02.

R&D Model, Strategy, & Portfolio

Building Innovative Partnerships to Deliver Better Treatments

Prioritising its efforts based on the most urgent treatment needs of patients, DNDi implements its R&D programmes with a wide variety of public & private partners around the world. The Scynexis researcher shown above works as a member of the HAT lead optimisation consortium.

DND*i*'s R&D portfolio has begun to bear fruit, with the registrations of ASAQ in 2007 and ASMQ in 2008, while continuing to grow as the strongest and most comprehensive kinetoplastid drug portfolio in history.

Having recently signed key, multi-year commitments with various partners who will serve as cornerstones in support of our pipeline, DND*i* continues to identify and engage partners who share our vision and commitment, and to ensure that a well-balanced pipeline is established for the 3 diseases of primary focus: sleeping sickness (HAT), visceral leishmaniasis (VL), and Chagas disease.

Maintaining a portfolio of projects at all stages of development, DND*i* harnesses the expertise of its partners by bringing together all current knowledge and capacities in a coordinated manner. With a strategic approach to identify and to bridge the gaps across the drug development pipeline, DND*i* implements its pharmaceutical R&D programmes in collaboration with public and private partners from around world and prioritises its efforts based on the most urgent treatment needs of the targeted patient populations.

DND*i*'s project portfolio balances long-term and short-term projects because R&D of new drugs is time-consuming, expensive, and highly risky when the process starts at the early discovery stage. DND*i* aims to ensure that access to improved treatment options is provided to patients in meaningful, incremental steps along the way to identify novel compounds for each kinetoplastid disease.

As DND*i* does not have its own laboratories or clinics, the organisation relies on partners to help to develop improved treatments for patients with neglected diseases. DND*i* seeks to maximise existing resources and available expertise so as to minimise costs, overlaps, and risks of attrition.

With dozens of partners spanning the globe and crossing various sectors related to neglected diseases and drug development, DND*i* is firmly on the way to meeting its objectives. However, drug development is both expensive and risky – additional support, from new research partners to governments and other donors, is needed in order to fully deliver the best science for the most neglected.

R&D PRIORITIES IN THE NEAR TERM

Research, in a dynamic process, to ensure the pipelines for HAT, VL, and Chagas are populated with the most promising compounds

- New projects to access state-of-the-art drug discovery technologies and the wealth of existing compounds with therapeutic potential
- Disease-focused lead optimisation partnerships

Develop new treatments that will improve upon the current options

- Ongoing trials to identify the most appropriate drug combinations for VL for specific regions
- Complete the development of the first-ever paediatric formulation of benznidazole for Chagas

Access improved treatment options

- Facilitate the adoption and proper use of the 2 currently available Fixed-Dose Artesunate-Based Combination Therapies (FACTs) for malaria
- Prepare the groundwork for the adoption of a nifurtimox-eflornithine combination for HAT.

> SCOPE OF ACTIVITIES FOR DND*i*: MAJOR FOCUS ON KINETOPLASTID DISEASES

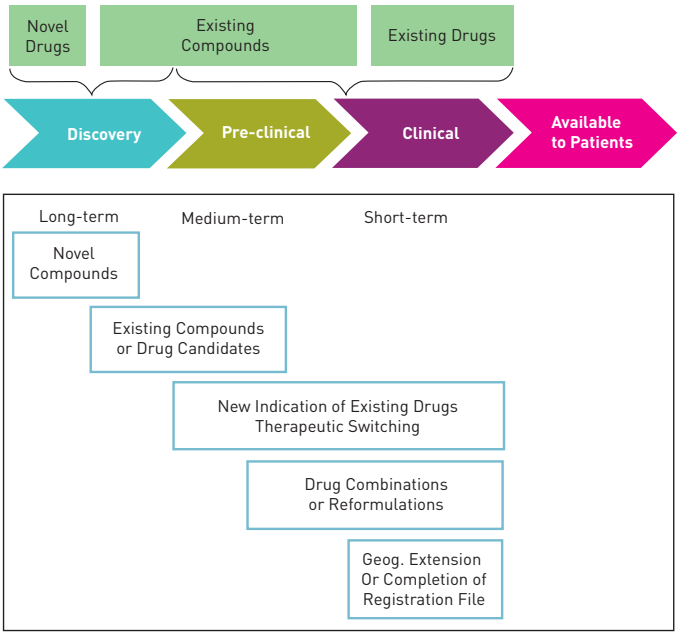
> ONLY 21 NEW DRUGS FOR NEGLECTED DISEASES (1975-2004)

Engaging in a collaborative mode of operation from the research laboratory to the patient clinic, DND*i* does not actually conduct research itself, but actively serves as project leader for its research projects from discovery through development. Together with these and other selected partners, DND*i* then acts as a facilitator to ensure effective

3 core diseases (HAT, VL, Chagas)

3 core diseases
+ malaria: complete the 2 FACTs
+ cutaneous leishmaniasis

SOURCING PROJECTS AT VARIOUS STAGES OF DEVELOPMENT



DND*i*'s portfolio continues to be a mix of projects in-sourced at any stage of the development process, from early discovery through post-registration, with the objective to bring new, field-relevant tools to patients in the shortest time and most efficient way possible.

