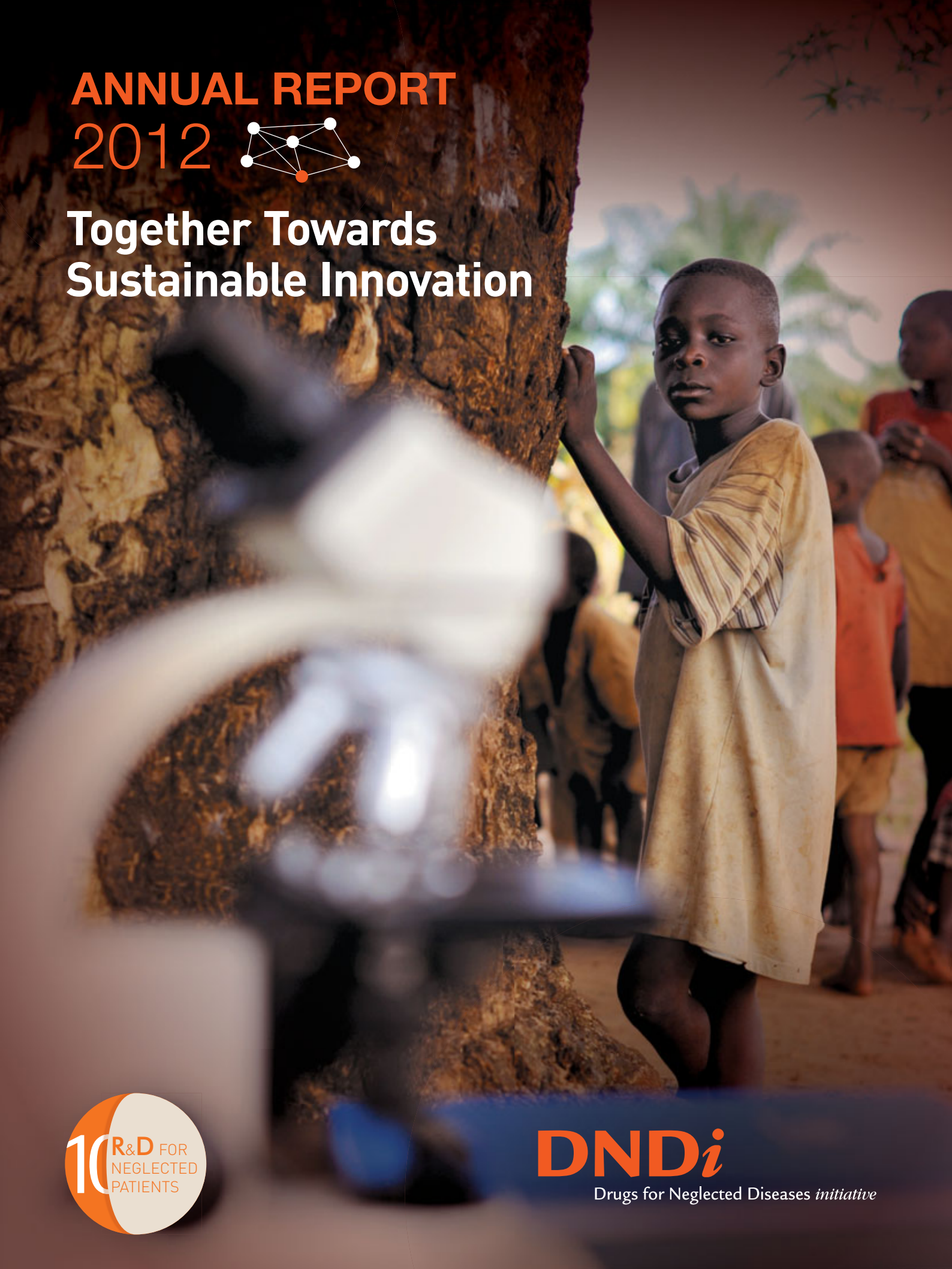
ANNUAL REPORT 2012

Together Towards Sustainable Innovation



10 R&D FOR NEGLECTED PATIENTS

DNDi

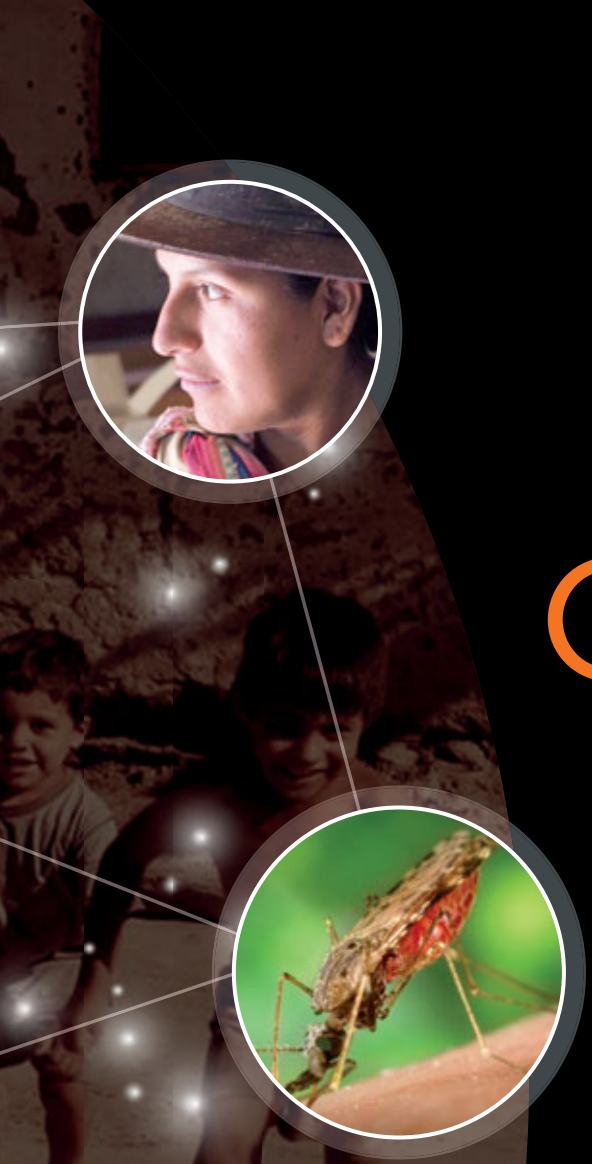
Drugs for Neglected Diseases *initiative*

DNDi
Drugs for Neglected Diseases *initiative*

Connect to Fight Neglect

ONE KEY GOAL, ONE PILL

A new short film explains DND*i* in a nutshell: our mission, how we partner to deliver new treatments, and what we have achieved in the past 10 years.



www.connect2fightneglect.org

DND*i* MARKS ITS 10-YEAR ANNIVERSARY WITH A SPECIAL WEBSITE:

CONNECT TO FIGHT NEGLECT

'Connect to Fight Neglect' is an interactive multimedia portal intended to connect neglected-disease actors worldwide, from patients to policy makers, by offering a forum to voice opinions and perspectives via short videos, photo essays, or opinion pieces.

'Connect to Fight Neglect' is a call to everyone involved, directly or indirectly, in neglected-disease R&D to step up and speak out about the successes, failures, needs, and solutions for innovation and access to much-needed health tools for neglected patients.

Objectives

- Highlight the diseases and issues DND*i* and partners are working on
- Give a voice to patients, healthcare workers, researchers, partners, policy makers, donors, activists, etc.
- Allow for critical reflection
- Highlight the many partnerships in which DND*i* is engaged
- Engage new stakeholders

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.

DND*i*

Drugs for Neglected Diseases *initiative*

The Drugs for Neglected Diseases *initiative* (DND*i*) is a patient-needs driven, not-for-profit research and development (R&D) organization that develops safe, effective, and affordable medicines for neglected diseases that afflict millions of the world's poorest people.

DND*i* focuses on developing new treatments for the most neglected patients suffering from diseases such as sleeping sickness (or human African trypanosomiasis), leishmaniasis, Chagas disease, malaria, specific filarial diseases, and paediatric HIV.

The initiative's primary objective is to deliver 11 to 13 new treatments by 2018 and to establish a strong R&D portfolio for these diseases.

CONTENTS 2012 ANNUAL REPORT

Dr Bernard Pécoul
Executive Director

Prof. Marcel Tanner
Chair of the Board
of Directors

When DND*i* was created ten years ago...

... there was a dearth of research and development (R&D) for neglected diseases. Treatments either did not exist, or did but were toxic, expensive, hard to come by, or difficult to administer: in short, ill-adapted to patients' needs. Pharmaceutical companies did not invest due to the lack of a lucrative market to recoup investments in R&D and scarce attention was paid to these patients. For HIV, R&D may have been active, but patient access to treatments was in a poor state, and little to nothing was being done for tuberculosis, malaria, and neglected tropical diseases (NTDs).

A decade later, despite the progress that we read about almost every day, still only 3.8% of newly approved drugs target the neglected diseases that account for 10.5% of the global disease burden.[1] Much of the progress in drug R&D over the past decade came about through drug reformulations and repurposing of existing drugs against these illnesses. As recently documented, only 1% of all health R&D investments in 2010 was for neglected diseases.[2] The neglect is still there, despite a decade of efforts and initial successes. To respond to a systemic crisis, we need more!

To help address the neglected disease gaps, new initiatives, including product development partnerships, have flourished and offer innovative ways to develop safe, effective, adapted, and affordable drugs, vaccines, and diagnostics for neglected patients. DND*i* was part of this movement, providing an alternative option in order to boost innovation and deliver effective treatments as quickly as possible to those in urgent need. Despite their relative 'youth', these initiatives have delivered new health tools and have begun to explore new thinking and practices such as open innovation models, echoed by several international initiatives including drug discovery consortia and intellectual property and patent-sharing mechanisms.

Indeed, most major pharmaceutical companies are now committed to neglected diseases R&D. Many provide access to compound libraries, data, and knowledge, whilst others limit their efforts to drug donations. Furthermore, emerging economies, and notably neglected disease-endemic countries, have begun to engage. These are all encouraging developments.

'Elimination' has become a real goal for some neglected diseases

Today we hear more and more about 'elimination', which was inconceivable a decade ago, and is illustrative of the progress made since. The WHO NTD Roadmap, for example, which defined very specific, time-bound targets for the prevention, control, elimination, or eradication of the 17 WHO-defined NTDs by 2020, is a clear sign that an end could be in sight for certain neglected diseases.

However, to ensure that the term 'elimination' is not just rhetoric, ongoing commitments will have to be sustained in order to radically change the course of these diseases. The WHO NTD Resolution, adopted at the 2013 World Health Assembly, is a major step forward by the international community, and emphasizes the paramount importance of strong leadership at country level, particularly in disease-endemic countries, for sustainability and success.

(1) Medical innovations for neglected patients, *DNDi-MSF, December 2012.* ***(2)*** *Rottingen J-A* et al. *(May 2013). Mapping of available health research and development data: What's there, what's missing, and what role is there for a global observatory?* Lancet. *doi:10.1016/S0140-6736(13)61046-6.*

Even if today the major actors in neglected disease R&D are still based in high-income countries, numerous innovative initiatives over the past decade have proven the importance and efficiency of building, in endemic countries, the research capacities, manufacturing capabilities, and implementation systems required to sustain a long-term response to the problems inherent in neglected disease R&D.

In addition, the commitment of the private sector, as illustrated by the January 2012 'London Declaration on Neglected Tropical Diseases', emphasized the private-sector support of the WHO NTD Roadmap and its objectives. The neglected disease landscape has benefited from the massive commitment of the Bill & Melinda Gates Foundation, having contributed over a billion dollars to global health, including R&D. Some governments, like those of the UK, The Netherlands, Spain, Germany, France, and Switzerland, also took important steps to increase their efforts, despite the financial crises that have hampered their economies. However, the financial stability of many high-income countries continues to deteriorate and the threat of funding cuts continues to loom.

"We need to progress from isolated and fragmented success to sustainable change"

A need for additional funding mechanisms

Moving into the next decade, additional resources are needed, particularly with a growing R&D drug pipeline with new chemical entities entering the more expensive phase of clinical development. There are very encouraging commitments from emerging economies, for example with Brazil's recent announcement to support neglected disease R&D. Additional funding has also come from new funding mechanisms such as UNITAID. The challenge today and for the coming years, however, will be to ensure that new funding sources are sustainable and include R&D, such as the Financial Transaction Taxes (FTTs).

For DND*i*, even though the six treatments we have delivered are substantial improvements for treatment of patients in the field, they are mainly incremental improvements of existing drugs, and have shortcomings, especially as 'tools for elimination' in the long term. As such, DND*i* will not have done its job until drugs that are oral rather than infusions or injections, are safe, efficacious, and cheap, and which will likely be used in drug combinations, are developed and delivered to neglected patients.

If we look at what the past decade has to tell us, as DND*i* we clearly need to further assess and learn lessons from the challenges we have faced and extract the best practices from our successes. The role of DND*i*'s regional offices in endemic regions, along with our founding partners, will certainly need to be strengthened to seize new scientific opportunities as well as to better respond to unmet medical needs. We also need stronger and more synergistic partnerships, and greater agility of the organization to explore innovative pathways to deliver adapted and cost-effective health tools.

The past decade has brought a lot of hope, but there is still a long road ahead in the fight against neglected diseases and the current momentum cannot stop after a few achievements. One thing we have definitely learned is that we need to revisit how we collaborate in order to progress from individual, one-shot, isolated, or fragmented achievements, and genuinely think out of the box about sustainable collaboration.

Connect to fight neglect

'Connect to Fight Neglect' is the motto for our 10-year anniversary website, and it is our hope that all of the actors now engaged in neglected disease R&D will reflect with us on what form of engagement that motto implies.

After a decade of innovation for neglected patients, we have learned that if we are to truly 'bring these diseases to their knees', we have to 'keep prodding, keep pushing, and keep searching' as Dr Margaret Chan recently put it. Indeed, we have to dare to take risks and invest, break down barriers, and move bravely towards our goals for the future.

Dr Bernard Pécoul

Prof. Marcel Tanner

DND*i* is an alternative model to develop treatments for neglected diseases and ensure equitable access for all patients.




Developing therapeutic innovation **for the most in need**

In January 2012, the World Health Organization (WHO) unveiled its Neglected Tropical Diseases (NTD) Roadmap, *Accelerating work to overcome the global impact of neglected tropical diseases: A roadmap for implementation.*[1]

This WHO report laid out the aims, objectives, and means by which 11 neglected tropical diseases are to be regionally or globally eliminated or eradicated by 2020, with targets for control for the remaining six diseases. This ambitious plan was followed and supported by a new NTD resolution,[2] adopted by all WHO member states during the 66th World Health Assembly (WHA) in May 2013.

The NTD Resolution is a comprehensive call on member states to ensure ownership of NTD programmes and strategies by expanding and implementing integrated interventions, strengthening capacities, and achieving universal coverage.

Endemic country engagement and the role of emerging economies

It calls on all WHO partners to support member states in these endeavours, and specifically calls for encouragement of discovery and development of new health tools and for collaboration with WHO to measure progress.

This unprecedented push for and by WHO member states to engage in the fight against neglected diseases comes at a time when positive signs from emerging economies, and particularly those of neglected disease-endemic countries, show that these countries are concretely placing resources in the field of R&D for these diseases.

In June 2011, UNAIDS set out a global plan to eliminate new cases of paediatric HIV infection in the *Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive.*[3] While one may argue that the dates set forth are overly ambitious, the mere fact that elimination has become a genuine target is important and has implications for how we prioritize projects and determine the profile of the 'tools for elimination' that are needed.

Brazil Unites in R&D

In 2012, the Brazilian Ministry of Health, the Oswaldo Cruz Foundation (FIOCRUZ), and DND*i* Latin America signed a Cooperation and Technical Assistance Agreement, uniting the three actors in a strategic partnership to collaborate on research and development (R&D) for new therapies and diagnostics for neglected diseases.

For DND*i*, this was the first such agreement with an emerging and endemic country to finance neglected disease R&D in this innovative way.

(1) Accelerating work to overcome the global impact of neglected tropical diseases: A roadmap for implementation, *WHO, January 2012. www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf* ***(2)*** *www.who.int/neglected_diseases/EB132_R7_en.pdf* ***(3)*** Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, *UNAIDS, June 2011.*

WHO OBJECTIVES BY 2020

DISEASE	TARGET
HUMAN AFRICAN TRYPANOSOMIASIS	**Global elimination** by 2020[3]
VISCERAL LEISHMANIASIS ASIA	**Regional elimination** in Indian subcontinent by 2020[3]
VISCERAL LEISHMANIASIS AFRICA	Detect and treat all cases in Africa by 2020[4]
CHAGAS DISEASE	Intra-domiciliary transmission interrupted in the Americas by 2020[3]
CUTANEOUS LEISHMANIASIS	Detect and manage 85% of CL cases in all endemic countries by 2020[4]
ONCHOCERCIASIS	**Elimination** in selected African countries by 2020[3]
LYMPHATIC FILARIASIS	**Global elimination** by 2020[3]
PAEDIATRIC HIV	**Elimination** of new paediatric infections by 2015[5]

In early 2013, the WHO published the primary reference document for the current state of each of the NTDs, *Sustaining the drive to overcome the global impact of neglected tropical diseases*, including the strategies for the NTD Roadmap targets and milestones.[1]

DND*i*'s project portfolio of treatments to address kinetoplastid diseases, filarial diseases, and paediatric HIV has matured to the extent that it can now support global strategies for sustainable control of neglected diseases, and therefore the elimination of targeted diseases, in addition to providing the tools necessary to support national programmes in the implementation of new, adapted, and affordable treatments.

Global elimination of sleeping sickness by 2020

The situation of Human African Trypanosomiasis (sleeping sickness) is significantly different than a decade ago. The number of cases is decreasing, and disease distribution and populations at risk are better understood. NECT has drastically changed the management of the late stage of the disease, and the tools necessary for disease elimination are working their way through the R&D pipeline, notably with two potential oral drug candidates in clinical trials. While this may seem to be reason to rejoice, the real challenge lies in going to the end of the road, getting a rapid diagnostic and a safe oral pill to treat both stages of the disease at the village level, to accompany sustained control and surveillance activities, and doing it in time. Specific and well-defined tools are needed to contribute to sustainable elimination. The WHO states: 'Reaching the roadmap's targets for eliminating human African trypanosomiasis depends on increasing access to early, accurate diagnosis; **delivering safer and effective treatment**; and continuing surveillance.'[2]

Unprecedented access to compounds and knowledge

In support of this hitherto unseen momentum for NTDs and of the WHO NTD Roadmap, DND*i* and many key NTD actors, both public and private, took part in a landmark event held in London, 'Uniting to Combat NTDs'. The 'London Declaration on Neglected Tropical Diseases', emanating from the event, has now garnered support from some 70 organizations worldwide.

DND*i* welcomed this mobilization, in particular to address the major gaps in R&D to develop new treatment and diagnostic tools to effectively support the elimination or control of targeted NTDs. Following the London Declaration, 11 pharmaceutical companies committed to negotiating licensing or collaboration agreements to share compounds and knowledge with DND*i*. The majority of the commitments have been honoured or are currently under negotiation.

Many of the agreements resulting from the London Declaration are material transfer agreements or licensing agreements. These agreements are a positive step, one which hopefully will lead to broader research collaborations such as those which DND*i* has negotiated with several partners. They include the

(1) Sustaining the drive to overcome the global impact of neglected tropical diseases: Second WHO report on neglected tropical diseases. *WHO, 2013. www.who.int/neglected_diseases/9789241564540/en/* ***(2)*** Ibid., *p. 63.* ***(3)*** Ibid., *p. 134.* ***(4)*** Ibid., *p. 70.* ***(5)*** Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, *UNAIDS, June 2011.*

sharing of compounds, knowledge, and expertise, with pro-access IP management that secures access to treatments at an affordable price in all endemic countries, and in some cases includes commitment of research resources, clinical development resources, and even implementation of the approved drug product.

In 2012 alone, new agreements for compound sharing were signed, for example, with AbbVie (formerly Abbott), Astellas, AstraZeneca, BMS, Dupont, GSK, Johnson & Johnson, Pfizer Ltd., and Sanofi. Other similar collaborations continued, for example, with Anacor, Celgene, Debiopharm, Eisai, and Merck (MSD), while development and distribution work with Cipla Ltd. for ASMQ continued and new work began in the field of HIV. While not an exhaustive list, these examples offer insight into the partnerships with pharmaceutical and biotechnology companies managed by DND*i* in 2012.

150,000 Compounds Screened

In 2012, DND*i* screened approximately **150,000 compounds, leading to 9 hit series from Pfizer, 7 from TDR, and 5 from Sanofi.**

The 21 series were progressed to lead optimization, and with an expected attrition rate, or statistical failure rate, of 90%, two or more of them could enter into the pre-clinical stage.

This level of output, which may seem trivial in absolute numbers, is actually the stepwise process of portfolio building.

Maintaining a robust portfolio this way directly expedites the R&D process to meet the 2020 NTD Roadmap goals.

'UNITING TO COMBAT NEGLECTED TROPICAL DISEASES' LONDON EVENT, JANUARY 2012

Dr Margaret Chan (WHO), Bill Gates (B&MGF), CEOs of 13 pharmaceutical companies, the U.S., U.K. and U.A.E governments, the World Bank and other global health organisations, namely DNDi, announced a coordinated push to accelerate progress toward eliminating or controlling 10 neglected tropical diseases (NTDs) by 2020, in support of WHO's NTD 2020 objectives.

Governance

DND*i* BOARD MEMBERS

Marcel Tanner
Chair; Swiss Tropical and Public Health Institute (Swiss TPH), *(2011-2015)*

Els Torreele
Secretary; Open Society Foundations, USA *(2011-2015)*

Derrick Wong
Treasurer; non-profit management consultant, France *(2011-2015)*

Alice Dautry
Institut Pasteur, France
(2009-2013)

Abul Faiz
Patient representative; Sir Salimullah Medical College, Bangladesh *(2009-2013)*

Unni Karunakara
Médecins Sans Frontières (MSF), *(2011-2015)*

Datuk Mohd Ismail Merican
Ministry of Health, Malaysia
(2009-2013)

Carlos Morel
Oswaldo Cruz Foundation (Fiocruz), Brazil *(2009-2013)*

Bennett Shapiro
Pure Tech Ventures, formerly with Merck & Co, USA *(2012-2016)*

Paulina Tindana
Patient representative; Navrongo Health Research Centre, Ghana *(2009-2013)*

John Reeder (Permanent Observer)
Special Programme for Research and Training in Tropical Diseases (WHO-TDR), Switzerland

- **Position currently vacant**
  Kenya Medical Research Institute (KEMRI)
- **Position currently vacant**
  Indian Council of Medical Research (ICMR)

DND*i* SCIENTIFIC ADVISORY COMMITTEE MEMBERS

Pierre-Etienne Bost, Chair; formerly with Institut Pasteur, France

Khirana Bhatt, University of Nairobi, Kenya

Chris Bruenger, IDEC Inc., Japan

François Chappuis, Médecins Sans Frontières & Geneva University Hospitals, Switzerland

J. Carl Craft, formerly with Medicines for Malaria Venture (MMV), Switzerland

Simon Croft, London School of Hygiene and Tropical Medicine, UK

Nilanthi de Silva, University of Kelaniya, Sri Lanka *(as of May 2012)*

Lisa Frigati, Tygerberg Hospital, South Africa *(as of December 2012)*

Federico Gomez de las Heras, formerly with GlaxoSmithKline, Spain

Chitar Mal Gupta, Central Drug Research Institute, India

Maria das Graças Henriquez, Oswaldo Cruz Foundation (Fiocruz), Brazil *(until May 2012)*

Paul Herrling, Novartis International AG, Switzerland

Dale Kempf, Abbott, USA

Ana Rabello, Oswaldo Cruz Foundation, (Fiocruz), Brazil *(as of June 2012)*

Murad Shahnaz, Institute for Medical Research, Malaysia *(as of December 2012)*

Nor Shahidah Khairullah, Infectious Diseases Research Center, Malaysia *(until October 2012)*

Shiv Dayal Seth, Indian Council of Medical Research (ICMR), India

Faustino Torrico, Universidad Mayor de San Simon, Cochabamba, Bolivia

Mervyn Turner, formerly with Merck Research Laboratories, USA

Muriel Vray, Institut Pasteur, France

Krisantha Weerasuriya, World Health Organization (WHO), Geneva

FRIENDS OF DND*i*

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

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

Abdallah Daar, Professor of Public Health Sciences and Surgery, University of Toronto, and Senior Scientist and Director of Ethics and Commercialization at the McLaughlin-Rotman Centre for Global Health, University Health Network and University of Toronto, Canada

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

Ahmed El Hassan, Emeritus Professor, Institute of Endemic Diseases, University of Khartoum, Sudan

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

Rowan Gillies, former President of MSF International Council, Australia

Lalit Kant, former Head of the Division of Epidemiology & Communicable Diseases, Indian Council of Medical Research, 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

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

Ricardo Preve, Film Director, Ricardo Preve Films LLC, Argentina

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

Eloan dos Santos, Public Health Policy Consultant, Brazil

José Gomes Temporão, former Minister of Health, Brazil

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

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

REGIONAL OFFICE BOARDS

DND*i* North America Board of Directors

Bennett Shapiro, Chair; Pure Tech Ventures, formerly with Merck & Co, USA

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Joelle Tanguy, International Federation of Red Cross and Red Crescent Societies, Switzerland

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Darin Portnoy, Montefiore Medical Center and Family Health Center, USA

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Vacant, Vice-president

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Fumiko Hirabayashi, Drugs for Neglected Diseases *initiative* (DND*i*), Japan

EXECUTIVE TEAM

DND*i* Headquarters, Geneva

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Shing Chang, Research & Development Director *(until June 2012)*
Graeme Bilbe, Research & Development Director *(from June 2012)*
(in alphabetical order)
Jean-François Alesandrini, Fundraising & Advocacy Director
Ralf de Coulon, Finance, Human Resources & Administration Director
Robert Don, Discovery & Pre-clinical Director
Jean-Pierre Paccaud, Business Development Director
Thomas Saugnac, Operations Director
Nathalie Strub Wourgaft, Medical Director

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Bhawna Sharma, Head of Regional Office, India
Eric Stobbaerts, Director of Regional Office, Brazil
Monique Wasunna, Head of Regional Office, Kenya

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Headquarters

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ASIA

INDIA
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MALAYSIA
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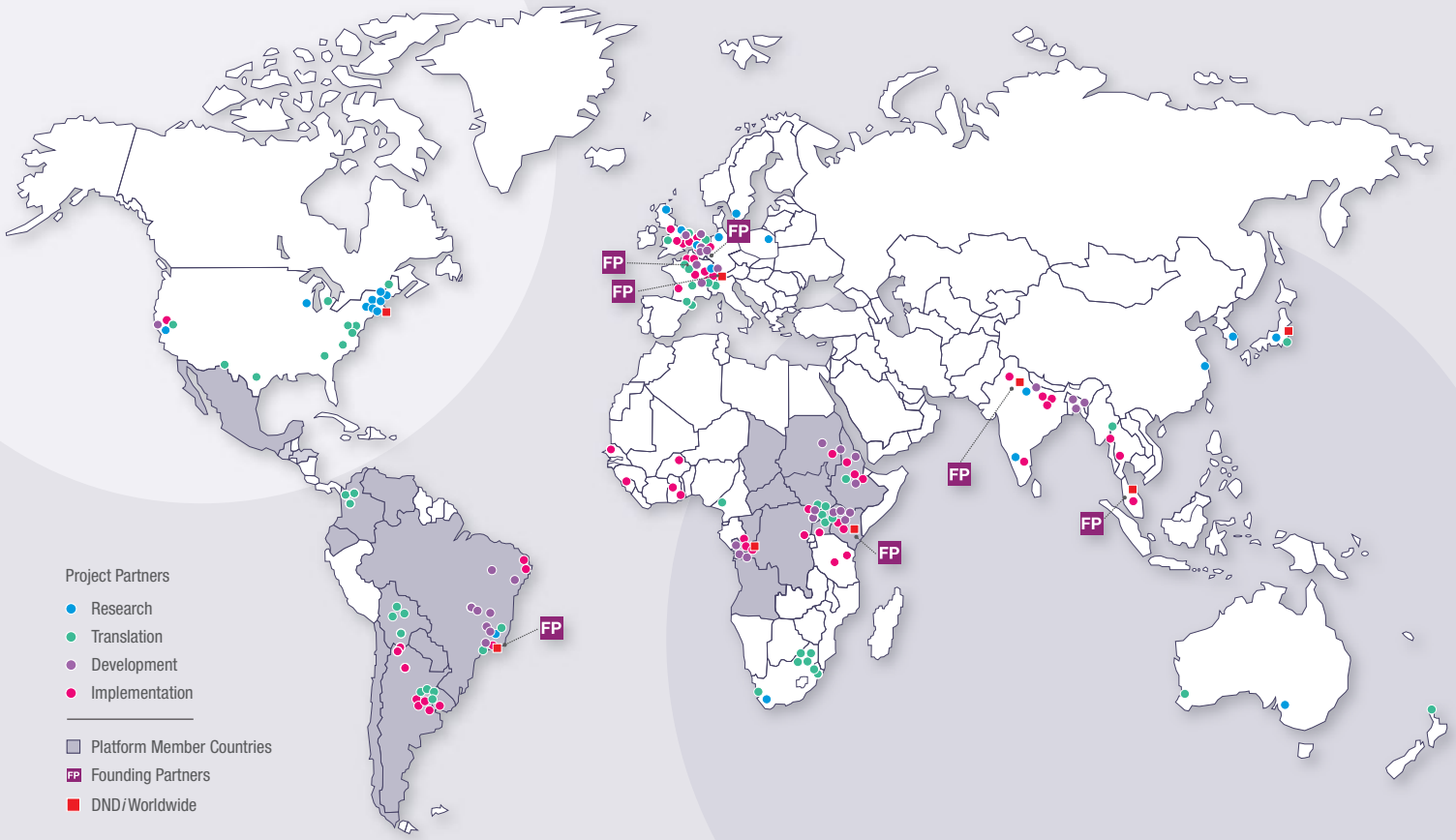
USA
Erin Conklin; Jennifer Duran; Jennifer Katz; Oliver Yun

Over 130 R&D partners worldwide



FOUNDING PARTNERS

In 2003, seven public and private institutions came together to form DND*i*:

- Médecins Sans Frontières (MSF) (Doctors Without Borders)
- Oswaldo Cruz Foundation, Brazil
- Indian Council for Medical Research, India
- Kenya Medical Research Institute, Kenya
- Ministry of Health, Malaysia
- Institut Pasteur, France
- The Special Programme for Research and Training in Tropical Diseases (WHO-TDR)

DND*i* WORLDWIDE

- DND*i* Headquarters (Geneva)
- DND*i* Latin America (Rio)
- DND*i* North America (New York)
- DND*i* Africa (Nairobi)
- DND*i* India (Delhi)
- DND*i* Malaysia (Penang)
- DND*i* Japan (Tokyo)
- DND*i* in DRC (Kinshasa)

CLINICAL RESEARCH PLATFORMS

LEAP PLATFORM

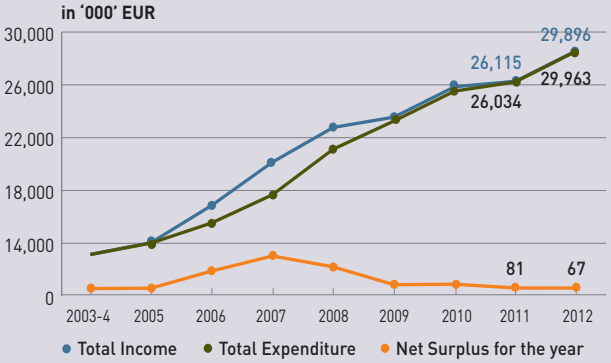
HAT PLATFORM

CHAGAS CLINICAL RESEARCH PLATFORM

2012 KEY FINANCIAL PERFORMANCE INDICATORS

Maintaining growth, achieving balance, with a greater network of partners worldwide

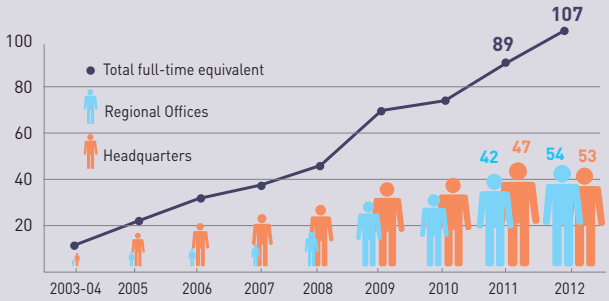
STATEMENT OF ACTIVITIES 2004-2012



DND*i* expenditure totals **EUR 150 million since its inception in 2003. In 2012**, expenditure amounted to **EUR 30 million**, +15% as compared to 2011. This increase is mainly due to the expansion of clinical activities in Africa and Asia. The operating loss of EUR 0.05 million is compensated by financial income and a positive exchange rate gain.

