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

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Eric Chatelain PhD

PSWC 2014, Melbourne, 15th April

The Landscape

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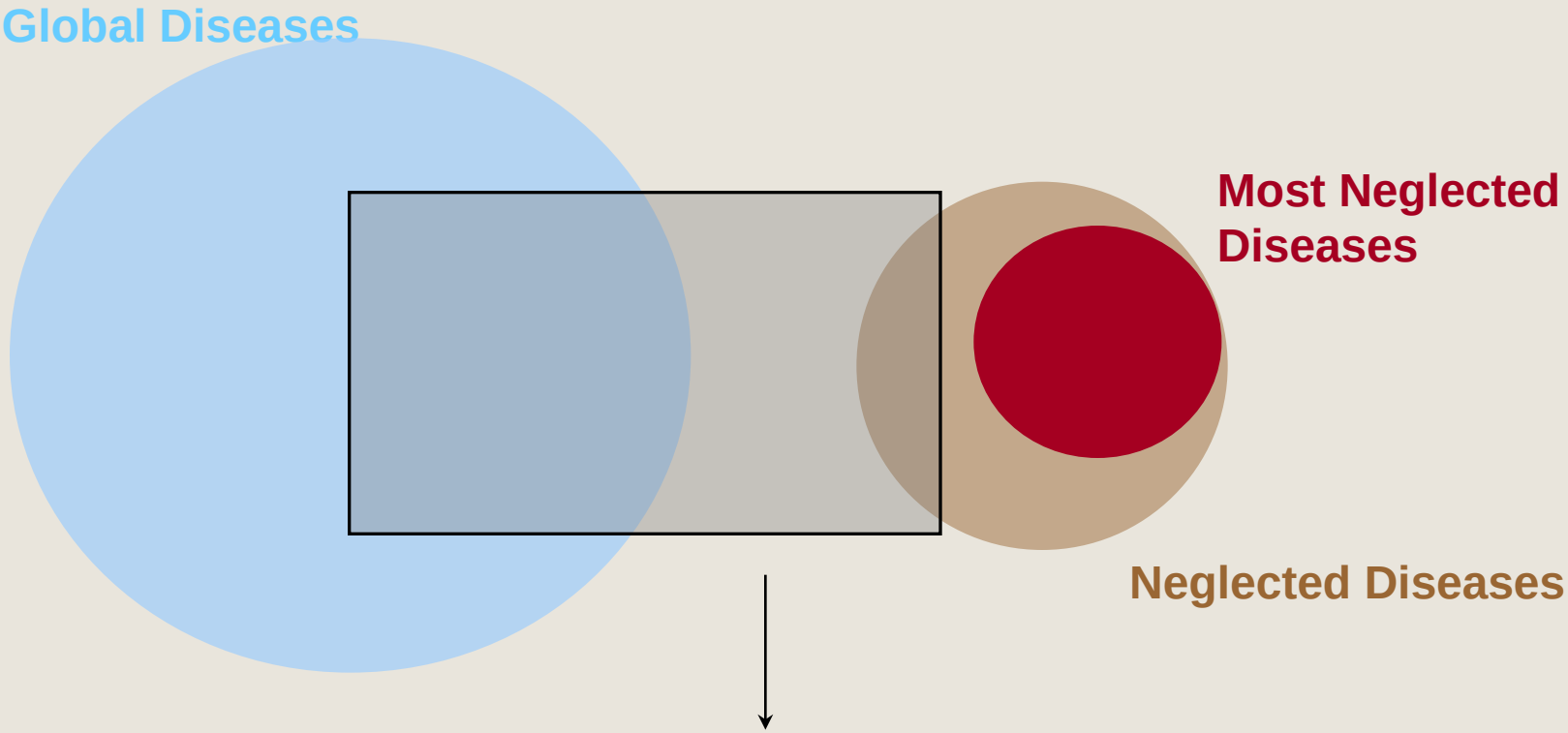
Neglected Diseases: Primarily Affect Developing Countries & Lie Outside the World Market



*Source: IMS Health

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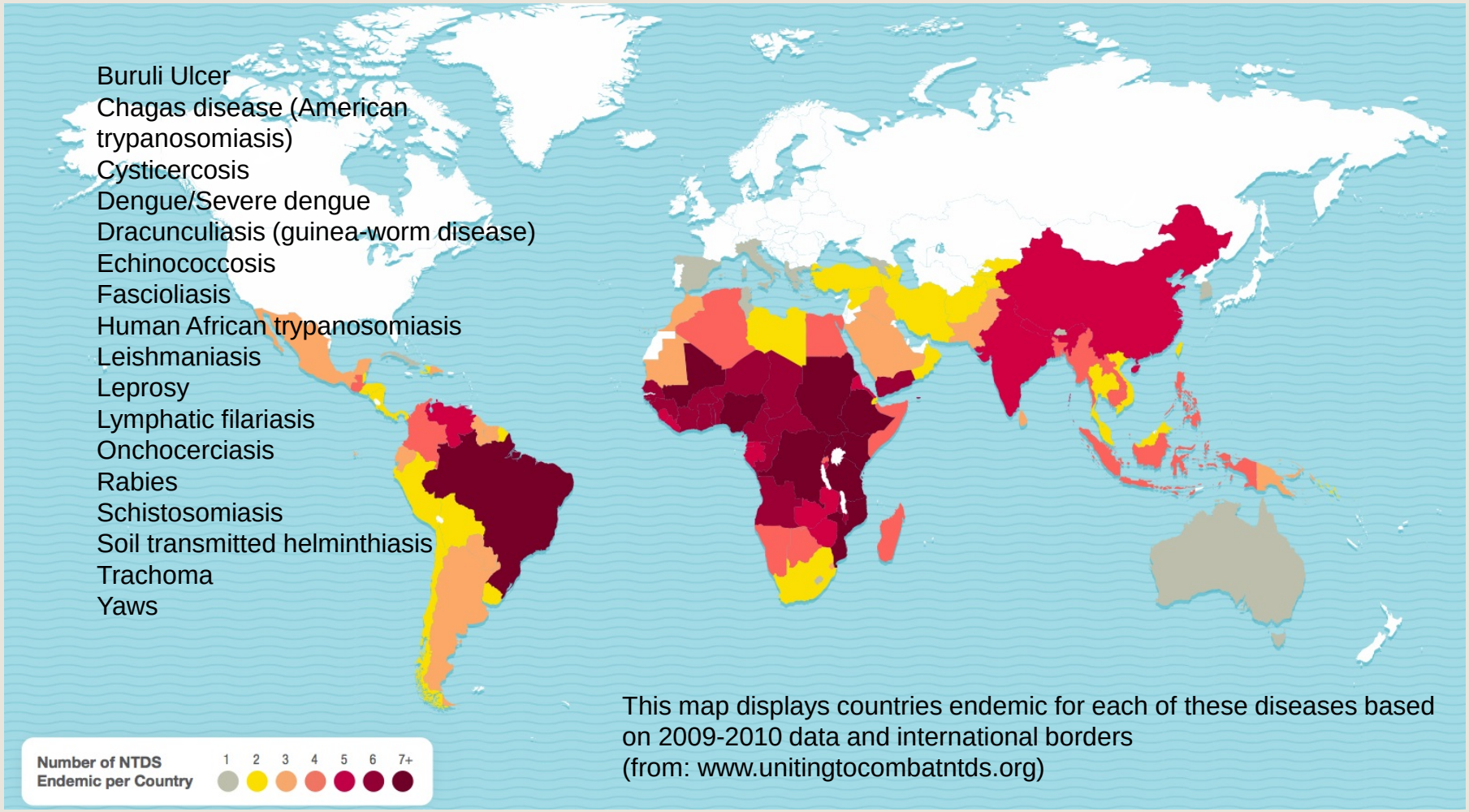
Burden of Neglected Tropical Diseases