DND*i* populates its portfolio by seeking out projects which fall into the following 5 categories, based on the nature of the compound/treatment under consideration and according to its stage of development or expected time to reach patients:

- New drugs from novel compounds identified through screening and lead optimisation
  → example: agreements for disease-focused lead optimisation for all 3 target diseases, and access to new drug discovery technologies with Institut Pasteur-Korea
- New drugs from compounds with known antimicrobial/antiparasitic activities (may start at lead optimisation or preclinical development)
  → example: progression of fexinidazole as a preclinical candidate
- New indications for existing medicines in the field of the most neglected diseases (therapeutic switching)
  → example: partnerships in place to investigate buparvaquone as a potential treatment for VL
- Reformulations and combinations better adapted to field conditions (paediatric, long-acting, new route of administration, fixed-dose combinations, co-packaging, or co-administration)
  → examples: both FACT products made available for malaria; completion of NECT study; agreement in place to develop paediatric formulation of benznidazole for Chagas disease
- Existing drugs for target diseases (geographical extension of registration; completion of regulatory dossiers of existing drug candidates)
  → example: paromomycin for visceral leishmaniasis in Africa.

STRENGTHENING AND STREAMLINING THE PORTFOLIO

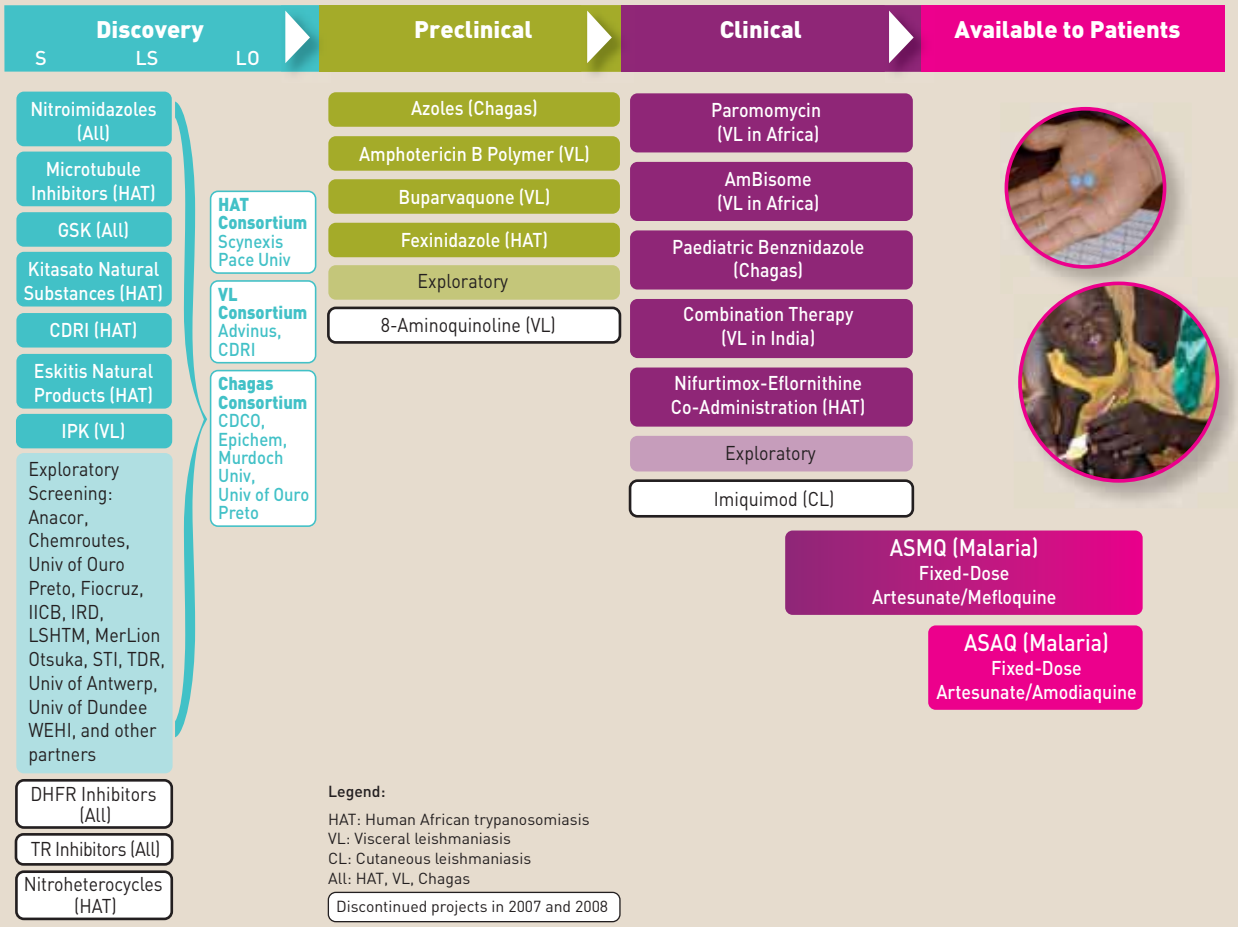
Through 2007 and into 2008, DND*i*'s portfolio continues to be strengthened and streamlined, with 21 projects across all stages of development and with numerous exploratory activities. These exploratory activities engage partners with drug development and parasite-specific expertise in providing compounds and in conducting *in vitro* and *in vivo* evaluation. The current portfolio ranges from discovery to post-registration projects, with a primary focus on three kinetoplastid diseases (HAT, VL, Chagas). Two ongoing projects in malaria have seen products made available to patients in the past year, and DND*i* remains open to later stage development projects for cutaneous leishmaniasis.

Individual Projects Discontinued in 2007 and 2008

DND*i* is grateful to the following project partners for their dedication during the lives of these projects.

