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From Molecular Targets to Drug Candidates

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Paul M. Selzer

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Drug Discovery for Neglected Diseases: View of A Public–Private Partnership

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DNDi
Drugs for Neglected Diseases *initiative*

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Rob Don and Eric Chatelain*

Abstract

In answer to the lack of modern and effective drugs for diseases such as human African trypanosomiasis (HAT; sleeping sickness) and Chagas' disease which present no financial viability for the pharmaceutical industry, new models of drug discovery have been developed. Public–private partnerships (PPPs) or product development partnerships (PDPs) aim to combine the skills and research capacity of academia, the pharmaceutical industry, and contract researchers to create focused research consortia which address all aspects of drug discovery. These consortia emulate the project teams within the pharmaceutical and biotechnology industry and include identification and screening of libraries, medicinal chemistry, pharmacology, and pharmacodynamics. The Drugs for Neglected Diseases initiative (DND*i*) has adopted a model closely related to that of a virtual biotechnology company for identifying and optimizing drug leads. This chapter outlines the application of this model to the development of drug candidates for the kinetoplastid infections of HAT, Chagas' disease, and leishmaniasis.

Introduction

During the past century, chemical and pharmaceutical industries made tremendous advances in the development of new therapeutics to treat many of the diseases which inflict humankind. This drug discovery and development process, which encompasses design of new drug candidates and clinical testing, has always been an expensive exercise, with costs continuing to escalate [1]. To a large extent, this cost has been borne by the consumers either directly or through taxes and insurance-based subsidies available only in wealthy countries. Those diseases which predominantly affect inhabitants of poorer nations, are of no military or strategic interest to wealthy countries and are not supported by markets or patients organizations capable of attracting the attention of politicians, have fallen below the radar of modern drug

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discovery. Moreover those afflicted are unable to bear the cost of development. These diseases have therefore been forgotten and often labeled as neglected diseases or, perhaps more appropriately, "diseases of the neglected." Examples of neglected diseases are malaria, dengue fever, tuberculosis (TB), human African trypanosomiasis (HAT), leishmaniasis, Chagas' disease, and buruli ulcer. There is a considerable global effort to bring awareness to these diseases and redress such inequity.

> *"Our greatest concern must always rest with the disadvantaged and vulnerable groups. These groups are often hidden, live in remote rural areas or shantytowns and have little political voice"*
>
> *Dr Margaret Chan – WHO Director General, 2007*

Unfortunately, the tools to treat these diseases fall woefully short of what many in wealthy nations would expect in a modern pharmacopoeia. For example, first-line therapy for stage 2 human African trypanosomiasis (HAT; sleeping sickness) in many regions is still melarsoprol, an arsenic-based drug developed at the turn of the twentieth century which causes fatal encephalopathy in up to 5% of those treated [2, 3].

Another example: long-term treatment with genotoxic drugs is the only choice for Chagas' disease in which a significant proportion of patients are children with a median survival measured in decades [4, 5]. There is an urgent need to bring the medicine chest for neglected diseases up to date for the sake of patients' wellbeing. To do so requires the development of different strategies to mobilize drug discovery from the "user pays" model in wealthy countries to one which can be sustained for those unable to pay.

Public–Private Partnerships

Over the past decade, a number of new ventures classified under the broad term of public–private partnerships (PPPs) have emerged to address the need for new drugs to treat neglected diseases [6]. Initially these were formed to focus on specific diseases and examples include the Medicines for Malaria Venture (MMV), Global Alliance for TB Drug Development (TB Alliance), the International Aids Vaccine Initiative (IAVI), and the Malaria Vaccine Initiative (MVI). More recently, ventures with a broader focus (efforts not concentrating on a single disease) have emerged such as the Institute for One World Health (iOWH) and the Drugs for Neglected Diseases initiative (DND*i*), and definitions of PPPs have expanded to include not-for-profit pharmaceutical companies and product development partnerships (PDPs) – perhaps a reflection of their different strategies to achieve a common goal, that is, to provide drugs for neglected patients [7].

DND*i* was formed in 2003 with the aim of developing new drugs for a group of "most neglected diseases," the kinetoplastid diseases. In the first instance theses diseases include a group of infectious parasitic diseases: human African trypanasomiasis, visceral leishmaniasis (VL), and Chagas' disease.

