. When the repository is set up it will need to have ongoing resources to replenish stocks.

In 'Creating and sharing community resources' we identified the importance of developing a single reference database to gather and share information about work being undertaken on potential antimalarial compounds. The information gathered in this data repository will inform better and quicker decision-making about the filtering process and thereby speed up drug

discovery. Access to the compound repository can be made dependent on sharing the results through the database and the two could be managed together.

A huge number of compounds have already been screened in the whole cell *P falciparum* HTS systems (GSK has screened 2 million [6]). The value of screening similar commercial libraries is diminishing as many of the compounds only duplicate those already assayed. However we believe that there remain untapped libraries that may take us into new chemical space. In particular the libraries of agrochemical companies offer a potential opportunity that needs to be explored.

In the past, too often, compounds have been taken through to development only for them to fail on toxicology or ADME grounds. More emphasis needs to be put on screening the positive hits in simple (and maybe fairly crude) animal models to get an early indication if the compound has potential issues in these areas, and so can be filtered out.

In 'Attacking artemisinin resistance' we highlighted the need to screen the current 15,000 positive hits in the public domain and further in drug development, against artemisinin resistant strains of *P falciparum*. In 'Delivering enabling technologies' we identified the importance of finding new drugs that have similar Pharmacodynamics (PD) properties to the current artemisinins and act on the early ring stages. Therefore another potentially important screening element is to look specifically for compounds that are particularly active in this important first 12 hours of the erythrocytic ring stage.

A potentially valuable source of information exists to understand the MoA of antimalarial drugs and to filter out early chemical classes that may not be suitable ultimately for development into practical drugs. This means using the information we already have on resistance to different chemical classes, and using systems biology tools to probe the underlying biological processes. We may then identify the structural elements that are either important for activity or being at risk for resistance development.

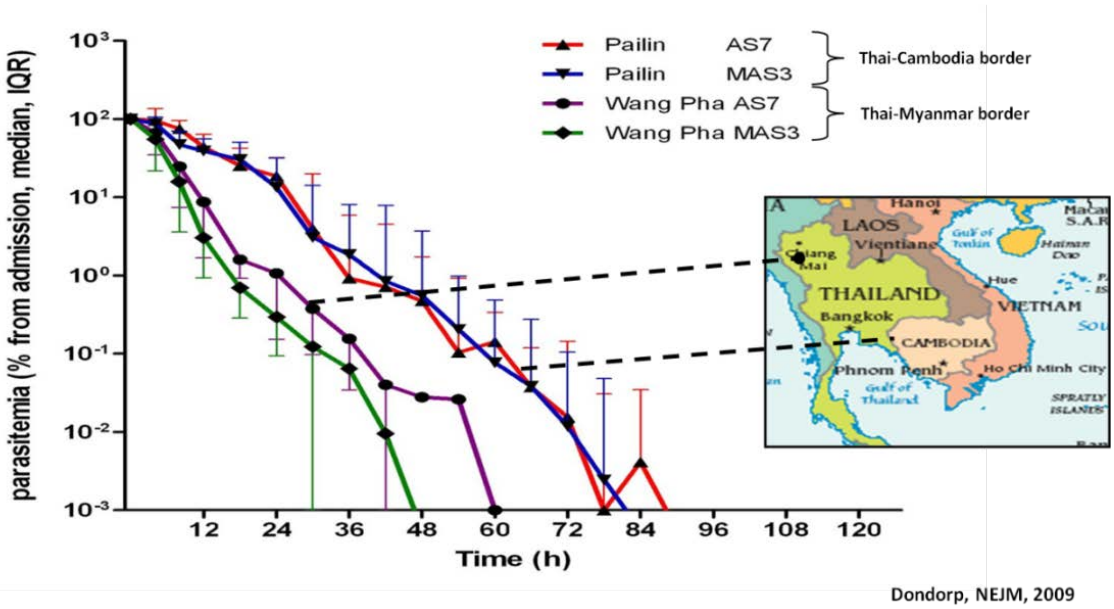
Key theme: attacking artemisinin resistance

Artemisinin-based Combination Therapy (ACT) is now the cornerstone of treatment and therefore control of *P falciparum* malaria. Recent increases in parasite clearance times (PCTs) seen in Cambodia is a matter of great concern [8]. If these tools are lost in a short space of time, the progress of GMAP would be put back by years, if not decades.

While the international community is throwing considerable resources at trying to stamp this out [9], many key questions remain unanswered. This phenomenon should be properly investigated as a matter of urgency to inform future drug discovery efforts. Many groups around the world are working on analogues of the artemisinin derivatives. If these new endoperoxides or other similar structures are also adversely affected, much of this work is wasted. It is crucial to the future of eliminating and eradicating malaria to establish the mechanism of the increased PCTs and the degree of 'cross-resistance' between the various peroxide structural types.