- **Trypanothione Reductase Inhibitors (HAT, VL, Chagas)** Partner: University of Dundee, UK
- **Dihydrofolate Reductase Inhibitors (HAT, VL, Chagas)** Partners: Institute of Parasitology and Biomedicine Lopez-Neyra, Spain; Basilea, Switzerland; Swiss Tropical Institute (STI), Switzerland; London School of Hygiene & Tropical Medicine (LSHTM), UK
- **Novel Nitroheterocycles (HAT)** Partners: University of Dundee, UK; Glasgow University, UK; University of Parma, Italy; Swiss Tropical Institute, Switzerland
- **NPC1161B, An 8-Aminoquinoline (VL)** Partners: University of Mississippi (UM), USA; Medicines for Malaria Venture (MMV), Switzerland; London School of Hygiene & Tropical Medicine (LSHTM), UK
- **Imiquimod (CL)** Partners: McGill University, Canada; Universidad Peruana Cayetano Heredia, Peru.

A ROBUST AND DYNAMIC PORTFOLIO FROM 2007-2008



CHARACTERISTICS OF A TPP

Indication
- **Which diseases?**

Population
- **Which patients and where?**

Clinical Efficacy
- **Does it kill the parasite effectively?**

Safety and Tolerability
- **What kind and how many adverse events?**

Stability
- **How long can it be stored in the field?**

Route of Administration
- **How is it given to patients?**

Dosing Frequency
- **How often and how long must it be given?**

Cost
- **Will it be affordable to target population?**

Time to Availability
- **How long will it take to develop?**

SELECTING FOR SUCCESS IN THE FIELD: THE TARGET PRODUCT PROFILE

As a prerequisite to building a portfolio strategy, the desired R&D outcome for each disease is defined as the target product profile (TPP). Each R&D project in the portfolio is selected, progressed, and managed according to well-defined decision matrices based on these TPPs.

Particularly during drug discovery, the TPP keeps research focused on the endgame – a medicine for the patient. Starting as a description of an 'ideal' drug, the TPP changes over the development process as new treatment options emerge. A common format in which to develop the TPP is as an ideal "package insert" which contains all of the information necessary for a medical practitioner to effectively prescribe the drug.

Sound knowledge of patient needs is essential to a credible TPP. Our clinical project managers work to develop in-depth knowledge about the field. In addition, a necessary part of their role is to solicit input from healthcare workers, patients, health regulators, and policymakers in disease-endemic countries where the drug will ultimately be made available. By engaging such partners at the early stages of the decision-making process, we ensure that the needs in the field are reflected in the final product.

Used properly, the TPP can play a central role in the entire drug discovery and development process. This role includes effective optimisation of drug candidates, decision-making within an organisation, design of clinical research strategies, and constructive communication with regulatory authorities.

Discovery Projects

Key discovery activities are consolidated screening efforts, with established reference screening centres, which feed hits into disease-specific lead optimisation consortia.

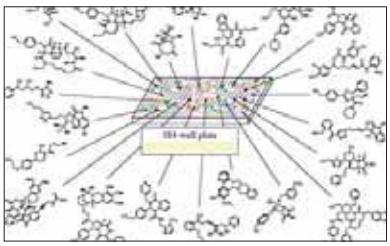
Discovery research is essential in bringing forward novel drugs that are significantly better than current therapies. To that end, DND*i* has established a variety of concerted efforts in this research phase to maximise success and to ensure a robust pipeline that will deliver in 2014 and beyond.

A diverse set of complementary projects in early-stage screening is utilised to identify new compound classes with anti-parasitic activity. These activities include:

- screens of compound classes which have shown promising anti-parasitic activity,
- target-based screens where a validated molecular target (like an enzyme) of the parasite is identified and then screened, and
- general screens (utilising synthetic compound libraries and natural products).

KEY CHARACTERISTICS OF DND*i*'S DISCOVERY ACTIVITIES

- Bring a thorough understanding of field conditions and patient needs
- Apply updated Targeted Product Profiles (TPP) to guide our disease-specific programmes
- Continue to harness existing knowledge and take an opportunistic approach to address urgent needs – e.g., therapeutic switching, mining for new drugs from abandoned programmes, etc.
- Have organised disease-focused consortia for centralized lead optimisation operation, which allows for needed flexibility, and for efficient decision making in the laboratories
- Take a balanced approach in targeting diverse sets of compounds and libraries, while also targeting selected classes of compounds, thereby leveraging existing drug discovery knowledge
- Work with partners who share our mission and commitment.



MICROTUBULE INHIBITORS

- Target disease:
  HAT
- Partners:
  Murdoch University, Australia; Epichem, Australia; Centre for Drug Candidate Optimization, Monash University, Australia
- DND*i* project manager and coordinator:
  Robert Don, Jean-Robert Ioset
- Project start:
  September 2006

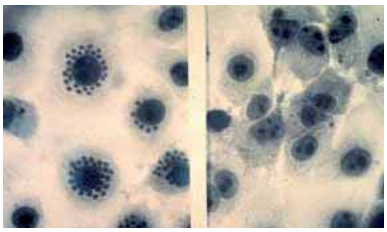
This lead optimisation project, which builds on data from a lead molecule shown to be highly selective for trypanosome α-tubulin, is to assess the development potential of this lead series. Previous studies have shown that novel compounds which bind to trypanosome α-tubulin have selective activity to *T. brucei* α-tubulin *versus* murine α-tubulin.
At the end of 2007, more than 80 compounds have been synthesized by Epichem *via* 3 different analogue programmes using a biphenyl scaffold. After assessing these compounds for *in vitro* antiparasitic activity and potential mutagenicity, Murdoch University then conducted a number of *in vivo* experiments to assess the compounds' acute model, bioavailabilities, and abilities to cross the blood-brain barrier. A lead molecule was identified for further investigation, which will include completion of ongoing dose response studies, further *in vivo* efficacy assessment, and exploration of the compounds' potential for mutagencity via *in vitro* and *in vivo* micronucleus testing. Work is also ongoing to improve solubility *via* synthesis of new analogues and different formulations.

