New compound blocks 'gatekeeper' enzyme to kill malaria

July 1 2014

Dr Justin Boddey (L), Dr Brad Sleebs and colleagues have developed a compound that blocks the action of a key 'gatekeeper' enzyme essential for malaria parasite survival. Credit: Walter and Eliza Hall Institute

Melbourne researchers are homing in on a new target for malaria treatment, after developing a compound that blocks the action of a key 'gatekeeper' enzyme essential for malaria parasite survival.

The compound, called WEHI-916, is the first step toward a new class of antimalarial drugs that could cure and prevent malaria infections caused by all species of the parasite, including those resistant to existing drugs.

Scientists at the Walter and Eliza Hall Institute developed WEHI-916 to

block the critical malaria enzyme Plasmepsin V. The research team has previously shown Plasmepsin V is a 'gatekeeper' enzyme responsible for controlling the transport of critical proteins in and out of the parasite.

Dr Brad Sleebs, Dr Justin Boddey, Mr Sash Lopaticki, Mr Matthew O'Neill, Professor Alan Cowman and colleagues from the Walter and Eliza Hall Institute published their findings today in *PLOS Biology*.

Dr Boddey said the research team used WEHI-916 to prove the importance of Plasmepsin V to malaria parasite survival. "In this study, we developed a novel compound to target Plasmepsin V and showed for the first time that the enzyme is essential for survival of the malaria parasite" he said. "WEHI-916 is really exciting because if you block Plasmepsin V, the malaria parasite dies."

Plasmepsin V was an ideal drug target because its inhibition effectively halted the transport of hundreds of malaria proteins, Dr Boddey said. "The Plasmodium parasite needs to produce and deliver over 300 different proteins to the red blood cell to survive in the body and hide from the host's immune system," he said. "Instead of targeting individual proteins, we can block Plasmepsin V and prevent all of those proteins from leaving the parasite."

Dr Sleebs said WEHI-916 could lead to drugs that were effective in curing malaria caused by all five species of Plasmodium parasite that cause malaria. "Of the five malaria species, Plasmodium falciparum is responsible for the most deaths and is highly prevalent in Africa, while Plasmodium vivax presents major health issues for the Asia-Pacific region," he said. "Our study has shown that Plasmepsin V is a key enzyme in these two important species of the parasite and WEHI-916 can inhibit Plasmepsin V isolated from both of them. Not only does this compound enable us to prove Plasmepsin V is an excellent drug target, it is a starting point for a research program that could lead to a new class of

antimalarial drugs."

Dr Boddey said WEHI-916 was a crucial tool in proving Plasmepsin V's importance. "Researchers – including us – had been trying without success to learn more about Plasmepsin V using standard genetic techniques," he said. "Our idea was to create a drug-like compound that would block Plasmepsin V so we could investigate its importance. We found that blocking Plasmepsin V kills malaria parasites and delivered a new and effective potential drug at the same time."

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.

Institute scientists will now turn their attention to developing WEHI-916 and related compounds for human use, Dr Boddey said. "We are now examining in our insectary whether Plasmepsin V could be a target during other stages of the malaria lifecycle," Dr Boddey said. "The enzyme is present in the parasites that first infect humans in the liver, as well as in parasite forms that exit humans and infect mosquitoes. If WEHI-916 kills the parasite during these stages as well, it will mean any drugs that target Plasmepsin V can be used as a preventative as well as a cure."

More information: Sleebs BE, Lopaticki S, Marapana DS, O'Neill MT, Rajasekaran P, et al. (2014) Inhibition of Plasmepsin V Activity Demonstrates Its Essential Role in Protein Export, PfEMP1 Display, and Survival of Malaria Parasites. *PLoS Biol* 12(7): e1001897. doi:10.1371/journal.pbio.1001897 . www.plosbiology.org/article/in … journal.pbio.1001897

Provided by Walter and Eliza Hall Institute