2010. ANNUAL REPORT

Developing, implementing, consolidating

DNDi

Drugs for Neglected Diseases *initiative*

DND*i*

Drugs for Neglected Diseases *initiative*

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 players collaborate to raise awareness of the need to research and develop drugs for those neglected diseases that fall outside the scope of market-driven R&D. They also build public responsibility and leadership in addressing the needs of these patients.

MISSION

- To develop new drugs or new formulations of existing drugs for patients suffering from the most neglected communicable diseases. Acting in the public interest, DND*i* will bridge existing R&D gaps 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.
- DND*i*'s primary focus will be the development of drugs for the most neglected diseases, such as sleeping sickness, leishmaniasis, and Chagas disease; and it will also consider engaging R&D projects on other neglected diseases. DND*i* will address unmet needs by taking on projects that others are unable or unwilling to pursue and, as means permit, will consider development of diagnostics and/or vaccines.
- In pursuing these goals, DND*i* will manage R&D networks built on South-South and North-South collaborations. While using the existing support capacities in countries where the diseases are endemic, DND*i* will help to build additional capacity in a sustainable manner through technology transfer in the field of drug research and development for neglected diseases.

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

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2010 ANNUAL REPORT

Message from the Chair of the Board and the Executive Director

Dr Bernard Pécoul
Executive Director

Prof. Marcel Tanner
Chair of the Board of Directors

The year 2010 was one of challenges and success for DND*i*. We are happy to announce the fourth treatment delivered from DND*i*'s portfolio, a combination therapy for visceral leishmaniasis – SSG&PM. With four treatments made available over the past four years, and the robust pipeline that has been built since the inception of DND*i*, the time was right for critical assessment and reflexion on the future orientations of DND*i*.

This year, the Board of Directors was called upon by international organizations and partners to **extend the DND*i* portfolio** to include two new 'mini-portfolios': paediatric HIV and helminth infections, with a particular focus on filariasis. This expansion of activities indicates **a natural progression of DND*i*'s capacity to deliver**, to capitalize on its assets, and to develop innovative partnerships with the private and public sectors as well as with other not-for-profit organizations. It also confirms the **efficiency of the DND*i* model**, unique in its fundamental rooting in endemic countries, with regional offices and disease-specific platforms, in addition to its founding partners – all pillars of DND*i*. By consolidating and further developing its business model, DND*i* aims to maintain the dynamic adaptability to continue **to go where others do not, where needs are unmet**. This is our purpose, our task, and our commitment. With the help of the entire DND*i* team and network, our founding partners, and our donors, we are confident that the model works and that it will continue to evolve in response to patient needs.

For DND*i*, the flexibility to adapt rapidly to needs and opportunities has become a guiding principle, both in its R&D approach and in its institutional development. Our regional offices and regional disease-specific platforms play a key role and have become invaluable resource centres for the DND*i* model. These developments will be further fostered in the coming years. Working throughout the R&D pipeline with regional decision-makers, regulatory authorities, researchers, and clinicians is an integral part of DND*i*'s *modus operandi*.

We are pleased to note that many positive changes are occurring in the field of the neglected diseases R&D landscape, particularly with new public donors committing resources, even amidst economic instability. This is a message that, even in periods of global crisis, **the needs of the poorest populations in the world are seen, heard, and addressed**. New pharmaceutical and biotechnology partners are engaging in diseases that can never and will never bring profit to the industry. Today, we are also happy to observe that among PDPs, efforts are being made to collaborate and share knowledge in ways that have never before been explored. DND*i* is committed to harnessing this momentum. Now eight years into its existence, DND*i* is part of an environment that has facilitated what we can qualify as the most robust pipeline for kinetoplastid diseases.

Many challenges remain and in our field, success is nothing but work in progress. Much is still to be done to ensure that priorities in research and global health reflect the millions suffering from neglected diseases. While the global increase in investment in R&D for neglected diseases is encouraging, it must be seen in proportion to the massive global investment in pharmaceutical development for other diseases, and must be coupled with sustainable funding in order to fill existing gaps. **R&D for neglected diseases requires innovation** as all other R&D does, but it requires **alternative models** to ensure that innovation is brought to bear on those who

“Time and experience have confirmed that DND*i* is as strong as its partnerships. We are most grateful to our donors, our partners at all levels, and our team worldwide for making DND*i* the organization it is today.”

need it most. DND*i* has responded to this requirement and, along with other PDPs, has brought new hope not only by delivering new medicines, but by unceasingly advocating for open IP, global access policy, government engagement, new funding mechanisms, and access to existing and new treatments. Indeed, **delivering treatments will not translate into access unless we join efforts with all partners** involved in the R&D process to increase access to medicines once they are made available. DND*i*, and all PDPs collectively, can and should go beyond drug development. It is our joint responsibility to demonstrate the value chain along the R&D pipeline and measure our collective impact on global health.

After eight years of existence, the time has come for DND*i* to evaluate its performance and take the necessary steps to consolidate and further develop its business model in order to remain vigilant and responsive to the needs of neglected patients. Time and experience have confirmed that DND*i* is as strong as its partnerships. We are most grateful to our donors, our partners at all levels, and our team worldwide for making DND*i* the organization it is today. Without the partnership we experience, DND*i* would not be what it is today.

Dr Bernard Pécoul

Prof. Marcel Tanner

01. OVERVIEW & GOVERNANCE

An alternative model to develop drugs for neglected diseases and ensure equitable access for all patients.

Fourth new treatment delivered in 2010

In 2010, DND*i* delivered its fourth treatment, a combination of sodium stibogluconate and paromomycin (SSG&PM) for visceral leishmaniasis in Africa. This follows the two fixed-dose anti-malarials (ASAQ – 2007 and ASMQ – 2008) and NECT (nifurtimox-eflornithine combination therapy – 2009) for sleeping sickness.

The WHO Expert Committee on the Control of Leishmaniases recommended SSG&PM as first-line treatment for VL in East Africa and at the close of the year, Sudan recommended SSG&PM as first-line treatment for VL. SSG&PM showed a similar safety and efficacy profile as the standard SSG monotherapy, with shorter treatment duration (17 days versus 30 days) in addition to lower cost.

A BALANCED APPROACH TO ADDRESS UNMET NEEDS

Seven years after DND*i*'s inception, this breakthrough for one of the most neglected diseases affecting the poorest people of the world, reinforces DND*i*'s strategy of maintaining a balanced R&D pipeline of long-term and short-term projects. The ultimate goal is to develop new treatments that are safe, efficacious, affordable, and field-adapted to support elimination programmes for human African trypanosomiasis and VL, and case management for Chagas disease. Through this balanced approach, DND*i* addresses both immediate patient needs, through improvement and/or combination of existing drugs, and the more long-term public health requirements, through the R&D for new chemical entities (NCEs). The latter are developed to correspond to the ideal target drug profiles that are established with a long-term vision of patient needs and with the aim of supporting elimination strategies where possible.

While SSG&PM provides confirmation of the efficiency of DND*i*'s model, other outcomes are illustrative of this as well:

- the implementation of ASAQ, launched in March 2007 in partnership with sanofi-aventis, is now registered and available in 30 African countries and India with more than 80 million treatments distributed in Africa by December 2010. Meanwhile, sanofi-aventis, MMV, DND*i*, and National Malaria Control Programmes are implementing a vast risk management plan with several studies throughout West and East Africa. This plan is one of the largest ever of its kind for the African continent.

The implementation of NECT, a simplified co-administration of eflornithine and nifurtimox for stage 2 HAT patients, included in the WHO Essential Medicines List in 2009, was running in 10 countries, which cover approximately 97% of all estimated HAT cases. NECT, used to treat over 60% of stage 2 HAT patients by the end 2010, is quickly replacing melarsoprol, an arsenic derivative that is painful, toxic, and even fatal for 5% of those who receive it.

- Oxaborole (SCYX-7158 compound), the first novel oral drug candidate developed through DND*i*'s lead optimization programme, is prepared to enter Phase I clinical trials in 2011, following promising results obtained from pre-clinical safety studies, in collaboration with Anacor, SCYNEXIS, Pace University (USA), and Advinus (India).
- Following the license agreement signed with the Japanese pharmaceutical company Eisai, DND*i* designed the clinical development plans for E-1224, a prodrug of ravuconazole. With CRESIB, DND*i* conducted the preliminary activities at the site level for a Phase II proof-of-concept clinical trial in adult patients, to start in 2011 in Bolivia, for chronic indeterminate Chagas disease.

PAVING THE WAY FOR INNOVATIVE PARTNERSHIPS

In order to bring to fruition the new generation of treatments coming from its discovery programmes, DND*i* actively seeks access to chemical libraries of pharmaceutical and biotechnology companies, with the aim of identifying the right candidates that will become innovative medicines. Securing this access to compound libraries of private companies is key as it gives a major head start for the otherwise expensive and time-consuming discovery phase.

In 2010, DND*i* pursued such partnerships resulting in, for instance, research collaboration with Pfizer for the screening of 150,000 compounds against all three kinetoplastid diseases at the Institut Pasteur Korea (IPK). Until recently, .../

OBJECTIVES BY 2014

DND*i*'s objective is to

- Develop 6-8 new, field-relevant treatments and a robust pipeline by 2014 for people suffering from neglected diseases

In doing this, DND*i* will also

- Use and strengthen existing research capabilities in countries where neglected diseases are endemic
- Raise awareness about the need to develop new drugs for neglected diseases and advocate for increased public responsibility

SSG&PM, a combination therapy to treat VL in East Africa made available in 2010, provides confirmation of the efficiency of DND*i*'s model.

/... the lack of high-throughput screening has hampered efforts to screen large-sized libraries for *Leishmania* (the parasite causing VL) and *T. cruzi* (the parasite causing Chagas). DND*i* has specifically commissioned IPK to develop a new methodology to address this bottleneck and therefore quickly identify hits/leads critical to the discovery programmes (see page 17). The commitment of IPK – supported by the Institut Pasteur, the Korean government, and DND*i*'s donors – showed the impact of collaborative models managed by product development partnerships (PDPs) in boosting innovation.

The partnership agreement with the TB Alliance for leishmaniasis treatment announced in 2010 is yet another illustration of the benefits of open innovation practices between PDPs. TB Alliance granted DND*i* access to a selected library of chemical entities (see page 26) and shared its scientific expertise and knowledge of the drug classes. The not-for-profit model demonstrates that there are innovative ways to share knowledge, to avoid duplication in research, and thereby save costs and speed up the R&D process for the benefit of patients. This unique PDP-to-PDP agreement maximizes the benefits from the global health community's investment in research and development, and may serve as a model for future collaborations. With more than 100 clinical research programmes among the 18 major global health PDPs, there may be opportunities to leverage other innovations across diseases, bringing a promise of more rapid progress.

In the past few years, DND*i* has formalized strong relationships with several pharmaceutical and biotechnology companies committed to R&D for neglected tropical diseases (NTDs). These business relationships occur at all stages of the R&D pipeline. Sanofi-aventis, GSK, Pfizer, Merck, Eisai, Cipla, Novartis, Anacor, SCYNEXIS, Genzyme, and Advinus are participating in these joint efforts.

These novel alliances between not-for-profit organizations and private companies, public institutions, and academia are heralding a new paradigm, with major opportunities to generate new pathways for innovation.

KEY MILESTONES IN 2010

JANUARY → FEBRUARY → MARCH → APRIL

→ LEAP/1,100

Last patient completed follow-up in a multi-centre, multi-country (Kenya, Ethiopia, Sudan, and Uganda) clinical trial for VL managed by the Leishmaniasis East Africa Platform (LEAP), with over 1,100 patients, to facilitate recommendation of one combination therapy for VL.

→ *1 $ for 1 Life*

A documentary film inspired by DND*i*'s activities for neglected patients is broadcast on Arte channel.

→ US Congress

Thirteen members of US Congress urge USAID to expand R&D funding for leishmaniasis, sleeping sickness, Chagas disease, and Buruli ulcer – diseases that impact millions in low-income countries.

→ Chagas Platform

First general meeting of the Chagas Clinical Research Platform in Buenos Aires, Argentina, attended by key stakeholders from Chagas national control programmes, international organizations, and pharmaceutical manufacturers.

→ CRESIB

DND*i* and CRESIB sign in Barcelona an agreement to join forces on clinical research for Chagas disease.

→ 350,000 compounds

Over 350,000 compounds are screened at Institut Pasteur Korea from libraries of private companies. Since 2008, for the first time in the field of neglected diseases a method called 'high-throughput image screening' allows the testing of thousands of compounds in a very short period of time.
This major technological breakthrough in drug discovery for neglected diseases is given DND*i*'s 'Partnership of the year' award.

MAY → JUNE → JULY → AUGUST → SEPTEMBER → OCTOBER → NOVEMBER → DECEMBER

→ Manifesto

The eight-point 'Manifesto', published in PLoS NTDs, co-authored by Peter Hotez and Bernard Pécoul, conveys the message that all NTDs need to implement existing tools and that increased investment in R&D for NTDs is urgent.

→ DOKA centre

The Leishmaniasis East Africa Platform opened the renovated and expanded Professor El Hassan Centre for Tropical Medicine in Doka, Sudan, the seventh research and treatment centre taking part in LEAP clinical studies.

→ HAT Platform

The platform and the East African Network for Trypanosomosis (EANETT) held their first joint scientific meeting in Nairobi, Kenya, to discuss further the implementation of NECT treatment.

→ SSG&PM

DND*i*'s fourth delivered treatment was recommended and implemented in Sudan end 2010. This combination therapy had been recommended in March 2010 by the WHO Expert Committee on the Control of Leishmaniases as first-line treatment for VL in East Africa.

→ Oxaborole

All safety studies indicate that Oxaborole (SCYX-7158), the first pre-clinical candidate for sleeping sickness developed through DND*i*'s lead optimization programme with SCYNEXIS, Anacor, and Advinus, should enter Phase I clinical studies in 2011.

→ Alliance

The Global Alliance for TB Drug Development (TB Alliance) and DND*i* announce the first-ever royalty-free license agreement between two not-for-profit drug developers, speeding progress toward improved therapies for multiple neglected diseases.

→ DND*i*'s Partners

Over 150 Indian and international health researchers, policy makers, and experts from 22 countries meet in New Delhi, India, for the third international DND*i* Partners' Meeting, organized in collaboration with Indian Council for Medical Research (ICMR).

→ International status

Special international status organization is granted to DND*i* by the Swiss Government.

→ Art.58

DND*i* and sanofi-aventis apply for joint EMA article 58 and US Food Drug and Administration Office (FDA) scientific advice on the clinical development plan for fexinidazole (drug candidate for HAT).

→ India

DND*i* 'Project of the year' is awarded to the Visceral Leishmaniasis Combination Therapies project in India. This clinical research study completed in 2010 showed that three combination therapies of existing drugs for visceral leishmaniasis (VL) are highly efficacious and are shorter, safer, and cheaper than current standard monotherapy available in the region. Results are published in *The Lancet* in January 2011.

DND*i* around the world

DND*i* NORTH AMERICA

Established in 2007. The DND*i* affiliate in North America supports advocacy, fundraising, and R&D efforts in the region. Based in New York City, DND*i* North America operates under the direction of a 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, Institut Pasteur is a non-profit private foundation dedicated to prevention and treatment of diseases such as yellow fever, tuberculosis, poliomyelitis, hepatitis, and HIV/AIDS. With 8 Nobel Prizes awarded to its researchers, Institut Pasteur is at 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

MÉDECINS SANS FRONTIÈRES (MSF)

MSF is an independent, private, medical aid organization 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, which it dedicated to finding long-term, sustainable solutions to the lack of essential medicines, ultimately leading to the founding of DND*i*.
www.msf.org

DND*i* LATIN AMERICA

Established in 2004. DND*i* Latin America, based in Rio de Janeiro, supports regional R&D activities for Chagas disease, malaria, and leishmaniasis, in addition to advocacy, communication, and fundraising activities to increase awareness of neglected diseases in the region. DND*i* Latin America operates under the direction of a Board of Directors.
www.dndi.org.br

OSWALDO CRUZ FOUNDATION (FIOCRUZ)

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

DND*i* Headquarters in Geneva

DND*i* IN THE DEMOCRATIC REPUBLIC OF THE CONGO

Established in 2005. The DND*i* project support office in Kinshasa, Democratic Republic of the Congo (DRC), provides essential logistical and financial support to the nifurtimox-eflornithine combination therapy (NECT) trials and studies, as well as to the HAT Platform.

DND*i* AFRICA

Established in 2003. DND*i* Africa, based at the Kenya Medical Research Institute (KEMRI) in Nairobi, provides support to R&D projects in the region, including clinical activities for leishmaniasis, as well as capacity building in the framework of the LEAP and HAT Platforms.

7 FOUNDING PARTNERS

6 REGIONAL OFFICES

1 AFFILIATE

At the founding of DND*i* in 2003, seven key stakeholders joined forces to propel the initiative. Each Founding Partner is a centre of excellence in neglected disease research and/or patient care. In addition, DND*i* has secured its regional rooting in countries where neglected diseases are endemic, as well as in other countries where its activities are prominent.

WHO/TDR - 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 major diseases of the poor and disadvantaged.
www.who.int/tdr

INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR)

Established in 1911 and re-designated in 1949 as the Indian Council of Medical Research, the ICMR is funded by the Government of India. ICMR's activities focus on the formulation, coordination, and promotion of biomedical research. The Council has a network of 21 Permanent Research Institutes throughout the country that conduct research on tuberculosis, leprosy, and visceral leishmaniasis.
www.icmr.nic.in

DND*i* INDIA

Established in 2004. DND*i* India, based at the Indian Council for Medical Research (ICMR) in New Delhi, supports DND*i*'s operational and advocacy activities in India and Bangladesh, primarily focusing on malaria and leishmaniasis in the region.

DND*i* JAPAN

Established in 2004. DND*i* Japan facilitates the development of research projects and relationships with Japanese academia, pharmaceutical companies, government agencies, donors, and the media. DND*i* Japan operates under the direction of a Board of Directors.
www.dndijapan.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 makes a significant contribution to regional research capacity building, with a focus on infectious and parasitic diseases, and on public health and biotechnology research.
www.kemri.org

MINISTRY OF HEALTH, MALAYSIA

The Institute for Medical Research (IMR), within the Ministry of Health was established in 1900 to carry out scientific and sustained research into the causes, treatment, and prevention of infectious tropical diseases. IMR is now comprised of eight centres which perform research, diagnostic services, training, and consultative services across diverse health fields.
www.imr.gov.my; www.moh.gov.my

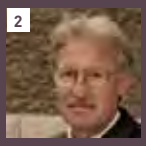
DND*i* MALAYSIA

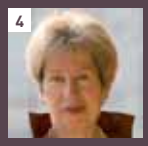
Established in 2004. The DND*i* office in Malaysia supports a wide range of R&D activities across the Asian region, including key pre-clinical and early clinical studies, and facilitates registration and implementation of DND*i* treatments in the region.

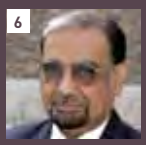
Governance

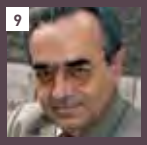
THE BOARD OF DIRECTORS

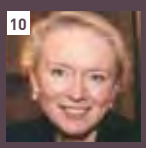
DND*i*'s Board of Directors is composed of ten to thirteen members, including at least one patient representative, who serve four-year terms. Each of the founding members nominates one Board member.

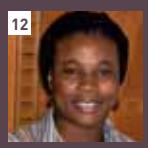


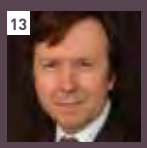












DND*i* BOARD MEMBERS

1 ▪ **Marcel Tanner**
Chair; Swiss Tropical and Public Health Institute (Swiss TPH)

2 ▪ **Reto Brun**
Secretary; Swiss Tropical and Public Health Institute (Swiss TPH)

3 ▪ **Bruce Mahin**
Treasurer; formely with Médecins Sans Frontières (MSF)

4 ▪ **Alice Dautry**
Institut Pasteur, France

5 ▪ **Abul Faiz**
Patient representative;
Sir Salimullah Medical College, Bangladesh

6 ▪ **Lalit Kant**
Indian Council of Medical Research (ICMR)

7 ▪ **Unni Karunakara**
Médecins Sans Frontières (MSF)

8 ▪ **Datuk Mohd Ismail Merican**
Ministry of Health, Malaysia

9 ▪ **Carlos Morel**
Oswaldo Cruz Foundation (Fiocruz), Brazil

10 ▪ **Gill Samuels**
Global Forum for Health Research, Foundation Council, Switzerland, formerly with Pfizer, UK

11 ▪ **Bennett Shapiro**
Pure Tech Ventures, formerly with Merck & Co, USA

12 ▪ **Paulina Tindana**
Patient representative; Navrongo Health Research Centre, Ghana

13 ▪ **Robert G. Ridley**
WHO-TDR (Permanent Observer)

Position vacant, Kenya Medical Research Institute (KEMRI)

THE SCIENTIFIC ADVISORY COMMITTEE (SAC)

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

DND*i* SCIENTIFIC ADVISORY COMMITTEE MEMBERS

- **Pierre-Etienne Bost**
  Chair; formerly with Institut Pasteur, France
- **Khirana Bhatt**
  University of Nairobi, Kenya
- **Marleen Boelaert**
  Institute of Tropical Medicine, Antwerp, Belgium
- **Chris Bruenger**
  IDEC, Japan
- **J. Carl Craft**
  formerly with Medicines for Malaria Venture, Switzerland
- **Simon Croft**
  London School of Hygiene and Tropical Medicine, UK
- **Federico Gomez de las Heras**
  formerly with GlaxoSmithKline, Spain
- **Chitar Mal Gupta**
  Central Drug Research Institute, India
- **Maria das Graças Henriques**
  Owaldo Cruz Foundation (Fiocruz), Brazil
- **Paul Herrling**
  Novartis International AG, Switzerland
- **Dale Kempf**
  Abbott, USA
- **Nor Shahidah Khairullah**
  Infectious Diseases Research Center, Malaysia
- **Shiv Dayal Seth**
  Indian Council of Medical Research (ICMR), India
- **Faustino Torrico**
  Universidad Mayor de San Simon, Cochabamba, Bolivia
- **Muriel Vray**
  Institut Pasteur, France
- **Krisantha Weerasuriya**
  World Health Organization (WHO), Switzerland
- **Haruki Yamada**
  Kitasato Institute for Life Sciences, Japan

AFFILIATE AND REGIONAL OFFICE BOARDS

DND*i* NORTH AMERICA BOARD OF DIRECTORS

- **Bennett Shapiro**, Chair; Pure Tech Ventures, formerly with Merck & Co., USA
- **Hellen Gelband**, Center for Disease Dynamics, USA
- **Joelle Tanguy**, Global Alliance for Vaccines and Immunization (GAVI), Switzerland
- **James Orbinski**, University of Toronto, Canada
- **Suerie Moon**, Harvard School of Public Health, USA
- **Bernard Pécoul**, Drugs for Neglected Diseases *initiative* (DND*i*), Switzerland

DND*i* LATIN AMERICA BOARD, EXECUTIVE MEMBERS

- **Michel Lotrowska**, Chair; Brazil
- **Carlos Morel**, Oswaldo Cruz Foundation (FIOCRUZ), Brazil
- **Tyler Fainstat**, Médecins Sans Frontières (MSF), Brazil

DND*i* JAPAN BOARD OF DIRECTORS

- **Haruki Yamada**, Chair; Kitasato Institute for Life Sciences, Japan
- **Koshin Nakahira**, Nakahira Certified Tax Accounting Office, Japan
- **Bernard Pécoul**, Drugs for Neglected Diseases *initiative* (DND*i*), Switzerland
- **Fumiko Hirabayashi**, Drugs for Neglected Diseases *initiative* (DND*i*), Japan

THE EXECUTIVE TEAM

DND*i* consists of a team of permanent staff based in Geneva and in seven regional and affiliate offices throughout the world. The Geneva team also coordinates a broad base of consultants and volunteers worldwide.

DND*i* HEADQUARTERS / GENEVA

Bernard Pécoul, Executive Director

Shing Chang, Research and Development Director

(in alphabetical order)

Hyo Jeung Ahn, Site and Travel Assistant

Jean-François Alesandrini, Fundraising and Advocacy Director

Manica Balasegaram, Head of Leishmaniasis Clinical Programme

Séverine Blesson, Project Coordinator

Pascale Boulet, Policy Research Officer

Gwenaëlle Carn, Project Coordinator

Eric Chatelain, Head of Chagas Discovery and Pre-clinical Programme

Brigitte Crotty, Executive & Board Assistant

Violaine Dällenbach, Communications Officer

Julia Fährmann, Fundraising Coordinator (as of January 2011)

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Sally Ellis, Clinical Manager

Caroline Gaere Gardaz, Fundraising Officer for Major Donors

Karin Génevaux, Fundraising Coordinator (until September 2010), Head of Fundraising (as of October 2010)

Federica Giovannini, Scientific Communications Officer (until January 2011)

Jean-Robert Ioset, Discovery Manager

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Delphine Launay, Project Coordinator

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Antoine Tarral, Head of HAT Clinical Programme

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Sarah de Tournemire, Administration and Development Manager, USA

02. R&D MODEL, STRATEGY & PORTFOLIO

A well-balanced and robust pipeline in order to develop new needs-driven treatments for neglected patients.

Streamlining efforts for efficient and effective R&D

In 2010, DND*i*'s drug portfolio continues to be enriched with the engagement of private and public partners who share DND*i*'s vision and commitment, and who bring complementary capabilities. DND*i*'s virtual R&D model allows for the outsourcing of R&D activities with active management by DND*i* personnel experienced in different aspects of pharmaceutical development. This model cuts costs while providing flexibility. Most importantly, it has allowed DND*i* to establish a well-balanced and robust pipeline in order to develop new treatments for sleeping sickness (HAT), visceral leishmaniasis (VL), Chagas disease, and malaria. One of DND*i*'s unique characteristics is its R&D scope of diseases: four diseases until 2010, plus two new disease areas as of 2011 (see page 2). According to each specific disease strategy, DND*i*'s activities range from discovery to pre-clinical and clinical phases, to implementation and access.

TPPs: ENSURING THE DEVELOPMENT OF NEEDS-DRIVEN TREATMENTS

As a guiding principle for building each disease portfolio, the desired key features for these new drugs/treatments are defined in the target product profiles (TPPs). Each R&D project in the portfolio is selected, progressed, and managed with decision matrices that ensure products will meet these TPPs, thus ensuring that patient needs are met.

TPPs are defined with input from disease experts, representatives of Ministries of Health, of National Control Programmes in endemic countries, WHO representatives, and specifically from leading clinicians and researchers, as well as with health workers who deal with each disease on a daily basis. DND*i*'s TPPs are reviewed and revised annually, and shared with other investigators openly. In 2010, for instance, the TPP for HAT was revised to reflect the change of the latest reference treatment (NECT; previously melarsoprol).

By implementing this strategy, DND*i* has delivered four treatments – for sleeping sickness, visceral leishmaniasis, and malaria – the latest of which is a combination therapy for visceral leishmaniasis in Africa (SSG&PM, see page 28). In 2010, the WHO Expert Committee on the Control of Leishmaniases recommended SSG&PM as first-line treatment for VL in East Africa, and it was recommended and implemented in Sudan during the year. For the three treatments previously launched, DND*i* has continued its efforts to facilitate access to these essential medicines.

In 2010, DND*i* projects continue to progress well in the pipeline. Thanks to the vital engagement of its partners, the following DND*i* projects have reached important milestones in the past year:

Overall Portfolio: One additional treatment made available, DND*i*'s first treatment for VL reaching this milestone; successful advancement of new leads and optimized leads in the discovery and pre-clinical phases in order to guarantee a robust pipeline for the coming years; clinical projects progressing successfully towards future implementation.

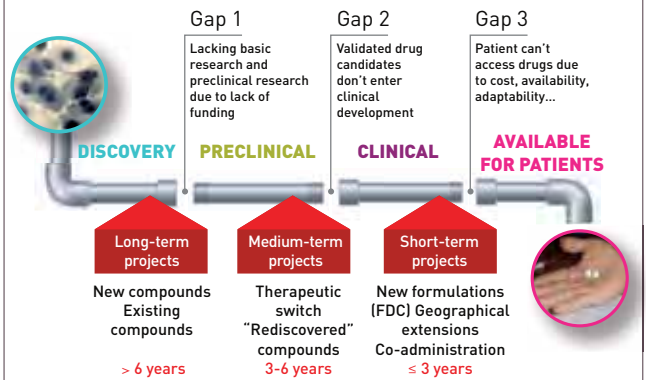
- **Discovery**: Increased and strengthened collaboration with pharmaceutical partners in order to ensure access to their compounds and expertise, as well as enhanced screening capacity through high-throughput screening (e.g. IPK). See page 15 for a list of these partners.

.../

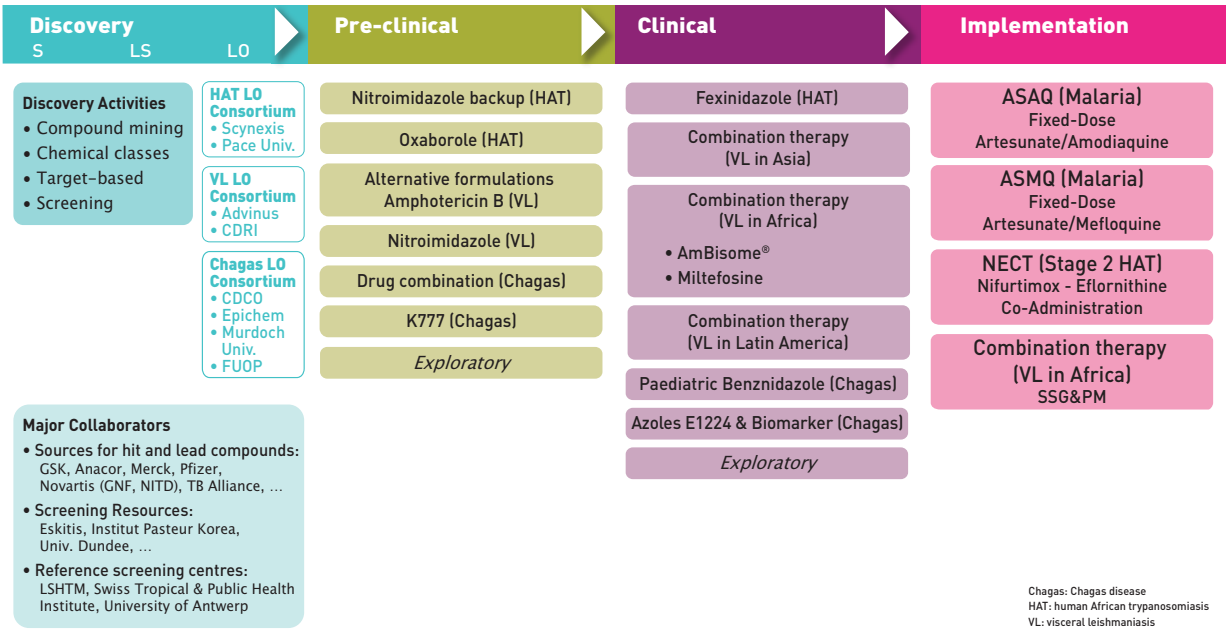
BY KEEPING THE FOCUS ON THE PATIENTS AND THEIR NEEDS, DND*i*'S PROJECT PORTFOLIOS BALANCE LONG-, MEDIUM- AND SHORT-TERM PROJECTS.

- **Long-term projects** - to develop innovative medicines with new chemical entities.
- **Medium-term projects** - to identify existing pre-clinical or clinical stage compounds suitable for therapeutic switching, or for further improvements via improved formulations.
- **Short-term projects** - to make existing drugs available in broader geographic areas and to develop better treatments, including combinations, from existing drugs.

DND*i*'S R&D PROJECTS – FILLING THE GAPS



DND*i* PORTFOLIO (as of December 2010)



/...

- **HAT**: NECT available in 10 countries; fexinidazole progressing in Phase I; the SCYX-7158 oxaborole, identified in lead optimization, in pre-clinical phase, as well as promising nitroimidazoles in lead optimization.
- **VL**: SSG&PM, recommended by WHO Expert Committee on the Control of Leishmaniases for East Africa, now available and implemented in Sudan; increasing number of sites for combination studies in Africa and Asia, with results of a large Phase III study in India with drug combination; one project in pre-clinical phase and promising leads in lead optimization.
- **Chagas disease**: Two projects in clinical phase: one paediatric treatment for which DND*i* and its partners prepare the dossier for registration, one in Phase II; one project in pre-clinical phase and promising perspectives in lead optimization.
- **Malaria**: Implementation phases for both ASAQ and ASMQ. Over 80 million treatments of ASAQ have been delivered in 21 countries (registered in 28) and a pharmacovigilance plan developed with sanofi-aventis and MMV; ASMQ: technology transfer from Brazil to India completed, preparation of submission dossiers for registration in Asia, preparation of clinical studies in Africa.
- **Platforms**: DND*i* is a founding partner of regional platforms for capacity strengthening and clinical research. One platform per kinetoplastid disease is now operational: HAT Platform for sleeping sickness, LEAP for VL, and the CCRP for Chagas disease (see pages 40-41).

Projects completed in 2010 (End of contract period)

- **GSK Screening (VL, HAT, Chagas disease);** Stage: Discovery; Partners: GlaxoSmithKline, Spain; Swiss Tropical and Public Health Institute, Switzerland
- **Eskitis Screening of Natural Products (HAT);** Stage: Discovery; Partners: Eskitis Australia; Griffith University, Australia
- **Kitasato Screening of Natural Products (HAT);** Stage: Discovery; Partners: Kitasato Institute, Japan.

