



Malaria vaccines

EDCTP Stakeholder meeting

Copenhagen

31 January 2007

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1. Introduction

The EDCTP stakeholders' meeting on malaria vaccines is the first stakeholders' meeting organised by EDCTP in the light of the amended strategy for funding new projects.

The aim of this meeting, which was hosted by Denmark, was to make recommendations to EDCTP in terms of suitable products in the pipeline for clinical trials; define potential sites to conduct the trials; and determine capacity building needs for the conduct of clinical trials in Africa. Additionally, EDCTP requested a recommendation on the funding procedure that should be applied to meet these aims.

The meeting was chaired by Dr Carter Diggs. Dr Diggs is the Senior Technical Advisor on malaria vaccine development for USAID. Carter has considerable experience working on malaria vaccines in developing countries and serves as an advisor to many malaria vaccine networks.

2. Participants

2.1 African Malaria Network Trust (AMANET)

AMANET was invited because of its role in malaria vaccine trials, training and capacity building. The mission of AMANET is to promote capacity strengthening performance and impact of Africa malaria R&D and training institutions in Africa. The AMANET Secretariat is based in Tanzania. Its objectives include:

1. To create global awareness of the Africa malaria disaster;
2. To promote cooperation and collaboration with stakeholders;
3. To advance essential human capacity for research development of malaria interventions;
4. To determine the needs and characterise potential sites for testing malaria interventions;
5. To strengthen infrastructure and provide equipment to prospective trial sites;
6. To sponsor clinical and field trials of interventions;
7. To promote good governance and networking of malaria R&D and training institutions.

More information on the activities of AMANET can be found at:

<http://www.amanet-trust.org>

2.2 European Commission

The European Commission (EC) is the main funder of EDCTP through Article 169 of the European Treaty. The representative of the European Commission DG Research expressed support of the EDCTP Stakeholders' meetings. He noted the broad involvement of many member states and mentioned that in addition to the member

states, EDCTP should partner with players on the global research arena. EDCTP should develop into a strong independent player in this field.

More information can be found at goals and activities of the European Commission can be found at: http://ec.europa.eu/index_en.htm

2.3 European and Developing Countries Clinical Trial Partnership (EDCTP)

EDCTP was represented through the Member State representatives, the Partnership Board (PB), the Developing Countries Coordinating Committee (DCCC), the High Representative and the Secretariat.

More information on EDCTP can be found at: <http://www.edctp.org>

2.4 European Malaria Vaccine Initiative (EMVI)

EMVI was established in 1998 by the European Commission and interested European Union Member States, in order to address identified structural deficiencies in public funded malaria vaccine development. Its goals are to provide a mechanism through which the development of experimental malaria vaccines can be accelerated within Europe and in developing countries.

More information on EMVI can be found at: <http://www.emvi.org>

2.5 Malaria Vaccine Initiative (MVI)

MVI was invited as a developer of malaria vaccines.

The mission of MVI is to accelerate the development of promising malaria vaccines and to ensure their availability and accessibility in the developing world. MVI is a focussed vaccine development program created in 1999 by a grant from the Bill & Melinda Gates Foundation (BMGF). MVI is a not-for-profit, public-private-partnership. MVI whose new cycle for core funding has started in 2007 has strategic goals that are linked to the millennium development goals and the malaria vaccine roadmap.

More information can be found at <http://www.malariavaccine.org>

2.6 Malaria Clinical Trial Alliance (MCTA)

The mission of MCTA is to facilitate site preparation for the effective conduct of clinical trials for life-saving malaria interventions and simultaneously promote the long-term development and sustainability of clinical trial sites in resource-constrained countries in the developing world. Mainly funded by the BMGF, MCTA aims to create a new networking environment.

More information on the organisation can be found at:

<http://www.indepth-network.org/mcta/mctaobj.htm>

2.7 Scientists

Members of the African scientific community working on the on malaria vaccines were invited. They were from various institutions and centres, representing different regions of sub-Saharan Africa. In addition each European member state was asked to bring one scientific expert.

2.8 US Agency for International Development Malaria Vaccine Development Program (USAID MVDP)

The mission of the USAID MVDP is to development malaria vaccines for introduction into malaria control programmes in the developing world to reduce morbidity and mortality due to malaria. The USAID MVDP has pursued this mission for more than 40 years through support of many institutions. Currently the USAID supports MSP1 and AMA1 vaccine development with the US Department of Defense Malaria Vaccine Program, GlaxoSmithKline Biologics and GenVec, Inc.

More information can be found at:

http://www.usaid.gov/our_work/global_health/id/malaria/techareas/vaccine.html

2.9 WHO Initiative for Vaccine Research (IVR)

The World Health Organisation (WHO) was represented by the Initiative for Vaccine Research (IVR), which plays a major coordinating role in the malaria vaccine field. IVR conducts and coordinates activities related to product research and development and implementation research for vaccines and delivery devices. Based at WHO headquarters in Geneva, the disease portfolio of the initiative includes tropical diseases, HIV/AIDS, tuberculosis, malaria, meningitis, respiratory diseases, diarrhoeal diseases, Japanese encephalitis, cervical cancer and measles.

More information can be found at: http://www.who.int/vaccine_research/about/en/

3. Science and Products

3.1 Malaria vaccine roadmap

The Malaria Vaccine Technology Roadmap provides a coherent framework for aligning resources, facilitating partnerships and identifying pathways to a viable malaria vaccine.

More than 230 experts representing 100 organizations from 35 countries have participated in the process of preparing the malaria vaccine roadmap. The resulting Roadmap presents a shared vision and goal and identifies the community's top

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priorities for accelerating malaria vaccine development. Members of the WHO-led malaria vaccine funders' group, who are each associated with agencies funding malaria vaccine development and contributors to the Roadmap process, have committed to greater coordination and partnership in support of the activities identified in the Roadmap. The Roadmap can be downloaded from the following website:

<http://www.malariavaccineroadmap.net/index.html>

3.2 Products in the pipeline

The WHO maintains a rainbow table which lists all malaria vaccine candidates currently in the pipeline. Currently there are 16 products in active clinical development. It was explained how candidates are selected for this list and the scientific complexities were stressed. Half of the current vaccine candidates are based on 3 proteins CSP, AMA1 and MSP 1. The table below specifies the main products with its target stage and expected clinical effect as presented by WHO.

Target Stage, clinical effect and possible immune mechanism of various malaria vaccine candidates		
Name of Product/Candidate	Target Stage	Clinical Effect
CSP, LSA1, LSA3	Sporozoite stage	Prevent infection and disease
MSP1, AMA1, MSP3, GLURP, SERA	Blood stage	Reduce clinical disease severity
PfS25	Mosquito stage	Interrupt transmission

Various presenters mentioned products in the pipeline. This information is summarised in the table below:

Malaria vaccine products in the pipeline presented at the meeting*		
Name of Product/Candidate	Presented by	Where in pipeline
pfAMA 1	EMVI	Phase 1a completed
pfAMA 1 ASO2	EMVI	Phase 1a completed
pfAMA1 DDA/TBD	EMVI	Phase 1a to commence Q3 of 2007
pfAMA1	AMANET/EMVI	Phase 1b scheduled for Q2 of 2007
AMA1 ASO1/ASO2	MVI	Phase 1a 1/2a
AMA1:MSP1 ISA720	MVI	Phase 1a 1/2a
GMZ2	EMVI	Phase 1a completed
GMZ2	AMANET/EMVI	Phase 1b scheduled for Q2 of 2007
GMZ2 DDA/TBD	EMVI	Phase 1a to commence Q3 of 2007
GMZ2 DDA/TBD	EMVI	Phase 2a conditional on proof of efficacy in phase 2b trials i.e. attempt

