New cells harnessed to ambush and kill malaria immediately upon transmission

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A change in the plan of attack against malaria—to target the infection as soon as it enters the bloodstream—has yielded exciting results for Burnet Institute scientists seeking to accelerate the development of a highly

protective malaria vaccine.

For decades global malaria vaccine research has focused overwhelmingly on immune responses that may block malaria from infecting liver cells, an essential stage of the malaria life cycle. The liver is where malaria migrates to replicate, subsequently causing massive infection of red blood cells.

Burnet's study, led by postdoctoral scientist Dr. Gaoqian Feng, set out to discover the potential for human immune cells to attack malaria from the first moment the infection is transmitted by mosquito bite.

"Immune cells that can destroy pathogens or infectious organisms are at the frontline of our immune defense, so we asked, could there be a component of the immune response that can act very early on, very soon after being bitten?" Dr. Feng said.

"We started looking at different immune cells—monocytes, macrophages—there's a range of them—and we were excited to find this early attack against malaria can happen, and the main cell that performs this attack is called a neutrophil."

The study, published in the journal *Nature Communications*, shows that neutrophils can work in concert with antibodies, which are proteins produced by the immune system that target a pathogen.

The antibodies coat the parasites, and the neutrophils deliver the knockout blow in a two-pronged attack.

"The current thinking in malaria vaccines is to stop malaria once it gets to the liver, which can take a couple of hours after the mosquito bite," Dr. Feng said.

"It's a bit like saying, we're going to build a big wall, and we'll let the invading troops come and we'll knock them off at the wall—but that's risky because if they find a way through, you're finished.

"Our thinking was that we want an immune response that happens straight away, and those two hours in the bloodstream present us with a special opportunity to attack, an opportunity that scientific research hasn't capitalized on before now."

The study's supervising author, Professor James Beeson, Head of Burnet's Malaria Immunity and Vaccines Laboratory, said little was previously known about neutrophils and their role.

"What this research has established for the first time is not just how neutrophils act, but their characteristics and an understanding of their molecular mechanisms," Professor Beeson said.

"Most importantly, what it's yielded is proof of principle to inform how to go forward with a vaccine to maximize protection against malaria."

Professor Beeson said new paths for vaccine development could include the modification of existing vaccines to better harness the antibody-neutrophil mechanism, or the redesign of vaccines based on the role of neutrophils and other approaches.

"The important thing is to harness the mechanism to get vaccines to act much earlier, and hopefully clear parasites before they have a chance to get to the liver," Professor Beeson said.

"We might find that it takes a combination of approaches to be effective—clearance of malaria from the blood by neutrophils and blocking infection of the liver."

Each year, more than 400,000 people globally die of malaria, with an estimated two-thirds of deaths among children aged under five.

The most advanced malaria vaccine, known as RTS, S, has shown only modest efficacy of 26-36 percent among infants and young children, well short of the global benchmark of 75 percent protection over two years.

More information: Gaoqian Feng et al. Mechanisms and targets of Fcγ-receptor mediated immunity to malaria sporozoites, *Nature Communications* (2021). DOI: 10.1038/s41467-021-21998-4

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