02.

R&D Model, Strategy, & Portfolio

DNDi acts as a virtual organisation which manages collaborative R&D projects. Utilising a stepwise, integrated model of drug R&D, DNDi primarily focuses its R&D efforts on trypanosomiasis and leishmaniasis, with needs-driven projects that can be sourced at any stage of the R&D pipeline.
Managing Collaborative R&D Projects to Bridge Gaps

DNDi follows the virtual research model, whereby most research is outsourced and actively managed by DNDi personnel experienced in different aspects of pharmaceutical development. DNDi proactively identifies research opportunities with the highest potential to translate into improved treatment options, in-sources the project, builds the full development plan, identifies and contracts the appropriate partners for each step, and manages the project as it progresses through the pipeline.

Including public and academic research institutions; governments and disease control programmes of neglected disease-endemic countries; individual pharmaceutical and biotechnology companies; NGOs, foundations and other institutions involved in R&D and/or advocacy for neglected diseases; and individual experts - DNDi’s collaborators in both developed and developing countries are essential.

Together with these selected partners, DNDi will also ensure effective post-registration management of these new treatments. Mechanisms must be put into place to ensure treatment, utilisation, and access through partnership with international and national programmes and to ensure timely hand-over of projects to commercial partners.

**STRATEGY**

As DNDi combines new drug discovery with optimisation of existing drugs and compounds, DNDi’s portfolio will be a mix of projects in-sourced at any stage of the development process, from early discovery through clinical development. Five project categories can be distinguished by the nature of the compound/treatment under consideration and by the stage of development or expected time to reach patients:

- New drugs from novel compounds identified through screening and lead optimisation;
- New drugs from compounds with known antimicrobial/antiparasitic activities [may start at lead optimisation or pre-clinical development];
- New indications for existing medicines in the field of the most neglected diseases [therapeutic switching];
- Reformulations and combinations better adapted to field conditions [paediatric, long-acting, new route of administration, fixed-dose combinations, co-packaging, or co-administration];
- Existing drugs for target diseases [geographical extension of registration; completion of regulatory dossiers of existing drug candidates];

The DNDi R&D team will proactively reach out and build a number of exploratory activities which, depending on outcomes, can be built-up to full drug development projects or maintained as backup pipeline projects. Through this approach DNDi will maintain a “feeder” system for the pipelines of each target disease. Successful initial links with the pharma/biotech sector will be used to build further contacts and partnerships, as well as provide some clear indicators of engagement with industry.

**PRIORITIES IN 2006**

- To continue to build a robust portfolio for HAT, leishmaniasis, and Chagas
- To develop projects from lead selection to lead optimisation, with progression of one candidate into lead optimization
- To conduct five clinical trials and to submit registration files for two Fixed-Dose Artesunate-Based Combination Therapies for malaria
In 2006, DNDi’s portfolio has grown to 22 projects from an initial three in 2003. The current portfolio ranges from discovery to Phase III clinical trials and focuses on three kentoplastic diseases: Chagas disease, visceral leishmaniasis, and sleeping sickness. DNDi’s drug development pipeline is focused on bringing together all current knowledge and capacities on a treatment in a coordinated manner. From discovery through clinical trials, and on to implementation, new, field-relevant tools will be brought to patients in the shortest possible time.

TARGET PRODUCT PROFILE

As a prerequisite to building a portfolio strategy, the desired R&D outcome, or the target product profile (TPP), has to be defined. Each R&D project in the portfolio will be selected, progressed, and managed according to well-defined decision matrices based on these TPPs. Particularly during drug discovery, the Target Product Profile (TPP) keeps research focused on the endgame – a medicine for a patient. A common format for the TPP is a package insert which contains all of the information necessary for a medical practitioner to effectively prescribe the drug. At DNDi, additional features include a low manufacturing cost, to make the drug more affordable to patients and governments, and a robustness to the extremes of climate that the drug will encounter. The TPP provides a statement of intent very early on in the drug’s development process as limitations in the potential drug emerge.

