



Perspectives in Neglected Diseases: DNDi strategy for development of new treatments for Chagas Disease

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DNDi

Drugs for Neglected Diseases *initiative*



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)

7 support offices

Coordination team Geneva + consultants

USA

DRC

Brazil

Kenya

India

Malaysia

Japan



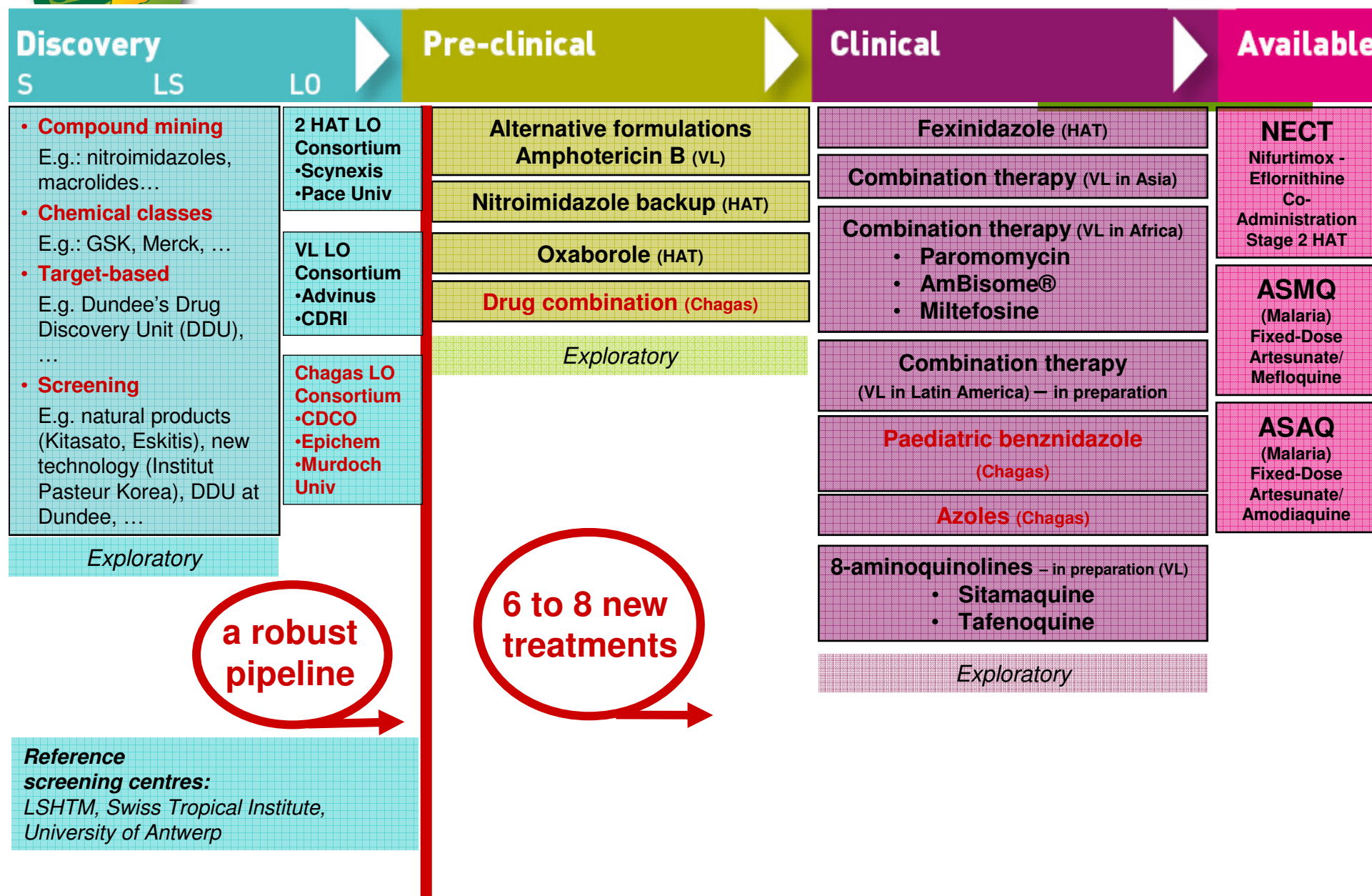
DNDi's Main Objectives

- Deliver **6 - 8 new treatments by 2014** for 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**