The answer to these questions will either close off peroxides as potential future antimalarials or will redirect drug discovery work towards related structures that are unaffected by the cause of the increased PCTs.Without a clear definition of what we all mean by 'artemisinin resistance', it is difficult for the community to study the phenomenon in a logical and aligned way. A definition should be based on

clinical endpoints (increased PCTs and treatment failures). It should also recognise the small but measurable geographical differences of response by the parasite to artemisinins. This is a high priority. When we have a clear definition of artemisinin resistance, it will be possible to start work to identify discriminatory markers of reduced susceptibility that can be developed into practical screening methods, preferably through simple, quick, cheap, and robust *in vitro* assays. Given the importance and urgency of this challenge, we judge it is important to bring as many different minds and investigative approaches to bear on the problem. This requires much greater access to parasites showing reduced susceptibility. To date it has not been possible to develop stable cell lines of the Cambodian parasites. These are needed so they can be shared around all groups who wish to study this phenomenon.



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Greater access to these resistant parasite lines will improve chances of developing stable models of artemisinin resistance and also facilitate work on identifying resistant phenotypes. It should then be possible to develop suitable assays to screen compounds. Once we have these tools and information in place, we should re-screen against the resistant parasites existing compounds

which have shown positive hits in the HTS programmes or are further on in development. This in turn will inform chemical strategies for developing the next generations of antimalarials.

We need to design new drugs that retain the important aspects of the artemisinins mode of action (leading to rapid clinical effects) coupled with further activity across a broad range of other lifecycle stages. This will be covered later in ‘Identifying novel drug targets’.

The main advantage of artemisinins in treating malaria is their effect on the early asexual blood ring stages of the parasite’s lifecycle. We need to study the impact of resistance on how and where in the lifecycle the artemisinins kill Plasmodium. It is still not clear if the mechanism of increased PCT is induced dormancy in the parasite or another mechanism. Therefore we need to develop the tools needed to probe these questions.

The use of as wide a range of systems biological tools developed in other fields may also shed light and so should be rapidly deployed to see if they can be of use. We would recommend to see these ‘-omic’ tools used both to generate testable hypotheses (through whole genome scans of resistant and sensitive parasites) and hypothesis testing (through correlations of possible markers of resistance and mechanisms suggested by the application of these tools).

Key theme: creating and sharing community resources

Today, more research work is undertaken on malaria, new drugs, and related tools than ever before. Since 2007, this work is being driven to develop and identify new tools to not just control malaria, but also to eliminate and eradicate it.

Unnecessary duplication of effort and the existence of gaps in work underway are inevitable without collaboration and sharing of knowledge and data. In the current economic climate, funding agencies are responding to other pressing demands on their resources and are considering cutting back on their support for malaria.

As such, we must try to reduce the amount of unnecessary overlap between different research groups. A degree of duplication is a necessary part of R&D to ensure that results are validated and key challenges are addressed by different routes, but this must be a conscious decision.

Sharing of information between researchers will help reduce duplication of effort and make clearer any gaps in work that need to be filled. The only way to do this, at present, is to look at what each funder is supporting. This is not easy, and is time consuming.

A wealth of data is now becoming available as groups (initially GlaxoSmithKline), co-ordinated by MMV, make public the structures of the positive hits from their whole cell *P falciparum* HTS campaigns [8, 9]. There is a risk however this information will be spread across a variety of databases, making access more difficult.

Funders may find their resources unintentionally applied to the same areas of chemical space. A single reference database that can be the first port-of-call for information on a particular structure would create more efficient and cost effective ways of working for researchers. Such a database can cross-reference to other databases with information on genomics, metabolic and biochemical pathways. In this way we can bring together all relevant information about a structure or structural series in one place.

For this proposed database to be of real value it must be a two-way communication tool. All groups working on malaria need to be encouraged to lodge new findings about structures there. Groups will only be prepared to share their information if they see the value of doing so. Other databases have been successful in achieving this and we can learn lessons from their experience. Different degrees of access are necessary in order to protect commercial confidentiality and academic priority.

A key requirement of success is to share procedures and protocols adopted for the various tests whose results are recorded on the database. Participants need to be required to lodge details of their testing protocols along with the test results. This will allow for peer review of their methodology and also ensure community ownership of the standards being adopted. In time this will evolve into a set of robust and well-defined testing methods available to the entire community. This is similar to the process used by the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) for antibacterial and anti-yeast testing procedures.

The design of the database will need to be undertaken in an open manner by the community but the core dataset must be kept to a manageable size. ‘Mission creep’ must be avoided at all costs. The database cannot be ‘all things to all people’. The report on Workshop 2 (Managing the wealth of new HTS data) gives more detail of how the proposed system can be designed, managed and curated [4].

