

# NEW MECHANISMS TO ACCELERATE DRUG DISCOVERY FOR NEGLECTED TROPICAL DISEASES (NTDs)

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**DNDi**

Drugs for Neglected Diseases *initiative*

ICOPA XIII

13<sup>th</sup> INTERNATIONAL CONGRESS OF PARASITOLOGY  
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HOTEL CAMINO REAL, MEXICO CITY

# Vision & Objectives

## ❑ Vision:

A collaborative, patients' needs-driven, virtual, non-profit drug R&D organisation to develop new treatments against the most neglected communicable diseases



## ❑ Objectives:

- ❑ Deliver **11 to 13 new treatments by 2018** for sleeping sickness, Chagas disease, leishmaniasis, malaria, paediatric HIV and specific helminth infections
- ❑ Establish a **robust pipeline** for future needs
- ❑ Use and strengthen existing **capacity in disease-endemic countries**

# Responding to the Needs of Patients Suffering from Neglected Diseases...



Malaria



Leishmaniasis



Paediatric HIV



Sleeping Sickness (HAT)



Chagas Disease




Filaria

- Published Target Product Profiles to meet patients' needs  
See: [www.dndi.org](http://www.dndi.org)

# 6 New Treatments Developed Since 2007


**ASAQ** 2007  
(Fixed-dose combination of artesunate + amodiaquine)

**malaria**

A collage of four images: a mosquito on a human arm, a healthcare worker in a white coat, a box of ASAQ tablets, and a group of people in a community setting.

**ASMQ** 2008  
(Fixed-dose combination of artesunate + mefloquine)

**malaria**

A collage of four images: a mosquito on a human arm, a healthcare worker in a white coat, a box of ASMQ tablets, and a group of people in a community setting.

**NECT** 2009  
(Nifurtimox-eflornithine combination therapy)

**sleeping sickness stage 2**

A collage of four images: a mosquito, a healthcare worker in a white coat, two bottles of NECT medication, and a person in a community setting.

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


**SSG&PM** 2010  
(Sodium stibogluconate & paromomycin combination therapy)

**VL**

A collage of four images: a mosquito on a human arm, a healthcare worker in a white coat, a box of SSG&PM tablets, and a group of people in a community setting.

**NEW VL TREATMENTS IN ASIA** 2011  
(SD AmBisome® / PM+M / A®+M /)

**VL**

A collage of four images: a mosquito on a human arm, a healthcare worker in a white coat, a box of NEW VL treatments, and a group of people in a community setting.

**Benznidazole** 2011  
12.5 mg  
Pediatric dosage form of benznidazole

**Chagas disease**

A collage of four images: a mosquito on a human arm, a healthcare worker in a white coat, a box of Benznidazole tablets, and a group of people in a community setting.

# DNDi Portfolio June 2014



## Research

## Translation

## Development

## Implementation

Screen

Hit to Lead

Lead Opt.

Pre-clinical

Phase I

Phase IIa/PoC

Phase IIb/III

Registration

Access

● HAT

SCYX2035811 ★  
SCYX1608210 ★

SCYX-7158 ★

Fexinidazole ★

NECT  
Nifurtimox-Eflornithine  
Combination Therapy

● Leishmaniasis

S  
C  
R  
E  
E

Nitroimidazole  
backups ★  
Oxaleish ★

VL-2098 ★

Fexinidazole ★

New VL treatments  
for Bangladesh

SSG&PM  
Sodium Stibogluconate  
& Paromomycin  
Combination Therapy  
for VL in Africa