TARGET PRODUCT PROFILE (TPP)

- **Indications:** which diseases?
- **Population:** which type of patients and where?
- **Clinical Efficacy:** does it treat the parasitic infection effectively?
- **Safety and Tolerability:** what level of acceptability for adverse events?
- **Stability:** how long is the shelf life of the drug(s), and storage conditions?
- **Route of Administration:** how is it administered to patients?
- **Dosing Frequency and Treatment Duration:** how often and how long must it be given?
- **Cost:** will it be affordable to the target population?
- **Time to Availability:** how long will it take to develop?

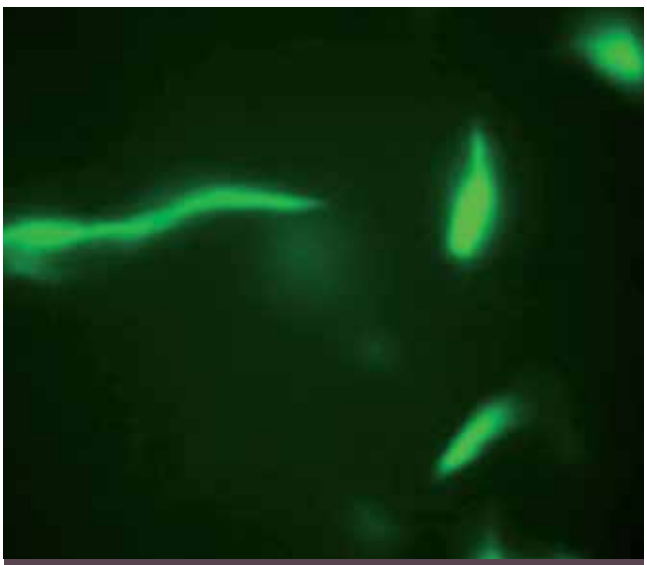
Discovery

A pragmatic strategy for more efficient R&D

In 2010, DND*i* has continued to remodel its discovery activities from a hunter-gatherer approach – identifying projects mostly based on networking interactions – to a fully integrated process-oriented platform in partnership with pharmaceutical and biotechnology companies. The sourcing of compounds is based on a clear strategy combining compound mining, access to specific chemical classes, extension of chemical diversity and target based approaches supported by high-throughput screening capacity for all three kinetoplastids.

DISCOVERY AND THE 'S' RULE

Discovery research – a three-stage process consisting of sourcing and screening compounds, lead selection, and lead optimization – is the earliest stage of drug research and development (R&D), helping to identify novel drugs that offer significant improvements over current therapies. Since 2003, DND*i* has built up a well-balanced and robust pre-clinical pipeline to develop new treatments for sleeping sickness, visceral leishmaniasis, and Chagas disease. To proceed, DND*i* has recently transitioned from a hunter-gatherer approach – identifying projects mostly based on networking interactions – to a more pragmatic and structured discovery strategy relying on partnerships with public (universities, academia, etc.) and private partners (pharmaceutical and biotechnology companies). Those partnerships include **S**ourcing and **S**creening of compounds followed by the **S**election of **S**eries to optimize.



GFP *Leishmania donovani* (promastigote stage) screened at Central Drug Research Institute, in Lucknow (India).

This discovery platform takes advantage of a dedicated and improved capacity for phenotypic screening as well as of lead optimization consortia funded by DND*i*. The nomination of SCYX-7158 as pre-clinical candidate for sleeping sickness is the first success achieved through this new model (see pages 21-22).

In 2010, important developments among DND*i*'s discovery efforts include:

- Committed support to strengthening the screening capacity against the parasites causing the three kinetoplastid diseases using high-throughput screening (HTS) assays, including *Trypanosoma brucei* (the parasite causing HAT) at the Institute Eskitis (Griffith University, Australia), and intracellular *Leishmania donovani* and *T. cruzi* assays at Institut Pasteur Korea (IPK).
- Agreements with pharmaceutical and biotechnology companies including Anacor, Merck, Pfizer.
- Streamlining and sharing with other Product Development Partnerships (PDPs) (Medicines for Malaria Venture, TB Alliance, and the Consortium for Parasitic Drug Development) and additional R&D industrial institutes and centres active in the field, such as the Novartis Institute for Tropical Diseases (NITD), Diseases of the Developing World at GlaxoSmithKline (GSK), the Drug Discovery Unit at the University of Dundee, the Genomics Institute of the Novartis Research Foundation (GNF) and the TI Pharma Consortium.

DND*i*'s discovery activities are dynamically evolving as DND*i* continues to take on new exploratory activities.

- **Target diseases**: HAT, VL, and Chagas disease
- **Partners**: Anacor, USA; Drug Discovery Unit (DDU) at the University of Dundee, UK; Eskitis Institute (Griffith University), Australia; Federal University of Ouro Preto, Brazil; Genomics Institute of the Novartis Research Foundation (GNF), USA; GlaxoSmithKline, Tres Cantos, Spain; Institut Pasteur Korea (IPK), South Korea; London School of Hygiene & Tropical Medicine (LSHTM), UK; Merck, USA; Novartis Institute for Tropical Diseases (NITD), Singapore; Pfizer, USA; SCYNEXIS Inc., USA; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; TB Alliance, USA; TI Pharma, The Netherlands; University of Antwerp, Belgium; the UNDP/World Bank/WHO's Special Programme for Research and Training in Tropical Diseases (TDR).
- **Management:** Discovery Manager, Jean-Robert Ioset

DND*i*'s discovery strategy includes several approaches for compound sourcing: .../

/... SOURCING

■ Compound mining

Proactive acquisition and investigation of compounds from selected series associated with a significant level of available information (biological activities, pre-clinical dossier, published data, safety profile, among others) in order to identify candidates with a potential for further development – ideally ready to enter into pre-clinical or later stage without further optimization – for the target diseases. An example of this approach is our compound mining effort undertaken in 2005 to explore new and old nitroimidazoles as drug leads against HAT. Over 700 compounds from 15 different sources were identified, accessed, and tested.

■ Chemical classes

Identification of promising chemical classes as sources for lead compounds. From libraries of collaborating pharmaceutical and biotech companies, promising compound classes can be identified by sampling a subset of representative compounds and testing them for antiprotozoal activities. Subsequent optimization from the selected classes would be more efficient as they result from existing know-how. Examples of interesting classes include oxaboroles (Anacor Pharmaceuticals), pyridones (GSK), and nitroimidazoles (TB Alliance).

■ Chemical diversity

Accessing diversity sets and libraries from various institutions and pharmaceutical companies (natural products, synthetic compounds, agriculture chemicals). This approach aims to mine new chemical territories to identify additional classes of molecules of potential interest in terms of drug development for DND*i* target diseases. Illustrating this approach is the recent research collaboration with Pfizer to screen the Pfizer DGRS II set (representative of the entire Pfizer library in terms of chemical diversity, i.e. 150,000 compounds) against all three kinetoplastid diseases at the Eskitis Institute (HAT) and IPK (VL and Chagas disease).

■ Target-based

Screening compounds and assessing their activity against a specific target essential for parasite growth (e.g. Drug Discovery Unit at the University of Dundee, UK for VL; TI Pharma consortium for HAT and VL]. This early discovery approach is used in combination with phenotypic screen of specific collections of compounds to allow the identification of inhibitors of targets essential to the growth of *Trypanosoma* and *Leishmania* pathogens.

SCREENING

■ High-throughput screening

High-throughput screening (HTS) of large-size libraries for *Leishmania* and *T. cruzi* (IPK), and *T. brucei* (Eskitis) have been developed and are used to identify novel hit compounds. Screening capacity is a key element of our discovery strategy as it enables the screening of large libraries/series of compounds and therefore a quicker identification of hits/leads critical to our discovery programmes.

■ Reference Screening Centres

The Swiss Tropical and Public Health Institute (Swiss TPH), the University of Antwerp, and the London School of Hygiene & Tropical Medicine (LSHTM) serve as reference screening centres to ensure that screening methodologies are comparable and that *in vitro* and *in vivo* assays at different sites and with different groups meet the same standard. The centres also provide expert parasitology advice that ensures the quality of our data and work.

Assay automation: 1) 384-Well plates containing host cells infected with parasites are loaded onto an automated platform for compound addition, incubation, and reading. 2) Robotic arm involved in the process (High-throughput screening at Institut Pasteur Korea).

HIGH-THROUGHPUT SCREENING AT INSTITUT PASTEUR KOREA (IPK)

IPK on the cutting edge of technology in service of research for NTDs

- **Target disease**: Leishmaniasis and Chagas
- **Major Partners**: Institut Pasteur Korea (IPK)
- **Management**: Head of Chagas Discovery and Pre-clinical Programme, Eric Chatelain; Discovery Manager, Jean-Robert Ioset
- **Project start**: May 2008

The overall goal of this project was the identification of novel compounds for the treatment of leishmaniasis (but also Chagas and HAT). In collaboration with Institut Pasteur Korea (IPK) – a renowned translational research institute with funding from South Korea's Ministry of Education, Science and Technology and the Gyeonggi Provincial Government – we have successfully developed and validated a unique HTS visual screening assay for *Leishmania*, and screened the IPK library. The main goal of this DND*i*-IPK partnership has been to develop a method allowing the evaluation of thousands of compounds in a very short period of time. Until 2008, it was only possible to assess hundreds of compounds over a period of a few months. Combining the parasitology expertise to the screening and image-analysis technology and know-how of IPK, this project seeks to develop a major methodological advance in drug development. Additionally, we have also developed a HTS visual screening assay for *Trypanosoma cruzi*, taking advantage of the knowledge gained in the development of HTS for *Leishmania*.

IPK and DND*i* have signed a broader collaboration agreement enabling the screening of third-party libraries at IPK for *Leishmania* and *T. cruzi* among others.

In November 2009, Pfizer Inc. and DND*i* signed an agreement designed to facilitate advancements in the battle against human African trypanosomiasis (HAT), visceral leishmaniasis (VL), and Chagas disease. Under the agreement, DND*i* obtained access to the Pfizer library of novel chemical entities and screened it for compounds that have the potential to be developed into new treatments. The screening of the Pfizer library at IPK against *L. donovani* is ongoing and completed for *T. cruzi* (over 150,000 compounds) using the newly developed assay.

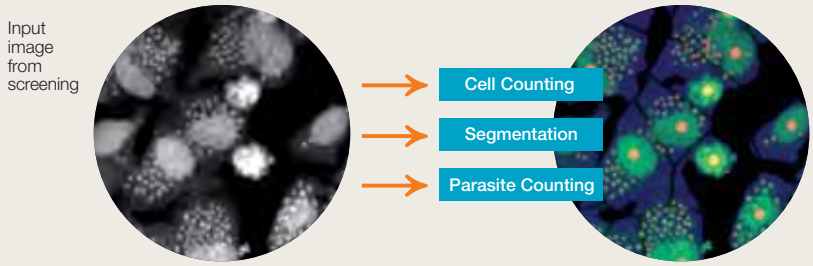
DND*i* Partnership of the Year 2010

The award went to the Partnership with Institut Pasteur Korea (DND*i* Partners' meeting in Delhi, India, December 2010).

IPK recently established the Center for Neglected Diseases Drug Discovery (CND3), affirming its commitment to neglected diseases. So far, a total of 210,000 compounds have been screened for VL from the compound libraries of IPK, Anacor, and the TB Alliance. With this new technology, the number of compounds screened for VL is probably higher than the total number of compounds that have ever been screened for this disease in the intracellular format. From this activity, one compound series has already shown very promising results — the aminothiazoles. This series is now in further development at the Indian pharmaceutical company, Advinus Therapeutics.

The success of this new technology has allowed IPK and DND*i* to develop high-throughput image screening for Chagas disease, leading to a broader collaboration between DND*i* and IPK. Today, DND*i* has access to compound libraries with a large number of compounds from different pharmaceutical companies that can now be screened with greater time efficiency than ever.

This collaboration will maximize the chances of identifying attractive starting points for a drug discovery programme, and marks an important step towards the fulfilment of DND*i*'s objectives.



Processing of *Leishmania donovani* High Content Screening (HCS) data: from image to determination of biological activity. Small dots are *Leishmania* parasites (intracellular amastigote form).

Human African Trypanosomiasis
Sleeping Sickness

Major progress in access to NECT treatment and promising new drug candidates

The year 2010 has seen the emergence of hope for elimination of sleeping sickness. According to WHO, the number of cases of human African trypanosomiasis (HAT) has substantially decreased. The current trend suggests that elimination of HAT is possible, and the efforts in the past decade by WHO and National Control Programmes, with MSF, sanofi-aventis, Bayer, DND*i*, and others contribute to this. In addition, the introduction of NECT, an improved therapy option for stage 2 HAT, is accelerating this trend. However, it is important to bear in mind that HAT has known periods of decline in the past, which have been followed by re-emergence due to a lack of surveillance and control efforts in known endemic areas. While the decrease of reported cases is encouraging, some geographical areas are still not covered at all by surveillance and control efforts. Furthermore, one-third of HAT patients are women of childbearing age and one-fourth are children under 15 years of age. Currently available treatments are not adapted for these particularly neglected patients.

Sustainable elimination necessitates maintaining and reinforcing current surveillance and control efforts in the known endemic areas. In addition, now more than ever, R&D investments to develop field-adapted diagnostic and treatment tools to reach and treat patients not accessed by current strategies have to be both boosted and secured.

Currently available treatments for HAT are complex regimens. In several regions, they have lost efficacy. Treatment is also stage-specific, with more toxic and more difficult-to-administer drugs for stage 2 disease. Taken together with the complicated and invasive diagnostic methods, the reality of HAT treatment has made it very challenging to integrate HAT control into already burdened health systems. There is an immediate need to improve current treatment options, particularly for patients with the stage 2 disease. Ideally, treatment should be orally administered and effective for both stages of the disease.

Since its inception in 2003, DND*i*'s short-term strategy has been to develop a combination therapy of existing drugs to improve current treatment options. In September 2009, DND*i* and its partners launched the first new treatment for sleeping sickness in 25 years: nifurtimox and eflornithine combination therapy (NECT). The combined use of these drugs has been included on the Essential Medicines List of the World Health Organization. As of December 2010, 10 HAT endemic African countries have signed the supply request with WHO and have been ordering this improved therapy option.

DND*i*'s medium-term strategy was to initiate a proactive compound mining effort shortly after its inception to identify existing chemical compounds with potential against kinetoplastid diseases. This resulted in the rediscovery of fexinidazole in 2007, a drug that went through early pre-clinical assessment in the mid-1980s, but was shelved by the pharmaceutical company Hoechst. DND*i* has since completed all necessary pre-clinical testing and has begun clinical development of fexinidazole for HAT as a potential oral drug to treat stage 2 disease. .../

A young girl treated for sleeping sickness lies on a bed, accompanied by her grand-mother, in Katanda HAT centre, Democratic Republic of the Congo.

IDEAL TARGET PRODUCT PROFILE FOR HAT

- **A new treatment for stage 1 + 2 HAT in adults and children**
  - Active against *Trypanosoma brucei (T.b.) gambiense* and *T.b. rhodesiense*
  - Ideally requiring no monitoring
  - Ideally <0.1% drug related mortality
- **Ideally safe during pregnancy and for lactating women**
- **Ideally >95% efficacy at 18 months follow-up**
- **Easy-to-use treatment**
  - Short course (ideally <7 days, up to 10 days is acceptable)
  - Preferably oral or, if injectable, intramuscular
  - Preferably once-a-day treatment
- **Affordable**
- **Stable in tropical climate (minimum 3-year shelf life)**

Human African Trypanosomiasis / SLEEPING SICKNESS

A threat to millions in 36 countries in sub-Saharan Africa

WHAT IS THE IMPACT OF HAT?

The estimated number of actual cases is currently approximately 30,000. Fatal if untreated. Displacement of populations, war, and poverty lead to increased transmission, with severe social and economic consequences. Some areas are still not covered by surveillance and control efforts.[1]

HOW IS HAT TRANSMITTED?

Transmitted by the parasite *Trypanosoma brucei (T. b.)* to humans through the bite of the vector tsetse fly, HAT is caused by two subspecies of the parasite: *T. b. gambiense* (West and Central Africa), *T. b. rhodesiense* (East Africa).

WHAT ARE THE SYMPTOMS?

HAT occurs in two stages:

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

A lumbar puncture is needed to differentiate between the 2 stages for the administration of proper treatment.

WHERE DOES HAT OCCUR?

Of the 36 countries considered endemic (i.e. countries that have presence of the tsetse fly) 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[2]. HAT primarily occurs in the poor and rural areas of Africa, where difficulty of diagnosis, political instability, and lack of health surveillance make estimates of disease prevalence difficult to ascertain.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

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

- **Stage 1** treatments, **pentamidine** and **suramin**, are fairly well-tolerated but still require injections and are ineffective for stage 2.
- **Stage 2** has three treatments available: **melarsoprol**, an arsenic derivative that is painful, toxic (killing 5% of those who receive it[3]), and increasingly ineffective (up to 50% resistance and treatment failure in certain areas); **eflornithine**, which requires trained health staff and extended hospital stay (56 intravenous infusions taking 2 hours each to administer, over 14 days and four times each day); **NECT** (nifurtimox-eflornithine combination therapy) with only 14 injections of eflornithine over 7 days and 10 days of oral treatment with nifurtimox has been available since September 2009. NECT, developed by DND*i* and its partners, is an improved therapy option for stage 2 sleeping sickness. While it is not the panacea for disease elimination, it provides an incremental improvement for case management in a hospital setting at the community level.

WHAT ARE THE PATIENT TREATMENT NEEDS?

A safe, effective, and orally administered stage 2 treatment is needed that improves and simplifies current case management. This drug should ideally work in both stages of the disease.

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

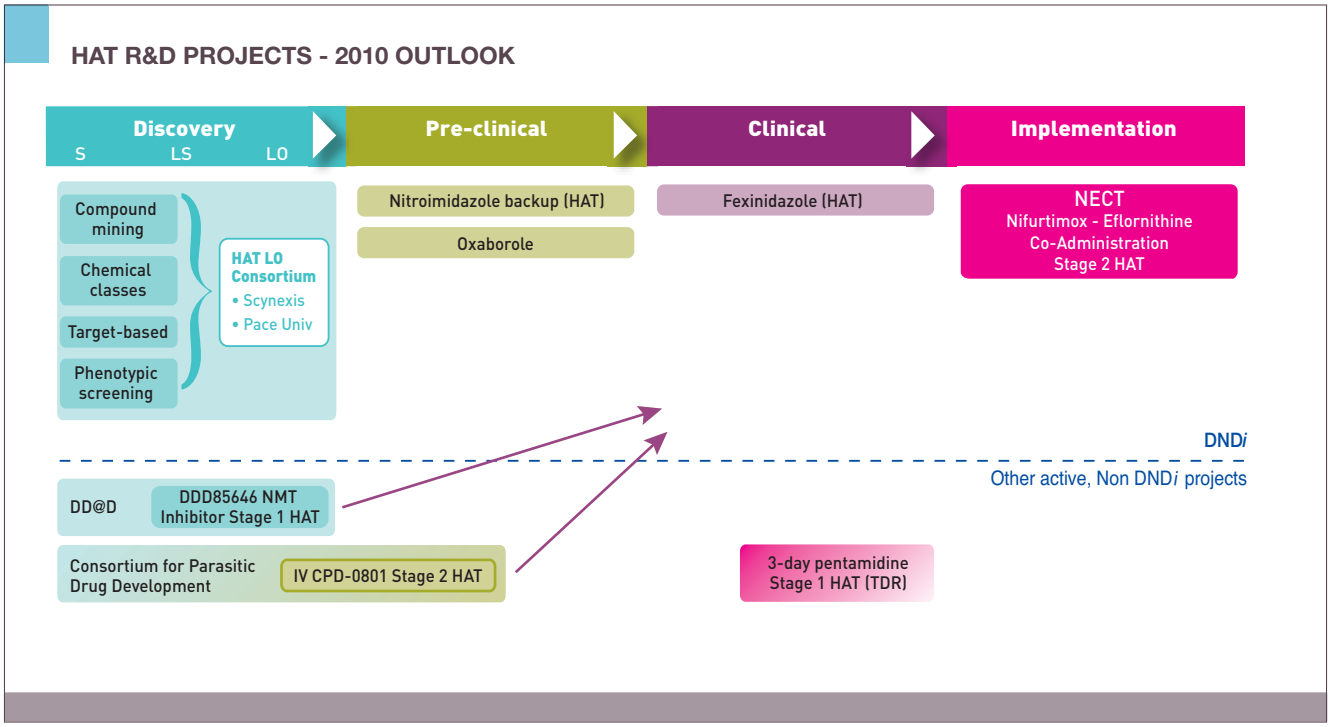
Short term: Nifurtimox-eflornithine combination therapy (NECT), the simplified treatment for stage 2 HAT, now in use.

Medium term: drug candidates identified through compound mining.
- Fexinidazole: first oral new drug candidate entered clinical development from the Nitroimidazoles Project

Long term: discovery of promising new drug candidates and improved clinical research capacity.
- New drugs developed from compounds identified (i.e. oxaboroles) in discovery research and progressed through HAT Lead Optimization Consortium to pre-clinical
- Multi-country, multi-partner HAT Platform to strengthen regional research capacity
- Back-up nitroimidazoles and oxaboroles

By 2014, DND*i* aims to deliver from its HAT-specific portfolio:
- 1 new combination therapy recommended by WHO (delivered)
- 2 new drugs in development
- A robust pipeline

(1) WHO 2010, http://www.who.int/mediacentre/factsheets/fs259/en/ **(2)** Simaro PP, Jannin J., Cattnd p; PLoS Med. 2008;5:e55 **(3)** Vincent IM, Creek D, Watson DG, Kamleh MA, Woods DJ, et al. 'A Molecular Mechanism for Eflornithine Resistance in African Trypanosomes'. PLoS Pathog. November 2010, 6(11): e1001204. doi:10.1371/journal.ppat.1001204



/... An agreement was signed in 2009 with sanofi-aventis as the industrial partner for this project.

To further build a pipeline for HAT drug R&D, DND*i* has established the HAT Lead Optimization Consortium, and built additional partnerships with pharmaceutical, biotechnology, and academic groups for research collaboration and for access to natural products, synthetic chemical libraries, process chemistry high-throughput screening (HTS), and biological models. A network of expert advisors has been formed to guide DND*i*'s discovery efforts with pharmacokinetic, pharmacodynamic, and toxicological expertise for selection and assessment of potential drug candidates.
One of the successful outcomes of the HAT Lead Optimization Consortium is the identification of one oxaborole as a promising lead series against the *T. brucei* parasite. SCYX-7158 oxaborole progressed steadily through pre-clinical development throughout the year.

In addition, DND*i* is one of the founders of the HAT Platform (see page 41), launched in 2005 in the Democratic Republic of the Congo, that supports the clinical trials for NECT and, since May 2009, NECT-Field. The platform is also very active in strengthening existing capacities.

DISCOVERY

HAT Lead Optimization Consortium

- **Partners:** SCYNEXIS Inc, USA; Pace University, USA
- **Management:** Discovery & Pre-clinical Director, Robert Don; Project Coordinator, Ivan Scandale
- **Project start:** April 2007

With the objective of developing optimized leads by progressing 'hit' molecules with a good safety profile and activity against *T. brucei* parasites, this consortium brings together expertise in chemistry, biology, screening, and pre-formulation. Optimization efforts are focused on improving the molecule's capacity to be absorbed into the bloodstream, to be distributed effectively to the infection sites, to survive in the body, to kill the parasite, and not to harm the patient. With two full lead optimization teams in place at SCYNEXIS (a total of 18 scientists), a number of hits identified from DND*i* screening partners are undergoing hit expansion. Scientists within the consortium use advanced techniques to study how the selected molecules interact with the therapeutic target (i.e. a protein or an enzyme, if known) and optimize the drug-like characteristics of these molecules to ensure that they comply with the target product profile (TPP).
This phase of discovery work requires a close, highly interactive collaboration between the biologists and chemists, who form a feedback loop: the biologists test the biological properties of compounds on biological systems, while the chemists perfect the chemical structure of these compounds based on information obtained by the biologists. Many compound series have been assessed. The current focus of the team is on the oxaborole series (see below).
The nitroimidazole class is another chemical series that is promising. One of the compounds in this class, fexinidazole, has been advanced into clinical development. DND*i*'s strategy for the Lead Optimization Consortium is to develop a back-up compound in each of the oxaborole and nitroimidazole series. In case of failure of one of the current developed compounds, the back-up should be able to replace it rapidly.

PRE-CLINICAL

Nitroimidazole backup

- **Partners:** Suwinski, Poland; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Global Alliance for Tuberculosis Drug Development (TB Alliance), USA
- **Management:** Discovery & Pre-clinical Director, Robert Don; Project Coordinator, Ivan Scandale
- **Project start:** April 2009

The nitroimidazoles are a well-known class of antibacterial and antiprotozoal drugs. Despite their widespread clinical and veterinary use, this family of drugs has been stigmatized, partly due to associated genotoxicity problems.
DND*i*, through extensive compound mining efforts, was able to develop anti-trypanosomal active and non-genotoxic molecules belonging to a new class of nitroimidazoles: 1-aryl-4-nitro-1*H*-imidazoles. In parallel, DND*i* accessed another very promising non-genotoxic nitroimidazole library from the Global Alliance for Tuberculosis Drug Development (TB Alliance). Approximately one thousand analogues belonging to this series have been tested at SCYNEXIS against *T. brucei*. Several active molecules have been identified and further assessments are ongoing at the University of Auckland, SCYNEXIS, and Pace University. Efforts for the identification of pre-clinical candidates within the nitroimidazole class will continue.

PRE-CLINICAL

Oxaborole

- **Partners:** Anacor Pharmaceuticals Inc., USA; SCYNEXIS Inc., USA; Pace University, USA
- **Management:** Discovery & Pre-clinical Director, Robert Don; Project Coordinator, Ivan Scandale
- **Project start:** December 2007

Oxaboroles, provided by Anacor – the originator of this unique boron-based chemical class – were identified as hits against *T. brucei* at the Sandler Center of the University of California San Francisco, and have shown activity in animal models of sleeping sickness. During the course of the subsequent 15 months, chemists at SCYNEXIS synthesized approximately 400 compounds and screened an additional 330 compounds from the Anacor libraries. Some compounds, in particular .../

CLINICAL

FEXINIDAZOLE

A new promising oral drug in clinical development

- **Major Partners**: sanofi-aventis, France; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; HAT Platform members
- **Management**: Medical Manager, Olaf Valverde Mordt; Project Coordinator, Séverine Blesson; Head of HAT Clinical Programme (as of November 2010), Antoine Tarral
- **Project start**: February 2007

Fexinidazole, a drug candidate for stage 2 HAT, is the first success of the proactive compound mining efforts DND*i* pursued in the Nitroimidazole Project. Fexinidazole was in pre-clinical development as a broad-spectrum antiprotozoal at Hoechst AG in the early 1980s, but was then abandoned. DND*i* 'rediscovered' it and an extensive profiling has shown that fexinidazole is orally active in animals, crosses to the brain in mice, and has cured in models for both acute and chronic infections with African trypanosomes. Additionally, fexinidazole is not mutagenic (i.e. is not capable of inducing mutation) in a panel of *in vitro* and *in vivo* mammalian genetic toxicology tests, confirming its favourable activity/toxicity profile as a drug candidate.
In 2007, a full pre-clinical programme was established to enable first-in-human studies. This included: process chemistry; GMP (good manufacturing practice) manufacturing of the active pharmaceutical ingredient; pre-clinical formulation; ADME-PK (absorption, distribution, metabolism, excretion, and pharmacokinetics) profiling and confirmatory studies in animal models of HAT; and the regulatory toxicology package. In May 2009, DND*i* signed an agreement with sanofi-aventis, whereby DND*i* is responsible for non-clinical, clinical, and pharmaceutical development, whereas sanofi-aventis is responsible for the industrial development, registration, and production of the drug at its manufacturing sites.
Fexinidazole entered into Phase I first-in-human studies in September 2009, which makes it the only new drug candidate currently in clinical development for sleeping sickness. By the end of 2010, the three planned studies (single ascending dose, food effect, multiple ascending dose) had been completed. Additional studies are planned in 2011 in order to find the adequate regimen and treatment duration.
In 2010, DND*i* and its partners submitted the protocol to the French ethical and regulatory authorities, for a new Phase I study assessing pharmacokinetic profile after administration with field food. Together with DND*i*'s partner sanofi-aventis, parallel scientific advice from EMA (under the article 58) and FDA on the clinical development plan of fexinidazole was requested and took place in 2010. Results of the consultation are expected in January 2011.

The first success of the proactive compound mining efforts, Fexinidazole, entered into Phase I.

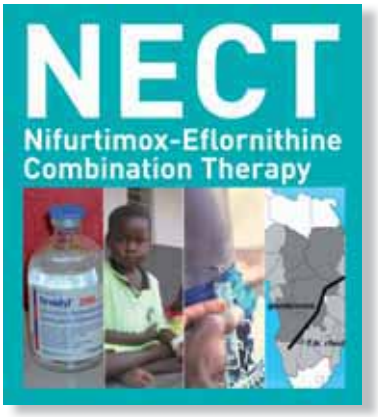
/... SCYX-6759, cured murine central nervous system infection but were actively transported from the brain and had to be administered at high doses. New compounds that are not effluxed from the brain have since been identified.
One of these compounds, SCYX-7158, was advanced as a pre-clinical candidate at the end of 2009. In 2010, the pre-clinical development progressed successfully. In particular, the early non-GLP safety studies demonstrated no issues of concern. Thus, a regulatory toxicology package is planned for early 2011. The drug candidate SCYX-7158 will enter into clinical development in 2011 and will be DND*i*'s first new chemical entity issued from lead optimization.

IMPLEMENTATION

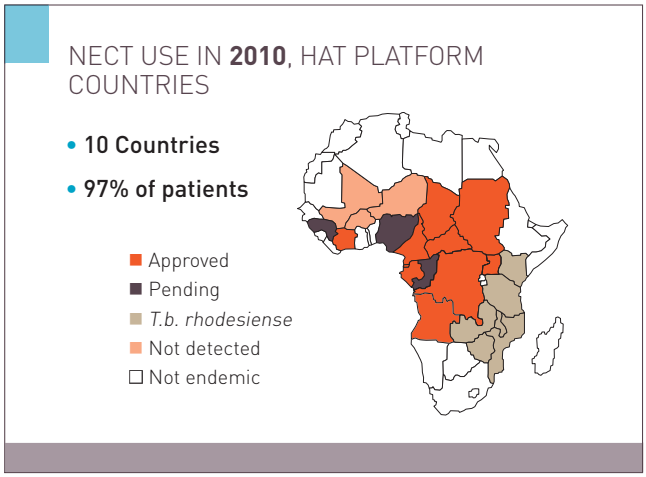
NECT (Nifurtimox-Eflornithine Combination Therapy)

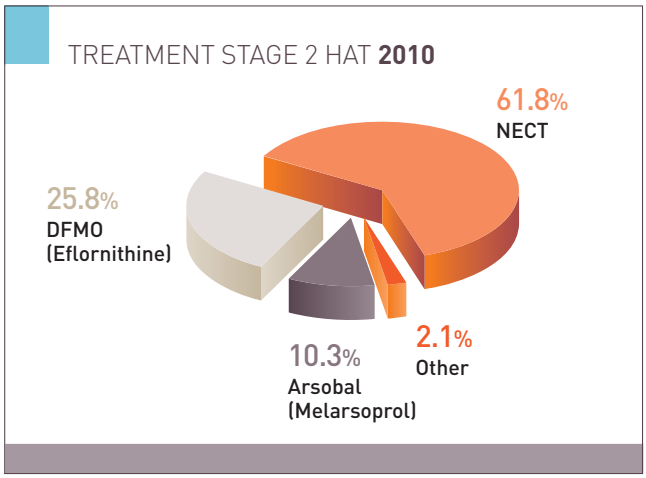
- **Partners:** Epicentre, France; Médecins Sans Frontières (MSF); Swiss Tropical and Public Health Institute (Swiss TPH); National Trypanosomiasis Control Programmes of the Republic of Congo and the Democratic Republic of the Congo (DRC); HAT Platform partners
- **Management:** Medical Manager, Olaf Valverde Mordt; Project Coordinator, Séverine Blesson
- **Project start:** 2004

NECT (Nifurtimox-Eflornithine Combination Therapy) has been available to patients since the end of 2009 and is the first new treatment for sleeping sickness in 25 years. NECT consists of a simplified co-administration of oral nifurtimox and intravenous eflornithine. Developed by DND*i*, Epicentre, Médecins Sans Frontières (MSF), the Swiss Tropical and Public Health Institute (Swiss TPH), and the National Trypanosomiasis Control Programmes of the Republic of Congo and the Democratic Republic of the Congo (DRC), NECT reduces the total number of infusions of eflornithine from 56 to 14, shortens hospitalization from 14 days to 10 and cuts the cost of treatment by half. Because NECT requires only two infusions a day that can be administered during daytime, it significantly reduces the burden on health staff, and makes the treatment far more adaptable for the resource-poor settings where HAT treatments take place.



