

New Drugs to Treat Neglected Tropical Diseases

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July 9, 2011

DNDi

Drugs for Neglected Diseases *initiative*



Outline

- Introduction & Background
- Example of Sleeping Sickness
- Snapshot of Other DNDi Projects, Access Strategy & Funding
- Global Policy Priorities & Conclusions

Neglected Diseases: Current Treatment Limitations



Melarsoprol



Eflornithine

- Ineffective (resistance)
- Toxic
- Expensive
- Painful when delivered
- Difficult to use
- Not registered in endemic regions
- Restricted by patents

We Need Safe, Effective, Easy-to-Use Drugs

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**

Project Portfolio (June 2011)

Discovery

HAT LO Consortium
- *Scynexis*
- *Pace Univ.*

VL LO Consortium
- *Advinus*
- *CDRI*

Chagas LO Consortium
- *CDCO*
- *Epichem*
- *Murdoch Univ.*
- *FUOP*

Major Collaborators:

- Sources for hit and lead compounds:
GSK, Anacor, Sanofi, Merck, Pfizer, Novartis (GNF, NITD), TB Alliance,...
- Screening Resources:
Eskitis, Institut Pasteur Korea, Scynexis, U. Dundee,...
- Reference screening centres:
LSHTM, Swiss Tropical & Public Health Institute, University of Antwerp

Pre-clinical

Nitroimidazole backup (HAT)

Oxaborole SCYX-7158 (HAT)

Alternative formulations of Amphotericin B (VL)

Nitroimidazole (VL)

Drug combination (Chagas)

K777 (Chagas)

Flubendazole
Macrofilaricide (Helminth)

Exploratory

Clinical

Fexinidazole (HAT)

New VL treatments –
Bangladesh

New VL treatments –
Africa

New VL treatments –
Latin America

Benznidazole
Paediatric dosage form
(Chagas)

Azoles E1224
& Biomarker (Chagas)

Paediatric HIV
(exploratory)

Exploratory

Implementation

ASAQ (Malaria)
Fixed-Dose Artesunate/
Amodiaquine

ASMQ (Malaria)
Fixed-Dose Artesunate/ Mefloquine

NECT (Stage 2 HAT)
Nifurtimox – Eflornithine
Co-administration

SSG&PM co-administration
VL in Africa

New VL treatments in Asia
(SD AmBisome[®],
PM+M / A[®]+M / PM+ A[®])

Available

Four Products Making a Difference

2007

ASAQ (Malaria)
Fixed-Dose
Artesunate/
Amodiaquine



Main Partners

sanofi-aventis
(France)

2008

ASMQ (Malaria)
Fixed-Dose
Artesunate/
Mefloquine



Farmanguinhos
(Brazil)
Cipla
(India)

2009

NECT
Nifurtimox -
Eflornithine
Combination
Therapy (HAT)



National Control Programs
MSF / Epicentre
Bayer / sanofi-aventis
WHO

2010

SSG&PM
SSG-paromomycin
co-administration
(VL)



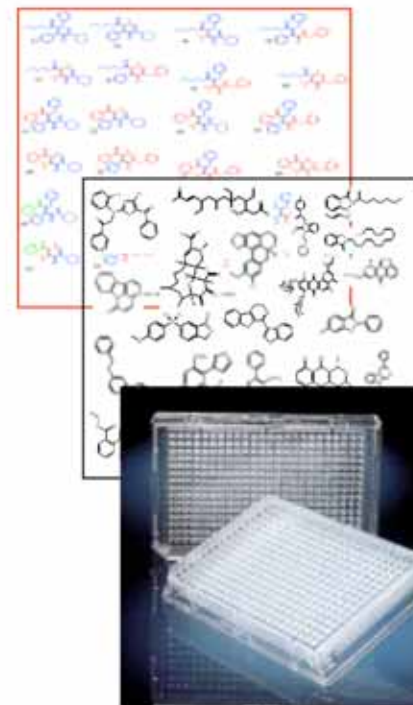
LEAP
National Programs
iOWH

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

Discovery - Building the Pipeline

2 Key Breakthroughs

- 1) Access to libraries of compounds for chemical diversity
 - Agreements with Merck, Pfizer, Sanofi, Genomics Institute of the Novartis Research Foundation (GNF), others in negotiation
- 2) Access to High Throughput Screening capacity for HAT, VL and Chagas
 - Available at Eskitis (HAT) and Institut Pasteur Korea (VL + Chagas)



