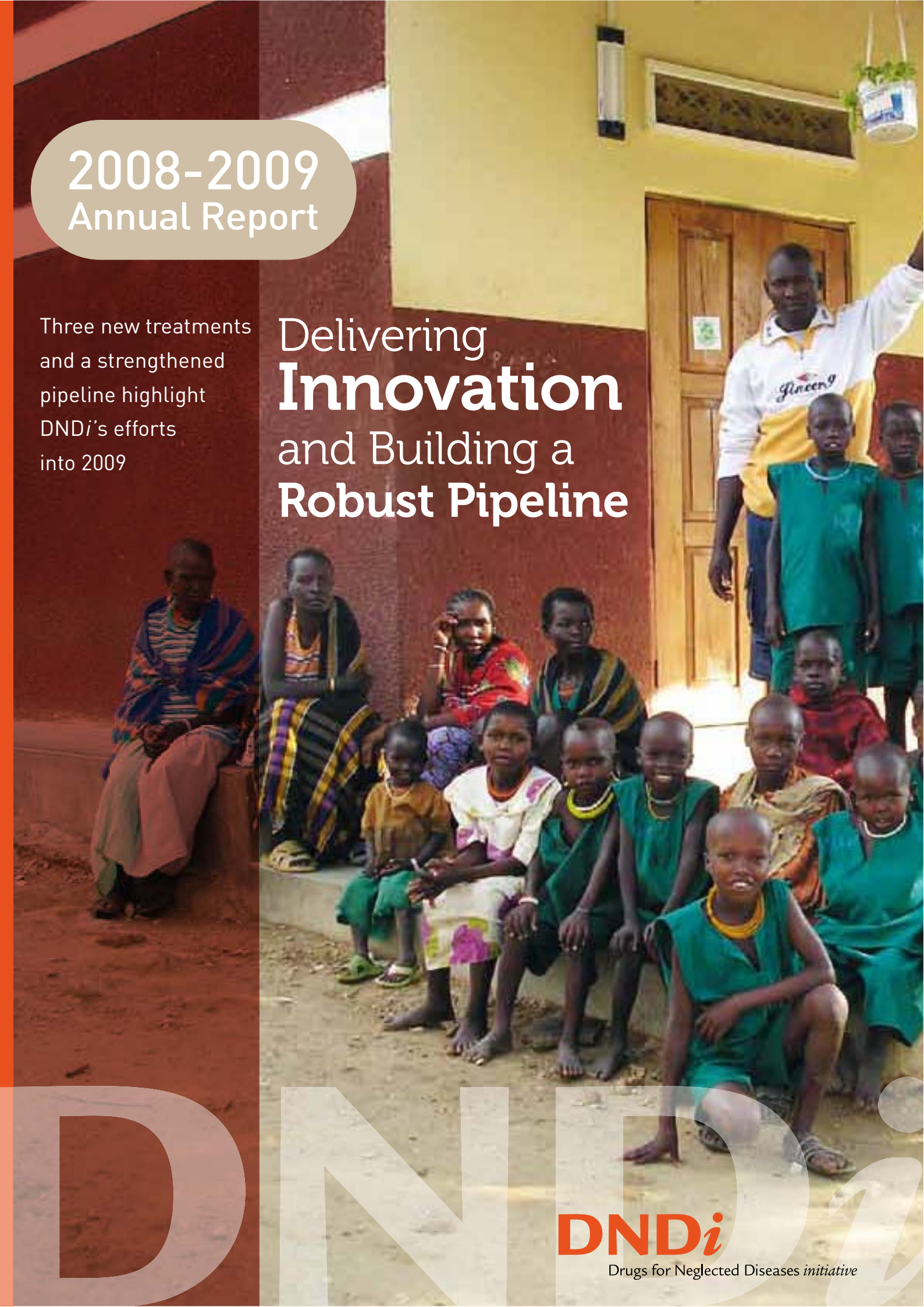
2008-2009 Annual Report

Three new treatments and a strengthened pipeline highlight DND*i*'s efforts into 2009

Delivering **Innovation** and Building a **Robust Pipeline**



DNDi

Drugs for Neglected Diseases *initiative*

The Drugs for Neglected Diseases *initiative* (DND*i*) is an independent, not-for-profit product development partnership working to research and develop new and improved treatments for neglected diseases such as leishmaniasis, human African trypanosomiasis, Chagas disease, and malaria. DND*i* was founded in 2003 by the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia, France's Pasteur Institute, Médecins sans Frontières (MSF) and WHO/TDR which acts as a permanent observer to the initiative.

Message

from the Chair of the Board and the Executive Director

In March 2009, the World Bank estimated that if the current global economic crisis persists, there could be between 200,000 and 400,000 additional child deaths every year – between 1.4 and 2.8 million before 2015-and **100 million of the world's poorest forced back into poverty**. The conclusion of the world leaders was eloquent: "Any reduction in investment in healthcare will have devastating consequences for the sick and untreated, and has the potential to plunge new groups and nations into poverty."

Now, as we are preparing our annual report, we have no option but to consider this economic breakdown which constitutes a dramatic challenge not only for DND*i* and our stakeholders, but also for all those committed to bringing innovation and new tools to those most in need.

Most neglected tropical diseases primarily affect the poor and marginalised who have few resources or possibilities to make a living. The high burden of disease and loss of productivity aggravate poverty which is further compounded by the high cost of long-term care.

For tropical diseases such as sleeping sickness, leishmaniasis, and Chagas disease, for which no adequate treatments or diagnostics exist, research is needed now more than ever, for new, practical, and effective tools, and efficient ways to implement them. With the strongest and most comprehensive drug portfolio for these neglected tropical diseases in history, DND*i* continues to engage partners who share our vision and commitment, and to ensure that a well-balanced pipeline is maintained.

For all these R&D disease strategies, DND*i* has made major progress in delivering quality, affordable and adapted treatments.

Specifically, advances in combatting one of the most neglected diseases - sleeping sickness - are significant, as this is the role, mission, and the "raison d'être" of DND*i*. To deliver an improved therapeutic option for this disease, strong partnerships have been set up with national programmes of most endemic countries, NGOs, public and private research institutions, and the World Health Organization (WHO). Oral nifurtimox and intravenous eflornithine combination therapy (NECT) has been included on the WHO Essential Medicines List. **NECT, the first improved treatment for sleeping sickness in 25 years**, is now available for

Contents

2008-2009 Annual Report

Dr. Bernard Pécoul,
Executive Director

Dr. Marcel Tanner,
Chairman of the Board of Directors

Bringing innovation and new health tools to those most in need.

use in treating the advanced stage of the disease and could save four to five lives of every 100 patients treated, as it is far less toxic than the arsenic drug that is still being used in some areas. It is a major improvement and source of satisfaction for all the partners who have been engaged in our organisation since its creation in 2003. However, delivering a truly simplified treatment which can be orally administered, implemented at the primary healthcare level, and effective against both stages of the disease, is still our ultimate goal.

One promising drug entering into clinical development this year is fexinidazole –the only new clinical candidate currently in the drug pipeline for sleeping sickness. This project holds great promise for patients and practitioners in the field. Both short- and long-term strategies are considered as the core of our scientific approach, which requires the best scientific resources at all stages of R&D to access compounds, technologies, expertise, and knowledge.

Sleeping sickness is one illustration of DND*i*'s continuous progress to boost innovation for the most neglected patients. Another example is our successful track record of collaboration with sanofi-aventis in delivering **ASAQ for the treatment of malaria**. In 2008, more than 5 million treatment courses were procured and 20 to 30 million more will be delivered in 2009.

Six years on from its founding, DND*i* is managing more than 300 partnerships with a wide range of public and private partners and NGOs, and ten clinical trials are ongoing in 2009, with more than 400 people engaged in our programmes.

With focused collaboration, innovative thinking, and political leadership, we will meet the noble goals set by our organisation. We remain firmly engaged in making a major and significant contribution to the Millennium Development Goals and bringing those forgotten patients out of the shadows.

The changes seen in the past decade offer a new landscape for collaboration to improve essential healthcare. At a time when the financial crisis could have significant consequences for the poorest, greater investment from governments and the private sector, complemented with new and adapted funding mechanisms, are needed to ensure that these efforts will be sustained and strengthened.

We would like to thank again all our donors for their support, and particularly those who have reinforced their commitment to most neglected diseases with significant multi-year contributions

We would also like to pay special tribute to our dedicated team working at DND*i* for their outstanding commitment and contribution to our successes. In particular, we would like to thank Els Torreele, one of the main sources of inspiration for our organisation, even prior to its creation, and who has played a major role in the successful implementation of our sleeping sickness projects. Els is moving on to new horizons but, no doubt, will remain committed to neglected diseases in her future job.

Investing in R&D for the most neglected patients goes hand in hand with better health and economic growth for affected marginalised communities. Help us meet our goal.

Simply because their wellbeing matters.

Dr. Bernard Pécoul **Dr. Marcel Tanner**

01.

Vision, Mission, & Governance

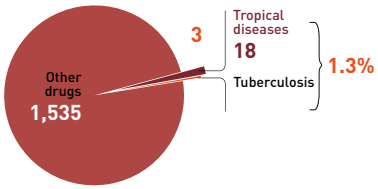
Major progress for most neglected diseases

Prospects set to improve dramatically for children threatened by sleeping sickness in Mwana-Mputu (Democratic Republic of the Congo), thanks to new treatments developed by DND*i* and its partners.

A landmark year for sleeping sickness with two major project milestones achieved: NECT a new and improved treatment approved by WHO and fexinidazole, a new possible drug brought into clinical development.

With the strongest and most comprehensive R&D portfolio in history for the most neglected diseases, DND*i* continues to identify and engage partners who share our vision and commitment, to ensure that a well-balanced pipeline is established for the three diseases of primary focus: sleeping sickness (human African trypanosomiasis, HAT), kala–azar (visceral leishmaniasis, VL), and Chagas disease.

Total of new drugs developped



Of the 1,556 new drugs registered between 1975 and 2004, only 21 drugs have indications for tropical diseases and tuberculosis even though these diseases constitute over 12% of the global disease burden. A mere 10% of the world's health research expenditure is spent on diseases that account for 90% of the global burden of disease.

Source: Chirac P. Torreele E, Lancet, 2006 May 12,1560-1561

Since the launching of two new anti-malarials in 2007 and 2008 - ASAQ and ASMQ – DND*i* has taken key steps towards ensuring their effective implementation in endemic countries, while advancing other projects from its portfolio, and expanding its worldwide partnerships. For example as a result of working with our partner sanofi-aventis, ASAQ is now registered in 24 countries, over 20 million treatments will be delivered in 2009.

Major progress has particularly been achieved in R&D with regard to sleeping sickness. NECT, a combination of nifurtimox and eflornithine for the treatment of the disease received approval by the WHO Expert Committee on the Selection and Use of Essential Medicines in April 2009. The approval came after positive efficacy and safety results from the clinical study that was run jointly by DND*i*, Médecins Sans Frontières, Epicentre, and national programmes. NECT does not only reduce the risk of resistance emerging but also reduces the duration of drug treatment (with infusions twice a day for ten days); and makes it easier to administer through oral doses.

The major breakthrough, however, is the prospect of a simple oral treatment or a pill to treat the disease. Fexinidazole, a compound 'rediscovered' by DND*i*, is entering into phase I clinical trial this year, in close collaboration with sanofi-aventis. It is the only new clinical candidate currently in the drug pipeline for sleeping sickness.

In the field of Chagas disease, DND*i* is also moving forward with its R&D strategies: we are currently developing a paediatric formulation with LAFEPE (a Brazilian public laboratory) and researching the therapeutic utility of azoles, which already have available drugs. However, more must be done, as the burden of Chagas is significantly underestimated in official statistics: few patients receive any treatment at all; and new diagnostics and treatments are still urgently needed. All these factors have prompted DND*i* to launch a Chagas campaign in 2009. (see Chapter 4)

OBJECTIVES

The primary objectives are to:

- Deliver 6-8 new treatments by 2014 for leishmaniasis, sleeping sickness, Chagas disease, and malaria
- Establish a robust portfolio for new generation of treatments

Secondary:

- Use and strengthen existing capacity in disease-endemic countries
- Raise awareness and advocate for increased public responsibility

VISION

To improve the quality of life and the health of people suffering from neglected diseases by using an alternative model to develop drugs for these diseases and ensuring equitable access to new and field-relevant health tools. In this not-for-profit model, driven by the public sector, a variety of partners collaborate to raise awareness of the need to research and develop drugs for those neglected diseases that fall outside the scope of market-driven R&D. They also build public responsibility and leadership in addressing the needs of these patients.

MISSION

To develop new drugs or new formulations of existing drugs for patients suffering from the most neglected communicable diseases. Acting in the public interest, DND*i* will bridge existing R&D gaps to find essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners.

DND*i*'s primary focus is the development of drugs for the most neglected diseases, such as sleeping sickness (Human African Trypanosomiasis, HAT), kala-azar (visceral leishmaniasis, VL), and Chagas disease, and it will also consider engaging in R&D projects for other neglected diseases. In pursuing these goals, DND*i* manages R&D networks built on South-South and North-South collaborations. While using and supporting existing capacity in countries where the diseases are endemic, DND*i* helps to strengthen additional capacity in a sustainable manner through technology transfer in the field of drug research and development for neglected diseases.

Over the past five years, the R&D landscape has changed significantly, with greater resources being given to global health and the development of new drugs for poverty-related neglected diseases. However, while much attention has been focused on combatting the 'big three' neglected diseases (HIV/AIDS, malaria, and tuberculosis), many others have failed to attract sufficient resources, and adequate drugs are not available for many diseases affecting poor, neglected populations in the developing world.

In 2007, less than 5 per cent of US$ 2.5 billion – the total funding allocated to R&D for neglected diseases - went to kinetoplastid diseases[1] although those tropical diseases (NTDs) kill more than 100,000 of people each year and aggravate poverty in the developing world.

Almost everyone in the bottom billion has at least one of these diseases, which reinforces the poverty trap. **These diseases prevent the achievement of the first six Millenium Development Goals** even though for some of them their control with low cost and cost-effective interventions could start long-term economic growth and development. For some kinetoplastid diseases, the few treatments available date back to colonial times and are simply inadequate by today's standards.

THREE CHALLENGES AHEAD...

Despite substantial progress proving that PDPs such as DND*i* can successfully manage R&D and translate knowledge into tangible results, we are still facing major challenges on three levels:

EXPANDING INNOVATIVE PARTNERSHIPS

DND*i* operates through a virtual model, whereby all of its R&D activities are outsourced, contributing to keeping development costs under control, while providing a high level of flexibility. A consequence of this strategic option is that fostering an efficient drug-development programme requires the establishment of strong agreements within the entire biomedical landscape, so as to leverage and mobilise private and public sector resources. The first DND*i* successes show how crucial it is to build new collaborative business models through efficient partnerships, alliances and consortia amongst a broad range of public and private players who share an objective driven by needs, not profit.

To put it in perspective: of the 350 agreements signed since the establishment of DND*i*, more than 100 have come about since 2008. These include research, technical, and funding agreements with public and private partners such as sanofi-aventis for the development of ASAQ and Fexinidazole, GlaxoSmithKline, Merck, Farmanguinhos, Advinus, Cipla, BDSI, Griffith University (Aus), University of Antwerp, University of Dundee, Anacor, Scynexcis, among many others.

FACILITATING ACCESS TO TREATMENTS

To immediately address the access barriers during the implementation phase, DND*i*'s role is upstream, early, and jointly with the implementers such as the national control programmes, NGOs and WHO. DND*i* aims to gather relevant information during the development of treatments so as to facilitate their transition to implementers, for rollout into the field, after registration.

The DND*i* access strategy and activities adopted by the board of directors in December 2008 are guided by the following principles:

- the need to facilitate equitable access to the new treatments developed by DND*i*
- the desire to transition these treatments, in the long run, to their natural implementers, i.e. national ministries of health (MOH) and control programmes (NCP), WHO, and NGOs such as MSF, in order for DND*i* to focus on its core activity of research and development, and
- a commitment to contribute to the development of approaches for improved access and dissemination of knowledge.

THE GANG OF 4!

Neglected tropical diseases (NTDs) are a group of thirteen major parasitic and bacterial infections that affect over one billion people and kill 500,000 people annually - most of whom live on less than US$ 2 per day. NTDs stigmatise, disable and inhibit individuals from being able to care for themselves or their families, and 6 many are fatal without treatment.

- Fortunately, there are inexpensive, safe and effective treatments available for the control or elimination of the seven most common NTDs: ascariasis, hookworm infections, trichuriasis, lymphatic filariasis (LF), onchocerciasis, schistosomiasis, and trachoma For these diseases, efficiency and effectiveness of mass treatment using existing products has recently been demonstrated, and the **Global Network for Neglected Tropical Diseases (GNNTD)** has begun a global campaign for integrated control in 56 countries where at least five diseases are coendemic. However, due to resistance, new antihelminthic drugs and vaccines will be needed.
- For the other NTDs such as sleeping sickness, leishmaniasis, Chagas disease, and Buruli ulcer, no adequate diagnostics or treatment exist today. The few treatments that are available for these neglected diseases often date back to colonial times and are simply inadequate by today's standards: they are often highly toxic, completely unaffordable, and extremely difficult to administer in resource-poor settings.

ENSURING A MORE FAVOURABLE ENVIRONMENT FOR R&D

Moreover, public leadership is needed to implement policy changes and to create a more favourable environment that will support the development of new, essential health tools. This leadership must strive to ensure that affected populations have equitable access to treatments and they must also contribute to the development of innovative needs-based measures. Such measures include intellectual property (IP) management policies to encourage a needs-driven R&D agenda, technology transfer, an enabling regulatory environment and the strengthening of research capacities in developing countries.

1 Moran, M. et al. PloS Med. 6, e1000030 (2009)

DNDi R&D Main Progress to 2009

Malaria

ASAQ – fixed-dose combination (FDC) of artesunate and amodiaquine for use in sub-Saharan Africa; launched in March 2007; registered in 24 disease-endemic countries; in landmark partnership with sanofi-aventis; obtained WHO prequalification in October 2008; 5 million treatment courses delivered in 2008 and more than 20 million forecast for 2009

ASMQ – FDC of artesunate and mefloquine for treatment in Latin America and Asia; registered in Brazil in March 2008 in partnership with Farmanguinhos/Fiocruz; South-South technology transfer underway to Cipla for availability in Asia and Africa; in use by Brazilian national authorities

Human African Trypanosomiasis

NECT - Clinical Trial of Nifurtimox-Eflornithine Coadministration Therapy– promising study presented at ASTMH in December 2008; full dossier submitted to WHO Essential Medicines List (EML) in 2008; in April 2009, NECT is included in the EML list

Fexinidazole – first compound mining success from DNDi 's nitroimidazoles project; preclinical studies finalised; entering into clinical development in 2009 and the only new clinical candidate currently in the drug pipeline for HAT; in May 2009, sanofi-aventis and DNDi sign agreement to develop and make it available

Lead Optimisation Partnership – two compound series have been advanced as attractive leads progressing from early-stage screening research through innovative partnership with U.S. partners: Scynexis & Pace University

Visceral Leishmaniasis

VL Combination Trials in Africa, Asia and Latin America – implemented for evaluating safe and short-course combination therapy, using existing drugs in three regions to stave off parasitic resistance and provide a shorter, more effective treatment course;

Fexinidazole entering into Phase I in 2009.

• Phase III trial (AmBisome, Miltefosine, Paromomycin) designed for India, Bangladesh and Nepal; patient recruitment began in June 2008 in two sites in Bihar (India).

• Paromomycin trial in Africa – more than 1,000 patients included in multi-centre trial in East Africa, aimed to register paromomycin and evaluate the shorter course combination of PM+SSG

• AmBisome in Africa. Recruitment started in 2009, aimed to achieve geographical extension and potential therapies combination

Lead Optimisation Partnership – partnership implemented in 2007; with two key partners in India: Advinus and Central Drug Research Institute (CDRI); 2 promising series of compounds identified in 2008

Chagas disease

Paediatric Benznidazole – agreement with LAFEPE to develop first benznidazole formulation

for children; to be affordable and publicly available in 2010

Lead Optimisation Partnership – the project started in 2008 with the aim of progressing molecules from early-stage screening research.Partners include: Centre for Drug Candidate Optimisation (CDCO), Epichem, & Murdoch University (Australia); Federal University of Ouro Preto (Brazil)

Agreement signed in May 2009 between DNDi and Institut Pasteur Korea (IPK).

Discovery Projects

Consolidation with strategic focus on compound collection, target identification, target validation, assay development, high-throughput screening (HTS), hit identification, and hit to lead selection. For HAT: HTS is available (Eskitis, Scynexis); for VL: HTS with Institut Pasteur Korea, and in development stage for Chagas. DNDi is working closely with Dundee University, London School of Hygiene & Tropical Medicine (LSHTM), University of Antwerp as well as developing synergies with Medicines for Malaria Venture (MMV), Global Alliance for TB Drug Development (GATB), and the Consortium for Parasitic Drug Development (CPDD). DNDi has established working relations with GSK, sanofi-aventis, Merck, and Novartis, and is currently building relations with Pfizer, Eisai, and many others.

Strengthening Research Capacities

• Three regional networks for research capacity strengthening.

Africa: the HAT Platform and the Leishmaniasis East Africa Platform (LEAP): GCP, ethics, and trial-monitoring training; establishment and training of data safety monitoring board (DSMB); workshops on clinical trial methodology and information sharing on recent clinical research developments.

Asia: Pan Asian Network for Neglected Diseases (PAN4ND): screening capacity strengthening in the Asian region for purification and identification of chemicals from plant, soil, and marine organisms.

DND*i* Founding Partners and Worldwide Presence

THE KEY ROLE OF THE FOUNDING PARTNERS

Since DND*i*'s founding in 2003, seven key stakeholders have helped to propel the initiative. Each Founding Partner is a centre of excellence in neglected disease research and/or patient care.

- 7 Founding Partners
- 4 Regional Support Offices
- 1 Affiliate
- 2 Project Support Offices

DND*i* NORTH AMERICA

Established in 2007, the affiliate of DND*i* in North America **supports the advocacy, fundraising, and R&D efforts of DND*i* in the region**. Based in New York City, USA, this affiliate operates under the direction of the DND*i* North America Board of Directors and collaborates with **key partners engaged in a variety of R&D activities.**

■ www.dndina.org

INSTITUT PASTEUR

Established in France in 1887, the Pasteur Institut is a non-profit private foundation dedicated to the prevention and treatment of diseases. It focuses on diseases like yellow fever, tuberculosis, poliomyelitis, hepatitis, and HIV/AIDS. With 8 Nobel Prizes awarded to its researchers, **the Pasteur Institut is on the forefront of medical research with discoveries of antitoxins, BCG, sulfamides, and anti-histamines, as well as key research in molecular biology and geneticengineering**.

■ www.pasteur.fr

OSWALDO CRUZ FOUNDATION (FIOCRUZ)

Founded in 1900, Fiocruz is the largest biomedical research institution in Latin America. Part of the Brazilian Ministry of Health, **Fiocruz has facilitated health tool R&D for neglected diseases via the establishment of dedicated centres for vaccine and drug development: Biomanguinhos and Farmanguinhos.**

■ www.fiocruz.br

DND*i* coordination team in Geneva

DND*i* LATIN AMERICA

Opened in 2004, the DND*i* Latin America regional support office is based in Rio de Janeiro. With the **primary aim to support regional R&D activities for Chagas disease, malaria, and VL,** the Latin American office also undertakes advocacy and communications activities to increase awareness of neglected diseases in the region.

■ www.dndi.org.br

DND*i* IN THE DRC

Since 2005, the DND*i* office in the Democratic Republic of the Congo (DRC) has provided **essential logistical and financial support for the nifurtimox-eflornithine clinical trial (NECT) and the HAT Platform**. Based in Kinshasa, the office shares space with key project partner, the Swiss Tropical Institute.

DND*i* AFRICA

Established in 2003, the DND*i* Africa regional support office is based at the Kenya Medical Research Institute (KEMRI) in Nairobi, Kenya. **DND*i* Africa provides support to R&D projects in the region, including the paromomycin study, the LEAP and HAT Platforms, and the FACT Project**.

■ www.dndiafrica.org

MÉDECINS SANS FRONTIÈRES (MSF)

MSF is an independent, private, medical aid organisation that has been operational in emergency medical aid missions around the world since 1971. **With offices in 19 countries and ongoing activities in over 80, MSF has also run the Campaign for Access to Essential Medicines since 1999**. MSF has received numerous international awards for its activities, including the Nobel Peace Prize in 1999. MSF dedicated this prize to finding long-term, sustainable solutions to the lack of essential medicines crisis (which ultimately led to the founding of DND*i* in 2003).
■ www.msf.org

THE SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES (TDR)

As an independent global programme of scientific collaboration, established in 1975 and co-sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO), TDR **aims to help coordinate, support, and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged**. TDR is a permanent observer of DND*i*'s Board of Directors.
■ www.who.int/tdr

INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR)

Established in 1911, it was re-designated in 1949 as the Indian Council of Medical Research (ICMR). Funded by the Government of India, ICMR's activities are **focused on the formulation, coordination, and promotion of biomedical research**. The Council has a network of 21 Permanent Research Institutes located in different parts of India that conduct research on **tuberculosis, leprosy, and visceral leishmaniasis**.
■ www.icmr.nic.in

DND*i* IN JAPAN

Since 2004, the DND*i* office in Japan has provided support in **developing discovery projects and on better positioning DND*i*** in the country by expanding its relationships with academia, pharmaceutical companies, government, and media.
■ www.dndijapan.org

DND*i* INDIA

Opened in 2004, the regional support office in India is based at the Indian Council for Medical Research (ICMR) in New Delhi. The office **functions as a relay for DND*i*'s operational activities in India, which are primarily focused on two diseases, malaria and visceral leishmaniasis**.
■ www.dndiindia.org

KENYA MEDICAL RESEARCH INSTITUTE (KEMRI)

Established in 1979, KEMRI conducts health sciences research and shares its research findings with the international community. One of the leading health research institutions in Africa, KEMRI has been making a significant contribution to regional research capacity for many years. With **a focus on infectious and parasitic diseases, and on public health and biotechnology research**.
■ www.kemri.org

MINISTRY OF HEALTH, MALAYSIA (IMR)

The Institut for Medical Research (IMR), within the Ministry, was established in 1900 to **carry out scientific and sustained research into the causes, treatment and prevention of infectious tropical diseases.** Initially, it principally focuses on **malaria, beriberi, cholera, and dysentery**. The IMR is now comprised of eight centres which perform research, diagnostic services, training, and consultative services across diverse health fields.
■ www.imr.gov.my; www.moh.gov.my

DND*i* MALAYSIA

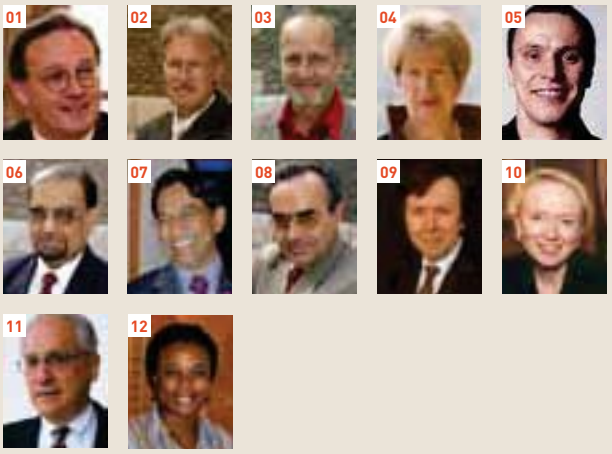
Since 2004, the DND*i* office in Malaysia has supported a variety of R&D activities across the Asian region, including key preclinical and early clinical studies for the FACT Project, as well as the fostering of the PAN4ND, **a regional research platform that is focused on the discovery and development of natural substances as therapeutics to neglected diseases**. Based at the Universiti Sains Malaysia, the office also works to facilitate the implementation of ASMQ in the region.
■ www.dndiasia.org

Governance & People

THE BOARD OF DIRECTORS

The **Board of Directors** is composed of between ten and thirteen members, including one patient representative. Each of the six funding members nominates one Board member. Board members serve for a term of four years.

