Enzymes possible targets for new anti-malaria drugs

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Researchers at the Perelman School of Medicine at the University of Pennsylvania, Monash University, and Virginia Tech have used a set of novel inhibitors to analyze how the malaria parasite, Plasmodium falciparum, uses enzymes to chew up human hemoglobin from host red blood cells as a food source. They have validated that two of these parasite enzymes called peptidases are potential anti-malarial drug targets. The research appeared in an early online edition of the *Proceedings of the National Academy Sciences.*

"The basis for this research was to use small molecule inhibitors to help understand the biology of the malaria parasite and to find new drug targets as drug-resistant parasites necessitate the discovery of new antimalarials," says Doron C. Greenbaum, PhD, assistant professor of Pharmacology at Penn, who lead the collaborative study.

The P. falciparum parasite, delivered in a mosquito bite, causes malaria once it takes up residence in the human host's red blood cells and begins to digest hemoglobin, the protein that carries oxygen. The parasite multiplies and is picked up from the bloodstream when the mosquito feeds. Scientists are interested in determining which enzymes are responsible for generating amino acids from the hemoglobin in the feeding process.

Two enzymes, called aminopeptidases, have been proposed as being responsible for releasing single amino acids from proteins, or peptides. However, "there has been controversy regarding where this takes place

and which enzymes are responsible," said Michael Klemba, associate professor of biochemistry with the Vector-Borne Infectious Disease Research Group at Virginia Tech, who collaborated on the evaluation of new aminopeptidase inhibitors with Greenbaum's lab. "It has been difficult to study their specific roles in breaking down hemoglobin."

The Penn team developed chemical genetic tools called activity-based probes that enabled the researchers to specifically inhibit one or the other of the enzymes. "When we inhibited the parasite enzyme PfA-M1, it blocked hemoglobin degradation, starving the parasite to death. While inhibition of the leucyl aminopeptidase showed it to have an important but distinct role earlier in the parasite's life cycle within the red blood cell. Our collective data suggest that these two MAPs are both potential antiparasitic drug targets," explains Greenbaum.

"Dr. Greenbaum's team developed the probes and Virginia Tech's researchers tested the probes on purified enzymes and determined the potency of the probes against each of the two aminopeptidases," said Klemba. "Dr. Whisstock's team at Monash University did the structural biology, providing the high-resolution atomic structure of the enzymes."

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