Modified bone drug kills malaria parasite in mice

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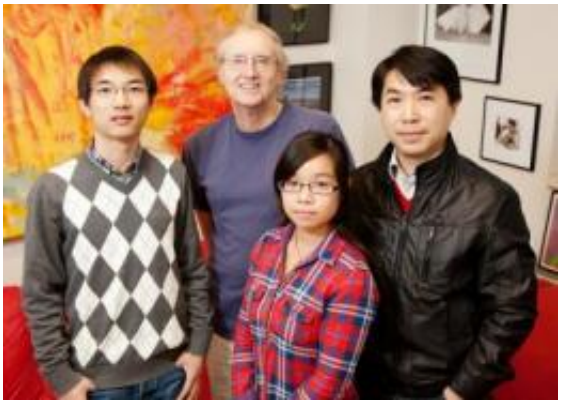

University of Illinois chemistry professor Eric Oldfield (in blue, center) and colleagues (from left to right) graduate assistant Wei Zhu, graduate student Xinxin Feng, and research scientist Yonghui Zhang found that a modified bone drug killed the malaria parasite in mice. Credit: L. Brian Stauffer

A chemically altered osteoporosis drug may be useful in fighting malaria, researchers report in a new study. Unlike similar compounds tested against other parasitic protozoa, the drug readily crosses into the red blood cells of malaria-infected mice and kills the malaria parasite. The drug works at very low concentrations with no observed toxicity to the mouse.

The study appears in the *Proceedings of the National Academy of Sciences*.

The researchers found the drug by screening a library of about 1,000 compounds used in previous efforts to target an important biochemical pathway (called isoprenoid biosynthesis) in cancer and in disease-causing organisms. The new drug lead, BPH-703, inhibits a key enzyme in isoprenoid biosynthesis that enables the malaria parasite to sustain itself and defend itself from the host immune system. The drug has little effect on the same chemical pathway in human or mouse cells, said University of Illinois chemistry professor Eric Oldfield, who led the study.

The lead compounds are chemically modified forms of the osteoporosis drugs Actonel (Risedronate) and Zometa (Zoledronate), Oldfield said. Risedronate and Zoledronate potently block isoprenoid biosynthesis, but are unable to get across the membrane of red blood cells to get to the parasite. The modified forms include a long lipid tail that helps them pass through the lipid-rich membrane of red blood cells, and also enhances the drug's ability to bind to the target enzyme, geranylgeranyl diphosphate synthase (GGPPS), he said.

"We found that compounds that were really active had a very long hydrocarbon chain," Oldfield said. "These compounds can cross the cell membrane and work at very low concentrations."

The World Health Organization estimates that malaria killed 708,000 to 1.003 million people in 2008, most of them in Sub-Saharan Africa and Asia. The malaria parasite has evolved resistance to nearly every drug used so far to combat it, and while some of these drugs still work – especially when used in combination – drug-resistant malaria strains are always emerging.

"It's important to find new drug targets because malaria drugs last only a few years, maybe 10 years, before you start to get resistance," Oldfield said. "The parasites mutate and then you lose your malaria drug."

"We are the first to show that the enzyme GGPPS is a valid target for malaria," said study co-author Yonghui Zhang, a research scientist in Oldfield's lab and inventor of the lead compound, BPH-703. "Our work gives a new direction to find new antimalarial drugs."

More information: "Lipophilic analogs of zoledronate and risedronate inhibit Plasmodium GGPPS and exhibit potent anti-malarial activity," *Proceedings of the National Academy of Sciences.*

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