Thanks to the inclusion in the WHO Essential Medicines List (May 2009), endemic countries have now begun ordering the new combination treatment through the WHO. As of December 2010, 10 countries – which together treat more than 97% of all HAT *T.b. gambiense* patients – have requested NECT as a treatment for HAT in their territories: Angola, Cameroon, Central African Republic, Chad, the Democratic Republic of the Congo, Equatorial Guinea, Gabon, Ivory Coast, South Sudan, and Uganda. Six of them have received the supplies from the WHO – nearly 6,000 treatments – and have begun to treat patients (2,176 patients treated with NECT by the end of 2010). Since the launch of NECT in the second half of 2009, melarsoprol and eflornithine in monotherapy are increasingly being replaced by NECT (see table below). The HAT Platform continues advocating for the use of NECT, which offers a safer and better field-adapted treatment for stage 2 sleeping sickness.





DND*i* and its partners are conducting a Phase IIIb 'NECT-Field' study, to further document the safety and ease of use of the combination in real-life field conditions and in special populations like children, pregnant women, and lactating women. The enrolment started in April 2009 and by December 2010, 630 patients had been enrolled for the study (including 100 children and more than 40 pregnant women). They will be followed up for 2 years.

Leishmaniasis

A new combination therapy available in East Africa and clinical studies worldwide to develop field-adapted treatments

Leishmaniasis occurs in several forms, the two most common of which are visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL). VL, also known as kala-azar or black fever, mainly occurs in poor, remote areas in South Asia, East Africa, and South America. Particularly affecting women and children, it is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anaemia. VL is life threatening. CL is characterized by lesions on the skin, either self-healing or chronic. Another form of leishmaniasis is post-kala-azar dermal leishmaniasis (PKDL), a complication of VL, and is important as it serves as a parasite reservoir for VL, thus contributing to transmission of the disease.
DND*i*, while focusing primarily on VL, also included cutaneous leishmaniasis (CL) in its portfolio and has ongoing exploratory activities to seek improved treatments.

There is a general agreement that chemotherapy remains one of the most important tools in the control of VL. Existing treatments have serious limitations such as potential of resistance development, low tolerability, long treatment duration, and difficulty in administration. Furthermore, they are high in cost. Established VL treatments include: pentavalent antimonials (given by injection, registered in East Asia and some African countries); amphotericin B (an intravenous treatment given over 30 days, registered in East Asia and some African countries); AmBisome® (a liposomal formulation of amphotericin B registered for VL in India, USA, and Europe); miltefosine (an oral drug registered in India in 2002, now in use as a monotherapy); and a low-cost parenteral (intramuscular) formulation of paromomycin, registered in India in 2007 by the Institute for OneWorld Health (iOWH).

In addition to developing novel therapies as a long-term goal, DND*i*'s short-term approach is to develop new treatments involving either optimal monotherapy regimens or combination therapies of drugs that are already available. This offers the following important advantages: shorter course of treatment; better tolerability; reduction of the burden on health systems in resource-limited areas; greater affordability; and with combinations, the potential to prevent or delay resistance development and therefore prolong the life-span of these drugs. Another short-term objective pertains to extending registration and availability of current drugs to additional countries in need. The goal is to make drugs that are available in India, for example, also available to patients in Bangladesh, Nepal, East Africa, and other countries and regions, provided that a favourable efficacy/safety profile is also shown in these regions.

Mother and child waiting for their medicines at the pharmacy of Kimalel Health Centre, in Kenya, where DND*i* and its partners conducted VL clinical trials.

Over 2009 and 2010, DND*i* and other partners made considerable headway in the development of new treatments for visceral leishmaniasis. In East Africa, the year 2010 saw the adoption of SSG&PM combination (sodium stibogluconate & paromomycin) - a new, improved treatment option which was recommended as first-line treatment for VL in the region by the World Health Organization (WHO) Expert Committee on the Control of Leishmaniases.
In India, significant progress was also made with the completion of two important Phase III clinical trials. One major study .../

IDEAL TARGET PRODUCT PROFILE FOR VL

Target product profile for a new chemical entity for VL

- **A new treatment for adults and children**
- **Efficacious (>95% clinical efficacy at 6 months after treatment) against all species of the parasite in all regions**
- **Ideally efficacious for PKDL**
- **Ideally efficacious in all geographical regions**
- **Favourable safety profile, ideally requiring no monitoring**
- **Easy-to-use treatment: Short course (ideally ≤7 days, once daily oral; shorter duration for intramuscular)**
- **Affordable (stable in tropical climates with minimum 3-year shelf life)**

/... was completed by DND*i* on three short-course combination therapies while another study, conducted by Sundar et al. on single-dose AmBisome® was published: both studies demonstrated the high efficacy (>95%) of these new treatment options.

VL CLINICAL STUDIES ON THREE CONTINENTS

The objective of the South Asia clinical project was to study short-course combination therapy using two of the three drugs registered in India: AmBisome®, paromomycin, and miltefosine (see Project of the Year, page 27). In parallel to this, another study was undertaken to develop an optimal single-dose regimen of AmBisome®. The goal is to have improved treatment options that can be implemented by National Control Programmes in India, Nepal, and Bangladesh.

The East Africa clinical projects, led by DND*i* and the Leishmaniasis East Africa Platform (LEAP, see page 41), aim to geographically extend all currently available VL drugs to East Africa and to develop new therapies suitable for the region, of which SSG&PM is the first.

DND*i* is also participating in multicentre clinical trials in Latin America. These studies are sponsored by the Brazilian Ministry of Health to assess the safety and efficacy of the currently recommended treatments for VL in Brazil (Glucantime®, amphotericin B deoxycholate, AmBisome®), as well as to assess the combination of AmBisome® with Glucantime®.

Furthermore, DND*i* aims to accelerate the development and registration of new VL drugs by building on existing pre-clinical and early clinical data. In addition, DND*i* has a lead optimization programme, which aims at bringing new candidates into clinical development.

DISCOVERY

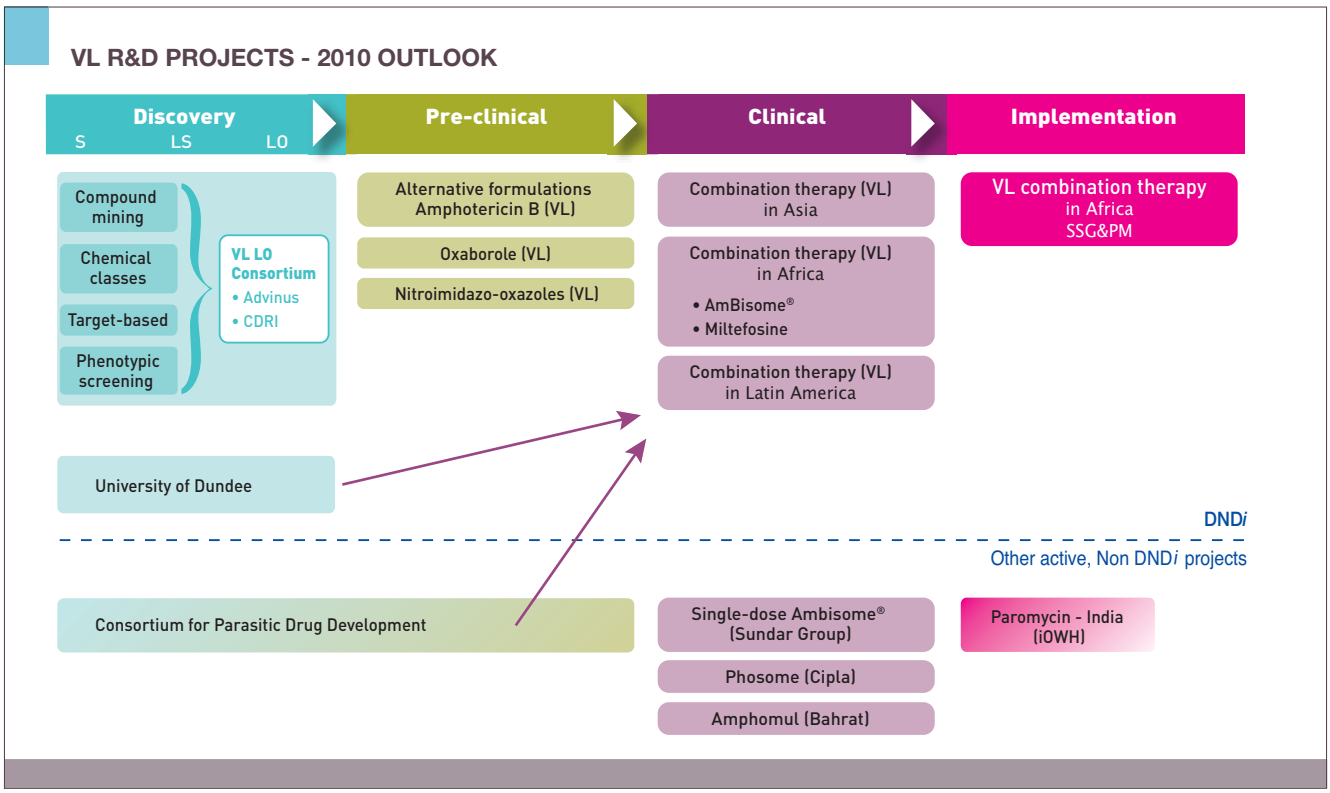
VL Lead Optimization Consortium

- **Partners:** Advinus Therapeutics, India; Central Drug Research Institute (CDRI), India
- **Management:** Head of Visceral Leishmaniasis Discovery and Pre-clinical Programme, Denis Martin; Project Coordinator, Delphine Launay
- **Project start:** November 2007

The goal of this project is to generate new drug candidates that meet the target product profile for the treatment of VL. DND*i* partnered in 2007 with Advinus Therapeutics, a drug discovery and development company based in Bangalore, India, and CDRI (Central Drug Research Institute), an Indian public institution located in Lucknow, India.

Compounds showing activities (hits) are identified from DND*i*'s ongoing screening projects carried out by our screening partners. The chemical structure of the best hits are then systematically modified, guided by a combination of medicinal chemistry, physicochemical properties, biological screening, and absorption, distribution, metabolism, excretion, and toxicology (ADMET) parameters, to ensure that the optimized compounds meet all the necessary drug-like criteria specified by the target product profile (TPP) for a new drug to treat VL. With a full team of eight chemists in place within the VL Lead Optimization Consortium, assessments of four series of synthetic compounds, provided by DND*i* partners, have been carried out or are ongoing.

Recently, the thiazole series identified from a large screening campaign performed at Institut Pasteur Korea (IPK) has yielded potent lead molecules. Additional efficacy and pharmacokinetics studies are underway to identify pre-clinical candidates from this promising series.



Leishmaniasis

98 countries affected with 350 million people at risk

WHAT IS THE ANNUAL IMPACT OF LEISHMANIASIS?[1]

- **500,000 cases of visceral leishmaniasis (VL)[1]**
- **1.5 million cases of cutaneous leishmaniasis (CL)[1]**
- **Approx. 50-60,000 deaths due to VL[2]**

HOW IS LEISHMANIASIS TRANSMITTED?

More than 20 species of the kinetoplastid protozoan parasite *Leishmania* can be transmitted to humans via some 30 species of phlebotomines sandflies.

WHAT ARE THE SYMPTOMS?

Leishmaniasis occurs in several forms, the two most common of which are:

- **VL**: characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anaemia. VL is life threatening.
- **CL**: characterized by lesions on the skin, which can either be self-healing or become chronic. CL is generally not life threatening.

WHERE DOES LEISHMANIASIS OCCUR?

Leishmaniasis occurs in 98 countries with 350 million people at risk. VL affects poor populations living in remote areas of around 70 countries across Asia, East Africa, South America, and the Mediterranean region. The seven most affected countries, which represent over 90% of new cases of VL, are Bangladesh, Brazil, Ethiopia, India, Kenya, Nepal, and Sudan. CL has a wider geographic range, with the majority of cases occurring in Afghanistan, Algeria, Islamic Republic of Iran, Saudi Arabia, Syrian Arab Republic, Bolivia, Brazil, Colombia, Nicaragua, and Peru[1].

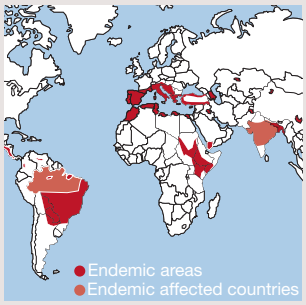
WHAT ARE THE CURRENT TREATMENTS FOR VL AND THEIR LIMITATIONS?

The number of treatment options has increased in the past decade, but each treatment still has numerous drawbacks. Treatments include:

- **Pentavalent antimonials** (sodium stibogluconate and meglumine antimoniate): toxic, increasing resistance and require 30-day parenteral treatment
- **Amphotericin B**: dose-limiting toxicity and requires 15-20 day treatment
- **Liposomal amphotericin B** (AmBisome®): effective, but expensive[3] and requires intravenous infusion
- **Paromomycin**: requires 3 weeks of intramuscular administration
- **Miltefosine**: first orally administered drug registered in India but expensive[3], requires a 28-day treatment and is teratogenic

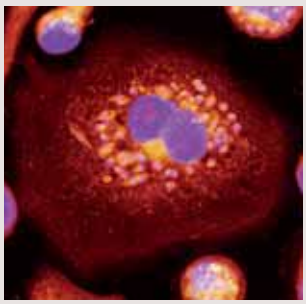
Taking into account latest evidence and in order to optimize these current treatments, in March 2010, a WHO expert committee recommended the following treatments for VL:

- **India**: Liposomal amphotericin B monotherapy; combinations involving miltefosine, paromomycin, and Liposomal amphotericin B
- **East Africa**: sodium stibogluconate & paromomycin combination treatment (SSG&PM)
- **Latin America**: Liposomal amphotericin B monotherapy



WHAT ARE THE PATIENTS' TREATMENT NEEDS FOR VL?

Patients with VL need a treatment which is oral, safe, effective, low cost, and short course.



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

Short term: better use of existing treatments through geographical extension and new treatments schedules for VL

- **Africa**: Registration of paromomycin, AmBisome®, miltefosine, and development of an AmBisome® based combination. SSG&PM combination treatment now available.
- **Asia**: Recommendation and implementation of single-dose AmBisome® and combinations involving miltefosine, paromomycin and Liposomal amphotericin B in India, Bangladesh, and Nepal by 2014.
- **Latin America**: Recommendation of a new treatment by 2013 involving Liposomal amphotericin B in monotherapy and/or in combination.

Medium or long term: registration of one new drug through new formulations of existing treatments and therapeutic switching. Potential compounds in-sourced at late pre-clinical phase – DND*i* is actively pursuing potential candidates ready for clinical development in the short term. New drugs developed from compounds identified through VL Lead Optimization Consortium. Multi-country, multi-partner LEAP to strengthen regional research capacity (see page 41).

By 2014, DND*i* aims to deliver from its VL-specific portfolio:

- 1 new drug at late stage of clinical development
- 1-3 geographical extensions in endemic regions of currently available drugs

(1) *Control of the Leishmaniases: Report of a Meeting of the WHO Expert Committee on the Control of Leishmaniases*, Geneva, 22-26 March 2010. WHO, Geneva, 2010.
(2) It is difficult to estimate the accurate incidence and case-fatality rate of VL due to frequent misdiagnosis and lack of surveillance systems. **(3)** Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of key endemic countries as of 2007.

PRE-CLINICAL

Alternative formulations of amphotericin B

- **Partners:** Polytherics, UK; London School of Pharmacy, UK; London School of Hygiene and Tropical Medicine (LSHTM), UK
- **Management:** Head of Visceral Leishmaniasis Discovery and Pre-clinical Programme, Denis Martin
- **Project start:** September 2006

The goal of this project is to identify an improved formulation of amphotericin B that shows the most promise in terms of *in vivo* efficacy, safety, heat stability, and cost. Amphotericin B, under various formulations, is one of the most efficacious treatments for VL. The standard formulations (oily suspension) have side effects. AmBisome®, a liposomal formulation, has overcome these limitations, but its high cost and lack of heat stability limit its utility in disease-endemic countries. Recently, new formulations have emerged and have either been approved or are under clinical development in India. However, they are still not field-adapted and there is no safety and VL efficacy data available yet. DND*i* and its UK partners are investigating improved polymer-based formulations to replace the lipid-based component with a narrow molecular weight range polymer. Ideally, the selected polymer can form an amphotericin B conjugate that is soluble, cheaper, better tolerated, and has increased thermal stability. Initial results show that reproducible *in vivo* activity could be achieved without signs of amphotericin-induced toxicity in test animals. Further characterization is in progress.

PRE-CLINICAL

Nitroimidazoles

- **Partners:** TB Alliance, USA; Advinus, India; CDRI, India, LSHTM, UK; Auckland University, New Zealand
- **Management:** Head of Visceral Leishmaniasis Discovery and Pre-clinical Programme, Denis Martin; Project Coordinators, Delphine Launay, Anne-Sophie Bessis
- **Project start:** May 2010

Nitroimidazoles, a class of novel anti-bacterial agents, have great potential for addressing major unmet medical needs in TB therapy. PA-824, the first compound in the TB Alliance portfolio is currently undergoing Phase II clinical development for the treatment of TB. It has many attractive characteristics as a TB therapy. Through a contractual agreement with TB Alliance, DND*i* was granted access to their nitroimidazole library. From the initially selected 70 nitroimidazoles belonging to 4 chemical subclasses, DND*i*-VL-2098 was identified as a very potent and safe molecule and was selected for in-depth evaluation of its efficacy, pharmacokinetic, and early safety profile on the basis of these preliminary results. This compound is potent and selective *in vitro* and shows efficacy in acute and chronic VL animal models. Appropriate exposure is obtained after oral dosing in rodents and the compound does not induce toxicity after one-week administration at several times the efficacious dose. The objective is to perform all pre-clinical activities needed to meet regulatory requirements, and to file an Investigational New Drug (IND) by the end of 2011 if further pre-clinical data support advancement to clinical. A well-focused back-up programme is ongoing at Auckland University.

TB ALLIANCE AND DND*i* JOIN FORCES IN 2010

The Global Alliance for TB Drug Development (TB Alliance) and DND*i* entered into a first-ever royalty-free license agreement between two not-for-profit drug developers in 2010. The TB Alliance granted rights to DND*i* to develop a class of potential anti-TB compounds that also show significant promise for treating other neglected diseases, such as those in DND*i*'s portfolio. Such collaboration not only strengthens the impact of investments in R&D for neglected diseases, it demonstrates the good will among PDPs in creating critical paths by reducing repetition in research.

CLINICAL

Combination therapy (VL in Latin America)

- **Major Partners:** René Rachou Research Institution – FIOCRUZ-MG, Brazil; Paediatric Hospital João Paulo II – FHEMIG, Brazil; Brasilia University, Brazil; Montes Claros State University, Brazil; Piauí Federal University, Brazil; Sergipe Federal University, Brazil; Tocantins Federal University, Brazil; Leishmaniasis Control Programme/Brazilian Ministry of Health, Brazil.
- **Management:** Head of Leishmaniasis Clinical Programme, Manica Balasegaram; Clinical Manager, Fabiana Piovesan Alves
- **Project start:** 2010

About 90% of VL cases in Latin America occur in Brazil, and most of them affect children. In 2007, Brazil reported around 3,500 new cases and a fatality rate of 5.4%. DND*i*'s objective is to assist the Brazilian Ministry of Health to evaluate the safety and efficacy of Glucantime®, AmBisome®, amphotericin B, and AmBisome® and Glucantime® combination to treat VL patients in Brazil. To this end, a feasibility assessment and VL site selection was performed over 2010, with potential study sites identified in different regions of the country. The broader objectives of the study, led by Dr Gustavo Romero of the University of Brasilia, and sponsored by the Brazilian Ministry of Health, include the assessment of the effectiveness of currently recommended treatments for VL in Brazil. The project is conducted in several reference centres, involving a total of 600 adults and children. The recruitment of patients commenced in Q1 2011.

About 90% of VL cases in Latin America occur in Brazil, and most of them affect children.

COMBINATION THERAPY (VL IN ASIA)

Good efficacy results in India for combination therapies

- **Major Partners**
  INDIA: Indian Medical Research Council (ICMR), Delhi; Kala-Azar Medical Research Centre (KAMRC), Muzaffarpur; Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna.
  BANGLADESH: International Centre for Diarrhoeal Disease Research (ICDDR, B), Dhaka; Shaheed Suhrawardy Medical College and Hospital (ShSMC), Dhaka; Community Based Medical College (CBMC), Mymensingh.
  NEPAL: BP Koirala Institute of Health Sciences, Dharan.
  USA: Institute for OneWorld Health, San Francisco.
  WHO's Special Programme for Research and Training in Tropical Diseases (TDR)
- **Management:** Senior Advisor for Leishmaniasis, Farrokh Modabber; Head of Leishmaniasis Clinical Programme, Manica Balasegaram; Clinical Manager, Sally Ellis; Head of DND*i* India, Bhawna Sharma
- **Project start:** June 2008

DND*i*'s objective is to identify a safe and effective short-course therapy using existing drugs, which could be easily deployed in control programmes and replace current treatment regimens which either lack efficacy (SSG in some regions), require long treatment courses (miltefosine, SSG, paromomycin) or are have some associated toxicity (conventional amphotericin B, SSG). Following preclinical and Phase II studies, an open label, randomized, prospective, non-inferiority Phase III trial was conducted to study the combination of drugs already registered in India: AmBisome®, miltefosine, and paromomycin. Three arms investigating the three possible 2-drug combinations with a maximum duration of 11 days were compared with the standard 30-day therapy (15 infusions every other day using amphotericin B). This study, involving a total of 634 patients, was completed in 2010. All three combination treatments were highly efficacious (>97.5% cure rate), and none was inferior to the standard treatment using amphotericin B.

This project has been developed in collaboration with ICMR, the Rajendra Memorial Research Institute of Medical Sciences (RMRI) in Patna and the Kala Azar Medical Research Centre (KAMRC) in Muzaffarpur.

DND*i* Project of the Year 2010

The complete results were published in *The Lancet* in January 2011[1].
A two-step Phase III trial (first in hospital settings followed by treatment in primary healthcare centres) using the same combinations have also been initiated in Bangladesh, with recruitment commencing in July 2010. In December 2010, about 100 patients had been enrolled in the study. Discussions are ongoing with authorities and partners such as iOWH to initiate a trial in Nepal to evaluate the safety of one or more combinations with the same drugs. In addition, discussions are in progress with the Indian National Vector Borne Disease Control Programme.
In parallel to this work, Sundar et al. conducted another Phase III study that showed the efficacy of a single dose of 10mg/kg of AmBisome® (n=304) given as an i.v. infusion, which cured 95.7% of patients at 6 months (95% CI 93.40-97.90). The treatment was shown to be non-inferior in both safety and efficacy to the standard treatment of amphotericin B 1mg/kg i.v. given as 15 infusions on alternate days (n=108).
In March 2010, the WHO Expert Committee on the Control of Leishmaniasis met in Geneva and recommended that all 4 of the new treatments (the 3 combinations and single dose AmBisome®) be used preferentially to current established monotherapy treatments for VL in South Asia.
DND*i* has actively developed a partnership with TDR and iOWH to facilitate the introduction of these new treatments for VL in South Asia. This will be done in collaboration with health authorities at state, national, and regional levels. DND*i* and its partners intend to implement effectiveness studies in the region to demonstrate that such treatments can be feasibly and safely implemented in primary healthcare settings in both the public and private sectors.

(1) Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial by Sundar S et al. *The Lancet*, 2011 January, DOI:10.1016/S0140-6736(10)62050-8.

The award went to the 'VL in Asia' Project
(DND*i* Partners' meeting in Delhi, India, December 2010).

COMBINATION THERAPY (VL IN AFRICA)

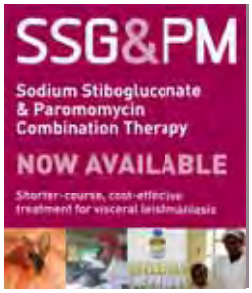
SSG&PM recommended for East Africa and further studies for new treatment options

- **Major Partners**
  Kenya Medical Research Institute (KEMRI), Kenya; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; University of Makerere, Uganda; London School of Hygiene and Tropical Medicine, UK; ASK (AMC, Slotervaart Hospital, KIT), The Netherlands; Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; Médecins Sans Frontières (MSF); i+ solutions, The Netherlands; Institute for OneWorld Health (iOWH), USA; LEAP (Leishmaniasis East Africa Platform)
- **Management:** Head of Leishmaniasis Clinical Programme, Manica Balasegaram; Clinical Manager, Sally Ellis
- **Project start:** November 2004

Due to various limitations such as toxicity, difficulty of use, and the high cost of existing drugs, VL is complex to treat in Africa. Sodium stibogluconate (SSG), a relatively toxic drug requiring a daily regimen of painful injections over 30 days, remains the mainstay of treatment. Other drugs, such as paromomycin (PM) and miltefosine, are neither registered nor available in the region. Since 2004, DND*i* and the Leishmaniasis East Africa Platform (LEAP) have embarked on a clinical research programme with two specific objectives: to geographically extend all currently available VL drugs and to develop one to two new treatments. In 2010, the first – a combination therapy – came out of this clinical research programme: SSG&PM.

In addition to the LEAP 0104 study, DND*i* also conducted two other clinical trials in the region during 2010 in order to develop a second treatment:

AmBisome® / LEAP 0106 Study
AmBisome®, a liposomal formulation of amphotericin B manufactured by Gilead, is approved to treat VL in Europe and USA. Gilead has worked with the World Health Organization and NGOs to provide AmBisome® at a preferential price for the treatment of leishmaniasis in resource-limited settings. Therefore, the goals of this project are 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 stays required, and to facilitate the registration and adoption of the drug in the region, in addition to its optimal use in combination therapies. Recruitment for the study was closed at the end of 2010. Results of this study will be presented in 2011.



This project was initiated to register paromomycin in East Africa and evaluate its use in a shorter-course combination with SSG as an improved treatment for VL.

In 2010, the Leishmaniasis East Africa Platform (LEAP) completed this multi-centre, multi-country clinical trial sponsored by DND*i* in Kenya, Ethiopia, Sudan, and Uganda. The LEAP 0104 study involved over 1,100 VL patients and showed that a short-course combination of PM (15mg/kg/day) and SSG (20mg/kg/day) had a similar safety and efficacy profile (efficacy at 6 months follow up post-treatment >90%) as the standard SSG monotherapy treatment (SSG 20mg/kg/day for 30 days). The trial also demonstrated that the use of PM (15 or 20 mg/kg/day) alone for 21 days resulted in significantly lower efficacy. Thus the use of the combination will be critical to prolonging the use of both drugs in the region, particularly PM.

In March 2010, the WHO Expert Committee on the Control of Leishmaniases recommended SSG&PM as first-line treatment for visceral leishmaniasis in East Africa. A few months later, Sudan was the first country to apply the recommendation and implement SSG&PM to treat patients (end 2010). DND*i* and LEAP will continue the process of ensuring the registration of paromomycin in the region in order to further implement the recommendation of SSG&PM as first-line treatment regimen for VL. These results were presented in PLoS (see publications, page 47).

Miltefosine-AmBisome® / LEAP 0208 Study
This study is to evaluate the safety and efficacy of miltefosine and AmBisome® combination treatment. Recruitment has started in Kenya and Sudan (Q2 2010). Miltefosine, a drug originally developed for the treatment of cancer, is the only orally administered drug against VL. Miltefosine is registered and used in India and in some countries in Latin America. The trial will collect safety, efficacy, and pharmacokinetic data on miltefosine to geographically extend the use of the drug into East Africa. In addition, combination treatments of AmBisome® with either miltefosine or SSG are evaluated. If the results are promising, it will be taken into Phase III development.

Chagas Disease
American Trypanosomiasis

Development of a paediatric treatment and of a new azole compound to treat adult chronic patients

After 40 years of scant clinical research on Chagas disease, DND*i* launched three studies in Latin America, one of which to test a totally new compound against the *T. cruzi* infection. Until recently, the primary focus for controlling Chagas disease was to interrupt transmission. This was done through vector control programmes and the screening of blood donors. In the Southern Cone of South America major initiatives began in 1991-92 and over the next decade most Central and South American countries joined the initiatives. The goal was to eliminate *T. cruzi* infections by 2010 through a new Global Network for Chagas Elimination. While these programmes have significantly reduced the incidence of infection in children and have hindered blood-transfusion related transmission, Chagas disease still affects an estimated 8 million worldwide. In 2005, according to PAHO, 1.8 million women of childbearing age were infected and 14,000 children were born with the disease in the Americas.[1]

Current therapy for Chagas disease is limited to two nitroheterocyclic drugs, nifurtimox and benznidazole. Both drugs require a long treatment duration (30-60 days), which increases the risk of patient noncompliance, and dose- and time-dependent toxicity is also frequent. Both are more effective in the acute form of the disease (mostly identified in children) than they are in the chronic phase. Unfortunately, most of the patients are diagnosed in the latter phase. Furthermore, no paediatric strength or formulation is currently available, meaning that caregivers are obliged to break and crush the only available adult formulation into small pieces for children, leading to potential errors in dosage.

The long-term goal is to develop new and effective treatments for chronically-infected patients. The near-term goal is to improve existing treatments through the development of new formulations that are better adapted to patients' needs, especially for newborns who acquire the infection through mother-to-child transmission. DND*i* currently has engaged in the development of a paediatric formulation of benznidazole, and in the clinical development of a new azole antifungal drug, E1224, against *T. cruzi* in adult chronic patients bringing new hope to Chagas patients. In parallel, DND*i* plans to evaluate selected biomarkers, which could shorten the patient follow-up for test of cure.

In the longer term, however, new chemical entities need to be developed that are safe and efficacious, as specified in DND*i*'s target product profile. DND*i* continues to identify and engage partners from private and public sectors to ensure that the goals in drug development for Chagas disease are met. Additionally, DND*i* is committed to strengthening existing clinical research capabilities through a regional platform of experts, the Chagas Clinical Research Platform (see page 40), launched in 2009, that supports GCP-standard clinical trials.

Children are the most vulnerable population at risk of contracting Chagas disease (Argentina).

IDEAL TARGET PRODUCT PROFILE FOR CHAGAS

- **A new treatment for acute and chronic disease**
  - Useful against most parasite species in all regions
- **Better safety profile than existing drugs**
  - Ideally requiring little or no monitoring
- **Non inferior efficacy to benznidazole**
- **Easy-to-use treatment**
  - Ideally once-a-day for less than 30 days
  - Oral
  - Preferably once-a-day treatment, ideally outpatient
- **Affordable**
- **Stable (3 years minimum) in tropical climates**

(1) PAHO, *Estimación cuantitativa de la enfermedad de Chagas en las Américas*, 2006

Chagas Disease - AMERICAN TRYPANOSOMIASIS

21 endemic countries and worldwide impact due to global migration

WHAT IS THE ANNUAL IMPACT OF CHAGAS DISEASE?

100 million people at risk[1]
Approximately 8 million cases[2]
12,000 deaths[3]

HOW IS CHAGAS DISEASE TRANSMITTED?

Caused by the kinetoplastid protozoan parasite *Trypanosoma cruzi*, Chagas disease is primarily transmitted by large, bloodsucking reduviid insects widely known as 'the kissing bugs' in endemic countries. Other routes of transmission include blood transfusion, organ transplantation, as well as congenital and oral routes through ingestion of contaminated food or beverage.

WHAT ARE THE SYMPTOMS?

The disease has two clinical phases:

- **Acute phase** (fatal for 2-8% of children[4]), often asymptomatic or unrecognized due to its non-specific symptoms, such as fever, malaise, generalized lymphoadenopathy, and hepatosplenomegaly, which spontaneously resolve in 4-6 weeks.
- **Chronic phase** can be divided into two stages:
  – The chronic asymptomatic 'indeterminate' stage, during which patients can transmit the parasite to others, especially through vertical transmission, while showing no signs of the disease, and which may last decades after infection.
  – The chronic symptomatic stage, which develops in up to 30% of infected patients and most often involves the heart or gastrointestinal tract.

Chagas disease is the leading cause of infectious heart disease (cardiomyopathy) in the region.

WHERE DOES CHAGAS DISEASE OCCUR?

Endemic in 21 countries across Latin America, but through population migration the disease has spread to Australia, North America, Japan, and Europe.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

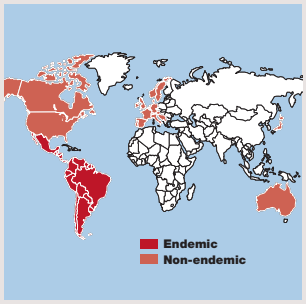
Current treatments have the highest efficacy in acute infection with limited evidence for efficacy in the chronic stages.

- **Benznidazole, nifurtimox** to treat acute and chronic phases:
  – Long treatment period (30-60 days)
  – Dose-dependent toxicity
  – High rate of patient non-compliance
  – No paediatric strengths

There is no treatment for chronic disease with target organ involvement.

WHAT ARE THE PATIENT TREATMENT NEEDS?

- A paediatric strength of benznidazole that is affordable and age-adapted.
- A new oral drug that is safe, efficacious, and adapted to the field, and ideally would work in both stages of the disease.



