DNDi Update: Global Partnership Addressing Needs of Most Neglected From Research to Access

Bernard Pécoul, Executive Director
Shing Chang, R&D Director
Monique Wasunna, Head of DNDi Africa

Outline of the presentation

1. Introduction - Understanding Patients’ Needs
2. DNDi’s Achievements
3. R&D Portfolio
4. Strengthening Capacities
5. Advocacy & Resources
6. Conclusions
Neglected Diseases:
- primarily affect developing countries
- lie outside the world market

*Source: IMS Health, 26.2.2008

Control of Neglected Tropical Diseases

Figure 1. The 10 Leading Causes of Life-Years Lost to Disability and Premature Death.
**What’s Needed to Combat NTDs?**

**Large scale interventions**
- Lymphatic filariasis
- Leprosy
- Onchocerciasis
- Schistosomiasis
- Helminthiasis
- Trachoma
- Yaws

Rapid Impact Interventions
*Improving access*

**Case management and development of new tools**
- Human African trypanosomiasis
- Chagas diseases
- Buruli ulcer
- Leishmaniasis
- Dengue

Focused interventions
*Improving innovation*

**A Fatal Imbalance**

Tropical diseases (including malaria) and tuberculosis account for:
- 12% of the global disease burden
- Only 1.3% of new drugs developed

Source: Chirac P, Torreele E. Lancet. 2006 May 12; 1560-1561.
Responding to the Needs of Patients Suffering from Neglected Diseases…

- Malaria
- Visceral Leishmaniasis (VL)
- Sleeping Sickness (HAT)
- Chagas Disease

**Human African Trypanosomiasis (HAT) or Sleeping Sickness**

- **60 million at risk** in sub-Saharan Africa
- Transmitted by the *tsetse fly*
- **Difficult to diagnose**: many patients go undiagnosed until late stage of disease
- Fatal if untreated

**Needs:**
- A safe, effective, and practical stage 2 treatment
- A simple stage 1 treatment
Visceral Leishmaniasis (VL)

- **200 million at risk** worldwide (in 70 countries)
- Transmitted by the **sandflies**
- **Symptoms:** prolonged fever, enlarged spleen & liver, substantial weight of loss, progressive anemia
- **Fatal if untreated**
- **Current drugs:** antimonials, Amphotericin B, AmBisome®, miltefosine, paromomycin
- **Needs:**
  - oral, safe, effective, low-cost and short-course treatment

Chagas Disease: A Silent Killer

- **100 million at risk** in Latin America
- **Kills more people in region than malaria**
- Patient number growing in non-endemic, developed countries
- Transmitted by ‘**kissing bug**’, blood transfusion, organ transplantation, as congenitally or orally
- **Majority of patients undiagnosed until late stage**
- **Needs:**
  - An affordable, age-adapted, safe, and efficacious paediatric strength
  - A new drug for early chronic stage
Best Science for the Most Neglected

Among the most neglected...

- Poorest of the poor
- Living in remote areas
- Socioeconomic burden on family and community
- Marginalised & voiceless patients

Neglected Diseases: Current Treatment Limitations

- Ineffective (resistance)
- Toxic
- Expensive
- Painful when delivered
- Difficult to use
- Not registered in endemic regions
- Restricted by patents

We Need Safe, Effective, Easy-to-Use Drugs
A New Model for Drug Development: DNDi created in 2003

- Non-profit drug research & development (R&D) organization founded in 2003
- Addressing the needs of the most neglected patients
- Harnessing resources from public institutions, private industry and philanthropic entities

7 Founding Partners

- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation Brazil
- Medecins Sans Frontieres (MSF)
- Institut Pasteur France
- WHO/TDR (permanent observer)

DNDi’s Main Objectives

- Deliver 6 - 8 new treatments by 2014 for sleeping sickness, Chagas disease, leishmaniasis and malaria
- Establish a robust pipeline for future needs
- Use and strengthen existing capacity in disease-endemic countries
- Raise awareness and advocate for increased public responsibility
Scope of Activities for DNDi

Major focus on kinetoplastids (HAT / VL / Chagas)

3 Core Diseases
- Malaria: complete the 2 FDC
- Cutaneous leishmaniasis

HAT: DNDi Achievements so far

Success & progress at each stage

Lead Opt. Consortium (Scynexis/Pace) => Boron-based preclinical candidate (Anacor)

Fexinidazole (STI, Accelera, Aptuit, Axyntis, Covance, Drugabilis, LPU, SGS; contract: sanofi-aventis)