CpG-D35  
(CL) ★

Anfoleish  
(CL) ★

New treatments for  
HIV/VL co-infection  
for Africa

New VL treatments  
for Latin America

Generic Ambisome

New VL  
Treatments  
for India

● Chagas

N  
I  
N  
G

Nitroimidazole ★  
Oxachagas ★

Biomarkers

Fexinidazole ★  
New Benz  
Regimens  
New  
Combinations ★

Benznidazole  
Paediatric  
Dosage Form

● Filaria

Emodepside ★

● Paediatric  
HIV

Two '4-in-1' LPV/r  
based FDC granules

RTV Superbooster  
for HIV/TB co-infection

LPV/r pellets with  
dual NRTI FDC

● Malaria

ASAQ FDC  
Artesunate-Amodiaquine  
Fixed-Dose Combination

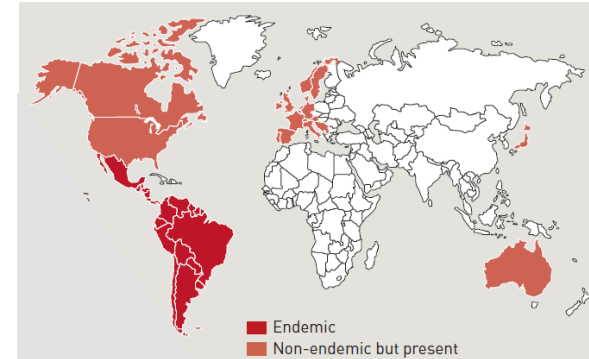
ASMQ FDC  
Artesunate-Mefloquine  
Fixed-Dose Combination

★New Chemical Entity (NCE); Fexinidazole (for HAT, VL, and Chagas disease) = 1 NCE



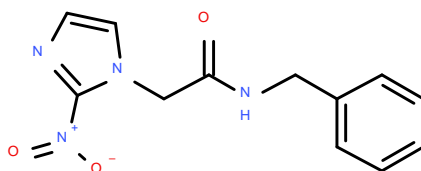
# Chagas Disease (CD)

- ❑ 100 million at risk in Latin America
  - ❑ Transmitted by triatomine insects, blood transfusion, organ transplantation, congenitally or orally
- ❑ 7.6 million people affected by CD
    - ❑ Largest parasitic cause of death in western hemisphere
    - ❑ Leading cause of cardiomyopathy
    - ❑ Kills more people in region than malaria
    - ❑ Patient number growing in non-endemic, developed countries
    - ❑ Majority of patients undiagnosed until late stage
- ❑ To date, geographical separation of CD and VL has led to little co-infection



# Drugs for Chagas Disease

*Limited options in one class*



MW 260, clogP 0.90

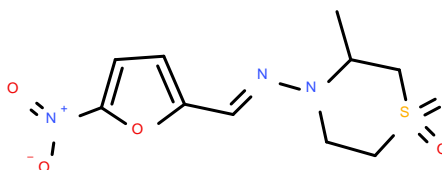
**Benznidazole**

po

5-7 mg/kg/day  
10 mg/kg/day in children  
40-80 days

variable efficacy

- GI toxicity
- dermatological



MW 287, clogP 0.02

**Nifurtimox**

po

8-10 mg/kg/day, TID, 12-20  
mg/kg/day in children  
60-120 days

variable efficacy

- GI toxicity
- dermatological
- dizziness
- headache

- Long treatments & variable efficacy
- Serious toxicities resulting in 20-30% discontinuations
- Urgent need for new effective, safe, and convenient treatments