<i>Malaria vaccine products in the pipeline presented at the meeting*</i>		
<i>Name of Product/Candidate</i>	<i>Presented by</i>	<i>Where in pipeline</i>
		<i>to validate a blood stage phase 2a challenge model. The earliest 2009.</i>
<i>Polyprotein</i>	<i>Oxford-Hill/EMVI</i>	<i>Phase 1a completed</i>
<i>Polyprotein</i>	<i>Oxford-Hill/EMVI</i>	<i>Phase 2 completed</i>
<i>pfMSP1 EBA175</i>	<i>EMVI</i>	<i>1-2 trials planned for late 2007 early 2008 in India optional trials in Africa mid 2008</i>
<i>MSP-C1 AIOH+CpG</i>	<i>MVI</i>	<i>Phase 1a 1/2a</i>
<i>MSP 3</i>	<i>AMANET</i>	<i>Phase 1b completed, phase 1b/2b scheduled for 2007</i>
<i>RTS.S AS01/AS02</i>	<i>MVI</i>	<i>Phase 2b</i>

**Table was amended by SJ post meeting*

3.3 Needs identified

At the meeting several needs were identified as priority areas for research and development. Some of these priorities are, however, beyond the scope of the EDCTP programmes. The identified priorities are as follows:

- Standard assays
- Access to potential adjuvants
- Pre-clinical studies
- Alternative vaccine delivery systems

It was agreed that there was an urgent need to have standardised assays for the evaluation of malaria vaccines. It was also pointed out that the delivery system of vaccines is very important and needs attention. Furthermore, it was also agreed that there a need for affordable, reliable and safe adjuvants.

3.4 Summary discussion on products and science

- Phase Ia Safety studies

There was a lively debate on the necessity and desirability of conducting the initial safety studies (Phase Ia) in Europe. Some African scientists preferred to omit Phase Ia trials in Europe, and conduct the entire clinical development of the vaccines in Africa, starting with Ib in adults, in order to accelerate the development of the vaccines, and save financial resources that could otherwise be utilised in Africa. There was also a concern that European clinical trial site capacity problems may arise. On the other hand it was argued that:

- Review by a European regulatory agency of the vaccine dossier, IMPD, IB, and review by ethics committees might greatly enhance the safeguarding of trial volunteers in Africa.
- Registration/licensure of a malaria vaccine via an opinion of EMEA (article 58) probably would be facilitated, if the initial safety trials (Ia) were conducted in Europe.

- Immunogenicity data from malaria non-exposed European adults could be valuable in predicting the immune response in African (non-exposed infants).

The general opinion, after discussion, was that the standard practise with initial Ia studies in Europe should be continued and be a prerequisite for EDCTP consideration.

- Phase IIa Challenge trials

Some malaria vaccine candidates are tested in human challenge models. These challenge trials are mainly carried out on healthy volunteers in Europe and the United States. The costs are around 300,000 euros. The aim of these trials is to assess safety as well as immune responses (protection) to the vaccine candidate after challenge with *P. falciparum* infected mosquitoes. EDCTP can only fund trials in Africa, not in Europe. Relevant questions surrounding human challenge models in non-exposed volunteers include:

- Can the results be reproduced in the field? To consider are the issue of background immune status which is very different in western volunteers compared to their peers in Africa
- What to do when a vaccine is not protective in a challenge trial? Can the vaccine candidate proceed to testing in the field or not? The view point of the regulatory officials was mentioned in this respect. Would they allow for a field trial after a negative challenge trial? However, it was generally agreed that challenge tests should not be neither the only nor the main criterion of go-no go in malaria vaccine development
- Should a challenge test be done before a trial in the field or vice versa? There were differing views on this matter
- Should capacity be built to do challenge tests in Africa? The general consensus was that this was not an urgent requirement
- How to validate challenge trials? Possibly the only way is to compare the results of such studies with the results of testing the same products in field trials under natural challenge. The issue of validation of diagnostic assays in general is of relevance to this topic. Also the limited knowledge on immunological correlates of protection is important to note. EMVI and other organisations are working on the technical validation of challenge models
- It was agreed that challenge models can be of relevance in prioritisation because it is important to know as much as possible before large scale field testing. End-point criteria can be set only if working model is understood.

- Discussion immunological correlates

Most trials use absence of clinical malaria as an end-point. In terms of markers of infection many issues remain to be resolved. The immunological markers for protection using a blood stage vaccine are not yet known. Rough immune correlates are known but more information is required. In phase IIb trials a vaccine may work in one place but not another depending on the immune status of the population immunised as a consequence of malaria transmission intensity.

There are no standardised correlates of protection. Technical assays are not yet standardised, although efforts are ongoing to achieve this. How to determine which vaccine candidate is the most promising to pursue when resources are limited? On what criteria should these decisions be based? How to maximise strong immune

responses in African setting? Unexpected things happen and are not fully understood.

EDCTP should invest in facilities for clinical testing. Guidelines on how to interpret the results of trials are also very important. There are many technical improvements to be made. Understanding on how natural immunity in adults develops may lead to knowledge of what is required to assess in the trials.

4. Sites in Africa

4.1 Represented sites

The table below lists Southern partner institutions that were represented in person at the meeting. In addition to these sites many other were represented through their association with either AMANET and/or MCTA.

<i>Southern partner institutions represented at the meeting</i>		
<i>Name of Institution</i>	<i>City</i>	<i>Country</i>
<i>Centre National de recherche et de Formation sur le paludisme (CNRF)</i>	<i>Ouagadougou</i>	<i>Burkina Faso</i>
<i>Institut de Recherche pour le Développement (IRD)</i>	<i>Dakar</i>	<i>Senegal</i>
<i>Walter Reed Project / KEMRI</i>	<i>Kisumu</i>	<i>Kenya</i>
<i>Malaria Research and Training Center, University of Bamako</i>	<i>Bamako</i>	<i>Mali</i>
<i>Ifakara Health Research and Development Centre</i>	<i>Ifakara</i>	<i>Tanzania</i>

4.2 Summary discussion on Sites in Africa

- Terminology

The term site was discussed and it was suggested that Southern partner institution or centre were more appropriate and politically correct rather than site. It was considered that the term site implies an extension or an outpost of a Northern institution. It was also stressed that research should be designed according to the view of all partners not only the Northern ones.

- Role of African universities

Development of universities is very important for the development of a country as a whole. It was suggested that university development is essential to nation building and that EDCTP should pay attention to universities as part of their capacity building approach. In some countries, such as Mali and Tanzania, there are strong links

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between research institutions and local universities. However, it was pointed out that since lecturers normally have other commitments such as teaching and clinical services, research may not always be their priority. This was not unique for Africa. Examples of hybrids are also present such as in Mali and Ghana where several successful examples of individuals who are both lecturers and successful researchers are enhancing the collaboration of universities and research institutions in their countries.

- Clinical trial sites development

The need for new clinical trial sites was highlighted. EDCTP intends to improve networking between trial sites with strong institution linked to weaker ones. Many trial sites can be developed through partnership between institutions.

- Map of institutions with clinical trial capacity in Africa

It was suggested that EDCTP should undertake a detailed mapping of institutions and centres with sites that are capable or have the potential to undertake clinical trials. It was also observed that surveys on these institutions are already being done by the BMGF, INDEPTH/MCTA, EDCTP (through DCCC) and AMANET. It was recommended that these efforts should be coordinated.