NECT (Epicentre/MSF, STI, WHO, Nat. Prog. DRC & Congo)

HAT Platform
VL: DNDi Achievements so far

Promising discovery & ambitious plan for drug combination

- High-Troughput Screening at IPK
- Combination Therapy

Chagas: DNDi Achievements so far

Consolidating our portfolio

- Lead Optimisation Consortium establishment
- Paediatric Benznidazole: Lafspo, CeNDIE, Liverpool Uni
ASAQ: Making a Difference in Fighting Malaria

Innovative partnership with sanofi-aventis
- A FDC of artesunate-amodiaquine
- Registered in 2007, prequalified by WHO in 2008
- 5.3 million treatments distributed in 2008
- More than 20 millions to be distributed in 2009
- Available in 24 countries
- Ambitious risk management plan (Pharmacovigilance)

- Adapted
- Simple
- Accessible
- Quality

ASMQ: Available in 2008

Public partnership with Brazil-funded Farmanguinhos
- A FDC of artesunate-mefloquine
- Registered in 2008
- Incorporated into Brazilian National Programmes
- Extension to other Latin American countries
- Technology transfer to Cipla
- Clinical studies:
  - Latin America (Brazil)
  - Asia (India, Myanmar, Malaysia)
  - Africa (Tanzania)
R&D Portfolio

Shing Chang
R&D Director

DNDi Portfolio-Building Model

- Long-term projects
  - Existing chemical libraries
  - New lead compounds

- Medium-term projects
  - New formulations
    (fixed-dose combinations)
  - New indications of existing drugs

- Short-term projects
  - Completing registration dossier
  - Geographical extension

Discovery  LS  LD  Preclinical  Clinical  Access to Patients
**Dynamic Portfolio – June 2009**

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Clinical</th>
<th>Available</th>
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<tbody>
<tr>
<td>S</td>
<td>LS</td>
<td>LO</td>
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- **Compound mining**
  - E.g.: nitroimidazoles, ...
- **Chemical classes**
  - E.g.: GSK, Merck, ...
- **Target-based**
  - E.g.: Dundee’s Drug Discovery Unit (DDU), Microtubule inhibitors ...
- **Screening**
  - E.g.: natural products (Kisasabo, Eskitis), new technology (Institut Pasteur Korea, DDU at Dundee, CDRI screening)

- **2 HAT LO**
  - Consent
  - Syntaxis
  - Pfizer

- **VL LO**
  - Consortium<br>Antiviral<br>CDDI

- **Chagas LO**
  - Consortium<br>CDC<br>Epicent<br>Munich Univ

**Alternative formulations**
- Amphotericin B – in preparation (VL)
- Buparvaquone (VL)

**Drug combination**
- Combination therapy (VL in Asia)
- AmBisome®
- Miltefosine – in preparation

**Combination therapy**
- Combination therapy (VL in Latin America) – in preparation
- Paediatric benznidazole (Chagas)
- Azoles (Chagas)
- NECT
  - Nitfurtimox – Eflornithine Co-Administration<br>Stage 2 HAT

**From Preclinical Phase**
- Nitfurtimox or Other Aminoquinolines (VL)

**On the Way to Deliver**
6 to 8 New Treatments by 2014

**DELIVERED**
- Nitfurtimox - Eflornithine Co-Administration
- AS/AQ - HAT<br>VL<br>Malaria
- AS/MQ

**New Opportunities**
- 8-aminoquinolines – in preparation (VL)
- Sitamaquine or Other Aminoquinolines (VL)

**Probability of Success in %**
- 70%
- 33%
- 33%

**Exploratory**
- a robust pipeline

Reference screening centres:
- LSHTM, Swiss Tropical Institute, University of Antwerp

### Best Science for the Most Neglected

**[Image of a woman with a microscope and a slide]**

**Nairobi, Kenya, June 23, 2009**
Discovery - Building the pipeline  
2 Breakthroughs in 2009

1) Access of libraries of compounds for chemical diversity

**Agreements with pharma**
- Merck
- GNF (Genomics Institute of the Novartis Research Foundation)
- Others in negotiation

2) Access to HTS capacity

<table>
<thead>
<tr>
<th>Disease</th>
<th>High Throughput Screening</th>
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<tbody>
<tr>
<td>HAT</td>
<td>HTS available</td>
</tr>
<tr>
<td>VL</td>
<td>HTS developed at Institut Pasteur Korea</td>
</tr>
<tr>
<td>Chagas</td>
<td>HTS in development at Institut Pasteur Korea</td>
</tr>
</tbody>
</table>
Discovery

