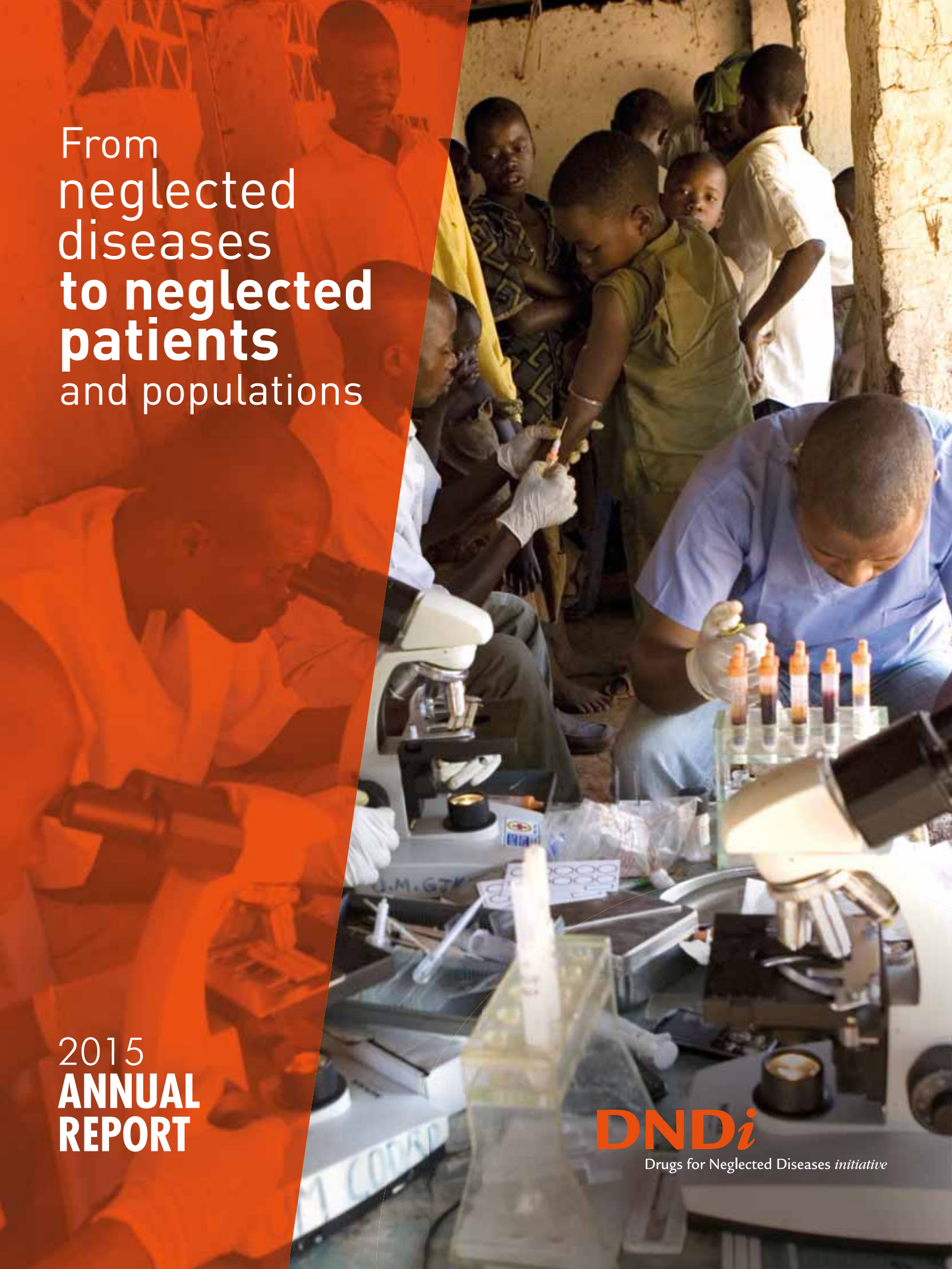

From
neglected
diseases
to neglected
patients
and populations

2015
ANNUAL REPORT

DNDi
Drugs for Neglected Diseases *initiative*

DND*i*'s 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 research and development (R&D). They also build public responsibility and leadership in addressing the needs of these patients.

DND*i*'s MISSION

- To develop new drugs or new formulations of existing drugs for **people living with neglected diseases**. Acting in the public interest, DND*i* bridges 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** has been the development of drugs for the **most neglected diseases**, such as human African trypanosomiasis (HAT, or sleeping sickness), leishmaniasis, and Chagas disease, while considering engagement in **R&D projects for other neglected patients** (e.g. malaria, paediatric HIV, filarial infections) and development of diagnostics and/or vaccines to address unmet needs that others are unable or unwilling to address.
- In pursuing these goals, DND*i* enables R&D networks built on global collaborations. While harnessing existing support capacities in countries where the diseases are endemic, DND*i* contributes to **strengthening capacities in a sustainable manner**, including through know-how and technology transfers in the field of drug R&D for neglected diseases.
- In order to address evolving needs of public health importance and maintain DND*i*'s commitment to delivering on the objectives of the current portfolio of diseases, **a dynamic portfolio approach** has been adopted. This enables DND*i* to take on new disease areas with various operating models, while completing objectives in current 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 the millions of neglected patients across the world.

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

The initiative's primary objective is to deliver a total of 16 to 18 treatments by 2023 and to establish a strong R&D portfolio for these diseases.

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2015 ANNUAL REPORT

Cover photo: A mobile team of the National Control Programme for sleeping sickness screens a young boy for sleeping sickness, in Mpata village, Democratic Republic of the Congo.

VISION, MISSION & STRATEGY

REMAINING RESPONSIVE TO EVOLVING RESEARCH AND PATIENT NEEDS

DND*i* is rooted in an ideal: to mobilize scientific innovation to create new medicines for the world's most neglected diseases and malaria. Our aim was to provide the structure to take the most promising projects ignored by commercial drug development through the pipeline, by capitalizing on existing capacity and expertise, particularly in affected countries.

Message from

Prof Marcel Tanner,
Chair of the Board of Directors,

and

Dr Bernard Pécoul,
Executive Director

Since its inception in 2003, DND*i* has defined itself as an experiment in 'innovation for access,' a laboratory for alternative mechanisms that deliver affordable products answering to an unaddressed medical need. Our scale is by definition small: our purpose is not, and never has been, to act as the solution to systemic failures of biomedical R&D.

Our six achievements to date, attained in collaboration with our partners, bear witness to the pertinence of that initial ideal and the success of the model – with two new antimalarial fixed-dose combinations, the world's first child-friendly medication for Chagas disease, and changes to national or international guidelines, thanks to successful clinical trials for sleeping sickness and for visceral leishmaniasis treatments in Africa and Asia.

More than a decade later, it is our pleasure to take stock once again.

An unchanged vision, an expanded mission

In 2014 and 2015, we embarked on an extensive consultation exercise with our founding partners and key stakeholders, as well as with leading global health actors, to ensure the organization remains attuned to current and emerging patients' needs and the evolving R&D landscape.

The outcome of the consultation, enshrined in the new Business Plan for 2015 to 2023, maintains our focus on the most neglected diseases by adopting a dual strategy: on the one hand, pursuing incremental innovation to bring therapeutic benefits to patients by repurposing, reformulating, or combining existing drugs; and on the other, seeking to discover and develop entirely new chemical entities, with the aim of bringing radically improved oral treatments without which sustainable control or elimination of these diseases can never become a reality.

Discovering and developing treatments to respond to neglected tropical diseases like sleeping sickness, visceral and cutaneous leishmaniasis, Chagas disease, and filaria remain at the core of our work. Adding to this focus on the most neglected of the neglected, a new research and development project will focus on new treatments for mycetoma, a devastating infection – recently introduced on the official WHO list of neglected tropical diseases – which, left untreated, eventually results in amputation.

While our core focus remains unchanged, we acknowledge that the shortcomings of the existing system of research and development extend far beyond the neglected diseases at the core of DND*i*'s portfolio.

From our consultations, three main findings emerged to help us draw lessons for the future of DND*i*'s model and operations: first, R&D priorities do not sufficiently originate from low- and middle-income countries (LMICs); secondly, patients' needs are not prioritized, and many treatment needs, for example for Ebola or mycetoma, are left unaddressed; and finally, market incentives that solely rely on intellectual property and exclusivity rights do not adequately address health needs in LMICs, with certain public health needs like antimicrobial resistance left unanswered as a result.

We also noted changes in global health epidemiology, with for example the

Prof Marcel Tanner (top) and Dr Bernard Pécoul (bottom) visiting DND*i* projects in Tanzania and in the Democratic Republic of Congo, 2015.

emergence of new infectious disease risks and LMICs facing a double burden of both communicable and non-communicable diseases. The political context of global health is also evolving, with the lack of equitable access to new health tools increasingly seen as a problem, including in high-income countries as, for example, in hepatitis C.

The challenge is therefore better understood as one of "neglected diseases, neglected patients and populations in neglected health and social systems"– that is, of ensuring that the global R&D system meets the needs of all, especially of the poorest and most vulnerable populations in the most neglected settings.

A dynamic and pragmatic approach to ensure DND*i* can respond to changing needs

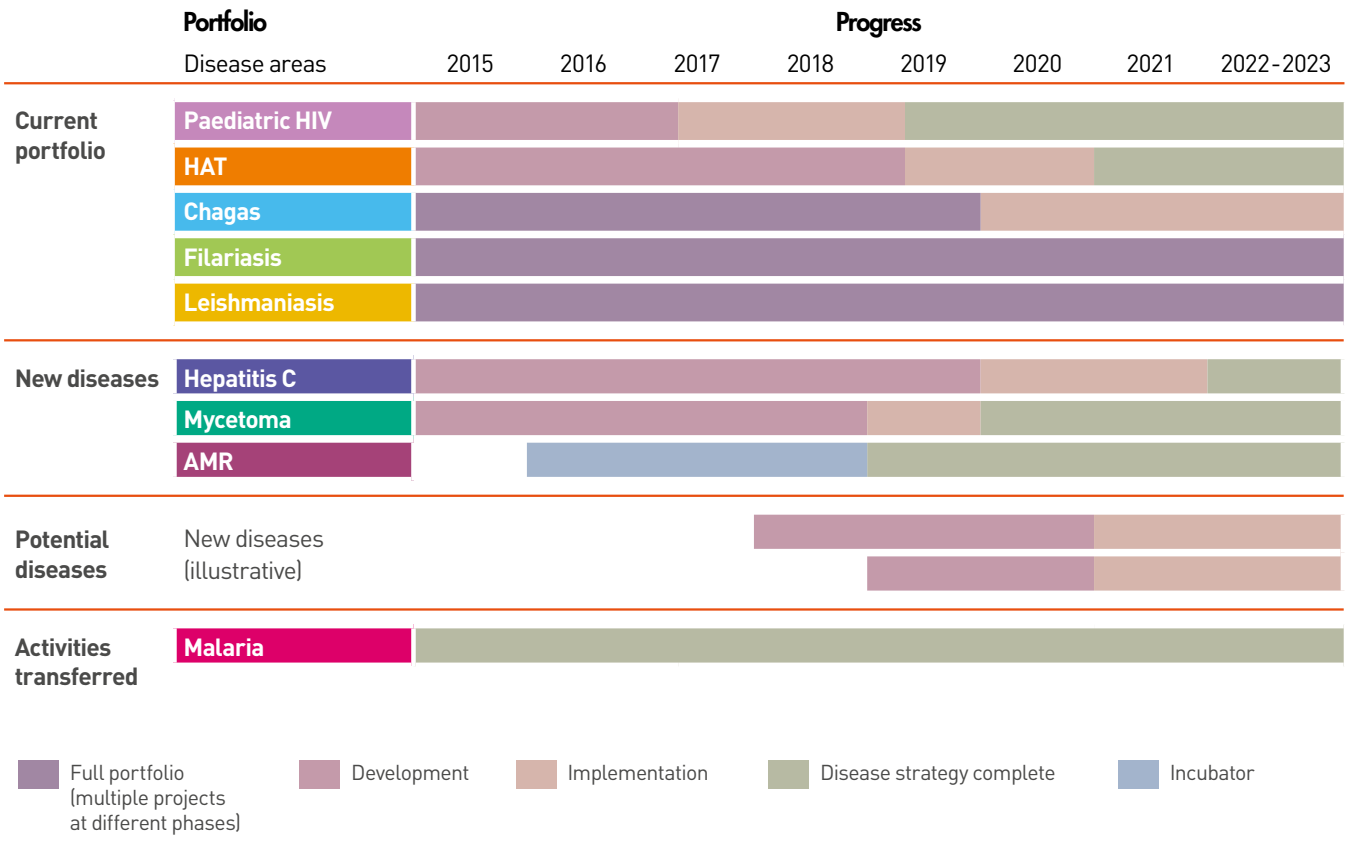
Given the complexities of drug discovery and development, the timelines of a research and development organization are lengthy. By essence, our commitments and objectives are long term. The challenge lies in continuing to meet these, while also ensuring DND*i* remains relevant and responsive to the evolving needs of patients.

Within this rapidly changing landscape, DND*i*'s new Business Plan for 2015 to 2023 aims to give the organization the flexibility to address urgent unmet patients' needs, by introducing the concept of a dynamic portfolio as a tool to guide the evolution of DND*i*'s activities. This will involve identifying and selecting new opportunities through a detailed decision-making and evaluation framework, as well as for phasing out projects when they reach completion and/or are not part of our core activities, as was recently the case for our malaria portfolio that was transferred to the Medicines for Malaria Venture.

Ultimately, decisions to enter into new projects will always be based on patients' needs, existing R&D opportunities, an absence of other actors in the field, and ability to engage operational partners.

The Chair of the Board of Directors and Executive Director launching DND*i*'s new Business Plan for 2015-2023 in Basel, Switzerland, September 2015.

DND*i*'s portfolio progression (2015-2023)



This is what led DND*i* to include paediatric HIV into its portfolio in 2011. Even though there is a strong R&D effort to develop better HIV/AIDS treatments for adults, very little research is done for HIV-positive children. Current treatment options are insufficient, as little investment has been made to ensure the safety and efficacy of antiretrovirals in treating children. They are neglected patients.

We now tackle hepatitis C: Despite an abundant pipeline of potential new drugs, developing country research needs are largely unaddressed, and existing products are unaffordable. The therapeutic advances brought about by direct-acting antivirals are not reaching patients. In an exciting new project launched in April 2016, DND*i* aims to foster a public health approach to the disease, by facilitating the development of an affordable pan-genotypic treatment.

DND*i* will also change *how* it does things. Not every disease area will require the same amount of effort and investment. A range of different operating models can be used, from integration into DND*i*'s R&D portfolio, to various levels of more time-limited support such as knowledge sharing, advocacy, building new resource platforms, or serving as an incubator for an idea that may ultimately be externalized.

By allowing for more flexible and diversified operational models, DND*i* can tailor the breadth and depth of its engagement to a specific global health R&D need as it arises without jeopardizing our focus or draining resources. Resistance to antibiotic treatments, for example, emerged as a key unmet medical need in our landscape analysis, and was considered best addressed through an incubator model, with a dedicated team (see p. 9).

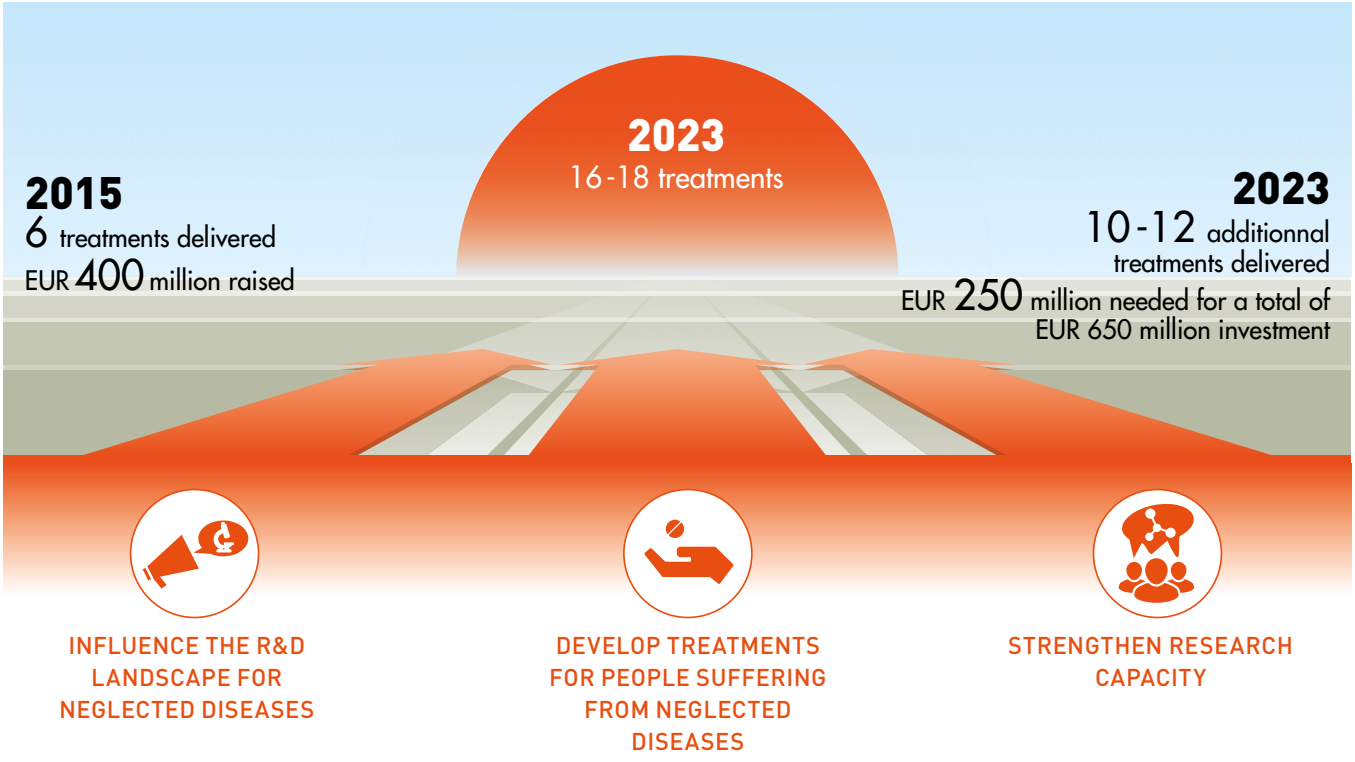
The roadmap towards 2023

In our 13 years of existence, DND*i* has developed, implemented, or delivered six new treatments, for malaria, sleeping sickness, Chagas, and leishmaniasis, and developed a pipeline of over 30 projects. By our 20th anniversary in 2023, our ambition is to have delivered 16 to 18 new treatments, including two to three new chemical entities.

Reaching this ambitious objective relies on an estimated budget of EUR 650 million covering the 20 year period since the creation of DND*i* until 2023,

of which close to EUR 400 million has already been secured to date.

We will stay focused on the key elements that have been essential to our success: our partnerships with private sector actors, key for us to access the necessary expertise and data to bring a treatment through to the hands of patients; the support of public actors, which has been the lifeline of our endeavours; and the participation of research communities and civil society in endemic countries to ensure patients' needs remain at the forefront of our efforts. For this particular reason, this business plan will be translated into a regional strategic plan, with the expansion and development of DND*i*'s regional offices, particularly those in neglected disease-endemic regions. These close associations, for some now more than a decade long, will remain a fundamental part of the set-up of DND*i* and assure the process of mutual learning for change for the benefit of the most neglected populations in the most neglected health and social systems.



In the new Business Plan, the founding principles upon which DND*i* is built are also reinforced:

- a patients' needs-driven approach;
- a steadfast commitment to promote open sharing of research knowledge and data while ensuring an access-oriented approach to intellectual property;
- the fostering of innovative, collaborative partnerships with public and private sectors;
- the diversification of funding sources to ensure independence.

GARD: A new partnership to fill critical gaps in antibiotic R&D

"Antimicrobial resistance threatens the very core of modern medicine and the sustainability of an effective, global public health response to the enduring threat from infectious diseases. Without harmonized and immediate action on a global scale, the world is heading towards a post-antibiotic era in which common infections could once again kill."

Global Action Plan on Antimicrobial Resistance,
World Health Organization, 2015

A joint initiative by WHO and DND*i*, the vision of the Global Antibiotic Research and Development (GARD) Partnership is to develop new antibiotic treatments addressing antimicrobial resistance and to promote their responsible use for optimal conservation, while ensuring equitable access for all, with a focus on global health needs.

The initiative ties in with the Global Action Plan on Antimicrobial Resistance adopted in 2015, which required the WHO Secretariat to propose options for the establishment of new partnerships to identify priorities for new treatments, diagnostics, and vaccines to fight resistant pathogens.

In November 2015, WHO and DND*i* jointly organized a technical consultation that reaffirmed the initiative, with participants from pharmaceutical and biotechnology companies, other product development partnerships, academia, civil society, and health authorities from countries of all income levels, including Brazil, Canada, Chile, China, Egypt, India, Japan, Malaysia, Qatar, South Africa, Thailand, the US, Zambia, and seven European countries and the European Commission.

In December 2015, the DND*i* Board of Directors approved the hosting of the incubation of the GARD Partnership, which was formally launched in May 2016.

New incentive mechanisms

A critical issue is the failure of current incentive mechanisms to replenish the empty antibiotic R&D pipeline. GARD will provide an important alternative to the traditional market-driven approach, by focusing on products that the pharmaceutical industry has not and will not develop for lack of profitability.

To overcome this hurdle, alternative business models and incentives need to be tested, including 'delinkage' of the cost of R&D from volume-based sales and price of treatments. Learning from DND*i*'s experience of the partnership model for product development in the field of neglected diseases, GARD will test new incentive mechanisms that stimulate R&D but also contribute to responsible use, while facilitating equitable access to new antibiotic treatments.

Political and financial support from governments

At the time of its launch, GARD secured seed funding commitments from the Federal Ministry of Health of Germany, the Netherlands' Ministry of Health Welfare and Sports, the South African Medical Research Council, and the United Kingdom Department for International Development as well as from Médecins Sans Frontières, totalling over EUR 2 million of the projected EUR 3 million required for the incubation phase.

Hosted by DND*i*, the GARD team is responsible for building the scientific strategy and a product pipeline, developing the GARD business plan, setting up a scientific working group and steering committee, and establishing the operational structure. GARD's governance is de facto embedded into DND*i*'s during this start-up phase.

WHO will provide support in priority setting, stewardship, and access; report back to its Member States; secure close collaboration with the AMR Secretariat, relevant WHO departments, the Essential Medicines List team, and the Global Health R&D Observatory; and provide other technical input where needed.

Staphylococcus Aureus bacteria culture.

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Krisantha Weerasuriya, World Health Organization (WHO), Geneva

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Nick White, Mahidol University, Bangkok, Thailand

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◆ Former DND*i*'s Board or SAC member

More details on each person available on DND*i*'s websites

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Monique Wasunna, Director, DND*i* Africa*

Chirac Bulanga Milemba, Head of DND*i*'s Project office, DRC (as of March 2016)

Fumiko Hirabayashi, Head of Liaison office, DND*i* Japan

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Jennifer Duran, Richard Feiner, Colin Forsyth▲, Robert Grembowitz, Ilan Moss, Jaxira Rodriguez

▲ Joined DND*i* in 2016 (as of April 2016).

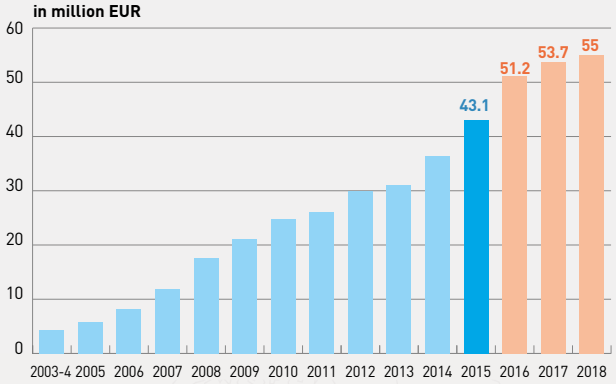
More details on each person available on DND*i*'s websites

EUR 43 MILLION BUDGET FOR 155 DND*i* CORE STAFF AND CLOSE TO 700 ESTIMATED FTEs WORLDWIDE

Major growth for HAT disease and in the recent portfolios, as well as in feasibility studies

Since its inception in 2003, DND*i* expenditure totals EUR 260 million. In 2015, expenditure amounted to EUR 43 million, +18% (+EUR 6.6 M) compared to 2014. This increase is principally due to HAT projects expenditure (+EUR 1.6 M) and the projects recently entered in the portfolio (+EUR 1.2 M for filarial diseases; +EUR 1.1 M for the HIV paediatric project, and +EUR 0.5 M for feasibility studies).
In addition, the variation of exchange rates in 2015, and particularly the higher price of the US dollar (+17%) and the Swiss franc (+9%) against the Euro, led to a significant increase in our accounts, as these are held in Euros (~+EUR 3 M, accounting for ~8% out of the total 18% 2015 growth). The operating gain of EUR 0.28 million is partly canceled because of exchange rate loss (EUR 0.16 million).

STATEMENT OF ACTIVITIES 2003-2015 AND FORECAST for 2016-2018

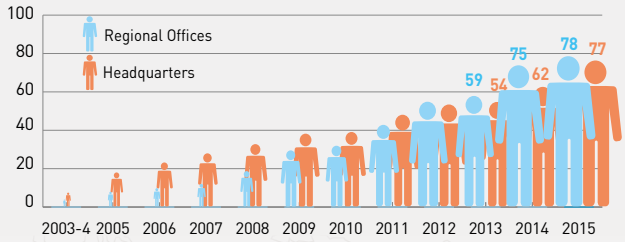


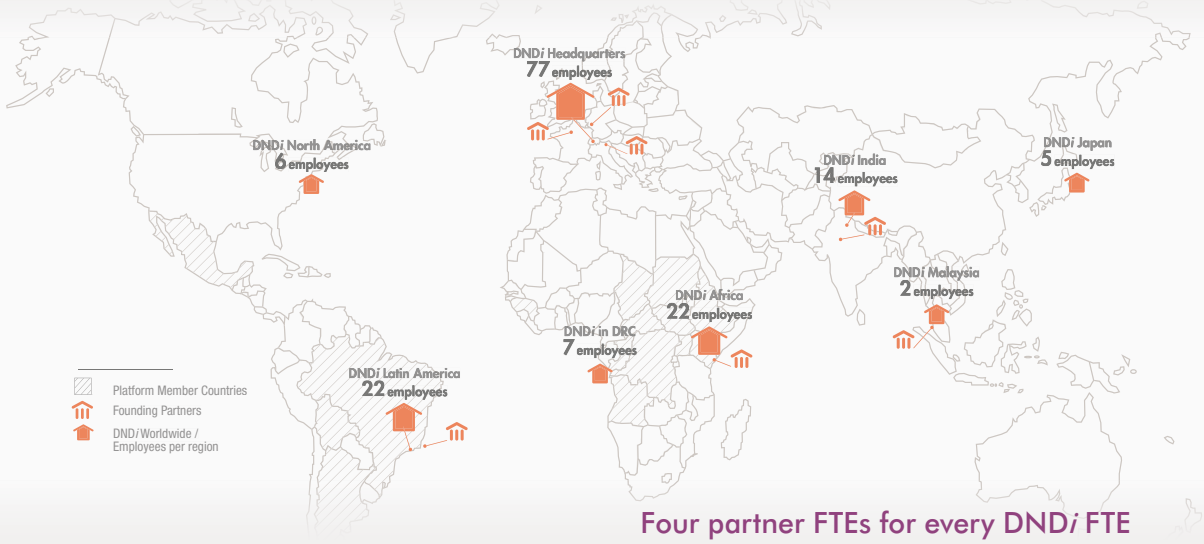
155 people worldwide, with most new positions dedicated to R&D coordination and External affairs

In 2015, DND*i* recruited an additional 18 people (24 people in 2014), which represents an increase of 13%. Recruitment occurred mainly at headquarters in Geneva, with 15 new people (+24%), and with 3 new positions in regional offices (ROs) - Kinshasa, Tokyo, and Rio de Janeiro (+4%). The increase in the Geneva R&D team is mainly due to the strengthening of the R&D coordination (4 FTE in Geneva and 2 in Japan) and HAT disease (+2 FTE in Geneva and 1 FTE in Kinshasa). Other new positions are mostly dedicated to External Affairs (Communication and Fundraising activities +4 FTE). Staff in ROs is now of an equivalent number (50%) to staff based in headquarters (50%). Also noteworthy: of the 16 recruitments completed in 2016 by the end of April, 5 are in the headquarters (4 replacements and 1 new position), and 11 implemented in ROs (3 replacements and 8 new positions).

For 2015, the exact amount of FTE working at DND*i* was calculated taking into account start date, end date, and percentage of time for each person working in DND*i*; giving a total of 139 FTE with 155 people working at DND*i*.

HUMAN RESOURCES EVOLUTION 2014-2015
Growth of activities (+18%) sustained by staff increase (+13%)



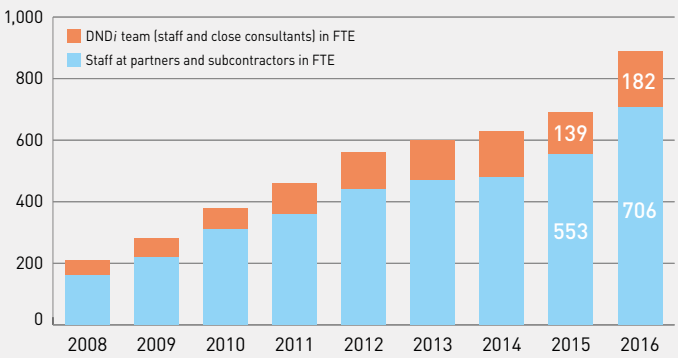


FOUNDING PARTNERS

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)

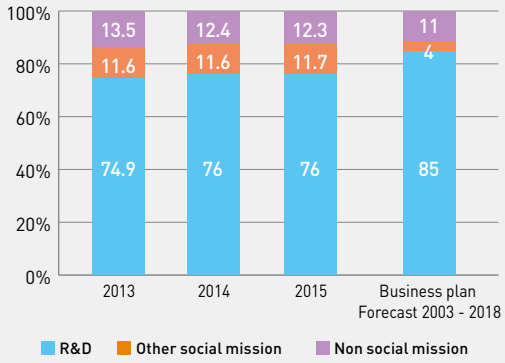
Four partner FTEs for every DND*i* FTE

692 FTES WORLDWIDE IN 2015 (888 FORECASTED IN 2016)



Stabilization of the Social Mission ratio

2015 SOCIAL MISSION BREAKDOWN: 87.7% OF EXPENDITURE

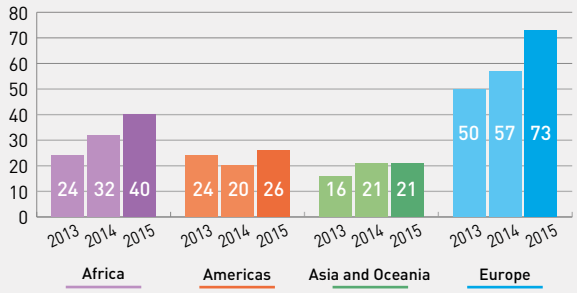


In 2015, DND*i*'s non-social mission ratio remains highly stable compared to 2014. The growth in non-social mission (+EUR 0.8 M) and social mission expenditures (+EUR 5.8 M) were balanced, at 18% each. However, these steady figures mask some specific points worth highlighting:

- The External Affairs department covering Communications, Advocacy, Policy affairs, and Fundraising activities experienced one of the highest growths in 2015 of all departments, with a 33% increase (+EUR 1.1 M).
- Activities related to Strengthening Capacities, with 7% growth (+EUR 0.2 M), and General Administration, with 10% growth (+EUR 0.3 M) maintained the same level of activity compared to 2014, with the rise in expenditure mostly due to the increase in the CHF & USD exchange rates against the EUR.

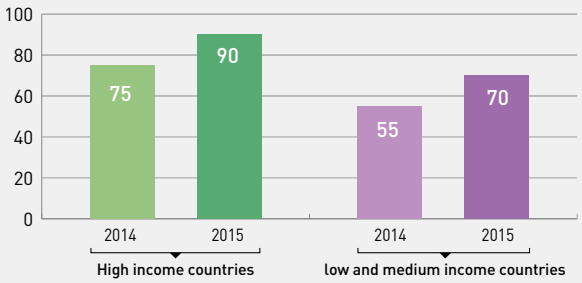
Partnerships increase of 23% to support the growth of R&D activities

MAIN R&D PARTNERS & SERVICE PROVIDERS PER CONTINENT, with financial compensation over EUR 5,000



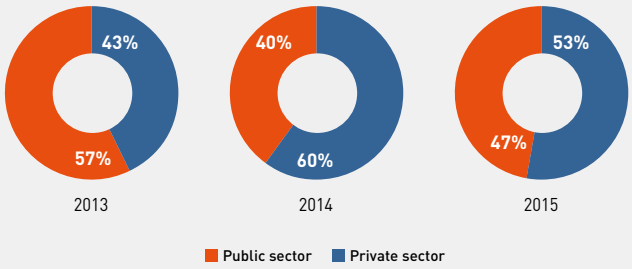
In 2015, the number of partners and service providers DND*i* had business relations valuing over EUR 5,000 with increased by 23% (160 in 2015, compared to 130 in 2014). All regions increased except Asia. The Americas saw a rise of 30% with 6 additional partners & service providers to support the new activities related to CL and Chagas access projects in Latin America. In Europe the figure progressed by 28% with 16 additional partners & service providers, reflecting the growth of the new diseases activities in 2015 in Europe. In Africa there was growth of 25%, with 8 additional partners & service providers, particularly with the Kenya office increasingly engaging local vendors for regional activities related to paediatric HIV, mycetoma, and leishmaniasis.

MAIN R&D PARTNERS: FASTER GROWTH IN LOW & MIDDLE-INCOME (+27%) THAN IN HIGH-INCOME COUNTRIES (+20%)



Private *versus* public sector ratio remains stable at around 50%/50% over the last 4 years

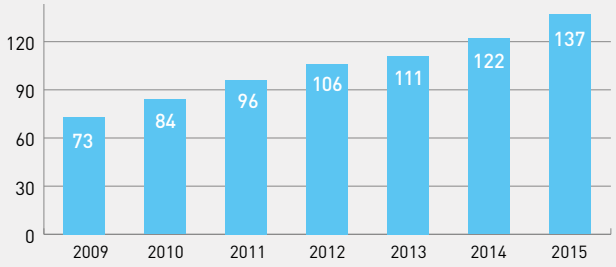
MAIN R&D PARTNERS AND SERVICES PROVIDERS with financial compensation over EUR 5,000



Comparison of percentage of partnerships with the public institutional sector (research institutes, public hospitals, academic groups, universities, PDPs, and other not-for-profit organizations) with numbers of partnerships with the private sector (pharmaceutical and biotechnology companies and contract research organizations).

