Update on novel treatments for filarial infections

Marc P. Hübner

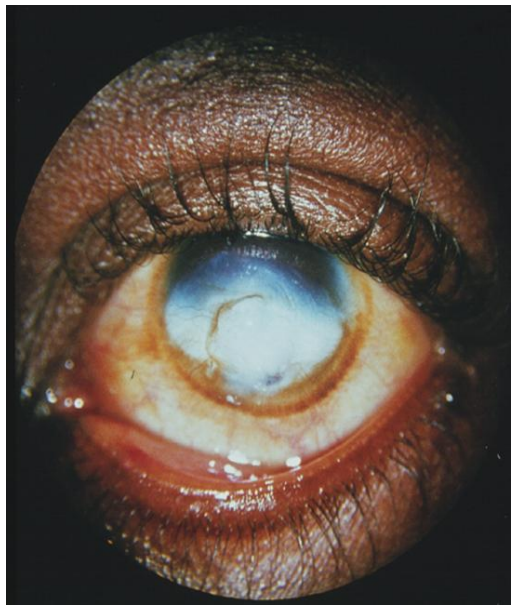
29. Jahrestagung der PEG, Weimar

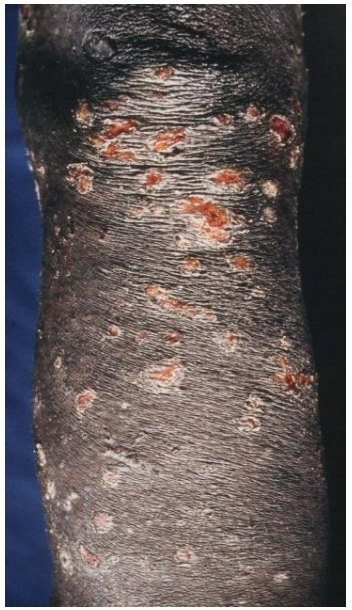
17th October 2024

Filariasis – Neglected Tropical Diseases

Onchocerciasis

Onchocerca volvulus





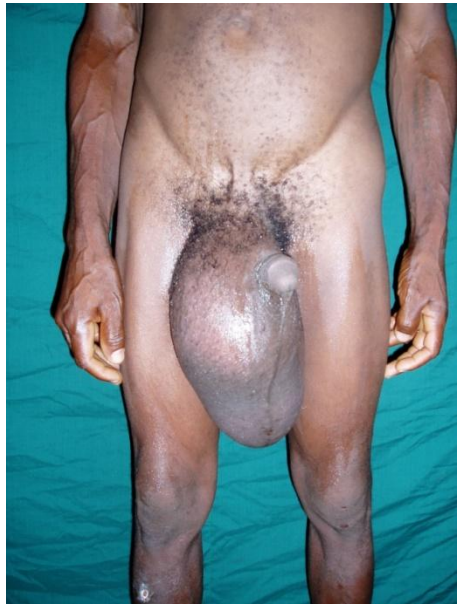
Ca. 265.000

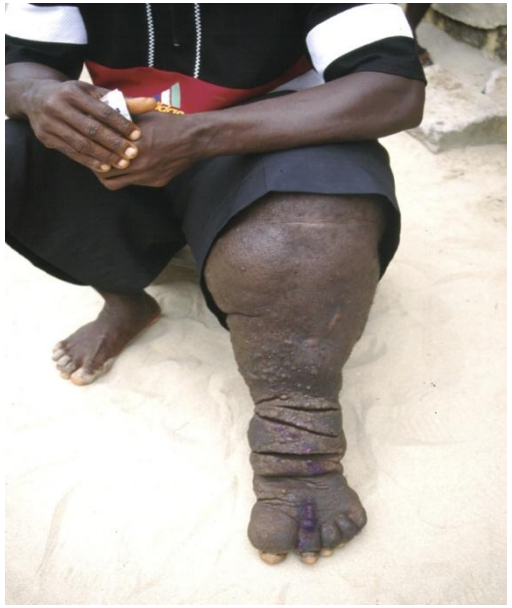
30-50%

- 99% of patients in Sub-Saharan Africa
- Visual impairment, blindness, severe dermatitis
- 21 million people infected

Lymphatic filariasis

Wuchereria bancrofti/ Brugia malayi/ B. timori





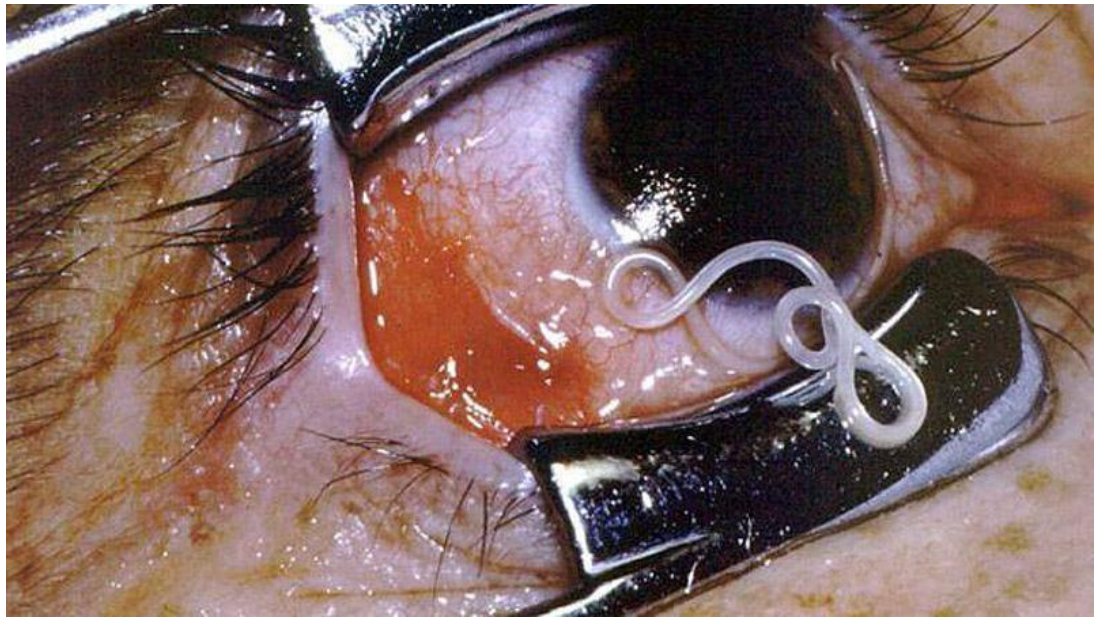
- Tropical Sub-Saharan Africa, South America, Asia
- Hydrocele, lymphedema
- ~51.4 million infected

NTD Road map 2012-2030
King, WHO Guideline Nov. 2017
Cantey, WHO Weekly epidemiological report Nov. 2017

Filariasis: not listed as Neglected Tropical Diseases

Loiasis (African Eye Worm)

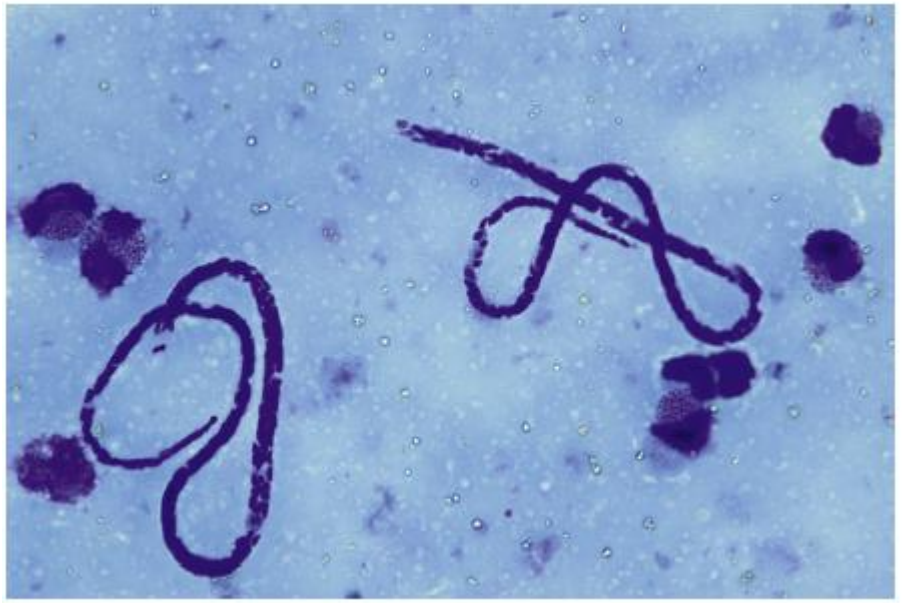
Loa loa



- Central and West Africa
- Itching, Calabar swelling, decreased life expectancy
- ~20 million infected

Mansonellosis

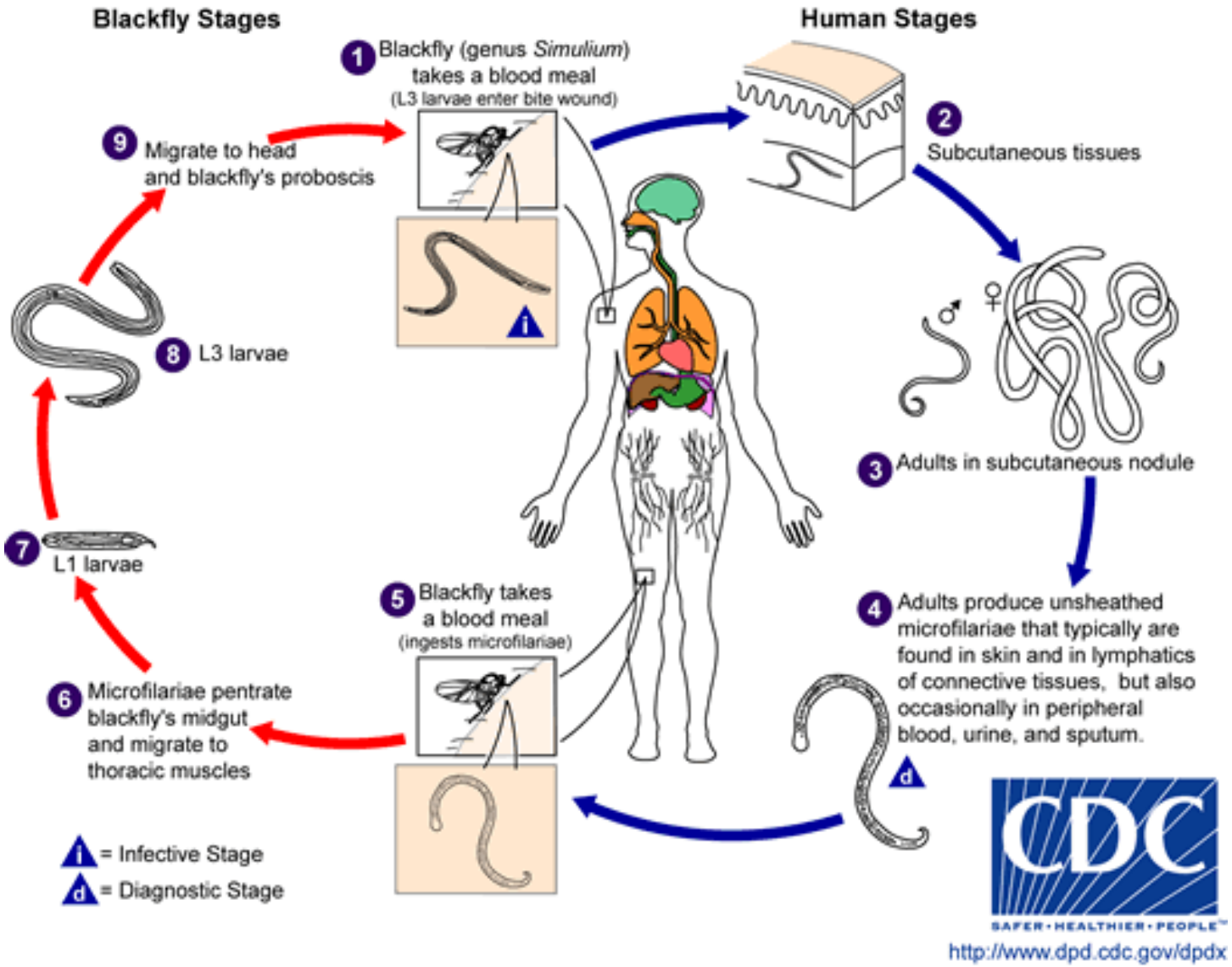
Mansonella perstans, M. ozzardi, M. streptocerca



- Africa, Central and South America
- Pruritus, fever, joint pain, severe abdominal pain
- 120 million infected with *M. perstans*

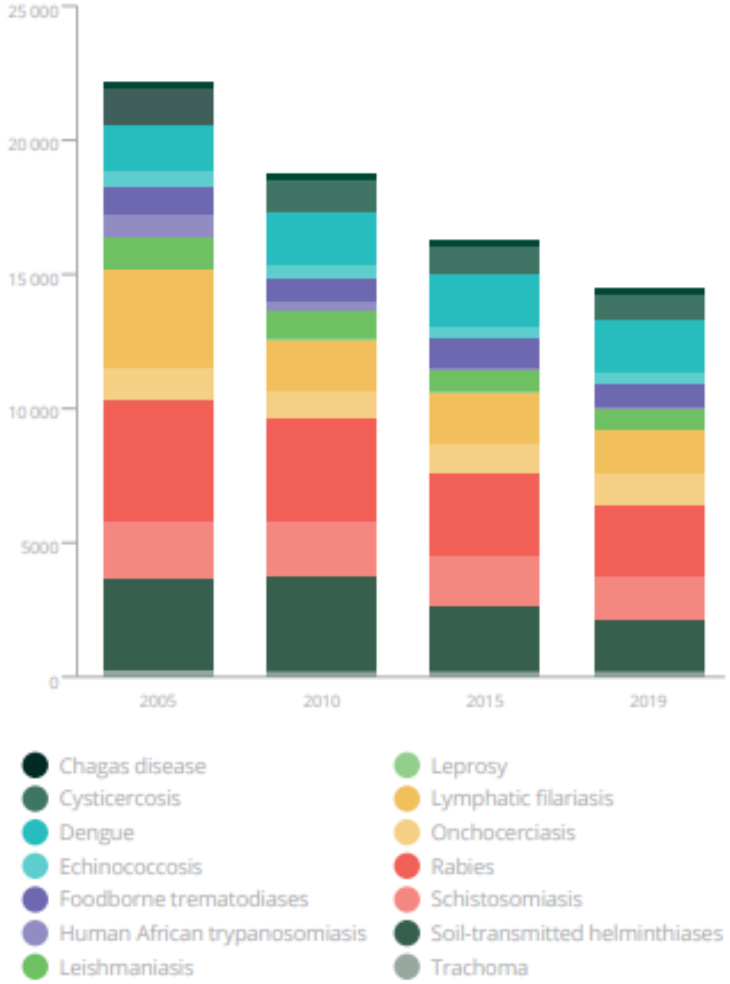
NTD Road Map 2021-2030
King, WHO Guideline Nov. 2017
Cantey, WHO Weekly epidemiological report Nov. 2017
Mansons „The Filariases“ Fischer PU., Hoerauf A., Weil Gj., 2023

Onchocerca volvulus – life cycle



DALYs caused by Neglected Tropical Diseases

Fig. 5. Burden of NTDs (overall and by disease) assessed using DALYs (in thousands), 2005–2019



Helminth infections:

Cysticercosis
Echinococcosis
Foodborne trematodiases
Lymphatic filariasis
Onchocerciasis

Schistosomiasis
Soil-transmitted helminths

WHO – Global Report on neglected tropical diseases 2023

DALYs caused by Neglected Tropical Diseases

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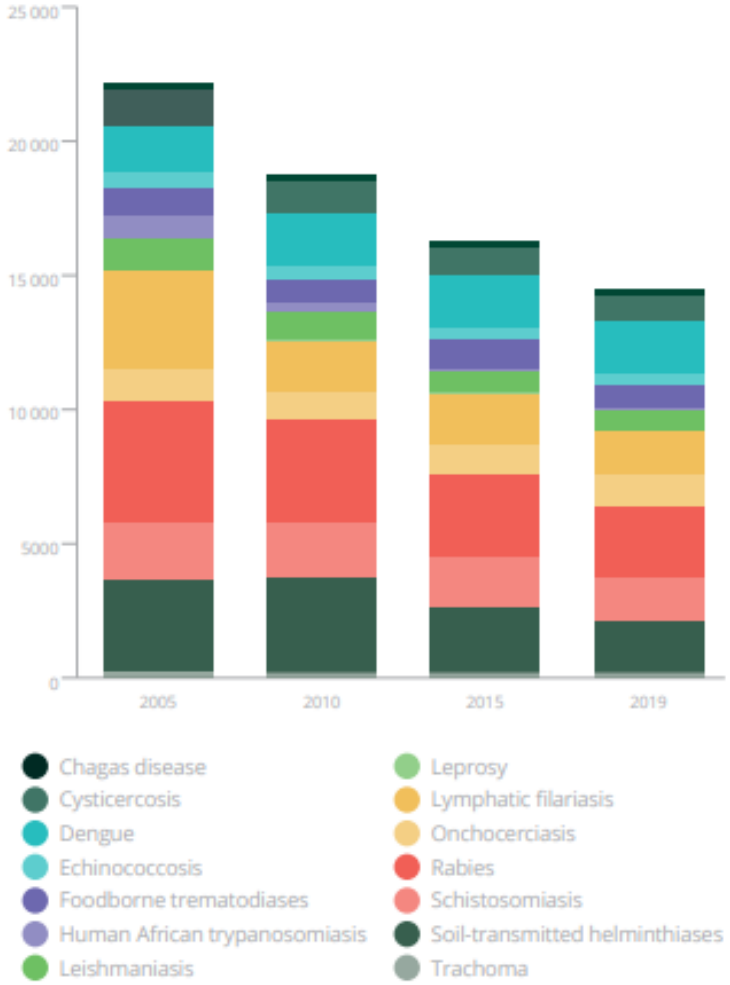

Helminth infections:

Cysticercosis
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Onchocerciasis

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WHO – Global Report on neglected tropical diseases 2023

Drugs Registered for Human Use:

Nematodes (roundworms)

- **Diethylcarbamazine (Banocide)**
- **Ivermectin (Stromectol)**
- **Moxidectin**
- Mebendazole (Vermox)
- **Albendazole (Albenza)**
- Pyrantel Pamoate (PIN-X)
- Thiabendazole (Mintezol)

Trematodes (flukes)

- Praziquantel (Biltricide)

Cestodes (tapeworms)

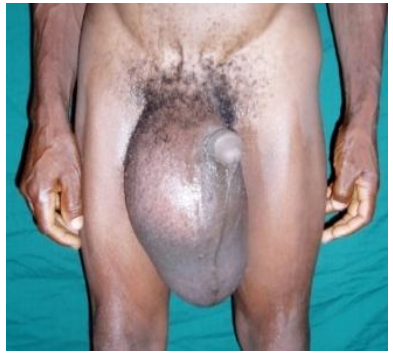
- Niclosamide

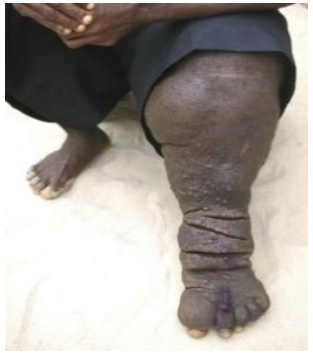
→ All are repurposed veterinary drugs

Filarial diseases – mass drug administration

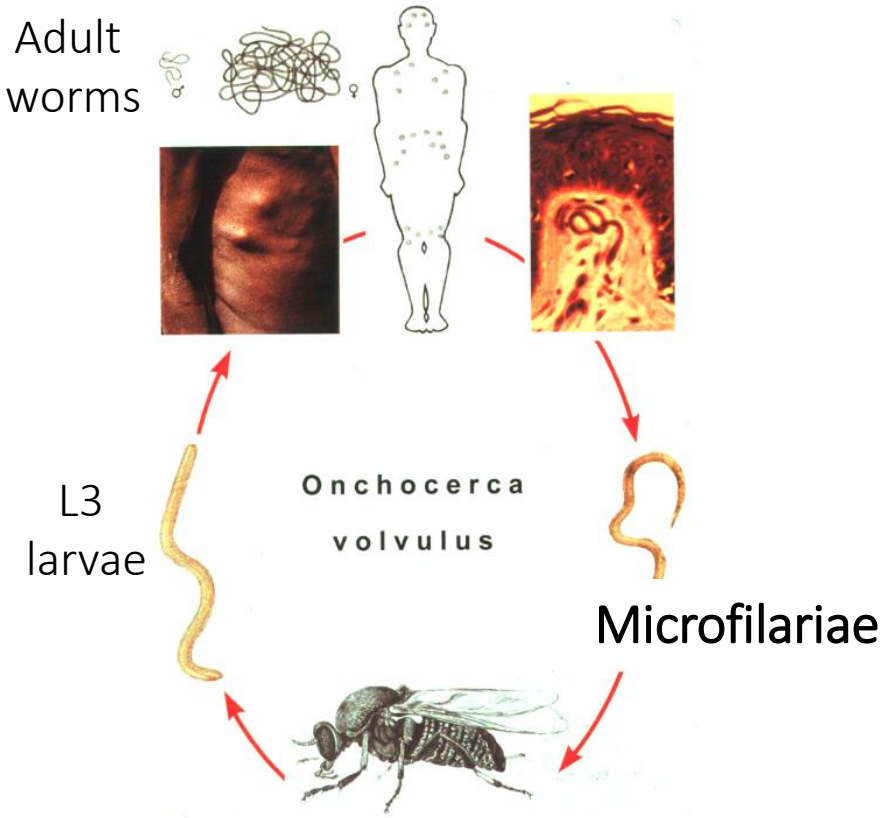
Lymphatic filariasis

Wuchereria bancrofti /
Brugia malayi / B. timori



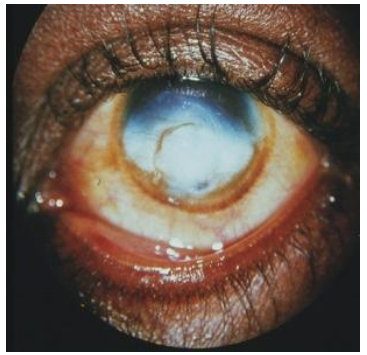


Ivermectin
DEC
Albendazole



Onchocerciasis

Onchocerca volvulus



Ivermectin /
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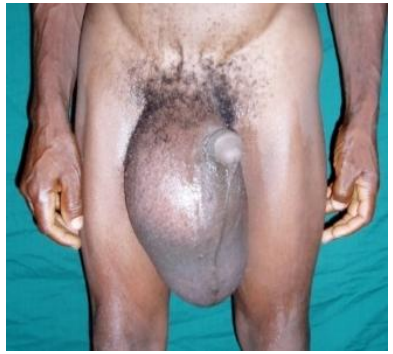

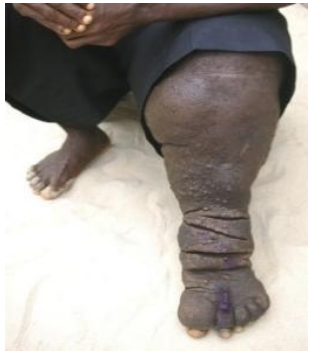

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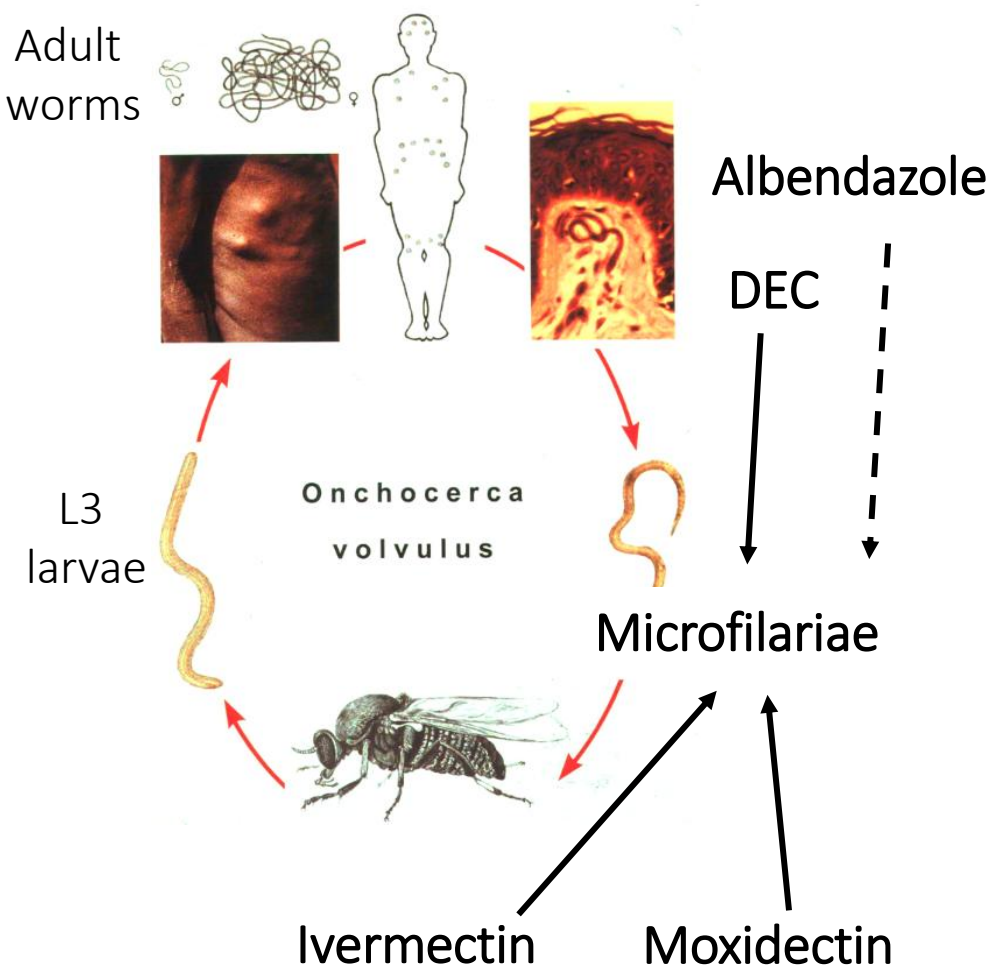

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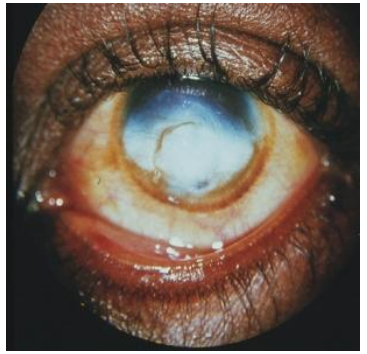

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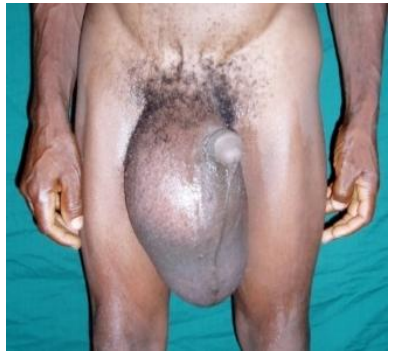
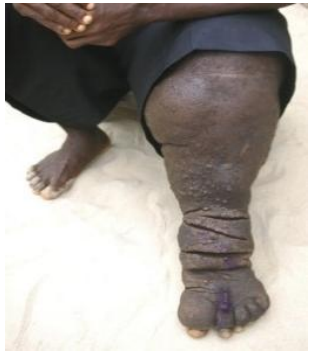
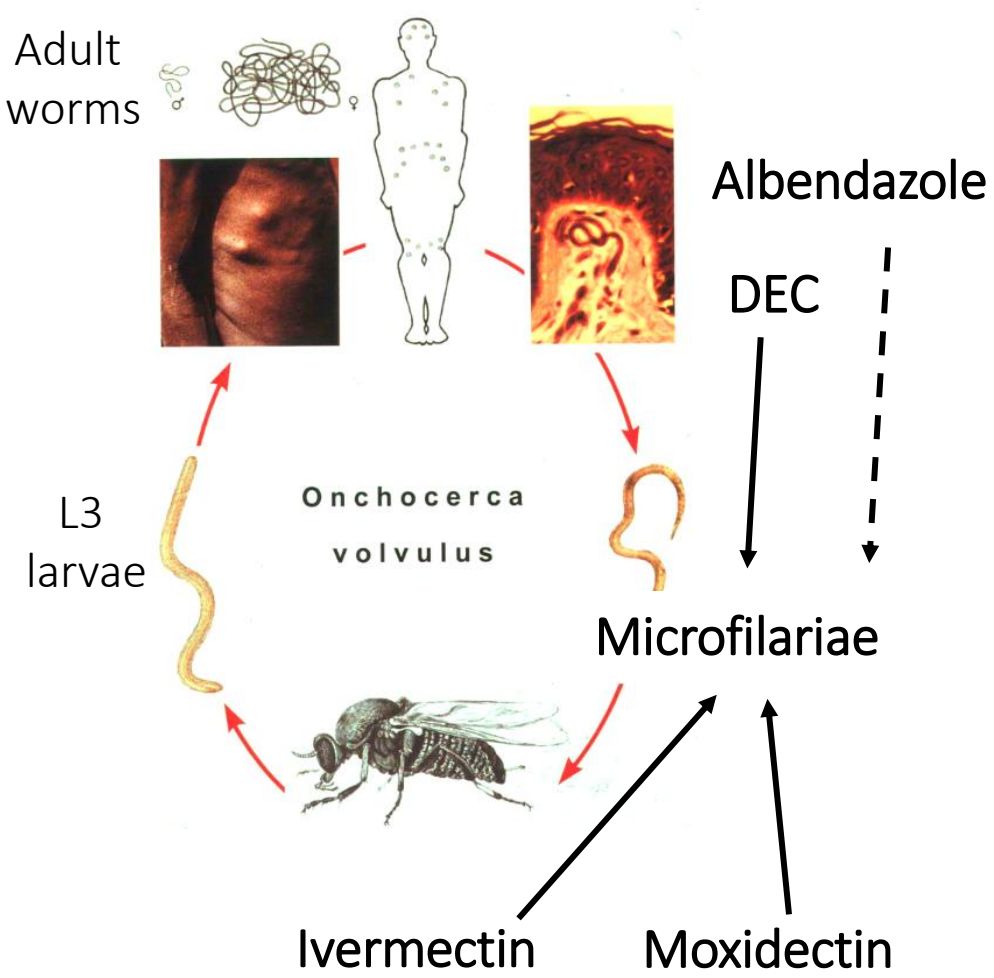




Ivermectin
DEC
Albendazole

→ no macrofilaricidal –
adult worm killing - efficacy



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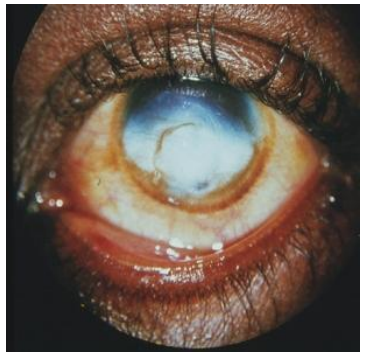

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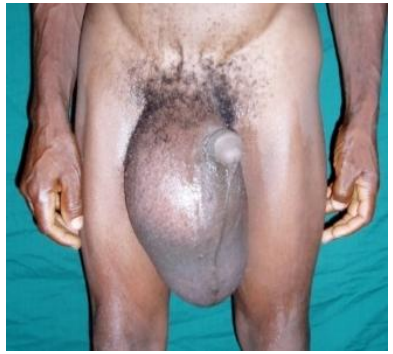

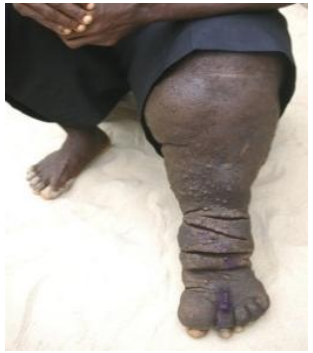

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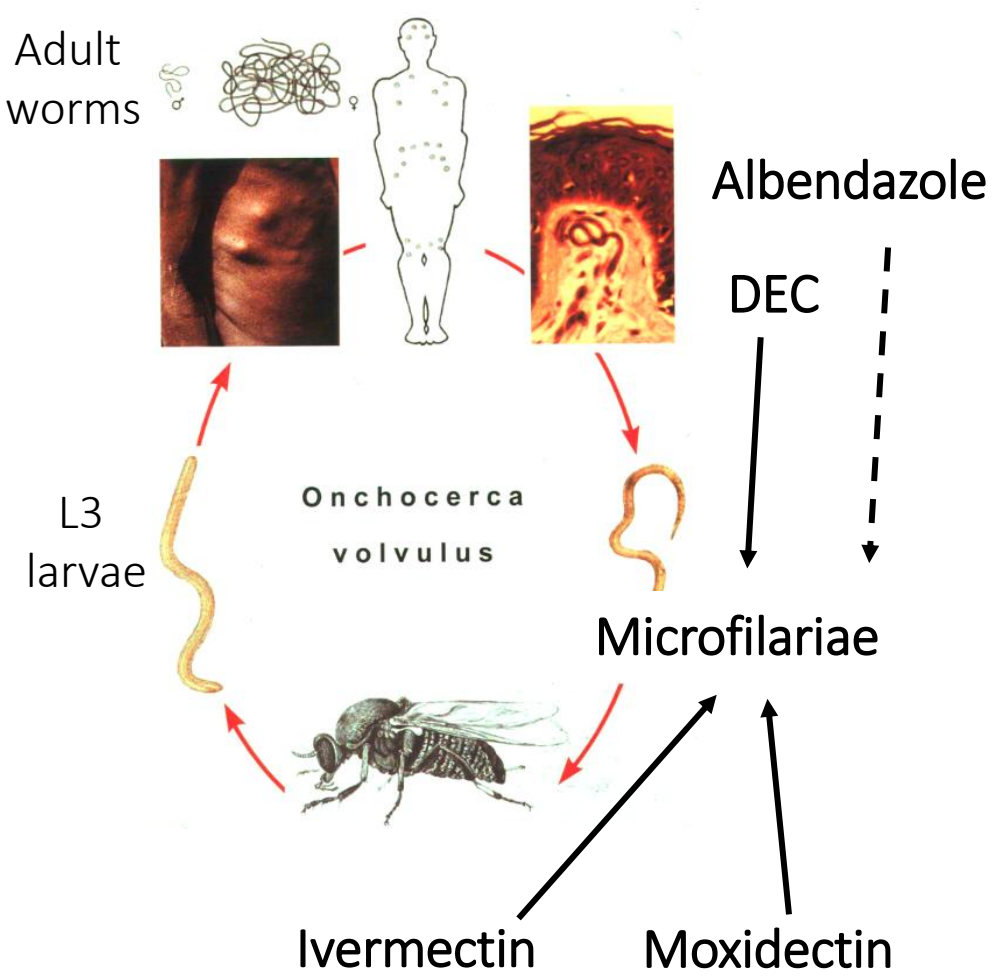

