The NTD Drug Discovery Booster: an innovative collaboration for hit expansion

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Discovery Director
Responding to the Needs of Patients Suffering from Neglected Diseases…

DNDi’s Mission

- To develop new drugs or new formulations of existing drugs
- To strengthen capacities in a sustainable manner
- To adopt a dynamic approach to portfolio diseases

DNDi’s PRIORITY: Neglected Patients

- Hep C
- Sleeping sickness
- Pediatric HIV
- Mycetoma
- Malaria
- Chagas disease
- Leishmaniasis
- Filarial diseases

…from Bench to Bedside
7 new treatments delivered, recommended, implemented

- 30 projects, 8 diseases areas
- 13 entirely new chemical entities (NCEs)
- Over 160 partnerships, most in endemic countries
- 160 staff, half in endemic countries & 700 people working on DNDi projects
- EUR 400 million raised equally from public and private sources
- 4 regional disease-specific clinical trial platforms/networks and several technology transfers

✓ Easy to use
✓ Affordable
✓ Field-adapted
✓ Non-patented
DNDi’s success is only possible through innovative partnerships

Over 160 partnerships worldwide

CRITERIA FOR SUCCESS
✓ Share the same vision
✓ Mutual understanding
✓ Involvement throughout the whole process

Universities & Research Institutes
PDPs
Int. Org., & NGOs
Biotechs
CROs
Pharmaceutical companies

Some current Japanese partners:
Eisai
Takeda
Shionogi
Daiichi-Sankyo
GeneDesign
Kitasato Institute
Riken Institute
IMC
GHIT Fund
## DNDi R&D Portfolio June 2017

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Screen</th>
<th>Hit to Lead</th>
<th>Lead Opt.</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase IIa/PoC</th>
<th>Phase IIb/III</th>
<th>Registration</th>
<th>Access</th>
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</thead>
<tbody>
<tr>
<td><strong>HAT</strong></td>
<td></td>
<td></td>
<td></td>
<td>SCYX-1330682</td>
<td>Acoziborole</td>
<td>Fexinidazole</td>
<td>NECT Nifurtimox-Eflornithine Combination Therapy</td>
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<td>SCYX-1608210 oxaborole</td>
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<tr>
<td><strong>Leishmaniasis</strong></td>
<td></td>
<td>Leish H2L</td>
<td>DNDI-5421 DNDI-5610 oxaborole</td>
<td>DNDI-6148 oxaborole</td>
<td>DNDI-0690 nitroimidazole</td>
<td>New Treatments for HIV/VL</td>
<td>New Treatments for PKDL</td>
<td>MF/Paromomycin Combo for Africa</td>
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<td></td>
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<td>Amino pyrazoles</td>
<td>GSK3186899 DDD853651</td>
<td>GSK3494245 DDD1305143 CgG-D35 (CL)</td>
<td>New CL Combination</td>
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<td>New VL Treatments Asia</td>
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<tr>
<td><strong>Chagas</strong></td>
<td></td>
<td>Chagas H2L</td>
<td>Chagas Lead Opt</td>
<td>Biomarkers</td>
<td>New Benz Regimens +/- fosravuconazole</td>
<td>Fexinidazole</td>
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<tr>
<td><strong>Filaria</strong></td>
<td></td>
<td>Screening</td>
<td>Screening</td>
<td>Screening</td>
<td>ABBV-4083 TylaMac</td>
<td>Emodepside</td>
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<tr>
<td><strong>Pediatric HIV</strong></td>
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<td>Two ‘4-in-1’ LPV/r/ABC/3TC</td>
<td>LPV/r pellets with dual NRTI</td>
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<tr>
<td><strong>HCV</strong></td>
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<td>Ravidasvir/Sofosbuvir</td>
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<td><strong>Mycetoma</strong></td>
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<td>Fosravuconazole</td>
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</tbody>
</table>

* New Chemical Entity (NCE); Fexinidazole (for HAT, VL, and Chagas disease) = 1 NCE; Fosravuconazole = 1 NCE
Projects with Japanese partnerships and support from the GHIT Fund providing NCEs

DNDi R&D Portfolio June 2017

Growing portfolio
- 8 Partners
- 20 projects

New Chemical Entity (NCE)
Unique compounds from Japan

- Screening of drug-like small molecules from Japanese pharmaceutical companies and research institutes
- Some interesting hits identified
- NTD Drug Discovery Booster used to accelerate these new discoveries
- Japanese natural products


Drug discovery for tropical diseases such as Visceral Leishmaniasis and Chagas Disease is neglected
  - Little interest, limited investment, few researchers, few tools

Parasites are very difficult to kill
  - High Throughput Screening hit rates:
    • L. donovani (intracellular) <0.05%
    • T. cruzi (intracellular) <0.15%

*Hits are scarce and precious – need to fully exploit them*

**The NTD Drug Discovery Booster Goals:**
  - Expand precious HTS hits and enable scaffold-hopping to find new hits
  - Benefit from the pooling of structures and information
  - Accelerate discovery and reduce costs
  - Experiment with a new open innovation approach to drug discovery
Booster Process - Representative Example

<table>
<thead>
<tr>
<th>Source</th>
<th># hits</th>
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<tbody>
<tr>
<td>Seed S01</td>
<td>1</td>
</tr>
<tr>
<td>Partner A</td>
<td>~90</td>
</tr>
<tr>
<td>Partner B</td>
<td>~90</td>
</tr>
<tr>
<td>Partner C</td>
<td>~90</td>
</tr>
<tr>
<td>Partner D</td>
<td>~40</td>
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</tbody>
</table>

• Complementary compound collections and different computational approaches efficiently explore chemical space around new hits
• Rapid SAR expansion and scaffold-hopping before expensive optimisation chemistry is needed
Booster: Progress to date

Status

Hit Series approved
Abandoned
2\textsuperscript{nd} Iteration ongoing
2\textsuperscript{nd} Iteration planned
1\textsuperscript{st} Iteration ongoing
1\textsuperscript{st} Iteration planned

Ongoing
Abandoned
Completed
Hit series identified
Innovative NTD Booster Project recognised by DNDi

Project of the year 2016
NTD Booster Summary

- A novel approach accelerating discovery of new drugs for NTDs
- A unique partnership of Japanese companies, the GHIT Fund and other international partners
- Diversity of chemistry and scientific approaches already yielding several promising projects
- Useful learning for growing partnership with applicability to other global health projects
- Special environment created in Japan by the GHIT Fund and Japanese pharmaceutical companies
- Global partnership committed to patients’ needs
- Precious Japanese contributions to synthetic and natural compound screening, the NTD Booster, and drug discovery and development projects
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NTD Drug Discovery Booster