107 FTEs working worldwide

HUMAN RESOURCES EVOLUTION 2004-2012



In 2012, DND*i* recruited an additional 18 FTEs (+15 FTEs in 2011), mainly in Regional Offices (ROs): +11 FTEs in Nairobi, New Delhi, Kinshasa, New York, and Rio de Janeiro (+25%) and +7 FTEs in Headquarters in Geneva (+15%). End 2012, DND*i* staff reached a first-ever balance between the ROs and the Headquarters, fully in line with the Business Plan 2011-2018.

Progression towards Business Plan objectives

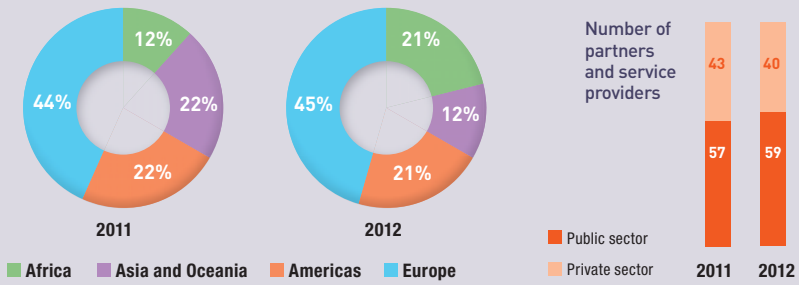
2012 SOCIAL MISSION BREAKDOWN

In 2012, DND*i*'s non-social mission ratio decreased by 1% since the same level of management and fundraising expenditure was maintained from 2011. Four budget lines increased: IT support to implement new tools, a new finance officer to support the increase of financial workload and reporting to donors (+1 FTE), a full-time Director of Operations in charge of implementing new practices and policies in Geneva and Regional Offices (ROs), and various consultants to improve project management. Other social mission ratio (including capacity strengthening and advocacy activities) increased due to larger involvement of ROs in Kenya, Brazil, and North America in advocacy and communication activities, the reinforcement of ROs and platforms by 14% to support increase of R&D activities, and additional resources added in the communications department to temporarily support preparations for the 10-year anniversary activities in 2013.

Steady increase in service provision partnerships in neglected disease-endemic regions to support clinical activities

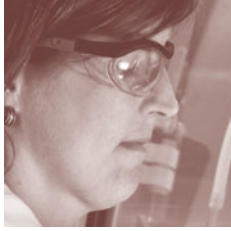
MAIN R&D PARTNERS & SERVICE PROVIDERS PER CONTINENT

(with financial compensation over EUR 5,000 in 2012)



In 2012, the number of partners and service providers with which DND*i* had business relations valuing over EUR 5,000 remained stable (99 in 2012 as compared to 100 in 2011). The increase in Africa is mainly linked to setting up clinical trials, namely fexinidazole for HAT, several studies for VL and HIV/VL co-infection, and paediatric HIV. In Asia in 2012, DND*i* ran clinical trials mainly with international organizations based in Asia (but not listed as Asian partners), such as WHO-TDR, OWH/PATH, and MSF, which partly explains the decrease. In addition, some projects in Asia were completed.

DND*i*'s objective is to deliver 11 to 13 new treatments by 2018 and to maintain a robust pipeline to support long-term objectives.






Beginning with the end in mind

Since its inception, DND*i* has delivered six new treatments and built a robust pipeline with 12 new chemical entities in pre-clinical and clinical stages. DND*i*'s portfolio matured in 2012, with six treatments now registered or available to patients, promising compounds progressing through the clinical pipeline, and new chemical libraries or compounds being screened.

DND*i*'s R&D strategy is defined by patients' needs and relies on the combination of long-term goals, through the development of new chemical entities (NCEs) to support sustainable control or elimination of neglected diseases, with short-term goals based on the optimization of existing drugs, to address more immediate and urgent needs. Building the future of novel and effective treatments for neglected diseases includes progressing promising compounds through the development pipeline, establishing collaborations with the pharmaceutical industry, biotechs, academia, and increasingly with other product development partnerships (PDPs), to access new chemical libraries or compounds using cutting-edge technologies, such as high-throughput screening (imaging technology-based high-content screening assays against intracellular *Leishmania* and *T. cruzi*), as well as developing strong lead optimization consortia. DND*i* also builds and consolidates capacity for clinical research in the field, by supporting regional platforms for each kinetoplastid disease. So far, DND*i* has delivered six new treatments for four diseases: malaria, sleeping sickness, visceral leishmaniasis, and Chagas disease.

The key features of the new drugs/treatments DND*i* seeks to develop are at the centre of the organization's target disease strategies, which define the patient need and desired outcome of each product, taking into account the current research landscape as well as the health systems in endemic countries. Because drug development can be a long process, it is essential to plan from the outset with the end in sight, i.e. agreeing on what the key features and attributes of the intended end-product are. These are summarized into Target Product Profiles (TPPs), taking the target population in need as the starting point, then defining the ideal technical attributes of efficacy, safety, and 'user-friendliness' (i.e. duration, mode of administration, storing conditions), as well as cost. TPPs are developed with input from disease experts, representatives of Ministries of Health and National Control Programmes in endemic countries, WHO representatives, leading clinicians and researchers, as well as health workers, all of whom deal with the realities of the diseases in the field. DND*i*'s target diseases call for clear TPPs that are based on epidemiological data and cater for the needs of specific populations – the poorest of the poor, both adults and children.

By Keeping the Focus on Patients and their Needs, DND*i*'s Project Portfolios Balance Long-term and Short/medium-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

With the right dose, the right formulation, the right taste, no refrigeration required, a well-designed product and adapted packaging, DND*i* and partners aim to ensure the best treatment is delivered to those in need in all endemic countries at an affordable price; by engaging and seeking early advice from regulatory authorities and the WHO, regulatory and field adoption can be greatly facilitated. This implies looking for treatments that can be delivered at the village or primary healthcare level to avoid the long distances that many patients must travel, as well as the time and money required for patients and family members to reach and stay at district hospitals (or secondary healthcare level). DND*i*'s TPPs are publicly available on the web (www.dndi.org).

Human African trypanosomiasis (HAT): In 2012, fexinidazole entered a pivotal Phase II/III study in the Democratic Republic of the Congo and the Central African Republic. If successful, fexinidazole could become the first oral-only treatment for sleeping sickness patients. SCYX-7158, also an oral drug candidate, entered first-in-human studies in healthy volunteers. Promising backups are in lead optimization and pre-clinical phases. NECT is now on the national essential medicines lists of 12 countries across Africa and has almost entirely replaced melarsoprol and eflornithine monotherapy as first-line treatment for second stage *T. b. gambiense* sleeping sickness. It is now included on the WHO Essential Medicines List for children.[1]

Leishmaniasis: Recruitment for the LEAP 0208 study in East Africa, which aims to evaluate the safety and efficacy of miltefosine alone as well as combination treatments for VL ended in March 2012 – results will be available at the beginning of 2013 and will inform the decision to evaluate one of the combinations in a Phase III trial. SSG&PM is available and implemented in Sudan and Uganda. In 2012, it was added to Kenya's national VL guidelines. New drug combination therapies are available for Asia. Backup compounds are at the pre-clinical stage and promising leads are in the lead optimization phase.

Chagas disease: The paediatric dosage form of benznidazole, registered in Brazil at the end of 2011, is now included on the WHO Essential Medicines List for children.[1] Recruitment for the E1224 Phase II clinical trial concluded in June 2012 and the first results will be available in the second half of 2013. In addition, in 2012, DND*i* received funding for the first-ever large-scale study involving treatment of non-human primates (macaques) naturally infected in their outdoor living environment with *Trypanosoma cruzi* with the aim of identifying new biological markers for the evaluation of treatment efficacy in Chagas disease.

Malaria: By the end of 2012, more than 180 million ASAQ treatments had been distributed in 30 African countries. In addition, more than 20 million treatments had been ordered for the private sector in seven countries in Africa within the Affordable Medicines Facility – malaria (AMFm). ASMQ received pre-qualification from the WHO and was registered in Malaysia and Myanmar. It is now included on the WHO Essential Medicines Lists for adults and children.[1]

In 2011, DND*i*'s portfolio was extended to paediatric HIV and filarial diseases:

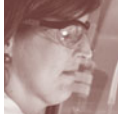
Paediatric HIV: The added arm to the CHAPAS-2 trial (sponsored by MRC), which aimed to clinically assess the protease inhibitor lopinavir/ritonavir in the existing sprinkle (minitablet) formulation in children between 1-4 years of age (additional CHAPAS-2 cohort), was concluded in 2012.

Filarial diseases: Work was undertaken to develop a pre-clinical formulation of flubendazole, a potential macrofilaricide that allows oral absorption, and non-clinical development progressed, notably studies required to file an Investigational New Drug (IND) application.

Target Product Profile (TPP)

- **Indications:** Which disease(s)?
- **Population:** Which type of patients and where?
- **Clinical Efficacy:** Does it treat the infection effectively?
- **Safety and Tolerability:** What level of acceptability for adverse events?
- **Stability:** How long is the shelf-life of the drug(s), and what are the 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?

(1) As of July 2013: *www.who.int/medicines/EMP_Website_notice_EML_July2013.pdf*



6 new treatments and 12 new chemical entities in the pipeline

Portfolio 2012

	Research			Translation			Development		Implementation
	Screen	Hit to Lead	Lead Opt.	Pre-clinical	Phase I	Phase IIa/PoC	Phase IIb/III	Registration	Access
HAT	SCREENING	Nitroimidazole backup ★ Oxaborole backup ★			Oxaborole SCYX-7158 ★		Fexinidazole ★		**NECT** Nifurtimox-Eflornithine Combination Therapy
LEISHMANIASIS		Nitroimidazole backup (VL) ★		VL-2098 ★	Fexinidazole (VL) ★ Anfoleish (CL) ★		New VL treatments for Bangladesh New VL treatments for Africa New treatments for HIV/VL co-infection for Africa New VL treatments for Latin America		**SSG&PM** Sodium Stibogluconate & Paromomycin Combination Therapy for VL in Africa **New treatments for VL in India**
CHAGAS DISEASE		Nitroimidazole ★		Fenarimol series ★ K777 ★ Biomarkers	Azoles E1224 ★				**Benznidazole Paediatric** dosage form
FILARIAL DISEASES				Flubendazole ★ Macrofilaricide					
PAEDIATRIC HIV				Improved PI for first-line treatment			PI Sprinkles (CHAPAS-2) Superboosting - TB-HIV		
MALARIA									**ASAQ FDC** Artesunate Amodiaquine Fixed-Dose Combination **ASMQ FDC** Artesunate-Mefloquine Fixed-Dose Combination

★ New Chemical Entity (NCE)
Fexinidazole (for HAT and VL) = 1 NCE

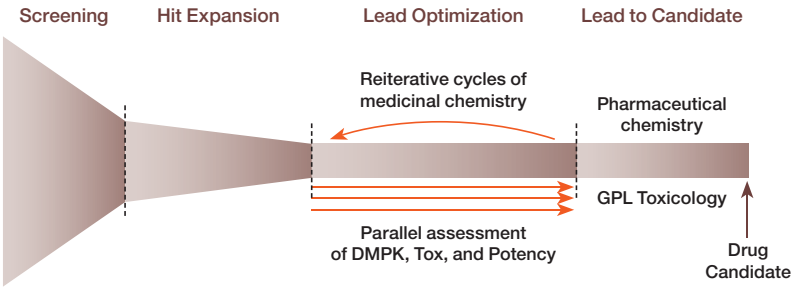
RESEARCH

Increasing efforts to discover new drugs

The earliest stages of drug discovery consist of three phases: sourcing and screening compounds, hit-to-lead expansion up to lead selection, and lead optimization (LO). In order to ensure an uninterrupted supply of quality active series to its lead optimization programmes, DND*i* screens libraries from its pharmaceutical, biotech, academic and PDP partners using defined selection criteria, then reviews/prioritizes series according to the probability of success. At the same time, DND*i* secures back-up series to address the attrition rate in optimization programmes.

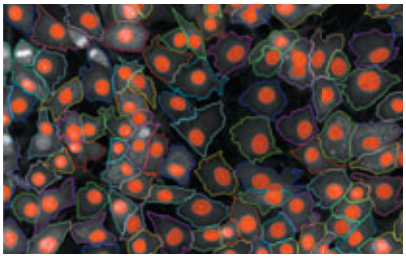
For 2012, DND*i* refocused its early discovery and LO efforts on the discovery and development of novel active lead series for leishmaniasis. This was achieved through a significant increase in the high throughput screening capacity against *Leishmania* parasites in collaboration with the University of Dundee, as well as prioritizing active hit series to enter the Hit-to-Lead and LO phases in order to bring additional pre-clinical candidates to the DND*i* discovery pipeline.

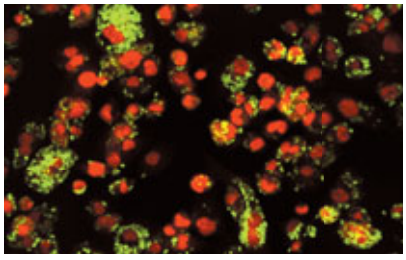
DND*i*'s discovery strategy relies on partnerships with public (e.g. universities and academia) and private partners (pharmaceutical and biotechnology companies); lead optimization activities are carried out by two consortia that work across all three kinetoplastid diseases, enabling cross-talk between diseases for each compound series being investigated.

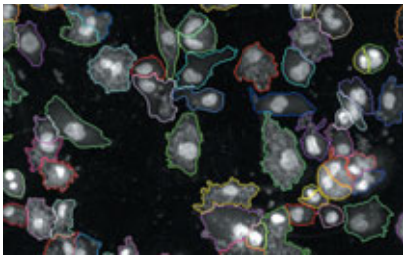


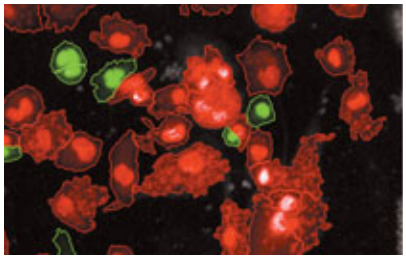
In 2012, DND*i* screened over **150,000** compounds in more than **420,000** screening assays

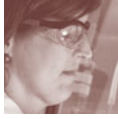
Over 20 active series have been advanced to the Hit-to Lead and Lead Optimization phases for the three kinetoplastid diseases with priority given to visceral leishmaniasis.


3T3 cells infected with *T. cruzi* (DRAQ5 staining, 20x Objective) Cytoplasm selection


THP1 cells infected with *L. donovani*-eGFP (DAPI staining, 20x Objective)


THP1 cells infected with *L. donovani*-eGFP (DAPI staining, 20x Objective) Cytoplasm selection


THP1 cells infected with *L. donovani*-eGFP (DAPI staining, 20x Objective) Infected cells



SCREENING

Main partners:
AbbVie (formerly Abbott), USA; Actelion, Switzerland; Anacor, USA; Astellas, Japan; AstraZeneca, Sweden; Bayer, Germany; Bristol-Myers Squibb, USA; Celgene, USA; E.I. du Pont de Nemours, USA; Eisai Co., Ltd, Japan; Genomics Institute of the Novartis Research Foundation, USA; GlaxoSmithKline, Tres Cantos, Spain; Institute of Medical Microbiology, Immunology, and Parasitology, Hospital University of Bonn, Germany; Medicines for Malaria Venture, Switzerland; Merck (MSD), USA; Northwick Park Institute for Medical Research, UK; Novartis Institute for Tropical Diseases, Singapore; Pfizer, USA; Pfizer Animal Health, USA; Sanofi, France; Sigma-Tau, Italy; WHO-TDR; TB Alliance, USA; Institut Pasteur Korea (IPK), South Korea; Drug Discovery Unit (DDU) at the University of Dundee, UK; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Laboratory of Microbiology, Parasitology, and Hygiene (LMPH), University of Antwerp, Belgium; and London School of Hygiene & Tropical Medicine (LSHTM), UK; TI Pharma, The Netherlands

Leadership:
Discovery and Pre-Clinical Director: Robert Don;
Discovery Manager: Jean-Robert Ioset

High-throughput screening

High-throughput screening (HTS) of large libraries for *Leishmania* (IPK and DDU) and *T. cruzi* (IPK) have been developed and used to identify novel hit compounds. Adequate screening capacity is a key element of DND*i*'s discovery strategy, as it enables the screening of large libraries/series of compounds and therefore a quicker identification of hits/leads for optimization.

Chemical diversity

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*'s target diseases. Illustrating this approach is the 2011 research collaboration with Pfizer to screen the Pfizer GDRS II set (representative of the entire Pfizer library in terms of chemical diversity, i.e. 150,000 compounds) against all three kinetoplastid diseases. In addition, DND*i* is evaluating access to various libraries based on chemical diversity with its pharmaceutical partners, including, among others, Sanofi and GSK.

Mining for chemical classes

Discovery activities are typically associated with high attrition rates, especially in the case of candidates not associated with any pre-clinical data other than *in vitro* efficacy. In order to lower this attrition rate, mining for chemical classes relies on the identification of promising chemical classes of which a member has been successfully advanced in drug development for other disease indications. From libraries originating from collaborating pharmaceutical and biotech companies, promising compound classes are identified by sampling a subset of representative compounds and testing for antiprotozoal activity. Examples of interesting classes include oxaboroles (Anacor Pharmaceuticals), pyridones (GSK), and nitroimidazoles (TB Alliance). Access to specific sets of compounds (inhibitors of a specific target and chemical classes) from DND*i*'s pharmaceutical partners (e.g. Sanofi, GSK, or MSD) was one of the major focuses of DND*i*'s discovery strategy in 2012.

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) enables identification of candidates with potential for further development – ideally ready to enter into pre-clinical or later stage without further optimization – for the target diseases. A successful example of this strategy is fexinidazole. DND*i* has extended and applied this strategy in collaboration with its pharmaceutical partners.

Reference screening centres

The Swiss Tropical and Public Health Institute (Swiss TPH), the University of Antwerp (LMPH), 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 standards. The centres also provide expert parasitology advice that ensures the quality of DND*i*'s data and work.

LEAD OPTIMIZATION

Main partners:
Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto (UFOP), Brazil; Institut Pasteur Korea (IPK), Korea; iThemba, South Africa; LMPH, University of Antwerp, Belgium; LSHTM, UK; Murdoch University, Australia; SCYNEXIS Inc., USA; TB Alliance, USA; University of Auckland, New Zealand; Pace University, USA; Pfizer, USA; WuXi AppTech, China

Leadership:
Discovery and Pre-Clinical Director: Robert Don; Head of Drug Discovery: Eric Chatelain; Head of Drug Discovery: Charles Mowbray; Project Coordinator: Stéphanie Braillard

DND*i*'s strategy for its lead optimization consortia is es advance new chemical classes identified through screening programmes, as well as to develop backup compounds that can rapidly replace frontrunner compounds in case of failure. These consortia bring together expertise in chemistry, biology, drug metabolism, and pharmacokinetics (DMPK), *in vivo* screening, drug safety assessment, and pre-formulation. Optimization efforts are focused on improving the lead compound's properties for absorption into the bloodstream following oral dosing, distribution of the compound to the site of infection(s), modification of residues in the compound that are prone to breakdown or clearance and which increase tolerability and safety for the patient.

HUMAN AFRICAN TRYPANOSOMIASIS (HAT)

Sleeping Sickness

Working together to develop the right tools for elimination

The WHO, in its recently published NTD Roadmap,[1] has slated human African trypanosomiasis for elimination by 2020, measuring elimination by an annual prevalence rate of less than 1 case per 10,000 population in historical foci.[2] This objective comes at a time when a steady decline in the numbers of reported cases has been recorded over 15 years, resulting from intensified efforts to detect and promptly treat patients and to control the disease. In 1995, there were 30,000 reported and 300,000 estimated cases of HAT. Today there are approximately 7,000 reported cases and approximately 30,000 estimated cases annually, thanks to the efforts and successes of National Control Programmes (NCPs) of endemic countries, together with WHO, MSF, Sanofi, Bayer, and many other key actors. A new combination therapy, NECT, that is effective and safe, but also simplifies treatment, was introduced by DND*i* and partners in 2009 for patients with stage 2 HAT, and two oral drugs are currently in clinical trials. Eliminating the disease, however, will not happen without concerted efforts to bring simple and safe oral drugs and rapid diagnostics to the field, supported by fine-tuned control strategies according to disease prevalence[3] and sustained surveillance programmes.

The reality of HAT management remains challenging, even more so in the most remote settings such as the small villages where the current treatments are not feasible for use, and where the current diagnostics still require specialized mobile teams. The rapid diagnostics, in addition to the two oral treatments in development by DND*i* and partners, could dramatically change diagnosis and treatment by making tools available in the rural health centres in sub-Saharan Africa, thus facilitating the decentralization of HAT services and surveillance, and so directly contributing to elimination targets.

In the current context of a declining number of patients that can participate in clinical research projects and with several promising tools still requiring clinical trial testing, the need for stronger collaboration and coordination of the key players is vital. It will later ensure that the right tools reach patients through national programmes.

Ideal Target Product Profile for HAT

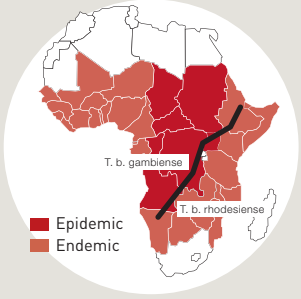
A new treatment for adults and children

- Effective against **both stages** of the disease
- Active against **both causative parasite sub-species:** *Trypanosoma brucei gambiense* and *T.b. rhodesiense*
- With less than **0.1%** drug-related mortality
- With at least **95%** efficacy at 18 months follow-up
- **Safe** for pregnant and lactating women
- **Easy to use:** short-course (7, maximum 10 days), oral, once a day, requiring no monitoring.
- **Affordable**
- **Adapted to tropical climates** (three-year shelf-life)

(1) Accelerating work to overcome the global impact of neglected tropical diseases: A roadmap for implementation*, WHO, January 2012. www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf*

(2) *Report of a WHO meeting on elimination of African trypanosomiasis (Trypanosoma brucei gambiense),* World Health Organization*, April 2013.*

(3) *Simarro PP.* et al. (2013) *Diversity of human African trypanosomiasis epidemiological settings requires fine-tuning control strategies to facilitate disease elimination.* Research and Reports in Tropical Medicine *4:1–6.*



FACT SHEET

Human African Trypanosomiasis
Sleeping Sickness

WHAT IS THE IMPACT OF HAT?

The number of reported cases is approximately 7,000, but the number of actual cases is estimated to be 30,000.[1] Fatal if untreated, the disease affects mainly those living in remote areas with limited access to adequate health services. Almost eliminated in the 1960s, transmission increased again as a result of war, population displacement, poverty, and the collapse of adequate support to the control activities conducted within health systems.

Recent successes and an impressive drop in the number of reported cases call for renewed hope, but there is still work to be done, as some areas are not covered by surveillance and control efforts.

HOW IS HAT TRANSMITTED?

HAT is transmitted to humans by two sub-species of the parasite *Trypanosoma brucei* (*T. b.*) through the bite of the tsetse fly: *T. b. gambiense* (West and Central Africa, responsible for the vast majority of cases) and *T. b. rhodesiense* (East Africa). The disease affects 36 countries in sub-Saharan Africa, but 8 countries report 97% of all cases (see map), and over two-thirds of those are reported in the Democratic Republic of the Congo.[2] Man is the essential reservoir for *T. b. gambiense*.

WHAT ARE THE SYMPTOMS?

HAT occurs in two stages:

→ **Stage 1:** the hemolymphatic 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 leads to serious sleep cycle disruptions, paralysis, progressive mental deterioration, and ultimately, without effective treatment, death.

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

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Available treatments are limited, difficult to administer, often toxic, and stage-specific.

→ **Stage 1: pentamidine** and **suramin**, require injections and are ineffective for stage 2.

→ **Stage 2: melarsoprol**, a toxic arsenic derivative that causes pain and fatal encephalopathies in up to 5% of those who receive it,[3] and is increasingly ineffective, with reports of drug resistance and treatment failure in some foci; **eflornithine**, difficult to administer as treatment requires trained health staff and an extended hospital stay (56 intravenous infusions taking two hours each to administer, over 14 days and four times each day); **NECT** (nifurtimox-eflornithine combination therapy), a simplified therapy option for stage 2 *T. b. gambiense* sleeping sickness, with only 14 infusions of eflornithine over 7 days and 10 days of oral treatment with nifurtimox. While not the most appropriate treatment to support elimination efforts as it requires a hospital setting, NECT does provide a major improvement in case management.

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

At its inception, DND*i*'s short-term strategy was to make better use of existing treatments by combining drugs already in use. In September 2009, DND*i* and partners **launched the first new treatment for sleeping sickness** in 25 years: nifurtimox-eflornithine combination therapy (NECT). **NECT** was included on the WHO Essential Medicines List (EML) in 2009 and is now recommended as first-line treatment in 12 endemic countries. In December 2012, it was submitted for inclusion on the WHO EML for children.

As a medium-term strategy, DND*i* initiated a compound mining effort to identify existing chemical compounds with potential against kinetoplastid diseases. This resulted in the rediscovery of fexinidazole, which completed Phase I clinical development in 2011. **Fexinidazole entered a pivotal Phase II/III study** in 2012 and is currently recruiting patients in the DRC. An agreement was signed in 2009 with Sanofi as the industrial partner for this project.

In order to build a strong pipeline for long-term drug discovery, DND*i* established a **HAT Lead Optimization Consortium**. The identification of the **oxaborole SCYX-7158** represents the first success of this consortium. SCYX-7158 successfully progressed through pre-clinical development and after some additional studies, entered **Phase I clinical** development in early 2012 and should be completed in 2013. Other backup compounds continue to be evaluated by the consortium.

In addition, DND*i* supports the **HAT Platform** (see page 49) that was launched in Kinshasa (Democratic Republic of the Congo – DRC) in 2005. The HAT Platform is a clinical research and access-supporting network that brings together key players in the fight against sleeping sickness from Angola, the Central African Republic, Chad, DRC, Republic of the Congo, Sudan, South Sudan, and Uganda.

By 2018, DND*i* aims to deliver from its HAT-specific portfolio:

→ An oral, safe, effective treatment for stage 2 HAT, ideally to be used with the same regimen for stage 1 HAT

(1) *www.who.int/mediacentre/factsheets/fs259/en/* ***(2)*** *Simarro PP.* et al. *(2008) Eliminating human African trypanosomiasis: where do we stand and what comes next?* PLoS Med *5: 55.* ***(3)*** *Blum J.* et al. *(2001) Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis.* Trop Med Int Health *6: 390-400.*

Research

Partners:
TB Alliance, USA; University of Auckland, New Zealand; SCYNEXIS Inc., USA; Pace University, USA; Wuxi AppTech, China

Leadership:
Discovery and Pre-clinical Director: Robert Don; Head of Drug Discovery: Charles Mowbray; Project Manager: Ivan Scandale; Project Coordinators: Delphine Launay, Stéphanie Braillard

Project start:
April 2007

Lead Optimization Consortium – Nitroimidazoles backup – Oxaborole backup

2012 OBJECTIVES:
- → **Continue the lead optimization programme with the goal of a backup oxaborole. Assess the front-running compounds SCYX-6086 and SCYX-8210 in rat toxicity studies**
- → **Evaluate the lead nitroimidazole backup RJ164 to determine if suitable to progress further**
- → **Initiate a new Lead Optimization (LO) programme with the LO USA Consortium to select a new chemical series for LO**

The prototype oxaborole SCYX-7158 is progressing through Phase I clinical trials. A range of structurally diverse oxaboroles with good activity against *T. brucei* were profiled in an animal pharmacokinetic (PK) study and several promising candidates with shorter half-lives than SCYX-7158 were identified. In depth DMPK and *in vitro* parasitology profiling narrowed the selection to SCYX-8210 and SCYX-0682, which may offer good backups to SCYX-7158 if needed. SCYX-7158 continues to make good progress in Phase I clinical trials, so at present there is no urgent need for a backup compound. Thus, only limited further development of SCYX-8210 and SCYX-0682 will be performed in 2013.

The nitroimidazole backup programme for HAT has been searching for a compound with a lower projected human dose than fexinidazole to simplify dosing and mitigate any potential issues with tolerance. Work at WuXi AppTech and the University of Auckland allowed the preparations of enantiomers of the nitroimidazole SN29971/SCYX-1227; after parasitology and *in vitro* DMPK profiling, the enantiomer SCYX-2035811 was identified as the active isomer and retained the good metabolic stability of the racemate. A synthetic route to SCYX-2035811 has been developed and scaled-up to provide active pharmaceutical ingredient (API) for further characterization. In the mouse acute model of HAT, SCYX-2035811 has shown excellent activity at doses down to 12.5 mg/kg for 7 days. The dose response for this compound will be further explored and a parallel PK assessment, including brain levels, will be carried out before the progression of this compound into the mouse stage 2 CNS model to enable a full comparison with fexinidazole. The nitroimidazole fexinidazole is progressing well in Phase II/III clinical trials. The need for a backup compound is therefore not urgent at this stage and only limited work will be carried out in 2013 on the backup programme.

Translation

Partners:
Anacor Pharmaceuticals Inc., USA; SCYNEXIS Inc., USA; Advinus Therapeutics, India; Penn Pharma, UK; Swiss TPH, Switzerland; Pace University, USA

Leadership:
Discovery and Pre-clinical Director: Robert Don; Head of HAT Clinical Programme: Antoine Tarral; Clinical Manager: Séverine Blesson; Head of Pharmaceutical Development: Steve Robinson; Project Coordinator: Delphine Launay

Project start: January 2010

Oxaborole SCYX-7158

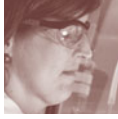
2012 OBJECTIVES:
- → **Completion of a GLP (Good Laboratory Practice) safety package (reprotox), process development, manufacture of the API, formulation, and be ready for regulatory submissions for Phase I clinical trials**
- → **Initiate oxaborole SCYX-7158 Phase 1 study**

SCYX-7158 belongs to a unique boron-based chemical class, the oxaboroles, which was originally provided by Anacor Pharmaceuticals and screened for activity against *T. brucei* at the University of California San Francisco. A unique collaboration between DND*i*, Anacor Pharmaceuticals (a biopharmaceutical company in Palo Alto, California, USA) and SCYNEXIS (a drug discovery and development company based in Research Triangle Park, North Carolina, USA), within a consortium that also included Pace University (USA) and Swiss TPH, enabled the identification of SCYX-7158, selected as a promising pre-clinical candidate in late 2009. In pre-clinical studies, SCYX-7158 was shown to be safe and efficacious to treat stage 2 HAT, as it is able to cross the blood-brain barrier. Pre-clinical development progressed successfully through 2010, and all pre-clinical data were published in *PLoS NTDs* in June 2011.[1] Batches of drug substance and drug product (capsules) were produced according to current good manufacturing practices (cGMP) and supplied for the Phase I clinical trial. In 2012, a robust tablet formulation was also developed in order to supply Phase II/III clinical trials, and manufacturing is planned for mid-2013.