Steady growth in number of partnerships

NUMBER OF CONTRACTS SIGNED ANNUALLY*



The number of contracts finalized each year follows a trend similar to that of R&D partners & service providers with a financial compensation of over EUR 5,000. There is a regular annual increase of between 5% and 15%, with 5% in 2013 and 12% in 2015.

**Except confidentiality agreements; some new contracts may be extensions.*

R&D MODEL & PORTFOLIO

ADAPTED TREATMENTS FOR THE BENEFIT OF NEGLECTED PATIENTS

The R&D strategies developed by DND*i* since its inception aim to address the immediate needs of patients by improving existing therapeutic options in the short term, whilst undertaking longer term research to identify and develop entirely new compounds which will be valuable adapted tools, particularly for elimination targets set by the World Health Organization. Although not necessarily breakthrough medicines, six new treatments have been delivered to date as a result of the short-term strategy, which have brought significant benefits to patients.

The year 2015 has been a turning point for DND*i*, as long-term investments have now filled the drug development pipeline with thirteen new chemical entities (NCEs) included by the end of the year, the vast majority of which are orally available compounds for systemic use. The most clinically advanced of these are for sleeping sickness: fexinidazole, which was identified from compound mining and is a ten day oral treatment, and SCYX-7158, which is entering Phase II trials as a potential single-dose oral treatment and is the first molecule to arise from DND*i*'s lead optimization programme.

Leishmaniasis is a complex family of diseases, and the identification of new compounds has proved challenging. Compound libraries from a variety of sources have been screened and, despite the inevitable loss of compounds to attrition, NCEs from the nitroimidazole, oxaborole, and aminopyrazole chemical families are undergoing lead optimization to combat *Leishmania* infections, with the nitroimidazole VL-0690 selected to go forward to

pre-clinical development in 2015. Additional drug candidates have come from the drug discovery programmes of GSK/Dundee Drug Unit (two classes), and Celgene (one class). These six classes are also undergoing testing in animal models of CL. The three classes from the DND*i* series have already shown efficacy against *L. major* in a mouse model of infection, with the aminopyrazole class showing sterile cure in animals. This is the first time this has been observed with a drug candidate. The NTD Drug Discovery Booster, a multilateral experiment launched in 2015, aims to speed up the discovery of new compounds for leishmaniasis and Chagas disease. The lack of clinical markers of disease, and of animal models capable of accurately predicting the translation of drugs from laboratory to patient, has proven to be a major obstacle in developing new drugs for Chagas disease.

A two-pronged approach aims to develop direct-acting or indirect-acting compounds for treating filarial diseases. Emodepside, used in veterinary healthcare, began its clinical evaluation in healthy volunteers in 2015 as a potential treatment for onchocerciasis. Additional NCEs are being sought by screening focused libraries with known anthelmintic activity from animal health companies and repurposing libraries from human health companies. Although drug repurposing is high risk, the wealth of information available for drugs which have already undergone clinical development can speed up the development process drastically, and new treatments reach patients faster. A macrofilaricide which indirectly leads to the death of the parasite by killing its *Wolbachia* symbiont entered the development pipeline in 2015.

This increased number of compounds in development has resulted in a concomitant increase in the number of clinical trials. At the end of 2015 more than 30 clinical trials were in preparation, on-going, or reporting results worldwide.

The extension of DND*i*'s portfolio with the new Business Plan 2015-2023 (see p. 6) led to the inclusion of two new diseases. Fosravuconazole, already available to DND*i* because of its previous evaluation for Chagas disease, is the most promising drug candidate for fungal mycetoma and DND*i* will begin recruiting 130 patients in Sudan in the first ever randomized clinical trial to be undertaken for eumycetoma.

DND*i* South East Asia

A combination of sofosbuvir with ravidasvir will be evaluated in 750 patients in Malaysia and Thailand as a potential public health tool to treat Hepatitis C.

29 ongoing clinical studies in 2015, on 4 continents, for 7 diseases

Phase I	Phase II	Phase III	Phase IV
3 STUDIES	11 STUDIES	10 STUDIES	5 STUDIES

DND*i* DRC

Efficacy studies with fexinidazole in human African trypanosomiasis (HAT) patients in the Democratic Republic of Congo and Central African Republic will ultimately collect information from 750 adults and children above the age of 6 years with both stages of *gambiense* disease, including an evaluation of its ease of use under real-life conditions. A later study will examine its efficacy in patients with *rhodesiense* HAT.

DND*i* Africa

Fexinidazole is also being investigated for treating patients with the related kinetoplastid diseases – leishmaniasis and Chagas disease. A combination of fexinidazole and miltefosine for the treatment of visceral leishmaniasis (VL) patients in eastern Africa could be the first oral-only combination therapy for VL: an allometric dosing study of miltefosine to address drug underexposure in children was undertaken in 2015. Twelve month follow-up of efficacy and safety data of fexinidazole in adult Chagas disease patients was concluded in 2015, with the results expected in early 2016. A planned study in 270 adult patients with chronic Chagas disease aims to determine if the safety and tolerability issues of benznidazole can be managed by reduced doses and treatment duration, or by combination with fosravuconazole.

DND*i* Latin America

DND*i* Africa

DND*i* is seeking to address the urgent need for better medicines for children living with HIV. In June 2015 lopinavir/ritonavir (LPV/r) pellets were awarded tentative approval for use by the U.S. Food and Drug Administration (FDA). This was followed by the initiation of an implementation study (the LIVING study) in 3,000 Kenyan children, which will provide information on their use as part of a combination treatment with AZT/3TC or ABC/3TC administered under normal living conditions. A "superboosting" study was undertaken in 96 African children infected with both HIV and tuberculosis (TB), aiming to compensate for the negative drug interactions between LPV/r and the TB-treatment rifampicin. The study was finalized in 2015 and results led the South African government to change its treatment guidelines for HIV/TB coinfected children.

BUILDING A ROBUST PORTFOLIO

PROJECTS ARE DIVIDED INTO FIVE CATEGORIES:

New treatments (involving NCEs) developed from novel compounds identified through screening, lead optimization, or licensing. These drugs must meet target product profiles (TPPs) and may be used in monotherapy or as part of combination therapies when appropriate.

★ New Chemical Entity (NCE); Fexinidazole (for HAT, VL, and Chagas disease) = 1 NCE

- **New treatments developed from compounds with known antimicrobial/ antiparasitic activities** aiming to maintain or improve efficacy and tolerability.
- **Compound repurposing for new indications of existing treatments in other diseases** (therapeutic switching).
- **Combinations or new formulations of existing drugs that are better adapted to field conditions and patient needs** (paediatric dosage forms, long-acting forms, new route of administration, fixed-dose combinations, co-packaging, or co-administration).
- **Geographical extension of existing treatments**, including completion of regulatory dossiers in new countries.

Implementation

Access

NECT
Nifurtimox-Eflornithine Combination Therapy

SSG&PM
Africa

New VL Treatments
Asia

Benznidazole
Paediatric Dosage form

Malaria
ASAQ FDC
ASMQ FDC

December 2015

KEY R&D MILESTONES IN 2015

DISCOVERY

- Successful implementation of NTD Drug Discovery Booster
- New series in H2L and lead optimization for leishmaniasis and Chagas disease
- Screening of 300,000 compounds from pharmaceutical and other libraries completed
- Two optimized lead candidates under review for VL with backup compounds in three different chemical classes – including one very potent for CL

HUMAN AFRICAN TRYPANOSOMIASIS (HAT)

- Recruitment to three fexinidazole studies (pivotal late stage, early stage, children) completed
- Phase I study for SCYX-7158 completed

LEISHMANIASIS

- DNDI-0690 nominated as new pre-clinical candidate for VL
- Miltefosine allometric dosing study recruitment completed in Africa
- Dose selection and decision to initiate drug-drug interaction study on fexinidazole/miltefosine as a potential oral combination in Africa
- Development of PKDL study for India and PKDL infectivity study in Bangladesh
- Study on new VL treatments in Latin America completed
- 12-month follow-up of VL-Asia study ongoing – collaboration with Kalacore for further implementation and pharmacovigilance monitoring

CHAGAS DISEASE

- Drug-drug interaction study completed for E1224/benznidazole
- Development of study protocol for short-course benznidazole as well as benznidazole/E1224 combination

FILARIAL DISEASES

- Pre-clinical development for emodepside completed

PAEDIATRIC HIV

- Interim positive results for TB Superboosting study
- LIVING study on the implementation of pellets initiated in Kenya

MALARIA

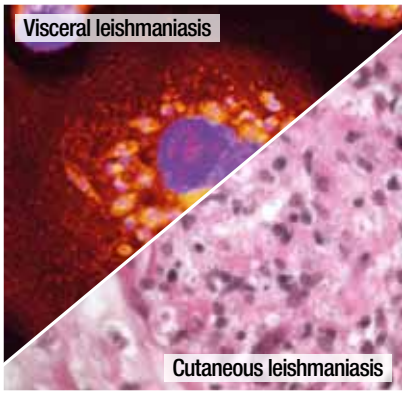
- ASAQ and ASMQ transferred to MMV
- ASAQ technology transfer to Zenufa: preparation of prequalification file
- >400 million ASAQ treatments delivered by Sanofi

TRANSMISSION

DND*i* works on diseases that are transmitted in a variety of ways, from parasites living in two different hosts to viruses, worms, and a fungus. Curing these diseases requires not only an understanding of the infectious agents, but also an understanding of the interplay between infection, vector, and host.

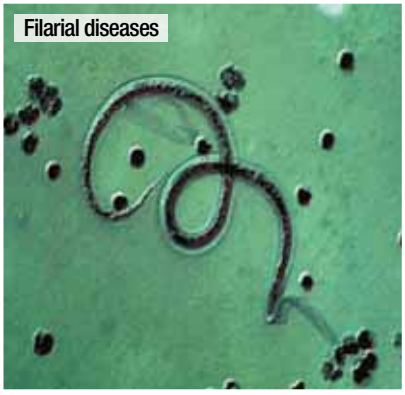
Chagas disease is caused by the **kinetoplastid protozoan parasite *Trypanosoma cruzi*.** It is primarily transmitted by large, blood-sucking **reduviid insects** widely known as **'kissing bugs'**.

HAT is caused by two sub-species of **kinetoplastid protozoan parasites: *Trypanosoma brucei (T.b.) gambiense*** (West and Central Africa) and ***T. b. rhodesiense*** (East Africa). Parasites are transmitted to humans by **tsetse flies**.



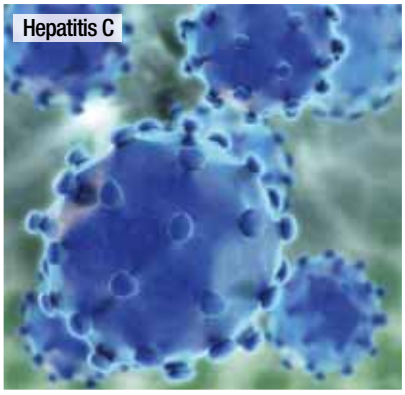
Leishmaniasis is a diverse and complex disease caused by more than 20 species of the **kinetoplastid protozoan parasite. *Leishmania*** parasites can be transmitted to humans by some 30 species of **phlebotomine sandflies.**

Malaria is caused by the ***Plasmodium* parasite**. Five species are involved: ***P. falciparum, P. malariae, P. vivax, P. ovale & P. knowlesi***. They are transmitted from person to person by the bite of infected **anopheline mosquitoes**.

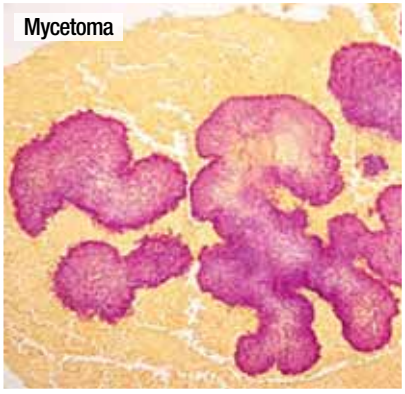


Onchocerciasis (River blindness), **Lymphatic filariasis** (Elephantiasis), and **Loiasis** (*Loa loa* infection) are all caused by **parasitic filarial nematode worms.** They are transmitted between humans by **blood-sucking insects**.

The **human immunodeficiency virus is a lentivirus** that causes **HIV infection** and acquired **immunodeficiency syndrome**. About **90%** of the infected infants acquire **the HIV virus from their HIV-positive mothers** during pregnancy, delivery, or through breast-feeding (known as mother-to-child transmission).



The **hepatitis C** virus exists in six genotypes that cause liver disease. It is a **blood-borne virus** that is commonly transmitted through **unsafe injection practices, contaminated medical equipment, and transfusion of unscreened blood**.



Mycetoma is a slow-growing **bacterial** (Actinomycetoma) or **fungal** (Eumycetoma) **infection**. The exact route of Eumycetoma infection is unknown but it is thought to enter the body after the **skin has been pricked** (e.g. by a thorn).

DISCOVERY

Drug discovery is a demanding process, particularly with the added constraints of working in a neglected area and within a limited budget. The standard "black box" approach involves screening compounds against parasites *in vitro*, to identify those which are able to kill the parasite under laboratory conditions.

Having identified initial hits, analogous compounds are synthesized and evaluated to identify even more potent molecules in a process known as hit-to-lead. The most promising of these undergo further optimization in order to maximize antiparasitic activity, increase tolerability and safety, and optimize the amount of time a compound stays in the body.

With compounds undergoing clinical development for HAT, DND*i*'s screening and lead optimization efforts are currently focused on identifying compounds for Chagas and leishmaniasis.

The mini-portfolio approach for filarial disease treatments aims to identify: (1) direct-acting compounds – by screening libraries from animal health companies and repurposing compounds for human use, and (2) indirectly-acting compounds – which kill the symbiotic *Wolbachia* bacteria – in partnership with the anti Wolbachia consortium (A-WOL) at the Liverpool School of Tropical Medicine, UK.

The NTD Drug Discovery Booster was launched in 2015 as an experiment aimed at speeding up the process and cutting the cost of finding new treatments for Chagas disease and leishmaniasis (see p. 21).

Medicinal chemistry with partners in the North and South

Over the last decade, DND*i* has worked with academic and industrial medicinal chemistry partners who are organized geographically into two consortia, in Australia (LO AUS) and the United States (LO US).

In 2013 we began building a new consortium in Latin America (LOLA), providing support and mentoring for young scientists in the region (see below). The consortia undertake hit-to-lead and lead optimization activities for visceral leishmaniasis and Chagas disease (see Leish H2L p. 29, and Chagas H2L p. 38), with HAT activities on hold in case of any future need.

A Latin American consortium for leishmaniasis and Chagas disease drug discovery

The Chemistry Team of Prof. Dr. Luiz Carlos Dias (centre), UNICAMP.

The "Partnership of the Year 2015" was awarded to LOLA, a Latin American Lead Optimization Programme. The LOLA project uses an international collaborative approach, working with UNICAMP (University of Campinas), Brazil, and with partners in the USA (AbbVie) and Europe (LMPH, University of Antwerp, Belgium) to carry out early stage drug discovery and sets a precedent for all emerging neglected disease endemic countries.

SCREENING

Screening for kinetoplastids (leishmaniasis, Chagas disease, human African trypanosomiasis)

OVERALL OBJECTIVE:
Establish a robust portfolio of drug discovery quality hits for the three kinetoplastid diseases, with a focus primarily on visceral leishmaniasis (VL) and Chagas disease

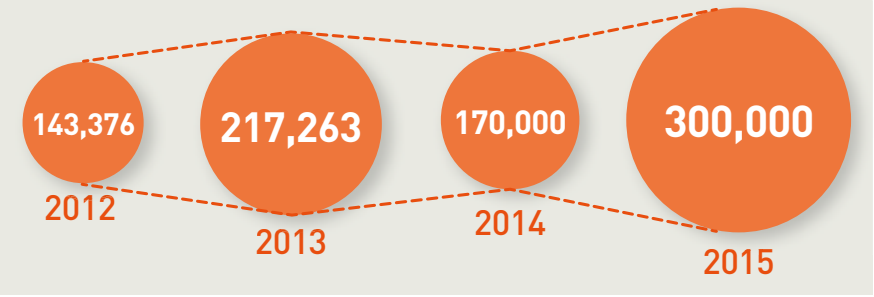
2015 OBJECTIVE: Focus high throughput screening on identification of novel hit series for VL and Chagas disease by screening larger size compound libraries, exploring new "chemical space" and open source drug discovery initiatives

During 2015, over 300,000 compounds (representing more than 820,000 wells) were evaluated, with a focus on visceral leishmaniasis and Chagas disease, in five DND*i*-Partner screening centres. This includes several chemical collections and sets of chemical analogues of hits/hit series from pharmaceutical and biotechnology companies. Commercial compound libraries from Axxam, Bioascent, and SPECS have been screened, together with TB Alliance's "Active" and MMV's "Biofocus" collections.

Drug candidates which target the enzyme CYP51 are very common hits in *T. cruzi* screens. However, recent clinical studies with fosravuconazole and posaconazole have shown that this is not a valid drug target in Chagas patients. A new *in vitro* protocol for *T. cruzi* amastigotes which can differentiate between CYP51 inhibitors (such as azoles and other scaffolds) and benznidazole by determining time kill and percentage kill profiles was developed in collaboration with Swiss TPH. This assay has been integrated into our discovery cascade and is routinely used to profile and prioritize non-CYP51 *T. cruzi* hits. Over 50 novel VL and Chagas active scaffolds were identified in 2015 from screening efforts.

DND*i* has actively collaborated with MMV on the development of a "Pathogen Box"- a collection of 400 drug-like compounds for multi-purpose screening – and has supplied a number of "hit" compounds for the kinetoplastids for consideration; seventy of these 400 compounds show activity against kinetoplastids.

Number of compounds screened



High throughput screening (large-size libraries)

for leishmaniasis (*Leishmania*) and Chagas disease (*Trypanosoma cruzi*)

PARTNERS: The Institut Pasteur Korea, South Korea, and the Drug Discovery Unit, University of Dundee, UK

Medium throughput screening

for kinetoplastids – leishmaniasis, Chagas disease, and HAT (*Trypanosoma brucei*)

PARTNERS: The Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; the Laboratory of Microbiology, Parasitology, and Hygiene (LMPH), University of Antwerp, Belgium; and the Walter Reed Army Institute of Research (WRAIR), USA

MAIN COMPOUND LIBRARIES: AbbVie, USA; Anacor Pharmaceuticals Inc., USA; Astellas Pharma, Japan; AstraZeneca, UK; Celgene, USA; Daiichi Sankyo, Japan; Eisai Co. Ltd, Japan; GSK, Tres Cantos, Spain; Institut Pasteur Korea, South Korea; London School of Hygiene and Tropical Medicine (LSHTM), UK; Medicines for Malaria Venture (MMV), Switzerland; Merck, USA; Microbial Chemistry Research Foundation, Japan; Pfizer Ltd, UK; University of Dundee, UK; Sanofi, France; Takeda Pharmaceutical Company Ltd, Japan; TB Alliance, USA

Screening for filarial diseases

OVERALL OBJECTIVE:
Identify new drug candidates using targeted compounds, primarily from repurposing libraries or focused sets with known antihelminthic activity from animal health companies

2015 OBJECTIVE: Identify 1-2 new candidates

With the limited throughput of phenotypic screening against filarial nematodes, screening large chemical libraries is not possible, and DND*i* has negotiated access to smaller focused chemical series that are more likely to give rise to drug candidates. These include indications sets (compounds that have progressed to pre-clinical or clinical research but failed to reach the market); well-annotated sets of compounds (e.g. bioavailable sets or compounds which have been through lead optimization); chemical series from veterinary anti-infective research programmes; or orthologous sets (compounds directed against human targets

with similar gene sequences to the parasites).
In total over 17,000 compounds have been provided by the companies and organizations listed below, in addition to the commercial MicroSource library. This effort yielded a considerable number of hits in the low micromolar range. However, further work is needed to make optimized antifilarial drugs before progressing any candidate into preclinical development. Resources for this project are mainly dedicated to profiling molecules from the optimisation programmes undertaken by AbbVie and Celgene.

PARTNERS: The Hospital of Bonn, Institute for Medical Microbiology, Immunology & Parasitology (IMMIP), Germany; the Muséum National d'Histoire Naturelle Paris, France; and the Northwick Park Institute for Medical Research (NPIMR), UK

MAIN COMPOUND LIBRARIES: AbbVie, USA; AstraZeneca, UK; BASF, Germany; Bristol-Myers Squibb (BMS), USA; Celgene, USA; GSK, Tres Cantos, Spain; E.I. DuPont Nemours, USA; Epichem, Australia; Janssen, Belgium; Mercachem, The Netherlands; Merck, USA; Merck Serono, Germany; MMV, Switzerland; National Institutes of Health (NIH), USA; Novartis Centre de la Recherche Santé Animale, Switzerland; Sanofi, France; TB Alliance, USA; WuXi AppTech, China

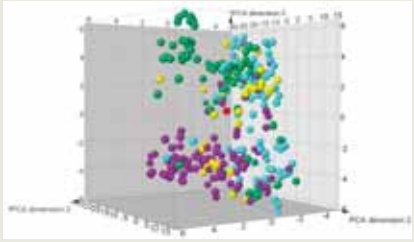
NTD Drug Discovery Booster to speed up compounds identification

OVERALL OBJECTIVE: Speed up the process and cut the cost of finding new treatments for leishmaniasis and Chagas Disease

OBJECTIVE 2015: Implement the NTD Drug Discovery Booster project with 3-6 pharmaceutical companies

More than 1,600 analogues tested

The NTD Drug Discovery Booster was launched in 2015 as an experiment aimed at speeding up the process and cutting the cost of finding new treatments for Chagas disease and leishmaniasis. Initially, the project brought together DND*i* and four pharmaceutical companies: Eisai Co Ltd, Shionogi & Co Ltd, Takeda Pharmaceutical Ltd, and AstraZeneca plc.



The chemical universe around a DND*i* lead molecule (red) is explored through sharing of molecules in pharma companies databases (green, cyan, yellow, purple spheres).

DND*i* supplies active "seed" compounds used by each company for *in silico* searches of chemical libraries for structurally-related compounds and entirely novel chemical scaffolds. The most interesting compounds are selected and undergo further testing *in vitro* to assess potency. In a multilateral, simultaneous search process across the pharmaceutical companies, DND*i* accesses millions of compounds, generated over decades of research. Identification of novel chemical entities acts as a starting point for optimization of potential treatments or cures for these diseases. The innovation of the Drug Discovery Booster not only lies in the multilateral and cross-company comparative approach, but also in the iterative nature of the search, in which companies continue to examine their compound libraries for better compound matches as the search is refined. This will significantly reduce the time it will take to find new, promising treatment leads.

NTD Drug Discovery Booster meeting in Tokyo with partners' representatives, November 2015.

By the end of 2015, six seed compounds had been submitted to the Booster for the first round of *in silico* screening and then the identified analogues were tested *in vitro* by the Institut Pasteur Korea and showed improvements in potency or the identification of novel chemical scaffolds. Further iterations will seek to build on these initial results.
Celgene joined the consortium in 2016, and it is hoped that more companies will join in the future.

PARTNERS: AstraZeneca, UK; Celgene, USA (since 2016); Eisai, Japan; Shionogi, Japan; Takeda Pharmaceutical, Japan

A sleeping sickness patient rests in the HAT ward in Katanda, Kasai, DRC.

› **Sleeping sickness** is usually deadly without treatment. Patient numbers have fluctuated with time, with disease outbreaks occurring intermittently, particularly when surveillance and control measures were relaxed. In the mid-1960s fewer than 5,000 cases were reported in the whole African continent, but the disease re-emerged, with a major epidemic from 1970, peaking in 1998 with over 38,000 cases detected. Since then, numbers have been falling consistently thanks to the combined efforts of WHO, National Control Programmes, NGOs, and Belgian and French bilateral aid. The most recent figures show that fewer than 3,000 new cases of *T.b. gambiense* HAT (g-HAT) were reported in 2015, the lowest figure ever recorded by WHO; 117 cases of *T.b.* rhodesiense (r-HAT) were recorded in 2014.

Sustained disease elimination requires new tools

Available treatment options depend on the stage of the disease and the parasite subspecies causing the infection, making the invasive and feared lumbar puncture – to determine if the parasite has entered the brain – mandatory for every patient diagnosed. Nifurtimox-eflornithine combination therapy (NECT), developed by Epicentre, MSF, DND*i*, and partners for treating stage 2 g-HAT, replaced melarsoprol, a highly toxic arsenic-containing drug which killed 1 in 20 patients. Eflornithine was initially introduced as a slow-infusion treatment administered 56 times (every 6 hours for 14 days). In NECT, the number of eflornithine infusions is reduced to 14, in combination with orally administered nifurtimox, shortening the time spent in hospital and reducing the burden on resources. For stage 1 disease, pentamidine (discovered in 1940) remains the current treatment for g-HAT and suramin (discovered in 1920) for r-HAT. The arsenic-derivate melarsoprol is still the only treatment available for stage 2 r-HAT.

WHO aims to eliminate g-HAT as a public health problem by 2020. A paradigm shift in diagnosis and treatment is therefore needed, with patients screened at home, referred to a nearby centre for diagnostic confirmation and sent back home with an oral treatment, obviating the need for staging of the disease by lumbar puncture. This will require a simple, reliable, rapid test, coupled with a safe and effective treatment that is easy to administer for both disease stages in g-HAT and r-HAT.

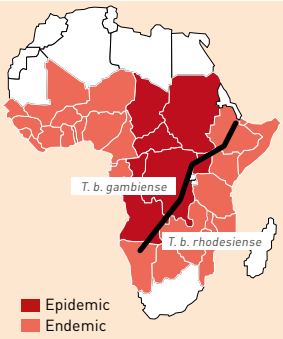
DND*i* has advanced oral candidates for HAT treatment in clinical development that are new chemical entities: fexinidazole, a 10-day treatment, and SCYX-7158, a potential single-dose treatment. The fexinidazole pivotal trial in adults with stage 2 g-HAT, and additional trials in adults with stage 1 disease and in children with both disease stages, had finished recruitment by the beginning of 2016. In addition, an implementation study to determine safety and efficacy in a 'real world' setting will provide further data on the use of fexinidazole for treating outpatients, including at home. This will inform HAT endemic countries on the widest possible use of the drug and guide treatment policy. A study is planned for fexinidazole in r-HAT. SCYX-7158 has completed studies in healthy human volunteers and DND*i* will start recruiting patients into a phase II/III trial in 2016.

During recruitment into the fexinidazole trials in the DRC, mobile teams from the National Control Programme for HAT, supported by DND*i*, travel to endemic villages to identify infected people who are then sent to specialized district hospitals for diagnosis confirmation and treatment. Mobile teams tested approximately 25% of the nearly 4 million people screened for g-HAT in the entire country in 2014 and 2015. As such, DND*i* is making a real contribution to the control and elimination of HAT through the work of mobile teams and conduct of clinical trials.

With the exciting prospect of wiping out this deadly disease, it is vital that funding is maintained to sustain elimination efforts and avoid previous scenarios where control and surveillance lapsed and the disease re-emerged.

13.1 million people were estimated to live in areas at moderate to very high risk in 2012 (more than one case per 10,000 population)

Disease is caused by two subspecies of *Trypanosoma brucei (T. b.) gambiense* (g-HAT; 98% of reported sleeping sickness cases) and *T. b. rhodesiense* (r-HAT), and occurs in two stages: the early stage has non-specific symptoms and is often un- or misdiagnosed, and the late stage, where the parasite crosses the blood-brain barrier, causing serious neurological disorders including sleep cycle disruptions, paralysis, and progressive mental deterioration. Without effective treatment, the disease usually leads to death. A lumbar puncture is needed to differentiate between stages in order to choose the appropriate treatment.



T. b. gambiense is endemic in

24 countries of West and Central Africa • Less than 3,000 new cases reported (2015)

T. b. rhodesiense is endemic in

13 countries of Eastern and Southern Africa • 117 cases (2014)

Current treatments are difficult to administer, and stage-specific:

TREATMENT OF STAGE 1 HAT

Pentamidine (1940) for g-HAT and **suramin** (1920s) for r-HAT, require injections and are ineffective for stage 2.

TREATMENT OF STAGE 2 HAT

NECT – nifurtimox-eflornithine combination therapy (2009): for stage 2 g-HAT, requires 14 slow intravenous infusions of eflornithine of 2 hours each over 7 days, together with three times a day oral nifurtimox for 10 days. Requires specialized hospital administration and trained staff. Since its addition to the EML, NECT is first-line treatment for stage 2 g-HAT.

Eflornithine (1981): today seldom used alone, requires an extended stay in hospital during administration (56 intravenous infusions – four times per day, over 14 days).

Melarsoprol (1949): No longer used for g-HAT. Remains the only drug available for stage 2 r-HAT – a toxic arsenic derivative that causes pain and fatal encephalopathy in up to 5% of patients who receive it.

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 option for sleeping sickness** in 25 years: nifurtimox and eflornithine combination therapy (NECT). NECT is included on the WHO Essential Medicines Lists (EML) for adults (since 2009) and children (since 2013), and virtually all *T. b. gambiense* endemic countries are now using NECT as first-line treatment for stage 2 g-HAT.

As a medium-term strategy, DND*i* initiated a compound mining effort to identify existing chemical compounds with potential against kinetoplastid diseases, resulting in the rediscovery of fexinidazole. After a complete Phase I programme, DND*i* engaged in g-HAT patient studies. Inclusion into a **pivotal Phase II/III study** in stage 2 g-HAT is complete and patient follow-up is ongoing. Two complementary studies will examine efficacy and safety in adults with stage 1 and early stage 2 g-HAT, in children aged 6-14 years, and a third one is being planned for r-HAT patients. Additional information will be obtained from a study in special population groups and to provide preliminary evidence on treatment compliance and effectiveness in ambulatory patients. Sanofi is the industrial partner.

In order to build a strong pipeline for **long-term drug discovery**, DND*i* established a HAT Lead Optimization Consortium resulting in identification of the oxaborole **SCYX-7158**, which successfully progressed through pre-clinical development. **Phase I clinical** development was completed in 2015 and preparations are underway for a prospective Phase II/III efficacy study in patients, to be initiated in 2016. Other backup compounds were evaluated by the consortium and remain available for further development if necessary.

In addition, DND*i* supports the **HAT Platform** (see p.59) that was launched in Kinshasa, Democratic Republic of the Congo (DRC) in 2005. The HAT Platform is a clinical research and access-supporting network for HAT endemic countries that brings together key players in the research on sleeping sickness in endemic countries and those involved in HAT from the international research arena, with partners having a role in developing HAT health policy participating in the Platform.

Ideally a new treatment for adults and children would be effective against **both stages** of the disease and **both parasite sub-species, non-toxic**, have at least **95% efficacy** at 18 months post end of dosing follow-up examination, be **safe** for pregnant and breastfeeding women, **easy to use** (short-course or once a day), **oral**, require no monitoring, **affordable,** and **adapted to tropical climates.**

By 2018, DND*i* aims to deliver from its HAT-specific portfolio: An oral, safe, effective treatment to be used for both stage 2 and stage 1 HAT.

RESEARCH

SCYX-1608210 and SCYX-1330682

PROJECT START: April 2007 and April 2009 respectively

OVERALL OBJECTIVE: Progress a backup oxaborole into pre-clinical development

2015 OBJECTIVE: Retain as a back-up compound in case of future need

Extensive pharmacokinetic profiling of possible oxaborole compounds led to the selection of SCYX-1608210 and SCYX-1330682, which demonstrated cure in the stage 2 mouse model of HAT, as a backup for SCYX-7158 in case of need. Given the current success of other projects for HAT, further development was put on hold in 2013 and will only recommence should problems be encountered with SCYX-7158 in clinical development.

PARTNERS: Anacor Pharmaceuticals Inc., Pace University, USA; LMPH, Belgium; SCYNEXIS Inc., USA

TRANSLATION

SCYX-7158

PROJECT START: January 2010

OVERALL OBJECTIVE: Develop and register SCYX-7158 as a new, single dose, oral treatment for the treatment of stage 2 HAT caused by *T. b. gambiense* (g-HAT), ideally also for stage 1

2015 OBJECTIVE: Complete single-ascending dose study in healthy human volunteers

An oxaborole originally provided by Anacor Pharmaceuticals was found to be active against HAT parasites at the University of California San Francisco, and further investigated by a consortium consisting of DND*i*, Anacor, SCYNEXIS, Pace University, and Swiss TPH. Compound optimization over two years and examination of over 1,000 compounds produced SCYX-7158 which was selected as a promising pre-clinical candidate for g-HAT in late 2009. In pre-clinical studies, SCYX-7158 was shown to be safe and efficacious in treating a brain form of the disease in animals, when administered orally in a single dose.

In March 2012, SCYX-7158 became DND*i*'s first new chemical entity resulting from its own lead optimization programme, to enter clinical development. SCYX-7158 was found to have an unusually long half-life when tested in healthy volunteers. This Phase I study was finalized in March 2015 and results were presented later that year at the European Congress on Tropical Medicine and International Health in Basel. The single-dose treatment will be tested in patients with stage 2 g-HAT in a Phase II/III trial, planned to start in the Democratic Republic of the Congo in 2016. The study will use several sites already active in fexinidazole development with addition of new sites selected from high-prevalence g-HAT areas. Patients will be followed up for 18 months after treatment to ensure long-lasting cure, with a preliminary evaluation of data performed after the first 12 months.

PARTNERS: Anacor Pharmaceuticals Inc., USA; Advinus Therapeutics Ltd, India; SCYNEXIS Inc., USA; Institut de Recherche pour le Développement (IRD), France.

DEVELOPMENT

Fexinidazole

PROJECT START: April 2007

OVERALL OBJECTIVE: Develop and register fexinidazole as a new oral drug for the treatment of HAT caused by *T. b. gambiense* (g-HAT), ideally also to be used for *T. b. rhodesiense* (r-HAT)

2015 OBJECTIVES:

- Complete recruitment of the pivotal Phase II/III study of fexinidazole versus the reference treatment (NECT)
- Complete recruitment of the studies in adults with stage 1/early stage 2 g-HAT and in children above 6 years of age and over 20 kg weight (both stages)

749 patients recruited at 10 sites

Fexinidazole, the result of successful compound-mining efforts pursued by DND*i* in 2005, entered clinical development in September 2009 and is being co-developed with Sanofi: DND*i* is undertaking clinical and pharmaceutical development whilst Sanofi is responsible for the industrial development and production. Fexinidazole is the most advanced oral candidate under development for HAT. DND*i* aims to evaluate and register it as a treatment for a wide range of patients, specifically in adults and children over 6 years of age and 20 kg body weight with either stage of disease.

