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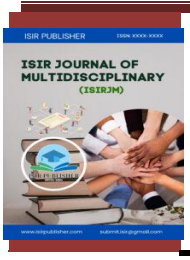

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POTENTIAL ANTIGENTS FOR MALARIA VACCINE DEVELOPMENT

By

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Abstract

Malaria remains a significant global health burden, with millions affected annually, despite significant advancement in the fight against malaria, nearly half of the global population remains at risk of contracting the disease. Developing an effective malaria vaccine has long been a daunting challenge for medical science. In 2021, the World Health Organization (WHO) approved the RTS, S/AS01 vaccine for widespread use, The RTS, S/AS01 vaccine, which has completed Phrase testing and received a favorable assessment, is a significant achievement in malaria vaccine development. Marking a major milestone in malaria vaccine development. This paper provides an overview of the progress made in malaria vaccine development, highlighting the challenges, successes, and future directions in the quest to combat this devastating diseases, including, pre-erythrocytic Vaccines; Targeting parasite proteins, such as: Circumsporozoite protein (CSP), Thrombospondin-Related Adhesion protein (TRAP),Liver Stage Antigen (LSA).Blood Stage Vaccines: Targeting: Merozoite Surface Protein 1 (MSP-1), Apical Membrane Antigen 1 (AMA-1),Erythrocyte-Binding Antigen (EBA). Transmission-Blocking Vaccines: Focusing on antigens expressed on: Gametes, Zygotes, Ookinetes.

Keywords: *Plasmodium falciparum, Malaria, Vaccine, Pre-erythrocytic Vaccines, Blood Stage Vaccines, Transmission-Blocking Vaccines*

INTRODUCTION

Malaria is a life-threatening disease caused by parasites in the genus Plasmodium (*Plasmodium falciparum*) that are transmitted to humans through the bites of infected female anopheles' mosquitos. It is a major public health concern in many tropical and subtropical regions of the world, particularly in the sub-Sahara Africa. According to World Health Organization (WHO) There's an estimated 22.9 million cases of malaria Worldwide in 2019 resulting in approximately 409,000 deaths (WHO, 2020). The parasite that causes malaria belongs to the plasmodium genius, with plasmodium falciparum being the deadliest species. Malaria can present with a wide range of symptoms which include fever and chills being the most common symptoms of malaria which are caused by a reaction of malaria antigens, also anemia which is caused by intra vascular rupture of the red blood, sand extra vascular hemolysis, which is caused by sequestration of parasitized and non-parasitic red blood cells(Pukama, 2022) Insecticide – treated bed nets, Indoor residual spraying and anti-malarial medications are key components in malaria prevention and control. Efforts to control the disease have been hindered by factors such as insecticides resistance in mosquitoes, drug resistance in parasites and limited access to healthcare in affected regions (Anderson et al., 2014).

The rise of drug resistant malaria strains has compromised the effectiveness of synthetic antimalarial medicines, undermining the benefits of chemoprophylaxis and chemotherapy. Meanwhile the surge in the new malaria cases in developing countries notably Nigeria, underscores the imperative for a shift strategy. It is time to move beyond reliance on chemoprophylaxis and chemotherapy and embrace vaccination as a vital component or malaria control and prevention (Ismail *et al,* 2022) A Malaria vaccine has the potential to reduce the number of severe cases and death caused by the disease, improving overall public health outcome (Ismail, *et a*l 2022) The malaria vaccine will work by stimulating the immune system to recognize and target the

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malaria parasite. i.e. the *Plasmodium* specie when it enters the body, thereby preventing infection, reducing disease severity, and interrupting the transmission cycle of the parasite. This study is sought to provide a comprehensive overview of the current stage of antigen research in malaria vaccine development. The paper will also examine emerging trends including antigen combinations and multistage vaccines and evaluate their potential impact on future vaccine development. By providing a comprehensive overview, this paper aims to contribute to the advancement of malaria vaccine research and development.

PATH WAY TO MALARIA VACCINE

The pursuit of malaria vaccine began in the early 20th Century, with scientists acknowledging the potential of vaccination as a key weapon against the disease: Initial attempts to create a vaccine involved Exposing people to weakened forms of the malaria parasite to trigger an immune response. Although these efforts did not yield a long-term protection, they paved the way for subsequent vaccine development approaches. (Sagara et al., 2009). Despite the progress made in malaria vaccine development, several challenges remain. One of the main challenges is the complex biology of the plasmodium parasite, which has multiple stages in its life cycle and can evade the host immune system through various mechanisms. This complexity makes it difficult to develop a single vaccine that provides long-lasting and broad protection against malaria (White et al., 2015).

