Taking a Bite Out of Mosquitoes: A New Drug to Block Transmission of Malaria

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(See the major article by Ojo et al on pages 275–84.)

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Despite concerted control efforts and decades of research, malaria remains a global scourge and the most important parasitic disease of humans. Infections caused by the parasite Plasmodium falciparum exact a huge toll, largely in sub-Saharan Africa, where nearly a million children die annually from complications of malaria. Integrated campaigns such as The Malaria Control and Evaluation Program in Africa (MACEPA) have adopted comprehensive strategies including insecticide-impregnated bed nets, artemisinin-based combination therapies, aggressive indoor insecticide spraying, and advanced diagnostics to reduce mortality in children by nearly 20 percent [1]. Such recent advances coupled with evolving prospects for a vaccine against malaria [2] suggest that the goal of malaria eradication may soon be attainable, using an arsenal of preventive practices.

For now, chemotherapeutic measures remain the mainstream of malaria management. Currently, combination therapy with artemisinin derivatives and agents such as mefloquine, lumefantrine, or amodiaquine are first-line therapies for uncomplicated malaria in most endemic regions of the world. Such treatments can be highly effective with resolution of parasitemia when administered soon after onset. Although artemisinin-based therapies have proven successful in many trials across Africa and Southeast Asia, there are growing concerns about evolving resistance of P. falciparum to these agents. Recently, Phyo et al [3] reported an alarming increase in rates of artemisinin resistance amongst P. falciparum isolates from patients seen in clinics along the Thailand-Myanmar border. Furthermore, resistance rates in Western Cambodia were reported to be greater than 40 percent. Assays of parasite clearance were correlated with genotypic changes in parasite populations and nearly two-thirds of the variation in parasite clearance over a 3-year period was attributable to genetic polymorphisms in populations of P. falciparum isolates from patients seen in clinics along the Thailand-Myanmar border. Furthermore, resistance rates in Western Cambodia were reported to be greater than 40 percent. Assays of parasite clearance were correlated with genotypic changes in parasite populations and nearly two-thirds of the variation in parasite clearance over a 3-year period was attributable to genetic polymorphisms in populations of P. falciparum isolates from patients seen in clinics along the Thailand-Myanmar border.

In this issue of the Journal, Ojo et al [4] report a very exciting new prospect for drug treatment of P. falciparum. The investigators describe a new class of antimalarial compounds that target the sexual stage of Plasmodium (Figure 1), specifically the parasite’s calcium-dependent protein kinase 4 (CDPK4), a signaling molecule that is essential for exflagellation of male gametocytes. This step is a precursor to the fusion of male and female gametocytes, which results in zygote formation in the mosquito. The sexual phase of the Plasmodium life cycle is critical and represents a potential target for drugs that would ultimately abort transmission of parasites by mosquitoes to humans.

Compound 1294, reported by Ojo et al is a synthetic inhibitor of Plasmodium CDPK4. The authors demonstrate convincingly that the synthetic CDPK4 inhibitor inhibits exflagellation of gametocytes and, by acting on a specific serine residue of the parasite, avoids cross-reactivity with mammalian kinase substrates. Furthermore, the mechanism by which this compound acts on parasites is cleverly elucidated, using transgenic lines of Plasmodium. By generating a mutant parasite with a modified target site for the enzyme, the authors demonstrate that EC50 exflagellation values are shifted relative to wild-type parasites exposed to the same inhibitor. Thus, both efficacy of compound 1294 and its mode of action are presented in this seminal article.

Gametocytes of P. falciparum begin maturation in the mammalian host and are taken up during a mosquito’s blood meal (Figure 1). Fusion of the gametocytes and formation of a zygote occur in the arthropod. Therefore, a CDPK4 inhibitor, taken as a drug by a human, would disrupt the parasite life cycle within the insect and prevent formation of infectious...
sporozoites. For this strategy to be effective, the drug would have to be widely bioavailable and have a long half-life, because release and persistence of gametocytes in humans occurs over a lengthy period of time. Through a strategy of N-methylation, Ojo et al developed compound 1294, which offers 8-fold increase in bioavailability after a single oral dose, when compared to precursors, and significantly prolonged serum half-life in a mouse model. Transmission studies using the mosquito, *Anopheles stephensi*, confirmed that insects feeding on blood that was pretreated with as little as 0.1 µM of compound 1294, had significantly reduced oocyst formation in the midgut, which would correlate with decreased capacity to transmit malaria.

Taken together, the studies of Ojo et al offer a new direction in antimalarial therapy. Current chemotherapeutic regimens against *P. falciparum* are primarily directed at the asexual stages of the parasite (Figure 1) and provide treatment to already infected individuals. Drugs such as compound 1294 could be used in concert with current regimens, thereby permitting dual modes of attack against malarial parasites and sites of action within humans and mosquitoes. Furthermore, drugs that target gametocytes could address a critical stage in parasite evolution. The sexual phase of *P. falciparum* gives rise to mutant parasites that carry drug-resistant traits. Compounds that disrupt the parasite life cycle at this phase could, theoretically, reduce the burden of escape mutants and slow the evolution of parasite resistance when used in combination with schizonticidal agents.

Hopefully, the next few years will witness an end to malaria. Efforts to reduce transmission via bed nets, targeted insecticides, and environmental management coupled with the latest advances in vaccines, even engineered insects that are incapable of transmitting parasites [5] could signal the end to this global menace. In the meantime, more effective drugs are desperately needed as resistance of *P. falciparum* to available agents spreads across the world. Let’s hope that the new class of compounds described by Ojo et al fits the bill and offers a new set of tools in the fight against malaria.

**Figure 1.** Life cycle of parasites of the genus *Plasmodium*. The sexual phase of the parasite cycle, resulting in zygote formation, occurs in the mosquito, and exflagellation of male gametocytes, the immediate precursor to zygote formation, is the target of compound 1294. Source: CDC - DPDx/Alexander J. da Silva, PhD, and Melanie Moser. Public Health Image Library, image #3405 (http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/M-R/Malaria/body_Malaria_il1.htm) (2002).
Notes

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