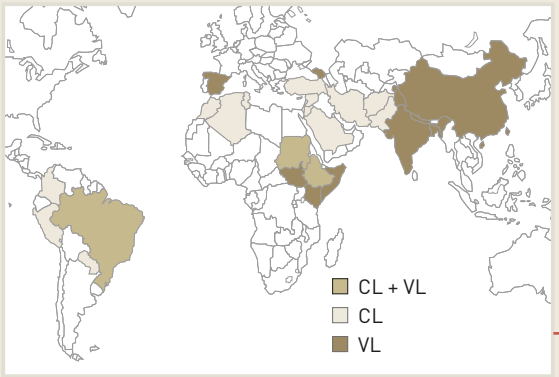
LEISHMANIASIS

- *Leishmania* parasite transmitted by the bite of a sandfly
- Three main forms of leishmaniasis: visceral (VL - fatal without treatment), cutaneous (CL), and mucocutaneous (MCL)
- Post-kala-azar dermal leishmaniasis (PKDL) is a disease causing skin lesions which mostly affects individuals after treatment for VL; PKDL may play a major role in disease transmission between epidemics
- VL in HIV co-infected patients is an increasing concern
- The treatment of leishmaniasis depends on several factors including type of disease, concomitant pathologies, parasite species, and geographic location

350

million people around the world at risk



Until recently, pentavalent antimonials like sodium stibogluconate (SSG) were the mainstay of treatment for VL and CL, despite numerous drawbacks (toxic, difficult to administer, expensive, and even poorly efficacious in many regions). These drugs nevertheless remain the therapy of choice for CL, in the absence of an effective, safe, and affordable alternative, so R&D needs for CL remain acute.

For visceral leishmaniasis, alternatives do exist, with liposomal amphotericin B, paromomycin (PM), and miltefosine either developed or made available over the last 15 years. In its first decade of operation, DND*i* research was aimed at optimizing regimens based on existing treatments.

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90% of new VL cases reported occur in seven countries:

- Brazil
- Ethiopia
- Kenya
- India
- Somalia
- South Sudan
- Sudan

Majority of CL cases reported occur in nine countries:

- Afghanistan,
- Algeria
- Brazil
- Colombia
- Iran
- Pakistan
- Peru
- Saudi Arabia
- Syria

20,000
to 30,000 deaths due to VL annually

200,000
to 400,000 cases of VL annually

5-10%
of VL patients develop PKDL

700,000
to 1.2 million cases of CL annually

Dr Márcia Hueb
Julio Müller Hospital, Cuiabá, Brazil

"Treatment for leishmaniasis involves complicated injectable drugs. The diagnosis isn't easy, it depends on skill and knowledge. We must move forward."

•••

As a result, the combination of SSG and PM (see p. 8) is now the standard treatment in East Africa, while in South Asia single-dose AmBisome® is the first option, with paromomycin and miltefosine as a second line. Yet, these treatments still present safety, logistical, affordability, and access drawbacks, and the search for entirely new treatments – more patient-friendly, effective, safe, and ideally oral – is still the basis for DND*i*'s long-term R&D strategy.

Research needs in leishmaniasis are further complicated by specific questions that are yet to be addressed. While the VL case load is falling to such a degree that elimination targets appear to be within reach in South Asia, the role in *Leishmania* transmission played by PKDL and asymptomatic patients must be clarified if elimination is to be sustained. And in both South Asia and East Africa, better treatments are required for patients co-infected with HIV as current options are unsatisfactory, requiring long and often repeated courses of treatment, including with antimonials.

"I feel ashamed of myself and don't feel like going anywhere. People around laugh at me with sarcasm and sometimes hatred. I felt humiliated because of these scars on my face."

Ruby Devi
PKDL patient diagnosed when seven months pregnant, New Delhi, India

DND*i* aims to deliver:

- **A safe, effective, low-cost and short-course, oral treatment** for VL
- **A new treatment for PKDL** that is shorter and better tolerated than current options
- **A new treatment regimen for patients co-infected** with HIV and VL
- **A safe, effective, and shorter-course treatment** for CL

"This disease has destroyed my life, my wife left me, I can't see my children as much as I used to and I was fired from my job because I was too weak to work. All that I had was used to pay medical bills."

