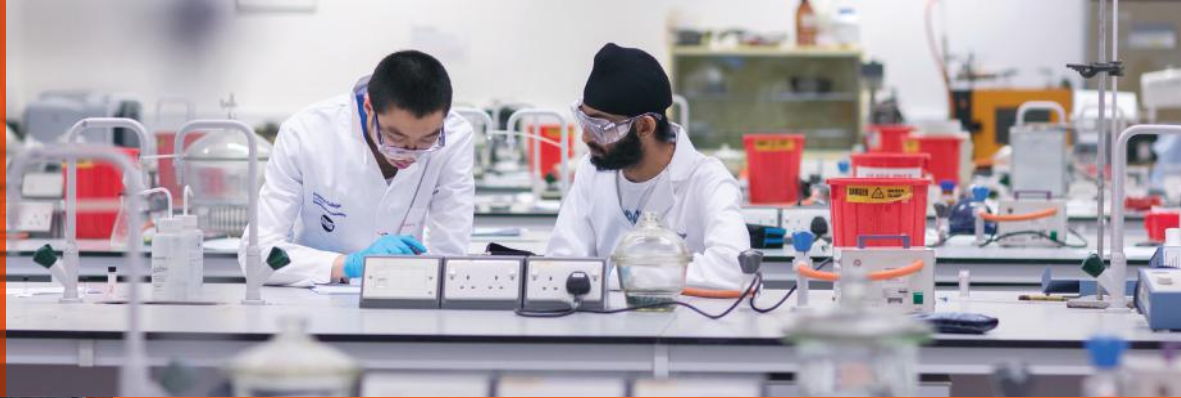


2016
ANNUAL
REPORT



Progress through Partnership



DNDi

Drugs for Neglected Diseases *initiative*

DNDi'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.

DNDi's MISSION

- To develop new drugs or new formulations of existing drugs for **people living with neglected diseases**. Acting in the public interest, DNDi 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.
- DNDi'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, DNDi enables R&D networks built on global collaborations. While harnessing existing support capacities in countries where the diseases are endemic, DNDi 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 DNDi's commitment to delivering on the objectives of the current portfolio of diseases, **a dynamic portfolio approach** has been adopted. This enables DNDi to take on new disease areas with various operating models, while completing objectives in current diseases.

DNDi

Drugs for Neglected Diseases *initiative*

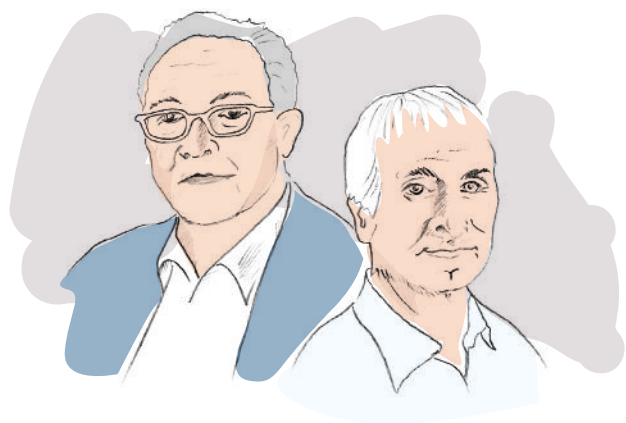


The Drugs for Neglected Diseases *initiative* (DNDi) is a collaborative, patient-needs driven, not-for-profit research and development (R&D) organization that develops safe, effective, and affordable treatments for the millions of people across the world affected by neglected diseases, notably human African trypanosomiasis (sleeping sickness), leishmaniasis, Chagas disease, filarial infections, paediatric HIV, mycetoma, and hepatitis C.

Launched in 2016 by the World Health Organization (WHO) and DNDi, the Global Antibiotic Research & Development Partnership (GARDP) aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists, while endeavouring to ensure sustainable access. GARDP is currently operating within DNDi, which provides its governance.

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Dr Bernard Pécoul
Executive Director

Message from the Chair of the Board and the Executive Director

We have evolved, expanded, and adapted. Our mission, however, remains unchanged: to bring the best science to neglected patients, by discovering and developing new treatments for diseases where commercial R&D is not enough.

For DNDi teams across the world, 2016 ended with exciting news. The topline results of the sleeping sickness clinical trial comparing fexinidazole with NECT came in, and they were most promising. This is the moment to rigorously pursue, together with Sanofi and all partners, the registration of fexinidazole as a new treatment for sleeping sickness. If successful, fexinidazole will be DNDi's first new chemical entity to get regulatory approval, expected in 2018.

Beyond this potential landmark for DNDi, thanks to effective partnerships we saw numerous other achievements over the past year.

There is indeed much to celebrate throughout the drug development pipeline.

At the final phase of the pipeline, the implementation phase, WHO guidelines for treating children co-infected with TB and HIV were modified as a result of a DNDi-led study in South Africa conducted with Cipla and South African partners. At the earliest part of the pipeline, in drug discovery, pharmaceutical companies Astra Zeneca, Celgene, Eisai, Shionogi, and Takeda participated in our innovative pre-competitive research programme, the 'NTD Discovery Booster'. In early 2017, they were joined by AbbVie and Merck.

We also successfully launched a new crowdsourcing project working with five universities in the UK, US, and India, to engage students in drug discovery.

There has also been progress across all disease areas, be it neglected diseases, viral diseases or drug-resistant infections.

With the nomination of several pre-clinical candidates for leishmaniasis, there is now hope that new oral treatments could replace today's suboptimal parenteral therapies. The inclusion of mycetoma on the WHO list of neglected tropical diseases was great recognition of the needs of these most neglected patients. Then in 2017, the first patient was enrolled in the first ever trial for an effective treatment for the disease, with the drug fosravuconazole. The trials are sponsored by the Mycetoma Research Centre in Sudan.

For hepatitis C, clinical trials of ravidasvir - developed by Egyptian manufacturer Pharco - were launched in Malaysia and Thailand. If successful, these could help encourage affordable scale up and enable a test-and-cure approach.

In May 2016, the Global Antibiotic Research and Development Partnership (GARDP), a joint initiative between DNDi and WHO, was launched. GARDP is an important component of the WHO Global Action Plan on Antimicrobial Resistance. The initiative was made possible through seed funding from Germany, the Netherlands, South Africa, Switzerland, the UK, and Médecins Sans Frontières.

GARDP's vision is a world where everyone in need of antibiotics receives effective, appropriate, and affordable treatment, irrespective of where they live. In its first six months, GARDP defined its strategy for antibiotic drug development, with a mix of short- and long-term approaches. Excitingly, its first R&D programmes are now set to be launched. The initial focus is on neonatal sepsis, sexually transmitted infections, and a 'memory recovery' project to ensure the knowledge, data, and assets of forgotten, abandoned, or withdrawn antibiotics are not lost.

As ever, none of this progress is DNDi's alone - it is only possible thanks to the partnerships forged with industry, academia, development agencies, ministries of health in endemic countries, civil society, and many others. We are extremely grateful for all of these close, innovative, and stimulating collaborations. In recognition of the central role these partners play, you will find many of their voices reflected throughout this report.

Of course, only continuous support from donors makes our work possible, and we particularly acknowledge their commitment to our cause. Notably, the renewal of support in 2016 from the German Federal Ministry of Education and Research (BMBF), through KfW, and the Japanese Global Health Innovative Technology Fund, and in 2017 from the UK's Department for International Development and the Swiss Agency for Development and Cooperation.

As Marcel Tanner prepares to leave as Chair after a decade, we are drawn to look back on the past ten years of the close collaboration between us. In this time, seven new treatments have been developed, the largest ever pipeline for NTDs built, and now the potential for new chemical entities which, if successful, could transform treatment options for the most neglected patients. The organization has evolved into one with true global reach, with increasing recognition for our work. With hepatitis C, we have expanded our mandate, and with GARDP, seen how we can adapt our operational model to take on new challenges.

Our mission, however, remains unchanged: to bring the best science to neglected patients, by discovering and developing new treatments for diseases where commercial R&D is not enough. In 2017, we hope to take further firm steps forward.

In closing, we wish to especially thank DNDi teams across the world - in field projects, in regional offices, and in our headquarters - it is only their enduring commitment and hard work that make any of our successes a reality.

Thank you Marcel! Welcome Marie-Paule!

After ten years of dedicated service, Professor Marcel Tanner, Chair of DNDi's Board of Directors, is moving on. We wish to again express our deep gratitude to Marcel for his tireless work, wise guidance, and passionate commitment.



In July 2017, he handed over the reins to Dr Marie-Paule Kieny, former WHO Assistant Director General. We are very pleased to welcome her on board, and look forward to a long and fruitful future together.

DNDi in numbers



7 **treatments**
delivered
since 2003



More than
3,000
people trained
since 2010



clinical research platforms
and networks in disease-
endemic countries
since **2003**

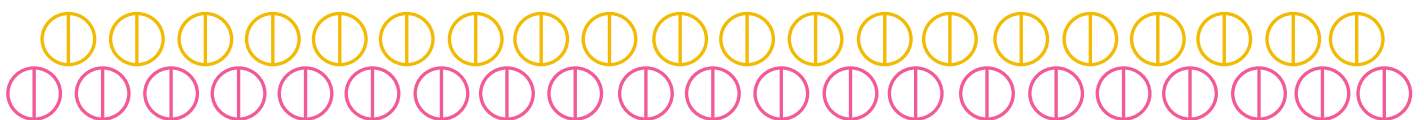


590,170
people screened for **sleeping sickness in DRC**
in 2016

MORE THAN

430 million

ASAQ treatments for malaria
distributed since 2007



RECOMMENDED IN 2016 BY WHO:
SUPERBOOSTER THERAPY FOR PAEDIATRIC HIV/TB

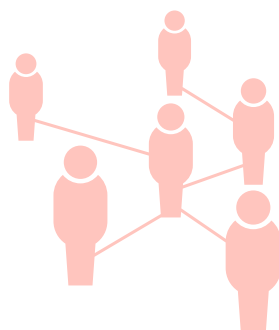


14
NEW CHEMICAL ENTITIES
IN DNDi's **R&D PIPELINE**
in 2016



388,461
COMPOUNDS SCREENED
in 2016

EUR 34 M
in-kind contributions
from PARTNERS since 2007



722
PEOPLE WORKING
FOR DNDi IN PARTNER
ORGANIZATIONS
in 2016

NOMINATION
OF 3 PRE-CLINICAL
CANDIDATES
(For leishmaniasis
and filarial diseases)
in 2016



5
UNIVERSITIES
FROM THE UK, THE US,
AND INDIA JOINED
THE OPEN SYNTHESIS NETWORK in 2016

7 new treatments delivered, recommended, and implemented since 2007

2007 ● **ASAQ*** Over 430 million treatments distributed

With older antimalarials increasingly ineffective due to growing resistance, WHO recommended in 2006 the use of artemisinin-based fixed-dose combinations (FDCs) to keep the malaria parasite from becoming resistant to new drugs.

- Partnership with Sanofi
- Once daily fixed-dose combination for 3 days
- 4 dosage forms based on a weight for-age-reference
- WHO prequalified (2008) and WHO Essential Medicines Lists (adults and children)
- Registered in 32 African countries (plus India, Ecuador, and Colombia)
- Technology transfer to Zenufa (Tanzania)



“Combining two drugs in a single tablet was a big step forward in the treatment of malaria which is now simplified, facilitating the adherence and reducing the risk of resistance.”

Dr Michel Queré
Medical coordinator, MSF, Chad

2008 ● **ASMQ*** Over 1.3 million treatments distributed

- Partnership with Farmanguinhos/Fiocruz (Brazil)
- Once daily fixed-dose combination for 3 days
- 4 dosage forms based on a weight for-age-reference
- South-South technology transfer to Cipla (India)
- WHO prequalified (2012; Cipla product) and WHO Essential Medicines Lists (adults and children)
- Registered in 11 countries in Asia, Latin America, and Africa

2009 ● **NECT** 100% of stage 2 patients treated with NECT

Before 2009, the best available treatment for sleeping sickness, involving over 50 intravenous infusions and 14 days in hospital, was so complex to distribute and administer in resource-poor settings, that all-too-often clinicians chose melarsoprol, a highly toxic, arsenic-based drug that kills 5% of those treated with it.

- Partnership with MSF, Epicentre, national control programmes, and WHO
- First new treatment for HAT in over 25 years
- 14 intravenous infusions of eflornithine over 7 days together with 3 times a day oral nifurtimox for 10 days
- WHO Essential Medicines Lists (adults and children)
- Free supply from WHO via drug donations by Sanofi and Bayer to endemic countries



“Arsobal/melarsoprol was very toxic, many patients died from this treatment. I was so very happy when NECT replaced it. With NECT, things are going very well. We haven't had a single death.”

Simeon Kwame Lundikisa
Nurse, Masi-Manimba hospital,
Democratic Republic of Congo

2010 ● **SSG&PM** Cheaper, more effective treatment in Africa

Following DNDi clinical trials in East Africa which showed that sodium stibogluconate & paromomycin (SSG&PM) was as safe and effective as the standard treatment to treat visceral leishmaniasis, WHO recommended the combination be used in the region.

- Partnership with the Leishmaniasis East Africa Platform (LEAP) and national control programmes
- Intramuscularly once a day for 17 days (instead of 30 days previously)
- Recommended by the WHO Expert Committee on the Control of Leishmaniasis (2010)
- Included in the national guidelines of Sudan, South Sudan, Kenya, Uganda, and Ethiopia



“Jamesta, my five-year-old son was unwell. He had fever, headache, and nose bleeds. After some investigation, we found out his symptoms were those of kala-azar.

His recovery was much faster than that of my older son. The shorter and better the treatment, the better for us all.”

Nancy Chemluo
Mother with two children affected by
visceral leishmaniasis, West Pokot, Kenya

* Handed over to MMV in 2015

2011 ● **Paediatric benznidazole** **First paediatric drug**

Despite recommendations to treat children with Chagas disease, benznidazole, the main drug of choice for treating Chagas, was only available in an adult tablet strength. Infants and children were treated with fractioned or macerated tablets, which complicated administration and made dosing imprecise.

- Partnership with LAFEPE (Brazil)
- Child-adapted dose of 12.5 mg per tablet twice daily for 60 days
- Registered in Brazil
- WHO Essential Medicines List (children)
- Collaboration with the Mundo Sano foundation to deliver a second source of treatment with Laboratorio ELEA, Argentina

2011 ● **New VL treatments Asia** **Adoption of new treatments**

Existing treatment options for visceral leishmaniasis in South Asia caused severe side effects and were growing ineffective due to resistance. DNDi convened a consortium of partners to identify the best combination therapies for South Asia.

- Four year-long implementation study assessing the safety and efficacy of, and patient compliance to, various new treatments (single dose AmBisome® and combination therapies)
- Recommended by the WHO Expert Committee on the Control of Leishmaniases
- Supported policy change for control and elimination of kala-azar in high endemic countries (India, Bangladesh, Nepal)

2016 ● **Superbooster therapy** **More effective treatment for children co-infected with HIV and TB**



Among the many challenges of treating children co-infected with HIV and tuberculosis (TB) is the fact that rifampicin, a key TB drug, negates the effectiveness of ritonavir - one of the main antiretrovirals (ARV) used to treat HIV.

DNDi carried out a pharmacokinetic study in 96 HIV/TB co-infected infants and young children at five sites in South

Africa, to demonstrate the safety and effectiveness of 'superboosting' - which involves adding extra ritonavir to the lopinavir/ritonavir (LPV/r) regimen.

An interim analysis, carried out in May 2015, demonstrated excellent safety and efficacy. The results were presented to the WHO Guidelines Review Committee, and in 2016 the WHO revised its guidelines to recommend 'superboosting' of ritonavir in treatment of co-infected children when on the LPV/r based therapy.

The final results showed that this approach counteracts the negative interactions between LPV/r and rifampicin, easing the co-administration of HIV and TB treatment for this particularly vulnerable population.



“TB is a major problem for HIV-positive children. The information gathered from the DNDi superboosting study helped to strengthen our knowledge on the treatment of small children who have TB and need lopinavir for their HIV treatment.”

Prof Helena Rabie
Paediatrician, Tygerberg
Hospital, South Africa

Regional offices to ensure good understanding of patients' needs

Regional offices are essential to the DNDi model as they entrench the organization both in endemic countries, providing proximity to neglected patients and to the doctors and researchers who understand field needs, conditions, and constraints, but also in countries where key partnerships with academia, industry, and public agencies are essential to fulfilling DNDi's mission.

Some regional offices play a key role in DNDi's R&D, access, facilitation of strategic networks of excellence, and capacity strengthening activities; others are more focused on building close partnerships with national and regional actors, or conducting advocacy, communications, and fundraising.

With the expansion of DNDi's portfolio to include diseases like hepatitis C, and with the creation of new initiatives like GARDP, DNDi's regional offices remain central to ensuring close connection with patients' needs, building strategic partnerships, taking on region-specific challenges, and facilitating delivery of operational and policy goals.



DNDi North America

Highlights 2016

- United Nations High-Level Panel on Access to Medicines issues a report that calls for new approaches to ensure innovation and access to health technologies
- UN Political Declaration on Antimicrobial Resistance highlights the need to improve access to existing medical tools, as well as the need to develop new products that are affordable and appropriately available to all who need them
- Huffington Post "Project Zero" campaign launches to raise awareness of NTDs and crowdfund for DNDi's sleeping sickness programme
- US Chagas Treatment Access Project launches to support Center of Excellence for Chagas Disease at UCLA-Olive View Medical Center in Los Angeles
- Biopharmaceutical company Celgene becomes the first US-based partner to join DNDi's Drug Discovery Booster
- Publication of feature piece on DNDi's model in Nature magazine by science journalist Amy Maxmen
- Open Synthesis Network launches with two US universities – Northeastern and Pace – to engage students in NTD drug discovery



DNDi Latin America

Highlights 2016

- Pilot project for access and implementation of Chagas diagnosis and treatment launches in four regions of Colombia, to boost national response in partnership with MoH
- Study results pave the way for treatment guidelines to change in Brazil, replacing Glucantime by AmBisome® as first-line VL treatment
- UNASUR (Union of South American Nations) High-Level Meeting with Health Ministry representatives discusses access to HCV treatment with DNDi participation
- DNDi Partners' Meeting in Rio de Janeiro gathers 300 neglected disease R&D stakeholders to debate regional and global issues, such as innovative funding and emerging public health challenges
- Newly-formed Social Movement against NTDs holds first meeting in Brazil, bringing together patients and public health actors in a new advocacy-focused initiative



DNDi India

Highlights 2016

- Retrospective study starts to determine occurrence of PKDL cases in previously treated VL patients
- DNDi becomes a founding member of newly-launched SPEAK India consortium, funded by the Gates Foundation, for post-elimination agenda for VL in South Asia
- Trainings in Good Clinical Practice and Good Clinical Laboratory Practice enable clinical staff to apply them in upcoming trials, particularly in Bihar, and to be briefed on specificities of regulations in India
- Two Indian universities join the Open Synthesis Network, a new open-source drug discovery project
- Experts' meeting with the Indian Council of Medical Research defines the most pressing medical needs and R&D gaps in drug-resistant infections in India

DNDi Democratic Republic of Congo

Highlights 2016

- Top-line results from the fexinidazole Phase III/IV study enable DNDi and Sanofi to pursue plans to submit for regulatory approval with the EMA in 2017
- Phase II/III study starts in seven sites in DRC to test SCYX-7158 as a single-dose treatment in 350 patients with stage 2 HAT

DNDi Japan

Highlights 2016

- Participation in the GGG (GHIT Fund, Gavi, Global Fund) high-level round table prepares policy inputs for the G7 Ise-Shima Summit
- 'Strategy on Drug Development for Neglected Tropical Diseases' symposium features at the 89th Annual Meeting of the Japanese Pharmacological Society
- TICAD6 post-event in Kenya gives massive impulse to science, technology, and innovation collaboration between Africa and Japan, with DNDi input
- DNDi seminar in Tokyo for academia, government representatives, and media highlights need to address mycetoma
- GHIT Fund supports DNDi's cutaneous leishmaniasis and screening projects

DNDi South-East Asia

Highlights 2016

- DNDi collaborates closely with the Malaysian MoH to develop and produce a new affordable HCV combination treatment
- Clinical trial starts in six sites in Malaysia to test the sofosbuvir and ravidasvir combination in 220 HCV patients
- DNDi engages R&D and civil society actors in Malaysia, Thailand, and other South-East Asian countries
- DNDi office moves to Kuala Lumpur and new Head of Office is hired

DNDi Africa

Highlights 2016

- Allometric pharmacokinetic study shows miltefosine remains an attractive option for combination with other drugs; conclusion is that for children, allometric dosing seems to be a better regimen and will be employed in future studies involving paediatric patients
- Paediatric HIV study extends to Uganda, with 5 new sites enrolling over 150 new patients by the end of the year



- LEAP 2.0 - the revamped Leishmaniasis East Africa Platform - launches, with expansion of R&D activities from VL to CL and PKDL, and inclusion of other countries (Eritrea, Somalia, South Sudan)
- Following advocacy from DNDi and the Mycetoma Research Centre in Sudan, mycetoma becomes the 18th disease to be included in the WHO NTD list
- Site initiation visits, protocol training, GCP and GCLP training pave the way for study of fosravuconazole as a potential mycetoma treatment





R&D STRATEGY & PORTFOLIO

Delivering a robust pipeline of new chemical entities

Since DNDi's inception in 2003, our research and development programme has combined both short- and longer-term strategies to maximize health impacts. The short-term approach, focusing the optimization of existing drugs to address immediate medical needs, has yielded six new treatments for neglected tropical diseases and malaria. In 2016, this total reached seven, as the results of a DNDi-led study confirmed the need to increase ritonavir dosages to counter drug-drug interactions for children co-infected with HIV and TB, prompting a change in WHO guidelines.



While the short-term approach unquestionably delivers improved treatment options for neglected patients, it still relies on using drugs that are suboptimal due to toxicity, safety, adaptability, or affordability issues. Our long-term strategy aims to develop entirely new chemical entities (NCEs) to treat neglected diseases, fight and prevent resistance, control these diseases, and ultimately achieve sustained elimination. NCEs must meet target product profiles that shape the design of pre-clinical candidates for development-stage testing, in terms of indications, targeted populations, clinical efficacy, safety and tolerability, route of administration, dosing frequency, cost, and time to availability.

Here, our portfolio is looking robust, with 14 NCEs, covering six out of the seven diseases in DNDi's remit. Nine of these NCEs were identified through DNDi's own drug discovery process, having completed screening, hit-to-lead, and lead optimization phases. The five others are the result of in-licensing with pharmaceutical industry partners. The recently launched 'Neglected Tropical Diseases Drug Discovery Booster' is a new approach bringing together pharmaceutical companies into a multilateral, simultaneous search for compounds. So far, four series have been identified and approved for further lead optimization by the five partners involved in this project.

In 2016, we saw the promising progression of NCEs through the development pipeline. Let us look at the three most salient examples. Firstly, fexinidazole became the first DNDi NCE to complete Phase II/III clinical trials successfully, with promising topline results encouraging us, together with industrial partners Sanofi, to seek to register fexinidazole as a new treatment for sleeping sickness in 2018 (see page 32). Secondly, we launched a Phase II/III hepatitis C clinical trial in Malaysia and Thailand, testing a combination of sofosbuvir, today's mainstay treatment, with the NCE ravidasvir from Egyptian manufacturer Pharco. If the trial is successful, it could help overhaul the approach to the disease by encouraging affordable scale up and providing one essential component of a test-and-cure approach (see page 45). Last but not least, our leishmaniasis pipeline has

produced eagerly awaited potential new oral treatments, with the nomination of two NCEs from the oxaborole and the nitroimidazole compound classes as pre-clinical candidates, with the promise of two more series producing development candidates from other compound classes (see page 26).

Maintaining an adequate translational pipeline of NCEs is critical to ensure the delivery of novel drugs. Often described as the 'valley of death' of drug development due to high attrition rates - 55% in pre-clinical studies and up to 70% in Phase I studies - the process of translating early discoveries from the laboratory, into effective treatments for patients is time-consuming and costly. The aim is to assess the liabilities of a drug candidate in terms of safety, efficacy, and tolerability. Should the drug candidate withstand the tests, it then progresses into efficacy trials in patients.



DNDi's pipeline in 2016 saw the advance of orally-active candidates from diverse structural classes along this translation pipeline. For filarial diseases, AbbV4083 (TylAMac) was nominated for pre-clinical development in collaboration with AbbVie. Emodepside, which DNDi will jointly develop as a treatment for onchocerciasis with Bayer, entered Phase I studies. SCYX-7158, which after fexinidazole could be the second new oral treatment for HAT, entered into a pivotal Phase II/III trial in the Democratic Republic of Congo. DNDI-6148 and DNDI-0690 entered into pre-clinical development for both visceral and cutaneous leishmaniasis (CL), while CpG-D35 for CL progresses with the initiation of two studies, one *in vitro* and one *in vivo*. For Chagas disease, a proof-of-concept study was initiated in Bolivia testing existing drugs, in combination with Eisai's NCE fosravuconazole, while a new proof-of-concept study was under development with fexinidazole. All of these efforts were made possible with the support and collaboration of the partnerships which are at the centre of DNDi's model to address patients' needs.

