



# INNOVATIVE APPROACHES FOR NEGLECTED DISEASES DRUG DISCOVERY

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**DNDi**

Drugs for Neglected Diseases *initiative*

ISNTD d<sup>3</sup>

The International Society for Neglected Tropical Diseases  
(drug discovery & development)  
Thursday May 15<sup>th</sup> 2014 - Wellcome Trust London

# 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**

# Responding to the Needs of Patients Suffering from Neglected Diseases...



Malaria



Leishmaniasis



Paediatric HIV



Sleeping Sickness (HAT)



Chagas Disease




Filaria

- Published Target Product Profiles to meet patients' needs  
See: [www.dndi.org](http://www.dndi.org)

# 6 New Treatments Developed Since 2007


**ASAQ** 2007  
(Fixed-dose combination of artesunate + amodiaquine)

**malaria**

A collage of four images: a mosquito on a human arm, a person in a white lab coat, a box of ASAQ medication, and a group of people in a community setting.

**ASMQ** 2008  
(Fixed-dose combination of artesunate + mefloquine)

**malaria**

A collage of four images: a mosquito on a human arm, a person in a white lab coat, a box of ASMQ medication, and a group of people in a community setting.

**NECT** 2009  
(Nifurtimox-eflornithine combination therapy)

**sleeping sickness stage 2**

A collage of four images: a mosquito, a person in a white lab coat, two bottles of NECT medication, and a person in a community setting.

✓ Easy to Use    ✓ Affordable    ✓ Field-Adapted    ✓ Non-Patented


**SSG&PM** 2010  
(Sodium stibogluconate & paromomycin combination therapy)

**VL**

A collage of four images: a mosquito on a human arm, a person in a white lab coat, a box of SSG&PM medication, and a group of people in a community setting.

**NEW VL TREATMENTS IN ASIA** 2011  
(SD AmBisome® / PM+M / A®+M /)

**VL**

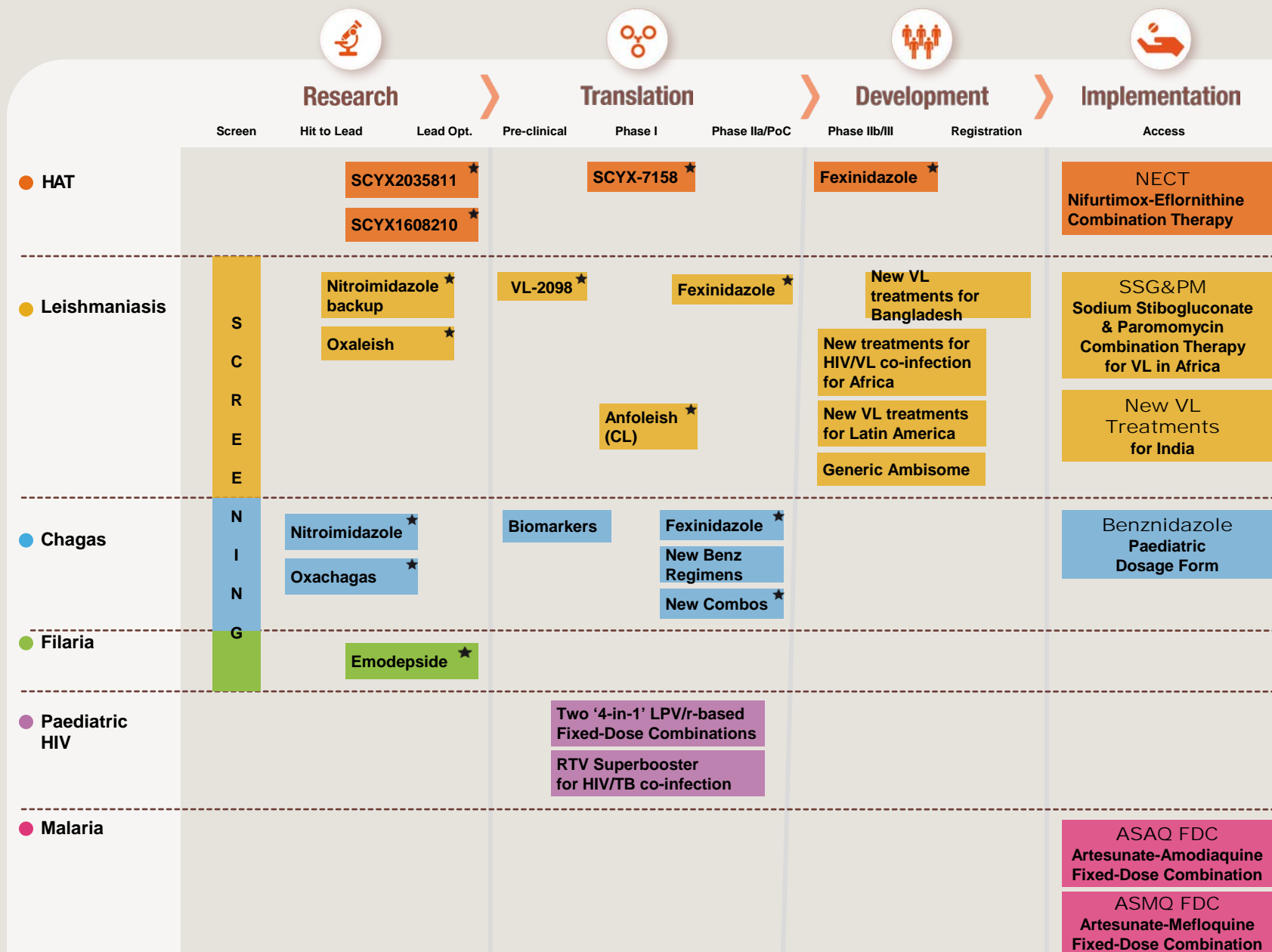
A collage of four images: a mosquito on a human arm, a person in a white lab coat, a box of NEW VL treatments, and a group of people in a community setting.

