



New Delhi, India, December 3, 2010

DNDi's  
**3rd Partners' Meeting**  
in collaboration  
**with ICMR**



Indian Council  
of Medical Research

**DNDi**

Drugs for Neglected Diseases *initiative*

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## Welcome address

3 December 2010

Dear guests, partners, friends, and colleagues,

Welcome to DNDi's 3<sup>rd</sup> Partners' Meeting organised in collaboration with the Indian Council for Medical Research (ICMR), which aims to present major progress from DNDi's research pipeline and ongoing partnerships in India. This event brings together DNDi's key partners, as well as world renowned health experts, researchers, clinicians, and pharmaceutical executives committed to tackle diseases that affect neglected patients. These leading experts will have the opportunity to examine ongoing DNDi projects in drug research and development, access, and capacity strengthening.

This meeting will be an excellent forum to share knowledge on the realities of conducting research, managing drug development, and ensuring access to new treatments for visceral leishmaniasis and malaria in India.

We are honoured to have distinguished guests from the public and private sectors among us: representatives of national and local authorities, pharmaceutical companies, health-related NGOs, academics, and research institutes. We would like to especially thank our Hon'ble Guest Sri Ghulam Nabi Azad, Minister of Health & Family Welfare and Dr. V.M. Katoch, Secretary to Government of India, Department of Health Research and Director General of the Indian Council of Medical Research (ICMR), as well as speakers and panellists who will bring their expertise to facilitate the debate.

We would like to acknowledge all our project partners and donors for their commitment and support. We also wish to pay a special tribute to our devoted Indian partners who provide invaluable contributions to our R&D activities: the ICMR, the Central Drug Research Institute (CDRI), the National Institute of Malaria Research (NIMR), the Kala-azar Medical Research Centre, the Rajendra Memorial Research Institute of Medical Sciences, Advinus Therapeutics, GVK BIO, Cipla and sanofi-aventis. We would also like to acknowledge our partners from Bangladesh: the Director General, DGHS, Ministry of Health, Bangladesh; the International Centre for Diarrhoeal Disease Research (ICDDR, B), Dhaka; and Shaheed Suhrawardy Medical College (ShSMC), Dhaka.

We are very pleased that you are here with us today and will have a chance to share your knowledge and expertise with all those present. We look forward to future engagements as we work together to make a true difference in delivering adequate treatments to the most neglected patients.

Best regards,

Dr. Bernard Pecoul  
Executive Director  
Drugs for Neglected Diseases  
*initiative*

Dr. Marcel Tanner  
Chair, Board of Directors  
Drugs for Neglected Diseases  
*initiative*

