MALARIA

A step closer to elimination?

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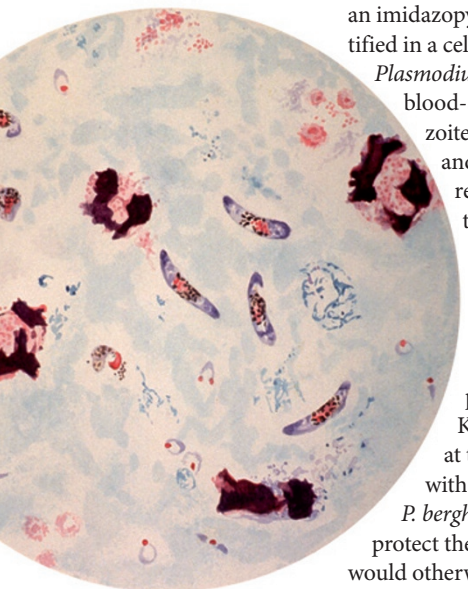

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Despite the fact that malaria — caused by the *Plasmodium* spp. parasite and spread by *Anopheles* mosquitoes — is mostly treatable and preventable, the goal of global eradication is distant, and resistance development is a major concern. Now, writing in *Nature*, a group of scientists from academia and industry report the discovery of a new class of antimalarials with promising preventive, therapeutic and transmission-blocking activity against a number of different *Plasmodium* species, including those that are resistant to conventional antimalarials.

A range of inhibitors, defined by an imidazopyrazine core, were identified in a cell-based screen against *Plasmodium falciparum* asexual blood-stage parasites (merozoites). Ensuing *in vitro* and *in vivo* experiments revealed potent activity of these compounds against a range of *Plasmodium* species and parasite stages. For example, in mice, a single oral dose of the imidazopyrazine compound KDU691, administered at the time of infection with the rodent parasite *P. berghei*, was sufficient to protect the animals from what would otherwise be fatal disease — demonstrating activity against sporozoites, the infectious form of the parasite.

In the normal course of the disease, sporozoites enter the liver, proliferate and emerge into the bloodstream as merozoites, causing symptomatic disease. In some species (notably *P. vivax*), hypnozoites can remain dormant in the liver and provide a reservoir for relapse. Live-imaging of mice infected with luciferase-expressing *P. berghei* demonstrated that a single dose of KDU691, administered after the establishment of disease, eliminated parasites from the liver. Activity against the liver stage of several other *Plasmodium* species (including *P. falciparum*, *P. yoelii* and hypnozoites of *P. vivax* and *P. cynomolgi*) was demonstrated in *in vitro* experiments.

Merozoites in the vertebrate host can sexually differentiate into gametocytes, which transfer the parasite back to the mosquito vector during a blood meal. Gametocytes are resistant to most antimalarials, with the exception of dihydroartemisinin (DHA). *In vitro* tests showed that KDU691 was significantly more active against gametocytes than DHA, and in a mosquito feeding assay, 1 μM of KDU691 completely inhibited transmission.

Microscopic investigation of imidazopyrazine-treated merozoites showed perturbed membrane ingression during daughter cell development, which indicates that the compounds impair membrane biogenesis. A forward-genetic approach, in which imidazopyrazine-resistant parasites were generated and the genomic differences to the parental strain determined, revealed the lipid kinase phosphatidylinositol 4-OH kinase (PI(4)K) as the molecular target of the imidazopyrazine compounds. *In silico* modelling indicated that they bind to the ATP binding pocket of PI(4)K, and further biochemical experiments showed dose-dependent ATP-competitive inhibition of PI(4)K. Imidazopyrazine treatment did not lead to a decrease in the levels of phosphorylation of PI(4), the substrate of PI(4)K, but instead led to a redistribution of phosphorylated PI(4) within the parasite.

These results validate *Plasmodium* PI(4)K as a potential target for next-generation antimalarials, with the potential to cure, block and prevent the transmission of the disease — a profile that is viewed as key for the success of worldwide malaria elimination efforts.

Alexandra Flemming

ORIGINAL RESEARCH PAPER McNamara, C. W. *et al.* Targeting *Plasmodium* phosphatidylinositol-4-OH kinase to eliminate malaria. *Nature* http:dx.doi.org/10.1038/nature12782 (2013)