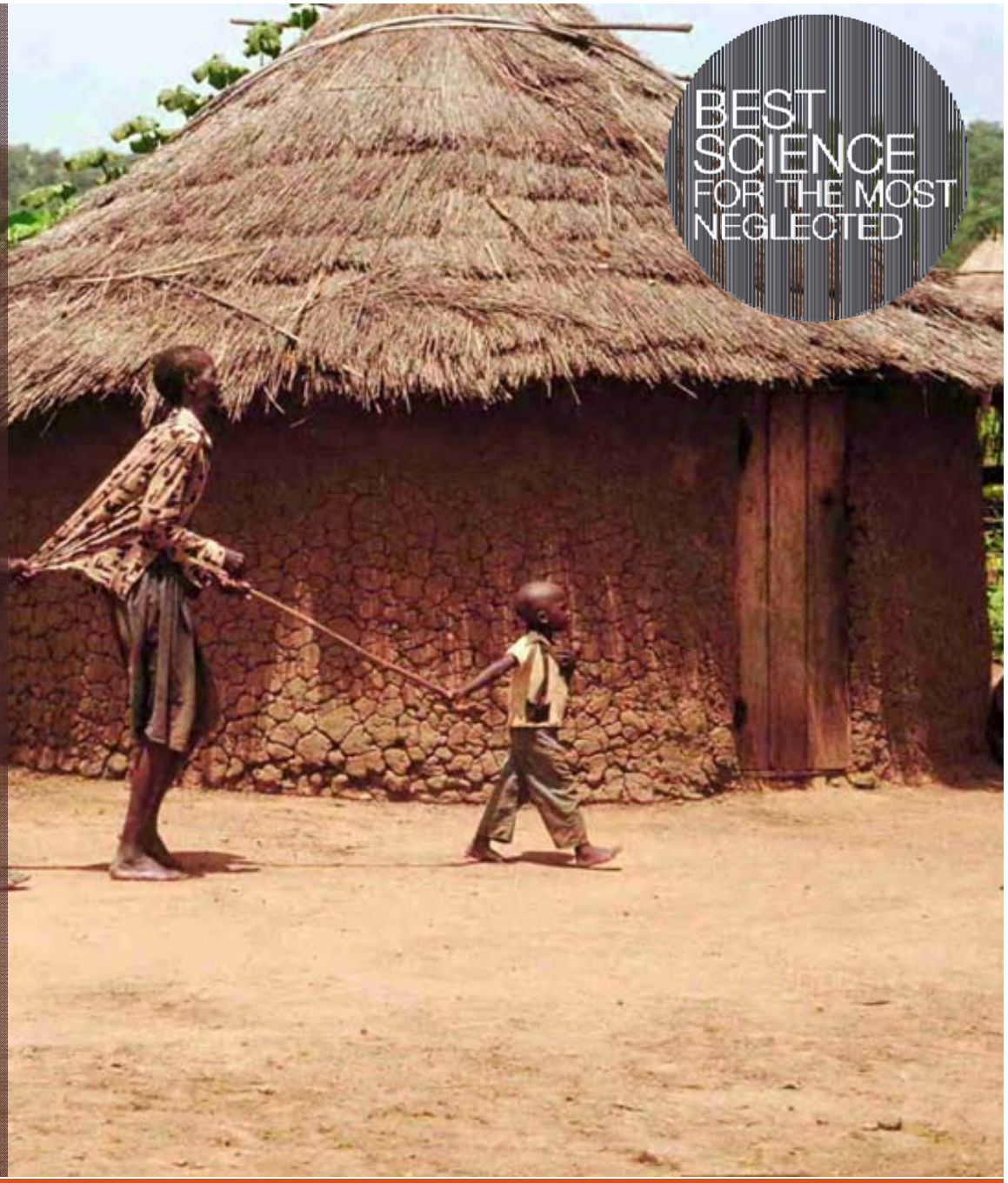
New molecules for parasites of animals and humans

XXIX Congress SolPa

Ivan Scandale



BEST SCIENCE FOR THE MOST NEGLECTED

DNDi
Drugs for Neglected Diseases *initiative*

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)

Responding to the Needs of Patients Suffering from Neglected Diseases…

Hepatitis C

Sleeping sickness

Mycetoma

DND*i*'s PRIORITY:

Neglected Patients

Malaria

Chagas disease

Paediatric HIV

Leishmaniasis

Filarial diseases

…from Bench to Bedside

DNDi Portfolio-Building Model:

Address Immediate Patient Needs & Deliver Innovative Medicines

- **New chemical entities (NCEs)**

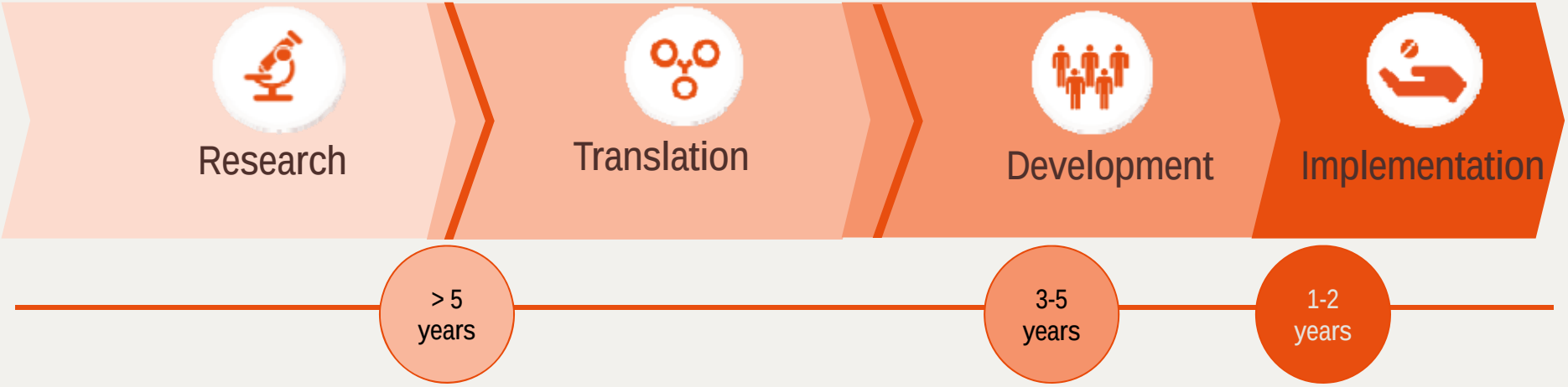
Long-term projects

- **New formulations (fixed-dose combinations)**
- **New indications of existing drugs**

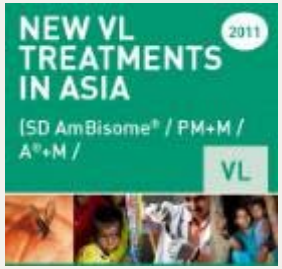
Medium-term projects

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

Short-term projects



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 DNDi projects
- **Over EUR 350 million** raised equally from public and private sources
- **3 regional disease-specific clinical trial platforms** and 2 technology transfers

Filarial Portfolio

Compounds providers

Filarial Screening based on a repurposing strategy

Lead Optimization

Research — Screen, Hit to Lead, Lead Opt.

Translation — Pre-clinical, Phase I, Phase IIa/PoC

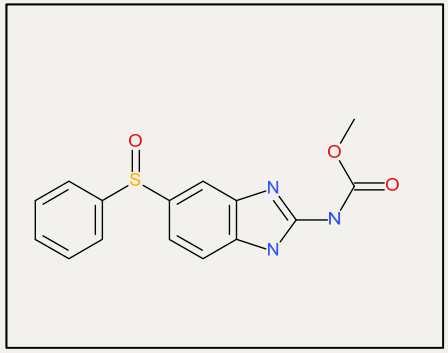
Development — Phase IIb/III, Registration