Bhawna Sharma  
Head  
DNDi India Regional Support Office



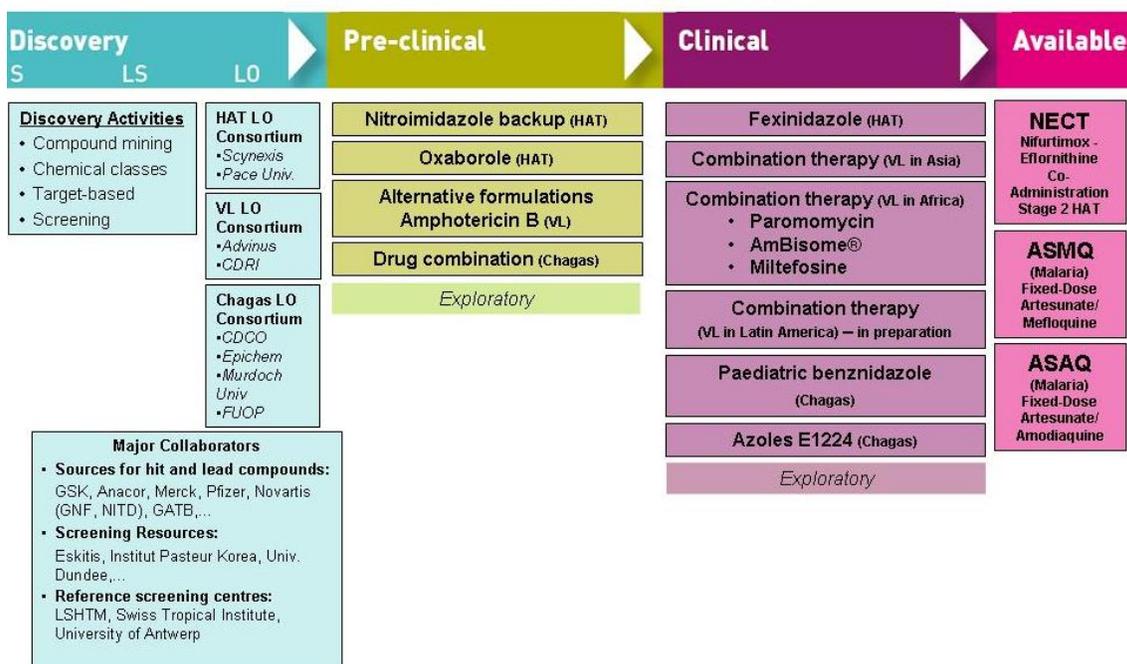
## DNDi in 2010

DNDi (Drugs for Neglected Diseases *initiative*) is a collaborative, patient-needs driven, not-for-profit drug R&D organization that is currently developing new treatments against the most neglected diseases such as sleeping sickness (or human African trypanosomiasis, HAT), visceral leishmaniasis (VL), Chagas disease and malaria. The initiative's primary objective is to deliver six to eight new treatments by 2014 and to establish a strong R&D portfolio for these diseases. In doing so, DNDi is also working to use and strengthen existing capacities in disease-endemic countries, and advocate for increased public responsibility.

DNDi was established in 2003 by the Indian Council for Medical Research (ICMR), Brazil's Oswaldo Cruz Foundation (Fiocruz), the Kenya Medical Research Institute (KEMRI), the Ministry of Health of Malaysia, the Pasteur Institute in France, and Médecins Sans Frontières/Doctors Without Borders (MSF), with the World Health Organization/TDR as a permanent observer.

Working in partnership with industry, NGOs, and academia, DNDi has built the largest ever R&D portfolio for kinetoplastid diseases and currently has seven clinical/post-registration projects, four preclinical projects, and three lead optimization projects underway, as well as several discovery activities.

## DNDi R&D Portfolio – 2010



Today, DNDi is managing more than 120 partnerships with a wide range of public and private partners and NGOs with more than 400 people engaged in our programmes. DNDi's work is led by a team of talented staff located in different regions, including a team of permanent staff in Geneva, and five regional support offices in Kenya, India, Brazil, Malaysia, and Japan; it has one affiliate in North America, as well as a regional project support office in the Democratic Republic of the Congo.

### Clinical research platforms to strengthen research capacities

DNDi and its partners in disease-endemic countries synergise efforts to build sustainable research capacities. The process of strengthening existing capacities, at the individual and institutional level, helps boost the R&D process not only locally, but also internationally. Three platforms bring together different partners (including



relevant scientists, research organizations, international organizations, NGOs, and national programmes) to work on HAT, VL, and Chagas disease, respectively:

- **The HAT Platform**, a research-strengthening network of clinicians, health agencies, and scientists in the seven African countries most affected by sleeping sickness (Sudan, Democratic Republic of the Congo, Republic of the Congo, Angola, Uganda, Chad, Central African Republic). The HAT Platform has trained site investigators and clinical monitors, implemented two clinical trials, and facilitated the adoption of NECT, a safe and effective combination therapy for HAT.
- **The Leishmaniasis East Africa Platform (LEAP)**, a research-strengthening network of health agencies and scientists in the four African countries most affected by visceral leishmaniasis (Uganda, Kenya, Sudan, and Ethiopia). The LEAP Platform has established seven trial sites and trained principle investigators, lab technicians, and monitors for clinical trials.
- **The Chagas Clinical Platform**, a network of health agencies and scientists in the Americas that is strengthening capacities through training and infrastructure, expanding community participation, and improving evaluation and delivery of new treatments across the region.

## DNDi's main progress into 2010

### Three new treatments delivered since 2007

DNDi has delivered three new treatments to patients, and is well on its way to meeting the objectives of 6–8 new treatments by 2014. In 2011, DNDi will make three new treatments available, including two combination treatments for VL (one for Africa and one for Asia) and paediatric benznidazole for Chagas disease, which is developed in collaboration with LAFEPE in Brazil.

### NECT for sleeping sickness (2009)

- Nifurtimox-eflornithine combination therapy (NECT) is an improved treatment option for the advanced stage of sleeping sickness. The development of NECT is the result of a collaborative partnership over six years between DNDi, Médecins Sans Frontières, Epicentre, the HAT platform, the Swiss Public Health Institute, the national control programmes of the Democratic Republic of the Congo (DRC) and Republic of Congo, with the support of the World Health Organization (WHO), with drugs donated by sanofi-aventis and Bayer Schering Pharma AG. NECT - the first new treatment in 25 years against sleeping sickness - replaces melarsoprol, a highly toxic, arsenic-based drug that kills 5% of treated patients. NECT is easier to administer than the monotherapies, with a reduced number of intravenous infusions of eflornithine (14 instead of 56) and a shorter treatment period (10 days instead of 14), and thus is more convenient for patients and puts less burden on the health staff, logistics and infrastructure. WHO included NECT in the Essential Medicines List (EML) in May 2009. Following the placement of an order for the first NECT kits by the Democratic Republic of the Congo (DRC) to treat 6000 patients, nine other countries have also ordered the combination therapy ([www.dndi.org](http://www.dndi.org)).

