

2007-2008 Annual Report



Delivering **Innovation**

Two new treatments
and a strengthened
pipeline highlight
DNDi's efforts into 2008

DNDi

Drugs for Neglected Diseases *initiative*

Main events

2007 2008

DND*i*

Drugs for Neglected Diseases *initiative*



► January 07

The first newsletter of the Human African Trypanosomiasis (HAT) Platform is published to improve communication among platform members. Since 2005, the HAT Platform has been providing training on the treatment of HAT patients and the conduct of clinical trials, including Good Clinical Practices (GCP), to platform members in Angola, the Democratic Republic of Congo (DRC), Republic of Congo, Uganda, and Sudan.



► September 07

DND*i* and the Leishmaniasis East Africa Platform (LEAP) organise a scientific symposium on visceral leishmaniasis (VL): "A step together in the right direction" at the centenary meeting of the Royal Society of Tropical Medicine and Hygiene (RSTMH), in London. More than 120 scientists attend the meeting.



► October 07

The NECT study, which examines the combination of oral nifurtimox plus intravenous eflornithine as a treatment of stage 2 sleeping sickness, shows promising interim safety data. An independent audit confirms the quality and integrity of the data as well as the respecting of patients' rights at an international standard. The final study report (including safety data) should be available by the end of 2008.



► November 07

Sanofi-aventis and DND*i* hold a symposium at 56th American Society of Tropical Medicine and Hygiene (ASTMH), in Philadelphia, about the implementation of a new artemesian combination therapy (ACT) in African endemic countries. Over 120 attendees from NGOs, academia, and the pharmaceutical sector were an audience to FACT project partners presentations on ASAO and ASMO.



► March 08

The Fexinidazole Project finishes preclinical studies for the treatment of sleeping sickness. In June 2008, the project receives approval from DND*i*'s Scientific Advisory Committee to move into clinical studies with the objective to enter first-in-human Phase I trials early in 2009.



► April 08

Farmanguinhos/Fiocruz and DND*i* launch ASMO, the new fixed-dose combination of artesunate (AS) and mefloquine (MQ), now registered in Brazil. Developed and delivered by a worldwide collaboration of public partners, ASMO will soon be available throughout Latin American and Southeast Asia.



► May 08

The World Health Assembly endorses a public health, innovation, and intellectual property strategy to promote new approaches to drug research and development, and improve access to medicines. After 2 years of discussions, it is viewed as a serious step to move forward.



► March 07

Sanofi-aventis and DNDi launch ASAQ, the new fixed-dose combination of artesunate (AS) and amodiaquine (AQ), which is now available in 21 countries throughout sub-Saharan Africa (June 08). ASAQ, the first drug developed by DNDi, is an innovative product to treat malaria that is adapted to the needs of patients of all ages, simple to use, accessible as a non-patented drug, and available at an affordable price.



► April 07

The French Ministry of Foreign and European Affairs (MAEE) provides DNDi a 3-year, EUR 6 million grant to support projects for HAT and VL. Spain's Agency for International Cooperation (AECI) grants core initiative funding of EUR 5 million over 2 years.



► July 07

DNDi welcomes Marcel Tanner as Chair of the Board of Directors, and Julio Urbina as Chair of the Scientific Advisory Committee. They are respectively replacing Yves Champey and Dyann Wirth, both of whom shared their expertise and enthusiasm throughout the first 4 years of DNDi's development.



► December 07

The Bill & Melinda Gates Foundation grants DNDi US\$ 25.7 million to support Lead Optimisation consortia for HAT and VL with Scynexis and Advinus.



► February 08

The 10th Leishmaniasis East Africa Platform (LEAP) meeting takes place in Khartoum, Sudan. A solid clinical trial network is being built, thanks to the serious commitment of all members. Capacity building is still ongoing, with one site in Kenya to be built and another in Uganda to be strengthened. In May 2008, DNDi and its partners inaugurate a new treatment centre in Gondar, Ethiopia, with a 24 bed capacity.



► February 08

Two training workshops of the Pan-Asian Screening Network (PASN) take place in Lucknow (India) for drug screening, and in Singapore for drug metabolism, pharmacokinetics, and toxicology.



► June 08

DNDi's First Stakeholders' meeting in New York brings together 150 scientists, researchers, academics, and global health leaders from 25 countries to discuss how international research partnerships can best develop and deliver new lifesaving drugs for neglected diseases.

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Message from the Chair of the Board and the Executive Director

“Delivering quality, affordable, and adapted treatment is our mission.”



Dr. Bernard Pécoul,
Executive Director



Dr. Marcel Tanner,
Chairman of the Board
of Directors

When a guest speaker ended his presentation with a picture of four children suffering from human African trypanosomiasis and the words, “They are waiting... and we have to work faster!”, there was a stunned silence at DNDi’s Stakeholders’ meeting in New York.

The image reminds us all of a sad reality, that despite an increasing awareness of the lack of tools to treat neglected patients, the speed of treatment delivery is still too slow. How can we respond to this need on behalf of millions and millions of people suffering or dying of diseases which should easily be treated? Here at DNDi, we are driven by the moral and scientific obligation to develop new treatments and to deliver them as soon as possible.

Product development partnerships (PDPs) such as DNDi are becoming increasingly prominent in neglected diseases, a field that had been largely deserted. These not-for profit organisations face an enormous challenge to succeed and respond adequately to these urgent needs.

Undoubtedly, in the past 10 years, the landscape of R&D has changed significantly, with greater attention given to global health and to research and development (R&D) of new drugs for poverty-related neglected diseases. Some novel approaches have emerged to stimulate R&D for needs-adapted

health tools. This new landscape offers fresh and diverse opportunities to succeed, not just by developing new tools; but also by collaborating with partners to deliver the necessary treatments faster.

In just 5 years since we opened our doors, DNDi is now in the process of building one of the most robust portfolios in the field, for some of the most neglected diseases such as visceral leishmaniasis, human African trypanosomiasis, and Chagas disease. Looking ahead, we plan to deliver a new generation of efficient and adapted drugs that will have a significant impact on the lives of affected poor populations. A case in point is one of DNDi’s most promising projects, “Fexinidazole for human African trypanosomiasis”. We are preparing to enter the first-in-human Phase I trials, in early 2009. This follows 3 years of intensive collaboration between experts, researchers, pharmaceutical companies, and biotech from public and private sectors.

Delivering quality, affordable, and adapted treatment is our mission. In 2007 and 2008 DNDi and its public and private partners within the FACT Project successfully launched 2 new fixed-dose, artesunate-based combination therapies (ACTs) for malaria, ASAQ and ASMQ. These new ACTs are easier to use, more affordable than current malaria treatments, and non-patented,

allowing for production of generics. The lessons DNDi has learned from this project, in areas such as pharmaceutical development, technology transfer, and regulatory strategies, will evolve as we move forward and will serve as efficient models of drug development for other diseases.

This success shows 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 sharing an objective driven by needs, not profit.

The launch of these 2 new malaria products was a major breakthrough, showing that PDPs can successfully manage R&D and translate knowledge from the bench to the bedside. Now, as we reach the implementation stage, the challenge is to make these drugs accessible to the patients as fast as possible. This can only be done with the active participation of a wider range of partners who can help ensure that the new medicines reach those most in need, whether they are at a central hospital or a remote community outpost.

This is why collaboration with other partners, particularly with other PDPs, should be enhanced. What we learn in one disease can be used to speed up the development of a treatment for another. Exchange of information,

selection of projects, shared communication, advocacy efforts, and “non-competitive” technology exchange in favour of patients should also frame our strategic plan.

However, just because PDPs can catalyse good science and gain win-win partnerships, they should not be considered as THE solution to solve global health R&D problems.

Some key challenges must be solved: how to ensure patients have better access to new medicines and diagnostics, how to adapt the regulatory environment to the particular needs of endemic countries, how to ensure sustainable funding to support both neglected diseases control programs and R&D initiatives, how to create a more relevant intellectual property management to facilitate access to the existing science, and how to strengthen research capacities in endemic regions. These are some of the daily challenges DNDi continues to confront and to raise at various public health fora, particularly through the WHO Intergovernmental Working Group on Public Health, Innovation, and Intellectual Property (IGWG).

No single institution can solve all these global health problems. Collaboration, innovative thinking and political leadership are needed to address these challenges. In our quest to deliver 6 to 8 treatments for the most neglected diseases by 2014, DNDi will continue to forge new and innovative partnerships. The patients at the other end are waiting!

Many people have generously contributed with their time, experience and guidance towards the success of DNDi in its first 5 years of existence; we would particularly like to thank **Yves Champey**, Chair of DNDi’s Board (2003-2007), **Simon Croft**, DNDi R&D Direc-

tor (2004-2007), and **Dyann Wirth**, Chair of the Scientific Advisory Committee (2003-2007), for their outstanding commitment. They will continue supporting DNDi either through its newly formed “Friends of DNDi”, or actively participating in DNDi’s scientific activities.

“No single institution can solve all these global health problems. Collaboration, innovative thinking, and political leadership are needed to address these challenges.”

As we move forward, DNDi remains dedicated to building strong and talented R&D teams composed of staff, researchers in the field, public and private partners, and donors - all of whom continue to demonstrate their commitment to result-oriented collaborative R&D efforts.

We know the patients are waiting and we know what they need. It is time to build on what we have learned, to be innovative, and to make it happen!

Dr. Bernard Pécoul

Dr. Marcel Tanner



01.

Vision, Mission,
& Objectives

**New and
Improved
Treatments
for the Most
Neglected**



A family in Acre, in the Legal Amazon, Brazil. Acre has been the focus of national malaria health authorities, who have found ASMQ, an antimalarial drug developed by Farmanguinhos/Fiocruz and DNDi, to be field effective in more than 17,000 patients.

Since its outset in 2003, DNDi has built the largest ever portfolio for kinetoplastid diseases. DNDi has also reached a new milestone in its evolution by delivering, in 2007 and 2008 respectively, 2 new treatments against malaria.

In the past months, DNDi has taken key steps towards strengthening and expanding its worldwide partnerships. These partnerships enable DNDi to continue to build its robust portfolio of drug candidates targeting 3 kinetoplastid diseases (human African trypanosomiasis, visceral leishmaniasis, and Chagas disease). DNDi delivered its first products for malaria by launching ASAQ and ASMQ through innovative partnerships with private and public sectors. Both products serve today as models to foster innovation for the most neglected diseases.

Through R&D networks built on South-South and North-South collaborations, DNDi aims to bring medical innovation

to patients by developing:

- New drugs from novel compounds identified through screening and lead optimisation
- New drugs from compounds with known antimicrobial/antiparasitic activities (could start at lead optimisation or pre-clinical development);
- New indications for existing medicines targeting the most neglected diseases (therapeutic switching)
- Reformulations and combinations better adapted to field conditions (paediatric, long-acting, new route of administration, fixed-dose combinations, co-packaging, or co-administration)
- Existing drugs for target diseases (geographical extension of registration



OBJECTIVES

The primary objectives are to:

- Deliver 6 - 8 new treatments by 2014 for leishmaniasis, sleeping sickness, Chagas disease, & 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

to additional geographical areas, completion of regulatory dossiers of existing drug candidates).

FACING CHALLENGES OF DEVELOPING TREATMENTS

Over past 5 years, the R&D landscape has changed significantly, with greater attention and resources given to global health and the development of new drugs for poverty-related neglected diseases. This new landscape offers opportunities to foster innovative and successful partnerships. However, in order to achieve its mission, DNDi has to address five critical challenges.

1. DNDi has to gain access to existing science by establishing win-win partnerships that could help build a strong portfolio. By obtaining access to relevant scientific libraries, capabilities, and knowledge, DNDi seeks to stimulate innovation and translate this knowledge into viable drug candidates.
2. It is also important to translate new knowledge into drugs that can be tested in patients. Through its network of partnerships, DNDi has succeeded in accessing promising drugs or drug candidates; a promising drug ●●●



VISION & MISSION

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 by 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, DNDi will bridge existing R&D gaps in 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.

DNDi's primary focus is the development of new treatments for the most neglected diseases, such as sleeping sickness (human African trypanosomiasis, HAT), kala-azar (visceral leishmaniasis, VL), and Chagas disease; it will also consider engaging R&D projects on other neglected diseases. In pursuing these goals, DNDi 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, DNDi helps to strengthen additional capacity in a sustainable manner through technology transfer in the field of drug R&D for neglected diseases.

●●● candidate yielded from these efforts in 2007 is Fexinidazole for HAT.

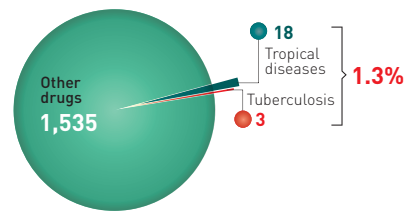
3. Strengthening research capacities through technology sharing, personnel training, and infrastructure upgrading is integral to ensure sustainable innovation in endemic countries. In this respect, DNDi brought together national, regional, and international partners in order to facilitate clinical studies research in the field. The HAT Platform and Leishmaniasis East Africa Platform (LEAP), along with the Fixed-Dose Artesunate-Based Combination Therapies (FACT) Project and the Pan-Asian Network for Neglected Diseases (PAN4ND), are concrete examples of such fora. Furthermore, the clinical research platforms in Africa continuously attract more partners and allow for clinical research to be conducted in extremely difficult rural settings.

4. Innovation is pointless if it does not ultimately reach patients living in remote areas. Delivering products to neglected patients and building conditions to improve access through solid national, regional, and international partnerships remain critical.

5. Increased commitment and sustainable funding from public and private donors are prerequisites to ensure successful outcomes. In order to deliver 6 to 8 new treatments by 2014 and build a robust and well-balanced portfolio for kinetoplastid diseases, DNDi has estimated a total expenditure of EUR 275 million.

> ONLY 21 NEW DRUGS IN 30 YEARS

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. Torrele E., *Lancet*, 2006 May 12, 1560-1561.



DNDi'S PRAGMATIC INTELLECTUAL PROPERTY (IP) POLICY

Contract terms with private and public partners are guided by DNDi's mission to develop safe, effective, and affordable new treatments for patients suffering from neglected diseases, and to ensure equitable access.

These contracts are guided by the following principles:

- The need to ensure that drugs are affordable and access is equitable for patients who need them
- The desire to develop drugs as public goods and at cost when possible
- Primacy of the Needs of Neglected Patients, negotiating the best possible conditions for them
- Pragmatism in decisions over acquisition of patents, ownership, and licensing terms on a case-by-case basis
- Contribution to ensuring access to essential drugs and encouraging further R&D innovation.

BUILDING STRONG PARTNERSHIPS

DNDi operates through a virtual model whereby all of its R&D activities are outsourced, contributing to keep development costs under control, while providing a high level of flexibility. As a consequence of this strategic option, the development of an efficient drug development pro-

gramme to address neglected diseases requires the establishment of strong agreements within the entire biomedical landscape, so as to leverage and mobilise private and public sector resources.

However, owing to the absence of foreseeable profit in the field of neglected diseases, these partnerships have to be built on different grounds,



Women and children waiting at a visceral leishmaniasis treatment centre in Ethiopia.

whereby each party obtains a tangible upside through a well-balanced agreement.

Since 2003, DNDi has demonstrated its capacity to successfully bring together academia, public health institutes, and the biotechnology and pharmaceutical industries. Since 2003, DNDi has managed 250 research, technical, and funding agreements with both public and private partners. In 2007/2008, DNDi has concluded several key agreements with the private sector and academia for the different stages of the R&D process (see Chapter 2). Successful partnership agreements require the management of divergent interests by solving critical issues like licensing rights, confidentiality concerns, intellectual property (IP) management, and/or lack of a visible profit. Defining the field (the diseases), territory (the geographical area), and the market (public vs. private distribution) are important issues that generally must be agreed upon by both parties in order for a private partner to provide DNDi access to a compound or technology.

THE WAY FORWARD

No single state, organisation, company, or community can meet neglected disease challenges alone. Cooperation and coordination are important elements to ensure an effective and rapid response to control these diseases. Partnership, public leadership, and increased private and public awareness are valuable in addressing urgent needs for patients suffering from these diseases. DNDi remains driven by a steadfast determination to make a difference for people affected by these diseases, in the most timely, and cost-effective way.

MAIN PROGRESS INTO 2008

DNDi has achieved a number of milestones since its establishment in 2003.

Malaria

- ASAQ – new fixed-dose combination of artesunate and amodiaquine for treatment of malaria in sub-Saharan Africa; launched in March 2007; registered in 21 countries; produced in partnership with sanofi-aventis; Good Manufacturing Practices (GMP) certification granted; WHO pre-qualification pending
- ASMQ – new fixed-dose combination of artesunate and mefloquine; successfully registered in Brazil in March 2008; produced in partnership with Farmanquinhos/Fiocruz; currently being used by Brazilian national authorities as part of ongoing intervention study (25,000 patients).

Visceral Leishmaniasis (VL)

- Lead Optimisation Partnership – with the aim to progress molecules proven to be safe and active in early-stage screening research, Indian partners implemented activities in 2007
- VL Combination Trial – evaluating use of approved drugs, such as miltefosine, paromomycin, and liposomal, amphotericin B, began patient recruitment in May 2008 in India
- Paromomycin Trial – more than 1,000 patients included in multi-centre trial in East Africa
- Leishmaniasis East Africa Platform (LEAP) - research capacity strengthening in Africa; 5 facilities upgraded in Sudan (2), Ethiopia (2), and Uganda (1), as well as a new site has been identified in Kenya.

Human African Trypanosomiasis (HAT)

- Lead Optimisation Partnership – with the aim to progress molecules proven to be safe and active in early-stage screening research, American partners implemented activities in 2007
- Fexinidazole – finalising preclinical studies; intend to enter first-in-human Phase I trials in early 2009
- Clinical Trial of Nifurtimox-Eflornithine Co-Administration – promising interim safety data observed; a full dossier will be submitted to WHO in order to obtain recommendation for the use of the combination treatment in 2009
- HAT Platform – provided training on HAT patient treatment and clinical trial conduct to platform members in Angola, Democratic Republic of Congo (DRC), Republic of Congo, Uganda, and Sudan.

Chagas Disease

- Lead Optimisation Partnership – agreements established with partners in Australia and Brazil; focuses on progressing molecules proven to be safe and active against Chagas in early-stage screening research
- Paediatric Benznidazole – agreement established to develop formulation of benznidazole for children to be affordable and available as public goods.

It is important to remember, though, that these milestones are only part of a much longer process.



ASAQ and ASMQ simplify treatment of malaria for children, the primary victims of malaria. A simple regimen for children and adults is as easy as 1-2-3, requiring only once-daily administration of 1 or 2 tablets, according to age, over 3 days.

