Winning the drugs war

We have the science to make new antimalarials, say Robert Ridley and Yeya Toure, but we need better mechanisms and resources to develop drugs and deliver them.

In the 1990s, prospects for antimalarial chemotherapy became increasingly bleak owing to growing parasite resistance to chloroquine and sulphadoxine-pyrimethamine. Artemisinin-based drugs showed great promise in southeast Asia, but were barely used in Africa because of their cost and a lack of clinical data. To make matters worse, the pipeline for new drugs was dry as nearly all pharmaceutical companies had pulled out of antimalarial research.

The outlook for new antimalarials is now better than it has been for decades, thanks to public–private partnerships and increased funds for countries to buy drugs. But to deliver on this promise we must integrate drug development into a broader research agenda and involve stakeholders in developing countries.

Whereas the science is the fundamental obstacle to developing malaria vaccines, the main bottlenecks in drug discovery are structural. Resources are lacking to translate basic science into drug leads. In addition, mechanisms and resources are needed for improved clinical evaluation of drugs.

The brighter outlook for new drugs is in large part due to the nonprofit organization Medicines for Malaria Venture (MMV), established in late 1999 to fund and manage the discovery, development and registration of antimalarials. With a US$20-million annual budget funded mainly by the public sector and philanthropic foundations, it now runs about 20 drug-discovery and development projects. It has also persuaded the pharmaceutical industry to re-engage in malaria drug development[1].

Despite renewed international commitment to research and control, the reality for many patients is much as it was in the late 1990s. Children are dying because they are unable to access treatment and often the drugs they are given no longer work[2]. Evidence from coordinated multicentre trials is now supporting a widespread rollout of artemisinin-based combination therapies in Africa[3], but converting this policy into practice and implementing it on a nationwide scale is not straightforward. The new treatment regimens are more complex and expensive. Appropriate systems and finances must be put in place to ensure that artemisinin combinations are widely available and appropriately used to ensure their effectiveness and to prevent parasite resistance.

Productive partnerships

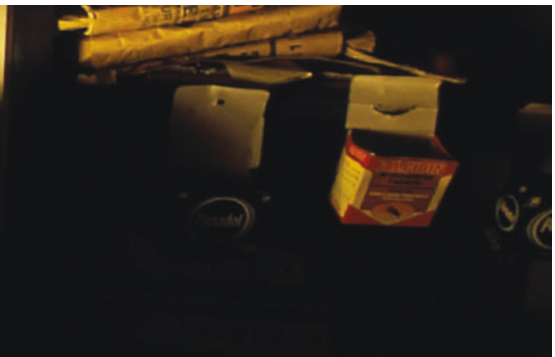
The current wave of antimalarial drug development has come from public–private partnerships. For example, registration of chlorproguanil-dapsone for the treatment of uncomplicated malaria resulted from a collaboration between GlaxoSmithKline and the Special Programme for Research and Training in Tropical Diseases (TDR)[4,5]. Several fixed-dose artemisinin combinations are in late-stage development. Particularly noteworthy is the partnership between MMV and the Indian manufacturer Ranbaxy to develop a new class of molecule: a fully synthetic peroxide (see page 900)[6] that may overcome several limitations of the artemisinins, including their short half-life, short shelf-life and cost.

This project is a marvellous example of how a public–private partnership can take an innovative approach to drug discovery. With initial TDR support, chemists at the University of Nebraska had generated several novel molecules of interest. But it was not until industry partnered the project and MMV provided substantial funding and support combined with a rigorous review process[7] that it could deliver a new drug-development target.

There is still a long way to go. Even if successfully developed and registered over the next four years, further research will be needed to assess just how the drug should be used in the fight against malaria.

Global support for such public–private partnerships remains insufficient. This is despite an annual increase of about US$20 million in resources from public-sector organizations and philanthropic foundations such as the Bill & Melinda Gates Foundation, plus 'in kind' industry contributions such as GlaxoSmithKline's new malaria and tuberculosis drug-discovery unit in Tres Cantos, Spain[1]. We need a significant scale-up of activity if we are to keep delivering new drugs.

We also need to research carefully how best to use such drugs. Development of fixed-dose combinations should be strongly encouraged to improve compliance and prevent the development of resistance. But such formulations have risks as well as benefits that need to be reviewed on a case-by-case basis, particularly for new drugs. The wrong choice of partner may limit the value of a new drug if it leads to problems in formulation, stability, toxicity or cost, or if resistance develops rapidly to the partner drug. Limitations on possible partner combinations may also



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A shop in Kilifi, Kenya, sells malaria drugs and provides advice, although some therapies are now losing their effectiveness. But the potent antimalarial artemisinin (below) from the plant *Artemisia annua* (bottom) could provide an alternative treatment.

