Mission possible

One billion people worldwide suffer from tropical diseases. **Andrew L. Hopkins**, **Michael J. Witty** and **Solomon Nwaka** explain how drug-discovery networks might be scaled up to address the lack of treatments cost-effectively.

New drugs are urgently needed for neglected tropical diseases and tuberculosis. Although one person in six suffers from such diseases, the few drugs available are not widely used, owing to problems with safety, administration, cost and — increasingly — resistance of the infectious agents[1]. Moreover, there is a shortage of potential drugs for these diseases. So how do we meet this challenge and accelerate the flow of drugs through the pipeline?

The dearth of new drugs entering development for tropical diseases results mainly from the gap between basic scientific research, which is usually publicly funded, and clinical development, which is usually funded by pharmaceutical companies or, more recently for diseases in the developing world, through public–private partnerships. This situation reflects, in part, a lack of commercial incentives to develop new drugs for use in the developing world.

There are several current strategies for tackling this problem. Pull mechanisms, for example, offer a guaranteed market for a product — or other rewards for the company — when the development phase is complete. Push mechanisms involve subsidies to support developing pharmaceutical products for unprofitable or unpredictable markets. Public–private partnerships and non-profit organizations have emerged as cost-efficient vehicles for clinical-product development, and they tend to focus on one or a few neglected diseases. Examples are the Medicines for Malaria Venture, the Institute for OneWorld Health and the Special Programme for Research and Training in Tropical Diseases (TDR).

> "About half of the drugs being developed to treat neglected diseases fail the criteria for being fully effective in the field."

But as most experimental drugs fail in the development phase, the challenge is to produce a sustainable pipeline of new drug candidates to enter development. In the past few years, research facilities to undertake drug discovery for tropical diseases have been established in both industry and academia. A simple calculation, however, shows why the discovery of new drugs for neglected infectious diseases is unrealistic for a company or institute acting alone.

There are at least eight diseases for which new drugs are urgently required, according to the TDR. If a realistic goal is set today to deliver at least one effective new medicine for each of these eight diseases by 2020, then at least six candidate compounds need to enter clinical trials for each disease (assuming a historical success rate of 16% for anti-infective drugs)[2]. At present, in the pharmaceutical industry, the research costs alone for each drug candidate ready to enter clinical development are in the order of US$20 million. So the drug-discovery costs for a minimum of 48 clinical candidates that could result in 8 new drugs are probably close to US$1 billion — more than the annual research budget of most drug companies.

A new collaborative mindset is required if we are to scale up drug discovery for tropical diseases. The TDR is now implementing a scalable, collaborative model for drug discovery that is based on networks and partnerships with industry and academia in developed and developing countries[3]. Scaling up or expanding innovative drug-discovery networks could be a way to mobilize resources from both public and private sectors. This approach would involve the creation of a transparent and flexible global portfolio of drug-discovery projects and research requirements. Capacity for drug discovery worldwide would then expand through the pooling of private- and public-sector resources, and the productivity of existing non-profit research would increase through the sharing of information, tools and ideas.

From lab to clinic

Investment in basic research for tropical diseases has created the scientific opportunity to develop a new generation of drugs. Compared with therapies for complex diseases, such as heart disease, type 2 diabetes and cancer, those for tropical diseases are generally simpler to test and optimize. This is because it is often possible to test compounds using highly predictive *in vitro* or *in vivo* screens in which death or elimination of the infectious organism can be evaluated directly. If a candidate successfully kills a parasite in a dish and a laboratory animal model, then there is a good chance that it will be effective in humans when it moves to clinical development, although further safety and dosing criteria will still need to be met.

WHO/TDR/LSTM

But many organisms that cause tropical diseases are difficult to maintain in the laboratory because of their complex life cycles. So it makes sense for specialist facilities and disease experts to work in a coordinated manner as screening centres for multiple drug-discovery groups, as in the TDR Screening Network.

New targets for drugs are also being identified as researchers finish sequencing the genomes of pathogenic organisms. Compared with whole-organism screening, mechanistic targets such as purified enzymes or receptors are usually more suitable for rapid screening using the libraries of many hundreds of thousands of compounds that are available in some pharmaceutical companies. Valuable lead compounds can be missed in whole-organism assays when they are rapidly metabolized or are unable to cross cell membranes to reach their mechanistic target. Unfortunately, genomics-based approaches have so far failed to deliver the predicted new generation of anti-infective drugs. This stems in part from a focus on the biological relevance of potential targets rather than on their 'druggability'[4] (the

Few effective medicines are available to treat diseases prevalent in tropical regions.

probability that the targets will bind to drug-like molecules).

