INFECTIOUS DISEASES

New leads for tackling malaria

With drug resistance threatening the effectiveness of currently available malaria therapies, the development of novel agents is crucial. Now, two studies reported in *Proc. Natl Acad. Sci. USA* identify promising new antimalarial compounds that are capable of treating and preventing disease in rodent models.

The semisynthetic peroxide-based artemisinin derivatives are the only drug class that are effective against multidrug-resistant strains of the *Plasmodium* parasite. However, their use is limited by their short half-lives, costly and laborious production, and concerns of emerging resistance. Other peroxide antimalarials under development are the synthetic ozonides, but the pharmacokinetic profile of first-generation agents such as OZ277 is not optimal. Vennerstrom and colleagues therefore set out to design and optimize a novel ozonide, OZ439, with the aim of developing a single-dose oral malaria treatment.

Although reactivity with Fe(II) in the blood is necessary for the activity of peroxide antimalarials, this reaction probably also underlies their rapid clearance. Interestingly, Vennerstrom and colleagues found that replacing the *cis*-8′-alkyl group in first-generation ozonides with a *cis*-8′-phenyl substituent reduced their blood Fe(II)-reactivity and increased their stability, which prolonged the blood concentration profile and increased the half-life of these agents in rats. Importantly, some Fe(II) reactivity was retained.

These second-generation ozonides exhibited potent *in vitro* and *in vivo* antimalarial activity. Indeed, OZ439 was more effective than all other comparative malaria therapies — a single oral dose completely cured mice that were infected with *Plasmodium berghei*. In addition, OZ439 displayed a rapid onset of action; it reduced parasitaemia to undetectable levels within 7–8 days of treatment, and this effect was maintained for up to 30 days post-infection. Furthermore, a single oral dose conferred complete protection when administered 48 hours prior to infection.

Meanwhile, Gazzinelli and colleagues set out to target the overactive immune response that is believed to be largely responsible for the clinical manifestations of malaria. Given that Toll-like receptors (TLRs) are critical for the production of pro-inflammatory cytokines during microbial challenge and a hyperresponsiveness of TLRs has been observed in malaria, they investigated the antimalarial potential of a synthetic small-molecule TLR antagonist, E6446.

E6446 demonstrated selectivity for the nucleic acid-sensing TLRs, and it most potently inhibited TLR9 and abolished production of downstream cytokines *in vitro* and in mice. Similarly, in mouse models of acute *Plasmodium* infection, oral administration of E6446 prevented the exacerbated TLR and cytokine responses. Furthermore, although it had no effect on parasitaemia, E6446 enhanced the survival of mice with lethal *Plasmodium berghei* ANKA-induced experimental cerebral malaria (ECM), when it was administered 1 day prior to and 12 days following infection. This agent was also effective in mice with established ECM, increasing survival and preventing ECM symptoms when administered up to 6 days post-infection.

These studies could lead to novel antimalarial strategies and therapies. Indeed, OZ439 has now successfully completed Phase I clinical trials, and Phase IIa trials in patients with malaria are underway.

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ORIGINAL RESEARCH PAPERS Charman, S. A. *et al.* Synthetic ozonide drug candidate OZ439 offers new hope for a single-dose cure of uncomplicated malaria. *Proc. Natl Acad. Sci. USA* 7 Feb 2011 (doi:10.1073/pnas.1015762108) | Franklin, B. S. *et al.* Therapeutical targeting of nucleic acid-sensing Toll-like receptors prevents experimental cerebral malaria. *Proc. Natl Acad. Sci. USA* **108**, 3689–3694 (2011)