



PATH Malaria Vaccine Initiative

Strategy for Developing Next-Generation Malaria Vaccines

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Strategy for Developing Next-Generation Malaria Vaccines

Background

The PATH Malaria Vaccine Initiative's (MVI) new strategy sets the stage for a push to develop an effective malaria vaccine that could help eliminate and eradicate one of the world's deadliest infectious diseases. Malaria kills nearly 900,000 people a year, most of them children in sub-Saharan Africa.

The MVI strategy represents a multi-pronged approach to developing a next-generation vaccine by 2025 that is at least 80 percent effective against clinical disease for at least four years. A key component of this approach will build on the success of GlaxoSmithKline Biologicals' RTS,S malaria vaccine candidate, which in Phase 2 studies was found to be 53 percent effective against clinical disease. RTS,S has begun a Phase 3 clinical trial at 11 sites throughout Africa, the only malaria vaccine candidate to reach this stage.

Since the introduction in 2006 of the Malaria Vaccine Technology Roadmap, intended to align and guide the malaria vaccine community, the primary goal of MVI has been the development of a vaccine for *Plasmodium falciparum* with at least 80 percent efficacy against clinical malaria in children through age five years and in pregnant women. Driven primarily by the global agenda toward control, elimination, and eventual eradication of malaria, the focus during recent years has expanded to include increased consideration and support for development of vaccines against *P. vivax*, as well as transmission-blocking vaccines (TBVs) directed at both *P. vivax* and *P. falciparum*. Accordingly, MVI has modified its vision to reflect a new, broader focus toward malaria vaccine development.

While MVI will continue to work closely with the malaria community, particularly with respect to antigens and evaluation tools, it is seeking to expand collaborations with vaccine developers outside the malaria community.

Principal axes of MVI's new research and development strategy

- Pre-erythrocytic (PE) vaccine approaches that target *P. falciparum*.
- Approaches that target *P. vivax*.
- Transmission-blocking vaccine approaches that target *P. falciparum* and *P. vivax*.
- Feasibility studies to ensure availability of vaccine approaches aligned with strategy.
- Blood-stage (BS) approaches limited to those related to combination *P. falciparum*/*P. vivax* transmission-blocking vaccines.
- Evaluation technologies across all program areas.

Research and development strategy

P. falciparum vaccine development

Our initial focus is the development of vaccines that reduce the morbidity and mortality associated with *P. falciparum*. Building on the success of RTS,S/AS01, we envisage next-generation PE *P. falciparum* vaccine candidates falling into one of four categories described below:

- Circumsporozoite (CSP)-based PE vaccines: We intend to build on the success of RTS,S by testing candidates that are associated with CSP-specific antibody and cell-mediated immune (CMI) responses of higher magnitude and quality. Heterologous prime-boost regimens are of particular interest, as they have already yielded promising preclinical data toward maximizing combined humoral and cellular immune responses.
 - Antibody responses to CSP: We are seeking better persistence of anti-CSP responses and vaccine approaches based on regions of CSP that are directly associated with the invasion process into hepatocytes.
 - T-cell responses: We hope to determine whether CSP-specific CD4+ T-cell responses of higher magnitude and quality are able to enhance protective efficacy. Further, the ability of CD8+ T-cell responses to enhance protective efficacy associated with robust antibody and CD4+ T-cell responses will also be studied.
- Multi-antigen, PE-stage vaccines incorporating CSP: Sporozoites can be neutralized by circulating anti-sporozoite antibodies or targeted post-hepatocyte invasion by cell-mediated mechanisms. Only a single antigen—CSP—has been shown to provide high levels of protective efficacy in both controlled human challenge studies and field studies in Africa. To complement the role of anti-CSP immunity, we aim to develop multi-antigen vaccines that incorporate additional sporozoite and liver-stage antigens that could prime additional antibodies to block hepatocyte invasion and T-cells to target infected hepatocytes. We are actively supporting efforts focused on identifying promising new vaccine targets expressed in sporozoites and during liver-stage infection.
- Multi-antigen, multi-stage, PE + BS vaccines incorporating CSP: In addition to supporting vaccine approaches that target PE-stage immunity, we will support a limited and focused effort on the development of multi-stage (PE + BS) vaccines incorporating BS antigens that target attachment and/or invasion mechanisms of merozoites. Leading candidates in this regard are the erythrocyte-binding antigen and reticulocyte-binding protein families that represent a complex network of invasion pathways that *P. falciparum* can mobilize to ensure effective invasion into erythrocytes.
- Whole sporozoite-based PE vaccines: MVI is supporting radiation-attenuated sporozoites as potential vaccines for *P. falciparum* malaria, and has a long-term interest in the potential advantages associated with a genetically attenuated parasite approach. Radiation-attenuated sporozoites have been shown to confer high levels of protective efficacy from experimental challenge in humans, when administered as ~1,000 immunizing bites. A Phase 1/2a clinical study designed to determine the protective efficacy of whole radiation-attenuated sporozoites, delivered for the first time by needle and syringe, was initiated in 2009.