Chemogenomics is therefore emerging as a useful strategy for target-based drug design[5] (see 'Drug discovery: from the genome to the clinic', overleaf). This approach exploits both chemical (for example, protein structure–activity data and drug binding-site features) and genomic (DNA sequence) information about the pathogenic organism. Its power lies in the ability to relate targets in a parasite back to likely chemical starting points *in silico*, enabling potential targets to be selected before expensive and time-consuming drug-screening and optimization studies are undertaken[6]. Researchers can assign priority to the most promising mechanistic drug targets for further investigation, building up a portfolio of potential projects, which can then be ranked on the basis of 'drug-hunting' criteria. Identifying promising chemical leads as early as possible could lower failure rates from screening initiatives and help reduce overall discovery costs.

Global portfolio

As well as being clinically effective, pharmaceuticals for developing countries need to be cheap to manufacture, stable during distribution and storage, and easy to administer to ensure wide usage. About half of the drugs being developed to treat neglected diseases fail some of these criteria[7], reflecting a lack of attention given to optimizing for desired properties, a paucity of lead structures and a reluctance to abandon the few unpromising leads. An agreed set of product profiles that describe the target clinical efficacy, route of administration, dosage regimen, safety and cost of treatment are widely used in industry to drive lead discovery and candidate selection. Emphasis should be placed on understanding the product profile of drugs required for the various neglected diseases[3].

One powerful way to help align global research on infectious diseases with patient needs is to use challenge-based innovation methods. Communication of specific public challenges by appropriate bodies could act as an impetus for innovation (see page 164).

Moreover, the efficiency of drug discovery would improve if a shared public portfolio of prioritized drug targets and candidate drug structures for optimization were available, because this would stimulate the pooling of research resources worldwide and attract new contributors. The recently announced TDR Drug Target Prioritization Database (http://tdrtargets.org) provides a central facility for information on drug targets, with targets ranked according to their predicted druggability, potential importance to the organism and selectivity compared with related human proteins. Specific risks and opportunities can be assessed from the known and inferred molecular properties of each putative drug target.

By listing specific projects and requirements, these portfolios could help to mobilize new resources. Interested participants could identify collaborators, and this would increase the diversity of expertise in, for example, optimization of lead candidates, screen development or drug screening. But each organization would carry out only modular research tasks appropriate for its facilities and expertise.

Innovation networks

Scaling up drug-discovery capacity for neglected diseases means designing a mechanism that is attractive to all stakeholders — such as industry, academia, governments and international agencies — involved in drug discovery. Despite a lack of market incentive, about half of the research projects currently focusing on neglected diseases are conducted by pharmaceutical companies. Several large companies, most notably GlaxoSmithKline, Novartis, AstraZeneca and Eli Lilly, have founded research institutes dedicated to research into tropical diseases. Industry also makes a substantial contribution in kind to public–private product-development partnerships. Also, in recent years, funding from governments and philanthropic foundations has helped to establish new drug-discovery units for tropical diseases in developed and developing countries.

More industrial enterprises and academic groups could be persuaded to participate if they could contribute advice, skills and infrastructure while avoiding the sustained and costly overheads of running separate, dedicated institutes or programmes, and if they could safeguard intellectual property through appropriate contractual arrangements. 'Virtual' drug-discovery networks may be the mechanism to enable research into neglected infectious diseases to be scaled up markedly, by attracting new private and public participants.