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Burden of Neglected Tropical Diseases (2)

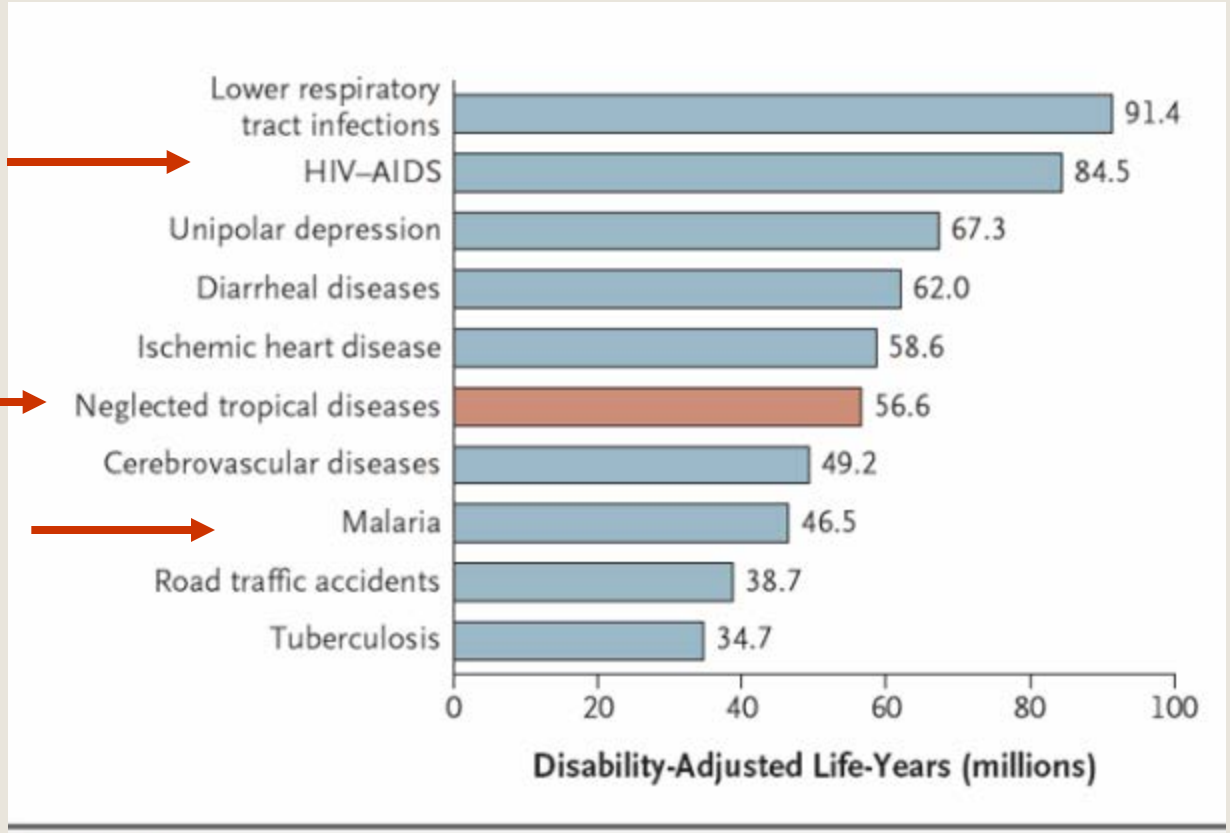

Figure 1. The 10 Leading Causes of Life-Years Lost to Disability and Premature Death.

CURRENT CONCEPTS

Control of Neglected Tropical Diseases

Peter J. Hotez, M.D., Ph.D., David H. Molyneux, Ph.D., D.Sc., Alan Fenwick, Ph.D., Jacob Kumaresan, M.B., B.S., Dr.P.H., Sonia Ehrlich Sachs, M.D., Jeffrey D. Sachs, Ph.D., and Lorenzo Savioli, M.D.

N ENGL J MED 357;10 WWW.NEJM.ORG SEPTEMBER 6, 2007

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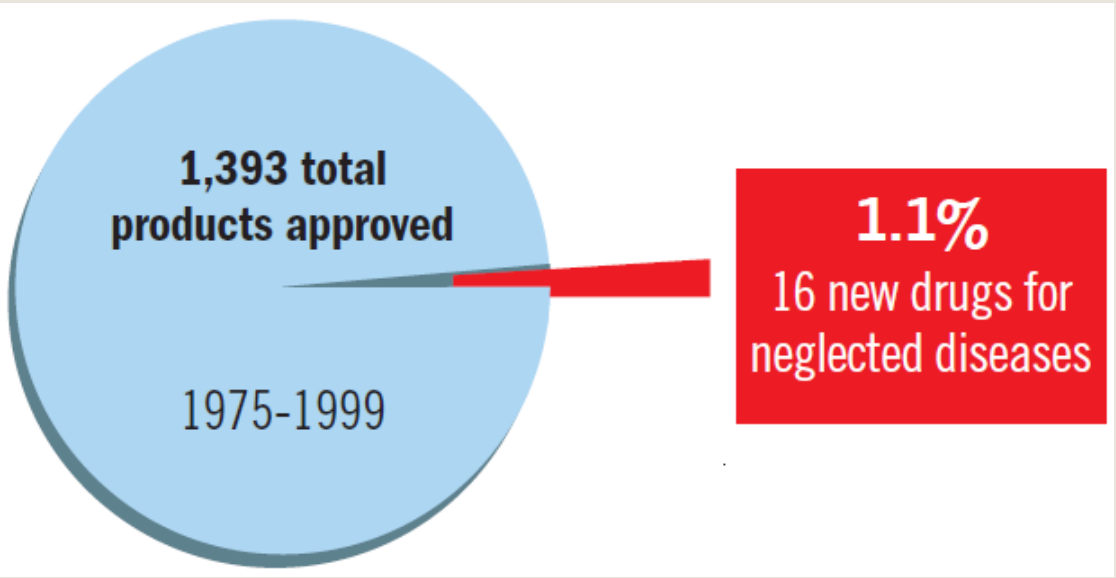
A Decade Ago, Pipeline Virtually Empty for Neglected Diseases

Health R&D (1975 – 1999)



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

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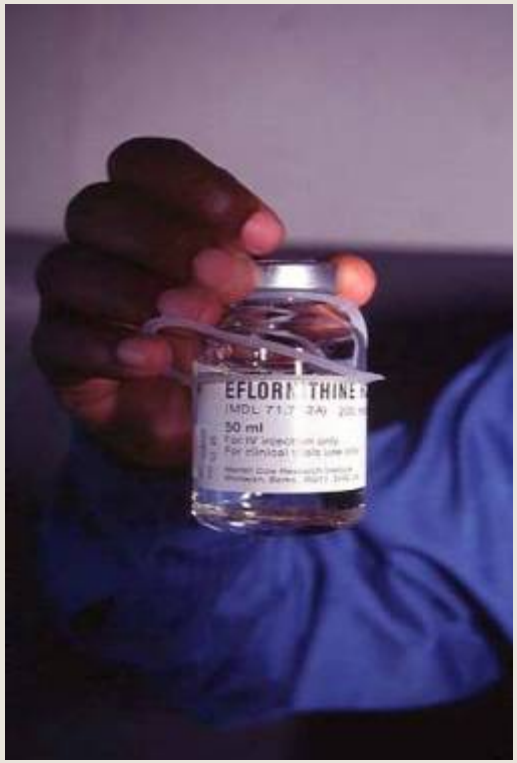
Neglected Diseases
Treatment Limitations 10 Years Ago

Melarsoprol



Eflornithine

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

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

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Neglected Tropical Diseases

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Human African Trypanosomiasis (HAT) or Sleeping Sickness