DNDi Founding Partners and Worldwide Presence

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

> THE KEY ROLE OF DNDi'S FOUNDING PARTNERS

Since DNDi's founding in 2003, 7 key stakeholders have helped to propel the initiative. Each of DNDi's original Board members represents one of DNDi's Founding Partners, all of which are centres of excellence in neglected disease research and/or patient care. Drawn primarily from the public sector in neglected disease-endemic countries, they have continued to serve as the backbone of DNDi by providing their expert advice, the benefit of their experience, and key project participation.

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**. Farmanguinhos/Fiocruz, one of the largest pharmaceutical laboratories in Brazil, has a long history of drug production in the field of neglected diseases, particularly for AIDS and now with the development of the antimalarial, ASMQ (see page 25).
• www.fiocruz.br

DNDi NORTH AMERICA

Established in 2007, the affiliate of DNDi in North America **supports the advocacy, fundraising, and R&D efforts of DNDi in the region**. Based in New York City, USA, this affiliate operates under the direction of the DNDi 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 genetic engineering**.

- www.pasteur.fr

DNDi coordination team in Geneva

DNDi LATIN AMERICA

Opened in 2004, the DNDi Latin America regional support office is based at the Médecins Sans Frontières offices 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 neglected diseases awareness in the region.

- www.dndi.org.br



DNDi IN THE DRC

Since 2005, the DNDi 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.

DNDi AFRICA

Established in 2003, the DNDi Africa regional support office is based at the Kenya Medical Research Institute (KEMRI) in Nairobi, Kenya. **DNDi Africa provides support to R&D projects in the region, including the paromomycin study, the LEAP and HAT Platforms, and the FACT Project**. Additionally, the office works to build awareness about neglected diseases and realities in the field through regional advocacy and communications activities.

- 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 DNDi 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 DNDi'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

DNDi IN JAPAN

Since 2004, the DNDi office in Japan has provided support in **developing discovery projects and on better positioning DNDi within the country.** Based in Tokyo, DNDi Japan is strengthening its presence in the country by expanding its relationships with academia, pharmaceutical companies, government, and media.

• www.dndijapan.org

DNDi 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 DNDi's operational activities in India, which are primarily focused on two diseases, malaria and visceral leishmaniasis.** R&D activities involve not only ongoing clinical trials but a number of earlier stage projects.

• www.dndiindia.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 focuses on **malaria, beriberi, cholera, and dysentery.** The IMR is now comprised of 8 centres which perform research, diagnostic services, training, and consultative services across diverse health fields.

• www.imr.gov.my; www.moh.gov.my

DNDi MALAYSIA

Since 2004, the DNDi 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

KENYA MEDICAL RESEARCH INSTITUTE (KEMRI)

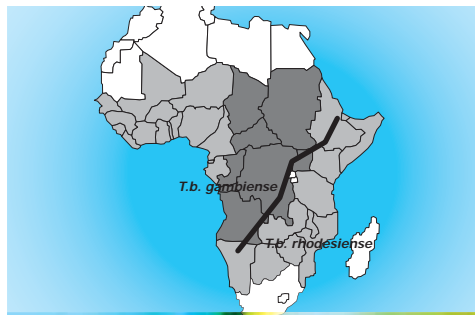
Established in 1979, KEMRI conducts health sciences research and shares its research findings with the international community. One of the leading health research institutions in Africa, KEMRI has and continues to make a significant contribution to regional research capacity. **With a focus on infectious and parasitic diseases, and on public health and biotechnology research.**

• www.kemri.org

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.

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.

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 SYMPTOMS/PRESENTATIONS?

HAT occurs in two stages:

- **stage 1** - the haemolympathic 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 ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Available treatments are **few, old, and stage-specific**. 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
- **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.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi's HAT-specific portfolio balances short- and long-term objectives.

Short term: better use of existing treatments and improved research capacity

- **Nifurtimox-eflornithine combination therapy (NECT)**, a simplified treatment for stage 2 HAT (see page 24)

Long term: new drugs and improved research capacity across region

- **Fexinidazole**: first drug candidate in preclinical development from nitroimidazoles project (see page 23)
- New drugs developed from compounds identified in discovery research (see pages 18-20) and progressed through HAT lead optimisation consortium (see page 21)
- **Multi-country, multi-partner HAT Platform** to strengthen regional research capacity (see pages 29-30)

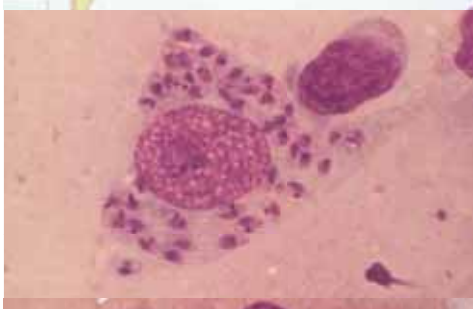
By 2014, DNDi aims to deliver from its HAT-specific portfolio:

- **1 new combination therapy recommended by WHO**
- **1 new drug registered**
- **A robust pipeline**

Kala-Azar

Visceral Leishmaniasis (VL)

200 million people at risk worldwide

**WHAT IS LEISHMANIASIS?**

Leishmaniasis is a poverty-associated disease with several different forms, of which the two following are most common:

- **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 DNDi, whereas CL is secondary, mainly because it is not a life-threatening disease in general.

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⁾.

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, and Sudan – represent over 90% of new cases.

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 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 ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

The number of treatments has increased in the past decade, but there are numerous drawbacks to each of the treatments, 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®)**: excellent, 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).

**WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?**

DNDi's VL-specific portfolio balances short- and long-term objectives.

Short term: better use of existing treatments through geographical extension and new combinations

- **Paromomycin and AmBisome®**: treatments for VL not yet registered in Africa and could be used in combination with existing treatment (see page 26)
- **Combination of existing therapies for VL in India**: a critical step in reducing course, toxicity, and cost of treatments (see page 26)

Long term: new drugs and improved research capacity

- **Buparvaquone and amphotericin B polymer**: compounds which could improve upon route of and length of current treatments (see page 22)
- **New drugs developed from compounds identified in discovery activities** (see pages 18-20) progressed through VL lead optimisation consortium (see page 21)
- **Multi-country, multi-partner LEAP** to strengthen regional research capacity (see pages 29-30)

By 2014, DNDi aims to deliver from its VL-specific portfolio:

- **1 new drug registered**
- **2 geographical extensions in endemic regions outside India by 2014**
- **2 new co-administrations 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.

South 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 workers with Chagas disease ⁽⁴⁾.

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 (eg. Australia, Canada, Japan, Spain, and the United States), due to increased migration of Latin American immigrants unknowingly carrying the parasite in their blood (see map).

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 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 cardiomyopathy worldwide.

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 CURRENT PATIENT TREATMENT NEEDS?

Improved treatment options are needed for all stages of Chagas infection:

- **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.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi's Chagas-specific portfolio balances short- and long-term objectives.

Short term: better use of existing treatments through new formulations, therapeutic switching, and combination therapy

- **Paediatric strength of benznidazole:** first treatment designed specifically for children (see page 24)
- **Azoles:** clinical development of a well-known compounds already used against fungal infections (see page 22)

Long term: new drugs and improved research & treatment capacity

- New drugs developed from promising compounds identified in discovery activities (such as GSK library of pyridones and cysteine protease inhibitors – see page 18) and progressed through Chagas lead optimisation consortium (see page 21)

By 2014, DNDi aims to deliver from its Chagas-specific portfolio:

- 1 new paediatric strength available
- 1 new drug registered

(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.

Malaria

3.2 billion people at risk



WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Effective treatments exist, but there are 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⁽¹⁾
- **Existing combination therapies**, now adopted as first-line treatment in most malaria-endemic countries, **can be expensive and have complicated treatment regimens**
- **Limited access** of 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.

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⁾.

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.

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 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 DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi'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. Medicines for Malaria Venture), DNDi 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 21 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

Into 2014, DNDi will support the proper use 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, Sudmack D, Irmwong M, Tanomsing N, Pongvongsa T, et al. Am J Trop Med Hyg. 77: 2007: 36-43

02.

R&D Model,
Strategy, & Portfolio

Building Innovative Partnerships to Deliver Better Treatments



Prioritising its efforts based on the most urgent treatment needs of patients, DNDi implements its R&D programmes with a wide variety of public & private partners around the world. The Scynexis researcher shown above works as a member of the HAT lead optimisation consortium.

DNDi's R&D portfolio has begun to bear fruit, with the registrations of ASAQ in 2007 and ASMQ in 2008, while continuing to grow as the strongest and most comprehensive kinetoplastid drug portfolio in history.



Having recently signed key, multi-year commitments with various partners who will serve as cornerstones in support of our pipeline, DNDi continues to identify and engage partners who share our vision and commitment, and to ensure that a well-balanced pipeline is established for the 3 diseases of primary focus: sleeping sickness (HAT), visceral leishmaniasis (VL), and Chagas disease.

Maintaining a portfolio of projects at all stages of development, DNDi harnesses the expertise of its partners by bringing together all current knowledge and capacities in a coordinated manner. With a strategic approach to identify and to bridge the gaps across the drug development pipeline, DNDi implements its pharmaceutical R&D programmes in collaboration with public and private partners from around world and prioritises its efforts based on the most urgent treatment needs of the targeted patient populations.

DNDi's project portfolio balances long-term and short-term projects because R&D of new drugs is time-consuming,

expensive, and highly risky when the process starts at the early discovery stage. DNDi aims to ensure that access to improved treatment options is provided to patients in meaningful, incremental steps along the way to identify novel compounds for each kinetoplastid disease.

As DNDi does not have its own laboratories or clinics, the organisation relies on partners to help to develop improved treatments for patients with neglected diseases. DNDi seeks to maximise existing resources and available expertise so as to minimise costs, overlaps, and risks of attrition.

With dozens of partners spanning the globe and crossing various sectors related to neglected diseases and drug development, DNDi is firmly on the way to meeting its objectives. However, drug development is both expensive and risky – 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.

R&D PRIORITIES IN THE NEAR TERM

Research, in a dynamic process, to ensure the pipelines for HAT, VL, and Chagas are populated with the most promising compounds

- New projects to access state-of-the-art drug discovery technologies and the wealth of existing compounds with therapeutic potential
- Disease-focused lead optimisation partnerships

Develop new treatments that will improve upon the current options

- Ongoing trials to identify the most appropriate drug combinations for VL for specific regions
- Complete the development of the first-ever paediatric formulation of benznidazole for Chagas

Access improved treatment options

- Facilitate the adoption and proper use of the 2 currently available Fixed-Dose Artesunate-Based Combination Therapies (FACTs) for malaria
- Prepare the groundwork for the adoption of a nifurtimox-eflornithine combination for HAT.

> SCOPE OF ACTIVITIES FOR DNDi: MAJOR FOCUS ON KINETOPLASTID DISEASES

> ONLY 21 NEW DRUGS FOR NEGLECTED DISEASES (1975-2004)

Engaging in a collaborative mode of operation from the research laboratory to the patient clinic, DNDi does not actually conduct research itself, but actively serves as project leader for its research projects from discovery through development. Together with these and other selected partners, DNDi then acts as a facilitator to ensure effective

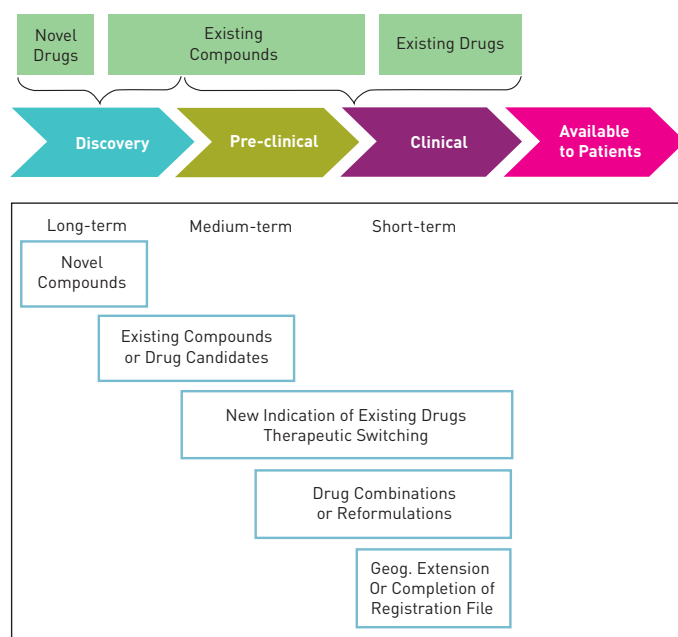


3 core diseases (HAT, VL, Chagas)

3 core diseases

+ malaria: complete the 2 FACTs
+ cutaneous leishmaniasis

SOURCING PROJECTS AT VARIOUS STAGES OF DEVELOPMENT



DNDi's portfolio continues to be a mix of projects in-sourced at any stage of the development process, from early discovery through post-registration, with the objective to bring new, field-relevant tools to patients in the shortest time and most efficient way possible.

DNDi populates its portfolio by seeking out projects which fall into the following 5 categories, based on the nature of the compound/treatment under consideration and according to its stage of development or expected time to reach patients:

- New drugs from novel compounds identified through screening and lead optimisation
 - example: agreements for disease-focused lead optimisation for all 3 target diseases, and access to new drug discovery technologies with Institut Pasteur-Korea
- New drugs from compounds with known antimicrobial/antiparasitic activities (may start at lead optimisation or preclinical development)
 - example: progression of fexinidazole as a preclinical candidate
- New indications for existing medicines in the field of the most neglected diseases (therapeutic switching)
 - example: partnerships in place

to investigate buparvaquone as a potential treatment for VL

- Reformulations and combinations better adapted to field conditions (paediatric, long-acting, new route of administration, fixed-dose combinations, co-packaging, or co-administration)
 - examples: both FACT products made available for malaria; completion of NECT study; agreement in place to develop paediatric formulation of benznidazole for Chagas disease
- Existing drugs for target diseases (geographical extension of registration; completion of regulatory dossiers of existing drug candidates)
 - example: paromomycin for visceral leishmaniasis in Africa.



STRENGTHENING AND STREAMLINING THE PORTFOLIO

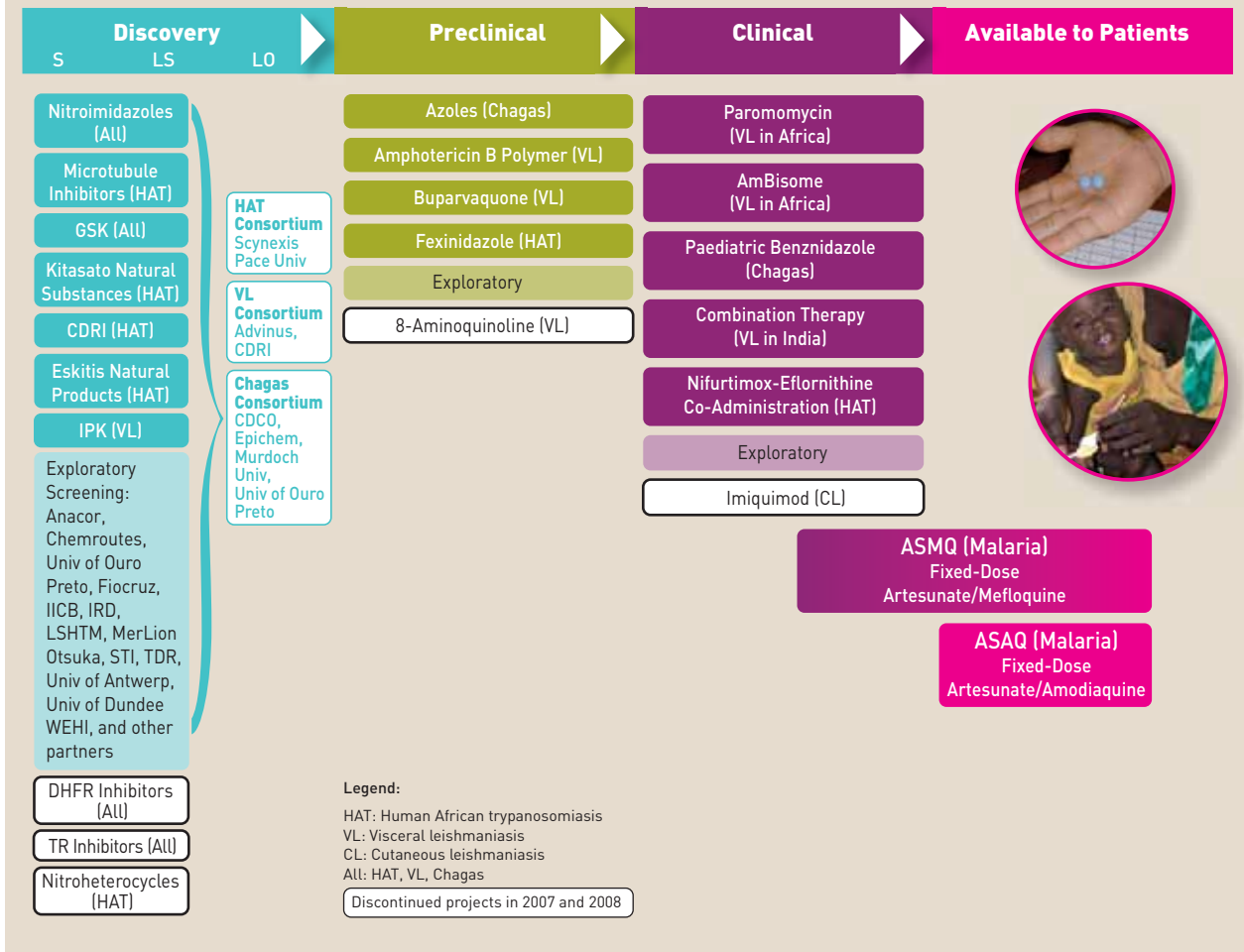
Through 2007 and into 2008, DNDi's portfolio continues to be strengthened and streamlined, with 21 projects across all stages of development and with numerous exploratory activities. These exploratory activities engage partners with drug development and parasite-specific expertise in providing compounds and in conducting *in vitro* and *in vivo* evaluation. The current portfolio ranges from discovery to post-registration projects, with a primary focus on three kinetoplastid diseases (HAT, VL, Chagas). Two ongoing projects in malaria have seen products made available to patients in the past year, and DNDi remains open to later stage development projects for cutaneous leishmaniasis.

Individual Projects Discontinued in 2007 and 2008

DNDi is grateful to the following project partners for their dedication during the lives of these projects.

