10 Years of Portfolio Building for Neglected Diseases: A DNDi Experience
DNDi Portfolio Building: Defining R&D Strategy

Perspectives by Prof. Simon Croft
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Former Director of Research and Development, DNDi (2004-2007)
Gaps Exist in the R&D Process for Neglected Diseases…

New knowledge on drug targets and lead compounds is published but pre-clinical research does not begin.

Validated candidate drugs do not enter clinical development because of strategic company choices.

New or existing drugs do not reach patients: registration problems, lack of production, high prices, or not adapted to the local conditions of use.
Long-term projects
• New chemical entities (NCEs)

Medium-term projects
• New formulations (fixed-dose combinations)
• New indications of existing drugs

Short-term projects
• Completing registration dossier
• Geographical extension

DNDi Portfolio-Building Model: Filling the Gaps
Address Immediate Patient Needs & Deliver Innovative Medicines
Stage 1 (2005-6): Move from Selection through Calls for Projects... towards a Proactive Strategy

**Discovery**
- TR inhibitors (leish, tryps)
- DHFR inhibitors (leish, tryps)
- Microtubule inhibitors (HAT)
- CP inhibitors (HAT, Chagas)
- Novel nitroheterocycles (HAT)
- Benzofuroxans (Chagas)
- Ascofuranone (HAT)
- Kitasato screening (HAT)
- Nitroimidazoles (tryps)
- Scynexis screening (HAT)
- CDRI screening (HAT)
- Genzyme screening (HAT)

**Pre-clinical**
- NPC1161B, an 8-aminoquinoline (VL)
- K 777 protease inhibitor (Chagas)
- Amphotericin B polymer (VL)
- Ravuconazole (Chagas)
- Drug combinations (VL)

**Call for projects**

**Proactive portfolio building**
Stage 2 (2006-7): Building the Chain of Partners from Discovery to the Clinic - Illustrated by the HAT Portfolio

TARGET BASED
TR Inhibitors (Fairlamb, Dundee)
CP inhibitors (McKerrow, UCSF)
DHFR Inhibitors (Basilea, Granada)
Microtubule inhibitors (Thompson, Perth)
Target X (…, Japan)
Target Y (…, Singapore)
Target Z (…, Germany)

CHEMISTRY BASED
Ascofuranone derivatives (Kita, Tokyo)
Nitroheterocycles (Gilbert, Dundee)
Nitroimidazoles (VARIOUS)
Series A (…, UK)
Series B (…, China)
Series C (…, USA)

CHEMICAL DIVERSITY
Kitasato Institute screen
CDRI, Lucknow screen
Library Q (…, USA)

LEAD OPTIMISATION
Medicinal Chemistry
Scynexis North Carolina
Advinus Therapeutics, Bangalore
CDCO, Monash university
Blood-Brain Barrier
Perfusion models, KO models, microdialysis (London Univ., Pharmidex)

DISEASE MODEL EVALUATION
Swiss Tropical Institute
KARI – TRC Nairobi
CROs or Pharma partners
ADME
(Geno)toxicity
CMC etc
Regulatory advise
Animal models
Acceptable activity/toxicity profile
Fast-tracking?

CLINICAL TRIAL
Nifurtimox – Efornithine co-administration for 2nd stage disease
Partners: Epicentre, MSF, STI, DRC
Nat. Prog, TDR, Roc and Uganda Natl programme

HAT PLATFORM
DNDi
Swiss Tropical Institute
WHO
National Programmes
FIND, TDR and others
Stage 3 (2005-7): Building Consortia to Generate Leads

Drug candidates:

- SCYX-7158
- VL-2098
- Fenarimol series
- Fexinidazole

HAT Lead Optimization Programme
- Scynexis, Genzyme, Pace

VL Lead Optimization Programme
- Advinus Therapeutics, Indian Institute for Chemical Biology

Chagas Lead Optimization Programme
- In preparation (in 2007)

HAT Data mining and re-purposing

Organizations involved:
- Anacor
- Basilea
- CDRI
- Chemroutes
- Epichem
- Eskitis
- Genzyme
- GSK
- Institut Pasteur Korea
- IRD
- Nycomed Altana
- Otsuka NITD
- Ranbaxy
- Sanofi-Aventis
- Scynexis
- Sigma-Tau
- SIMM
- Swiss Tropical Institute
- UCSF
- Uni Washington
- WEHI