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

Short term: better use of existing treatments through the development of paediatric-strength benznidazole

Medium term:

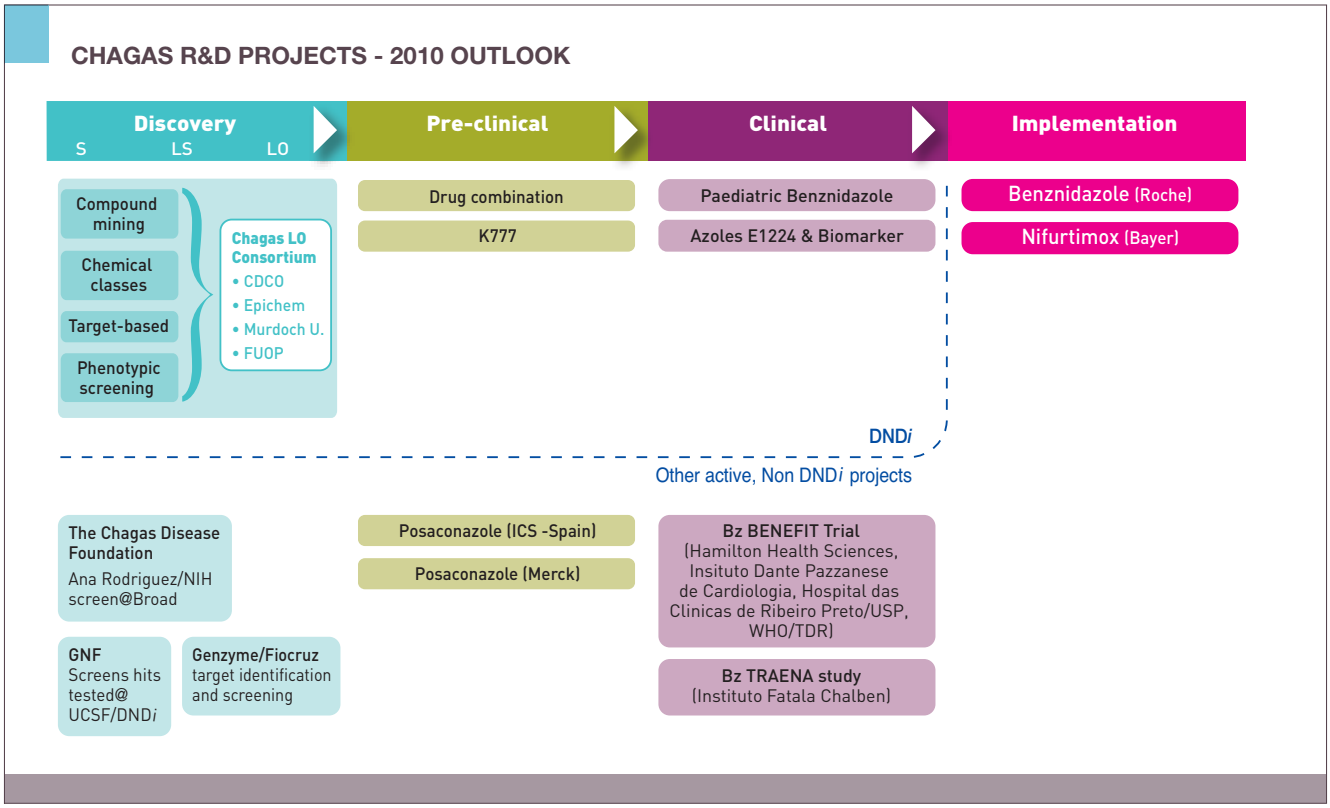
1) Azoles: clinical assessment of known compounds already in development against fungal infections. Specifically, clinical studies of E1224, in collaboration with Eisai are being conducted.

2) Development of new treatments through combination therapy – in exploratory pre-clinical stage.

Long term: New drugs developed from promising compounds identified in discovery activities (such as GSK library of pyridones and cysteine protease inhibitors) and progressed through Chagas Lead Optimization Consortium.

By 2014, DND*i* aims to deliver from its Chagas-specific portfolio
– 1 new paediatric-strength benznidazole
– 1 new drug registered for chronic Chagas disease

(1) PAHO, *Estimación cuantitativa de la enfermedad de Chagas en las Américas*, 2006 **(2)** PAHO 2010, http://new.paho.org/blogs/cd50/?p=1527&lang=en
(3) Ibid. **(4)** Parada H, Carrasco HA, Anez N, Fuenmayor C, Inglessis I. Cardiac involvement is a constant finding in acute Chagas disease: a clinical, parasitological and histopathological study. *Int J Cardiol*. 1997. 60: 49–54.



DISCOVERY

Chagas Lead Optimization Consortium

- **Partners:** Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto, Brazil
- **Management:** Head of Chagas Discovery and Pre-clinical Programme, Eric Chatelain; Project Coordinator, Ivan Scandale
- **Project start:** July 2008

In mid-2008, a Lead Optimization Consortium devoted to Chagas drug discovery was set up by DND*i*. Members of this consortium are engaged in a complex, iterative process to optimize the efficacy and pharmacological properties of lead compounds while minimizing their toxicity. Rapid turnaround of compound assessment is achieved by a group of analytical and medicinal chemists (Epichem, Australia), pharmacologists (Monash University, Australia), and parasitologists (Murdoch University, Australia and Universidade Federal de Ouro Preto, Brazil). The objective is to develop at least one new optimized lead for Chagas disease by the first quarter of 2012 and to identify a new chemical series of interest.

One of the current chemistry efforts is on the fenarimol series. Several high-potency compounds have been generated, and some have shown efficacy *in vivo*.

At the same time, the team is evaluating the oxaboroles series, taking advantage of the compounds generated from the lead optimization programme for human African trypanosomiasis (HAT). Over 2,000 oxaboroles have been screened for their activity against *T. cruzi in vitro*, and some have shown activity. Other series originating from DND*i* screening efforts will serve as leads for further optimization in the future.

PRE-CLINICAL

Drug combination

- **Partners:** Federal University of Ouro Preto, Brazil
- **Management:** Head of Chagas Clinical Programme, Isabela Ribeiro; Project Coordinator, Bethania Blum
- **Project start:** September 2008

The main treatment limitation in Chagas disease is the poor tolerability with currently available treatments. Side effects of benznidazole and nifurtimox are both time- and dose-dependent. Combination therapy could improve treatment efficacy and reduce dosage, treatment duration, and toxicity, and could also prevent the potential development of resistance to existing drugs. Azole derivatives have shown synergistic anti-*T. cruzi* effects, *in vitro* and *in vivo*, with benznidazole or nifurtimox and with other inhibitors of the sterol biosynthesis pathway. DND*i* has thus initiated pre-clinical studies to systematically evaluate, in animal models, treatments combining azole drugs with either one of the two available drugs for Chagas disease therapy. Preliminary *in vivo* results demonstrate a clear beneficial effect for such combination treatment. The data will be further validated in future studies and will help to inform subsequent clinical evaluation of the azole class in combination therapy.

PRE-CLINICAL

K777

- **Partners:** University of California San Francisco (UCSF), USA
- **Management:** Head of Chagas Discovery and Pre-clinical Programme, Eric Chatelain
- **Project start:** September 2010

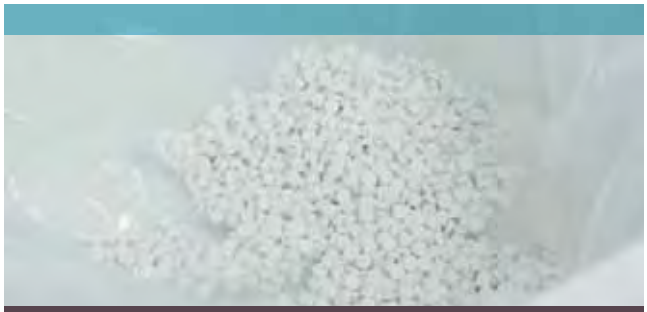
K777 is a vinyl sulfone cysteine protease inhibitor which irreversibly inhibits cruzain, a key protease required for viability of *Trypanosoma cruzi*, the parasite responsible for Chagas disease. A novel chemical entity originally characterized at University of California San Francisco (UCSF), K777 has since been shown to be safe and effective in models of acute and chronic Chagas disease in animals. The main objective of the project is to collaborate with the UCSF team in completing the pre-clinical drug development requirements to allow K777 to move into Phase I clinical trials.

CLINICAL

Paediatric benznidazole

- **Major Partners:** Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE), Brazil; Hospital de Niños Ricardo Gutierrez, Argentina; Instituto Nacional de Parasitología, Dr M Fatala Chabén, Argentina; Hospital de Niños de Jujuy, Argentina; Ministério de Salud, Província de Jujuy, Argentina; Hospital Público Materno Infantil – Salta, Argentina; Centro de Chagas y Patologia Regional, Argentina; CONICET/INGEBI, Argentina; Centro Nacional de Diagnóstico e Investigación de Endemo-epidemias (CeNDIE), Ministry of Health, Argentina; University of Liverpool, UK; NUDFAC, Brazil; CRO - LAT Research, Argentina;
- **Management:** Head of Chagas Clinical Programme, Isabela Ribeiro; Clinical Trial Manager, Jayme Fernandes; Project Coordinator, Bethania Blum
- **Project start:** June 2008

Benznidazole, a nitroimidazole introduced by Roche in 1971, and licensed to the Brazilian LAFEPE, is one of the two products registered for Chagas disease treatment and is included in the WHO Essential Medicines List. It is supplied in 100 mg tablets and administered twice daily for 60 days at a dose of 5 mg/kg bodyweight/day for adults and 5-10 mg/kg bodyweight/day for children. Extemporaneous formulations and fractionation are needed for most children because no paediatric formulation of the drug exists. Fractionation of tablets is far from ideal because of the high risk of delivering improper dosages, thereby raising concerns about efficacy, safety, and decreased stability.



Production of paediatric benznidazole at the pharmaceutical company LAFEPE in Recife, Brazil.

With the goal of developing an adapted dispersible tablet of benznidazole suitable for very young children, DND*i* and LAFEPE signed a development agreement in July 2008.

Using current benznidazole dose recommendations, and data from dosing practices and patient age and weight profiles from reference centres that treat children with *T. cruzi* infections as a guide, the team has determined the most appropriate paediatric tablet formulation, strength, and associated dosing regimen (12.5 mg tablets). Biobatch production was carried out in early 2010 and submission for registration is planned for the first quarter of 2011. A population pharmacokinetics study is to start in 2011 in Argentina, involving 80 paediatric Chagas disease patients, to obtain additional information on pharmacokinetics, treatment safety, and efficacy for this targeted population.

In rural areas of Latin America, where Chagas disease is highly endemic, families are at high risk of contracting the disease.

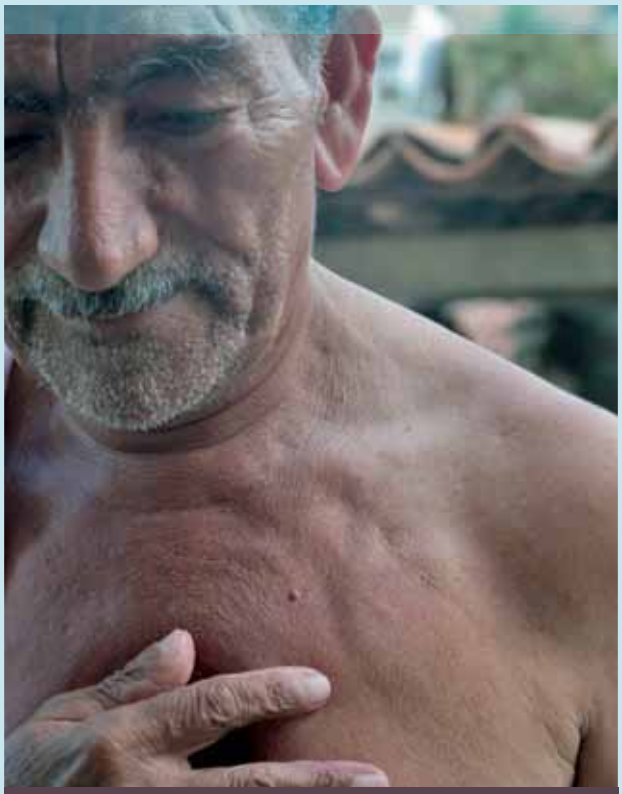
AZOLES E-1224 & BIOMARKERS

A promising alternative treatment for Chagas disease

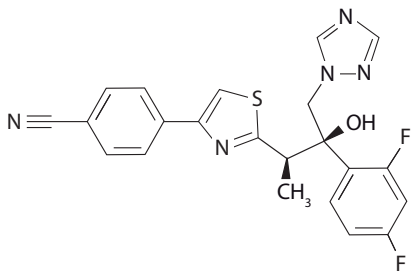
- **Major Partners:** Eisai Pharmaceuticals, Japan; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Universidad Mayor de San Simon, Bolivia; Federal University of Ouro Preto, Brazil; CONICET, Argentina; MSF-Spain; Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain
- **Management:** Head of Chagas Clinical Programme, Isabela Ribeiro; Clinical Manager, Fabiana Piovesan Alves; Project Coordinator, Bethania Blum
- **Project start:** June 2008

New antifungal azole derivatives offer a promising alternative treatment for Chagas disease. They potently inhibit *T. cruzi* ergosterol biosynthesis and possess desired pharmacokinetic properties (long terminal elimination half-life and large volume of distribution) suitable for the treatment of this disseminated intracellular infection. The current project evaluates E-1224, a new generation azole compound, as a new tool for the treatment of Chagas disease.

E-1224 is a water-soluble monolysine salt form of a pro-drug of ravuconazole, which is rapidly converted to ravuconazole *in vivo*. Ravuconazole has been evaluated extensively in animal models and in human trials, including Phase II safety and efficacy studies for fungal infections. E-1224, discovered and developed by Eisai Pharmaceuticals (Japan), has completed pre-clinical evaluation and five Phase I clinical studies.
DND*i* and Eisai Pharmaceuticals signed a collaboration and licensing agreement in September 2009. They will jointly conduct the safety and efficacy assessment of the compound in Chagas disease. DND*i* is responsible for the clinical development to assess the safety and efficacy in patients with Chagas disease in endemic countries.
In partnership with Eisai Pharmaceuticals and the Platform of Integral Care for Patients with Chagas Disease - that brings together scientists from CRESIB, Spain and universities in Bolivia - DND*i* will start a Phase II study to evaluate safety and efficacy of E-1224 in (adult) patients with chronic indeterminate Chagas infection. Sites will be located in Bolivia, where Chagas is highly endemic. They have been properly equipped and staff received appropriated training during 2010. The protocol has been approved by three different ethical committees and sites will be ready to start recruitment by second quarter of 2011.
Also in the scope of azoles compounds, DND*i* will carry out, in partnership with the Federal University of Ouro Preto, Brazil, evaluations of the activity of ravuconazole in different strains of *T. cruzi*, *in vivo* and *in vitro* and in combination with benznidazole.
A study is ongoing to optimize procedures for the use of the polymerase chain reaction (PCR) blood test as a measure of treatment response in Chagas disease. This study is being conducted in collaboration with MSF Spain, with PCR assay support provided by the Universidad Mayor de San Simon (UMSS) in Bolivia and quality assurance from INGEBI-CONICET in Buenos Aires, Argentina.
In parallel, DND*i* decided at the end of 2010 to start assessing biomarkers for Chagas disease with respect to their potential for application to clinical research (e.g. shortening of patient follow-up for test of cure, possible staging of the patients). This evaluation will be undertaken in 2011 in order to define a clear strategy for 2012 and years thereafter.



This elderly man suffers from Chagas disease and has undergone surgery for placement of his 4th pacemaker. For most Chagas patients, the first symptom of the disease can be heart failure.



Ravuconazole.

Malaria

Implementing ACTs on three continents is urgent

In sub-Saharan Africa, malaria is the largest cause of death for children under five. It kills one child every 45 seconds.

The majority of the 225 million cases of malaria reported worldwide in 2009 were uncomplicated (or simple) malaria. Some 3.3 billion people – half of the world's population – are at risk, in 106 endemic countries. More than half of all estimated *P. falciparum* clinical cases occurred in the Democratic Republic of the Congo, India, Myanmar, and Nigeria, where an estimated 1.4 billion people are at risk. Of an estimated 781,000 *P. falciparum* malaria-related deaths reported in 2009 of which about 85% are children under the age of five years, 90% occurred on the African continent. Malaria continues to be the leading cause of death in African children.

Malaria control requires an integrated approach, including diagnosis, vector control, and prompt treatment with effective antimalarials. In 2001, in response to the increasing failure of treatment with chloroquine, and to contain and control the spread of drug resistance in malaria-endemic regions, the World Health Organization (WHO) recommended worldwide abandonment of chloroquine and the use of artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated *P. falciparum* malaria. Artemisinin derivatives include dihydroartemisinin, artesunate, and artemether. Fast-acting artemisinin-based compounds are combined with a drug from a different class. These companion drugs include amodiaquine, lumefantrine, mefloquine, piperaquine and sulfadoxine/pyrimethamine. The advantages of ACTs are their high efficacy, fast onset of action, very good patient tolerance, and the reduced likelihood of development of resistance. They can be taken for a shorter duration than artemisinin alone and can be used by pregnant women.

In 2002, the Fixed-Dose Artesunate-Based Combination Therapies (FACT) Consortium, created by DND*i* started to develop two fixed-dose artesunate (AS)-based combination therapies (out of the four initially recommended by WHO) – ASMQ fixed-dose combination (artesunate and mefloquine) and ASAQ fixed-dose combination (artesunate and amodiaquine) – for the treatment of uncomplicated *P. falciparum* malaria to improve compliance and be available in all countries depending on their resistance profile. The development of the two fixed dose combinations (FDCs), ASAQ and ASMQ, registered respectively in 2007 and 2008, strengthened the existing ACT portfolio of fixed-dose combinations – adding to artemether-lumefantrine. The portfolio will be expanded by the addition of artesunate-pyronaridine FDC and dihydroartemisinin-piperaquine FDC under development by the Medicines for Malaria Venture (MMV).

Despite the substantial progress made worldwide over the past five years in the number of countries that have adopted and deployed ACTs as first-line treatment, their access is still limited in many parts of Africa and in some areas in Asia.

In 2010, the revised malaria treatment guidelines published by WHO strongly recommended the use of intravenous artesunate in place of quinine for the treatment of severe *P. falciparum* malaria in children and in adults.

Within the landscape of increased availability of affordable ACTs and innovative financing mechanisms for antimalarials, DND*i* in collaboration with National Malaria Control Programmes conducted market surveys in Ghana (2010), after Burundi and Sierra Leone (both in 2009). The three countries have adopted AS+AQ as first-line treatment for malaria. The main conclusions indicated that both the public and private sectors have actions to undertake to strengthen policies that lead to the replacement of loose blister packs with fixed-dose ACT products, develop strategies to ban inappropriate antimalarials and regulate those bans, and facilitate technology and knowledge transfer to scale up production of fixed-dose ACT products, which should be readily available and affordable to those patients who are in the greatest need of these medicines.[1] Translating evidence into policy and then again into practice, improving quality supply, decreasing drug costs through various mechanisms put in place by the private and the public sectors and ensuring the availability of artemisinin to also impact the cost of artesunate are the key components to facilitate access to new and available quality ACT treatments.

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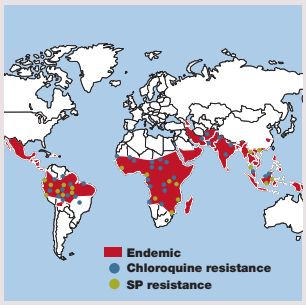
Half of the world population at risk with 106 endemic countries



WHAT IS THE IMPACT OF MALARIA?

- One of the three most deadly diseases in Africa
- 225 million cases of malaria worldwide each year, with nearly 1 million deaths[1]
- Every 45 seconds a child in Africa dies of malaria

HOW IS MALARIA TRANSMITTED?

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

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

- In addition to the widespread resistance to chloroquine, the marketing of oral monotherapies, including artemisinin, threatens the continued efficacy of artemisinins
- Access to ACTs is still limited in many parts of Africa and in some areas of Asia, particularly for children, the primary victims of malaria worldwide, who do not have access to the paediatric strengths of fixed-dose ACTs
- Countries with the highest prevalence of 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, simple, safe, and field-adapted quality drugs
- Access to diagnostic testing needs to be expanded

WHERE DOES MALARIA OCCUR?

Malaria is endemic in 106 countries worldwide and threatens half of the world's population. In sub-Saharan Africa, where it is the single largest cause of death for children under 5 years of age, malaria kills one child every 45 seconds. The disease accounts for 20% of all childhood deaths.

WHAT ARE THE SYMPTOMS/ PRESENTATIONS?

Malaria is considered uncomplicated when symptoms are present without clinical or laboratory signs to indicate severity or vital organ dysfunction. The symptoms of uncomplicated malaria are non-specific and include fever.

Infection with *P. falciparum*, if not treated, can quickly progress to severe malaria. The main symptoms include: severe breathing difficulties, low blood sugar, and low blood haemoglobin (severe anaemia), and coma. Children are particularly vulnerable as they have little or no immunity to the parasite. If untreated, severe malaria can quickly become life-threatening.

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

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

DND*i* will complete its malaria activities, including emphasis on technology transfer and sustained access, by shifting its malaria activities to other partners by 2014.

The FACT Project has produced two 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 proportion
– 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 30 African countries and in India

• **ASMQ** – FDC of artesunate and mefloquine registered in Brazil in 2008 and integrated in the national policy for treating uncomplicated malaria.

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

(1) World Malaria Report 2010, WHO.

/... DND*i*'s FACT projects will reach completion by 2014, with a gradual transfer of access and implementation projects for ASAQ and ASMQ being made to DND*i*'s industrial partners, the Medicines for Malaria Venture (MMV), and others.

IMPLEMENTATION

ASMQ – Artesunate-Mefloquine fixed-dose combination

Successful South-South technology transfer from Brazil to India

- **Major Partners:** Farmanguinhos, Brazil; Cipla, India; Shoklo Malaria Research Unit, Thailand; Universiti Sains Malaysia; Oxford University, UK; WHO/TDR; Indian Council of Medical Research (ICMR), India; Epicentre, France; Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland; National Institute of Medical Research, Tanzania; Kenya Medical Research Institute (KEMRI), Kenya; Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso.
- **Management:** Senior Pharma Advisor & Product Manager, Jean-René Kiechel; Project Coordinator, Gwenaëlle Carn; Senior Access Advisors: Florence Camus-Bablon, Eric Stobbaerts
- **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 *P. falciparum* malaria. Used in the field for many years, the combination of AS and MQ is one of the four ACTs recommended by WHO since 2001 as first-line treatment for uncomplicated *P. falciparum* malaria.

ASMQ fixed-dose combination treatment (ASMQ FDC) was first developed in 2002 through an innovative partnership between the Brazilian government-owned pharmaceutical company, Farmanguinhos/Fiocruz and the FACT consortium, coordinated by WHO/TDR and MSF. The latter turned the project over to DND*i* upon its foundation in 2003. ASMQ FDC was registered in Brazil in March 2008.

ASMQ offers four dosage forms adapted to age and weight so that patients are more likely to receive the dose they need.

A phase IV clinical trial was initiated in 2009-10 in Africa to assess the efficacy and safety of ASMQ in children under five.

ASMQ FDC tablets (25/55 mg and 100/220 mg) offer an easy-to-use treatment regimen with one single daily dose of one or two tablets of two highly effective, combined products to be taken over three days. In addition, the three-year shelf-life of ASMQ FDC facilitates deployment and availability in rural health centres.

Following a major intervention study in Acre, a State of the of Amazon River Basin, sponsored by the National Malaria Control Programme, ASMQ FDC is now an alternative first-line treatment for uncomplicated *P. falciparum* malaria according to National Malaria Policy in Brazil. Over 180,000 treatments have been ordered by Brazilian government agencies.

In addition, the ASMQ FDC registration process is underway in three additional malaria-endemic countries in Latin America – Peru, Bolivia, and Venezuela, which have already adopted the combination of AS+MQ for treating uncomplicated *P. falciparum* malaria.

Following an agreement signed in 2008, the transfer of technology between Farmanguinhos in Brazil and the Indian generic pharmaceutical company Cipla was successfully completed in 2010. This technology transfer will facilitate and support the deployment of the treatment throughout the Indian sub-continent, in Central and Southeast Asia, as well as in other parts of the world.

Cipla, DND*i*'s industrial partner, submitted the ASMQ registration file to regulatory authorities in India, Malaysia, and Myanmar. DND*i*, in collaboration with National Malaria Control Programmes and other key malaria actors, is preparing the implementation of ASMQ FDC in countries where its

(1) Anti-malarial market and policy surveys in sub-Saharan Africa by Diap G, et al. *Malaria Journal Supplement,* BioMed Central 2010 April, 9(1):S1.

registration is imminent. In order to render ASMQ eligible for international funds, DND*i* and partners submitted a full dossier for WHO pre-qualification in 2010.
According to WHO recommendations, AS+MQ could be considered for use in Africa. To provide additional information on the tolerability of ASMQ FDC, DND*i* is sponsoring a multicentre Phase IV study in Tanzania, Burkina Faso, and Kenya to assess efficacy, safety, and pharmacokinetics of ASMQ FDC as compared to that of artemether-lumefantrine treatment in children with uncomplicated *P. falciparum* malaria.

IMPLEMENTATION

ASAQ – Artesunate-Amodiaquine fixed-dose combination

80 million treatments distributed in Africa at the end of 2010

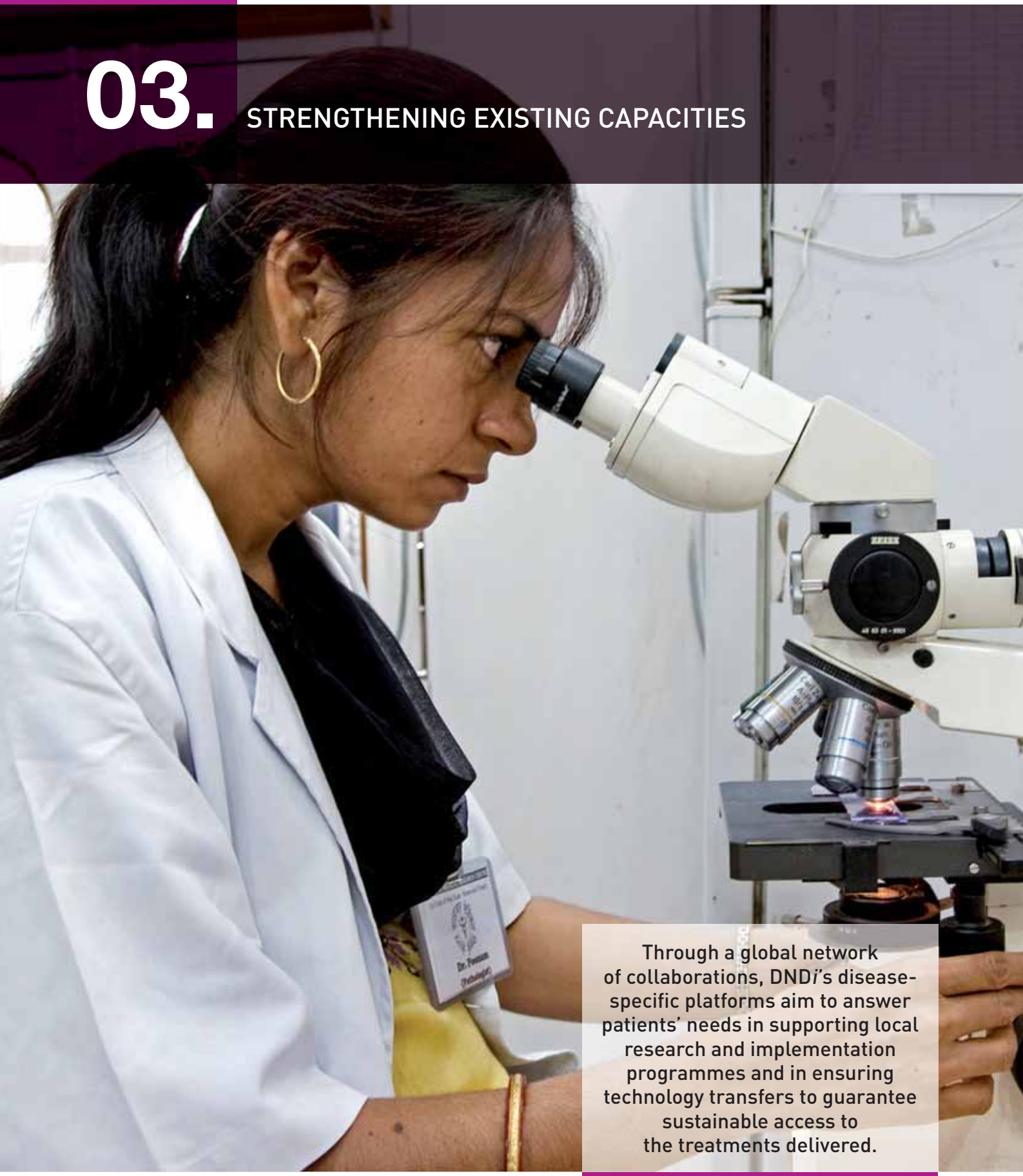
- **Major Partners:** sanofi-aventis, France; Medicines for Malaria Venture, Switzerland; National Centre for Research and Development on Malaria, Burkina Faso; Universiti Sains Malaysia; Oxford University, UK; Institute of Research for Development (IRD), Senegal; Université de Bordeaux Faculté de Pharmacie, France; Mahidol University, Thailand; Ellipse Pharmaceuticals, France; Médecins Sans Frontières; Epicentre, France; WHO/TDR; Kenya Medical Research Institute (KEMRI), Kenya; Indian Council of Medical Research (ICMR), India; National Malaria Control Programme, Ministry of Health, Burundi; WHO, Burundi; Ministry of Health, Sierra Leone; Komfo Anokye Teaching Hospital (KATH), Ghana
- **Management:** Senior Pharma Advisor & Product Manager, Jean-René Kiechel; Project Coordinator, Gwenaëlle Carn; Medical Coordinator FACT Project, Graciela Diap
- **Project start:** January 2002

ASAQ Winthrop, the fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ), was the first treatment made available by DND*i* in 2007 through an innovative partnership with sanofi-aventis. ASAQ Winthrop was pre-qualified by WHO in October 2008. Over 80 million treatments were distributed by the end of 2010 throughout 29 African countries. It is estimated that an additional 55 million will be made available to malaria patients in Africa in 2011. First registered in Morocco, where it is manufactured, ASAQ is now registered in 30 African countries and India.
ASAQ truly represents an improvement for patients as it requires treatment regimens of once-a-day dosing. ASAQ is available at less than USD 0.5 for children and USD 1 for adults.
In 2010, ASAQ Wintrop obtained WHO authorization for its three-year shelf life, giving the product the longest shelf-life of any pre-qualified FDC artemisinin-based treatment available for malaria. In partnership with MMV, DND*i*, and National Malaria Control Programmes, sanofi-aventis is implementing an ambitious and comprehensive risk management plan for ASAQ, which aims at collecting high-quality data on ASAQ's effectiveness and safety profile in the field. Being the first ever of its kind submitted to WHO, this risk management plan will ensure that appropriate post-marketing data is available as quickly as possible on safety and effectiveness of ASAQ in the field. The plan consists of several studies currently underway in West and East Africa, spanning from randomized, comparative, clinical trials in a limited number of patients treated under well-controlled conditions, to large-scale studies assessing the drug's safety in 'real-life' conditions. Among these is a Phase IV efficacy and tolerability study conducted in Ivory Coast. The study recruited more than 1,800 patients in four different sites in the country by the end of 2010. Delays, however, are expected due to current instability in the country.
Two additional clinical studies included in the above-mentioned plan have been managed by DND*i* in collaboration with MSF, Epicentre, and the National Malaria Control Programme in Liberia, the results of which were made available in 2010. They show that ASAQ is highly efficacious, safe, and well tolerated in children and adults in Liberia.
In parallel, the evaluation and selection process of a second industrial partner for the production of ASAQ in Africa was conducted in 2010 by OTECI with the support of AEDES and Bertin Pharma, and technology will be transferred to Zenufa in Tanzania as of 2011.
Following the antimalarial market assessments conducted by DND*i* in Burundi and Sierra Leone in 2009,[1] DND*i* and its partner Komfo Anokye Teaching Hospital, Kumasi (KATH) are performing outlet surveys in Ghana, as part of the independent evaluation of the Affordable Medicines Facility–Malaria (AMFm) Phase I. This contribution, funded by the Global Fund to Fight AIDS, Tuberculosis, and Malaria, will provide data on the availability, affordability, use, and market share of ACTs in Ghana. The conclusions of the Burundi and Sierra Leone surveys, where ASAQ is the first-line treatment for malaria, were published in 2010 in *Malaria Journal*[2] and offered a set of recommendations at global, national, and community levels to facilitate broad implementation of ACTs.

Over 80 million treatments were distributed by end 2010 throughout 29 African countries in Africa. It is estimated that 55 million more will be made available in 2011.

(1) Access to artesunate-amodiaquine, quinine and other anti-malarials: Policy and markets in Burundi by Amuasi JH et al. *Malaria Journal.* 2011, 10:34. **(2)** Anti-malarial market and policy surveys in sub-Saharan Africa by Diap G et al. *Malaria Journal Supplement*, BioMed Central 2010 April, 9(1):S1.

03. STRENGTHENING EXISTING CAPACITIES



Through a global network of collaborations, DND*i*'s disease-specific platforms aim to answer patients' needs in supporting local research and implementation programmes and in ensuring technology transfers to guarantee sustainable access to the treatments delivered.

Regional networks working to ensure sustainable solutions

True to its vision and mission, DND*i* works closely with partners in disease-endemic countries to strengthen existing clinical research capacity as well as to build new capacity where necessary. These efforts to support research and implementation programmes are also vital to ensuring sustainable access to the treatments delivered. Furthermore, with this vision of sustainability, DND*i* also aims at transferring technology, in particular manufacturing processes, to industrial partners in endemic regions.