CYSTEINE PROTEASE INHIBITORS AND PYRIDONES

- Target diseases:
  HAT, VL, Chagas
- Partners:
  University of California, San Francisco, USA; GlaxoSmithKline, Spain
- DND*i* project manager and coordinator:
  Denis Martin, Jean-Robert Ioset
- Project start:
  October 2005

With the objective to identify novel

inhibitors of parasite cysteine proteases (CP) that could be progressed as lead compounds, this project targets the CP family because they are nearly ubiquitous in protozoan parasites, play a number of key roles in parasite survival (from nutrition to immune evasion among others), and have well-known structure-activity relationships.
In 2007, none of the CP inhibitors from previously accessed libraries were found to meet the targeted profile, and this specific project was not further pursued.



GSK signs on…
In early 2008, GSK and DND*i* formalised an ambitious collaboration which makes available a large GSK library of new CP inhibitors and a library of pyridone compounds to DND*i* in order to examine their specific activities against kinetoplastid parasites.

NITROIMIDAZOLES

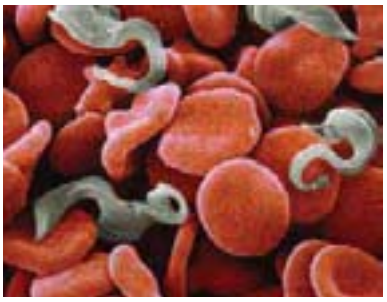
- Target diseases:
  HAT, VL, Chagas
- Partners:
  Swiss Tropical Institute, Switzerland; Fiocruz, Brazil; Ouro Preto University, Brazil; Covance, UK; Absorption Systems, USA; BioDynamics, UK; and a range of worldwide collaborators who have made compounds of interest available for testing, including ENH Research Institute, USA; Tehran Univ of Medical Sciences, Iran; Silesian Univ of Technology, Poland; LaSapienza Univ, Italy; Univ of Alberta, Canada; Univ of Tennessee, USA; Tokushima Univ, Japan; Univ of Auckland, Australia; sanofi-aventis, France; Roche, Switzerland; Novartis/NITD, USA-CH-Singapore; Alkem, India; TB Alliance, USA
- DND*i* project manager:
  Els Torreele
- Project start:
  January 2005

Nitroimidazoles are a well-known class of anti-infective compounds, however, the risk for genetic toxicity linked to the nitro-group has been a concern for drug development. An extensive compound mining effort was undertaken by DND*i* to explore new and old nitroimidazoles as drug leads against HAT, leishmaniasis, and/or Chagas disease. Over 600 existing compounds from 15 different sources were identified, accessed, and tested for anti-parasitic activity (*in vitro* and *in vivo*). Active compounds underwent extensive druggability profiling, including possible mutagenic activity, ADME, and pharmacokinetics. This approach has already led to the discovery and characterisation of fexinidazole as a promising development candidate for HAT (see page 23), while several other compounds with potential for either HAT, leishmaniasis, or Chagas disease are still undergoing profiling in 2008.

KITASATO SCREENING

- Target disease:
  HAT
- Partners:
  Kitasato Institute (KI), Japan
- DND*i* project manager and coordinator:
  Eric Chatelain, Jean-Robert Ioset
- Project start:
  April 2005

Natural products from microbial and plant sources, such as avermectin and artemisinin, have played an important role in the history of parasitic chemotherapy. Likewise, KI has a long history in the research and discovery of anti-infectious drugs from natural products, such as microbial metabolites and plant products. The objective of this specific project is to discover new types of anti-trypanosomal molecules from KI natural products via *in vitro* and *in vivo* screening.
Through March 2008, over 24,000 natural products and their synthetic derivatives have been screened, with 9 compounds having been identified as having high activity. These compounds are now being evaluated for possible lead optimisation at Scynexis, where researchers are currently undertaking hit expansion on one of the compounds (see page 21); KI will concurrently continue in search of further 'hits' to feed the pipeline.



COMPOUND SCREENING WITH CDRI

- Target disease:
  HAT
- Partners:
  Central Drug Research Institute (CDRI), India
- DND*i* project manager and coordinator:
  Eric Chatelain, Jean-Robert Ioset
- Project start: February 2006

With the goal of this project to identify some chemically diverse compounds with *in vitro* activity against *T. brucei*, CDRI – based in Lucknow, India – has established an *in vitro* medium-throughput screen and has begun to screen its compound library which includes 8,000 synthetic compounds. In 2007, approximately 5000 compounds were screened, and over 200 compounds (belonging to 11 different chemical scaffolds) have shown activity by inhibiting more than 90% of *T. brucei* growth. As

of June 2008, the screening has been completed, and hits are being reviewed in terms of promising activity (IC50) and cytotoxicity profiles in order to determine the whether or not to progress any of them through further lead identification.

ESKITIS NATURAL PRODUCTS SCREENING

- Target disease:
  HAT
- Partners:
  Eskitis Institute, Australia; Griffith University, Australia
- DND*i* project manager and coordinator:
  Robert Don, Jean-Robert Ioset
- Project start:
  November 2007

As part of early exploratory activities, DND*i* accessed the natural products' wealth and drug discovery expertise of Eskitis to examine the *in vitro* trypanocidal activity of 64,000 natural products from a diverse screening library of over 200,000 extracts. This unique lead-like peak library of natural products, which possess well-characterised physicochemical properties optimised for drug development, includes representatives of 60% of global plants and 9,500 marine invertebrates. The proprietary lead-like enhancement technology used by Eskitis is a two-step process which enriches extracts in lead-like and drug-like components prior to pre-fractionation; this process maximises the chance of a positive outcome, ie. detecting a "hit". In 2008, the first "hit", a marine invertebrate, has been identified. As the project continues through 2009, the remaining 136,000 compounds will be screened, and promising compounds will undergo hit expansion.