Implementation — Access

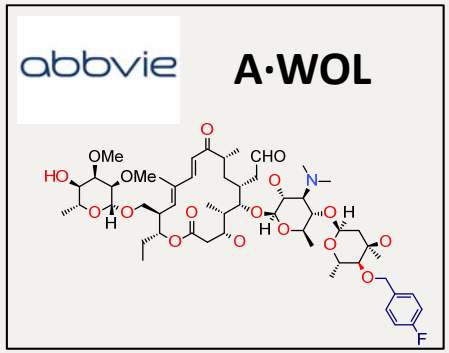
TylAMac ★ | Emodepside ★

Oxfendazole ★

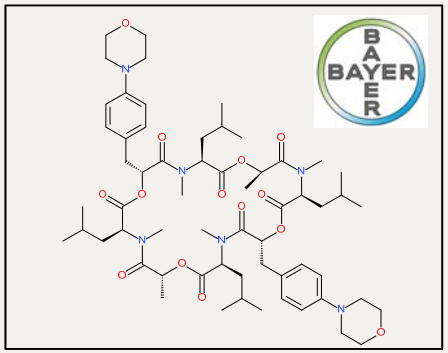
Oxfendazole



Tylosin Analogue

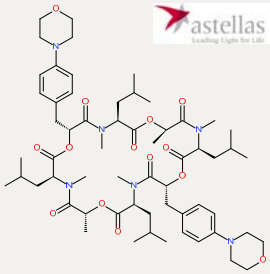


Emodepside



Emodepside

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



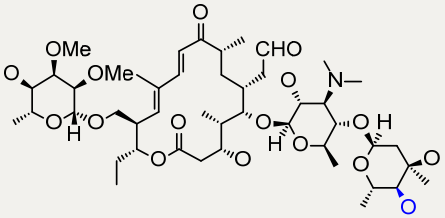
License to Bayer

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

- DNDi 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

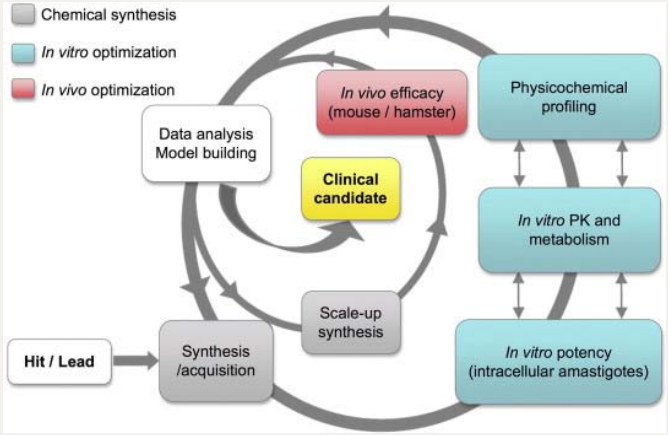


- Tylosin target the endosymbiont Wolbachia bacterium present in *O. volvulus* and *W. bancrofti*. This causes:
  - Inhibition of fertility (absence of microfilariae)
  - Possible macrofilaricide activity
- Tylosin is poorly bioavalible:

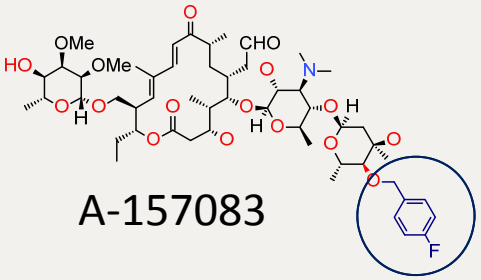
Optimization program conducted by:

abbvie

A·WOL ANTI-WOLBACHIA CONSORTIUM



Analogues:



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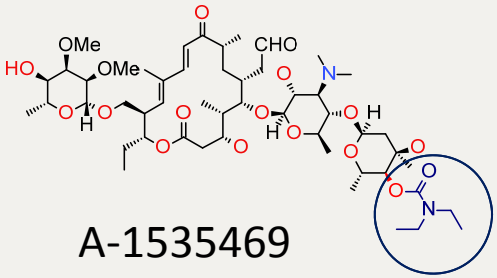
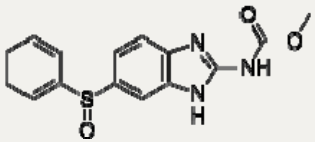


