Lead discovery for infectious tropical diseases

TDR BUSINESS LINE 3
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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADME</td>
<td>Absorption, distribution, metabolism and excretion</td>
</tr>
<tr>
<td>AiBST</td>
<td>African Institute of Biomedical Science and Technology</td>
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<tr>
<td>ANDI</td>
<td>African Network for Drugs and Diagnostics Innovation</td>
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<tr>
<td>APOC</td>
<td>African Programme for Onchocerciasis Control</td>
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<tr>
<td>BL</td>
<td>Business line</td>
</tr>
<tr>
<td>BMGF</td>
<td>The Bill &amp; Melinda Gates Foundation</td>
</tr>
<tr>
<td>CDCO</td>
<td>Centre for Drug Candidate Optimisation, Monash University</td>
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<tr>
<td>CDRI</td>
<td>Central Drug Research Institute</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P</td>
</tr>
<tr>
<td>DEC</td>
<td>Disease endemic country</td>
</tr>
<tr>
<td>DHFR</td>
<td>Dihydrofolate reductase</td>
</tr>
<tr>
<td>DMPK</td>
<td>Drug metabolism and pharmacokinetics</td>
</tr>
<tr>
<td>DNDi</td>
<td>Drugs for Neglected Diseases Initiative</td>
</tr>
<tr>
<td>EDAC</td>
<td>Expert Drug Discovery Advisory Committee</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>GATB</td>
<td>Global Alliance for TB Drug Development</td>
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<tr>
<td>GSPOA</td>
<td>The Global Strategy and Plan Of Action</td>
</tr>
<tr>
<td>HAT</td>
<td>Human African trypanosomiasis</td>
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<tr>
<td>HAT</td>
<td>Helminth Drug Initiative</td>
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<tr>
<td>HEOS</td>
<td>Hit Explorer Operating System</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HTS</td>
<td>High-throughput screening</td>
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<tr>
<td>IC</td>
<td>Inhibitory concentration</td>
</tr>
<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers &amp; Associations</td>
</tr>
<tr>
<td>LF</td>
<td>Lymphatic filariasis</td>
</tr>
<tr>
<td>LSHTM</td>
<td>London School of Hygiene &amp; Tropical Medicine</td>
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<tr>
<td>MMV</td>
<td>Medicines for Malaria Venture</td>
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<tr>
<td>NCDS</td>
<td>The National Center for Drug Screening</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>NIPRD</td>
<td>The National Institute for Pharmaceutical Research and Development</td>
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<tr>
<td>NPIMR</td>
<td>Northwick Park Institute for Medical Research</td>
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<tr>
<td>OECD</td>
<td>Organization for Economic Cooperation and Development</td>
</tr>
<tr>
<td>PHI</td>
<td>Secretariat on Public Health, Innovation and Intellectual Property</td>
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<tr>
<td>PPP</td>
<td>Public–private partnerships</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and development</td>
</tr>
<tr>
<td>SAC</td>
<td>Strategic and Scientific Advisory Committee</td>
</tr>
<tr>
<td>SAR</td>
<td>Structure–activity relationship (analysis)</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
<tr>
<td>STAC</td>
<td>Scientific and Technical Advisory Committee</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TBRI</td>
<td>Theodor Bilharz Research Institute, Egypt</td>
</tr>
<tr>
<td>TDR</td>
<td>The Special Programme for Research and Training in Tropical Diseases</td>
</tr>
<tr>
<td>TPP</td>
<td>Target product profile</td>
</tr>
<tr>
<td>UCT</td>
<td>University of Cape Town, South Africa</td>
</tr>
<tr>
<td>WHA</td>
<td>World Health Assembly</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Overview and highlights

The gap in the availability of drug leads and candidates to sustain the development pipeline for infectious tropical diseases is well documented through the work of TDR (The Special Programme for Research and Training in Tropical Diseases) and others (Fig. 1). The primary objective of the Lead Discovery business line (BL3) is to help fill this “translational innovation gap” through an integrated north–south drug discovery network. Established in 2005, this innovative network is producing significant results following the increasing locus, coordination and external leverage achieved through TDR’s new strategy.

In addition to the discovery of novel drug leads, this business line is supporting the empowerment and stewardship functions of TDR as follows:

a) Through the strong participation of developing-country scientists and institutions coupled with training opportunities in drug discovery;

b) By contributing critical resources in support of the international drug discovery community, for example, the development and publication of standard operating procedures (SOPs), compound progression criteria and databases to support project coordination.

Specific activities of the business line include target selection and validation in support of target-based screens; compound evaluation through parasite screens in vitro and in animal models in vivo; and iterative medicinal chemistry linked to drug metabolism/pharmacokinetics. The major strengths of this north–south drug discovery network include:

1) the strong technical and financial leverage attained through in-kind support provided by partners, for example access to compound libraries;

2) the potential for rapid GO/NO-GO decisions on projects due to a closer monitoring and review process, helping to reduce cost and enhance chances of success;

3) the added advantage of promoting innovation in disease endemic countries (DECs) through the network activities; and,

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1 Collaborative network between developed and developing countries.

