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COMMENTARY

Current Status of Malaria Vaccines

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Malaria remains a major global health problem, which still accounts for around one million deaths annually primarily in young children and pregnant women residing in the most impoverished countries of the world. Currently there is no licensed vaccine available against malaria or any other human parasitic disease. Efforts to develop malaria vaccines have been hindered by the enormous complexity of the parasite, widespread antigenic polymorphisms, and inadequate knowledge of host-parasite interactions. While, naturally acquired immunity develops among people residing in endemic areas and does protect against severe disease and death, it is not clearly understood as to how this protection works and what are the correlates of protection.

The malaria life cycle is highly complex and involves the *Plasmodium* parasite residing in two hosts – the human host and the *Anopheles* mosquito, both of which offer many targets for the development of malaria vaccines. In humans, the parasites (sporozoites) first invade the liver hepatocytes in which they undergo massive multiplication to form a huge number of merozoites that get released in the blood stream, where they invade red blood cells (RBC). Within the RBC, the parasite grows and multiplies over a 48 h cycle. The clinical symptoms and pathology associated with malaria emanate from these blood stages. During the blood stages, the parasites form male and female gametocytes that are taken up by the mosquito during a blood meal. The sexual stage of the parasite cycle occurs in the mosquito vector, which is responsible for transmitting the parasites and the disease.

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Malaria vaccine development efforts have employed strategies that target the three different stages of the parasite life cycle - Pre-erythrocytic or liver stage, Blood stage and transmission blocking vaccines that target the sexual stages in the mosquito. A number of reviews in literature have described malaria vaccine development in great detail [1, 2]. The aim of the authors in this commentary is to give a brief overview on the current status of malaria vaccine development against *Plasmodium falciparum*, the causative agent of the most severe form of malaria and most disease mortality across the world.

The most advanced malaria candidate vaccine is RTS,S, a pre-erythrocytic vaccine that has been developed by GSK (Glaxo Smithkline, Belgium) and PATH-MVI (Program for Appropriate Technology in Health – Malaria Vaccine Initiative) , and is currently being tested in a Phase III clinical trial in Africa, in which it is being co-administered with other EPI vaccines [3]. RTS,S comprises of the NANP repeat region of the circumsporozoite protein (outer coat protein of the sporozoite) fused with the Hepatitis B surface antigen that forms a virus like particle. RTS,S formulated with a potent adjuvant ASO1B (TLR4 agonist) exhibited 50 % protection in Phase II efficacy trials, which was consistently observed against both clinical and severe malaria in the 5–17 mo old children group of the Phase III trial [3]. However, recently the trial results for the 6–12 wk old group of infants reported only a modest protection against both clinical and severe malaria [3]. Although these results may be lower than expected, the RTS,S trial and its development story has proven that malaria vaccine is a realistic possibility and that further research efforts are crucial to develop a vaccine with ~90 % efficacy as observed for many vaccines against bacteria and virus.

There is a growing consensus in the field that a successful malaria vaccine would be multivalent that simultaneously targets several parasite antigens at the three different stages of its life cycle – liver, blood and sexual stage. While, the

identification of more pre-erythrocytic target antigens is the subject of further intense research efforts, CSP has attracted the most attention as the leading antigen for the development of a pre-erythrocytic malaria vaccine. However, the scenario is quite different for blood stage vaccines. *P. falciparum* has evolved a large repertoire of parasite molecules that mediate erythrocyte invasion [4]. This redundancy in ligand-receptor interactions allows the parasite to invade the erythrocyte through multiple alternate invasion pathways and as a result there is no human erythrocyte variant that is known to be completely refractory to invasion by *P. falciparum*.

Global efforts to develop blood stage malaria vaccines against *P. falciparum* have focussed on few antigens mostly tested individually in clinical trials. Unfortunately, the leading blood stage vaccine candidates, MSP-1_{42} and AMA-1, while being essential for the parasite have elicited very limited protection in field trials, which is attributed to their extensive polymorphisms that enable immune escape [1, 2]. Therefore, it is crucial to identify and validate novel, efficacious *P. falciparum* blood stage targets that would elicit strain-transcending invasion inhibitory antibodies.

