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 a 10 de julho de 2009 • Hotel Sofitel • Rio de Janeiro - RJ

Centenário da descoberta da Doença de Chagas 1909 • 2009

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DNDi

July 2009

DNDi

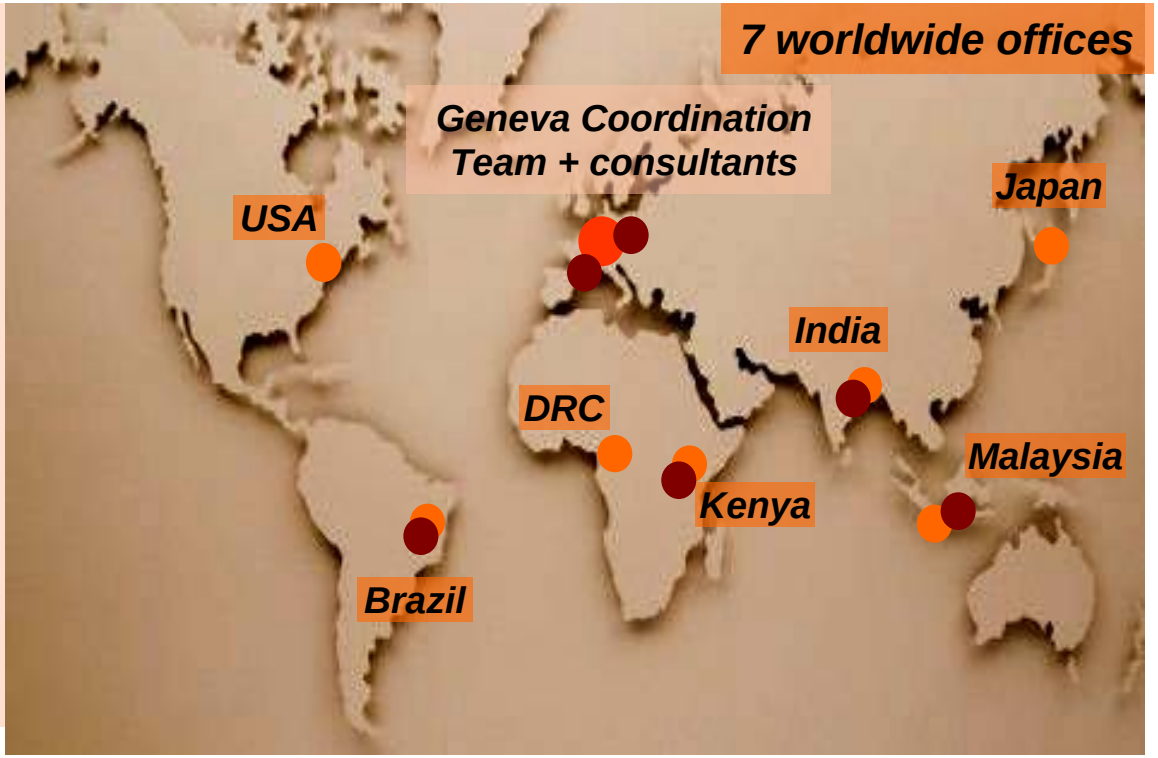
Drugs for Neglected Diseases *initiative*

DND*i* 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)***



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DND*i* 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

Long-Term projects	Medium-term projects	Short-term projects
New compounds Screening of existing libraries	Therapeutic switch "Rediscovered" compounds	New formulations (FDC) Geographical extensions Co-administration
>6 years	3-6 years	≤3 years

