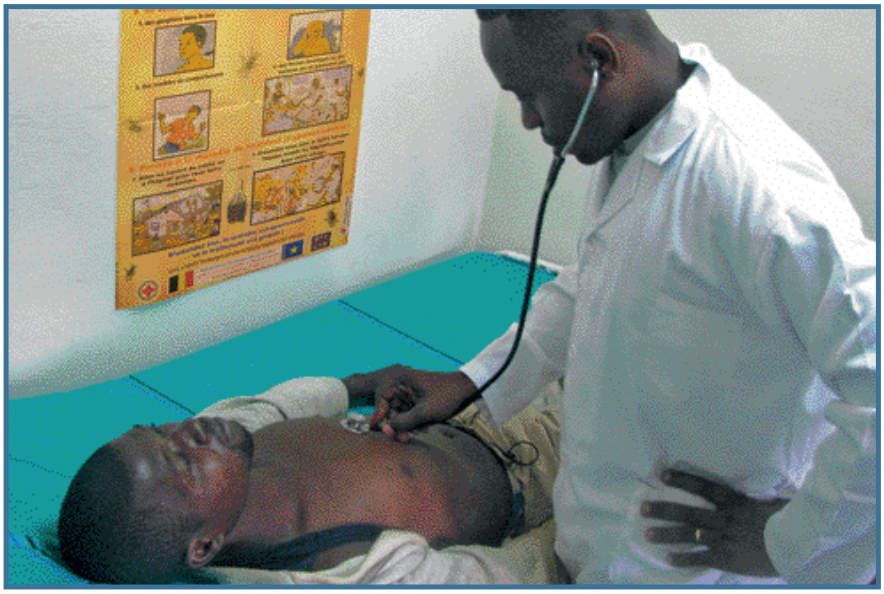
SLEEPING SICKNESS

Human African Trypanosomiasis (HAT)

Major progress seen, punctuated by first improved treatment for stage 2 sleeping sickness in 25 years



PRIORITY TARGET PRODUCT PROFILE FOR HAT

- **A new treatment for stage 2 HAT in adults and children**
  - Preferably useful for stages 1 and 2
  - Active against *Trypanosoma brucei (T. b.) gambiense* and *T. b. rhodesiense*
- **Better safety profile than existing drugs**
  - Ideally requiring little or no monitoring
- **Equal or better efficacy profile than existing drugs**
  - Ideally ≥ 95% clinical efficacy at 18 months after treatment
- **Easy-to-use treatment**
  - Short course (ideally ≤ 7 days, up to 14 days is acceptable)
  - Preferably oral; if injectable, intramuscular preferred
  - Preferably once-a-day treatment
- **Affordable**
- **Stable in tropical climate (minimum 2-year shelf life)**
  - Preferably 3-year shelf life

At the forefront of DND*i*'s efforts to develop new treatments is the need to understand the realities and treatment needs of patients and health care staff in the field.

The ultimate goal for human African trypanosomiasis (HAT) is a truly simplified treatment which can be orally administered, implemented at the primary health care level, and effective against both stages of the disease. Currently, both diagnosis and treatment require a complicated series of tests and trained medical supervision.

A key issue with HAT is that it affects hard-to-access communities in regions with poor health infrastructure. Poor access to medical facilities, a lack of resources and skills, and misdiagnosis contribute to underreporting. Due to the resource-poor areas where the disease occurs, control efforts are often mobilised into vertical programmes. Consisting of a series of specifically equipped and trained diagnosis and treatment centres and mobile teams in endemic areas, but these programmes are not integrated into regional health centres. There is an immediate need to improve current treatment options, particularly for patients with advanced stage of the disease where the few drugs that are available are either toxic, and increasingly ineffective in killing the parasite, or difficult to use. Ideally, a treatment will be safe enough to be used in the first stage of the disease and effective enough in the second stage of the disease. In addition to lead optimisation programmes, DND*i* has conducted proactive compound mining activities to identify existing compounds with potential against kinetoplastid diseases. The compound mining activities of DND*i* have led to the revival of the nitromidazole class as potential drug candidates: the most notable