Discovery – Building the Pipeline Capacity to Optimize Leads



HAT Lead Optimization Consortium

Scynexis, Pace University



VL Lead Optimization Consortium

Advinus Therapeutics,
Central Drug Research Institute

Chagas Lead Optimization Consortium

CDCO, Epichem, Murdoch University,
University of Ouro Preto

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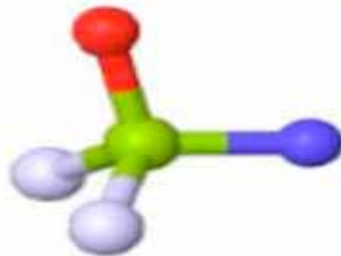
Sleeping Sickness: Success & Progress at Each Stage



Discovery

Preclinical

Oxaboroles



Anacor, Scynexis
Inc, Pace
University,
HIKMA

Clinical

Fexinidazole
Phase I



Sanofi

Implementation

NECT



WHO, Nat. Prog., MSF

Oxaboroles SCYX-7158

First DNDi Preclinical Candidate Issued from Lead Optimization Program



Key partners include:

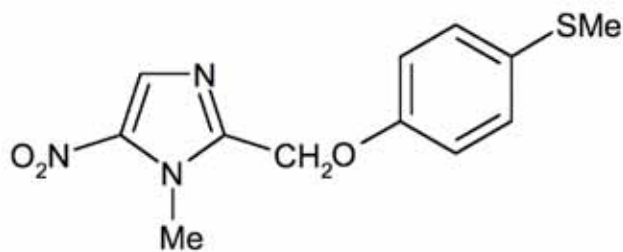
- Anacor Pharmaceuticals
- SCYNEXIS
- Pace University

- Identified as hits against *T. brucei* at the Sandler Center, University of California, San Francisco, and have shown activity in animal models of sleeping sickness
- Innovative partnership between 2 US biotechs, 1 US university
- Completion of preclinical study; results published in PLoS NTD (June 2011)
- Ready to enter clinical development
- Potential to be oral, effective against both stage 1 and 2

Fexinidazole

In Phase I through Compound Mining

Objective: Drug candidate to become an oral, short course treatment for stage 1+ 2 sleeping sickness treatment, caused by either *T.b. gambiense* or *T.b. rhodesiense*



- 5-nitroimidazole
- In preclinical development by Hoechst in 1980s as broad-spectrum anti-protozoal
- Oral activity, distributes to the brain
- Curative in mouse models of HAT (both acute and chronic)
- Good safety profile in animal studies, including no evidence of mammalian genotoxicity
- Preclinical development including ADME-PK, GLP-toxicology and safety pharmacology completed; prototype tablets available
- Phase I clinical trials started in September 2009 in Paris
- Agreement to co-develop with Sanofi

NECT

Implemented in 10 Countries Since 2009

- Nifurtimox-eflornithine combination therapy (NECT): A simplified, safe & effective treatment for stage 2 HAT
- NECT included on WHO Essential Medicines List (May 2009)
- Over 6,000 treatments distributed
 - End 2010: >60% of all stage 2 patients treated with NECT
- 600 patients included in NECT-Field study
- **Work with WHO and national programs to facilitate availability**



