DNDi
Fighting Neglected Tropical Diseases Through Partnering

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Neglected Tropical Diseases (NTD)

Control of Neglected Tropical Diseases

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Figure 1. The 10 Leading Causes of Life-Years Lost to Disability and Premature Death.
## Neglected Tropical Diseases (NTD)

<table>
<thead>
<tr>
<th>Category</th>
<th>Disease</th>
<th>Currently used drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protozoan infections</strong></td>
<td>Chagas disease</td>
<td>Nifurtimox, Benznidazole</td>
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</tbody>
</table>
|                                   | Human African trypanosomiasis (Sleeping sickness)                       | *Early stage:* Pentamidine, Suramin  
*Late stage:* Efornithine, Melarsoprol, Combination Nifurtimox-efornithine |
|                                   | Leishmaniasis                                                          | *Visceral L.::* Ambisome, Paromomycin, Miltefosine  
*Cutaneous L.::* Glucantime, SSG                                                   |
| **Helminth infections**           | Cysticercosis, zoonotic helminthias                                     | Praziquantel, Triclabendazole                                                        |
|                                   | Guinea-worm disease                                                    | -                                                                                    |
|                                   | Lymphatic filariasis                                                   | Albendazole, Ivermectin, DEC                                                         |
|                                   | Onchocerciasis (River blindness)                                       | Ivermectin                                                                           |
|                                   | Schistosomiasis                                                        | Praziquantel                                                                          |
|                                   | Soil-transmitted helminth infections (ascariasis, trichuriasis, hookworm) | Albendazole/Mebendazole, Pyrantel, Levamisole                                        |
| **Bacterial infections**          | Buruli ulcer                                                           | Rifampicin, Streptomycin, Clarithromycin, Moxifloxacine                               |
|                                   | Leprosy                                                                | MDT (Rifampicin, clofazimine, dapsone)                                               |
|                                   | Trachoma                                                               | Tetracycline eye ointment, Azythromycin                                              |
|                                   | Yaws                                                                   | Benzathine penicillin                                                                 |
| **Viral**                         | Dengue, Dengue haemorrhagic fever                                      | Need for antiviral drugs                                                             |
Neglected Tropical Diseases (NTD)

- primarily affect the poorest populations in developing countries
- lie outside the world pharmaceutical market

Global Diseases

Neglected Tropical Diseases

Neglected Diseases

World pharmaceutical market
$837 bn in 2009*

*Source: IMS Health, 20.04.2010
Neglected Tropical Diseases (NTD)

A Fatal Imbalance:

Tropical diseases and TB: 21 registered drugs in 30 yrs

Total: 1,556

Tropical diseases and tuberculosis account for 12% of the global disease burden but only 1.3% of new drugs developed.

Source: Chirac P, Torreele E. Lancet. 2006 May 12; 1560-1561.
NTDs affect the most neglected patients

- Poorest of the poor
- Living in remote areas
- Socio-economic burden on family and community
- Marginalised & voiceless patients
Current Treatment Limitations

- Ineffective (resistance)
- Toxic
- Expensive
- Painful when delivered
- Not adapted to the health system capabilities
- Not registered in endemic regions
- Restricted by patents
Product Development Partnerships (PDPs)

- Public health driven not-for-profit organizations that steer NTD drug development
- Main functions:
  - Fill the gaps in translational research and product development
  - Integrate and coordinate multiple industry and academic partners along the drug development pipeline
  - Allocate philanthropic and public funds to the “right“ kinds of R&D projects
  - Manage neglected disease R&D portfolios
PDPs work across different diseases and modalities

- **Vaccine**
  - HIV/AIDS
  - TB
  - Malaria
  - NTD
  - Diarrhea
  - Respiratory

- **Microbicides & preventatives**

- **Therapeutic product**

- **Diagnostics**

**Source:** Bill & Melinda Gates Foundation & BCG
DNDi: a Global Foundation

- 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
  - Médecins Sans Frontières (MSF)
  - Institut Pasteur France
  - WHO/TDR (permanent observer)

