Advancing R&D Projects Through Partnering

Shing Chang, PhD
R&D Director, DNDi
Research, Development, Access

- **Research**
  - Building a pipeline for the future

- **Development**
  - 6 to 8 new treatments

- **Access**
  - Patients access to improved treatments
Characteristics of Our Discovery Strategy

- Understanding of the field conditions and patient needs
- TPP (Targeted Product Profile) to guide our programs
- “Low hanging fruits” approach to address urgent needs
- Consortia for centralized LO
- Targeting selected classes of compounds
- Working with partners with shared mission and commitment
Diverse Compounds and Libraries through Partnerships

<table>
<thead>
<tr>
<th>Hits &amp; leads</th>
<th>Screening center</th>
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<tbody>
<tr>
<td>Scynexis</td>
<td>London School of Hygiene &amp; Tropical Medicine</td>
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<td>IPK</td>
<td>Swiss Tropical Institute</td>
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<td>Epichem</td>
<td>Antwerp University</td>
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<td>LicA</td>
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<td>Anacor</td>
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<td>Chemroutes</td>
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<td>Eskitis</td>
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<td>Kitasato Institute</td>
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<td>Genzyme</td>
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<td>Nycomed Altana</td>
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<td>CDRI</td>
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<td>Otsuka</td>
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<td>U.Washington</td>
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Accessing Compound Classes with Known Activity Against Parasites

• Partnership with GSK
  – To identify promising compounds via screening of existing GSK libraries and tapping into MMV-GSK research on malaria
  – Initial work focused on two classes known to be active against parasites
    • 4 (1H) pyridones and cysteine protease inhibitors

• Partnership with Anacor
  – Interesting exaborolo compounds active against *T. brucei* and *T. cruzi* in vitro
Accessing the Wealth of Natural Products Screening

• Partnership with Eskitis Institute, Australia
  – Screening a unique library of natural product extracts that are enriched for drug-like molecules using proprietary “Lead-like Enhancement Technology

• Partnership with Kitasato Institute, Japan
  – Screening a unique library of microbial secondary metabolites and plant extracts
Accessing New Drug Discovery Technologies

• Partnership with Institute Pasteur of Korea
  – High throughput Image Screen for *leishmania*
  – Use macrophage infected with intracellular amastigotes under BSL-3 conditions
Best Science for the Most Neglected

Lead Optimization

Screening  Hit Expansion  Lead to Candidate

Reiterative cycles of medicinal chemistry

each scaffold

Hits

Parallel assessment of DMPK Tox And Potency

GLP Toxicology

Pharmaceutical chemistry

Drug Candidate
Optimizing Leads Through Disease-focused Consortia

HAT Lead Optimization
- Scynexis, Pace

VL Lead Optimization
- Advinus
- Central Drug Research Institute

Chagas Lead Optimization
- CDCO, Murdoch, Epichem, Ouro Preto

Hits & Leads from Screening Partners
A Robust and Dynamic Portfolio 2004-2008

**Discovery**
- S
- LS
- LO

**Pre-clinical**
- Azoles (Chagas)
- Amphotericin B Polymer (VL)
- Buparvaquone (VL)
- Fexinidazole (HAT)

**Clinical**
- Paromomycin (VL in Africa)
- AmBisome (VL in Africa)
- Paediatric Benznidazole (Chagas)
- Combination Therapy (VL in India)
- Nifurtimox - Eflornithine Co-Administration (HAT)

**Available**
- ASMQ (Malaria)
  Fixed-Dose Artesunate/Mefloquine
- ASAQ (Malaria)
  Fixed-Dose Artesunate/Amodiaquine

**Exploratory**
- Nitroimidazoles (All)
- Microtubule Inhibitors (HAT)
- GSK (All)
- Kitasato Natural Substances (HAT)
- CDRI (HAT)
- Eskitis Natural Products (HAT)
- IPK (VL)
- HAT Consortium: Scynexis, Pace Univ
- VL Consortium: Advinus, CDRI
- Chagas Consortium: CDCO, Epichem, Murdoch Univ

**Exploratory Screening:**
- Anacor, Chemroutes, Univ of Ouro Preto, Fiocruz, IICB, IRD, Lica
- LSHTM, MerLion, Otsuka, STI, TDR, Univ of Antwerp, University of Dundee, WEHI, ...
DNDi Preclinical & Clinical Portfolio - Human African Trypanosomiasis
HAT Strategy Challenges

• Make combination of nifurtimox and eflornithine available for patients
• Develop an accelerated clinical plan for fexinidazole
• Select best regulatory strategy
• Identify new preclinical candidates
• Success with lead optimization projects
DNDi Preclinical & Clinical Portfolio - Visceral Leishmaniasis