Flowing from the successful sharing of information through the use of the proposed database, there will be increased demands to share compounds. A mechanism alongside the database will be needed to ensure that supplies of actual ‘powders’ can be made available readily. This challenge is dealt with under the theme ‘Acceleration of HTS Hits’.

Key Theme: delivering enabling technologies

We are currently hampered by significant gaps in the platform technologies needed to find and evaluate new drug candidates. We have many of the tools necessary to rapidly identify and progress novel compounds active against acute *P. falciparum* blood stage infections. In contrast, there are significant gaps in the platform technologies necessary for other species of Plasmodium and acting against other stages in the parasite lifecycle.

For example, a Single Encounter Radical Cure and Prophylaxis (SERCaP) drug [2] will require activity against the blood-stages and mature gametocytes in *P. Falciparum*, both the blood-stages and the hypnozoites (dormant liver stage) in *P. vivax*. Our inability to efficiently screen for all these types of activity is a major block to developing tools for elimination.

P. vivax

Guerra *et al.* [10] recently made very clear the growing need for us to focus more resources on *vivax* malaria if the goal of elimination is to be achieved.

Our main focus until now has been on falciparum malaria but this is increasingly untenable. *Vivax* malaria is more widely distributed globally with 2.85 billion people at risk. It is less amenable to control, and (despite past thinking) it can cause severe clinical problems. Our main tools to fight *P vivax* – chloroquine and primaquine – are failing, with well-documented reports of resistance to both. The asymptomatic hypnozoite stage of infection is a reservoir of further infection that must be cleared in an elimination programme, but the requirements of drugs to achieve this are considerably different from those needed to treat acute symptomatic infections.

Despite the importance of this parasite, we lack the practical technologies needed to study it and especially the effect of drugs on the key part of the parasite lifecycle – the liver stages. Liver cells cannot be easily cultured. Robust and easy-to-use assay methods for new drugs do not exist. We have little understanding of the process under which an infected hepatocyte becomes dormant or the hypnozoite becomes reactivated. Therefore we have no markers for infected hypnozoites to use in drug screening.

If we are to make any real progress in developing the tools to tackle this major part of the control and elimination challenge, then we urgently need to develop the culture methods, models, and assays needed to study liver stages. As with all useful assays, they will need to be simple, cheap, quick, robust, and transferable.

Transmission blocking

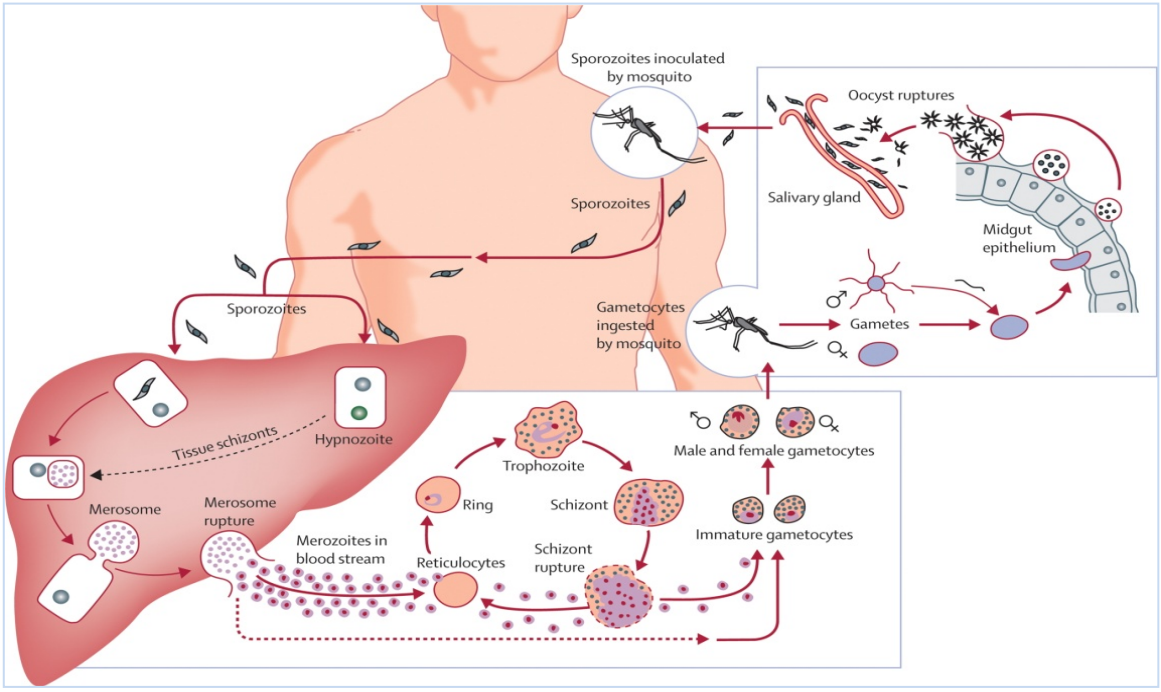
Another key challenge for the elimination of malaria is to break transmission of the disease and bring the basic reproduction rate to below 1. To do this, we need tools that both reduce the reservoirs of infection (especially in the liver for *vivax*) and to reduce the rate at which infections are spread. Transmission blocking agents are key to the latter. To find new agents, we need to be able to study gametocytes and to screen drugs for activity against them. As with all screening systems, they will need to be robust, reproducible, inexpensive, and high throughput. Once we have the tools to study this stage, we would expect to find a wealth of potential targets for new drugs as the parasite is undergoing a large number of biochemical changes which could be interfered with.