Human African Trypanosomiasis (HAT)

HAT, known as sleeping sickness, is caused by two subspecies of *Trypanosoma* parasites which are transmitted to humans by tsetse flies. Sleeping sickness, which WHO estimates to infect 50 000 to 70 000 people and puts 50 million at risk, occurs only in subSaharan Africa [8]. The disease takes one of two forms, depending on the parasite subspecies (either *T. b. gambiense* or *T. b. rhodesiense*). Sleeping sickness has two stages. The early stage entails bouts of fever, headaches, pain in the joints, and itching. The second, known as the neurological phase, begins when the parasite crosses the blood–brain barrier and invades the central nervous system. Without treatment, the disease is fatal. Currently available treatments for HAT – melarsoprol, eflornithine, pentamadine, and suramin – are few and limited due to age, high toxicity, and lost efficacy in several regions. Treatment is stage-specific, with more toxic and more difficult-to-administer treatments (melarsoprol, eflornithine) for stage 2 disease. Few projects for improved treatments are currently in clinical development and none has the potential to dramatically change either the treatment or control options for this disease. With regard to treatment, most drugs are old, difficult to administer in resource-limiting conditions and by no means always successful [9, 10].

Visceral Leishmaniasis

Transmitted by the sandfly, the protozoan parasite *Leishmania* causes three different forms of disease, of which visceral leishmaniasis (VL) is the most severe. Leishmaniasis affects over 12 million people and puts over 350 million people at risk in 88 countries. Fatal if left untreated, VL (also known as black fever or kala-azar in India) persists today in poor, remote, and sometimes politically unstable areas, in countries where patients have little access to preventive measures and affordable drugs. A significant proportion of clinical cases occurs in children. Approximately 500 000 new cases are reported to occur each year, though it is estimated that only 30% of cases are reported. VL is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anemia and is complicated by co-infection with other infectious diseases, such as HIV, malaria, or pneumonia [10–12].

Chagas' Disease

Chagas' disease is another human form of trypanosomiasis (human American trypanosomiasis) and occurs almost exclusively in the Americas where an estimated eight to 11 million people are infected. Transmitted to humans by a triatomine insect containing the parasite *Trypanosoma cruzi*, the disease is contracted through the bite of insects widely known as the kissing bug. There are three stages of the disease: acute, indeterminate, and chronic. In the acute form (in which 5% of children die), Chagas' disease manifests generally as fever, malaise, facial edema, generalized lymphadenopathy, and hepatosplenomegaly. The acute illness often spontaneously

resolves itself in four to six weeks, at which time patients enter an asymptomatic, indeterminate phase, which can last from 10 years onwards. The chronic stage of Chagas' disease develops in 10–30% of infected persons and most commonly affects the heart. Death usually results from cardiac arrhythmia or congestive heart failure. The two current treatments, benznidazole (which requires 60 days of treatment in acute infections and is only effective in 50% of cases) and nifurtimox (primarily acute and early indeterminate stages of the disease) are very limited. There are no treatments for indeterminate and chronic stages of the disease [10, 13].

DND*i*'s Partners and Strategy

DND*i*'s founding partners are Médecins Sans Frontieres, the Oswaldo Cruz Foundation for Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health in Malaysia, the Pasteur Institute in France, and the Special Programme for Research and Training in Tropical Diseases (TDR). Their vision was the creation of a drug discovery and development entity using the assets of organizations spread across the world to respond to the dire need of safe, affordable, easy-to-use, and efficacious treatments for neglected patients [14]. Since its inception, DND*i* has invested resources in preclinical and clinical development as well as drug discovery programs with the intent to bring "low-hanging fruits" to patients in the shortest possible timeframe. This approach has been so far implemented with two products now registered for treatment of malaria: (i) fixed-dose artesunate-amodiaquine, "AS/AQ" (www.actwithasaq.org), and (ii) fixed-dose artesunate-mefloquine, "AS/MQ" (www.actwithasmq.org), programs in phase II and III clinical trials for visceral leishmaniasis and sleeping sickness, and a strong network of clinical researchers and trial sites in disease-endemic regions. Nonetheless, the organization remains acutely aware of the high attrition rate associated with drug discovery and development and strives to maintain a full pipeline, which includes development of innovative new drugs through longer-term lead optimization programs [15].

