Microscopic CCTV reveals secrets of malaria invasion

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State-of-the-art video microscopy has enabled researchers at WEHI, Australia, to see the molecular details of how malaria parasites invade red blood cells—a key step in the disease.

The researchers used a custom-built lattice light sheet microscope—the first in Australia—to capture high-resolution videos of individual parasites invading red blood cells, and visualize the molecular and cellular changes that occur throughout this process. The research has provided critical new information about malaria parasite biology that may have applications for the development of much-needed new antimalarial medicines.

The research, which was published today in *Nature Communications,* was led by Ms Cindy Evelyn, Dr. Niall Geoghegan, Dr. Lachlan Whitehead, Professor Alan Cowman and Dr. Kelly Rogers.

Focusing on a deadly parasite

Malaria is a mosquito-borne disease that kills around 400,000 people globally each year. Many of the serious symptoms of malaria occur because of the invasion and growth of the Plasmodium parasite in an infected person's red blood cells, said Dr. Rogers, who is the head of WEHI's Centre for Dynamic Imaging.

"Understanding in better detail exactly how the parasite invades red blood cells may reveal new ways to stop this stage of the parasite life cycle, potentially leading to much-needed new therapies," she said.

"We used microscopy—specifically a state-of-the-art approach, lattice light sheet microscopy (LLSM) - to follow the intricate cellular and molecular changes that occur when the malaria parasite invades red blood cells. We captured the first ever high-resolution, real time and dynamic views of the parasite in action."

Ms Evelyn, who began the research as an honors student, said the research revealed many previously unrecognized aspects of parasite invasion.

"The videos we recorded showed the 'push and pull' interactions as the parasite landed on the red blood cell, and then entered the cell in an enclosed chamber—called a vacuole—where it grew and multiplied.There has long been contention in the field about whether the vacuole is derived from the parasite or the host cell. Our research resolved this question, revealing it was created from the red blood cell's membrane," she said.

Most antimalarial therapies and vaccines target the initial binding of malaria to red blood cells.

"By visualizing these processes in more detail, our research may contribute in several ways to the development of new antimalarial therapies. For example, now that we know that the parasite vacuole relies on components of the red blood cell membrane, it might be possible to target these components with medicines to disrupt the parasite life cycle. This host-directed approach could be one way to bypass the malaria parasite's propensity to rapidly develop drug resistance," Dr. Rogers said.

"LLSM may also have applications for observing the specific steps of parasite invasion that are blocked by potential new drugs—an area we are now very interested in pursuing."

New views of cells

LLSM is an advanced imaging technology that enables researchers to visualize cells and organs in unprecedented detail and in real time. Dr. Geoghegan said LLSM had changed how cells could be studied.

"In the past, the choice of microscope for an experiment had to be a compromise between capturing a lower resolution video, which revealed dynamic processes like shape changes or movement, and capturing much higher-definition still images, which provided much more detail about

how the cells and molecules are functioning," he said.

"LLSM allows us to obtain high-resolution videos of cells, which has been a game-changer for many fields of biological research.

We custom built a LLSM at WEHI—the first version of this technology in Australia. This groundbreaking microscopy has enabled us to progress multiple areas of research, including this malaria study. To achieve this, we brought together a multidisciplinary team with expertise in physics, engineering and biology—and the results of this current study have vindicated our approach."

The research was supported by the Australian National Health and Medical Research Council, an EMBO Long Term Fellowship, a Sir Henry Wellcome Fellowship and the Victorian Government.

More information: Niall D. Geoghegan et al, 4D analysis of malaria parasite invasion offers insights into erythrocyte membrane remodeling and parasitophorous vacuole formation, *Nature Communications* (2021). DOI: 10.1038/s41467-021-23626-7

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