DND*i* BOARD MEMBERS



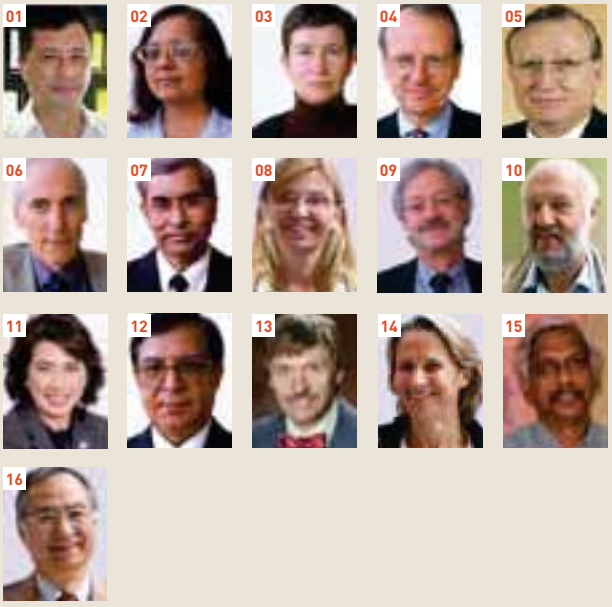
01 **Marcel Tanner**, Chair; Swiss Tropical Institute (STI)
02 **Reto Brun**, Secretary; Swiss Tropical Institute (STI)
03 **Bruce Mahin**, Treasurer
04 **Alice Dautry**, Institut Pasteur, France
05 **Christophe Fournier**, Médecins Sans Frontières (MSF)
06 **Lalit Kant**, Indian Council of Medical Research (ICMR)
07 **Datuk Mohd Ismail Merican**, Ministry of Health, Malaysia
08 **Carlos Morel**, Oswaldo Cruz Foundation (FIOCRUZ), Brazil
09 **Robert G Ridley**, TDR (Permanent Observer of Board)
10 **Gill Samuels**, Global Forum for Health and Research, Genev
11 **Bennett Shapiro**, Pure Tech Ventures, formerly with Merck & Co, USA
12 **Paulina Tindana**, Patient Representative, Navrongo Health Research Centre, Ghana

- **Representative of KEMRI: vacant post**

THE SCIENTIFIC ADVISORY COMMITTEE (SAC)

The **SAC** is composed of sixteen prominent scientists with expertise in various scientific disciplines related to drug discovery and development, and/or the specific reality of neglected diseases and neglected patients. They operate independently of the Board of Directors and the Executive team. The SAC has the mandate to advise the Board of Directors on matters related to research and development and choice of projects, as well as the quality of the scientific output.

DND*i* SCIENTIFIC ADVISORY COMMITTEE MEMBERS



01 **Julio Urbina**, Chair; Venezuelan Institute for Scientific Research (IVIC), Venezuela
02 **Kirana Bhatt**, University of Nairobi, Kenya
03 **Marleen Boelaert**, Institute of Tropical Medicine, Antwerp, Belgium
04 **Pierre-Etienne Bost**, Institut Pasteur, France
05 **J Carl Craft**, Formerly with Medecines for Malaria Ventures, Switzerland
06 **Alan Hutchinson Fairlamb**, University of Dundee, UK
07 **Chitar Mal Gupta**, Central Drug Research Institute, India
08 **Maria das Graças Henriquez**, Owaldo Cruz Foundation, Fiocruz, Brazil
09 **Paul Herrling**, Novartis International AG, Switzerland
10 **Marcel Hommel**, Institut Pasteur, France
11 **Nor Shahidah Khairullah**, Infectious Diseases Research Center, Malaysia
12 **Shiv Dayal Seth**, Indian Council of Medical Research (ICMR), India
13 **Mervyn Turner**, Merck Research Laboratories, USA
14 **Muriel Vray**, Institut Pasteur, France
15 **Krisantha Weerasuriya**, World Health Organization, (WHO),Geneva
16 **Haruki Yamada**, Kitasato Institute for Life Sciences, Japan

THE EXECUTIVE TEAM (as of June 2009)

DND*i* HEADQUARTERS, GENEVA (AS OF DECEMBER 2008)

Bernard Pécoul, Executive Director
Shing Chang, R&D Director
Hyo Jueng Ahn-Degras, Site and Travel Assistant
Jean-François Alesandrini, Fundraising and Advocacy Director
Manica Balasegaram, Clinical Project Manager
Severine Blesson, Project Coordinator (as of July 2009)
Bethania Blum de Oliveira, Project Support Officer, (based in Brazil)
Gwenaëlle Carn, Clinical Project Coordinator
Eric Chatelain, Senior Project Manager
Brigitte Crotty, Executive Assistant
Violaine Dällenbach, Communications Officer
Ralf De Coulon, Finance, HR, and Administration Director
Robert Don, Senior Project Manager
Sally Ellis, Clinical Project Coordinator
Karin Génevaux, Fundraising Coordinator
Caroline Gaere Gardaz, Fundraising Officer for Major Donors
Jean-Robert Ioset, Screening Coordinator
Sadia Shafaqoj-Kaenzig, Media and Corporate Communications Manager
Jennifer Katz, Head of Fundraising
Jean-René Kiechel, Senior Product Manager, FACT Project, and Expert, (based in Paris, France)
Delphine Launay, Lead Optimisation Coordinator (as of March 2009)
Denis Martin, Senior Project Manager
Janine Millier, Accountant
Béatrice Mouton, Human Resources & Legal Affairs Manager
Jean-Pierre Paccaud, Business Development Director
Sylvie Renaudin, Research & Development Assistant
Isabela Ribeiro, Senior Project Manager, (based in Rio de Janeiro, Brazil)
Jerôme Saint-Denis, Fundraising Coordinator (as of March 2009)
Ivan Scandale, Lead Optimisation Coordinator
Ann-Marie Sevcsik, Scientific Communications Manager
Nathalie Strub-Wourgaft, Clinical Development Director (as of March 2009)
Els Torreele, Senior Project Manager
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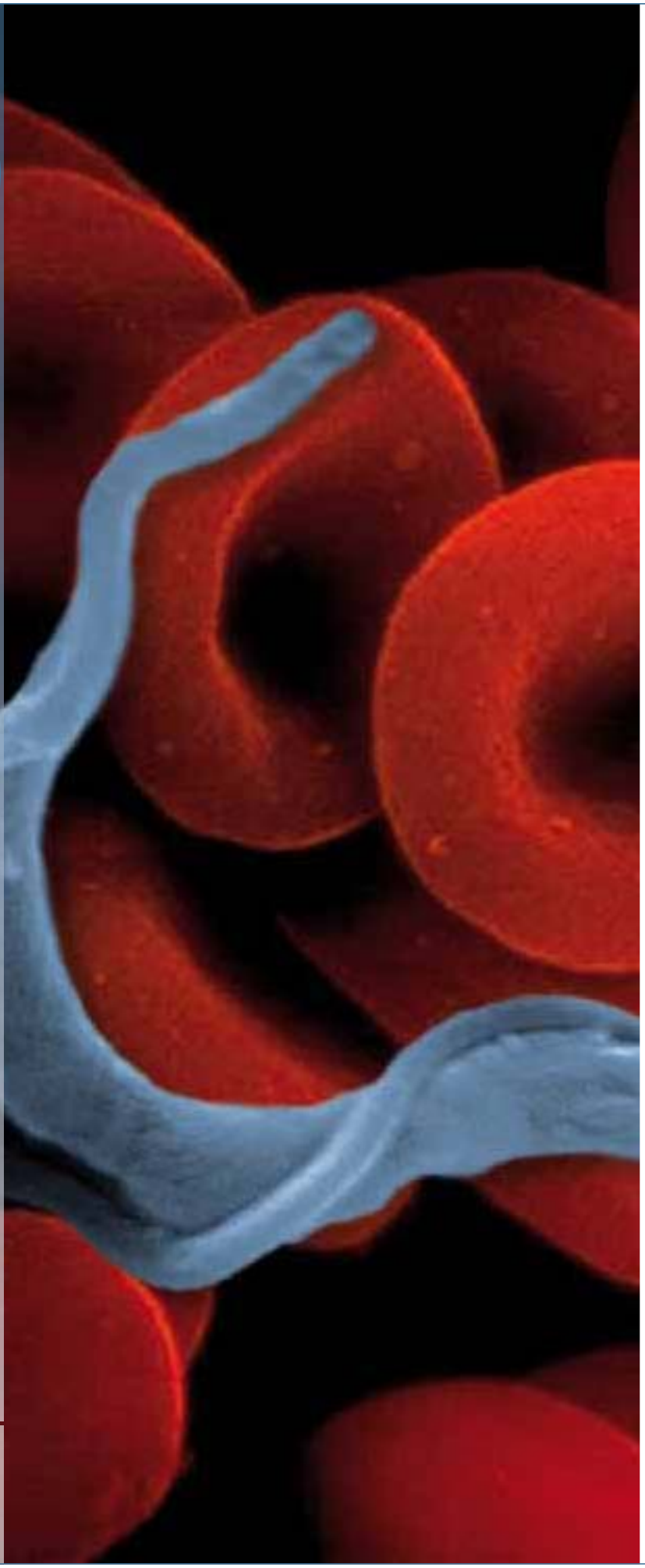
02.

R&D Model, Strategy, & Portfolio

Consolidating efforts to research and deliver better treatments



One century after Chagas disease was first described, research has provided better understanding of the disease-causing parasite (shown under magnification). However, more activities and partnerships are needed in order to **develop and deliver better-adapted diagnostics and treatments** for this and other neglected diseases.

Major progress towards addressing the most neglected diseases with better medicines, including DND*i*'s 1st treatment for sleeping sickness.

DND*i* has made significant progress in establishing a well-balanced pipeline for the 3 diseases of our current primary focus: sleeping sickness (human African trypanosomiasis; HAT), visceral leishmaniasis (VL), and Chagas disease; and in addressing issues on access to these essential medicines.

Promising developments can be seen in each of the disease-specific and discovery portfolios:

- **Discovery phase:** new commitments from pharmaceutical partners like Anacor and GlaxoSmithKline, as well as key academic groups, such as the Drug Discovery Unit at the University of Dundee, and Institute Pasteur Korea
- **HAT:** positive Phase III results and inclusion of NECT onto the WHO Essential Medicines List, advancement of fexinidazole towards clinical development, and promising lead series from Scynexis and Anacor
- **VL:** combination studies in Asia and Africa are progressing, with new sites and studies added; development of combination strategy for Latin America; excellent progress seen from lead optimisation consortium
- **Chagas disease:** agreement with LAFEPE to develop the only available paediatric formulation for a Chagas treatment, investigation of azoles as potential combination treatment in preclinical studies, and continued efforts to access promising azoles for Chagas treatment
- **Malaria:** prequalification by the World Health Organization and growing use in public market of "ASAQ" (ASAQWinthrop®), with 20 million treatments expected to be distributed in 2009; further transition into the access phase with partners including sanofi-aventis and Medicines for Malaria Venture (MMV); registration of ASMQ in Brazil and continuing efforts to further roll out ASMQ into Latin America and Southeast Asia.

The strongest and most comprehensive kinetoplastid drug portfolio in history continues to be fortified with engagement of partners who share DND*i*'s vision and commitment, and who bring complementary capabilities. By keeping our focus on the patients and their needs, DND*i*'s project portfolio balances long-term and short-term projects because R&D of new drugs is time-consuming, resource-intensive, and exceedingly risky, particularly at the early discovery stage. DND*i* utilises a combination of approaches to achieve the ultimate goal of developing new treatments that are safe, efficacious, and field-adapted, while also balancing the urgent needs for incrementally improved treatments that offer meaningful improvements.

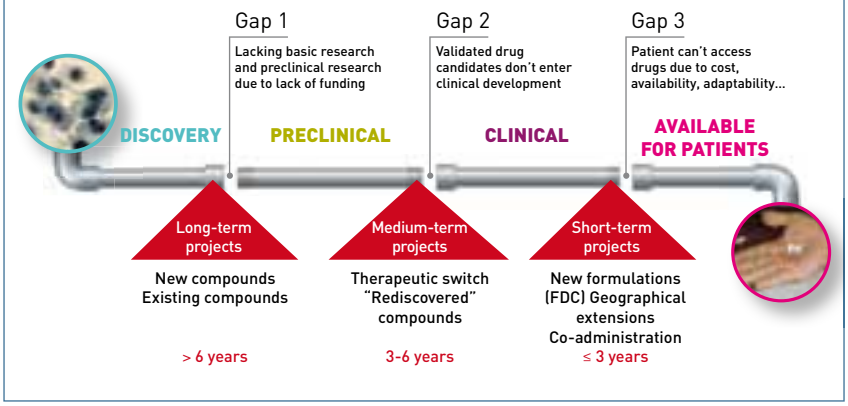
Each of the disease portfolios consists of a balance of projects designed to serve:

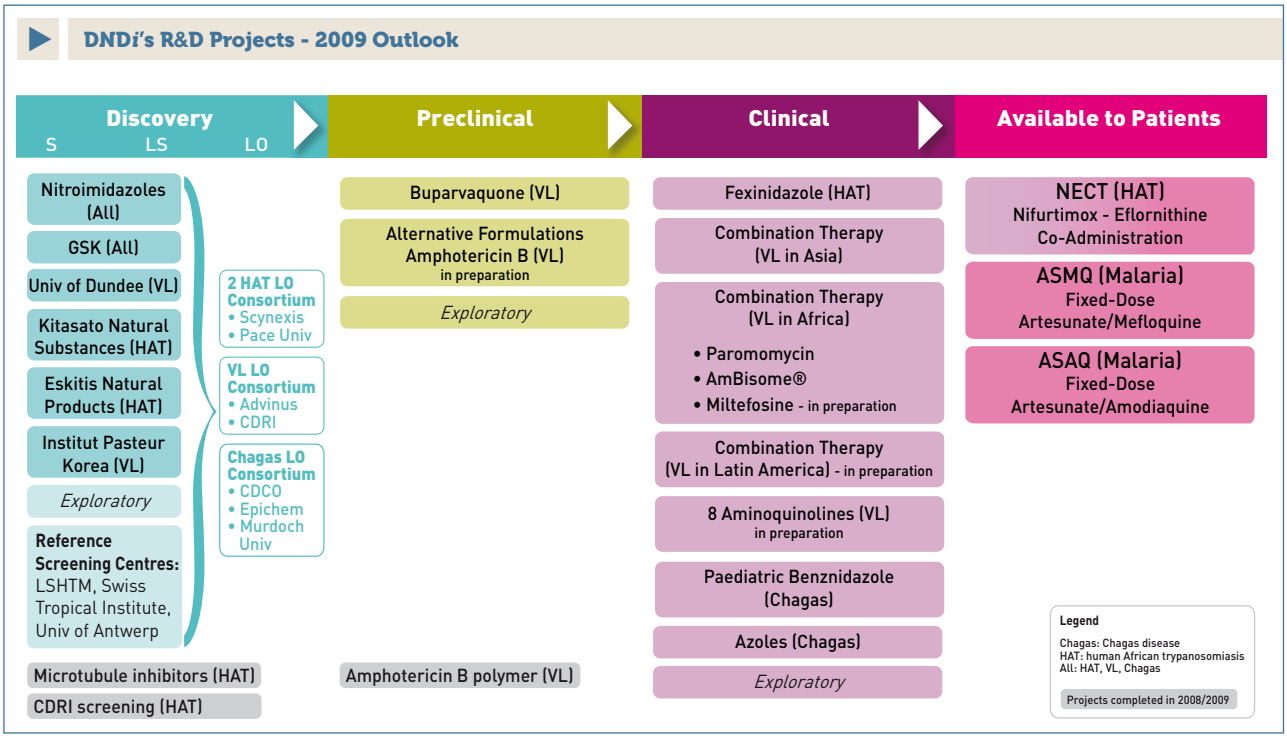
- Long-term objectives of developing innovative medicines from new chemical entities
- Medium-term objectives of identifying existing preclinical or clinical stage compounds suitable for therapeutic switching, or for further improvements via alternative or new formulations
- Short-term objectives of making existing drugs available in broader geographic areas and developing better treatments from existing drugs; examples include conducting necessary studies to register drugs not yet available in selected regions, developing fixed-dose combinations, and identifying combinations of existing drugs to reduce treatment duration, improve tolerability and lower the risk of resistance development.

By this balanced approach of portfolio-building, DND*i* is able to address patient needs in the near and long term, while also ensuring that a sustainable pipeline is established.

With the aim to deliver improved treatments for patients with neglected diseases, DND*i* manages a spectrum of skilled partners with unique and varied expertise in the research and development of improved treatments for patients with neglected diseases. Discovery efforts are consolidated to allow the maximum efficiency for uncovering compounds with potent antiparasitic activities. Preclinical

DND*i*'s R&D Projects – Filling the Gaps





and clinical development activities are organised by disease area, and each is focused on the ultimate goal of developing new treatments which reach patients and contribute to improved disease control.

STRENGTHENING AND STREAMLINING THE PORTFOLIO

Into 2009, DND*i*'s portfolio continues to be strengthened and streamlined. Within the drug research and development process, milestones are defined for each project. Each year, a number of projects reach completion, and resources are reallocated to new projects.

We'd like to acknowledge our partners' contributions to the following projects that have reached completion in the past year. DND*i* continues to work with many of these partners on other projects:

- COMPOUND SCREENING WITH CDRI (HAT); Stage: Discovery; Partner: Central Drug Research Institute (CDRI), India,
- MICROTUBULE INHIBITORS (HAT); Stage: Discovery; Partners: Murdoch University, Australia; Epichem, Australia; Centre for Drug Candidate Optimisation, Monash University, Australia,
- AMPHOTERICIN B POLYMER (VL) Partners: Imperial College, UK; London School of Pharmacy, UK; LSHTM, UK

The R&D portfolio represents a collection of projects that are in-sourced at all stages along the drug R&D process, from early discovery through clinical development, with **the objective to bring new, field-relevant tools to patients in the shortest time and most efficient way possible**. DND*i* utilises a target product profile (TPP) which is a hypothetical "package insert" that guides the development process. The TPP plays a key role in guiding lead optimisation of drug candidates, decision-making within the team, design of clinical research strategies, and constructive communication with regulatory authorities. TPPs can be found for each of DND*i*'s target diseases in the following pages.

Sound knowledge of patient needs is essential to a credible TPP. Our clinical project managers have in-depth knowledge about the patients in the field. They solicit input from healthcare workers, patients, health regulators, and policy-makers in disease-endemic countries where the drug will ultimately be made available. Input from key opinion leaders and the R&D landscape for each disease area are also important and influential in shaping the TPPs.

With dozens of partners spanning the globe and crossing various sectors related to neglected diseases and drug development, DND*i* is firmly on its way to meeting its objectives. However, additional support, from new research partners to governments and other donors, is needed in order to fully deliver the best science for the most neglected.

CHARACTERISTICS OF A TPP

Indication
- Which diseases?

Population
- Which patients and where?

Clinical Efficacy
- Does it kill the parasite effectively?

Safety and Tolerability
- What kind and how many adverse events?

Stability
- How long can it be stored in the field?

Route of Administration
- How is it given to patients?

Dosing Frequency
- How often and how long must it be given?

Cost
- Will it be affordable to target population?

Time to Availability
- How long will it take to develop?

DISCOVERY

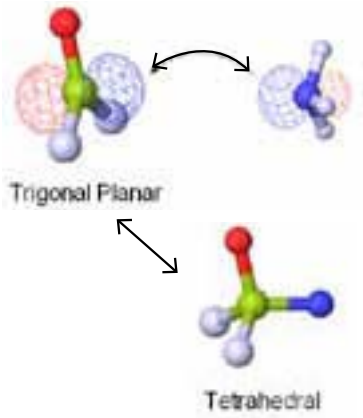
Consolidated efforts in discovery are feeding a pipeline that will deliver

Discovery research – a three-stage process consisting of screening, lead selection, and lead optimisation – is the one of the earliest stage of drug research and development, and contributes to bringing forward novel drugs that are significantly better than current therapies. DND*i* continues its screening efforts into 2009 by consolidating and strengthening activities **to ensure a robust pipeline that will deliver.**

Many molecular targets or chemicals with therapeutic potential never make it into the drug development process. Although a lot of research has been conducted on the kinetoplastid parasites over the past century, culminating in the publishing of sequencing of its genomes and proteomes in 2005, basic research has yet to translate into new therapeutic tools.

DND*i* is working to overcome this gap in the discovery stage by: (1) **accessing broad chemical diversity** through a number of different sources and partnerships such as a natural products screening network and collaborations with pharmaceutical companies, (2) **evaluating antiparasitic activity** of compounds *in vitro* and *in vivo* according to standard operating procedures to ensure that screening at different sites and with different groups are comparable, and (3) **increasing screening capacity** for the kinetoplastid diseases. A resourceful and pragmatic approach, with a variety of strategies and partnerships, is used to feed the pipeline and deliver suitable leads to the lead optimisation (LO) programme.

Oxaboroles: A Promising Lead Series



Oxaboroles, now a promising lead series being optimised as part of the HAT lead optimisation consortium, have a unique boron-based chemistry that allows researchers at Anacor to use rational drug design in creating compounds with unique properties beyond traditional small-molecule drugs.
As shown above, boron's reactive P-orbital allows it to form a tetrahedral structure under certain conditions.

Into 2009, important developments within DND*i*'s discovery efforts include:

- a high-throughput screening (HTS) assay for the intramacrophagic *Leishmania* parasite, with the goal to have HTS for all 3 kinetoplastid diseases by end of 2009 – this is already available for *T. brucei* (the parasite causing human African trypanosomiasis), but remains a rate-limiting step for both *Leishmania* and *T. cruzi*
- agreements with pharmaceutical and biotechnology companies – GSK, Anacor, Merck, and many others in discussion
- streamlining/sharing with other PDPs (MMV, TB Alliance), new research agreements with the Drug Discovery Unit at the University of Dundee, and information sharing with the Consortium for Parasitic Drug Development at the University of North Carolina.

DND*i* has taken efforts in the past year to consolidate its activities with strategic focus on proactive compound mining, chemical class screening, improved throughput of screening intracellular parasites, and general phenotypic screening. The following projects are part of DND*i*'s discovery activities but are by no means comprehensive as DND*i* continues to take on new exploratory activities.

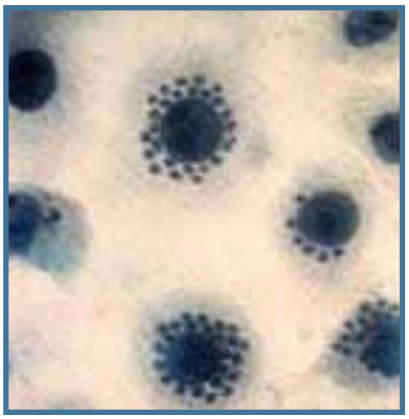
REFERENCE SCREENING CENTRES

Dedicated research groups at the London School of Hygiene and Tropical Medicine (LSHTM), Swiss Tropical Institute (STI), and the University of Antwerp serve as reference screening centers for DND*i* in our efforts to harness existing expertise as well as to help ensure that screening results are comparable and standard for *in vitro* and *in vivo* assays at different sites and with different groups.

SCREENING OF PROMISING CHEMICAL CLASSES

▶ GSK - CYSTEINE PROTEASE INHIBITORS AND PYRIDONES

- **Target diseases:** HAT, Chagas, and VL
- **Partners:** GlaxoSmithKline, Spain; Swiss Tropical Institute, Switzerland
- **DNDi project manager and coordinator:** Denis Martin, Jean-Robert Ioset
- **Project start:** March 2008

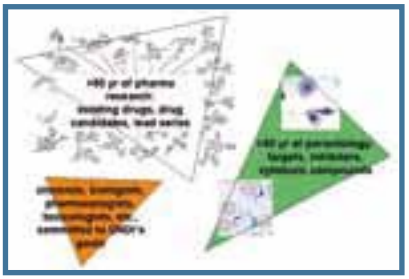


In early 2008, GSK and DND*i* formalized an ambitious collaboration which makes available a large GSK library of new cysteine protease inhibitors and a library of pyridone compounds to DND*i* in order to examine their specific activities against kinetoplastid parasites as both compound libraries have shown good parasitic activity. Cysteine proteases (CP) are nearly ubiquitous in protozoan parasites, play a number of key roles in parasite survival (from nutrition to immune evasion), and have well-known structure-activity relationships. Pyridones have demonstrated potent in vitro and *in vivo* antimalarial activity. In 2009, over 500 compounds have been screened *in vitro*, and a number of compounds have been selected for further pharmacokinetic and *in vivo* efficacy testing.

▶ NITROIMIDAZOLES – PROACTIVE COMPOUND MINING

- **Target diseases:** HAT, Chagas, and VL
- **Partners:** Swiss Tropical Institute, Switzerland; Fiocruz, Brazil; Ouro Preto University, Brazil; Covance, UK; Absorption Systems, USA; BioDynamics, UK; and a range of worldwide collaborators who have made compounds of interest available for testing, including ENH Research Institute, USA; Tehran Univ of Medical Sciences, Iran; Silesian Univ of Technology, Poland; LaSapienza Univ, Italy; Univ of Alberta, Canada; Univ of Tennessee, USA; Tokushima Univ, Japan; Univ of Auckland, Australia; sanofi-aventis, France; Roche, Switzerland; Novartis/NITD, USA-CH-Singapore; Alkem, India; TB Alliance, USA; Sigma-Aldrich, USA
- **DNDi project manager:** Els Torreele
- **Project start:** January 2005

Nitroimidazoles are a well-known class of anti-infective compounds; however, the risk for genotoxicity linked to the nitro-group has been a concern for drug development. An extensive, proactive compound mining effort was undertaken by DND*i* to 'revive' nitroimidazoles as drug leads against the kinetoplastid parasites. Over 700 existing compounds from 15 different sources were identified, accessed, and tested for *in vitro* and *in vivo* activity. Active compounds underwent extensive druggability profiling, including possible mutagenic activity, ADME, and pharmacokinetics. This approach has led to the discovery and characterization of fexinidazole as a promising drug candidate for HAT (see page 18) and with promising activity against *T. cruzi* (the parasite causing Chagas disease). Additionally, N-aryl-4-nitroimidazoles have been identified as a new lead series for HAT as a possible back-up for fexinidazole, should it fail in the clinic. Other nitroimidazoles have shown promising activity against *Leishmania* and *T. cruzi*, and are being assessed for their potential for further development. This research shows that it's possible to select non-mutagenic nitroimidazoles with good antiparasitic activity.



Proactive mining requires harnessing of fragmented knowledge.

PHENOTYPIC SCREENING

▶ DRUG DISCOVERY UNIT AT THE UNIVERSITY OF DUNDEE

- **Target disease:** VL
- **Partners:** Drug Discovery Unit at the University of Dundee
- **DNDi project manager and coodinator:** Eric Chatelain, Jean-Robert Ioset
- **Project start:** December 2008

The collaboration between the Drug Discovery Unit at the University of Dundee is focused on identifying molecules capable of killing the *Leishmania* parasite, which are suitable for further development into safe and effective medicines for clinical trials by DND*i*'s partners. The DDU will use, as a starting point, the current knowledge and potential medicines developed within its African sleeping sickness programme. Researchers will utilise both a phenotypic and target-based screening approach in order to identify any promising 'hits' to be further developed.

▶ ESKITIS SCREENING OF NATURAL PRODUCTS

- **Target disease:** HAT
- **Partners:** Eskitis, Australia; Griffith University, Australia
- **DNDi project manager and coodinator:** Eric Chatelain, Jean-Robert Ioset
- **Project start:** November 2007

As part of early exploratory activities, DND*i* accessed the natural products' wealth and drug discovery expertise of Eskitis Institute for Cell and Molecular Therapies to examine the *in vitro* trypanocidal activity of 64,000 natural products from a diverse screening li-

brary of over 200,000 extracts. This unique lead-like peak library of natural products, which possess well-characterized physicochemical properties optimised for drug development, includes representatives of 60% of global plants and 9,500 marine invertebrates. The proprietary lead-like enhancement technology used by Eskitis is a two-step process which enriches extracts in lead-like and drug-like components prior to pre-fractionation; this process maximizes the chance of a positive outcome, i.e., detecting a 'hit'. In 2008, the first 'hit', a marine invertebrate, was identified. As the project continues through 2009, the remaining 136,000 compounds have been screened, and hit expansion with 2 series is due to begin later in the year.

▶ KITASATO SCREENING OF NATURAL SUBSTANCES

- **Target disease:** HAT
- **Partners:** Kitasato Institute (KI), Japan
- **DND*i* project manager and coodinator:** Eric Chatelain, Jean-Robert Ioset
- **Project start:** April 2005

Natural products from microbial and plant resources, such as avermectin and artemisinin, have played an important role in the history of parasitic chemotherapy. Likewise, KI has a long history in the research and discovery of anti-infectious drugs from natural products, such as microbial metabolites and plant products. The objective of this specific project is to discover new types of antitrypanosomal molecules from KI natural products via *in vitro* and *in vivo* screening.

Through March 2009, over 25,000 natural products and their synthetic derivatives have been screened, with 9 compounds having been identified as having high activity. These compounds are now being evaluated for possible lead optimisation at Scynexis, where researchers are currently undertaking hit expansion on one of the compounds, malonomycine; at the same time, KI will continue searching for further 'hits' to feed the pipeline.

