Perspectives in Neglected Diseases: DND*i* strategy for development of new treatments for Chagas Disease

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Colloquium on
Neglected Tropical Diseases of Latin America
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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**

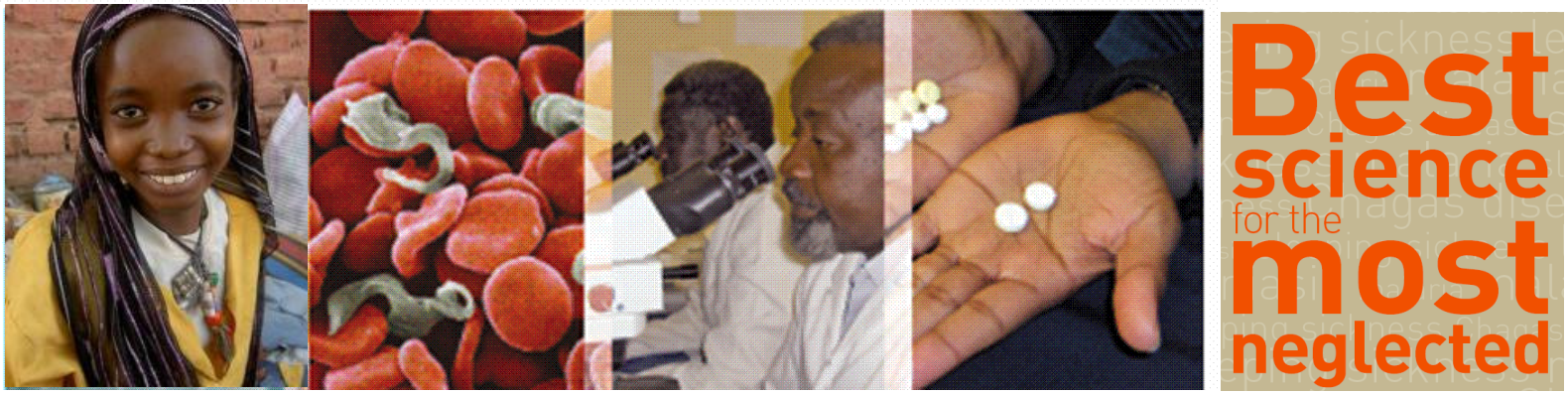
7 Founding Partners

- 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)