- Relationship with African national policies and strategies

It was also pointed out that for the EDCTP programme to be more meaningful, it must be integrated and incorporated with national programme policies and strategy. The EDCTP interaction with political leaders and integration of the programme into national strategic development should be done with the assistance of DCCC and ENNP constituencies. Research framework for Africa was prepared by African Heads of States.

- Capacity Building

Capacity Building should be done carefully. Clinical trials should be used as vehicles for capacity development. This capacity should be developed to enable conduct of quality trials following ICH-GCP guidelines. This will ensure both the successful conduct of the trials, utilisation, retention and sustainability of the developed capacity and through learning by doing. This should be enhanced by promoting networks using south-south networking for mentorship and support of the weaker institutions and south-north networks for support and technology transfer.

- Sustainability of sites in between trials

Sustainability of sites in between trials was raised as a very important issue. Many sites derive their main income from grants and lose experienced staff when the grants are over until new ones are awarded. Centres should be able to retain their core staff.

5. EDCTP procedures

5.1 Overview EDCTP procedures

EDCTP can fund proposals through an open call or a brokering procedure. Both were explained to the audience. More information can be found in the Guidelines for Stakeholder meetings (see Annex 2).

5.2 Summary discussion EDCTP funding procedure and timelines for initiating funding procedure

It was generally agreed that an open call would be the appropriate funding procedure for malaria vaccines. EDCTP should aim to support several products to increase the chance of supporting a successful product. In an ideal world EDCTP should support large trials in which several competing products would be tested head to head but it was acknowledged that this may be very difficult to achieve.

The need to focus the call text was stressed. The call text should contain a clear definition and scope. It was suggested only phase II trials should be funded. Issues such as validation of assays and correlates of protection are outside the scope of EDCTP but could be asked for as part of the trials and should be considered for inclusion in the call text. The involvement of sites not attached to an existing network should be considered.

Funds for malaria vaccines are limited. Therefore, EDCTP should work in synergy with other partners including EMVI, MVI, BMGF, WHO/IVR, the Wellcome Trust, USAID and US NIAID and avoid overlap and duplication of efforts.

It was debated if EDCTP should opt for a one-stage (full proposal only) or a two-stage procedure (first submitting a letter of intent followed by full proposal for the selected candidates). Although a one-stage procedure would be faster some participants suggested that using a letter of intent stage may facilitate merger or potential collaboration between 2 proposed trials of competing products.

Because the proposals comprise clinical trial, capacity building and networking elements the issue of how to review them was also discussed. One possibility would be to ask each reviewer to assess only a specific part of the proposal. It was also generally agreed that the Scientific Review Committee should be broad-based and include capacity development expertise.

Consensus recommended procedure

The result of the discussion was consensus that EDCTP should issue an open call for final proposals which will be reviewed by broad based committee which will consider capacity building as well as product evaluation aspects.

Possible funding partners:

The table below lists the European countries that were represented at the meeting:

Country	Type of support
Belgium	Was not in a position to make a pledge because they were represented by a scientific expert only
Denmark	Did not specify but pledged to contribute funds, and in kind
France	Capacity building for a site in Senegal
Germany	Germany will be able to support German applicants
Netherlands	Indicated willingness to recommend to programme board to participate to this call
Norway	Did not make a pledge
Spain	<p>Specific products:</p> <p>Currently at preclinical stage:</p> <ul style="list-style-type: none"> • Attenuated Pf sporozoite vaccine (Sanatia) • MSP 1-19/EBA-175 F1 (ICGEB) <p>Currently at clinical stage:</p> <ul style="list-style-type: none"> • RTS,S/ASO2 ASO1 (MVDU) • AMA-1 C1/AOH+CPG (SMMHS/Wanxing/MVI/WHO)
Sweden	Happy to support call using core funding previously donated to EDCTP
Switzerland	<p>Specific products:</p> <ul style="list-style-type: none"> • PEV 301 (CSP)/PEV 302 (AMA-1) in combination for Phase I trial, a challenge trials is already done • PEV 303, PEV 304, PEV 305 which are ready for testing as single components or in combination with PEV 301 and PEV 302
United Kingdom	All products

6. Recommendations to EDCTP

1. An open call for proposals
2. The total sum for malaria vaccines, i.e. €14.7 million. Should be allocated to this call. In the event that not all this amount is allocated, there could be a second call for malaria vaccines at a later stage
3. The call text should emphasise that EDCTP requires integrated project proposals with - if possible - several vaccine candidates included, and that the candidates - if scientifically and technically possible - should be compared using the same assays, clinical trial protocols and have the same definition of end-points, providing for comparison of results
4. The text should call for malaria vaccine clinical trials of Phase II, including age de-escalating trials in target populations, which could be infants or children, depending on transmission intensity (prior exposure)
5. The call text should emphasise that a proposal comprises three components, (1) the clinical trial, (2) capacity building and (3) networking, and that the secretariat should institute a review with experts in the various areas. The Review Committee should be broad and include experts in these three areas.
6. EDCTP should aim to invest in the development of several products to increase the chance to support a successful candidate.
7. Artificial challenge IIa studies in Europe of pre-erythrocytic vaccines could be of value in prioritisation, but should not be a pre-requisite. It was also generally accepted that artificial challenge with insectary-bred mosquitoes in endemic countries could not be recommended.
8. There was a general agreement that it was important to advance to efficacy trials in target populations in Africa as fast as possible. Although data from field efficacy trials may be useful in validation of the possible predictive value of artificial phase IIa challenge studies in Europe, this is outside the scope of EDCTP.

Annexes

Annex 1: Hosting country contribution to the stakeholder meeting

Estimate of all costs covered by hosting country	
Item	Amount
Travel	
Hotel	
Catering	1200 euros
Administration support	
Venue	
Other	
Sum	1200 euros

Annex 2: EDCTP Guidelines for Stakeholder meetings

Introduction

This document aims to describe all aspects related to the aim, organisation and outcome of the EDCTP stakeholder meetings.

EDCTP aims to organise to 2 types of stakeholder meetings: 7 meetings will focus on disease specific topics and one meeting will concentrate on Nodes of Excellence. The disease-specific topics will have a focus on products in the pipeline. These topics are listed below:

- Malaria treatment and malaria in pregnancy (combined meeting)
- Malaria vaccines
- TB treatment
- TB vaccines
- HIV treatment
- HIV vaccines
- HIV microbicides

The Nodes of excellence meeting will focus on the integrated approach of EDCTP towards the establishment of regional nodes of excellence in sub-Saharan Africa with particular focus on reference laboratories and centres specialised in data management encompassing clinical trials design, conduct, and analysis skills, building on sites with existing capacities and competences in these areas.

These guidelines aim to describe the generic approach towards organising both types of meetings. All stakeholder meetings on disease related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP. The expected outcome, communication aspects, timelines and financial issues concerning stakeholder meetings will be clarified. In addition the role of the hosting member state, the organising committee including the independent chair as well as the expected list of participants are described.

To ensure transparency these guidelines are made public and the EDCTP Secretariat will ensure that the implementation will be carried out and documented correctly.

Aim and objectives of a stakeholder meeting

A stakeholder meeting is a one day meeting. It is the start of a process that leads towards EDCTP funding one or more projects through a call or brokering procedure.

The expected outcome of these meetings is:

1. To make recommendations to EDCTP for:
 - The development of cooperative projects and coordination of efforts
 - Priorities for EDCTP:
 - for disease specific topics EDCTP requires priorities in terms of product and sites whereas
 - for nodes of excellence EDCTP needs priorities in terms of sites, location as well as required skills and capacity
2. Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms. These will be followed up by the EDCTP secretariat.
3. Establishment of trust in the EDCTP approach with our stakeholders.