IPK HIGH-CONTENT SCREENING

- Target disease:
  VL
- Partners:
  Institut Pasteur Korea (IPK)
- DND*i* project manager and coordinator:
  Eric Chatelain, Jean-Robert Ioset
- Project start:
  December 2007

A cell-based high-content screening system for *Leishmania* parasites offers the possibility to quickly generate new hits against novel targets. Utilising both the intellectual and technological capacity of the Institute Pasteur-Korea, this project seeks to develop a major methodological advance in antileishmanial drug development as this will be the first high-content screening assay for intracellular *Leishmania* amastigotes in macrophages. *Leishmania* amastigotes are the clinically relevant intracellular form of the parasite. Beginning in 2008, the project seeks to develop and validate the assay in the first year so as to then use it in the second year of the project to test confirmed "hits" against *Leishmania*. If the project is successful, this assay will be the first of its kind in the world, and it may then be expanded to include testing against *T. cruzi* as such an assay could represent a huge advance for antitrypanosomal screening as well.

Landmark agreements cement DND*i*'s optimisation efforts

In 2007, key multi-year partnerships were formed in terms of research and funding that will enable DND*i* to apply best drug discovery science for the most neglected. Capped off with the financial commitment of the Bill & Melinda Gates Foundation to support both of these programmes in December (see page 37), DND*i* signed 5-year collaborative agreements with Scynexis and Advinus as primary partners in lead optimisation consortia for HAT and VL, respectively. In July 2008, a Chagas disease consortium was also finalised.

The projects are to obtain optimised leads by progressing "hit" molecules with a good safety profile and active against *Trypanosoma* and *Leishmania* parasites, these consortia bring together expertise in chemistry, biology, screening, and pre-formulation, in order to optimise 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.

Scientists within the consortia use very advanced techniques to study how the selected molecules link themselves to the therapeutic target (ie. a protein or an enzyme) in order to optimise the drug-like characteristics of these molecules. This phase requires a close, highly responsive 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.

By early 2008, both HAT and VL consortia partners had dedicated teams (shown below: Scynexis, left; Advinus, right), processes, and milestones in place so as to ensure that this critical gap in the drug development pipeline is filled. In July 2008, contracts have been signed with partners who will serve as cornerstones of the Chagas consortium. In addition, DND*i* has agreements in place with a number of other sources of novel compounds that can feed all of the drug discovery programmes (see page 17).

It is planned that by end of 2011, all programmes will have a number of back-ups ready to sustain the pipeline should the 1st candidate fail, and will have progressed a molecule with a good safety profile and active against the respective parasite in early-stage screening research through the first steps of regulatory safety assessment in the preclinical phase.

Scynexis team

Advinus team

LEAD OPTIMISATION PROGRAMMES

- Target disease: HAT
- Partners: Scynexis, USA; Pace University, USA
- DND*i* project manager and coordinator: Robert Don, Ivan Scandale
- Project start: April 2007
- Status: With two full lead optimisation teams in place, a number of hits identified from DND*i* screening partners are undergoing hit expansion. A review will take place later in the year to begin "hit to lead" activities.

- Target disease: VL
- Partners: Advinus, India; CDRI, India
- DND*i* project manager and coordinator: Denis Martin, Ivan Scandale
- Project start: November 2007
- Status: With a full team in place, assessment of the first series of synthetic compounds has been conducted and chemistry-biology activities have been initiated. Dedicated screening facilities at CDRI will be established by the end of 2008.

- Target disease: Chagas
- Partners: Centre for Drug Candidate Optimization (CDCO), Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto, Brazil
- DND*i* project manager: Robert Don
- Project start: July 2008
- Status: Key contracts have been signed in July 2008, and work has begun to populate a full lead optimisation team who will assess promising hits from DND*i* screening partners.

Preclinical Development

To address the relatively sparse preclinical landscape of drug research and development for kinetoplastid diseases, DND*i* has a proactive programme which aims to identify compounds that can be rapidly advanced to clinical trials.

These may include:

- Drugs used to treat related diseases such as fungal infections which are also potent against kinetoplastid parasites
- Drug candidates which have been partially developed for kinetoplastid infections and abandoned by pharmaceutical companies. This can happen when companies change focus after mergers or review of their target markets
- Compounds developed in universities or research institutes which have stalled because funding mechanisms do not exist to take them to the next step.

DND*i* also recognises the need for new disease-specific models to improve the selection of drugs in the development phases, and is working with partners to identify new potential candidates.

AZOLES

- Target disease: Chagas
- Partners: Federal University of Ouro Preto, Brazil; and companies who will provide compounds of interest
- DND*i* project managers: Robert Don, Isabela Ribeiro
- Project start: 2007

Preclinical studies with antifungal triazoles have shown considerable efficacy in the treatment of Chagas disease in animal models. One of these compounds, posaconazole (Schering Plough), was recently registered for treatment of invasive fungal infections in Europe and USA. In addition, several other companies have taken other azole compounds into clinical trials for fungal infections. These also show strong activities against *T. cruzi*. The team is assessing the treatments in animal models, of several compounds as monotherapy and combination with existing drugs to treat Chagas disease. In 2008, DND*i* is progressing on the goal to advance either posaconazole or another azole into clinical research on Chagas disease patients, and to examine other molecules from the same family as potential drug candidates.