In the 1960s and 1970s, researchers began exploring the use of whole parasite vaccines, which involved administering radiation-attenuated or genetically attenuated parasites to induce immunity against malaria. These vaccines showed promise in animal models and early clinical trials, but the development was concerned about safety and efficacy (Wiersma et al., 2009). In the 1980s, advances in molecular biology and immunology led to the identification of specific malaria antigens that could serve as vaccine targets. Researchers focused on developing sub unit vaccines that contains purified antigens from the malaria parasite, such as the circumsporozoite protein (CSP) and the merozoite surface protein (MSP) These subunit vaccines were designed to stimulate a specific immune response against key stages of the parasite's life cycle. (Birkett et al., 2013).

One of the most well-known malaria vaccine candidates is RTS, S/ASCO1 which was developed by Glaxo smith Kline in collaboration with path malaria vaccine initiative. It is a prominent contender in the fight against malaria by targeting the circumsporozioite protein of the *Plasmodium falciparum* parasite, RTS, S/ASOT has demonstrated partial efficacy in preventing malaria in clinical trials, particularly among children residing in areas where malaria is prevalent (Lancet et al, 2015). By genetically modifying the carboxyl terminus of the circumsporozoite antigen (amino acids 207-394) the RTS, S/ASOT vaccine directs the immune system to recognize and respond to the primary protein on the surface of infecting sporozoites. (Ismail *et al* 2022) According to Ismail in 2019 the protein plays a crucial role in the sporozoites attachment to hepatocytes during the initial stage of parasites infection. However Anti-circomsporozoite antibodies have been shown to compromise vaccine effectiveness overtime, leading to a resurgence of malaria cases. The RTS, S vaccine is designed to prevent infection by *plasmodium falciparum*, the deadliest of the malaria parasites that infect humans, the vaccine works by inducing antibodies against the circumsporozoite protein, which is a key protein on the surface of the malaria parasite that is involved in invasion of liver cells. (Lancet et al, 2015). The vaccine includes RTS, S antigen which is a fusion protein that combines a portion of the circumsporozoite protein which is hepatitis B surface. This allows the immune system to generate both antibodies and T-cell response against malaria parasite. The AS01 adjuvant is included in the vaccine to enhance the immune response and boost efficacy of the vaccine. The adjuvant contains a combination of two immune stimulants, MPL (Monophosphoryl Lipid A) and QS21(a plant saponin). (Arama et al, 2014). In December 2021, the board of Gavi, the vaccine Alliance, approved a program to support the broader rollout of malaria vaccines in Gavi-eligible countries. RTS, S was granted WHO prequalification in July 2022, allowing UNICEF to procure the vaccine. Cameroon made history in January 2024 by becoming the first country to integrate the RTS, S malaria vaccine into its national immunization program outside pilot initiatives. This milestone marks a significant step forward in the fight against malaria, particularly in Africa, where the disease claims hundreds of thousands of lives annually. Nine countries are expected to introduce the RTS,S vaccine into their routine immunization programs by 2025. Some of these countries include Benin who already received vaccine shipments, Burkina Faso who are preparing for rollout, Sierra Leone who received vaccine shipments and Liberia who received shipments. Additionally, 20 African countries plan to introduce malaria vaccines, with seven using RTS, S and eight using the R21 vaccine. The widespread adoption has potential to significantly reduce malaria cases and deaths across the continent. (WHO 2024).

POTENTIAL ANTIGENS FOR VACCINE DEVELOPMENT

According to Amal A, El- Moamly and Mohammed A.El-sweify in 2023 malaria vaccines are categorized according to the parasites targeted development stage: Pre-erythrocytic stage antigens ; Circumsporozoite protein (CSP), Liver stage Antigen 1(LSA-1) and Liver stage Antigen 3 (LSA-3). Erythrocytic stage Antigens; Merozoite Surface Protein 1 (MSP-1), Merozoite Surface Protein 2 (MSP-2) and Apical Membrane Antigen 1 (AMA-1) and Erythrocyte-Binding Antigen 175 (EBA-175) and Transmission-Blocking Antigens; Pfs25 and Pfs48/45.