### ASMQ for malaria (2008)

- ASMQ is a fixed-dose combination therapy of artesunate (AS) and mefloquine (MQ) for the treatment of uncomplicated *P. falciparum* malaria in South America and Southeast Asia. This new co-formulation, manufactured by Farmanguinhos/Fiocruz, was developed by a worldwide public partnership coordinated by DNDi. ASMQ is a simple regimen consisting of a single daily dose of one tablet (for children) or two tablets (for adults) over three days, available at cost and as public good. Since its registration in Brazil in 2008, ASMQ is part of the recommended treatment in Brazil since April 2009 by the Brazilian Government. After a successful transfer of technology from Farmanguinhos/Fiocruz in Brazil to Cipla in India, ASMQ is on its way to be pre-qualified by WHO and registered in several countries in Southeast Asia ([www.actwithasmq.org](http://www.actwithasmq.org)).



### ASAQ (2007)

- ASAQ Winthrop® is a combination treatment for uncomplicated *P. falciparum* malaria. The combination therapy of artesunate (AS) and amodiaquine (AQ) developed with sanofi-aventis is a non-patented fixed-dose treatment for malaria that has been pre-qualified by WHO. ASAQ Winthrop® is easy to use for patients, easily crushable and consisting of a single-dose regimen with one tablet a day for three days for children and two tablets a day for three days for adults. ASAQ Winthrop® has been the first drug to be made available by DNDi in an innovative partnership with sanofi-aventis in 2007. ASAQ Winthrop® is approved in 25 African countries and in India, and over 70 million treatments have been distributed since 2007. The WHO has recently approved an extension of ASAQ shelf-life from 24 to 36 months, thus making it the first pre-qualified antimalarial treatment with such a long shelf-life ([www.actwithasaq.org](http://www.actwithasaq.org)).

### Funding for lifesaving drugs

DNDi's proven, cost-effective drug development process requires sustainable and diversified investments to deliver safe, effective medicines to those suffering from neglected diseases. DNDi relies on financial support of individuals, foundations, public institutions, and private enterprises to deliver lifesaving drugs to millions of patients in the world. Thanks to its donors, since 2003 DNDi has successfully secured 150 Million Euros out of the 230 Million Euros needed to achieve the goal of delivering 6–8 new treatments by 2014.

**DNDi would like to thank the following donors for their support of its activities since July 2003:**

#### Public donors

- Republic and Canton of Geneva, Switzerland
- Department for International Development (DFID), United Kingdom
- German Agency for Technical Cooperation (GTZ) on behalf of the Government of the Federal Republic of Germany
- European Union – Framework Partnership 5, 6 and 7
- French Development Agency (AFD), France
- Ministry of Foreign Affairs (DGIS), The Netherlands
- Ministry of Foreign and European Affairs (MAEE), France
- National Institutes of Health – National Institute of Allergy and Infectious Diseases (NIAID), USA
- Region of Tuscany, Italy
- Spanish Agency for International Cooperation and Development (AECID), Spain
- Swiss Agency for Development and Cooperation (DDC), Switzerland

#### Private donors

- Bill & Melinda Gates Foundation, USA
- Fondation André & Cyprien, Switzerland
- Guy's, King's and St Thomas' Giving Week, UK
- Leopold Bachmann Foundation, Switzerland
- Médecins Sans Frontières, International
- Medicor Foundation, Liechtenstein
- Fondation Pro Victimis, Switzerland
- Sasakawa Peace Foundation, Japan
- Starr International Foundation, Switzerland
- UBS Optimus Foundation, Switzerland

### DNDi's activities in India

With support from its founding member, the India Council of Medical Research (ICMR), DNDi opened the regional support office in India in 2005 to support and catalyse DNDi's operational activities, mainly for malaria and VL. These two diseases are prevalent in India and affect more than 3 million Indian people each year, according to Indian Government estimates.



India has been the focus of medical research as it bears the burden of two diseases: neglected tropical diseases, which represent major health problems, and non-communicable diseases. Consequently, it is clear that India has become an emerging pharmaceutical hub where research costs are low and pools of skilled medical research and drug development experts are abundant. These elements make India a key country in the fight against neglected diseases, which is why DNDi has been active in the country since 2004.