Lead Optimization at DND*i*: Building the Pipeline

During the five years since its inception, DND*i*'s model of drug discovery has evolved from funding research projects in response to "letters of interest" to building a virtual and fully integrated, patient-need driven, not-for-profit, R&D organization. The initial model (i.e., responding to "letters of interest") which very successfully reviewed the research landscape for neglected diseases also led to the risk of DND*i* being perceived as a research funding agency rather than a drug discovery organization. As such, if initial research projects were successful, an expectation existed for DND*i* to increase

commitment and expand the projects – a natural progression based on the model of competitive research funding. Keeping the "letter of interest" approach would have required:

- Expanding a team which had commitment and expertise frequently limited to one particular molecular scaffold and/or target;
- Building the capacity in teams which did not span all of the research disciplines necessary for drug discovery;
- Losing the ability to prioritize projects because of a need to fund projects on a medium term basis at research institutions and therefore commit limited resources on a "first come/first served" basis.

In building such lead optimization teams, considerable expense and time would be needed during the expansion phase and, if the team was focused on a particular scaffold or target, considerable time and expense would also be required to wind the project down if that target proved not amenable to lead optimization. To acknowledge the high rate of attrition in drug discovery and counter the probability of disbanding research programs because of drug candidate failure, DND*i* has adopted the approach of contracting lead optimization teams independent from specific targets or scaffolds. In doing so, DND*i* can feed each team with hits and leads which are identified from a range of different sources. Scaffolds which prove not to be amenable to optimization can also be "killed" without disrupting the research integrity of the dedicated lead optimization team.

To maintain the capacity of optimizing one lead series at all times, each team is comprised of 5–6 chemists, 2–3 pharmacologists, and a dedicated screening facility to assess potency and efficacy with guaranteed infrastructure to support medicinal chemistry, *in vitro* and *in vivo* distribution–metabolism–pharmacokinetic (DMPK), toxicology (Tox.), and efficacy studies. In addition, DND*i* works with consultants who are expert in different disciplines to provide ongoing critical review of the programs. The programs are also regularly reviewed by the Scientific Advisory Committee (SAC) of DND*i*. The SAC is a group of 15 respected scientists who volunteer their time to assess and guide DND*i* scientific activities.

To produce new drug candidate as efficiently as possible, it is very important that all players are focused on the lead optimization program and not distracted by other research efforts. To that end:

- Once a lead is introduced into a lead optimization program, it enters a critical path [16] which promises development through to patient access unless the compound series fails because structural liabilities prevent optimization as a drug candidate;
- Sufficient resources are allocated to guarantee the rapid turnaround of data necessary to support the medicinal chemistry effort;
- A research group associated with the program is encouraged to pursue more discovery research associated with the disease so that the lead optimization (LO) programs are constantly fed with promising leads. This implies that a separate

group of staff conducts the supporting assays for lead optimization and commits 100% of its time to the medicinal chemistry effort.

To date, DND*i* has brought together three LO teams, two for HAT, and one for VL. DND*i* has chosen to work with companies and partners with a commitment to research for neglected diseases at the senior management and CEO level to ensure that research goals are aligned. The researchers are funded as full "fee for service" contractors and make no claim to any intellectual property generated during the lead optimization programs. As such, DND*i* remains free to manage the intellectual property in a manner the organization deems to be most appropriate to guarantee access for those suffering from neglected diseases.

Lead Optimization at DND*i*: Supporting the Pipeline

Target Product Profiles

DND*i* is a needs-driven organization, that is, the needs of patients suffering from neglected diseases are the driving force behind all drug discovery and development programs. DND*i* partners work with patients in disease endemic countries and DND*i* has actively participated in bringing together stakeholders like physicians, local disease control programs, regulators, and patient representatives, as well as local and global public health bodies to gauge the true needs of patients. It is through consultation with expert committees that DND*i* is able to draft target product profiles (TPPs), which define effective therapies for patients in normal field conditions.

The TPP is an organized list that prioritizes key features of the drug and guides all players to work with the same end in mind [17]. It lists both ideal and acceptable values for each feature. On a strong note of caution, one should exercise care not to lower development standards and use the acceptable values as the TPP. They should be viewed as the lowest acceptable value for a particular feature in isolation. If this value becomes part of the TPP then other values originally listed as acceptable may be compromised and the TPP should be revised. For example, if parenteral administration instead of oral is deemed acceptable then a previously acceptable treatment duration of two months may no longer be tenable.