The meetings with a disease-specific topic will have the following objectives:

- Identify products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend priority in terms of product and sites
- Recommend if the funding procedure is a call or brokering or no-go
- Recommend EDCTP timelines concerning the initiation of funding for each topic area

The stakeholder meeting on Nodes of Excellence has similar priorities:

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- Identify potential sites
- Identify needs in terms of skills and capacity
- Recommend priorities in terms of needs and sites
- Recommend if the funding procedure is a call or brokering or no- go
- Recommend EDCTP timelines concerning the initiation of funding

Organisational aspects

All stakeholder meetings on disease-related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP.

All meetings will be organised by an Organising Committee that consists of:

- An independent expert to chair
- A representative of the hosting country. For the European Member States this is the European Networking Officer (ENO) representing the country while for the Nodes of Excellence meeting this role should be fulfilled by the relevant member of the Developing Country Coordinating Committee (DCCC),
- The Partnership Board (PB) and DCCC disease experts
- The Executive Director and Operations Manager from the EDCTP Secretariat

The independent chair will be identified by EDCTP Secretariat, PB and DCCC representatives of the organising committee before the date of the stakeholder meeting is set. The candidate will be approved by the GA in a written procedure. If the hosting country is identified before a chair is selected the representative of the hosting country will also be involved in selecting the chair. The Terms of reference for the Independent chair are the following:

To work with the EDCTP stakeholders' meeting planning group to ensure that the meeting is planned and implemented transparently avoiding or declaring any conflict of interest to give an optimal, independent and objective advice to the EDCTP. This, via the EDCTP Secretariat should take into account the following:

1. The presence of appropriate representation of all significant bodies including industry, private-public partnerships and other stakeholders that are relevant to the topic; ensuring that the representation at the meeting is sufficiently senior to contribute with authority
2. There are appropriate and effective arrangements for conducting the meeting including drafting and approving of the agenda; noting of the attendance; ensuring of adequate participation and deliberation of all the relevant issues
3. Provision in an agreed timescale of a good quality report of the meeting.

Travel and hotels are arranged in close collaboration between the hosting country and the EDCTP Secretariat and the hosting country is expected to play an active role in this. The hosting country should organise location, catering and administrative support as well as assist delegates with their visa requirements. In addition the hosting country is responsible for sending out the invitations to participants. The final list of participants to be invited will be provided by the EDCTP Secretariat in collaboration with the Organising Committee.

Participants

It is a requirement that the following parties are represented at the stakeholder meeting:

- Funders both from the European Member States and if applicable third parties. Each European Member State will be asked to send one representative. It is up to the individual country to accept this invitation or not
- Product developers, Public Private Partnerships and/or industry (disease specific topics only)
- Representatives of African sites that have the capacity to carry out phase II or III trials
- Experts in the field. Each European Member State may bring one expert of their own choosing

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- Independent experts if applicable.

Most participants will be identified by the Organising Committee with the exception of the representatives of the European Member States. Each European Member State is free to send one expert in the field and one representative of their funding body of their own choosing.

It is normally expected that a stakeholder meeting will have no more than around 40 participants.

Invitations to the participants need to go out at least 6 weeks in advance.

Agenda

The agenda for the stakeholder meeting is set by the Organising Committee using the format developed by the EDCTP Secretariat. The generic format for the meetings on disease specific topics is shown below.

EDCTP Stakeholder Meeting
Topic
location, date 2007
Address
Contact

Agenda items	By	Timelines
<i>Coffee/Tea</i>	<i>All</i>	
1.0 Welcome by host	host	
2.0 Approval of the Agenda	All	
3.0 Science and products 3.1 Scientific overview of the field 3.2 Products in the pipeline: relevant stakeholder (more added if required) More added if required		
Coffee break	All	
4.0 Discussion on products and science	All	
5.0 Sites in Africa 5.1 Relevant stakeholder (more added if required) 5.3 DCCC		
Lunch	All	
6.0 Discussion on sites	all	
7.0 EDCTP procedures	SEC	
8.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	
9.0 Summary of recommendation	Chair	

Communication

Because EDCTP stakeholder meetings should demonstrate transparency and independence it is important that the meetings are widely advertised and that the hosting country does not have a perceived conflict of interest with the topic. EDCTP will however, not publish a call for participants. The advertisements for the stakeholder meetings will focus on announcement of topics, locations, aims and dates. They should list a contact address and encourage those that would like more information to make contact. If someone contacts EDCTP with a wish to participate, this request will be passed on to the Organising Committee who will make a decision.

Advertising of the stakeholder meetings will be through the following means:

- Internet:
 - EDCTP website
 - Requesting constituency members to publish at their websites
 - Other relevant websites
- Paper advertisement:
 - Publishing of adverts in Lancet as soon as all the dates are set
- Ask EDCTP constituencies to communicate to appropriate parties
- If the opportunity arises mention of EDCTP stakeholder meetings in presentations or meetings

Timelines

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The dates for the various stakeholder meetings will be set as soon as the independent chair and hosting country have been identified and once the chair agrees to the Terms of Reference. It is expected that the stakeholder meetings for TB vaccines, malaria vaccines, HIV vaccines and HIV treatment will take place during the first quarter of 2007. The stakeholder meetings for Nodes of Excellence, malaria treatment/pregnancy, TB treatment and HIV microbicides are scheduled for the second quarter of 2007.

Financial issues

If the stakeholder meeting is hosted by a European country, it is expected that this country will at least as a minimum cover the costs for use of the location, catering during the meeting, administrative support and any other local expenses. If the hosting country is African these costs need to be discussed with the EDCTP Finance Manager. EDCTP will normally pay for travel and hotel for external participants as well as for PB and DCCC members. EDCTP expects that the European Member states will at least pay for travel and hotel of the participants they delegate. EDCTP will pay for travel and hotel of European MS participants and experts only if the European Member State is unable to do so.

Outcome/follow up

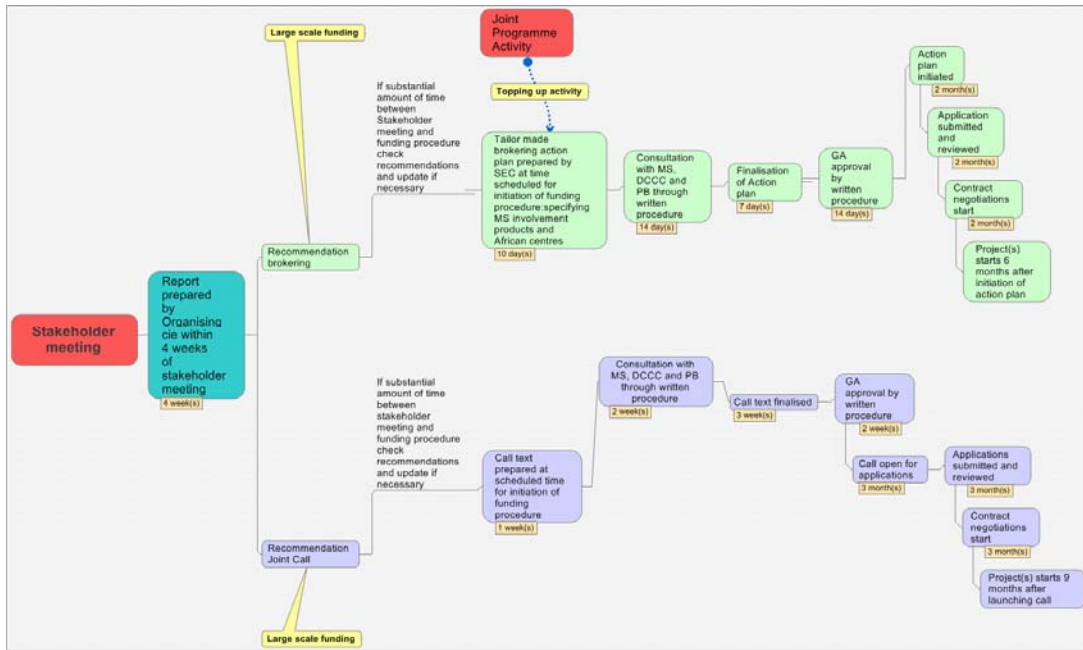
The organising committee will produce a report of the meeting within 4 weeks. The report will be presented to EDCTP. EDCTP will initiate its funding procedures at the appropriate time after considering the report. The timing for launching calls or brokering initiatives can range from 2007-2009 depending on the on the availability of products and sites. A final list of expected dates for initiation of funding procedures will be prepared after all stakeholder meetings have taken place. The diagram below summarises both funding procedures. More information on the EDCTP funding procedures can be found at the website.

