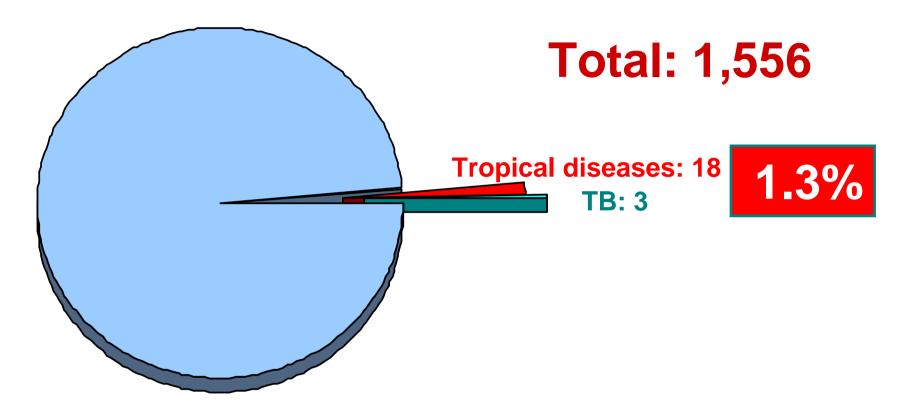
# Développement des nouvelles thérapeutiques pour la leishmaniose et la trypanosomose humaine africaine

Bernard Pécoul Directeur Exécutif, DNDi Bordeaux, Juin 2006



## New drugs developed from 1975-2004



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

Source: Chirac P, Torreele E. Lancet. 2006 May 12; 1560-1561.



 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** 

**Pre-Clinical Development** 

**Clinical Development**  **Availability** to patients

**Trypanothione reductase** inhibitors (leish & tryps)

**Novel nitroheterocycles** (HAT)

**Benzofuroxans (Chagas)** 

**Cysteine protease** inhibitors (HAT)

**Ascofuranone (HAT)** 

Dihydrofolate reductase inhibitors (leish, tryps)

Ravuconazole (Chagas)

**Nitroimidazoles (tryps)** 

**Kitasato screening (HAT)** 

**CDRI screening (HAT)** 

Microtubule inhibitors (HAT)

8-aminoquinoline (VL)

**Drug combinations (VL)** 

**Amphotericin B polymer** (VL)

AmBisome (leish in Africa)

Exploratory screening, compound 'mining', 'switching' (leish, HAT, Chagas)

**Nifurtimox - Eflornithine (HAT)** 

**Artesunate-Amodiaguine** combination (malaria)

**Artesunate-Mefloquine** combination (malaria)

Paromomycin (VL in East Africa)

Imiquimod (CL - S America)

**HAT: Human African trypanosomiasis** 

**Ongoing** 

In contractual discussion or pro-active

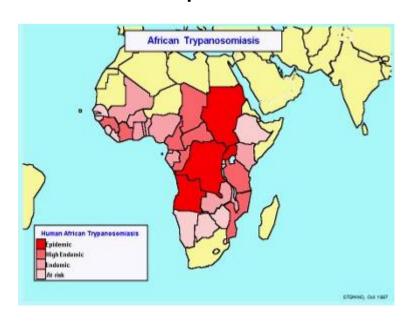
Leish: Leishmaniasis Tryps: Trypanosomiasi Chagas: South Americ

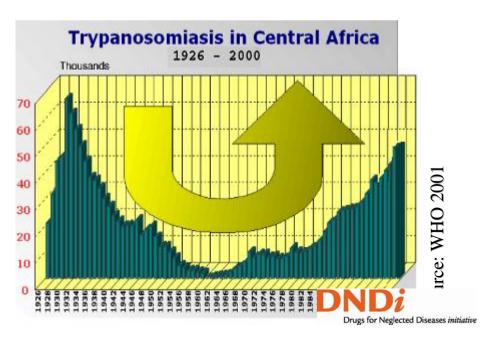
American trypanosomiasis

**Trypanosomiasis** 

# 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





**Current pipeline for HAT** 

**Discovery** 

Pre-Clinical Development

**Clinical Development** 

Availability to patients

**Trypanothione reductase inhibitors (leish & tryps)** 

**Nifurtimox - Eflornithine** 

**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)

**Diamidines** 

**Short-course pentamidine** 

Pafuramidine (DB289)

