New molecules for parasites of animals and humans

XXIX Congress SoIPa

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)
Responding to the Needs of Patients Suffering from Neglected Diseases…

DNDi’s PRIORITY: Neglected Patients

...from Bench to Bedside
DNDi Portfolio-Building Model:
Address Immediate Patient Needs & Deliver Innovative Medicines

- Long-term projects
  - New chemical entities (NCEs)
  - New formulations (fixed-dose combinations)
  - New indications of existing drugs

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

- Short-term projects

Research:
- >5 years
Translation:
- 3-5 years
Development:
- 1-2 years
Implementation:

DNDi Portfolio-Building Model:
Drug for Neglected Diseases Initiative
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
Filarial Portfolio

Compounds providers

Filarial Screening based on a repurposing strategy

Lead Optimization

Research

Screen

Hit to Lead

Lead Opt.

Pre-clinical

Phase I

Phase II/III

Registration

Implementation

Access

TyloAnalogue

Emodepside

Oxfendazole

Oxfendazole

Tylosin Analogue

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 Macrofilaricide (TylAMac)

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

\[
\begin{align*}
\text{Tylosin Target} & \quad \text{Endosymbiont Wolbachia bacterium present in } O. \text{volvulus} \\
& \quad \text{and } W. \text{bancrofti. This causes:} \\
& \quad \quad \text{Inhibition of fertility (absence of microfilariae)} \\
& \quad \quad \text{Possible macrofilaricide activity}
\end{align*}
\]

- Tylosin is poorly bioavailable:

Optimization program conducted by:

Analogues:

- A-157083
- A-1535469
Oxfendazole

- Oxfendazole is a benzimidazole, anthelmintic treatment for farm and pet animals.

- 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**

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

- **O. Lienalis**
  - microfilariae
  - Parameters:
    - Motility
  - Monkey kidney cells
  - Feeder cell layer
  - No toxicity at 10 \( \mu M \) or SI (cells/worms) > 5X

**Batch 2**

- **Mouse**: 200 mg
- **Jird**: 800 mg

**in vivo efficacy**

- Mouse or jird model
  - \( L. \) sigmodontis
  - Dose–response
  - At least three dose groups
  - \( \text{Reduction of adult worms} \geq 70\% \)
  - No toxicity

**in vivo ADME**

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

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

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

**In vitro, in vivo safety profiling**

**Reduction of adult worms establishment**
### AbbVie program

#### In vitro (Onchocerca gutturosa)

- 760 compounds (Bioavailable)
- 24 “score 3” hits
- No overlap!
- Re-test against O. gutturosa adults
- 14/24 re-confirm as “score 3”, EC<sub>50</sub> < 4 uM

#### AbbVie program

#### In vivo (Litomosoides sigmodontis)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>Average Adult worm</th>
<th>Reduction adult worms</th>
<th>Reduction microfilaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>17.1 (12.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flubendazole</td>
<td>6 mg/kg QD x 5 days</td>
<td>0</td>
<td>100 % (P=0.01)</td>
<td>100 % (P=0.01)</td>
</tr>
<tr>
<td>A-697365</td>
<td>100 mg/kg QD x 5 days</td>
<td>24.0 (29)</td>
<td>Not significant</td>
<td>96.3 % (P=0.01)</td>
</tr>
<tr>
<td>A-973584</td>
<td>100 mg/kg QD x 5 days</td>
<td>2.7 (4.7)</td>
<td>84.4% (P=0.02)</td>
<td>100 % (P=0.01)</td>
</tr>
<tr>
<td>A-1066844</td>
<td>40 mg/kg BID x 5 days</td>
<td>16.7 (8.8)</td>
<td>Not significant</td>
<td>86 % (P=0.02)</td>
</tr>
</tbody>
</table>

Values expressed as mean (SD)

**Natural infection** (L. sigmodontis, BalbC mice)  
**Treatment (5 Days)**  
**Worm Recovery and Analysis:**  
- Parasite number  
- Microfilariae count

---

**AbbVie program**

**In vitro (Onchocerca gutturosa)**

- 760 compounds (Bioavailable)
- 24 “score 3” hits
- No overlap!
- Re-test against *O. gutturosa* adults
- 14/24 re-confirm as “score 3”, EC<sub>50</sub> < 4 uM
Active analogs contain mono- or bicyclic, amine-containing ring.

All active analogs contain isoquinoline.

