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Review

The march toward malaria vaccines

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ABSTRACT

In 2013 there were an estimated 584,000 deaths and 198 million clinical illnesses due to malaria, the majority in sub-Saharan Africa. Vaccines would be the ideal addition to the existing armamentarium of anti-malaria tools. However, malaria is caused by parasites, and parasites are much more complex in terms of their biology than the viruses and bacteria for which we have vaccines, passing through multiple stages of development in the human host, each stage expressing hundreds of unique antigens. This complexity makes it more difficult to develop a vaccine for parasites than for viruses and bacteria, since an immune response targeting one stage may not offer protection against a later stage, because different antigens are the targets of protective immunity at different stages. Furthermore, depending on the life cycle stage and whether the parasite is extra- or intra-cellular, antibody and/or cellular immune responses provide protection. It is thus not surprising that there is no vaccine on the market for prevention of malaria, or any human parasitic infection. In fact, no vaccine for any disease with this breadth of targets and immune responses exists. In this limited review, we focus on four approaches to malaria vaccines, (1) a recombinant protein with adjuvant vaccine aimed at *Plasmodium falciparum* (Pf) pre-erythrocytic stages of the parasite cycle (RTS,S/AS01), (2) whole sporozoite vaccines aimed at Pf pre-erythrocytic stages (PfSPZ Vaccine and PfSPZ-CVac), (3) prime boost vaccines that include recombinant DNA, viruses and bacteria, and protein with adjuvant aimed primarily at Pf pre-erythrocytic, but also asexual erythrocytic stages, and (4) recombinant protein with adjuvant vaccines aimed at Pf and *Plasmodium vivax* sexual erythrocytic and mosquito stages. We recognize that we are not covering all approaches to malaria vaccine development, or most of the critically important work on development of vaccines against *P. vivax*, the second most important cause of malaria. Progress during the last few years has been significant, and a first generation malaria candidate vaccine, RTS,S/AS01, is under review by the European Medicines Agency (EMA) for its quality, safety and efficacy under article 58, which allows the EMA to give a scientific opinion about products intended exclusively for markets outside of the European Union. However, much work is in progress to optimize malaria vaccines in regard to magnitude and durability of protective efficacy and the financing and practicality of delivery. Thus, we are hopeful that anti-malaria vaccines will soon be important tools in the battle against malaria.

1. Introduction

In 2013 at least $2.6 billion was invested in malaria control programs, which utilize tools including insecticide impregnated bednets, residual insecticide spraying, and early diagnosis and treatment [1]. These programs have had a tremendous impact on reducing malaria morbidity and mortality during the past decade [1]. However, even in the face of this large investment, in 2013 there were an estimated 584,000 deaths and 198 million clinical illnesses due to malaria, the majority in sub-Saharan Africa [1].

Vaccines would be the ideal addition to the existing armamentarium of anti-malaria tools. A vaccine was used to eradicate smallpox from the world and polio from the Western hemisphere, and vaccines have had dramatic impacts on many infectious diseases. It is because of these successes that vaccines are considered the most cost effective single intervention for control, prevention, elimination, and eradication of infectious diseases.

However, malaria is caused by parasites, and parasites are much more complex in terms of their biology than the viruses and bacteria for which we have vaccines. For example their genomes are

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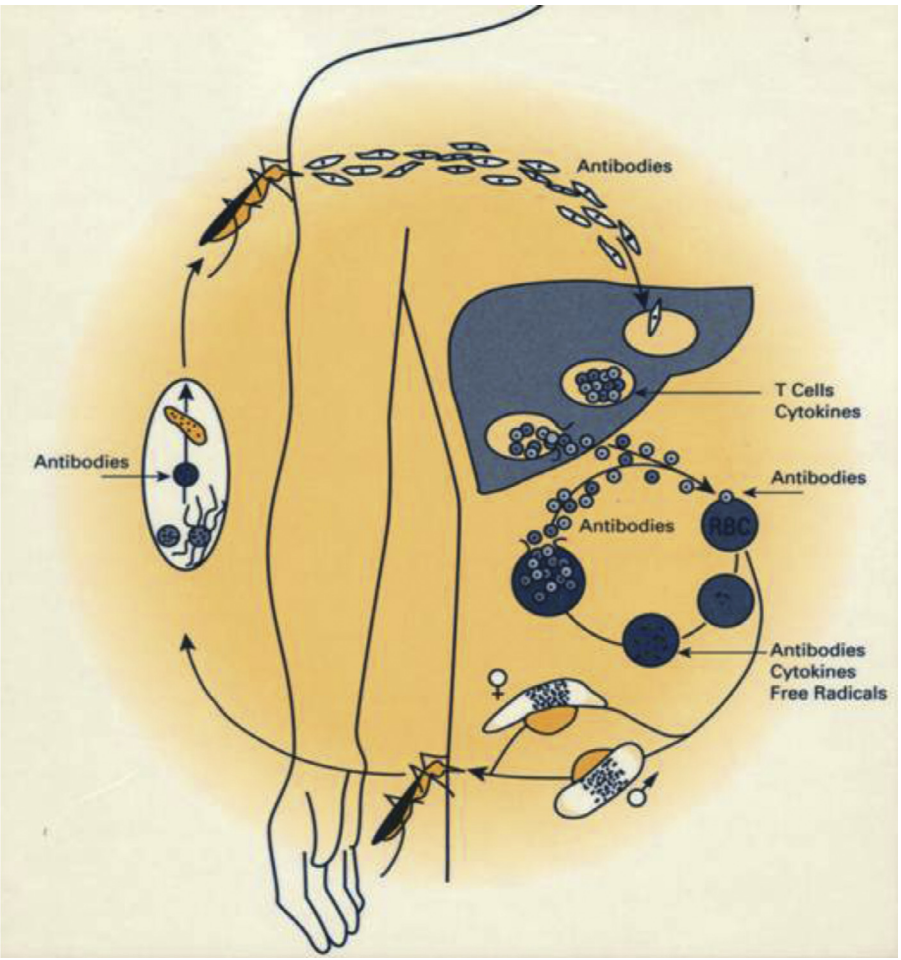

