VACCINE FOR MALARIA – HOW FAR?

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This is a review of the progress made so far in the effort to produce a malaria vaccine. The problems that have made it impossible to get an effective vaccine for malaria are discussed. Also examined are the current efforts to produce the vaccine and the prospects for an effective vaccine in the future.

Key words: Vaccine, malaria, review.

INTRODUCTION

Vaccines are one of the most cost-effective and logistically feasible means of disease control, and have remarkable success in the control of many infectious diseases [1]. Examples include the eradication of smallpox and the near-eradication of polio [2]. It is surprising that a licensed potent vaccine for malaria has not arrived. The difficulties on the way of production of this vaccine have been identified for a long time but every advance towards the resolution of this problem, like chasing a mirage, has resulted in illusion.

Yet, the increasing resistance of the Plasmodium species to chemotherapeutic agents and the increasing resistance of the vectors, Anopheles mosquitoes, to insecticides [3] pinpoint the critical need for an effective vaccine against this infection. Although protective immunity is conferred by naturally acquired infection and by irradiated sporozoite immunization, no subunit malaria vaccine candidate so far has proven sufficiently efficacious for commercial development [4].

Hope for a potent malaria vaccine was raised when an international body of genome scientists and funding agencies was formed in 1996 [3]. This hope was on course with the publication of the genomic sequence of Plasmodium falciparum in 2002 [5] and simultaneous publication of the Plasmodium falciparum proteome representing stage-specific sporozoites, merozoites, trophozoites and gametocytes [6, 7].

Also completed is the gene expression profile of the parasite during the different stages of its life cycle [8]. The hope is that this knowledge will be exploited to identify and prioritize antigens and epitopes that may be targets of anti-malarial protective immunity. However, identification of the most effective epitopes is difficult because the genome of Plasmodium falciparum is large.

PROBLEMS HINDERING THE PRODUCTION OF AN EFFECTIVE MALARIA VACCINE

Despite intense research efforts over close to half a century now, which has resulted in clinical trials of many candidate vaccines, few humans have been protected from malaria through vaccination [4]. Unlike in the development of vaccines against bacteria and viruses, developing a vaccine against the malarial parasite is complicated
by the complexity of the parasite and that of
the host's response [3].

The identification of antigens that
will stimulate the most effective immunity
against Plasmodium is problematic because
of: (a) the multistage parasitic life cycle, (b) a
large genome encoding more than 5,300
proteins, and (c) distinct proteins expressed
at different stages of the parasite. Added to
these problems is the poor understanding of
what constitutes the protective immune
mechanisms that target the different
parasite stages; and sequence polymorphism
of identified target epitopes.

It is well established that
immunization of humans with radiation-
attenuated Plasmodium sporozoites confers
sterile protective immunity [9-12]. Irradiated
sporozoites could invade hepatocytes and
undergo limited development but could not
mature into blood-stage parasites [13] thus
eliminating clinical symptoms of the disease
and transmission of the parasite. However,
immunization with heat-killed, formalin-
inactivated or lysed sporozoites was not
effective [3], making sporozoite-based
vaccine production difficult. These
observations seem to emphasize the
requirement for live sporozoites targeting the
liver. Even then the targets of cellular
immunity, induced by irradiated sporozoites
are largely unknown, and correlates of
protection after immunization are not clearly
elucidated.

A dilemma is suggested by the
possibility that the protective immunity
induced by irradiated sporozoite
immunization is due to the summation of
many immune responses of low magnitude
against multiple targets which result from
low density of epitopes [3]. Thus, responses
against characterized hepatic-stage antigens
recognized by sporozoite-induced cellular
immune responses are not as potent as
those induced by subunit vaccination [14].

Repeated natural infections confer
immunity against severe infection but this
immunity is normally species and strain
specific; and it is dependent on continuous
boosting and is usually short-lived. A potent
vaccine based on this type of natural
immunity will then be required to generate
"super-natural" immunity [15].

CURRENT APPROACHES TO MALARIA
VACCINE DEVELOPMENT

Presently, most candidate malaria
vaccines are designed to protect against pre-
erythrocytic and/or erythrocytic stage
antigens. Transmission blocking vaccines
are formulated to protect the entire
community by inducing protective
antibodies directed at sexual stage antigens
[3]. These vaccines have been developed with
potency against a single or a few key
antigens, such as Plasmodium falciparum
circumsporozoite protein (CSP) and
merozoite surface protein-1 (MSP1), by
immunizing with synthetic peptides or
recombinant proteins in an adjuvant [15].
Results of trials with these subunit vaccines
[16] leave us with the question of whether all
the antigens are the same and it is the
vaccine delivery system that matters. It is
also not clear yet whether key protective
antigens have already been identified or not.