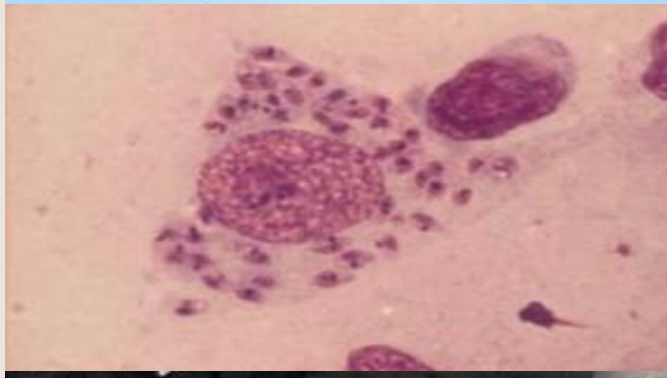
- 36 countries at risk in sub-Saharan Africa; estimated current cases: 20,000
- Transmitted by the tsetse fly
- Difficult to diagnose; many patients go undiagnosed until late stage of disease (CNS or Stage 2)
- Fatal if untreated
- Needs

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

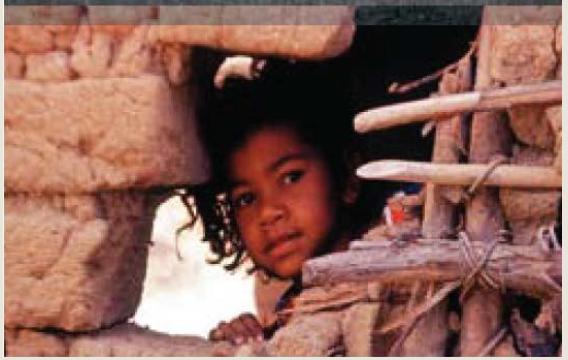


Chagas Disease

- 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

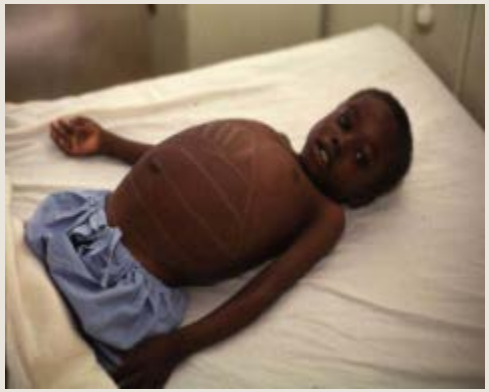
An affordable, age-adapted, safe, and efficacious paediatric strength

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

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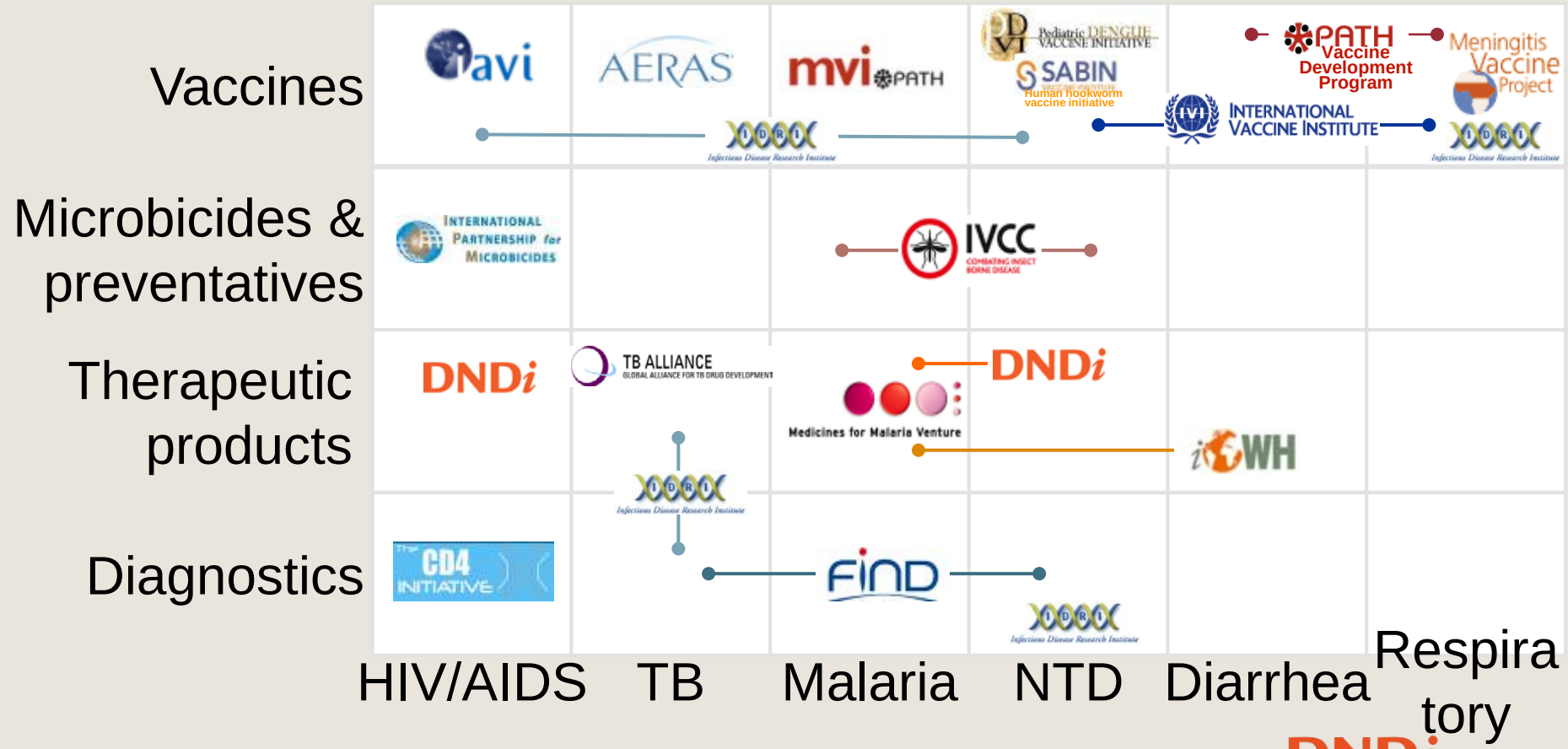
Product Development Partnerships (PDPs)

Filling the Gaps in Translational Research and Product Development

PDPs work across different diseases and modalities



Source: Bill & Melinda Gates foundation & BCG The Boston Consulting Group

DNDi Drugs for Neglected Diseases initiative

Drugs for Neglected Diseases *initiative* (DND*i*) Model

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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 DND*i* (7 founding members)
- 2007
  - First DND*i* treatment registered…
- 2013
  - 10 years of DND*i* and 6 treatments made available