### The first initiative in Bangladesh

In early 2010, DNDi has initiated its first VL study in Bangladesh in partnership with the Director General, DGHS, Ministry of Health, Bangladesh, International Centre for Diarrhoeal Disease Research (ICDDR, B), Dhaka, and Shaheed Suhrawardy Medical College (ShSMC), Dhaka. It is a study of three short-course combination regimens (AmBisome<sup>®</sup>, miltefosine, paromomycin) compared with AmBisome<sup>®</sup> alone for the treatment of VL in Bangladesh. The overall objective is to identify a safe and effective short-course combination treatment for VL, which could be easily deployed in a control programme in Bangladesh. The study is designed in two steps with sites in the Community Based Medical College (CBMC), Mymensingh and Upa Zila Health Complexes (UZHC) in its periphery.

### **Discovery activities**

In December 2007, DNDi signed a 5-year collaborative agreement with Advinus Therapeutics as primary partner in the lead optimization consortium for VL. The project aims to obtain optimized leads by processing "hit" molecules with good safety profiles and proven activity against *Leishmania* parasites.

This consortium brings together expertise in chemistry, drug screening, pharmacology, and pre-formulation in order to optimize a molecule's drug properties — to be orally absorbed and reach the bloodstream, to be distributed effectively to infection sites, to remain intact in the body to kill the parasites, and yet not to harm the patient. With a full team in place, Advinus Therapeutics in Bangalore has conducted an assessment of series of compounds, and initiated chemistry and biology activities. Dedicated screening facilities at the Central Drug Research Institute (CDRI), in Lucknow, have been established in 2008 for investigating *in vitro* and *in vivo* biological activity. The consortium has recently worked on the oxaborole series from Anacor Pharmaceuticals, USA, that has shown *in vivo* efficacy. The nitroimidazole series, accessed through the collaboration with TB Alliance, produced a number of highly potent compounds, several of which also proved to be efficacious in a VL animal model. Additional pharmacokinetics and safety studies are underway to identify preclinical candidates from these promising series.

### **Clinical development activities**

#### MALARIA

Malaria is unevenly distributed in India: 80% of the population lives in low-transmission areas and 20% in a high-transmission belt. The annual burden reported by the national malaria control program is 2 million confirmed cases and 1,000 deaths, whereas the WHO estimates 15 million cases and 20,000 deaths. India holds 77% of the Southeast Asia malaria burden. The region has also a large number of *P. falciparum* cases (up to 50%) and chloroquine resistance.

- **ASAQ:** In collaboration with the Indian Council of Medical Research (ICMR), National Institute of Malaria Research (NIMR) and supported by GVK, DNDi implemented in 2007 and 2008 an open randomized, multi-centric clinical study for ASAQ versus Amodiaquine (AQ) in India (States of Orissa and Jharkhand). This multicenter study showed that the fixed dose combination of ASAQ is efficacious and well tolerated in the treatment of acute, uncomplicated Plasmodium falciparum malaria in highly endemic, chloroquine resistant areas of Orissa and Jharkhand. The Indian regulatory authority approved ASAQ in 2009 and DNDi and sanofi-aventis are planning for implementation actions in 2011.



- **ASMQ**, the fixed-dose combination of artesunate (AS) and mefloquine (MQ) developed by DNDi and Farmanguinhos/Fiocruz, was successfully registered in Brazil in March 2008. ASMQ is being submitted for registration in countries where Artesunate plus Mefloquine Combination is part of the National Malaria Policy as well as in areas of multidrug resistance where this FDC could be of benefit to patients suffering uncomplicated malaria. In February 2008, the principles of a technology transfer agreement between Farmanguinhos/Fiocruz and Cipla, the Indian pharmaceutical company, were agreed; with the support and facilitation of DNDi it was successfully concluded in 2010. Cipla, in charge of ASMQ FDC manufacturing, will shortly make the product available in Southeast Asia and in India following approval from regulatory authorities.

### VISCERAL LEISHMANIASIS (VL)

Visceral leishmaniasis affects poor, remote populations in 70 countries across Asia, East Africa, South America, and the Mediterranean region. The seven most affected countries represent over 90% of all reported new cases. India has about 100,000 new cases of VL annually, of which approximately 90% are from the region of Bihar.

