Update of DNDi’s Filarial portfolio

ISTND d³
May 16-17th 2017
Wellcome Trust London

Ivan Scandale
Origins of DNDi

1999
- First meeting to describe the lack of R&D for neglected diseases
- MSF commits the Nobel Peace Prize money to the DND Working Group
- JAMA article: ‘Access to essential drugs in poor countries - A Lost Battle?’

July 2003
- Creation of DNDi

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 offices worldwide
DNDi Portfolio-Building Model:
Address Immediate Patient Needs & Deliver Innovative Medicines

- Long-term projects
  - New chemical entities (NCEs)

- Medium-term projects
  - New formulations (fixed-dose combinations)
  - New indications of existing drugs

- Short-term projects
  - Completing registration dossier
  - Geographical extension

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Research
Translation
Development
Implementation

> 5 years
3-5 years
1-2 years
Filarial diseases

Loiasis
- Lyssia (Loa loa)
- Human stages:
  1. Fly stage (genus Chrysops) takes a blood meal (5-10 times per day
  2. Migrate to head and fly through nostrils
  3. Adults in subcutaneous tissue
  4. When full of eggs, adults migrate to the eyes
  5. Microfilariae shed off host, can exist in fly's midgut, and migrate to thoracic muscles

Onchocerciasis
- Onchocerca volvulus
- Human stages:
  1. Blackfly stage (genus Simulium) takes a blood meal (1-3 times per week)
  2. Migrate to head and attach to larynx
  3. Adults in subcutaneous tissue
  4. When full of eggs, adults migrate to the skin
  5. Microfilariae penetrate blackfly's midgut and migrate to thoracic muscles

Lymphatic filariasis
- Wuchereria bancrofti
- Brugia spp.
- Mosquito stages:
  1. Mosquito takes a blood meal (1-3 times per week)
  2. Migrate to head and mosquito's proboscis
  3. Adults in lymphatics
  4. Microfilariae shed sheaths, penetrate mosquito's midgut, and migrate to thoracic muscles

CDC
http://www.dpd.cdc.gov/dpfdbx

DNDi
Drugs for Neglected Diseases initiative
Filarial Portfolio

Compound providers

Filarial Screening based on a repurposing strategy

Lead Optimization

Research → Translation → Development → Implementation

Screen → Hit to Lead → Lead Opt. → Pre-clinical → Phase I → Phase IIa/PoC → Phase IIIb/III → Registration → Access

LO  ABBV-4083  Emodepside

Oxfendazole

Lead Optimisation

ABBV-4083

Oxfendazole

Emodepside
Emodepside

- Anthelmintic veterinary drug for cats and dogs in combination with praziquantel (Profender®) and in combination with toltrazuril (Procox®).

- Emodepside showed remarkable *in vivo* and *in vitro* activity against a variety of filarial nematodes including *O. volvulus*.

- DNDi has an agreement with Bayer to develop emodepside for the treatment of onchocerciasis.
Tylosin Analogue Macrofilaricde (TylAMac)

- Tylosin is a macrolide antibiotic used as food additive in veterinary medicine

- Tylosin targets the endosymbiont Wolbachia bacterium present in *O. volvulus* and *W. bancrofti*. This causes:
  - Inhibition of fertility (absence of microfilariae)
  - Possible macrofilaricide activity

- Tylosin is poorly bioavailable:

Optimization program conducted by:

![AbbVie](image1)

Analogues:

- A-157083
- A-1535469
Oxfendazole

• Oxfendazole is a benzimidazole, anthelmintic treatment for farm and domestic animals.

![Chemical Structure of Oxfendazole]

• Oxfendazole is potent *in vivo* against a variety of filarial nematodes (*L. sigmodontis, B. malayi, A. viteae*)

• A Phase I trial evaluating safety and pharmacokinetics of oxfendazole is ongoing for two inductions:
  - Neurocysticercosis. Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)
  - Tenia Solium Infection. Sponsor: Johns Hopkins Bloomberg School of Public Health
**Batch 1**

50 mg

- **O. Gutturosa**
  - Adult worm (male)
  - Parameters:
    - Motility
    - MTT
  - \( EC_{50} \leq 1 \mu M \)
  - Cytotoxicity

**Batch 2**

Mouse: 200 mg

- **L. sigmodontis**
  - Adult worm
  - Parameters:
    - Motility
    - MTT
  - \( EC_{50} \leq 1 \mu M \)

Jird: 800 mg

- **O. Lienalis**
  - microfilariae
  - Parameters:
    - Motility
  - Solubility > 0.01 mg/ml at pH 7.4
  - Metabolic Stability: medium or high
  - Permeability: medium or high

---

**in vitro efficacy**

- Mouse or jird model
  - \( L. \) *sigmodontis*
  - Dose - response
  - At least three dose groups

- Reduction of adult worms > 70%
- No toxicity

**in vitro ADME / Chem. Charact.**

- Solubility, logD, permeability (MDCK-MDR1), protein binding, metabolism in liver microsomes (human + in vivo target species)
- Solubility > 0.01 mg/ml at pH 7.4
- Metabolic Stability: medium or high
- Permeability: medium or high