- 7 worldwide offices
- Geneva Coordination Team + consultants
- USA
- DRC
- India
- Malaysia
- Japan
- Kenya
- Brazil
DNDi’s Main Objectives

- Deliver **6 - 8 new treatments by 2014** for:
  - Human African Trypanosomiasis (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**
**Projects Portfolio – January 2010**

### Discovery Activities

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<tr>
<td><strong>HAT LO Consortium</strong></td>
<td><strong>VL LO Consortium</strong></td>
<td><strong>Chagas LO Consortium</strong></td>
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<tr>
<td>Scynexis</td>
<td>Advinus</td>
<td>CDCO</td>
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<td>Pace Univ.</td>
<td>CDRI</td>
<td>Epichem</td>
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<td>Murdoch Univ.</td>
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**Pre-clinical**

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<tr>
<td>Nitroimidazole backup (HAT)</td>
<td>Oxaborole (HAT)</td>
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<tr>
<td>Alternative formulations Amphotericin B (VL)</td>
<td>Drug combination (Chagas)</td>
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**Clinical**

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<tr>
<td>Fexinidazole (HAT)</td>
<td>Combination therapy (VL in Asia)</td>
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<tr>
<td>Combination therapy (VL in Africa)</td>
<td>Combination therapy (VL in Latin America) in preparation</td>
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<tr>
<td>Paediatric benznidazole (Chagas)</td>
<td>Azoles E1224 (Chagas)</td>
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**Available**

**NECT**
- Nifurtimox - Eflornithine Co-Administration Stage 2 HAT

**ASMQ**
- (Malaria) Fixed-Dose Artesunate/Mefloquine

**ASAQ**
- (Malaria) Fixed-Dose Artesunate/Amodiaquine

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**a robust pipeline**

**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

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**Discovery**

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<tr>
<td>S</td>
<td>LS</td>
<td>LO</td>
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**Clinical**

- Combination therapy (VL in Asia)
- Combination therapy (VL in Africa)
- Combination therapy (VL in Latin America) in preparation
- Paediatric benznidazole (Chagas)
- Azoles E1224 (Chagas)

**Available**

- NECT: Nifurtimox - Eflornithine Co-Administration Stage 2 HAT
- ASMQ: (Malaria) Fixed-Dose Artesunate/Mefloquine
- ASAQ: (Malaria) Fixed-Dose Artesunate/Amodiaquine

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**6 to 8 new treatments by 2014**
Three products making the difference

Available

2007
ASAQ (Malaria)
Fixed-Dose Artesunate/ Amodiaquine

2008
ASMQ (Malaria)
Fixed-Dose Artesunate/ Mefloquine

2009
NECT
Nifurtimox - Eflornithine Co-Administration Stage 2 HAT

Strategic Partners

sanofi-aventis
(France)

Farmanguinhos
(Brazil)
Cipla
(India)

National Control Programs
MSF / Epicentre
Bayer / sanofi aventis
WHO
DNDi Operational Model

**Discovery**
- S
- LS
- L0

**Pre-clinical**

**Clinical**

**Available**

**Long-Term projects**
- New lead compounds

**Medium-term projects**
- Fixed dose combinations;
- New indications of existing drugs

**Short-term projects**
- Completing registration;
- Co-administration;
- New formulations
DNDi business model

DNDi’s Collaboration Model:

• At early discovery stage:
  – Compounds come mainly from pharma partners
  – Biological characterizations are conducted at major parasitology research centers

• Clinical trials:
  – Collaborating partners include institutions and experts from disease-endemic countries, health authorities, and regulatory experts, and frequently MSF teams

• Registration and manufacturing:
  – Pharmaceutical partners provide essential capabilities to ensure sustainability
DNDi Guidelines for Partnerships

- To develop treatments free of any rights, so as to insure affordability for patients

- To provide treatments responding to the medical needs of the patients in endemic countries (simple, stable, affordable)

- To actively contribute to the usage of the product in endemic countries

- To make freely available all information generated about the product during its development
Drug development in partnership

Accessing resources across the entire development process:

- Quality Chemical libraries
- Screening centers
- Lead optimization
- ...