INSTITUT PASTEUR KOREA (IPK)

Developing a technological breakthrough: IPK visual high-throughput screening (HTS)

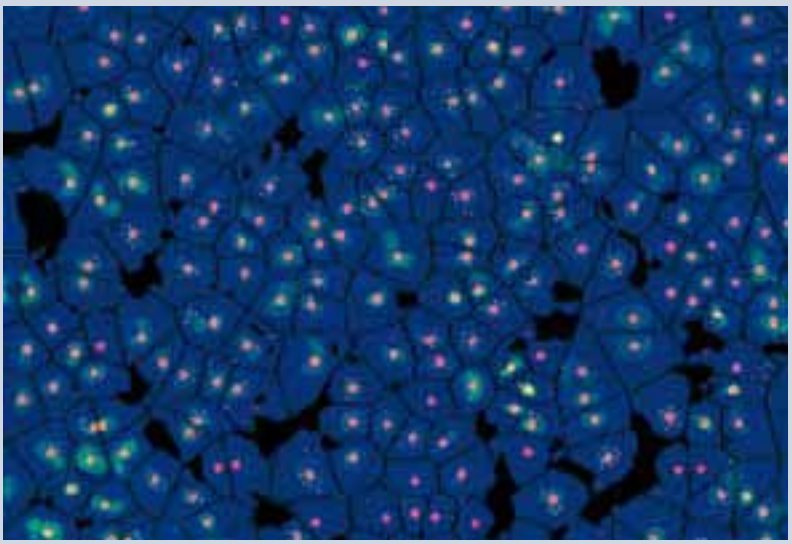
- **Target disease:** Visceral leishmaniasis (VL)
- **Partners:** Institut Pasteur Korea (IPK)
- **DND*i* project manager and coodinator:** Eric Chatelain, Jean-Robert Ioset
- **Project start:** December 2007

In May 2009, DNDi and IPK agreed to extend HTS collaboration for another three years.

A cell-based, high-throughput visual screening system for *Leishmania* parasites offers the possibility to quickly generate new hits against novel targets. Utilising both the intellectual and technological capacity of the Institute Pasteur Korea, this project seeks to develop a major methodological advance in antileishmanial drug development as this will be the first HTS visual screening assay for the clinically relevant intracellular form of the parasite: intracellular *Leishmania* amastigotes in macrophages.

Having operationally begun in May 2008, the project first sought to develop and validate the visual assay in the first year so as to then use it in the second year of the project to test confirmed 'hits' against *Leishmania*. The project is now at a stage where a 200,000 compound library is being screened, with results expected later in 2009.

When the methodology is validated with the current screening run, this assay will be the first of its kind in the world, and it will then be expanded to include testing against other intracellular parasites such as *T. cruzi*. Such a visual screening would represent a huge advance for antitrypanosomal screening as well. Highlights of the ongoing research efforts were presented during the World Leishmaniasis Congress in February 2009, and the presentation is available on the DND*i* website.



Visualization of intracellular *Leishmania* amastigotes in macrophages.

R&D Portfolio
BY DISEASE

Major progress seen, punctuated by first improved treatment for stage 2 sleeping sickness in 25 years.

SLEEPING SICKNESS
Human African Trypanosomiasis (HAT)

At the forefront of DND*i*'s efforts to develop new treatments is the need to understand the realities and treatment needs of patients and health care staff in the field.

The ultimate goal for human African trypanosomiasis (HAT) is **a truly simplified treatment which can be orally administered, implemented at the primary health care level, and effective against both stages of the disease**. Currently, both diagnosis and treatment require a complicated series of tests and trained medical supervision.

A key issue with HAT is that it affects hard-to-access communities in regions with poor health infrastructure; as a result, there is probably considerable underreporting of the condition. Poor access to medical facilities, a lack of resources and skills, and misdiagnosis all contribute to underreporting. Due to the resource-poor areas where the disease occurs, control efforts are often mobilised into vertical programmes. Consisting of a series of specifically equipped and trained diagnosis and treatment centres and mobile teams in endemic areas, but these programmes are not integrated into regional health centres.

There is an immediate need to improve current treatment options, particularly for patients with advanced stage of the disease where the few drugs that are available are toxic, increasingly ineffective in killing the parasite, and difficult to use. Ideally, a treatment will be safe enough to be used in the first stage of the disease and effective enough in the second stage of the disease.

In addition to lead optimisation programmes, DND*i* has conducted proactive compound mining activities to identify existing compounds with potential against kinetoplastid diseases. The compound mining activities of DND*i* have led to the revival of the nitromidazole class as potential drug candidates: the most notable example is fexinidazole, upon which DND*i* has begun clinical development for HAT.

Several groups worldwide have specific established expertise and knowledge in drug discovery that are readily applicable to the discovery of new antitrypanosomal drugs. In this context, DND*i* has established:

- Partnerships with pharmaceutical / biotechnology / academic groups for interaction and access to natural product as well as synthetic chemical libraries, chemistry, HTS, biological models, and drug design
- A network of key international laboratories to support discovery efforts with pharmacokinetic, pharmacodynamic, and toxicological expertise, and defined synergy between these laboratories.

At the clinical stage of development, DND*i* is working to both investigate new medicines and to also strengthen capacity for clinical research on HAT. With the recent inclusion of NECT onto the WHO Essential Medicines List, DND*i* is well on its way to meeting its short-term objective to bring a new, short-course, co-administration treatment for stage 2 HAT to the patients. Through this project, DND*i* has also built important relationships with other groups involved in HAT clinical research as well as with the WHO, national HAT control programmes and NGOs working to control HAT.

Key to developing new treatments is understanding the realities and treatment needs of patients and health care staff in the field. Here a DNDi team visits a village in the Democratic Republic of the Congo with a mobile team of the national sleeping sickness control programme.

PRIORITY TARGET PRODUCT PROFILE FOR HAT

- **A new treatment for stage 2 HAT in adults and children**
  - Preferably useful for both stages 1 and 2
  - Active against *Trypanosoma brucei (T. b.) gambiense* and *T. b. rhodesiense*
- **Better safety profile than existing drugs**
  - Ideally requiring little or no monitoring
- **Equal or better efficacy profile than existing drugs**
  - Ideally ≥95% clinical efficacy at 18 months after treatment
- **Easy-to-use treatment**
  - Short course (ideally ≤7 days, up to 14 days is acceptable)
  - Preferably oral; if injectable, intramuscular preferred
  - Preferably once-a-day treatment
- **Affordable**
- **Stable in tropical climate (minimum 2-year shelf life)**
  - Preferably 3-year shelf life

SLEEPING SICKNESS – **Human African Trypanosomiasis (HAT)**

60 million people at risk in sub-Saharan Africa

WHAT IS THE ANNUAL IMPACT OF HAT?

50,000-70,000 cases [1]
48,000 deaths [2]
1,525,000 DALYs [2] [3]
Large proportions of communities can be affected by HAT, with serious social and economic consequences. Epidemics at the end of the 20th century infected up to 50% of population in several villages across rural Africa.

HOW IS HAT TRANSMITTED?

Transmitted to humans by tsetse flies, **HAT is caused by two sub-species of the kinetoplastid protozoan parasite,** *Trypanosoma brucei: T. b. gambiense* (west African), *T. b. rhodensiense* (east African).

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

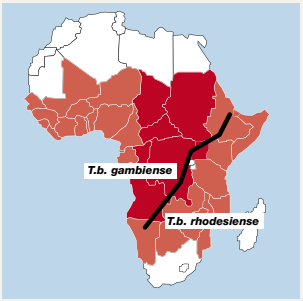
Available treatments are **few, old, and stage-specific.**
Stage 1 treatments, pentamadine and suramin, are fairly well-tolerated but stll require injections and are mostly ineffective in stage 2.
For stage 2 (where most patients are diagnosed and thus treated),
2 available treatments exist:
– **melarsoprol**, an arsenic derivative: painful, toxic (killing 5% of those who receive it), increasingly (ineffective up to 50% resistance and treatment failure).
– **eflornithine**: difficult to administer and requires trained health staff and constant hospitalisation (requiring 56 infusions of 2 hours over 14 days), and resistance an increasing concern.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?

Improved treatment options for this fatal disease are urgently needed, particularly for stage 2.
– **A safe, effective, and practical stage 2 treatment** would improve and simplify current case management. This drug should ideally work in both stages of disease.
– **A simple stage 1 treatment**, to be used at the local health centre level, would increase access to treatment and coverage.

WHERE DOES HAT OCCUR?

Of the 36 countries considered endemic for HAT, the 7 most affected countries represent 97% of all reported cases (see map).
The Democratic Republic of the Congo (DRC) alone accounts for 2/3 of reported cases [4].
HAT primarily occurs in the poorest, most rural areas in Africa, where difficulty of diagnosis, political instability, and lack of health surveillance make estimates of disease prevalence difficult to ascertain.



WHAT ARE THE SYMPTOMS/ PRESENTATIONS?

HAT occurs in two stages:
– **stage 1** - the haemolymphatic phase – includes non-specific symptoms like headaches and bouts of fever (**generally goes undiagnosed** without active HAT surveillance).
– **stage 2** - the later, neurologic phase – occurs when the parasite crosses the blood-brain barrier (BBB) and can lead to serious sleep cycle disruptions, paralysis, progressive mental deterioration, and, ultimately, **results in death without effective treatment**.

WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

Short term: better use of existing treatments
– **Nifurtimox-eflornithine combination therapy (NECT)**, a simplified treatment for stage 2 HAT, now ready for use

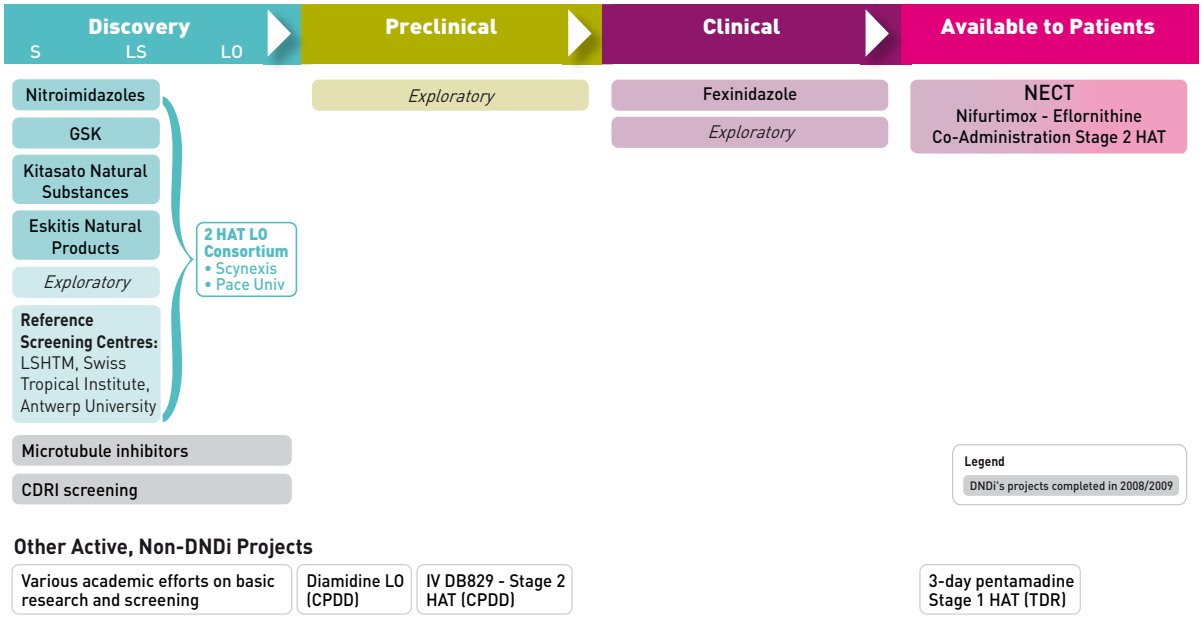
Medium term: rediscovered compounds
– **Fexinidazole**: first drug candidate entering clinical development from nitroimidazoles project
– Back-up nitroimidazoles

Long term: new compounds and improved research capacity
– **New drugs** developed from compounds identified (**i.e. oxaboroles**) in discovery research and progressed through **HAT lead optimisation consortium**
– Multi-country, multi-partner **HAT Platform** to strengthen regional research capacity (see Section 3).

By 2014, DND*i* aims to deliver from its HAT-specific portfolio:
– 1 new combination therapy recommended by WHO
– 1 new drug registered
– A robust pipeline

(1) World Health Organization (WHO). Wkly Epidemiol Rec. 2006:81;71-80. **(2)** WHO. The World Health Report. Geneva; 2004. Available from http://www.who.int/whr/2004. Accessed Aug 12, 2008. **(3)** DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. **(4)** Simarro PP, Jannin J, Cattand P. PLoS Med. 2008;5:e55.

HAT R&D Projects - 2009 Outlook



DISCOVERY

LEAD OPTIMISATION CONSORTIUM

- **Partners:** Scynexis, USA; Pace University, USA
- **DND*i* project manager and coordinator:** Robert Don, Ivan Scandale
- **Project start:** April 2007

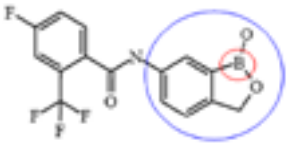
With an objective to develop optimised leads by progressing 'hit' molecules with a good safety profile and activity against *T. brucei* parasites, these consortia bring together expertise in chemistry, biology, screening, and pre-formulation. Optimisation focuses on the molecule's capacity to be absorbed into the bloodstream, be distributed effectively to the infection, survive in the body, kill the parasite and not harm the patient. With two full lead optimisation teams in place (a total of 18 scientists), a number of hits identified from DNDi screening partners are undergoing hit expansion. Scientists within the consortia use advanced techniques to study how the selected molecules interact with the therapeutic target (ie. a protein or an enzyme) and optimise the drug-like characteristics of these molecules to ensure that they comply with the target product profile. This phase requires a close, highly interactive collaboration between the biologists and chemists, who form a feedback loop: the biologists test the biological properties of compounds on biological systems while the chemists perfect the chemical structure of these compounds based on information obtained by the biologists. Two compound series have been chosen as lead series:

- oxaboroles, provided by Anacor and possessing a unique boron-based chemistry, were identified as hits against *T. brucei* at the Sandler Centre of the University of California San Francisco, and have shown *in vivo* activity.
- kinase inhibitors, of which approximately 300 analogs have been synthesized to date. Significant in vitro potency has been developed but only moderate in vivo activity, so further study is ongoing. These two series will continue to be optimised, with the goal to enter preclinical develoment in 2010 and 2011.

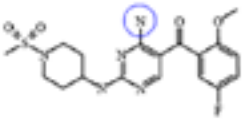
This strategy and the promising early results were presented during the 2008 meeting of American Society of Medicine & Tropical Hygiene, and are available at www.dndi.org.

Sample compound structure of oxaboroles and kinase inhibitors

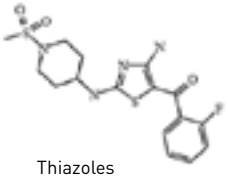
Oxaboroles



Kinase inhibitors



Pyrimidines



Thiazoles

Ongoing collaboration with Dundee University

CLINICAL

FEXINIDAZOLE

- **Stage:** preclinical moving clinical development
- **Partners:** Accelera, Italy; Aptuit, UK; Axyntis, France; Covance, UK; Drugabilis, France; Labor für "Pharma and Umweltanalytik", Germany; Germany sanofi-aventis, France; Swiss Tropical Institute, Switzerland
- **DND*i* Project Manager:** Els Torreele
- **Project start:** February 2007

Fexinidazole as a drug candidate for stage 2 HAT is the first success of the proactive compound mining efforts DND*i* has pursued in particular in the nitroimidazoles project (see page 13).

A 5-nitroimidazole that was in preclinical development as a broad-spectrum anti-protozoal by Hoechst in the early 1980s, fexinidazole was rediscovered by DND*i* after being an abandoned compound. Extensive profiling by DND*i* has shown that fexinidazole is orally active, and readily distributes to the brain and cures mouse models for both acute and chronic infection with African trypanosomes. Importantly, fexinidazole is not mutagenic in a panel of *in vitro* and *in vivo* mammalian genetic toxicology tests, confirming its favorable activity/toxicity profile as a drug candidate.

In 2007, a full preclinical programme was established to enable first-in-human studies. This included process chemistry and GMP-manufacturing of the active pharmaceutical ingredient, its preclinical formulation, extensive ADME-PK profiling and confirmatory studies in animal models of HAT, and the regulatory toxicology package (4-weeks repeated dose toxicokinetics in rat and dog, safety pharmacology, and an extensive genetic toxicology package). In June 2008, a full review of the data by DND*i* concluded that fexinidazole is suitable for progression into clinical development.

Tablets of fexinidazole in development

Preparation for first-in human phase I studies are underway, including clinical tablet formulation considered a promising development candidate for HAT. Fexinidazole will enter into Phase I clinical studies in 2009, which would make it the only new drug candidate in clinical development for sleeping sickness. DND*i*; and sanofi-aventis have announced in May 2009 an agreement for the development, manufacturing and distribution of fexinidazole. Under the terms of the agreement, DND*i* will be responsible for non-clinical, clinical, and pharmaceutical development and sanofi-aventis will be responsible for the industrial development, registration, and production of the drug at its manufacturing sites.

This project and the preclinical results were presented during the 2008 meeting of American Society of Medicine & Tropical Hygiene, and are available at www.dndi.org.

NIFURTIMOX-EFLORNITHINE COMBINATION THERAPY (NECT)

Now available for use after being added to the WHO Essential Medicines List as treatment against stage 2 sleeping sickness

- **Stage**: clinical
- **Partners:** Epicentre, France; MSF; the national HAT control programmes of the Democratic Republic of the Congo (DRC) and the Republic of the Congo; SCIH/STI, Switzerland
- **DND*i* project manager:** Els Torreele
- **Project start:** April 2004

With the ultimate goal to enable a WHO recommendation on the use of the nifurtimox- eflornithine combination therapy (NECT), **the NECT project has shown that the combination is as effective and safe as standard eflornithine monotherapy, but easier to use, and safer than melarsoprol** (toxic though still widely used in ~70% of patients with stage 2 HAT).

Begun originally as a single centre study by MSF-Holland and Epicentre in the Republic of Congo (Brazzaville) in 2003, this study was extended, as of 2004, to additional sites in the DRC by DND*i* in collaboration with Epicentre, MSF, STI and the national HAT control programmes of the DRC.

This multi-centre clinical study, which enrolled 287 patients and was completed in 2008, compared the safety and efficacy of NECT, a coadministration of the oral drug nifurtimox and the intravenous drug eflornithine, with eflornithine monotherapy, the current first-line treatment for stage 2 *T. b. gambiense* HAT. As is requisite to establish efficacy in this disease, patients were actively followed up for 18 months after treatment.

The study conclusively demonstrated that NECT is as well-tolerated and efficacious as eflornithine. At the end of 2008, the final efficacy and safety results of the Phase III study were available and led to DND*i*'s submission of NECT for inclusion on the WHO Essential Medicines List (EML). The final results are in the process of being published, and were presented by Epicentre during the 2008 meetings of American Society of Medicine & Tropical Hygiene and the HAT Platform, and are available at www.dndi.org. The EML application and support statements of the HAT community are available on the website of the WHO Essential Medicines List.

In May 2009, MSF, Epicentre, and DND*i* announced that NECT had been included on the EML. According to the WHO, NECT can now be used in patients and will provide an opportunity to improve the management of HAT cases. The WHO has already made preparations for the arrival of this improved therapeutic opportunity and is working to ensure that patients have access to NECT by providing appropriate training and supplying the drugs and necessary equipment to disease-endemic countries.

DND*i* and partners are conducting a field study, which began enrolling patients in April 2009, to further document the safety and ease of use of the combination in real-life field conditions and in special populations like children.

Recognised as
"Project of the Year in 2008"

R&D Portfolio
BY DISEASE

From combination therapies to the potential of an oral, short-course drug, the R&D portfolio for VL holds promise

KALA-AZAR
Visceral Leishmaniasis (VL)

Based on the current R&D landscape, the realities in VL-endemic regions, the limited treatment options, DND*i* and partners have determined that the ideal product should be **oral, safe, effective, low cost, and short course (≤10-day)**. Ideally, this treatment will be effective against all forms of the disease and is adequate for use in rural health settings.

As it can take five to ten years to bring a compound through the preclinical and clinical phases of development, DND*i* is currently building on previous research by extending the registration and availability of current drugs, while maximizing their potential and minimizing their drawbacks.

geographically extend other existing drugs in South Asia and East Africa and to develop other combination treatments for East Africa. For Latin America, a similar strategy of combination of current drugs will be undertaken.

In parallel, DND*i* also aims to accelerate the development and registration of new VL drugs by building on existing preclinical and early clinical data in order to offer new medium-term options to patients. As the existing drugs are few and are mostly parenteral, there is a need to increase the number of therapeutic options focusing on new drugs that can be administered orally and that can be new components of

Combination therapies of these new treatments represent a critical path forward because they could offer the following important advantages: shorter course of treatment, better tolerability, reduction in the work load on the health systems in resource-limited areas, better affordability, and potential to prevent or retard resistance development and prolong the life span of these drugs.

DND*i* has three clinical (active) projects: one examining combination treatments (AmBisome®, paromomycin, miltefosine) in India and two ongoing studies in East Africa. In addition to completing these projects, DND*i* will conduct further work to improved combination treatments. Several products including new oral formulations of amphotericin B, 8-aminoquinolines, and potential compounds at late preclinical phase are considered and could be made available to patients as early as possible. In addition, DND*i* has a lead optimisation programme which will bring new candidates into clinical development over the next few years. All of these new drugs will also be considered for combination therapy.

Using a multi-disciplinary approach, DND*i* will bring practical, safe and effective treatments to VL patients that will be a significant step in helping to control the disease in South Asia, East Africa, and Latin America.

PRIORITY TARGET PRODUCT PROFILE FOR VL

- **A new treatment for adults and children**
  - Efficacious against all species in all regions
- **Comparable or better safety profile than existing drugs**
  - Ideally requiring no monitoring
- **Equal or better efficacy profile than existing drugs**
  - ≥95% clinical efficacy at 6 months after treatment
- **Easy-to-use treatment**
  - Short course (ideally ≤7 days, up to 11 days is acceptable)
  - Preferably oral; if injectable, intramuscular depot
  - Preferably once-a-day treatment, ideally outpatient
- **Affordable**
- **Stable in tropical climate**
  - Preferably 3-year shelf life

KALA-AZAR – **Visceral Leishmaniasis (VL)**

200 million people at risk worldwide

WHAT IS THE ANNUAL IMPACT OF LEISHMANIASIS?

500,000 cases of VL; 1.5 million cases of CL[1]
51,000 deaths [2]
2,357,000 DALYs [2] [3]
A lack of surveillance systems and frequency of misdiagnosis means that it is difficult to estimate the true incidence and case-fatality rate of VL [1].

HOW IS LEISHMANIASIS TRANSMITTED?

Diversity and complexity mark the disease of leishmaniasis: more than 20 species of the kinetoplastid protozoan parasite *Leishmania* are transmitted to humans by ~30 species of phlebotomines sandflies.

WHAT IS LEISHMANIASIS?

Leishmaniasis is a disease with several forms. The two most common are:
– **VL: fatal without treatment**
– **cutaneous leishmaniasis (CL)**: has a spectrum of presentations; typically with self-healing or chronic lesions on the skin.
VL is the primary disease target for DND*i*, whereas CL is secondary, mainly because it is typically not life-threatening.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

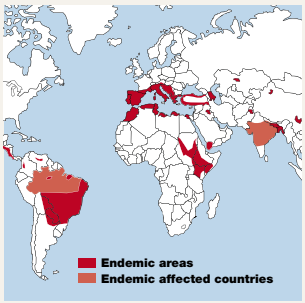
The number of treatment options has increased in the past decade, but each treatment has numerous drawbacks, such as **difficulty to administer, length to treat, toxicity, cost, and increasing parasitic resistance to treatment**:
– **Pentavalent antimonials**: toxic & increasingly ineffective due to resistance; 30-day, hospital-based parenteral treatment
– **Amphotericin B**: dose-limiting toxicity; 15-20 day, hospital-based IV treatment
– **Liposomal amphotericin B (AmBisome®)**: effective, but expensive [4]
– **Paromomycin**: registered in India, but efficacy in Africa not yet determined
– **Miltefosine**: first orally available drug registered in India, but expensive [4] and teratogenic.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?

Patients need a treatment which is **oral, safe, effective, low cost, and short course** (≤10-day course).

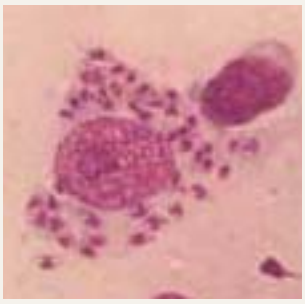
WHERE DOES LEISHMANIASIS OCCUR?

Leishmaniasis infects approximately 12 million people in 88 countries.
VL affects poor, remote populations in 70 countries across Asia, East Africa, South America, and the Mediterranean region (see map) [1] [2].
The 7 most affected countries – Bangladesh, Brazil, India, Ethiopia, Kenya, Nepal and Sudan – represent over 90% of new cases.



WHAT ARE THE SYMPTOMS/ PRESENTATIONS OF VL?

VL is characterised by **prolonged fever, enlarged spleen & liver, substantial weight loss, and progressive anemia**. These symptoms occur progressively over a period of weeks or even months.
Coinfection with other infectious diseases is an increasing concern: HIV-VL coinfection has been reported in 35 countries worldwide.
Almost all clinically symptomatic patients die within months if untreated.



WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

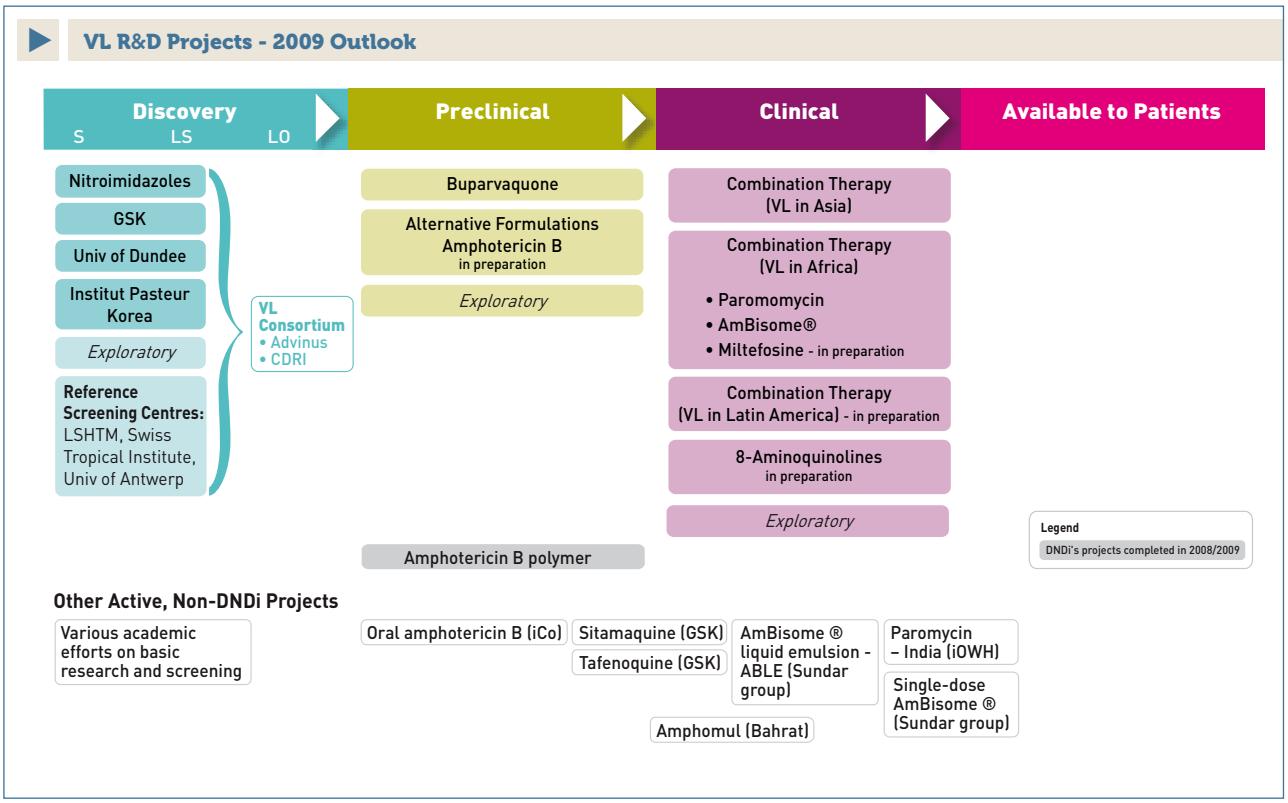
Short term: Better use of existing treatments through geographical extension and new combinations.
– **Combination in Africa:** Registration of paromomycin in 2010, recommendation of combination including paromomycin + sodium, stibogluconate (SSG), registration of AmBisome® in 2011, registration of miltefosine, development of combination with short-course AmBisome®
– **Combination in India:** Recommendation in India, Bangladesh and Nepal by 2011
– **Combination in Latin America:** Recommendation in 2013

Medium term: Registration of one new drug through new formulations of existing treatments and therapeutic switching
– **Alternative formulations of amphotericin B** – DND*i* is evaluating an oral formulation developed by BioDelivery Sciences International (BDSI)
– **8-aminoquinolines** – DND*i* is in discussion with GlaxoSmithKline (GSK) abouttafenoquine and sitamaquine for clinical development
– **Potential compounds** in-sourced at late preclinical phase – DND*i* is actively pursuing potential candidates ready for clinical development in the short term

Long term: New compounds and improved research capacity
– **New drugs** developed from compounds identified (i.e. 2-quinolines) in discovery research and progressed through VL lead optimisation consortium
– **Multi-country, multi-partner LEAP** to strengthen regional research capacity (see Section 3).