The pivotal study compares fexinidazole in patients with late stage g-HAT versus NECT, and completed inclusions of all 394 patients between October 2012 and April 2015. The 18 month follow-up period will end in 2016, and results processed for regulatory submission in Q3 2017. Additional safety and efficacy data from the two complementary studies will also be included; the first reached 230 early stage adult patients and the second 125 children aged 6-14 years (approximately equal numbers of early stage and late stage patients) in an open, non-comparative study, using the same regimen with doses adapted to children's weight. In total therefore, information collected from 749 individuals will be included in the safety database.

More information from special population groups not included in trials to date, such as pregnant and breastfeeding women, patients with poor nutritional status or with chronic diseases, will be obtained in a planned Phase IIIb trial. This will also include a cohort of outpatients and will provide preliminary information about treatment compliance and use on an outpatient basis.

The protocol for a study to be undertaken in r-HAT patients is being finalized, sites in Uganda and Malawi have been identified, and the study is planned to commence in 2017.

The submission of a regulatory dossier to the European Medicines Agency (EMA) under Article 58 is planned for 2017, for the treatment of g-HAT with fexinidazole. This provision allows the EMA's Committee for Medicinal Products for Human Use (CHMP) to give scientific opinions, in co-operation with the World Health Organization (WHO), on drugs to prevent or treat diseases of major public health interest and intended exclusively for markets outside the European Union. It aims to ensure faster WHO prequalification of medicines by removing barriers to simultaneous prequalification. A Risk Management Plan to further monitor safety and efficacy in the field is under preparation in collaboration with Sanofi and WHO.

PARTNERS: Sanofi, France; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Institute of Tropical Medicine (ITM) – Antwerp, Belgium; Médecins Sans Frontières; Institut de Recherche pour le Développement (IRD), France; Institut National de Recherche Biomédicale (INRB), DRC; HAT Platform; National Control Programmes of the Democratic Republic of Congo and the Central African Republic.

IMPLEMENTATION

NECT: Nifurtimox-Eflornithine Combination Therapy

PROJECT START: May 2004

OVERALL OBJECTIVE: Develop and make available a safe, effective, easier to administer and more cost-effective combination therapy which requires shorter hospitalization

2015 OBJECTIVE: Prepare the field for change of policy and implementation

365 NECT kits distributed, sufficient to treat 1,460 patients

NECT, a co-administration of intravenous eflornithine and oral nifurtimox, was developed by Epicentre, MSF, DND*i*, Swiss TPH, and the national HAT control programmes of the Republic of the Congo and DRC. After inclusion in the WHO Essential Medicines List in 2009, it quickly became the first-line treatment for second stage g-HAT. NECT has been a game-changer in the treatment of sleeping sickness – it has reduced the number of eflornithine infusions required, compared to when it is used as a monotherapy, from 56 to 14. More importantly, however, it has had a major impact on patients, by removing the fear of treatment they had when the only option was melarsoprol, a product so toxic that it killed up to 5% of all patients who received it. NECT is available in all endemic countries, who receive free supplies from WHO *via* drug donations by Sanofi and Bayer.

In 2015, 365 NECT kits containing four treatments each were distributed in all disease endemic countries, sufficient to treat 1,460 patients with second stage g-HAT.

MAIN PARTNERS: Epicentre, France; Médecins Sans Frontières (MSF), Holland; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Ministry of Health, Republic of Congo; HAT Platform; National Trypanosomiasis Control Programme, DRC

LEISHMANIASIS

Visceral leishmaniasis patients waiting to see a healthcare worker at the Kala-Azar Medical Research Centre (KAMRC), Muzaffarpur, Bihar, India.

Leishmaniasis affects the poorest of the poor and has strong links with malnutrition, low-quality housing, and lack of resources. Some 350 million people around the world are at risk of developing leishmaniasis in one of its many forms. There are more than 20 species of *Leishmania* parasite, transmitted to humans by approximately 30 species of phlebotomine sand flies found throughout the tropics and subtropics, as well as in temperate zones.

One of the two most common forms of disease, visceral leishmaniasis (VL) or kala-azar, is fatal without treatment. There are 200,000-400,000 new cases per year, albeit with a large reduction recently in South Asia. The WHO's roadmap for elimination - published in 2012 and supported by the London Declaration the same year - targets elimination of kala-azar as a public health problem by the end of 2020 in South Asia.

Surprisingly, the response of visceral leishmaniasis to treatment is not homogenous across continents, nor even within the same region, and different drugs and/or regimens are needed, particularly in eastern Africa. Intermediate results from an implementation trial which was underway in India, carried out by DND*i* and partners, led the government to change its treatment guidelines in 2014, abandoning miltefosine monotherapy in favour of single-dose AmBisome® as first-line and a combination of paromomycin/miltefosine as second-line treatment. These changes were subsequently also taken up by the governments of Bangladesh and Nepal. Similarly in Latin America, the interim results of an implementation trial carried out by DND*i* with partners in Brazil led to Ambisome® being included as second-line treatment after Glucantime®, with the final results now suggesting it would be more suitable as first-line treatment. In addition, Ambisome® alone or in combination with miltefosine is being evaluated in Ethiopia for treating VL patients who are co-infected with HIV.

Post kala-azar dermal leishmaniasis (PKDL) is a complication of VL. Treating PKDL patients, which may also remove a reservoir for reinfection and outbreaks, is likely to be key for sustained elimination of the disease. The safety and efficacy of Ambisome® alone or in combination with miltefosine will be assessed for treating PKDL patients in India and Bangladesh, whilst patients in Sudan will receive Ambisome® or paromomycin in combination with miltefosine.

Cutaneous leishmaniasis, although not life-threatening, is more common than the visceral form and is the cause of serious socio-economic problems in populations with already limited resources. Initial approaches will explore opportunities to better use the existing treatments in combination, together with the development of a topical formulation for small numbers of ulcerated, uncomplicated CL lesions. However, an oral treatment will be needed to treat multiple or large lesions, to be selected from compounds at early clinical stages or from the DND*i* discovery programme. PKDL and complicated forms of CL may be treatable with an immune modifier combined with chemotherapy.

Multiple approaches needed to address a complex family of diseases

DND*i* has recently identified new chemical entities from its drug discovery efforts and it is hoped that these, together with other leads expected to emerge from the NTD Drug Discovery Booster, launched in 2015, will lead to a generation of safe and effective oral treatments for VL and CL.

DND*i* is a member of the consortium for the Control and Elimination of Visceral Leishmaniasis, known as KalaCORE, which aims to tackle VL in South Asia and East Africa by supporting national efforts and coordinating with national VL control programmes.

Following the acceptance of a joint submission in 2015 by DND*i* and the Instituto de Salud Carlos III (ISCIII), a Madrid-based WHO collaborating Center for leishmaniasis for 19 years, the 6th World Congress on Leishmaniasis will take place in Toledo, Spain from 16 to 20 May 2017, with some 1500 attendees expected (see www.worldleish2017.org).

What are the current treatments and their limitations?

Existing drugs have serious drawbacks in terms of safety, resistance, stability, and cost. They have low tolerability, long treatment duration, and are difficult to administer. These drugs are used either as monotherapy or in combination for the various forms of leishmaniasis.

Pentavalent antimonials (sodium stibogluconate – SSG – and meglumine antimoniate): used for VL and CL for over 60 years. Acquired resistance in areas of high prevalence and high transmission has been reported. Serious cardiotoxicity leading to death is well documented. In monotherapy, they require a 30-day parenteral treatment for VL. For CL: intramuscular injections for 21 days; in the Old World, generally 1-2 intralesional applications per week for 3-7 weeks, sometimes alternating with cryotherapy (not used in the New World). Registered in South East Asia, Latin America, and some Mediterranean and African countries.

Amphotericin B deoxycholate: only an alternative treatment for VL in areas with high rates of unresponsiveness to antimonials where no other options are available. Need for hospitalization, constant renal monitoring of patients, 28-day duration of treatment, and infusion-related adverse events are notable drawbacks. Amphotericin B displays dose-limiting toxicity. Registered in South Asian countries and some countries in Africa and Latin America.

AmBisome®: a liposomal formulation of amphotericin B, which is comparatively much safer and highly efficacious. A single infusion of 10mg/kg has shown a 96.4% cure rate in Asia. However, high cost and the need for a cold chain limit widespread use. Registered for VL in India, USA, and Europe and used as a second-line drug for the treatment of VL in East Africa at higher doses than in India and for VL in Brazil. It is also used to treat PKDL cases in Sudan. A donation to WHO facilitates free distribution of AmBisome® to the three countries involved in the elimination strategy in South Asia for primary VL patients, and as a rescue treatment for African VL. It is not properly evaluated for cutaneous leishmaniasis (CL).

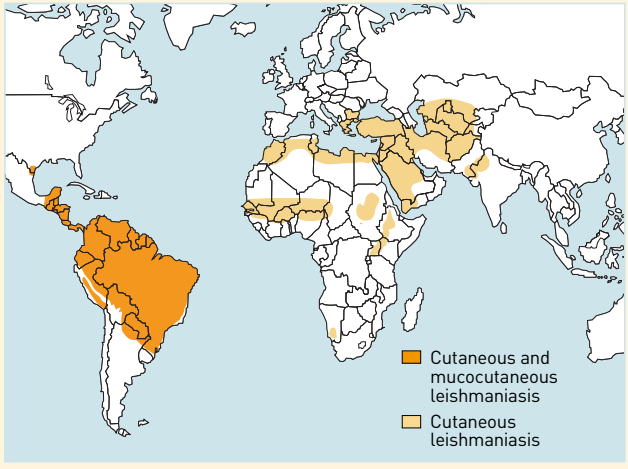
Miltefosine: an oral drug administered twice daily, registered for use in India for VL, and requires 28-day treatment. Major limitations include low compliance, risk of resistance, contraindication in pregnancy, and mandatory contraception for women of child-bearing age for the duration of therapy and three months beyond. A recent study in Asia indicated an emerging lack of efficacy of monotherapy in the region, probably associated with drug underexposure in children, and the same has been observed in Africa. For CL, currently approved for lesions caused by three *Leishmania* species. Miltefosine is not registered in many endemic countries and is consequently not available.

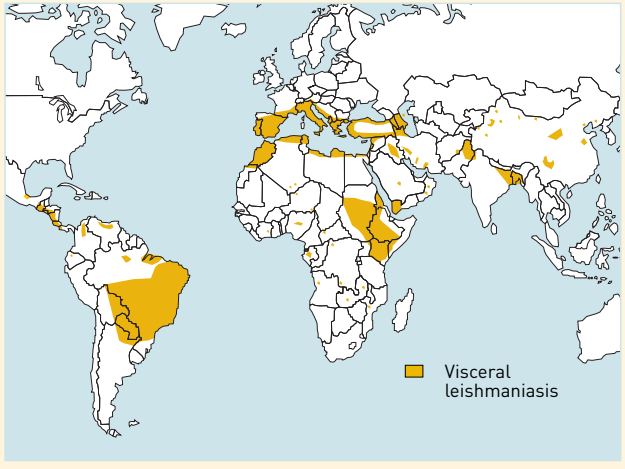
Paromomycin: a low-cost parenteral formulation that requires three weeks of painful intramuscular administration is also highly efficacious in Asia but is associated with some degree of renal and ototoxicity; limited efficacy as monotherapy in East Africa.

350
million people
at risk in
98
countries

0.7-1.2
million cases
of CL annually

0.2-0.4
million cases
of VL annually,
although with a marked reduction in the number of cases observed in the Indian subcontinent





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

VISCERAL LEISHMANIASIS

Improved treatment options for VL patients in some areas have already been delivered. DND*i*'s **short-term approach** has been 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, and the geographical extension of existing drugs in other countries and regions. In 2010, DND*i* and LEAP partners **delivered the SSG&PM combination therapy for East Africa**, now recommended as first-line treatment for VL in the region. In **India**, a Phase III trial demonstrated the efficacy of combination therapies of already-registered drugs (see p. 35). In 2014, based on the evidence generated by this trial and one conducted by Sundar *et al.*, the government of **India** recommended use of single-dose AmBisome® as a first option and paromomycin/miltefosine combination as the second option for treatment instead of using miltefosine as monotherapy, with the same policy change also taken up in Bangladesh and Nepal. DND*i* later collaborated 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 effectiveness and safety of these new treatments at the primary healthcare level and facilitate their introduction. 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. The national control programme has extended the use of AmBisome® as second-line treatment based on the interim safety data from this trial.

***Leishmania* and HIV co-infection** is a growing problem, difficult to manage clinically due to poor response to treatment with frequent relapses of disease, and is eventually fatal. DND*i* is working with partners towards better treatment for HIV/VL co-infected patients in **Africa and Asia**.

In the **medium term**, DND*i* is assessing the combination of fexinidazole and miltefosine for the treatment of VL patients in eastern Africa. This could be the first oral-only combination therapy for VL.

The role of **Post-Kala Azar Dermal Leishmaniasis** (PKDL, a common complication of VL) in infectivity is poorly understood and treatment options remain limited, requiring long and often repeated courses of treatment including with antimonials. It is a particular problem in Sudan and Bangladesh, and needs to be addressed if VL is to be controlled. DND*i* is working with partners to facilitate additional research in epidemiology, diagnosis, pathogenesis, and treatment.

DND*i*'s **long-term** strategy for VL is to bring new oral drug candidates into clinical development through its lead optimization programme with the ultimate goal of improving the safety profile and efficacy of the existing tools with a second oral-only combination treatment.

In addition, DND*i* supports the **Leishmaniasis East Africa Platform** (LEAP) (see p. 58).

A new VL treatment for adults and children based on a new chemical entity would ideally be **efficacious against all species of *Leishmania* in all regions as well as against resistant strains, have at least 95% efficacy, be short course** (once a day for 10 days oral; or 3 shots over 10 days), **easy to use**, compatible for **combination therapy, safe** in pregnant and breastfeeding women and for immunocompetent/immunosuppressed patients, **affordable**, and adapted to tropical climates. The TPP for the combination treatment will be reviewed in 2016.

By 2020, DND*i* aims to deliver from its VL-specific portfolio:

- **A safe, effective, low-cost, and short-course combination treatment**
- **A new treatment for PKDL that is shorter course and better tolerated than current options**
- **Treatment options for HIV/VL co-infected patients**
- **A new first-line treatment regimen for VL in Latin America**

CUTANEOUS LEISHMANIASIS

For CL, DND*i*'s objective is to develop short, safe, efficacious, affordable, and field-adapted treatments, at least for lesions caused by *L. tropica* and *L. braziliensis*. As a **medium-term** strategy, DND*i* is developing a topical treatment based on amphotericin B. In addition, we aim to improve treatment strategies using currently available treatment modalities and will be evaluating a single application of heat therapy combined with a short course of oral miltefosine. In the **medium to long term**, DND*i* aims to develop an oral drug and an immune-modulator for use in combination with chemotherapy. This novel approach aims to initially eliminate parasites with chemotherapy, followed by enhancement of the patient's immune response with an immune-stimulating agent.

A new topical or oral treatment for CL would ideally be **efficacious against all species**, show at least **95% efficacy**, be **easy to use, short course** (14-28 days), compatible for combination therapy, produce **minimal scarring**, be **safe** in pregnant and breastfeeding women, **affordable,** and **adapted to tropical climates**.

By 2020, DND*i* aims to deliver from its CL-specific portfolio: A safe, effective, and shorter-course treatment for CL

RESEARCH

Leish H2L

(Leishmaniasis Hit to Lead)

PROJECT START: On-going

OVERALL OBJECTIVE: Identify new leads series from current ongoing Hit-to-Lead activities by taking advantage of the optimization consortia platform screening of compounds for VL

2015 OBJECTIVE: Progress two new chemical classes into lead optimization

Hit to lead is a dynamic phase in the drug discovery cascade in which small molecule hits from high throughput screens are evaluated and undergo limited optimization to identify promising lead compounds. Series from a number of different partners have shown activity against *L. donovani*; work on these series to bring forward suitable candidates for lead optimization is on-going.

A notable success in January 2015 was the successful advancement of the aminopyrazole series from the hit to lead stage into the next lead optimization stage. This early work has recently been published in *J. Med. Chem.* In addition, the NTD Drug Discovery Booster project commenced in April 2015 working with four pharmaceutical companies: Eisai, Shionogi, Takeda, and Astra Zeneca and has so far conducted hit expansion on six different hits which are being developed for leishmaniasis and Chagas disease.

A number of pharmacokinetic and pharmacodynamic studies have been conducted in animal models of VL using existing and experimental drugs to build improved PK/PD models and ameliorate the translation of new drugs from discovery into clinical studies.

MAIN PARTNERS: Epichem, Australia; UNICAMP (University of Campinas, Brazil); Centre for Drug Candidate Optimization, Monash University, Australia; TCG Lifesciences, India; Sandexis, UK; WuXi AppTech, China; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; London School of Hygiene and Tropical Medicine, UK; Griffith University, Australia; GSK, Tres Cantos, Spain; Sanofi, France; Anacor Pharmaceuticals Inc., USA; Merck, USA; AstraZeneca, UK; AbbVie, USA; Pfizer, UK.

Oxaborole

(previously known as Oxaleish)

PROJECT START: January 2010

OVERALL OBJECTIVE: Select an oxaborole for pre-clinical evaluation

2015 OBJECTIVES:

- Select an oxaborole for pre-clinical evaluation
- Complete profiling of lead oxaboroles

DND*i* and Anacor have been working together over the last few years to identify oxaborole compounds, initially for the HAT programme, and this has expanded to include both leishmaniasis and Chagas disease. DNDI-6148 has emerged as a promising lead candidate and by the end of 2015, studies including exploratory toxicology necessary for possible progression to pre-clinical development had been successfully completed. It is anticipated that pre-clinical development of DNDI-6148 will commence following a review meeting in January 2016. Approximately four additional oxaborole compounds continue to be developed behind DNDI-6148 as potential back-ups in case an insurmountable issue should be identified.

MAIN PARTNERS: Anacor Pharmaceuticals Inc., USA; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; London School of Hygiene and Tropical Medicine (LSHTM), UK; Wuxi AppTech, China; Sandexis, UK

Aminopyrazoles

PROJECT START: February 2012

OVERALL OBJECTIVE: Select an aminopyrazole for pre-clinical evaluation

2015 OBJECTIVE: Identify compounds suitable for pre-clinical evaluation

Compound mining of well-annotated chemical compound libraries has been used to identify a new class of compounds active against VL. In June 2014, the first *in vivo* proof of concept for VL series 12 (aminopyrazoles) from Pfizer was achieved in the hamster early curative model of VL. An initial compound gave 93% and 95% reductions in parasitaemia in liver and spleen respectively after five days oral dosing at 50mg/kg BID, with a subsequent compound showing even better *in vivo* activity (>99% reduction in parasitaemia in both liver and spleen). The project moved into the lead optimization stage in January 2015, with GHIT Fund support and expert scientific assistance from Takeda from April 2015. Further compounds are being designed and tested. Profiling of current and new leads in a panel of drug sensitive and drug resistant strains of *Leishmania*, exploration of the *in vivo* dose response, rat pharmacokinetics, and initial *in vitro* safety assays are all underway. A full lead optimization programme is ongoing and we aim to select an optimized lead in 2016.

MAIN PARTNERS: Takeda Pharmaceutical Company Ltd, Japan; Wuxi AppTech, China; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; London School of Hygiene and Tropical Medicine, UK; Pfizer, UK; Sandexis, UK

TRANSLATION

VL2098 (completed)

PROJECT START: July 2010

OVERALL OBJECTIVE: Fully investigate the profile of VL-2098 as an NCE for VL

2015 OBJECTIVE: Decision on whether or not to move the candidate forward

VL-2098 was chosen for development from a selection of 70 nitroimidazoles belonging to four chemical sub-classes as a very potent and safe molecule. An in-depth evaluation of its efficacy, pharmacokinetic, and early safety profile showed the compound to be potent against *L. donovani in vitro* and efficacious in acute and chronic VL animal models after oral dosing. However, toxicology and pharmacokinetic studies performed in three animal species indicated a link between dose, length of treatment, and testicular toxicity. Further studies of longer duration were undertaken in order to determine the safety margin, but as it was not possible to establish any therapeutic window between plasma exposures in the most sensitive animal model and efficacious exposures in the two rodent species, the decision was taken to close the project in early 2015.

MAIN PARTNERS: TB Alliance, USA; Advinus Therapeutics, India; Endolytics, USA; Accelera, Italy; Aptuit, Italy; London School of Hygiene & Tropical Medicine (LSHTM), UK; Laboratory for Microbiology, Parasitology and Hygiene (LMPH), Belgium

Fexi sulfone (completed)

PROJECT START: January 2015

OVERALL OBJECTIVE: Investigate the potential of developing fexinidazole sulfone as a treatment for VL

2015 OBJECTIVE: Take decision on whether to develop fexinidazole sulfone

Oral fexinidazole is under development as a treatment for our kinetoplastid diseases, and is most advanced for HAT. When absorbed it functions as a pro-drug for the rapidly formed sulfoxide (M1) and sulfone (M2) metabolites which are 10x more active than fexinidazole itself in *in vitro* tests and also exhibit a higher drug exposure at all dose levels. Fexinidazole sulfone was considered for development as a drug to replace fexinidazole, and the dossier was reviewed in 2015. In October 2015 the decision was taken not to progress fexinidazole sulfone as there was no clear advantage over fexinidazole; the latter continues to undergo evaluation for VL in combination with miltefosine.

PARTNERS: None

DNDI-0690

PROJECT START: September 2015

OVERALL OBJECTIVE: Progress and evaluate a nitroimidazole as a potential treatment for VL

2015 OBJECTIVE: Select a compound to progress from the nitroimidazooxazine backup programme

Following the termination of the VL-2098 project in early 2015, the decision was taken to progress with lead compounds from two sub-series previously identified from the nitroimidazooxazine backup programme (DNDI-8219 and DNDI-0690) which had good efficacy *in vivo*, better solubility, and lower potential for cardiotoxic effects. A 14-day toxicity evaluation carried out in 2015 led to DNDI-0690 nomination as a pre-clinical candidate in September 2015. In addition, with other potential lead compounds for VL, DNDI-0690 was profiled *in vitro* against CL-causing strains of *Leishmania* at the London School of Hygiene & Tropical Medicine and the Walter Reed Army Institute of Research and showed good to excellent activity, consistent with their activity against *L. donovani* and *L. infantum*.

MAIN PARTNERS: London School of Hygiene and Tropical Medicine (LSHTM), UK; TB Alliance, USA; Auckland University, New Zealand; Laboratory of Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, Belgium; WuXi AppTech, China; Aptuit, Italy; Accelera, Italy

TRANSLATION

Fexinidazole/Miltefosine Combination

PROJECT START: 2013

OVERALL OBJECTIVE: Develop an oral-only therapy for VL by 2022

2015 OBJECTIVES: Initiate allometric dosing study of miltefosine in children. Prepare for a drug-drug interaction study on fexinidazole-miltefosine

30 paediatric patients recruited at 4 sites

Fexinidazole has shown potent activity against *L. donovani in vitro* and *in vivo* in a VL mouse model, and studies in healthy volunteers found it to be safe when given as a single dose or as repeated dosing after 14 days. Furthermore, fexinidazole is in late stage development for HAT with a good safety profile.

A Phase II proof-of-concept study initiated in 2013 assessed the safety and efficacy of fexinidazole for the treatment of primary VL adult patients in Sudan, and enrolled 14 patients. All patients showed clinical improvement during treatment and the majority had parasite clearance (by microscopy) at the end of treatment. Three patients remained cured until 6 months follow-up, however the response was not sustained in other patients and relapses were observed. The study was interrupted in 2014 as it failed to show conclusive efficacy in the majority of patients. Miltefosine is the only other oral drug currently available and will be evaluated in combination with fexinidazole in Eastern Africa. A previous study carried out in Africa indicated miltefosine was underdosed in children as compared to adults, and that dose adjustment was required. A study to assess safety and efficacy of miltefosine using an allometric dosing in children with VL was initiated in Kenya and Uganda in June 2015, recruitment completed in September, and patient follow up will end in 2016.

As the ultimate goal is to develop a combination of fexinidazole and miltefosine, a drug-drug interaction study in normal healthy volunteers to assess the pharmacokinetics and safety of the concomitant administration of fexinidazole and miltefosine has been prepared.

MAIN PARTNERS: Institute of Endemic Disease (IEND), Khartoum University, Sudan; Kenya Medical Research Institute (KEMRI), Kenya; Makerere University, Uganda; Amudat Hospital, Uganda; Leishmaniasis East Africa Platform (LEAP); Kacheliba District Hospital, Kenya; Uppsala University, Sweden; Utrecht University, The Netherlands; London School of Hygiene and Tropical Medicine (LSHTM), UK; Koninklijk Instituut voor de Tropen (KIT), The Netherlands; The Netherlands Cancer Institute, The Netherlands; PhinC, France; Centres d'Investigation Clinique des Centres Hospitaliers Universitaires de Clermont-Ferrand, Lille et Bichat-Claude Bernard, France; SGS, Belgium; Cardiabase, France; Optimed, France; UBC, Switzerland.

TRANSLATION

CpG-D35 (CL)

PROJECT START: June 2014

OVERALL OBJECTIVE: Characterize and produce GMP-grade D35 to evaluate its protective cellular immunity and its effectiveness to treat PKDL and CL in chemotherapy combinations

2015 OBJECTIVE: Advance the pre-clinical development of CpG-D35

CpG-D35 is being developed as a combination therapy for the treatment of complicated cutaneous leishmaniasis and post kala-azar dermal leishmaniasis (PKDL). *Leishmania* parasites are able to persist in host cells by evading or exploiting immune mechanisms. Modulating the immune response with CpG oligonucleotides may improve the effectiveness of chemotherapies. The project has four phases: production and characterization of GMP-grade CpG-D35, pre-clinical studies in two species to assess potential toxicities, Phase I clinical trials in healthy volunteers, and proof-of-concept clinical trials in patients for CpG-D35 and the combination of CpG-D35 with chemotherapy. In 2015 IND-enabling pre-clinical safety prerequisites and service providers for entry into Phase I proof-of-concept clinical trials were identified.

MAIN PARTNERS: US FDA, USA; National Institutes of Health (NIH), USA; Ohio State University, USA; Nagasaki University, Japan; University of Osaka, Japan; GeneDesign Inc., Japan

Anfoleish (CL)

PROJECT START: September 2011

OVERALL OBJECTIVE: Develop at least one modality of treatment for CL

2015 OBJECTIVE: Continue enrolment in the Phase Ib/II exploratory study and have an indication of the safety, PK, and efficacy

80 patients recruited at 1 site

The rationale for development of a topical formulation of amphotericin B was to provide a treatment to be applied locally at the CL lesion, showing high anti-parasitic effect, but without the systemic toxicity associated with amphotericin B. A Phase Ib/II open-label, randomized, non-comparative, two-arm exploratory study is being conducted in Colombia. Initially planned to include only patients with CL caused by *L. braziliensis*, recruitment was widened to include patients with CL caused by *L. panamensis*. Enrolment of all 80 patients was completed in November 2015, and preliminary data on cure will be available in 2016.

If Anfoleish is shown to be efficacious against *L. braziliensis* and *L. panamesis*, a multi-country Phase III study will be planned in Latin America.

MAIN PARTNERS: Humax Pharmaceutical, Medellin, Colombia; Programa de Estudio y Control de Enfermedades Tropicales, Universidad de Antioquia, Medellin, Colombia

New CL combination therapies

PROJECT START: June 2015

OVERALL OBJECTIVE: Develop an improved treatment for CL based on existing treatments used in combination

2015 OBJECTIVE: Obtain approval of the proposed study

The efficacy of currently available and approved CL treatment approaches (antimonials, miltefosine, and thermotherapy) is approximately 70-75% worldwide. The safety profiles of these approaches when administrated alone is very well established. Using a combination of therapies may both improve this efficacy rate and reduce the length of treatment and rate of adverse events. A combination of one single application of thermotherapy at 50°C for 30 seconds with a 3 week course of oral miltefosine will be tested in order to gain information about safety and efficacy, with no anticipated safety problems and in a short period of time. The study protocol was finalized and submitted for review by local ethics committees in 2015; approval was received from Peru and Colombia in December 2015. It will be submitted to regulatory authorities in 2016 and patient enrolment is expected to begin the same year.

MAIN PARTNERS: Programa de Estudio y Control de Enfermedades Tropicales, Universidad de Antioquia, Medellin, Colombia; Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru

DEVELOPMENT

New treatments for HIV/VL co-infection for Africa

PROJECT START: September 2011

OVERALL OBJECTIVE: Develop a new treatment regimen for patients co-infected with HIV/VL

2015 OBJECTIVE: Finalize recruitment into HIV/VL coinfection study and conduct three interim analyses

59 patients recruited at 2 sites

This study, initiated in 2014, aimed to 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. The AmBisome® monotherapy arm was dropped due to lower than expected efficacy at the time of the first interim analysis in April 2015, and recruitment into the remaining combination arm was also interrupted after the 2nd interim analysis in July for the same reason. Efficacy and safety data for the treatment period is currently under analysis. All 59 patients recruited continue the 12 months follow-up with pentamidine prophylaxis. The final clinical trial report is expected in 2016.

In anthroponotic transmission areas (where disease is transmitted by the vector from human to animals), the WHO recommends secondary prophylaxis with drugs not given in treating primary VL cases to avoid resistance development. As part of the Africoleish consortium, the results from a separate study to assess pentamidine as prophylaxis to prevent VL relapses in HIV-VL population demonstrated monthly pentamidine infusions led to lower rates of VL relapses in HIV co-infected patients following one year of treatment.

MAIN PARTNERS: Gondar University Hospital, Ethiopia; Addis Ababa University, Ethiopia; London School of Hygiene and Tropical Medicine (LSHTM), UK; Institute of Tropical Medicine (ITM) – Antwerp, Belgium; Médecins Sans Frontières (MSF), The Netherlands; Uppsala University, Sweden; Gilead Sciences, USA; LEAP; The Netherlands Cancer Institute, The Netherlands; Utrecht University, The Netherlands; BaseCon, Denmark; UBC, Switzerland

New treatments for PKDL for Asia/Africa

PROJECT START: March 2015

OVERALL OBJECTIVE: Evaluate the role of PKDL in transmission and epidemiology of *Leishmania* parasites and to develop a new treatment

2015 OBJECTIVE: Carry out preparations for epidemiological, infectivity, and PK and treatment studies

DND*i* is prioritizing the management of PKDL patients who are believed to constitute a reservoir of infection for visceral leishmaniasis in the Indian Sub-continent and East Africa. A synopsis has been developed for a Phase II clinical trial of AmBisome® alone or in combination with miltefosine, to assess the safety and efficacy for the treatment of PKDL patients in India and Bangladesh, and AmBisome® or paromomycin in combination with miltefosine for the treatment of PKDL in Sudan.

An infectivity study will also be conducted in both countries, to explore the role of PKDL as a potential reservoir of *L. donovani* parasites which can be spread by the sandfly. This is of particular concern in the period between epidemics, and the trial aims to ascertain if there is a need for chemotherapy for all PKDL patients to reduce transmission. It also aims to identify immunological biomarkers of infectivity in VL and PKDL cases. In preparation of the study, an insectarium was constructed at the SK hospital in Mymensingh, Bangladesh in 2015.

MAIN PARTNERS: International Centre for Diarrhoeal Disease Research (ICDDR,B), Bangladesh; Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), India; Kala Azar Medical Research Centre, India; Institute of Medical Sciences, Banaras Hindu University, Varanasi, India; Safdarjung Hospital, Delhi, India; Uppsala University, Sweden; Institute of Endemic Disease (IEND), Khartoum University, Sudan; Ministry of Health, Sudan; LEAP

DEVELOPMENT

New VL treatments for Latin America

PROJECT START: February 2011

OVERALL OBJECTIVE: 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

2015 OBJECTIVE: Complete VL trial

378 patients recruited at 5 sites (2 active in 2015)

More than 95% of VL cases in Latin America occur in Brazil, and most of them are children. In 2013, Brazil reported 3,253 new cases with a fatality rate of 6.7%. DND*i* is supporting the implementation of a Phase IV clinical trial, sponsored by the Brazilian Ministry of Health, to assess current treatments used for VL in Brazil (Glucantime®, AmBisome®, and amphotericin B as monotherapies, and an AmBisome®/Glucantime® combination proposed by DND*i*). In 2014, patient recruitment was stopped based on the interim analysis of 50% of the recruited patients, and the five trial sites concluded six months follow-up of the 378 patients enrolled in the study. Data management and sites close-out were finalized in 2015 and study results show that, although there is no statistically significant difference in efficacy between treatment arms, AmBisome® monotherapy shows a statistically better safety profile in terms of frequency and severity of adverse events, and early treatment suspension due to toxicity. These results, associated with a shorter administration time, suggest that AmBisome® monotherapy would be a more adequate first line treatment of VL in Brazil and in Latin America. All final results will be published in 2016. Follow-up discussions will be held with the Brazilian Ministry of Health and PAHO in 2016 for evidence-based policy changes in the treatment of VL patients in Brazil, and to discuss plans for further studies to improve efficacy with good safety profile for treatment of VL in Brazil. The Ministry of Health already changed treatment recommendations in 2013, expanding the use of AmBisome® monotherapy as a second-line treatment, based on interim safety data provided by the trial.

PARTNERS: BRAZIL: Rene Rachou Research Center – Fiocruz-MG, Belo Horizonte; Paediatric Hospital Joao Paulo II – FHEMIG, Belo Horizonte; Brasilia University; Montes Claros State University; Piaui Federal University, Teresina; Sergipe Federal University, Aracaju; Leishmaniasis Control Programme/Ministry of Health; Universidade Estadual do Rio de Janeiro; Hospital Sao José de Doencas Infecciosas, Fortaleza

IMPLEMENTATION

SSG&PM Sodium Stibogluconate/ Paromomycin Combination Therapy

PROJECT START: April 2011

OVERALL OBJECTIVE: Include SSG&PM as the new first line treatment for primary VL in the national guidelines of countries in the region, disseminate results to the region's VL stakeholders and update registration status of SSG&PM

2015 OBJECTIVES: Renew retention of SSG&PM in the register for Kenya and Uganda and register SSG and PM in Ethiopia and Sudan

More than 10,000 patients treated

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); this shorter course lessens the burden on patients and health systems, and is more cost effective. WHO recommended SSG&PM combination as first line treatment for primary VL in Eastern Africa in March of the same year, and a large Pharmacovigilance (PV) study was implemented in Sudan, Ethiopia, Uganda, and Kenya between April 2011 and May 2014. The PV study results showed a 95% cure rate at the end of treatment with the SSG&PM therapy with no new safety concerns.

SSG&PM is recommended as first-line treatment for VL in Sudan, Ethiopia, South Sudan, Somalia, and Kenya. SSG&PM has been included in the national guidelines of Sudan, South Sudan, Ethiopia, Somalia, and Kenya, and the guidelines are under review in Uganda. PM is registered in Uganda (2011) and Kenya (2013), and is in the process of registration in Sudan and Ethiopia.

