BL 3
Business Plan
2008-2013

Lead discovery for drugs

Draft Business Plan for JCB

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Business plan: Business line 3 - Lead discovery for drugs

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EXECUTIVE SUMMARY

Needs and Opportunities

In recent years there has been an expansion of product development activities for tropical diseases through a number of new public-private partnerships (PPPs) for malaria, tuberculosis and certain neglected tropical diseases. However, there is a dearth of credible drug leads to feed the development pipeline of these PPPs and 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 for the helminthiases there is a need to go beyond lead discovery and identify drug candidates that can be further developed by partners or within TDR.

Pharmaceutical and animal health companies often have relevant compounds that have not been assessed for their potential to treat tropical diseases. Experience shows that companies are willing to avail their compounds for testing but are unsure about an appropriate mechanism in view of the risk of exposing their intellectual property to competitors. TDR has played a pioneering role in establishing win-win agreements with industry in which they partner and contribute compounds for evaluation through the TDR coordinated network of compound assessment centres. Availability of parasite genome sequences also present opportunity for de novo discovery of new chemical entities.

Overall Objective

To facilitate and support the discovery of new drug leads for tropical diseases through networks and partnerships between pharmaceutical companies, academia and disease endemic country (DEC) institutions

Specific Objectives

- Identify quality drug leads for tropical diseases and facilitate the transfer of those leads to PPPs, industry, and other innovative partnerships for further development
- Identify drug candidates for helminth infections (initially focusing on schistosomiasis, lymphatic filariasis and onchocerciasis) through the Helminth Initiative and transfer the candidates to appropriate partners for development
- Promote the global coordination of drug discovery activities through the network and partnership model
- Promote technology transfer and innovative drug discovery in DECs through the North/ South collaboration networks and partnerships
- Support targeted fundamental research on generation of new tools to facilitate drug discovery
Activities

The discovery of quality drug leads against infectious diseases associated with poverty will involve the establishment of a portfolio of prioritized targets, progressing validated targets through high throughput screening, in vitro and in vivo screening through the TDR compound assessment and pharmacological networks, as well as iterative medicinal chemistry and exploratory toxicology on promising leads. New partners for compound supply will be proactively identified, and transfer of leads to relevant development partners implemented. DEC researchers and institutions will be engaged in these partnerships.

End-Products

- 10 leads discovered by 2013, 1 lead transferred to a partner every other year
- Open access database of drug targets (starting 2007)
- Helminth Drug Initiative fully functional by 2008
- 2 drug candidates for helminthiases identified by 2013
- Coordinated drug discovery strategy, based on networks and partnership
- DEC scientists and institutions participating in lead discovery
- Open access high-impact publications and standard operating procedures for lead discovery

Comparative Advantage

TDR is well positioned to play the leading role in the discovery of new leads based on its track record and current progress. TDR has considerable experience in virtual drug discovery and an understanding of the desired product profiles and needs of DECs. TDR has helped create some of the existing PPPs (e.g. MMV, DNDi, FIND) and also provided some of the lead series currently being progressed by them. TDR has the convening power to assemble global experts from academia and industry to review and select promising projects. It has unrivalled access to thousands of compounds through its unique network of compound assessment centres, and it has established win-win agreements with industry (e.g. with Pfizer, Serono, Chemtura) to enable them to contribute to the network. TDR has experience in creating networks between the North and South and in linking lead discovery with fellowships and capacity development in DECs. In fact, a new drug discovery strategy for tropical diseases based on networks between academia, industry in developed and developing countries is already in place and delivering leads.
1. OBJECTIVE

1.1. OVERALL OBJECTIVE

The overall objective of this business line (BL) is to facilitate and support the discovery of new drug leads for tropical diseases through networks and partnerships between pharmaceutical companies, academia and DEC institutes.

1.2. SPECIFIC OBJECTIVES

1.2.1. Identify quality lead compounds for tropical diseases (specifically malaria, leishmaniasis, African trypanosomiasis, Chagas, schistosomiasis, lymphatic filariasis, onchocerciasis and tuberculosis) and facilitate the transfer of those leads to PPPs, industry, and other innovative partnerships in the North or South for further development.

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

1.2.3. Stewardship function - promote the coordination of drug discovery activities through the network and partnership model.

1.2.4. Empowerment function - promote technology transfer and innovative drug discovery in DECs through North-South collaborative networks and partnerships.

1.2.5. Support targeted fundamental research on generation of new tools to facilitate drug discovery through calls for "Bright Innovative Ideas" on new screening tools, target validation around TDR’s drug target database, animal models, bioinformatic tools.