Within the merozoite surface proteins, both MSP-1_{19} and MSP-3 are considered leading blood-stage candidates. Epidemiological studies have reported that antibodies to both proteins are clearly associated with a reduced incidence of *P. falciparum* malaria [5]. We now know that the target of protective antibodies in the MSP-1_{42} protein is the 19 kDa C-terminal region, MSP-1_{19} [6]. MSP-1_{19} has a highly conserved sequence that elicits cross-reactive invasion inhibitory antibodies [6].

While MSP-1_{19} has been tested in a clinical trial only as a fusion with AMA-1 [1], a new Phase Ia trial of MSP-1_{19} in combination with the erythrocyte binding antigen, EBA-175 (JAIVAC-1) has been recently completed by ICGEB through the support of the European Vaccine Initiative (EVI). The results of the trial are being analyzed and will soon be published. This trial was the first malaria clinical study conducted in India with indigenously produced antigens and has demonstrated the translational competence of research institutes based in India.

However, the problem with MSP-1_{19} is that it is poorly immunogenic as it lacks T cell epitopes and thus vaccine groups have focused on the larger protein, MSP-1_{42} [1, 2]. The ICGEB Malaria Vaccine Group has developed a fusion protein, MSP-Fu_{24}, comprising of the conserved regions of MSP-3 and MSP-1_{19} [6]. MSP-3 contains T-cell epitopes that help in boosting antibody responses against MSP-1_{19} and also its antibodies have been reported to neutralize parasite growth by monocyte mediated antibody dependent cellular inhibition (ADCI) [6]. MSP-3 has been tested in a Phase Ib human clinical trial in a malaria endemic area in which it was found to induce protection against clinical malaria [7]. MSP-Fu_{24} elicits potent parasite neutralizing antibodies that block red cell invasion and inhibit growth by ADCI, thus making it promising to pursue for clinical development.

Apart from MSP-1 and AMA-1, a number of erythrocyte binding proteins such as EBA-175, AARP (Apical Asparagine Rich protein) and the RH (Reticulocyte binding-like homologous) proteins especially RH5 have gained prominence as major determinants of erythrocyte invasion [4, 8, 9]. However, none of these proteins are essential (except PfRH5) for the parasite and their antibodies individually do not completely block invasion in a strain-transcending manner. PfRH5 is the only parasite ligand known to be essential for the parasite and whose antibodies potently block erythrocyte invasion [9, 10]. *P. falciparum* has the ability to switch its invasion phenotype and enable immune escape [4]. Thus, analogous to the anti-malarial combinatorial drugs administered to prevent onset of drug resistance, a combination vaccine approach that targets multiple antigens may be more effective in limiting the parasite's ability to escape host immunity. In this regard, the ICGEB Malaria Vaccine Group has identified potent antigen combinations that elicit strain-transcending invasion inhibitory antibodies [11]. Thus, ICGEB and other vaccine groups across the world are developing new generation combination blood-stage vaccines and validating their delivery through different platforms [10, 11].

Transmission blocking vaccines (TBVs) represent a new innovative approach of targeting the sexual stages of the parasite in the mosquito so as to block transmission through the vector [12]. The basis of TBV is to induce antibodies against the sexual stage antigens in immunized humans that would be taken up by the mosquito during a blood meal. In this regard, the major target antigens are Pfs25, Pfs48/45 and Pfs230 [12]. In pre-clinical studies, antibodies raised in small animals when fed to live mosquitoes have produced a significant decrease in the number of oocysts (sexual stage parasites) thus establishing a proof of principle [12]. However, the TBV approach will require vast immunization coverage among endemic populations in order to be effective. After the call for malaria eradication from major funding agencies, TBVs have gained immense prominence in the global malaria vaccine strategy.

The quest to produce an efficacious malaria vaccine to counter this deadly disease has proven to be a long battle but recent developments have shown great promise and have positioned the field at a very exciting stage.

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