---

**in vivo ADME**

- In vivo mouse or jird pharmacokinetic profile
  - at \( \leq 50 \) mg/kg

**Achievable plasma levels above \( EC_{50} \) for 24 hours**

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**in vivo efficacy**

- Mouse or jird model
  - \( L. \) *sigmodontis*
  - Dose - response
  - At least three dose groups

- Exposure in mouse
- Dosing groups overlap with in vivo study

- Reduction of adult worms > 70%
- PK/PD established

- In vitro, in vivo safety profiling
Celgene program

**In vivo Results (Litomosoides sigmodontis)**

<table>
<thead>
<tr>
<th>Day:</th>
<th>0</th>
<th>30</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment (5 Days)</strong></td>
<td>Vehicle</td>
<td>FBZ</td>
<td>Compounds</td>
</tr>
<tr>
<td><strong>Worm Recovery and Analysis:</strong></td>
<td>Parasite number</td>
<td>Microfilariae count</td>
<td></td>
</tr>
</tbody>
</table>

**In vitro (Onchocerca species)**

- **158 compounds**
  - O. lienalis microfilariae
  - 32 “score 3” hits
  - Single digit micromolar and sub-micromolar activity
  - Re-test 158 compounds against O. gutturosa adults
  - 61 “score 3” hits
  - Single digit micromolar and sub-micromolar activity
  - 43 compounds specific for adults only

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>Average Adult worms</th>
<th>Reduction Adult worms</th>
<th>Reduction Microfilaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td></td>
<td>11 (26)</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>Flubendazole</td>
<td>2 mg/kg 5 days</td>
<td>0</td>
<td>100% (P=0.007)</td>
<td>NA</td>
</tr>
<tr>
<td>Compound A</td>
<td>3x30 mg/kg 5 days</td>
<td>2 (1.7)</td>
<td>68% (p=0.032)</td>
<td>NA</td>
</tr>
<tr>
<td>Vehicle</td>
<td></td>
<td>11 (26)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flubendazole</td>
<td>2 mg/kg 5 days</td>
<td>0.2 (0.5)</td>
<td>98% (P=0.019)</td>
<td>100% (P=0.034)</td>
</tr>
<tr>
<td>Compound B</td>
<td>3x30 mg/kg 5 days</td>
<td>2.17 (1.3)</td>
<td>80% (p=0.044)</td>
<td>98% (p=0.042)</td>
</tr>
<tr>
<td>Compound C</td>
<td>3x30 mg/kg 5 days</td>
<td>5.5 (2.7)</td>
<td>56% (p=0.125)</td>
<td>78% (p=0.078)</td>
</tr>
<tr>
<td>Compound D</td>
<td>3x30 mg/kg 5 days</td>
<td>10.2 (9.4)</td>
<td>18% (p=0.685)</td>
<td>86% (p=0.058)</td>
</tr>
</tbody>
</table>

Values expressed as mean (SD)
In vivo Data: Gerbil *L. sigmodontis* Model

**Adult worm burden gerbil**

- Untreated
- FBZ 2 mg/kg 5d QD
- Compound D 30 mg/kg 10d QD
- Compound D 30 mg/kg 5d QD
- Compound B 30 mg/kg 10d BID

**Microfilariae burden gerbil**

- MF + 1/10 µl blood

**Graphs:**
- Recovery of adult worms over time.
- Burden of microfilariae over time.
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UBS Optimus Foundation

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The Starr Foundation

BNDES

Ruta

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INSTITUTO CASTRO JIMÉNEZ DE LA SALUD

medicor foundation

THE SASAKAWA PEACE FOUNDATION
Responding to the Needs of Patients Suffering from Neglected Diseases...

DNDi’s PRIORITY: Neglected Patients

- Hepatitis C
- Sleeping sickness
- Mycetoma
- Malaria
- Paediatric HIV
- Chagas disease
- Leishmaniasis
- Filarial diseases

...from Bench to Bedside
In vivo Data: Murine *L. sigmodontis* Model

**Reduction of Adult Worms**

5 days of dosing:
- 100% reduction
- 80% reduction
- 56% reduction

10 days of dosing:
- 100% reduction
- 98% reduction
- 93% reduction

**Compound B** (Ser A)
- *O. gutt* EC$_{50}$ = 270nM
- *O. lien* EC$_{50}$ = 3100nM

**Compound C** (Ser B)
- *O. gutt* EC$_{50}$ = 699nM

**Compound E** (Ser A)
- *O. gutt* EC$_{50}$ = 27nM

1 day dosing
In a decade of R&D, 6 new treatments delivered

- 30 projects, 6 diseases areas
- 15 entirely new chemical entities (NCEs)
- Over 130 partnerships, most in endemic countries
- 150 staff, half in endemic countries & 600 people working on DNDi projects
- Over EUR 350 million raised equally from public and private sources
- 3 regional disease-specific clinical trial platforms and 2 technology transfers

✓ Easy to use
✓ Affordable
✓ Field-adapted
✓ Non-patented