- **Trypanothione Reductase Inhibitors (HAT, VL, Chagas)** Partner: University of Dundee, UK
- **Dihydrofolate Reductase Inhibitors (HAT, VL, Chagas)** Partners: Institute of Parasitology and Biomedicine Lopez-Neyra, Spain; Basilea, Switzerland; Swiss Tropical Institute (STI), Switzerland; London School of Hygiene & Tropical Medicine (LSHTM), UK
- **Novel Nitroheterocycles (HAT)** Partners: University of Dundee, UK; Glasgow University, UK; University of Parma, Italy; Swiss Tropical Institute, Switzerland
- **NPC1161B, An 8-Aminoquinoline (VL)** Partners: University of Mississippi (UM), USA; Medicines for Malaria Venture (MMV), Switzerland; London School of Hygiene & Tropical Medicine (LSHTM), UK
- **Imiquimod (CL)** Partners: McGill University, Canada; Universidad Peruana Cayetano Heredia, Peru.

A ROBUST AND DYNAMIC PORTFOLIO FROM 2007-2008



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?

SELECTING FOR SUCCESS IN THE FIELD: THE TARGET PRODUCT PROFILE

As a prerequisite to building a portfolio strategy, the desired R&D outcome for each disease is defined as the target product profile (TPP). Each R&D project in the portfolio is selected, progressed, and managed according to well-defined decision matrices based on these TPPs.

Particularly during drug discovery, the TPP keeps research focused on the endgame – a medicine for the patient. Starting as a description of an “ideal” drug, the TPP changes over the development process as new treatment options emerge. A common format in which to develop the TPP is as an ideal “package insert” which contains all of the information necessary for a medical practitioner to effectively prescribe the drug.

Sound knowledge of patient needs is essential to a credible TPP. Our clinical project managers work to develop in-depth knowledge about the field. In addition, a necessary part of their role is to solicit input from healthcare workers, patients, health regulators, and policymakers in disease-endemic countries where the drug will ultimately be made available. By engaging such partners at the early stages of the decision-making process, we ensure that the needs in the field are reflected in the final product.

Used properly, the TPP can play a central role in the entire drug discovery and development process. This role includes effective optimisation of drug candidates, decision-making within an organisation, design of clinical research strategies, and constructive communication with regulatory authorities.

Discovery Projects

Key discovery activities are consolidated screening efforts, with established reference screening centres, which feed hits into disease-specific lead optimisation consortia.

Discovery research is essential in bringing forward novel drugs that are significantly better than current therapies. To that end, DNDi has established a variety of concerted efforts in this research phase to maximise success and to ensure a robust pipeline that will deliver in 2014 and beyond.

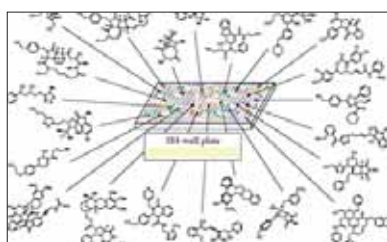
A diverse set of complementary projects in early-stage screening is utilised to identify new compound classes with anti-parasitic activity. These activities include:

- screens of compound classes which have shown promising anti-parasitic activity,
- target-based screens where a validated molecular target (like an enzyme) of the parasite is identified and then screened, and
- general screens (utilising synthetic compound libraries and natural products).



KEY CHARACTERISTICS OF DNDi'S DISCOVERY ACTIVITIES

- Bring a thorough understanding of field conditions and patient needs
- Apply updated Targeted Product Profiles (TPP) to guide our disease-specific programmes
- Continue to harness existing knowledge and take an opportunistic approach to address urgent needs – e.g., therapeutic switching, mining for new drugs from abandoned programmes, etc.
- Have organised disease-focused consortia for centralized lead optimisation operation, which allows for needed flexibility, and for efficient decision making in the laboratories
- Take a balanced approach in targeting diverse sets of compounds and libraries, while also targeting selected classes of compounds, thereby leveraging existing drug discovery knowledge
- Work with partners who share our mission and commitment.



▶ MICROTUBULE INHIBITORS

- Target disease: HAT
- Partners: Murdoch University, Australia; Epichem, Australia; Centre for Drug Candidate Optimization, Monash University, Australia
- DNDi project manager and coordinator: Robert Don, Jean-Robert Ioset
- Project start: September 2006

This lead optimisation project, which builds on data from a lead molecule shown to be highly selective for trypanosome α -tubulin, is to assess the development potential of this lead series. Previous studies have shown that novel compounds which bind to trypanosome α -tubulin have selective activity to *T. brucei* α -tubulin versus murine α -tubulin.

At the end of 2007, more than 80 compounds have been synthesized by Epichem via 3 different analogue programmes using a biphenyl scaffold. After assessing these compounds for *in vitro* antiparasitic activity and potential mutagenicity, Murdoch University then conducted a number of *in vivo* experiments to assess the compounds' acute model, bioavailabilities, and abilities to cross the blood-brain barrier. A lead molecule was identified for further investigation, which will include completion of ongoing dose response studies, further *in vivo* efficacy

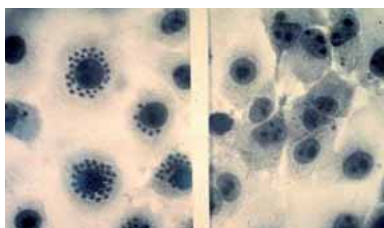
assessment, and exploration of the compounds' potential for mutagenicity via *in vitro* and *in vivo* micronucleus testing. Work is also ongoing to improve solubility via synthesis of new analogues and different formulations.

▶ CYSTEINE PROTEASE INHIBITORS AND PYRIDONES

- Target diseases: HAT, VL, Chagas
- Partners: University of California, San Francisco, USA; GlaxoSmithKline, Spain
- DNDi project manager and coordinator: Denis Martin, Jean-Robert Ioset
- Project start: October 2005

With the objective to identify novel

inhibitors of parasite cysteine proteases (CP) that could be progressed as lead compounds, this project targets the CP family because they are nearly ubiquitous in protozoan parasites, play a number of key roles in parasite survival (from nutrition to immune evasion among others), and have well-known structure-activity relationships. In 2007, none of the CP inhibitors from previously accessed libraries were found to meet the targeted profile, and this specific project was not further pursued.



GSK signs on...

In early 2008, GSK and DNDi formalised an ambitious collaboration which makes available a large GSK library of new CP inhibitors and a library of pyridone compounds to DNDi in order to examine their specific activities against kinetoplastid parasites.



▮ NITROIMIDAZOLES

- Target diseases: HAT, VL, Chagas
- 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

- DNDi project manager: Els Torrelee
- Project start: January 2005

Nitroimidazoles are a well-known class of anti-infective compounds, however, the risk for genetic toxicity linked to the nitro-group has been a concern for drug development. An extensive compound mining effort was undertaken by DNDi to explore new and old nitroimidazoles as drug leads against HAT, leishmaniasis, and/or Chagas disease. Over 600 existing compounds from 15 different sources were identified, accessed, and tested for anti-parasitic activity (*in vitro* and *in vivo*). Active compounds underwent extensive druggability profiling, including possible mutagenic activity, ADME, and pharmacokinetics. This approach has already led to the discovery and characterisation of fexinidazole as a promising development candidate for HAT (see page 23), while several other compounds with potential for either HAT, leishmaniasis, or Chagas disease are still undergoing profiling in 2008.

▮ KITASATO SCREENING

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



Natural products from microbial and plant sources, 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 anti-trypanosomal molecules from KI natural products via *in vitro* and *in vivo* screening.

Through March 2008, over 24,000 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 (see page 21); KI will concurrently continue in search of further 'hits' to feed the pipeline.



▮ COMPOUND SCREENING WITH CDRI

- Target disease: HAT
- Partners: Central Drug Research Institute (CDRI), India
- DNDi project manager and coordinator: Eric Chatelain, Jean-Robert Ioset
- Project start: February 2006

With the goal of this project to identify some chemically diverse compounds with *in vitro* activity against *T. brucei*, CDRI – based in Lucknow, India – has established an *in vitro* medium-throughput screen and has begun to screen its compound library which includes 8,000 synthetic compounds. In 2007, approximately 5000 compounds were screened, and over 200 compounds (belonging to 11 different chemical scaffolds) have shown activity by inhibiting more than 90% of *T. brucei* growth. As

Discovery Projects

of June 2008, the screening has been completed, and hits are being reviewed in terms of promising activity (IC50) and cytotoxicity profiles in order to determine the whether or not to progress any of them through further lead identification.



ESKITIS NATURAL PRODUCTS SCREENING

- Target disease: HAT
- Partners: Eskitis Institute, Australia; Griffith University, Australia
- DND*i* project manager and coordinator: Robert Don, 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 to examine the *in vitro* trypanocidal activity of 64,000 natural products from a diverse screening library of over 200,000 extracts. This unique lead-like peak library of natural products, which possess well-characterised 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 maximises the chance of a positive outcome, ie. detecting a "hit". In 2008, the first "hit", a marine invertebrate, has been identified. As the project continues through 2009, the remaining 136,000 compounds will be screened, and promising compounds will undergo hit expansion.



IPK HIGH-CONTENT SCREENING

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

A cell-based high-content 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 Institut Pasteur-Korea, this project seeks to develop a major methodological advance in antileishmanial drug development as this will be the first high-content screening assay for intracellular *Leishmania* amastigotes in macrophages. *Leishmania* amastigotes are the clinically relevant intracellular form of the parasite. Beginning in 2008, the project seeks to develop and validate the assay in the first year so as to then use it in the second year of the project to test confirmed "hits" against *Leishmania*. If the project is successful, this assay will be the first of its kind in the world, and it may then be expanded to include testing against *T. cruzi* as such an assay could represent a huge advance for antitrypanosomal screening as well.



Landmark agreements cement DNDi's optimisation efforts

In 2007, key multi-year partnerships were formed in terms of research and funding that will enable DNDi to apply best drug discovery science for the most neglected. Capped off with the financial commitment of the Bill & Melinda Gates Foundation to support both of these programmes in December (see page 37), DNDi signed 5-year collaborative agreements with Scynexis and Advinus as primary partners in lead optimisation consortia for HAT and VL, respectively. In July 2008, a Chagas disease consortium was also finalised.

The projects are to obtain optimised leads by progressing "hit" molecules with a good safety profile and active against *Trypanosoma* and *Leishmania* parasites, these consortia bring together expertise in chemistry, biology, screening, and pre-formulation, in order to optimise 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.

Scientists within the consortia use very advanced techniques to study how the selected molecules link themselves to the therapeutic target (ie. a protein or an enzyme) in order to optimise the drug-like characteristics of these molecules. This phase

requires a close, highly responsive 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.

By early 2008, both HAT and VL consortia partners had dedicated teams (shown below: Scynexis, left; Advinus, right), processes, and milestones in place so as to ensure that this critical gap in the drug development pipeline is filled. In July 2008, contracts have been signed with partners who will serve as cornerstones of the Chagas consortium. In addition, DNDi has agreements in place with a number of other sources of novel compounds that can feed all of the drug discovery programmes (see page 17).

It is planned that by end of 2011, all programmes will have a number of back-ups ready to sustain the pipeline should the 1st candidate fail, and will have progressed a molecule with a good safety profile and active against the respective parasite in early-stage screening research through the first steps of regulatory safety assessment in the preclinical phase.



Scynexis team



Advinus team

LEAD OPTIMISATION PROGRAMMES

• Target disease: HAT

- Partners: Scynexis, USA; Pace University, USA
- DNDi project manager and coordinator: Robert Don, Ivan Scandale
- Project start: April 2007
- Status: With two full lead optimisation teams in place, a number of hits identified from DNDi screening partners are undergoing hit expansion. A review will take place later in the year to begin "hit to lead" activities.

• Target disease: VL

- Partners: Advinus, India; CDRI, India
- DNDi project manager and coordinator: Denis Martin, Ivan Scandale
- Project start: November 2007
- Status: With a full team in place, assessment of the first series of synthetic compounds has been conducted and chemistry-biology activities have been initiated. Dedicated screening facilities at CDRI will be established by the end of 2008.

• Target disease: Chagas

- Partners: Centre for Drug Candidate Optimization (CDCO), Australia; Epicchem, Australia; Murdoch University, Australia; Federal University of Ouro Preto, Brazil
- DNDi project manager: Robert Don
- Project start: July 2008
- Status: Key contracts have been signed in July 2008, and work has begun to populate a full lead optimisation team who will assess promising hits from DNDi screening partners.

Preclinical Development

To address the relatively sparse preclinical landscape of drug research and development for kinetoplastid diseases, DNDi has a proactive programme which aims to identify compounds that can be rapidly advanced to clinical trials.

These may include:

- Drugs used to treat related diseases such as fungal infections which are also potent against kinetoplastid parasites
- Drug candidates which have been partially developed for kinetoplastid infections and abandoned

by pharmaceutical companies. This can happen when companies change focus after mergers or review of their target markets

- Compounds developed in universities or research institutes which have stalled because funding mechanisms do not exist to take them to the next step.

DNDi also recognises the need for new disease-specific models to improve the selection of drugs in the development phases, and is working with partners to identify new potential candidates.



▶ AZOLES

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

Preclinical studies with antifungal triazoles have shown considerable efficacy in the treatment of Chagas disease in animal models. One of these compounds, posaconazole (Schering Plough), was recently registered for treatment of invasive fungal infections in Europe and USA. In addition, several other companies have taken other azole compounds into clinical trials for fungal infections. These also show strong activities against *T. cruzi*. The team is assessing the treatments in animal models, of several compounds

as monotherapy and combination with existing drugs to treat Chagas disease. In 2008, DNDi is progressing on the goal to advance either posaconazole or another azole into clinical research on Chagas disease patients, and to examine other molecules from the same family as potential drug candidates.



▶ AMPHOTERICIN B POLYMER

- Target disease: VL
- Partners: Imperial College, UK; London School of Pharmacy, UK; LSHTM, UK
- DNDi project manager: Denis Martin
- Project start: September 2006

The goal of this project is to develop a low-cost and heat stable version of liposomal amphotericin B (AmBisome®). This efficacious yet highly expensive formulation of amphotericin B has been

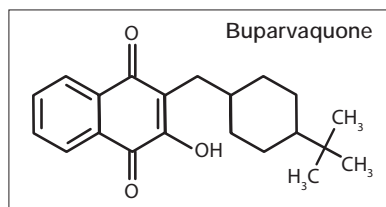
increasingly used to treat VL but has seen very limited use in VL-endemic regions of Africa and Asia, where disease burden is greatest, because of its high cost. Using a less expensive, modified metacrylic polymer has shown promise in experimental work conducted by the Imperial College team. In 2007, Imperial College has moved forward to establish adequate efficacy in an *in vivo* model of the disease and is examining key characteristics related to the size of the polymer, the ratio of the polymer to amphotericin B, and the actual dose of amphotericin B. While this project moves ahead in 2008, DNDi is conducting parallel investigations into other amphotericin B-based formulations which show promise *in vivo* and will plan to advance the most promising one by early 2009.

▶ BUPARVAQUONE

- Target disease: VL
- Partners: Advinus Therapeutics, India; Drugabilis, France; University Sains, Malaysia; LSHTM, UK
- DNDi project manager: Denis Martin
- Project start: Approved in October 2007; start in January 2008

In 2007, DNDi-commissioned work by partners at the Universiti Sains Malaysia and at Advinus Therapeutics has shown that a new self-emulsifying drug delivery system (SEDDS) could improve the oral bioavailability of buparvaquone to greater than 60%. Earlier research with buparvaquone – a hydroxynaphthoquinone antiprotozoal drug related to well-known anti-infective drug, atovaquone – has shown it to have good antileishmanial activity *in vitro* and *in vivo* but with limited efficacy in a canine model of VL, possibly due to low bioavailability. In 2008, with these promising early results, DNDi has identified partners to assess buparvaquone as a potential optimised lead, and ongoing studies are examining toxicology, pharmacokinetics / pharmacodynamics in animal models (mouse, hamster),

and reconfirmation of oral bioavailability using the SEDDS formulation. If acceptable, development will be progressed with the aim of satisfying the criteria specified for a clinical candidate.



A rediscovered nitroimidazole progresses into preclinical development

► FEXINIDAZOLE

- Target disease: HAT
- Partners: Accelera, Italy; STI, Switzerland; Axyntis, France; Covance, UK; Aptuit, UK; KARI Trypanosomiasis Research Center, Kenya
- DNDi project manager: Els Torrelee
- Project start: February 2007

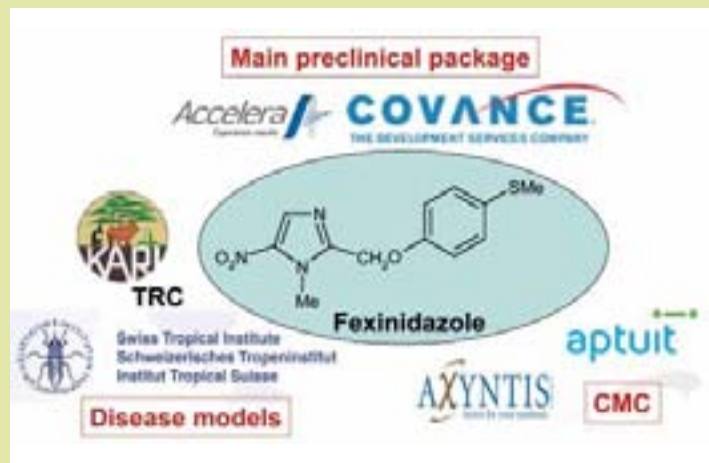
The progression of fexinidazole as a drug candidate for stage 2 HAT is the first success of the compound mining efforts DNDi has pursued in particular in the nitroimidazoles project (see page 19).

Fexinidazole is a 5-nitroimidazole that has been in preclinical development as a broad-spectrum anti-protozoal by Hoechst in the early 1980s. Rediscovery of this abandoned compound and extensive profiling by DNDi has shown that fexinidazole is orally active, 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 late 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 DNDi concluded that fexinidazole is suitable for progression into clinical development.

Preparation for first-in-human Phase 1 studies is underway, including clinical tablet formulation.

Recognised as “Project of the Year 2008”



Clinical Development & Post-Registration

The seven clinical and post-registration projects in DNDi's portfolio are near-term opportunities which can make a significant difference in improving upon current treatment options for each of the diseases on which DNDi is focused.

They represent the potential for meaningful, incremental improvements in terms of both treatment and strengthening clinical research capacity that can be utilised in DNDi's longer term projects evaluating novel compounds (currently in earlier stages of R&D). They also address immediate treat-

ment concerns like development of drug resistance when effective drugs are used in monotherapy, enhancement of patient compliance, and availability of paediatric strengths.

The clinical projects mainly consist of projects which are new formulations of existing drugs, drugs switched from other indications, or drug combinations. Two of DNDi's clinical projects have successfully progressed into the post-registration process, where the products are now available to patients in Africa and Latin America.