DNDi Portfolio – September 2009





The disease described by Carlos Chagas, 1909



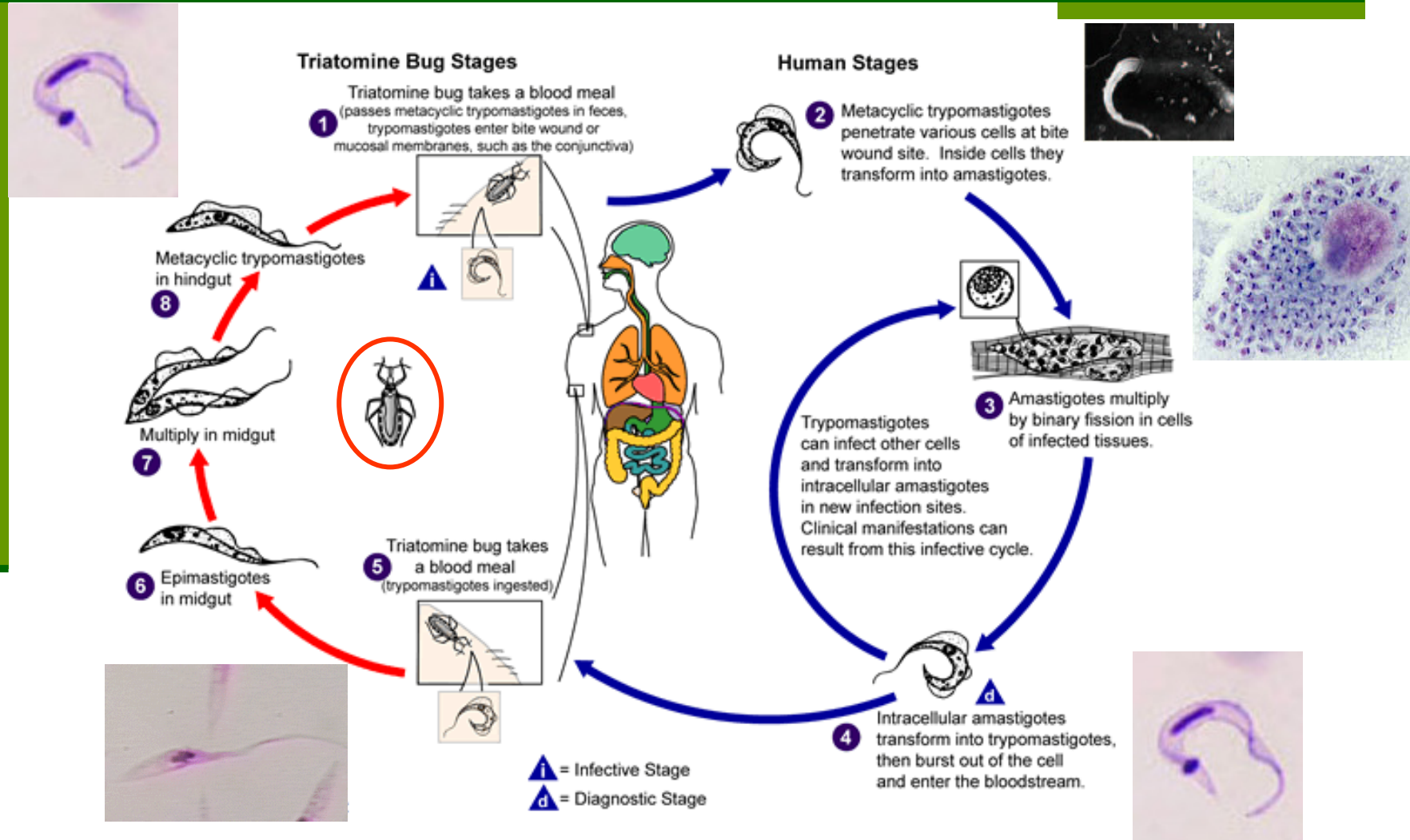
Hospital in Lassance



One of the first cases, Rita.



T. cruzi life cycle



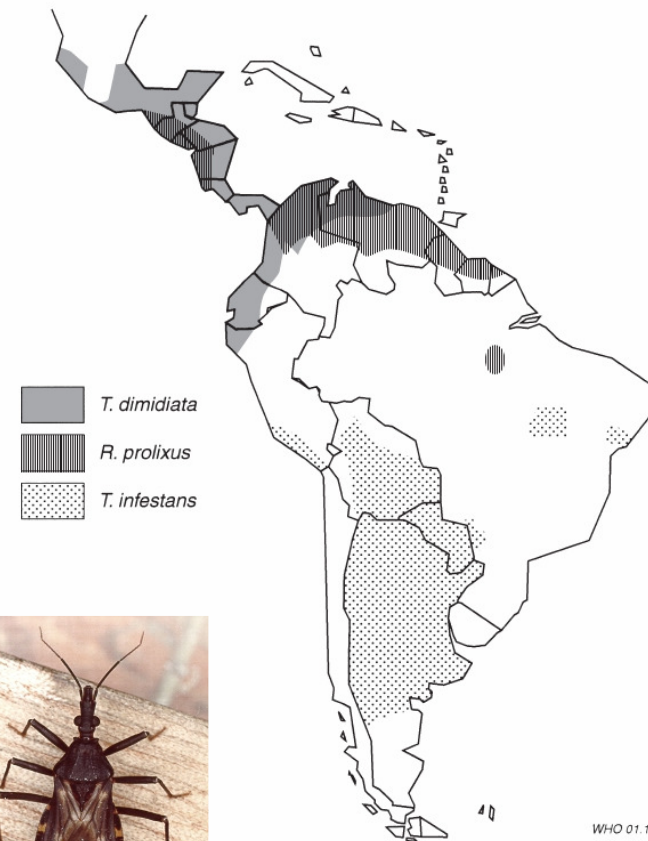
Source: CDC



The burden of Chagas' Disease

- **21 endemic countries in the Americas**
- **1980s - 17 million cases**
 - 4.8–5.4 million with clinical symptoms
 - Incidence of 700,000-800,000 new cases
 - 45,000 deaths - cardiac form of the disease
- **1990 - 2.7 million DALYs**
- **2001 – 9.8 million cases**
 - 586.000 DALYs
- **2006 – PAHO assessment**
 - ~8 million cases
 - 100 million individuals at risk in LA

