Is the tide turning for new malaria medicines?

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Tim Wells, MMV's Chief Scientific Officer, gives his perspective in *Science* on the optimal methods to discover the antimalarials of the future.

Every so often, the tide turns in a field of science. In malaria research, for a while an approach called "rational design" held sway, with great optimism that new drugs would emerge from understanding the biology of the malaria parasite at the molecular level. On page 1175 of Vol. 329 of *Science*, however, Rottmann *et al.* (1) take our thinking back up to the level of the parasite.

Using older screening methods that involve whole malaria parasites and cells, the authors identify a new class of compounds, spiroindolones, that show promise for treating malaria. Low concentrations of one spiroindolone, NITD609, kill the parasite's erythrocytic (bloodstream) stages by blocking protein synthesis, and preliminary tests in animals suggest that it could be developed into a safe drug. The timing here is important: Researchers in Cambodia have reported the first signs of resistance to artemisinin, the essential ingredient of existing malaria treatments for 100 million patients annually (2).There is thus an urgent need for candidates for new drugs that can overcome the challenges of resistance.

In the past decade, the availability of genome data and high-throughput systems for screening compounds was heralded as a breakthrough for discovering new anti-infective drugs. These molecular based approaches promised to identify new "hits," or compounds that could inhibit key enzymes or cell receptors at submicromolar concentrations. Unfortunately, this promise has not been fulfilled. Payne *et al.* (3), for instance, concluded that the molecular approach was not efficient in identifying validated "targets," such as specific genes or cellular pathways, for antimicrobial compounds. Targets are not validated until molecules can be tested in the clinic; and even then, getting the hits to kill the microbe was far from simple. Their recommendation was twofold: Researchers should either work on families of compounds already shown to be clinically active, or return to screening compounds against whole microorganisms.

This message was not lost on the industrial partners of the antiparasitic research community. Over the last few years, companies have screened several million compounds against the erythrocytic stages of the malaria parasite. They identified more than 20,000 compounds that, at submicromolar concentrations, show some effect on the parasites—a hit rate of 0.5% (4–6). This hit rate was startlingly higher than most predictions (3), and higher than the 0.1% hit rate that, in my experience, was considered a success for molecular-based screening programs. It also suggested that several years could be shaved off the drug development process (see the fi gure) if researchers could optimize, or further develop, the compounds identified by parasite-based screens without knowing exactly the molecular target they affected or the mechanism of action.

Rottmann et al. show that such “blind” optimization can be done rapidly. Their hit, initially identified by screening some 12,000 natural compounds and structurally similar synthetics against cells taken from malaria parasites, was optimized into a preclinical candidate in just 3 years. That is a turbocharged pace. Indeed, the first hints of NITD609’s mechanism of action didn’t come until the researchers studied how it acted against various mutant strains of the malaria parasite. These tests revealed that NITD609 blocks protein synthesis by inhibiting the gene that encodes the P-type cation-transporter ATPase4 (PfATP4).

One advantage of parasite-based screening is that it identifi es compounds that may act on more than one molecular target. Clinical experience has shown that drugs targeting a single molecular pathway, such as folate synthesis (targeted by pyrimethamine) or electron transport (atovaquone), can rapidly generate resistant strains (6). Medicines that have a more ambiguous molecular target or targets, such as artemisinin or quinine, tend to fare better in the clinic. So it is reassuring that Rottmann et al. had diffi culty producing parasites resistant to NITD609 *in vitro* and that the molecule is active against malaria strains from Thailand, where resistance to arteminisin is a growing problem. Both results suggest that the compound may affect more than one cellular process.

A final twist in this story is that Rottmann *et al.’s* hit is a fully synthetic compound that was accidentally included in a collection of naturally occurring molecules; none of the other natural products were as interesting. Cell-based screening has not yet led us to new natural products that might replace artemisinin and quinine. It also suggests that future work on natural products should go back to its roots by focusing only on purifying natural molecules that have some clinical evidence of activity in humans.

Do these developments mean that the days of searching for molecular targets for antiparasitic drugs are over? Far from it. Target-based approaches are extremely useful once you know the target, and cell-based screening is one way of fi nding new molecular targets. Moreover, target-based approaches can help develop drugs that attack other stages of the malaria parasite’s life cycle. This is important in the context of malaria eradication (7), which will require new classes of medicines that can stop transmission to other patients by blocking the sexual stages of the parasite (8,9). There is also a need for new medicines to block reactivation by dormant parasites in the liver, which occurs in the case of infection by *Plasmodium vivax* (9), the major strain in Asia and South America (10). Rational, molecular-based drug design also remains important in rapidly indentifying second generation compounds that can overcome resistance.

Can NITD609 replace artemisinin? Unfortunately, as in most drug development, the answer is “wait and see.” Artemisinin has two major strengths: It works quickly to reduce parasite levels in the bloodstream and resistance to it occurs less rapidly than for classical enzyme inhibitors. Meanwhile, NITD609’s route to regulatory approval is a long one. In vitro and animal data are often poor surrogates for clinical reality. Even the most optimistic observer would note that less than 20% of new compounds make it to fi nal approval, and that the process can take up to 8 years. The speed at which NITD609 has moved from a hit to a preclinical drug candidate, however, suggests that we may not have to wait too long.

References

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