By 2014, DND*i* aims to deliver from its VL-specific portfolio:
– 1 new drug registered
– 1-3 geographical extensions in endemic regions outside India by 2014
– 1-3 coadministrations recommended by WHO
– A robust pipeline

(1) Desjeux P. Comp Immunol Microbiol Infect Dis. 2004; 27:305. **(2)** WHO. Report of the 5th Consultative Meeting on Leishmania/HIV Coinfection. Geneva; 2007. **(3)** WHO. The World Health Report. Geneva; 2004. Available from http://www.who.int/whr/2004. Accessed Aug 12, 2008. DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. **(4)** Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of developing countries as of 2007.



DISCOVERY

LEAD OPTIMISATION CONSORTIUM

- **Partners:** Advinus, India; CDRI, India
- **DND*i* project manager and coordinator:** Denis Martin, Delphine Launay
- **Project start:** November 2007

With a full team in place, including 12 team members at the two primary partner sites, assessment of three series of synthetic compounds has been conducted and chemistry-biology activities have begun to bear fruit, with the promising lead series of 2-quinolines. Partners at the "Institut de Recherche et Development" (IRD) originally isolated the 2-quinolines from Bolivian plants, which are used in traditional medicine to treat cutaneous leishmaniasis and malaria. After some promising early results, the DND*i*-managed LO consortium has synthesised more than 250 diverse analogues of 2-quinolines. These modified quinolines were significantly more effective than the parent compounds and a few compounds have shown >90% parasite killing at <1.0 µM. Metabolic stability, which is a known liability of this series, has been improved through the introduction of halogen substituents in more than ten compounds. Further studies of the most promising compounds are underway to confirm the druggability and *in vivo* efficacy and safety. More hits from the other chemical series, including oxaboroles and licochalcones, provided by DND*i* screening partners will be continue to be examined by Advinus.

This strategy and the promising early results were presented during the World-Leish4 meeting in February 2009 and are available at www.dndi.org.

PRECLINICAL

BUPARVAQUONE

- **Partners:** Advinus Therapeutics, India; Drugabilis, France; University Sains, Malaysia; LSHTM, UK
- **DND*i* project manager:** Denis Martin
- **Project start:** January 2008

Buparvaquone has been shown to exhibit antileishmanial activity *in vitro* and *in vivo*. However treatment of dogs infected with visceral leishmaniasis failed to halt disease progression. It was postulated that the disappointing *in vivo* data, when compared to in vitro potency may be a result of low plasma levels in the experimental animals. Preliminary animal studies at the Universiti Sains, Malaysia, and DND*i*-commissioned studies at Advinus Therapeutics have shown that oral absorption of buparvaquone is dissolution-rate limited and that a self-emulsifying drug delivery system (SEDDS) can increase absolute oral bioavailability to greater than 60%. Such an increased bioavailability should be reflected by an improved efficacy.

Buparvaquone efficacy was further tested

The Kala Azar Medical Research Centre is one of the clinical research partners for the VL combination studies in Asia.

at LSHTM in a mouse model. In parallel, the toxicology profile was also assessed. Buparvaquone was tested under conditions allowing maximum exposure. As solubility is a limiting factor even in lipid-based formulations, the intravenous (iv) route was preferred. Buparvaquone, when using an iv formulation leading to maximum exposure, did not show activity within the non toxic dose range. It was therefore decided not to move further with this compound.

Meanwhile, a focused medicinal chemistry program was initiated at Advinus, so as to increase solubility while ensuring the structure-activity relationship. The rationale is based on the assumption that buparvaquone's efficacy is limited by its poor solubility. A limited number of scaffolds have been synthesized, and decisions will be made by the end of the 2009 as to whether to move forward with any of the scaffolds.

ALTERNATIVE FORMULATION OF AMPHOTERICIN B POLYMER

- **Partners:** Polytherics, UK; London School of Pharmacy, UK; Imperial College, UK; LSHTM, UK; BioDelivery Sciences International (BDSI), United States
- **DND*i* Project Manager:** Denis Martin
- **Project start:** September 2006

The goal of this project is to identify an amphotericin B-based formulation which shows the most promise in terms of in vivo efficacy, safety, low cost, and heat stability. Amphotericin B, under various formulations, has become one of the most efficient treatments for VL. The standard formulations (oily suspension) have limitations related to side effects. AmBisome®, a liposomal formulation has overcome these limitations, but its cost and stability are serious limits to its wide-spread use. There has been very limited use in VL-endemic regions of Africa and Asia, where disease burden is greatest, because of its high cost. Recently, new formulations have emerged and are approved or under clinical development in India. However, their intravenous route of administration is still a barrier for appropriate use in the field. Studies aimed at replacing the lipid-based component with a narrow molecular weight polymer are ongoing, with the goal of developing a soluble complex, cheaper, and exhibiting increased thermal stability. Polymers can also prevent the systemic toxicity of amphotericin B to which they are conjugated, still allowing the drug intracellular delivery. The team in the UK has been investigating a less expensive, modified metacrylic polymer; efforts to establish adequate *in vivo* efficacy in a disease model while optimising key characteristics of the polymer did not yield promising results, so this part of project was concluded in early 2009. Recently, two new formulations of amphotericin B – phospholipid-based cochleates and a lipid-based form with enhanced gastrointestinal tract absorption – have been reported to show activity as antifungals when administered orally in animal models. Early reports suggest that they also exhibit activity in murine models of visceral leishmaniasis. BDSI has developed an oral formulation that is currently in Phase I, targeting fungal infections. DND*i* is conducting an exploratory preclinical evaluation of this oral formulation for VL and, if successful, will proceed to clinical development.

CLINICAL

COMBINATION THERAPY FOR VL IN ASIA (INDIAN SUBCONTINENT)

- **Partners:** ICMR, India; Kala Azar Medical Research Centre, India; Rajendra Memorial Research Institute of Medical Sciences, India; GVK BIO, India
- **DND*i* project manager and coordinator:** Farrokh Modabber, Sally Ellis
- **Project start:** December 2006; revised protocol approved October 2007

With the objective to identify a safe and effective short-course combination therapy using existing drugs which could be easily deployed in control programmes, this four-armed, definitive phase III combination therapy study is using drugs already registered in the region: AmBisome®, miltefosine, and paromomycin. Three arms with a combination of 2 drugs/arm for a maximum of 15-day treatment will be compared with the standard 30-day therapy using amphotericin B. In June 2008, the first patient was enrolled into the study. Enrolment should be completed in June 2009, and results are expected by early 2010. The study has been designed to provide data for authorities in India, Bangladesh and Nepal to make informed recommendations for combination treatment which can be used in the elimination programme. Discussions are ongoing to initiate bridging trials in Bangladesh and Nepal to evaluate the safety of the same combinations, followed by larger trials for further evaluation of safety and efficacy. It is anticipated that these combination treatments will be shorter, safer and cheaper than the standard treatment.

VL COMBINATION IN AFRICA

A step together in the right direction

LEAP and DNDi study combination therapy for Africa: making the best of what we have, making it better and protecting it for the future

In the next year, DND*i* and LEAP will embark on additional clinical research to examine new potential combination therapies, including a geographical extension study on miltefosine, one of the few oral drugs effective against leishmaniasis.

PAROMOMYCIN FOR AFRICA

- **Partners:** LEAP (Leishmaniasis in East Africa Platform) group including Kenya Medical Research Institute, Kenya; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; University of Makarere, Uganda; Ministries of Health in LEAP countries; Médecins Sans Frontières (MSF); I+ Solutions, the Netherlands; LSHTM, UK; University of Nairobi, Kenya; Institute for OneWorld Health, USA
- **DND*i* project manager & coordinator:** Manica Balasegaram; Sally Ellis
- **Project start:** November 2004

In Africa, visceral leishmaniasis is difficult to treat with existing drugs due to various issues, such as toxicity, emerging resistance, difficulty of use, and cost. Paromomycin (PM), an aminoglycoside antibiotic that was identified as an antileishmanial in the 1960s, has the potential to be an improved treatment at a lower cost when combined with the standard treatment of sodium stibogluconate (SSG).

Currently being made available throughout the Indian subcontinent by fellow PDP, Institute for One World Health (IOWH), paromomycin is being studied in parallel by DND*i* and the Leishmaniasis East Africa Platform (LEAP) in Ethiopia, Kenya, Sudan, and Uganda. The aim is to register paromomycin as a new treatment in each region, to have it adopted in national treatment guidelines, and to evaluate the shorter course combination of PM+SSG as an alternative treatment for VL.

After early results showed the initial dosage of paromomycin did not work as well in Africa as it did in India, LEAP decided to increase the dose and is now examining a higher-dosage regimen to determine if it is more effective. Over 1000 patients have been recruited so far into the various arms of the study.

In 2008, the study is continuing to recruit patients at sites where infrastructure has been improved or built (see section 3). Initial data was presented during the 2007 RSTMH symposium, and final results of the early part of the study were presented during the WorldLeish4 meeting in February 2009, are in the process of being written up for publication, and are available at www.dndi.org. The study is due to complete in 2009, with final results being ready by the spring of 2010.

AMBISOME® FOR VL IN AFRICA

- **Partners:** LEAP (Leishmaniasis in East Africa Platform) group including Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LSHTM, UK; Ministry of Health, Ethiopia; Kenya Medical Research Institute, Kenya; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; University of Makarere, Uganda; Ministries of Health in LEAP countries; I+ Solutions, the Netherlands; LSHTM, UK; Gilead, USA
- **DND*i* project manager & coordinator:** Manica Balasegaram; Sally Ellis
- **Project start:** Approved in May 2006; study start in May 2009

AmBisome®, a liposomal formulation of amphotericin B manufactured by Gilead, has been used with increasing frequency to treat VL, especially in Europe, over the past decade. Unfortunately, in Africa and Asia, where disease burden is high, drug access is poor because of the high cost of the drug. With recent preferential pricing offered by the manufacturer to patients in the public sector in East Africa, it is possible that AmBisome® could become economically feasible for treatment, even in resource-poor countries.

The goal of this project, therefore, is to determine the minimum dose of AmBisome® that is efficacious, safe, and cost effective in the treatment of VL in Africa, to reduce the length of hospital stay, and to facilitate registration and adoption of AmBisome® in the region. Identifying the minimum dose for monotherapy will be an important step in developing combinations for Africa and in preventing the development of drug resistance. Early in 2009, DND*i* has received approval from both the national ethics committees and from the Ethiopian regulatory authority. The study began enrolling patients in May 2009.

LEAP, who coordinates and runs both of these studies, has been recognised as "Partnership of the Year in 2008"

R&D Portfolio
BY DISEASE

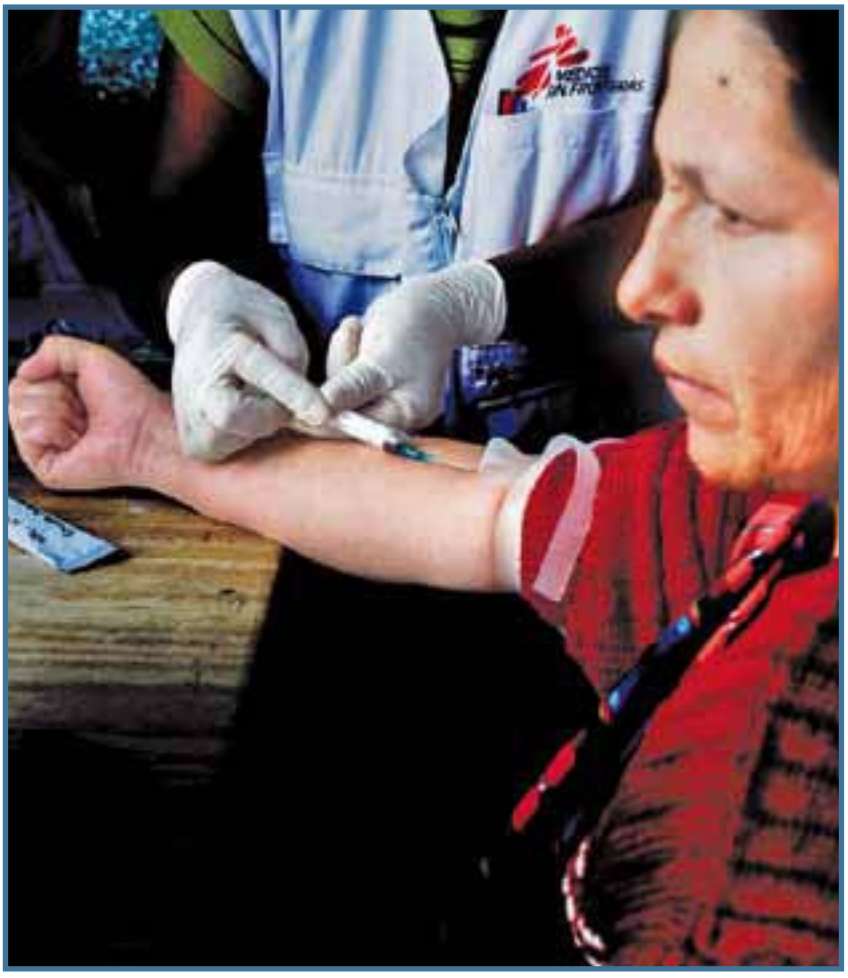
Making inroads on treatments for Chagas disease, from a paediatric formulation to combination therapies

Chagas Disease

Until recently, the primary focus for disease control has been interruption of transmission by vector control programmes and screening of blood donors. Major initiatives began in the Southern Cone countries in 1991 and 1992. Most central and southern American countries joined the initiative over the following decade. Despite these advances in reducing the incidence of *T. cruzi* infection, the burden of Chagas heart disease is expected to continue in the future since virtually all of the burden of Chagas heart disease comes from individuals already infected who progress from the indeterminate phase to the chronic phase.

Current therapy for Chagas disease is limited to two nitroheterocyclic drugs, nifurtimox and benznidazole. Unfortunately, these drugs are limited to treatment of acute infection in children with conflicting evidence for treatment of indeterminate disease and no evidence to support their use as therapy for symptomatic chronic disease. Even in children, who are more able to tolerate the considerable toxicity associated with treatment, the cure rate is only around 60%. No new anti-*T. cruzi* drugs are in the clinical development pipeline and only one class of drugs, the antifungal triazoles, have demonstrated potential for therapeutic switching to the treatment of Chagas disease.

The Chagas disease-specific portfolio is a balance of objectives. In the short- and mid-term, the aim is for better use of existing treatments through new formulations, therapeutic switching and combination therapy. In the long term, new chemical entities must be developed. Another important element in DND*i*'s strategy in Chagas disease is to address the methodological constraints that impact the design of clinical studies.



PRIORITY TARGET PRODUCT PROFILE FOR CHAGAS

- **A new treatment for adults and children for acute and early chronic disease**
  - Priority is a pediatric formulation
  - Useful against both parasite species in all regions
- **Better safety profile than existing drugs**
  - Ideally requiring little or no monitoring
  - Suitable for immuno-compromised patients
- **Equal or better efficacy profile than existing drugs**
- **Easy-to-use treatment**
  - Ideally less than 30 days
  - Oral
  - Preferably once-a-day treatment, ideally outpatient
- **Affordable**
- **Stable in tropical climate**

AMERICAN TRYPANOSOMIASIS – **Chagas Disease**

100 million people at risk

WHAT IS THE IMPACT OF CHAGAS DISEASE?

Approximately 8 million cases [1]
14,000 deaths [2]
667,000 DALYs [2] [3]

Chronic Chagas disease results in significant disability with great social and economic impact including unemployment and decreased earning ability. **In Brazil alone, losses of over US$ 1.3 billion in wages and industrial productivity** were due to Chagas disease [4].

HOW IS CHAGAS DISEASE TRANSMITTED?

Caused by the kinetoplastid protozoan parasite Trypanosoma cruzi, Chagas disease is **primarily transmitted by large, blood-sucking reduviid insects widely known as "the kissing bugs"** in endemic countries. Other ways of transmission are **blood transfusion, organ transplantation**, as well as congenital and oral transmissions.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments can cure infected patients, but highest efficacy is seen early in infection.

– Benznidazole, nifurtimox to treat acute & early indeterminate disease:
  • Long treatment period (30-60 days)
  • Dose-dependent toxicity
  • High rate of patient non-compliance
  • No paediatric strengths

No treatment for chronic disease.

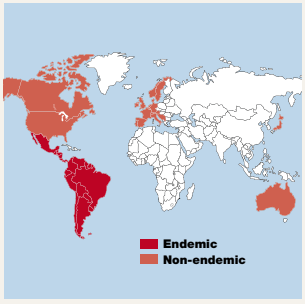
WHAT ARE THE PRIORITY PATIENT TREATMENT NEEDS?

– **A paediatric strength which is affordable, age-adapted, safe, and efficacious** would cure patients early on in the disease.
– **A new drug for chronic disease** that is safe, efficacious, and adapted to the field, and ideally would work in both stages of the disease.

WHERE DOES CHAGAS DISEASE OCCUR?

Endemic in 21 countries **across Latin America, Chagas disease kills more people in the region each year than any other parasite-born disease, including malaria.**

Patient numbers are growing in non-endemic, developed countries, due to increased movement of unknowingly infected people unknowingly carrying the parasite in their blood (see map).



WHAT ARE THE SYMPTOMS/ PRESENTATIONS?

The disease has two clinical stages:

– **acute (in which 5% of children die)** - characterised by fever, malaise, facial oedema, generalised lymphadenopathy, and hepatosplenomegaly - often spontaneously resolves in four to six weeks
– **chronic** disease has two phases:
  – **chronic asymptomatic "indeterminate" disease**, during which patients can transmit the parasite to others while showing no signs of the disease, can last 10 years to life
  – **chronic symptomatic disease develops in 10% to 30% of infected patients** and most often involves the heart or gastrointestinal tract.

Chagas disease is a leading cause of infectious heart disease (cardiomyopathy) worldwide.

WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

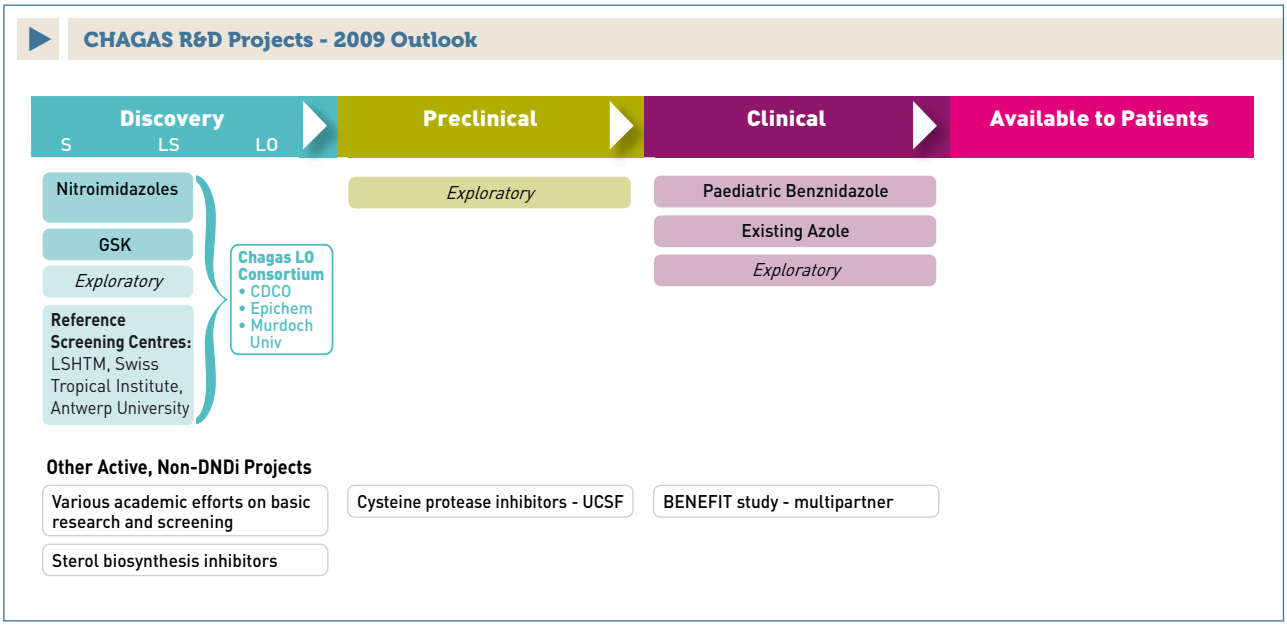
Short term: better use of existing treatments through new formulations
– **Paediatric strength of benznidazole**: first treatment designed specifically for children

Medium term: development of new treatments through therapeutic switching and combination therapy
– **Azoles**: clinical development of a well-known compounds already developed against fungal infections for use as Chagas disease monotherapy and/or in combination with existing drugs

Long term: new drugs, and improved research & treatment capacity across region
– **Nitroimidazoles**: a well-known class of anti-infective compounds
– New drugs developed from promising compounds identified in discovery activities (such as GSK library of pyridones and cysteine protease inhibitors) and progressed through **Chagas lead optimisation consortium.**
– A multi-country, multi-partner Chagas clinical research platform in preparation (see Section 3).

By 2014, DND*i* aims to deliver from its Chagas-specific portfolio:
– 1 new paediatric strength available
– 1 new drug registered
– A robust pipeline

(1) PAHO. http://www.paho.org/English/AD/DPC/CD/psit-nd-poster.htm. Accessed August 18, 2008. **(2)** WHO. The World Health Report. Geneva; 2004. Available from http://www.who.int/whr/2004. Accessed August 12, 2008. **(3)** DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. **(4)** Moncayo A, Ortiz Yanine M. Ann Trop Med Parasitol. 2006;100:1-15.



DISCOVERY

CHAGAS LEAD OPTIMISATION CONSORTIUM

- **Target disease:** Chagas disease
- **Partners:** Centre for Drug Candidate Optimisation (CDCO), Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto, Brazil
- **DNDi project manager and coordinator:** Robert Don, Ivan Scandale
- **Project start:** Project start: July 2008

In 2008, a lead optimisation consortium was set up by DNDi so to engage in a critical, iterative process that helps to optimise the efficacy of a lead compound while minimizing its toxicity. This consortium includes institutions in Australia (Monash and Murdoch Universities and Epichem) and Brazil (Universidade Federal de Ouro Preto) and consists of a group of analytical and medicinal chemists, pharmacologists and parasitologists with rapid turnaround facilities or compound assessment. A full lead optimisation team has been now been put in place to assure the speed of the highly iterative process. Into 2009, five classes of compounds identified in DNDi screening programmemes were further assessed in hit-to-lead studies. Work is ongoing to select a single series for lead optimisation by the end of the year.

CLINICAL

AZOLES

- **Partners:** Federal University of Ouro Preto, Brazil; and companies who will provide compounds of interest
- **DNDi project managers and coordinator:** Robert Don, Isabela Ribeiro, Bethania Blum
- **Project start:** 2007

Patients with Chagas disease often live in rural and remote settings. Chagas disease both afflicts the poor and, like other neglected tropical diseases, "promotes poverty" through its impact on worker productivity, premature disability, and death.

A new generation of antifungal triazoles including posaconazole, voriconazole and ravuconazole show considerable promise as antitrypanosomal agents. The marketed antifungal drug posaconazole (Noxafil®, Schering-Plough), has previously been shown to induce parasitological cure in mice with acute and chronic infections, including benznidazole-resistant strains. It is considered the leading azole candidate for proof-of-concept evaluation. DNDi has been in discussion and negotiation with Schering-Plough since 2006. Two other triazole derivatives, ravuconazole (Eisai) and TAK-187 (Takeda) have shown encouraging in vitro and in vivo results. Both products have completed Phase I testing and are good candidates for further assessment as potential treatments. In 2009, DNDi continues to progress on the goal of advancing either posaconazole or another azole into clinical research on Chagas disease patients, if data and conditions are favorable, and to examine other molecules from the same family as potential drug candidates.

Chagas disease leaves a memorable impression in the areas where the disease is endemic.

Preclinical combination studies with azoles. A main treatment limitation in Chagas disease is the poor tolerability reported with currently available treatments. Side effects of benznidazole and nifurtimox are both time- and dose-dependent. Combination therapy could improve treatment efficacy, reduce dose, treatment duration and toxicity, and could also prevent the potential development of resistance to anti-infective drugs. Azole derivatives have shown synergistic anti-T. cruzi effects, in vitro and in vivo, with benznidazole and other compounds involved in the sterol biosynthesis pathway. Taking these results into consideration, DND, has begun preclinical studies with the objective of reducing the dose and duration of current Chagas treatments by systematically evaluating, in animal models, several azole compounds as monotherapy and in combination with the two existing drugs available for Chagas disease. Preliminary in vivo results demonstrated a clear synergistic effect for both combinations with posaconazole, with reduction of mortality and parasitaemia suppression observed in animals. These data will be confirmed in further studies, and will help to inform future clinical evaluation of the azole class.

PAEDIATRIC BENZNIDAZOLE

Meeting an acute patient need...

By developing and making available the only paediatric formulation for Chagas disease

- **Stage:** clinical
- **Partners:** Pharmaceutical Laboratory of Pernambuco State (LAFEPE), Brazil; Tulane University – Centro Nacional de Diagnostico e Investigacion de Endemo-epidemias (CeNDIE), Ministry of Health, Argentina; University of Liverpool, UK
- **DND*i* project manager and coordinator:** Isabela Ribeiro, Bethania Blum
- **Project start:** June 2008

Since the 1990s, there is consensus for early diagnosis and treatment of children and adolescents in the early indeterminate (chronic) phase of Chagas disease. Young children remain an important target population for treatment despite decreasing vectoral transmission, because congenital infection may remain an important mode of transmission for at least another generation.

This is not reflected in the current treatment options as current drugs are formulated as tablets for adults, not adapted to children weights. Tablet fractionation and extemporaneous formulations are needed to treat most children: these procedures increase the likelihood of improper dosages and raises safety concerns, particularly in the very young and malnourished, reduced efficacy (due to the addition of diluents) and stability concerns.

Benznidazole, one of only two products registered for Chagas disease, can be highly efficacious in children yet no paediatric formulation exists. For the majority of children, the 100-mg tablet must be fractionated (broken into pieces). A number of approaches have been examined to best meet the need of developing a new paediatric formulation which is affordable, age-adapted, and easy to comply with.

With the goal to develop an adapted, dispersible tablet of benznidazole, DND*i* and LAFEPE signed a development deal in July 2008. Since then, the project team has been engaged in pre-formulation and analytical development activities. Using current benzinadozole dose recommendations, dosing practices, and patient age and weight profiles from 10 centers which treat children with *T. cruzi* infections as a guide, the team has determined the most appropriate paediatric tablet formulation, strength and associated dosing regimen. Work is progressing, with batch production and stability testing planned for later in 2009.

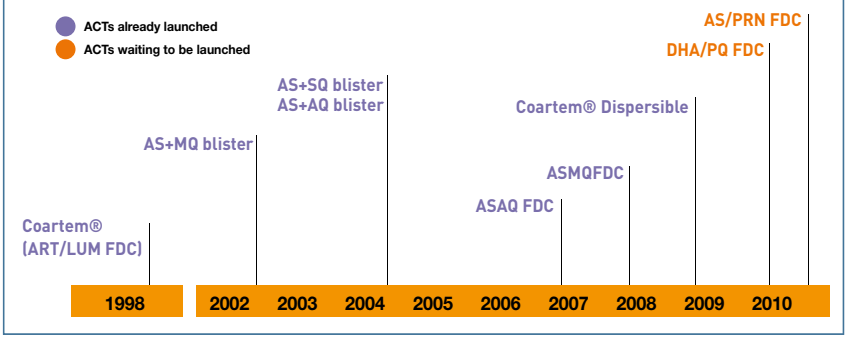
Currently, benznidazole tablets are fractionated by hand into 1/2 and 1/4 tablets (as seen at a health post in Honduras). Fractionation of tablets is not ideal - a paediatric formulation would improve the proper use of benznidazole.

R&D Portfolio
BY DISEASE

Further progress made in fighting an old disease as FACT products gain ground in Africa and Latin America

Malaria

Availability of New ACTs: Recent and Projected Launches



The past year has seen efforts by DND*i* and our industrial partners take further hold in the field of malaria treatment, particularly with the WHO prequalification of ASAQ, its growing use in the public market, and the proactive monitoring plan of ASAQ in "real-life" conditions, which includes the most ambitious proactive pharmacovigilance programme ever launched in Africa, for any drug. Important progress has also been seen with ASMQ as the first purchase was made by Brazilian authorities in April 2009, and plans for technology transfer to Asia and study of its possible use in Africa are afoot.