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Fig. 1. Translational innovation gap in drug discovery for infectious tropical diseases (Nwaka et al., 2009).
4) the potential for spin-off of mature activities that would otherwise not be well-resourced from within TDR.

Highlights of progress made by BL3 in 2009 include:

1) Development of clear lead progression and candidate selection criteria with input from network partners and our Expert Drug Discovery Advisory Committee (EDAC).

2) Publication and dissemination of the progression and candidate selection criteria.

3) Continued interface with other partners, including public–private partnerships (PPPs) and developing country centres and networks especially through the establishment of regional innovation networks being implemented through business line 4 (which covers innovation for product development in disease endemic countries).

4) Two leads declared for malaria through collaboration with Pfizer and Merck Serono.

5) Conclusion of a second agreement with Chemtura for lead optimization and progress towards the finalization of stage 2 agreement with Pfizer and Merck Serono for lead optimization and eventual development.

6) Conclusion of first high-throughput screening (HTS) against a TB target at the National Center for Drug Screening (NCDS) Shanghai. This is part of a collaboration between TDR, Novo Nordisk and the NCDS. Two postdoctoral fellows from Africa (Kenya and Nigeria) are being trained as part of this project.

7) Continued progress with TDR compounds in medical chemistry centres at the University of Cape Town (South Africa) and the University of São Paulo (Brazil).

8) Continued improvement of the TDR targets database (www.tdrtargets.org), which is a global open source resource. The target used for screening at the NCDS was selected from the TDR target database.

9) As a result of the global economic crises, our new compound management partner (ASDI Delaware, USA) had major management changes that negatively impacted our compound-handling activities. Consequently the contract with ASDI was terminated and we are now seeking a new partner.

The current TDR drug discovery portfolio highlighting projects in the different stages of the drug discovery process is presented in Fig. 2.

**Fig. 2.** TDR drug discovery portfolio
1. Context, strategic objectives and framework

1.1 Context and rationale

The gap in the availability of drug leads and candidates to sustain the development pipeline for infectious tropical diseases is well documented (Nwaka et al., 2009, Fig. 1). In recent years there has been an increase in product development activities for tropical diseases through a number of public–private partnerships (PPPs) for malaria, tuberculosis and certain neglected tropical diseases. Examples include: MMV (Medicines for Malaria Venture), DNDi (Drugs for Neglected Diseases Initiative) and GATB (Global Alliance for TB Drug Development).

However, there is a dearth of credible drug leads to feed the development pipeline of these PPPs or to support sustained product innovation activities in developing countries. There is an urgent need for a vibrant drug discovery initiative to produce such leads. Furthermore, for helminth diseases there is currently no PPP for product development, and there is a need to go beyond lead discovery to identify drug candidates that can be further developed through new partnerships. TDR is well positioned to play the leading role in the discovery of new leads. TDR has already played a pioneering role in establishing win–win agreements with industry, obtaining compounds from pharmaceutical and animal-health companies to support lead discovery through a coordinated network of compound assessment centres.

Additionally, the recent availability of parasite genome sequences presents an opportunity for de novo discovery of new chemical entities. This business line furthers TDR’s vision of fostering an effective research effort on infectious diseases of poverty in which disease endemic countries play a pivotal role. They help by filling the innovation gap, identifying new lead series and contributing to empowerment and stewardship functions.

1.2 Strategic objectives

BL3’s overall objective is to facilitate and support the discovery of new drug leads for infectious tropical diseases through networks and partnerships between pharmaceutical companies, academia and DEC institutions.

The specific objectives are to:

1.2.1 Identify quality drug leads for tropical diseases and facilitate the transfer of those leads to PPPs, industry, and other innovative partnerships for further development.

1.2.2 Identify drug candidates for helminth infections (initially focusing on schistosomiasis, lymphatic filariasis and onchocerciasis) through the Helminth Drug Initiative (HDI), and transfer the candidates to appropriate partners for development.

1.2.3 Support targeted fundamental research on generation of new tools to facilitate drug discovery.

1.2.4 Promote the global coordination of drug discovery activities through the network and partnership model (stewardship function).

1.2.5 Promote technology transfer and innovative drug discovery in DEC through north–south collaboration networks and partnerships (empowerment function).
1.3 Strategic framework

The implementation strategy (business model) for this business line is based on a coordinated network of partners from industry and academia in developed and developing countries working on different areas of the drug discovery process (Fig. 3). This innovative drug discovery network includes: 1) the drug target portfolio; 2) in vitro and in vivo screening or evaluation; 3) medicinal chemistry; and, 4) drug metabolism and pharmacokinetics (DMPK) networks.

