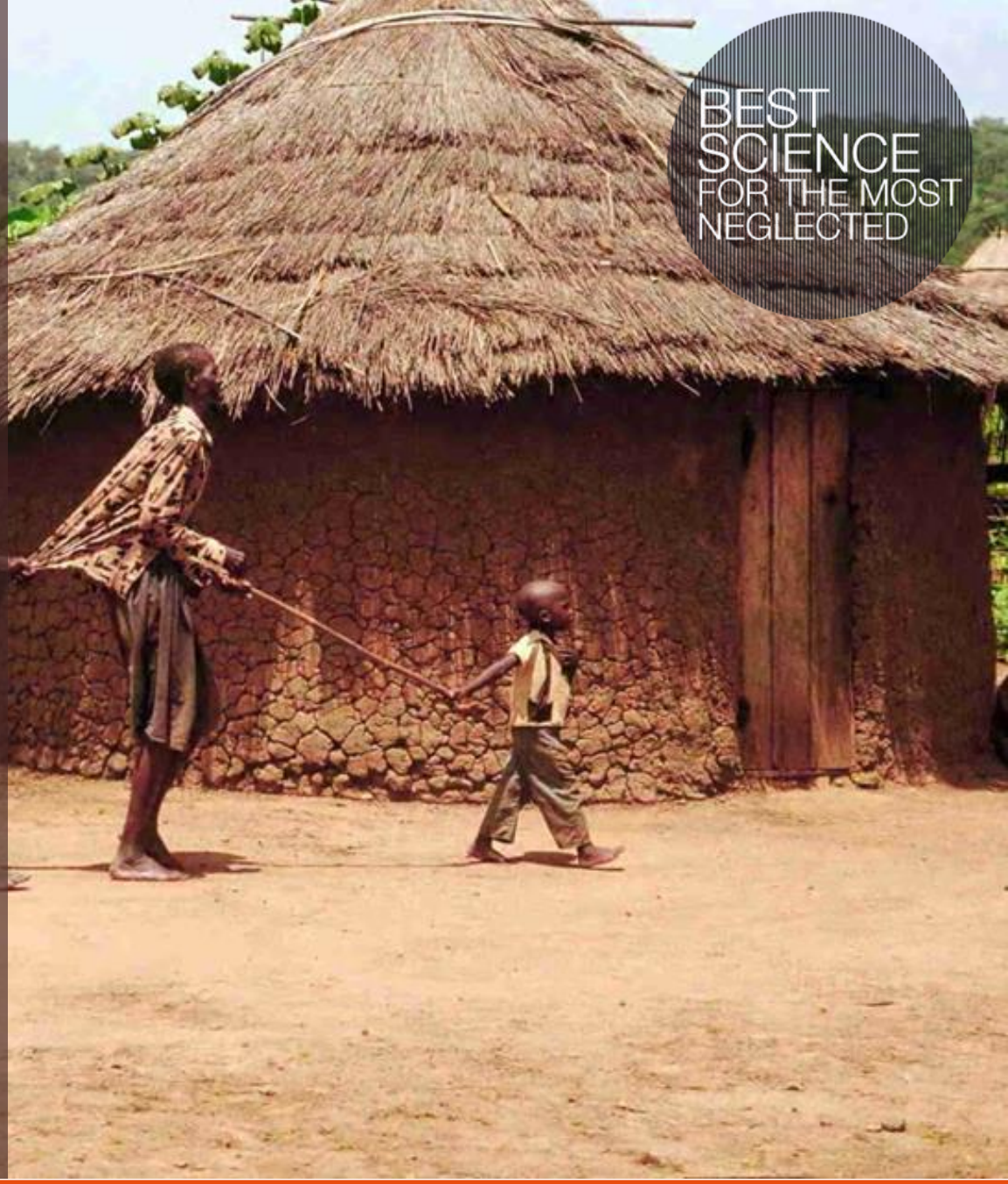
Update of DND*i*'s Filarial portfolio



ISTND d^3

May 16-17th 2017

Wellcome Trust London

Ivan Scandale

Origins of DND*i*

1999

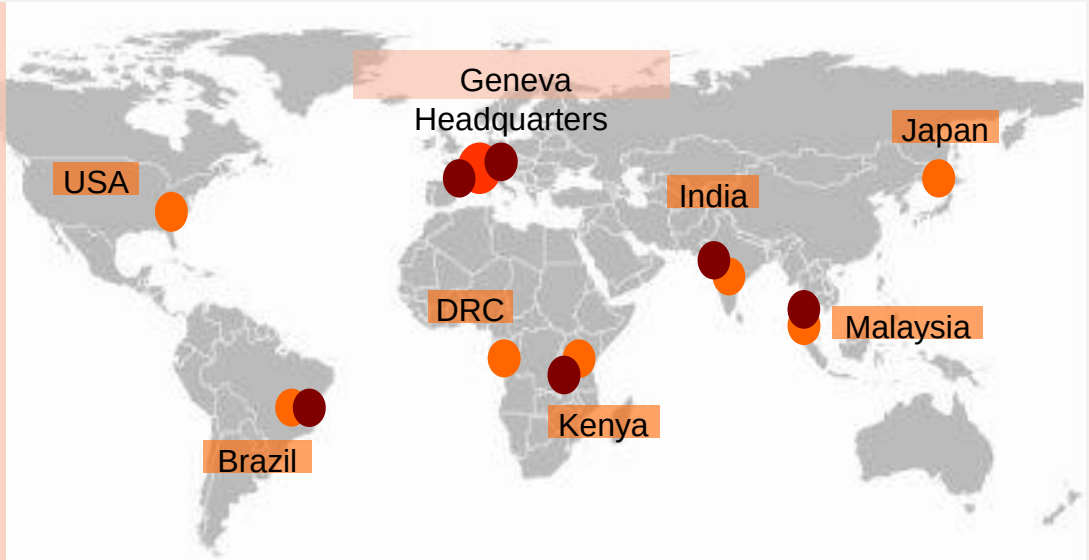
- First meeting to describe the lack of R&D for neglected diseases
- MSF commits the Nobel Peace Prize money to the DND Working Group
- JAMA article: *'Access to essential drugs in poor countries - A Lost Battle?'*

July 2003

- Creation of DND*i*

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)