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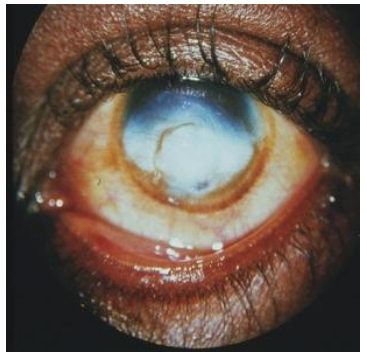
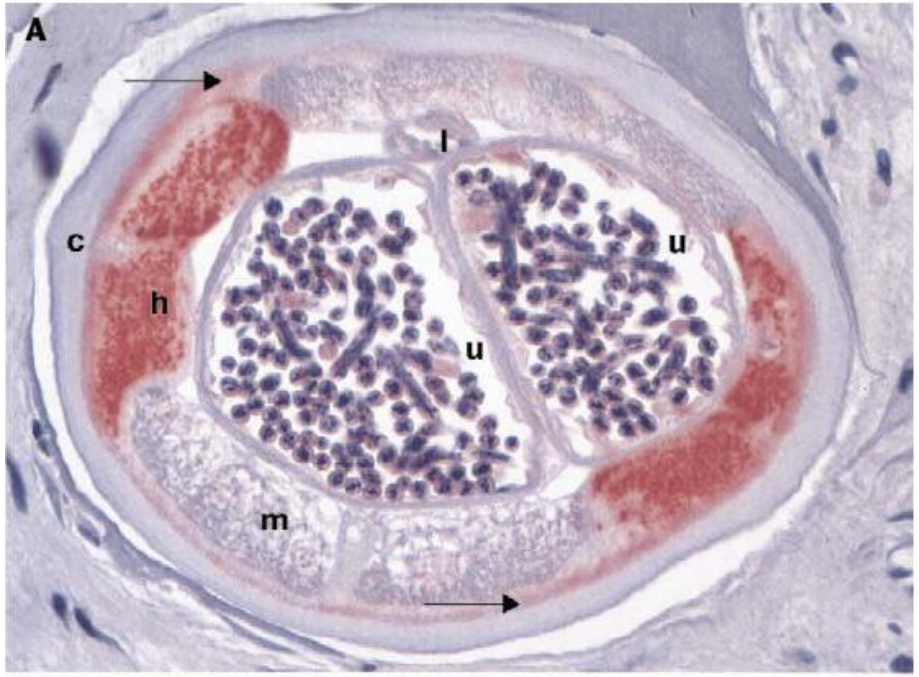


DEC contraindicated in onchocerciasis patients:
- **Severe dermatitis**
- **Risik of blindness**

Loiasis:
- **Risk of life-threatening adverse events after DEC or ivermectin treatment**

← Caused by dying microfilariae

Targeting *Wolbachia* endosymbionts of filarial nematodes



O. volvulus female
from an untreated patient

***Wolbachia* bei:**

- *O. volvulus*
- *W. bancrofti, Brugia spec.*
- *M. perstans, M. ozzardi*
- **NOT *Loa loa***

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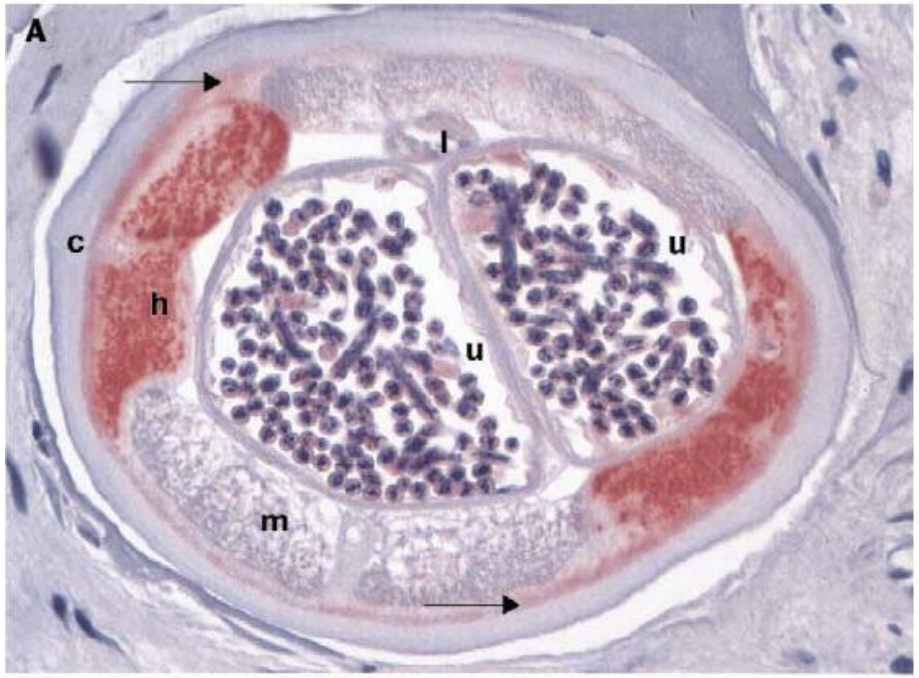

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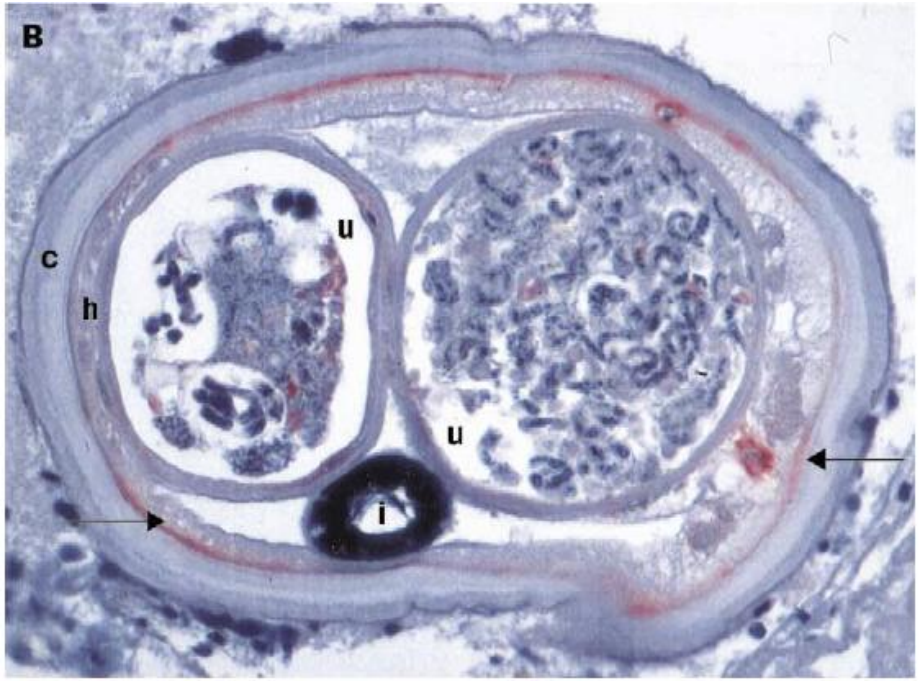


O. volvulus female after 6 weeks of
100 mg/kg **doxycycline** therapy

Hoerauf et al. Lancet 2000

***Wolbachia* bei:**
- *O. volvulus*
- *W. bancrofti, Brugia spec.*
- *M. perstans, M. ozzardi*
- **NOT *Loa loa***

Depletion of *Wolbachia* leads to:
- **Sterilization** of the adult filariae
- Gradual **depletion of microfilariae**
- Slow **killing of adult worms** alongside an improved safety profile

Current recommendations for doxycycline treatment in onchocerciasis and LF

»Onchocerciasis

Doxy 200 mg/d for 6 weeks for macrofilaricidal efficacy

Doxy 200 mg/d for 4 weeks or 100 mg/d for 5 weeks if only adult worm sterility is required

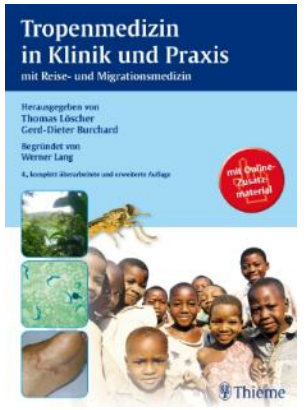
»Lymphatic Filariasis

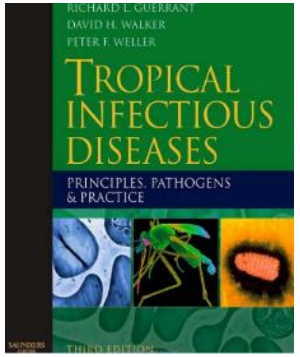
Doxy 100 mg/d for 4 weeks for macrofilaricidal efficacy

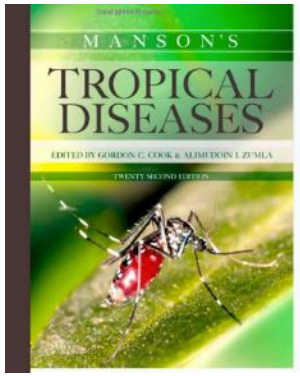
Exclusion criteria:

- Children <8 years
- Pregnancy
- Breast feeding mothers

Hoerauf, Curr Opin Infect Dis 2008,
Taylor-Hoerauf-Bockarie Lancet 2010
Mand et al., Clin Infect Dis 2012



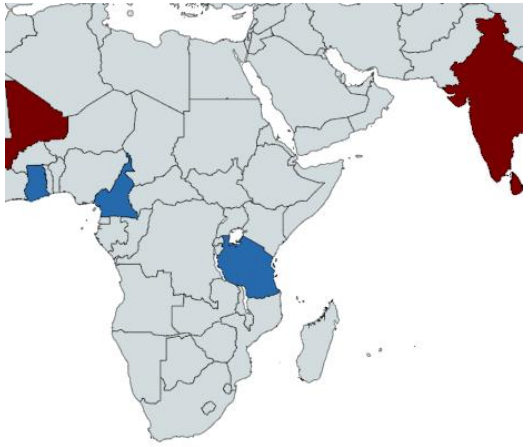




→ **Doxycycline is not in accordance with TPP**

Management of filarial lymphedema

Tackling the Obstacles to Fight Filarial Infections and Podoconiosis



Multicenter study:
TAKeOFF in Ghana, Cameroon, Tanzania
TFGH in Mali, India, Sri Lanka

Prof. Hörauf

Dr. Klarmann-Schulz

Prof. Debrah

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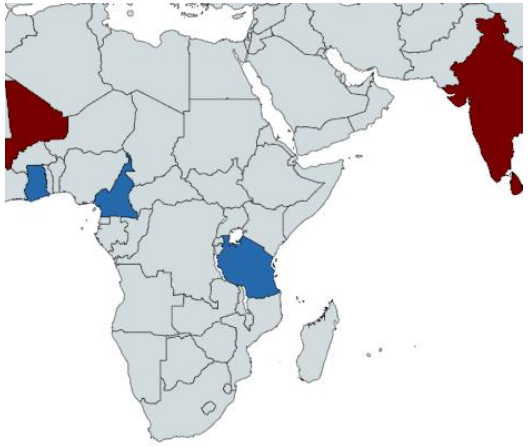

Multicenter study:
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»Lymphatic Filariasis

Doxy 200 mg/d for 6 weeks as treatment of lymph edema and hydrocele?

Management of filarial lymphedema

Hygiene measurements improve quality of life, reduce acute adenolymphangitis and holt lymphedema progression

Doxycycline treatment has an potential **additional benefit** by **preventing acute adenolymphangitis attacks** and **holt of lymphedema progression**

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doi:10.4269/ajtmh.24-0337

Efficacy and Safety of Adding 6 Weeks of Doxycycline to the Essential Package of Care to Treat Filarial Lymphedema: A Double-Blind, Randomized, Controlled Trial in Southern India

Suma Krishnasastry,[1*] Anuja Ashok,[1] Ammu Devidas,[1] Sarah Sullivan,[2] Mariana Stephens,[2] Jayla Norman,[2] Elianna Paljug,[2] Andrew Deathe,[2] Andrew Majewski,[2] John Horton,[3] Joseph P. Shott,[4] Ute Klarmann-Schulz,[5] Achim Hoerauf,[5] Eric Ottesen,[2] and Charles D. Mackenzie[2,6]

[1]*WHO Collaborating Centre for Lymphatic Filariasis Morbidity Management and Disability Prevention, Government TD Medical College, Alappuzha, India;* [2]*Neglected Tropical Disease-Supporting Centre (NTD-SC), Task Force for Global Health, Decatur, Georgia;* [3]*Tropical Projects, Hitchin, United Kingdom;* [4]*Division of Neglected Tropical Diseases, Office of Infectious Diseases, Global Health Bureau, US Agency for International Development, Washington, District of Columbia;* [5]*Institute for Medical Microbiology, Immunology and Parasitology, German Centre for Infection Research (DZIF), University Hospital Bonn, Bonn, Germany;* [6]*Reaching the Last Mile Fund (RLMF), The Ending Neglected tropical Diseases (END) Fund, New York, New York*

Am. J. Trop. Med. Hyg., 111(Suppl 4), 2024, pp. 66–82
doi:10.4269/ajtmh.24-0313

Adherence to Hygiene Protocols and Doxycycline Therapy in Ameliorating Lymphatic Filariasis Morbidity in an Endemic Area Post-Interruption of Disease Transmission in Ghana

Linda Batsa Debrah,[1,2,3†] Ute Klarmann-Schulz,[4,5,6†] Jubin Osei-Mensah,[1,7] Janina M. Kuehlwein,[4,5] Yusif Mubarik,[1] Jennifer Nadal,[4,6] Nana Kwame Ayisi-Boateng,[8] Arcangelo Ricchiuto,[4,6] Vera Serwaa Opoku,[1] Sarah M. Sullivan,[9] Derrick Adu Mensah,[1,2] John Horton,[10] Abu Abudu Rahamani,[1,2] Philip J. Budge,[11] Stephen Gbedema,[12] Patricia Jebett Korir,[4,5] John Opoku,[1] Kenneth Pfarr,[4,5] Derrick Boateng Kontoh,[12] Angelika Kellings,[13] Charles Gyasi,[1] Michael Agyemang Obeng,[1] Barbara Gruetzmacher,[4] Fatima Amponsah Fordjour,[14] Inge Kroidl,[15,16] Sacha Horn,[15] Eunice Kyaakyile Kuutiero,[1] Caroline Wauschkuhn,[4,5] Abdallah Ngenya,[17] Charles Mackenzie,[9] Samuel Wanji,[18] Akili Kalinga,[17] Eric A. Ottesen,[9] Achim Hoerauf,[4,5,19‡] and Alexander Yaw Debrah[1,3,20,‡]

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doi:10.4269/ajtmh.24-0049

Efficacy of Intensified Hygiene Measures with or without the Addition of Doxycycline in the Management of Filarial Lymphedema: A Randomized Double-Blind, Placebo-Controlled Clinical Trial in Tanzania

Abdallah Ngenya,[1†] Ute Klarmann-Schulz,[2,3,4,*†] Winfrida John,[1] Patricia Jebett Korir,[2,3] Mathias Kamugisha,[1] Jennifer Nadal,[2,4] Dennis Moshi,[1] Arcangelo Ricchiuto,[2,4] Ndekya Oriyo,[1] Sarah Mary Sullivan,[5] Ruth Laizer,[6] John Horton,[7] Max Demitrius,[1] Anja Feichtner,[8,9] Thomas F. Marandu,[10] Yusuph Mgaya,[1] Angelika Kellings,[11] Inge Kroidl,[8,9] John Ogondiek,[1] Janina M. Kuehlwein,[2,3] Leonard Masagati,[1] Charles Mackenzie,[5] Maureen Mosoba,[1,12] Sacha Horn,[8] Kheri Kagya,[13] Samuel Wanji,[14] Wilfred Mandara,[1] Linda Batsa Debrah,[15,16,17] Eric A. Ottesen,[5] Alexander Yaw Debrah,[15,17,18] Upendo Mwingira,[1,19] Achim Hoerauf,[2,3,20†] and Akili Kalinga[1†]

LEDoxy-SL: A Placebo-Controlled, Double-Blind, Randomized, 24-Month Trial of Six Weeks of Daily Doxycycline Plus Hygiene-Based Essential Care for Reducing Progression of Filarial Lymphedema in Sri Lanka

Thishan Channa Yahathugoda,[1*] Nirmitha Lalindi De Silva,[1] Janaka Ruben,[1] Sharmini Gunawardena,[2] Mirani Vasanthamala Weerasooriya,[1] John Horton,[3] Philip Budge,[4] Eric Ottesen,[5] Sarah Mary Sullivan,[5] Mariana Stephens,[5] John Shen,[5] Ute Klarmann-Schulz,[6] Achim Hoerauf,[6] Joseph Patrick Shott,[7] and Charles Mackenzie[5]

[1]*Filariasis Research Training and Service Unit, Department of Parasitology, Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka;* [2]*Department of Parasitology, Faculty of Medicine, University of Colombo, Sri Lanka;* [3]*Tropical Projects, Hitchin, United Kingdom;* [4]*Washington University School of Medicine, St. Louis, Missouri;* [5]*Neglected Tropical Disease Support Center, Task Force for Global Health, Decatur. Georgia;* [6]*Institute for Medical Microbiology, Immunology and Parasitology (IMMIP), German Centre for Infection Research (DZIF), Bonn-Cologne Site, University Hospital Bonn, Bonn, Germany;* [7]*Division of Neglected Tropical Diseases, U.S. Agency for International Development, Washington, District of Columbia*

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doi:10.4269/ajtmh.23-0908

Part 2: Clinical Trials For Treating and Managing Filarial Lymphedema

Effect of Adding a Six-Week Course of Doxycycline to Intensive Hygiene-Based Care for Improving Lymphedema in a Rural Setting of Mali: A Double-Blind, Randomized Controlled 24-Month Trial

Yaya I. Coulibaly,[1,2*] Abdoul F. Diabate,[1] Moussa Sangare,[1] Sekou O. Thera,[1] Housseini Dolo,[1] Salif S. Doumbia,[1] Siaka Y. Coulibaly,[1] Ayouba Diarra,[1] Lamine Diarra,[1] Diadje Tanapo,[1] Michel E. Coulibaly,[1] Lamine Soumaoro,[1] Abdallah A. Diallo,[1] Amatigue Zeguime,[1] Yacouba Sanogo,[1] Adama Berthe,[1] Fatoumata Dite Nene Konipo,[1] Charles Mackenzie,[3,4] Mariana Stephens,[3] Joseph P. Shott,[5] Jayla Norman,[3] Ute Klarmann-Schulz,[6] Achim Hoerauf,[6] Andrew Majewski,[3] John Horton,[7] Sarah Sullivan,[3] Eric A. Ottesen,[3] and Thomas B. Nutman[8]

[1]*International Center for Excellence in Research, Bamako, Mali;* [2]*Dermatology Hospital of Bamako, Bamako, Mali;* [3]*Neglected Tropical Diseases Support Center, Task Force for Global Health, Decatur, Georgia;* [4]*The Reaching the Last Mile Fund, The End Fund, New York, New York;* [5]*Division of Neglected Tropical Diseases, Global Health Bureau, Bethesda, Maryland;* [6]*Institute for Medical Microbiology, Immunology and Parasitology, German Centre for Infection Research (DZIF), Bonn-Cologne Site, University Hospital Bonn, Bonn, Germany;* [7]*Tropical Projects, Hitchin, United Kingdom;* [8]*National Institute of Allergy and Infectious Diseases, Bethesda, Maryland*

Elimination of filarial diseases

SUSTAINABLE DEVELOPMENT GOALS KNOWLEDGE PLATFORM

World Health Organization

NTD Roadmap 2021–2030

SUSTAINABLE DEVELOPMENT GOAL 3

Ensure healthy lives and promote well-being for all at all ages

Goal: **By 2030, end the epidemic of neglected tropical diseases** (NTDs)

← 90% reduction in the number of people requiring interventions against NTDs by 2030

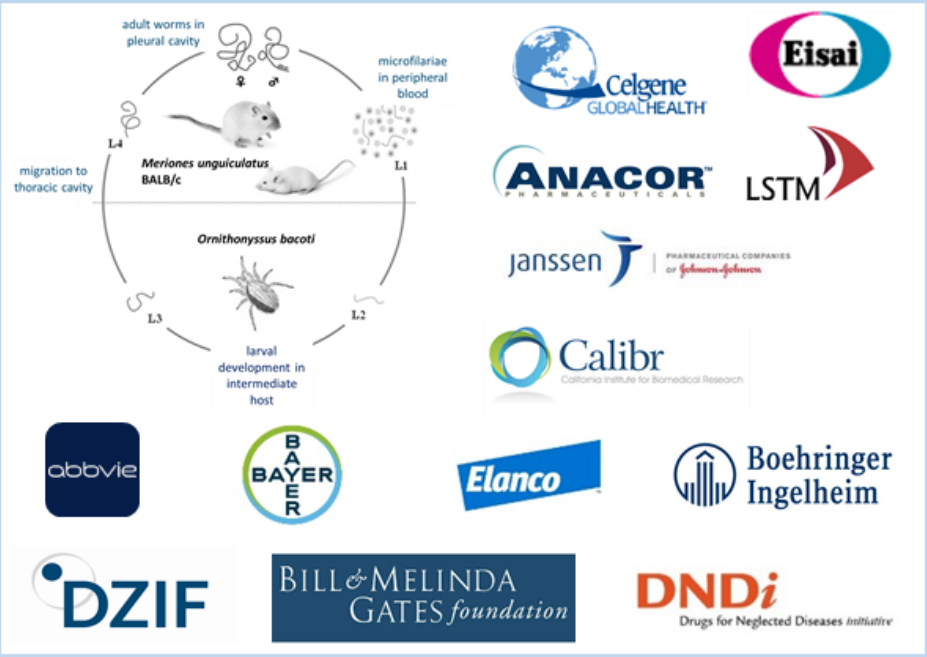
← **Onchocerciasis**:
Confirmed **elimination of transmission** in 12 endemic countries (31%)

← **Lymphatic filariasis**:
80% of endemic countries (58 of 72) validated as achieving **elimination as public health problem**

Macrofilaricidal candidates for onchocerciasis

Preclinical

- Intern. hit to lead program (>500K candidates)
- Collaboration with industry & academia
- > 450 candidates tested in the *Litomosoides sigmodontis* rodent model



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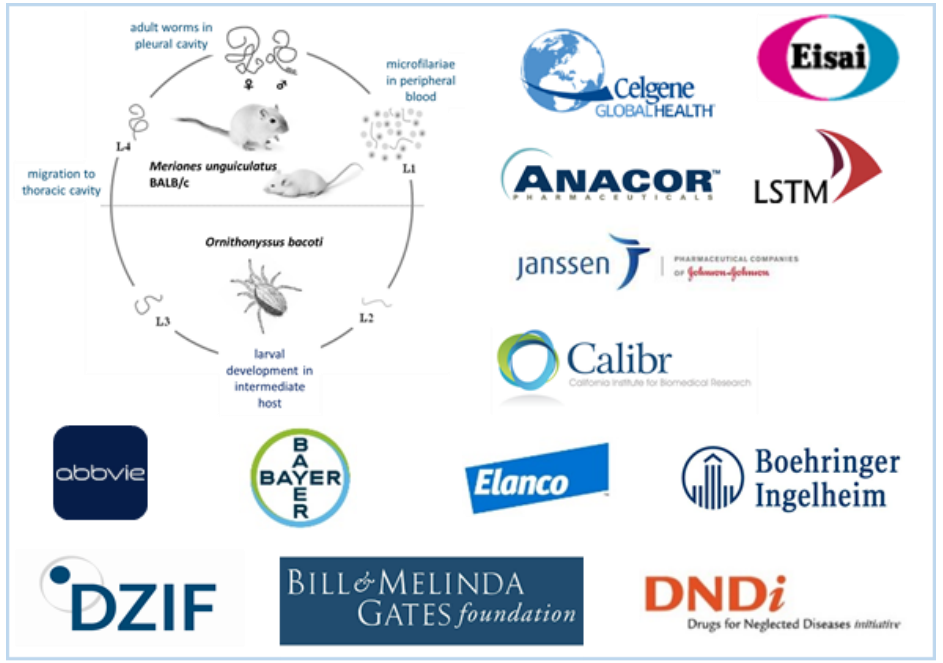

Phase 1:

- **CorA** (scheduled for 2026)
- **AWZ-1066**

Phase 2:

- **Flubentylosin/ABBV-4083**
- **Emodepside**
- **Oxfendazole** (in 2025)

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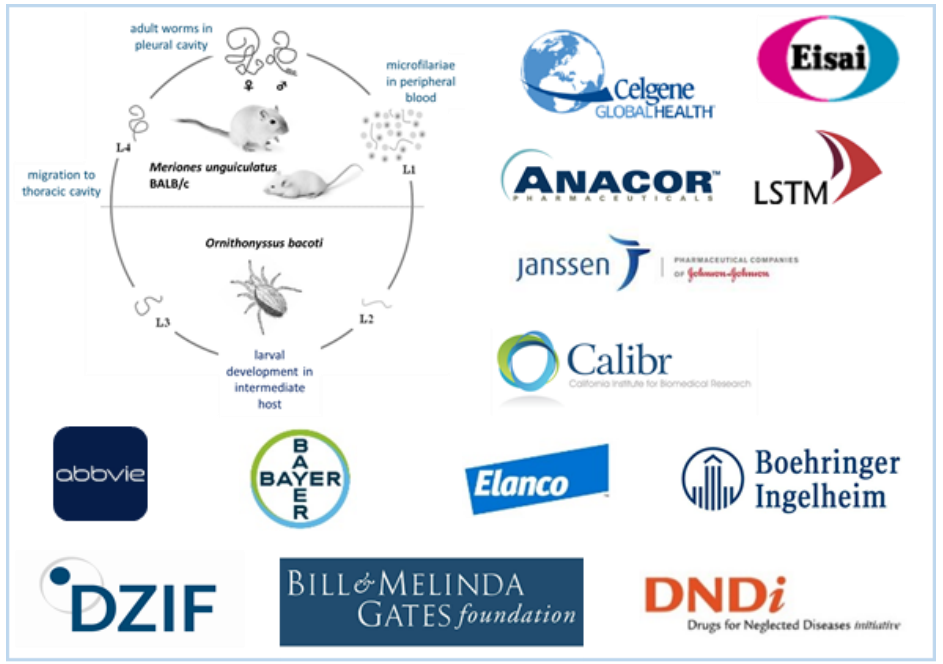

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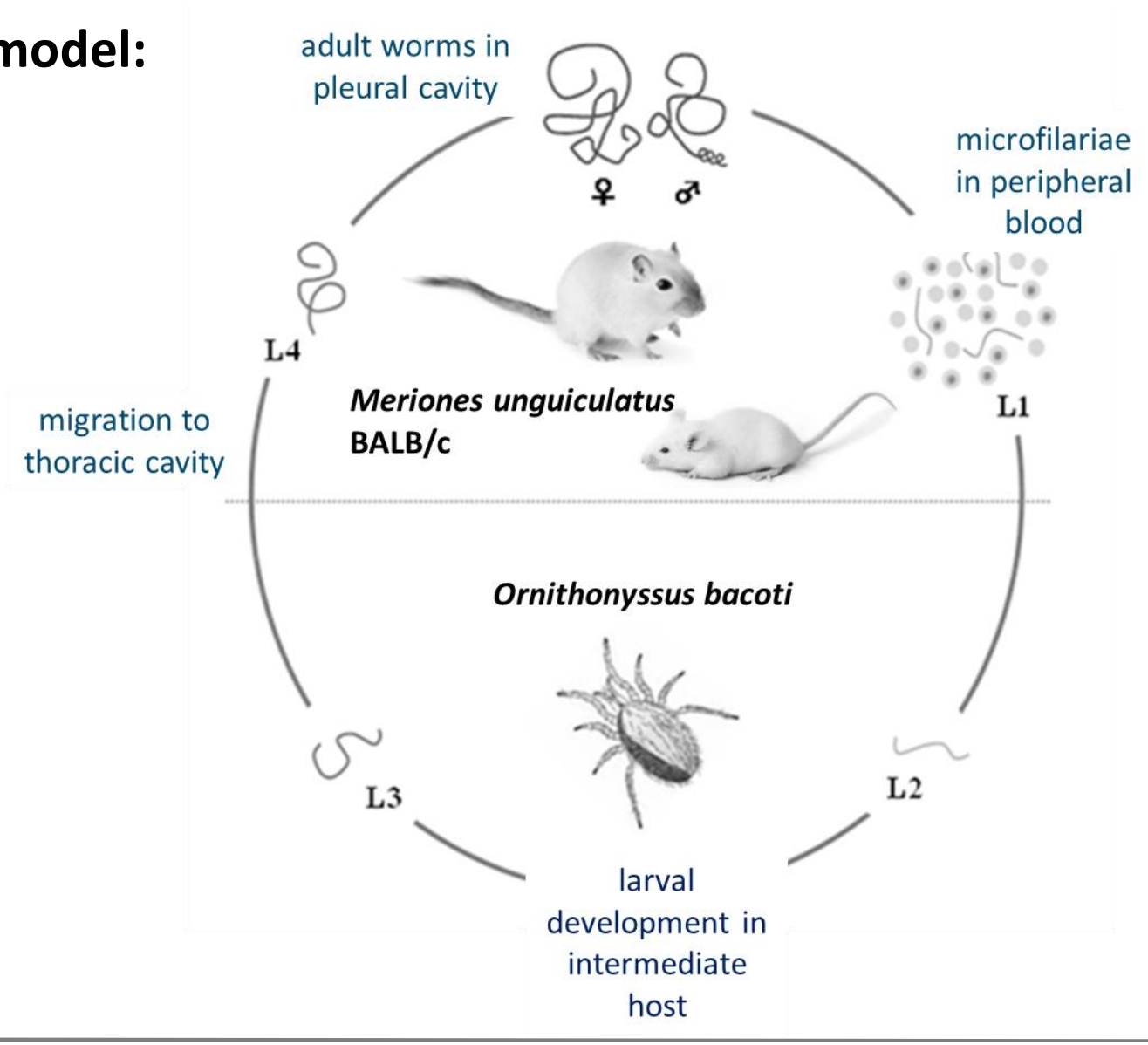
Preclinical development and testing of novel anthelmintics

Litomosoides sigmodontis rodent model:

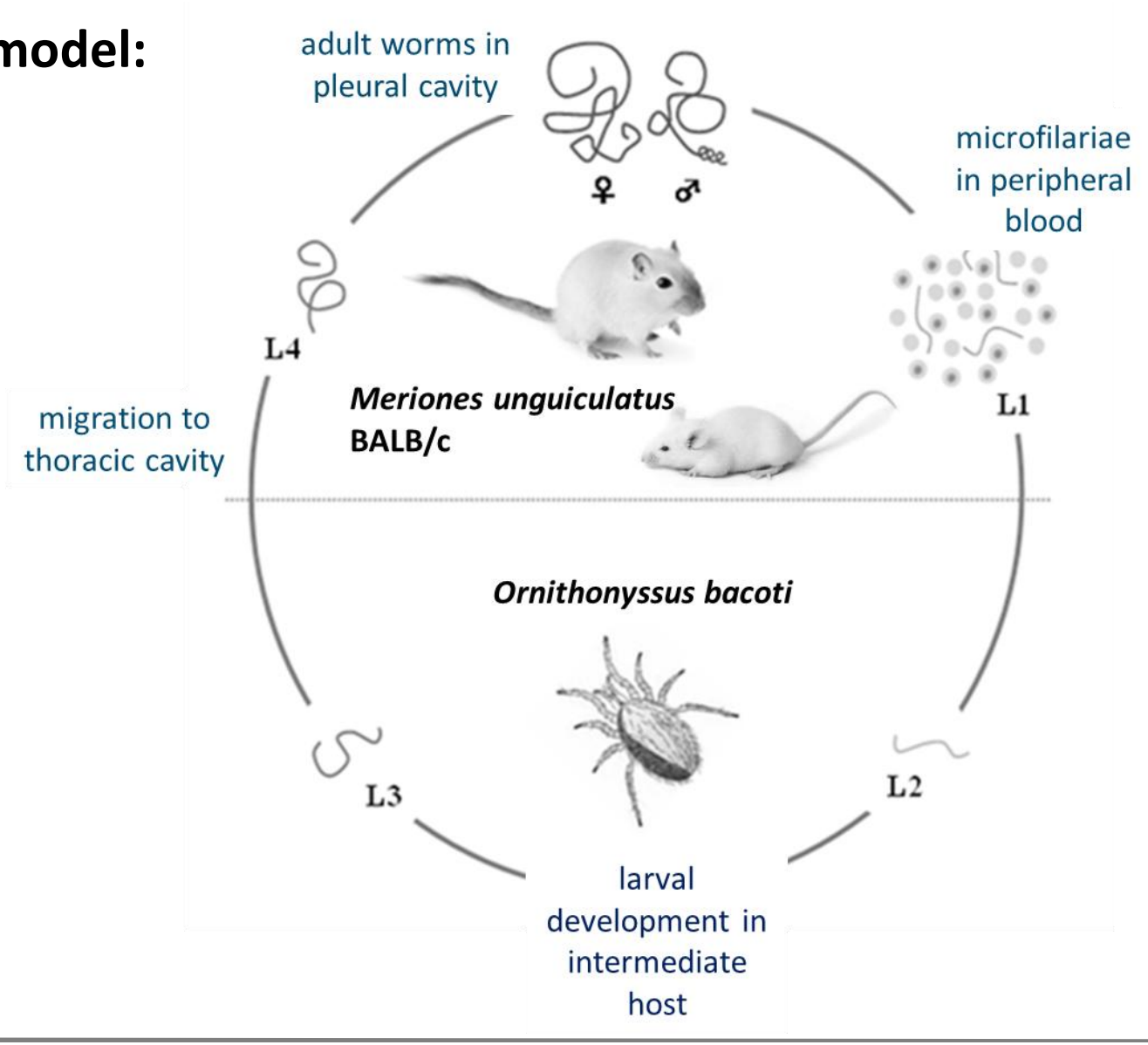


Preclinical development and testing of novel anthelmintics

***Litomosoides sigmodontis* rodent model:**

Identification of:

- anti-*Wolbachia* candidates
- direct acting compounds



Preclinical development and testing of novel anthelmintics

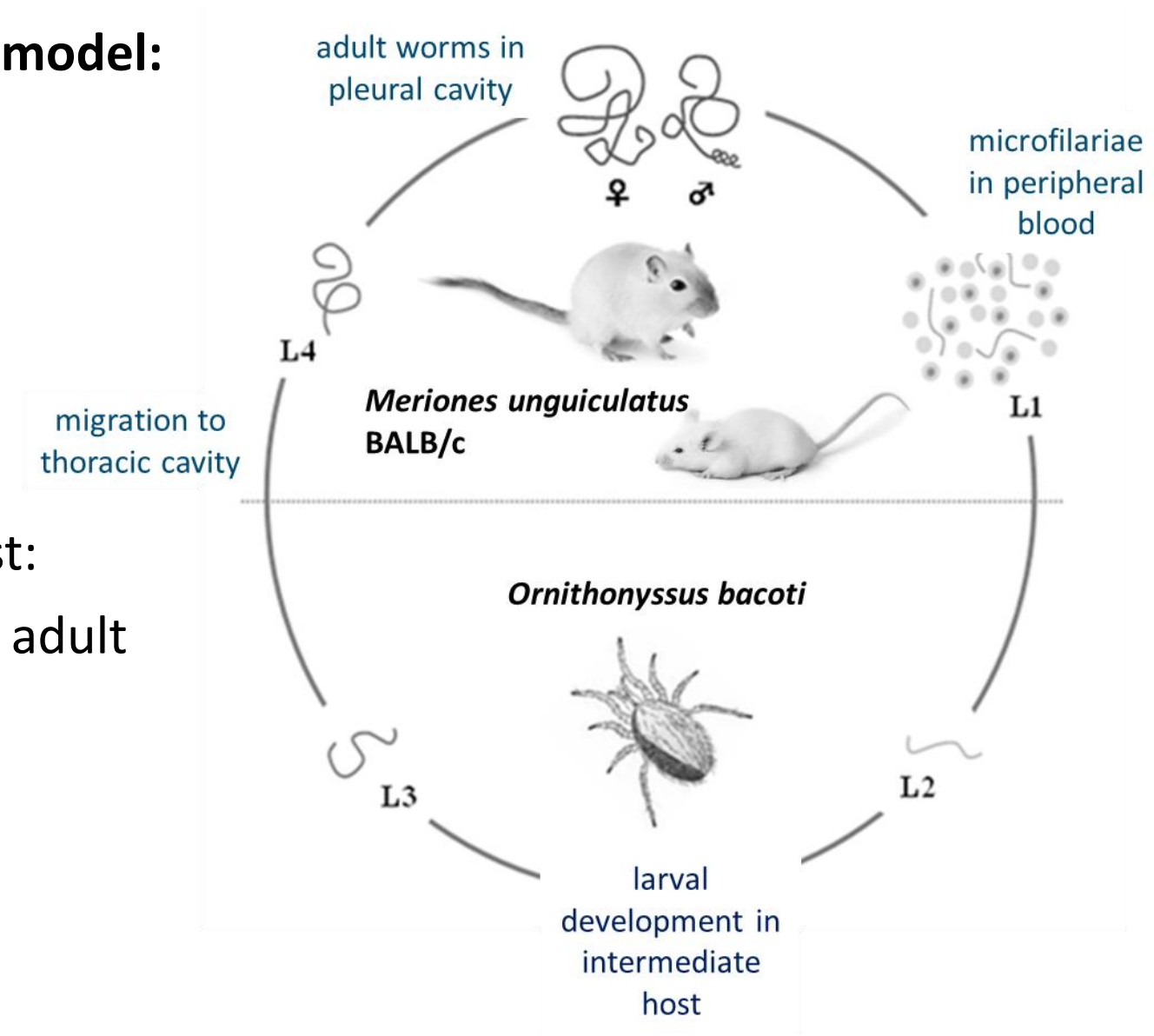
***Litomosoides sigmodontis* rodent model:**

Identification of:

- anti-*Wolbachia* candidates
- direct acting compounds

Assessment of drug efficacy against:

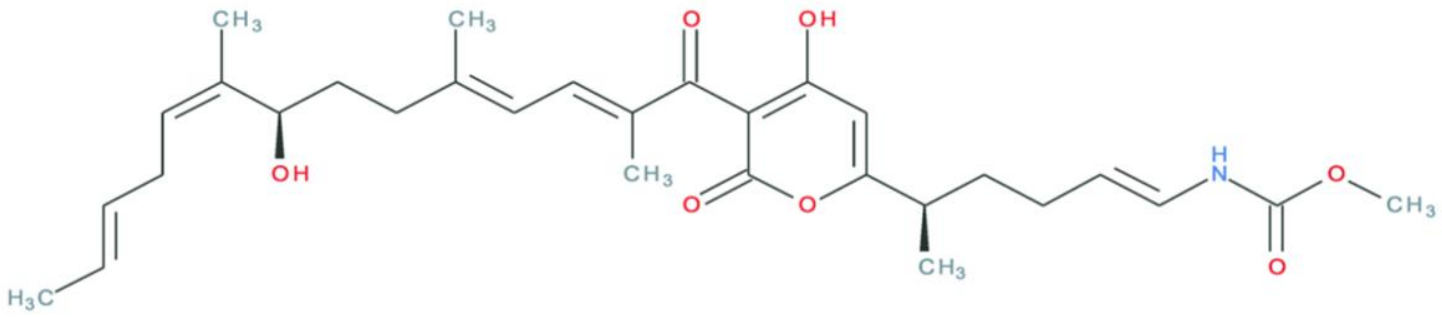
- Different life cycle stages (L3, L4, adult filariae, microfilariae)
- Filarial development
- Development of microfilaremia

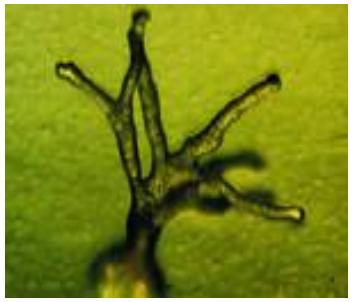


Corallopyronin A

Phase 1 clinical trial
scheduled for 2026

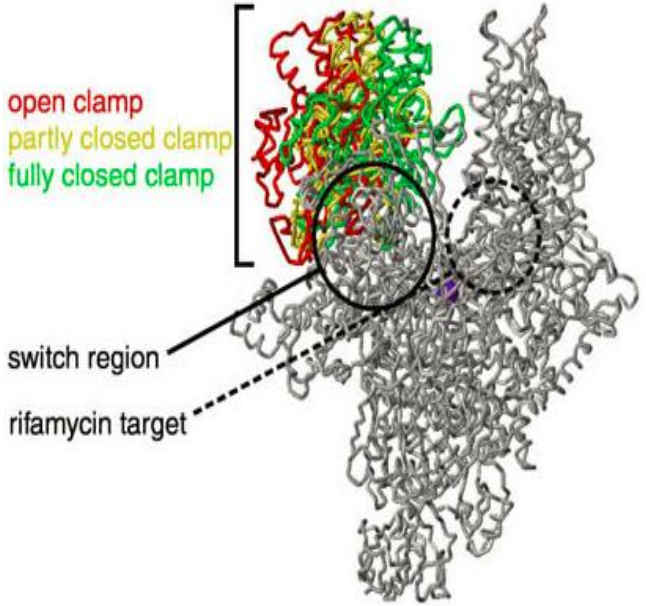
Background: Corallopyronin A (CorA)





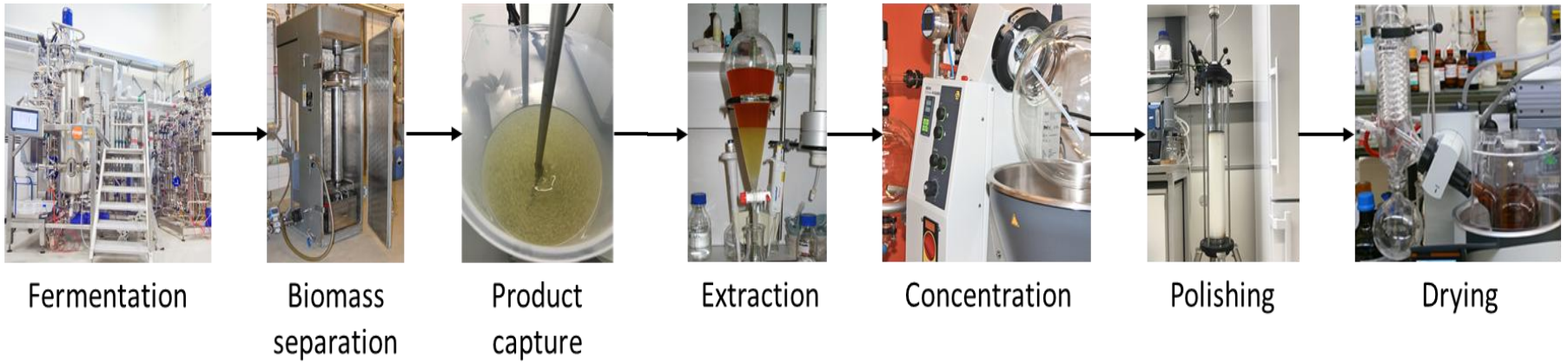
Corallococcus coralloides

- **Natural product of *Corallococcus coralloides***
  - Soil Myxobacteria
- **Inhibits bacterial DNA dependent RNA polymerase**
- **Novel MoA: different from rifamycins**
  - Switch region – blocks entrance of DNA template
  - Effective against rifampicin-resistant *S. aureus*
- **Effective against many Gram-positive bacteria**
  - *E. coli* ΔtolC mutants are sensitive

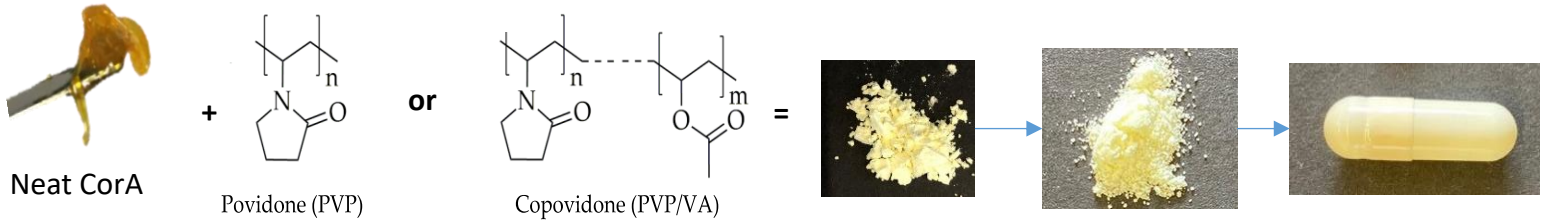


Background: Corallopyronin A (CorA)

- **USP & DSP** process established for **15,000 L bioreactor** (industrial scale!)



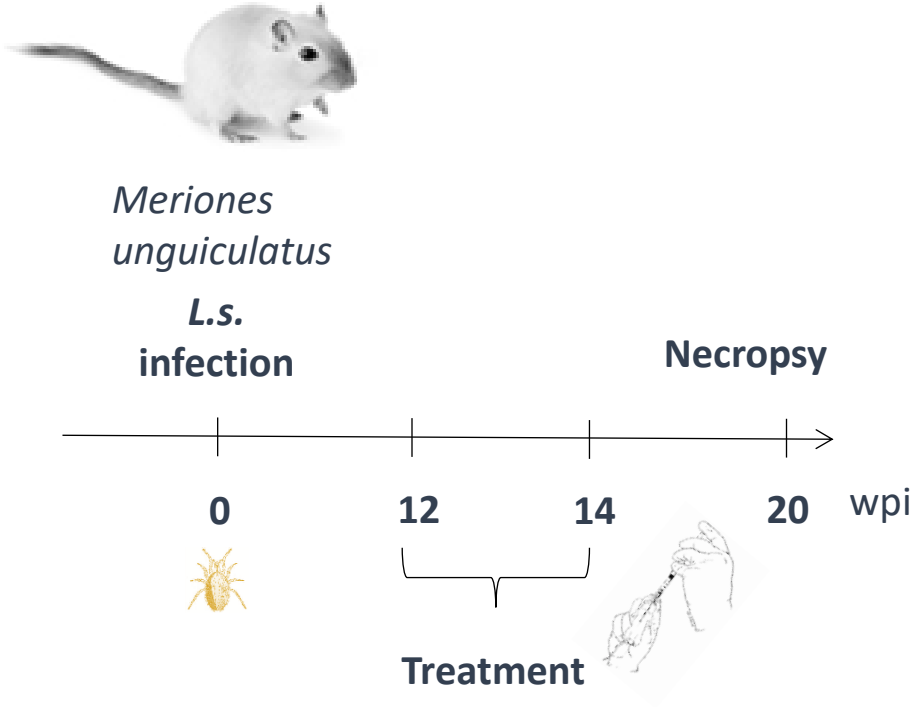
- **GLP** appropriate **oral formulations** developed



- **GMP-compliant Master Cell Bank** established

Primary Indication: Treatment of Filariasis

- **CorA has efficacy against *Wolbachia* bacterial endosymbionts of filariae**
  - *in vivo* **depletion of *Wolbachia*** → blocked filarial development, worm death
  - **Kills adult worms**



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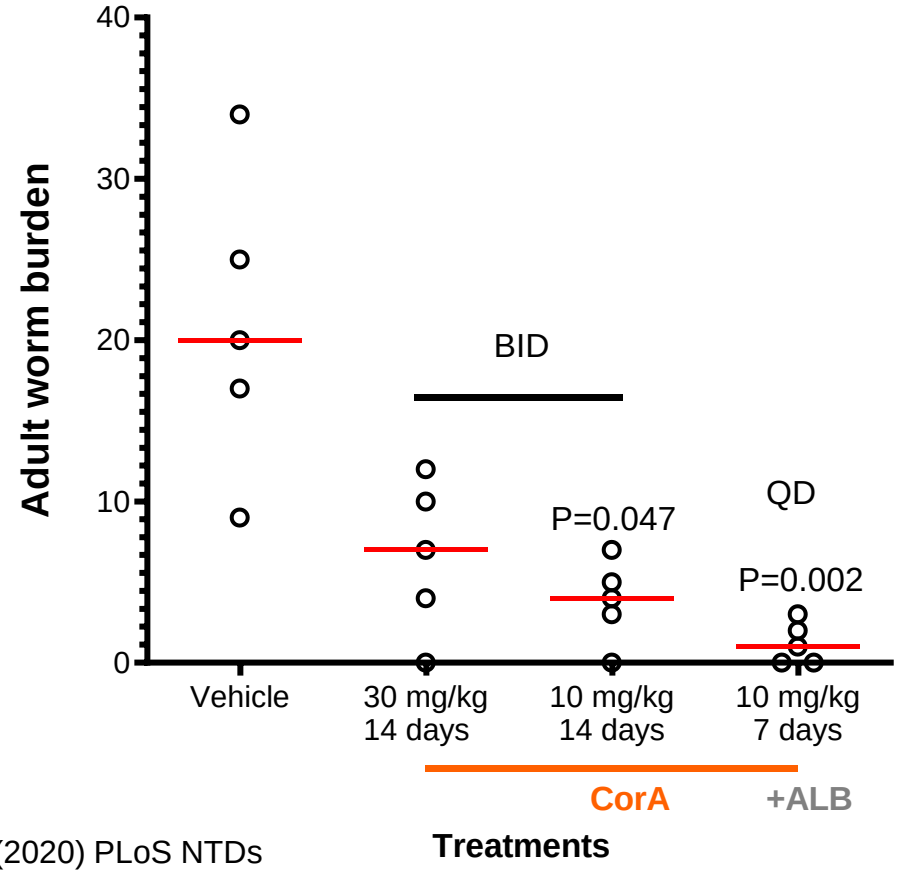
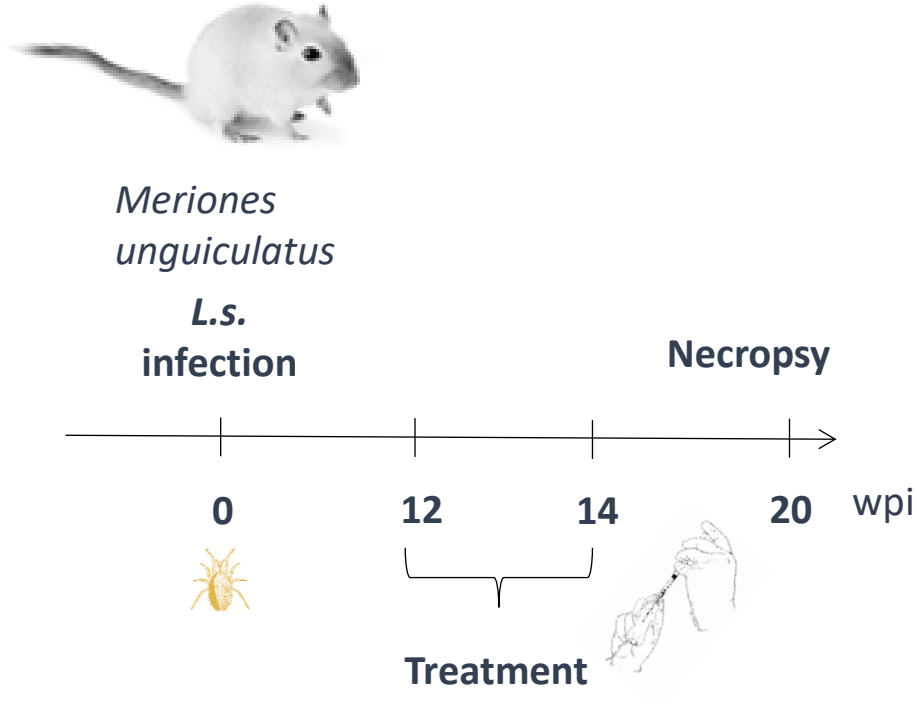


Schiefer et al. (2020) PLoS NTDs



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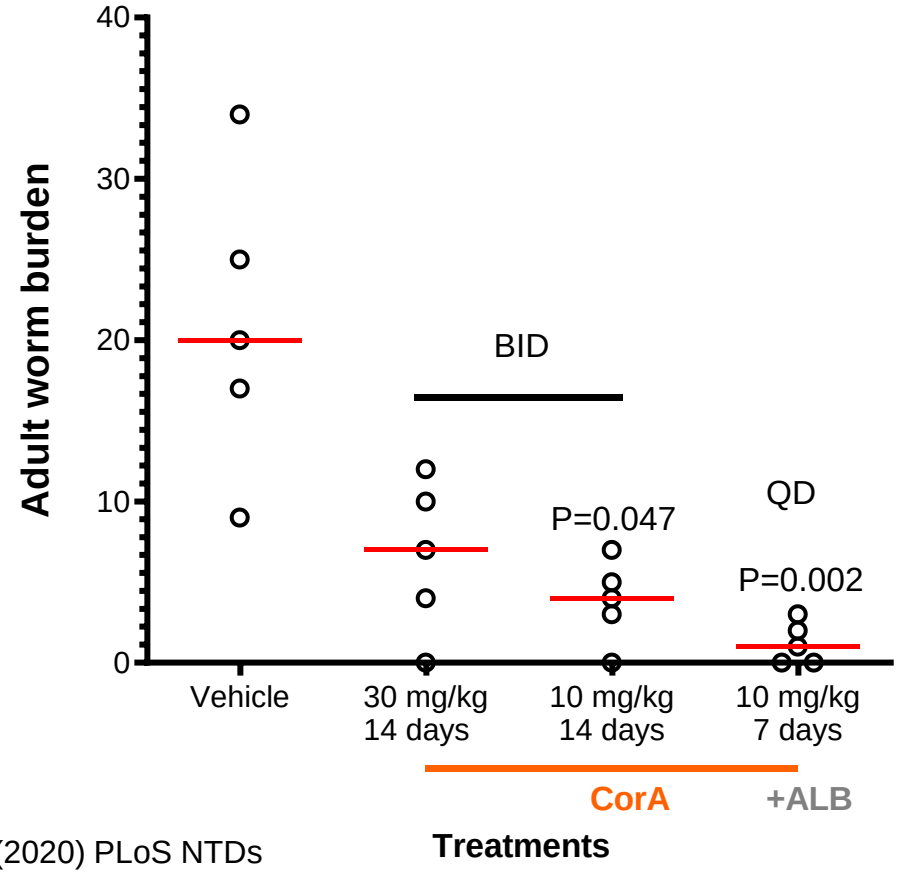


Schiefer et al. (2020) PLoS NTDs

Prediction of HED according to FDA

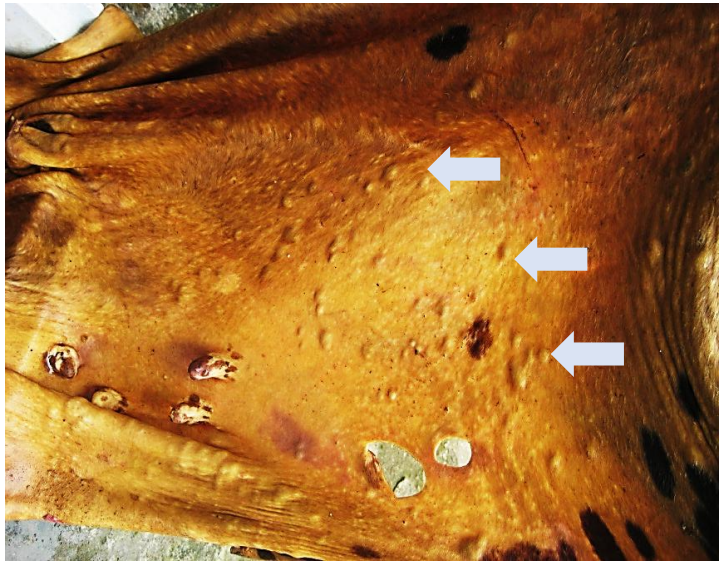
(Guidance for Industry 07/06/05)

Minimal effective dose CorA-PVP, oral	Human
Jird therapy: 30 mg/kg TID 14 days	4 mg/kg
Mouse prophylaxis: 12 mg/kg BID 14days	1.5 mg/kg

Primary Indication: Treatment of Filariasis

➢ ***Onchocerca ochengi*** **in SCID mice**

Hide from infected cattle

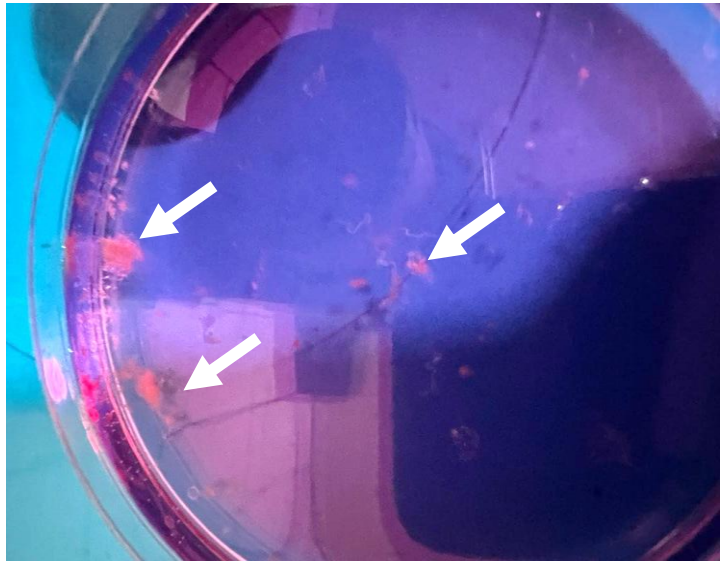


Excision of nodules

Worms/nodules from skin

Implantation and treatment

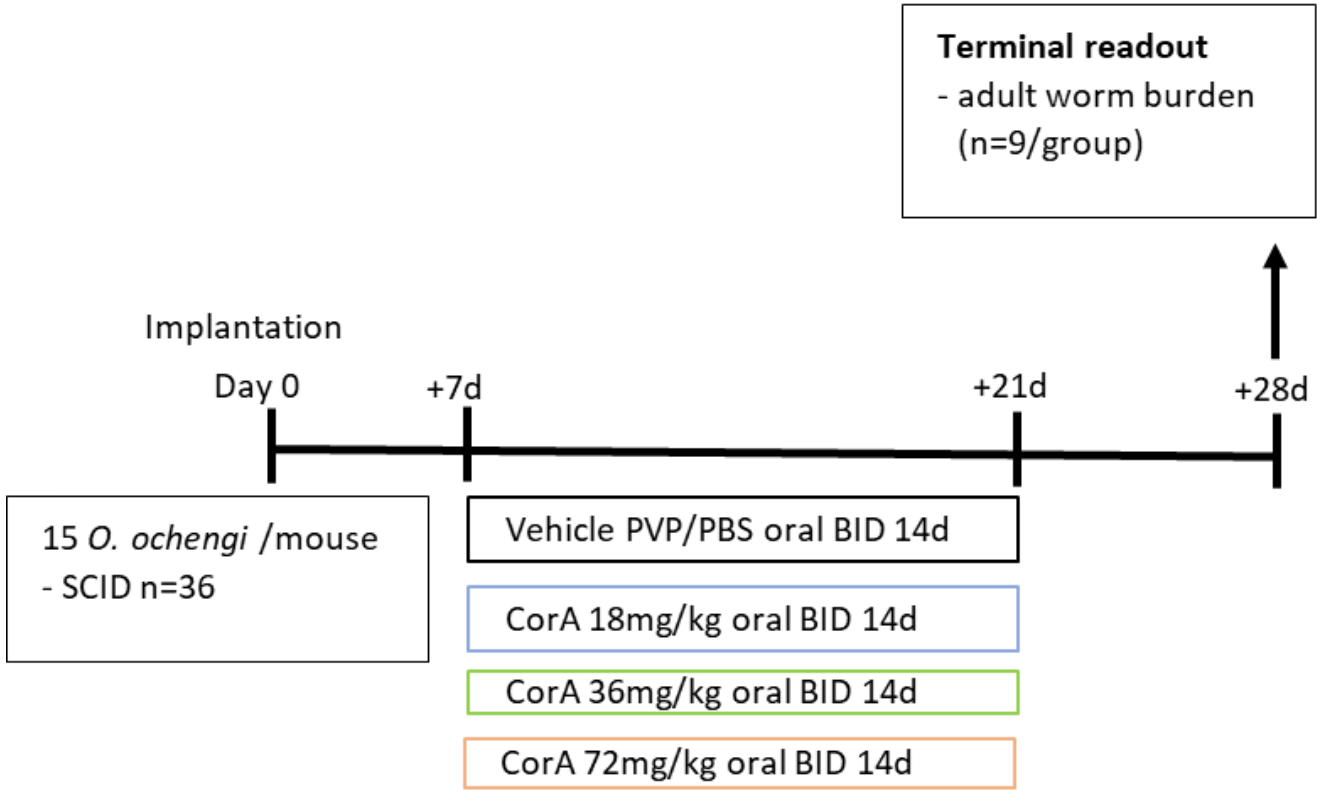
Recovery of worms



Collaboration with Prof. Samuel Wanji
University of Buea, Cameroon

Primary Indication: Treatment of Filariasis

➢ **CorA has efficacy vs *Onchocerca ochengi* in SCID mice**



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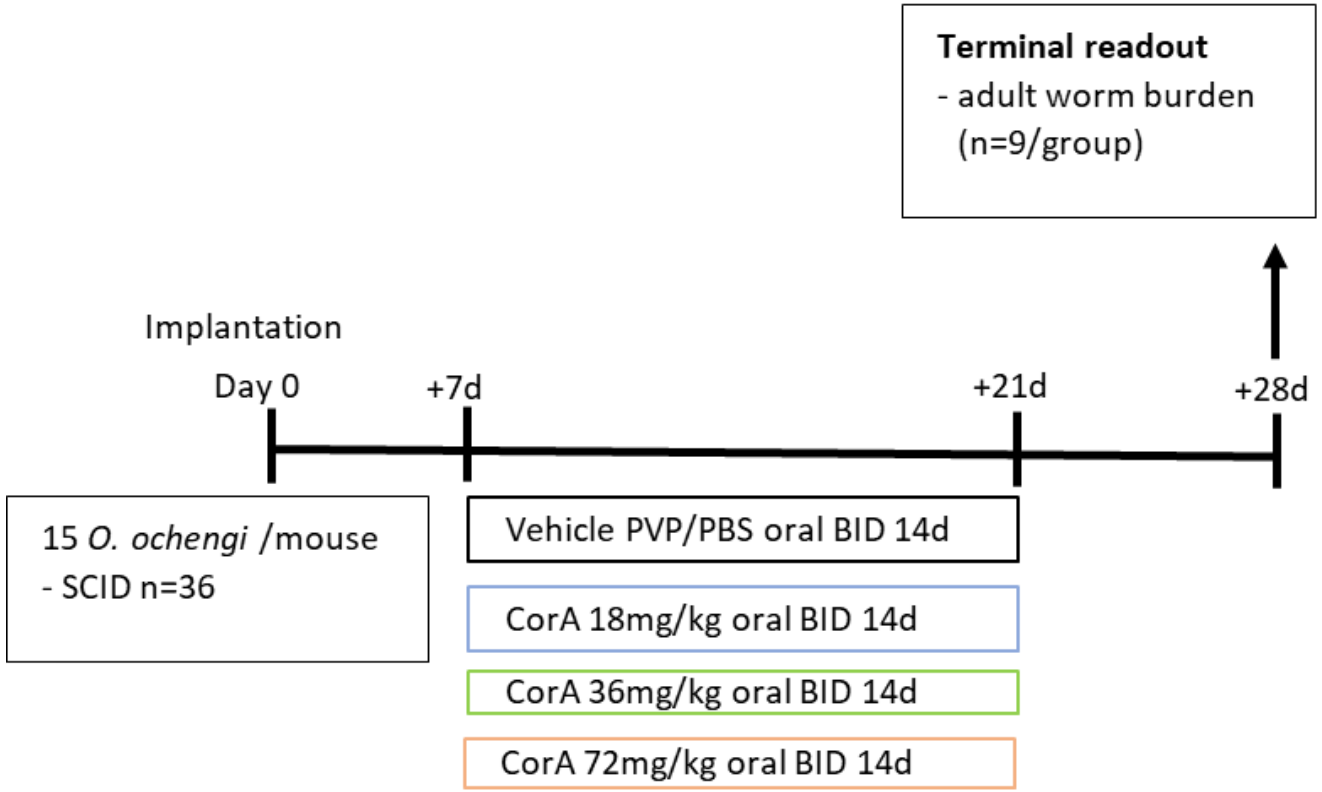
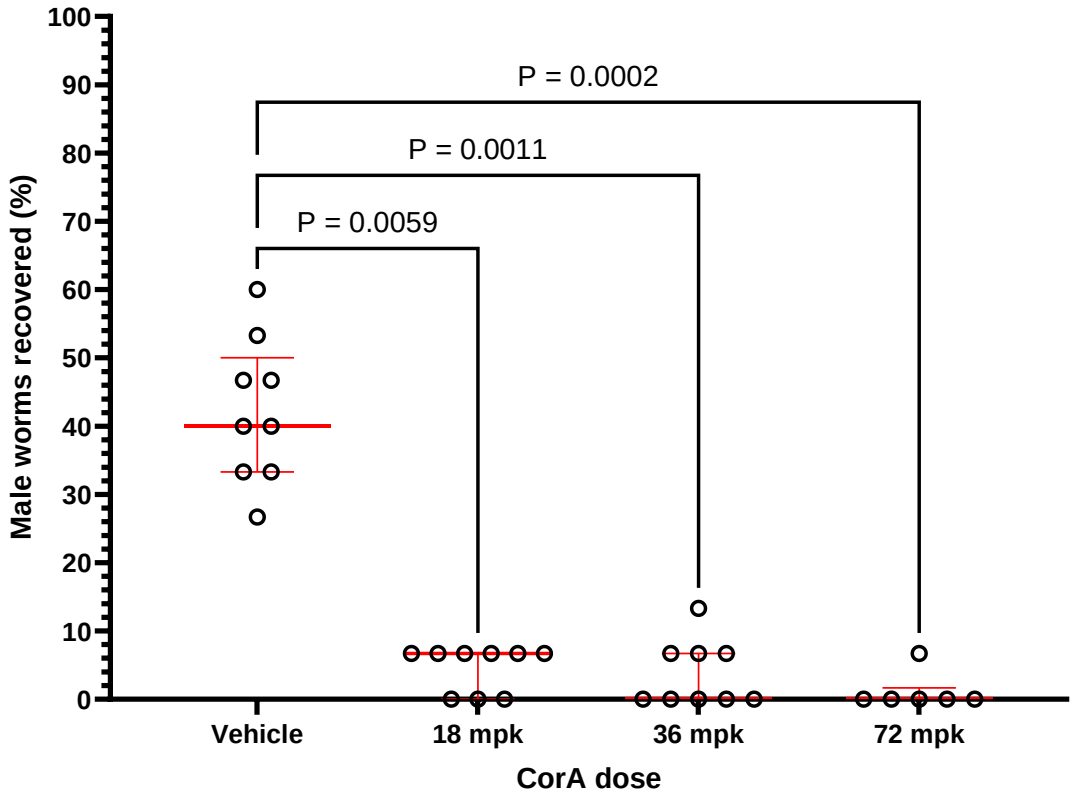




Kruskal-Wallis P < 0.0001; Dunn's multiple comparison shown

Collaboration with Prof. Samuel Wanji
University of Buea, Cameroon

CorA non-GLP *in vitro* and *in vivo* toxicity

In vitro and *in vivo* safety data		Conclusion
Off target profiling		No major events
Cyp inhibition		No inhibition of six recombinant human CYPs; inhibition of 2CP
CYP 3A4 induction via PXR		Minimal inducer: 12 µM CorA vs 1.5 µM Rifampicin, DDI unexpected
Non-GLP Micronucleus		No induction of chromosomal damage, no genotoxicity
Non-GLP AMES (5 strains)		No evidence of genotoxicity
Phototoxicity		No phototoxicity up to limit of solubility (38 µM)
Liver toxicity		No toxicity in hepatocytes from rats or humans (200µM)
Non-GLP hERG		Predicted IC_{50} = > 10 µM
MTD rat		1000 mg/kg; mild clinical symptoms
MTD dog		1000 mg/kg; moderate, transient symptoms
7d repeated-dose rat: 0, 250, 1000 mg/kg/d		**LOAEL**: 250 mg/kg/d, no effects seen
7d repeated-dose dog: 0, 150, 450, 750 mg/kg/d		**NOEL**: 150 mg/kg; [conversion in **HED NOEL** = 83.3 mg/kg]

➢ **CorA has no relevant safety issues**

Corallopyronin A – secondary indications & future

- Effective against ***Neisseria gonorrhoeae, Chlamydia spp.*** and ***Staphylococcus aureus***
  - Effective vs. MDR/XDR clinical strains
    - Balansky et al. (2022) Antibiotics; Edwards et al. (2022) mSphere; Shima et al. (2018) Int J Antimicrob Agents
  - Medium (*S. aureus*) to no (*N. gonorrhoeae* and *Wolbachia* spp.) resistance
    - Balansky et al. (2022) Antibiotics; Balthazar et al. (2024 Microbiol Spectr; Behrman et al. (2024) Int J Antimicrob Agents
- Potential to treat **biofilm-associated bacteria**
- **GLP toxicology and safety pharmacology begin in Q4/2024**
- **Phase 1 study** scheduled for **2026**

HELP
Helminth Elimination Platform


Prof. Hörauf


Dr. Pfarr


Dr. Schiefer


Dr. Risch

Bundesministerium für Bildung und Forschung
HORIZON 2020
EFRE.NRW Investitionen in Wachstum und Beschäftigung
DZIF
Eisai
Else Kröner Fresenius Stiftung

Conclusions Corallopyronin A

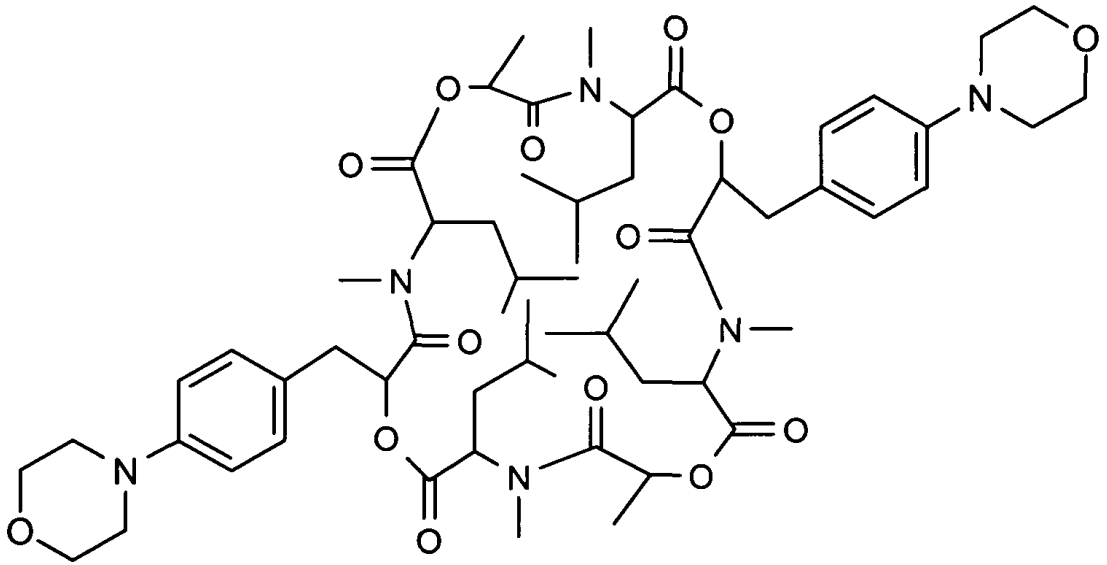
→ **Corallopyronin A** is an anti-*Wolbachia* candidate that allows shorter treatment regimens in comparison to doxycycline

→ **Corallopyronin A** is also effective against *Staphylococcus aureus, Chlamydia spp., Neisseria gonorrhoeae*

Emodepside

Phase 2 clinical trial
for onchocerciasis completed
– results pending

Emodepside - anthelmintic used in cats and dogs



- Emodepside is used in combination with praziquantel (Profender) for the treatment of parasitic worms in cats and dogs

- Inhibits Ca^{2+}-gated K^{+}-channel Slo-1 of nematodes (Kulke et al. PLOS NTDs 2014)

Emodepside - broad activity against filarial species and life cycle stages

in vitro

Filarial species	Life cycle stage	IC_{50} / EC_{50}
Litomosoides sigmodontis	Adult worms	1×10^{-8} M
	L3	9×10^{-9} M
Brugia malayi	MF	9×10^{-9} M
Onchocerca gutturosa	Adult male worms	9×10^{-9} M
Brugia pahangi	Adult female worms	4.3×10^{-7} M
	Adult male worms	6×10^{-8} M

in vivo

Filarial species	Life cycle stage	Dose
Acanthocheilonema viteae	MF clearance	100mg/kg
	Adult worm clearance	100mg/kg
Litomosoides sigmodontis	MF clearance	100mg/kg
	Adult worm clearance	5x 100mg/kg
Brugia malayi	Adult worm clearance	5x 100mg/kg

Krücken et al. PLOS Pathog 2021

Hübner et al. Int J Parasitol Drugs Drug Resist 2021

Emodepside Phase II trial for Treatment of Onchocerciasis as well as *T. trichiura* and hookworm infections

Phase 2 clinical studies performed:

- **onchocerciasis patients**

Concentration	Treatment duration
15 mg QD	1 day
30 mg QD	1 day
15 mg QD	7 days
15 mg QD	14 days
15 mg BID	10 days

- ***Trichuris trichiura*** and **hookworm patients**

Concentration (single treatment)
5 mg QD
10 mg QD
15 mg QD
20 mg QD
25 mg QD
30 mg QD

Emodepside Phase II trial for Treatment of Onchocerciasis as well as *T. trichiura* and hookworm infections

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DNDi
Drugs for Neglected Diseases *initiative*

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Swiss TPH

The NEW ENGLAND JOURNAL of MEDICINE

05/2023

ORIGINAL ARTICLE

Emodepside for *Trichuris trichiura* and Hookworm Infection

Emmanuel C. Mrimi, M.Sc., Sophie Welsche, Ph.D., Said M. Ali, M.Sc., Jan Hattendorf, Ph.D., and Jennifer Keiser, Ph.D.