The TDR targets database (www.tdrtargets.org) developed by the target portfolio network is already supporting drug target prioritization, high-throughput screening (HTS) and in silico screening efforts for infectious tropical diseases (Aguero et al., 2008). Two HTSs have been completed at Pfizer and NCDS, using targets selected from this database. Hits emerging from HTS are assessed in whole parasites (in vitro) through the compound screening network. In addition, select compounds (small molecules and natural products) are sourced and channelled into the compound screening network for whole-cell and cytotoxicity screening, with actives subsequently tested in animal disease models. Through iterative medicinal chemistry and DMPK network activities, leads are identified. The leads are taken forward into lead optimization either in partnership with other institutions or handed off to appropriate partners. It should be stressed that transfer of leads or handoff requires contractual agreements that will ensure compounds are further developed and made available to the public according to WHO principles. The closer alignment of business lines 3 and 4 makes the handoff of leads for optimization and further assessment as seamless as possible.

Fig. 3. Innovative lead discovery strategy for tropical diseases (Nwaka & Hudson, 2006)
The integrated lead discovery strategy involves experienced consultants and mentors who support and provide guidance on various aspects of the preclinical process – including support for research fellows from disease endemic countries (Fig. 3). These DEC fellows are trained in drug discovery methods at pharmaceutical and academic research laboratories as part of BL3 activities supporting the empowerment objectives of TDR. Interactions between the different networks and quality control are managed by the BL3 staff, the Expert Drug Discovery Advisory Committee (EDAC) and consultants. A central drug discovery database known as the Hit Explorer Operating System (HEOS) supports BL3’s management of individual projects, as well as data and compounds exchange.

1.4 End-products (2009–2013)

The milestones and end-products for BL3 (up to the end of 2013) are presented in Fig. 4 and Table 1.
## TABLE 1. INDICATORS FOR END-PRODUCTS AND OUTCOMES (UNTIL 2013)

<table>
<thead>
<tr>
<th>BL objectives</th>
<th>End-products</th>
<th>Indicators for end-products</th>
<th>Expected outcomes</th>
<th>Indicators for expected outcomes</th>
</tr>
</thead>
</table>
| **Strategic objective 1:** Identify quality drug leads for tropical diseases and facilitate the transfer of those leads to PPPs, industry and other innovative partnerships for further development | Ten leads (with novel chemotypes) discovered for one or more TDR target diseases by 2013 | - Two leads discovered every year  
- One lead transferred to a partner every other year  
- A portfolio of projects delivering leads  
- Open access database containing drug targets in support of high-throughput and in silico screening for lead discovery starting 2007 | Six leads entering optimization through partnerships including through BL4 to support innovation in developing countries | Three leads transferred to BL4 or centres in the south for further optimization |
| **Strategic objective 2:** Identify drug candidates for helminth infections (initially focusing on schistosomiasis, lymphatic filariasis and onchocerciasis) through the Helminth Drug Initiative (HDI) and transfer the candidates to appropriate partners for development | Two drug candidates identified through the Helminth Drug Initiative by 2013 | - HDI fully functional, utilizing existing network and partnerships model  
- HDI Task Force in place to help further develop the framework for the initiative, including the development of a focused business plan  
- Two new centres for helminth screens identified and supported through funding and technical support to contribute to sustainability | One drug candidate entering development pipeline | Two drug candidates identified which meet target product profiles |
| **Strategic objective 3:** Support targeted fundamental research on generation of new tools to facilitate drug discovery | Target database maintained (supporting target-based drug discovery and supporting translation of research into drug leads) | - Continued management and curation of the TDR target database  
- Three new targets validated and one assay developed for at least one TDR target disease  
- One new in vitro or in vivo drug screening tool developed  
- Support the translation of genomics and basic research into product leads and their further development | - Eight diseases covered in the database  
- Two targets progressed to HTS | |
### TABLE 1 (CONT). INDICATORS FOR END-PRODUCTS AND OUTCOMES (UNTIL 2013)

<table>
<thead>
<tr>
<th>BL objectives</th>
<th>End-products</th>
<th>Indicators for end-products</th>
<th>Expected outcomes</th>
<th>Indicators for expected outcomes</th>
</tr>
</thead>
</table>
| **Strategic objective 4:** Promote the global coordination of drug discovery activities through the network and partnership model (stewardship function) | • Coordinated drug discovery strategy based on networks and partnerships published and publicized  
• Target product profiles and compound progression criteria as well as standard operating processes in support of drug discovery established  
• Web-based SOPs/compound submission requirements | • Managed portfolio of lead discovery projects with partners available, delivering leads and transferring these to appropriate partners for further development | • Improved coordination, management and sharing of information in support of drug discovery activities  
• Publications or processes contributing to harmonization of global research efforts | • Portfolio review through EDAC, the Helminth Drug Initiative Task Force and network meetings to promote drug discovery for public health  
• Two product innovation publications  
• Four meetings on innovation in the developing countries |
| **Strategic objective 5:** Promote technology transfer and innovative drug discovery in developing countries through north–south collaboration networks and partnerships (empowerment function) | Empowerment of DEC scientists and institutions to participate in north–south and south–south networks to produce leads | • North–south and south–south networks for drug discovery established and contributing to innovation in developing countries through institutional strengthening and training  
• Six fellows from developing countries trained through drug fellowships. Workshops and training on innovative lead discovery in developing countries including structure-based drug design, medicinal chemistry, in vitro ADME, whole cell screening and natural products | Increased capacity building and training of leaders in drug discovery in developing countries | Ten developing country scientists trained or institutions strengthened |
2. Key stakeholders and partnerships: roles and responsibilities