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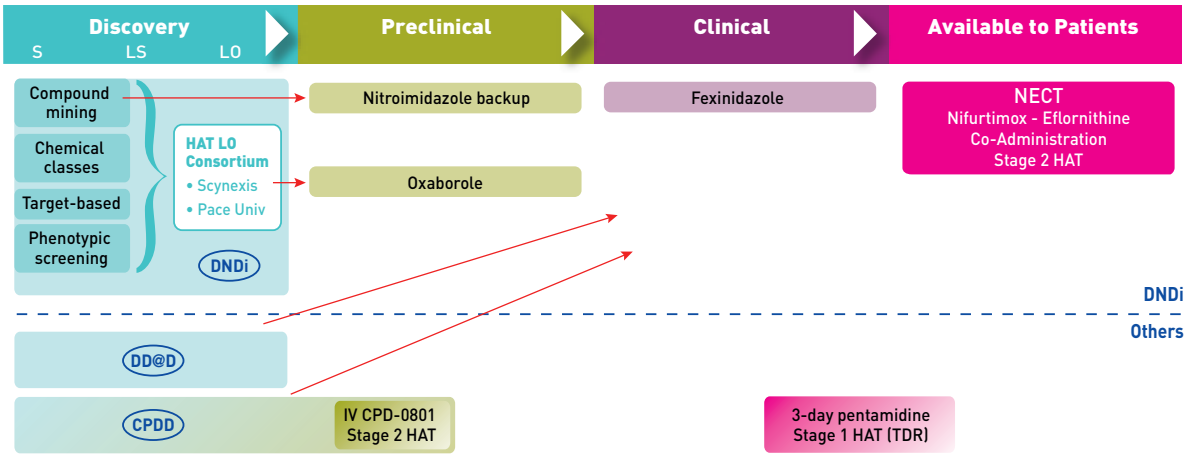
HAT R&D Projects - 2010 Outlook



example is fexinidazole, upon which DND*i* has begun clinical development for HAT.

Several groups worldwide have specific established expertise and knowledge in drug discovery that are readily applicable to the discovery of new antitrypanosomal drugs. In this context, DND*i* has established:

- Partnerships with pharmaceutical / biotechnology / academic groups for interaction and access to natural product as well as synthetic chemical libraries, chemistry, HTS, biological models, and drug design.
- A network of key international laboratories to support discovery efforts with pharmacokinetic, pharmacodynamic, and toxicological expertise, and defined synergy between these laboratories.

At the clinical stage of development, DND*i* is working to both investigate new medicines and to also strengthen capacity for clinical research on HAT. With the recent inclusion of NECT onto the WHO Essential Medicines List, DND*i* is well on its way to meeting its short-term objective to bring a new, shortcourse, co-administration treatment for stage 2 HAT to the patients. Through this project, DND*i* has also built important relationships with other groups involved in HAT clinical research as well as with the WHO, national HAT control programmes and NGOs working to control HAT.

DISCOVERY

LEAD OPTIMISATION CONSORTIUM

- **Partners:** Scynexis, USA; Pace University, USA
- **DND*i* project manager and coordinator:** Robert Don, Ivan Scandale
- **Project start:** April 2007

With an objective to develop optimised leads by progressing 'hit' molecules with a good safety profile and activity against *T. brucei* parasites, these consortia bring together expertise in chemistry, biology, screening, and pre-formulation. Optimisation focuses on the molecule's capacity to be absorbed into the bloodstream, be distributed effectively to the infection, survive in the body, kill the parasite and not harm the patient. With two full lead optimisation teams in place (a total of 18 scientists), a number of hits identified from DND*i* screening partners are undergoing hit expansion. Scientists within the consortia use advanced techniques to study how the selected molecules interact with the therapeutic target (ie. a protein or an enzyme) and optimise the drug-like characteristics of these molecules to ensure that they comply with the target product profile.