Conclusions emodepside

→ **Emodepside** is a pan-nematode drug candidate, which targets all life-cycle stages of filariae, including microfilariae

Oxfendazole

Phase 2 clinical trial
scheduled for 2025

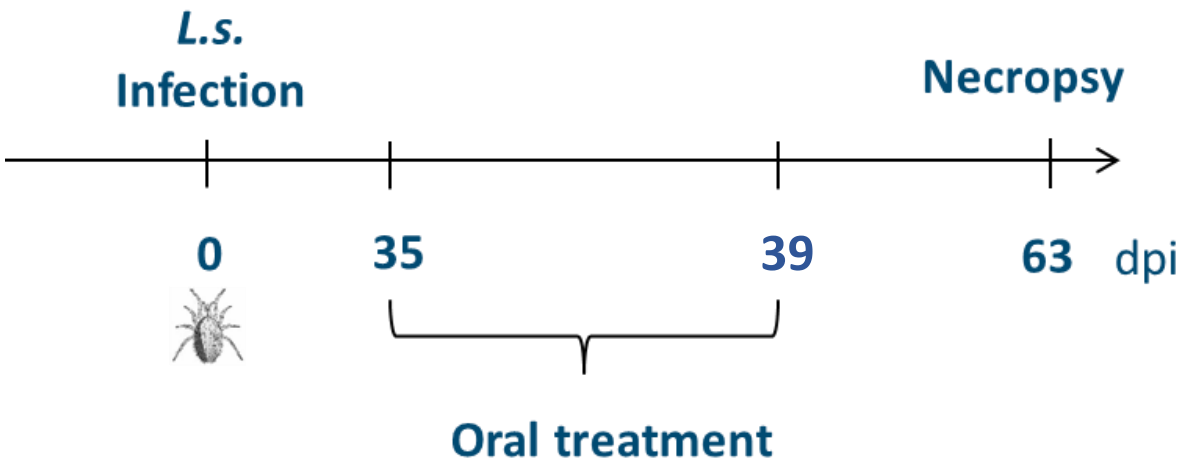
Oxfendazole

- **Broad spectrum anthelmintic** used as dewormer in the veterinary field
- **Multiple ascending dose phase 1 studies** using up to 15 mg/kg for 5 days were **completed** (Bach et al. 2020)
- **Field applicable formulation** developed by DNDi via USAID
- **Bioavailability study** was performed in Tanzania via HELP

→ **Pan-nematode candidate**: efficacy against filariae and STH?

Assessment of the oxfendazole efficacy in the *Litomosoides sigmodontis* model

BALB/c J
females



Assessment of the oxfendazole efficacy in the *Litomosoides sigmodontis* model

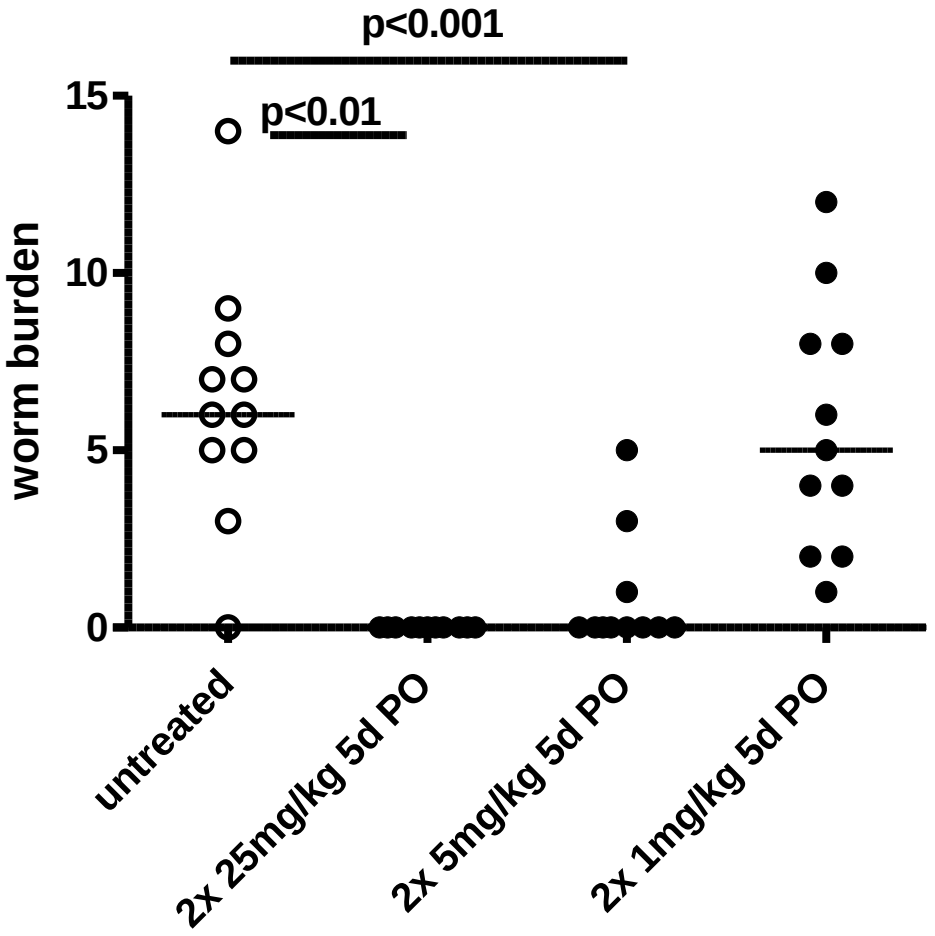
BALB/c J females

L.s. **Infection**

Necropsy

0 **35** **39** **63** dpi

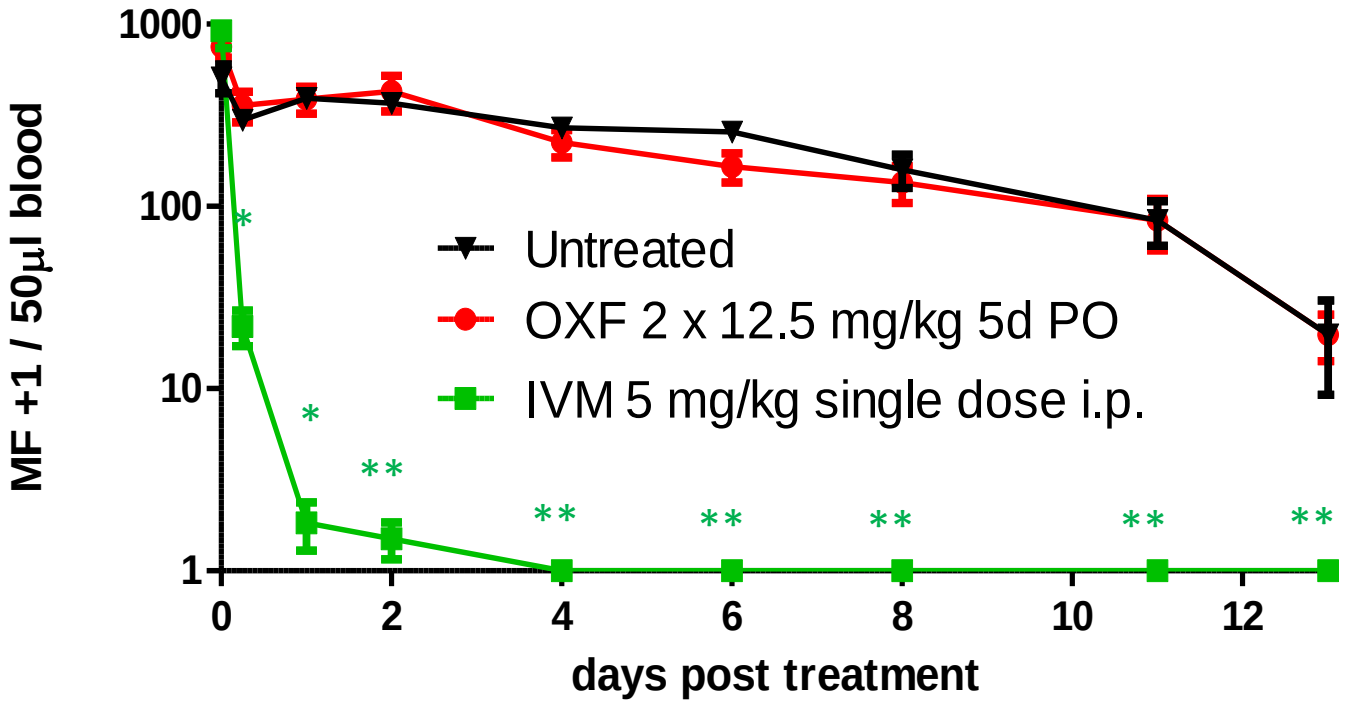
Oral treatment



→ **Oral oxfendazole treatment provides sterile cure**

Hübner et al. PLOS NTDs 2020

In vivo assessment of the direct microfilaricidal efficacy of oxfendazole



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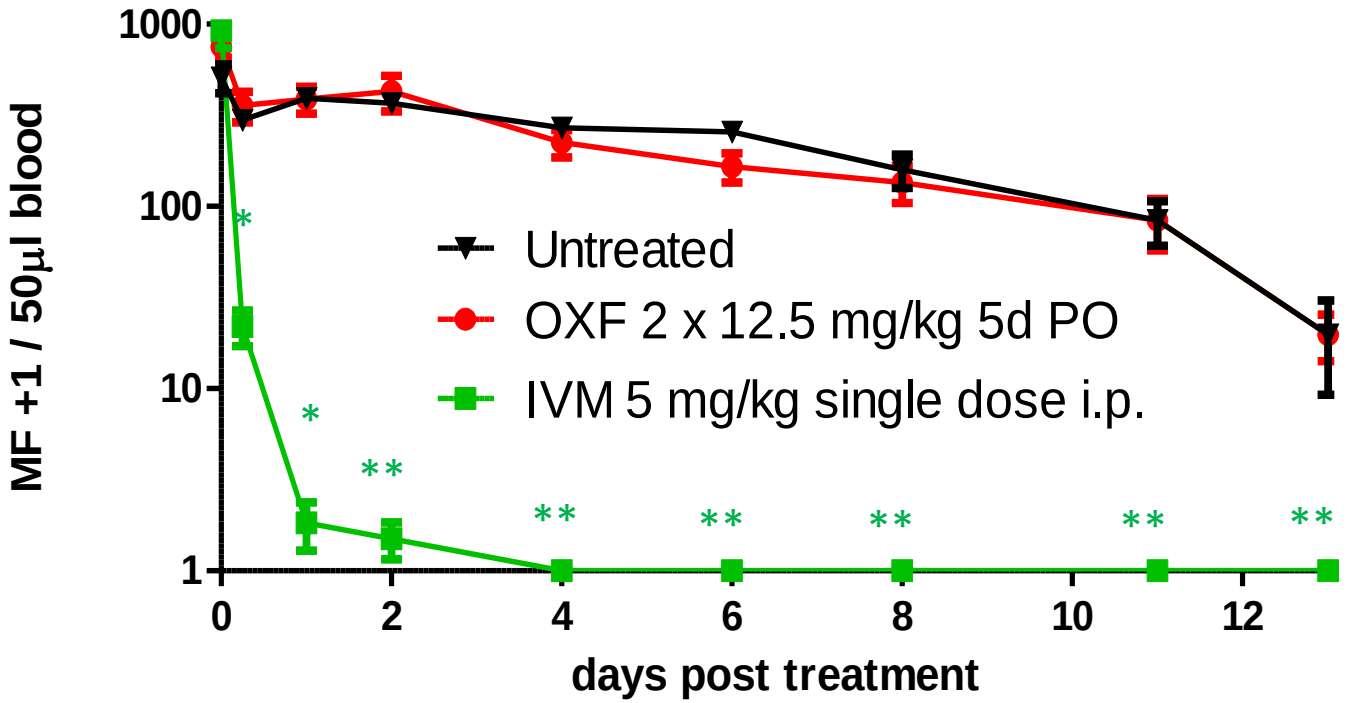

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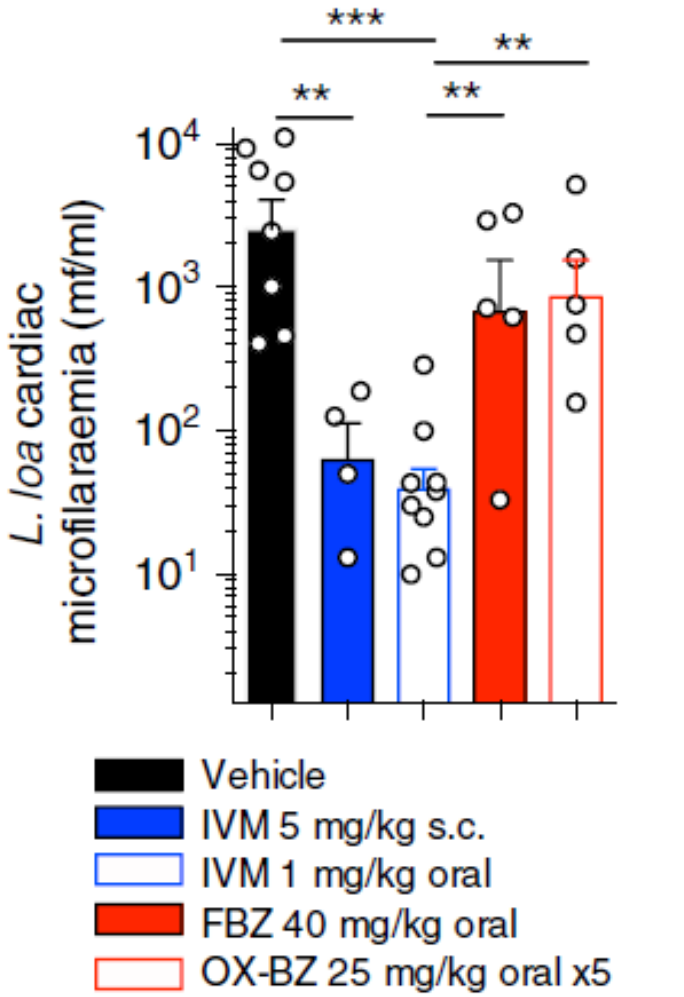

Pionnier et al. Nat Commun 2019

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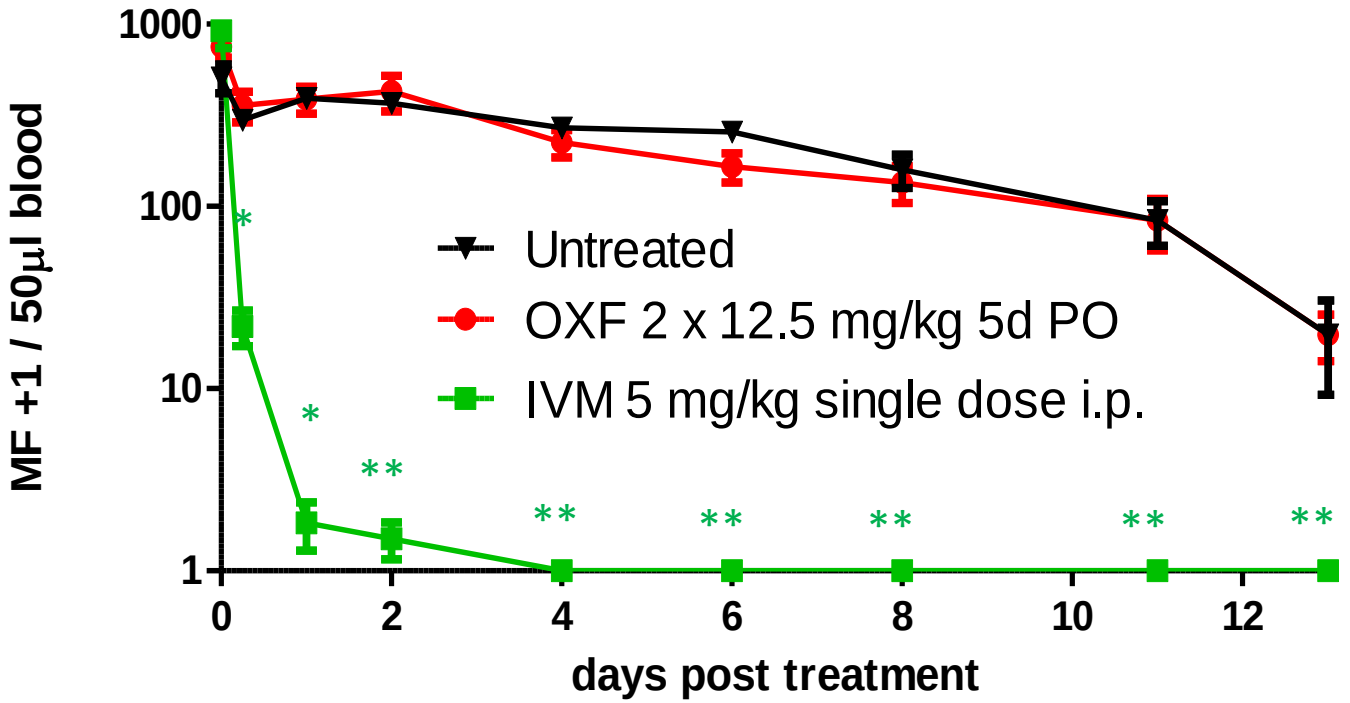

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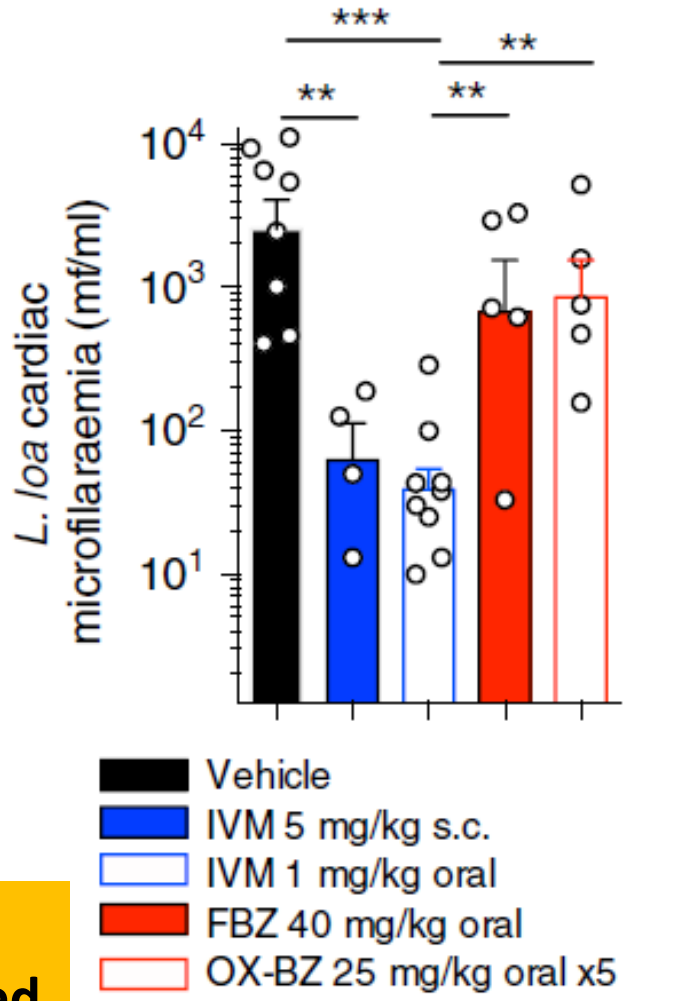

Pionnier et al. Nat Commun 2019

→ Oral oxfendazole treatment has **no strong direct microfilaricidal efficacy**
→ **No microfilariae-induced SAE** in onchocerciasis & loiasis patients **expected**
→ **Potential macrofilaricidal candidate for loiasis**

eWHORM

www.ewhorm.org

Global Health EDCTP3

Co-funded by the European Union

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Eliminating Worm Infections in Sub-Saharan Africa and **e**nabeling the **WHO R**oad **M**ap 2030

enabling the WHO Road Map

Common problems across helminthiases

- **Lack** of **drug pipeline**
- **Drug development** is **complex, risky** and **expensive**
- Current model: **testing one target, one drug at a time**

enabling the WHO Road Map

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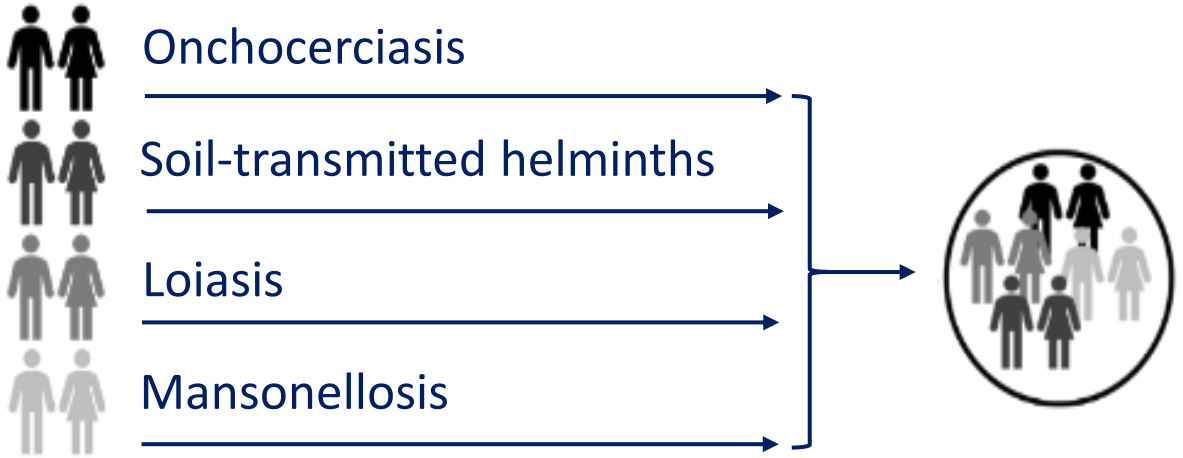
Adaptive basket trial design: A collaborative approach to R&D

- **One candidate** – **multiple indications** at the same time (!)

Oxfendazole – multiple indications at the same time



enabling the WHO Road Map

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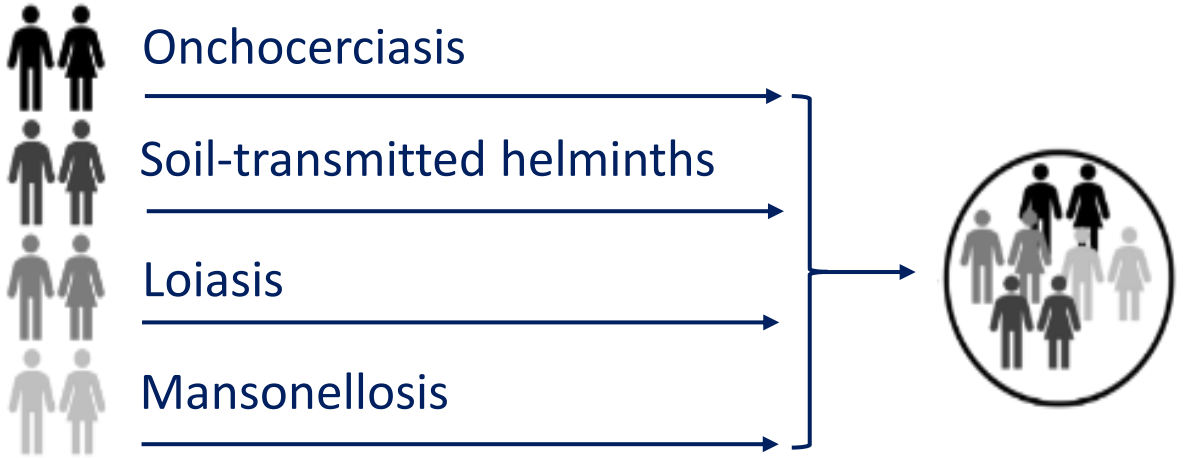
Adaptive basket trial design: A collaborative approach to R&D

- **One candidate** – **multiple indications** at the same time (!)
- **Minimizing number** of **trial participants**
  - **Reduce** the need of **redundant trials**
  - **Patient centricity** (coinfection)
  - **Mid-course adaptations** to avoid repetition
  - Detection of **country-specific drug differences**

Oxfendazole – multiple indications at the same time



Adaptive clinical trial platform in Gabon, Cameroon, Democratic Republic of the Congo and Tanzania

enabling the WHO Road Map

Common problems across helminthiases

- **Lack** of **drug pipeline**
- **Drug development** is **complex, risky** and **expensive**
- Current model: **testing one target, one drug at a time**

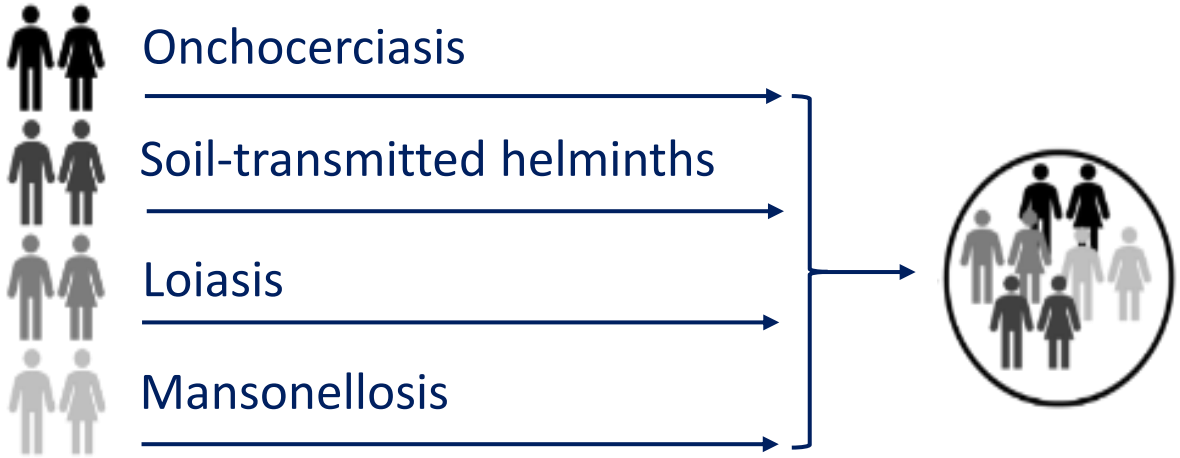
Adaptive basket trial design: A collaborative approach to R&D

- **One candidate** – **multiple indications** at the same time (!)
- **Minimizing number** of **trial participants**
  - **Reduce** the need of **redundant trials**
  - **Patient centricity** (coinfection)
  - **Mid-course adaptations** to avoid repetition
  - Detection of **country-specific drug differences**

- Allow academics/pharma/NGO to **collaborate**
- Expedite drugs to market and more **quick decisions** overall

→ Proof of concept for the **pan-nematode** drug candidate **oxfendazole**

Oxfendazole – multiple indications at the same time



Adaptive clinical trial platform in Gabon, Cameroon, Democratic Republic of the Congo and Tanzania

Conclusions oxfendazole

→ **Oxfendazole** is the only drug candidate with a predicted **selective adulticidal efficacy** and the only **macrofilaricidal candidate** available for ***Loa loa***

→ **Phase 2 clinical trial in STH, onchocerciasis, loiasis** and **mansonellosis patients** scheduled for **2025**

Global Health EDCTP3
Co-funded by the European Union
Schweizerische Eidgenossenschaft
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Confederazione Svizzera
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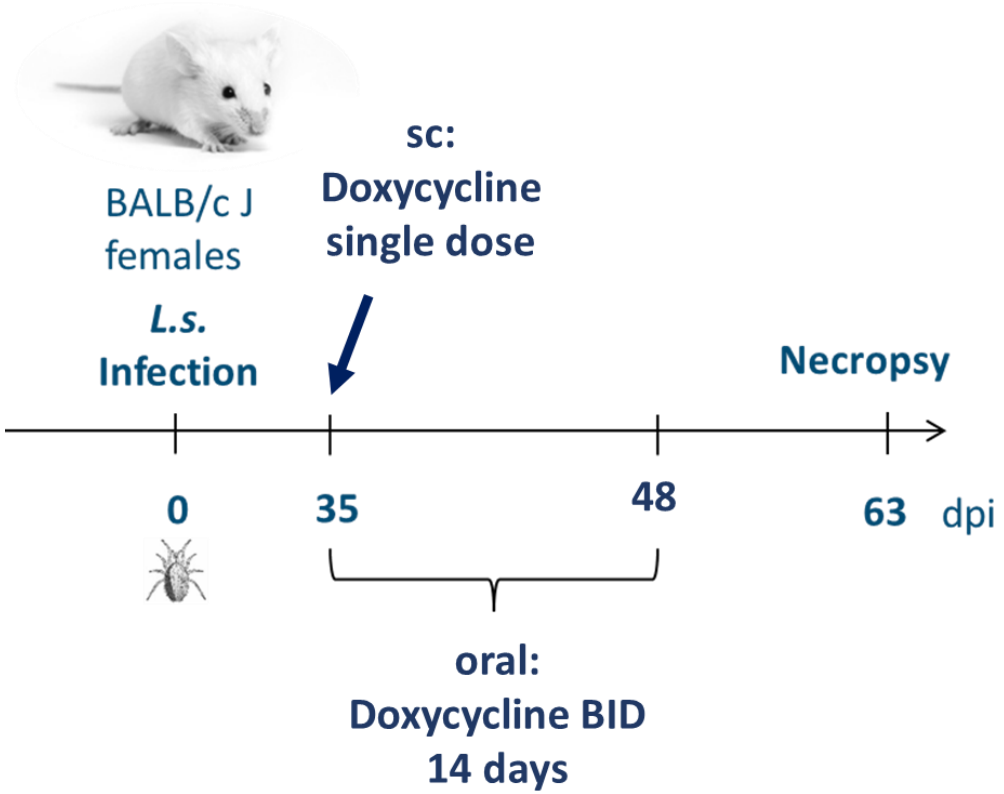
Improvement of treatments

Development of a parenteral controlled release formulation of doxycycline and oxfendazole

Doxycycline controlled release formulation improves *Wolbachia* reduction after single injection in *L. sigmodontis*-infected mice



Martin-Luther-Universität
Halle-Wittenberg

Prof. Karsten Mäder

Doxycycline controlled release formulation improves *Wolbachia* reduction after single injection in *L. sigmodontis*-infected mice

