Global drug development pipeline for Chagas disease

Chagas Disease in the Americas:
Improving Access and Tools for Patient Diagnosis and Treatment
2 October, 2009
Los Angeles, California, USA

Isabela Ribeiro

A Fatal Imbalance

Tropical diseases (including malaria and tuberculosis) account for:
• 12% of the global disease burden
• But only 1.3% of new drugs developed
• None for Chagas disease

Source: Chirac P, Torreele E. Lancet. 2006 May 12; 1560-1561.
Specific Funds for Chagas Disease

Total funding: 10,099,322 USD; Drugs: 972,031 USD (2007)

Existing Chagas Treatments: Major Limitations

- Only two drugs available: nifurtimox and benznidazole
  - Safety issues
  - No general medical consensus as to their optimal use
  - Long treatment period (1-2 months)
  - High rate of non-compliance
  - No pediatric formulations available
A New Model for Drug Development: DNDi

- 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)

Coordination team
Geneva + consultants

7 support offices

Brazil
USA
DRC
India
Kenya
Malaysia
Japan

Chagas Portfolio – Assembling & Evolving

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Clinical</th>
<th>Available</th>
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<tbody>
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<td>LS</td>
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<td>L0</td>
<td>Drug combination</td>
<td>Existing azoles</td>
<td>Paediatric benznidazole</td>
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<td>• Compound mining</td>
<td>Chagas LO Consortium:</td>
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<td>• Chemical classes</td>
<td>• CDCO</td>
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<td>• Target-based</td>
<td>• Epichem</td>
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<td>• Phenotypic screening</td>
<td>• Murdoch Univ.</td>
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Sterol biosynthesis inhibitors

Cysteine protease inhibitors - UCSF

Diamidines and reversed amidines - FIOCRUZ/CPDD

BENEFIT Trial – McMaster University

Selenium Adjuvant Therapy & Heart Dz - FIOCRUZ

Cell therapy & Chagas CMP - MoH Brazil

DNDi
Others
Global Chagas Discovery Patent Search

- Cysteine Protease Inhibitors
- Ergosterol Byosynthesis Inhibitors
  - C14 demethylase
  - Oxidosqualene cyclase or lanosterol synthase
- Synthesis of Poliisoprenoids
- Trypanothione reductase inhibitors
- DHFR inhibitors
- Acidocalcisome nucleus – DNA binder antimitotic drugs topoisomerase II
- Neuraminidase /sialidase inhibitors
- Natural compound and its derivatives - nd

DNDi’s Chagas R&D Strategy

**Short-term objectives:**
Better use of existing treatments through new formulations
  - Paediatric formulation of benznidazole

**Medium-term objectives:**
Development of new treatments through therapeutic switching and combination therapy
  - Azoles

**Long-term objectives:**
New drugs and improved research & treatment capacity
  - Improved screening methodologies
  - Nitroimidazoles, cysteine protease inhibitors, …
  - Chagas lead optimisation consortium

Recent Patents on Anti-Infective Drug Discovery, 2007, Vol. 2, No. 1
Long-term projects

**Discovery**

- Evaluation of compound libraries
- Pharmacophore based screens -- access interesting compound classes from pharma companies: GSK & Merck
- Compound mining – e.g., nitroimidazoles
- Development of new techniques for increased screening capacity

  -- collaboration with Institute Pasteur-Korea for High Throughput Screening for *T. cruzi*

  -- collaboration with USP, UFOP on *in vivo* models

Long-term projects

**Lead Optimisation Consortium**

- Initiated mid-2008
- Key partners include:
  - Centre for Drug Candidate Optimisation, Australia
  - Epichem, Australia
  - Murdoch University, Australia
  - Federal University of Ouro Preto, Brazil
Long-term projects

**Hit-to-lead: Status**

<table>
<thead>
<tr>
<th>Series 1: WEHI</th>
<th>Series 2: Fenarol</th>
<th>Series 3: derived from Series 2</th>
<th>Natural Product: Purine NH Dehydrogenase</th>
</tr>
</thead>
</table>

*Hit to lead and lead optimisation activities are pursued on Series 1, 2 & 3*

- **Series 1**
  - There is a clear direction for the SAR progression in this series.
  - Good trypanocidal activity (IC50 = 190nm)

- **Series 2**
  - SAR has been greatly expanded over the last 6 months.
  - 127 new analogues have been prepared
  - Potency has been improved to IC50 2nM.