A summary of both procedures is described below:

- *Call for proposals*
A call text is drafted based on the recommendations that came out of the stakeholder meeting. After consultation of the various EDCTP constituencies and approval of the General Assembly the call will be published. An EDCTP call is normally open for applications for a period of 3 months. The applications are then checked against the eligibility criteria as defined in the call text and eligible applications will be reviewed by at least 2 external experts as well as the EDCTP Scientific Review Committee (SRC). The SRC ranks the applications and makes a recommendation for funding. This recommendation is examined by the PB which ensures the quality of the review procedure and also assess if the proposal is in line with the EDCTP strategy. The PB make the final recommendation for funding to the General Assembly who approve the application.
- *Brokering*
A brokering action plan is prepared by the EDCTP Secretariat and requires to be approved by the General Assembly after consultation with the EDCTP constituencies. The action plan will be initiated resulting in an application for funding. This application is checked for eligibility as described in the brokering action plan and reviewed by at least two external experts as well as the relevant EDCTP SRC. The SRC make a recommendation for funding or rejection which is examined by the PB which examines both the procedure as well as the alignment of the project with the EDCTP strategy. Upon recommendation of the PB the GA make the decision to fund the project or not.

EDCTP Stakeholder meeting: Malaria vaccines

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Annex 3: Instructions for presentations

Expected outcome of the meeting

The expected outcome of the EDCTP stakeholder meetings is to make recommendations to EDCTP for:

- The development of cooperative projects and coordination of efforts
- Priorities for EDCTP in terms of product and sites
- Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms.
- Establishment of trust in the EDCTP approach with our stakeholders

The stakeholder meeting is considered the start of a process that leads towards EDCTP funding of one or more projects through an open call or brokering.

Audience

The audience will be a mixture of experts in the field and people who represent funding agencies and may not have a scientific/medical background. Therefore we would like to suggest that your presentation should be aimed at a general audience.

Expected contents of your presentation

Given the expected outcome of the meeting and the composition of the audience EDCTP would like to provide you some points regarding the expected contents of your presentation.

If you talk about science and products

- A short introduction on the organisation you are representing
- Without going into too much scientific details basic information about the products in the pipeline:
 - Basic principles of the product
 - Status with respect to clinical testing: what has been done/what is ongoing and what is planned/needed
 - Availability of the product
 - Restrictions with respect to the use of the product: is it only available for persons associated with your organisation/is it for sale?

In addition to the presentation could you provide a short summary document on each product that should enable the participants to the meeting to assess its scientific validity and potential.

If you talk about sites in Africa

- A short introduction on the organisation you are representing
- Basic information about the sites you are representing:
 - Capacity and trial experience
 - Commitment to other trials/availability to do the trial
 - Local malaria situation

Duration of your presentation

The time available per presentation is limited to 15 minutes. The presentations will be followed by an initial discussion of 1 hour.

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Annex 4: Agenda**EDCTP Stakeholder Meeting****Malaria vaccines**

Copenhagen, 31 January 2007

Statens Serum Institut, Artillerivej 5, Copenhagen

0930-1700

Aim of the meeting:

- Identify and prioritise potential products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend if the funding procedure of EDCTP will be an open call, brokering or whether EDCTP should fund this topic at all
- Recommend EDCTP 's timeline concerning the initiation of funding for this topic

Agenda items	By	Timelines
<i>Coffee/Tea</i>	<i>All</i>	<i>9:15 – 9:30</i>
1.0 Welcome	Charles Mgone and Klaus Winkel	9:30 – 9:40
2.0 Approval of the Agenda	All	9:40-9:45
Brief word of European Commission	Andreas Hottel	
3.0 Science and products		
3.1 Scientific overview of the field	Zarifa Reed	9:45-10:00
3.2 Products in the pipeline: EMVI	Odile Leroy	10:00-10:15
3.3 Products in the pipeline: MVI	Carolyn Petersen	10:15-10:30
Coffee break	All	10:30-10:45
4.0 Discussion on products and science	All	10:45-11:45
5.0 Sites in Africa		
5.1 MCTA	Bernard Ogotu	11:45-12:00
5.2 AMANET	Wen Kilama	12:00-12:15
5.3 DCCC	Andrew Kitua	12:15-12:30
Lunch	All	12:30-13:30
6.0 Discussion on sites	all	13:30-14:30
7.0 EDCTP procedures	Cynthia Naus	14:30-14:45
8.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	14:45-16:00
9.0 Summary of recommendation	Chair	16:00-16:20

Annex 5: List of participants

Salim Abdullah

Ifakara Health Research and Development
Centre,
Box 53, Ifakara,
Tanzania
Phone: 255-23-2625164,
Fax: 255-23-2625312,
E-mail: mndejembi@ifakara.mimcom.net

Umberto D'Alessandro

Epidemiology Unit
Department of Parasitology,
Prince Leopold Institute of Tropical Medicine,
Nationalestraat 155,
B-2000 Antwerp,
Belgium
Phone : +32-(0)3-247.66.66
Email : udalessandro@itg.be

Christian Burri

Swiss Tropical Institute
Socinstrasse 57
P.O. Box
CH-4002 Basel
Switzerland
Phone: +41 61 225 26 61
Fax: +41 61 225 26 78
Email: christian.burri@unibas.ch

Roma Chilengi

AMANET
Tanzania Commission for Science and
Technology Building
P.O. Box 33207,
Dar es Salaam, Tanzania
Phone +255 22 270 0018
Email: chilengi@amanet-trust.org

Hannah Akuffo

Swedish International Development Agency (SIDA),
Dept. of Research SAREC
Sveavägen 20
SE – 10525 Stockholm
Sweden
Phone.: +46/ 8-6985053
Fax: +46 8 698 5656
Email: hannah.akuffo@sida.se

Carmen Audera

Spanish European Office at ISCIII
Sinesio Delgado, nº 6 (Pabellón Nº 4). 28029 – Madrid
Spain
Phone.: +34 91 82 22508
Fax: +34 91 38 77766
E-mail: caudera@isciii.es

Qijun Chen

Department of Microbiology, Tumour and cell biology
(MTC)
Karolinska Institutet, MTC, Box 280
171 77 Stockholm
Sweden
Email : Qijun.Chen@ki.se