AMPHOTERICIN B POLYMER

- Target disease: VL
- Partners: Imperial College, UK; London School of Pharmacy, UK; LSHTM, UK
- DND*i* project manager: Denis Martin
- Project start: September 2006

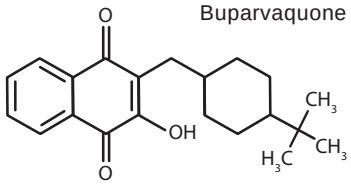
The goal of this project is to develop a low-cost and heat stable version of liposomal amphotericin B (AmBisome®). This efficacious yet highly expensive formulation of amphotericin B has been increasingly used to treat VL but has seen very limited use in VL-endemic regions of Africa and Asia, where disease burden is greatest, because of its high cost. Using a less expensive, modified metacrylic polymer has shown promise in experimental work conducted by the Imperial College team.
In 2007, Imperial College has moved forward to establish adequate efficacy in an *in vivo* model of the disease and is examining key characteristics related to the size of the polymer, the ratio of the polymer to amphotericin B, and the actual dose of amphotericin B.
While this project moves ahead in 2008, DND*i* is conducting parallel investigations into other amphotericin B-based formulations which show promise *in vivo* and will plan to advance the most promising one by early 2009.

BUPARVAQUONE

- Target disease: VL
- Partners: Advinus Therapeutics, India; Drugabilis, France; University Sains, Malaysia; LSHTM, UK
- DND*i* project manager: Denis Martin
- Project start: Approved in October 2007; start in January 2008

In 2007, DND*i*-commissioned work by partners at the Universiti Sains Malaysia and at Advinus Therapeutics has shown that a new self-emulsifying drug delivery system (SEDDS) could improve the oral bioavailabilty of buparvaquone to greater than 60%. Earlier research with buparvaquone – a hydroxynaphthoquinone antiprotozoal drug related to well-known anti-infective drug, atovaquone – has shown it to have good antileishmanial activity *in vitro* and *in vivo* but with limited efficacy in a canine model of VL, possibly due to low bioavailability.
In 2008, with these promising early results, DND*i* has identified partners to assess buparvaquone as a potential optimised lead, and ongoing studies are examining toxicology, pharmacokinetics / pharmacodynamics in animal models (mouse, hamster), and reconfirmation of oral bioavailability using the SEDDS formulation. If acceptable, development will be progressed with the aim of satisfying the criteria specified for a clinical candidate.

Buparvaquone

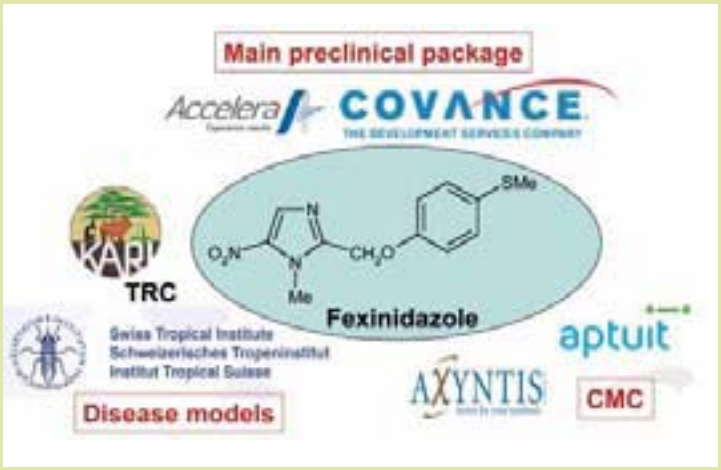


A rediscovered nitroimidazole progresses into preclinical development

FEXINIDAZOLE

- Target disease: HAT
- Partners: Accelera, Italy; STI, Switzerland; Axyntis, France; Covance, UK; Aptuit, UK; KARI Trypanosomiasis Research Center, Kenya
- DND*i* project manager: Els Torreele
- Project start: February 2007

The progression of fexinidazole as a drug candidate for stage 2 HAT is the first success of the compound mining efforts DND*i* has pursued in particular in the nitroimidazoles project (see page 19).



Fexinidazole is a 5-nitroimidazole that has been in preclinical development as a broad-spectrum anti-protozoal by Hoechst in the early 1980s. Rediscovery of this abandoned compound and extensive profiling by DND*i* has shown that fexinidazole is orally active, readily distributes to the brain, and cures mouse 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 late 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, extensive 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 is suitable for progression into clinical development.

Preparation for first-in-human Phase 1 studies is underway, including clinical tablet formulation.

Recognised as “Project of the Year 2008”

Clinical Development & Post-Registration

The seven clinical and post-registration projects in DND*i*'s portfolio are near-term opportunities which can make a significant difference in improving upon current treatment options for each of the diseases on which DND*i* is focused.

They represent the potential for meaningful, incremental improvements in terms of both treatment and strengthening clinical research capacity that can be utilised in DND*i*'s longer term projects evaluating novel compounds (currently in earlier stages of R&D). They also address immediate treatment concerns like development of drug resistance when effective drugs are used in monotherapy, enhancement of patient compliance, and availability of paediatric strengths.

The clinical projects mainly consist of projects which are new formulations of existing drugs, drugs switched from other indications, or drug combinations. Two of DND*i*'s clinical projects have successfully progressed into the post-registration process, where the products are now available to patients in Africa and Latin America.

PAEDIATRIC BENZNIDAZOLE

- Target disease: Chagas
- Partners: Pharmaceutical Laboratory of Pernambuco State (LAFEPE), Brazil; University of Liverpool, UK
- DND*i* project manager: Isabela Ribeiro
- Project start: June 2008

Benznidazole, one of only two products registered for Chagas disease, can be highly efficacious in children yet no paediatric strengths exist. For the majority of children, the 100-mg tablet must be fractionated (broken into pieces). A fractionated tablet is not the ideal form of treatment; with fractionation, there is the potential for improper dosage - raising safety concerns, especially in the very young and malnourished, reduced efficacy (due to coating modification or diluent addition), and decreased stability.