Drug development is a long journey filled with pitfalls and risks. Though the translation phase is one of the most challenging parts, it is also perhaps the most exciting and promising, in that it gives hope that scientific breakthroughs will lead to innovative medicines, and enable DNDi to fulfill its mission of bringing the best science to the most neglected.



Global Antibiotic Research & Development Partnership officially launched

May 2016 saw the launch of the Global Antibiotic R&D Partnership (GARDP), a joint WHO/DNDi initiative incubated by DNDi in support of the Global Action Plan for Antimicrobial Resistance. GARDP aims to develop new antibiotic treatments, promote responsible use, and ensure access for all in need.

The launch was celebrated on the occasion of the 69th World Health Assembly in Geneva, in presence of its seed funders – the Federal Ministry of Health of Germany, the Netherlands' Ministry of Health Welfare and Sports, the South African Medical Research Council, the United Kingdom Department for International Development, and Médecins Sans Frontières.

1. **Bernard Pécoul**, Executive Director, DNDi
2. **John-Arne Rottingen**, Chief Executive, Research Council, Norway
3. **Jeanette R Hunter**, Deputy Director General, Primary Health Care, Department of Health, South Africa
4. **Manica Balasegaram**, Director, GARDP
5. **Marie-Paule Kieny**, former Assistant Director General, WHO
6. **Mercedes Tatay**, International Medical Secretary, Médecins Sans Frontières
7. **Dagmar Reitenbach**, Head of Division, Federal Ministry of Health, Germany
8. **Marja Esveld**, Senior Policy Advisor, Department for Social Development, Ministry of Foreign Affairs, The Netherlands
9. **Lord Jim O'Neill**, Honorary Professor of Economics, University of Manchester

30 projects and 14 new chemical entities in the pipeline

	 Research			 Translation			 Development	
	Screen	Hit to Lead	Lead Opt.	Pre-clinical	Phase I	Phase IIa/PoC	Phase IIb/III	Registration
Human African Trypanosomiasis			SCYX-1330682 ★ SCYX-1608210 Oxaborole			SCYX-7158 oxaborole* ★	Fexinidazole ★	
Leishmaniasis	Screening	Leish H2L	DNDI-5421 ★ DNDI-5610 Oxaborole Amino pyrazoles ★ CGH VL Series 1 ★	DNDI-6148 Oxaborole ★ DNDI-0690 Nitroimidazole ★ CpG-D35 (CL) ★			New Treatments for HIV/VL New Treatments for PKDL MF/Paromomycin Combo for Africa	New VL Treatments Latin America
Chagas disease	Screening	Chagas H2L	Chagas Lead Opt Biomarkers			New Benz Regimens +/- fosravuconazole ★ Fexinidazole ★		
Filarial diseases	Screening		Macro Filaricide 3 ★	ABBV-4083 TylAMac ★	Emodepside ★			
Paediatric HIV					Two '4-in-1' LPV/r/ABC/3TC			LPV/r pellets with dual NRTI
Hepatitis C							Sofosbuvir/Ravidasvir ★	
Mycetoma							Fosravuconazole ★	

★ New Chemical Entity (NCE); fexinidazole (for HAT and Chagas disease) = 1 NCE; fosravuconazole (for Chagas and Mycetoma) = 1 NCE

* As of 2017, SCYX-7158 oxaborole will be named 'acoizaborole'.

7 achievements

(see pages 8 et 9)

Implementation	
Access	
NECT Nifurtimox-Eflornithine Combination Therapy	
SSG&PM Africa	
New VL Treatments Asia	
Benznidazole Paediatric Dosage form	
Superbooster Therapy Paediatric HIV/TB	
Malaria ASAQ FDC	Malaria ASMQ FDC

Key R&D milestones in 2016

Discovery

- Identification of three improved hit series by the NTD Drug Booster for VL and Chagas
- Start of the open source chemistry project with collaboration with five US, UK, and Indian universities

HAT

- Completion of three clinical studies on fexinidazole in children
- Last stage of clinical development of fexinidazole before potential submission to regulatory authorities in 2017
- Start of a Phase II/III on SCYX-7158 in stage 2 HAT patients

Leishmaniasis

- Nomination of DNDi-6148 as pre-clinical candidate for VL and CL
- Start of a Phase II study on a new combination treatment for CL in Peru
- Design of two Phase II studies on new treatments for PKDL in India/Bangladesh and Sudan
- Design of two PKDL infectivity studies in Bangladesh and Sudan
- Completion of a Phase III study for HIV/VL co-infected patients in Ethiopia

Chagas disease

- Start of a proof-of-concept (PoC) study on new benznidazole regimens and in combination with fosravuconazole in patients with chronic Chagas disease in Bolivia (and soon in Argentina)

Filarial diseases

- Start of Phase I in healthy human volunteers of Emodepside for onchocerciasis
- Nomination of AbbV4083 (TylAMac) as a pre-clinical candidate for filarial diseases

Paediatric HIV

- Uganda revises paediatric HIV treatment guidelines to include LPV/r pellets
- TB-HIV co-infection superboosting study results prompted a change in WHO guidelines increasing the dose of ritonavir to counter drug-drug interactions

Hepatitis C

- Start of the Phase II/III study on combination therapies, sofosbuvir plus ravidasvir, for HCV in Malaysia and soon in other countries

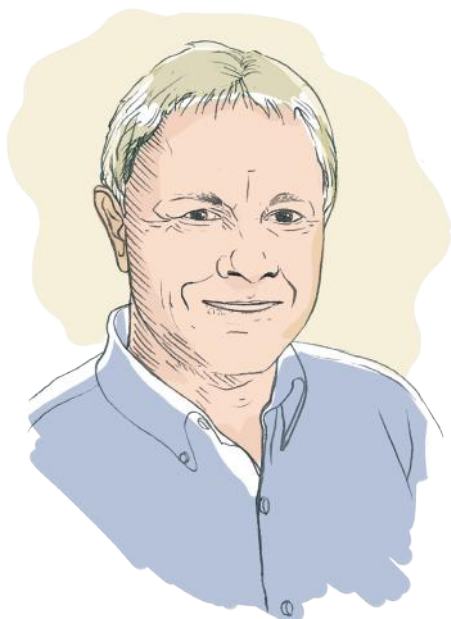
Mycetoma

- Design of a Phase II/III study on fosravuconazole for mycetoma in Sudan

December 2016

» FOCUS

DRUG DISCOVERY



Dr Robert Don

Discovery and Pre-Clinical Director
at DNDi (2005-2017)

How has drug discovery at DNDi evolved over the past decade?

Dr Robert Don reflects on challenges and achievements in drug discovery at DNDi over the last 12 years.

“ I joined DNDi in March 2005 to work in discovery – a three-stage process consisting of screening, lead selection, and lead optimization – essential to bringing forward new drugs.

At that point, there were no pre-existing consortia working on ‘our’ diseases as there were for other product development partnerships (PDPs). We were just working through bilateral agreements with pharmaceutical companies and screening centres. Over the last twelve years, we have consolidated our efforts, built up teams, and followed the usual pharmaceutical process for discovering new drugs.

We set up three consortia that undertake hit-to-lead and lead optimization activities for visceral leishmaniasis (VL) and Chagas disease in the US, Australia and, since 2013, Brazil. The latter is particularly significant as it is DNDi’s first neglected disease early-stage research programme launched in an endemic region.

DNDi is now starting to explore ‘open innovation’, an approach to drug discovery in which different actors actively collaborate without the restraints of intellectual property. We are venturing into this by three routes:

Firstly, **open source drug discovery**, in which all data and ideas are freely and immediately shared, and anyone may participate at any level. Typically, after a single hit has been identified, a large number of analogues are synthesized and tested. In the search for a pre-clinical candidate for Chagas disease, we produced and characterized 1,000 analogues of the antifungal agent fenarimol. This data set has been shared with the Open Source Drug Discovery project at the University of Sydney to facilitate the search for drugs for mycetoma.

The second approach is the **NTD drug discovery booster**, in which five pharmaceutical companies conduct a multilateral, simultaneous search of the millions of compounds in their compound libraries based on an active seed compound supplied by DNDi.

The most interesting compounds are tested and fed back into the process, refining the search in an iterative manner. This beautiful example of a productive collaboration between pharmaceutical companies and PDPs has surpassed my expectations: four hit series have been approved already thanks to a vastly accelerated process. The Booster runs at very little cost to either side – we estimate that each iteration saves about USD 90,000 compared to running the process in a conventional manner, and we have done 22 iterations so far. Although precompetitive research is not a new idea, the Booster takes it in a new direction.

...

"DNDi has demonstrated that it can build a credible drug discovery pipeline. As I retire, I am leaving an organization that is facing future challenges in a spirit of openness and innovation."

NTD Drug Discovery Booster

2016

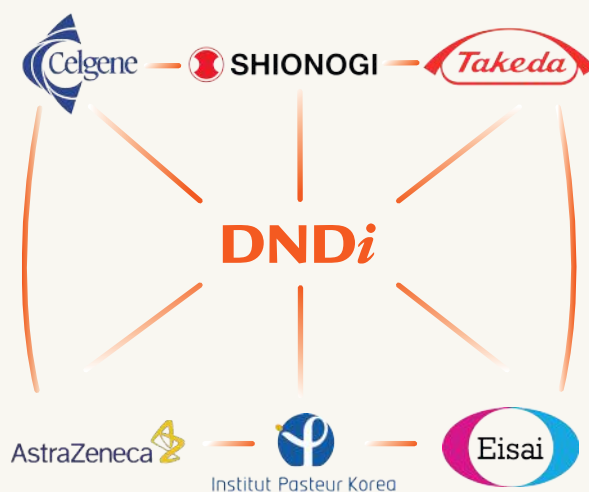
- Celgene became the 5th partner and the 1st US one
- 10,000 compounds from 7 different chemical series analysed at Institut Pasteur Korea (IPK)
- 4 series approved for further optimization



David Shum

Group Leader, Assay Development & Screening, Institut Pasteur Korea, South Korea

“IPK joined DNDi’s new initiative, the NTD Drug Discovery Booster programme, that cuts the cost of early-stage drug discovery, accelerates and expands discovery of new drugs for NTDs. In 2016, we identified four hit series that are currently advancing to further development. It is our hope that we can soon identify a breakthrough compound for patients.”





“This partnership will contribute to real-life medicinal chemistry projects featuring neglected disease research. By participating in the OSN project, our students will get an opportunity to enhance their skills in medicinal chemistry research and will develop an interest to work on real drug discovery projects.”

Dr Kapil Juvele

Assistant Professor, Narsee Monjee
Institute of Management Studies, India

Thirdly, we have been looking at ways to incentivize **crowd-sourcing**. We have approached universities with real problems from our lead optimization programme and suggested analogues of hits that we would like to test. Final year undergraduates and graduate students, who would otherwise synthesize well-known compounds that are then discarded, are given the challenge of synthesizing these analogues. These are then tested and the data returned to the students, who may then propose further analogues for testing, building up a rich source of information that may ultimately lead to the development of a life-saving drug. We are running a pilot with five universities – Imperial College London (UK), Pace University, New York, and Northeastern University, Boston (US), the Indian Institute of Chemical Technology, Hyderabad, and the Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management at Narsee Monjee Institute of Management Studies, Mumbai (India) – who are very enthusiastic about this approach. This project is open to expansion to other universities in the coming months.

The biggest challenge for open innovation lies ahead, in the next step of the drug discovery process, getting beyond an optimized lead. This ‘valley of death’, in which the vast majority of compounds fail, is expensive and requires good laboratory practice capacity, both are major barriers to academic involvement.

With the development of fexinidazole and SCYX-7158 for sleeping sickness and a promising pipeline of new compounds from oxaborole and nitroimidazole series for VL, DNDi has demonstrated that it can build a credible drug discovery pipeline. As I retire, I am leaving an organization that is facing future challenges in a spirit of openness and innovation.”

Highlights from drug discovery in 2016

Successful drug repurposing

2016 3 chemical series in development for visceral leishmaniasis (VL) – nitroimidazoles, aminopyrazoles, and oxaboroles – have shown remarkable *in vitro* and *in vivo* efficacy for cutaneous leishmaniasis (CL). A VL to CL pre-clinical candidate repurposing approach will accelerate access to patients, with very low impact on development cost.

High throughput screening

Two sorts of libraries are being screened for kinetoplastids:

Commercial compound libraries, screened at the Drug Discovery Unit at Dundee University. The large numbers of compounds available are important given the low hit rate for VL. Intellectual property rights are secured up-front allowing DNDi to publish, develop, and share results without further negotiation.

2016 New series for VL have been identified and are transitioning to our lead optimization programmes, mainly LOLA (Lead Optimization Latin America project).

Libraries from pharma and biotech companies, and other R&D organizations, screened by Institut Pasteur Korea. These well-characterized compounds allow DNDi to determine whether it is worth progressing a series.

2016 A collaboration with Daiichi Sankyo has identified 3 series for Chagas and VL that are progressing into hit-to-lead, with support from the GHIT Fund.



Compound libraries shared by the following partners:

AbbVie ■ Anacor ■ Astra Zeneca ■ BASF ■ Bristol-Myers Squibb ■ Broad Institute ■ Celgene ■ Daiichi Sankyo ■ Dupont ■ Eisai ■ GlaxoSmithKline ■ Janssen ■ Merck ■ Merck Serono ■ Merial ■ Medicines for Malaria Venture ■ Merck Sharp and Dohme ■ National Institutes of Health ■ Novartis ■ Pharmakon ■ Sanofi ■ Takeda ■ TB Alliance.

New assay to characterize drug activity profile

Swiss TPH has established and validated a number of VL and Chagas disease assay protocols on a new high content image analysis platform, allowing an understanding of the action of drugs over time in natural host cells (mouse macrophages).



Manu De Rycker

Portfolio Leader, Kinetoplastid Drug Discovery, Drug Discovery Unit (DDU), University of Dundee, UK

“Since 2014, DNDi, in partnership with the DDU, has accessed and screened over 550,000 molecules from commercial collections against VL and more recently Chagas disease. This screening effort aims at profiling around one million compounds by end of 2017 and identifying 10-15 novel active series to feed the DNDi preclinical pipeline for VL and Chagas.”

Promising screen results for filariasis

More than 20'000 compounds have been evaluated against *Onchocerca* species in the context of early screening, hit-to-lead, and lead optimization projects since 2012. The primary early screening aiming at identifying repurposing opportunities has shown promising opportunities.

2016 Resulting from this work, AbbVie and Celgene have agreed to support a lead optimization programme that provided 4 optimized leads.

➔ FOCUS

CLINICAL DEVELOPMENT

56 clinical sites, in 14 countries, for 7 diseases

The year 2016 marked a cornerstone in the clinical development of the potential first new oral treatment for sleeping sickness. The Phase III study with fexinidazole entered into the last stage of testing before potential submission to regulatory authorities in 2017, while SCYX-7158, another potential oral treatment, moved to Phase II/III.

New clinical activities were planned for leishmaniasis as two Phase II studies to test new treatments for PKDL - AmBisome® monotherapy and in combination with miltefosine in India and Bangladesh, and AmBisome® in combination with miltefosine, and paromomycin in combination with miltefosine in Sudan – were designed for launch in 2017. Two PKDL infectivity studies were also under preparation in Bangladesh and Sudan to establish the infectivity of PKDL patients to sandflies and determine if PKDL patients maintain inter-epidemic transmission of VL. A Phase III study to test the combination of miltefosine and paromomycin for VL was also planned for a launch in 2017.

In Bolivia, a proof-of-concept (PoC) study started in patients with chronic Chagas disease testing new regimens and durations of benznidazole, in monotherapy and in combination with fosravuconazole. This latest compound was also selected to be tested in a Phase II/III study in eumycetoma patients in Sudan in 2017, representing the first ever randomized clinical trial for the disease.

In Malaysia, a Phase II/III study was launched - soon to be extended to other countries – combining ravidasvir and sofosbuvir to develop a pan-genotypic regimen that works for all patients, including the most vulnerable.

Emodepside entered Phase I studies for the treatment of onchocerciasis.

The results of the Phase III HIV/TB co-infection 'super-boosting' study prompted a change in WHO guidelines, confirming the evidence around the need to increase ritonavir dosages to counter drug-drug interactions.

14 ongoing clinical trials

Phase I Research on safe dosage with healthy volunteers	Filarial diseases <ul style="list-style-type: none"> Emodepside single ascending dose for onchocerciasis (UK)
Phase II Early safety and proof-of-concept in patients	Leishmaniasis <ul style="list-style-type: none"> Thermotherapy & miltefosine combination proof-of-concept (Colombia, Peru) Chagas disease <ul style="list-style-type: none"> Evaluation of different single and combined regimens with benznidazole & fosravuconazole (Bolivia) Mycetoma <ul style="list-style-type: none"> Fosravuconazole proof-of-concept for eumycetoma patients (Sudan)
Phase III Larger scale safety and efficacy trials	Human African Trypanosomiasis <ul style="list-style-type: none"> Fexinidazole pivotal study (DRC) Fexinidazole study in adults with early stage 1 + stage 2 (DRC) Fexinidazole study in children with both stage 1 + stage 2 HAT (DRC) Study of fexinidazole in adults and children with option to take treatment at home (DRC) SCYX-7158 pivotal study in adults with stage 2 HAT (DRC) Leishmaniasis <ul style="list-style-type: none"> New treatments for HIV/VL co-infection (Ethiopia) Infectivity study for PKDL patients (Bangladesh) Paediatric HIV <ul style="list-style-type: none"> Lopinavir/ritonavir pellets with dual NRTIs implementation study in infants and young children (Kenya, Uganda) Hepatitis C <ul style="list-style-type: none"> Sofosbuvir/ravidasvir combination therapy study (Malaysia, Thailand)
Phase IV Post-registration trials for additional data	Leishmaniasis <ul style="list-style-type: none"> Follow-up study of PKDL in VL patients (India)

Protocols approved by at least one authority, Feb. 2017

Active sites in 2016

5 sites in Europe

- Spain
- UK

4 sites in Latin America

- Bolivia
- Peru

14 sites in India and South East Asia

- India
- Thailand
- Malaysia

33 sites in Africa

- Central African Republic
- Democratic Republic of the Congo
- Ethiopia
- Kenya
- South Africa
- Sudan
- Uganda

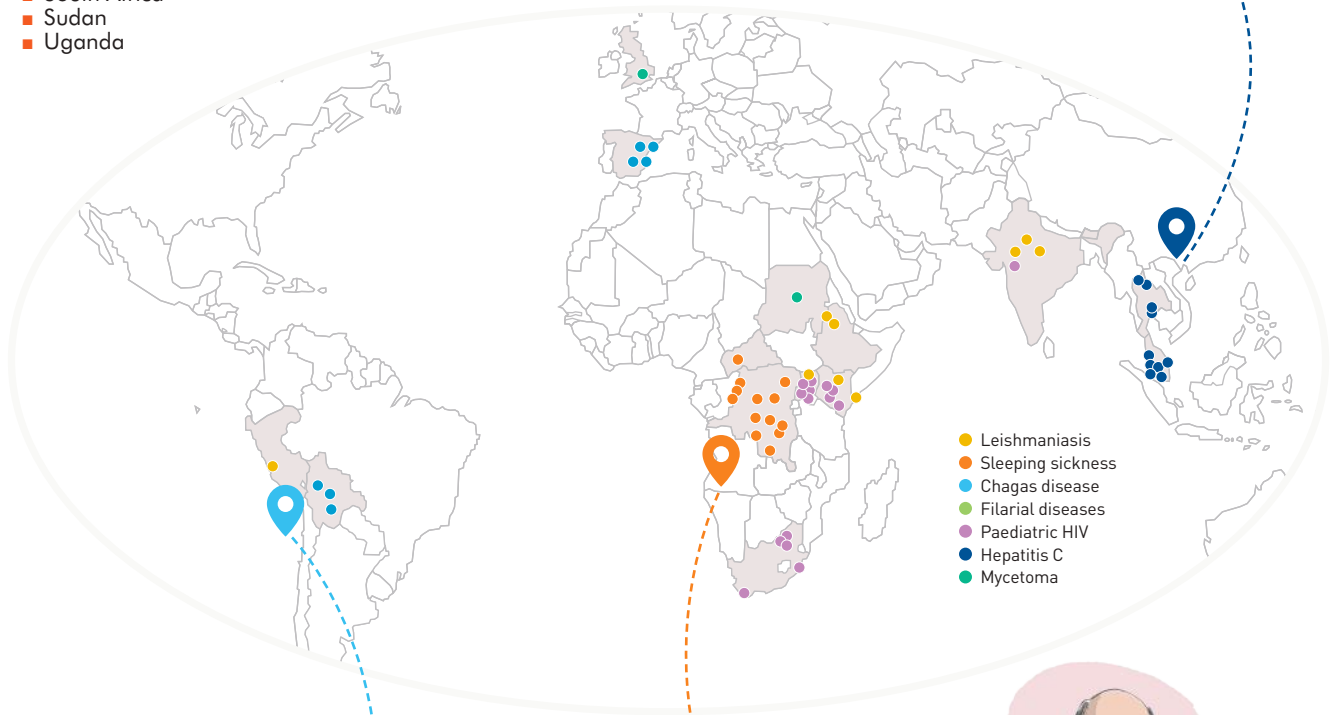


YB Datuk Seri Dr S Subramaniam

Minister of Health, Malaysia

“Because of the high prices of new hepatitis C medicines, it has been almost impossible for governments to provide access to treatment at the necessary scale. We hope data from these studies will support our efforts to introduce this combination as soon as possible and scale up to reach all patients in need.”

DNDi press release, April 2016



Dr Faustino Torrico

President, Collective of Applied Studies and Social Development (CEADES), Bolivia

“After 6 years of collaboration, CEADES and DNDi are pursuing joint activities as part of the BENDITA study. We hope that the results will provide the information needed on the best treatment regimen of benznidazole for Chagas patients.”



Dr Luc Kuykens

Senior Vice President, Global Head Medical Data Dissemination and Access to Medicines, Sanofi

“Sanofi has a long-standing partnership with the WHO to fight HAT, and fexinidazole will be a decisive new tool to ensure HAT elimination. In 2016, Sanofi, following the conclusion of clinical trials fully executed by DNDi and its local partners, have worked hard to anticipate all the work that will be needed to submit the fexinidazole registration file to Regulatory Authorities, and provide access to patients in the best possible timeframe.”



LEISHMANIASIS

- *Leishmania* parasite transmitted by the bite of a sandfly
- Three main forms of leishmaniasis: visceral (VL - fatal without treatment), cutaneous (CL), and mucocutaneous (MCL)
- Post-kala-azar dermal leishmaniasis (PKDL) is a disease causing skin lesions which mostly affects individuals after treatment for VL; PKDL may play a major role in disease transmission between epidemics
- VL in HIV co-infected patients is an increasing concern
- The treatment of leishmaniasis depends on several factors including type of disease, concomitant pathologies, parasite species, and geographic location

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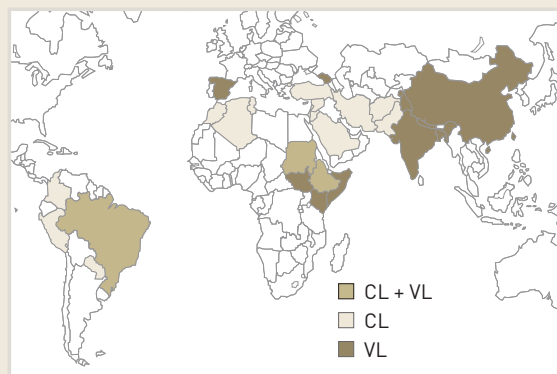
million people around
the world at risk



Until recently, pentavalent antimonials like sodium stibogluconate (SSG) were the mainstay of treatment for VL and CL, despite numerous drawbacks (toxic, difficult to administer, expensive, and even poorly efficacious in many regions). These drugs nevertheless remain the therapy of choice for CL, in the absence of an effective, safe, and affordable alternative, so R&D needs for CL remain acute.

For visceral leishmaniasis, alternatives do exist, with liposomal amphotericin B, paromomycin (PM), and miltefosine either developed or made available over the last 15 years. In its first decade of operation, DNDi research was aimed at optimizing regimens based on existing treatments.

...



→ 90% of new VL cases reported occur in seven countries:

- Brazil
- Ethiopia
- Kenya
- India
- Somalia
- South Sudan
- Sudan

→ Majority of CL cases reported occur in nine countries:

- Afghanistan,
- Algeria
- Brazil
- Colombia
- Iran
- Pakistan
- Peru
- Saudi Arabia
- Syria

20,000
to 30,000 deaths due
to VL annually

200,000
to 400,000 cases
of VL annually

5-10%
of VL patients
develop PKDL

700,000
to 1.2 million cases
of CL annually



Dr Márcia Hueb
Julio Müller Hospital,
Cuiabá, Brazil

“Treatment for leishmaniasis involves complicated injectable drugs. The diagnosis isn't easy, it depends on skill and knowledge. We must move forward.”

