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Malaria vaccines and human immune responses

Carole A Long[1] and Fidel Zavala[2]

Despite reductions in malaria episodes and deaths over the past decade, there is still significant need for more effective tools to combat this serious global disease. The positive results with the Phase III trial of RTS,S directed to the circumsporozoite protein of *Plasmodium falciparum* have established that a vaccine against malaria can provide partial protection to children in endemic areas, but its limited efficacy and relatively short window of protection mandate that new generations of more efficacious vaccines must be sought. Evidence shows that anti-parasite immune responses can control infection against other stages as well, but translating these experimental findings into vaccines for blood stages has been disappointing and clinical efforts to test a transmission blocking vaccine are just beginning. Difficulties include the biological complexity of the organism with a large array of stage-specific genes many of which in the erythrocytic stages are antigenically diverse. In addition, it appears necessary to elicit high and long-lasting antibody titers, address the redundant pathways of merozoite invasion, and still seek surrogate markers of protective immunity. Most vaccine studies have focused on a single or a few antigens with an apparent functional role, but this is likely to be too restrictive, and broad, multi-antigen, multi-stage vaccines need further investigation. Finally, novel tools and biological insights involving parasite sexual stages and the mosquito vector will provide new avenues for reducing or blocking malaria transmission.

Addresses
[1] Laboratory of Malaria and Vector Research, 12735 Twinbrook Parkway, National Institute of Allergy and Infectious Diseases, National Institute of Health, Rockville, MD 20852, United States
[2] Department of Molecular Microbiology and Immunology, Malaria Research Institute, Bloomberg School of Public Health, Johns Hopkins University, 615 N. Wolfe Street, Baltimore, MD 21205, United States

Corresponding author: Long, Carole A (clong@niaid.nih.gov)

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Introduction

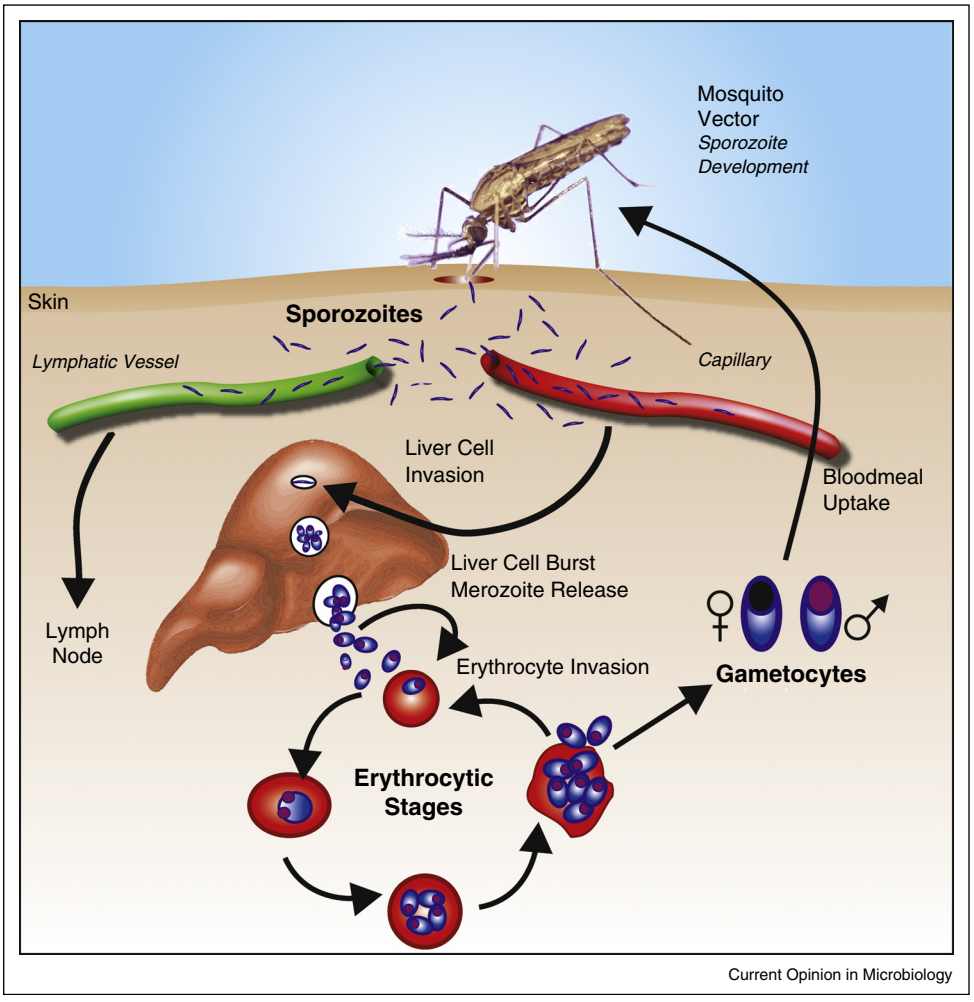
Despite considerable efforts over decades, we do not yet have a highly effective vaccine for any of the five plasmodial species which cause human malaria. While malaria deaths are reported to have declined between 2000 and 2013 [1], further inroads into this global scourge will require new tools, including a vaccine. Development of such a vaccine is complicated by the complex life cycle of the parasite involving both a vertebrate and an invertebrate host (Figure 1). Infectious sporozoites from the Anopheline vector enter the liver, replicate and differentiate there to asexual stage merozoites which can invade erythrocytes. Replication in red cells and accompanying host innate and acquired immune responses are responsible for all the clinical symptoms of disease. Finally small numbers of parasites differentiate into male and female gametocytes which can be picked up by the insect vector and thus complete the cycle. This review summarizes the status of malaria vaccine development, particularly focusing on *Plasmodium falciparum* since *P. vivax* vaccine approaches have been recently reviewed [2], and why it has been so difficult to achieve protective immune responses to the various stages of these fascinating organisms.