7 offices worldwide

DNDi 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**

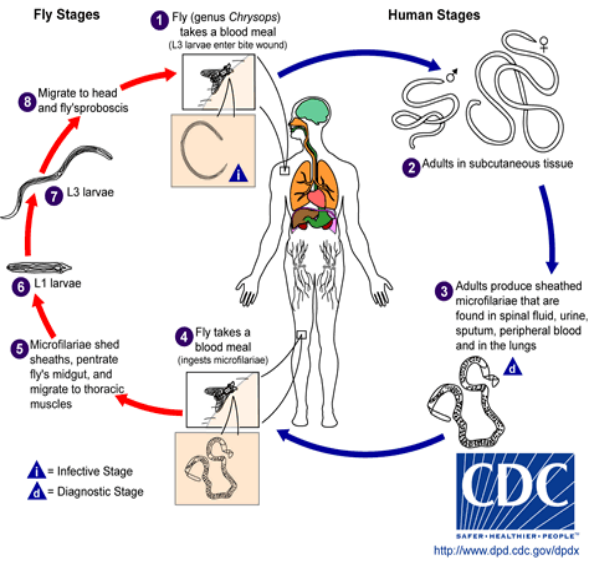
Medium-term projects

- **Completing registration dossier**
- **Geographical extension**

Short-term projects

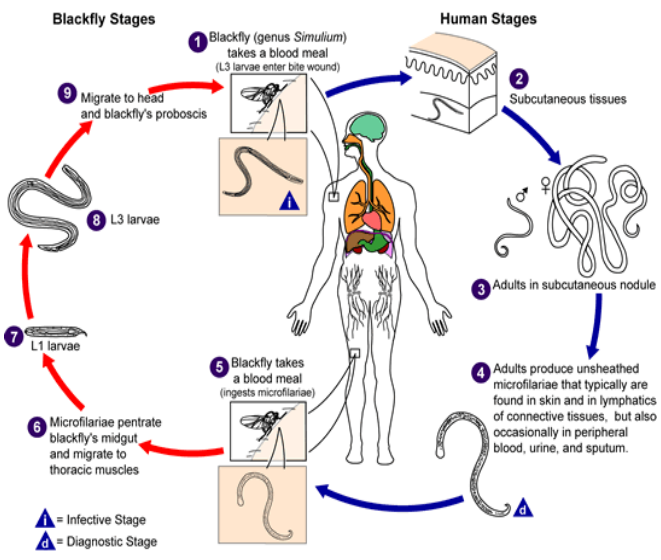
Filarial diseases

Loiasis



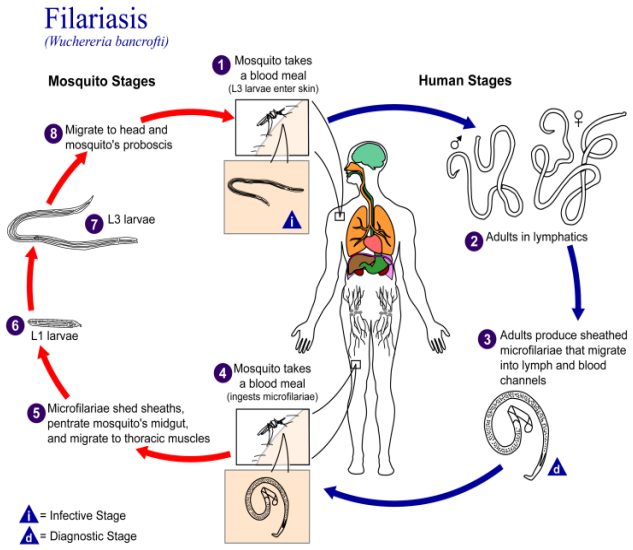
Loa loa

Onchocerciasis



Onchocerca volvulus

Lymphatic filariasis



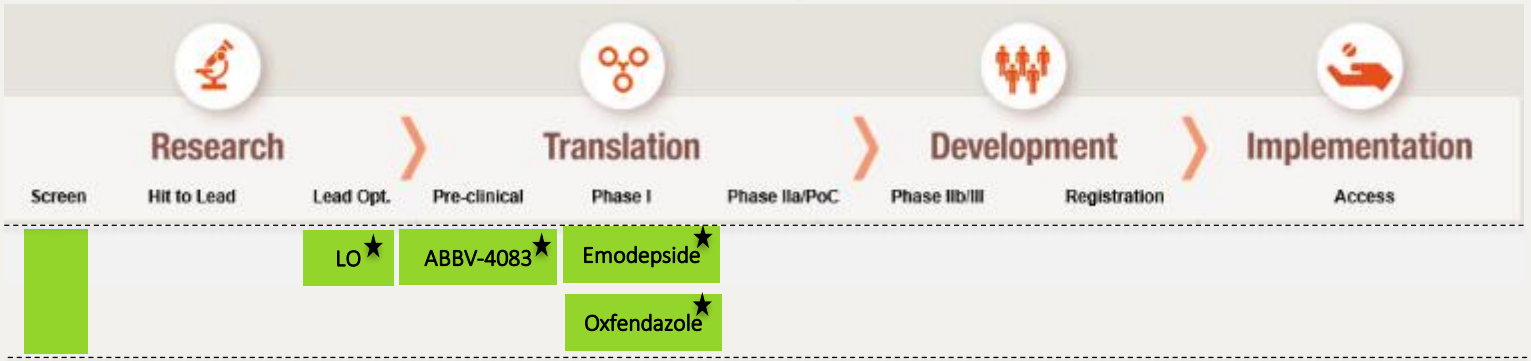
Wuchereria bancrofti
Brugia spp.

Filarial Portfolio

Compound providers

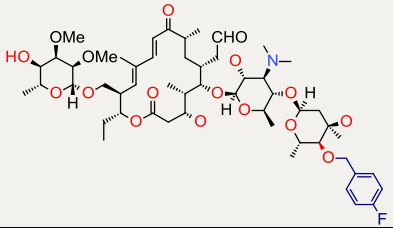
Filarial Screening based on a repurposing strategy

Lead Optimization