...

As a result, the combination of SSG and PM (see p. 8) is now the standard treatment in East Africa, while in South Asia single-dose AmBisome® is the first option, with paromomycin and miltefosine as a second line. Yet, these treatments still present safety, logistical, affordability, and access drawbacks, and the search for entirely new treatments – more patient-friendly, effective, safe, and ideally oral – is still the basis for DNDi's long-term R&D strategy.

Research needs in leishmaniasis are further complicated by specific questions that are yet to be addressed. While the VL case load is falling to such a degree that elimination targets appear to be within reach in South Asia, the role in *Leishmania* transmission played by PKDL and asymptomatic patients must be clarified if elimination is to be sustained. And in both South Asia and East Africa, better treatments are required for patients co-infected with HIV as current options are unsatisfactory, requiring long and often repeated courses of treatment, including with antimonials.



“I feel ashamed of myself and don't feel like going anywhere. People around laugh at me with sarcasm and sometimes hatred. I felt humiliated because of these scars on my face.”

Ruby Devi

PKDL patient diagnosed when seven months pregnant,
New Delhi, India

DNDi aims to deliver:

- A safe, effective, low-cost and short-course, oral treatment for VL
- A new treatment for PKDL that is shorter and better tolerated than current options
- A new treatment regimen for patients co-infected with HIV and VL
- A safe, effective, and shorter-course treatment for CL



“This disease has destroyed my life, my wife left me, I can't see my children as much as I used to and I was fired from my job because I was too weak to work. All that I had was used to pay medical bills.”

Tsadik

35 years old, HIV-VL patient, Abdurafi, Ethiopia



Leish H2L

Hit-to-lead for leishmaniasis

OBJECTIVE: Identify new leads series from current ongoing hit-to-lead activities by taking advantage of the optimization consortia and screening platforms for leishmaniasis.

Background: 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 optimization to identify promising lead compounds.

2016 This process of hit-to-lead optimization is ongoing with multiple series from several pharmaceutical companies. If promising activity can be demonstrated in pre-clinical models of leishmaniasis, the series will be advanced into full lead optimization.



DNDI-5421 & DNDI-5610 oxaboroles

OBJECTIVE: Maintain back-up oxaboroles which could replace the pre-clinical candidate DNDI-6148 in case it does not succeed in development.

Background: These two compounds from the oxaborole class from Anacor Pharmaceuticals serve as back-ups to DNDI-6148. Their further development is currently on hold and will only recommence should problems be encountered with the pre-clinical development of DNDI-6148.



Aminopyrazoles

OBJECTIVE: Select a pre-clinical candidate from the aminopyrazole series for the treatment of leishmaniasis.

Background: The aminopyrazole class of compounds originally from Pfizer has shown promising early profiles for the treatment of both VL and CL. 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, pharmacokinetics, and initial *in vitro* safety assays are all underway. The ongoing lead optimization programme in collaboration with Takeda and supported by the GHIT Fund aims to select an optimized lead.

2016 Preparation of active pharmaceutical ingredient (API) and formulation for the second generation leads to enable the exploratory toxicology studies early 2017.



CGH VL series 1

OBJECTIVE: Select a pre-clinical candidate from the CGH VL series for the treatment of VL.

Background: A novel series of heterocyclic compounds for VL has been optimized by Celgene in collaboration with London School of Hygiene and Tropical Medicine and Advinus, and with advice from DNDi.

2016 An *in vivo* proof-of-concept has been achieved for this series. An intensive lead optimization programme is ongoing with Celgene to identify an optimized lead.



TRANSLATION

DNDI-6148 oxaborole

OBJECTIVE: Progress the pre-clinical development of DNDI-6148, a selected oxaborole for the treatment of leishmaniasis.

Background: The Lead Optimization US programme has progressed the compound DNDI-6148 into pre-clinical development. DNDI-6148 resulted from medicinal chemistry optimization of hits with activity against *Leishmania* originally identified from screening of Anacor's oxaborole library.

2016 In January, DNDI-6148 was nominated as a pre-clinical candidate for the treatment of VL. Pharmaceutical development activities (drug substance and drug product development and manufacture) have now been initiated, and the toxicity/safety pre-IND package was launched, starting with dose range finding studies, along with refinement of ADME (absorption, distribution, metabolism, and elimination), and efficacy and safety profiles to ensure a smooth transition from pre-clinical to Phase I clinical studies, which should happen over the course of 2017.



TRANSLATION

DNDI-0690 nitroimidazole

OBJECTIVE: Progress the pre-clinical development of DNDI-0690, a selected nitroimidazole for the treatment of VL and possibly CL.

Background: Following the termination of the VL-2098 project in early 2015, two lead compounds from the nitroimidazooxazine back-up programme were progressed. One of these, DNDI-0690, showed good to excellent activity *in vitro* against both VL and CL-causing strains of *Leishmania* and was nominated as a pre-clinical candidate in September 2015.

DNDI-0690 and other potential lead compounds for VL were 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.

2016 DNDI activities focused on pharmaceutical development activities (drug substance and drug product development and manufacture), launching of toxicity/safety pre-IND package with dose range finding studies, as well as refinement of ADME, efficacy and safety profile to ensure a smooth transition from pre-clinical to Phase I studies, which should happen over the course of 2017.



CpG-D35 for CL

OBJECTIVE: Produce an immunomodulator to stimulate the innate immune system to fight the parasitic infection causing CL as an adjunct to drug therapy.

Background: CpG-D35 is being developed as a combination therapy for the treatment of complicated CL and post-kala-azar dermal leishmaniasis (PKDL) in partnership with GeneDesign. *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.

2016 Two studies, one *in vitro* and one *in vivo*, were initiated. The *in vivo* study aims to demonstrate if CpG-D35 – whether alone or in combination with antimonials chemotherapy – will lead to improved *Leishmania* infection outcomes, compared with antimonials alone. The *in vitro* study aims to assess the stimulatory capability of CpG-D35 in both peripheral blood mononuclear cells and whole blood samples from patients with both CL and PKDL, and to determine which host genes are modulated in these two conditions. Results of both studies are expected by the end of 2017.



New CL combination therapies

OBJECTIVE: Further explore opportunities to better use the existing approved treatment approaches for CL when used in combination.

Background: When administrated alone, the safety and efficacy profiles of current CL treatments are well established. A combination of therapeutic approaches may improve efficacy rates, reduce treatment duration, and improve the rate of adverse events. A combination of one single application of thermotherapy at 50°C for 30 seconds with a three-week course of oral miltefosine will be tested in order to gain information about safety and efficacy.

2016 After official approvals were obtained, a site initiation visit was conducted and the first patients were enrolled in Peru at the end of 2016. Final approvals are expected by early 2017 for a second site in Colombia.



Fexinidazole/miltefosine combination [completed]

OBJECTIVE: Develop an oral-only therapy for the treatment of VL.

Background: Before proceeding to a proof-of-concept study in patients, a drug-drug interaction study was to be conducted in up to 60 healthy volunteers to assess the combination's pharmacokinetics, tolerability, and safety.

While ethical approval was granted, French regulatory authorities stated that there was not sufficient information available to justify a study in healthy volunteers. Considering the excellent activity of the new oral chemical entities currently in pre-clinical development for VL, the development of the fexinidazole/miltefosine combination was stopped.



Anfoleish for CL [completed]

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

Background: The aim was to develop a topical formulation of amphotericin B to be applied at the CL lesion, that showed high anti-parasitic effect without the systemic toxicity associated with amphotericin B. A Phase Ib/II open-label, randomized, non-comparative, two-arm exploratory study was conducted in Colombia. Enrolment of all 80 patients with CL caused by *L. braziliensis* and *L. panamensis* was completed in November 2015.

Study results did not support continuation of the clinical development of Anfoleish in its current formulation. Alternative options are currently under consideration.





New treatments for HIV/VL

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

Background: In 2014, a Phase III study testing both AmBisome® monotherapy (at a higher dose than current practice) and a combination of AmBisome® and miltefosine was initiated in Ethiopia for the treatment of HIV/VL co-infection. After 132 patients had been enrolled, recruitment was interrupted at the time of the second interim analysis, as efficacy at the end of treatment was lower than expected. Patients who had not achieved cure at the end of treatment were given a second cycle of the same treatment.

2016 Results obtained with the extended duration of the combination treatment were very promising; the majority of patients achieving VL cure. These results were based on a limited number of patients; a new HIV/VL study is therefore under consideration to confirm this.



New treatments for PKDL

OBJECTIVE: To determine the safety and efficacy of two treatment regimens for patients with PKDL, mainly in the Indian Sub-continent and East Africa.

Background: DNDi is prioritizing the management of PKDL patients who are believed to constitute a potential reservoir of infection for VL in the Indian Sub-continent and East Africa. Early treatment of PKDL patients could be critical elements of any VL public health and elimination strategy.

2016 A Phase II study testing both AmBisome® monotherapy and a combination of AmBisome® and miltefosine is underway in India and Bangladesh to assess the safety and efficacy for patients with PKDL. A separate Phase II study to assess the safety and efficacy of both AmBisome® in combination with miltefosine, and paromomycin in combination with miltefosine, is planned in Sudan. Site visits have been undertaken at all participating sites in the three countries, and protocols and study documents are under finalization for submission to ethical and regulatory review. In addition, two PKDL infectivity studies are under preparation in Bangladesh and Sudan. Their objective is to establish the infectivity of PKDL patients to sand flies, to determine if PKDL patients maintain inter-epidemic transmission of VL.



Dr Pradeep Das

Director, Rajendra Memorial Research Institute, Patna, India

“After a long collaboration with DNDi for research for VL, we are now entering into bringing new treatments for PKDL patients. This collaboration will definitely help the poor patients

standing last in the queue with better and affordable treatment. To invest in research on the precise role of PKDL patients is critical as they could maintain transmission of visceral leishmaniasis during inter-epidemic periods. Early treatment of the most infective PKDL patients should be a priority element of any VL public health and elimination strategy.”



DEVELOPMENT

Miltefosine/paromomycin combinations for Africa

OBJECTIVE: Assess the efficacy and safety of two combination regimens of paromomycin (PM) and miltefosine as compared to SSG&PM for the treatment of primary VL patients in Eastern Africa.

Background: A Phase III clinical trial will be conducted in East Africa to compare the efficacy and safety of two combination regimens of miltefosine and PM with the current standard VL treatment sodium stibogluconate (SSG)&PM, in both paediatric and adult patients. Sites will be located in Kenya, Sudan, Uganda, and Ethiopia. If the combination is proven safe and efficacious, current treatment would no longer rely on SSG, an injectable drug, but would be replaced with miltefosine, an oral drug. A safer, more field-adapted, patient-friendly treatment would particularly benefit children, who represent a high proportion of the population at risk in East Africa.

2016 The trial protocol is under finalization and will be submitted to ethics committees and regulatory authorities in early 2017.



DEVELOPMENT

New VL treatments in Latin America

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, supporting the Brazilian Ministry of Health and its partners.

Background: In 2011, a Phase IV study sponsored by the Brazilian Ministry of Health (FINEP) was initiated at five sites in Brazil to evaluate the efficacy and safety of Amphotericin B deoxycholate, AmBisome®, and a combination of AmBisome® and Glucantime®, in comparison to Glucantime®, the existing first-line treatment of VL. 378 patients were recruited. Brazil's national guidelines for VL were revised in 2013 based on the interim safety data from the trial. While Glucantime® remains the first-line treatment, AmBisome® replaced Amphotericin B deoxycholate as a second-line treatment.

2016 The final results of this trial were presented to the Ministry of Health, and are expected to guide further policy change in Brazil as of 2017.

378
patients
recruited
at 5 sites





HUMAN AFRICAN TRYPANOSOMIASIS

Sleeping Sickness

- Caused by two subspecies of *Trypanosoma brucei* (*T. b.*) *gambiense* (g-HAT; 98% of reported sleeping sickness cases) and *T. b. rhodesiense* (r-HAT)
- Transmitted by the tsetse fly
- Occurs in two stages:
 - the early stage (stage 1) with non-specific symptoms, often un- or misdiagnosed
 - the late stage (stage 2) where the parasite crosses the blood-brain barrier, causing serious neurological disorders including sleep cycle disruptions, neurological manifestations, and progressive mental deterioration
- Without effective treatment, the disease usually leads to death
- The WHO Roadmap objective: to eliminate HAT as a public health problem by 2020



The combination therapy Nifurtimox-Eflornithine (NECT), developed in 2009 (see p. 8), replaced the toxic treatments for HAT. NECT is now used to treat 100% of stage 2 HAT identified patients infected with *T. b. gambiense*, and has contributed to the fall in the case load. But treatment remains cumbersome, difficult to ship, store, and administer; patients must be hospitalized and undergo a complex and painful lumbar puncture to first determine the stage of the disease.

New oral treatments in combination with rapid diagnostic tests would shift the treatment paradigm, and are needed to reach the final mile of WHO's elimination target⁽¹⁾ and ensure its sustainability, particularly as HAT has a history of resurging in epidemics.

13
million people
estimated
to live in areas at
moderate to very
high risk

65
million people
at risk



T. b. gambiense
is endemic in

24

countries of West
and Central Africa
2,733 new cases
reported (2015)

T. b. rhodesiense
is endemic in

13

countries
of Eastern and
Southern Africa
71 new cases
reported (2015)



“I began to feel tired and weak. I was cold all the time even when it was hot. My bones ached terribly. I could sleep during the day but not at night. I didn't know what was wrong until I was diagnosed with sleeping sickness.”

Jean de Dieu Liyande Walo

52, a survivor of sleeping sickness, a cassava and rice farmer, and a part-time preacher. Yalikombo, a village located on the Congo river, DRC

DNDi aims to deliver:

- A safe, effective, and orally administered drug to replace current first-line HAT treatments, and to improve and simplify current case management
- The ideal goal is to develop two drugs that are effective against both stage 1 and 2 HAT and both subspecies of the parasite

If successful, this would represent a fundamental shift in disease management, as it would remove the need both for a risky and painful lumbar puncture test to confirm the disease stage, and for hospitalization, as treatment would no longer rely on administering a drug intravenously.

⁽¹⁾ Less than one case per 10,000 inhabitants in at least 90% of endemic foci is expected.



RESEARCH

SCYX-1330682 and SCYX-1608210 oxaboroles

OBJECTIVE: Maintain back-up oxaboroles which could replace the drug candidate SCYX-7158 in case it does not succeed in development.

Background: These two back-up candidates from the oxaborole class have demonstrated cure for stage 2 of the disease in the mouse model. 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.



TRANSLATION

SCYX-7158 oxaborole⁽¹⁾

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.

Background: SCYX-7158 was selected as a pre-clinical candidate for g-HAT in late 2009. This resulted from DNDi's own lead optimization project starting with an initial hit identified in the Anacor chemical library. In 2012, it became DNDi's first new chemical entity resulting from its own lead optimization programme to enter clinical development. SCYX-7158 is expected to be administered directly at home.

Phase I trials were completed in 2015, and allowed the therapeutic dose to be determined at 960mg administered orally in a single dose of three tablets.

11
patients
recruited
at 7 sites

2016 A pivotal Phase II/III study started in seven clinical sites – Katanda, Isangi, Dipumba, Ngandajika, Masi Manimba, Kwamouth, and Bolobo – in the Democratic Republic of the Congo (DRC). Eleven patients (out of a target 350) had been recruited by the end of 2016.

The submission of a regulatory dossier to the European Medicines Agency under Article 58 is planned for 2021.



(1) As of 2017, SCYX-7158 oxaborole will be named 'acoziborole'.



DEVELOPMENT

Fexinidazole

OBJECTIVE: Develop and register fexinidazole as a new oral drug for the treatment of stage 2 HAT caused by *T. b. gambiense*, ideally also for stage 1 HAT and for children between 6 and 14 years old.

Background: Fexinidazole, the result of successful compound-mining efforts pursued by DNDi in 2005, entered clinical development in September 2009 and is being co-developed with Sanofi. The 10-days oral-only treatment could be administered at the primary healthcare level, ideally allowing patients to take the medicine at home.

In 2015, DNDi and the National HAT Control Programme (PNLTHA) of the DRC completed the recruitment of 394 adult patients with stage 2 HAT at nine clinical sites in the DRC and one (supported by MSF) in the Central African Republic, for a pivotal Phase II/III study.

2016 Two complementary cohorts to the Phase II/III study were completed in 2016, one including 230 adult patients with stage 1 and early stage 2 of the disease, and another including 125 children between six and 14 years, both in DRC sites. Follow up of patients will be completed in 2017.

A Phase IIIb study aimed at getting more information about special population groups not included in previous fexinidazole trials (pregnant or lactating women, and patients with poor nutritional status or with chronic diseases) started in 2016. Patients will be treated either in hospital, or at home, thereby also providing preliminary information about the treatment compliance and final effectiveness in ambulatory patients. Three sites were initiated (Bandudu, Mushie, and Bagata) and six patients (out of a target of 174) had been recruited by the end of 2016.

The results of the Phase II/III study support the submission of a regulatory dossier to the European Medicines Agency under Article 58, planned for late 2017 for the treatment of g-HAT with fexinidazole. It aims to facilitate faster WHO prequalification of the medicine as well as regulatory approvals and implementation in endemic countries. A risk management plan to further monitor safety and efficacy in the field is under preparation in collaboration with Sanofi and WHO.

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

755
patients
recruited
at 10 sites



The challenge of conducting clinical studies in remote areas

Masi-Manimba hospital in the province of Bandundu, DRC, one of the sites where DNDi clinical trials for sleeping sickness take place

As fexinidazole enters the final stages of its clinical development, the fact it may become both DNDi's first new chemical entity and a new oral treatment that could radically transform sleeping sickness patient management, means there may be much to celebrate. Even more so when one considers how much of a daunting challenge running clinical trials in the remoter areas of a country like the Democratic Republic of the Congo (DRC) can be.

Because sleeping sickness occurs in very remote areas of the country, there are two major operational challenges that need to be overcome.

The first major challenge is infrastructure. Ensuring local physical capacities, including in-patient wards and onsite labs, are up to the task of conducting Good Clinical Practice (GCP) compliant clinical research and can deliver quality results is imperative. In the DRC, nine referral treatment units were renovated for the fexinidazole trials. Buildings were refurbished, with solar energy equipment and generators installed to ensure the regular supply of electricity needed to operate lab equipment and computers, and even to maintain the cold chain to store reagents. Emergency medical equipment such as defibrillators and technical equipment such as the Piccolo analyser, a fully automated system for blood testing, were brought in. Internet access was installed to enable transmission of electronic case report forms, particularly necessary for the monitoring of safety parameters.

Overcoming the lack of trained staff is the second big hurdle. Through the HAT Platform (a regional disease-specific clinical research network supported by DNDi) trainings were provided in diagnostic techniques and treatment procedures, pharmacovigilance, GCP

guidelines, in the performing and interpreting of electrocardiogram results, and even medical waste management.

Ensuring real-life field conditions are included in any trial set up is critical to its success. The joint experience of DNDi, Médecins Sans Frontières, and the national sleeping sickness control programme in the DRC - notably thanks to the committed mobile teams - shows it is possible to build an environment conducive to running high quality clinical trials. In overcoming these challenges, our hope is that this effort serves not only to build and sustain the capacity to conduct a high standard of clinical research in endemic countries and particularly remote areas, but also to bring lasting benefits to researchers, staff and hospitals, as well as to health systems more broadly, and thus ultimately to local communities and patients ■



Dr Crispin Lumbala
Director, National Control
Programme for Sleeping
Sickness, DRC

“I have been involved in DNDi's clinical trials on NECT and fexinidazole. To ensure that they were Good Clinical Practice compliant, we needed to strengthen capacities in terms of infrastructure and expertise. These improvements will be useful to the Congolese research community and should last for future studies. More importantly, this will benefit our patients and will help us on our way to eliminate sleeping sickness as public health problem.”



CHAGAS DISEASE

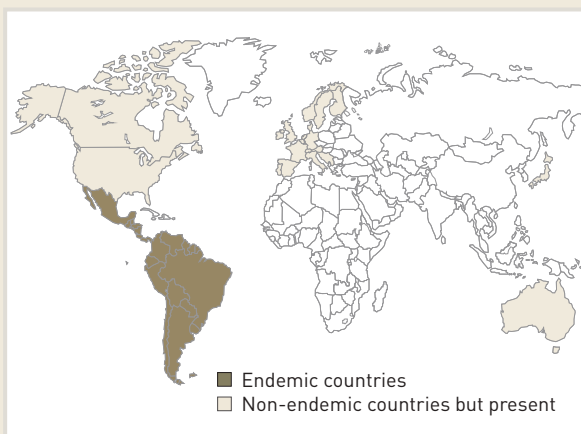
- *Trypanosoma cruzi* parasite transmitted by the bite of a triatomine vector known as the 'kissing bug'
- Congenital transmission, blood transfusion, organ transplantation, or ingestion of contaminated food or beverages also possible
- Endemic in 21 countries in Latin America but also in Europe, North America, Japan, and Australia
- Occurs in two phases:
 - the initial acute phase, with no or unspecific symptoms in most cases; lasts for about two months after infection, and
 - the chronic phase, where the parasites are hidden mainly in the heart and digestive muscles.
- Up to 30% of chronically infected people develop cardiac alterations and up to 10% develop digestive, neurological, or mixed alterations. In later years, can lead to sudden death due to cardiac complications

70

million people at risk,
mainly in Latin America

6 to 8

million people infected



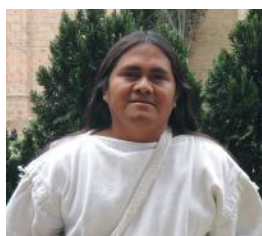
About
12,000
deaths annually

Less than
1%
of infected people have
access to diagnosis
and current treatments



Current available treatments are more than 40 years old, and while they show good efficacy in the acute phase, they need to be used in long regimens and cause significant side effects. The efficacy and safety of shorter treatment courses and/or at lower doses need to be explored. New drugs and new combinations are also needed, and there is currently no approved treatment for the chronic form of the disease.

Lastly, the dire situation of access and extremely limited use of existing drugs needs to be tackled, caused by a lack of guidelines and policies supporting implementation and the poor availability of medicines.



“I am dedicated to informing my community about Chagas disease, especially the children and youth. But what can I say to those adults that access treatment?”

Duámaco Escribano

Chagas patient and community health activist, Palomino, Colombia

DNDi aims to deliver:

- Alternative regimens of existing drugs (lower doses, shorter treatment duration, and combinations)
- A safe and efficacious new drug treatment of chronic Chagas patients, ideally efficacious for acute Chagas patients, also safe to use during pregnancy
- An early test of cure and/or markers of therapeutic response



Chagas H2L

Hit-to-lead for Chagas disease

OBJECTIVE: Identify new lead series from current ongoing hit-to-lead activities by taking advantage of the optimization consortia and screening platforms for Chagas disease.

Background: The project evaluates hits identified from screening and begins the process of optimizing new chemical series. If promising activity can be demonstrated in *in vivo* models of Chagas disease, the series will be advanced into full lead optimization programmes. This process of hit-to-lead optimization is ongoing with multiple series identified following DNDi screening efforts and coming from several pharmaceutical companies.



Chagas lead optimization

OBJECTIVE: Optimize leads issued from hit-to-lead series and identify pre-clinical candidates with the potential to fulfill the target product profile.

Background: In order to guarantee a robust pipeline for new drug candidates, a lead optimization strategy is being followed that explores a range of chemical scaffolds.

2016 Two new compounds issued from two new chemical classes showed curative activities against chronic infection of Chagas disease in a bioluminescence imaging mouse model developed by the London School of Hygiene & Tropical Medicine. It was the first time that non-nitroimidazoles compounds have been found to be curative in this model.



New benznidazole regimens +/- fosravuconazole



OBJECTIVE: Evaluate new therapeutic regimens of benznidazole, in monotherapy and in combination with fosravuconazole, for the treatment of adult patients with chronic indeterminate Chagas disease.

Background: Benznidazole, the standard treatment for Chagas, has sustained efficacy until 12 months post-therapy, but is associated with side effects that can result in treatment discontinuation. In 2013, a proof-of-concept trial showed that fosravuconazole, an azole-class antifungal drug discovered by Eisai, had good safety and was effective at clearing the parasite, but efficacy was not sustained. A Phase I drug-drug interaction study 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.

2016 Regulatory approvals were secured in Bolivia to start a Phase II Proof of Concept study to determine if the safety and tolerability issues of benznidazole could be managed by reduced doses and treatment duration, or by combining it with fosravuconazole. Benznidazole in monotherapy or in combination with fosravuconazole at selected doses and treatment durations will be assessed versus placebo in 210 patients with chronic Chagas disease. Recruitment started at the end of November; 10 patients had been enrolled by the end of 2016.



