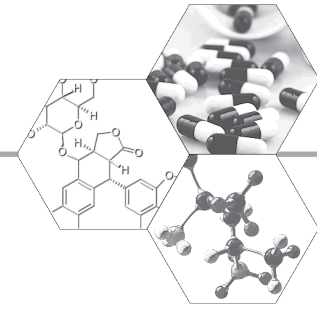

Drugs for Neglected Diseases *initiative* model of drug development for neglected diseases: current status and future challenges

The Drugs for Neglected Diseases *initiative* (DND*i*) is a patients' needs-driven organization committed to the development of new treatments for neglected diseases. Created in 2003, DND*i* has delivered four improved treatments for malaria, sleeping sickness and visceral leishmaniasis. A main DND*i* challenge is to build a solid R&D portfolio for neglected diseases and to deliver preclinical candidates in a timely manner using an original model based on partnership. To address this challenge DND*i* has remodeled its discovery activities from a project-based academic-bound network to a fully integrated process-oriented platform in close collaboration with pharmaceutical companies. This discovery platform relies on dedicated screening capacity and lead-optimization consortia supported by a pragmatic, structured and pharmaceutical-focused compound sourcing strategy.

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Drugs for Neglected Diseases *initiative*'s mission & business model

■ Scope of diseases, unmet needs & activities covered by Drugs for Neglected Diseases *initiative*

The Drugs for Neglected Diseases *initiative* (DND*i*) is an international and nongovernmental not-for-profit organization committed to the development of novel and/or improved treatments for neglected diseases. The diseases chosen initially included visceral leishmaniasis (VL), Chagas disease and human African trypanosomiasis (HAT, also commonly known as sleeping sickness). They are caused by different but related flagellate **protozoa**, known as kinetoplastids. In addition, DND*i* selected two fixed-dose antimalaria drug projects in response to a well-defined need [1–3]. These neglected diseases, together with other tropical parasitic and viral infections, such as onchocerciasis, schistosomiasis, lymphatic filariasis, Buruli ulcer and dengue (included in WHO's official list of 17 neglected tropical diseases [101]), account for substantial morbidity and mortality in endemic countries [4,5]. According to the WHO, these diseases are strongly related to poverty, remain endemic in tropical countries, affect populations with low visibility causing stigma and discrimination, and have an important impact on morbidity and mortality. Neglected tropical diseases are also insufficiently addressed from an R&D perspective. As a consequence there is a lack of safe, effective and field-adapted treatments made available to the patients affected by these pathologies. This is illustrated by the fact that only 16 out of 1393 (1.1%) new chemical entity (NCE) marketed drugs from 1975 to 1999 were developed for neglected diseases including malaria and tuberculosis [6]. Although these diseases account for 11.4% of the global disease burden, the efforts to improve the situation have remained marginal in recent years, with only 21 (1.3%) out of 1556 approved molecules that were specifically developed to address neglected diseases between 1975 and 2004 [7]. This poor performance can be explained by the lack of a profitable market, as well as by the absence of stimulating mechanisms leading to funding and execution of R&D activities to efficiently combat these diseases [102]. Fully aware of these issues based on its field experience, Médecins Sans Frontières (Doctors without Borders) committed its 1999 Nobel Peace Prize funds to develop an alternative R&D model for new drugs for neglected diseases that eventually led to the creation of DND*i* in 2003.

■ A business model based on product-development partnership

The Drugs for Neglected Diseases *initiative*'s objectives and activities are driven by patient needs that have been identified with the help of various stakeholders with strong field experience [8]. To address these needs, DND*i* has adopted a pragmatic **product-development partnership** (PDP) approach based on a virtual model with all its R&D activities

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Key Terms

Protozoa: Diverse group of single-cell eukaryotic (nucleus-containing) organisms, many of which are motile thanks to the presence of flagella.

Product-development partnerships: Public–private partnerships between not-for-profit organizations and partners aimed at developing pharmaceutical products (such as treatments, vaccines and diagnostics) and preventative tools, for the treatment of neglected diseases.

Target product profile: An organized list, developed in agreement with multiple stakeholder perspectives, which prioritizes the key features and attributes of the intended end product (e.g., drug).

Drug repositioning: Application of known drugs and compounds to new indications, such as new diseases. Also known as therapeutic switching.

outsourced [9,10]. This model requires the establishment of strong collaborations with various partners from both nonendemic and endemic countries including WHO, national health programs, regulatory agencies, public and private research institutions, pharmaceutical companies and NGOs that share DND*i*'s vision and commitment. Since its creation in 2003, DND*i* has developed an innovative, flexible and efficient approach to conduct drug development. This is achieved through its unique hybrid organizational culture and involves worldwide partnerships that rely on state-of-the-art R&D expertise. DND*i* plays a leading role in identifying partners and securing funding to initiate key projects, in line with its objectives across scientific disciplines as well as cultural and organizational boundaries. A catalytic role is played by DND*i* in the day-to-day management, coordination and empowerment of the project stakeholders with a common defined objective. As clearly stated in its mission, DND*i* also aims to utilize and strengthen existing capacities in disease-endemic countries through, among other means, technology transfer related to R&D. This has led, for instance, to the establishment of three specific clinical platforms: HAT Platform for Sleeping Sickness in Africa, Leishmaniasis East Africa Platform for VL in Africa and the most recently launched Chagas Clinical Research Platform for Chagas disease in Latin America. The platforms, centering around DND*i* clinical projects, bring together regional and international actors: ministries of health, national-control programs, regulatory agencies, academia, clinicians, civil-society groups and pharmaceutical companies, with a common vision of addressing patient needs in the local and national contexts where the diseases are endemic. They utilize, capitalize upon, and reinforce laboratory and clinical capacities in endemic regions, and address infrastructural requirements where necessary, as well as providing on-site training in clinical research [103].

