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Scientists from Merck and the Walter and Eliza Hall Institute of Medical Research Discover Novel Class of Candidate Anti Malaria Agents that Block Multiple Stages of the Lifecycle of the Parasite

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

KENILWORTH, N.J. & MELBOURNE, Australia--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, and the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, today 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.*

“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,” said 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. “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.”

“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,” said Dr David B. Olsen, Distinguished Scientist, Infectious Diseases Discovery, Merck Research Laboratories and study co-author. “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.”

Design and results of preclinical research

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.

The researchers conducted optimization studies to identify compounds with required drug-like properties, resulting in the identification of WM382, a compound that acts as a dual inhibitor of PMIX and PMX, and inhibits growth of *P. falciparum* and *P. knowlesi,* a parasite that causes malaria in humans and other primates. Oral administration of WM382 cured mice of *P. berghei* and prevented blood infection from the liver. It also was efficacious against *P. falciparum* asexual infection in humanized mice and prevented transmission to mosquitoes. The ability of WM382 to block transmission is an important attribute for an antimalarial drug as this characteristic could reduce both the incidence and spread of malaria.

The collaborative research was funded in part by the Wellcome Trust (UK), National Health and Medical Research Council (Australia) and the Victorian Government (Australia).

About Malaria

Malaria is one of the most severe public health problems worldwide. According to the US Centers for Disease Control (CDC), it is a leading cause of death and disease in many developing countries, where the groups most affected are young children, who have not yet developed partial immunity to malaria, and pregnant women, whose immunity is decreased by pregnancy. In 2016, malaria caused an estimated 216 million clinical episodes and 445,000 deaths – most of whom were young children in sub-Saharan Africa. An estimated 90% of deaths in 2016 were in the WHO African Region. According to the World Health Organization's World Malaria Report 2017, nearly half the world's population lives in areas at risk of malaria transmission in 91 countries and territories. Direct costs of malaria (e.g., illness, treatment, premature death) have been estimated to be at least $12 billion per year.

About the Walter and Eliza Hall Institute of Medical Research

The Institute is one of Australia's leading biomedical research organisations, with a national and international reputation for performing highly influential basic and translational research. We are addressing some of the major health challenges of our time, with a focus on cancer, immune health and infection, and development and ageing. We are at the forefront of research innovation, with a strong commitment to excellence and investment in research computing, advanced technologies and developing new medicines and diagnostics. For more information, visit https://www.wehi.edu.au.

Merck's commitment to infectious diseases

For more than 80 years, Merck has contributed to the discovery and development of novel medicines and vaccines to combat infectious diseases. In addition to a combined portfolio of antibiotic and antifungal and antiviral medicines and vaccines, Merck has multiple programs that span discovery through late-stage development including four programs in Phase 2/Phase 3 clinical trials for the potential treatment or prevention of infectious diseases.

About Merck

For more than 125 years, Merck, known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2019 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

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