Fexinidazole

OBJECTIVE: Evaluate fexinidazole for treatment of chronic Chagas disease.

Background: A Phase II Proof of Concept study of fexinidazole was initiated in 2014 in Cochabamba and Tarija, Bolivia. A total of 47 patients were included, but the study was interrupted due to safety and tolerability issues. Analyses of key outcomes demonstrated high efficacy findings at the lowest dose tested and for all treatment durations, with safety concerns about treatment at high doses tested for more than 14 days. In addition, acceptable safety and tolerability were found at low doses and short treatment durations. Taken together, these results warrant further investigation of fexinidazole for Chagas disease.

2016 A new PoC study has been designed and will be run in four sites in Spain. Recruitment of patients is planned for 2017.



Biomarkers

OBJECTIVE: Identify and evaluate new biological markers of therapeutic efficacy in chronic Chagas disease.

Background: DNDi has been seeking to identify and/or evaluate biomarkers of therapeutic response to treatment, as the only measurable outcomes to date have been the disappearance of anti-Chagas antibodies which, with the exception of children, can take several decades, and clinical benefit. The initial focus has been on optimizing blood sampling procedures and validation of DNA quantification through polymerase chain reaction, one of the key outcome measures in use for clinical trials in Chagas disease.

2016 Pre-clinical studies are ongoing to identify and validate potential biological markers of therapeutic response in Chagas disease patients. In addition, through the Ibero-american network NHEPACHA, DNDi is fostering and encouraging work on testing four biomarkers to assess the response to treatment of Chagas.





A young woman in the village of Jerusalem, close to Rio Claro in the Andes, Colombia

Bringing Treatment to the Forgotten 99%

The treatment access pilot programme in Colombia

Treatment of Chagas disease with existing drugs is recommended worldwide but less than 1% of those infected have access to diagnosis and treatment. There are over six million people around the globe infected with *T. cruzi*, the parasite that causes Chagas disease. The disease impact is high in the lives of those affected. It has an important economic burden on countries, with high health care costs and a significant loss of productivity from cardiovascular disease-induced early mortality. This represents a missed opportunity for adding to patients' healthy, productive years of life while reducing the economic burden on the public system.

People with Chagas disease are prevented from receiving the medical attention they need due to many factors that lead to a cycle of neglect. Political and economic inequalities offer structural barriers for access to diagnosis and treatment, as well as the gaps on the health systems, availability of diagnostic and treatment options, and the associated stigmatization, misconceptions, and prejudices about Chagas disease.

In different settings across the world, people are taking action to overcome these obstacles. In Colombia, stakeholders from Government, academia, NGOs, and patient organizations are working in partnership with DNDi aiming to eliminate barriers to diagnosis and treatment for Chagas disease in the country for its estimated 437,000 patients.

This cooperation started in 2015, with a seminar in Bogota that identified four different key barriers to access in Colombia: a lengthy, complex diagnostic process that created long delays; low awareness of Chagas disease among providers and patients; the absence of registered medications and availability; and the fact that specialists who were providing treatment were far from patients' communities.

This analysis led to two initiatives in 2016: first, a patient-centred roadmap was created for Chagas disease and implemented in pilot projects in selected endemic communities in Colombia. Four endemic municipalities volunteered and were selected to join the pilot project in the departments of Boyacá, Santander, Casanare, and Arauca. Second, a new diagnostic model was proposed to the health representatives of each department of the country.

The first capacity building training for health and laboratory workers from Casanare, one of the Colombian departments with the highest prevalence of Chagas disease in the country, took place in December.

Once the model has been tested, it is expected to be extended to the rest of the country – with the support of the Ministry of Health, territorial entities, the National Health Institute, and DNDi – in order to guarantee the diagnosis, care, and timely treatment of patients with Chagas disease. Also, this model could be replicated by other countries in Latin America after the identification of local barriers and a consideration of the contextual analysis ■

Partnering for Access

Drug registration is an important step to overcoming barriers to accessing medicine.

In June 2016, DNDi and the pharmaceutical company Chemo Group, together with non-profit foundation Mundo Sano, signed a formal collaboration to register benznidazole, the first-line treatment for Chagas disease, in affected countries mainly in Latin America. It also includes the USA, through the Food and Drug Administration (FDA).

DNDi and Mundo Sano's strategy, with partners, is, to scale up access to diagnostics and treatment for Chagas patients – supported by a comprehensive action plan – in both endemic and non-endemic countries.

Alejandro Gaviria

Minister of Health and Social Protection, Colombia

“Colombia wants to lead the way in the fight against neglected diseases. Nobody can do this alone and the collaboration with DNDi has shown that it is feasible to address the long-term challenge of Chagas disease in the country. We want to step away from a legacy of human suffering and disease and pave the way to a better future.”





FILARIAL DISEASES

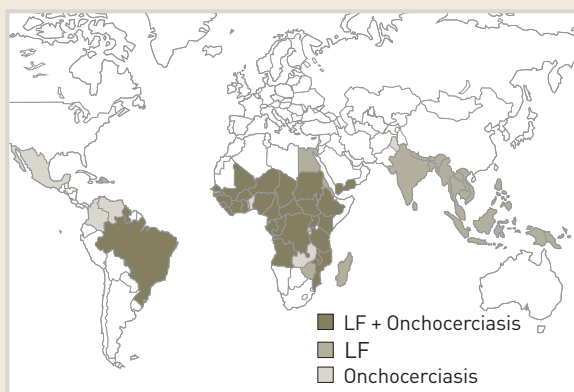
- Filarial diseases from parasitic filarial nematode worms are transmitted to humans by blood-sucking insects
- There are three filarial diseases: lymphatic filariasis (LF, also known as elephantiasis), onchocerciasis (also known as river blindness) and loiasis (also known as *Loa loa*, or African eye-worm)
- Filarial diseases are rarely fatal but can inflict immense hardship on millions of people. Onchocerciasis and lymphatic filariasis cause life-long disabilities such as blindness, severe itching, dermatitis, and swollen limbs and genitals
- Lymphatic filariasis is endemic in 54 countries worldwide
- Onchocerciasis is endemic in 31 African countries

947

million people
at risk of LF

Over 120

million people
infected with LF



169

million people at risk
of onchocerciasis

Over 37

million people infected
with onchocerciasis



Existing treatments, such as ivermectin - the microfilaricide used in mass drug administration (MDA) programmes - take years to be effective. This is because although they kill juvenile worms, they do not kill adult worms which continue to reproduce. MDAs therefore need repeating once or twice a year, for over a decade. A short-course treatment that kills adult worms, and reduces the number of MDA cycles is needed.

Further complications include serious safety issues preventing people infected with loiasis from being treated with ivermectin. Meanwhile, reported suboptimal responses to the treatment in patients with onchocerciasis may indicate resistance to it.

There are also no effective treatments to slow or stop the progression of the disease pathology or prevent those infected from developing lymphoedema.



“People are scared to take the drugs — they are scared of side effects. People don’t understand why they have to take a drug that doesn’t cure them. This is because they still have the nodules even after taking medicines.”

Anyasi

Community distributor of ivermectin
and head of the Regional Health Centre
Committee, Bababgulu, DRC

DNDi aims to deliver:

- A new oral, short-course macrofilaricide treatment, with potential application to treat both onchocerciasis and lymphatic filariasis



Macro-filaricide 3

OBJECTIVE: Develop a third macrofilaricide candidate for filarial diseases.

Background: Following a drug repurposing strategy, screening of compounds against *Onchocerca gutturo* and *Onchocerca lienalis* identified several candidates from compound libraries provided by pharmaceutical companies. These compound collections are well-characterized chemical series which have been extensively optimized for use in other indications. Although the project was quite successful, none of the identified candidates had a drug profile with utility for filarial diseases.

Screening of several more companies yielded further candidates. With funding from the Bill & Melinda Gates Foundation, these companies are conducting a hit-to-lead and lead optimization programme, which aims to develop a drug candidate for filarial indications. DNDi has contributed to this effort by providing biological resources, expertise, and the target product profile to select the best candidates.

2016 In conjunction with industrial partners, Abbvie and Celgene, further lead optimization was carried out. These efforts will continue throughout 2017, with the aim of delivering a pre-clinical candidate for filarial diseases.



ABBV-4083 TylAMac

OBJECTIVE: Develop TylAMac as an anti-Wolbachia therapy and assess its macrofilaricidal efficacy.

Background: ABBV-4083 is a derivative of tylosin, a veterinary antibiotic which targets the worm-symbiont Wolbachia. DNDi is working in partnership with AbbVie and AWOL to develop the compound for filarial diseases, it is currently in full pre-clinical development. ABBV-4083 is orally available, induces a robust anti-Wolbachia effect in several *in vivo* models, demonstrates clear superiority over doxycycline, and is effective after a shorter dosing regimen.

2016 Preliminary safety and toxicology profiling of this compound suggests a favourable safety profile. Upon completion of toxicology studies and the development of an oral formulation, a Phase I study will be conducted in 2017. The aim will be to assess the safety, tolerability, and pharmacokinetics of ABBV-4083.



Emodepside

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

Background: Emodepside was originated by Astellas, and developed and commercialized by Bayer Animal Health as an anthelmintic treatment for companion animals. DNDi has a collaboration agreement with Bayer to jointly develop emodepside for the treatment of onchocerciasis. DNDi is responsible for clinical development, and Bayer for pre-clinical, pharmaceutical development, manufacturing, registration, and supply of the drug at the lowest sustainable price.

71
patients
recruited
at 1 site

2016 Phase I trials of emodepside were started. A Single Ascending Dose Study will be completed in 2017, and the the protocols for the Multiple Dose Study will be initiated. The design of a Phase Ib study to be performed in patients in Africa is also being finalized.



Prof Andreas Busch

Head of Drug Discovery and Member of
Executive Committee, Bayer Pharmaceuticals

“We are excited to see first promising results of emodepside from Phase I clinical studies in healthy volunteers. The compound's unique mode of action targeting the adult worm could result in a single course of treatment for patients with river blindness.”





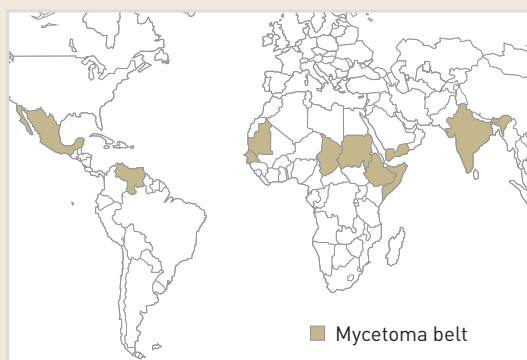
MYCETOMA

- Chronic inflammatory disease, in a fungal (eumycetoma) and a bacterial (actinomycetoma) form. Eumycetoma, mainly endemic in Africa, is much more difficult to treat
- Attacks the skin, deep muscle structures and the bone, believed to enter the body via thorn pricks or lesions on the feet
- Affects poor people in rural areas and in particular young males aged between 15 and 30
- Causes devastating deformities, often resulting in amputation and morbidity
- No global surveillance systems exist, so epidemiological data is lacking. The Mycetoma Research Centre in Khartoum, Sudan, has recorded around 6,500 patients since 1991
- Mycetoma is endemic in tropical and subtropical regions. The 'mycetoma belt' includes Chad, Ethiopia, Mauritania, Sudan, Senegal, and Somalia, as well as India, Mexico, Venezuela, and Yemen

80% of known patients develop deformities that need to be amputated

Global burden

Unknown



Eumycetoma treatments are extremely long, toxic, ineffective, and expensive. The disease is slow-growing and people often only seek treatment when it has reached later stages, by which time antifungal treatments are only 25-35% effective. Treatment is often followed by surgical removal of the remaining mass, leading to multiple amputations and, ultimately, the loss of entire limbs – with the risk of complications and death. An effective, safe, and affordable treatment for use in rural settings is urgently needed.

In 2016, mycetoma became the 18th disease to be added to the WHO list of NTDs, giving the disease political prominence and potentially paving the way for governments to monitor the disease, and for donors to fund research.



“I was in excruciating pain. I had to use a lot of pain killers just to be able to walk from one point to another. At some point, I got tired and decided to have my leg amputated.”

Alsadik Mohamed Musa Omer

Infected with mycetoma 19 years ago while playing football at school in Sudan

DNDi aims to deliver:

- A new safe, effective, and affordable treatment for patients with limited eumycetoma



Fosravuconazole

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

Background: The anti-fungal drug fosravuconazole, an orally bioavailable azole discovered by Eisai and under development for Chagas disease (see p. 35 'New benzimidazole regimen +/- fosravuconazole' project), may be an effective and affordable treatment for eumycetoma. A Phase II/III randomized controlled trial will be conducted to study the efficacy of fosravuconazole in moderate lesions compared to the current treatment, itraconazole. The primary objective of this double-blind, randomized, single-centre study will be to demonstrate the superiority of fosravuconazole over itraconazole after 12 months' treatment.



Dr Haruo Naito
Representative Corporate
Officer and CEO,
Eisai Co., Ltd

“Eisai places an emphasis on initiatives that lead to increase non-financial value, including ESG (Environmental, Social and Governance). Eliminating NTDs, one of the major social issues which is affecting more than 1 billion people mainly in developing countries, is in alignment with Eisai's *hbc* philosophy, and we believe these endeavors will ultimately lead to increase our corporate value. We are proud of our collaboration with DNDi to develop treatments for Chagas disease and mycetoma, and are proactively and continuously working to solve access to medicine problems in developing countries.”

2016 Protocols were finalized. Recruitment of patients (with a target of 136 participants) started in early 2017. An interim analysis will be conducted at three months.

MYCETOMA

➔ SPOTLIGHT

Political recognition at last: mycetoma added to WHO list of neglected tropical diseases

In 2016, mycetoma was added to WHO's official list of 'neglected tropical diseases' during the 69th World Health Assembly, making it the 18th disease in the list. By adding this devastating infection to the list, WHO Member States took an important step in boosting national and global responses to this woefully neglected disease and addressing the suffering of patients. This inclusion will give the disease the political prominence it so desperately needs to help increase donors, funders, and pharmaceutical bodies' awareness and attention leading to more research and development, health education, and advocacy programmes. This will eventually lead to better medicines and diagnostic tests ■

Dr Najwa Jouda in the laboratory of the Mycetoma Research Centre, Sudan



Prof Ahmed Hassan Fahal
Director, Mycetoma Research Centre, Sudan

“I was representing the Sudanese Government when I gave a statement to support the inclusion of mycetoma in the WHO neglected tropical diseases list that was discussed at the World Health Assembly in Geneva in May. Its adoption was a memorable event. I could not control my deep emotions and feelings and in fact I went into tears.”



PAEDIATRIC HIV

- 90% of infected infants acquire HIV from their mothers, during pregnancy, delivery, or through breast-feeding
- Without treatment, 1 in 3 children die in their first year of life; and half before they reach their second birthday
- Fewer than half of children (<15 years) living with HIV are on antiretroviral medication
- Opportunistic infections such as tuberculosis (TB) are common

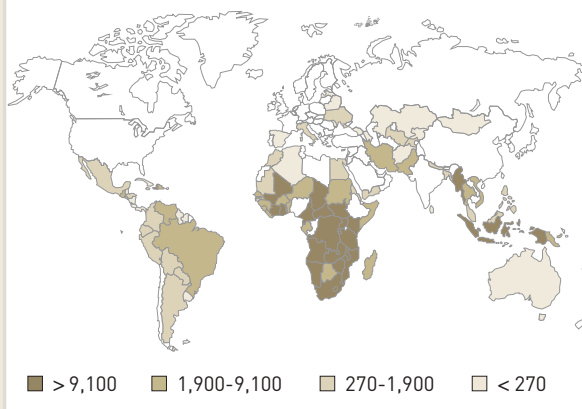
1.8

million children
living with HIV
in 2015

150,000

children newly infected
with HIV in 2015

▼ Children (<15 years) living with HIV in 2015



Nearly
90%
of cases are in
sub-Saharan Africa

300
child deaths every day



Infants and young children need treatments that are safe, efficacious, and easy to swallow, to ensure their best chance of survival to adulthood. Because children are frequently co-infected with TB, any paediatric HIV treatment also needs to be TB treatment-compatible. In 2016, based on the interim results of a DNDi-sponsored study (see p. 9), the WHO revised its guidelines to recommend the 'superboosting' of ritonavir in treatment of children co-infected with HIV and TB.

Today, the only approved protease inhibitor for young children is a foul-tasting lopinavir/ritonavir solution with a high alcohol content that requires refrigeration and is difficult to store, making it unsuitable for use in resource-poor settings. A taste-masked, oral formulation is needed.

Ultimately, it would be combined with other antiretrovirals into a single 4-in-1 capsule, thus radically simplifying treatment of HIV in children.



“I face a lot of difficulties with the medicine. I really have to battle in order for my baby to take them. It's heart-breaking to give a child four medicines at a time.”

Sani Nojiyeza

23-year-old mother to baby Mel. Sani and Mel are both HIV positive, Mel is also co-infected with TB. Durban, South Africa

DNDi aims to deliver:

- Develop a solid taste-masked first-line LPV/r-based fixed-dose formulations in combination with two NRTIs, 3TC and prioritizing ABC as the second NRTI.
- Immediate introduction of the recently US FDA approved LPV/r-pellets, before the availability of better-adapted 4-in-1 products



Comparison of the current treatment, lopinavir/ritonavir pellets plus the 2 NRTIs dispersible tablets which need to be taken dispersed in water (on the left), vs the future treatment, the granules of lopinavir/ritonavir mixed with the granules of NRTIs as the '4-in-1' treatment (on the right)



4-in-1' fixed-dose combination with LPV/r

OBJECTIVE: Develop and register a solid taste-masked first-line LPV/r-based fixed-dose formulation with two NRTIs, 3TC and prioritizing ABC as the second NRTI.

Background: The objective is to combine the four drugs needed for the treatment of paediatric HIV into an easy-to-use single unit, or fixed-dose combination, which is heat-stable, taste-masked, solid, does not contain alcohol or inappropriate solvents.

2016 Following preliminary studies, the best formulation candidates in terms of bioavailability and taste-masking have been chosen – out of the 30 formulations evaluated since 2014 – for testing in healthy human volunteers in on-going Phase I studies.



LPV/r pellets with dual NRTI

OBJECTIVE: Evaluate the effectiveness of LPV/r pellets in addition to AZT/3TC (or ABC/3TC) paediatric fixed-dose combination tablet in an implementation study in HIV-infected infants and young children who cannot swallow tablets.

Background: Cipla Inc has developed LPV/r pellets in capsules which can be opened and administered orally to small children; they are alcohol-free, do not require a cold chain and are less costly to transport. However, they must be given with two other antiretrovirals which come in dispersible tablet form.

The DNDi project includes large-scale implementation studies (known as the LIVING study) to provide supportive clinical data on the acceptability, feasibility, efficacy, safety, and pharmacokinetics of LPV-based therapies in routine treatment settings and to provide early access to better formulations and facilitate registration in the countries concerned.

2016 Patients were recruited in Kenya (221 patients out of a target 350) and Uganda (167 patients out of a target 350) for the implementation study. Clinical trials will also be initiated in South Africa, Tanzania, Zambia in 2017.

388
patients
recruited
at 9 sites

PAEDIATRIC HIV

SPOTLIGHT



Access: Rolling out LPV/r pellets in Uganda

In 2016, Uganda announced its intention to begin using lopinavir/ritonavir (LPV/r) pellets to treat children living with HIV, starting from January 2017.

Until the development of the pellets in 2015, the only available version of LPV/r for kids was a harsh-tasting syrup that requires refrigeration and contains 40% alcohol. Through the LIVING study being conducted in Kenya and Uganda, DNDi has developed extensive experience in understanding the use of the pellets and was asked to help strengthen the capacity of health workers to help patients and caregivers in using them. Information, education, and communication materials developed for use in the LIVING study sites were shared with ministries of health for translation and adaptation as training materials.

Uganda joins Kenya in including pellets in national treatment guidelines, with Cameroon, Nigeria, Zimbabwe, and the Democratic Republic of Congo all expressing interest in adopting pellets for use from 2017 ■



Dr Cordelia Katureebe

National coordinator,
Paediatric and adolescent
care and treatment, AIDS
Control Programme,
Ministry of Health, Uganda

“The pellets will provide an opportunity for our children to have better and simpler treatment formulations. We are happy to introduce them in 2017 here in Uganda and believe that the study currently being conducted by DNDi will provide important lessons towards a seamless launch.”



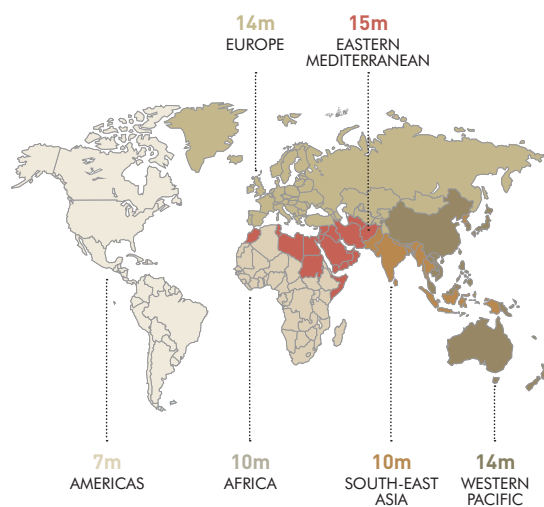
HEPATITIS C

- Inflammatory liver disease caused by the hepatitis C virus (HCV) is transmitted through exchange of body fluids, mostly through exposure to contaminated blood
- 55-85% of patients develop chronic infection; of those, 15-30% are at risk of cirrhosis of the liver within 20 years
- The virus exists as six major genotypes (GTs); prevalence varies by region with GT1 most prevalent in high-income countries and GT3 in low- and middle- income countries
- Current treatments are effective, but few patients have access to diagnosis and treatment, notably due to exorbitant prices

71

million people worldwide chronically infected in 2015

▼ Million of patients with Hepatitis C



81%

of patients live in low- and middle-income countries

400,000

deaths from HCV-related liver diseases in 2015



Direct-acting antivirals have revolutionized the therapeutic landscape. With cure rates of 95%, these 12-week oral treatments have replaced less effective, injection-based 48-week regimens associated with side effects. But their price is a major barrier to access, with treatment reserved for the most severe cases, and middle-income countries often excluded from price discounts.

The development of an affordable pan-genotypic regimen that works for all patients, including the most vulnerable, combined with innovative models of care that allow test-and-cure strategies, would set the foundations for a public health approach to the HCV epidemic to be implemented.



Dr SS Tan

Head of Hepatology Services, Ministry of Health, Malaysia and Head of the Department of Hepatology, Hospital Selayang, Batu Caves, Selangor, Malaysia

“Sofosbuvir has been registered in Malaysia since September 2015, but it is beyond the reach of my patients. It is not available in government hospitals and it is unlikely to be with the current price tag.”

DNDi aims to deliver:

- A safe, effective, and easy-to-use direct-acting antiviral regimen, to be used as an affordable combination paving the way for a public health approach to HCV



DEVELOPMENT

Ravidasvir/sofosbuvir

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

Background: More than one million people in Thailand, and 400,000 in Malaysia are estimated to be infected with chronic HCV. The most prevalent genotypes are 1, 3, and 6. Yet, both countries are excluded from global voluntary licensing agreements that enable access to generic HCV treatments.

A Phase II/III study started in Malaysia and Thailand aims to assess, in real-world settings, the efficacy, safety, tolerability, pharmacokinetics, and acceptability of a 12-week regimen containing sofosbuvir in combination with the drug candidate ravidasvir, supplied by Egyptian manufacturer Pharco. Participants are included regardless of genotype, source of transmission (including intravenous drug use), or HIV co-infection. Patients with compensated liver disease with or without cirrhosis, will also be included (for participants with compensated liver cirrhosis, treatment duration will be 24 weeks). A total of 750 patients will be enrolled, including up to 30% with compensated cirrhosis and up to 20% who inject drugs, providing data on efficacy and safety of the combination, as well as on treatment compliance.

164
patients
recruited
at 6 sites



2016 At the end of 2016, six study sites in Malaysia had recruited 164 patients (out of a target of 300) and four sites in Thailand had been initiated, with the full cooperation of the Ministries of Health in these countries. Sites in additional countries including Vietnam should be initiated in the coming months.

▼ Innovative licencing agreement to ensure affordable access.
Ravidasvir licencing territory



- Non-exclusive licence granted to DNDi
- DNDi has an option to take a licence after March 2018
- Exclusive licence granted to other partners
- No licence required/no patent claims have been filed/granted

“We hope that Pharco’s collaboration with DNDi to develop a combination treatment that costs \$3.50 per day or less — as opposed to \$1,000 per day for only one pill — will save millions of lives, and lead to widespread access to safe, effective and affordable treatment for hepatitis C patients around the world.”