BL3 activities are implemented through collaborations with several academic and industry partners, donors and government agencies. Table 2 lists current network partners and their roles. In addition, there is close cooperation within WHO, especially with the Secretariat on Public Health, Innovation and Intellectual Property (PHI) in support of the global strategy and plan of action approved through World Health Assembly resolutions WHA61.21 and WHA62.16. There is also a significant interaction between BL3 and the WHO legal office in support of contractual negotiations with partners. This time-sensitive contractual negotiation is mandatory for initiating new drug discovery projects with partner institutions. There is also close interaction with PPPs such as the MMV and DNDi. Contractual negotiation is ongoing with MMV on antimalarial lead optimization projects at the University of Cape Town and DNDi is implementing hit-to-lead projects using screening hits identified by TDR for Chagas disease.

TDR also interacts with philanthropic foundations such as The Bill & Melinda Gates Foundation and The Wellcome Trust, through information sharing and observer attendance at project review meetings. In addition to partnerships with specific pharmaceutical companies, there is ongoing collaboration with the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) in support of drug discovery for tropical diseases. In terms of national or multilateral agencies and institutions, BL3 also has ongoing interactions with the USA-based National Institutes of Health (NIH), for example through its new programme, “Therapeutics for Rare and Neglected Diseases” and the European Union (EU)’s drug research and development (R&D) programme for malaria. (TDR’s BL3 leader chairs the EU Antimalarial Expert Scientific Advisory Committee.)
### TABLE 2. LIST OF NETWORK PARTNERS (IMPLEMENTORS)

<table>
<thead>
<tr>
<th>Network</th>
<th>Partners</th>
<th>Role</th>
</tr>
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<tbody>
<tr>
<td>Compound screening</td>
<td>Swiss Tropical Institute, Switzerland; Laboratory for Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; London School of Hygiene &amp; Tropical Medicine, United Kingdom; Northwick Park Institute for Medical Research (NPIMR), United Kingdom; Theodor Bilharz Research Institute (TBRI), Egypt; University of Washington, USA (until April 2009); University of Buea, Cameroon; Central Drug Research Institute, India; Kenya Medical Research Institute, Kenya; National Centre for Drug Screening, China; University of São Paulo, Brazil</td>
<td>In vitro and in vivo whole parasite screens</td>
</tr>
<tr>
<td>Compound supply and management</td>
<td>Chemtura, USA; Merck Serono, Switzerland; Pfizer, United Kingdom; Life Chemicals, Ukraine; Novo Nordisk, Denmark; ASDI, USA (until August 2009); Scynexis, USA</td>
<td>Compound supply, storage and management</td>
</tr>
<tr>
<td>Medicinal chemistry</td>
<td>University of Cape Town, South Africa; Merck Serono, Switzerland; University of Dundee, United Kingdom; University of São Paulo, Brazil; Pfizer, United Kingdom; Chemtura, USA</td>
<td>Synthetic chemistry, molecular modelling, pharmacology to discover and design new drugs</td>
</tr>
<tr>
<td>Drug metabolism and pharmacokinetics (DMPK)</td>
<td>Merck Serono, Switzerland; Pfizer, United Kingdom; African Institute of Biomedical Science and Technology, Zimbabwe; Centre for Drug Candidate Optimisation, Monash University, Australia</td>
<td>In vitro and in vivo DMPK assessment</td>
</tr>
<tr>
<td>Drug target prioritization</td>
<td>University of Washington, USA; University of Pennsylvania, USA; The Wellcome Trust Sanger Institute, United Kingdom; Walter and Eliza Hall Institute of Medical Research, Australia; Biotech Institute, Argentina; Inpharmatica, USA; New England Biolabs, USA; University of California, San Francisco, USA</td>
<td>Development and curation of TDR drug target database, discovery of new therapeutic targets through modern approaches (genomics/proteomics/bioinformatics)</td>
</tr>
</tbody>
</table>
3. Implementation plan 2008–2013 and progress

3.1 Scope of activities

The activities of BL3 cover lead discovery for protozoan and helminth diseases. A major focus of activities is in the area of helminths through the Helminth Drug Initiative (HDI), which aims to support the preclinical development of new compounds for helminths. In the area of protozoan diseases, the major focus is hit-to-lead activities. All discovery activities are implemented through the TDR network (comprising several industry/academia partnerships).

