

STRENGTHENING EXISTING
CAPACITIES

DNDi works closely with partners in disease-endemic countries to strengthen existing clinical research capacity.





REINFORCING RESEARCH AND MANUFACTURING CAPACITIES IN ENDEMIC COUNTRIES

An integral part of its business model, DNDi has endeavoured to build regional disease networks to ensure that research capacity is where it needs to be – where the diseases occur – and that it is sustained. In addition, DNDi facilitates technology transfer as a vital means to sustaining production, notably in endemic countries, and increasing patient access to treatments.

The health R&D landscape in neglected disease-endemic countries has undergone a change over the past decade, with several initiatives being undertaken in and by developing countries. However, research capacity remains a hindrance to sustainable R&D in many such countries, which is why DNDi has maintained endemic country capacity utilization and strengthening at the core of its mission. By 2009, one disease-specific research platform per kinetoplastid disease (human African trypanosomiasis, leishmaniasis, and Chagas disease) was in



place. These platforms promote South-South collaboration and bring together the most important actors in each region to address patient needs from 'A to Z': from defining patient needs, to training clinical researchers, to facilitating registration, to expediting implementation. An integral part of the DNDi model, these platforms have achieved several important milestones, including: LEAP's delivery of SSG&PM for visceral leishmaniasis in East Africa; the HAT Platform's continued support for implementation of NECT for sleeping sickness in 11 endemic countries; and the Chagas Clinical Research Platform's network that oversaw three new clinical studies for Chagas disease in Argentina and Bolivia.

Disease platforms in 2011

Leishmaniasis East Africa Platform (LEAP)

Founded: 2003 in Khartoum, Sudan



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

- Approx. 60 individual members, representing over 20 institutions
- Over 1,300 patients enrolled in clinical trials by the end of 2011
- Approx. 700-800 patients treated outside clinical trials in 2011
- 1,000 patients on Pharmacovigilance Phase IV study (all patients received SSG&PM combination therapy)

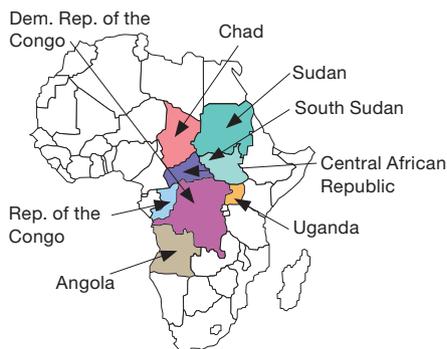
Overall objectives:

- Strengthen clinical research capacity, which is lacking in part due to the remoteness and geographic spread of the patients, most of whom live in the most impoverished regions of Africa
- Serve as a base for ongoing educational cooperation among East African countries and for standardization of procedures and practices in the region, as far as possible within the confines of local regulations
- Evaluate, validate, and facilitate registration of new treatments for VL in the region



Human African Trypanosomiasis HAT Platform

Founded: 2005 in Kinshasa, Democratic Republic of the Congo



Members from the following institutions:

National Control Programmes of most affected endemic countries: Angola, Central African Republic, Chad, Democratic Republic of the Congo, Republic of Congo, South Sudan, Sudan, Uganda; Swiss Tropical and Public Health Institute (Swiss TPH); Institute of Tropical Medicine-Antwerp, Belgium; Institut National de Recherche Biomédicale (INRB), DRC; Kenya Agricultural Research Institute - Trypanosomiasis Research Centre (KARI-TRC), Kenya; Tropical Medicine Research Institute (TMRI), Sudan; Institut Pasteur Bangui, CAR; Médecins Sans Frontières (MSF); Epicentre; Foundation for Innovative New Diagnostics (FIND); regional networks such as Eastern Africa Network for



Trypanosomiasis (EANETT), Centre interdisciplinaire de Bioéthique pour l'Afrique Francophone (CIBAF); Special Programme for Research and Training in Tropical Diseases (WHO-TDR) as observer.

- With the independence of South Sudan in July 2011, the HAT Platform now counts eight member countries.

