Drugs for Neglected Tropical Diseases: New Approaches, Current Status, Challenges

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The Landscape
Neglected Diseases: Primarily Affect Developing Countries & Lie Outside the World Market

Global Diseases

Most Neglected Diseases

Neglected Diseases

World pharmaceutical market
$962 bn in 2012*

*Source: IMS Health
Burden of Neglected Tropical Diseases

This map displays countries endemic for each of these diseases based on 2009-2010 data and international borders (from: www.unitingtocombatntds.org)

- Buruli Ulcer
- Chagas disease (American trypanosomiasis)
- Cysticercosis
- Dengue/Severe dengue
- Dracunculiasis (guinea-worm disease)
- Echinococcosis
- Fascioliasis
- Human African trypanosomiasis
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Onchocerciasis
- Rabies
- Schistosomiasis
- Soil transmitted helminthiasis
- Trachoma
- Yaws
Burden of Neglected Tropical Diseases (2)

Figure 1. The 10 Leading Causes of Life-Years Lost to Disability and Premature Death.

Control of Neglected Tropical Diseases

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A Decade Ago, Pipeline Virtually Empty for Neglected Diseases

Health R&D (1975 – 1999)

1,393 total products approved

1975-1999

1.1%
16 new drugs for neglected diseases

A Fatal Imbalance

From 1975-1999:

- 16 of 1393 new products for neglected tropical diseases + malaria and TB (1.1%) despite these diseases representing 12% of global disease burden

- Approx. 10% of R&D dedicated to illnesses that affect 90% of global disease burden (‘10/90 gap’)

Source: Fatal Imbalance: The Crisis in Research and Development for Neglected Diseases, MSF, 2001
Neglected Diseases
Treatment Limitations 10 Years Ago

We Need Safe, Effective, Easy-to-Use Drugs

- Ineffective (resistance)
- Toxic
- Expensive
- Painful when delivered
- Difficult to use
- Not adapted to the field
- Not registered in endemic regions
- Restricted by patents

Melarsoprol  Eflornithine
Human African Trypanosomiasis (HAT) or Sleeping Sickness

- 36 countries at risk in sub-Saharan Africa; estimated current cases: 20,000
- Transmitted by the tsetse fly
- Difficult to diagnose; many patients go undiagnosed until late stage of disease (CNS or Stage 2)
- Fatal if untreated
- Needs a safe, effective, and orally administered stage 2 treatment
Leishmaniasis

- 350 million at risk worldwide (in 98 countries)
- Transmitted by the sandflies
- 2 types of leishmaniasis
  - Visceral (VL): fatal without treatment
  - Cutaneous (CL): has a spectrum of presentations; typically with self-healing or chronic lesions on the skin.
- Symptoms of VL: prolonged fever, enlarged spleen & liver, substantial weight of loss, progressive anemia
- Needs for VL
  - Oral, safe, effective, low-cost and short-course treatment
Chagas Disease

- 100 million at risk in Latin America
  - Kills more people in region than malaria
  - Patient number growing in non-endemic, developed countries
- Transmitted by ‘kissing bug’, blood transfusion, organ transplantation, as congenitally or orally
- Majority of patients undiagnosed until late stage
- Needs

An affordable, age-adapted, safe, and efficacious paediatric strength

A new drug for early chronic stage
Responding to the Needs of Patients Suffering from Neglected Diseases…

- Malaria
- Leishmaniasis
- Paediatric HIV
- Sleeping Sickness (HAT)
- Chagas Disease
- Filaria
Product Development Partnerships (PDPs)
Filling the Gaps in Translational Research and Product Development

PDPs work across different diseases and modalities

Vaccines
Microbicides & preventatives
Therapeutic products
Diagnostics

HIV/AIDS  TB  Malaria  NTD  Diarrhea  Respiratory

Source: The Bill & Melinda Gates Foundation & BCG
Drugs for Neglected Diseases initiative (DNDi) Model
Since 1999, from ideas to realization …

- 1999
  - First meeting to describe the lack of R&D for neglected diseases
  - MSF commits the Nobel Peace Prize money to the DND Working Group
  - JAMA article: ‘Access to essential drugs in poor countries - A Lost Battle?’

