Latest drug development and innovation for kinetoplastid diseases

Dr Nathalie Strub Wourgaft
Medical Director

DNDi
Drugs for Neglected Diseases initiative
Iniciativa Medicamentos para Enfermedades Olvidadas
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)

98.7%
1,535 new drugs
for other diseases

Tropical diseases:
18 new drugs
(incl. 8 for malaria)

Tuberculosis:
3 new drugs

1.3%
21 new drugs
for neglected
diseases

Product Development Partnerships (PDPs): Filling the Gaps in Translational Research and Product Development

PDPs work across different diseases and modalities

- Vaccine
- Microbicides & preventatives
- Therapeutic product
- Diagnostics

DNDi

Source:

Bill & Melinda Gates Foundation & BCG
DNDi: An innovative R&D model

- 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)
Kinoplastid diseases / Protozoan Infection: most NTDs

Essentially represented by:

- African Trypanosomiasis (HAT) or sleeping sickness
- American Trypanosomiasis or Chagas Disease
- Leishmaniasis
  - Visceral (and PKDL) or Kala-Azar
  - Cutaneous
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

- New indications of existing drugs
- Compilng registration dossier
- Geographical extension
## Portfolio – June 2011

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Clinical</th>
<th>Implementation</th>
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<tbody>
<tr>
<td>HAT LO Consortium</td>
<td>Nitroimidazole backup (HAT)</td>
<td>New VL treatments – Bangladesh</td>
<td>ASAQ (Malaria) Fixed-Dose Artesunate/ Amodiaquine</td>
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<tr>
<td>- Scynexis</td>
<td>Oxaborole SCYX7158 (HAT)</td>
<td>New VL treatments – Africa</td>
<td>ASMQ (Malaria) Fixed-Dose Artesunate/ Mefloquine</td>
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<tr>
<td>- Pace Univ.</td>
<td>Alternative formulations of Amphotericin B (VL)</td>
<td>New VL treatments – Latin America</td>
<td>NECT (Stage 2 HAT) Nifurtimox – Eflornithine Co-administration</td>
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<tr>
<td>VL LO Consortium</td>
<td>Drug combination (Chagas)</td>
<td></td>
<td>SSG&amp;PM co-administration VL in Africa</td>
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<tr>
<td>- Advinus</td>
<td>Nitroimidazole (VL)</td>
<td></td>
<td>New VL treatments in Asia (SD AmBisome®, PM+M / A®+M / PM+ A®)</td>
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<tr>
<td>- CDRI</td>
<td>K777 (Chagas)</td>
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<tr>
<td>Chagas LO Consortium</td>
<td>Flubendazole Macrofilaricide (Helminth)</td>
<td></td>
<td>Benznidazole Paediatric dosage form (Chagas) Filed - awaiting approval</td>
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<td>- CDCO</td>
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<td>- Epichem</td>
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<td>- Murdoch Univ.</td>
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<td>- FUOP</td>
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<tr>
<td><strong>Major Collaborators:</strong></td>
<td></td>
<td></td>
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<tr>
<td>- Sources for hit and lead compounds:</td>
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<tr>
<td>GSK, Anacor, Sanofi, Merck, Pfizer, Novartis (GNF, NITD), TB Alliance,...</td>
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<tr>
<td>- Screening Resources:</td>
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<tr>
<td>Eskitis, Institut Pasteur Korea, Univ. Scynexis, U. Dundee,...</td>
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<tr>
<td>- Reference screening centres:</td>
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<tr>
<td>LSHTM, Swiss Tropical &amp; Public Health, University of Antwerp</td>
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Sleeping sickness
36 countries at risk
Estimated 30000 cases

Fatal if untreated

G- 6 years boy with probable relapse of late stage HAT
NECT in 12 countries since 2009

- NECT (nifurtimox-eflornithine combination therapy): a simplified, shorter, safe & effective treatment
- WHO Essential Medicines List (May 2009)
- > 6000 Tx (end 2010)
  - melarsoprol use (36% to 12%)
- 629 patients in NECT-Field study
- WHO, National Programmes and MSF-logistics ensure availability
Fexinidazole

TPP: oral, short course treatment for both stages caused by either 
*T.b. gambiense* or *T.b. rhodesiense*