Overall objectives:

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

Chagas Clinical Research Platform (CCRP)

Founded: 2009 in Uberaba, Brazil



The Platform includes representatives from:

Pan American Health Organization (PAHO); Department for the Control of Neglected Tropical Diseases, WHO; Ministries of Health and National Control Programmes of high-burden endemic countries (Argentina, Bolivia, Brazil, Mexico); Hospital de Niños Ricardo Gutiérrez, Argentina; Instituto Nacional de Parasitología Dr M Fátala Chabén, Argentina; Hospital de Niños de Jujuy, Argentina; Hospital Público Materno Infantil - Salta, Argentina; Centro de Chagas y Patología Regional, Santiago del Estero, Argentina; Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina; Instituto Oswaldo Cruz, Brazil; Instituto de Pesquisa Evandro Chagas-Fiocruz, Brazil; Centro de Pesquisas René Rachou-Fiocruz, Brazil; Universidad Mayor de San Simón - Platform of Integral Care for Patients with Chagas Disease, Bolivia; CRESIB - Hospital Clinic Barcelona, Spain; Médecins Sans Frontières; Institut de Recherche pour le Dével-

oppement, France; Eisai Co. Ltd, Japan; FINDECHAGAS; Mundo Sano, Argentina.

- More than 70 institutions represented from 20 countries

Overall objectives:

- Deliver concrete support for R&D, such as training, capacity building, definition and compliance to standards and regulations, integration of ethical principles across different populations and countries
- Discuss access challenges to new and existing technologies, through a flexible and needs-driven platform





Achievements and Activities in 2011

Treatments: Following the results of the study comparing paromomycin (PM) and sodium stibogluconate (SSG) in monotherapies, and the shorter course combination SSG&PM, the WHO Expert Committee on the Control of Leishmaniases recommended, in March 2010, the use of SSG&PM as first-line treatment for VL in East Africa. Sudan applied this recommendation at the close of 2010, implementing SSG&PM as first-line treatment. Since then, the process of registration of PM has been initiated in LEAP countries, of which Uganda will be the first (early 2012).

Clinical trials: Patient follow-up and data collection and analysis for DNDi and LEAP AmBisome®/AMBI 0106 Study were completed in 2011 (see page 29). In 2011, recruitment progressed for Miltefosine-AmBisome®/LEAP 0208 study (see page 29). In addition, a pharmacovigilance study to monitor safety and effective-

ness of SSG&PM was initiated (see page 31). Another study, the Rapid Diagnostics Tests (RDT) study in Kenya (MSF and KEMRI) was completed.

Capacity strengthening: Good Clinical Practice (GCP), Good Clinical and Laboratory Practice (GCLP) and study-specific training courses were held in 2011 for lab technicians, nurses, pharmacists, monitors, and investigators. LEAP also provides post-graduate training to researchers and health workers: in 2011, one person from Uganda, three from Kenya, one from Sudan, and three from Ethiopia. A total of 108 people were trained in 2011. In addition, an exchange programme was initiated between the laboratory staff at the Kimalael site in Kenya and the Amudat site in Uganda. Launched in November 2011 in Kimalael, the programme will continue in 2012 in Amudat.

Infrastructure: In 2011, the renovation of laboratories at Gondar clinical site, Ethiopia, started and will be finalized in 2012.

Access: LEAP countries are in the process of reviewing National VL Guidelines in light of WHO recommendation of SSG&PM as first-line treatment for VL in the region. In parallel, the update of Essential Medicines Lists in each country is ongoing in order to reflect the addition of SSG&PM as a VL treatment.

Communication: The first LEAP brochure was released. SSG&PM treatment was featured in regional media following a press conference in Nairobi in September 2011.

Meetings: The 16th LEAP meeting & LEAP stakeholders workshop held in Nairobi, Kenya, in September 2011 brought together more than 150 participants for a week-long meeting. Principal investigators' meetings and DSMB & monitors' meetings took place at this occasion; other scientific congresses.