David Coles

EDCTP
P.O. Box 93015
2509 AA The Hague
The Netherlands
Phone: +31 70 344 0880/0897
Fax: +31 70 344 0899
Email : coles@edctp.org

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Alassane Dicko

PO Box 1805
Bamako
Mali
Phone : +223 222 81 09
Fax : +223 222 4987
Email : adicko@mrtcbko.org

Diana Dunstan

Medical Research Council
20 Park Crescent
London
W1N 1AL
United Kingdom
Phone : +44 (20) 76365422 extension 6227
Email : diana.dunstan@headoffice.mrc.ac.uk

Andreas Heddini

Karolinska Institutet
171 77 Stockholm
Sweden
Phone. 070 757 4562
Email : andreas.heddini@mtc.ki.se

Adrian Hill

Hill Group
The Wellcome Trust Centre for Human Genetics
Roosevelt Drive
Oxford
OX3 7BN
UK
Phone number: +44 1865 287759
Email: adrian.hill@well.ox.ac.uk

Carter Diggs

USAID
Washington, D.C. 20523
USA
Phone: 001 202 712 5728
Email: CDiggs@usaid.gov

Caterina Guinovart

Center for International Health,
Hospital Clínic i Provincial de Barcelona ,
Rosselló 132, 4-2
E-08036 Barcelona, Spain
Phone: +34 93 2275400 ext. 3288
Email: cguinova@clinic.ub.es

Claudia Herok

Bundesministerium für Bildung und Forschung
Referat 612
Hannoversche Str. 28-30
10115
Berlin
Germany
Phone: +49 1888-57 5296
Fax: + 49 1888-57 8 5296
E-mail: Claudia.Herok@BMBF.BUND.DE

Andreas Holtel

European Commission
Directorate General F3
Brussels B-1049
Belgium
Phone : +32 2 2953716
Email : s.sirima.cnlp@fasonet.bf

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Marcel Hommel

Institut Pasteur
25,28 rue du Docteur Roux
75724 Paris CEDEX 15
France
Phone : +33 1 45 68 80 00
Email: mhommel@paris.ird.fr

Søren Jepsen

State Serum Institute
Artillerivej 5
DK – 2300 Copenhagen
Denmark
Phone.: +45/32 68 31 88
Fax: +45/32 68 32 28
Email: sje@ssi.dk

Wen Kilama

The African Malaria Network Trust [AMANET]
Tanzania Commission for Science and
Technology Building
P.O. Box 33207,
Dar es Salaam,
Tanzania
Phone: +255 (022) 2700018
Email: wkilama@amanet-trust.org

Andrew Kitua

National Institute for Medical Research (NIMR),
Luthuli Road/Sokoine Drive,
P.O. Box 9653,
Dar es Salaam,
Tanzania.
Phone: +255222131864 / 2125185,
Email: akitua@nimr.or.tz and akitua@hotmail.com

Peter Kremsner

University of Tuebingen
Wilhelmstrasse 27
72074 Tuebingen
Germany
Phone: +49 7071 29 85 7179
Fax: +49 7071 295 189
Email : Peter.kremsner@uni-tuebingen.de

Judith de Kroon

NACCAP
P.O. Box 93120
2509 AC
The Hague
The Netherlands
Phone: + 31 (0)70 3440553
Fax: + 31 (0)70 3819874
E-mail: kroon@nwo.nl

Odile Leroy

European Malaria Vaccine Initiative
Secretariat
c/o Statens Serum Institut (SSI)
Artillerivej 5
DK-2300 Copenhagen S
Denmark
Phone.: +45 32 68 37 98
Fax: +45 32 68 31 44
e-mail: oly@ssi.dk

Bernt Lindtjorn

Centre for International Health
Arm. Hansens Hus, Haukelandsv. 28
N-5021 Bergen
Norway
Phone : +47 55 97 49 82
Email : Bernt.Lindtjorn@cih.uib.no

Kårstein Måseide

The Research Council of Norway
Department of Global Issues
P.O Box 2700
St. Hanshaugen
N-0131
Oslo, Norway
Phone: + 47 22037457
Fax: + 47 22037362
E-mail: kmaa@forskningsradet.no

Christoph Meier

Division Biology and Medicine
Swiss National Science Foundation
Wildhainweg 3
CH-3001 Bern – Switzerland
cmeier@snf.ch

Charles Mgone

EDCTP
PO Box 19070
Tygerberg 7505
South Africa
Phone: +27 21 938 0819
Fax: +27 21 938 0569
Email : mgone@edctp.org

Pascoal Mocumbi

EDCTP
P.O. Box 93015
2509 AA The Hague
The Netherlands
Phone: +31 70 344 0880/0897
Fax: +31 70 344 0899
Email : mocumbi@edctp.org

Cynthia Naus

EDCTP
P.O. Box 93015
2509 AA The Hague
The Netherlands
Phone: +31 70 344 0880/0897
Fax: +31 70 344 0899
Email : naus@edctp.org

Claire Newland

Medical Research Council, UK
20 Park Crescent
London
W1B 1AL
United Kingdom
Phone: +41 31 308 2362
Fax: +41 31 305 2977
E-mail:

Francine Ntoumi

EDCTP
P.O. Box 93015
2509 AA The Hague
The Netherlands
Phone: +31 70 344 0880/0897
Fax: +31 70 344 0899
Email : ntoumi@edctp.org

Bernhard Ogutu

Walter Reed Project / KEMRI
P.O. Box 54
Kisumu
Kenya
Email : bogutu@wrp-ksm.org

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Carolyn Petersen

The PATH Malaria Vaccine Initiative
7500 Old Georgetown Road, Suite 1200
Bethesda, MD, USA 20814
Phone: +240 395 2700
Fax: +240 395 2591
Email: cpetersen@malariavaccine.org

Robert Sauerwein

Medical Microbiology
P.O. Box 9101
6500 HB Nijmegen
The Netherlands
Phone: +31 24 3610577
Email : r.sauerwein@ncmls.ru.nl

Cheikh S. Sokhna

UR Paludisme Afro-Tropical,
Institut de Recherche pour le Développement,
BP 1386, Dakar,
Senegal
E-mail: sokhna@ird.sn

Klaus Winkel

c/o Statens Serum Institut,
Artillerivej 5,
DK-2300 Copenhagen
Denmark
Phone : +45 45 88 11 30
Fax : +45 32 68 32 38
Email: WIN@ssi.dk

Zarifah Reed

Research on Parasitics and Other Pathogens
Initiative for Vaccine Research
Immunization, Vaccines and Biologicals
World Health Organization (WHO)
20 Avenue Appia
1211 Geneva 27
Switzerland
Phone: +41 (22) 791 43 95
Fax: +41 (22) 791 48 60
Email: reedz@who.int

Sodimon Sirima

Centre National de Recherche et de Formation sur le
Paludisme (CNRFP)
01 BP 2208 Ouagadougou 01
Burkina Faso
Phone +226 50 32 46 95
Fax : + 226 50 30 12 86
Email: s.sirima.cnlp@fasonet.bf

Alfred Tiono

Centre National de recherche et de
Formation sur le paludisme (CNRFP ex
CNLP)
01 BP 2208 Ouagadougou 01
Burkina Faso
Phone: + 226 32 46 95/6
Fax: + 226 30 12 86 or + 226 31 04 77
Email: t_alfred@fasonet.bf