Strengthening Clinical Trial Capacity

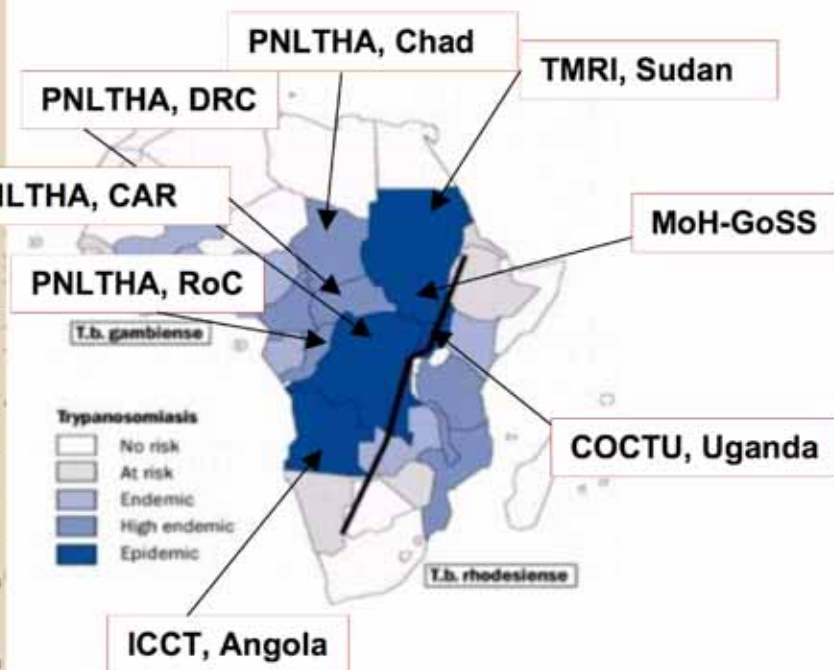


Objectives:

- To strengthen clinical trial capacity for sleeping sickness
- To overcome health system challenges for clinical research
- To share information on HAT research progress
- To improve HAT clinical trial methodologies

Partners:

- National HAT control programs of most affected endemic countries
- DNDi, Swiss TPH
- Research institutes like ITMA, INRB, CDC, KARI-TRC
- NGOs like MSF, Epicentre
- FIND, WHO
- Regional networks - eg. EANETT, PABIN, AMANET



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Leishmaniasis: A Strong Pipeline



From innovative discovery to
clinical demonstration of efficacious
combination treatments

Discovery

Preclinical

Clinical

Implementation

High-Troughput
Screening at IPK

Nitroimidazoles



Synergy between
PDPs

New VL
Treatments –
Asia (India, Nepal,
Bangladesh)

