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Unveiling Malaria Vaccine Miracle

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ABSTRACT

Malaria is a major public health problem, affecting most of the world population. Although efforts have greatly reduced the burden of malaria through centuries, but it still endangers millions of children's life. An important approach in control strategies of malaria is the development of an efficient vaccine. Malaria vaccination has made significant contributions to public health. There are many obstacles such as intricate nature of parasite life cycle, immune dodging and diverse parasite genome for the development of effective malaria vaccine. Out of five *Plasmodium* species only two species i.e. *P. falciparum* and *P. vivax* are in use for the development of malaria vaccine. Many strategies including pre-erythrocytic vaccine, blood stage vaccine, placental stage malarial vaccine and subunit vaccine has been evolved for the development of malaria vaccine. Further research on the use of the parasite targets as well as the evaluation of different vaccine candidates in the process through vaccine trials are highly suggested because a malaria vaccine would be a significant tool for the eradication of malaria.

Key words: Malaria, *Plasmodium*, Vaccination, Elimination

Introduction

Malaria, a fatal disease caused by *Plasmodium*, is a major public health concern affecting children below five years of age and pregnant women of the third world countries, mainly residing in sub-Saharan Africa (1). To control malaria various strategies are developed such as Artemisinin-based combination therapy, the anti-malarial drugs and insecticides treated bed nets with other vector control programs. Although these medicines have temporarily declined the incidence of malaria in many endemic zones but unfortunately, the poor health care infrastructure in many malaria-endemic countries obstructs the implementation of these strategies. Moreover, microorganisms are developing resistance against these anti-malarial drugs. So, an effective vaccine is needed to control, eliminate or even eradicate malaria (2).

Vaccines are among the highly effective tools in promoting individual and public health. Among all other human interventions, vaccination against infectious diseases has made the most significant contributions to public health (3). Presently, there is no licensed or registered vaccine for malaria. Out of the five plasmodium species that cause malaria in humans, only two species i.e., *P. falciparum* and *P. vivax* are in use for the development of malaria vaccine (4). For the development of effective vaccine of *falciparum* malaria, there are many complications such as diverse parasitic genome, intricate nature of parasite infectious cycle, immune dodging and complex life cycle of malarial parasite (5). According to WHO guidelines, the malarial vaccines against *P. falciparum* and *P.* vivax should not have protective efficiency less than 75% (1). Different phases of clinical trials are conducted on candidates for malaria vaccine. Presently, the stages of pathogen life cycle including human, and mosquitoes are targeted for malaria vaccine development. Only few proteins are considered for the development of effective vaccine (2).

Malaria Vaccine Development

The pre-erythrocytic stage, erythrocytic stage and transmission blocking vaccine against asexual stages are the prime targets of *P. falciparum* for the development of malaria vaccine. Table 1 lists current malarial vaccine and their respective target mechanism.

Pre-erythrocytic vaccine

A highly potent pre-erythrocytic vaccine against *P. falciparum* prevents infectious sporozoites to invade hepatocytes. To prevent sporozoites from entering dermis during blood biting of Anopheles mosquito and before they had a chance to travel from capillary network to the liver, immunity induced by vaccine would need to function fast and effectively. Hepatocyte's invasion can be prevented by using antibodies that block sporozoites movement and opsonize them. Successful pre-erythrocytic activity can be achieved by *Plasmodium* specific CD8 T cells that target antigens at liver stage, resulting in sterile immunity (6).

The attenuation of sporozoites achieved by radiation is dependent on randomized mutations that inhibit the development at liver stage. Consequently, the immune individuals support diverse population of these attenuated sporozoites, but this is only limited to experimental purposes because of genetically disintegrated sporozoites (7). Immunity against transmission of malaria at liver stage in humans and mice has been shown to be provided by experimental sporozoites (8). Deletion in US13 gene of *Plasmodium berghei* parasite makes parasite unable to mature in merozoites. Sterile immunity even for a prolonged time can be achieved by attenuating animals with three consecutive doses of removed US13 gene. This experiment should be revised for *P. falciparum* (9).