- **Clinical trials on VL combination therapies in India of Ambisome® (lipid formulations of Amphotericin B), paromomycin, and miltefosine**  
Until recently, pentavalent antimony was one of very few VL treatments, despite all its limitations (toxicity, lengthy treatment, and growing resistance). Presently, amphotericin B, paromomycin, and miltefosine have been evaluated and officially approved by all relevant authorities for the treatment of VL in India. All these drugs have advantages and disadvantages with regard to cost, toxicity, length, and ease of administration. Therefore, to reduce treatment duration, to increase compliance, and to reduce the possibility of development of resistance, DNDi and its partners have investigated the possibility to use combinations of these drugs to treat VL. A clinical study to assess various drug combinations has been initiated in collaboration with the ICMR and the Rajendra Memorial Research Institute (RMRI), at Patna, the Kala-azar Medical Research Centre (KMRC), and GVK Bio at Muzaffarpur. This project has been extended to Nepal and Bangladesh.

The combination study was designed to provide data for authorities in India, Bangladesh, and Nepal to make informed recommendations for combination treatment, which can be used in the VL elimination programmes in the region. This study involving 634 patients was completed in 2010. All three combination treatments were highly efficacious ( $\geq 97.5\%$  cure rate) and none was inferior to the standard treatment with amphotericin B.

The VL Combination project in India was awarded DNDi's Project of Year 2010 (see separate).

- **Clinical trial on VL combination therapies in Bangladesh**  
A study of three short-course combination regimens (AmBisome®, miltefosine, paromomycin) compared with AmBisome® alone for the treatment of VL in Bangladesh. The overall objective is to identify a safe and effective short-course combination treatment for VL that could be easily deployed in a control programme in Bangladesh. The study is designed in two steps in the Community Based Medical College (CBMC), Mymensingh, and Upa Zila Health Complexes (UZHC) in its periphery.

### **Advocacy activities in India**

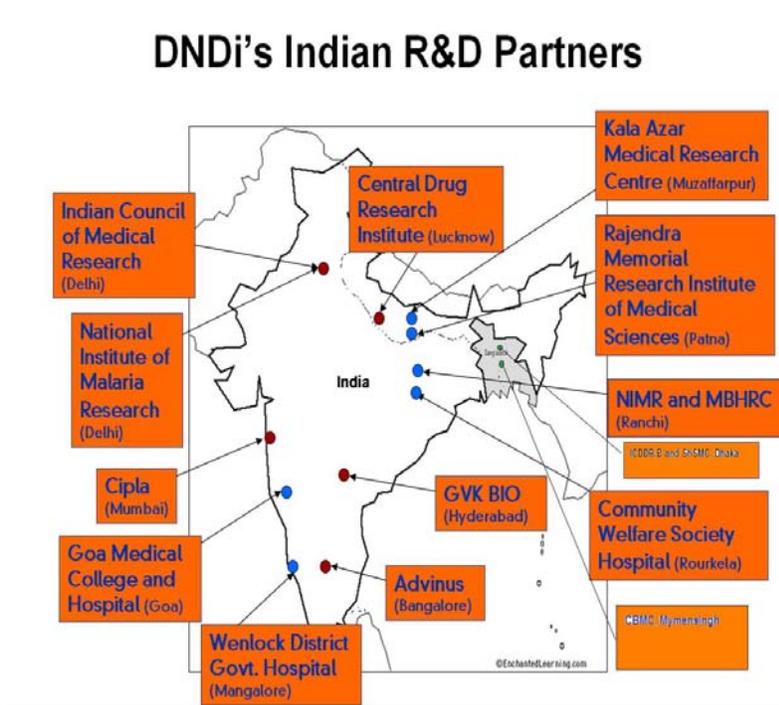
DNDi India has undertaken several initiatives to strengthen its role in advocacy for patients affected by neglected diseases and to raise awareness for their plight. Likewise, DNDi's communication activities focus on providing an accurate image of DNDi's mission and objectives by promoting a widespread commitment to neglected diseases, in particular by the Indian Government. Key messages are expanded upon to convey neglected disease concerns to those who can make a difference in this field.



Some examples of activities in India in the field of neglected diseases are:

- The vision and mission of DNDi was translated into Hindi and published in the ICMR bulletin, which is circulated to all relevant professionals throughout the country.
- DNDi India Public Symposium "India (October 13, 2008 in New Delhi): Catalyst in Drug Development for Neglected Diseases?". More than 100 scientists and researchers convened to discuss the present and future role of India in R&D, access, and capacity strengthening to develop and deliver new treatments for neglected patients.
- DNDi was a sponsor of the WorldLeish4 event that took place February 3-7, 2009 in Lucknow. The DNDi symposium covered the DNDi's R&D programme for VL, from early-stage discovery research done by the Institut de Recherche pour le Développement (IRD) to the Advinus-led lead optimization consortium, and all clinical activities on VL 'Improved Treatments for Visceral Leishmaniasis – Status of Ongoing Studies, and Challenges & Opportunities Ahead'.