Achievements and Activities in 2011

Treatments: In December 2011, NECT was used in 11 African countries after becoming the first-line treatment for second stage *T.b. gambiense* infected patients. In 2011, the Republic of Congo was the latest country to adopt NECT as first-line treatment.

Clinical trials: **NECT:** Participation in the ongoing NECT-Field studies (six sites in DRC); **Fexinidazole:** Preparation of the clinical trials for a new oral drug in DRC during 2011: discussions with ethical and regulatory authorities of DRC; training; and selection of sites. This study will start in 2012 in three countries: DRC, Central African Republic (CAR), and South Sudan. In addition, by strengthening collaboration with FIND, the platform contributed to a trial for a new Rapid Diagnostic Test. With ITM-Antwerp, it was involved

in the preparation of the trial for the neurological diagnosis decision trees (NIDIAG).

Capacity strengthening: In 2011, the platform organized two training courses in Kinshasa: A pharmacovigilance training with 40 participants (DRC, Chad, CAR, and Angola) and a Clinical Research and Good Clinical Practice training with 22 participants, mainly from DRC and CAR.

Infrastructure: The HAT Platform helps to identify the needs of each member country and sites involved in the clinical studies, namely by facilitating the selection of equipment and products to purchase. In 2011, Kwamouth and Katanda clinical sites in DRC benefited from several infrastructure upgrades, such as solar energy systems, kitchen, warehouses, and painting of rooms.

Access: Advocacy in member countries towards quick adoption of NECT as first-line treatment for second stage HAT. NECT is rapidly replacing previous treatments for stage 2 HAT: in 2011, 93% of stage 2 sleeping sickness patients in DRC were treated with NECT.

Communication: Two HAT platform newsletters were published in 2011; the first HAT platform brochure was released.

Meetings: The HAT Platform Steering Committee took place in Bangui, CAR, in May 2011, with 20 participants. The Annual Scientific Meeting of the HAT Platform was held in Bamako, Mali, in September 2011, with 37 participants. Other scientific congresses: presentations of HAT research activities at the 31st ISCTRC meeting (Bamako) and at the 7th ECTMIH (Barcelona, Spain).



Achievements and Activities in 2011

Clinical trials: In 2011, three studies that receive support from the Platform were initiated: a population pharmacokinetics (PK) study of the use of benznidazole in children, including the new paediatric dosage form (Argentina); a study to evaluate and optimize the polymerase chain reaction method (PCR) for diagnosis and assessment of therapeutic response in patients with chronic indeterminate Chagas disease (Bolivia); a study to evaluate the safety and efficacy of E1224, a pro-drug of ravuconazole (Bolivia, see page 36).

Capacity Strengthening: In 2011, Good Clinical Practice training courses and investigators meetings were held in Bolivia and Argentina for team members involved in the ongoing clinical studies on Chagas disease supported by the platform. 70 participants were trained in 2011.

Infrastructure: As part of the start-up and preparatory activities for the implementation of the clinical trials (E1224, Bolivia, and the paediatric dosage form of benznidazole, Argentina), equipment and infrastructure building took place in 2011 (upgrade of laboratory equipment and construction of separate laboratory areas of the Platform of Integral Care for Patients with Chagas Disease).

Access: The CCRP collaborated on the development of an Information, Education, and Communication (IEC) Tool Box for rational use of the paediatric dosage form of benznidazole. In addition, the Platform was active in mediating and addressing the 2011 crisis in the production of benznidazole.

Communication: The first edition of the CCRP Newsletter was published in August 2011 in

Portuguese, Spanish, and English, and a Web Forum was launched, bringing together over 120 members from 73 organizations and 20 countries within this virtual working space for discussions and sharing of information on access to treatments.

Meetings: In 2011, the Ibero-American research network NHEPACHA, member of the CCRP, organized two meetings in Spain and Argentina to launch the network and review priorities in research on biological markers for Chagas disease and facilitate long-term follow-up. The 2nd CCRP meeting took place end 2011 in Brazil with over 90 participants including PAHO, WHO, control programme managers from key endemic countries, investigators, and patient representatives. All the current projects on Chagas disease were reviewed and discussed.