PILLARS OF DND*i*'S BUSINESS MODEL

Since its inception in 2003, DND*i* has worked to integrate capacity strengthening in all of its projects as well as to promote technology transfer where possible in order to increase the chances of registration, uptake, and sustainable access of new treatments. The regional platforms, set up at the outset of DND*i* as part and parcel of its business model, are essential pillars of DND*i*'s work. At the cornerstone of their mission, the platforms define patient needs and provide a solid basis for appropriate and sustainable research, by creating clinical trial methodologies in compliance with Good Clinical Practices (GCP) standards, while taking into consideration the local conditions in which such trials are conducted.

Three regional disease-specific platforms in Latin America and Africa collaborate to support R&D programmes on Chagas disease (Chagas Clinical Research Platform), visceral leishmaniasis (Leishmaniasis East Africa Platform – LEAP), and sleeping sickness, or Human African Trypanosomiasis (HAT Platform). They have the specificity of bringing together regional actors, notably Ministries of Health and National Control Programmes, regulatory agencies, academia, clinicians, civil society groups, and pharmaceutical companies with a common goal of addressing patient needs in the local and national contexts where the diseases are endemic. The platforms utilize, capitalize upon, and reinforce clinical capacities in endemic regions, and address infrastructural requirements where necessary. They provide on-site training in clinical research in sometimes very remote settings, which are the most challenging research environments.

In 2010, the LEAP platform was critical to making available DND*i*'s first new treatment for visceral leishmaniasis – the combination of SSG&PM, see page 28 – and in obtaining recommendation of SSG&PM by the WHO Expert Committee on the Control of Leishmaniases as first-line treatment for VL in East Africa. The HAT Platform was instrumental in facilitating the implementation and access of NECT for stage 2 sleeping sickness in 10 endemic countries by working closely with national authorities.

A YEAR OF COLLABORATION AND ACHIEVEMENTS

In addition, training was a vital part of DND*i*'s regional efforts to strengthen existing capacities in 2010. In the field of sleeping sickness, a Good Clinical Practices (GCP) training course was organized in Kenya, while Ethics Committee training courses were delivered in Rwanda and Central African Republic by the HAT Platform. The Leishmaniasis East African Platform (LEAP) organized GCP training in Kenya and the newly launched Chagas Clinical Research Platform (CCRP) held a GCP course at its first platform meeting in Argentina.

Clinical trial training with investigators from DND*i*-supported site of Doka, Kassab, Sudan, January 2010.

TWO TECHNOLOGY TRANSFER PROJECTS PAVE THE WAY TO INCREASING ACCESS

For DND*i*, the transfer of technology consists of transferring the industrial development know-how to partners in endemic regions to ensure a wide-spread distribution of new treatments. It implies providing the required regulatory files and information in order to maintain competitive prices and to reinforce the technological and scientific capacities of endemic countries. In 2010, DND*i* actively participated in the process of technology transfer between Farmanguinhos and Cipla (for ASMQ) and is preparing the transfer of technology to an additional partner for ASAQ.

ASMQ: FROM BRAZIL TO INDIA AND BEYOND

In order to facilitate access of ASMQ in Southeast Asia, a South-South technology transfer between Farmanguinhos/Fiocruz in Brazil and Cipla Ltd in India, the agreement for which was signed in 2008, came to completion in 2010 with support and facilitation by DND*i*. This technology transfer for the artesunate-mefloquine fixed-dose combination (ASMQ FDC, see page 36) was the first of its kind between a company in Brazil and one in India, and was even more unique in that it involved a transfer from a public entity, Farmanguinhos, to a private company, Cipla Ltd.

Successful transfer of technology necessitates true partnership, as it is more than just a question of offering acquired information. The Farmanguinhos-Cipla technology transfer required the alignment of procedures to Good Manufacturing Practices (GMP) to achieve similar and comparable products that meet international requirements in order to benefit patients in all endemic countries.

ASAQ: ON THE STARTING BLOCKS FOR TECHNOLOGY TRANSFER IN AFRICA

ASAQ, the artesunate-amodiaquine fixed-dose combination (see page 37), was the first treatment developed by DND*i* in partnership with sanofi-aventis (launched in 2007), and is produced in Morocco. Developed as a non-patented product, the technology transfer for ASAQ to a second partner in Africa is a vital part of DND*i*'s strategy to increase patient access to this treatment, according to the market demand forecast of 100 million treatments.

In 2010, DND*i*, with support from a group of experts, assessed various potential partners in Africa in order to ensure that all criteria for a successful technology transfer were met. By the close of 2010, a partner in Tanzania – Zenufa – was selected and negotiations are well underway.

CHAGAS CLINICAL RESEARCH PLATFORM

Founded: 2009 in Uberaba, Brazil

Representatives from the following organizations participated in the first CCRP meeting: Pan American Health Organization (PAHO); Department for the Control of Neglected Tropical Diseases, WHO; Ministries of Health and National Control Programmes of high burden endemic countries (Argentina, Bolivia, Brazil, Mexico); Hospital de Niños Ricardo Gutiérrez, Argentina; Instituto Nacional de Parasitología Dr. M Fatala Chabén, Argentina; Hospital de Niños de Jujuy, Argentina; Hospital Público Materno Infantil – Salta, Argentina; Centro de Chagas y Patologia Regional, Santiago del Estero, Argentina; Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina; Instituto Oswaldo Cruz, Brazil; Instituto de Pesquisa Evandro Chagas–Fiocruz, Brazil; Centro de Pesquisas René Rachou–Fiocruz, Brazil; Universidad Mayor de San Simon– Platform of Integral Care for Patients with Chagas Disease, Bolivia; CRESIB - Hospital Clinic Barcelona, Spain; Médecins Sans Frontières; Institut de Recherche pour le Développement, France; Eisai, Japan.

Objectives: To support its R&D activities on Chagas disease, DND*i* launched the Chagas Clinical Research Platform (CCRP). The platform brings together partners, experts, and stakeholders to provide support for evaluation and development of new treatments for Chagas disease. The CCRP aims to facilitate clinical research, provide a forum for technical discussions, develop a critical mass of expertise, and strengthen institutional research capacities. In addition, it will identify and review priority needs, work towards standardization of methodology to assess drug efficacy to treat *T. cruzi* infection, review alternatives for using current drugs approved (new schemes, doses, combination) and special scenarios (resistance).

Achievements and Activities in 2010

- **Meetings:** The CCRP held its first meeting in Buenos Aires, Argentina, in March 2010 to update the target product profile (TPP) for Chagas disease.
- **Clinical trials:** Three studies are planned for 2011 for which the CCRP will provide support in terms of preparation and implementation. A population pharmacokinetics study of the paediatric formulation of benznidazole will be conducted in Buenos Aires, Argentina, and in endemic areas of the north of the country. With its partners in Bolivia, the CCRP will also implement a study to evaluate and optimize the polymerase chain reaction (PCR) for diagnosis and assessment of therapeutic response in patients with chronic indeterminate Chagas disease, and a study to evaluate the safety and efficacy of E-1224, a pro-drug of ravuconazole.
- **Capacity Strengthening:** A training course on Good Clinical Practices (GCP) was offered to investigators involved in the planned studies. 38 people trained in 2010.
- **Access:** The CCRP will increasingly work as a channel to raise awareness on issues related to access to existing drugs and will be involved in the implementation of paediatric benznidazole, developed through a partnership between DND*i* and the Brazilian public laboratory LAFEPE, planned for 2011.

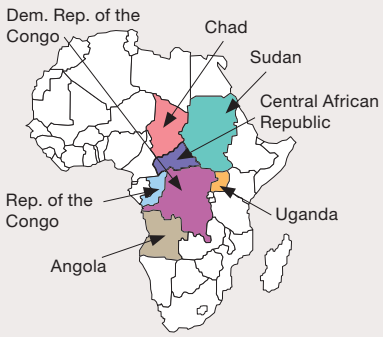
networks for global impact

HUMAN AFRICAN TRYPANOSOMNIASIS HAT PLATFORM

Founded: 2005 in Kinshasa, Democratic Republic of the Congo

Members: National Control Programmes of most affected endemic countries; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Institute of Tropical Medicine in Antwerp (ITMA), Belgium; Institut National de Recherche Biomédicale (INRB), DRC; Centers for Disease Control and Prevention (CDC), USA; Kenya Agricultural Research Institute – Trypanosomiasis Research Centre (KARI-TRC), Kenya; MSF/Epicentre; Foundation for Innovative New Diagnostics (FIND); WHO-TDR; Regional networks such as Eastern Africa Network for Trypanosomosis (EANETT), Pan African Bioethics Initiative (PABIN), the African Malaria Network Trust (AMANET).

Objectives: To build and strengthen treatment methodologies and clinical trial capacity in HAT-endemic countries, so that new treatments for this fatal disease can be rapidly and effectively evaluated, registered, and made available to patients. After the success of the Nifurtimox-Eflornithine Combination Therapy (NECT), included in the WHO List of Essential Medicines for the treatment of stage 2 HAT, the primary goals of the HAT Platform are to develop appropriate clinical trial methodologies for HAT, overcome system challenges related to administrative and regulatory requirements, strengthen clinical trial capacity (human resources, infrastructure, equipment), and share information and strengthen ties among endemic countries.



Achievements and Activities in 2010

- **Treatments:** As of December 2010, NECT was available in 10 African countries and 2,176 patients were treated. More than half (62%) of the patients are now treated with NECT in African endemic countries.
- **Clinical trials:** Participation in the ongoing NECT-Field studies. Preparation of the clinical trials for a new oral drug (Fexinidazole) in the Democratic Republic of the Congo for 2011.
- **Capacity Strengthening:** Good Clinical Practices (GCP) training for researchers; Ethics Committee training; HAT patient examination training for clinical monitors and general practitioners. 208 people trained in 2010.
- **Communication:** Two newsletters were published in 2010. TV and radio presentations were given on NECT.
- **Meetings:** Joint HAT Platform-EANETT Annual Scientific Meeting, Nairobi, 2010: contributions to this meeting provided suggestions for a profile to target research for new molecules for HAT; other scientific congresses.
- **Supply:** Advocacy in member countries towards quick adoption of NECT as first-line treatment for second stage HAT.

LEISHMANIASIS EAST AFRICA PLATFORM (LEAP)

Founded: 2003 in Khartoum, Sudan

Members: Center for Clinical Research, Kenya; Medical Research Institute, Kenya; Ministry of Health, Kenya; Institute of Endemic Diseases, University of Khartoum, Sudan; Federal Ministry of Health, Sudan; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Federal Bureau of Health, Ethiopia; Makerere University, Uganda; Ministry of Health, Uganda; Médecins Sans Frontières; i+ Solutions; Institute for OneWorld Health (iOWH); AMC/KIT/University of Sloter-vaart, Amsterdam, The Netherlands; London School of Hygiene and Tropical Medicine (LSHTM), UK.

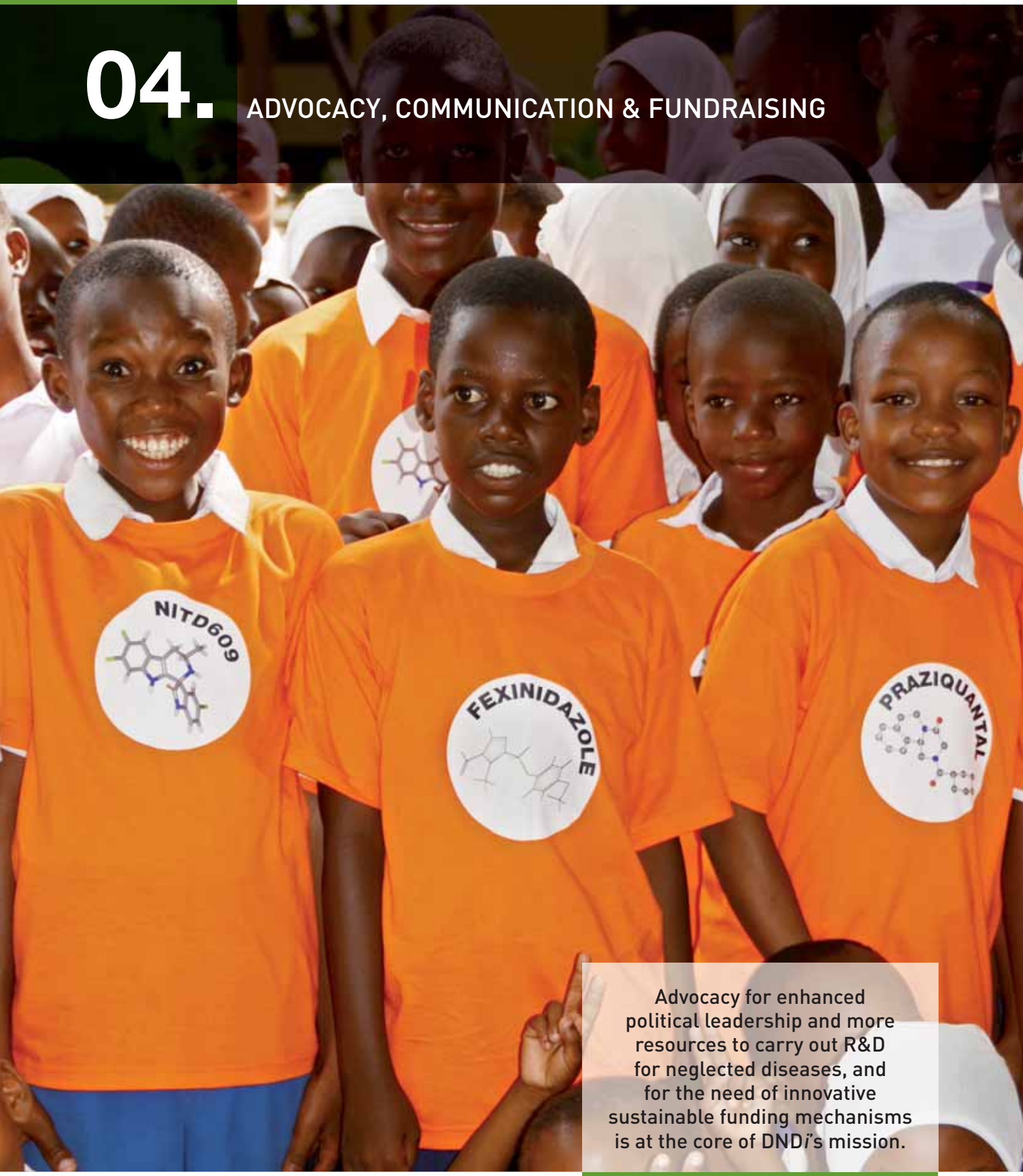
- 50 individual members, representing over 20 institutions
- Over 1,100 patients enrolled in clinical trials by the end of 2010
- Approximately 1,000 patients treated outside clinical trials per year

Objectives: The overall aim of the platform is to strengthen clinical research capacity, which is lacking in part due to the remoteness and geographic spread of the patients, most of whom live in the most impoverished regions of Africa. This platform also serves as a base for ongoing educational cooperation between the countries in the East African region and standardization of procedures and practices within the region, as far as is possible within the confines of local regulations. LEAP evaluates, validates, and registers new treatments that address regional needs for VL.

Achievements and Activities in 2010

- **Treatments:** Following up on the results of the study comparing the paromomycin (PM) and sodium stibogluconate (SSG) in monotherapies, and the shorter course combination of PM and SSG, the WHO Expert Committee on the Control of Leishmaniases recommended, in March 2010, the use of the SSG&PM as first-line treatment for VL in East Africa. Sudan applied this recommendation at the close of 2010, implementing SSG&PM as a first-line treatment.
- **Clinical trials:** DND*i* and LEAP have completed the study **LEAP 0104**, a multi-centre clinical trial comparing the paromomycin (PM) and sodium stibogluconate (SSG) as monotherapies, and the shorter course combination of SSG and PM. The **AMBI 0106** study aims at determining the minimum effective single dose of AmBisome® in Ethiopia and Sudan. The objective of the **LEAP 0208** study is to assess the safety and efficacy of miltefosine in monotherapy and in combination with AmBisome® in Kenya and Sudan as a second shorter-course combination treatment. Evaluation of rapid diagnostic kits for VL is also ongoing in Kenya.
- **Capacity Strengthening:** Clinical monitors, Data and Safety Monitoring Board (DSMB) members, and investigators received training in Good Clinical Practices (GCP); key members were trained on a case-by-case basis in career development, and researchers were trained in parasite classification research through technology transfer and training courses. 63 people trained in 2010.
- **Infrastructure:** A treatment and laboratory training centre was opened in Doka, Sudan, in 2010. Ongoing improvements were made to a data centre in Nairobi to set up a GCP-compliant data-management system using open source software.

04. ADVOCACY, COMMUNICATION & FUNDRAISING



Advocacy for enhanced political leadership and more resources to carry out R&D for neglected diseases, and for the need of innovative sustainable funding mechanisms is at the core of DND*i*'s mission.

Photo: courtesy of MMV

An enabling Global Framework for R&D

The fight to bring new health tools to end the suffering of millions of neglected patients is more than just about developing medicines. Since its inception, DND*i* has actively advocated for a new and more favourable environment for neglected diseases R&D. In 2010, three policy research projects developed or commissioned by DND*i* – on regulatory environment, IP management, and sustainable funding – came to completion or were presented at international meetings.

NEW INCENTIVES FOR INNOVATION

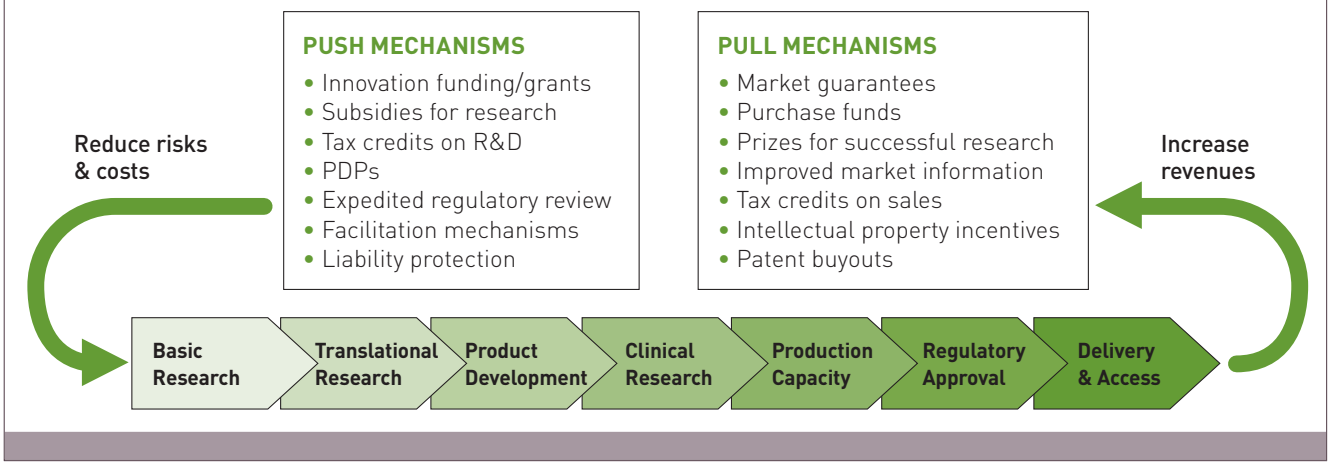
Despite positive signs from donors, funding for scientific and medical innovation for neglected diseases remains inadequate. Global neglected disease R&D funding in 2009 totalled USD 3.2 billion (including malaria, tuberculosis, and HIV/AIDS)[1] which is still insufficient to support development efforts. Of this amount, only USD 162 million – slightly over 5% – was spent on the kinetoplastid diseases (sleeping sickness, leishmaniasis, and Chagas disease).

To contribute to discussions on R&D financing and coordination at WHO and in other fora, and to support its own long-term funding strategy, DND*i* conducted in 2010 an evaluation of existing and proposed R&D incentives and funding mechanisms. This analysis, **'Financing Neglected Diseases R&D: Principles and Options'**, was published on DND*i*'s website and discussed with various stakeholders including WHO, UNITAID, the EU, other PDPs, and NGOs. Although DND*i*'s analysis and recommendations naturally focused on innovative options to support the development of new treatments for the 'most neglected' diseases, many are applicable to other diseases and product types.

Substantial rewards for attaining specified milestones could act as useful supplements to grants and other 'push' funding to boost innovation for diseases for which market incentives are deficient, and to attract new R&D players. As with other 'pull' mechanisms (see chart), prizes are advantageous in that sponsors only pay for success. In addition, milestone prizes promise far earlier pay-outs than advance market commitments, Priority Review Vouchers, or prizes for licensed products, and are thus more likely to attract new actors such as biotechs, which cannot make major investments in pursuit of rewards that may be more than a decade away.

PDPs have now advanced several compounds to clinical development, but financing is not ensured for large efficacy trials, manufacturing scale-up, registration, and other activities required to ensure adoption and equitable access in disease-endemic countries. The urgency of providing the necessary health tools to address the global neglected disease burden requires an expeditious and efficient response from the international community. In considering innovative and sustainable financing mechanisms for health R&D, we should build upon the successes of existing international organizations and mechanisms that are already addressing market and public policy failures, such as UNITAID.

'PUSH' MECHANISMS TO FINANCE R&D AND 'PULL' INCENTIVES TO SPUR PRIVATE SECTOR INVESTMENT[2]



(1) G-Finder 2010, Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?, by M. Moran et al. Policy Cures, Sydney and London, 2011. **(2)** 'Financing neglected disease R&D: principles and options', DND*i* study based on an analysis from Paul Wilson, 2010.

STRENGTHENING OF REGULATORY CAPACITY IN ENDEMIC REGIONS

What would be the best registration strategy for the approval of a new drug to treat sleeping sickness, which primarily affects neglected patients in Central and West Africa? What would be the best way to support African regulatory authorities in their evaluation of new drugs developed to treat their own populations? How should essential standards for the conduct of clinical trials be defined? These are some of the issues addressed in the report, ***Registering New Drugs: The African Context***, sponsored by DND*i* and commissioned to the George Institute for International Health. The report was launched in Pretoria, South Africa, at the COHRED (Council on Health Research for Development) & NEPAD (New Partnership for Africa's Development) meeting on pharmaceutical innovation in Africa, in February 2010.

While new tools have been developed and others are soon to be made available, the registration of new drugs in endemic countries, particularly in Africa, remains problematic. Most African regulatory authorities are experienced in registering generic treatments, but lack resources to evaluate the safety, efficacy, and quality of new medicines, generally relying on registration by regulatory authorities in developed countries, notably the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The latter, however, do not have the necessary field-knowledge and political responsibility to make appropriate risk-benefit assessments for the populations most affected. The experts involved in this study expressed that African regulators have a crucial role to play in assessing health tools being used to respond to specific patient needs in their countries. The report issued key recommendations to strengthen regulatory authorization processes in Africa:

- ensure closer collaboration between developing and developed countries by involving regulators of endemic countries in all regulatory assessment of new drugs for neglected diseases;
- extend WHO's role in the prequalification process of new tools against neglected tropical diseases, in addition to HIV/AIDS, malaria, and tuberculosis;
- strengthen regulatory capacity in Africa through the creation of Regional Centres of Excellence in each of Africa's main sub-regions.

ACCESS-ORIENTED MANAGEMENT OF IP AND OPEN INNOVATION

The lack of funding and incentives for R&D in neglected diseases calls for a open model of sharing knowledge and research data to create a more enabling environment for neglected disease R&D.

DND*i* has partnered with the Program on Global Health and Technology Access of Duke University to draw lessons from its experience, notably in access to compound libraries and licensing agreements. The aim was to gain insight into what an open innovation platform for neglected disease R&D might look like. Preliminary conclusions of this research project were presented at a DND*i* workshop, organized in New Delhi.

From the GSK pool launched in 2009 to the Medicines Patent Pool Foundation for HIV/AIDS, launched by UNITAID, initiatives for open innovation are flourishing, a clear indication of a more open environment to boost innovation within the private sector.

DND*i*'s experience in licensing agreements and management of intellectual property (IP) is driven by its IP policy, based on two fundamental principles: (1) the need to ensure that treatments are ultimately affordable to patients and that access is equitable; (2) the desire to develop drugs as public goods when possible, disseminating results of DND*i*'s research work as widely as possible to encourage the research community to engage in additional or follow-on research in the field of neglected diseases.

Hence, none of the new treatments developed by DND*i*, e.g. ASAQ and ASMQ, are protected by patents.

DND*i* negotiates access to and licensing of IP on a routine basis for all products under development to ensure access to all neglected patients. Operating on a virtual basis, DND*i* needs to negotiate sub-licensable licensing rights to have access to compounds, knowledge, and data, as well as to coordinate R&D activities on a worldwide basis. As the IP generated may be individually or jointly owned by DND*i* and/or its partners, DND*i* secures a non-exclusive, sub-licensable royalty-free license on the IP generated from the research partnership to keep control of the outcome of the joint research in the field of neglected diseases. To ensure affordable and equitable access to the final products, DND*i* negotiates to secure sustainable manufacture and distribution of the product at the lowest possible price in endemic countries. For neglected diseases, a field in which competition between manufacturers hardly exists, affordability can be reached through agreements with industrial partners committing to produce at the lowest possible cost and include a reasonable margin in the price to ensure long-term production, thereby delinking the costs of R&D from the final price of the product.

EUR 153 MILLION SECURED

TARGET:
EUR 230 million

TO DATE:
EUR 153 million

By December 2010, DND*i* secured a total of EUR 153 million (see page 59) of the EUR 230 million needed by 2014 to achieve the objectives laid forth in its business plan.

In line with its vision and mission, DND*i*'s funding strategy aims to ensure a balance in funding from public and private donors. To ensure the greatest possible flexibility in decision making needed for its R&D portfolio management strategy and maximum operational independence, DND*i*'s priority is given to securing unrestricted core funding versus project-specific or earmarked funding. In cases in which this is not possible, DND*i* will pursue project-specific or earmarked funding without requirements that may interfere with the objectives of the project.

DND*i* would like to thank Médecins Sans Frontières (MSF), the UK Government (DFID), the Dutch Government (DGIS), the Spanish Government (AECID), and the Swiss Government (SDC) as well as private foundations and individuals who have provided unrestricted core/portfolio funding.

Multiyear project-specific commitments from the Bill & Melinda Gates Foundation, the French Government (MAEE/AFD), the EU (FP7 and EDCTP), the US Government (NIH/NIAID), the Republic and Canton of Geneva, Switzerland, the Global Fund and private foundations have also been critical to the success of DND*i*.

With the support of its financial partners, DND*i* is moving towards the achievement of its objective of developing 6 to 8 new, field-relevant treatments and a robust pipeline by 2014 for people suffering from neglected diseases.

NEW GRANTS RECEIVED IN 2010

EUR 14 Million
Dutch Ministry of Foreign Affairs (DGIS)

The Ministry of Foreign Affairs of The Netherlands (DGIS) granted EUR 14 million to DND*i* to fight neglected tropical diseases. The grant will be disbursed over four years (2011-2014) and will provide critical funding for DND*i*'s core disease programmes for human African trypanosomiasis, Chagas disease, and leishmaniasis. While this is the second time that the Dutch Government has awarded funding to DND*i*, it is first that is targeted at the most neglected diseases. Mrs Reina Buijs, Head of the Health and Aids Division of the Dutch Government, said that one of *'the strongest points of DNDi is that it works very actively to share information and to build capacity between partners in industrialized and developing countries'*. In 2006, the first grant (EUR 3M) from The Netherlands to DND*i* helped develop and give access to two new WHO–recommended artemisinin-based combination therapies (ACTs) for malaria.

CHF 4 Million
Swiss Agency for Development and Cooperation (SDC)

The Swiss Agency for Development and Cooperation (SDC) granted CHF 4 million to DND*i*. The grant will be disbursed over three years (2010-2012) and will contribute to DND*i*'s core disease programmes. This grant reaffirms SDC's increasing role as a major supporter of development and implementation of new treatments to fight neglected diseases.

CHF 600,000
Republic and Canton of Geneva, Switzerland

The Republic and Canton of Geneva granted CHF 600,000 to DND*i* to be disbursed over three years (2010-2012) to document the use of NECT in real-life conditions (including pregnant and lactating women and children). The funds are also being used to promote patient access to NECT and to conduct further research in improved treatments. Prior funding supported the VL programme (total of CHF 1 million, 2004- 2009). This grant was allocated to the Paromomycin Project which resulted in the SSG&PM combination to treat VL (4th treatment delivered by DND*i*).

EUR 1.3 Million & 0.5 Million
French government (AFD & MAEE)

The French Development Agency (AFD) and Ministry of Foreign and European Affairs (MAEE) granted EUR 1.3 million and 0.5 million respectively for the period 2009-2011/12. These grants support specific discovery and pre-clinical projects (IPK screening, HAT lead optimization, Oxaborole for HAT) and a DND*i* malaria project (FACT). The French Government has supported DND*i* since 2006 through four grants reaching a total amount of EUR 9.3 million.

EUR 380,000
European and Developing Countries Clinical Trials Partnership (EDCTP)

EDCTP granted EUR 380,000 to DND*i*. The grant will be disbursed over three years (2010-2012) to support clinical studies in Burkina Faso, Kenya, and Tanzania to assess the fixed-dose combination of artesunate and mefloquine (ASMQ) developed by DND*i* and its partners, as an alternative antimalarial treatment for children in Africa.

EUR 221,900
The Global Fund to Fight AIDS, Tuberculosis, and Malaria

The Global Fund to Fight AIDS, Tuberculosis, and Malaria granted EUR 221,900 to DND*i*. The grant was for the year 2010-2011 and supports a study that aims to evaluate the availability, affordability, use, and market share of artemisinin-based combination therapies (ACTs) in Ghana, in collaboration with Komfo Anokye Teaching Hospital, Kumasi (KATH).

FRIENDS OF DND*i*

The 'Friends of DND*i*', comprised of select, internationally-renowned individuals, share in DND*i*'s mission and vision by engaging global influencers, policy-makers, and supporters to help DND*i* in vital ways. Their role is key to the achievement of DND*i*'s objectives.

Yves Champey, former Chair of DND*i* Board of Directors. Served as Medical and Scientific Director, and then as Senior Vice President, International Drug Development, at Rhone Poulenc, France

John Bowis, former Member of the European Parliament (MEP) for London and the spokesman on the Environment, Health, and Food Safety in the European Parliament, UK

Nirmal K. Ganguly, former Director General of the Indian Council of Medical Research (ICMR), India

Stephen Lewis, Chair of the Board of the Stephen Lewis Foundation, former Minister of Foreign Affairs of Canada, former United Nations Special Envoy for HIV/AIDS in Africa, Canada

Morten Rostrup, former international President of Médecins Sans Frontières, Norway

Dyann Wirth, Chair of the Department of Immunology and Infectious Diseases, Harvard School of Public Health, USA

Yongyuth Yuthavong, former Minister of Science and Technology, Thailand

Sheba K. Meymandi, Director of the Center of Excellence for Chagas Disease at Olive View-UCLA Medical Center, in Sylmar, California, USA

Darin Portnoy, former President of the MSF USA Board of Directors, USA

Rafael Vila San Juan, Director Laboratorio de Ideas, Institute for Global Health of Barcelona (ISGlobal), Spain

Rowan Gillies, former President of MSF International Council, Australia

Samih T. Darwazah, Founder and Chairman of Hikma Pharmaceuticals, Jordan

Paulo Buss, Professor of Health Planning, National School of Public Health, Oswaldo Cruz Foundation (Fiocruz), Brazil

Awareness-

«1$ for 1 life» documentary on ARTE

The French and German TV channel ARTE broadcast this documentary on malaria, neglected diseases, and DND*i*. The documentary has been realized by the French filmmaker Frédéric Laffont, who followed several projects worldwide to give a voice to the most neglected.

raising for neglected patients

DND*i* has enjoyed worldwide media coverage in 2010. In addition to television and radio coverage, DND*i* was featured in the following press articles.

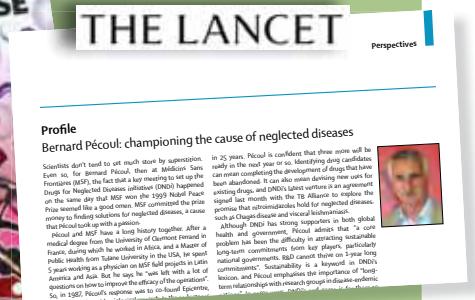
DND*i* IN INTERNATIONAL PRINT MEDIA

- **The Lancet,** 'Bernard Pécoul: Championing the Cause of Neglected Diseases', 28 August 2010.
- **CheckOrphan,** 'Sanofi-Aventis Receives Award for Innovative Malaria Access to Medicines Partnership Programme', 27 May 2010.
- **Nature,** 'Neglected Diseases Fund Touted', 18 May 2010.
- **Centre Daily News,** 'White House Needs to Tackle All Diseases', 5 May 2010.
- **The Lancet,** 'Building Medical Regulatory Authorities in Africa', April 2010, Vol. 10.
- **Neue Zürcher Zeitung,** 'Neue Forschungsmodelle für vernachlässigte Krankheiten', 19 February 2010.
- **La Recherche,** 'Nous créons des médicaments innovants pour les plus pauvres', February 2010.
- **SciDev.net,** 'Challenge: Potential Drug Targets for Kinetoplastid Infectious Diseases', 1 February 2010.
- **Le Point,** 'Des maladies très fréquentes et pourtant négligées', 1 February 2010.
- **Outlook Business,** 'Middle Ground', 23 January 2010.
- **The Lancet,** 'Killer Coma: The Evolving Story of Sleeping Sickness Treatment', 9 January 2010.

SCIENTIFIC PUBLICATIONS BY DND*i* TEAM AND PARTNERS

An increase in the number of scientific publications occurred in 2010 in comparison to previous years, an important marker of DND*i*'s activities and advancement of its projects.