The Drugs for Neglected Diseases *initiative* actively seeks public and private funding for its projects. In order to reach its objectives for 2014, DND*i* had secured €153 million (by the close of 2010) of the €230 million targeted, with overall funding balanced between public and private sources. DND*i*'s total annual budget in 2010 was €25 million, of which 80% is committed to R&D activities. In the coming years, DND*i* will continue to advocate for sustainable and diversified (public and private balance) funding mechanisms for neglected disease R&D, increasing its efforts for the creation of innovative funding mechanisms.

■ An access & open-innovation-oriented approach to intellectual property management

The Drugs for Neglected Diseases *initiative*'s R&D approach is needs-driven and patient-focused, ensuring that the concrete needs of patients affected by neglected diseases are the driving force of all research efforts and opportunities. An intellectual property (IP) policy has been established by DND*i* to guide IP negotiations related to its R&D activities [104]. This policy aims to ensure that treatments are ultimately affordable to patients and, whenever possible, that they be made available as public goods in order to ensure equitable access for all patients and encourage further innovation. DND*i* has adopted a pragmatic and case-by-case approach regarding ownership of patents and licensing terms. Typically, DND*i* does not seek IP ownership on molecules and technologies considered promising for development, rather it negotiates freedom to operate to ensure the access for the neglected patients. When negotiating access to a given proprietary technology, DND*i* carefully examines the issues related to the field (diseases concerned), the territory (countries where the diseases are endemic), and the market to be addressed (distribution through the public and/or private sector). Clear definitions and agreement on these terms are the key factors to moving forward and to allocating, with confidence, substantial resources to a specific project or program. In addition, this approach offers partners the potential to benefit from a for-profit market outside of the field of the agreement. It is important to note that so far DND*i* has not filed a patent on any discovery emanating from its R&D activities. However, such an option could be exerted on a case-by-case basis, for instance, through defensive patenting to prevent third parties from blocking the use of a specific technology or to secure freedom to operate in a risky IP environment. Clearly, DND*i*'s IP policy is not aimed at preventing its partners from patenting discoveries made in the frame of DND*i*-funded projects, as long as DND*i* is granted licensing rights necessary to achieve its mission and related R&D objectives. In addition, DND*i* embraces the dissemination of its research data to the scientific community

to encourage additional or follow-on research in the field of neglected diseases. Guidelines of DND*i*'s IP and licensing policies are available on the DND*i* website [104].

DND*i* organization, objectives & key accomplishments

■ DND*i* as an organization

The Drugs for Neglected Diseases *initiative* was founded by seven institutions with the aim of responding to the need for safe, efficacious, affordable and field-adapted treatments for neglected patients. The seven institutions are the Indian Council for Medical Research, Kenya Medical Research Institute, Malaysian Ministry of Health, Oswaldo Cruz Foundation in Brazil, Médecins Sans Frontières and Institut Pasteur in France, with the UNICEF/UNDP/World Bank/WHO's Special Programme for Research and Training in Tropical Diseases as a permanent observer on the Board. DND*i* is governed by a Board of Directors that receives advice and recommendations from an independent Scientific Advisory Committee on matters related to choice of R&D projects and quality and progression of the scientific activities. The DND*i* executive team is based in Geneva and consists of 30 permanent scientific staff and various professionals. The organization has an affiliate in North America along with five regional support offices in Kenya, India, Brazil, Malaysia and Japan, and one regional project support office in the Democratic Republic of the Congo. The executive team is responsible for the implementation of the R&D strategy, management of the global portfolio, allocation of resources to supported projects, fundraising and advocacy. **FIGURE 1** provides an overview of DND*i*'s governance and operational management chart [104].

■ Building the DND*i* portfolio

The Drugs for Neglected Diseases *initiative*'s primary objective is to deliver six to eight new treatments by 2014 for HAT, VL, Chagas and malaria. Short-term projects have been defined to address urgent patient needs for better, effective, safe, adequate and accessible new treatments. To date, late-stage development has rendered two fixed-dose combinations based on artesunate for malaria (artesunate + amodiaquine [105–108] and artesunate + mefloquine [109]), one combination therapy based on existing drugs for the treatment of VL (paromomycin and sodium stibogluconate, in East Africa) and one simplified co-administration for the treatment of second-stage sleeping sickness (nifurtimox–eflornithine combination therapy) [110]. These treatments are now available to patients. Besides these important achievements, DND*i* has built the largest ever R&D portfolio for kinetoplastid diseases, with three clinical projects (including two new clinical candidates) and four preclinical projects (including three new NCEs) currently underway **(FIGURE 2)**. The inclusion of new projects is continuously considered at the various stages of development of the pipeline to further consolidate the current portfolio. This requires that the selected projects match closely with the identified needs as defined in its **target product profiles** (TPPs) (see 'Discovery tools' section in this article). Other key criteria in project selection relate to funding and IP management to ensure equitable access to treatments, and identification of committed expert partners to ensure the maximal prospects of success for a given project.

