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РАЗРАБОТКА ВАКЦИНЫ ОТ МАЛЯРИИ: ПРОБЛЕМЫ И ПЕРСПЕКТИВЫ

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РЕЗЮМЕ. Разработка лицензированных вакцин против малярии являлась сложной задачей из-за многоступенчатого жизненного цикла, антигенной изменчивости и большого генетического разнообразия плазмодия, что создавало проблему подбора подходящего кандидата на вакцину среди тысяч антигенов плазмодия. Разработано несколько вакцин для различных стадий плазмодия, которые включают вакцину на предэритроцитарной стадии, вакцины на стадии крови с использованием белков плазмодия, вакцины из плаценты и вакцины, блокирующие передачу инфекции (TBV), которые подавляют половую стадию развития малярийных паразитов. Однако нет такой вакцины, которая являлась бы полностью эффективной и обладала высокой реактогенностью. Из-за неспособности разработать эффективные вакцины для борьбы с одной стадией жизненного цикла плазмодия продолжается разработка эффективной многоступенчатой или многовалентной вакцины против малярии (Мультимальвакс), которая могла бы стать наилучшим подходом для нейтрализации спорозоитов, превращающихся в мерозоиты, а также мерозоитов, выходящих из гепатоцитов и эритроцитов, для прекращения распространения спорозоитов и блокирования половой стадии развития малярийного плазмодия. Таким образом, глубокое понимание потенциальных мишеней вакцины и того, как действует иммунитет, является ключевым этапом разработки полностью эффективной вакцины против малярии.

КЛЮЧЕВЫЕ СЛОВА: малярия; иммунитет; *Plasmodium falciparum*; вакцина.

MALARIA VACCINE DEVELOPMENT: CHALLENGES AND PROSPECTS

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ABSTRACT. This is a review on malaria vaccine development: challenges and prospects. The development of licensed malaria vaccines has been challenging because of the multi-stage life cycle,

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antigenic variation, and great genetic diversity of *Plasmodium* making it difficult for the right vaccine candidate among the thousands antigens of *Plasmodium.* Several vaccines for different stages of *Plasmodium* which include pre-erthrocytic stage vaccine, blood stage vaccines, using *Plasmodium* proteins, placenta vaccines and transmission-blocking vaccines (TBVs) which inhibit sexual stage of malaria parasites. However, none of these vaccines are completely effective and have high reactogenicity. Due to the failure to formulate effective vaccines to tackle a single stage of *Plasmodium* life cycle, the development of effective multistage or multivalent malaria vaccine (MultiMalVax) is ongoing which could be the best approach to neutralize the sporozoites from developing to merozoites; and the merozoites emerging from hepatocytes and erythrocytes and; to break the sexual stage transmission. Therefore, great understanding of the potential vaccine targets and how immunity acts is a key road-map to develop a fully effective vaccine against malaria.

KEY WORDS: malaria; immunity; *Plasmodium falciparum*; vaccine.

INTRODUCTION

The formulation of artemisinin-based combination therapy (ACT) has led to great advancements in malaria control. However, clinical resistance to artemisinin and its derivatives has been well established and this appears to be the main threat to malaria eradication of malaria in the world [2]. In the eradication of some other infections, vaccination remains the most effective method [97].

However, constant polymorphisms in the biology of *Plasmodium* species have made the identification of the right vaccine candidate among the thousands antigens of *Plasmodium* very difficult [98]. Hence, there is need for malaria vaccine and there is no licensed malaria vaccine at the moment [3]. The aim of this study is to describe the progress, challenges and future expectation of malaria vaccine development.

PROGRESS IN MALARIA VACCINE DEVELOPMENT

The journey towards the development of modern malaria vaccine started since 1960s immunizing rodents, primates and human volunteers with irradiated sporozoites [5, 72]. In 1967, mice were immunized with radiation-attenuated *Plasmodium berghei* sporozoites [72]. In a study conducted in 2002, the gamma radiation-attenuated sporozoites inside infected *Anopheles* mosquitoes led to a total protection in human. This irradiation approach was however not cost-effective and not practical on a large scale [46]. The early 1980s ushered in the advent of technologies such as monoclonal antibodies and recombinant DNA methodologies. Though several antigens were cloned and sequenced with these technologies, their roles in protective immunity were only assessed by testing homologues in experimental infections [1, 30].