James Orbinski,
ex-President, MSF Int, 1999

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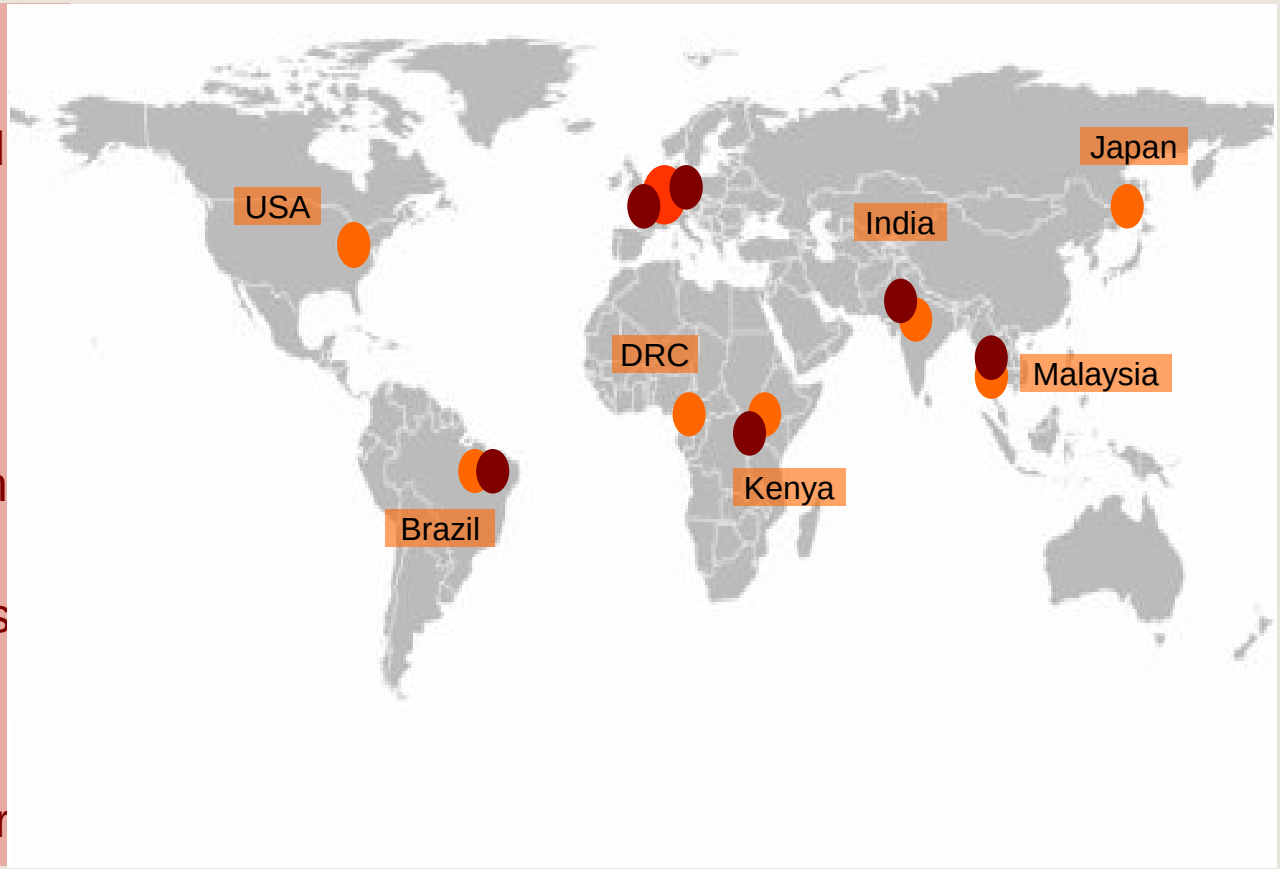
DNDi “Structure”

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

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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**

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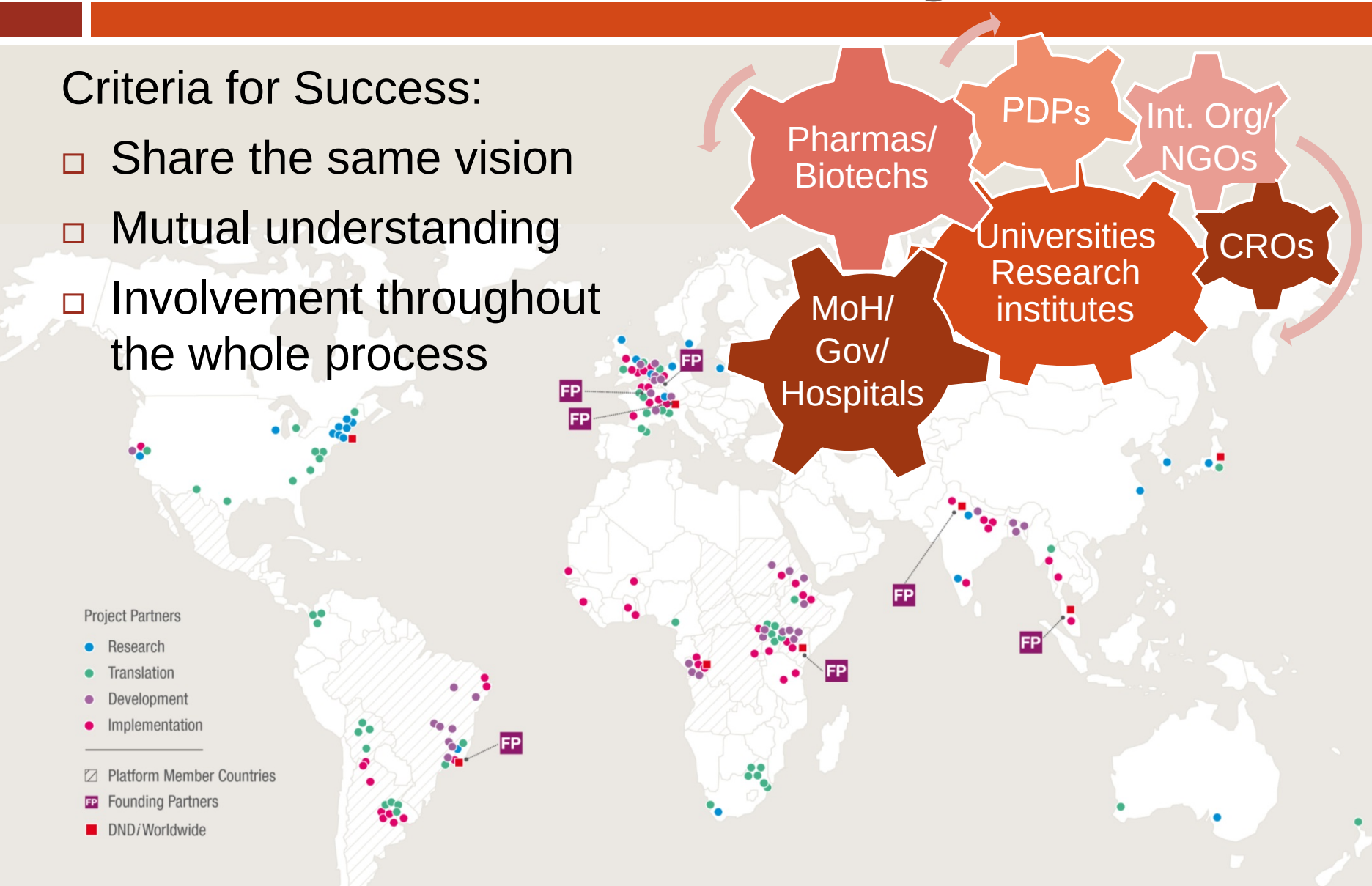
Partners(hips): No One Can Do It Alone
A Global Network to Leverage Resources

Criteria for Success:

- Share the same vision
- Mutual understanding
- Involvement throughout the whole process



Utilizing and Strengthening Research Capacities in Disease-Endemic Countries

VL

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

HAT

PLATEFORME REGIONALE DE RECHERCHE CLINIQUE
TRYPANOSOMIASE HUMAINE AFRICAINE
HUMAN AFRICAN TRYPANOSOMIASIS
REGIONAL PLATFORM FOR CLINICAL RESEARCH

CHAGAS

PLATAFORMA DE INVESTIGACION CLINICA EN ENFERMEDAD DE CHAGAS
CHAGAS DISEASE CLINICAL RESEARCH PLATFORM

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)

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Challenge to Conduct Clinical Trials in Very Difficult Settings