HAT Data mining and re-purposing

VL Lead Optimization Programme
- VL-2098

Fenarimol series
- Fexinidazole
Selection of Existing Treatments to Develop Improved Formulations

- **NECT** for sleeping sickness
- **Paromomycin** alone and in combination with SSG for VL in East Africa
- **FACT Consortium** for FDCs for malaria (**ASAQ, ASMQ**)
- **Paediatric** dosage form of benznidazole for children with Chagas disease
Utilizing and Strengthening Research Capacities in Disease-Endemic Countries

Major Role of Regional Disease Platforms:

- Defining patients’ needs and target product profile (TPP)
- Strengthening local capacities
- Conducting clinical trials (Phase II/III studies)
- Facilitating registration
- Accelerating implementation of new treatments (Phase IV & pharmacovigilance studies)
Launch of ASAQ for Malaria in 2007: Reference Partnership with Sanofi Leading to First Pipeline Delivery

- DNDi licensed the product to Sanofi in Dec. 2004
- Public price ‘at cost’
  - <USD1 for adults, USD 0.50 for children
- Non-exclusive
- Scale up, registration, distribution, and medical information support by Sanofi
- Collaboration in implementation and post-registration
DNDi Portfolio Consolidation

Perspectives by Dr Shing Chang
Consultant & Former Director of Research and Development, DNDi (2007-2012)
Consolidation of Short- and Medium-term Strategy

**Discovery**
- DHFR inhibitors, LT
- CP inhibitors, T
- TR inhibitors, LT
- Microtubule inhibitors, H
- Scynexis screening, T
- CDRI screening, T
- Genzyme screening, T
- Kitasato screening, T
- Novel nitro-heterocycles, H
- Ascofuranone, H
- Nitroimidazoles 1, LT

**Pre-clinical**
- NPC1161B, an 8-aminooquinoline, VL

**Clinical**
- FDC Artesunate-Amodiaquine, M
- FDC Artesunate-Mefloquine, M
- Nifurtimox-Eflornithine, H
- Paromomycin, VL
- Imiquimod, CL
- Ambisome, L

**Implementation**
- Drug combinations, VL

**Portfolio 2007**
- L: Leishmaniasis
- VL: Visceral leishmaniasis
- CL: Cutaneous leishmaniasis
- T: Trypanosomiasis
- C: Chagas disease
- H: Human African trypanosomiasis
After ASAQ, 5 Additional New Treatments Delivered to Respond to Urgent Patients’ Needs

- Easy to Use
- Affordable
- Field-Adapted
- Non-Patented
ASAQ FDC Implementation with Sanofi

More than 200M Treatments Distributed by End 2012

- Registered in 2007, prequalified by WHO in 2008
- Non patented product
- Registered in 30 sub-Saharan African countries, in India, Bangladesh and Colombia
- Only FDC with a 3-year shelf-life
- Ambitious risk management plan (Pharmacovigilance) with MMV and Sanofi
- Transfer of technology to Zenufa (Tanzania)
Addition of Mini-Portfolios to Meet Patient Needs Flexibility and Adaptability of DNDi’s Portfolio Model

- **Paediatric HIV**
  - Need for a Fixed-Dose Combination ARV, 4-in-1 for children <3 y.o.

- **Filarial infections**
  - Need for a macrofilaricde

Diagram:
- **Discovery**
- **L.O.**
- **Pre-clinical**
- **Clinical**
- **Reg.**
- **Access**

**Leishmaniasis**
- (VL – CL – PKDL – HIV/VL)
- **HAT**
- **Chagas**
- **Malaria**
  - **Filaria**
  - **Paediatric HIV**

**DNDi**
Drugs for Neglected Diseases initiative
Long-term Strategy
New Chemical Entities Filling the Pipeline

Two oral drug candidates:

- **Fexinidazole for sleeping sickness**
  - After data mining, pre-clinical development
  - Clinical Phase I study
  - Agreement to co-develop with Sanofi

- **E1224 for Chagas disease**
  - Partnership with Eisai
  - Phase II clinical trial in adult chronic patients
  - First-ever Phase II in Bolivia
Two oral drug candidates:

- Oxa SCYX-7158 for sleeping sickness
  - First candidate from DNDi LO programme
  - Innovative partnership with biotechs and universities (Anacor, Pace University, Sandler Center UCSF, Swiss TPH, Scynexis)
  - Clinical Phase I study ending

