

Innovative lead discovery strategies for tropical diseases

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Abstract | Lead discovery is currently a key bottleneck in the pipeline for much-needed novel drugs for tropical diseases such as malaria, tuberculosis, African sleeping sickness, leishmaniasis and Chagas disease. Here, we discuss the different approaches to lead discovery for tropical diseases and emphasize a coordination strategy that involves highly integrated partnerships and networks between scientists in academic institutions and industry in both wealthy industrialized countries and disease-endemic countries. This strategy offers the promise of reducing the inherently high attrition rate of the early stages of discovery research, thereby increasing the chances of success and enhancing cost-effectiveness.

There is a continuing and compelling need for new and improved treatments for developing-world diseases. These include bacterial, protozoan and helminth infectious diseases such as tuberculosis, malaria, African sleeping sickness, leishmaniasis, Chagas disease, onchocerciasis, lymphatic filariasis and schistosomiasis^{1–3}. A number of factors limit the utility of existing drugs in resource-poor settings, such as high cost, poor compliance, drug resistance, low efficacy and poor safety². Because the evolution of drug resistance is likely to compromise every drug in time, the demand for new therapies is continuous. Accordingly, a vibrant drug discovery pipeline is needed to help to ensure the availability of new products that will reduce mortality and morbidity resulting from these infections^{4,5}.

Discovering lead compounds with the potential to become usable drugs is a crucial step to ensuring a sustainable global pipeline for innovative products^{4,6}. In recognition of this need a number of agencies, including the Special Programme for Research and Training in Tropical Diseases at the World Health Organization (WHO/TDR), various international/national bodies and philanthropic foundations, have been supporting the discovery of such agents for tropical diseases (see Further information for organizations likely to support this type of research). Some of the fruits of these programmes have already been taken forward by public–private partnerships (PPPs)^{5,7,8}.

Drug development PPPs that focus on product identification for specific tropical diseases often require quality lead compounds to feed into their preclinical pipelines. Some of these organizations are making significant

progress in trying to bring products to the market through enhanced development programmes, but place less emphasis on the risky early phases of the discovery process^{2,9,10}. However, owing to the paucity of robust lead series, these organizations are now trying to invest more in the early stages of drug discovery. For example, the Medicines for Malaria Venture (MMV) has recently initiated a focused call for drug discovery projects to boost its antimalarial pipeline. In addition, a number of the diseases mentioned above (lymphatic filariasis, onchocerciasis and schistosomiasis) lack dedicated PPPs for innovative product discovery and development. Recent reports have highlighted the gaps, needs and opportunities for increased investment and activity in translational research for new product leads^{10–12}. It should be noted that lead discovery tends not to receive much funding from the normal scientific granting bodies, and so there is less incentive for academia to work in this area.

The majority of international R&D funding and aid for infectious diseases affecting the developing world is focused on the ‘big three’ healthcare problems — HIV, tuberculosis and malaria^{9,13}. This is understandable given the high burden of these diseases. However, there is a compelling need to invest in innovative strategies to address the other largely neglected infectious diseases prevalent in the developing world via enhanced translational research for new products, as well as capacity building and utilization in disease-endemic countries^{11,14,15}. We lack a robust pipeline of products in discovery and development to deliver drugs that meet the desired target product profiles (TABLE 1) for these diseases^{2,5,16,17}.

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So, there is an urgent requirement for a coordinated approach involving multi-disciplinary networks of investigators, as well as partnerships between industry and the public sector in both developed and developing countries. One such approach that considers networks, partnerships and capacity building in an integrated lead discovery process is illustrated in FIG. 1. The present paper discusses strategies to meet the need for lead compounds for further development for tropical diseases. Specific examples are drawn from the work of the WHO/TDR covering a broad range of tropical diseases and from the approaches taken by other agencies in these areas.

Strategies for drug discovery

The discovery of novel therapeutics for tropical diseases has largely relied on three strategies: label extension, piggy-back discovery and *de novo* drug discovery.

Label extension. Until recently, the primary strategy for drug discovery for tropical diseases was based on extending the indications of existing treatments

for other human and animal ailments to tropical diseases^{5,18,19}. This fast-track approach has been successful and has resulted in some of the most important antiparasitic drugs in use today, such as ivermectin for filariasis/onchocerciasis, and praziquantel for schistosomiasis^{20–23} (TABLE 2). It continues to have a major role in the global drug discovery and development strategy for tropical diseases. For example, the veterinary anthelmintic product moxidectin, an analogue of ivermectin²⁴, is being taken into Phase II clinical trials for the treatment of lymphatic filariasis and onchocerciasis. The main attractions of this approach are the reductions in cost and time to market that can be achieved. In addition, over the past three decades there have been few specific drug discovery programmes supported by the pharmaceutical industry that target tropical diseases. However, concern related to over-reliance on label extensions has arisen in recent years: many companies have been reluctant to allow their products to be developed for tropical diseases in case their economic potential is blighted by unexpected

Table 1a | **Limitations of available drugs for parasitic diseases and proposed target profile for new drugs**

Some available drugs and their limitations*	Proposed target profile
Malaria	
<ul style="list-style-type: none"> • Quinine (1930): compliance, safety, resistance • Chloroquine (1945): resistance • Primaquine (1948): safety • Sulfadoxine/pyrimethamine (1961): resistance • Mefloquine (1984): resistance, safety • Artemisinins (1994): compliance, cost, Good Manufacturing Practice • Atovaquone/proguanil (1999): cost 	<ul style="list-style-type: none"> For uncomplicated falciparum malaria • Orally active • Low cost of goods (~US\$1 per full course treatment) • Effective against drug-resistant parasites; low propensity to generate rapid resistance • Curative within 3 days • Fast acting • Potential for combination with other agents • Paediatric formulation • Stable under tropical conditions (shelf life of >2 years)
	<p>Further profiles</p> <ul style="list-style-type: none"> • Intermittent treatment in pregnancy and early infancy • <i>Plasmodium vivax</i> malaria • Severe malaria • Prophylaxis • Single dose cure
Leishmaniasis	
<ul style="list-style-type: none"> • Pentamidine (1939): safety and efficacy/resistance issues, injectable • Antimonials (1950): safety and efficacy/resistance issues, injectable • Liposomal Amphotericin B (1990): cost, injectable • Miltefosine (2002): contraindicated in pregnancy 	<ul style="list-style-type: none"> • Active against all visceral and cutaneous leishmaniasis • Short course of treatment (≤14 days) • Single daily dose, but alternate days or weekly dosing acceptable • Injectable with reduced treatment time acceptable • Oral drug desired • Safer than available treatment • Safe in children and pregnancy desired • Cost less than current treatments (US\$200–400) • Stable under standard tropical conditions (shelf life >2 years)
	<p>Further profiles</p> <ul style="list-style-type: none"> • Topical application for cutaneous leishmaniasis desired • Potential for combination with existing agents
Human African trypanosomiasis	
<ul style="list-style-type: none"> • Suramin (1920): safety, not effective in late-stage disease, injectable • Pentamidine (1939): safety and resistance issues, injectable, not effective in late-stage disease • Melarsoprol (1949): safety and resistance issues, injectable • Eflornithine (1991): cost, injectable, only effective in <i>Trypanosoma gambiense</i> 	<ul style="list-style-type: none"> • Active against both major species <i>Trypanosoma rhodesiense</i> and <i>T. gambiense</i> • Active against known resistance strains for example, melarsoprol failures • Treatment for early-stage diseases acceptable but efficacy against both early- and late-stage desired • Parenteral administration for late-stage disease • Oral formulation for early-stage disease desired • Cure in 14 days or less • Cost less than current treatment for early stage disease (\$100–140) • Safe in pregnancy • Stable under tropical conditions (shelf life >2 years)

*The dates in parentheses are the approximate dates when the drugs were first used (information adapted and modified from REFS 2,5,22).

toxicities in these patient classes⁵. This, and other factors, has driven the quest for novel products for tropical diseases using additional discovery strategies^{5,25}.

'Piggy-back' discovery. The 'piggy-back' strategy is most useful when a molecular target present in parasites is being pursued for other (commercial) indications as it facilitates the identification of chemical starting points²⁶. Specific examples of this approach include the antimalarial screening of lead series of histone deacetylase inhibitors²⁷ that were originally developed for cancer chemotherapy, and cysteine protease inhibitors that are being developed for osteoporosis¹⁸. It should be noted that structure–activity relationships emerging from the parasite assays are unlikely to be the same as those observed for the original indication. It is therefore likely that optimized clinical candidates emerging from this strategy will be disease-specific.