BUILDING A ROBUST PORTFOLIO

The objectives of DNDi’s portfolio strategy are to bridge the gaps seen in the drug development pipeline by bringing together all current knowledge and capacities on a treatment in a coordinated manner. From discovery through clinical trials and on to implementation, new, field-relevant tools will be brought to patients in the shortest possible time.

DNDi implements its pharmaceutical R&D programs in collaboration with public and private partners based upon the priority needs of the populations. The organisation is using existing science and R&D capacity in different countries to develop essential medicines and ensure that they are suitable for, and accessible to, the millions of people suffering from neglected diseases, often living in poverty and in remote areas. DNDi maintains a portfolio of projects at all stages of drug development and has screening to drug registration, and has the project management skills to support all aspects of their advancement through the pipeline.

As a prerequisite to building a portfolio strategy, the desired R&D outcome, or the target product profile (TPP), has to be defined. Each R&D project in the portfolio will be selected, progressed, and managed according to well-defined decision matrices based on these TPPs. Particularly during drug discovery, the Target Product Profile (TPP) keeps research focused on the endgame – a medicine for a patient. A common format for the TPP is a package insert which contains all of the information necessary for a medical practitioner to effectively prescribe the drug. At DNDi, additional features include a low manufacturing cost, to make the drug more affordable to patients and governments, and a robustness to the extremes of climate that the drug will encounter. The TPP provides a statement of intent very early on in the drug’s development process as limitations in the potential drug emerge.
**APRAGMATIC IP POLICY**

Contract terms with private and public partners are guided by DNDi’s mission to develop safe, effective, and affordable new treatments for patients suffering from neglected diseases, and to ensure equitable treatment access. Contracts are entered into with these principles in mind and according to its IP policy, which is “guided” by the following principles as laid down in the business plan:

- The need to ensure that drugs are affordable and access is equitable for patients who need them;
- The desire to develop drugs as public goods when possible.

The DNDi IP approach is pragmatic, and decisions regarding the possible acquisition of patents, ownership, and licensing terms is made on a case-by-case basis. DNDi puts the needs of neglected patients first, and negotiates for them. DNDi’s decisions regarding IP will contribute to ensuring access and encouraging further innovation. DNDi regards drug research as a public good that should primarily lead to the advancement of health. In addition to a pragmatic day-to-day approach on IP, DNDi is committed to contributing to the development of IP approaches in health R&D that are aimed at serving the public good.
Radical improvement of therapies for the leishmaniases and the trypanosomiases requires the identification, evaluation, and development of novel compounds that are significantly better than current therapies.

The growth in DNDi’s project number to 22 in 2006 from four in 2003 has been largely in discovery (with twelve projects at the end of 2006). The large number of projects in discovery is due to the need to ‘feed’ three different disease programmes and to compensate for the high attrition rate of the drug development pipeline.

Massive, concerted efforts focused on discovery must and are being undertaken in order to achieve a robust R&D pipeline.

In order to maximize resources, compounds in discovery projects are initially tested against all kinetoplastids. Based on the data at this stage, DNDi then makes a decision on whether to focus the project on a specific disease in further development.

Discovery includes:
• Screening of compounds against the pathogens that cause the target disease;
• Hit expansion, where chemical modification is applied on the hits for improved efficacy and selectivity;
• Lead identification, where further in vitro, in vivo, and administration, distribution, metabolism, and extraction (ADME) studies identify a small series of compounds for lead optimisation.

### TRYANOTHIONE REDUCTASE INHIBITORS

- **Target disease:** trypanosomiasis and leishmaniasis
- **Partner:** University of Dundee, UK.
- **DNDi Project Manager:** Denis Martin
- **Project start:** June 2004

The enzyme trypanothione reductase (TR) is a validated drug target for trypanosomiasis and leishmaniasis. With that in mind, the project objective is to identify new chemotypes, via the automated screening of large compound libraries and performing rational design and chemistry on possible hits, which potently and selectively inhibit trypanothione reductase.

