Review of DNDi activities

Bernard Pécoul, Executive Director, DNDi
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)

- 7 worldwide offices
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 / Leishmaniasis / Chagas)

3 Core Diseases

+ malaria: complete the 2 FDC
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
  - S
  - LS
  - LO

- Preclinical

- Clinical

- Access to Patients
**Project Portfolio – End of 2010**

**Discovery**
- Discovery Activities
  - Compound mining
  - Chemical classes
  - Target-based
  - Screening
  - HAT LO Consortium
    - Scynexis
    - Pace Univ.
  - VL LO Consortium
    - Advinus
    - CDRI
  - Chagas LO Consortium
    - CDCO
    - Epichem
    - Murdoch Univ
    - FUOP

**Pre-clinical**
- Nitroimidazole backup (HAT)
- Oxaborole (HAT)
- Alternative formulations of Amphotericin B (VL)
- Nitroimidazole (VL)
- Drug combination (Chagas)
- K777 (Chagas)
  - Exploratory

**Clinical**
- Fexinidazole (HAT)
- Combination therapy (VL in Asia)
  - AmBisome®
  - Miltefosine
- Combination therapy (VL in Africa)
- Combination therapy (VL in Latin America)
- Paediatric benznidazole
  - (Chagas)
- Azoles E1224 (Chagas)
  - Exploratory

**Available**
- ASAQ
  - (Malaria)
  - Fixed-Dose Artesunate/ Amodiaquine
- ASMQ
  - (Malaria)
  - Fixed-Dose Artesunate/ Mefloquine
- NECT
  - Niturtimox - Efionithine
  - Co-Administration
  - Stage 2 HAT
- VL Combi. Therapy
  - Africa - SSG/PM

**Major Collaborators**
- Sources for hit and lead compounds:
  - GSK, Anacor, Merck, Pfizer, Novartis (GNF, NITD), GATB,…
- Screening Resources:
  - Eskitis, Institut Pasteur Korea, Univ. Dundee,…
- Reference screening centres:
  - LSHTM, Swiss Tropical Institute, University of Antwerp

**Discovery Activities**

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

DELIVERED

AS/AQ  AS/MQ

Paediatric Benznidazole

Nitfurtimox - Eflornithine Co-Administration

Combination VL Therapy India

Combination VL Therapy Latin America

AmBisome Africa

- HAT - Chagas - Malaria

Probability of Success in %

70%

33%

Fexinidazole

Azoles

New forms of Amphotericin B

AS/AQ

2007 2008 2009 2010 2011 2012 2013 2014

2007 2008 2009 2010 2011 2012 2013 2014

2007 2008 2009 2010 2011 2012 2013 2014
From innovative discovery to clinical demonstration of efficacious combination treatments
Leishmaniasis – Breakthrough technology from Institut Pasteur Korea

- Removes the bottleneck of drug screening for *Leishmania sp.*
- + 350,000 Compounds screened (IPK & Pfizer)
- One chemical series currently in Lead Optimization at Advinus
A global collaborative effort to build the pipeline

Screening → Hit Expansion → Lead Optimization

Reiterative cycles of medicinal chemistry

Parallel assessment of DMPK Tox and Potency

Pharmaceutical chemistry

GLP Toxicology

Lead to Candidate

Drug Candidate

Candidate

Anacor

IRD

ADVINUS

CDRI

TB Alliance

Institut Pasteur Korea

New Delhi, India, December 3, 2010

DNDi’s 3rd Partners’ Meeting in collaboration with ICNR
Leishmaniasis: A strong pipeline

From innovative discovery to clinical demonstration of efficacious combination treatments

Discovery

Preclinical

Clinical

Available to patients

High-Throughput Screening at IPK

Advinus, CDRI, IRD, Anacor

Nitroimidazoles

Synergy between PDPs – TB Alliance

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT
Promising leads from TB Alliance: Nitroimidazole series

- Compounds developed by TB Alliance showed great promise for leishmaniasis treatment

- Synergy between two PDPs – collaboration to benefit patients

- Further studies at:
  - Advinus Therapeutics, India
  - CDRI, India
  - Auckland University, NZ
  - LSHTM, UK
Leishmaniasis: A strong pipeline

From innovative discovery to clinical demonstration of efficacious combination treatments