Another possible target to interrupt transmission is to interfere with the sporozoites before they have a chance to infect liver cells. On its own, this is more likely to be a target for a vaccine, but it would be of interest to screen potential drugs to see if they have this as an additional activity to their main one. Therefore we need to develop a suitable assay method, which will also require us to develop a robust and reliable supply of both *falciparum* and *vivax* sporozoites. Without this we will not be able to share them between laboratories.

Upgrading and extending current assays

Too often, we rely on models and assays that act as surrogates for human malaria (*e.g. P berghei* in rodents). It would be preferable to study the human species of Plasmodium. Recently the development of the humanised mouse model has allowed us to do this to some extent, but the model is expensive and is only available in a few centres. The development of an affordable model system is potentially a valuable additional enabling technology.

In addition to finding new assays, we need to upgrade our current set of assay systems to reflect changes in the particular stages in the parasite lifecycle we would like to target. For example, if we are to focus more on finding drugs that mimic the artemisinins in their activity in the early ring stages in the red blood cells, we need systems and assays to screen drugs for activity in this time period. Similarly we need to develop the tools to screen potential drugs for their activity against active infected liver cells, a key stage in the lifecycle of all Plasmodium species. We need to upgrade our array of assays so that they are simple, cheap, quick, robust, and transferable.



Mueller et al. (2009) Key gaps in the knowledge of Plasmodium vivax, a neglected human malaria parasite. Lancet Infectious Diseases 9: 555-566.

Key theme: Identifying novel targets

The current antimalarial drugs we use to control malaria are targeted at a limited number of biological pathways in the parasite's lifecycle. Most of them are in the asexual blood stages as they have been the easiest stage to access and study. But the parasite has been very successful in overcoming each class of drugs that we have deployed. As in most areas of anti-infective therapy, we need to be developing drugs that target new pathways in order to stay one step ahead and also to meet the different needs of the elimination and eradication stages of GMAP. The focus on *P falciparum* has meant that, with the increased reports of resistance to chloroquine and primaquine, there is now a growing gap in our tools to treat *P vivax* infections – a key challenge for elimination outside Sub-Saharan Africa.

We are constrained in our search for new drug targets by our poor understanding of much of the underlying biology of the parasite's lifecycle. If we can extend our knowledge to other lifecycle stages, then we greatly improve our chances of finding new targets to kill the parasite. Similarly we do not understand as much as we should about the similarities and differences between the underlying biology of *vivax* and *falciparum* infections. Part of the problem is the lack of appropriate platform technologies that we can use to study this (as mentioned in 'Delivering enabling technologies'). However greater understanding of the biology is not solely dependent on platform technology, but also on the priorities of the research agenda. In the past this has focused on *falciparum*, due to its greater mortality and the faster loss of drugs effective against it. The continued effectiveness of chloroquine and primaquine against *P vivax* has given us a false sense of security. Resources focused on new drug discovery for *vivax* need to be greatly increased.

In the interactive workshops, proper target validation was identified as a clear need, along with a process for the community to review the validation of potential new targets. This has been referred to above in 'Creating and sharing community resources', but it needs to be emphasised again here.

Targets should have the following characteristics:

- *Be validated either chemically or genetically, both in vitro and in vivo, at a credible stage of the lifecycle of the parasite.*
- *Should be druggable, i.e. should be amenable to treatment with small molecules at low concentrations.*
- *Have a reliable functional assay.*

A range of mathematical and systems biological tools have been used with some effect in the study of other diseases. Application of these to the lifecycle of the various species of Plasmodium may throw light on the underlying biology, allow hypotheses to be developed and tested, and so may identify possible new targets for drug discovery.

Similarly identifying and phenotyping Plasmodium strains that are differently affected by each class of compounds may help to identify characteristics in the chemistry that also can be used to identify possible new targets. Drugs to eliminate malaria will have different requirements to those needed to control the disease. This will be reflected in differences in potential new targets.