There are numerous ways new projects can be considered for inclusion in the current DND*i* portfolio at the different stages of development:

- Discovery level: new chemical series identified through screening and early profiling efforts;
- Discovery/preclinical level: molecules associated with an advanced development profile could enter lead optimization (LO) or preclinical development. Some of these molecules are also referred to as 'low-hanging fruits'. Examples of low-hanging fruits are drug candidates that have previously been developed for other indications;
- Preclinical/clinical level: new indications for existing medicines in the field of the most neglected diseases (i.e., therapeutic switching, **drug repositioning**), combinations or new formulations of existing drugs and/or more adapted to field conditions (i.e., paediatric, long-acting, new route of administration, fixed-dose combinations, co-packaging or co-administration), geographic extension of registration for existing drugs and completion of regulatory dossiers of existing drug candidates.

In addition to its main R&D objectives, DND*i* also aims to use and strengthen existing capacities in disease-endemic countries, to raise awareness about the need to develop new drugs for neglected diseases and to advocate for increased public responsibility.

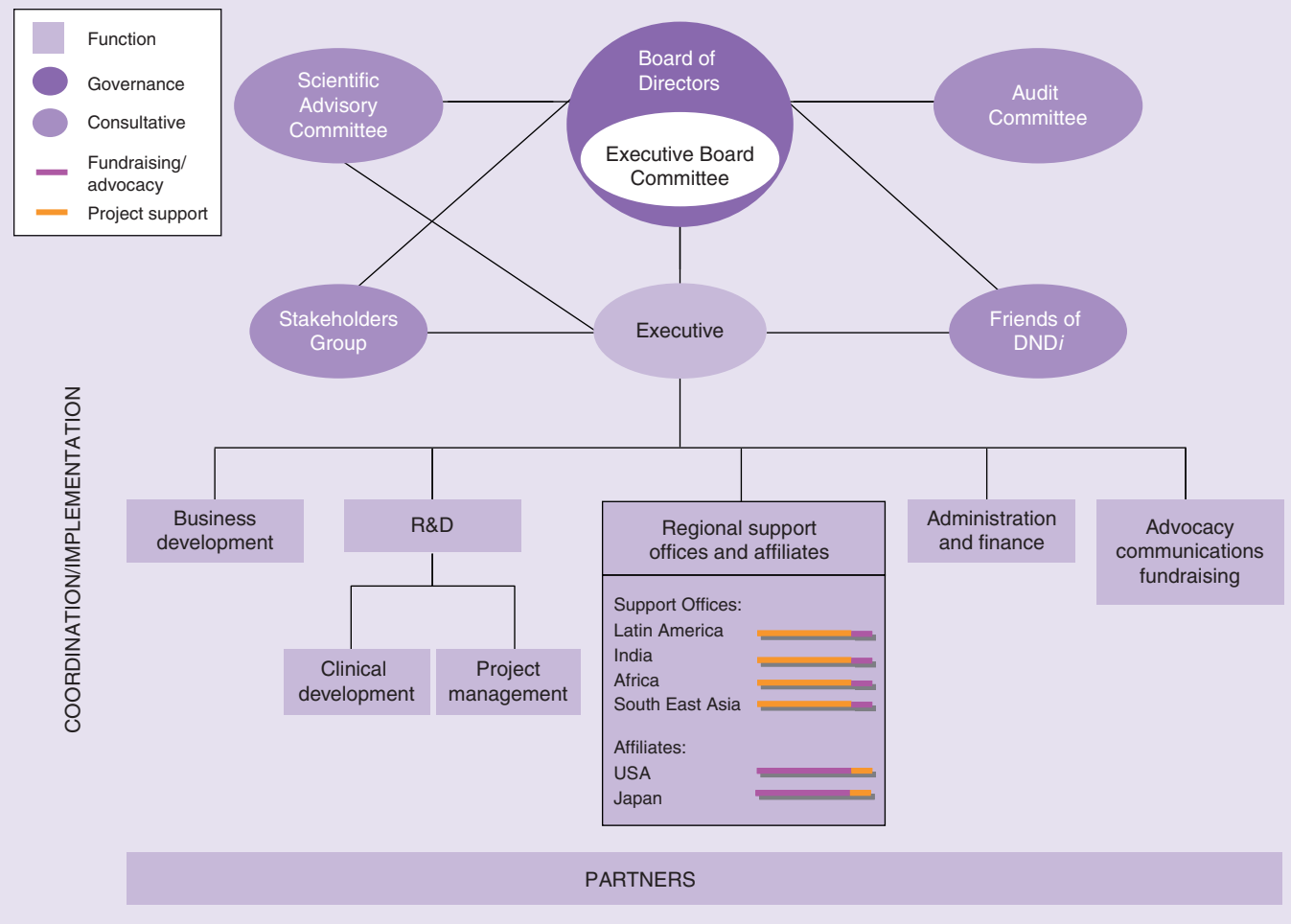

Figure 1. Drugs for Neglected Diseases *initiative*'s governance and operational management chart.