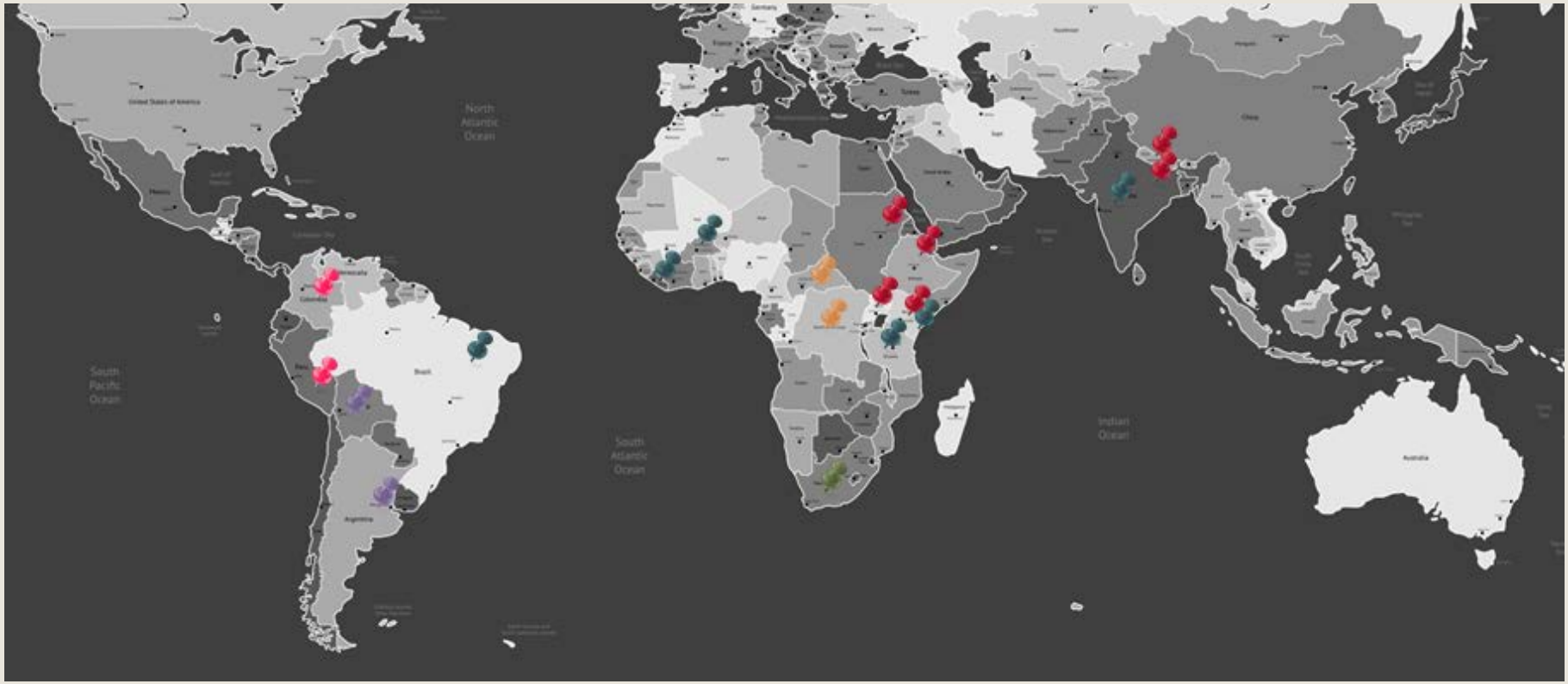
- Access to Sites
- Status of Infrastructure
- Staff Limitations

TB

JS

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



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DND*i*'s Portfolio

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DND*i* Portfolio-Building Model

Address Immediate Patient Needs & Deliver Innovative Medicines

- **New chemical entities (NCEs)**

Long-term projects

- **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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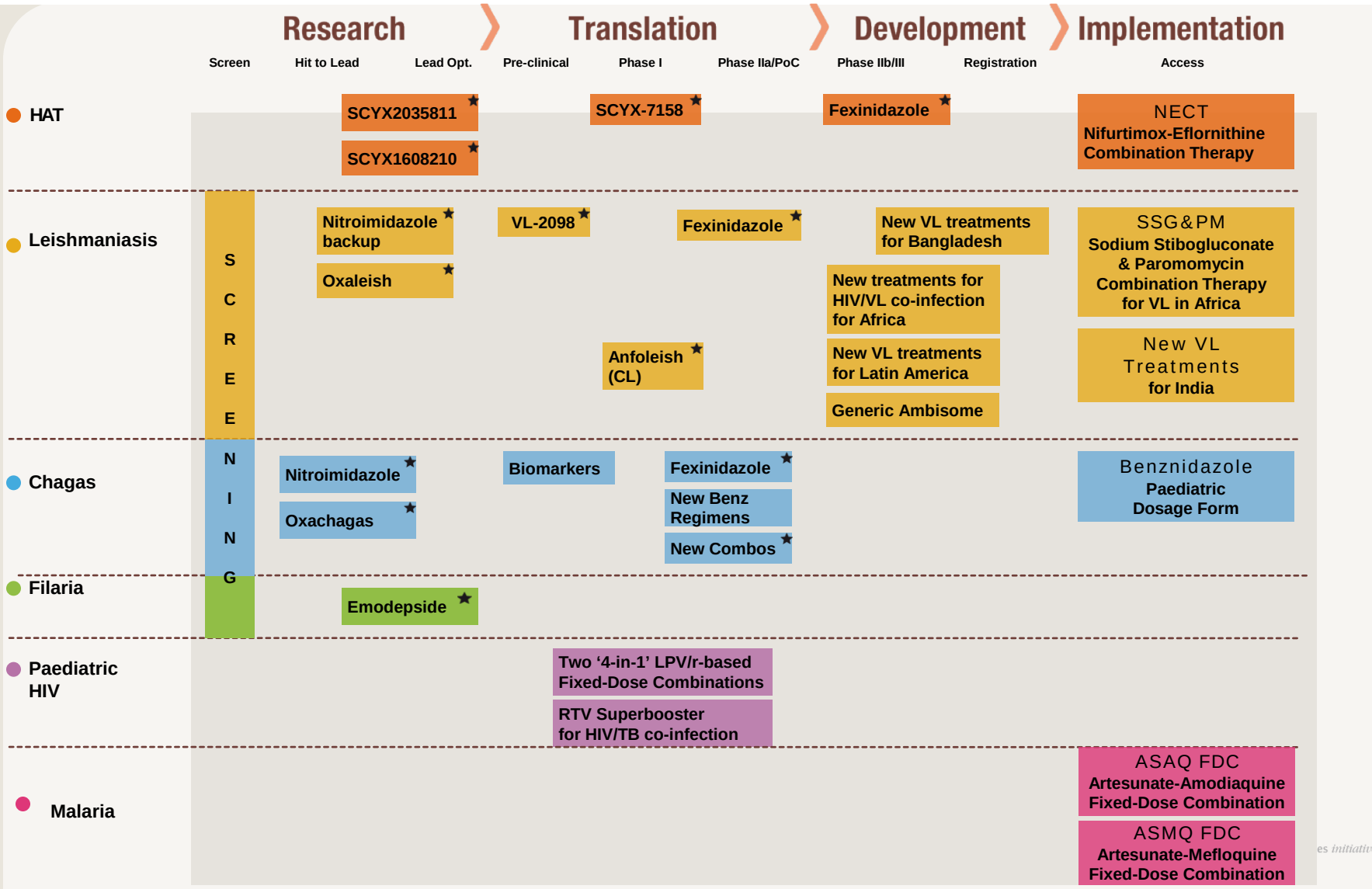
DND*i* Portfolio: A Mix of Exisiting Drugs & NCEs