Targets for malaria control

The main focus of malaria control is the treatment of symptomatic patients. Drugs primarily need to treat the asexual blood stages of the parasite lifecycle, which cause the symptoms and are when patients present for treatment. We would argue that the 'must have' characteristic for a good target here would be that the effect should be 'cidal' in 48 hours through either inhibition of the target or

interaction of the chemical compound with the target. The early and rapid kill achieved by the artemisinins is due to their effect on the early stages of the asexual blood stage and new targets should also be active, especially in the first 12 hours after the parasite invades the red blood cell. To identify more targets here, then we need to better understand the biology of this stage and how the artemisinins act against it.

Similarly the last 12 hours of the asexual blood stage, when the schizont ruptures and releases the merozoites, is another potentially promising point to attack. The multiple biochemical changes going on at this time should yield new targets.

Targets for malaria elimination

Here the main focus is the use of drugs to reduce and interrupt the cross-infection between people, often asymptomatic, through the clearance of parasite reservoirs especially in the liver. The need for better tools to study the liver stages, especially hypnozoites in *P vivax*, has been highlighted in 'Delivering enabling technologies'. Priority areas to study for potential new targets should be:-

- *Reactivation of hypnozoites (including compounds that either block reactivation or kill hypnozoites).*

- *Causes of dormancy and ways to block the switch to a dormant state.*

The known activity of the 8-aminoquinolines (primaquine and tafenoquine) should be a useful starting point for target identification in this lifecycle stage of *P vivax*. This approach may also be of value with other chemical classes.

Other stages of the parasite lifecycle may also be of value in this context. Looking for drugs that specifically target sporozoites and gametocytes would not be productive, but adding activity against these stages to blood and/or liver stage activity could be of value. Gametocytes are a potentially interesting point to interrupt transmission of the parasite. A purely anti-gametocyte drug would not directly benefit the patient and so would impose a high safety requirement on the compound. On the other hand, a drug targeting gametocytes would be a valuable asset in preventing the escape of genotypes that confer resistance against anti-asexual blood stage drugs.

Thus one of the main benefits of transmission-blocking activity would be the protection (and thus lifespan extension) of co-administered curative drugs. The mechanisms of action of existing blood-stage active compounds against gametocytes should therefore be investigated. There are multiple possible targets to attack gametocytes worthy of investigation – especially gametocytogenesis (where many metabolic processes are active) and egress mechanisms.

Five Year Roadmap – Time to Impact

Recommended activities will impact at different periods from now. Some work on the recommended activities may need to start in the near-term in order to have an impact at the right time.

Funders and policy-makers will wish to focus their attention on the themes most closely aligned to where they want to make an impact. However it is important that the right mix of time horizons is addressed by the malaria community. This will ensure that all the recommendations in this report are implemented according to the priorities and timescales needed to properly contribute to improved antimalarial drug discovery.

Near-term impact: exploiting what we have better

In the near-term, we will increase the productivity of existing tools and information by applying the recommendations in the following three themes: 'Attacking artemisinin resistance', 'Creating and sharing community resources' and 'Exploitation of HTS hits'.

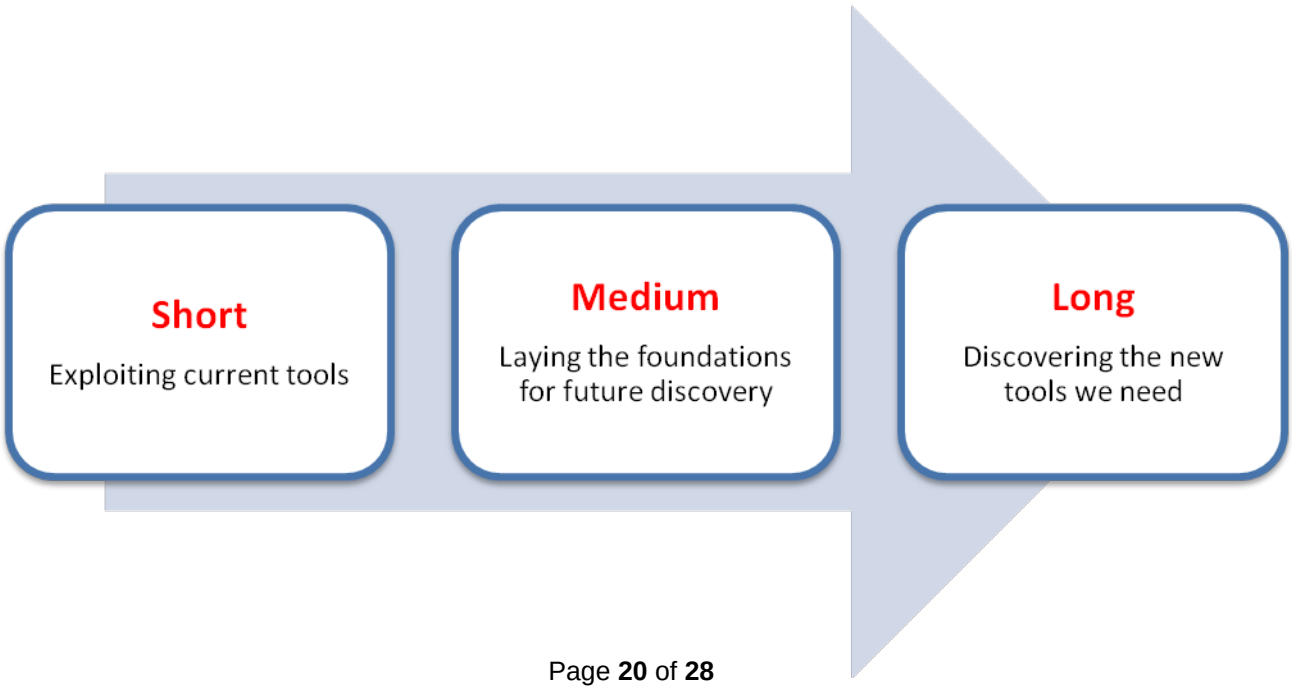
We will also increase the number of research groups that are able to contribute by removing barriers to participation, as well as putting in place tools, systems, and information that can inform work that will have impact in the longer term.