# Chagas Disease – Target Product Profile

	Acceptable	Ideal
<b>Target population</b>	Chronic	Chronic and Acute (Reactivations)
<b>Strains</b>	TcI, TcII, TcV and TcVI (according to new 2009 classification)	All according to new classification (2009)*
<b>Distribution</b>	All areas	All areas
<b>Adult/children</b>	Adult	All
<b>Clinical efficacy</b>	Non inferior to benznidazole in all endemic regions (parasitological)	Superiority to benznidazole to different phases of disease (acute and chronic) (parasitological)
<b>Safety</b>	Superiority to benznidazole ** 3 CE plus 2 standard LE or ECG during treatment	Superiority to benznidazole or nifurtimox No CE or LE or ECG needed during treatment
<b>Activity against resistant strains</b>	Not necessary	Active against nitrofurantoin- and nitroimidazole-resistant <i>T. cruzi</i> strains
<b>Contraindications</b>	Pregnancy/lactation	None
<b>Precautions</b>	No genotoxicity; No pro-arrhythmic potential	No genotoxicity; No teratogenicity; No negative inotropic effect; ; No pro-arrhythmic potential
<b>Interactions</b>	No clinically significant interaction with anti-hypertensive, anti-arrhythmic and anticoagulants drugs	None
<b>Presentation</b>	Oral	Oral
<b>Stability</b>	3 years, climatic zone IV	5 years, climatic zone IV
<b>Dosing regimen</b>	Comparable to systemic antifungal treatments	Once daily/ 30days



# Lessons for Discovery from DNDi'S first 10 years

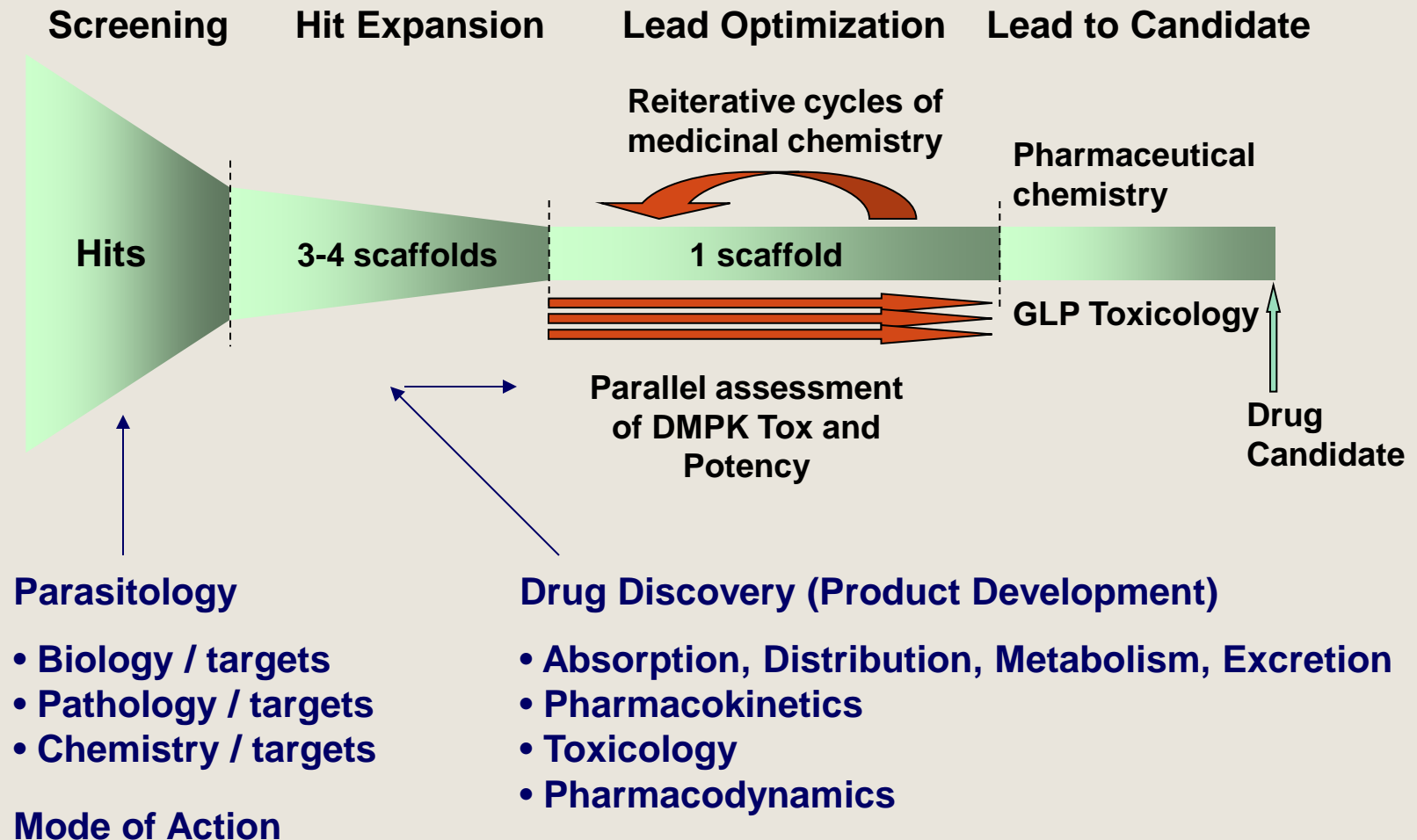
- An evolving Discovery model
  - ▣ Switch from awarding grants to building focused consortia
  - ▣ Increased engagement with Pharma companies
- Phenotypic focus
  - ▣ Paucity of well validated drug targets
  - ▣ Success with phenotypic approach
- Compound sources
  - ▣ Access to large, high quality Pharma libraries - AbbVie, Astellas, AZ, Eisai, GSK, Merck, Pfizer, Sanofi,...
  - ▣ Re-purposing & large diverse collections
- Screen platforms
  - ▣ Huge leaps in screening through application of new technologies and industrial approaches – HCS, logistics and data management
- H2L & LO consortia
  - ▣ Successful biotech/academic/pharma/consultant collaborations yielding NCEs