Figure 2
Current geographical distribution of the three triatomine vector species of major epidemiological importance in Chagas disease



Triatoma infestans



Existing Chagas Treatments: Major Limitations



Médecin Sans Frontières

- 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



DNDi's Chagas R&D Strategy

Goal: to deliver effective, non-toxic, inexpensive treatment(s) proven effective for the acute and chronic phases of CD

Long-term projects:

New drugs and improved research & treatment capacity

- Improved screening methodologies
- Nitroimidazoles, cysteine protease inhibitors, ...
- Chagas lead optimisation consortium
- Chagas Platform

Medium-term projects:

Development of new treatments through therapeutic switching and combination therapy

- Azoles
- Combinations

Short-term projects:

Better use of existing treatments through new formulations

- Paediatric formulation of benznidazole



Long-term projects

Discovery

- Evaluation of compound libraries
 - Pharmacophore based screens -- access interesting compound classes from pharma companies: GSK, Merck and Anacor
 - 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 UNIFESP, UFOP on *in vivo* models



Long-term projects

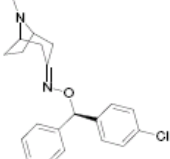
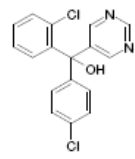
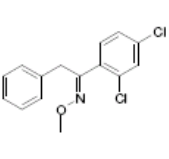
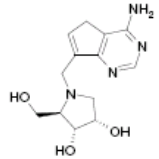
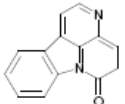
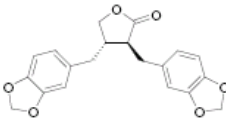
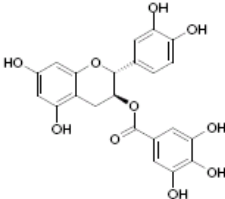
Lead Optimisation Consortium

- Initiated mid-2008
- Key partners include:
 - Centre for Drug Candidate Optimisation, Australia
 - Epichem, Australia
 - Murdoch University, Australia
 - Federal University of Ouro Preto, Brazil
 - UNIFESP, São Paulo, 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 ($IC_{50} = 190nm$)
- *Series 2*
 - SAR has been greatly expanded over the last 6 months.
 - 210 new analogues have been prepared
 - Potency has been improved to $IC_{50} 2nM$.
- *Series 3*
 - Further chemistry work on SAR is on-going



Medium Term Projects

Evaluation of Combination Therapy

Rationale:

- 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

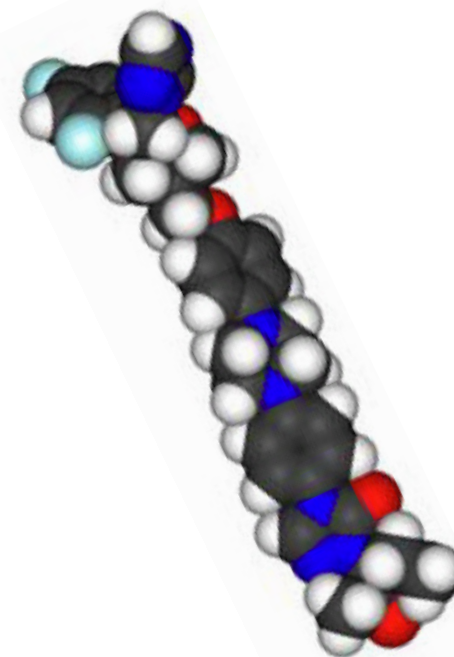
Azoles

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- 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

- Registration by Roche in 1971, licensed to Brazilian government in 2003
- Supplied in 100 mg tablets, regimen twice daily for 60 days

Current ways to administer in children:

- 100 mg tablet fractionated into $\frac{1}{2}$ (50mg) or $\frac{1}{4}$ (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

DNDi-Lafepe agreement in 2008 for development of a paediatric formulation



Short Term Project

A Paediatric Benznidazole therapy available in 2010

- 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

Population Pk study planned for 2010, in Argentina

Partner: Lafepe (Brazil), July 2008





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
- Forum of discussion of technical issues relevant to clinical research and development of new tools
- Support an environment conducive to quality research
- Facilitate effective and efficient trials to deliver improved treatment for Chagas disease



RESEARCH ON NEGLECTED DISEASES
TIME TO TREAT
CHAGAS DISEASE!



coming soon WWW.TREATCHAGAS.ORG

Chagas Campaign:

Raising Awareness of
Silent Killer

www.treatchagas.org



THANK YOU!