The limitations of these methods are that they lack inflammatory cytokines triggered by most subunit vaccine and the vaccines could not target the liver-stage malaria parasite [94]. In attempts to induce higher efficacy vectored vaccines were introduced using Chimpanzee adenoviruses (ChAds) encoding TRAP pre-erythrocytic antigen. This process was boosted by another viral vector, modified vaccinia virus Ankara (MVA) encoding the same TRAP insert. This prime-boost induced much higher T-cell responses than immunization with single vector [44, 88].

Despite evidence that since the 1970s, whole sporozoite vaccines confer sterilizing immunity against sporozoite challenge of humans, whole sporozoites vaccines were not followed up as a product owing to the impression that the production of irradiated sporozoites was impractical for a vaccine [114]. Sanaria in 2010 introduced a technology that enables the harvesting *Plasmodium falciparu*m sporozoties (*Pf*SPZ) from the salivary glands of aseptic mosquitoes infected by cultured laboratory parasites after which they are purified,put in vials, and preserved at low temperature in liquid nitrogen vapour phase [47]. The attenuation of *Pf*SPZ into different vaccine candidate products has advanced quickly into three main technologies which include: radiation attenuation called *Pf*SPZ Vaccine, chemoattenuation achieved in vivo by concomitant administration of antimalarial drugs called *Pf*SPZ-CVac for chemoprophylaxis vaccination and genetic attenuation by deletion of genes required to complete liver-stage development called *Pf*SPZ-GA1 for the first genetically attenuated *Pf*SPZ candidate [NCT03163121] [50, 69, 90].

For *Pf*SPZ Vaccine to convey sterile immunity against sporozoites, it has to be inoculated

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directly into the vein [99]. The challenges of implementing whole sporozoite vaccines will include maintaining liquid nitrogen cold chain, intravenous inoculation and scale-up of manufacture. The efficacy of whole sporozoite vaccines has been tested in humans but this efficacy depends on the regimen and dosage of the vaccine administered. The efficacy against homologous or heterologous sporozoite challenge in malaria-naive individuals with either *Pf*SPZ Vaccine or *Pf*SPZ-CVac has been shown to convey high levels of sterile immunity [31, 32, 66, 101]. The efficacy of *Pf*SPZ-CVac is however, higher than *Pf*SPZ Vaccine. This probably could be due to to expression of more liver stage antigens and development of larger antigen loads than radiation-attenuated Spz. Furthermore, human immunization with whole sporozoites combines the bites of non-attenuated fully infectious *Plasmodium falciparum*-infected mosquitoes with prophy-laxis [8]. This rout of immunization by bite might induce more potent immune responses than IV immunization with radiation-attenuated Spz [65]. Development of *Pf*SPZ-CVac as a viable vaccination strategy will require safe and reliable delivery through coformulation of non-attenuated highly infective sporozoites and long-lived chemoprophylactic agents to ensure full chemoattenuation in vivo [28].

In genetically attenuated parasites (GAP), the deletion of two pre-erythrocytic genes (p52-/p36-) in the NF54 strain resulted in introducing of the first generation *Plasmodium falciparum* GAP [110]. The first mice experiments showed that the deletion of a single gene using (p52-/p36 genetically attenuated parasites (GAP) could trigger immune protection mediated by CD8+T cells which could last for a long period of time [110]. GAP parasites induced larger and broader CD8+T cell responses and long-lasting effector memory CD8+T cells than radiation-attenuated Spz parasites in mice [16, 26]. In more recent times, triple KO *Pf* GAP (p52-/p36-/SAP-) and alternative *Plasmodium falciparum* GAP vaccine based on b9/slarp deficient sporozoites was introduced [62, 111]. Radiation attenuated sporozoites Sanaria® *Pf*SPZ-GA1 is another genetically attenuated strain with deletions of the b9 and slarp genes [111]. Genetically attenuated parasites recognize antigens in both the late liver stages and blood and elicit stage transcending immunity. This may lead to identification of novel approach for development of a multi-stage subunit vaccine [93]. Genetically attenuated parasite vaccines are being tested in malaria-naive individuals for safety, immunogenicity and protective efficacy [50].

