CUTANEOUS LEISHMANIASIS: DNDi STRATEGY

Byron Arana, Joelle Rode, Marina Boni
DNDi is a collaborative, patients’ need-driven, non profit drug research and development organization that is developing new treatments for neglected diseases.

HQ in GVA, Regional offices in Rio de Janeiro, Nairobi and New Delhi, Japan, USA, Malaysia.
6 New Treatments Developed Since 2007

- ASAQ (Fixed-dose combination of artesunate + amodiaquine)
- ASMQ (Fixed-dose combination of artesunate + mefloquine)
- NECT (Nifurtimox-eflornithine combination therapy)
- SSG&PM (Sodium stibogluconate & paromomycin combination therapy)
- NEW VL TREATMENTS IN ASIA
- Benznidazole 12.5 mg

- Easy to Use
- Affordable
- Field-Adapted
- Non-Patented
DNDi Portfolio June 2015
6 New Treatments since 2003

**HAT**
- SCYX1330682
- SCYX1608210
- Fexinidazole
- SCYX-7158

**Leishmaniasis**
- Nitroimidazoles
- Oxaleish
- Leish H2L
- Amino pyrazoles
- CpG-D35 (CL)
- Anfoleish (CL)
- New CL Combos

**Chagas**
- Chagas H2L
- Biomarkers
- New Benz Regimens/Combos

**Filaria**
- Macro Filaricide 2
- Emodepside
- Macro Filaricide 2

**Paediatric HIV**
- Two ‘4-in-1’ LPV/r based FDC granules
- LPV/r pellets with dual NRTI FDC

**Mycetoma**
- E1224

**New Treatments for HIV/VL**
- Benznidazole Paediatric Dosage Form

**New VL Treatments**
- Asia
- Africa

**NECT**
- Nifurtimox-Eflornithine Combination Therapy

**Research**
- Screen
- Hit to Lead

**Translation**
- Pre-clinical
- Phase I
- Phase Ila/PoC

**Development**
- Phase IIb/III
- Registration

**Implementation**
- Access

**Biomarkers**
- Fexinidazole

**New Chemical Entity (NCE)**
Cutaneous Leishmaniasis Program

2010  CL included in DNDi portfolio
2011  CL strategy approved and endorsed by SAC and BoD

Q1 2012  Anfoleish selected for its clinical development
Q1 2014  Enrolment of first patient
Q2 2015  Enrolment of first 30 patients completed. DSMB met and recommended continuation of the enrolment.

Q2 2015  Combinations approach approved by R&D and SAC

2012  Literature review completed
Q1 2013  In vitro – in vivo studies of selected compounds (none selected for further studies)
Q4 2014  Inclusion of CL strains in the screening of VL compounds
Q2 2015  Firsts orals compounds identified (in vitro and in vivo studies)

Q1 2014  CpG D35 approved by SAC and Q2 2014 by BoD
Q4 2014  CpG D35 Demo project merged with VL Demo project
Q3 2015  Licence agreement with NIH and CRADA with FDA completed
Q3 2015  Initiation of CMC and Tox package studies
### Spectrum of the disease, current treatment options and gaps

#### Diseases Severity

<table>
<thead>
<tr>
<th>No Tx</th>
<th>Topical</th>
<th>Syst oral</th>
<th>Syst parenteral</th>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable self healing rate (0-40% at 6M)</td>
<td>Multiple applications</td>
<td>Variable efficacy</td>
<td></td>
<td></td>
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<tr>
<td>Might take long time</td>
<td>Painful</td>
<td>Teratogenic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission in ACL</td>
<td>Equipment</td>
<td>GI and renal problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Access</td>
<td>Availability</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Cosmetic problems</td>
<td>Cost</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Toxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teratogenic</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Difficult to administrate</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Compliance</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Efficacy is ↓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### The “gap”

Topical & oral drugs, safe, effective against all forms of CL, with superior cosmetic results, at a low-cost and easy to use in rural areas.
DNDi CL Strategy: Objective

To achieve short, safe, non-invasive, efficacious, affordable and field-friendly treatments for CL or at least for lesions caused by *L. tropica* and *L. braziliensis*.

