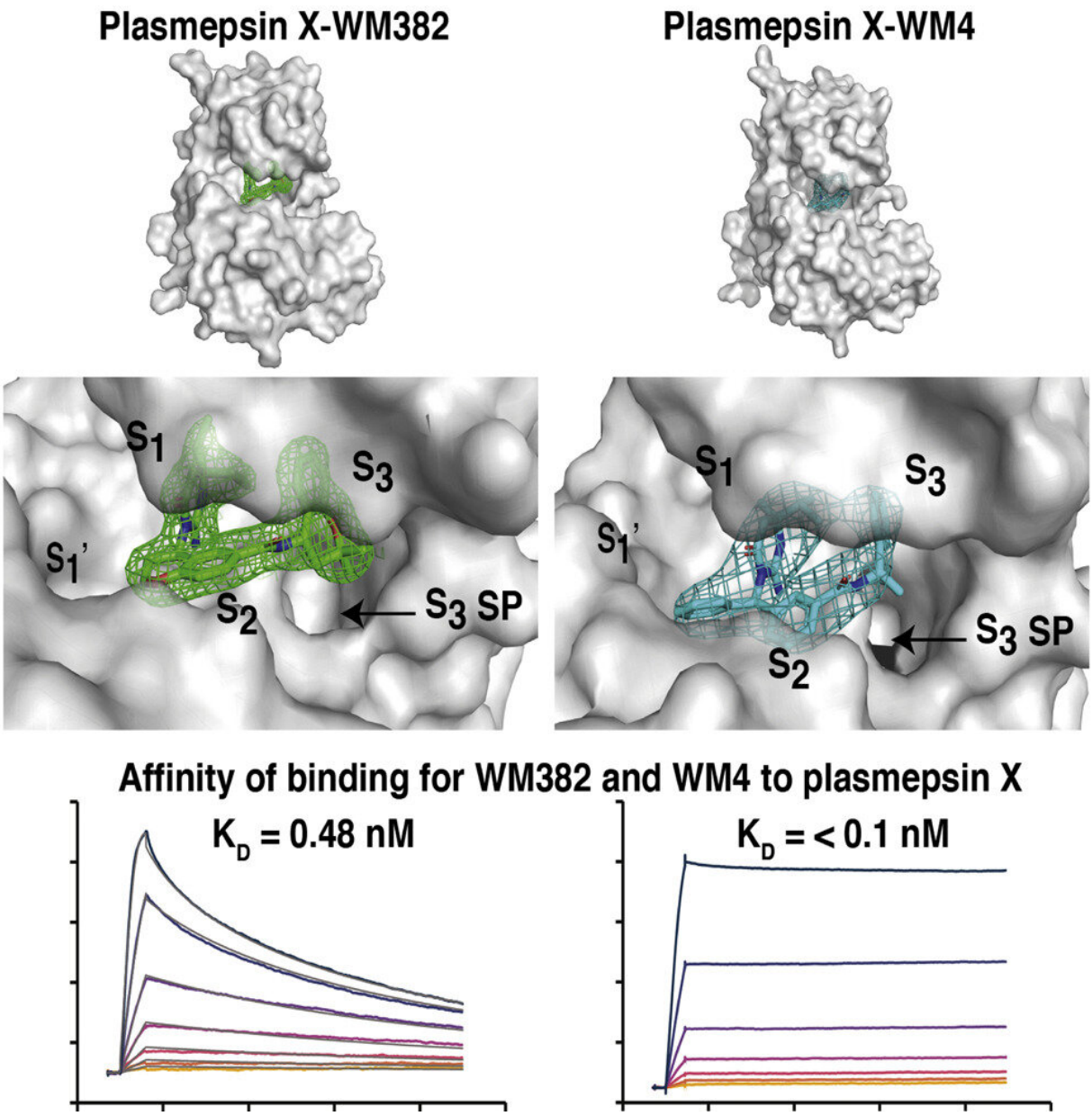
Insights into malaria parasites strengthen drug discovery pipeline

May 16 2022



Graphical abstract. Credit: *Structure* (2022). DOI: 10.1016/j.str.2022.03.018

Revolutionary 3D images have enabled researchers to understand how new anti-malaria compounds kill malaria parasites, paving the way for the next generation anti-malarial treatments.