- **'Fexinidazole – A New Oral Nitroimidazole Drug Candidate Entering Clinical Development for the Treatment of Sleeping Sickness'**, by Torreele E, Bourdin Trunz B, Tweats D, Kaiser M, Brun R, Mazué G, Bray M A, Pécoul B. *PLoS NTD*, 2010 December, Vol. 4, Issue 12, e923.
- **'Effectiveness of Five Artemisinin Combination Regimens with or without Primaquine in Uncomplicated Falciparum Malaria: An Open-label Randomised Trial'**, by Smithuis F, Kyaw Kyaw M, Phe O, Win T, Phyo Aung P, Pyay Phyo Oo A, Naing A L, Yee Nyo M, Htun Myint N Z, Imwong M, Ashley E, Lee S J, White N J. *The Lancet Infectious Diseases*, 2010 September, Vol. 10, Issue 10, pp. 673-81.
- **'Paromomycin for the Treatment of Visceral Leishmaniasis in Sudan: A Randomized, Open-Label, Dose-Finding Study'**, by Musa A, Younis B, Fadlalla A, Royce C, Balasegaram M, wasunna M, Hailu A, Edwards T, Omollo R, Mudawi M, Kokwaro G, El-Hassan A, Khalil E. *PLoS NTD*, 2010 October, 4(10):e855



- **'Geographical Variation in the Response of Visceral Leishmaniasis to Paromomycin in East Africa: A Multicentre, Open-Label, Randomized Trial'**, by Hailu A, Musa A, Wasunna M, Balasegaram M, Yifru S, Mengistu G, Hurissa Z, Hailu W, Weldegebreal T, Tesfaye S, Makonnen E, Khalil E, Ahmed O, Fadlalla A, El-Hassan A, Raheem M, Muellerm, Koummuki Y, Rashid J, Mbui J, Mucee G, Njoroge S, Manduku V, Musibi A, Mutuma G, Kirui F, Lodenyo H, Mutea D, Kirigi G, Edwards T, Smith P, Muthami L, Royce C, Ellis S, Alobo M, Omollo R, Kesusu J, Owiti R, Kinuthia J, for the Leishmaniasis East Africa Platform (LEAP) group. *PLoS NTD*, 2010 October, 4(10):e709.
- **'Safety and Effectiveness of Meglumine Antimoniate in the Treatment of Ethiopian Visceral Leishmaniasis Patients with and without HIV Co-infection'**, by Hailu W, Weldegebreal T, Hurissa Z, Tafes H, Omollo R, Yifru S, Balasegaram M, Hailu A. Trans R Soc Trop Med Hyg. 2010 November, 104(11):706-12. Epub 2010 Sep 27.
- **'Cost-Effectiveness Analysis of Combination Therapies for Visceral Leishmaniasis in the Indian Subcontinent'**, by Meheus F, Balasegaram M, Olliaro P, Sundar S, Rijal S, Faiz Md. Al, Boelaert M. *PLoS NTD*, 2010 September, 4(9):e818.
- **'Leishmaniasis Vaccines: Past, Present and Future'**, by Modabber F. *International Journal of Antimicrobial Agents*, 2010 Nov 36, Suppl 1:S58-61. Epub 2010 Aug 30.
- **'Discovery of Novel Orally Bioavailable Oxaborole 6-carboxamides that Demonstrate Cure in a Murine Model of Late-stage Central Nervous System African Trypanosomiasis'**, by Nare B, Don R, et al. *Antimicrob Agents Chemother.* 2010 October, 54(10):4379-88. Epub 2010 Jul 26.
- **'Nature Outlook Chagas Disease Supplement'**. *Nature Supplement*, 2010 June, Vol. 465, No. 7301 suppl., pp. S3-S22. Sponsored by DND*i*.
- **'Antileishmanial High-Throughput Drug Screening Reveals Drug Candidates with New Scaffolds'**, by Siqueira-Neto J L, Song O-R., Oh H, Sohn J-H, Yang G, Nam J, Jang J, Cechetto J, Lee C B, Moon S, Genovesio A, Chatelain E, Christophe T, Freitas-Junior L H. *PLoS Neglected Tropical Diseases*, 2010 May, Volume 4, Issue 5.
- **'"Manifesto" for Advancing the Control and Elimination of Neglected Tropical Diseases'**, by Hotez P, Pécoul B. *PLoS NTD.* 2010 May, Vol. 4, Issue 5, e 718.
- **'Pharmacokinetics and Comparative Bioavailability of Artesunate and Mefloquine Administered Separately or as a Fixed Combination Product to Healthy Volunteers and Patients with Uncomplicated Plasmodium falciparum Malaria'**, by Olliaro P, Ramanathan S, Vaillant M, Reuter S, Evans A, Krudsood S, Looareesuwan S, Kiechel J-R, Taylor W, Navaratnam V. *Journal of Bioequivalence & Bioavailability*, 2010 May, Volume 2(3):59-66.
- **'Anti-malarial Market and Policy Surveys in Sub-Saharan Africa'**, by Diap G, Amuasi J, Boakye I, Sevcsik A-M, Pécoul B. *Malaria Journal Supplement, BioMed Central*, 2010 April, 9(1):S1.
- **'Population Pharmacokinetics and Pharmacodynamic Considerations of Amodiaquine and Desethylamodiaquine in Kenyan Adults with Uncomplicated Malaria Receiving the Artesunate-Amodiaquine Combination Therapy'**, by Jullien V, Ogutu B, Juma E, Carn G, Obyono C, Kiechel J-R. *Antimicrobial Agents and Chemotherapy*, 2010 April 5, 01496-09.
- **'In Vitro and In Vivo Experimental Models for Drug Screening and Development for Chagas Disease'**, by Romanha A J, de Castro S L, de Nazaré Correia Soeiro M, Lannes-Vieira Ribeiro I, Talvani A, Bourdin B, Blum B, Olivieri B, Zani C, Spadafora C, Chiari E, Chatelain E, Chaves G, Calzada J E, Bustamante J M, Freitas-Junior L H, Romero L I, Bahia M T, Lotrowska M, Soares M, Andrade S G, Armstrong T, Degrave W, de Araújo Andrade Z. *Mem Inst Oswaldo Cruz*, 2010 March, Vol. 105 (2):233-8.
- **'Combination Therapy for Visceral Leishmaniasis'**, by van Griensven J, Balasegaram M, Meheus F, Alvar J, Lynen L, Boelaert M. *Lancet Infect Dis* 2010; 10:184–94.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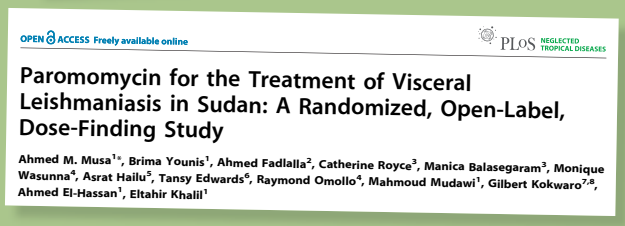
PLoS NEGLECTED TROPICAL DISEASES

Fexinidazole – A New Oral Nitroimidazole Drug Candidate Entering Clinical Development for the Treatment of Sleeping Sickness

Els Torreele[1*], Bernadette Bourdin Trunz[1], David Tweats[1,2], Marcel Kaiser[3,4], Reto Brun[3,4], Guy Mazué[1], Michael A. Bray[1], Bernard Pécoul[1]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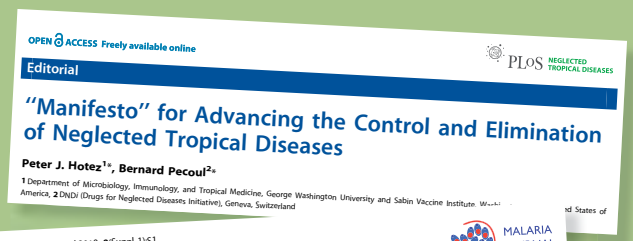
PLoS NEGLECTED TROPICAL DISEASES

Paromomycin for the Treatment of Visceral Leishmaniasis in Sudan: A Randomized, Open-Label, Dose-Finding Study

Ahmed M. Musa[1*], Brima Younis[1], Ahmed Fadlalla[2], Catherine Royce[3], Manica Balasegaram[3], Monique Wasunna[4], Asrat Hailu[5], Tansy Edwards[6], Raymond Omollo[4], Mahmoud Mudawi[1], Gilbert Kokwaro[7,8], Ahmed El-Hassan[1], Eltahir Khalil[1]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PLoS NEGLECTED TROPICAL DISEASES

Editorial

"Manifesto" for Advancing the Control and Elimination of Neglected Tropical Diseases

Peter J. Hotez[1*], Bernard Pecoul[2*]

1 Department of Microbiology, Immunology, and Tropical Medicine, George Washington University and Sabin Vaccine Institute, [illegible] America, 2 DNDi (Drugs for Neglected Diseases Initiative), Geneva, Switzerland


Diap et al. Malaria Journal 2010, 9(Suppl 1):S1
http://www.malariajournal.com/content/9/S1/S1

MALARIA JOURNAL

PROCEEDINGS

Open Access

Anti-malarial market and policy surveys in sub-Saharan Africa

Graciela Diap[1*], John Amuasi[2], Isaac Boakye[2], Ann-Marie Sevcsik[1], Bernard Pecoul[1]

From Meeting on Public and Private Antimalarial Markets and Policy Surveys
Geneva, Switzerland. 18 September 2009

DND*i* SYMPOSIA AND MAIN CONFERENCES

DND*i* 3rd Partners' Meeting in collaboration with Indian Council of Medical Research (ICMR)

New Delhi, India, 3-4 December 2010

- DND*i* and ICMR brought together more than 150 Indian and international health researchers, policy makers, and experts from 22 countries to stimulate greater regional research partnership to fight the most neglected diseases.
- In collaboration with partners from the Program on Global health and Technology Access of Duke University, DND*i* organized **a workshop on intellectual property** and open innovation that gathered around 50 participants including DND*i* partners, representatives of Indian civil society, and DND*i* staff.

American Society of Tropical Medicine and Hygiene (ASTMH)

Washington DC, USA, 3-7 November 2010

- **Joint symposium**, DND*i* and Central Drug Research Institute (CDRI): 'Current Challenges and Opportunities in Managing Visceral Leishmaniasis in the Indian Subcontinent'
- **Joint symposium**, DND*i* and *Leishmania* East Africa Platform (LEAP): 'VL in East Africa- Current Needs and Latest Clinical Developments'
- **Satellite symposium**, 'Challenges and Successes of the FACT Project through Innovative Partnerships for the Development of Artesunate Combination Therapies for Malaria'

XIIth International Congress of Parasitology (ICOPA)

Melbourne, Australia, 15-20 August 2010

- DND*i* symposium, 'Artesunate-based Combination Treatments for Malaria'
- DND*i* symposium, 'The DND*i* Model for Drug Discovery Programmes of Neglected Diseases'

Partnering for Global Health Forum 2010

Chicago, USA, 4 May 2010

MEDTROP 2010: XLVI Congresso da Sociedade Brasileira de Medicina Tropical

Foz do Iguaçu, Brazil, 14-18 March 2010

- 'Azoles Compounds in Chagas Disease: The Current Situation'
- 'Evaluation of Extemporaneous Formulations of Benznidazole for the Paediatric Treatment of Chagas Disease'

Congressional Malaria & NTD Caucus Briefing

Washington DC, USA, 22 February 2010

- 'Controlling Deadly Neglected Tropical Diseases: Opportunities to Expand the US Impact'
- DND*i* session: 'Game Changing New Treatments in Less than 5 Years'

COHRED & NEPAD Meeting: Strengthening Pharmaceutical Innovation in Africa

Pretoria, South Africa, 18-20 February 2010

- DND*i* presented the background need for strengthened regulatory capacity in Africa
- DND*i* held a regulatory workshop

05. FINANCIAL & PERFORMANCE REPORT

Significant progress towards providing safe, affordable, and effective new treatments, with a fourth new treatment available in 2010.

Performance report

SUMMARY

In 2010, DND*i* completed its seventh year of activities to develop and deliver new treatments to patients suffering from the most neglected diseases, with a fourth new treatment available: a combination of sodium stibogluconate and paromomycin (SSG&PM).
Since 2003, EUR 93.7 million has been spent (EUR 24.9 million in 2010 compared to EUR 21.1 million in 2009) to build a strong and robust portfolio. Among other projects and activities, 2010 was marked by the following:

- The **fourth new treatment** developed by DND*i*, SSG&PM, a short-course combination treatment against visceral leishmaniasis (VL) was launched. SSG&PM showed a similar safety and efficacy profile to that of the standard SSG monotherapy and provides shorter treatment duration (17 days *versus* 30 days for SSG alone) in addition to lower cost. The WHO Expert Committee on the Control of Leishmaniases recommended SSG&PM as first-line treatment for VL in East Africa. At the close of 2010, Sudan recommended SSG&PM as first-line treatment for VL;
- ASAQ, the first new treatment against malaria developed by DND*i* in partnership with sanofi-aventis, which was launched in March 2007, is now **registered and available in 30 African countries in addition to India with more than 80 million treatments courses distributed** by December 2010;
- On 14 December 2010, along with two other Product Development Partnerships (PDPs), DND*i* was granted the status of 'other **International Organization**' by the Swiss Government with effect as of 1 January 2011. This provided important recognition of DND*i*'s goals of developing and implementing effective, low-cost, and innovative drugs to fight neglected diseases.

In 2010, DND*i* reached EUR 24.9 million in expenditure, an increase of 18% from 2009, continuing the growth pattern of previous years (+20% in 2009).
In 2010, contributions from donors and other revenue brought the level of income to EUR 24.9 million, leaving a small excess of income over expenditure of EUR 0.5 million, mainly due to net exchange rate gains related to the high volatility of currencies in 2010. This excess is due to the re-evaluation of DND*i*'s short-term cash position in USD and GBP as per 31 December 2010.
The operating surplus in 2010 amounted to EUR 55,757, consisting of royalties received from one of DND*i*'s main partners (see explanation in note 6) sanofi-aventis for EUR 54,071, the use of which is restricted, alongside an unrestricted operating surplus of EUR 1,686.

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 organizations.**
- **The report provides financial information and some efficiency indicators regarding DND*i*'s activities in 2010, 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.**

Therefore the *Restricted Operating Fund* created in 2009 and dedicated to projects and activities related to the use of antimalarial treatments, totalled EUR 205,155 at the close of the year.
DND*i*'s reserve of unrestricted funds reached EUR 10 million in 2010 compared to EUR 9.5 million by end of 2009. This reserve is crucial for DND*i* and represents four months of activities.

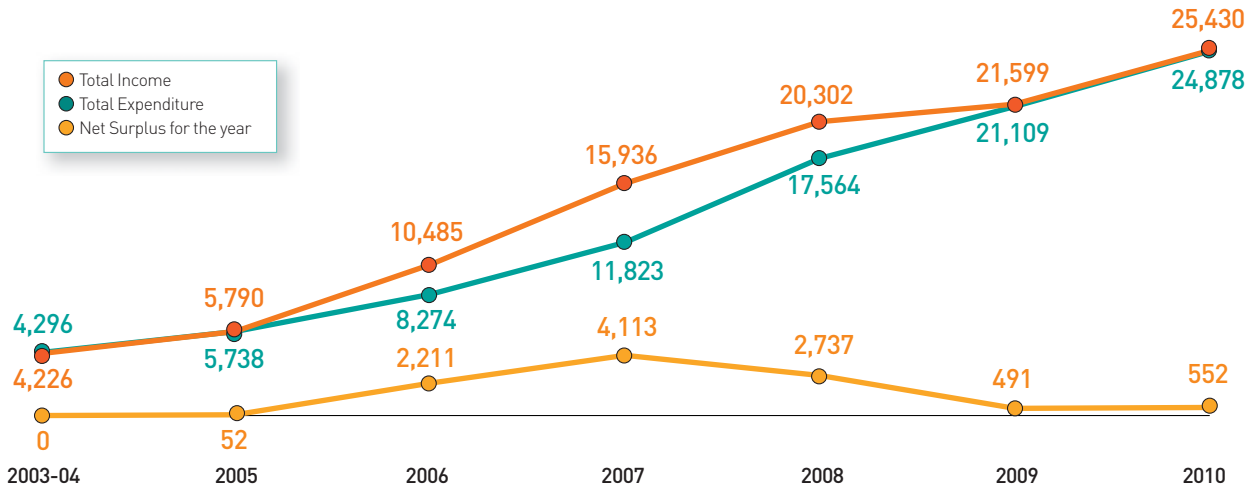
DND*i*'s work was led by a team of talented staff throughout the world. This team remained relatively stable, increasing from 69 full time equivalents (FTEs) in 2009 to 74 FTEs in 2010. Among them, 46% are working in DND*i* Regional Offices and its Affiliate, in Nairobi, Rio de Janeiro, New Delhi, Penang, Kinshasa, Tokyo, and New York, respectively. This demonstrates the increasingly international rooting of DND*i*, and continues a trend that was 43% in 2009, up from 25% in 2004. Additionally, over 80 partners and sub-contractors enabled DND*i* to carry out its mandate in 2010 (+12% as compared to 2009).

The Finance, Human Resources, and Administration Department was composed of eight staff members in 2010 (six staff members in 2009): a Director, Financial Controller, Senior Accountant, Finance Assistant, Finance Officer, HR & Administration Manager, Travel Assistant, and Receptionist. In 2010, a Receptionist and a Finance Assistant joined to help the Senior Accountant manage the increased workload, raising the total of FTEs from 5.2 to 6.9. They are supported in the Regional Offices by six additional staff members (four of whom have been with DND*i* since 2008), who maintain vital links with local authorities and partners.

.../

STATEMENT OF ACTIVITIES 2004-2010 (SUMMARY)

(Euro '000s)	2010	2009	2008	2007	2006	2005	2003-4
INCOME							
Public Institutional Funding	11,890	11,768	9,895	9,563	4,902	377	1
Private Resources	13,044	9,499	10,175	6,290	5,398	5,364	4,225
Total Income	**24,934**	**21,267**	**20,071**	**15,852**	**10,300**	**5,741**	**4,226**
EXPENDITURE							
Research & Development	19,810	16,394	13,649	8,577	5,855	3,687	2,292
Strengthening Capacities	1,414	1,322	1,111	974	558	448	157
Advocacy	941	1,194	864	658	650	537	492
Fundraising	1,175	890	694	363	250	213	81
General & Administration	1,538	1,309	1,247	1,251	961	853	1,274
Total Expenditure	**24,878**	**21,109**	**17,564**	**11,823**	**8,274**	**5,738**	**4,296**
Operating Surplus	56	159	2,506	4,029	2,026	3	-70
Other Income (net)	496	332	231	83	185	49	70
Net Surplus for the year	**552**	**491**	**2,737**	**4,113**	**2,211**	**52**	**0**



/... The Department is in charge of accounting, budget, internal control, cash management, human resources, administration, logistics, and IT services for the entire organization. DND*i*'s auditors, Deloitte SA, conducted the 2010 financial audit in accordance with Swiss Auditing Standards.

RESEARCH & DEVELOPMENT EXPENDITURE

In 2010, DND*i* continued to strengthen a large R&D portfolio for kinetoplastid diseases (leishmaniasis, human African trypanosomiasis, and Chagas disease) with ten clinical and post-registration projects, five pre-clinical projects and three lead optimization projects underway, in addition to discovery activities.

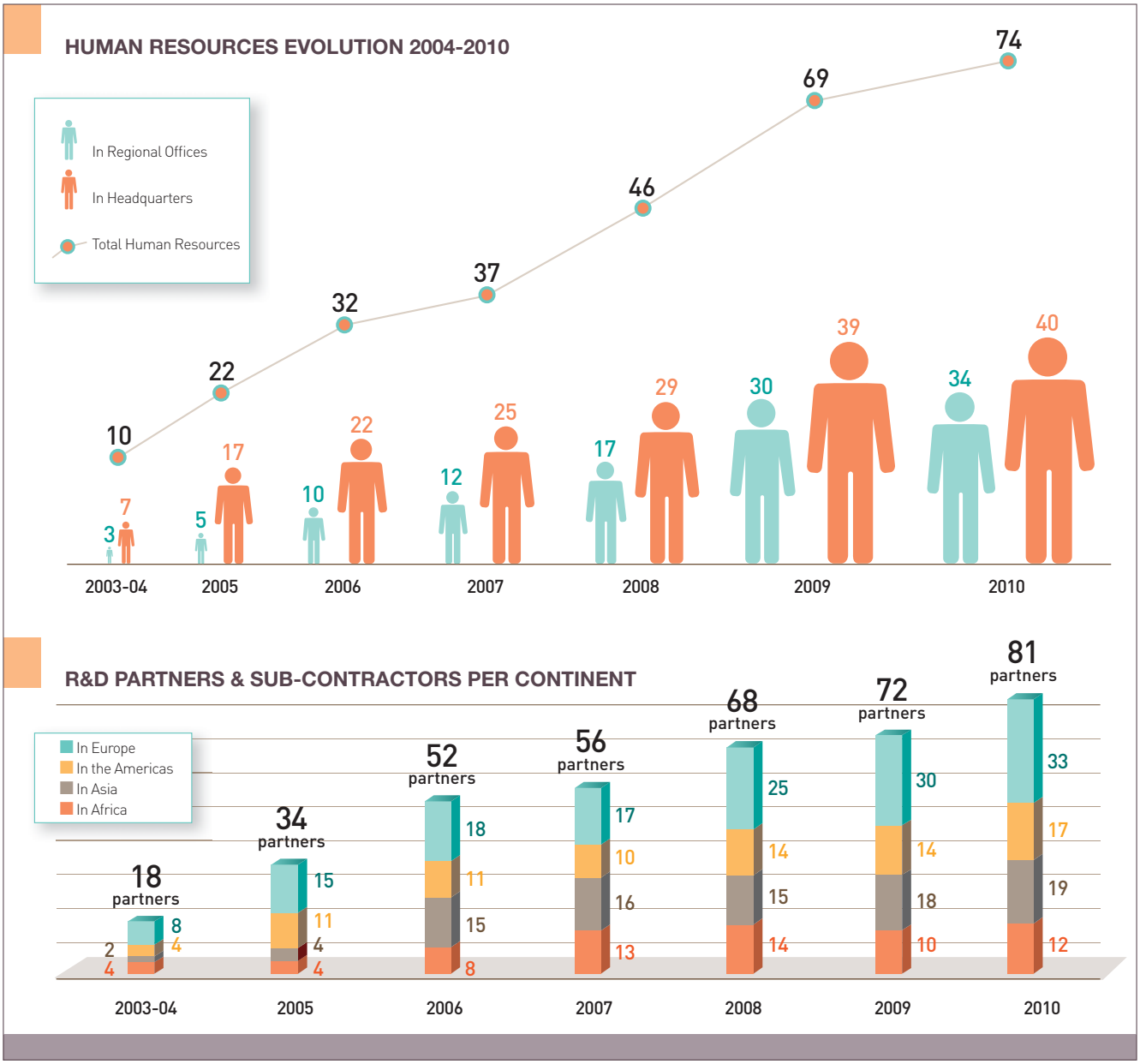
The growth of DND*i*'s R&D department continues with EUR 19.8 million in 2010, an increase of 21% compared to 20% in 2009.

As of December 2010, 21 R&D projects and several exploratory activities were being managed with a restructured team: five Heads of Programme, six Project Managers, six Project Coordinators, and two Senior Advisors. This team is supported by the R&D Coordination Team.

R&D COORDINATION & SUPERVISION

R&D coordination & supervision expenditure remained stable with a slight increase of 4% in 2010: EUR 1.69 million compared to EUR 1.63 million in 2009.

The R&D Coordination Team, driven by the Research & Development Director, his assistant, and one Clinical Development Director, has been reinforced with a new Discovery & Pre-clinical Director. The Business Development Director, as part of the R&D Coordination Team, recruited a Legal Officer in January



2010 in order to increase internal capacity for contractual and complex negotiations issues.
This growth accounts for the EUR 0.1 million increase in R&D Coordination costs. However, expenses related to coordination (office of the R&D Director, Medical Director & Pre-clinical Director) and IP, and regulatory research decreased mainly because fewer consultants supported these activities in 2010 compared to 2009.

The R&D Coordination Team also undertook specific work on intellectual property and regulatory issues. DND*i* launched a report on regulatory issues during the first quarter of 2010 in collaboration with the Georges Institute.
The team under R&D coordination and supervision in December 2010 consisted of 9 staff members (7.8 FTEs, plus 1 FTE) including 1.5 staff members in Tokyo, Japan.

LARGE USE OF ASAQ IN AFRICA & POSITIONING OF ASMQ ON THREE CONTINENTS

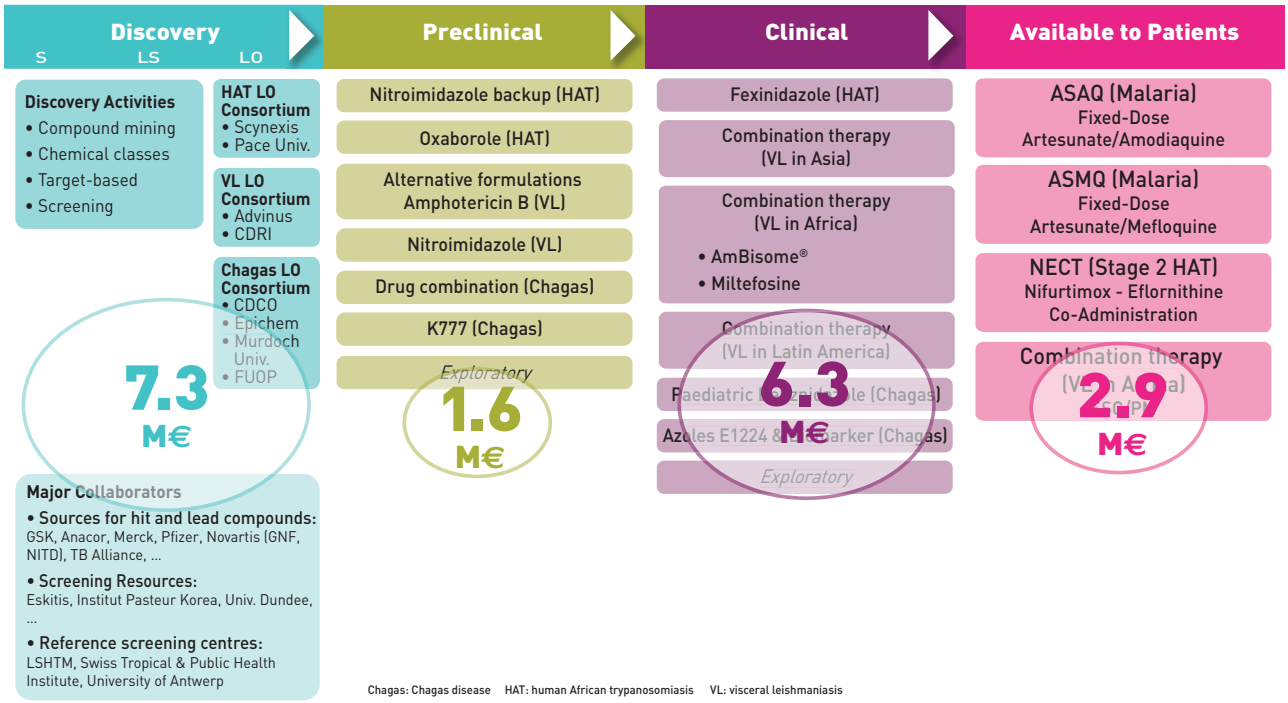
ASAQ, the fixed-dose combination of artesunate and amodiaquine, was the first drug to be made available by DND*i* through an innovative partnership with sanofi–aventis in 2007.
The main activities regarding ASAQ in 2010 were as follows:

- With the support of Epicentre, the analysis of the Phase IV efficacy & tolerability study (1,350 patients) in Liberia (EUR 0.35 million in 2010) was completed;
- MMV, sanofi-aventis, and DND*i* collaborated in Ivory Coast to implement a pharmaco-vigilance study. DND*i* provided financial support to the study's monitoring activities (EUR 0.08 million);
- DND*i*, in collaboration with Komfo Anokye Teaching Hospital, Kumasi (KATH), assessed the distribution of .../

BREAKDOWN BY DEVELOPMENT STAGE

The total R&D expenditure increased by 21%, which is superior to the increase for the other DND*i* activities (strengthening capacity, advocacy, and general management +7.5%). The greatest expenditure (40%) is in discovery projects, mainly because the lead optimization activities (80% of the discovery investment) continued to work on 4 series (1 for VL, 2 for HAT, and 1 for Chagas).
Two new projects entered pre-clinical activity in 2010: Oxaborole for HAT and Nitroimidazole for VL. These 2 new projects account for the 28% increase from 2009 to 2010. The increase of expenditure dedicated to clinical development doubled between 2009 and 2010 (+EUR 3.2 M) as DND*i* invested in a Phase I clinical trial for the Fexinidazole project (EUR 2.150 M in 2010 compared to EUR 0.550 M in 2009) and that VL combination projects increased by EUR 1M because of the launch of 2 new projects (Bangladesh and Latin America).
The investment (16% of R&D) for availability to patients remains stable: despite the combination therapy (VL in Africa, SSG&PM) entering in this phase, the malaria project expenditure decreased.

BREAKDOWN PER STAGE (PORTFOLIO 2010)



/... malaria treatments in 1,500 outlets in Ghana (EUR 0.18 million) as part of the *Baseline Outlet Survey for the Affordable Medicines Facility* (Global Fund);

- OTECI actively supported DND*i*'s selection of its second industrial partner for the production of ASAQ in Africa (EUR 0.09 million). With the support of AEDES and Bertin Pharma, technology will be transferred to Zenufa in Tanzania as of 2011.

Expenditure for ASAQ decreased from EUR 0.9 million (in 2009) to EUR 0.7 million (in 2010).
DND*i*'s 2010 investment in **ASMQ**, a fixed-dose combination of artesunate and mefloquine, was aimed at ensuring that this treatment progressively be made available over three continents. In 2010 the Brazilian Ministry of Health ordered 150,000 treatments from Farmanguinhos and Bolivia committed to implement ASMQ. The main activities regarding ASMQ in 2010 were:

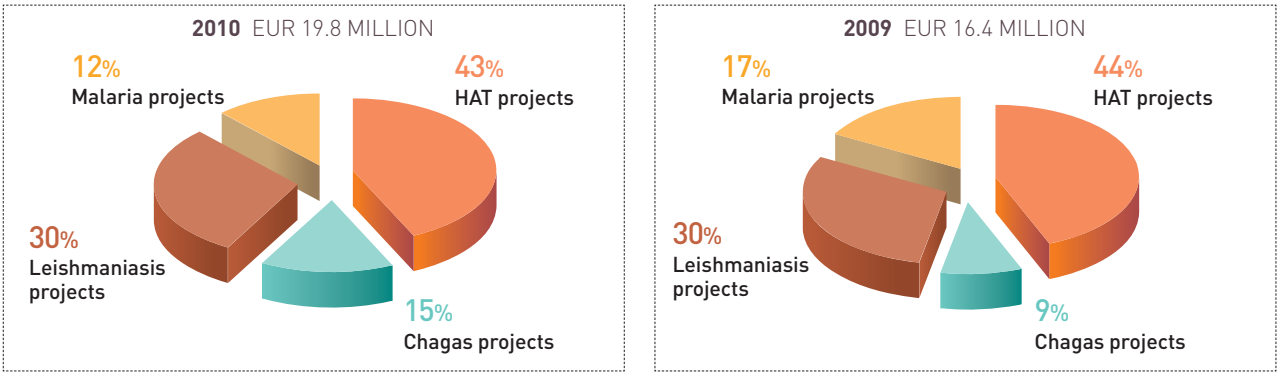
- Cipla in India manufactured the registration batches according to those produced by Farmanguinhos in Brazil, thus successfully concluding this South-South **technology transfer** facilitated by DND*i* (EUR 0.200 million);
- A dossier was submitted to **WHO for ASMQ prequalification**. The DND*i* Malaria team supported the filing of the registration dossier by Cipla for ASMQ in South East Asia (EUR 0.375 million);
- Active support was provided for a series of clinical studies on ASMQ in Cambodia, Myanmar, and India and regional expert meetings were held in Myanmar, Malaysia, Cambodia, and Kenya (EUR 0.4 million). DND*i* prepared a **multicentric study** to assess the efficacy, safety, and population pharmacokinetics (PK) of ASMQ in children in Burkina Faso, Kenya, and Tanzania (EUR 0.575 million). The clinical study started in Burkina Faso in 2010 with 26 children enrolled by the end of March 2011.

Approximately EUR 1.5 million was invested in ASMQ in 2010, equivalent to the 2009 investment.

BREAKDOWN BY DISEASE

The percentage breakdown of R&D expenditure by disease highlights the major efforts exerted for the Chagas portfolio in 2010, resulting in an increase of 195% compared to 2009 (242% compared to 2008). Indeed, the finalization of the registration dossier for Paediatric Benznidazole (+EUR 200 K) and the preparation of the clinical trial sites in Bolivia for Azole E1224 Project (+EUR 300 K) demonstrate this increase. Clinical trials for VL combinations in Bangladesh started in early 2010 and the 7 clinical sites operational in Africa for VL increased the expenditure for VL clinical projects by 32% (+EUR 600 K). In addition, a new pre-clinical project, Nitrimidazole for VL (+EUR 400 K), explains the increase of VL diseases in 2010 (Total + EUR 1,000 K). The HAT clinical programme increased by EUR 1,100 K, mainly because of the Fexinidazole Project entering in a clinical Phase I package (+EUR 1,300 K) with decrease of NECT field study I of EUR 200 K. Regarding pre-clinical HAT program, the Oxaborole Project entering in a full pre clinical package in 2010 increased by 215% (+EUR 500 K). The proportion of malaria projects in terms of the total expenditure is decreasing (-EUR 200 K).