Fig. 1. Life cycle of *P. falciparum* and stages at which antibodies and cellular immune responses are primary for protection. When an infected female *Anopheles* spp. mosquito feeds on a human, she inoculates uninucleated sporozoites into the tissues or directly into the bloodstream. Sporozoites rapidly pass through the bloodstream to the liver (probably within 2 min, but less than 60 min). In hepatic sinusoids they may penetrate and pass through Kupffer cells and invade hepatocytes. Sporozoites may invade several hepatocytes before finding the correct hepatocyte in which to develop. During a minimum of 5.5 days, the uninucleated *P. falciparum* sporozoite develops to a mature liver-stage schizont with an average of 30,000 and range of 10,000–40,000 uninucleated merozoites. The hepatocyte containing mature liver-stage schizonts die or rupture releasing "sacks" containing merozoites called merosomes containing thousands of uninucleated merozoites, each of which can invade a normal erythrocyte. In the erythrocyte, the invading merozoite develops during approximately 2 days to a mature asexual erythrocytic-stage schizont with an average of 16 uninucleated merozoites. When fully mature, the infected erythrocyte ruptures, releasing the merozoites, which then invade normal erythrocytes, initiating the cycle of intraerythrocytic-stage development, rupture, and reinvasion that leads to a 10–20-fold increase in the numbers of *P. falciparum* parasites in the bloodstream approximately every 2 days and to all the clinical manifestations and pathology of malaria. Alternatively, erythrocytic-stage parasites can develop to sexual-stage parasites, gametocyte. In the gut of the mosquito, gametocytes escape from erythrocytes and form gametes. The male gamete fuses with the female, forming a zygote. By 18–24 h, the zygote has transformed into an ookinete. The ookinete traverses the midgut wall by passing through epithelial cells and comes to rest adjacent to the basal lamina. Here it begins to transform into an oocyst in which sporozoites are produced. By day 12, they are released into the hemocele of the mosquito and migrate to the salivary glands. In the salivary glands, they become infectious for humans and are released into the human host when the mosquito feeds.

Source: Figure is from Hoffman, SL. *Malaria vaccine development, a multi-immune response approach*. 1996. ASM Press, Washington, DC.

much larger than those of viruses and bacteria (Pf has >5400 genes) and they have multiple stages of their life cycles, which viruses and bacteria do not have (Fig. 1). These different stages, (1) must be attacked by different arms of the immune system, depending on whether the parasites are inside or outside of host cells and (2) are in many cases antigenically distinct. For example, protective antibodies against sporozoites injected by mosquitoes do not recognize the asexual erythrocytic stages that cause all disease. Thus, if one sporozoite evades vaccine-induced protective antibodies, a week later 10,000–40,000 merozoites will escape the liver. Each can invade a different erythrocyte, and none of these erythrocytic stage parasites are recognized by antibodies to the circumsporozoite protein (CSP), the major antigen on the sporozoite surface.

This complexity makes it more difficult to develop a vaccine for parasites than for viruses and bacteria. In fact there is no vaccine on the market for prevention of any human parasitic infection. There are five species of *Plasmodium* that cause malaria in humans, *Plasmodium falciparum* (Pf), *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi*. Pf is responsible for more than 98% of malaria mortality and has the most significant drug resistance of all the human malaria parasites. Furthermore, the most progress has been made on Pf vaccines. For these reasons, in this review we focus primarily on anti-Pf vaccines.

The malaria parasite has a complex life cycle and significant antigenic diversity. Hence, there are many different approaches to the development of malaria vaccines [2]. They include targeting the production of antigen specific protective antibodies, CD4+ T cells, and/or CD8+ T cells. Some are focused on the sporozoite and/or liver stages of the life cycle (pre-erythrocytic stages), some on the asexual erythrocytic stages, and some on the sexual erythrocytic and mosquito stages. Some are focused on preventing infection to prevent all disease, some in reducing the morbidity and mortality of the asexual erythrocytic stages by reducing the rate at which individuals become infected and/or reducing asexual erythrocytic