BALB/c J females

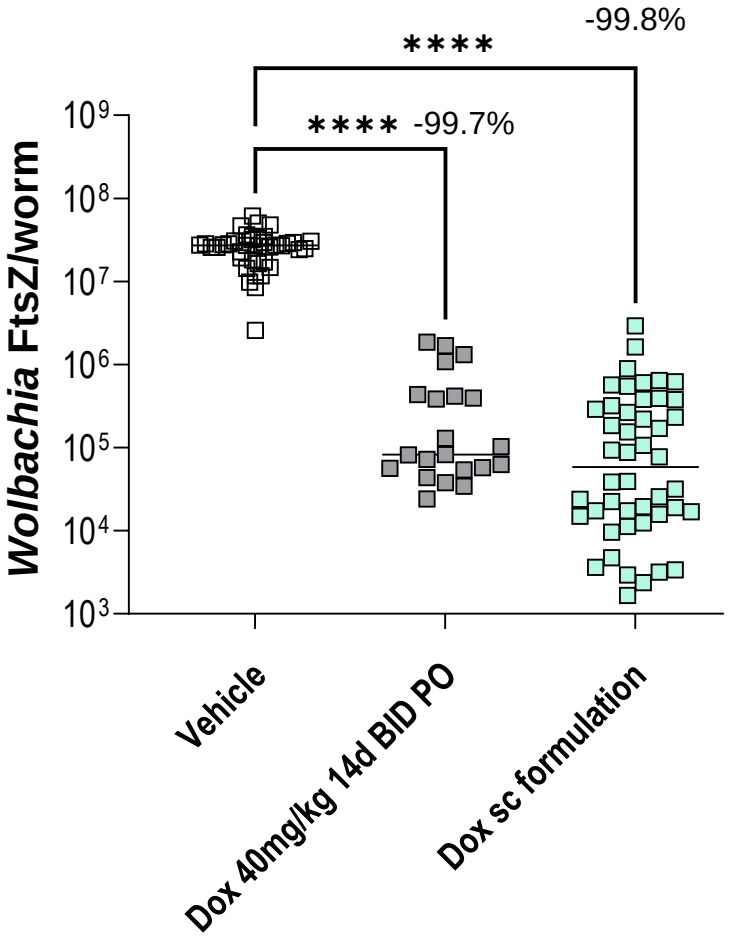
L.s. Infection

sc: Doxycycline single dose

Necropsy

0 35 48 63 dpi

oral: Doxycycline BID 14 days



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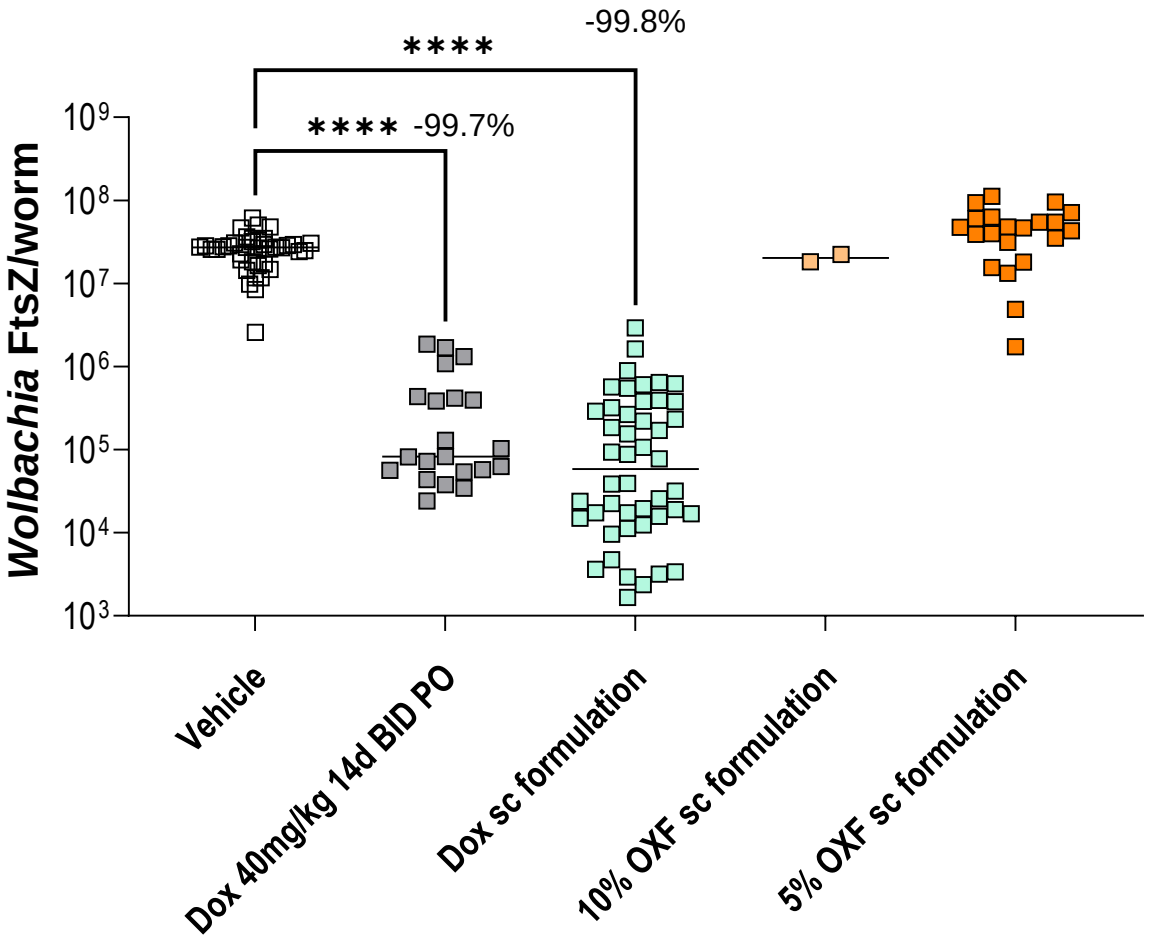


Martin-Luther-Universität Halle-Wittenberg

Prof. Karsten Mäder

Oxfendazole controlled release formulation improves worm clearance after single injection in *L. sigmodontis*-infected mice

BALB/c J females

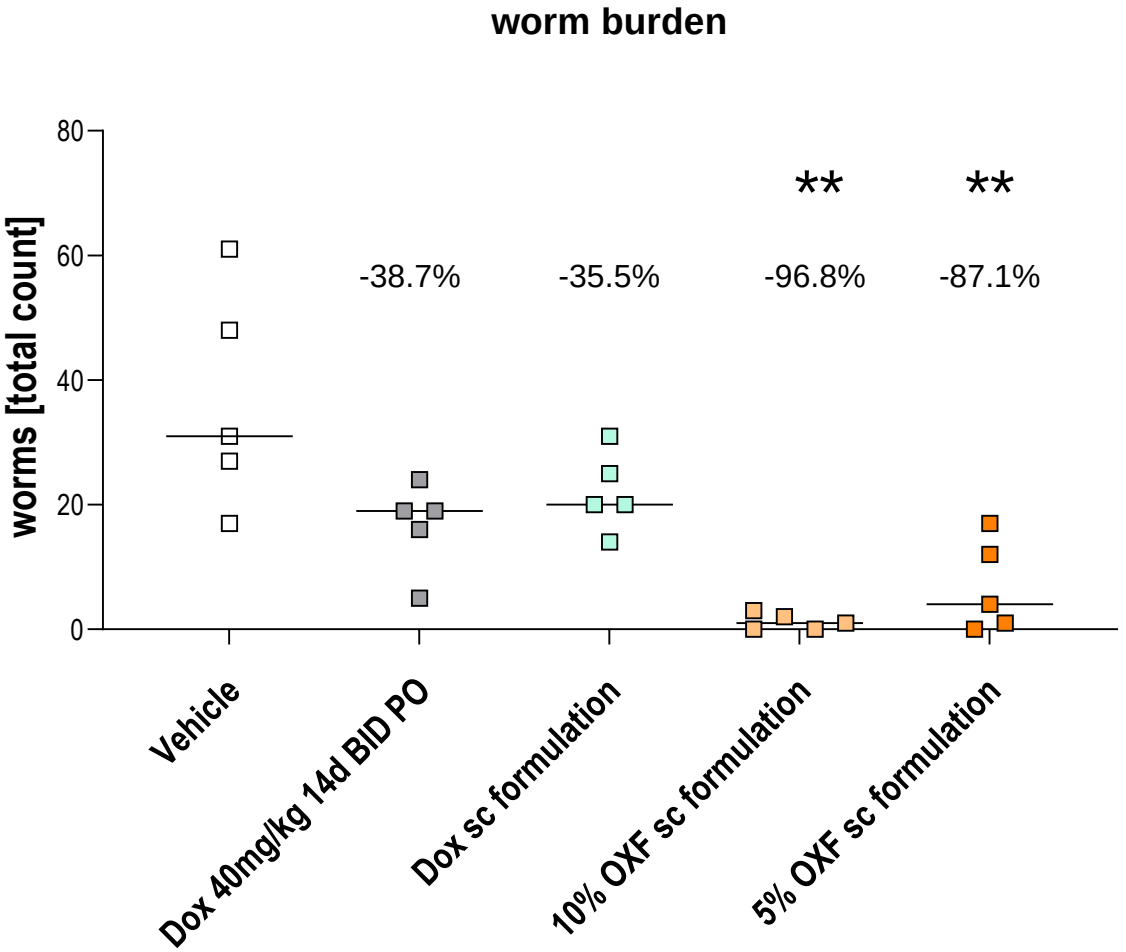
L.s. Infection

sc: Doxycycline single dose

Necropsy

0 35 48 63 dpi

oral: Doxycycline BID 14 days



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Prof. Karsten Mäder

Controlled release formulation for single dose treatments

→ Single parenteral controlled release formulations are possible

→ Optimization of the formulation is ongoing

→ Similar formulations are possible for other candidates (e.g. Corallopyronin A)

Combinations of anti-wolbachials & benzimidazoles

PNAS

Albendazole and antibiotics synergize to deliver short-course anti-*Wolbachia* curative treatments in preclinical models of filariasis

Joseph D. Turner[a,1], Raman Sharma[a,1], Ghaith Al Jayoussi[a], Hayley E. Tyrer[a], Joanne Gamble[a], Laura Hayward[a], Richard S. Priestley[a], Emma A. Murphy[a], Jill Davies[a], David Waterhouse[a], Darren A. N. Cook[a], Rachel H. Clare[a], Andrew Cassidy[a], Andrew Steven[a], Kelly L. Johnston[a], John McCall[b], Louise Ford[a], Janet Hemingway[a,2], Stephen A. Ward[a], and Mark J. Taylor[a]

[a]Research Centre for Drugs and Diagnostics, Department of Parasitology, Liverpool School of Tropical Medicine, Liverpool L3 5QA, United Kingdom; and [b]TRS Laboratories, Athens, GA 30605

→ **Combination** of anti-wolbachials with benzimidazoles allow **shorter treatment regimens** and treatments with **lower doses**

frontiers | Frontiers in Microbiology

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Combinations of the azaquinazoline anti-*Wolbachia* agent, AWZ1066S, with benzimidazole anthelmintics synergise to mediate sub-seven-day sterilising and curative efficacies in experimental models of filariasis

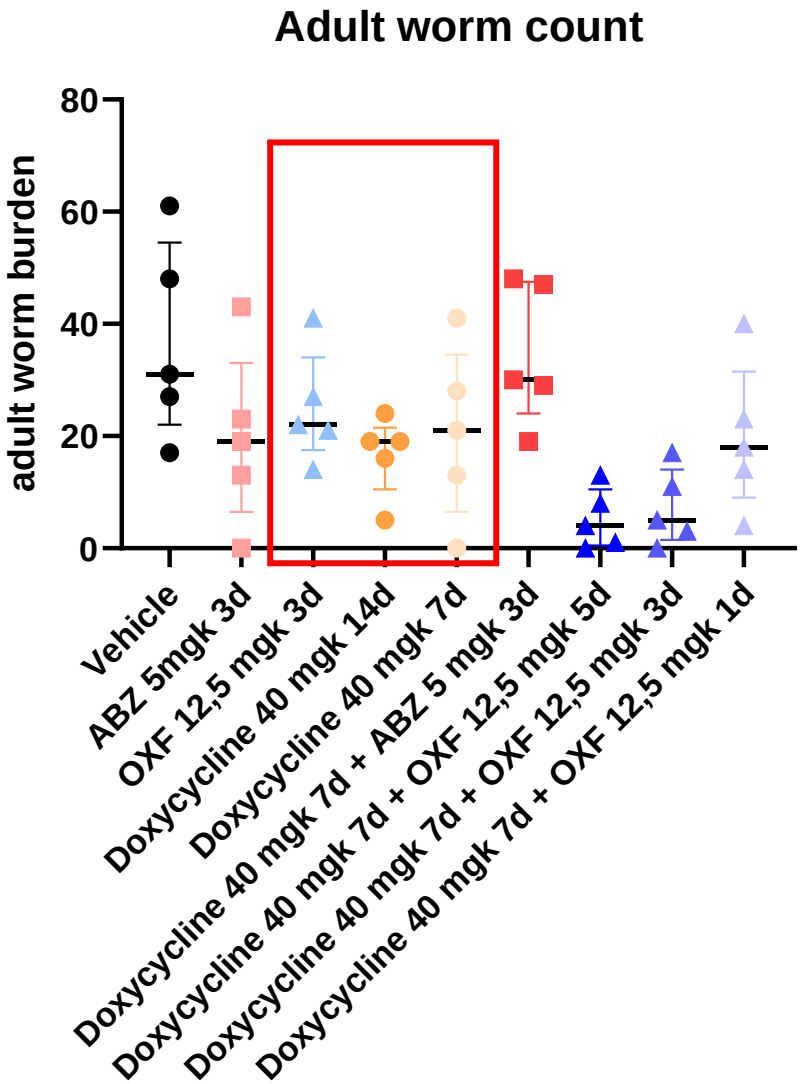
Shrilakshmi Hegde[1], Amy E. Marriott[1], Nicolas Pionnier[1†], Andrew Steven[1], Christina Bulman[2], Emma Gunderson[2], Ian Vogel[2], Marianne Koschel[3], Alexandra Ehrens[3], Sara Lustigman[4], Denis Voronin[4†], Nancy Tricoche[4], Achim Hoerauf[3,5], Marc P. Hübner[3,5], Judy Sakanari[2], Ghaith Aljayyoussi[1†], Fabian Gusovsky[6], Jessica Dagley[1], David W. Hong[7], Paul O'Neill[7], Steven A. Ward[1], Mark J. Taylor[1] and Joseph D. Turner[1*]

Combinations of doxycycline and oxfendazole

BALB/c J
females

L.s.
Infection

Hannah Wegner



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Oral treatment

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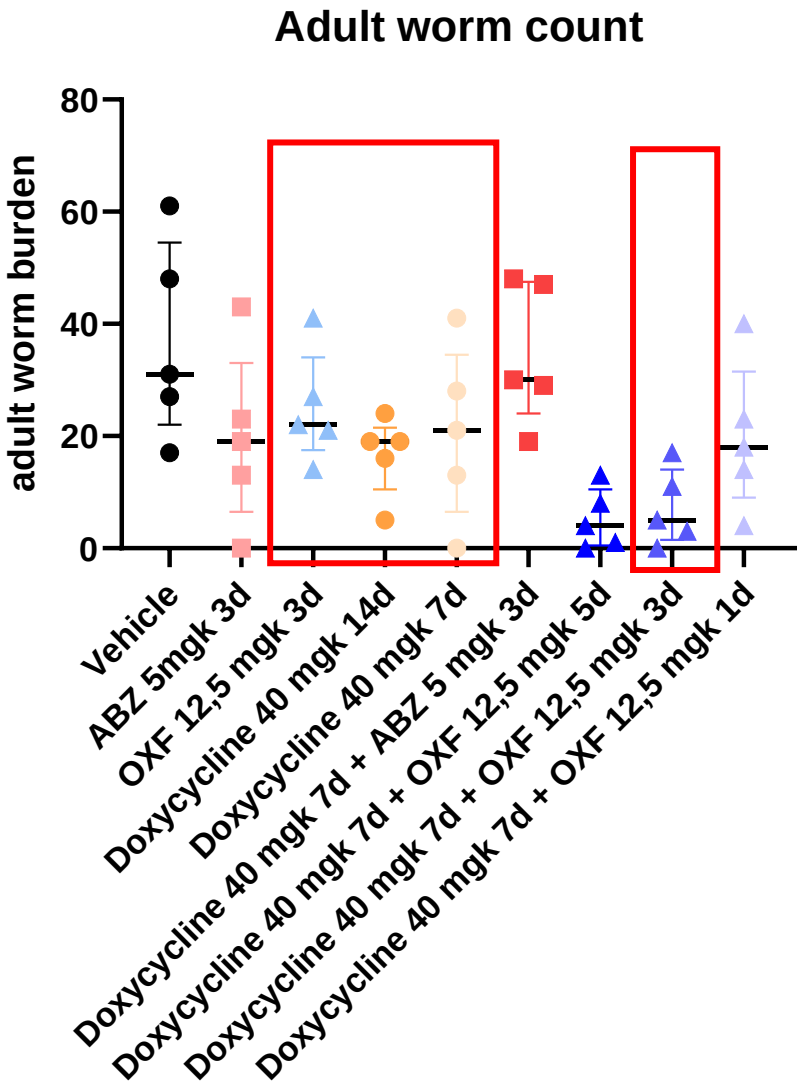

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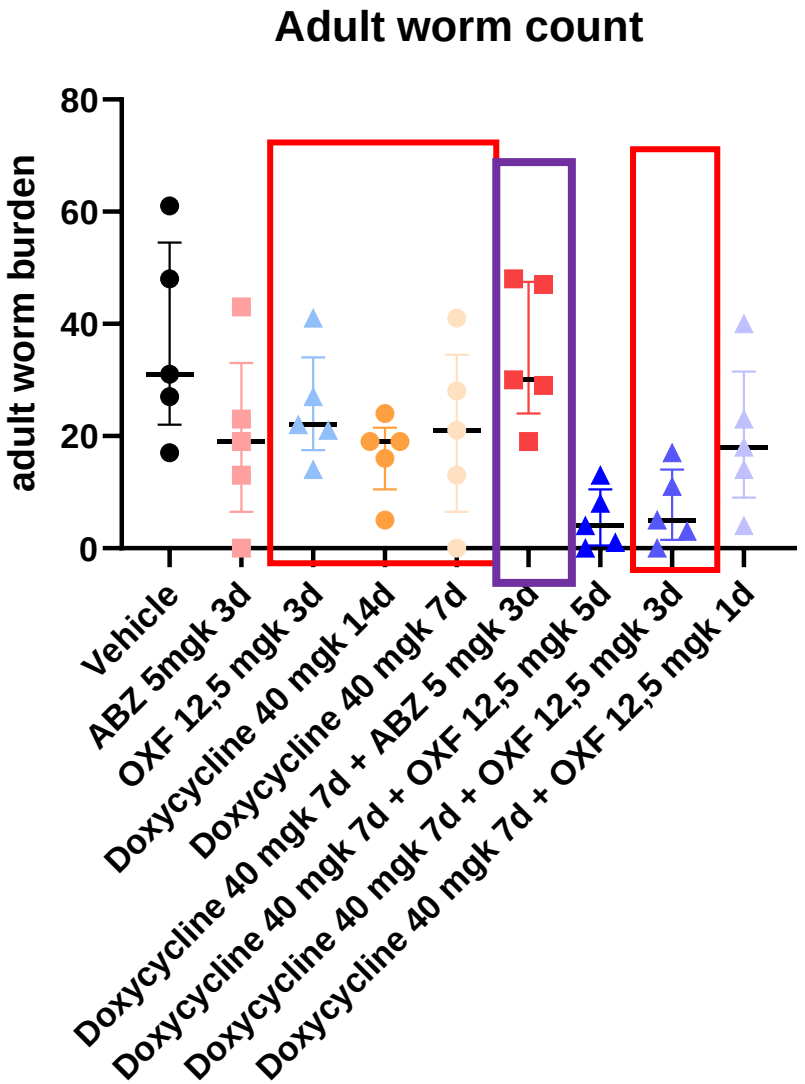

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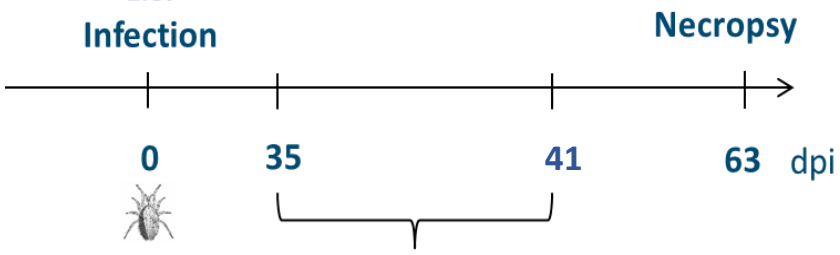

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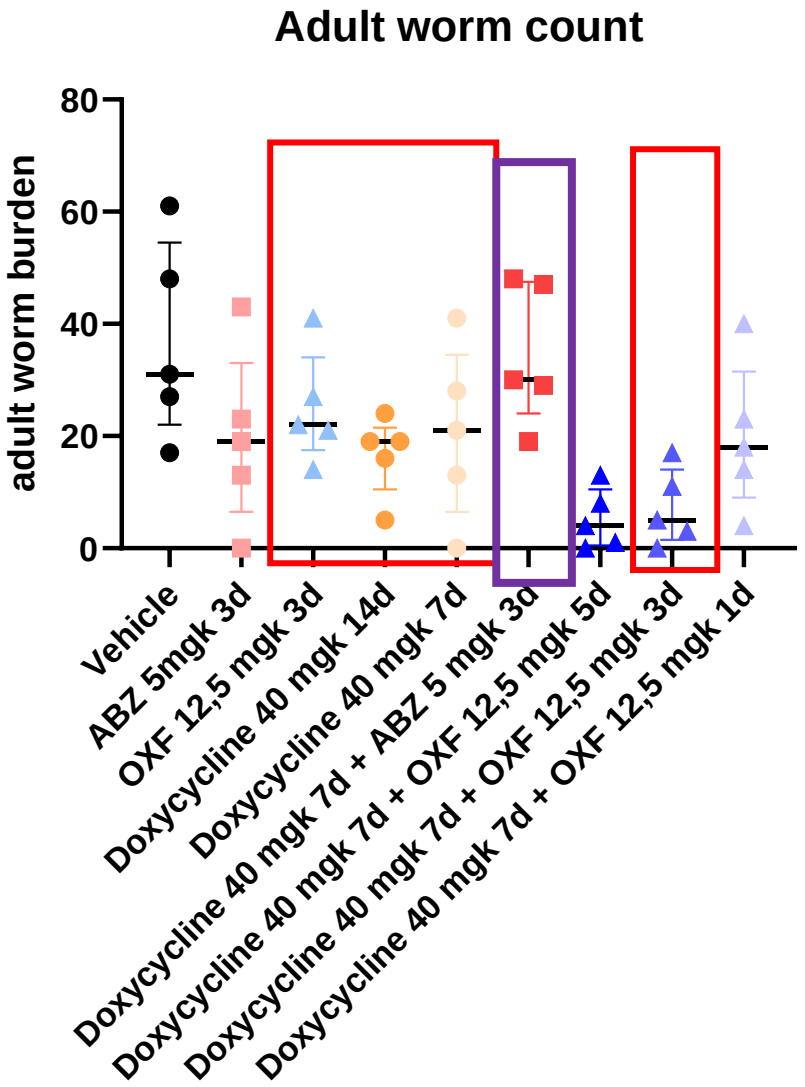
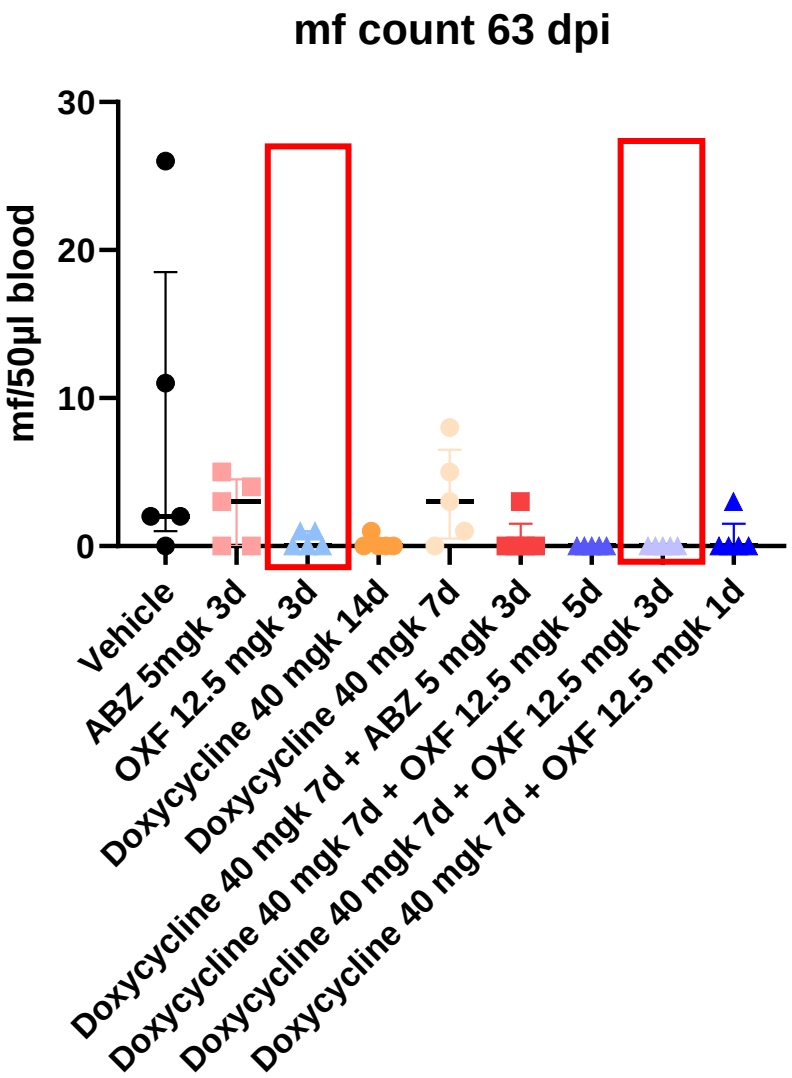
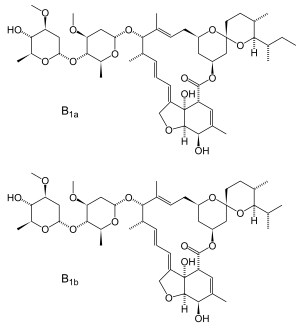




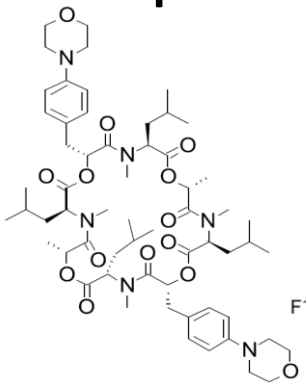
Immune stimuli to improve oxfendazole efficacy?

Involvement of immune responses on drug efficacy?

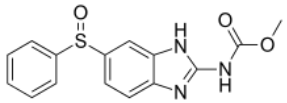
Ivermectin



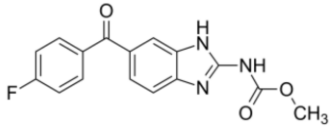
Emodepside

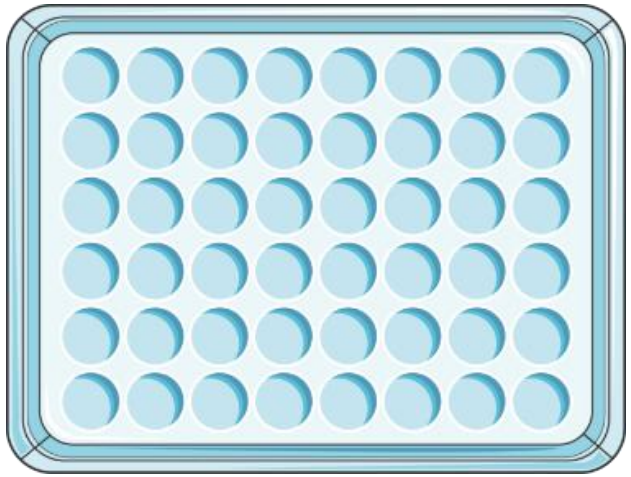


Oxfendazole

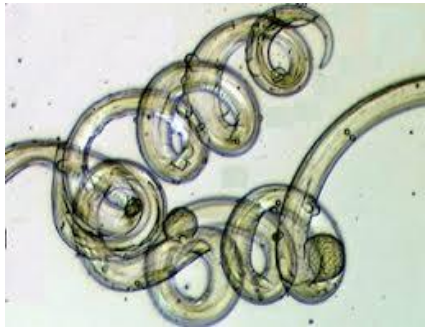


Flubendazole



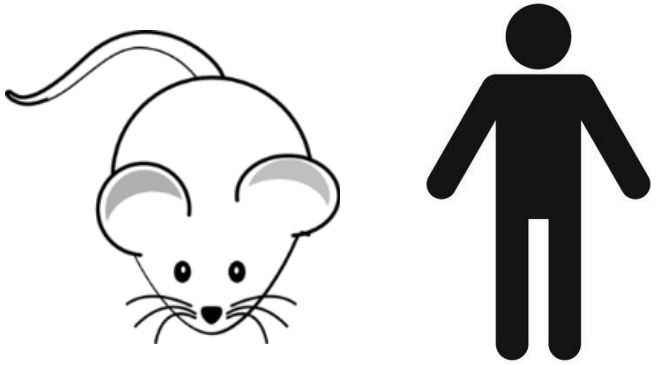


Many anthelmintics have **limited efficacy *in vitro*…**



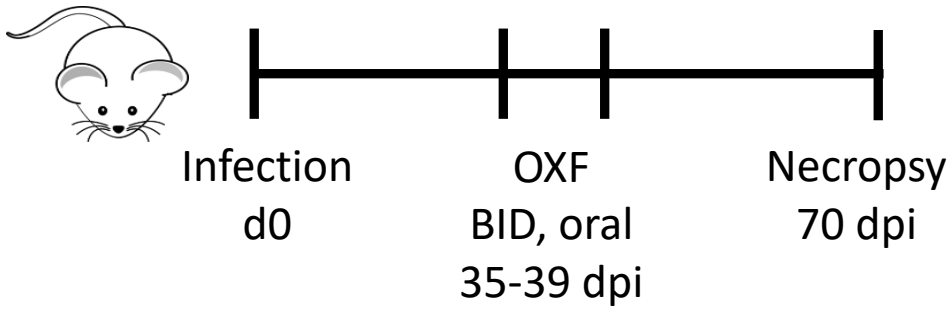
Hypothesis
Anthelmintics require the immune system for an effective response

Dr. Risch

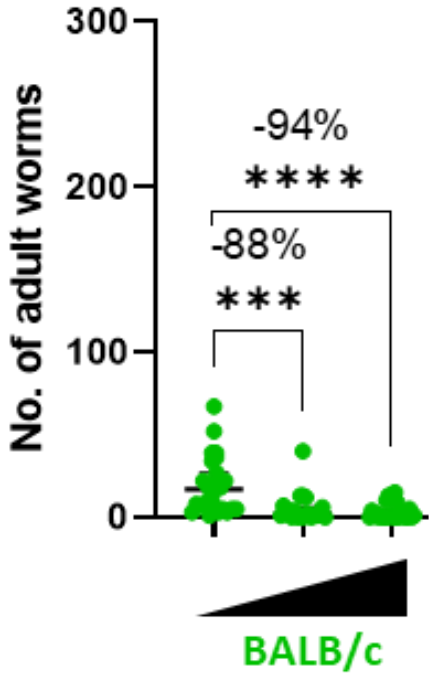


… but are **efficacious *in vivo***

Involvement of immune responses on drug efficacy?



Oxfendazole 5d BID	5 mg/kg	12.5 mg/kg
	% worm free	% worm free
BALB/c	22.2%	50.0%



- BALB/c: wild-type

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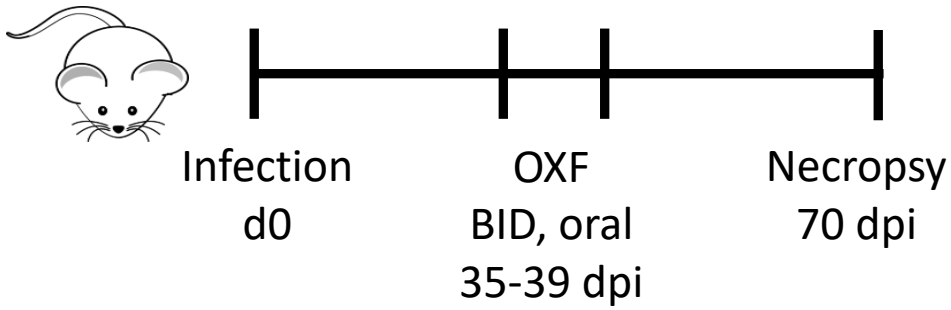
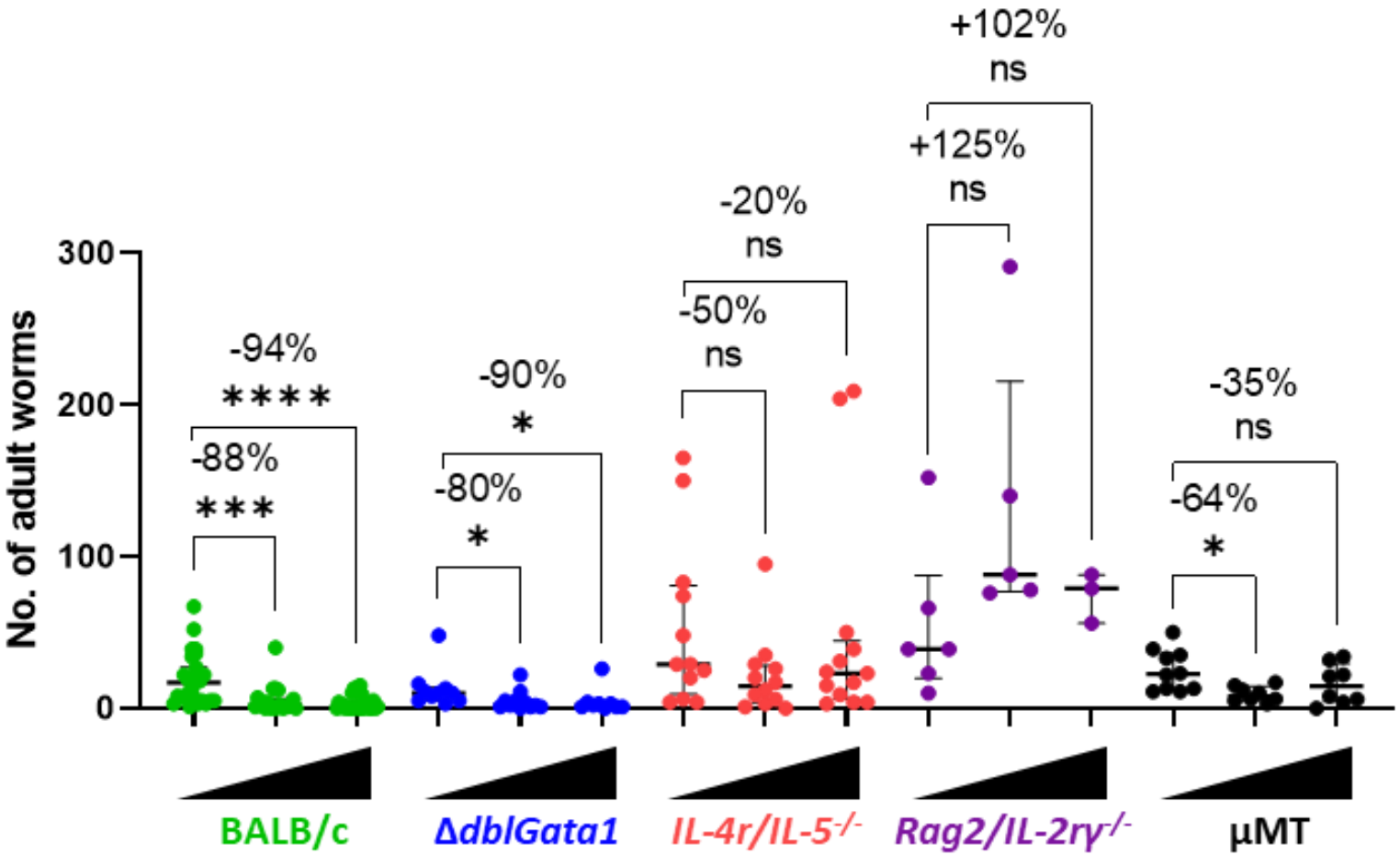
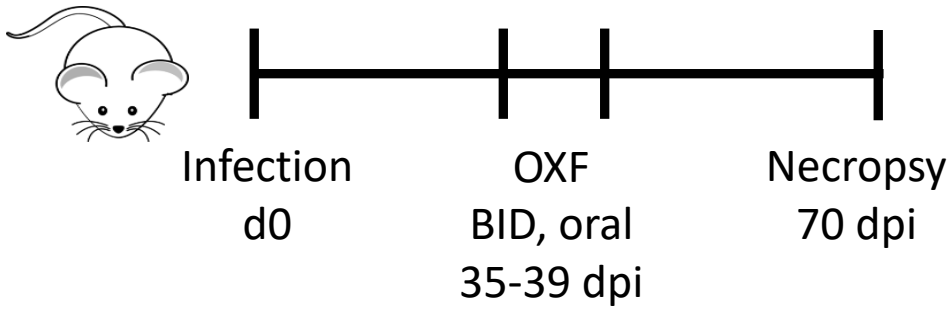


Oxfendazole 5d BID	5 mg/kg	12.5 mg/kg
	% worm free	% worm free
BALB/c	22.2%	50.0%
dblGATA	9.1%	11.1%
IL-4R/IL-5 $^{-/-}$	0.0%	0.0%
RAG2/IL-2Rγ	0.0%	0.0%
µMT	0.0%	11.1%



- BALB/c: wild-type
- dblGATA: no eosinophils
- IL-4R/IL-5$^{-/-}$: no eosinophils and M2 macrophages
- RAG2/IL-2Rγ$^{-/-}$: no T, B & NK cells and no ILCs
- µMT: no mature B cells and antibodies

Involvement of immune responses on drug efficacy?



