

# Malaria-infected mice cured by 1 dose of new drug

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Johns Hopkins University researchers have cured malaria-infected mice with single shots of a new series of potent, long lasting synthetic drugs modeled on an ancient Chinese herbal folk remedy.

The team also has developed several other compounds which defeated the febrile disease in rodents after three oral doses.

These peroxide compounds, containing a crucial oxygen-oxygen unit, promise not only to be more effective than today's best malaria remedies, but also potentially safer and more efficient, said research team leader Gary Posner, Scowe Professor of Chemistry in the Krieger School of Arts and Sciences at Johns Hopkins.

An article about the team's work is slated to appear on the Web on April 17 in the ASAP section of *The Journal of Medicinal Chemistry*.

"We are disclosing, for the first time, the curative activity of a new generation of compounds that are long-lasting and therapeutic, even when used by themselves," Posner said. "Older drugs in this family of peroxide antimalarials also are known to be fast-acting, but they are unfortunately short-lived and not curative when used by themselves."

Though they say their results are very promising, the researchers caution that the new compounds must be thoroughly tested for safety and for how they are absorbed, distributed and metabolized in, and eliminated from, rodents' bodies before human tests begin.

Malaria afflicts between 300 million and 500 million people a year, killing between 1.5 million and 3 million, mostly children and mostly in developing nations. The parasite that causes the disease is spread by female mosquitoes feeding on human blood. The most commonly fatal species of the malaria parasite now shows strong resistance to most current treatments, making the development of effective new drugs a worldwide priority.

Since 1992, Posner and his team, which includes collaborator Theresa Shapiro, professor and chair of clinical pharmacology at the Johns Hopkins School of Medicine, have been tackling that challenge by designing a series of peroxide compounds, called trioxanes.

"As a class, these compounds have proven to be unusually valuable in several ways, from their brisk and potent antimalarial activity to their lack of resistance and cross-resistance with other antimalarial agents," Shapiro said.

The Johns Hopkins trioxanes mimic artemisinin, the active agent in a Chinese herbal drug used to treat malaria and other fevers for thousands of years. Artemisinin comes from the *Artemisia annua* plant, an herb also known by a variety of names including sweet wormwood.

The oxygen-oxygen unit in the peroxides causes malaria parasites essentially to self-destruct. The parasites digest hemoglobin, the oxygen-carrying pigment of red blood cells, and, in the process, release a substance called heme, a deep-red iron-containing blood pigment. When the heme encounters peroxides, a powerful chemical reaction occurs, releasing carbon-free radicals and oxidizing agents that eventually kill the parasites.

But the first generation of trioxane drugs also had a number of shortcomings, including a half-life of less than one hour. (A drug's half-

life is the amount of time it takes for half of it to be metabolized.) Posner and team believe that their new compounds address those disadvantages.

"Our semi-synthetic artemisinin-derived compounds successfully overcome the disadvantages of their first-generation predecessors," he said. "Most important is their curative activity after a single, low dose, which is distinctly unusual. But based on our intentional design, they may also have a longer half-life in animals. We also designed them to be more lipophilic, meaning they have an enhanced ability to dissolve in fats and thus to arrive inside malaria-infected red blood cells."

In addition, the new compounds are far less likely to break down into toxic substances when they are metabolized in the test animals' bodies, making them potentially safer than their predecessors.

Although the substance is inexpensive by Western standards, the widespread use of artemisinins in the developing world remains limited, in part by availability and the cost of separating the active ingredient from the *Artemisia annua* plant. Posner and his team contend that the potency and curative activity of their compounds provide "a substantially more efficient and economical use of the price-setting natural product."

Source: Johns Hopkins University

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