Rapid evaluation of Plasmodium falciparum Transmission Blocking Vaccine (PfTBV) candidates through enhanced African Resource Centers (ARC) for integration into malaria control and elimination

Background:

Malaria transmission blocking vaccines (PfTBV) halt parasite transmission to mosquitoes, and are needed for elimination. The most advanced PfTBV (Pfs230D1M-EPA/AS01) induces high and durable functional serum activity in African adults, providing an essential benchmark for our partnership to rapidly identify the optimal candidate for Phase 3 trials. PfTBV address WHO Goal 3 Target 3.3, aiming to "end the epidemic of malaria diseases" by 2030 since a highly effective malaria vaccine is currently unavailable. Malaria vaccine development has been thwarted by the stepwise approach to assess one protein in the clinic at a time, thereby delaying evaluations and diverting resources from other targets.

We circumvent these challenges by directly comparing lead vaccine candidates, delivery platforms and adjuvants, providing definitive down-selection of optimal candidates for later efficacy trials. The resulting PfTBV could be used alongside RTS,S, or "anti-infection" vaccine components (outside this proposal). Multi-stage vaccines would directly protect and halt onward parasite transmission. Four African, two European, and one US institution will liase with the NIH as third party and form the PfTBV consortium, leveraging past/current investments.

Project objectives:

The *Pf*TBV consortium has three main objectives to be achieved by the interrelated activities described below.

Objective 1: Bridge the product development gap by accelerating lead *Pf*TBV candidates into the clinic (WP3-8)

Promising vaccines are often lost between development and clinical evaluation, due to the stepwise candidate approach. We will:

- Accelerate leading candidates into the clinic for definitive comparative evaluation and down-selection. Our prior investments position the leading *Pf*TBV candidates for clinical evaluation as proposed here.
- Conduct comparative testing of *Pf*s230- and *Pf*s48/45-based vaccines, delivery platforms and adjuvants in malaria-exposed populations.
- Establish and qualify bioassays and endpoints for future Phase 2 and 3 efficacy trials.
- Pioneer a regulatory path for clinical development of elimination vaccines.

Objective 2: Support capacity development and technology transfer that accelerates malaria vaccine development (WP2)

- Reinforce existing infrastructure at leading research centers in west Africa (USTTB, Mali; NPHIL, Liberia; CNFRSRM, Guinea; GRAS, Burkina Faso).
- Provide training including graduate thesis work to enhance human infrastructure for clinical trials research.
- Facilitate networking and knowledge/technology transfer between sites.
- Foster a regional approach to collaborative trials among national research and regulatory bodies.

Objective 3: Advance the understanding of mechanisms of reactogenicity, immunogenicity and efficacy of a *Pf*TBV (WP3-6)

- Determine reactogenicity, antibody responses, and functional activity of *Pf*TBV candidates.
- Determine endpoints for definitive efficacy assessment of *Pf*TBV.
- Survey novel protein arrays with archived and project-generated samples to identify key malaria antigens.
- Establish a biobank of clinical samples at each host African institutions for future studies.
    - Immunology samples will be stored at clinical sites and shipped to USTTB, RUMC, and NIH at regular intervals throughout the trial for the ELISA and SMFA to be conducted. Samples for correlates will be kept at USTTB, RUMC, and NIH until the analysis has been completed as outlined in the propsal and specified in the Consortium Agreement. Hereafter, the biobank will be made available via Proposals which will be evaluated by the Scientific Advisory Committee as described in the Consortium Agreement. Inventory management of specimen data will be located in the PfTBV Biorepository - an electronic database for samples and sample data. The purpose of the PfTBV Biorepository is to act as a human biospecimen repository and database for malaria research. The biorepository follows the principles documented in the PfTBV Biorepository Charter. The Charter is to outline general principles that shall be implemented for the management and good governance of the biorepository to ensure that the interests of donors and all other stakeholders are safeguarded. The Charter applies to all the biospecimens and associated data managed by USTTB, RUMC, and NIH on the PfTBV Biorepository system for which we have permission to share.
    - Freezerworks or similar sample tracking platform will be used at each site
    - Will not require additional funding for maintenance after establishment, each institution will be responsible for maintaining