This phase requires a close, highly interactive collaboration between the biologists and chemists, who form a feedback loop: the biologists test the biological properties of compounds on biological systems while the chemists perfect the chemical structure of these compounds based on information obtained by the biologists. Two compound series have been chosen as lead series:

- **Oxaboroles**, provided by Anacor and possessing a unique boron-based chemistry, were identified as hits against *T. brucei* at the Sandler Centre of the University of California San Francisco, and have shown *in vivo* activity.

During the course of the last 15 months, chemists at Scynexis have synthesized approximately 400 compounds and screened an additional 330 compounds from the Anacor libraries. Some compounds and in particular, SCYX 6759 cured murine central nervous system infection but appeared to be actively transported from the brain. Compounds which are not effluxed from the brain have been synthesised. One of these compounds such as SCYX-7158 is expected to become a preclinical candidate in 2010.

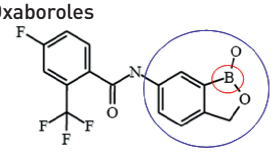
- **Kinase inhibitors**, of which approximately 300 analogs have been synthesized to date. Significant *in vitro* and *in vivo* potency has been developed across the series. However no activity is expected in the second stage of the disease and the series has been abandoned.

To replace kinase inhibitors hit to lead program has been restarted at Scynexis and another optimized lead is expected to be delivered in 2011.

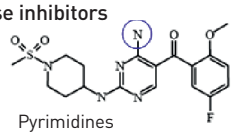
This strategy and the promising early results were presented during the 2008 meeting of American Society of Medicine & Tropical Hygiene, and are available at www.dndi.org.

Sample compound structure of oxaboroles and kinase inhibitors

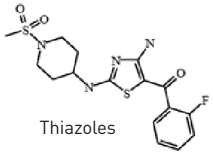
Oxaboroles



Kinase inhibitors



Pyrimidines



Thiazoles

Ongoing collaboration with Dundee University

CLINICAL

FEXINIZADOLE

- **Stage:** Phase I clinical development
- **Major Partners:** sanofi-aventis, France; Swiss Tropical Institute, Switzerland; HAT Platform partners
- **DND*i* Project Manager:** Olaf Valverde Mordt
- **DND*i* Project Coordinator:** Séverine Blesson
- **Project start:** February 2007

Fexinidazole as a drug candidate for stage 2 HAT is the first success of the proactive compound mining efforts DND*i* has pursued in particular in the nitroimidazoles project.

A 5-nitroimidazole that was in preclinical development as a broad-spectrum antiprotozoal by Hoechst in the early 1980s, fexinidazole was rediscovered by DND*i* after being an abandoned compound. Extensive profiling by DND*i* has shown that fexinidazole is orally active, crosses to the brain and has cured *in vivo* models for both acute and chronic infection with African trypanosomes. Importantly, fexinidazole is not mutagenic in a panel of *in vitro* and *in vivo* mammalian genetic toxicology tests, confirming its favorable activity/toxicity profile as a drug candidate.

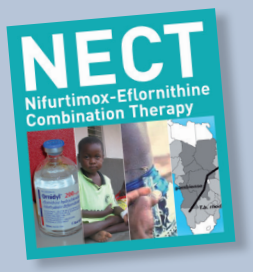
In 2007, a full preclinical programme was established to enable first-in-human studies.

This included process chemistry and GMP-manufacturing of the active pharmaceutical ingredient, its preclinical formulation, ADME-PK profiling and confirmatory studies in animal models of HAT, and the regulatory toxicology package (4-weeks repeated dose toxicokinetics in rat and dog, safety pharmacology, and an extensive genetic toxicology package). In June 2008, a full review of the data by DND*i* concluded that fexinidazole was suitable for progression into clinical development.