Annex 6: Discussion paper

Malaria Vaccine Development

A brief background

Prepared by Zarifah Reed and Carter Diggs

Introduction and Overview

It is estimated that *Plasmodium falciparum* malaria kills around 1 million children and causes 300-500 million clinical episodes of malaria annually. While scale-up and implementation of existing intervention measures to reduce the burden of disease caused by malaria, such as vector control, insecticide-treated bed-nets and anti-malarial therapy is imperative, the development and availability of a malaria vaccine for young children would address a critical public health need

As evidenced by the "Rainbow Table" produced by WHO IVR, malaria vaccine development is an active and complex enterprise worldwide, with more than 75 vaccine concepts, currently at various stages of development. Most of these concepts are based on a handful of known antigens despite the fact that the malaria parasite has some 5000 genes, each of which could theoretically serve as an antigen in a vaccine formulation. The numbers of potential vaccine concepts that could be result from various combinations of antigens, adjuvants, as well as delivery systems is staggering. The challenge of testing them is formidable, given the lack of relevant and predictive tools to preclinically screen and prioritize all the possibilities. Ultimate proof of vaccine concept requires clinical efficacy trials, even more unlikely for all possible candidates, Fortunately there are some insights which limit the number of vaccine concepts which should seriously be pursued. But making selections among the alternatives is both art and science and, in truth, sometimes driven by politics and funding. In this brief account, an attempt is made to classify this diversity and provide some suggestions as to how to approach parsing of the various alternatives.

Categories of malaria vaccines based on mode of action

Malaria antigens fall into three broad categories depending on their putative mode of action when used in vaccine formulations: (1) preerythrocytic, (2) blood stage, and (3) transmission blocking.

Preerythrocytic vaccines target parasites before they reach the blood stream and thus have the potential to prevent disease (which is due entirely to blood stage infection). There are many antigens of this type, all related to parasite forms which are injected by mosquitoes or develop in the liver before being released into the blood stream.

Early observation that antibodies to the sporozoite surface antigen, the circumsporozoite (CS) protein, neutralized sporozoites, and that such antibodies were present following protective immunization with irradiated sporozoites led to the development and testing of various CS-based vaccines. Ability to test for efficacy in an artificial challenge model has greatly facilitated progress and in fact the most advanced malaria vaccine in clinical development (RTS,S) is based on the CS protein. Anti-CS antibodies have not been shown to be correlated to vaccine induced protection and the underlying mechanisms are not definitively known although it seems likely that other cell-mediated immune responses are the more relevant responses. Although RTS,S has not demonstrated an optimal level of efficacy, it is thought that a partially efficacious, first-generation vaccine of 30-50% could still provide great public health impact in disease endemic areas. Sponsored by a development partnership between PATH MVI and GSK

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Biologicals, multi-center, multi-nation trials are being planned to gather the necessary data in the infant age group required for regulatory submission and market authorization, aimed for 2011.

Another strategy being pursued involving mainly pre-erythrocytic antigens is the prime-boost approach. While plasmid DNA-based vaccine approaches for pre-erythrocytic antigens failed to protect in challenge studies as they did in animal studies, the heterologous prime-boost vaccination approaches delivers plasmid DNA vaccines as primers, and viral vectored vaccines as the prime or as the boost. The pre-erythrocytic antigen, thrombospondin-related adhesive protein (TRAP) and a string of T-cell epitopes (ME; multiple epitopes) using modified viruses and plasmid DNA, have been tested with modified vaccinia Ankara (MVA) and attenuated fowlpox-virus 9 viral vectors. Despite impressive cellular immune responses in preclinical studies and delay in development of parasitemia in challenge studies, there was no protective efficacy against natural exposure trials in the Gambia and Kenya.

Artificially induced immunity to malaria has been achieved through immunization with irradiated sporozoites and comparative screening of reagents obtained through these experiments with a subset of expression library clones led to the identification of several antigens of vaccine potential such as liver stage antigens 1 (LSA1) and 3(LSA3). A formulation based on LSA1 failed in recent challenge trials. LSA3, a molecule with evidence of protection from animal efficacy studies in *Aotus* monkeys and chimpanzees is about to enter clinical trials.

The blood stage vaccine concept is based on a different principal, namely that mimicking the immunity which occurs in nature could be an effective vaccination strategy. Naturally acquired immunity is induced by multiple bouts of clinical disease resulting from parasite multiplication and growth by invasion of erythrocytes. The assumption is that inhibition of parasite invasion will lead to an impact on parasite multiplication leading to reduced parasite burden and to decreased morbidity and mortality from malaria. The majority of blood-stage vaccine concepts can be clustered around the hypothesized mechanism of protection such as induction of antibodies that inhibit merozoite invasion, or attack intra-erythrocytic parasites, either directly or indirectly, or through Th1 responses, demonstrated via *in vitro* assay systems or protection in animal models. No blood-stage candidates have proven protective in efficacy trials, and thus the predictive nature of these systems and their relevance remains open to question. Additionally, inhibition of parasite invasion is not always predictive of immune status in endemic areas.

Leading blood stage vaccine candidates include the merozoite surface protein 1 (MSP1) and apical membrane antigen 1 (AMA1). Various recombinant versions are being developed, differing in construct, strains, expression systems and formulations. The most advanced of these candidates, known as FMP1 (Falciparum Merozoite Protein 1), formulated with the same adjuvant as RTS,S has shown disappointing efficacy results in Kenya despite the apparently good safety and immunogenicity profile that led to further clinical development. Several formulations of AMA1 are being developed and have been safely tested with efficacy trials ongoing for one formulation and planned another over the coming months.

Observations from passive transfer experiments of sera from malaria immune adults into parasitemic individuals provided evidence that antibodies were critical in mediating protection against malaria disease due to blood-stage parasites. Further study of the underlying mechanisms of this protection identified an antibody-dependent cellular inhibition (ADCI) mechanism of parasite killing mediated through monocytes. This assay has been used as a selection tool for molecules of vaccine potential such as Merozoite Surface Protein 3 (MSP3), Glutamate Rich Protein (GLURP) and Serine Repeat Antigen (SERA). An MSP3 based candidate was safely tested in Burkina Faso and further clinical trials are planned. GLURP based vaccine candidates are in early clinical trials in Europe and a subunit candidate vaccine based on SERA is currently being tested in a Phase 1a trial in non-immune Japanese volunteers.

The challenge of inducing a broad spectrum of immune responses thought to be needed for maximum protection as well as overcome the potential challenge of antigenic polymorphism has led to the development of the multi-component strategy.

Components may be target antigens corresponding to the same or to different stages. Some leading examples of multi-component, same-stage vaccine candidates include a hybrid molecule of AMA1 and MSP1, and of MSP3 and GLURP. Both candidates are in Phase 1 clinical trials. Most other multi-component vaccines are all in early development.

The above approaches all aim to prevent infection and disease in a vaccinated individual. An alternative approach being pursued is the development of transmission-blocking vaccines. Transmission blocking vaccines are unusual in that they need not protect the vaccinated individual to be effective; rather antibodies taken up by mosquitoes inactivate the parasites within the mosquitoes, thus protecting other individuals, who need not have been vaccinated. Several examples of this kind of vaccine appear in the Rainbow Table. The challenge for this vaccine approach, however, is in field efficacy testing and it would seem that such a concept will be easier to test as a component of a combination vaccine.