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

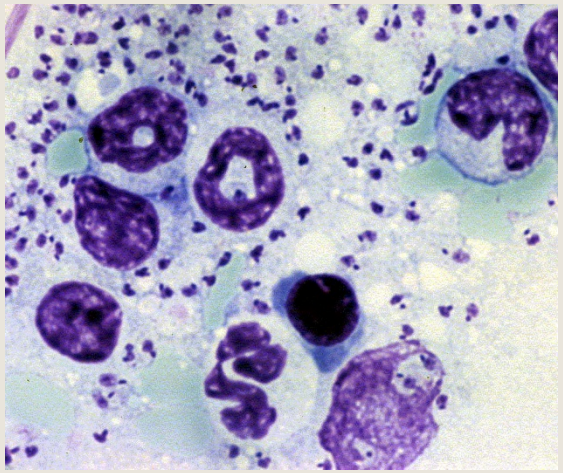


Discovery:Entering a New Era

NCEs Are Still Needed for Chagas and VL

Research

- Transform discovery capabilities
  - HTS/HCS for all diseases developped
  - 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)



Leishmania donovani intracellular amastigotes in murine peritoneal macrophage
Courtesy of SwissTPH

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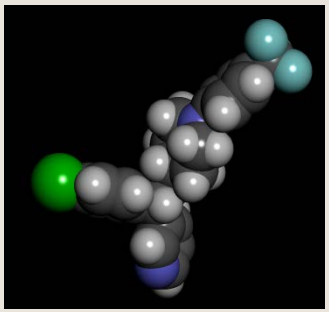
Lead Optimization Consortia

From Hit to Potential Pre-Clinical Candidate

Research



- 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 developped
  - Better understanding of PK/PD relationship for these diseases

Key partners:

CDCO/Monash University, Epichem, Griffith University, WuXi, Sandexis, Anacor, LMPH, LSHTM, Unicamp

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Sleeping Sickness: From Unacceptable To Better, Towards Tools for Elimination

10 years ago

Eflornithine

Melarsoprol

Since 2009

NECT

2016

Oral treatment & rapid diagnostic test?

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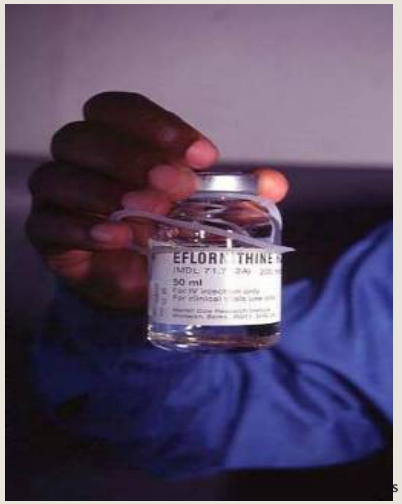
10 Years Ago: A Dire Situation

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

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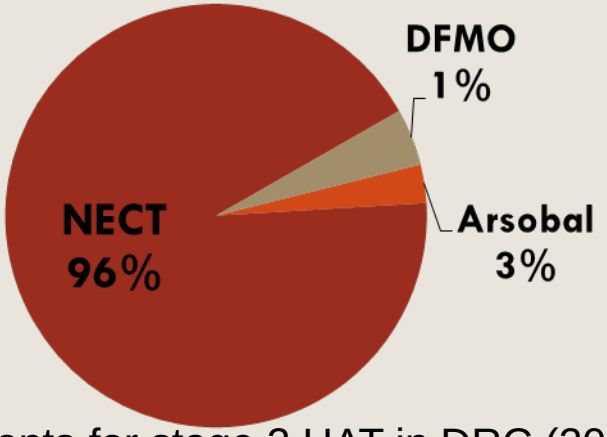
Since 2009, NECT
Improved Treatment But Still Not Ideal in Remote Areas

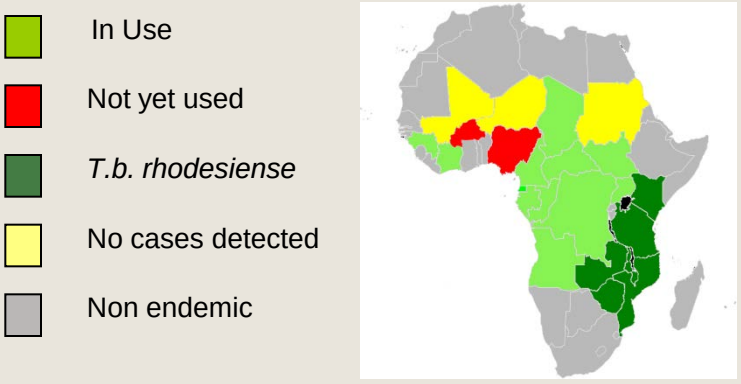
Nifurtimox-eflornithine combination therapy

- 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



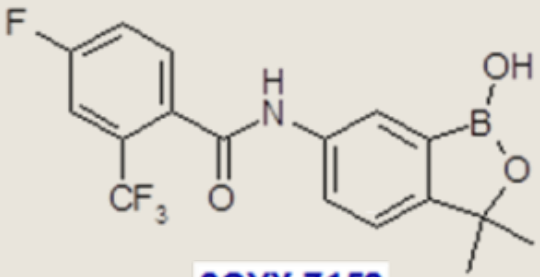
Treatments for stage 2 HAT in DRC (2012)

NECT Use (May 2013)

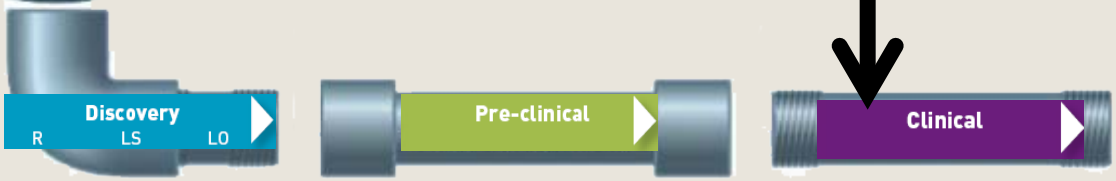


Oxaborole SCYX-7158 for HAT

From Lead Optimization to Clinical Candidate



SCYX-7158



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

- Identified as hits against *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*i* Lead Opt. Programme
- Clinical Phase I study ending

Key partners: Scynexis, Anacor, Pace University, Sandler Center

UCSF, Swiss TPH

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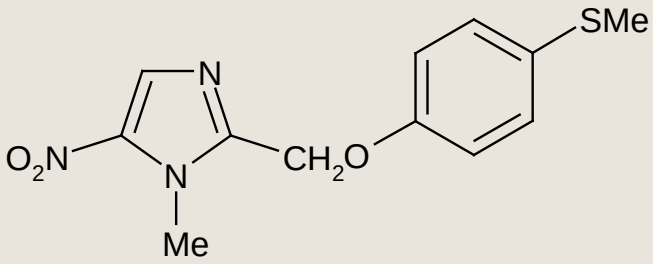
Fexinidazole, a Rediscovered New Chemical Entity in Phase II/III Clinical Study for HAT

