



# Annual Report to the US Agency for International Development

October 1, 2005 – September 30, 2006



**Cooperative Agreement No.**

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### Annual Report Submitted by The PATH Malaria Vaccine Initiative November 3, 2006

#### **Executive Summary**

The PATH Malaria Vaccine Initiative (MVI) carried out the following activities from October 1, 2005 through September 30, 2006. The cooperative agreement (CA) between MVI and the US Agency for International Development (USAID) was signed on October 8, 2004. Subsequent conversations led to a defined scope of work and budget submitted November 23, 2004, and approved by USAID on December 3, 2004. For the following USAID fiscal year of 2005, a scope of work was submitted on October 21, 2005 and approved on January 6, 2006.

John McNeil, who has taken over from Melinda Moree as MVI's CA principal, has had preliminary meetings with USAID (Dr. Carter Diggs) to begin a bilateral strategic planning process for the following year's activities.

#### **Science & Technical Activities**

##### ***MVDB – MSP1-C (3D7 + FVO) Recombinant Protein Vaccine***

The Malaria Vaccine Development Branch (MVDB) at the National Institute of Allergy and Infectious Diseases/National Institutes of Health (NIAID/NIH) has manufactured two alleles of MSP1 (3D7 and FVO) that have entered clinical development. MVI supported a first-in-human, open-label, dose-escalation trial of each individual allele through a Phase 1 trial contract with Quintiles in Lenexa, Kansas. For each vaccine, 10 volunteers in each of three dose groups (5 µg, 20 µg, and 80 µg) were vaccinated at 0, 28, and 180 days (N=60). The vaccines were well tolerated, with pain at the injection site being the most common reaction. Anti-MSP1<sub>42</sub> antibodies were detected by enzyme-linked immunosorbent assay (ELISA) in 20/27 (74 percent) and 22/27 (81 percent) of the volunteers receiving three vaccinations of MSP1<sub>42</sub>-FVO/Alhydrogel<sup>®</sup> or MSP1<sub>42</sub>-3D7/Alhydrogel<sup>®</sup>, respectively. Reactivity of sera from the volunteers with *P. falciparum* was demonstrated by immunofluorescence assay. However, in-vitro inhibition of FVO or 3D7 parasites was not observed.

A Phase 1 trial of the two alleles co-formulated on alum compared to alum+CpG (Coley 7909) at two dose groups (40 µg and 80 µg) is ongoing. The trial is being conducted through the MVDB contract with the Johns Hopkins University (the trial site is at George Washington University in Washington, DC). The trial is designed to characterize the immune responses generated by the different doses and formulations. Anticipated conclusion of the trial is March 2007.

##### ***WRAIR – MSP1(3D7)/AS02 Recombinant Protein Vaccine***

The Kenya Medical Research Institute and the Walter Reed Army Institute of Research (WRAIR) jointly conducted a pediatric test-of-concept clinical trial in Kenya. The project, jointly supported by USAID and MVI, has been completed and closed. A manuscript is being submitted to the *Public Library of Science* (PLOS) journal, and the results of the trial will be presented at the American Society of Tropical Medicine and Hygiene meetings in Atlanta, Georgia on November 15, 2006. The trial was conducted in Kombewa Division, Nyanza Province in Western Kenya, an area of intense, perennial transmission of *P. falciparum*. Four hundred children ages 12 months to 47 months who were in general good health were enrolled. They were drawn from 13 field stations within a one-mile radius in the Kombewa district. Children were randomized in a 1:1 fashion to receive either FMP1/AS02A or rabies vaccine. Vaccinations were administered on a 0-, 1-, and 2-month schedule, using 50 µg of FMP1/AS02A.

The primary study endpoint was time to first clinical episode of *P. falciparum* malaria (temperature  $\geq 37.5^{\circ}\text{C}$  with asexual parasitemia of  $\geq 50,000$  parasites/ $\mu\text{L}$  of blood) occurring between 14 days and six months after a third dose. Case detection was both active and passive. Safety and immunogenicity were evaluated for eight months after first immunizations; vaccine efficacy (VE) was measured over a six-month period following third immunizations.

Three hundred and seventy-six of 400 children received all three doses and completed six months of follow-up. FMP1/AS02A was safe and well-tolerated but more reactogenic than the comparator. Geometric mean anti-MSP1<sub>42</sub> antibody concentrations increased from .33 µg/mL to 27.3 µg/mL in the FMP1/AS02A recipients but were unchanged in controls. Ninety-seven children in the FMP1/AS02A group and 98 controls had a primary endpoint episode. Overall VE was 5.1% (95 percent confidence interval: -26 percent to +28 percent; p-value = 0.72).

**Conclusions:** FMP1/AS02A is not a promising candidate for further development as a monovalent malaria vaccine.

### ***ELISA Service Center***

A Commercial Test Agreement has been executed between PATH and WRAIR to provide for enzyme-linked immunosorbant assay (ELISA) analysis of 2,400 clinical samples from malaria vaccine trials in a one-year period. WRAIR's Malaria Serology Laboratory has capabilities to perform highly reproducible ELISAs for a select number of malaria antigens. Advertisements have been placed with the Multilateral Initiative on Malaria, *Trends in Parasitology*, and *The American Journal of Tropical Medicine and Hygiene* to announce this service to the global malaria community. To date, 300 samples have been evaluated, and approximately 1,500 samples have been selected for analysis in the near future. Other laboratory activity included production of new lots of circumsporozoite surface protein plate antigens.