De novo drug discovery. This strategy focuses on the identification of new chemical entities, both synthetic compounds and natural products, as novel antiparasitic drugs. It is more long-term than the approach discussed above and integrates discovery research based on target-based

high-throughput screening (HTS) and medium throughput screening (MTS) in whole-parasite assays against specific proteins and whole parasites.

Target-based HTS campaigns have been emphasized in recent years as a way of harvesting the significant investment made in parasite genomics programmes by the international community^{28–31}. However, difficulties encountered in moving resultant hits through the pipeline — for example, in demonstrating a correlation between enzyme inhibition and activity against whole parasites — has generated interest in developing HTS techniques for whole-organism screening^{25,32–35}. Recent whole-cell-based HTS campaigns using compound libraries containing registered drugs have yielded encouraging results^{34,35}. In addition, chemoinformatic methodologies linked to genomics, *in silico* screening^{36–38}, as well as the structural determination of proteins and their co-crystallization with small molecules, are now being applied for antibacterial and antiparasitic drug discovery^{39–42}.

MTS in whole-parasite assays using compounds chosen on the basis of a biological, biochemical or structural rationale remains the most pursued screening option for parasitic diseases^{5,25,43}. The main disadvantage of

Table 1b | **Limitations of available drugs for parasitic diseases and proposed target profile for new drugs**

Some available drugs and their limitations*	Proposed target profile
Chagas disease (American trypanosomiasis)	
<ul style="list-style-type: none"> • Nifurtimox (1970): safety, long treatment compliance, activity limited to acute stage of disease • Benznidazole (1974): safety, activity limited to acute stage of disease 	<ul style="list-style-type: none"> • Active against blood and tissue forms of disease • Active in chronic forms of the disease • Parental administration with reduced treatment time acceptable • Oral drug desired • Improved safety over current products (free of cardiac effects) • Paediatric formulation • Safe for use in children and pregnancy • Inexpensive • Stable under tropical conditions (shelf life >2 years)
Schistosomiasis	
<ul style="list-style-type: none"> • Oxamniquine (1967): only effective against <i>Schistosoma mansoni</i>, multiple dosing, cost • Praziquantel (1975): does not kill young worms and eggs; possible resistance reported 	<ul style="list-style-type: none"> • New chemical class; alternative to praziquantel is important in the context of resistance development • New mechanism of action: drug active against mature and immature forms of parasites including eggs • Active against all major types of schistosome infections • Safety equal or better than praziquantel • Oral use • Inexpensive • Short treatment courses (ideally single oral dose) • Safety profile compatible with use without diagnosis • Safe in children, pregnant women desired • Stable under tropical conditions (shelf life >2 years)
Lymphatic filariasis and onchocerciasis	
<ul style="list-style-type: none"> • Diethylcarbamazine (1949): safety, not a macrofilaricide, not used in <i>Onchocerca volvulus</i> endemic areas • Albendazole: only used in combination therapy, little acute microfilaricidal effect • Ivermectin (1989): not a macrofilaricide, regular administration needed to kill young worms 	<ul style="list-style-type: none"> • New chemical class: alternative to ivermectin and albendazole, important in the context of resistance development • Macrofilaricidal or permanent sterilization of adult worms (in addition to being microfilaricidal) • Slow action (avoid rapid death of worms to prevent side effects due to immune responses) • Oral use • Inexpensive • Safety equal or better than ivermectin or combinations for LF • Short treatment courses (ideally single oral dose) • Safety profile compatible with use without diagnosis • Safe in children, pregnant women • Stable under tropical conditions (shelf life >2 years)

*The dates in parentheses are the approximate dates when the drugs were first used (information adapted and modified from REFS 2,5,22).

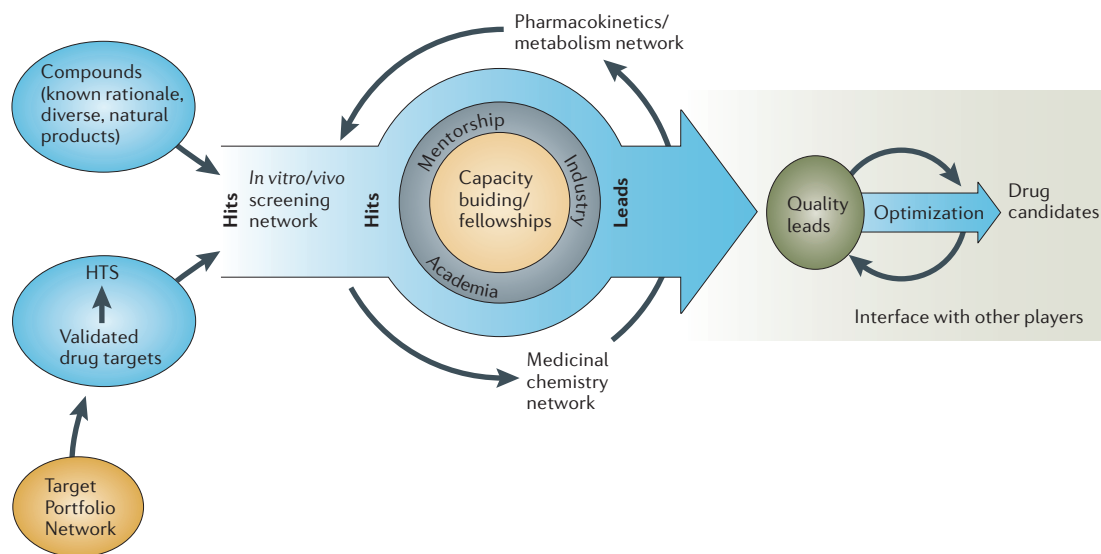


Figure 1 | An innovative lead discovery strategy for tropical diseases. This strategy involves networks and partnerships with industry and academic institutions worldwide to deliver specific drug discovery objectives. The portfolio of prioritized and validated molecular targets developed by the target portfolio network will be used in high-throughput screening (HTS) efforts at various institutions (academia and industry). Hits* emerging from the screening are assessed in whole parasites (*in vitro*) through the compound-evaluation network. In addition, compounds with an established biological/biochemical rationale or diverse structures, as well as natural products, are sourced and channelled into the compound-evaluation network for whole-parasite screening, with actives subsequently being tested in animal disease models. Through iterative medicinal chemistry and pharmacological profiling using the appropriate network, structure–activity relationships are developed and used to guide synthesis of analogues with enhanced activity. The resulting drug-like lead compounds will then be progressed into focused optimization programmes in collaboration with other partners. The integrated lead discovery strategy of the Special Programme for Research and Training in Tropical Diseases at the World Health Organization (WHO/TDR) involves experienced consultants or mentors who support and provide guidance on various aspects of the preclinical process and to the postdoctoral fellows from disease-endemic countries who are working and being trained on the programme. The involvement of institutions worldwide in the various network activities calls for increased management and fruitful capacity building, especially in the disease-endemic countries. Interactions between the different networks and quality control are managed by WHO/TDR. In this respect, a central database housed at WHO/TDR is a crucial resource for managing individual projects and processing data and compounds. *A 'hit' is compound with selective *in vitro* activity (usually $IC_{50} < 1\mu M$) against the target whole organism and/or protein; a 'lead' is a compound with druggable characteristics, that is efficacious in disease animal models with no overt toxicity; a 'drug candidate' is an optimized lead compound with *in vitro* and *in vivo* activity equivalent or better than drug standards, acceptable pharmacokinetic and toxicity profile, with a synthesis that is amenable to cost-effective scale-up. Activity criteria for 'hit' and 'lead' compounds are presented in BOX 1.

this approach is the low throughput of available assays (especially those using filariae and schistosomes), and the limited investment in the development of new robust assays. A recurring difficulty for all screens (HTS or MTS) for neglected diseases is the availability of high-quality compound libraries. Efforts are now being made to establish compound libraries and HTS screening capacity at public institutions (TABLE 3).