TRANSFERRING TECHNOLOGY TO BOOST LOCAL INNOVATION CAPACITY

DNDi develops non-patented treatments notably to facilitate their production by different pharmaceutical partners, namely in endemic countries, to ensure the sustainability of production, to ensure a second source of treatments, and ultimately better support patient access to the treatments. To do so, a process of transfer of technology is needed to share the drug development know-how between industrial partners. DNDi is committed to two technology transfers (TT), for ASAQ and ASMQ, the two ACT fixed-dose combinations for malaria.

ASMQ: From Brazil to India

In order to facilitate access of the ASMQ fixed-dose combination (see page 40) in Southeast Asia, a South-South TT between Farmanguinhós/Fiocruz in Brazil and Cipla Ltd in India came to completion in 2010 with support from DNDi. The first TT of its kind between a company in Brazil and one in India – even more unique since it involved a public entity (Farmanguinhós) and a private company (Cipla) – the results of this transfer continue to bear fruits. An application for registration was submitted in India and ASEAN countries (Cambodia, Laos,



Malaysia, Myanmar, Philippines, Thailand, and Vietnam) in 2011. In addition, responses and complementary information for the submission to the WHO for pre-qualification were provided throughout the year. In November 2011, the registration of ASMQ by the Drugs Controller General of India (DCGI), launched the implementation process of ASMQ for Asia and the Southeast Asian region. More ASEAN countries are set to register ASMQ in 2012 in order to ensure wide-spread distribution of the life-saving treatment in the region.



ASAQ: From Morocco to Tanzania

Developed as a non-patented product, the ASAQ fixed-dose combination (see page 41) – produced by Sanofi in Morocco since 2007 – will undergo technology transfer. In 2010, DNDi, with support from a group of experts from OTECI, assessed potential partners in Africa to become the second producer of ASAQ in an endemic area of Africa. By the close of 2010, the Tanzanian industrial group Zenufa was selected, one of the critical characteristics of the partner being its ability to pass pre-qualification by WHO.



In 2011, the terms of the agreement were finalized and the contract with Zenufa was signed. The first transfer activities began, among them audits of Zenufa to define the steps of the analytical and technical transfer plans, to assess in detail Good Manufacturing Practice (GMP) for pre-qualification, and to develop a business plan. To manage the TT, a team formed by Aedes, Bertin Pharma, OTECI, DNDi, and Zenufa was formed.