For clarity, description of ongoing networks and partnerships in the TDR's drug discovery are presented in Annex 1 (see also ref. 1):

The network/partnership approach (see also Fig 1 below and reference 1) is helping to facilitate drug discovery and also to reduce the high risk and cost associated with this process. This approach promises to create value that will be transferred to development partners or leveraged for additional funding to support further progression of the leads. The networks are also a strong instrument to facilitate capacity building, institutional strengthening and technology transfer to DECs. The activities of the network will continue to be managed by TDR staff (including external consultants), and reviewed on a regular basis by an external Expert Discovery Advisory Committee (EDAC). Members of EDAC will be leading experts in drug discovery and infectious diseases drawn from both the disease endemic and developed countries.
Figure 1. The Network and Partnership Strategy for Drug Discovery for Tropical Diseases (Nwaka S. and Hudson A. Nature Reviews Drug Discovery 5, 941 - 955 (2006))

Definitions and activity criteria for hits and leads are presented in Annex 2 (see also ref 1).
2. NEEDS AND OPPORTUNITIES

2.1. NEEDS

- There is a continuing and compelling need for new and better drugs for tropical diseases caused by protozoal, helminthic and bacterial infections - malaria, African sleeping sickness, the leishmaniasis, Chagas disease, filarial diseases, schistosomiasis and tuberculosis. 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 safety. Because the evolution of drug resistance is likely to compromise every drug in time, the demand for new medicaments is a continuum. Accordingly, a vibrant drug discovery pipeline is needed to help to ensure the availability of new products that will reduce mortality/morbidity caused by these diseases\(^1, 2, 3\). In addition, most tropical diseases lack easy to use and cost-effective diagnostic tools to detect infection and monitor response to drug treatment and increased effort is needed in the pursuit of such reagents.

- PPPs that focus on product development for tropical diseases often require quality leads to feed their pre-clinical pipelines. Some of these organizations are making significant progress in trying to bring products to the market through enhanced product development, with less emphasis on the risky early phases of the discovery process\(^1, 4\). In addition, a number of the diseases mentioned above (for example filariasis, onchocerciasis, 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\(^1, 2, 4, 5\).

- It should be noted that lead discovery tends not to receive much funding from the traditional scientific granting agencies, and there is less incentive for academia to work in this area\(^1\).

- There is an urgent need for a coordinated mechanism to fill this gap and support the translation of available scientific knowledge (for example genomics) into product leads.

- Meeting these needs requires a multi-disciplinary network of investigators working together as well as partnerships between industry and the public sector.
2.2 OPPORTUNITIES

- Clear opportunities exist for this business line:
  
  o Pharmaceutical, animal health, agrochem, and specialty chemical companies often have compounds with drug-like properties that have not been assessed for their potential to treat tropical diseases. Experience shows that companies are willing to avail their compounds for testing but are not well informed about an appropriate mechanism to do so especially when the risk of exposing their intellectual property to competitors is considered.
  
  o Genomics data are available to facilitate the identification of novel molecular targets which in turn should permit identification of small molecular weight inhibitors and their subsequent conversion into lead structures. TDR is supporting and managing a network of academic and industrial centres that is establishing a portfolio of drug targets across tropical diseases using the wealth of available genomics information. This drug target portfolio will be a global resource to help facilitate the prioritization of drug targets for high throughput screens. This business line will share lessons (from TDR target network) with the diagnostics business line in establishing a prioritized diagnostic target database.
  
  o We have witnessed global interest in the promotion of innovation for new treatments for developing world diseases. The G8 meeting in 2005, as well as the Millennium Development Goals, emphasized the need for partnerships to solve health problems. The WHO Commission on Intellectual Property and Health also emphasized the need for innovation. Indeed, enhanced lead discovery efforts 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 lead discovery for tropical diseases.

- In cognizance of the changing nature of drug research for tropical diseases TDR has now positioned itself to play the leading role in the discovery of new leads which can then be made available to other organizations for further progression. TDR's track record and current progress in lead discovery presents a clear opportunity and continuity for the business line. For example, TDR’s leadership on the discovery of leads and drug candidates for helminth infections supported by various companies will be maintained by this business line. The discovery and development of novel anthelmintics presents unique opportunities as well as challenges: no product discovery/development PPPs exist, novel screening methodologies are needed, funding is limited for this area of work. Nonetheless progress is being made in the identification of new leads through industry partnerships. The new Helminth Initiative in TDR will strengthen this area of work.

In summary, the past 2 years has witnessed a boost in TDR’s lead discovery efforts through the establishment of North/South based networks and partnerships to meet clear objectives. Examples of these include the TDR networks for compound screening (which covers the diseases mentioned above), medicinal chemistry, PK/metabolism, and the development of a prioritized drug target portfolio. These activities supported by enhanced industry participation are testimony to the opportunities for this BL.
3. COMPARATIVE ADVANTAGE

3.1 TDR COMPARATIVE ADVANTAGE

3.1.1 Proven technical and field experience

- TDR has a clear understanding and experience in virtual drug discovery and portfolio management as evidenced by the opportunities already discussed. In 2003, the current Director of TDR and present manager of discovery research (then at MMV) published the strategy and management needs for virtual drug discovery in contrast to drug development. This expertise to manage these activities remains available in TDR.

- The engine of TDR’s drug discovery strategy is the unique global network of compound assessment centres that allows scientists from academia and industry to submit compounds for test free of charge. This gives TDR unrivalled access to thousands of compounds in the search for new anti-parasitic leads. The investigators responsible for the individual test centres are world-renowned parasitologists (Annex 1).

- TDR's understanding of tropical diseases, desired therapeutic product profiles and needs of DECs are key considerations in the discovery of relevant molecules for further development.

- The target product profile for each of the TDR’s target diseases is available and will be used to guide discovery of new leads. A major consideration is the need for products that are safe in pregnancy, in women of child bearing potential and in early infancy.