It should be mentioned that so far in the field of anti-infective (including antiparasitic) drug discovery, the target-based HTS approach has yielded few success stories^{6,44–46}. In part this reflects the high rate of attrition in the process of progression from early-stage biochemical hits to robust lead compounds. Many compounds active in protein-based assays are inactive in whole cells. This can be due to failure to enter intact cells but can also occur because the chosen molecular targets are not in fact essential to the microbes. The latter issue suggests that more work on target validation is needed to

increase confidence levels in the selection of protein candidates for HTS campaigns. The initial challenge of identifying molecular targets that are crucial to parasite survival, coupled with the identification of whole-cell active compounds, is formidable — and this challenge is made harder by the need to achieve efficacy in small animal disease models combining an appropriate level of potency with suitable pharmacokinetics. With the possible exception of the cysteine protease inhibitor K777, which is in development for Chagas disease⁴⁷, the authors are not aware of any compound in late discovery phase or development for a human protozoan or helminth disease that has resulted from a target-based HTS campaign. The strategy is still valid but needs to be augmented by increased efforts to select and focus on validated molecular targets and to improve the quality of compound libraries selected for the initial screening exercise. It should be seen as complementary to whole-cell screening and not as a substitute for it.

Table 2 | Some available drugs for tropical diseases

Diseases	Drug	Origin
Chagas' disease	Benznidazole	Veterinary R&D (Roche)
	Nifurtimox	Veterinary R&D (Bayer)
Human African trypanosomiasis	Eflornithine (DFMO)	Anticancer R&D (MMD/TDR)
Leishmaniasis	Lipo. Ampho. B	(NexStar/WHO)
	Miltefosine	Anticancer R&D (Zentaris/TDR)
Schistosomiasis	Praziquantel	Veterinary R&D (Pfizer/TDR)
	Oxamnaquine	Veterinary R&D (Pfizer)
Helminth infections	Albendazole	Veterinary R&D (SKB)
Onchocerciasis	Ivermectin	Veterinary R&D (Merck/TDR)
Malaria	Mefloquine	(WRAIR/H-LaRoche/TDR)
	Halofantrine	(WRAIR/SKB/TDR)
	Artemether	(China/RPR/TDR)
	Atovaquone/prog.	(Wellcome (now GSK))
	Arteether	(Artecef/TDR)
	Lapdap	(GSK/TDR)
	Lumefantrin/Artemeter	(Novartis)

Companies and partners involved in their development are indicated. The original indications for some of the drugs are highlighted. MMD, Marion Merrell Dow; SKB, SmithKline Beecham (now GSK, Glaxo SmithKline); RPR, Rhône-Poulenc Rorer.

The tripartite strategy pursuing 'label extension,' 'piggy-back' and '*de novo* drug discovery' is integrated into the network and partnership model described below.

Network/partnership models for lead discovery

In recent years, a number of networks, partnerships and consortia have been established specifically to pursue tropical disease research. Important examples include the following:

- A collaborative network of institutions supported under the Grand Challenges in Global Health initiative (funded by the Gates Foundation and Wellcome Trust; see Further information) to address infectious disease problems — for example, those with the goal to discover drugs and delivery systems that limit drug resistance for infectious diseases (see Further information, Grand Challenges in Global Health initiative — Limit drug resistance)⁴⁸.
- The various European Union drug discovery initiatives, such as the FP6, support consortia (for example, the Antimal Drug Discovery network for malaria, which consists of scientists from over 20 institutions, including academia and industry; see Further information, EU Commission — Poverty-Related Diseases) as well as the network focusing on new drugs for persistent tuberculosis (see Further information, EU Commission — New TB Drugs).
- Several drug discovery projects present within the portfolio of PPPs such as MMV, Drugs for Neglected Diseases Initiative (DNDi) and Global Alliance for TB Drug Development (GATB). For example, the anti-malarial synthetic peroxide project is based on the network paradigm⁷, as is the 8-aminoquinoline project at the

University of Mississippi, which is supported by both MMV and DNDi for malaria and leishmaniasis.

- A consortium supported by the Gates Foundation for the discovery of new drugs for African sleeping sickness is focused on the dicationic structure scaffold^{49,50}. The team consists of investigators from the University of North Carolina, the Swiss Tropical Institute (STI), Ohio State University, Kenya Trypanosomiasis Research Institute, London School of Hygiene and Tropical Medicine (LSHTM) with Immtech International as the industrial partner.

Another fairly recent development is the emergence of dedicated academic and public initiatives that focus on various aspects of drug discovery for tropical and non-tropical diseases^{2,10,51–53}. Such initiatives are largely supported with external funding and aim to approach the level of drug discovery resources and expertise present in small-to-medium-size biopharmaceutical companies. Efforts of these centres include HTS and MTS using synthetic small-molecule and natural-product libraries (TABLE 3). Examples include the University of Dundee's drug discovery initiative for trypanosomiasis and leishmaniasis, funded by the Wellcome Trust and other agencies, which encompasses HTS screening capability, molecular and parasite biology, and medicinal chemistry supported by ADME (absorption, distribution, metabolism and excretion) assays. Another example is the University of California San Francisco Sandler Center and Tropical Diseases Research Unit (supported by the Sandler Family Foundation and the National Institute of Allergy and Infectious Diseases (NIAID)), which is a consortium of laboratories dedicated to the discovery and development of new drugs for tropical diseases with core competences in genomics and proteomics, structural biology, chemistry, cell-based screens as well as pharmacokinetics. Other relevant organizations maintaining antiparasite screening operations include the Harvard/Broad initiative, the Walter Eliza Hall Institute for Medical Research and the St Jude Children's Research Hospital Memphis (TABLE 3).

The above organizations are all making valuable contributions in one way or another in the search for new therapies for specific tropical diseases. However, as the goal of these initiatives is to discover new leads or drug candidates for tropical diseases, we now need a strategy to track and monitor the progress of these activities and to avoid unnecessary duplication of effort. A coordination strategy that enhances networking and exchange of information between these entities would help to maximize the return on the investment made by the various stakeholders. One possible way of enhancing information flow is to set up a website on which investigators are encouraged to record what HTS campaigns they have conducted or which are ongoing.

The integrated and centrally coordinated strategy discussed below represents a focused attempt by WHO/TDR to address a specific gap in the earlier phases of the discovery pipeline: the identification of robust lead compounds for tropical diseases. The idea is to share some lessons that might be helpful for institutions

Box 1 | Definitions and activity criteria for hits and leads:**Hit activity criteria for protozoa**

- *Plasmodium falciparum* (K1) IC₅₀ <0.2 µg per ml, SI* >100
- *Trypanosoma brucei rhodesiense* (STIB 900) IC₅₀ <0.2 µg per ml, SI* >100
- *Trypanosoma cruzi* (Tulahuen) IC₅₀ <1.0 µg per ml, SI* >50
- *Leishmania donovani* (L82)

Axenic amastigotes IC₅₀ <0.5 µg per ml, SI* >20

Amastigotes in macrophage IC₅₀ <1 µg per ml, SI* >20

SI* = IC₅₀ L-6/IC₅₀ parasite

Lead activity criteria for protozoa

- Active *in vivo* (mice) in 10% dimethyl sulphoxide (DMSO) formulation at $n \leq 100$ mg per kg as measured by >90% reduction in parasitaemia* and/or increase in life span**;
n = number of doses given intraperitoneally, subcutaneously or per orally daily, and varies usually from 1–5

Malaria: *Plasmodium berghei* (ANKA strain), usually at 4 × 50 mg per kg*.**

African trypanosomiasis: *T. b. brucei* (STIB 795 strain), usually at 4 × 50 mg per kg*.**

American trypanosomiasis: *T. cruzi* (Tulahuen)**

Leishmaniasis: *L. donovani* (HU3)*

- Not overtly toxic in animals at efficacious dose
- Active *in vitro* against relevant parasite strains (for example, drug-resistant)

Hit activity criteria for helminths

- Schistosomiasis: *Schistosoma mansoni* adults 100% inhibition of motility at 5 µg per ml
- Onchocerciasis: *Onchocerca lienalis mf* 100% inhibition of motility at 1.25 × 10⁻⁵M

Onchocerca gutturosa adults 100% inhibition of motility or formazan formation at 1.25 × 10⁻⁵M with no obvious sign of toxicity to the monkey kidney feeder cell layer

Lead activity criteria for helminths

- Active *in vivo* (mice) when given intraperitoneally or subcutaneously in 10% DMSO formulation at 5 × 100 mg per kg as measured by a statistically significant reduction in worms (>80% is highly active)

Schistosomiasis: *S. mansoni* adults

Onchocerciasis: *O. lienalis mf*

- Not overtly toxic in animals at efficacious dose

Values are illustrative and are based on experience with compounds that have moved through the evaluation network³.

working on drug discovery for tropical diseases. For many years, WHO/TDR has focused its drug discovery resources on funding a network of compound assessment centres (FIG. 2). The need to follow up actives emerging from these test centres with dedicated medicinal chemistry backed up by pharmacokinetic investigations has now been recognized and supported with the establishment of two further specialist networks. Furthermore, in order to harness the output from the various parasite genome programmes^{28–30}, an additional network has been created to triage bioinformatic data and to identify a pipeline of molecular targets for various disease-causing parasites. These networks are described below.