**Benznidazole 12.5 mg** 2011  
Pediatric dosage form of benznidazole

**Chagas disease**

A collage of four images: a mosquito on a human arm, a person in a white lab coat, a box of Benznidazole medication, and a group of people in a community setting.

# Published DNDi Portfolio December 2013

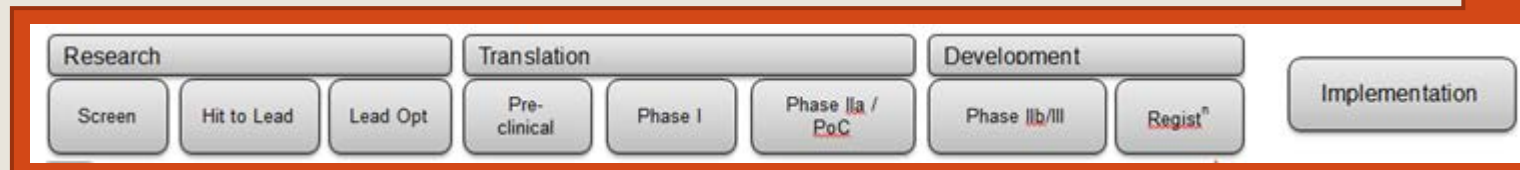






# Share and use open data

- ❑ Science works through sharing and collaborating
- ❑ A continuum of more or less 'open' approaches
  - ❑ What is shared?
  - ❑ When is it shared
  - ❑ With whom is it shared?
- ❑ Do not need to share everything, immediately & with everyone to have a useful impact!
- ❑ Innovations focussed on bottlenecks most impactful
  - ❑ Some current examples for Research...



# Some Drug Discovery challenges for DNDi

**Innovative collaborations and open source approaches can help**



- Accessing and exploiting public and private data  
→ **“Know your molecule” & predictive activity models**
- Maximising the potential of hard won HTS hits  
→ **The NTD Drug Discovery Booster**
- Mobilising increased & sustainable resources for lead optimisation  
→ **LOLA & open chemistry partnerships**



# The changing discovery landscape

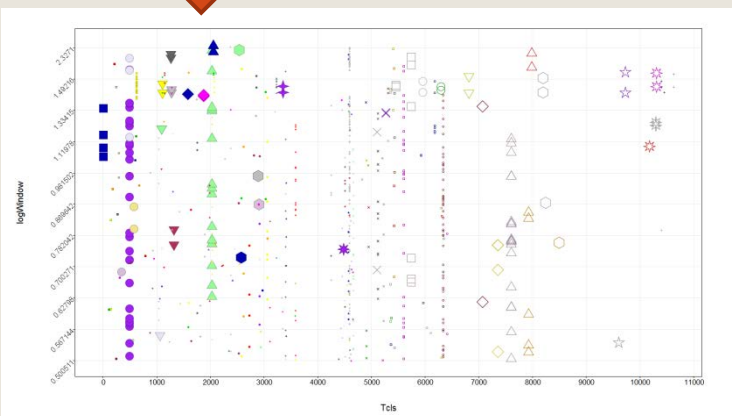
- Screening for new leads against kinetoplastid parasites is evolving
  - ▣ Throughput increased & some new hits identified
  - ▣ But insufficient number and variety of starting points to give high confidence of delivering new clinical candidates
  