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*Iniciativa Medicamentos para Enfermedades Olvidadas*



# The Science(s) of Lead Optimization

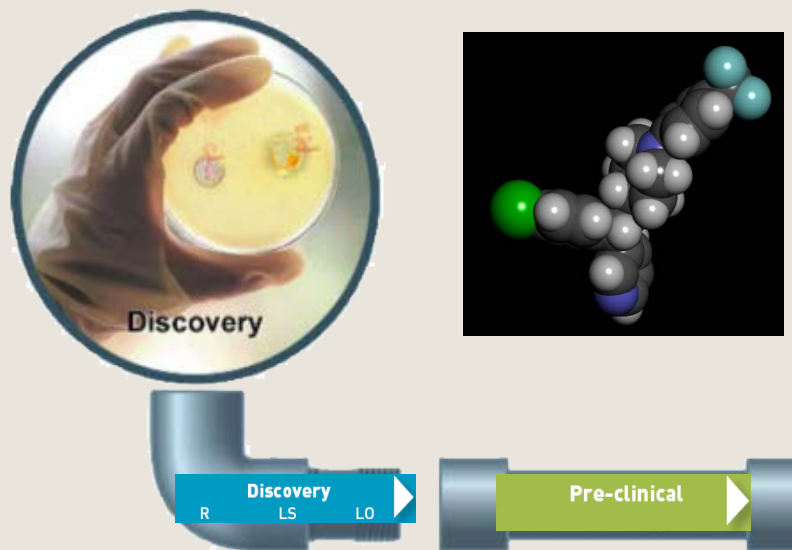


# Lead Optimization Consortia

## From Hit to Potential Pre-Clinical Candidate



Research



### Key partners:

CDCO/Monash University, Epichem, Griffith University, WuXi, iThemba, Sandexis, LMPH, LSHTM, Swiss TPH, UNICAMP, Anacor, Pfizer, Sanofi, AbbVie, GSK