Ongoing In contract

In contractual discussion or pro-active

Other groups



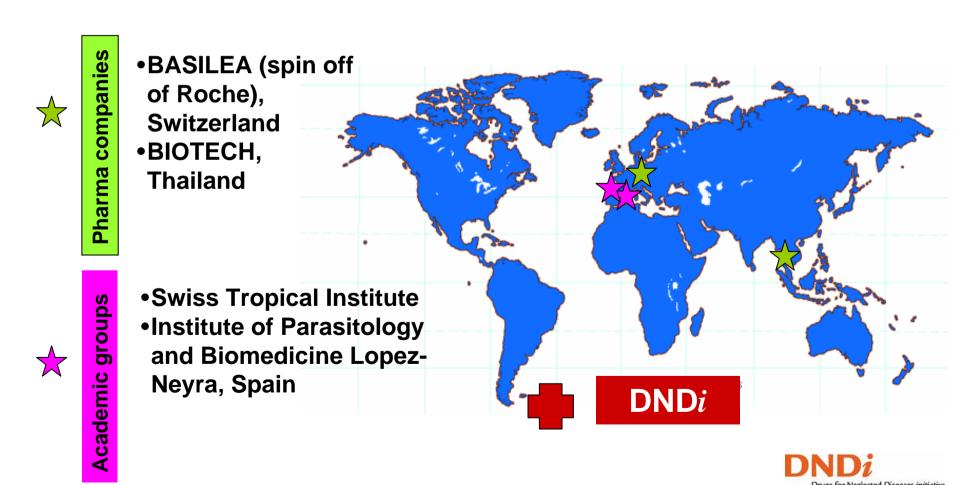
# Discovery Nitroimidazoles project for trypanosomiasis

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

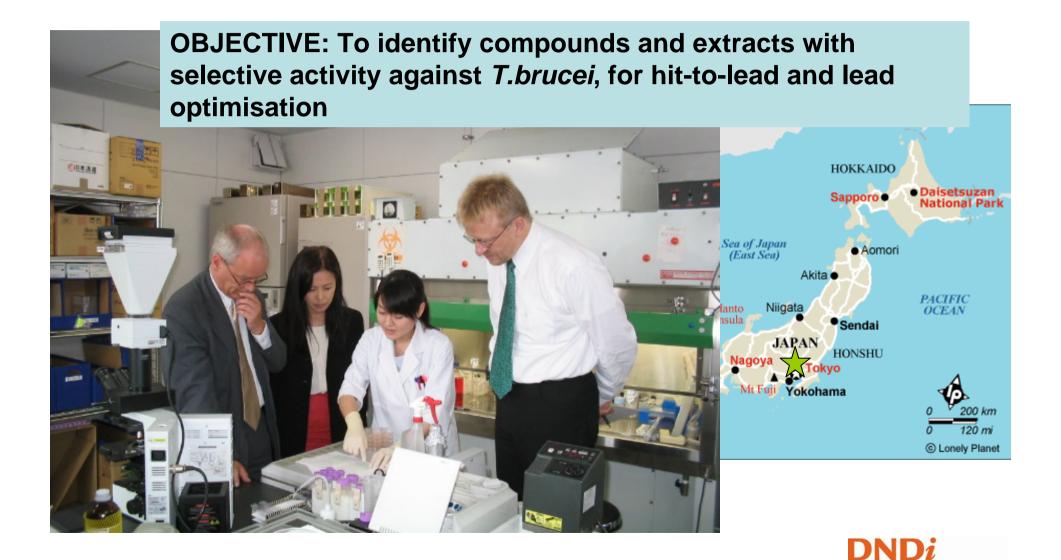
 Sanofi-aventis, France Chiron, USA Novartis, Switzerland, **Singapore** Alkem, India Swiss Tropical Institute •Fiocruz, Brazil •U of Sao Paolo, Brazil •U of Kerman, Iran •U of Bologna, Italy •U of Marseille, France •Prof Nagarajan, India

# Discovery DHFR inhibitors

OBJECTIVE: To screen DHFR inhibitors against the enzymes from *T.brucei, T.Cruzi, L. donovani* and humans



# Discovery Screening at Kitasato



Drugs for Neglected Diseases initiative

# 2<sup>nd</sup> stage sleeping sickness – NECT nifurtimox- effornithine combination

**Baver** Start 2004: DNDi -TDR collaboration **Nifurtimox** to study safety and efficacy of **NECT** combination in Democratic Clinical Trials Material Supply Agreement Republic of Congo WHO / TDR TDR/DNDi WHO CPE expert group Named patient program TDR-sponsoring Controlled cohort studies "Compassionate use" DNDi-sponsoring-PI initiated Clinical data to establish risk benefit in HAT as a basis for treatment recommendationand

