KNOW YOUR ENEMY: THE PATH TO MALARIA ELIMINATION

Scientists are exposing the *Plasmodium* parasite's inner workings to FIND NEW DRUG AND VACCINE TARGETS, and stop infections from taking hold.

Every two minutes, a child in Africa dies from malaria, according to the World Health Organization. And while malaria deaths declined each year between 2000 and 2019, the disease is far from being eliminated worldwide.

In some areas, infection numbers are creeping up again. Pandemic-related disruptions to essential services, such as distributing insecticide-treated bed nets, saw 13.4 million more malaria cases and 63,000 more malaria deaths than expected over 2020 and 2021, most of which were in Africa.

"We are looking for cheap, effective and safe drugs for malaria, and to develop vaccines to protect children, especially, in sub-Saharan Africa," says Kiyoshi Kita, dean of the School of Tropical Medicine and Global Health at Nagasaki University. To find new therapeutic targets, researchers at Nagasaki University are revealing details about the parasite's life cycle and biology in the hope they can be exploited.

"IN AFRICA, I SAW SO MANY SMALL CHILDREN SUFFERING FROM MALARIA. HELPING THEM IS MOST IMPORTANT."

Of the handful of parasite species that cause malaria in humans, *Plasmodium falciparum* is the deadliest. When an infected female Anopheles mosquito feeds on a person, it injects saliva into the skin, along with the *Plasmodium* parasite in a form called a sporozoite. These sporozoites migrate to the person's liver, invade hepatocytes — the main cell type in the liver — and develop into another stage called merozoites, which are released into the bloodstream.

As a merozoite sidles up to a red blood cell, it then secretes a set of molecules that, when arranged in a specific way, allow it to slip inside. The merozoites then multiply, and burst out to infect yet more red blood cells. At this point the human host gets sick, and because their immune system is less developed, children are particularly vulnerable to illness and death.

Osamu Kaneko, from Nagasaki University's Institute of Tropical Medicine, is untangling the molecular mechanisms involved in merozoites infecting red blood cells.

He's using rodent malaria parasites because the invasion process is longer and thus easier to analyse than *P. falciparum*. "It's different from human malaria but it can help us understand how parasites invade cells," Kaneko said.

"I want to understand how the parasite is able to coordinate the molecules that are released, one by one," Kaneko said. That knowledge could lead to the development of vaccines that target one or more of these molecules, thus stopping an infection in its tracks.

▲ **A team installing insecticide-treated mosquito nets from the ceiling. These nets cover an entire room from the inside, rather than just a bed.**