Medium-term impact: laying the foundations for future discovery

We will have greater capacity to extend drug discovery research into new areas if we develop enabling technologies that allows us to do so. These will be the foundations on which the tools necessary for malaria elimination are built. The theme that contains recommendations with medium term impact is: 'Delivering enabling technologies'.

Long term impact: discovering the new tools we need

The discovery of new targets will take some time to achieve and is an ongoing, long-term process. Recommendations under the theme of 'Identifying novel drug targets' provide such a long-term vision. Once targets are established, compounds need to be screened against them, and filtered with other assays. Eventually a few candidate compounds will be taken through to full development (and hopefully become drugs).



- **How long will it take and how much will it cost?**

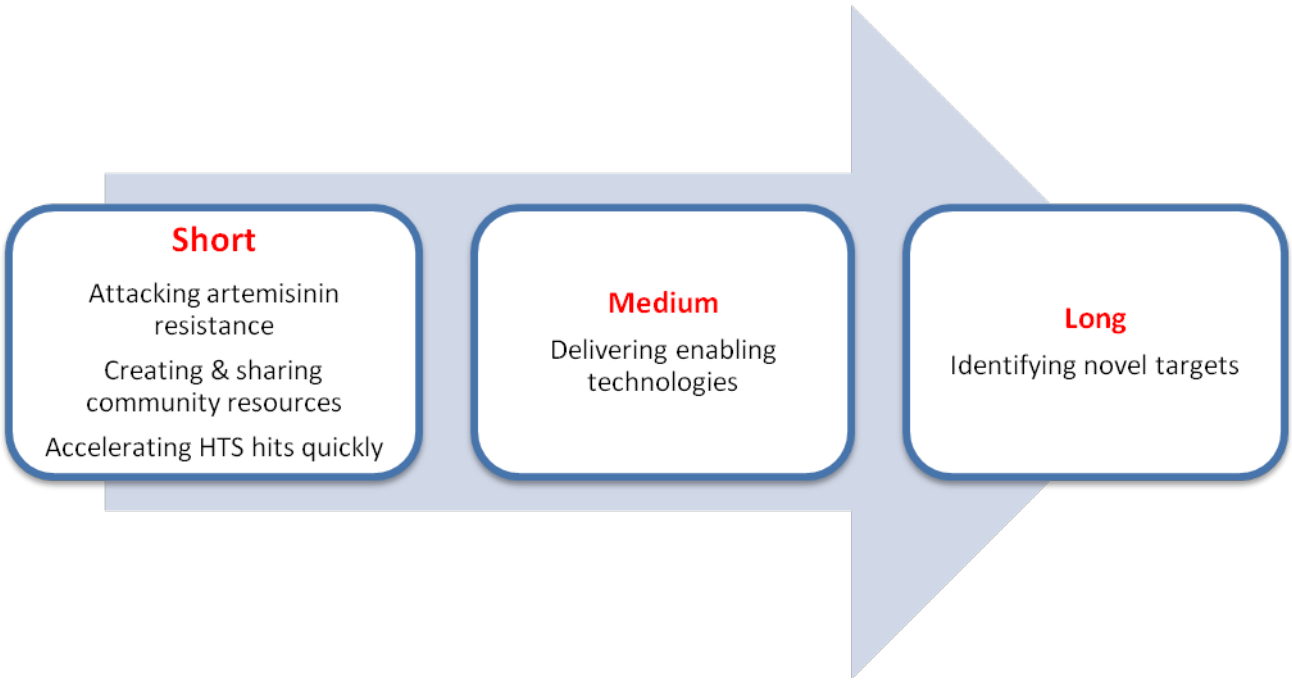
One of the principal objectives in the CRIMALDDI Project was to go beyond a long list of activities in antimalarial drug discovery. Too often the malaria community presents funders and policy makers with such lists, but gives them no guidance on the priorities, the costs, and the phasing of the proposed projects or recommendations.

