DND*i* R&D progress to tackle sleeping sickness

1 DISCOVERY

Discovery is a three-stage process consisting of compound screening, lead selection, and lead optimization. The objective is to identify drug candidates that meet a predetermined set of criteria to enter the clinical development process. DND*i* has entered into a number of partnerships aimed at ensuring that a robust portfolio is built by 2018.

> SCREENING > LEAD SELECTION > LEAD OPTIMIZATION

SCREENING PROCESS

> Compound mining
Extensive proactive investigation of small series of compounds, on which some biological tests have already been performed, to assess them as potential drug leads against the kinetoplastid parasites (Chagas, HAT, VL), e.g. nitroimidazoles.
Partners: Sanofi, France; Pfizer, USA; GlaxoSmithKline Tres Cantos, Spain.

> Screening
Identification of new active compounds via low- to high-throughput screening assays in dedicated centres:

- High-throughput screening
High-throughput screening of large-size libraries for T. b. brucei (Eskitis) has been developed and is used to identify novel hit compounds. Screening capacity is a key element of DND*i*'s discovery strategy as it enables the screening of large libraries/ series of compounds and therefore a quicker identification of hits/leads critical to discovery programmes.
Partners: Eskitis Institute (Griffith University), Australia.

- Reference Screening Centres
The Swiss Tropical and Public Health Institute (Swiss TPH), the Laboratory of Microbiology, Parasitology, and Hygiene (LMPH) of the University of Antwerp, and the London School of Hygiene & Tropical Medicine (LSHTM) serve as reference screening centres to ensure that screening methodologies are comparable, and that in vitro and in vivo assays at different sites and with different groups meet the same standard. The centres also provide expert parasitology advice that ensures the quality of data and work.
Partners: Swiss TPH, Switzerland; LMPH, University of Antwerp, Belgium; LSHTM, UK.

LEAD OPTIMIZATION (as of May 2011)

HAT Consortium

Objective: To obtain optimized leads by progressing 'hits' with a good safety profile and activity against Trypanosoma brucei parasites.
Partners: Anacor, USA; SCYNEXIS, USA; Pace University, USA; with the support of Swiss TPH, Switzerland.

2 PRE-CLINICAL DEVELOPMENT

Nitroimidazole Back-up (HAT)

Objective: In case the clinical development of a potential drug in development for HAT fails to meet the expected profiles, DND*i* is undertaking the pre-clinical development of a back-up drug candidate from the nitroimidazole s proactive screening project.
Partners: TB Alliance, USA; Swiss TPH, Switzerland; Suwinski, Poland.

Oxaborole SCYX-7158 (HAT)

Objective: To undertake the pre-clinical development of oxaboroles – a boron-based compound series originated by Anacor. During the course of the collaboration, chemists at SCYNEXIS synthesized several hundreds of new compounds and screened additional compounds from the Anacor libraries. One of the optimized compounds, SCYX-7158, a promising new drug candidate for HAT, will be advanced into Phase I first-in-human clinical studies in 2011.
Partners: Anacor, USA; SCYNEXIS, USA; Pace University, USA; Advinus Therapeutics, India.