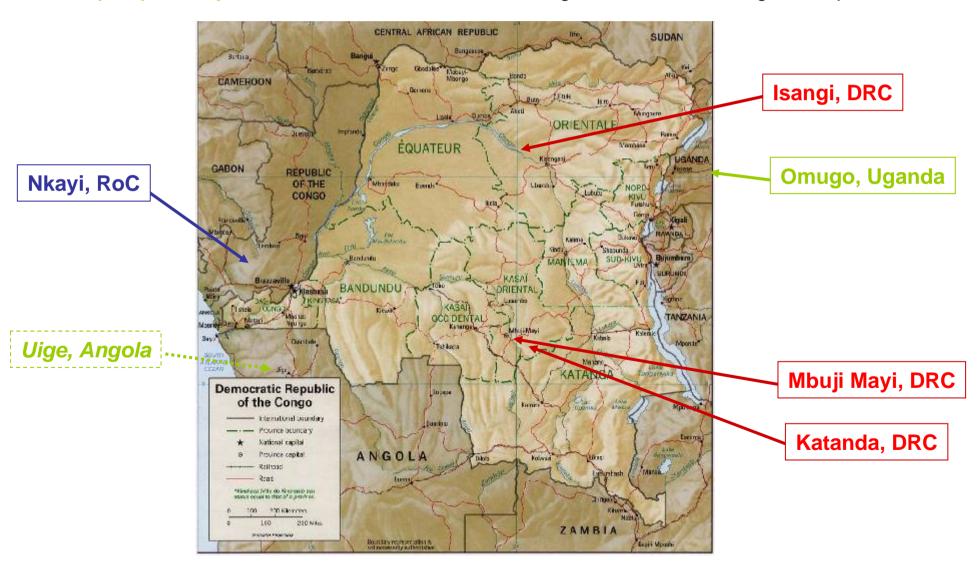
decision on option of publication based registration

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

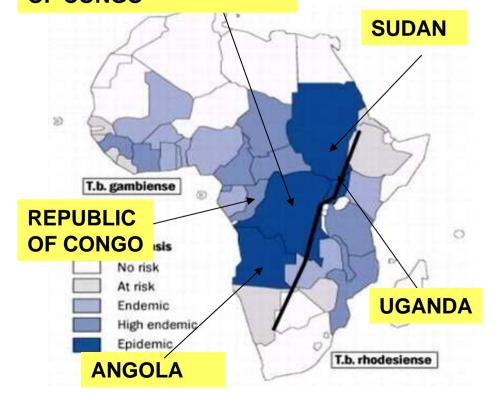
Partners include: Epicentre, MSF-H, MSF-B, STI, PNLTHA DRC, PNLTH RoC, COCTU Uganda, ICCT Angola, WHO/TDR, Belgian cooperation



### **HAT Clinical Trials Platform**



DEMOCRATIC REPUBLIC OF CONGO



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



National HAT control programmes of most affected endemic countries

#### Other partners:

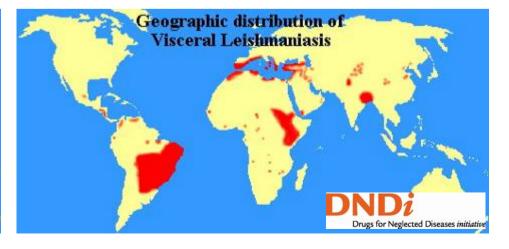
- NGOs working in HAT control
- National and international research groups involved in HAT