Pre-erythrocytic vaccines (PEVs)

According to experts most effective vaccine is the one that target the early stages of infection and transmission (Moamly et al., 2023)The pre-erythrocytic stage is also referred to as liver stage, aim to prevent infection by targeting sporozoites, the sexual forms of the parasites transmitted to humans through mosquito bites. PEVs are designed to elicit a dual immune response: antibodies that recognize sporozoite

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surface antigens and prevent inner cell infection, and T cells that target and clear infected inner cells (Duffy & Gorres, 2020). PEVs target the crucial early phase of sporozoite infection, when the parasites invade a small number of liver cells and require about a week to develop, allowing sufficient time foe the vaccine to take effect. Moreover, infected hepatocytes display parasite antigens that can activate T-cells to recognize and eliminate these cells, thereby preventing merozoites from entering the blood stream (Clemens & Jodar, 2005). They comprise antigenic fragments of the circumsporozoite protein, specifically from sporozoite stage of the parasite (Okie et al, 2005) whole sporozoite vaccines are developed by attenuating sporozoites using radiation, chemicals, or genetic modification. The attenuated sporozoites are then delivered to recipients through mosquito bites, when they enter liver cells and undergo limited development. This approach stimulates broad and protective immune response without causing illness, offering a promising strategy for malaria prevention (Arama et al,. 2014). Vaccines can be designed to target antigens present during the early and late stages of liver schizogony, potentially triggering cell-mediated immunity and suppressing the growth of intracellular parasites. Additionally, this vaccine approach may be particularly effective in targeting the dormant stages of *Plasmodium vivax* which are responsible for recurring nature of the infection. (Ismail *et al*.,2022). For vaccine targeting pre-erythrocytic Plasmodium to be truly effective, it must achieve 100% protection rate. Currently three major parasite proteins are being explored as potential candidate antigens for the development of such vaccine they are; Plasmodium falciparum circumsporozoite protein (CSP), Thrombospondin-related adhesion protein (TRAP) and Liver stage antigen (LSA). (Ismail *et al*.,2022). LSA-1 is expressed early in liver stage (sporozoite and initial hepatocyte infection) it is involved in parasite invasion and initial hepatocyte infection. LSA-3 is expressed later in liver stage (after parasite multiplication in hepatocytes) it induces T-cell and antibody responses, but with different epitope specificity (Raj et al.,2020).

Erythrocytic Vaccine

These vaccines take effect when the merozoites released from the liver, enter the bloodstream to infect red blood cells (erythrocyte). Therefore, these vaccines are also referred to as blood stage vaccines. The goal is to block the invasion of red blood cells by the merozoite and prevent the parasite asexual reproduction and elicit invasion and disease response (Moamly et al., 2023). Several blood stage antigens have been tried: erythrocyte-binding antigen 175(EBA-175) ((Sallusto et al., 2010),Apical membrane antigen 1(AMA-1) ,Glum ate rich protein (GLURP)(Moamly et al., 2023) ,Serine repeat antigen 5(SERA5),and merozoite surface protein(MSP-1)(Ogutu et al., 2009),MSP-2(Genton et al., n.d.),MSP-3(K. Singh et al., 2018).Although the previously mentioned antigens are abundantly expressed on the merozoite surface, they have failed to demonstrate a substantial impact on chemical malaria. This disappointment has led to the exploration of alternative antigens with robust immunogenicity and promising potential as blood-stage vaccine candidates. For instance, the plasmodium falciparum reticulocyte binding protein homologue 5 (PfRH5) has emerged as a promising candidate as it has been shown to elicit neutralizing antibodies that recognize common genetic variants of protein (Bustamante et al., 2013). Notably, PfRH5 has demonstrated minimal polymorphism, making it an attractive target for vaccine development. Pre-clinical studies have shown that thus antigen is the first highly conserved blood-stage antigen capable of including broadly neutralizing antibodies, providing a promising foundation for vaccine development (Palacpac et al., 2013) new blood stage vaccine candidate AMA1-RON, has gained attention its potential to prevent malaria this combination antigen; targets the merozoite-erythrocyte junction, where it can block invasion has shown improved immunogenicity compared to AMA1 alone, induces more effective anti-invasion antibodies(Srinivasan et al., 2017).PFEMP1, is another immunodominant virulence antigen that facilitates sequestering of the Plasmodium falciparum parasite and its targeted by naturally acquired immunity(Palacpac et al., 2013).Unfortunately the development of a vaccine targeting PFEMP1 has stalled due to several challenges which are; large antigen size, genetic polymorphism and complicated structure. As a result, no further progress has been made in evaluating efficacy of a PFEMP1 vaccine. Another erythrocyte surface protein called PFGARP has been described as target for protective antibodies (Raja et al., 2017). Plasmodium falciparum schizont Egress antigen-1 (PFSEA-1) which emerges from infected blood cells has also been identified (Raj et al., 2020). Due to previous disappointments with blood stage vaccine candidates, Scientists have explored alternative approaches including; chemically attenuated erythrocytic-stage parasites (CAP) created by culturing parasites with a DNA-binding agent called Tafuramycin-A, CAP induces immunity in mice, providing protection against homologous (same strain) and heterologous (different strain) parasites. CD4+ T cells plays a crucial role in this protection (Raj et al., 2020).

