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## New Malaria Drug Candidate Holds Promise

By GAUTAM NAIK

An international team of scientists has identified a promising drug candidate that represents an entirely new class of medicines to treat malaria, one of the biggest killers in the developing world.

The new drug was shown to be effective when tested in a small number of mice, according to a study appearing in the journal *Science*. Human trials, backed by Swiss pharmaceutical giant Novartis AG, could begin later this year.



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People give blood at a malaria screening near the Thai-Cambodian border. Health officials are always on the lookout for drug-resistant parasites.

The discovery comes amid two key developments in the fight against the mosquito-borne illness. Several parts of Africa are showing a decline in malaria deaths, thanks to wider use of insecticides and bed nets to ward off mosquitoes that carry the disease, as well as use of artemisinin, a potent drug.

At the same time, there are worrying signs that the malaria parasite in parts of Southeast Asia is becoming resistant to artemisinin, which is the mainstay of combination therapy for as many as 100 million patients world-wide. Resistance has already rendered some older therapies less effective.

"We welcome a new class of drug because it could help us stay one step ahead of the parasite," said Robert Newman, director of the global malaria program at the World Health Organization, who wasn't involved in the *Science* study. However, he cautioned, "it's a long route to making the drug marketable ... many drugs fall by the wayside."

The malaria parasite can cause fever, joint pain and death. Last year, there were an estimated 240 million cases of malaria. Of total deaths, 91% occurred in Africa and 85% were children under the age of five, according to the WHO. But the battle against malaria is making progress, and a potent new drug could help sustain the momentum.



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A mosquito on the prowl

In 2009, malaria deaths world-wide fell to 836,000 from more than one million a few years earlier, including declines in Eritrea, Rwanda, Zambia and Zanzibar. Over the past decade, malaria cases have fallen in nine countries in Africa and in 29 elsewhere.

Most anti-malaria compounds being tested today are derivatives of existing drugs. Many common medicines treat malaria by essentially making the parasite's blood meal toxic. For other medicines, the mechanism is more of a mystery, said Thierry Diagana, co-author of the Science study and

malaria program head at the Novartis Institute of Tropical Diseases in Singapore. Finding a drug that can kill malaria in a new way is hard.

When malarial parasites infect people, they spend part of their life cycle in the blood and part of it in the liver. In 2007, Elizabeth Winzeler of the Scripps Research Institute in La Jolla, Calif., who also works for Novartis, used robots to screen 12,000 naturally occurring chemicals against *Plasmodium falciparum*, the deadliest malaria parasite. The chemicals were supplied by Novartis, which leads a big effort to develop drugs for tropical diseases. Dr. Winzeler and colleagues at Novartis and elsewhere came up with NITD609, a compound that killed two species of parasites in their blood stage and also proved effective against drug-resistant strains.

The drug, a class of compounds known as spiroindolones, was then tested in mice. A mouse with malaria usually dies within a week. But when NITD609 was orally given to five infected mice, they were cured with no side effects. Other mouse tests also showed promising results.

"The next step would be to go into humans" for early-stage safety testing, said Dr. Winzeler. "As far as I can tell, there are no red flags."

Further studies are in the works, and "provided the outcomes of these studies are favorable, the compound could progress to clinical trials later this year," a Novartis spokeswoman said.

What makes the discovery unusual is that it harks back to an older way of finding novel drugs. The modern, "molecular" approach is to first identify a protein vital to the survival of the malaria parasite, and then screen various drugs until one is found that targets the protein. In the past few years, this approach has been tried on millions of compounds against malaria, with modest success.

The more traditional way is to bombard the entire parasite with various chemical compounds, and see what happens. The hitch is that even if a particular compound is effective, no one knows exactly how it worked. That uncertainty can make it harder to develop the drug for people.

Still, Dr. Winzeler opted for the traditional approach, which yielded a pre-clinical candidate in three years—quick by industry standards. She and her co-authors then figured out that the compound acted on a protein called PfATP4, which allows substances to cross cell membranes. No other malaria drug acts on this protein, though its exact mechanism has yet to be pinned down.

"This approach is upside down. It flies in the face of modern drug discovery," said Tim Wells, chief scientific officer at the Medicines for Malaria Venture, a Swiss-based nonprofit group that helped pay for the Science study.

Other funders, besides Novartis, included U.K.-based Wellcome Trust, the U.S. National Institutes of Health and the Keck Foundation.

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