DNDi's discovery model & strategy

■ Discovery in DNDi's early days

The earliest stage of the drug-discovery research process consists of three stages: sourcing and screening compounds, hit-to-lead expansion up to lead selection and LO. In its early days, DND*i* built its discovery portfolio mainly relying on opportunities arising from academic and biotechnology collaborations, which were identified through networking interactions, as well as requests for proposals within the scientific community. The *in vitro*/*in vivo* assessments of molecules of interest were mostly conducted with research parasitology laboratories that included the Swiss Tropical and Public Health Institute (formerly the Swiss Tropical Institute), the University of Antwerp (Belgium) and the London School of Hygiene and Tropical Medicine (UK). Those molecules were generally supplied to the project as hits. Occasionally, the biological assessments mentioned above were performed at the project partner's site when such capabilities were available locally. Frequently, the chemistry laboratories where the compounds originated would perform further development of these hits, although these laboratories usually had limited **drug metabolism and pharmacokinetics** (DMPK) support and expertise to advance the hits aggressively. This type of collaborative research arrangement facilitated the coupling of biology to chemistry capacity and successfully delivered several leads to the DND*i* discovery pipeline. However, serious limitations and constraints were observed with this early discovery model. Major concerns were related to the low throughput for drug screening, the limited capacity to generate timely *in vitro* and *in vivo* DMPK and toxicity assay data for compound evaluation, and insufficient allocation of chemistry resources in most of the medicinal chemistry laboratories. While many of the academic laboratories are well equipped and staffed with excellent researchers, the educational mission frequently conflicts with the need to make daily 'go/no-go'

Key Term

Drug metabolism and pharmacokinetics: Preclinical studies that form part of a larger battery of studies often referred to as ADME, which aim to describe the disposition of a pharmaceutical compound within an organism.

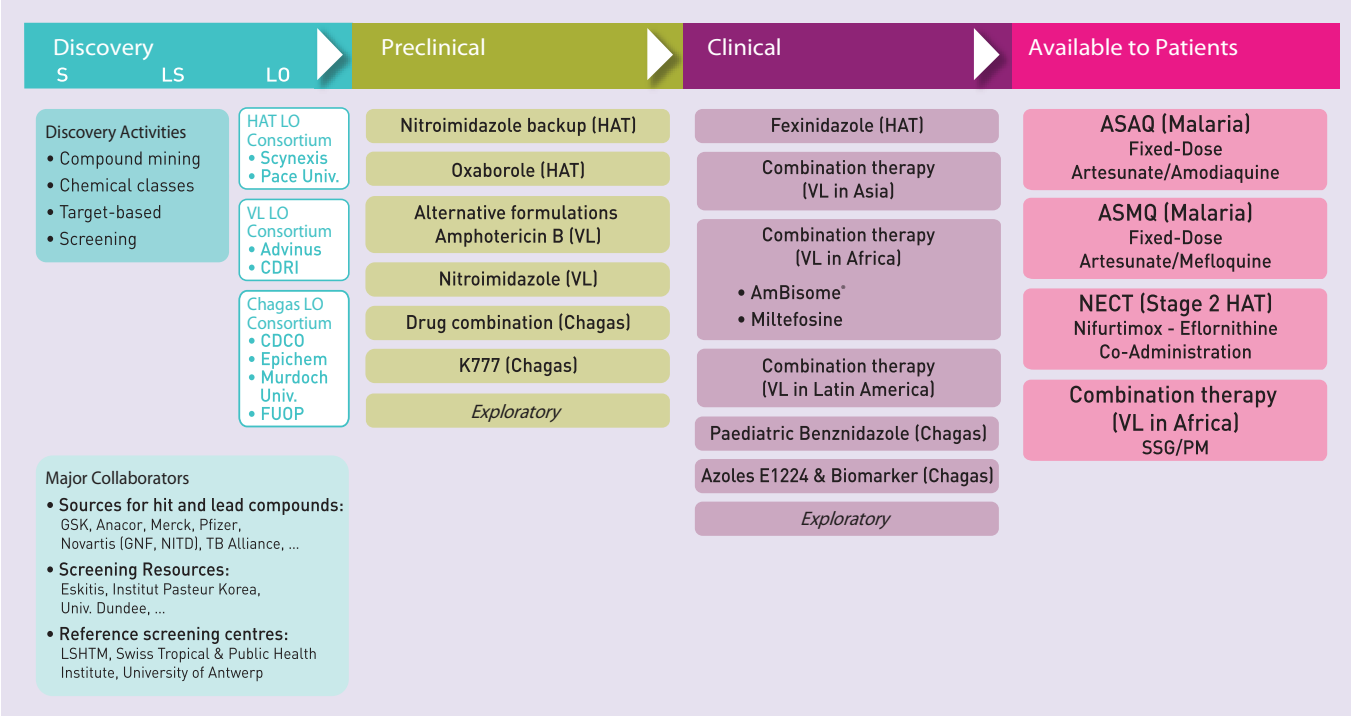

Figure 2. Drugs for Neglected Diseases *initiative* R&D portfolio as of January 2011.
ASAQ: Artesunate + amodiaquine; ASMQ: Artesunate + mefloquine; Chagas: Chagas disease; GNF: Genomics Institute of the Novartis Research Foundation; HAT: Human African trypanosomiasis; LO: Lead optimization; LS: Lead selection; LSHTM: London School of Hygiene & Tropical Medicine; NECT: Nifurtimox–eflornithine combination therapy; NITD: Novartis Institute for Tropical Diseases; PM: Paromomycin; S: Sourcing; SSG: Sodium stibogluconate; VL: Visceral leishmaniasis.

decisions for each compound series by individual chemists, and the requirement for flexibility to scale-up/-down projects as drug discovery priorities shift. Medicinal chemistry in the early stage of drug discovery is inherently risky with a high intrinsic attrition rate [11] due to the low success rate and the empirical nature of the work. Decisions need to be made for each compound and each chemical series under investigation as the biological data are generated, frequently on a daily basis. These challenges prompted DND*i*'s decision to adopt a more dynamic, integrated and cost-effective model.

