Developing Drugs for Neglected Diseases
Bernard Pecoul, MD, MPH, Executive Director
A Fatal Imbalance

Tropical diseases (including malaria) and tuberculosis account for:

- 12% of the global disease burden
- Only 1.3% of new drugs developed

(1975-2004)

18 new drugs (incl. 8 for malaria)

98.7%
1,535 new drugs for other diseases

1.3%
21 new drugs for neglected diseases

Burden of Neglected Tropical Diseases

This map displays countries endemic for each of these diseases based on 2009-2010 data and international borders. (from: www.unitingtocombatntds.org)

Buruli Ulcer
Chagas disease (American trypanosomiasis)
Cysticercosis
Dengue/Severe dengue
Dracunculiasis (guinea-worm disease)
Echinococcosis
Fascioliasis
Human African trypanosomiasis
Leishmaniasis
Leprosy
Lymphatic filariasis
Onchocerciasis
Rabies
Schistosomiasis
Soil transmitted helminthiasis
Trachoma
Yaws
Human African Trypanosomiasis (HAT) or Sleeping Sickness

- 36 countries at risk in sub-Saharan Africa; estimated current cases: 30,000
- Transmitted by the tsetse fly
- Difficult to diagnose; many patients go undiagnosed until late stage of disease
- 1/3 of patients are child-bearing age women and 1/4 are children < 15 years old (4% being children < 5 y.o.)
- Fatal if untreated

Needs:
- A safe, effective, and orally administered stage 2 treatment
Paediatric HIV

- Virtual elimination of paediatric HIV in high-income countries…
- …but 390,000 new infant infections each year and 3.4 million children with HIV/AIDS (91% in sub-Saharan Africa)
  - > 1,000 new pediatric HIV infections daily
  - > 700 deaths in HIV+ children daily
- HIV disease progression in children more rapid than in adults if no treatment is given
  - 1/3 of HIV+ infants will die by 1 yr old
  - 50% of HIV+ children will die by 2 yrs old
  - 80% of HIV+ children will die by 5 yrs old
Children (<15 years) estimated to be living with HIV | 2011

Total: 3.4 million [3.1 million – 3.9 million]

- North America: 4500 [4000 – 5800]
- Caribbean: 18 000 [15 000 – 21 000]
- Latin America: 40 000 [29 000 – 54 000]
- Western & Central Europe: 1800 [1400 – 2100]
- Eastern Europe & Central Asia: 17 000 [14 000 – 21 000]
- East Asia: 16 000 [11 000 – 22 000]
- Middle East & North Africa: 19 000 [12 000 – 26 000]
- South & South-East Asia: 180 000 [100 000 – 230 000]
- Sub-Saharan Africa: 3.1 million [2.8 million – 3.4 million]
- Oceania: 3600 [2800 – 4600]
**Product Development Partnerships (PDPs): Filling the Gaps in Translational Research and Product Development**

PDPs work across different diseases and modalities

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Microbicides &amp; preventatives</th>
<th>Therapeutic product</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="#">Avi</a></td>
<td><a href="#">AERAS</a></td>
<td><a href="#">mvi</a></td>
<td><a href="#">PATH</a></td>
</tr>
<tr>
<td><a href="#">Sabin</a></td>
<td><a href="#">Human Hookworm Vaccine Initiative</a></td>
<td><a href="#">PATH Vaccine Development Program</a></td>
<td><a href="#">International Vaccine Institute</a></td>
</tr>
<tr>
<td><a href="#">INN</a></td>
<td><a href="#">IVCC</a></td>
<td><a href="#">Meningitis Vaccine Project</a></td>
<td><a href="#">INN</a></td>
</tr>
</tbody>
</table>

Source: [Bill & Melinda Gates Foundation](#) & [BCG](#)

![DNDi](#)
Pipeline Now Begins to Be Filled
143 Candidates

104 biopharmaceutical candidates in development...

<table>
<thead>
<tr>
<th>Stage</th>
<th># Candidates</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre Clinical</td>
<td>59</td>
<td>57%</td>
</tr>
<tr>
<td>Phase I</td>
<td>15</td>
<td>14%</td>
</tr>
<tr>
<td>Phase II</td>
<td>12</td>
<td>12%</td>
</tr>
<tr>
<td>Phase III</td>
<td>10</td>
<td>10%</td>
</tr>
<tr>
<td>Registration</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Launched</td>
<td>6</td>
<td>6%</td>
</tr>
</tbody>
</table>

57% of candidates are in Pre Clinical stage.