14 PATIENTS out of 120 recruited at 1 site

Following clearance by the French ethics committee and regulatory authority, SCYX-7158 entered first-in-human studies in March 2012 and became DND*i*'s first entity resulting from its own lead optimization efforts to enter Phase I clinical studies. These studies are performed in order to assess its safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy volunteers of sub-Saharan origin. Following the first dose of SCYX-7158, pharmacokinetic results showed a longer than expected half-life in human plasma. Additional cohorts in humans assessed the safety profile, and following results from the intermediate dog study, the ascending dose study re-started in early 2013.

(1) *Jacobs RT.* et al. *(2011) SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 human African trypanosomiasis.* PLoS Negl Trop Dis *5: e1151.*



Fexinidazole

2012 OBJECTIVES:
- → **Start pivotal Phase II/III trial in three African countries**
- → **Launch the trial in Q2 in three sites (DRC) and Q3 in the remaining sites (CAR, DRC, South Sudan)**
- → **Prepare EMA discussion for stage 1 of the disease**
- → **Collaborate with FIND to develop new tools for diagnosis and follow up**

17 PATIENTS out of 510 recruited at 4 sites

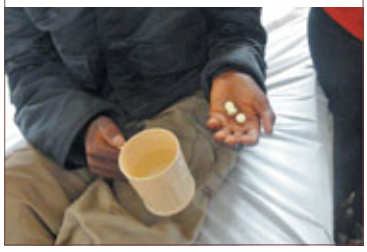
Fexinidazole is the first success of the extensive compound mining efforts pursued by DND*i* within the nitroimidazole project initiated in 2005. This drug entered Phase I first-in-human studies in September 2009 and Phase II/III in October 2012. This single pivotal Phase II/III study aims to prove the safety and efficacy of fexinidazole, with NECT as the active comparator. The study was initiated and is conducted by DND*i* in collaboration with the Swiss TPH and the human African trypanosomiasis national control programmes of the Democratic Republic of the Congo (DRC) and Central African Republic (CAR), in addition to MSF. DND*i* is co-developing the drug with Sanofi: DND*i* is responsible for pre-clinical, clinical, and pharmaceutical development, while Sanofi is responsible for the industrial development, registration, and production of the drug at its manufacturing sites. A safe API manufacturing process, able to be commercialized, has been developed in collaboration with Sanofi. The study will recruit patients at six clinical sites in DRC and one in CAR. By the end of 2012, 17 patients had been recruited at four active sites in DRC. Two additional sites will open in 2013: one in CAR, another in DRC ready to start Q2 2013. No site was chosen in South Sudan.

Partners:
Sanofi, France; Swiss TPH, Switzerland; Programme National de la Lutte Contre la Trypanosomiase Humaine Africaine (PNLTHA) DRC; Médecins Sans Frontières; and other HAT Platform members

Leadership:
Head of HAT Clinical Programme: Antoine Tarral; Medical Manager: Olaf Valverde; Clinical Manager: Séverine Blesson; Head of Pharmaceutical Development: Steve Robinson

Project start:
April 2007

Development



NECT – Nifurtimox-Eflornithine Combination Therapy

2012 OBJECTIVES:
- → **Support replacement of melarsoprol by NECT as first-line treatment for 2nd stage HAT in remaining sites**
- → **Increase advocacy for continued international support to R&D activities (including diagnostics) for HAT**

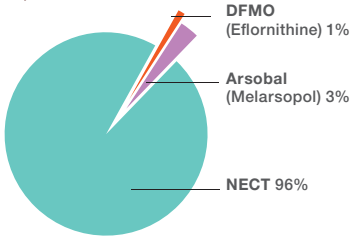
3,000 TREATMENTS in 2012, 2,618 of which in DRC. On the EML of 12 countries

NECT was developed by Epicentre, MSF, DND*i*, Swiss TPH, and the national HAT control programmes of the Republic of the Congo and DRC as a combination of eflornithine and nifurtimox. It quickly became first-line treatment for the neurological stage of *T. b. gambiense* sleeping sickness, as it is simpler to administer than eflornithine alone, making it more adapted to field conditions. NECT was included on the WHO Essential Medicines List in 2009. As of December 2012, all countries endemic to *T. b. gambiense* had added NECT to their national essential medicines list. Apart from Angola, all receive free supplies from WHO: 3,000 treatment kits were distributed in 2012.

The HAT Platform continues to advocate for the use of NECT, including supporting its inclusion in the WHO Essential Medicines List for children, for which a decision will be taken in 2013.

In September 2012, DND*i* and its partners concluded the follow-up of patients included in the 'NECT-Field' study, launched in 2009. The final report is being prepared, and results will be shared through scientific publications. This Phase IIIb study documents the safety, effectiveness, and ease-of-use of NECT in real-life conditions, in specific populations such as children and pregnant and breastfeeding women. A total of 630 patients were enrolled in the study, including 100 children, 13 pregnant women, and 34 breastfeeding women.

Distribution of stage 2 HAT treatments in DRC, 2012



Partners:
Médecins Sans Frontières (MSF); Swiss TPH; PNLTHA DRC; HAT Platform members

Leadership:
Head of HAT Clinical Programme: Antoine Tarral; Medical Manager: Olaf Valverde

Project start:
May 2004

Implementation

LEISHMANIASIS

Overcoming geographical variations to implement the most effective treatments

Leishmaniasis, caused by more than 20 species of *Leishmania*, is comprised of complex diseases which range from localized skin ulcers to lethal systemic disease. Visceral leishmaniasis (VL) is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anaemia, and is usually fatal within two years if left untreated. Cutaneous leishmaniasis (CL) is characterized by lesions of the skin that can become chronic and/or disfiguring, while post-kala azar dermal leishmaniasis (PKDL) is a disseminated skin infection. A common sequel of VL, PKDL serves as a parasite reservoir, thus contributing to the transmission of the disease.

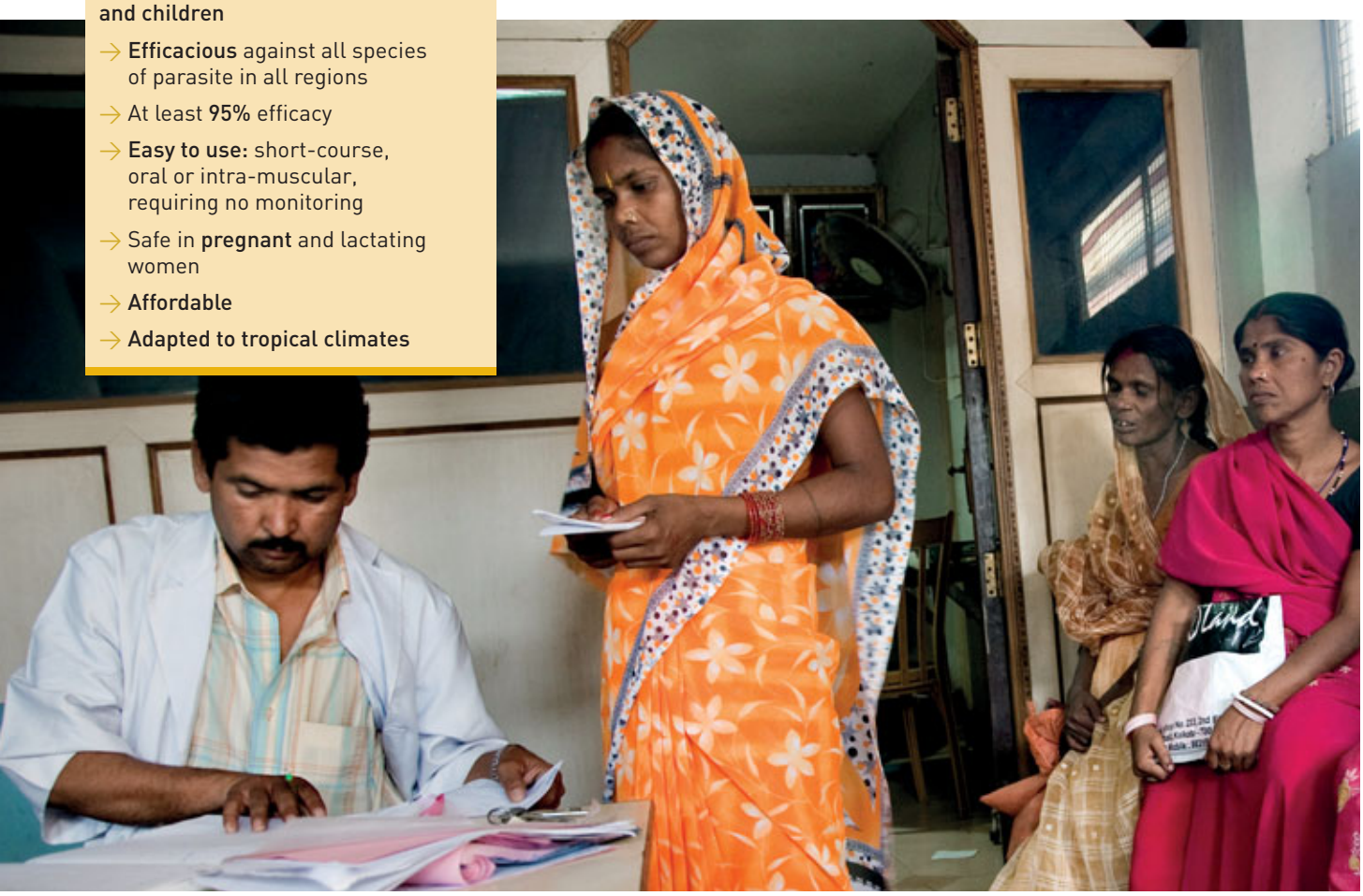
The natural history of VL is itself complex, its transmission fuelled by poverty and environmental degradation, the latter allowing the interplay of the different elements in the disease cycle (vectors and reservoirs) with humans. The different *Leishmania* species and their adaptation to specific reservoirs determine the cycle, zoonotic (transmission from animals to humans via the vector) or anthroponotic (transmission from humans to humans via the vector), which has implications for disease control.

The last decade has seen improvements in the treatment, diagnosis, and prevention of leishmaniasis in South Asia, notably through the development of liposomal amphotericin B, paromomycin, and miltefosine. Through a combination of active case detection, early treatment, vector control, and social mobilization, the WHO expects to reach its aim

Ideal Target Product Profile for VL

A new treatment for adults and children

- **Efficacious** against all species of parasite in all regions
- At least **95%** efficacy
- **Easy to use:** short-course, oral or intra-muscular, requiring no monitoring
- Safe in **pregnant** and lactating women
- **Affordable**
- **Adapted to tropical climates**



of eliminating anthroponotic visceral leishmaniasis from the Indian sub-continent by 2020.[1] More work, however, is needed to achieve similar results in other parts of the world, particularly East Africa and Latin America. Response to treatment varies between regions, requiring higher doses of the VL drugs, notably in East Africa, than in South Asia. Furthermore, there is evidence of geographical variations within East Africa. While the progress achieved has led to a clearer notion of how to treat patients across different continents, existing treatments are not ideal: potential of resistance development, low tolerability, long treatment duration and difficulty in administration, as well as high cost are still major drawbacks. New treatments that address these issues and address geographical variations and local realities are essential, notably in East Africa.

Although cutaneous leishmaniasis (CL) is not life-threatening, it can have devastating effects on local communities. Indeed, the disfiguring lesions it causes can lead to social stigmatization, with consequences such as ostracism, impaired education, and economic loss – all of this in populations with already limited resources. There is currently no satisfactory treatment for any form of CL, as none bring significant advantages while some have unacceptable safety profiles.

The ideal treatment for VL is a safe, effective, oral, short-course (10 days maximum) drug that would be efficacious in all geographic regions as well as against PKDL. The ideal treatment for CL is a safe, short-course, affordable, field-friendly topical or oral agent that cures lesions fast, with minimal scarring.

Ideal Target Product Profile for CL

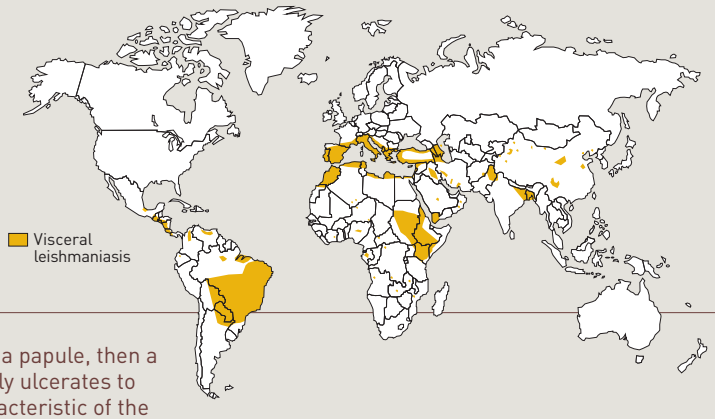
A new or oral treatment

- **Efficacious** against all species of *Leishmania*
- At least **95%** efficacy
- **Easy to use:** short-course, requiring no monitoring
- Leaving minimal scarring
- Safe in **pregnant** and lactating women
- **Affordable**
- **Adapted to tropical climates** (minimum three-year shelf-life)

(1) *Sustaining the drive to overcome the global impact of neglected tropical diseases: second WHO report on neglected tropical diseases World Health Organization, 2013.*

FACT SHEET

Leishmaniasis



WHAT IS THE IMPACT OF LEISHMANIASIS?

A total of 98 countries and 3 territories on 5 continents reported endemic leishmaniasis transmission. Among parasitic diseases, morbidity and mortality caused by leishmaniasis are surpassed only by malaria and lymphatic filariasis. 350 million people are at risk of the disease, most of them children. The annual incidence is estimated at approximately 0.7 to 1.2 million CL cases and 0.2 to 0.4 million VL cases, with a case-fatality rate of 10% for VL per year (i.e. 20,000 to 40,000 deaths per year).[1] However, mortality data are extremely sparse and generally represent hospital-based deaths only, so actual figures are expected to be higher. Co-infection with other infectious diseases is an increasing concern: HIV-VL co-infection has been reported in 35 countries worldwide.

HOW IS LEISHMANIASIS TRANSMITTED?

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

VL is usually caused by *L. donovani* and *L. infantum*.

CL is most frequently caused by *L. major*, *L. tropica*, and *L. aethiopica* in the Old World, and *L. braziliensis*, *L. mexicana*, and related species in the New World. Mucocutaneous leishmaniasis **(MCL)** can develop as a complication of CL.

PKDL occurs during, or more often after, recovery from VL. It is caused by *L. donovani* and is believed to be a parasite reservoir for human VL.

WHAT ARE THE SYMPTOMS?

VL is characterized by progressive fever, weight loss, enlarged spleen and liver, and anaemia. Untreated symptomatic VL is fatal in almost all cases.

CL is a small erythema that develops after a variable period at the site where an infected sandfly has bitten the host. The erythema develops into a papule, then a nodule that progressively ulcerates to become the lesion characteristic of the disease. Depending on the species, CL usually heals spontaneously within one to two years, but results in lifelong scars, which, depending on the size and location, may cause substantial trauma in affected individuals, particularly children.

MCL is characterized by partial or total destruction of mucous membranes of the nose, mouth, and throat.

PKDL is characterized by a macular, maculopapular, and nodular rash; starting from the face, it spreads to other parts of the body. PKDL is subject to geographical variations and can spontaneously heal, but can also develop into severe or persistent forms, requiring long courses of treatment.

CURRENT TREATMENTS AND THEIR LIMITATIONS

Existing therapies for VL have serious drawbacks in terms of safety, resistance, stability, and cost.[2] They have low tolerability, long treatment duration, and are difficult to administer.

→ **Pentavalent antimonials** (sodium stibogluconate – **SSG** – and meglumine antimoniate, such as Glucantime®): used for VL and CL for over 60 years. Acquired resistance in areas of high prevalence and high transmission. Serious cardiotoxicity leading to death is well documented. Require a 30-day parenteral treatment for VL. Registered in South-East Asia, Latin America, and some Mediterranean and African countries.

→ **Amphotericin B deoxycholate:** first-line treatment for VL in areas with high rates of unresponsiveness to antimonials and second-line treatment elsewhere. Need for hospitalization, constant renal monitoring of patients, 15-20 day treatment, and infusion-related adverse events are notable drawbacks. Amphotericin B displays dose-limiting toxicity. Registered in South Asia and some countries in Africa and Latin America.

→ **AmBisome®**: a liposomal formulation of amphotericin B, much safer and highly efficacious. A single infusion of 10 mg/kg has shown a 96.4% cure rate in Asia.[3] However, high cost and the need for a cold chain limit its widespread use.[4] Registered in India, USA, and Europe and used as a second-line drug for PKDL in East Africa and for VL in Brazil.

→ **Miltefosine:** oral drug registered and recommended in India, but expensive[5] and requires 28-day treatment. Major

(1) Alvar J. et al. *(2012) Leishmaniasis worldwide and global estimates of its incidence.* PLoS ONE *7: e35671.* *(2)* Seifert K. *(2011) Structures, targets and recent approaches in anti-leishmanial drug discovery and development.* Open Med Chem J *5: 31–9.* *(3)* Sundar S. et al. *(2011) Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial.* Lancet *377: 477-86.* *(4)* Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of key endemic countries as of 2007. *(5)* Ibid.

FACT SHEET

limitations include low compliance, with risk of resistance, and contraindication in pregnancy and mandatory contraception for women of child-bearing age for the duration of therapy and three months beyond. A recent study in Asia indicated an emerging lack of efficacy in monotherapy in the region.[1]

→ **Paromomycin (PM)**: a low-cost parenteral formulation that requires three weeks of painful intramuscular administration and is associated with some degree of renal and ototoxicity.

In 2010, DND*i* and LEAP partners **delivered the SSG&PM combination therapy for East Africa** that is now recommended as first-line treatment for VL in the region by the WHO Expert Committee on the Control of Leishmaniases. In India, DND*i* also conducted a Phase III trial to evaluate the combination of already registered drugs: AmBisome®, miltefosine, and paromomycin. They are now recommended by the WHO Expert Committee on the Control of Leishmaniases (see page 29).

Together with OWH/PATH and TDR, DND*i* is collaborating with the National Control Programmes of India and Bangladesh, MSF, the Bihar State Health Society, and the Indian Council for Medical Research to assess the feasibility of these new treatments at the primary health care level and facilitate their introduction for the treatment of VL in South Asia.

In Latin America, DND*i* is participating in a study sponsored by the Brazilian Innovation Agency (FINEP) to evaluate the safety and efficacy of Glucantime®, AmBisome®, and amphotericin B as monotherapies, and of AmBisome®-Glucantime® combination to treat VL patients.

Existing treatments for CL are not satisfactory. Many treatment regimens are associated with significant failure rates and considerable toxicity. Relapses are common and there are increasing reports of drug resistance emergence.

→ **Pentavalent antimonials**: given as first-line drugs through a series of intramuscular, intravenous, or intralesional injections. Serious side effects, require long treatment, not affordable for most patients and difficult to administer in poor rural areas.

→ Alternative treatments: **Liposomal amphotericin-B**, not fully tested on CL. Even if efficacious, cannot be deployed widely because of cost and delivery requirements. **Miltefosine**, potentially teratogenic and has side effects that make it unsuitable to treat CL. Registered in Colombia. Other treatments, such as thermotherapy and cryotherapy are used in certain clinics, but are expensive.

→ A promising approach is to combine **chemotherapy with immune-modulation**: initial elimination of parasites with chemotherapy, followed by modification of the patient's immune response by an immune-enhancing agent (either a **therapeutic vaccine** or an appropriate adjuvant) could lead to quick recovery and control of persisting parasites. Therapeutic vaccines have yielded positive results for CL in Brazil and Venezuela. Several chemical immunomodulators have been tested for cancer and other diseases, and could be useful for CL therapy.

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

DND*i*'s **short-term** approach was to develop new treatments by combining existing drugs and/or shortening treatment duration in order to increase tolerability, reduce burden on health systems, and offer greater affordability, whilst also preventing or delaying emergence of resistance. Another objective was to assess efficacy and safety of existing drugs in other countries and regions to extend registration and availability to patients.

Leishmania-HIV co-infection is a newly emerging problem. It is very difficult to manage, due to poor response to treatment with frequent relapses of disease, and is eventually fatal. DND*i* is working towards a new treatment for HIV/VL co-infected patients in Africa.

DND*i*'s **long-term** strategy is to bring new drug candidates into clinical development through its lead optimization programme.

For CL, DND*i*'s objective is to develop short, safe, efficacious, affordable, and field-adapted treatments against *L. tropica* and *L. braziliensis* – because of the severity of the disease and its public health importance. As a **short-term** strategy, DND*i* is developing a topical treatment of an existing drug. In the **longer term**, DND*i* aims to develop a novel field-adapted modality of treatment that would combine anti-parasite and immune-modifying agents, with a strong emphasis on safety, efficacy, cost, quality of scar and reduced need for follow-up and interaction with health systems.

In addition, DND*i* supports the **Leishmaniasis East Africa Platform** (LEAP) (see page 48) that aims to geographically extend all currently available VL drugs in East Africa and to develop new therapies suitable for the region, as well as to build and sustain capacity in the region for conducting clinical trials.

By 2018, DND*i* aims to deliver from its VL-specific portfolio:

→ An oral, safe, effective, low-cost and short-course treatment

→ A new treatment for PKDL that is shorter course and better tolerated than current options

→ Treatment options for HIV/VL co-infected patients

By 2018, DND*i* aims to deliver from its CL-specific portfolio:

→ A safe, effective, and shorter-course treatment for CL

(1) Rijal S. et al. *(2013)* Increasing failure of miltefosine in the treatment of kala-azar in Nepal and the potential role of parasite drug resistance, reinfection, or noncompliance. Clin Infect Dis *56: 1530-8.*

Research

Partners:
TB Alliance, USA; Advinus Therapeutics, India; Central Drug Research Institute, India; LSHTM, UK; Auckland University, New Zealand; Laboratory of Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, Belgium; WuXi AppTech, China

Leadership:
Head of Drug Discovery: Eric Chatelain; Project Coordinator: Delphine Launay

Project start:
July 2010

Nitroimidazole backup

2012 OBJECTIVE:
→ **Profile potential backup candidates to VL-2098 for the treatment of VL**

In 2010, the Global Alliance for Tuberculosis Drug Development (TB Alliance) and DND*i* entered into a first-ever royalty-free license agreement between two not-for-profit drug developers. 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 VL. Within TB Alliance's nitroimidazole library, VL-2098 was identified as a candidate with potent efficacy against VL (see below). A focused programme is ongoing to identify a backup pre-clinical candidate in case VL-2098 does not successfully complete pre-clinical testing. Over 200 analogues have been prepared so far.

A number of backup compounds have now been identified as meeting the targets set at the start of the project, including *in vivo* efficacy. Additional studies are in progress to further characterize these and select the compound with the best chance of becoming a successful clinical candidate meeting the criteria for good *in vivo* efficacy and an acceptable safety profile.

Translation

Partners:
TB Alliance, USA; Advinus Therapeutics, India; Central Drug Research Institute, India; LSHTM, UK; Auckland University, New Zealand; Bertin Pharma, France; ChemDepo Inc., USA

Leadership:
Discovery & Pre-clinical Director: Robert Don; Project Coordinators: Stéphanie Braillard, Delphine Launay

Project start:
July 2010

VL-2098

2012 OBJECTIVE:
→ **Complete the pre-clinical package (regulatory safety studies and API and drug product manufacturing) in order to start a clinical Phase I study in 2015**

From 70 nitroimidazoles belonging to four chemical sub-classes, VL-2098 was identified as the most potent molecule with a favourable safety profile for in-depth evaluation as a clinical candidate. VL-2098 profiles as selective for *L. donovani* with efficacy in acute and chronic VL animal models following oral dosing. Safety testing with administrations at several multiples of the efficacious dose is ongoing and we expect to complete these studies and propose VL-2098 as a clinical candidate late in 2013.

Translation

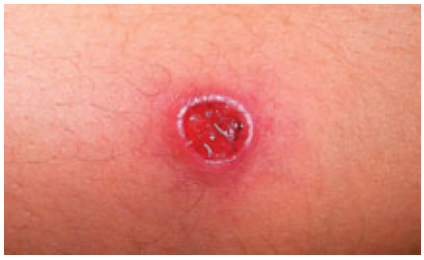
Partners:
PECET (Program for the Study and Control of Tropical Diseases), Universidad de Antioquia Medellin, Colombia; Humax Pharma, Columbia; Imperial College of Science, Technology and Medicine, UK; Centro de Pesquisas René Rachou, Brazil

Leadership:
Head of CL Clinical Programme: Farrokh Modabber / Byron Arana; Clinical Managers: Fabiana Alves, Gwenaëlle Carn

Project start:
September 2011

Anfoleish (Cutaneous Leishmaniasis)

2012 OBJECTIVE:
→ **Develop a topical anti-parasitic treatment containing amphotericin B for the treatment of CL**



The rationale for development of a topical formulation of amphotericin B was to provide a treatment to be applied locally at the CL lesion, with high anti-parasitic effect, but without the systemic toxicity associated with amphotericin B. Anfoleish was selected by DND*i* for clinical development after completion of pre-clinical assessments. The first study will be a Phase Ib/II trial aiming to assess the safety, PK, and efficacy of an amphotericin B cream in patients with CL caused by *L. braziliensis*. If this trial shows that Anfoleish is efficacious against *L. braziliensis*, a multi-country Phase III study will be planned in several endemic countries in Latin America.

Fexinidazole

2012 OBJECTIVE:
→ **Initiate a Phase II proof-of-concept study to determine the efficacy and safety of using fexinidazole for the treatment of visceral leishmaniasis**

Fexinidazole has shown potent activity against *L. donovani in vitro* and *in vivo* in a VL mouse model. It was assessed in three Phase I studies in healthy volunteers and was shown to be safe when given as a single dose or as repeated dosing after 14 days. This Phase II proof-of-concept study will evaluate fexinidazole for the treatment of primary VL patients in Sudan. If successful, it will be followed by a Phase II/III programme in South Asia, East Africa, and Brazil.

Partners:
Kenya Medical Research Institute (KEMRI), Kenya; Institute of Endemic Diseases (IEND), University of Khartoum, Sudan; MSF; LEAP; BaseCon, Denmark; Utrecht University, The Netherlands

Leadership:
Head of VL Clinical Programme: Manica Balasegaram; Clinical Manager: Sally Ellis; Project Coordinator: Clélia Bardonneau

Project start: September 2012

Translation

New VL treatments – Bangladesh

2012 OBJECTIVE:
→ **Conduct Phase III/IV study to demonstrate feasibility of implementing new treatment modalities recommended by WHO (miltefosine-paromomycin, AmBisome®-miltefosine, AmBisome®-paromomycin, single-dose AmBisome®) in primary healthcare settings in Bangladesh**

The Phase III trial conducted by DND*i* and its partners in 2010 demonstrated the efficacy of combination therapies based on AmBisome®, miltefosine, and paromomycin. This two-step Phase III study (first in hospital settings, then in primary healthcare centers) is using these combination therapies in Bangladesh. By the end of 2012, 431 out of 674 patients had been recruited. The trial is expected to end in 2013 and results will be available in 2014.

Partners:
Ministry of Health and Family Welfare, Bangladesh; International Centre for Diarrhoeal Disease Research (ICDDR,B), Bangladesh; Shaheed Suhrawardy Medical College and Hospital (ShSMC), Bangladesh

Leadership:
Head of Leishmaniasis Clinical Programme: Manica Balasegaram; DND*i* India Director of R&D Operations: Bhawna Sharma; Clinical Managers: Sally Ellis and Vishal Goyal; Project Coordinator: Abhijit Sharma; Assistant Project Coordinator: Pankaj Kumar

Project start: July 2010

Development

New VL treatments – Africa

2012 OBJECTIVES:
→ **Develop new shorter-course treatments for VL in East Africa and geographically extend available anti-leishmanial drugs to all countries of the region**
→ **Support ongoing registration activities for use of SSG&PM**
→ **Assess the efficacy and safety of miltefosine combinations for East Africa**

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.

The LEAP 0208 Study, coordinated by DND*i* and LEAP, to assess combinations of existing drugs to treat VL in Africa, aimed to evaluate the safety and efficacy of miltefosine monotherapy, AmBisome®-SSG, and AmBisome®-miltefosine combination treatments. Recruitment started in Kenya and Sudan in 2010 and ended in March 2012. The trial collected 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 were evaluated. Preliminary safety and efficacy results available at the beginning of 2013 will inform the decision to evaluate one of these combinations in a Phase III trial.

The LEAP AMBI 0106 trial which aimed to determine the minimum dose of AmBisome® that is efficacious, safe, and cost-effective to treat VL in Africa was completed in 2011 and results have been submitted for publication.

Partners:
KEMRI, Kenya; IEND, University of Khartoum, Sudan; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; University of Makerere, Uganda; LSHTM, UK; Slotervaart Hospital, The Netherlands Cancer Institute, The Netherlands; Royal Tropical Institute (KIT), The Netherlands; Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; MSF; i+solutions, The Netherlands; OneWorld Health (OWH/PATH), USA; LEAP; Institute of Tropical Medicine-Antwerp, Belgium

Leadership:
Head of DND*i* Africa: Monique Wasunna; Head of VL Clinical Programme: Manica Balasegaram; Clinical Manager: Sally Ellis; Project Coordinator: Clélia Bardonneau

Project start:
November 2004

Development

Development

Partners (AfriCoLeish):
LSHTM, UK; Institute of Tropical Medicine-Antwerp, Belgium; MSF, The Netherlands; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; IEND, University of Khartoum, Sudan; LEAP; Slotervaart Hospital, The Netherlands Cancer Institute, The Netherlands; Utrecht University, The Netherlands

Leadership:
Head of Leishmaniasis Clinical Programme: Manica Balasegaram; Clinical Manager: Sally Ellis; Project Coordinator: Clélia Bardonneau

Project start:
September 2011

HIV/VL

2012 OBJECTIVE:
→ **Identify and deliver a safe and highly effective treatment for VL in HIV co-infected patients that will improve long-term survival of these patients**

A first study will evaluate the efficacy of a combination regimen of AmBisome® with miltefosine, and of AmBisome® (at a higher dose) monotherapy in Ethiopian patients co-infected with VL and HIV. A secondary objective is to assess relapse-free survival at day 390 (after initial cure at day 28 or at day 56 after extended treatment). Viral load and CD4 count will be measured in all patients, and the pharmacokinetics of antiretrovirals, AmBisome®, and miltefosine, as well as immune function markers will be examined in a subset of patients.

In anthroponotic transmission areas, the WHO recommends secondary prophylaxis with drugs not given in treating primary VL cases to avoid resistance development. A second, follow-up study, sponsored by the Institute of Tropical Medicine-Antwerp, Belgium, will assess the use of pentamidine as secondary prophylaxis for HIV/VL co-infected patients.

Development

Partners:
René Rachou Research Institution – Fiocruz-MG, Brazil; Paediatric Hospital Joao Paulo II – FHEMIG, Brazil; Brasilia University, Brazil; Montes Claros State University, Brazil; Piaui Federal University, Brazil; Sergipe Federal University, Brazil; Leishmaniasis Control Programme/Ministry of Health, Brazil; Universidade Estadual do Rio de Janeiro, Brazil

DND*i* support:
Clinical Manager: Fabiana Alves

Project start:
February 2011

New VL treatments – Latin America

2012 OBJECTIVE:
→ **Support the Brazilian Ministry of Health and its partners to conduct a Phase III trial assessing the efficacy and safety of amphotericin B deoxycholate, AmBisome®, and AmBisome®-Glucantime® combination for the treatment of VL in Latin America**

About 90% of VL cases in Latin America occur in Brazil, and most of them affect children. In 2011, Brazil reported 3,894 new cases with a fatality rate of 6.7%. DND*i* is supporting the implementation of a Phase III clinical trial sponsored by the Brazilian Ministry of Health to assess treatments for VL. The primary objective of the study is to assess the efficacy and safety of amphotericin B deoxycholate, AmBisome®, and AmBisome® combined with Glucantime®, as compared to the first-line treatment, Glucantime®, for the treatment of VL patients in Brazil. The study progressed well during 2012, with five active sites and a total of 205 patients recruited (out of 426 total), and is expected to be completed by 2014. Evidence provided by this project will guide policies on the treatment of VL caused by *L. infantum* in Brazil.