The effect of substitution patterns is unclear.
Murine model of filariasis: 
*Litomosoides sigmodontis*

- **D0** 30 days post infection
- **75 days post infection**
- **Natural infection** Or injection of L3
- **Randomization** (weight)
- **When the treatment begins**, adult worms are not fully mature and do not produce microfilariae (mf)
- **Begining of treatment**
- **Worm recovery & analysis** parasite numbers microfilariae counts
5-HT6 Series – profiles of Lead Compounds

A-1687262.21

In vivo testing: 100mg/kg 10d QD

A-738799.0

Do not belong to the 5-HT6 series

A-738799.0

In vivo testing: 100mg/kg 10d BID

A-1356925.0

In vivo testing: 100mg/kg 10d BID

p<0.01

untreated A-1687262.21 A-1356925.0 A-738799.0
## In vitro (Onchocerca species)

- **158 compounds**
  - 32 “score 3” hits
    - Single digit micromolar and sub-micromolar activity
  - 61 “score 3” hits
    - Single digit micromolar and sub-micromolar activity
  - 43 compounds specific for adults only

### In vivo Results (Litomosoides sigmodontis)

#### Day: 0
1. Injection of L3
2. Natural infection
   - L. sigmodontis, Bellini mice

#### Treatment (5 Days)
- Vehicle
- FBZ
- Compounds

#### Worm Recovery and Analysis:
- Parasite number
- Microfilariae count

<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</td>
<td>0</td>
<td>100% (p=0.007)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>5 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7025101</td>
<td>3 x 30 mg/kg</td>
<td>2 (1.7)</td>
<td>68% (p=0.032)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>5 days</td>
<td></td>
<td></td>
<td></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</td>
<td>0.2 (0.5)</td>
<td>98% (p=0.019)</td>
<td>100% (p=0.034)</td>
</tr>
<tr>
<td></td>
<td>5 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7033019</td>
<td>3 x 30 mg/kg</td>
<td>2.17 (1.3)</td>
<td>80% (p=0.044)</td>
<td>98% (p=0.042)</td>
</tr>
<tr>
<td></td>
<td>5 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7033021</td>
<td>3 x 30 mg/kg</td>
<td>5.5 (2.7)</td>
<td>56% (p=0.125)</td>
<td>78% (p=0.078)</td>
</tr>
<tr>
<td></td>
<td>5 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7033023</td>
<td>3 x 30 mg/kg</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: Murine L. sigmodontis model**

Reduction of Adult Worms

**5 days of dosing**

- **Vehicle**
- FBZ SC 2 mg/kg
- 7033019 3x30 mg/kg
- 7033021 3x30 mg/kg

**7033019 (Ser A)**
- *O. gutt* EC$_{50}$ = 270nM
- *O. lien* EC$_{50}$ = 3100nM

**7033021 (Ser B)**
- *O. gutt* EC$_{50}$ = 699nM
- *O. lien* EC$_{50}$ > 12500nM

**10 days of dosing**

- 100% **red**
- 98% **red**
- 93% **red**

**Vehicle**
- FBZ 5d SC 2 mg/kg
- 7033019 3x30 mg/kg
- 7011002 3x30 mg/kg

**7011002 (Ser A)**
- *O. gutt* EC$_{50}$ = 27nM

**1 day dosing**
Acknowledgments

Natalie A. Hawryluk,
Stacie S. Canan,
Vikram Khetani
Jerome B. Zeldis

Simon Townson
Suzanne Gokool
Andrew Freeman

Marc Hübner
Achim Hoerauf

Ivan Scandale
Claudia Pena Rossi
Robert Don

Zhongyuan Wang
Songling Yu
Zhyuan Zhang
Hongjuan Liu
Jia Wang
Jingyu Zhang
MeijingWang
THANK YOU
TO ALL OUR
PARTNERS &
DONORS

Global Health Innovative Technology Fund

Bill & Melinda Gates Foundation

UKaid from the British people

Ministry of Foreign Affairs

wellcome trust

Sustainable Development Goals

Global Ministries

Fondation de la Familles

Public Health Foundation

UNICEF

World Health Organization

USAID

UBS

The Global Fund

United States Agency for International Development

KfW

Agence Française du Développement

GHTC

Medicor Foundation

The Sasakawa Peace Foundation

The Starr Foundation

BBVA Foundation

EDCTP

Ministerio de Asuntos Exteriores

CAEID

Secretaria de Desarrollo Social

SAPOR

USP

Instituto Carlos Slim

Regione Toscana

UBS Optimus Foundation

Brasil

The Rockefeller Foundation

The Starr Foundation
**O. lienalis** mf microplate assay
cytotoxicity Evaluation

Inhibition motility at 1.25·10^{-5} M
toxicity to monkey kidney cell feeder layer
50% reduction motility vs untreated controls

**Compounds**

**O. gutturosa adult worms**

Inhibition of motility and MTT at 1.25·10^{-5} M
100% reduction motility vs untreated controls

**O. lienalis** mf microplate assay

EC_{50} (1 in 4 dilutions) readout:
motility (activity 2 or 3)

**Compounds**

**O. gutturosa adult worms**

EC_{50} (1 in 4 dilutions) readout: motility and MTT

**HIT**

EC_{50} < 10^{-6} M

**In vivo PK (exposure, plasma levels > IC_{50})**

**In vivo jird model B. malayi & in vitro B. malayi**

Toxicity
- receptor profiling
- AMES
- hERG
- in vivo explo. tox.

**Dose response**

Activity comparable to flubendazole
(2 mpk, 5 days, subcutaneous)

**In vivo jird or mouse model L. sigmodontis & in vitro L. sigmodontis**

**Lead**

**Preclinical Candidate**