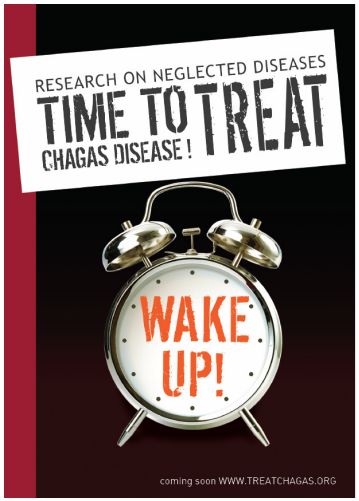
R&D challenges to develop new treatments for Chagas disease



An Overview of DNDi's activities in Chagas

Dr Nathalie Strub-Wourgaft
Clinical Development Director

September 2009

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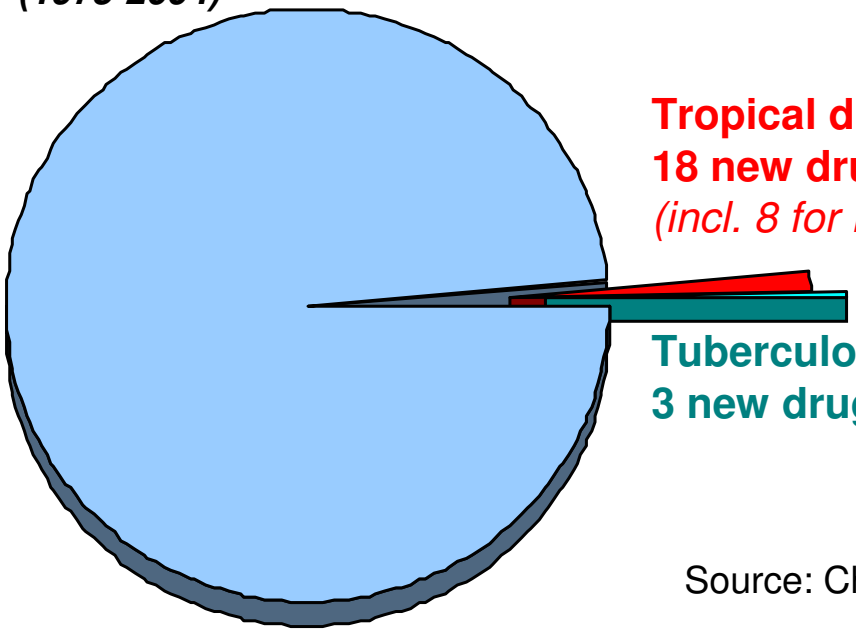
A Fatal Imbalance

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, Torreele E. *Lancet*. 2006 May 12; 1560-1561.

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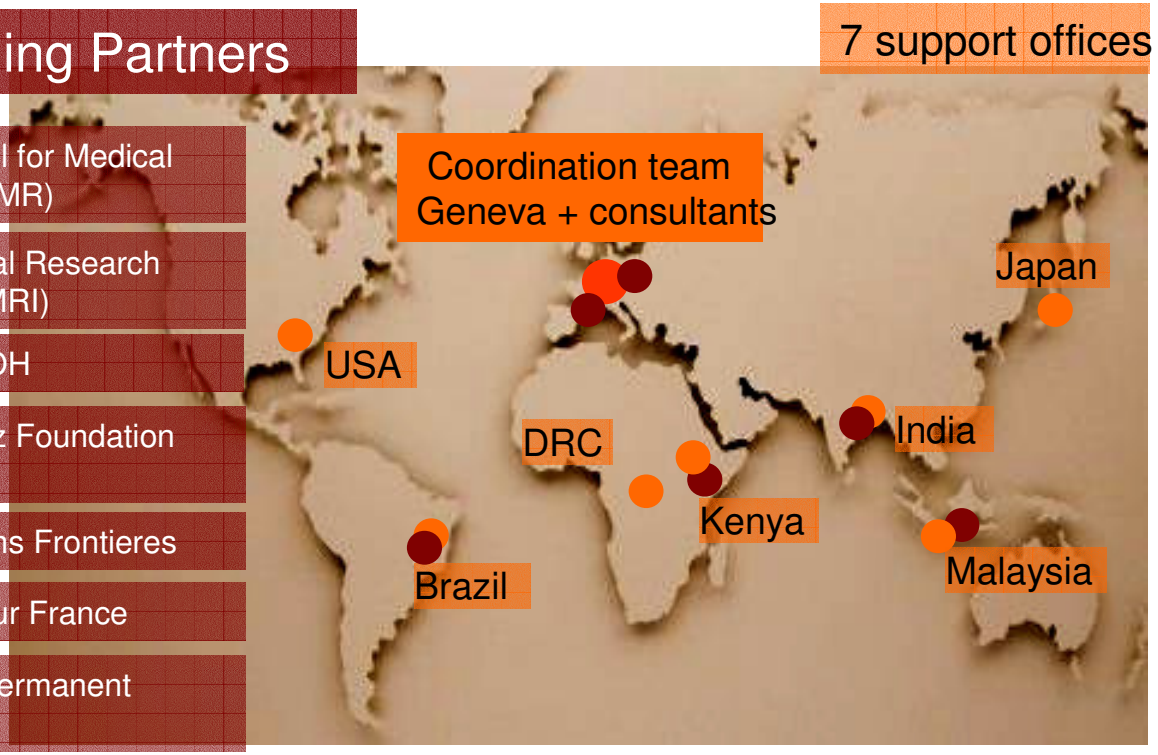
A New Model for Drug Development: DNDi

