TOWARDS THE FUTURE...
THE DEVELOPMENT OF NEW MACROFILARICIDE TREATMENTS

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Filaria Program
DNDi: a Patient Needs-Driven & Innovative R&D Model

- Created in July 2003 (7 founding members)
- Deliver **11 to 13 new treatments by 2018**
- Establish a robust pipeline
- Use and strengthen existing capacity in disease-endemic countries
- Raise awareness and advocate for increased public leadership

**Founding Partners**

- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation, Brazil
- Médecins Sans Frontières (MSF)
- Institut Pasteur France
- TDR (permanent observer)

7 worldwide offices
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**
  - SD Ambisome® / PM+M / A®+M /
- **Benznidazole** (12.5 mg Pediatric dosage form of benznidazole)

- Easy to Use
- Affordable
- Field-Adapted
- Non-Patented
Overcoming Challenges in the Field With Partners in Endemic Countries

In 10 years: >33,000 patients enrolled in >20 clinical studies
Onchocerciasis (River Blindness)

- An estimated 37 million people infected (99% of cases in Africa)
- 300,000 people blind (second highest infectious cause of blindness)
- 500,000 people visually impaired
- 6.5 million with severe itching or skin disease

Current treatment recommended by WHO: Ivermectin one or twice a year for MDA
Ivermectin is donated by Merck to Onchocerciasis Control Programs for MDA since 1989
Onchocerciasis: a disease with high socioeconomical impact

Onchocercal Skin Disease

- Acute papular onchodermatitis
- Chronic papular onchodermatitis
- Lichenified onchodermatitis
  - Oedema and secondary infections
- Skin atrophy 'lizard skin'
- Depigmentation 'leopard skin'

Onchocercal Eye Disease

- "River Blindness"
- Death of microfilaria and secondary inflammatory changes

- Stigmatism and discrimination
- Limited ability to work
The unmet medical need

Limitations of available treatments:

- Ivermectin, the only approved treatment (1989):
  - not a macrofilaricide
  - regular administration needed for 12-15 years to eliminate adult worms.
  - Limited use in regions with concomitant *Loa loa* infection
  - Potential resistance to ivermectin*

* defined as individuals with microfilaria (mf) counts in skin >10 mf/snip after nine or more rounds of ivermectin treatment Lancet 2007; 369: 2021–29
DNDi objectives

- To develop a new drug with macrofilaricide activity to:
  - Improve individual case management and cure patients
  - Provide treatment in areas with Loa-loa co-infection
  - Accelerate progress towards WHO elimination goal (ATS)
DNDi’s Discovery Strategy

- Repurposing of drugs from human health applications through an active screening program of drug compounds (e.g. AbbVie, Astra Zeneca, Sanofi, GSK, Merck, Bayer)
- Identification of drugs from Animal Health applications and determination of their suitability for development as a macrofilaricide for human use
- Assessment of new candidates to be brought into the drug development pipeline from pharmaceutical, biotechnology, and academic partners

- Approximately 14,000 compounds were screened in vitro, of which 450 were found to be active (HIT)
- Around 100 compounds have been evaluated in vivo
- **Emodepside** has completed the preclinical phase
- Other compounds active in vivo are currently under evaluation
Emodepside is a synthetically modified fermentation product, belonging to the chemical class of cyclooctadepsipeptides, active against nematodes.

Its fermentation product, PF1022A, is obtained from a fungus living on the leaves of Camellia japonica.

**Novel mode of action:**
- LAT-1 dependent inhibition of the pharynx
- SLO-1 dependent hyperpolarization of the presynaptic neurons and post synaptic muscle cells
Emodepside is commercialized by Bayer under license from Astellas as an anthelmintic veterinary drug for cats and dogs in combination with praziquantel (Profender®) and in combination with toltrazuril (Procox®).

DNDi has an agreement with Bayer to develop emodepside for the treatment of onchocerciasis

- Bayer will be responsible for the pharmaceutical development, investigational medicinal product supply, registration and later the manufacture and distribution of the product.
- DNDi is in charge of preclinical and clinical development
Emodepside: Murine and Jird models of filariasis

- Adult worms are not fully mature and do not produce microfilariae (mf) when treatment begins.
- Adult worms are fully mature and produce microfilariae (mf) when treatment begins.