205 PATIENTS
recruited
at 5 sites

SSG&PM – Sodium stibogluconate & paromomycin

2012 OBJECTIVE:
→ **Facilitate implementation of and access to SSG&PM in key endemic areas of East Africa by supporting registration of paromomycin (PM) and document safety through a pharmacovigilance study**

In 2010, DND*i* and LEAP successfully showed that the combination of SSG and PM (17 days) was as efficacious as SSG monotherapy (30 days), with the advantage of being shorter course, therefore lessening the burden on patients and health systems, and more cost-effective. Since then, DND*i* and LEAP have worked with local ministries of health to ensure recommendation and uptake of the new treatment following its recommendation as first-line therapy for VL patients in East Africa by the WHO Expert Committee on the Control of Leishmaniases. First registration (of PM) was obtained in Uganda at the end of 2011, and registration was obtained in Kenya in January 2013. The registration process is underway in Sudan and Ethiopia. Nonetheless, implementation has already begun in the region, as the treatment was recommended. In addition, it has been included in the national drugs lists of Sudan, South Sudan, and Ethiopia and in Kenya's national VL guidelines. SSG&PM treatment has been rolled out in Sudan and Uganda in public health structures, as well as in MSF centres. A pharmacovigilance study with MSF to monitor safety and effectiveness of SSG&PM was initiated in 2011 and, by the end of 2012, approximately 2,300 patients had been treated in Ethiopia, Sudan, Kenya, and Uganda. SSG&PM is also being used to treat VL patients in South Sudan as part of its national programme.

2,332 PATIENTS in the pharmaco-vigilance study treated since 2011 in 4 countries

Partners:
KEMRI, Kenya; IEND, University of Khartoum, Sudan; University of Makerere, Uganda; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LSHTM, UK; Slotervaart Hospital, The Netherlands Cancer Institute, The Netherlands; KIT, The Netherlands; Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; MSF; i+ solutions, The Netherlands; OWH/PATH, USA; LEAP

Leadership:
Head of Leishmaniasis Clinical Programme: Manica Balasegaram; Clinical Manager: Sally Ellis; Head of DND*i* Africa: Monique Wasunna

Project start:
November 2004

Implementation

New VL treatments – Asia

2012 OBJECTIVE:
→ **Conduct effectiveness studies in South Asia to demonstrate feasibility in implementing the new treatment modalities recommended by WHO (miltefosine-paromomycin, AmBisome®-miltefosine, AmBisome®-paromomycin, single-dose AmBisome® 10 mg/kg) in primary healthcare settings in India with a view to extending their use in the region to support control and elimination strategies in the countries of highest prevalence in South Asia**

The Phase III trial conducted by DND*i* and its partners in 2010 demonstrated the efficacy of combination therapies based on AmBisome®, miltefosine, and paromomycin. An additional study by Sundar *et al.* showed the efficacy of single-dose AmBisome® given as an intravenous infusion. To facilitate the introduction of these new treatments for VL in South Asia, DND*i* developed a partnership consortium with TDR and OWH/PATH, in collaboration with health authorities at state and national levels. DND*i* will work to implement single-dose AmBisome® in the public sector in India (with TDR) and new combination therapies in the private sector (with OWH/PATH). Effectiveness studies are being implemented in the region to demonstrate that such treatments can be safely implemented through primary healthcare systems in both the public and the private sectors. This includes a pilot project in the Bihar State of India implementing combination therapies at the primary healthcare level and single-dose AmBisome® at the hospital level. The project is monitoring pharmacovigilance as well as treatment effectiveness of the different treatment options when used outside of a clinical trial by the public sector. The study began in 2012 in two districts in India. By the end of the year, 213 patients had been recruited, out of 7,000 planned. The trial is expected to end in 2015 and results will be available in 2016.

213 PATIENTS out of 450 recruited at 10 sites in India

431 PATIENTS out of 674 recruited at 3 sites in Bangladesh

Partners:
Indian Medical Research Council (ICMR); Rajendra Memorial Research Institute of Medical Sciences (RMRI), India; Kala Azar Medical Research Centre, India; State Health Society, Bihar (BSHS), India; National Vector Borne Disease Control Programme (NVBDCP), India; Community Based Medical College (CBMC), Mymensingh, Bangladesh; Ministry of Health and Family Welfare, Bangladesh; ICDDR,B, Bangladesh: ShSMC, Bangladesh; University of Tokyo, Japan; OWH/PATH, USA; Institute of Tropical Medicine-Antwerp, Belgium; LSHTM, UK; WHO-TDR; WHO (SEARO, Geneva); MSF

Leadership:
Head of Leishmaniasis Clinical Programme: Manica Balasegaram; DND*i* India Director of R&D Operations: Bhawna Sharma; Clinical Managers: Sally Ellis and Vishal Goyal; Project Coordinator: Abhijit Sharma; Assistant Project Coordinator: Pankaj Kumar

Project start:
December 2006

Implementation

CHAGAS DISEASE
American trypanosomiasis

Treat now and boost innovation for tomorrow – millions are waiting

Over a century after its discovery, Chagas disease is still endemic to 21 countries in Latin America, where PAHO estimates that approximately 8 million people are infected and 100 million are at risk of the disease.[1] Imported Chagas disease affecting patients from endemic regions is increasingly recognized as an emerging problem in the USA and Europe, due to migration from Latin America. The Centers for Disease Control and Prevention (CDC) estimates that over 300,000 persons with *Trypanosoma cruzi* infection live in the USA. Most of the true burden of Chagas disease can remain hidden for years – many infected people remain asymptomatic for more than a decade.[2] Despite an economic burden equivalent to that of other prominent global diseases, such as rotavirus,[3] Chagas disease is among the neglected diseases that receive the least investment for R&D – less than USD 25 million in 2011, only half of which was invested in drug discovery for the disease [4] – of the more than USD 3 billion spent for R&D for neglected diseases.

Ideal Target Product Profile for Chagas Disease

A new treatment for **both acute and chronic** phases:

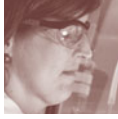
- Useful against most parasite species in all regions
- Better **safety** profile than existing drugs
- Non-inferior **efficacy** to benznidazole
- **Easy-to-use** treatment: oral, once-a-day for less than 30 days, requiring no hospitalization and little or no monitoring
- **Affordable**
- **Adapted to tropical climates** (minimum three-year shelf-life)

The only two drugs approved for treating acute Chagas disease were developed over 40 years ago and are far from ideal. Symptom management has generally been the only treatment option for patients with cardiac or digestive involvement at the chronic stage of the disease. There is no vaccine and no appropriate test of cure. Until recently, the main focus of the fight against Chagas disease was to interrupt transmission through the deployment of vector-control strategies and the screening of blood donors. Sustaining and consolidating advances made in controlling the disease is a key challenge, as well as expanding availability of diagnosis and treatment of patients.

For the existing drugs, benznidazole and nifurtimox, which have been used for decades, strong clinical trial evidence for the efficacy of either drug for the treatment of adults with chronic disease is lacking,[5] though this is likely to change with upcoming results of TRAENA and BENEFIT studies. Safety and tolerability remain important concerns. Side effects range from skin rashes to seizures and other nervous system disorders.[6] In addition, long treatment periods (60-90 days) make patient compliance challenging, with increased risk of drug resistance development. Despite these issues, there is consensus that in the lack of better options, drug treatment should be offered to adults (19-50 years of age) without advanced Chagas heart disease and be considered optional for those older than 50.

In order to effectively fight the disease, new treatments that are safe and effective against the chronic phase of the disease – which is when most patients are diagnosed – are sorely needed. Today, approximately 99% of people who require treatment for Chagas disease are not receiving it. In addition, to gain understanding of the disease progression and ease the development of test-of-cure diagnostic tools that support drug development, identification of biomarkers is essential.

(1) *http://new.paho.org/hq/index.php?option=com_content&view=article&id=5856&Itemid=4196.* ***(2)*** *Bruce YL.* et al. *(2013) Global economic burden of Chagas disease: a computational simulation model,* Lancet Infect Dis *13: 342-8.* ***(3)*** Ibid. ***(4)*** *G-FINDER Neglected Disease Research and Development: a five year review, Policy Cures, December 2012: http://policycures.org/downloads/GF2012_Report.pdf.* ***(5)*** *Clayton, J. (2010) Chagas disease: pushing through the pipeline.* Nature *465: S12–5.* ***(6)*** Ibid.



FACT SHEET

Chagas Disease
American Trypanosomiasis

WHAT IS THE IMPACT OF CHAGAS DISEASE?

Chagas disease is endemic to 21 countries in Latin America, where 100 million people are at risk. It is estimated that 8 million people are infected, leading to approximately 12,000 deaths every year in the region[1] Approximately 55,000 new cases arise each year.[2] Increased migration and population movements have changed the epidemiology and geographic distribution of Chagas disease, which is now found outside Latin America, including in the United States, Europe, Australia, and Japan.

HOW IS CHAGAS DISEASE TRANSMITTED?

Chagas disease is caused by the kinetoplastid protozoan parasite *Trypanosoma cruzi*, transmitted through the bite of a triatomine vector known as the 'kissing bug'. Other routes of transmission include blood transfusion, organ transplantation, as well as congenital and, less often, oral routes through ingestion of contaminated food or beverage especially in Amazonia.

WHAT ARE THE SYMPTOMS?

The disease has two clinical phases:

→ **The acute phase** (fatal for 2-8% of children),[3] often asymptomatic or unrecognized due to non-specific symptoms, such as fever, malaise, and enlarged lymph nodes, spleen, and liver. In less than half the cases, first visible signs can be a skin lesion or a purplish swelling of one eyelid (known as Romaña's sign). These symptoms spontaneously resolve in 4-6 weeks.

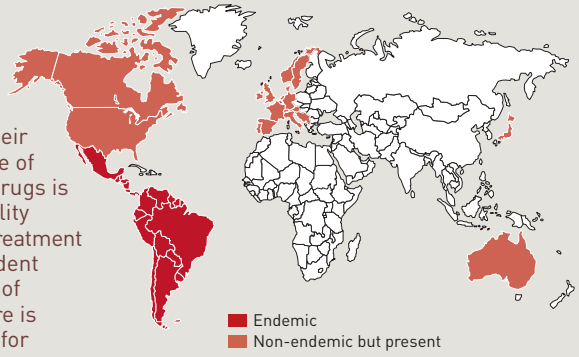
→ **The chronic phase**, which can be divided into two stages:

• The chronic, silent, and asymptomatic 'indeterminate' stage, during which patients can transmit the parasite to others, especially through vertical transmission or transfusion, while showing no signs of the disease, and which may last decades after infection.

• The chronic, symptomatic stage, developing later in up to 30% of infected patients, causes cardiopathies, digestive tract pathologies, and nervous system irregularities.[4] Chagas disease is the leading cause of infectious heart disease (cardiomyopathy) in Latin America.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments, **benznidazole and nifurtimox**, are effective against the acute phase of infection, and while there is increasing evidence of their efficacy against the chronic phase of the disease, broad use of these drugs is limited due to safety and tolerability issues. Drawbacks include long treatment periods (60-90 days), dose-dependent toxicity, and a high drop-out rate of patients due to side-effects. There is currently no approved treatment for chronic disease with target organ involvement. In 2011, DND*i* and partners produced a paediatric dosage form of benznidazole to fill the treatment gap for this population.



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

DND*i*'s **short-term** goal was to make better use of existing treatments, notably through the development of a paediatric dosage form of benznidazole – a goal which was achieved: this treatment was granted registration by the Brazilian regulatory authorities in December 2011 and DND*i* is working with LAFEPE, the manufacturer, to ensure it is widely accessible to all those in need.

As a **medium-term** strategy, DND*i* is assessing known compounds already in development against fungal infections, such as the new azole antifungal drug, E1224, for activity against *T. cruzi* in adult chronic patients. Also, we are searching for potential biomarkers of treatment response to enhance clinical trial capabilities of new substances.

As part of its **long-term** strategy, DND*i* continues to identify and engage partners from private and public sectors in order to identify, characterize, and advance the development of promising compounds as well as to pursue discovery efforts for innovative therapies.

In addition, DND*i* supports clinical research capabilities through the Chagas Clinical Research Platform (see page 50), which was launched in 2009.

By 2018, DND*i* aims to deliver from its Chagas-specific portfolio:

→ An effective and safe oral treatment for the treatment of chronic Chagas disease, ideally effective also against the acute form of the disease

→ Biomarkers to gain understanding of disease progression and ease the development of test-of-cure diagnosis tools that support drug development

(1) http://new.paho.org/hq/index.php?option=com_content&task=view&id=5856&Itemid=4196. *(2) Organizacion Panamericana de la Salud. Estimacion cuantitativa de la enfermedad de Chagas en las Americas. Montevideo, Uruguay: Organizacion Panamericana de la Salud, 2006.* *(3) Parada H.* et al. *(1997) Cardiac involvement is a constant finding in acute Chagas' disease: a clinical, parasitological and histopathological study.* Int J Cardiol *60: 49–54.* *(4) www.msfaccess.org/sites/default/files/MSF_assets/NegDis/Docs/NEGDIS_report_Chagas_UpdateOnProgress_ENG_2006.pdf.*

Research

Partners:
University of Auckland, New Zealand; TB Alliance, USA; Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto (UFOP), Brazil; Institut Pasteur Korea (IPK), South Korea

Leadership:
Head of Drug Discovery: Eric Chatelain; Project Coordinator: Delphine Launay

Project start:
April 2012

Nitroimidazole

2012 OBJECTIVE:
→ **Assess the nitroimidazole series (developed by TB Alliance) for its potential to identify a candidate for Chagas disease treatment, with the goal of proposing a pre-clinical candidate**

Lead optimization activities have provided a better understanding of the essential features for a drug to be efficacious for the treatment of Chagas disease. This insight will be used to propose a new pre-clinical candidate from the nitroimidazole class that is more potent and with a better safety profile than the drugs currently used (nifurtimox and benznidazole). Work on the nitroimidazooxazines series has concentrated on compounds from the VL-2098 backup programme (see page 26).

Fexinidazole is a nitroimidazole currently in Phase IIb/III development for HAT. It is very efficacious in a wide variety of rodent Chagas disease models and current work aims to assess fexinidazole suitability for development as a Chagas disease therapy. As safety, pre-clinical and clinical data are available, we aim to rapidly progress fexinidazole to clinical proof-of-concept studies.

Translation

Partners:
University of California San Francisco (UCSF), USA

Leadership:
Head of Drug Discovery: Eric Chatelain; Project Coordinator: Stéphanie Braillard

Project start:
September 2010

K777

2012 OBJECTIVE:
→ **Review the potential of K777 as a clinical candidate: progress IND-enabling studies**

K777 is a vinyl sulfone cysteine protease inhibitor, which inhibits cruzain, a key protease required for the survival of *T. cruzi*. K777 was originally characterized by the Sandler Center for Research in Tropical Parasitic Disease at UCSF and has since been shown to be safe and efficacious in animal models of acute and chronic Chagas disease. The main objective of the project is to perform the required pre-clinical studies (safety pharmacology and toxicology) in order to complete the Investigational New Drug (IND) application for clinical evaluation of K777 for the treatment of Chagas disease. Safety pharmacology studies were completed, and no effects on electrocardiogram (ECG) or respiratory function were observed, even at the high dose. Dose Range Finding/Maximum Tolerated Dose (DRF/MTD) in non-human primates and 28-day toxicity study will be performed in 2013 in order to finalize writing of IND for submission by early 2014.

Biomarkers

2012 OBJECTIVE:
→ **Identify and evaluate biomarkers to be used in Chagas disease Phase III clinical trials and future registration**

An important hurdle for the development of new drugs for chronic Chagas disease is the lack of clear and early markers that can indicate treatment parasitological outcome and later indicate definite cure. To date, the only definite outcome is seroconversion, which may take up to ten or more years. There is therefore a need to measure treatment effect via an indirect, surrogate marker.

Short-term objectives aim to assess the best sampling strategy to measure parasite clearance via *Trypanosoma cruzi* DNA quantification through polymerase chain reaction (PCR) and validate PCR as a measure of treatment response in Chagas disease, i.e. as a surrogate marker for Phase III clinical trials and regulatory submission:

- A clinical trial conducted in collaboration with MSF-Spain, with PCR assay support provided by the UMSS in Bolivia and quality assurance from INGEBI-CONICET in Buenos Aires, Argentina aims to evaluate sampling procedures for PCR. Patient recruitment was finalized in December 2011 and patients were followed-up for 12 months. Results are expected by mid-2013.
- In 2012, evaluation of samples from the TRAENA study (a collaboration to support the use of PCR as a method to evaluate treatment response) was concluded. Results are expected in 2013.
- Funding from the Wellcome Trust was obtained in 2011 for a study on naturally infected macaques to evaluate candidate biomarkers, and determine whether blood PCR assays can differentiate between parasitological cure and treatment failure. The study, conducted in collaboration with the Texas Biomedical Research Institute and the University of Georgia, will be completed at the end of 2014.

PCR STUDY:
220 patients

- Finally, DND*i* is working with FIND and PAHO/TDR to optimize PCR (in particular the extraction step).

In the longer-term, DND*i* is working towards identifying new biomarkers of treatment response and to understand the progression of Chagas disease:

- The study on macaques will evaluate lytic antibodies, T-cell assays, multiplex serodiagnostic assay and gene expression profiling.
- In the context of the E1224 study, markers of treatment response, such as conventional and non-conventional serology, multiplex serodiagnostic assays, selected pro-thrombotic factors and apolipoprotein A1, will be assessed.
- A project with Geneva University Hospitals and McGill University will assess the use of proteomic signatures and other biomarkers as potential test of efficacy in sera samples of nifurtimox-treated Chagas patients. A first study was concluded in 2012, for which results will be available in 2013. Results from available proteomic studies will be compiled and additional evaluation may be conducted using adult sera from larger cohorts (e.g. TRAENA and NHEPACHA), and an exploratory study using children sera will be carried out.
- DND*i* is part of the NHEPACHA network of investigators created for the long-term cohort evaluation of potential biomarkers.

Translation

Partners:
Médecins Sans Frontières (MSF); Universidad Mayor de San Simon, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Barcelona Centre for International Health Research (CRESIB), Spain; Dr Mario Fatala Chaben National Institute of Parasitology (INP), Argentina; University of Georgia, USA; Texas Biomedical Research Institute, USA; University of Texas at El Paso, USA; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina; McGill University, Canada; Geneva University Hospitals, Switzerland; NHEPACHA network

Leadership:
Head of Drug Discovery: Eric Chatelain; Head of Chagas Clinical Programme: Isabela Ribeiro; Clinical Trial Manager: Jayme Fernandes; Project Coordinator: Bethania Blum

Project start:
February 2010

Fenarimol

2012 OBJECTIVE:
→ **Complete studies needed for the nomination of the pre-clinical candidate out of the optimized leads from the fenarimol series**

Two interesting candidates from the fenarimol series of compounds were identified through lead optimization efforts. The project is now in its non-regulatory pre-clinical phase, with further profiling of candidates before nominating one candidate for further regulatory pre-clinical development. The objective is to perform Good Laboratory Practice (GLP) safety studies, as well as Chemistry, Manufacturing, and Control (CMC) studies on the selected candidate compound in order to file a formal investigational new drug (IND) application and move the candidate to first-in-man studies.

Translation

Partners:
Centre for Drug Candidate Optimisation (CDCO)/Monash University, Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto (UFOP), Brazil; Institut Pasteur Korea (IPK), Korea

Leadership:
Head of Drug Discovery: Eric Chatelain; Project Coordinator: Delphine Launay

Project start:
December 2011

Translation

Partners:
Eisai Co. Ltd, Japan; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Universidad Mayor de San Simon, Bolivia; Universidad Autónoma Juan Misael Saracho, Bolivia; Collective of Applied Studies and Social Development (CEADES), Bolivia; NUDFAC – Nucleus of Pharmaceutical and Cosmetics Development, Brazil; Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina

Leadership:
Head of Chagas Clinical Programme: Isabela Ribeiro; Clinical Trial Manager: Glaucia Santina; Project Coordinator: Erika Correia, Bethania Blum

Project start:
February 2010

Azole E1224

2012 OBJECTIVE:
→ **To evaluate the safety and efficacy of E1224 for the treatment of adult patients with chronic indeterminate Chagas disease; conclude recruitment of Phase II study and start planning for Phase III**

231 PATIENTS recruited at 2 sites

In 2009, DND*i* joined forces with Eisai Co. Ltd – the Japanese pharmaceutical company that discovered E1224 – to develop this new chemical entity for Chagas disease. E1224 is a pro-drug which converts to the active drug ravuconazole in the human body, leading to improved absorption and bioavailability. The Phase II proof-of-concept study started in July 2011 in Cochabamba and Tarija, Bolivia, the country which carries the world's largest Chagas disease burden.

The study evaluates the potential of E1224 as an oral, easy-to-use, safe, and affordable treatment for Chagas disease and will explore promising biomarkers of therapeutic response in Chagas disease (see also 'Biomarkers' project). This randomized, multicentre, placebo-controlled, safety and efficacy study will evaluate three oral E1224 dosing regimens (high dose for four weeks and eight weeks; low dose for eight weeks) and includes benznidazole (5 mg/kg/day) as a positive control.

The study concluded recruitment of 231 adult patients with chronic indeterminate stage of Chagas disease in June 2012. Twelve month follow-up will be completed mid-2013 and results will be available Q4 2013.

Implementation

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, Hospital Independencia, Santiago del Estero, Argentina; CONICET/INGEBI, Argentina; Centro Nacional de Diagnóstico e Investigación de Endemo-epidemias (CeNDIE), Ministry of Health, Argentina; University of Liverpool, UK; NUDFAC, Brazil; Administración Nacional de Laboratorios e Institutos de Salud (ANLIS), Argentina

Leadership:
Head of Chagas Clinical Programme: Isabela Ribeiro; Clinical Trial Manager: Jayme Fernandes; Project Coordinator: Bethania Blum

Project start:
May 2011

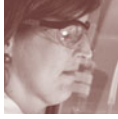
Paediatric dosage form of benznidazole

2012 OBJECTIVE:
→ **Implement an access plan for broad availability and implementation of paediatric benznidazole in Latin America**

REGISTERED in Brazil, **17,550 TABLETS** distributed

Until recently, adequate treatment options for children were lacking: benznidazole was only available as an adult formulation. In July 2008, DND*i* and LAFEPE entered a joint development programme that led to the determination and production of the most appropriate paediatric dosage formulation, strength, and dosing regimen of benznidazole. The paediatric formulation, adapted for babies and children up to two years of age, was granted registration by Brazil's National Health Surveillance Agency (ANVISA) in December 2011.

DND*i* is collaborating with LAFEPE to make the drug widely available, notably in the priority countries where Chagas disease prevalence is high and treatment is urgently needed. The institutions also worked together for the submission for the WHO Essential Medicines List for Children. As an additional component of the paediatric programme, a population pharmacokinetic study involving 80 Chagas disease patients was conducted in Argentina to gain more information on pharmacokinetics, treatment safety, and efficacy in children aged 0-12 years. The results of the study will be available in 2013.



FILARIAL DISEASES

Aiming for a faster cure for filarial patients

Filarial diseases are caused by a sub-group of helminths, the nematodes, which are transmitted by insect vectors to humans. Onchocerciasis (or river blindness), lymphatic filariasis (LF, or elephantiasis) and loiasis (*Loa loa*, or African eye-worm) affect millions across the world, particularly in Africa. While they do not kill, filarial diseases cause life-long disabilities, such as blindness (onchocerciasis) and swelling of the limbs and genitals (LF), causing great suffering and social stigmatization of those infected.

Ideal Target Product Profile for Filarial Diseases

A new treatment for adults and children

- **Macrofilaricide**: Efficacious against the adult form of worms
- **Oral**, short-course treatment
- **No side-effects** following death of worms
- **Safe** in pregnant and breastfeeding women
- **Affordable**
- **Adapted to tropical climates** (minimum three-year shelf-life)

The success of programmes such as the Global Programme to Eliminate Lymphatic Filariasis (GPELF) and the African Programme for Onchocerciasis Control (APOC) has made it possible to consider eliminating LF (defined as 70% of countries verified free of LF and 30% engaged in post-intervention surveillance activities) and controlling onchocerciasis by 2020.[1] These programmes have been in place for over twenty years and rely on mass drug administration (MDA) of safe and donated anti-helminthic drugs: community-directed treatment with ivermectin, albendazole, and diethylcarbamazine citrate (DEC) .

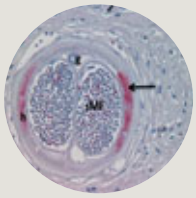
These drugs kill the juvenile form of the worms: the microfilariae cause most of the symptoms and are transmitted to insect vectors.

However, the drugs used in MDA programmes need to be administered repeatedly at regular intervals until adult forms of the worms (macrofilariae) die naturally and there are no more microfilariae in the body. For LF, patients are treated annually or bi-annually for 4-6 years and for onchocerciasis, the treatment duration is 10 years. Importantly, MDA cannot be undertaken in areas of loiasis co-endemicity: indeed, even though loiasis is not life-threatening and is usually not treated, infected patients often have a high burden of microfilariae, and the sudden death of juvenile forms causes a serious adverse reaction, known as *Loa loa* encephalopathy, which can be fatal or leave long-term sequelae.[2] The risk of severe adverse reactions is considered to be unacceptable in areas where the microfilarial prevalence exceeds 20%.[3]

A macrofilaricide drug, which would kill the adult form of the worm, would enable not only the treatment of patients in regions of loiasis co-endemicity, but could also be used in individual case management at the end of MDA programmes, known as 'mopping up', when the incidence rate is too low to justify initiating a new round of MDA. In addition, if sufficiently safe, the drug could potentially be used for MDA, in which case one or two rounds of treatment would be sufficient to eliminate the diseases from a given community.

(1) *Sustaining the drive to overcome the global impact of neglected tropical diseases: second WHO report on neglected tropical diseases* World Health Organization, *2013.* ***(2)*** *Boussinesq M. (2006) Loiasis.* Ann Trop Med Parasitol *100: 715-31.* ***(3)*** *Boussinesq M.* et al. *(2001) Relationships between the prevalence and intensity of* Loa loa *infection in the Central province of Cameroon.* Ann Trop Med Parasitol *95: 495-507.*

FACT SHEET



Filarial diseases

WHAT IS THE IMPACT OF FILARIAL DISEASES?

Onchocerciasis (or river blindness): A total of 18 million people are affected worldwide, in 36 countries in Africa, as well as in Guatemala, southern Mexico, some areas of Venezuela, small areas in Brazil, Colombia, and Ecuador, and in the Arabian Peninsula.[1]

Lymphatic filariasis (LF, or elephantiasis): More than 1.4 billion people in 73 countries worldwide are threatened by LF, commonly known as elephantiasis. Over 120 million people are currently infected, with about 40 million disfigured and incapacitated by the disease.[2] The infection is usually acquired in childhood, but its visible manifestations usually occur later in life, causing temporary or permanent disability.

Loiasis (African eye-worm): On the basis of the rapid assessment procedure of *Loa loa* (RAPLOA) results, it is tentatively estimated that some 14.4 million people live in high risk areas where the estimated prevalence of eye worm history is greater than 40%, and 15.2 million in intermediate areas with estimated eye worm prevalence between 20 and 40%.[3] The number of people at high risk varies considerably between countries. While the overlap with the geographic distribution of onchocerciasis or lymphatic filariasis is not well documented, where it does exist, there is significant risk of severe adverse events with ivermectin treatment.

HOW ARE FILARIAL DISEASES TRANSMITTED?

The parasitic worms that cause filarial diseases are transmitted by insect vectors to humans.

→ Onchocerciasis is a parasitic disease caused by *Onchocerca volvulus*, a thin parasitic worm that can live for up to 14 years in the human body. The disease is transmitted from one person to another through the bite of a blackfly. The transmitted worm larvae develop into adult worms and settle into fibrous nodules in the human body close to the surface of the skin or near the joints.

→ LF is caused by nematodes of the *Filarioidea* family, mainly *Wuchereria bancrofti*, transmitted to humans through mosquitoes. When a mosquito with infective stage larvae bites a person, the parasites are deposited on the person's skin and from there they enter the body. The larvae then migrate to the lymphatic vessels where they develop into adult worms in the human lymphatic system.

→ Loiasis is caused by the parasitic worm *Loa loa*. The adult worms migrate throughout the body just under the skin and sometimes cross into the sub-conjunctival tissue of the eye where they can easily be seen. It is transmitted through the repeated bites of deerflies (also known as mango flies or mangrove flies) of the genus *Chrysops*.

WHAT ARE THE SYMPTOMS?

Onchocerciasis is the world's second leading infectious cause of blindness.[4] The WHO estimates that there are about half a million blind people due to onchocerciasis. It also causes intense itching, skin discoloration, rashes, and eye disease.

LF can become chronic, and when it does, it leads to lymphoedema (tissue swelling) or elephantiasis (skin/tissue thickening) of limbs and fluid accumulation (hydrocele) in the testes. Such body deformities lead to social stigma, as well as financial hardship from loss of income and increased medical expenses. The socio-economic burden of isolation and poverty are immense.

Loiasis leads to recurrent episodes of itchy swellings and to 'eye-worm', the visible migration of the adult worm across the surface of the eye, which resolves after a few days.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments for onchocerciasis and LF are based on mass drug administration (MDA) of anti-parasitic drugs through programmes directed by the WHO. Drugs used by MDA programmes include **ivermectin** for onchocerciasis, **albendazole** plus either ivermectin in areas where onchocerciasis is also endemic or **diethylcarbamazine citrate (DEC)** in areas where onchocerciasis is not endemic for LF. These drugs remove existing microfilariae from skin, thus preventing vector-borne transmission, and provide long-term sterilization of adult worms, preventing re-population of the patient with microfilariae for six months or longer. However, in patients co-infected with *Loa loa*, the sudden death of large numbers of microfilariae can lead to serious adverse events, such as encephalopathy, which can be fatal or leave patients with severe sequelae. Patients infected only with *Loa loa* are not usually treated.

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

DND*i*'s **short-term strategy** is to assess flubendazole, an anti-helminthic drug with proven efficacy against gastrointestinal infections of soil-transmitted helminths in animals and man. The aim is to produce a reformulated version of flubendazole with properties for systemic exposure in the patient for use as a safe and field-adapted macrofilaricidal drug candidate in MDA programmes and/or for patient case management.

As a **medium-term strategy**, DND*i* is assessing additional opportunities through an active screening programme of drugs emanating from animal health and pharmaceutical companies, with the goal of selecting one or two candidates for proof-of-concept trials in patients.

By 2015, DND*i* aims to deliver from its filarial diseases portfolio a new oral drug candidate, available for proof of concept in patients that could be used for case management of onchocerciasis and lymphatic filariasis, especially in *Loa loa* co-endemic regions.