In July 2008, DND*i* has successfully concluded contract negotiations with LAFEPE for the development of paediatric-strength benznidazole tablets. Pharmaceutical and clinical development workplans are being designed, with the ultimate goal to make this affordable, age-adapted formulation available for the treatment of Chagas disease in endemic countries.

NIFURTIMOX-EFLORNITHINE CO-ADMINISTRATION

- Target disease: HAT
- Partners: Epicentre, France; MSF; the national HAT control programmes of the Democratic Republic of Congo (DRC) and the Republic of Congo; SCIH/STI, Switzerland
- DND*i* project manager: Els Torreele
- Project start: April 2004

Begun as a single centre study by MSF-Holland and Epicentre in the Republic of Congo (Brazzaville) in 2003, NECT is a multi centre clinical study to test a simplified combination of oral nifurtimox co-administered with intravenous eflornithine for stage 2 HAT. With the ultimate goal to enable a WHO recommendation on the use of the combination, the project aims to demonstrate that the combination is as effective and safe as standard eflornithine monotherapy, but easier to use. The number of slow, intravenous infusions of eflornithine is reduced from 56 to 14, the treatment duration is reduced from 14 to 10 days, and packaging is minimised. This reduces costs related to drugs, storage, and shipping.
In 2007, an early safety analysis showed that the combination was as well-tolerated as eflornithine monotherapy, and initial, single-centre results were published by Epicentre in the journal *Clinical Infectious Diseases*. By the end of 2008, final efficacy and safety results will be available after all data, including the 18-month efficacy follow-up of all 280 patients, has been analysed.
A submission for inclusion on the WHO Essential Medicines List will be made by the end of 2008. A field study is also being planned to further document the safety and ease of use of the combination in real-life field conditions.

A public good developed and supported by public partners is made available

ASMQ, FIXED-DOSE ARTESUNATE/MEFLOQUINE COMBINATION THERAPY

- Target disease:
  malaria
- Partners:
  Farmanguinhos, Brazil; Shoklo Malaria Research Unit, Thailand; Universiti Sains Malaysia; Oxford University, UK; TDR; Cipla, India; Catalent, USA; ICMR, India; GVK BIO, India; Quintiles, USA
- DND*i* project managers and coordinator: Jean-René Kiechel, Isabela Ribeiro, Gwenaelle Carn
- Project start: January 2002

Among the most studied ACTs is the three-day treatment with artesunate (AS) and mefloquine (MQ), which has shown to be a highly effective therapy against uncomplicated *falciparum* malaria. Used in the field for 16 years, the combination of AS and MQ has been one of four ACTs recommended by WHO since 2001 as first-line treatment for uncomplicated *falciparum* malaria.

ASMQ, the new co-formulation of AS and MQ manufactured by Farmanguinhos/Fiocruz, offers a simple regimen for children and adults that is as easy as 1-2-3: a single daily dose of one or two tablets over three days. This co-formulation was one of two malaria projects undertaken in 2002 by a number of public and private partners coordinated by TDR and MSF (who turned over the project to DND*i* upon its foundation) as part of the FACT (Fixed-Dose, Artesunate-Containing Therapy) Project.

In 2007 and throughout the first half of 2008, ASMQ project partners made significant progress. ASMQ was successfully registered in Brazil by public industrial partner Farmanguinhos/Fiocruz in March 2008. The coformulation is currently being used by Brazilian national authorities as part of an ongoing intervention study; preliminary results after one year show a 70% drop in *P. falciparum* malaria cases and a greater than 60% reduction in malaria-related hospital admissions. The study, which continues through 2008 and 2009, has now treated 25,000 patients with ASMQ.

The future holds even more promise for ASMQ: it will navigate the registration processes of other countries in Latin America; it will be submitted for PAHO pre-qualification; and Farmanguinhos/Fiocruz will continue its technology transfer to the Indian generics manufacturer, Cipla, in order to facilitate its future availability in Southeast Asia. Further clinical research with partners will also be conducted to examine the potential therapeutic value of ASMQ in pregnancy and in Africa.

Recognised as “Partnership of the Year 2008” as part of the FACT Project

PAROMOMYCIN FOR AFRICA

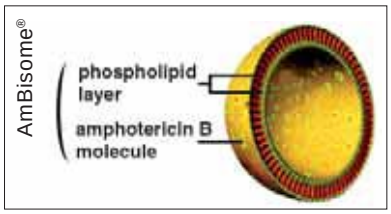
- Target disease: VL
- Partners: Kenya Medical Research Institute, Kenya; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; University of Makarere, Uganda; MSF; IDA Solutions, the Netherlands; LSHTM, UK; Institute for OneWorld Health, USA
- DND*i* project managers and coordinator: Catherine Royce (until February 2008); Manica Balasegaram (as of February 2008), Sally Ellis
- Project start: November 2004

In Africa, visceral leishmaniasis is difficult to treat with existing drugs due to various issues, such as toxicity, emerging resistance, difficulty of use, and cost. Paromomycin (PM), an aminoglycoside antibiotic that was identified as an antileishmanial in the 1960s, has the potential to be an improved treatment at a lower cost when combined with the standard treatment of sodium stibogluconate (SSG).
Currently in Phase IV development throughout the Indian subcontinent by fellow PDP, Institute for One World Health (IOWH), paromomycin is being studied in parallel by DND*i* and the Leishmaniasis East Africa Platform (LEAP) in Ethiopia, Kenya, Sudan, and Uganda. The aim is to register paromomycin as a new treatment in each region, to have it adopted in national treatment guidelines, and to evaluate the shorter course combination of PM+SSG as an alternative treatment for VL.
Early results showed the initial dosage of paromomycin did not work as well in Africa as it did in India. A dose escalation study was undertaken to determine if a higher-dosage regimen could meet its efficacy target.
In 2008, the study is continuing to recruit patients at sites where infrastructure has been improved or built (see pages 29 & 30). First interim analysis was concluded in February 2008, and a decision was made to pursue recruitment. The study is due to complete in 2009, with final results being ready by the end of that year.