## DNDi's Indian R&D Partners



## Project Partners: Descriptions

**Advinus Therapeutics:** Advinus is one of the leading R&D alliances and pharmaceutical research outsourcing companies, promoted by the Tata group, one of India's largest and most respected business houses, with total revenues of more than USD 17 billion and a market capitalization of more than USD 31 billion. With a history of leadership that goes back almost a century, the Tata group is renowned for its high standards of quality, ethics, and commitment.

Advinus is the principal partner of the VL Lead Optimization Consortium, which identifies screened compounds with promising profiles to advance into preclinical studies. Advinus works with DNDi also on the preclinical development of buparvaquone, a promising oral treatment candidate for VL.

**Central Drug Research Institute (CDRI):** CDRI is a pioneer research organisation in the field of biomedical research. Infrastructure and expertise are available to develop a drug from its concept to the market. The very latest techniques and methodologies are employed for developing drugs, diagnostics, and vaccines to combat most prevalent diseases worldwide and among the Indian population in particular.



CDRI acts as a screening centre for DNDi on both HAT- and VL-related projects that feed promising candidates into the respective lead optimization consortiums. CDRI has already screened approximately 8,000 compounds against HAT and VL.

**Cipla:** Founded in 1935 as the Chemical, Industrial & Pharmaceutical Laboratories (CIPLA), Cipla is a prominent Indian pharmaceutical company, best known worldwide for producing generics, namely low-cost anti-AIDS drugs for HIV-positive patients in developing countries. Cipla also makes drugs to treat cardiovascular disease, arthritis, diabetes, obesity, depression and many other health conditions. Its products are distributed in more than 180 countries worldwide. Cipla is renowned both locally and internationally for its high standards, quality, efficacy, and affordability of medicines.

Cipla serves as DNDi's Indian pharmaceutical development and manufacturing partner for ASMQ, facilitating the drug's availability across Southeast Asia.

**GVK BIO:** GVK BIO is a part of the USD 1 billion GVK group. GVK is a diversified enterprise having interests in infrastructure, services, and manufacturing. GVK BIO is one of India's premier contract research organisations (CROs), providing an integrated platform of research services across the pharmaceutical R&D value chain to a growing number of global pharmaceutical and biotechnology companies.

GVK Bio assists in managing DNDi's VL combination therapy, ASAQ, and ASMQ clinical trials.

**Indian Council of Medical Research (ICMR):** ICMR, the apex body in India for the formulation, coordination, and promotion of biomedical research, is one of the oldest medical research bodies in the world. The Council promotes biomedical research in the country through intramural (Permanent Research Institutes and Regional Medical Research Centres), as well as extramural research (Centres for Advanced Research, Task Force and Open-ended research).

ICMR is one of DNDi's founding partners, and continues to provide clinical trial and research support for DNDi's VL combination therapy, ASAQ, and ASMQ projects.

**Kala-azar Medical Research Centre:** The first of its kind, the Kala-azar Medical Research Centre, founded in 1994, is a recognised centre dedicated to VL (or kala-azar) treatment. So far, it has successfully treated thousands of patients affected by this disease across India and collaborates with worldwide experts in clinical research. Its many achievements include conducting the first trials on miltefosine and leading a pivotal phase III miltefosine trial, which contributed to the drug's registration in India, the first country in the world to do so. The centre also conducted the first testing of the rK39 strip test and led a pivotal phase III trial on paromomycin, leading to its registration.

The Kala-azar Medical Research Centre is a clinical trial site for DNDi's VL combination therapy project.

**National Institute of Malaria Research (NIMR):** Established in 1977 as the Malaria Research Centre, it was renamed as the National Institute of Malaria Research in November 2005. NIMR is one of the institutes of the Indian Council of Medical Research (an autonomous body under the Ministry of Health & Family Welfare, Govt. of India). The primary task of the Institute is to find short-term as well as long-term solutions to the problems of malaria through basic, applied, and operational field research. The Institute also plays a key role in manpower resource development through trainings/workshops and transfer of technology. It has more than 50 scientific experts with a network of well-developed laboratories in Delhi carrying out research on all aspects of malaria, along with ten field laboratories in malaria-endemic areas, which serve as testing grounds for new technologies and help in the transfer of technologies.

NIMR assists in conducting DNDi's ASAQ and ASMQ clinical trials in India.