Dr Sherine Helmy
CEO, Pharco Pharmaceuticals, Egypt



An unattainable cure: Countries rich, poor, and in the middle all struggling to access HCV drugs

Advocacy campaign of Médecins du Monde for access to hepatitis C treatment, 2016

The powerful generation of new direct-acting antivirals (DAAs) to treat HCV have become the poster child for the prohibitive price of medicines in many countries.

New treatment regimens combining DAAs cost upwards of USD 100,000 in the US, and EUR 40,000 in European countries. Pricing of HCV drugs has led to treatment rationing in Europe and the US, where countless headlines have lamented a situation where “only the sickest receive treatment.” Politicians, activists, and patients are angry. Gilead’s USD 84,000 price tag for sofosbuvir in the US even triggered a Congressional investigation.

Pharmaceutical companies have offered DAAs at vastly reduced prices for low-income countries, with voluntary licensing deals allowing generic production. But 73% of the world’s chronic HCV patients live in middle-income countries. Most of these countries – from Brazil to Malaysia – are excluded by licensing deals. Sofosbuvir in Brazil costs anywhere from USD 5000 to USD 10,000 per patient – simply too high for the country.

The result: More people are getting infected than being put on treatment. There were 1.75 million new HCV infections globally in 2015 but only 1.1 million people started treatment. With no animal reservoir of HCV and drugs that are almost 100% effective, elimination of this viral disease is a real possibility – if we first eliminate the many barriers to access around the world.

Many activists have turned to the courts, employing the same tactics used to reduce the prices of HIV drugs in the 2000s. Patent oppositions are one option, where a third party can oppose the granting of a patent on grounds that it does not meet patentability standards. In 2015, India’s

patent office rejected Gilead’s patent on sofosbuvir after activists argued that it represented only minor changes to a previous formulation. But the decision was overturned in 2016. Patent oppositions have been filed in other countries, including France and Ukraine.

Latin America is a battleground in this access showdown. A sofosbuvir patent was recently rejected in Brazil, while civil society groups in Argentina have filed an opposition to a patent request for sofosbuvir. Meanwhile the patent has been granted for sofosbuvir in other Latin American countries like Colombia, Chile, and Mexico. The Strategic Fund of the Pan American Health Organization (PAHO) will play a key role in obtaining treatments in these countries at affordable prices.

Others countries are leading by example. Egypt has approximately 12 million HCV infected patients, but thanks to local generic production of new DAAs and a public health approach, one million people have been treated. The Indian state of Punjab launched a comprehensive HCV test-and-treat programme for its 28 million inhabitants that could also be an excellent model.

DNDi’s R&D approach is synergistic with all these efforts. In conjunction with Egyptian manufacturer Pharco we are seeking to develop an affordable regimen of ravidasvir/sofosbuvir, with a target price of USD 300-500 a treatment course. Critically, the combination is intended to treat all HCV genotypes.

Our comprehensive strategy incorporates HCV education, surveillance, screening, testing, and links to care and prevention. It is also country-driven, with the ministries of health in Malaysia and Thailand co-sponsoring DNDi’s trial and providing public leadership.

MAIN R&D PARTNERS

Screening

AbbVie (USA) ■ AstraZeneca (UK) ■ Institute of Medical Microbiology, Immunology and Parasitology, Bonn University Hospital (Germany) ■ Celgene Corporation (USA) ■ Eisai Co Ltd (Japan) ■ Eskitis Institute for Cell and Molecular Therapies, Griffith Institute for Drug Discovery, Griffith University (Australia) ■ Institut Pasteur Korea (South Korea) ■ Muséum National d'Histoire Naturelle (France) ■ Northwick Park Institute for Medical Research, Northwick Park and St Mark's Hospital (UK) ■ Shionogi & Co Ltd (Japan) ■ Swiss Tropical and Public Health Institute (Switzerland) ■ Takeda Pharmaceutical Company Ltd (Japan) ■ Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp (Belgium) ■ Drug Discovery Unit, University of Dundee (UK) ■ Walter Reed Army Institute of Research (USA)

List of partners providing compound libraries on page 21.

Leishmaniasis

AbbVie (USA) ■ Academic Medical Centre, University of Amsterdam (The Netherlands) ■ Accelera (Italy) ■ Addis Ababa University (Ethiopia) ■ Advinus Therapeutics Ltd (India) ■ Amudat General Hospital (Uganda) ■ Anacor Pharmaceuticals (now Pfizer since 2017, USA) ■ Aptuit (Italy) ■ AstraZeneca (UK & Sweden) ■ Institute of Medical Sciences, Banaras Hindu University (India) ■ Bihar State Health Society (India) ■ University of Brasília (Brazil) ■ Cardiabase (France) ■ Catalent (USA) ■ Celgene Corporation (USA) ■ Centre d'Investigation Clinique (CIC), Hôpital Bichat-Claude Bernard, Paris (France) ■ Centre d'Investigation Clinique (CIC), Hôpital Cardiologique de Lille (France) ■ Centres d'Investigation Clinique des Centres Hospitaliers Universitaires de Clermont-Ferrand (France) ■ Eisai Co Ltd (Japan) ■ Epichem (Australia) ■ Eskitis Institute for Cell and Molecular Therapies, Griffith Institute for Drug Discovery, Griffith University (Australia) ■ Eurofins-Optimed (France) ■ Federal University of Sergipe (Brazil) ■ Fiocruz - Research Center René Rachou (Brazil) ■ Food and Drug Administration (USA) ■ GeneDesign Inc (USA) ■ Gondar University Hospital (Ethiopia) ■ GlaxoSmithKline (Spain) ■ GVK Biosciences Ltd (India) ■ Hospital Infanto João Paulo II - FHEMIG (Brazil) ■ Hospital Sao José de Doenças Infecciosas, Fortaleza (Brazil) ■ Humax Pharmaceutical (Colombia) ■ i-solutions (The Netherlands) ■ IDA Foundation (The Netherlands) ■ Indian Council of Medical Research (India) ■ Institut Pasteur Korea (South Korea) ■ Instituto de Salud Carlos III (Spain) ■ International Centre for Diarrhoeal Disease Research (Bangladesh) ■ Institute of Tropical Medicine, University of Antwerp (Belgium) ■ Kacheliba Hospital (Kenya) ■ Kala-Azar Medical Research Centre (India) ■ Kenya Medical Research Institute (Kenya) ■ Institute of Endemic Diseases, University of Khartoum (Sudan) ■ Laboratory of Microbiology Parasitology and Hygiene, University of Antwerp (Belgium) ■ Leishmaniasis Control Programme/Ministry of Health (Brazil) ■ London School of Hygiene & Tropical Medicine (UK) ■ Makerere University (Uganda) ■ Merck (USA) ■ Ministry of Health (Ethiopia) ■ Ministry of Health (Kenya) ■ Ministry of Health (Sudan) ■ Ministry of Health (Uganda) ■ Monash University, Centre for Drug Candidate Optimisation (Australia) ■ Médecins Sans Frontières ■ Muzaffarpur Hospital (India) ■ National Institute of Pathology (India) ■ National Vector Borne Disease Control Programme (India) ■ Netherlands Cancer Institute (The Netherlands) ■ OneWorld Health/PATH (USA) ■ Penn Pharmaceuticals Services (UK) ■ PhnC (France) ■ Programa Nacional de Leishmaniasis (Colombia) ■ Rajendra Memorial Research Institute of Medical Sciences (India) ■ Sandexis (UK) ■ Sanofi (France) ■ Sanofi Chinoin (Hungary) ■ Sara Pharm (Romania) ■ Scynexis (USA) ■ SGS (Belgium) ■ Shaheed Suhrawardy Medical College and Hospital (Bangladesh) ■ Shionogi & Co Ltd (Japan) ■ SK Hospital, Mymensingh (Bangladesh) ■ State University of Montes Claros (Brazil) ■ Swiss Tropical and Public Health Institute (Switzerland) ■ Syngene (India) ■ Takeda Pharmaceutical Company Ltd (Japan) ■ TCG Lifesciences Private Limited (India) ■ Thermosurgery Technologies, Inc (USA) ■ Universidade Estadual do Rio de Janeiro (Brazil) ■ Universidade Federal do Piauí, Campus Universitário Ministro Petrônio Portella (Brazil) ■ Universidad Peruana Cayetano Heredia (Peru) ■ Universidad Sao Paulo, Sao Carlos (Brazil) ■ Universidade Estadual de Campinas, UNICAMP (Brazil) ■ University of Antioquia, Programa de Estudio y Control de Enfermedades Tropicales (Colombia) ■ Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp (Belgium) ■ Drug Discovery Unit, University of Dundee (UK) ■ University of Gedaraf (Sudan) ■ University of Osaka (Japan) ■ Uppsala University (Sweden) ■ WHO Neglected Tropical Diseases department (Switzerland) ■ WHO-TDR (Switzerland) ■ Wil Research (Charles River Laboratories) (France) ■ WuXi AppTech (China)

Human African Trypanosomiasis

Anacor Pharmaceuticals (now Pfizer since 2017, USA) ■ Aptuit (Italy) ■ Avista Pharma Solutions (USA) ■ Bertin Pharma (France) ■ BIOTRIAL (France) ■ Cardiabase (France) ■ CBCO (DRC) ■ Luxembourg Institute of Health

(Luxembourg) ■ Creapharm (France) ■ Eurofins Optimed (France) ■ HAT Platform ■ Institut National de Recherche Biomédicale (DRC) ■ Institut de Recherche pour le Développement (IRD) (France) ■ Institute of Tropical Medicine, University of Antwerp (Belgium) ■ Médecins Sans Frontières ■ National Trypanosomiasis Control Programmes (DRC, CAR, Angola, Chad, Rep. of Congo, Guinea, South Sudan, Sudan, Uganda) ■ Patheon (UK) ■ PhnC (France) ■ RCTs (France) ■ Sanofi (France) ■ SGS (Belgium and France) ■ Swiss Tropical and Public Health Institute (Switzerland) ■ Theradis Pharma (France) ■ WHO Neglected Tropical Diseases department (Switzerland)

Chagas disease

AbbVie (USA) ■ Anacor Pharmaceuticals (now Pfizer since 2017, USA) ■ AstraZeneca (UK & Sweden) ■ Celgene Corporation (USA) ■ Chemo Group (Argentina) ■ Collective of Applied Studies and Social Development - CEADES (Bolivia) ■ Barcelona Centre for International Health Research - CRESIB (Spain) ■ Eisai Co Ltd (Japan) ■ Epichem (Australia) ■ Eskitis Institute for Cell and Molecular Therapies, Griffith Institute for Drug Discovery, Griffith University (Australia) ■ GlaxoSmithKline (Spain) ■ Hospital de Niños Dr Ricardo Gutiérrez (Argentina) ■ Hospital de Sant Joan Despi Moisés Broggi, Consorci Sanitari Integral (Spain) ■ Centro de Chagas y Patología Regional, Hospital Independencia (Argentina) ■ Vall d'Hebron University Hospital (Spain) ■ Institut Pasteur Korea (South Korea) ■ Instituto Nacional de Epidemiología - Dr Mario Fátala Chaben (Argentina) ■ ISGlobal, Instituto de Salud Global Barcelona (Spain) ■ London School of Hygiene & Tropical Medicine (UK) ■ Luxembourg Institute of Health (Luxembourg) ■ McGill University (Canada) ■ Médecins Sans Frontières ■ Merck (USA) ■ Centre for Drug Candidate Optimisation, Monash University (Australia) ■ Mundo Sano (Argentina) ■ National Council of Scientific and Technological Research - INGEBI/CONICET (Argentina) ■ NHEPACHA Network Projects ■ PAHO ■ Platform of Integral Care for Patients with Chagas Disease (Bolivia) ■ Sandexis (UK) ■ Sanofi (France) ■ Shionogi & Co Ltd (Japan) ■ Swiss Tropical and Public Health Institute (Switzerland) ■ Takeda Pharmaceutical Company Ltd (Japan) ■ TCG Lifesciences Private Limited (India) ■ Texas Biomedical Research Institute (USA) ■ Unidad de Enfermedades Infecciosas, Sección de Salud Internacional y Consejo al Viajero, Valencia (Spain) ■ Laboratory of Microbiology, Parasitology and Hygiene, University of Antwerp (Belgium) ■ Universidad Autónoma Juan Misael Saracho (Bolivia) ■ Brazil Biosciences National Laboratory, University of Campinas (Brazil) ■ Drug Discovery Unit, University of Dundee (UK) ■ Universidade Estadual de Campinas - UNICAMP (Brazil) ■ University of Georgia Research Foundation (USA) ■ Universidad Mayor de San Simón (Bolivia) ■ Universidad São Paulo (Brazil) ■ University of Texas at El Paso (USA) ■ University of Texas Rio Grande Valley (USA) ■ WuXi AppTech (China)

Filarial diseases

AbbVie (USA) ■ Bayer Healthcare (Germany) ■ Institute of Medical Microbiology, Immunology and Parasitology, Bonn University Hospital (Germany) ■ London School of Hygiene & Tropical Medicine (UK) ■ Northwick Park Institute for Medical Research, Northwick Park and St Mark's Hospital (UK) ■ Geneva University Hospitals (Switzerland)

Mycetoma

Eisai Co Ltd (Japan) ■ Erasmus University Medical Centre (The Netherlands) ■ Vrije University Amsterdam (The Netherlands) ■ Institute of Endemic Diseases, University of Khartoum (Sudan) ■ Mycetoma Research Centre, Soba University Hospital (Sudan) ■ Radboud University Medical Center (The Netherlands) ■ WHO Neglected Tropical Diseases department (Switzerland)

Paediatric HIV

AbbVie (USA) ■ Moi Teaching and Referral Hospital/AMPATH (Kenya) ■ Associated Medical Services/PHPT Research Unit (Thailand) ■ Astellas Pharma Inc. (Japan) ■ AstraZeneca (UK) ■ Avista Pharma Solutions (USA) ■ Bayer Healthcare (Germany) ■ Baylor College of Medicine Children's Foundation (Uganda) ■ Bristol-Myers Squibb (USA) ■ Cipla Inc (India) ■ Clinton Health Access Initiative (USA) ■ Debiopharm (CH) ■ FACES Project (Kenya) ■ Gertrude's Children's Hospital (Kenya) ■ Joint Clinical Research Centre (Uganda) ■ Kenya Medical Research Institute (Kenya) ■ Kenyatta National Hospital (Kenya) ■ Management and Development for Health (MDH) (Tanzania) ■ Ministry of Health (Kenya) ■ Swiss Tropical and Public Health Institute (Switzerland) ■ UNITAID (Switzerland) ■ University of Nairobi (Kenya)

Hepatitis C

Pharco Pharmaceuticals Inc (Egypt) ■ Clinical Research Malaysia, Ministry of Health (Malaysia) ■ Presidio Pharmaceuticals (USA) ■ Ministry of Health and Ministry of Industry, Science and Technology (Thailand)



GARDP launched with three programmes starting for drug-resistant infections

Building on DNDi's experience in developing a research & development (R&D) pipeline for neglected diseases, the Global Antibiotic Research & Development Partnership (GARDP) was officially launched in May 2016. A joint initiative between WHO and DNDi, with seed funding from Germany, the UK, Switzerland, the Netherlands, South Africa, and Médecins Sans Frontières, GARDP's vision is a world where everyone in need of antibiotics receives effective, appropriate, and affordable treatment, irrespective of where they live.

GARDP's strategy for antibiotic drug development comprises a mix of short- and long-term approaches, and will focus on drug-resistant bacterial infections, including serious infections for which adequate treatment is not available. Bacterial infections are spread globally, so GARDP will maintain a global focus, including attention to the needs of low- and middle-income countries.

Guided by the group of Scientific Advisors that oversee the creation of its R&D portfolio, in 2016 GARDP defined its initial programmes:

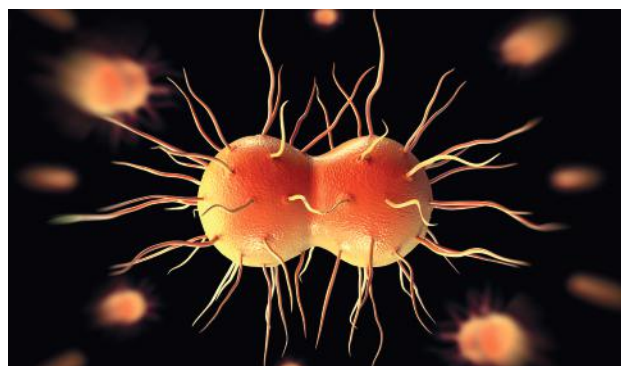
- **Neonatal Sepsis:** to provide an evidence base for the use of old and new antibiotics in neonates with serious bacterial infections, as the current standard of care in many countries becomes increasingly less effective due to drug resistance. The longer-term objective includes the development of new treatment regimens for babies with neonatal sepsis;
- **Antimicrobial Memory Recovery Initiative (AMRI):** to recover the knowledge, data, and assets of forgotten, abandoned, or withdrawn antibiotics so that potential opportunities are not missed. By building a global panel of world experts in antibiotic drug discovery and development, the longer-term objective is to identify drug opportunities, including 'early-stage, forgotten and abandoned' antibiotics, suitable for GARDP's infectious disease focus;
- **Sexually Transmitted Infections (STIs):** In its short-term strategy, GARDP will focus on *Neisseria gonorrhoeae* (gonorrhoea) as the spread and incidence of drug-resistant gonorrhoea is rapidly outpacing the development of new drugs needed to treat it. This programme will accelerate the entry of new antibiotics and explore the use of combinations, including old and new antibiotics, while focusing development on specific public health needs.



**Ms Malebona
Precious Matsoso**
Director General,
Department of Health,
South Africa

“There is a dire need for cooperative solutions that assist countries in strengthening systems to address the risks of antimicrobial resistance. No country can safeguard itself from resistant bacteria unless the world collectively heeds the call.”

GARDP Business plan 2017-2023



Neisseria gonorrhoeae bacteria

GARDP's Objectives 2017 – 2023



- **Develop** and deliver up to four new treatments through improvement of existing antibiotics and acceleration of the entry of new chemical entities. **Build** a robust pipeline of pre-clinical and clinical candidates with up to four candidates brought into pre-clinical or clinical development.



- **Secure** EUR 270 million to execute its R&D programmes, build a highly experienced R&D team, and establish a dedicated entity.



- **Support** and advocate for appropriate use of antibiotics, sustainable access, and suitable financing of R&D for new antibiotic treatments.

For GARDP, a comprehensive and sustainable approach to access comprises innovation, access, and stewardship of new antibiotic treatments. It also implies that stewardship of antibiotic treatments is framed within an access-oriented approach and not vice-versa.

Recent global policy meetings confirmed the critical need for R&D and access in the field of drug resistant infections. In her final address to the World Health Assembly in May 2017, WHO Director General Margaret Chan noted how reconciling the question of access to new products with the need to support R&D was 'the most contentious issue' of her time in office. The same month, the G20 Health Ministers' meeting delivered the 'Berlin Declaration' calling for initiatives, such as GARDP, which 'reinvigorate R&D in science and industry for antimicrobials'. This broad recognition of the importance and need of new and global R&D initiatives is key, as GARDP now moves from the incubation phase to programme implementation.



Dr Margaret Chan

Director General (until May 2017),
World Health Organization

“The rise of antimicrobial resistance is a severe threat that is rendering more and more life-saving medicines useless. WHO together with DNDi has set up GARDP as a proactive initiative, within a larger global response, that can bring new products into the R&D pipeline.”

GARDP Business plan 2017-2023

Expert consultations held in 2016

Scientific Expert Meetings

In 2016, GARDP and WHO convened several thematic expert meetings on disease areas as well as on sustainable access. Below is a selection of key meetings.

- **February:** a scientific consultation with 42 participants (11 countries) at the Institut Pasteur in Paris to help GARDP evolve from its initial **scientific strategy** to determining priority areas and short- to medium-term projects.
- **June:** an expert meeting with 26 participants (9 countries) to review and evaluate the needs and potential development of new and effective treatment options for **gonorrhoea**, and define a roadmap for future R&D activities.
- **August:** a neonatal sepsis expert meeting co-organized by DNDi and WHO with 25 participants (8 countries) to review and evaluate GARDP's **neonatal sepsis** programme proposal, and define future preparatory work for clinical trials.

- **September:** a group of 20 renowned experts in antimicrobial drug discovery and development met to develop a programme proposal for the **recovery of forgotten or abandoned antibiotics** from the 'golden era' of antibiotic drug development, and to consolidate experts, knowledge, and resources via a web portal.

Regional Consultations

The most pressing medical needs related to drug-resistant infections, R&D gaps, the potential to address them, and opportunities for collaboration differ vastly from region to region. In September, GARDP organized a first expert consultation in South Africa. The event was co-hosted with the South African Medical Research Council, and brought together 45 participants from 11 African countries. In December, a second regional event, co-hosted with the Indian Council of Medical Research, brought together 40 South Asian experts and stakeholders in the field of drug-resistant infections.

A close-up photograph of a man with dark skin, wearing a white lab coat over a pink and white striped shirt, looking through the eyepiece of a white and black microscope. The microscope is on a wooden table. The background is a plain, light-colored wall. The text 'KACHE' is visible on the side of the microscope's base.

STRENGTHENING CAPACITIES

Strengthening endemic country capacity to advance new treatments

Conducting clinical trials on neglected diseases means that research must often be conducted in some of the most remote areas of the world, where there is little infrastructure of any kind, let alone health infrastructure. In some areas, there can also be a risk of political instability. While carrying out clinical research at international standards of quality in such conditions is possible, it requires considerable effort to ensure adequate infrastructure, well trained staff, as well as specialized ethics committees, and well-functioning regulatory authorities are in place.

Since its inception in 2003, DNDi has worked to integrate capacity strengthening into its projects in a sustainable manner, through knowledge sharing and technology transfers. The objective is to increase the chances of registration, uptake, and sustainable access of new treatments for neglected diseases and, ultimately, to support the transfer of ownership to disease-endemic countries.

To support strengthening of capacities and ensure sustainability, DNDi's activities include:

- **Maintaining and building R&D regional platforms** (see p. 52-53). As an integral part of DNDi's model, R&D regional research platforms form part of a broader, positive trend of research networks to maximize worldwide collaborations. The objective is to bring together key regional actors (ministries of health, national control programmes, regulatory authorities, academia, civil society groups, pharmaceutical companies, clinicians and health professionals) to share different experiences, knowledge, and problem-solving techniques.



“Diseases don't respect political boundaries or geographic borders — so countries must work together to tackle them. Thanks to DNDi and the LEAP platform, Sudan and other East African countries are now tackling the challenge of leishmaniasis together. LEAP has made this change!”

Prof Ahmed El Hassan

Doctor and 'father of leishmaniasis' working on the disease for over 60 years, The Institute of Endemic Diseases, University of Khartoum, Sudan

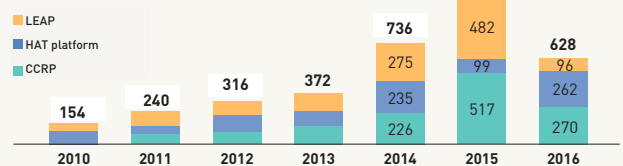
- **Building health infrastructure**, creating R&D training spaces, and setting up research facilities in clinical trial sites. The physical upgrading of facilities needed for clinical research (such as patient wards and diagnostics laboratories) is undertaken by DNDi at trial sites to ensure they are compliant with Good Clinical Practice (GCP) international standards and remain the property of the local public health provider.

2016 The clinical sites of Kwamouth, Ngandajika, and Bolobo, in the Democratic Republic of Congo, were rehabilitated to prepare for the inclusion of sleeping sickness patients into the SCYX-7158 Phase II study.

- **Training to support R&D efforts in disease-endemic countries.** Trained staff are needed to carry out GCP-compliant trials. Training is important not just at the start of a trial, but is a continuous process which involves upgrading existing skill-sets and training new staff members. From external consultants to experienced trial site staff, the sharing of better practice principles helps to motivate teams working in difficult field conditions.

2016 628 people trained across the Leishmaniasis East Africa Platform (LEAP), the HAT platform, and the Chagas Clinical Research Platform (CCRP).

628 people trained in 2016



The decrease in overall training numbers in 2016 (by 43%) is related to the exceptional number of trainings given in 2015 to prepare for new clinical studies.