PAEDIATRIC BENZNIDAZOLE

- Target disease: Chagas
- Partners: Pharmaceutical Laboratory of Pernambuco State (LAFEPE), Brazil; University of Liverpool, UK
- DNDi project manager: Isabela Ribeiro
- Project start: June 2008

Benznidazole, one of only two products registered for Chagas disease, can be highly efficacious in children yet no paediatric strengths exist. For the majority of children, the 100-mg tablet must be fractionated (broken into pieces). A fractionated tablet is not the ideal form of treatment; with fractionation, there is the potential for improper dosage - raising safety concerns, especially in the very young and malnourished, reduced efficacy (due to coating modification or diluent addition), and decreased stability.

In July 2008, DNDi has successfully concluded contract negotiations with LAFEPE for the development of paediatric-strength benznidazole tablets. Pharmaceutical and clinical development workplans are being designed, with the ultimate goal to make this affordable, age-adapted formulation available for the treatment of Chagas disease in endemic countries.



NIFURTIMOX-EFLORNITHINE CO-ADMINISTRATION

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

Begun as a single centre study by MSF-Holland and Epicentre in the Republic of Congo (Brazzaville) in 2003, NECT is a multi centre clinical study to test a simplified combination of oral nifurtimox co-administered with intravenous eflornithine for stage 2 HAT. With the ultimate goal to enable a WHO recommendation on the use of the combination, the project aims to demonstrate that the combination is as effective and safe as standard eflornithine monotherapy, but easier to use. The number of slow, intravenous infusions of eflornithine is reduced from 56 to 14, the treatment duration is reduced from 14 to 10 days, and packaging is minimised. This reduces costs related to drugs, storage, and shipping.

In 2007, an early safety analysis showed that the combination was as well-tolerated as eflornithine monotherapy, and initial, single-centre results were published by Epicentre in the journal *Clinical Infectious Diseases*. By the end of 2008, final efficacy and safety results will be available after all data, including the 18-month efficacy follow-up of all 280 patients, has been analysed. A submission for inclusion on the WHO Essential Medicines List will be made by the end of 2008. A field study is also being planned to further document the safety and ease of use of the combination in real-life field conditions.

A public good developed and supported by public partners is made available



▶ ASMQ, FIXED-DOSE ARTESUNATE/MEFLOQUINE COMBINATION THERAPY

- Target disease: malaria
- Partners: Farmanguinhos, Brazil; Shoklo Malaria Research Unit, Thailand; Universiti Sains Malaysia; Oxford University, UK; TDR; Cipla, India; Catalent, USA; ICMR, India; GVK BIO, India; Quintiles, USA
- DNDi project managers and coordinator: Jean-René Kiechel, Isabela Ribeiro, 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 manufactured by Farmanguinhos/Fiocruz, 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 DNDi upon its foundation) as part of the FACT (Fixed-Dose, Artesunate-Containing Therapy) Project.

In 2007 and throughout the first half of 2008, ASMQ project partners made significant progress. ASMQ was successfully registered in Brazil by public industrial partner Farmanguinhos/Fiocruz in March 2008. The coformulation is currently being used by Brazilian national authorities as part of an ongoing intervention study; preliminary results after one year show a 70% drop in *P. falciparum* malaria cases and a greater than 60% reduction in malaria-related hospital admissions. The study, which continues through 2008 and 2009, has now treated 25,000 patients with ASMQ.

The future holds even more promise for ASMQ: it will navigate the registration processes of other countries in Latin America; it will be submitted for PAHO pre-qualification; 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 will also be conducted to examine the potential therapeutic value of ASMQ in pregnancy and in Africa.

Recognised as “Partnership of the Year 2008” as part of the FACT Project

Clinical Development



▶ PAROMOMYCIN FOR AFRICA

- Target disease: VL
- Partners: Kenya Medical Research Institute, Kenya; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; University of Makerere, Uganda; MSF; IDA Solutions, the Netherlands; LSHTM, UK; Institute for OneWorld Health, USA
- DNDi project managers and coordinator: Catherine Royce (until February 2008); Manica Balasegaram (as of February 2008), 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 in Phase IV development throughout the Indian subcontinent by fellow PDP, Institute for One World Health (IOWH), paromomycin is being studied in parallel by DNDi 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.

Early results showed the initial dosage of paromomycin did not work as well in Africa as it did in India. A dose escalation study was undertaken to determine if a higher-dosage regimen could meet its efficacy target.

In 2008, the study is continuing to recruit patients at sites where infrastructure has been improved or built (see pages 29 & 30).

First interim analysis was concluded in February 2008, and a decision was made to pursue recruitment. The study is due to complete in 2009, with final results being ready by the end of that year.

▶ COMBINATION THERAPY FOR VL IN INDIA

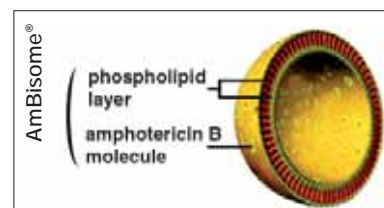
- Target disease: VL
- Partners: ICMR, India; Kala Azar Medical Research Centre, India; Rajendra Memorial Research Institute of Medical Sciences, India; GVK BIO, India
- DNDi project manager and coordinator: Farrokh Modabber, Sally Ellis
- Project start: December 2004; Phase II duration from 2005 to 2007; revised Phase III protocol approved in October 2007



A number of new therapeutic options for VL have been developed, but they are generally expensive and have long treatment periods (of up to one month). Combination therapies of these new treatments represent a critical path forward because of their potential for ease of use, shorter course of treatment, prevention of parasite resistance, and cost containment. Additionally, combination regimens using already existing drugs offer a short-term solution to assist in protecting the useful life of available drugs while new chemical entities are developed.

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 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. This past year was spent assembling a project team, and drafting and receiving ethical approval on a revised clinical study protocol. Enrolment will continue through 2009, and results are expected by early 2010.



▶ AMBISOME FOR VL IN AFRICA

- Target disease: VL
- Partners: Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LSHTM, UK; Ministry of Health, Ethiopia; Armauer Hansen Research Institute (AHR), Ethiopia; other members of the LEAP network
- DNDi project managers and coordinator: Catherine Royce (until February 2008), Manica Balasegaram (as of February 2008); Sally Ellis
- Project start: Approved in May 2006; start by end of 2008

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.

Post-Registration

A dose of innovation is delivered as ASAQ reaches African malaria patients



ASAQ, FIXED-DOSE ARTESUNATE/AMODIAQUINE COMBINATION THERAPY

- Target disease:
malaria
- Partners:
sanofi-aventis, France; National Centre for Research and Development on Malaria, Burkina Faso; Universiti 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; Office of Technical Studies and of International Cooperation (OTECI), France
- DNDi project manager and coordinators: Jean-René Kiechel, Gwenaëlle Carn, Graciela Diap (Medical Coordinator)
- 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 DNDi in an innovative partnership with sanofi-aventis. Now available and registered in 21 countries in sub-Saharan Africa, with more than 1,500,000 treatments procured, the continuing focus of this post-registration project is to support the implementation of ASAQ for the treatment of uncomplicated *falciparum* malaria after its registration in endemic countries, mainly in sub-Saharan Africa, and in Indonesia.

ASAQ provides a true innovation in patient treatment by being a tropical-stable bilayer coformulation, 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.

The year 2007 was a milestone year for ASAQ as it was made available to patients. Launched in March 2007, ASAQ achieved 1st registration in Morocco, the country where ASAQ is manufactured by sanofi-aventis. This registration has paved the way for further registration across sub-Saharan Africa, where ASAQ can be of substantial public health benefit.

In 2008, further progress has been made as the ASAQ production facility in Morocco has been granted Good Manufacturing Practices (GMP) certification; such a certification allows ASAQ to be procured by malaria-endemic countries via international funding mechanisms, such as the Global Fund (which pays for 70% of malaria medicines made available).

There is still much work to be done with ASAQ: WHO prequalification is pending, and DNDi is regularly convening a group of external experts as part of the FACT Implementation Advisory Group to advise on Phase IV clinical studies, which are being implemented to study the drug's tolerability and effectiveness in real-life conditions. DNDi and sanofi-aventis are also working with MMV and the INDEPTH network on a pharmacovigilance strategy.

Further work will also focus efforts to inform on the proper use of ASAQ as part of reinvigorated global efforts to eradicate malaria.

Recognised as "Partnership of the Year 2008" as part of the FACT Project

03.

Strengthening Existing Capacities

Working Together to Face Research Challenges



Making a solid impact on the ground, DNDi has built partnerships with researchers and health officials in endemic regions that help to strengthen the region's research capacity. Such strengthening relates to both personnel and infrastructure: for example, this laboratory technician working at Dipumba Hospital, in Mbuji-Mayi (DRC), has been trained on HAT diagnostic tools as part of the activities related to the NECT study.

Developing drugs is a long and arduous process that requires skilled and knowledgeable partners throughout all stages of the pipeline and into the field. In order to bridge some of the gaps seen in drug R&D for neglected diseases, DNDi uses and strengthens existing research capacity in disease-endemic countries.



CLINICAL TRIALS

Conducting clinical trials on neglected diseases often means that research must be conducted in some of the most remote areas where little infrastructure

of any kind, yet alone health, exists and where political instability is also frequent. Diagnosis and treatment of patients is difficult in itself, but DNDi and partners

must also ensure that clinical research is carried out at international standards of quality.



NEEDS ASSESSMENT

DNDi has identified several key components to be met:

- Fostering trust and building partnerships with local communities, patients, and healthcare workers. As many local partners have long historical relationships with local populations, they are vital in facilitating the process
- Improving local infrastructure and ensuring that the entire logistical chain in place is compliant with Good Clinical Practices (GCP)
- Recruiting, training, and supporting relevant human resources. Quality healthcare workers at a local level must not only be identified but must be maintained and enhanced through training. Such personnel include both the staff conducting the clinical trials (doctors, laboratory technicians, and nurses) as well as those monitoring the trial (clinical monitors and data safety monitoring boards)
- Working with governing and regulatory authorities at local, national, and regional levels. These authorities play a crucial role in evaluating and approving clinical protocols, ensuring drug availability (by registering drugs and by facilitating drug importation, in terms of logistics), and making changes to national treatment guidelines and protocols. National ethics committees also play a critical role
- Ensuring prioritisation and sustainability of clinical research worldwide, through increased public awareness in donor countries and among local communities.



Before

Capacity strengthening can involve the physical upgrading of facilities related to clinical research (such as patient wards and diagnostic laboratories). When research and treatment of visceral leishmaniasis began in Gondar, Ethiopia, it was in a tent.



After

Now, DNDi and LEAP partners have built and are using a new building which was completed in May 2008.

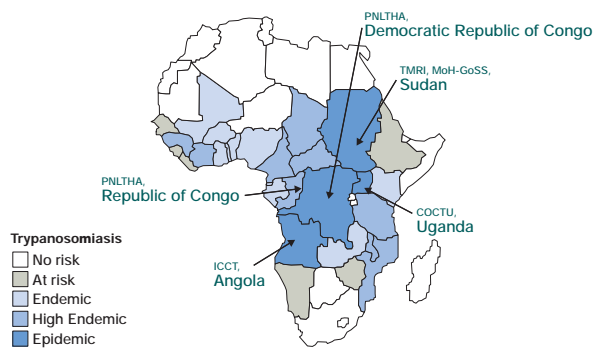
DNDi'S SYSTEMATIC RESPONSE

DNDi and partners are tackling each of these issues by adopting strategic and integrated approaches as clinical trials are implemented:

- In partnership with groups and investigators in endemic regions, the regional research platforms of the Human African Trypanosomiasis (HAT) Platform and the Leishmaniasis East Africa Platform (LEAP) aim to ensure that clinical research capacity is strengthened in a coherent regional approach that overcomes system barriers and facilitates the availability of new medicines when they are developed
- The national control programmes of the most affected countries are essential members of both platforms as they play a key role in areas where clinical investigations are taking place
- Acting as transnational support networks, the platforms enable partners to share different experiences, knowledge, and problem-solving techniques. Through sharing of information and expertise at a regional level, fundamental problems at the field level can also be addressed
- Physical upgrading of facilities related to clinical research (such as patient wards and diagnostic laboratories) is undertaken by DNDi at trial sites so as to ensure they meet GCP standards. These facilities are not owned by DNDi.



> THE HAT PLATFORM



• **Target disease:**
HAT

• **Core partners:**

STI; national HAT control programmes of most affected endemic countries (see map on left); national and international research groups (eg. ITMA, INRB, CDC, and KARI-TRC); NGOs like MSF; FIND; WHO; TDR; regional networks (eg. EANETT, PABIN, AMANET)

• **DNDI contact:** Augustin K. Ebeja

• **Project start:**

August 2005; Kinshasa, DRC



- In addition to physical infrastructure, trained staff are needed in order to carry out GCP-compliant trials. Training is important not just at the start of a trial, but is a continuous process which updates existing staff and trains new members. From external consultants to the experienced trial site staff, the sharing of better practice 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 at international standards
- At the final R&D step, there is the challenge to make new treatments available to patients. The post-registration phase requires that all partners actively monitor the safety (pharmacovigilance), efficacy (monitoring of resistance), and field effectiveness of the products in real-life conditions. But, even before doing this, it's imperative to determine how the drug will be made available through a well-defined implementation strategy
- These platforms also have an advocacy role to play at community, national, and international levels. As representatives of countries most affected by neglected diseases, they have the legitimacy to showcase the plight of what patients endure and how best to meet their urgent needs.

CLINICAL RESEARCH PLATFORM ACHIEVEMENTS INTO 2008

HAT Platform

- **Training:** for members on Good Clinical Practice (GCP) training, ethics, and clinical monitoring; for general practitioners, a programme on how to examine patient with HAT
- **Communications:** 3 platform newsletters published, presentations at various scientific congresses
- **Meetings:** launch in August 2005, and annual platform meetings (Nairobi, 2006; Khartoum, 2007); 6 steering committee meetings held as well – both in conjunction with annual meetings as well as in Basel (June 2007), and Kampala (June 2008).

LEAP

- **Training:** Good Clinical Practice (GCP), pharmacovigilance, and ethics sessions for clinical monitors, Data and Safety Monitoring Board (DSMB) members, Ethics Committees, and investigators
- **Strengthening capacities:** 6 clinical trial sites established in Ethiopia (2), in Sudan (2), in Kenya (1), and in Uganda (1); the building and opening of leishmaniasis research and treatment centres in Arba Minch, Ethiopia, and Gondar, Ethiopia; treatment centre and laboratory training site under construction in Dooka, Sudan (opening in 2008)
- **Communications:** a newsletter, biannual meetings, and presentations at various scientific congresses.

> LEISHMANIASIS EAST AFRICA PLATFORM (LEAP)



• **Target disease:** VL

• **Core partners:**

KEMRI, Kenya; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Drug Administration & Control Authority, Ethiopia; Institute of Endemic Diseases, University of Khartoum, Sudan; Makerere University, Uganda; MSF; WHO; TDR; Ministries of Health in Kenya, Ethiopia, Sudan, and Uganda.

• **DNDI contact:** Monique Wasunna

• **Project start:**

August, 2003; Khartoum, Sudan



Skilled and appropriately trained staff are needed in order the best research and treatment to be delivered at all stages of the R&D pipeline, as shown above. On the left, clinical monitors visit a principal investigator at the LEAP clinical trial site in Kassab, Sudan; on the right, a training workshop on trypanosomiasis screening is being held as part of PAN4ND activities.

SCREENING NETWORK

With the objectives to leverage the biodiversity potential of the Asian region in drug discovery efforts for neglected diseases, the Pan-Asian Network for Neglected Diseases (PAN4ND) brings together scientists from research institutions across Asia and the Pacific region (see below). The network, which first formed as Pan-Asian Screening Network (PASN), aims to translate the discovery of new bioactive molecules from natural local resources into drugs against neglected diseases by sharing screening technologies between institutions. To fulfill its objectives, PASN interacts with a Natural Products Working Group, representing several institutions involved in the purification and identification of

chemicals from plant, soil, and marine organisms in the region.

There is a strong rationale to explore natural resources in the search for new antiprotozoal medicines, as several anti-infective drugs, including ones

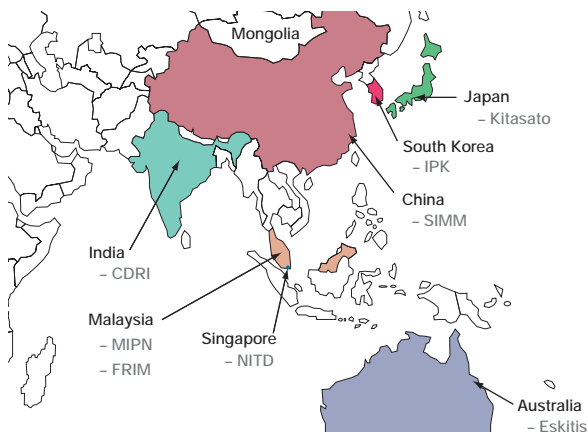
targeting parasitic diseases, are from natural origin or derived from it. Two striking examples, first identified by Asian researchers, are artemisinin, for the treatment of malaria, and ivermectin, as a cure for river blindness.



PAN4ND ACHIEVEMENTS INTO 2008

- **Training:** Drug screening workshop at CDRI, Lucknow (February 2007); drug metabolism, pharmacokinetics, and toxicology workshop at NITD, Singapore (February 2008)
- **Strengthening capacities:** 3 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 antiprotozoal drug screening in collaboration with LSHTM, STI, and CDRI; organisation of 5 regional scientific events: 3 annual meetings (Tokyo, May 2006; Shanghai, June 2007; and Tokyo, June 2008) and 2 Natural Substances Drug Discovery and Development meetings (Kuala Lumpur, November 2006 and 2007).

> DISCOVERY RESEARCH PAN-ASIAN NETWORK FOR NEGLECTED DISEASES (PAN4ND) NATURAL SUBSTANCES SCREENING



- **Target disease:** HAT, VL, Chagas
- **Core 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 Nutraceuticals (MIPN), Malaysia; Novartis Institute of Tropical Diseases (NITD), Singapore; Shanghai Institute of Materia Medica (SIMM), China.
- **DNDi contact:** Jean-Robert Ioset
- **Project start:** May 2006; Tokyo, Japan

04.

Advocacy,
Communication,
& Fundraising

Key Steps to Boost Innovation



As DNDi and its partners blaze the trail together, communications and advocacy play a key role in promoting and supporting projects which address the needs of neglected patients in the most timely and cost-effective way.

In the past few years, awareness of the lack of effective treatments for neglected diseases has been growing. With increasing media attention, essential health R&D has also been included in new policy proposals and funding initiatives.

Established to accelerate innovation for neglected diseases, product development partnerships (PDPs), such as DNDi, are increasingly seen as a new model that provides the drive for collaborative R&D efforts, bringing together public and private donors and researchers. PDPs aim to stimulate R&D, produce needs-adapted health tools, build robust portfolios, and attract new sources of funding from public and private donors.

