NEW ANTIMALARIAL TARGET IS FOUND

Discovery could lead to a new class of drugs to treat malaria

Scientists have found a compound that potently inhibits a novel target protein in the malaria parasite, including forms of the parasite resistant to the classic antimalarial drug chloroquine. The compound could portend a new class of agents to fight malaria.

Malaria, an infection caused by the protozoan Plasmodium falciparum and transmitted by mosquitoes, causes high fever, body aches, and often death, particularly among children. Despite decades of effort to eradicate the disease, it still kills more than 1 million people per year, mostly in Africa. Current medications can’t adequately address the problems posed by malaria worldwide, and new treatments that are more effective, cheaper, and easier to distribute are urgently needed.

One problem is that few targets for antimalarial drugs are known. Now, pharmacology professor Jun O. Liu of Johns Hopkins University School of Medicine and coworkers have identified a methionine aminopeptidase (MetAP) enzyme from P. falciparum as a new molecular target for malaria treatment. And by screening a 175,000-compound library, they were able to find a lead compound called XCII that inhibits the enzyme with good potency (Proc. Natl. Acad. Sci. USA 2006, 103, 14548).


XCII inhibits MetAP Ib selectively without blocking the activity of the other three MetAPs encoded in the P. falciparum genome. The compound shows good activity against both chloroquine-sensitive and chloroquine-resistant strains of the malaria parasite in a mouse model. Improving the selectivity and in vivo potency of XCII analogs, efforts the researchers are currently pursuing, “may lead to the development of a novel class of antimalarial agents,” they note in their paper.

Peter K. Chiang, chief scientific officer of Pharmadyn, in Sunnyvale, Calif., says that the new study is proof of concept of earlier observations by his group that inhibiting MetAP enzymes has antimalarial and antiparasitic effects. The Johns Hopkins study “is an important milestone discovery pointing to a new paradigm in using MetAP inhibitors as novel antimalarial agents to circumvent malaria drug resistance,” Chiang says.

Chemistry professor David H. Peyton of Portland State University, in Oregon, a specialist in antimalarial drug design, says, “It is to be hoped that this lead compound will yield a productive search for a class of drugs that might help to alleviate the disaster that is found through much of the developing world—drug-resistant strains of malaria.”

MetAPs are protease enzymes, and “there are currently no protease-directed antimalarial drugs in use,” says assistant professor of pathology Matthew S. Boggo of Stanford University School of Medicine, “so compounds like XCII are likely to be active against the current resistant strains of the parasite.” Boggo notes that it will be interesting to compare XCII and related agents with another set of protease inhibitors that are being developed by professor of medicine Philip Rosenthal of the University of California, San Francisco, in collaboration with GlaxoSmithKline through the Medicines for Malaria Venture, a cooperative public-private effort to discover, develop, and distribute new antimalarial drugs.

Rosenthal, whose group is investigating inhibitors of cysteine proteases, notes that the key advance in the new study is not that XCII is a protease inhibitor per se but that the Johns Hopkins group found a new antimalarial target, of which there are currently very few, and used high-throughput screening to identify a lead compound that hits it.

MALARIA FIGHTERS Liu (far right), Sullivan (from left), grad student Curtis R. Chong, and postdoc Xiaochun Chen discovered XCII by high-throughput screening of a large compound library.