MAIN PARTNERS: Ministries of Health of Uganda, Sudan, Kenya, and Ethiopia; Institute of Endemic Disease (IEND), Khartoum University, Sudan; Kenya Medical Research Institute (KEMRI), Kenya; Gondar University Hospital, Ethiopia; Addis Ababa University, Ethiopia; Arba Minch Hospital, Ethiopia; Makerere University, Uganda; Amudat Hospital, Uganda; LEAP; Médecins Sans Frontières (MSF), Switzerland and Holland; London School of Hygiene and Tropical Medicine (LSHTM), UK; IDA Foundation, The Netherlands

IMPLEMENTATION

New VL treatments - Asia

PROJECT START: July 2010 (Bangladesh)/December 2006 (India)

OVERALL OBJECTIVE: Develop one to two new (combination) treatments and support recommendations from the authorities in the main endemic countries. Provide evidence for adoption of combination treatment as a second line option in national policy in Bangladesh

2015 OBJECTIVE: Advocate for the adoption of combinations as second line treatment in Bangladesh

1,761 patients recruited at 12 sites in India

The Phase III trial conducted in India in 2008-2010 demonstrated the efficacy of combination therapies based on AmBisome®, miltefosine, and paromomycin, and 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* conducted safety and effectiveness studies, including a pilot project in the Bihar State of India (2012-2015) implementing combination therapies at the primary healthcare level, and single-dose AmBisome® at the hospital level.

These regimes were observed to be safe and effective and, based on the study results, the Indian National Roadmap for Kala-Azar Elimination in August 2014 recommended use of single dose AmBisome® as a first option treatment for the treatment of VL patients, with paromomycin and miltefosine as a second option at all levels; a policy also reflected in Bangladesh and Nepal. This removal of miltefosine monotherapy is an important policy change. The pilot study continued following up patients, documenting 12 month treatment outcomes, at the request of the national programme; this follow up was completed in September 2015. Site close out activities will be completed in January 2016.

In Bangladesh, a two-step Phase III study conducted from 2010-2014 in 602 patients (first in hospital settings, then in primary healthcare centres) used the same combination therapies as those tested in India. All tested treatments demonstrated excellent cure rates and were well tolerated by patients, in support of policy change in the country.

MAIN PARTNERS: INDIA: Indian Council of Medical Research (ICMR); Rajendra Memorial Research Institute of Medical Sciences (RMRIMS); Bihar State Health Society; National Vector Borne Disease Control Programme (NVBDCP); Kala Azar Medical Research Centre; GVK Biosciences; BANGLADESH: Ministry of Health and Family Welfare; International Centre for Diarrhoeal Disease Research (ICDDR,B); Shaheed Suhrawardy Medical College and Hospital; OTHER: Médecins Sans Frontières (MSF), Spain; London School of Hygiene and Tropical Medicine (LSHTM), UK; WHO-TDR, Switzerland; Institute of Tropical Medicine-Antwerp, Belgium

Health workers at the Mizque health care centre, Cochabamba, Bolivia.

› **Chagas disease** is endemic in 21 Latin American countries and in the USA, and is of increasing concern in Europe due to migrant populations. The asymptomatic nature of chronic disease means that it is difficult to know exactly how many people are infected, but current estimates are of 5.7 million people in Latin America alone, indicating that more than 6 million people are likely to be affected worldwide. It is the leading cause of infectious cardiomyopathy in the Western hemisphere. Chagas disease mostly affects those living in poverty, and to date less than 1% of people infected with *Trypanosoma cruzi* have access to diagnosis and treatment, despite the fact that more than one-half of Chagas disease sufferers live in Latin America's wealthiest countries – Argentina, Brazil, and Mexico. The only drugs developed which successfully kill *T. cruzi* parasites are nifurtimox and benznidazole, both more than 40 years old, and although effective, they are used as long treatment regimens and cause frequent side effects. Benznidazole is currently produced in Brazil and Argentina.

Improving treatments and access to medicines

The benznidazole/fosravuconazole (E1224) trial carried out by DND*i* and partners confirmed the long-term efficacy of benznidazole, although with the already observed side effects, and further trials are planned to evaluate shorter treatment courses and lower doses of benznidazole with and without fosravuconazole, aiming to maintain or increase efficacy and improve safety. In addition, the recently completed Merck-sponsored STOP Chagas trial in adults with asymptomatic chronic disease confirmed the efficacy of benznidazole and the lack of sustained effect by the azole class of compounds as treatment for Chagas. However, the BENEFIT (Benznidazole Evaluation for Interrupting Trypanosomiasis) trial showed benznidazole treatment was not effective in preventing progression of disease in patients with known Chagas cardiac involvement. These results highlighted the importance of early diagnosis and treatment of Chagas patients. Fexinidazole is also being evaluated in adults with chronic indeterminate disease and early stage drug discovery efforts are aiming to identify entirely new chemical entities for development.

In response to the lack of access to treatments, DND*i* proposed a project to assess the feasibility of scaling up treatment and access to benznidazole, in five countries in the Americas. Previous work undertaken has shown an important paradigm shift over the past two years, from discussing vector control to focusing on the urgent need to scale up access to diagnosis and treatment in Latin America. Throughout 2015, DND*i* has worked closely with the Colombian Chagas National Control Programme, providing technical support to create the enabling environment needed to scale up access to diagnosis and treatment for Chagas in Colombia. As a result of meetings and discussions between the Ministry of Health, the National Control Programme, and the Red Chagas Colombia programme, a comprehensive roadmap for Chagas has been developed which defines operational interventions – such as implementation of pilot projects in four different regions in the country, registration of benznidazole, and support for validation of a new national diagnostic protocol for Chagas disease – which are due to start in 2016. A project in Mexico will focus on short- and medium-term approaches to further assess the disease burden, raise awareness, and ultimately improve patient access by working with the Ministry of Health and other stakeholders. Furthermore, there is the aim to identify and address barriers to access diagnosis and treatment in the USA, as there are large numbers affected by Chagas disease in areas with large populations from endemic countries – such as in California, Florida, and Texas – who are excluded from the healthcare system.

The disease has two clinical phases, the **acute phase** (fatal for 2-8% of children), which is often asymptomatic or poorly symptomatic and unrecognized, and the **chronic phase**, which can be divided into two stages:

- The **chronic, asymptomatic (or indeterminate)** stage, during which patients can transmit the parasite to others (mostly through blood, congenital transmission, or occasionally organ transplant) and which may last decades after infection.
- The **chronic, symptomatic** stage, developing later in up to 30% of infected patients. Chagas disease causes abnormal dilation of the large intestine (megacolon), is the leading cause of infectious heart disease (cardiomyopathy) in the world, and the leading cause of death from a parasitic disease 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 in the chronic indeterminate phase of the disease, broad use of these drugs has been limited due to lack of guidelines and policies supporting implementation. 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 the chronic form of the disease with target organ involvement (chronic symptomatic stage).

Endemic in
21 countries
IN LATIN AMERICA

70 million
people at risk

5.7 million
people infected, leading to approximately 7,000 deaths every year

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

DND*i*'s **short-term** goal was to make better use of existing treatments, for example through the development of a paediatric dosage form of benznidazole – a goal which was achieved in 2011. The treatment is registered in Brazil by LAFEPE (2011), and was included on the WHO Essential Medicines List for children in 2013. An agreement signed in 2013 with the Mundo Sano Foundation ensures a second source of the paediatric dosage form to be produced by ELEA. Collaborative activities will continue to support country registration and adoption, and greater treatment availability to patients.

As a **medium-term** strategy, DND*i* has been assessing known families of compounds, such as nitroimidazoles and the new triazole antifungals, for activity against *T. cruzi* in adult chronic patients. A proof-of-concept trial showed fosravuconazole (E1224) monotherapy did not show sustained efficacy, as measured by sustained parasite clearance one year after end of treatment. In contrast, the current regimen of benznidazole was very efficacious over the period of 12 months of follow-up. Alternative benznidazole regimens, including reduced dosing and duration of treatment in monotherapy, and combination treatment with fosravuconazole, are now being explored.

Fexinidazole, a non-genotoxic nitroimidazole currently in development for HAT and VL, is also being evaluated for treatment of adult indeterminate Chagas disease. Additionally, DND*i* continues to search for potential biomarkers of treatment response to enhance clinical trial capabilities for evaluation of new compounds.

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 and access through the Chagas Clinical Research Platform (see p. 60), which was launched in 2009.

Ideally, a new treatment would target **both acute and chronic** phases of the disease, with activity against most parasite species in all endemic regions, with a better **safety** profile than existing drugs and non-inferior **efficacy** to benznidazole, being **easy-to-use** (oral, once-a-day for less than 30 days, requiring no hospitalization, and little or no monitoring), **affordable, and adapted to tropical climates.**

By 2020, DND*i* aims to deliver from its Chagas-specific portfolio:

- **An effective, safe, new oral treatment regimen for chronic indeterminate Chagas disease, ideally also effective against the acute form of the disease**
- **Biomarkers to gain understanding of disease progression and support evaluation of treatment response to support drug development**

RESEARCH

Nitroimidazole

PROJECT START: April 2012

OVERALL OBJECTIVE: **Generate new drug candidates for the treatment of Chagas to be assessed in clinical trials**

An opportunistic approach was undertaken to assess compounds issuing from the VL-2098 back-up programme (nitroimidazooxazine series) showing activity against *T. cruzi in vitro*, evaluating the most promising candidates in *in vivo* models of Chagas disease. Given the ongoing clinical development of fexinidazole for Chagas disease, further progression was put on hold and will only recommence if a need arises.

PARTNERS: TB Alliance, USA; Auckland University, New Zealand; Laboratory of Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, Belgium; WuXi AppTech, China; LSTMH, UK

Chagas H2L (Chagas Hit to Lead)

PROJECT START: On-going

OVERALL OBJECTIVE: **Identify new leads series from current ongoing Hit-to-Lead activities to move them into lead optimization**

2015 OBJECTIVE: **Identify new chemical series to progress into Hit-to-Lead and lead optimization stages**

Multiple hits from screening with several pharmaceutical partners or from other sources have been progressed into hit confirmation and expansion studies. Several promising series, issued from the published hit list from "GSK kinetoplastid Boxes" and Celgene, have been identified and are currently moving into the hit-to-lead stage; one series showed Proof of Principle *in vivo* and is in Lead Optimization. In order to identify hit series with a different mechanism of action, the screening cascade has been modified to filter out potential CYP51 inhibitors (same mechanism of action as posaconazole or ravuconazole), and prioritizing trypanocidal compounds early on. The insights gained from additional *in vitro* assays, coupled with a new *in vivo* model based on BioLuminescent Imaging, was developed at the LSHTM. The model predicts the outcome of benznidazole and posaconazole in clinical trials, enabling compounds to be moved forward with more confidence.

Opportunities for new candidates to include in the pipeline are continually under review. Preliminary mapping and set-up of discovery activities are continuing in Latin America in accordance with the global DND*i* strategy of empowerment of and funding from the regional offices.

MAIN PARTNERS: Centre for Drug Candidate Optimization, Monash University, Australia; Epichem, Australia; Griffith University, Australia; London School of Hygiene and Tropical Medicine, UK; WuXi AppTech, China; LNBio/CNPEM, Brazil; University of Campinas (UNICAMP), Brazil; AbbVie, USA; Sanofi, France; Sandexis, UK; Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp, Belgium; TCG Life Sciences, India; AbbVie, USA

TRANSLATION

Biomarkers

PROJECT START: 2010

OVERALL OBJECTIVE: **Identify and evaluate new biological markers of therapeutic efficacy in chronic Chagas disease and to promote research**

2015 OBJECTIVES:

- **Follow-up validation and characterization studies on selected markers identified through proteomic-based platforms and other studies**
- **Progress Non-Human Primate Study through 12 month assessment and immunosuppression phase**

DND*i* has been seeking to identify and/or evaluate biomarkers of therapeutic response to treatment, as the only measurable outcomes to date have been clinical benefit and seroconversion, and, with the exception of children, the latter can take several decades. The initial focus has been on optimizing blood sampling procedures and validation of DNA quantification through polymerase chain reaction (PCR), one of the key outcome measures in use for clinical trials in Chagas disease. The assessment of proteomic signatures in serum samples from nifurtimox-treated Chagas patients previously led to the identification of possible biological markers of therapeutic response. Children show faster seroconversion than adults. In 2015, analysis of sera from children treated with benznidazole was undertaken in order to evaluate a potential correlation between seroconversion and the presence or absence of biological markers. Early indications are that these can be used to classify patients as cured or not, and results of confirmatory experiments are expected in 2016.

DND*i* is collaborating with the University of Georgia and the Texas Biomedical Research Institute in a Wellcome Trust funded, non-human primate study in naturally infected animals with chronic Chagas disease, to further determine PCR and other markers as sensitive tools to consistently differentiate parasitological cure from treatment failure. The dosing period of the non-human primate study in naturally infected animals with chronic Chagas disease ended in 2015, and a 12-month follow-up assessment was completed in August 2015. The study immunosuppression phase was initiated in October 2015 and will end in mid-2016, at which point blood and tissue sample PCR and assessment of other biomarkers will be undertaken to determine if they can differentiate parasitological cure from treatment failure.

DND*i* is a member of the NHEPACHA network of investigators created for the long-term cohort evaluation of potential biomarkers.

MAIN PARTNERS: Texas Biomedical Research, USA; University of Georgia Research Foundation, USA; McGill University, Canada; 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 Texas at El Paso, USA; National Council of Scientific and Technological Research (INGEBI-CONICET), Argentina; NHEPACHA network; Universidad San Martin, Argentina

DEVELOPMENT

New benznidazole regimens/ combinations

PROJECT START: December 2013

OVERALL OBJECTIVE: Develop a new improved regimen of benznidazole and a benznidazole/fosravuconazole combination treatment regimen for chronic Chagas disease

2015 OBJECTIVE: Initiate plans for Phase II studies for simpler benznidazole monotherapy regime or in combination with fosravuconazole

Benznidazole, the standard treatment for Chagas, had sustained efficacy until 12 months post-therapy, but was associated with side effects that resulted in treatment discontinuation. A proof-of-concept trial carried out in 2013 showed that fosravuconazole (previously known as E1224) had good safety and was effective at clearing the parasite, but efficacy was not sustained. A Phase I drug-drug interaction study, undertaken in 2014 in 28 healthy human volunteers in Buenos Aires, Argentina, assessed the safety and pharmacokinetic interactions of fosravuconazole and benznidazole administered separately and in combination: no major clinically relevant safety or tolerability issues were identified. A proof of concept study in approximately 270 patients with chronic Chagas disease will determine if the safety and tolerability issues of benznidazole can be managed by reduced doses and treatment duration, or by combining it with fosravuconazole. The protocol for this study, composed of eight arms with benznidazole in monotherapy or in combination with fosravuconazole at selected doses and treatment durations versus placebo, was finalized in 2015. Sites in Argentina, Bolivia, and Spain were identified, and patient recruitment is expected to start in 2016.

MAIN PARTNERS: ARGENTINA: Fundación Mundo Sano and ELEA; Administración Nacional de Laboratorios e Institutos de Salud (ANLIS); Instituto Nacional de Epidemiología Dr Fatala Cháben; Instituto de Investigaciones en Ingeniería Genética y Biología Molecular "Dr. Héctor N. Torres" - INGEBI-CONICET; Centro de Chagas y Patologia Regional, Hospital Independencia, Santiago del Estero; Fundación Para el Estudio de las Infecciones Parasitarias y Enfermedad de Chagas (FIPEC); BOLIVIA: Collective of Applied Studies and Social Development (CEADES); Universidad Autónoma Juan Misael Saracho; Universidad Mayor de San Simon; SPAIN: IS Global, Centre de Recerca en Salut Internacional de Barcelona (CRESIB); Hospital General de Valencia; SPAIN/BOLIVIA: Platform of Integral Care for Patients with Chagas Disease; JAPAN: Eisai Co. Ltd

DEVELOPMENT

Fexinidazole

PROJECT START: December 2013

OVERALL OBJECTIVE: Evaluate fexinidazole for treatment of chronic Chagas disease

2015 OBJECTIVE: Conclude the 12-month assessments of the PoC Phase II and proceed to the data cleaning and analysis

47 patients recruited at 2 sites

Comprehensive pre-clinical results evaluation of fexinidazole supported its clinical evaluation in patients. A Phase II Proof-of-Concept trial was initiated in adult patients with chronic Chagas disease in Bolivia in 2014, but after recruiting 47 participants, the study was interrupted due to safety and tolerability issues. A safety review did not identify the same frequency or severity of adverse events for fexinidazole when used in other indications. Patient monitoring continued for 12 months post-treatment to assess if there was sustained suppression of parasites as assessed by PCR and the final study results are expected in early 2016.

MAIN PARTNERS: ARGENTINA: Instituto de Investigaciones en Ingeniería Genética y Biología Molecular "Dr. Héctor N. Torres" INGEBI-CONICET; BOLIVIA: Collective of Applied Studies and Social Development (CEADES); Platform of Integral Care for Patients with Chagas Disease, Tarija and Cochabamba; Universidad Autónoma Juan Misael Saracho; Universidad Mayor de San Simon; SPAIN: Centre de Recerca en Salut Internacional de Barcelona (CRESIB)

IMPLEMENTATION

Paediatric Dosage Form of Benznidazole

PROJECT START: May 2011

OVERALL OBJECTIVE: **Develop and make available an easily dispersible, simpler to administer, safer, age-adapted dosage for children under two years old**

2015 OBJECTIVES:

- **Ensure paediatric benznidazole is available in endemic countries in Latin America and together with ELEA**
- **Submit a regulatory dossier for second source of paediatric benznidazole**

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. A population pharmacokinetic study in children aged 0 to 12 years with Chagas disease was conducted and showed complete parasitic clearance in all children immediately after treatment. Sustained response at 12 months was assessed in a subset of patients with longer follow-up. The study also showed that children have lower blood levels of benznidazole than previously documented in adults, suggesting that reduced adult dose regimen should be considered for evaluation. An easy to use and adapted paediatric dosage form was developed and registered in Brazil (2011), and subsequently included on the WHO Essential Medicines List for children (2013). The Mundo Sano Foundation and DND*i* signed a collaboration agreement (2013) to deliver a second source of the treatment in partnership with ELEA. ELEA produced pilot and scale-up batches in 2014, and stability testing is underway. Submission for marketing authorization was carried out by ELEA in Argentina at the end of 2015, and will proceed in other endemic countries. Through this project, DND*i* has also stepped up efforts to support the scale up of treatment with benznidazole for adult patients with Chagas disease.

MAIN PARTNERS: BRAZIL: LAFEPE; ARGENTINA: Fundación Mundo Sano and ELEA; Centro Nacional de Diagnóstico e Investigación de Endemo-epidemias (CeNDIE), Administración Nacional de Laboratorios e Institutos de Salud (ANLIS); Centro de Chagas y Patologia Regional, Hospital Independencia, Santiago del Estero; Hospital de Niños de Jujuy; Hospital de Niños Dr. Ricardo Gutiérrez; Hospital Público Materno Infantil – Salta; Instituto Nacional de Parasitología Dr M Fatala Chabén; Ministry of Health; Ministério de Salud, Província de Jujuy

Foot measurement of a lymphatic filariasis patient in Sukala, Satyavadi, Puri district, Odisha, India.

› **The helminth** worms responsible for causing parasitic disease in animals and humans are classified into three species – roundworms or nematodes (including filarial worms and soil-transmitted helminths), flatworms, and flukes. Filarial worms are spread by blood-feeding insect vectors, and invade different parts of the human body causing chronic disease. *Wucheria bancrofti*, *Brugia malayi,* and *B. timori* adult worms invade the lymphatic system, and *Onchocerca volvulus* and *Loa loa* form deep tissue and subcutaneous nodules.

Onchocerciasis is predominantly found in West and Central Africa where it causes river blindness, so-called because the black flies which spread disease breed in fast-flowing rivers and streams, and can produce blindness after many years of chronic infection. Before large control programmes started, blindness was highly prevalent in villages along rivers infested with blackflies, leading to the abandonment of fertile land, and increased poverty. An estimated 37 million people are infected with *O. volvulus* worms, which cause severe itching and may result in blindness or impaired vision.

Lymphatic filariasis (LF) is more widespread, found in tropical areas principally in Africa and Asia. Worms migrate to the lymph glands, resulting in swollen limbs and genitals, a disabling, painful, and highly stigmatizing affliction. Over 67 million people are infected and over 36 million are estimated to be clinically affected by the symptoms.

Loiasis, also known as African eyeworm because of the migration of the adult worm through the conjunctiva, has less direct impact, with symptoms not considered to be as severe. But loiasis infection has important implications for LF and onchocerciasis control programmes using preventive mass drug administration (MDA) chemotherapy, as serious adverse events can occur in co-infected patients.

MDA programmes depend on donations from pharmaceutical companies, and although the drugs are effective in killing the different juvenile worms (microfilariae) of the *O.volvulus*, *W. bancrofti*, and *Brugia* worms, they do not kill adult worms (macrofilariae) which continue to reproduce during most of their long lifespan. MDA chemotherapy therefore needs repeating once or twice annually for over a decade. A short-course treatment that kills adult worms is needed to cure patients, and may also be useful in reducing the number of cycles of MDA to achieve disease control or elimination.

Treatments are needed for juvenile as well as adult worms

DND*i* is aiming to develop a safe and effective field-adapted macrofilaricidal drug with its partners, based on drugs used to treat animal helminth infections. A parallel approach is to target *Wolbachia*, a symbiotic intracellular bacterium present in *Onchocerca*, *Wucheria*, and *Brugia* worms, aiming to identify drugs which kill the *Wolbachia* and impact worm survival and reproduction.

The year 2015 was a defining one for filarial diseases. In October, one half of the Nobel Prize for Medicine was awarded jointly to William Campbell and Satoshi Omura for their discovery of the antifilarial drug ivermectin, used in MDA programmes. Meanwhile, the 20-year old African Programme for Onchocerciasis Control, considered to be one the most successful public health initiatives ever, closed at the end of the year. While both milestones bear testament to the progress made in treating these diseases, millions of people remain affected and in need of a curative treatment.

What are the current treatments and their limitations?

Current treatments for onchocerciasis and lymphatic filariasis are based on repeated mass drug administration (MDA) of antiparasitic drugs through programmes directed by the WHO. WHO recommends MDA for onchocerciasis at least once yearly for 10-15 years, and for lymphatic filariasis once yearly for at least five years. The drugs used in MDA programmes are **ivermectin** for onchocerciasis; **albendazole** for lymphatic filariasis; and **albendazole** plus either **ivermectin** in areas where onchocerciasis is also endemic (i.e. African countries), or **diethylcarbamazine** (DEC) in areas where onchocerciasis is not co-endemic (i.e. non-African countries).

A bite from an infected insect allows filarial larvae to pass into the blood and migrate through the human body. These mature into adults that produce microfilariae, which the insect ingests during a blood meal, and the cycle goes on. MDA drugs can prevent this vector-borne transmission for several months by killing mainly the microfilariae, and inducing a temporary sterilization of adult worms. However, because adult worms (macrofilariae) continue to live in the body, they eventually produce new microfilariae, often before the next MDA, thus requiring repeated MDAs for several years to decades.

Ivermectin treatment is safe and has been used widely in MDA programmes. However, the use of ivermectin in patients co-infected with high levels of *Loa loa* microfilaria in the blood can result in safety issues such as the occurrence of encephalopathy that can be fatal if not properly managed. Additionally, a suboptimal response to ivermectin in patients with onchocerciasis has been reported which may be a sign of resistance development. Furthermore, the morbidity associated with onchocerciasis and LF infection (itching, dermatitis, lymphedema, and blindness) are only partially improved or prevented and require repeated treatment with the current drugs.

ONCHOCERCIASIS

37 million infected worldwide, with 99% cases in **31 African countries**

746,000 visually impaired

265,000 blinded and more than 4 million suffering from severe itching

169 million were estimated at risk in 2014

LYMPHATIC FILARIASIS

Over **1.1 billion** people at risk worldwide, 57% in South East Asia region

Over **36 million** suffering from clinical illness (19.4 million with hydrocele, and 16.6 million with lymphedema)

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

DND*i*'s strategy is to develop a new compound with macrofilaricide activity (to kill adult worms) for use as a safe and field-adapted macrofilaricidal drug for patient case management and possibly later MDA if needed.

As a **medium-term strategy**, DND*i* is assessing emodepside which is commercialized by Bayer under license from Astellas as an anthelmintic veterinary drug for cats and dogs in combination with praziquantel (Profender®) and in combination with toltrazuril (Procox®). DND*i* has an agreement with Bayer to develop emodepside for the treatment of onchocerciasis.

Other compounds targeting *Wolbachia*, a worm symbiotic bacteria present in the parasites causing onchocerciasis and LF, will also be explored.

As a **long-term strategy**, DND*i* is assessing additional opportunities through an active screening programme of drug compounds emanating from animal health/pharmaceutical companies and academic institutions, with the goal of selecting one or two candidates to move into clinical development.

DND*i* aims to deliver a **safe, efficacious, affordable,** and **field-adapted macrofilaricidal drug** for onchocerciasis and/or lymphatic filariasis for the treatment of patients, and as a **possible alternative in mass drug administration programmes**.

TRANSLATION

Macrofilaricide 2

PROJECT START: March 2015

OVERALL OBJECTIVE: **Develop a macrofilaricide effective against worm-symbiotic *Wolbachia* bacteria**

Two derivatives of a veterinary antibiotic, which target the worm-symbiont *Wolbachia* bacterium, are currently in development for treatment of filarial diseases. These compounds can be delivered orally, induce a robust anti-*Wolbachia* effect in several *in vivo* models, demonstrate clear superiority over doxycycline, and are effective after a shorter dosing regimen. Preliminary safety and toxicology profiling of these compounds carried out in 2015 suggests a favourable safety profile. Upon successful completion of the necessary toxicology studies, expected in 2016, and development of an oral formulation, a Phase I single rising dose study in healthy human volunteers will be performed to determine the safety, tolerability, maximum tolerated dose, and pharmacokinetics of single oral doses of the selected compound. If appropriate pharmacokinetic characteristics are demonstrated and are suggestive of sufficient therapeutic margins, the safety, tolerability, and pharmacokinetics of multiple ascending doses of an oral formulation of the compound will be determined. To demonstrate proof of concept for filarial disease, a Phase Ib programme will be conducted in patients. This programme will be designed to provide data on which a collective decision can be made to proceed into Phase II studies in patients with either onchocerciasis or lymphatic filariasis.

MAIN PARTNERS: AbbVie, USA; Liverpool School of Tropical Medicine, UK

Emodepside

PROJECT START: March 2013

OVERALL OBJECTIVE: **Develop emodepside as a new macrofilaricidal treatment for patients suffering from onchocerciasis**

2015 OBJECTIVES:

- **Complete pre-clinical package for first-in-human study**
- **Progress emodepside into first-in-human study**

Emodepside is a semi-synthetic product (originated by Astellas and out-licensed to Bayer for animal and human use); its precursor is synthesized by a fungus living in the leaves of Camellia japonica. It is a potent antihelminthic drug used in combination with praziquantel (as Profender®) and in combination with toltrazuril (as Procox®) for the treatment of parasitic worms in cats and dogs. DND*i* and Bayer Pharma AG are jointly developing emodepside for the treatment of onchocerciasis patients. DND*i* will be responsible for the pre-clinical and clinical development of emodepside and Bayer for the pharmaceutical development, manufacturing, registration, and supply of the drug at the lowest sustainable price. The pre-clinical package to start Phase I studies was completed and recruitment into a single-ascending dose study was initiated in December 2015.

MAIN PARTNER: Bayer HealthCare, Germany

Filling knowledge gaps

As is frequently the case with neglected diseases, there are a number of knowledge gaps. DND*i* partners are carrying out modelling studies aiming to quantify and characterize the future needs of patients suffering from onchocerciasis and lymphatic filariasis, and to provide information on the size and profile of target populations for the new treatments in development. There is also a need for reliable biomarkers of disease evolution which can assess the effect of new treatments as an alternative to existing invasive skin biopsies and nodulectomies. A new medical optical imaging technique is being evaluated, which aims to find an optical signature of live versus dead *O. volvulus* worms in subcutaneous nodules.

PARTNERS: Erasmus University, the Netherlands; CEA-LETI[1], France; REFODTE, Cameroon; Institut de Recherche pour le Développement, France.

(1) LETI a French state-owned research entity, (*Commissariat à l'énergie atomique et aux énergies alternatives* (CEA), *Laboratoire d'Électronique et de Technologies de l'Information* (LETI).

A mother of an HIV+ baby boy administering him bitter tasting ARV medication, Belville South, Cape Town, South Africa.

Developing treatments for children living with HIV/AIDS

› **HIV** continues to be a major public health problem worldwide, particularly in sub-Saharan Africa, even though international efforts to combat HIV/AIDS since the turn of the millennium have led to an overall decrease in the number of new cases diagnosed and in the number of AIDS-related deaths. Children are the worst affected, and the majority of babies born with HIV are still not diagnosed or treated. Of the approximately 2.6 million children currently living with HIV, only 32% receive treatment. Although efforts in preventing mother-to-child transmission should reduce the market size of paediatric HIV in the long term, the increased testing of pregnant women and their children is paradoxically expected to increase the paediatric market in the short to medium term, and the need for paediatric treatment will continue to increase until at least 2020. Antiretroviral therapy is not able to cure the disease and needs to be taken for life, but it can control the virus and enable the patient to live a healthy life. Early treatment is essential, as without it 50% of children infected will die before their second birthday, and 80% before their fifth. Adapted paediatric treatments are needed for infants and young children that are safe, efficacious, and easy for the child to swallow, thus ensuring their best chance of survival to adulthood. Children in Africa are frequently also co-infected with tuberculosis (TB), so HIV and TB treatments need to be compatible.

Antiretroviral treatments typically combine three or more drugs with different modes of action. The only approved protease inhibitor for young children, lopinavir boosted with ritonavir (LPV/r), comes as an unpleasant tasting oral solution with a high alcohol content. It also requires refrigeration, is difficult to store due to its large volume, and expensive, making it unsuitable for resource-poor settings. DND*i* and partners have been working on developing a taste-masked, solid LPV/r oral formulation adapted for infants and young children, which would ultimately be combined with two nucleoside reverse transcriptase inhibitors (NRTIs) into a single '4-in-1' unit or capsule. As a first step, LPV/r has been formulated into pellets by Cipla Ltd., which received the U.S. Food and Drug Administration (FDA) tentative approval for use in June 2015. These pellets can be sprinkled onto food, are alcohol-free, do not require a cold chain, and are cheaper to transport, although they still have an unpleasant taste. As such, the formulation provides a better treatment option for children and is currently undergoing evaluation in DND*i*'s LIVING study in Africa, which will give valuable information on its use under normal living conditions.

What are the current treatments and their limitations?

The 2013 WHO guidelines recommend early diagnosis and immediate treatment of HIV-positive infants and children under the age of five, regardless of immunological status; infants under the age of three should be treated with an antiretroviral treatment (ART) combination that includes protease inhibitors, regardless of whether they have been exposed to ARVs, for the prevention of mother-to-child transmission (PMTCT).
The combination of a **boosted protease inhibitor (PI) with two nucleoside reverse transcriptase inhibitors** (NRTIs), ABC + 3TC or ZDV + 3TC, is considered by the WHO as the most effective first-line therapy for infants and children.

However, this combination therapy is not being widely used. According to a WHO survey performed in 45 countries, in 2010 only 12.2% of children with HIV were receiving a first-line treatment containing 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 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 difficult to store and transport.

In some places, the levels of co-infection with TB and HIV in infants and children are high. 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 antiretroviral (ARV) treatment. In order to counteract this interaction, extra ritonavir (RTV) needs to be added to the standard proportion of LPV/r. This is called 'superboosting'. The currently available ritonavir formulation suffers the same limitations as the current formulation of RTV with regard to taste, high alcohol content, and logistical constraints imposed by its short shelf-life.

2.6 million children below the age of 5 living with HIV/AIDS

More than **86%** of all new infections in sub-Saharan Africa

150,000 children under 15 years of age died of AIDS-related illness in 2014 globally

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.

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

1. Develop and register **two solid first-line '4-in-1' LPV/r-based fixed-dose combinations** (FDCs) with two NRTIs. All components of the combination will be developed in the form of taste-masked granules, which are stable with no need for refrigeration, presented in a single unit with appropriate strengths to accommodate weight band dosing.
2. **Evaluate the superboosting strategy:** i.e. increasing the LPV:RTV ratio that can effectively and safely counteract the negative drug-drug interactions between PIs and rifampicin-containing **TB** treatments.

As a **short-term strategy**, DND*i* will start testing the use of PI-based treatment with Cipla's LPV/r-based pellets before the '**4-in-1' FDC** becomes available, 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 pellets to the LPV/r liquid formulation. These pellets are being used in combination with NRTI dispersible tablets in implementation studies (LIVING study), which started in 2015. In the **longer-term**, DND*i* is working with Cipla, its industrial partner, on combining taste-masked LPV/r granules or pellets 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 order to address the needs of **HIV/TB co-infected** children, DND*i* aims to assess the addition of ritonavir for superboosting LPV/r at a 1:1 LPV:RTV ratio. DND*i* is conducting a study to establish the pharmacokinetics, efficacy, and safety of superboosted LPV/r in children in South Africa with the existing ritonavir solution. Interim results look promising for this approach and the study is being extended to include all solid formulations.

The ideal first-line treatment for paediatric HIV would be a protease inhibitor-based **all-in-one** antiretroviral regimen for HIV-infected children which is **safe and efficacious, is an adapted formulation** suitable for infants and children, is an **easy-to-use** fixed-dose combination, **is palatable, addresses drug-drug interaction** with medicines for tuberculosis, and is **adapted to tropical climates** (no refrigeration needed).

By 2019, DND*i* aims to deliver from its paediatric HIV portfolio:

- **Two new '4-in-1' paediatric formulations containing a PI (LPV/r) and two NRTIs (ABC or AZT and 3TC)**
- **One new regimen recommended to treat HIV/TB coinfection**

TRANSLATION

Two '4-in-1' LPV/r based FDC granules

PROJECT START: 2012

OVERALL OBJECTIVE: Develop and register two solid taste-masked first-line LPV/r-based fixed-dose formulations with two NRTIs, 3TC plus ABC or AZT

2015 OBJECTIVES:

- Perform pilot comparative bioavailability studies of the most promising taste-masked LPV/r granule or pellet formulations in adult volunteers
- Perform as-needed bioequivalence studies in healthy human volunteers using all components of the '4-in-1' FDC

Pharmacokinetic modelling was carried out to determine drug dosages within potential '4-in-1' formulations, and the proposed dosing for the two '4-in-1' LPV/r based FDCs and RTV booster were incorporated into Annex 7 of the WHO's new Consolidated Guidelines on The Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, under 'urgently needed ARV drugs for children recommended by the Paediatric ARV Working Group' in 2013.