At the end of 2006, the medium-throughput screening, performed at Dundee, has identified a number of interesting ‘hits’ among tricyclics and a number of other chemical structures from libraries provided by Sigma and GlaxoSmithKline. Further screening - including molecular target-based, whole cell, and rodent - and additional chemistry of compounds related to the current tricyclic leads and hits will be performed.

### DIHYDROFOLATE REDUCTASE INHIBITORS

- **Target diseases:** trypanosomiasis and leishmaniasis
- **Partners:** Institute of Parasitology and Biomedicine Lopez-Neyra, Spain; BIOTEC, Thailand; Basilea, Switzerland; Swiss Tropical Institute, Switzerland.
- **DNDi Project Manager:** Denis Martin
- **Project start:** August 2005

Enzymes involved in folate metabolism, especially dihydrofolate reductase (DHFR), have been successfully targeted for cancer and antimicrobial infections by limiting the energy supply to the infectious cell. Most DHFR inhibitors are not suitable candidates for parasitic diseases because they are more selective towards the human
enzyme than towards the parasite enzyme. There may also be a second enzyme, which must also be inhibited in order for DHFR inhibitors to successfully kill the parasite. The objective of the project is to identify, via in vitro and in vivo screens, parasite-specific DHFR inhibitors that kill the parasite. At the end of 2006, compounds from Basilea have been screened against the enzyme at the Institute of Parasitology and Biomedicine Lopez Neyra; hits have also been identified for in vitro parasite screening at STI. For 2007, STI will study the compounds’ in vivo efficacies in a mouse model so that a short list of candidates for lead expansion will be ready by the end of the year.

**CYSTEINE PROTEASE INHIBITORS**

- **Target disease:**
  human African trypanosomiasis (HAT)
- **Partner:**
  University of California, San Francisco, USA.
- **DNDi Project Manager:** Denis Martin
- **Project start:** October 2005

Cysteine proteases (CP), especially a subgroup of the papain family which is nearly ubiquitous in protozoan parasites, have been identified as promising targets for the development of antiparasitic chemotherapy. These proteases play a number of key roles in parasite survival (from nutrition to immune evasion among others), and much is known about the structure/function relationship of the enzyme family. A number of mammalian homologues exist to many of the parasitic enzymes, which means there has been a considerable amount of pharmaceutical research done on inhibitors of this protein family. Therefore, this enzyme family has great potential as a target for discovery research. The objective is to identify novel inhibitors of parasite CPs from three classes (vinyl sulfones, dihydrazides, and thiosemicarbazones) so as to generate lead compounds capable of eliminating the parasitaemia in animal disease models of HAT.

**MICROTUBULE INHIBITORS**

- **Target disease:**
  human African trypanosomiasis (HAT)
- **Partners:**
  Murdoch University, Australia (Principal Investigator and in vitro T. brucei assays); Swiss Tropical Institute, Switzerland (in vivo models); Epichem, Australia (medicinal chemistry); Centre for Drug Candidate Optimization, Monash University, Australia (pharmacokinetics, ADME, and toxicology).
- **DNDi Project Manager:** Robert Don
- **Project start:** September 2006

Previous studies have shown that novel compounds which bind to trypanosome alpha-tubulin have selective activity to T. brucei alpha-tubulin versus murine alpha-tubulin. The purpose of this project is to assess the development potential of this lead series. At the end of 2006, more than 50 compounds have been synthesized and are being assessed in vitro for antiparasitic activity and potential mutagenicity. In 2007, this reiterative medicinal chemistry and screening work will be continued. If promising leads are identified, in vivo toxicology may be undertaken.