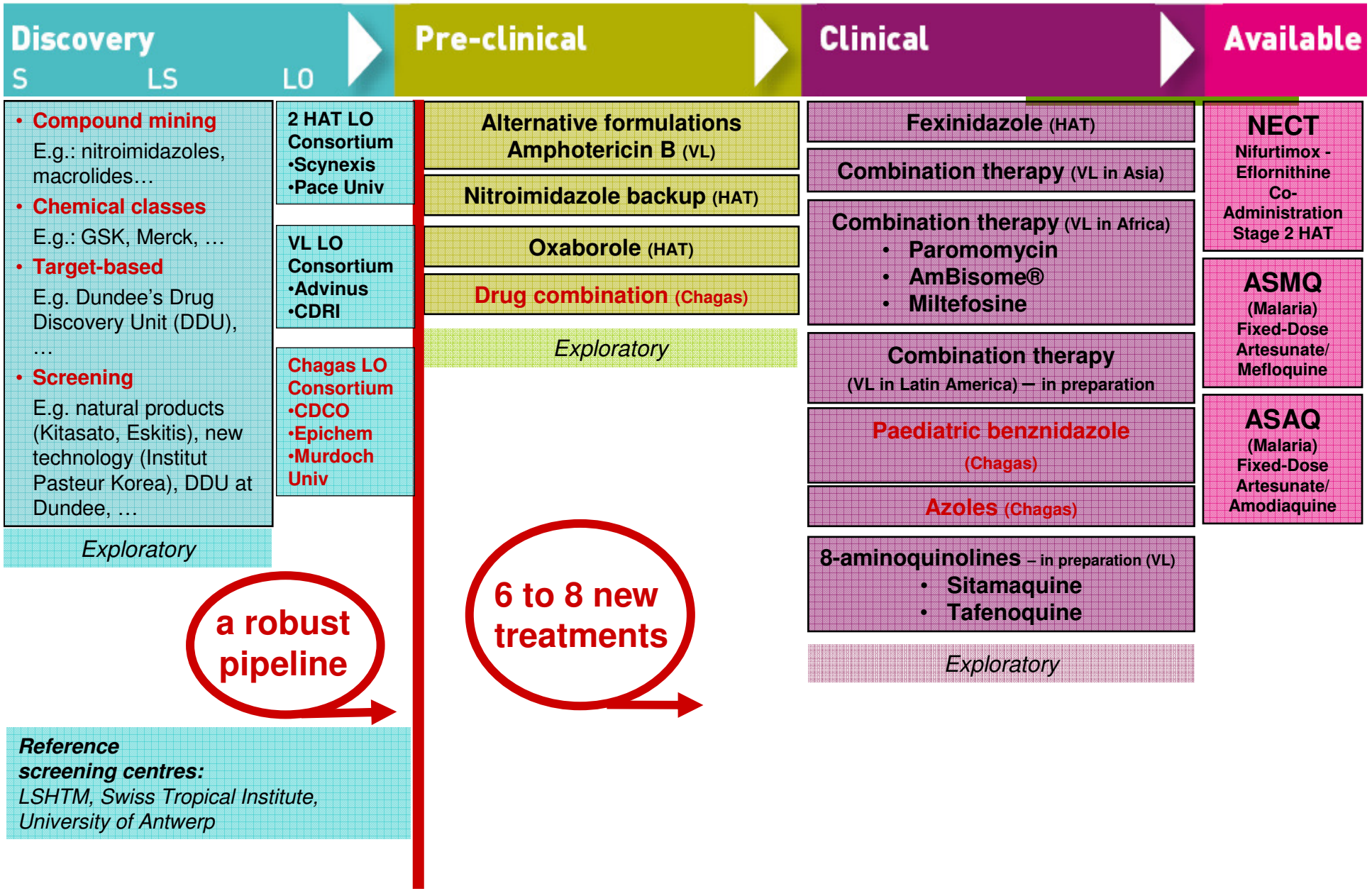
DNDi
Drugs for Neglected Diseases initiative

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

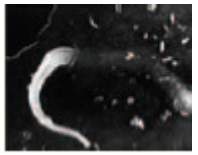


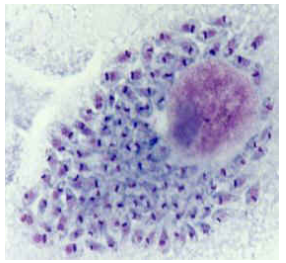
The disease described by Carlos Chagas, 1909

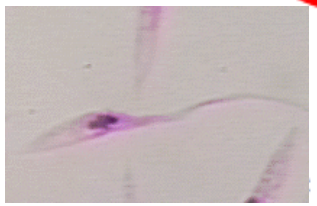
Hospital in Lassance

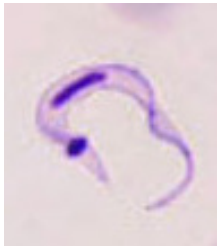
One of the first cases, Rita.

T. cruzi life cycle









Triatomine Bug Stages

Triatomine bug takes a blood meal
1 (passes metacyclic trypomastigotes in feces, trypomastigotes enter bite wound or mucosal membranes, such as the conjunctiva)

Metacyclic trypomastigotes in hindgut
8

Multiply in midgut
7

Epimastigotes in midgut
6

Triatomine bug takes a blood meal
5 (trypomastigotes ingested)

Human Stages

2 Metacyclic trypomastigotes penetrate various cells at bite wound site. Inside cells they transform into amastigotes.

3 Amastigotes multiply by binary fission in cells of infected tissues.

Trypomastigotes can infect other cells and transform into intracellular amastigotes in new infection sites. Clinical manifestations can result from this infective cycle.

4 Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream.