#### Leishmaniasis: 350 million at risk

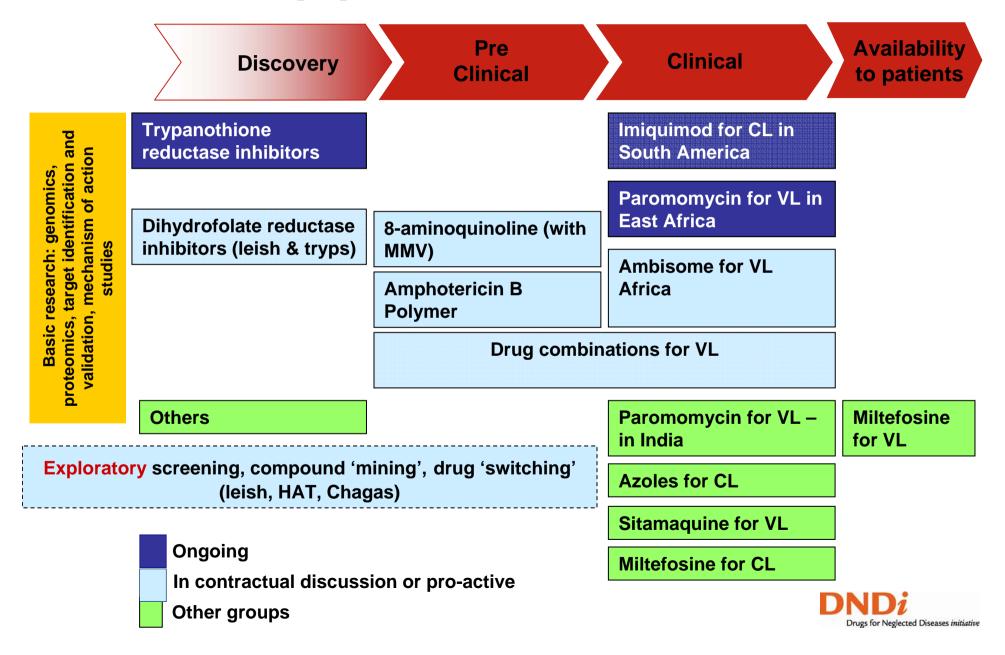
- An estimated 12 million people affected in 88 countries
  - Different forms: visceral, (muco)cutaneous, PKDL
- Per year:1-1.5 million new cases of CL/MCL; 500,000 cases of VL
- VL is fatal if left untreated
- Existing drugs: old, toxic, resistance, difficult to use, expensive



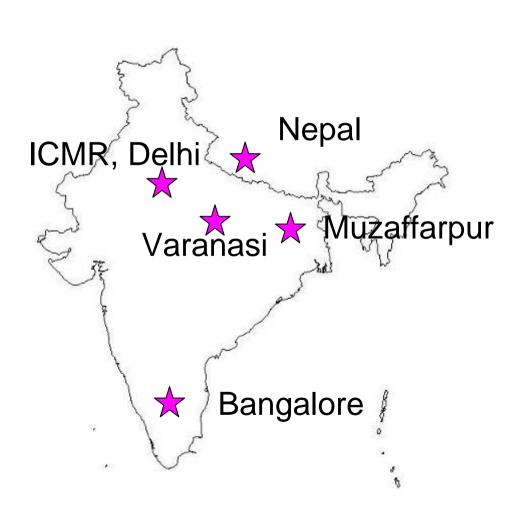




## **Current pipeline for Leishmaniasis**



# Pre-clinical development 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

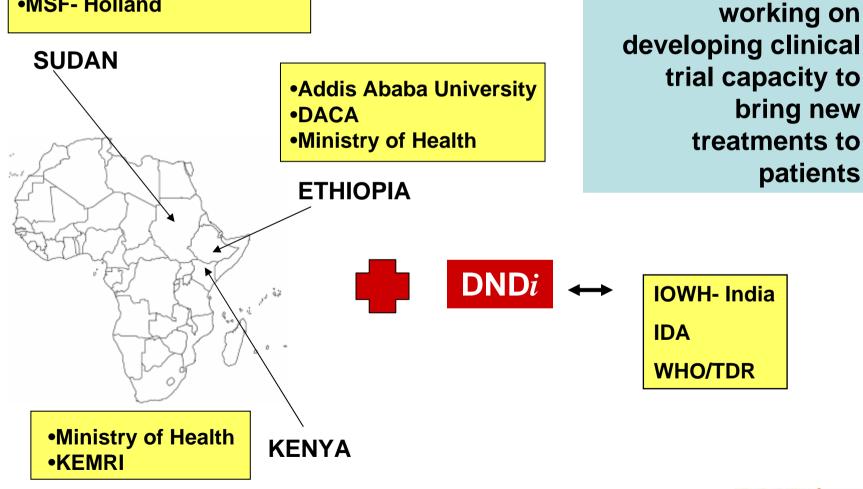
#### **Objectives**

- 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)

- University of Khartoum
- •Federal Ministry of Health
- •MSF- Holland





A group of scientists

and institutions

## EVERY DAY 35,000 PEOPLE DIE FROM NEGLECTED DISEASES



#### Government leadership must urgently:

- set global public health priorities
- fund R&D for neglected diseases
- provide new rules for essential health R&D



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