3.2 Plan, progress and key milestones

3.2.1 Identify quality drug leads for tropical diseases and facilitate the transfer of those leads to PPPs, industry and other innovative partnerships for further development.

Summary of screens, hit and lead identification activities:

• Screening of TDR compounds
  - The antiprotozoan (malaria, Chagas, Leishmania, and human African trypanosomiasis – HAT) whole cell screening of 10 000 compounds purchased by TDR have been completed at the University of Antwerp. Several confirmed hits resulted from this activity with several compounds identified as new starting points for lead identification as follows:
    - 1 hit series identified for Chagas (TDR21944 and analogues) have been sent to the University of São Paulo in Brazil for hit-to-lead and structure–activity relationship (SAR) analysis.
    - 3 new hit series identified for HAT (TDR84116, TDR81098, TDR83420) have been sent to Merck Serono for hit-to-lead and SAR analysis.
  - Additional hits are being prioritized for leishmaniasis and malaria.

Antihelminthic screening of the same 10 000 compounds is ongoing at NPIMR and the University of Buea against onchocerciasis, at LSHTM and TBRI against schistosomiasis and at the Central Drug Research Institute in India against lymphatic filariasis (LF).

• Screening of compounds supplied by industry partners
  - Pfizer compounds
    - A set of antiprotozoan and antihelminthic library screening was finalized in Q1 2009 at the Swiss Tropical Institute allowing the identification of new hit series for malaria and onchocerciasis which are now being prioritized.
    - HTS against GSK3 from T. brucei (using about 1 million compounds) was finalized in Q2 2009 at Pfizer. Hit series identified from the screens are being prioritized.
  - Chemtura compounds
    - Screening of about 700 Chemtura compounds was completed at the University of Washington, the University of Antwerp and TBRI. Following analysis and clustering of hits, several compounds have been prioritized for follow up:
      - 2 new hit series identified for onchocerciasis have been selected for hit-to-lead medicinal chemistry at Chemtura and the University of Manitoba (TDR55404 and TDR72301).
      - Hit analysis and validation are ongoing for schistosomiasis, malaria, leishmaniasis, HAT and Chagas disease.
Screening at the National Centre for Drug Screening (Shanghai, China). The first HTS campaign with 32,000 compounds against Mycobacterium tuberculosis DHFR (dihydrofolate reductase) was completed at NCDS with the support of two fellows from Africa (Dr Shittu Hafsat, National Institute for Pharmaceutical Research and Development (NIPRD), Nigeria and Dr Charles Mutai, Centre for Traditional Medicine and Drug Research-Kenya Medical Research Institute, Kenya) being trained as part of the project. Two identified confirmed hits are now available for whole pathogen testing.

- **Hit-to-lead or optimization activities**
  - **Merck Serono**
    - Initial agreement focusing on lead discovery successfully completed with one malaria lead compound proposed to enter the next phase of lead optimization in Q4/2009. Work on a new legal agreement covering lead optimization to clinical candidate is expected to be signed soon.
    - One HAT project based on TDR20939 terminated.
    - One schistosomiasis project based on TDR35811 transferred to Merck Serono for medicinal chemistry.
    - Four new hit series (3 HAT and 1 schistosomiasis) submitted for hit validation for future hit-to-lead programmes.
  - **Pfizer**
    - Initial agreement covering screening and lead discovery successfully concluded with 2 malaria leads and some potential new onchocerciasis hits.
    - Work on a new legal agreement covering follow-up activities to clinical candidate is expected to be finalized by the end of the year.
    - The initial focus of the second stage agreement will be the malaria leads.
    - Pfizer has committed in-house resources to support this effort with the goal to declare development candidate by Q2 2010.
  - **Chemtura**
    - Second phase agreement concluded to support lead optimization.
  - **University of Dundee**
    - Hit-to-lead activity on TDR32750 and analogues ongoing. Oral activity for the series is low and the project is working to resolve some DMPK issues.
  - **University of Sáo Paulo**
    - Hit-to-lead activity on new bioactive compounds (TDR26631 and TDR30139) against Trypanosoma cruzi. Initial SAR on the series ongoing with encouraging oral activity.
  - **University of Cape Town (UCT)**
    - Ongoing early malaria lead optimization studies for TDR76133 and the bis-hydrochloride salt TDR86919. Agreement with MMV on optimization presently stalled. The plan in 2010 is to implement this project through BL4 and eventually transfer it to the African Network for Drugs and Diagnostics Innovation (ANDI).

3.2.2 Identify drug candidates for helminth infections (initially focusing on schistosomiasis, lymphatic filariasis and onchocerciasis) through the Helminth Drug Initiative, and transfer the candidates to appropriate partners for development.

