

# DNDi Strategy for the Development of New Treatments for Chagas Disease



SIMPÓSIO  
INTERNACIONAL  
comemorativo do  
CENTENÁRIO  
da descoberta da  
DOENÇA DE CHAGAS  
1909 • 2009  
8 e 10 de julho de 2009 • Hotel Sofitel • Rio de Janeiro • RJ

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& Shing Chang

DNDi

July 2009



**DNDi**

Drugs for Neglected Diseases *initiative*

# DNDi Created in 2003: A New Model for Drug Development

- *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)*

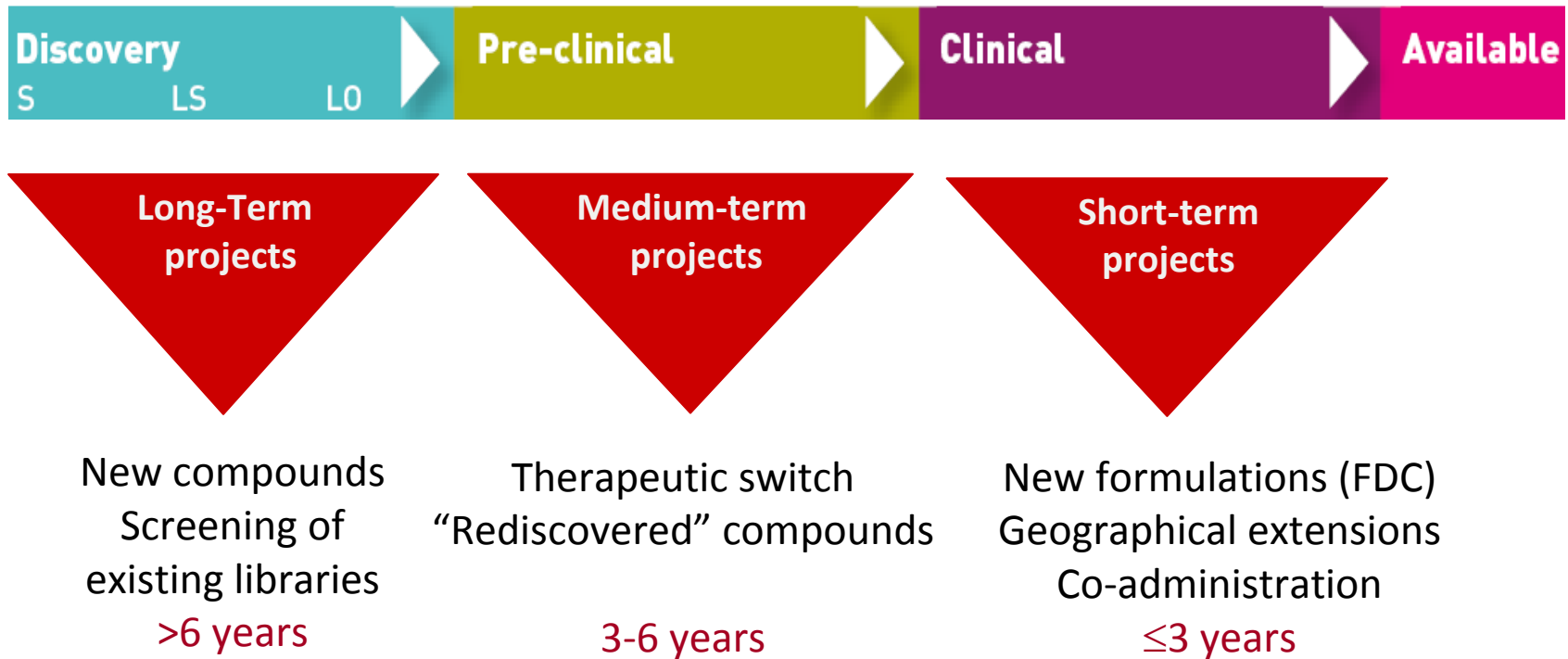


# DNDi Portfolio-Building Model

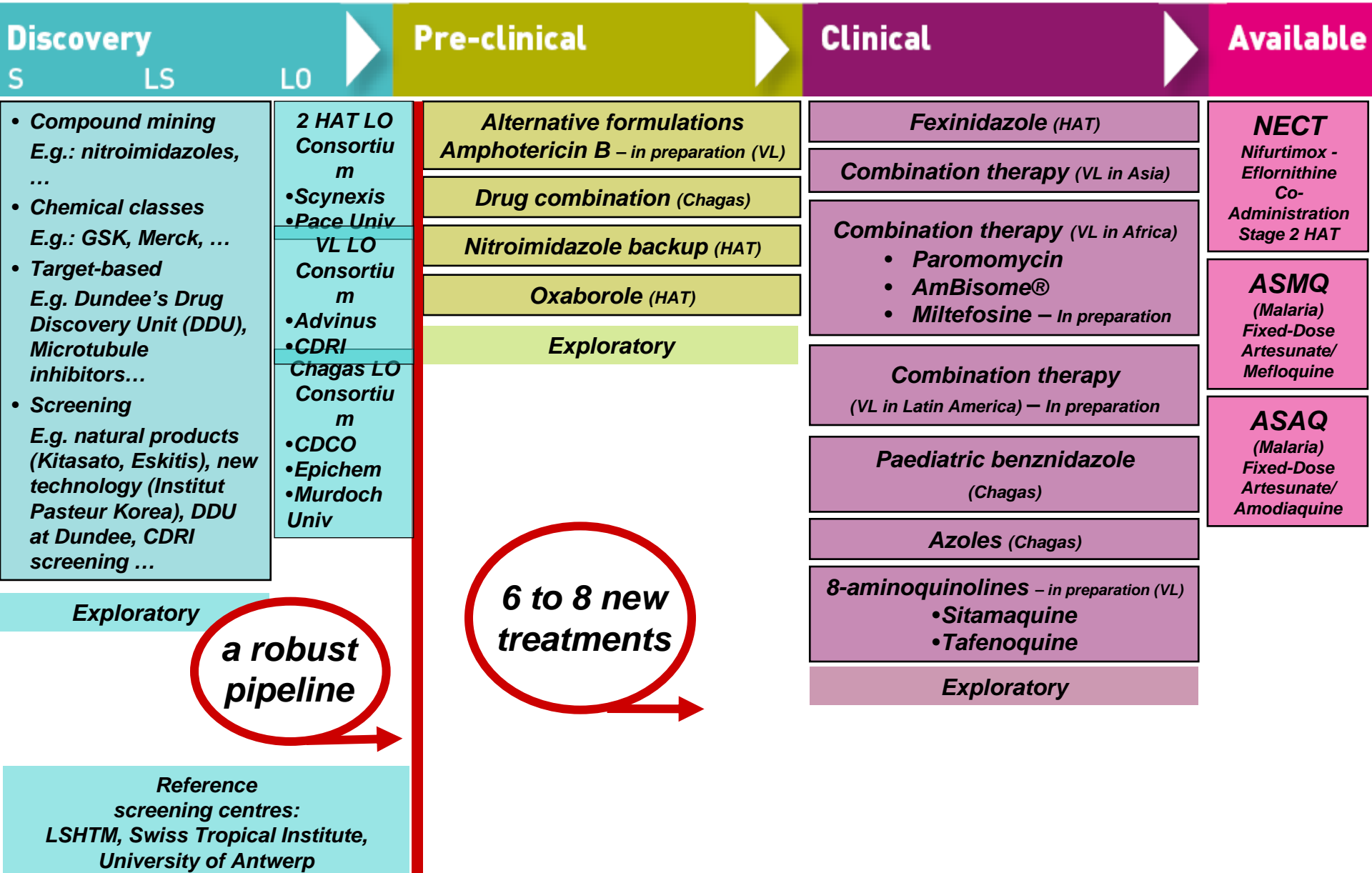
## Mission

- Deliver 6 - 8 new treatments by 2014 for neglected diseases, with robust pipeline (malaria, Chagas, sleeping sickness, leishmaniasis)
- Use and strengthen research capacity; build awareness

## Strategy



# DNDi Portfolio – June 2009



**a robust pipeline**

**6 to 8 new treatments**

# 3 New Treatments Delivered: Making a Difference with Partners

2007

**ASAQ** (Malaria)  
Fixed-Dose  
Artesunate/  
Amodiaquine



## Partners

**sanofi-aventis**  
(France)

2008

**ASMQ** (Malaria)  
Fixed-Dose  
Artesunate/  
Mefloquine



**Farmanguinhos**  
(Brazil)  
**Cipla** (India)

2009

**NECT**  
Nifurtimox -  
Efornithine  
Co-Administration  
(HAT)



**National Control  
Programs**  
**MSF**  
**WHO**

- Easy to Use
- Affordable
- Field-Adapted
- Non-Patented

# Chagas Disease: A Silent Killer

## Major Limitations of Existing Chagas Treatments:

- Only two drugs available:
  - nifurtimox and benznidazole
  - Long treatment period (1-2 months)
  - Toxicity profile
  - High rate of non-compliance
  - No pediatric formulations available
- Limited data on efficacy and safety of treatments for chronic disease