- VL-2098 for visceral leishmaniasis
  - Identified in TB Alliance Nitroimidazoles library
  - Very potent against VL
  - Showed efficacy and no major toxicity \textit{in vivo}
  - Pre-clinical development ongoing
Dynamic Industrial Partnerships at All Stages of Development

**Discovery**
- HAT: AbbVie, Advinus, Anacor, Astellas, AstraZeneca, Bayer, BMS
- Leish: AbbVie, Advinus, Anacor, Eisai, GSK, MSD, Novartis, Pfizer, Scynexis
- Chagas: AbbVie, Advinus, Anacor, Eisai, Scynexis

**Pre-clinical**
- HAT: AbbVie, Advinus, Anacor, Eisai, Scynexis
- Leish: AbbVie, Advinus, Anacor, Eisai, Scynexis
- Chagas: AbbVie, Advinus, Anacor, Eisai, Scynexis

**Clinical**
- HAT: Eisai, Gilead, Gland Pharma, Sanofi
- Leish: Bayer, Gilead, Gland Pharma, Lafepe, Sanofi
- Chagas: J&J

**Implementation**
- HAT: Cipla
- Leish: Cipla
- Chagas: Sanofi, Farmanguinhos, Cipla, Zenufa
Global actors form a coalition to support WHO’s 2020 NTD Roadmap:

- Pharmaceutical companies
- World Bank
- Donor Countries (UK, USA, UAE)
- BMGF and other private donors (Mundo Sano, Brazil)
- Endemic country MoHs
- DNDi

The outcome for DNDi?

- New, renewed, or expanded commitments from 12 major pharmaceutical companies.
- Greatest ever access to compound libraries for DNDi.
Short-, Medium- and Long-Term Strategy Come Together

Perspectives by Dr Graeme Bilbe
Director of Research and Development, DNDi (2012-present)
DNDi Portfolio: A Mix of Existing Drugs & NCEs
6 new treatments available and 12 new chemical entities in the pipeline

Dec. 2013
★ New Chemical Entity (NCE); Fexinidazole (for HAT, VL, and Chagas) = 1 NCE
Two examples of the challenges

- **Chagas disease**
  - Paediatric dosage form of benznidazole: guarantee access from a 2nd source
  - Benznidazole efficacy confirmed in a recent clinical trial => strengthen access infrastructure to deliver to patients

- **Visceral leishmaniasis (VL) in India**
  - Drugs for effective combination therapies are available and recommended by WHO
    - *Now, there is a real need for political change*

- **Endemic countries have a crucial role to play**
Improving Existing Therapies and Advancing NCEs in Development

- Improve benznidazole regimens for Chagas disease
  - A shorter-course treatment is needed
- Safe *and* effective treatments for VL
  - Develop new combination therapies for Africa
  - New manifestations like HIV/VL
- Meet the needs of Paediatric HIV patients with 4-in-1 Fixed-Dose Combinations
- Register Fexinidazole for sleeping sickness
  - First NCE
    ✓ Phase II/III in DRC and CAR
Sleeping Sickness
- SCYX-7158: Phase I ongoing
- Entering Phase II/III in 2014

VL and Chagas
- Potent nitroimidazoles e.g., VL-2098
- New compound classes like oxaboroles

Helminth infections
- Repurpose drugs from animal or human health applications
Accessing Diversity

NCEs Are Still Needed for Chagas and VL

- Transform discovery capabilities
  - Access new chemical space
  - Innovate in translation to the clinic
- Build on endemic country expertise
  - Latin America
    - LOLA (Lead Optimization in Latin America)
  - India
    - CSIR (Council of Scientific & Industrial Research)
- Improve and expand research partnerships

Leishmania donovani intracellular amastigotes in murine peritoneal macrophage

Courtesy of SwissTPH
Boosting Discovery
From Bilateral Collaborations

DNDi
Disease knowledge
Discovery resources
Development expertise
Implementation

Partner A
Compound libraries
Screening
Lead Optimisation

Partner B
Research projects
Compounds
Clinical candidates

Partner C
Compounds

Partner D

Partner E
Boosting Discovery

..To Exploiting Knowledge from Multilateral Partnerships

NEW OPTIONS FOR ORALLY-ACTIVE THERAPIES
On Track to Deliver 6 Additional Treatments by 2018

Total = 6-8
Preparing the Future

- Business plan revision for the 10 years to come
- Keep Patients at the Core of Our Mission!
Thank You to All Our Partners & Donors

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