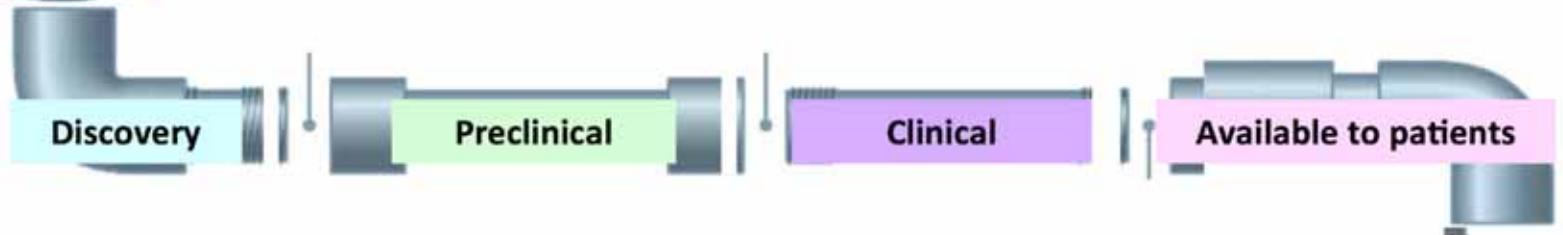


New VL
Treatments –
Africa /
SSG&PM

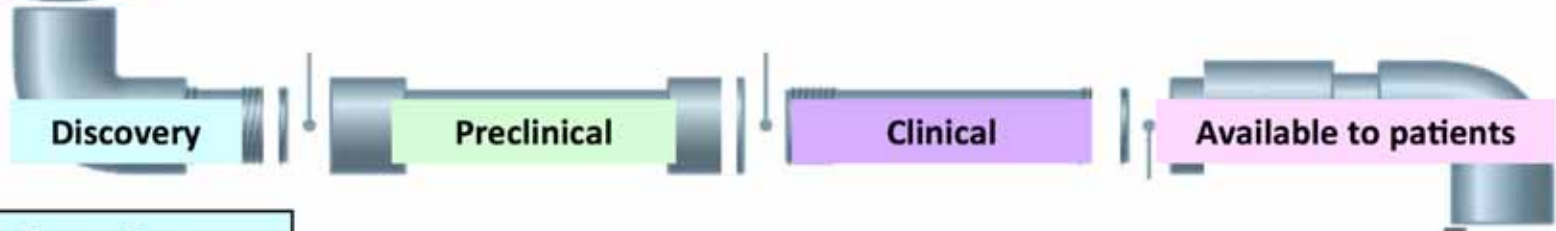


Advinus, CDRI,
IRD, Anacor

Chagas: Consolidating our Portfolio



Chagas: Consolidating our Portfolio



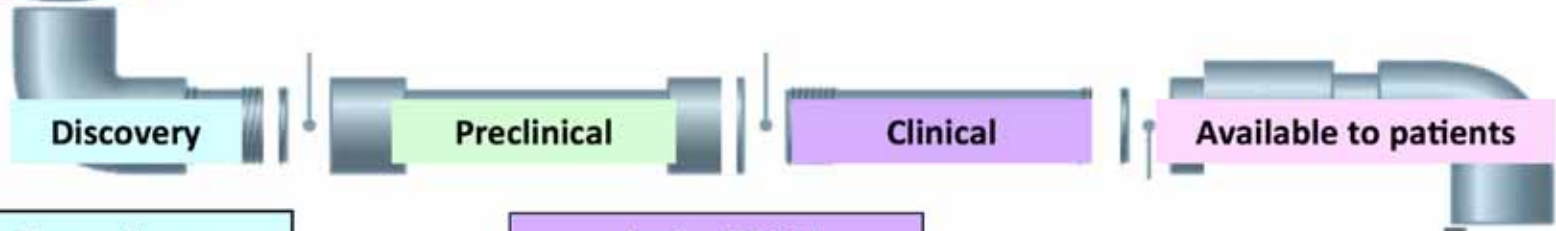
Lead opt. Consortium



Chagas: Consolidating our Portfolio



Discovery



Discovery

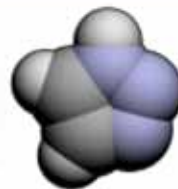
Preclinical

Clinical

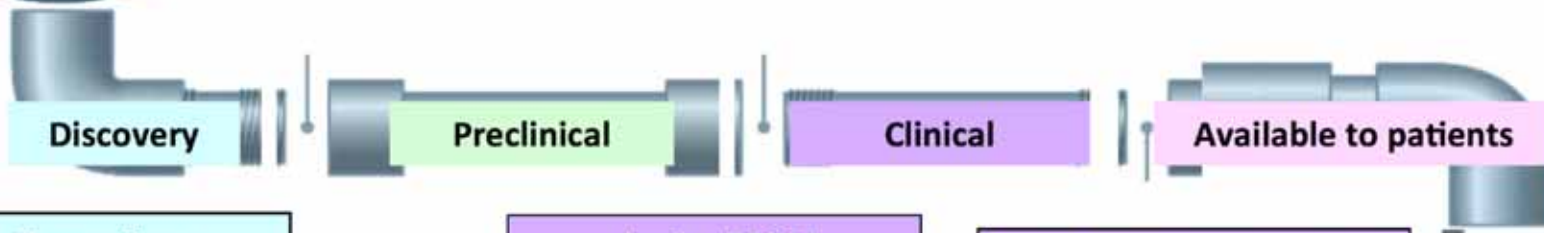
Available to patients

Lead opt. Consortium

Azoles E1224
Phase II



Chagas: Consolidating our Portfolio



Lead opt. Consortium

Azoles E1224
Phase II

Paediatric Benznidazole

cdco
Murdoch UNIVERSITY
epichem
UFOP

Eisai
CRESIB BARCELONA
Chagas

LAFEPE