- TDR incubated and helped in the creation of some of the existing PPPs. It has a clear understanding of lead discovery paradigms and the strength of industry and the public sector in those processes. Many lead compounds currently being progressed by PPPs benefited from initial TDR funding, for example, the antimalarial ozonides, bis amidines, dihydrofolate reductase inhibitors (MMV) and trypanothione reductase and farnesy transferase inhibitors (DNDi).

- TDR is now incubating a Helminth Initiative to help facilitate drug discovery for filariasis/onchocerciasis and schistosomiasis. A series of articles focusing on the initiative is being prepared for publication as part of the business line.

- A secure database for managing compounds and drug discovery data from different partners has been established. This is being up-graded to a more interactive database to enhance communication/exchange with partners.
3.1.2. Demonstrated stewardship/facilitation of agenda setting

- TDR's global convening power and ability to assemble expert scientists from academia and industry to review and select promising projects from across the globe helps to reduce the inherently high attrition in lead discovery.

- TDR is attracting companies and good public laboratories to partner in its discovery activities. TDR has played a pioneering role in establishing win-win agreements with industry to enable them to partner and contribute compounds to the TDR network of compound assessment centres. Agreements concluded with industry in the past year include:
  - the collaboration with Pfizer and Chemtura where thousands of biologically/biochemically-relevant compounds are currently being tested against target parasites in TDR centres.
  - high throughput screening with Serono where the Company uses its comprehensive compound libraries to screen against putative new drug targets selected by TDR.
  - the collaboration between TDR and the Japanese pharmaceutical industry in the search for new antimalarial and antifilarial leads.
  - Ongoing discussion with Bayer in the assessment of veterinary anthelmintics as potential macrofilaricides – this resulted in Emodipside being selected as a potential candidate for further development.

These agreements provide a solid platform for this business line to engage other partners and to flourish in the lead discovery process.

Annex 4 is a list of companies collaborating with TDR in drug discovery.

We are unaware of any other organization coordinating this level of early discovery activity for tropical diseases. Indeed, the helminth initiative meeting in Tokyo encouraged TDR to intensify partnership with the animal health industry in the discovery of new anthelmintics for human disease.

- **Helminth Initiative**: A broad TDR consultation has identified the need for an initiative to facilitate the discovery and development of new products for the helminth diseases. TDR has aligned its ongoing anthelmintic discovery activities (focusing on filariasis/onchocerciasis and schistosomiasis) to kick start the Helminth Initiative. Ongoing collaborations with industry, for examples Pfizer and Chemtura (see Annex 4), are providing a strong platform for the Initiative. It is expected that success in the next 2-3 years will help build a case for a focused PPP for anthelmintic drug R&D. Several new hits are now emerging from our anthelmintic screens. The need for additional screening centres to support our work has led us to conduct a survey to identify potential new drug screening centres for helminth diseases under the Initiative. The result of this survey is encouraging and has provided some indication of potential new anthelmintic screening centres. The TDR target portfolio network has started collecting helminth data for the TDR target database.
3.1.3. Capacity building capabilities in developing countries

- TDR has wide experience in the creation of networks between institutions in the North and South. It has been successful in the management of lead discovery linked with fellowships and capacity development in DECs. Sustainable capacity can be developed in DECs if the most talented scientists and institutions are engaged in these partnerships for lead discovery with the same level of rigor as scientists in the North. Our track record in this area shows that this goal is achievable.

In summary, a new drug discovery strategy for tropical diseases based on networks and partnerships between academia, industry in developed and developing countries is in place and functioning (see Figure 1). This strategy incorporates TDR empowerment function in relation to both institutional and individual development in DECs. It also emphasizes a new stewardship role through the coordination of these efforts and the generation of global resources such as lead compounds and a database of drug and diagnostic targets.

3.2 SYNERGIES WITH OTHER ORGANIZATIONS

The business line will exploit the extensive partnerships already established with industry, academia, PPPs and philanthropic foundations.

- Industry: this business line will build on TDR's track record in partnering with industry to identify new drug leads. Industry typically provides chemical libraries, infrastructure and know how for high throughput screening, medicinal chemistry, and ADMET profiling. TDR brings 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, personnel (including fellows from developing countries) are funded to work on projects, and industry/academic collaborations are managed.

- Academia and public agencies: through this business line, TDR will partner with academic laboratories in the North and South to translate research into new leads. Academic laboratories will help in the selection and validation of new targets, and development of assays for HTS campaigns as well as in vitro and in vivo parasite screens. This business line will collaborate with such laboratories to develop new drug screening tools and models, especially for diseases caused by helminths as these are urgently needed. TDR will invest and manage work at academic laboratories to deliver new product leads through network activities and partnerships with industry. Some national research agencies, for example in the USA (e.g. NIH) and EU, are encouraging translational research and supporting small companies and academic laboratories to participate (but tropical diseases is not the only focus).

- PPPs: the business line will complement and synergize with the PPPs located in the North, for examples MMV, GATB, FIND, DNDi. Some of the products being developed by these PPPs resulted from early TDR funding. Indeed, TDR is now negotiating a contract with MMV to enable collaboration to progress a TDR antimalarial lead series (TDR 22093) which has recently emerged from the TDR compound assessment network. Some of existing PPPs are not investing sufficient funds in the early stages of lead
discovery (e.g. HTS against molecular targets and MTS against parasites in vitro) to produce a sustainable portfolio of lead compounds for further optimization.