**High level**

- **Disease**: Cutaneous Leishmaniasis
- **Indication or presentation**
  - 1-4 ulcerated lesions
  - Non-ulcerated multiple / large lesions
  - Special Forms PKDL / Others
- **Approach**
  - Topical Combination
  - Systemic Oral
  - Immuno-modulator + drug(s)

**More detailed**

- Anfoleish TT + Milt
- Alone / Combo
- CpG D35 +

**Overall strategy**
- General positioning
- Could include multiple approaches

**Individual project**
- Highly specific
CL Roadmap

- **Anfoleish**
  - Phase 1b/2
  - Phase 1b/2
  - Phase 3 (NW)

- **Combinations**
  - PoC (NW)
  - Phase 3 (NW)

- **Orals**
  - Screening
  - In vitro/ vivo
  - CMC-Tox
  - Phase I
  - Phase II

- **CpG - D35**
  - CMC – Tox Pre-clinical
  - Phase 1a
  - Phase 1b

**Go / No Go decisions**
Anfoleish is a topical formulation containing 3% of AmB

The 3% concentration was based on previously available AmB topical products in the market (Fungizone cream, which is no longer available).

Formulations in the range 0.3%-3% w/w were evaluated and was found that Amphotericin B concentrations at 3% offered the best option.

Pre-clinical studies showing encouraging results in animal models.

Open label study in humans shows to be very efficacious (10 out 11)
Safety, PK, and Efficacy of topical 3% Amphotericin B cream (Anfoleish) for the treatment of uncomplicated cutaneous leishmaniasis in Colombia

* Enrollment will be paused after enrolling 15 subjects per arm.
Systemic → Oral Drugs

- Literature review (DNDi Brazil)
- Screening of drugs/compounds against cutaneous leishmaniasis *in vitro* (Imperial College London)
  
  ~ 50 compounds already in the market or in late stage of development were screened against *L. tropica* and *L. braziliensis*

- Effect of ravuconazole (E1224) in BALB/c mice infected with *L. tropica* (Pasteur Institute, Iran) and in gold hamster model infected with *L. braziliensis* (PECET, Medellin, Colombia)

- *In vitro and In vivo* evaluation of fexinidazole against CL *Leishmania* strains (FIOCRUZ)
## Literature Review