■ The current LO model adopted by the DND*i*

In early 2008, DND*i* began to centralize its LO operations and established three fully funded disease-focused consortia dedicated to HAT, leishmaniasis and Chagas. The LO consortia aim to consolidate all necessary expertise and direct the progression of chemical series from the hit-to-lead stage to the optimized lead stage, with the capacity to support the preclinical package for drug candidates ready to enter Phase I clinical trials **(FIGURE 3)**. This includes access to relevant *in vitro* and *in vivo* parasitological assay support adapted to the required LO throughput and turnaround time in the reiterative cycle **(FIGURE 2)**. These dedicated LO consortia allowed smooth progression of hits and leads, and addressed the need to drop specific chemical series and replace them with new ones in a timely manner, while maintaining the stable commitment of supporting each research team. This centralized and disease-focused LO model also facilitated effective project management by DND*i*, since each team in these LO consortia is dedicated to and accountable for the progress towards the goal of producing drug candidates that meet the TPP. Stable collaborative relationships between research teams within each of the LO programs, and a shared commitment to a common neglected disease target, create a positive working environment [12]. This LO model has proven to be successful and led to the identification of SCYX-7158, a drug candidate from the unique boron-containing oxaborole series originating from Anacor and optimized by the HAT LO Consortium that included SCYNEXIS Inc., Pace University (USA) and the Swiss Tropical and Public Health Institute. This compound

Key Term

Phenotypic screening: Screening against a whole-cell organism (in our case: protozoan parasites). This term is often used in contrast to target-based screening where the screening is run against an isolated drug target (typically a protein receptor or an enzyme).

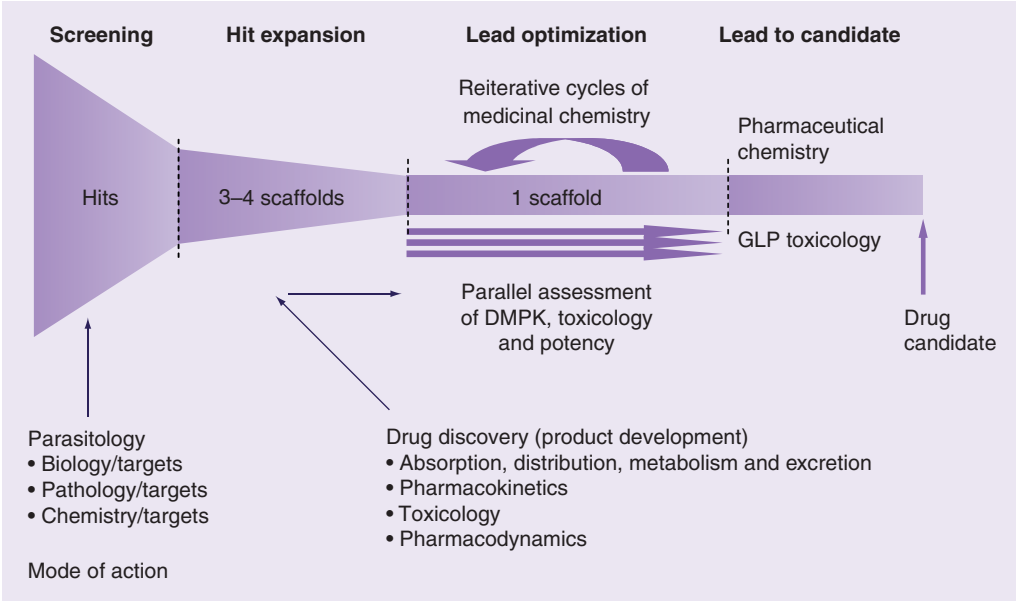

Figure 3. Current discovery process at the Drugs for Neglected Diseases *initiative*.
DMPK: Drug metabolism and pharmacokinetics; GLP: Good laboratory practice.

was nominated as a preclinical candidate at the end of 2009 (see article by Jacobs *et al.* for more details [13]).

■ Discovery tools: TPPs, discovery manuals & data management system

The objectives of the LO consortia are based on the disease strategies and the associated TPPs [14]. DND*i*, in consultation with its various partners (physicians, national and local disease control programs, regulators, patient representatives and global public-health bodies) involved in the treatment of patients in disease-endemic countries, have generated TPPs to ensure that the drugs developed by the project teams meet the patients' needs. Additional tools to guide the consortia's work, such as drug-discovery manuals and derived operational decision matrices, have also been produced. These tools provide a clear outline of the physiochemical properties, *in vitro*/*in vivo* efficacy as well as toxicity and DMPK end points. They are valuable in enabling objective decision-making at the hit, lead, optimized lead and drug-candidate selection levels [12]. Data generated during the various steps of the discovery process in all programs are managed via a proprietary, fully-secured, web-based data management system known as HEOS®, operated by SCYNEXIS Inc. HEOS provides the project/program partners with an easy worldwide access to report, search, review, analyze and extract biological and chemical data. In addition, an embedded web-based portal can also be used to store and share among partners more complex types of information, such as activity reports, scientific articles, presentations or patent searches [15].