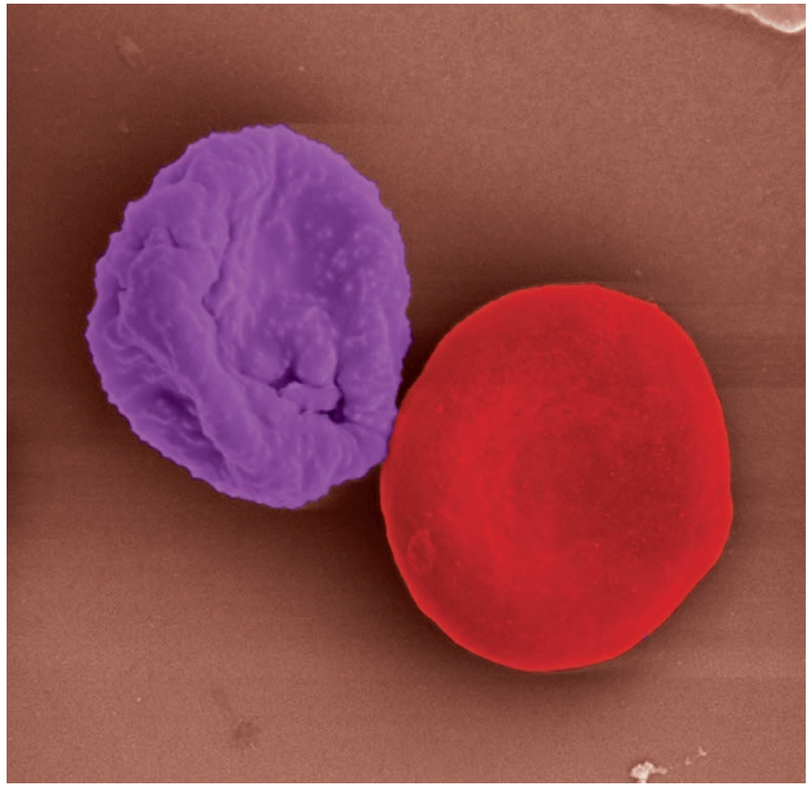
TOWARDS ELIMINATION

Nagasaki University malaria research has already moved from the lab to the real world, with human trials in malaria-endemic areas trying to slow the parasite's spread or stamp it out altogether. In 2013, Kita and colleagues reported that a combination of a commercially available supplement called 5-aminolevulinic acid (5-ALA) and sodium ferrous citrate killed *P. falciparum in vitro*. Two years later, they showed a daily oral dose of the 5-ALA/sodium ferrous citrate combination cured 60% of mice infected with a deadly form of rodent malaria and protected recovered mice from reinfection for more than 230 days.

In light of these promising preclinical results, in 2019, and supported by pharmaceutical manufacturer, neopharma Japan, researchers conducted a human trial of 5-ALA/sodium ferrous citrate against asymptomatic malaria patients in villages in Laos.

"To eliminate malaria we need to treat asymptomatic patients and clear the parasite from them too," Kita said. The data are currently being analysed, but Kita is keen to extend the trial to other parts of the world, including Africa.

To accelerate development of more drug and vaccine candidates, Nagasaki University partnered with Japanese pharmaceutical company, Shionogi & Co., Ltd. to create a collaborative research division called the Shionogi Global Infectious Diseases Division (SHINE). Shionogi senior director, Shinya Omoto said while the company is noted for its infectious disease treatments, it is also looking to expand into prophylaxis and vaccine production.



▲ ***P. falciparum*** **malaria parasites modify parasitized red blood cells to build protruding structures called knobs (right, uninfected red blood cell; left, infected red blood cell).**

DESIGNING BETTER NETS

While Kita and his colleagues are working on drugs and vaccines, Nagasaki University malaria mosquito ecologist, Noboru Minakawa, is trying to stop Anopheles mosquitoes from getting within biting distance of children in the first place. A widespread malaria control method is to sleep under a bed net, which is hung up at night and taken down again in the morning. Bed nets are usually treated with an insecticide too, but mosquitoes can rapidly develop resistance to those chemicals.

Minakawa and his colleagues conducted a trial, in western Kenya, of bed nets treated with an insecticide as well as piperonyl butoxide or PBO. Supplied by Japanese chemical company Sumitomo Chemical, PBO is a synergist that inhibits an enzyme that confers insecticide resistance in Anopheles mosquitoes. After 12 months, 45% of children living in houses without the PBO bed nets contracted malaria during that time, compared to 33% of children using PBO-insecticide nets.

But the problem with bed nets is that they tend to develop holes from constantly being hung up and brought down, or taken between houses. Sleeping children can also roll around and press against the net. Moreover, many children still sleep without nets. In another trial, Minakawa and his team gave households in western Kenya a ceiling net too — larger than bed nets, and designed to cover an entire room from the inside.

After 18 months of using ceiling nets (or not, depending on the group), Minakawa and his colleagues found 42% of children living in houses with only bed nets had been infected with malaria, and only 23% in the ceiling net cohort. "It's a huge reduction," Minakawa said.

He's currently running a trial that combines the two previous studies: installing ceiling nets made from the chemo-protective PBO-insecticide material. He expects to see an even bigger reduction in malaria rates in children, and potentially for longer than a couple of years. Because ceiling nets stay where they are all day and night — they're not exposed to the same daily wear and tear as a bed net — he's seen them last six or even seven years. "Plus there's enough insecticide in the nets to last more than five years," Minakawa said.

What is clear is that malaria won't be eliminated by nets alone, or even drugs alone — it requires multiple avenues of attack. So will the WHO meet its ambitious goal of reducing malaria incidence and deaths by more than 90% compared to 2015 levels by 2030? It's a tough ask, says Shusaku Mizukami, a researcher in malaria vaccine development at Nagasaki University.

But whether it be thwarting parasites or mosquitoes, Kita keeps his reason for Nagasaki University's malaria research front of mind: "In Africa, I saw so many small children suffering from malaria. Helping them is most important." ■

This article has been produced with assistance from Shionogi & Co., Ltd.

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