- **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
- Institut Pasteur France
- WHO/TDR (permanent observer)



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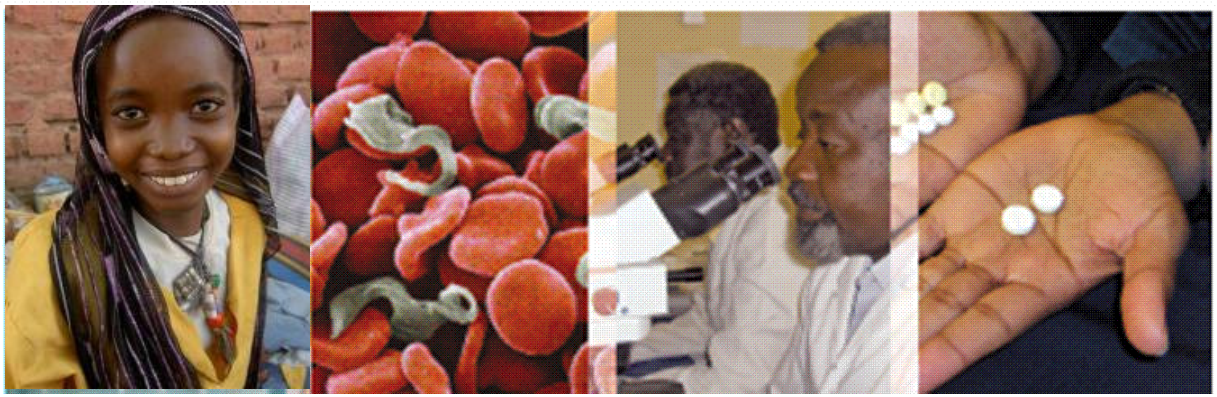
DNDi's Main Objectives