■ Consolidating & feeding the pipeline with the new discovery model

In parallel to the implementation of the new model involving LO consortia, DND*i* has taken steps in the past few years to address two main concerns: the low throughput in screening against intracellular protozoa (*Leishmania* and *Trypanosoma cruzi*), and the sourcing of quality compounds. This has led to the changes described in the following two sections. These recently adapted approaches are starting to yield positive results in accelerating the pace of drug discovery.

■ Increasing capacity for phenotypic screening

In the kinetoplastid field, there are currently very few validated targets amenable to drug screening. A notable but rare success is the recent report on the validation of *Trypanosoma brucei N*-myristoyltransferase as a promising target for HAT and the discovery of associated *N*-myristoyltransferase lead compounds [16]. Hitherto, target-based screening campaigns run on the best putative targets, such as trypanothione reductase for HAT [17,18], have yielded a limited number of novel scaffolds associated with potent *in vitro* activity against target protozoan

organisms. In addition, hits against biochemical targets *in vitro* must reach the target in a parasite that is often sequestered in a hostile environment in the host. Considerable LO is often required to overcome these barriers and the attrition rate is quite high. As such, DND*i* relies mainly on **phenotypic screening** to generate hits and has successively supported the development and validation of medium- to high-throughput *in vitro* assays using whole-cell assays against *Trypanosoma brucei brucei* (SCYNEXIS and the Eskitis Institute for Cell and Molecular Therapies at Griffith University [19]). In addition, the Institut Pasteur Korea, in partnership with DND*i*, has developed imaging technology-based high-content screening assays against intracellular *Leishmania* and *T. cruzi*. These newly developed assays have significantly increased DND*i*'s capacity to screen compound collections against its target pathogens. Access to a panel of *in vitro* and *in vivo* assays, run at lower throughput in parasitology research laboratories (Swiss Tropical and Public Health Institute, University of Antwerp, London School of Hygiene and Tropical Medicine) together with access to the newly developed higher throughput *in vitro* assay mentioned earlier, allowed DND*i* to evaluate the diverse types and sizes of libraries provided by third parties in a timely manner. These screens are producing valuable hits for LO consortia.

■ New strategy for compound sourcing

Compound sourcing at DND*i* has evolved from a hunter–gatherer approach (harnessing partners by identifying project opportunities from networking within the neglected diseases scientific community and from literature findings) to a more structured partnership-based approach with pharmaceutical companies and biotechnology organizations [20]. Libraries are accessed under specific terms as part of a negotiated partnership agreement between pharmaceutical and biotechnology companies and DND*i*. These libraries contain numerous chemical structure series that have been optimized or partially optimized for various drug targets (generally human targets related to past and current indications of the partners' R&D portofolio) and therefore have more biological and chemical information associated with them from prior work. These libraries also contain carefully chosen compounds to ensure representation of considerable chemical diversity. The ability to access these libraries, combined with the availability of conducting high-throughput *in vitro* assays, represents a turning point in drug discovery for kinetoplastid diseases.

■ Compound mining

This approach involves the proactive acquisition and investigation of compounds from selected series that are associated with a significant level of available information (biological activities, preclinical dossier, published data and safety profile, among others) in order to identify candidates with potential for the further development for the target diseases. Ideally, they will be ready to enter into preclinical or later stages without further optimization. An example of this approach is the compound-mining effort undertaken in 2005 examining nitroimidazoles. A review and profiling of over 700 nitroheterocyclic compounds (mostly nitroimidazoles) obtained from various sources were undertaken, and included an assessment of their antiprotozoal activity as well as their mutagenic potential. This led to the identification of fexinidazole as a clinical drug candidate for HAT [21]. Fexinidazole, a 5-nitroimidazole, had been in preclinical development as a broad-spectrum antiprotozoal by Hoechst in the early 1980s, but was abandoned. Extensive profiling by DND*i* confirmed an earlier report [22] that showed that fexinidazole is orally active, capable of penetrating into the brain compartment and is efficacious in animal models for both acute and chronic infection with African trypanosomes [22]. After the completion of preclinical testing, confirming the previously determined favourable efficacy and safety profile of fexinidazole as a drug candidate [22], fexinidazole entered into Phase I first-in-human clinical studies in September 2009. Fexinidazole is currently the only new drug candidate in clinical development for sleeping sickness. Additional compound-mining efforts have been undertaken at DND*i* in association with several partners. Examples include the review of historical *in vitro* and *in vivo* screening data made available to DND*i* by the Swiss Tropical and Public Health Institute, the University of Antwerp and the Walter Reed Army Institute of Research. DND*i* has also searched various databases (including SciFinder® and Derwent World Patent Index®) in order to identify any molecules that could be considered for further development. Promising hits resulting from these searches were reviewed and a few selected molecules pursued through early discovery or full LO programs, but were eventually discontinued. Examples include canthinones for Chagas and 2-substituted quinolines for Leishmaniasis (Institut de Recherche et Développement) as well as licochalcones for Leishmaniasis (Lica Pharmaceuticals). One of the limiting factors of this approach is that there

are only a small number of chemical series with antiparasitic activities reported in the literature. Therefore, there are only a finite number of opportunities to be discovered. Extending this approach to the identification of low-hanging fruits by searching proprietary libraries and databases (e.g., drug candidates associated with a preclinical package or previously investigated in clinical trials) in collaboration with pharmaceutical companies remains a promising avenue to explore.