Edwin Abner

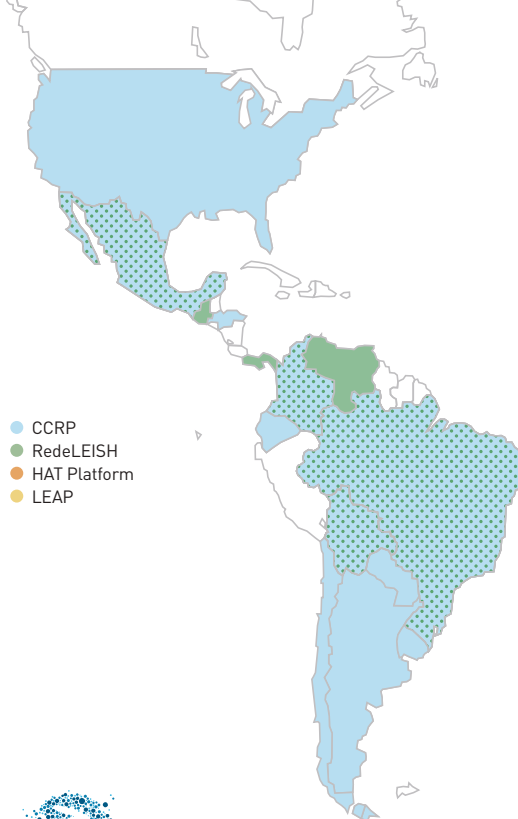
Lab technologist, Kacheliba sub-county Hospital, Kenya

“This was my first GCP and GCLP training course. A great opportunity to learn the key principles for getting accurate and quality results. I am now fully informed of international standards and I am applying them to how I handle subjects and samples.”

- **Transferring technology to local manufacturers.** For DNDi, the transfer of technology consists of transferring the industrial development know-how to partners in disease-endemic regions to ensure a wide-spread distribution of treatments. It involves providing the required regulatory files and information needed to maintain competitive prices and reinforce the technological and scientific capacities of disease-endemic countries.

2016 Technology transfer to Tanzanian company Zenufa as a second source of production for the antimalarial ASAQ was finalized. This is in addition to the one produced by Sanofi. Zenufa's production site in Tanzania is now 'Good Manufacturing Practice' certified by the Tanzanian authorities and its prequalification dossier is being finalized for submission to the WHO.

Platforms & Networks



Chagas Clinical Research Platform (CCRP)

Founded: 2009 in Uberaba, Brazil
376 members, representing over 100 institutions

3
clinical sites

Highlights 2016

- 3 clinical trial sites were active in Bolivia to support the Phase II proof-of-concept BENDITA trial (benznidazole new doses improved treatment and associations).
- At the Chagas Platform Annual Meeting, about 270 people were trained on key areas, including: qPCR validation and quality control for diagnosis and monitoring, discovery of new drugs, congenital Chagas disease, civil society movements, new research fields and guidelines for Chagas disease, new landscape for chronic patients, integrative therapy approach.

270
people trained



RedeLEISH Network

Founded: 2014, Rio de Janeiro, Brazil
117 members, representing 54 institutions

Highlights 2016

- Completion of a collaborative research project of species identification conducted in Pará, Mato Grosso, and Acre (Brazil), and preliminary results presented during annual meeting
- INFOLEISH, the network's first newsletter was launched in May

A joint workshop of the **Chagas Platform and the redeLEISH**, 'Interface between civil society and NGOs to tackle neglected diseases: prospective on opportunities and challenges', led to the creation of the Brazilian Social Forum for Confronting Infectious and Neglected Diseases. The Forum was officially launched in August, at the Annual Meetings of Applied Research on Chagas Disease and Leishmaniasis at the Brazilian Society of Tropical Medicine Congress, in Maceio.

Filarial clinical research network

DNDi and its partners are working jointly to establish a network of expertise and research capacity on filarial diseases. In 2016, DNDi's filaria team met with experts in Cameroon, DRC, Ghana, and Ivory Coast to discuss trial design and identify potential partners for clinical trials. In October, DNDi hosted an Onchocerciasis Clinical and Regulatory Technical meeting to present unmet medical needs, and obtain feedback from experts on the endpoints chosen for the development of a macrofilaricidal treatment. This was followed up with another meeting to discuss study design with endemic country experts.

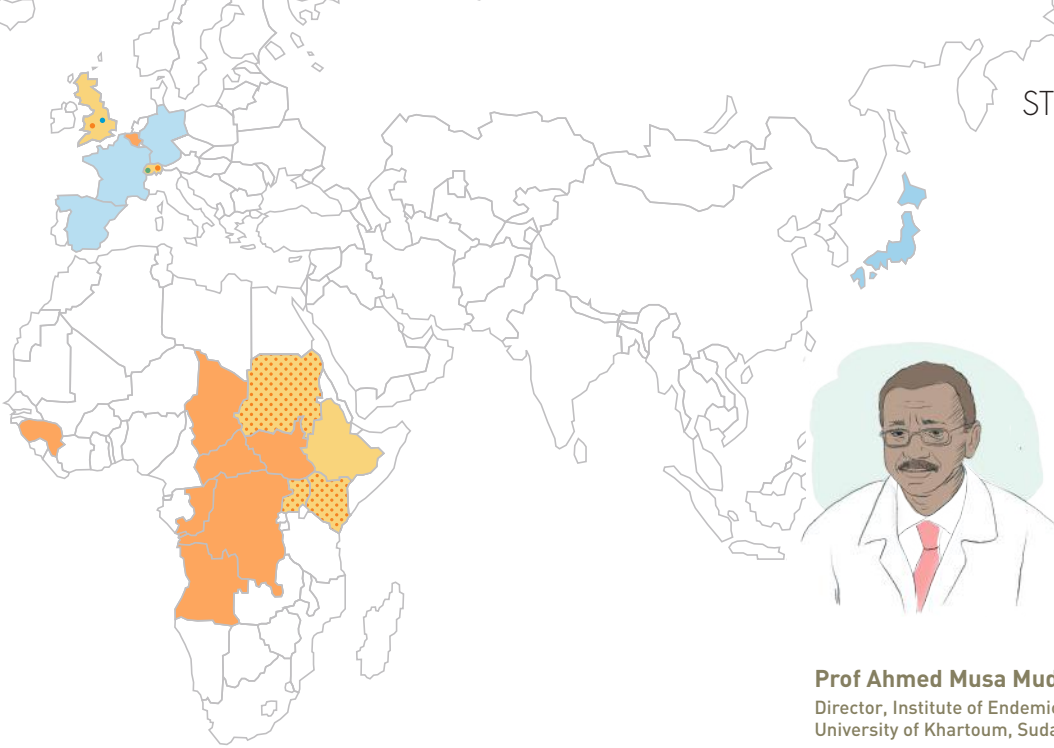
MAIN MEMBERS

HAT Platform

National sleeping sickness control programmes, research institutions and national laboratories of public health of the most affected endemic countries: Angola, Central African Republic, Chad, Democratic Republic of the Congo, Republic of Congo, South Sudan, Sudan, Uganda, Guinea; Drugs for Neglected Diseases initiative (DNDi), Switzerland; Swiss Tropical and Public Health Institute, Switzerland; Institute of Tropical Medicine–Antwerp, Belgium; Institut National de Recherche Biomédicale, DRC; University of Makerere, Uganda; Kenya Agricultural Research Institute – Trypanosomiasis Research Centre, Kenya; Tropical Medicine Research Institute, Sudan; Institut Pasteur Bangui, CAR; Médecins Sans Frontières (MSF); Foundation for Innovative New Diagnostics (FIND), Switzerland; Eastern Africa Network for Trypanosomiasis, Centre interdisciplinaire de Bioéthique pour l'Afrique Francophone, DRC; World Health Organization (WHO) Department of Neglected Tropical Diseases as observer; INZI project, University of Edinburgh, UK; Juba University, South Sudan.

LEAP

Center for Clinical Research, Kenya Medical Research Institute, Kenya; Ministry of Health, Kenya; Institute of Endemic Diseases, University of Khartoum, Sudan; Federal Ministry of Health, Sudan; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Federal Bureau of Health, Ethiopia; Makerere University, Uganda; Ministry of Health, Uganda; MSF; London School of Hygiene & Tropical Medicine, UK; WHO; DNDi, Switzerland; FIND, Switzerland.



“I was just a young doctor when the Leishmaniasis East Africa Platform was launched 13 years ago. LEAP has developed me as a researcher over the years. Through this exposure, I have acquired a desire to mentor others as researchers in the field of endemic neglected diseases.”

Prof Ahmed Musa Mudawi

Director, Institute of Endemic Diseases,
University of Khartoum, Sudan



Human African Trypanosomiasis (HAT) Platform

Founded: 2005 in Kinshasa, DRC
Over 120 members, representing over 20 institutions

10

clinical sites

Highlights 2016

- The HAT platform was operational in 10 clinical trial sites supported by 10 mobile teams dedicated to the screening of patients: 7 sites for the Phase II/III clinical trial for SCYX-7158 and 3 sites for the recruitment of patients for the fexinidazole Phase IIIb study.
- Training activities were sizeable – 262 people trained (compared to 99 in 2015) – to prepare for the Phase II/III clinical trial for SCYX-7158, and covered diagnosis for mobile team technicians, active screening for community health workers, and waste management in clinical trial sites.

262

people trained



Leishmaniasis East Africa Platform (LEAP)

Founded: 2003 in Khartoum, Sudan
Over 60 members, representing over 13 institutions

6

clinical sites

Highlights 2016

- The LEAP Platform handled 6 clinical trial sites in Ethiopia, Kenya, Uganda, and Sudan, as well as maintaining clinical trial sites even though they were not involved in R&D activities. Outside of the trials, 1,156 people were treated, and 3,069 screened.
- Launch of LEAP 2.0: the platform was restructured to adjust to expanding clinical trial needs in the region; with expansion of disease areas – from VL only to CL and PKDL –, extension of member countries (Eritrea, South Sudan, Somalia), and for a focus on new areas of activities (access, Phase I studies, data sharing)

1,156

people trained

CCRP

Pan American Health Organization (PAHO); Department of Neglected Tropical Diseases, WHO; Ministries of Health and National Control Programmes of high-burden endemic countries (Argentina, Bolivia, Brazil, Mexico, Paraguay, Honduras); MSF; International Federation of People Affected by Chagas Disease and patient associations. ARGENTINA: Hospital de Niños Ricardo Gutiérrez; Instituto Nacional de Parasitología Dr M. Fátala Chabén; Hospital de Niños de Jujuy; Hospital Público Materno Infantil – Salta; Centro de Chagas y Patología Regional, Santiago del Estero; Consejo Nacional de Investigaciones Científicas y Técnicas; Fundación Mundo Sano, ELEA. BRAZIL: Instituto Oswaldo Cruz; Instituto de Pesquisa Evandro Chagas–Fiocruz; Centro de Pesquisas René Rachou–Fiocruz; LAFEP. BOLIVIA: Universidad Mayor de San Simón; Platform of Integral Care for Patients with Chagas Disease; Collective of Applied Studies and Social Development. COLOMBIA: Centro de Investigaciones en Microbiología y Parasitología Tropical, Universidad de los Andes; Centro Internacional de Entrenamiento e Investigaciones Médicas; Programa de Estudio y Control de Enfermedades Tropicales, Universidad de Antioquia (PECET); Red Chagas Colombia. FRANCE: Institut de Recherche pour le Développement. GERMANY: Bayer HealthCare. JAPAN: Eisai Co. Lt. MEXICO: Instituto Carlos Slim de la Salud; Instituto Nacional de Salud Pública. SPAIN: ISGlobal and Barcelona Centre for International Health Research; Hospital Clínic Barcelona; Instituto de Parasitología y Biomedicina López Neyra; Consejo Superior de Investigaciones Científicas; Instituto Catalán de la Salud. SWITZERLAND: DND; Geneva University Hospitals. UK: The Global Health Network. USA: Merck; Sabin Vaccine Institute.

RedeLEISH

BOLIVIA: Fundación Nacional de Dermatología. BRAZIL: Centro de Pesquisa Gonçalo Moniz–Fiocruz; Centro de Pesquisa René Rachou–Fiocruz; Fiocruz/Plataforma de Pesquisa Clínica; Fundação de Medicina Tropical Heitor Vieira Dourado; Ministério da Saúde; Instituto Evandro Chagas/SVS/MS, Universidade do Estado do Pará; Instituto Nacional de Pesquisa da Amazônia; Secretaria Municipal de Saúde Unidade Referência em Atenção Primária Drª Claudia Vitorino; Universidade de Brasília – Núcleo de Medicina Tropical; Universidade Federal de Mato Grosso/Hospital Universitário Júlio Müller; Universidade de São Paulo; Universidade Federal do Pará; Universidade do Rio de Janeiro. COLOMBIA: Centro Dermatológico Federico Lleras Acosta; Centro Internacional de Entrenamiento e Investigaciones Médicas; Instituto Colombiano de Medicina Tropical; Instituto Nacional de Salud; PECET. GUATEMALA: Universidad del Valle. MEXICO: Universidad Nacional Autónoma. PANAMA: Instituto Conmemorativo Gorgas de Estudios de la Salud. PERU: Department of Parasitology, Public Health Training Program – U.S. Naval Medical Research Unit No. 6; Universidad Peruana Cayetano Heredia. SWITZERLAND: DND; FIND. VENEZUELA: Instituto Medico la Floresta. WHO. PAHO.



POLICY, ADVOCACY, COMMUNICATIONS, AND FUNDRAISING

What norms and principles should govern the financing of health R&D?

The need for alternative models such as DNDi, to boost innovation and access for neglected tropical diseases (NTDs), where the commercial model clearly fails to meet the needs of patients in low- and middle-income countries, has long been recognized. But in recent years, the global environment has evolved.

“The system is broken but change is underway to fix it [...]. We need meaningful efforts by both the pharmaceutical industry and governments to invest in new medicines, provide full transparency on costs, prices, and who pays what beforehand, and respect the legal space for governments to protect public health. [...] Without fixing this broken system we will not reach the Sustainable Development Goal to ensure healthy lives and wellbeing for all, at all ages.”

Better life through medicine—let's leave no one behind, The Lancet, November 2016

Lilianne Ploumen Minister for Foreign Affairs and
Edith Schippers, Minister for Health, The Netherlands

First, the problem is no longer perceived as one of a lack of appropriate treatments for some diseases. Concerns around the high prices of drugs have thrown into greater relief the need to link alternative models and incentives for R&D to issues around access to medicines. Witness for example, recent oppositions filed by civil society organizations

against patents on hepatitis C drugs, and the statements by WHO in relation to high prices of medicines included in the Essential Medicines List.

Second, the emerging crisis around drug-resistant infections have pointed to deficiencies of the existing model in the area of innovation

Highlights from DNDi's advocacy work in 2016

UN High-Level Panel on Access to Medicines: balancing trade, IP, and public health

The High-Level Panel (HLP) was created by the UN Secretary General (UN SG) to recommend solutions to remedy the policy incoherence between the rights of inventors, international human rights law, trade rules and public health.

Five of the eight recommendations made by DNDi were reflected in the final report, released in September.

The report called on the UN SG to:

- Launch a political process to lead to a binding global agreement on the financing, prioritization, coordination, and norms;
- Support countries to use TRIPS flexibilities to allow innovation and access;
- Encourage governments, industry, and academia to increase access medical technologies and data;
- Advocate for a declaration by key public and private R&D funders ensuring that R&D funding will be tied to implementation of set norms;
- Expand the remit of existing pooled funds, or develop funds to cover all areas of need, tied to agreed priorities and norms.

Progress of the implementation of the report's recommendations is due to be discussed at the UN General Assembly, before September 2018.



UN High-Level Declaration on Antimicrobial Resistance (AMR)

In September, at a UN High-Level Meeting on AMR, governments took an important step by approving a UN Political Declaration that recognized the many global challenges caused by AMR. The Declaration endorsed key principles to guide R&D, namely that it should be 'needs-driven, evidence-based, and guided by the principles of affordability, effectiveness, efficiency, and equity'.

The importance of delinking the cost of R&D from the price and volume of sales of treatments to facilitate access was acknowledged.

DNDi welcomed the Declaration as another encouraging sign, after the UN HLP, that governments have elevated the debate on biomedical innovation and access to medicines to the highest political levels, and as a strong acknowledgement that 'business as usual' is not enough to stimulate innovation for AMR. DNDi also urged support for the WHO to proceed with the development of a Global Development and Stewardship Framework, based on the key principles outlined in the Declaration to support the development, appropriate use of, and access to new and existing antibiotics.

and access to new antibiotics. Significantly, the issue is now recognized in all countries, and is no longer relegated to a developing world problem. Concerns around innovation and access to medicines – and not just for NTDs, but for all issues of public health importance – have been elevated to the highest level of the global policy agenda. Throughout 2016, a series of expert panels or recommendations (see box) in which DNDi played an active role, discussed these questions. While only some are outlined below, DNDi policy advocacy has been actively involved in many others, such as the Lancet Commission, the Fair Prices Forum, or at the WHO on the follow up to the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) including the Global Observatory on Health Research and Development.

Many governments are showing growing willingness to defend more robustly the need for public return on public investment in R&D, notably with calls for price and cost transparency. Interest in delinkage – where the costs and risks associated with R&D should be rewarded, and incentives for R&D provided, by means other than through the price of the

product – and the R&D models that apply it are increasing. This brings sustained interest from policy makers in some of the key lessons learnt from DNDi's experience, including open knowledge innovation, pro-public health management of intellectual property, and partnerships to ensure equitable and sustainable access to new medical technologies.

Some progress was made towards DNDi's call for sustainable global R&D frameworks with Governments' endorsement of a R&D framework for pandemic preparedness. Governments also agreed to support a framework for development and stewardship for AMR.

The year 2016 saw an increased recognition of the need to support new policies and models to ensure sustainable and equitable R&D that meets the public health needs of neglected patients. Further progressive policy steps must still be taken to create global R&D agreements that are connected by a common set of norms and principles to address all areas of public health need. Translating this political momentum into sustainable financing mechanisms and concrete action is the next challenge.

DNDi Innovation and Access: Partners' Meeting 2016: Promoting science for the most neglected in Latin America

In June 2016, DNDi, in partnership with the Brazilian Development Bank (BNDES) and with the support of Fiocruz, organized its Partners' Meeting, as well as meetings and workshops of the Chagas Platform and the redeLEISH Network, in Rio de Janeiro, Brazil. This event brought together more than 300 participants from the field of neglected diseases, including patients, international scientists, product developers, policy-makers, and civil society organizations.

At the Partners' Meeting, DNDi wished to recognize the work of Latin American partners and programmes in NTD research. Ruta N, an organization based in Medellin, Colombia, was awarded the Innovative Funding Mechanism Award for its funding of leishmaniasis.

The Partnership of the Year Award was presented to LOLA, the Lead Optimization Latin America Project, which uses an international collaborative approach, working with UNICAMP (University of Campinas), and partners in the USA (AbbVie) and Europe (LMPH, University of Antwerp, Belgium) to carry out early-stage drug discovery.



Selected press coverage

HUFFPOST **THE HUFFINGTON POST**
This Group Helps Fight Devastating Diseases The World Ignores
The illnesses it combats affect the world's poorest people.
 1 December 2016

EBC Agência Brasil
Pesquisadores discutem formas de incentivar estudo de doenças negligenciadas
 "Researchers want to encourage the study of neglected diseases"
 6 June 2016

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DNDiと製薬企業によるグローバルコンソーシアム「隠れた病い熱帯病(NTDs)研究ブースター」にセルゲン社が参加
 "Celgene joins global consortium "Neglected Tropical Diseases drug discovery booster" with DNDi and pharmaceutical companies"
 15 June 2016

Deutsches Ärzteblatt **Mehr Geld für die Forschung zu armutsbedingten Erkrankungen**
 1 December 2016

FINANCIAL TIMES
 "Waking up to sleeping sickness"
 29 April 2016

LA STAMPA
 "Alla ricerca dei vecchi scienziati per studiare i nuovi antibiotici"
 29 May 2016

nature
Busting the billion-dollar myth: how to slash the cost of drug development
 A non-profit organization is proving that new drugs don't have to cost a fortune. Can its model work more broadly?
 24 August 2016

الوفد
 دواء مصري يُخفض كلفة علاج فيروس سي عالميًا
 "Egyptian drug reduces the cost of HCV treatment worldwide"
 14 April 2016

Le Monde
La guerre contre les « superbactéries » est déclarée
 6 June 2016

the guardian
Hepatitis C treatment for under \$300 coming soon
 13 April 2016

excite
マイセトマ(Mysetoma:菌症)が WHOの「隠れた病い熱帯病(NTDs)」のリストに新たに加わる
 Mycetoma is added to the list of "neglected tropical diseases" (NTDs), by the WHO
 1 July 2016

Selected scientific publications

The BENEFIT Trial: Where do we go from here? by Pécoul B, Batista C, Stobbaerts E, Ribeiro I, Vilasanjuan R, Gascon J, Pinazo MJ, Moriana S, Gold S, Pereiro A, Navarro M, Torrico F, Bottazzi ME, Hotez PJ. *PLOS Neglected Tropical Diseases*, February 2016

Eliminating the neglected tropical diseases: Translational science and new technologies by Hotez PJ, Pécoul B, Rijal S, Boehme C, Aksoy S, Malecela M, Tapia-Conyer R, Reeder JC. *PLOS Neglected Tropical Diseases*, March 2016

An analysis of volumes, prices and pricing trends of the pediatric antiretroviral market in developing countries from 2004 to 2012 by Lee JSF, Teyssier LS, Nguimack BD, Collins IJ, Lallemand M, Perriens J and Moatti JP. *BMC Pediatrics*, March 2016

The Leishmaniasis East Africa Platform (LEAP): strengthening clinical trial capacity in resource-limited countries to deliver new treatments for visceral leishmaniasis by Wasunna M, Musa, A, Hailu A, Khalil EAG, Olobo J, Juma R, Wells S, Alvar J, Balasegaram M. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, June 2016

Comparison of artesunate-mefloquine and artemether-lumefantrine fixed-dose combinations for treatment of uncomplicated *P. falciparum* malaria in children under 5 years in sub-Saharan Africa: a randomised, multicentre, phase 4 trial by Sodiomon BS, Ogutu B, Lusingu JPA, Mtoro A, Mrango Z, Ouedraogo A, Yaro JB, Onyango KO, Gesase S, Mnkande E, Ngocho JS, Ackermann I, Aubin F, Vanraes J, Strub N, Carn G. *The Lancet Infectious Diseases*, July 2016

Transmission dynamics of visceral leishmaniasis in the Indian subcontinent – A systematic literature review by Hirve S, Boelaert M, Matlashewski G, Mondal D, Arana B, Kroeger A, Olhiano P. *PLOS Neglected Tropical Diseases*, August 2016

Efficacy and safety of AmBisome in combination with sodium stibogluconate or miltefosine and miltefosine monotherapy for African visceral leishmaniasis: Phase II randomized trial by Wasunna M, Njenga S, Balasegaram M, Alexander N, Omollo R, Edwards T, Dorlo TPC, Musa B, Sharaf Ali MH, Elamin MY, Kirigi G, Juma R, Anke E. Kip, Schoone GJ, Hailu A, Olobo J, Ellis S, Kimutai R, Wells S, Khalil EAG, Strub Wourgaft N, Alves F, Musa A. *PLOS Neglected Tropical Diseases*, September 2016

Evaluation of parameters impacting drug susceptibility in intracellular *T. cruzi* assay protocols by Yang G, Lee N, Ioset JR, No JH. *Journal of Biomolecular Screening*, October 2016

Essential medicines for universal health coverage by Wirtz VJ, Hogerzeil HV, Gray AL, Bigdeli M, de Joncheere CP, Ewen MA, Gyansa-Lutterodt M, Jing S, Luiza VL, Mbindyo RM, Möller H, Moucheraud C, Pécoul B, Rago L, Rashidian A, Ross-Degnan D, Stephens PN, Teerawattananon Y, 't Hoen EFM, Wagner AK, Yadav P, Reich MR. *The Lancet*, November 2016

EUR 13.6 million secured in 2016 with an additional EUR 63 million committed

Accomplishing the objectives of the DNDi 2015-2023 business plan requires an overall budget of EUR 650 million. In 2016, DNDi was grateful to renew a number of partnerships, ensuring continued stability for the organization's work for neglected patients. The vast majority of the EUR 13.6 million received in 2016 was granted by public institutions, including the German Government (BMBF through KfW), the GHIT Fund (Japan), the Norwegian Agency for Development Cooperation (Norad), and the Canton of Geneva (Switzerland).

Core funding gives DNDi the agility to manage its scientific portfolio in a dynamic manner, and steer investments to ensure alignment with ever-changing R&D priorities in a way that reflects project attrition and unforeseen opportunities. Core funding commitments pledged in 2016 included support from the German Federal Ministry of Education and Research (covering the years 2016-2021, see 'Major contributions' box), GBP 48 million from the UK Department for International Development (DFID, 2017-2021), and CHF 8 million from the Swiss Agency for Development and Cooperation (SDC, for 2017-2020), reaching a total commitment of EUR 63 million.

DNDi has also cultivated **collaborative funding** sources, after approaching partners with the intent of submitting joint funding applications, which would result in funding going directly to the partner. Grants of this type - which are listed in the 2016 Financial and Performance Report - have been received from Australia, Malaysia, Thailand, and the Colombian business and innovation centre Ruta N.

In addition, DNDi has sought to develop new sources of funding from public and private sources, which has come from four new donors - three of which are seed funders of GARDP.