- Make best use of **all** the available data to
  - ▣ To better understand the hits we have
  - ▣ Construct computational models to guide further screening

# Global review of HTS hits from DNDi VL discovery program

## VL Actives in ScienceCloud

(in vitro intracellular hits with  $IC_{50} > 10 \mu M$ ,  $SI > 10$ )

data  
curation/clustering/annotation  
workflow



*ongoing*

Hit analog purchase  
followed by  
confirmatory screening

Q2 2014

6 priority series

- “Know your molecules”
- Data from collaborations
- Published data from ChEMBL

## preliminary selection

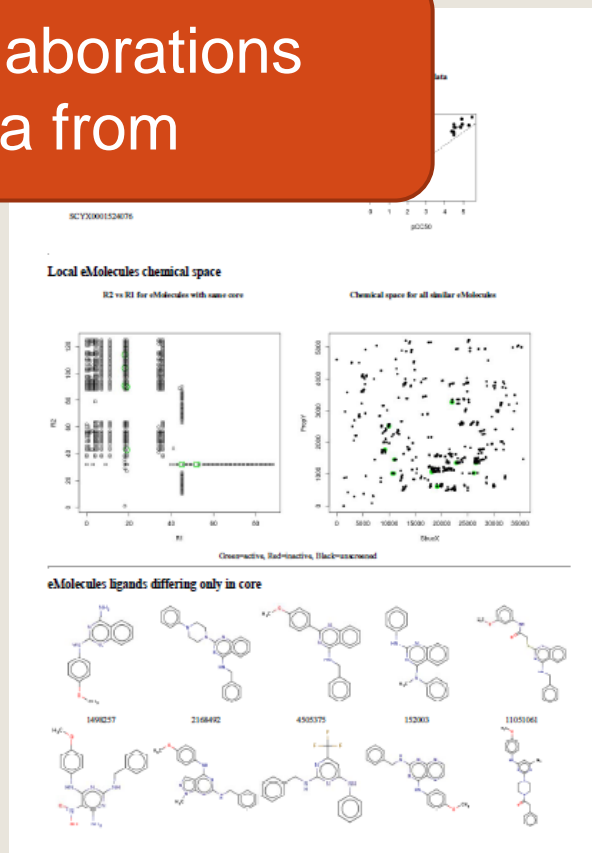
- activity/selectivity
- novelty
- Toxicity/reactivity

...

Med Chem  
review

58 clusters **DNDi**

Drugs for Neglected Diseases initiative





# Predictive activity models



**Objective:** Use existing data to identify novel active series for VL, Chagas disease & HAT

- 2- and 3-D model building (training sets of actives/inactives) ✓
- *in silico* prediction of activity using commercial libraries (compound list) ✓
- *In vitro* screening to validate models *ongoing* Data available end Q2 2014
- Sharing of models with partners to select compounds from their libraries *next*

Data sources: IPK, GNF, DDU, AbbVie, GSK, ChEMBL, DNDi, PubChem

Sharing of selected data with key partner(s) can be enormously enabling



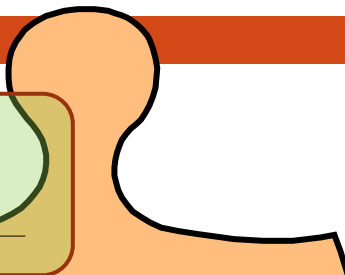
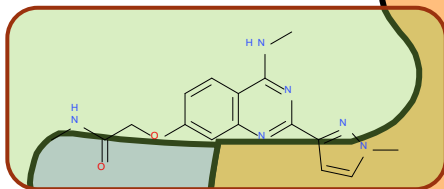
# The changing discovery landscape

- Screening for new leads against kinetoplastid parasites is evolving
  - Throughput increased & some new hits identified
  - But insufficient number and variety of starting points to give high confidence of delivering new clinical candidates
  
- The NTD Drug Discovery Booster will
  - Expand the hits from screening and enable scaffold-hopping to identify related series
  - Benefit from the pooling of structures and information from the consortium members to inform decision-making
  - Accelerate discovery and reduce costs

