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ASIA EDITION

Merck & WEHI discover novel class of Candidate Anti Malaria Agents

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Preclinical Data on Candidate Anti Malaria Agents Published in Cell Host & Microbe

Merck and Australia's leading biomedical research organisations Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia has announced the publication of research on the discovery of a novel class of candidate antimalarial agents that block multiple stages of the lifecycle of the parasite that causes the disease. Specifically, they identified novel dual inhibitors of plasmepsins IX and X (PMIX and PMX), two proteases that are essential to Plasmodium falciparum, the predominant cause of the most severe form of the disease.

The research was published in the latest issue of the peer-reviewed journal Cell Host & Microbe.

Professor Alan F. Cowman, Ph.D., Deputy Director, Science Strategy, Division of Infectious Diseases and Immune Defence at the Walter and Eliza Hall Institute of Medical Research and study co-author said, "Our goal is to develop new antimalarial treatments that will kill the parasite once it's present inside the human body, and we're excited to be working with Merck scientists and other leaders in the field to advance this novel class of compounds that inhibit PMIX and PMX. With drug resistance a continuing concern in our malaria-endemic world, a drug regimen that could act on novel targets at multiple stages of the malaria parasite's lifecycle would not only enhance the utility of the regimen but may potentially help eliminate a major cause of malaria in the future."

Dr David B. Olsen, Distinguished Scientist, Infectious Diseases Discovery, Merck Research Laboratories and study co-author said, "Resistance against existing treatments remains a concern, underscoring the need for new antimalarial drugs with novel mechanisms of action that can be used to treat, eliminate and eradicate malaria. We are excited about the potential of novel dual inhibitors of PMIX and PMX as potential drugs for the treatment and prevention of malaria infection."

In the blood, successive broods of malaria-causing parasites grow inside erythrocytes (red blood cells) and destroy them, releasing daughter parasites, called merozoites, that continue the cycle by invading other erythrocytes. Plasmepsins PMIX and PMX are targets in antimalarial drug discovery because they are involved in the process in which the malaria parasite invades erythrocytes and also in egress of the parasite from cells. Inhibiting PMIX and PMX blocks this process, as well as prevents maturation of certain proteins required for replication. Proper functioning of PMX is also required within merozoites to enter fresh erythrocytes.

In this preclinical research, scientists from Merck and the Walter and Eliza Hall Institute of Medical Research and the Swiss Tropical and Public Health Institute in Basel, screened a targeted library of protease inhibitors that kill the P. falciparum parasite. The two most potent in inhibiting the replication of P. falciparum in vitro were administered to mice to determine in vivo activity against P. berghei infection (a parasite that causes malaria in rodents). Although both compounds suppressed P. berghei parasitemia, they did not have desirable pharmacokinetic attributes.

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