With its 5 years of experience, DNDi contributes to accelerate the above momentum by strengthening its advocacy, communications, and fundraising activities. DNDi has undertaken a series of initiatives to strengthen its

role in advocacy for neglected disease patients and to raise awareness over their plight. In tandem, DNDi's communications activities focus on providing an accurate image of DNDi's mission and objectives by promoting a more widespread commitment to neglected diseases. Key messages are expanded upon to convey neglected disease concerns to those who can make a difference in this field.

Throughout 2007/2008, DNDi and its scientific experts actively attended numerous scientific congresses and symposia and provided donors, inter-governmental organisations, NGOs, PDPs, UN bodies, scientists, and the media with experience-based analyses



on the challenges facing researchers in the field of neglected diseases and an explanation of DNDi's role within this field.

POLITICAL LEADERSHIP

The dynamic process launched by the Organisation for Economic Cooperation and Development (OECD) in June 2007, which resulted in the Noordwijk medicines agenda resolution asking "governments of OECD and developing countries to demonstrate political leadership to improve the availability of and access to medicines, vaccines, and diagnostics for neglected and emerging infectious diseases," was a great step forward, yet the WHO Inter-governmental Working Group (IGWG) has been perhaps the most significant process set up to design a global framework for accelerating innovation and improving access to medicines in the developing world.

The elements of the strategy adopted by governments during the 61st World Health Assembly (WHA) in May 2008 include: providing an assessment of health needs in developing countries and prioritising R&D; implementing possible incentive schemes for R&D; improving R&D capacity in developing countries; boosting technology transfer; improving delivery and access to all health products; and promoting sustainable R&D financing mechanisms.

CONCERTED ADVOCACY EFFORTS

DNDi has positioned itself, along with other PDPs, as a credible advocate of neglected disease patients, by voicing its concerns and calling upon governments to increase their mobilisation for medical R&D in the field. ●●●

AWARDS

DNDi receives Goodwin Award for its social entrepreneurial approach



In May 2008, the University of Siena honoured DNDi with its Goodwin Award in the presence of Nobel Prize-winning economist Joseph Stiglitz (left in picture). The award was given to DNDi for its innovative needs-driven approach in making 2 new antimalarials available as public goods, and in engaging public and private partners worldwide, especially in neglected disease-endemic countries. The Goodwin Award is given

to entities that – through concrete actions and initiatives – promote well-being and demonstrate entrepreneurship.

DNDi honoured by the Société de Pathologie Exotique (France)

In June 2008, on the occasion of the centenary celebration of the prestigious Société de Pathologie Exotique, DNDi, represented by Marcel Tanner, Chairman of DNDi's Board of Directors, received the Society's Gold Medal Award given by SPE's President, Pierre Ambroise Thomas.



Dr. Bernard Pécoul voted "Doctor of the Year 2007"

Readers of the French magazine "Impact Médecine" nominated Dr. Bernard Pécoul, the Executive Director of DNDi, as the "Doctor of the Year 2007" for his remarkable work, reflected in the activities undertaken by DNDi in the field of neglected diseases.

●●● In April 2008, a joint statement to IGWG, signed by the International AIDS Vaccine Initiative (IAVI), Medicines for Malaria Venture (MMV), the TB Alliance, the Pediatric Dengue Vaccine Initiative (PDVI), Combating Insect Disease Borne (IVCC), AERAS, and DNDi, called for *"adequate and secure funding and on well-coordinated national and international policies that encourage innovation, facilitate collaboration and technology transfer, and ensure access to new health technologies."* Furthermore, and in parallel with these efforts, DNDi released in June 2008 a public statement endorsed by World Health Organization (WHO) urging the world's wealthiest nations, before the G8 summit in Japan, *"to commit resources for appropriate and sustainable financial mechanisms to strengthen existing efforts and to support innovation that are required to meet the health needs priorities of developing countries."*

RSTMH 2007: A STEP TOGETHER IN THE RIGHT DIRECTION

At the centenary meeting of the Royal Society of Tropical Medicine and Hygiene (RSTMH) in September 2007, in London, DNDi and the Leishmaniasis East Africa Platform (LEAP) held a symposium on investigating paromomycin to treat visceral leishmaniasis in Africa. More than 120 key scientists from the Tropical Medicine community attended the symposium to discuss this project.

Visceral leishmaniasis is particularly difficult to treat in Africa. The few existing drugs have limited use in the region due to concerns about toxicity, emerging resistance, difficulty of administration, cost, and the often low base level of patient health. The most widely used treatment for VL is sodium stibogluconate (SSG).

"The LEAP group, funded and facilitated by DNDi in Geneva, is currently engaged in discovering what might be the cause for this regional difference," stated current LEAP Chair, Dr. Ahmed Mudawi Musa of the Institute for Endemic Diseases in Sudan. "It appears that Sudanese patients are not only younger than those in India, but also sicker, as they suffer more concomitant infec-



INCREASING AWARENESS

Various tools (newsletters, videos, website, etc.) have been developed to raise awareness about kinetoplastid diseases and DNDi's activities. Worldwide media coverage included the following:

- *Le Monde*, "L'ASAQ, la pilule qui bouscule l'industrie pharmaceutique", February 27, 2007
- *New York Times*, "Malaria Pills Without Profit", March 3, 2007
- *Washington Post*, "A Dose of Innovation", March 29, 2007
- *Lancet*, "Hope for improved leishmaniasis treatment in Africa", October 2007
- *New York Times*, "Jump-Start on Slow Trek to Treatment for a Disease", January 8, 2008
- *Fortune*, "A new approach to an old disease", February 25, 2008
- *El País*, "Hay dolencias fuera del 'marketing' farmacéutico", March 11, 2008
- *Libération*, "Lutte générique contre le palu", April 28, 2008

tions, including malaria and pneumonia, during treatment. These factors probably contribute to a poorer clinical response.”

Dr. Monique Wasunna, of the DNDi Africa office at the Kenya Medical Research Institute, commented, “More region-specific research is needed to evaluate new potential treatments. LEAP has the expertise and presence on the ground to do it!”

Dr. Ahmed M. El Hassan, from the Department of Epidemiology and Clinical Sciences, at the Institute of Endemic Diseases of the University of Khartoum, Sudan, chaired this symposium, and his concluding remarks were: “A lot of effort and expertise has

gone into this project, with meticulous attention to detail and close follow-up. Important is not only the effort to find a new drug or a combination of drugs to treat VL, but other critical issues have been addressed by the project: capacity building with excellent training of African scientists and support staff, and concrete community participation in development and infrastructure strengthening in rural areas. I must underscore the fact that the project has brought African scientists in the region together to tackle a disease that knows no political boundaries: an example par excellence of South-South collaboration, about which we talk a lot and do very little.”

> SCIENTIFIC PUBLICATIONS IN 2007 BY TEAM AND PARTNERS

- “L’ASAO, une avancée dans la lutte contre le paludisme”
Kiechel JR, Pécoul B. *Med Trop.* 2007; 67:109.
- “Topical buparvaquone formulations for the treatment of cutaneous leishmaniasis”
Garnier T, Mantyla A, Jarvinen T, Lawrence MJ, Brown MB, Croft SL. *J Pharm Pharmacol.* 2007; 59:41-49.
- “Neglected diseases: progress in drug development”
Croft SL. *Curr Opin Investig Drugs.* 2007; 8:103-10.
- “Consultative meeting to develop a strategy for treatment of cutaneous leishmaniasis. Institute Pasteur, Paris. 13-15 June, 2006”
Modabber F, Buffet PA, Torreele E, Milon G, Croft SL. *Kinetoplastid Biol Dis.* 2007; 6:3.
- “Artesunate-amodiaquine for the treatment of uncomplicated malaria”
Sirima SB, Gansane A. *Expert Opin Investig Drugs.* 2007; 16:1079.
- “Sustainable health R&D and equitable access: harnessing momentum for the most neglected”
Dentico N, Sevcsik AM. *The Commonwealth Health Ministers Book.* 2007: 154-155.
- “Nifurtimox-eflornithine combination therapy for second-stage *Trypanosoma brucei gambiense* sleeping sickness: A randomized clinical trial in Congo”
Priotto G, Kasparian S, Nguoua D, Ghorashian S, Arnold U, Ghabri S, et al. *CID.* 2007; 45:1435-1442.
- “Efficacy and safety of artesunate plus amodiaquine in routine use for the treatment of uncomplicated malaria in Casamance, southern Sénégal”
Brasseur P, Agnamey P, Gaye O, Vaillant M, Taylor WR, Olliaro PL. *Malar J.* 2007 15; 6:150.
- “The challenges of Chagas disease – Grim outlook or glimmer of hope?”
Tarleton RL, Reithinger R, Urbina JA, Kitron U, Gürtler RE. *PLoS Negl Trop Dis.* 2007; 12:e332.
- “An analytical method with a single extraction procedure and two separate high performance liquid chromatographic systems for the determination of artesunate, dihydroartemisinin and mefloquine in human plasma for application in clinical pharmacological studies of the drug combination”
Lai CS, Nair NK, Mansor SM, Olliaro PL, Navaratnam V. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2007; 857:308.



DNDi SYMPOSIA IN 2007

Biovision

Lyon, France, March 11-14, 2007

- DNDi/session on “Diseases of poverty: disease burden and regulatory and legal issues with R&D for drugs for neglected diseases”

5th European Congress on Tropical Medicine and International Health



Amsterdam, the Netherlands, May 24-28, 2007

- Satellite Symposium: “The sanofi-aventis/DNDi partnership against malaria: first achievements”

Centenary Meeting of the Royal Society of Tropical Medicine and Hygiene (RSTMH)



London, UK, September 13-15, 2007

- DNDi/LEAP Symposium: “A step together in the right direction – LEAP investigates paromomycin to treat visceral leishmaniasis in Africa”

American Society of Tropical Medicine and Hygiene (ASTMH)



Philadelphia, USA, November 4-8, 2007

- sanofi-aventis/DNDi Symposium: “Implementation of a new ACT in African endemic countries: opportunities and challenges for documenting safety and effectiveness in the field”



FRIENDS OF DNDi

In 2007, DNDi inaugurated "Friends of DNDi", a group established to recognise select individuals who support DNDi's mission and vision by engaging global influencers, policymakers, and donors to help DNDi succeed in reaching its objectives. The first "Friends of DNDi" are (as of June 2008):

John Bowis: 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: Chair of Genethon Laboratory (France); former Chair of DNDi'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 DNDi.

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 DNDi Board member (2003-2005).

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

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

DNDi's FIRST STAKEHOLDERS' MEETING

DNDi's first Stakeholders' meeting took place in New York in June 2008 and brought together 150 scientists, researchers, academics, NGOs, "Friends of DNDi", and global health leaders from 25 countries to discuss how international research partnerships can best develop and deliver new lifesaving drugs for neglected diseases.

All speakers shared their operational experiences on different aspects of R&D activities, framing a comprehensive, open-minded, and rich discussion with stakeholders on a diverse range of issues, such as: intellectual property rights (IPR); regulatory strategy; development costs; the role and contribution of public and private partners in fostering innovation; the challenges in strengthening research capacities to conduct trials in remote areas; and the respective roles of PDPs and partners in implementing access plan strategies to better deliver tools to the patients. Marcel Tanner, Chair of DNDi's Board of Directors, commented, "To strengthen cross-border and public-private collaboration, our scientific partners from around the world shared critical insights on meeting patient needs, conducting clinical trials, and fostering R&D innovation." Dr. Bennett Shapiro, Chair of



Rashmi Barbhaiya, CEO of Advinus Therapeutics, and Monique Wasunna, Acting Director, Kenya Medical Research Institute (KEMRI), at DNDi's Stakeholders' meeting, June 2008.

DNDi's North American Board of Directors, and formerly with Merck, also noted: "In its short existence, DNDi has already shown remarkable capabilities in executing drug discovery and development programmes, as demonstrated by its launch of 2 new drugs for malaria, which were registered in record time. The opportunity to relieve the suffering of neglected patient populations is immense. I am personally delighted to be part of this effort."

Attendees were also reminded of the urgent needs that are driving efforts in the field of neglected diseases by Argentinian doctor Sergio Sosa-Estani, who remarked, "The patients are waiting. They are waiting for the researcher to research, the politician to decide, and the health worker to act."



During DNDi's first Stakeholders' meeting, the needs of patients took centre stage as participants were reminded that patients are waiting for new and improved tools for essential health. Participants agreed that PDPs can, and must, be strong advocates for policy change. "Let's move forward, let's maintain and consolidate", said Marcel Tanner as he concluded the meeting.

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.

A total of EUR 74 million has been committed to DND*i* as of April 2008 (see Financial Report). However, DND*i* still needs a total of EUR 200 million to achieve its business plan objectives by 2014.

EUR 200 million still needed!

Throughout the past 5 years, DND*i* has moved from an organisation mainly funded by one founding partner to an organisation with a diverse pool of 12 donors. When DND*i* was founded, Médecins Sans Frontières (MSF) - as its sole donor - provided EUR 25 million that was disbursed over its first five years. DND*i* has since succeeded in diversifying its funding from both public and private sectors, but is still seeking to achieve a balance between the two. To date:

- DND*i* has secured funding from national and local governments including France, Switzerland, Italy (Region of Tuscany), the United Kingdom, Spain, the Netherlands, the USA, and the European Union.
- DND*i* secured the other half of its funding from the private sector through donors such as MSF, the Bill & Melinda Gates Foundation, other private foundations, and individual donors.

In its fundraising efforts, DND*i* actively pursues donations from its Founding Partners, foundations, and major donors.

New major GRANTS RECEIVED in 2007



US\$ 25.7 million from the Bill & Melinda Gates Foundation

DND*i* received a 5-year, US\$ 25.7 million grant from the Bill & Melinda Gates Foundation to support its HAT and VL lead optimisation programmes as well as the progression of promising drug candidates through preclinical development.



EUR 6 million from the French Ministry of Foreign and European Affairs

The MAEE awarded DND*i* a 3-year, EUR 6 million grant to support preclinical and clinical projects for VL and HAT, as well as two clinical trial platforms in Africa.



EUR 5 million from the Spanish Agency for International Cooperation

AECI granted EUR 5 million to DND*i* for essential R&D of drugs for neglected diseases. The 2-year grant of the Spanish government will provide core initiative funding for DND*i*.



US\$ 2.3 million from the US National Institute of Allergy and Infectious Diseases

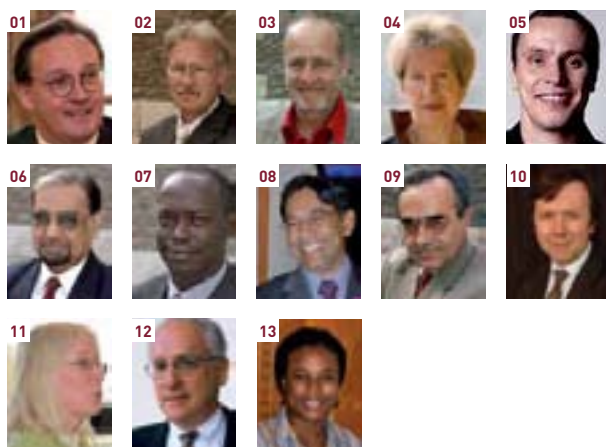
NIAID, part of the US National Institutes of Health (NIH), awarded DND*i* a 3-year, US\$ 2.3 million grant for the R&D of a low-cost formulation of amphotericin B to treat VL.

Governance & People

► THE BOARD OF DIRECTORS

The **Board of Directors** (as of June 2008) is composed of 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/ BOARD MEMBERS



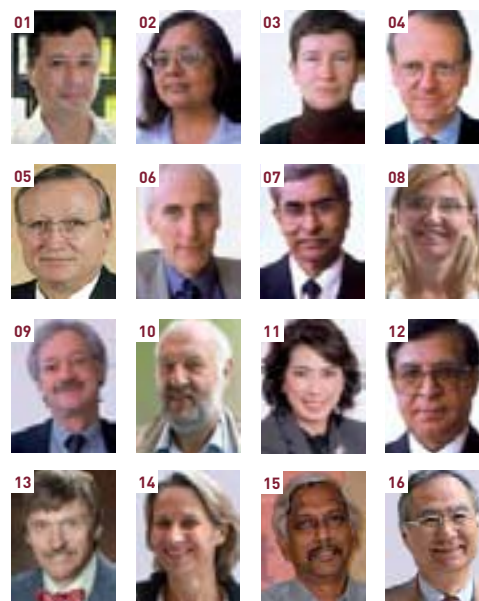
- 01 **Marcel Tanner**, Chair; Swiss Tropical Institute (STI)
- 02 **Reto Brun**, Secretary; Swiss Tropical Institute (STI)
- 03 **Bruce Mahin**, Treasurer; Médecins Sans Frontières (MSF)
- 04 **Alice Dautry**, Institut Pasteur, France
- 05 **Christophe Fournier**, Médecins Sans Frontières (MSF)
- 06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

► THE SCIENTIFIC ADVISORY COMMITTEE (SAC)

The **SAC** (as of June 2008) is composed of sixteen prominent scientists with expertise in various scientific disciplines relating to drug discovery & 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/ SCIENTIFIC ADVISORY COMMITTEE MEMBERS



- 01 **Julio Urbina**, Chair; Venezuelan Institute for Scientific Research (IVIC), Venezuela
- 02 **Khirana 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 Medicines for Malaria Venture, Switzerland
- 06 **Alan Hutchinson Fairlamb**, University of Dundee, UK
- 07 **Chitar Mal Gupta**, Central Drug Research Institute, India
- 08 **Maria das Graças Henriques**, Farmanguinhos/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)
- 13 **Mervyn Turner**, Merck & Co., USA
- 14 **Muriel Vray**, Institut Pasteur, France
- 15 **Krisantha Weerasuriya**, World Health Organization (WHO), India
- 16 **Haruki Yamada**, Kitasato Institute for Life Sciences, Japan

► THE EXECUTIVE TEAM (as of June 2008)

DNDi consists of a team of permanent staff based in Geneva, four regional support offices, a North American affiliate, and two project support offices. The Geneva team also coordinates a broad base of consultants and volunteers worldwide.