As we in the world malaria community move forward in meeting the needs of those suffering from malaria, one of the main strategies for malaria prevention and control is prompt and effective treatment. It has been well established that drug combinations are a strategic and viable option in improving efficacy, and in delaying development and selection of resistant parasites (after lessons learned with widespread resistance to chloroquine and SP).

Artemisinin-based combination therapy is nowadays the best therapeutic option for treating drug-resistant malaria and retarding the development or spread of parasite resistance. Since 2001, the WHO has recommended combination therapies containing an artemisinin derivative and, in 2006, strengthened its recommendations to say that fixed-dose combinations (FDCs) should be used wherever possible.

The advantages of using FDCs have been well documented in several disease areas, including malaria, tuberculosis and HIV/AIDS. FDCs offer several potential advantages: increasing patient adherence to treatment, delaying the development of parasite resistance, decreasing total treatment cost (including production, storage, and transport), reducing the risk of me-

In 2009, ASAQ is reaching more and more patients, including at this MSF treatment programme in Guinea.

Malaria

3.2 billion people at risk

WHAT IS THE ANNUAL IMPACT OF MALARIA?

350 to 500 million new cases [1]
Over 1 million deaths [1]
42,280,000 DALYs [2]

Malaria is the leading parasitic cause of morbidity and mortality worldwide, especially in developing countries where it has serious economic and social costs.

Malaria is thought to slow annual economic growth by 1.3% in endemic areas with high prevalence. The economic cost of malaria in Africa alone is estimated at US$12 billion every year [3].

HOW IS MALARIA TRANSMITTED?

Transmitted from person to person **by the bite of anopheline mosquitoes, malaria is caused by the Plasmodium parasite.** Four species are involved: *P. falciparum, P. malariae, P. vivax,* and *P. ovale. P. falciparum* is the main cause of severe clinical malaria and death.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

• **Widespread drug resistance**: chloroquine, one of the easiest to use and most available malaria treatments, is no longer effective, with parasite resistance at more than 90% in some parts of the world (4)

• **Existing combination therapies**, now adopted as first-line treatment in most malaria-endemic countries, can be expensive and have complicated treatment regimens

• **Limited access o**f neglected patients **to the few paediatric strength, fixed-dose ACTs which are available**

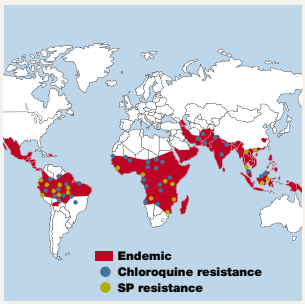
• The countries suffering the most from malaria lack the necessary capacity and funding to deliver the drugs to the patients who need them.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?

Patients in malaria-endemic countries need inexpensive, efficacious, and field-adapted drugs.

WHERE DOES MALARIA OCCUR?

Malaria is present in over 100 countries and threatens half of the world's population. **In sub-Saharan Africa, where it is the single largest cause of death for children under five, malaria kills one child every 30 seconds** – approximately 3,000 children every day.



WHAT ARE THE SYMPTOMS/ PRESENTATIONS?

Malaria begins as a flu-like illness 8 to 30 days after infection. Symptoms include fever (with or without other signs or symptoms such as headache, muscular aches and weakness, vomiting, diarrhea). Typical cycles of fever, shaking chills, and drenching sweats may then develop. Death may be due to brain damage (cerebral malaria), or damage to vital organs.

WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

DND*i*'s malaria-specific portfolio aims to facilitate the widespread availability of the two products delivered by its diverse partners in the Fixed-Dose Artesunate Combination Therapy (FACT) Project.

Because of numerous antimalarial R&D activities (eg. Medecines for Malaria Venture), DND*i* is phasing out its malaria activities to focus on the kinetoplastid diseases.

The FACT Project has produced 2 fixed-dose ACTs which are:

– Easy to use as given in a single daily dose of 1 or 2 tablets for 3 days

– A 2-in-1 fixed-dose combination (FDC) of drugs that ensures both drugs are taken together and in correct proportions

– Age-based dosing to facilitate proper dosing in rural, remote areas

• ASAQ – FDC of artesunate and amodiaquine for treatment of malaria in sub-Saharan Africa; now registered in 24 countries

• ASMQ – FDC of artesunate and mefloquine registered in Brazil in March 2008 and in use by Brazilian national authorities as part of ongoing intervention study

Through 2014, DND*i* will support the proper use to work to facilitate access to of these FACTs along with the other effective ACTs so as to maintain the effectiveness of artemisinin as a first-line treatment.

(1) World Health Organization. Introduction. In: World Malaria Report. Geneva, Switzerland: World Health Organization; 2005. **(2)** DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. **(3)** Global Forum for Health Research. Monitoring Financial Flows for Health Research. Geneva: 2005, p. 59. **(4)** Mayxay M, Nair S, Sudimack D, Imwong M, Tanomsing N, Pongvongsa T, et al. Am J Trop Med Hyg. 77; 2007: 36-43

dication errors by prescribers or patients themselves, and preventing the risk of medication given in combination to be taken only as monotherapy.
Following the recommendations of WHO and independent malaria experts, DND*i* developed fixed-dose combination of ACTs (FDC-ACTs or 'FACT's) as part of its overall R&D efforts begun in 2003.
In building partnerships with industrial partners – sanofi-aventis for ASAQ and Farmanguinhos/Fiocruz for ASMQ - from an initial network of public partners, DND*i* has ensured that these products be developed as non-exclusive public goods and at cost so that the largest potential global health benefit could be attained
As a result of these efforts, new effective, easy-to-use and affordable FDC-ACTs are now available or under development. Through DND*i* and its partners, artesunate-amodiaquine (ASAQ), and artesunate-mefloquine (ASMQ) are now available. In addition, efforts by Medicines for Malaria Venture (MMV), have led to the availability of a paediatric version of artemether-lumefantrine (AL), and the development of dihydroartemisinin-piperaquine (DHA/PQ), which is expected to become available in the second quarter of 2010.

Although the existing armamentarium of FDCs for the treatment of uncomplicated malaria is relatively limited nowadays, there are an increasing number of FDC-ACT manufacturers. With the April 2009 launch of the AMFm, DND*i* joined MSF in its call for the exclusive use of FDC to further incentivise drug makers to enlarge the FDC-ACT pipeline.

ASMQ, FIXED-DOSE ARTESUNATE/MEFLOQUINE COMBINATION THERAPY

A public good developed and supported by public partners crosses continents

- **Stage:** Phase IV post-registration monitoring and access
- **Partners:** Farmanguinhos, Brazil; Epicentre, France; MSF International; Shoklo Malaria Research Unit, Thailand; University Sains Malaysia; Oxford University, UK; TDR; Cipla, India; Catalent, USA; ICMR, India; GVK BIO, India; Tanzania; Quintiles, USA
- **DND*i* project managers and coordinator:** Jean-René Kiechel, Patrice Piola, Gwenaëlle Carn
- **Project start:** January 2002

Among the most studied ACTs is the three-day treatment with artesunate (AS) and mefloquine (MQ), which has shown to be a highly effective therapy against uncomplicated falciparum malaria. Used in the field for 16 years, the combination of AS and MQ has been one of four ACTs recommended by WHO since 2001 as first-line treatment for uncomplicated falciparum malaria.

ASMQ, the new co-formulation of AS and MQ, offers a simple regimen for children and adults that is as easy as 1-2-3: a single daily dose of one or two tablets over three days. This co-formulation was one of two malaria projects undertaken in 2002 by a number of public and private partners coordinated by TDR and MSF (who turned over the project to DND*i* upon its foundation) as part of the FACT (Fixed-Dose, Artesunate-Containing Therapy) Project.

April 2008 marked an important milestone for ASMQ as the first public order was completed by Brazil. DNDi's public industrial partner Farmanguinhos/Fiocruz successfully registered ASMQ in April 2008, and the co-formulation has been used by Brazilian national authorities as part of an intervention study, where preliminary results after one year show a greater than 70% drop in *P. falciparum* malaria cases and an approximate 65% reduction in malaria-related hospital admissions.
The study has now treated over 23,000 patients with ASMQ. Work is ongoing to clean the data set and finalise the results.

In 2009, registration processes for ASMQ in 2 or 3 other countries in Latin America are being navigated; it will be submitted for PAHO prequalification; and Farmanguinhos/Fiocruz will continue its technology transfer to the Indian generics manufacturer, Cipla, in order to facilitate its future availability in Southeast Asia. Further clinical research with partners is in preparation to examine the potential therapeutic value of ASMQ in pregnancy and in Africa. A clinical study in India has recently been completed, with analysis ongoing, and a dossier for registration in India will be submitted by the end of 2009.

ASMQ is the only fixed-dose ACT available with a 3-year shelf life. Optimised for rural and remote settings. An innovative weight- and age-based dosing regimen, of ≥180,000 individuals, This work, as well as preliminary results from the Brazilian intervention study, was presented during the 57th American Society of Tropical Medicine & Hygiene in December 2008 and is available at www.dndi.org

The color-coded and age-based packaging of ASMQ provides clear information that is meant to facilitate proper use in the most remote of settings.

ASAQ, FIXED-DOSE ARTESUNATE/AMODIAQUINE COMBINATION THERAPY

More than 20 million of ASAQ treatments to be delivered for African malaria patients during 2009

- **Stage:** Phase IV post-registration monitoring and access
- **Target disease:** malaria
- **Partners:** sanofi-aventis, France; Medicines for Malaria Venture, Switzerland; National Centre for Research and Development on Malaria, Burkina Faso; University Sains Malaysia; Oxford University, UK; Institute of Research for Development (IRD), Senegal; Mahidol University, Thailand; Ellipse Pharmaceuticals, France; MSF; Epicentre, France; TDR; Catalent, USA; KEMRI, Kenya ; ICMR, India; GVK BIO, India; Quintiles, USA; Cardinal Systems, France; Epicentre, France; MS; Komfo Anokye Teaching Hospital, Ghana
- **DND*i* project managers and coordinator:** Jean-René Kiechel, Gwenaëlle Carn
- **Project start:** January 2002.

ASAQ, the new fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ), was the first drug to be made available by DND*i*. Over 5.3 million treatments were distributed in 2008. Now available in 24 countries in sub-Saharan Africa, with over 20 million treatments to be delivered in 2009, the continuing focus of this post-registration project is to support sanofi-aventis the implementation of ASAQ for the treatment of uncomplicated falciparum malaria after its registration in endemic countries, mainly in sub-Saharan Africa, India, and Indonesia.

ASAQ provides a true innovation in patient treatment by being a tropical-stable bilayer co-formulation, which allows AS and AQ to be taken together and in the correct proportions in a simplified three-day dosing regimen where the most vulnerable population, children under the age of five, take one tablet per day.

To continue their pioneering efforts as the 1st public-private partnership to deliver a needs-adapted antimalarial medicine, sanofi-aventis and DND*i* continue to work to enlarge the partnership by involving national malaria control programs and pharmacovigilance systems, as well as international organizations and agencies.

DND*i*, sanofi-aventis and additional partners, in particular MMV and national malaria control programmes, are implementing a comprehensive "ASAQ Deployment Monitoring Plan" that aims to collect high-quality data on ASAQ effectiveness and safety profile in "the field". This programme includes a series of proactive clinical studies conducted in several countries of sub-Saharan Africa with different levels of disease transmission. Some of the studies are underway while others are still in the design phase.

Key ongoing studies include two post-registration studies being done in collaboration with MSF, Epicentre, and the national malaria control programme in Liberia: 1300 patients have been enrolled in these studies, which will assess the tolerability and efficacy of ASAQ in comparison with artemether-lumefrantine (Coartem™). In Ivory Coast, two clinical studies are being set up in a collaboration between sanofi-aventis, MMV, and DND*i*: these studies will collect relevant 'real-life' efficacy, effectiveness and pharmacovigilance data in over 15,000 patients at a district level.

Ultimately, more than 20,000 patients will be followed as part of this monitoring plan. These results will provide a comprehensive overview of the efficacy and safety of ASAQ in the long run and will also allow innovative pharmacovigilance methods to be developed, suited to the needs and resources of countries in sub-Saharan Africa.

The deployment monitoring plan as well as additional clinical data supporting the use of ASAQ has been presented over the past 6 months at international meetings such as ASTMH and the 3rd Annual East African Health Sciences in March 2009. Highlights of these data and the plan can be found on www.actwithasaq.org.

- **Just published:** ASAQ is found to be efficacious and well-tolerated in pivotal Phase III field study carried out in Burkina Faso children: the study showed 28-Day PCR-corrected parasitological and clinical cure rates were ≥95% in both arms comparing the fixed-dose ASAQ combination with the non-fixed AS+AQ association in 750 children with uncomplicated *P. falciparum* malaria. Sirima SB, et al. *Malar J.* 2009 8(1):48.

- A recent population pharmacokinetic analysis has shown that there is a pharmacological equivalence of ASAQ with the well-established separate products

- Meta-analyses – individual and aggregate – presented at ASTMH and in the process of publication

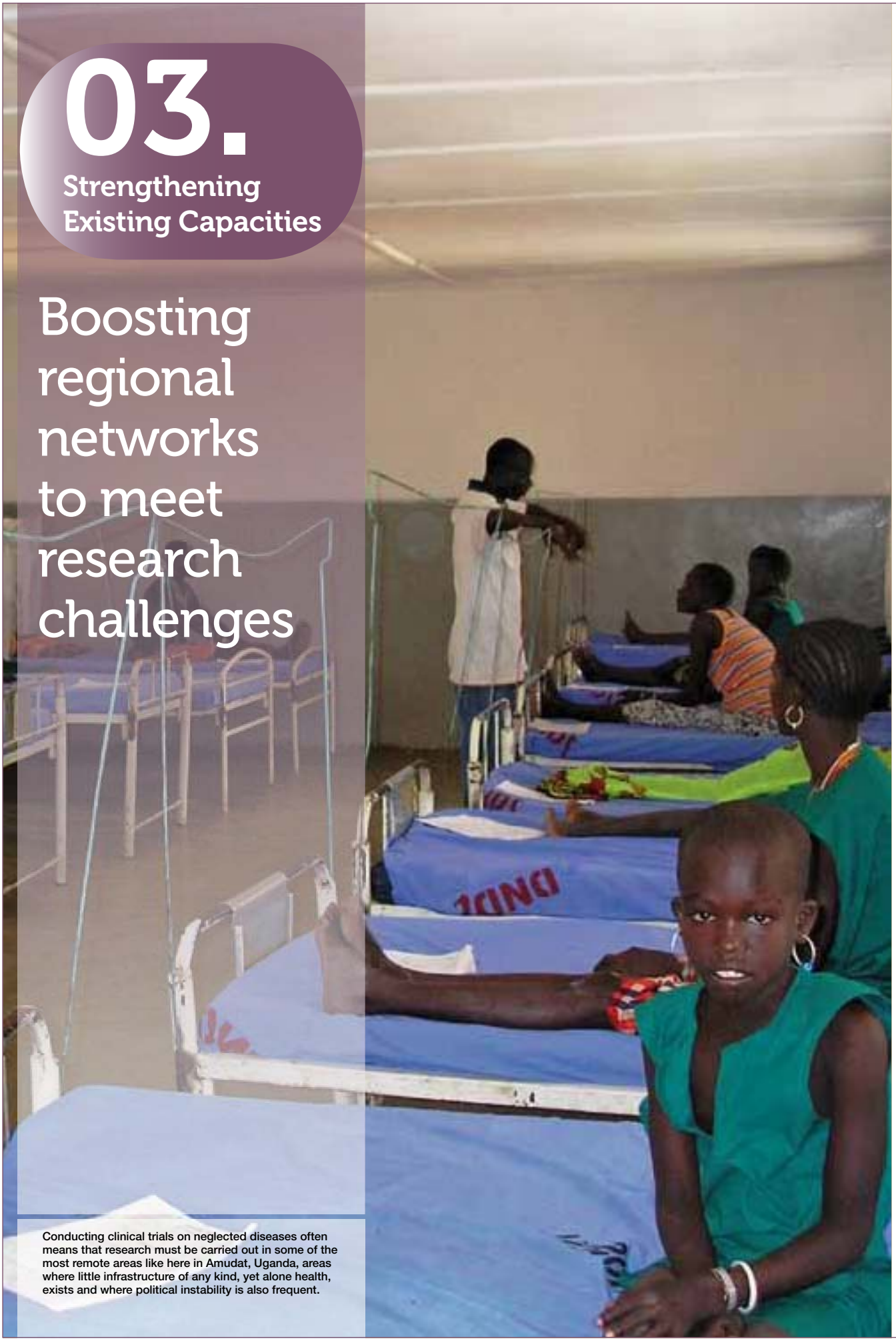
- Results published in Eur J Clin Pharmacol in May 2009 show that ASAQ is well-tolerated and with a comparable pharmacokinetic profile as the separate products

- A multi-center, non-inferiority trial comparing ASAQ with Coartem® (fixed-dose artemether-lumefantrine) in Cameroon, Madagascar, Mali, and Senegal, has shown that ASAQ is as efficacious and well-tolerated as Coartem® in a total of 941 patients including in 112 paediatric patients less than 5 years old. Nadiaye et al. *Malaria J*; 8 (125)

03.

Strengthening Existing Capacities

Boosting regional networks to meet research challenges



Conducting clinical trials on neglected diseases often means that research must be carried out in some of the most remote areas like here in Amudat, Uganda, areas where little infrastructure of any kind, yet alone health, exists and where political instability is also frequent.

As part of its mission and objectives, DND*i* synergises efforts to build sustainable research capacities in disease-endemic countries. The process of strengthening existing capacities, at the individual and institutional level, helps in transferring ownership of the solutions and responsibility to the affected country.

INVESTING IN INFRASTRUCTURE, TRAINING, RESEARCH, AND PARTNERSHIPS

Effective clinical research requires adequate infrastructure, solid partnerships, and leadership of ethical and regulatory authorities to ensure that good clinical practices are observed through the entire process of clinical development. In disease-endemic countries, where many of DND*i* clinical trials are taking place, challenges are huge as most of these trials take place in very remote areas.

■ **Building infrastructure, training, and research capacities in the trial sites**. The physical upgrading of facilities related to clinical research (such as patient wards and diagnostics laboratories) is undertaken by DND*i* at trial sites so as to ensure they are compliant with Good Clinical Practices (GCP) standards.These facilities are not owned by DND*i*. In addition to physical infrastructure, trained staff are needed to carry out GCP-compliant trials. Training is important not just at the start of a trial, but is a continuous process which involves upskilling existing staff and training new members. From external consultants to the experienced trial site staff, the sharing of better practices principles helps to motivate teams working in difficult field conditions. Independent monitors are encouraged to make site visits on a regular basis to ensure that sites are following good clinical and laboratory practices, and standard operating procedures. This monitoring and auditing further educates staff and reinforces the importance of conducting clinical trials to international standards. In 2008-2009, DND*i* constructed clinical trials wards in the Dooka clinical trials site, Sudan, and upgraded wards used for the same purpose in two new trials sites – Kimalel centre, Kenya, and Amudat hospital, Uganda. Moreover, DND*i* has installed solar panels and repaired the incinerator at the Katanda health centre in the Democratic Republic of the Congo (DRC). More than 164 principle investigators, lab technicians, and monitors have received GCP training and 24 people attended the AmBisome trial initiation. DND*i* has also sponsored 16 members of the three platforms to attend different international scientific events. Out of a total of 134 staff involved in the clinical trials and paid by DND*i*, 98 are staff at DND*i* partners, 5.3 are DND*i* core staff, and 30.7 are DND*i* associated staff and consultants.

DND*i* has taken a number of steps to help improve local infrastructure.

■ **Building sustainable partnerships**. In partnership with scientists and academics in endemic regions, the regional research platforms of the human African trypanosomiasis (HAT) Platform and the Leishmaniasis East Africa Platform (LEAP) aim to strengthen clinical research capacity in a coherent manner to facilitate the availability of new medicines developed. The national control programmes of the most endemic countries are essential members of both platforms, and they play a key role in areas where clinical investigations are taking place. In order to leverage the biodiversity potential of the Asian region in drug discovery efforts for neglected diseases, the Pan-Asian Network for Neglected Diseases (PAN4ND) aims to translate the discovery of new bioactive molecules from natural, local resources into drugs effective against neglected diseases by sharing screening technologies between institutions. Acting as transnational support networks, these platforms enable partners to share different experiences, knowledge, and problem-solving techniques.

■ **Building transparent working relations with regulatory authorities and national ethics committees at all levels**. In many of the countries where trials could be conducted, the governing and regulatory authorities at local, regional and national levels play a crucial role in evaluating and approving clinical protocols, ensuring drug availability (by registering drugs and facilitating drug importation, in terms of logistics), and making changes to national treatment guidelines and protocols. National ethics committees also play a critical role.

REGIONAL PLATFORMS

LEAP
Leishmaniasis East Africa Platform

- **2003**: founded in Khartoum
- **4** endemic countries
- **44** members
- More than **1,000 patients enrolled** in clinical trials
- More than **802 patients treated** outside the clinical trials in 2008/09

Dr Ahmed Mudawi Musa of the Institute for Endemic Diseases, and LEAP Chair, Sudan: "As important as the effort to find a new drug or a combination

of drugs to treat VL is, LEAP is addressing other critical issues associated with clinical research for neglected populations: capacity- building with excellent training of African scientists and support staff, and concrete community participation in development and infrastructure strengthening in rural areas. With the help of LEAP and DND*i*, we have facilities that allow us to serve unprivileged and marginalised communities with medicines at village level at the Kassab Hospital and Dookah Centre."

Objectives

- Facilitate clinical testing and registration of new treatments for VL in the region (Ethiopia, Kenya, Sudan and Uganda)
- Evaluate, validate, and register improved options that address regional needs for VL
- Provide capacity strengthening for drug evaluation and clinical studies in the region

The DND*i* Scientific Advisory Committee (SAC) voted LEAP as 'The Best Partnership of the Year 2009': The selection was based on the following three criteria: quality and effectiveness of the partnership; strengthening capacities in disease-endemic countries; and knowledge gained that can lead to therapeutic innovation.

Recognised as "Partnership of the Year in 2008"

Partners

- Center for Clinical Research, Kenya Medical Research Institute, Kenya
- Ministry of Health, Kenya
- Institute of Endemic Diseases at University of Khartoum, Sudan
- Federal Ministry of Health, Sudan
- Addis Ababa University, Ethiopia
- Gondar University, Ethiopia
- Federal Bureau of Health, Ethiopia
- University of Makarere, Uganda
- Ministry of Health, Uganda
- Médecins Sans Frontières
- I+ Solutions
- Institute for OneWorld Health
- London School of Hygiene and Tropical Medicine

Financial support

- International Solidarity, Canton of Geneva, Switzerland
- Ministry of Foreign and European Affairs (MAEE), France
- Region of Tuscany, Italy
- Medicor Foundation, Liechtenstein

In addition, core organisational funding from the following donors has been used by DND*i* to support its research efforts with the HAT Platform:

- Department for International Development (DFID), UK
- Médecins Sans Frontières (MSF)
- Spanish Agency of International Cooperation for Development (AECID), Spain

HAT PLATFORM

- **2003**: Founded in Kinshasa
- **5** endemic countries

"There is limited clinical research activity to assess and/or improve treatments and diagnostics for HAT, in part because patients are usually very spread out, living in remote areas. The national control programmes of the five most affected countries, in collaboration with DND*i*, the Swiss Tropical Institute (STI), and a number of other partners, have established this platform for capacity-building in

clinical trials for HAT. The overall aim is to build and strengthen clinical trial capacities in these endemic countries so that new and promising interventions for this fatal disease can be rapidly and effectively evaluated, registered and made available to the patients," said **Dr Victor Kande, Director of the HAT National Control Programme of the DRC, member of the HAT Platform.**

Objectives

- To strengthen clinical trial capacity for sleeping sickness
- To overcome health system challenges for clinical research
- To share information on HAT research progress
- To improve HAT clinical trial methodologies

Partners

- National HAT control programmes of most affected endemic countries: Democratic Republic of the Congo, Republic of the Congo, Angola, Uganda, and Sudan
- DND*i*, Swiss Tropical Institute (STI)
- Research institutes including Institute of Tropical Medicine in Antwerp (ITMA), Institut National de Recherche Biomédicale (INRB), Centers for Disease Control and Prevention (CDC), Kenya Agricultural Research Institute – Trypanosomiasis Research Centre (KARI-TRC)
- NGOs as MSF, Epicentre
- FIND, WHO
- Regional networks - e.g. Eastern Africa Network for Trypanosomosis (EANETT), Pan-African Bioethics Initiative (PABIN), The African Malaria Network Trust (AMANET)

PAN4ND
Pan Asian Network for neglected diseases

- 2006, founded in Tokyo, Japan

"This network forms part of a long-term research collaboration between DND*i* and the Kitasato Institute, that will make a significant contribution to bringing new treatments to patients suffering from neglected diseases," says **Professor S. Ōmura, President of the Kitasato Institute.**

Objectives

- To link natural products researchers and institutes as a collaborative network
- To incorporate neglected diseases into our drug candidate screening programmes
- To standardise network screening methodologies against parasitic targets and other pathogens

40.3% of new chemical entities (NCEs) approved by the FDA from 1981 to 2002 were natural products or natural-product derivatives.

DND*i* has been acting as a catalyst by supporting the creation and initial steps of the Pan-Asian Screening Network over a three-year period.

Partners

- Central Drug Research Institute (CDRI), India; Eskitis Institute, Australia; Forest Research Institute Malaysia (FRIM); Institut Pasteur Korea (IPK); Kitasato Institute (KI), Japan; Malaysian Institute of Pharmaceuticals and Neutraceuticals (MIPN), Malaysia; Novartis Institute of Tropical Diseases (NITD), Singapore; Shanghai Institute of Materia Medica (SIMM), China.

Financial support

Financial support from the Sasakawa Peace Foundation, DND*i* and MOSTI (Ministry of Science,Technology and Innovation, Malaysia).

• Other private foundations and individual donors who whish to remain anonymous

Achievements

Capacity-building infrastructure

• Building and opening leishmaniasis research and treatment centres in Ethiopia: Arba Minch 2006; Gondar 2008

• Upgrading infrastructure at Amudat Hospital and initiating it as a clinical trial site

• Treatment centre opened in Kimalel, Kenya in January 2009 and treatment centre / laboratory training centre is planned to open in Dooka (late 2009)

• Ongoing improvements to data centre in Nairobi to set up a GCP-compliant data-management system using open source software

Capacity building – training

• Training of clinical monitors, Data and Safety Monitoring Board (DSMB) members, and investigators in good clinical practice (GCP)

• Providing career development training on a case- by-case basis for key members of the LEAP group / trial site teams

• Capacity strengthening of parasite classification research through technology transfer and training

Clinical trials

• Development and conduct of the LEAP 0104 paromomycin multi-centre clinical trial comparing paromomycin, sodium stibogluconate (SSG), and combination of paromomycin and SSG for treatment of VL (expected to be completed in Q4 2009. see page 25)

• Adoption by LEAP of phase II study AMBI 0106 to determine the minimum effective single dose of AmBisome

• Development of phase II clinical trial to assess safety and efficacy of miltefosine alone, AmBisome + miltefosine and AmBisome + SSG

Financial support

• European Union FP6

• Ministry of Foreign and European Affairs (MAEE), France

In addition, core organisational funding from the following donors has been used by DND*i* to support its research efforts with the HAT Platform:

• Department for International Development (DFID), UK

• Médecins Sans Frontières (MSF)

• Spanish Agency of International Cooperation for Development (AECID), Spain

• Other private foundations and individual donors who wish to remain anonymous

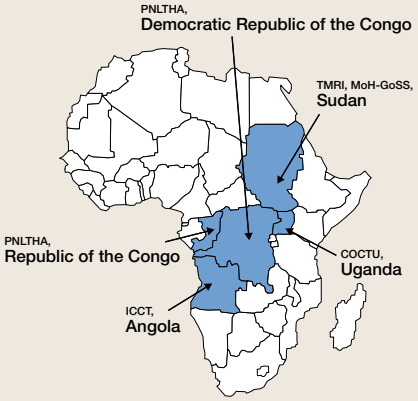
Achievements

• **Training**: Members - training on Good Clinical Practice (GCP) , ethics, and clinical monitoring General practitioners - a programme on how to examine patients with HAT

• **Communications**: four platform newsletters published in English and French; presentations at various scientific congresses

• **Meetings**: launch in August 2005, and annual platform meetings (Nairobi, 2006; Khartoum, 2007; Brazzaville, 2008); seven steering committee meetings held – in conjunction with annual meetings as well as in Basel (June 2007), and Kampala (June 2008).

