A new lead in malaria

By Joanne Kotz, Senior Editor

A consortium of researchers led by the **Novartis Institute for Tropical Diseases** has identified a potent new class of antimalarials that could provide a much needed safeguard against parasites resistant to the largely artemisinin-based armamentarium of malaria drugs. The consortium's experience suggests that directly screening in whole parasites—instead of first identifying a potential drug target—may be the most effective path to discovering new compounds.

Novartis AG hopes to begin a Phase I trial of the lead compound as early as year end.

In 2006, the **World Health Organization** (WHO) began recommending artemisinin-based combination therapies (ACTs) as first-line therapy for uncomplicated *Plasmodium falciparum* malarial infection. The move was a response to the spread of parasites resistant to chloroquine and sulphadoxine-pyrimethamine.¹

Fixed-dose artemisinin combinations are now the preferred mode for treating malaria,² and there are at least four such products on the market or in registration. The problem is that virtually the entire late-stage pipeline of malaria therapeutics relies on derivatives of artemisinin, and resistance to the parent molecule could dampen the efficacy of a broad swath of antimalarials.

WHO-recommended fixed-dose ACTs are Coartem, an artemether-lumefantrine combination marketed by Novartis, and Coarsucam, an artesunate-amodiaquine combination marketed by **sanofi-aventis Group**.

Combinations under regulatory review include Pyramax artesunate-pyronaridine from **Shin Poong Pharmaceutical Co. Ltd.** and Eurartesim dihydroartemisinin-piperaquine from **Sigma-Tau S.p.A.** and **Pfizer Inc.**

Now, a team led by Thierry Diagana, malarial program head at the Novartis Institute for Tropical Diseases, and Elizabeth Winzeler, an associate professor at **The Scripps Research Institute** and head of the Department of Infectious Diseases at the **Genomics Institute of the Novartis Research Foundation**, have found a new class of compounds based on a chemical scaffold called spiroindolone.³

Using a whole-cell assay measuring *P. falciparum* proliferation in red blood cells, researchers at the Genomics Institute screened about 12,000 compounds and identified 275 with submicromolar EC₅₀ values.^{3,4}

Medicinal chemistry-based optimization of one of the hits led to the identification of NITD609, the spiroindolone-based compound.^{3,5} NITD609 inhibited proliferation of drug-sensitive and drug-resistant

strains of *P. falciparum* and *P. vivax* in red blood cells at low nanomolar concentrations, demonstrating that the compound had activity against the blood stage of the parasite.

In a mouse model of malaria, a single oral dose of 100 mg/kg NITD609 increased survival and was the only compound to cure infection compared with the same dose of artesunate, artemether, chloroquine or mefloquine.

The mechanism of action of NITD609 is not yet known but appears to be distinct from those of known antimalarials. *In vitro*, the compound rapidly blocked *P. falciparum* protein synthesis, whereas artemisinin or mefloquine had little effect.

Moreover, resistance to NITD609 was slow to develop. When parasites were grown under selective drug pressure for three to four months, only low levels of resistance were observed.

"Further regulatory pharmacological and safety evaluations are ongoing and, provided the outcomes of these studies are favorable, NITD609 could progress to clinical trials later this year," Diagana told SciBX.

"NITD609 would not have been discovered without a whole-organism screening approach."

— **Thierry Diagana,**
Novartis Institute for Tropical Diseases

Following a whole-istic path

Richard Davis, business development manager at **Wellcome Trust**, said NITD609 is the result of a collaborative effort that started in 2006 and had a five-year goal of identifying a new single-dose cure for malaria. Novartis Institute for Tropical Diseases is leading the consortium, which includes a global network of collaborators.

Funding for the consortium comes from Wellcome Trust, the **Singapore Economic Development Board**, **Medicines for Malaria Venture** (MMV) and Novartis.

NITD609 is the first clinical candidate to emerge from the consortium. According to Diagana, "NITD609 would not have been discovered without a whole-organism screening approach."

In fact, for the past four years, the portfolio taken on by the group has had a balance of both target-based and cell-based approaches, said Davis. However, nearly all target-based projects have been killed, and those that are still active are in earlier stages of preclinical development than NITD609.