R&D EXPENDITURE BY DISEASE



HUMAN AFRICAN TRYPANOSOMIASIS (HAT): NECT IMPLEMENTATION AND DEVELOPMENT OF NEW CHEMICAL ENTITIES TO SUPPORT THE ELIMINATION STRATEGY

HAT expenditure increased in 2010 (EUR 7.7 million) as compared to 2009 (EUR 6.5 million) mainly because of the Fexinidazole Project (EUR from 1.3 million in 2009 to 2.6 million in 2010) entering Phase I.

The main activities regarding the development of new treatments for HAT in 2010 were:

- **NECT**, a simplified co-administration of Eflornithine and Nifurtimox for stage 2 HAT patients, was included on the WHO Essential Medicines List in 2009. Since then, DND*i*, the national programme against human African trypanosomiasis (PNLTHA) of the Democratic Republic of the Congo, and the Swiss Tropical and Public Health Institute (Swiss TPH) have implemented the NECT Field study to document its safety and effectiveness in field conditions as well as the feasibility of its implementation. The NECT Field study recruited 630 patients including 100 children and 47 pregnant or lactating women. Patient follow-up will continue in 2011 (EUR 0.5 million in 2010 compared to EUR 0.7 million in 2009). By end of December 2010, **10 countries, which cover approximately 97% of all HAT estimated cases, had ordered NECT kits from WHO to use as first-line treatment**.
- **The promising oral drug candidate for HAT, fexinidazole,** moved from pre-clinical to Phase I in 2009. Since then, some 100 volunteers have been included in a Phase I study conducted by SGS (France) and Chemistry, Manufacturing, and Control (CMC) work with sanofi-aventis was undertaken (EUR 2.1 million) while pre-clinical work was finalized (expenditure of EUR 0.5 million in 2010 compared to EUR 0.7 million in 2009). Thus, total expenditure for the Fexinidazole Project reached EUR 2.6 million in 2010. Following review by WHO, the eligibility of fexinidazole for an evaluation through article 58 of the European regulatory agency (EMA) has been confirmed. In 2010, DND*i* and sanofi-aventis (see in-kind contribution table) applied for joint EMA article 58 and US Food Drug and Administration Office (FDA) scientific advice on the clinical development plan. In 2011, DND*i* will complete the Phase I programme before starting the pivotal Phase II-III study.
- **Oxaborole** (SCYX-7158 compound) is the first pre-clinical candidate developed through DND*i*'s lead optimization program. In 2010, pre-clinical safety studies for oxaborole (oral candidate) have been carried out in collaboration with SCYNEXIS (USA) and Advinus (India), and thus increasing pre-clinical expenditure for the project from EUR 0.4 million in 2009 to EUR 0.9 million in 2010. **All safety studies indicate so far that oxaborole should enter Phase I clinical studies in 2011.**
- **The Lead Optimization** Consortium (partnership with SCYNEXIS and Pace University, USA) for HAT continued working in 2010 on two promising series. Expenditures reached .../

/... EUR 3.3 million, the same as in 2009 and 2008. The consortium aims to identify and optimize back-up compounds in order to replace fexinidazole or oxaborole in a timely manner should they fail to progress successfully in clinical phases.

LEISHMANIASIS: DEVELOPMENT AND USE OF VL COMBINATIONS WHILE ADVANCING NOVEL THERAPIES ALONG THE R&D CHAIN

The expenditures for leishmaniasis projects increased by EUR 0.6 million in 2010 and reached EUR 4.7 million compared to EUR 4.1 million in 2009. Major efforts have been devoted to clinical trials to test **combinations of existing treatments**.

- In **Africa**, DND*i* and the Leishmaniasis East African Platform (LEAP) completed a multi-centre, multi-country (Kenya, Ethiopia, Sudan, and Uganda) clinical trial with patient follow-up ending in February 2010; clinical study reports and two publications have been produced (EUR 0.150 million). This study involved over 1,100 VL patients and showed that the short-course combination of SSG&PM (17 days) had a similar safety and efficacy profile as the standard SSG monotherapy treatment (30 days).
- DND*i* and LEAP conducted two clinical trials in 2010: AmBisome® and miltefosine to develop a second shorter combination. Through this work, approximately 1,000 patients in 2010 were treated both within and outside the trials. The costs for these activities in 2010 totalled EUR 1.8 million against EUR 0.5 million in 2009.
- In **India,** DND*i* and Sitaram, Kala-Azar Medical Research Center, and GVK completed a Phase III clinical trial assessing three combinations of drugs registered in India, (AmBisome®, miltefosine, and paromomycin). The results presented at the ICMR/DND*i* meeting in New Delhi in March 2010 and published in *The Lancet* in 2010, indicated that all three shorter duration combination therapies were highly efficacious and caused fewer adverse reactions than the standard Amphotericin B treatment. Expenditure for this study was EUR 0.7 million in 2009, and EUR 0.2 million in 2010 (632 patients enrolled).
- A Phase III trial testing the same combination treatments started in 2010 in **Bangladesh** in order to facilitate their registration. As of March 2011, 60 patients have been recruited in partnership with Shaheed Surawhady Medical College Hospital and the International Centre for Diarrhoeal Disease Research, Bangladesh. (EUR 0.450 million)
- A VL combination study started in **Brazil** in 2010 with Centro de Pesquisa René Rachou and Fiocruz. The Brazilian Ministry of Health sponsored (see in-kind contribution table) DND*i* for its support in evaluating the safety and efficacy of the currently recommended treatments for VL in Brazil as well as the combination of AmBisome® + Glucantime (EUR 0.1 million). The first patients for the study were recruited in February 2011.
- The **VL Lead Optimization Consortium**, Advinus and Central Drug Research Institute (CDRI), Lucknow, India, worked in 2010 on the oxaborole and nitroimidazoles series and produced a number of highly potent compounds. Pharmacokinetics and safety studies were underway to validate a pre-clinical candidate from these promising series. The expenditure remains stable at EUR 1.1 million in 2009 and EUR 1.2 million in 2010.
- In 2010, DND*i* conducted **pre-clinical** studies with the **nitroimidazoles series** accessed through collaboration with the TB Alliance. As of September 2010, a promising compound demonstrated significant efficacy in acute (mouse) and chronic (hamster) animal models (EUR 0.4 million).
- In 2010, DND*i* invested EUR 0.1 million to explore potential treatment options for **cutaneous leishmaniasis** (CL) projects.

CHAGAS DISEASE: PREPARING PAEDIATRIC BENZNIDAZOLE FOR AVAILABILITY TO PATIENTS AND NEW CHEMICAL ENTITIES AT DISCOVERY AND CLINICAL PHASE

Expenditure for **Chagas disease projects** reached EUR 2.4 million in 2010 against EUR 1.4 million in 2009. This increase highlights DND*i*'s efforts to mobilize R&D to develop a new treatment for Chagas by 2014.

- DND*i* and LAFEPE (Brazil) are developing a paediatric formulation of benznidazole for children with Chagas disease. In 2010, the bio batches were manufactured and underwent the required stability testing. In March 2011, the regulatory dossier was submitted to the regulatory agency ANVISA (Agência Nacional de Vigilância Sanitária). The **paediatric benznidazole formulation** should be available in 2011. 2010 expenditure of EUR 0.45 million was double that of 2009.
- Following the signature in 2009 of a license agreement with the Japanese pharmaceutical company Eisai Inc. DND*i* developed the clinical development plans for **E-1224, a prodrug of ravuconazole** in 2010. In partnership with CRESIB (Spain), DND*i* conducted the preliminary activities at the site level to start a Phase II proof-of-concept clinical trial in adult patients with chronic indeterminate Chagas disease in Cochabamba, Bolivia. The 2010 expenditure reached EUR 0.5 million.
- The **Chagas Lead Optimization Consortium** includes institutions in Australia (CDCO/Monash and Murdoch Universities, Epichem Ltd) with the support of Universidade Federal de Ouro Preto (Brazil) and Institut Pasteur Korea. In 2010, DND*i* assessed seven classes of compounds in hit-to-lead studies. One of these series was selected and is currently in lead optimization. The 2010 expenses reached EUR 1.45 million, compared to EUR 0.8 million in 2009.

DISCOVERY STAGE: ACCESS TO QUALITY LIBRARIES

The expenditure for early discovery increased by EUR 0.2 million in 2010 (EUR 1.5 million in 2010 against EUR 1.3 million in 2009). Since end of 2009, the **high-throughput screening** (HTS) capacity for all diseases with Eskitis (for HAT) and Institut Pasteur Korea (for VL and Chagas) has enabled DND*i* to fully implement its discovery strategy.

- DND*i* gained access to **chemical diversity** through key agreements and partnerships with pharmaceutical companies (Merck, Pfizer, Genzyme). The cost of the screening of these new libraries was EUR 0.6 million.
- The partnership with the Drug Discovery Unit (DDU) at the **University of Dundee** provides DND*i* a broader access to early-stage discovery and state-of-the-art technology in order to discover new lead compounds against *Leishmania* spp. This accounted for expenditure of EUR 0.45 million in 2010.
- In addition, DND*i* continued to work in 2010 with reference screening partners including Swiss TPH, Antwerp University. The costs related to partners, screening centres in 2010 totalled EUR 0.35 million against EUR 0.6 million in 2009.

EXPLORATORY WORK: PREPARING FOR EXTENSION OF THE PORTFOLIO

Exploratory expenditure in 2010 totalled EUR 0.2 million. Half of this budget was dedicated to assess patient needs and R&D opportunities for helminth-related diseases and half to assess patient needs and R&D opportunities for paediatric HIV (see page 53 below).

STRENGTHENING CAPACITIES EXPENDITURE

Strengthening capacity expenditure increased to EUR 1.4 million in 2010 compared to EUR 1.3 million in 2009. This includes:

Chagas Clinical Trial Platform (since 2009)

The first general meeting of the Chagas Clinical Trial Platform took place in Buenos Aires (Argentina, 22-24 March 2010) with the attendance of key stakeholders, Chagas control programme members, international organizations, and manufacturers. The objectives were to revise the Chagas disease Target Product Profile (TPP), present the Chagas disease strategy, provide an update on clinical studies and projects, and offer a Good Clinical Practices (GCP) training course. The total reached EUR 0.1 million.

HAT Platform (since 2007)

The annual scientific meeting of the HAT Platform was organized in October 2010 in Nairobi in collaboration with EANETT (Eastern African Network on Trypanosomosis) and was attended by more than 75 participants, including leaders from the National Control Programmes of the most endemic countries. Updates were given on epidemiological data of the first semester of 2010 and researchers presented the latest findings.

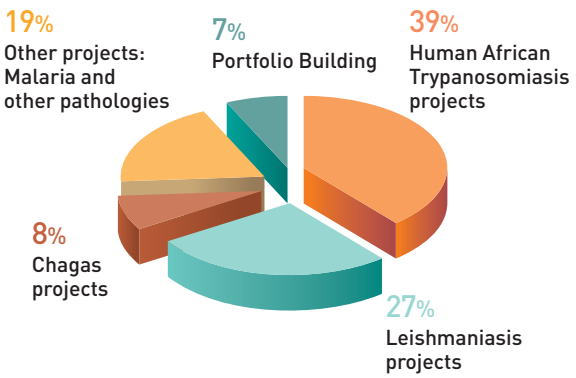
The HAT Platform creates synergy with regional partners to strengthen the overall national capacities in clinical research. The main challenges for the HAT Platform are to overcome the difficulties of the remote settings, improve access to the sites, reinforce infrastructures, and address staff limitations in order to conduct the research-related activities. The 2010 total reached EUR 0.2 million.

LEAP Platform (since 2003)

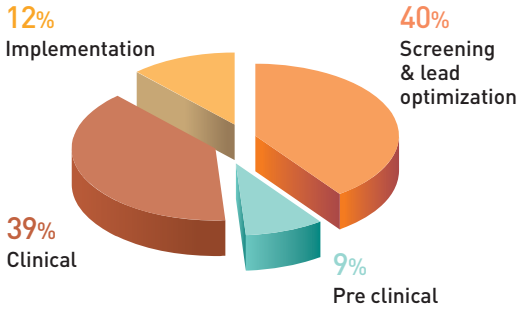
The Leishmaniasis East Africa Platform (LEAP) is a regional clinical research network collaborating to study new treatments for African patients suffering from visceral leishmaniasis (VL). It incorporates over 20 institutional members from four countries across the spectrum of clinical research and disease control organizations. In 2010, LEAP conducted two bi-annual meetings in Uganda and Sudan. LEAP continued to update the national treatment policies. The recommendation of SSG&PM by the Sudanese MoH followed one of these meetings. LEAP continued to coordinate clinical trials and .../

R&D CUMULATED COST BREAKDOWN, 2004-2010, 70.3 MILLION EURO, INCLUDING R&D COORDINATION (75% OF TOTAL EXPENDITURE)

R&D EXPENDITURES BY DISEASE **2004-2010**



ACTUAL EXPENDITURES BY R&D STAGE **2004-2010**



/... studies and conducted several trainings for site personnel, health workers, and laboratory staff. In September 2010, an additional LEAP trial site was inaugurated in Doka (the site was equipped in 2010) in the State of Gedaref. Expenditure totalled EUR 0.2 million.

CL Platform (since end of 2009)

A CL platform was built in partnership with LSHTM and with the support the European Union-Framework Programme 7 (EU FP7) in order to strengthen clinical research for CL vaccines. The consortium will prepare clinical study facilities and enhance sites through GCP training and infrastructure building. Expenditure totalled EUR 0.1 million.

Regional Support Offices

Networking in disease endemic countries (e.g. national control programmes, Founding Partners, other existing networks) as well as management/support of local/regional activities were carried out through DND*i* regional offices based in Nairobi, Rio de Janeiro, Penang, and New Delhi. Total expenditure was EUR 0.7 million in 2010 against EUR 0.6 million in 2009.

COMMUNICATION & ADVOCACY EXPENDITURE

Communication and Advocacy expenditures decreased by 21% in 2010 (EUR 0.94 million) compared to (EUR 1.19 million) in 2009.

This decrease is explained by the investment in an important campaign in 2009, the Chagas Campaign, which did not continue in 2010.

DND*i* advocacy efforts were mainly focused on the organization of a major event in December 2010: the **Third DND*i* Partners' Meeting** in collaboration with the Indian Council for Medical Research (ICMR) in New Delhi. DND*i* brought together more than 150 Indian and international health researchers, policy makers, and experts from 22 countries, to stimulate greater regional research partnerships to fight the most neglected diseases. These leading experts used this opportunity to examine ongoing DND*i* projects in drug research and development, access, and capacity strengthening.

During this meeting, two projects were highlighted as **DND*i*'s successes of the year 2010**: a combination therapy for visceral leishmaniasis – a new hope for patients suffering from this disease – and the partnership with Institut Pasteur Korea, which was deemed the year's most innovative and important breakthrough to boost innovation for neglected tropical diseases.

The DND*i* Communication and Advocacy team also worked to: raise awareness of the lack of tools to treat neglected patients; facilitate meetings at regional and national levels; produce educational material (newsletters, video, and websites); publish the results of clinical studies in peer-reviewed medical journals; and participate in international congresses such as ASTMH 2010 in Atlanta (USA). During the latter, DND*i* organized a joint symposium with Central Drug Research Institute (CDRI) on visceral leishmaniasis in the Indian Continent and in East Africa, and a satellite symposium on 'Challenges and Successes of the FACT Project for Malaria'. DND*i* also participated in the XIIth International Congress of Parasitology (ICOPA) in Australia, at which the movie *1$ for 1 Life* was presented.

The Communication and Advocacy team in December 2010 was composed of 5 staff members (4 FTEs, plus 0.5 FTE since 2009) with the support of temporary staff and consultants at headquarters and in North America and Latin America.

FUNDRAISING & GENERAL MANAGEMENT EXPENDITURE

Fundraising expenditure increased by 32% in 2010 (EUR 1.18 million in 2010 and EUR 0.99 million in 2009).

This increase is a consequence of the reinforcement of the Fundraising team with consultants in various countries to support the achievement of DND*i*'s 2010 fundraising objectives to address the balance of funds in 2010, and beyond; to renew existing commitments from current government donors; to secure additional multi-year contracts with new governments; to secure new grants from major private foundations; to develop private fundraising strategies in high-income countries; to explore public and private targets in other countries; and to advocate for new funding mechanisms.

Fundraising expenses represent the costs to raise funds: personnel, travel, and document production. The Fundraising team was composed in 2010 of 6 staff members (4.5 FTEs), compared to 4 FTEs in 2009, and had the support of 2 staff members at DND*i* North America, dedicated to fundraising in North America, as well as additional consultants.

General Management & Administration total expenditure increased by 18% (EUR 1.54 million in 2010 compared to EUR 1.31 million in 2009).

The increase was due to the reinforcement of the administrative and financial team with two new staff members; the growing costs of IT support to the organization and the support of a consultant to help DND*i* develop a new business plan for the period 2011-2018, including the potential extension of DND*i* scope of diseases.

General Management and Administration expenses represented the costs of managing the organization: expenses incurred by the Board of Directors, the Executive Director, and the Financial and Administration Department. In 2010, with the addition of a new Finance Officer, the team was composed of 10 staff members (9 FTEs) as compared with 8 staff members (7 FTEs) in 2009.

PREPARING THE FUTURE

DND*i*'s **business plan,** developed in 2003 and updated in 2007, for the 2004-2014 period serves as a framework and guide for DND*i* activities. In 2010, DND*i* launched a process to think beyond 2014 and to **update** its business plan for the period **2011-2018**. This was an opportunity for DND*i* to review its objectives and reforecast expenditure. DND*i*'s Board of Directors is scheduled to approve the updated business plan in June 2011.

Having confirmed the strengths, potential, and key assets of its **business model**, DND*i* was able to identify the essential building blocks for a more dynamic approach to its disease portfolio, including the development of mini-portfolios (carefully selected projects, limited in number, for specific disease areas) to address well-defined unmet needs for other poverty-related diseases. In-depth needs assessments were conducted by expert working groups, which led DND*i* to decide upon an **expansion of its scope of diseases**, guided by the same vision and mission laid forth in its original business plan. While remaining fully committed to neglected diseases such as sleeping sickness, leishmaniases, and Chagas disease, DND*i*'s Board of Directors decided in December 2010 to take on specific projects for two new disease areas: **paediatric HIV** and specific **helminth** infections.

Paediatric HIV: Over 85 % of the 2.5 million children infected with HIV (as of 2009) are not treated. DND*i* aims at developing a mini-portfolio in 2011 to offer a better combination treatment for this population under the age of 3**.**

Helminths: Millions of people suffer from filaria diseases (onchocerciasis, lymphatic filariasis, and loiasis). DND*i* aims to develop a mini-portfolio to provide one new treatment for lymphatic filariasis in *Loa loa* co-endemic areas.

Until the approval of the updated business plan 2011-2018, the current 2004–2014 business plan, which foresees the delivery of six to eight new treatments by 2014 at an estimated EUR 230 million, is the benchmark against which the seven years (2004 – 2010) of DND*i*'s accomplishments are to be measured. By 2010, DND*i* delivered four new treatments at a cumulative cost of EUR 94 million and commitments from donors for EUR 153 million.

This comparison and the forecast's review of the three years to come (2011 – 2013) shows that DND*i* is well on its way to succeed in delivering at least six new treatments for neglected diseases and creating a healthy portfolio of projects by 2014 for the target current business plan estimation of EUR 230 million.

Cumulative Breakdown DND*i* 2004 – 2010 (in million Euro) and social mission ratio			
R&D	70.3	(75%)	(80% in 2010)
Strengthening Capacities	6.0	(6%)	(6% in 2010)
Advocacy	5.3	(6%)	(4% in 2010)
Fundraising	3.7	(4%)	(5% in 2010)
General Management	8.4	(9%)	(6% in 2010)
Total	**93.7**	**(100%)**	

The cumulative breakdown illustrates that the vast majority of funds are devoted to R&D (75%), with a secondary programmatic focus on strengthening capacities (6%) and advocacy (6%). This focus shows a clear emphasis on the social mission with 87% of the funds allocated to this area. From a disease perspective, two-thirds of overall expenses are devoted to visceral leishmaniasis and human African trypanosomiasis R&D, which shows DND*i*'s commitment to these two diseases.

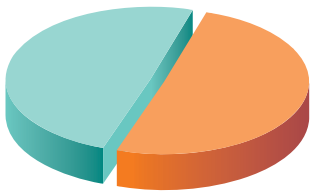
DIVERSIFICATION OF PUBLIC AND PRIVATE DONORS

To develop its activities and achieve its objectives, DND*i* seeks diverse funding including grants, in-kind contributions, and cash donations from governments, public institutions, foundations, NGOs, companies, individuals, and other mechanisms. After more than seven years of operations, DND*i* has secured diversified funding which includes a mix of public and private donors for project, portfolio, and initiative funding.

DND*i* aims to obtain half of its funding from public sources. By the end of 2010, DND*i* achieved an overall balance of public and private funding, with total public institutional contributions of EUR 75,839,603 (49.5% of total commitment received by end of 2010).

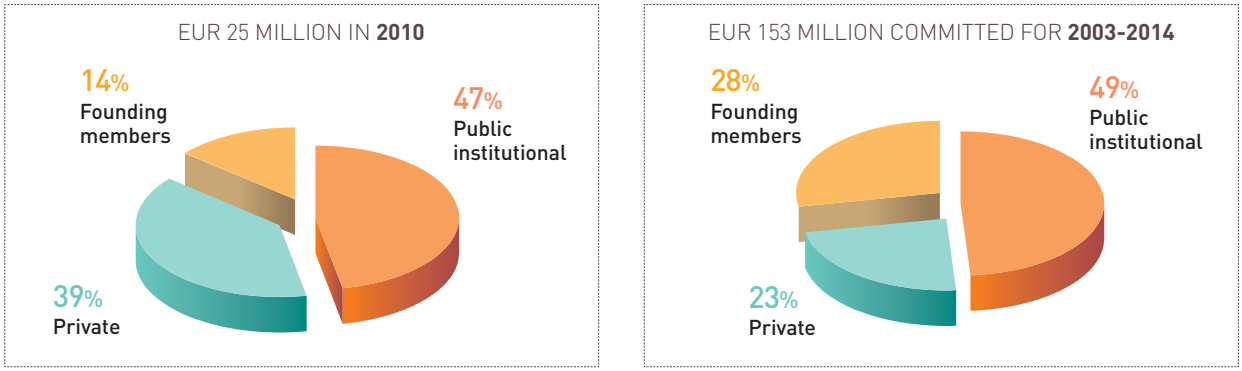
Despite the ripple effects of the on-going economic crisis, DND*i* was able to generate enough income to cover its total expenses. This achievement is the result of sound financial management, ongoing multi-year grants, renewed and increased commitments of past and current donors, as well as new partnerships with key institutions. .../

AS OF JANUARY 2011, EUR 153 MILLION HAS BEEN COMMITTED TO DND*i* TO FUND ITS ACTIVITIES FROM 2003-2014



Médecins Sans Frontières	28.1%
Bill & Melinda Gates Foundation	20.1%
The Various private donors	2.4%
Private Contributions	**50.6%**
UK (DFID)	20.6%
The Netherlands (DGIS)	11.1%
Spain (AECID)	6.5%
France (MAEE and AFD)	6.0%
Switzerland (SDC and Republic and Canton of Geneva)	2.8%
European Union: FP5, FP6, FP7, EDCTP	0.8%
Various Gov: Germany, Tuscany, USA	1.6%
Public Institutional Contributions	**49.4%**

PUBLIC INSTITUTIONAL *VERSUS* PRIVATE AND FOUNDING MEMBER FUNDING IN 2010 COMPARED TO TOTAL COMMITTED BETWEEN 2003 AND 2014



/... In 2010, DND*i* received contributions from the American, British, Dutch, and French governments, EU FP7, Médecins Sans Frontières, and The Bill & Melinda Gates Foundation. Demonstrating their confidence in DND*i*'s objectives and achievements, the Spanish government (EUR 2.5 million), the Republic and Canton of Geneva, Switzerland (CHF 0.6 million), and the Medicor Foundation (USD 0.4 million) renewed their commitments in 2010, while the UK government (GBP 1.4 million) increased its support to DND*i*. Two governments decided in 2010 to support the development of new treatments for neglected tropical diseases by partnering with DND*i*: the Dutch (EUR 14 million – 2011 to 2014) and Swiss governments (CHF 4 million – 2010 to 2012). DND*i* also received a donation from ICMR, India. As of 2010, EDCTP and the Global Fund AMFm worked with DND*i* on some specific malaria activities. Four private foundations decided to support DND*i* for the first time in 2010, thereby further diversifying DND*i*'s donor portfolio.

At the end of 2010, a total of EUR 24,880,077 (plus EUR 54,071 of royalties – see financial section) had been raised compared to EUR 21,116,173 in 2009 (an increase of 18%). The cumulative funding mix of EUR 153 million was 34% restricted funds (36% by the end of 2009) and 66% unrestricted funds (64% by the end of 2009).

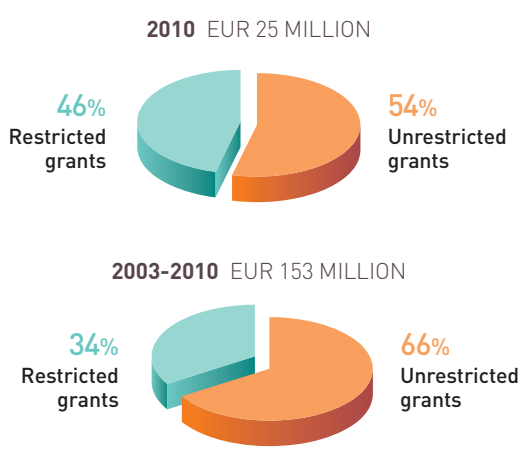
Significant and multi-year commitments will be critical to the success of DND*i* in the coming years. These include: unrestricted and multi-year initiative funding from Médecins Sans Frontières of EUR 42.6 million (2003-2014), the UK Department for International Development of GBP 24.5 million (2006-2013), the Swiss Agency for Development and Cooperation of CHF 4 million, and the portfolio funding from the Dutch government (14 million EUR – 2011 to 2014).

In-kind donations grew from EUR 1.1 million in 2009 to EUR 2.3 million in 2010, showing the increasing involvement of both public and private partners. Nearly 80% of all in-kind contributions to DND*i* in 2010 can be attributed to six main sources: Epichem Pty Ltd (Australia), Eisai (Japan), sanofi-aventis (France), Monash University (Australia), CNPq - Universidade de Brasilia (Brazil), and Insitut Pasteur Korea.

As of March 2011, a total of EUR 153 million was committed to DND*i*, which has enabled all of its activities to be funded since 2003. However, DND*i* still needs a total of EUR 77 million by 2014 to achieve its business plan objectives.

Thanks to all its donors DND*i* has delivered four new treatments for the most neglected patients and built a robust pipeline of innovative drug candidates, while strengthening the capacity of endemic countries in their fight against neglected diseases.

EVOLUTION OF RESTRICTED *VERSUS* UNRESTRICTED GRANTS BETWEEN 2003 AND 2010



DND*i* WOULD LIKE TO THANK THE FOLLOWING DONORS FOR SUPPORTING ITS ACTIVITIES SINCE JULY 2003:

PUBLIC INSTITUTIONAL DONORS:

- Department for International Development (DFID) / United Kingdom
- Dutch Ministry of Foreign Affairs (DGIS) / The Netherlands
- European Union – Framework Programmes 5, 6, and 7
- European and Developing Countries Clinical Trials Partnerships (EDCTP) with co-funding from Member States / International
- French Development Agency (AFD) / France
- The Global Fund to Fight AIDS, Tuberculosis and Malaria (AMFm) / International
- German International Cooperation (GIZ) on behalf of the Government of the Federal Republic of Germany / Germany
- Ministry of Foreign and European Affairs (MAEE) / France
- National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) / USA
- Region of Tuscany / Italy
- Republic and Canton of Geneva / Switzerland
- Spanish Agency of International Cooperation for Development (AECID) / Spain
- Swiss Agency for Development and Cooperation (SDC) / Switzerland

PRIVATE DONORS:

- The Bill & Melinda Gates Foundation / USA
- Médecins Sans Frontières (Doctors without Borders) / International
- Medicor Foundation / Liechtenstein
- The Peter and Carmen Lucia Buck Foundation/ USA
- Fondation André & Cyprien / Switzerland
- Fondation ARPE / Switzerland
- Fondation de bienfaisance de la banque Pictet / Switzerland
- Fondation Pro Victimis / Switzerland
- Starr International Foundation / Switzerland
- UBS Optimus Foundation / Switzerland
- Leopold Bachmann Foundation / Switzerland
- The Sasakawa Peace Foundation / Japan
- Guy's, King's and St Thomas, Giving Week / UK
- Other private foundations who would like to remain anonymous
- Numerous individual donors

Financial statements

BALANCE SHEET

at December 31, 2010

Assets *(expressed in EUR)*	*Notes*	2010	2009
CURRENT ASSETS			
Cash and cash equivalents			
Cash and banks at headquarters		3,985,617	13,609,027
Cash and banks at RSOs and affiliate		285,943	159,774
Time deposits		12,815,450	0
Total cash and cash equivalents		**17,087,010**	**13,768,801**
Stocks of drugs	*3*	**81,041**	**35,000**
Current accounts and receivables			
Advances to officers and liaison offices		47,700	44,103
Advances to partners related to projects		330,715	658,542
Receivables from public institutional donors		2,899,330	1,653,715
Receivables from founders		6,745	6,745
Other receivables		14,430	15,490
Prepaid expenses		119,064	120,756
Total current accounts and receivables		**3,417,984**	**2,499,351**
Total current assets		**20,586,035**	**16,303,152**
NON-CURRENT ASSETS			
Tangible fixed assets, net	*4*	86,051	153,166
Bank guarantee deposits		28,938	23,888
Total non-current assets		**114,989**	**177,054**
TOTAL		**20,701,024**	**16,480,206**

Liabilities & Capital *(expressed in EUR)*	*Notes*	2010	2009
CURRENT LIABILITIES			
Payables to partners related to projects		589,209	263,390
Other payables and accrued expenses		2,882,574	1,237,251
Deferred income		6,791,274	5,112,172
Provisions	*5*	248,614	229,750
Total current liabilities		**10,511,671**	**6,842,563**
CAPITAL OF THE ORGANISATION			
Paid-in capital		32,510	32,510
Restricted operating funds	*6*	205,155	151,084
Internally generated unrestricted funds		9,951,688	9,454,049
Total capital of the organisation		**10,189,353**	**9,637,643**
TOTAL		**20,701,024**	**16,480,206**

STATEMENT OF OPERATIONS

for the year ended December 31, 2010 *(with 2009 comparative figures)*

(expressed in EUR)	*Notes*	2010	2009
INCOME			
Govern. & public int. organiz. unrestricted		7,769,967	7,517,316
Govern. & public int. organiz. restricted		4,119,969	4,250,944
Total public institutional funding		**11,889,936**	**11,768,260**
Private foundations, corporations, and individuals, unrestricted		36,689	196,233
Private foundations, corporations, and individuals, restricted		9,322,111	5,659,380
Royalties on drug sales	*6*	54,071	151,084
Total private resources		**9,412,871**	**6,006,697**
Resources from founders			
Médecins Sans Frontières, unrestricted		3,165,075	3,392,300
Médecins Sans Frontières, restricted		465,000	100,000
Indian Council for Medical Research, unrestricted		1,266	
Total resources from Founders		**3,631,341**	**3,492,300**
Total income	*7*	**24,934,148**	**21,267,257**
SOCIAL MISSION EXPENDITURE			
Research & development expenditure	*8*		
Research & development coordination and supervision		1,687,659	1,629,330
Human African trypanosomiasis projects		7,308,575	5,998,437
Leishmaniasis projects		4,678,495	4,066,409
Chagas disease projects		2,356,588	1,396,556
Other projects		2,217,335	2,448,972
Portofolio building		1,561,311	854,121
Total research & development expenditure		**19,809,963**	**16,393,825**
Strengthening capacities	*9*	**1,414,184**	**1,322,228**
Advocacy expenses	*10*	**941,318**	**1,193,540**
Total social mission expenditure		**22,165,465**	**18,909,593**
NON-SOCIAL MISSION EXPENDITURE			
Fundraising	*10*	1,174,883	890,154
General and administration	*10*	1,538,043	1,308,822
Total non-social mission expenditure		**2,712,926**	**2,198,976**
Total expenditure		**24,878,391**	**21,108,569**
Operating surplus		55,757	158,688
OTHER INCOME (EXPENSES)			
Financial income, net		30,453	58,909
Exchange gain (loss), net		381,468	203,751
Other income		84,033	69,215
Total other income, net		**495,954**	**331,875**
Net surplus for the year prior to allocations		551,711	490,563
Allocation to restricted operating funds	*6*	(54,071)	(151,084)
Allocation to internally gener. unrestricted funds		(497,640)	(339,479)
Net surplus for the year after allocations		**-**	**-**

FUNDS FLOW STATEMENT

for the year ended December 31, 2010 *(with 2009 comparative figures)*

(expressed in EUR)	2010	2009
FUNDS FLOW FROM OPERATIONS		
Net surplus for the year, unrestricted	497,640	339,479
Net surplus for the year, restricted	54,071	151,084
Depreciation of fixed assets	88,815	79,977
Increase (decrease) in provisions	18,863	(53,354)
(Increase) decrease in stocks	(46,041)	(35,000)
(Increase) decrease in advances	324,231	(169,525)
(Increase) decrease in receivables from donors	(1,245,615)	(572,305)
(Increase) decrease in Founders and other receivables	1,059	116,916
(Increase) decrease in prepaid expenses	1,693	(31,231)
Increase (decrease) in payables to partners related to projects	325,819	185,502
Increase (decrease) in other payables and accrued expenses	1,645,323	(769,211)
Increase (decrease) in deferred income	1,679,102	143,480
Funds flow from operations	**3,344,960**	**(614,188)**
FUNDS FLOW FROM INVESTING ACTIVITIES		
(Increase) decrease of investments in tangible fixed assets	(21,700)	(82,489)
(Increase) decrease in bank guarantee deposits	(5,050)	2,287
Funds flow from investing activities	**(26,750)**	**(80,202)**
FUNDS FLOW FROM FINANCING ACTIVITIES	-	-
Cash increase (decrease)	3,318,210	(694,390)
Cash and cash equivalents - beginning of year	13,768,800	14,463,190
Cash and cash equivalents - end of year	**17,087,010**	**13,768,800**

STATEMENT OF CHANGES IN CAPITAL

Internally generated funds *(expressed in EUR)*	Opening balance	Allocation	Internal fund transfers	Closing balance
Paid-in capital	32,510	-	-	32,510
Surplus for the year	-	551,711	(551,711)	-
Restricted operating funds	151,084	-	54,071	205,155
Internally generated unrestricted funds	9,454,049	-	497,640	9,951,689
Capital of the organisation	9,637,643	551,711	-	10,189,354

NOTES TO THE FINANCIAL STATEMENT FOR THE YEAR ENDED 31 DECEMBER 2010

1. GENERAL INFORMATION

a) Legal aspects

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

With its headquarters in Geneva, DND*i* aims to:

a) stimulate and support research and development of drugs, as well as vaccines and diagnostics for neglected diseases;
b) seek equitable access and development of new drugs, to encourage the production of known effective drugs, diagnostic methods and/or vaccines for neglected diseases;
c) adapt new treatments for neglected diseases, to meet patients, needs, as well as to meet the requirements of delivery and production capacity in developing countries;
d) raise awareness of the need to research and develop drugs for neglected diseases.

