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## AFRICAN MALARIA NETWORK TRUST

### Workshop on Malaria Vaccinology in Developing Countries

14 -18 March 2005, Bagamoyo, Tanzania

### Workshop Report

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#### Introduction

AMANET organized a five-day training workshop on “Malaria Vaccinology in Developing Countries” in Bagamoyo, Tanzania, from 14 to 18 March 2005. The aim of the workshop was to update participants with recent advances in research and development of malaria vaccines and also, among others, discuss malaria vaccine research problems in Africa. Secondly, the workshop aimed at equipping the participants’ capacity to influence decision making towards the acceleration of malaria vaccines as viable intervention tools.

Thirty four (34) participants from Burkina Faso, Cameroon, Ghana, Kenya, Malawi, Nigeria, Sudan, Tanzania, Zambia, and Zimbabwe attended the workshop. Facilitators came from AMANET, European Malaria Vaccine Initiative (EMVI), Gates Malaria Partnership-LSTM, GSK Biologicals, Tanzania Commission for Science and Technology, Tanzania National Institute for Medical Research, Rooster Training Solutions, Radboud University Nijmegen Medical Centre, Statens Serum Institut, MRTC Bamako and MacNaughton Limited (representing AstraZeneca)

The workshop was divided into five themes, one for each day. The following is a summary of the proceedings.

#### Immunity in malaria

The history of immunoprophylaxis dates as far back as 1000 AD, in China, where some form of small pox variolation was practiced as a method of disease prevention. Parenteral variolation spread from the Indian sub-continent to Europe in the 1700s and this progressed to culminate in eradication of Small pox in 1977.

There are six vaccine targets or approaches that can be adopted in searching for a workable malaria vaccine; two each against infection and disease, one against transmission and a live attenuated parasite vaccine. Transmission blocking agents have been successfully used against Lyme disease.

The ideal malaria vaccine candidate against blood stage should have antigens that are recognized by human antibodies acting through biological mechanisms that are effective only in clinically immune individuals, that are highly conserved because an antigen that

constantly changes its sequence is a major challenge to vaccine development, and when used will generate the same response as was used in its identification in the first place. Different vaccine targets require induction of different immune mechanisms, a prior knowledge of this is required to allow careful design of combinations, avoiding potential problems of interference or suppression.

On the current state of affairs of malaria vaccine candidates, there is a clear need for a public-private partnership, a few vaccine candidates have undergone phase Ia up to phase II trials and some of the lessons learnt are the following: there is the need of a clear definition of roles and responsibilities of all the players including sponsor, investigator, regulatory authorities and other stakeholders; insurance and indemnification, personal and institutional liability; need for validated assays including challenge and surrogate markers; and many small phase I trials may be needed.

### **Evaluation of malaria vaccines and experiences in vaccine trials in Africa**

In general the development, execution and orderly termination of a clinical trial is often a complicated and time consuming requiring significant resources in personnel, funding, facilities, equipment and supplementary support activities. The take home message was that there should be a manual of procedures and there should be systematic back up of equipment and personnel and remember that “if it is not written it did not happen!”

Some of the experiences and lessons learnt from the DNA ME-TRAP/MVA vaccine trial in The Gambia were that, there should be established criteria for moving a candidate malaria vaccine from phase I to phase IIb field trials. Study designs should be more robust i.e. clearly defined as to whether the study looks at clinical disease or parasitaemia as the end point. Length of post trial follow up, data management issues and clinical trial monitoring roles should be clearly defined.

Other lessons from the AMA-1 vaccine trial in Mali were that, there is a need for intense continuous learning and capacity building and that sites need to have a vision of their own development in discussions with potential sponsors and product manufacturers. Investigators should also build a long term relationship with the population

### **Regulatory and ethical issues**

The important issues that came out of this discussion are the need for Africans to have:

- clear guidelines for the ethical and regulatory approval process for vaccine trials
- increased capacity for ethical and regulatory review
- common agreements to decrease “IRB shopping”.

An important part of ethical considerations is the informed consent process, which involves disclosure of all necessary information to a competent potential research subject or acceptable legal representative. Potential subjects should be given enough time to consider the information provided and understand it before giving their consent. Decision making must be completely voluntary and information must be updated whenever necessary.