- Institutions in the South: through its network activities, this business line will promote innovation and partnership for lead discovery in the South. It will proactively identify and engage industry, both in the least and most advanced developing countries, to participate in lead discovery through technology transfer. Where appropriate, the business will promote local IPR management as a catalyst for innovation. In this regard a successful meeting on the promotion of innovation and technology transfer was organized by TDR as part of the MIM meeting in Yaoundé in 2005. In addition, TDR organized a successful meeting on Innovative Drug Discovery Strategies for Tropical Diseases at the American Society for Tropical Medicine and Hygiene in December 2006. These meetings generated a lot of interest and exemplify TDR's stewardship role in this area. Through this business line, the innovation meetings will continue.

- Philanthropic Foundations: the business line will solicit lasting relationships with foundations such as the Bill and Melinda Gates, Wellcome Trust and Rockefeller. These organizations recognize the importance of investing in lead discovery and are willing to make appropriate contributions. TDR is currently engaging some of these foundations - for example in the helminth initiative. Activities of the Gates Grand Challenges may be more upstream of this BL. In the area of TB, the Gates Foundation has developed a strategy for TB drug discovery. It is anticipated that TDR's target portfolio development exercise which encompasses TB will be synergistic with this. It is noteworthy that a recent meeting organized by MSF in New York (January 11-12, 2007) on "Overcoming Gaps in Drug Research and Development - No Time to Wait" identified our work and the model described here\(^1\) as one of three background-meeting materials. The Wellcome Trust have recently funded a Drugs for Tropical Diseases Initiative in the University of Dundee (focusing on kinetoplastids), and extended this to there Seeding Drug Discovery but this is not directed specifically towards tropical diseases and can encompass any human disease.

In general the work this BL is unique, synergistic to other initiatives and presents a platform for enhanced search for new antiparasitic medicaments.
4. ACTIVITIES AND END PRODUCTS

4.1 KEY ACTIVITIES

4.1.1. Activities supporting the discovery of quality leads (specific objectives 1.2.1 to 1.2.5):

- Establish and maintain a portfolio of prioritized molecular targets to facilitate discovery of new leads for tropical diseases. Work on the open access database containing prioritized drug targets is at an advanced stage. Data on TB, malaria, human African sleeping sickness, Chagas disease and leishmaniasis targets are available in the database. Continuous curation of the database and work on helminth targets are ongoing. This experience with drug target prioritization will guide the establishment of a prioritized list of potential diagnostic targets to be assessed by the TDR's diagnostics business line or other agencies. This target portfolio exercise will be very useful for vaccine discovery and this business line will encourage appropriate players to invest in this.

- Progress validated targets to high throughput screening campaigns
  - Through the target portfolio work (database), promote the establishment of an in silico platform for tropical diseases drug discovery

- In vitro and in vivo screening through the TDR compound assessment network comprising leading centres and investigators in the North and South (see Annex 1)

- Development of improved in vitro parasitic screens and in vivo models through fundamental research ("Bright Ideas proposals").

- Medicinal chemistry and pharmacological analysis through the respective networks (see Annex 1), as well as the exploratory toxicology of promising leads

- Proactive identification of new partners for: compound supply (for example compounds with established biological and biochemistry rationale for helminth diseases coming from animal health companies), real/virtual high throughput screening against molecular targets/whole cells or model systems, lead identification and optimization as appropriate

- Define a strategy that will facilitate the transfer of innovative lead molecules to the most relevant development partners e.g. pharmaceutical companies, PPPs, innovative South-based initiatives. Proactively engage DEC researchers and institutions in these partnerships

4.1.2. Activities supporting the Helminth Initiative (see specific objectives 1.2.2):

- Establish and incubate the Helminth Drug Initiative - establish a Working Group to help follow up on the recommendations of the expert meeting held in Tokyo in March 2006 and January 2007. The Working Group will help to shape the technical agenda, future scope and framework of the Helminth Initiative.
The screening networks, medicinal chemistry and other networks will support the Initiative (see Annex 1)

Exploratory toxicological analysis will be undertaken to support candidate selection

Proactive sourcing of compounds through partnership with pharma, animal health and agrichemical companies

4.1.3. Activities providing stewardship function (see specific objective 1.2.3):

- Establish good practices for project and portfolio management to deliver lead discovery objectives. Promote the use interactive database for data and project management
- promote the global coordination of drug discovery activities through the network and partnership model and transfer leads or compounds to appropriate partners
- Coordinate the Helminth Initiative and help identify new screening tools to support the Initiative
- Identify funding to support the Helminth Initiative

4.1.4. Activities providing empowerment function (see specific objective 1.2.4):

- North-South collaboration networks and partnerships to promote technology transfer and innovative drug discovery in DECs
- Postdoctoral fellowships and training of DEC scientists in drug discovery through North-South networks, an example is the placing of scientists from DECs in industry to work on TDR or network projects

4.1.5. Activities supporting fundamental research on generation of new tools to facilitate drug discovery (1.2.5)

- Targeted call for application ("Bright Innovative Ideas") on new screening tools, target validation around TDR’s drug target database, animal models, bioinformatics
- Promote helminth genome sequencing as a catalyst for translational research in this area