Over the next five years, we anticipate most clinical advancement to be associated with two program areas—the attenuated sporozoites and improved CSP-based PE vaccines. However, we regard preclinical work in the other two areas to be essential for building a portfolio that has depth and sustainability. Our plan is to maintain sufficient flexibility such that if one of our more advanced approaches is highly successful, we will realign the strategy to ensure that resources are available to accelerate its development. We will not continue the development of individual BS antigens as stand-alone vaccine

candidates as part of our revised strategy. While we do see significant value in *P. falciparum*/*P. vivax* combination vaccines, we believe that it is too early for such investments.

***P. vivax* vaccine development**

MVI is pursuing the clinical testing of two leading *P. vivax* antigens, CSP and RII domain of the Duffy binding protein (DBP), in human challenge studies. Significant progress has been made in recent years toward the development of a reliable human challenge model for *P. vivax*, which we regard as a critical tool for accelerating the development of *P. vivax* vaccines. The approaches are described below.

- **Single-antigen PE and BS vaccines:** The two most promising vaccine candidates for *P. vivax* are CSP and the DBP. Interest in CSP stems from the successful work with *P. falciparum*, so this antigen is currently considered “low-hanging fruit” in the quest for an effective *P. vivax* vaccine.
 - MVI has supported preclinical studies of a novel full-length *P. vivax* CSP antigen, developed by the Walter Reed Army Institute of Research, and expects to initiate human clinical safety, immunogenicity, and efficacy studies in 2010.
 - While single BS antigens do not align well with our research and development strategy for *P. falciparum*, the DBP is somewhat unique in that it appears to be the obligate invasion antigen for *P. vivax*. We anticipate advancing a DBP-based candidate (*P. vivax* R2) to human clinical safety, immunogenicity, and efficacy studies in the coming years.
- **Multi-antigen/multi-stage PE + BS:** Our focus in this area is limited to the combination of CSP- and DBP-based vaccines, where there is a reasonable expectation for synergy, and will depend on the outcome of challenge studies for the two individual antigens, as detailed above.

***P. falciparum*/*P. vivax* transmission-blocking vaccine development**

The development of vaccines that could block the cycle of transmission of *Plasmodium* species that infect humans is widely regarded as a key tool in the global control, elimination, and eradication effort. MVI recognizes that the most effective TBV for malaria is a highly effective PE vaccine that not only blocks the cycle of transmission in the human host but also protects from clinical disease. MVI has identified two additional approaches—*Plasmodium* sexual-stage antigens and *Anopheles* mid-gut antigens—that we expect to support over the coming years. A key challenge in the development of this class of vaccines will be identification of an effective clinical development and licensure strategy, given that the approaches offer no direct benefit to the vaccinee, but rather, reduce transmission and clinical disease via a reduction in the mosquito-born reservoir of infection. MVI plans to seek expert consultation in this regard early in the development process.

Evaluation technologies

The development and maintenance of effective preclinical and clinical evaluation technologies to support our programs is essential for MVI to successfully execute its strategy. Additional resources have been applied to the effort, and our focus in the area of evaluation technologies is being brought into alignment with the vaccine target categories outlined above. The primary areas we are supporting are preclinical and clinical challenge models and immunological assays, including those related to the development of newly supported *P. vivax* and TBVs. The development of these evaluation tools has suffered from a chronic lack of investment. Some of the major efforts anticipated for support during the current core grant funding period are outlined below.