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Trials</th>
<th># CT</th>
<th>In Vivo studies</th>
<th>#</th>
<th>In Vitro studies</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>Weak OW &amp; NW (45% - 83%)</td>
<td>8</td>
<td>La, Lb, Lm (Weak)</td>
<td>3</td>
<td>Lm, La, Lb (Strong)</td>
<td>3</td>
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<tr>
<td>Chloroquine</td>
<td>Weak</td>
<td>1</td>
<td>No evidence</td>
<td>0</td>
<td>No evidence</td>
<td>0</td>
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<tr>
<td>Chlorpromazine</td>
<td>Weak (Case report)</td>
<td>Lm, L mex, L aeth (Weak)</td>
<td>2</td>
<td>Lm, L mex, Lm, L aet (Strong)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Weak</td>
<td>1</td>
<td>La, L mexicana (Strong)</td>
<td>2</td>
<td>No evidence</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofl oxacin</td>
<td>Weak</td>
<td>1</td>
<td>No evidence</td>
<td>0</td>
<td>Lp (Strong)</td>
<td>2</td>
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<tr>
<td>Clofazimine</td>
<td>Weak</td>
<td>1</td>
<td>La, Lm (Weak)</td>
<td>1</td>
<td>La, Lm, Lb, Lt, L. mex (Strong)</td>
<td>2</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>Weak</td>
<td>1</td>
<td>L, Lm (Weak)</td>
<td>1</td>
<td>L (Weak)</td>
<td>1</td>
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<tr>
<td>Dapsone</td>
<td>Strong to weak</td>
<td>5</td>
<td>L?</td>
<td>1</td>
<td>Lm (Strong)</td>
<td>1</td>
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<tr>
<td>Furazolidone</td>
<td>Weak</td>
<td>1</td>
<td>No evidence</td>
<td>0</td>
<td>Lm, La, Lb, L chagasi (Strong)</td>
<td>3</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Strong - Controversial</td>
<td>10</td>
<td>Strong</td>
<td>1</td>
<td>Lm (Weak)</td>
<td>1</td>
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<tr>
<td>Mefloquine</td>
<td>Weak - Controversial</td>
<td>7</td>
<td>La (Weak)</td>
<td>1</td>
<td>No evidence</td>
<td>0</td>
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<tr>
<td>Miconazole</td>
<td>Weak</td>
<td>3</td>
<td>La, Lm (Weak)</td>
<td>1</td>
<td>L (Weak)</td>
<td>1</td>
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<tr>
<td>Omeprazole</td>
<td>Strong (in combination)</td>
<td>2</td>
<td>Lb (Weak)</td>
<td>1</td>
<td>No evidence</td>
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<tr>
<td>Rifaximic</td>
<td>Strong to weak</td>
<td>13</td>
<td>Lm (Weak)</td>
<td>3</td>
<td>La, Lm, Lt (Weak-Controversial)</td>
<td>4</td>
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<tr>
<td>Terbinacine</td>
<td>Weak</td>
<td>1</td>
<td>La, Lm (Weak)</td>
<td>2</td>
<td>Lb, La, Lm, L mex. Sinerg. w Ket</td>
<td>4</td>
</tr>
<tr>
<td>Fluocoanazol</td>
<td>Strong but methodol prob</td>
<td>2</td>
<td>No evidence</td>
<td>0</td>
<td>No evidence</td>
<td>0</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Case report (Strong)</td>
<td>La (Strong)</td>
<td>1</td>
<td>La, Lm, Lb, Lp, L mexicana (Weak)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Zinc Sulphate</td>
<td>Weak</td>
<td>1</td>
<td>?</td>
<td></td>
<td>Lm (Weak)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Weak:** efficacy < 60% and/or < standard treatment; Efficacy range variable but < 60% and/or < standard treatment in RC trials

**Controversial:** efficacy range variable according to clinical trials and methodological issues (nC,nR trials, small number of patients. < 3mFU)

**Strong:** efficacy > or = 60%, or > or = standard treatment
**Oral Drugs: IC50 of the most active compounds against *L. braziliensis* and *L. tropica***

<table>
<thead>
<tr>
<th></th>
<th>IC50 (µM)</th>
<th>L. tropica</th>
<th>L. braziliensis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravuconazole</td>
<td>0.006543</td>
<td>0.004242</td>
<td>0.005043</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.009452</td>
<td>0.03391</td>
<td>0.009544</td>
</tr>
<tr>
<td>EPL-BS967</td>
<td>0.05981</td>
<td>0.443</td>
<td>0.05591</td>
</tr>
<tr>
<td>HOC</td>
<td>0.5303</td>
<td>1.283</td>
<td>0.5293</td>
</tr>
<tr>
<td>Clotrimazol</td>
<td>1.673</td>
<td>5.194</td>
<td>1.673</td>
</tr>
<tr>
<td>Fex-sulfone</td>
<td>1.729</td>
<td>6.108</td>
<td>1.729</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>1.792</td>
<td>6.376</td>
<td>1.792</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>3.849</td>
<td>6.72</td>
<td>3.849</td>
</tr>
<tr>
<td>Butenafine hyd.</td>
<td>4.041</td>
<td>6.409</td>
<td>4.041</td>
</tr>
<tr>
<td>Miconazole</td>
<td>4.676</td>
<td>8.409</td>
<td>4.676</td>
</tr>
<tr>
<td>Butenafine hyd.</td>
<td>5.344</td>
<td>8.875</td>
<td>5.344</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>9.544</td>
<td>14.71</td>
<td>9.544</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>13.1</td>
<td>27.41</td>
<td>13.1</td>
</tr>
<tr>
<td>Fex-sulfoxide</td>
<td></td>
<td>29.6</td>
<td></td>
</tr>
</tbody>
</table>
Class D CpG ODN D35 was selected based on its activity profile, the results on animal studies, the quality of the studies and the willingness for collaboration of the patent’s owner.