DNDi HEADQUARTERS, GENEVA

Bernard Pécoul, Executive Director
Shing Chang, Research & Development Director
Jean-François Alesandrini, Fundraising & Advocacy Director
Manica Balasegaram, Clinical Project Manager (from February 2008)
Gwenaëlle Carn, Clinical Project Coordinator
Eric Chatelain, Senior Project Manager
Brigitte Crotty, Executive & Board Assistant
Violaine Dällenbach, Communications Officer (from May 2008)
Ralf de Coulon, Finance, Human Resources & Administration Director
Robert Don, Senior Project Manager
Sally Ellis, Clinical Project Coordinator
Karin Genèveaux, Fundraising Coordinator
Caroline Gaere, Fundraising Officer for Major Donors (from March 2008)
Jean-Robert Ioset, Screening Coordinator (from January 2008)
Sadia Shafaqj Kaenzig, Senior Communications & Press Officer
Jennifer Katz, Fundraising Manager
Jean-René Kiechel, Senior Project Manager, FACT Project (based in Paris, France)
Denis Martin, Senior Project Manager
Céline Méot, Site & Travel Secretary
Janine Millier, Accountant
Béatrice Mouton, Human Resources & Legal Affairs Manager
Jean-Pierre Paccaud, Business Development Director
Sylvie Renaudin, Research & Development Assistant (from February 2008)
Isabella Ribeiro, Senior Project Manager (based in Rio de Janeiro, Brazil)
Ivan Scandale, Lead Optimisation Coordinator (from May 2008)
Ann-Marie Sevcsik, Scientific Communications Manager
Els Torreele, Senior Project Manager
Laurence Vielfaure, Financial Controller

REGIONAL SUPPORT OFFICES

Africa

Monique Wasunna, Head of Regional Support Office, Kenya
Simon Bolo, Finance and Administration Officer, Kenya
Joy Malongo, Administrative Assistant, Kenya

Malaysia

Visweswaran Navaratnam, Head of Regional Support Office, Malaysia

India

Bhawna Sharma, Head of Regional Support Office, India
Sharmila Roy, Finance & Administration Officer, India (from April 2008)

South America

Carolina Larriera, Head of Regional Support Office, Brazil
Bethania Blum de Oliveira, Project Support Officer, Brazil

AFFILIATE

DNDi North America, Inc.

Jana Armstrong, DNDi North America Director, USA
Sarah de Tournemire, Development & Administration Manager, USA (from April 2008)

PROJECT SUPPORT OFFICES

Democratic Republic of Congo

Augustin Kadima Ebeja, Regional Human African Trypanosomiasis Platform Coordinator, Democratic Republic of Congo (DRC)
Angèle Ngo-On, Logistician, NECT Project, DRC

Japan

Fumiko Hirabayashi, Japan Representative, Japan
Chris Brünger, Drug Development Advisor, Japan

CONSULTANTS AND VOLUNTEERS

DNDi would like to thank all of the consultants and volunteers who have played a significant role in DNDi's activities around the world:

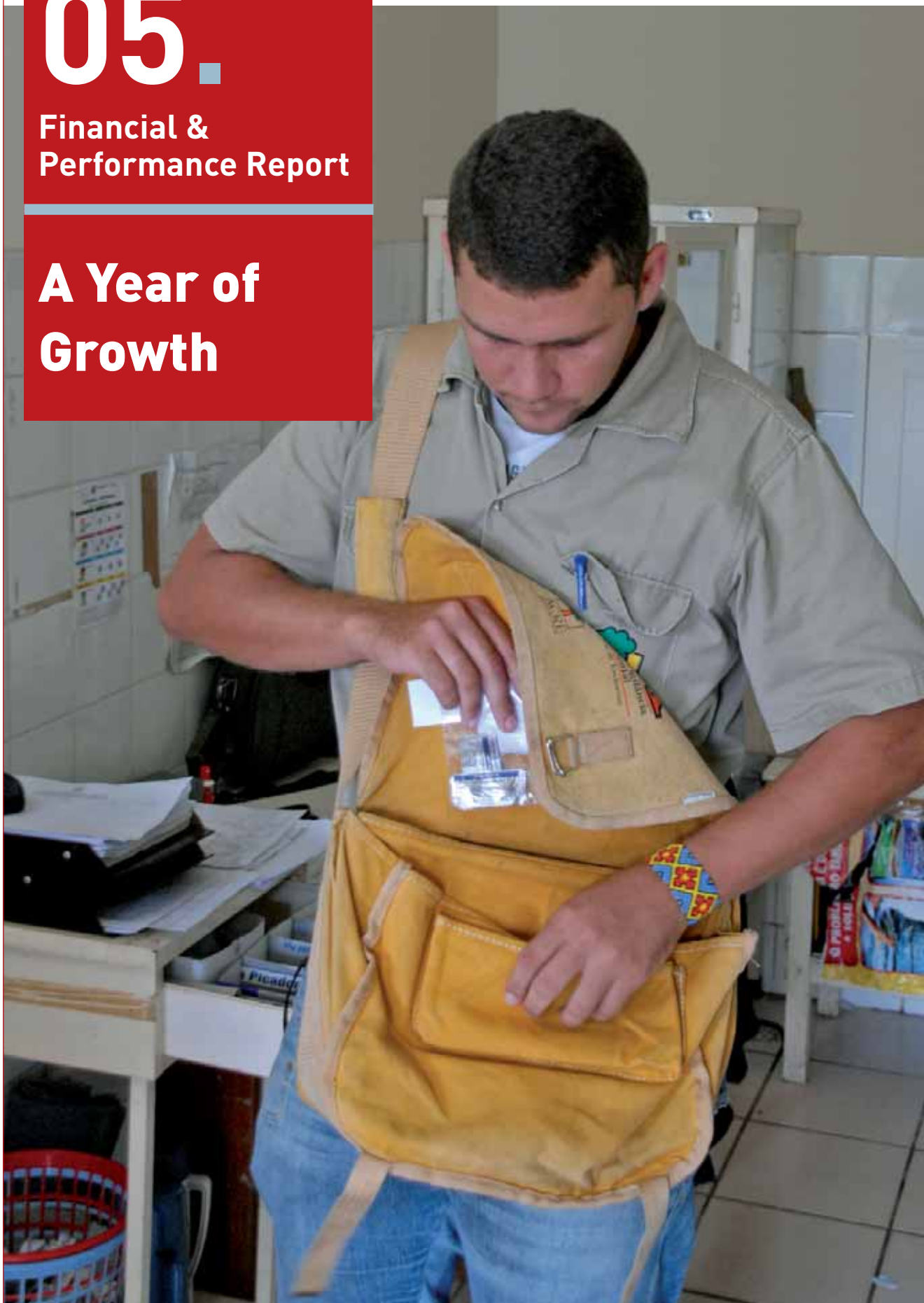
Moses Alobo, John Amuasi, Bineta Ba, Franck Ekow Baiden, Luciana de Barros, Samantha Bolton, Bernadette Bourdin, Philippe Brasseur, Michael Bray, Cécile Bridel, François Chappuis, Noëlle Chehab, Francis Crawley, Binod Dhungana, Graciela Diap, Nicoletta Dentico, Matthias Dormeyer, Eloan Dos Santos Pinheiro, Anouk Dunne, Virginie Emery, Michelle French, Nirmal Ganguly, Eva Gawronski-Renaud, Hellen Gelband, Corinne Ginfrey, Anne Gurnett, Alan Hudson, Kubinhe Kim, John Kinuta, Yuh Wen Ling, Karen Leon Guerrero, Michel Lotrowska, Marta Lucas, Ivan Maillet, Dirce de Matos, Guy Mazué, Farrokh Modabber, Evelyne Murenbeeld, Maristela de Oliveira Suare, Raymond Omolo, Emmanuel Petrault, Fabiana Piovesan Alves, Gustavo Romero, Morten Rostrup, Catherine Royce, Daniela Sassella, Karien Stuetzle, Olena Sushchenko, Jerzy Suwinski, Bob Taylor, Jessica Thomas, David Tweats, Michel Vaillant, Christina Zackiewicz.

DNDi would also like to extend a most sincere thanks to all of the experts, such as the FACT Implementation Advisory Group, who provide advice on various activities.

05.

Financial & Performance Report

A Year of Growth



As DNDi and its projects mature, health authorities play a key role in helping us to make products available. Such as is the case with ASMQ, where Brazilian health agents have traveled long and far to distribute ASMQ to thousands of patients as part of an intervention study undertaken by health authorities in the Amazonian state of Acre.

During its fourth year of operation, DNDi continued its growth, with overall expenditures increasing by 43% (as compared with 44% in 2006).



SUMMARY

In line with DNDi's business plan, 2007 was a year of continuing growth and development as DNDi's expenditures (Statement of Operations) grew to EUR 11.8 million from EUR 8.3 million in 2006. This growth in expenditure was matched with income growth as total contributions rose to EUR 15.9 million in 2007 (as compared with EUR 10.3 million in 2006 and EUR 5.7 million in 2005). These contributions demonstrate the confidence that donors have in DNDi as a product development partnership and their support of DNDi's social mission.

This income growth has enabled DNDi to increase its unrestricted operating funds to secure the continuity of its activities and the long-term viability of the organisation. As of December 2007, DNDi had a total of EUR 6.4 million in net assets (EUR 2.3 million as of December 2006). Unrestricted operating funds represent 3.8 months of DNDi's 2008 revised operating budget in-line with the spe-

cific objective outlined by the Board of Directors to create net assets totaling three months of the annual operating budget by the end of 2007.

In response to the growth of its activities, DNDi has accordingly grown its team of staff and consultants. In 2007, four scientists were hired to the R&D team, the position of Business Development was filled, and an additional staff member has reinforced the Department of Fundraising, Communications & Advocacy.

The Financial and Human Resources department, which is composed of four staff members: a Finance & Administration Director, a Financial Controller, an Accountant, and a Human Resources & Legal Affairs Manager (equivalent to 3.7 FTEs), has managed the growth by improving the organization's procedures. DNDi's financials are now being managed using the enterprise resources planning software Navision™. This software enables DNDi to manage its finances in a more efficient way and to notably improve its

financial reporting to its various donors. DNDi's auditors, Deloitte SA, conducted the organization's 2007 financial audit according to Swiss auditing standards and International Standards on Auditing (ISA).



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 2007, 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 <i>for the year ended December 31, 2007 (Summary in Euros)</i>	2007	2006
INCOME <i>(in Euros)</i>		
Public Institutional Funding	9,562,743	4,902,153
Private Resources	6,289,570	5,398,048
Total Income	15,852,313	10,300,201
EXPENDITURE		
Research & Development	8,577,253	5,855,204
Strengthening Capacities	974,041	557,741
Advocacy	657,580	649,292
Fundraising	363,084	249,587
General & Administration	1,251,076	961,344
Total Expenditure	11,823,035	8,273,168
Operating Surplus	4,029,278	2,027,033
Other income (net)	83,383	184,568
Net surplus for the year	4,112,661	2,211,601

RESEARCH & DEVELOPMENT EXPENDITURE

During 2007, DNDi continued to build a strong portfolio of screening, lead optimisation, preclinical, and clinical projects. As of December 2007, 18 R&D projects and several exploratory activities were being managed by five DNDi project managers with total Research and Development expenditures of EUR 8.6 million.

DNDi launched its first new treatment – **ASAQ** – in collaboration with sanofi-aventis in March 2007. ASAQ, a fixed dose combination therapy of artesunate (AS) and amodiaquine (AQ) for the treatment of malaria in sub-Saharan Africa is easy to use (one tablet-a-day dosing regimen for the most at-risk population, children), sold at low price in public markets (less than 1 USD for adults and less than 0.5 USD for children) and not patented. As of December 2007, ASAQ is registered in 21 countries in Africa. Approximately, EUR 1.0 million was spent in 2007, compared to EUR 0.8 million in 2006.

DNDi's second fixed-dose combination – **ASMQ** – is being developed in collaboration with Farmanguinhos, a public Brazilian pharmaceutical company. ASMQ is a fixed-dose combination of artesunate (AS) and mefloquine (MQ) for the treatment of malaria in Latin America and Southeast Asia. In December 2007, pharmaceutical development and registration activities were progressing well. EUR 0.7 million was spent in 2007, compared to EUR 1.0 million in 2006.

Highlighted below are several promising projects for human African trypanosomiasis (HAT) and visceral leishmaniasis (VL). Each of these projects achieved their 2007 milestones, raising the HAT project expenditure from EUR 1.3 million in 2006 to EUR 2.9 million, and the VL project expenditure from EUR 1.4 million in 2006 to EUR 2.1 million in 2007.

Among DNDi's promising projects are two in clinical development: a **nifurtimox-eflonithine co-administration therapy** for stage 2 HAT, EUR 0.4 million was spent in 2007, as compared to EUR 0.6 million in 2006; and **paromomycin**, a treatment for VL in East Africa, EUR 1.3 million was spent in 2007, as compared to EUR 0.9 million in 2006.

Several early-stage projects were also initiated in 2007: a preclinical project for HAT, a lead optimisation project for HAT, and a lead optimisation project for VL. In preclinical development, the fexinidazole project began in January 2007.

Fexinidazole, a new molecule synthesised by Hoechst, is active against the human African trypanosomiasis parasite and has been studied for its relative efficacy and safety compared to nifurtimox. The drug candidate is anticipated to enter Phase I clinical trials in 2008. EUR 0.5 million was spent in 2007.

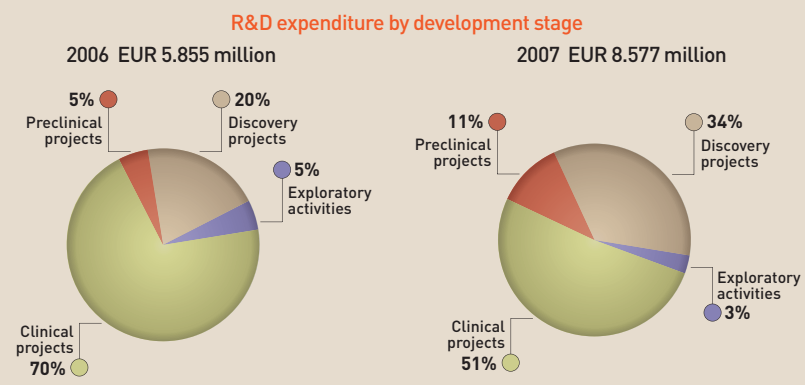
The two new **lead optimisation projects** were initiated together with two sets of industrial and institutional partners: one in the USA with Scynexis Inc., in North Carolina, and Pace University, in New York, to investigate potential HAT treatments; and the other in India

with Advinus Therapeutics, in Bangalore, and the Central Drug Research Institute (CDRI), in Lucknow, for compounds to treat VL. The total estimated budget of approximately EUR 22.6 million is anticipated to fully fund the program for the entire five years planned for the lead optimisation phase. EUR 1.3 million was spent in 2007.

Consequently, R&D expenditure increased by 46% (EUR 8.6 million in 2007, as compared to EUR 5.9 million in 2006). In December 2007, DNDi had seven projects in clinical development amounting to EUR 3.7 million; three projects in the preclinical stages, EUR 0.8 million; eight projects in the discovery stages, EUR 2.4 million; and pro-actively developed exploratory activities, EUR 0.2 million. Coordination and supervision amounted to EUR 1.3 million.

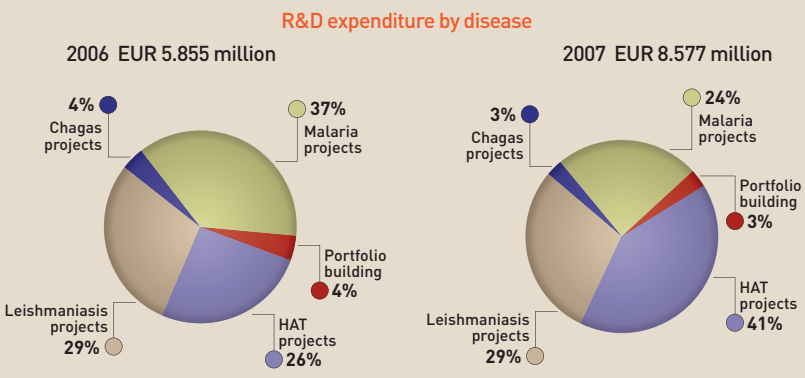
> BREAKDOWN BY DEVELOPMENT STAGE

The larger expenditures were in clinical development, but discovery projects represent 34% of the total R&D expenditure in 2007, as compared to 20% in 2006, due to the initiation of two lead optimisation projects. Likewise, the addition of the fexinidazole project accounts for the increase in preclinical expenditures (11% in 2007, as compared to 5% in 2006).



> BREAKDOWN OF TOTAL R&D EXPENDITURE BY DISEASE

The breakdown of expenditure by disease highlights DNDi's investment in HAT R&D in 2007.



STRENGTHENING CAPACITIES EXPENDITURE

Strengthening capacities expenses increased to EUR 974,041 in 2007, as compared to EUR 557,741 in 2006. These expenses comprise costs for construction and rehabilitation of clinics and hospital wards that are used for clinical trials in East Africa; training costs of partners' medical and paramedical staff to enhance their skills and knowledge; and the cost of local representatives to support DNDi's field activities.

COMMUNICATIONS & ADVOCACY EXPENDITURE

Communications and Advocacy expenses remained stable at EUR 657,580 in 2007, as compared to EUR 649,292 in 2006. The 2007 activities focused on: raising DNDi's profile in key targeted international scientific congresses; increasing awareness of the need to research and develop drugs for those neglected diseases; and building public responsibility for and leadership in addressing the needs of these patients.

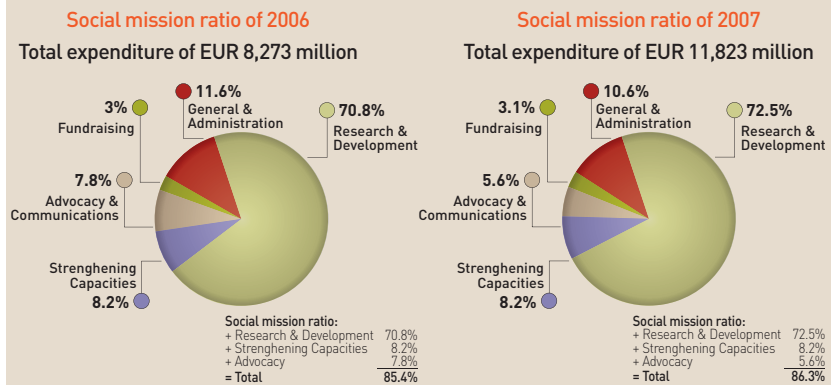
FUNDRAISING & GENERAL MANAGEMENT EXPENDITURE

The 2007 fundraising objective was to continue securing new funds from a mixture of public and private sources

> SOCIAL MISSION EXPENDITURE: MORE THAN 86% FOR THE SOCIAL MISSION

Social mission expenditures comprise the operational expenses to implement the mission of DNDi as defined in its charter (Research & Development, Strengthening Capacities and Advocacy), as opposed to non-social mission expenditures represented by the supporting costs (Fundraising and General & Administration). Social mission expenditures increased by 44% from EUR 7.1 million in 2006 to EUR 10.2 million in 2007.