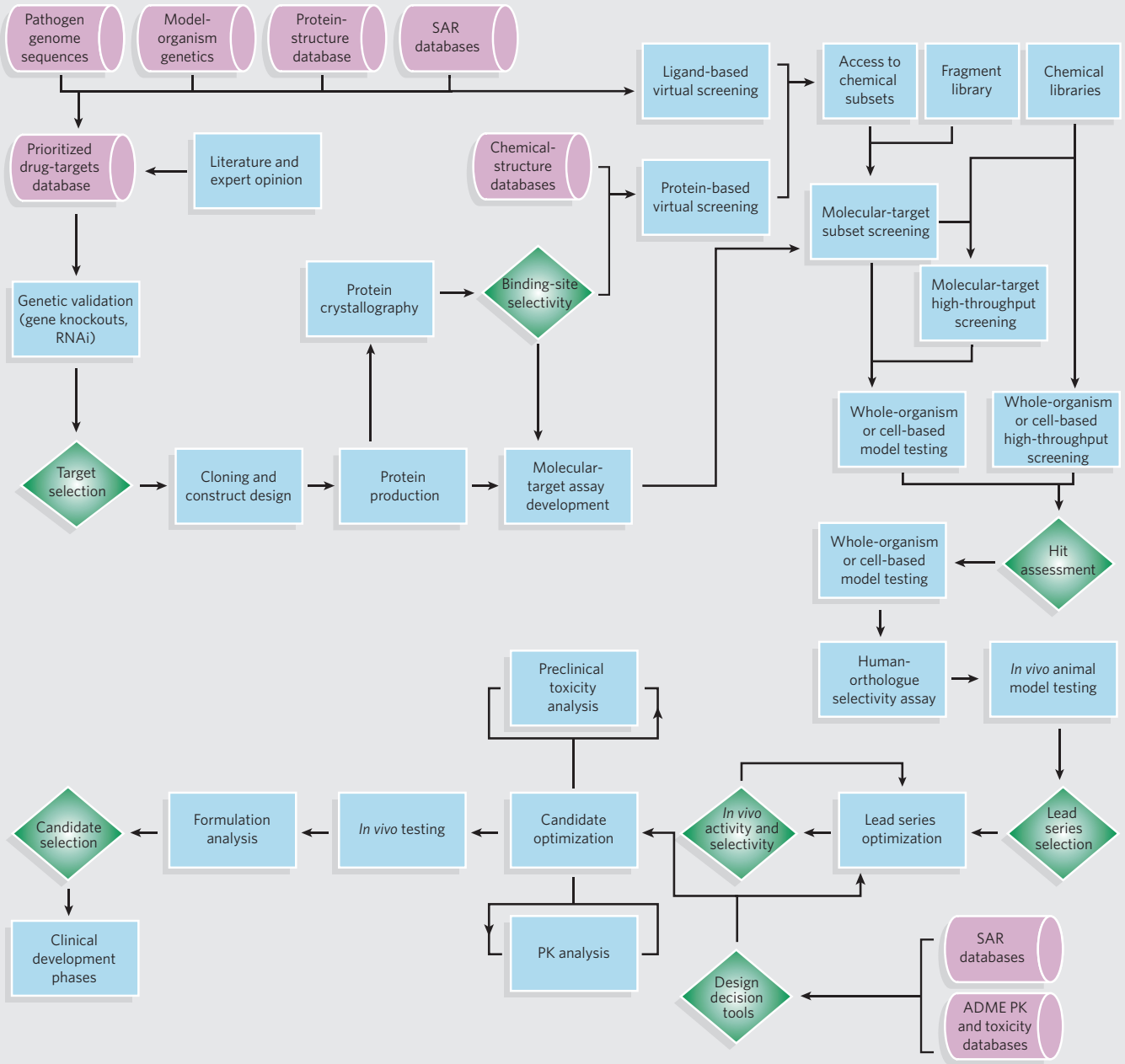
Partnering industry

Partnerships between the pharmaceutical industry, the public sector and non-governmental organizations are the foundations for the success of the innovation-network concept. By creating a framework in which industry can contribute to its expertise, knowledge, compound libraries and infrastructure, considerable cost savings could be obtained.

Industrial ventures might contribute expertise with sponsored sabbatical or fellowship schemes, or training in medicinal chemistry, for example, which is rare in the public sector. Industrial scientists could form part of a virtual multidisciplinary project team, collaborating with scientists at public and private institutes so that skills and experience are transferred in

DRUG DISCOVERY: FROM THE GENOME TO THE CLINIC

Drug discovery consists of discrete decision stages (diamonds), with iterative experimentation at each step (boxes). The early stage involves identifying 'hits' by exploiting information (cylinders) from the biochemical properties and genome sequence of an organism in a lead-discovery strategy. Proteins that are found to be essential by chemogenomic analysis and are predicted to have promising drug-like properties can be prioritized for genetic validation. Suitable molecular-screening assays for validated targets are subset screening (10–1,000 compounds), fragment screening (1,000–2,000 compounds) and high-throughput screening (10,000–1,000,000 compounds). Chemoinformatics and 'virtual' screening methods can be used on selected subsets of compounds from various databases and then tested before scaling up an assay for high-throughput screening. Hits that pass this step can then be assessed for efficacy, selectivity and druggability. Successful hit compounds are then usually clustered into chemical series, which need to be chemically optimized into lead compounds with suitable efficacy and selectivity. Lead compounds are then optimized for their pharmaceutical properties (absorption, distribution, metabolism and excretion; ADME) and absence of overt drug toxicity. This is an iterative, time-consuming process of medicinal-chemistry design, which is assisted by design-decision tools. Ideally, several lead series are run in parallel to increase the overall chance of success. PK, pharmacokinetics; RNAi, RNA interference; SAR, structure–activity relationships. **A.L.H., M.J.W. & S.N.**




PFIZER

Pharmaceutical companies, such as Pfizer (pictured), are increasingly sharing tools with non-profit organizations to accelerate drug discovery.

both directions, helping to build global innovation capacity.

The infrastructure of industrial laboratories for research into tropical diseases could be made accessible to sponsored scientists within a collaborative framework. This might include access to facilities such as high-throughput screening equipment, automated synthesis and computer-aided drug design, under joint academic–industrial doctoral and postdoctoral training programmes. The TDR postdoctoral fellowship programme, which funds scientists to work in pharmaceutical companies on specific tropical-disease projects, is an example of how public funding can be used in an effective collaboration with industry.