DNDi’s Capacity to Optimize Leads

- **HAT Lead Optimisation Consortium**
  - Scynexis, Pace University

- **VL Lead Optimisation Consortium**
  - Advinus Therapeutics, Central Drug Research Institute

- **Chagas Lead Optimisation Consortium**
  - CDCO, Epichem, Murdoch University, University of Ouro Preto

Chagas Portfolio – Assembling & Evolving

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<th>Clinical</th>
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<tr>
<td>LS</td>
<td>Drug combination</td>
<td>Paediatric benznidazole</td>
<td>Sterol biosynthesis inhibitors</td>
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<tr>
<td>LO</td>
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<td>Others</td>
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<td>S</td>
<td></td>
<td></td>
<td>Cysteine protease inhibitors - UCSF</td>
</tr>
</tbody>
</table>

- **Chagas LO Consortium**
  - CDCO
  - Epichem
  - Murdoch Univ.

- **Sterol biosynthesis inhibitors**
- **Cysteine protease inhibitors - UCSF**
DNDi’s Chagas Strategy

**Paediatric Benznidazole**
- Unmet need: age-adapted, easy-to-use paediatric formulation
- Anticipated introduction in 2010

Key partners include:
- Pharmaceutical Laboratory of Pernambuco State (LAFEPE)
- Centro Nacional de Diagnostico e Investigacion de Endemio-epidemias (CeNDIE), Argentina
- University of Liverpool

**Azoles**
- Therapeutic switching
- Candidates include posaconazole (Schering Plough) and E1224 (Eisai)
- Drug combination with existing drugs

Key partners include:
- Federal University of Ouro Preto, Brazil
- Companies which provide compounds of interest
**DNDi’s Chagas Strategy**

**Key partners include:**
- Centre for Drug Candidate Optimisation
- Epichem
- Murdoch University
- Federal University of Ouro Preto

**Fenarimol series**

**Lead Optimisation Consortium**

*Initiated mid-2008*

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**VL Portfolio – Consolidation & Growing**

**Alternative formulations**
- Amphotericin B – in preparation

**Combination therapy**
- using existing drugs
  - Africa
  - Asia
  - Latin America

**Sitamaquine or Tafenoquine**

- in preparation

**DNDI**

**DD@D**

**Others**

**CPDD**

**Oral amphotericin B (iCu/CPDD)**

**Single-dose AmBisome®**
- (Sundar group)

**Paromomycin**
- India (QWH)

**Amphomul (Bahrat)**
DNDi’s VL Strategy

**VL Combination Therapy in Asia**

- Identify the optimal 2-drug combination therapy from the following 3 drugs:
  - AmBisome®
  - Miltefosine
  - Paromomycin
- Trial completion India: end of 2009; analysis completion in early 2010
- Recommendation in India, Bangladesh and Nepal by 2011

**Key partners include:**
- Indian Council for Medical Research
- Kala Azar Medical Research Centre
- Rajendra Memorial Research Institute of Medical Sciences
- GVK BIO

**VL Combination Therapy in Africa**

- Geographical extension for broader treatment options; Paromomycin / AmBisome® / Miltefosine
- Recommendation of combination incl. paromomycin + sodium stibogluconate (SSG)
- Development of combination treatment containing short-course AmBisome®

**Key partners include:**
- LEAP partners
DNDi’s VL Strategy

Medium-term projects

Amphotericin B polymer and oral AmphoB

Key partners include:
- BioDelivery Sciences International
- Imperial College
- London School of Pharmacy
- London School of Hygiene and Tropical Medicine

Long-term projects

Lead Optimisation Consortium
- Promising lead series of 2-quinolines
- Some compounds show >90% parasite killing in vitro
- One lead compound with >85% efficacy in vivo
- Oxaboroles and licochalcones under evaluation

Key partners include:
- Advinus
- Central Drug Research Institute
- Institut de Recherche pour le Développement
- Anacor
HAT Portfolio – Robust & Dynamic

DNDi’s HAT Strategy

Nifurtimox-Eflornitine Combination Therapy (NECT)

- Simplified treatment with less infusions, shorter course, safe & efficacious
- Added to WHO Essential Medicines List in May 2009
- NECT-FIELD study ongoing

Key partners include:
- National HAT control programmes
- Epicentre
- MSF
- Swiss Tropical Institute
- WHO
- Drug donors: s-a, Bayer
Fexinidazole
- “Rediscovered” by DNDi after extensive review of existing data
- Completed preclinical development
- Entering into Phase I clinical studies in 2009