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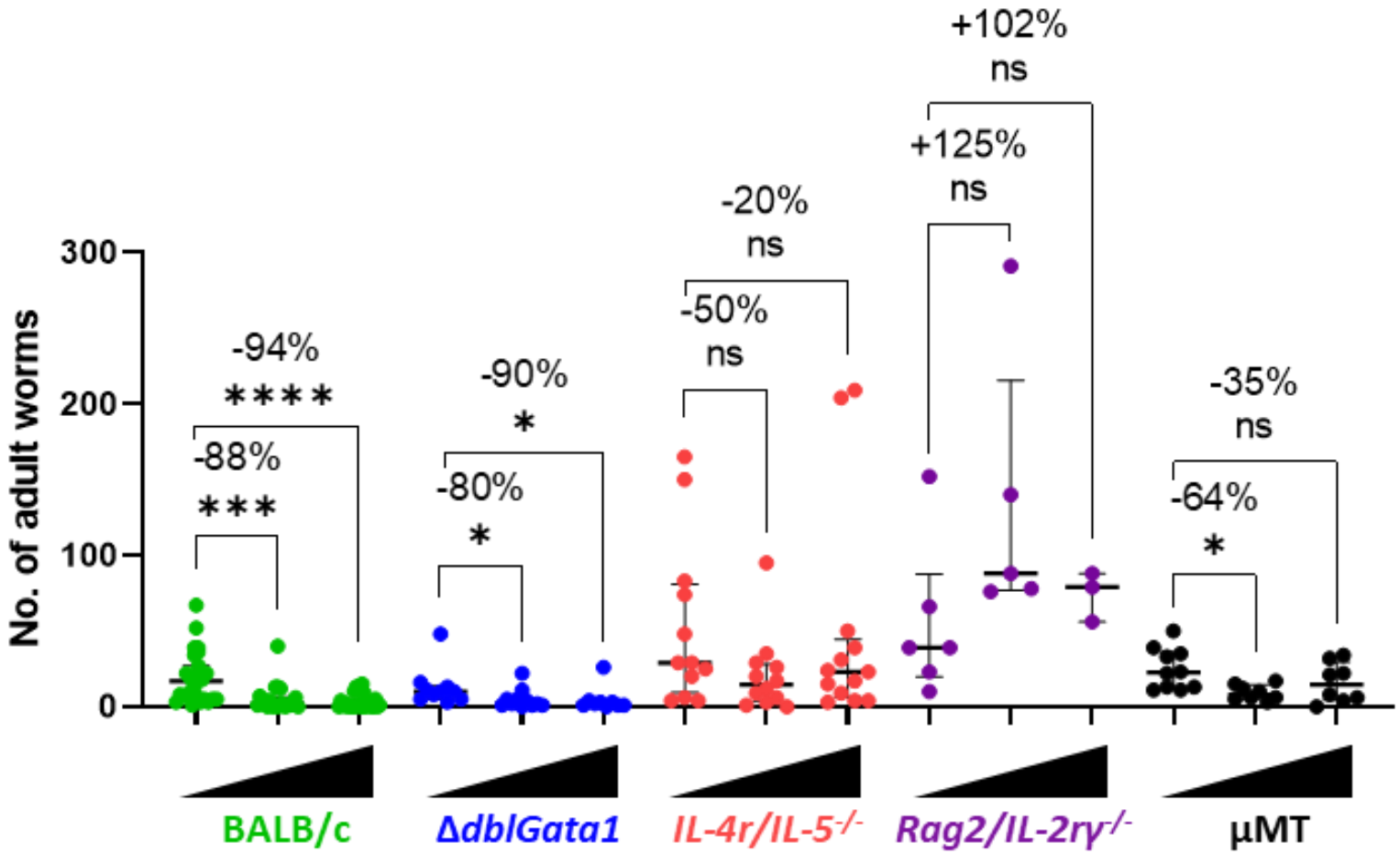
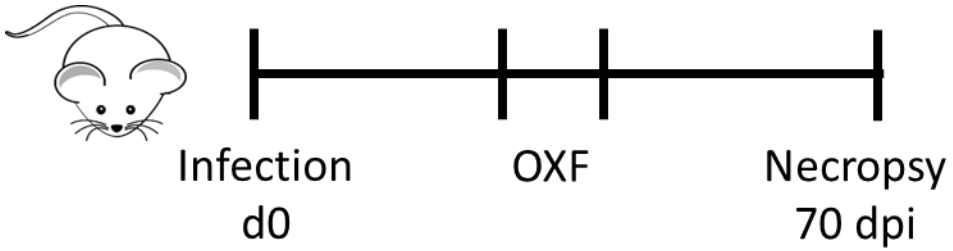


➢ Macrofilaricidal efficacy of oxfendazole is dependent on the adaptive and innate immune system

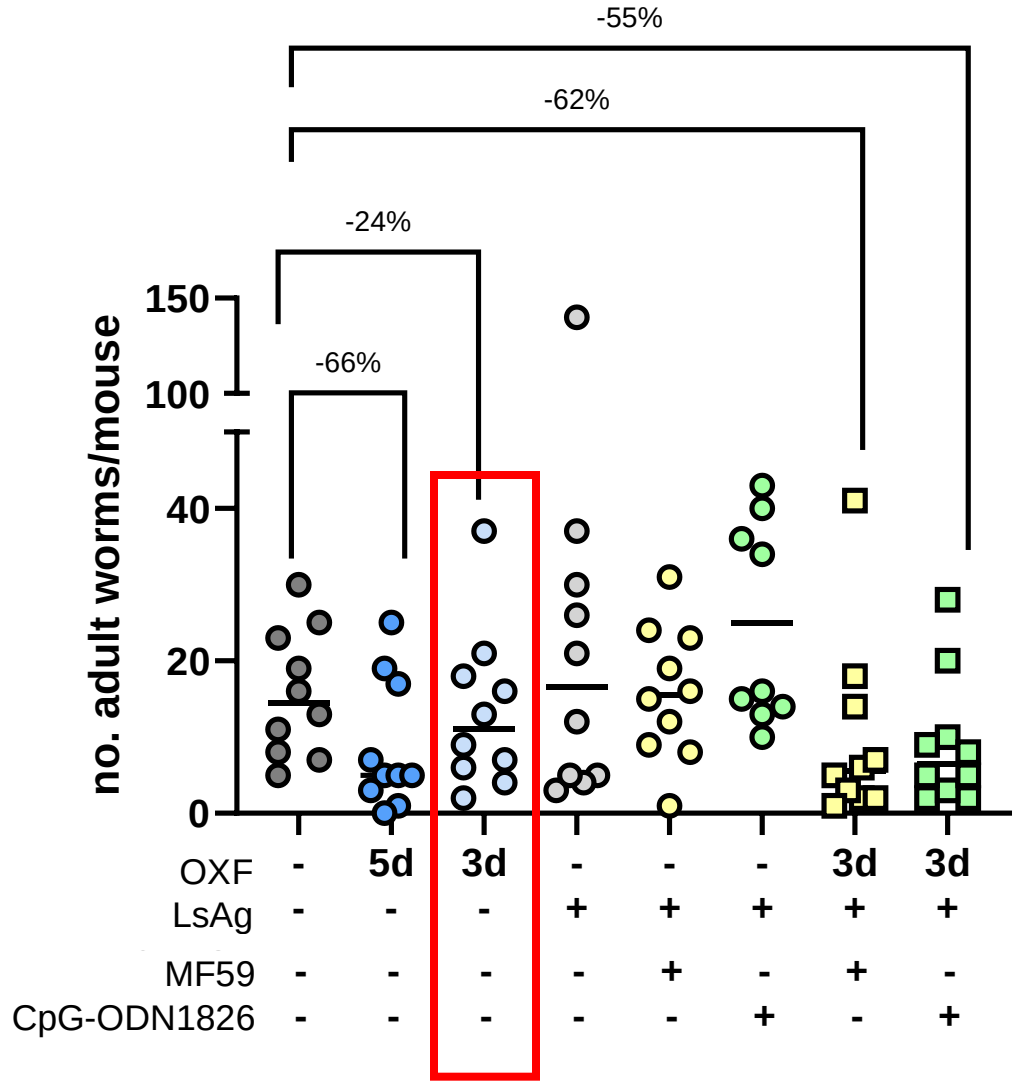
Risch et al. Front Microbiol 2023

Combination of oxfendazole and type 2 cytokines for shorter treatment regimens



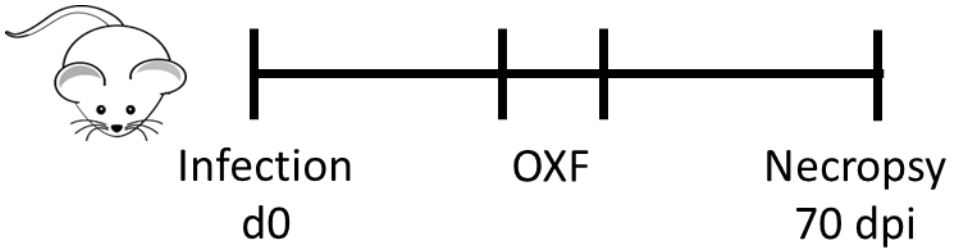
Vaccine adjuvants were given intraperitonially QD for 3 days

Oxfendazole 12.5 mg/kg BID oral



- Co-administration with vaccine adjuvants improves drug efficacy

Combination of oxfendazole and type 2 cytokines for shorter treatment regimens



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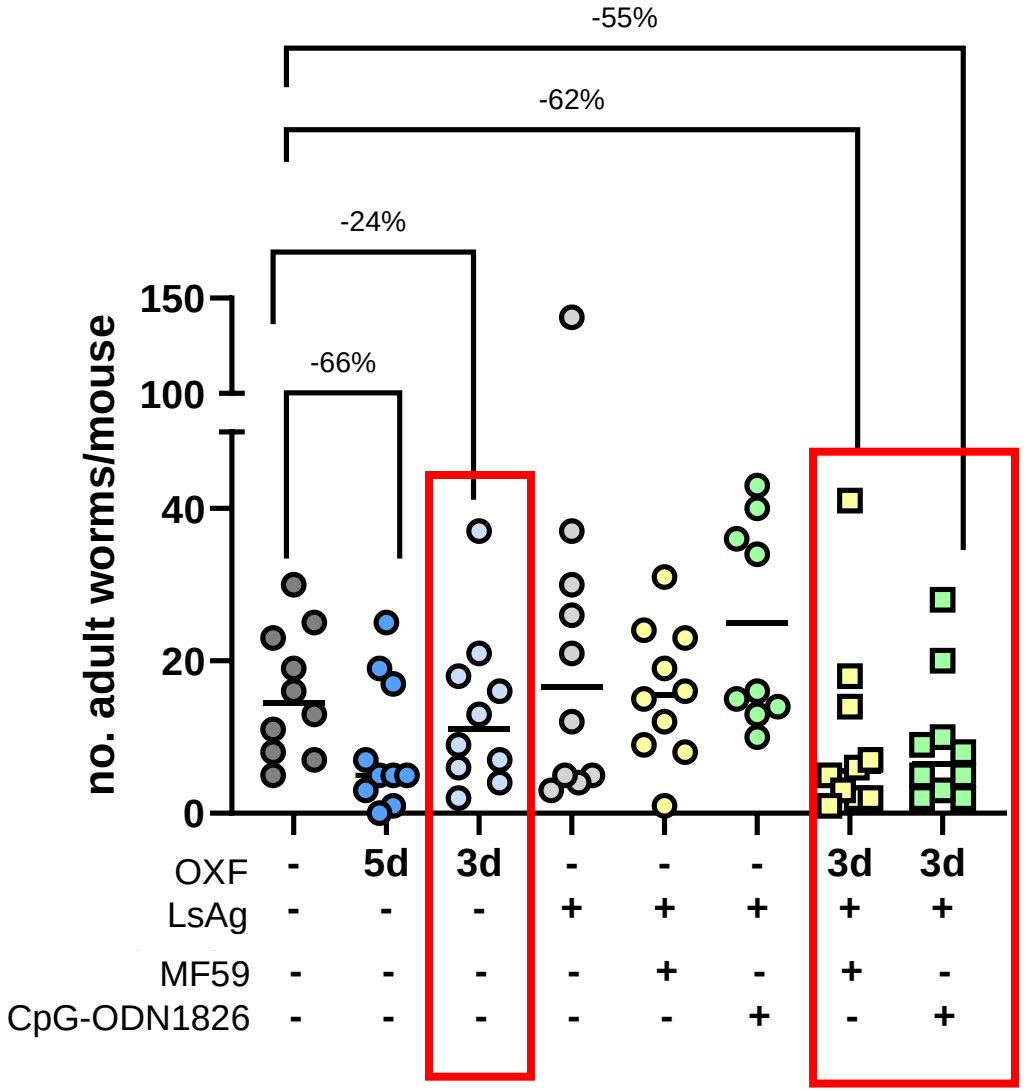

- Co-administration with vaccine adjuvants improves drug efficacy

Immune stimuli to improve drug efficacy

→ **Vaccine adjuvants may be an option to boost the immune system and improve drug efficacy** to allow **shorter treatment regimens / lower drug doses**

Summary

New candidates are identified which are expected to provide a macrofilaricidal – adult worm killing – efficacy in filariasis patients

- Those candidates will allow oral treatments as short as 5-14 days

- Candidates have different **benefits**:
  - **Corallopyronin A** effective against filariae, *Staphylococcus aureus, Chlamydia spp., Neisseria gonorrhoeae*
  - **Emodepside** effective against filariae and soil-transmitted helminths
  - **Oxfendazole** is a pan-nematode candidate and only macrofilaricidal candidate for *Loa loa* and provides a synergistic effect with anti-Wolbachials

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Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Helminth Elimination Platform

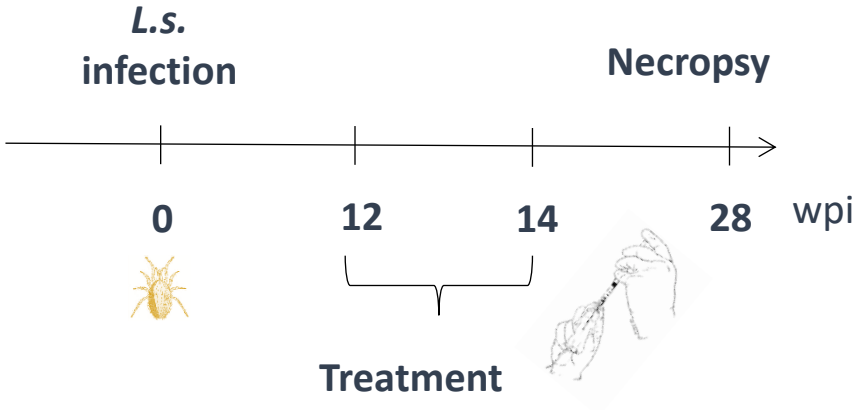
enabeling the WHO Road Map

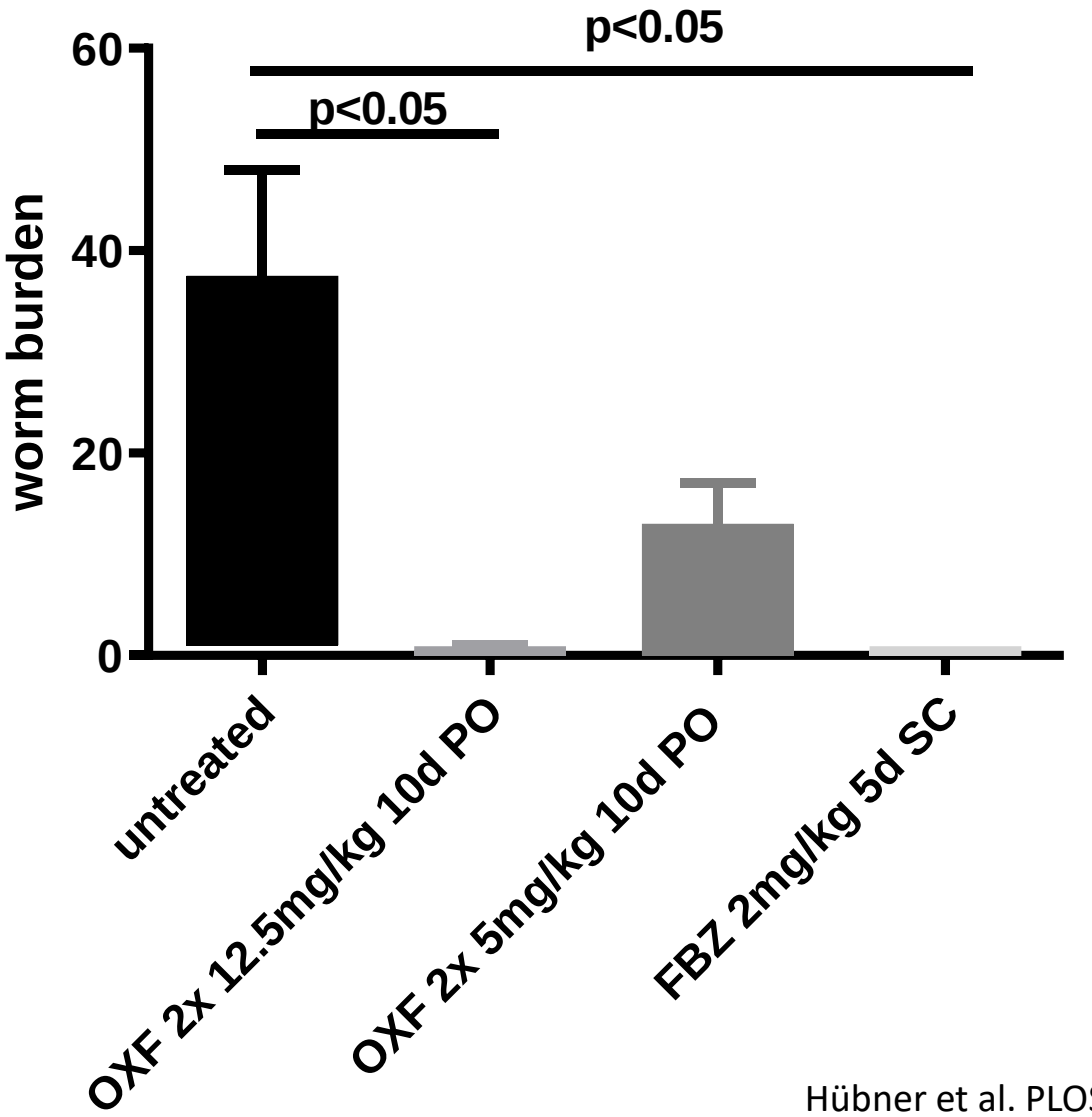
Disease Pathogen	Pathology	Treatment & Limitations	Endemic in study site of
Onchocerciasis ***O. volvulus*** **~ 21 Mio infected**	Blindness, severe dermatitis	Ivermectin, Moxidectin: do not kill the adult worms Doxycycline: daily 5-6 week treatment to kill adult worms; children and pregnant women excluded	DRC, Cameroon
Loiasis ***L. loa*** **~ 13 Mio infected**	Eye worm, angioedema, Calabar swelling	DEC, Ivermectin: may cause life-threatening adverse events; daily 2-4 week treatment, currently not within MDA programs Albendazole: limited efficacy against mf (twice daily 3-week treatment to reduce mf load) -> not on the NTD list!	DRC, Gabon, Cameroon
Mansonellosis ***M. perstans*** **~ 120 Mio infected?**	Mainly asymptomatic	DEC, Ivermectin: MDA treatment (single dose) not efficacious; twice daily 3-week DEC or twice daily 4- week albendazole treatment reduces mf load, currently not within MDA programs -> not on the NTD list!	DRC, Gabon, Cameroon
Trichiuriasis ***T. trichiura*** **>600 Mio infected**	Delayed child development, anemia	Albendazole, mebendazole, levamisole and pyrantel pamoate: all with poor efficacy at single dose; Emodepside promising candidate for Phase 3	DRC, Gabon, Cameroon, Tanzania

Gruppe	Tierzahl und Tierspezies	Substanz	Route	Dosis pro Applikation; Behandlungsintervall ; Behandlungstage	Applikationsvolumen	Vehikel	
1	10 BALB/c	Vehikel (Negativkontrolle)	PO	BID, 3 Tage	5 ml/kg	Maisöl	63
2	10 BALB/c	Oxfendazol (Positivkontrolle)	PO	12.5 mg/kg BID, 5 Tage	5 ml/kg	Maisöl	63
3	10 BALB/c	Oxfendazol	PO	12.5 mg/kg BID, 3 Tage	5 ml/kg	Maisöl	63
4	10 BALB/c	MPL-A/LsAg	s.c.	2µg /2µg QD 3 Tage	10 ml/kg	0,9% NaCl-Lösung	63
5	10 BALB/c	Alhydrogel/LsAg	s.c.	1:1 vol, 2µg QD 3 Tage	10 ml/kg	0,9% NaCl-Lösung	63
6	10 BALB/c	MF59/LsAg	s.c.	1:1 vol, 2µg QD 3 Tage	10 ml/kg	0,9% NaCl-Lösung	63
7	10 BALB/c	CpG-ODN1826/LsAg	s.c.	20µg/2µg QD 3 Tage	10 ml/kg	0,9% NaCl-Lösung	63
8	10 BALB/c	LsAg	s.c.	2µg QD 3 Tage	10 ml/kg	0,9% NaCl-Lösung	63
9	10 BALB/c	Oxfendazol + MPLA/LsAg	PO + s.c.	12.5 mg/kg BID PO 3 Tage + 2µg/2µg QD 3 Tage	5 ml/kg + 10 ml/kg	Maisöl + 0,9% NaCl Lösung	63
10	10 BALB/c	Oxfendazol + Alhydrogel/LsAg	PO + s.c.	12.5 mg/kg BID PO 3 Tage + 1:1 v/v, 2µg QD 3 Tage	5 ml/kg + 10 ml/kg	Maisöl + 0,9% NaCl Lösung	63
11	10 BALB/c	Oxfendazol + MF59/LsAg	PO + s.c.	12.5 mg/kg BID PO 3 Tage+ 1:1 v/v, 2µg QD 3 Tage	5 ml/kg + 10 ml/kg	Maisöl + 0,9% NaCl Lösung	63

Assessment of the oxfendazole efficacy on the adult worm burden in patently *L. sigmodontis*-infected jirds

Meriones unguiculatus

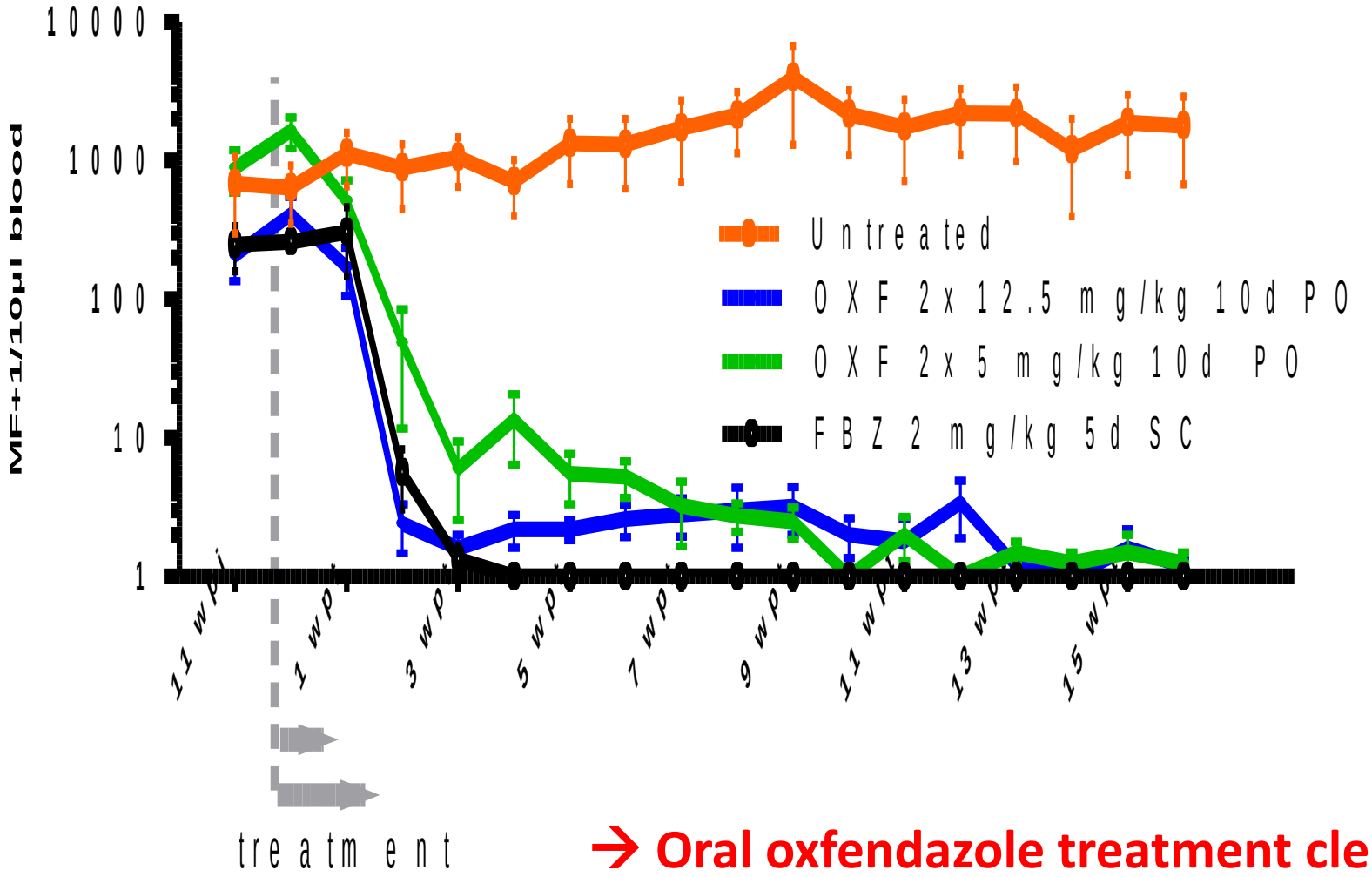




→ **Oral oxfendazole treatment is macrofilaricidal**

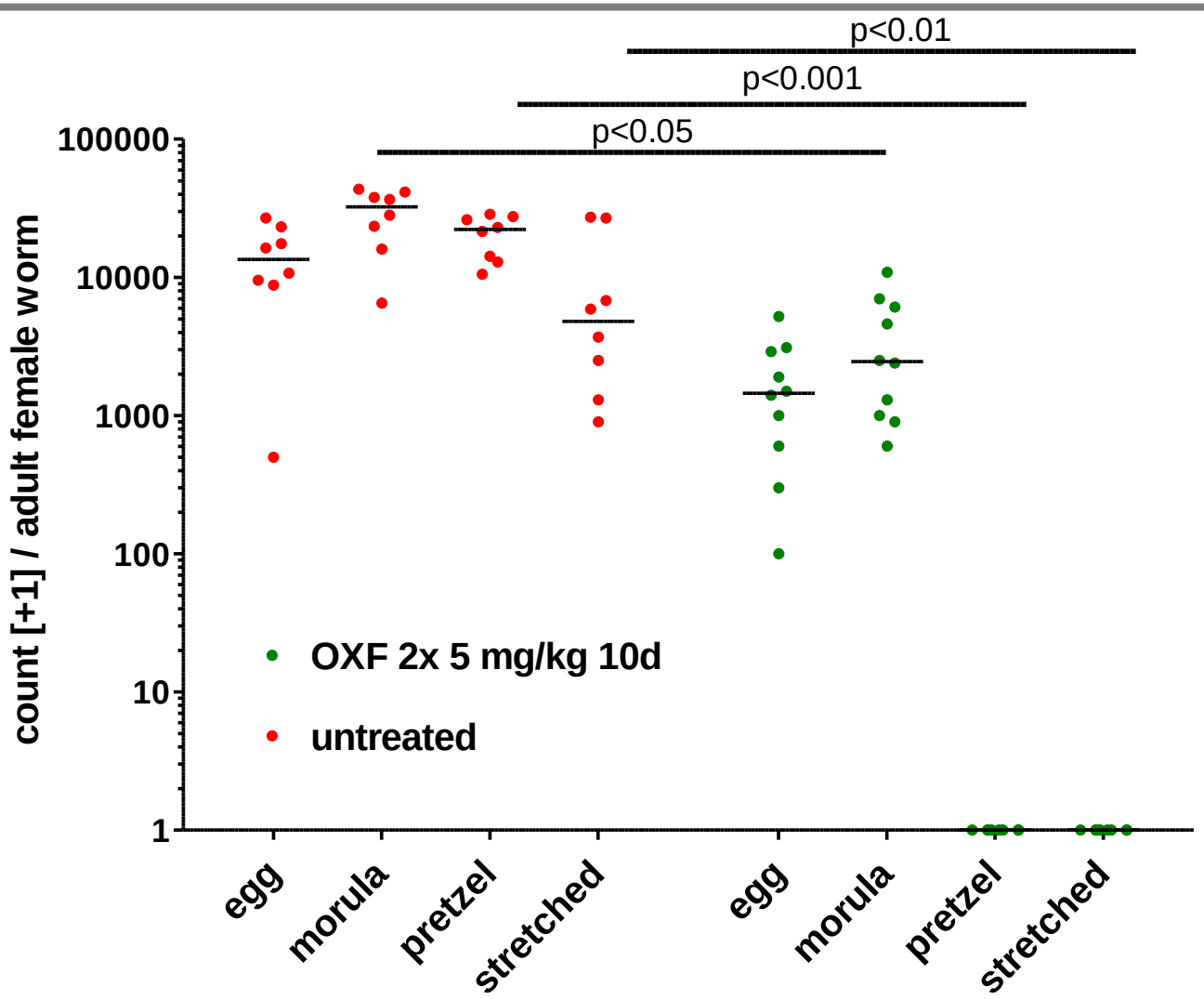
Hübner et al. PLOS NTDs 2020

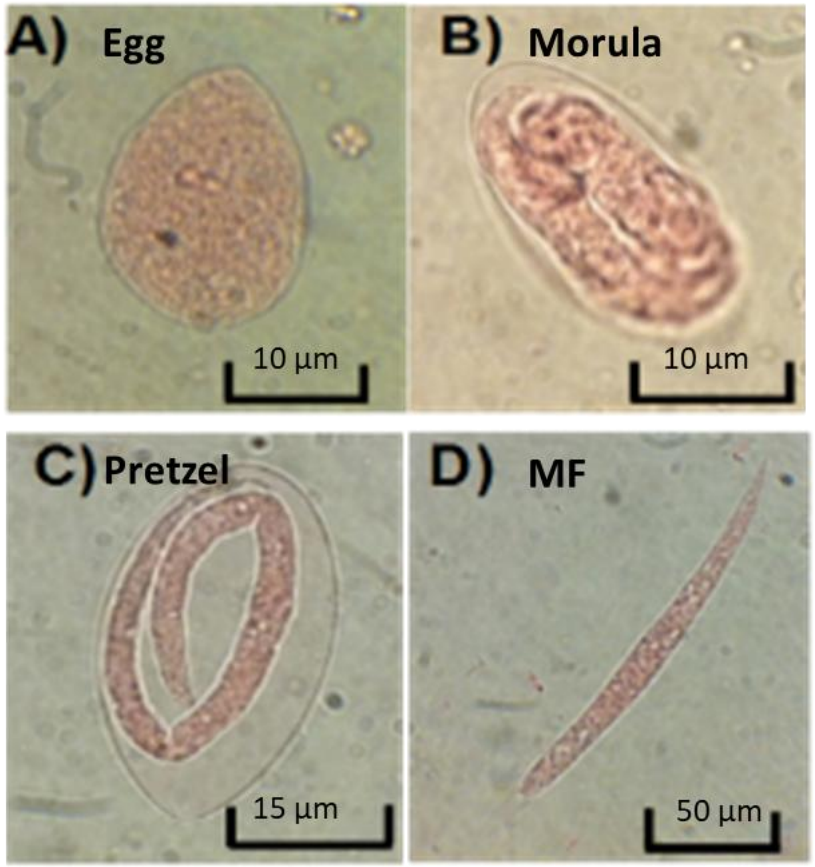
Assessment of the oxfendazole efficacy on microfilaremia in patently *L. sigmodontis*-infected jirds