■ Chemical diversity

This approach aims to mine new chemical territories to identify novel classes of molecules of potential to the target diseases. **Table 1** illustrates compound screening of several medium-sized libraries conducted in the past few years in collaboration with various DND*i* partners.

Hit rates resulting from screening efforts can vary quite dramatically depending on the nature of the library: diversity libraries generally yield low hit rates, typically less than 1%, whereas preselected compound sets may reach 10% or higher. The pathogen under consideration also has an influence on hit rate: *L. donovani* repeatedly provides lower hit rates than *T. cruzi* assays, while *T. brucei* screening generally yields the highest hit rates. Such a ranking can be tentatively explained by the relative intrinsic susceptibilities of the aforementioned protozoa as well as by the presence of restricted access to the pathogen in the case of *Leishmania donovani* and *T. cruzi* intracellular assays. Other parameters, such as quality of the library, type of assay used and screening of pure compounds, compared with fractions/extracts from natural-product libraries, also have a significant impact on the hit rate.

From the screening work, only a small number of scaffolds (~20) have been selected for progression to hit-to-lead. The reasons for this relatively low rate include: the lack of chemical tractability (mostly related to natural products); metabolic and stability-related issues; known unsuccessful scaffolds previously explored; identification of toxicophores; lack of initial structure–activity relationships related to the hit series; identification of hits as singletons; or the lack of selectivity towards mammalian cell lines. Limited hit-to-lead capacity also restricted the number of scaffolds that could be progressed. One scaffold identified from the Institut Pasteur Korea screen is currently under further optimization as part of our LO program against VL, run in partnership with Advinus Therapeutics and the Central Drug Research Institute in India. Overall, this type of screening has generated hits at a rate that is consistent with that of other disease targets.

The Drugs for Neglected Diseases *initiative* has more recently entered into a collaboration with Pfizer to screen the Pfizer global diversity research set (150,000 compounds) against *T. brucei*, *L. donovani* and *T. cruzi* with the hope of identifying several novel scaffolds to be progressed for its target diseases.

■ Mining for promising chemical classes

One of the lessons learnt from DND*i*'s past discovery activities relates to the challenge of progressing scaffolds that were not associated with any preclinical data other than *in vitro* efficacy. Hit-to-lead and LO are indeed time-consuming and resource-intensive processes because of the high attrition rate associated with these activities. However, if the hit is a member of one of the classes of compounds that have been successfully advanced in drug development for other disease indications, the attrition rate may be significantly lower. This approach can only be effectively pursued in collaboration with pharmaceutical and biotechnology companies. Some examples of

Table 1. Examples of libraries screened in collaboration with Drugs for Neglected Diseases *initiative*.

Drugs for Neglected Diseases *initiative* partner	Compounds class	Samples screened	Disease target
SCYNEXIS	Synthetic compounds	108,000	Human African trypanosomiasis
Kitasato Institute	Natural product collections as pure compounds, fractions and extracts	35,000	Human African trypanosomiasis
Eskitis Institute for Cell and Molecular Therapies	Natural products	200,000	Human African trypanosomiasis
Walter and Eliza Hall Institute	Synthetic compounds	100,000	Human African trypanosomiasis
Institut Pasteur Korea	Synthetic compounds	200,000	Visceral leishmaniasis

chemical classes that have been/are under investigation at DND*i* are oxaboroles (see paper by Jacobs *et al.* [13]), pyridones, quinolines and protease inhibitors. The following is not an exhaustive list, as many more promising chemical series associated with successful track records in drug development could be included: anti-infective classes (fluoroquinolones, macrolides and nitroimidazoles), those acting via relative mechanisms of action or targets, together with chemicals that have been partially validated for kinetoplastids, are all parameters for including chemical series for evaluation. In addition, subsets of compounds associated with a specific ADME profile (CNS penetrant series for HAT, compounds known to penetrate cell membranes and possibly accumulate into human monocyte-macrophage cells for *Leishmania*) could be prioritized. Hits identified through screening of commercial libraries could also offer interesting starting points to interrogate proprietary databases and compound collections.

When a hit is discovered from one of these well-characterized classes, quick access to a collection of chemical analogs, knowledge related to routes of synthesis and structure–activity relationship information related to pharmacokinetics and toxicity are readily available from the collaborating partners. This knowledge can greatly accelerate the subsequent LO efforts and reduce the attrition rate. In addition, some classes have the potential to be active in multiple parasites, as the target organisms are phylogenetically related. Indeed, there are compound classes that are active against two, or all three, kinetoplastid parasites. Therefore, 'broad-spectrum' classes exist and can be identified.

■ Target-based screening

In 2009, DND*i* entered into a strategic partnership with the Drug Discovery Unit (DDU) at the University of Dundee (UK) to address early-stage discovery research, with the aim of identifying one to three lead series against VL. This decision was largely motivated by the strong expertise and unique capabilities of the DDU in lead generation, from their active engagement in molecular target screening, cell and organism-based phenotypic screening, structure-based drug design, computational and medicinal chemistry, DMPK, and access to *in vivo* animal models. In the absence of thoroughly genetically validated and druggable targets for *L. donovani*, the DDU and DND*i* have opted for a phenotypic-screen approach to chemically validate targets in *L. donovani,* using chemical series issued from the DDU's ongoing HAT target program as well as from various focused libraries assembled by the University of Dundee. Selected hit series are followed up by the DDU as part of an internal hit-to-lead program, with the opportunity to identify essential targets by reverse chemical genetics. The validation and development of molecular-target assays is performed by the DDU in collaboration with third parties.