Tsadik
35 years old, HIV-VL patient, Abdurafi, Ethiopia

RESEARCH

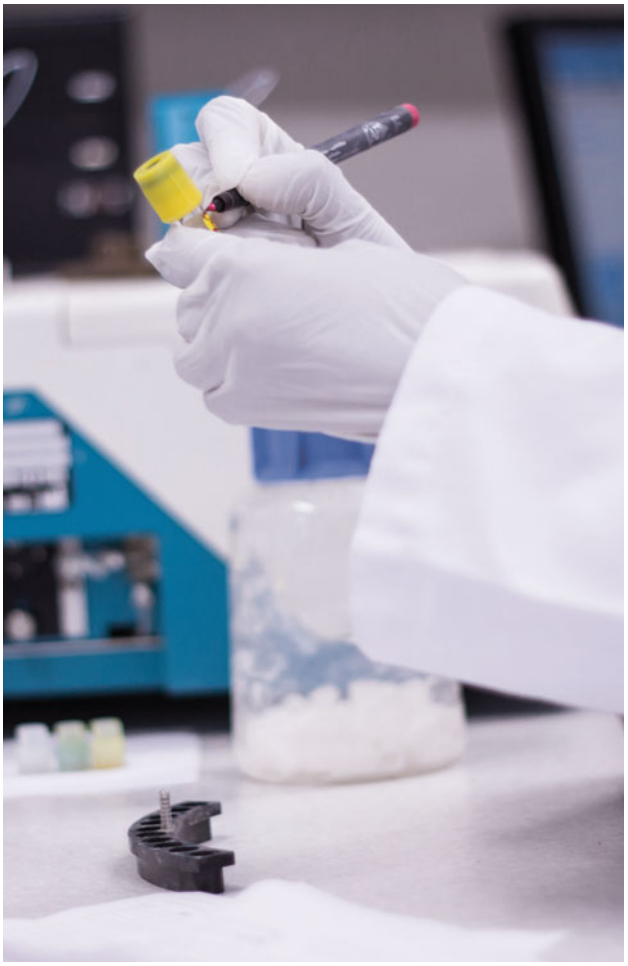
Leish H2L

Hit-to-lead for leishmaniasis

OBJECTIVE: Identify new leads series from current ongoing hit-to-lead activities by taking advantage of the optimization consortia and screening platforms for leishmaniasis.

Background: Hit-to-lead is a dynamic phase in the drug discovery cascade in which small molecule hits from high throughput screens are evaluated and undergo optimization to identify promising lead compounds.

2016 This process of hit-to-lead optimization is ongoing with multiple series from several pharmaceutical companies. If promising activity can be demonstrated in pre-clinical models of leishmaniasis, the series will be advanced into full lead optimization.



RESEARCH

DNDI-5421 & DNDI-5610 oxaboroles

OBJECTIVE: Maintain back-up oxaboroles which could replace the pre-clinical candidate DNDI-6148 in case it does not succeed in development.

Background: These two compounds from the oxaborole class from Anacor Pharmaceuticals serve as back-ups to DNDI-6148. Their further development is currently on hold and will only recommence should problems be encountered with the pre-clinical development of DNDI-6148.

RESEARCH

Aminopyrazoles

OBJECTIVE: Select a pre-clinical candidate from the aminopyrazole series for the treatment of leishmaniasis.

Background: The aminopyrazole class of compounds originally from Pfizer has shown promising early profiles for the treatment of both VL and CL. Profiling of current and new leads in a panel of drug-sensitive and drug-resistant strains of *Leishmania*, exploration of the *in vivo* dose response, pharmacokinetics, and initial *in vitro* safety assays are all underway. The ongoing lead optimization programme in collaboration with Takeda and supported by the GHIT Fund aims to select an optimized lead.

2016 Preparation of active pharmaceutical ingredient (API) and formulation for the second generation leads to enable the exploratory toxicology studies early 2017.

RESEARCH

CGH VL series 1

OBJECTIVE: Select a pre-clinical candidate from the CGH VL series for the treatment of VL.

Background: A novel series of heterocyclic compounds for VL has been optimized by Celgene in collaboration with London School of Hygiene and Tropical Medicine and Advinus, and with advice from DND*i*.

2016 An *in vivo* proof-of-concept has been achieved for this series. An intensive lead optimization programme is ongoing with Celgene to identify an optimized lead.

TRANSLATION

DNDI-6148 oxaborole

OBJECTIVE: Progress the pre-clinical development of DNDI-6148, a selected oxaborole for the treatment of leishmaniasis.

Background: The Lead Optimization US programme has progressed the compound DNDI-6148 into pre-clinical development. DNDI-6148 resulted from medicinal chemistry optimization of hits with activity against *Leishmania* originally identified from screening of Anacor's oxaborole library.

2016 In January, DNDI-6148 was nominated as a pre-clinical candidate for the treatment of VL. Pharmaceutical development activities (drug substance and drug product development and manufacture) have now been initiated, and the toxicity/safety pre-IND package was launched, starting with dose range finding studies, along with refinement of ADME (absorption, distribution, metabolism, and elimination), and efficacy and safety profiles to ensure a smooth transition from pre-clinical to Phase I clinical studies, which should happen over the course of 2017.