- 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**



Best science for the most neglected

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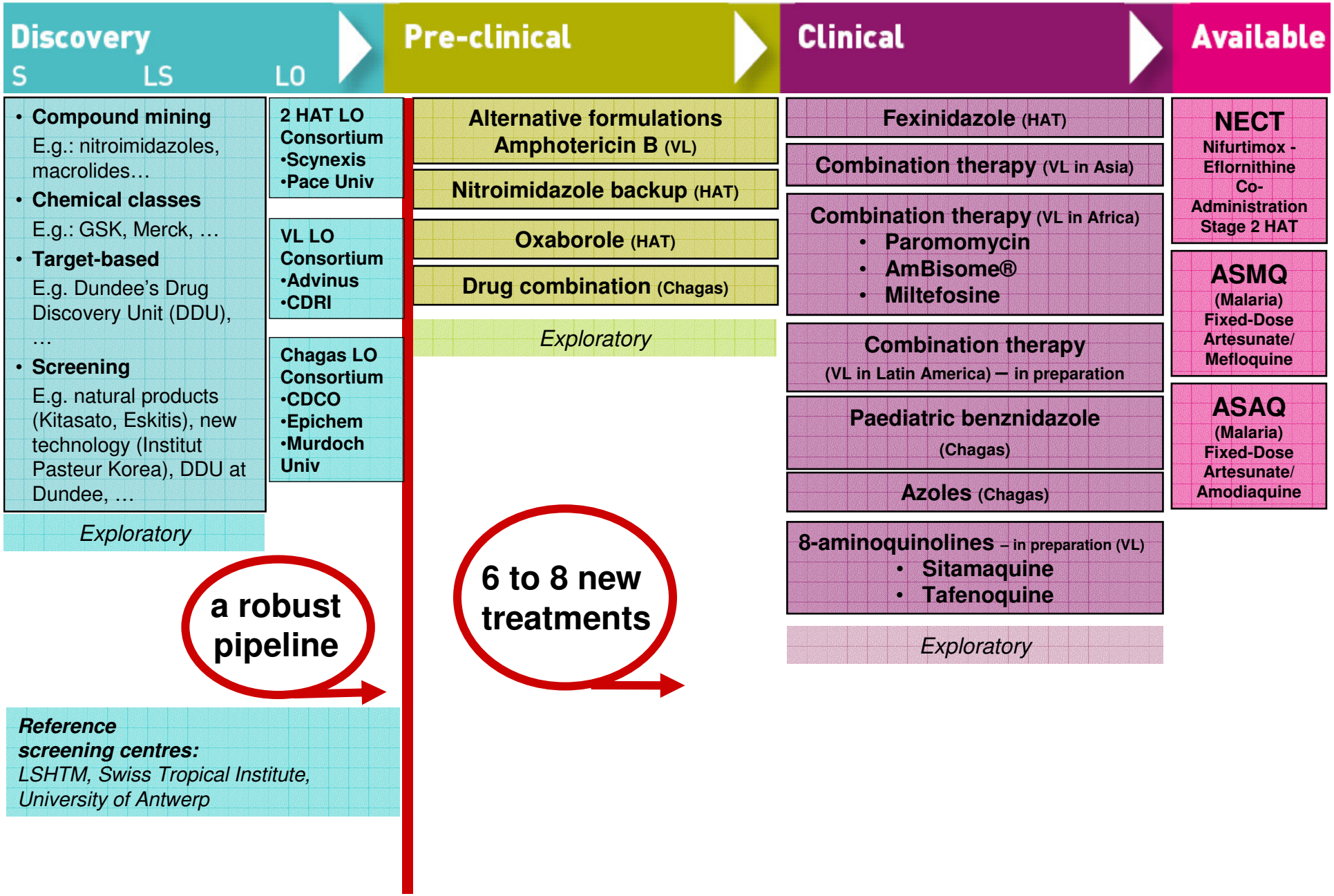
DNDi Portfolio – September 2009



Chagas Disease:
100 years of discovery but still 100 million at risk !

- Caused by protozoal parasite *Trypanosoma cruzi*
- Transmitted by 'kissing bug', blood transfusion, organ transplantation, as well as congenitally (or orally)
- Impacts:
  - **100 million people at risk in 21 endemic countries of South and Central America**
  - **Kills 14,000 per year => 40 deaths per day**
  - **Estimated 8 million people infected**
  - **Less than 0,5% of the infected receive treatment (<20,000/year)**
  - **0,4% of total invested in R&D for neglected diseases in 2007 to Chagas**
  - **Patient number growing with globalisation ie. USA, Canada, Japan, Spain, France, Italy and Switzerland**

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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
- No treatments for chronic disease

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Chagas: a silent disease

- Chagas disease: synonym of inattention, silent and silenced
- Important achievements in prevention
  - **And what about the infected?**
- The number of non treated patients in unclear and existing estimates are extremely low
- New tools for diagnosis and

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Chagas: More patients treated in Geneva than in State of Mexico !!!

Inadequate systems for surveillance and reporting

- Underreporting of new Chagas cases
  - 2008: 140 cases reported in Geneva – 200 cases in whole Mexico
- Lack of clinical consensus and harmonisation of standards and practices for treatment of scaling
- Need for active notification of specific populations (pregnant women, blood banks, programs for the donation of organs)
- Need for new options of diagnosis

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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

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Chagas Portfolio – Assembling & Evolving

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

Chagas LO Consortium:

- CDCO
- Epichem
- Murdoch Univ.

