3-D image of malaria 'conductor' aids search for antimalarial drugs

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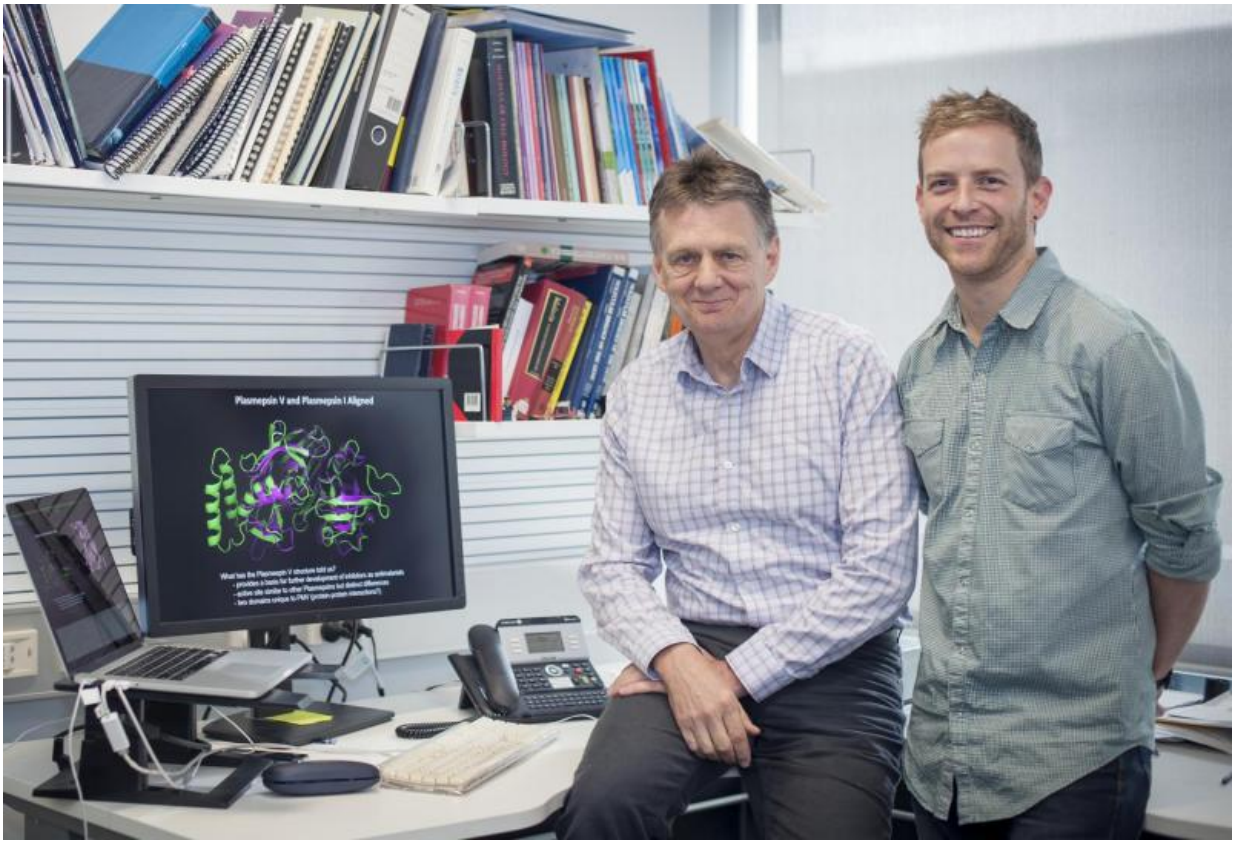

Professor Alan Cowman (left) and Dr Justin Boddey have captured the first 3-D image of a critical malaria 'conductor' protein, which could lead to new antimalarial drugs.Researchers from Melbourne's Walter and Eliza Hall Institute developed WEHI-842, a drug that blocks the malaria parasite protein plasmepsin V, killing the parasite. The discovery is a new step towards developing much needed new drugs for treating and preventing malaria. Credit: Walter and Eliza Hall Institute

The first three-dimensional image capturing a critical malaria 'conductor' protein could lead to the development of a new class of antimalarial drugs.

Researchers from Melbourne's Walter and Eliza Hall Institute developed WEHI-842, a drug that blocks the malaria parasite protein plasmepsin V, killing the parasite. The discovery is a new step towards developing much needed new drugs for treating and preventing malaria.

The research, led by Professor Alan Cowman, Dr Justin Boddey, Dr Tony Hodder, Dr Brad Sleebs and Dr Peter Czabotar was published today in the journal *Nature Structural and Molecular Biology*.

Professor Cowman said the detailed, three-dimensional molecular structure of the protein plasmepsin V was a significant step towards a new antimalarial drug.

"Plasmepsin V acts like a bus conductor, giving each protein that needs to leave the parasite a stamp of approval and a ticket to the correct destination," Professor Cowman said. "It is an important target given its critical role in the survival of malaria parasites and expression at all stages of its lifecycle".

"There has been significant interest in solving the structure of plasmepsin V, which has been a very tricky venture given the nature of the protein. Using the potent drug WEHI-842, we were able to stabilise the protein sufficiently to detail its molecular structure, which will be critical in developing this new class of antimalarial drugs."

Dr Boddey said targeting plasmepsin V would effectively kill the two species of malaria that caused significant death and disease.

"WEHI-842 is a very effective agent in preventing the growth and

survival of Plasmodium falciparum," Dr Boddey said. "Plasmodium falciparum is the most deadly form of malaria parasite, causing most of the 800,000 deaths from malaria each year. Plasmodium vivax is also particularly insidious because it can hide in the body for long periods of time without symptoms, causing disease relapses much later."

Approximately half of the world's population is at risk of contracting malaria each year, with more than 200 million people infected. Malaria kills up to 700,000 people each year, predominantly children under the age of five. Current antimalarial drugs are becoming less effective as the parasite develops resistance to the drugs, making the search for new targets that can kill all species of malaria critical.

Dr Boddey said malaria parasites were shape shifters, changing how they look and how they act throughout their lifecycle to help them evade detection and elimination in the body. "WEHI-842 is able to strongly bind to and disrupt the function of plasmepsin V, preventing the release of proteins that are critical for shaping the parasite's environment and, effectively, killing it," Dr Boddey said. "Plasmepsin V is expressed by the different shapeshifters across the lifecycle so we should be able to kill these different forms as well."

Professor Cowman said the biggest challenge for the team was developing an agent that could cross the barriers that protect the malaria parasite as it hides within the cell.

"The malaria parasite hides exceptionally well in the liver and red blood cells, with four walls between the bloodstream and the protein we are targeting," Dr Boddey said.

"We are now collaborating with a pharmaceutical company to identify drugs that act in the same way as WEHI-842, but are able to find a way through these four walls to access the parasite hidden deep inside the red

blood cell."

More information: Structural basis for plasmepsin V inhibition that blocks export of malaria proteins to human erythrocytes, *Nature Structural and Molecular Biology*, DOI: 10.1038/nsmb.3061

Provided by Walter and Eliza Hall Institute