Malaria infections are driven by Plasmodium parasites that enter the bloodstream and destroy red blood cells.

WEHI researchers, in collaboration with Merck Sharp & Dohme (MSD), have now captured the first three dimensional (3D) images that reveal how compounds work to stop the parasites from spreading in the blood.

Plasmepsin IX (PMIX) and Plasmepsin X (PMX) are enzymes made by the Plasmodium parasite family, which process and activate key proteins that enable the parasites to move in and out of red blood cells. Blocking these two enzymes stops the parasite replication in its tracks, leaving the parasite unable to multiply in the bloodstream.

WEHI researchers Dr. Anthony Hodder, Dr. Janni Christensen (now at Denmark's ExpreS2ion Biotechnologies) and Professor Alan Cowman collaborated with Dr. David Olsen and his team at MSD to create world-first 3D images that show how the activity of PMIX and PMX can be blocked through interactions with drug-like molecules.

In laboratory models, the compounds have been shown to inhibit the functions of these enzymes which blocks the parasitic lifecycle, resulting in the death of the parasite and stopping further transmission.

Published in *Structure*, the findings have allowed researchers at WEHI and MSD to make informed improvements to the design of a new

generation of compounds that could be developed for use in the fight against malaria.

Pacman effect

The two compounds used in the study, known as WM4 and WM382, are the result of a six-year collaboration between WEHI and MSD.

While the compounds have been known to kill malaria parasites, little was understood about how or why they worked.

Now researchers have visualized, for the first time, the interaction between these compounds and the PMIX and PMX enzymes at a molecular level, to show how they kill malaria parasites.

They found the compounds bind in the active site of both enzymes.

"PMIX and PMX are the equivalent of molecular scissors and can be likened to a game of pacman, where the binding site becomes the pacman's mouth," lead researcher Dr. Anthony Hodder said.

"The enzymes essentially bind the compounds in the pacman's mouth, and this stops these molecular scissors from cutting other proteins that would normally allow the parasites to freely move between and infect red blood cells."

This binding stops the Plasmodium parasites from being able to move out of an infected red blood cell and invade uninfected red blood cells.

"Using our world-first 3D images, we were able to show exactly how and why these compounds block PMIX and PMX—or the pacman," Dr. Hodder said.

Revolutionary imaging

Dr. Janni Christensen said the findings would not have been possible without the Australian Synchrotron and WEHI's X-ray crystallography technology.

"This technology allowed us to capture the first 3D images of these enzymes that can be magnified up to 100 million times in size," Dr. Christensen said.

"Seeing this with such exquisite molecular detail allowed us to make this significant finding showing how these compounds can block the activity of PMIX and PMX and stop the parasites from growing."

Collaborative power

Professor Alan Cowman, an international malaria expert and deputy director at WEHI, said his team worked alongside MSD scientist and U.S. team leader Dr. David Olsen, to gain the crucial new insights.

More than 600,000 people die from malaria every year, highlighting the urgent need for novel drugs that can be used in place of, or in combination with, existing medicines.

Professor Cowman said the 3D images have laid the foundation for new drugs to be discovered to block the Plasmepsins more effectively and prevent the invasion of these malaria parasites.

"When we know how something works, we can use this knowledge to spearhead the design of novel and even more potent compounds," he said.

"We now have the ability to engineer a new class of anti-malarial compounds to attack this disease, which continues to be a global health crisis."

More information: Anthony N. Hodder et al, Basis for drug selectivity of plasmepsin IX and X inhibition in Plasmodium falciparum and vivax, *Structure* (2022). DOI: 10.1016/j.str.2022.03.018

Provided by Walter and Eliza Hall Institute of Medical Research