

# Fighting Malaria on His Home Turf

*With a mix of lab studies and field trials, this scientist and his research partner are stopping the malaria parasite from disarming the immune system.*

FOR LOUIS SCHOFIELD, THE MALARIA PROBLEM IN PAPUA NEW GUINEA IS more than a passing interest. When he was a boy, his family lived on the Pacific island, where his father worked as a physician treating patients with tropical diseases such as dengue fever, typhoid, and malaria. Schofield says, “I got both metaphorically and literally exposed to some of those infections. I have no doubt that it planted some seeds in my mind.”

Now at the Walter and Eliza Hall Institute of Medical Research (WEHI) in Melbourne, Australia, Schofield has merged his laboratory studies with field trials involving children in Papua New Guinea to better understand how molecules in mosquito-borne protozoa make malaria so difficult for the human immune system to fight.

“Malaria causes more than a million fatalities every year, mainly in kids,” Schofield says. “I believe strongly that inappropriately regulated immunological reactions are responsible for a lot of those fatalities. So the thing is to identify the parasite molecules that alter the immune response.”

Most recently, Schofield and Alan Cowman, both HHMI international research

scholars at WEHI, found the molecule used by *Plasmodium falciparum*—the protozoa that causes the deadliest form of malaria—to turn off the body’s immune response.

Typically, a protein known as interferon-gamma (INF-gamma) alerts white blood cells when a pathogen enters the body. But when *P. falciparum* protozoa infect a red blood cell, they send a molecule called PfEMP-1 to the surface of the cell. PfEMP-1 shuts down the INF-gamma alarm pathway.

In 2002, Schofield discovered how another malaria parasite molecule called GPI triggers an inflammatory response in the body, sometimes with fatal side effects. He and his team suspected that other parasite molecules also contributed to skewing

the balance of the immune system. They set their sights on PfEMP-1 because they knew it mediates contact between parasites and white blood cells.

To study the function of PfEMP-1 in malaria infection, Schofield needed a parasite with an inactive form of the molecule to compare its effects on the immune system with those caused by unaltered protozoa. Schofield collaborated with Cowman, a parasite molecular biologist who had been studying the biology of PfEMP-1, to design his experiment.

PfEMP-1 had been difficult to investigate because every malaria parasite contains 50 to 60 slightly different alleles, or variants, of the gene that encodes PfEMP-1. The protozoa’s ability to switch these gene variants on and off allows it to escape detection by the immune system.

Cowman could not knock out all 60 genes. He did, however, engineer a *P. falciparum* mutant that switched off all PfEMP-1 expression.

