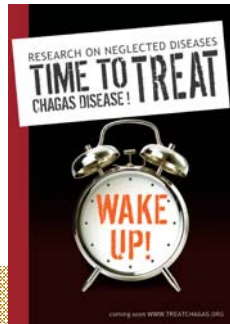


Global drug development pipeline for Chagas disease



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

Isabela Ribeiro



DNDi

Drugs for Neglected Diseases *initiative*

Best Science for the Most Neglected

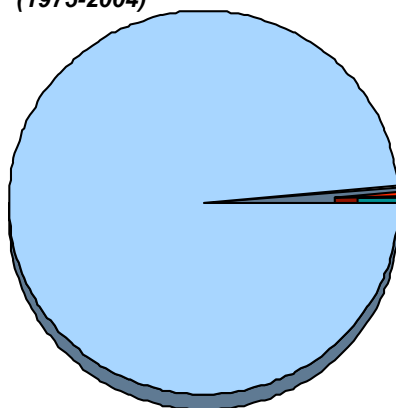
A Fatal Imbalance

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



(1975-2004)



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

Tuberculosis:
3 new drugs

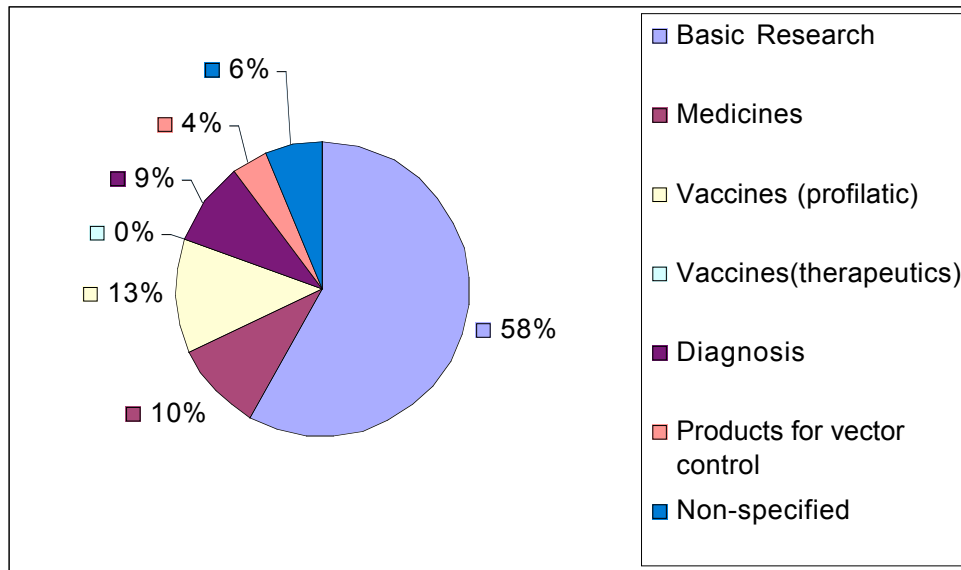
1.3%
21 new drugs
for neglected diseases

Source: Chirac P, Torrele E. *Lancet*. 2006 May 12; 1560-1561.

DNDi

Specific Funds for Chagas Disease

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



Moran M, Guzman J, Ropars A-L, McDonald A, Jameson N, et al. 2009 Neglected Disease Research and Development: How Much Are We Really Spending?. PLoS Med 6(2): e1000030. doi:10.1371/journal.pmed.1000030