- **Series 3**
  - Further chemistry work on SAR is on-going

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**Medium Term Projects**

**Evaluation of Combination Therapy**

**Objectives:**

- Improvement of safety and tolerability
- Improvement of efficacy
- Reduction of dose and duration of therapeutic regimen
- Potential reduction of resistance development for the individual components of the combination

**Initial target:**

- Evaluation of combination therapy of Nifurtimox/Benznidazole + Azole compounds in animal model
- Investigation on-going; preliminary results promising
Existing antifungal drugs with promising activity against Chagas pathogen

- Potent inhibitors of *T. cruzi* with interesting PK properties
- In negotiation with pharmaceutical companies

• 3 compounds represent the most near-term hope & opportunity
  - E1224 (Eisai)
  - Posaconazole (SP)
  - TAK-187 (Takeda)

Medium Term Projects

**Azoles**

E1224- Promising clinical development starting in 2010

- License agreement with Eisai for clinical development - Sept 29, 2009
- Water-soluble prodrug monolysine form of ravuconazole
- PK properties – large volume of distribution, t _ 4.42-11.75 days
Short Term Project
Paediatric Benznidazole

- **Objective:**
  An affordable, age-adapted, easy to use, pediatric formulation for Chagas disease

- **Definition of Tablet Strength and Formulation:**
  Target: 12.5 mg dispersible tablets for <20 kg children

**Partner:** Lafepe (Brazil), July 2008

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Short Term Project
**A Paediatric Benznidazole option therapy available in 2010**

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

**Current ways to administer in children**

- 100 mg tablet fractionated into _ (50mg) or _ (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**

C. Zuniga, Programa Nacional de Controle e Prevenção, Honduras
Short Term Project

Chagas Platform
to Strengthen Clinical Research

Based on platforms models developed for HAT and VL in Africa

• Making clinical research “less difficult”
• Develop a critical mass of expertise
• Strengthen institutional research capacity
• Support an environment conducive to quality research
• Facilitate effective and efficient trials to deliver improved treatment for Chagas disease

Symposium

“Chagas disease in the Americas: Improving Access and Tools for Patient Diagnosis and Treatment”

Dr Davi Santana

Industrial Director

LAFEPE - Laboratório Farmacêutico do Estado de Pernambuco Governador Miguel Arraes S/A

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Los Angeles, octobre 2009
Best Science for the Most Neglected Symposium

“Chagas disease in the Americas: Improving Access and Tools for Patient Diagnosis and Treatment”

LAFEPE - founded in 1966
Second public pharmaceutical industry in Brazil
Located in Northeast Brazil
Manufactures 1,200,000,000 pharmaceutical units per year
Main areas of production: Liquids, Semi-solids and solids dosage forms
Main Therapeutic Class: Antihypertensive; anti-diabetes; analgesic; anti-HIV, anti-inflammatory, tuberculostatics,...

Exchange of BENZNIDAZOLE technology

2006
- LAFEPE Product registration in ANVISA
- Number of tablets sold by Roche®: since 1978 to 2003
(47,899,970.00 un)
- Consumer Countries: Brasil, Argentina, Bolivia, Ecuador, Venezuela, Costa Rica, Honduras, Colombia, Mexico, Panama
### Retrospective information about the production and distribution of BENZNIDAZOL

**2007/2008/2009**

- Amount manufactured by LAFEPE: 07 Batches (~ 400,000 un)
- Acquisition of API benznidazole by LAFEPE from Roche®
- PAHO Pre-qualification - July, 2008
- GMP certification, valid also for Mercosul/2009
- PAHO acquisition: 800 tablets / 2008
- PAHO acquisition: 3,200 tablets / 2009
- WHO acquisition: 50,000 tablets / 2009
- Brazilian Ministry healthy: 500,000 tablets / 2008
- Brazilian Ministry healthy: 1,000,000 tablets / 2009

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**Venezuela**

- 580,300 tablets / 2008

- Masters (international supply): 300 tablets / 2008
- BENEFIT project/partners: 16,000 tablets / 2008
- Punction Changes / 2009

- Tablets stored: 425,300 units / 2009
- API Benznidazole stored: 261,531 Kg / 2009
Challenges

Pediatric presentation of Benznidazole

- Partnership with DNDi - signature of agreement / 2008
- Pediatric demand - to be defined
- Dosage Form: 12.5 mg tablet -
  - Liverpool School of Tropical Medicine, using retrospective data from: Bolivia, Honduras, Argentina e Paraguay
- Dosage form: tablet, October 2010?

API development - New synthesis strategy (Cost x Price)

Registration status Bz

- 5/17 countries with Benznidazole in treatment guidelines

Registration status Nifurtimox

- 10/16 countries with Nifurtimox in treatment guidelines

Essential Medicines List

- 8/17 countries Benznidazole in treatment guidelines
- 5/16 countries with Nifurtimox in treatment guidelines
Obrigado !