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Researchers Identify New Target for Malaria Drug Development

Deducing the role of a crucial protein, researchers have discovered one of the malaria parasite's top survival strategies. Their findings could lead to desperately needed drugs against the disease.

Daniel E. Goldberg of HHMI at Washington University School of Medicine in St. Louis and colleagues have figured out how the malaria parasite, *Plasmodium*, transforms the potentially lethal remains of its food into harmless solid waste.

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— Daniel E. Goldberg

Living inside red blood cells, the malaria parasite feeds on the oxygen-carrying pigment hemoglobin. But like a gourmet who dines on puffer fish—a delicacy that can prove poisonous—*Plasmodium* must be careful to avoid being killed by heme, a toxic byproduct of hemoglobin digestion.

"So *Plasmodium* ingests hemoglobin and deposits it into a digestive vacuole," Goldberg explained. "The heme that pops out is polymerized into a non-toxic crystalline lattice called hemozoin, and the parasite then feeds on the globin."

Publishing in the January 12 issue of the journal *Science*, Goldberg, David J. Sullivan, Jr., an HHMI associate and postdoctoral fellow at Washington University, and research associate Ilya Y. Gluzman showed that an enzyme called histidine-rich protein II (HRP II) catalyzes this heme polymerization.

In the lab, the researchers first demonstrated HRP II's presence in the malaria parasite's digestive vacuole. They then incubated HRP II in test tubes filled with heme. HRP II readily converted the toxic heme to harmless, sludgy hemozoin.

Now that heme detoxification is understood, researchers can learn more about how top antimalarial drugs like chloroquine work. The team found that

chloroquine inhibits HRP-mediated polymerization, leaving free-floating heme to kill the malaria parasite.

Scientists may now be able to modify chloroquine or design other drugs to block heme's breakdown. "There is an urgent need for new drugs now that vast areas of the world have substantial chloroquine resistance," Goldberg noted.

The World Health Organization estimates that 300 million people are infected by the malaria parasite. Malaria kills more than 1 million people—mostly children—every year.