# Growing a series from a seed

## Consortium members add pieces

Seed from HTS





# NTD Drug Discovery Booster

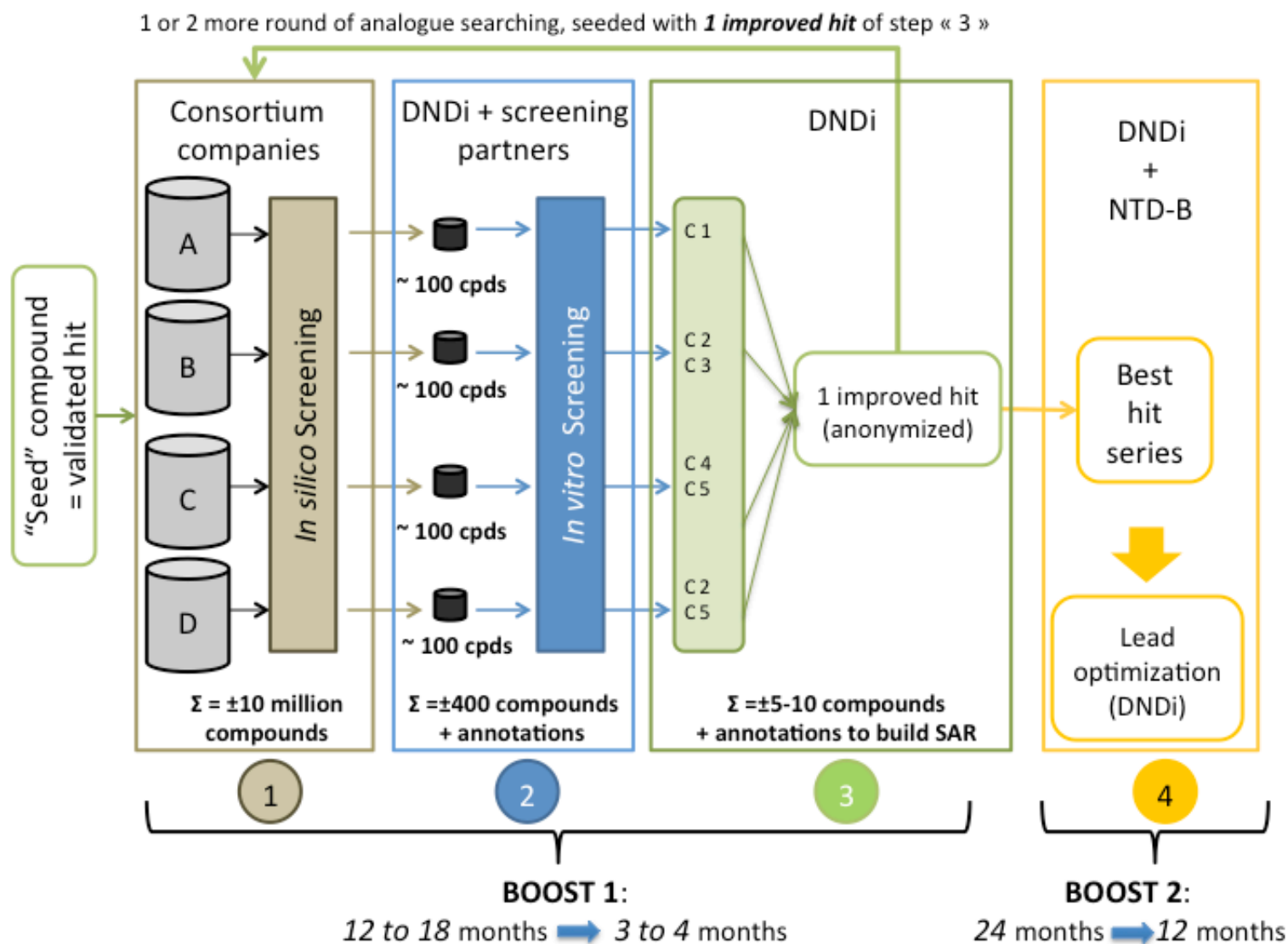
- The goal is faster, cheaper drug discovery for NTDs
- Rapid expansion of new screening hits through cross-collaboration with several Pharma
- DNDi would be able to generate additional SAR **before** commencing time consuming and expensive chemistry to make new analogues
- The expanded series produced could benefit from annotation by multiple partners

