News & views

Medical research

Malaria vaccine gets a parasite boost in the liver

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Effective malaria vaccines are urgently needed. Now, clinical evidence indicates that a vaccination approach that uses live parasites growing in the liver can generate high levels of immune protection from infection. **See p.289**

Malaria has long remained among the worst infectious-disease threats to human health. There were 229 million clinical cases of malaria and more than 400,000 deaths from this disease reported during 2019, according to the World Health Organization[1]. Although more than 140 years have passed since *Plasmodium* parasites were identified as the causative agents of malaria, a vaccine that offers a high level of protection against *Plasmodium* infection has not yet reached the market. Creation of such a vaccine has been hindered by the genomic complexity of *Plasmodium*, which has approximately 5,300 genes[2], and by the parasite's elaborate life cycle.

On page 289, Mwakingwe-Omari *et al.*[3] report a vaccination strategy using live, whole *Plasmodium falciparum* parasites that provides unmatched, high levels of protection against infection. This work represents a major advance in the quest for an effective malaria vaccine.

Human infection by *P. falciparum* begins when the mosquito-transmitted parasite (in a form known as a sporozoite) moves from the bloodstream to the liver and infects the organ's main cells, called hepatocytes (Fig. 1), in which the parasite grows and replicates. This liver stage of its life cycle is not associated with any disease symptoms. Within a week, tens of thousands of parasites are generated in a form that can infect red blood cells. These enter the blood, multiply in red blood cells, and can cause disease and death.

Sporozoites and liver-stage parasites, which together are called pre-erythrocytic (PE) parasites, have been the target of vaccine development since observations more than 50 years ago sparked interest in them as a promising target. Those observations showed that immunization with high doses of sporozoites weakened by radiation treatment can confer protection from subsequent parasite infection (termed sterile immunity) in animal models and in humans challenged with the malaria parasite in a controlled human malaria infection (CHMI) trial setting[4,5]. However, subsequent vaccine efforts focused instead on the development of a malaria vaccine that targets a single parasite protein (called CSP) that is expressed in PE stages. These efforts culminated in a licenced vaccine that confers moderate, short-lived protection against malaria[6]. An updated version of a CSP-based vaccine achieved improved levels of protection in a phase II clinical trial[7].

Given the limitations of a vaccine approach using a single parasite protein, vaccines using whole, live PE parasites that infect the liver but do not cause malaria have been revived as a promising alternative strategy[8]. Immunization with replication-deficient *P. falciparum* radiation-attenuated sporozoites (*Pf*SPZ-RAS), which infect the liver but cannot develop into a liver-stage parasite, remains the most-studied whole-parasite vaccine so far. At high doses, this type of vaccine induces robust protection against CHMI. When tested in Africa, it provided protection against natural transmission of malaria, albeit with reduced efficacy compared with that observed in CHMI[9].

In a whole-parasite vaccine approach called chemoprophylaxis vaccination, fully infectious sporozoites are administered together with a drug, such as chloroquine, that kills the blood-stage form of the parasite. The chloroquine-assisted form of this vaccine was shown to confer sterile immunity in CHMI studies, even when scientists used 18-fold fewer parasites than the quantity used in trials of *Pf*SPZ-RAS vaccines. However, the possibility

