Development of Flubendazole as a macrofilaricide

Robert Don
Discovery and Preclinical Director

DNDi
Drugs for Neglected Diseases initiative
DNDi’s Main Objectives

- Deliver **11-13 new treatments by 2018** for sleeping sickness, Chagas disease, leishmaniasis and malaria, and specific helminth infections and paediatric HIV
- Establish a **robust pipeline** for future needs
- Use and strengthen existing **capacity in disease-endemic countries**
- Raise awareness and advocate for increased **public responsibility**
DNDi Portfolio-Building Model

- **Existing chemical libraries**
- **New lead compounds**

**Long-term projects**

- **New formulations** (fixed-dose combinations)
- **New indications of existing drugs**

**Medium-term projects**

- **Completing registration dossier**
- **Geographical extension**

**Short-term projects**

**Best Science for the Most Neglected**
Evolution of DNDi Disease Portfolio

Discovery | L.O. | Pre-clinical | Clinical | Reg. | Access
---|---|---|---|---|---

Leishmaniases (VL – CL – PKDL – HIV/VL)

HAT

Chagas

Malaria

Helminths

Paediatric HIV

“Mini portfolios”
- Green: To be built
- Red: To complete
Flubendazole as a Macrofilaricide
Filariasis

Loiasis

1. Fly goes through a blood meal to become infective L3 larvae
2. Migrate to head and eyes
3. L3 larvae
4. Moth flies to L3 larvae
5. Microfilariae shed sheaths, penetrate posterior muscles, and migrate to thoracic muscles
6. Moth flies to infective L3 larvae
7. Fly takes a blood meal (microfilariae are ingested)
8. Adults in subcutaneous tissue

Lymphatic filariasis

1. Mosquito takes a blood meal (L3 larvae enter skin)
2. L3 larvae
3. Migrate to head and moquito’s proboscis
4. L3 larvae
5. Insect vector sheds sheath, microfilaria is ingested, and migrates to thoracic muscles
6. Mosquito takes blood meal (microfilariae are ingested)
7. L3 larvae
8. Adults in lymphatics

Loa loa

Onchocerciasis

1. Blackfly stages
2. Blackfly takes a blood meal (microfilariae are ingested)
3. L3 larvae
4. Migrate to head and blackfly’s proboscis
5. L3 larvae
6. Microfilariae penetrate blackfly’s midgut, and migrate to thoracic muscles
7. Blackfly takes a blood meal (microfilariae are ingested)
8. Adults in subcutaneous nodule

Wuchereria bancrofti

Onchocerca volvulus

Brugia spp.
Filariasis Treatment

Onchocerciasis
• Ivermectin

Lymphatic Filariasis
• Diethylcarbamazine (DEC) + Albendazole

Loiasis
• Usually untreated

Limitations
• Ivermectin and DEC are microfilaricides
• Preventive chemotherapy must be maintained for long periods (up to 15 years for Oncho)
• DEC and Ivermectin can induce encephalopathy in *Loa loa* infected patients with high microfilarial loads
• Ivermectin is not recommended for Preventative Chemotherapy in populations coinfected with *L. loa*
The Need

A safe, short course macrofilaricidal drug for treatment of Onchocerciasis and Lymphatic filariasis in Loa Loa coendemic regions

1. Mass Drug Administration (MDA) in Loa Loa coendemic regions
2. As a companion or alternative to MDA programs in other regions → Reduction in treatment duration
3. Case management of filarial infections
Flubendazole
(LF-Onchocerciasis)

Objectives
• Short course for MDA (1 day)
• 10-14 days p.o./i.m. for case mgt

• Most promising
• Small human study reported in literature
• “Low-hanging fruit” opportunity
• + Explore other new drugs in animal health
Flubendazole and DEC in treatment of Onchocerciasis

10 Men  Flubendazole - 750mg, QWK 5 for weeks i.m.
9 Men    Diethylcarbamazine - 100mg, b.i.d. for 14 days p.o.

<table>
<thead>
<tr>
<th></th>
<th>2 MONTHS POST Rx</th>
<th>3 MONTHS POST Rx</th>
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<tbody>
<tr>
<td></td>
<td>DEC</td>
<td>FLUB</td>
</tr>
<tr>
<td>Degenerated Adults</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Intact Adults Worms</td>
<td>44</td>
<td>11</td>
</tr>
<tr>
<td>Females with Empty Uteri</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Females with Only Oocytes</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Reduction in Dermal Microfilariae</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

Effect of flubendazole (FLUB) and diethylcarbamazine (DEC) on adult *Onchocerca volulus* isolated from human nodules.