SEED FUNDING FOR GARDP

In 2016, GARDP attracted a first round of seed funding from the governments of Germany (EUR 500,000), the Netherlands (EUR 500,000), South Africa (ZAR 6 million), Switzerland (CHF 360,000), and the UK (GBP 75,000 for seed funding in 2016, and GBP 3 million for 2017-2018), as well as support from Médecins Sans Frontières (EUR 600,000), for a total commitment of nearly EUR 6 million. DNDi is delighted to welcome three of those as new donors (the German Federal Ministry of Health, the South African Medical Research Council, and the Swiss Federal Office of Public Health).

GARDP continues to engage donors from the DNDi network and beyond, to secure funding needs of EUR 270 million, in line with the 7-year business plan (2017-2023).

MAJOR CONTRIBUTIONS RECEIVED IN 2016

Federal Ministry of Education and Research (BMBF) through KfW / Germany (2016-2021) renewed core support of EUR 10 million for 5 years to support the development of improved and innovative treatments for HAT, leishmaniasis, Chagas disease, and filarial diseases.

Republic and Canton of Geneva, International Solidarity Office / Switzerland (2016-2018) renewed its support with a grant of CHF 480,000 over three years (2016-2018), for sleeping sickness control activities in the DRC.

Australian Government - Austrade (2016-2018) awarded AUD 250,000 (EUR 168,000) directly to DNDi's pre-clinical partner, Epichem, for studies on pre-clinical candidates for leishmaniasis as part of the Australian Tropical Medicine Commercialisation Programme.

The Global Health Innovative Technology (GHIT) - Japan. With over EUR 11 million in grants since 2013, DNDi has established a solid partnership with the GHIT Fund, an innovative funding mechanism established to fill a gap in the R&D of new tools for infectious diseases sponsored by the Japanese government, several Japanese pharmaceutical companies, the Bill & Melinda Gates Foundation, and the Wellcome Trust. GHIT has supported various DNDi projects to build a solid discovery pipeline of new chemical entities, translating into an increase of pre-clinical candidates and later-stage clinical trials. In 2016, GHIT expanded its support with two new grants for JPY 561 million (EUR 4.4 million), both for pre-clinical development of a combination treatment on cutaneous leishmaniasis.

NEW INTEGRATED HAT CAMPAIGN

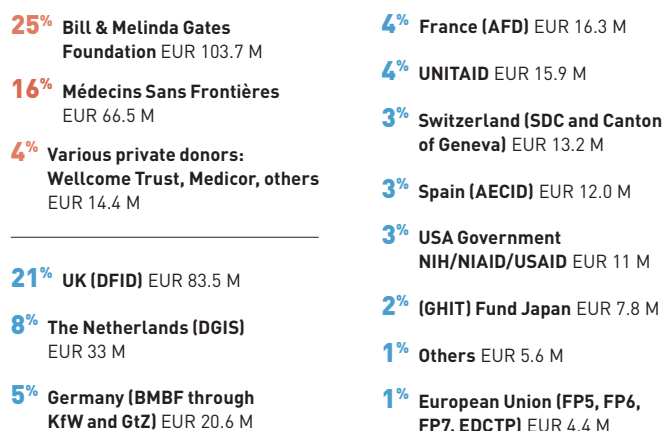
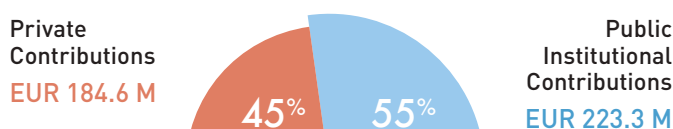
DNDi launched its human African trypanosomiasis (HAT) campaign, a two-year integrated fundraising campaign with the goal of securing USD 5 million in financial support from new private funding sources. In addition to diversifying funds for the HAT programme, the campaign allows DNDi to pilot new approaches to raise private support that could potentially be adapted to other DNDi R&D programmes or other priority initiatives. Secondary objectives include increasing awareness about HAT (and other neglected diseases), the need for new treatments, and the possibility of disease elimination.

2016 KEY PERFORMANCE INDICATORS

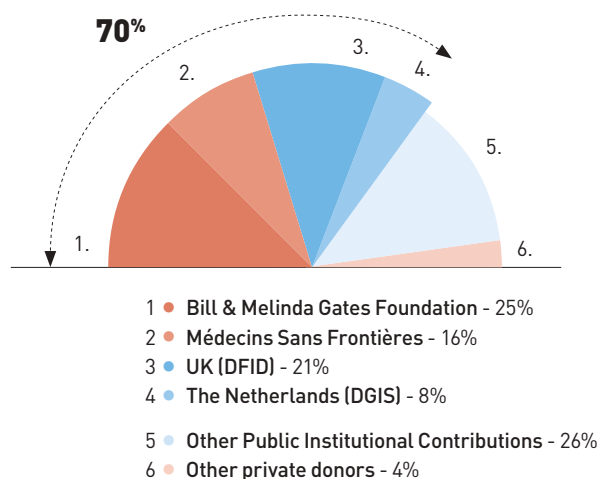
CONTRIBUTIONS

Maintaining balanced and diversified funding

- DNDi seeks diversified sources of funding from public and private sources, and this diversification increased in 2016 with four new donors, all of which are from public sources including one from an endemic country. DNDi welcomed new grants from the Australian Government – Austrade (through collaborative funding); the German Federal Ministry of Health (for GARDP); the South African Medical Research Council (for GARDP); and the Federal Office of Public Health, Switzerland (for GARDP).
- Concerted efforts were made to ensure that no single donor contributes more than around 25% towards DNDi's business plan.
- DNDi also seeks to ensure that around half its budget is covered by public funds and half by private funds. In 2016, with secured funds until 2021, the split remains balanced with public funding accounting for 55% (54% in 2015) and 45% for private support (46% in 2015).
- The vast majority (96%) of the EUR 13.6 M of new funding granted in 2016 for the period 2016-2021 was granted by public institutions, including by the German Government (BMBF through KfW); the GHIT Fund, Japan; the Norwegian Agency for Development Cooperation (Norad), Norway; the Canton of Geneva, Switzerland; and the new donors for GARDP mentioned above.



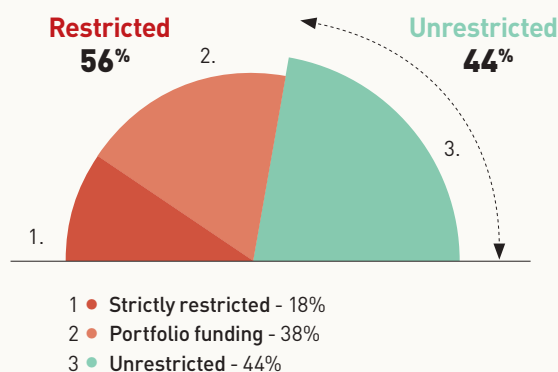
Between 2003-2021, four funders account for 70% of the funds committed to DNDi: the Gates Foundation, DFID (UK), Médecins Sans Frontières, and DGIS (the Netherlands).



A successful shift toward unrestricted funding

- Over the last five years, DNDi managed to maintain a balance between restricted and unrestricted grants. Unrestricted funding allows the organization to respond quickly to research opportunities and also terminate projects that do not meet targeted goals set forth in DNDi's Business Plan.
- In 2016, cumulative portfolio funding reached 38% (EUR 155.2 M), which allows a certain degree of risk mitigation within restricted grants as it can be allocated towards activities in the five neglected tropical disease areas in DNDi's portfolio. The share of portfolio grants has progressively increased from 18% in 2011, to 22% in 2012, to 29% in 2013, to 33% in 2014, and to 37% in 2015.
- Looking at cumulative funding to 2021 since DNDi's inception in 2003, restricted funding accounts for 56% of the total (of which 38% is portfolio funding allocated toward the full range of R&D activities related to a specific disease, and 18% is strictly restricted to an R&D project in the portfolio), and core funding for 44%.

Cumulative 2003-2021: EUR 407.9 Million



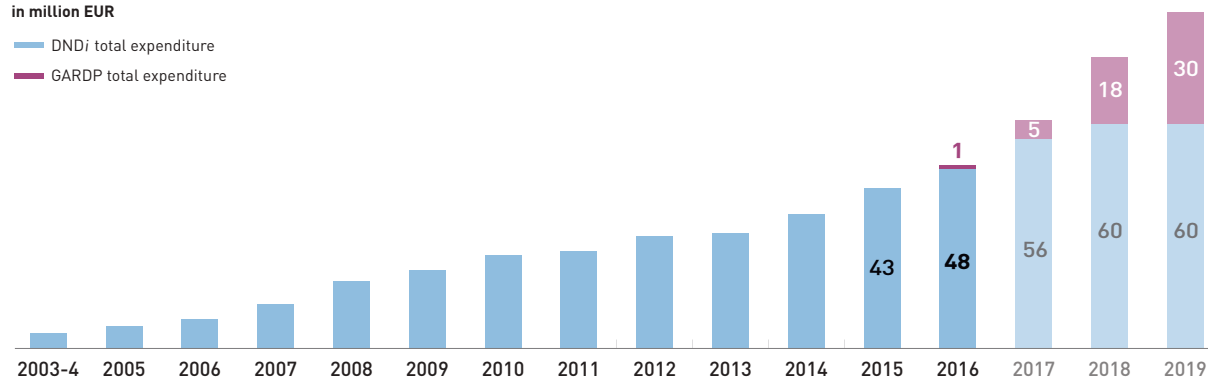
EXPENDITURE

Steady growth in spending, concentrated on R&D

- In 2016, expenditure reached EUR 48.8 M, up by 13% (+EUR 5.8 M) compared to 2015.
- Overall R&D expenditure (EUR 37.3 M) increased by 14% (+EUR 4.6 M) compared to 2015.
- The operating gain in 2016 (EUR 0.26 M) is largely negated by exchange rate losses (EUR 0.24 M).
- Since the inception of DNDi in 2003, the organization's expenditure totals EUR 309 M.

in million EUR

— DNDi total expenditure
— GARDP total expenditure



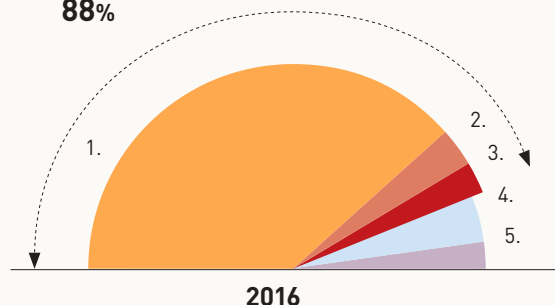
Statement of activities 2003-2016 and forecast 2017-2019

88% of spending dedicated to the social mission

- DNDi's ratio of social mission to non-social mission spending improved slightly, with the percentage of non-social mission spending reduced from 12.3 % in 2015 to 11.8% in 2016.
- Social mission expenditure grew by 14% (+EUR 5.3 M), due to the significant growth of R&D activities with new diseases added to DNDi's portfolio (+EUR 3.6 M) and projects transitioning from the discovery to translational phase (+EUR 1.3 M).
- Non-social mission expenditure grew by 9% (+EUR 0.5 M), largely due to growth in support teams (+6 FTE).

Social mission

88%



1. R&D - 77%
2. Strengthening capacities - 6%
3. Advocacy - 5%
4. General management - 8%
5. Fundraising - 4%

EXPENDITURE

R&D spending increases concentrated in leishmaniasis & new diseases entering DNDi portfolio

- Overall R&D expenditure increased by 14% between 2015 and 2016 to reach a total of EUR 37.3 M.
- The increase in R&D spending is principally due to substantial increases in expenditures on leishmaniasis (+EUR 1.9 M), together with spending on diseases recently added to DNDi's portfolio (+EUR 0.9 M for GARDP; +EUR 0.5 M for HCV, +EUR 0.5 M for mycetoma).

Neglected tropical diseases remain at the heart of the portfolio, counting for 85% of R&D expenses

Leishmaniasis

With a total of EUR 10.1 M spent in 2016, leishmaniasis represents the most substantial R&D expenditure (30%). In 2016, leishmaniasis expenditure increased by EUR 1.9 M. This increase is mostly due to the progress of new chemical entities in the portfolio (DNDi-0690 & VL-6148 for visceral leishmaniasis, and CpG for cutaneous leishmaniasis), from the discovery to the pre-clinical phase (+EUR 1.7 M).

HAT

With a total of EUR 7.5 M, HAT disease represents 23% of R&D expenditure. Investments decreased in 2016 by EUR 1.2 M (from EUR 8.7 M in 2015) because the cost of patients' follow-up in the clinical activities for fexinidazole is inferior to the cost of the recruitment of the 749 patients which was completed in 2015 (-EUR 2 M). The progress of the SCYX-7158 project into the development stage and the recruitment of patients for the phase II/III trial started Q4 2016 offsets some of this drop in spending (+EUR 0.8 M).

Chagas disease

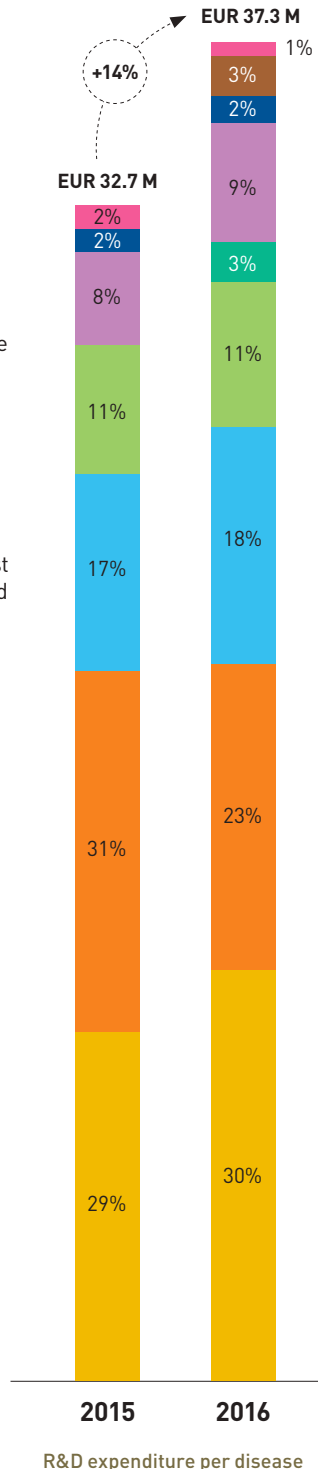
Chagas projects account for 18% of R&D expenditure (EUR 6 M). Spending increased in 2016 (+EUR 1.2 M), owing to the recruitment of patients in Bolivia and Argentina for the proof-of-concept study for the new benznidazole regimens/combinations project (+EUR 1.2 M).

Filaria

Filarial disease spending totaled EUR 3.5 M in 2016, accounting for 11% of R&D expenditure. Spending increased in 2016 (+EUR 0.5): while the flubendazole project was stopped (-EUR 0.1 M) and the Phase I studies initiated in 2015 for emodepside continued (-EUR 0.2 M), the progress of TylAMac to the pre-clinical stage more than offset these spending drops (+EUR 0.8).

Mycetoma

Mycetoma accounts for 2% of R&D expenditure (EUR 0.6 M). Spending is concentrated on the preparation of a randomized clinical trial with fosravuconazole in Sudan (+EUR 0.5).



As HCV projects get underway, viral diseases spending increases by 42%

Viral diseases now account for 12% of the R&D expenditures compared to 9% in 2015, as total spending on HIV and HCV increased by EUR 1.1 M.

Paediatric HIV

Paediatric HIV accounts for 9% of R&D expenditure (EUR 2.9 M). The LIVING study added a tenth clinical trial site, with 388 children enrolled in 2016 (+EUR 1.2 M). The ritonavir superboosting study for children co-infected with HIV and tuberculosis was completed in South Africa (-EUR 0.1 M) and spending on the development of a '4-in-1' formulation was reduced, as most equipment had been purchased in 2015 (-EUR 0.5 M).

Hepatitis C (HCV)

HCV accounts for 3% of R&D expenditure (EUR 0.9 M). Increase in spending was due to Phase III clinical studies in Malaysia and the preparation of a clinical study in Thailand (+EUR 0.5 M).

With the launch of GARDP, antimicrobial resistance now accounts for 3% of R&D spending

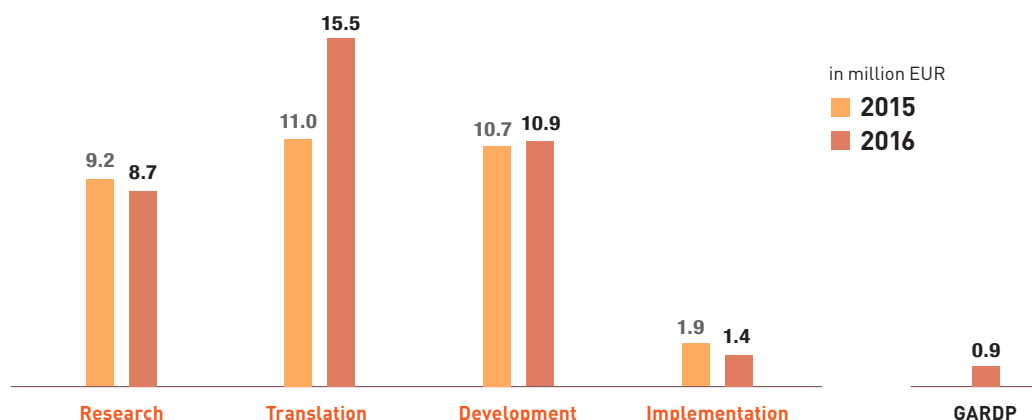
Antimicrobial resistance (AMR) / GARDP

Antimicrobial resistance (AMR) is a new area of intervention for DNDi with the launch in Q2 2016 of GARDP. GARDP's Business Plan is under development, with some projects in the exploratory phase. R&D spending in 2016 reached EUR 0.9 M, or 3% of total R&D expenditures.

Malaria

EXPENDITURE

Spending on translational research increases as projects enter pre-clinical development



R&D expenditure per stage of development

R&D coordination & supervision costs for NTDs, HIV, and HCV (EUR 4.7 M) are included proportionally in the R&D expenditure per stage. GARDP expenditures are presented separately and refer to activities related to the preparation and exploration of projects.



Discovery/Research

- Discovery/Research activities account for 23% of R&D expenditure.
- Screening and lead optimization activities decreased by 5% (-EUR 0.5 M). Two of the three candidates in late-stage lead optimization in 2015 progressed to the translational phase in 2016 (DNDi-0690 nitroimidazole and DNDi-6148 oxaborole, both for leishmaniasis). This reflects a focus on hit-to-lead series instead of full lead optimization work. Therefore, fees for services costs decreased in 2016. In addition, we benefitted from some in-kind contributions from pharmaceutical partners who conducted experimental profiling of lead compounds.
- This drop was partly offset by expansion of the NTD Drug Discovery Booster in 2016 (+EUR 0.3 M), with six committed partners as of May 2016. Three hit series are advancing and more than 5,000 compounds have been screened.



Translation

- Translational activities account for 42% of R&D expenditure, to reach a total of EUR 15.5 M in 2016.
- Spending on translational projects (including pre-clinical, Phase I, together with the preparation of Phase II/proof of concept) increased by 42% (+EUR 4.5 M). Five projects are driving this increase:
 - the TylAMac project for filaria progressing into the pre-clinical stage (+EUR 0.5 M);
 - new chemical entities (DNDi-0690, VL-6148, and CpG) progressing into the pre-clinical stage for leishmaniasis (+EUR 1.7 M);
 - SCYX-7158 completing Phase I and preparation of development phase (+EUR 0.8 M);
 - the beginning of recruitment for a proof-of-concept study on new benznidazole regimens and combinations for Chagas disease (+EUR 1.2 M);
 - the cutaneous leishmaniasis combination project progressing to Phase II (+EUR 0.3 M).



Development

- Development activities account for 29% of R&D expenditure.
- At EUR 10.9 M, spending on clinical development projects remained stable in 2016 compared to 2015 (+EUR 0.2 M).



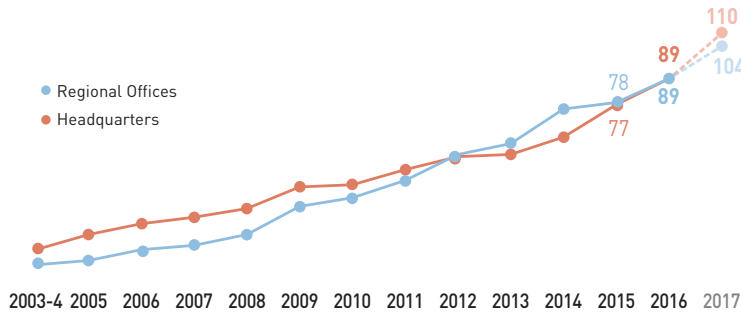
Implementation

- Implementation activities account for 4% of R&D expenditure.
- Spending decreased by 28% (-EUR 0.5 M) in 2016 compared to 2015 as implementation projects are nearing completion. However, in 2016, a new project was added: with the change in the WHO and South Africa guidelines, activities related to the superboosting of ritonavir for children co-infected with HIV and tuberculosis are now included in the implementation phase.

HUMAN RESOURCES

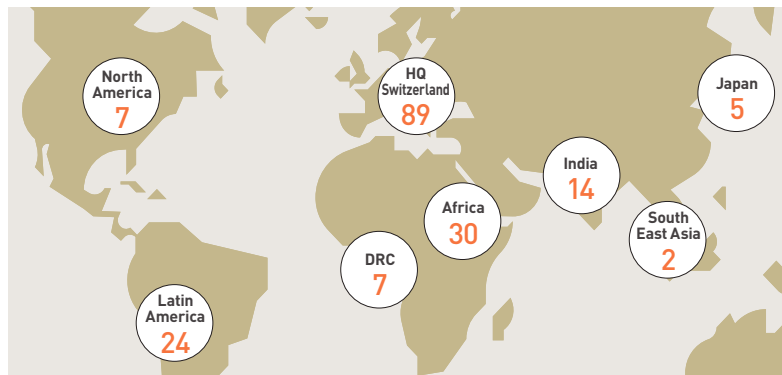
178 people worldwide, with HR growth split across regions but concentrated on R&D teams

Growth of activities (+13%) sustained by HR increase (+15%)



Human resources evolution 2004-2017

2017 forecast includes GARDP.

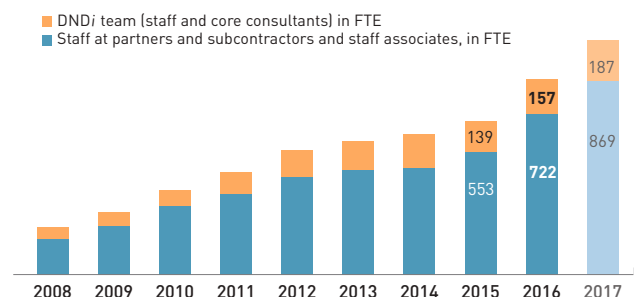


DNDi people in each office

- In 2016, DNDi recruited an additional 23 people, compared to 18 recruited in 2015. This represents an increase of 15% in staff numbers compared to 2015.
- The newcomers are almost equally split between Geneva Headquarters (HQ, 12 people) and Regional Offices (RO, 11 people), meaning exactly the same number of people are employed at HQ as in ROs (89).
- Growth was concentrated in the R&D team, both in HQ and in RO, and largely dedicated to the management of diseases recently added in DNDi's portfolio (+5 for HIV & HCV, +3 for NTDs, +3 for GARDP, +2 for R&D coordination, and +1 for the transitioning diseases unit dedicated to exploratory projects).
- Other new positions are dedicated to support functions such as Human Resources (+2 FTE), Finance (+2), RO Operations (+1) and assistant positions (+2). New position were created for Policy/Advocacy (+1) and for DNDi's international development (+1).
- Taking into account all employees' start and end dates and the percentage of time worked for each position in DNDi, the 2016 total staff count is 157 FTE, with 178 people working at DNDi.

Every DNDi FTE generates four FTEs through sub-contracted research activities

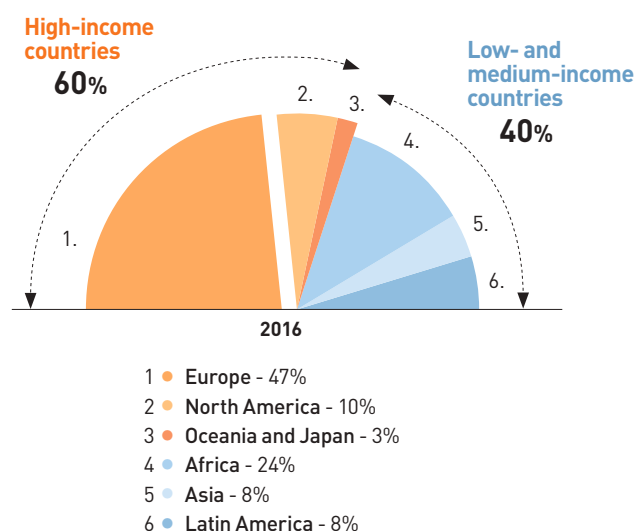
- As a virtual R&D organization, DNDi sub-contracts its research activities to partners. The number of FTEs thus created in partner organizations, and working on DNDi activities has been tracked over recent years, giving a trend of four FTEs in partner organizations for every DNDi FTE.
- In 2016, this trend was maintained, with 722 FTEs in partner organizations and staff associates for 157 FTEs at DNDi.
- The forecast for 2017 based on an analysis of contracts gives 869 FTEs in partner organizations and staff associates for 187 FTEs at DNDi.