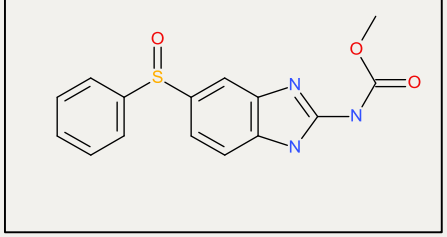


Lead Optimisation

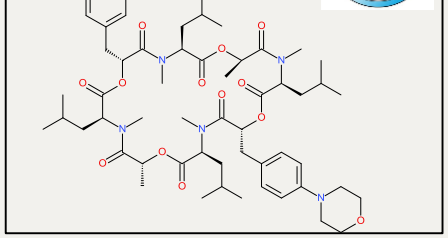
ABBV-4083



Oxfendazole

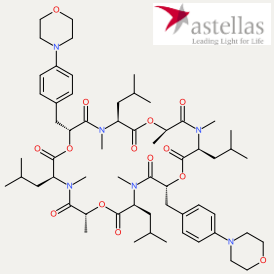


Emodepside



Emodepside

- Anthelmintic veterinary drug for cats and dogs in combination with praziquantel (Profender®) and in combination with toltrazuril (Procox®).



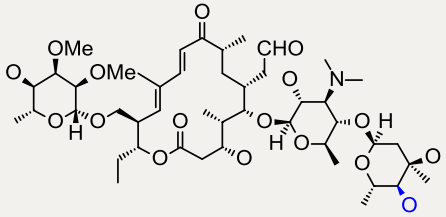
License to Bayer

- Emodepside showed remarkable *in vivo* and *in vitro* activity against a variety of filarial nematodes including *O. volvulus.*

- DND*i* has an agreement with Bayer to develop emodepside for the treatment of onchocerciasis

Tylosin Analogue Macrofilaricde (TylAMac)

