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MALARIA

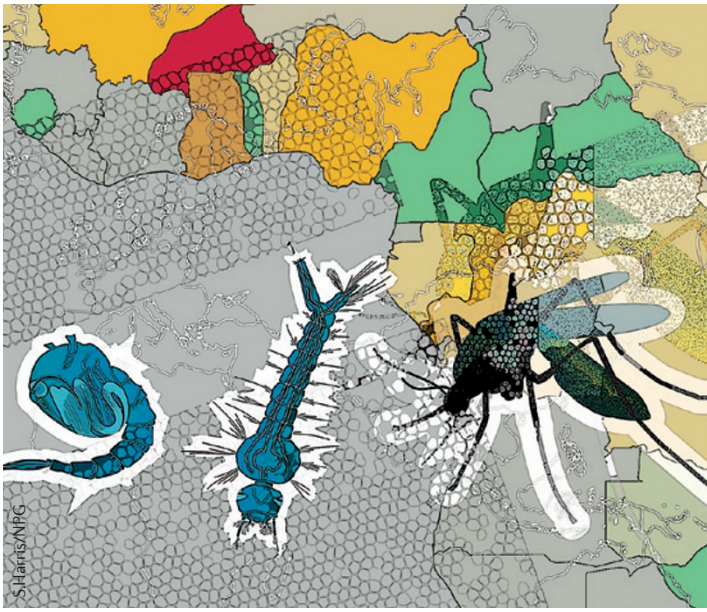
Hitting all stages of the parasite life cycle

The goal of malaria eradication requires compounds with novel mechanisms of action. These should ideally provide single-dose cures and act against all stages of the parasite life cycle in order to prevent infection and transmission. Now, a group of researchers from the University of Dundee (United Kingdom), in partnership with the Medicines for Malaria Venture (MMV), report the initial development of such a compound in *Nature*.

The compound originated from a phenotypic screen of a library of ~4,700 small molecules against the blood stage of *Plasmodium falciparum*. Chemical optimization led to the development of DDD107498, which showed potent *ex vivo* activity against clinical isolates of *P. falciparum* and *Plasmodium vivax*. In animal models, DDD107498 displayed excellent pharmacokinetic properties, including good oral availability and a long plasma half-life, as well as a favourable safety profile. It also showed comparable or greater efficacy than current antimalarials in several different mouse models. For example, a single oral administration led to a 90% reduction in parasitaemia in mice infected with the rodent parasite *Plasmodium berghei*.

Because intra-hepatic parasites (liver schizonts) are the first stage of human infection, agents active against this stage have potential for use in chemoprotection. DDD107498 showed potent activity against liver schizonts *in vitro*, and treatment with the drug 2 hours before infection with *P. berghei* was fully curative in mouse models. Moreover, the compound was also shown to be active against the erythrocyte form of the parasite, which is asymptomatic but can infect mosquitos and thereby promote transmission. When mice were treated with the drug 24 hours before mosquitos took a blood meal there was a 90% reduction in infected mosquitos and a similar reduction in the infection of mice that were subsequently bitten.

To determine the molecular target of DDD107498, *P. falciparum* was cultured in the presence of the drug until resistance developed (the rate of resistance development was comparable to other antimalarials). Ensuing whole-genome sequencing of ten resistant parasite lines identified a shared mutation in *P. falciparum* translation elongation factor 2 (PfeEF2). This protein is required for protein synthesis at all stages of the parasite life cycle and was validated as the target of DDD107498 in further experiments.



The authors note that owing to general concerns about resistance development, all antimalarials should be developed as combination therapies. Moreover, the therapies need to be cheap; the estimated cost of DDD107498 is US$1 per treatment. With its potent activity against multiple stages of the parasite life cycle, novel mode of action, excellent drug-like properties and low cost, DDD107498 meets the key criteria for new antimalarials. It is undergoing late-stage preclinical development with a view to entering clinical trials in the near future.

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ORIGINAL RESEARCH PAPER Baragaña, B. *et al.* A novel multiple-stage antimalarial that inhibits protein synthesis. *Nature* **522**, 315–320 (2015)
FURTHER READING Wells, T. N. C. *et al.* Malaria medicines: a glass half full? *Nat. Rev. Drug Discov.* **14**, 424–442 (2015)