# DNDi's Chagas Strategy

## Short-term objectives:

Better use of existing treatments through new formulations, therapeutic switching, and combinations

- Paediatric formulation of benznidazole
- Azoles

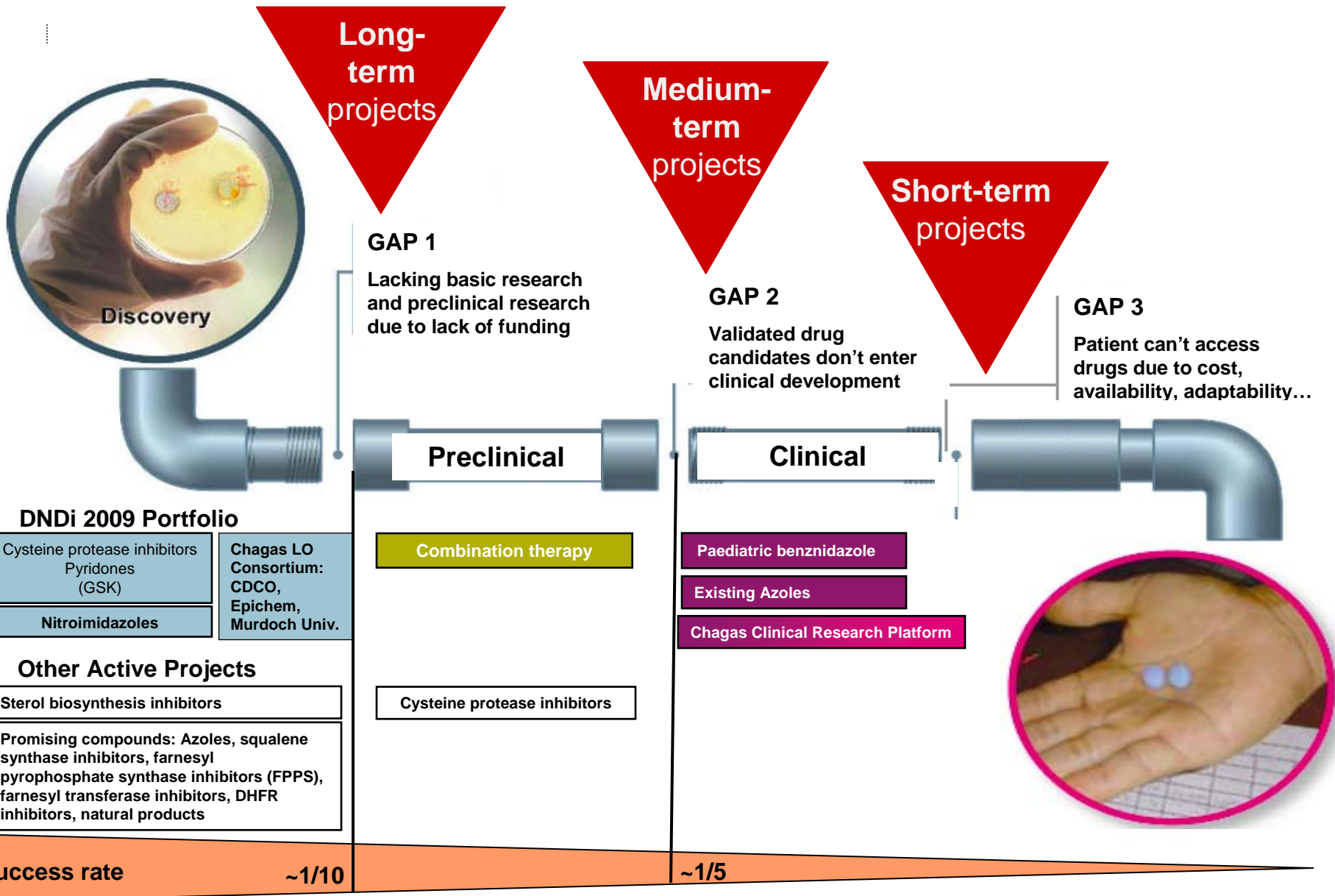
## Long-term objectives:

New drugs and improved research & treatment capacity

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

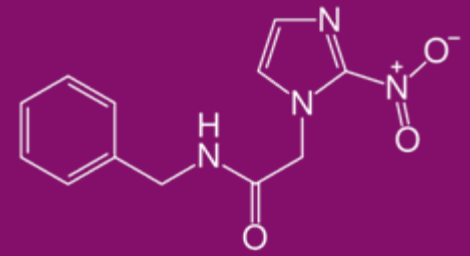


# DNDi - Chagas Disease Projects





# Paediatric Benznidazole



- Registration by Roche in 1971, now licensed to Lafepe
- Supplied in 100 mg tablets, twice daily for 60 days
- 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**



