Filarial Disease Program
S. Specht, F. Monnot, B. Pedrique, K. Dequatre, J. Lopatar, I. Scandale, JY Guillon
To fill the gap in R&D for neglected patients: Product Development Partnerships (PDPs)

Current PDP landscape working areas include:

• Vaccine R&D
• Diagnostics R&D
• R&D for new or improved treatments
### DNDi R&D Portfolio June 2018

7 new treatments available and up to 16 new chemical entities in the pipeline

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Screen</th>
<th>Hit to Lead</th>
<th>Lead Opt.</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase Ila/PoC</th>
<th>Phase IIb/III</th>
<th>Registration</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HAT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Leishmaniasis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Screening</td>
<td>Leish H2L</td>
<td>DNDI-5421</td>
<td>DNDI-6148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Booster H2L</td>
<td>DNDI-6148</td>
<td>DNDI-6148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daiichi-Sankyo LH2L</td>
<td>Amino</td>
<td>DNDI-6148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pyrazoles</td>
<td>DNDI-6148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CGH VL Series 1</td>
<td>DNDI-6148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Leish L205 Series</td>
<td>DNDI-6148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chagas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Screening</td>
<td>Chagas H2L</td>
<td>Biomarkers</td>
<td>DNDI-6148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Booster H2L</td>
<td>Chagas C205 series</td>
<td>DNDI-6148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daiichi-Sankyo CH2L</td>
<td>Amino pyrazoles</td>
<td>DNDI-6148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Filaria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Screening</td>
<td>Macro Filaricide 4</td>
<td>Oxfendazole</td>
<td>Emodepside</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pediatric HIV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HCV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mycetoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**New Chemical Entity (NCE)**

- SCYX-1330682
- SCYX-1608210
- DNDI-5421
- DNDI-6148
- DNDI-5561
- DNDI-5610
- Amino pyrazoles
- CGH VL Series 1
- Leish L205 Series
- New CL Combination
- New Benz Regimens +/- fosravuconazole
- Emodepside
- ABBV-4083
- ‘4-in-1’ LPV/r/ABC/3TC
- LPV/r pellets with dual NRTI
- Ravidasvir
- Sofosbuvir
- Ravidasvir
- Posravuconazole
- NECT Nifurtimox-Eflornithine Combination Therapy
- SSG&PM Africa
- New VL Treatments Asia
- Benznidazole Paediatric Dosage Form
- Superbooster Therapy Paediatric HIV/TB
- Malaria FDC ASAQ
- Malaria FDC ASMQ
Filarial Diseases: Unmet Medical Needs

- Unmet medical needs:
  - IVM is microfilaricidal (repeated application)
  - No macrofilaricidal treatment available
  - Morbidity management
  - *Loa-loa* coinfections with risk of serious adverse events
Elimination Scenario (beyond 2045)
Tailored interventions (1.3 billion treatments)
- Dependent on starting prevalence
- DRC, South Sudan, Central Africa,
- Conservative and optimistic models
BUT NOT BY 2030!

Major feasibility concerns (2015):
- *Loa loa* coinfection without treatment
- Political and economical situations
- Recrudescence
- Resistance
Filarial Diseases: Unmet Medical Needs

- Unmet medical needs:
  - IVM is microfilaricidal (repeated application)
  - No macrofilaricidal treatment available
  - Morbidity management
  - Loa-loa coinfections with risk of serious adverse events

- The aim is to:
  - deliver a short-course safe and efficacious macrofilaricidal/longterm sterilizing drug for onchocerciasis to be extended to LF

- Alternative therapy for:
  - case management / morbidity management
  - “mop-up” campaigns to contribute to elimination as public health problem
  - Test and Treat (TNT) approaches
  - Safe treatment in Loa loa coendemic regions
Major changes in the filarial landscape

- Mass drug administration activities are increasing, but:
  - Elimination as one goal of the SDG cannot be reached with MDA
  - Tipping point expected, when test and treat becomes cheaper
  - Resistance development (clearly proven in veterinary medicine), not shown in MDA environment, as people are not followed up

- IVM/DEC/ALB (IDA) is highly effective in LF:
  - Currently investigated for onchocerciasis
  - Safety risk due to DEC?
  - Cost and logistics (treat and retreat approach)

- Moxidectin with strongly improved microfilaricidal efficacy over ivermectin, but:
  - Will be registered in the US only
  - As IVM, it is not macrofilaricidal
  - Same class as IVM, therefore high chance of (cross)resistance
Drug targets: direct vs indirect

Onchocercoma containing male and female adult worms

*Courtesy of Prof. DW Büttner*

Cross-section of a female *Onchocerca volvulus* worm showing *Wolbachia* (red) in the lateral hypodermal cords.