The need for regulatory control in the production of biologicals has to a large extent been prompted by tragedy. Tragedy can occur anywhere down the supply chain from manufacture to the use of the product and hence regulatory control is necessary at all these stages. The regulatory body keeps an eye on all the processes an investigative drug or vaccine goes through, from concept through clinical trials, it facilitates the availability, accessibility and desirability of the product.

African countries need to harmonize their regulatory requirements so they can have mutual recognition agreements among themselves and with other countries. There was a call for AMANET to act as the driving force to facilitate such an achievement through the African Union (AU), NEPAD and WHO.

On Intellectual Property Rights (IPR) the importance of contractual agreements was emphasised to be critical especially in research and development. It was learnt that intellectual properties were not only in a finished product, but could also be in the process. The advantages and disadvantages of patents in medical products and their implications were discussed. It was recommended that research institutions participating in product development need to articulate their own IPR policies to guide them in collaborative work. The subject of Material Transfer Agreements (MTA) was also discussed as a potential source of problems in research if the issues are not well articulated.

### **Conducting Malaria Vaccine Trials**

There are many guidelines which direct the evaluation of malaria vaccines in endemic areas. Good Clinical Practice (GCP) was presented as the international scientific and ethical standard of designing, conducting, documenting and reporting clinical trials. Compliance with this standard provided public assurance that the trial participants were not abused and that the data collected are credible.

Generally safety is evaluated in all trial phases. The profile of the candidate is compared to other vaccines/known data in terms of frequency and nature of adverse events, serious adverse events. Efficacy measures are widely varied depending on the perceived mode of action of the vaccine and may include: time to infection, parasite density, clinical episodes, time to clinical episodes, disease severity, overall mortality, etc. The crucial issue is to carefully standardise all definitions so that data are consistent and comparable. The role of the principal investigator was emphasised especially in collection of accurate data, reporting and record keeping. Completeness of the investigator file with all essential documents for the conduct of a clinical trial was said to be central to GCP and product development research. Adverse events following the immunization process must be reported according to a pre-determined protocol criteria.

During the Private-Public partnerships in malaria vaccine development session, it was noted that the perceived lack of profitable market is a major hindrance to malaria vaccine development. Solutions to this under-investment in product development for poverty related diseases depend on increased research funding by the public/not for profit sector. Private enterprise would be attracted by mechanisms that minimise their investment into

the process i.e. streamlined regulatory and ethical processes, capacity for GCP trials in disease endemic countries, commitment by government to improve absorption capacity for the product and partnerships with the public sector.

### **Vaccine delivery and logistics**

The search for a malaria vaccine is an enormous task. But even when an effective vaccine is found there are still problems related to mechanisms of introducing the vaccine and the public finding it acceptable.

Information dissemination is very important in research as well as public health as it is the means to improved service/product utilization. In a general sense, scientists may not be the best publicists. It is thus important whenever possible that expert advice is sought for transmitting information to the public. It is desirable that institutions have publication policies that guide information dissemination. In collaborative research, it is also important to develop publication strategies right at the beginning of the work, so that appropriately packaged information is disseminated in a targeted and controlled manner. Caution was raised on the role that the media and journalists play; they are potentially a very useful vehicle for information, but can also be very destructive.

African governments need to create functional vaccine delivery systems that would ensure that once a vaccine is deployed, it is delivered to the needy in a conducive manner. It is their duty to ensure cold chains, adequate supplies, need health workers, sterility and safety of the vaccines. Health workers need to be well educated on the subject of injection safety, importance of sterility, prevention of needle stick accidents and how to deal with them.

Another important consideration in vaccinology is Post Licensure Monitoring. Having a product licensed is not the end in itself, but the end of one phase and the beginning of another. The product has to be marketed; issues of pricing, equity, distribution and access must be resolved. The sponsor is still responsible for the product, a Marketing Authorization Holder must be committed to present an adequate post marketing surveillance programme. Post marketing surveillance information contributes to update on side effect information leaflets and in extreme cases withdrawal of a registered product from the market. Post marketing surveillance is necessary because there is still much to learn on the product; its impact on larger populations, rarer adverse events and serious adverse events in real living conditions in communities.; safety and efficacy of product in different ethnicities and socio-cultural backgrounds; assessment of compliance and new indications.