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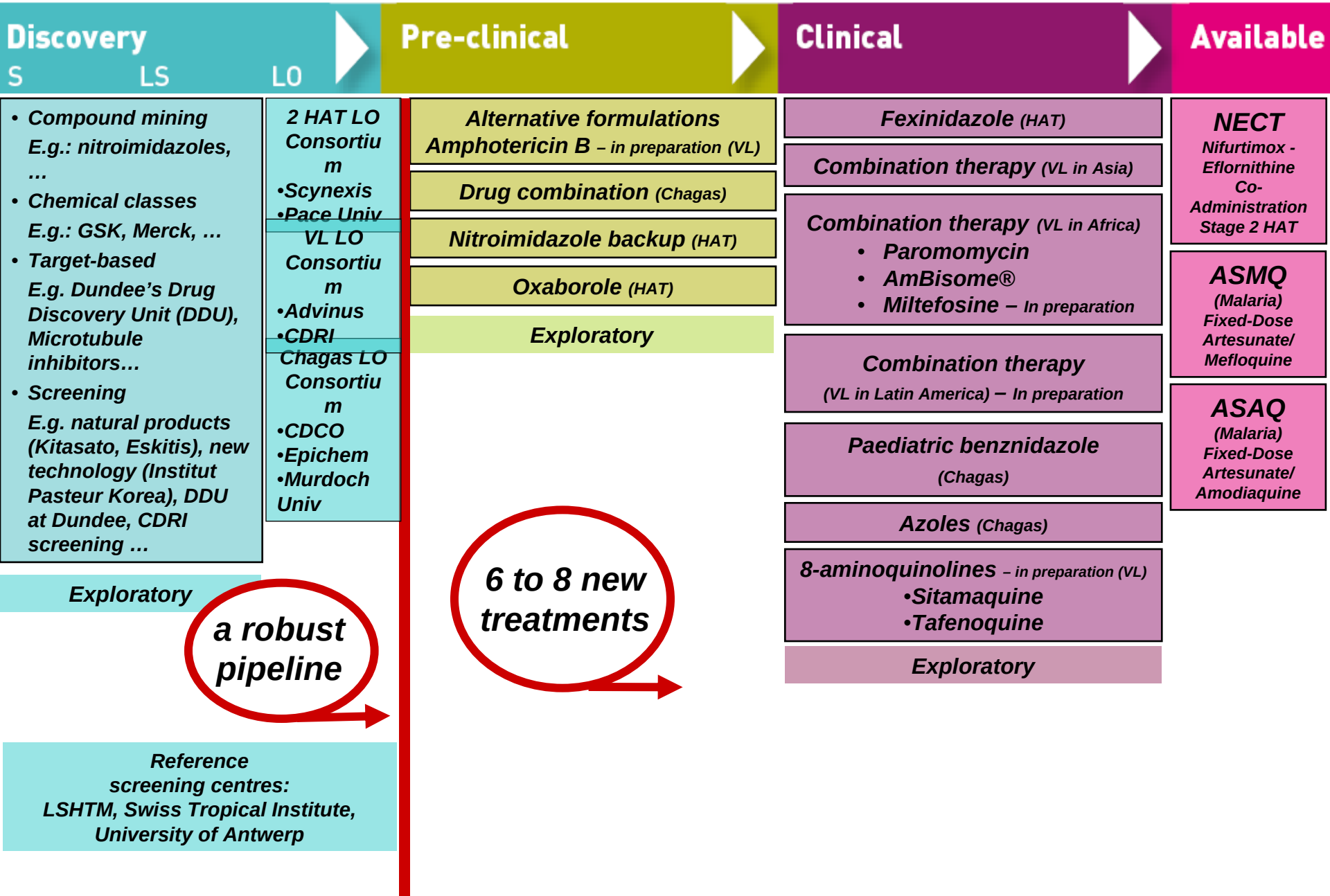
DND*i* Portfolio – June 2009



3 New Treatments Delivered: Making a Difference with Partners

2007

ASAQ (Malaria)
Fixed-Dose
Artesunate/
Amodiaquine

2008

ASMQ (Malaria)
Fixed-Dose
Artesunate/
Mefloquine

2009

NECT
Nifurtimox -
Eflornithine
Co-Administration
(HAT)

Partners

sanofi-aventis

(France)

Farmanguinhos

(Brazil)

Cipla **(India)**

National Control Programs

MSF

WHO

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

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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

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DND*i* - Chagas Disease Projects

Long-term projects

Medium-term projects

Short-term projects

GAP 1

Lacking basic research and preclinical research due to lack of funding

GAP 2

Validated drug candidates don't enter clinical development

GAP 3

Patient can't access drugs due to cost, availability, adaptability…

Preclinical

Clinical

DNDi 2009 Portfolio

Cysteine protease inhibitors Pyridones (GSK)	**Chagas LO Consortium: CDCO, Epichem, Murdoch Univ.**
Nitroimidazoles	