Transmission blocking chain (TBVs) (mosquito stage vaccines)

Transmission blocking vaccines (TBVs) target specific proteins essential for the parasite's development in mosquitoes, aiming to elicit antibodies that can neutralize these proteins and prevent further transmission (S. K. Singh et al., 2021). TBVs focus on antigens expressed on the gametes, zygote and ookinetes, which are crucial stages in the parasite's life cycle within the mosquito(Arama & Troye-blomberg, 2014). The Transmission-Blocking vaccine candidates, Pf48/45 and Pf230, are gametocyte- expressed antigens that are present in both humans and mosquito vectors. These antigens form a protein complex on the surface of Plasmodium falciparum gametes, making them ideal targets for vaccine development. (Moamly et al., 2023) While significant research and funding have focused on developing vaccines against Plasmodium falciparum, Plasmodium vivax is a major contributor to malaria-related morbidity and mortality in various regions, necessitating increased efforts to develop effective vaccines against this species. (Baird &

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Baird, 2013) Researchers have made notable progress in developing a Plasmodium vivax vaccine, exploring various targets and approaches including; pre-erythrocytic vaccines targeting the Circumsporozoite protein (Pv-CSP), Blood stage vaccines targeting the merozoite and Duffy Binding protein (Pv-DBP) and Transmission-Blocking vaccines targeting (Pv-s25). These vaccine candidates have shown promising results in pre-clinical trials, including; viral vector vaccines, which have advanced to various stages of clinical trials demonstrating, encouraging efficacy and safety profiles. (Payne et al., 2016), the progress of these candidates is a significant step forward in development of an effective Plasmodium vivax vaccine, offering hope for improved malaria control and prevention. Recombinant antigen-based vaccines are also being developed against Plasmodium vivax, showing promise in pre-clinical and clinical trials as a potential tool for malaria prevention. (S. K. Singh et al., 2021). Transmission-Blocking vaccines approaches using Pv-DBP and Pv-s25 have shown encouraging results including; Pv-DBP's potential to induce antibodies that block transmission and Pv-s25's demonstrated transmission-blocking activity, with a well-tolerated and modest antibody response in mosquito studies. (Wiersma et al., 2009). These findings suggest that Pv-DBP and Pv-s25 could be valuable components of a transmission-blocking vaccine against Plasmodium vivax helping to prevent spread of malaria.

Conclusion

A malaria vaccine is on the horizon, thanks to the identification of various potential antigens throughout the parasite's life cycle, including; sporozoite stage (blood and liver), merozoite stage (erythrocyte) and zygote and ookinete stages in the vector. To achieve effective malaria control, a combination of vaccines targeting these three stages is necessary. This multi-stage approach will; prevent infection, reduce parasite transmission and minimize the risk of resistance. A successful malaria vaccine will complement existing control measures, reduce reliance on antimalarial drugs, and prevent resistance development, save lives and reduce morbidity and enable elimination efforts in endemic areas. The potential impact of a malaria vaccine is significant, and its development is crucial for achieving a free malaria world.

Recommendations

Developing innovative vaccine candidates is essential to achieve a lasting and effective malaria control. By exploring multi-component vaccines approaches, researchers can; address limitations of current vaccines, enhance immune response and efficacy, minimize risk of parasite resistance and mutations and develop vaccines that provide durable protection against malaria.

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