New Drugs in Clinical Development

The Causes and Impacts of Neglected Tropical and Zoonotic Diseases - Implications for Global Health and Opportunities for Novel Intervention Strategies

INSTITUTE OF MEDICINE
FORUM ON MICROBIAL THREATS
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R&D Director
Drugs for Neglected Diseases initiatives
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
- USA
- DRC
- Kenya
- DRC
- Brazil
- India
- Malaysia
- Japan

Geneva Coordination Team + consultants
A collaborative, patients’ needs-driven, virtual, non-profit drug R&D organization to develop new treatments against the most neglected communicable diseases

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

The Neglected Diseases
- Difficult to manage
  - Sleeping sickness, Chagas, leishmaniasis,
  - Gaps: Burden, diagnosis, treatment, and follow-up
- Inadequate drugs – toxic, difficult to use, lengthy treatment, costly
- Low R&D investment
Responding to the Needs of Patients…

Malaria

Visceral Leishmaniasis (VL)

Sleeping Sickness (HAT)

Chagas Disease
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
- Preclinical
- Clinical
- Access to Patients
Combination Therapy

• Combination therapy offers the following potential benefits:
  – Retarding of resistance development
  – Shorter treatment duration
  – Better tolerance
  – Improved compliance
  – Lower burden on health systems
Human African Trypanosomiasis (HAT) or Sleeping Sickness

Transmitted by the tsetse fly
Human African Trypanosomiasis

Caused by protozoal parasites *Trypanosoma brucei*, transmitted by tsetse fly:

- *T. brucei gambiense*
  - Chronic disease, progresses during 1-2 years, 95% of cases

- *T. brucei rhodesiense*
  - Acute disease, kills within weeks
# HAT – Current Treatment Options

## Stage 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentamidine (1940)</td>
<td>7-10 daily intramuscular (i.m.) injections; only efficacious for stage 1</td>
</tr>
<tr>
<td>Suramin (1920s)</td>
<td>Used primarily for stage 1 <em>T. b. rhodesiense</em> HAT</td>
</tr>
</tbody>
</table>

## Stage 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melarsoprol (1949)</td>
<td>10 painful daily intravenous injections; highly toxic, with 5-10% treatment-related mortality Increasing number of treatment failures (up to 30% in some regions)</td>
</tr>
<tr>
<td>Eflornithine (1981)</td>
<td>Administration difficult – 4 intravenous infusions per day required for 14 days; primarily used as 2nd line for <em>T. b. gambiense</em> HAT;</td>
</tr>
<tr>
<td>Nifurtimox-eflornithine (2009)</td>
<td>Simplified stage 2 treatment combining 7 days eflornithine (2 infusions/day) and 10 days oral Nifurtimox</td>
</tr>
</tbody>
</table>
NECT (nifurtimox-eflornithine combination therapy)

A simplified, safe & effective treatment for stage 2 HAT

- Pivotal Phase III RCT at 4 clinical sites completed
  - Partners include: Epicentre, MSF, STI, HAT control programs of DRC and RoC
  - Good safety and efficacy of NECT established
- NECT included for HAT in WHO Essential Medicines List (April 2009)
- NECT-FIELD study initiated Q1-2009 recruitment to end in June 2010
- Work with WHO and national programmes to facilitate availability & implementation
Fexinidazole

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*

- 5-nitroimidazole
- In preclinical development by Hoechst in 1980s as broad-spectrum anti-protozoal
- Oral activity, distributes to the brain
- Curative in mouse models of HAT (both acute and chronic)
- Good safety profile in animal studies, including no evidence of mammalian genotoxicity

- Preclinical development including ADME-PK, GLP-toxicology and safety pharmacology completed; prototype tablets in use. Reproductive toxicology ongoing.
- Phase I clinical trials started in September in Paris. Single Ascending Dose and Food effect completed, Multiple Ascending Dose on-going
- Agreement to co-develop with sanofi-aventis
SCYX7158 - Preclinical Candidate
Stage 2 HAT

- Curative in the mouse CNS model
- Curative in mouse stage 1 model at low dose
- Orally Available (85% in monkeys and Rats)
- Metabolically stable – T1/2 ~ 20 hr in monkeys
- (q.d. dosing in humans)
- BCSII type molecule (Oral formulation should be straightforward)
- High brain exposure
- Plasma PK can predict CNS PK which can predict effective dose
- Five step synthesis with good yield
- Preliminary toxicology shows no alerts
  - hERG – Cardiotoxicity
  - Ames – Genotoxicity
HAT Landscape

**Discovery**
- Compound mining
- Chemical classes
- Target-based
- Phenotypic screening

**Pre-clinical**
- Nitroimidazole backup

**Clinical**
- Fexinidazole
  - NECT Nifurtimox - Eflornithine Co-Administration Stage 2 HAT
- Oxaborole

**Available**
- DNDi

Others

- 3-day pentamidine
  - Stage 1 HAT (TDR)