(1) *www.who.int/water_sanitation_health/diseases/oncho/en/* ***(2)*** *www.who.int/mediacentre/factsheets/fs102/en/* ***(3)*** *Zouré HGM,* et al. *(2011) The geographic distribution of* Loa loa *in Africa: results of large-scale implementation of the rapid assessment procedure for loiasis (RAPLOA).* PLoS Negl Trop Dis *5: e1210.*
(4) *www.who.int/blindness/partnerships/onchocerciasis_home/en/index.html*

Translation

Partners:
Johnson & Johnson, USA; Michigan State University, USA; AbbVie (formerly Abbott Laboratories), USA; University of Buea, Cameroon; McGill University, Canada

Leadership:
Discovery and Pre-clinical Director: Robert Don; Project Manager: Ivan Scandale

Project start:
April 2011

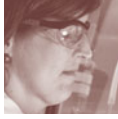
Flubendazole

2012 OBJECTIVE:
→ **Reformulate flubendazole for the treatment of onchocerciasis and lymphatic filariasis**

This project aims to develop flubendazole as a safe, highly efficacious, and field-usable macrofilaricidal drug candidate for the treatment of onchocerciasis and LF. Flubendazole belongs to the benzimidazole class of molecules. Developed by Janssen Pharmaceuticals (a pharmaceutical company of Johnson & Johnson) in the mid-1970s, it is a potent and efficacious anti-helminthic drug for gastrointestinal nematode infections in swine, poultry, companion animals, and humans. In Europe, flubendazole is marketed for human use as Fluvermal. In several animal models[1] and in a small human clinical trial for onchocerciasis, in which the drug was administered parenterally,[2] flubendazole showed very specific potency against the adult stage of the worm. Despite this selective potency, it has not been considered as a treatment for filarial infections, as all of the current formulations have very low bioavailability and these oral forms would not provide sufficient systemic exposure. The first step of this project was to develop, with the help of AbbVie, a new pre-clinical formulation of flubendazole that allows oral absorption.

Non-clinical development of flubendazole is ongoing in collaboration with Janssen Pharmaceuticals: in particular, the necessary studies required to file an Investigational New Drug (IND) application followed by submission of a dossier to the FDA are supported by Janssen Pharmaceuticals, which will also provide DND*i* with drug supplies to support clinical development. DND*i* will conduct extensive PK/PD studies to guide/refine the selection of human therapeutic doses.

(1) *Zahner H., Schares G. (1993) Experimental chemotherapy of filariasis: comparative evaluation of the efficacy of filaricidal compounds in* Mastomys coucha *infected with* Litomosoides carinii, Acanthocheilonema viteae, Brugia malayi *and* B. pahangi. Acta Trop *52: 221-66.* ***(2)*** *Dominguez-Vazquez A.* et al. *(1983) Comparison of flubendazole and diethylcarbamazine in treatment of onchocerciasis.* Lancet *1: 139-43.*



PAEDIATRIC HIV

Optimizing antiretroviral therapy for infants and young children in resource-poor settings

Despite the successes of programmes rolled out to reduce the number of new HIV infections in children, 330,000 children acquired HIV infection in 2011, more than 90% of whom were in sub-Saharan Africa. An estimated 3.3 million children under the age of fifteen were living with HIV in 2011 and 230,000 died of AIDS-related causes.[1] While the absolute number of infants newly infected with HIV is now declining due to progress in prevention of mother-to-child transmission (PMTCT), the need for paediatric treatment will continue to increase until 2020 at least.

The majority of children with HIV are infected through perinatal transmission during foetal development, birth, or whilst being breastfed. Whereas in high-income countries, HIV transmission in young children has largely been eliminated due to effective PMTCT interventions, in low- and middle-income countries many pregnant women do not have access to antenatal care and HIV testing. Therefore they do not benefit from interventions to prevent transmission to their child: in those countries, coverage of effective antiretroviral regimens for PMTCT reached only 57% in 2011.[2]

Provision of adequate treatment to those children who do become infected is vital. HIV-infected infants frequently develop illness within their first months of life. In the absence of antiretroviral therapy (ART), almost one-third of them die before their first birthday, and about half die before they are two years old.[3] Even though the 2010 WHO guidelines recommend that all children younger than two years start immediately on ART, less than one-third of eligible children under the age of fifteen were receiving the life-saving medicines in 2011.[4] ART coverage is even lower in children under the age of five, notably because of the lack of appropriate tools to diagnose HIV early in the child's life and of therapeutic options adapted to their needs. Although more than 25 drugs are approved for adults, many have not yet been tested and approved for use in children, limiting the number of therapeutic options for caregivers and children. The drugs that are approved for children need to be associated to act synergistically in order to suppress HIV replication. These combination antiretroviral therapies (cARTs) of three or four drugs are few, complex to administer, and will have to be taken for life.

With growing evidence of its superiority in infants and young children with very high viral loads, protease inhibitor (PI)-based cART is increasingly preferred as first-line therapy in low- and middle-income countries, as recommended by the 2013 WHO guidelines.[5] However, currently available PI-based paediatric formulations have serious limitations. They are in an alcohol-based liquid form with poorly tolerated taste, are difficult to administer, and carry a high risk of dosing errors. In addition, they have a short shelf-life, require a cold chain, and are voluminous and expensive.

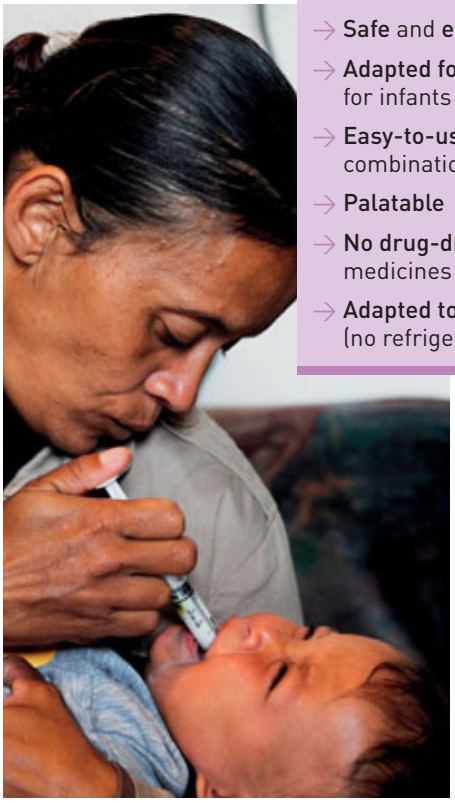
Finally, many children need to be treated for both HIV and tuberculosis (TB) and there are significant negative drug-drug interactions between anti-TB drugs and anti-HIV drugs. HIV-infected children co-infected with TB have a particularly poor prognosis.[6] These drug interactions need to be addressed either by new drugs or adapted dosages.

Improved first-line therapies for children are urgently needed.

Ideal Target Product Profile for Paediatric HIV

A first-line, protease inhibitor-based **all-in-one** antiretroviral regimen for HIV-infected children:

- **Safe** and **efficacious**
- **Adapted formulation** suitable for infants and children
- **Easy-to-use** fixed dose combination
- **Palatable**
- **No drug-drug interaction** with medicines for tuberculosis
- **Adapted to tropical climates** (no refrigeration needed)



(1) Global report: UNAIDS report on the global AIDS epidemic 2012, Geneva, 2012. *(2)* Ibid. *(3) Newell, M.* et al. *(2004) Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis.* Lancet *364: 9441.* *(4) Global report: UNAIDS report on the global AIDS epidemic 2012, Geneva, 2012.* *(5) Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, WHO, June 2013.* *(6) Children and AIDS: Fifth Stocktaking Report. New York, UNICEF/ UNAIDS/WHO/UNFPA/UNESCO, 2010.*

FACT SHEET

Paediatric HIV

WHAT IS THE IMPACT OF PAEDIATRIC HIV?

At the end of 2011, an estimated 3.3 million children below the age of 15 were living with HIV, more than 90% of whom in sub-Saharan Africa. An estimated 230,000 children under 15 years of age died of AIDS-related illness in 2010. In low- and middle-income countries, access to treatment has expanded to reach an estimated 562,000 HIV-infected children under the age of 15. Still, only 28% of HIV-positive children are estimated to be on antiretroviral therapy (ART), compared to 68% of adult women and 47% of adult men.[1]

HOW IS PAEDIATRIC HIV TRANSMITTED?

In children, HIV transmission can occur during pregnancy through the placenta, during delivery through exposure to body fluids and cervical secretions, and through breastfeeding. In the absence of antiretroviral preventive treatment, 30 to 40% of children born to an HIV-infected mother acquire infection themselves. However, with antiretroviral prophylaxis throughout pregnancy, delivery, and breastfeeding, transmission can be decreased to a few percent.

WHAT ARE THE SYMPTOMS?

HIV is difficult to diagnose in children and infants: indeed, signs and symptoms are non-specific and are very common in resource-poor settings, such as chronic diarrhea, recurrent infection, and failure to thrive. However, the disease progresses rapidly and can lead to death before HIV has been diagnosed or even suspected. All children born to HIV-infected mothers carry maternal anti-HIV antibodies, and are thus seropositive. A positive serological test therefore does not necessarily indicate HIV infection. Only very expensive diagnostic tests that detect the virus itself can give an accurate diagnosis in the first months of life. New tests are currently under development.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

The 2010 WHO guidelines recommend early diagnosis and immediate treatment of HIV-positive infants and children under the age of two; for those with prior exposure to PMTCT, PI-based first-line therapy is recommended, but results of a superior response to such therapy in children without prior exposure to PMTCT have also been reported.[2] The combination of a **boosted protease inhibitor** with **two nucleoside reverse transcriptase inhibitors** (NRTIs) is considered by many experts as the most effective first-line therapy for infants and children, regardless of prior exposure to ARVs.

However, this combination therapy is not being widely used. According to a WHO survey performed in 45 countries, only 12.2% of children with HIV were receiving a first-line treatment containing a PI (mostly lopinavir/ritonavir, LPV/r), 97% of whom were in South Africa. The only available PI for young children, LPV/r does not come in a child-friendly formulation: the oral solution formulation is unpalatable, contains 42% alcohol, and is not adapted to resource-poor settings due to major logistical constraints: it requires refrigeration, has a short shelf-life when exposed to heat, is expensive, and is difficult to store and transport.

In many areas, HIV-positive infants and children are co-infected with tuberculosis (TB). Drug-drug interactions between PIs in particular and rifampicin, one of the drugs used to treat TB, greatly diminish the blood levels of PIs and hinder the efficacy of the ARV treatment. In order to counteract this interaction, extra ritonavir needs to be added to the standard proportion of LPV/r. This is called 'superboosting', and requires the development of an infant-friendly formulation of ritonavir. The currently available ritonavir formulation suffers the same limitations as the current formulation of LPV/r with regard to taste, high alcohol content, and logistical constraints.

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

In 2010, DND*i* was called on by various organizations, including Médecins Sans Frontières, WHO, and UNITAID, to apply its expertise to the development of paediatric HIV treatments. DND*i*'s position, notably that paediatric HIV is a neglected disease, was published as a 'Perspective' in the *New England Journal of Medicine* in August 2011.[3]

DND*i* is pursuing **two objectives** to address the needs of HIV-infected children:

- Develop and register two solid first-line 4-in-1 LPV/r-based fixed-dose combinations (FDCs) with 2 NRTIs. All components of the combination will be developed in the form of taste-masked granules, stable with no need for refrigeration, presented in a single unit with appropriate strengths to accommodate weight band dosing.
- Develop and register a stand-alone ritonavir booster formulation that can be added to any PI-based paediatric ARV regimen and can be used to counteract the negative drug-drug interactions between PIs and rifampicin-containing TB treatments.

As a **short-term strategy**, DND*i* will start implementing the use of PI-based treatment with existing LPV/r-based products before the availability of the 4-in-1 FDC, in order to provide better treatment for infants today and promote in-country adoption. DND*i* participated in the CHAPAS-2 trial that compared LPV/r sprinkles (hereafter referred to as minitablets) to the LPV/r liquid formulation. These minitablets will be used in association with NRTI dispersible tablets in implementation studies as part of this short-term strategy.

In the mid-term, DND*i* is working with its industrial partner, Cipla Ltd., on combining LPV/r granules with two NRTIs into a single unit dose. This modular concept is flexible, so that any of the components can eventually be substituted to provide new fixed-dose combinations.

In addition, in order to address the needs of HIV/TB co-infected children, DND*i* is developing a formulation of ritonavir for superboosting LPV/r at a 1:1 ratio. A pharmacokinetic study to establish the efficacy and safety of superboosted LPV/r is ongoing in South Africa with the existing ritonavir solution.

By 2015-2016, DND*i* aims to deliver from its paediatric HIV portfolio:

→ Two new all-in-one paediatric formulations containing a PI and two NRTIs

→ One stand-alone paediatric booster for HIV-TB co-infected children

(1) *Global report: UNAIDS report on the global AIDS epidemic 2012, Geneva, 2012.* ***(2)*** *Violari A.* et al. *(2012) Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children.* N Engl J Med *366: 2380-9.* ***(3)*** *Lallemant M.* et al. *(2011) Pediatric HIV - A Neglected Disease?* N Eng J Med *365: 581-3.*

Improved PI for first-line treatment

2012 OBJECTIVE:
→ **Develop an improved PI that can be incorporated into a fixed-dose combination**

The project aims to improve the formulation of PI-based first-line treatment for young infants and children living with HIV. The development plan includes putting together all four drugs needed for the treatment of HIV in children into a single unit, also known as a fixed-dose combination (FDC), which is heat-stable, well taste-masked, solid, does not contain alcohol or inappropriate solvents and, most importantly, is easy to dose (using WHO-recommended weight band dosing) for the caregiver. The two FDCs in development are AZT/3TC/LPV/r and ABC/3TC/LPV/r. In order to counteract negative drug interactions between PIs and rifampicin-containing TB treatment, a stand-alone booster ritonavir (RTV) formulation will be developed.

A paediatric pharmacokinetic expert group has been created to determine the optimal weight band dosing of LPV/r and NRTIs in order to deliver all components in an FDC. These doses are modelled using WHO weight band recommendations.

The two 4-in-1 FDCs and the stand-alone RTV booster will be tested in healthy human volunteers in 2013.

Partners:
Cipla Ltd., India

Leadership:
Head of Paediatric HIV Programme: Marc Lallemant;
Project Coordinator: Janice Lee;
Senior Pharma Advisor & Product Manager: Jean-René Kiechel

Project start:
December 2011

Translation

PI Sprinkles (minitablets) (Chapas-2)

2012 OBJECTIVE:
→ **Clinically assess the pharmacokinetics and acceptability of LPV/r in the existing sprinkle (minitablet) formulation in children between 1-4 years of age (additional CHAPAS-2 cohort)**

The results of the PK study of LPV/r minitablets versus syrup (CHAPAS 2) in children aged 1 to 4 years were presented at CROI 2013.(1) Exposure to LPV/r minitablets was slightly higher than that to the liquid formulation. LPV exposure in this age group was similar to that observed in infants, older children, and adults. Variability in LPV/r pharmacokinetic parameters was similar in both formulations and neither formulation resulted in sub-therapeutic concentrations. Caretakers preferred the minitablet formulation, particularly for storage/transport reasons. For this group of children, acceptability of both formulations was similar, in particular as regards to taste (these minitablets are not taste-masked).

Partners:
DND*i* joined this trial sponsored by the Medical Research Council (MRC), UK, as an additional partner. Other partners include Cipla Ltd., India; Joint Clinical Research Centre, Uganda; Makerere University/Mulago Hospital, Uganda; Radboud University Nijmegen Medical Centre, The Netherlands

Leadership:
Head of Paediatric HIV Programme: Marc Lallemant; Project Coordinator: Janice Lee

Project start:
May 2012

Development

'Superboosting' – TB/HIV

2012 OBJECTIVE:
→ **Evaluate the safety and pharmacokinetics of increasing LPV/r boosting ratio from 4:1 to 1:1 in HIV/TB co-infected infants and children in order to counteract the negative drug-drug interactions between PIs and rifampicin-containing TB treatments**

This study is essential to support and prepare the development of a stand-alone ritonavir booster formulation that can be added to any PI-based paediatric ARV regimen. It will be performed in infants and young children co-infected with TB and HIV at 5 sites in South Africa. Site initiation visits were conducted in October 2012, and the first ethics approval was received from Cape Town Tygerberg Hospital at the end of the year.

The study is expected to end in 2014 and results will be available at the beginning of 2015.

Partners:
SOUTH AFRICA: Stellenbosch University and Tygerberg Children's Hospital; Perinatal HIV Research Unit; Shandukani Research Centre; Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital; Enhancing Care Foundation; Department of Health; Department of Science and Technology

Leadership:
Head of Paediatric HIV Programme: Marc Lallemant; Project Coordinator: Janice Lee

Project start:
May 2012

Development

(1) Kitaka S. et al. *Pharmacokinetics and acceptability of a new generic lopinavir/ritonavir sprinkle formulation in African, HIV+ children 1-4 Years: CHAPAS-2. CROI 2013. Poster 975b.*

MALARIA

Ensuring access to ACTs to fight malaria

Malaria is a major public health problem that continues to affect millions across the world, mainly children under the age of five. The development of multi-drug resistant *Plasmodium falciparum* parasites and resulting failure of treatment with chloroquine and sulfadoxine-pyrimethamine led the World Health Organization (WHO) to recommend the use of artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated *P. falciparum* malaria in 2001. Recently, delayed parasite clearance indicative of resistance to artemisinin has been reported in some areas of South-East Asia, sparking a global response to contain resistant parasites before they spread around the world. Despite these concerns, ACTs remain the best available antimalarial medicines and are still highly effective in the majority of malaria endemic areas. Fixed-dose combinations (FDCs) of ACTs are preferred and recommended, as they promote adherence to treatment and reduce the potential of selective use of the medicines as monotherapy. Since 2005, the number of ACT treatment courses procured by the public sector has increased from 11.2 million to 76 million in 2006, and reached 181 million in 2010.

In 2002, the Fixed-Dose Artesunate-Based Combination Therapies (FACT) Consortium, created by the DND Working Group and TDR, started to develop two fixed-dose artesunate (AS)-based combination therapies (out of the four initially recommended by WHO):

- **ASAQ**, the FDC of artesunate and amodiaquine developed in partnership with Sanofi, was first registered in 2007 and pre-qualified by WHO in 2008;
- **ASMQ**, the FDC of artesunate and mefloquine developed in partnership with Farmanguinhos (first registered in Brazil in 2008) and then, after a technology transfer, also produced by Cipla Ltd. (first registered in India in 2011), and pre-qualified by WHO in 2012.

FSCs enable simple treatment regimens, therefore increasing patient compliance. ASAQ and ASMQ, together with CoArtem® (the FDC of artemether and lumefantrine developed by Novartis and the first ACT pre-qualified by the WHO in 2001), Pyramax® (the FDC of artesunate-pyronaridine) and Eurartesim® (the FDC of dihydroartemisinin-piperaquine (DHA/PQP)), both developed by the Medicines for Malaria Venture (MMV) and approved in 2011, strengthen the global ACT portfolio of FDCs now available for the treatment of uncomplicated *P. falciparum* malaria. Fixed doses of some of these combinations, developed by other manufacturers, have recently been developed and pre-qualified by the WHO. Together with diagnosis and vector control tools, they represent a key improvement of the antimalarial arsenal.

FACT SHEET

Malaria

WHAT IS THE IMPACT OF MALARIA?

The WHO estimates that there were 216 million of cases of malaria in 2010, and that 660,000 deaths were attributable to the disease, 86% of which occured in children under five and 91% in sub-Saharan Africa. A study by C. Murray *et al.*, however, estimates that in 2010 malaria was the underlying cause of death for 1.24 million individuals, including 714,000 children younger than five years.[1]

Recent successes and a reduction in the number of cases are reason for optimism, but many people at risk of malaria still lack access to critical treatment and prevention options, including to ACTs, and malaria control continues to face serious challenges.[2]

HOW IS MALARIA TRANSMITTED?

Malaria is caused by *Plasmodium* parasites, spread to people through the bite of an infected female anopheles mosquito. Four species of the parasite cause malaria in humans: *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. *P. vivax* and *P. falciparum* are the most common, with *P. falciparum* the most deadly.

Approximately half of the world's population is at risk of malaria. Most malaria cases and deaths occur in sub-Saharan Africa, but Asia, Latin America, and to a lesser extent the Middle East and parts of Europe are also affected. In 2010, 99 countries and territories had active malaria transmission.

WHAT ARE THE SYMPTOMS?

Malaria is an acute febrile illness with initial symptoms that can be difficult to recognize. Symptoms of uncomplicated malaria include fever, headache, chills, and vomiting. If treatment is not given within 24 hours, *P. falciparum* malaria can progress to severe illness, which can lead to death or serious brain damage, especially in children, who are particularly vulnerable due to their lack of immunity to the parasite.

(1) *Murray, CJL* et al. *(2012) Global malaria mortality between 1980 and 2010: a systematic analysis.* Lancet *379: 413–31.*
(2) *A Decade of Partnerships and Results, Progress and Impact Series, number 7, World Health Organization, Geneva, 2011.*

ASMQ FDC

2012 OBJECTIVES:

→ **Technology transfer and registration:**
- **Support activities for prequalification by WHO and PAHO**
- **Obtain registration authorization in India and South-East Asia**
- **Reduce cost of mefloquine to decrease the price of ASMQ FDC**

→ **Clinical studies**
- **Progress the multicentre comparative study conducted in three African countries**

PHASE IIIB
study in children:
751/940 patients recruited by end 2012 at 4 sites in 3 countries

The ASMQ fixed-dose combination (FDC) was developed by the FACT consortium created by DND*i* and TDR in 2002. Within FACT, the Brazilian government-owned pharmaceutical company, Farmanguinhos/Fiocruz, was the first manufacturer of ASMQ FDC, which was registered in Brazil in March 2008. Through a South-South technology transfer, ASMQ FDC production was transferred to the Indian pharmaceutical company Cipla Ltd. in 2010 to ensure availability in India and Asia at affordable, pre-agreed prices. The product was registered in India in 2011, in Malaysia in March 2012, and in Myanmar in October 2012. In September 2012, Cipla Ltd.'s ASMQ FDC received WHO prequalification, an important step in accelerating access in Asia.

Additional clinical studies are ongoing that will provide information on use in children, adults, and pregnant women in Africa. According to WHO recommendation, AS+MQ could be considered for use in some countries in Africa. To provide information on the efficacy and tolerability of ASMQ FDC, DND*i* is sponsoring a multicentre Phase IIIB study in Tanzania, Burkina Faso, and Kenya to assess its efficacy, safety, and pharmacokinetics compared to artemether-lumefantrine in children below the age of 5. The study is expected to end in October 2013 and the first results will be available at the beginning of 2014.

Partners:
Farmanguinhos, Brazil; Cipla Ltd., 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, Switzerland; National Institute of Medical Research, Tanzania; Kenya Medical Research Institute (KEMRI), Kenya; Centre National de Recherche et de Formation sur le Paludisme, Burkina Faso; Medicines for Malaria Venture (MMV), Switzerland; Ifakara Health Institute, Tanzania

Leadership:
Senior Pharma Advisor & Product Manager: Jean-René Kiechel; Clinical Manager: Gwénaëlle Carn; Medical Coordinator FACT Project: Graciela Diap

Project start: January 2002

Implementation

ASMQ FDC WHO Prequalified

At a special DND*i* event in Kuala Lumpur, Malaysia, on 3 October 2012, WHO prequalification of the Cipla-manufactured ASMQ FDC is announced at a press conference with Malaysia's Minister of Health, Dato' Sri Liow Tiong Lai. A prequalified status makes ASMQ FDC eligible to tenders that receive funding from international procurement agencies, such as UNICEF and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

ASAQ Winthrop

2012 OBJECTIVE:

→ **Diversify ASAQ suppliers by transferring technology to a partner in Africa**

→ **Facilitate implementation of ACTs FDC in general and specifically ASAQ, in all countries where it could benefit patients and abides by local practices**

180 MILLION
treatments distributed in 30 African countries by the end of 2012

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. ASAQ Winthrop was pre-qualified by WHO in October 2008 and included on the WHO Essential Medicines List (EML) in 2011.

By the end of 2012, over 180 million treatments had been distributed in 30 African countries. First registered in Morocco, where it is manufactured, ASAQ is now registered in 30 African countries, as well as in India, Bangladesh, and Colombia. In 2010, ASAQ Winthrop obtained WHO authorization for a 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 Sanofi, MMV, and National Malaria Control Programmes, high-quality data on ASAQ effectiveness and safety in the field is being collected, as part of a Risk Management Plan (RMP). This was the first RMP submitted to the WHO, and the first to be set up entirely in Africa. It is expected to contribute to building capacity on drug safety and efficacy monitoring in sub-Saharan African countries and could set the precedent for further real-life assessment studies of new ACTs. Together with partners, DND*i* is also working on the transfer of technology to a second manufacturer in Africa, Zenufa, in Tanzania.

Partners:
Sanofi, France; MMV, Switzerland; AEDES, Belgium; Zenufa, Tanzania; National Centre for Research and Training on Malaria, Burkina Faso; Universiti Sains Malaysia; Oxford University, UK; Institute of Research for Development (IRD), Senegal; Université Bordeaux Segalen, Faculté de Pharmacie, France; Mahidol University, Thailand; Bertin Pharma, France; Médecins Sans Frontières; Epicentre, France; WHO-TDR; KEMRI, Kenya; ICMR, India; National Malaria Control Programme, Ministry of Health, Burundi; Ministry of Health, Sierra Leone; Ministry of Health, Ghana; Komfo Anokye Teaching Hospital (KATH), Ghana

Leadership:
Senior Pharma Advisor & Product Manager: Jean-René Kiechel; Clinical Manager: Gwénaëlle Carn; Medical Coordinator FACT Project: Graciela Diap

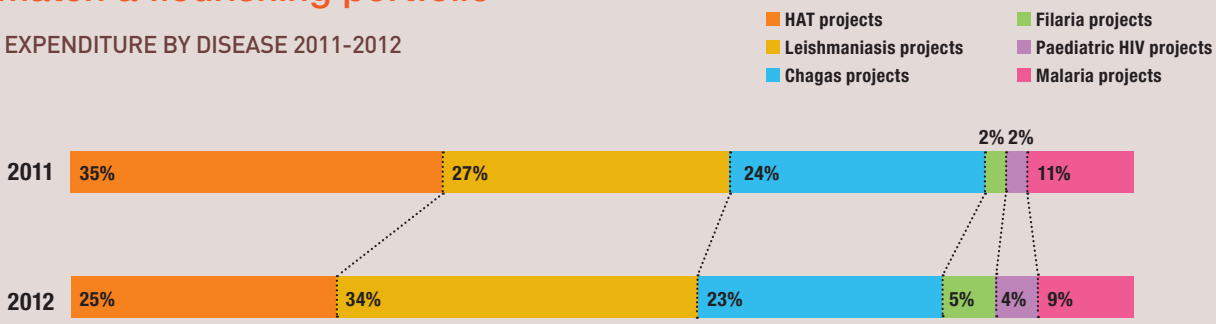
Project start:
January 2002

Implementation

2012 KEY FINANCIAL PERFORMANCE INDICATORS

EUR 22.8 million in R&D expenditures to match a flourishing portfolio

R&D EXPENDITURE BY DISEASE 2011-2012



Overall R&D expenditure of EUR 22.8 M increased by 13.5 % (EUR 2.7 M) in 2012. The percentage breakdown of 2012 R&D expenditure by disease highlights:

HAT: With a total of EUR 5 M, investments decreased (- EUR 1.3 M) due to redirecting screening and lead optimization to an external partner (- EUR 1.1 M), and clinical activities starting for fexinidazole (+ EUR 0.5 M); the oxaborole SCYX-7158 project expenditure was mainly dedicated to pharmacological studies and PK analysis (- EUR 0.5 M); and NECT two-year follow-up was completed (- EUR 0.2 M).

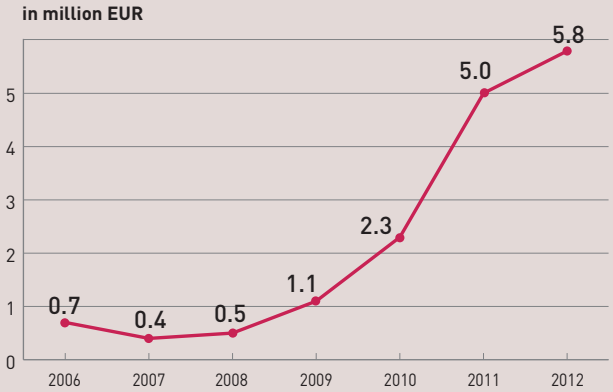
Leishmaniasis: For the first time, leishmaniasis projects became the most substantial part of R&D expenditure (34%) as projected in the Business Plan, with EUR 1.9 M. Expenditure increase illustrates substantial activity: patient recruitment in the Asia implementation study (+ EUR 0.8 M); cutaneous leishmaniasis topical treatment ready to enter clinical phase at end 2012 (+ EUR 0.5 M); preparation of two new clinical trials in Africa for fexinidazole (+ EUR 0.1 M) and HIV/VL co-infection (+ EUR 0.3 M); total investment for the lead optimization (LO) consortium and screening activities was EUR 2.5 M (approx. 43% of the LO and screening costs, + EUR 0.2 M).

Chagas disease: Projects remained stable in 2012 with EUR 4.7 M (23% of R&D expenditure).

Portfolio expansion: Expansion to include two new diseases areas represents 9% of R&D expenditure. **Paediatric HIV** expenditure doubled, with two activities: preparation of a clinical study for the super-boosting project (ritonavir for superboosting LPV/r) in South Africa (EUR 0.25 M) and DND*i*'s participation to the PI sprinkles (minitablets) CHAPAS project (EUR 0.25 M) in Ghana. The **filaria** project increased by 270% due to preparing the Investigational Medicinal Product Dossier for flubendazole and to the development of an oral formulation suitable for human clinical use (+ EUR 0.35 M), in addition to screening activities (+ EUR 0.25 M).

Stark increase in leveraging of partner resources

IN-KIND CONTRIBUTIONS 2006-2012



In order to present a comprehensive picture of its activities, DND*i* values the in-kind contribution of its generous partners (private companies, academic groups, and individuals).

In seven years, in-kind contributions have increased eight-fold. This reflects the investment by DND*i* in consolidating such partnerships and the increasing engagement of these partners in neglected disease R&D.

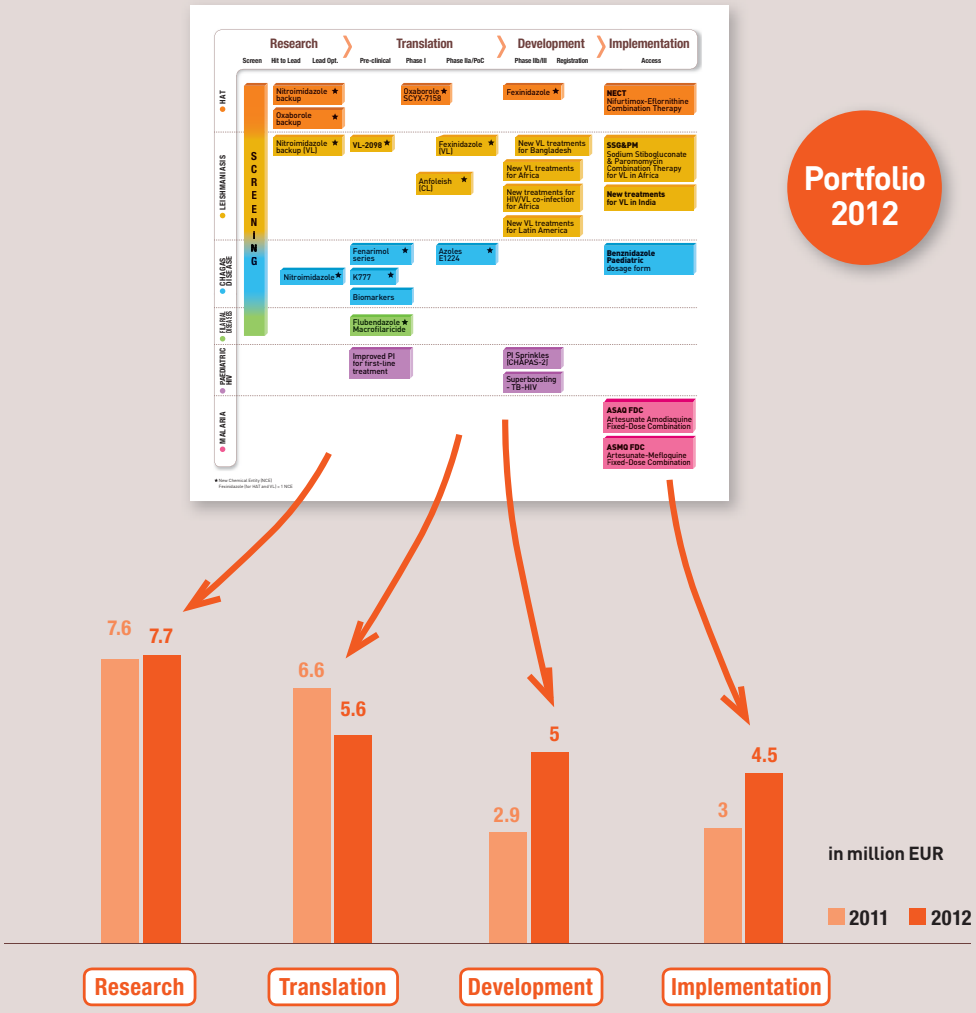
The major contribution reported, 50% of all annual totals from 2009 to present, relates to pharmaceutical development of azole E1224 (Chagas disease) and fexinidazole (HAT) with industrial partners.