Malaria: DNDi's FACT Project

2 New Antimalarial Treatments Delivered

- Initial objectives:
 - **Response** to public health need
 - **Easy** to use
 - **Affordable**
 - **Available** as public goods
- Today: support implementation of **ASAQ** (artesunate-amodiaquine) and **ASMQ** (artesunate-mefloquine)
 - **ASAQ**: Prequalified; 3 year shelf life; **over 80 million treatments distributed in 30 countries.**
 - **ASMQ**: Registered and implemented in Brazil; technology transfer to Cipla completed; registration ongoing in Asia; further development in Africa started.

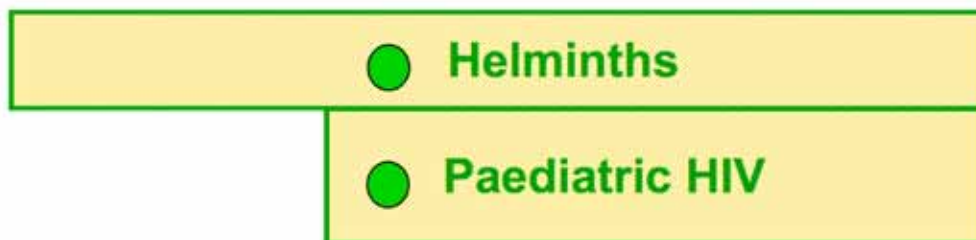
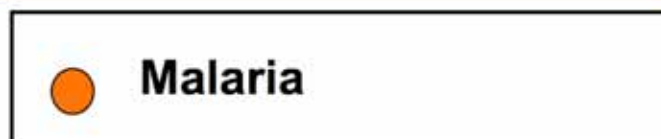
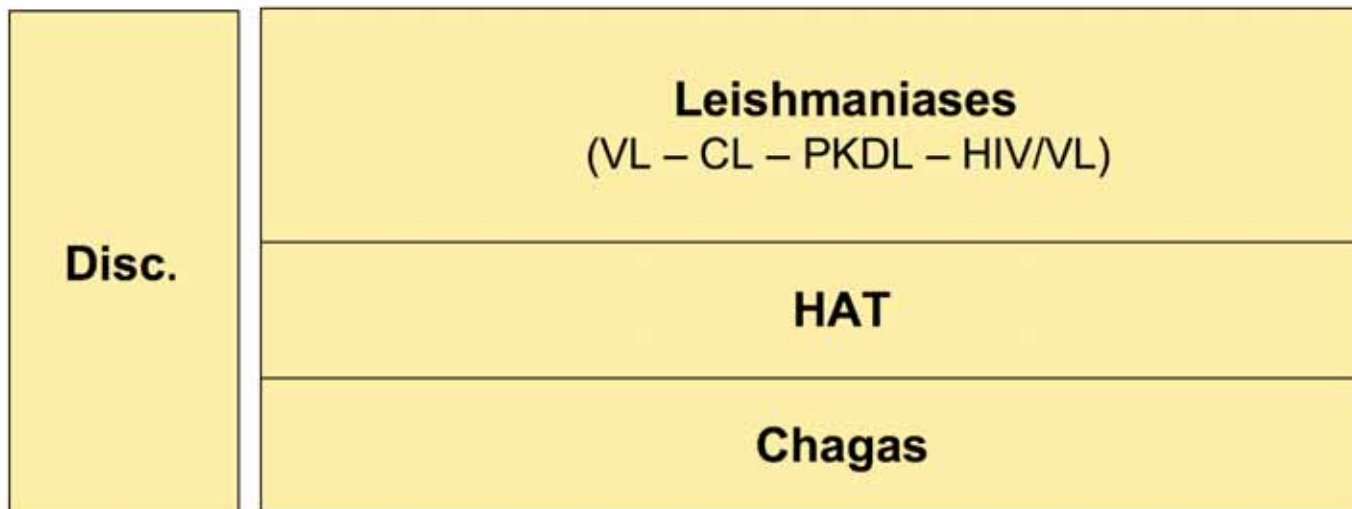
ASAQ (Sanofi)