The use of whole sporozoite vaccines to produce sterilized immunity in humans was at a time of the development of genetic engineering and the first malaria gene to be cloned was circumsporozoite protein (CSP). The gene encodes the major surface antigen of sporozoites and it is used for the production of subunit vaccines [5, 20]. Although subunit vaccines can eliminate the risk of reversion and have good safety compared to inactivated or attenuated pathogen vaccines, they have weakness in immune stimulation. Nanoparticles are introduced in the era of subunit vaccine development and they can enhance the efficacy of these vaccines by the duration of the antigen release and circulation [56]. However, there was no success in the production of a full-length CSP which led to the production of several subunits like R16tet32, R32tet32, R48tet32, and R32LR [4].

The RTS,S vaccine is another subunit vaccine based on *Plasmodium falciparum* CSP fragments containing C-terminal repeat regions (R) and T cell epitopes (T) combined with hepatitis B surface antigen (S) and a chemical adjuvant called AS01 made up of TLR4 ligand and the saponin derivative (QS-21) was added to increase the immune system response. Together, the vaccine was called RTS,S/AS01. The RTS is also expressed in yeast that carry hepatitis B "S" expression cassettes, and thus synthesize S and RTS polypeptides that spontaneously co-assemble into mixed lipoprotein particles (or "RTS,S") with the CSP fragment on their surface. RTS,S, til date remains the most advanced pre-erythrocyte vaccine [15, 49]. The RTS, S/AS01 induce CD4 T cell and antibody responses to the *Plasmodium falciparum* circumsporozoite protein [*Pf*CSP] [6]. Although this vaccine has been recommended for license by European Medicines Agency (EMA) and is the first vaccine to undergo large-scale phase 3 evaluations in seven African countries, the efficacy of this vaccine in infants is relatively low, and the vaccine apparently will not meet the goal of malaria eradication by itself [57].

Blood-stage parasites are important targets because this is the stage that disease development occurs. Passive transfer of IgG purified from semi-immune African adults was shown to clear parasitemia from African children 6 decades ago and later in Thai adults [15, 29, 92]. Hence, blood stage vaccines target the asexual parasite forms that undergo repeated multiplicative cycles in erythrocytes and cause disease and death. The challenges in the development of an-

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ti-merozoite vaccines include: the short time in seconds when merozoites pass between erythrocytes and are accessible to antibodies, polymorphisms of the antigens, redundant invasion pathways, and the large number of targeted parasites when compared to those of preerythrocyte vaccine and transmission-blocking vaccines [28].

Plasmodium falciparum erythrocyte membrane protein 1 (*Pf*EMP1), expressed on the surface of infected erythrocytes during erythrocytic satge was first cloned in 1995 and was considered as the prime target for an anti-complication vaccine [58]. At present, researchers have carried out several clinical trials with many erythrocytic stage antigens. In two separate studies in Mali, AMA1 vaccine with AS02 adjuvant was applied in 383 children and another vaccine trial with AMA-13D7 and AMA1-FVO and ALhydrogel in 279 children was studied. There was no significant impact of these vaccines on clinical malaria [77]. Although MSP1 vaccine could produce protective responses in monkeys, the phase II trial of this vaccine with AS02 adjuvant showed no significant effect on clinical malaria in Kenyan children [76]. This could be due to the high polymorphisms in the vaccine structures [104]. In a malaria vaccine with combined antigens of MSP-1, MSP-2 and RESA antigens with Montanide adjuvant, there was no efficacy at the completion of phase 2 trial on 120 children between the ages of 5 to 9 years old [63]. Attention has now been shifted to identifying novel blood-stage vaccine antigens or refining the approach to existing targets. Two vaccine candidates have been considered as a potential candidate to address the issue of redundant invasion pathways. They are: *Pf*RH5 and the AMA1-RON2 complex.