New formulations of LPV/r pellets are required to optimize bioavailability and taste-masking, but this has proved to be very challenging. In 2015, three of the most promising formulations tested in previous *in vivo* studies were assessed, and were found to be highly bioavailable in Phase I studies in man. Additional bioavailability studies and standardized electronic tongue taste-testing (e-tongue) of granules with modified coatings and different polymers will be performed in 2016.

MAIN PARTNERS: Cipla Ltd., India; Department of Health, South Africa; UNITAID; President's Emergency Plan for AIDS Relief (PEPFAR), USA; Médecins Sans Frontières; Necker Institute, Paris; various academic partners in South Africa and Kenya; AbbVie, USA; WuXi AppTech, China

DEVELOPMENT

Superbooster therapy for paediatric HIV/TB co-infection

PROJECT START: 2012

OVERALL OBJECTIVE: Evaluate the pharmacokinetic enhancer/booster formulation to be added to any PI-based paediatric ARV regimen

2015 OBJECTIVES:

- Finish recruitment of the RTV superboosting study performed in South Africa (using LPV/r and RTV originator's liquid formulations)
- Ensure guideline change
- Prepare for the evaluation of superboosting with solid formulations (LPV/r granules/pellets plus RTV solid booster)

96 patients recruited at 5 sites

In Africa, a large proportion of HIV-positive infants and children are co-infected with tuberculosis (TB). Rifampicin is commonly used to treat TB in children, however it has negative interactions with protease inhibitors (PIs) included in treatments used to combat HIV infection: concomitant administration of rifampicin leads to a decrease in LPV/r exposure of up to 90%. To counteract this effect, the amount of ritonavir (RTV) in the LPV/r combination must be quadrupled in a procedure known as superboosting. A stand-alone RTV booster formulation is needed that can be added to any PI-based paediatric ARV regimen. Like LPV/r, RTV has a high alcohol content, is unstable, and completely unpalatable.

A pharmacokinetic study has been carried out in infants and young children co-infected with TB and HIV at five sites in South Africa to supplement existing information and evaluate the effect of the 'super-boosting' strategy. At the end of November 2015 all 96 patients had been included. Interim results show that LPV exposure during TB/HIV cotreatment using the superboosting approach is as good as that when children return to standard LPV/r based therapy. Superboosting was safe and well tolerated. This study is being extended to include all solid formulations. Results were shared with the South African government and WHO to support a change in guidelines for the management of TB/HIV co-infections in children. The South African government changed its guidelines in December 2015 and WHO is expected to do so by summer 2016.

MAIN PARTNERS: Department of Health and Department of Science and Technology, South Africa; Stellenbosch University and Tygerberg Children's Hospital, South Africa; Perinatal HIV Research Unit University of Witswatersrand, South Africa; Shandukani Research Centre, Wits Reproductive Health and HIV Institute, South Africa; Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital, South Africa; Enhancing Care Foundation, South Africa; Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa.

DEVELOPMENT

LPV/r pellets with dual NRTI FDC

PROJECT START: 2014

OVERALL OBJECTIVE: **Start implementing LPV/r based products immediately, before the availability of the final, better-adapted 4-in-1 products**

2015 OBJECTIVES:

- **Provide early access to the solid LPV formulation**
- **Gain knowledge on the acceptability of these LPV/r pellets in youngest infants in order to inform the choice of formulations for the '4-in-1s'**

18 paediatric patients recruited at 3 sites

Cipla has developed LPV/r pellets in capsules which can be opened and administered orally to small children, allowing the drug to be sprinkled on food and offering the advantage, over the current liquid formulation of these drugs, of being alcohol-free. These pellets do not require a cold chain and are less costly in terms of weight of product for transport; however, their poor taste is still a barrier.

The implementation study aims to provide supportive clinical data on the feasibility, efficacy, safety, and PK of LPV/r pellet-based therapies in routine treatment settings in order to facilitate registration, recommendation in national guidelines, and adoption in treatment programmes in the countries concerned. The LIVING study started in Kenya in September 2015 and is planned to expand to Uganda, South Africa, Tanzania, Zimbabwe, and Zambia in 2016.

MAIN PARTNERS: Joint Clinical Research Centre (JCRC), Uganda; Baylor College of Medicine Children's Foundation, Uganda; Epicentre, Uganda; University of Nairobi, Kenya; Gertrude's Children's Hospital, Kenya; Kenya Medical Research Institute (KEMRI), Kenya; Associated Medical Sciences/PHPT International Research Unit (AMS-PHPT), Thailand; Department of Health, South Africa; Cipla Ltd., India; UNITAID; St Lumumba Health Centre, Kisumu, Kenya; Moi Teaching and Referral Hospital, Kenya; Ministry of Health, Kenya; Clinton Health Access Initiative (CHAI), USA

HEPATITIS C

Rosalyn, Kamaal, and Mohd Rashid Bin Hashim: activists and community leaders living with hepatitis C, at the Hospital Selayang, Batu caves, Selangor, Malaysia.

› **Hepatitis C** causes chronic liver disease, including inflammation, cirrhosis, and hepatocellular carcinoma; an estimated 130-150 million people are chronically infected with HCV worldwide. This blood-borne virus is most commonly spread through unsafe injection practices, inadequate sterilization of medical equipment, and insufficient screening of blood products. HCV can also be transmitted sexually and from an infected mother to her baby, although this is less common. The virus exists with six major genotypes (GTs), but prevalence varies by region with GT1 most prevalent in high-income countries and GT3 in low- and middle-income countries (LMICs).

In the last few years, direct acting antivirals (DAAs) have revolutionized the therapeutic landscape. These well-tolerated oral treatments have a cure rate of 95% or more and are taken once daily for 12 weeks, replacing the less effective regimen of weekly pegylated interferon injections, frequently administered with twice-daily oral ribavirin for up to 48 weeks, a therapy associated with unpleasant side effects. R&D efforts have focused principally on registering a product for the lucrative market in high-income countries, with little data available on efficacy in populations carrying the genotypes that are predominant in LMICs. The price of drugs is a major barrier to treatment access, with sofosvubir treatment costing $84,000 in the US, for example, and $94,000 when combined with lepidasvir.

A drug development strategy based on a public health approach

DND*i* aims to meet the specific needs of patients in LMICs by developing a short-course, affordable, highly efficacious, safe, and all-oral pan-genotypic regimen that will enable countries to implement a "public health approach" to the epidemic. It aims to identify and treat not only those in immediate need of therapy but all those infected, in order to prevent the long-term morbidity and mortality associated with HCV, and to reduce further transmission of the virus. This approach will build on the lessons learned from efforts to scale up HIV/AIDS treatment in resource-limited settings, and includes simplified models of care that allow for decentralization to the primary healthcare level, task-shifting of clinical and nonclinical services, and reduced dependence on genotyping and other expensive and sophisticated laboratory monitoring.

In April 2016, in partnership with the governments of Malaysia and Thailand, DND*i* and the Egyptian generic drug manufacturer Pharco Pharmaceuticals announced an agreement to test an affordable HCV regimen. Phase III clinical studies will evaluate sofosbuvir plus the drug candidate ravidasvir. The efficacy, safety, and pharmacokinetics of the sofosbuvir and ravidasvir combination will be evaluated in approximately 1,000 patients with various levels of liver fibrosis, different genotypes, and with/without HIV co-infection. The company has also agreed to supply the sofosbuvir plus ravidasvir combination at a price of less than $300 per treatment course, both for and after the studies, if they are successful.

What is hepatitis C?

Hepatitis C is an inflammatory liver disease caused by infection with the hepatitis C virus (HCV). HCV is transmitted parenterally through exchange of body fluids, mostly through exposure to contaminated blood. Most patients are unaware of their infection status and furthermore, access to treatment remains beyond reach in most developing countries where the burden of disease is the greatest, and no vaccine is available.

The incubation period for hepatitis C infection lasts from 2 weeks to 6 months. Approximately 15-20% of people clear the infection spontaneously. While they have developed HCV-specific antibodies, after a few months HCV RNA can no longer be detected in their blood. However, about 75-85 % of newly infected people develop chronic infection; HCV infects their liver cells and can cause severe inflammation of the liver with long-term complications. About 60-70% of chronically infected people develop chronic liver disease; 5-20% develop cirrhosis within the first two decades of infection and 5% liver cancer. In addition to liver disease, HCV persistent infection is associated with chronic fatigue, diabetes, depression, cryoglobulinaemia, and kidney disease.

Due to the high genetic heterogeneity of HCV, it is classified into six major genotypes. Disease expression and response to therapy may vary according to the genotype.

130-150 million people globally have chronic HCV infection,

of which

85% live in low- and middle-income countries

2.3 million people suffer from HIV/HCV co-infection worldwide

500,000 deaths per year from HCV-related liver diseases

What are the current treatments and their limitations?

Up until 2011, pegylated-interferon with ribavirin was the standard treatment for chronic HCV, but management of the treatment is complex and many patients do not finish their 48-week treatment course because interferon is not well tolerated and can be difficult to access in some settings. Recent scientific advances have led to the development of new antiviral drugs for HCV, **the direct acting antivirals (DAAs)**, which have revolutionized the therapeutic landscape. In recognition of this, in 2016 the WHO updated its treatment guidelines to recommend that DAA regimens be used for the treatment of people with hepatitis C infection rather than regimens with pegylated interferon and ribavirin. DAAs are much more effective (with cure rates of >95% in clinical trials, including in previously hard-to-treat populations), safer, and better tolerated than existing therapies. Their use has simplified HCV treatment by decreasing the duration of treatment, simplifying monitoring and laboratory requirements, and increasing cure rates. However, despite the low cost of production, access to these treatments remains quite limited, due mostly to the high price charged by innovator pharmaceutical companies.

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

DND*i* plans to enable the use of DAAs as a public health tool to treat HCV. A public health approach for resource-limited settings will be taken, including simplified models of care that allow for decentralization to the primary healthcare level, task shifting of clinical and non-clinical services, and reduced dependence on genotyping and other sophisticated lab monitoring.

DND*i* is proposing a two-step project with a focus on:

1. Regional research & development (R&D):
In the **medium term**, DND*i* and partners will conduct Phase III clinical trials in Malaysia, Thailand, and other countries to test the efficacy of a combination of sofosbuvir (SOF, already registered for HCV) + ravidasvir (RDV, a promising drug candidate) as a pan-genotypic treatment and public health for tackling the HCV epidemic.

2. Support affordable access:
An actively engaged Advisory Group has been created to advise the project on the rapidly-changing HCV treatment access landscape. There are many avenues for access, including but not limited to: developing alternative treatments with favourable licensing/access terms, patent oppositions, compulsory licensing, and voluntary licensing. Multi-stakeholder projects will be piloted in key countries.

By 2020, DND*i* aims to deliver from its HCV-specific portfolio:

Evidence for the safety, efficacy, and ease of use of direct-acting antiviral regimens to be used in an affordable combination as a public health approach

DEVELOPMENT

Sofosbuvir/Ravidasvir treatments

PROJECT START: Clinical trial to start 2016

OVERALL OBJECTIVE: Conduct Phase II/III clinical trials to test the efficacy of a combination of sofosbuvir + ravidasvir

OBJECTIVE 2015: Exploratory work

More than 1 million people are estimated to be chronically infected with HCV in Thailand and 400,000 in Malaysia (genotypes 1, 3, and 6). Both countries have been excluded from all global voluntary licensing agreements with drug companies that have developed effective treatments for HCV that include low and some middle income countries. In the short term, DND*i* will focus on combining SOF –already registered for hepatitis C– and RDV– a drug candidate developed by Presidio and licensed to Pharco – to evaluate pan-genotypic activity in Thai and Malaysian populations. The study will assess, in real-world settings, the efficacy, safety, tolerability, pharmacokinetics, and acceptability of a 12-week regimen containing SOF plus RDV in participants infected with HCV, regardless of the HCV genotype, source of transmission (including intravenous drug use), or HIV co-infection, and also in patients with compensated liver disease with or without cirrhosis. For participants with compensated liver cirrhosis, treatment duration will be 24 weeks. A total of 750 subjects will be enrolled, including up to 30% with compensated cirrhosis and up to 20% people who inject drugs, providing data on efficacy and safety of the SOF-RDV combination as well as on treatment compliance.

In 2015 the HCV project was undertaking exploratory work on assessing patient needs and project opportunities, recruitment of patients, and fund-raising.

MAIN PARTNERS: Pharco Pharmaceuticals, Inc., Egypt; Presidio Pharmaceuticals, Inc., USA; Clinical Research Malaysia (CRM), Ministry of Health, Malaysia

Almina, a mycetoma patient, showing her lesions to Prof Fahal and his team at the Mycetoma Research Centre, Sudan.

› **Mycetoma** is a truly neglected disease on every level. Although many suffer from this devastating infection, the global burden of disease is unknown, as those affected live in remote villages in the tropics and subtropics where there is no disease surveillance. The route of transmission is also unknown, and although it is thought that the infection may come from the soil or from animal dung, entering the body after the skin has been pricked, by a thorn for example, there have been no comprehensive studies to prove this theory.

Newly recognized as a neglected disease by WHO

Mycetoma was included in the official list of Neglected Tropical Diseases during discussions at the World Health Assembly in May 2016 – the 18th disease to be included – giving the disease the political prominence it so desperately needs. Such an important step will allow governments as well as other funding bodies to consider providing resources to set up research programmes for the development of new treatments and diagnostics to combat the disease.

What are the current treatments and their limitations?

There are two groups of microbial agents which cause disease. Actinomycetoma – the form caused by filamentous bacteria (actinomycetes) – responds well to antibiotics (amikacin and co-trimoxazole) and has a 90% cure rate. However eumycetoma – the fungal form – develops into a chronic skin infection which, without treatment, invades the surrounding tissue and bone. Children and young adults, particularly men working outdoors, are most at risk.

Early treatment has a higher chance of being effective, but patients live a long way from health centres and tend to present with advanced disease, if at all, by which time antifungal cure is only 25-35% effective. Treatment is most often followed by surgical removal of the remaining mass and there is a high chance of recurrence, often leading to multiple amputations and ultimately the loss of entire limbs, with the associated risk of complications and death. Current antifungals are expensive and cause serious side effects, and an effective, safe, and affordable curative treatment for use in rural settings is desperately needed.

Ketoconazole and **itraconazole** are the antifungal agents that are currently in use, however these have serious side effects. Concerns about liver toxicity have lead the FDA and EMA to restrict the use of ketoconazole. Both the duration (twelve months) and cost of treatment are significant barriers to access for patients and health authorities in endemic areas, and as a result drop-out rates are high: at 10,000 USD per annum, the treatment represents between 50-100% of the average annual wage of patients.

A stigmatizing disease that causes devastating deformities, often resulting in amputation and morbidity.

Basic epidemiological information is missing for this very neglected disease.

The causative organisms of mycetoma are **endemic in tropical and subtropical areas of the 'mycetoma belt'.**

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

Recognizing an opportunity to test the effectiveness of fosravuconazole in treating mycetoma after experience with this drug as a Chagas agent, DND*i* included its clinical testing for the disease in its Business Plan 2015-2023 as a short-term, pragmatic, mini-portfolio approach, and in 2016 will begin a clinical study in partnership with the Mycetoma Research Centre in Sudan.

DEVELOPMENT

Fosravuconazole

PROJECT START: September 2015

OVERALL OBJECTIVE: **Conduct a randomized controlled clinical trial to investigate the efficacy of fosravuconazole compared to the current treatment, itraconazole.**

Treating eumycetoma is a challenge. Currently, the antifungals ketoconazole and itraconazole are the only therapies available but these are expensive, ineffective, and have serious side effects. Patients often have to undergo amputation, and often more than once, sometimes resulting in death. Safe, effective antifungal agents that are appropriate for use in rural settings are urgently needed.

Fosravuconazole (E1224), an orally bioavailable azole that is under development for Chagas disease, may be an effective and affordable treatment for eumycetoma. Fosravuconazole, a prodrug, is rapidly converted to ravuconazole, which has been shown to have potent *in vitro* activity against one of the causative agents of eumycetoma, *Madurella mycetomatis*. Its pharmacokinetic properties are favourable and its toxicity is low. A randomized controlled trial will be conducted with the WHO Collaborating Centre on Mycetoma in Khartoum to study the efficacy of fosravuconazole in moderate lesions in comparison with the current treatment, itraconazole. The primary objective of this double-blinded, randomized, single-centre study (with an interim analysis at three months) will be to demonstrate superiority of fosravuconazole over itraconazole after 12 months treatment. The study is due to begin in 2016.

MAIN PARTNERS: Eisai Co. Ltd, Japan; Erasmus Medical Center, The Netherlands; Radboud University Medical Center, Nijmegen, The Netherlands; Mycetoma Research Centre (MRC), Soba University Hospital, Khartoum, Sudan; Institute of Endemic Diseases (IEND), Khartoum University, Sudan

Mustafa Alnour Alhassan, a young university student aged 26, with mycetoma, sitting on the rickshaw he took to the Mycetoma Research Centre (MRC) in Khartoum, Sudan. Despite the treatments he received, the flesh-eating fungal disease continued to progress and his leg was amputated in July 2015. The disease unfortunately spread to his groin and lungs. He died in March 2016.

ASAQ and ASMQ, the two antimalarial treatments developed by DND*i* and partners.

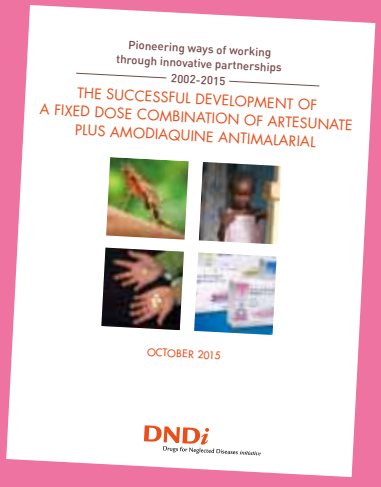
› **ASAQ and ASMQ**, fixed-dose combinations of artesunate (AS) with amodiaquine (AQ) or mefloquine (MQ), were the first projects to be undertaken by DND*i*; their development was based on WHO recommendations for artemisinin-combination therapies to treat malaria in 2001. Their development was overseen by the Fixed-Dose Combination Therapy (FACT) Consortium, formed in 2002, with the aim of developing field-adapted formulations that would be easy to administer to all age/weight categories of patients, but particularly infants and young children, and which were able to withstand tropical conditions.

ASAQ-Winthrop®, a generic fixed-dose combination (FDC) of ASAQ, was the first product launched by DND*i* in 2007 and was followed by ASMQ FDC the following year. Both feature on the WHO Essential Medicines Lists for adults and children.

The malaria projects were formally handed over to Medicines for Malaria Venture in May 2015, who will continue to implement these treatments in the field. Sanofi produces the generic ASAQ-Winthrop® in Morocco, and a commercial version, Coarsucam™. DND*i* is finalizing the technology transfer of ASAQ-Winthrop® to a second manufacturer based in Tanzania, Zenufa, and an application for WHO prequalification will be submitted in 2016. Cipla Ltd., in India, manufactures prequalified ASMQ FDC, following a successful technology transfer from the Brazilian manufacturer Farmanguinhos/Fiocruz. The shelf-life under tropical conditions for both products was extended from two to three years in March 2016.

By the end of 2015, more than 437 million treatments of ASAQ FDC produced by Sanofi had been distributed, and over 900,000 treatments of ASMQ FDC.

An innovative approach for the successful development of patient-adapted treatments



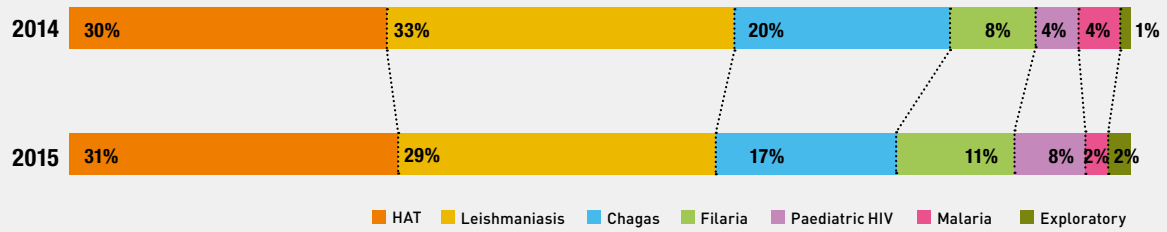
In 2016 DND*i* published an analysis of the lessons learned during the development of ASAQ FDC. The development of ASAQ FDC was characterized by innovation in its development approach (with public and private partners), formulation development, partnership with a major pharmaceutical company, implementation strategy, Risk Management Plan, and choice of a regulatory strategy.

The document reviews the development of ASAQ FDC, and forms part of a broader reflection on DND*i*'s business model and the lessons learned over a decade since its creation in 2003.

1. www.dndi.org/ASAQreport

EUR 32.7 million: moving toward a more dynamic R&D portfolio while maintaining a robust Kinetoplastids disease pipeline

R&D EXPENDITURE BY DISEASE (2014-2015)



Overall R&D expenditures (EUR 32.7 M) increased by 18% (EUR 5.1 M) compared to 2014.
Percentage breakdown highlights of 2015 R&D expenditures per disease (screening and lead optimization expenditures are split and allocated towards disease expenditures)

• **Kinetoplastids diseases** remain at the heart of the portfolio with 77% of the expenses:

Human African trypanosomiasis (HAT)

With a total of EUR 8.7 M, HAT represents the most substantial R&D expenditure (31%). Investments increased due to the growth in clinical activities for fexinidazole (+EUR 1.6 M), with the Phase IIb/III clinical study and the two additional cohorts (for stage 1 & early stage 2 and for children) with 10 operational sites in the DRC plus the preparation of three new clinical trial sites. The SCYX-7158 project completed Phase I, with Phase II/III now being prepared (writing synopsis, getting scientific advice from EMA, meeting with CARSAC (Cameroon) to present and evaluate the protocol, and finally submission to the Ethics Committee in the DRC). More details on page 25, "Development".

Leishmaniasis

Overall expenditures remained stable between 2014 and 2015 at EUR 8.4 M. Some projects are entering into the portfolio or progressing, such as the preclinical work for VL with DNDI-0690 (+EUR 0.4 M), the CPG for CL project (+EUR 0.1 M), the preparation of clinical trial study for PKDL treatment (+EUR 0.1 M), the combination fexinidazole/miltefosine project, and the completion of the recruitment of 30 patients for the Miltefosine Allometric Study (+EUR 0.4 M). Other projects are completed, such as the preclinical package for VL-2098 (-EUR 0.7 M) and the VL Combo study in Asia (-EUR 0.2 M), or progressing in a different phase, like the VL India implementation (-EUR 0.2 M).

Chagas disease

Projects remained stable in 2015 (- EUR 0.2 M), accounting for a total of EUR 4.8 M (17%) of R&D expenditure. The screening and lead optimization work toward Chagas disease increased by EUR 0.7 M. The Chagas access projects (+EUR 0.2 M) are developing activities in Latin America and North America. The completion of the study of fexinidazole for Chagas and the closure of the E1224 project incurred a decrease of EUR 0.7 M. The biomarker project was put on hold due to safety issues at the end of 2015, which entailed a budget decrease of EUR 0.4 M.

• **Portfolio expansion:** The three new disease and exploratory areas represent 23%, compared to 17% in 2014. Their increase (+EUR 2.3 M, +55%) is the most significant of the DND*i* portfolio.

Filaria

Project expenditures increased by 66% (+EUR 1.2 M). Screening work is ongoing and increased (+EUR 0.2 M) as well as the preclinical activities (+EUR 0.3 M), with two new candidates (oxfendazole and TylAMac). The flubendazole project was however closed in early 2015 (-EUR 0.8 M). The main increase is related to the Phase I for emodepside (+EUR 1.5 M).

Paediatric HIV

Project expenditure increased by 108% (+EUR 1.1 M). The implementation study for a "4-in-1" product (+EUR 0.3 M) is developing with three countries and 9 sites involved in the project, and 49 patients recruited in January 2016. The clinical 'superbooster' study (ritonavir for super boosting LPV/r) in South Africa (+EUR 0.1 M) is ongoing with the purchase of equipment (+EUR 0.7 M) for the formulation development of the "4-in-1" with Cipla Ltd as an industrial partner to enable the production of treatments for the implementation study.

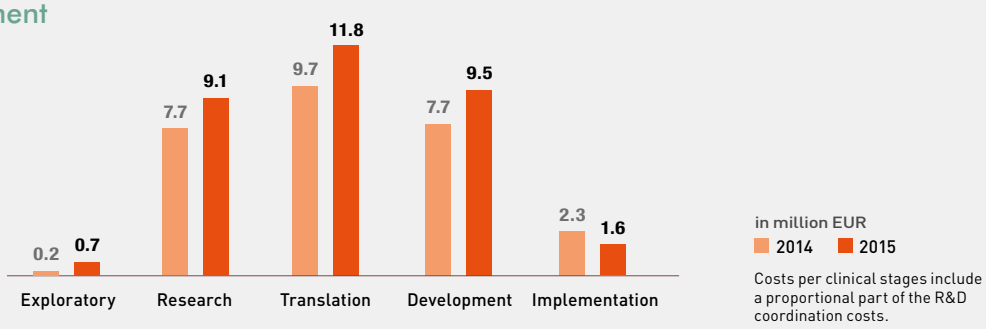
Malaria

Handover to MMV is complete (-EUR 0.5 M), however the ASAQ technology transfer was still ongoing in 2015.

Dynamic portfolio - Exploratory and feasibility studies

Based on the new business plan objectives, and as a part of the 'dynamic portfolio' concept, various feasibility studies were undertaken in 2015 to evaluate the possibility of adding new projects to the portfolio, including for hepatitis C, anti-infectives, and mycetoma (+EUR 0.5 M).

Development and translation increase with several new projects entering into pre-clinical stage or clinical development



Overall R&D expenditure increased by 18% between 2014 and 2015 to reach a total of EUR 32.7 M.

The most important fluctuation relates to growth of development projects (+23%), and the progress of translational projects including pre-clinical, Phase I, and Phase IIa/proof of concept (+22%). The R&D coordination & supervision costs (EUR 4.3 M) are included proportionally in the R&D expenditure per stage (+EUR 1.2 M).

Implementation

Projects costs decreased by 31% (-EUR 0.7 M) in 2015 compared to 2014.

With six projects in implementation (the first one entered in 2007), four projects are now terminated:

ASMQ for Malaria, NECT for HAT, and SSG&PM combination therapy for VL in Africa were finalized in 2014, with some expenses related to publication still ongoing (-EUR 0.4 M). The paediatric benznidazole for Chagas project was closed in 2015 (-EUR 0.1 M). The activity of New Treatments for VL in Asia is decreasing since the adoption of the treatment policy by the Indian Ministry of Health (-EUR 0.2 M).

Development

Projects costs increased by 23% (+EUR 1.8 M) in 2015 compared to 2014.

This progression is mainly due to the clinical activities for fexinidazole for HAT in the DRC. 88% of data concerning the 359 patients included in the fexinidazole Phase II/III clinical study have been cleaned. The complementary cohort trials, for stage 1 and early stage 2 in adults completed recruitment, with 230 patients and 95% of data cleaned. The clinical trial with children aged between 6 and 14 years completed recruitment, with 125 patients (last patient included mid-January 2016) and 95% of data cleaned. A total of 714 patients are thus included in the three clinical trials. Expenditures related to the HIV/VL co-infection and the new VL treatment in Latin America projects remain stable.

Translation

Expenditures increased by 22% (+EUR 2.1 M) in 2015 compared to 2014.

The three main drivers of this growth are the following:
- the paediatric HIV projects (+EUR 1.1 M), with development work including the bioequivalence CMC work, and equipment purchase with Cipla in order to select the best formulation for the "4-in-1";
- the filarial portfolio (+EUR 1.2 M), with the first-in-human Single Ascending Dose Study (SAD), the emodepside study, and the on-going evaluation - *via* pre-clinical activities - of opportunities from partners, including rifampicin, oxfendazole, and TylAMac;
- and the fexinidazole projects for Chagas disease: the Phase II study is on hold (-EUR 0.6 M), while the fexinidazole/miltefosine combination for VL in phase II is ongoing (+EUR 0.4 M).

Research

Screening and lead optimization expenditure increased by 18% (+EUR 1.4 M) in 2015 compared to 2014.

This was mainly due to more work on PK, chemistry, efficacy studies, API scale up, and exploratory toxicity studies (+EUR 0.9 M). In addition, three series were in late-stage lead optimization instead of the usual two series and candidate selection stage (DND*i*-0690; DND*i*-6148). The NTD Drug Booster project was also implemented during the entire year (+EUR 0.3 M) and a special effort was made for the Lead Optimization Latin America programme (LOLA), with an increase of chemist FTE from 1 to 4 during the last part of the year (+EUR 0.2 M). Screening and lead optimization efforts were entirely redirected towards leishmaniasis and Chagas disease.

Exploratory

In relation to the new business plan launched in 2015, exploratory activities were implemented for hepatitis C, mycetoma, and anti-infectives (+EUR 0.5 M).

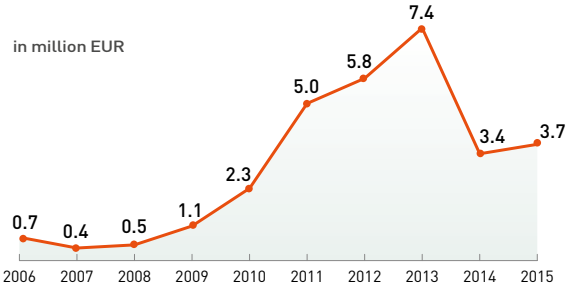
Leveraging partners' resources

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

The cumulated in-kind contribution over nine years amounts to EUR 30.3 M, reflecting DND*i*'s investment in building strong partnerships. The 11% increase in 2015 compared to 2014 (+EUR 0.3 M) is largely due to the support from several pharmaceutical companies towards the NTD Drug Discovery Booster experiment.

DND*i* has access to pharmaceutical libraries that will allow the development of innovative medicines with new chemical entities. The pharmaceutical companies provide compound libraries for screening and lead optimization at no cost. It is difficult for companies to value such contributions given the number of internal and external collaborators involved in this important effort and the existence of many indirect and intangible contributions.

To illustrate this contribution, the total number of compounds screened in 2012, 2013, 2014, and 2015 was consolidated and compared; it showed an increase of 76% between 2014 and 2015 with 300,000 compounds



screened (representing a total of more than 820,000 wells) in priority against visceral leishmaniasis and Chagas disease.

By the end of 2015, 34 partnership agreements had been signed between DND*i* and research companies (pharmaceutical and biotech companies), including access to compound libraries, pre-clinical activities, and industrial development.

STRENGTHENING EXISTING CAPACITIES

EXPANDING AND CONSOLIDATING CLINICAL RESEARCH CAPACITIES

In line with its vision and mission, DND*i* has worked closely with partners in disease-endemic countries to strengthen existing clinical research capacity and build new capacity where necessary.

The year 2015 has been a time for consolidation of the three existing platforms – LEAP, HAT Platform, and CCRP, which have been highly involved in clinical studies, treatment access, and personnel training – as well as of the recently created RedeLEISH network, which took off with a dense programme of activities mainly for R&D for cutaneous leishmaniasis.

DND*i* has always been committed to putting in place processes that, if successful, will ensure a wide-spread distribution of new treatments, and maintain competitive prices, such as by the development of non-patented products. The technological and scientific capacities of endemic countries have been reinforced, including through technology transfers, particularly of manufacturing processes, to industrial partners in endemic regions. The technology transfer of the antimalarial ASAQ – developed in partnership with Sanofi and others – to the Tanzanian drug company Zenufa, made significant progress in 2015. This required stability and bioequivalence studies, together with the preparation of the WHO prequalification and registration dossier to be submitted in 2016 which could ultimately result in the production of three to five million treatments per year for distribution in Africa.

Building strong R&D collaborations to answer the needs of filariasis patients

In 2015, DND*i*'s filariasis programme pursued its analysis of filariasis patients' needs. Clinical expert meetings held in May and October resulted in the definition of a Target Product Profile (TPP) of a new treatment for onchocerciasis, and the team visited research centres in Cameroon to assess possible sites for clinical studies. The team also attended two meetings of the African Programme for Onchocerciasis Control (APOC), its 40th Technical Consultative Committee in Burkina Faso (March) and the APOC closure meeting at its Joint Action Forum in Uganda (December).

Building strong R&D partnerships with disease experts is the first step towards answering patients' needs quickly and efficiently. To reach this common objective, DND*i* has started collaborations in 2015, notably with the Department of Public Health of the University Medical Center of Rotterdam, the Netherlands for an epidemiological modelling study on onchocerciasis and lymphatic filariasis; with CEA/LETI, France and the Research Foundation in Tropical Diseases and the Environment, Cameroon (REFOTDE), for an optical, non-invasive approach for clinical studies on drug effectiveness for onchocerciasis; with CEA/LETI, REFOTDE, the Institut de Recherche pour le Développement (IRD), France, and the National Natural History Museum, France for research on biomarkers and surrogate endpoints, and has regular interactions with key stakeholders in clinical research for filarial diseases.

MISSION OF THE PLATFORMS

- Define patients' needs, taking into consideration the local settings
- Bring together key regional actors in the disease field, namely representatives of ministries of health, national control programmes, regulatory authorities, academia, civil society groups, and pharmaceutical companies, as well as clinicians and health professionals
- Utilize, capitalize upon, and reinforce clinical capacities in endemic regions, and address infrastructural requirements where necessary
- Provide on-site training in clinical research in sometimes very remote settings
- Contribute to regulatory processes, uptake, and sustainable access of new treatments.

redeLEISH

FOUNDED: 2014 in Rio de Janeiro, Brazil

This network was built to give support and strengthen capacities for the implementation of clinical trials for the evaluation of new therapeutic tools for leishmaniasis, according to GCP, and to promote technical and scientific information sharing between participants. RedeLEISH also aims to promote consensus on research priorities and on harmonization of clinical trial design and methodology, and to promote discussion on the R&D challenges in leishmaniasis and on strategies to ensure the public health impact of the new treatment options developed.

Over 70 representatives from 38 institutions in 8 Latin American countries (Bolivia, Brazil, Colombia, Guatemala, Mexico, Peru, Panama, Venezuela).

2015 HIGHLIGHTS

- Originally created as a Brazilian network, redeLEISH included reference centres and experts from other Latin American countries.
- The second meeting was held in Medellin, Colombia with the collaboration of PECET (Programme for the Study and Control of Tropical Diseases/University of Antioquia), and Ruta N. 65 representatives from 35 institutions – namely PAHO, TDR/WHO, FIOCRUZ, and the Colombian and Brazilian MoHs – attended to identify the capacity of clinical research in Latin America. The agenda included discussions on the target product profile of a rapid diagnostic test for cutaneous leishmaniasis.
- A collaborative project for *Leishmania* species identification in three Brazilian States was implemented in 2015.

Second redeLEISH meeting in Medellin, Colombia.

