Malaria vaccination strategy provides model for superior protection

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Malaria is a devastating disease caused by the Plasmodium parasite which is transmitted to humans by infected mosquitoes. Hundreds of millions of new cases of malaria are reported each year, and there are more than 750,000 malaria-related deaths annually. As a result, there is an urgent need for vaccines to combat infection. Now, a new study uncovers a powerful strategy for eliciting an immune response that can combat the parasite during multiple stages of its complex life cycle and describes what may be the most effective next-generation vaccination approach for malaria. The research will be published online on June 15 by Cell Press in the journal *Cell Host and Microbe.*

When an infected mosquito bites a human, the parasite "sporozoite" stage is deposited in the skin. From there, it travels to the liver cells where it copies itself many times and matures for about a week into new forms that infect red blood cells and cause the clinical symptoms of malaria. "Halting Plasmodium infection during the clinically silent liver stage represents an attractive goal of antimalarial vaccination, but is challenging because, if not complete, some parasites can get into the blood and cause disease," explains study co-author Dr. Stefan Kappe, from the Seattle Biomedical Research Institute. "Unfortunately, the complexity of the parasite and the diverse types of protection needed against malaria are the main reason why, despite decades of effort, no fully protective vaccine is ready for licensing"

Guiding the search for a better malaria vaccine thus far has been the "gold-standard" of protection from Plasmodium: vaccination with

radiation-attenuated sporozoites. Irradiating the parasites elicits extensive and random DNA damage that arrests the parasite early in the liver and provides the immune system with an opportunity to develop an immune response that can combat the native parasite. However, very high irradiated-sporozoites doses are needed to generate full liver-stage protection and there is no protection against blood stages. "In our study, we examined whether genetically attenuated parasites (GAP) generated by targeted gene deletions to stop replication late in liver-stage development were a better vaccine option," says co-author Dr. John Harty from the University of Iowa.

Using mouse malaria models, the researchers discovered that immunization with late-liver-stage-arresting GAP provided superior and long-lasting protection against liver-stage infection when compared with irradiated parasites or early-liver-stage arresting GAP. Importantly, late-liver-stage-arresting GAP also provided protection at the blood stage of infection and across different malaria parasite species, as well as by the route of immunization that can be used in humans. These findings suggest that weakening the parasite and arresting it as late in the liver as possible may have a powerful payoff, providing a large and diverse array of immune cells with optimal targets that are very effective for neutralizing the native parasite.

"Collectively, our data indicate that late-liver-stage-arresting GAP constitute a superior vaccination strategy. This underscores the potential utility of late-arresting GAP as broadly protective second-generation live-attenuated malaria vaccine candidates and a powerful model to find new parasite protein-based vaccine candidates that protect against infection in the liver and the blood," conclude Dr. Kappe and Dr. Harty.

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