- **Human challenge studies:** Our *P. falciparum* malaria vaccine strategy places a heavy emphasis on development of PE vaccines that will require proof-of-concept human challenge studies. This model

has been used effectively in the clinical development of RTS,S, particularly to identify optimal adjuvant formulations and immunization regimens. Despite the advancement of RTS,S to Phase 3 clinical trials, the correlates of protection for this vaccine have not yet been clearly defined. It is important for both the continued development of RTS,S and other CSP-based candidates in our portfolio that we better define the protective mechanism of CSP in humans. To this end, we are establishing multi-partner collaborations to focus on better defining the immune correlates of protection of RTS,S in both controlled human challenge and field studies. We are focusing on the evaluation and development of functional assays to assess the ability of antibodies to neutralize sporozoites and block invasion into liver cells.

- CMI-based techniques: MVI has increased support for the use of novel CMI-based techniques to better evaluate the quality of the immune responses, in both preclinical and clinical candidate studies. This work will determine whether quality parameters are more reliable and complementary predictors of efficacy compared to the more traditional measurement of the magnitude of the response.
- Preclinical studies: The use of preclinical studies to support comparative immunogenicity and efficacy studies is critical in supporting go/no-go development decisions, particularly relative to down-selection decisions around delivery systems and adjuvants. We are evaluating a range of different systems, including the *P. knowlesi* nonhuman primate challenge model and chimeric rodent and nonhuman primate parasites expressing vaccine target genes from *P. falciparum*, to facilitate streamlined testing of *P. falciparum* vaccine concepts using preclinical models.
- Functional assays: To address the increased focus on the development of *P. vivax* and TBVs, there are several key areas in which evaluation technologies need to be applied. The relapse infections caused by liver-stage hypnozoites, not seen in *P. falciparum*, and the absence of a culture system for *P. vivax* (and hypnozoites) are important considerations that MVI will need to address. An effective functional assay to support the preclinical and clinical development of TBVs, namely the membrane feeding assay, is available but requires standardization. Further, less complex assays with higher throughput capacity (e.g., ELISA surrogate) must be developed to effectively support preclinical and clinical studies of this class of vaccines.

How MVI structures its vaccine programs

MVI's vaccine development effort is divided into three areas, which reflect the stage of development of various programs.

- Preclinical feasibility: Preclinical studies are designed to evaluate technologies, such as delivery systems, adjuvants, and antigens, using standardized preclinical assays and models. They are short (typically 6 to 18 months) and require low levels of investment. Supporting these studies will ensure that vaccine development opportunities that may transition into the portfolio are effectively aligned with our long-term strategic goals.
- Translational programs: These are typically multi-year, multi-million dollar projects for which preclinical immunogenicity/efficacy testing has been completed and the commitment to clinical testing has been made. A cross-functional team manages these programs, with guidance from an external technical advisory group that assists in reviewing the scientific integrity of the approach.
- Vaccine candidates: Only those programs that have completed human proof-of-concept testing (Phase 2b) and are on a path toward Phase 3 and eventual licensure are considered vaccine candidates. Of the programs currently supported by MVI, only RTS,S/AS01 is considered a vaccine candidate.

Summary

MVI's research and development strategy has recently been realigned to support the global elimination and eradication paradigm for malaria and to build on the success of RTS,S. The successful development of RTS,S has been highly dependent on effective use of the human challenge model, and we believe that this model will be critical for developing improved *P. falciparum* vaccines. Our strategies for developing improved PE vaccines are primarily based on alternative delivery of CSP to improve humoral and cellular immune responses and inclusion of additional antigens to prime supplemental protective immune responses directed at invading sporozoites and/or liver-stage parasites, as well as whole attenuated sporozoites. We believe that the greatest potential for future success of BS vaccines will be in combination with partially effective PE vaccines; therefore, we will no longer support the development of single BS antigens as vaccine targets.

To effectively meet the needs of the community with renewed focus on control, elimination, and eventual eradication of malaria, we are diversifying our strategy to target *P. vivax*. Also, we are beginning to develop vaccines that could interrupt transmission of malaria parasites at the point of transmission from the human host to the mosquito vector.

A critical component of our revised strategy is the effective use of preclinical feasibility studies that will enable us to identify the most promising approaches to advance to translational programs that are on a clinical track. We believe that this strategy will most effectively replenish the portfolio with vaccine approaches that are optimally aligned with our overall strategy. Further, we believe that this strategy will yield near-, mid-, and long-term candidates to ensure that the portfolio has the sustainability to maximize our potential for success.