4.2 END PRODUCTS

4.2.1. The end products from lead discovery activities (see specific objectives 1.2.1 to 1.2.4):

- 10 leads (with novel chemotypes) will be discovered for one or more TDR target diseases by 2013
  - This translates to about 2 leads discovered every year starting 2007
  - 1 lead to be transferred to a partner every other year starting 2007/2008
  - A portfolio of projects and network activities delivering leads starting 2007
Business plan: Business line 3 - Lead discovery for drugs

- Open access database containing drug targets in support of high throughput and \textit{in silico} screening for lead discovery starting 2007
- 2 new centres for kinetoplastid screens identified and supported (2009)

4.2.2. End products from the Helminth Initiative activities (see specific objective 1.2.2)
- 2 drug candidates identified through the Helminth Initiative by 2013
  - Helminth Initiative fully functional, utilizing existing network and partnerships model (2006-2008)
  - Working Group established to help further develop the framework for the Initiative, including the development of a focused business plan (2007 - 2008)
  - 2 new centres for helminth screens identified and supported (2008)

4.2.3 End products from the stewardship activities (see specific objective 1.2.3):
- Coordinated drug discovery strategy based on networks and partnerships published and publicized (2006 - 2013)
- Coordinately managed portfolio of lead discovery projects with partners available (2007 see Annex 5), delivering leads and transferring these to appropriate partners for further development
  - Expert Discovery Review and Scientific Working Group meetings to promote drug discovery for public health starting 2007
  - Coordination of the Helminth Initiative, and publications focusing on the Initiative starting 2007
  - Meetings on Innovation in the North and South (examples, 2005 at MIM conference Cameroon, and 2006 at the ASTMH meeting Atlanta)

4.2.4. End products from the empowerment activities (see specific objective 1.2.4):
- DEC scientists and institutions participating in our North-South networks and producing leads (2006 - 2013)
  - North-South networks for drug discovery established and functional 2006
  - About 6 fellows from DECs trained - from 2006 - 2013
  - Workshops and training on innovative lead discovery in DEC including structure-based drug design, medicinal chemistry, \textit{in vitro} ADME, whole cell screening, and natural products - started in 2005

4.1.5. End products supporting fundamental research on generation of new tools to facilitate drug discovery (1.2.5):
- 1 new \textit{in vitro} or \textit{in vivo} drug screening tool developed by 2013
- 1 new target validated and assay developed for one of the TDR target diseases by 2008
4.2.5 Other end products or success indicators.

- Establish target product profile for each disease and use this to guide lead discovery (2006)¹
  - Review and revise the target profile on regular basis due to changing landscape
- Transition current networks as part of this business line (2006 - 2007)
- Drug candidate criteria defined for helminths (2008)
- Where appropriate, patents filed for promising leads by partners or in collaboration. Open access high-impact publications, including standard operating procedures, in different aspects of lead discovery. This will help to promote lead discovery in academia and DECs (2006 - 2013)
- Web based SOPs/compound submission requirements - molecular mass, solubility, structure etc.

4.3 INTERIM IMPLEMENTATION MILESTONES

4.3.1. Implementation milestones for lead discovery (see specific objectives 1.2.1 to 1.2.4):

- Transition relevant on-going lead discovery work/networks/partnerships into business line 3 (4Q 2006 - 2Q 2007)
- Replace existing Genomics and Discovery Research steering committee with a strategic Expert Discovery Advisory Committee - EDAC (June 2007)
- Establish criteria for new project selection/review to guide EDAC (2007)
- Review, with the help of EDAC, ongoing activities and strengthen existing networks (2007 till 2008)
- Initial launch of database of prioritized drug targets for TB, malaria, leishmaniasis, African sleeping sickness, Chagas (2007)
- Continue curation of the database and incorporate helminth targets (2007 -2013)
- Promote the establishment an in silico drug discovery platform the drug target database
- Identify 2 leads each year starting in 2007
- Transfer leads to appropriate partners - Pharma, PPPs, or innovative partnerships in the South - for further development (2007-2013)
4.3.2. Implementation milestones for Helminth Initiative (see specific objective 1.2.2.):

- Proposed Helminth Initiative fully functional under BL 3, utilizing existing network and partnerships to kick start activities (2006-2008)
- Scientific Working Group meeting to review progress to date and advice on future direction of the Initiative (held January 2007)
- Establish smaller Working Group (5 - 8 persons) to help further develop the framework (including focused business plan if warranted) for the Initiative (2007 - 2008)
- Identify 2 drug candidates for helminth diseases through the Helminth Initiative (2013)
  - Plan for progression of drug candidates for development by identifying appropriate partners or business line (2008 -2009)

4.3.3. Implementation milestones for stewardship (see specific objectives 1.2.3.):

- Expert discovery review meetings starting 2007
- Coordination of the Helminth Initiative, and publications focusing on the Initiative starting 2007
- Meetings on Innovation started 2005 (Cameroon) , 2006 (ASTMH Atlanta)
- Drug target portfolio available through an open access database (2007 - 2008)
  - Support the diagnostic business line to initiate diagnostic target prioritization work based on experience of the TDR drug target network
  - Promote the extension of the target portfolio work to vaccine discovery through other organizations
- Open access high impact publications, updated standard operating procedures established and where appropriate patents (2006-2013)

