Screening for anthelmintic drugs: new molecules, new mechanisms?

Kathryn Else
Lydia Becker Institute of Immunology & Inflammation
University of Manchester
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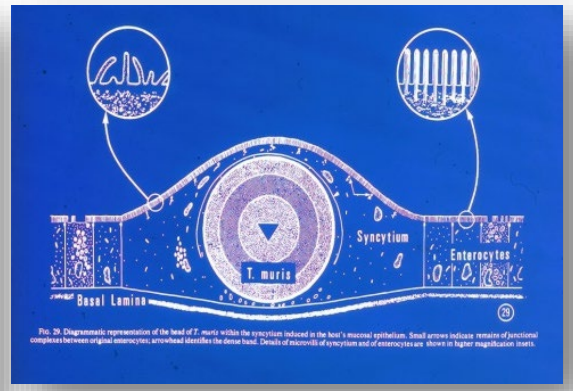
Neglected Tropical Diseases and the Soil Transmitted Helminths

- By every measurable health statistic, low/low-middle income countries are disproportionately affected by NTDs
- Poverty is considered the root cause of NTDs
- Current anti-NTD drugs are being rendered ineffective by parasite resistance.
- Novel drugs are urgently needed

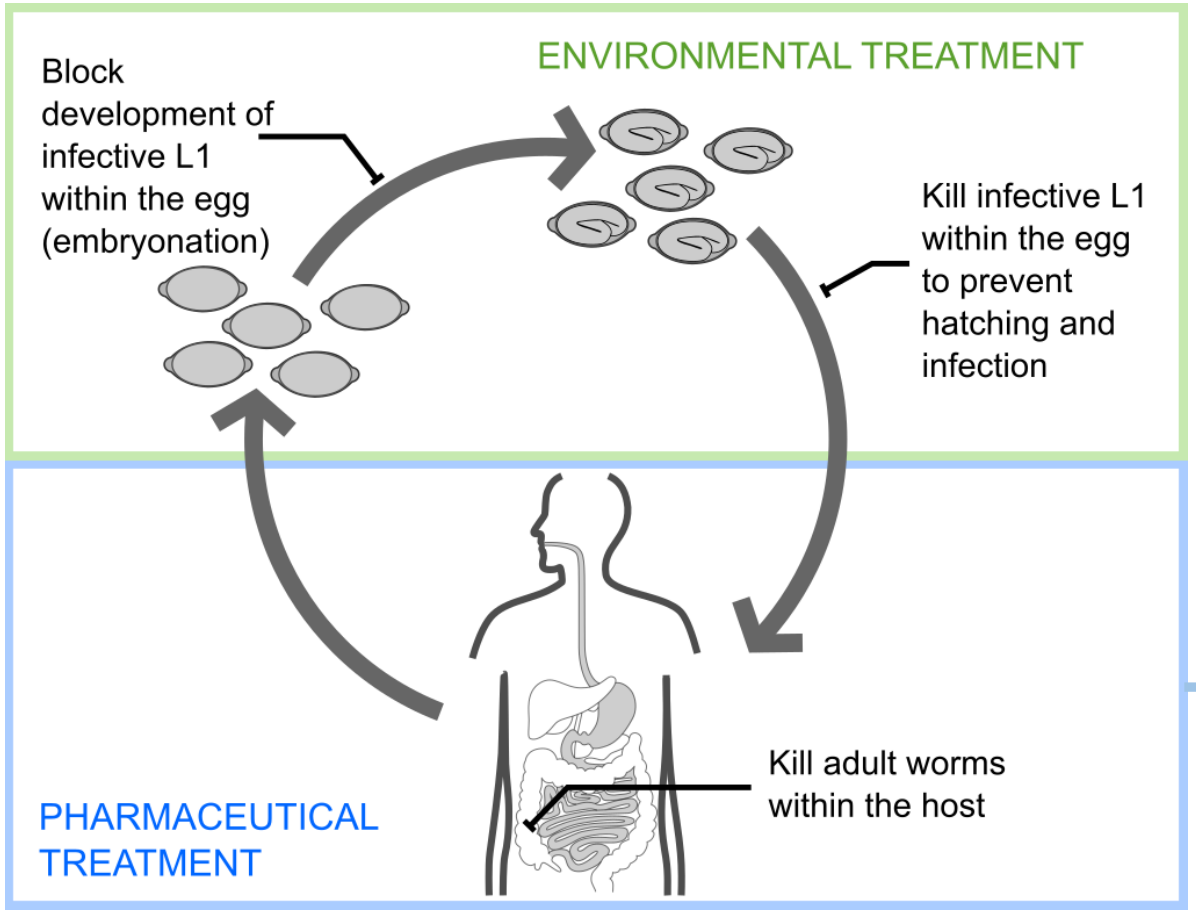
Introducing the whipworms

- ***Trichuris trichiura*** - Intestinal parasitic worm that infects ~500 million people world-wide
- One of the 3 major soil transmitted nematode parasites (whipworm, hookworm and *Ascaris*)
- Tends to cause morbidity not mortality
- Causes child growth delay, stunting and anaemia