Before starting the project, a GCP introduction training was given at Tomé-Açu Hospital and at Unidade Referência em Atenção Primária Dr Claudia Vitorino – Rio Branco

- The creation of a Web Forum, a virtual platform serving as a real space to share experiences in leishmaniasis R&D and access to treatments.

RedeLEISH is essential for the implementation of DND*i*'s strategy for cutaneous leishmaniasis (see p.28).

LEISHMANIASIS EAST AFRICA PLATFORM (LEAP)

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

Founded: **2003, Khartoum, Sudan**
Over 60 individual members, representing over 20 institutions

2015 HIGHLIGHTS

- 22nd LEAP meeting in Khartoum, Sudan in October 2015, with 68 participants, with 22nd LEAP principal investigators (PIs) meeting and 1st Project Advisory Committee (PAC) of the AfriCoLeish Project
- "New combination treatments for VL in Africa" and Fexinidazole studies completed.

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

Treatments & Access

LEAP facilitated and organized the Stakeholders and MoH dissemination meetings regarding the pharmacovigilance results of SSG&PM, in Nairobi and in Kampala (Nov.) and reviewed the national guidelines for VL diagnosis and management to clearly state that SSG&PM combination is the new first line treatment for primary VL patients in Eastern Africa.

Clinical trials

- **Miltefosine pharmacokinetic and safety in children with VL:** Completed recruitment, with 30 patients in August 2015 (21 in Kacheliba, Kenya and 9 in Amudat, Uganda). 2 DSMB meetings (July and Oct.)
- **HIV/VL treatment study:** 60 patients recruited by end of 2015 (32 in Gondar and 28 in Abdurafi, Ethiopia). The study is evaluating the efficacy of AmBisome®+miltefosine combination and of a higher-dose AmBisome® monotherapy. 2 DSMB meetings (April and May).

Capacity strengthening

LEAP organized trainings in Marsabit (with 22 attendees) and Turkana (14) counties, Kenya on the National Diagnosis and Management of VL Guidelines. Protocol specific, Good Clinical Practice (GCP), and GCLP courses were provided to **363 health staff of clinical sites**, in Gondar and Abdurafi (Ethiopia), Amudat (Uganda), and Kacheliba (Kenya). Data management events were attended by LEAP members: the 4th ADMIT Workshop organized by the Institute of Tropical Medicine (ITM) in Antwerp, Belgium (3), and the OpenClinica Global Conference 2015 in Amsterdam, Netherlands (6).

Communications

The fourth edition of the LEAP Newsletter was published in November 2015.

> "I am proud to be part of a team that gained new knowledge through training and participation in a clinical trial for the first time."
>
> **Martin Sunguti Kundu,**
> Lab. head, Kacheliba,
> West Pokot, Kenya

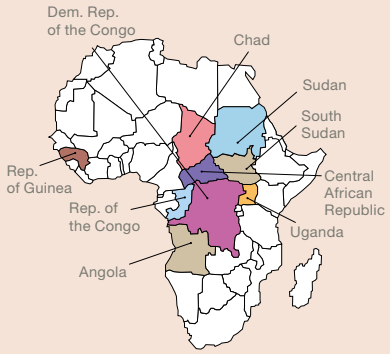
MEMBERS: Center for Clinical Research, Kenya Medical Research Institute (KEMRI), Kenya; Ministry of Health, Kenya; Institute of Endemic Diseases, University of Khartoum, Sudan; Federal Ministry of Health, Sudan; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Federal Bureau of Health, Ethiopia; Makerere University, Uganda; Ministry of Health, Uganda; Médecins Sans Frontières; IDA Foundation, The Netherlands; OneWorld Health (OWH/PATH), USA; AMC/KIT/Slotervaart Hospital, The Netherlands; London School of Hygiene & Tropical Medicine (LSHTM), UK.

HUMAN AFRICAN TRYPANOSOMIASIS (HAT) PLATFORM

Founded: **2005 in Kinshasa, Democratic Republic of the Congo**
Over 120 individual members, representing over 20 institutions

2015 HIGHLIGHTS

- Recruitment of patients to the fexinidazole Phase II/III study completed (394 patients)
- Participation in the 33rd International scientific council of research and control of trypanosomiasis in Ndjamena, Chad, with 53 attendees (Sept.)



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

Treatments & Access

In 2015, NECT improved therapy has been used as first-line treatment for stage 2 sleeping sickness in almost all *T. b. gambiense* detected patients. The platform attended the meeting of the Consultative Scientific Committee to the national control programme of DRC in Kinshasa, DRC (Sept.), where the DRC national HAT policy was reviewed and recommendations were issued. This could help other national programmes to revise and update their policies, particularly considering WHO's new target for elimination of the disease by 2020.

Clinical trials

- **Fexinidazole Phase II/III study:** Inclusion of all 394 patients completed in April. Two additional cohort studies have enrolled the following: 230 stage 1 and early stage 2 adult patients and 125 children aged 6-14 years (all stages). A total of 749 patients have been included.
- **SCYX-7158 Phase II/III study:** This single dose oral treatment will be tested in 210 stage 2 and around 150 stage 1 patients in DRC. Recruitment is planned to start in 2016. Three new clinical sites, N'gandajika, Bolobo, and Kwamouth (DRC), were selected and prepared in 2015.

Capacity strengthening

Training on Trypanosomiasis management was co-organized between Chad's national sleeping sickness control programme and the HAT Platform in Dinamadji district (Chad) with the support of DRC national control programme; 22 doctors and nurses attended (August). The platform also supported HAT clinical training in South Sudan, with 36 attendees (Nov). An investigators' meeting on fexinidazole trials was organized in Kinshasa, DRC, with 18 attendees (July).

Communications

The 16th edition of the HAT Platform newsletter was published in 2015.

> "The training in Good Clinical Practice and the site initiation of the clinical study help me on a daily basis to improve the way we take care of all patients."
>
> **Tawaba Say Watson,**
> Nurse head, Bagata,
> Kwilu province, RDC

MEMBERS: National sleeping sickness control programmes and national laboratories of public health of the most affected endemic countries: Angola, Central African Republic, Chad, Democratic Republic of the Congo, Guinea, Republic of Congo, South Sudan, Sudan, Uganda; Drugs for Neglected Diseases initiative (DND*i*), Switzerland; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Institute of Tropical Medicine – Antwerp, Belgium; Institut de Recherche pour le Development (IRD), France; 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; University of Juba, South Sudan; Institut Pasteur Bangui, CAR; Médecins Sans Frontières (MSF); Foundation for Innovative New Diagnostics (FIND), Switzerland; Eastern Africa Network for Trypanosomosis (EANETT), Centre interdisciplinaire de Bioéthique pour l'Afrique Francophone (CIBAF), INZI project, University of Edinburgh, UK; WHO Department of Neglected Tropical Diseases as observer.

CHAGAS CLINICAL RESEARCH PLATFORM (CCRP)

Countries highlighted on the map represent Chagas disease-endemic Latin American countries with platform members. Other CCRP members' countrie are listed below.

The CCRP brings together partners, experts, and stakeholders to provide support for the evaluation and development of new treatments for Chagas disease. This patient-centred platform aims to facilitate clinical research, provide a forum for technical discussions, develop a critical mass of expertise, and strengthen institutional research capacities. In addition, it identifies and reviews priority needs, works towards standardization of methodology to assess drug efficacy, and reviews alternatives for using current approved drugs (new schemes, doses, combination).

> **"Enabling discussions among researchers is an important tool for the improvement of efficiency, diagnosis, and treatment."**
>
> **Concepción Zúniga Valeriano,** Medical doctor, Head of CHAGAS-Honduras

Founded: **2009 in Uberaba, Brazil**
Over 90 institutions represented from 23 countries, bringing together over 300 people

2015 HIGHLIGHTS

- **Number of CCRP members grew by 23%; about 40% of new members come from non-endemic countries.**
- **The Annual Chagas Clinical Research Platform Meeting in Buenos Aires, Argentina (Aug.) in the context of the National Chagas Week, with 230 attendees (from 17 countries) from, among others, national programmes, patient associations, research and clinical care centres, NGOs, and pharmaceutical companies.**

Treatments & Access

In 2015, the Platform continued its engagement on access issues, namely with Global Chagas Coalition and Regional Initiatives meetings convened by PAHO and the national programmes, for instance at the Andean Countries Initiative meeting (Peru, Sept.) or at the Central America & Mexico Initiative meeting (Costa Rica, Nov.) CCRP also contributed to the Chagas Access Implementation Project on access to diagnosis and treatment, through pilot projects in Colombia (as of April); Mexico, USA, Brazil, and Gran Chaco will follow in 2016-17. The CCRP continued to strongly support the registration process for benznidazole in Mexico.

Clinical Trials

- The Phase II **New Benznidazole Regimens** study: protocol finalization and study design definition, consensus on the study read-outs, and quality systems.
- The Phase II **Fexinidazole** study in Bolivia to evaluate the treatment of adult patients with chronic Chagas disease: in 2015, the enrolled patients were monitored for 12 months post-treatment.
- The Phase I **Drug-drug interaction** study of fosravuconazole with benznidazole in Argentina was concluded: no clinically relevant PK, safety, or tolerability issues identified.

In addition, the CCRP worked towards integration of clinical trial results from different research groups and institutions, as well as harmonization of clinical trial designs in Chagas disease.

Capacity Strengthening

In 2015, 12 experts' and technical meetings were held in Mexico, Argentina, Bolivia, and Spain, namely a Target Product Profile workshop in Barcelona with 25 participants (March); the Experts' Meeting (NHEPACHA Network) in Barcelona & Buenos Aires; and the Latin-American Chagas Summit, organized by the National Programme in Mexico, with 235 attendees (July). The DND*i* Chagas Team also taught two courses to CCRP members: Introduction to Clinical Trials (Córdoba, Argentina) and Introductory Course on Research (Tarija, Bolivia).

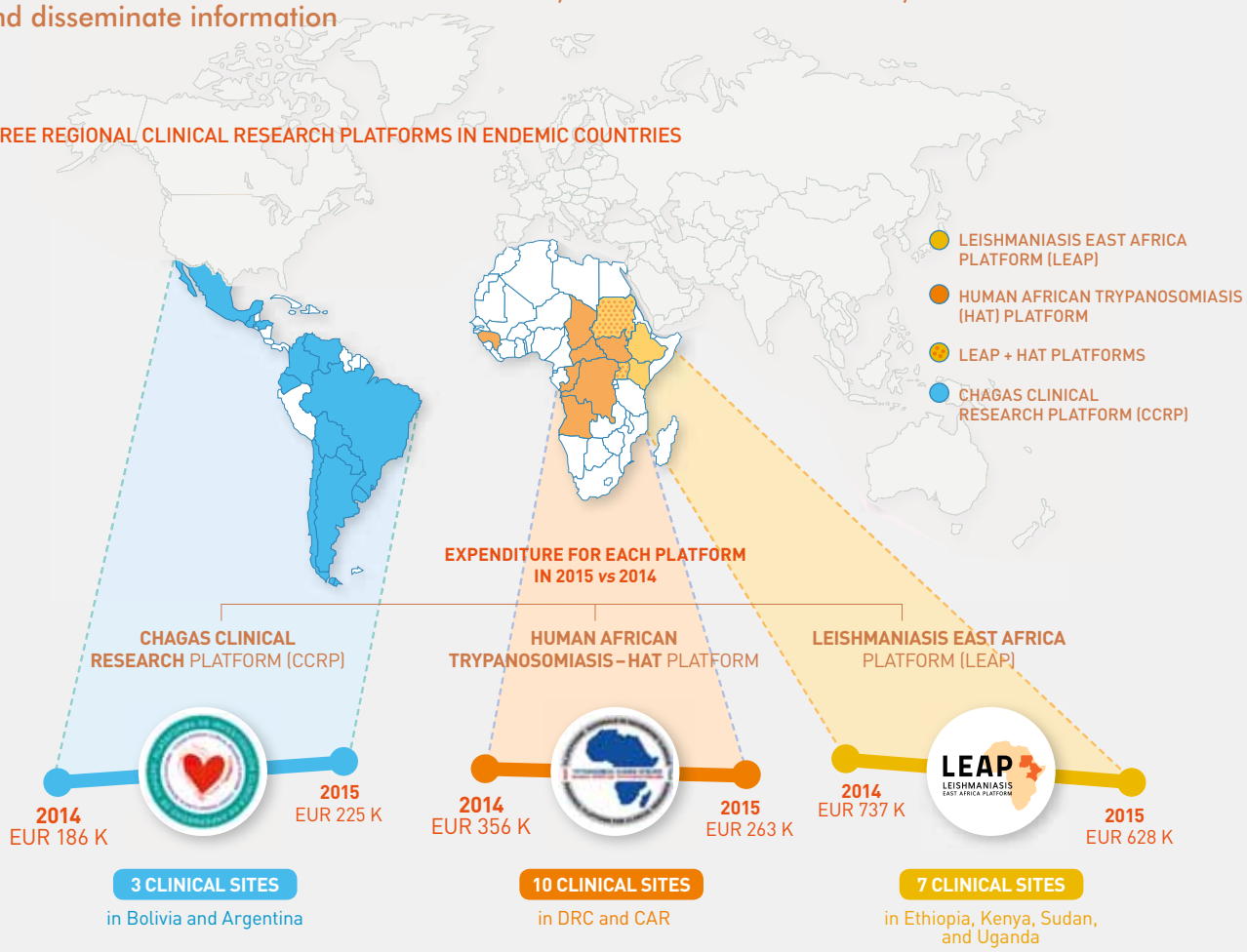
Communications

The fourth edition of the CCRP newsletter was published in July. The Web Forum has been actively used by CCRP members as an online workspace for discussion, sharing of information, and debate.

MEMBERS: Pan American Health Organization (PAHO); Department for the Control of Neglected Tropical Diseases (WHO); Ministries of Health and National Control Programmes of high-burden endemic countries (Argentina, Bolivia, Brazil, Colombia, Chile, Paraguay, Ecuador, Mexico, Honduras, Costa Rica, Guatemala); Global Chagas Coalition; NHEPACHA; Médecins Sans Frontières; International Federation of People Affected by Chagas Disease (FINDECHAGAS) and several patient associations **ARGENTINA:** Hospital de Niños Ricardo Gutiérrez; Instituto Nacional de Parasitología Dr. M. Fatala Chabén; Hospital Eva Perón; 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); INGEBI; Fundación Mundo Sano; ELEA; Grupo Hablamos de Chagas **BRAZIL:** Instituto Oswaldo Cruz; Instituto de Pesquisa Evandro Chagas – Fiocruz; Centro de Pesquisas René Rachou – Fiocruz; IFSC – Universidade de São Paulo; UNICAMP; Universidade federal de Ouro Preto; Universidade de Pernambuco; Faculdade de Medicina – Universidade Federal do Ceará; LAFEPE **BOLIVIA:** Universidad Mayor de San Simón; Platform of Integral Care for Patients with Chagas Disease; CEADES **SPAIN:** ISGlobal and Barcelona Centre for International Health Research (CRESIB); Hospital Clinic Barcelona; Hospital Vall d'Hebron; Instituto de Parasitología y Biomedicina López Neyra; Consejo Superior de Investigaciones Científicas; Instituto Catalán de la Salud; Instituto de Salud Tropical, Universidad de Navarra **MEXICO:** Instituto Carlos Slim de la Salud; Instituto Nacional de Salud Pública de México; UADY; UNAM **COLOMBIA:** CIMPAT; CIDEIM; PECET; Universidad de los Andes; Chagas Network **VENEZUELA:** Venezuelan Institute for Scientific Research; Central University of Venezuela; IDEA SWITZERLAND: Geneva University Hospitals **FRANCE:** Institut de Recherche pour le Développement **USA:** Sabin Vaccine Institute; Broad Institute of MIT; TULANE University; Baker Institute; The University of Texas at El Paso; UCLA; Merck **JAPAN:** Eisai Co. Ltd **GERMANY:** Bayer **UNITED KINDOM:** The Global Health Network **CANADA:** McMaster University; IRDC; EndoParagon **ITALY:** Centro per le Malattie Tropicali – Ospedale Sacro Cuore **OTHER:** Researchers from others Universities and media in endemic and non-endemic countries.

Stabilization of investment in regional disease-specific networks to build capacity, conduct clinical research in endemic countries, facilitate treatment access, and disseminate information

THREE REGIONAL CLINICAL RESEARCH PLATFORMS IN ENDEMIC COUNTRIES



The overall platform budgets decreased by 13% between 2014 and 2015 (from EUR 1'279 K in 2014 to EUR 1,115 K in 2015).

• **The Chagas** platform expenditure (CCRP) increased by 21% because 2015 was a year of transition characterized by a consolidation of the main clinical research groups, with a specific agenda for each one. Consequently, the number of trainings between 2014 and 2015 increased by 129%. In addition the number of members of the platform grew by 23% (~40% of new members come from non-endemic countries) and this has a direct impact on the cost of the annual platform meeting.

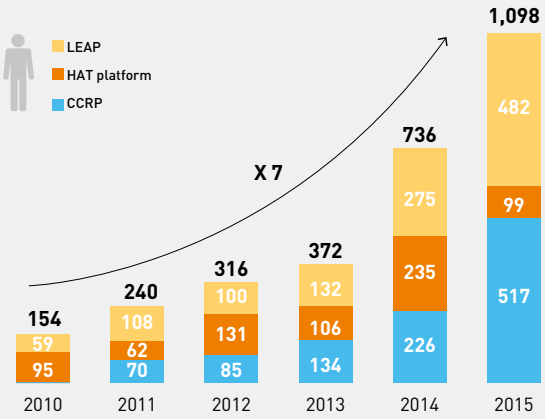
• **The HAT** platform expenditure decreased by 26% while the recruitment of the new coordinator was ongoing. Since mid-2015, with the arrival of the new coordinator of the HAT platform, the activities have fully resumed.

• **The Leishmaniasis East Africa** platform (LEAP) costs decreased by 15%, due to the fact that the LEAP meeting was not organized together with a scientific day meeting as in 2014. LEAP continues to maintain clinical trial sites (mainly the team) even though they were not involved in R&D activities in 2015. The costs of these sites (Kimalel clinical trial site of KEMRI in Kenya, Abdu Rafi in Ethiopia, Kassab and Dooka in Sudan) were removed from R&D expenditures and allocated toward the strengthening capacities budget. Patients treated outside clinical trials in 2015 in the seven VL clinical trial sites reached 1,363 (3,910 people screened).

People trained between 2014 and 2015 increased by almost 50%

DEVELOPING RESEARCH CAPACITIES IN ENDEMIC REGIONS

In six years, platforms have been able to multiply by 7 the number of people trained every year.



ADVOCACY, COMMUNICATIONS & FUNDRAISING

MEDICAL INNOVATION ON THE POLITICAL AGENDA LIKE NEVER BEFORE

The early 2000s saw a massive boost in the political prominence of health, and with it, the question of access to medicines and health financing. The Millennium Development Goals defined health as a priority intervention for reducing poverty. The Doha Declaration reaffirmed the right of countries to act when intellectual property acts as a barrier to public health. And financial commitments were ramped up through the creation of the Global Fund, following calls by Kofi Annan to establish "a war chest to fight the diseases of poverty".

Today, health has once more erupted into the political spotlight. The Sustainable Development Goals call for more efforts to "eradicate a wide range of diseases and address many different persistent and emerging health issues". The Ebola crisis of 2014 brought to the world's attention the lack of technologies to deal with potential pandemics. The threat of antibiotic resistance demonstrates how traditional incentive mechanisms fail to spur innovation to answer critical public health needs. And the price of new medications for cancer and hepatitis C in particular have raised questions about what constitutes a fair reward for research and development in countries across the globe.

Public leadership is essential

DND*i*'s collaborative model has shown at a small scale that alternative approaches to R&D that address pressing public health needs are possible. To fully address the scale of public health needs, public leadership is needed on a more fundamental level, to redefine the 'rules of the game' that govern biomedical innovation.

In 2015, in response to these and other concerns, DND*i* called on governments to act to address the core problems that need to be tackled:

- the lack of a global body to identifying R&D gaps and needs;
- the lack of global agreed priority setting;
- the lack of effective monitoring and coordination of R&D efforts;
- and the lack of globally agreed norms that guide R&D initiatives to ensure sharing of data and knowledge and the affordability of end products.

DND*i* has advocated that a series of progressive policy steps be taken to re-orient the global biomedical R&D system so that it responds to patient needs, neglected by our predominant reliance on commercial incentives to spur drug development. In particular, a political process should be launched to negotiate a binding global agreement on the financing, prioritization, and coordination of medical innovation, and on the norms required to enable the discovery, development, and delivery of and equitable access to innovations of public health importance. Norms should be developed that guide R&D actors and condition funding of research in order to ensure innovation with access.

DND*i*'S INNOVATIVE FUNDING MECHANISM AWARD TO RUTA N

Ruta N Medellín, an organization based in Medellin, Colombia, which focuses on knowledge as a primary source for research and development, was awarded DND*i*'s Innovative Funding Mechanism Award for its funding of DND*i*'s cutaneous leishmaniasis project Anfoleish (see page 32) for 2015-2016.

Carlos Castro and Elkin Echeverri (two first from the left), Ruta N, receiving DND*i*'s Award with Cecilia Castillo (centre), DND*i*, from Prof Marcel Tanner, Chairman of the Board.

A call in PLOS from 13 international health experts

In a 2015 call published in PLOS, DND*i*, together with a group of renowned global health experts, called for the creation of an R&D fund and mechanism. The proposal centred on the creation of a pooled fund that would complement existing funding mechanisms and secure long-term and sustainable financing primarily from governments but also other donors. It would be owned and overseen by governments with a strong link to an intergovernmental agency like the World Health Organization (WHO), but private and philanthropic actors and civil society would be involved as stakeholders. Existing multilateral funds such as the Global Fund, GAVI, or UNITAID, could serve as models. In addition to the fund, the proposal called for a mechanism that could act as an umbrella framework to cover all disease areas that suffer from chronic under-investment in R&D.

PLOS | MEDICINE

A Global Biomedical R&D Fund and Mechanism for Innovations of Public Health Importance

Demonstrating the impact of the DND*i* model as a part of the WHO CEWG process

In 2015, DND*i* also actively raised these messages in multiple policy processes now looking at questions of innovation and access. Foremost among these is a decade-long process at WHO on coordination and financing of R&D, known as the CEWG. It includes a recommendation for the establishment of a global agreement as the most appropriate way to underpin priority setting, coordination, and sustainable financing of affordable biomedical innovations of public health importance.

DND*i* has actively participated in this process, including with one of the "demonstration projects" chosen to show the effectiveness of alternative, innovative, and sustainable financing and coordination approaches. DND*i*'s proposal for a large-scale R&D project for leishmaniasis was thus awarded $2.3 million from a pilot pooled fund for health R&D hosted by WHO TDR in 2015.

ICMR AND DND*i* REINFORCING R&D COLLABORATION

DND*i* India | On the occasion of DND*i*'s Stakeholders' Event 'New R&D Pathways to Address Neglected Patients' Needs in the Indian Sub-Continent', the Indian Council of Medical Research (ICMR) and DND*i* signed a Memorandum of Understanding to reinforce the research and development technical collaboration in the field of neglected diseases and the patronage of the ICMR as a key institutional partner of DND*i*.

Dr Bernard Pécoul, Executive Director, DND*i*, Dr Suman Rijal, Head, DND*i* India, and Dr Soumya Swaminathan, Secretary, Department of Health Research and Director General, ICMR, New Delhi, October 2015 (from left to right)

The UN High-Level Panel to address policy incoherence

Beyond WHO, a High-Level Panel was formed at the UN to discuss "the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health". DND*i*'s submission drew lessons from our experience – which serves as a practical illustration of how R&D can be conducted in the public interest, if a de-linked approach is implemented, with R&D costs at a fraction of the traditional pharmaceutical business model.

In addition, global responses to pandemic diseases and antibiotic resistance are swiftly being established. While it is encouraging that so many multiple processes are looking at the issue of global health innovation, the response is currently highly fragmented. Governments need to "join the dots" between multiple frameworks and develop an overarching framework for all R&D actors and for all areas of public health importance.

Going forward, DND*i* will continue to engage with WHO, the G7, G20, and other UN processes, with a view to encouraging the taking of progressive steps towards this R&D framework, in order to ensure innovation with access.

ECTMIH 2015 and launch of new business plan: DND*i* more committed than ever to neglected patients

In September 2015, the DND*i* team attended the 9th European Congress on Tropical Medicine and International Health (ECTMIH) in Basel, Switzerland. ECTMIH brings together over 2,000 of the most distinguished scientists and experts in the field of tropical diseases. DND*i* organized five symposia on visceral leishmaniasis, open source drug discovery, helminth infections, sleeping sickness, and mycetoma, as well as participating in seven other symposia. DND*i*'s Executive Director, Dr Bernard Pécoul, also participated in the Roundtable 'Challenges in Global health' at the plenary closing session.

On the margins of the conference, DND*i* also organized a public event to unveil its new business plan for 2015-2023, to develop 16-18 treatments for neglected patients in need of safe, effective, affordable, and accessible medicines.

Attending DND*i*'s new Business plan launch: Dr David Reddy, MMV, and Dr Robert Sebbag, Sanofi (top left); Dr Alwyn Gladwyn Zebron Mwinga, Zambia AIDS-Related Tuberculosis Project and patient representative at DND*i*' Board of Directors (top right) ; Dr Susanna Hausmann Muela, Swiss Agency for Development and Cooperation (bottom left); Dr Guy Morin, Mayor of Basel, and Dr Nkandu Luo, Gender Minister, Zambia (bottom right).

SELECTED SCIENTIFIC ARTICLES AND PRESS COVERAGE

Special Issue: Novel therapeutic approaches for neglected infectious diseases
Editorial: *Novel Therapeutic Approaches for Neglected Infectious Diseases* by Martin-Plaza J and Chatelain E. *Journal of Biomolecular Screening*, January 2015

Novel 3-nitrotriazole-based amides and carbinols as bifunctional antichagasic agents by Papadopoulou MV, Bloomer WD, Lepesheva GI, Rosenzweig HS, Kaiser M, Aguilera-Venegas B, Wilkinson SR, Chatelain E, Ioset JR. *Journal of Medicinal Chemistry*, January 2015

Repurposing of the Open Access Malaria Box for kinetoplastid diseases identifies novel active scaffolds against trypanosomatids by Kaiser M, Maes L, Tadoori LP, Spangenberg T, Ioset JR. *Journal of Biomolecular Screening*, February 2015

How can we end paediatric HIV? by Celletti F, Cohen J, Connor C, Lallemant M, Lee J. *The Lancet HIV*, March 2015

Enantiomers of nifurtimox do not exhibit stereoselective anti-*T. cruzi* activity, toxicity or pharmacokinetic properties by Moraes CB, White KL, Braillard S, Perez C, Goo J, Gaspar L, Shackleford DM, Cordeiro-da-Silva A, Thompson RC, Freitas-Junior L, Charman SA, Chatelain E. *Antimicrobial Agents Chemotherapy*, April 2015

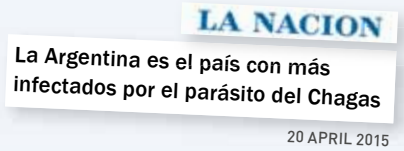
Infectious diseases: Overcoming neglect of kinetoplastid diseases by Bilbe G. *Science*, May 2015

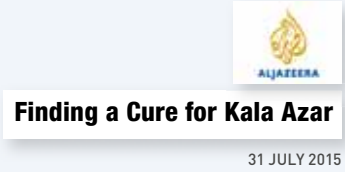
Translational challenges of animal models in Chagas disease drug development: A review by Chatelain E and Konar N. *Drug Design, Development and Therapy*, August 2015

Development and validation of a novel *Leishmania donovani* screening cascade for high-throughput screening using a novel axenic assay with high predictivity of leishmanicidal intracellular activity by Nühs A, De Rycker M, Manthri S, Comer E, Scherer CA, Schreiber SL, Ioset JR, Gray DW. *PLOS Neglected Tropical Diseases*, September 2015

Hit and lead criteria in drug discovery for infectious diseases of the developing world by Katsuno K, Burrows JN, Duncan K, Hooft van Huijsduijnen R, Kaneko T, Kita K, Mowbray CE, Schmatz D, Warner P, and Slingsby BT. *Nature Reviews Drug Discovery*, October 2015

Novel amino-pyrazole ureas with potent *in vitro* and *in vivo* antileishmanial activity by Mowbray C, Braillard S, Speed W, Glossop P, Whitlock G, Gibson K, Mills J, Brown A, Gardner JM, Cao Y, Hua W, Morgans G, Feijens P-B, Matheeussen A, Maes L. *Journal of Medicinal Chemistry*, November 2015





EUR 30 million secured in 2015

Since its inception in 2003, DND*i* has secured EUR 395 million from loyal supporters and a growing network of new funders. As DND*i* expands its R&D activities during its second decade, it is worth noting that a committed group of funders have provided significant long-term contributions to DND*i*. The Bill & Melinda Gates Foundation (BMGF), UK Department for International Development (DFID), Médecins Sans Frontières (MSF), and the Dutch Ministry of Foreign Affairs (DGIS) account for approximately 73% of overall funds awarded since 2003 (see chart p. 67). Unrestricted and portfolio funding also remains highly important as it provides the necessary flexibility to easily react to opportunities or inherent attrition in our R&D activities. In an effort to maintain a sustainable funding pipeline, DND*i* continues to make efforts to secure unrestricted and portfolio funding – representing 81% of DND*i*'s funding resources.

Innovative funding mechanisms continue to play an important role in DND*i*'s funding strategy. The Global Health Innovation Technology (GHIT) Fund, a public-private partnership involving the Government of Japan, leading life science companies, the Bill & Melinda Gates Foundation, the Wellcome Trust, and UNDP, played an important role in supporting DND*i*'s leishmaniasis and Chagas disease early discovery activities for an amount of ¥482 million in 2015. The most notable example of its success is the funding of the Japanese portion of the Neglected Tropical Diseases Drug Discovery Booster consortium (see p. 21).

DND*i* Japan

Resulting from a process that began over a decade ago to ensure that R&D for public health needs of developing countries are prioritized, the creation by WHO Members States of a pilot pooled funding mechanism hosted by WHO-TDR to foster innovation for neglected diseases provided EUR 2.3 million to DND*i*'s Leishmaniasis Global R&D & Access initiative. This project is based on new R&D incentives and mechanisms following the core principles identified by the WHO Consultative Expert Working Group (CEWG) that includes affordability, effectiveness, efficiency, and equity.

DND*i* Latin America

Lastly, Brazil's National Development Bank (Banco Nacional de Desenvolvimento Econômico e Social – BNDES) granted R$ 3.5 million over three years in support of DND*i* Latin America's lead optimization project for the Chagas and leishmaniasis clinical research platforms, where 10% would be complemented by Fiocruz – one of DND*i*'s founding partners.

DND*i* North America

DND*i* also continues to make investments in its private fundraising programme. In 2015, DND*i* received renewed contributions and attracted new support from private grant-making institutions and individuals worldwide. In the United States alone, DND*i* has significantly diversified its funding portfolio and has attracted support from key geographic areas, mainly in the New York, Philadelphia, and Silicon Valley regions.

As DND*i* initiates activities in line with the new dynamic portfolio strategy and the 2015-2023 Business Plan, new challenges remain ahead for DND*i* in terms of funding its R&D portfolio and new disease areas. To reach its goal of delivering 16-18 treatments by 2023, DND*i* needs to secure an additional EUR 255 million for an investment total of EUR 650 million. Maintaining the support of committed funders will be important in helping DND*i* reach its funding goal. It will be just as important to secure new support from additional governments and private entities in order to diversify the funding portfolio and thus solidify the sustainability of DND*i*'s R&D programmes.

KEY CONTRIBUTIONS RECEIVED IN 2015

Dutch Ministry of Foreign Affairs (DGIS), The Netherlands (2015–2020)
The Directorate-General for International Cooperation provided portfolio funding support of EUR 16 million over 5 years for mycetoma, sleeping sickness, leishmaniasis, Chagas disease, and early discovery activities.

Department for International Development (DFID), UK (2015)
DFID provided supplemental funding of GBP 3 million for the year 2015 to support Chagas disease, VL & CL, sleeping sickness, discovery activities and attend scientific conferences to present DND*i*'s NTD research. DFID's total contribution to date is GBP 64.4M.

WHO-TDR Pool Funding (2015–2016)
WHO-TDR awarded DND*i* EUR 2.34 million in support of a large-scale R&D project for leishmaniasis. The 'Leishmaniasis Global R&D and Access Initiative' project is based on the principle of de-linkage, which dissociates the cost of R&D from the price of the resulting products.

French Development Agency (AFD), France (2015–2018)
AFD and DND*i* signed a partnership agreement of EUR 2 million for the development of a new, safe, and effective oral treatment to support efforts to control leishmaniasis in East Africa (Sudan, Ethiopia, Kenya, and Uganda).

Global Health Innovation Technology Fund, Japan (2015–2017)
The GHIT Fund invested EUR 3.2 million in a partnership between Takeda Pharmaceutical Company and DND*i* for the development of a new drug for visceral leishmaniasis based on a promising new series of aminopyrazoles. GHIT also awarded EUR 550K to DND*i* and three Japanese pharmaceutical companies in support of the NTD Drug Discovery Booster.

Banco Nacional de Desenvolvimento Econômico e Social (BNDES), Brazil (2015–2017)
BNDES supported a partnership between DND*i* and Fundação Oswaldo Cruz (Fiocruz) with a grant of R$ 3.5 million for local efforts in Brazil, mainly around lead optimization and capacity strengthening for leishmaniasis and Chagas disease.