4.3.4. Implementation milestones for empowerment (see specific objective 1.2.4.):

- Full integration of DEC institutions in our networks (screening, medicinal chemistry (2007 -2008)
- Training of DEC fellows through our networks and partnerships (2007 - 2013)
- Transfer of specific discovery technology or projects to centres of excellence in developing countries (2007 - 2013)
ADDITIONAL PERFORMANCE METRICS OR INTERMITTENT SUCCESS INDICATORS

- Number of companies and public institutions engaged and supplying compounds, initiating HTS and providing lead discovery know-how.
- Number of hits emerging from HTS campaigns and progressed to whole cell screens
  - TDR’s experience is that about 100 hits emerging from HTS can be progressed to whole cell screen per annum and analogues sourced for whole cell actives.
- Number of compounds progressed to in vitro (whole cell) and in vivo (animal) screens
  - TDR’s experience in the past years is about five thousand compounds can be progressed to whole cell testing for protozoal and helminth, and about 150 compounds in vivo per annum. However, these numbers have increased in the past year due to enhanced compound acquisition from industry by TDR.
- Number of projects benefiting from medicinal chemistry and PK/metabolism analysis
- Number of projects stopped early for lack of progress
- Number of leads identified and progressed to optimization and/or development
- Number of drug candidates identified

KEY DECISION/REVIEW POINTS:

- Compounds: quality, diversity and novelty of compounds supplied for testing or used for HTS campaigns (evaluated by our medicinal chemistry consultants)
- HTS: availability of hits against molecular target. Review chemical structures. Review of the correlation between enzyme and whole cell activity
- MTS screens on whole cells: availability of active compounds that meet established in vitro activity and selectivity criteria. Mammalian cell line counter screen. Review of chemical structures and prioritization of compounds. Generation of in vivo data in relevant animal model of disease
- Medicinal Chemistry/Pharmacokinetics work: on the basis of above data, assign medicinal chemistry resources for compound scale up, SAR exploration and additional animal testing including PK/metabolism (DMPK) to help define a quality lead
- Exploratory toxicology: where appropriate, exploratory toxicology data will be generated and made available for review

INTERFACES WITH WHO/TDR RELATED ENTITIES

- Interaction with product development committees
- Interaction with the WHO secretariat on Public Health, Innovation and Intellectual Property. This BL will continue to support the work of the secretariat's work
- Interaction with NTD department on the Helminth Drug Initiative managed by this BL
5. FUNDING

### 5.1 RESOURCE REQUIREMENTS

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<thead>
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<th>Activity</th>
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<th>2008</th>
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<td>Drug target portfolio database (covering protozoa, helminths and TB targets)</td>
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<td>500</td>
<td>900</td>
<td>1,200</td>
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<td>Helminth Initiative - (covering additional cost for lead optimization)</td>
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<td>6 external consultants (chemists, PK, Tox, general drug discovery)</td>
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<td>Targeted fundamental research</td>
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<td>10</td>
<td>Portfolio management (Advisory meetings, portfolio review/analysis, Consultations, lead/candidate selection)</td>
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**Activities**  
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**Personnel Costs**  
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**Total**  
5,727 6,515 7,864 10,164 10,864 10,864

### 5.2 RATIONALE FOR RESOURCES REQUIRED

The budget requested is based on our current lead discovery experience and that of some PPPs and industry figures\(^7\). For example, in the past year the screening network cost TDR about US$ 1.1 million (excluding the cost of compound storage and database). However, the increase in compound supply due to new collaborations with industry has put pressure on the screening centres. The requested budget will help in strengthening the existing centres and identifying about 2 more centres to support enhanced drug discovery for helminth and kinetoplastid infections. The same rationale is true for medicinal chemistry and other networks. The budget for medicinal chemistry, PK, HTS and exploratory toxicology are lower than normal due to in-kind support from industry. Please note that these figures may increase significantly in the coming years.
Additional justification:

Lead discovery - on average a typical lead identification project takes about 2 to 3 years with a cost of about US$ 4 million using estimates from the MMV Business Plan 2003. This does not include the cost of hit identification through high or medium throughput screening campaigns. Typically each HTS campaign costs US$ 250,000 for screening a sizeable compound library (say 100,000 compounds or more). To deliver 10 drug leads by 2013, this business line will continue to source and screen compounds with known biological and biochemical rational from industry as well as diverse libraries of compounds (including natural products) from different sources. The business line will also continue to invest in target-based drug design using novel targets progressed to HTS campaigns (both real and virtual screens). We estimate that about 2 or 3 HTS campaigns per annum (using good and sizeable compound libraries, and validated targets) will help in initiating "hit to lead" projects based on genomic targets. For both target and non target based approaches, the scale of our operation across parasites brings added advantages. Because the parasite screens are available at our screening centres it is cost-effective to profile available compounds against a panel of disease-causing parasites rather than individual protozoa or helminths. This also provides early information on the selectivity or toxicity of a particular set of compounds (cytotoxicity assessments are carried out simultaneously). Our budget estimate translates to about US$ 6 million for 2 lead compounds per year (plus limited lead optimization activities - see below). This is value for money considering that this average cost is lower than the experience of the few PPPs involved in lead discovery today. However, a certain degree of budgetary flexibility is required for discovery research and these numbers can change.

Lead optimization: the budget presented also covers the cost of 2 drug candidates for helminths by 2013. This is also an added benefit considering the high cost of lead optimization. In-kind support from industry is one of the reasons for the significant cost savings. Estimates from MMV suggest that it takes about 3 years for a lead optimization programme with an annual cost of about US$ 2 million per project.