→ **Oral oxfendazole treatment clears microfilaremia**

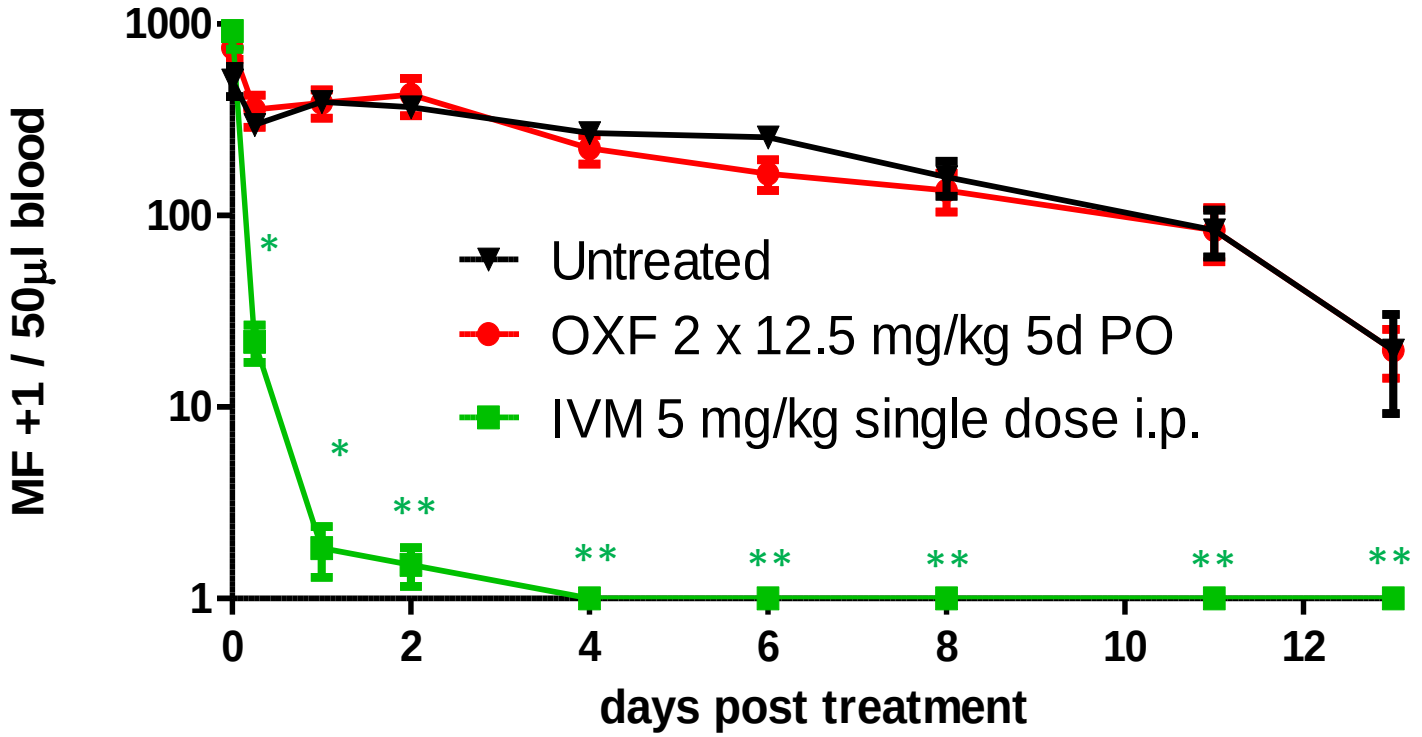
Impact of oxfendazole treatment on filarial embryogenesis





→ **Oral oxfendazole treatment inhibits embryogenesis**

In vivo assessment of the direct microfilaricidal efficacy of oxfendazole



*p<0.05

**p<0.01

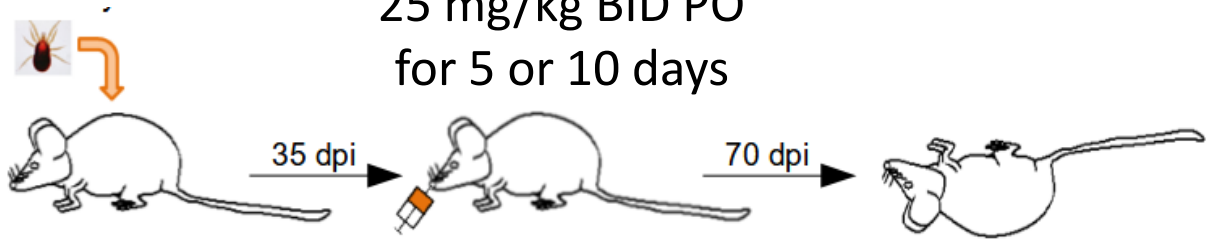
→ Oral oxfendazole treatment has **no direct microfilaricidal efficacy**

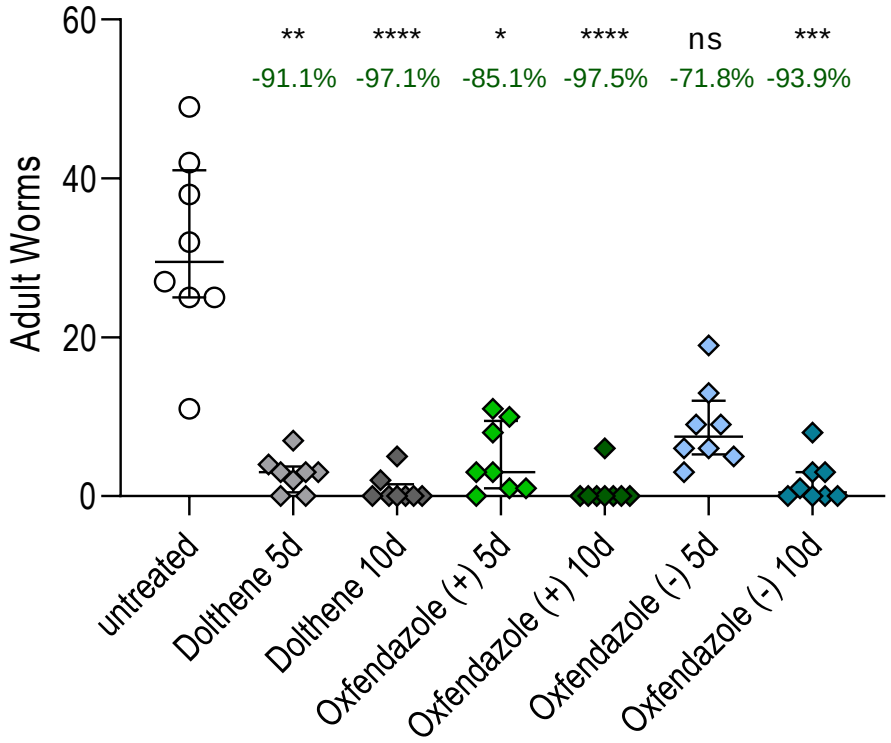
→ **No microfilariae-induced SAE** in onchocerciasis and loiasis patients **expected**

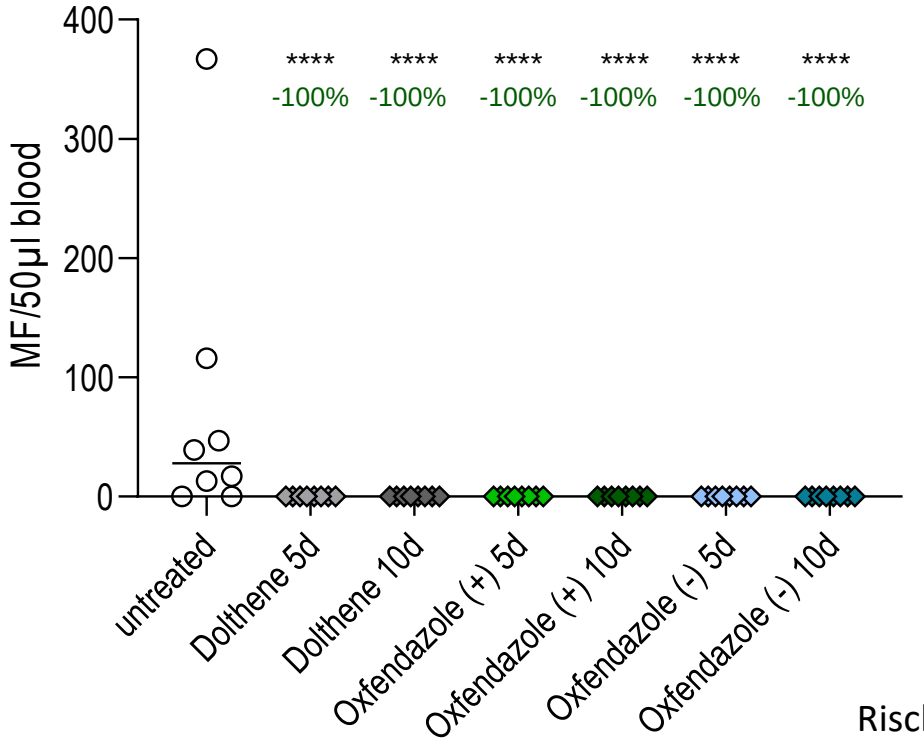
→ **Potential macrofilaricidal candidate for loiasis**

Are oxfendazole isomers equally active as the racemic formulation?

In vivo assessment of the efficacy of oxfendazole isomers







Risch et al. submitted

→ Oxfendazole isomers have a similar macrofilaricidal efficacy as the racemic formulation (Dolthene)

Conclusions oxfendazole

- Oxfendazole is **active** against ***Onchocerca gutturosa*** adult and ***O. volvulus*** pre-adult worms *in vitro*
  (Hübner et al. PLOS NTDs 2020)

- Oral oxfendazole treatment is **macrofilaricidal** against *L. sigmodontis*

- Oral oxfendazole treatment **inhibits embryogenesis**, but has **no direct microfilaricidal efficacy**
  → no microfilariae-induced SAE in onchocerciasis and loiasis patients expected

- **Oxfendazole isomers** display **similar anti-filarial activity** and our data do not support the development of a single isomer for future use in human patients

- **Oxfendazole efficacy** is **dependent on immune responses**

- **Predicted human efficacious dose** (1.5 and 4.1 mg/kg) is **within the range** of previously **tested multiple ascending phase 1 studies** (Hübner et al. PLOS NTDs 2020)

→ **Oxfendazole is the only drug candidate with a predicted selective adulticidal efficacy for human filariae and the only potential macrofilaricidal treatment available for *Loa loa***

Summary on Clinical Candidates for filariasis patients I

- **Clinical candidates currently tested in phase 2 clinical studies in onchocerciasis patients**
  - ABBV-4083 (anti-*Wolbachia*) → Accelerator √, *Loa loa* endemicity √
  - Emodepsid → **Replacement** for ivermectin, moxidectin √
- **Clinical candidate for phase 2 clinical studies in onchocerciasis patients**
  - Oxfendazol → Accelerator √, *Loa loa* endemicity √
    → **Candidate for *Loa loa* patients**
- **Clinical candidate currently tested in phase 1 clinical studies**
  - AWZ1066 (anti-*Wolbachia*) → Accelerator √, *Loa loa* endemicity √
- **Candidates prepared for phase 1 clinical studies**
  - Corallopyronin A (anti-*Wolbachia*) → Accelerator √, *Loa loa* endemicity √
  - CC6166 → Accelerator √, *Loa loa* endemicity √

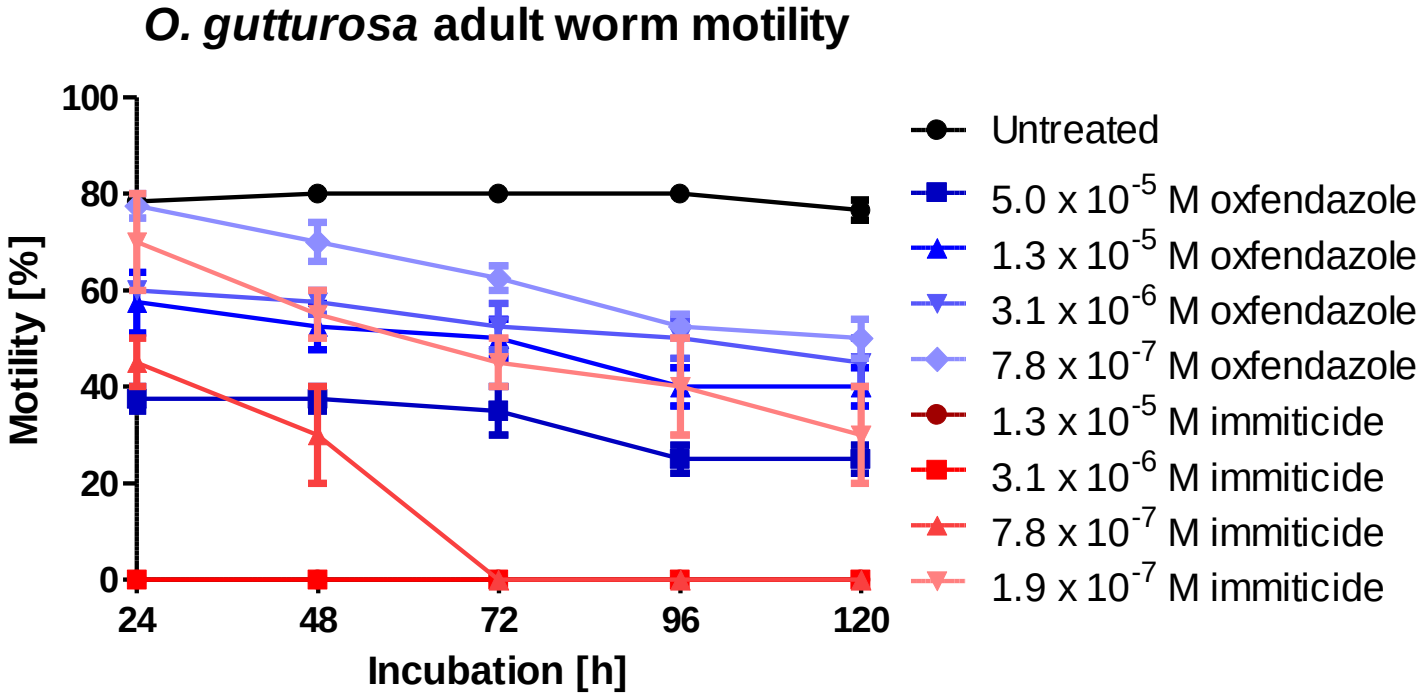
Human pharmacokinetic prediction for oxfendazole

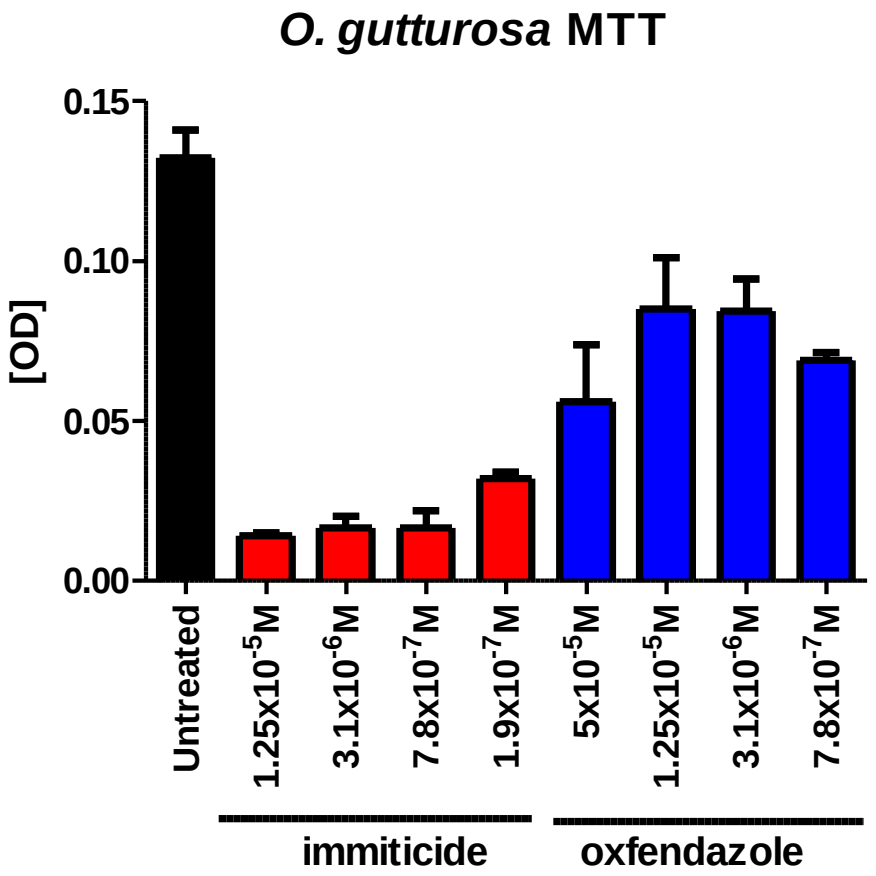
Human PK Prediction for Oxfendazole[a]		
Clearance (CL)	**(mL/min/kg)**	**Comments[b]**
rat-dog allometry	8.0	$CL = \alpha \times BW^{\beta}$
rat-dog allometry (+PPB[c])	0.4	unbound $CL = \alpha \times BW^{\beta}$
hepatocyte CL scaling	0.4	well-stirred model using fu x CL_{int}
Final	**0.4**	
Vol. of Distribution (V_{ss})	**(L/kg)**	**Comments[b]**
rat-dog allometry	1.2	$V_{ss} = \alpha \times BW^{\beta}$
via rat (with PPB[c])	0.2	$V_{ss,h}$ = mean fu,h x ($V_{ss,y}$/fu,y)
via dog (with PPB[c])	0.1	
Final	**0.5**	
Half-Life (HL)	**(h)**	**Comments**
via predicted Vss/CL	14.4	$T_{1/2} = \ln_2 \times (V_{ss}/CL)$
rat-hum correlation	12.1	$\log(T_{1/2}$ human) = 0.906 log ($T_{1/2}$ rat) + 0.723
dog-hum correlation	4.2	$\log(T_{1/2}$ human) = 0.934 log ($T_{1/2}$ dog) + 0.433
Final	**10.2**	
Bioavailability (F)	**(%)**	**Comments**
rat/sheep/cattle	>50	published data[37]
rat	~35	Published data[22]
dog	~10	in-house data at high dose of 25 mg/kg
Final	**30**	

The resulting daily doses needed to reach all assumed **target concentrations** for these scenarios in humans were calculated to be **between 1.5 and 4.1 mg/kg** (average all methods: 2.7 mg/kg assuming a 70 kg subject).

→ **Reasonable dose with an acceptable range.**

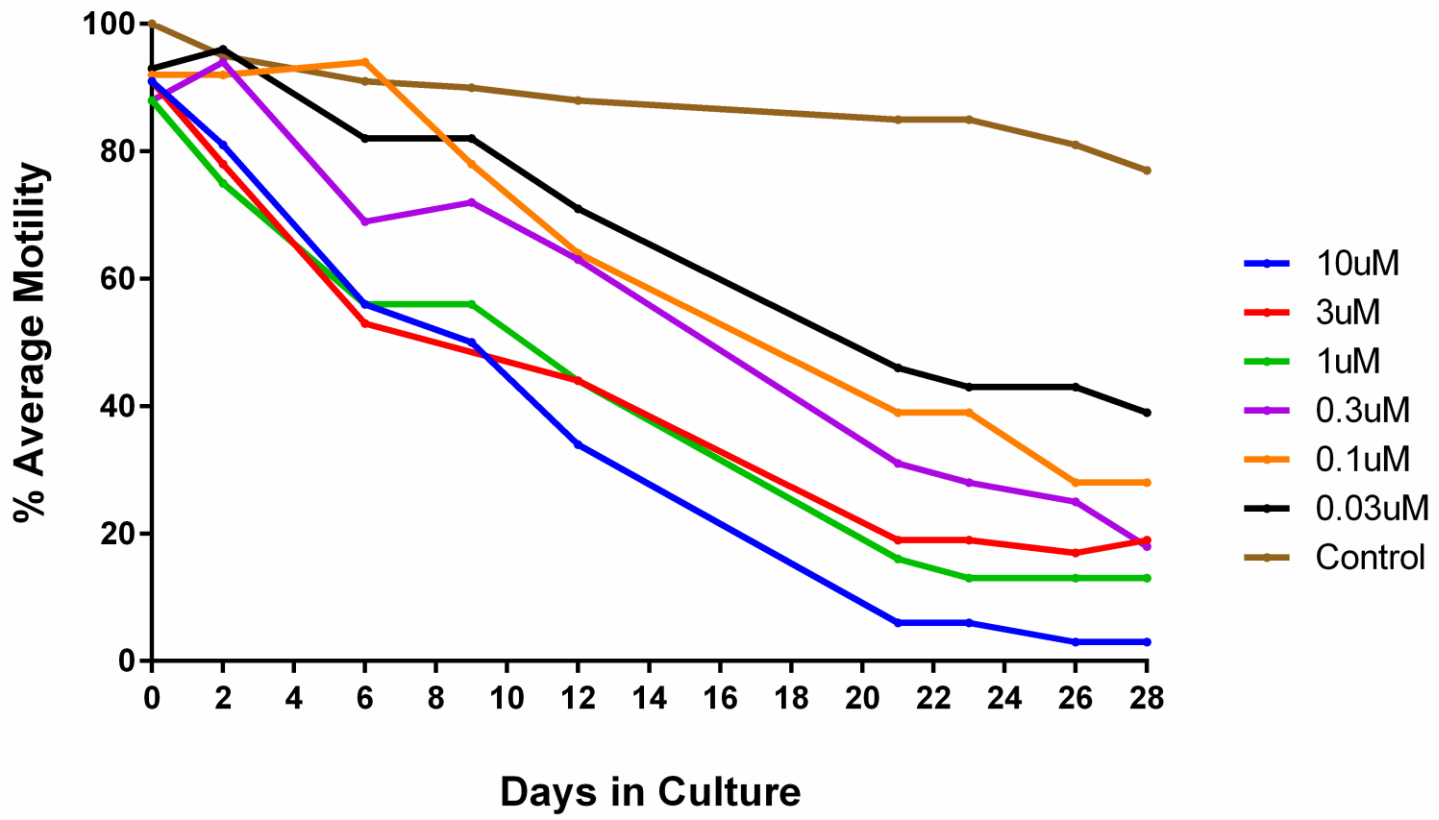
In vitro assessment of the efficacy of oxfendazole against *O. gutturosa* adult worms





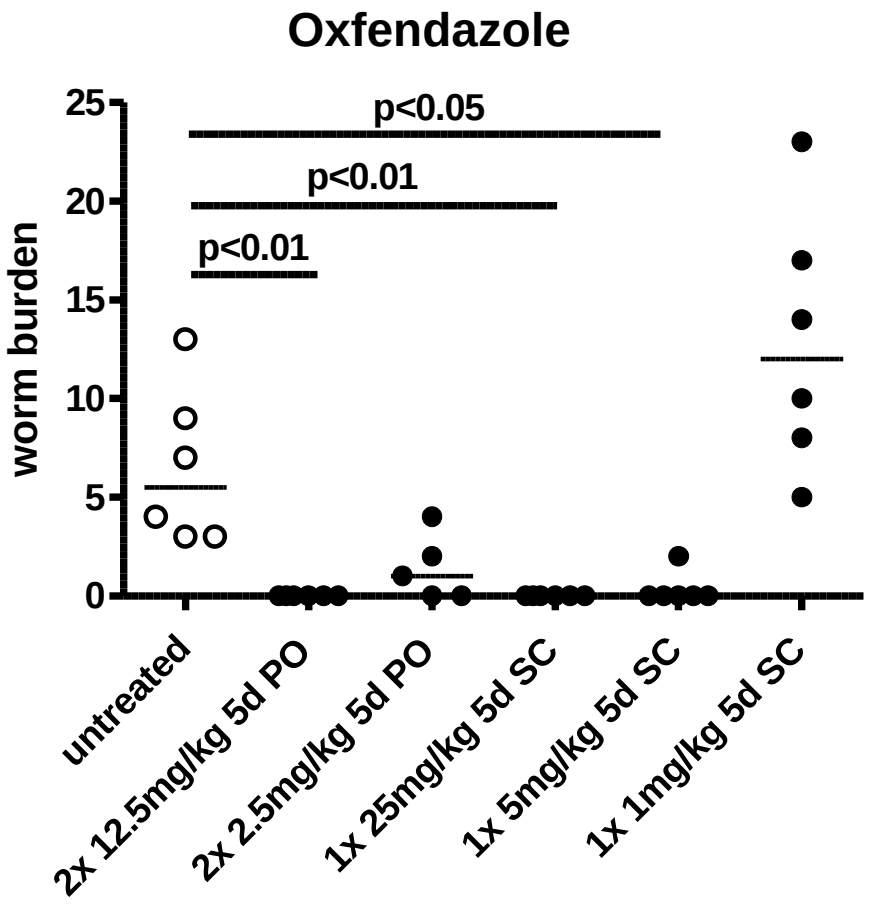
→ **Oxfendazole is macrofilaricidal for *O. gutturosa***

In vitro assessment of the efficacy of oxfendazole against *O. volvulus* L5s

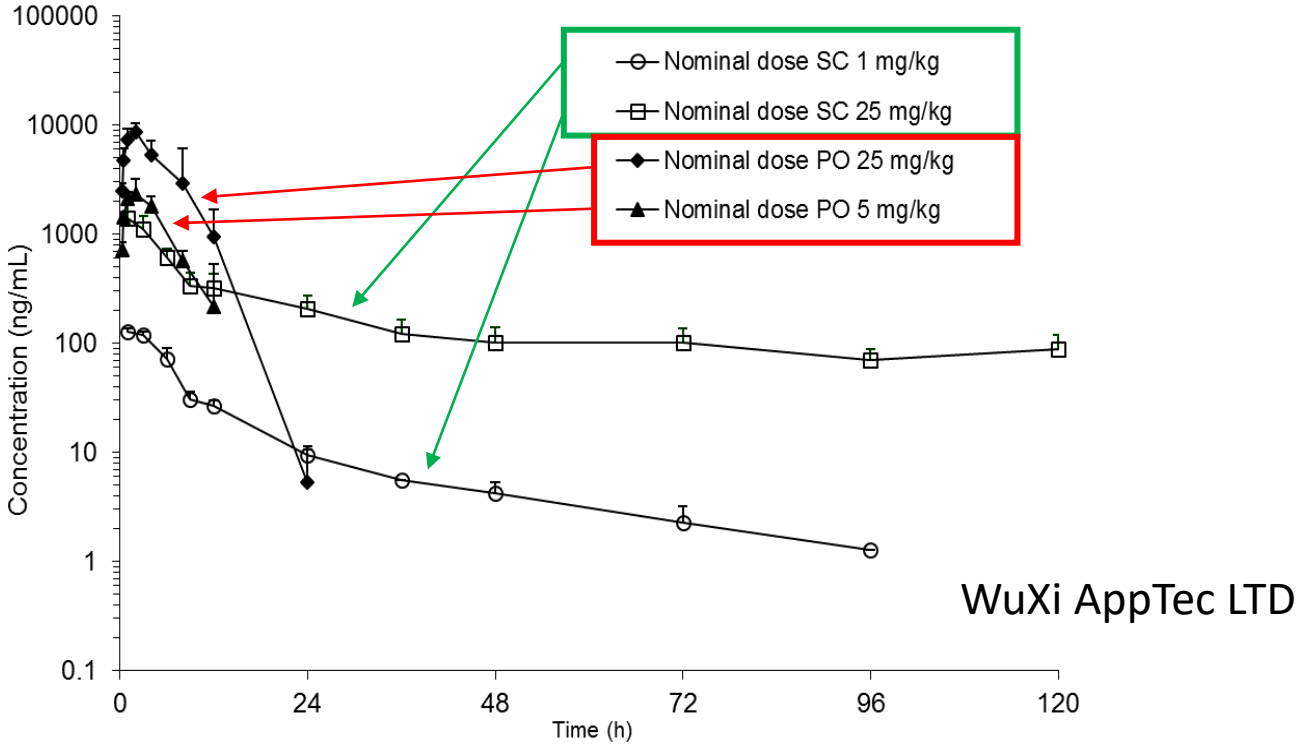


→ **Oxfendazole inhibits the motility of *O. volvulus* L5s**

Identification of the PK driver of efficacy



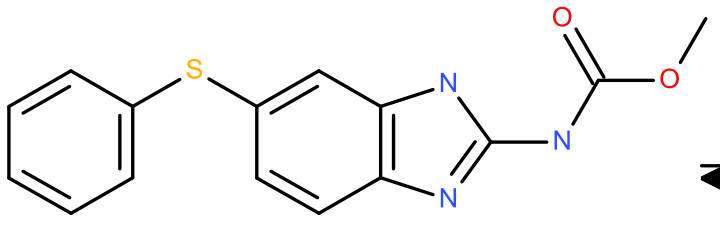
→ Maintenance of C_{min} determines efficacy



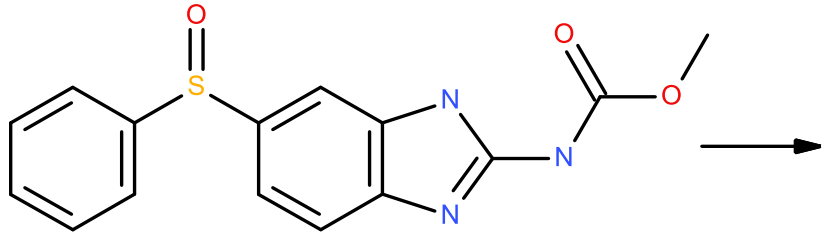
WuXi AppTec LTD

oxfendazole	PO (5mg/kg)	PO (25mg/kg)	SC (1mg/kg)	SC (25mg/kg)
C_{max} (ng/ml)	2530	8593	131	1447
T_{max} (h)	1,67	2,00	1,67	2,33
$T_{1/2}$ (h)	2,87	1,87	24,8	76
$AUC_{0\text{-last}}$	14673	50311	1284	20817

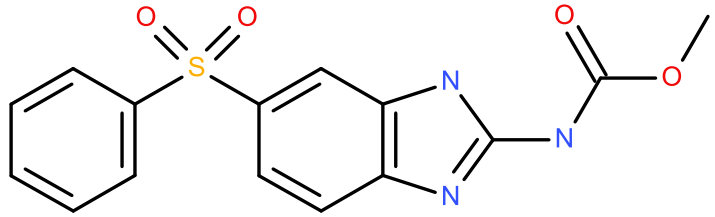
Oxfendazole isomers are metabolized at different rates into fenbendazole sulfone



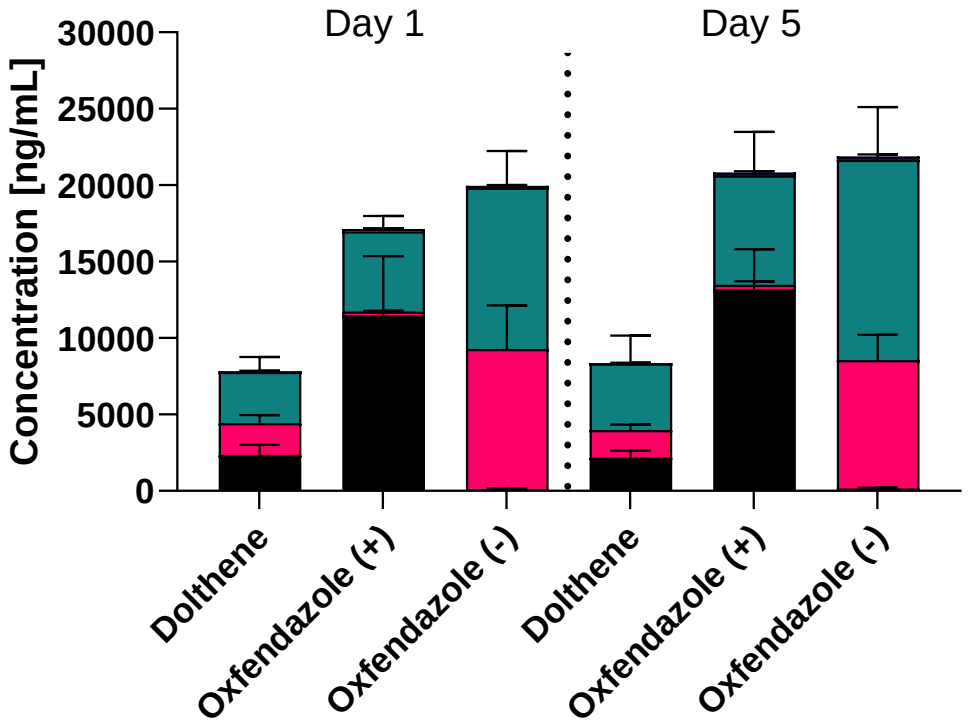
Fenbendazole

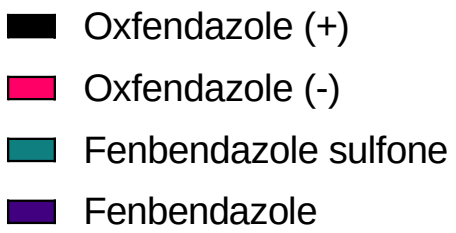


Oxfendazole (=fenbendazole sulfoxide)



Fenbendazole sulfone





Fenbendazole sulfone has been described to be **inactive against several helminths** but both isomers have **similar activity against *L. sigmodontis***