**NOVEL NITROHETEROCYCLES**

- **Target disease:**
  human African trypanosomiasis (HAT)
- **Partners:**
  University of Dundee, UK (Principal investigator); Glasgow University, UK; University of Parma, Italy; Swiss Tropical Institute, Switzerland.
- **DNDi Project Manager:** Els Torreele
- **Project start:** June 2005

The objective is to identify lead compounds for HAT from a new series of melamine-nitrofuram conjugates. Proof-of-principles to determine if compounds with good antiparasite activity in vivo could be identified. The goal is to establish screens of natural substances as a possible source of new compounds for similar compounds. The goal is to identify new nitroheterocycle compounds, however, is genotoxicity, which is likely to be an issue for the hybrid compounds as well. A second challenge is to generate compounds that can cross the BBB and can cure the CNS-stage of the disease. At the end of 2006, 50 more compounds had been reviewed and their activity/toxicology profile assessed.

**KITASATO SCREENING**

- **Target disease:**
  human African trypanosomiasis (HAT)
- **Partners:**
  Kitasato Institute (KIT), Japan; Swiss Tropical Institute (STI), Switzerland.
- **DNDi Project Manager:** Simon Croft
- **Project start:** April 2005

The goal of this project is to establish screens of natural substances as a possible source of new compounds with activity against Trypanosoma brucei, with a research partner who has years of experience in natural products’ screening and demonstrated success with the identification of widely used antibiotic, ivermectin. Staff from another partner, STI, with expertise in kinetoplastid research, were trained in in vitro and in vivo techniques for T. brucei.
assays, then transferred the methods to KIT. At the end of 2006, over 12,000 natural products and their synthetic derivatives have been screened, with ten compounds identified as having high activity and not being known anti-cancer compounds. In 2007, further work will be carried out in vivo to study the activity of the ten promising compounds, and leads will also be tested against T. cruzi and L. donovani.

**COMPOUND SCREENING WITH SCYNEXIS**
- **Target disease:** human African trypanosomiasis (HAT)
- **Partner:** Scynexis, USA
- **DNDi Project Team:** Robert Don, Denis Martin
- **Project start:** July 2006

The current objective is to establish a T. brucei in vitro screen at Scynexis, to screen the Scynexis library of 25,000 compounds in a whole cell in vitro screen and to select compounds with selectivity for a full lead optimization programme. At the end of 2006, an action plan and agreement are in place, with T. brucei cultures established. Validation of the screening procedures is ongoing. Project-specific templates for the HEOS online database have also been designed.

**ASCOFURANONE**
- **Target disease:** human African trypanosomiasis (HAT)
- **Partners:** University of Tokyo School of Medicine, Japan (Principal Investigator); Tottori University, Japan; Nagoya University, Japan.
- **DNDi Project Manager:** Simon Croft
- **Project start:** October 2004

Several years ago, researchers at the University of Tokyo School of Medicine identified the *in vitro* and *in vivo* activity of ascofuranone against Trypanosoma brucei, the parasite responsible for sleeping sickness. In the veterinary field, subsequent published research has studied the mechanism of action and anti-trypanosomal activity in ungulates like cows and sheep. However, there are a number of limitations to this activity which must be further studied. Submitted via a letter of interest and approved by the SAC in October 2004, the project objective is to identify ascofuranone derivatives with high selectivity for the HAT parasite and with drug-like properties in a lead refinement project. In 2006, negotiations continued with the Japanese biotech company that owns the IP on the molecules so that the research partners can continue their work on the activity profile and chemistry of this compound in 2007.

**COMPOUND SCREENING WITH GENZYME**
- **Target disease:** human African trypanosomiasis (HAT)
- **Partner:** Genzyme
- **DNDi Project Team:** Robert Don, Denis Martin
- **Project start:** July 2006

Genzyme will provide a number of compounds that impact on the polyamine biosynthesis for screening against *T. brucei* at the Swiss Tropical Institute. These have been studied as part of their oncology programme and this pathway is also the target for DFMO (Eflornithine) in *T. brucei*. A contract has been signed. All compounds have been supplied to STI and screened. Twelve ceramide analogues show >75% growth inhibition of *T. brucei* in vitro at 0.8 μg/ml.