**DNDi**

Design for Neglected Diseases Initiative
Leishmaniasis

Transmitted by the sand fly
Best Science for the Most Neglected

Leishmaniasis in the World

2,000,000 cases/year
97 countries affected
Major health problem:
5 countries Visceral
14 Countries Cutaneous leishmaniasis

VL/CL

VL Estimated:
500,000/yr
Death 59,000/year mostly children.
Cyclic epidemics

CL

1-5 million per year
Current Treatment Options for VL

- **Pentavalent antimonials**
  - Toxic, parasite resistance growing, 30-day IV treatment in hospital.
- **Amphotericin B**
  - Used in case of antimonial resistance but dose limiting toxicity, 15 IV treatment in hospital on alternate days
- **Liposomal amphotericin B (AmBisome)**
  - Less toxic but prohibitively expensive – WHO price $840
- **Miltefosine**
  - Teratogenic, only registered in India, expensive; 28 days p.o.
- **Paromomycin**
  - IM, registered in India; in phase 4 trial, 21 days
Geographical Extension and Combination Strategy

VL Combo Asia
- Combination trials and recommendation in India, Bangladesh & Nepal

VL Combo Africa
- Register Paromomycin, AmBisome, Miltefosine
- Combination trials and recommendation of optimal treatment using PM, AmB, Milt and SSG

VL Combo Latin America
- Working with MoH of Brazil
VL Combination Therapy Asia
in India, Bangladesh & Nepal

- Identify the optimal 2-drug combination therapy from the following 3 drugs:
  - AmBisome®
  - Miltefosine
  - Paromomycin
- Trial completion India: end of 2009; analysis May 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
# Efficacy -- VL Combination Therapy in India

## Definitive cure at 6 months

<table>
<thead>
<tr>
<th></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>
VL Combination Therapy 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
LEAP 0104B Interim Analysis

- Table with Efficacy (cure) at 6 months by site (ITT complete-case analysis) - LEAP 0104B interim analysis: data are in n and (%)
- The unadjusted (for site) difference in efficacy between the SSG and PM arms was 8.6% (95% CI: 2.7% to 14.5%).
- The difference in efficacy between the SSG and SSG + PM combination arms of 0.6% (95% CI: -4.2 to 5.4%) suggests that there may be no real difference between these two arms.
- There were no new major safety concerns that arose from this part of the trial

<table>
<thead>
<tr>
<th>Site (N=596)</th>
<th>SSG 20 mg/kg – 30 days N=200</th>
<th>PM 20 mg/kg – 21 days N=199</th>
<th>Combination SSG 20 + PM 15 mg/kg -17 days N=197</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cure (all sites)</td>
<td>188 (94.0)</td>
<td>170 (85.4)</td>
<td>184 (93.4)</td>
</tr>
<tr>
<td>Kassab, Sudan (N=409)</td>
<td>131 (94.2)</td>
<td>116 (85.3)</td>
<td>126 (94.0)</td>
</tr>
<tr>
<td>KEMRI, Kenya (N=103)</td>
<td>32 (94.1)</td>
<td>29 (82.9)</td>
<td>32 (94.1)</td>
</tr>
<tr>
<td>Gondar, Ethiopia (N=39)</td>
<td>10 (83.3)</td>
<td>11 (84.6)</td>
<td>13 (92.9)</td>
</tr>
<tr>
<td>Arba Minch, Ethiopia (N=45)</td>
<td>15 (100)</td>
<td>14 (93.3)</td>
<td>13 (86.7)</td>
</tr>
</tbody>
</table>
Collaboration: From TB to VL drugs

- DNDi sampled TB Alliance’s compound collection & identified oxazole and 7-substituted oxazine subclasses for *Leishmania* (2008)
- Expanded SAR analysis of 74 compounds conducted at CDRI, India, and at LSHTM (Dec. 2009)
- Licensed to DNDi (2010)
- Univ. of Auckland assisted in scaling up of 13 compounds for *in vivo* evaluation
- TB Alliance shared their extensive knowledge on PK and tox SAR, made possible for DNDi to select from current leads the most suitable candidates for visceral leishmaniasis in the coming months

- To develop 2nd generation nitroimidazole & backup candidate for PA-824
- Funded Univ. of Auckland on nitroimidazoles work since 2006
Current Nitroimidazole Leads

**Lead compounds**

<table>
<thead>
<tr>
<th></th>
<th>SN 31644</th>
<th>SN31178</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vivo Efficacy (parasite reduction)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>99% @ 25 mg/kg</td>
<td>98% @ 6.25 mg/kg</td>
</tr>
<tr>
<td>Hamster on day 7</td>
<td>94% @ 25 mg/kg</td>
<td>86% @ 50 mg/kg</td>
</tr>
<tr>
<td>Hamster on day 28</td>
<td>TBD</td>
<td>72 % @ 50 mg/kg</td>
</tr>
</tbody>
</table>