- ‘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



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DND*i*'s Funding Strategy

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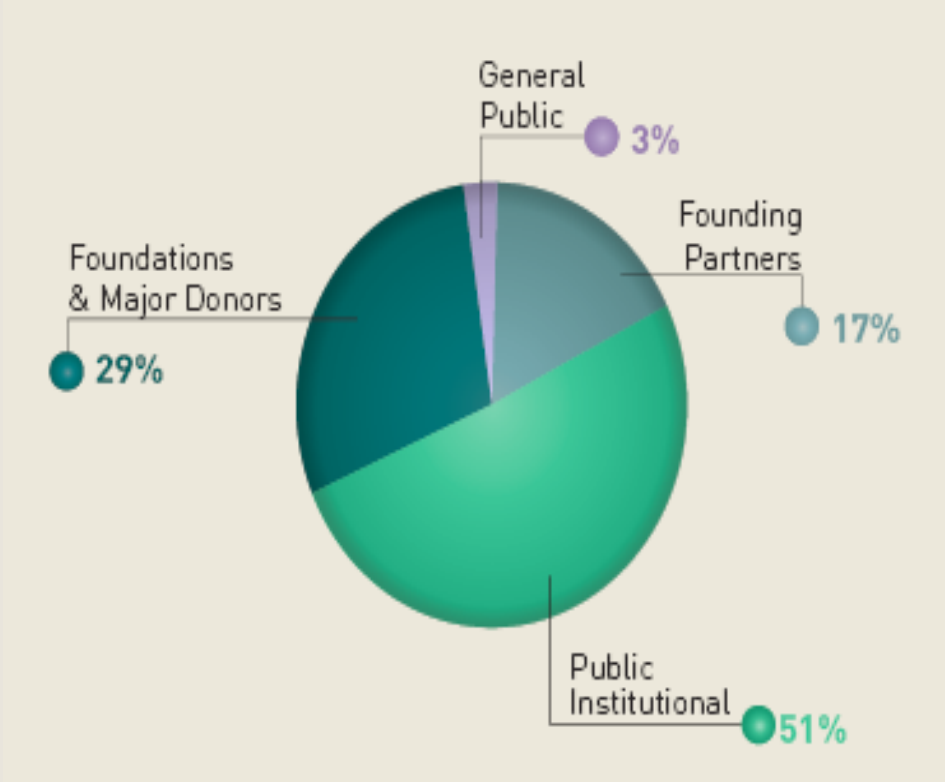
DND*i*'s Funding Strategy

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)



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Challenges

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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

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But There is HOPE……

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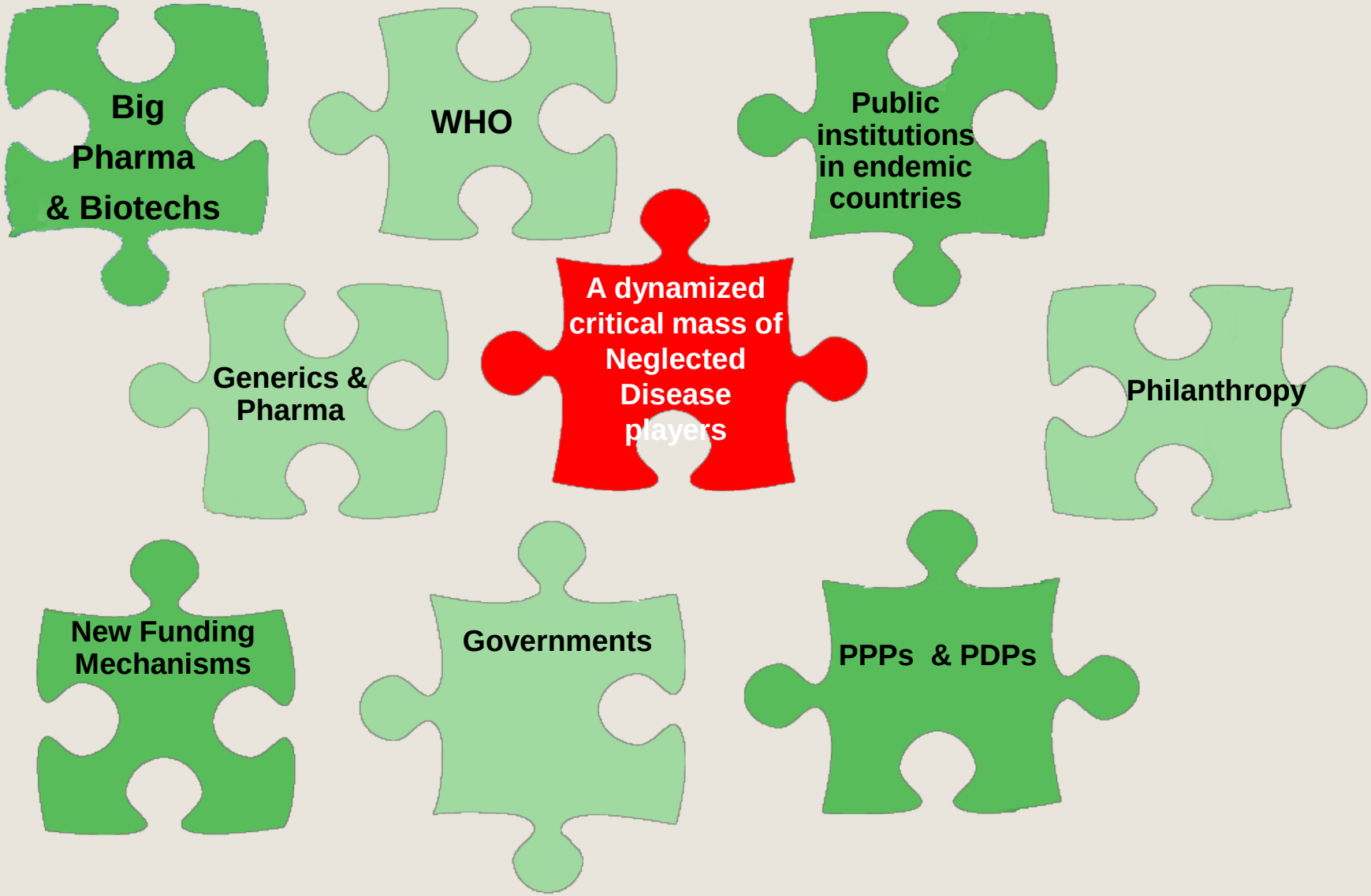
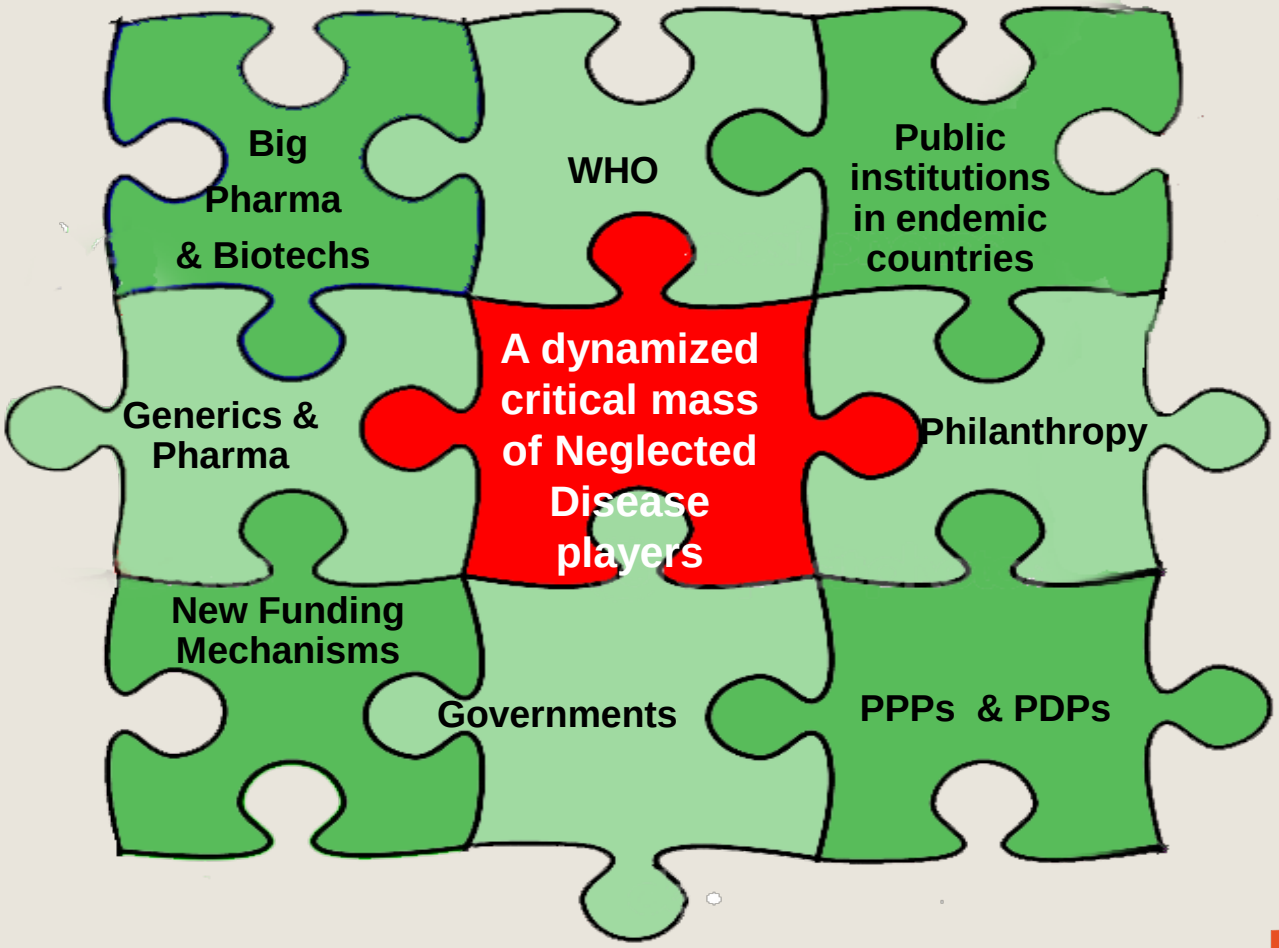
From a Fragmented Landscape for Neglected Diseases R&D