A-1535469

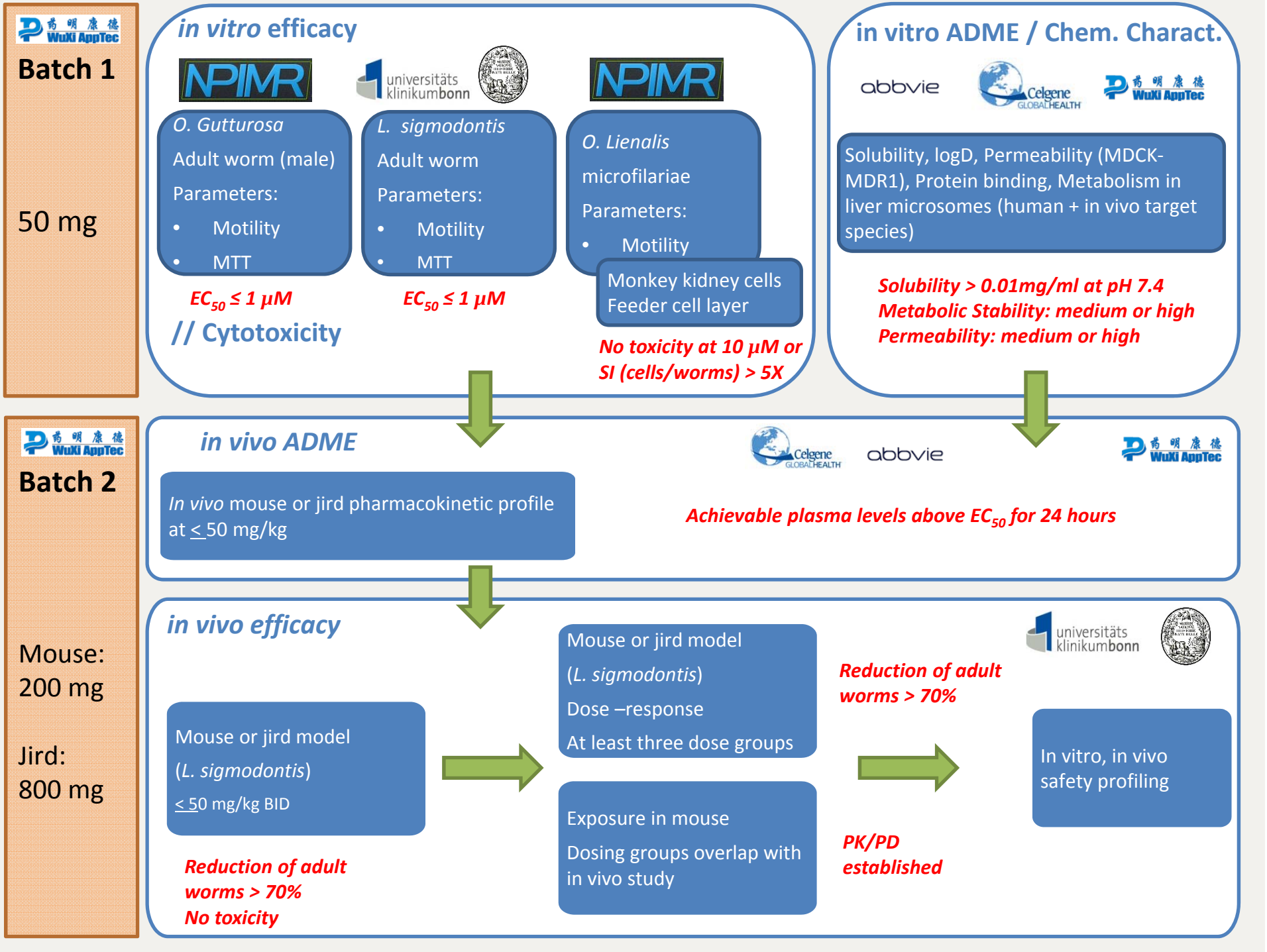
Oxfendazole

- Oxfendazole is a benzimidazole, anthelmintic treatment for farm and pet 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
EC50 ≤ 1 µM
L. sigmodontis
Adult worm
Parameters:
• Motility
• MTT
EC50 ≤ 1 µM
O. Lienalis
microfilariae
Parameters:
• Motility
Monkey kidney cells
Feeder cell layer
No toxicity at 10 µM or
SI (cells/worms) > 5X
// Cytotoxicity
in vitro ADME / Chem. Charact.
abbvie
Celgene GLOBAL HEALTH
WuXi AppTec
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
WuXi AppTec
In vivo mouse or jird pharmacokinetic profile at ≤ 50 mg/kg
Achievable plasma levels above EC50 for 24 hours
in vivo efficacy
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
universitäts klinikumbonn
In vitro, in vivo safety profiling

AbbVie program

abbvie

In vitro
(Onchocerca gutturosa)

760 compounds
(Bioavailable)

O. gutturosa adults

24 "score 3" hits

O. lienalis microfilariae

No overlap!

Re-test against O. gutturosa adults

14/24 re-confirm
as "score 3",
EC_{50} < 4 uM

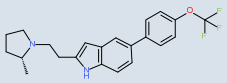
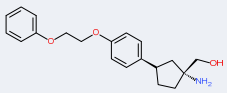
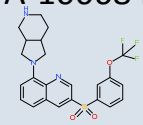
In vivo (Litomosoides sigmodontis)

Day: 0 — 30 — 75 — 105

Natural Infection (*L. sigmodontis*, BalbC mice)

Treatment (5 Days)
- Vehicle
- FBZ
- Compounds

Worm Recovery and Analysis:
- **Parasite number**
- **Microfilariae count**

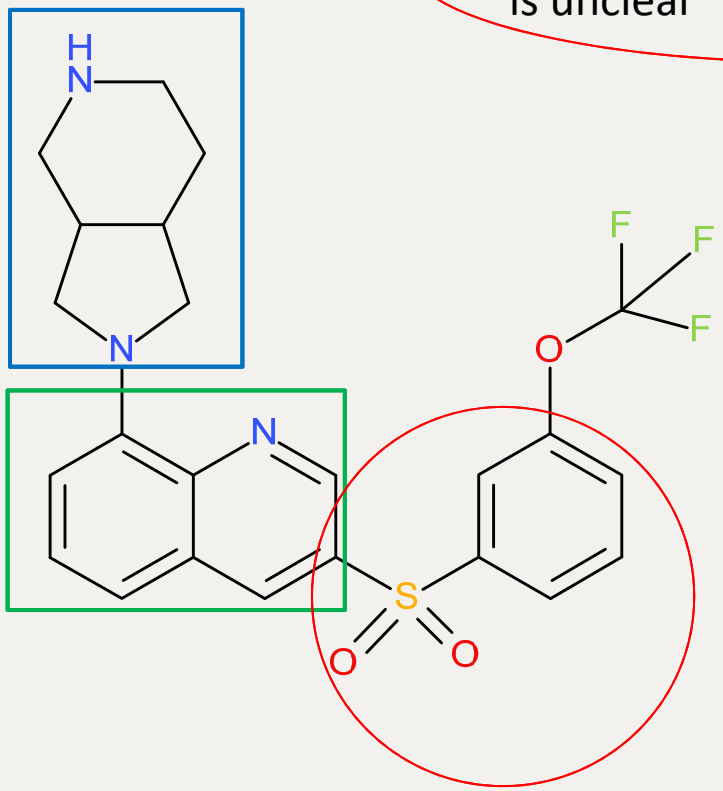
Compound	Dose	Average Adult worm	Reduction adult worms	Reduction microfilaria
Vehicle		17.1 (12.4)	-	-
Flubendazole	6 mg/kg QD x 5 days	0	100 % (P=0.01)	100 % (P=0.01)
A-697365 	100 mg/kg QD x 5 days	24.0 (29)	Not significant	96.3 % (P=0.01)
A-973584 	100 mg/kg QD x 5 days	2.7 (4.7)	84.4% (P=0.02)	100 % (P=0.01)
A-1066844 	40 mg/kg BID x 5 days	16.7 (8.8)	Not significant	86 % (P=0.02)