**PROJECTS DISCONTINUED IN 2006**

**DISCOVERY:**
Protein farnesyltransferase inhibitors (HAT).
Partner: University of Washington, USA.

Benzofurans (Chagas).
Partners: Universidad de la Republica, Uruguay (Principal Investigator); Universidad de Navarra, Spain; IIBCE, Uruguay; Universidad Nacional de Salta, Argentina.

**PRECLINICAL:**
Protease inhibitor K777 (Chagas).
Partners: Federal University of Minas Gerais, Brazil; University of California, USA; Einstein School of Medicine, USA.

DNDi is grateful to the project partners for their dedication during the lives of these projects.
Rediscovering nitroimidazoles as promising drug candidates

In 2004, DNDi commissioned a literature/patent review to explore past and ongoing research activities on megazol and related nitroimidazole compounds as possible leads for antitrypanosomal drug development because they had previously been shown to possess good antimicrobial activity, including anti-protozoal activity. In the case of megazol, which had proven highly active in vitro and in vivo as a trypanocidal compound and a promising potential drug candidate against Chagas disease and HAT, it was orally active and could cross the blood-brain barrier. However, due to its toxicity (specifically mutagenicity, or possibility of causing genetic mutation), it was not developed further.

After establishing the potential of the class, DNDi undertook a project to identify a range of new and old nitroheterocycles, to (re)assess their in vitro and in vivo trypanocidal activity, and evaluate their activity/genotoxicity profile through a series of standard genotoxicity tests. In parallel, other drugability characteristics were summarily compiled to allow comparison of the most promising compounds. Near the end of 2006, the project was also expanded to include leishmaniasis as a target, as several compounds demonstrated good in vitro activity against L. donovani.

At the end of 2006, over 500 compounds from 15 different sources have been identified, accessed, and tested at STI for in vitro antiparasitic activity, and further assessed for in vivo selectivity. Several interesting compound series have been identified and selected for further exploration. Two compounds from Roche and sanofi-aventis (ex-Hoechst) were identified as preclinical candidates (see Nitroimidazoles-2).
Preclinical Projects

A look at the current status of R&D research for the trypanosomiases and leishmaniases, reveals a clear shortage of projects in preclinical development, which raises concern about potential new drugs in five to ten years time. To redress the balance, DNDi is taking a proactive approach to identify new drugs and projects that have the possibility of filling this preclinical gap. Already, projects on nitroimidazoles and aminoquinolines have been established to fill this immediate need. DNDi 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.

**NITROIMIDAZOLES – 2**

- **Target disease:** human African trypanosomiasis (HAT)
- **Partners:** Swiss Tropical Institute (STI), Switzerland (compound evaluation); several CRO’s including Covance UK; BioDynamics, UK, Absorption Systems, US; sanofi-aventis, France; Roche, Switzerland.
- **DNDi Project Manager:** Els Torreele
- **Project start:** December 2006

In December of 2006, the two most advanced compounds (coming from Roche and sanofi-aventis) of the “Nitroimidazoles-1” re-discovery project were separated into their own project. This separation was done in order to further characterize them and to select the most promising of the two to advance into preclinical development in 2007. Further characterization will include metabolic profile, PK, and mutagenic potential of the two candidates.