TRANSLATION

DNDI-0690 nitroimidazole

OBJECTIVE: Progress the pre-clinical development of DNDI-0690, a selected nitroimidazole for the treatment of VL and possibly CL.

Background: Following the termination of the VL-2098 project in early 2015, two lead compounds from the nitroimidazooxazine back-up programme were progressed. One of these, DNDI-0690, showed good to excellent activity *in vitro* against both VL and CL-causing strains of *Leishmania* and was nominated as a pre-clinical candidate in September 2015.

DNDI-0690 and other potential lead compounds for VL were profiled *in vitro* against CL-causing strains of *Leishmania* at the London School of Hygiene & Tropical Medicine and the Walter Reed Army Institute of Research.

2016 DND*i* activities focused on pharmaceutical development activities (drug substance and drug product development and manufacture), launching of toxicity/safety pre-IND package with dose range finding studies, as well as refinement of ADME, efficacy and safety profile to ensure a smooth transition from pre-clinical to Phase I studies, which should happen over the course of 2017.

TRANSLATION

CpG-D35 for CL

OBJECTIVE: Produce an immunomodulator to stimulate the innate immune system to fight the parasitic infection causing CL as an adjunct to drug therapy.

Background: CpG-D35 is being developed as a combination therapy for the treatment of complicated CL and post-kala-azar dermal leishmaniasis (PKDL) in partnership with GeneDesign. *Leishmania* parasites are able to persist in host cells by evading or exploiting immune mechanisms. Modulating the immune response with CpG oligonucleotides may improve the effectiveness of chemotherapies.

2016 Two studies, one *in vitro* and one *in vivo*, were initiated. The *in vivo* study aims to demonstrate if CpG-D35 – whether alone or in combination with antimonials chemotherapy – will lead to improved *Leishmania* infection outcomes, compared with antimonials alone. The *in vitro* study aims to assess the stimulatory capability of CpG-D35 in both peripheral blood mononuclear cells and whole blood samples from patients with both CL and PKDL, and to determine which host genes are modulated in these two conditions. Results of both studies are expected by the end of 2017.

TRANSLATION

New CL combination therapies

OBJECTIVE: Further explore opportunities to better use the existing approved treatment approaches for CL when used in combination.

Background: When administrated alone, the safety and efficacy profiles of current CL treatments are well established. A combination of therapeutic approaches may improve efficacy rates, reduce treatment duration, and improve the rate of adverse events. A combination of one single application of thermotherapy at 50°C for 30 seconds with a three-week course of oral miltefosine will be tested in order to gain information about safety and efficacy.

2016 After official approvals were obtained, a site initiation visit was conducted and the first patients were enrolled in Peru at the end of 2016. Final approvals are expected by early 2017 for a second site in Colombia.

TRANSLATION

Fexinidazole/miltefosine combination [completed]

OBJECTIVE: Develop an oral-only therapy for the treatment of VL.

Background: Before proceeding to a proof-of-concept study in patients, a drug-drug interaction study was to be conducted in up to 60 healthy volunteers to assess the combination's pharmacokinetics, tolerability, and safety.

While ethical approval was granted, French regulatory authorities stated that there was not sufficient information available to justify a study in healthy volunteers. Considering the excellent activity of the new oral chemical entities currently in pre-clinical development for VL, the development of the fexinidazole/miltefosine combination was stopped.

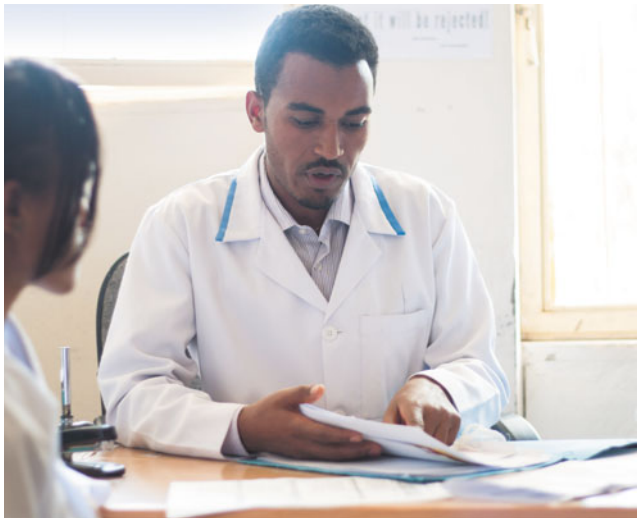
TRANSLATION

Anfoleish for CL [completed]

OBJECTIVE: Develop at least one modality of treatment for CL.