# Paediatric Benznidazole - The need

## 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**



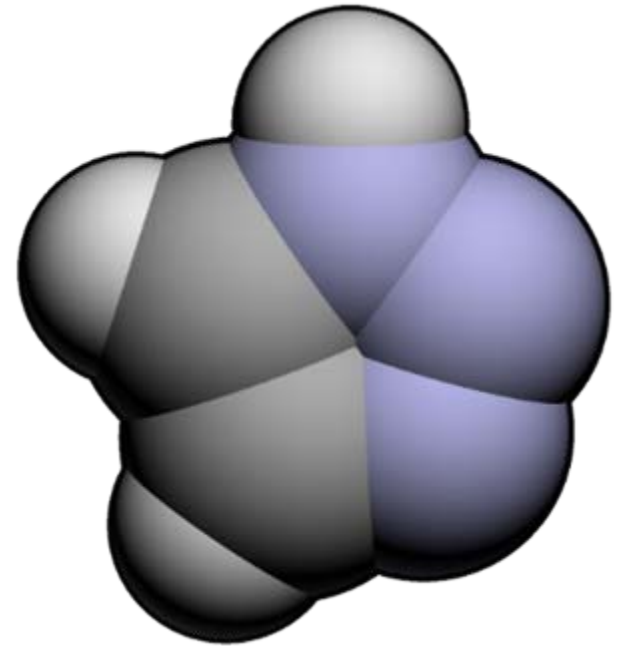
C. Zuniga, Programa Nacional de Controle e Prevenção, Honduras

# Azoles

## Triazole derivatives:

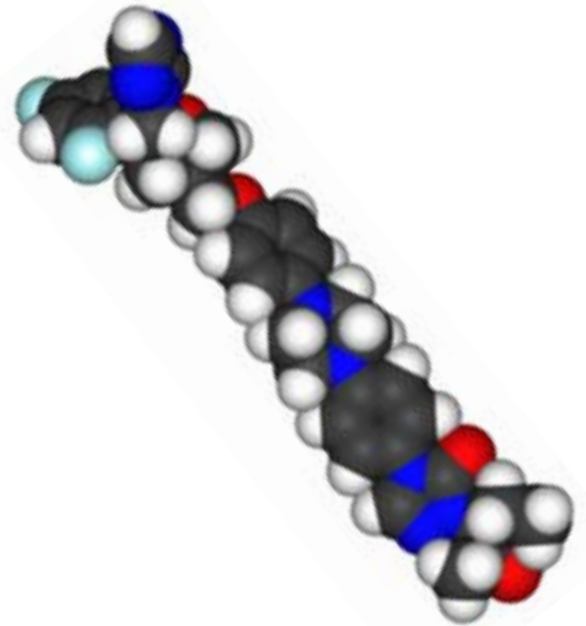
Existing antifungal drugs with promising activity against Chagas pathogen

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



# Azoles - posaconazole

- Most desirable azole, marketed by Schering-Plough
- Represent the most near-term hope & opportunity for Chagas patients
- DNDi in negotiation with SP since 2006 – numerous discussions with CEO & senior R&D management
- Unable to reach agreement on protocol and access issue so far



# Chagas Platform to Strengthen Clinical Research



- 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

# 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/ Benznidazol + Azole compounds in animal model
- Investigation on-going; preliminary results promising
- To guide future clinical studies