**NPC1161B, AN 8-AMINOQUINOLINE**

- **Target disease:** visceral leishmaniasis
- **Partners:** University of Mississippi (UM), USA (Principal Investigator); Medicines for Malaria Venture (MMV), Switzerland; London School of Hygiene & Tropical Medicine (LSHTM), UK.
- **DNDi Project Manager:** Denis Martin
- **Project start:** December 2005

8-aminoquinolines are a class of compounds with considerable anti-parasitic activity, but their potential has been limited in the past due to human toxicity. A team of researchers led by the University of Mississippi recently developed NPC1161B, a new lead compound from the 8-aminoquinoline class, which is very effective against parasites for both malaria and leishmaniasis, and offers promise for reduced hematological toxicity in man. MMV has been working in collaboration with UM to further preclinical development of NPC1161B because of promising oral efficacy against P. vivax infection. Through a cooperative agreement, DNDi and MMV will share clinical information, as well as significant scientific findings regarding the non-clinical safety data, metabolism, or other relevant findings. In 2006, DNDi has provided financial support for additional studies on the in vivo antileishmanial/trypansomal activity of NPC1161B. DNDi will undergo a review process with its SAC in May 2007 to decide whether to pursue this project or other 8-aminoquinolines further advanced in the drug development pipeline.

**RAVUCONAZOLE**

- **Target disease:** Chagas disease
- **Partners:** Federal University of Ouro Preto, Brazil; Instituto Venezolano de Investigaciones Científicas, Venezuela; EISAI Co. Ltd., Japan.
- **DNDi Project Team:** Robert Don, Isabela Ribeiro
- **Project start:** 2005

Preclinical studies with antifungal triazoles have shown considerable efficacy in the treatment of Chagas disease in animal models. Two of these compounds have been in development for fungal infections: ravuconazole (Eisai) is currently in Phase III studies, and posaconazole (Schering Plough) was recently registered for treatment of fungal infections in Europe and as an antifungal prophylactic in the USA. At the end of 2006, two of three animal studies have been completed with ravuconazole because of promising oral efficacy against P. vivax infection. Through a cooperative agreement, DNDi and MMV will share clinical information, as well as significant scientific findings regarding the non-clinical safety data, metabolism, or other relevant findings. In 2006, DNDi has provided financial support for additional studies on the in vivo antileishmanial/trypansomal activity of NPC1161B. DNDi will undergo a review process with its SAC in May 2007 to decide whether to pursue this project or other 8-aminoquinolines further advanced in the drug development pipeline.
Finding a safe and affordable alternative

**AMPHOTERICIN B POLYMER**

- **Target disease:** visceral leishmaniasis (VL)
- **Partners:**
  - Imperial College, UK (Principal Investigator); London School of Pharmacy, UK; London School of Hygiene and Tropical Medicine (LSHTM), UK; Advinus, India; Shanta Biotech, India.
- **DNDi Project Manager:** Denis Martin
- **Project start:** September 2006

Liposomal amphotericin B (AmBisome), an efficacious yet highly expensive formulation of amphotericin B, has been increasingly used to treat VL. However, its use in the VL-endemic regions of Africa and Asia has been limited due to its high cost, which prices it out of use in developing countries with the highest burden of disease. Instead, patients there still receive the acutely toxic, yet more affordable, amphotericin B, a 70-year-old drug which kills 10% of the patients treated with it. This project aims to combine the amphotericin molecule in a way that is similar yet different from the way AmBisome is modified. Instead, in this project, amphotericin B will be surrounded by a less expensive methacrylic acid derived polymer, which is expected to make a drug that is stable in hot climates, highly soluble, relatively inexpensive, safe, and effective in short-term therapy of VL. The early stage proof-of-concept of the efficacy of a modified methacrylic has been shown by the Imperial College team.

At the end of 2006, experimental work has begun in *in vivo* mouse models at LSHTM, where initial efficacy and safety data look promising. In 2007, researchers will optimize the *in vitro* and physicochemical properties of the amphotericin-polymer complex with the aim to have a well-defined polymer weight and ratio between amphotericin B and polymer.
Clinical Projects

The six clinical projects in DNDi’s portfolio at the end of 2006 are mainly constituted of a cluster of new formulations of established drugs, drugs switched from other indications, or drug combinations. While there are few novel compounds in this area in R&D for neglected diseases, all of the treatments under investigation can have a real impact on improving patient treatment in the near future and serve to strengthen clinical research capacity that will be used in the future for evaluating novel compounds. Two of the clinical projects, which are currently undergoing the registration process, are expected to be available to patients in Africa and Latin America in 2007.