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

b) Income tax

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

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

DND*i* has seven Regional Support Offices and Affiliates to help identify patients, needs, support heads of disease programmes, identify and support regional partners, and undertake regional advocacy work for DND*i*. The RSOs, together with regional networks, ensure the participation of disease-endemic countries notably in clinical and post-clinical activities and foster South-South collaboration. In addition, RSOs can explore fundraising opportunities in their regions. Their tasks and duties are further developed in the DND*i* Business Plan.

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

As of December 2010, DND*i* has established legal entities in Kenya (in 2006), in Brazil (in 2008) and in India (2009) in the form of branches. The fourth DND*i* RSO is in Penang, Malaysia, and is in the process of being registered as a branch. Additionally DND*i* has one Project Support Office in the Democratic Republic of Congo. RSO accounting is fully incorporated into DND*i* accounts.

In June 2009, the Board of Directors approved the creation of a Regional Support Office in Japan, under the form of a 'specified non-profit organization,, a legal entity registered with the city of Tokyo. DND*i* Japan was established in November 2009.

The aim of DND*i* Japan is exclusively charitable, and includes but shall not be limited to: assisting people in developing countries who are suffering from tropical diseases and contributing to the health and welfare of people in developing countries by supporting activities of the Drugs for Neglected Diseases *initiative* (DND*i*) by promoting medical treatment; encouraging scientific research; liaising, advising, and assisting bodies performing these activities. The DND*i* Japan Board of Directors met for the first time in February 2010.

DND*i* Japan presents an annual report comprising the financial statements of the calendar year. This report is certified by an independent Certified Public Accounting (CPA) firm selected by its Board of Directors. The firm auditing DND*i* Japan accounts as of 2010 is Deloitte Touche Tohmatsu LLC, Tokyo, Japan.

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

DND*i* Japan's 2010 financial position as of 31 December 2010 is the following:

- Total liabilities and net assets: JPY 2,801,553;
- Total revenue: JPY 6,036,900 which represents a grant from DND*i* to DND*i* Japan;
- Of this grant, JPY 2,506,168 is deferred to 2011 and JPY 150,000 was considered as net assets and carried forward for 2011.

Affiliate: Drugs for Neglected Diseases *initiative* North America, Inc., a Delaware not-for-profit corporation exempt from U.S. Federal income taxation pursuant to Section 501(c) (3) of the U.S. Internal Revenue Code (DND*i* NA), was established in February 2007. This affiliate is based in New York City, New York, USA and operates under the Direction of the DND*i* NA 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* (DND*i*), such as conferring grants to support programmes, projects, and activities to stimulate and support research and development of drugs for neglected .../

/... diseases and raising awareness in the region about the need for increased research and development for neglected diseases.

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

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

DND*i* NA's 2010 financial position as of 31 December 2010 is the following:

- Total liabilities and net assets: USD 106,760;
- Total revenue and other support: USD 580,750, of which a total grant from DND*i* to DND*i* NA, amounting to USD 524,407 and contributions (unrestricted) from twenty individuals and one private foundation (restricted) ranging from USD 25 to 25,000 for a total of USD 56,250;
- Total expenses: USD 601,560, and an excess of the expenses over revenue (change of net assets) of USD 20,810.

In June 2009, the Board of Directors approved the change in legal status of DND*i* in Brazil from a branch to a not-for-profit legal entity under the form of Associação de direito privado, sem fins lucrativos e de fins não econômicos, DND*i* Latin America. The process was terminated during the first semester 2010.

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

2. SIGNIFICANT ACCOUNTING POLICIES

a) Statement of compliance

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

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

These financial statements present all activities by the Foundation. A list of in-kind income and expenditures is disclosed in Note 12.

b) Basis of preparation

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

c) Social mission expenditure

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

d) Functional currency

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

e) Foreign currency translation

Transactions in currencies other than the entity's measurement and reporting currency (EUR) are converted at the average monthly rates 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:

	2010	2009
USD	0.7496	0.6943
CHF	0.8006	0.6725
GBP	1.1597	1.1184
100 CDF	0.0801	0.0740
100 INR	1.6733	1.4862
100 KES	0.9287	0.9213
100 JPY	0.9210	0.7525
100 BRL	45.0999	39.8454

f) Income

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

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

Other donations are recorded on a cash basis.

g) Funding committed to projects

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

a) according to a financial report presenting expenditures incurred during the year on an accrual basis; or
b) if financial reports are unavailable as per the deadline of the 15th of March of the following year, an estimated amount

is calculated on a *prorata temporis* basis, based on the time between the contract signing date and 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) Expenditure incurred for projects and activities

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

i) Credit risk, cash-flow management

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

j) Tangible fixed assets

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

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

Office fittings and equipment	20%
IT equipment	33%

k) Bank guarantee deposits

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

l) Provisions

A provision is recognized on the balance sheet when the organization 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 organization

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

3. DRUG INVENTORY

During the fourth quarter of 2010, DND*i* purchased a total of 8,750 vials of SSG of an estimated value of EUR 51,000 from IDA Foundation, a Dutch not-for-profit drug seller, to be used in planned pharmaco-vigilance programmes for SSG, plus paromomycin combinations and patients, treatments at six clinical trial sites, mainly hospitals, in four countries: Ethiopia, Kenya, Sudan, and Uganda. In addition, stocks of AmBisome®, miltefosine, paromomycin, and glutamine, of an estimated value of EUR 30,041, were available at the clinical trial sites in Ethiopia, Kenya, Sudan, Uganda, as well as at a clinical trial site in Bangladesh. These stocks are stored at the clinical trial sites in the different countries.

4. TANGIBLE FIXED ASSETS, net

(expressed in EUR)	Computer Equipment	Office fittings & Installations	Office Equipment	Total
Net carrying amounts 1.1.2009	**29,357**	**56,130**	**65,169**	**150,656**
Gross values of cost				
Beginning of the period 1.1.2009	169,300	115,905	106,050	391,225
Additions	40,698	10,580	31,211	82,489
Disposals	-	-	-	-
End of the period 31.12.2009	209,998	126,485	137,261	473,744
Cumulated amortisation				
Beginning of the period 1.1.2009	(139,943)	(59,776)	(40,882)	(240,600)
Systematic amortisation	(35,869)	(18,548)	(25,560)	(79,977)
End of the period 31.12.2009	(175,812)	(78,324)	(66,441)	(320,577)
Net carrying amounts 31.12.2009	**34,186**	**48,162**	**70,820**	**153,168**
Net carrying amounts 1.1.2010	**34,186**	**48,162**	**70,820**	**153,168**
Gross values of cost				
Beginning of the period 1.1.2010	209,998	126,485	137,261	473,744
Additions	16,358	5,342	-	21,700
Disposals	-	-	-	
End of the period 31.12.2010	226,356	131,827	137,261	495,444
Cumulated amortisation				
Beginning of the period 1.1.2010	(175,812)	(78,324)	(66,441)	(320,577)
Depreciation	(36,616)	(22,996)	(29,204)	(88,816)
End of the period 31.12.2010	(212,428)	(101,320)	(95,645)	(409,393)
Net carrying amounts 31.12.2010	**13,928**	**30,507**	**41,616**	**86,051**

5. PROVISIONS

(expressed in EUR)	Provision for taxes	Provision for HR expenses (holidays not taken)	Provision for running expenses (other)	Total
Carrying amount as per 1.1.2009	**139,613**	**73,534**	**69,957**	**283,104**
Creation	24,507	62,985	23,624	111,116
Utilization	(23,712)	(70,801)	(69,957)	(164,470)
Reversal	-	-	-	-
Carrying period as per 31.12.2009	**140,408**	**65,718**	**23,624**	**229,750**
Carrying period as per 1.1.2010	**140,408**	**65,718**	**23,624**	**229,750**
Creation	42,963	75,624	14,588	133,175
Utilization	(24,507)	(62,985)	(26,819)	(114,311)
Reversal	-	-	-	-
Carrying period as per 31.12.2010	**158,864**	**78,357**	**11,393**	**248,614**

6. ROYALTIES

In December 2004, DND*i* signed an agreement with sanofi-aventis pertaining to the implementation of co-formulation treatments against malaria developed originally by DND*i* together with sanofi-aventis (ASAQ). Article VI of the contract states that 3% royalties resulting from net sales of this drug whose brand name is CoArsucam® to the private sector in developing countries are to be paid to DND*i*.
DND*i* has decided to allocate this money to supporting pharmacovigilance projects or activities such as the implementation of ASAQ treatment in developing countries, notably in Africa.
Hence, DND*i* decided to allocate the total amount of the 3% royalties on the 2009 sales of CoArsucam® amounting to EUR 54,071 to the *Restricted operating fund*, which will be used for collaborative projects with various partners for an observational study at the district level in Africa. The total amount of this restricted fund amounted to EUR 205,155 as per 31 December 2010.

7. INCOME

a) Cumulative donations committed to DND*i* and/or received by 2010 (in EUR):

DONORS		Total Commitment in currencies*	Total Commitment in EUR	As per Statement of Operations 2010 in EUR	To be used after 2010 in EUR
Médecins Sans Frontières	EUR	43,031,228	43,031,228	3,630,075	10,908,109
UK Government DFID**	GBP	25,881,529	31,507,947	6,220,601	9,942,138
Bill & Melinda Gates Foundation	USD	42,229,285	30,864,728	8,983,751	12,681,647
Dutch Government DGIS	EUR	16,975,000	16,975,000	68,000	14,000,000
Spanish Government AECID	EUR	10,000,000	10,000,000	2,500,000	0
French Government MAEE/AFD***	EUR	9,255,000	9,255,000	1,024,801	585,253
Swiss Government SDC	CHF	4,120,000	3,164,963	1,467,044	1,620,874
Medicor Foundation	EUR	1,360,245	1,360,245	305,305	0
European Union FP5-6-7, EDCTP	EUR	1,216,134	1,216,134	90,411	518,126
USA Government NIH/NIAID	USD	1,600,659	1,186,821	208,583	397,078
Republic and Canton of Geneva	CHF	1,600,000	1,111,777	149,328	320,240
German Government GTZ	EUR	1,000,000	1,000,000	0	0
UBS Optimus Foundation	CHF	1,250,000	791,045	0	0
Sandoz Family Foundation	CHF	500,000	308,700	0	0
Various private donors	EUR	247,200	247,200	71,011	4,659
Sasakawa Peace Foundation	EUR	241,336	241,336	0	0
Global Fund (AMFM)	EUR	221,961	221,961	161,168	60,793
Tuscany Region	EUR	200,000	200,000	0	0
Various other donor(s)	EUR	170,060	170,060	0	0
Starr International Foundation	USD	200,000	141,388	0	0
Anonymous donation	CHF	201,229	138,108	0	0
Leopold Bachmann Foundation	EUR	91,900	91,900	0	0
TOTAL DONATIONS (€)*			**153,225,541**	**24,880,078**	**51,038,917**

* Exchange rates used for Total Commitment in EUR, and As per Statement of Operations 2010, are real exchange rates following the DND*i* exchange rate policy. Exchange rates used for To be used after 2010, appear in EUR at the USD/EUR, CHF/EUR, and GBP/EUR exchange rates as per 31 December 2010 (see note 2). Total Donations, therefore yield an approximate value as exchange rates will vary over time.

** The UK Government, DFID, funded DND*i* with 3 grants. A first unrestricted grant of GBP 6,500,000 in 2006 for the period 2006–2008, a second unrestricted grant of GBP 18,000,000 in 2009 for the period 2009–2013 and a third restricted grant of GBP 1,381,529 in 2010 for the period 2010–2011, of which GBP 808,504 (EUR 950,634) was used in 2010 and GBP 491,496 to be used before 31 March 2011.

*** The French Government, Ministry of Foreign and European Affairs, funded DND*i* with 4 grants. From the MAEE: EUR,5,955,000 in April 2007 for the period 2007-2010; from the MAEE: EUR 1,300,000 in December 2009 for the period 2009-2010; from the AFD: EUR 1,500,000 in June 2006 for the period 2006-2008, and from the AFD, EUR 500,000 in December 2009 for the period 2009–2010.

b) Funding per project (restricted and unrestricted):

		UK Government DFID[1] (Unrestricted)	French Government MAEE & AFD[2] (Restricted)	Spanish Government AECID (Unrestricted)	Dutch Government DGIS (Restricted)	United States Government NIH[3] (Restricted)	Switzerland SDC (Unrestricted)
CLINICAL& POST-CLINICAL	FACT (ASAQ & ASMQ) for Malaria	1,785,401	179,844	18,598	56,968		
	Nifurtimox + Eflornithine (NECT) for HAT	555					141,348
	Paromomycin for VL						118,071
	Combination therapy for VL (Asia, Africa, Latin America)	755,321	291,372	133,521			517,678
	Fexinidazole for HAT						
	Azole E1224 for Chagas	15,003		447,865			
	Pediatric Benznidazole for Chagas	83,974		4,814			
PRE-CLINICAL	Alternative formulation of Amphotericin B for VL					181,302	
	Oxaborole for HAT						
	Nitroimidazole for VL						
	Drug combination for Chagas & VL	6,934					
DISCOVERY	VL Consortium Lead Optimization						
	Chagas Consortium Lead Optimization	254,382	68,688	612,087			
	HAT Consortium Lead Optimization						
	Discovery Projects, (Dundee, GSK, IPK,...)	814,066	332,256	33,090			259,906
	Exploratory activities	43,947		20,146			
	R&D Coordination, Supervision costs	514,064		310,442	11,032	16,231	92,481
	HAT LEAP & Chagas Platforms	153,488	87,774	108,978			107,180
	Other Strengthening Capacity activities	296,321	34,532	275,372			3,943
	Advocacy	531,920	7,244	223,202			94,554
	Fundraising	397,753		84,548		317	123,921
	General Management	567,472	23,091	227,337		10,733	7,962
	Restricted funds						
	Year-end result						
	TOTAL GRANTS ONLY	**6,220,601**	**1,024,801**	**2,500,000**	**68,000**	**208,583**	**1,467,044**

(1) DFID grants include: 1) An unrestricted grant of 5,269,967 € and 2) A restricted grant of 950,634 € for Malaria projects (Oct-Dec 2010).
(2) MAEE & AFD: MAEE grants considered in 2010 cover 2 different grants, 1) A first grant for various clinical projects for HAT and Leish (Jan-Apr 2010 - 444,013 €) and 2) A second grant for discovery projects (Jan-Dec 2010 - 400,944 €).
(3) NIH: the grant considered in 2010 is part of a multi year grant. Year 3 = January - August 2010 with a no cost extension for the period September - December 2010.
(4) B&M Gates Foundation: two grants in 2010: 1) A grant pertaining to Lead Optimization for HAT & VL pre-clinical projects covering the period January - December 2010 and 2) A grant related to Fexinidazole project for the same period.

Switzerland Republic and Canton of Geneva (Restricted)	AMM - Global Found (Restricted)	European Union EU FP7 (Restricted)	European Union EDCTP (Restricted)	Bill & Melinda Gates Foundation[4] (Restricted)	Médecins S. Frontières[5] (Restricted/ Unrestricted)	Medicor Foundation (Restricted)	Private Foundations & Other Revenue[6] (Restricted/ Unrestricted)	Royalties on drug sales[7]	TOTAL
	148,360		11,545		8,974		7,645		2,217,335
142,214					205,241		10,709		500,066
					5,516		10,316		133,903
					694,391	305,305	15,950		2,713,538
				2,662,362	216				2,662,577
					4,192				467,060
					300,000		15,094		403,882
									181,302
				873,837					873,837
				397,432					397,432
					11,975				18,909
				1,179,856					1,179,856
					488,830		108		1,424,095
				3,272,096					3,272,096
				5,535	29,581		2,024		1,476,458
					135,866				199,959
				125,359	616,939		1,111		1,687,659
7,115		78,866			151,494		2,674		697,569
					106,447				716,615
					80,704		3,694		941,318
				35,683	532,661				1,174,883
	12,808			431,592	257,049				1,538,044
								54,071	54,071
							1,685		1,685
149,328	**161,168**	**78,866**	**11,545**	**8,983,751**	**3,630,075**	**305,305**	**71,010**	**54,071**	**24,934,148**

(5) MSF donation comprises 1 unrestricted grant for 3,165,075 € and 2 restricted grant: 1) A grant for the 'Pediatric Benznidazole' project for 300,000 € and 2) A grant related to the assessment of new diseases for 165'000 €.
(6) Private Foundations: Fondation Pro Victimis (10,316 €), Fondation Pictet (6,831 €), Arpe Foundation (7,645 €), Buck Foundation (15,094 €).
(7) Royalties from Sanofi-Aventis for 54,071 € earmarked to Monitoring study on pharmacovigilance of ASAQ (see note 6).

8. R&D PROJECT-RELATED EXPENDITURE

Recognized in		2010	2009
CLINICAL/POST-REGISTRATION PROJECTS:			
Artesunate+Amodiaquine for Malaria[1]		678,703	932,861
Artesunate+Mefloquine for Malaria[2]		1,538,633	1,516,111
Nifurtimox - Eflornithine co-administration for stage 2 T.b.gambiense HAT[3]		500,066	716,471
Fexinidazole for HAT[4]		2,662,577	554,522
Combination therapy for VL in Africa[5]			
- Paromomycin for VL		133,903	978,751
- AmBisome® for VL		257,191	472,324
- Miltefosine for VL		1,554,349	
Combination therapy for VL in Asia, Latin America[6]		901,998	698,709
Paediatric Benznidazole for Chagas[7]		403,882	224,279
Azole E1224 for Chagas[8]		467,060	82,487
Total Clinical/Post-Registration Projects		**9,098,362**	**6,176,516**
PRE-CLINICAL PROJECTS:			
Fexinidazole for HAT[4]	(Clinical phase I as of Sept. 2009)	0	725,400
Alternative formulations of Amphotericin B for VL[9]		181,302	212,429
Drug combination for Chagas[10]		18,909	140,643
Buparvaquone for VL	(terminated in 2009)	0	67,111
Oxaborole for HAT[11]		873,837	0
Nitroimidazole for VL[12]		397,432	0
Nitroimidazole backup for HAT		34,620	
Total Pre-clinical Projects		**1,506,100**	**1,145,582**
DISCOVERY (SELECTION & OPTIMIZATION) PROJECTS:			
Kitasato screening for Trypanosomiasis	(terminated in 2009)	0	137,198
Nitroimidazoles for HAT	(Pre-clinical as of 2010)	0	146,027
Screening Resources (Dundee, Eskitis, IPK)13		1,139,512	641,156
Reference Screening Centers (STPH, LSHTM, Antwerp)[14]		336,945	373,276
HAT Consortium Lead Optimization[15]		3,272,096	3,745,776
VL Consortium Lead Optimization[16]		1,179,856	1,114,998
Chagas Consortium Lead Optimization[17]		1,424,095	844,411
Total Discovery Projects		**7,352,504**	**7,002,843**
OTHER EXPLORATORY ACTIVITIES TO BUILD THE PORTFOLIO:			
Other exploratory activities[18]		165,338	439,554
Total Exploratory projects		**165,338**	**439,554**
PROJECT-RELATED VARIABLE EXPENDITURE			
- Coordination & Supervision[19]		1,687,659	1,629,330
Total of Projects related expenditure		**19,809,963**	**16,393,825**

See notes on following page

Main R&D partners & sub-contractors:

1. Sanofi-aventis, France / Institute of Research for Development (IRD), Senegal / Ellipse Pharmaceuticals, France / Médecins Sans Frontières Logistiques, France / Epicentre, France / KATH, Ghana / OTECI, France / AEDES, Belgium / Zenufa, Tanzania.
2. Farmanguinhos, Brazil / University Sains Malaysia / Cipla, India / ICMR, India; National Institute of Medical Research, Tanzania; Centre Hospitalier Universitaire Vaudois (CHUV) , Switzerland / Ministry of Health, Cambodia / Catalent, UK / TDR, WHO / CIPLA, India / CNRPF, Burkina Faso / KEMRI, Kenya.
3. Epicentre, France / Médecins Sans Frontières (MSF) / the HAT National Control Programmes, Democratic Republic of the Congo / Swiss Tropical and Public Health Institute (STPH); HAT Platform partners (PNLTH, the Republic of Congo / TMRI Sudan / ICCT, Angola / COCTU, Uganda / PNLTHA Centrafrique / PNLTHA Chad); RCTS, France.
4. Sanofi-Aventis, France / Swiss Tropical and Public Health Institute / HAT Platform partners (see point 3 above) / Aptuit, UK / Accelera, Italy / SGS, Belgium and France / Epicentre, France / Xcentipharm, France / Covance, UK.
5. Kenya Medical Research Institute, Kenya / Institute of Endemic Diseases (IED) and University of Khartoum, Sudan / Addis Ababa University, Ethiopia / Gondar University, Ethiopia / University of Makarere, Uganda / Amudat Hopital, Uganda / LSHTM, UK / ASK (AMC, Slotervaart Hospital, KIT), The Netherlands / GILEAD, Irland / IDA Foundation, The Netherlands.
6. Universidade de Brasilia (UNB), Brazil / CNPQ, Brazil / GVK, India / Sitaram Kala Azar Medical center, India / RMRIMS (ICMR), India / ICDDR, Bangladesh / SHSMC, Bangladesh / SK Hospital Bangladesh.
7. Pharmaceutical Laboratory of Pernambuco State (LAFEPE), Brazil / Centro Nacional de Diagnostico e Investigacion de Endemo-epidemias (CeNDIE) / Ministry of Health, Argentina / LAT Research, Argentina / FITEC, Argentina.
8. Eisai, Japan / Cardinal System, France / CRESIB, Spain / CEADES, Bolivia / CONICET, Argentina.
9. Federal University of Ouro Preto, Brazil / Polytherics, UK / London School of Pharmacy, UK / LSHTM, UK / BioDelivery Sciences International (BDSI), USA.
10. Federal University of Ouro Preto, Brazil.
11. Scynexis, USA / Advinus Therapeutics, India / Drugabilis, France / Penn Pharma, UK.
12. Global Alliance for TB, USA / Advinus Therapeutics, India.
13. Eskitis Institut at Griffith University, Australia / Institut Pasteur Korea, South Korea / University of Washington, USA / STPH, Switzerland / GlaxoSmith-Kline (GSK-Tres Cantos), Spain / University of Dundee, UK.
14. STPH, Switzerland / LSHTM, UK / Institute of Tropical Medicine, Antwerp, Belgium.
15. SCYNEXIS Inc, USA / Pace University, USA.
16. Advinus Therapeutics, India /CDRI, India / LSHTM, UK / Drugabilis, France / Anacor, USA.
17. Epichem Pty Ltd, Australia / Institut Pasteur Korea, South Korea / Murdoch University, Australia / Monash University, CDCO, Australia.
18. Anacor, USA / Eskitis (Griffith University), Australia / Institut Pasteur Korea, South Korea / Institut de Recherche pour le Développement (IRD), France / GlaxoSmithKline (GSK-Tres Cantos), Spain; LSHTM, UK.
19. R&D Coordination & Supervision.

	2010	2009
Coordination	888,695	907,658
Scientific Advisory Commission	99,209	94,504
Business Development	377,565	253,090
Japan representation office	206,835	188,793
Research: IP & Regulatory affairs	115,355	185,285
Total	1,687,659	1,629,330

Consultants involved in R&D projects:

Amuasi John; Barros Gonçalves Luciana; Bray Michael; Bruning Karin; Clarck Jeffrey; Crawley Peter; Dormeyer Mathias; Dorre Daniel; Fernandes Jaime; Ghabri Salah; Grislain Luc; Hailu Asrat; Hudson Alan; Mac Cerri; Mazue Guy; Mechali Daniel; Molyneux David; Moody Anthony; Mudawi Ahmed; Pierron Evelyne; Pinheiro Eloan; R.K. Singh; Sasella Daniela; Scherrer Bruno; Schijman Alejandro; Seltzer Jonathan; Smithuis Frank; Sosa-Estani Sergio; Taylor Bob; Thenot Jean-Paul; Tweats David; Vaillant Michel; Von Geldern Thomas; Yardley Vanessa; Zijlstra Ed; Zwang Julien.

Additional major partners involved in DND*i* R&D projects without financial implications:

Fiocruz, Brazil; Genzyme, USA; Hospital de Ninos Ricardo Gutierrez, Argentina; Institut René Rachou, Brazil; Institute for OneWorld Health, USA; Medical Malaria Venture MMV, Switzerland; Novartis Institute for Tropical Diseases NITD, Singapore; Pfizer, USA; University of Auckland, New Zealand; Universidade Federal do Piaui, UFP, Brazil; Universidade Federal de Tocantins, Brazil.

9. STRENGTHENING CAPACITIES EXPENDITURE

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

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

(expressed in EUR)	2010	2009
Regional Support Offices: Brazil, India, Kenya, Malaysia	716,615	596,295
For VL combo, Ward Construction & Equipment in Ethiopia and in Sudan	78,654	183,389
Leishmaniasis East African Platform (LEAP)	155,355	234,824
Human African Trypanosmiasis (HAT) Platform	207,075	214,460
Chagas Platform	118,526	44,752
LeishDNAvax Consortium Agreement	99,183	26,262
Pan-Asian Natural Substances Network	38,776	22,246
TOTAL	1,414,184	1,322,228

Consultants: Vanessa Daniel-Boscoraj, Gan Eng Seong, Michel Lotrowska, Christina Zackiewicz.

HAT Platform: WHO, Ministries of Health and National Control Programmes of the major endemic countries (Angola, Democratic Republic of the Congo, Republic of Congo, Sudan, Uganda, Chad, and the Central African Republic), Swiss Tropical and Public Health Institute, Médecins Sans Frontières, DND*i*.

Leishmaniasis East African Platform: University of Khartoum, Sudan; Addis Abeba University, Ethiopia; Makerere University, Uganda; Kenya Medical Research Institute; Ministries of Health of Kenya, Uganda, Ethiopia, and Sudan; London School of Hygiene and Tropical Medicine, UK; Médecins Sans Frontières; ANC-Slotervaart University, The Netherlands; i+ Solutions, The Netherlands; DND*i*.

10. ADVOCACY & FUNDRAISING AND GENERAL & ADMINISTRATION EXPENSES

	ADVOCACY		FUNDRAISING		GENERAL & ADMINISTRATION	
	2010	2009	2010	2009	2010	2009
Human resources	487,445	573,056	919,307	678,534	938,799	829,420
Office charges	47,950	40,422	66,778	52,118	95,132	69,491
Travel expenses	29,072	55,230	46,559	54,307	103,848	80,011
Administration	31,820	36,727	92,905	56,778	160,719	99,606
IT & telecommunications	18,242	40,272	14,644	16,077	177,921	132,305
Communication	301,518	433,942	24,032	20,592	37,730	74,522
Depreciation	11,546	12,796	10,658	9,597	23,092	21,594
Exceptional expenses	13,725	1,095	0	2,151	802	1,873
TOTAL	941,318	1,193,540	1,174,883	890,154	1,538,043	1,308,822

Consultants: Samantha Bolton, Pernille Brodhal, Nina Holzhauer, Karly Louie, Rachel Kiddle-Monroe, Ivan Maillet, Masako Matsudaira, Thomas Saugnac, Catrin Schulte Hillen, Daniel Stein, Marta Lucas Subirats, Ulrike Von Pilar, Lina Walid Abu Rous.

11. INDEMNITIES & REMUNERATIONS GIVEN TO DIRECTORS

All members of the Board are appointed on a voluntary basis. The Board members have not received any remuneration for their mandate in 2010, nor in 2009.

12. VALUATION OF IN-KIND CONTRIBUTIONS

DND*i* operations are funded through financial contributions and donations. In addition to financial funding, generous partners – private companies, academic groups, and individuals – provide DND*i* with goods and services at zero cost as gifts-in-kind (see note 2o, DND*i* In-Kind Policy). DND*i* aims at reflecting this increasing contribution in the 2010 financial statements in order to present a comprehensive picture of its activities. The in-kind contribution of DND*i*'s partners doubled between 2009 and 2010, from EUR 1.1 million in 2009 to EUR 2.3 million in 2010.

Gifts-in-kind in EUR evaluated for the year 2010 per category and per project:

	Staff Scientific	Staff non-Scientific	R&D Services	Office, furniture & admin.	TOTAL
FACT	21,416	14,559			35,974
NECT Field			52,800		52,800
VL-Combo	160,893		131,708		292,601
Fexinidazole	450,000		57,200		507,200
Azole E1224 for Chagas	547,602				547,602
Drug Combination for Chagas	28,196				28,196
Chagas Lead Optimization	203,239	34,642	107,926	34,642	380,448
Early Discovery	154,568		77,284		231,852
Regional Support Offices				55,985	55,985
R&D Coordination	136,291	8,789			145,079
TOTAL	1,702,204	57,989	426,917	90,627	2,277,737

Main in-kind contributors: Expert C. Brunger, Japan; Volunteers for Administrative work in Tokyo; ICMR, India; Sains University, Malaysia; Institut Pasteur Korea (IPK); sanofi-aventis, France; CNPq, Brazil; WHO, Switzerland; Gilead, Irland; Paladin, Canada; Eisai, Japan; Expert P. Olliaro/TDR Switzerland; Epichem Pty Ltd, Australia; Monash University, Australia; European Medicine Agency, UK; GSK, France; Kyorin University, Japan; University Federal Ouro Preto, Brazil.

13. ASSETS PLEDGED AS GUARANTEE FOR COMMITMENTS

At year-end, a bank of the Foundation had provided two rental letters of guarantee of CHF 70,000 (EUR 56,042) and CHF 20,000 (EUR 16,012) in favour of a third party. Cash for an equivalent amount is pledged at the corresponding bank.

Report of the statutory auditor

Deloitte.

Report of the statutory auditor

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

Report of the statutory auditor on the financial statements

As statutory auditor, we have audited the accompanying financial statements of Drugs for Neglected Diseases initiative (DNDi), which comprise the balance sheet, statement of operations, funds flow statement, statement of changes in capital, notes and performance report for the year ended December 31, 2010. In accordance with Swiss GAAP RPC 21, the content of the performance report is not audited.

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

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

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

Opinion
In our opinion, the financial statements for the year ended December 31, 2010 give a true and fair view of the financial position, the results of operations and the cash flows in accordance with Swiss GAAP RPC and comply with Swiss law as well as with the charter of foundation and regulations.

Audit. Fiscalité. Conseil. Corporate Finance.

Deloitte.

Report on other legal requirements

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

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

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

Deloitte SA

Peter Quigley
Licensed audit expert
Auditor in charge

Jürg Gehring
Licensed audit expert

Geneva, May 9, 2011
PBO/JGE/rshe

Enclosures : Financial statements (balance sheet, statement of operations, funds flow statement, statement of changes in capital, notes and performance report)

Photos credits: cover : Anita Khemka-DND*i*; 4: João Roberto Ripper-DND*i*; 7: Anita Khemka-DND*i*; 8: João Roberto Ripper-DND*i*; 9: Anita Khemka-DND*i*; 12: Alex Mansour-Farmanguinhos; 15 : Central Drug Research Institute; 16-17: Institut Pasteur Korea; 18-19: Benoît Marquet-DND*i*; 25: Anita Khemka-DND*i*; 26-29-30-32-33: João Roberto Ripper-DND*i*; 32: Lafepe; 38: Anita Khemka-DND*i*; 42: Mira Shibaru-MMV; 50: João Roberto Ripper-DND*i*

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Best science
for the most neglected

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