- **Emodepside** - There are ongoing discussions with Bayer Healthcare on Emodepside, a semisynthetic broad spectrum antihelminthic for companion animals and livestock. Interestingly, Emodepside was shown to have potent in vitro activity against Onchocerca volvulus adult worms (screens done at NPIMR). Emodepside also shows a significant antinematodal spectrum with activity against hookworms, roundworms and whipworms. There are ongoing discussions between Bayer Health Care and TDR regarding the possible advancement of Emodepside for human use. Dr Achim Harder and Dr Klemens Krieger of Bayer Animal Health (Germany) attended TDR’s 2009 Expert Drug Discovery Advisory Committee meeting where data on Emodepside, including mode of action studies, were also presented.

- Extensive analysis of available hits and leads from screens planned in 2010.
3.2.3 Support targeted fundamental research on generation of new tools to facilitate drug discovery.

- **TDR target database** ([www.tdrtargets.org](http://www.tdrtargets.org)). Excellent progress was made in the optimization of the database with new data and features such as helminth targets and compound association, despite financial difficulties due to budget cuts encountered by the TDR target network.

- The TDR target database has also supported target selection for HTS campaigns at Pfizer (UK) and NCDS (Shanghai, China).

- As a global resource, the database is also supporting the work of other organizations involved in drug discovery.

3.2.4 Promote the global coordination of drug discovery activities through the network and partnership model (stewardship function).

- Publication and dissemination of compound progression criteria and candidate selection criteria, as well as a list of available pathogen strains used for screens (see Nwaka et al., 2009, Annex 5.1).

3.2.5 Promote technology transfer and innovative drug discovery in DECs through north–south collaboration networks and partnerships (empowerment function).

- Training of two fellows from Kenya (at Pfizer) and India (at the University of Dundee) in medicinal chemistry.

- Training of two African scientists in DMPK and medicinal chemistry at the UCT South Africa and AiBST Zimbabwe.

3.3 Financial analysis

Table 3 provides a breakdown of the financial implementation between 2008 and 2009.

3.4 Implications of progress/delays and global context changes on 2009–2013 plans

**Implications of progress/delays on 2009–2013 plans**

Delays in funding projects this year negatively affected the activities of our investigators. Despite this, BL3 has delivered on its key objectives, but it is not clear how this will affect delivery in the next biennium. There were also delays in hiring approved staff which placed stresses on meeting deadlines.

**Implication of changes in global context**

As reflected in Fig. 1, a significant innovation gap remains despite some ongoing activities in drug R&D for malaria, tuberculosis and some neglected diseases through product development partnerships based in developed countries. At the same time, there has been increased donor interest in promoting early-stage innovation, for instance from The Bill & Melinda Gates Foundation Grand Challenges Grants and recent efforts by The Wellcome Trust, as well as government initiatives through the European Commission and NIH in the United States of America.

The Global Strategy and Plan Of Action (GSPOA), adopted through World Health Assembly resolutions WHA61.21 and 62.16, presents a unique opportunity for BL3 and other related TDR business lines to support rapid implementation of this historic plan. In the context of empowering developing countries to participate and take leadership in the innovation process, the GSPOA represents a forward-looking agenda that could contribute to sustaining long-term access to health products in developing countries. As always, the
### TABLE 3. FINANCIAL IMPLEMENTATION 2008–2009

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>BL3 Lead Discovery</td>
<td>7 600 000</td>
<td>5 730 000</td>
<td>4 418 825</td>
<td>77%</td>
</tr>
<tr>
<td>Lead identification</td>
<td>2 520 780</td>
<td></td>
<td>2 185 346</td>
<td></td>
</tr>
<tr>
<td>Drug targets</td>
<td>1 204 725</td>
<td></td>
<td>484 689</td>
<td></td>
</tr>
<tr>
<td>Lead optimization</td>
<td>2 580 372</td>
<td></td>
<td>1 020 415</td>
<td></td>
</tr>
<tr>
<td>Helminth initiative</td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Coordination</td>
<td>1 294 123</td>
<td></td>
<td>728 375</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 4. APPROVED BUDGET FOR 2010–11

<table>
<thead>
<tr>
<th>Title</th>
<th>JCB approved budget 2010–2011 US$ 121 million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead identification</td>
<td>3 455 000</td>
</tr>
<tr>
<td>Drug targets</td>
<td>700 000</td>
</tr>
<tr>
<td>Lead optimization</td>
<td>1 730 000</td>
</tr>
<tr>
<td>Helminth drug initiative</td>
<td>100 000</td>
</tr>
<tr>
<td>Coordination</td>
<td>890 000</td>
</tr>
<tr>
<td><strong>Total – BL3 Lead discovery for infectious tropical diseases</strong></td>
<td><strong>6 875 000</strong></td>
</tr>
</tbody>
</table>
challenge lies in translating plans or resolutions into concrete action. The concept of regional innovation networks, exemplified by the African Network for Drugs and Diagnostics Innovation (more on ANDI available in the BL4 Annual Report), represents a practical approach for concrete implementation in developing countries. Promoting innovation for products in developing countries is likely to be the future terrain for many new product R&D efforts for neglected diseases.