The TPP (see Table 3.1 for an example) is the foundation of all drug discovery management tools designed to support lead optimization programs.

Discovery Manuals

To direct a lead optimization program, a drug discovery manual is drafted which defines key decision points during the preclinical drug discovery process and provides objective measures for making those decisions with reference to potency,

Table 3.1 Example of a TPP for human African trypanosomiasis.

Desirable	Acceptable: improvement to current standard treatment
Effective against stage 1 and 2	Effective against stage 2
Broad spectrum (*T. gambiense, T. rhodesiense*)	Efficacy against *T. gambiense* only
Clinical efficacy >95% at 18 mo follow up	Clinical efficacy no worse than current treatment
Effective in melarsoprol refractory patients	
<0.1% drug related mortality	1% drug related mortality
Safe during pregnancy and for lactating women	
Formulation adapted to adults and children	
No monitoring for AEs	Weekly simple laboratory testing (field testing)
<7 d p.o. once daily (DOT)	<20 d p.o. (DOT)
<7 ds i.m. once daily	<20 d i.m.
	<5 d i.v. if no toxicity
Stability in zone 4 for >3 yr	Stability in zone 4 for >12 mo
Cidal	
multitarget	Unique target (but no uptake via P2 transporter only)
< €30/course (only drug cost)	< €100/course
	< €200/course; ok if very good on other criteria

This TPP is revised on a regular basis.
Considering that some 20 000 to 50 000 patients per year might require treatment, it is still expected that donor agencies rather than the patients themselves take care of these costs.

physicochemical properties, and *in vitro* and *in vivo* DMPK/Tox. The major decision points are listed below and shown in Figure 3.1:

- Hit Selection – The decision to proceed to *in vivo* studies and hit expansion based on identification of a single compound from library screening or literature search.
- Lead Selection – The decision to proceed with chemical optimization based on review of a series of chemical analogs of the "Hit."
- Optimized Lead Selection – The decision to proceed to regulatory preclinical toxicology, drug metabolism and pharmacokinetic (DMPK)/Tox., and "good manufacturing practice" pharmaceutical development of one compound or a small number of compounds from the same chemical class.
- Drug Candidate Selection – The decision to proceed to clinical evaluation of one compound or a small number of compounds from the same chemical class.

In addition, key activities and partners are listed for each stage of drug discovery to ensure that sufficient resources have been allocated to the program and that research progresses in the shortest timeframe as activities are conducted in parallel wherever possible. At each decision point, the information may be sufficient to result

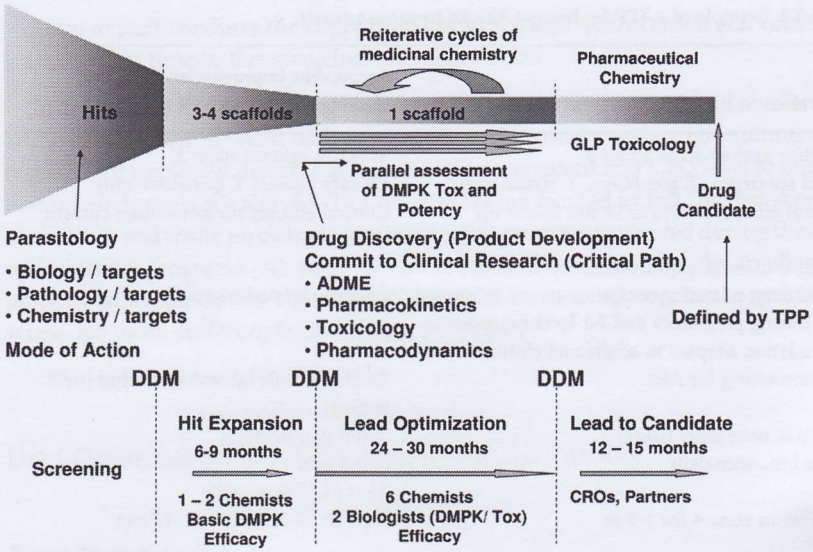

Figure 3.1 DNDi's drug discovery process with decision-making tools and key decision points (DDM: drug discovery manual; TPP: target product profile).

in a "go/no go" decision. In other instances, it may highlight additional research required before fully committing to the next stage of drug discovery.

The key activities for each decision point and the expected outcomes/values for these activities are defined to guarantee that continued development will address the expectations defined in the TPP.