### **Market Assessment**

During this past year, MVI both continued and extended its work with the market assessment and accompanying demand model, a project originally developed (with USAID support) in 2004–2005 in collaboration with the Boston Consulting Group. During 2006, MVI worked independently to achieve two objectives: 1) to generate a demand-model analysis to support

discussions with countries, industry, and potential malaria vaccine donors; and 2) to conduct additional primary research in sub-Saharan Africa.

### ***Analysis***

MVI used the demand and investment case model in 2006 to generate specific analysis supporting a range of discussions with stakeholders in the malaria vaccine field. MVI served as a technical advisor to the World Bank, the Global Alliance for Vaccines and Immunization, and key donor governments (including the United Kingdom and Italy) in their analyses of the use of advanced market commitment (AMC) mechanisms for select vaccines that target developing countries. Using the model, MVI analyzed various demand and investment case scenarios that were used to support a malaria vaccine AMC proposal. MVI further used analysis from the model to support discussions with industry (seeking additional industry involvement in malaria vaccine development) as well as ongoing discussions with stakeholders in malaria-endemic countries.

### ***Primary Research***

MVI undertook additional primary market research in sub-Saharan Africa to enhance the quality of data in the demand model and more accurately reflect the drivers of public-sector demand at the country level, particularly related to product profile. Countries selected for expanded research included four previously researched during 2004-2005 (Ghana, Senegal, Tanzania, and Mozambique) and four additional countries (Kenya, Ethiopia, Mali, and Gabon). By the end of October 2006, primary research activities were completed in Tanzania, Mozambique, Kenya, Ethiopia, and Gabon. Research was collected via five to ten interviews, primarily with individuals but sometimes with small groups. Interviewees included ministry of health officials (malaria control and immunization), the World Health Organization, bilateral donors, nongovernmental organizations (NGOs), and researchers. This new data will be incorporated into the demand model and will be used to generate new demand data, particularly as it relates to a first-generation malaria vaccine.

## **Malaria Vaccine Decision-Making Framework**

In 2006, in partnership with ministries of health in African countries, the World Health Organization (WHO), and other international partners, MVI led the “Malaria Vaccine Decision-Making Framework,” a multi-stakeholder process to help countries make decisions regarding the potential use of a malaria vaccine in their national health systems. MVI and the WHO Regional Office for Africa (WHO AFRO) share the responsibility for meeting planning and coordination in eight countries in Africa, including: Ethiopia, Gabon, Ghana, Kenya, Mali, Mozambique, Senegal, and Tanzania.

The process in 2006 began with a consultation in Benin that brought together more than 30 participants from 13 African countries. The participants reflected a wide range of disciplines from public health, immunization, malaria, research, planning, and financing. The purpose of the meeting was to develop a first draft Decision-Making Framework (DMF) that could provide a foundation for more in-depth, individual country consultations. The draft drew heavily on recent country experience in deciding on and implementing new vaccine and malaria interventions. It also drew on WHO normative documents and on the seven briefing papers reported on in the 2005 MVI report to USAID.

The process has included a series of briefings that inform policymakers on the state of malaria vaccine development worldwide. The DMF seeks to understand country information requirements that would reduce the time between licensure of a malaria vaccine and the decision by a country to use it. Traditionally, there has been a long lag time between the licensing of a vaccine and its actual deployment in Africa.

The two-day meetings in each country include representatives of the health, policy, and planning ministries; donors; representatives from the WHO, the United Nations Children's Fund, NGOs, and malaria scientists and donors.

MVI hopes this activity will enable national governments to have information to make timely and well-informed decisions about the appropriate use of a malaria vaccine within one to three years of licensure.

In addition to support from USAID, this activity receives funding from the Bill & Melinda Gates Foundation. The activity is overseen by a Steering Committee made up of leaders from the sponsor organizations and other global leaders in the malaria and immunization communities.

Progress to date includes:

- Development and implementation of initial consultation in Benin to construct the first draft framework.
- Design and development of DMF process methodology to evaluate the draft Benin framework.
- Coordination of logistics and administration of eight meetings (in partnership with WHO AFRO).
- Five two-day, in-country DMF meetings (Tanzania, Kenya, Gabon, Mozambique, and Mali).
- Final reports resulting from Tanzania and Kenya meetings;
- Monthly Steering Committee calls.
- Design and launch of DMF Website ([www.malvacdecision.net](http://www.malvacdecision.net)).
- Translation of seven English-language briefing papers into French and Portuguese for dissemination.

Forthcoming activities include:

- Three two-day, in-country meetings in 2006 (Ethiopia, Ghana, and Senegal).
- Reports from Gabon, Mozambique, Mali, Ethiopia, Ghana, and Senegal.
- Analysis of framework meetings.
- Modification of framework and creation of new framework, based on eight country meetings.
- Final report resulting from process.

## **Financial Review**

PATH's quarterly financial report will be submitted per the agreement terms.