...and 39 diagnostic & vector control candidates

<table>
<thead>
<tr>
<th>Stage</th>
<th># Candidates</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility</td>
<td>7</td>
<td>26%</td>
</tr>
<tr>
<td>Test Development</td>
<td>7</td>
<td>26%</td>
</tr>
<tr>
<td>Evaluation</td>
<td>6</td>
<td>22%</td>
</tr>
<tr>
<td>Demonstration</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Country Adoption</td>
<td>6</td>
<td>22%</td>
</tr>
</tbody>
</table>

CD4: 7 candidates
FIND: 6 candidates
IDRI: 1 candidate

Diagnostics

Vector control

Early Stage In Development

DNDi
Drugs for Neglected Diseases initiative

Notes: Includes products not funded by Gates Foundation.
Biopharmaceutical candidates in development include: IAVI, IPM, IVI, GATB, Aeras, MMV, MVI, MVP, PVS, DNDi, iOWH, PDVI, HHVI.
Source: PDPs
DNDi: Patient Needs-Driven & Innovative R&D Model

- Deliver **11 to 13 new treatments by 2018** for sleeping sickness, Chagas disease, leishmaniasis, malaria, paediatric HIV and specific helminth infections
- Establish a **robust pipeline** for future needs
- Use and strengthen existing **capacity in disease-endemic countries**

**Founding Partners**
- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation, Brazil
- Médecins Sans Frontières (MSF)
- Institut Pasteur France
- TDR (permanent observer)

**7 worldwide offices**
A Global Network to Leverage Resources
More Than 100 R&D Partners

- Balance of public and private partnerships worldwide

- Academia: 42%
- Pharmas/Biotechs: 19%
- NGOs/PDPs: 13%
- MoH/Gov. org./Hospitals: 12%
- CROs: 14%

December 2011
Global actors form a coalition to support WHO’s 2020 NTD Roadmap:

- Pharmaceutical companies
- World Bank
- Donor Countries (UK, USA, UAE)
- BMGF and other private donors (Mundo Sano, Brazil)
- Endemic country MoHs
- DNDi

The outcome for DNDi?

- New, renewed, or expanded commitments from 12 major pharmaceutical companies.
- Greatest ever access to compound libraries for DNDi.
DNDi Portfolio-Building Model:
Address Immediate Patient Needs & Deliver Innovative Medicines

Long-term projects
- New chemical entities (NCEs)

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

Short-term projects
- Completing registration dossier
- Geographical extension

- Discovery
  - R
  - LS
  - LO
- Pre-clinical
- Clinical
- Implementation
DNDi Portfolio: A Mix of Existing Drugs & NCEs

**Discovery**

- HAT
  - Nitroimidazole backup
  - Oxaborole backup

- Leish.
  - Alternative formulations of Amphotericin B (VL)
  - VL-2098 (VL)
  - Nitroimidazole backup (VL)
  - Topical Amp B (CL)

- Chagas
  - Nitroimidazole
  - Fenarimol series
    - K777

- Helminths
  - Flubendazole - Macrofilaricide

- Paed. HIV
  - Improved PI for 1st-line
  - PI sprinkles (CHAPAS-2)

- Malaria
  - ‘Superboosting’ – TB/HIV

**Pre-clinical**

- Fexinidazole

**Clinical**

- NECT (Stage 2 HAT) Nifurtimox - Eflornithine Co-administration
- SSG&PM co-administration VL in Africa
- New VL treatments in Asia (SD AmBisome®, 3 drug combinations)
- New VL treatments in Asia (SD AmBisome®, Miltefosine)

**Implementation**

- Nitroimidazole backup
- Oxaborole backup
- Oxaborole SCYX-7158
- New VL treatments – Bangladesh
- New VL treatments – Africa (AmBisome® • Miltefosine)
- New VL treatments – (Latin America)
- HIV / VL
- Fexinidazole (VL)

✓ : NCE

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May 2012

Drugs for Neglected Diseases initiative

**June 2012**
6 New Treatments Developed Since 2007

- **Easy to Use**
- **Affordable**
- **Field-Adapted**
- **Non-Patented**

**ASAQ**
(Fixed-dose combination of artemisinine + amodiaquine)

**ASMQ**
(Fixed-dose combination of artemisinine + mefloquine)

**NECT**
(Nifurtimox-eflornithine combination therapy)

**SSG&PM**
(Sodium stibogluconate & paromomycin combination therapy)

**NEW VL TREATMENTS IN ASIA**
(SD AmBisome® / PM+M / A®+M /)

**LAFEPE**
Benznidazol 12.5 mg
(Paediatric dosage form of benznidazole)

**Sleeping sickness stage 2**
ASAQ Implemented in Partnership with Sanofi
More than 150M Treatments Distributed

- Registered in 2007, prequalified by WHO in 2008
- Registered in 30 sub-Saharan African countries, in India, Bangladesh and Colombia
- Only FDC with a 3 year shelf life
- Ambitious risk management plan (Pharmacovigilance)
Simplified 3-Day Dose Regimen of ASAQ