Plasmodium falciparum reticulocyte-binding protein homolog 5 (*Pf*RH5) binds with the essential red cell receptor basigin and shows limited polymorphism and entered clinical trials using a viral-vectored prime-boost immunogen [17, 81]. The *Pf*RH5 is the first significantly conserved merozoite antigen which has been shon to elicit largely neutralizing antibody in preclinical studies [23]. In different combinations of *Pf*RH5 viral-vectotred and/oradjuvanted protein immunogens, protective immunity against parasitemia as produced after an initial challenge with virulent heterogenous parasite [24]. Natural infections have been reported to produce poor immunogenicity against *Pf*RH5 [23, 108, 113]. and *Pf*RH5 in monkey studies has shown good immunity against virulent blood-stage parasite but poor immunogenicity by vaccine-induced antibody. This may limit the duration of protection conferred by a vaccine [24].

Anti-*Pf*RH5 IgG requires dosage as high 200μg/mL in order for vaccination to be achieved and sustained. In order to improve the efficacy of RH5 vaccine candidate, several efforts like presentation in virus-like particles (VLP) and production of a protein vaccine Drosophila cells [45, 51]. Also, studies at Jenner Institute have reported the production of human *Pf*RH5 vaccine-induced monoclonal antibodies (mAbs) to identify epitopes targeted by neutralizing, non-neutralizing and potentiating antibodies. The potentiating antibodies reduced the invasion of merozoites and facilitate the activity of neutralizing antibodies [41]. This knowledge will inform the design of improved Rh5 immunogens that focus the antibody response on neutralizing and potentiating epitopes [28].

Although the efficacy of AMA was poor in the previous trials, it is an essential protein for blood stage parasite growth. The study on the binding of AMA1 with RON2 at the merozoite-red blood cell interface for invasion to begin has brought back the interest in AMA1 as an immunogen in complex with RON2. When AMA1 forms complex with RON2 peptide, the antigenicity of AMA1 changes to produce more potent antibodies that can stop invasion than monomeric AMA1 antigen [103]. The study of AMA1-RON2 in monkey has shown significant protective immunity against heterologous blood-stage challenge against AMA1 alone, and conferred sterile protection in half the animals [103]. Vaccines with AMA1 may be improved by structural studies of antigenantibody complexes to determine epitopes to be included or excluded in redesigned immunogens. Unlike Rh5, AMA1 displays extensive sequence polymorphism, and therefore future studies will need to assess the number of alleles or chimeric sequences that will be required for AMA1-RON2 to confer broadly effective immunity [28].

The search for new blood-stage vaccine candidates has progressed beyond the merozoites targets. The antigens of the parasites are transported to the surface of infected red blood cells where they are exposed to antibody attacks for hours. Prominent among these antigens is the variant surface antigen family *Pf*EMP1. This antigen is very important facilitating parasite sequestration thereby making *Plasmodium falciparum* to be virulent. It is therefore a target of naturally acquired protective antibody [107]. However, due to its high polymorphism, large size, presence of cysteine-rich interdomain regions hindered vaccine development and lack of

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reported trials of *Pf*EMP1-based vaccines have limited its usage for viable malaria vaccine.

A non-*Pf*EMP1-infected erythrocyte surface protein called *Plasmodium falciparum* glutamic acid rich protein (*Pf*GARP) found on the surface of infected red blood cells by early-to-late-trophozoite-stage parasites has just been described as the target of protective antibodies [86]. Anti-*Pf*GARP which triggered apoptesis of intraeythrocytic trophozoites in vitro and naturally acquired *Pf*GARP antibodies was associated with *Plasmodium falciparum* parasitemia control and protection from severe malaria. There was partial protection with *Pf*GARP-based vaccines against *Plasmodium falciparum* in monkey studies [28].

The egression of malaria parasite from the red blood cells has been identified as a target for protective immunity. *Plasmodium falciparum* Schizont Egress Antigen 1 (*Pf*SEA-1) which facilitates schizont egression in red blood cells is very important in protective immunity. In *in vitro* studies, there was rupturation of recombinant *Plasmodium falciparum* and a reduction of parasitaemia after vaccination of mice with *Plasmodium berghei* which delayed death after infection with virulent *Plasmodium berghei*. Screening of the sera of children who controlled and those who did not control parasite density during infection was associated with antibody protection against *Plasmodium falciparum* [85].