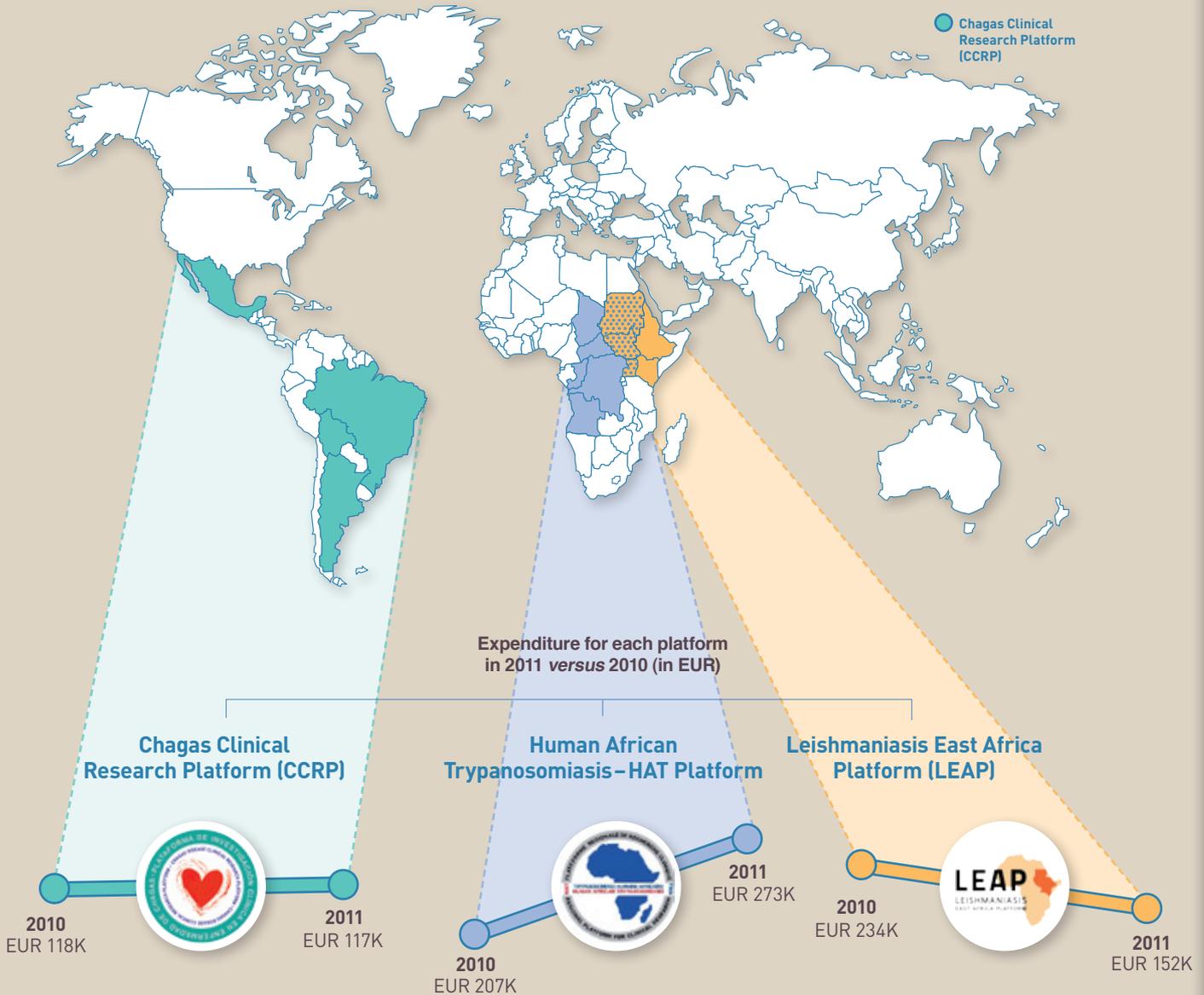
2011 KEY FINANCIAL PERFORMANCE INDICATORS



Three Regional Clinical Research Platforms

Bringing together key actors to address patient needs from A to Z

-  Leishmaniasis East Africa Platform (LEAP)
-  Human African Trypanosomiasis-HAT Platform
-  LEAP + HAT
-  Chagas Clinical Research Platform (CCRP)



The **Chagas Clinical Research Platform (CCRP)** is operational at two sites for the E1224 Phase II study (Bolivia) and five sites for paediatric benznidazole pharmacokinetics (Argentina). The CCRP expenses remain stable, and include the organization of a platform meeting in December 2011 in Rio de Janeiro, Brazil. **In 2011, 70 people were trained.**

The **HAT Platform** is operational at six sites for the NECT study. In addition, five to six sites are in preparation in DRC (Bandundu-Ville, Vanga, Masi-Manbimba) and in CAR (Batangafo) for the fexinidazole Phase II/III study expected to start in 2012. The increase of expenses is due to human resource strengthening to support the preparation of clinical trial sites for this study. **In 2011, 62 people were trained.**

In 2011, clinical trial activities are conducted at seven sites managed by the **LEAP platform**: two in Sudan (Kassab, Dooka), one in Uganda (Amudat), one in Kenya (Kimalel), and two in Ethiopia (Arba Minch, Gondar). In addition, in 2011, MSF and MoH sites in Sudan have implemented studies for SSG&PM co-administration. No rehabilitation was undertaken in 2011, whereas the site in Dooka was rehabilitated in 2010 (EUR 0.1 Million) and opened as a new LEAP clinical site in 2011 for the VL studies. **Over 100 people were trained in 2011.**