Fexinidazole has entered into Phase I first-in human clinical studies in September 2009, which makes it the only new drug candidate in clinical development for sleeping sickness. A tablet formulation is underway. In May 2009, DND*i* and sanofi-aventis have signed an agreement for the development, manufacturing and distribution of fexinidazole. Under the terms of the agreement, DND*i* will be responsible for non-clinical, clinical, and pharmaceutical development and sanofi-aventis will be responsible for the industrial development, registration, and production of the drug at its manufacturing sites.

This project and the preclinical results were presented during the 2008 meeting of American Society of Medicine & Tropical Hygiene, and are available at www.dndi.org.

NIFURTIMOX-EFLORNITTHINE COMBINATION THERAPY (NECT)



Now available and added to the WHO Essential Medicines List as treatment against stage 2 sleeping sickness

- **Stage:** available (field studies ongoing)
- **Major Partners:** Epicentre, France; Médecins Sans Frontières (MSF); the HAT National Control Programmes of the Democratic Republic of the Congo and the Republic of Congo; the Swiss Tropical Institute (STI); HAT platform
- **DND*i* project manager:** Olaf Valverde Mordt
- **Project start:** April 2004

The DND*i* project has shown that the use of the nifurtimox-eflornithine combination therapy (NECT) is as effective and safe as standard eflornithine monotherapy, but easier to use, and safer than melarsoprol (toxic though still widely used in 50% of patients with stage 2 HAT). NECT is the first new treatment developed for sleeping sickness in 25 years.

Begun originally as a single centre study by MSF-Holland and Epicentre in the Republic of Congo (Brazzaville) in 2003, this study was extended, as of 2004, to additional sites in the DRC by DND*i* in collaboration with Epicentre, MSF, STI and the national HAT control programmes of the DRC.

This multi-centre clinical study, which enrolled 287 patients and was completed in 2008, compared the safety and efficacy of NECT, a coadministration of the oral drug nifurtimox and the intravenous drug eflornithine, with eflornithine monotherapy, the current first-line treatment for stage 2 T. b. gambiense HAT. As is requisite to establish efficacy in this disease, patients were actively followed up for 18 months after treatment.

The study conclusively demonstrated that NECT is as well-tolerated and efficacious as eflornithine. At the end of 2008, the final efficacy and safety results of the Phase III study were available and led to DND*i*'s submission of NECT for inclusion on the WHO Essential Medicines List (EML). The final results were published in The Lancet[1] and were presented by Epicentre during the 2008 meetings of American Society of Medicine & Tropical Hygiene and the HAT Platform, and are available at www.dndi.org. The EML application and support statements of the HAT community are available on the website of the WHO Essential Medicines List.

In May 2009, MSF, Epicentre, and DND*i* announced that NECT had been included on the EML. According to the WHO, NECT can now be used in patients and will provide an opportunity to improve the management of HAT cases. The WHO has already made preparations for the arrival of this improved therapeutic opportunity and is working to ensure that patients have access to NECT by providing appropriate training and supplying the drugs and necessary equipment to disease-endemic countries.

The treatment is now available for countries to use. In September 2009, the Democratic Republic of the Congo (DRC), Chad, and the Central African Republic (CAR) have ordered NECT kits to treat patients.

DND*i* and partners are conducting a field study, which began enrolling patients in April 2009, to further document the safety and ease of use of the combination in real-life field conditions and in special populations like children.

Recognized by the board of DND*i* as "Project of the Year 2008"

(1) Nifurtimox-eflornithine combination therapy for second-stage African Trypanosoma brucei gambiense trypanosomiasis: a multicentre, randomised, phase III, non inferiority trial", Priotto G, Kasparian S, Mutombo W, Ngouama D, et al.,Lancet, 4 July 2009;. 374 (9683): 56 – 64.

SLEEPING SICKNESS – **Human African Trypanosomiasis (HAT)**

60 million people at risk in sub-Saharan Africa

WHAT IS THE ANNUAL IMPACT OF HAT?