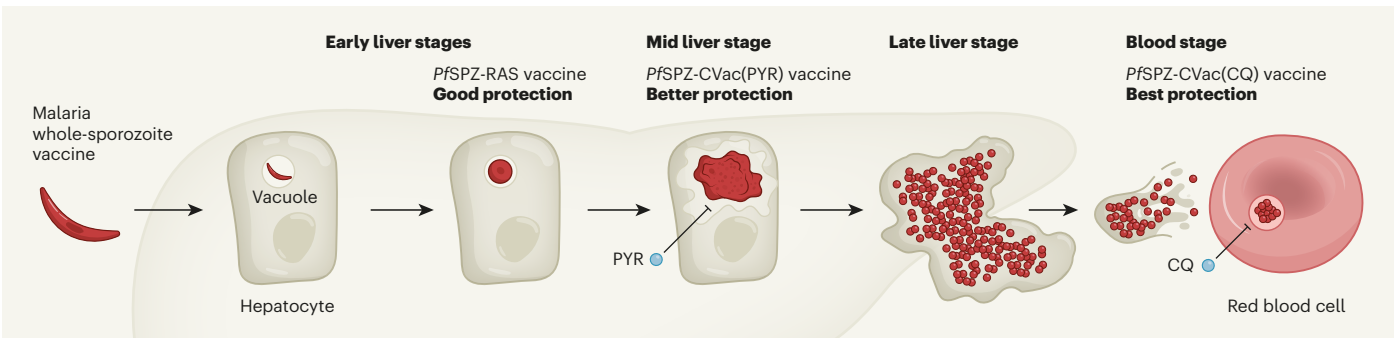

Figure 1 | Vaccine strategies. Attention is turning towards malaria-vaccination approaches that use whole *Plasmodium falciparum* (*Pf*) parasites, which are the disease-causing agent. After the parasite enters the bloodstream in a form called a sporozoite, it reaches the liver, where it resides inside a vacuole in cells called hepatocytes. The parasite develops in the liver and then returns to the bloodstream to infect red blood cells and cause illness. Previous work[8,9] indicates that vaccination using a weakened form of the parasite (*Pf*SPZ-RAS), which cannot develop in the liver, offers some protection against malaria. Mwakingwe-Omari *et al.*[3] report a clinical trial of vaccines containing whole, live parasites given with drug treatments to kill the parasite at a particular developmental stage. The *Pf*SPZ-CVac(PYR) vaccine, which harnesses the drug pyrimethamine (PYR), offered improved protection against malaria compared with that reported[8,9] for *Pf*SPZ-RAS vaccines. The best vaccine results were for the *Pf*SPZ-CVac(CQ) vaccine, which requires the drug chloroquine (CQ).

that the introduced parasites might transition to a lethal blood-stage infection, as well as evidence that blood-stage infection might itself compromise protective liver-stage immunity, has raised concerns about this approach[10].

To address these issues, Mwakingwe-Omari and colleagues report a whole-parasite vaccine, in which immunization with infectious sporozoites is followed by the administration of the drug pyrimethamine a few days later. This timing of the drug administration kills liver-stage parasites halfway through their development in the liver (Fig. 1). A low-dose vaccination using this approach was minimally protective against CHMI when tested with the same (homologous) parasitic strain (NF54, which is of African origin) as that used for vaccination. However, a fourfold increase in the dose of parasites resulted in sterile immunity in nearly 90% of vaccinated individuals. This level of protection is comparable to that achieved against the homologous parasite strain using the vaccination approach with chloroquine[10,11]. A high level of protection from the homologous strain as a consequence of vaccination using chloroquine was also confirmed by Mwakingwe-Omari and colleagues.

A considerable obstacle to the development of a successful malaria vaccine is the substantial global diversity in *P. falciparum* strains. This partially explains the lower protection conferred by high-dose *Pf*SPZ-RAS in Africa compared with the results from the CHMI trial that tested protection against the homologous strain[12,13]. To test how whole-parasite vaccination with pyrimethamine treatment might perform outside a laboratory setting, Mwakingwe-Omari and colleagues carried out CHMI using a different strain (the 7G8 strain, which is found in Brazil) from the NF54 strain used for vaccination. Impressively, the authors' vaccination strategy maintained nearly 80% sterile immunity in the 7G8 CHMI, even though the 7G8 strain is very different from the hundreds of African *P. falciparum* strains characterized so far[14], including NF54.

The immune responses underlying whole-parasite-mediated vaccination protection in humans are poorly understood. Animal models indicate that immune cells called CD8 T cells, which eliminate parasite-infected hepatocytes, have a key role[15]. Immune protection in Mwakingwe-Omari and colleagues' study correlated with higher frequencies of circulating subsets of γδ T cells, a type of immune cell shown to promote superior responses by CD8 T cells in animal models[16].

Rodent models of malaria[17] have indicated that, to mount an effective defence response to the parasite, it is important to have encounters between components of the parasite (protein fragments called antigens) that are undergoing liver-stage development and components of the immune system. Now, Mwakingwe-Omari *et al.* establish for the first time in humans that antigens from the liver-stage parasite are crucial for the induction of durable, strain-transcending immunity against *P. falciparum* infection. Furthermore, the authors' observation that pyrimethamine was not quite as protective as chloroquine hints at the potential to further enhance the immune response by using a type of vaccination in which the parasites undergo full liver-stage development but cannot progress to the blood stage of infection.

However, several issues remain that limit this type of vaccine approach for the half of humanity that is at risk of malaria. The foremost concern is that these live-parasite vaccines, administered in three doses, require stringent compliance in taking the accompanying drug, to prevent malaria caused by vaccination. This is feasible in controlled clinical trials but would be difficult to implement if vaccinating billions of people. Thus, although there is strong evidence for liver-stage-directed immunity in humans as a result of live-parasite vaccination and drug treatment, a way to intrinsically weaken the parasite in the vaccine is desirable. This would remove the need for the accompanying parasite-killing drugs and would avoid the associated safety issues. Genetically attenuated parasite vaccines, in which the parasite is weakened by an engineered deletion of genes that are essential for its liver-stage development[18], might represent a future strategy.

"There is strong evidence for liver-stage-directed immunity in humans as a result of live-parasite vaccination and drug treatment."

Another matter to consider is that any whole-parasite vaccine strategy currently requires sporozoite production in live mosquitoes, and therefore faces formidable challenges in scaling up production. This might be overcome by investments in technologies that allow large-scale manufacturing of whole-sporozoite vaccines.

Ultimately, this study by Mwakingwe-Omari *et al.* has reinforced the importance of PE antigens in the induction of protective immunity after whole-parasite vaccination. Future efforts to identify which PE antigens are recognized by CD8 T cells should also re-energize the individual-antigen vaccine approach. Both of these immunization avenues, as well as investigations into the immune responses to vaccination, should be priorities for the malaria-vaccine field, and should certainly receive renewed impetus from the work of Mwakingwe-Omari and colleagues.

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