Existing Chagas Treatments: Major Limitations



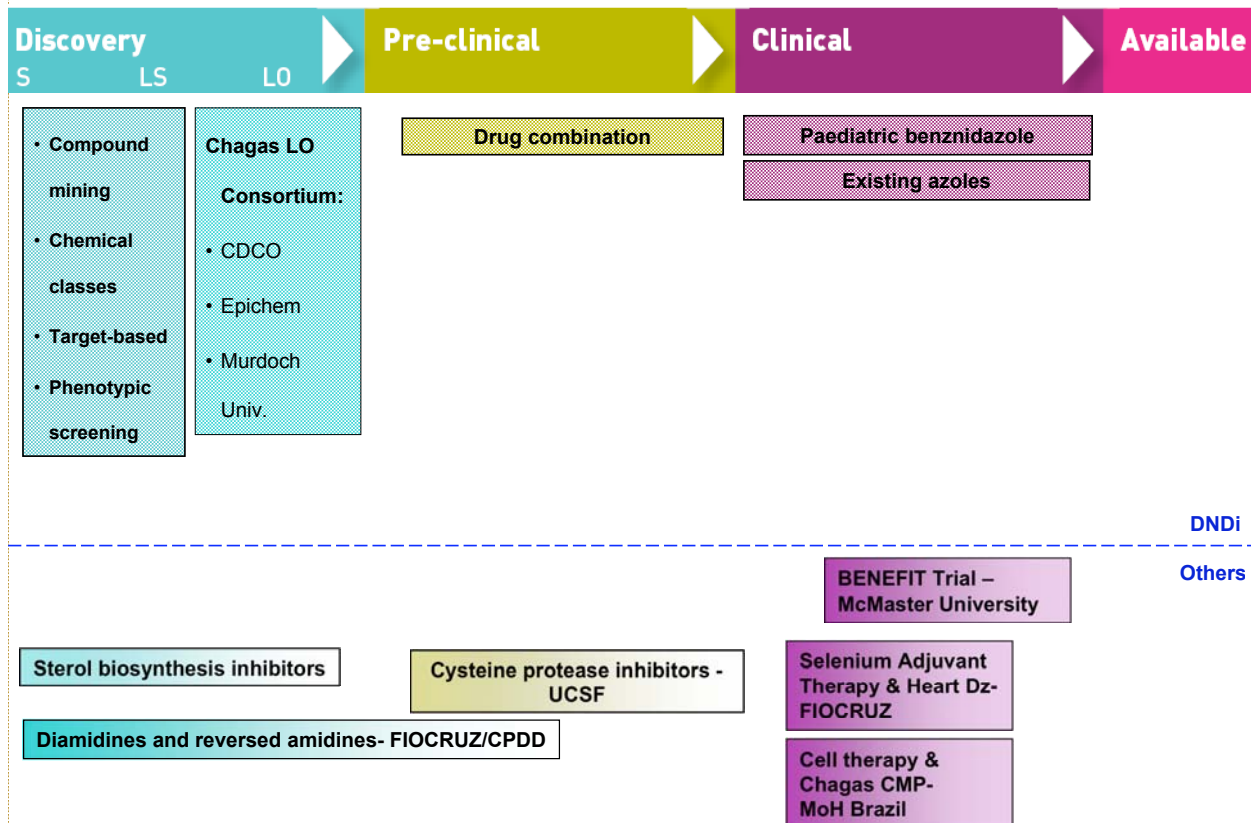
- Only two drugs available: nifurtimox and benznidazole
 - Safety issues
 - No general medical consensus as to their optimal use
 - Long treatment period (1-2 months)
 - High rate of non-compliance
 - No pediatric formulations available

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



Chagas Portfolio – Assembling & Evolving



Global Chagas Discovery Patent Search

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

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

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

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

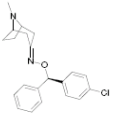
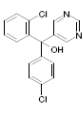
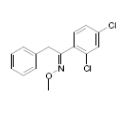
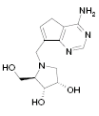

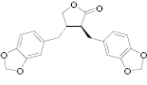
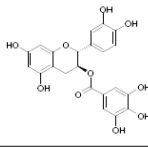
Long-term projects Lead Optimisation Consortium

- 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

			
Series 1: WEHI	Series 2: Fenarimol	Series 3 is derived from series 2	Natural Product: Purine NH Dehydrogenase
			
Natural Product: Canthinones	Natural Product: Hinokinin	Natural Product: Catechin	

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*

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:

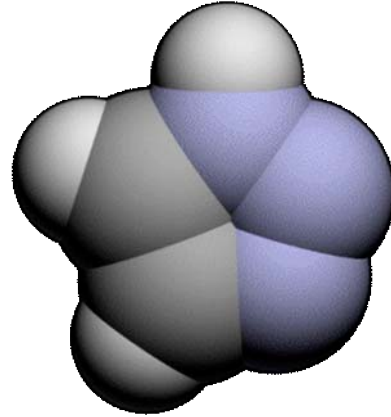
- Evaluation of combination therapy of Nifurtimox/Benznidazole + Azole compounds in animal model
- Investigation on-going; preliminary results promising

Medium Term Projects

Azoles

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

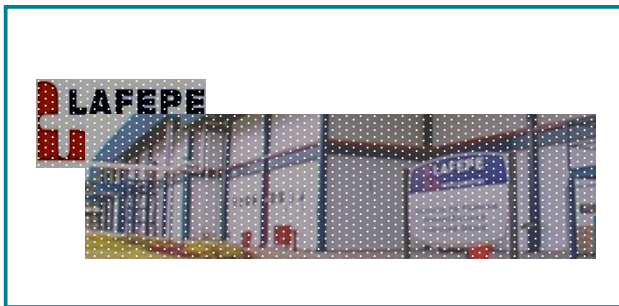
- License agreement with Eisai for clinical development - Sept 29, 2009
- Water-soluble prodrug monolysine form of ravuconazole
- PK properties – large volume of distribution, $t_{1/2}$ 4.42-11.75 days

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



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

E-mail: davi.santana@lafepe.pe.gov.br

Los Angeles, octobre 2009

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,...



Symposium

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

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



Symposium

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

**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



Symposium

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

**Retrospective information about
the production and distribution of BENZNIDAZOL**

2007/2008/2009

- 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





Symposium

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

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)



Symposium

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

Challenges

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 !