Background: The aim was to develop a topical formulation of amphotericin B to be applied at the CL lesion, that showed high anti-parasitic effect without the systemic toxicity associated with amphotericin B. A Phase Ib/II open-label, randomized, non-comparative, two-arm exploratory study was conducted in Colombia. Enrolment of all 80 patients with CL caused by *L. braziliensis* and *L. panamensis* was completed in November 2015.

Study results did not support continuation of the clinical development of Anfoleish in its current formulation. Alternative options are currently under consideration.



DEVELOPMENT

New treatments for HIV/VL

OBJECTIVE: Identify and deliver a safe and highly effective treatment for VL in HIV co-infected patients that will improve long-term survival of these patients.

Background: In 2014, a Phase III study testing both AmBisome® monotherapy (at a higher dose than current practice) and a combination of AmBisome® and miltefosine was initiated in Ethiopia for the treatment of HIV/VL co-infection. After 132 patients had been enrolled, recruitment was interrupted at the time of the second interim analysis, as efficacy at the end of treatment was lower than expected. Patients who had not achieved cure at the end of treatment were given a second cycle of the same treatment.

2016 Results obtained with the extended duration of the combination treatment were very promising; the majority of patients achieving VL cure. These results were based on a limited number of patients; a new HIV/VL study is therefore under consideration to confirm this.

DEVELOPMENT

New treatments for PKDL

OBJECTIVE: To determine the safety and efficacy of two treatment regimens for patients with PKDL, mainly in the Indian Sub-continent and East Africa.

Background: DND*i* is prioritizing the management of PKDL patients who are believed to constitute a potential reservoir of infection for VL in the Indian Sub-continent and East Africa. Early treatment of PKDL patients could be critical elements of any VL public health and elimination strategy.

2016 A Phase II study testing both AmBisome® monotherapy and a combination of AmBisome® and miltefosine is underway in India and Bangladesh to assess the safety and efficacy for patients with PKDL. A separate Phase II study to assess the safety and efficacy of both AmBisome® in combination with miltefosine, and paromomycin in combination with miltefosine, is planned in Sudan. Site visits have been undertaken at all participating sites in the three countries, and protocols and study documents are under finalization for submission to ethical and regulatory review. In addition, two PKDL infectivity studies are under preparation in Bangladesh and Sudan. Their objective is to establish the infectivity of PKDL patients to sand flies, to determine if PKDL patients maintain inter-epidemic transmission of VL.

Dr Pradeep Das
Director, Rajendra Memorial Research Institute, Patna, India

"After a long collaboration with DND*i* for research for VL, we are now entering into bringing new treatments for PDKL patients. This collaboration will definitely help the poor patients standing last in the queue with better and affordable treatment. To invest in research on the precise role of PKDL patients is critical as they could maintain transmission of visceral leishmaniasis during inter-epidemic periods. Early treatment of the most infective PKDL patients should be a priority element of any VL public health and elimination strategy."

DEVELOPMENT

Miltefosine/paromomycin combinations for Africa

OBJECTIVE: Assess the efficacy and safety of two combination regimens of paromomycin (PM) and miltefosine as compared to SSG&PM for the treatment of primary VL patients in Eastern Africa.

Background: A Phase III clinical trial will be conducted in East Africa to compare the efficacy and safety of two combination regimens of miltefosine and PM with the current standard VL treatment sodium stibogluconate (SSG)&PM, in both paediatric and adult patients. Sites will be located in Kenya, Sudan, Uganda, and Ethiopia. If the combination is proven safe and efficacious, current treatment would no longer rely on SSG, an injectable drug, but would be replaced with miltefosine, an oral drug. A safer, more field-adapted, patient-friendly treatment would particularly benefit children, who represent a high proportion of the population at risk in East Africa.

2016 The trial protocol is under finalization and will be submitted to ethics committees and regulatory authorities in early 2017.

DEVELOPMENT

New VL treatments in Latin America

OBJECTIVE: Assess the efficacy and safety of amphotericin B deoxycholate, AmBisome®, and AmBisome® combined with Glucantime®, as compared to the first-line treatment, Glucantime®, for the treatment of VL patients in Brazil, supporting the Brazilian Ministry of Health and its partners.

Background: In 2011, a Phase IV study sponsored by the Brazilian Ministry of Health (FINEP) was initiated at five sites in Brazil to evaluate the efficacy and safety of Amphotericin B deoxycholate, AmBisome®, and a combination of AmBisome® and Glucantime®, in comparison to Glucantime®, the existing first-line treatment of VL. 378 patients were recruited. Brazil's national guidelines for VL were revised in 2013 based on the interim safety data from the trial. While Glucantime® remains the first-line treatment, AmBisome® replaced Amphotericin B deoxycholate as a second-line treatment.

2016 The final results of this trial were presented to the Ministry of Health, and are expected to guide further policy change in Brazil as of 2017.

378
patients recruited at 5 sites