The cost of pharmaceutical drug discovery is not fixed. Due to the high attrition and FTE costs, estimates for discovery expenditure alone may range from US$ 200 to US$ 400 million/ product based on industry figures. It is likely that for infectious diseases the true cost will be to the lower, rather than higher end of this scale due to some of the points already discussed as well as the availability of reasonably good predictive animal models. This said, it is vital for neglected disease drug discovery to be run like a business, but with a clear mandate to reduce the cost of operation and resulting products. The need to rise to the challenge and consider innovative solutions to reduce costs of drug discovery is a fundamental principle of the proposal outlined in this business plan. Indeed, low-cost drug discovery does not imply a low quality operation. In fact the opposite may be true because this effort is guided by target product profiles geared for use in resource-poor settings. Careful a priori application of available drug discovery knowledge to target selection, lead selection and optimization can be a key factor in improving the overall quality of the tropical diseases drug discovery portfolio, thus increasing the chance of success and cost reductions.
6. RISKS

Technical
- Drug discovery is inherently high risk with attendant attrition rates. However our strategy, project selection and review procedure involving leading experts promises to reduce attrition and the cost of lead discovery. Also, extensive due diligence is carried out on the compounds sourced for screening and the projects funded using seasoned consultants with wide industry experience (for example, medicinal chemists and leading drug discovery experts).

Financial and administrative
- Lack of funding for projects, inability to raise funds
- Administrative bottlenecks in implementation of funds and lack of flexibility in managing projects. We hope that the business line approach will solve this problem.

Environmental
- Lack of infrastructure in DECs may impede progress and technology transfer. So far, southern investigators involved in our network activities have world class infrastructure and internationally competitive scientists working locally.

Project execution related
- Inability or inadequate incentives to attract industry to supply compounds
- Intellectual property issues can sometimes prevent concluding agreement. An IP strategy that builds on TDR's successful win-win approach to partnership will be emphasized in line with the guidelines of WHO.

Others
- Perceived redundancy with other TDR business lines might cause confusion internally and externally. TDR business lines should be synergistic and complementary, but not repetitive with each other.

In conclusion, this business plan is a realistic attempt to clarify and reinstate TDR as a key player in the discovery of new antiparasitic agents. The focus on innovative lead discovery based on a networks/partnership model (see Figure 1) fills a critical gap in the drug development pipeline for tropical diseases required for health impact in developing countries. A robust drug discovery portfolio based on this model is already being managed by TDR (see Annex 5). The plan recognizes the important role of partnerships as well as participation of developing country scientists and institutions in achieving the Millennium Development Goals and providing lasting solutions to the product access crises.
ANNEXES

ANNEX 1: EXAMPLES OF ONGOING NETWORKS AND PARTNERSHIPS

Examples of ongoing networks and partnerships in the TDR's drug discovery are as follows:

1. Compound Screening/Evaluation Network: this consists of the Swiss Tropical Institute (STI) Basel, which provides in vitro and in vivo screens for malaria, African and South American trypanosomiasis, leishmaniasis - this laboratory is led by Dr. Reto Brun; the London School of Hygiene and Tropical Medicine (LSHTM), which provides in vivo screens for schistosomiasis also in vitro, malaria, leishmaniasis and Chagas - the laboratory is led by Dr. Quentin Bickle; the Northwick Park Institute for Medical Research (NPIMR) London, which provides in vitro and in vivo screens for filariasis and onchocerciasis - the laboratory is led by Dr. Simon Townson; the Theodor Bilharz Research Institute (TBD) Cairo, which provides in vitro and in vivo screens for schistosomiasis - the laboratory is led by Dr. Fouad Yousif; Laboratory for Microbiology, Parasitology and Public Health (LMPH) Antwerp, which provides in vitro screens for malaria, leishmaniasis and African and South American trypanosomiasis - the laboratory is led by Dr. Louis Maes. This network is capable of processing about 20,000 compounds per annum through the in vitro screens and about 1,000 compounds per annum in vivo based on the funding currently provided by TDR. The compounds assessed by these centres are largely sourced by TDR through its pharmaceutical and academic partners. Hits emerging from the screens are further progressed through the TDR medicinal chemistry and pharmacokinetic networks to generate leads.

2. The new TDR Medicinal Chemistry and Pharmacokinetics Networks: these networks were initiated in late 2005 but they are now fully functional. The medicinal chemistry network consists of Pfizer, Serono, Pharmacopeia, University of Nebraska, University of Dundee, University of Cape Town, Ohio State University and St. Jude Children's Research Hospital Memphis. These centres work on the hits or potential leads coming out of the compound assessment network as well as those emerging from the high throughput screening campaigns. Several postdoctoral fellows linked to institutions in developing countries are supported to work at these centres. Compounds generated through this network are further evaluated by the screening centres (see above). The pharmacokinetics network consists of the companies providing chemistry support as well as Monash University. The network provides essential ADME (absorption, distribution, metabolism and excretion) data to guide the chemists. Additional pharmacokinetics centres are sought to augment the network.