COMBINATION THERAPY
- Target disease: visceral leishmaniasis (VL)
- Partners:
  - ICMR, India; Kala-azar Medical Research Centre, India; Rajendra Memorial Research Institute, India; University of Varanasi, India
- DNDi Project Team: Catherine Royce, Bhawna Sharma
- Project start: December 2006

At the end of 2006, preclinical studies for efficacy and toxicology have been completed. In 2007, a project team will be assembled and a clinical study protocol drafted in the first quarter; and by the end of the year, patient enrolment will be initiated.

IMIQUIMOD ADJUNCT IMMUNOTHERAPY
- Target disease: cutaneous leishmaniasis (CL)
- Partners:
  - McGill University, Canada (Principal investigator); Universidad Peruana Cayetano Heredia, Peru.
- DNDi Project Team: Catherine Royce, Isabela Ribeiro
- Project start: June 2005

Current treatments for CL are administered systematically and require protracted treatment by daily intramuscular injections. With DNDi’s ultimate goal to develop a better tolerated, more convenient, and cheaper therapy for CL than current standards, the study objective is to determine the efficacy and safety of a topical administration of imiquimod, an immunomodulator that is used extensively as a topical treatment for genital warts. Imiquimod’s mechanism of action is to stimulate a local immune response at the lesion site and therefore resolve the infection. As imiquimod is already available as a generic in a few countries with endemic leishmaniasis, it has the potential to be a readily affordable and available treatment. The primary endpoint of the clinical study, analysis of 3-month follow-up data, was made in December 2006. In 2007, the 12-month follow-up data will be available.
ASAQ, FIXED-DOSE ARTESUNATE/AMODIAQUINE COMBINATION THERAPY

- **Target disease:** malaria
- **Partners:** Centre National de Recherche et de Formation sur le Paludisme, Burkina Faso; University Sains Malaysia; Oxford University, UK; Mahidol University, Thailand; Tropival, France; Ellipse Pharmaceuticals, France; Rottendorf Pharma, Germany; Médecins Sans Frontières; TDR; sanofi-aventis.
- **DNDi Project Team:** Jean-René Kiechel, Graciela Diap
- **Project start:** January 2002

ASAQ, the new fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ), will be the first drug to be delivered by DNDi and is intended to treat paediatric and adult uncomplicated falciparum malaria, with a primary focus on Africa and some countries in Asia where amodiaquine resistance is low.

With resistance a major threat to malaria control, artemisinin-based combination therapies (ACTs) offer a way to counter resistance: the combination of AS and AQ was one of four ACTs recommended by WHO in 2001 as first-line treatment for uncomplicated falciparum malaria, but it did not yet exist as a FDC nor was it in FDC development. Hence, the FACT (Fixed-Dose, Artesunate-Containing Therapy) Project was undertaken in 2002 by a number of public and private partners coordinated by TDR and MSF (who turned over the project to DNDi upon its foundation).

AS and AQ are well-known drugs, with scientific evidence supporting the use of the combination of AS and AQ in approximately 10,000 patients. 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.

In December 2004, sanofi-aventis signed on as industrial partner and has been involved in industrial, preclinical, and clinical product development, as well as in preparation of all of the registration files. ASAQ will be a quality, easy-to-use product that will be readily available and affordable at cost price (<US$1 for adults and <US$0.50 for children in public markets) as a non-patented public good.

The year 2006 was a milestone year for ASAQ: in February, the pivotal Phase III field study, which enrolled 750 children in Burkina Faso, successfully concluded and showed final results of >95% efficacy, which were presented at the American Society for Tropical Medicine and Hygiene (ASTMH) annual meeting in November; also in November, sanofi-aventis filed for registration in Morocco, the country where ASAQ is manufactured.