High-Troughput Screening at IPK

Advinus, CDRI, IRD, Anacor

Nitroimidazoles

Synergy between PDPs – TB Alliance

Combination Therapy VL Combo

DOI: 10.13

ADVINUS. A TARA Enterprise

CDRI. SURA SURA
Highly efficacious results with 3 combination treatments in India

<table>
<thead>
<tr>
<th>Definitive cure at 6 months</th>
<th>Ampho B (N=157)</th>
<th>AmB-5 + Milt-7 (N=160)</th>
<th>AmB-5 + Paro-10 (N=158)</th>
<th>Milt-10 + Paro-10 (N=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients Randomized (634)</td>
<td>157</td>
<td>160</td>
<td>158</td>
<td>159</td>
</tr>
<tr>
<td>No. Of patients Cured</td>
<td>146</td>
<td>156</td>
<td>154</td>
<td>157</td>
</tr>
<tr>
<td>Percent</td>
<td>93.0%</td>
<td>97.5%</td>
<td>97.5%</td>
<td>98.7%</td>
</tr>
<tr>
<td>95% CI</td>
<td>[87.50, 96.27]</td>
<td>[93.32, 99.20]</td>
<td>[93.24, 99.19]</td>
<td>[95.06, 99.78]</td>
</tr>
<tr>
<td>Per-Protocol population (627)</td>
<td>156</td>
<td>158</td>
<td>155</td>
<td>158</td>
</tr>
<tr>
<td>No. Of patients Cured</td>
<td>146</td>
<td>155</td>
<td>153</td>
<td>156</td>
</tr>
<tr>
<td>Percent</td>
<td>93.6%</td>
<td>98.1%</td>
<td>98.7%</td>
<td>98.7%</td>
</tr>
<tr>
<td>95% CI</td>
<td>[88.21, 96.71]</td>
<td>[94.12, 99.51]</td>
<td>[94.93, 99.78]</td>
<td>[95.03, 99.78]</td>
</tr>
</tbody>
</table>

Excellent safety profile with no treatment discontinuation in the combination arms

affordable and field adapted tools are now close to availability

Partners:
- KAMRC, Muzaffarpur and Banaras Hindu Univ, Varanasi
- RMRI, Patna
- ICMR, Delhi
- GVK BIO, Delhi
- Gilead, Paladin, Gland Pharma
- DSMB: Dr C.P. Thakur, Dr Ravindra Mohan Pandey, Dr Narendra Kumar Arora, Dr P. G. Smith (Chair)
Leishmaniasis: A strong pipeline

From innovative discovery to clinical demonstration of efficacious combination treatments

High-Throughput Screening at IPK

Advinus, CDRI, IRD, Anacor

Synergy between PDPs – TB Alliance

Nitroimidazoles

Combination Therapy VL Combo

Combination Therapy VL Combo Africa

Available to patients
No difference between standard SSG (30 days) and shorter and cheaper combination treatment in terms of safety and efficacy

- Combination now recommended for East Africa in WHO expert committee report
- Combination recommended as first line treatment by the Ministry of Health in Sudan
Chagas: Consolidating our Portfolio

Discovery

Preclinical

Clinical

Available to patients

Lead opt. Consortium

Azoles E1224 Phase 2

Paediatric Benznidazole

Chagas Platform, CRESIB

Lafepe
Sleeping Sickness: Success & progress at each stage

- **Discovery**
  - Oxaboroles
    - Anacor, Scynexis Inc, Pace University, HIKMA

- **Preclinical**
  - Fexinidazole Phase 1
    - sanofi-aventis

- **Clinical**
  - NECT

- **Available to patients**
  - WHO, Nat. Prog., MSF
NECT implemented in 9 countries since 2009

- NECT (nifurtimox-eflornithine combination therapy): A simplified, safe & effective treatment for stage 2 HAT
- NECT included into WHO Essential Medicines List (May 2009)
- 600 patients included into NECT-FIELD
- Work with WHO and national programmes to facilitate availability
Malaria: from a stronger Global Portfolio

The priority is to implement ACTs

Source MMV 2010
ASAQ: A successful implementation in Africa

Innovative partnership with sanofi-aventis

- Registered in 2007, prequalified by WHO in 2008
- 70 million treatments distributed
- Only FDC with a 3 year shelf life
- Ambitious risk management plan (Pharmacovigilance)

India:

- Registered in 2009
- Clinical studies with high efficacy results

- Easy to Use
- Affordable
- Field-Adapted
- Non-Patented
ASMQ
(Fixed Dose Combination of Artesunate /Mefloquine): From Brazil to the rest of the world

- Registered by Farmanguinhos in Brazil in 2008 and implemented by the Brazilian national programme
- Successful Technology transfer to Cipla
- Cipla filing to WHO pre-qualification and Indian / ASEAN registration
- Positioning ASMQ:
  - Clinical studies completed: Latin America (Brazil), Asia (India, Myanmar)
  - Clinical studies on going: Africa (Tanzania, Burkina Faso, Kenya), Asia (Malaysia)
Use and strengthen existing capacity in disease-endemic countries
Challenges

- Access to patients
- Infrastructure
- Political instability
- Health system barriers
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

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

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

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

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

**DNDi**
Drugs for Neglected Diseases initiative
Use and strengthen existing capacity in Asia

- Working with experienced clinical sites in malaria and VL
- Using existing clinical CROs
- Strengthening infrastructure to establish a centre of excellence for VL in Mymensingh (Bangladesh)
- Proposal to work at the PHC level in partnership with NVBCP in Bihar for the treatment of VL
Resources & Advocacy

- People
- Partners
- Funding
- Advocacy
Governance members including from disease endemic countries provide strategic guidance

Board

Scientific Advisory Committee
DNDi today = 391 people worldwide
(DNDi staff & Partners’ staff working on DNDi’ projects)
DNDi’s success hinges on expertise and involvement of partners all over the world
India, a major DNDi partner

DNDi’s Indian R&D Partners

- Indian Council of Medical Research (Delhi)
- National Institute of Malaria Research (Delhi)
- Cipla (Mumbai)
- Goa Medical College and Hospital (Goa)
- Wenlock District Govt. Hospital (Mangalore)
- Central Drug Research Institute (Lucknow)
- Kala Azar Medical Research Centre (Muzaffarpur)
- Rajendra Memorial Research Institute of Medical Sciences (Patna)
- NIMR and MBHRC (Ranchi)
- GVK BIO (Hyderabad)
- Community Welfare Society Hospital (Rourkela)
- Advinus (Bangalore)
Well-balanced partnerships (public/private)
Funding strategy

Independence through diversified sources of funding

Approximately 50% of funding from public institutional donors in line with DNDi’s advocacy objective (public responsibility for NDs)

- Approximately 50% from private sector (foundations, major donors, general public)
- Key contributions to come from Founding Partners
- Maximum of 25% per donor

Sources of funding - Projection

Projected commitments from previous BP
€150M of €230M Secured (2004-2014)

Private Donors
- Médecins Sans Frontières (€42M)
- Bill & Melinda Gates Foundation (€30 M)
- Other Private Foundations (incl. Medicor, €1M)

Public Donors
- United Kingdom - DFID (€31 M)
- France – AFD & MAEE (€9.3 M)
- Spain – AECID (€10 M)
- Netherlands – DGIS (€17 M)
- USA – NIH/NIAID (€1.8 M)
- Germany – GTZ (€1 M)
- Switzerland - SDC (€4.2 M)
- European Union - FP 5, 6,7, EDCTP (€1.2 M)
- Italy - Region of Tuscany
- The Global Fund -AmFm
Future sustainable funding needs political commitment from emerging economies

India, the 5th larger public funder of NTD’s R&D

Source: Moran et al., G-Finder, 2009
Advocacy: Ensure Public Leadership

Waking Up to “Essential Health R&D”

• Public leadership to define R&D priorities
• Significant investment with sustainable funding
• Ensure better access to knowledge
• Enable better regulatory environment
• Devise new IP management policies to encourage needs-driven R&D
• Transfer technology and strengthen research capacities in developing countries
7-Year Results

- 2 new malaria treatments
- 1 new sleeping sickness combination
- 1 new visceral leishmaniasis combination for Africa
- Largest pipeline ever for the kinetoplastid diseases
- Clinical research platforms in Africa
- €150M of €230M needed raised
- On track to deliver new treatments per business plan
3 Key Challenges for the Future

- To build a solid portfolio
- To ensure sustainability of the PDP model
- From research to implementation – Advocacy for access – To roll out treatments to patients
We look forward to continuing to work with our partners in India, as this will bring us a step closer to DNDi’s ultimate goal to develop new, effective and affordable drugs for the most neglected patients!