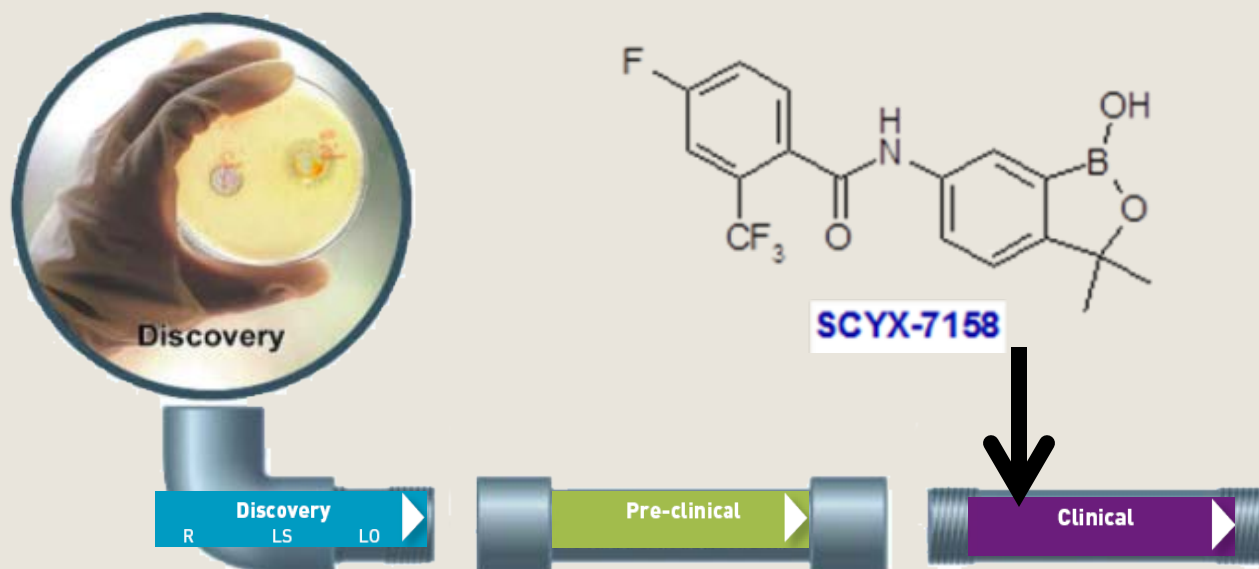
### A global network:

Australia, Belgium, Brazil, China, South Africa, Spain, Switzerland, UK, USA

- ❑ Continued evolution
  - ❑ 3 Consortia (1 in endemic country, LOLA)
  - ❑ Shared resources
- ❑ VL and Chagas are priority
- ❑ Access to series from Pharma
- ❑ New candidates already issued from:
  - ❑ Oxaboroles series (Anacor, USA)
  - ❑ Nitroimidazoles (Univ. of Auckland, NZ)
- ❑ Further chemical series in optimization
- ❑ Translational challenges being tackled
  - ❑ New tools/assays developed
  - ❑ Better understanding of PK/PD relationship for these diseases

# Oxaborole SCYX-7158 for HAT

## From Lead Optimization to Clinical Candidate



Potential to be oral,  
effective against  
both stages 1 and 2

- Identified as hits against *T. brucei* at Sandler Center, showed activity in animal models of HAT
- Innovative US partnership with 2 biotechs and 1 university
- First candidate issued from DNDi Lead Optimization Programme
- Clinical Phase I study nearly complete

Key partners:

Scynexis, Anacor, Pace University,

Sandler Center UCSF, Swiss TPH

# Future directions for discovery

- Build on progress of last 10 years
- Increased number of contributors in NTD drug Discovery
  - e.g. GSK, DDU, GNF, ...
- Bilateral and multilateral collaborations with pharma companies
  - NTD Drug Discovery Booster
- New technologies, open innovation & exploiting more of the data
  - Identification of new series and more rapid optimisation
- Harnessing scientific expertise & capacity in endemic regions
  - Lead Optimisation Latin America (LOLA)

Richard Glynne, GNF  
José M. Fiandor, GSK

James Mills, Sandexis

Luiz Carlos Dias,  
UNICAMP

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# Thank you!

## Science:



## Libraries:



## Funding:



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