The drug target portfolio network. In order to interpret and capitalize on the data emerging from parasite genome programmes, a network has been created to develop a globally accessible database populated with a prioritized list of potential drug targets. A comprehensive

listing of putative drug targets from human protozoan and helminth parasites has not been carried out systematically to date. The project will help address this issue and provide published recommendations for selected molecular targets suitable for progression to HTS campaigns. This should help promote the strategy in both industry and academia. The TDR drug target portfolio network consists of groups based at the University of Washington, Seattle, USA; the University of Pennsylvania, USA; the Sanger Centre, Cambridge, UK; the Walter Eliza and Hall Institute for Medical Research (WEHI), Melbourne, Australia; and the Institute for Research in Biotechnology (UNSAM), Argentina. The participation of an institution from a disease-endemic country in this global consortium adds a novel capacity-building dimension.

In addition to the above, a recent drug discovery collaboration between Pfizer and WHO/TDR is being extended to include support for the target portfolio project. Pfizer is already supporting this network by bringing its own genome triaging expertise and techniques³⁶ to bear on the selection and prioritization of molecular targets. A recent publication on target prioritization for *Mycobacterium tuberculosis*⁵⁵ demonstrates the utility of this exercise across tropical diseases. Pfizer is working with the University of Pennsylvania, the University of California San Francisco Sandler Center, and Inpharmatica to identify parasite homologues of their own commercial targets for other indications. The ‘druggability’ of such parasite targets will be assessed and ranked in order to facilitate prioritization by the drug target network. The triaged information will be made available through a database that is being developed by the network. The synergistic, overlapping and coordinated activities of the different groups present an opportunity for building a chemoinformatics and *in silico* drug discovery platform for tropical diseases.

Compound screening and evaluation network. The biological assessment network has been the engine of TDR’s drug discovery strategy for many years. It is a unique integrated global collection of compound assessment centres that allows scientists from academia and industry to submit compounds for test free of charge. This has given the network unrivalled access to many thousands of diverse compounds in the search for new antiparasitic leads. However, in the process of assessing these diverse collections, various recurring problems have been noted. For example, the turn-around time has been a contentious issue, particularly with the assessment of individual compounds or small collections. This arises because of the need of the screening centres to amass sufficient samples to make it time-effective to run multiple parasite assays at once. However, the screening centres are now focused on evaluating agreed numbers of compounds based on available budgets to ensure an efficient turn-around of data. Another problem encountered is that many samples supplied for test and subsequently found active enough to justify progression have not been available in sufficient quantity. Consequently, only preliminary test data have

Table 3 | Academic and public institutes offering drug screening opportunities for tropical and other diseases

Region	HTS screens	Whole-parasite screening and disease type
North America	<ul style="list-style-type: none"> • NIH USA: Chemical Genomics Initiative and Molecular Libraries Screening Center Network (http://nihroadmap.nih.gov) • University of California San Francisco Sandler Center and Tropical Diseases Research (http://www.ucsf.edu/mckerrow/protocol.html) • Harvard and Broad Institute Initiative (www.broad.harvard.edu/chembio/plaform/screening/index.htm) • Stanford University: High Throughput-Bioscience Center (http://www.htbc.stanford.edu) • Purdue Center for Combinatorial Chemical Biology (http://www.chem.purdue.edu/CCCB/index/shtml) • Yale University: Chemical Genomics (http://www.yale.edu) • St. Jude Children's Research Hospital HTS efforts (http://www.stjude.org) • McGill University: HTS facility (www.medicine.mcgill.ca/biochem/htsfacility/index.htm) • McMaster: HTS lab (www.hts.mcmaster.ca) • Canadian Institute for Health Research, network for chemical biology (http://www.cihr.irc.gc.ca/e/28269.html) 	<ul style="list-style-type: none"> • Walter Reed Army Institute for Research WRAIR — malaria, leishmaniasis and others (http://wrair-www.army.mil/) • University of Washington Seattle — malaria, trypanosomiasis (http://depts.washington.edu/daid/) • University of California San Francisco — malaria, trypanosomiasis (http://www.ucsf.edu/) • University of Mississippi — malaria, leishmaniasis (http://www.pharmacy.olemiss.edu/ncnpr/) • University of Southern Florida — malaria
Europe	<ul style="list-style-type: none"> • University of Dundee Drug Discovery Initiative (http://www.welcome.ac.uk/doc_wtx027342.html) • European Molecular biology Laboratory: Chemical Genomics Core Facility (http://www.embl.org) • HT-Technology Development Studio, Max Planck Institute (http://tds.mpi-cbg.de/webtds/4.html) • Medical Research Council London — malaria (http://www.mrc-technology.org) • WISDOM: Initiative for grid-enabled drug discovery against neglected diseases (http://wisdom.healthgrid.org/) 	<ul style="list-style-type: none"> • Swiss Tropical Institute — malaria, leishmaniasis, trypanosomiasis, helminths (www.sti.ch) • London School of Hygiene and Tropical Medicine — malaria, leishmaniasis, trypanosomiasis, schistosomiasis (www.lshtm.ac.uk) • Northwick Park Institute for Medical Research — filariasis, onchocerciasis • Institute Pasteur — malaria, trypanosomiasis (http://www.pasteur.fr) • University of Anwerp, Laboratory of Microbiology, Parasitology and Hygiene — malaria, trypanosomiasis, leishmaniasis (http://www.ua.ac.be/lmph) • University of Liverpool — malaria (www.liv.ac.uk)
Asia/Australia	<ul style="list-style-type: none"> • Walter Eliza Hall Institute for Medical Research (http://www.wehi.edu.au) • Griffith University, Eskin Institute (www.griffith.edu.au/centers/eskitits/) 	<ul style="list-style-type: none"> • Kitasato Institute Japan — malaria, leishmaniasis, schistosomiasis (www.kitasato.or.jp) • Indian Central Drug Research Institute Lucknow — expertise on malaria, leishmaniasis, filariasis (www.cdriindia.org) • Institute of Parasitic Diseases Shanghai China — malaria, schistosomiasis • National Center for Genetic Engineering and Biotechnology, Thailand — malaria, tuberculosis (http://www.biotec.or.th)
Africa and Middle East	<ul style="list-style-type: none"> • Tel Aviv University: National center for HTS of Novel Bioactive Compounds (http://www.tau.ac.il/~nchts/main.htm) 	<ul style="list-style-type: none"> • Theodor Bilharz Research Institute Cairo — schistosomiasis (http://www.tbri.sci.eg/main.htm) • Kenya Medical Research Institute — malaria, leishmaniasis (http://www.kemri.org/kemri_centres.asp) • University of Ibadan Nigeria — malaria (http://www.ui.edu.ng/)
South America		<ul style="list-style-type: none"> • Instituto Oswaldo Cruz — malaria, trypanosomiasis (www.ioc.fiocruz.br) • Instituto Venezolano de Investigaciones Científicas, Venezuela — trypanosomiasis • Institute for Advanced Scientific Investigation and High Technology — malaria, leishmaniasis

Some of the institutions involved in high-throughput screening (HTS) are not primarily focused on tropical diseases (see also REF. 51). The list might not be exhaustive.

been obtained, which, once provided to the supplier, have often been published without any further action being planned. There is now increasing due diligence being performed to assess the quality of the compounds supplied for test and to ascertain that a commitment to follow them up will be made by the supplier.