**Rajendra Memorial Research Institute of Medical Sciences:** Rajendra Memorial Research Institute of Medical Sciences (RMRI), Agamkuan, Patna, is one of the permanent Institutes of the Indian Council of Medical Research. Its main thrust is research into the different aspects of VL, including clinical, vector



biology and control, immunological, biochemical, molecular biology, pathological, parasitological and social. The Institute's laboratories are assessed regularly by WHO/TDR clinical monitors.

RMRI assists in conducting clinical trials for DNDi's VL combination therapy project.

**sanofi-aventis:** sanofi-aventis is one of the leading pharmaceutical companies. It is present in over 100 countries and has about 100,000 employees worldwide. sanofi-aventis has several key assets in the global pharmaceutical market: worldwide presence; an extensive portfolio of prescription medicines; market leadership in vaccines, major biological products, generics medicines, consumer healthcare, animal healthcare; and has a strong and long-established presence in both traditional and emerging markets.

In India, sanofi-aventis operates through two entities — Aventis Pharma Limited and Sanofi-Synthelabo (India) Limited.

## Bangladesh

**The Director General, DGHS, Ministry of Health, Bangladesh:** DGHS is the largest executing authority under the Ministry of Health and Family Welfare (MOHFW). It operates the healthcare delivery system for the Ministry all over the country, extending as much as to the village level. DGHS also provides technical guidance to the Ministry. The activities of DGHS are implemented both through the regular revenue set ups and under the development programmes.

**International Centre for Diarrhoeal Disease Research (ICDDR, B), Dhaka:** ICDDR, B is the International Centre for Diarrhoeal Disease Research, Bangladesh, an international health research institution located in Dhaka. Dedicated to saving lives through research and treatment, ICDDR, B addresses some of the most critical health concerns facing the world today, ranging from improving neonatal survival to HIV/AIDS. In collaboration with academic and research institutions throughout the world, ICDDR, B conducts research, training, and extension activities, as well as programme-based activities, to develop and share knowledge for global lifesaving solutions.

**Shaheed Suhrawardy Medical College (ShSMC), Dhaka:** ShSMC is the fourteen government medical college, situated at Sher-e-Bangla Nagar, Dhaka, Bangladesh. It is also the first ever government medical college in New Dhaka. The government set up the college to spread medical knowledge. Awarded "Best Medical College" by the NDF (National Debate Federation) festival in 2008, it has been included in the Avicenna Directory of Medical Schools (Formerly WHO directory) in May, 2010.

## DNDi's 2010 Project of the Year: Visceral Leishmaniasis Combination Therapies in India

### Background

Visceral leishmaniasis (VL), also known as kala azar or black fever, mainly occurs in poor, remote areas in South Asia, East Africa, and South America, and is caused by the parasite *Leishmania* transmitted by the sand fly. VL is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anemia. If left untreated, the disease is fatal.

To this day, existing treatments have serious limitations such as potential of resistance, low tolerability, long treatment duration, and difficulty in administration. Furthermore, they can be expensive. Current monotherapies (*treatment of a condition by means of a single drug*) include: pentavalent antimonials (*given by injection*); amphotericin B (*an intravenous treatment administered over 30 days*); AmBisome® (*a liposomal formulation of amphotericin B registered for VL*); miltefosine (an oral drug registered in India in 2002, now in use as a monotherapy), and a low-cost parenteral (*intramuscular*) formulation of paromomycin, registered in India in 2007 by Gland Pharma and the Institute for OneWorld Health (iOWH).



## Needs

DNDi have determined that the ideal treatment to be developed should be oral, safe, effective, short course, and low cost. This treatment should be effective against all stages of the disease and adequate for use in difficult health settings.

## Solutions

New treatment regimens involving combination therapies of drugs that are already available offer important advantages, such as shorter courses of treatment; better tolerability; reduction of the burden on health systems in resource-limited areas; better affordability; and the potential to prevent or delay resistance development and therefore prolong the lifespan of these drugs.

## Objectives

DNDi is conducting several VL clinical studies in three continents (Asia, East Africa and Latin America). The objective of the Asia clinical project is to identify a safe and efficacious short-course combination therapy using the three drugs registered in India: AmBisome®, paromomycin, and miltefosine. The goal is to have improved treatment options that can be implemented by national control programmes in India, Nepal, and Bangladesh.

## Results

Together with its partners from India, Bangladesh, and Nepal, DNDi has worked to find VL combination treatments, which are efficacious in Asia. Recently completed studies in India show a high efficacy of single dose of AmBisome® alone (95% cure rate) and combinations treatments (AmBisome® and paromomycin, AmBisome® and miltefosine, paromomycin and miltefosine), all for the treatment of VL in India. The combination study was designed to provide data for authorities in India, Bangladesh, and Nepal to make informed recommendations for combination treatments, which can be used in the VL elimination programmes in the region.