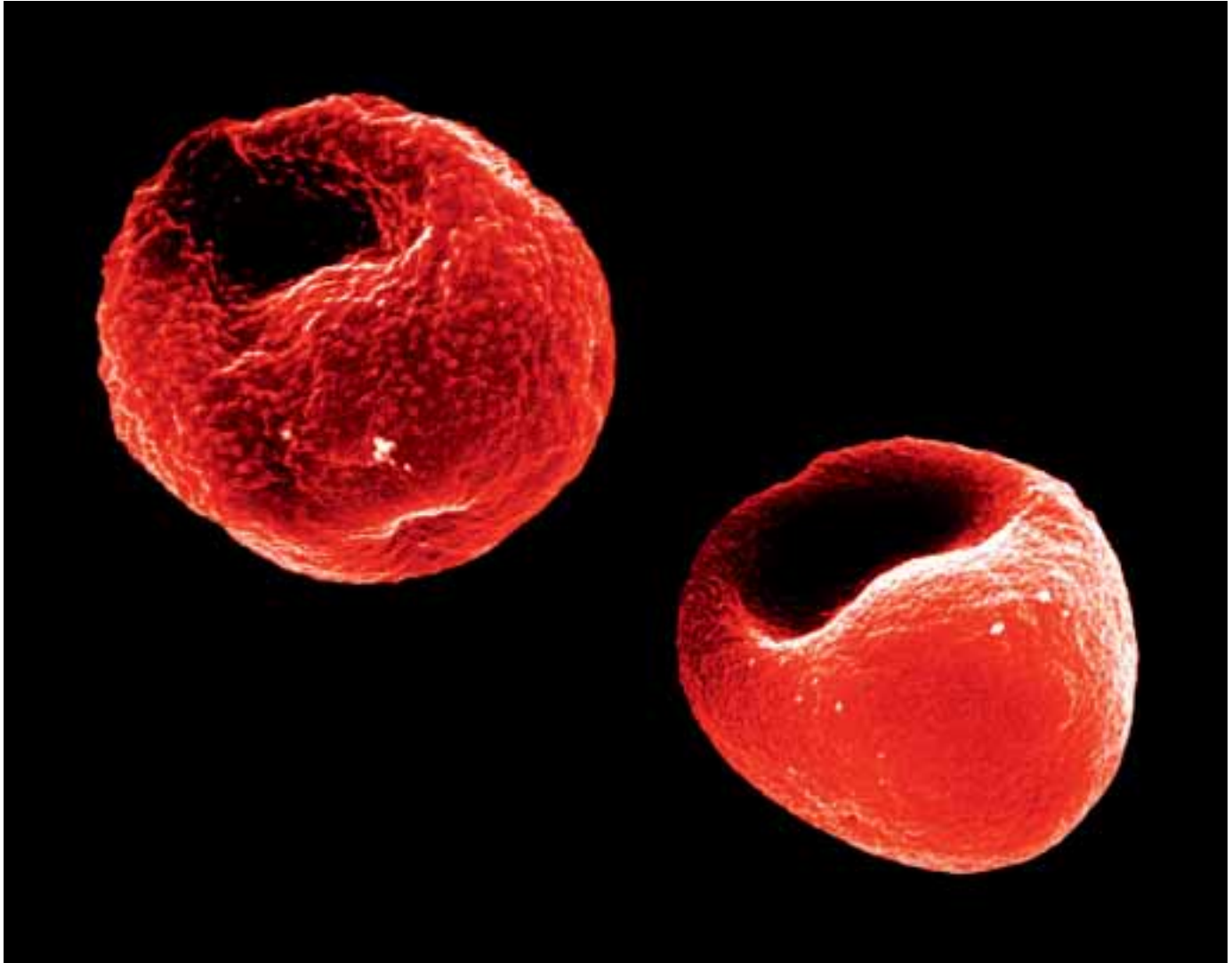
Schofield exposed isolated adult white blood cells to unmodified, or wild-type, protozoa, and to Cowman’s mutant *P. falciparum*. The mutant protozoa prompted a normal inflammatory immune response while the wild-type protozoa down-regulated INF-gamma and remained undetected by the host immune system. Schofield and

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LOUIS SCHOFIELD



Paul Fetters



Surface protrusions, called knobs, on *Plasmodium falciparum*-infected red blood cells display aggregates of PfEMP1, a protein that shuts down part of the immune system alarm pathway. The smooth appearance of the red cell on the right is due to a mutation in another protein, KAHRP, required for knob formation.

Science image: Ross Waller and Alan Cowman Photo: Czestia Markiewicz

Cowman published their results in the August 2007 issue of *Cell Host and Microbe*.

Next, Schofield intends to identify PfEMP-1's receptor in white blood cells. Then he hopes to design a field study that examines the response of white cells to wild-type *P. falciparum* or Cowman's mutant protozoa in children with different levels of susceptibility to disease. Schofield will incorporate this study into his ongoing program at the Papua New Guinea Institute of Medical Research.

At the Institute, Schofield's team works both on hospital-based studies with patients and on a longitudinal, population-based study with a group of children

in Papua New Guinea. The researchers look at genetic variation within the group to learn how it might affect the children's immune function and their risk of developing malaria.

Schofield has been studying malaria for nearly three decades, since he was 21 years old. He says that he's kept his focus because of malaria's widespread impact. Although there is practically no malaria in Australia, the disease thrives in neighboring countries—along with Papua New Guinea, it is epidemic in Indonesia and East Timor. "That's one of the motivations," adds Cowman, "It's a big problem. But also, scientifically it's incredibly interesting." ■ -SHELLEY DUBOIS



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ALAN COWMAN