The investigators responsible for the individual test centres funded by TDR are world-renowned parasitologists. Collectively, they offer a comprehensive range of *in vitro* (whole parasite) screens and animal disease models, permitting in-depth profiling against a range of parasites and detailed assessment in various *in vivo*

systems to guide lead identification/optimization (FIG. 2). The network consists of five centres: the Swiss Tropical Institute (STI), Basel, which provides *in vitro* and *in vivo* screens for malaria, African trypanosomiasis, leishmaniasis and Chagas disease; the London School of Hygiene and Tropical Medicine (LSHTM), which provides *in vitro* and *in vivo* screens for schistosomiasis, as well as *in vivo* assays for leishmaniasis and Chagas disease; the Northwick Park Institute for Medical Research (NPIMR), London, which provides *in vitro* and *in vivo* screens for filariasis and onchocerciasis; the Theodor Bilharz Research Institute (TBRI), Cairo, which provides

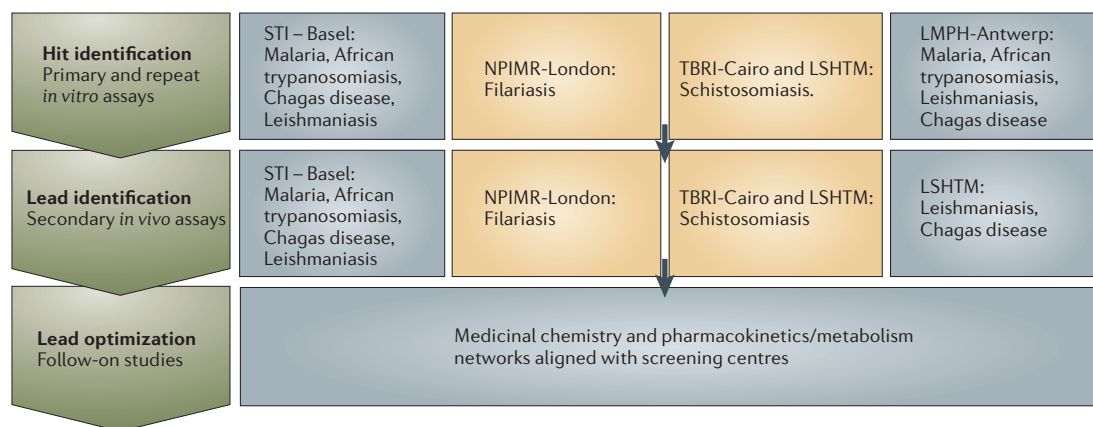


Figure 2 | **WHO/TDR-funded compound evaluation network.** The compound evaluation network performs primary *in vitro* screens against the various parasites. Compounds that meet the *in vitro* activity and cytotoxicity criteria ('hits') are progressed to *in vivo* analysis, and subsequently medicinal chemistry and pharmacokinetic analysis to identify 'leads'. LMPH, Laboratory of Microbiology, Parasitology and Hygiene (Antwerp); LSHTM, London School of Hygiene and Tropical Medicine; NPIMR, Northwick Park Institute for Medical Research (London); STI, Swiss Tropical Institute (Basel); TBRI, Theodor Bilharz Research Institute (Cairo); WHO/TDR, Special Programme for Research and Training in Tropical Diseases at the World Health Organization. Activity criteria for 'hits' and 'leads' are presented in BOX 1.

in vitro and *in vivo* screens for schistosomiasis; and the Laboratory of Microbiology, Parasitology and Hygiene at the University of Antwerp (LMPH), which provides *in vitro* screens for malaria, leishmaniasis and trypanosomiasis. Overall, the network is capable of processing about 20,000 compounds per annum through the *in vitro* screens and evaluating approximately 1,000 compounds per annum *in vivo*, based on the funding currently provided by WHO/TDR. The turn-around time for generating data varies for the various *in vitro* and *in vivo* models used. On average, most *in vitro* test data is available within 4–8 weeks of receiving the compound whilst the turn around time for *in vivo* assessment is about 8 weeks.

The compounds fed into these centres are sourced from both industrial and academic partners and in most cases the supply is under contractual agreement. In recent years, hits emerging from these screens have largely been pursued through the acquisition of analogues, either from the original suppliers or from commercial purveyors of compound libraries. Although this has allowed development of preliminary structure–activity relationships, often it has not allowed the work to progress sufficiently to allow identification of lead compounds that are orally efficacious in animal disease models. The lack of a coordinated strategy encompassing medicinal chemistry, pharmacology and toxicology is now being addressed — active compounds are further supported through the TDR medicinal chemistry and pharmacokinetic networks in order to optimize activity and generate robust leads. The activity criteria used for some of these screens are presented in BOX 1.

There are other well-established screening centres for various tropical diseases (TABLE 3), although these tend not to cover the range of parasite assays embraced by the TDR network. These include the Walter Reed Army Institute for Research (WRAIR), which has worked closely with TDR for many years in seeking

antimalarial leads; the Indian Central Drug Research Institute, Lucknow; the Kitasato Institute, Japan; the Institute for Parasitic Diseases, China; the University of Washington, the University of North Carolina, the University of Mississippi and the University of California San Francisco, USA.

Database and compound storage resource in project management. Another important element in the management of network and partnership activities is the use of a secure interactive database for data, project and communication management. The database managed centrally by TDR enables the organization, collation and management of all compounds sourced as well as the resultant data subsequently generated from the test centres. Compounds are organized with clear identification numbers. A planned update of the TDR database will enable relevant partners to enter data directly onto the database from a remote location using a password-protected mechanism. The database promotes enhanced communication, as recent results or presentations can be shared as needed with relevant partners at different locations in real time — for example, during tele- or video conferencing. The integrated database is secure and respects all confidential structures from collaborators. Another equally important type of database is the open-source database that contains various research reagents^{67,68}.

Linked to the function of the database is a central compound storage facility where all the samples sourced by TDR are collated and distributed to screeners in an appropriate format. For the past few years, TDR has retained RCC, Basel (TABLE 4), as its compound storage facility. The need for various types of databases (whether secure or open-source) as well as compound management^{69,70} and storage exemplifies additional elements of managing virtual drug discovery that are not often discussed.

Table 4 | TDR drug discovery collaborations

Name of company	Type of business	Type of collaborations with TDR
Pfizer	Pharma/animal health	<ul style="list-style-type: none"> • Compound supply for testing • Medicinal chemistry/ pharmacokinetics • Potential HTS campaigns • Cheminformatics • Training
Serono	Pharma	<ul style="list-style-type: none"> • HTS campaigns • Medicinal chemistry/ pharmacokinetics • Training
Bayer	Pharma/Animal Health	<ul style="list-style-type: none"> • Compound supply for testing
Sanofi-Aventis	Pharma	<ul style="list-style-type: none"> • Compound supply for testing • Other collaboration
Pharmacopeia	Pharma	<ul style="list-style-type: none"> • Medicinal chemistry/ pharmacokinetics • Training
TopoTarget	Pharma	<ul style="list-style-type: none"> • Compound supply for testing • Lead optimization for malaria
Paratek	Pharma	<ul style="list-style-type: none"> • Compound supply for testing
Meiji	Pharma/Animal health	<ul style="list-style-type: none"> • Compound supply for testing
Chemtura	Crop protection/vector control	<ul style="list-style-type: none"> • Compound supply for testing
Syngenta	Agrochemicals	<ul style="list-style-type: none"> • Compound supply for testing
Dow AgroSciences	Agrochemicals	<ul style="list-style-type: none"> • Compound supply for testing
ChemDiv	Chemical libraries and contract synthesis	<ul style="list-style-type: none"> • Compound supply for testing
Princeton BioMolecular Research	Chemical libraries and contract synthesis	<ul style="list-style-type: none"> • Compound supply for testing
Specs	Chemical libraries and contract synthesis	<ul style="list-style-type: none"> • Compound supply for testing
ChemRoutes	Chemical libraries and contract synthesis	<ul style="list-style-type: none"> • Compound supply for testing
RCC	Contract Research	<ul style="list-style-type: none"> • Compound storage and handling

HTS, high-throughput screening.

The medicinal chemistry and pharmacokinetics/metabolism networks. The medicinal chemistry effort currently involves one large pharmaceutical company (Pfizer) partnering with TDR, and two biopharmaceutical companies, Serono and Pharmacopeia (TABLE 5). Several academic institutions are also part of this network: the University of Nebraska, USA; University of Dundee, UK; University of Cape Town, South Africa; Ohio State University, USA; and St. Jude Children's Research Hospital, Memphis, USA. These centres work on the active compounds emerging from either the screening network (whole cells) or from the HTS campaigns (protein-based assays directed towards specific molecular targets). Some of the recent active compounds (validated hits) emerging from TDRs screening of commercially sourced compounds are part of the series being progressed through the medicinal chemistry network. These include seven leads for various tropical diseases: four for malaria, one for leishmaniasis, one for African sleeping sickness and two for helminths.