- ***Trichuris muris*** – caecal dwelling nematode of mice
- A model of human trichuriasis caused by *T. trichiura*
- A partly *intracellular* parasitic worm that lives in the *large intestine*



Current and aspirational approaches to treat *Trichuris trichiura*



Treatment	Mechanism of action	*T. trichiura* infection		
		Preventive chemotherapy[a]	Cure rate (%)[b]	Egg reduction rate (%)[b]
Albendazole	β-Tubulin binding	Once	32.1	64.3
Mebendazole	β-Tubulin binding	Once	44.4	80.7
Albendazole–ivermectin	NA	Once	60.0	95.5
Levamisole	L-subtype nAChR agonist	Once	23.4	41.8
Pyrantel pamoate	L-subtype nAChR agonist	Once	28.5	62.3

World Health Organization

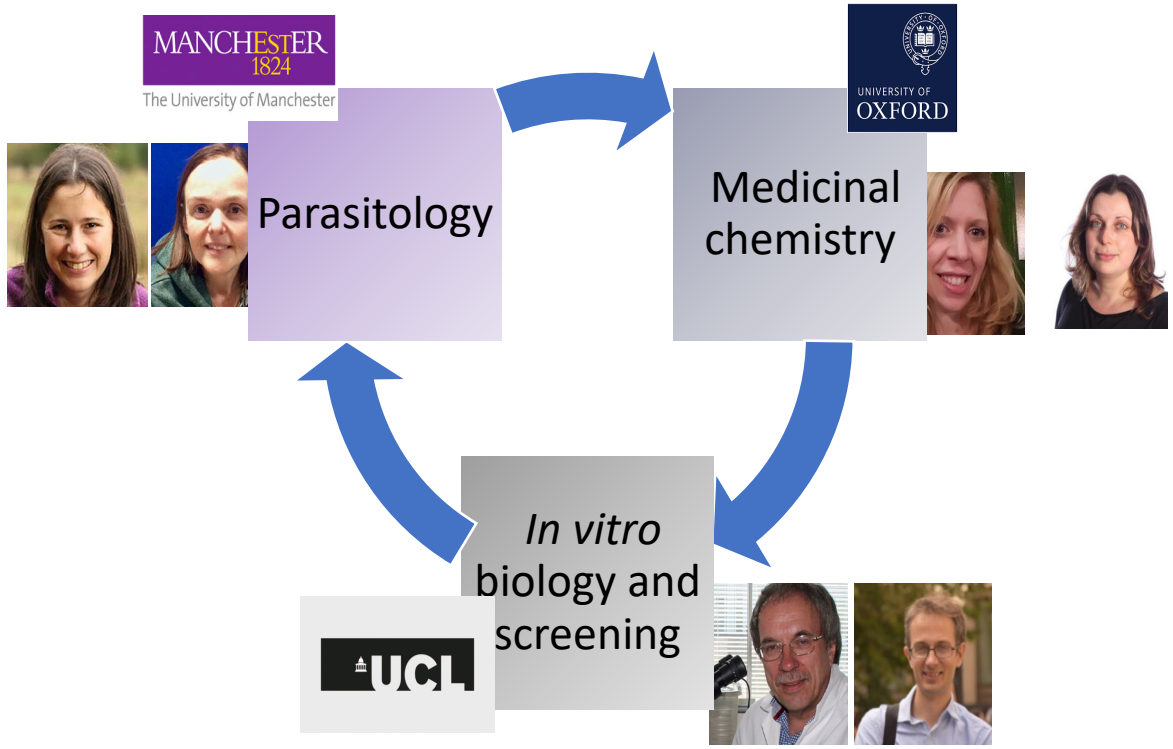
About 700 million children at risk are treated with anthelmintic drugs each year as preventative chemotherapy

Single dose, once or twice per year

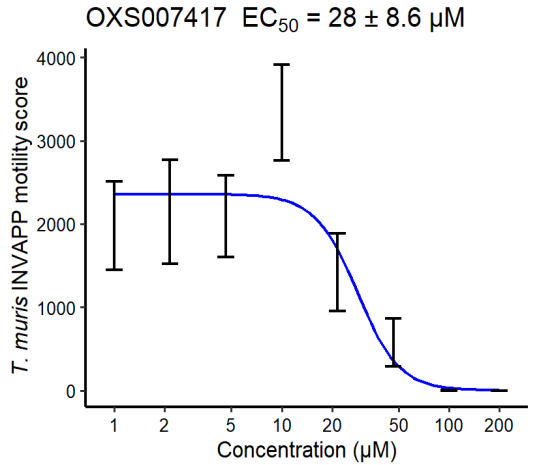
nature reviews disease primers

Else, K.J., Keiser, J., Holland, C.V. et al. Whipworm and roundworm infections. Nat Rev Dis Primers 6, 44 (2020).