**Pharmacokinetic & Genotoxicity Properties**

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro Metabolism (metabolized in 30’ w microsome)</strong></td>
<td>Mouse: 42 %; Hamster: 58 % Human: 12%</td>
<td>Mouse: 21%; Hamster: 51 % Human: 14 %</td>
</tr>
<tr>
<td>Bioavailability (mouse)</td>
<td>35%</td>
<td>37%</td>
</tr>
<tr>
<td>T1/2 (mouse)</td>
<td>3.8h</td>
<td>1.7h</td>
</tr>
<tr>
<td>Mini-Ames Test:</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>
VL Landscape

Screening - Lead Optimisation

- Discovery Activities
  - Compound mining
  - Chemical classes
  - Target-based
  - Screening

Preclinical

- Alternative formulations
  - Amphotericin B (VL)

- Oxaborole (VL)

- Nitroimidazole (VL)

Clinical Development

- VL combination therapy
  - (in Bangladesh and Nepal)

- VL Combination therapy
  - (in Africa)
    - AmBisome®
    - Miltefosine

- VL Combination therapy
  - (in Latin America)

Available

- VL Combi. Therapy
  - India

- VL Combi. Therapy
  - Africa
    - SSG/PM

Other

- Single-dose AmBisome®
  - (Sundar group)

- Phosome (Cipla)

- Amphomul (Bahrat)

- Paromomycin – India
  - (iOWH)

U. Dundee

CPDD

DNDi

Best Science for the Most Neglected

VL LO Consortium
- Advinus
- CDRI

VL Combi. Therapy
- India

Others

DNDi

Design for Neglected Diseases Initiative
Chagas Disease

caused by *Trypanosoma cruzi* infection
Chagas Disease
(American Trypanosomiasis)

- ~ 8M infected; 100M at risk in Central & South America
- Less than 1% of the infected receive treatment
- Bloodstream invasive form
- Intracellular in macrophages, muscle and nerve cells

from Rubem Figueiredo - Instituto Oswaldo Cruz
João Roberto Ripper DNDi
Chagas Existing Treatment: Major Limitations

- Only two drugs available: nifurtimox (Lampit) and benznidazole (Rochagan)
  - 40 years old
  - Long treatment period (1-2 months)
  - Dose-dependent toxicity
  - High rate of non-compliance
  - No pediatric formulations available

- No treatments for chronic disease
Paediatric Strength Benznidazole Available in 2010

- Registration by Roche in 1971, licensed to Brazilian government in 2003
- DNDi-Lafepe agreement in 2008 for development of pediatric formulation
- Supplied in 100 mg tablets, twice daily for 60 days

Current ways to administer in children

- 100 mg tablet fractionated into ½ (50mg) or ¼ (25mg).
- 100 mg tablet macerated
  - Dilution in liquid suspension
  - Manipulation and production of capsules
  - Manipulation and placement in envelopes

40-160% of Target BZ content
Azoles

Existing antifungal drugs with promising activity against Chagas disease pathogen

- Ergosterol biosynthesis: pathway effectively targeted for antifungal therapy, similarity with the trypanosome pathway
- Potent inhibitors of *T. cruzi* with adequate PK properties
- **E1224**, pro-drug of ravuconazole
- Ravuconazole’s lack of curative activity possibly related to the PK characteristics of the compound in the animals
- E1224 not specifically evaluated for CD in animals models BUT its PK characteristics show increased bioavailability, reliable oral absorption
- T½: mice (4.5h) ‡ dogs (8.8h) ‡ humans (4.42-11.75 days)
- **Posaconazole** – Marketed broad-spectrum antifungal marketed by Merck; excellent in vitro and in vivo profiles for Chagas indication
Chagas Landscape

**Discovery Activities**
- Compound mining
- Chemical classes
- Target-based
- Screening

**Chagas LO Consortium**
- CDCO
- Epichem
- Murdoch University
- UFOP

**IPK**
- High content screening

**University of Washington**
- Tipifarnib analogs (JK36)
- Disubstituted Imidazoles

**Merck**
- Cysteine protease inhibitors

**The Chagas Disease Foundation**
Ana Rodriguez/NIH
screen @ Broad

**GNF**
Screens hits
tested @
UCSF/DNDi

**Genzyme/Fiocruz**
Target identification and screening

**Drug combination**

**Pre-clinical**

**Clinical**
- Ruvuconazole (E1224) Eisai
- Benznidazole pediatric formulation LAFEPE

**Available**
- Benznidazole LAFEPE
- Nifurtimox Bayer

**DNDi**
- K777 Sandler/NIAID/SRI
- Posaconazole (Merck)
  (ICS – Spain)

**Others**
- Bz BENEFIT Trial
  Hamilton Health Sciences,
  Instituto Dante Pazzanese de Cardiologia,
  Hospital das Clínicas de Ribeiro Preto/USP,
  WHO/TDR
- Bz TRAENA study – Instituto Fatala Chalben
By working together in a creative way, PDPs, large and small pharma, and the public sector can bring innovation to neglected patients!