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NIH-funded investigators develop therapeutic compound effective against malaria

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An international team that includes NIH-funded researchers at Stanford University has developed a therapeutic compound that is effective in inhibiting *Plasmodium falciparum*, one of five species of parasite that infects people with malaria, and the strain which causes the highest number of malaria deaths. The compound specifically inactivates an enzyme complex in the parasite that is required for all of the parasite life cycle stages. This enzyme target is also important for parasite resistance to a current front-line antimalarial drug, called artimisinin.

"The impact of malaria is widespread and devastating, and there is an urgent need for approaches to maximize clinical efficacy while minimizing side effects and drug resistance," said Richard Conroy, Ph.D., director of the Division of Applied Science and Technology at the National Institute of Biomedical Imaging and Bioengineering (NIBIB), part of NIH. "This research presents a novel drug discovery approach and a new drug candidate that is selective in its target and could be used to enhance the efficacy of existing antimalarial drugs."

People who get malaria can become sick with high fevers, shaking chills, and flu-like illness. Each year, malaria sickens millions and causes hundreds of thousands of deaths. The disease poses greatest risk in warmer regions close to the equator—particularly in sub-Saharan Africa and South Asia—but there is a persistent threat that malaria could be reintroduced in the United States. It was a significant public health problem in the U.S. until about 1950.

In the study that appeared in the Feb. 11, 2016 issue of *Nature*, the research team used electron microscopy to study the structure of the proteasome, a protein complex that human cells need for recycling of proteins and to complete their cell cycle, and that the parasites rely on to rapidly divide inside host cells.

Senior author, Matthew Bogyo, Ph.D., is a professor in the Department of Pathology and the Department of Microbiology and Immunology at Stanford University. He has studied the function of the proteasome for more than 20 years, during a time when the first proteasome-based drugs became viable for treatment of multiple myeloma, a blood plasma cancer.

"I've always had an interest in the proteasome as a target," Bogyo said. "Potentially, if you could inhibit this enzyme you could inhibit the parasites at all stages of their different life-cycle stages to prevent their transmission. So it would be both curative and potentially transmission blocking." However, the first studies that demonstrated the effectiveness of proteasome inhibitors in killing malaria in mice were also toxic to the malaria-infected animals.

"We decided we needed to take a systematic approach and really screen for differences between the human and the parasite proteasome," Bogyo said. His lab teamed up with researchers at the University of California, San Francisco, who used a chemical analysis technique called mass spectrometry to develop a profile of both the malaria and human proteasome. They looked for particular protein segments that each proteasome preferred to act upon. "That tells you how the human and malaria enzymes differ from one another," Bogyo said.

The testing led the team to identify specific sequences of amino acids that the parasite and not the human proteasome preferred to act on. With this knowledge, the team designed and tested three therapeutic compounds, one of which proved superior as an inhibitor of the parasite's proteasome activity. While it was deadly to the parasite, it did not disrupt human cell proteasomes. They next tested that compound in mice with a form of malaria and showed that the proteasome-inhibiting compound almost completely eliminated the parasite, without causing any toxicity to the mice.

To advance their study further, Bogyo's team collaborated with a team at the Medical Research Council-funded Laboratory of Molecular Biology, Cambridge, U.K., to use cryo-electron microscopy (cryo-EM) to generate a high resolution image of the structure of the malaria proteosome. The researchers obtained highly refined images (to 3.6 Angstroms—or 3.6 ten-billionths of a meter) which provided a detailed view of the proteosome's molecular structure, including the inhibitor compound bound to the proteasome. "You previously weren't able to get such high-resolution images by cryo-EM, but recent advances in both instrumentation and the methods used to refine the images have dramatically changed the field of structural biology" Bogyo said.

Using these images, Bogyo's team determined that the parasite is most sensitive to the inhibitor compound during

two stages of the parasite's life cycle that occur within the human or animal host's blood. When mosquitos draw blood from a host treated with the protease inhibitor, the blood no longer contains parasites that the mosquito can subsequently transmit to another host.

The potential for malaria parasites to become resistant to medication is an ever present concern for the global health community. Bogyo's collaborators at the University of Melbourne, Australia, recently showed that P. falciparum has slowly been acquiring mutations that make it more resistant to artimisinin, which is one of the front line therapies currently used to treat malaria. They had shown that the mutations strengthen a pathway that helps the parasites deal with the stress from the drug. Moreover, they showed that the stress pathway requires the proteasome. Inhibiting the proteasome in the parasite, therefore, has the potential to prevent the emergence of artimisinin-resistant parasites.

"That's what we're really excited about," Bogyo said. "Even at a low dose of the drug you could potentially put enough pressure on the parasite so that resistance to artimisinin would be much harder to attain for the parasite. There is also the possibility that different types of drugs may also work by inducing stress in the parasite. If you add on top of that a proteasome inhibitor, you're going to get a synergistic effect."

Bogyo and his team continue to work to improve the potency of the compound and to develop a formulation that could be administered orally so that the new compound could be used in combination with existing anti-malarial drugs. They will need to conduct more optimization and testing before the compound can be tested in humans.

"The paper was a proof of concept that it's a viable strategy," Bogyo said of his study. "It was hard to sell the viability of the proteasome as a drug target because it was hard to convince people that it is possible to get around the toxicity issues of proteasome inhibitors. It's finally becoming clear that it is a feasible approach."

Source:
National Institute of Biomedical Imaging and Bioengineering