Table 1: Malarial vaccines and their respective target mechanism

Vaccine	Mechanism
Pre-erythrocytic vaccine	Targets antigens at liver stage, prevents infectious sporozoites to invade hepatocytes (6)
Blood stage vaccine	Prevents asexual reproduction and invasion of parasite in red blood cells (10)
Subunit vaccine (RTS, S/AS01)	Induces antibody and CD4 T cells reaction (16)
Vectored vaccine	Induces T-cells response higher than single vector vaccination (18,19)
Placental stage malarial vaccine	Targets chondroitin sulphate A (CSA) (21)

Blood Stage Vaccine

The aim of blood stage vaccine is to inhibit the asexual reproduction and invasion of parasite in red blood cells. Effective blood stage immunization will prevent problems such as renal failure and every clinical sign of deadly malaria in pregnancy. The main target to develop effective anti-complication vaccine is *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), expressed on infected red blood cells surface (10).

Currently many clinical trials are performed on antigens of blood stage which includes erythrocytes binding antigen-175 (EBA-175), merozoites surface proteins (MSP) 1, MSP2, MSP3, glutamate rich protein (GLURP), apical membrane antigen 1 (AMA1) (11,12) and serine repeat antigen 5 (SRA5) (13). Although MSP1 vaccine has the potential to produce protective results in monkeys, there are no significant impacts of these clinical trials against clinical malaria (14). There is no strong efficiency of blood stage vaccines in higher clinical trials of phase 2 &3, so it is strongly recommended to discover novel antigen (15).

Subunit Vaccines

In case of a subunit vaccines, an antigen or a segment of antigen is selected from a pathogen that on vaccination provides immunity against entire pathogen. A subunit vaccine known as RTS, S/ASO1 induces antibody and CD4 T cells reactions to *P. falciparum* circumsporozoite protein (PFCSP) (16). It is the first vaccine to undergo extensive phase three clinical trials in seven African countries but its efficiency in newborns is quite poor and it

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seems that the vaccine alone will not achieve the aim of eradicating malaria (17).

Vectored vaccines

To achieve higher efficiency, vector vaccines were designed. Chimpanzee Adenoviruses (ChAds) that encodes the thrombospondin-related adhesion proteins (TRAP) pre erythrocytic antigens was used to initiate immune response as shown in Fig.1 and then this immune response was boosted by other viral vector named as modified vaccinia virus Ankara, this vector encodes the similar TRAP insert (18,19). This approach induces T-cell response higher than single vector vaccination.

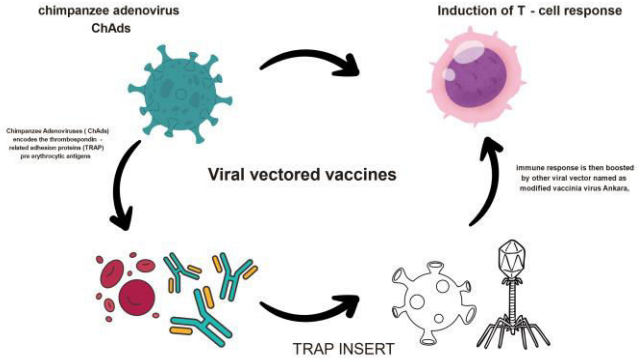

Figure 1: Stimulation of immune response by vectored vaccine

Placental malarial vaccine

The Chondroitin sulphate A (CSA) which binds to the parasite and accumulates them in placenta is the target of placental malarial vaccine. Pregnant women can receive protection from malaria through pre-erythrocytic and erythrocytic stage vaccination that safeguard the population against diseases. After multiple pregnancies, antibodies against the CSA naturally develop to defend against malaria. The *P. falciparum* erythrocyte membrane protein 1, a component of VAR2CSA that binds to CSA binding site, is expressed by placental parasites (20). The VAR2CSA induced antibodies prevent the parasite from attaching to the CSA. With six BDL domains, an extracellular domain larger than 300kd and certain interdomain regions, VAR2CSA is a complicated target. Seven to eight domains have been identified in recent experimental case (21).

Conclusion

The development of malarial vaccine has been continued from many years but the formulation that satisfies the requirements of safety, accessibility, cost and efficiency has not been yet achieved. The search for novel approach needs sustained attempts and resources. Further research on the use of different parasite targets as well as the evaluation of different vaccine candidates in the process through vaccine trials are highly suggested because a malaria vaccine would be significant tool for the prevention and cure of the disease.

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