Sporozoites and pre-erythrocytic stages of infection

The notion that vaccine-induced immune responses against Plasmodium sporozoites could have a protective effect, inhibiting parasite infectivity in the vertebrate host, arises from early studies indicating that immunization of mice [3] and humans [4] with radiation-attenuated malaria sporozoites conferred sterile protection. Importantly, human vaccine trials demonstrated that sterile immunity induced by exposure to radiation-attenuated *Plasmodium falciparum* sporozoites was not strain specific and could last for at least 10 months (reviewed in [5]). From these seminal studies two main streams of research developed. One of them has focused on the development of subunit vaccines consisting of well-defined parasite antigens. More recently, a second line of research proposes the development of a vaccine based on the use of whole attenuated sporozoites. Both vaccine candidates have advanced to the point of human clinical trials involving large numbers of volunteers living in endemic areas.

RTS,S, the most advanced subunit malaria vaccine now known as Mosquirix^{TM}, contains the conserved central repeat and C-terminal regions of the *P. falciparum* Circumsporozoite Protein (CSP) which is expressed on sporozoites and in early liver stages. Phase III clinical trials in over 15 000 African children demonstrated that the vaccine efficacy of RTS,S ranges from 25 to 55%, depending on the age of the children and the intensity of transmission [6••], and that this protection appears to be

Figure 1



Life cycle of malaria parasites.

mediated by antibodies and perhaps also CD4+ T cells [7]. The partial efficacy of the RTS,S vaccine wanes over time with a significant reduction by 3 years post-immunization [6••]. Thus, while these results are encouraging, it is generally accepted that improvements in the efficacy of this vaccine will be needed.

The limited efficacy of this vaccine may be due, at least in part, to the narrow breadth of the immune responses induced by RTS,S, which consists mostly of antibodies against the repeat domain of the CSP, which are known to neutralize sporozoite infectivity. While this vaccine also induces some antibody and CD4+ T cell responses against the C-terminal region [7], the anti-parasite effect of these immune mechanisms has not been demonstrated. Thus, the protective capacity of the RTS,S-induced immune responses may be quite limited, relying mostly on the recognition of few or perhaps single epitopes. The efficacy of this vaccine might be significantly improved if additional antigens were included in this construct. This would broaden the specificity of the anti-parasite immune response and help achieve additive anti-parasite effects from responses specific for the other antigens. In fact there are a number of sporozoite and liver stage antigens that have been identified, some of them several years ago, that could be part of a more complex vaccine construct. Unfortunately, very few studies have been done to evaluate their potential as components of a multi-antigen vaccine. In addition, optimization of the vaccination schedule might elicit more effective antibody responses, as had been seen in an early Phase I trial of this vaccine [8,9].

Another significant limitation of the RTS,S vaccine is the fact that it does not induce CD8+ T cell responses, which represent an efficient anti-parasite mechanism that eliminates malaria liver stages in rodent model systems (reviewed in [10]). Development of vaccines capable of