Key partners include:
- Swiss Tropical Institute, Accelera, Aptuit, Axyntis, Covance, Drugabilis, LPU, SGS
- Agreement signed with sanofi-aventis for joint development

Oxaboroles
- Innovative chemistry with potent anti-protozoal activity
- Candidate chosen to enter preclinical development by Q4 2009

Key partners include:
- Scynexis, Pace University
- Anacor Pharmaceutical
Strengthening Research Capacities in Disease-Endemic Countries

Monique Wasunna
Assistant Director, KEMRI & Head of DNDi Africa

Challenges

- Access to patients
- Infrastructure
- Political instability
- Health system barriers
Clinical research capacity

- Research infrastructure in endemic regions has either:
  - Not been sustained
  - Never existed

Idea for Platforms Started in 2003

- **1st DNDi Africa meeting**
  - 7-9 May 2003, Nairobi: 18 African Countries, 71 participants
- Neglected, marginalized, forgotten, invisible diseases
- Consensus conclusion: more action, fewer words
- Desire to collaborate to solve many health crises plaguing Africa
  - For diseases urgently needing improvement of treatments: LEAP, HAT Platform
Aims of Clinical Research Platforms

- Strengthen regional capacity in endemic regions
  - training
  - infrastructure

- Identify unmet treatment needs
  - safe
  - efficacious
  - short course
  - affordable
  - registered
  - field adapted

- Testing new treatments
  - LEAP studies focused on combination strategy
    - Paromomycin, Ambisome®, miltefosine

Where Are We Today? Achievements

- DNDi Africa office at KEMRI established
  - Building and coordination of African network
  - Two-way information with the network
  - 2 international conferences held in Nairobi; numerous operational meetings hosted and coordinated
  - Advocacy campaigns: African neglected diseases
  - Coordination of & support to DNDi research projects and platforms in Africa:
    - LEAP, HAT, FACT
Leishmaniasis East Africa Platform (LEAP)

SUDAN: 2 sites (Kassab, Dooka)
Univ. of Khartoum
Federal Ministry of Health

ETHIOPIA: 2 sites
(Gondar, Arba Minch)
Addis Ababa Univ.
Gondar Univ.
Ministry of Health

UGANDA: 1 site (Amudat)
• Makerere Univ.
• Ministry of Health

KENYA: 2 sites (Nairobi, Kimalel)
KEMRI
Ministry of Health

A group of scientists and institutions working on developing clinical trial capacity to bring new treatments to patients

MSF
I+ solutions
LSH&TM
AMC/ SU/ KIT (ASK)
IOWH -India
Industry partners

HAT Clinical Trial Platform

Objectives
• To strengthen clinical trial capacity for sleeping sickness
• To overcome health system challenges for clinical research
• To share information on HAT research progress
• To improve HAT clinical trial methodologies

Partners:
• National HAT control programs of most affected endemic countries
• DNDi, STI
• Research institutes like ITMA, INRB, CDC, KARI-TRC
• NGOs like MSF, Epicentre
• FIND, WHO
• Regional networks – e.g. EANETT, PABIN, AMANET
Strengthening Clinical Research Capacity
Platform Accomplishments

• Active in conducting and sharing research – things are happening!
• Both platforms have strengthened clinical trial capacity in member countries
  – Personnel
  – Communications
  – Infrastructure

Accomplishments
Research activities

• Facilitated multi-country, multi-centre studies
  – LEAP: clinical studies in 2009 include paromomycin, AmBisome®, and miltefosine (in preparation)
  – FACT: numerous field studies completed, ongoing or planned to serve as evidence base on value and proper use of ASAQ and ASMQ in Africa
• Regional pools of clinical trial expertise has been created
  – HAT Platform serving as forum for members to share their clinical research experience
  • National sleeping sickness control programme of DR Congo engaged in NECT and NECT-FIELD
Personnel

• A needs-driven approach, adapted per region
  • Training of trial staff (needs, level, methods)
  • Ethics concepts (GCP, informed consent etc)
  • Standard operating procedures (SOPs)
Communications

- Overcoming regional barriers (differences in laws, guidelines, methods, languages, concepts etc.) through regular communications:
  - Platform meetings, newsletters
  - Sharing with regional and international community
  - Various presentations and symposia at key international meetings including RSTMH in 2007, ASTMH in 2008, EAHS in 2009, and WorldLeish2009
Infrastructure

• LEAP
  – Building of 2 research and treatment centres in Ethiopia and 1 in Sudan
    • Arba Minch in February 2006; Gondar in May 2008; Dooka planned for late 2009
  – Upgrading of facilities in Kenya and Uganda