Values expressed as mean (SD)

5-HT6 Series Structure Activity Relationship Summary

Active analogs contain mono- or bicyclic, amine-containing ring

The effect of substitution patterns is unclear

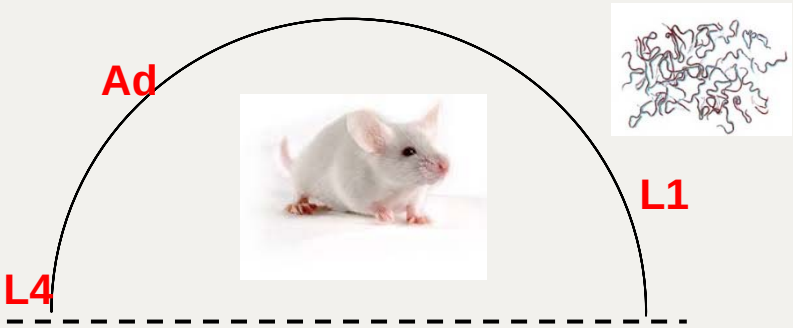


All active analogs contain isoquinoline

Murine model of filariasis:

Litomosoides sigmodontis

2



When the treatment begins, adult worms are not fully mature and do not produce microfilariae (mf)

D0

Natural infection
Or injection of L3

30 days post infection

Randomization
(weight)

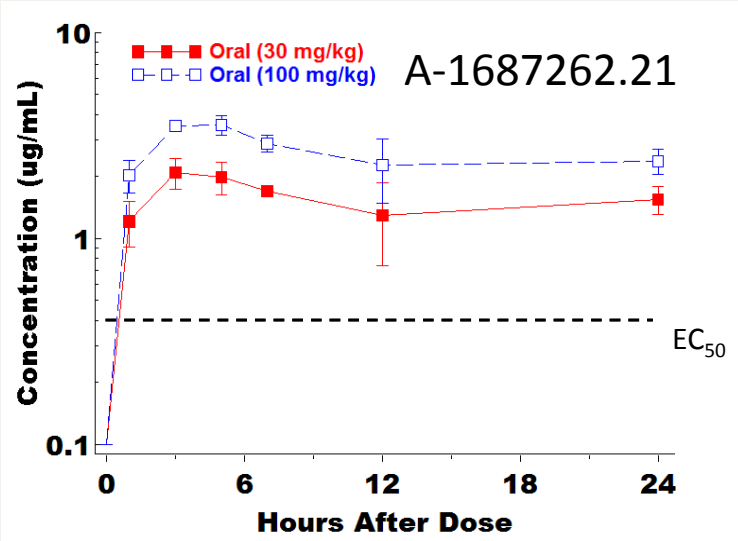
Begining of treatment

75 days post
infection

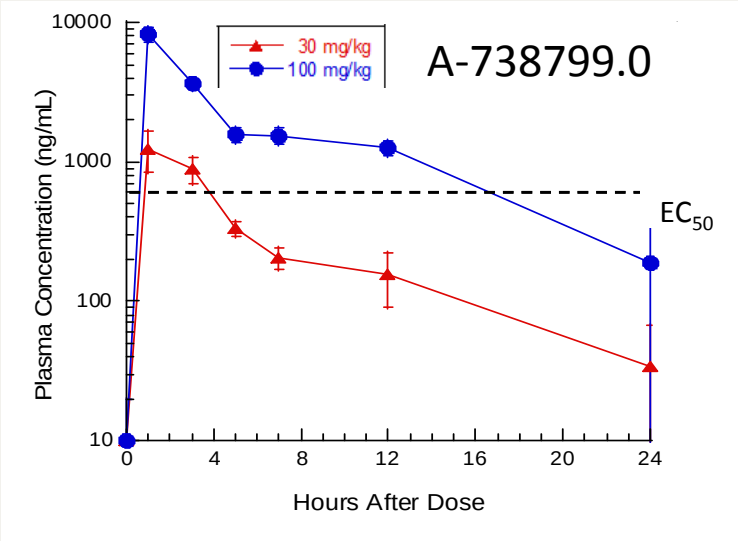
Worm recovery & analysis
parasite numbers
microfilariae counts