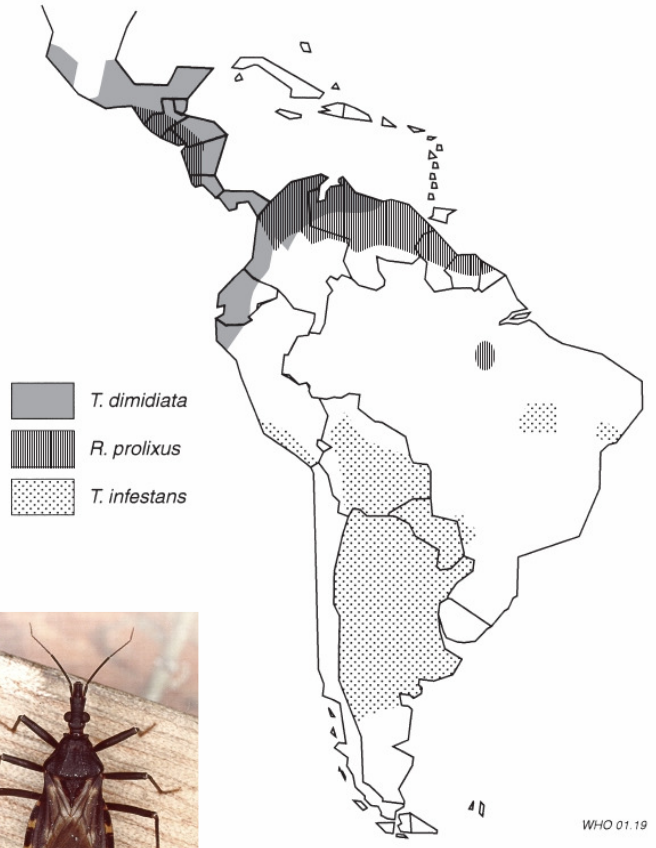
i = Infective Stage
d = Diagnostic Stage

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

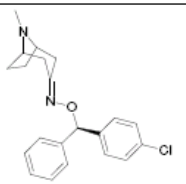
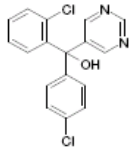
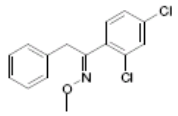
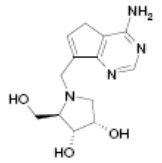
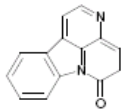
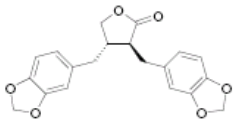
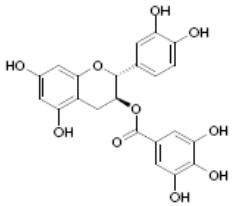
Long-term projects

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:

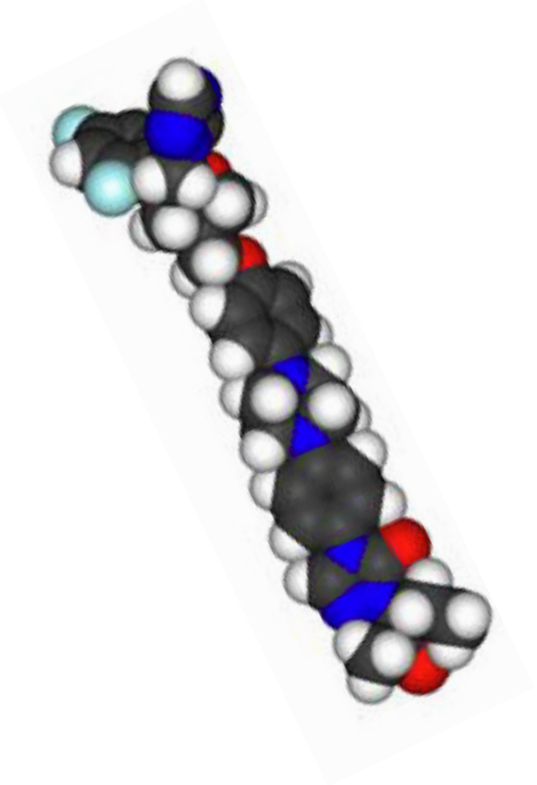
- Evaluation of combination therapy of Nifurtimox/Benznidazole + Azole compounds in animal model
- Investigation on-going; preliminary results promising

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 ½ 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 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