ASMQ (Farmanguinhos)



Evolution of DNDi Disease Portfolio



“Mini portfolios”

- To be built
- To complete

Helminths

(LF-Onchocerciasis)

Need safe and efficacious macrofilaricide

- To offer case management tool
- To achieve control of oncho. and LF worldwide
- To offer MDA in *Loa loa* co-endemic areas (Africa)

Objectives

- Short course for MDA (1 day)
- 10-14 days p.o./i.m. for case mgt

Flubendazole

- Promising “low-hanging fruit” opportunity
- Small human study reported in literature
- Will explore other new drugs in animal health

US\$ 239M Secured of US\$ 330M Needed (2004-2014)

Private Donors

- Doctors Without Borders/Médecins Sans Frontières (US\$ 62M)
- Bill & Melinda Gates Foundation (US\$ 59M)
- Other Private Foundations (US\$ 1.4M)

Public Donors

- United Kingdom - DFID (US\$ 44.5M)
- Netherlands – DGIS (US\$ 24.5 M)
- Spain – AECID (US\$ 14.4M)
- France – AFD & MAEE (US\$ 13.4M)
- Switzerland – SDC & Geneva (US\$ 6M)
- USA – NIH/NIAID (US\$ 2.6M)
- European Union – FP 5,6,7& EDCTP (US\$ 1.7M)
- Germany – GTZ (US\$ 1.4M)
- The Global Fund – AMFm (US\$ 0.3M)



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- Key NTD Policy Issues
- **Global Policy Priorities & Conclusions**

Role of the US Government

- Largest financial supporter of neglected disease R&D and significant increased attention to NTDs in past 5 years
- Key opportunities in 2011 and beyond
 - **NIH:** Long-standing support for basic research/early clinical development; traditional grant structures can be challenging for product development partnerships
=> **New initiatives (e.g. new translational sciences center) could potentially bridge key gaps**
 - **USAID:** Focus only on 7 NTDs and existing tools
=> **NTD Program could expand disease scope and invest in late-stage product development (aligning with other disease areas, e.g. HIV/AIDS, TB, malaria)**

Global Policy Priorities to Increase Needs-Driven R&D and Ensure Access

1. Increase resources and incentives for neglected disease R&D
 - **Innovative sustainable financing** mechanisms, particularly for late-stage product development (key role for USAID, UNITAID, etc.)
 - Pilot milestone **prizes** (and/or final product prizes) to stimulate discovery
 - Ensure that **access** is addressed as fundamental goal of any R&D incentives or financing mechanisms
2. Improve efficiency and reduce duplication in R&D efforts
 - **Innovative IP management, open innovation, sharing of knowledge**
3. Enable innovative regulatory pathways to expedite access
 - **Involve endemic country regulators** in regulatory assessments
 - **Extend WHO's prequalification** role to NTDs
 - **Strengthen regulatory capacity**, particularly in Africa

Conclusions

- **Significant progress made in delivering new treatments (DNDi is just one example):**
 - ✓ 2 new malaria treatments; 1 new HAT combination; 1 new VL combination for Africa
 - ✓ Promising new drug candidates in pipeline
- **Key policy changes at USG and international level needed to increase NTD R&D and ensure a “global framework for essential health R&D”**
 - ✓ Expand scope of NTD Program to include other diseases and support late-stage product development
 - ✓ Maintain central role of WHO to define priorities, develop guidelines, etc.
 - ✓ Ensure key role for endemic countries to identify needs, participate as R&D partners, take part in regulatory reviews



Best
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most
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www.dndi.org