DGIS: A LONG-TERM SUPPORTER OF DND*i*

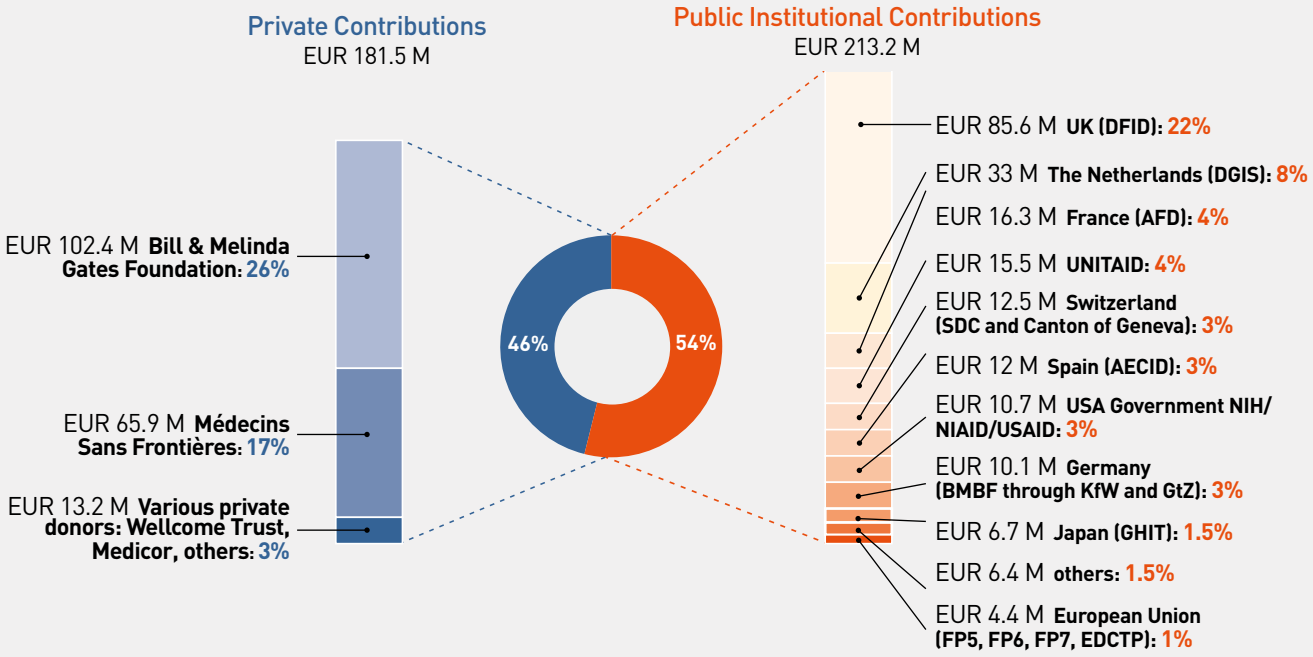
DND*i* has a robust and longstanding partnership with the Dutch Ministry of Foreign Affairs (DGIS) and the Government of the Netherlands. In the past decade, Dutch funding of nearly EUR 33 million provided in 2006, 2011, and 2015 has supported multiple projects related to malaria, sleeping sickness, leishmaniasis, Chagas disease, early discovery, and most recently mycetoma. The funding provided has contributed to the development of new medicines for children and adults suffering from neglected tropical diseases as well as the progression of new chemical entities towards clinical development and ultimately support of elimination programmes.

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

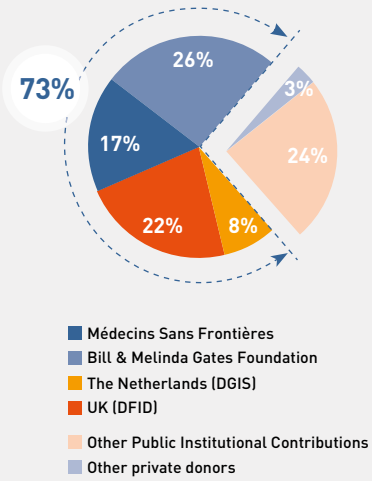
To develop its activities and meet its objectives, DND*i* seeks diversified sources of funding from public and private sources, which include financial contributions from governments, public institutions, private individuals, foundations, founding partners, and innovative funding mechanisms. The diversification of donors increased in 2015 with three new donors. DND*i* welcomed WHO-TDR, the Ministry of Health of Brazil, and Kalacore, all public sources of financing, and one from an endemic country.

Concerted efforts were made to ensure that no one donor contributes more than around 25% towards 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 2014, public funding (projected to 2019) was at 51%, with private support at 49%. In 2015, with secured funds until 2020, the split remains balanced with public funding at 54% and 46% for private support. This is mainly due to the fact that most (EUR 30.2 M, 98%) of the new funding granted in 2015 for the period 2015-2020 are contributions from public institutions, including the UK (DFID), WHO-TDR, France (AFD), Japan (GHIT), Brazil (BNDS), Germany (KfW), and the Netherlands (DGIS).



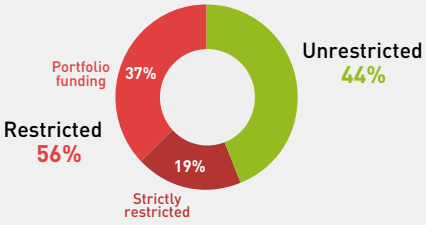
FOUR MAIN FUNDERS BETWEEN 2003-2020 CUMULATE 73% OF THE FUNDS COMMITTED TO DND*i*



A successful shift toward unrestricted funding

Over the last five years, DND*i* managed to maintain a balance between restricted and unrestricted grants. While the ratio is relatively balanced, this requires substantial effort. Unrestricted funding has been part of DND*i*'s success to date as it allows 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 2015, DND*i* continued to receive significant portfolio funding (EUR 21.2 M, 69%) from various donors including the Netherlands (DGIS), France (AFD), WHO-TDR, and Brazil (BNDS). This allows a certain degree of risk mitigation within restricted grants, as it supports three diseases and various projects within each disease. Portfolio grants accounted for 18% of total income in 2011, 22% in 2012, 29% in 2013, 33% in 2014, and 37% in 2015.

CUMULATED 2003-2020: EUR 394.7 MILLION



FINANCIAL REPORT

2015 FINANCIAL STATEMENTS AND AUDIT REPORT

Financial Report

2015 Financial statements and audit report

BALANCE SHEET

AT 31 DECEMBER 2015 (with 2014 comparative figures)

(Expressed in EUR)	Notes	2015	2014
CURRENT ASSETS			
Cash and cash equivalents:			
Cash and banks at head office		11,219,157	13,138,390
Cash and banks at regional offices and affiliate		603,453	775,596
Time deposits		12,762,861	18,885,961
Total cash and cash equivalents		24,585,471	**32,799,947**
Stocks of drugs	3	156,537	**173,164**
Current accounts and receivables:			
Advances to officers and liaison offices		76,672	88,625
Receivables from public institutional donors		1,798,808	1,434,538
Other receivables		692,398	880,820
Prepaid expenses		609,580	595,381
Total current accounts and receivables		3,177,458	**2,999,364**
TOTAL CURRENT ASSETS		**27,919,466**	**35,972,475**
NON-CURRENT ASSETS			
Tangible fixed assets, net	4	261,722	69,806
Bank guarantee deposits	12	229,500	89,483
Total non-current assets	2.k.	491,222	**159,289**
TOTAL		**28,410,688**	**36,131,764**
CURRENT LIABILITIES			
Payables		3,238,685	2,433,459
Accrued expenses		1,563,337	1,991,183
Deferred income	7	12,639,386	20,955,657
Provisions	5	331,251	233,442
Total current liabilities		17,772,659	**25,613,741**
CAPITAL OF THE ORGANIZATION			
Paid-in capital		32,510	32,510
Restricted operating funds	6	53,364	114,547
Unrestricted operating funds		10,552,155	10,370,966
Total capital of the organization		10,638,029	**10,518,023**
TOTAL		**28,410,688**	**36,131,764**

STATEMENT OF OPERATIONS

FOR THE YEAR ENDED 31 DECEMBER 2015 (with 2014 comparative figures)

(Expressed in EUR)	Notes	2015	2014
INCOME			
Public institutional funding:			
Govern. & public int. organiz. unrestricted		13,589,613	13,460,530
Govern. & public int. organiz. restricted		11,745,627	10,396,427
Total public institutional funding		25,335,240	**23,856,957**
Private resources:			
Private foundations, corp. and individuals, unrestricted		286,879	215,633
Private foundations, corp. and individuals, restricted		13,572,650	8,383,666
Royalties on drug sales	6	304	5,762
Total private resources		13,859,833	**8,605,061**
Resources from founders:			
Médecins Sans Frontières, unrestricted		4,000,000	4,000,000
Médecins Sans Frontières, restricted		14,944	19,102
Total resources from Founding Partners		4,014,944,0	**4,019,102**
Other income:			
Sundry income & reimbursements		73,328	74,352
Other income net		73,328	**74,352**
TOTAL INCOME	7	**43,283,345**	**36,555,473**
SOCIAL MISSION EXPENDITURE			
Research & development expenditure:	8		
Research & development coordination and supervision		4,320,562	3,109,458
Human African trypanosomiasis projects		8,723,041	7,137,019
Leishmaniasis projects		4,380,683	4,398,588
Chagas disease projects		1,872,551	2,803,540
Filarial diseases projects		3,025,486	1,821,335
Paediatric HIV projects		2,240,641	1,078,126
Other diseases projects (malaria, HCV, mycetoma, and anti-infective)		1,196,696	1,271,557
Lead optimization & Portfolio building		6,948,617	6,026,487
Total research & development expenditure		32,708,277	**27,646,111**
Strengthening capacities	9	2,754,649	**2,574,948**
Advocacy expenses	10	2,265,997	**1,653,489**
TOTAL SOCIAL MISSION EXPENDITURE		**37,728,923**	**31,874,548**
NON-SOCIAL MISSION EXPENDITURE			
Fundraising	10	2,035,629	1,579,783
General and administration	10	3,238,280	2,942,777
Total non-social mission expenditure		5,273,909	**4,522,560**
TOTAL EXPENDITURE		**43,002,832**	**36,397,108**
Operating surplus		280,513	158,365
OTHER INCOME (EXPENSES)			
Financial income, net		**21,862**	10,290
Exchange gain (loss), net	1.i	(182,369)	(103,065)
TOTAL OTHER INCOME (EXPENSES)		**(160,507)**	**(92,776)**
Net surplus for the year prior to allocations		120,006	65,589
Release from restricted operating funds	6.a-6.b	61,183	45,299
Allocation to unrestricted operating funds		(181,189)	(110,888)
NET SURPLUS FOR THE YEAR AFTER ALLOCATIONS			**-**

FUNDS FLOW STATEMENT

FOR THE YEAR ENDED 31 DECEMBER 2015 (with 2014 comparative figures)

(Expressed in EUR)	**2015**	2014
FUNDS FLOW FROM OPERATIONS		
Net surplus for the year, unrestricted	181,189	110,888
Net allocations for the year, restricted	(61,183)	-45,299
Depreciation of fixed assets	114,824	53,368
Increase (decrease) in provisions	97,809	96,883
(Increase) decrease in stocks	16,627	16,250
(Increase) decrease in advances	11,953	-15,426
(Increase) decrease in receivables from donors	(364,270)	-1,182,411
(Increase) decrease in Founders and other receivables	188,423	489,771
(Increase) decrease in prepaid expenses	(14,199)	-166,082
Increase (decrease) in payables	805,226	93,764
Increase (decrease) in accrued expenses	(427,846)	676,892
Increase (decrease) in deferred income	(8,316,270)	10,751,691
Funds flow (used in) from operations	(7,767,718)	**10,880,289**
FUNDS FLOW FROM INVESTING ACTIVITIES		
(Increase) decrease of investments in tangible fixed assets	(306,741)	-74,795
(Increase) decrease in bank guarantee deposits	(140,017)	-15,324
Funds flow from investing activities	(446,758)	-90,119
FUNDS FLOW FROM FINANCING ACTIVITIES		
Cash increase (decrease)	(8,214,475)	10,790,170
Cash and cash equivalents – beginning of year	32,799,946	22,009,776
Cash and cash equivalents – end of year	24,585,471	**32,799,946**

STATEMENT OF CHANGES IN CAPITAL

FOR THE YEAR ENDED 31 DECEMBER 2015 (with 2014 comparative figures)

Internally generated funds *(Expressed in EUR)*	Opening balance	Allocation	Internal fund transfers	Closing balance
FUNDS FLOW FROM OPERATIONS				
Paid-in capital	32,510	-	-	32,510
Surplus for the year	-	120,006	(120,006)	-
Restricted operating funds	114,547	-	(61,183)	53,365
Unrestricted operating funds	10,370,966	-	181,189	10,552,155
Capital of the organization	10,518,023	120,006	-	10,638,029

NOTES TO THE FINANCIAL STATEMENT

FOR THE YEAR ENDED 31 DECEMBER 2015

1 GENERAL INFORMATION

a) Legal aspects

The Drugs for Neglected Diseases *initiative* (DND*i*) is a Swiss foundation registered in Geneva under statutes dated 17 July 2003 as a not-for-profit legal entity, with its headquarters in Geneva. DND*i* is monitored by the Swiss Federal Supervisory Board for Foundations, and was granted 'Other International Organisation' status in 2011. DND*i* is compliant with Swiss law and with Swiss GAAP FER.

The annual average number of full-time positions in the reporting year, as well as in the previous year, did not exceed 250.

DND*i* aims to, as per the Charter:

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 governed by the Board of Directors, with the Scientific Advisory Committee, Audit Committee, and Executive Board Committee providing key scientific and management guidance for decision making. The DND*i* Executive Team implements the R&D strategy, manages the global portfolio, allocates resources, raises funds, and advocates.

The DND*i* Executive Team is led by the Executive Director and includes the R&D Director, the Operations Director, and the Fundraising, Advocacy and Communication Director.

The Strategic Committee, in addition to the Executive Team members, includes the Finance and Planning Director, the Business & Legal Development Director, the Medical Director, the Discovery & PreClinical Director, and the Directors of Regional Offices.

b) Income tax

An agreement was signed with the Swiss Federal Council under provisions of the promulgated Swiss Host State Act, to grant DND*i* certain privileges effective as of 1 January 2011 for an indeterminate period. The principal advantages for DND*i* as a Swiss foundation with 'Other International Organisation' status are:

- Exoneration from all indirect federal, cantonal, and communal taxes
- Exoneration from VAT on all goods and services acquired for the sole use of the foundation within Switzerland and abroad
- Unrestricted access to work permits for non-Swiss, non-EU nationals

DND*i* is exonerated from income tax from the Swiss federal income tax and from the Geneva cantonal and communal taxes for a ten-year period granted in September 2008 until 2018.

c) Situation of Regional Offices

DND*i* has seven Regional Offices (RO) that help identify patients' needs, support Heads of Disease Programmes, identify and support regional partners, and undertake regional advocacy work for DND*i*. Their strategic role is defined in DND*i*'s Business Plan. Their operational contributions are defined in the context of the yearly Action Plan and budget approved by the Board of Directors of DND*i*.

From an operational perspective, the ROs can be characterized either as a Regional office, a Liaison Office, or a Project Support Office depending on the purpose of their mission.

From a legal standpoint, DND*i* can establish the RO as a simple office (e.g. branch, representation, or Liaison Office) of the DND*i* Foundation or as an independent legal entity, depending on needs, local regulations, and requirements. Establishment of a DND*i* RO outside Switzerland requires the authorization of the Board of Directors. Such ROs are set up according to the DND*i* vision and mission, and model (in particular as a Not-for-Profit organization). DND*i* is compliant with all local laws and regulations, where it operates.

RO accounting is fully incorporated into DND*i* accounts, following the method of full integration (i.e. all income and expenditures are incorporated into DND*i* financial statements).

The chart below gives an overview of the relationships established between DND*i* Geneva and the different Regional Offices:

As of December 2015, DND*i* has established branches in Kenya (2006), Brazil (2008), India (2009), and in Penang, Malaysia. Additionally, DND*i* has one Project Support Office in the Democratic Republic of Congo (2006).

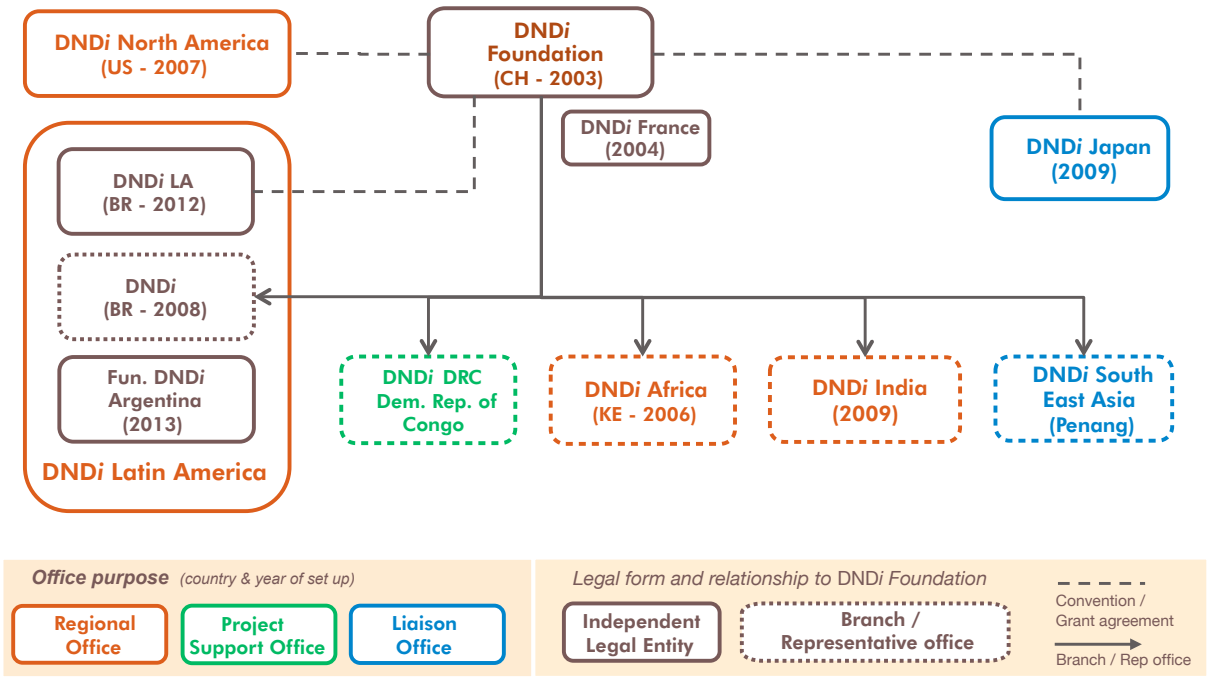
In June 2009, the Board approved the creation of a liaison office in Japan, under the form of a 'specified non-profit organization', a legal entity registered with the city of Tokyo. DND*i* Japan was established in November 2009.

Drugs for Neglected Diseases *initiative* North America, Inc., (DND*i* NA), 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, 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.

In June 2009, the Board approved the creation of a new legal entity in Brazil, in addition to the branch in the form of an 'Organização da Sociedade Civil de Interesse Público', DND*i* Latin America. The process was completed in October 2012. Since 2012 accounts were audited by an external auditor and by Deloitte Touche Tohmatsu as from 2014 accounts.

In 2013, DND*i* decided to setup a new legal entity in Argentina with the initial purpose of addressing regional fundraising needs.

DND*i* legal framework



This entity was named Fundacion DND*i* Argentina "*Iniciativa* medicamentos para enfermidades olvidadas" with a legal status to operate in Argentina under AFIP and IGJ regulations.

In addition, a legal entity was set up in France in September 2004 in the form of a not-for-profit association.

2 SIGNIFICANT ACCOUNTING POLICIES

a) Statement of compliance

The financial statements have been prepared in accordance with the statutes and by-laws of DND*i*, the applicable provisions of the Swiss Code of Obligations and 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.

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

b) Scope of the financial statements

The scope of the financial statements of DND*i* includes all the offices presented under 1.c) above, which are controlled by DND*i*. Some are separate legal entities.

These financial statements present all activities of the Foundation and the controlled offices.

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 recognised in the statement of operations.

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

	2015	2014
USD	0.9152	0.8226
CHF	0.9245	0.8315
GBP	1.3563	1.2804
100 CDF	0.1017	0.0915
100 INR	1.3867	1.2971
100 KES	0.8967	0.9146
100 JPY	0.7604	0.6875
100 BRL	23.1027	31.0965

f) Income

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

Unrestricted public and private institutional donations based on annual or multi-year agreements are recorded on an accrual basis over the life of the agreement. A reconciliation between donations committed to DND*i* and income recognized in the statement of operation is shown in table 7.b. 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*, 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 policy. Thereafter, funds are allocated to the partner(s) in charge of the project.

Partners' expenditures are recorded:

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

b) If financial reports are unavailable as per the deadline of the 15 March of the following year, an estimated amount is calculated on a pro rata temporis basis, based on the time between the contract signing date and 31 December. This estimated amount is considered as an accrued expense following Swiss GAAP FER to be regularised in the following year. The unpaid portion remaining at year-end is included under current liabilities.

h) Expenditures incurred for projects and activities

The annual action plan and budget as well as the revised budgets are approved by the Board.

They include funding for projects subcontracted to partners (see point g) and current expenditures required (mainly via vendors) to achieve the objectives of the 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, market risk, and liquidity 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. Any form of speculation is prohibited.

The main financial risk for DND*i* is the volatility of foreign exchange rates that can affect the value of its holding in various currencies (USD, EUR, GBP, and CHF). DND*i* is exposed to currency risk on donations received, projects expenditure and general and administrative expenses that are denominated in a currency other than the functional currency (EUR). These transactions are mainly denominated in EUR, CHF, USD, GBP, BRL, KES, INR, JPY, and AUD.

DND*i* ensures that its net exposure is kept to an acceptable level by buying or selling foreign currencies at spot rates when necessary to address short-term imbalances. The diversity of fundraising currencies represents a 'natural hedging' mechanism (income in BRL, CHF, EUR, GBP, JPY, and USD).

j) Tangible fixed assets

Tangible fixed assets are stated at cost in EUR 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) 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.

l) 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.

m) 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.

n) 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 and in line with DND*i*'s mission and objectives.

Partners' voluntary involvement in joint projects and activities, in particular if the partner does not aim to achieve DND*i*'s project objectives, are not considered as gifts-in-kind. For goods or services paid at prices below market prices, the difference between real payment and current market price is not considered as a gift-in-kind.

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 STOCKS OF DRUGS

In 2015, DND*i* purchased vials of SSG, lipossomal amphotericin B (Ambisome®), paromomycin, and caps of miltefosine 10mg and 50mg at an estimated value of EUR 154,357 from various partners (MSF Logistique, MSF supply, IDA Foundation), for use in the routine VL patient management and on-going VL clinical trials (HIV/VL co-infection study and Miltefosine Allometric Study). Stocks of SSG, AmBisome®, miltefosine, and paromomycin at an estimated value of EUR 156,537 are stored at clinical trial sites in Ethiopia, Kenya, Sudan, and Uganda.The stock held in India in 2014 was donated to the Indian Ministry of Health in 2015.

2014	Quantity Vials			Quantity Caps		
Countries / drugs	SSG [1]	AmBisome® [2]	Paromomycin	Miltefosine 50mg	Miltefosine 10mg	**Total in EUR**
India		2,895	13,050	15,894	38,022	107,496
Ethiopia	500	1,839	3,000	2,300	-	34,546
Kenya	1,070	128	4,060	-	-	13,342
Sudan	1,000	160	930	-	-	10,170
Uganda	650	140	1,100	-	-	7,610
Total vials/caps	3,220	5,162,00	22,140	18,194	38,022	
Total in EUR	**22,540**	**72,268**	**22,140**	**18,194**	**38,022**	**173,164**

(1) SSG Cost per vial = EUR 7; (2) AmBisome® Cost per vial = EUR 14; paromomycin & miltefosine are valued at EUR 1 per unit

2015	Quantity Vials			Quantity Caps		
Countries / drugs	SSG [1]	AmBisome® [2]	Paromomycin	Miltefosine 50mg	Miltefosine 10mg	**Total in EUR**
India		-	-	-	-	-
Ethiopia	4,367	555	2,150	-	-	38,342
Kenya	4,769	1,726	4,620	3,150	3,822	71,274
Sudan	1,825	835	2,105	-	-	28,085
Uganda	800	541	700	840	2,758	18,836
Total vials/caps	11,761	3,657	9,575	3,990	6,580	-
Total in EUR	**70,566**	**65,826**	**9,575**	**3,990**	**6,580**	**156,537**

(1) SSG Cost per vial = EUR 6; (2) AmBisome® Cost per vial = EUR 18; paromomycin & miltefosine are valued at EUR 1 per unit

4 TANGIBLE FIXED ASSETS, NET

(Expressed in EUR)	Computer Equipment	Office fittings & Installations	Office Equipment	**Total**
Net carrying amounts 1.1.2014	46,854	1,524	1	48,379
Gross values of cost				
Beginning of the period 1.1.2014	421,791	167,367	172,526	761,684
Additions	53,275	5,037	16,483	74,795
Disposals				-
End of the period 31.12.2014	475,066	172,404	189,009	836,479
Accumulated depreciation				-
Beginning of the period 1.1.2014	(374,938)	(165,843)	(172,525)	(713,306)
Change of the year	(47,539)	(2,531)	(3,298)	(53,368)
End of the period 31.12.2014	(422,477)	(168,374)	(175,823)	(766,674)
Net carrying amounts 31.12.2014	**52,589**	**4,030**	**13,186**	**69,805**
Net carrying amounts 1.1.2015	52,589	4,030	13,186	69,805
Gross values of cost				-
Beginning of the period 1.1.2015	475,066	172,404	189,009	836,479
Additions	110,312	147,870	48,559	306,741
Disposals				-
End of the period 31.12.2015	585,378	320,274	237,568	1,143,220
Accumulated depreciation				-
Beginning of the period 1.1.2015	(422,477)	(168,374)	(175,823)	(766,674)
Change of the year	(71,234)	(30,581)	(13,008)	(114,824)
End of the period 31.12.2015	(493,711)	(198,955)	(188,831)	(881,498)
Net carrying amounts 31.12.2015	**91,667**	**121,319**	**48,736**	**261,722**

5 PROVISIONS

(Expressed in EUR)	Provision for taxes (Social taxes)	Provision for HR expenses (holidays not taken)	Provision for pension plan (DRC team) *	**Total**
Carrying period as per 1.1.2014	-	136,558	0	136,558
Creation	15,386	213,945	4111	233,442
Utilization		(136,558)		(136,558)
Reversal				-
Carrying period as per 31.12.2014	**15,386**	**213,945**	**4,111**	**233,442**
Carrying period as per 1.1.2015	15,386	213,945	4,111	233,442
Creation		309,630	14,750	324,380
Utilization	(11,211)	(213,945)	-1,416	(226,571)
Reversal				-
Carrying period as per 31.12.2015	**4,175**	**309,630**	**17,445**	**331,251**

** In the Democatric Republic of Congo the pension plan for the DND*i *team is saved and cumulated on a specific bank account.*

6 RESTRICTED OPERATING FUNDS

Restricted Funds	Increased	Utilization	**Net utilization**
Royalties	304	(43,092)	(42,788)
Donor Advance		(18,395)	(18,395)
Total	**304**	**(61,487)**	**(61,183)**

a) Royalties

In December 2004, DND*i* signed an agreement with Sanofi, a pharmaceutical company, pertaining to the implementation of coformulation treatments artesunate + amodiaquine (ASAQ) against malaria, developed originally by DND*i* together with Sanofi. 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 and ASMQ treatment in developing countries, notably in Africa, or the ASMQ clinical trial in Africa.

The 3% royalties on the 2014 sales of Coarsucam® amounting to EUR 304 were entirely allocated to the malaria (ASAQ and ASMQ) projects.

The total costs of this project in 2015 amount to EUR 43'092. The balance of EUR 42'788 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 for ASAQ and ASMQ treatments. After the 2015 utilization, the total amount of the restricted fund incurred by the payment of the royalties amounts to EUR 53'364 as per 31 December 2015.

b) Restricted operating funds

In December 2014, the Drugs for Neglected Diseases *initiative* North America raised a grant from the Rockefeller Brothers Fund of USD 25,000. Out of this grant, USD 2,083 was allocated against 2014 accounts and USD 22'916 (EUR 18'395) against 2015 accounts. On 31 December 2015 the grant was entirely released from restricted operating funds.

7 INCOME

a) Deferred income

The total deferred income decreased by EUR 8,316,270 in 2015 compared to 2014, mainly because a donor grant advance related to a five-year grant signed in 2014 (for the period 2015-2019) paid in 2014 as a 15-month advance payment was significantly used in 2015 (~80%). As per the contract, the advance payment was not renewed in 2015. The next advance payment related to this grant (i.e. the second payment) is scheduled for May 2016.

b) Cumulative donations committed to DND*i* and/or received by 2015 (in EUR)

DONORS	Currency	Total Commitment in currencies [5]	Total Commitment in EUR [5]	As per Statement of Operations 2015 in EUR	To be used after 2015 in EUR
Bill & Melinda Gates Foundation	USD	123,766,688	102,422,200	12,571,477	45,089,648
UK Government DFID [1]	GBP	67,389,550	85,585,249	11,734,008	18,988,200
Médecins Sans Frontières	EUR	65,933,920	65,933,920	4,014,944	12,121,356
Dutch Government DGIS	EUR	32,975,000	32,975,001	800,000	15,200,000
French Government MAEE / AFD [2]	EUR	16,255,000	16,255,000	1,040,335	3,161,808
UNITAID	USD	17,335,304	15,543,461	2,077,688	11,888,172
WHO-TDR	EUR	2,340,000	2,340,000	967,566	1,372,434
Spanish Government AECID	EUR	12,000,000	12,000,000	-	-
Swiss Government SDC [3]	CHF	13,020,000	10,924,703	1,855,605	1,849,000
US Government NIH/NIAID/USAID	USD	11,896,405	10,745,270	536,843	8,583,869
German Government [4]	EUR	10,101,383	10,101,383	1,910,606	789,337
European Union, FP5, FP6, FP7, EDCTP	EUR	4,413,112	4,413,102	1,373,096	506,223
Wellcome Trust UK	EUR/USD	4,999,801	4,371,296	324,399	142,615
Medicor Foundation	EUR/USD	3,219,424	3,027,821	240,000	240,000
GHIT	USD/JPY	866,047,081	6,678,599	2,043,154	4,509,303
Norwegian Government NORAD	NOK	15,000,000	1,713,787	553,423	0
Canton of Geneva	CHF	2,100,000	1,546,741	154,874	0
UBS Optimus Foundation	CHF	2,000,000	1,448,640	125,152	247,841
Brazil Government MoH, BNDS and FINEP	BRL	5 029 948	1 250 306	246 441	0
Various other donors (ARPE Found., found. NA, individual NA, royalties, Brian Mercer Charitable Trust, Rockefeller Brothers Fund)	EUR/GBP	1,077,824	1,159,736	267,536	27,126
Family Moreau	BRL	3,500,000	1,059,339	288,096	115,514
Sasakawa Peace Found., Tuscany Region, and others	EUR	611,396	611,396	-	-
Global Fund (AMFm)	EUR	532,809	532,809	-	-
BBVA	EUR	400,000	400,000	-	-
Starr International Foundation	USD	625,000	491,402	116,503	0
Ruta N Medellin	EUR	317,500	290,576	0	290,576
Sandoz Family Foundation & anonymous donation	CHF	701,229	446,808	-	-
Kalacore	GBP	213,900	290,808	49,496	241,312
Rockefeller Found. & Carlos Slim Found.	USD	200,000	147,549	-	-
TOTAL DONATIONS (EUR)			**394,706,902**	**43,291,243**	**125,364,336**

*(1) The UK Government, DFID, funded DND*i* with 6 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; a fifth restricted grant of GBP 3.5 million in 2012 for the period 2011-2013; and a sixth unrestricted grant of GBP 33 million for the period 2013-2018.*

*(2) The French Government, Ministry of Foreign and European Affairs, funded DND*i* with 5 portfolio 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 2012-2017.*

*(3) The Swiss Government, SDC, funded DND*i* with 4 grants. A first restricted grant of CHF 0.12 million in 2008 for the period 2008-2009; a second unrestricted grant of CHF 4 million in 2010 for the period 2010-2012; a third restricted grant of CHF 0.9 million in 2012 for period November 2012 to November 2013; and a fourth unrestricted grant of CHF 8 million in 2013 for the period 2013 to 2016.*

*(4) The German Government funded DND*i* with 2 portfolio grants. From the GtZ: 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.*

*(5) Exchange rates used for 'Total Commitment in EUR' and 'As per Statement of Operations 2014' are real exchange rates following the DND*i* exchange rate policy. Exchange rates used for 'To be used after 2014' appear in EUR at the USD/EUR, CHF/EUR, and GBP/EUR exchange rates as per 31.12.2014 (see note 2). 'Total Donations' therefore yield an approximate value as exchange rates will vary over time.*

c) Funding per project (restricted and unrestricted)

Operational Income (Grand TOTAL = 43,283,345) *(Expressed in EUR)*

		UK Government DFID [1] (Unrestricted)	Dutch Government DGIS [2] (Restricted)	German Government KfW-BMBF (Restricted)	Switzerland SDC (Unrestricted)	French Government AFD [3] (Restricted)	EU FP7 (Restricted)	UNITAID (Restricted)	Norwegian Government (Restricted)	Switzerland Canton of Geneva (Restricted)
Implementation & Development	FACT (ASAQ & ASMQ fixed-dose) for Malaria	123,368			12,871	329,771				
	Nifurtimox + Eflornithine co-administration (NECT) for stage 2 for HAT				16,295					
	New VL treatments (Asia, SSG & Paromo, Latin America; co infection HIV/VL)	27,826	15,909		81,501		357,207			
	Fexinidazole for HAT	1,329,949	191,831			212,922			306,516	75,186
	Chagas Access	103,495								
Translation	Nitroimidazole VL-2098 (& back-up VL0690) for VL	270,684		227,431						
	Macrofilaricide for Filaria (Flubendazole, Emodepside, TylAMac, Oxfendazole)	4,113		176						
	Combination Fexinidazole/ Miltefosine for VL	116,667	65,481	158,450	59,334	30,532	706,010			
	Fexinidazole for Chagas	294,792		133,963	150,523					
	Oxaborole SCYX-7158 for HAT	3,586		252,921					199,851	
	Biomarkers for Chagas	194,871								
	New Benz Regimen for Chagas	69,972		2,138						
	Anfoleish for CL & CL Combination	412,486	44,171		27,000					
	CpG-D35 (CL) + PKDL	60,229	2,758		41,172	4,631				
	Paediatric HIV: PI sprinkles CHAPAS-2 & super boosting T. b./ HIV					240,997		1,881,666		
Research	Lead Optimization Consortia (for VL, Chagas, and HAT), including Fenarimol series and Nitroimidazole & Oxaborole back-ups	2,477,820	147,653	391,487	198,818					
	Discovery & Exploratory Kinetoplastids	457,120	29,102	324,836	51,609					
	Filariasis Screening	3,843		27,986						
Exploratory	HCV, Mycetoma, Anti-infective	56,830								
	R&D Coordination, Supervision costs	1,345,294	108,295	139,914	457,956			71,383		
	HAT, LEAP, Filaria & Chagas Platforms	439,273	71,535	74,022	35,734	109,812	90,401		9,578	58,086
	Other Strengthening Capacity activities	1,270,520			210,529	114				
	Advocacy	1,036,269	34,376		366,667	33	6,372	27,055		
	Fundraising	671,190	7,057	95,310	11,465	29,857	53,887	23,807	4,783	9,319
	General Management	963,812	81,832	81,974	134,130	64,742	151,321	73,777	32,696	12,282
	Net surplus allocated to unrestricted funds					16,924				
	Net surplus allocated to restricted funds									
	TOTAL Income + other income	**11,734,008**	**800,000**	**1,910,606**	**1,855,605**	**1,040,335**	**1,365,198**	**2,077,688**	**553,423**	**154,874**