The network seeks to carry out medicinal chemistry using postdoctoral fellows based at those centres. These pursue 'hit to lead' or early stage 'lead optimization' in the normal iterative cycle of synthesis and biological assessment, feeding compounds back into the screening centres (FIG. 1). A number of fellows are linked to institutions in developing countries. The participation of a first-rate medicinal chemistry laboratory in a disease-endemic country provides an opportunity for the establishment in Africa of a centre of excellence to help promote innovation in this core area of lead discovery.

The pharmacokinetics/metabolism network, which provides essential data for the chemists, presently consists of the Monash University, Australia, and various TDR collaborating companies such as Pfizer, Serono and Pharmacopeia that are providing this service in-kind as part of the ongoing collaboration. Additional academic centres are being sought to augment this network.

Another approach to providing chemical support for tropical disease research (one widely used by large pharma for other therapeutic areas) is to draw on the services of contract research organizations and institutions located in advanced developing countries such as India and China⁵⁴. These are probably most productively deployed to synthesize focused chemical libraries rather than engaging in the more specific process of lead optimization. In general, it will be beneficial to establish coordination mechanisms similar to the integrated approach discussed in this paper, to help harness the huge resources available in these technologically advanced developing countries. The risk of poor commercial return might explain why some companies in these countries are not investing in product discovery for tropical diseases endemic to these geographic regions. However, an increasing number of companies in China, India, Korea, South Africa and Singapore are participating in PPPs to develop products for various developing world diseases^{2,9}.

Partnership characteristics and opportunities

The past 6 years has witnessed a dramatic increase in interest in R&D directed towards producing new drugs for tropical diseases. This has been fuelled by the creation of various partnerships involving academia, industry and PPPs, and the arrival of new funding from both governments and philanthropic foundations, in particular the Gates, Wellcome Trust and Rockefeller Foundations^{2,56} (BOX 2; TABLE 6). Industry is increasing its participation^{2,9}: GSK has dedicated its Tres Cantos facility in Spain to developing world diseases (mainly malaria and tuberculosis) and continues to collaborate with MMV and GATB; the Novartis Institute in Singapore is focusing on tuberculosis (in partnership with GATB) and dengue and has recently extended to malaria in partnership with MMV and the Wellcome Trust; AstraZeneca India is investing in tuberculosis drug R&D, as is Johnson & Johnson; and Sanofi-Aventis has established an Impact Malaria programme and continues to collaborate with TDR and DNDi.

These efforts are required to sustain the drug development pipeline for tropical diseases in the medium and long term. In addition, drug R&D for certain diseases

Table 5 | **The medicinal chemistry network**

Workstations (pharma/academia)	Number of post-doctoral fellows
Pfizer	Two fellows
Serono	Two fellows
Pharmacopeia	One fellow
University Cape Town	Two fellows
University of Nebraska	One fellow
University of Dundee	One fellow
St Jude Children Hospital	One fellow
Ohio State University	One fellow

Some of the postdoctoral fellows are from disease-endemic countries. They receive on-the-job training in order to contribute to specific projects in the network. The interface between medicinal chemistry and the networks engaged in compounds assessment and pharmacokinetic profiling is managed jointly by WHO/TDR and partners.

continues to be neglected, such as those encompassed by kinetoplastids (which DNDi is investing in, as well as helminth infections, for which a new initiative is being created (BOX 3)). In a new development, Pfizer has recently signed an agreement with the WHO/TDR to provide compounds and other drug discovery support to help identify leads for a wide range of tropical diseases: malaria, African sleeping sickness, Chagas, leishmaniasis, lymphatic filariasis, onchocerciasis and schistosomiasis. A similar collaboration directed at progressing various HTS campaigns has been secured with Serono. These new partnerships present a unique opportunity for tropical diseases and will probably help draw other companies into this field of research.

The recent re-emergence of interest in tropical disease research from the pharmaceutical sector is also supported by the involvement of the animal health and agrochemical industries, as well as specialty chemical companies, who are all contributing compounds for evaluation for human infectious diseases. This is exemplified by the collaboration of WHO/TDR with such companies as Syngenta, Chemtura and Bayer Animal Health (TABLE 4). Forte Dodge is partnering with TDR in clinically progressing the animal-health product moxidectin for the treatment of onchocerciasis²⁴.

Although TDR maintains a network of screening centres with a substantial overall capacity for testing compounds in whole-cell screens, it can be difficult to source samples with an appropriate rationale for testing and in sufficient quantity to facilitate follow-up assessment. Increasing efforts are being put into sourcing high-quality compounds with a defined testing rationale. Companies are sought that might have biologically, biochemically or pharmacophore-relevant compounds that they would be willing to provide for assessment for their potential to treat tropical diseases. Experience shows that although many scientists in industry are extremely willing to provide compounds for testing, higher management is often more reticent due to perceived problems in exposing their intellectual property to competitors or putting at risk drugs in commercial development. Such issues,

although often requiring protracted discussion, can usually be addressed satisfactorily, and TDR plus other PPPs have been successful in establishing agreements with industry to enable them to partner and contribute compounds for evaluation against tropical diseases.

Partnerships for drug discovery with both industry and academia typically involve the following: the supply of biologically or biochemically relevant compounds, or natural products, for screening against parasites; supporting investigators to validate and obtain proteins as molecular targets for HTS campaigns; accessing or supporting centres to conduct HTS campaigns using diverse or focused compound libraries; funding medicinal chemistry, pharmacokinetics/metabolism and toxicological assessment for lead identification and optimization, as well as supporting the establishment and maintenance of databases to facilitate drug discovery for tropical diseases.

These collaborations are normally covered by 'materials transfer' or 'collaborative' contracts as exemplified by the recent agreements between WHO/TDR and Pfizer, Serono and Chemtura. The Pfizer collaboration focuses initially on lead discovery, with the company supplying thousands of compounds (including those with a known biological/biochemical rationale) to be tested against target parasites in TDR's screening network. Hits emerging from this programme will be expanded using TDR-funded medicinal chemists based at Pfizer. The collaboration is being extended to pursue HTS campaigns against molecular targets, and to use cheminformatics to identify new targets and compounds^{36,37,57}.

The Serono–WHO/TDR collaboration centres on drug discovery through HTS campaigns and allows for hit expansion with medicinal chemistry support. Serono is using its compound libraries for HTS against putative new drug targets selected by TDR in association with collaborators based in academia. Hits identified in these protein-based assays are assessed in the TDR parasite screens. Whole-cell actives are then further elaborated to develop SAR using TDR-funded medicinal chemistry resources based in Serono. The Chemtura–WHO/TDR agreement focuses initially on supply of test compounds. These and other companies helping TDR in the discovery of new leads are highlighted in TABLE 4. Collectively, these represent a significant coordinated level of early discovery activity for multiple tropical diseases.

The globally integrated and focused strategy depicted in FIG. 1 is helping to stimulate industry worldwide to participate in lead discovery for tropical diseases. It is also attracting more academic investigators to work in the field of 'neglected diseases' drug discovery. It complements and synergizes with the activities of PPPs such as MMV, DNDi and GATB by facilitating the progression of new leads into the development pipeline of these organizations or other institutions. It is noteworthy that a number of lead series currently being developed by PPPs benefited from initial involvement with WHO/TDR, either by direct support for synthesis programmes or by access to the compound-assessment network. Examples include the antimalarial ozonides⁷, *bis*-amidines⁴⁹ and dihydrofolate reductase inhibitors³⁹ being developed by

MMV, and trypanothione reductase¹⁶ and farnesyltransferase inhibitors⁵⁸ previously supported by DNDi. This has provided these organizations with sufficient data to allow critical assessment of the work and to commence funding at the lead optimization stage.

