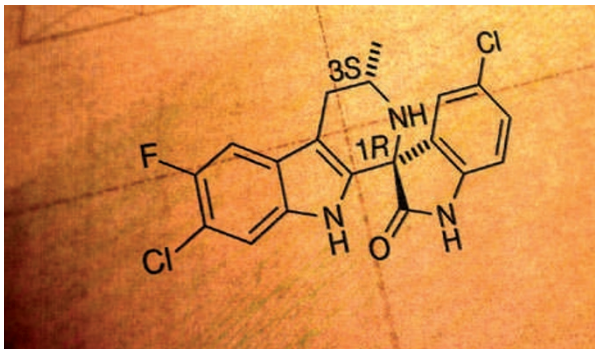
ANTIMALARIAL DRUGS

Speeding to a new lead

A public–private partnership has identified a promising new antimalarial compound that is potently effective against a range of *Plasmodium* species — including some that are resistant to currently used agents — and possesses the pharmacokinetic properties needed to become a viable drug. The lead candidate, named NITD609, was optimized in just 3 years from a class of compounds called the spiroindolones that were identified in a whole-cell screen of a library comprising 12,000 natural products and synthetic compounds.

NITD609 had half-maximal inhibitory concentration (IC_{50}) values of 0.5–1.4 nM against a laboratory panel of *Plasmodium falciparum* strains. Moreover, IC_{50} values of <10 nM were also seen when NITD609 was tested against clinical isolates of *P. falciparum* and *Plasmodium vivax*; samples were obtained from patients on the Thai–Burmese border, an area where resistance to chloroquine (a widely used antimalarial) has been reported. In addition, standard toxicity screens indicated a minimal risk of cytotoxicity, cardiotoxicity and genotoxicity.



Structure of NITD609; the 1*R*,3*S* configuration is fundamental for its antimalarial activity

Mice infected with the highly virulent *Plasmodium berghei* were completely cured with a single oral dose (100 mg per kg) of NITD609, an effect that was not seen with similar doses of the current standard antimalarial drugs artesunate, artemether, chloroquine or mefloquine. The mechanism of action of NITD609 remains to be elucidated; however, it was shown to block protein synthesis in *P. falciparum* to a similar degree as two compounds commonly used in research: anisomycin (a peptidyl transferase inhibitor) and cyclohexamide (a translational elongation inhibitor).

Importantly, resistance development to NITD609 was slow, as IC_{50} values only increased to a mean of 3–11 nM after 3–4 months of constant exposure to a cultured *P. falciparum* clone that has a high rate of mutations. Further analysis identified mutations in the *pfatp4* gene that seemed to confer the resistance. Although PfATP4 is known to be a cation transporter, its specific molecular functions and its role in resistance development are yet to be investigated.

Overall, the discovery of NITD609 highlights the potential to rapidly move from whole-cell screening to a lead candidate that so far seems to meet the stringent efficacy and pharmacokinetic criteria needed to become a novel antimalarial drug. Further assessment of its safety profile, to support its progression into clinical trials, is currently ongoing.

Man Tsuey Tse

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