C. Zuniga, Programa Nacional de Controle e Prevenção, Honduras

DNDi-Lafepe agreement in 2008 for development of a peadiatric 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

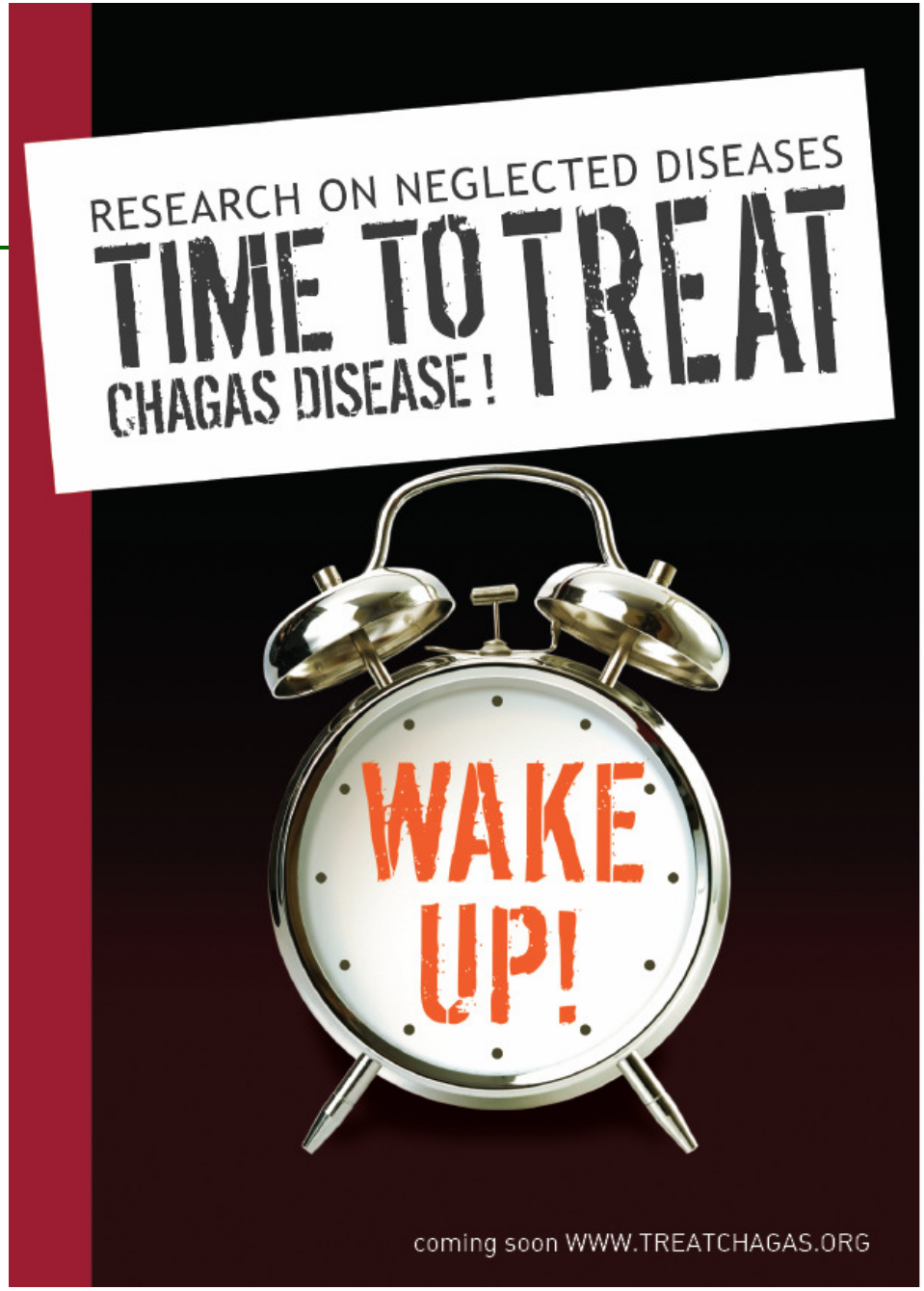
Population Pk study planned for 2010, in Argentina

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



Chagas Campaign:

Raising Awareness of Silent Killer

www.treatchagas.org

THANK YOU!