At the placenta, chondroitin sulfate A (CSA) is the primary receptor for infected erythrocytes sequestration [95]. Variant surface antigen 2-CSA (VAR2CSA) is a family member of *Pf*EMP1 responsible for cytoadhesion to CSA in the infected erythrocytes. Indeed, *var2csa* is the only *var* gene expressed in CSA-binding selected infected erythrocytes [37, 75, 96]. While prerythrocyte vaccine and blood-stage vaccine candidates which protect every group of individual may be beneficial to pregnant women, naturally-acquired protection against placental malaria provides a focus towards placenta malaria vaccine approach [36]. Naturally-acquired antibodies to CSA binding parasites are significant in providing protection against placental malaria and are acquired over successive pregnancies as there are reports that women in endemic areas become resistant to placental malaria. Therefore, CSA-binding parasites become a target for placenta malaria vaccines [28, 36, 40, 91].

Variant surface antigen 2-CSA (VAR2CSA) is a large extracellular protein of 350 kDa comprising of six Duffy-Binding Like (DBL) domains, one Cysteine-rich Inter-Domain Regions (CIDR) and several inter-domain regions [38]. Current studies have identified a unique VAR2CSA with functional seven or eight DBL domains in some isolates in the field [22]. With the first trials of VAR2CSA-based vaccines conducted more than half a decade ago, VAR2CSA vaccine development has focused on individual domains or domain combinations due to its large size [67]. Single recombinant domains have though been shown to bind CSA, latest studies report that complete ectodomain of VAR2CSA fully produces high affinity binding with CSA [54, 103].

Two placenta malaria vaccine candidates (PRIMVAC and PAMVAC) have been formulated based on N-terminal VAR2CSA fragments with high affinity for CSA and are currently under clinical development [13, 67]. The testing of Drosophila cell expressed PAMVAC using different human adjuvants was carried out and had proven to be safe, well tolerated and immunological functional against homologous parasites [67]. Duffy & Gorres (2020) reported a trial that was carried out in females who have never been pregnant and second subunit VAR2CSA candidate, PRIMVAC was said to be immunologically safe and functional against parasites with homologous VAR2CSA variant expressed by NF54-CSA in the erythrocytes [28]. There is however, poor cross-reaction against heterologous VAR2CSA variants by the placenta vaccine candidate and the reaction with the homologous variant occurred with very dose [18, 102]. Researchers have suggested that an alternate schedule of immunization, antigen dose, and combinations with other VAR2CSA-based vaccines could improve the cross-reactivity against heterologous VAR2CSA variants [28].

Transmission-blocking vaccines include surface antigens of sexual-stages of the parasites (gametes and zygotes) in humans and mosquitoes in order to produce antibodies against the parasites in the mosquito blood meal and block the parasite from being transmitted through the vector [12]. Early works using avian and murine *Plasmodium* species clearly showed that monoclonal antibodies against gametes bind to the surfaces of gametes and inhibit the development of parasite in the midgut of mosquito [42, 53, 61].

In vitro studies of *Plasmodium falciparum* made it possible for gametes which were used in the production of murine monoclonal antibodies, recognized and inhibit the development of oocyts to be isolated in an experimented mosquito feeding [53, 84, 87, 112]. The mosquitoes fed on gametocyte-erythrocytes added with the test antibodies and this became the gold standard

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for measuring transmission-blocking activity [10, 64].

The first monoclonal antibodies with transmission-reducing activity were used in the identification of specific desired proteins on the gamete surface. The proteins were *Pf*s48/45, *Pf*s230, *Pf*s25 and later *Pf*s28. These four proteins are considered as the leading TBV candidates and are under development [27]. Other proteins secreted by ookinete which are the target for TBVs are Chitinase 1, von Willebrand factor-A domain-related protein, TRAP, membrane-attack ookinete protein, secreted ookinete adhesive protein (SOAP) and cell-traversal protein for ookinetes and sporozoites [CelTIOS] [21, 52].

Antibodies against *Pf*s28 were also shown to be very effective but enhanced the TBA of antibodies against *Pf*s25 [27]. Polyclonal antibodies for the male gamete protein, hapless 2 (HAP2) and a monoclonal antibody for female-specific *Pf*s47, a paralog of *Pf*s48/45 have been reported to produce great reduction in transmission [9]. Midgut antigen of *Anopheles* (AnAPN1) has been reported to exhibit the ability to block malaria transmission in a parasite strain- and species-transcending manner [3].