# Annotations

- Annotations on the final 'boosted' series
  - Inform decision to move into LO
  - Highlight risks and benefits of series
  - Guide medicinal chemistry strategy
  - Accelerate lead optimisation and reduce costs

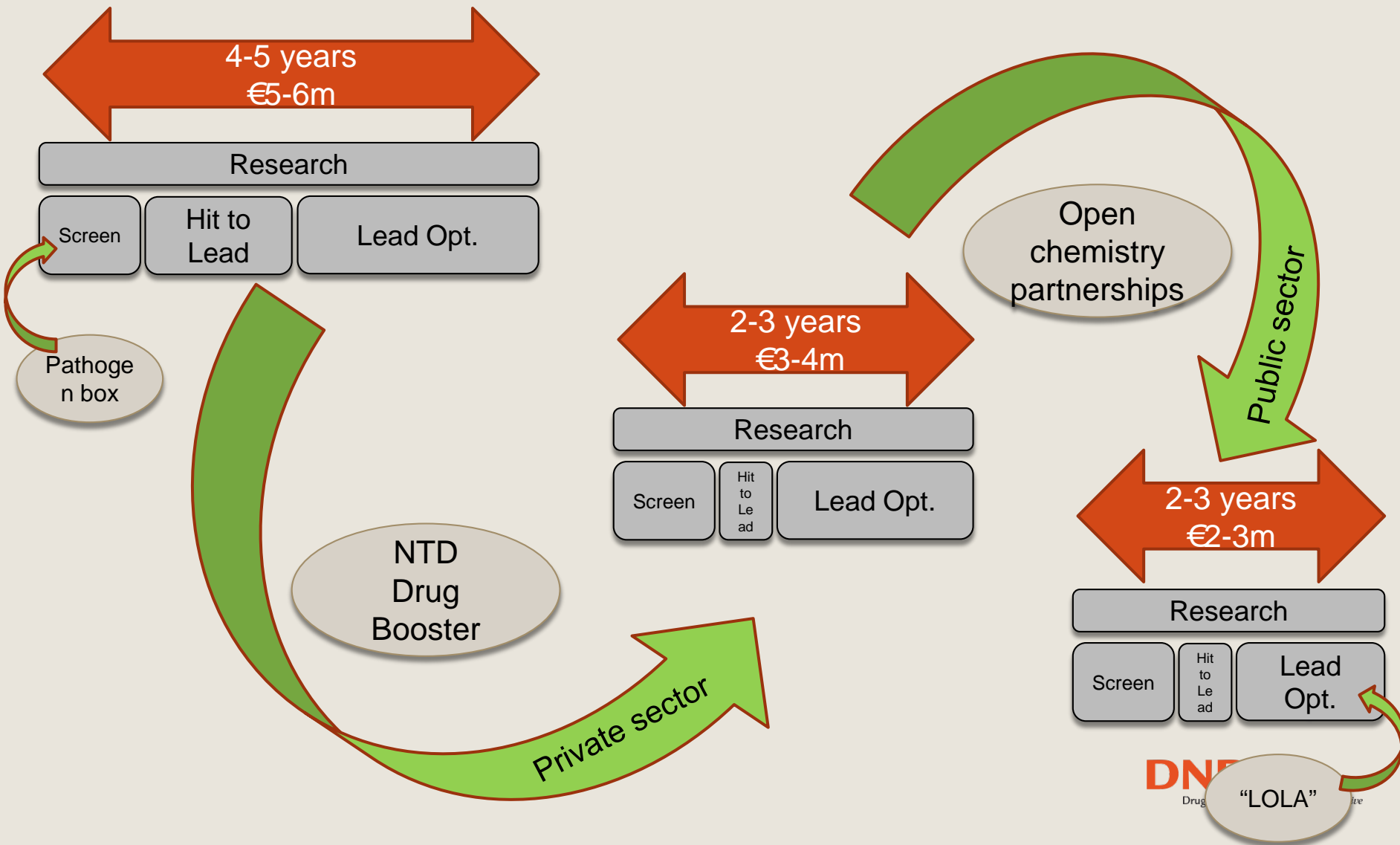
# NTD Drug Discovery Booster: How Would it Work?

## Moving from bilateral to multilateral collaborations



# Drug Booster and Open Source innovations

→ faster, cheaper, sustainable & more efficient Research





THANK YOU

[www.dndi.org](http://www.dndi.org)