Drug combination

Paediatric benznidazole

Existing azoles

DNDi

Others

Sterol biosynthesis inhibitors

Cysteine protease inhibitors - UCSF

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

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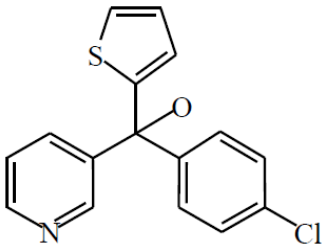
Long-term projects

Lead Optimisation Consortium



Fenarimol series

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

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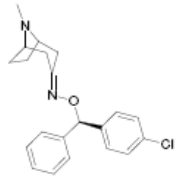
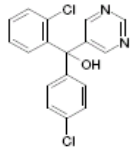
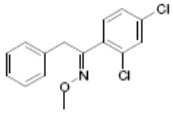
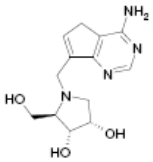
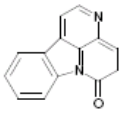
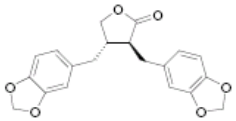
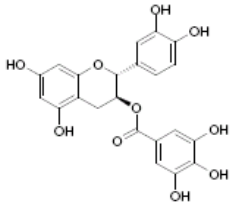
Long-term projects

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*

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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

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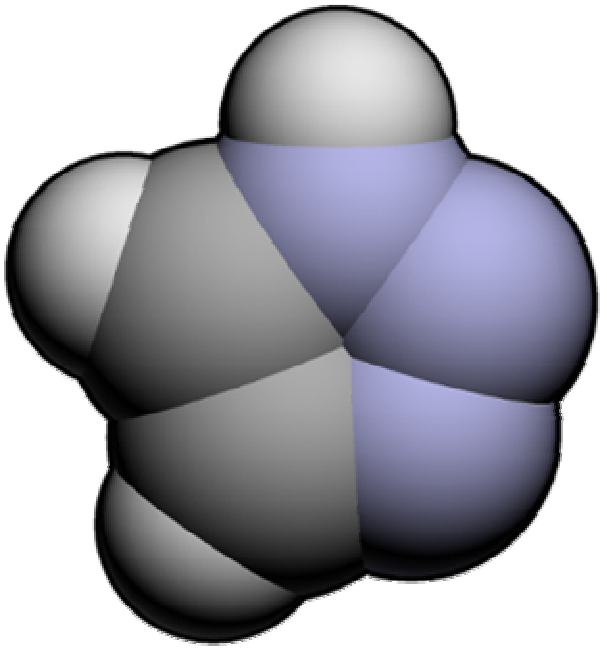
Medium Term Projects

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

- Posaconazole (SP)
- E1224 (Eisai)
- TAK-187 (Takeda)

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Medium Term Projects

Azoles

Promising clinical development starting in 2009 or 2010 ?

- Close to reach a license agreement with one pharma company for clinical development
- After 3 years of discussion, unable to conclude agreement with SP (discussion on access issue)

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Short Term Project

A Paediatric Benznidazole option therapy available in 2010 !

- Registration by Roche in 1971, licensed to Brazilian governement 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 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

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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

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

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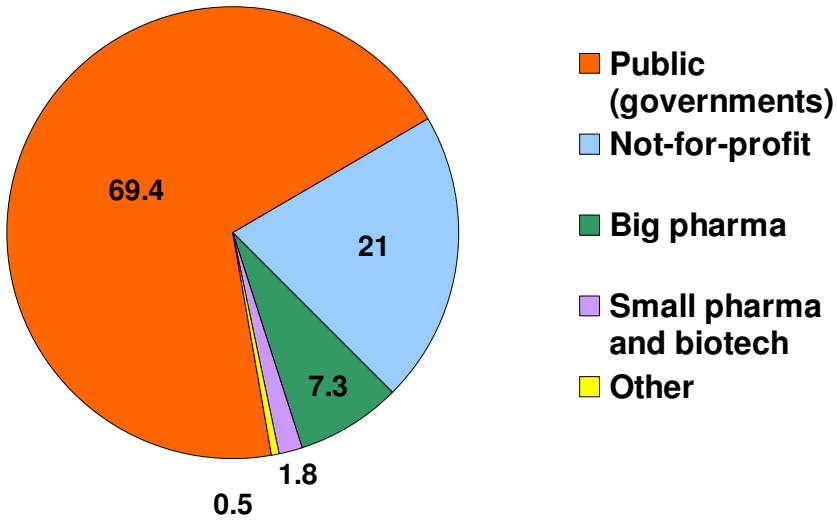
$2.5 billion funding for R&D for neglected diseases* in 2007



Only 0.4% allocated to Chagas disease !