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be imposed by the need for drugs to be available for niche applications, for example to treat severe disease or malaria in pregnancy, or for prophylaxis, including intermittent presumptive treatment in pregnancy and in infants (see 'An attack on all fronts', page 930). Decisions on whether and how to combine drugs may often need to be left until after initial regulatory approval of a single agent, or at least until late in development.

Taking the lead

To boost discovery of new lead compounds and exploit the potential of genomics (see 'Know thine enemy', page 944) we need innovations in administrative, managerial and funding systems as much as we need technical innovation[7–9]. We need to improve academics' access to high-throughput screening facilities in conjunction with parasite testing, exploratory chemistry and pharmacokinetics. Such approaches are now within the reach of some academic laboratories through non-proprietary chemical libraries and robotic technologies.

> "We need innovations in administrative, managerial and science partnership funding systems as much as we need technical innovation."

For some drug targets in the parasite, such as the cysteine proteinases and farnesyltransferases, the process can be simplified by 'piggybacking' on relevant industry-based chemistry to identify leads. A judicious mix of public-sector investment and public–private partnership needs to be further extended into this area.

Obtaining regulatory approval for a drug is just the first step. The efficacy and safety data required for approval, although critical, do not necessarily predict effectiveness in a real-life situation. For example, poor patient compliance with treatment regimens may have an impact on effectiveness, especially in settings where professional dispensing and medical supervision are lacking and patients are too poor to pay for a full course of treatment.

The thousand or so patients in a phase III clinical trial are too few to demonstrate fully a drug's safety. Rare adverse events occurring in sub-groups of patients — for example pregnant women, HIV-infected individuals, or patients taking other drugs — may not be noticed. Patients with different genetic susceptibilities, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, may also require special consideration. We need further post-registration studies on safety, patient compliance and effectiveness. We should also explore alternative formulations and improved drug-delivery strategies.

If properly managed, such studies would reduce the time it takes to decide whether and how a drug should be included within national policies. We simply do not have the luxury of waiting many years for these data to accumulate in an ad hoc way. A more coordinated, comparative assessment of new drug options needs to take place in local settings to ensure best practice for rapid, timely and cost-effective treatment[10].

Examples of such studies partnered by the TDR include assessment of rectal artesunate prior to hospital referral for patients unable to take oral medication, evaluation of chlorproguanil-dapsone in G6PD-deficient patients, and an assessment of Coartem in very young children. Attention is also turning towards the use of drugs during pregnancy.

We still fail to recognize the research and development role of scientists and organizations in developing countries. Agencies such as the US National Institutes of Health, the UK medical charity the Wellcome Trust and the new European and Developing Countries Clinical Trials Partnership are giving researchers in developing countries a greater stake in clinical research, but there is still a long way to go. The wealth of opportunities provided by traditional medicines offers particular promise for developing capacity for drug research and development and we should build on this through the Multilateral Initiative on Malaria and other organizations.

Although we now have considerably greater hope of developing a strong armamentarium of antimalarials, we still need to ensure that new drugs are optimally used and made accessible to patients. This will involve interactions across multiple disciplines, institutions and organizations. In particular, it demands coordinated action and dialogue between research and disease-control communities, both within countries and internationally. ■

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1. *Medicines for Malaria Venture Annual Report 2003* (MMV, Geneva, 2004); available at www.mmv.org/filesupld/184.pdf.
2. *Africa Malaria Report 2003* (WHO/UNICEF, Geneva, 2003); available at www.rbm.who.int/amd2003/amr2003/amr_toc.htm
3. Adjuik, M. *et al. Lancet* **363,** 9–17 (2004).
4. Lang, T. & Greenwood, B. *Lancet Infect. Dis.* **3,** 162–168 (2003).
5. Alleouche, A. *et al. Lancet* **363,** 1843–1848 (2004).
6. Vennerstrom, J. L. *et al. Nature* **430,** 900–904 (2004).
7. Nwaka, S. & Ridley, R. G. *Nature Rev. Drug Discov.* **2,** 919–928 (2003).
8. Ridley, R. G. *Nature* **415,** 686–693 (2002).
9. Fidock, D. A., Rosenthal, P. J., Croft, S. L., Brun, R. & Nwaka, S. *Nature Rev. Drug Discov.* **3,** 509–520 (2004).
10. *Scaling up Home-Based Management of Malaria: From Research to Implementation* (WHO, Geneva, 2004); available at www.who.int/tdr/publications/publications/pdf/home_2004.pdf.