Decision Matrices

The decision matrix is an operational tool which is designed to support the drug discovery manual. In addition to the key assays specified for the decision points, simpler surrogate assays are listed to enable more rapid screens of molecules which are synthesized as part of medicinal chemistry programs. For instance, membrane permeability may be used to predict bioavailability or ability to cross the blood–brain barrier. As the program progresses, more complex assays with greater predictive value should be used. Ideal and acceptable values together with data for comparator drugs are included in the decision matrix to facilitate assessment of new compounds with respect to the TPP and current drugs. A simple spreadsheet in which values for each new compound are entered allows for ready comparison with ideal and acceptable values. By color coding the cells, based on the value entered (green for ideal, orange for acceptable, red for unacceptable), it is possible to rapidly assess progress during the synthesis of a particular chemical series. In addition, it is recommended that representatives from major compound classes with defined biological activity should be regularly tested in key assays to assess the true predictive value of the surrogate assays.

Data Management

Regular and spontaneous communication between all members of a research team is essential for efficient progression of a lead optimization program. In most cases, not all members are located at the same site. For instance, it is rare that efficacy studies for tropical infectious diseases can be sourced to commercial contract researchers carrying out medicinal chemistry. Such studies are usually contracted to a University research group. To provide all participants in the research exercise with ready access to data as generated, DND*i* uses a proprietary web-based data management system. All researchers enter data in templates which have been formatted to suit the data they generate, be it chemical or biological. The data is structure and substructure-searchable and every researcher can review all data within the context of their specific expertise. A web-linked based portal has the capacity to store files in a variety of formats and is used for circulation of reports and for storing complex supporting data and background information such as papers and patents.

Lead Optimization at DND*i*: Feeding the Pipeline

Access to an adequate chemical diversity of hits and leads is essential to guarantee success for each lead optimization team. By generating such diversity, new chemical series can be introduced to the lead optimization process when scaffolds fail due to the natural attrition associated with drug discovery. In line with DND*i*'s approach to develop compounds as far downstream as possible ("low-hanging fruits"), DND*i* identifies small series of compounds in which structure activity relationships may already be available or may be readily discerned rather than large libraries of compounds for early stage hits.

Compounds and compound series may be focused around inhibitors of a specific target or a molecular scaffold known to be associated with antiparasitic activity. They are sourced from pharmaceutical companies, biotechnology companies, and academic institutes. To prevent diluting the effort of the lead optimization teams, DND*i* aims to support hit to lead chemistry with the partners who provide access to their compound libraries when possible. To support the constant feeding of hits in the LO process, DND*i* also sponsors a network of natural product screening centers worldwide. Natural product screening is conducted with the goal of identifying hits and/or leads which can be subsequently optimized as new chemical entities.

Negotiation of terms for access to intellectual property associated with the libraries is done on a case-by-case basis. It is DND*i*'s policy to disseminate intellectual property associated with neglected diseases research as widely as possible. Nonetheless, DND*i* remains pragmatic while negotiating and respects more stringent restrictions in return to access to new compounds which may lead to new therapies for treatment of neglected diseases, keeping in mind patient's interest. DND*i* is also aware of the risk

for contamination of intellectual property through sharing of information on closely related chemical series developed by different companies.

Conclusion

The product development partnership for neglected-disease drug development relies both on forging a strong relationship between industry and academia and on sharing knowledge which different partners often hold as proprietary. As well as the application of best research practices (e.g., TPPs, drug discovery manuals, critical paths), the building of trust and open communication are paramount to success. While the concept of PDP is still in its infancy, many productive alliances have been built, and the DND*i*-coordinated Fixed-Dose Artesunate-Containing Therapy (FACT) Project Consortium has developed and made available two new, improved treatments for malaria. In 2007, DND*i* registered its first product, the antimalarial "ASAQ," by applying its innovative R&D model, in collaboration with Sanofi-Aventis for the treatment of noncomplicated *Plasmodium falciparum* malaria. In 2008, DND*i* launched its second product for malaria, "AS/MQ," in Brazil using a similar model in partnership with a public institution (Farmanguinhos, Brazil). However, there remains a continuing need to advocate for increased awareness of the plight of those suffering from these neglected diseases. It is only by doing so that we can ensure that truly modern treatments – safe, efficacious, easy to administer – will become available for those afflicted by these "diseases of the neglected."

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