As in 2011, the total 2012 in-kind contribution reached approximately 20% of total expenses.

2012 KEY FINANCIAL PERFORMANCE INDICATORS

Development and implementation expenditure increases as treatments approach the end of the pipeline

R&D EXPENDITURE BY R&D STAGE



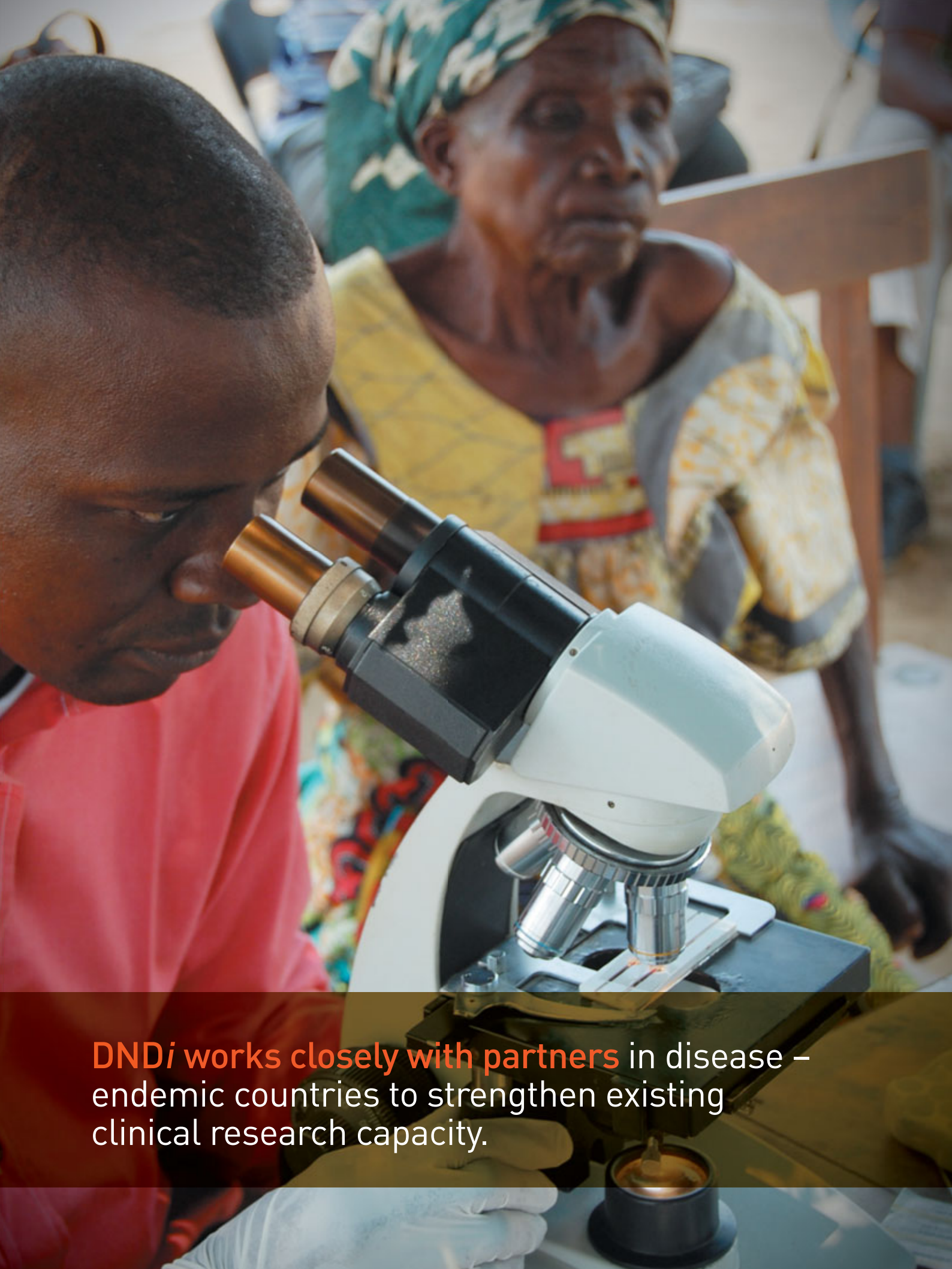
In 2012, the most important fluctuations relate to growth of clinical development and progress of implementation activities (+ EUR 3.7 M).

Research: Screening and lead optimization activities remain stable (+EUR 0.1 M). However, some changes occurred in the set-up of activities, namely in screening for filarial diseases and in the partnerships that have been redesigned in a more suitable way, allowing for greater cost efficiency.

Translation: Expenditure decreases between 2011 and 2012 (- EUR 1 M), mainly due to: progression of fexinidazole for HAT to clinical development; four projects in transition phase (VL-2098, oxaborole SCYX-7158, azole E1224 and biomarkers, and K777); increasing activities of the two new disease areas of the portfolio, filarial diseases and paediatric HIV.

Development: The progression of two projects to clinical development led to an increase of expenditure (+ EUR 2.1 M): fexinidazole for HAT started Phase II/III study, and the VL and HIV/VL co-infection study started Phase IIb/III.

Implementation: With six projects in implementation phase, expenditure increased by 50% (+ EUR 1.5 M) mainly due to the paediatric dosage form of benznidazole implementation after registration in December 2011, and the start of recruitment in India for the VL Asia study, with 300 patients recruited.



DND*i* works closely with partners in disease – endemic countries to strengthen existing clinical research capacity.




Building **strong & sustainable research capacities** in endemic countries

According to its vision and mission, DND*i* works closely with partners in disease-endemic countries to strengthen research capacities and to promote technology transfer in order to facilitate registration, uptake, and sustainable access of new treatments.

By 2009, one disease-specific research platform for each of the kinetoplastid diseases (human African trypanosomiasis, leishmaniasis, and Chagas disease) was in place.

Three regional platforms for sustainable response

These platforms promote South-South collaboration and bring together the most important actors in each region in order to define patient needs, train clinical researchers, facilitate registration, and expedite implementation. An integral part of the DND*i* model, these platforms have achieved several milestones, including: LEAP's delivery of SSG&PM for visceral leishmaniasis in East Africa; the HAT Platform's continued support for implementation of NECT for sleeping sickness in all endemic countries; and the Chagas Clinical Research Platform's overseeing of clinical studies for Chagas disease in Argentina and Bolivia.

These regional platforms, included from the outset of DND*i* as part of its original business model, are essential pillars of DND*i*'s work, and aim to support and reinforce the locally grown R&D initiatives addressing neglected diseases in endemic countries.

Leishmaniasis East Africa Platform (LEAP)

Founded: 2003 in Khartoum, Sudan

→ Approximately 60 individual members, representing over 20 institutions

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; OneWorld Health (OWH/PATH); AMC/KIT/ Slotervaart Hospital, The Netherlands; London School of Hygiene & Tropical Medicine (LSHTM), UK.

- → **Over 3,500 patients enrolled in clinical trials by the end of 2012**
- → **Over 2,700 patients treated outside clinical trials by the end of 2012**
- → **Over 2,750 patients treated in pharmacovigilance Phase IV study (all patients received SSG&PM combination therapy)**

OVERALL OBJECTIVES

- → **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**
- → **Serve as a base for ongoing educational cooperation among East African countries and for standardization of procedures and practices in the region, as far as possible within the confines of local regulations**
- → **Evaluate, validate, and facilitate registration of new treatments for VL in the region**

Treatments

Following recommendation of SSG&PM as first-line treatment for VL in East Africa by the WHO Expert Committee on the Control of Leishmaniases (2010), Sudan was the first country to implement SSG&PM (end 2010). Registration of PM has been initiated in LEAP countries, Uganda being the first (end 2011) and Kenya the second (Feb. 2013) to register it.

Clinical trials

The miltefosine-AmBisome®/LEAP 0208 study (started 2010) to assess safety and efficacy of the combination of SSG+single-dose AmBisome®; miltefosine+single-dose AmBisome®; and miltefosine alone ended recruitment March 2012. In addition, the SSG&PM pharmacovigilance study (started 2011) to monitor safety and effectiveness of SSG&PM combination recruited 2,332 patients in Ethiopia, Sudan, Kenya, and Uganda by end 2012. In early 2013, a new study will evaluate the efficacy of AmBisome®+miltefosine combination and of a higher-dose AmBisome® monotherapy in Ethiopian patients with HIV-VL co-infection.

Capacity strengthening

Good Clinical Practice (GCP)/Good Clinical and Laboratory Practice (GCLP) and pharmacovigilance courses were delivered in 2012 to 78 lab technicians, nurses, pharmacists, monitors, and investigators in Ethiopia, Kenya, and South Africa. Six post-graduate trainings were supported by LEAP. In addition, an exchange programme, initiated in late 2011, between the laboratory staff at the Kenyan Kimalel site and the Ugandan Amudat site was successfully carried out.

Infrastructure

Renovation of laboratories at the Ethiopian Gondar clinical site was finalized in 2012.

Access

Kenya's Ministry of Health launched its National VL Guidelines in September 2012, recommending SSG&PM first-line treatment. SSG&PM was included in the national drugs lists of Sudan, South Sudan, and Ethiopia.

Human African Trypanosomiasis (HAT) Platform

Founded: 2005 in Kinshasa, Democratic Republic of the Congo
→ 8 member countries

OVERALL OBJECTIVES

- → **Build and strengthen treatment methodologies and clinical trial capacity in HAT-endemic countries, so that new treatments can be rapidly and effectively evaluated, registered, and made available to patients**
- → **Develop appropriate clinical trial methodologies for HAT and strengthen clinical trial capacity (human resources, infrastructure, equipment)**
- → **Overcome system challenges related to administrative and regulatory requirements**
- → **Share information and strengthen ties among endemic countries**

Treatments

In 2012, 96% of stage 2 sleeping sickness patients were treated with NECT. In 2012, 11 countries reporting cases of HAT *T.b. gambiense* (98% of cases) were using NECT as first-line treatment for stage 2 HAT.

Clinical trials

Fexinidazole: Preparation of six clinical trial sites in DRC and CAR, support for submission to the ethical and regulatory authorities of DRC and CAR; staff training. Study recruitment started 2012 at four sites in DRC. Strengthening collaboration with FIND, the platform contributed to a trial for a new rapid diagnostic test and molecular test (LAMP). With ITM-Antwerp, the platform is involved in monitoring of the NIDIAG trial, notably on neurological diagnosis decision trees, in Mosango, DRC.

NECT Field studies (six sites in DRC) were completed in 2012.

Capacity strengthening

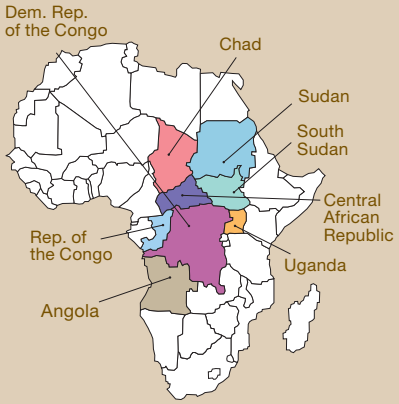
Training sessions were given to 130 professionals in DRC, Uganda, South Sudan, and Chad, mainly for the start of the fexinidazole Phase II/III study: preparation of staff (65 people); Good Clinical/Laboratory Practice (46), and pharmacovigilance (19).

Infrastructure

In 2012, Bandundu, Masi Manimba, and Vanga clinical sites in DRC benefited from several infrastructure upgrades, such as laboratory upgrades and equipment, solar energy systems, VSAT for internet, kitchen, warehouses, and waste disposal spaces, including incinerators, and painting and renewal of the beds as needed in patient wards.

Members

National Sleeping Sickness Control Programmes and National Laboratories of Public Health of most affected endemic countries: Angola, Central African Republic, Chad, Democratic Republic of the Congo, Republic of Congo, South Sudan, Sudan, Uganda; Swiss Tropical and Public Health Institute (Swiss TPH); Institute of Tropical Medicine-Antwerp, Belgium; Institut National de Recherche Biomédicale (INRB), DRC; University of Makerere, Uganda; Kenya Agricultural Research Institute – Trypanosomiasis Research Centre (KARI-TRC), Kenya; Tropical Medicine Research Institute (TMRI), Sudan; Institut Pasteur Bangui, CAR; Médecins Sans Frontières (MSF); Foundation for Innovative New Diagnostics (FIND); Eastern Africa Network for Trypanosomosis (EANETT), Centre interdisciplinaire de Bioéthique pour l'Afrique Francophone (CIBAF); WHO Department of Neglected Tropical Diseases as observer.



Chagas Clinical Research Platform (CCRP)

Founded: 2009 in Uberaba, Brazil

→ Over 70 institutions represented from 22 countries

Members

Ministries of Health and National Control Programmes of high-burden endemic countries (Argentina, Bolivia, Brazil, Mexico, Paraguay, Honduras); Pan American Health Organization (PAHO); Department for the Control of Neglected Tropical Diseases, WHO; Médecins Sans Frontières; International Federation of People Affected by Chagas Disease (FINDECHAGAS) and several patients associations

ARGENTINA: Hospital de Niños Ricardo Gutiérrez; Instituto Nacional de Parasitología Dr. M. Fatala Chabén; Hospital de Niños de Jujuy; Hospital Público Materno Infantil – Salta; Centro de Chagas y Patologia Regional, Santiago del Estero; Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET); Fundación Mundo Sano, ELEA

BRAZIL: Instituto Oswaldo Cruz; Instituto de Pesquisa Evandro Chagas–Fiocruz; Centro de Pesquisas René Rachou–Fiocruz; LAFEPE

BOLIVIA: Universidad Mayor de San Simón; Platform of Integral Care for Patients with Chagas Disease; CEADES

MEXICO: Instituto Carlos Slim de la Salud

SPAIN: ISGlobal and Barcelona Centre for International Health Research (CRESIB)

USA: Merck; Sabin Vaccine Institute

JAPAN: Eisai Co. Ltd

FRANCE: Institut de Recherche pour le Développement

GERMANY: Bayer

OTHER: researchers from Universities of Colombia, Venezuela, Bolivia, USA, Canada, Brazil, and Paraguay.

OVERALL OBJECTIVES

→ **Deliver concrete support for R&D, such as training, capacity building, definition and compliance to standards and regulations, integration of ethical principles across different populations and countries**

→ **Discuss access challenges to new and existing technologies, through a flexible and needs-driven platform**

Clinical trials

In 2012, three studies (started 2011) have been receiving support from the Platform: a population pharmacokinetics (PK) study of the use of benznidazole in children, including the new paediatric dosage form (Argentina); a study to evaluate and optimize the polymerase chain reaction (PCR) method for diagnosis and assessment of therapeutic response in patients with chronic indeterminate Chagas disease (Bolivia); and a study to evaluate the safety and efficacy of E1224 (Bolivia). During 2012, all these studies ended the recruitment of their patients and started their final visits of follow up.

Countries highlighted on the map represent Chagas disease-endemic Latin American countries with platform members. Other CCRP members' countries not indicated on this map are listed on the left.

Capacity strengthening

During 2012, training courses were held in Bolivia, Argentina, and Brazil for CCRP members involved in ongoing Chagas disease-related trials with 100 professionals trained. Two technical meetings in Brazil were held, engaging over 35 researchers.

Infrastructure

For the Phase II E1224 clinical trial in Bolivia, a backup site was prepared in 2012 (training, equipment, and infrastructure) to support enrollment.

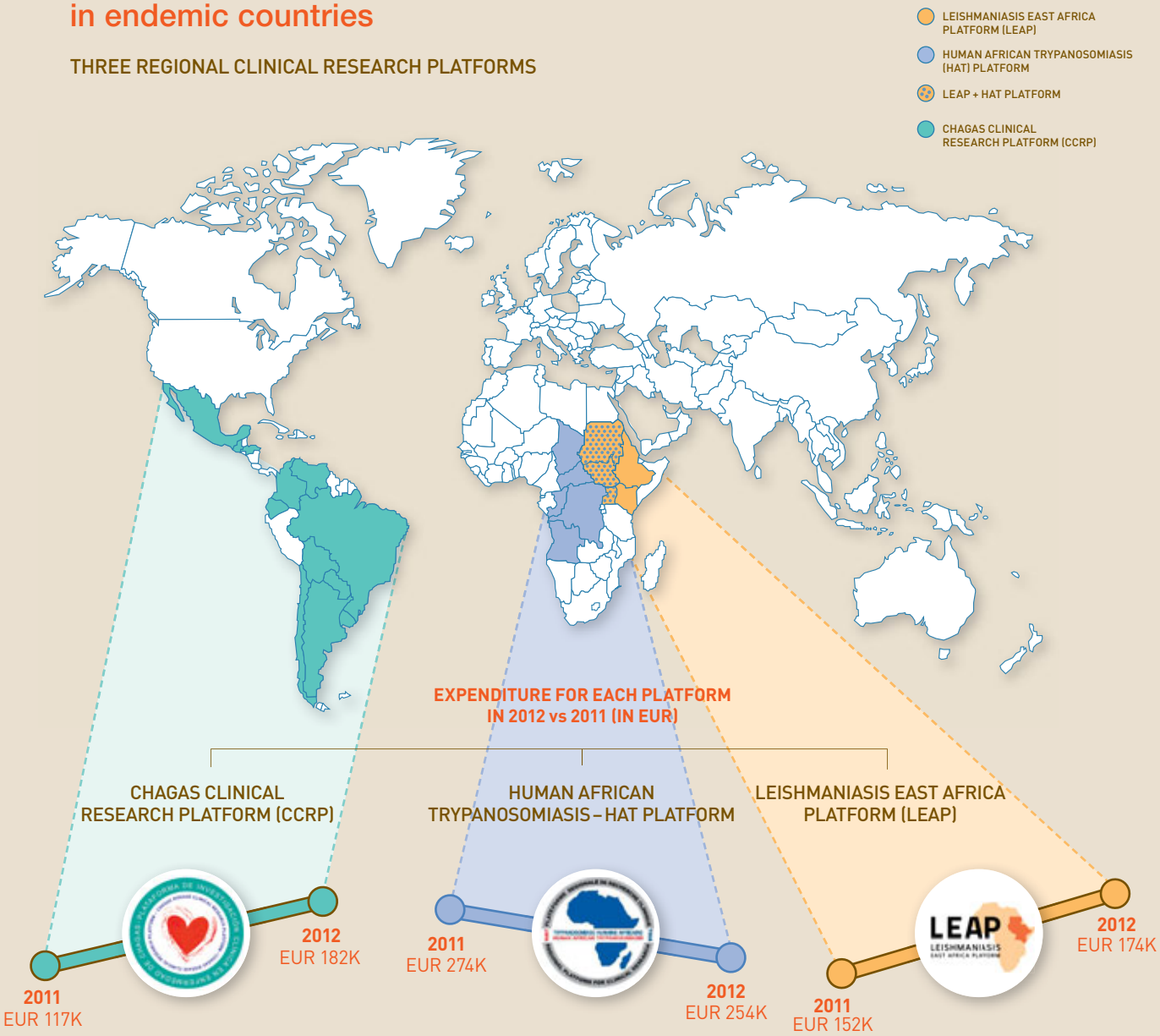
Access

The CCRP collaborated on the distribution of an Information, Education, and Communication (IEC) Tool Box for rational use of the paediatric dosage form of benznidazole. It also took part, with the Brazilian MoH, PAHO, and MSF, in the demand forecast for Chagas treatment for 14 endemic countries, and in the dossier submission for inclusion of benznidazole 12.5mg to the WHO Model List of Essential Medicines for children.

2012 KEY FINANCIAL PERFORMANCE INDICATORS

Building lasting clinical research capacities in endemic countries

THREE REGIONAL CLINICAL RESEARCH PLATFORMS



The overall LEAP and HAT Platform budgets remain stable between 2011 and 2012. The Chagas Clinical Research Platform (CCRP) costs increased by 50 % due to a meeting in August 2012 in Rio and to strengthening a regional network for Chagas drug access (Chagas meeting in Mexico, NHEPACHA meeting in Barcelona, communication activities).

CLINICAL SITES IN 2012	7
PEOPLE TRAINED IN 2012	85

In 2012, the **Chagas Clinical Research Platform** was operational at two sites for the E1224 study (Bolivia) and five sites for paediatric benznidazole Pop PK (Argentina). One new site was in preparation end of 2012 as a backup site for E1224 clinical trial.

CLINICAL SITES IN 2012	10
PEOPLE TRAINED IN 2012	131

In 2011, the **HAT Platform** was operational at six sites for the NECT study. In 2012, four additional sites were opened in Democratic Republic of the Congo for the fexinidazole study (Bandundu, Vanga, Masi Manimba, and Dipumba).

CLINICAL SITES IN 2012	7
PEOPLE TRAINED IN 2012	100

In 2012, the **LEAP Platform** was operational at seven DND*i* clinical trial sites (same as 2011): Kassab and Doka (Sudan), Amudat (Uganda), Kimalel and Kacheliba (Kenya), and Arba Minch and Gondar (Ethiopia).

DND*i*'s advocates for increased public responsibility and a more enabling environment for neglected disease R&D.



A Decade of R&D for Neglected Diseases

Despite Progress, 'Fatal Imbalance' Persists and a Global Framework Is Still Needed.

In December 2012 in New York, *Lives in the Balance: Delivering Medical Innovations for Neglected Patients and Populations*, an event co-organized by MSF, DND*i*, and Mount Sinai School of Medicine, brought together over 300 participants from civil society, academia, the pharmaceutical and biotechnology industry, ministries of health, and funding bodies to look at the progress and shortcomings of the last decade in medical innovations for neglected diseases. This conference took place precisely 10 years after MSF had hosted a major gathering in the same city to examine the crisis in R&D for neglected diseases, which ultimately led to the creation of DND*i* in 2003.

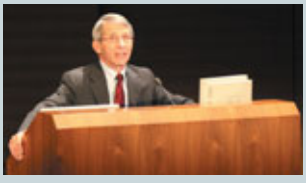
Despite incremental progress over the past decade, the essential health needs of the vast majority of the world's population are still largely unmet, current R&D efforts are still too fragmented, and financing is still far too fragile. The December conference focused on the urgent need for genuine therapeutic breakthroughs for patients dying from drug-resistant tuberculosis (DR-TB), Chagas disease, and vaccine-preventable illnesses. New therapies to fundamentally transform the treatment of these and other neglected diseases, notably those with the highest death rates, have yet to make their way through costly clinical trials and reach patients in need.

Furthering the reflections of 10 years of R&D for neglected diseases, DND*i*, MSF, and other partners undertook their own specific analysis of the R&D pipeline for neglected diseases. The study showed that while important inroads have been made, only a small fraction of new medicines developed between 2000 and 2011 were for the treatment of neglected diseases. It concluded that the 'fatal imbalance'

New York DND*i*-MSF Event (Dec. 2012): A Global Call For Action

"[T]he current model of health innovation is failing millions of the world's poorest and most vulnerable people. [W]e must work on two fronts. We need robust research and development mechanisms, producing new technologies for the diseases that afflict poor people. This means adequate, sustainable, global research investment, as well as more open approaches to sharing research knowledge. On the other hand, we must support countries to strengthen the delivery systems that will give poor people effective access to new drugs and technologies."

Dr Jim Yong Kim
President, World Bank Group

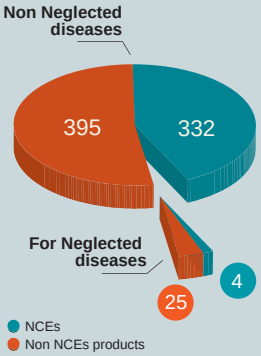


"The US is the largest public funder of neglected diseases... I say this not as a kudos to us, but as almost a challenge that we absolutely need to do more, and there's no doubt about that. And despite the constraints in resources, because it's neglected diseases doesn't mean that we should continue to neglect."

Dr Anthony S. Fauci
Director, National Institute of Allergy and Infectious Diseases, US National Institutes of Health

Progress Made but Fatal Imbalance Remains

→ **Between 2000 and 2011, only 3.8%** of newly approved drugs (excluding vaccines) were for tropical diseases, TB, and other neglected infections, which together account for 10.5% of the global disease burden.



→ **Much of the progress** in the treatment of neglected diseases and important patient benefit during this time came about through **drug reformulations** and repurposing of existing drugs against these illnesses.

→ **Only four of the 336 brand-new medicines** (new chemical entities, NCEs) developed between 2000 and 2011 were for the treatment of neglected diseases.

→ **Three of the four brand-new medicines** approved for neglected diseases in the past decade were **for malaria**, with **none for the 17 neglected tropical diseases** (NTDs) defined by the World Health Organization (WHO), nor TB.

→ As of December 2011, **only 1.4%** of a total of nearly 150,000 registered clinical trials were focused on neglected diseases.

→ **Product development partnerships (PDPs) were responsible for over 40%** of neglected disease products registered between 2000 and 2011, including new TB diagnostics and malaria combination treatments.

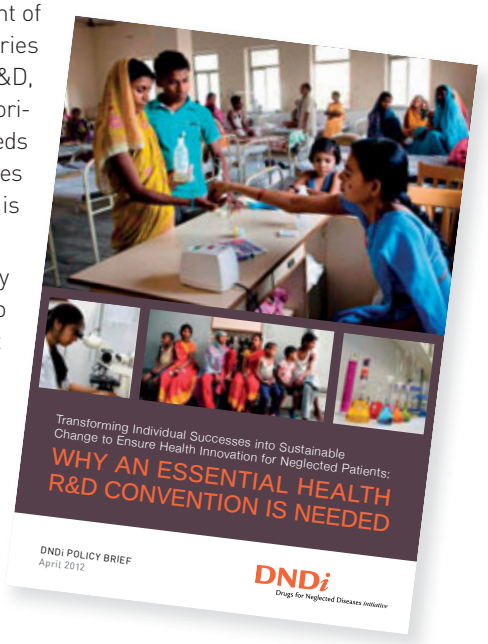
Medical innovation for neglected patients, MSF-DNDi, December 2012.

between global disease burden and drug development for some of the world's most devastating illnesses, which was the reason MSF took the first steps to found DND*i* a decade ago, was still present, despite encouraging progress made in certain areas.

The study was also prompted by the need to gain insights into neglected-disease R&D, given the 2012 recommendations of the WHO Consultative Expert Working Group (CEWG) on Research and Development: Financing and Coordination. The CEWG produced an analysis indicating that, indeed, at such a crucial time in the history of neglected diseases, it is vital to establish essential health needs-based R&D priorities and ensure that additional and sustainable financing is guaranteed. This was substantiated by a recommendation that all countries initiate formal negotiations towards a global framework that would strengthen coordination and financing of R&D and ensure that the cost of R&D be de-linked from the price of products in order to meet the needs of developing countries. In addition, the WHO's essential role in setting R&D priorities would be reinforced in the process.

DND*i* published in 2012 a policy brief, *Why an Essential Health R&D Convention Is Needed*, to relate the findings of the CEWG report to its decade of experience in drug R&D for neglected diseases. DND*i*'s 'lessons learned' included four key components:

- New financing mechanisms are necessary to provide adequate and sustainable funding, secure new funding sources, and engage public responsibility in addressing global health needs.
- R&D strategies based on open innovation models are critical to boost innovation globally, reduce duplication and costs of R&D, and speed up delivery of new medicines to patients. Such open innovation initiatives supported by public funding should be designed to secure access for patients by delinking the costs of R&D from the price of products, delivered as public goods.
- Increased involvement of disease-endemic countries in the coordination of R&D, especially in defining priorities based on patient needs and in allocating resources to identified priorities, is essential.
- Innovative regulatory pathways are needed to ensure timely patient access to treatments, reduce total costs of delivering treatments, and ultimately support greater capacity strengthening in disease-endemic countries.



DND*i* AWARDS 2013

Three Awards in 2013!

DND*i* receives prestigious awards from the BBVA Foundation, the Carlos Slim Health Institute, and the Rockefeller Foundation

In early 2013, DND*i* was honoured with the *BBVA Foundation Award for Development Cooperation* for Delivering New Treatments for Neglected Diseases with a EUR 400,000 prize. DND*i* Latin America received the 2013 *Carlos Slim Award for Innovations in Neglected Disease Drug Development* with USD 100,000 for 10 years of exceptional work in the region. In addition, DND*i* won a public voting competition for the Rockefeller Foundation's Next Century Innovators Award.

DND*i* in the news

Nearly 30 articles in mainstream media following 'Uniting to Combat NTDs' event in early 2012, and another 30 throughout the year.

Open Access to Research Results – Over 20 Scientific Publications in 2012

Neglected Diseases

More efficient ways of assessing treatments for neglected tropical diseases are required: innovative study designs, new endpoints, and markers effects by Olliaro P, Vaillant M, Sundar S, Balasegaram M. *PLoS Negl Trop Dis*, May 2012, Vol 6, Issue 5, e1545.

Novel 3-nitro-1H-1,2,4-triazole-based amides and sulfonamides as potential antitrypanosomal agents by Papadopoulou MV, Bloomer WD, Rosenzweig HS, Chatelain E, Kaiser M, Wilkinson SR, McKenzie C, and Ioset JR, *Journal of Medicinal Chemistry*, 2012 May, 55 (11), 5554-5565.

Human African Trypanosomiasis (Sleeping Sickness)

Human African Trypanosomiasis in the Democratic Republic of the Congo: a looming emergency? by Hasker E, Lutumba P, Chappuis F, Kande V, Potet J, De Weggheleire A, Kambo C, Depoortere E, Pécoul B, Boelaert M. *PLoS Negl Trop Dis*, December 2012, 6(12): e1950.

In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (nect) for *T. b. gambiense* sleeping sickness by Schmid C, Kuemmerle A, Blum J, Ghabri S, Kande V, Mutombo W, Ilunga M, Lumpungu I, Mutanda S, Nganzobo P, Tete D, Mubwa N, Kisala M, Blesson S, Valverde Mordt O, *PLoS Negl Trop Dis*, November 2012, 6(11): e1920.

Identification of compounds with anti-proliferative activity against *Trypanosoma brucei brucei* strain 427 by a whole cell viability based HTS campaign by Sykes ML, Baell JB, Kaiser M, Chatelain E, Moawad SR, Ganame D, Ioset JR, Avery VM, *PLoS Negl Trop Dis*, November 2012, 6(11): e1896.