Of all the TBVs, *Pv*s25 is the most advanced and with its *Plasmodium vivax* ortholog *Pv*s25 and *Pf*s230 have reached human clinical trials. Earlier studies revealed that clinical trials on *Pf*s25 and *Pv*s25 was poor either due to poor production of antibodies with transmission-blocking activity or to high reactogenicity from adjuvant formulations [59, 74, 118]. Human studies have shown that *Pf*s25 and *Pv*s25 are immunologically effective when they are administered in high dose [59, 105]. The challenges of TBVs have been addressed by developments in vaccine expression systems, delivery platforms, and formation of adjuvant formulations. Recombinant TBV antigens have been studied *in vivo* to produce better-folded proteins which are stable in solution and recreate conformational epitopes [79, 116].

Many others ways in improving the reactogenicity of vaccine candidates are vaccine conjugation such as *Pseudomonas aeruginosa* exoprotein A [EPA] and bacterial outer membrane protein complex [OMP]) or proteins recombination such as C4 bp oligomerization domain [IMX313] expressed in *Escherichia coli* or modified lichenase carrier (LiKM) produced in *Nicotiana benthamiana* [55, 75, 83, 117]. Viral vector vaccines, such as Chad63/Modified Vaccinia Ankara are also being studied produce good immunogenicity [55]. Studies using adjuvants like Alhydrogel® and Montanide had been employed in preclinical and clinical trials of TBV. However, issues on reactogenicity were associated with the two adjuvants. Recent studies using Alhydrogel®-formulated TBV have shown good safety and reactogenicity quality. Considerations have been made in the use of GSK®'s liposomal adjuvant AS01 for the production of TBV [25].

Due to the failure in the development of efficacious vaccines for a particular stage of *Plasmodium* life cycle, research on vaccine to tackle more than one malaria parasite stage referred to as multistage or multivalent malaria vaccine (MultiMalVax) is on going. The International Centre for Genetic Engineering and Biotechnology (ICGEB) Malaria Vaccine Group has discovered high profile antigenic formulations which evoke antibodies that inhibit the development of strain transcending parasite invasion. Other vaccine groups in the world are also embarking on this research [44, 80, 115]. At the moment, MultiMalVax trial is being championed by the Oxford University and funded by the European Union's seventh Framework Programme (FP7). This vaccine has already undergone phase II in Europe and has further been tried in malaria endemic community [109]. (University of Oxford, 2017). This multistage vaccine is already promising for all the *Plasmodium* species because (i) the newly vectored chimpanzee adenovirus vaccination regime has evoked great high quality CD8+T-cell responses and the high quantity antibodies which retard the development of multiple malaria antigens; (ii) the development of an enhanced virus like particle (VLP) from parts of RTS,S vaccine candidate, termed R21, that lacks excess part of HBsAg in RTS,S; (iii) recognition of the blood stage antigen, RH5, by using a vector approach to evoke strong strain-specific antibodies inhibitory to the blood stage parasites in in vitro assays; and (iv) demonstration of the new nanoparticle vaccine, which have triggered antibodies which have completely inhibited the transmission of the *Plasmodium falciparum* isolates in Africa [109]. Combination vaccine studies with several antigens like Polyoma virus (Py) and Paul-Bunnell (P-B) either alone or in combination with CSP have been carried out and it has been reported that PyLISP1 and PyS-LARP, PbLISP1, PbSLARP and PbPF3D7 produced very high protection than that seen with CSP [33].

CHALLENGES OF VACCINE DEVELOPMENT

The major challenge of vaccine development is the inability to identify malaria vaccine candidates alongside understanding the mechanism of the disease caused by the malaria parasite and

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the host immune response interactions. This is because of the complexity in the life cycle of the parasite. Furthermore, *Plasmodium falciparum* has many antigens which could be the target of the host immune system protection. But these antigens are mostly polymorphic, and even exhibit clonal variation through differential multigene expression. These genetic polymorphisms have aid the malaria parasites to evade immune attack [70]. Significant strides have been made in vaccine development through which more vaccines have progressed to the clinical phase. However, this may also show inability to predict immunity efficacy of a particular vaccine candidate in early phases thus, substantially increasing the risks of investment by forcing investigators to make go-decisions based on immune measures tested to decide if the approach is promising in large scale trials [14].