Arguably, one of the more novel and attractive elements of this innovative lead discovery approach is the integration of capacity building through clear project deliverables. Such capacity building in lead discovery, as shown in FIG. 1, is not restricted to the developing world — through network activities it can also be pursued in

institutions in developed countries. In the context of disease-endemic countries, this approach will encourage local technology development — for example, through exploration of natural products as potential leads, and technology transfer through the various network activities. TDR is supporting two natural-product screening centres in Kenya and Nigeria. Sustainable capacity can be developed in disease-endemic countries if the most talented scientists and institutions are engaged in these partnerships for lead discovery with the same level of rigour as their colleagues in developed countries. In

Box 2 | Synergies of partners in lead discovery for tropical diseases

Academia. The role of academic laboratories is indispensable in lead discovery for tropical diseases. Tropical disease expertise in *in vitro* and *in vivo* screening (TABLE 3), development of new screening tools, improved animal models, genomics, and target identification/validation resides within academia. In addition, academic laboratories are making great strides in high-throughput screening (HTS), medicinal chemistry and pharmacokinetic analysis to aid the discovery and progression of leads into development candidates for tropical diseases, and this should be encouraged. For example, TDR has collaborated with the Walter Eliza and Hall Institute for Medical Research in Melbourne to run HTS against three parasite targets: trypanothione reductase (from *Trypanosoma cruzi*), farnesyl pyrophosphate synthetase (*Trypanosoma brucei*) and pyrophosphokinase (*Plasmodium falciparum*). The initial hits emerging from the three campaigns have been evaluated in whole parasites at the WHO/TDR compound screening centres, and follow-up medicinal chemistry/pharmacokinetic studies are now under consideration. Similar HTS campaigns have been commissioned by Drugs for Neglected Diseases Initiative (DNDi) at other academic institutions. Such laboratories (TABLE 3), as discussed previously, are well established for HTS campaigns. Further participation from academia will probably be encouraged by such success stories as the selection of a synthetic peroxide OZ277 by the Medicines for Malaria Venture (MMV) for development for malaria (now in Phase II clinical trials)⁷. This involved participation from both industry and academia, as well as input from experts with pharma experience. Although the increasing role of academic centres in drug discovery for tropical diseases is a welcome development, partnership with industry and other centres will help to maximize output.

Industry. TDR and the new private–public partnerships (PPPs) have a track record in collaborating with industry to identify new drug candidates for human health⁶⁴. Indeed, a focused lead discovery effort that incorporates a clear milestone-driven approach and a ‘win–win’ intellectual property strategy promises to attract more industry involvement. Industry typically provides compound libraries, infrastructure and know-how for HTS, medicinal chemistry and ADMET (absorption, distribution, metabolism, excretion and toxicity) profiling. However, academia is increasingly starting to have a significant role in the provision of chemistry and pharmacokinetic expertise and in developing HTS capabilities^{7,34,35,53,64,65}. TDR or other public-sector participants typically bring knowledge of the disease and target product profile to guide discovery, molecular targets for screening from academic collaborators and funding from its stakeholders to leverage the investment of industry (for example, by funding personnel, including fellows from developing countries, to work on projects as well as portfolio management).

PPPs. Some PPPs involved in tropical disease R&D (TABLE 6) are focusing on product development with less investment in the early stages of lead discovery (for example, HTS against molecular targets and medium-throughput screening against parasites *in vitro*). Investment in early drug discovery is essential in order to ensure a sustainable portfolio of lead compounds for further optimization and development. The focused lead discovery strategy and the work of academic centres discussed here will complement and synergize with PPPs such as MMV, Global Alliance for TB Drug Development (GATB) and DNDi.

Philanthropic foundations. Organizations such as the Bill and Melinda Gates Foundation, Rockefeller Foundation and the Wellcome Trust are investing in discovery (TABLE 6). They make funding available for such work as long as a clear rationale exists supported by the appropriate technical and management expertise to achieve agreed objectives. Some of the projects supported through the Gates Grand Challenges initiative should help to stimulate lead discovery in the medium to long term. In response to the gap in the availability of new tuberculosis leads, the Gates Foundation has developed a new strategy for tuberculosis drug discovery, which is much needed (See Further information, Bill & Melinda Gates Foundation: Call For Proposals — Tuberculosis). It would seem that the strategy for this programme is similar in many respects to the network and partnership approach discussed in this paper. It is anticipated that the target prioritization exercise discussed above, which encompasses tuberculosis (see also REF. 55), will complement this new effort.

In addition to supporting the University of Dundee’s drug discovery efforts, the Wellcome Trust is also funding a more general initiative focused on early stages of lead discovery/optimization. However, this is not directed specifically towards tropical diseases and can encompass any human disease.

National and international research agencies. Some national and international agencies (TABLE 6) might have opportunities for funding and capacity building in various areas of tropical diseases.

These various initiatives, some with varied scope, funding and strategy are an excellent demonstration of the progress being made in tropical disease R&D. It also shows the need to increase coordination in order to better manage interfaces, gaps and data flow from these efforts.

Table 6 | **Organizations funding (or likely to fund) research into tropical diseases**

Organization	Website
Philanthropic foundations	
Bill & Melinda Gates Foundations	http://www.gatesfoundation.org
Burroughs Wellcome	http://www.bwfund.org
Grand Challenges	http://www.grandchallengesgh.org
Rockefeller Foundation	http://www.rockfound.org
Wellcome Trust	http://www.wellcome.ac.uk
Public organizations/institutions*	
European Union	http://ec.europa.eu/research/health/poverty-diseases
UK DFID	http://www.dfid.gov.uk/research
US National Institute of Health	http://www.nih.gov ; http://www.niaid.nih.gov
International Development Research Council Canada	http://www.idrc.ca
Canadian Institute for Health Research	http://www.cihr-irsc.gc.ca
Public-private partnerships	
Drugs for Neglected Diseases Initiative	http://www.dndi.org
Global Alliance for TB Drug development	http://www.tballiance.org
Medicines for Malaria Venture	http://www.mmv.org
Institute for One World Health	http://www.iowh.org
International organizations and development banks	
Special Programme for Research and Training (TDR) at WHO	http://www.who.int/tdr
The World Bank	http://www.worldbank.org
Regional Development Bank	http://www.iadb.org ; http://www.afdb.org ; http://www.adb.org
United Nations Education, Scientific and Cultural Organization (UNESCO)	http://www.unesco.org

This list is not exhaustive. *Certain national agencies concerned with international development and research such as United States Agency for International Development USAID (www.usaid.gov), Japan International Cooperation Agency JICA (<http://www.jica.go.jp>), Swedish International Development Agency (<http://www.sida.se>), German Agency for Technical cooperation (<http://www.gtz.de/home/english>), Swiss Agency for Development and Cooperation (www.sdc.admin.ch), Danish International Development Agency DANIDA, Canadian International Development Agency (www.cida.gc.ca), Netherlands Ministry of Development Cooperation, and other national as well as research councils and ministers.

contrast to past capacity-building activities in developing countries, this approach is linked to clear project deliverables, management and accountability. There have already been some successes through the fellowship component of this approach, with scientists involved with HTS campaigns at Serono going back to their countries to put their new-found experience into practice⁵⁹.

Currently, global interest in the promotion of innovation for new treatments for developing-world diseases is high. The G8 meeting in 2005 (REF. 60), as well as the Millennium Development Goals⁶¹, emphasize the role of partnerships in providing worldwide healthcare solutions. The WHO Commission on Intellectual Property Rights, Innovation and Public Health also highlighted the need for innovative product discovery for diseases affecting developing countries¹¹. Indeed, increased emphasis on innovative lead discovery will help ensure sustainability in the availability of new products for the control of tropical diseases both in the medium and long term. The hope is that public donor agencies and foundations will invest more resources in this area. Some recent indication of such improved funding comes from a call from the Gates

Foundation for proposals for discovery research directed towards TB (see Further information, Bill & Melinda Gates Foundation: Call For Proposals — Tuberculosis).

In view of the changing nature of drug research for tropical diseases, more robust coordination mechanisms are needed for lead discovery. A promising vehicle for delivering and coordinating the discovery of new lead compounds is exemplified by the integrated networks embracing compound screening, medicinal chemistry, pharmacokinetics/metabolism, and the development of a prioritized drug target portfolio (FIG. 1). This strategy offers a cost-effective solution to filling the demand for robust lead compounds suitable for further development^{62,63}. Initial cost assessment based on TDR's lead discovery experience using the network and partnership method described here suggests that two high-quality lead compounds can be discovered every year with an annual budget of about US\$7 million. This includes investment in the development of new technologies — such as new drug screening tools and prioritization of drug targets to facilitate HTS campaigns, as well as capacity building — that will help sustain lead discovery

Box 3 | A new initiative focusing on helminth drug discovery

In recognition of the urgent need for new anthelmintics, WHO/TDR is currently coordinating and facilitating drug discovery for helminth infections. An informal consultation meeting convened by TDR in February 2005 identified the need for an initiative to facilitate the discovery and development of new products for diseases resulting from infections with schistosoma and the filariae. The Genomics and Discovery Research committee of TDR endorsed proceeding with such an initiative but recommended that a focused meeting of world experts from industry, academia and the donor community be convened to provide further guidance. Subsequently, the meeting was held in Tokyo in March 2006 and the concept of the helminth initiative fully endorsed. TDR was tasked with the establishment and incubation of the Helminth Initiative, focusing on antihelminthic drug discovery to identify new candidates that can be advanced to development. It is expected that success in the next 2–3 years might help to build a case for an independent public–private partnership for anthelmintic R&D.

for tropical diseases in the medium to long term. This is good value for money considering the high attrition rate in early drug discovery. Obviously this estimate does not include in-kind contributions from the industry.