3.5 Activities for 2010 and budget for 2010–2011

A major activity for 2010 will be the merger of BL3 and BL4, if approved by the Scientific and Technical Advisory Committee (STAC). While the proposed merger might impact on the proposed BL3 2010 activities and how they are organized, it is foreseen that most of the activities will be retained in a manner that supports coherent and seamless product R&D efforts in developing countries.

Activities for 2010 are highlighted below:

3.5.1 Hit-and-lead identification:
- Compound and data management
- Establishment of partnerships (public and private) drug discovery
- Hit-to-lead activities through screening, medicinal chemistry, and drug metabolism and pharmacokinetics (DMPK) networks.

3.5.2 Lead optimization for helminths through the Helminth Drug Initiative:
- Lead optimization through screening, medicinal chemistry, DMPK networks and toxicology
- Development of new assay for helminth
- Finalization of target product profiles for schistosomiasis, onchocerciasis and lymphatic filariasis.

3.5.3 Drug targets and fundamental research:
- Continued support and improvement of the TDR target database (www.tdrtargets.org) as a global resource
- Increase the participation and leadership of developing country scientists in the work of the TDR target network
- Ensure enhanced curation of helminth and other pathogen data in the database.

3.5.4 Empowerment activities:
- Continue the training of developing country fellows as part of network activities — ensure that two fellows are trained in 2010
- Support and validate developing country institutions participating in network activities
- Support workshops and training on innovation in developing countries.

3.5.5 Stewardship activities:
- Continue to develop tools and share information globally in support of drug discovery for infectious tropical diseases for example through (www.tdrtargets.org)
- Finalize and share target product profiles for neglected diseases
- Continue to publish on innovation.
4. Leverage and contributions to empowerment and stewardship

4.1 Leverage

The achievements described above and in the past years would not have been possible without the significant leverage achieved through the network model. This includes: substantial in-kind contributions through various industrial and academic partners; economies of scale achieved through the ability to evaluate available compounds against multiple diseases; support from members of TDR’s Expert Drug Discovery Advisory Committee, and consultants who contribute their time and efforts at costs that are far below commercial rates.

Summary of the leverage achieved through BL3:

4.1.1 Access to compound collection and industry support. Although TDR purchases compounds for screening from time to time, a significant proportion of the thousands of drug-like compound collections used are supplied by industry at no cost to TDR. Since the cost of preparing, acquiring and maintaining good compound libraries runs into the millions of dollars, TDR leverage achieved is thus represented by comparable cost savings. Specific examples of such leverage include the ongoing collaborations between TDR and Merck Serono, Pfizer, Chemtura and Novo Nordisk. In addition, some of these companies provide medicinal chemistry training for TDR-supported fellows from developing countries. It must, however, be acknowledged that achieving this leverage means significant investment in time and resources to identify partners willing to collaborate and to negotiate win-win contractual agreements.

4.1.2 Economy of scale due to disease scope. Our network model for drug discovery focusing on multiple diseases presents a significant advantage both in terms of cost savings and reducing overall compound attrition (Nwaka and Hudson, 2006, Nwaka et al., 2009). For example, the screening for multiple diseases implemented by BL3 makes it easy to rapidly evaluate scarce compound collections across eight diseases in a very short time. This, in turn, supports rapid prioritization of compounds for further assessment.

4.1.3 The TDR target database (www.tdrtargets.org) is now a global resource leveraged by several investigators and institutions to get external funding for work on infectious tropical diseases. For example, this work has supported grant applications by other institutions to the USA-based National Institutes of Health. Several investigators from industry and academia are contributing to the work at no cost to TDR.

4.1.4 Co-funding or collaborative opportunities with PPPs on specific projects, such as through MMV and DNDi.

4.2 Contributions to overall empowerment and stewardship objectives

The lead discovery business line is supporting significant stewardship and empowerment functions (see Section 3). Stewardship efforts include sharing lessons with the international community through the development and publication of compound progression and candidate selection criteria, as well as target product profiles for various diseases. These materials, including SOPs, are also disseminated through databases and meeting presentations and attendance. Empowerment activities include training developing country researchers in drug discovery in state-of-the-art pharmaceutical company laboratories, as well as initiatives supporting compound screening and medicinal chemistry centres in developing countries. Several
fellows from developing countries including India, Kenya, Nigeria, South Africa and Zambia have been trained. This work is also helping to empower and foster collaboration and networking activities between developing country laboratories in the area of product innovation. BL3 coordinates with TDR's empowerment function (BL2) to implement these training and fellowship aspects of drug discovery.

### 4.3 Disease endemic countries playing a pivotal role in BL3 activities

The work in Africa and other disease endemic regions helped to kickstart BL4 with the implementation of the African Network for Drugs and Diagnostics Innovation (ANDI) and other regional innovation networks. The leadership of African scientists in the launch of the ANDI concept and the development of the strategic and business plans for ANDI is a clear demonstration of the pivotal role of the disease endemic countries in R&D.