Many factors may be contributing to the comparative success of whole-organism screening, according to Timothy Wells, CSO of MMV. In a target-based approach, genetically validating targets can be difficult because it is a negative experiment in which the parasite does not survive. In addition, small molecules rarely achieve the total target inhibition of a genetic knockout. The combination of these factors, Wells said, "always leaves a nagging doubt about any potentially new targets coming through."

Whole-organism screening also offers important advantages, Wells added. Active compounds from screens have to be getting into the parasite, which is not necessarily true for compounds identified by *in vitro* screening. Also, compounds can be identified that inhibit multiple or nonprotein targets.

According to Wells, although the mechanism of action of NITD609 remains to be elucidated, “what is nice is that you can investigate this in parallel with moving forward with taking the compound through preclinical steps and into humans.”

Diagana and Winzeler both told *SciBX* they are pursuing the drug target and mechanism of action.

Wells noted that whole-organism screens in malaria are not new. Pharma companies were looking for malaria drugs using whole-cell screens seven or eight years ago, but these were done in 96-well plates and screening 1,000 compounds was considered substantial.

Now the screens are being done in 1,584-well plates, with better imaging capabilities and lower cost, he said. Novartis was able to screen nearly 2 million compounds across multiple whole-parasite assays in a few weeks.

Indeed, other groups have turned to whole-organism screens in the search for new antimalarials. For example, a team led by Jose Garcia-Bustos, head of malaria drug discovery activities at the Tres Cantos Medicines Development Campus of **GlaxoSmithKline plc**, screened nearly 2 million compounds and identified more than 8,000 that had activity against a multidrug-resistant malarial strain.⁶

“We have identified several novel chemical structures which we think are possible winners and are currently developing them,” said Garcia-Bustos. He estimated that the most advanced is about a year behind the Novartis compound.

A separate collaborative effort led by R. Kiplin Guy, chair of the Chemical Biology & Therapeutics Department at **St. Jude Children's Research Hospital**, found more than 1,000 antimalarials from a 320,000-compound screen.⁷ “We are prosecuting our top candidates and are also focusing on getting exemplar compounds into the hands of parasite biologists to start

understanding detailed mechanisms,” said Guy.

NITD609 is patented by Novartis and is not available for licensing.

Kotz, J. *SciBX* 3(39); doi:10.1038/scibx.2010.1167

Published online Oct. 7, 2010

REFERENCES

1. Wells, T.N.C. *et al. Nat. Rev. Drug Discov.* **8**, 879–891 (2009)
2. Dondorp, A.M. *et al. Nat. Rev. Microbiol.* **8**, 272–280 (2010)
3. Rottmann, M. *et al. Science*; published online Sept. 30, 2010; doi:10.1126/science.1193225
Contact: Thierry T. Diagana, Novartis Institute for Tropical Diseases, Singapore
e-mail: thierry.diagana@novartis.com
Contact: Elizabeth A. Winzeler, The Scripps Research Institute, La Jolla, Calif.
e-mail: winzeler@scripps.edu
4. Plouffe, D. *et al. Proc. Natl. Acad. Sci. USA* **105**, 9059–9064 (2008)
5. Yeung, B.K.S. *et al. J. Med. Chem.* **53**, 5155–5164 (2010)
6. Gamo, F.-J. *et al. Nature* **465**, 305–310 (2010)
7. Guiguemde, W.A. *et al. Nature* **465**, 311–315 (2010)

COMPANIES AND INSTITUTIONS MENTIONED

Genomics Institute of the Novartis Research Foundation, San Diego, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Medicines for Malaria Venture, Geneva, Switzerland
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Novartis Institute for Tropical Diseases, Singapore
Pfizer Inc. (NYSE:PFE), New York, N.Y.
sanofi-aventis Group (Euronext:SAN; NYSE:SNY), Paris, France
Shin Poong Pharmaceutical Co. Ltd. (KSE:019170), Seoul, South Korea
Sigma-Tau S.p.A., Rome, Italy
Singapore Economic Development Board, Singapore
St. Jude Children's Research Hospital, Memphis, Tenn.
The Scripps Research Institute, La Jolla, Calif.
Wellcome Trust, London, U.K.
World Health Organization, Geneva, Switzerland