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Cancer-fighting drugs might also stop malaria early

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Scientists searching for new drugs to fight malaria have identified a number of compounds—some of which are currently in clinical trials to treat cancer—that could add to the anti-malarial arsenal.

Duke University assistant professor Emily Derbyshire and colleagues identified more than 30 enzyme-blocking molecules, called protein kinase inhibitors, that curb malaria before symptoms start.

By focusing on treatments that act early, before a person is infected and feels sick, the researchers hope to give malaria –- especially drug-resistant strains –- less time to spread.

The findings appear online and are scheduled to appear in a forthcoming issue of the journal *ChemBioChem*.

Malaria is caused by a single-celled parasite called Plasmodium that spreads from person to person through mosquito bites. When an infected mosquito bites, parasites in the mosquito's saliva first make their way to the victim's liver, where they silently grow and multiply into thousands of new parasites before invading red blood cells—the stage of the disease that triggers malaria's characteristic fevers, headaches, chills and sweats.

Most efforts to find safe, effective, low-cost drugs for malaria have focused on the later stage of the infection when symptoms are the worst. But Derbyshire and her team are testing chemical compounds in the lab

to see if they can identify ones that inhibit malaria during the short window when the parasite is still restricted to the liver, before symptoms start.

One of the advantages of her team's approach is that focusing on the liver stage of the malaria lifecycle—before it has a chance to multiply—means there are fewer parasites to kill.

Using a strain of malaria that primarily infects rodents, Derbyshire and Jon Clardy of Harvard Medical School tested 1,358 compounds for their ability to keep parasites in the liver in check, both in test tubes and in mice.

"It used to be that researchers were lucky if they could identify one or two promising compounds at a time; now with advances in high-throughput screening technology we can explore thousands at once and identify many more," said Derbyshire, an assistant professor in the Departments of Chemistry and Molecular Genetics and Microbiology at Duke.

Focusing on a particular group of enzyme-blocking compounds called protein kinase inhibitors, they identified 31 compounds that inhibit malaria growth without harming the host. Several of the compounds are currently in clinical trials to treat cancers like leukemia and myeloma.

The same compounds that stopped the stage of malaria that lurks in the liver also worked against the stage that lives in the blood.

Malaria-free mice that received a single dose before being bitten by infected mosquitos were able to avoid developing the disease altogether.

Medicines for malaria have been around for hundreds of years, yet the disease still afflicts more than 200 million people and claims hundreds

of thousands of lives each year, particularly in Asia and Africa. Part of the reason is malaria's ability to evade attack. One of the most deadly forms of the parasite, Plasmodium falciparum, has already started to outsmart the world's most effective antimalarial drug, artemisinin, in much of southeast Asia. Infections that used to clear up in a single day of treatment now take several days.

Diversifying the antimalarial arsenal could also extend the lifespan of existing drugs, since relying less heavily on our most commonly used weapons gives the parasite fewer opportunities to develop resistance, Derbyshire said.

Another advantage is that the compounds they tested suppress multiple malaria proteins at once, which makes it harder for the parasites to develop ways around them.

"That makes them like a magic bullet," she said.

More information: "Chemical interrogation of the malaria kinome," Derbyshire, E. and Clardy, J., et al. *ChemBioChem*, 2014. dx.doi.org/10.1002/cbic.201400025

Provided by Duke University

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