Vaccine delivery systems

Vaccines consist of two main types of components: antigens and delivery systems. The latter involve either the physical form of the antigen or additional components (adjuvants) which enhance the immune response usually through stimulation of the innate immune system; most vaccines involve both. The most widely used delivery system or formulation involves adsorption of antigen onto insoluble aluminum phosphate or hydroxide ("alum"), but experimental systems are quite wide ranging and include oil in water and water in oil emulsions (AS02A is an example), liposomes, virus like particles (of which RTS,S is an example), or live attenuated recombinant viruses which express malaria antigens. Examples of all of these can be seen in the Rainbow Table. However, the subunit vaccine approach continues to dominate malaria vaccine development, The majority of candidates are made in heterologous expression systems (*E. coli*, *Pichia Pastoris*, Baculovirus) but advancement in the peptide synthetic technology has led some developers to choose the long synthetic peptide production method as an alternative.

Alternative approaches based on whole parasites are also being investigated for both the sporozoite and the blood-stages of the parasite including development of knock-out sporozoites.

Principles of selection among vaccine concepts and investigational vaccines.

Designing a malaria vaccine involves the identification of suitable antigens, and the presentation of these antigens in a formulation that induces an appropriate immune response. Selection of vaccine approaches must be made at several levels. Choice of antigen should be based on evidence or sound theory that an immune response against the candidate antigen could interfere with parasite function. Evidence of this type can come from animal models which have characteristics in common with the human situation, from functional assays demonstrating antiparasitic effects by cells and/or cell products from immune humans, or from epidemiological observations to name a few. Choice of form of antigen should be based on the fidelity with which the manufactured substance emulates the native material, its purity, the feasibility of its reproducible production in appropriate quantities, as well as other factors.

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Choices of delivery systems are made in attempts to improve on past results and should be made by comparing the old and the new approaches in terms of meaningful functional measurements of the effects of immunization on the parasite. Obviously the earlier such assessments are made during the development progress, the more time and resources are conserved. Unfortunately, opportunities to make such comparisons are not abundant, thus leaving outstanding questions as to the appropriateness of parallel efforts.

Choice among competing vaccines that are very similar in composition and not otherwise distinguishable should be made on the basis of the level of development of each. Strong justification is needed for parallel development of such similar vaccines.

Challenges

A global research agenda and strategy has been formulated and published, known as The malaria vaccine Roadmap in a collaborative effort, jointly funded by BMGF and Wellcome Trust and endorsed by major funders of malaria vaccine R&D including EDCTP. Launched recently at the Global Forum for Vaccines Research from a process that sought ideas, and consensus from a highly diverse group of malaria vaccine stakeholders, the strategy was articulated around a vision for developing a malaria vaccine by 2025 that would have a protective efficacy of more than 80 percent against clinical disease and provide protection for longer than four years.

The question must be asked if continued pursuit of multiple variations of the same antigen with marginal differences diverts resources that could be used to identify alternative and potentially superior 'second generation' antigens and approaches, which might be needed to realize the vision. After all, current antigens account for less than one percent of the total number of potential antigens. The commitment should be to ensure that clearly defined hypothesis and rationale justify the selection and development of future antigens and formulations. Optimization of assays and animal models will facilitate better definition of go/ no go criteria at critical decision-making points.

Assay systems that are used as evidence of vaccine potential and measures of performance (such as the growth inhibition assay (GIA) which measures the capacity of antibodies to limit invasion or subsequent growth of *P. falciparum* parasites in red cells for MSP1 and AMA1 based candidates; the antibody-dependent cellular inhibition (ADCI) assay assesses the parasite growth inhibition resulting from the cooperative mechanism between monocytes and IgG in sera for MSP3 and GLURP) should be held to scrutiny and with recent data from efficacy trials, an opportunity to validate their concept now exists. Efforts to optimize and standardize the conduct and interpretation of these assays will also play a key role for validation. Selection is also hampered by the lack of a reliably predictive small-animal model. Access to formulations and manufacturing capacity and know-how is also lacking with only a handful of adjuvants exist, and even fewer are accessible.

Without a correlate of protection, clinical trials are the *only* means to screen malaria vaccine candidates for efficacy in humans. Candidate vaccines need to proceed through at least Phase II trials to determine their preliminary efficacy. Critical in their role of gathering safety, immunogenicity as well as preliminary efficacy data, the exploratory nature of these trials must be well thought through. They are a means of examining the expected performance of a particular candidate, but also as a means to advance scientific understanding including in better defining vaccine immune mechanisms and potential correlates of immunity. Improved trial design could potentially reduce the size of proof-of-concept trials, including the possibility that under well-characterized endemic conditions, the sample size required to demonstrate efficacy would be much smaller. The design and conduct of trials with biological end-points should also be explored and correlation with end-points of clinical and public health significance

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investigated as the validation of such an approach could allow these trials to be used not only for preliminary efficacy, but also to optimize dosing, schedule or routes of vaccination as well as early exploration of efficacy of combination or multistage vaccines.

Meeting the capacity needs to build an enabling environment to properly evaluate candidate vaccines and conduct trials are wide-ranging and involve promoting proper research infrastructure, including personnel with critical research skills to lead and manage trials and trial sites. Systems ensuring the basics of good research governance such as ethical review committees and regulatory bodies must be nurtured and supported. Networks, region-based initiatives and transfer of skills and technology through effective and targeted research partnerships should be appropriately expanded.

The role of funding agencies in malaria vaccine development

Progress in the current state of the art of malaria vaccine development has undoubtedly been facilitated by the participation of organizations such as the European Malaria Vaccine Initiative (EMVI) and the Malaria Vaccine Initiative (MVI). Some degree of fragmentation and duplication of activities could be desirable for some aspects of discovery and research, but on the other hand poses the risk that key gaps in research that warrants intense collaborative efforts remain unaddressed. What about potentially promising candidates or concepts not supported by these two leading groups? What about the need to establish an environment that facilitates comparative development and testing of promising vaccines? In recent years it has been estimated that less than US\$75 million has been available world wide for malaria vaccine development, far less than optimal. In spite of this, there are some 80 vaccine efforts listed in the Rainbow Table. The questions are: how many should there be? Does this large number of efforts portend early success through one or two of the many being successful because of characteristics that cannot be judged *a priori*? Or do many continue because they have not been adequately assessed with respect to their possible redundancy and the relative risk that they will not contribute to the final goals in a meaningful way. Commercial enterprises will address this question in their own way. But public sector agencies have a responsibility to evaluate programs in the context of the state of the art globally and array resources in a manner designed to minimize the time until an effective vaccine can make a major impact on malaria morbidity and mortality.

The malaria vaccine roadmap process attempted this and proposes a framework of 11 priorities within four major areas of work on which to act to realize the vision. Among these are:

- **Research:** standardizing procedures to compare immune responses generated by vaccine candidates, using state-of-the-art approaches and sharing information via the web to strengthen the connection between laboratories and clinics.
- **Vaccine development:** diversify the portfolio, including pursuing multi-antigen, multi-stage, and weakened whole-parasite vaccine approaches.
- **Key capacities:** establishing readily accessible formulation and scale-up development capacity, and building good clinical practice and clinical trial capacity in Africa.
- **Policy and commercialization:** dialoguing with countries and providing data to facilitate policy decisions; securing sustainable financing; and developing novel regulatory strategies to expedite the approval of a safe vaccine.

The major funding agencies, including EDCTP, all played a role in the development and endorsement of the Roadmap. The roadmap also provides a framework or 'home' for on-going activities by various organizations, including EDCTP and the members of the malaria vaccine funders' group and will be used for mapping and tracking of on-going and up-coming activities being planned. It is meant to catalyze leadership and action by malaria vaccine R&D stakeholders to take on the opportunities and

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needs identified in the priority areas on the Roadmap. These opportunities and needs are available for EDCTP to seize and address.

This is the challenge that EDCTP faces. Good choices could be world changing.