• **Clinical trials**: Support to the NECT Phase III and to the ongoing NECT-Field Studies

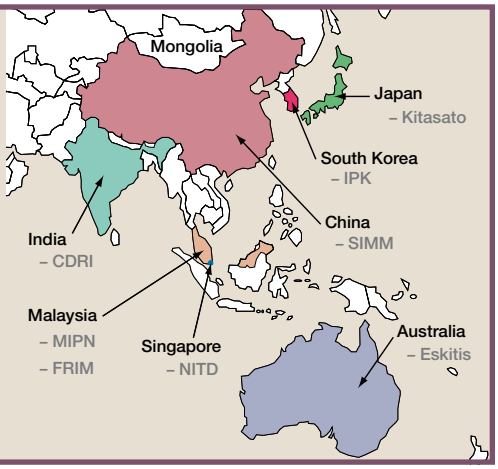


Achievements

• **Training**: Drug screening workshop at CDRI, Lucknow (February 2007); drug metabolism, pharmacokinetics, toxicology workshop at NITD, Singapore (February 2008); and a training programme in Kuala Lumpur December 2008 which covered natural product extraction and purification together with a seminar series on structure elucidation.

• **Strengthening capacities**: three training visits of platform scientists to reference screening centres (Kitasato Institute, Swiss Tropical Institute, University of Antwerp) between June and December 2007

• **Communications**: Development of manual on drug screening for kinetoplastid diseases in collaboration with LSHTM, STI, and CDRI; organisation of five regional scientific events: four annual meetings (Tokyo, May 2006; Shanghai, June 2007; and Tokyo, June 2008; Kuala Lumpur, December 2008) and two natural substances drug discovery and development meetings (Kuala Lumpur, November 2006 and 2007). Development of a website dedicated to PAN4ND: www.pan4nd.org



04.

Advocacy, Communications, & Fundraising

Increasing awareness and mobilising resources for neglected diseases

People are denied access to drugs by a variety of factors, including a lack of tools, a lack of funding, and a lack of healthcare infrastructure.

Product Development Partnerships (PDPs) are proving to be an effective means of delivering innovation to the most neglected.

Of the five new treatments delivered for neglected diseases in the past five years, DND*i* has delivered three. However, governments and global actors need to scale up efforts to foster innovation on a broader scale. A range of alternative market, policy and financing mechanisms must be developed and implemented to stop the suffering of millions of patients. Sustainable funding and strong public support for research and development (R&D) are urgently needed to develop new health tools, including diagnostics and treatments. Recognising the importance of fostering a supportive environment for neglected tropical disease (NTD) research, DND*i* works to raise awareness of critical NTD issues and to mobilise public and private resources to meet the needs of the most neglected patients.

For example, in June 2008, before the G8 Summit in Japan, DND*i* released a statement endorsed by the **World Health Organization (WHO)** urging the G8 governments to support both control programmes and R&D initiatives for NTDs. The Summit Leaders Declaration issued at the close of the conference asserts that the G8 will ramp up commitments to neglected diseases, and includes a specific reference to neglected disease research.

In February 2009, in conjunction with the UN Special Event on Philanthropy and the Global Public Health Agenda [see box], DND*i* and Médecins Sans Frontières called for a scale-up of R&D in the form of increased governmental and private-sector commitments to combat deadly neglected diseases that afflict millions of the world's poorest.

In July 2009, on the occasion of the centenary of the discovery of Chagas disease, DND*i* and its partners will launch a campaign to draw attention to the huge gaps in treatments for Chagas patients. The Chagas Advocacy Campaign, with the theme '**Wake Up. Chagas kills – Time to Treat!**' will bring to light the stark realities surrounding the disease. The burden of Chagas disease is significantly underestimated in official statistics, and few infected patients receive any treatment at all. The only available treatments today are two medicines developed more than 30 years ago with limited efficacy in the chronic phase, toxic side effects, and which are not readily accessible to patients due to complicated supply, procurement and drug registration limitations. New, improved diagnostics and treatments are urgently needed.

These initiatives represent some of DND*i*'s continuous worldwide activities aimed at increasing awareness about most neglected diseases in various forums.

MORE SUSTAINABLE RESOURCES NEEDED

Despite the establishment of PDPs like DND*i* and new commitments from public and private donors, funding for scientific and medical innovation for diseases that disproportionably affect the developing world remains inadequate. The R&D funding gap is particularly severe for the most neglected tropical diseases, which offer virtually no commercial market to product developers. Greater investment, complemented with innovative funding mechanisms and incentives, are needed from both governments and the private sector to ensure that these efforts are sustained and strengthened.

Global neglected disease R&D funding in 2007 totalled US$ 2.5 billion, (including malaria, tuberculosis and HIV/AIDS). Of this amount, only US$ 125 million – less than 5% – was spent on the kinetoplastid diseases (sleeping sickness, leishmaniasis, and Chagas disease), which are the focus of DND*i*'s efforts. DND*i* requires a total of EUR 274 million to achieve its objectives of building a robust pipeline and delivering 6-8 new treatments by 2014. As of April 2009, EUR 110 million

UN SPECIAL EVENT ON PHILANTHROPY AND GLOBAL PUBLIC HEALTH AGENDA

In February 2009, Dr Bernard Pécoul spoke at the UN Special Event on Philanthropy and Global Public Health Agenda, which was attended by more than 400 executives, philanthropy leaders, global health experts, and representatives of UN member states. The main topic was how to strengthen partnerships towards achieving the Millennium Development Goals (MDGs), especially in the areas of neglected tropical diseases and maternal and child health, where progress has been slow.

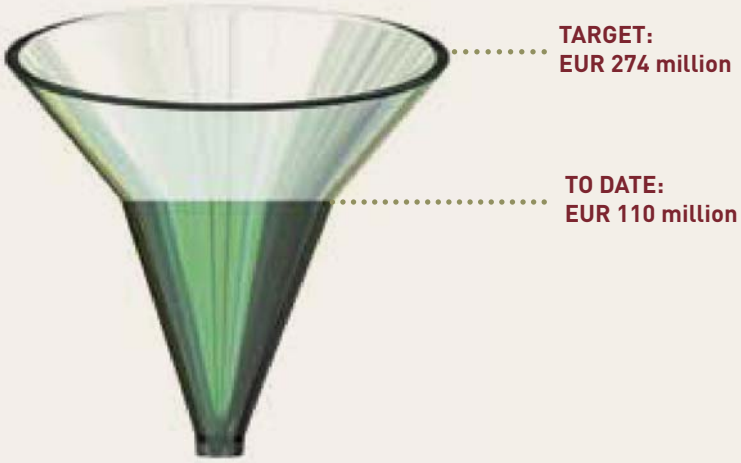
Secretary-General **Ban Ki-moon** made the opening speech, and former U.S. President, **Bill Clinton** offered closing remarks. Both highlighted the heavy burden of neglected tropical diseases on developing nations, and the need for increased commitments from governments, the private sector, academia, and civil society to scale up action against them. Bill Clinton mentioned DND*i* as a contributor to the "staggering amount of progress made in this decade" towards reaching the MDGs, even though he acknowledged that much more work must be done to solve global health problems.

Dr Pécoul also participated in the UN press conference preceding the event, where **DND*i* and Médecins Sans Frontières** called for a scale-up of R&D in the form of increased governmental and private-sector commitments to combat deadly neglected diseases that afflict millions of the world's poorest.

EUR 110 MILLION SECURED

DND*i* seeks to ensure balanced financial support from public and private sectors, allowing the organisation more flexibility and sustainability, while also preserving its independence. Accordingly, to promote responsible management, DND*i* ensures transparency regarding its decision making and use of donors' funds.

Up to April 2009, a total of EUR 110 million had been committed to DND*i* (see Financial Report), which enabled all of its activities to be funded since 2003. However, DND*i* still needs a total of EUR 164 million by 2014 to achieve its business plan objectives.



NEW GRANTS RECEIVED IN 2008/2009

GBP 18 Million from the UK Department for International Development (DFID)

The UK Department for International Development granted DND*i* GBP 18 million over five years in unrestricted initiative funding. This grant builds on the 2005 grant from DFID, which provided the first major government funding to DND*i* over the three-year period 2005 – 2008. The grant covers a broad spectrum of drug research, development, and access activities undertaken by DND*i* and its partners.

EUR 18 Million from Médecins Sans Frontières (MSF)

MSF has committed EUR 18 million over the next six years to DND*i* and continues to provide support through its field programmes to the operational and clinical research needed to advance DND*i*'s drug-development portfolio. As a founding partner, MSF committed EUR 25 million in start-up funding to DND*i* in 2004.

EUR 1 Million from the German Agency for Technical Cooperation (GTZ)

The GTZ, on behalf of the Government of the Federal Republic of Germany, granted DND*i* EUR 1 million to support discovery, lead optimisation and preclinical projects for Chagas disease and HAT.

US$ 200,000 from the Starr International Foundation, Switzerland

The Starr International Foundation granted DND*i* US$ 200,000 of unrestricted initiative funding to be used in 2009. The Foundation supports DND*i*'s mission to develop new drugs for patients suffering from HAT, VL and Chagas disease.

was committed to DND*i* from a diversified group of public and private donors.

ENABLING R&D ENVIRONMENT

Public leadership is needed to implement policy changes that will support development of new, essential health tools, to ensure equitable access for affected populations; and to contribute to the development of innovative, needs-based measures such as intellectual property management policies to encourage needs-driven R&D, technology transfer, an enabling regulatory environment and strengthening of research capacities in developing countries.

VARIOUS ADAPTED "PUSH" AND "PULL" MECHANISMS

Although a comprehensive, sustainable solution to the problem of neglected disease R&D has not yet emerged, governments, experts, and industry have proposed a number of new ideas, including both "push" mechanisms to finance R&D, and "pull" incentives to spur private sector investment.

Some new mechanisms specifically focused on neglected diseases have been launched by donor governments, such as the U.S. FDA's Tropical Disease Priority Review Voucher, and a number of other public and private initiatives have been proposed or initiated, such as prize funds, UNITAID, the Fund for R&D in Neglected Diseases (FRIND), and the Advance Market Commitment for Pneumococcal Vaccines, or patent pools.

PATENT POOLS

In July 2008, UNITAID approved a proposal to establish a patent pool for medicines. The initiative aims to provide patients in low- and middle-income countries with increased access to more appropriate and affordable medicines. Through a collective management structure for medicine patents, **UNITAID seeks to improve access** to patents and foster the development and production of more affordable and more suitable medicines. The initial focus will be in the area of paediatric antiretroviral medicines (ARVs) and

new combinations. The principle is to facilitate the availability of new technologies by making patents and other forms of intellectual property (IP) more readily available to entities other than the patent holder.

In February 2009, GlaxoSmithKline (GSK) announced that it is making its IP available to help bridge the gap in research, development, and access to medicines for treatment of 16 NTDs in the least developed countries. GSK offered to put its patents and processes relevant to NTDs into a pool to allow third party access for the development of new drugs and formulations for NTDs to be used in least developed countries.

DND*i* welcomes these initiatives. Obtaining access to proprietary IP is one of DND*i*'s primary challenges and can take up to two years of negotiations. Accessing proprietary IP through standardised licensing terms incorporated in patent pools could save precious time in delivering new treatments to patients.

At the same time, the WHO has established an expert working group to examine current financing and coordination of R&D, as well as new proposals to stimulate innovation related to Type II (that occur in both rich and poor countries such as HIV/AIDS and tuberculosis) and Type III diseases (those overwhelmingly or exclusively occurring in the developing countries such as sleeping sickness and African river blindness). This group, which will build on **the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property** adopted by the 2008 World Health Assembly, is accepting and evaluating submissions during 2009 and should deliver a plan to the World Health Assembly (WHA) in 2010. While the potential value of some of the new mechanisms for malaria, HIV/AIDS, and TB has been assessed, there has been little analysis of their potential impact on neglected disease research. To help inform the debate, DND*i* has commissioned a research study to analyse the value of different funding mechanisms and incentives for the most neglected diseases.

DND*i* SUPPORTS CALLS FOR INCREASED U.S. GLOBAL HEALTH R&D COMMITMENT

The U.S. government is one of the largest funders of medical research in the world, yet today a disproportionately small level of funding goes to neglected disease research. Recognising this imbalance, DND*i* has actively supported calls by the Institute of Medicine, Families USA and the Global Health Technologies Coalition (GHTC) for the U.S. government to increase its commitment to R&D for neglected diseases.

The **Institute of Medicine**, in a report entitled 'The U.S. Commitment to Global Health: Recommendations for Public and Private Sectors', calls for the U.S. to make global health a key component of foreign policy, to double global health spending by 2015, and to support neglected disease research and PDPs like DND*i*. Dr Bennett Shapiro, Board member of DND*i*, serves on the **Committee on the U.S. Commitment to Global Health**, which prepared the report.

Families USA's report, 'The World Can't Wait: More Funding Needed for Research on Neglected Infectious Diseases', found that U.S. government spending on neglected infectious disease research totalled only US$ 366 million in 2007, an "inadequate" sum for diseases that affect 1 billion people. Of that, just US$ 8 million was dedicated to drug development for three of the most neglected diseases – Chagas, HAT and VL.

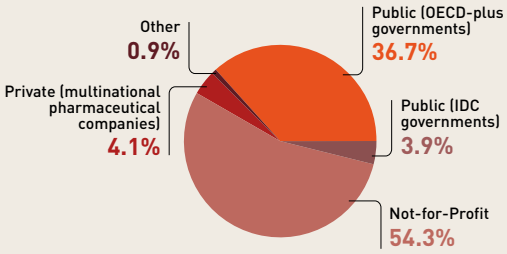
The **Global Health Technologies Coalition**, a coalition of over two dozen nonprofit organizations, including DND*i*, works to accelerate the development and delivery of new health products to prevent HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases. GHTC educates U.S. policymakers about the benefits of new vaccines, microbicides, drugs, and diagnostics to improve health in developing countries, and has made specific funding and policy recommendations to both the Administration and Congress.

As it has from its inception, DND*i* continues to advocate for increased resources to carry out R&D for neglected diseases, and the need for innovative sustainable mechanisms to finance and stimulate it (see box). Moreover, DND*i* is itself an example of a push mechanism that has successfully attracted new public and private funding to this field.

DND*i* is encouraged by the breadth of ongoing discussions and proposals aimed at stimulating innovation and creating sustainable funding for NTD research. These discussions are critical to moving forward. However, concrete action must be taken if we are to bring new treatments to patients who desperately need them.

Kinetoplastids R&D funding by funder type in 2007

Funding for kinetoplastids R&D was predominantly from philanthropic organisations ($67.9 million or 54.3%) and public funders in the West and IDCs (40.6% of funding or $50.9 million), making up 94.9% of total global funding.



Source: G-Finder Report, 2008.

FRIENDS OF DND*i*

In 2007, DND*i* inaugurated "Friends of DND*i*", a group established to recognise select individuals who support DND*i*'s mission and vision by engaging global influencers, policymakers, and donors to help DND*i* succeed in reaching its objectives.

John Bowis: Former member of the European Parliament (EP) for London; Spokesman on the Environment, Health and Food Safety; Author of the report on "Major and Neglected Diseases in Developing Countries" adopted by the EP (2005).

Yves Champey: Former Chair of Genethon Laboratory (France); former Chair of DND*i*'s Board of Directors (2003-2007); former Senior Vice President, International Drug Development, at Rhone Poulenc (1995-1997).

Nirmal K. Ganguly: Former Director General of the Indian Council of Medical Research (ICMR), Founding Partner of DND*i*.

Stephen Lewis: Chair of the Board of the Stephen Lewis Foundation (Canada); former Minister of Foreign Affairs in Canada; former member of the United Nations Special Envoy for HIV/AIDS in Africa.

Morten Rostrup: Physician in the Department of Acute Medicine at Ullevaal University Hospital in Oslo, Norway; former International President of Médecins Sans Frontières (2001-2004); former DND*i* Board member (2003-2005).

Dyann Wirth: Chair of the Department of Immunology and Infectious Diseases, Harvard School of Public Health; former Chair of DND*i*'s Scientific Advisory Committee (2003-2007).

Yongyuth Yuthavong: Former Minister of Science and Technology of Thailand; former member of DND*i*'s Scientific Advisory Committee (2003-2006).

INCREASING AWARENESS

SCIENTIFIC PUBLICATIONS IN 2008 BY TEAM AND PARTNERS

'Drug discovery for neglected diseases: View of a public-private partnership' Chatelain E, Don R. In: 'Antiparasitic and antibacterial drug discovery. To molecular targets to drug candidates', Selzer PM (Ed.).Weinheim, Germany: Wiley-Blacwell; 2009; 33-43.

'Dosing accuracy of artesunate and amodiaquine as treatment for falciparum malaria in Casamance, Senegal'. Brasseur P, Agnamey P, Gaye O, et al. Trop Med Int Health. 2009; 14: 79-87.

'Validation of high performance liquid chromatography-electrochemical detection methods with simultaneous extraction procedure for the determination of artesunate, dihydroartemisinin, amodiaquine and desethylamodiaquine in human plasma for application in clinical pharmacological studies of artesunate-amodiaquine drug combination'. Lai CS, Nair NK, Muniandy A, Mansor SM, Olliaro PL, Navaratnam. V. J Chromatogr B Analyt Technol Biomed Life Sci. 2009; 877: 558-562.

'The efficacy and safety of a new fixed-dose combination of amodiaquine and artesunate in young African children with acute uncomplicated Plasmodium falciparum'. Sirima SB, Tiono AB, Gansane A, et al. Malar Journal. 2009; 8: 48.

'Natural products for neglected diseases: a review'. Ioset JR. Current Organic Chemistry. 2008; 12: 643-666

'New lycorine-type alkaloid from Lycoris traubii and evaluation of antitrypanosomal and antimalarial activities of lycorine derivatives'. Toriizuka Y, Kinoshita E, Kogure N, Kitajima M,

VARIOUS TOOLS, EVENTS AND PUBLICATIONS HAVE BEEN DEVELOPED TO RAISE AWARENESS ABOUT KINETOPLASTID DISEASES AND DND*i*'S ACTIVITIES. SOME EXAMPLES OF WORLDWIDE MEDIA COVERAGE:

- **The Lancet Infectious Diseases, 'Ongoing neglect of leishmaniasis'**, May 15, 2009
- **The Guardian, 'New treatments rise hope of cutting sleeping sickness deaths'**, May 15, 2009
- **Journal of the American Medical Association, 'Attention sought for neglected diseases'**, May 5, 2009
- **Voice of America, In focus, 'Malaria Day'**, April 23, 2009
- **British Medical Journal, 'Patent pools: an idea whose time has come'**, April 20, 2009
- **Chemical & Engineering News, 'Paying attention to neglected diseases. The Drugs for Neglected Diseases initiative is mobilizing public/private partnerships'**, April 20, 2009
- **Radio France Internationale, Priorité Santé, 'L'OMS et DND*i* parlent des maladies négligées'**, April 13, 2009
- **Europa Press, 'Una de cada cuatro enfermedades en el mundo tiene como origen el descuido del medio ambiente, según la OMS'**, March 27, 2009
- **Global Post, 'When two drugs are less deadly than one'**, February 24, 2009
- **PharmaTimes, 'R&D for neglected diseases needs political leadership'**, March 4, 2009
- **Nature, 'Neglected Disease Boost'**, February 11, 2009
- **Agence Congolaise de Presse, 'NECT: Une amélioration thérapeutique contre la maladie du sommeil'**, February 5, 2009

- **Le Monde, 'Bernard Pécoul à la recherche de traitements contre les maladies négligées'**, December 25, 2008
- **Science NOW, 'A 1-2 Punch against sleeping sickness'**, December 5, 2008
- **The Parliament, 'Sending out the message'**, November 10, 2008
- **SCRIP, 'DND*i* invests EUR 8.5 million in neglected disease R&D'**, October 21, 2008
- **BioTechnologyNews.net, 'US$3M for Murdoch and EpiChem's neglected disease work'**, August 19, 2008
- **Canadian Medical Association Journal, 'G8 attention to neglected diseases research welcomed'**, August 12, 2008
- **El Tiempo, 'Brasil producirá para Latinoamérica versión pediátrica de fármaco contra Chagas'**, July 7, 2008
- **SCRIP, 'G8 urged to address neglected diseases'**, July 1, 2008

Ishiyama A, Otoguro K, et al. Bioorg Med Chem. 2008; 16:10182-9.

'In vitro and in vivo antitrypanosomal activitiy of two microbial metabolites, KS-505a and alazopeptin'. Ishiyama A, Otoguro K, Namatame M, Nishihara A, Furusawa T, Masuma R, et al. J Antibiot. 2008; 61:627-32.

'Acylated pregnane glycosides from Caralluma tuberculata and their antiparasitic activity'. Abdel-Sattar E, Harraz FM, Al-ansari SMA, El-Mekkawy S, Ichinio C, Kiyoara, H, et al. Phyto-chemistry. 2008; 69: 2180-2186.

'Synthesis and biological properties of ten-syuic acids B, C, and E, and investigation of the optical purity of natural tensyuic acid B'. Matsumaru T, Sunazuka T, Hirose T, Ishiyama A, Namatame M, Fukuda T. Tetrahedron. 2008; 64: 7369-7377.

DND*i* SYMPOSIA IN 2008-2009

MEDTROP 2009: XLV Congresso da Sociedade Brasileira de Medicina Tropical
Recife, Brazil, March 8-12, 2009
- DND*i* presented 'Perspectives on New Drugs for Neglected Diseases'

4th World Congress on Leishmaniasis
Lucknow, India, February 3-7, 2009
- DND*i* Symposium : 'Challenges for and Potential in the Early-Stage R&D Pipeline to Develop New Antileishmanial Drugs'
- Session on: 'Improved Treatments for Visceral Leishmaniasis – Status of Ongoing Studies, and Challenges & Opportunities Ahead'

American Society of Tropical Medicine and Hygiene (ASTMH)
New Orleans, USA, December 7-11, 2008
- DND*i* HAT-related Symposium: 'Addressing the R&D Challenges in Making New Drugs Available for Human African Trypanosomiasis: Potential in the Pipeline and Recent Clinical Results'

DND*i* India Public Symposium
New Delhi, India, October 13, 2008
- DND*i* focused on: 'India: Catalyst in Drug Development for Neglected Diseases?'

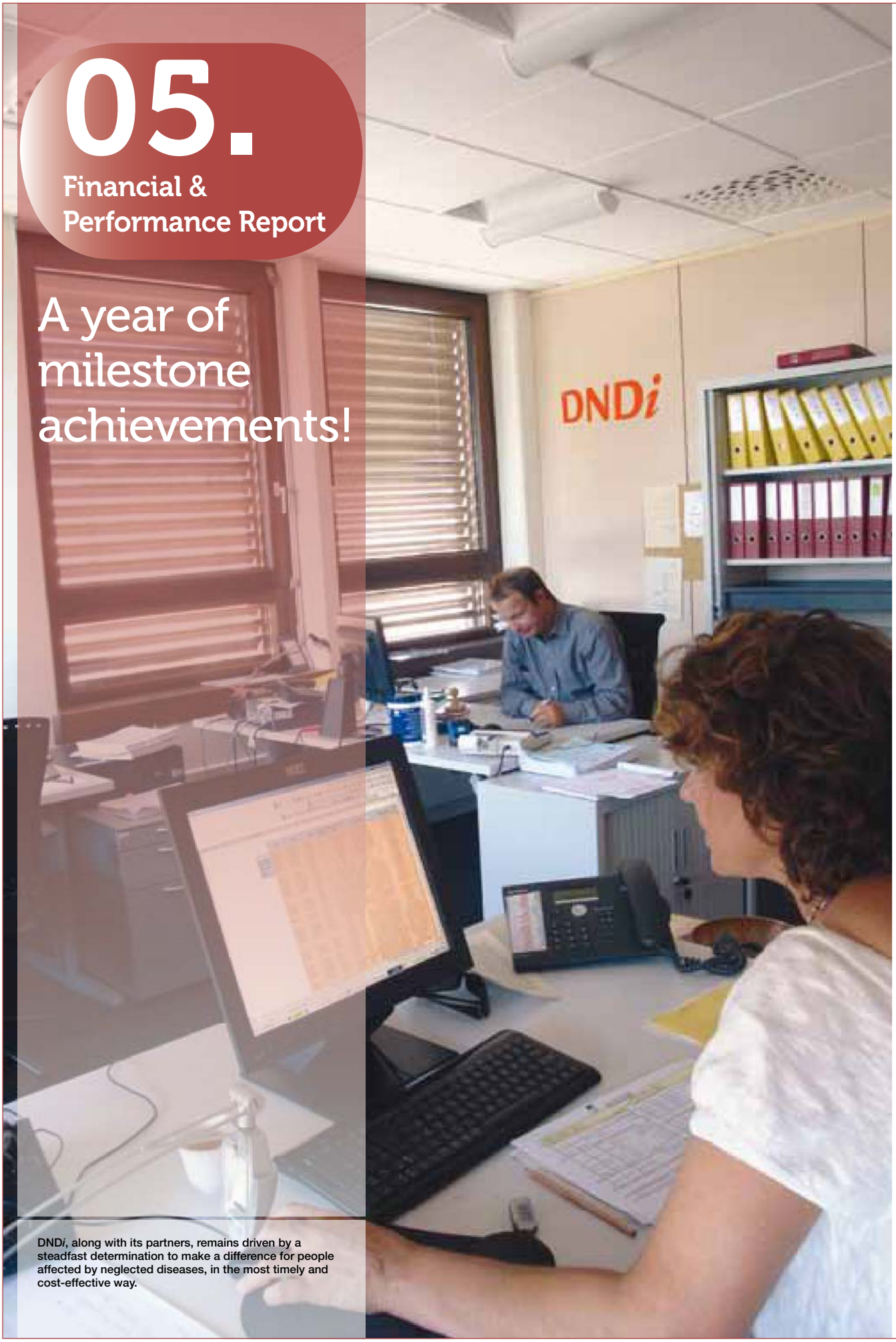
XVIIth International Congress for Tropical Medicine and Malaria - from Bench to Field
Jeju Island, Korea, September 29-October 3, 2008
- DND*i* and sanofi-aventis session: 'Antimalarial medicines: artesunate-amodiaquine and beyond'

13th International Congress on Infectious Diseases (ICID)
Kuala Lumpur, Malaysia, 19-22 June, 2008
- DND*i* Symposium on 'Neglected Diseases Drug R&D'

05.

Financial & Performance Report

A year of milestone achievements!



DND*i*, along with its partners, remains driven by a steadfast determination to make a difference for people affected by neglected diseases, in the most timely and cost-effective way.

PERFORMANCE REPORT

SUMMARY

In 2008, DND*i* delivered a second combination drug for malaria. ASMQ, a new fixed-dosed combination of artesunate and mefloquine was registered and made available for patients in Brazil, through a partnership with a public Brazilian pharmaceutical company.

In addition to delivering a new treatment, DND*i* continued to develop a robust R&D portfolio of potential new treatments for Chagas disease, leishmaniasis, and sleeping sickness, consisting of 20 projects and several exploratory screening activities with the diverse range of DND*i* partners, from the pharma industry, the academic world and organisations involved in the fight against neglected diseases.

DND*i*'s expenditure reflected this dynamism and grew to EUR 17.6 million from EUR 11.8 million in 2007. This growth in expenditure was matched with income growth, as total donations and contributions rose to EUR 20 million in 2008 compared with EUR 15.9 million in 2007. For the fifth year of its existence, DND*i*'s donors demonstrated the confidence they have in the initiative and their support for DND*i*'s strategy to produce new treatments for neglected diseases.

As in previous years, DND*i* was able to increase its unrestricted funds reserve to secure the continuity of its activities and the long-term viability of the organisation. As of December 2008, DND*i* had a total of EUR 9.1 million in net assets (total capital of the organisation). These funds represent five months of DND*i*'s 2009 revised operating budget.

In response to the growth of its activities, DND*i* has continued to develop a team of talented staff and consultants throughout the world. In December 2008, DND*i* had a total of 57.3 full-time equivalent (FTE) staff and consultants - 26.9 FTE working at headquarters and 30.4 in regional offices or with projects, on five continents. This can be compared with 43.4 FTE in December 2007 (22.4 FTE in headquarters and 21 FTE in regional offices and projects).

The Finance, Human Resources and Administration Department is composed of five staff members: a Director, Financial Controller, Accountant, Human Resources Manager and a Travel Assistant/Receptionist. In 2008, an amendment was made to the Swiss Code of Obligations (CO) articles 728a and 728b making it mandatory for large organisations to verify that well-designed, effective internal control systems are being implemented. The reinforcement and formalisation of the Internal Control System has enabled DND*i* to improve its management procedures. Large organisations shall also assess the risks facing their organisation. In this regard, DND*i* has taken steps to upgrade its general risk management procedure. DND*i*'s auditors, Deloitte SA, conducted the organisation's 2008 financial audit in accordance with Swiss Auditing Standards.

DISCLAIMER

- The present financial and performance report is written in accordance with the regulations of the Swiss Generally Accepted Accounting Principles, Swiss GAAP, specifically FER/RPC 21, which is applicable to charitable and social not-for-profit organisations.
- The report provides financial information and some efficiency indicators regarding DNDi's activities in 2008, notably the social mission ratio and the breakdown by stage of development and disease. It also highlights the evolution of public institutional versus private sources of funds and the independence ratio pertaining to the diversity of resources.