- Tylosin is a macrolide antibiotic used as food additive in veterinary medicine

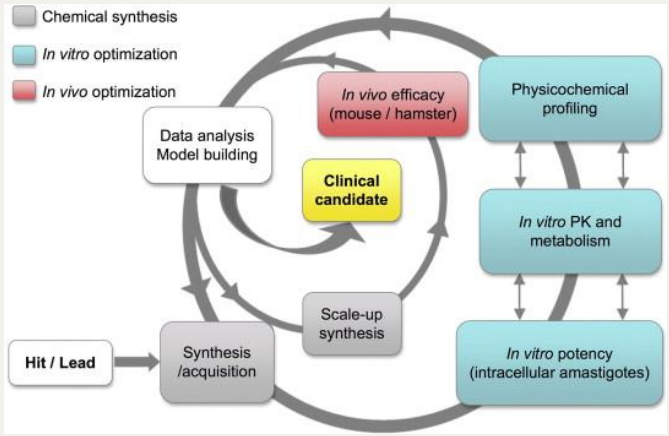


- Tylosin targets the endosymbiont Wolbachia bacterium present in *O. volvulus* and *W. bancrofti*. This causes:
  - Inhibition of fertility (absence of microfilariae)
  - Possible macrofilaricide activity
- Tylosin is poorly bioavalible:

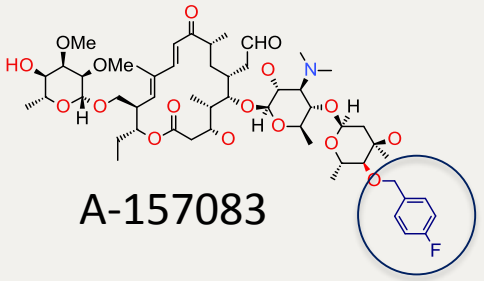
Optimization program conducted by:

abbvie

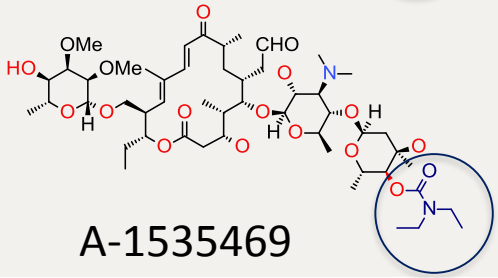
A·WOL ANTI-WOLBACHIA CONSORTIUM



Analogues:



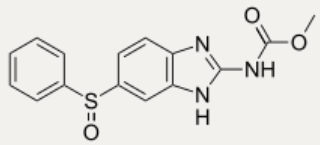
A-157083



A-1535469

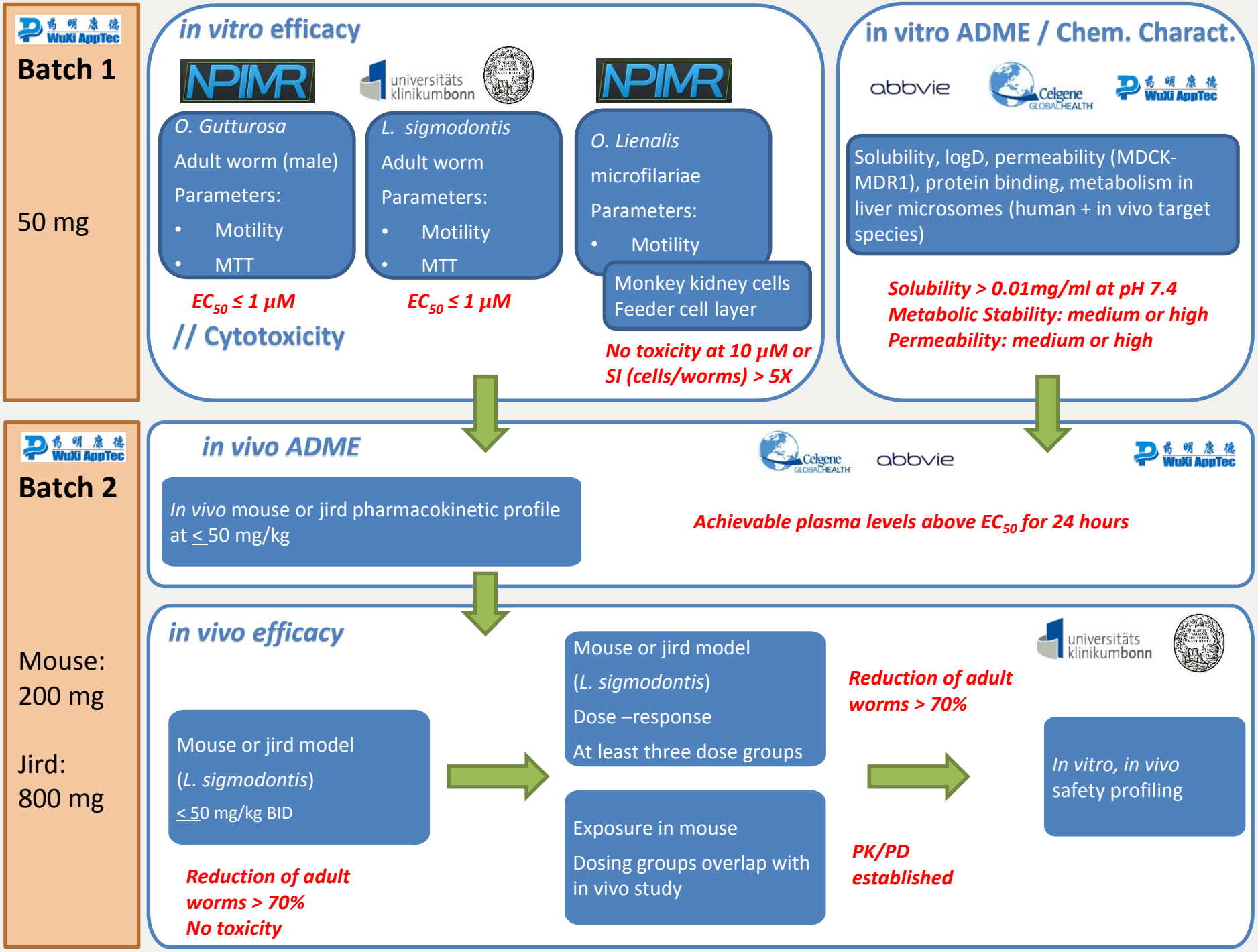
Oxfendazole

- Oxfendazole is a benzimidazole, anthelmintic treatment for farm and domestic animals.



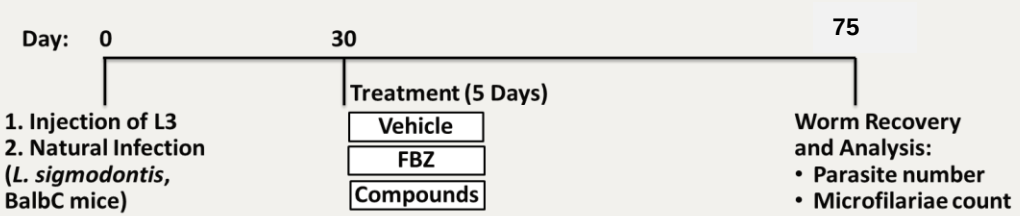
- Oxfendazole is potent *in vivo* against a variety of filarial nematodes (*L. sigmodontis*, *B. malayi*, *A. viteae*)

- A Phase I trial evaluating safety and pharmacokinetics of oxfendazole is ongoing for two inductions:
  - Neurocysticercosis. Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)
  - Tenia Solium Infection. Sponsor: Johns Hopkins Bloomberg School of Public Health


Batch 1
50 mg
in vitro efficacy
NPIMR
universitäts klinikumbonn
NPIMR
O. Gutturosa
Adult worm (male)
Parameters:
• Motility
• MTT
L. sigmodontis
Adult worm
Parameters:
• Motility
• MTT
O. Lienalis
microfilariae
Parameters:
• Motility
Monkey kidney cells
Feeder cell layer
EC50 ≤ 1 µM
EC50 ≤ 1 µM
// Cytotoxicity
No toxicity at 10 µM or
SI (cells/worms) > 5X
in vitro ADME / Chem. Charact.
abbvie
Celgene GLOBAL HEALTH
Solubility, logD, permeability (MDCK-MDR1), protein binding, metabolism in liver microsomes (human + in vivo target species)
Solubility > 0.01mg/ml at pH 7.4
Metabolic Stability: medium or high
Permeability: medium or high
Batch 2
Mouse:
200 mg
Jird:
800 mg
in vivo ADME
Celgene GLOBAL HEALTH
abbvie
In vivo mouse or jird pharmacokinetic profile at ≤ 50 mg/kg
Achievable plasma levels above EC50 for 24 hours
in vivo efficacy
universitäts klinikumbonn
Mouse or jird model
(L. sigmodontis)
≤ 50 mg/kg BID
Reduction of adult worms > 70%
No toxicity
Mouse or jird model
(L. sigmodontis)
Dose –response
At least three dose groups
Exposure in mouse
Dosing groups overlap with in vivo study
Reduction of adult worms > 70%
PK/PD established
In vitro, in vivo safety profiling

Celgene program

In vivo Results (*Litomosoides sigmodontis*)



Compound	Dose	Average Adult worms	Reduction Adult worms	Reduction Microfilaria
Vehicle		11 (26)	-	NA
Flubendazole	2 mg/kg 5 days	0	100 % (P=0.007)	NA
Compound A	3x30 mg/kg 5 days	2 (1.7)	68 % (p=0.032)	NA
Vehicle		11 (26)	-	-
Flubendazole	2 mg/kg 5 days	0.2 (0.5)	98 % (P=0.019)	100 % (P=0.034)
Compound B	3x30 mg/kg 5 days	2.17 (1.3)	80 % (p = 0.044)	98 % (p = 0.042)
Compound C	3x30 mg/kg 5 days	5.5 (2.7)	56 % (p = 0.125)	78 % (p=0.078)
Compound D	3x30 mg/kg 5 days	10.2 (9.4)	18 % (p = 0.685)	86% (p=0.058)

Values expressed as mean (SD)

In vitro (*Onchocerca species*)