The social mission ratio increased to 86.3% in 2007 compared to 85.4% in 2006. Hence, Fundraising and General Management expenses, as a percentage of total expenses, decreased from 14.6% to 13.7%.



to achieve a ratio of approximately 1:1 from both sources, while securing sustainable funding for the future (see below). Fundraising (EUR 363,084 in 2007 and EUR 249,587 in 2006) and General Management & Administration (EUR 1,251,076 in 2007 and EUR 961,344 in 2006) expenses represent the costs to raise funds (personnel, travel, and

document production) and the costs to manage the organisation (expenses incurred by the Board, the Executive Director, and the Financial & Administration department). The increase of the latter in 2007, as compared to 2006, is due to the cost of creating a Business Development department and the recruiting of its Director.

STATEMENT OF FINANCIAL POSITION

CAPITAL

DNDi increased its internally generated unrestricted funds by EUR 4.1 million reaching a total of EUR 6.4 million as of 31 December 2007, enabling DNDi to have 54% of its 2007 overall expenditure covered by total capital, representing 3.8 months of 2008 activities.

BALANCE SHEET at December 31, 2007 (summary in Euros)

ASSETS	2007	2006	LIABILITIES AND CAPITAL	2007	2006
Cash & securities	12,042,426	2,308,397	Payables & accruals	1,270,836	1,069,837
Receivables	3,579,870	1,882,388	Deferred income	7,840,730	759,110
Non-current assets	68,870	64,954	Provisions	169,995	129,849
			Total liabilities	9,281,562	1,958,796
			Paid-in capital	32,510	32,510
			Intern. generated unrestricted funds	6,377,094	2,264,433
			Total capital	6,409,604	2,296,943
Total Assets	15,691,166	4,255,739	Total Liabilities and Capital	15,691,166	4,255,739

STATEMENT OF CHANGES IN CAPITAL, for the year ended December 31, 2007 *(in Euros)*

	Opening balance	Allocation	Internal fund transfers	Closing balance
Paid-in capital	32,510	-	-	32,510
Internally generated unrestricted funds	2,264,433	-	4,112,661	6,377,094
Surplus for the year	-	4,112,661	(4,112,661)	-
Total Capital	2,296,943	4,112,661	-	6,409,604

CASH FLOW

The increase in cash flow in 2007, due to the development of internally generated reserves, lead to the need to strengthen DNDi's treasury management. UBS SA, a major Swiss bank, is providing these services, as well as global banking relationships. As a consequence, financial income increased in 2007 to EUR 134,338, as compared to EUR 61,099 in 2006.

THE FUTURE

In 2006, DNDi launched a process to review and update its Business Plan, with the support of Ernst & Young Business Advisory Services, to reflect significant changes in the landscape of neglected disease research and incorporate new information gathered during the first years of DNDi'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. DNDi will dedicate the majority of funding towards the development of treatments for visceral leishmaniasis (34%), human African trypanosomiasis (35%), and Chagas disease (17%). 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 optimisation or pre-clinical 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 co-administration)

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

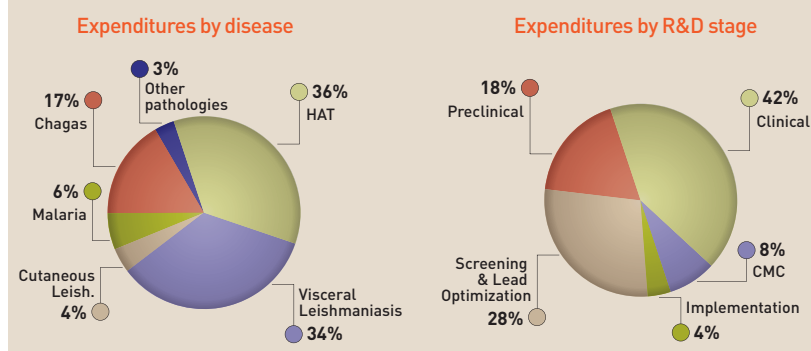
will be devoted to R&D (84%), with a secondary programmatic focus on strengthening capacities (4%) and advocacy (3%). This focus shows a clear emphasis on the social mission with 91% of the funds allocated in this area. From a disease perspective, two-thirds of overall expenses are devoted to visceral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

FORECASTED SOCIAL MISSION BREAKDOWN DNDi 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%)

> R&D COST APPORTIONMENT, 2004 - 2014, EUR 230 MILLION (84% of total expenditure)



DIVERSIFICATION OF FUNDING

DNDi was founded in 2003 with one of its founding partners, Médecins Sans Frontières (MSF), providing EUR 5 million per year for the first five years of operation. That financial contribution of MSF, as well as its operational support over the past five years, has been instrumental to give DNDi the independence and flexibility needed for the start-up of the initiative: to support the development of a robust pipeline for the target diseases; to launch its first products and to develop its fundraising capacity. Since that time, DNDi has been working to diversify its funding on several fronts to include both a mix of public and private donors and of project, portfolio, and initiative funding. Specifically, DNDi seeks diverse funding including: cash donations, in-kind contributions, grants, sponsorships, and legacies from individuals, governments, public institutions, companies, foundations, NGOs, and new alternative financial mechanisms. DNDi accepts donations of core funding to the organisation, earmarked support to a project, or a contribution to several projects pertaining to one or multiple diseases. However, to allow for the great-

THANKS TO OUR DONORS

DNDi would like to thank the following donors for their support of DNDi's activities since July 2003:

Public Institutional Donors

- Canton of Geneva, Switzerland
- Department for International Development (DFID), United Kingdom
- Dutch Ministry of Foreign Affairs (DGIS)
- European Union – Framework Partnership 5 and 6
- French Development Agency (AFD)
- French Ministry of Foreign and European Affairs (MAEE)
- Region of Tuscany, Italy
- Spanish Agency for International Cooperation (AECI)
- Swiss Development and Cooperation Agency (DDC)
- United States National Institutes of Health – National Institute of Allergy and Infectious Diseases (NIAID)

Private Donors

- Bill & Melinda Gates Foundation, USA
- Leopold Bachmann Foundation, Switzerland
- Médecins Sans Frontières, International
- Sasakawa Peace Foundation, Japan
- UBS Optimus Foundation, Switzerland
- Other Private Foundations and Private Individual Donors

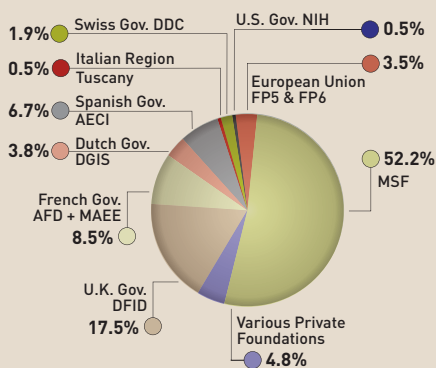
est flexibility in decision making needed for the R&D portfolio management strategy and to allow for the greatest independence in its operations, DNDi's priority is to raise unrestricted initiative funding. In cases where this is not possible, DNDi will pursue project specific or earmarked

funding without requirements that may interfere with the objectives of the project. In 2007, while MSF is still the largest donor contributing 33% of the 2007 funding (50% since 2003, cumulative funding), this is a significant reduction from the 87% funding in 2005 and 49% in 2006. As a key component of the ●●●

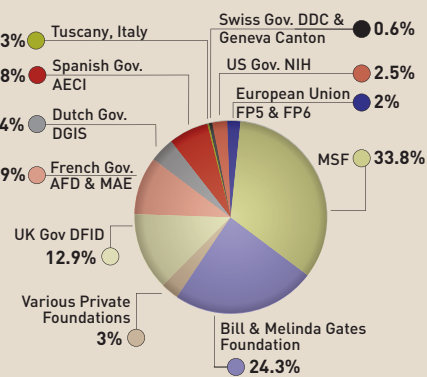
> FROM 2003 TO THE END OF 2007, A TOTAL OF EUR 37 MILLION WAS CONTRIBUTED TO DNDI

In 2007, DNDi was pleased to welcome the French Ministry of Foreign & European Affairs, the Spanish Agency for International Cooperation, and the US National Institute of Allergy and Infectious Diseases part of the National Institutes of Health, as important new public donors. In November 2007, DNDi obtained the commitment of the Bill & Melinda Gates Foundation with the signature of a five year grant agreement for USD 25.7 million (~ EUR 18 million), with funding to begin in 2008.

From 2003 to end of 2007, a total of EUR 37 million was contributed to DNDi



As of April 2008, EUR 74 million has been committed to DNDi to fund its activities from 2003 through 2010

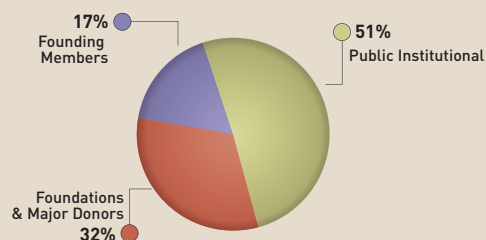


mission of DNDi is to stimulate increased involvement and responsibility of national governments and international organisations in R&D for neglected diseases, DNDi strives to obtain half of its funding from public sources. DNDi works to achieve a balance of public and private funding, with total public institutional contributions amounting to EUR 9,562,743 (60%), as compared to EUR 6,289,570 (40%) in private grants in 2007. This increase in public funding was a result of new actors entering the field of Product development partnerships (PDPs) and neglected diseases research. With the NIAID of the US NIA releasing a call specifically for PDPs, under which DNDi was awarded a grant of USD 1.4 million. The French and Spanish governments also demonstrated their commitment to neglected diseases with awards of EUR 5.95 million over 3 years and EUR 5 million over 2 years, respectively. In addition the Region of Tuscany, Italy joined this group of public donors. To ensure the other 50% of DNDi's funding, DNDi is actively pursuing private funding from its founding members, foundations, and major donors. In November 2007, DNDi obtained the commitment of the Bill & Melinda Gates Foundation with the signing, of a five-year grant agreement for USD 25.7 million (around EUR 18 million), with funding to begin in 2008. In addition, DNDi North America, an affiliate, is launching a major fundraising effort following the long history of private philanthropy in North America. Thanks to all its donors, DNDi is able to deliver new treatments for the most neglected patients.

> EVOLUTION OF PUBLIC/INSTITUTIONAL VERSUS PRIVATE AND FOUNDING MEMBERS FUNDING IN 2006 AND 2007, AS COMPARED TO FORECAST FROM DNDi BUSINESS PLAN

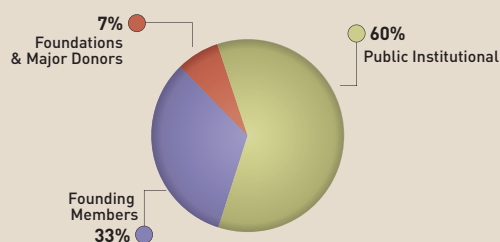
Sources of funds: Public institutional, Private and Founding Members

Total: EUR 276 million forecast from 2004 to 2014

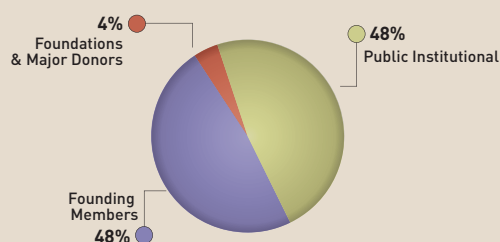


Source: DNDi Business Plan

Total: EUR 15.9 million in 2007



Total: EUR 10.3 million in 2006



Financial Statements and Audit Report

DRUGS FOR NEGLECTED DISEASES INITIATIVE (DNDI), Geneva BALANCE SHEET at December 31, 2007 *(with 2006 comparative figures)*

ASSETS <i>(expressed in EUR)</i>	Notes	2007	2006
Current assets			
Cash and marketable securities			
Cash and banks at head office		901,226	976,726
Cash and banks at subsidiaries		87,880	31,671
Time deposits		11,053,320	1,100,000
Marketable securities		0	200,000
Total cash and marketable securities		12,042,426	2,308,397
Current accounts and receivables			
Advances to officers and liaison offices		79,968	32,227
Advances to partners related to projects		524,959	623,238
Receivables from public institutional donors		2,766,989	817,433
Receivables from founders		37,887	270,750
Other receivables		54,492	51,731
Prepaid expenses		115,575	87,009
Total current accounts and receivables		3,579,870	1,882,388
Total current assets		15,622,296	4,190,785
Non-current assets			
Tangible fixed assets, net	3	53,379	50,259
Bank guarantee		15,491	14,695
Total non-current assets		68,870	64,954
TOTAL		15,691,166	4,255,739
LIABILITIES & CAPITAL <i>(expressed in EUR)</i>			
Current liabilities			
Payables to partners related to projects		251,962	339,227
Accounts payable to founders		0	1,596
Other payables and accrued expenses		1,018,873	729,014
Deferred income		7,840,731	759,110
Provisions	4	169,995	129,849
Total current liabilities		9,281,562	1,958,796
Capital of the organisation			
Paid-in capital		32,510	32,510
Internally generated unrestricted funds		6,377,094	2,264,433
Total capital of the organisation		6,409,604	2,296,943
TOTAL		15,691,166	4,255,739

Statement of activities

STATEMENT OF OPERATIONS for the year ended December 31, 2007 *(with 2006 comparative figures)*

<i>(expressed in EUR)</i>	<i>Notes</i>	2007	2006
Income			
Public institutional funding			
Government & public institutional organisation, unrestricted		5,440,744	3,597,640
Government & public institutional organisation, restricted		4,121,999	1,304,513
Total public institutional funding		9,562,743	4,902,153
Private resources			
Private foundations, corporations, and individuals, unrestricted		152,035	156,925
Private foundations, corporations, and individuals, restricted		892,735	241,123
Total private resources		1,044,770	398,048
Resources from founders			
Médecins Sans Frontières, unrestricted		5,244,800	5,000,000
Total resources from founders		5,244,800	5,000,000
Total income	5	15,852,313	10,300,201
Social mission expenditure			
Research & development expenditure			
Research & development coordination and supervision	6	1,329,644	963,873
Human African trypanosomiasis projects		2,907,810	1,293,323
Leishmaniasis projects		2,118,230	1,416,658
Chagas disease projects		230,382	179,524
Other projects		1,744,814	1,782,759
Portfolio building		246,373	219,067
Total research & development expenditure		8,577,253	5,855,204
Strengthening capacities	7	974,041	557,741
Advocacy expenses	8	657,580	649,292
Total social mission expenditure		10,208,874	7,062,237
Non-social mission expenditure			
Fundraising	8	363,084	249,587
General and administration	8	1,251,076	961,344
Total non-social mission expenditure		1,614,160	1,210,931
Total expenditure		11,823,034	8,273,168
Operating surplus		4,029,279	2,027,033
Other income (expenses)			
Financial income (expenses), net		134,338	61,099
Exchange loss, net		(72,850)	(42,455)
Other income		21,894	165,924
Total other income, net		83,382	184,568
Net surplus for the year prior to allocations		4,112,661	2,211,601
Allocation to internally generated unrestricted funds		(4,112,661)	(2,211,601)
Net surplus for the year after allocations		-	-

DRUGS FOR NEGLECTED DISEASES INITIATIVE (DND), Geneva
FUNDS FLOW STATEMENT FOR THE YEAR ENDED DECEMBER 31, 2007 *(with 2006 comparative figures)*

(expressed in EUR)

	2007	2006
Funds flow from operations		
Operating surplus for the year	4,112,661	2,211,601
Depreciation of fixed assets	34,768	43,778
Increase (decrease) in provisions	40,147	75,532
(Increase) decrease in advances	50,538	(460,407)
(Increase) decrease in receivables from donors	(1,949,556)	(522,376)
(Increase) decrease in founders and other receivables	230,101	(288,683)
(Increase) decrease in prepaid expenses	(28,565)	(65,417)
Increase (decrease) in payables to partners related to projects	(87,265)	(171,443)
Increase (decrease) in accounts payable to founders	(1,596)	(58,612)
Increase (decrease) in other payables and accrued expenses	289,858	131,921
Increase (decrease) in deferred income	7,081,621	683,333
Funds flow from operations	9,772,712	1,579,227
Funds flow from investing activities		
(Increase) decrease of investments in tangible fixed assets	(37,888)	(34,959)
(Increase) decrease in bank guarantee	(795)	416
Funds flow from investing activities	(38,683)	(34,543)
Funds flow from financing activities		
Cash increase	9,734,029	1,544,684
Cash and marketable securities - beginning of year	2,308,397	763,713
Cash and marketable securities - end of year	12,042,426	2,308,397

DRUGS FOR NEGLECTED DISEASES INITIATIVE (DND), Geneva
STATEMENT OF CHANGES IN CAPITAL, for the year ended December 31, 2007 *(expressed in Euros)*

	Opening balance	Allocation	Internal fund transfers	Closing balance
Internally generated funds				
Paid-in capital	32,510	-	-	32,510
Internally generated unrestricted funds	2,264,433	-	4,112,661	6,377,094
Surplus for the year	-	4,112,661	(4,112,661)	-
Capital of the organisation	2,296,943	4,112,661	-	6,409,604

NOTES TO THE FINANCIAL STATEMENT FOR THE YEAR ENDED DECEMBER 31, 2007

1. GENERAL INFORMATION

a) Legal aspects

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

With its head office in Geneva, DNDi 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, DNDi is monitored by the Swiss Federal Supervisory Board for Foundations.

b) Income tax

DNDi is exonerated from income tax from the Geneva Cantonal tax authorities for a five-year period commencing 2003 and from Swiss federal income tax for an indeterminate period.

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

DNDi has four Regional Support Offices to help identify patients' needs, support project managers, identify and support regional partners, seek funding, and undertake regional advocacy work for DNDi. 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 DNDi 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 DNDi. For local or operational reasons, DNDi may deem it necessary to establish the RSOs as a legal entity, usually a branch of DNDi Foundation. Establishment of a DNDi legal entity outside Switzerland requires the authorization of the Board of Directors.

As of December 2007, DNDi has established legal entities in Kenya and Brazil in the form of branches for its African and Latin American RSOs. The establishment of a branch in India is still pending.

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 ("DNDi North America"), was established in February 2007. This affiliate is based in New York City, New York, USA, and operates under the direction of the DNDi North America Board of Directors. The purposes for which it was formed are exclusively charitable and educational and include conducting activities to support or benefit the Drugs for Neglected Diseases *initiative* (DNDi), such as making grants to support programs, 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.

A legal entity has been set up in France in the form of a not-for-profit Association for administrative purposes; this legal body is not a RSO. The final DNDi RSO is in Malaysia. Additionally, DNDi has two Project Support Offices: in Japan and the Democratic Republic of Congo.

RSO accounting is fully incorporated into DNDi accounts. Start-up funding for the affiliate is provided via a grant from DNDi and is accounted for in the DNDi financial statements.