Flubendazole

- Toxicity,
  - Aneugenic / Teratogenic

- Formulation
  - Low solubility
  - A suspension is not bioavailable (Commercial product is used to treat intestinal infections)
  - An experimental formulation in cyclodextrin showed dramatically improved bioavailability (Potential to examine safety of orally administered drug in animals)
Flubendazole Research Plan

Year 1
- Draft TPPs and Safety Rules
- Preliminary PK/PD
- Preliminary Safety
- Develop formulation for Tox Species
- Preliminary assessment of options for human formulation

Assessment of Safety Margin
- Develop as a candidate for preventative chemotherapy and case management (A)
- Terminate project (B)

Year 2
- Conduct extensive PK/PD studies for human dose prediction
- Conduct IND enabling safety studies
- Develop an oral formulation for clinical trials

Year 3
- Draft IND / IMPD
- Manufacture GMP batch of drug product
CMC

Review of formulation options

Non clinical and clinical

- Lipids: deprioritized due to low solubility
- Cyclodextrin based complexes
- Nanosuspension
- Amorphous Solid Dispersion
Flubendazole Research Plan

![Graph showing area under the curve vs dose and plasma concentration vs hours after dose for different formulations.]

### Formulation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>$t_{1/2}$ (hr)</th>
<th>$C_{max}$ (µg/ml)</th>
<th>$T_{max}$ (hr)</th>
<th>AUC (µg·hr/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD (Cyclodextrin Solution)</td>
<td>3.5</td>
<td>0.29 (0.04)</td>
<td>0.8</td>
<td>2.63 (0.71)</td>
</tr>
<tr>
<td>CD (Cyclodextrin Solution) (n=2)</td>
<td>-</td>
<td>1.58 (0.30)</td>
<td>-</td>
<td>2.19 (1.07)</td>
</tr>
<tr>
<td>Nano (Nanosuspension)</td>
<td>4.4</td>
<td>0.19 (0.05)</td>
<td>4.7</td>
<td>2.28 (0.19)</td>
</tr>
<tr>
<td>Nano (Nanosuspension) (n=2)</td>
<td>-</td>
<td>1.58 (0.30)</td>
<td>-</td>
<td>1.50 (0.30)</td>
</tr>
<tr>
<td>ASD (Amorphous Solid Dispersion)</td>
<td>4.5</td>
<td>0.29 (0.02)</td>
<td>1.7</td>
<td>2.66 (0.36)</td>
</tr>
<tr>
<td>ASD (Amorphous Solid Dispersion)</td>
<td>6.5</td>
<td>0.78 (0.23)</td>
<td>4.7</td>
<td>12.65 (2.31)</td>
</tr>
</tbody>
</table>

Data provided as Mean (SD; n=3); $^*$ harmonic mean; $t_{1/2}$ [hr]; $C_{max}$ [µg/mL]; $T_{max}$ [hr]; AUC [µg·hr/mL]; All formulations administered using a 10 ml/kg dose volume in non-fasted rats.
ASD: Dose Escalation

- 10 ml/kg dose: aqueous suspension
- 20 ml/kg at 402 mg/kg
- Minimal animal to animal variability
- Increasing concentrations with increasing dose
  - Less than proportional to the dose
- Plasma concentrations maintained for >24 hr

Data provided as Mean (SD; n=3)
Flubendazole Research Plan

Next Steps

Year 1
- Draft TPPs and Safety Rules
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- Preliminary Safety
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Assessment of Safety Margin
A: Develop as a candidate for preventative chemotherapy and case management
B: Terminate project

Year 2
- Conduct extensive PK/PD studies for human dose prediction
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Year 3
- Draft IND / IMPD
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Safety

1. Flubendazole binds tubulin and blocks formation of the mitotic spindle

- Aneugenic → Aneuploidy, Teratogenicity, embryotoxicity
  - Benzimidazoles have
    - A common mechanism of action
    - A threshold of action
  - NOAEL has been determined for Benomyl / carbendazim (Committee on mutagenicity of chemicals in food UK)

- Determine threshold of action by dose response in an *in vitro* micronucleus assay
- Toxicity to rat whole embryo culture
- Preliminary reproductive toxicology (Seg 2)
Pharmacodynamics

Review of models of infection with safety experts to gain insight into therapeutic window

1. in vitro
   Brugia malayi (macrofilariae and microfilariae)

2. in vivo
   Brugia malayi in jirds and rats
   Onchocerca ochengi in cattle