Pharmaceutical companies can also provide access to a subset of their extensive libraries of proprietary chemical compounds — on a contractual and usually confidential basis — to help spread their corporate mandate across a broad range of tropical diseases. The TDR has ongoing partnerships with Pfizer, Merck Serono and Chemtura that exemplify this approach: subsets of compounds are selected by companies for screening by the TDR Compound Evaluation Network (which follows the process shown in the middle portion of the graphic, opposite).

Because shipping large amounts of proprietary chemicals to external screening laboratories can be costly and impractical, several high-throughput screening campaigns are ongoing within companies against tropical-disease targets. Virtual screening of patent and literature compound databases could also be used to help companies and collaborators select small subsets of compounds for initial screening experiments.

> "All of the tools needed to create a sustainable and scalable model of drug innovation are within our reach."

Making global networks work

Virtual drug-discovery networks[8] for infectious diseases prevalent in the developing world are already functioning on a small scale. Various researchers and institutes are called on by public–private partnerships to contribute their diverse expertise, technology and resources for a limited duration. Compared with established pharmaceutical companies, which have a relatively fixed resource and skills base, these networks have the flexibility to reprioritize projects and to outsource as needed to academia, industry and contract research organizations.

The TDR has developed a virtual drug-discovery capability by using a series of portfolio, screening, medicinal chemistry and ADME (absorption, distribution, metabolism and excretion) networks. But to be scalable and sustainable, additional components, including funding, are required to attract and coordinate more participants from the private and public sectors. To work effectively, innovation networks need to be coordinated. This includes communicating the portfolio to network participants and beyond; establishing win–win collaborations; and encouraging innovative measures to lower the costs of drug discovery and delivery. Within the framework of an enhanced innovation network, large and small companies can make worthwhile contributions to the overall mission depending on what level of commitment they can afford. This concept is already being implemented by the TDR on a small scale.

Pharmaceutical companies contain business units that benefit from shared services and enabling technologies to support their portfolio of projects. Likewise, network 'enablers', such as shared contract services, discovery tools, databases and knowledge management, would help the public–private product-development partnerships and drug-discovery networks to scale up their activity.

A coordinated, information- and knowledge-sharing 'clearing house' would be a key requirement for the active management of an enhanced virtual drug-discovery network. It would provide a place to attract new participants to public–private drug-discovery partnerships and match them to individual portfolio projects and collaborators, while brokering confidentiality agreements and contract research[9]. The modular nature of the network would allow projects to be undertaken by self-organizing, self-motivated, virtual teams with a common goal. Productivity would be increased by sharing, for example, ADME and toxicology data, as well as workflows and research tools, such as physicochemical prediction models.

Our capacity to combat neglected tropical diseases must now be mobilized to include a pan-industry effort using an open innovation[10] approach to drug discovery. All of the tools needed to create a sustainable and scalable model of drug innovation for many of these devastating scourges are within our reach. The challenge now is for industry, governments and philanthropists to unite in undertaking this mission. ■

Andrew L. Hopkins is head of chemical genomics at Pfizer Global Research and Development, Sandwich, UK. Michael J. Witty is group director of global portfolio management at Pfizer Animal Health, Sandwich, UK. Solomon Nwaka is leader of drug-discovery activities at the Special Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland.

1. Pink, R., Hudson, A., Mouries, M.-A. & Bendig, M. *Nature Rev. Drug Discov.* **4,** 727–739 (2005).
2. Kola, I. & Landis, J. *Nature Rev. Drug Discov.* **3,** 711–715 (2004).
3. Nwaka, S. & Hudson, A. *Nature Rev. Drug Discov.* **5,** 941–955 (2006).
4. Payne, D. J., Gwynn, M. N., Holmes, D. J. & Pompliano, D. L. *Nature Rev. Drug Discov.* **6,** 29–40 (2007).
5. Bredel, M. & Jacoby, E. *Nature Rev. Genet.* **5,** 262–275 (2004).
6. Hopkins, A. L. & Groom, C. R. *Nature Rev. Drug Discov.* **1,** 727–730 (2002).
7. Moran, M., Ropars, A.-L., Guzman, J., Diaz, J. & Garrison, C. *The New Landscape of Neglected Disease Drug Development* (London School of Economics/Wellcome Trust, London, 2005).
8. Nwaka, S. & Ridley, R. G. *Nature Rev. Drug Discov.* **2,** 919–928 (2003).
9. Munos, B. *Nature Rev. Drug Discov.* **5,** 723–729 (2006).
10. Chesbrough, H. *Open Business Models: How to Thrive in the New Innovation Landscape* (Harvard Business School Press, Boston, 2006).

Acknowledgements We thank G. Samuels, T. Wood, B. Callan and R. Ridley for useful discussions.