• HAT
  – NECT study strengthened sites in DRC
HAT & LEAP Platforms
Strengthening Regional Research Capacity

• A new approach in which platforms serve as bridges for the region
  – Allow effective problem solving at a local level
  – Reference points for DNDi’s global network to show how regional partnership can deliver

Lessons learned

• Difference in cultural backgrounds appreciated in order to continue working as a team
• Communication and frequent consultations key to success of platform
• Consultative meetings of PIs crucial and play a major role in steering the platforms research activities
• A wide membership of the platform: MoH of member countries, regulatory authorities that provide desired support towards achieving the platforms objectives
• Each member institution appreciated as an equal partner that plays an integral part towards the success of the platform
Chagas Platform to Strengthen Clinical Research

- Inspired by African platforms
- In preparation for endemic countries within Latin America
- Develop a critical mass of expertise
- Strengthen institutional research capacity
- Support an environment conducive to quality research
  - Facilitate registration and recommendation of new therapies

Facilitating Regional Approach From Screening to Production

- Important to engage regions affected by diseases to strengthen capacity in all stages
  - Early-stage discovery research
    - PAN4ND: regional network linking natural products researchers to include neglected diseases in screening
      - 8 countries involved; www.pan4nd.org
  - Technology transfer with FACT products
    - ASAQ: identifying local African manufacturer in process
    - ASMQ: ongoing South-South transfer between public Farmanghuinos and private Cipla
Asante Sana!

Resources & Advocacy

- People
- Partners
- Money
- Advocacy

Bernard Pécoul
Executive Director
DNDi = 287 people worldwide

Governance members provide strategic guidance
Diverse yet complementary expertise

Board
SAC
A motivated group committed to the same vision

A harmonised mix of cultures & skills

DNDi’s success hinges on expertise and involvement of partners
Well-balanced partnerships (public/private)

Increased number of partners: 204 in June 09 (128 in June 08)

Partnership distribution (June 2009)

Partners working together from all over the world
Global R&D funding in 2007

Neglected Diseases
$2.5 billion (US)

Kinetoplastids
$125 million (US)

Source: Moran et al., G-Finder report, 2009

Funding Strategy - Diversity
€110M of €274M Secured (2004-2014)

Private Donors
• Médecins Sans Frontières (€43M)
• Bill & Melinda Gates Foundation (€18M)
• Other Private Foundations (€2.3M)

Public Donors
• UK (€28M)
• France (€7.5M)
• Spain (€5M)
• Netherlands (€3M)
• USA – NIH (€1M)
• Germany (€1M)
• Canton de Genève - Switzerland (€0.7M)
• European Union (€0.6M)
• Tuscany (Italy) (€0.2M)
€164M Still Needed

2004-2014 Projected:

Advocacy: Ensure Public Leadership
Waking Up to “Essential Health R&D”

World Health Assembly, towards a new Global R&D Framework:

- R&D priorities
- Sustainable funding
- Intellectual property
- Regulatory environment
- Research capacity and technology transfer
Conclusions:
3 Key Challenges for the Future

• Access
• Sustainability
• Regulatory

Access

1. Access to compounds and knowledge
   • Innovative Agreements
   • Explore Patent Pools, etc.

2. Reaching patients
   • DNDi plays a facilitating role with many partners
Partnership is Key

Best Science for the Most Neglected

Implementers
NCP, WHO, NGOs (MSF)

Other PDPs
FIND, iOWH, MMV,

Platforms
LEAP, HAT, FACT, Chagas

Manufacturers
sanofi-aventis, Farmanguinhos, Cipla, Lafpe

Distributors
IDA

Networks - studies
INESS, WWARN, Epicentre, TDR

Sustainability

• Funding
  – New mechanisms are key (Prize incentives, Global Fund, UNITAID, etc.)

• Strengthening capacities & technology transfer
**Regulatory**

- Major obstacles: delays in product registration
  - Role of National Regulatory Authorities in Disease Endemic Countries
  - Support of WHO
  - Facilitating role of more experienced agencies (FDA, EMEA and others)

- Innovative IP Management

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**6-Year Results**

- 2 new malaria treatments developed
- 1 new sleeping sickness combination developed
- Largest pipeline ever for the kinetoplastid diseases
- Clinical research platforms in Africa
- €110M of €274M needed raised
- On track to deliver new treatments per business plan
By working together in a creative way, PDPs, large and small pharma, and the public sector can bring innovation to neglected patients!

www.dndi.org