3 CLINICAL DEVELOPMENT

Phase I

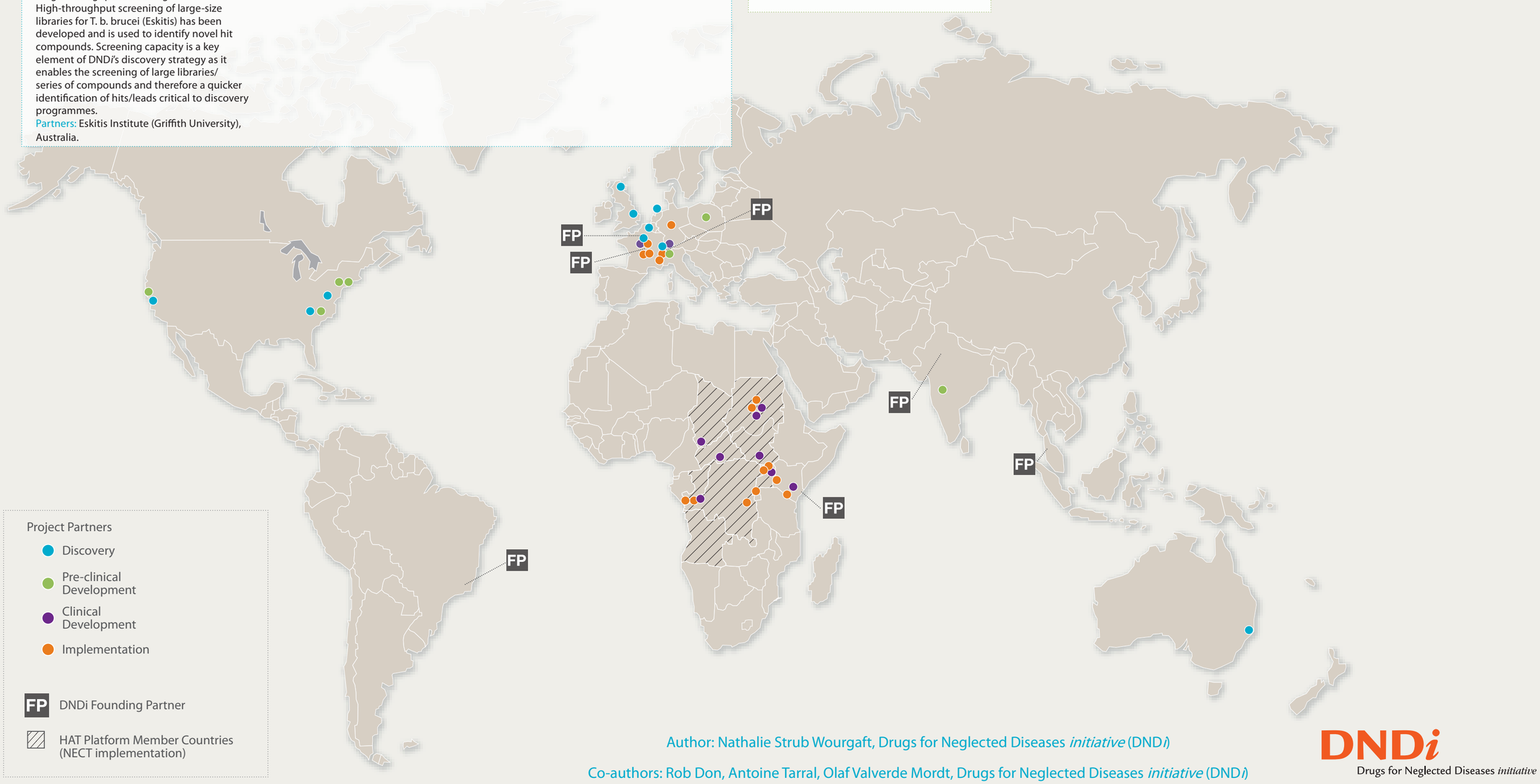
Fexinidazole (HAT)

Objective: To undertake the clinical development of fexinidazole, the first orally administered drug candidate in clinical phase for sleeping sickness. Fexinidazole entered into Phase I first-in-human clinical studies in September 2009. Phase II clinical studies will start in early 2012. DND*i* and Sanofi have signed an agreement for the development, manufacturing, and distribution of fexinidazole.
Major Partners: Sanofi, France; Swiss TPH, Switzerland; HAT Platform partners.

4 IMPLEMENTATION

NECT-Field – Nifurtimox-Eflornithine Co-administration Therapy (HAT)

Objective: The Phase IIIb NECT-Field study in DRC will further document the safety and ease of use of the combination in real-life field conditions and in new populations, such as pregnant and breastfeeding women, and children.



Author: Nathalie Strub Wourgaft, Drugs for Neglected Diseases *initiative* (DND*i*)
Co-authors: Rob Don, Antoine Tarral, Olaf Valverde Mordt, Drugs for Neglected Diseases *initiative* (DND*i*)

DNDi
Drugs for Neglected Diseases *initiative*