DNDi Strategy for the Development of New Treatments for Chagas Disease

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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
**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**
- **2 HAT LO Consortiu m**
  - Scynexis
  - Pace Univ
- **VL LO Consortiu m**
  - Advinus
  - CDRI
- **Chagas LO Consortiu m**
  - CDCO
  - Epichem
  - Murdoch Univ

**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
- Paediatric benznidazole (Chagas)
- Azoles (Chagas)
- 8-aminoquinolines – in preparation (VL)
  - Sitamaquine
  - Tafenoquine

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

**Exploratory**
- 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 ...

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

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**

**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**
- ~1/10

**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**
- Combination therapy
- Cysteine protease inhibitors

**Clinical**
- Paediatric benznidazole
- Existing Azoles
- Chagas Clinical Research Platform
Paediatric Benznidazole

- Registration by Roche in 1971, now licensed to Lafeppe
- 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:** Lafeppe (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
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

- Data Analysis
  - Model Building
- Drug Candidate
- Scale-up Synthesis
- Synthesis/Acquisition
- In vitro Activity
  - In vitro PK
- In vivo Activity
  - In vivo PK
- In vitro PK and Metabolization
- Physicochemical Profiling

Legend:
- In vitro optimization
- In vivo optimization
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
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