5-nitroimidazole (> 700 compound mining)

Phase I - 2009 to 2011 in Paris
S advice art. 58 EMA & FDA in Q1 2011
Pivotal phase II/III - Q1 2012
DRC, CRA, SS

Oxaborole SCYX-7158
First DNDi Preclinical Candidate Issued from Lead Optimisation Program

- Belongs to new class
- Identified as hits against *T. b. brucei*
- Showed activity in animal models
- Innovative partnership between 2 US biotechs and University and 1 NGO
- Completion of preclinical package
- Results published in PLoS NTD (June 2011)
- FIM study Q4 2011/ Q1 2012

Potential for oral early and late stages
Visceral Leishmaniasis

200 Millions at risk
Half Million cases / year
50000/60000 deaths year

Fatal if untreated
Highly efficacious results in India

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Recommended for region in WHO bluebook (2010)
Large implementation study in India

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<thead>
<tr>
<th></th>
<th>AmB SD</th>
<th>Ampho B</th>
<th>Ampho B</th>
<th>AmB+M</th>
<th>AmB+PM</th>
<th>M+PM</th>
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<tbody>
<tr>
<td>ITT</td>
<td>304</td>
<td>108</td>
<td>157</td>
<td>160</td>
<td>158</td>
<td>159</td>
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<tr>
<td>Cure at M6 % 95 CI</td>
<td>291 95.7% 93.4-97.9</td>
<td>104 98.1% 95.5-100</td>
<td>146 93.0% 87.5-96.3</td>
<td>156 97.5% 93.3-99.2</td>
<td>154 97.5% 93.2-99.2</td>
<td>157 98.7% 95.1-99.8</td>
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<tr>
<td>PP</td>
<td>304</td>
<td>106</td>
<td>148</td>
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SSG/PM: effective, safer & cheaper treatment for East Africa

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<thead>
<tr>
<th></th>
<th>SSG 30 days IM</th>
<th>PM 20mg/kg 21 days IM</th>
<th>SSG 30 days IM</th>
<th>SSG+PM 15mg/kg 17 days IM</th>
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<tbody>
<tr>
<td>N</td>
<td>200</td>
<td>198</td>
<td>359</td>
<td>359</td>
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<tr>
<td>Efficacy at 6 months FU, n (%)</td>
<td>188 (94.0)</td>
<td>167 (84.3)</td>
<td>337 (93.9)</td>
<td>328 (91.4)</td>
</tr>
<tr>
<td>Unadjusted difference the 2 arms [95% CI]</td>
<td>9.7% [3.6 – 15.7%] *</td>
<td>2.5 [-1.3 to 6.3%] NS</td>
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*p= 0.002 in favor of SSG, NS = non significant

1st line treatment for the region in WHO bluebook (2010)
Included in National guidelines in Sudan (2010)
Cutaneous Leishmaniasis

82 endemic countries

1-1.5 M new cases/year

Permanently disfiguring

Exploratory work
Chagas Disease
21 countries
108 Million at risk
7.7 Million estimated
Chagas Progress

Pediatric dosage form of benznidazole: Efficacy demonstrated in children with acceptable safety BUT

- Supplied in 100 mg tablets, twice daily for 60 days
- No available formulation for children

An affordable, age-adapted, easy to use, pediatric formulation

E1224: a new clinical candidate

- Prodrug or ravuconazole (very potent against T. Cruzi)
- Favourable PK
- Now in phase II proof of concept in Bolivia
Clinical studies

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<tr>
<th>I</th>
<th>II</th>
<th>III</th>
<th>post approval</th>
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<tr>
<td>VL</td>
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<tr>
<td>Africa</td>
<td>M / SSG &amp; M / LamB &amp; M</td>
<td>LamB &amp; M vs SSG &amp; PM</td>
<td>PharmacoVigilance SSG/PM</td>
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<td></td>
<td>Combination Bangladesh</td>
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<tr>
<td>Asia</td>
<td>Large implementation India</td>
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<td>Fexi SCYX7158</td>
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<td>BZN pop PK</td>
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Challenges ahead

- Implementation
- Registration
- Clinical demonstration of efficacy
- Research & Discovery

2018 Business Plan
Gracias - Thank you