Combination therapy

Paediatric benznidazole

Existing Azoles

Chagas Clinical Research Platform

Other Active Projects

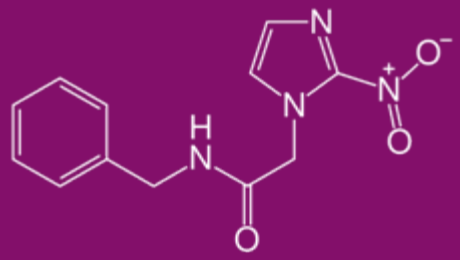
Sterol biosynthesis inhibitors

Promising compounds: Azoles, squalene synthase inhibitors, farnesyl pyrophosphate synthase inhibitors (FPPS), farnesyl transferase inhibitors, DHFR inhibitors, natural products

Cysteine protease inhibitors

Success rate **~1/10** **~1/5**

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

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Paediatric Benznidazole - The need

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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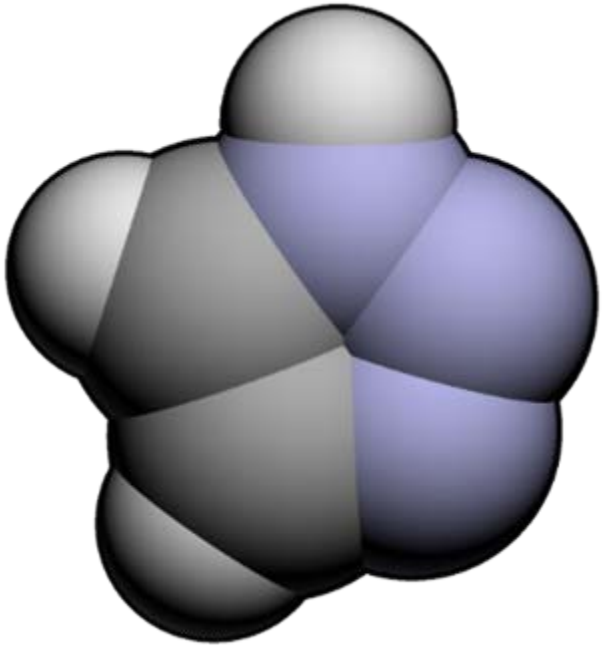
Azoles

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



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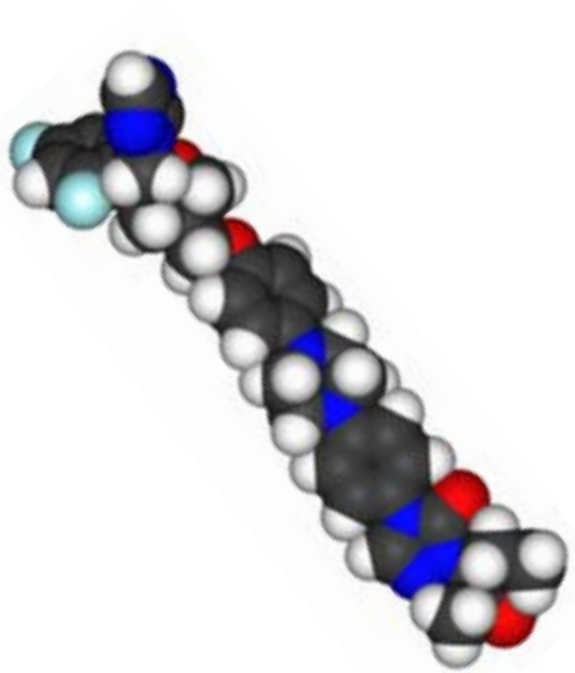
Azoles - posaconazole

- 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



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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

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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

