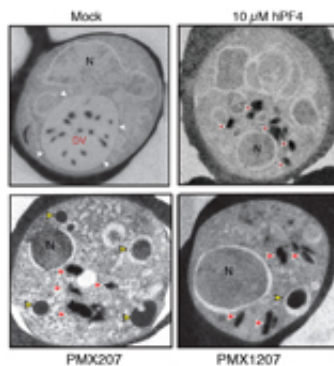


# Team mimicking a natural defense against malaria to develop new treatments

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Transmission electron micrograph images reveal lysis of the parasite digestive vacuole (DV) upon treatment with human PF4 (top right), or the small molecules PMX207 and PMX1207 (bottom) as shown by the dispersal of hemozoin fragments throughout the cytoplasm (red arrowheads) and undigested hemoglobin-containing vesicles (yellow arrowheads). Mock-treated control (top left) shows complete integrity of the DV membrane (white arrowheads), encapsulating all hemozoin crystals. (N: parasite nucleus). Credits: Melanie G. Millholland and Doron C. Greenbaum, Perelman School of Medicine, University of Pennsylvania

(Medical Xpress)—One of the world's most devastating diseases is malaria, responsible for at least a million deaths annually, despite global efforts to combat it. Researchers from the Perelman School of Medicine at the University of Pennsylvania, working with collaborators from Drexel University, The Children's Hospital of Philadelphia, and Johns Hopkins University, have identified a protein in human blood

platelets that points to a powerful new weapon against the disease. Their work was published in this month's issue of *Cell Host and Microbe*.

Malaria is caused by parasitic microorganisms of the *Plasmodium* genus, which infect [red blood cells](#). Recent research at other universities showed that [blood platelets](#) can bind to infected red blood cells and kill the parasite, but the exact mechanism was unclear. The investigators on the [Cell Host and Microbe](#) paper hypothesized that it might involve host defense peptides (HDP) secreted by the platelets.

"We eventually found that a single protein secreted when platelets are activated called human platelet factor 4 [hPF4] actually kills parasites that are inside red cells without harming the red cell itself," explains senior author Doron Greenbaum, PhD, assistant professor of Pharmacology, whose team studies innovative ways to fight malaria. The hPF4 targets a specific organelle of the [Plasmodium falciparum](#) parasite called the digestive vacuole, which essentially serves as its "stomach" for the digestion of hemoglobin. The investigators found that hPF4 destroys the vacuole with a deadly speed of minutes or even seconds, killing the parasite without affecting the [host cell](#).

While host defense peptides appear to be attractive [therapeutic agents](#), the expense of manufacturing this protein lessens its potential impact on the treatment of malaria. Greenbaum and colleagues set out to discover whether [synthetic molecules](#) mimicking the structure of HDPs could have similar beneficial effects against the *Plasmodium* parasite. After screening approximately 2000 small molecule HDP mimics (smHDPs) developed by biotech company PolyMedix, Inc. of Radnor, PA, Greenbaum and his team found that "all of the best hits had the same mechanism of action against *Plasmodium* parasites."

Like the natural hPF4 found in platelets, the most effective smHDPs tested targeted only infected red blood cells, attacking and destroying the

parasite in exactly the same way, but with even greater potency and speed. "The smHDPs get into infected red cells and lyse or basically destroy the digestive vacuole or stomach of the parasite more rapidly than the hPF4 protein," Greenbaum notes. "The protein from platelets is about 25 times less potent, but the surprising thing is they act with the same mechanism. With ease, within seconds, they destroy the vacuole of the parasite."

Greenbaum's team settled on two compounds, PMX1207 and PMX207, for testing in mouse models of malaria. Both compounds significantly decreased parasitic growth and greatly improved survival rates, providing further confirmation of the potential of smHDPs as antimalarial agents. The work, Greenbaum says, shows that "we can translate a natural arm of the innate immune system in platelets to drug-like small molecules that we are honing to become potent, selective, potentially less toxic, and cheaper to make as an antimalarial."

Aside from their great effectiveness, smHDPs may have several other advantages over other antimalarial therapies. As *Plasmodium* inevitably adapts and becomes resistant to a particular drug therapy, the efficacy of that treatment decreases and survival rates drop. By mimicking the body's own natural defenses, the new HDP-centered approach could avoid that pitfall. "Certainly with malaria we've had a lot of problems in the last 20 years with resistance," Greenbaum explains. "One of the unique features of the synthetic HDPs is that studies show that pathogens have a difficult time generating resistance to them, because they attack membranes, not proteins. So they might be intrinsically more difficult to become resistant against."

Although Greenbaum's team focused mostly on the chronic red-blood-cell stage of malaria, their HDP-mimic also shows promise against other stages of the disease. "We think that the mimics would be useful as a transmission-blocking therapeutic," Greenbaum says. "In other words,

you prevent transmission from human to mosquito and therefore back to human again. We have positive data for those two stages. It's becoming increasingly more important in antimalarial drug development that people think more and more about multistage inhibition."

The next step for Greenbaum's team is to further hone the selectivity and potency of the smHDP compounds, while developing them into drugs that can be orally administered. As Greenbaum explains, practical antimalarials need to be "taken as pills rather than having to be used intravenously, which is not going to be appropriate for treatment in endemic countries, especially in more rural environments."

Provided by University of Pennsylvania School of Medicine

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