

New insights into immune responses to malaria

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Advanced technologies have been used to solve a long-standing mystery about why some people develop serious illness when they are infected with the malaria parasite, while others carry the infection

asymptomatically.

An international team used [mass cytometry](#)—an in-depth way of characterizing [individual cells](#)—and machine learning to discover 'immune signatures' associated with symptomatic or asymptomatic infections in people infected with the [Plasmodium vivax parasite](#). This uncovered an unexpected role for immune T cells in protection against [malaria](#), a finding that could help to improve the development of much-needed malaria vaccines.

The research, which was published in the journal [JCI Insight](#) was led by WEHI's Dr. Lisa Ioannidis and Associate Professor Diana Hansen, in collaboration with Professor Ric Price from the Menzies School of Health Research, Darwin, and Dr. Rintis Noviyanti from the Eijkman Institute for Molecular Biology, Indonesia.

Variable immune responses

Malaria is a parasitic disease impacting hundreds of millions of people each year. After infection, people develop immunity to the Plasmodium parasite that causes malaria—but this immunity only reduces the disease severity rather than preventing infection altogether. Despite the immense global impact of malaria, there are not yet vaccines in [clinical use](#) to prevent this disease.

The immune response to malaria is a 'double-edged sword,' Associate Professor Hansen said. "While an immune response to the parasite can prevent severe disease, in some people it is an excessive immune response—driving severe inflammation—that exacerbates malaria, causing the most severe, and potentially fatal, symptoms," she said.

"Our research has investigated the longstanding question of how immune responses differ between people with symptomatic and asymptomatic

malaria infections. We focussed on the Plasmodium vivax form of malaria, which is most common in the Asia-Pacific and Latin America. This species is a particular challenge to control as infected people can carry it for many months in the liver without symptoms."

Using the University of Melbourne's mass cytometry facility, the research team were able to undertake in-depth, multi-dimensional assessments of the immune cells in blood samples provided by people living in a vivax malaria-endemic region of Indonesia. Dr. Ioannidis said the team compared many aspects of immunity in samples from people who were uninfected, asymptotically infected, or symptomatically infected with *P. vivax*.

"In collaboration with a WEHI bioinformatics team led by Professor Gordon Smyth, we used machine learning to develop an 'immune signature' that distinguished between these three categories of samples. These signatures could be applied to new blood samples from people infected with malaria, to accurately predict the severity of their [infection](#)," Dr. Ioannidis said.

Enhancing malaria control

Dr. Ioannidis said the immune signatures revealed the key components of the [immune response](#) that drive immunity to malaria. "Antibodies produced by B cells were one important component, especially in people with high parasite loads and symptomatic disease, but we also discovered that certain types of CD4 T cells were critical to keep infections in check, preventing symptoms," she said.

"This is the first time CD4 T cells have been shown to be important for controlling asymptomatic *P. vivax* infections."

Associate Professor Hansen said the discovery could lead to better

approaches to controlling—or even eliminating—malaria. "Malaria vaccine development has focussed almost entirely on measuring antibody responses as a marker of vaccine success. Our research has revealed the important role of CD4 T cells in controlling malaria infections—and we think these cells need much more consideration when designing malaria vaccines. Because vivax malaria can persist in asymptomatic people, it is critical that vaccines activate CD4 T [cells](#) to control these low-grade infections," Associate Professor Hansen said.

More information: Lisa J. Ioannidis et al, High-dimensional mass cytometry identifies T cell and B cell signatures predicting reduced risk of Plasmodium vivax malaria, *JCI Insight* (2021). [DOI: 10.1172/jci.insight.148086](#)

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