- Begining of treatment: Emodepside:
  - Murine and Jird models of filariasis

- Randomization (weight or mf): 30 months post infection
- Natural infection: 75 days post infection
- Animal sacrificed and worm recovery & analysis: 9-12 week post infection
Emodepside has a macrofilaricide effect in vivo

**Jirds infected with L. sigmodontis**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Reduction of adult worms compare to control group</th>
<th>Formulation</th>
<th>Route of administration</th>
<th>Readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/kg (3 days)</td>
<td>55 %</td>
<td>Suspension in 2% Cremophor EL</td>
<td>Oral gavage</td>
<td>9 weeks post treatment</td>
</tr>
<tr>
<td>50 mg/kg (5 days)</td>
<td>86 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg/kg (5 days)</td>
<td>22 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.5 mg/kg (5 days)</td>
<td>0 %</td>
<td></td>
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</tr>
</tbody>
</table>

- **5 x 50 mg/kg**
- \( C_{\text{max}} = 145 \text{ ng/ml} \)
- \( \text{AUC}_{0-\text{last}} = 2097 \text{ ng·h/ml} \)

**Mice infected with L. sigmodontis**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Reduction of adult worms compare to control group</th>
<th>Formulation</th>
<th>Route of administration</th>
<th>Readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/kg (3 days)</td>
<td>73 %</td>
<td>Solution 100% capmul MCM</td>
<td>Oral gavage</td>
<td>75 days post treatment</td>
</tr>
<tr>
<td>12.5 mg/kg (5 days)</td>
<td>82 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/kg (5 days)</td>
<td>72 %</td>
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</tbody>
</table>

- **5x 1 mg/kg**
- \( C_{\text{max}} = 84 \text{ ng/ml} \)
- \( \text{AUC}_{0-\text{last}} = 1399 \text{ ng·h/ml} \)
Emodepside summary

- Emodepside has a macrofilaricide effect in vivo in both animal models
- Reduction of adult worms is about 80%
- PK parameters of efficacious doses in both mouse and the jird model are approximatively in the same ballpark
- Emodepside has completed preclinical development
- Planned to enter in Clinical development in Q4 2015
Other Drugs

- Moxidectin
  - Macrocyclic lactone
- Doxycycline
  - Bacterial endosymbiont, essential for growth, development and survival
- Flubendazole
  - Benzimidazole drug
- Auranofin
- Other anti-wolbachia compounds
- Oxfendazole
Challenges for Clinical Development of macrofilaricidal drugs

- No regulatory guidance on primary endpoint measures for registration
- No precedent of regulatory approval of a macrofilaricidal drug
- Clinical trials to verify potentially macrofilaricidal effects of drugs currently lack methods for repeatable long-term observation of adult living filaria in onchocerciasis
  - Difficult to quantify
  - Moderate specificity
  - Does not allow several time point assessments
- Effects of drugs are currently assessed by histological examinations of the nodules (number of male and female worms, size, embryogenesis and spermiogenesis)
- Low sensitivity of nodule palpation (up to 1/2 of nodules may be located in deep tissues)
- Mf in skin snip: inference the presence of fertile adult females, low sensitivity in light infections, invasive test, infection vs re-infection issues

Need to develop robust endpoints and biomarkers to measure macrofilaricidal effect
Early Decision Points: Progression of candidates

- Research
- Phil POC
- Phase II
- Phase III
- Phase IIIb IV

- Discovery strategy
- Safety/PK
- Clinical strategy
- Clinical operations
- HA submission
- Patient access

Decision Point: GO/NO GO criteria
Summary

- Emodepside to enter in clinical phase in Q4 2015
- Establish a robust pipeline
  - Identify four clinical drug candidates
  - Other compounds found to have activity in vivo are currently under evaluation
- Need for identification of clinically significant surrogate endpoints for clinical trials in both early and later development
- Opportunities to shape the clinical development by early interactions with HA

Get new treatment tools to meet patients needs timely
Acknowledgement

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- Muséum National d’Histoire Naturelle

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- U.S. Agency for International Developmen
THANK YOU

www.dndi.org