New lead on malaria treatment: Variation of natural compound cures malaria in mice

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Approximately 350 million to 500 million cases of malaria are diagnosed each year mostly in sub-Saharan Africa. While medications to prevent and treat malaria do exist, the demand for new treatments is on the rise, in part, because malaria parasites have developed a resistance to existing medications. Now, researchers at the Johns Hopkins University School of Medicine have discovered one way to stop malaria parasite growth, and this new finding could guide the development of new malaria treatments.

"Our research on malaria is in line with Johns Hopkins' mission to address health problems on a global level," says Jun O. Liu, Ph.D., a professor of pharmacology and molecular sciences. "Our findings offer both a new potential molecular target for treating malaria and a compound that interacts at that target. These are important steps in discovering drugs that could help to treat malaria." The results of the research were published in the February 27 issue of Chemistry & *Biology*.

Liu's research team has for many years studied MetAP2 proteins, which are found in all organisms — from humans to single-celled bacteria — and essential for cell survival. They reasoned that if the malaria parasite has its own MetAP2, finding a chemical that disrupts MetAP2 function may lead to a new drug to stop parasite growth and malaria spread. So they searched a computer database of the sequence of the malaria parasite genome and found one protein very similar to human MetAP2, which they named PfMetAP2 for plasmodium falciparum, the parasite

that causes malaria.

Recently other researchers reported that the natural antibiotic fumagillin can stop malaria parasites from growing, possibly by interfering with MetAP2. But the man-made version of fumagillin causes brain cells to die, so Liu's team made several compounds chemically related to fumagillin in hopes of finding one less toxic but still effective in interfering with PfMetAP2. They chose to further study one of these compounds, fumarranol, because it interacts with human MetAP2 and is less toxic to mice.

The team first tested whether fumarranol can stick to and interfere with PfMetAP2 by treating mouse cells containing PfMetAP2 with different amounts of fumarranol and fumagillin and comparing them to untreated cells. In treated cells, fumarranol stuck to PfMetAP2 and stopped it from working.

They next asked whether fumarranol could stop malaria parasites from growing in a culture dish. They treated both drug-resistant and multidrug-resistant strains of Plasmodium falciparum and found that fumarranol could stop the parasite from multiplying.

The team then gave mice infected with malaria fumarranol for four days after infection and measured the parasite load in the blood. They found that after four days, fumarranol worked as well as fumagillin to slow infection. After another 26 days they again measured parasites in the blood, found that some mice carried no observable level of parasites and considered these animals cured.

"The next step for establishing a new treatment for malaria would be to test whether fumarranol is the most optimal treatment or if new compounds that are similar to fumarranol might be even more specific to malaria parasites," Liu says.

Source: Johns Hopkins Medical Institutions