5-HT6 Series – profiles of Lead Compounds

abbvie

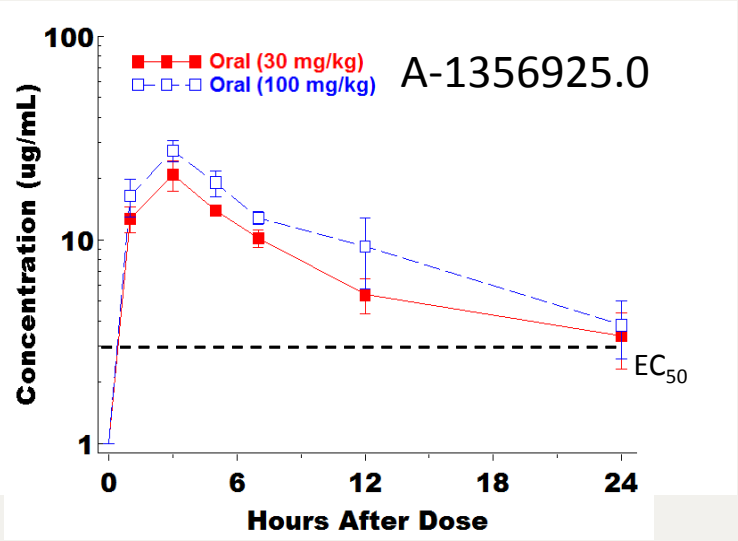


In vivo testing: 100mg/kg 10d QD

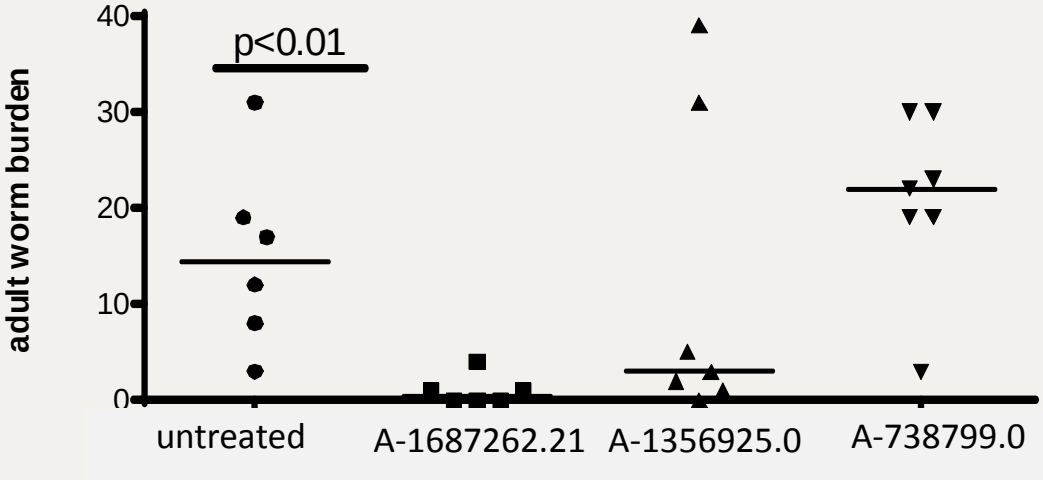


A-738799.0
Do not belong to the 5-HT6 series

In vivo testing: 100mg/kg 10d BID



In vivo testing: 100mg/kg 10d BID



Celgene program

In vitro (*Onchocerca species*)

158 compounds

O. lienalis microfilariae

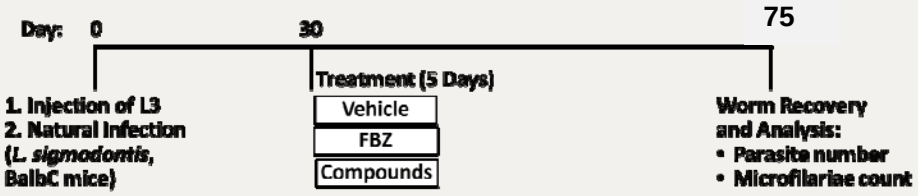
32 "score 3" hits
Single digit micromolar and sub-micromolar activity

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 Results (*Litomosoides sigmodontis*)