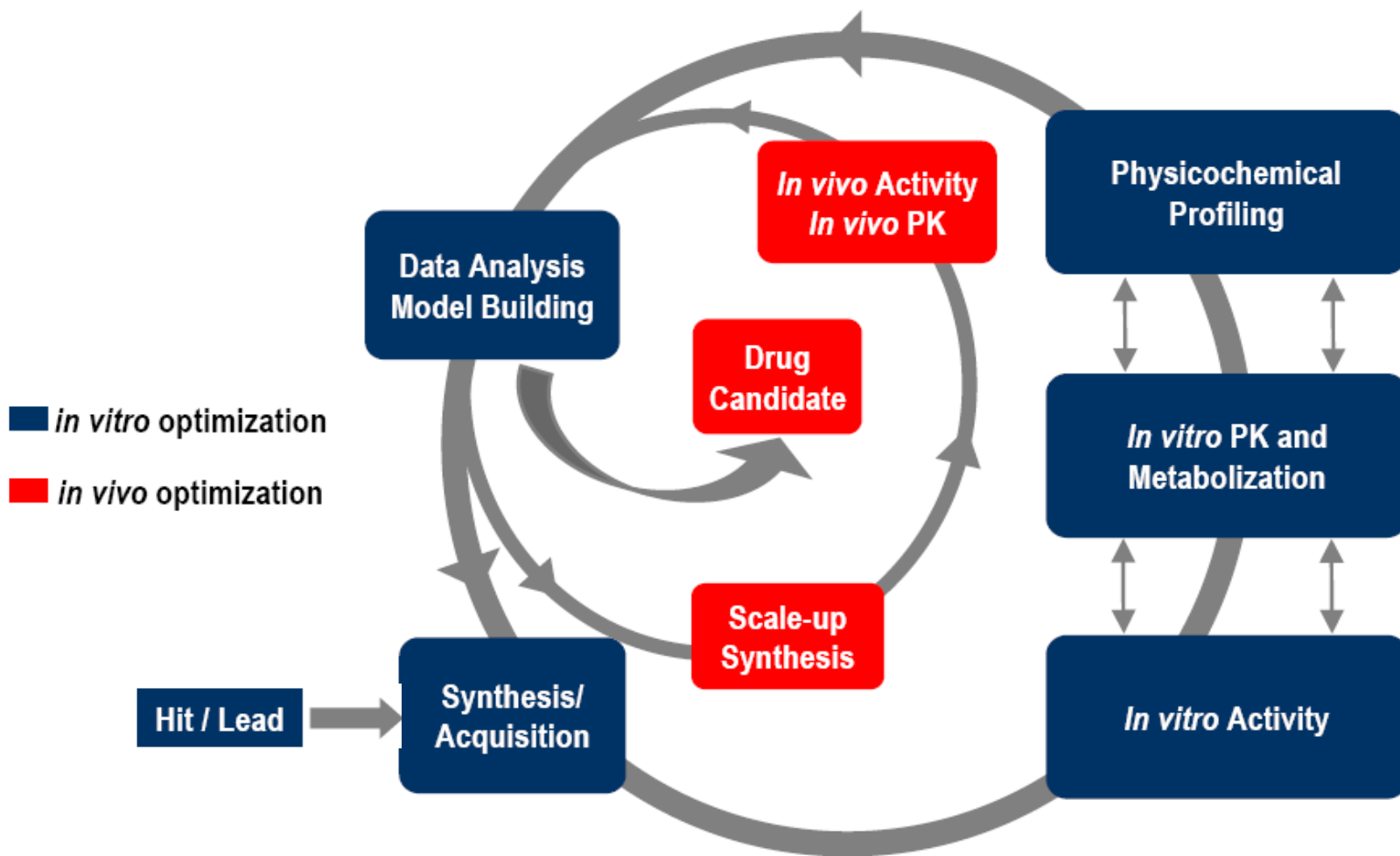
# Long-term projects - Discovery

- 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*

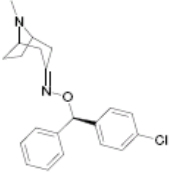
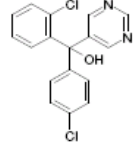
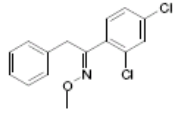
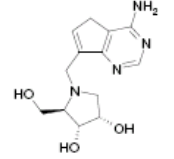
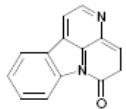
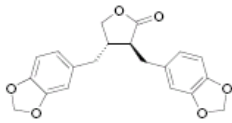
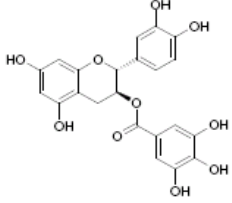


# CHAGAS Lead Optimization Consortium

## Hit to Lead and Lead Optimization



# 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 optimization 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<sub>50</sub> = 190nm)*
- Series 2
  - *SAR has been greatly expanded over the last 6 months.*
  - *127 new analogues have been prepared*
  - *Potency has been improved to IC<sub>50</sub> 2nM.*
- Series 3
  - *Further chemistry work on SAR is on-going*

RESEARCH ON NEGLECTED DISEASES  
**TIME TO TREAT**  
CHAGAS DISEASE!



coming soon [WWW.TREATCHAGAS.ORG](http://WWW.TREATCHAGAS.ORG)

Chagas  
Campaign:

Raising  
Awareness of  
Silent Killer

[www.treatchagas.org](http://www.treatchagas.org)

# Thank you to all our donors including:



**... as well as to all of our partners !**

**[www.dndi.org](http://www.dndi.org)**