Screening of the Malaria Box against kinetoplastids: a concrete example of Open Innovation collaborative research
OUTLINE

- Introduction to DNDi vision and R&D model
- Screening of Malaria Box against kinetoplastids
- Follow up on actives
- Data sharing
- The Malaria Box experience: DNDi’s view
DNDi’s Model
DNDi: Vision & Objectives

Vision:
A collaborative, patients’ needs-driven, virtual, non-profit drug R&D organisation to develop new treatments against the most neglected communicable diseases

Objectives:
- Deliver 11 to 13 new treatments by 2018 for sleeping sickness, Chagas disease, leishmaniasis, malaria, paediatric HIV and specific helminth infections
- Establish a robust pipeline for future needs
- Use and strengthen existing capacity in disease-endemic countries
Dedicated Teams Worldwide
Over 660 People Committed to DNDi’s Vision
IP & Open Innovation Practices

- Access to compounds, know-how and knowledge
- Increase access to innovation
- Ensure equitable access to all patients & affordable treatment

⇒ Medicines Patent Pool
⇒ WIPO Re:Search
⇒ Open & equitable licensing
⇒ Open Innovation portal/CHEMBL

www.dndi.org/diseases-projects/open-innovation.html
Screening of Malaria Box against kinetoplastids

Collaboration with

- Medicines for Malaria Venture
- LMPH at University of Antwerp (DNDi)
- Swiss Tropical and Public Health Institute (DNDi)
Screening outcome

- Quick access to Malaria Box (compounds and structures)
- screened against Tryp. b. rhod., T. cruzi, L. inf. and MRC-5 cell line

### HAT
- 55 hits
- 13.7% (0.45%)

### Chagas
- 21 hits
- 5.2% (0.55%)

### VL
- 8 hits
- 2% (0.06%)
Hit analysis and priority setting: an example

Hit triaging criteria

- cluster analysis
- duplication with DNDi
- discovery program
- drug-like properties

4 priority hit for HAT
1 priority hit for VL
Follow up on actives
Priority hits: progressing in a collaborative mode

- resupply of material
- Activity reconfirmation of priority hits
- preclinical profiling (ADMET, PK)
- Screening of analogs
- Follow-up in vitro profiling drug action assays (time-kill, reversibility)

Go/no-go decision
For in vivo efficacy assays (PoC)
HAT priority hit: data annotation for decision-making

<table>
<thead>
<tr>
<th>KS</th>
<th>Kinetic Solubility pH=7.4 (µg/mL)</th>
<th>&lt;0.37</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kinetic Solubility pH=7.4 (µM)</td>
<td>&lt;1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HMS</th>
<th>Mouse</th>
<th>t½ (min)</th>
<th>213.26</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CL (mL/min/kg)</td>
<td>38.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL_int (mL/min/kg)</td>
<td>30.5</td>
</tr>
</tbody>
</table>

| Human | t½ (min) | 79.08 |
|       | CL (mL/min/kg) | 31.67 |

<table>
<thead>
<tr>
<th>MMS</th>
<th>Human</th>
<th>T½ (min)</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CL (µL/min/mg)</td>
<td>30.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CL_int (mL/min/kg)</td>
<td>30.5</td>
<td></td>
</tr>
</tbody>
</table>

| Mouse | T½ (min) | 100.43 |
|       | CL (µL/min/mg) | 27.6 |
|       | CL_int (mL/min/kg) | 109.3 |

<table>
<thead>
<tr>
<th>PLS</th>
<th>% Remaining after Incubation (60 min)</th>
<th>Human Plasma</th>
<th>88.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CD-1 Mouse Plasma</td>
<td>91.0</td>
</tr>
</tbody>
</table>

| MPB     | CD-1 Mouse Liver Microsome | Fu | 0 |
|         |                          | Fb | 1.0 |
|         |                          | % Recovery | 37.4 |

| PPB     | Human Plasma | % Unbound | 0.7 |
|         |              | % Bound | 99.3 |
|         |              | % Recovery | 89.2 |

| CD-1 Mouse Plasma | % Unbound | 0.1 |
|                  | % Bound | 99.9 |
|                  | % Recovery | 95.8 |

| DDI | 1A2 | Inhibition | *IC₅₀ (µM) | 11.8 |
|     | 2C9 | Inhibition | *IC₅₀ (µM) | 94.0 |
|     | 2C19 | Inhibition | *IC₅₀ (µM) | >100 |
|     | 2D6 | Inhibition | *IC₅₀ (µM) | 4.2 |
|     | 3A4-M | Inhibition | *IC₅₀ (µM) | No inhibition |
|     | 3A4-T | Inhibition | *IC₅₀ (µM) | 99.0 |

| Administered dose (mg/kg) (PO) | 59.13 |
| Administered dose (µmol/kg) (PO) | 161 |
| Cmax (µmol/L) | 3.57 |
| Tmax (h) | 1.66 |
| T½ | NR |
| Tlast (h) | 9 |
| AUC₀-last (h*µmol/L) | 24.13 |
| AUC₀-inf (h*µmol/L) | NR |
| MRT₀-last (h) | 4.44 |
| MRT₀-inf (h) | NR |
| AUC₀-inf/AUC₀-last (%) | NR |

| hERG % I (11µM) | 82.69 |
| hERG % I (1µM) | 14.22 |

**HAT in vitro**

T. b. rhod. STIB 900
IC₅₀ 0.36 µM
IC₉₀ 1.41 µM

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**Plasma Concentration after PO Administration**

- **M1**
- **M2**
- **M3**
- **Mean PO**

**IC₉₀**

**Medicines for Malaria Venture**
### Findings

In vitro activity does not always translate to in vivo activity. The compound, not the model, is the question.