**Discovery**
- General screening
  - VL Consortium
    - Advinus, CDRI
  - By chemical structure
  - By target
  - Natural products
  - Screening centers

**Preclinical**
- Amphotericin B Polymer
- Buparvaquone
- Oral Ampho B

**Clinical**
- AmBisome (in Africa)
- Paromomycin in Africa
- Combination Therapy (in India)

**Available**

- Screen: 30%
- Lead ID: 65%
- Lead Optimization: 55%
- Preclinical Efficacy & Safety: 55%
- Ph I: 70%
- Ph II: 50%
- Ph III: 65%
- Registration Access: 95%
VL Strategy Challenges

• Select the most appropriate drug combination tailored for different regions:
  – Asia
  – East Africa
  – Latin America

• Develop better preclinical candidates to be used in combination therapy
  – efficacy/safety
  – easy use
  – affordability

• Select new compounds from lead optimization program
## DNDi Preclinical & Clinical Portfolio - Chagas

### Discovery

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<tr>
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<th>Clinical</th>
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<tbody>
<tr>
<td>General screening By chemical structure By target Natural products Screening centers</td>
<td>Chagas Consortium: CDCO, Epichem Murdoch U</td>
<td>Comb. Azoles/Benznidazole</td>
<td>Azoles</td>
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<tr>
<td>Cysteine Protease Inhibitors</td>
<td>Washington U Buckner/Gelb</td>
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### DNDi Preclinical & Clinical Portfolio - Chagas

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<th>Preclinical Efficacy &amp; Safety</th>
<th>Ph I</th>
<th>Ph II</th>
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<tbody>
<tr>
<td>30%</td>
<td>65%</td>
<td>55%</td>
<td>55%</td>
<td>70%</td>
<td>50%</td>
<td>65%</td>
<td>95%</td>
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- **Available**
  - Paediatric Benznidazole Lafepe
Chagas Challenges: Need for new drugs at all stages

- **Therapeutic switching**
  - Azole class such as ravaconazole (Eisai) and posaconazole (Schering-Plough)
  - Active in animal efficacy models

- **Paediatric strength of benznidazole**
  - Currently not available; known to be effective in children in acute phase

- **Develop a new treatment for indeterminate/early chronic disease through the advancement of lead optimization**
  - One project per year
Preclinical and Clinical Projects – Portfolio in the Field by Disease

**Chagas**
- Azoles combo
- Paed. Benz
- CPI
- Azoles

**HAT**
- Next DB
- Fexi
- DB289
- Fexi backups
- NECT

**VL**
- Amphotericin B Polymer
- Oral Amphotericin B (BDSI)
- Combination - India
- Amphomul
- Oral Amphotericin B (iCo)
- AmBisome - Africa
- Miltefosine + Amphotericin B - India
- PM & PM-SSG combo - Africa
- Buparvaquone
- PM - India

- DNDi projects
- Non-DNDi
- In discussion


Registration: Amphotericin B Polymer, oral Amphotericin B (BDSI), oral Amphotericin B (iCo), AmBisome - Africa, Miltefosine + Amphotericin B - India, PM & PM-SSG combo - Africa, Buparvaquone.

Ph IV: Amphotericin B Polymer, oral Amphotericin B (BDSI), oral Amphotericin B (iCo), AmBisome - Africa, Miltefosine + Amphotericin B - India, PM & PM-SSG combo - Africa, Buparvaquone.
Access

- DNDi has delivered 2 projects
  - Challenges remain
- Solid partnerships being built
- Post-registration: an ongoing challenge & process
  - How to deliver?
Strategic Partnering to Address Access for Neglected Patients

As facilitator, DNDi ensures:

- Timely registration in endemic countries (WHO prequalification)
- Implementation through successful procurement and distribution strategy
- Changing international and national treatment guidelines
- Rational use of new treatment
- Pharmacovigilance
- Monitoring of drug resistance
- Advocacy to support implementation
Overcoming Access Challenges
Reaching Neglected Patients
Strategic Partnering to Implement Tools: ASAQ

- Registered by sanofi-aventis in 21 countries
- Prequalification pending
- sanofi-aventis distributes ASAQ and Coarsucam
- 1.5 M treatments distributed
- Global fund, Unitaid, AFMm
- Recommended in 16 countries as first line treatment, and by WHO (geographic extension: India)
- Rational use (Effectiveness study in Liberia/Specific groups, DNDi, MSF, Epicentre)
- Pharmacovigilance study in Ghana (DNDi, MMV, sanofi-aventis, In-depth)
- Information materials
As DNDi and our partners blaze the trail together...

...we continue to advance our projects, and to address the needs of the neglected patients