Favorable characteristics includes:
- Structure optimized for humans
- *In vitro* stimulation profiles of cells from monkey and human are similar
- Tested in a monkey CL model (with *L. major*) with encouraging results (reduction of pathogenicity, enhanced healing - even without a drug)
- No apparent toxicity
- Single or two low doses required
- Simple production amenable to large scale manufacturing at affordable cost (depending on needed dose for humans – to be reviewed further)
- Should results be favorable, D35 could be applicable for treatment of other disease forms.
CpG D35 Mode of Action

- Tested in a monkey CL model (with *L. major* and *L. amazonensis*) with encouraging results (reduction of pathogenicity, enhanced healing - even without a drug).
- No apparent toxicity in animal models.
- One dose of 100 µg/kg produce the desired immune response and efficacy in animal models.
- Effect evident even when administrated therapeutically (10-15 d after lesion development)
Can CpG ODN be used to treat established L. major skin lesions?

- 4-6 macaques per group challenged with $10^6$ metacyclic promastigotes
- Treated 15 days after challenge with 500 ug CpG ODN ID or SC (0.5 mg/kg).
Thermotherapy (1 application, 50°C x 30”) + Miltefosine for 3 weeks.

- Even though progress has been made for VL treatment, for CL it seems that what is currently available will probably represent almost the entire therapeutic arsenal for the coming years. *(Filling the gap with other formulations: CR-RCT: Sbv 53-78%; Milt 78%, LH 71%)*

- Multiples treatment combinations have been tested in the past and at least two are currently in use, specially in the EMRO region *(SOP for TT dev. by WHO available)*

- Theoretically, combining a topical with a systemic treatment offers the best chances to increase efficacy and reduce the length of treatment. *(Efficacy from ~75% to ≥ 90%; Length of Tx from 28d – 14-21d and GII AEs from ~10% to ≤5%)*

- A combination which requires the less contact with health providers and easily to implement in the field. *(Fits TPP)*
Annex 4.
Standard operating procedure for thermotherapy

Thermotherapy is an available technique for the treatment of cutaneous leishmaniasis patients by application of local heat at the site of lesion with a portable, battery-operated, localized current field radiofrequency generator (ThermoMed 1.8; Thermo-surgery Technologies).

Indication
- Papule, nodule or ulcer < 4 cm.
- Number of lesions < 4 cm.
- Location of the lesion should not be close to the eyes, nose or lips.

Method
A single thermotherapy treatment (one or more applications of localized heat of 50°C for 30 seconds, depending on lesion size). The area between the electrodes covers 49–73 mm². Therefore, several thermotherapy applications may be required to cover a lesion.

Procedure
- Disinfect the lesion and 2 cm border of healthy skin around the lesion with antiseptic (e.g. 0.1% chlorine dioxide solution).
- Anaesthetize the lesion with 1% lidocaine HCl.
- Moisturize the lesion with sterile saline solution.
- Apply the heat locally for 30 seconds.
- Apply chlorine dioxide gel to the lesions and then cover them after treatment.

Patient follow-up
To evaluate the outcome of thermotherapy, follow-up after completion of treatment should be scheduled at 14, 30, 45 and 180 days. It will be important to explain to patients that in case the lesion does not improve they should return to the health facility at any time.
A randomized, double blind, multicenter study to determine the efficacy and safety of combining thermotherapy and a short course of Miltefosine for the treatment of uncomplicated cutaneous leishmaniasis in the New World’
Thank You