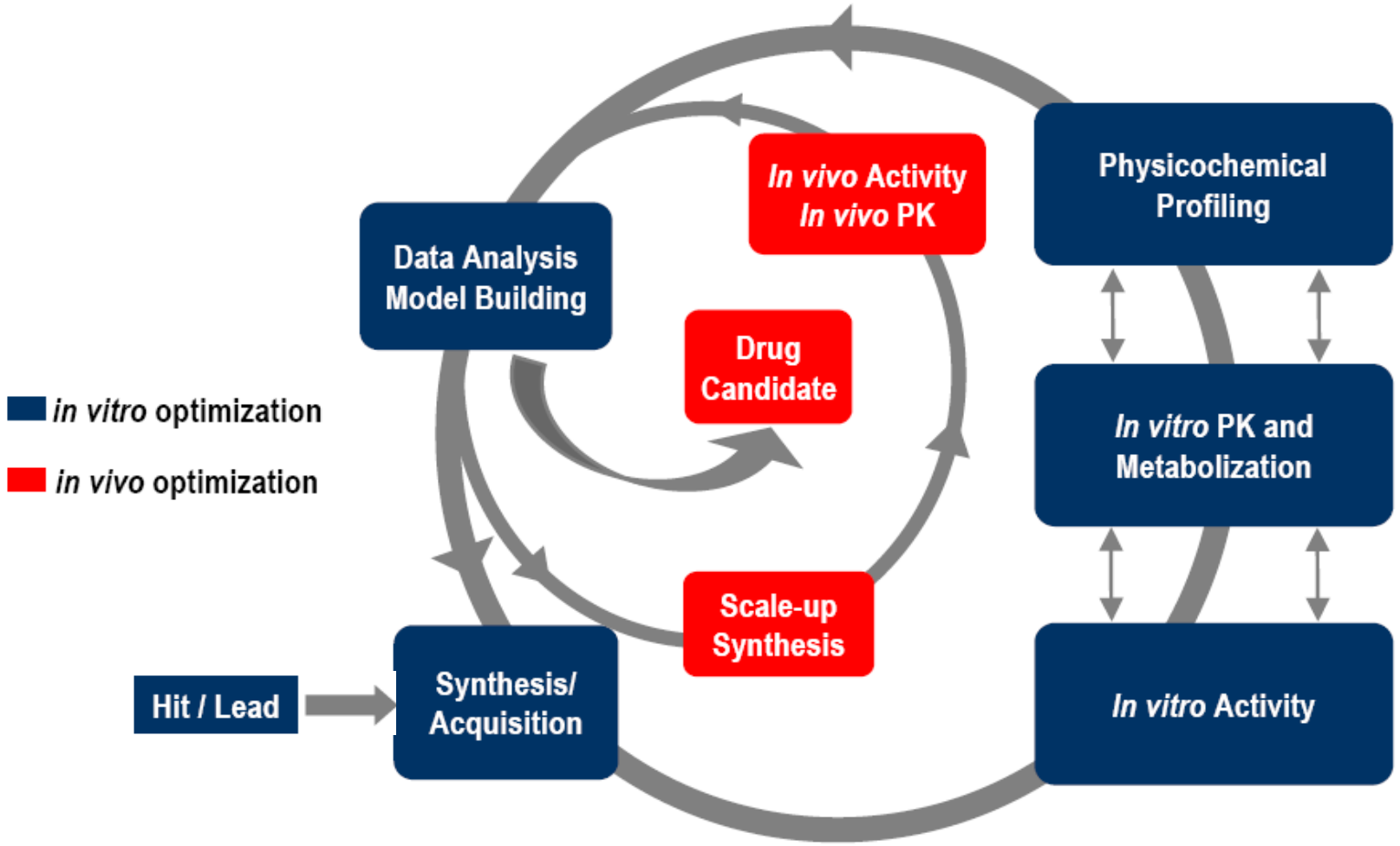
Initial target:

- Evaluation of combination therapy of Nifurtimox/ Benznidazol + Azole compounds in animal model
- Investigation on-going; preliminary results promising
- To guide future clinical studies

Long-term projects - Discovery

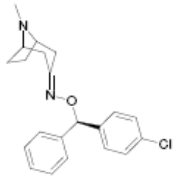
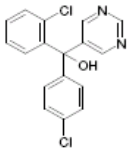
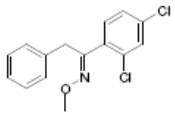
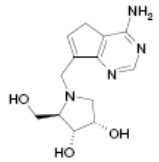
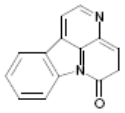
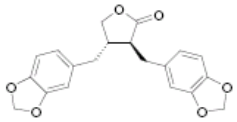
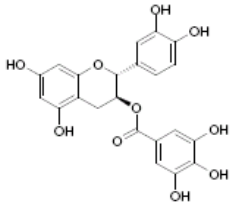
- Evaluation of compound libraries
- Pharmacophore based screens -- access interesting compound classes from pharma companies: GSK & Merck
- Compound mining – e.g., nitroimidazoles
- Development of new techniques for increased screening capacity -- collaboration with Institute Pasteur-Korea for High Throughput Screening for *T. cruzi*