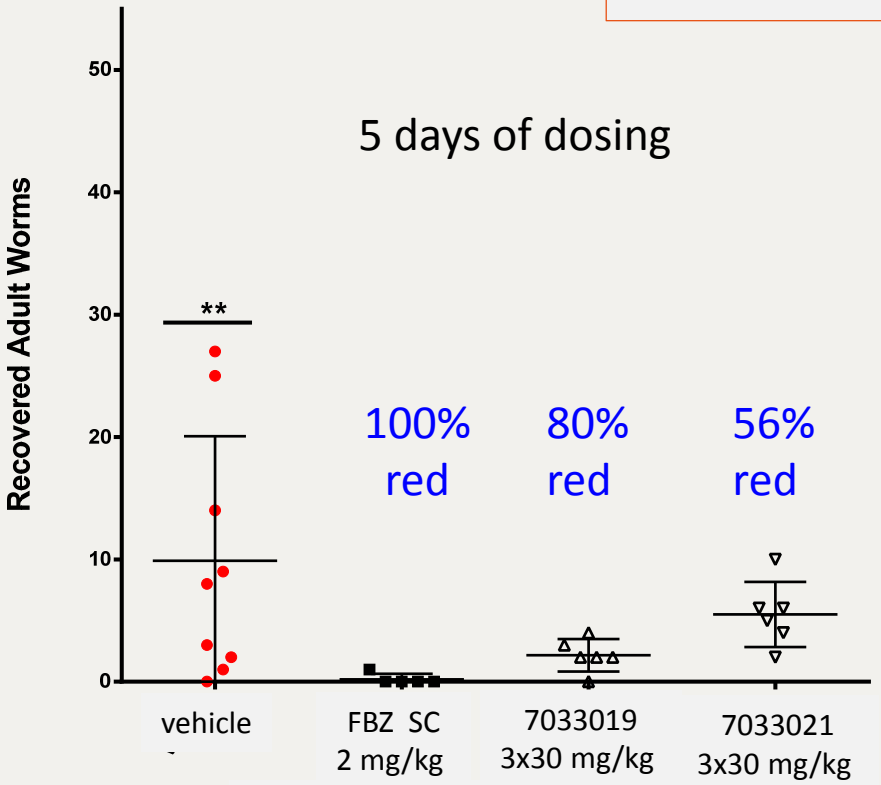


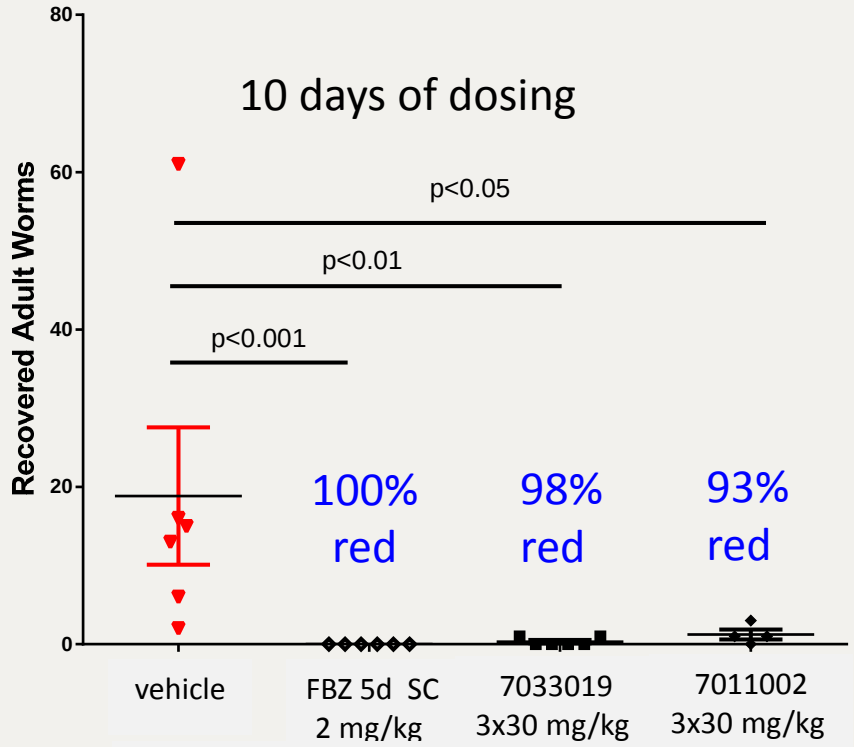
Compound	Dose	Average Adult worms	Reduction Adult worms	Reduction Microfilaria
Vehicle		11 (26)	-	NA
Flubendazole	2 mg/kg 5 days	0	100 % (P=0.007)	NA
7025101	3x30 mg/kg 5 days	2 (1.7)	68 % (p=0.032)	NA
Vehicle		11 (26)	-	-
Flubendazole	2 mg/kg 5 days	0.2 (0.5)	98 % (P=0.019)	100 % (P=0.034)
7033019	3x30 mg/kg 5 days	2.17 (1.3)	80 % (p = 0.044)	98 % (p = 0.042)
7033021	3x30 mg/kg 5 days	5.5 (2.7)	56 % (p = 0.125)	78 % (p=0.078)
7033023	3x30 mg/kg 5 days	10.2 (9.4)	18 % (p = 0.685)	86% (p=0.058)

Values expressed as mean (SD)

In vivo Data: Murine *L. sigmodontis* model

Reduction of Adult Worms





7033019 (Ser A)
O. gutt EC_{50} = 270nM
O. lien EC_{50} =3100nM

7033021 (Ser B)
O. gutt EC_{50} = 699nM
O. lien EC_{50} >12500nM

7011002 (Ser A)
O. gutt EC_{50} = 27nM

1 day dosing

Acknowledgments

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Dale Kempf

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Zhyuan Zhang
Hongjuan Liu
Jia Wang
Jingyu Zhang
MeijingWang