Risch et al. submitted

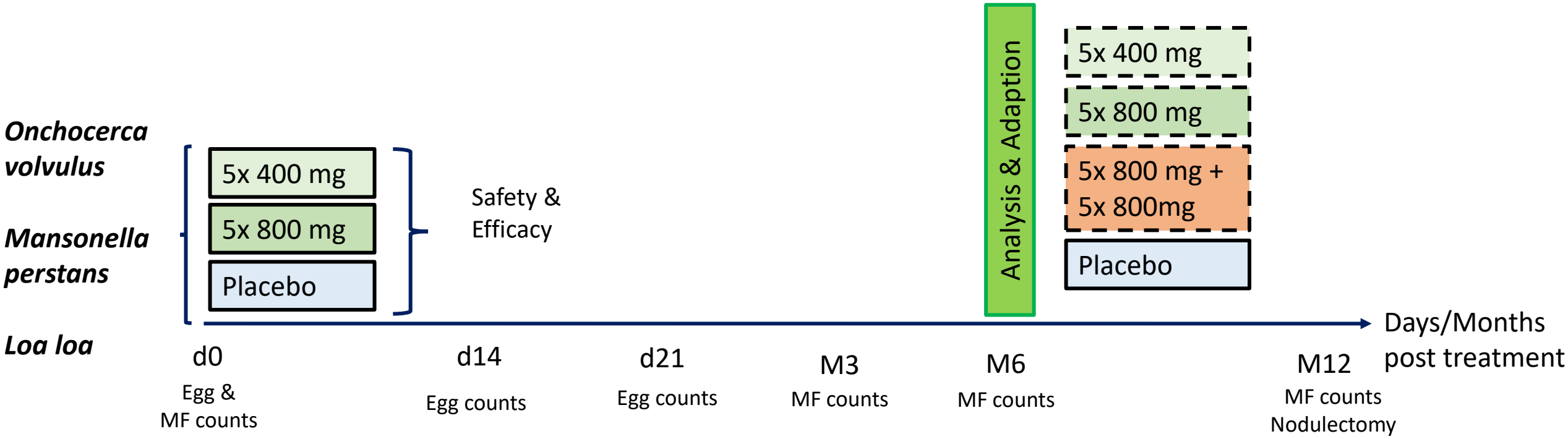
Oxfendazole basket trial

Co-infected will be included

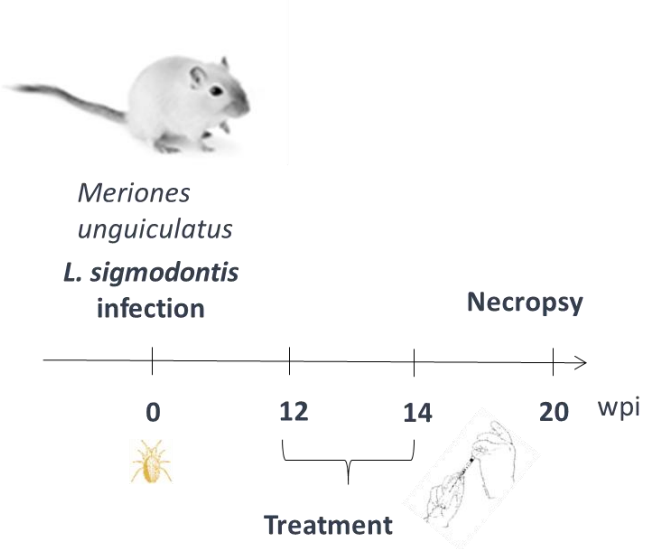
75% randomized, Adaptation

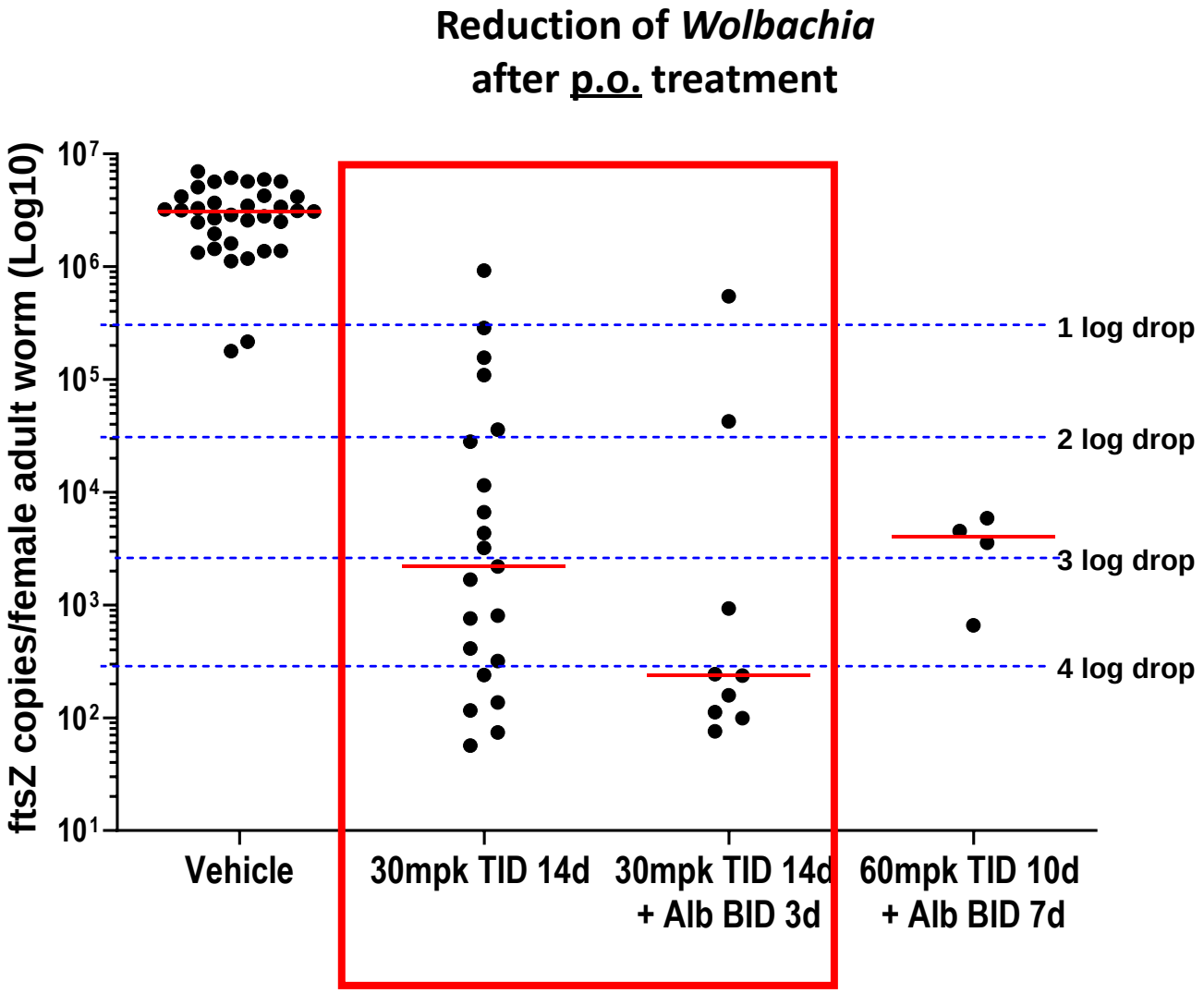
If no effect visible: Recruitment into 5x800 mg+ 5x800 mg

If effective: continue with effective arm



Combinations of CorA and albendazole





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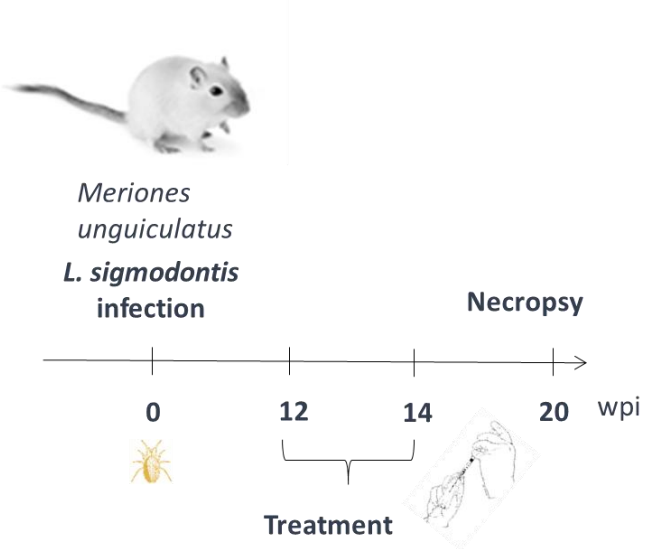

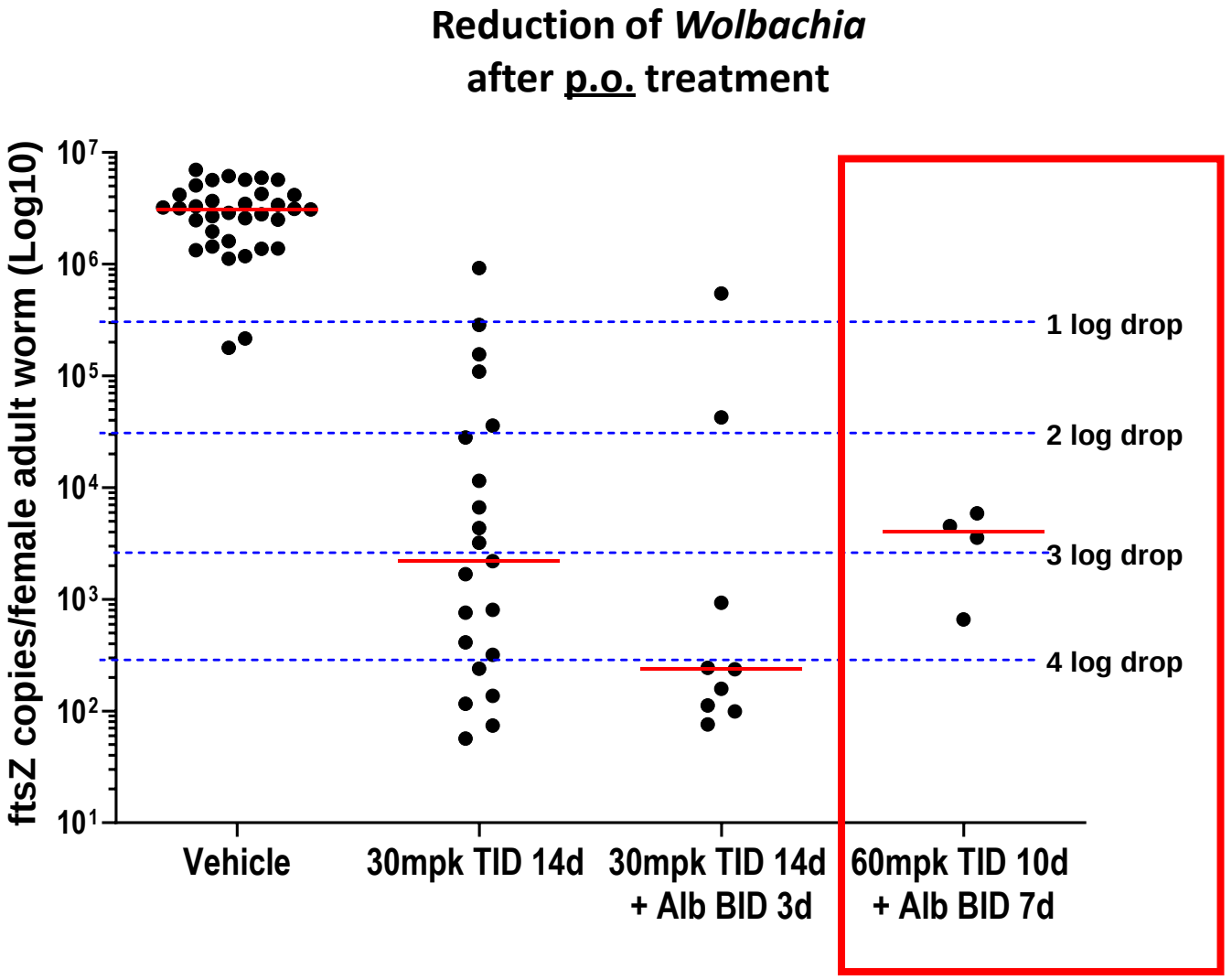

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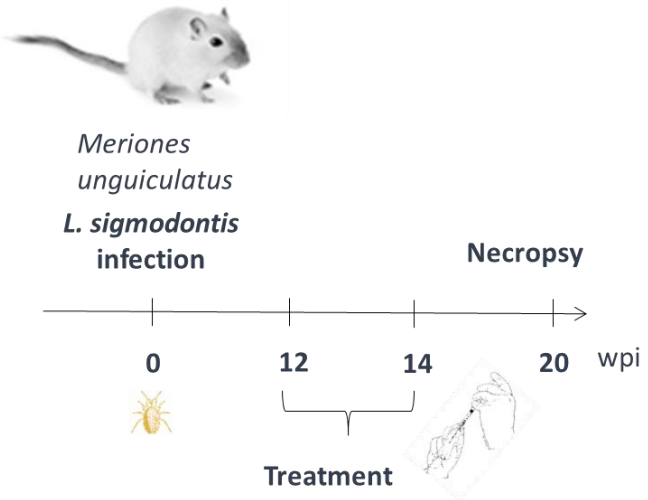
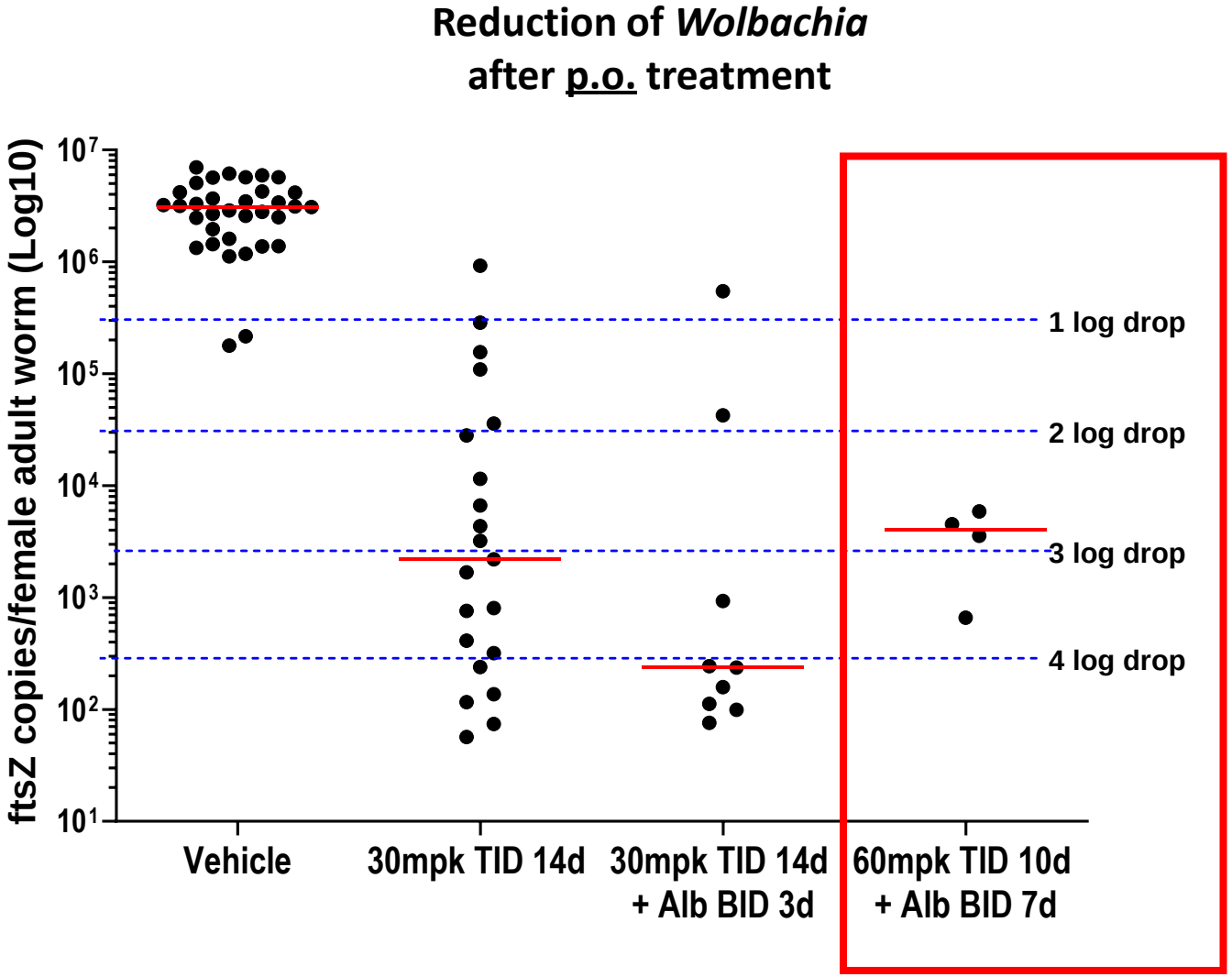




Co-administration with albendazole improves drug efficacy and shortens treatment time

Combinations of doxycycline and oxfendazole

BALB/c J
females

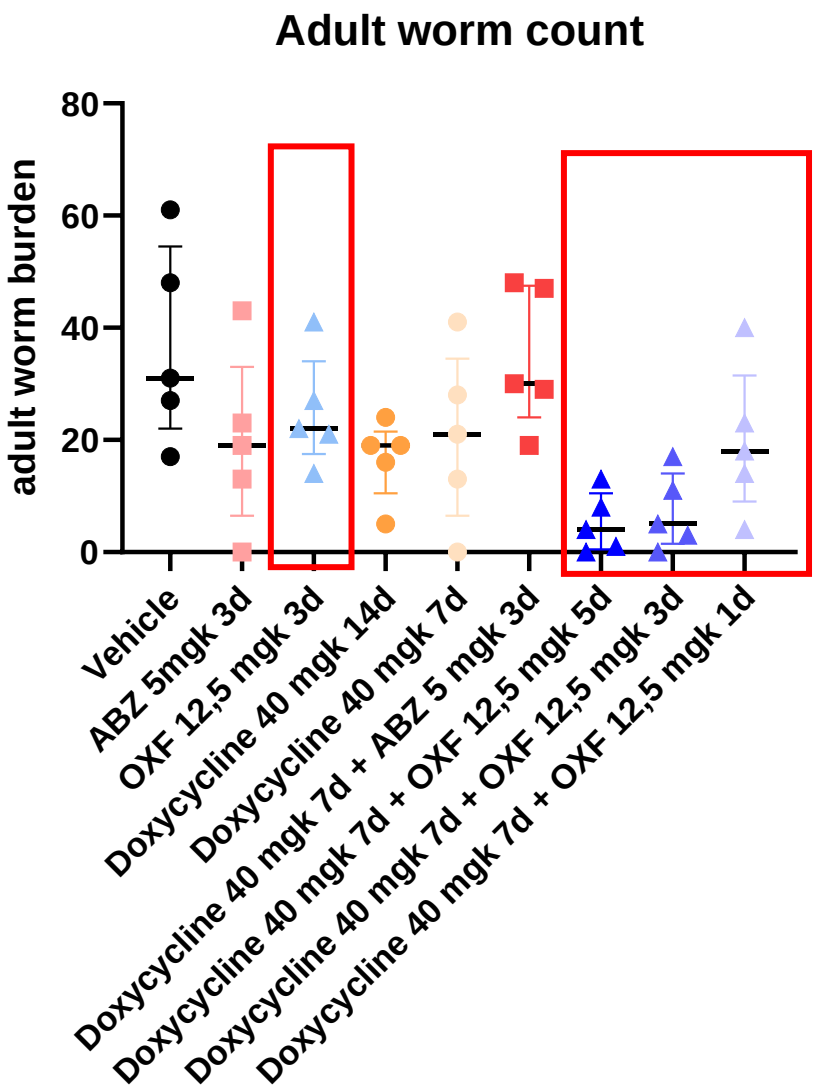
L.s.
Infection

Necropsy

0 35 41 63 dpi

Oral treatment

Hannah Wegner



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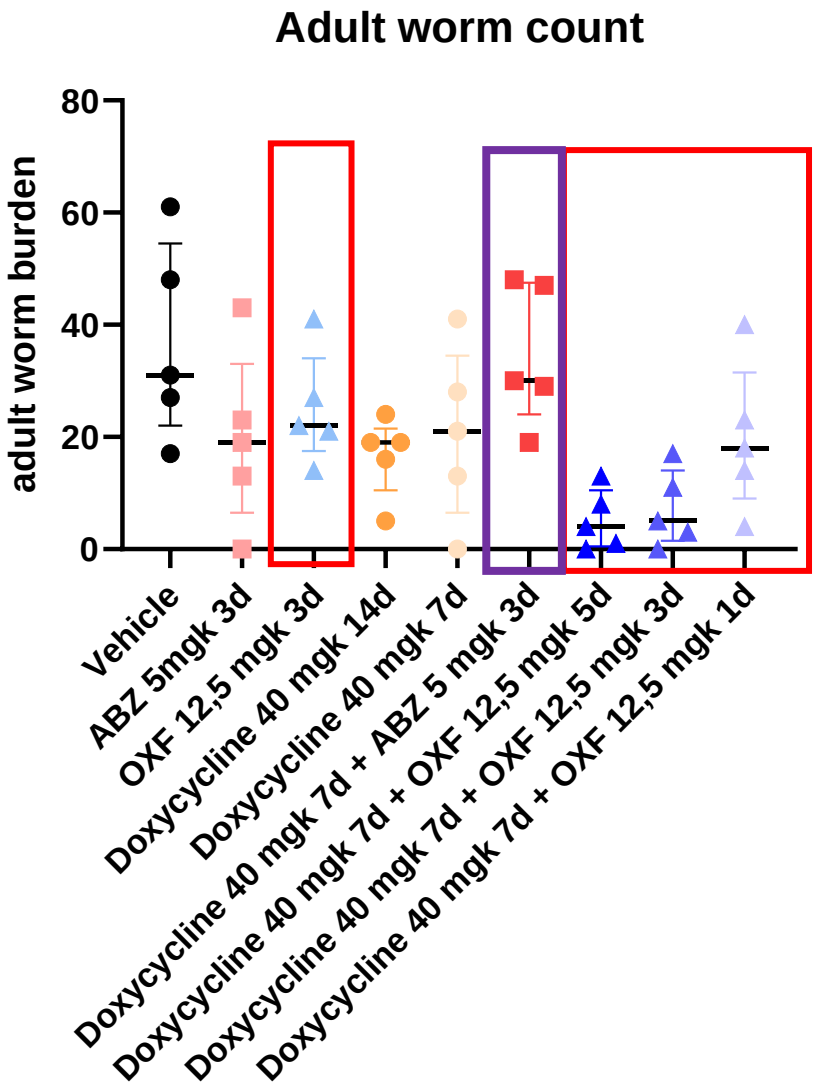

Combinations of doxycycline and oxfendazole

BALB/c J
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0 35 41 63 dpi

Oral treatment

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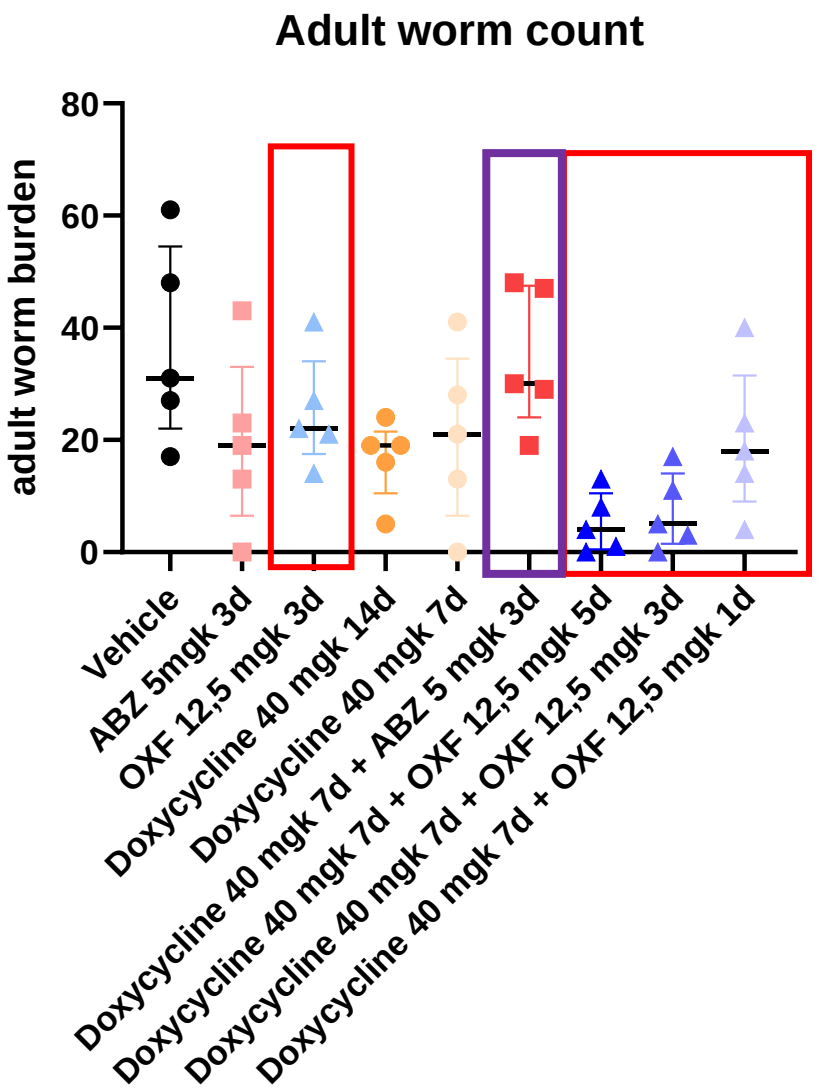
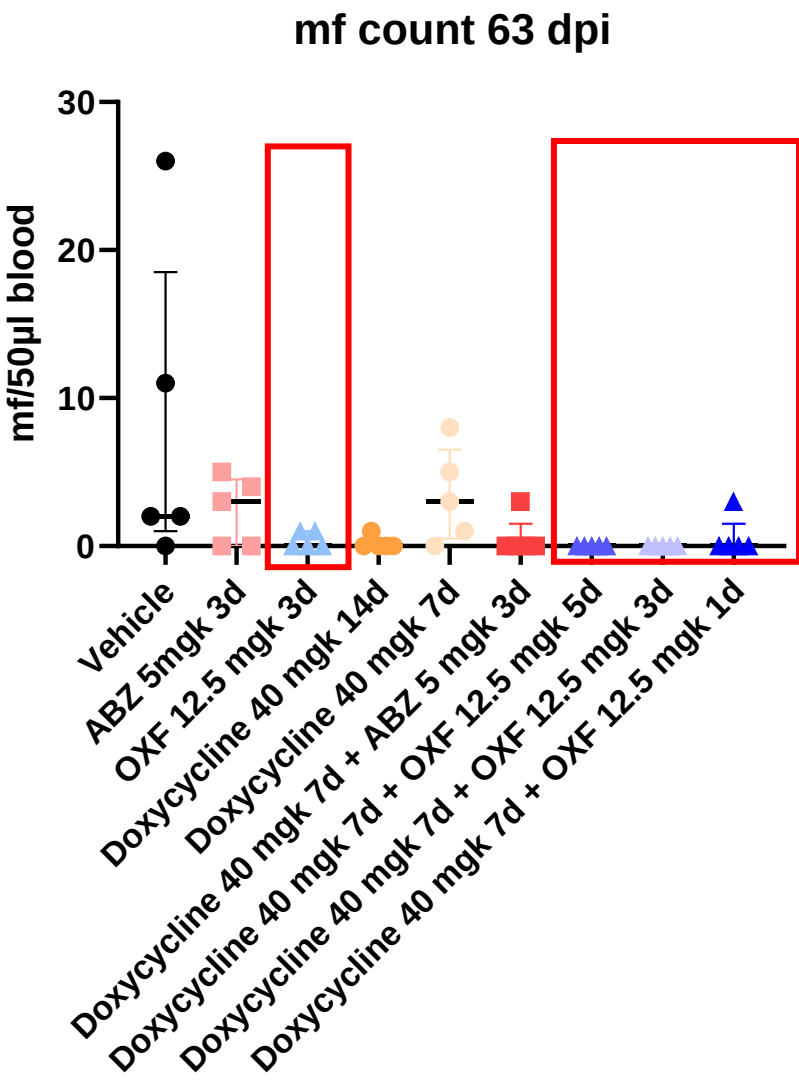
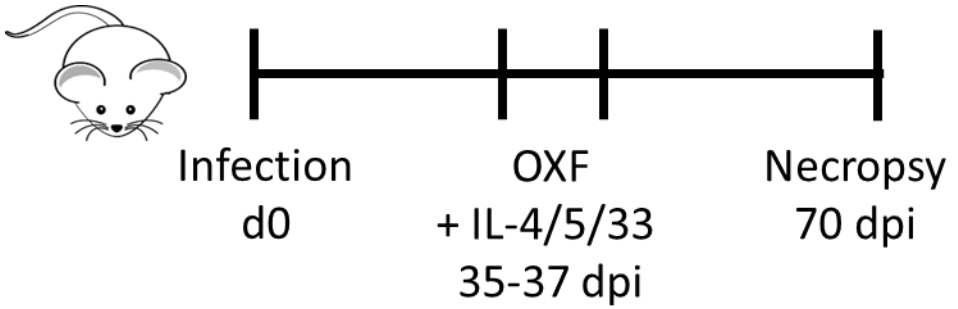


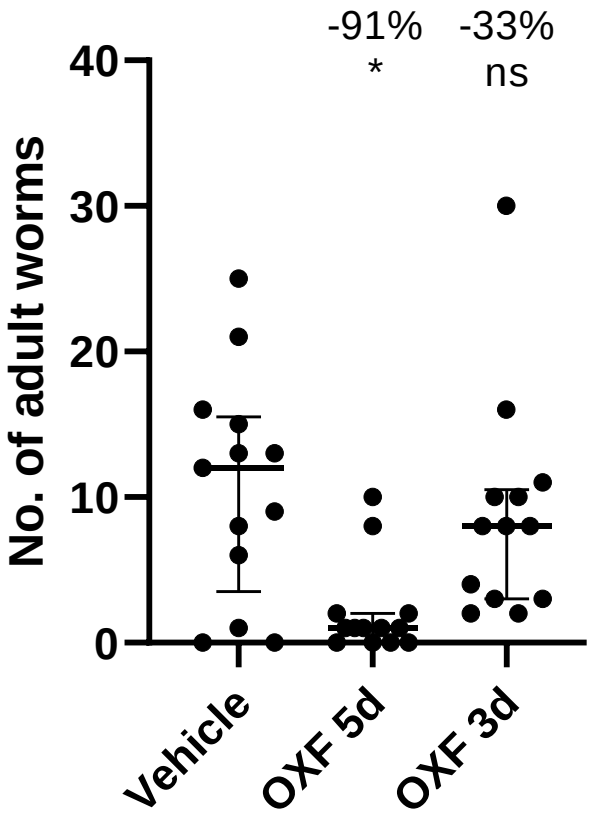


Combination of oxfendazole and type 2 cytokines for shorter treatment regimens

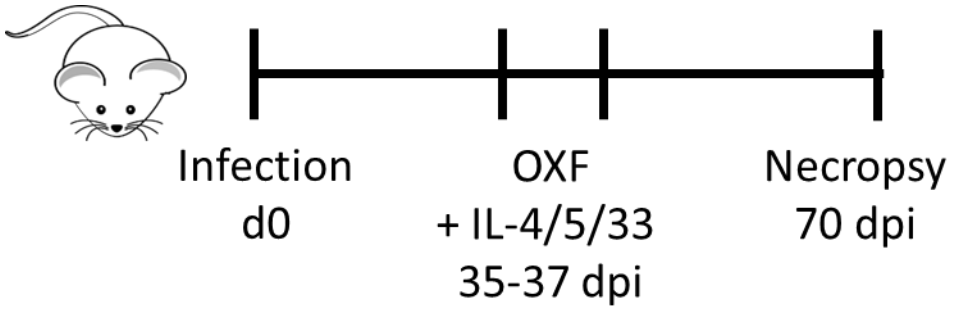


IL-4, IL-5, IL-33 were given intranasally
(2 µg, QD for 3 days)

Oxfendazole 12.5 mg/kg BID oral



Combination of oxfendazole and type 2 cytokines for shorter treatment regimens



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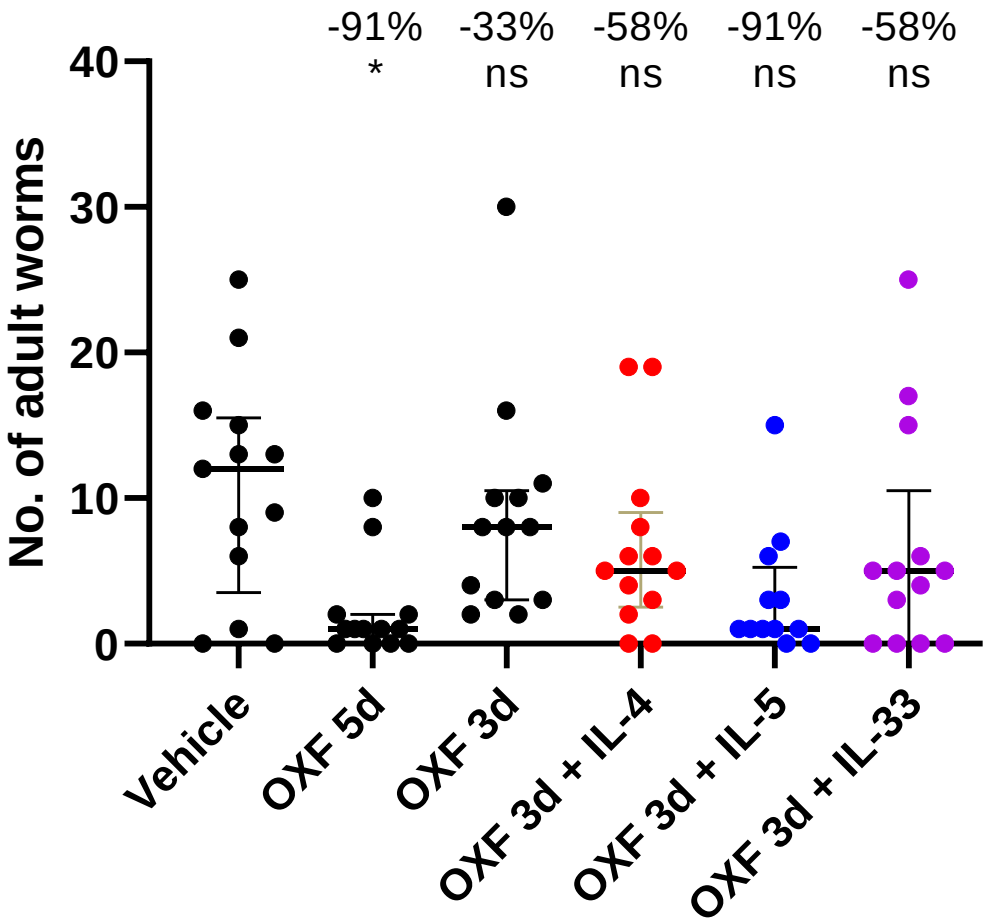
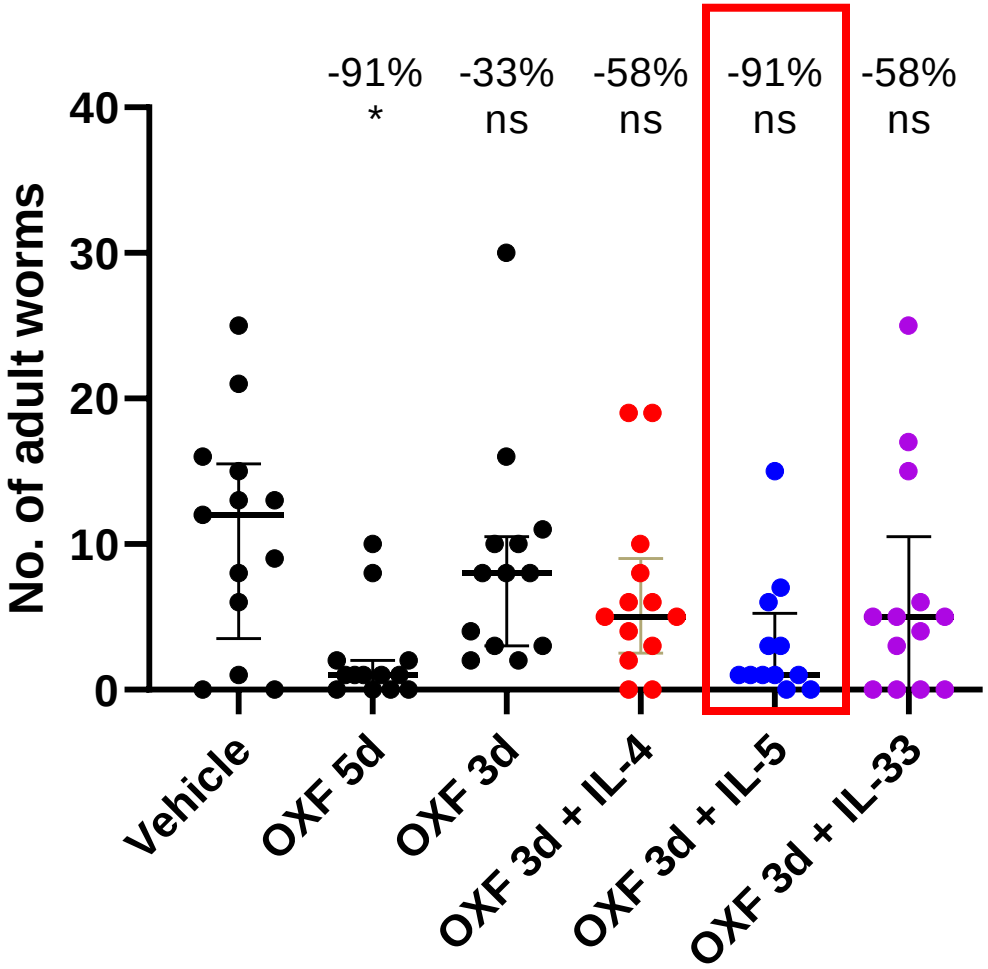


Combination of oxfendazole and type 2 cytokines for shorter treatment regimens

Infection d0 — OXF + IL-4/5/33 35-37 dpi — Necropsy 70 dpi

IL-4, IL-5, IL-33 were given intranasally (2 µg, QD for 3 days)

Oxfendazole 12.5 mg/kg BID oral



➢ Co-administration of IL-5 improves drug efficacy

Risch et al. Front Microbiol 2023