Compounds, screens & Chemistry
Drug development in partnership

Accessing resources across the entire development process:

Deal characteristics:

- Access to proprietary class of compounds:
  - no upfronths or milestones
  - collaboration with Anacor's scientists

- IP generated gets back to Anacor:
  - rights for NTDs in endemic countries
  - no royalties on sale in public markets
Drug development in partnership

Accessing resources across the entire development process:

**Compounds, screens & Chemistry**

**Deal characteristics:**

- Access to the **most valuable compound libraries** of Pfizer
- Access to the information on selective actives (**know-how**)
- Framework Agreement containing provisions:
  - Pfizer has option to perform hit to lead and to become DNDi’s industrial partner
  - Royalty-free, out-licensable licenses if Pfizer is not the industrial partner
  - “at cost” distribution in the public sector
Drug development in partnership

Accessing resources across the entire development process:

Deal characteristics:

- Access to selected Merck’s *compounds libraries*
- Access to Merck’s *know-how*
- **Joint IP** generated through early development
- Non-exclusive, royalty-free, and sub-licensable license granted to DNDi for NTDs
- **Opt-in option** for Merck to undertake late clinical development and registration:
  - at its own expenses
  - commitment to provide the final product at the least possible cost to the public sector
Drug development in partnership

Accessing resources across the entire development process:

- Toxicology
- PK/PD
- Formulation
- Process Chemistry
- ....
Drug development in partnership

Accessing resources across the entire development process:

- **Scynexis**: lead optimization, pilot batches
- **Advinus**: lead optimization, toxicology
- **Aptuit**: formulation
- ...

Proof of concept cGMP batches
Drug development in partnership

Accessing resources across the entire development process:

- NCE
- Repurposing
- Re-formulation
- Combination therapy
- ...

IND compounds
Drug development in partnership

Accessing resources across the entire development process:

Deal characteristics:

- License signed with Eisai for clinical development of **Ravuconazole** for treatment of Chagas’ disease funded by DNDi (September 29, 2009)
  - E1224, pro-drug of ravuconazole, an anti-fungal drug discovered by Eisai
  - Joint clinical development team
  - Phase 2 clinical studies to be started in Bolivia (2010)
  - Eisai to secure manufacturing of E1224
  - Eisai can elect to become the development partner of DNDi
  - Rights to insure best pricing for endemic countries
Drug development in partnership

Accessing resources across the entire development process:

- Manufacturing
- Registration
- Distribution
- ...

Best Science for the Most Neglected

DNDi: Drugs for Neglected Diseases initiative
Drug development in partnership

Accessing resources across the entire development process:

Deal characteristics:

- ASAQ is a fixed-dose artesunate/amodiaquine combination product against malaria developed by DNDi
- **Out-licensed** to sanofi-aventis:
  - scale-up, manufacture, registration, distribution,
  - collaboration through post-registration
- **Not patented**
- Public price: “at cost”
- Distribution in private sector on a commercial basis (Coarsucam™)
Recipe for a successful partnership:

- Full understanding of DNDi’s business model by partner
- Endorsement of the project by the top management
- Building trust between project leaders from both sides
- Partnership “of equals”
- Identification of upsides for the partner (generally no monetary incentives…)
- Clear path forward through well structured agreements
Partnering is key

- Early stage research
- Compound mining
- Medicinal chemistry
- Product manufacturing
- Registration
- .....
By working together in an innovative way, PDPs, the public sector, and large and small pharma can bring new treatments to neglected patients.

www.dndi.org

药物忽视疾病倡议

www.dndi.org