NEW Fixed-dose ASAQ
Artesunate/amodiaquine

3 dosage strengths available

<table>
<thead>
<tr>
<th>Dosage</th>
<th>AS</th>
<th>AQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (4.5-8 kg)</td>
<td>25 mg</td>
<td>67.5 mg</td>
</tr>
<tr>
<td>Young Children (8-17 kg)</td>
<td>50 mg</td>
<td>135 mg</td>
</tr>
<tr>
<td>Children (17-35 kg)</td>
<td>100 mg</td>
<td>270 mg</td>
</tr>
<tr>
<td>Adults (≥36 kg)</td>
<td>100 mg</td>
<td>270 mg</td>
</tr>
</tbody>
</table>

Co-blistered non-fixed AS+AQ
Artesunate-amodiaquine

<table>
<thead>
<tr>
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<th>AS</th>
<th>AQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS: 50 mg; AQ 135 mg</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
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Oxaboroles SCYX-7158 for HAT
From Lead Optimization to Clinical Candidate

- Identified as hits against *T. brucei* at Sandler Center, showed activity in animal models of HAT
- Innovative US partnership with 2 biotechs and 1 university
- First candidate issued from DNDi Lead Opt. Programme
- Start of Phase I in March 2012

Key partners:
Scynexis, Anacor, Pace University,
Sandler Center UCSF, Swiss TPH
Objective: Drug candidate to become an oral, short course treatment for stage 1+2 sleeping sickness treatment, caused by either *T.b. gambiense* or *T.b. rhodesiense*

- Preclinical development including ADME-PK, GLP-toxicology and safety pharmacology
- Phase I clinical trials in Paris - completed
- Agreement to co-develop with Sanofi
- Phase II ready to start with Sanofi in DRC, CAR, and possibly South Sudan
NECT, an Improved Therapy Option for HAT Implemented in 12 Countries (99% of reported cases)

Nifurtimox-eflornithine combination therapy

- A simplified, safe & effective treatment for stage 2 HAT
- WHO Essential Medicines List (2009)
- > 60% of stage 2 HAT patients treated with NECT in 2010
  - melarsoprol use (36% to 12%)

[Map of Africa showing NECT use in 12 countries]
HAT Treatments in 2011 in DRC

Treatments for stage 2 HAT

<table>
<thead>
<tr>
<th>Treatment</th>
<th># treatments 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>NECT</td>
<td>1,711</td>
</tr>
<tr>
<td>DFMO</td>
<td>55</td>
</tr>
<tr>
<td>ARSOBAL</td>
<td>37</td>
</tr>
<tr>
<td>Lampit</td>
<td>0</td>
</tr>
</tbody>
</table>

# treatments 2011
Paediatric HIV: Most Urgent Treatment Needs (TPP)

- Formulations/regimens that are simple, easy to administer, and more tolerable (once daily or less, heat-stable, dispersible/sprinkles, tolerable taste)
- Durable (forgiving and minimal requirement for repeated immunological or virological testing; minimal risk for developing resistance)
- Suitable for infants (< 2 mos - 3 yrs)
- TB treatment compatible
- Affordable
Innovative PI Formulation: The Cipla-MRC Collaboration

- LPV/r sprinkles by Cipla*
- CHAPAS-2: Pharmacokinetics and acceptability of sprinkle formulation compared with syrup/tablets**

- Sprinkles preferred: better to swallow, store, transport; important advantage for caregivers
  - 71% (<1 y.o.) chose to continue sprinkles over syrup after study
- Inspired DNDi, leading to the concept of “4-in-1” sachet

* [http://www.retroconference.org/2012b/PDFs/982.pdf](http://www.retroconference.org/2012b/PDFs/982.pdf)
• Address the need for a PI-based first-line ARV FDC
• Adaptable for use in treating TB co-infected children
Main Challenges for Sustainable R&D for Neglected Patients

- IP & Open Innovation Platforms
- Overcoming Regulatory Barriers
- Sustainable Financing & New Incentives for R&D
Thank You to All Our Partners & Donors

www.dndi.org