Source: Moran et al., G-Finder report, 2009

*** Including HIV/AIDS, malaria and tuberculosis**

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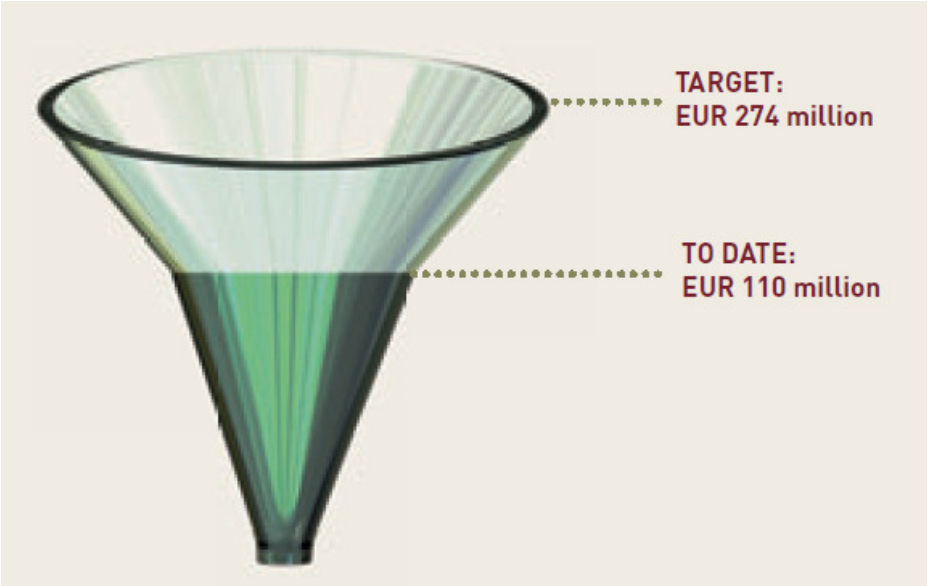
Funding Strategy - Diversity

€110M of €274M Secured (2004-2014)



Private Donors

- Médecins Sans Frontières
- Bill & Melinda Gates Foundation
- Other Private Foundations

Public Donors

- UK
- France
- Spain
- **Netherlands**
- USA – NIH
- Germany
- Canton de Genève - Switzerland
- European Union
- Tuscany (Italy)

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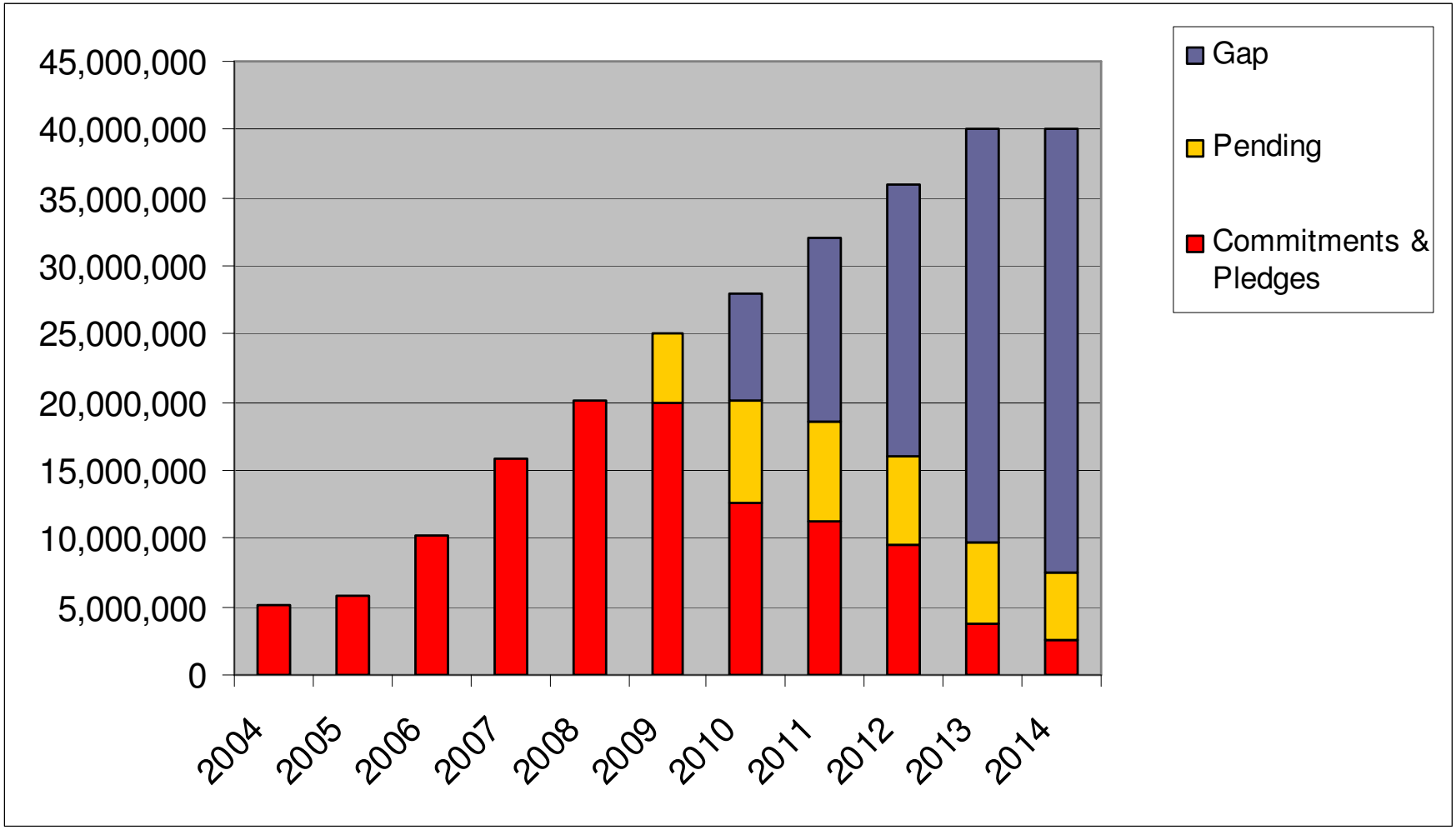
€164M Still Needed