PARTNERSHIPS

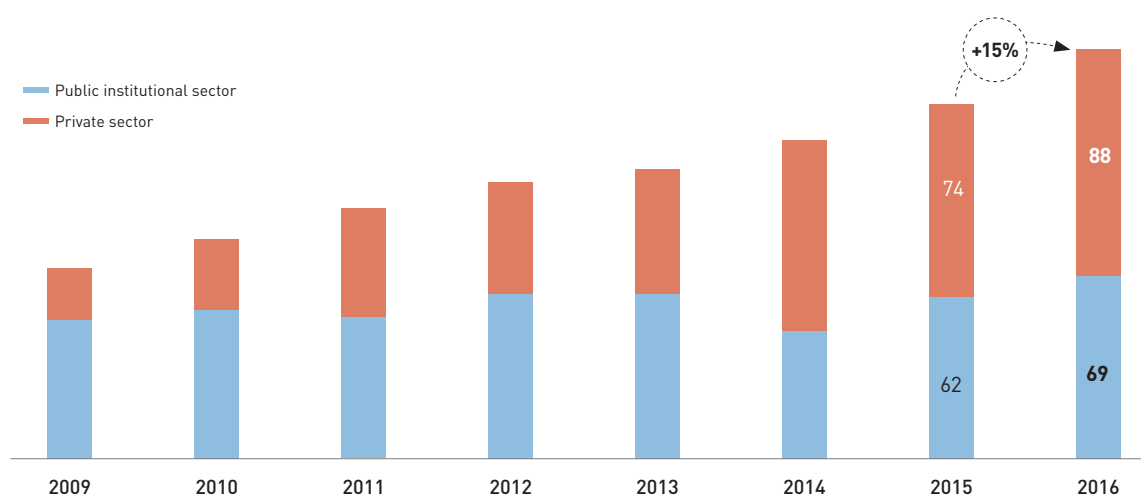
Rise in partnerships to support the growth of R&D activities

- In 2016, the number of partners and service providers with whom DNDi had business relations valued at over EUR 5,000 remained relatively stable, with a 4% increase (167 in 2016, from 160 in 2015). Note that these figures do not include some substantive and close partnerships that present no financial element.
- Partnerships increased significantly in two regions:
 - in North America, with four (+30%) additional partners and service providers to support filarial and Chagas diseases' pre-clinical activities;
 - in Europe, with six (+8%) additional partners and service providers, reflecting the preparation of activities in the diseases recently added to DNDi's portfolio.
- The ratio of low- and middle-income country partners to high-income country partners is relatively stable, at around 40% versus 60%.



More contracts with private rather than public sector partners

- The evolution of contracts finalized each year follows a similar trend to the growth in activity. Since 2010, the annual increase of new contracts has been between 10% and 15%, with 12% in 2015 and 15% in 2016.
- In 2016, a total of 157 new contracts were signed. Note the figures below exclude confidentiality agreements, but include as 'new' some contracts that may be extensions.
- Organizations from the public institutional sector (including research institutes, public hospitals, academic groups, universities, product development partnerships, and other not-for-profit organizations) accounted for 69 (44%) of contracts signed in 2016, with the private sector (including pharmaceutical and biotechnology companies and contract research organizations) accounting for 88 (56%).



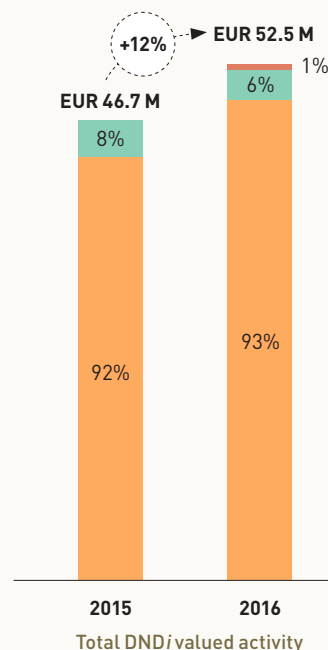
Number of contracts signed 2004-2016

LEVERAGING PARTNERS' RESOURCES

Collaborative funding and in-kind contributions

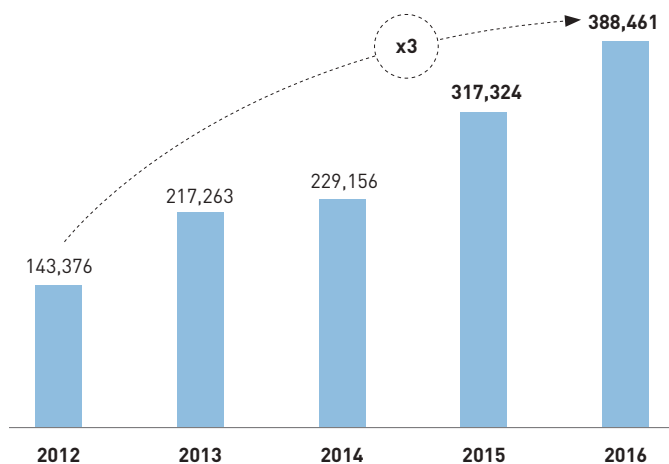
- To present a comprehensive picture of its activities, DNDi accounts for collaborative funding (funding secured from local donors which helps offset R&D and is given directly to our partners and vendors for DNDi R&D-related initiatives) and attributes an estimate value to the generous in-kind contributions from its partners, be they private companies, academic groups, or individuals.
- In 2016 collaborative funding was valued at EUR 0.6 M and in-kind contributions at EUR 3.1 M. This is stable compared to 2015, when the total of in-kind contributions were valued at EUR 3.7 M (collaborative funding was not accounted separately in 2015 and was embedded in the in-kind contribution).
- The cumulated in-kind contributions for the last ten years amount to EUR 34 M, reflecting DNDi's continued investment in building strong partnerships. This represents more than 11% of the total expenditure for the same period.

- DNDi total expenditure
- In-kind contributions
- Collaborative funding

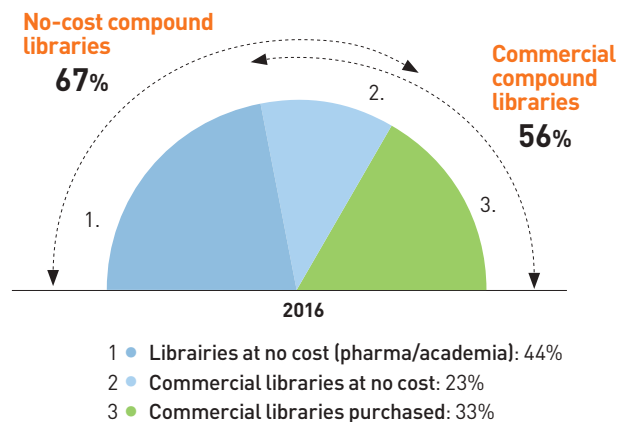


Access to compound libraries

- As well as paying for access to commercial libraries, DNDi has access to pharmaceutical compound libraries for its work on the development of new chemical entities for neglected patients. The pharmaceutical companies provide this access at no cost. Despite DNDi's attempts to estimate more precisely the in-kind value of this access, it is complicated 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.
- One attempt to illustrate this contribution is the total number of compounds screened. More than 1.3 million compounds were screened since 2012, with an increase of 22% between 2015 and 2016. Visceral leishmaniasis and Chagas disease are the priority targets of this activity.
- Commercial libraries represent 56% of the screened compounds since 2012. 40% of these libraries are transferred to DNDi at no cost.
- Therefore, two-thirds of screened compounds (869,950 compounds) were provided at no cost as in-kind contributions.



Number of compounds screened 2012-2016



Extract of the 2016 Financial and Performance Report

BALANCE SHEET

At 31 December 2016 with 2015 comparative figures

(Expressed in EUR)

	2016	2015
CURRENT ASSETS		
Cash and cash equivalents:		
Cash and banks at Headquarters	21,338,896	11,219,157
Cash and banks at Regional and Affiliate Offices	1,310,387	603,453
Time deposits	3,408,386	12,762,861
Total cash and cash equivalents	26,057,668	24,585,471
Stocks of drugs	287,735	156,537
Current accounts and receivables:		
Advances to staff and Regional Offices	45,370	76,672
Receivables from public institutional donors	1,487,890	1,798,808
Other receivables	597,053	692,398
Prepaid expenses	684,552	609,579
Total current accounts and receivables	2,814,866	3,177,458
TOTAL CURRENT ASSETS	29,160,269	27,919,466
NON-CURRENT ASSETS		
Tangible fixed assets, net	324,369	261,722
Bank guarantee deposits	242,091	229,500
Total non-current assets	566,460	491,222
TOTAL	29,726,729	28,410,688
CURRENT LIABILITIES		
Payables	6,648,043	3,238,685
Accrued expenses	1,718,804	1,563,337
Deferred income	10,248,121	12,639,386
Provisions	452,166	331,251
Total current liabilities	19,067,134	17,772,659
CAPITAL OF THE ORGANIZATION		
Paid-in capital	32,510	32,510
Restricted operating funds	0	53,364
Unrestricted operating funds	10,627,084	10,552,155
Total capital of the organization	10,659,595	10,638,029
TOTAL	29,726,729	28,410,688

Extracted from DNDi's '2016 Financial and Performance report' audited by Deloitte. The full report is available on DNDi's website at: www.dndi.org/key-financial-figures

Extract of the 2016 Financial and Performance Report

STATEMENT OF OPERATIONS

At 31 December 2016 with 2015 comparative figures

(Expressed in EUR)

	2016	2015
INCOME		
Public institutional funding:		
Governments & public international org., unrestricted	14,608,068	13,589,613
Governments & public international org., restricted	16,536,879	11,745,626
Total public institutional funding	31,144,948	25,335,240
Private resources:		
Private foundations, corp. and individuals, unrestricted	161,135	286,879
Private foundations, corp. and individuals, restricted	13,387,722	13,572,650
Royalties on drug sales	0	304
Total private resources	13,548,857	13,859,834
Resources from founding partners:		
Médecins Sans Frontières, unrestricted	4,275,025	4,000,000
Médecins Sans Frontières, restricted	15,556	14,944
Total resources from Founding Partners	4,290,581	4,014,944
Other income:		
Sundry income & reimbursements	54,878	73,328
Other income net	54,878	73,328
TOTAL INCOME	49,039,263	43,283,345
SOCIAL MISSION EXPENDITURE		
Research & development expenditure:		
Research & development coordination and supervision	4,691,590	4,320,562
Human African trypanosomiasis projects	7,486,589	8,723,041
Leishmaniasis projects	6,303,749	4,380,683
Chagas disease projects	3,202,400	1,872,551
Filarial diseases projects	3,528,799	3,025,486
Paediatric HIV projects	2,901,795	2,240,641
Hepatitis C projects	890,530	422,104
Mycetoma projects	566,903	121,455
Other diseases projects (malaria and exploratory)	243,230	653,137
Lead optimization & portfolio building	6,630,788	6,948,617
Global Antibiotic Research & Development Partnership (GARDP)	887,256	0
Total research & development expenditure	37,333,628	32,708,277
Strengthening capacities	3,177,076	2,754,649
Advocacy expenses	2,500,878	2,265,997
TOTAL SOCIAL MISSION EXPENDITURE	43,011,582	37,728,923
NON-SOCIAL MISSION EXPENDITURE		
Fundraising	1,912,520	2,035,629
General and administration	3,848,785	3,238,280
Total non-social mission expenditure	5,761,305	5,273,909
TOTAL EXPENDITURE	48,772,887	43,002,832
Operating surplus	266,375	280,513
OTHER INCOME (EXPENSES)		
Financial income (loss), net	(9,436)	21,862
Exchange gain (loss), net	(235,374)	(182,369)
TOTAL OTHER INCOME (EXPENSES)	(244,810)	(160,507)
Net surplus for the year prior to allocations	21,566	120,006
Release from restricted operating funds	53,364	61,183
Allocation to unrestricted operating funds	(74,930)	(181,189)
NET SURPLUS FOR THE YEAR AFTER ALLOCATIONS	-	-

Extracted from DNDi's '2016 Financial and Performance report' audited by Deloitte. The full report is available on DNDi's website at: www.dndi.org/key-financial-figures

Extract of the 2016 Financial and Performance Report

INCOME

a) Deferred income

The total deferred income decreased by EUR 2,391,265 in 2016 compared to 2015, mainly because two donors advanced grant payment in 2015 for two years of activities (covering 2015 and 2016). These advances (EUR 1.1 M and EUR 0.9 M) have mostly been exhausted in 2016. As per the contract, the advance payments were not renewed in 2016. One grant is now terminated and the next advance payment will be done for the other one in 2017.

b) Cumulative donations committed to DNDi and/or received by 2016

DONORS (Notes)	Currency	Total initial commitment in currency	Total initial commitment in EUR	As per statement of operations 2016 in EUR	Remaining commitment to be used after 2016 in EUR
Bill & Melinda Gates Foundation	USD	123,777,824	103,671,686	11,735,344	34,603,788
UK Government DFID	GBP	67,364,550	83,371,641	12,685,191*	4,089,400
Médecins Sans Frontières (MSF)	EUR	65,924,009	65,924,009	4,015,556	8,096,633
Dutch Government DGIS	EUR	32,975,000	32,975,000	3,198,833	12,000,000
German Government BMBF through KfW	EUR	20,101,381	20,101,381	1,989,336	8,800,000
French Government MAEE/AFD	EUR	16,255,006	16,255,006	1,321,067	1,840,741
UNITAID	USD	17,335,304	15,908,857	2,498,752	9,754,815
Spanish Government AECID	EUR	12,000,000	12,000,000		-
US Government NIH/NIAID/USAID	USD	12,196,791	11,049,243	729,835	8,158,007
Swiss Government SDC	CHF	13,020,000	10,912,707	1,837,004	
GHIT Fund, Japan	USD/JPY	958,968,632	7,820,966	3,885,002	1,766,668
Wellcome Trust, UK	EUR/USD	5,579,614	4,913,759	685,078	-
European Union, FP5, FP6, FP7, EDCTP	EUR	4,413,101	4,413,101	514,121	-
Medicor Foundation, Liechtenstein	EUR/USD	3,650,000	3,027,821	240,000	-
Various other donors (Fondation ARPE, Brian Mercer Charitable Trust, Rockefeller Brothers Fund, Fondation de Famille Sandoz, Sasakawa Peace Foundation, Tuscany Region and anonymous individuals and foundations) and royalties ^[12]	EUR/GBP	2,781,260	2,496,970	246,212	11,684
WHO-TDR	EUR	2,340,000	2,340,000	1,256,101	116,333
Norwegian Government NORAD	NOK	18,000,000	2,045,671	276,436	55,448
Canton of Geneva, Switzerland	CHF	2,580,000	1,992,083	138,376	306,966
UBS Optimus Foundation, Switzerland	CHF	2,000,000	1,445,021	203,380	40,841
Associação Bem-Te-Vi Diversidade, Brazil	BRL	5,000,000	1,437,545	493,720	-
Global Fund (AMFm)	EUR	532,809	532,809	-	-
Starr International Foundation, US	USD	625,000	491,402	-	-
Brazil Government, MoH and FINEP	BRL	1,384,212	409,611	20,876	-
BBVA, Spain	EUR	400,000	400,000	-	-
Kalacore	GBP	213,900	260,340	67,857	142,988
Rockefeller Found. & Carlos Slim Foundation	USD	200,000	147,549	-	-
MSF for GARDP	EUR	600,000	600,000	275,025	324,975
German Government, Bundesministerium für Gesundheit (BfG- MOH) for GARDP	EUR	500,000	500,000	457,459	42,541
Swiss Government OFSP for GARDP	CHF	360,000	333,294	182,829	150,465
UK Government DFID for GARDP	GBP	75,000	85,873	85,873	-
TOTAL DONATIONS (EUR)			407,863,346	49,039,263	90,302,292

Extracted from DNDi's '2016 Financial and Performance report' audited by Deloitte. The full report is available on DNDi's website at: www.dndi.org/key-financial-figures

Extract of the 2016 Financial and Performance Report

EXPENDITURE

a) R&D projects related expenditure

Recognized in (Expressed in EUR)	2016	2015
IMPLEMENTATION PROJECTS		
ASAQ - Fixed-dose combination of artesunate-amodiaquine (malaria)	180,457	330,026
ASMQ - Fixed-dose combination of artesunate-mefloquine (malaria)	34,175	248,622
NECT - Nifurtimox-eflornithine combination therapy for stage-2 HAT	7,554	16,295
SSG & paromomycin combination therapy for visceral leishmaniasis in Africa	-	20,279
New visceral leishmaniasis treatments in South Asia	340,465	536,953
Chagas disease - access	424,087	228,753
Superboosting ritonavir for TB/HIV co-infected children	209,472	276,447
TOTAL IMPLEMENTATION PROJECTS	1,196,211	1,657,376
DEVELOPMENT PROJECTS (PHASE IIB/III; REGISTRATION)		
Fexinidazole (HAT)	5,392,577	7,447,957
New visceral leishmaniasis treatments in Latin America	94,726	111,936
New visceral leishmaniasis treatments in Africa	209,094	-
HIV / visceral leishmaniasis co-infection	594,485	684,752
HIV - 'LIVING' study	1,701,790	461,178
Hepatitis C	890,530	422,104
Mycetoma	566,903	121,455
TOTAL DEVELOPMENT PROJECTS	9,450,105	9 249 382
TRANSLATION PROJECTS (PRE-CLINICAL; PHASE I; PHASE IIA/PROOF-OF-CONCEPT)		
Fexinidazole (Chagas disease)	292,977	640,021
SCYX-7158 (HAT)	2,086,459	1,258,789
Fexinidazole/miltefosine combination (visceral leishmaniasis)	1,563,690	1,693,469
Anfoleish (cutaneous leishmaniasis)	255,492	405,377
Cutaneous leishmaniasis combination	418,665	93,564
CpG-D35 (cutaneous leishmaniasis)	721,524	318,472
Post Kala-Azar Dermal Leishmaniasis	341,054	-
New combination therapies including benznidazole (Chagas disease)	1,599,290	431,643
Biomarkers (Chagas disease)	886,045	572,133
4-in-1 LPV/r-based fixed-dose combination (paediatric HIV)	990,532	1,503,016
Nitroimidazole (VL-2098) + VL-0690 + VL-6148 (visceral leishmaniasis)	1,764,553	515,882
Flubendazole macrofilaricide (Filaria)	-	123,618
Emodepside macrofilaricide (Filaria)	1,458,439	1,584,830
Oxfendazole macrofilaricide (Filaria)	23,702	19,007
TylAMac macrofilaricide (Filaria)	1,097,214	323,758
TOTAL TRANSLATION PROJECTS	13,499,637	9,483,579
RESEARCH PROJECTS (SCREENING; HIT-TO-LEAD; LEAD OPTIMIZATION)		
Lead Optimization Consortia	4,933,020	5,614,961
Screening resources & reference screening centres	1,697,768	1,333,656
Screening filaria	949,444	974,272
TOTAL RESEARCH PROJECTS	7,580,231	7,922,889
GARDP	887,256	-
Exploratory Activity	28,598	74,489
R&D coordination, supervision and exploratory activities	4,691,590	4,320,562
TOTAL PROJECTS-RELATED EXPENDITURE	37,333,628	32,708,277

Extracted from DNDi's '2016 Financial and Performance report' audited by Deloitte. The full report is available on DNDi's website at: www.dndi.org/key-financial-figures

DNDi BOARD OF DIRECTORS



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Chair; University of Basel, formerly
with Swiss Tropical and Public Health
Institute, Switzerland



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USA



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Sir Salimullah Medical College,
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Joanne Liu
Médecins Sans Frontières



Alwyn Mwinga
Patient representative; Zambart,
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Kenya Medical Research Institute
(KEMRI), Kenya



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



John Reeder
Permanent observer;
Special Programme for Research
and Training in Tropical Diseases
(WHOTDR), Switzerland

DNDi SCIENTIFIC ADVISORY COMMITTEE



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Chair (since April 2016);
Mahidol University, Bangkok, Thailand



Pierre-Etienne Bost
Chair (until March 2016);
formerly with Institut Pasteur, France



Rashmi Barbhaiya
formerly with Advinus, India
(since Dec. 2015)



Kirana Bhatt
University of Nairobi, Kenya



Shing Chang
formerly with DNDi USA
(until June 2016)



J. Carl Craft
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Cochabamba, Bolivia



Muriel Vray
Institut Pasteur, France



Krisantha Weerasuriya
World Health Organization, Geneva
(until June 2016)



John Westwick
Imperial College,
London University, UK

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of DNDi's Board of Directors, France

Pierre-Etienne Bost, Former Chair
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France

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of Health, Malaysia

Bernhards Ogutu, Kenya Medical
Research Institute, Kenya

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

Tankred Stoebe, Médecins Sans
Frontières, Germany

Bernard Pécoul, DNDi, Switzerland
Thomas Saugnac, DNDi, Switzerland

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Barbara Kessler, formerly with Novartis, Switzerland

Statutory auditors: Deloitte

Bernard Pécoul, DNDi, Switzerland

Marcel Tanner, Chair of DNDi's Board of Directors

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* Former DNDi's Board or SAC member

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Joelle Tanguy, Treasurer; UN Women, Switzerland

Shing Chang, formerly with DNDi, USA

Suerie Moon, Harvard School of Public Health and Harvard Kennedy School of Government, USA (until June 2016)

Bernard Pécoul, DNDi, Switzerland

Kristina Torgeson, The Alliance for International Medical Action, USA

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Joelle Tanguy, UN Women, Switzerland

George Tyler, formerly with the World Bank, USA

Derrick Wong, non-profit management consultant, France

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Vacant, Vice-president

Susana de Deus, Secretary; Médecins Sans Frontières, Brazil

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DNDi Latin America Advisory Board

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Pedro Carpenter Genescá, Lawyer, Brazil

Sergio Alejandro Sosa Estani, Ministry of Health, Argentina (until Nov. 2016)

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Laurence Vielfaure, Auditor; DNDi, Switzerland

Fumiko Hirabayashi, DNDi, Japan

DNDi LEADERSHIP

Executive Team

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Jean-François Alesandrini, External Affairs Director

Manica Balasegaram, GARDP Director

Graeme Bilbe, Research & Development Director

Thomas Saugnac, Operations Director

Headquarters

Robert Don, Discovery & Pre-Clinical Director

Jana Jauffret, Human Resources and Organization Director (since June 2016)

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Serge Sagodira, Business Development and Legal Director (since Dec. 2016)

Eric Stobbaerts, International Development and Coordination Director (since Dec. 2016)

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Laurence Vielfaure, Finance and Planning Director

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Monique Wasunna, Director, DNDi Africa

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Fumiko Hirabayashi, Head of Liaison office, DNDi Japan (until Sept. 2016)

Daisuke Imoto, Head of Liaison office, DNDi Japan (since May 2017)

Jean-Michel Piedagnel, Head of Liaison office, DNDi South East Asia

DNDi TEAM WORLDWIDE

List of all programme, regional, and functional leaders available on DNDi's website: <https://www.dndi.org/about-dndi/our-people/leadership/>

Biographical details available on DNDi websites

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To date, DNDi has delivered seven new treatments and aims to bring 16-18 treatments to patients living with neglected diseases by 2023. DNDi is grateful for the support received from the following donors, have contributed toward the advancement of our mission and goals. Supporters who have given a cumulative contribution in excess of USD or EUR 10,000, are listed below.

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NOTES



Drugs for Neglected Diseases *initiative*

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Former patients and people living with the diseases in DNDi's portfolio have been represented in photo format throughout this report, and medical staff, scientists, researchers, academics, ministers, and civil servants through illustrations realized by Agnès Rastoin and Léna Bousquet.

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Drugs for Neglected Diseases *initiative*

The Drugs for Neglected Diseases *initiative* (DNDi) is a collaborative, 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, filarial infections, paediatric HIV, mycetoma, and hepatitis C.

In 2016, in collaboration with the World Health Organization, DNDi launched the Global Antibiotic Research and Development Partnership, a not-for-profit research and development organization that addresses global public health needs by developing and delivering new or improved antibiotic treatments while endeavouring to ensure sustainable access.

DNDi's primary objective:

- Deliver 16 to 18 new treatments by 2023 for targeted neglected diseases, ensure equitable access to these treatments, and establish a robust R&D portfolio of new drug candidates that addresses patients' treatment needs

In doing this, DNDi 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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