158 compounds

↓ *O. lienalis* microfilariae

32 "score 3" hits
Single digit micromolar and sub-micromolar activity

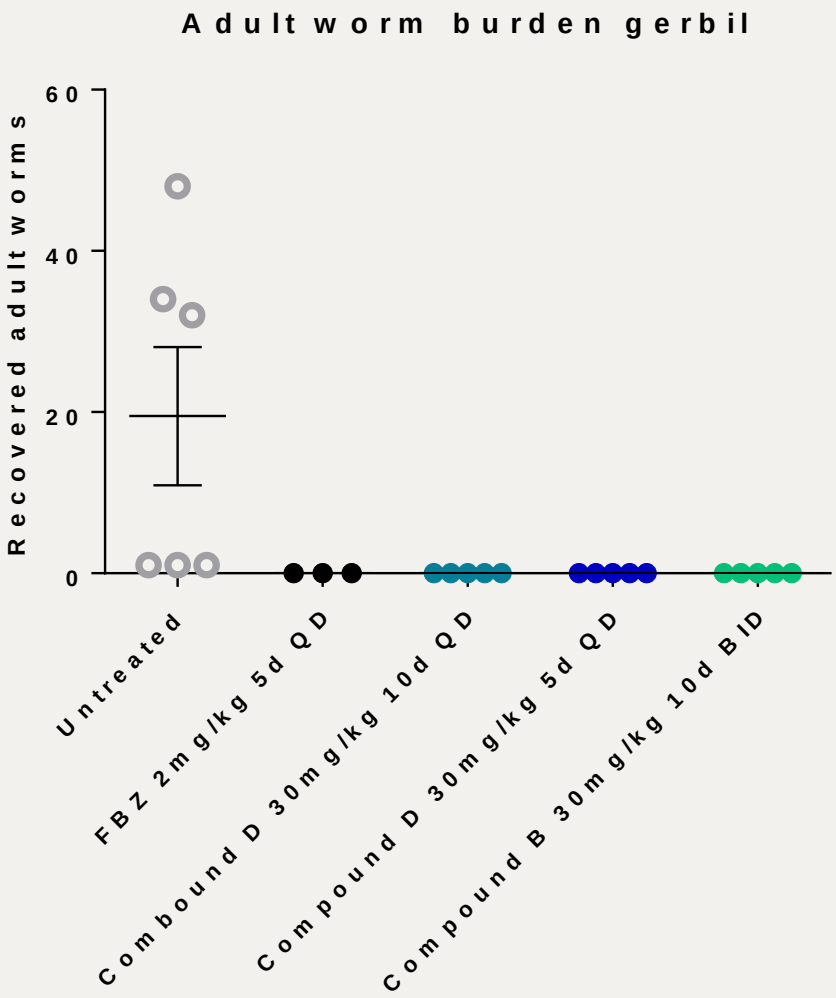
↓ *Re-test 158 compounds against O. gutturosa* adults

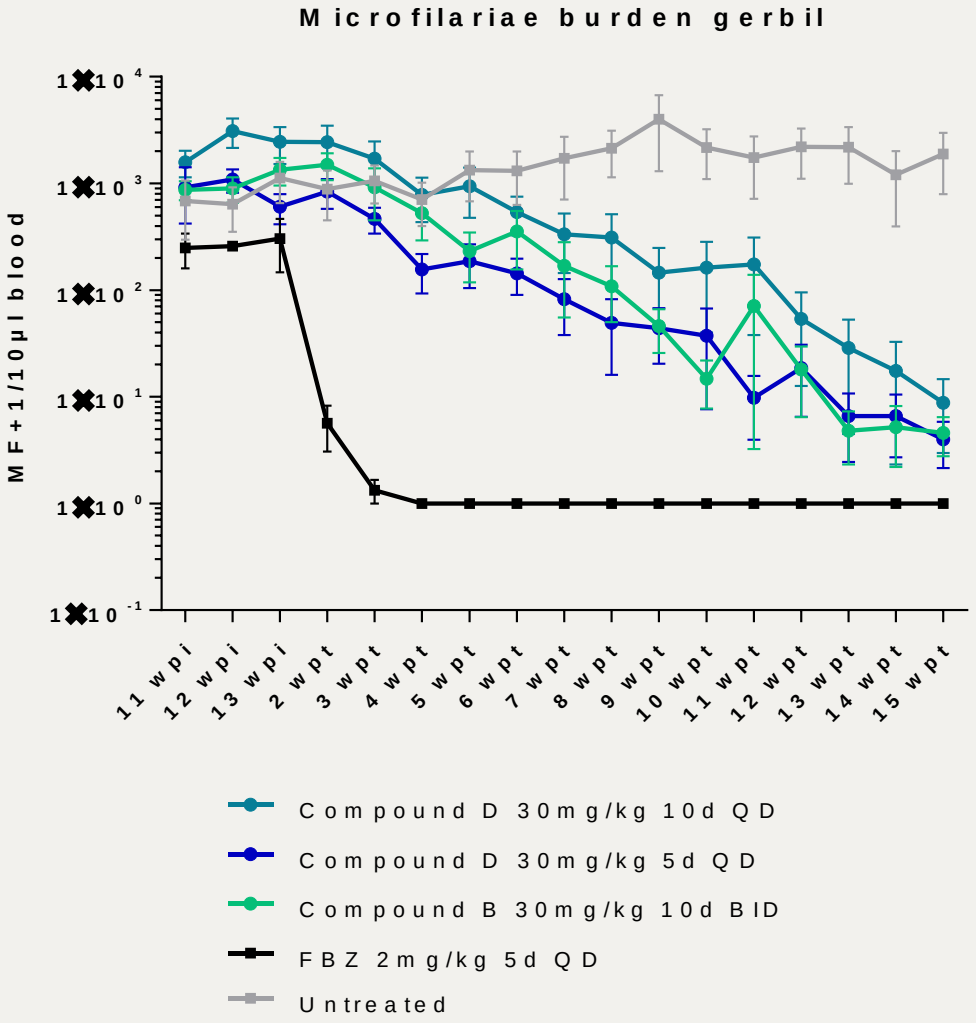
61"score 3" hits
Single digit micromolar and sub-micromolar activity

