Développement des nouvelles thérapeutiques pour la leishmaniose et la trypanosomose humaine africaine

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Tropical diseases and tuberculosis account for 12% of the global disease burden but only 1.3% of new drugs developed.

• DNDi 2003: a new collaborative, patient’s-needs driven, not-for-profit drug R&D model for neglected diseases

• **Primary Objective:**
  – To deliver 6 - 8 new treatments by 2014 for leishmaniasis, sleeping sickness, Chagas disease, malaria
20 projects in DNDi’s portfolio, May 2006

**Discovery**
- Trypanothione reductase inhibitors (leish & tryps)
- Novel nitroheterocycles (HAT)
- Benzofuroxans (Chagas)
- Cysteine protease inhibitors (HAT)
- Ascofuranone (HAT)
  - Dihydrofolate reductase – inhibitors (leish, tryps)
  - Nitroimidazoles (tryps)
- Kitasato screening (HAT)
- CDRI screening (HAT)
- Microtubule inhibitors (HAT)
  - Ravuconazole (Chagas)

**Pre-Clinical Development**
- Nifurtimox - Eflornithine (HAT)
- Artesunate-Amodiaquine combination (malaria)
- Artesunate-Mefloquine combination (malaria)
- Paromomycin (VL in East Africa)
- Imiquimod (CL – S America)
  - Drug combinations (VL)
  - Amphotericin B polymer (VL)
  - AmBisome (leish in Africa)

**Clinical Development**
- In contractual discussion or pro-active

**Availability to patients**
- Ongoing
Sleeping sickness is a most neglected disease

- An estimated 300,000 infected
- 55 million at risk in sub-Saharan Africa
- Difficult to diagnose
- **Fatal** if untreated
- Existing drugs: old, toxic, resistance, difficult to use, expensive

Source: WHO 2001
Current pipeline for HAT

**Discovery**
- Trypanothione reductase inhibitors (leish & tryps)
- Novel nitroheterocycles
- Cysteine protease inhibitors
- Ascofuranone
- Dihydrofolate reductase inhibitors (leish & tryps)
- Nitroimidazoles (tryps)
- Kitasato screening
- CDRI screening
- Microtubule inhibitors
- **Exploratory** screening, compound ‘mining’, drug ‘switching’ (leish, HAT, Chagas)

**Pre-Clinical Development**
- Nifurtimox - Eflornithine
- Short-course pentamidine
- Pafuramidine (DB289)

**Clinical Development**
- **Ongoing**
- In contractual discussion or pro-active
- Other groups

**Availability to patients**
- Diamidines
Discovery
Nitroimidazoles project for trypanosomiasis

OBJECTIVE: To identify new drug candidates amongst old and new nitroimidazoles for trypanosomiasis

- Sanofi-aventis, France
- Chiron, USA
- Novartis, Switzerland, Singapore
- Alkem, India
- Swiss Tropical Institute
- Fiocruz, Brazil
- U of Sao Paolo, Brazil
- U of Kerman, Iran
- U of Bologna, Italy
- U of Marseille, France
- Prof Nagarajan, India
OBJECTIVE: To screen DHFR inhibitors against the enzymes from *T. brucei*, *T. Cruzi*, *L. donovani* and humans.
OBJECTIVE: To identify compounds and extracts with selective activity against *T. brucei*, for hit-to-lead and lead optimisation
2nd stage sleeping sickness – NECT nifurtimox- eflornithine combination

Start 2004: DNDi -TDR collaboration to study safety and efficacy of NECT combination in Democratic Republic of Congo

Bayer Nifurtimox

Clinical Trials Material Supply Agreement

WHO / TDR

TDR-sponsoring
DNDi-sponsoring

TDR/DNDi expert group
Controlled cohort studies
PI initiated

WHO CPE
Named patient program
"Compassionate use"

Clinical data to establish risk-benefit in HAT as a basis for treatment recommendations and decision on option of publication based registration

DNDi
Drugs for Neglected Diseases initiative
Clinical trial sites for NECT study for stage 2 HAT

- 3 DNDi sponsored sites
- 1 MSF-sponsored site
- 1 (or 2) TDR sponsored sites

Partners include: Epicentre, MSF-H, MSF-B, STI, PNLTHA DRC, PNLTH RoC, COCTU Uganda, ICCT Angola, WHO/TDR, Belgian cooperation
HAT Clinical Trials Platform

National HAT control programmes of most affected endemic countries

- DNDi
- Swiss Tropical Institute
- FIND Diagnostics
- WHO / TDR

Other partners:
- NGOs working in HAT control
- National and international research groups involved in HAT

Map showing affected countries:
- Democratic Republic of Congo
- Sudan
- Angola
- Uganda
- Republic of Congo

T. b. gambiense

T. b. rhodesiense

At risk
Endemic
High endemic
Epidemic
No risk
Leishmaniasis: 350 million at risk

- An estimated 12 million people affected in 88 countries
  - Different forms: visceral, (muco)cutaneous, PKDL
- Per year: 1-1.5 million new cases of CL/MCL; 500,000 cases of VL
- VL is fatal if left untreated
- Existing drugs: old, toxic, resistance, difficult to use, expensive
Current pipeline for Leishmaniasis

**Discovery**
- Trypanothione reductase inhibitors
- Dihydrofolate reductase inhibitors (leish & tryps)
- 8-aminoquinoline (with MMV)
- Amphotericin B Polymer

**Pre Clinical**
- Ambisome for VL (Africa)
- Drug combinations for VL

**Clinical**
- Paromomycin for VL in East Africa
- Imiquimod for CL in South America
- Paromomycin for VL in India
- Miltefosine for VL
- Azoles for CL
- Sitamaquine for VL
- Miltefosine for CL

**Availability to patients**
- Paromomycin for VL in India

**Basic research:** genomics, proteomics, target identification and validation, mechanism of action studies

**Exploratory** screening, compound ‘mining’, drug ‘switching’ (leish, HAT, Chagas)

**Ongoing**

**In contractual discussion or pro-active**

**Other groups**
Proposed partnerships for kala azar drug combinations in India & Nepal

Objective:
Combine existing kala azar drugs such as miltefosine, paromomycin, and liposomal amphotericin B to provide a shorter treatment regime & avoid resistance.
Clinical development
Paromomycin for visceral leishmaniasis in Africa

Objectives
- To register paromomycin (PM) as a new alternative treatment for VL in East Africa (Sudan, Ethiopia and Kenya)
- To confirm efficacy and safety of paromomycin (and SSG)
- To confirm efficacy and safety of a shorter combination course of PM/SSG
Leishmaniasis East Africa Platform (LEAP)

A group of scientists and institutions working on developing clinical trial capacity to bring new treatments to patients.

- University of Khartoum
- Federal Ministry of Health
- MSF - Holland
- Addis Ababa University
- DACA
- Ministry of Health
- Ministry of Health
- KEMRI

IOWH - India
IDA
WHO/TDR

DNDi

Countries:
- SUDAN
- ETHIOPIA
- KENYA
Every day 35,000 people die from neglected diseases.

For research on neglected diseases:

Wake up your government. Too many have sleeping sickness.

Government leadership must urgently:
- set global public health priorities
- fund R&D for neglected diseases
- provide new rules for essential health R&D

Sign the appeal
www.researchappeal.org

Urges your government to take leadership
Sign up at
www.researchappeal.org

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www.dndi.org