2007 holds great promise as the next steps for ASAQ are to: obtain regulatory approval in Morocco, undergo submission for WHO prequalification, and continue to be registered in all sub-Saharan African countries where it can be of substantial public health benefit.
Clinical Projects

- **Fixed-dose Artesunate/Mefloquine (AS/MQ) Combination Therapy for Malaria**
  - **Target disease:** malaria
  - **Partners:** Farmanguinhos, Brazil; Mahidol University, Thailand; Shoklo Malaria Research Unit, Thailand; University Sains Malaysia; Oxford University, UK; Médecins Sans Frontières; TDR.
  - **DNDi Project Team:** Jean-René Kiechel, Isabela Ribeiro
  - **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 malaria. ASMQ, the new co-formulation of AS and MQ, offers a single daily dose of one or two tablets over three days and provides added regimen simplicity.

Consistent with 2006 WHO treatment guidelines, ASMQ will serve as a fixed-dose combination to treat uncomplicated *falciparum* malaria in paediatric and non-pregnant adult populations. Drug deployment efforts are initially focused on areas of low transmission, including Southeast Asia and South America, but ASMQ can potentially be used in all endemic regions including those affected by multi-drug resistant *P. falciparum* strains.

In the year 2006, significant progress was made. Results were published and showed the efficacy and side-effect profile of ASMQ to be equivalent to the non-fixed combination of AS and MQ, with a number of clinical trials undertaken by the Brazilian national control programme.

- **Paromomycin for Africa**
  - **Target disease:** visceral leishmaniasis
  - **Partners:** Kenya Medical Research Institute, Kenya; University of Nairobi, Kenya; University of Addis Ababa, Ethiopia; Institute of Endemic Diseases, University of Khartoum, Sudan; Gedeeref University, Sudan; National Ribat University, Sudan; IDA; Médecins Sans Frontières-Holland; TDR; London School of Hygiene and Tropical Medicine, UK.
  - **DNDi Project Manager:** Elis Torreele
  - **Project start:** November 2004

Paromomycin, an aminoglycoside antibiotic that was identified in the 1960s as an antileishmanial, represents an improved treatment at a lower cost that will allow it to be adopted in developing countries suffering the largest disease burden of VL. A critical milestone was met for paromomycin development in 2006 as our partner PDP, the institute for One World Health (OWH), successfully registered paromomycin intramuscular (IM) injection in India in August.

At the end of 2006, patient recruitment at the three DNDi sites in DRC was completed after reaching the 280 patient target for the trial (when taking account the number of patients enrolled at the Congo-Brazzavile site). A full safety analysis will be completed by mid 2007. Final results of the trial, including the efficacy analysis at the 18-month follow-up, are expected by the fourth quarter of 2008.
is to register paromomycin as a new treatment in each region and to have it adopted in national treatment guidelines.

At the end of 2006, the study is currently recruiting patients at six sites in Ethiopia, Kenya, and Sudan, five of which have been improved or built using the experience gained from the Trypanosomiasis Control Unit built by DNDi in Atesha (Mara), Ethiopia. The next step for the project will be an interim analysis to be completed by early 2008.

AMBISOME

- **Target disease:** Visceral leishmaniasis (VL)
- **Partners:** Addis Ababa University, Ethiopia; London School of Hygiene and Tropical Medicine, UK.
- **DNDi Project Manager:** Catherine Royce
- **Project start:** upon completion of the paromomycin study

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, there is a possibility that AmBisome could become economically feasible for use in resource-poor countries. The goal of this project is, therefore, to determine the minimum dose of AmBisome that is efficacious, safe, and cost-effective in the treatment of VL, to reduce length of hospital stay, and to facilitate registration and adoption of AmBisome in Ethiopia. Identifying the minimum dose for monotherapy will be an important step in developing combinations by Africa.