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 by 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 DNDi statutes. They are defined in the present general notes under point 1.a Legal aspects. Research & Development, Strengthening existing capacities, and Advocacy are the three chapters that comprise "Social mission expenditure."

d) Functional currency

The Board of DNDi 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 recognized 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:

	2007	2006
USD	0.6796	0.7587
CHF	0.6034	0.6222
GBP	1.3563	1.4914
100 CDF	0.1207	0.1493
100 INR	1.7257	1.7111
100 KES	1.0740	1.0951
100 JPY	0.6063	0.6384

f) Income

Public and private donations are recorded on an accrual basis. Individual and spontaneous donations are recorded on a cash basis.

g) Funding committed to projects

After Board approval of grants for projects, one or more contracts are drawn up and signed by the Executive Director. Thereafter, funds are allocated to the partner(s) in charge of the project. Expenditures are recorded:

- according to a financial report presenting expenditures incurred during the year on an accrual basis; or
- if financial reports are unavailable as per the deadline of the 15th of March of the following year, an estimated amount is calculated on a *pro rata temporis* basis, based on the time between the contract signing date and December 31. This estimated amount is considered as an accrued expense

following Swiss GAAP RPC to be regularized 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 grants for projects 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 one guarantee representing a deposit related to an office rental and a letter of guarantee pertaining to the new premises DND*i* will rent from February 2008. 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 utilized 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 and valued 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, excluding the involvement of a monetary transfer.
- They must be clearly identifiable and part of DND*i*'s projects and activities as defined by DND*i*'s action plans and budgets.
- Recognizable as a visible contribution to DND*i*'s projects and activities,

benefiting to DNDi's, and in-line with DNDi's mission and objectives.

- Partners' voluntary involvements in joint projects and activities, in particular if the Partner does not aim to achieve DNDi's project objectives, are not considered as gifts-in-kind.
- For goods or services paid at prices below market prices, the difference

between real payment and a current market price is not considered as a gift-in-kind, but the current market price reached after negotiations is.

- Fair market value is defined as the price DNDi would have paid to utilize the good or service. Fair market value can be suggested by partners. However, DNDi will be careful not to over-

estimate 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 DNDi 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.	15,915	25,655	8,689	50,259
Gross values of cost				
Beginning of the period 1.1	108,649	42,156	14,328	165,132
Additions	27,108	2,743	8,038	37,889
Disposals	-	-	-	-
End of the period 31.12	135,757	44,899	22,366	203,022
Cumulated amortisation				
Beginning of the period 1.1	(92,734)	(16,501)	(5,639)	(114,874)
Systematic amortisation	(21,438)	(8,884)	(4,446)	(34,768)
End of the period 31.12	(114,172)	(25,385)	(10,085)	(149,642)
Net carrying amounts 31.12	21,586	19,513	12,280	53,379

4. PROVISIONS

	Provision for taxes	Provision for HR expenses (holidays not taken)	Provision for running expenses (other)	Total
Carrying amount as per 1.1.2006	54,317	0	0	54,317
Creation	69,462	0	6,070	75,532
Utilization	0	0	0	0
Reversal	0	0	0	0
Carrying period as per 31.12.2006	123,779	0	6,070	129,849
Carrying period as per 1.1.2007	123,779	0	6,070	129,849
Creation	48,682	54,787	0	103,469
Utilization	(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

5. INCOME

a) Cumulative donations committed to DNDi and/or received by 2007 (in EUR)

		Total commitment in currencies*	As per Statement of Operations 2007 in EUR	To be used after 2007 in currencies*
Bill & Melinda Gates Foundation (signed in 2007)	USD	25,729,285	0	25,729,285
Canton of Geneva	CHF	600,000	124,440	0
Dutch Government DGIS	EUR	2,975,000	1,300,000	1,550,000
EU FP6 HAT	EUR	340,000	113,613	226,387
French Government AFD	EUR	1,500,000	568,720	0
French Government MAEE	EUR	5,955,000	1,668,060	4,286,940
Medicor Foundation	EUR	650,000	650,000	0
Médecins Sans Frontières	EUR	25,000,000	5,244,800	5,529,846
Sandoz Family Foundation	CHF	500,000	151,775	0
Sasakawa Peace Foundation	EUR	161,650	78,818	21,200
Spanish Government AECI	EUR	5,000,000	2,500,000	2,500,000
Tuscany Region	EUR	200,000	200,000	0
UBS Optimus Foundation	CHF	540,000	163,917	0
UK Government DFID	GBP	6,500,000	2,940,744	2,000,000
USA Government NIAID	USD	1,375,633	147,166	1,159,435
Various individual donors	EUR	260	260	0
TOTAL DONATIONS*	<i>EUR</i>	70,222,102*	15,852,313	35,100,547*

*"Total donations" amounts appear in Euro at the USD/EUR, CHF/EUR and GBP/EUR exchange rates as per 31.12.2007 (see note 2).

They give an approximate value of "total commitment in currencies" and "total to be used after 2007 in currencies" as exchange rates vary over time.

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

	Medecins Sans Frontieres* (Unrestricted)	Sandoz Family Foundation (Unrestricted)	Medecins Sans Frontieres (Restricted)	Spanish Government AECI (Unrestricted)	Canton of Geneva (Unrestricted)	UK Government DFID (Unrestricted)	French Government AFD (Restricted)	French Government MAEE (Restricted)	Dutch Government DGIS (Restricted)	European Union FP6 HAT (Restricted)	Medicor Foundation (Restricted)	United States Government NIAD (Restricted)	Sasakawa Peace Foundation (Restricted)	Tuscany Region (Restricted)	UBS Optimus Foundation (Restricted)	Other Revenue	TOTAL
R&D Coordination, Supervision costs	24,572	3,331	8,117	422,933	0	805,965	0	0	645	0	46,899	17,194	0	0	0	0	1,329,644
Paromomycin for VL	0	0	219,129	4,533	32,844	0	0	542,265	0	0	345,126	0	0	137,695	0	0	1,281,593
FACT (ASAQ & ASMQ) for Malaria	0	0	0	0	0	0	566,160	0	1,178,654	0	0	0	0	0	0	0	1,744,814
Nifurtimox + Eflornithine for HAT	0	0	0	15,105	0	0	0	300,918	0	0	75,560	0	0	0	0	0	391,583
Other Clinical Projects	0	0	0	259,884	0	0	0	0	0	0	18,481	0	0	0	0	0	278,365
HAT Consortium (Scynexis) Lead Optim.	0	0	0	321,469	0	978,274	0	0	0	0	0	0	0	0	0	0	1,299,743
VL Consortium (Advinus) Lead Optim.	0	0	0	56,025	0	0	0	0	0	0	0	0	0	0	0	0	56,025
Other Preclinical projects	0	5,401	0	157,760	0	6,197	0	407,118	0	0	0	129,972	0	0	113,752	0	820,200
Discovery Projects	0	68,043	0	721,266	0	554,211	0	17,261	0	0	0	0	78,687	0	50,485	0	1,489,953
HAT & LEAP Platforms	7,648	0	0	12,605	91,615	0	0	161,026	0	113,685	73,125	0	0	62,240	0	0	521,943
Other Strengthening Capacities activities	0	0	0	45,210	0	208,114	0	0	0	0	84,106	0	0	0	0	0	337,430
Advocacy	225,513	0	17,666	72,882	0	123,134	0	112,822	105,583	0	0	0	0	0	0	0	657,580
Fundraising	119,795	0	0	242,874	0	0	0	0	415	0	0	0	0	0	0	0	363,084
General Management costs	628,872	75,000	(92)	167,454	(19)	264,850	2,560	126,650	14,703	(72)	6,713	0	131	65	(320)	210,622	1,497,117
Year-end result	3,993,600	0	0	0	0	0	0	0	0	0	0	0	0	0	0	119,062	4,112,662
TOTAL	5,000,000	151,775	244,800	2,500,000	124,440	2,940,744	568,720	1,668,060	1,300,000	113,613	650,000	147,166	78,818	200,000	163,917	329,684	16,181,737
TOTAL GRANTS ONLY	5,000,000	151,775	244,800	2,500,000	124,440	2,940,744	568,720	1,668,060	1,300,000	113,613	650,000	147,166	78,818	200,000	163,917		15,852,053

*Medecins Sans Frontieres' donation is fully unrestricted and can be used to increase total capital, whereas Sandoz Family Foundation, UK, and Spanish Government grants are only partially unrestricted.

6. R&D PROJECTS RELATED EXPENDITURE

Recognized in	2007	2006
Clinical/Post-Registration Projects:		
Nifurtimox-Eflornithine co-administration for stage 2 <i>T.b.gambiense</i> HAT ¹	391,583	615,755
Paromomycin for VL in East Africa ²	1,281,593	859,270
Artesunate+Amodiaquine for Malaria ³	1,041,260	803,696
Artesunate+Mefloquine for Malaria ³	703,554	979,063
Imiquimod for Cutaneous Leishmaniasis ⁴	93,737	178,256
Combination therapy for VL ⁵ (Preclinical phase until 2006)	165,858	0
Ambisome for VL ⁶	18,770	251
Exploratory Clinical (Ped. Benznidazole, Posaconazole, ...)	28,870	9,994
Total Clinical/Post-Registration Projects	3,725,225	3,446,285
Preclinical Projects:		
Fexinidazole HAT ⁷	526,344	0
Combination therapy for VL ⁵ (Clinical phase as from 2007)	0	249,731
Amphotericin B polymer ⁸	293,856	1,883
Buparvaquone VL ⁹	6,880	0
Total Preclinical Projects	827,080	251,614
Discovery (Selection & Optimization) Projects		
Benzofuroxans for Chagas	0	45,754
Cysteine Protease Inhibitors for HAT	2,197	85,169
DHFR Inhibitors	0	27,698
Kitasato Screening for Trypanosomes ¹⁰	155,482	91,960
Nitroimidazoles (+ Nitroheterocycles 2006) for HAT ¹¹	226,767	368,850
Protein Farnesyl-transferase inhibitors for Trypanosomes	0	23,880
Trypanothione Reductase Inhibitors for Leishmania & Trypanosomes ¹²	104,182	20,922
8 Aminoquinoline NPC1161B for VL	0	2,214
Ascofuranone for HAT	0	1,086
Microtubule Inhibitor ¹³	189,295	74,716
HAT Consortium (Scynexis) Lead Optimisation ¹⁴	1,299,743	0
VL Consortium (Advinus) Lead Optimisation ¹⁵	56,025	0
Pan-Asian Natural Substances Network (Strengthening Existing Capacities in 2007)	0	54,351
Exploratory Screening Assays (STI, LSHTM, Antwerp, Murdoch)	292,587	0
Exploratory Discovery (Scynexis, CDRI)	122,653	158,952
Total Discovery Projects	2,448,931	955,552
Other Exploratory Activities		
Other Exploratory Activities	246,373	237,880
Total Exploratory Projects	246,373	237,880
Project-Related Variable Expenditure		
Coordination & Supervision	1,329,644	963,873
TOTAL OF PROJECTS RELATED EXPENDITURE	8,577,253	5,855,204

Main partners:

- Swiss Tropical Institute (STI), Switzerland / Epicentre, France / National Programs for the Fight Against Human African Trypanosomiasis (PNLTHA), Democratic Republic of Congo & the Republic of Congo/ Coordinating Office for the Control of Trypanosomiasis (COCTU), Uganda / Médecins Sans Frontières (MSF) / WHO-TDR
- Kenya Medical Research Institute (KEMRI), Kenya / Institute of Endemic Diseases, Sudan / University of Addis Ababa, Ethiopia / MSF / WHO-TDR, Gondar University, Ethiopia/ Gedaref MoH, Sudan/ IDA Solutions, The Netherlands, London School of Hygiene and Tropical Medicine (LSHTM), UK
- sanofi-aventis, University of Bordeaux-Tropival, Epicentre, IRD & Ellipse, France / National Centre for Research and Development on Malaria (CNRFP), Burkina Faso / KEMRI, Kenya / Indian Council of Medical Research (ICMR), India / MSF / University of Oxford, UK, Rottendorf Pharma, Germany/Farmanguinhos, Brazil/ University Sains, Malaysia / Oxford University, UK / Cipla, India / Mahidol University Shoklo Malaria Research Unit in Mae Sot, Thailand / Catalent, ICMR & GVK, India / WHO-TDR
- McGill University, Canada / Universidade Peruana Cayeto Heredia, Peru / 3M Pharmaceuticals, USA

- ICMR, India / Kala Azar Medical Research Center, India/ RMRI, India/ University of Varanasi, India/ GVK-BIO, India
- University of Addis Abeba & Gondar University, Ethiopia/ London School of Hygiene and Tropical Medicine, UK
- Axyntis, France / STI, Switzerland / Nerviano, Italy / Covance & Aptuit, UK / KARI-TRC, Kenya
- Imperial College London & London School of Hygiene and Tropical Medicine (LSHTM), UK/ Shantha Biothec, India
- Advinus Therapeutics, India / University Sains, Malaysia / LSHTM, UK
- Kitasato University & Institute, Japan
- STI, Switzerland / Fiocruz Institute & Ouro Preto University, Brazil / Covance & BioDynamics, UK / Absorption Systems, USA
- Venezuelan Institute for Scientific Research (IVIC) / Ouro Preto University, Brazil
- Murdoch University, Monash University & Epicheim, Australia
- Scynexis Inc & Pace University, USA
- Advinus & CDRI, India / LSHTM, UK

7. STRENGTHENING CAPACITIES EXPENDITURE

DNDi 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.

	2007	2006
Regional Support Offices: Brazil, India, Kenya, Malaysia	337,430	332,224
Paromomycin for VL, Ward constructions Gondar, Ethiopia & Dooka, Sudan	157,548	37,043
Leishmaniasis East Africa Platform (LEAP)	163,249	97,990
Human African Trypanosomiasis (HAT) Platform	201,146	90,484
Pan-Asian Natural Substances Network*	114,668	0
TOTAL	974,041	557,741

*Discovery Project in 2006

8. ADVOCACY, FUNDRAISING, AND GENERAL & ADMINISTRATION EXPENSES

	ADVOCACY		FUNDRAISING		GENERAL & ADMINISTRATION*	
	2007	2006	2007	2006	2007	2006
Human resources	333,670	333,515	274,469	185,023	837,653	540,151
Office charges	13,909	16,365	14,256	7,013	32,857	24,754
Travel expenses	41,660	77,895	23,052	13,236	110,055	85,159
Administration	62,217	31,458	23,946	35,550	145,376	197,096
IT & telecommunications	25,590	24,569	19,454	4,215	63,311	59,802
Communication	173,894	155,762	3,902	1,038	44,427	38,396
Depreciation	5,608	8,064	4,006	3,456	9,133	11,982
Exceptional expenses	1,032	1,664	0	56	8,264	4,004
TOTAL	657,580	649,292	363,084	249,587	1,251,076	961,344

*Including Business Development in 2007

9. INDEMNITIES & REMUNERATIONS GIVEN TO DIRECTORS

All members of the Board are volunteers. The Board members have not received any remuneration for their mandate in 2007. In 2006, the Treasurer was involved in the capacity of a consultant. In this

capacity, he was remunerated as an employee of Médecins Sans Frontières, France. Part of the Treasurer's salary, which amounted to EUR 11,017 in 2006, was invoiced to DNDi. DNDi received

the authorization from the Swiss Federal Supervisory Board for Foundations to remunerate a member of the Council until June 2007.

10. VALUATION OF IN-KIND

Drugs for Neglected Diseases Initiative (DNDi), as an independent needs-driven not-for-profit organization, 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 DNDi with goods or services at zero cost, as gifts-in-kind.

Gifts-in-kind in Euros evaluated for the year 2007, per category and per project

	Staff scientific	Staff non-scientific	R&D services	Legal & comm. services	Office, furniture & admin.	TOTAL
FACT	120,000					120,000
NECT & HAT Platform			7,800			7,800
Paromomycin		14,818				14,818
Natural Substances					37,883	37,883
Exploratory: Buparvaquone			76,330			76,330
HTS Assay for VL			35,185			35,185
Regional Support Offices	72,061	6,125			43,762	121,948
Fundraising				23,037		23,037
General Management		5,000				5,000
TOTAL	192,061	25,943	119,315	23,037	81,645	442,001

Main in-kind contributors: J.-R. Kiechel, France; C. Brünger, Japan; Simpson Thacher & Bartlett LLP, USA; KEMRI, Kenya; Sains University, Malaysia; Institut Pasteur, Korea.

11. ASSETS PLEDGED AS GUARANTEE FOR COMMITMENTS

At year-end, a bank of the Foundation provided a rental guarantee of EUR 42,238 in favour of a third party. Cash for an equivalent amount is pledged at the corresponding bank.

AUDITOR'S REPORT

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

As statutory auditors, we have audited the accounting records and the financial statements (balance sheet, statement of operations, funds flow statement, statement of changes in capital and notes) of Drugs for Neglected Diseases initiative (DNDi), presented on pages 47 to 57, for the year ended December 31, 2007. In accordance with Swiss GAAP RPC 21, the content of the performance report presented on pages 41 to 46 is not audited.

These financial statements are the responsibility of the Board. Our responsibility is to express an opinion on these financial statements based on our audit. We confirm that we meet the legal requirements concerning professional qualification and independence.

Our audit was conducted in accordance with Swiss Auditing Standards as well as with International Standards on Auditing (ISA), which require that an audit be planned and performed to obtain reasonable assurance about whether the financial statements are free from material misstatement. We have examined on a test basis evidence supporting the amounts and disclosures in the financial statements. We have also assessed the accounting principles used, significant estimates made and the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

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

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

DELOITTE SA



Peter Quigley
Auditor in charge

Jürg Gehring

May 29, 2008



Photos credits: Cover: Edmundo Caetano; Main events: April07-Andrea Branca, Cambodia, 2005; May08-World Health Organization (WHO): Oliver O'Hanlon; 8: Edmundo Caetano; 9: Médecins Sans Frontières (MSF); 11: WHO; MSF; 12: James Gathany/U.S. Centers for Diseases Control and Prevention (CDC); MSF; 13: James Gathany/CDC; Shoklo Malaria Research Unit (SMRU); 14: Scynexis; 16: SMRU; 17: SMRU; 19: University of California, San Francisco; 20: Eskitis; Institut Pasteur Korea; 21: Scynexis; Advinus; 23: SMRU; 24: MSF; 25: Farmanguinhos/Fiocruz; 37: SMRU; Edmundo Caetano; 40: Edmundo Caetano.

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HOW YOU CAN HELP

In order to meet its objective to build a robust pipeline and to deliver 6 to 8 new treatments by 2014 for leishmaniasis, human African trypanosomiasis, Chagas disease, and malaria, DNDi still needs EUR 200 million in funding. Your support to meet this challenge is greatly appreciated as you will help to provide new tools that will improve the lives of patients suffering from these neglected diseases.

To join our efforts, please contact the DNDi Fundraising Manager at +41.22.906.9240 or supportdndi@dndi.org.

Best science
for the most neglected

DNDi

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