3. The TDR Drug Target Portfolio Network: this consists of the University of Washington Seattle (led by Dr. Wes Van Voorhis), the University of Pennsylvania (led by Dr. David Roos), the Sanger Center (led by Dr. Matt Berriman), the Walter Eliza and Hall Institute for Medical Research - WEHI (led by Dr. Stuart Ralph) and the Institute for Research in Biotechnology at UNSAM Argentina (led Dr. Fernan Aguero). Additional support is
provided by Pfizer, Inpharmatica, and University of California San Francisco. This network has made excellent progress in the development of a globally accessible database with a prioritized list of potential drug target (emerging from genomics) that can be progressed to HTS by TDR or other players. The hits emerging from the HTS campaigns will be evaluated in the TDR compound screening network. The first year of this network has already generated a database containing targets from Mycobacterium tuberculosis, Plasmodium falciparum, Leishmania donovani, Trypanosoma brucei, and Trypanosoma cruzi. See sample of the database in the Annex Section - Annex 3.

4. Partnerships: these are various public-private partnerships focusing on drug discovery including compound supply. These partnerships are covered by agreements. Examples include: the Pfizer/TDR partnership for drug discovery - compound supply, medicinal chemistry etc; the Serono/TDR partnership for drug discovery - high throughput screening campaigns, medicinal chemistry, compound supply and the Chemtura/TDR partnership - compound supply. Companies collaborating or supporting TDR in drug discovery are presented in a table in the Annex Section - Annex 4 (see also ref 1)

ANNEX 2: DEFINITIONS AND ACTIVITY CRITERIA FOR HITS & LEADS

Definitions*:

‘Hit’ - compound with selective in vitro activity (usually IC50≤1uM) against target whole organism and/or protein

‘Lead’ - compound with drug characteristics, and efficacious in disease animal model with no overt toxicity

‘Development candidate’ – optimized lead compound with in vitro and in vivo activity equivalent or better than current drug standards, acceptable pharmacokinetic and toxicity profile, amenable to cost-effective scale-up

‘Clinical candidate’ – development candidate which has passed additional stringent toxicity, pharmacokinetic, formulation and stability studies

Hit activity criteria for protozoa

- *P. falciparum* (K1) IC50 <0.2ug/ml, SI*>100
- *T. b. rhodesiense* (STIB 900) IC50 <0.2ug/ml, SI* >100
- *T. cruzi* (Tulahuen) IC50 <1.0ug/ml, SI* >50
- *L. donovani* (L82)
  - Axenic amastigotes IC50 <0.5ug/ml, SI* >20
  - Amastigotes in macrophage IC50 <1ug/ml, SI* >20
  SI* = IC50 L-6/IC50 parasite
Lead activity criteria for protozoa

- Active *in vivo* (mice) in 10% DMSO formulation @ n x \( \leq 100 \) mg per kg as measured by > 90% reduction in parasitaemia* and/or increase in life span**, n = no. of doses given ip, sc or po daily and varies usually from 1-5
  - Malaria *P. berghei* (ANKA strain), usually at 4 x 50 mg/kg* **
  - African trypanosomiasis *T. b. brucei* (STIB 795 strain), usually at 4 x 50 mg/kg * **
  - *S. American trypanosomiasis T. cruzi* (Tulahuen)**
  - Leishmaniasis *L. donovani* (HU3)*
- Not overtly toxic in animals at efficacious dose
- Active *in vitro* against relevant parasite strains (e.g. drug-resistant)

Hit activity criteria for helminths

- Schistosomiasis: *S. mansoni* adults 100% inhibition of motility @ 5ug/ml
- Onchocerciasis: *O. lienalis* mf 100% inhibition of motility @ 1.25 x 10-5M
  - *O. gutturosa* adults 100% inhibition of motility or formazan formation @ 1.25 x 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 po, ip or sc in 10% DMSO formulation @ 5 x 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

Development candidate criteria:

Development candidates must have a good chance of meeting therapeutic target profile (based on animal data) in terms of efficacy, safety, metabolism, chemistry, route of administration, and treatment regimen⁶. A generic set of information required for drug candidate selection has been described (see ref 6). However, specific candidate criteria vary for every disease. The specific criteria are being developed for the TDR target diseases (especially helminthiasis), and will be discussed by the Scientific Working Group on the Helminth Drug Initiative and the Expert Discovery Advisory Committee in due course.
ANNEX 3 : SAMPLE OF TDR TARGET PORTFOLIO DATABASE

WHO/TDR Drug Discovery

Apply global weights

*Note:* Zero-weight queries are automatically omitted from weighting results. Mark the **Include** checkbox to include zero-weight queries in weighting calculations.

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# ANNEX 4: TDR Drug Discovery Collaborations

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<td>• Medicinal Chemistry/PK</td>
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<tr>
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<td>• Potential HTS campaigns</td>
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<td>Meiji</td>
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<td>Chemtura</td>
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Annex 5: TDR DRUG DISCOVERY PORTFOLIO

TDR Drug Discovery portfolio to be further developed and managed by BL 3

TDR Drug Discovery Portfolio

- Genomics: Portfolio of drug targets and database being developed
- HTS: WEHI 3 targets, Malaria 4 lead series, African Tryps 1 lead series, Leishmaniasis 1 lead series, Helminths 1 lead series
- Lead ID: HDAC Inhibition Malaria, TDR 22093 With MMV, Cyclodepsipeptides
- Preclinical Development: Pfizer collaboration, Serono Collaboration, Helminth Initiative
REFERENCES