- July 2003
  - Creation of DNDi (7 founding members)

- 2007
  - First DNDi treatment registered…

- 2013
  - 10 years of DNDi and 6 treatments made available
DNDi “Structure”

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

7 worldwide offices
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**
  
  - **Raise awareness** and advocate for increased **public responsibility**
Partnerships: No One Can Do It Alone
A Global Network to Leverage Resources

Criteria for Success:
- Share the same vision
- Mutual understanding
- Involvement throughout the whole process
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)
Challenge to Conduct Clinical Trials in Very Difficult Settings

- Access to Sites
- Status of Infrastructure
- Staff Limitations
Overcoming Challenges in the Field
Thanks to Our Partners in Endemic Countries

In 10 years: >33,000 patients enrolled in >20 clinical studies in five disease areas
DNDi’s Portfolio
DNDi Portfolio-Building Model
Address Immediate Patient Needs & Deliver Innovative Medicines

- Long-term projects
  - New chemical entities (NCEs)
  - New formulations (fixed-dose combinations)
  - New indications of existing drugs

- Medium-term projects
  - Completing registration dossier
  - Geographical extension

- Short-term projects

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[Image of a timeline with stages: Discovery (R, LS, LO), Pre-clinical, Clinical, Implementation]
DNDi Portfolio: A Mix of Existing Drugs & NCEs

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

**HAT**
- SCYX2035811
- SCYX1608210

**Leishmaniasis**
- Nitroimidazole backup
- Oxaleish
- VL-2098
- Fexinidazole
- New VL treatments for Bangladesh
- New VL treatments for Latin America
- New VL treatments for India
- Anfoleish (CL)
- 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
Transform discovery capabilities
- HTS/HCS for all diseases developed
- Access new chemical space (Pharma files)
- Better understanding of the diseases

Development of secondary assays
- Innovate in translation to the clinic

Improve and expand research partnerships

Build on endemic country expertise
- Latin America: LOLA (Lead Optimization in Latin America)
- India: CSIR (Council of Scientific & Industrial Research)
Lead Optimization Consortia
From Hit to Potential Pre-Clinical Candidate

- Continued evolution
  - 2.5 Consortia (1 in endemic country, LOLA)
  - Shared resources (WuXi)
- VL and Chagas are priority
- Access to series from the Pharma
- Potential VL candidates issued from:
  - Oxaboroles series (Anacor, USA)
  - Nitroimidazoles (Univ. of Auckland, NZ)
- New chemistry starting points for Chagas
- Translational challenges being tackled
  - New tools/assays developed
  - Better understanding of PK/PD relationship for these diseases

Key partners:
CDCO/Monash University, Epichem, Griffith University, WuXi, Sandexis, Anacor, LMPH, LSHTM, Unicamp
Sleeping Sickness: From Unacceptable To Better, Towards Tools for Elimination

Since 2009
NECT

Eflornithine
Melarsoprol

10 years ago

2016
Oral treatment & rapid diagnostic test?
10 Years Ago: A Dire Situation

Melarsoprol

- Toxic (~5% mortality)
- Ineffective (resistance)
- Painful when delivered
- 1940
- 10 days i.v.

Eflornithine

- Expensive
- Difficult to use
- Not registered in endemic regions
- 1980
Eflornithine
14 days q.i.d. infusion

1 cubic metre
No roads
No power
Since 2009, NECT
Improved Treatment But Still Not Ideal in Remote Areas

Nifurtimox-eflornithine combination therapy
- MSF & Epicentre initiated trial
- A simplified, safe & effective treatment for stage 2 HAT
- WHO Essential Medicines List (2009)
- Implemented in 12 Countries (99% of cases)
  - Over 13,000 treatments distributed
- Drastic decrease in melarsoprol use

Treatments for stage 2 HAT in DRC (2012)

NECT Use (May 2013)
Oxaborole SCYX-7158 for HAT
From Lead Optimization to Clinical Candidate

- Identified as hits against \textit{T. brucei} at Sandler Center, showed activity in animal models of HAT.
- Innovative US partnership with 2 biotechs and 1 university.
- First candidate issued from DND\textit{i} Lead Opt. Programme.
- Clinical Phase I study ending.