CHAGAS Lead Optimization Consortium
Hit to Lead and Lead Optimization



DNDi Drugs for Neglected Diseases initiative

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 (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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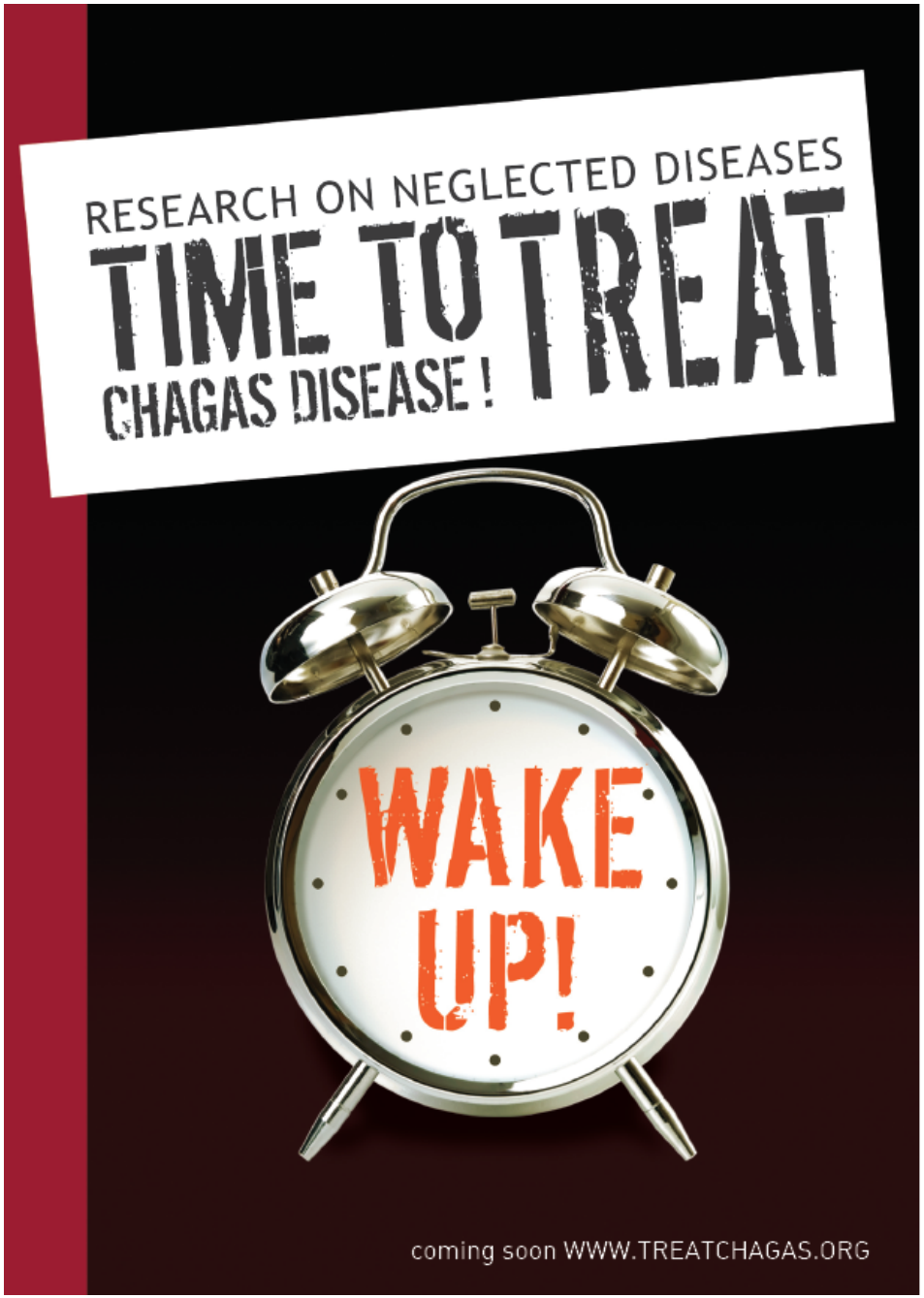

Chagas Campaign:

Raising Awareness of Silent Killer

www.treatchagas.org

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Thank you to all our donors including:

… as well as to all of our partners !

www.dndi.org