DNDi Strategy for the Development of New Treatments for Chagas Disease

Isabela Ribeiro & Shing Chang
DNDi
July 2009
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)

7 worldwide offices

- Geneva Coordination Team + consultants
- USA
- Japan
- DRC
- India
- Malaysia
- Kenya
- Brazil
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

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- **Long-Term projects**
  - New compounds
  - Screening of existing libraries
  - >6 years

- **Medium-term projects**
  - Therapeutic switch
  - “Rediscovered” compounds
  - 3-6 years

- **Short-term projects**
  - New formulations (FDC)
  - Geographical extensions
  - Co-administration
  - ≤3 years
DNDi Portfolio – June 2009

**Discovery**
- Compound mining
  - E.g.: nitroimidazoles, ...
- Chemical classes
  - E.g.: GSK, Merck, ...
- Target-based
  - E.g. Dundee’s Drug Discovery Unit (DDU), Microtubule inhibitors...
- Screening
  - E.g. natural products (Kitasato, Eskitis), new technology (Institut Pasteur Korea), DDU at Dundee, CDRI screening ...

**Pre-clinical**
- Alternative formulations
  - Amphotericin B – in preparation (VL)
- Drug combination
  - (Chagas)
- Nitroimidazole backup (HAT)
- Oxaborole (HAT)
- Exploratory

**Clinical**
- Fexinidazole (HAT)
- Combination therapy (VL in Asia)
- Combination therapy (VL in Africa)
  - Paromomycin
  - AmBisome®
  - Miltefosine – In preparation
- Combination therapy (VL in Latin America) – In preparation
- Pediatric benznidazole
  - (Chagas)
- Azoles (Chagas)
- 8-aminoquinolines – In preparation (VL)
  - Sitamaquine
  - Tafenoquine
- Exploratory

**Available**
- NECT
  - Nifurtimox - Eflornithine Co-Administration Stage 2 HAT
- ASMQ
  - (Malaria) Fixed-Dose Artesunate/Mefloquine
- ASAQ
  - (Malaria) Fixed-Dose Artesunate/Amodiaquine

**Reference screening centres:**
- LSHTM, Swiss Tropical Institute, University of Antwerp

**Exploratory**
- a robust pipeline

6 to 8 new treatments
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
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**

**Long-term projects**
- GAP 1: Lacking basic research and preclinical research due to lack of funding
- Preclinical: Combination therapy
- Clinical: Paediatric benznidazole
  - Existing Azoles
  - Chagas Clinical Research Platform

**Medium-term projects**
- GAP 2: Validated drug candidates don’t enter clinical development
- Preclinical: Cysteine protease inhibitors

**Short-term projects**
- GAP 3: Patient can’t access drugs due to cost, availability, adaptability…

**DNDi 2009 Portfolio**
- Cysteine protease inhibitors
- Pyridones (GSK)
- Nitroimidazoles
- Chagas LO Consortium: CDCO, Epichem, Murdoch Univ.

**Other Active Projects**
- Sterol biosynthesis inhibitors
  - Promising compounds: Azoles, squalene synthase inhibitors, farnesyl pyrophosphate synthase inhibitors (FPPS), farnesyl transferase inhibitors, DHFR inhibitors, natural products

**Success rate**
- Long-term: ~1/10
- Medium-term: ~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
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
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 desirableazole, 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
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*
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
Reasearch on Neglected Diseases
Time to Treat
Chagas Disease!

WAKE UP!

Coming soon WWW.TREATCHAGAS.ORG

Chagas Campaign:
Raising Awareness of Silent Killer

www.treatchagas.org
Thank you to all our donors including:

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

www.dndi.org