*Courtesy of PD Dr. Sabine Specht*
## Possible mode of actions: direct vs indirect

<table>
<thead>
<tr>
<th>Onchocerciasis only areas</th>
<th>Onchocerciasis + Loiasis coendemic areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macro- and microfilaricidal drug can be used in the total population</td>
<td>Microfilaricidal drug has to be used with caution (“test and not treat”)</td>
</tr>
</tbody>
</table>

### Direct acting drugs: Emodepside, Oxfendazole

**PoC:**
- Macrofil. (Oncho-Loa coinfected areas)
- Macrofil. + microfil. (Oncho only areas)*

**Advantage:**
- Proven MoA in veterinary medicine
- Fast-killing, morbidity management*
- Potentially used for multiple nematodes

**Disadvantage:**
- Risk of AE due to microfil. activity (Emod.)

**Possible:** Combination treatments

### Indirect-acting drugs (anti-wolbachial): TylAMac

**PoC:**
- Macrofil. (Oncho-Loa coinfected areas)

**Advantage:**
- slow-killing, MoA well known,
- Reduction of inflammation due to removal of *Wolbachia*
- No side effects in loiasis infected individuals

**Disadvantage:**
- long time to death of the adult parasite

**Possible:** Combination treatments

---

High attrition rates: need for a variety of candidates
Pursue both approaches are valuable and build up the anti-filarial tool-kit
Drug targets: SLO-1 (emodepside)

SLO-1 K+ channel / big potassium channel:
- inhibition of pharyngeal pumping activity and locomotion
- slow, irreversible, concentration-dependent hyperpolarization
- Human SLO-1 is 10-100-fold less sensitive
- SLO-1 orthologues in many nematodes, correlates with spectrum of activity
Drug targets: *Wolbachia* (TylAMac)

*Wolbachia*:  
- Inhibits binding of tRNA  
- bacteriostatic  
- Validated target with macrofilaricidal activity and longterm sterilizing effect
Anti-wolbachial drug: TylAMac

• Synthetic derivative of tylosin A (common veterinary macrolide antibiotic)

• Highly potent against *Wolbachia* (>200-fold more potent than doxycycline)

✓ Tox-package completed

✓ IND (Investigational New Drug) application 11/2017

✓ Phase 1 Single Ascending Dose study ongoing

Dale Kempf
Phase 1 clinical trials

• Aim:
  • Determine the maximum tolerated dose (MTD) of the new treatment
  • MTD is found by escalating the treatment dose until dose-limiting toxicity (DLT) is reached

• Design:
  • To assess the safety, tolerability, PK and PD of the drug
  • Healthy volunteers (often male)
  • Duration: 6-12 months

• Types of Phase 1:
  • SAD: single ascending dose
  • MAD: multiple ascending dose
  • Food Effect
  • Relative bioavailability
Find new tools for elimination and case management

**Discovery programs = New Clinical Entities**

**Long-term projects**
- Research
  - Long-term
    - AbbVie (anti-Wolbachia), Celgene (lead optimization macrofilaricide)
    - Filarial Clinical Trial and Research Platform

**New indications for existing drugs = Repurposing Strategy**

**Medium-term projects**
- Translation
  - Medium-term
    - Repurposing of veterinary: Emodepside (Bayer), oxfendazole
      - Based on known mode of action: TylAMac (AbbVie)
      - Fingerprint studies

**Supportive Activities**

**Short-term projects**
- Development
  - Short-term
    - Explore pediatric IVM
    - Modelling of distribution/morbidity to address the patients needs
- Implementation
  - Modelling of CT endpoints
  - Surrogate Biomarker
Thank you