Novel drug wipes out deadliest malaria parasite through starvation

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An antimalarial agent developed by researchers at Albert Einstein College of Medicine of Yeshiva University proved effective at clearing infections caused by the malaria parasite most lethal to humans – by literally starving the parasites to death. The novel research, carried out on a small number of non-human primates, could bolster efforts to develop more potent therapies against one of the world's leading killers. The study, published in the November 11, 2011 issue of *PLoS ONE,* was led by senior author Vern Schramm, Ph.D., professor and Ruth Merns Chair in Biochemistry at Einstein.

Malaria is a mosquito-borne disease caused by single-celled parasites belonging to the *Plasmodium* genus. The U.S. Centers for Disease Control and Prevention estimated that in 2008 (the latest year for which figures are available) between 190 million and 311 million cases of malaria occurred worldwide and between 708,000 and 1.003 million people died, most of them young children in sub-Saharan Africa. *Plasmodium falciparum*, the malaria species most likely to cause severe infections and death, is very common in many countries in Africa south of the Sahara desert.

The Einstein researchers exploited what is arguably *P. falciparum*'s Achilles' heel: it can't synthesize purines, vital building blocks for making DNA. Instead, the parasite must make purines indirectly, by using an enzyme called purine nucleoside phosphorylase (PNP) to make a purine precursor called hypoxanthine. By inhibiting PNP, the drug BCX4945 kills the parasites by starving them of the purines they need to

survive.

After BCX4945 showed potency against laboratory cultures of *P. falciparum*, owl monkeys were chosen as the non-human primate model for further testing of the drug. Three animals were infected with a strain of *P. falciparum* that is consistently lethal without antimalarial therapy. Orally administering BCX4945 twice a day for seven days cleared the infections from all the animals between the fourth and seventh day of treatment. The monkeys remained parasite-negative for up to nine days post-treatment. Parasitic infection eventually returned in all three monkeys after treatment ended, although a lower rate of parasitic growth was observed. No signs of toxicity were observed during the study period (30 days after the first dose).

BCX4945 belongs to a class of drugs known as transition state analogs that Dr. Schramm has been developing since 1994. Transition states form in every chemical change and whenever an enzyme does its job of converting one chemical (the substrate) into another (the product). The fleeting transition-state molecule is neither substrate nor product, but something in between—a ghostly intermediate to which the enzyme clings for just one billionth of a millionth of a second.

After figuring out the brief-lived transition-state structure for a particular enzyme, Dr. Schramm is able to design transition-state analogs to knock that enzyme out of action. The analogs closely resemble the actual transition-state structure but with one big difference: they powerfully inhibit the enzyme by binding to it and not letting go.

The transition-state analog BCX4945 was chosen for this study because of its high affinity for both *P. falciparum* PNP and human PNP (which the parasite obtains from the red blood cells it infects). Since PNP is abundant in mammalian red blood cells and those cells are constantly replaced, BCX4945 is toxic only to the parasite and not its mammalian

hosts. (Two of Dr. Schramm's other PNP inhibitors—one for T-cell cancers, the other for gout—are being evaluated in clinical trials.)

"Inhibiting PNP differs from all other current approaches for treating malaria," said Dr. Schramm. "For that reason, BCX4945 fits well with the current World Health Organization protocols for malaria treatment, which call for using combination-therapy approaches against the disease."

More information: The paper is titled "Plasmodium falciparum Parasites Are Killed by a Transition State Analogue of Purine Nucleoside Phosphorylase in a Primate Animal Model."

Provided by Albert Einstein College of Medicine