The CRIMALDDI Management Team has taken the recommendations and themes developed during the project and prioritised them. It has (in collaboration with MMV) estimated the time needed to achieve the recommendations and an order of magnitude cost of each. Obviously this is a first step. Detailed costing and timelines would need to be developed as funding decisions are arrived at. The results of this work are shown in the tables below.

We believe that recommendations prioritised as 'Important quick wins' and "Responses to key roadblocks' have to start as soon as possible. We have therefore shown them as starting in 2012 (to allow time for necessary planning and decision-making processes to find funding and resources).

The recommendations prioritised as 'Speeding up drug discovery' can follow as resources become available and funding agencies / policy-makers decide they want to see progress on them. As this timing is uncertain, we have shown them only in years from commencement, without giving actual dates.

'Nice to Have' recommendations have not been included in the forecast costs and timelines. We believe that these should only be undertaken if and when all resources needed by the other priorities have been allocated.



Quick wins

Theme	Recommendation	2012	2013	2014	2015	2016	Est. Cost	Comments
Artemisinin Resistance	Establish a clear definition of 'artemisinin resistance'						$100,000	Requires one meeting of relevant experts from a range of disciplines including clinical development, drug discovery and public health
	Shipping of resistant parasites to the malaria community						$30,000 Per Year	Budget to grow and ship parasites until resistance challenge is overcome
Identifying Novel Targets	Define what constitutes target validation to ensure that putative targets are real and practical						$100,000	Requires one meeting of relevant experts from a range of disciplines including clinical development, drug discovery and public health

Removing key roadblocks

Theme	Recommendations	2012	2013	2014	2015	2016	Est. Cost	Comments
Accelerating exploitation of HTS	Establish a single repository for compounds identified as positive hits: - synthesis of ca. 20,000 compounds - replenishment of repository compound holdings						$10-20 mill 2 mill/yr	Initial synthesis positive hits Replacing compounds as they are used
Artemisinin Resistance	Define the molecular & cellular basis of artemisinin-induced dormancy & develop easier to measure markers						$10-20 mill	Funding of multiple groups to bring as many different approaches and lines of thought to the problem
	Identify discriminatory phenotypes by systematic re-evaluation all of the *in vitro* assays available						$5-10 mill	
Creating & Sharing Community Resources	Develop & roll-out a single reference database. Development Maintenance						$6 mill $2 mill/yr	The existence & proper use of the database should facilitate improved communication throughout the Community
Delivering Enabling Technologies	Develop *in vitro* & *in vivo* culture methods, models & assays that can be used to study *P. vivax* infections across all stages of the parasite lifecycle						$150 mill	
	Elucidate the causes/biology of hypnozoite dormancy in *P. vivax* infections & so develop markers to differentiate hypnozoites from active infected hepatocytes						$10-20 mill 3-5 years	

Theme	Recommendation	Year 1	2	3	4	5	Est. Cost	Comments
Accelerating exploitation of HTS	Continue routine screening of compound libraries and prioritisation of positive hits in secondary screening. Agrochemical libraries are a particular priority.						$1 mill/yr $1 mill/yr	Based on 1,000 compounds per year
	Expand early use of ADME & toxicology screens to filter positive HTS hits						$500,000/ yr	Based on 2,000 compounds per yr & 10 different assays
	Utilise information on resistance to each drug class to probe underlying biological processes and drug targets						$2.5 mill/yr	Continue until resistance is gone
	Evaluate speed of action and stage specificity of current HTS hits to identify new chemotypes with similar PD to artemisinins (including activity against artemisinin-resistant strains)							
Attacking Artemisinin Resistance	Establish stable resistant parasite lines to improve access and broaden the number of groups able to study resistance mechanisms. Identify and evaluate an appropriate range of "omic" approaches to search for discriminatory tools and markers of artemisinin resistance.						$5 mill	Continue & expand work already underway
Delivering Enabling technologies	Precisely define and develop novel methods and assays for evaluating drug activity against each stage of the *f. Falciparum* lifecycle							
	❖ Disseminate existing tools to all interested parties						$1 mill	
	❖ Enhance existing tools						$2 mill/yr	Ongoing programme
	Precisely define and develop novel methods and assays for evaluating drug activity against non-blood stages of *P. falciparum* lifecycle							
	❖ Disseminate existing tools to all interested parties						$2 mill/yr	Ongoing programme
	❖ Enhance existing tools						$2 mill/yr	Ongoing programme
	Precisely define and develop novel methods and assays for evaluating transmission-blocking drug activity against *P. falciparum*							
	❖ Disseminate existing tools to all interested parties						$7 mill/yr	Ongoing programme
	❖ Enhance existing tools						$2 mill/yr	Ongoing programme
Identifying Novel Targets	Focus on looking for novelty in 1st & last 12 hours of the ring stages						$250 mill/yr	
	Phenotype parasite strains to identify differential chemotype activity & identify novel targets							
	❖ Phenotyping							
	❖ Identify novel targets from phenotyping information						$2 mill/yr	
	Develop mathematical tools from other biological fields to be used in malaria						$5 mill/yr	
	Focus on increasing understanding of activity of current antimalarial in high priority areas						$2 mill/yr	Depends on data availability & duration
							$2 mill/yr	