Towards a Global Framework for NTDs R&D



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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

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BILL & MELINDA GATES foundation

UKaid from the British people

Ministry of Foreign Affairs

UNITAID

afd AGENCE FRANÇAISE DE DÉVELOPPEMENT

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gtz Partenaire mondial pour un avenir commun.

UBS

UBS Optimus Foundation

National Institutes of Health

USAID FROM THE AMERICAN PEOPLE via the 4th Sector Health Project implemented by Abt Associates, Inc.

Norad

medicor foundation

BBVA Foundation

THE STARR FOUNDATION

Ministério da Saúde

GOVERNO FEDERAL BRASIL PAÍS RICO É PAÍS SEM POBREZA

The Global Fund To Fight AIDS, Tuberculosis and Malaria

INSTITUTO Carlos Slim DE LA SALUD

WELLSPRING ADVISORS

SPF THE SASAKAWA PEACE FOUNDATION

Sandoz SANDOZ FONDATION DE FAMILLE

www.connect2fightneglect.org

www.dndi.org

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Paediatric HIV

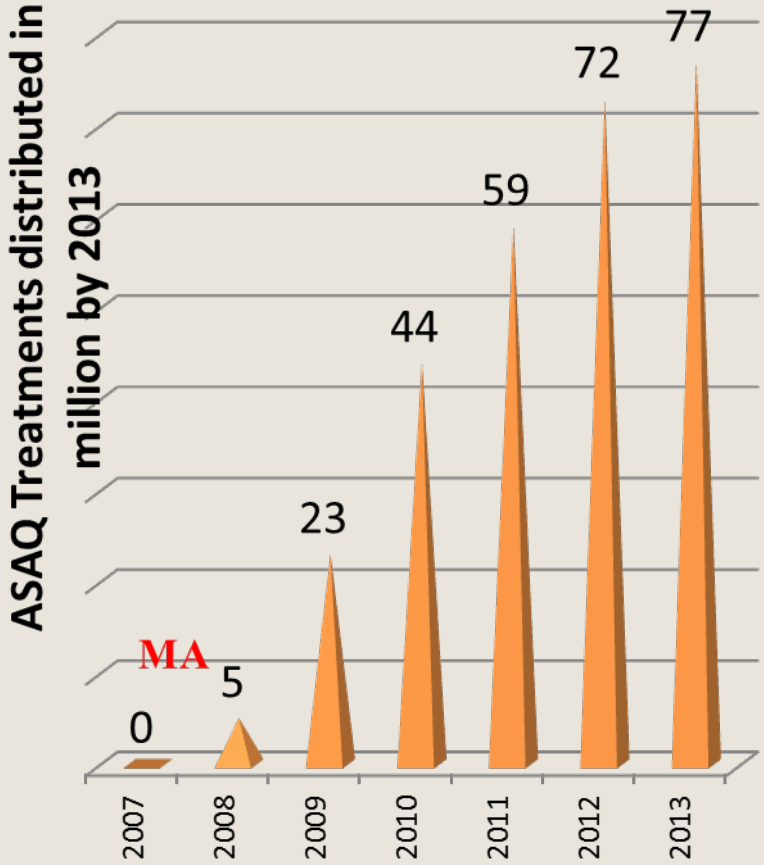
- Virtual elimination of paediatric HIV in high-income countries…
- …but 330,000 new infant infections each year and 3.4 million children with HIV/AIDS (91% in sub-Saharan Africa)
  - > 900 new pediatric HIV infections daily
  - > 600 deaths in HIV+ children daily
- HIV disease progression in children 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

THANK YOU

www.dndi.org

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)



Source: Sanofi

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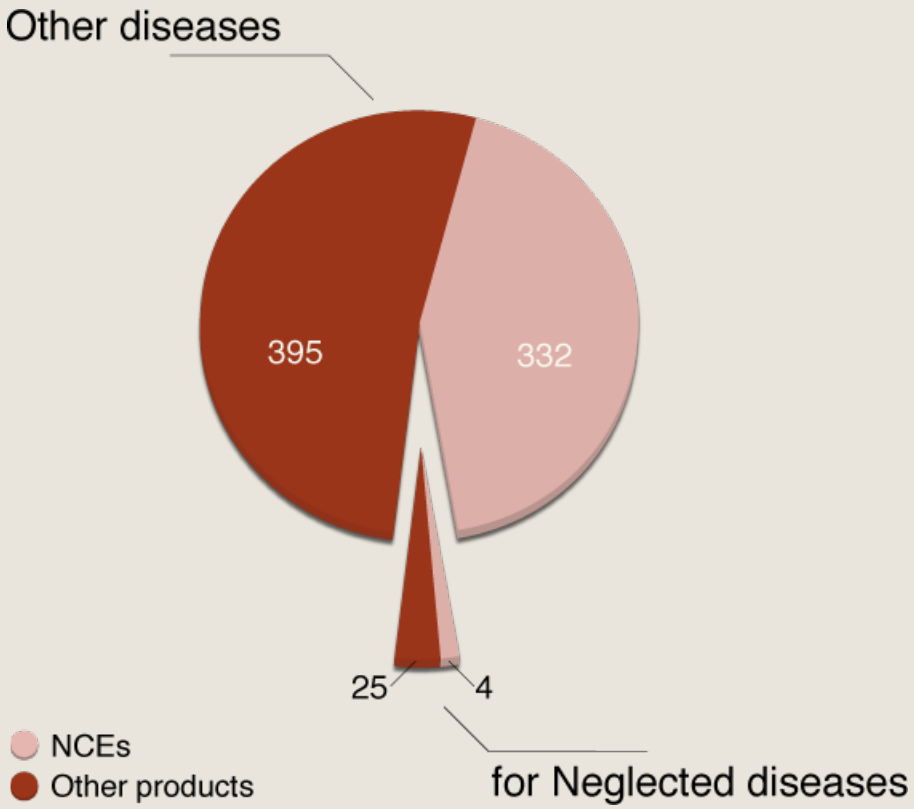
Fatal Imbalance Remains Despite Progress Over A Decade

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



Source: 'The drug and vaccine landscape for neglected diseases (2000-2011): a systematic assessment' Pedrique B et al. *Lancet*, Oct 2013

- 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

30 January 2012, London: ‘Uniting to Combat NTDs’
A Turning Point in the NTD Landscape

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
- DND*i*

The outcome for DND*i*?

- New, renewed, or expanded commitments from 12 major pharmaceutical companies.

- Greatest ever access to compound libraries for DND*i.*