### Transition from in vitro to in vivo

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (µM)</th>
<th>IC90 (µM)</th>
<th>IC50 (µM)</th>
<th>IC90 (µM)</th>
<th>IC50 (µM)</th>
<th>IC90 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMV665961 IC50</td>
<td>0.023</td>
<td>0.145</td>
<td>0.002</td>
<td>0.084</td>
<td>0.602</td>
<td>1.13</td>
</tr>
<tr>
<td>MMV665961 IC90</td>
<td>0.077</td>
<td>0.285</td>
<td>0.013</td>
<td>0.165</td>
<td>1.13</td>
<td>1.83</td>
</tr>
<tr>
<td>MMV019017 IC50</td>
<td>0.002</td>
<td>0.084</td>
<td>0.011</td>
<td>0.251</td>
<td>0.602</td>
<td>1.13</td>
</tr>
<tr>
<td>MMV019017 IC90</td>
<td>0.013</td>
<td>0.165</td>
<td>0.002</td>
<td>0.429</td>
<td>0.602</td>
<td>1.83</td>
</tr>
</tbody>
</table>

### Activity of MMV019017

MMV019017 is a slow-killer.

### Treatment Period

<table>
<thead>
<tr>
<th>Treatment period (days)</th>
<th>Dose (mg/kg/day)</th>
<th>Route</th>
<th>Cured / infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td>0/4</td>
</tr>
<tr>
<td>MMV019017</td>
<td>4</td>
<td>60</td>
<td>p.o. 0/4</td>
</tr>
</tbody>
</table>

MMV019017 is not active in vivo.

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**DNDi**

Drugs for Neglected Diseases initiative
Data sharing
Data sharing

- **Malaria box screening data set released in CHEMBL-NTD**
  https://www.ebi.ac.uk/chembl/malaria  13 Noc 2012

- **Publication of data under preparation**
  submission end of May to Journal of Biomolecular Screening (Special issue on Novel Therapeutic Approaches for Neglected Infectious Diseases)

- **Annotation data** to be made public domain by MMV in near future

Data will benefit the NTD scientific community
Malaria Box experience: the DNDi’s view
Clear gain in time and resources by working in a collaborative and open way

• Immediate access to structures (waiving negotiation)
• Direct access to compounds for screening and profiling assays
• High quality collection: QC, favourable biological properties (high hit rate)
• Timely access to key preclinical data for decision-making purpose
  readily available or generated on ad hoc basis

• Fast data sharing among project partners … and beyond
• Facilitate Identification of synergies
• Data generated beneficial to other development projects
• New data can “resuscitate”/encourage work on discarded/low priority active
• Keep away from duplication

Welcome to the Pathogen Box!
THANK YOU

www.dndi.org
DNDi:
Patient Needs-Driven & Innovative R&D Model

- 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)

- **Geneva Headquarters**
- **USA**
- **DRC**
- **India**
- **Japan**
- **Malaysia**
- **Brazil**
- **Kenya**

- **7 worldwide offices**
10-Year Results

- 2 new malaria treatments
- 1 new sleeping sickness combination
- 1 new visceral leishmaniasis combination for Africa
- 1 set of VL treatment modalities for Asia
- 1 Chagas paediatric dosage form
- Largest pipeline ever for the kinetoplastid diseases
- Clinical research platforms in Africa
- €277M of €400M needed raised
- On track to deliver new treatments per business plan
6 New Treatments Developed Since 2007

☑ Easy to Use  ☑ Affordable  ☑ Field-Adapted  ☑ Non-Patented
### DNDi Portfolio: A Mix of Existing Drugs & NCEs

6 new treatments available and 12 new chemical entities in the pipeline

<table>
<thead>
<tr>
<th>Research</th>
<th>Translation</th>
<th>Development</th>
<th>Implementation</th>
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</thead>
<tbody>
<tr>
<td>Screen</td>
<td>Pre-clinical</td>
<td>Phase I</td>
<td>Registration</td>
</tr>
<tr>
<td>Hit to Lead</td>
<td></td>
<td>Phase Ila/PoC</td>
<td></td>
</tr>
<tr>
<td>Lead Opt.</td>
<td></td>
<td>Phase IIb/III</td>
<td>Access</td>
</tr>
</tbody>
</table>

#### HAT
- **SCYX2035811**
- **SCYX1608210**
- **Fexinidazole**

- **NECT**
  - Nifurtimox-Eflornithine Combination Therapy

#### Leishmaniasis
- **Nitroimidazole**
- **Oxaleish**
- **VL-2098**
- **Fexinidazole**
- **Anfoleish (CL)**

- **SSG&PM**
  - Sodium Stibogluconate & Paromomycin Combination Therapy for VL in Africa

- **New VL Treatments for Bangladesh**
- **New VL Treatments for Latin America**
- **Generic Ambisome**

#### Chagas
- **Nitroimidazole**
- **Oxachagas**
- **Biomarkers**
- **Fexinidazole**
- **New Benz Regimens**
- **New Combos**

- **Benznidazole**
  - Paediatric Dosage Form

#### Filaria
- **Emodepside**

#### Paediatric HIV
- **Two ‘4-in-1’ LPV/r-based Fixed-Dose Combinations**
- **RTV Superbooster for HIV/TB co-infection**

#### Malaria
- **ASAQ FDC**
  - Artesunate-Amodiaquine Fixed-Dose Combination
- **ASMQ FDC**
  - Artesunate-Mefloquine Fixed-Dose Combination

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★ New Chemical Entity (NCE); Fexinidazole (for HAT, VL and Chagas Disease) = 1 NCE

Jan. 2014
Risks in R&D of Pharmaceutical Drugs