STATEMENT OF ACTIVITIES

▶ **STATEMENT OF OPERATIONS** *for the year ended December 31, 2007 (Summary in EUR)*	**2008**	**2007**
INCOME *(in thousand Euros)*		
Public Institutional Funding	9,895	9,563
Private Resources	10,175	6,290
Total Income	**20,071**	**15,852**
EXPENDITURE		
Research & Development	13,649	8,577
Strengthening Capacities	1,111	974
Advocacy	864	658
Fundraising	694	363
General & Administration	1,247	1,251
Total Expenditure	**17,564**	**11,823**
Operating Surplus	2,506	4,029
Other Income (net)	231	83
Net Surplus for the year	**2,737**	**4,113**

RESEARCH & DEVELOPMENT EXPENDITURE

During 2008, DND*i* continued to build a dynamic portfolio for the three diseases: visceral leishmaniasis, human African trypanosomiasis, and Chagas disease. As of December 2008, 20 R&D projects and several exploratory activities were being managed by seven DND*i* Project Managers and four Project Coordinators with total project expenditures of EUR 13.6 million.

In 2008, DND*i* continued its steady growth with an increase of 59% in R&D expenditure compared to the previous year (46% growth increase in 2007).

In March 2008, DND*i* launched its second new treatment in Brazil – **ASMQ** – in collaboration with Farmanguinhos, a Brazilian public pharmaceutical company. ASMQ is the first fixed-dose combination therapy of artesunate (AS) and mefloquine (MQ) for the treatment of malaria in South America and Asia. The 2-in-1 combination of ASMQ ensures that both drugs are taken together in correct proportions (easy to use with one daily administration of 1 or 2 tablets, according to age, over 3 days). As of December 2008, ASMQ is being used by the Brazilian authorities as part of an ongoing intervention study (more than 25, 000 patients treated). In addition, ASMQ is planned to be registered in ten countries in Latin America and Asia. Approximately EUR 0.9 million was spent in 2008, compared to EUR 0.7 million in 2007. The main efforts were dedicated to the production of ASMQ and the transfer of technology between Farmanguinhos and Cipla in India.

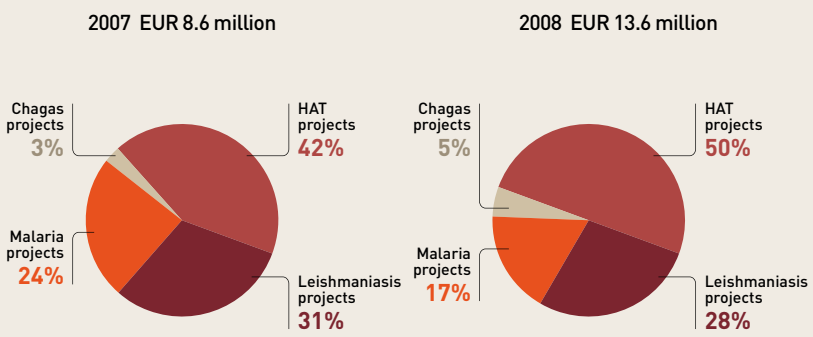
Fixed-dose combination therapy of artesunate (AS) and amodiaquine (**ASAQ**), the first new treatment launched by DND*i* in 2007, is now registered in 24 disease-endemic countries. Produced in a landmark partnership with sanofi-aventis, the new treatment obtained WHO prequalification in October 2008. More than 5.4 million treatments were distributed in 2008. Expenditure remained stable between 2007 (EUR 1 million) and 2008 (EUR 1.1 million). The main effort was focused on post-registration activities including pharmaco vigilance studies, complementary studies in India, and communication with national programmes about ACT (Artesunate Combination Therapy) and ASAQ.

Highlighted below are the projects for human African trypanosomiasis (HAT) which represented the main expenditure increase in 2008: EUR 5.9 million in 2008 as compared to EUR 2.9 million in 2007.

Breakdown by disease

The percentage breakdown of R&D expenditure by disease highlights the continuation of DND*i*'s investment in HAT R&D in 2008. The percentage of Chagas projects increased because the lead optimisation project started at the beginning of 2008. The proportion of malaria projects in terms of total project expenditure, decreased since the project entered the post-registration phase (see above). Leishmaniasis project expenditure remained stable. Most of the expenses concern three ongoing clinical trials.

R&D expenditure by disease



DND*i* KEY ACCOMPLISHMENTS

For HAT

- The multicentre clinical trials in DRC were completed (287 patients) for the Nifurtimox-Eflornithine combination therapy (NECT) - a simpler, less toxic treatment for stage 2 sleeping sickness. The partners that support this project in 2008 are PNLTHA (National Programme in DRC), Epicentre (France) and Swiss Tropical Institute (Switzerland). This combination therapy was added to the WHO Essential Medicines List in April 2009. EUR 0.5 million was spent in 2008.
- In 2008, the lead optimisation consortium for HAT progressed with Scynexis and Pace University, its partners in the USA. Two compounds series have been advanced from early-stage screening to attractive leads. Expenditure in 2008: EUR 3.3 million as compared to EUR 1.3 million in 2007 when the project started (Q4 2007). This is the most significant increase in DND*i* expenditure (about + 250%) for 2008.
- The preclinical studies for the fexinidazole project were successfully finalised in 2008. The project will enter phase I clinical trials in 2009. The main partners are based in Europe and include: Aptuit, Covance and Nerviano. Expenditure reached EUR 1.3 million in 2008 as compared to EUR 0.5 million in 2007.

For VL

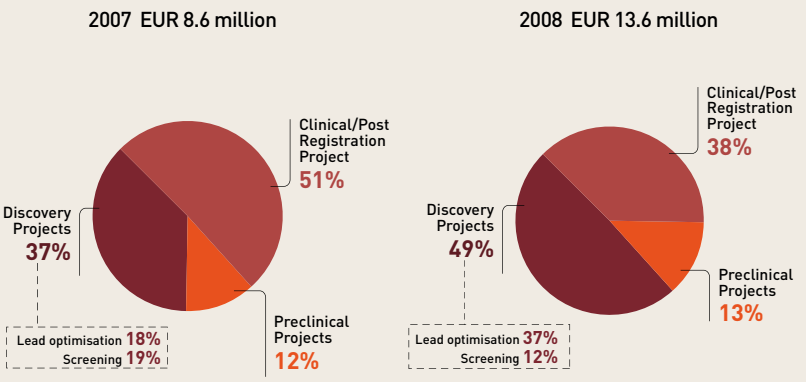
- The budget increased by EUR 1 million in 2008 and reached EUR 3.1 million.
- Three clinical trials are underway to test combinations of existing medicines for less toxic, more affordable shorter-course treatments and to retard the onset of drug resistance. The actual costs for these clinical trials in 2008 reached EUR 1.9 million against EUR 1.5 million in 2007.

1. More than 1,000 patients have been included in the paromomycin multi-

Breakdown by development stage

The total R&D expenditure increased by 59% in 2008 as compared with 21% for other DND*i* activities (Strengthening capacities, Advocacy and General Management). The larger growth occurred with discovery projects (33% in 2008 as compared with 16% in 2007) due to the two VL and HAT lead optimisation projects.

R&D expenditure by development stage



centre trials in Ethiopia, Kenya, Sudan, and Uganda.

2. More than 200 patients were recruited between May and December 2008 for the VL combination trials in India.
3. Preparation for the AmBisome clinical trials has been ongoing in 2008: staff training, protocol approval and drug shipment.

- In addition, the VL lead optimisation consortium identified two promising series of compounds. Key partners for this project are Advinus and Central Drug Research Institute (CDRI) in India. A new agreement was signed in 2008 with Institut de Recherche et Développement (IRD), France. Another agreement was signed with a new partner in 2008 - Anacor (USA). This early-stage project was initiated at the end of 2007 with expenditure of EUR 0.1 million, which grew to EUR 0.9 million in 2008.

For Chagas disease

The budget reached EUR 0.6 million in 2008 against EUR 0.2 million in 2007.

The consortium for Chagas lead optimisation was established in 2008 with three partners: Centre for Drug Candidate Optimisation (CDCO, Australia) Epichem & Murdoch University (Australia) and the Federal University of Ouro Preto (Brazil). The consortium is testing promising drug candidates identified by DND*i* 's global network of discovery research partners. 2008 expenditure equalled EUR 0.4 million. DND*i* established an agreement with the Pharmaceutical Laboratory of Pernambuco (LAFEPE) of Brazil in 2008 to develop the first benznidazole formulation for children. 2008 expenditure equalled EUR 0.2 million.

In 2008, the **discovery stage** was consolidated with nine projects underway to bring new drug candidates to the preclinical stage.

- DND*i* has a global network of partners who specialise in screening chemical libraries: Institut Pasteur Korea, Kitasato Institute Japan, Eskitis and Epichem Australia, CDRI India, and Fiocruz Brazil. Total EUR 1.3 million in 2008.
- Following screening, promising compounds are fed into DND*i*'s three lead optimisation consortia. Total EUR 4.5 million in 2008.
- Potential drug candidates are tested for safety and efficacy in the laboratory in preparation for clinical trials.

In 2008, four projects were in the preclinical stage, for a total EUR 1.1 million. In December 2008, DND*i* had seven projects in clinical development, amounting to EUR 4.7 million.

STRENGTHENING CAPACITIES EXPENDITURE

Strengthening capacities expenses increased to EUR 1,110,724 in 2008 as compared to EUR 1 million in 2007. These expenses integrate the cost of disease platforms for strengthening existing research capacity in Africa for VL and HAT. The main activities included:

- Construction (Dooka clinical trial site in Sudan), and rehabilitation (Kimalel centre in Kenya and Amudat Hospital in Uganda) of wards that are used for clinical trials in East Africa.
- Training of partners' staff to enhance their skills and knowledge: GCP (Good Clinical Practice), ethics, trials monitoring and methodology, and information sharing on recent clinical research development.
- Local representatives and offices to support DND*i*'s field activities (Penang, New Delhi, Nairobi and Rio).

COMMUNICATIONS & ADVOCACY EXPENDITURE

Communications and Advocacy expenses increased by 31% between 2007 (EUR 657,580) and 2008 (EUR 864,009). In 2008, DND*i* Advocacy efforts were focused on: raising awareness of the lack of tools to treat neglected patients; exchange of information; and shared communication. DND*i* facilitated meetings at regional and national level, participated in international congresses and conferences, produced educational material (newsletters, video and websites) regarding the three target diseases and malaria, and published the results of its ongoing clinical studies in peer-reviewed medical journals. A key event in 2008 was the launch of ASMQ on 17-18 April in Rio de Janeiro, Brazil.

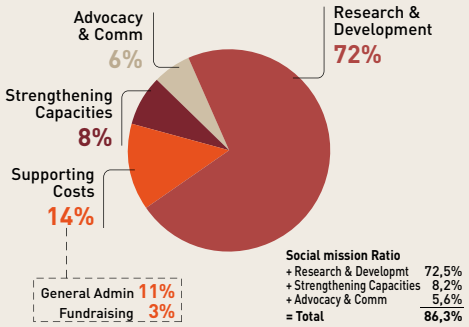
The Communications and Advocacy activities were essential to influence countries and national programmes for the deployment of ASAQ and prepare the ground for the implementation of ASMQ and NECT, as well as to facilitate DND*i* fundraising activities.

Social mission expenditure: 89% for the social mission

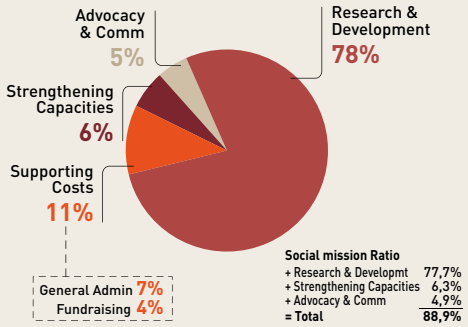
The social mission ratio increased to 89% in 2008 compared to 86% in 2007 and 85% in 2006. Fundraising and General Management expenses, as a percentage of total expenses, thus decreased from 15% 2006 to 14% in 2007 and 11% in 2008.

Social mission ratios

2007 Total expenditure of EUR 11.8 million



2008 Total expenditure of EUR 17.6 million



FUNDRAISING & GENERAL MANAGEMENT EXPENDITURE

Fundraising expenditure increased by 91% in 2008 (EUR 694,486 in 2008 and EUR 363,084 in 2007). This increase is mainly due to the activity of the New York office, which opened at the end of 2007 and was officially launched in 2008. This office is dedicated to private fundraising in North America and complements the fundraising team based in Geneva. In line with the expenditure, the 2008 fundraising objective was to actively pursue private fundraising in North America. DND*i*'s overall fundraising priorities remain the same: securing sustainable and diversified new funds from a mixture of public and private sources and raising unrestricted core funding. Fundraising expenses represent the costs to raise funds: personnel, travel and document production.

General Management & Administration total expenditure remains relatively constant in 2008 (EUR 1,246,694 in 2008 and EUR 1,251,076 in 2007). Expenditures increased slightly due to normal inflation, though total expenses were higher in 2007 due to exceptional costs related to the recruitment of a new R&D Director, the setting up of a new position of Business Development Director and consultant fees related to writing the 2007-2014 Business Plan. General Management and Administration expenses represent costs of managing the organisation: expenses incurred by the Board of Directors, the Executive Director and the Financial and Administration Department.

THE FUTURE

In 2006, DND*i* launched a process to review and update its Business Plan, with the support of Ernst & Young Business Advisory Services, to reflect the significant changes in the landscape of neglected disease research and to incorporate new information gathered during the first years of DND*i*'s operations. The outcome, approved in July 2007 by the Board of Directors, constitutes a benchmark for the development of new treatments by 2014 for visceral leishmaniasis, human African trypanosomiasis, and Chagas disease. The annual budget is projected to grow from EUR 4 million in 2004 to EUR 40 million in 2014. The overall expenditure during this period is projected to be EUR 274 million, with a possible outcome of six to eight new treatments for neglected diseases and the creation of a healthy portfolio of projects throughout the development pipeline. DND*i* will dedicate the majority of funding towards the development of treatments for visceral leishmaniasis (34%), human African trypanosomiasis (35%), and Chagas disease (17%).

Forecasted Social Mission Breakdown DND*i* 2004-2014 *(in million Euros)*

R&D	230	(84%)
Strengthening Capacities	11	(4%)
Advocacy	10	(3%)
Fundraising	10	(4%)
General Management	13	(5%)
Total	**274**	**(100%)**

Projects will be divided into five categories:

1. New drugs developed from novel compounds identified through screening and lead optimisation
2. New drugs from compounds with known antimicrobial/antiparasitic activities (could start at lead optimi-

sation or preclinical development)
3. New indications for existing medicines in the field of the most neglected diseases (therapeutic switching)
4. Reformulations and combinations better adapted to field conditions (paediatric, long acting, new route of administration; fixed-dose combinations, co-packaging, or coadministration)
5. Existing drugs for target diseases (geographical extension of registration to additional geographic areas; completion of regulatory dossiers of existing drug candidates)

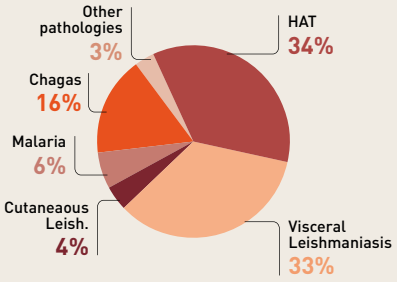
On average, the vast majority of funds will be devoted to R&D (84%), with a secondary programmatic focus on strengthening capacities (4%) and advocacy (3%). This focus shows a clear emphasis on the social mission with 91% of the funds allocated to this area. From a disease perspective, two thirds of overall expenses are devoted to visceral leishmaniasis and human African trypanosomiasis R&D, which shows DND*i*'s commitment to these two diseases.

An update of the Business Plan will be made in 2010.

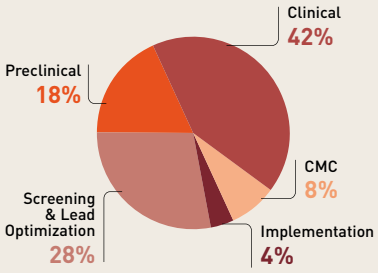
R&D cost apportionment, 2004 – 2014

EUR 230 million (84% of total expenditure)

Expenditures by disease



Expenditures by R&D stage



DIVERSIFICATION OF DONORS

To develop its activities and achieve its objectives, DND*i* seeks diverse funding including: cash donations, in-kind contributions, grants, sponsorships, and legacies – from individuals, governments, public institutions, companies, foundations, NGOs, and other mechanisms. Since its founding, DND*i* has been working to diversify its funding to include a mix of public and private donors and project, portfolio and initiative funding. As a key component of its mission is to stimulate increased involvement and to compel national governments and international organisations to assume their responsibilities in R&D for neglected diseases, DND*i* strives to obtain half of its funding from public sources. DND*i* works to achieve a balance of public and private funding, with total public institutional contributions amounting to EUR 9,895,423 (49%) as compared to EUR 10,175,249 (51%) in private grants in 2008. In addition to its continued funding from the American, British, Dutch, French, and Spanish governments, the Canton of Geneva, Switzerland, and the EU, the German government joined the public funders of DND*i* with a grant of EUR 1 million for 2008-2009. The increase in private funding is a result of the grant from the Bill & Melinda Gates Foundation, awarded in 2007, with funding beginning in 2008.

In 2008, DND*i* launched a major fundraising effort with the opening of DND*i* North America, and also began actively pursuing private funds in the Swiss market where DND*i* is headquartered. The results of these efforts started to bear fruit at the end of 2008 and beginning of 2009 with

DND*i* WOULD LIKE TO THANK THE FOLLOWING DONORS FOR THEIR SUPPORT OF DND*i* ACTIVITIES SINCE JULY 2003

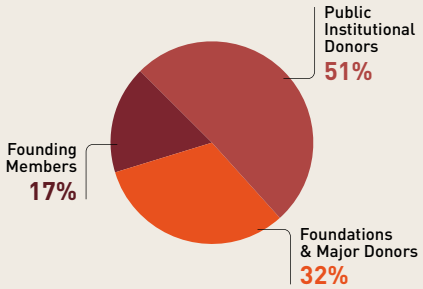
Public Institutional Donors
- Canton of Geneva, Switzerland
- Department for International Development (DFID), United Kingdom
- German Agency for Technical Cooperation (GTZ) on behalf of the Government of the Federal Republic of Germany
- European Union – Framework Partnership 5 and 6
- French Development Agency (AFD), France
- Ministry of Foreign Affairs (DGIS), Netherlands
- Ministry of Foreign and European Affairs (MAEE), France
- National Institutes of Health – National Institute of Allergy and Infectious Diseases (NIAID), USA
- Region of Tuscany, Italy
- Spanish Agency for International Cooperation and Development (AECID), Spain
- Swiss Agency for Development and Cooperation (DDC), Switzerland

Private Donors
- Bill & Melinda Gates Foundation, USA
- Fondation André et Cyprien, Switzerland
- Guy's, King's and St Thomas' Giving Week, UK
- Leopold Bachmann Foundation, Switzerland
- Médecins Sans Frontières
- Medicor Foundation, Liechtenstein
- Fondation Pro Victimis, Switzerland
- Sasakawa Peace Foundation, Japan
- Starr International Foundation, Switzerland
- UBS Optimus Foundation, Switzerland
- Other private foundations and private individual donors who wish to remain anonymous

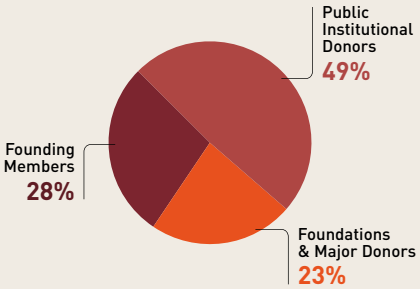
Evolution of public/institutional versus private and founding members funding since 2004 and in 2008, as compared to forecast from the DNDi business plan

Sources of Funds: Public Institutional, Private and Founding Members

Total: EUR 274 million forecast from 2004 to 2014



Total: EUR 20 million in 2008



several new grants awarded for 2009 funding, including grants from Fondation André et Cyprien, Fondation Pro Victimis and the Starr International Foundation, all in Switzerland. From North America, US$ 34,655 was raised from different private donors by the end of 2008.

DND*i* accepts donations of unrestricted initiative funding (core funding) to the organisation, restricted or earmarked support to a project, or a contribution to several projects pertaining to one or multiple diseases. However, to allow for maximum flexibility in decision making needed for the R&D portfolio management strategy, and to allow greater independence in its operations, DND*i* 's priority is to raise unrestricted initiative funding. In cases where this is not possible, DND*i* will pursue project-specific or earmarked funding without requirements which might interfere with the objectives of the project.

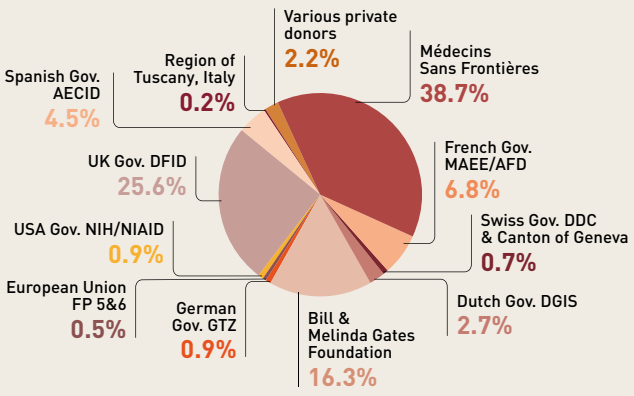
At the end of 2008, the cumulative funding mix of EUR 110 million was 31% restricted and 69% unrestricted grants. This bias toward unrestricted funding is both by design and a result of two new grants awarded at the end of 2008 of unrestricted initiative funding from the UK Department for International Development of GBP 18 million and from Médecins Sans Frontières of EUR 18 million (2009-2014). These significant and multi-year commitments are critical to the success of DND*i* for the next years.

As the financial crisis impacts on private and public budgets and thus, fundraising efforts, we cannot stress enough the importance of commitments such as these to ensure that the advances made towards achieving the Millennium Development Goals and other commitments are not lost. Thanks to all its donors DND*i* is able to deliver new treatments for the most neglected patients.

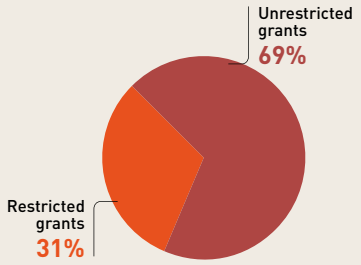
From 2003 to the end of 2008, a total of EUR 110 million was contributed to DNDi

In 2008, DND*i* was pleased to welcome the German Agency for Technical Cooperation (GTZ) on behalf of the Government of the Federal Republic of Germany as a new public donor.

As of April 2009, EUR 110 million has been committed to DND*i* to fund its activities from 2003 - 2014



Restricted versus unrestricted grants committed to DNDi from 2003 – 2014



Statement of activities

FINANCIAL STATEMENTS AND AUDIT REPORT

BALANCE SHEET AT DECEMBER 31, 2008 *(with 2007 comparative figures)*

ASSETS *(expressed in EUR)*	Notes	2008	2007
CURRENT ASSETS:			
Cash and cash equivalent:			
Cash and banks at head office		2,445,817	901,226
Cash and banks at RSOs and affiliate		295,373	87,880
Time deposits		11,722,000	11,053,320
Total cash and cash equivalent		14,463,190	12,042,426
Current accounts and receivables:			
Advances to officers and liaison offices		27,349	79,968
Advances to partners related to projects		505,771	524,959
Receivables from public institutional donors		1,081,410	2,766,989
Receivables from founders		6,746	37,887
Other receivables		132,405	54,492
Prepaid expenses		89,525	115,575
Total current accounts and receivables		1,843,206	3,579,870
Total current assets		**16,306,396**	**15,622,296**
NON-CURRENT ASSETS:			
Tangible fixed assets, net			
Bank guarantee	*3*	150,655	53,379
Total non-current assets		26,175	15,491
Total non-current assets		**176,830**	**68,870**
TOTAL		**16,483,226**	**15,691,166**

LIABILITIES & CAPITAL *(expressed in EUR)*			
Current liabilities			
Bank overdraft		544,153	0
Payables to partners related to projects		77,888	251,962
Accounts payable to founders		0	0
Other payables and accrued expenses		1,462,309	1,018,873
Deferred income		4,968,692	7,840,731
Provisions	*4*	283,104	169,995
Total current liabilities		**7,336,146**	**9,281,562**
Capital of the organisation			
Paid-in capital		32,510	32,510
Internally generated unrestricted funds		9,114,570	6,377,094
Total capital of the organisation		**9,147,080**	**6,409,604**
TOTAL		**16,483,226**	**15,691,166**

Statement of activities

STATEMENT OF OPERATIONS for the year ended December 31, 2008 *(with 2007 comparative figures)*

(expressed in EUR)	*Notes*	2008	2007
Income			
Public institutional funding			
Govern. & public int. organis. unrestricted		6,289,508	5,440,744
Govern. & public int. organis. restricted		3,605,915	4,121,999
Total public institutional funding		**9,895,423**	**9,562,743**
Private resources			
Private foundations, corporations, and individuals, unrestricted		177,694	152,035
Private foundations, corporations, and individuals, restricted		4,466,965	892,735
Total private resources		**4,644,659**	**1,044,770**
Resources from founders			
Médecins Sans Frontières, unrestricted		5,530,590	5,244,800
Total resources from founders		**5,530,590**	**5,244,800**
Total income	*5*	**20,070,672**	**15,852,313**
Social mission expenditure			
Research & development expenditure	*6*		
Research & development coordination and supervision		1,265,594	1,329,644
Human African trypanosomiasis projects		5,934,243	2,907,810
Leishmaniasis projects		3,118,089	2,118,230
Chagas disease projects		577,108	230,382
Other projects		2,057,398	1,744,814
Portofolio building		696,074	246,373
Total research & development expenditure		**13,648,506**	**8,577,253**
Strengthening capacities	*7*	**1,110,724**	**974,041**
Advocacy expenses	*8*	**864,009**	**657,580**
Total social mission expenditure		**15,623,239**	**10,208,874**
Non-social mission expenditure			
Fundraising	*8*	**694,486**	**363,084**
General and administration	*8*	**1,246,694**	**1,251,076**
Total non-social mission expenditure		**1,941,180**	**1,614,160**
Total expenditure		**17,564,420**	**11,823,034**
Operating surplus		2,506,253	4,029,278
Other income (expenses)			
Financial income (expenses), net		373,862	134,338
Exchange loss, net		(199,476)	(72,850)
Other income		56,837	21,895
Total other income, net		**231,223**	**83,383**
Net surplus for the year prior to allocations		2,737,476	4,112,662
Allocation to internally generated unrestricted funds		(2,737,476)	(4,112,662)
Net surplus for the year after allocations		**–**	**–**

DRUGS FOR NEGLEGTED DISEASES *initiative* (DND*i*), GENEVA

▶ FUNDS FLOW STATEMENT for the year ended December 31, 2008 *(with 2007 comparative figures)*

(expressed in EUR)	2008	2007
Funds flow from operations		
Net surplus for the year	2,737,475	4,112,661
Depreciation of fixed assets	90,959	34,768
Increase (decrease) in provisions	113,109	40,147
(Increase) decrease in advances	71,807	50,538
(Increase) decrease in receivables from donors	1,685,578	(1,949,556)
(Increase) decrease in founders and other receivables	(46,772)	230,101
(Increase) decrease in prepaid expenses	26,050	(28,565)
Increase (decrease) in payables to partners related to projects	(174,074)	(87,265)
Increase (decrease) in accounts payable to founders	0	(1,596)
Increase (decrease) in other payables and accrued expenses	987,589	289,858
Increase (decrease) in deferred income	(2,872,039)	7,081,621
Funds flow from operations	**2,619,682**	**9,772,712**
Funds flow from investing activities		
(Increase) decrease of investments in tangible fixed assets	(188,234)	(37,888)
(Increase) decrease in bank guarantee	(10,684)	(795)
Funds flow from investing activities	**(198,918)**	**(38,683)**
Funds flow from financing activities	–	–
Cash increase (decrease)	2,420,765	9,734,029
Cash and cash equivalent - beginning of year	12,042,426	2,308,397
Cash and cash equivalent - end of year	**14,463,190**	**12,042,426**

▶ STATEMENT OF CHANGES IN CAPITAL for the year ended December 31, 2008 *(with 2007 comparative figures)*

(expressed in EUR)

Internally generated funds	Opening balance	Allocation	Internal fund transfers	Closing balance
Paid-in capital	32,510	–	–	32,510
Internally generated unrestricted funds	6,377,094	–	2,737,476	9,114,570
Surplus for the year	–	2,737,476	(2,737,476)	–
Capital of the organisation	**6,409,604**	**2,737,476**	**–**	**9,147,080**

NOTES TO THE FINANCIAL STATEMENT FOR THE YEAR ENDED DECEMBER 31, 2008

1. GENERAL INFORMATION

a) Legal aspects

The Drugs for Neglected Diseases initiative (DND*i*) is a Swiss foundation, established as a not-for-profit legal entity, registered in Geneva under statutes dated July 17, 2003. DND*i* is managed by a Board, an Executive Director, and three senior managers.