50,000-70,000 cases [1]
48,000 deaths [2]
1,525,000 DALYS [3]

Large proportions of communities can be affected by HAT, with serious social and economic consequences. Epidemics at the end of the 20th century infected up to 50% population in villages across rural Africa.

HOW IS HAT TRANSMITTED?

Transmitted to humans by tsetse flies, **HAT is caused by two sub-species of the parasite**, Trypanosoma brucei: *T.b. gambiense* (west and central African), *T.b. rhodensiense* (east and southern African).

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Available treatments are **few, old, and stage-specific**. Stage 1 treatments, pentamidine and suramin are fairly well-tolerated but still require injections and are mostly ineffective in stage 2. For stage 2 (where most patients are diagnosed and thus treated), 3 available treatments exist:

melarsoprol, an arsenic derivative that is painful, toxic (killing 5% of those who receive it), and increasingly ineffective (up to 50% resistance and treatment failure).

eflornithine, difficult to administer, requires trained health staff and constant hospitalization (requiring 56 infusions of 2 hours each over 14 days), and resistance is an increasing concern.

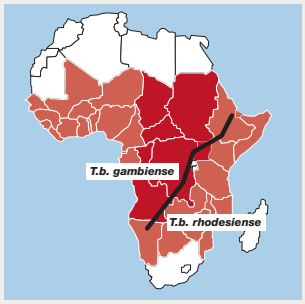
NECT (nifurtimox-eflornithine combination therapy), is available since September 2009. NECT was developed by DND*i* and its partners and is an improved therapy option for sleeping sickness. But is still far from an ideal, treatment that would improve management case at the community level.

WHAT ARE THE PATIENT TREATMENT NEEDS?

– A safe, effective, and practical stage 2 treatment would improve and simplify current case management. This drug should ideally work in both stages of the disease.
– A simple stage 1 treatment, to be used at the local health centre level, would increase access to treatment and coverage.

WHERE DOES HAT OCCUR?

Of the 36 countries considered endemic for HAT, the 7 most affected countries represent 97% of all reported cases (see map). **The Democratic Republic of the Congo (DRC) alone accounts for 2/3 of reported cases** [4]**. HAT primarily occurs in the poor and rural areas of Africa**, where difficulty of diagnosis, political instability, and lack of health surveillance make estimates of disease prevalence difficult to ascertain.



WHAT ARE THE SYMPTOMS AND PRESENTATIONS?

HAT occurs in two stages:

Stage 1 – the haemolymphatic phase – includes non-specific symptoms like headaches and bouts of fever (generally goes undiagnosed without active HAT surveillance).

Stage 2 –the later, neurologic phase – occurs when the parasite crosses the blood-brain barrier and can lead to serious sleep cycle disruptions, paralysis, progressive mental deterioration, and, ultimately, results in death without effective treatment.

WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

Short term: better use of existing treatments
– **Nifurtimox-eflornithine combination therapy (NECT)**, a simplified treatment for stage 2 HAT, now ready for use

Medium term: drug candidates identified through compound mining
– **Fexinidazole:** first drug candidate entered clinical development from nitroimidazoles project
– Back-up nitroimidazoles identified

Long term: discovery of promising new drug candidates and improved clinical research capacity
– **New drugs** developed from compounds identified **(i.e. oxaboroles)** in discovery research and progressed through **HAT lead optimisation consortium**
– Multi-country, multi-partner **HAT Platform** to strengthen regional research capacity (see Section 3).

By 2014, DND*i* aims to deliver from its HAT-specific portfolio:
– 1 new combination therapy recommended by WHO
– 1 new drug registered
– A robust pipeline

(1) World Health Organization (WHO). Wkly Epidemiol Rec. 2006:81;71-80. **(2)** The World Health Report. Geneva; 2004. Available from http://www.who.int/whr/2004. Accessed Aug 12, 2008. **(3)** DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. **(4)** Simaro PP, Jannin J., Cattnd p; ploS Med. 2008;5:e55.