Potential oral treatment with a single pill, effective against both stages 1 and 2.

Key partners: Scynexis, Anacor, Pace University, Sandler Center, UCSF, Swiss TPH.
Fexinidazole, a Rediscovered New Chemical Entity in Phase II/III Clinical Study for HAT

- ‘Rediscovered’ through compound mining
- Preclinical development including DMPK, GLP-toxicology, safety pharmacology and CMC
- Phase I clinical trials completed
- Drug candidate to become an oral, short course treatment for stage 1+2 sleeping sickness treatment
- In partnership with sanofi
- Phase II/III ongoing in DRC and CAR
DNDi’s Funding Strategy
DNDi’s Funding Strategy

**Independence** through diversified sources of funding

- 50% of funding from public institutional donors in line with DNDi’s advocacy objective (public responsibility for NDs)
- 50% from private sector (foundations, major donors, general public)
- Key contributions to come from Founding Partners
- Maximum of 25% per donor

**Sources of funding**
Projected commitments (business plan)

- 51% Public Institutional
- 29% Foundations & Major Donors
- 17% Founding Partners
- 3% General Public
Challenges
Main Challenges for Sustainable R&D for Neglected Patients

- **R&D**
  - Access to chemical diversity, Know-How and knowledge, IP (FTO in the field), Data-sharing, Avoid duplication

- **Overcome Regulatory Barriers**
  - Need to strengthen regulatory agencies in endemic regions (regional collaboration)

- **Access**
  - Ensure equitable access to all patients & affordable treatment

- **Sustainable funding**
  - Innovative Mechanisms
But There is HOPE.............
From a Fragmented Landscape for Neglected Diseases R&D

A dynamized critical mass of Neglected Disease players

- Big Pharma & Biotechs
- WHO
- Generics & Pharma
- Governments
- PPPs & PDPs
- Philanthropy
- Public institutions in endemic countries
- New Funding Mechanisms

Public institutions in endemic countries
Towards a Global Framework for NTDs R&D

A dynamized critical mass of Neglected Disease players

Big Pharma & Biotechs
Generics & Pharma
New Funding Mechanisms
Governments
WHO
Public institutions in endemic countries
Philanthropy
PPPs & PDPs
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 and LA
- €277M of €400M needed raised
- On track to deliver new treatments per business plan
Thank You to All Our Partners & Donors

www.connect2fightneglect.org  www.dndi.org
Paediatric HIV

- Virtual elimination of paediatric HIV in high-income countries...
- ...but 330,000 new infant infections each year and 3.4 million children with HIV/AIDS (91% in sub-Saharan Africa)
  - > 900 new pediatric HIV infections daily
  - > 600 deaths in HIV+ children daily
- HIV disease progression in children more rapid than in adults if no treatment is given
  - 1/3 of HIV+ infants will die by 1 yr old
  - 50% of HIV+ children will die by 2 yrs old
  - 80% of HIV+ children will die by 5 yrs old
Malaria: ASAQ FDC Implemented in Partnership with Sanofi 280M Treatments Distributed

- 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)
Fatal Imbalance Remains Despite Progress Over A Decade

756 products developed (excluding vaccines) (2000-2011)

- 3.8% of new products for neglected diseases (reformulations, combinations)
- 1.2% of NCEs for neglected diseases
- Only 1.4% clinical trials (of nearly 150,000 trials) focus on neglected diseases
- Only 1% of global health investment for neglected diseases*


Source: 'Mapping of available health research and development data: what’s there, what’s missing, and what role is there for a global observatory?' Rottingen et al. Lancet, May 2013
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, Argentina)
- 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.