This study involving 634 patients was completed in 2010. All three combination treatments were highly efficacious ( $\geq 97.5\%$  cure rate), and none was inferior to the standard treatment amphotericin B. Our data therefore indicate that these combination treatments offer shorter, safer, and cheaper treatment options than the current standard monotherapy treatment available in the region. A two-step phase III trial (*first in hospital settings followed by treatment in primary health care centres*) using the same combinations has now been initiated in Bangladesh.

DNDi is now actively collaborating with the National control programmes and health authorities, and with other international partners including WHO-TDR and iOWH, to facilitate introduction of new treatments for VL in South Asia.

## Project partners

Indian Medical Research Council (ICMR), Delhi; Kala-Azar Medical Research Centre (KAMRC), Muzaffarpur; Rajendra Memorial Research Institute of Medical Sciences (RMRI), Patna; Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, GVK BIO, Delhi. DNDI would like also to acknowledge the following drug companies: Gilead, Paladin and Gland Pharma.

## **DNDi's 2010 Partnership of the Year: High Throughput Image Screening at Institut Pasteur Korea**

### Background

More than 1 billion people are still affected by at least one of the 17 diseases listed by the World Health Organization as neglected tropical diseases. These diseases affect millions of people each year, aggravate poverty in the developing world, and add up to a worldwide burden greater than road traffic accidents or tuberculosis. Despite the phenomenal changes in medicine over the past half-century, with therapeutic advances saving millions of lives, adequate drugs are still not available for many of the diseases that affect the world's poorest populations.



## Needs

DNDi, a not-for-profit product development partnership, has determined that, while better treatments need to be developed from existing drugs, it is also necessary to advance new chemical entities toward clinical development to bring to fruition new drugs that are effective, safe, patient-friendly, and low-cost. Visceral leishmaniasis (or kala azar), Chagas disease, and Human African trypanosomiasis (or sleeping sickness), are among the most neglected diseases. To this day, existing treatments have serious limitations, such as potential resistance, low tolerability, long duration, and difficulty in administration. Furthermore, they can be expensive. There is an urgent need for new drugs, and for research and development to be advanced without further delay.

## Solutions

To that end, new compounds have to be found that are active against the parasites that cause disease in order to identify a series of compounds that could eventually be developed into drugs. At the same time, it needs to be done quickly, with technology that can test as many compounds as possible in a short period of time. For this, the use of a cell-based high throughput image screening is a clear asset. Using this technique, parasites in cells can be visualized with the help of a specific microscope. Using robot technology, compounds are added to cells, and the data is analyzed and then displayed on a computer screen, which shows whether these compounds have had an effect on the parasite or not, without killing the cell. Institut Pasteur Korea (IPK) has already successfully used live cell-based screens to generate novel active compounds for HIV, malaria, and tuberculosis.

To quickly advance the research and development of new drugs for visceral leishmaniasis, IPK and DNDi started collaborating in 2008 to find new compounds that could potentially be developed into effective treatments against the disease.

## Objectives

The main goal of the partnership has been to develop a method that would allow the testing of thousands of compounds in a very short period of time. Until 2008, it was only possible to assess hundreds of compounds in a few months. DNDi and IPK have developed a new method called “high throughput image screening” for visceral leishmaniasis. Utilising both the intellectual and technological capacity of IPK, this project seeks to develop a major methodological advance in drug development.

## Results

The collaboration between DNDi and IPK has led to a breakthrough in the field of visceral leishmaniasis drug discovery. Today, with this method, around 35,000 compounds can be screened in a week. So far, 210,000 compounds have been screened from the compound libraries of IPK, the biotech company Anacor, and the organisation TB Alliance. An additional 156,000 compounds from the pharmaceutical company Pfizer will be screened soon. With this new technology, the number of compounds screened for visceral leishmaniasis is probably higher than the total number of compounds that have ever been screened for this disease. From this screening activity, one compound series has already shown very promising results—the aminothiazoles. This series is now in further development at the Indian pharmaceutical company, Advinus Therapeutics.

The success of this new technology has allowed IPK and DNDi to go further and to develop high throughput image screening for Chagas disease, leading to a broader collaboration between DNDi and IPK. Today, DNDi has access to compound libraries with a huge number of compounds from different pharmaceutical companies that can now be screened in a very short period of time. This brings DNDi closer to its ultimate goal of developing effective, low-cost drugs for patients suffering from neglected diseases.



# DNDi

Drugs for Neglected Diseases *initiative*

Best science  
for the most neglected

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