2004-2014 Projected:



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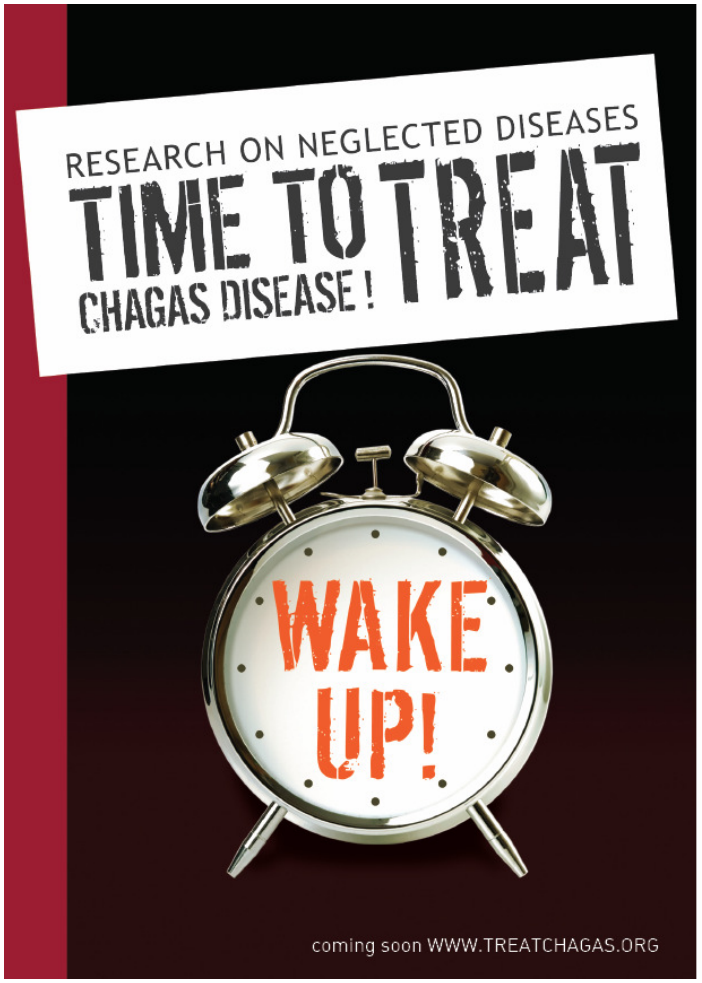
Chagas Campaign
Raising Awareness of Silent Killer



Objectives of the Campaign:

1) **Raise awareness on the disease and its reality. The silence must be broken.**
2) **Public leadership to prioritise Chagas on the agenda of policy makers. It is time for increased political will.**
   - **WHA/PAHO Resolution in May 2010**
3) **Boost R&D to develop new tools for diagnostics and new treatments.**
4) **More sustainable funding from public & private donors and promote new innovative funding mechanisms**

www.treatchagas.org

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