Regardless of the success in the development of malaria vaccines, there is still a lack of understanding of individual immunity against malaria. Since the work of Koch at the end of the 19th Century which showed acquisition of highly effective immunity among adults who survived malaria infection, the operation the immune system remains partly unknown, although the antibody that blocks the invasion of merozoites into erythrocytes appears to play a crucial role [1]. Several studies have been carried out to determine the protective antigens or epitopes which can be used in the recombinant or subunit construction or synthetic malaria vaccines [39, 44, 82, 98]. The assays which are used to evaluate the efficacy of surrogate markers of antibodies are in vitro. These assays are very laborious and difficult; unclear to if such in vitro assays can predict functional immunity in humans due to absence of animal model which allow the growth of *Plasmodium falciparum* [48]. Currently, there are no clear correlation between immunity and the parasites at pre-erythrocytic and blood stages. Immuno-assays can become valid only when a vaccine shows efficacy in a clinical trial. Once a correlation between immune correlate for protection is identified, it can be used for decision making in clinical development [71].

IMPROVING THE EFFICACY OF MALARIA VACCINES

One of the important ways of improving vaccine efficacy is by using optimal adjuvant. This has however being badly affected by few numbers of adjuvants approved for human use. An effective adjuvant should enhance immunogenicity without negatively affecting vaccine safety. Therefore, more understanding of the required immune responses for immune protection and the nature of vaccine-induced responses with specific adjuvants may further improve the selection of adjuvant [7, 35].

Vaccine candidates have been formulated to trigger a strong CD8+T cell responses at the pre-erythrocytic staged. Some of these formulations are in recombinant with viruses and administered by heterolpgous prime-boost strategies. These have been promising for malaria epitopes thrombospondin-Related Adhesion Protein [ME-TRAP] vaccine [33]. Some prime-boost strategies have produced a significant improvement in immune responses using animal models and humans in other infections like human immunodeficiency virus (HIV) and influenza [2, 60]. With other delivery platforms and formulations like micro needle skin patch delivery, nanoparticles, and virus like particles (VLPs), to improve retention of antigens and uptake by lymph nodes and antigen presentation or using specific strategies for targeting antigen presenting cells, there may be improvements in other humoral and cellular responses [1, 60].

There are several criteria to be considered in order to identify and choose the right antigens and epitopes for the development of vaccines. These include the location of antigen cells and function, abundance, polymorphisms, data from in vitro functional assays, evidence of protective associations in studies of naturally acquired immunity, and data from animal models [20]. Induction of protective antibodies may also be improved by identifying key epitopes targeted by protective responses. Current vaccine strategies to whole antigens or whole parasites typically consist of a range of protective and non-protective epitopes. Refining vaccine immunogens and responses to predominantly target key functional or protective epitopes and response types may enable protective immunity to be better maintained as the overall immune response wanes [7, 43].

Antigenic polymorphisms used in vaccines development facilitate immune escape and these have been a challenge in several vaccines including RTS,S and vaccines based on MSP2 and AMA1. Vaccine efficacy was higher against infection of vaccine-like strains compared to vaccine dissimilar strains [71, 72, 74]. Therefore, implementation of RTS,S could shift the burden of malaria to vaccineescape strains over time, decreasing its effectiveness. This highlights the need for nextgeneration vaccines capable of

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inducing more potent crossstrain protective responses. Strategies to address this include the inclusion of multiple alleles of an antigen [e.g., AMA1], combinations of different antigens, or whole parasite vaccines. Antibodies induced in a phase 1 trial by immunization with two different MSP2 alleles surprisingly shifted antibody targeting to conserved epitopes, in contrast to naturally acquired antibodies that are overwhelmingly allele specific [34, 78, 106]. To focus on conserved epitopes or less polymorphic antigens like CSP and *Pf*RH5 is another approach towards improving malaria vaccine efficacy [7, 86, 97].

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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