COMBINATION THERAPY FOR VL IN INDIA

- Target disease: VL
- Partners: ICMR, India; Kala Azar Medical Research Centre, India; Rajendra Memorial Research Institute of Medical Sciences, India; GVK BIO, India
- DND*i* project manager and coordinator: Farrokh Modabber, Sally Ellis
- Project start: December 2004; Phase II duration from 2005 to 2007; revised Phase III protocol approved in October 2007

A number of new therapeutic options for VL have been developed, but they are generally expensive and have long treatment periods (of up to one month). Combination therapies of these new treatments represent a critical path forward because of their potential for ease of use, shorter course of treatment, prevention of parasite resistance, and cost containment. Additionally, combination regimens using already existing drugs offer a short-term solution to assist in protecting the useful life of available drugs while new chemical entities are developed.
With the objective to identify a safe and effective short-course combination therapy using existing drugs which could be easily deployed in control programmes, this four-armed study is using drugs already registered in the region: AmBisome, miltefosine, and paromomycin. Three arms with a combination of 2 drugs/arm for a maximum of 15-day treatment will be compared with the standard 30-day therapy using amphotericin B.
In June 2008, the first patient was enrolled into the study. This past year was spent assembling a project team, and drafting and receiving ethical approval on a revised clinical study protocol. Enrolment will continue through 2009, and results are expected by early 2010.



AMBISOME FOR VL IN AFRICA

- Target disease: VL
- Partners: Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LSHTM, UK; Ministry of Health, Ethiopia; Armaur Hansen Research Institute (AHRI), Ethiopia; other members of the LEAP network
- DND*i* project managers and coordinator: Catherine Royce (until February 2008), Manica Balasegaram (as of February 2008); Sally Ellis
- Project start: Approved in May 2006; start by end of 2008

AmBisome®, a liposomal formulation of amphotericin B manufactured by Gilead, has been used with increasing frequency to treat VL, especially in Europe, over the past decade. Unfortunately, in Africa and Asia, where disease burden is high, drug access is poor because of the high cost of the drug. With recent preferential pricing offered by the manufacturer to patients in the public sector in East Africa, it is possible that AmBisome® could become economically feasible for treatment, even in resource-poor countries.
The goal of this project, therefore, is to determine the minimum dose of AmBisome® that is efficacious, safe, and cost effective in the treatment of VL in Africa, to reduce the length of hospital stay, and to facilitate registration and adoption of AmBisome® in the region. Identifying the minimum dose for monotherapy will be an important step in developing combinations for Africa and in preventing the development of drug resistance.

Post-Registration

A dose of innovation is delivered as ASAQ reaches African malaria patients

ASAQ, FIXED-DOSE ARTESUNATE/AMODIAQUINE COMBINATION THERAPY

- Target disease:
  malaria
- Partners:
  sanofi-aventis, France; National Centre for Research and Development on Malaria, Burkina Faso; Universiti Sains Malaysia; Oxford University, UK; Institute of Research for Development (IRD), Senegal; Mahidol University, Thailand; Ellipse Pharmaceuticals, France; MSF; Epicentre, France; TDR; Catalent, USA; KEMRI, Kenya ; ICMR, India; GVK BIO, India; Quintiles, USA; Cardinal Systems, France; Office of Technical Studies and of International Cooperation (OTECI), France
- DND*i* project manager and coordinators: Jean-René Kiechel, Gwenaelle Carn, Graciela Diap (Medical Coordinator)
- Project start: January 2002

ASAQ, the new fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ), was the first drug to be made available by DND*i* in an innovative partnership with sanofi-aventis. Now available and registered in 21 countries in sub-Saharan Africa, with more than 1,500,000 treatments procured, the continuing focus of this post-registration project is to support the implementation of ASAQ for the treatment of uncomplicated *falciparum* malaria after its registration in endemic countries, mainly in sub-Saharan Africa, and in Indonesia.

ASAQ provides a true innovation in patient treatment by being a tropical-stable bilayer coformulation, which allows AS and AQ to be taken together and in the correct proportions in a simplified three-day dosing regimen where the most vulnerable population, children under the age of five, take one tablet per day.

The year 2007 was a milestone year for ASAQ as it was made available to patients. Launched in March 2007, ASAQ achieved 1st registration in Morocco, the country where ASAQ is manufactured by sanofi-aventis. This registration has paved the way for further registration across sub-Saharan Africa, where ASAQ can be of substantial public health benefit.

In 2008, further progress has been made as the ASAQ production facility in Morocco has been granted Good Manufacturing Practices (GMP) certification; such a certification allows ASAQ to be procured by malaria-endemic countries via international funding mechanisms, such as the Global Fund (which pays for 70% of malaria medicines made available).

There is still much work to be done with ASAQ: WHO prequalification is pending, and DND*i* is regularly convening a group of external experts as part of the FACT Implementation Advisory Group to advise on Phase IV clinical studies, which are being implemented to study the drug's tolerability and effectiveness in real-life conditions. DND*i* and sanofi-aventis are also working with MMV and the INDEPTH network on a pharmacovigilance strategy.

Further work will also focus efforts to inform on the proper use of ASAQ as part of reinvigorated global efforts to eradicate malaria.

Recognised as "Partnership of the Year 2008" as part of the FACT Project