Challenges of lead discovery

Managing multiple partners (FIG. 1; BOX 2) from diverse cultures and with a wide range of expertise in a network charged with a unique drug discovery objective is not an easy undertaking^{2,21}. The success of these networks largely depends on the people doing the work, the available facilities, the mechanism(s) put in place for programme management by the coordinating body and the incentives

provided for reaching defined goals. Perhaps the single most important stimulus is the appreciation that the work being performed is for the public good, not for profit. Many scientists in industry are willing to contribute their expertise to help advance projects focused on developing-world diseases. This is also true of academic scientists who are increasingly pursuing product-driven research for tropical diseases even though it is often perceived to be less rewarding in terms of career prospects than some of the more fashionable healthcare issues. Attracting younger academic investigators into this field will require an increase in targeted funding. However, good science alone is not sufficient to ensure success — in all the programmes discussed the science has to be supported by strong management. In this context, the importance of a project champion cannot be overemphasized, and without such a leader many promising avenues of drug discovery will fail to make progress. The overall balance of good science, appropriate funding, enthusiasm and clear management will determine the outcome of all science-based programmes.

It should also be noted that a key element in successfully managing virtual drug discovery is flexibility in decision making². This includes the ability to prioritize projects, re-allocate resources and terminate projects that are not going well. However, the industry mantra ‘kill quick, kill cheap’ often does not find ready acceptance in an academic setting, and the different management styles resulting from the varying cultural experience of all the partners (academia, industry and donors) in a network/partnership setting can sometimes cause difficulty in decision making.

Mitigation of risks in lead discovery

Lead discovery is an inherently high-risk activity, as demonstrated by the corresponding attrition rates. Some of the challenges highlighted above can be overcome through the establishment of clear processes for project and portfolio management in order to deliver lead discovery objectives. The need for competitive project selection and review procedure by external experts promises to reduce attrition and the cost of lead discovery. Expert scientists from academia and industry are readily available to support and invest their time at no or limited cost for the purposes of reviewing and recommending promising projects for such endeavours.

A clear understanding of tropical diseases, desired product profiles for new drugs to guide R&D, and the needs of disease-endemic countries, are key to the discovery of relevant molecules for further development². The use of focused target product profiles (TABLE 1) to guide lead discovery and development candidate selection increases the chances of successful control programmes if and when such products reach the market.

The focus on innovative lead discovery fills a crucial gap in the tropical diseases drug development pipeline. The plan recognizes the important role of partnerships, as well as the participation of developing country scientists and institutions, in order to achieve the Millennium Development Goals and to provide a lasting solution to the product-access crises.

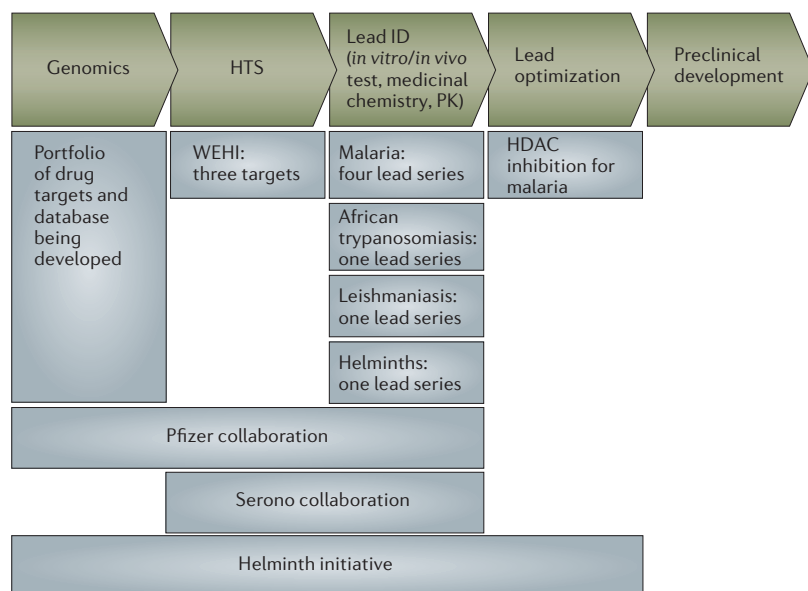


Figure 3 | The growing WHO/TDR drug discovery portfolio. Molecular targets being pursued as part of the Serono/TDR collaboration include: a *Plasmodium falciparum* serine protease, PfSub-1, provided by M. Blackman (MRC, London), a *P. falciparum* Ca²⁺-dependent protein kinase, PfCDK-1, supplied by B. Kappes (U. Heidelberg) and a cysteine peptidase from *Leishmania mexicana*, LmCPB, provided by J. Mottram (University of Glasgow). The targets pursued at WEHI include *Trypanosoma cruzi* trypanothione reductase from A. Fairlamb (University of Dundee), *Trypanosoma brucei* farnesyl pyrophosphate synthase provided by E. Oldfield (University of Illinois), and *P. falciparum* pyrophosphokinase from Sirawiraporn (Mahidol University). HDAC, histone deacetylase; WEHI, Walter Eliza and Hall Institute for Medical Research; WHO/TDR, Special Programme for Research and Training in Tropical Diseases at the World Health Organization.

Future perspectives

The concept of integrated drug discovery for tropical diseases through networks/partnerships (FIG. 1) using virtual and portfolio methodology² promises to revolutionize translational research not only for tropical diseases but for other diseases too. In the past, it was often thought that pharmaceutical companies had drug candidates ‘sitting on the shelf’ for tropical diseases and that these could be liberated given the appropriate financial inducement. This thinking is somewhat naive given that pharmaceutical companies are now involved in nearly half of new neglected-disease drug development activity on a non-commercial basis^{2,9,10,19}. The fact is that industry is also trying to identify efficient and cost-effective ways to increase their productivity in drug discovery^{19,44,45}. Some companies now see value in supporting tropical disease drug discovery as a way of boosting their lead discovery efforts for profitable diseases. For example, a ‘hit to lead’ programme targeting a parasite enzyme might help a company build a chemical library around the lead for testing against a human isoenzyme germane to a commercial market. This concept is increasingly gaining acceptance. Furthermore, the animal health industry is in need of new chemical entities for the veterinary market. Investment in lead discovery for human parasitic diseases might be seen as an avenue to identify new potential animal-health products.

The implications of this approach for the public health sector and pharma, animal health and agrochemical industries are considerable. Overall, the approach will help to reduce the high risk and cost associated with lead discovery^{62,63} as well as stimulating the pipelines

of the various sectors. For public health, this approach promises to create value through managed lead discovery portfolio efforts such as the ones being pursued by TDR (FIG. 3) and other organizations. The fruits of these endeavours can then be transferred to development partners or leveraged for additional resources to support future lead discovery efforts for diseases that have little or no potential of commercial return.

The networks are also a strong instrument for facilitating capacity-building in drug discovery, institutional strengthening and technology transfer to disease-endemic countries. They might also present a good platform for harnessing available drug discovery expertise in advanced developing countries. Clearly, networking, partnerships and capacity-building are useful and have yielded good results and should be seen as part of the solution. Strong political will and local commitment to research and economic development are also needed. In the words of the WHO Commission on Intellectual Property Rights, Innovation and Public Health¹¹, “In the longer term, the development of innovative capacity for health research in developing countries will be the most important determinant of their ability to address their own need for appropriate health-care technologies.” As the report goes on to say, “The formation of effective networks, nationally and internationally, between institutions in developing countries and developed countries, both formal and informal, are an important element to building innovative capacity.” This reflects the views expressed in this paper on the need for increased investment in upstream drug discovery for tropical diseases.

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Competing interests statement

The authors declare no competing financial interests.

FURTHER INFORMATION

Medicines for Malaria Venture: <http://www.mmv.org>
Grand Challenges in Global Health — Limit Drug Resistance: <http://www.gcgh.org/subcontent.aspx?SecID=396>
EU Commission — Poverty-Related Diseases: http://europe.eu.int/comm/research/health/poverty-diseases/projects/124_en.htm
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