Another approach to malaria
disease vaccine development focuses on all of the
currently known promising candidate
antigens to give rise to a multivalent and
multistage vaccine; produced mainly
through the technology of DNA-based
vaccines [17, 18]. First generation DNA
vaccines were found suboptimal but
immune enhancement strategies, such as the use of adjuvants, show promise [19-21]. This approach to vaccine production faces limitations regarding the size of antigens that can be included in a given vaccine delivery system and the number that can be formulated for simultaneous administration without inducing antigenic competition.

Despite the challenges facing malaria vaccine production, there are lines of evidence showing that a vaccine is feasible. These include the age-related acquisition of immunity against severe clinical malaria in endemic regions [22, 23] and the ability of passively transferred antibodies from immune adults to protect against natural and challenge infections with *Plasmodium falciparum* [24-26]. Blood-stage vaccines against the parasite are aimed at preventing complications of the infection, such as cerebral malaria and anaemia.

Both *Plasmodium falciparum* and *Plasmodium vivax* can cause severe anaemia but only *Plasmodium falciparum* causes the many complications of cerebral malaria: hypoglycaemia, metabolic acidosis and respiratory distress [15]. Most effort has been devoted to the production of *Plasmodium falciparum* vaccines because it is responsible for majority of deaths from malarial infections.

Among the recombinant blood-stage antigens that have been proposed for development as candidate vaccines, the leading erythrocyte stage antigens, merozoite surface protein 1 (MSP1) and apical membrane antigen 1 (AMA-1) are expressed in all species of *Plasmodium* [15]. A phase I trial of a vaccine based on MSP1 was fused to CD4 T cell epitopes from tetanus toxoid concluded that the vaccine was immunogenic but had a high rate of adverse reactions [27]. MSP1<sub>42</sub> formulated in ASO2 adjuvant has gone into phase 1 trials in the United States and Kenya [28-30]. Also, *Escherichia coli*-produced MSP1<sub>42</sub> and RTS, S combined with MSP1<sub>42</sub> has been phase 1 tried in the United States [31].

It is likely that many recombinant blood-stage vaccines will undergo safety and immunogenicity studies in malaria endemic regions soon. The short time of exposure of the merozoites to antibodies between release from one infected red blood cell and attachment and entry into another dictates that very high antibody levels are required to block entry [32]. Such levels of antibody may not be achieved with alum; therefore, a lot of effort is focused on the testing and development of new adjuvants for asexual blood-stage antigens.

The choice of adjuvants for use in man includes alum, MF 59, Montanide ISA 720, Montanide ISA 51. These are combined with immuno-stimulators, which include MPL, QS 21 and CpG [15]. A number of human phase II trials have been carried out using SPF 66 [33, 34], a multi-component vaccine which includes a blood-stage antigen.

**PROSPECT FOR A POTENT MALARIA VACCINE**

Will an effective vaccine against malaria parasite eventually emerge? Advances in the fields of genomics, proteomics and molecular immunology offer new hope for the development of a malaria vaccine. However, algorithms that can effectively identify the targets of protective immune effectors for malaria from genomic data are just being developed [35]. Doolan et al [3] have indicated data showing that
protective immune responses induced by immunization with irradiated sporozoites are directed against multiple epitopes on multiple antigens, with variable potency. Thus, a multi-antigen vaccine that induces cell-mediated immune responses against antigens of the liver stage may be required to mimic irradiated sporozoite-induced protection. A vaccine that prevents blood stage infection and clinical disease is likely to emerge if the antigenic targets of irradiated sporozoite-induced immunity are identified and packaged in a vaccine formulation that is immunogenic and suitable for manufacture and administration.

Evidence that natural exposure to Plasmodium falciparum results in acquisition of anti-malarial immunity in humans include the observation of decrease in the incidence of infections, reduction in prevalence and density of parasitaemia and the lowering of morbidity and mortality associated with repeated infection [36-38]. The existence of naturally acquired immunity and the fact that erythrocytic stage immunity can be induced by natural exposure [36, 37] to repeated blood stage infection provide a strong rationale for the identification of the antigenic targets of naturally acquired immunity and the development of vaccines designed to include high levels of antibody responses against these antigens.

CONCLUSION

A malaria vaccine that is potent and protective against the infection is likely to emerge in the near future but disappointing experiences of the past counsels caution concerning a time-frame prediction. It is difficult to say now whether such a vaccine will target pre-erythrocytic stage parasite or blood stage infection or both.

REFERENCES


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