(1) *UK Government, DFID: 1) an unrestricted grant of GBP 5.5 M (EUR 5,540,990), and an exceptional unrestricted grant of GBP 3 M (EUR 4,193,018) covering the period from Aug to Dec 2015 only.* ***(2)*** *The Netherlands Government, DGIS EUR 0.8 M with a new grant starting in Oct 2015.* ***(3)*** *French Government, AFD 1) A portfolio grant for malaria, HAT, and paediatric HIV EUR 912,462 and 2) a restricted grant to VL projects EUR 127,873. Requirement to open a specific bank account which bears its own financial result* ***(4)*** *GHIT 2015: a restricted grant of JPY 37,688,293 (EUR 282,129) for Chagas disease, a restricted grant of JPY 206,772,882 (EUR 1,549,753) for an early discovery project, and a restricted grant of JPY 28,409,954 (EUR 211,272) for NTD Booster project.* ***(5)*** *B&M Gates Foundation, includes four restricted grants and one portfolio grant: 1) EUR 729,455 for new VL treatments in Asia project; 2) EUR 147,771 for flubendazole macrofilaricide for the filarial programme terminated in Mar 2015; 3) EUR 97,206 for the Filarial screening programme terminating Mar 2015, 4) EUR 707,359 for an innovative fund terminating Dec 2015, and 5) EUR 12,240,783 as Portfolio grant for HAT, filarial programme, and discovery for leishmaniasis projects. Interests resulting from deferred incomes are*

GHIT [4] (Restricted)	MOH Brazil (Restricted)	USAID (Restricted)	Bill & Melinda Gates Foundation [5] (Restricted)	Médecins Sans Frontières [6] (Restricted/ Unrestricted)	Wellcome Trust (Restricted)	Medicor Foundation (Restricted)	WHO-TDR [7]	UBS OPTIMUS (Restricted)	Foundations & Other [8] (Restricted/ Unrestricted)	**Financial income (Net) =**	**Utilization of restricted reserves**	**TOTAL Expenditure = 43,002,832**
				55,441					14,408		42,788	578,648
												16,295
			536,953	272,497		27,894			34,132			1,353,920
			5,230,411	101,143								7,447,957
	2,175								123,083			228,753
				17,766								515,882
		265,108	1,780,709						1,107			2,051,213
				318,451		89,394	111,757		37,394			1,693,469
				33,852					26,892			640,021
			799,973	2,458								1,258,789
	40,393			4,754	324,399				7,716			572,133
263,673	31,373			36,556					27,932			431,643
	10,320			4,963								498,941
				17,700			191,982					318,472
				3,987				113,991				2,240,641
1,383,170	44,411		214,052	554,534			190,330		12,688			5,614,961
140,384				51,681			185,653		93,271			1,333,656
			930,025						12,418			974,272
			413,775	147,444								618,048
28,560	558	2,962	816,640	1,176,148			103,570		69,282			4,320,562
		94,594		84,074		85,375			60,282			1,212,765
						15,644			45,076			1,541,884
			39,892	721,729			23,012		10,590			2,265,996
70,670		95,830	763,933	109,136			41,109		48,275			2,035,629
156,697		78,348	1,055,495	188,748		21,693	120,152	11,161	9,420			3,238,280
			(10,380)	111,882					223,271	(160,507)		181,190
									(18,395)		(42,788)	(61,183)
2,043,154	**129,229**	**536,843**	**12,571,477**	**4,014,944**	**324,399**	**240,000**	**967,566**	**125,152**	**838,843**	**(160,507)**	**-**	**43,122,838**

reallocated to projects funded by the donor. ***(6)*** *MSF: 1) a multi-year unrestricted grant of EUR 4,000,000; 2) EUR 14,944 for the payment for services of the data management centre based in Nairobi in 2015.* ***(7)*** *WHO-TDR portfolio grant started in August 2015 EUR 967,566.* ***(8)*** *ARPE Foundation (EUR 10,000); Kalacore consortium (EUR 49,496), Rockefeller Brothers Fund (EUR 18,395); Starr International Foundation (EUR 116,503); Family Moreau (EUR 288,096); Brian Mercer Charitable Trust (EUR 13,526); FINEP- Brazil (EUR 117,212); Various individual donations from Individual donors, private foundations and corporations (EUR 170,932) mainly from North America; Royalties from Sanofi for EUR 304 earmarked for FACT activities (see note 6). In addition, DNDi in Geneva has collected various reimbursements and participation of partners throughout the year for a total of EUR 55,883 plus exceptional incomes for the year for a total of EUR17,445.* ***(9)*** *The restricted operating fund has been partially used (EUR 42,788) to fund and support the total expenditure attached to this project.*

8 EXPENDITURE

a) R&D projects related expenditure

Recognized in *(Expressed in EUR)*	2015	2014
IMPLEMENTATION PROJECT		
ASAQ - Fixed-dose Artesunate - Amodiaquine (Malaria)[1]	330,026	386,214
ASMQ - Fixed-dose Artesunate - Mefloquine (Malaria)[1]	248,622	698,075
NECT - Nifurtimox - Eflornithine co-administration for stage 2 (HAT)[4]	16,295	57,259
SSG & Paromomycin Combination Therapy for VL in Africa[2]	20,279	96,869
New VL treatments in Asia[3]	536,953	659,246
Paediatric Benznidazole (Chagas)	-	143,790
TOTAL IMPLEMENTATION PROJECTS	**1,152,176**	**2,041,453**
DEVELOPMENT PROJECTS (PHASE IIB/III; REGISTRATION)		
Fexinidazole (HAT)[4]	7,447,957	5,843,148
New VL treatments for Bangladesh	-	205,824
New VL treatments in Latin America	111,936	110,517
Coinfection HIV / Visceral Leishmaniasis[5]	684,752	698,094
TOTAL DEVELOPMENT PROJECTS	**8,244,645**	**6,857,581**
TRANSLATION PROJECTS (PRE-CLINICAL; PHASE I; PHASE IIA/POC)		
Fexinidazole (Chagas)[6]	640,021	1,212,669
Oxaborole SCYX-7158 (HAT)[7]	1,258,789	1,236,612
Combination Fexinidazole/Miltefosine (VL)[2]	1,693,469	1,252,599
Anfoleish (CL)[8]	405,377	350,718
CL Combination[9]	93,564	
CpG-D35 (CL)[10] + PKDL[11]	318,472	216,251
Azoles E1224 (Chagas)	-	46,892
New Combination including New Benz Regimen (Chagas)[12]	431,643	268,908
Biomarkers (Chagas)[13]	572,133	1,131,282
Paediatric HIV ("4-in-1" LPV/r based fixed-dose combination & Superbooster T. b./HIV)[14]	2,240,641	1,078,126
Nitroimidazole (VL-2098) + VL 0690[15]	515,882	808,472
Flubendazole Macrofilaricide (Filaria)[16]	123,618	938,583
Emodepside Macrofilaricide (Filaria)[17]	1,584,830	58,828
Oxfendazole Macrofilaricide (Filaria)[18]	19,007	0
TylAMac Macrofilaricide (Filaria)[19]	323,758	0
TOTAL TRANSLATION PROJECTS	**10,221,204**	**8,599,939**
RESEARCH PROJECTS (SCREEN; HIT TO LEAD; LEAD OPTIMIZATION)		
Lead Optimization Consortia[20]	5,614,961	4,667,142
Screening Resources & Reference Screening Centres[21]	1,333,656	1,359,345
Screening Filaria[22]	974,272	823,924
TOTAL RESEARCH PROJECTS	**7,922,889**	**6,850,411**
Project-related variable expenditure		
HCV, Mycetoma, and Anti-infective	**618,048**	187,268
Chagas Access[23]	228,753	0
R&D Coordination & Supervision[24]	4,320,562	3,109,458
TOTAL OF PROJECTS RELATED EXPENDITURE	**32,708,277**	**27,646,111**

MAIN R&D PARTNERS & SUB-CONTRACTORS:

Partners and service providers with financial compensation above EUR 5,000 in 2015 are:

(1) SITEC, India / Bertin Pharma, France / AEDES, Belgium / Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland / VENN Life Sciences, France / Mahidol Oxford, Thailand / National Institute of Medical Research, Tanzania

(2) Kenya Medical Research Institute, Kenya / Amudat Hospital, Uganda / Uppsala University, Sweden / Biomedic, France / MSF Logistique, France / UBC United Biosource, Switzerland / Institute of Endemic Diseases (IEND) and University of Khartoum, Sudan / IDA Solution, the Netherlands / Organisation for Social Science Research in Eastern and Southern Africa (OSSREA), and Addis Abeba University, Ethiopia / Arba Minch Hospital, Ethiopia / Makerere University, Uganda / MDL Srl, Italy / i+solutions, the Netherlands

(3) Rajendra Memorial Research Institute of Medical Sciences (RMRI), India / GVK Biosciences, India

(4) Swiss TPH, Switzerland / PNLTHA, DRC / INRB Kinshasa, DRC / Jeffery travels, DRC / La Référence Médicale, DRC / UBC United Biosource, Switzerland / Biotrial, UK / Institute of Tropical Medicine-Antwerp, Belgium / SGS, Belgium and France / VENN life Science, France / Vanga CBCO Clinic, DRC / RCTS, France / Phinc Development, France / Cardiabase, France / MSF-Logistique, France and Switzerland / Aptuit, UK / Scinopsis, France / Bertin Pharma, France / Theradis Pharma, France / Biomedic, France / Sanofi Aventis, France / Sunnikan, France / PNLTHA, Chad

(5) Gondar University, Ethiopia / LSHTM, UK / UBC United Biosource, Switzerland / Institut Tropical Medicine (ITM), Belgium / NLADF Research Foundation, the Netherlands / Appledown, UK / Uppsala University, Sweden

(6) CEADES, Bolivia / JSS, Canada / Phinc, France / UBC United Biosource, Switzerland / Cardiabase, France

(7) AVISTA (SCYNEXIS), USA / Patheon, UK / Eurofins Optimed, France / SGS, Belgium & France / Voisin consulting, France / Phinc, France / Cardiabase, France

(8) PECET Universidade de Antioquia, Colombia / JSS, Canada / CECIF, Colombia / Allianz, Brazil

(9) Universidad Peruana Cayetano Heredia, Peru

(10) Genedesign, Japan / Ohio University, USA

(11) ICDDRB, Bangladesh / Hospital Universitario de Fuenlabrada (FCSAI), Spain

(12) Fundacion Instituto De Biologica Y Medicinal, Argentina / Núcleo de Desenvolvimento Farmacêutico e Cosmético (NUDFAC), Brazil / Phinc, France / LAT Reasearch, Argentina /

(13) Texas Biomedical Research Institute, USA / McGill University, Canada / University of Georgia, USA / Barcelona Center for International Health Research (CRESIB), Spain

(14) CIPLA, India / University of Stellenbosch, South Africa / Kenya Paediatric Research Consortium, Kenya / WuXi AppTech, China / Associated Medical Sciences, Thailand / Joint Clinical Research Centre, Uganda / Kenya Medical Research Institute, Kenya / Baylor College of Medecine, USA / Kotak, India / Epicentre, France / Gertude Hospital Foundation, Kenya / Biomedic, France

(15) Aptuit, UK / Bsys, Switzerland / Advinus, India / Diane Creasy, USA

(16) Juniper Pharma, UK / Swansea Innovations, UK / Wuxi App Tec, China

(17) Hammersmith Medicine, UK / Bayer, Germany / UBC United Biosource, Switzerland / Creapharm, France / Syngene, India / MC Toxicology Consul, Austria

(18) Wuxi App Tec, China

(19) Abbvie, USA / Wuxi App Tec, China

(20) Epichem Pty Ltd, Australia / Syngene, India / CEMSA Laboratory, Brazil / WuXi AppTech, China / Monash University, Australia / TCG Life Science Ltd, India / Advinus, India / London School of Hygiene & Tropical Medecine LSHTM, UK / Griffith University, Australia / Antwerp University, Belgium / Centro Nacional de Energia em Energia e Materiels (CNPEM), Brazil / Sandexis, UK / Accelera, Italy / Wil Research, France / Advinus, India / CEREP, France / Selvita, Poland / Pharmaterials Limited, UK / Sara Pharm, Romania / Eurofins, France

(21) Swiss TPH, Switzerland / University of Antwerp, Belgium / GlaxoSmithKline (GSK-Tres Cantos), Spain / IPK, South Korea / Exquiron, Switzerland / Dundee University, UK / Bio ascent, UK

(22) Northwick Park Institute for Medical Research (NPIMR), UK / National Museum of Natural History, France / University Hospital of Bonn, Germany / WuXi AppTec, China / University of Bari, Italy / CEA LETI, France / REFOTDE, Cameroon

(23) Elea, Argentina / ISGlobal Barcelona Institut for Global Health, Spain

(24) R&D Coordination & Supervision: Sunnikan, UK / VOLT Europe Limited: UK / M Benton, UK

Breakdown of R&D coordination expenditure per activities

(Expressed in EUR)	**2015**	2014
Coordination	2,379,164	1,790,898
Scientific Advisory Committee	130,771	94,713
Business Development	1,220,343	847,990
Japan Representation Office	453,506	255,461
Medical, Access and Medical Coordination Latin America	136,779	120,396
TOTAL	**4,320,562**	**3,109,458**

CONSULTANTS AND PROJECT STAFF INVOLVED IN R&D PROJECTS:

Latin America office: Rodrigues, Belaine; De Jesus, Teresinha; Pinheiro, Eloan; Garcia, Facundo; Gonçalves, Luciana; Caicedo, Andres; Mechali, Daniel (in memoriam); Valencia, Carlos; Marchiol, Andrea; Zicker, Fabio; Barbeitas, Mady; Bernal, Oscar; Marques, Tayná; Boni, Marina; Christmann, Leandro; Dessoy, Marco; Martinez, Pablo; De Oliveira, Celso; Noya, Oscar; Barp, Cristiane; Certo, Marina

India office: Sharma, Bhawna

DRC office: Dinanga Muzadi, Joses; Kabangu Mundidimbi, Patrice; Ngolo Tete, Digas; Kande, Victor; Ciebue Bilumbu, Laurent; Diyi Lobo, Michel; Cimanga Kabongo, Dieudonne; Kabulu, Jean-Albert; Solo, Monique; Kabangu, Gabriel; Maki, Baudouin; Babingwa, Delon; Lenvo, Dally; Tsaku, Justin; Malenge, Lazare; Konga, Raymond; Pambala, Odette

Geneva office: Ansong, Daniel; Api J. Seltzer, Jonathan; Bacchi, Cyrus; Benmabrouk, Charles; Benton, Marcus; Bessis, Anne-Sophie; Besson, Dominique; Den Boer, Margriet; Boulet, Pascale; Bray, Mike; Brenner, Jennifer; Campbell, Simon; Carmody, Lesley; Chang, Shing; Chappuis, François; Clay, Robert; Courtemanche, Gilles; Cressey, Timothy; Evans, Dean; Dormeyer, Matthias; Duke, Jeff; Elango,Varalakshmi; Flamion, Bruno; French, Edward; Frey, Reiner; Gardner, Mark;T Hoe, Elisabeth; Hooft Van Huijsduijnen, Rob; Hulbert, Kuemmerle, Andrea; Last, Paul; Larrey, Dominique; Leping, Li; Love, James; Mazué, Guy; Modabber, Farrokh; Monnerat, Séverine; Moya Alonso, Laura; O,Reilly, Terry; Paillasseur Effi, Jean-Louis; Piedangnel, Jean-Michel; Rithea, Leang; Porkony, Rolf; Rosenkranz, Bernd; Ross, Fiona; Rowan, Tim; Salerno, Katia Sasella, Daniella; Scherrer, Bruno; Schilling, Cristophe; Schijmann, Alejandro; Schneider, Manfred; Smith, Graham Seixas, Jore; Sosa Estani, Sergio; Speed, Bill; Taylor, Bob; Than-in-at, Kanchana; Thenot, Jean-Paul; Tweats, David; Vaillant, Michel; Vie de Dieu N'goko-Zenguet; Viotti, Rodolfo; Voigt, Linda; Von Geldern, Thomas; Walker, Don; Walmsley, Andrea; Williams, Mike; Zijlstra, Eduard.

Africa office: Mbui, Jane; Asrat, Hailu; Olobo, Joseph; Ahmed Mudawi, Eltahir Khalil; Mudawi, Musa; Wamalwa, Dalton.

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

Recognized in *(Expressed in EUR)*	2015	2014
PERSONNEL		
Personnel at Headquarters	11,411,975	8,892,611
Personnel at Regional Offices	3,061,737	2,429,564
Consultants	2,100,159	1,762,857
Travel and Accommodation	1,715,373	1,386,652
TOTAL PERSONNEL	**18,289,244**	14,471,684
OPERATIONAL R&D		
Purchase & Logistics	1,039,351	1,360,232
Equipment	1,116,423	621,995
Discovery & Lead Optimization (partners & services)	6,472,712	5,484,863
Pre-clinical (partners & services)	1,571,039	1,844,174
Training for partners	141,961	200,516
Clinical & post-clinical (partners & services)	8,058,268	7,520,003
Product manufacturing & CMC (partners & services)	1,203,390	749,349
TOTAL OPERATIONAL R&D	**19,603,145**	17,781,131
OTHER		
Communication (tools, meetings, documents)	1,646,284	1,371,668
Administration & IT (depreciation, furniture, service providers)	3,464,159	2,772,625
TOTAL OTHER	**5,110,443**	4,144,293
GRAND TOTAL	**43,002,831**	36,397,108

9 STRENGTHENING CAPACITIES EXPENDITURE

DND*i* expenditure on strengthening existing capacities in developing countries aims 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)	2015	2014
Regional Offices, managmt. costs: Rio, Delhi, Nairobi, Penang	**1,541,884**	1,267,631
Leishmaniasis East Africa Platform (LEAP)	**627,608**	737,444
Human African Trypanosomiasis (HAT) Platform	**263,347**	355,522
Chagas Clinical Research Platform	**224,517**	185,928
Filariasis Platform	**97,293**	
Exceptional expenditure (HAT Platform)	-	28,422
TOTAL	**2,754,649**	**2,574,948**

10 ADVOCACY, FUNDRAISING, AND GENERAL & ADMINISTRATION EXPENSES

	Advocacy		Fundraising		General & Administration	
(Expressed in EUR)	**2015**	2014	**2015**	2014	**2015**	2014
Human resources	1,560,290	1,171,479	1,524,010	1,253,638	2,296,603	1,907,229
Office charges	72,195	50,895	109,619	89,464	187,707	127,237
Travel expenses	69,658	76,479	144,270	97,766	160,161	116,276
Administration	56,997	38,215	124,903	66,411	245,045	252,576
IT & telecommunications	102,193	44,906	90,789	43,743	226,172	419,772
Communication	390,358	266,171	29,257	19,377	89,766	104,075
Depreciation	11,482	5,337	11,482	6,404	29,854	13,342
Exceptional expenses	2,824	7	1,300	2,979	2,971	2,270
TOTAL	**2,265,996**	**1,653,489**	**2,035,629**	**1,579,783**	**3,238,280**	**2,942,777**

Consultants: ***Latin America office:*** *Lotrowska, Michel; Mortensen, Claudio; Pontes, Flavio; Enciso Peláez, Lucía; Childs, Michelle; Drumond, Madalena; Rojas, Nubia; Mccarthy, Robert; Paiva, Luciano; Martin, Jorge; Abi-Saab, Mariana; Schermutzki, Pierre, Cavedon, Felipe; Alapenha, Julia.* ***North America office:*** *Biddle Reath, Driker; Katz, Jennifer; Curtis, Jodie.* ***India office:*** *Sunil Prakash, Goel; Agarwal.* ***Africa office:*** *Apamo, Bruce; Apamo, James; Ngoye, Ben; Ogolla, Fred.* ***Geneva office:*** *Bowen, Sian; Burrows, Louise; Piper Roche, Lynda; Tissot, Raphael; Bloemen, Sophie; El Thir, Ghada; Furrer, Mariella; Langbein, Lena; Mahon, Anette; Njoroge, Andrew; Sarumaru, Michiko; Haberstroh Sabine, Allizzatti, Vincent.*

11 INDEMNITIES & REMUNERATIONS GIVEN TO BOARD MEMBERS AND DIRECTORS

All members of the Board are appointed on a voluntary basis. The Board members did not receive any remuneration for their mandate in 2015, nor did they in 2014.

The top five salaries (including salaries and all benefits) cumulated at DND*i* in 2015 amount to CHF 1,560,298 or EUR 1,453,319.

12 ASSETS PLEDGED AS GUARANTEE FOR COMMITMENTS AND BANK GUARANTEE DEPOSITS

a) Assets pledged: At year end, a bank of the Foundation provided two letters guaranteeing rental deposits of CHF 70,000 (EUR 64,715) and CHF 20,000 (EUR 18,490) in favour of a third party. Cash for an equivalent amount is pledged at the corresponding bank.

b) Bank guarantee deposits: Guarantees are presented as non-current assets. To date, DND*i* has six guarantees representing six deposits related to office rental in Tokyo, New Delhi, and Geneva (office and parking) and deposits for a travel agent and petrol in Kinshasa. In addition, a letter of guarantee pertaining to the Geneva premises is still valid.

It is recoverable, subject to prevailing contract terms, upon vacating the premises.

	2015				2014		
	Currency	Amount in Currency	Amount in EUR		Currency	Amount in Currency	Amount in EUR
Guarantees office Geneva	CHF	135,925	125,662	Guarantee office Geneva	CHF	56,186	46,719
Guarantee office Tokyo	JPY	2,682,000	20,383	Guarantee office Tokyo	JPY	770,000	5,290
Guarantee office New Delhi	INR	2,475,000	34,328	Guarantee office New Delhi	INR	630,000	8,171
Guarantee office Kinshasa	USD	18,000	16,474	Guarantee office Kinshasa	USD	18,000	14,807
Guarantee travel agency and petrol Kinshasa	USD	6,500	5,949	Guarantee travel agency and petrol Kinshasa	USD	6,500	5,347
Guarantee office Nairobi	KES	1,977,000	17,734				
Guarantee Nairobi credit cards	KES	1,000,000	8,970	Guarantee Nairobi credit cards	KES	1,000,000	9,150
Total guarantees			**229,500**	**Total guarantees**			**89,483**

13 CONTRIBUTIONS IN-KIND

(Expressed in EUR)	Staff Scientific	Staff non-Scientific	R&D Services	Office, furniture & admin.	TOTAL
Lead Optimization Consortia (Australia)	149,242	68,828		58,335	276,405
Screening Resources & Reference Screening Centres	545,030	63,949	264,963	338,901	1,212,843
Macrofilaricide Filaria	633,802	0	-		633,802
Azole E1224 (Chagas)	1,313,787	56,420	-183,431	0	1,186,776
Regional Offices	14,596	13,019	2,853	5,848	36,316
New VL treatments: Asia, America	128,936	671	32,835	-	162,442
ASMQ Fixed-dose Artesunate - Mefloquine (Malaria)					-
Cutaneous Leishmaniasis projects	3,715	-	-	0	3,715
Paediatric HIV (4-in-1, LPV/r-based fixed-dose combination)	157,109	-	-	72,390	229,499
TOTAL	**2,946,217**	**202,887**	**117,220**	**475,473**	**3,741,798**

Main in-kind contributors: AbbVie, USA; Eisai Ltd, Japan; ARC-Australian Research Council, Australia; University of Dundee, UK; University of Brasilia, Brazil; Monash University, Australia; KEMRI, Kenya; Astellas Pharma Inc, Japan; Cipla, India; Fiocruz, Brazil; Shionogi, Japan; Sanofi ID, France; GeneDesign, Inc., Japan; Swiss TPH, Switzerland; Takeda Pharmaceutical Company Ltd, Japan; Institut Pasteur Korea, Korea; Daniela Sassela, Italy; Epichem Pty Ltd, Australia

14 STRUCTURED PRODUCT AND OPEN DERIVATIVE

In January 2015, after the Swiss National Bank dropped its 1.2 EUR/CHF floor, the Foundation decided to put in place a hedging strategy for balancing probability of loss from fluctuation of CHF. In June 2015, after Audit Committee endorsement and Board approval, the Foundation started a hedging strategy of at least 50% of needs in CHF at six months, renewable (extended by one month at the end of each monthly period). As the Foundation is long in GBP and USD these two currencies are used to cover the needs in CHF. Two tools are used: Forward (FWD) and options (the Risk Reversal – RR and Kick Into Forward - KIF). The RR and KIF offer the potential of a better rate than the current market forward rate with a predefined Strike.

Derivative financial instruments

DND*i* uses forward contracts and options to hedge its exposure to foreign currency risks arising from its future cash flows.
The financial instruments are recognised at fair value, initially on the date on which the contract is entered into and subsequently at each reporting date.
Any gains or losses arising from changes in fair value of the financial instruments during the year are reported directly in the statement of operations.

See below the total commitment toward the year 2016 at year-end 2015.

Buy	Sell	Solution	Expiry	Strike	Instrike	Net present value
FORWARDS						
CHF 221,306	GBP 150,000	FWD	16-Mar-16	1.4798	-	**220,985**
CHF 221,625	GBP 150,000	FWD	18-Apr-16	1.4775	-	220,899
CHF 221,310	GBP 150,000	FWD	18-May-16	1.4754	-	220,903
CHF 220,980	GBP 150,000	FWD	16-Jun-16	1.4732	-	220,849
OPTIONS						
CHF 300,000	GBP	RR	18-Jan-16	1.3900	1.5180	
CHF 300,000	USD	KIF	18-Jan-16	0.9350	1.0105	
CHF 300,000	GBP	RR	18-Feb-16	1.4250	1.4900	
CHF 300,000	USD	KIF	18-Feb-16	0.9350	1.0151	
CHF	USD 300,000	RR	16-Mar-16	0.9300	1.0010	
CHF	GBP 150,000	KIF	16-Mar-16	1.4700	1.5270	
CHF	USD 300,000	RR	18-Apr-16	0.9300	1.0015	
CHF	USD 300,000	RR	18-May-16	0.9300	1.0010	
CHF	USD 300,000	RR	16-Jun-16	0.9300	1.0000	

RR Strategy: If spot at expiry trades at or below the Lower Strike, the client sells USD or GBP buys CHF at the Lower Strike. If spot at expiry trades at or above the Upper Strike, the client sells USD buys CHF at the Upper Strike.

KIF Strategy: If spot trades at or above the Instrike at any time during the life of the structure, the long option position turns into a forward with the conversion rate at the Strike.

15 SWISS FRANC EQUIVALENT OF KEY FIGURES

The Foundation maintains its accounting records in Euro. The key figures below have been translated into CHF for information purposes only, using a closing rate of EUR/CHF 0.9245 (2014: 0.8315).

(Expressed in EUR)	**2015**	2014
Total assets	**30,730,868**	43,453,714
Capital of the organization	**11,506,791**	12,649,456
Total income	**46,818,112**	43,963,286
Total social mission expenditure	**40,810,084**	38,333,791
Total non-social mission expenditure	**5,704,607**	5,439,038

16 AUDIT FEES

Fees for audit services and other services: Audit services include statutory audit, audit of projects, and donor's audit. To date, Deloitte is not providing other services such as tax and legal services.

(Expressed in EUR)	**2015**	2014
Total Audit services	**124,167**	**106,543**

17 SUBSEQUENT EVENTS

DND*i* Kinshasa Office informed the headquarters on March 31th, 2016 that BIAC, the financial services provider, may be at risk of bankruptcy.

Mitigation strategy: DND*i* is evaluating a new banking set-up and exploring Western Union Business Solutions as a potential answer, after Citibank refused DND*i* as a new client. In addition DND*i* is working on a rapid opening of a new bank account at ECOBANK or at Standard Bank; due diligence is ongoing. In the meantime local payments are temporarily covered by DND*i* headquarters in Geneva to ensure activities continue as planned.

BIAC's track record: DND*i*, along with other BIAC clients, received communication from the Government of DRC and the Congo Central Bank that this incident was a temporary situation to be resolved. DND*i* chose BIAC as its financial service provider in December 2009, a decision approved by FR-AFD in May 2013 when they pledged to support our HAT activities over a five-year period. BIAC is the third largest bank in DRC which provides financial services in the communities where DND*i* has activities. It is the first time DND*i* has faced such a situation with a bank. Bank ratings for such banks in Africa do not exist. In February 2016, the long-term rating of the country was revised by Standard & Poor's from stable to negative, due to the fall in the price of copper, political instability, and the lack of visibility over the election.

In April, DND*i* Geneva was returned three transfers of USD 18,000, USD 30,000 and USD 65,000 from BIAC Kinshasa accounts. In addition, since the beginning of the crisis we have been able to make local payments to vendors who have an account at the BIAC (~USD 12,000).

Our Head of DRC Project Office and the DND*i* Geneva Finance Department and the Executive Team are following the situation very closely, and expect the resolution of all funds located in the accounts of the BIAC to take time to be regularized. To date, the risk is considered low, an assessment based on the money already recovered (~30%). Today, the amount at risk (~USD 200,000) should be recovered by the end of the year 2016. No provision has thus been recorded at this stage.

18 CONSOLIDATED ACCOUNTS

These consolidated financial statements include the activities of the Swiss Foundation, its branches, and subsidiaries. The table below summarizes the detail by legal entity:

Amount are in '000 EUR	Income transferred by DND*i* Geneva **(1)**	Income raised by legal entity **(2)**	**Total income 2015 (1) + (2)**	% of the income raised by legal entity	**Total expenditure 2015**	% of the expenditure by legal entity
DND*i* Geneva and branches	-3,396	42,451	39,180	98.1%	39,266	91.3%
DND*i* Japan	327	1	328	0.0%	336	0.8%
DND*i* North America	1,018	297	1,190	0.7%	1,026	2.4%
DND*i* Latin America	2,051	535	2,586	1.2%	2,375	5.5%
Total consolidated accounts	**0**	**43,284**	**43,284**	**100.0%**	**43,003**	**100.0%**

REPORT OF THE STATUTORY AUDITOR

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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 Consolidated Financial Statements

As statutory auditor, we have audited the accompanying consolidated financial statements of Drugs for Neglected Diseases initiative (DNDi), which comprise the consolidated balance sheet as at 31 December 2015, the consolidated statement of operations, the consolidated funds flow statement, the consolidated statement of changes in capital and notes to the consolidated financial statements, presented on pages 69 to 87, for the year then ended. In accordance with Swiss GAAP FER 21, the content of the performance report presented on pages 4 to 67 is not audited.

Board's Responsibility
The Board is responsible for the preparation of these consolidated financial statements in accordance with Swiss GAAP FER, 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 consolidated 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 consolidated 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 consolidated financial statements are free from material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the consolidated financial statements. The procedures selected depend on the auditor's judgment, including the assessment of the risks of material misstatement of the consolidated 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 consolidated 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 consolidated financial statements. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

Deloitte.

Drugs for Neglected Diseases initiative (DNDi)
Report of the Statutory Auditor
for the year ended
31 December 2015

Opinion
In our opinion, the consolidated financial statements for the year ended 31 December 2015 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.

Report on Other Legal Requirements

We confirm that we meet the legal requirements on licensing according to the Auditor Oversight Act (AOA) and independence (article 83b Civil Code (CC) in connection with article 728 Code of Obligations (CO)) and that there are no circumstances incompatible with our independence.

In accordance with article 728a para. 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 consolidated financial statements according to the instructions of the Board.

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

Deloitte SA

Annik Jaton Hüni
Licensed Audit Expert
Auditor in Charge

Jürg Gehring
Licensed Audit Expert

Geneva, 24 May 2016

A WORD OF THANKS

DND*i* would like to thank all of the donors worldwide for their loyal commitment and collaboration since 2003. To date, DND*i* has delivered six new treatments and aims to bring 16-18 treatments in total to patients suffering from neglected diseases by 2023. DND*i* is grateful for the support received from the following donors who contributed toward the advancement of its mission and goals. Listed are supporters who have given a contribution of USD or EUR 10,000 cumulatively.

Public Institutional Support

- Banco Nacional de Desenvolvimento Econômico e Social (BNDES), Brazil
- Department for International Development (DFID), UK
- 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
- Federal Ministry of Education and Research (BMBF) through KfW, Germany
- French Development Agency (AFD), France
- German International Cooperation (GIZ) on behalf of the Government of the Federal Republic of Germany, Germany
- Global Health Innovative Technology Fund (GHIT Fund), Japan
- The Global Fund to Fight AIDS, Tuberculosis and Malaria (AMFm), International
- Minister of Foreign Affairs and International Development (MAEDI), France
- Ministry of Health, Brazil
- National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), USA
- Norwegian Agency for Development Cooperation (Norad), Norway
- Republic and Canton of Geneva, Switzerland
- Region of Tuscany, Italy
- Ruta-N, City of Medellin, Colombia
- Science and Technology Innovation Agency (FINEP), Brazil
- Spanish Agency for International Development Cooperation (AECID), Spain
- Swiss Agency for Development and Cooperation (SDC), Switzerland
- World Health Organization - Special Programme for Research and Training in Tropical Diseases (WHO-TDR)
- UNITAID, International
- United States Agency for International Development (USAID), USA

Private Support

- Anonymous individuals and organizations
- Associação Bem-Te-Vi Diversidade, Brazil
- Bennett Shapiro and Fredericka Foster, USA
- Bill & Melinda Gates Foundation, USA
- BBVA Foundation (through the 'Frontiers of Knowledge Award in Development Cooperation'), Spain
- Brian Mercer Charitable Trust, UK
- Carlos Slim Foundation through the Carlos Slim Health Award, Mexico
- David and Lisa U'Prichard, USA
- Family of Richard Rockefeller, USA
- Fondation André & Cyprien, Switzerland
- Fondation ARPE, Switzerland
- Fondation de bienfaisance du groupe Pictet, Switzerland
- Fondation Pro Victimis, Switzerland
- George H. Stout, USA
- Goldman, Sachs & Co., USA
- Guy's, King's and St Thomas', Giving Week, UK
- Harlan and Sally Weisman, USA
- Jeffrey Nelson, USA
- Leopold Bachmann Foundation, Switzerland
- Marsha Fanucci, USA
- Médecins Sans Frontières International and the MSF sections of Italy, Norway, and Brazil
- Medicor Foundation, Liechtenstein
- Rockefeller Brothers Fund, USA
- The Rockefeller Foundation (through the 'Next Century Innovators Award'), USA
- The Peter and Carmen Lucia Buck Foundation, USA
- The Stainman Family Foundation, USA
- The Wellcome Trust, UK
- Steve Rabin and Jonathan Winslow, USA
- Sandoz Family Foundation, Switzerland
- Sasakawa Peace Foundation, Japan
- Starr International Foundation, Switzerland
- UBS Optimus Foundation, Switzerland
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DND*i*
Drugs for Neglected Diseases *initiative*

DNDi

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 the millions of people across the world affected by neglected diseases, notably human African trypanosomiasis (sleeping sickness), leishmaniasis, Chagas disease, filariasis, paediatric HIV, mycetoma, and hepatitis C.

DND*i*'s primary objective:

→ Deliver 16 to 18 new treatments by 2023 for targeted neglected diseases and establish a robust 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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