Catechol pyrazolinones as trypanocidals: fragment-based design, synthesis, and pharmacological evaluation of nanomolar inhibitors of trypanosomal phosphodiesterase B1 by Orrling KM, Jansen C, Lan Vu X, Balmer V, Bregy P, Shanmugham A, England P, Bailey D, Cos P, Maes L, Adams E, van den Bogaart E, Chatelain E, Ioset JR, van de Stolpe A, Zorg S, Veerman J, Seebeck T, Sterk GJ, de Esch IJP, and Leurs R. *J. Med. Chem.*, September 2012, 55 (20), pp 8745–8756.

Genotoxicity profile of fexinidazole - a drug candidate in clinical development for human African trypanomiasis (sleeping sickness) by Tweats D, Bourdin Trunz B, Torreele E. *Mutagenesis*, September 2012, 27(5):523-32.

Leishmaniasis

Liposomal amphotericin B as a treatment for human leishmaniasis by Balasegaram M, Ritmeijer K, Lima MA, Burza S, Ortiz Genovese G, Milani B, Gaspani S, Potet J, Chappuis F. *Expert Opinion on Emerging Drugs*, December 2012, Vol. 17, No. 4, Pages 493-510.

Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis by Dorlo TPC, Balasegaram M, Beijnen JH, and de Vries PJ. *Journal of Antimicrobial Chemotherapy*, July 2012.

Sodium stibogluconate (SSG) & paromomycin combination compared to SSG for visceral leishmaniasis in East Africa: a randomised controlled trial by Musa A, Khalil E, Hailu A, Olobo J, Balasegaram M, *et al. PLoS Negl Trop Dis*, 6(6): e1674. June 2012.

An image-based high-content screening assay for compounds targeting intracellular '*Leishmania donovani*' amastigotes in human macrophages by Siqueira-Neto JL, Moon S, Jang J, Yang G, Lee C, Moon HK, Chatelain E, Genovesio A, Cechetto J, Freitas-Junior LH. *PLoS Negl Trop Dis*, June 2012, 6(6): e1671.

Translational pharmacokinetics modelling and simulation for the assessment of duration of contraceptive use after treatment with miltefosine by Dorlo TPC, Balasegaram M, Lima MA, de Vries PJ, Beijnen JH, Huitema ADR. *Journal of Antimicrobial Chemotherapy*, doi: 10.1093/jac/dks164, May 10, 2012.

Visceral leishmaniasis treatment: What do we have, what do we need and how to deliver it? by Freitas-Junior LH, Chatelain E, Kim HA, Siqueira-Neto JL. *International Journal for Parasitology: Drugs and Drug Resistance*, Volume 2, January 2012.

Chagas Disease

Fexinidazole: a potential new drug candidate for Chagas disease by Bahia MT, Mayer de Andrade I, Fontes Martins TA, da Silva do Nascimento AF, de Figueiredo Diniz L, Santana Caldas I, Talvani A, Bourdin Trunz B, Torreele E, Ribeiro I, *PLoS Negl Trop Dis*, November 2012.

Pharmacological characterization, structural studies, and *in vivo* activities of anti-Chagas disease lead compounds derived from tipifarnib by Buckner FS, Bahia MT, Suryadevara PK, White KL, Shackleford DM, Chennamaneni NK, Hulverson MA, Laydbak JU, Chatelain E, Scandale I, Verlinde CL, Charman SA, Lepesheva GI, Gelb MH, *Antimicrob Agents Chemother.* 2012 September; 56(9):4914-21.

Analogues of fenarimol are potent inhibitors of *Trypanosoma cruzi* and are efficacious in a murine model of Chagas disease by Keenan M, Abbott MJ, Alexander PW, Armstrong T, Best WM, Berven B, Botero A, Chaplin JH, Charman SA, Chatelain E, von Geldern TW, Kerfoot M, Khong A, Nguyen T, McManus JD, Morizzi J, Ryan E, Scandale I, Thompson RA, Wang SZ, White KL, *J. Med. Chem.*, April 2012, 55 (9), pp 4189–4204.

Malaria

Access to artemisinin-combination therapy (ACT) and other antimalarials: national policy and markets in Sierra Leone Amuasi JH, Diap G, Blay Nguah S, Karikari P, Boakye I, Jambai A, Kumba Lahai W, Louie KS, Kiechel J-R, *PLoS One*, October 2012.

Effect of the Affordable Medicines Facility – malaria (AMFm) on the availability, price, and market share of quality-assured artemisinin-based combination therapies in seven countries: a before-and-after analysis of outlet survey data by Tougher S, the ACTwatch Group, Ye Y, Amuasi JH, Diap G, *et al. The Lancet*, October 31 2012, 6(11): e1870.

Effect of artesunate-mefloquine fixed-dose combination in malaria transmission in Amazon basin communities by Santelli AC, Ribeiro I, Daher A, Boulos M, Marchesini PB, La Corte dos Santos R, Lucena MB, Magalhães I, Leon AP, Junger W, and Ladislau JL. *Malaria Journal*, 11:286, August 2012.

Artesunate-amodiaquine fixed dose combination for the treatment of *Plasmodium falciparum* malaria in India by Anvikar AR, Sharma B, Shahi BH, Tyagi PK, Bose TK, Sharma SK, Srivastava P, Srivastava B, Kiechel JR, Dash AP, Valecha N. *Malaria Journal*, 30 March 2012, 11:97.

Comparing changes in haematologic parameters occurring in patients included in randomized controlled trials of artesunate-amodiaquine vs single and combination treatments of uncomplicated falciparum in sub-Saharan Africa by Zwang J, Ndiaye JL, Djimde A, Dorsey G, Martensson A, Karema C, Olliaro P. *Malaria Journal*, 25 January 2012.

EUR 217 Million Secured

DND*i* experienced a successful year of fundraising in 2012, securing over EUR 33 million, up from EUR 25.8 million in 2011 (28%). This increase was directly linked to the UNITAID funding in support of the paediatric HIV mini-portfolio. Since the creation of UNITAID in 2006, this was the first time the organization allocated resources for late-stage development and treatment implementation. DND*i* also received funding from the French government and the Wellcome Trust, and additional support from the UK Department for International Development, Médecins Sans Frontières, and others.

Since its inception, DND*i* has recognized that the contribution of both public and private donors is essential to ensure the initiative's independence. Every effort is made to secure diversified funding from multiple sources and minimize earmarked donations to maintain the agility required to support research opportunities and deliver quickly.

In 2012, DND*i* made important strides in securing funding from endemic emerging economies, notably the government of Brazil. An agreement was signed with the Ministry of Health of Brazil, the Oswaldo Cruz Foundation (FIOCRUZ), and DND*i*, uniting the three actors in a strategic partnership to collaborate on R&D for new therapies and diagnostics for neglected diseases in the region.

At year-end, donors had committed over EUR 217 million, building on the EUR 184 million in 2011, since the launch of the initiative. The overall funding goal for DND*i* is to secure EUR 400 million by 2018. However, considering the financial crisis in Europe and economic constraints of a number of important donor countries, new funding mechanisms will be vital to bringing additional and sustainable resources to support DND*i* and others. Much expectation resides with the Global Health Innovation Technology Fund (GHIT Fund), set up by the government of Japan together with Japanese pharmaceutical companies and the Bill & Melinda Gates Foundation, launched in 2013. Encouragingly, the European and Developing Countries Clinical Trials Partnership (EDCTP) announced in 2012 an expansion of its scope to include all phases of clinical trials and neglected infectious diseases.

New Grants in 2012

UNITAID
USD 17.3 million (2012-2015)

This grant is to bolster development and delivery of a child-adapted antiretroviral (ARV) formulation and to begin market penetration, create a demand for the product and to promote in-country adoption. The funding will help expedite the production of 4-in-1 ARVs adapted for babies and toddlers with HIV/AIDS, including those co-infected with tuberculosis. DND*i* and partners will build on advances made in the field of paediatric HIV to date, and drive specific research and development to deliver ARV formulations that do not require refrigeration, are easy-to-administer, and are palatable, with simplified dosing.

French Government / AFD
EUR 5 million (2012-2016)

This is the third round of support DND*i* has received since 2006 from the Agence Française de Développement. This latest grant is directed toward DND*i*'s sleeping sickness portfolio activities, specifically the NECT and fexinidazole projects, as well as paediatric HIV and malaria projects.

UK Government / DFID
GBP 3.5 million (2012-2013)

The Department for International Development provided an additional grant to further implement the six treatments DND*i* delivered to date, to develop new chemical entities through high-quality clinical programmes, and to sustain discovery efforts to mitigate the risk of attrition inherent to R&D activities. Innovative drug candidates that can emanate from such efforts will play a critical role to support control or elimination strategies for leishmaniasis, sleeping sickness, Chagas disease, and filarial diseases.

Médecins Sans Frontières
EUR 3.5 million (2012-2013)

MSF's additional funding was directed toward DND*i*'s overall disease portfolio, ranging from early discovery activities to clinical trials and access. MSF's support also funded DND*i* operations to ensure the smooth running of all projects. Beyond the financial contribution, MSF provided invaluable support for clinical trials, and for expanding treatment uptake by governments, ministries of health, health systems, healthcare workers, and patients.

European Union / EDCTP (2012-2013) and FP7 Programmes
EUR 3.2 million (2012-2015)

DND*i* received two grants in 2012 from the European Union. The first came from the European & Developing Countries Clinical Trials Partnership (EDCTP) and supported malaria portfolio activities and specifically an ASMQ clinical trial project. The second came from the EU's Seventh Framework Programme, which supported the AfriCoLeish project, which aims to develop and deliver a package of care to address the needs of visceral leishmaniasis (VL) patients in East Africa. The project will test an alternative co-administration of two drugs to shorten current treatment duration, a preventive intervention for VL in HIV co-infected patients, as well as a safe and effective treatment for VL in HIV co-infected patients.

Wellcome Trust
USD 3 million (2012-2015)

This contribution enabled DND*i* to search for new biological markers to measure treatment efficacy (test of cure) for the leading parasitic killer of the Americas, Chagas disease. The three-year study is taking place in Texas, USA.

Swiss Government / SDC
CHF 0.9 million (2012-2013)

This supplemental funding was directed toward DND*i*'s malaria portfolio, which consists of running an extensive clinical trial programme in three countries in Africa, targeting children under five, to validate the efficacy and safety of the fixed-dosed combination ASMQ, and supporting the technology transfer for production of the malaria treatment to Zenufa, a Tanzanian industry partner.

Medicor Foundation
USD 0.8 million (2012-2013)

Medicor's funding was directed toward DND*i*'s visceral leishmaniasis (VL) portfolio. While SSG&PM was developed and recommended by the WHO in 2010 as a safer, effective, and less cumbersome first-line treatment for VL in East Africa, DND*i* set about developing a second alternative short-course combination therapy for VL in the region.

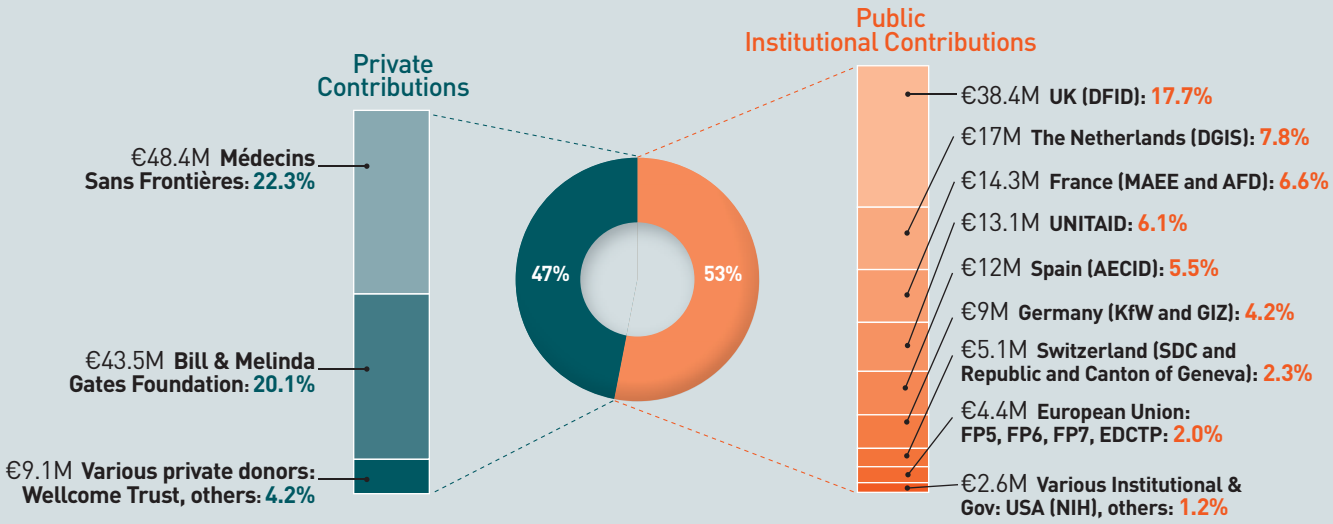
Starr International Foundation
USD 0.1 million (2012-2013)

The renewed support of the foundation to DND*i* was focused on the Chagas disease strategy in the Americas.

2012 KEY FINANCIAL PERFORMANCE INDICATORS

Maintaining balanced and diversified funding – essential to DND*i*'s vision and independence

EUR 217 MILLION COMMITTED TO DND*i* FOR 2003-2016 (AS PER DECEMBER 2012)

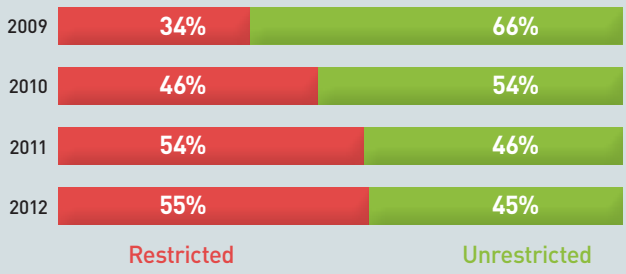


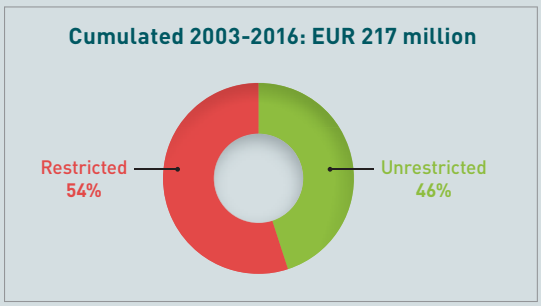
The diversification of donors increased in 2012. DND*i* welcomed additional donors including UNITAID, which pledged EUR 13.1 million toward paediatric HIV activities. To develop its activities and meet its objectives, DND*i* seeks diversified sources of funding from public and private donors, which include financial contributions from governments, public institutions, private individuals, foundations, founding partners, and innovative funding mechanisms.

Concerted efforts are made to ensure that no one donor contributes more than 25% toward DND*i*'s Business Plan, and that at maturity, half of DND*i*'s budget is covered by public funds and half by private funds. In 2012, the public-private balance was maintained as per DND*i*'s fundraising strategy. The ratio grew to 53% public support and 47% private support due to funding received from the EU Seventh Framework Programme Grant, the Agence Française de Développement, UNITAID, and the Swiss Agency for Development and Cooperation and DFID's additional contributions. New grants from private donors included the Wellcome Trust and Médecins Sans Frontières.

Challenge of a growing tendency toward restricted grants – limiting portfolio management flexibility

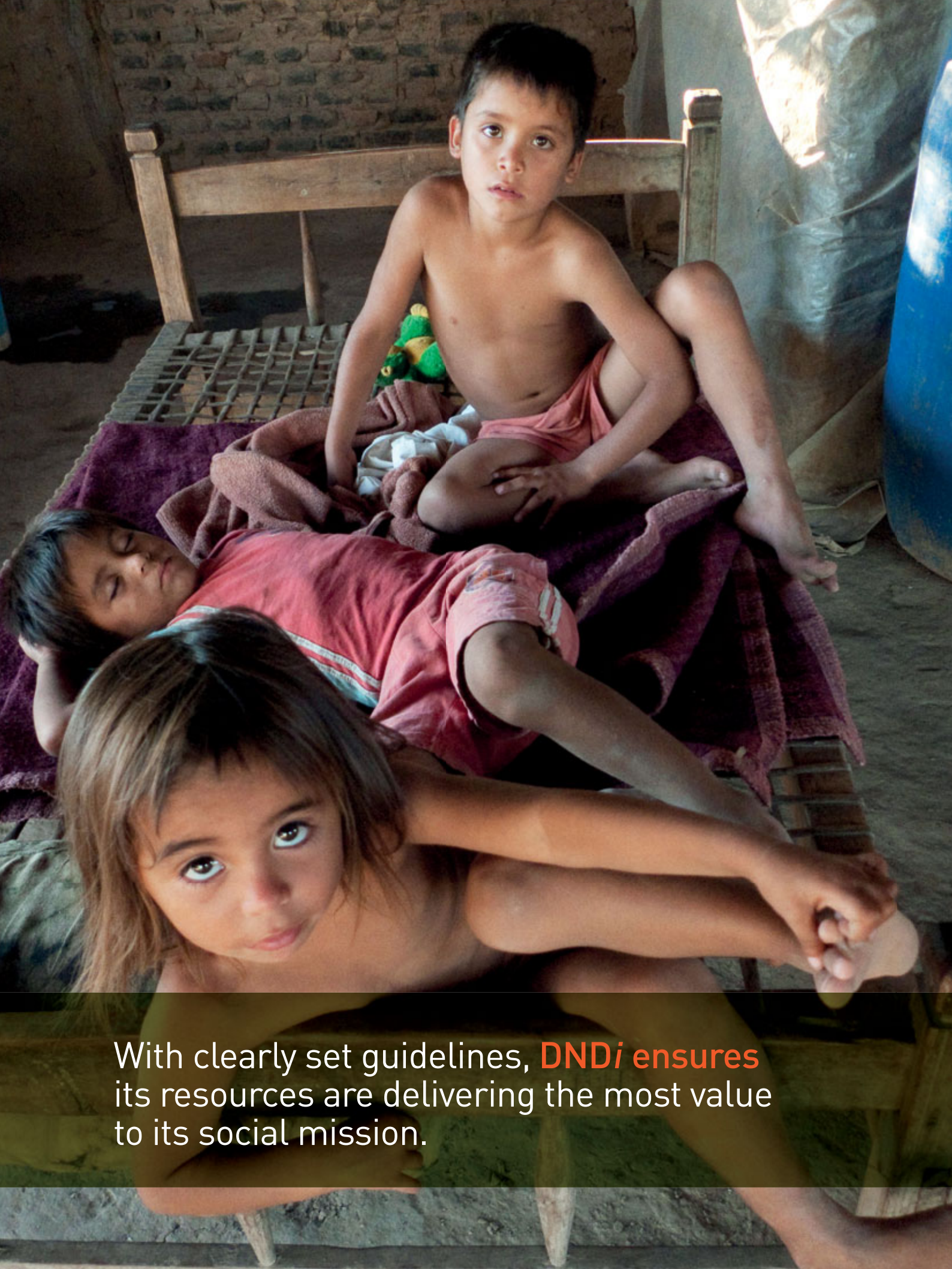
EVOLUTION OF RESTRICTED VERSUS UNRESTRICTED GRANTS BETWEEN 2009 AND 2012





Over the past four years, DND*i* has experienced a slight shift toward restricted funding. Ever so minimal, the percentage of grant funding is leaning toward specific diseases or R&D projects. While the ratio is still relatively balanced, greater efforts will be exerted in the coming years to recalibrate the proportion of restricted versus unrestricted funding. Unrestricted funding has been key to DND*i*'s success to date as it allowed the organization to respond quickly to research opportunities and also terminate projects that do not meet targeted goals set forth in the Business Plan. In 2012, DND*i* received significant earmarked contributions from UNITAID and the Wellcome Trust, shifting the scale to restricted funding. MSF and DFID (UK) also contributed additional funding to support core activities.

Restricted grants currently include a new category, increasingly proposed by donors: "portfolio grants". These grants are attributed to various diseases and various projects. While still restricted, they do allow for a certain degree of risk mitigation within restricted grants overall. Portfolio grants were estimated at 18% of the 2011 total income and 22% for 2012 total income.



With clearly set guidelines, DND*i* ensures its resources are delivering the most value to its social mission.

Financial statements and audit report

BALANCE SHEET

AT 31 DECEMBER 2012 (with 2011 comparative figures)

(expressed in EUR)	*NOTES*	2012	2011
CURRENT ASSETS			
Cash and cash equivalents:			
Cash and banks at head office		**10,070,432**	11,096,606
Cash and banks at regional offices and affiliate		**275,936**	347,002
Time deposits		**7,735,510**	8,182,670
Total cash and cash equivalents		**18,081,878**	19,626,278
Stocks of drugs	3	**164,173**	80,797
Current accounts and receivables:			
Advances to officers and liaison offices		**96,393**	66,651
Receivables from public institutional donors		**1,436,144**	2,475,541
Other receivables		**1,445,747**	1,147,388
Prepaid expenses		**179,818**	380,290
Total current accounts and receivables		**3,158,102**	4,069,870
Total current assets		**21,404,153**	23,776,945
NON-CURRENT ASSETS			
Tangible fixed assets, net	4	**50,985**	85,459
Bank guarantee deposits		**29,475**	32,108
Total non-current assets		**80,460**	117,567
TOTAL		**21,484,613**	23,894,512
CURRENT LIABILITIES			
Payables		**1,615,786**	2,588,190
Accrued expenses		**1,155,589**	759,073
Deferred income		**8,149,154**	10,077,858
Provisions	5	**226,904**	199,347
Total current liabilities		**11,147,433**	13,624,468
CAPITAL OF THE ORGANIZATION			
Paid-in capital		**32,510**	32,510
Restricted operating funds	6	**181,027**	219,888
Unrestricted operating funds		**10,123,643**	10,017,646
Total capital of the organization		**10,337,180**	10,270,044
TOTAL		**21,484,613**	23,894,512

STATEMENT OF OPERATIONS

FOR THE YEAR ENDED 31 DECEMBER 2012 (with 2011 comparative figures)

(expressed in EUR)	*NOTES*	2012	2011
INCOME			
Public institutional funding:			
Govern. & public int. organiz. unrestricted		**4,988,767**	8,729,076
Govern. & public int. organiz. restricted		**11,290,893**	4,728,028
Total public institutional funding		**16,279,660**	13,457,104
Private resources:			
Private foundations, corp. and individuals, unrestricted		**84,481**	71,060
Private foundations, corp. and individuals, restricted		**8,645,004**	8,192,695
Royalties on drug sales	6	**26,068**	56,693
Total private resources		**8,755,553**	8,320,448
Resources from founders:			
Médecins Sans Frontières, unrestricted		**4,146,208**	3,091,937
Médecins Sans Frontières, restricted		**603,967**	864,557
Total resources from Founding Partners		**4,750,175**	3,956,494
Other income:			
Sundry income & reimbursements		**60,780**	96,894
TOTAL INCOME	7	**29,846,168**	25,830,940
SOCIAL MISSION EXPENDITURE			
Research & development expenditure:	8		
Research & development coordination and supervision		**2,584,492**	2,017,738
Human African trypanosomiasis projects		**3,486,515**	3,654,972[(1)]
Leishmaniasis projects		**4,351,392**	3,473,871[(1)]
Chagas disease projects		**2,333,031**	1,720,880[(1)]
Other diseases projects (malaria, filaria, HIV)		**3,219,130**	2,393,102[(1)]
Lead optimization & Portfolio building		**6,815,215**	6,822,777[(1)]
Total research & development expenditure		**22,789,775**	20,083,340
Strengthening capacities	9	**1,630,531**	1,460,091
Advocacy expenses	10	**1,453,622**	866,543
TOTAL SOCIAL MISSION EXPENDITURE		**25,873,928**	22,409,974
NON-SOCIAL MISSION EXPENDITURE			
Fundraising	10	**1,484,849**	1,484,841
General and administration	10	**2,537,220**	2,139,433
Total non-social mission expenditure		**4,022,069**	3,624,274
TOTAL EXPENDITURE		**29,895,997**	26,034,248
Operating surplus / (loss)		**(49,829)**	(203,308)
OTHER INCOME (EXPENSES)			
Financial income, net		**4,256**	34,323
Exchange gain (loss), net		**112,709**	249,676
TOTAL OTHER INCOME, NET		**116,965**	283,999
Net surplus for the year prior to allocations		**67,136**	80,691
Allocation to restricted operating funds	6	**38,861**	(14,733)
Allocation to unrestricted operating funds		**(105,997)**	(65,958)
NET SURPLUS FOR THE YEAR AFTER ALLOCATIONS		**-**	-

***(1)** Numbers for 2011 may differ from those published in the Annual report 2011 due to modifications in the manner in which Lead Optimization budgets are allocated.*

FUNDS FLOW STATEMENT

FOR THE YEAR ENDED 31 DECEMBER 2012 (with 2011 comparative figures)

(expressed in EUR)	2012	2011
FUNDS FLOW FROM OPERATIONS		
Net surplus for the year, unrestricted	**105,997**	65,958
Net surplus for the year, restricted	**(38,861)**	14,733
Depreciation of fixed assets	**113,454**	105,153
Increase (decrease) in provisions	**27,557**	(49,267)
(Increase) decrease in stocks	**(83,376)**	244
(Increase) decrease in advances	**(29,743)**	(18,951)
(Increase) decrease in receivables from donors	**1,039,397**	423,790
(Increase) decrease in Founders and other receivables	**(298,360)**	(752,296)
(Increase) decrease in prepaid expenses	**200,472**	(304,428)
Increase (decrease) in payables	**(972,404)**	(485,247)
Increase (decrease) in accrued expenses	**396,518**	319,603
Increase (decrease) in deferred income	**(1,928,704)**	3,327,708
Funds flow from operations	**(1,468,053)**	2,647,000
FUNDS FLOW FROM INVESTING ACTIVITIES		
(Increase) decrease of investments in tangible fixed assets	**(78,980)**	(104,562)
(Increase) decrease in bank guarantee deposits	**2,633**	(3,170)
Funds flow from investing activities	**(76,347)**	(107,732)
FUNDS FLOW FROM FINANCING ACTIVITIES	**-**	-
Cash increase (decrease)	**(1,544,400)**	2,539,268
Cash and cash equivalents – beginning of year	**19,626,278**	17,087,010
Cash and cash equivalents – end of year	**18,081,878**	19,626,278

STATEMENT OF CHANGES IN CAPITAL

FOR THE YEAR ENDED 31 DECEMBER 2012

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	-	67,136	(67,136)	-
Restricted operating funds	219,888	-	(38,861)	181,027
Unrestricted operating funds	10,017,646	-	105,997	10,123,643
Capital of the organization	10,270,044	67,136	-	10,337,180

NOTES TO THE FINANCIAL STATEMENT

FOR THE YEAR ENDED 31 DECEMBER 2012

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 seven 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.

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 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 Offices (RO)

DND*i* has seven Regional Offices to help identify patients' needs, support Heads of Disease Programmes, identify and support regional partners, and undertake regional advocacy work for DND*i*. These offices, together with regional networks, ensure the participation of disease-endemic countries notably into clinical and post-clinical activities and foster South-South collaboration. In addition, Regional Offices can explore fund-raising opportunities in their regions. Their tasks and duties are further developed in the DND*i* Business Plan.

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

As of December 2012, DND*i* has established legal entities in Kenya (2006), in Brazil (2008), and in India (2009) in the form of branches. The fourth DND*i* RO is in Penang, Malaysia, and is still in the process of being registered as a branch in the country. Additionally, DND*i* has one Project Support Office in the Democratic Republic of Congo. RO accounting is fully incorporated into DND*i* accounts.

In June 2009, the Board of Directors approved the creation of a country 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; and liaising, advising, and assisting entities performing these activities.

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. Deloitte Touche Tohmatsu LLC Tokyo, Japan performs certain audit procedures on the financial statements of DND*i* 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 2012 financial position as of 31 December 2012 is the following:

- Total liabilities and net assets: JPY 3,298,377;
- Total revenue: JPY 12,004,955 which represents a grant from DND*i* to DND*i* Japan;
- Of this grant, there is JPY 0 carried forward for 2013.

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 awarding 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 since 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 2012 financial position as of 31 December 2012 is the following:

- Total liabilities and net assets: USD 122,134;
- Total revenue and other support: USD 2,347,990, of which a total grant from DND*i* to DND*i* NA, amounting to USD 823,010 and contributions (unrestricted) from individuals, corporate and private foundations ranging from USD 15 to 997,526.18 for a total of USD 1,524,745. One donor provided approximately 62% of the total contributions, including seed funding from DND*i* NA;
- Total expenses: USD 2,444,999, and an excess of expenses over revenue leading to a reduction of net assets of USD 97,009.

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 completed 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 body is not a Regional Office.

2. SIGNIFICANT ACCOUNTING POLICIES

a) Statement of compliance

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

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

These financial statements present all activities of the Foundation. A list of in-kind income and expenditures is disclosed in Note 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 made according to the purposes defined in Article 5 of the DND*i* statutes. They are defined in the present general notes under point 1.a Legal aspects. 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:

	2012	2011
USD	**0.7578**	0.7728
CHF	**0.8282**	0.8212
GBP	**1.2249**	1.1913
100 CDF	**0.0828**	0.0821
100 INR	**1.3831**	1.4536
100 KES	**0.8862**	0.9116
100 JPY	**0.8799**	0.9962
100 BRL	**37.0714**	41.4388

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 & Pre-clinical Director and/or the Medical Director for important and complex agreements and contracts above EUR 50,000, as detailed in the agreement signature process. Thereafter, funds are allocated to the partner(s) in charge of the project. Expenditures are recorded:

a) according to a financial report presenting expenditures incurred during the year on an accrual basis; or

b) if financial reports are unavailable as per the deadline of 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 FER to be regularized in the following year. The unpaid portion remaining at year-end is included under current liabilities.

h) Expenditures incurred for projects and activities

The annual action plan and budget are approved by the Board. They include 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 office rental in Tokyo and 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 paid in.

n) Restricted and unrestricted reserves

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

o) In-kind donations

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

- Goods transferred to a DND*i* project or services rendered to DND*i* must be free, excluding the involvement of a monetary transfer.
- They must be clearly identifiable and part of DND*i*'s projects and activities as defined by DND*i*'s action plans and budgets.
- Recognizable as a visible contribution to DND*i*'s projects and activities, benefiting DND*i*, and in line with DND*i*'s mission and objectives.
- Partners' voluntary involvements in joint projects and activities, in particular if the Partner does not aim to achieve DND*i*'s project objectives, are not considered as gifts-in-kind.
- For goods or services paid at prices below market prices, the difference between real payment and current market price is not considered as 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 goods 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 FER 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

In 2012, in addition to the existing stock of drugs, DND*i* purchased vials of SSG, AmBisome®, paromomycin, and caps of miltefosine 10mg and 50mg at an estimated value of EUR 83,350 from various partners (IDA Foundation, Gilead, Gland Pharma, and Paladin), for use in the on-going clinical trials and the SSG&PM combination pharmacovigilance programme. Stocks of SSG, AmBisome®, miltefosine, and paromomycin at an estimated value of EUR 164,173 are stored at clinical trial sites in Ethiopia, Kenya, Sudan, and India.