↓

43 compounds specific for adults only

In vivo Data: Gerbil *L. sigmodontis* Model





Acknowledgments

Celgene GLOBAL HEALTH

Stacie S. Canan,
Natalie A. Hawryluk,
Vikram Khetani

NPIMR

Andrew Freeman
Simon Townson
Suzanne Gokool

Coralie Martin

A·WOL ANTI-WOLBACHIA CONSORTIUM

Gemma Molyneux
Laura Myhill
Gemma Nixon
Nicolas Pionnier
Raman Sharma
Hanna Sjoberg
Andrew Steven
Mark Taylor
Joe Turner
Hayley Tyrer
Stephen Ward
David Waterhouse
Ghaith Alijayyoussi
Andy Cassidy
Ana Castro Guimaraes
Rachel Clare
Darren Cook
Susie Crossman
Jill Davies
Louise Ford
Joanne Gamble
Laura Hayward
Kelly Johnston
Susan Jones

abbvie

Milan Bruncko
Kevin Cusack
Karla Drescher
Tom von Geldern
Herve Geneste
Paul Jung
Joe Kalcsits
Dale Kempf
Kennan Marsh
Shaun McLoughlin
Marc Scanio
Irini Zanze

universitäts klinikum bonn

Dominique Blömker
Achim Hoerauf
Marc Hübner

WuXi AppTec

Hongjuan Liu
Jia Wang
MeijingWang
Zhongyuan Wang
Songling Yu
Jingyu Zhang
Zhyuan Zhang

DNDi Drugs for Neglected Diseases initiative

Rob Don
Frederic Monot
Ivan Scandale

THANK YOU

TO ALL OUR

PARTNERS & DONORS

DNDi
Drugs for Neglected Diseases *initiative*

MEDECINS SANS FRONTIERES

BILL & MELINDA GATES foundation

UKaid
from the British people

Ministry of Foreign Affairs of the Netherlands

afd
AGENCE FRANÇAISE DE DÉVELOPPEMENT

UNITAID

Federal Ministry of Education and Research
by KFW

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
MINISTÈRE DES AFFAIRES ÉTRANGÈRES

aecid
Agencia Española de Cooperación Internacional para el Desarrollo

EDCTP

GHIT Fund
Global Health Innovative Technology Fund

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

wellcome trust

NATIONAL INSTITUTES OF HEALTH

Ministério da Ciência, Tecnologia e Inovação
GOVERNO FEDERAL BRASIL
PAÍS RICO É PAÍS SEM POBREZA

USAID
FROM THE AMERICAN PEOPLE

Norad

TDR

giz Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH

Fundación BBVA

UBS
UBS Optimus Foundation

The Global Fund
To Fight AIDS, Tuberculosis and Malaria

Regione Toscana

REPUBLIQUE ET CANTON DE GENEVE

Rockefeller Foundation
Innovation for the Next 100 Years

BNDES

ruta n
MEDELLÍN

SANDOZ-FONDATION DE FAMILLE

INSTITUTO Carlos Slim DE LA SALUD

medicor foundation

THE SASAKAWA PEACE FOUNDATION

THE STARR FOUNDATION

Responding to the Needs of Patients Suffering from Neglected Diseases…

Hepatitis C

Sleeping sickness

Mycetoma

DNDi's PRIORITY:

Neglected Patients

Malaria

Chagas disease

Paediatric HIV

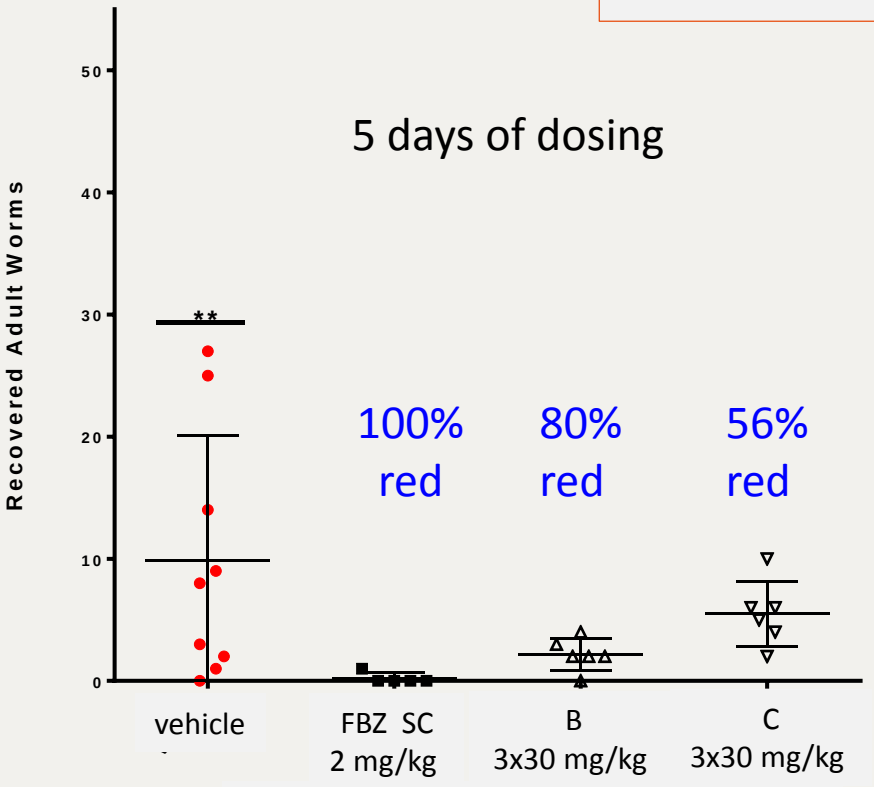
Leishmaniasis

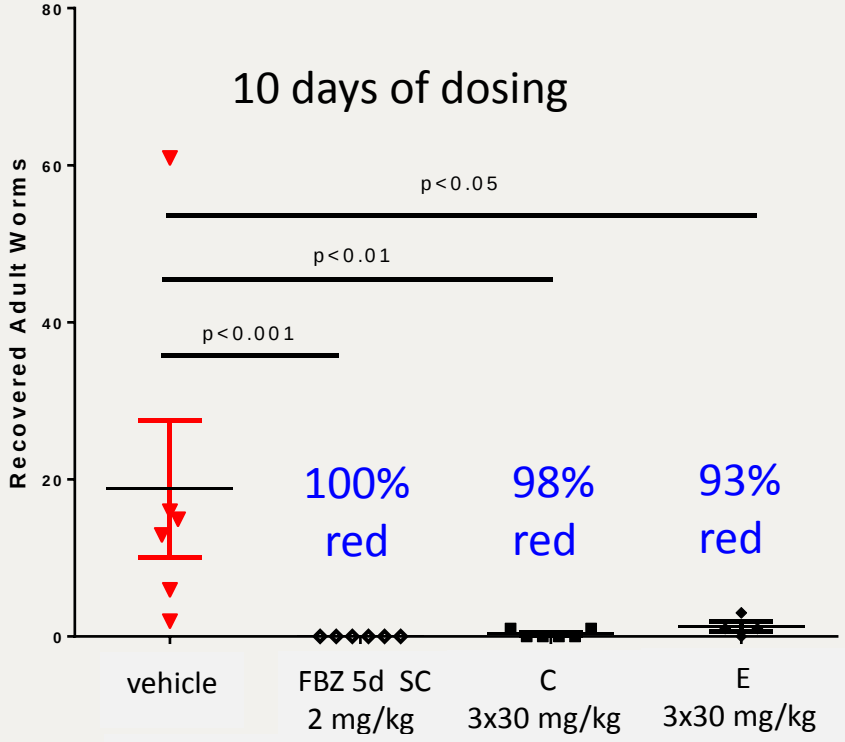
Filarial diseases

…from Bench to Bedside

In vivo Data: Murine *L. sigmodontis* Model

Reduction of Adult Worms





Compound B (Ser A)
O. gutt EC_{50} = 270nM
O. lien EC_{50} =3100nM

Compound C (Ser B)
O. gutt EC_{50} = 699nM
O. lien EC_{50} >12500nM

Compound E (Ser A)
O. gutt EC_{50} = 27nM

1 day dosing

In a decade of R&D, 6 new treatments delivered

- ✓ Easy to use
- ✓ Affordable
- ✓ Field-adapted
- ✓ Non-patented

- **30 projects, 6 diseases areas**
- **15 entirely new chemical entities (NCEs)**
- **Over 130 partnerships,** most in endemic countries
- **150 staff**, half in endemic countries & 600 people working on DND*i* projects
- **Over EUR 350 million** raised equally from public and private sources
- **3 regional disease-specific clinical trial platforms** and 2 technology transfers