New compound shows promise against malaria

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Credit: CDC

Malaria parasites cause hundreds of millions of infections, and kills hundreds of thousands of people annually, mostly in Africa. And in recent years the most dangerous malaria parasite, *Plasmodium falciparum*, has become increasingly resistant to the main anti-malarial drugs. Now, an international team of researchers shows that some members of a class of compounds called oxaboroles, which contain the

element, boron, have potent activity against malaria parasites. The research is published ahead of print June 6 in *Antimicrobial Agents and Chemotherapy*, a journal of the American Society for Microbiology.

"We demonstrated that certain oxaboroles, selected from a large library produced by collaborating chemists, had potent activity both against cultured malaria parasites, and in an animal model of malaria," said Philip Rosenthal, MD, Professor, Department of Medicine, the University of California, San Francisco.

Additionally, the researchers gained insight into the mechanism of action of the compounds, knowledge that could be important for refining new antimalarial drugs based on oxaboroles, said Rosenthal. "New antimalarial drugs, ideally directed against novel targets, are greatly needed."

To that end, the investigators demonstrated that the mechanism of action likely involved an enzyme that is required for protein synthesis. They accomplished this by growing the malaria parasites in the laboratory and treating them with the oxaboroles, over generations. With time and generations, the parasites became increasingly resistant to the oxaboroles.

The investigators then performed whole genome sequencing, both on the resistant parasites, and on the original non-resistant P. falciparum, which had been stored for this comparison. They used the sequences to look for mutations in the resistant parasites that were absent from the non-resistant ones. "We consistently found them in this one gene," said Rosenthal. That gene, for the aforementioned enzyme that is involved in protein synthesis, is called the leucyl tRNA-synthetase (LeuRS) gene.

Thus, the interaction between the oxaboroles and the LeuRS enzyme is presumably what inhibits that enzyme, killing P. falciparum, said

Rosenthal. Ultimately, Rosenthal's collaborators at Anacor Pharmaceuticals, Inc., Palo Alto, CA, may study that interaction, so that they can tweak oxaboroles to improve their properties, said Rosenthal.

As for the resistance to oxaboroles that developed in the lab, Rosenthal said did not mean that resistance would develop under clinical conditions. "You can select for just about anything in the lab," said Rosenthal. Furthermore, in malaria, as in the case of other dangerous diseases, such as HIV infection and tuberculosis, usually more than one drug is given to patients, which makes it much harder for the pathogen to develop resistance.

Although the research is an important first step, the investigators noted in their paper that developing antimalarials is particularly challenging. "In addition to obvious requirements for safety and effectiveness, antimalarial drug candidates should meet additional criteria, including rapid clinical response, requirement for no more than three days of treatment (and ideally single-dose treatment), oral bioavailability, low tendency to select for drug resistance, lack of cross resistance with existing antimalarials, safety in children and pregnancy, and low cost of production."

Oxaboroles appear promising on all counts. Among other things, safety of the general class has been demonstrated even in human trials of class members, though for purposes other than as antimalarials. Oxaboroles are also not difficult to synthesize, which would make them relatively inexpensive.

Nonetheless, no drug is ever a sure bet at this stage of development, and in the best case, a number of years will pass between the present, and approval of a new drug for malaria. But the potential prize is mitigation of untold misery.