Appendix One

Expert advisory group membership

The following people attended at least one meeting of the Expert Advisory Group:-

Image courtesy of LSTM: CRIMALDDI Executive Advisory Group:

Prof Simon Croft (Chair)	London School of Hygiene and Tropical Medicine
Prof John Adams	University of South Florida
Dr Ken Duncan	Bill and Melinda Gates Foundation
Prof David Fidock	Columbia University
Dr Laurent Fraisse	sanofi aventis
Dr Federico Gomez de las Heras	*formerly* GlaxoSmithKline
Dr Saman Habib	Central Drug Research Institute, Lucknow
Dr Jean-Rene Kiechel	Drugs for Neglected Diseases Initiative
Prof Dominique Mazier	INSERM
Prof Odile Mercereau-Puijalon	Institut Pasteur
Prof Chris Plowe	University of Maryland
Prof Geoff Targett	London School of Hygiene and Tropical Medicine

Appendix two: references

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Appendix Three

Workshop attendees

The following people gave generously of their time in attending and participating in at least one of the five interactive workshops:

Prof Pietro Alano	Istituto Superiore di Santa
Dr Neil Berry	University of Liverpool
Dr Ted Bianco	Wellcome Trust
Dr Giancarlo Biagini	Liverpool School of Tropical Medicine
Prof Steffen Borrmann	KEMRI – Wellcome Trust Centre, Kilifi
Dr Fred Bost	Scynexis
Dr Thierry Diagana	Novartis Institute for Tropical Diseases
Dr Ken Duncan	Bill and Melinda Gates Foundation (VTC)
Dr Sean Ekins	Collaborative Drug Discovery
Dr Laurent Fraisse	sanofi aventis
Dr Javier Gamo-Benito	GlaxoSmithKline
Dr Jose Garcia-Bustos	GlaxoSmithKline
Dr Val Gillett	University of Sheffield
Prof Hagai Ginsburg	Hebrew University of Jerusalem
Prof Roy Goodacre	University of Manchester
Dr Dean Goodman	University of Melbourne
Prof Ian Graham	CNAP, University of York
Prof Kip Guy	St Jude's Children's Research Hospital
Prof Annette Habluetzel	Università di Camerino
Prof Neil Hall	University of Liverpool
Dr Ian Hastings	Liverpool School of Tropical Medicine
Dr Richard Heidebrecht	Broad Institute
Prof David Hornby	University of Sheffield
Dr Marcel Kaiser	Swiss Tropical and Public Health Institute
Dr Sumalee Kamchonwongpaisan	National Centre for Genetic Engineering and Biotechnology, Bangkok
Dr Clemens Kocken	Biomedical Primate Research Centre, Netherlands
Prof Gilbert Kokwaro	University of Nairobi
Prof Sanjeev Krishna	St George's. University of London
Prof Dennis Kyle	University of South Florida
Dr Didier Leroy	Medicines for Malaria Venture
Prof Louis Maes	University of Antwerp
Prof Maria Manuel Mota	Universidade de Lisboa
Prof Maurizio Muraca	Osepadale Pediatrico Bambino Gesu
Prof Harald Noedl	Medical University, Vienna
Dr Alexis Nzila	University of Cape Town
Prof Odile Mercereau-Puijalon	Institut Pasteur
Dr John Overington	European Molecular Biology Laboratories, Cambridge
Dr Tanya Parkinson	Pfizer
Dr Bernadette Ramirez	TDR
Prof Sergio Romeo	University of Milan
Prof David Roos	University of Pennsylvania
Prof Phil Rosenthal	University of California, San Francisco

Dr Ilaria Russo	University of Perugia
Dr Raman Sharma	University of Liverpool
Prof Robert Sinden	Imperial College, London
Dr Georges Snounou	Université Pierre et Marie Curie/INSERM UMR S 945, Paris
Prof Roberta Spaccapelo	Università di Perugia
Dr Chairat Uthaipibull	National Centre for Genetic Engineering and Biotechnology, Bangkok
Prof Jonathon Vennestrom	University of Nebraska
Prof Mike White	University of Liverpool
Prof Andrew Wilks	Monash University
Prof Elizabeth Winzeler	The Scripps Research Institute (VTC)
Dr Sergio Wittlin	Swiss Tropical and Public Health Institute
Prof Paul Wyatt	University of Dundee