With its head office in Geneva, DND*i* aims to:

a) stimulate and support research and development of drugs, as well as vaccines and diagnostics for neglected diseases;

b) seek equitable access and development of new drugs, to encourage the production of known effective drugs, diagnostic methods and/or vaccines for neglected diseases;

c) adapt new treatments for neglected diseases, to meet patients' needs, as well as to meet the requirements of delivery and production capacity in developing countries;

d) raise awareness of the need to research and develop drugs for neglected diseases.

As with all Swiss foundations, DND*i* is monitored by the Swiss Federal Supervisory Board for Foundations.

b) Income tax

DND*i* is exonerated from Swiss federal income tax for an indeterminate period, and from income tax from the Geneva Cantonal tax authorities for a five-year period, commencing 2003, which was renewed in September 2008 for a period of ten years until 2018.

c) Situation of Regional Support Offices (RSO) and Affiliate

DND*i* has five Regional Support Offices and one Affiliate to help identify patients' needs, support Project Managers, identify and support regional partners, seek funding, and undertake regional advocacy work for DND*i*. The RSOs, together with regional networks, ensure the participation of disease-endemic countries and foster South-South collaboration. In addition, RSOs can explore fundraising opportunities in their regions. Their tasks and duties are further developed in the DND*i* Business Plan.

RSOs are usually hosted by a Founding Partner, often at no cost, and are represented by an experienced senior person as the RSO Director bearing a consultant contract with DND*i*. For local or operational reasons, DND*i* may deem it necessary to establish the RSO as a legal entity, usually a branch of the DND*i* Foundation or as a corporation, in accordance with the needs and local regulations and requirements. Establishment of a DND*i* legal entity outside Switzerland requires the authorisation of the Board of Directors.

As of December 2008, DND*i* has established legal entities in Kenya (2006) and in Brazil (2008) in the form of branches for its African and Latin American RSOs. The establishment of a branch in India is still pending. The fourth DND*i* RSO is in Penang, Malaysia and the process to have it registered as a branch in this country is already underway. Additionally DND*i* has two Project Support Offices in Japan, and the Democratic Republic of Congo. RSOs' accounting is fully incorporated into DND*i* accounts.

Affiliate: Drugs for Neglected Diseases *initiative* North America, Inc., a Delaware not-for-profit corporation exempt from U.S. Federal income taxation pursuant to Section 501(c)(3) of the U.S. Internal Revenue Code (DND*i* NA (North America)), was established in February 2007. This affiliate is based in New York City, New York, USA and operates under the Direction of DND*i* NA Board of Directors. The affiliate was formed exclusively for charitable and educational purposes including conducting activities to support or benefit the Drugs for Neglected Diseases *initiative* (DND*i*). It awards grants to support programmes, projects and activities to stimulate and support research and development of drugs for neglected diseases, and raising awareness in the region about the need for increased research and development for neglected diseases.

DND*i* NA presents an annual report comprising the financial statement of the calendar year. This report is certified by an independent Certified Public Accounting (CPA) firm selected by its Board of Directors. The firm auditing DND*i* NA accounts as of 2008, is Tait, Weller & Baker LLP, Philadelphia, Pennsylvania, USA.

Start-up funding is provided via annual grants from DND*i* and is accounted for in the DND*i* financial statements by combining DND*i* NA accounts, following the method of full integration (i.e. all income and expenditures are incorporated into the DND*i* financial statement).

DND*i* NA's 2008 financial position as of December 31, 2008 is the following:

- Total liabilities and net assets: US$ 128,011;
- Total revenue and other support: US$ 530,980, of which a total grant from DND*i* to DND*i* NA, amounting to US$ 496,000 and unrestricted contributions from eight individuals and one student association ranging from US$ 5 to US$ 20,000 for a total of US$ 34,655 plus US$ 1,500 as in-kind services donated ;
- Total expenses: US$ 464,092 including US$ 1,500 as professional consultancy in-kind services, and
- An excess of revenue over expenses (change of net assets) of US$ 68,388.

Lastly, in September 2004, a legal entity was set up in France in the form of a not-for-profit association for administrative purposes.This legal body is not a RSO.

2. SIGNIFICANT ACCOUNTING POLICIES

a) Statement of compliance

The financial statements have been prepared in accordance with Swiss GAAP RPC. They include:

a) Balance sheet,

b) Statement of operations (activity based method),
c) Funds flow statement,
d) Statement of changes in capital,
e) Notes, and
f) Performance report.

These financial statements present all activities of the Foundation. A list of in-kind income and expenditures is disclosed in Note 10.

b) Basis of preparation

The financial statements have been prepared on a historical cost basis. The principal accounting policies are set out below.

c) Social mission expenditure

Social mission expenditures represent expenses made according to the purposes defined in Article 5 of the DND*i* statutes. They are defined in the present general notes under point 1.a Legal aspects. R&D, strengthening existing capacities, and advocacy are the three chapters that comprise "Social mission expenditure."

d) Functional currency

The Board of DND*i* has determined that the assets, liabilities, and operations should be measured using EUR as the functional currency. The environment in which the entity primarily generates and expends cash determines this decision. All amounts presented in the financial statements are stated in EUR, except when otherwise specifically stated.

e) Foreign currency translation

Transactions in currencies other than the entity's measurement and reporting currency (EUR) are converted at the average monthly rate of exchange. Year-end balances in other currencies are converted at the prevailing rates of exchange at the balance sheet date. Resulting exchange differences are recognised in the statement of operations.

The following are the principal rates of exchange used at the end of the year to revalue the balance sheet items to EUR for reporting purposes:

	2008	2007
USD	0.7100	0.6796
CHF	0.6706	0.6034
GBP	1.0259	1.3563
100 CDF	0.1274	0.1207
100 INR	1.4619	1.7257
100 KES	0.9120	1.0740
100 JPY	0.7868	0.6063
100 BRL	30.4247	38.1709

f) Income

Restricted public and private institutional donations based on annual or multi-year agreements are recorded over the life of the agreement, as and when the milestones set out in the agreement are achieved.

Unrestricted public and private institutional donations based on annual or multiyear agreements are recorded on an accruals basis over the life of the agreement.

Other donations are recorded on a cash basis.

g) Funding committed to projects

After Board approval of the annual action plan and budget comprising the approved projects to be funded by DND*i*, one or more contracts are drawn up and signed by two Directors, including the Executive Director or the R&D Director for contracts above EUR 50,000, as detailed in the agreement signature process. Thereafter, funds are allocated to the partner(s) in charge of the project.

Expenditures are recorded:

a) according to a financial report presenting expenditures incurred during the year on an accrual basis; or
b) if financial reports are unavailable as per the deadline of 15 March of the following year, an estimated amount is calculated on a *prorata temporis* basis, based on the time between the contract signing date and 31 December. This estimated amount is considered as an accrued expense following Swiss GAAP RPC to be regularised in the following year. The unpaid portion remaining at year-end is included under current liabilities.

h) Expenditures incurred for projects and activities

The annual action plan and budget are approved by the Board. They include funding for projects subcontracted to partners and current expenditures required to achieve the objectives for the year. A budget revision is approved by the Board at mid-year. All expenditures incurred on behalf of a project or for any activity of DND*i* are recorded on an accrual basis.

i) Credit risk, cash-flow management

DND*i*'s liquid assets are maintained in cash, low-risk, short-term deposits or capital guaranteed investments. At the balance sheet dates, there are no significant concentrations of credit risk. The maximum exposure is primarily represented by the carrying amounts of the financial assets in the balance sheet, including accounts receivable and cash.

j) Tangible fixed assets

Tangible fixed assets are stated at cost less accumulated depreciation. Depreciation is charged to the statement of operations on a straight-line basis over the estimated useful lives of the tangible fixed asset items.

The rates of depreciation used are based on the following estimated useful lives:

Office fittings and equipment	20%
IT equipment	33%

k) Bank guarantee

Guarantees are presented as non-current assets. To date, DND*i* has four guarantees representing three deposits related to office rental in Tokyo, New York and parking space rental in Geneva; and a letter of guarantee pertaining to the Geneva premises. It is recoverable, subject to prevailing contract terms, upon vacating the premises.

l) Provisions

A provision is recognised on the balance sheet when the organisation has a legal

or constructive obligation as a result of a past event, and it is probable that an outflow of economic benefits will be required to settle the obligation.
Provisions are measured at the management's best estimates of the expenditure required to settle that obligation at the balance sheet date.

m) Capital of the organisation

The founding capital (paid-in capital) of EUR 32,510 (CHF 50,000) referenced in the statutes was received from the founding members of DND*i*, including the Indian Council of Medical Research, the Institut Pasteur, the Kenya Medical Research Institute, and the International office of Médecins Sans Frontières. The capital is fully subscribed.

n) Restricted and unrestricted reserves

Restricted and unrestricted reserves represent the excess of income over expenditure since the inception of DND*i*. Restricted reserves are available to DND*i* for future operations and project funding costs as its evolving research and development project pipeline dictates. Unrestricted reserves will be utilised for expenditures of DND*i* as incurred.

o) In-kind donations

Gifts-in-kind are not recorded but disclosed in the notes to the financial statements at fair market values according to the following principles:

- Goods transferred to a DND*i* project or services rendered to DND*i* must be free.
- They must be clearly identifiable and part of DND*i*'s projects and activities as defined by DND*i*'s action plans and budgets.
- Recognisable as a visible contribution to DND*i*'s projects and activities, benefiting DND*i*, and in-line with DND*i*'s mission and objectives.
- Partners' voluntary involvement in joint projects and activities, in particular if the partner does not aim to achieve DND*i*'s project objectives, are not considered as gifts-in-kind.
- For goods or services paid at below market prices, the difference between real payment and current market price is not considered as gifts-in-kind, but the current market price reached after negotiations is.
- Fair market value is defined as the price DND*i* would have paid to utilise the good or service. Fair market value can be suggested by partners. However, DND*i* will be careful not to overestimate such valuations in compliance with Swiss GAAP RPC 3 basic principles of materiality and prudence.
- Gifts-in-kind estimated at EUR 5,000 and above are taken into account. Exceptions can be made by DND*i* when it serves the purpose of providing consistency and completeness of a project's accounts.

3. TANGIBLE FIXED ASSETS, NET

	Computer Equipment	Office fittings & Installations	Office Equipment	Total
Net carrying amounts 1.1.	**21,586**	**19,513**	**12,280**	**53,379**
Gross values of cost				
Beginning of the period 1.1	135,757	44,899	22,366	203,022
Additions	33,543	71,006	83,684	188,233
Disposals	–	–	–	–
End of the period 31.12	169,300	115,905	106,050	391,255
Cumulated amortisation				
Beginning of the period 1.1	(114,172)	(25,385)	(10,085)	(149,642)
Systematic amortisation	(25,771)	(34,390)	(30,796)	(90,958)
End of the period 31.12	(139,943)	(59,775)	(40,881)	(240,600)
Net carrying amounts 31.12	**29,357**	**56,130**	**65,169**	**150,655**

4. PROVISIONS

	Provision for taxes	Provision for HR expenses (holidays not taken)	Provision for running expenses (other)	Total
Carrying amount as per 1.1.2007	**123,779**	**0**	**6,070**	**129,849**
Creation	48,682	54,787	0	103,469
Utilisation	(57,253)	0	(6,070)	(63,323)
Reversal	0	0	0	0
Carrying period as per 31.12.2007	**115,208**	**54,787**	**0**	**169,995**
Carrying period as per 1.1.2008	**115,208**	**54,787**	**0**	**169,995**
Creation	24,405	70,801	69,957	165,163
Utilisation	0	(52,054)	0	(52,054)
Reversal	0	0	0	0
Carrying period as per 31.12.2008	**139,613**	**73,534**	**69,957**	**283,104**

5. INCOME

a) Cumulative donations committed to DND*i* and/or received by 2008 *(in EUR)*

		Total Commitment in currencies*	Total Commitment in EUR	As per Statement of Operations 2008 in EUR	To be used after 2008 in EUR
Médecins Sans Frontières	EUR	42,566,228	42,566,228	5,530,590	17,565,484
UK Government DFID	GBP	24,500,000	28,203,392	3,789,508	17,875,500
Bill & Melinda Gates Foundation	USD	25,729,285	17,906,784	4,203,373	13,703,411
French Government MAEE/ AFD	EUR	7,455,000	7,455,000	1,835,526	2,451,415
Spanish Government AECID	EUR	5,000,000	5,000,000	2,500,000	0
Dutch Government DGIS	EUR	2,975,000	2,975,000	1,000,000	550,000
German Government GTZ	EUR	1,000,000	1,000,000	324,190	675,810
USA Government NIAID	USD	1,375,633	958,954	190,364	621,424
UBS Optimus Foundation	CHF	1,250,000	792,193	166,588	181,062
Medicor Foundation	EUR	650,000	650,000	0	0
Canton of Geneva	CHF	1,000,000	643,860	126,860	134,120
European Union FP5 & FP6	EUR	581,335	581,335	128,975	49,412
Sandoz Family Foundation	CHF	500,000	308,700	0	0
Sasakawa Peace Foundation	EUR	241,350	241,350	97,004	3,896
Tuscany Region	EUR	200,000	200,000	0	0
Various other donor(s)	EUR	170,060	170,060	0	0
Anonymous Donation	CHF	201,229	138,108	138,108	0
Leopold Bachmann Foundation	EUR	91,900	91,900	0	0
Swiss Government DDC	CHF	120,000	77,045	0	0
Various individual donors	EUR	41,997	41,997	39,586	0
TOTAL DONATIONS (EUR)*			**110,001,906**	***20,070,672***	***53,811,534***

*Exchange rates used for "Total Commitment in Euros" and "As per Statement of Operations 2008" are real exchange rates following DND*i* exchange rate policy. Exchange rates used for "To be used after 2008" appear in Euro at the USD/EUR, CHF/EUR and GBP/EUR exchange rates as per 31.12.2008 (see note 2). "Total Donations" yield therefore an approximate value, as exchange will vary over time.

▶ b) Funding per project (restricted and unrestricted) *(in EUR)*

		UK Government DFID* (Unrestricted)	Spanish Government AECID (Unrestricted)	French Government MAEE (Restricted)	Dutch Government DGIS (Restricted)	German Government GTZ (Restricted)	United States Government NIH** (Restricted)
Clinical & Post Clinical	FACT (ASAQ & ASMQ) for Malaria	514,030	485,442		901,648		
	Nifurtimox + Eflornithine for HAT	58,619		467,353			
	Paromomycin for VL	16,572		384,415			
	Ambisome for VL		2,228	137,757			
	Combination therapy for VL	13,444	273,903				
	Clinical Projects for Chagas		202,692				
Preclinical	Amphotericin B polymer for VL	10,965	48,896				159,228
	Buparvaquone for VL	3,386	0	49,338			
	Feixinidazole for HAT	665,888	63,856	300,509		197,573	
Discovery	VL Consortium Lead Optimisation		31,071			13,960	
	Chagas Consortium Lead Optimisation	36,100	313,521			16,813	
	HAT Consortium Lead Optimisation		0				
	Exploratory activities (Dundee, Otsuka,..)	114,238	42,381			403	
	Discovery Projects (Screening, 7 projects)	657,508	75,842	39,115		4,921	
	R&D Coordination, Supervision costs	684,708	435,622		23,091		
	HAT & LEAP Platforms	0	0	276,790			
	Other Strengthening Capacities activities	201,918	273,175	13,242			
	Advocacy	334,787	161,647	144,528	70,833		
	Fundraising	112,892	82,974	22,479		2,057	3,622
	General Management before retreatment	364,453	6,750	0	4,428	88,463	27,514
	Year-end result						
	TOTAL GRANTS ONLY	**3,789,508**	**2,500,000**	**1,835,526**	**1,000,000**	**324,190**	**190,364**

* DFID: the grant considered for 2008 is comprised of 2 grants = 1st grant: 2005-2008 and 2nd grant 2008-2013
** NIH: the grant considered in 2008 covers 2 NIH periods: part of year 1 = January to August 2008 and part of year 2 = September to December 2008
*** MSF donation includes a restricted grant for the "Paramomycin for VL" project of EUR 530,597 and an unrestricted grant of EUR 5,000,000

European Union FP6 HAT (Restricted)	Switzerland Canton of Geneva (Restricted)	Médecins S. Frontières*** (Unrestricted & Restricted)	Bill & Melinda Gates Foundation (Restricted)	UBS Optimus Foundation (Restricted)	Anonymous Grant (Unrestricted)	Sasakawa Peace Foundation (Restricted)	Individual Donors from USA (Unrestricted)	Guy's, King's & St.Thomas giving week (Unrestricted)	TOTAL
		156,278							2,057,398
		13,539							539,511
	126,724	598,377			117,337			16,074	1,259,498
		0							139,985
		169,774							457,121
		0		7,983					210,675
		0							219,089
		0							52,724
		99,760							1,327,586
		69,467	752,588						867,086
		0							366,434
		0	3,310,426						3,310,426
		95,572	496	5,740			23,513		282,343
		361,435	2,595	151,620					1,293,036
		92,820	29,353						1,265,594
115,311	136	63,736							455,973
		79,310				87,106			654,751
		143,302				8,912			864,009
13,664		439,706	17,092						694,486
		641,261	90,823	1,245,	20,771	986			1,246,694
		2,506,253							2,506,253
128,975	**126,860**	**5,530,590**	**4,203,373**	**166,588**	**138,108**	**97,004**	**23,513**	**16,074**	**20,070,672**

6. R&D PROJECTS RELATED EXPENDITURE

Recognised in	2008	2007
Clinical/Post-Registration Projects		
Nifurtimox – Eflornithine coadministration for stage 2 *T.b.gambiense* HAT[1]	539,511	391,583
Paromomycin for V Leish. in East Africa[2]	1,259,498	1,281,593
Artesunate+Amodiaquine for Malaria[3]	1,122,506	1,041,260
Artesunate+Mefloquine for Malaria[3]	934,892	703,554
Imiquimod for Cutaneous Leishmaniasis[4]	832	93,737
Combination therapy for VL[5]	457,121	165,858
Ambisome for VL[6]	139,985	18,770
Clinical projects for Chagas (Ped. Benznidazole, Posaconazole...)[7]	210,675	28,870
Total Clinical/Post-Registration Projects	**4,665,020**	**3,725,225**
Preclinical Projects		
Fexinidazole HAT[8]	1,327,587	526,344
Amphotericin B polymer[9]	219,089	293,856
Buparvaquone VL[10]	52,724	6,880
Total Preclinical Projects	**1,599,400**	**827,080**
Discovery (Selection & Optimisation) Projects		
Cysteine Protease Inhibitors for HAT	0	2,197
Kitasato screening Tryps[11]	180,825	155,482
Nitroimidazoles for HAT[12]	230,081	226,767
Trypanothione reductase inhibitors for Leishmania & Trypanosomes	0	104,182
Microtubule Inhibitor[13]	163,147	189,295
Eskitis Natural Product Screening for HAT[14]	182,666	0
HTS Image Screening / Institut Pasteur Korea[15] (exploratory in 2007)	122,585	0
Screening Assays (STI, LSHTM, Antwerp, Murdoch)[16]	356,832	292,587
Various Discovery (CDRI & Scynexis in 2008)[17]	56,067	122,653
HAT Consortium Lead Optimisation[18]	3,310,426	1,299,743
VL Consortium Lead Optimisation[19]	867,085	56,025
Chagas Consortium (...) Lead Optimisation[20]	366,434	0
Total Discovery Projects	**5,836,148**	**2,448,931**
Other Exploratory Activities to Build the Portfolio		
Other exploratory activities (Dundee, Otsuka, Ouro Preto, FUNDEP...)	282,343	246,373
Total Exploratory Projects	**282,343**	**246,373**
Project-Related Variable Expenditure		
Coordination & Supervision	1,265,594	1,329,644
TOTAL OF PROJECT RELATED EXPENDITURE	**13,648,505**	**8,577,253**

Main partners:

1 Swiss Tropical Institute; Epicentre, France; PNLTHA, Democratic Republic of the Congo; COCTU, Uganda; Médecins Sans Frontières; WHO-TDR; sanofi-aventis, France; Bayer, Germany; Roche, Switzerland

2 Kenya Medical Research Institute, Kenya; Institute of Endemic Diseases, Sudan; Gondar University & University of Addis Abeba, Ethiopia; Makerere University, Uganda; Médecins Sans Frontières; LSHTM, UK; IDA, Netherland

3 University of Bordeaux, Tropival, Epicentre, IRD & Ellipse, France; CNRFP, Burkina Faso; KEMRI, Kenya; ICMR, India; Médecin Sans Frontières; University of Oxford, UK; WHO-TDR University Sains, Malaysia; University Oxford, UK; CIPLA, India; Mahidol University Shoklo Malaria Research Unit in Mae Sot, Thaïland; Catalent, UK; ICMR & GVK, India; Institut FarManguinhos, Brazil; WHO-TDR

4 McGill University, Canada; Universidade Peruana Cayeto Heredia, Peru; 3M Phamaceuticals

5 ICMR & GVK-BIO, India

6 University of Addis Abeba & Gondar University, Ethiopia; Armaur Hansen Research Institut & LSHTM, UK

7 Lafepe & Universidade Federale de Ouro Preto, Brazil; Tulasne University, USA; University of Liverpool, UK

8 Axyntis, France; Swiss Tropical Institute; Nerviano, Italy; Covance & Aptuit, UK; KARI-TRC, Kenya

9 Imperial College London, London School of Pharmacy & LSHTM, UK

10 Advinus, India; University Sains Malaysia; LSHTM, UK; Tetra Q, Australia; Drugabilis, France

11 Kitasato University & Institute, Japan

12 Swiss Tropical Institute; Fiocruz Institute & Ouro Preto University, Brasil; Covance & BioDynamics, UK; Absorption Systems, USA

13 Murdoch University, Monash University & Epichem, Asutralia

14 Eskitis Institut at Griffith University, Australia

15 Institut Pasteur, Korea - France

16 Swiss Tropical Institut; LSHTM, UK; Antwerp Tropical Institut, Belgium; Murdoch University, Australia

17 CDRI, India

18 Scynexis Inc & Pace University, USA

19 Advinus Therapeutics & CDRI, India; LSHTM, UK; Drugabilis, France; Anacor, USA; GSK-Tres Cantos, Spain

20 CDCO Monash University, Epichem & Murdoch University, Australia; University of Washington, USA; University of Ouro Preto, Brazil

7. STRENGTHENING CAPACITIES EXPENDITURE

DND*i* expenditures on strengthening existing capacities in developing countries aim to:

- build networks around specific projects between researchers from developing and developed countries;
- establish working partnerships, including technology transfers, with public and private institutions, and researchers from developing and developed countries; and
- invest in sustainable capacity and leadership in developing countries at all stages of research and development.

	2008	2007
Regional Support Offices: Brazil, India, Kenya, Malaysia	527,087	337,430
Paromomycin for VL, Ward Construction Gondar, Ethiopia & Dooka, Sudan	163,737	157,548
Leishmaniasis East Africa Platform	35,363	163,249
Human African Trypanosomiasis (HAT) Platform	256,873	201,146
Pan-Asian Natural Substances Network	127,663	114,668
TOTAL	**1,110,724**	**974,041**

8. ADVOCACY, FUNDRAISING, AND GENERAL & ADMINISTRATION EXPENSES

	ADVOCACY		FUNDRAISING		GENERAL & ADMINISTRATION*	
	2008	2007	2008	2007	2008	2007
Human resources	370,462	333,670	504,588	274,468	790,591	837,653
Office charges	38,975	13,909	52,146	14,256	71,353	32,857
Travel expenses	52,961	41,660	31,812	23,052	97,291	110,055
Administration	76,350	62,217	43,781	23,946	90,274	145,376
IT & telecommunications	42,496	25,590	28,484	19,454	88,755	63,311
Communication	268,525	173,894	24,479	3,902	65,718	44,427
Depreciation	14,240	5,608	9,197	4,006	24,208	9,133
Exceptional expenses	0	1,032	0	0	18,504	8,264
TOTAL	**864,009**	**657,580**	**694,486**	**363,084**	**1,246,694**	**1,251,076**

*Including Business Development in 2007

9. INDEMNITIES & REMUNERATIONS GIVEN TO DIRECTORS

All members of the Board are volunteers. The Board members did not receive any remuneration for their mandate in 2008, or in 2007.

10. VALUATION OF IN-KIND CONTRIBUTIONS

The Drugs for Neglected Diseases *initiative* (DND*i*), as an independent needs-driven not-for-profit organisation, is developing drugs for people suffering from the most neglected diseases around the world. Its operations and activities are funded through financial donations. In addition to funding, generous partners, companies, and individuals provide DND*i* with goods or services at zero cost, as gifts-in-kind.

▶ Gifts-in-kind evaluated in Euros for the year 2008 per category and per project

	Staff scientific	Staff non-scientific	R&D services	Office, furniture & admin.	TOTAL
FACT	120,000				120,000
Natural Substances	10,031	5,261		750	16,042
Institut Pasteur Korea IPK	145,888				145,888
Kitasato Institut	47,712				47,712
Regional Support Offices	78,431	6,667	13,128	61,447	159,673
General Management		6,000			6,000
TOTAL	**402,062**	**17,928**	**13,128**	**62,197**	**495,315**

Main in-kind contributors: Experts J.-R. Kiechel, France and C. Brünger, Japan; Volunteers for administrative work in Geneva and Tokyo; ICMR, India; KEMRI, Kenya; Sains University, Malaysia; Institut Pasteur, Korea (IPK); Kitasato Institute, Japan.

11. ASSETS PLEDGED AS GUARANTEE FOR COMMITMENTS

At year-end, a bank of the Foundation provided a rental letter of guarantee for CHF 70,000 (EUR 46,942) in favour of a third party. Cash for an equivalent amount is pledged at the corresponding bank.

Deloitte.

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REPORT OF THE STATUTORY AUDITOR

To the Board of
Drugs for Neglected Diseases initiative (DNDi), Geneva

Report on the financial statements

As statutory auditor, we have audited the financial statements of Drugs for Neglected Diseases initiative (DNDi), which comprise the balance sheet, statement of operations, funds flow statement, statement of changes in capital and notes, presented on pages 51 to 62, for the year ended December 31, 2008. In accordance with Swiss GAAP RPC 21, the content of the performance report presented on pages 45 to 50 is not audited.

Board's Responsibility
The Board is responsible for the preparation of the financial statements in accordance with the requirements of Swiss GAAP RPC and the requirements of Swiss law as well as with the charter of foundation and regulations. This responsibility includes designing, implementing and maintaining an internal control system relevant to the preparation of financial statements that are free from material misstatement, whether due to fraud or error. The Board is further responsible for selecting and applying appropriate accounting policies and making accounting estimates that are reasonable in the circumstances.

Auditor's Responsibility
Our responsibility is to express an opinion on these financial statements based on our audit. We conducted our audit in accordance with Swiss law and Swiss Auditing Standards. Those standards require that we plan and perform the audit to obtain reasonable assurance whether the financial statements are free from material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statements. The procedures selected depend on the auditor's judgment, including the assessment of the risks of material misstatement of the financial statements, whether due to fraud or error. In making those risk assessments, the auditor considers the internal control system relevant to the entity's preparation of the financial statements in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control system. An audit also includes evaluating the appropriateness of the accounting policies used and the reasonableness of accounting estimates made, as well as evaluating the overall presentation of the financial statements. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

Opinion
In our opinion, the financial statements for the year ended give a true and fair view of the financial position, the results of operations and the cash flows in accordance with Swiss GAAP RPC and comply with Swiss law as well as with the charter of foundation and regulations.

Deloitte.

Report on Other Legal Requirements

We confirm that we meet the legal requirements on licensing according to the Auditor Oversight Act (AOA) and independence (articles 83b paragraph 3 CC and 728 CO) and that there are no circumstances incompatible with our independence.

In accordance with articles 83b paragraph 3 CC and 728a paragraph 1 item 3 CO and Swiss Auditing Standard 890, we confirm that an internal control system exists, which has been designed for the preparation of financial statements according to the instructions of the Board.

We recommend that the financial statements submitted to you be approved.

DELOITTE SA

Peter Quigley
Licensed audit expert
Auditor in charge

Jurg Gehring
Licensed audit expert

May 26, 2009

Photos credits: All photos are DND*i*'s apart from 5: Médecins Sans Frontières (MSF), Institut Pasteur Korea (IPK); 6: Edmundo Caetano; 14: Eskitis;15: IPK; 21: WHO; MSF; 26: Anna Surinyac (MSF); 28: Anna Surinyac (MSF); 29: C. Zuniga, National Chagas and Leishmaniasis Control Program of Honduras; 30: MSF; 31: James Gathany (CDC); Shoklo Malaria Research Unit (SMRU); 64: Edmundo Caetano; Acre, Amazon, Brazil.

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Best science
for the most neglected

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