THANK YOU

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PARTNERS & DONORS

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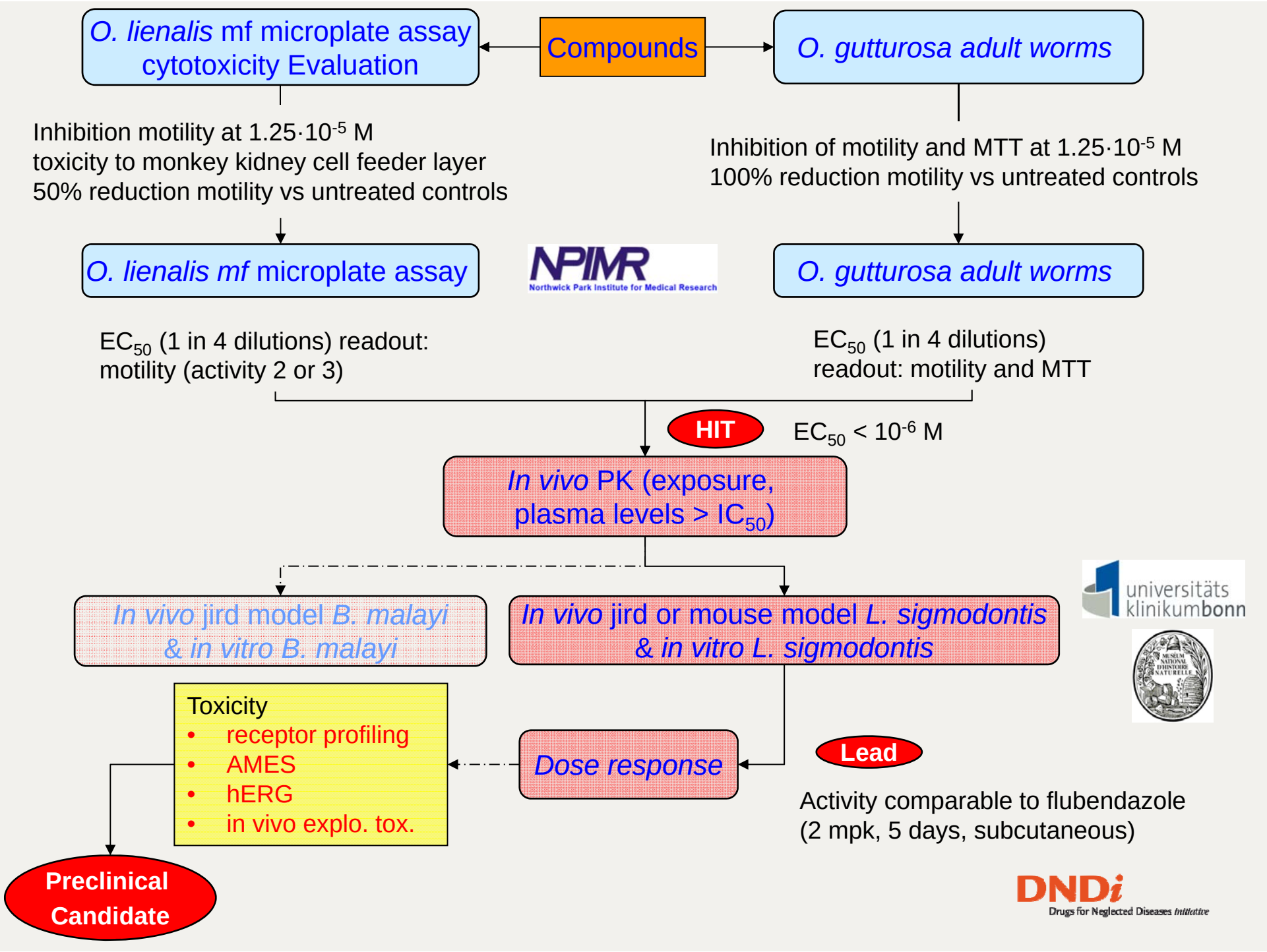
O. lienalis mf microplate assay cytotoxicity Evaluation
Compounds
O. gutturosa adult worms
Inhibition motility at 1.25·10-5 M
toxicity to monkey kidney cell feeder layer
50% reduction motility vs untreated controls
Inhibition of motility and MTT at 1.25·10-5 M
100% reduction motility vs untreated controls
O. lienalis mf microplate assay
NPIMR
Northwick Park Institute for Medical Research
O. gutturosa adult worms
EC50 (1 in 4 dilutions) readout:
motility (activity 2 or 3)
EC50 (1 in 4 dilutions)
readout: motility and MTT
HIT
EC50 < 10-6 M
In vivo PK (exposure, plasma levels > IC50)
In vivo jird model B. malayi & in vitro B. malayi
In vivo jird or mouse model L. sigmodontis & in vitro L. sigmodontis
universitäts klinikumbonn
Toxicity
• receptor profiling
• AMES
• hERG
• in vivo explo. tox.
Dose response
Lead
Activity comparable to flubendazole
(2 mpk, 5 days, subcutaneous)
Preclinical Candidate
DNDi
Drugs for Neglected Diseases initiative