Countries / drugs	Vials			Caps		Total in EUR
	SSG	AmBisome®	Paromomycin	Miltefosine 50mg	Miltefosine 10mg	
India		3,498	8,960	32,056	24,909	**114,897**
Ethiopia		759		8,400		**19,026**
Kenya				1,400		**1,400**
Sudan	2,450	500	9,600			**28,850**
Total vials/caps	2,450	4,757	18,560	41,856	24,909	
TOTAL IN EUR	**12,250**	**66,598**	**18,560**	**41,856**	**24,909**	**164,173**

4. TANGIBLE FIXED ASSETS, net

(expressed in EUR)	Computer Equipment	Office fittings & Installations	Office Equipment	Total
Net carrying amounts 1.1.2011	13,928	30,507	41,616	**86,051**
Gross values of cost				
Beginning of the period 1.1.2011	226,357	131,828	137,260	**495,445**
Additions	77,811	6,697	20,053	**104,561**
Disposals				
End of the period 31.12.2011	304,168	138,525	157,313	**600,006**
Accumulated amortization				
Beginning of the period 1.1.2011	(212,428)	(101,320)	(95,645)	**(409,393)**
Change of the year	(48,834)	(22,300)	(34,019)	**(105,153)**
End of the period 31.12.2011	(261,262)	(123,620)	(129,664)	**(514,546)**
NET CARRYING AMOUNTS 31.12.2011	42,906	14,905	27,649	**85,460**
Net carrying amounts 1.1.2012	42,906	14,905	27,649	**85,460**
Gross values of cost				
Beginning of the period 1.1.2012	304,168	138,525	157,313	**600,006**
Additions	50,677	23,314	4,989	**78,980**
Disposals				
End of the period 31.12.2012	354,845	161,839	162,302	**678,986**
Accumulated amortization				
Beginning of the period 1.1.2012	(261,262)	(123,620)	(129,664)	**(514,546)**
Change of the year	(49,383)	(28,852)	(35,390)	**(113,625)**
Non systematic amortization(1)		(2,583)	2,753	**170**
End of the period 31.12.2012	(310,645)	(155,055)	(162,301)	**(628,001)**
NET CARRYING AMOUNTS 31.12.2012	44,200	6,784	1	**50,985**

(1) Notably correction for impact of foreign exchange rates EUR/CHF on valuation of office furniture in CHF.

5. PROVISIONS

(expressed in EUR)	Provision for taxes	Provision for HR expenses (holidays not taken)	Provision for running expenses (other)	Total
Carrying period as per 1.1.2011	158,864	78,357	11,393	**248,614**
Creation		73,815	9,818	**83,633**
Utilization	(45,840)	(75,624)	(11,435)	**(132,899)**
Reversal	-	-	-	**-**
CARRYING PERIOD AS PER 31.12.2011	113,024	76,548	9,776	**199,348**
Carrying period as per 1.1.2012	113,024	76,548	9,776	**199,348**
Creation		108,270		**108,270**
Utilization		(73,815)	(6,899)	**(80,714)**
Reversal	-	-	-	**-**
CARRYING PERIOD AS PER 31.12.2012	113,024	111,003	2,877	**226,904**

6. ROYALTIES

In December 2004, DND*i* signed an agreement with Sanofi, a pharmaceutical company, pertaining to the implementation of co-formulation treatments against malaria developed originally by DND*i* together with Sanofi (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 the ASAQ treatment in developing countries, notably in Africa.

The 3% royalties on the 2011 sales of Coarsucam® amounting to EUR 26,068 have been allocated entirely to the artesunate + amodiaquine (FACT-ASAQ in Africa) project.

The total costs of this project in 2012 amount to EUR 64,929. The balance of EUR 38,861 was taken from the 'Restricted operating fund', which is used for collaborative projects for observational studies and other access-related expenses in Africa and in Asia. After the 2012 utilization, the total amount of the restricted fund amounts to EUR 181,027 as per 31 December 2012.

7. INCOME

a) Cumulative donations committed to DND*i* and/or received by 2012 (in EUR)

DONORS		Total Commitment in currencies[4]	Total Commitment in EUR	As per Statement of Operations 2012 in EUR	To be used after 2012 in EUR
Médecins Sans Frontières	EUR	48,354,973	48,354,973	4,750,175	7,525,185
Bill & Melinda Gates Foundation	USD	59,016,944	43,524,440	7,218,131	11,035,464
UK Government DFID[1]	GBP	31,389,550	38,382,771	7,324,955	1,932,658
Dutch Government DGIS	EUR	16,975,000	16,975,000	4,000,000	8,000,000
French Government MAEE / AFD[2]	EUR	14,255,000	14,255,000	190,331	4,809,669
UNITAID	USD	17,335,304	13,136,693	0	13,136,693
Spanish Government AECID	EUR	12,000,000	12,000,000	1,000,000	0
German Government[3]	EUR	9,000,000	9,000,000	2,000,000	5,598,561
European Union, FP5, FP6, FP7, EDCTP	EUR	4,413,112	4,413,112	237,547	3,150,974
Wellcome Trust UK	EUR/USD	4,999,801	4,274,789	1,084,451	2,470,841
Swiss Government SDC	CHF	5,020,000	3,957,272	901,500	674,281
Medicor Foundation	EUR/USD	2,519,424	2,329,970	231,646	378,900
USA Government NIH/NIAID	USD	2,488,363	1,846,169	346,450	383,166
Canton of Geneva	CHF	1,600,000	1,119,035	165,874	0
UBS Optimus Foundation	CHF	1,250,000	791,045	0	0
Various private donors	EUR	547,535	547,535	115,779	0
Global Fund (AMFm)	EUR	532,809	532,809	113,003	0
Sandoz Family Foundation	CHF	500,000	308,700	0	0
Starr International Foundation	USD	400,000	296,646	79,478	75,780
Sasakawa Peace Foundation	EUR	241,336	241,336	0	0
Tuscany Region	EUR	200,000	200,000	0	0
Various other donor(s)	EUR	170,060	170,060	0	0
Anomymus donation	CHF	201,229	138,108	0	0
TOTAL DONATIONS (EUR)[4]			216,795,463	29,759,320	59,172,172

*__(1)__ The UK Government, DFID, funded DND*i* with 5 grants. A first unrestricted grant of GBP 6.5 million in 2006 for the period 2006-2008; a second unrestricted grant of GBP 18 million in 2009 for the period 2009-2013; a third restricted grant of GBP 1,381,529 in 2010 for the period 2010-2011; a fourth restricted grant of GBP 2 million in 2011 for 2011; and a fifth restricted grant of GBP 3.5 million in 2012 for the period 2011-2013. __(2)__ The French Government, Ministry of Foreign and European Affairs, funded DND*i* with 5 grants. From the MAEE: EUR 5.955 million in April 2007 for the period 2007-2010; from the MAEE: EUR 1.3 million in December 2009 for the period 2009-2011; from the AFD: EUR 1.5 million in June 2006 for the period 2006-2008; from the AFD: EUR 0.5 million in December 2009 for the period 2009-2010; and from the AFD: EUR 5 million in November 2012 for the period 2011-2015. __(3)__ The German Government funded DND*i* with 2 grants. From the GiZ: EUR 1 million for the period 2008-2009; and from the BMBF through KfW: EUR 8 million in November 2011 for the period 2011-2015. __(4)__ Exchange rates used for 'Total Commitment in EUR' and 'As per Statement of Operations 2012' are real exchange rates following the DND*i* exchange rate policy. Exchange rates used for 'To be used after 2012' appear in EUR at the USD/EUR, CHF/EUR, and GBP/EUR exchange rates as per 31.12.2012 (see note 2). 'Total Donations' therefore yield an approximate value as exchange will vary over time.*

b) Funding per project (restricted and unrestricted)

Operational Income (Grand TOTAL = 29,846,168) *(expressed in EUR)*

		UK Government DFID[1] (Unrestricted)	French Government AFD (Restricted)[2]	Spanish Government AECID (Unrestricted)	Dutch Government DGIS (Restricted)	German Government KfW-BMBF (Restricted)	United States Government NIH (Restricted)[3]	Switzerland SDC (Restricted/ Unrestricted)[4]	Switzerland Canton of Geneva (Restricted)
Implementation & Development	FACT (ASAQ & ASMQ fixed-dose) for Malaria	980,095	118,107					71,271	
	Nifurtimox + Eflornithine co-administration (NECT) for stage 2 for HAT	85,256	15,000						106,041
	New VL treatments (Asia, Africa, SSG & Paromo, Latin America; co infection HIV/VL)	214,532		211,203	706,380	327,965		333,969	
	Fexinidazole for HAT		8,018						22,385
	Benznidazole Paediatric dosage form for Chagas				183,555				
	Paediatric HIV: PI sprinkles CHAPAS-2 & super boosting TB/HIV (Preclinical until 2011)		43,490						
Translation	Alternative formulations of Amphotericin B for VL	43,236					103,309		
	Nitroimidazole VL-2098 (& back-up) for VL				20,271	55,769			
	Flubendazole Macrofilaricide for Filaria					7,043			
	Fenarimol for Chagas				11,506	34,465			
	Oxaborole SCYX-7158 for HAT (Preclinical until 2011)				70,514	284,840		113,349	
	Azoles E1224 & Biomarkers for Chagas	284,595			188,262				
	Anfoleish for CL (Exploratory until 2011)	51,690		157,325					
	K777 for Chagas				11,885		196,615		
Research	Lead Optimization Consortia (for VL, Chagas, and HAT), including Fenarimol series and Nitroimidazole & Oxaborole back-ups	1,872,884		142,719	1,442,343	778,511	389		
	Discovery & Exploratory activities (Kinetoplastids and Filaria)	145,822				135,968			
	R&D Coordination, Supervision costs	1,011,888		144,866	593,114	81,527	31,799	103,958	
	HAT, LEAP & Chagas Platforms	128,566	5,716	38,553	251,600	59,647		81,599	32,781
	Other Strengthening Capacity activities	578,808						51,709	
	Advocacy	767,520		84,028		34,298		32,326	1,518
	Fundraising	429,285		121,972	159,754	30,147	272		3,149
	General Management	730,777		99,334	360,816	169,820	8,843	113,319	
	Net surplus allocated to unrestricted funds						5,223		
	TOTAL INCOME = 29,846,168 +116,965	**7,324,955**	**190,331**	**1,000,000**	**4,000,000**	**2,000,000**	**346,450**	**901,500**	**165,874**

(1) *DFID grants include: 1) an unrestricted grant of EUR 3,988,768; 2) an exceptional unrestricted grant of EUR 3,336,187covering the period from April to December 2012 only.* ***(2)*** *French Government AFD restricted multiyear grant started as of November 2012 with an amount of EUR 190,331.* ***(3)*** *NIH grants include two multiyear grants: 1) a restricted grant with a no-cost extension until April 2012 of EUR 123,597 (including a correction of EUR 5,223 related to 2008) for alternative formulations of Amphotericin B for VL programmes; and 2) a restricted grant of EUR 222,853 for K777 for the Chagas disease programme.* ***(4)*** *Switzerland SDC grants include: 1) an unrestricted grant of EUR 830,229; and 2) a one-year restricted grant of 71,271 which started in December 2012 for the FACT malaria programme.* ***(5)*** *AMFm-Global Fund includes one restricted grant, which started in 2010 and has been amended and increased in 2012 to reach a total amount of EUR 532,809.* ***(6)*** *European Union (EU) FP7: this grant was terminated in June 2012, together with the LeishDNAvax for the cutaneous leismaniasis programme, with a last grant of EUR 69,123.* ***(7)*** *European Union EDCTP: amendment of the grant signed with an increase of EUR 196,976 and an extension of the EDCTP programme and the funding until October 2013.* ***(8)*** *B&M Gates Foundation includes five restricted grants in 2012: 1) a grant of EUR 1,135,706 pertaining to lead optimization/pre-clinical for HAT, VL, and nitroimidazole for VL programmes; 2) a grant of EUR 2,825,149 for the fexinidazole for HAT programme; 3) a grant of EUR 1,486,722 for new VL treatments in Asia; 4) a grant of EUR 754,314 for flubendazole macrofilaricide for the filarial*

	AMFm - Global Fund (Restricted)[5]	European Union EU FP7 (Restricted)[6]	European Union EDCTP (Restricted)[7]	Bill & Melinda Gates Foundation (Restricted)[8]	Médecins Sans Frontières (Restricted/ Unrestricted)[9]	Wellcome Trust (Restricted)[10]	Medicor Foundation (Restricted)	Foundations & Other (Restricted/ Unrestricted)[11]	Royalties on drug sales[12]	**Financial income (Net) = 116,965**	**Utilization of restricted reserves**	**TOTAL Expenditure = 29,895,997**
	102,738		157,295		371,537			16,448	26,068		38,861	**1,882,420**
												206,297
				1,288,756	179,268		173,557	11,218				**3,446,848**
				2,500,023								**2,530,426**
					211,466			71,828				**466,849**
					701,159			19,824				**764,473**
												146,545
				170,892								**246,932**
				559,349	5,845							**572,237**
												45,971
				281,089								**749,792**
					45,714	1,084,451		8,689				**1,611,711**
					293,793			8,258				**511,066**
												208,500
				562,728	432,711			10,799		116,965		**5,360,049**
				850,719	315,824			6,833				**1,455,166**
				267,200	328,067			22,073				**2,584,492**
		60,625			7,829		24,737	467				**692,120**
				20,367	276,945		10,531	51				**938,411**
				13,107	501,555			19,270				**1,453,622**
			6	116,047	610,699			13,518				**1,484,849**
	10,265	8,498	11,123	587,854	389,244		22,821	24,506				**2,537,220**
					78,518			22,256		0	-38,861	**67,136**
	113,003	**69,123**	**168,424**	**7,218,131**	**4,750,174**	**1,084,451**	**231,646**	**256,038**	**26,068**	**116,965**	**0**	**29,963,133**

(helminths) programme; and 5) a grant of EUR 1,016,241 for the NTD screening programme. ***(9)*** *MSF includes 4 grants: 1) an unrestricted grant of EUR 2,646,208; 2) a restricted grant of EUR 392,500 for Paediatric HIV; 3) a restricted grant of EUR 211,467 for benznidazole paediatric dosage form for Chagas disease; and 4) an exceptional unrestricted grant of EUR 1,500,000 for 2012.* ***(10)*** *Wellcome Trust grants include: 1) a restricted multiyear grant amounting to EUR 963,998 for the Azoles E1224 project for Chagas disease; and 2) a restricted multiyear grant of EUR 120,453 for biomarkers for Chagas disease.* ***(11)*** *Private Foundations: Buck Foundation (EUR 4,574); Fondation ARPE (EUR 8,273); Fondation Pro Victimis (EUR 3,200); Starr Foundation (EUR 79,478). Other Revenue: various individual donations of a total of EUR 99,731, of which EUR 79,686 come from North America and EUR 20,045 come from Switzerland. In addition, DNDi in Geneva has collected various reimbursements and participations of partners all along the year for a total amount of EUR 60,780.* ***(12)*** *Royalties from Sanofi for EUR 26,068 earmarked to a monitoring study on pharmacovigilance of ASAQ (see note 6). The restricted operating fund has been partially used (EUR 38,861) to fund and support the total expenditure attached to this project (EUR 64,229).*

8. EXPENDITURE

a) R&D projects related expenditure

Recognized in (expressed in EUR)	2012	2011
IMPLEMENTATION PROJECTS		
ASAQ Fixed-dose Artesunate - Amodiaquine (Malaria)[1]	**812,945**	649,207
ASMQ Fixed-dose Artesunate - Mefloquine (Malaria)[2]	**1,069,475**	1,254,886
NECT Nifurtimox - Eflornithine co-administration for stage 2 (HAT)[3]	**206,297**	347,044
SSG & Paromomycin Combination Therapy for VL in Africa[4]	**206,472**	32,576
New VL treatments in Asia[5]	**1,244,486**	371,450
Paediatric Benznidazole (Chagas)[6] (*development until 2011*)	**466,849**	0
TOTAL IMPLEMENTATION PROJECTS	**4,006,524**	2,655,163
DEVELOPMENT PROJECTS (PHASE IIb/III; REGISTRATION)		
Fexinidazole for (HAT)[7] (*translation until 2011*)	**2,530,426**	0
New VL treatments for Bangladesh[5]	**341,146**	444,416
New VL treatments in Africa[4]	**1,187,533**	1,567,016
New VL treatments in Latin America	**132,389**	123,316
Coinfection HIV / Visceral Leishmaniasis[8]	**264,768**	0
Paediatric Benznidazole (Chagas)[6] (*implementation as of 2012*)	**0**	501,619
TOTAL DEVELOPMENT PROJECTS	**4,456,262**	2,636,367
TRANSLATION PROJECTS (PRE-CLINICAL; PHASE I; PHASE IIa/PoC)		
Fexinidazole for (HAT)[7] (*Development as of 2012*)	**0**	2,043,071
Oxaborole SCYX-7158 (HAT)[9]	**749,792**	1,264,857
Fexinidazole for (VL)[10]	**70,054**	0
Anfoleish (CL)[11]	**511,067**	0
Azoles E1224 & Biomarkers (Chagas)[12]	**1,611,711**	1,099,841
Fenarimol (Chagas)[13]	**45,971**	0
Paediatric HIV (PI sprinkles CHAPAS-2 & Superboosting TB/HIV)[14]	**764,473**	292,712
Alternative formulations of Amphotericin B (VL)[15]	**146,545**	166,178
Nitroimidazole (VL-2098)[16]	**246,932**	768,919
K777 for Chagas[17]	**208,500**	119,420
Flubendazole Macrofiliaricide (Filaria)[18]	**572,237**	196,297
TOTAL TRANSLATION PROJECTS	**4,927,283**	5,951,295
RESEARCH PROJECTS (SCREEN; HIT TO LEAD; LEAD OPTIMIZATION)		
Lead Optimization Consortia[19]	**5,360,049**	5,223,126
Screening Resources & Reference Screening Centres[20]	**1,455,166**	1,375,006
Other exploratory activities	**0**	224,645
TOTAL RESEARCH PROJECTS	**6,815,215**	6,822,777
Project-related variable expenditure		
Coordination & Supervision[21]	**2,584,492**	2,017,738
TOTAL OF PROJECTS RELATED EXPENDITURE	**22,789,775**	20,083,340

Main R&D partners & Subcontractors:

Partners and service providers with financial compensation above EUR 5,000 in 2012 are:

(1) Sanofi, France / Institute of Research for Development (IRD), Senegal / Epicentre, France / KATH, Ghana / OTECI, France / AEDES, Belgique / Zenufa, Tanzania.

(2) National Institute of Medical Research, Tanzania / Catalent, UK / WHO-TDR, Switzerland / CNRPF, Burkina Faso / KEMRI, Kenya / Ifakara, Tanzania / Epicentre, France / Cardinal Systems, France.

(3) PNLTHA, Democratic Republic of Congo / Swiss Tropical and Public Health Institute (Swiss TPH) / HAT Platform partners (PNLTHA, Republic of the Congo; TMRI, Sudan; ICCT, Angola; COCTU, Uganda; PNLTHA Central African Republic; PNLTHA, Chad) / RCTS, France.

(4) Kenya Medical Research Institute, Kenya / Institute of Endemic Diseases (IEND) and University of Khartoum, Sudan / Addis Ababa University, Ethiopia / University of Makerere, Uganda / Amudat Hospital, Uganda / LSHTM, UK / Gilead, Ireland / IDA Foundation, The Netherlands / i+solutions, The Netherlands / Torkke & Dreher, Switzerland.

(5) MSF-Logistique, France / Gilead, Ireland / WHO-TDR, Switzerland / OneWorld Health (OWH/PATH), USA / Médecins Sans Frontières / MSF-Supply, Belgium / GVK Biosciences, India / Shaheed Surawhady Medical College Hospital (SHSMC), Bangladesh / International Centre for Disease Diarrheal Research (ICDDR), Bangladesh.

(6) LAT Research, Argentina / F.I.P.E.C. Argentina / Fundacion Innova-T, Argentina.

(7) Sanofi, France / Swiss TPH / HAT Platform partners (see point 3 above) / Aptuit, UK / SGS, Belgium and France / Xcentipharm, France / Vanga CBCO Clinic, DRC / Médecins Sans Frontières / MSF-Logistique, France / Bertin Pharma, France / Institute of Tropical Medicine-Antwerp, Belgium / Cardiabase, France / Phinc Development, France / Cardinal Systems, France / Theradis, France / Qualilab, France.

(8) Gondar University, Ethiopia / Addis Ababa University, Ethiopia.

(9) SCYNEXIS, USA / Drugabilis, France / Penn Pharma, UK / Greenwich University, UK / Absorption Systems, UK / SGS, Belgium & France / Cardiabase, France / Patheon, UK.

(10) Phinc Development, UK.

(11) Imperial College, UK / PECET Universidade, Colombia / Calvert Laboratories, USA / Institut Pasteur, Iran.

(12) Barcelona Center for International Health Research (CRESIB), Spain / CEADES, Bolivia / Texas Biomedical Research Institute, USA / Fundep + René Rachou Institute, Brazil / Corlab Partners, USA / McGill University, Canada / University of Georgia, USA / Cardinal Systems, France / Clin Data First, France / Fundacion Ingebi, Argentina.

(13) Drugabilis, France / Accelera, Italy.

(14) WuXi AppTech, China / Medical Research Council (MRC), UK.

(15) Polytherics, UK / LSHTM, UK.

(16) Advinus Therapeutics, India / Drugabilis, France / ChemDepo Inc, USA / Huntingdon, USA.

(17) Harlan Laboratories, Switzerland / University of California, USA.

(18) Accelera, Italy / Covance, UK / Michigan State University, USA.

(19) Epichem Pty Ltd, Australia / CDRI, India / Advinus, India / Murdoch University, Australia / Monash University, Australia / WuXi Apptec, China / TB Alliance, USA / Cangenix, UK / IPK, Korea / Drugabilis, France / Phinc Development, France / SCYNEXIS, USA / Pace University, USA / Anacor Pharmaceuticals Inc., USA / LSHTM, UK / iThemba Pharma, South Africa / Antwerp University, Belgium / Sandexis, UK.

(20) Swiss TPH, Switzerland / LSHTM, UK / Antwerp University, Belgium / GlaxoSmithKline (GSK-Tres Cantos), Spain / IPK, Korea / Dundee University, UK / Northwick Park Institute for Medical Research (NPIMR), UK.

(21) R&D Coordination & Supervision.

(expressed in EUR)	2012	2011
Coordination	1,651,256	1,151,350
Scientific Advisory Commission	120,403	113,567
Business Development	589,818	420,761
Japan representation office	223,015	234,291
Research: IP & Regulatory affairs (under Advocacy & Comm in 2012)	0	97,769
TOTAL	2,584,492	2,017,738

Consultants involved in R&D projects:

Ansong, Daniel; Bacchi, Cyrus; Banks, Michael; Bennett, John; Bray, Michael; Buffet, Pierre; Campbell, Simon; Chang, Shing; Chappuis, François; Clark, Jeff; Daher, André; Diap, Graciela; Dinanga Munzadi, Jos; Duke, Jeff; Etienn, Paula; French, Edward; Garcia, Facundo; Geary, Timothy; Gradner, Mark; Hudson, Alan; Larrey, Dominique; Last, Paul; Massuyeau, Laurent; Mazué, Guy; Mechali Daniel; Mestra Laureano; Mutombo Kalonji, Wilfried; Oliveira, Ana Luiza; Paillasseur, Jean-Louis; Parkinson, Tanya; Pedrique, Maria Belen; Pinheiro, Eloan; Pouit, Sylvie; Prescott, Kim; Scherrer, Bruno; Schijmann, Alejandro; Smith, Dennis; Somme, Claudette; Sosa-Estani, Sergio; Speed, Bill; Taylor, Bob; Thénot, Jean-Paul; Tweats, David; Vacus, Joël; Vaillant, Michel; Voiriot, Pascal; Von Geldern, Thomas; Williams, Mike; Zijlstra, Edward; Zwang, Julien.

b) Presentation of the DND*i* expenditure per nature of expenses

Recognized in (expressed in EUR)	2012	2011
PERSONNEL		
Personnel at Head	**6,744,482**	5,409,964
Personnel at Regional	**2,012,990**	1,277,579
Consultant	**1,812,230**	2,016,288
Travel and Accomodation	**1,353,807**	1,215,779
TOTAL PERSONNEL	**11,923,509**	9,919,610
OPERATIONAL R&D		
Purchase & Logistics	**920,912**	472,562
Equipment	**253,032**	63,328
Discovery & Lead Optimization (partners & service)	**6,043,795**	5,795,563
Pre-clinical (partners & service)	**1,091,235**	1,409,435
Training for partners	**132,861**	97,016
Clinical & post-clinical (partners & service)	**5,511,870**	5,032,206
Product manufacturing & CMC (partners & service)	**690,396**	382,757
TOTAL OPERATIONAL R&D	**14,644,101**	13,252,867
OTHER		
Communication (tools, organization of)	**1,099,561**	954,702
Administration & IT (depreciation, furniture, service providers)	**2,228,826**	1,907,069
TOTAL OTHER	**3,328,387**	2,861,771
GRAND TOTAL	**29,895,997**	26,034,248

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)	2012	2011
Regional Offices, manage. costs: Rio, Delhi, Nairobi, Penang	**938,413**	842,514
Leishmaniasis East Africa Platform (LEAP)	**174,309**	151,760
Human African Trypanosmiasis (HAT) Platform	**253,578**	273,552
Chagas Clinical Research Platform	**182,147**	117,382
LeishDNAvax Consortium Agreement	**82,084**	74,883
TOTAL	**1,630,531**	1,460,091

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

Leishmaniasis East Africa Platform: *University of Khartoum, Sudan; Addis Ababa 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; ASK (AMC-Slotervaart Hospital, KIT), The Netherlands; i+solutions, The Netherlands;* DND*i.*

Chagas Clinical Research Platform: *Ministries of Health and National Control Programmes of high-burden endemic countries (Argentina, Bolivia, Brazil, Mexico); PAHO; Dept for the Control of Neglected Tropical Diseases, WHO; 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; 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; MSF; Institut de Recherche pour le Développement, France; Eisai Co. Ltd., Japan; FINDECHAGAS; Mundo Sano, Argentina.*

10. ADVOCACY, FUNDRAISING AND GENERAL & ADMINISTRATION EXPENSES

	Advocacy		Fundraising		General & Administration	
(expressed in EUR)	**2012**	2011	**2012**	2011	**2012**	2011
Human resources	**904,841**	453,778	**1,191,778**	1,170,773	**1,570,746**	1,215,285
Office charges	**41,752**	45,079	**72,565**	74,397	**121,081**	106,550
Travel expenses	**73,381**	39,506	**70,691**	86,787	**168,220**	141,789
Administration	**41,133**	26,861	**91,748**	86,989	**191,623**	284,561
IT & telecommunications	**55,215**	23,548	**29,144**	24,139	**358,324**	248,619
Communication	**319,171**	265,659	**16,443**	28,086	**85,109**	112,037
Depreciation	**11,345**	11,567	**12,480**	13,670	**32,902**	27,340
Exceptional expenses	**6,784**	545	**0**	0	**9,215**	3,253
TOTAL	**1,453,622**	866,543	**1,484,849**	1,484,841	**2,537,220**	2,139,433

Consultants: *Bolton, Samantha; Castillo, Cecilia; Chaves, Gabriela; Collins, Intira; Fiori, Valéria; Goel, Sunil Prakash; Lotrowska, Michel; Lucas Subirats, Marta; Matsudaira, Masako; Menghaney, Leena; Paccaud, Léa; Pontes, Flavio; Salamin, Alain; Thorens, Isaline; Van de Weerd, Hans; Vieira, Marcela; Wells, Susan; Wong, Peng Lin.*

11. INDEMNITIES & REMUNERATIONS GIVEN TO DIRECTORS

All members of the Board are appointed on a voluntary basis. The Board members have received no remuneration for their mandate in 2012, nor in 2011.

12. CONTRIBUTIONS IN-KIND

Drugs for Neglected Diseases *initiative* (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 no cost as gifts in kind (see note 20, DND*i* In-Kind Policy). DND*i* aims at reflecting this increasing contribution in the 2012 financial statements in order to present a comprehensive picture of its activities. The in-kind contribution of DND*i* partners increased between 2011 and 2012 from EUR 5,000,000 in 2011 to EUR 5,750,000 in 2012.

Gifts-in-kind evaluated for the year 2012 per category and per project

(expressed in EUR)	Staff Scientific	Staff non-Scientific	R&D Services	Office, furniture & admin.	**Total**
Lead Optimization Consortia (Australia)			115,714		**115,714**
Screening Resources & Reference Centres	216,128	114,266	230,651	41,834	**602,879**
Fexinidazole for HAT	80,000		88,714		**168,714**
K777 for Chagas			356,736		**356,736**
Fenarimol for Chagas			356,736		**356,736**
Flubendazole Macrofiliaricide	185,232		310,050		**495,282**
Regional Offices	113,275	10,669	2,339	52,812	**179,095**
New VL Treatments: Africa, Asia, America	125,834		310,249	13,589	**449,672**
Azoles E1224	1,459,453	35,699	1,510,478		**3,005,630**
Paediatric Benznidazole	1,798	499	10,087		**12,384**
ASMQ Fixed-dose (Malaria)	200	1,198	5,992		**7,390**
TOTAL	2,181,920	162,331	3,297,746	108,235	**5,750,232**

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 57,974 – 2011 CHF 70,000) and CHF 20,000 (EUR 16,564 – 2011 CHF 20,000) in favour of a third party. Cash for an equivalent amount is pledged at the corresponding bank.

Report of the statutory auditor

Deloitte.

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Report of the statutory auditor

To the Board of
DRUGS FOR NEGLECTED DISEASES INITIATIVE (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 and notes, presented on pages 59 to 73, for the year ended December 31, 2012. In accordance with Swiss GAAP FER 21, the content of the performance report presented on pages 8 to 57 is not audited.

Board's Responsibility
The Board is responsible for the preparation and the fair presentation of the financial statements in accordance with Swiss GAAP FER and the requirements of Swiss law and the charter of the foundation. 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, 2012 give a true and fair view of the financial position, the results of operations and the cash flows in accordance with Swiss GAAP FER and comply with Swiss law and the charter of the foundation.

Deloitte.

Drugs for Neglected Diseases initiative (DNDi)
Report of the statutory auditor
for the year ended
December 31, 2012

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 CC in connection with article 728 CO) and that there are no circumstances incompatible with our independence.

In accordance with article 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, June 3, 2013

A WORD OF THANKS

DND*i* is grateful for the support received from the following donors who contributed toward the advancement of its mission and goals. To date, DND*i* has delivered six new treatments and aims to bring eleven to thirteen treatments in total to patients suffering from neglected diseases by 2018. DND*i* would like to thank all of the donors and partners for their loyal commitment and partnership since 2003.

Public institutional support

Department for International Development (DFID) / United Kingdom
Dutch Ministry of Foreign Affairs (DGIS), The Netherlands
European Union – Framework Programmes 5, 6 and 7, International
European and Developing Countries Clinical Trials Partnerships (EDCTP) with co-funding from Member States, International
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German International Cooperation (GIZ) on behalf of the Government of the Federal Republic of Germany, Germany
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Ministries of Foreign and European Affairs (MAEE), France
National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), United States of America
Spanish Agency for International Development Cooperation (AECID), Spain
Swiss Agency for Development and Cooperation (SDC), Switzerland
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Fondation Pro Victimis, Switzerland
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Guy's, King's and St Thomas', Giving Week, United Kingdom
Leopold Bachmann Foundation, Switzerland
Médecins Sans Frontières (Doctors Without Borders), International
Medicor Foundation, Liechtenstein
The Peter and Carmen Lucia Buck Foundation, United States of America
Steve Rabin and Jonathan Winslow, United States of America
Richard Rockefeller, United States of America
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DND*i*
Drugs for Neglected Diseases *initiative*

DND*i*

Drugs for Neglected Diseases *initiative*

The Drugs for Neglected Diseases *initiative* (DND*i*) is a patient-needs driven, not-for-profit research and development (R&D) organization that develops safe, effective, and affordable treatments for neglected diseases that afflict millions of the world's poorest people, notably human African trypanosomiasis (sleeping sickness), leishmaniasis, Chagas disease, paediatric HIV, specific filarial diseases and malaria.

DND*i*'s primary objective is to:

→ Deliver 11 to 13 new treatments by 2018 for targeted neglected diseases and establish a strong R&D portfolio that addresses patients' treatment needs

In doing this, DND*i* has two further objectives:

→ Use and strengthen capacities in disease-endemic countries via project implementation

→ Raise awareness about the need to develop new drugs for neglected diseases and advocate for increased public responsibility

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