### 4.4 Elements enhancing sustainability of BL3 outcome

The following activities and linkages help to ensure sustainability of the BL activities.

The north–south discovery networks are already contributing to the identification and recognition of DEC drug discovery research leaders and research centres, thereby supporting the sustainability of their activities. The transfer of knowledge and leads from BL3 to partners and to BL4 for further development, particularly in DEC networks and institutions, is contributing to sustainability.
5. Annexes

5.1 Full list of publications resulting from BL3 or related activities

- Publications from the TDR Drug Discovery Network:
  14. Musonda CC et al. Synthesis and evaluation of 2-pyridyl pyrimidines with in vitro...


25. A poster was presented during the September 2009 European Society of Tropical Medicine meeting in Verona, Italy by Dr Richard Oduor (Jomo Kenyatta University of Agriculture and Technology, Kenya), TDR fellow training at Pfizer.

5.2 BL3 Strategic and Scientific Advisory Committee (SAC) membership and responsibilities

Expert Drug Discovery Advisory Committee (membership will change in 2010):

- Dr Frank DOUGLAS, Chair (innovation, research and development), Ewing Marion Kauffman Foundation, USA.
- Dr Susan CHARMAN (pharmacokinetics, metabolism), Department of Pharmaceutics, Victorian College of Pharmacy, Monash University, Australia.
- Dr Gaik-Lean CHEE (chemistry), University of Manitoba, Canada.
- Dr Ken DUNCAN (drug discovery), Global Health Program, The Bill & Melinda Gates Foundation.
- Dr Simon EFANGE (medicinal chemistry, natural products), University of Buea, Cameroon.
- Dr Timothy GEARY (helminths), Institute of Parasitology, McGill University, Canada.
- Professor Andrew HOPKINS (informatics), Division of Biological Chemistry and Drug Discovery, College of Life Sciences, University of Dundee, United Kingdom.
- Dr Ivan IDEA-MENSAH (medicinal chemistry, natural products), University of Ghana, Ghana.
- Dr Collen MASIMIREMBWA (drug metabolism and pharmacokinetics), African Institute of
Biomedical Science and Technology (AiBST), Zimbabwe.

- **Dr Valerie Mizrahi** (genomics), MRC/NHLS/WITS Molecular Mycobacteriology Research Unit, ST/NRF Centre of Excellence for Biomedical TB Research, National Health Laboratory Service and University of the Witwatersrand, South Africa.

- **Dr Alexis Nzila** (parasitology), Kenya Medical Research Institute/The Wellcome Trust Collaborative Research Programme, Kenya.

- **Dr Philip Rosenthal** (biology, medicine), San Francisco General Hospital, USA.

- **Dr Rakesh Tuli** (biology), Central Drug Research Institute, India.

- **Dr Michael Witty** (drug discovery, medicinal chemistry), Ex-Pfizer Animal Health, United Kingdom.

- **Dr Carlos Zanni** (natural products), Instituto Oswaldo Cruz, FIOCRUZ, Brazil.

**Helminth Drug Initiative Task Force (membership will change in 2010):**

- **Dr Graham Mitchell**, Chair (helminths), FOURSIGHT Associates, Australia (ex-Chair of TDR STAC).

- **Dr Sanaa Botros** (pharmacology), Pharmacology Department, Theodor Bilharz Research Institute, Egypt.

- **Dr Clotilde Carlow** (parasitology), New England Biolabs, USA.

- **Dr Kelly Chibale** (medicinal chemistry), Department of Chemistry, University of Cape Town, South Africa.

- **Dr Timothy Geary** (helminths), Institute of Parasitology, McGill University, Canada.

- **Dr Bertram Nwoke** (helminths, epidemiology), Imo State University, Nigeria.

- **Dr Yves Ribeill** (medicinal chemistry, industry), Scynexis, USA.

- **Dr Vincent TitANJI** (helminth biology), University of Buea, Cameroon.

- **Dr Juerg Utzinger** (parasitology), Swiss Tropical Institute, Switzerland.

- **Dr Michael Witty** (helminth research and development), Ex-Pfizer Animal Health, United Kingdom.

Observers are invited for both EDAC and the HDI Task Force meetings. They include interested parties from:

- The Bill & Melinda Gates Foundation;
- European Union;
- Country and national institutes of health;
- African Programme for Onchocerciasis Control (APOC);
- Organization for Economic Cooperation and Development (OECD);
- International Federation of Pharmaceutical Manufacturers and Associations (IFPMA);
- WHO’s Neglected Tropical Diseases department;
- WHO regional offices.
The Special Programme for Research and Training in Tropical Diseases (TDR) is a global programme of scientific collaboration established in 1975. Its focus is research into neglected diseases of the poor, with the goal of improving existing approaches and developing new ways to prevent, diagnose, treat and control these diseases. TDR is sponsored by the following organizations:
Lead discovery for infectious tropical diseases