■ Research collaboration with PDPs & R&D institutions active in neglected diseases

The Drugs for Neglected Diseases *initiative*'s uniqueness as an organization lies in the fact that its portfolio covers several neglected diseases, its funding is consistently diversified, and, in addition to its stepwise business model, it has established both disease-focused LO consortia as well as regional clinical-research platforms. The latter both utilize and reinforce research capacities in endemic countries, in addition to ensuring that DND*i*'s work keeps patient needs at its core. In addition, DND*i* has established links and research collaborations with other PDPs, including Medicines for Malaria Venture and The Global Alliance for TB, as well as private and public R&D institutes active in the field of neglected diseases such as the Consortium for Parasitic Drug Development, Novartis Institute for Tropical Diseases, Tres Cantos Medicines Development Campus, at GlaxoSmithKline, Genomics Institute of the Novartis Research Foundation, and the DDU at the University of Dundee. The scope of these collaborations ranges from access to compounds for screening, to medicinal chemistry for hit expansion and lead identification, to information and data sharing to avoid duplication of activities and to identify further collaborative opportunities.

A recent example of a successful PDP collaboration is the identification of a nitroimidazole series highly active against *L. donovani* both *in vitro* and *in vivo*. The design and synthesis of this series of compounds were carried out at the University of Auckland (New Zealand), under a collaborative agreement with The Global Alliance for TB originally intended for new TB drug discovery. Access to this promising nitroimidazole series for kinetoplastid diseases [105] has allowed DND*i* to leapfrog from screening to the identification of an optimized lead in one step. This productive collaboration illustrates the benefit of sharing knowhow, and that open-innovation models have accelerated the development of new therapies for treating neglected diseases.

Future direction of the R&D model at the DND*i*

The existing drug R&D process as practiced today in the pharmaceutical industry is cost prohibitive. One of the reasons is the competitive nature of the pharmaceutical industry. This demands secrecy, which unavoidably results in unnecessary duplication. DND*i*'s R&D model, while continuing to evolve in response to the changing landscape, remains anchored in collaboration and partnership. This collaborative model is based on sharing of information, experiences, compounds and resources with partners and the wider neglected diseases research community.

Driven by the urgent need for improved therapies for neglected patients, and considering the global R&D resource constraints in this field, DND*i* will continue to seek improved approaches to achieve timely development of these therapies. Much of the expertise for drug R&D resides in the pharmaceutical and biotechnology industries. An increasing number of collaboration agreements with companies in these industries have been signed in recent years and more are expected. This is an encouraging trend. DND*i* has a growing need to access annotated, information-rich chemical scaffolds to feed its current LO pipeline. DND*i* intends to stimulate and promote an elevated level of participation and contribution from pharmaceutical and biotechnology companies in the development of NCEs for neglected diseases.

The Drugs for Neglected Diseases *initiative*'s new discovery focus is on mining for promising compound classes and it will expand its efforts in this area in the next few years. Innovation in new discovery technologies, together with a better understanding of pathogenesis and parasitology, is critical to achieving DND*i*'s goals in the long term. While DND*i*'s R&D efforts will not be focused on these early-stage research activities, facilitating such development will remain an important task for DND*i*.

Future perspective

The landscape for R&D in the field of neglected diseases has changed drastically over the past 10 years. New actors, donors, financial incentives, and a more favorable political environment have contributed to a much better outlook for neglected disease R&D. However, this momentum must be accompanied by stronger collaboration among all actors. DND*i* will continue to play a leading role in discovery, development and delivery of new treatments for neglected diseases, to advocate for greater public leadership, to catalyze new commitments from governments and philanthropic donors, and to raise awareness of the need for R&D in this field. In order to increase the chances of further advancing NCE in the neglected disease pipeline, strong partnerships with pharmaceutical and biotechnology companies, as well as with other PDPs, are required, in order to share knowledge, avoid duplication in research, save costs and speed up the R&D process for the benefit of patients.

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Executive summary

Drugs for Neglected Diseases* initiative*'s mission & business model

- The need for an organization dedicated to finding new drugs for neglected diseases.
- Product-development partnerships.
- No need for patent protection.

Organization, objectives & key accomplishments

- Development of an R&D portfolio based on target product profiles.
- 'Low-hanging fruits' approach.
- Future direction of R&D model at Drugs for Neglected Diseases *initiative*.
- Sharing information leads to more cost-effective research.

Discovery model & strategy

- Optimizing the drug-development process.
- Advantages of lead-optimization consortia and the tools they use.
- Improved screening and compound sourcing.
- Lessons learned from compound mining.
- Extensive collaboration leads to effective research.

Financial & competing interests disclosure

The Drugs for Neglected Diseases initiative *(DNDi) is grateful to its donors, public and private, who have provided funding since its inception in 2003. With the support of these donors, DND*i *is well on its way to achieving the objectives of a robust pipeline that aims to deliver 6–8 new treatments by 2014. A full list of DND*i*'s donors can be found at: www.dndi.org/index.php/donors.html?ids=8. The donors had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

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