An academic multidisciplinary anthelmintic discovery collaboration



Screened a library of drug-like small molecules screened, the IMPs, utilising an in vitro viability screen with adult *T. muris*

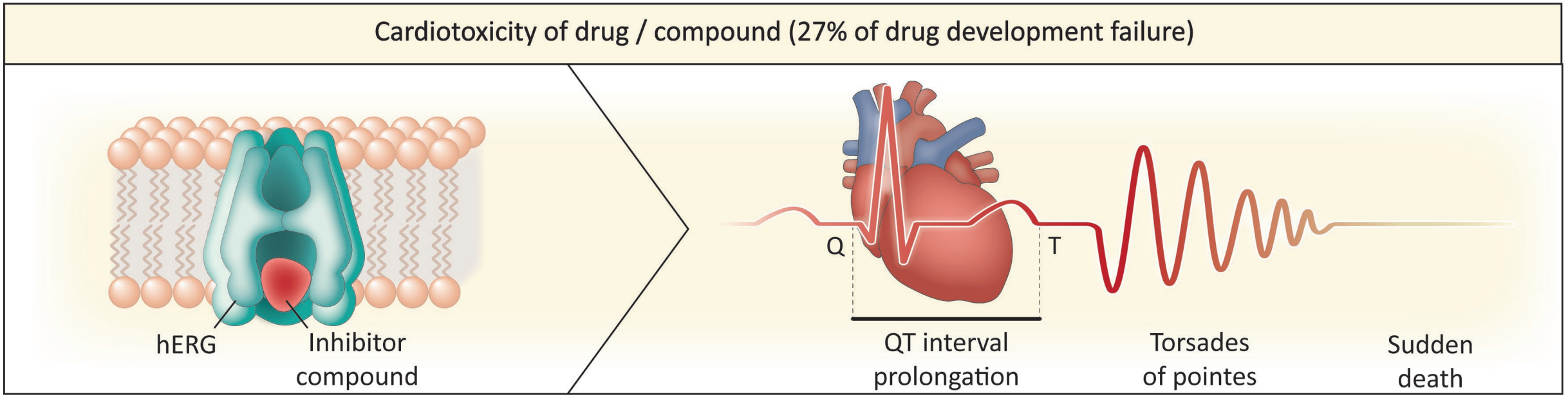


With proof of concept lead compound targeting whipworm wrote preproposal MRC DPFS 2020

Declined at preproposal as lead compound had in the panel's opinion unacceptable hERG activity

hERG activity

- hERG encodes the inward rectifying voltage gated potassium channel in the heart
- Block of this channel causes QT prolongation and can degenerate into a potential fatal ventricular arrhythmia called Torsades de pointes.
- A number of drugs have been withdrawn from late stage clinical trials due to these cardiotoxic effects, therefore it is important to identify inhibitors early in drug discovery.



Stergiopoulos *et al* 2021

Our block: the need to identify a lead compound with anti-Trichuris activity *and* acceptable hERG

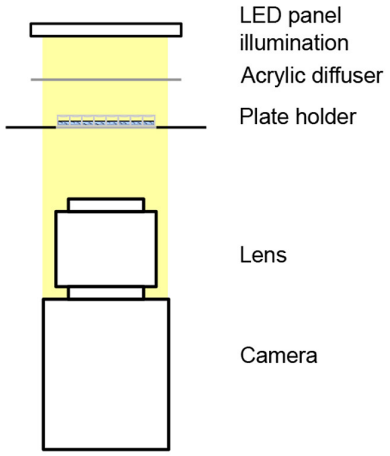
We were at D3 in the translational pathway

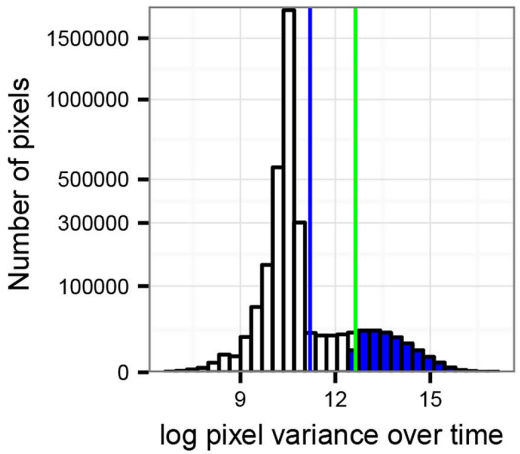
Had initial proof of concept lead compound targeting whipworm.

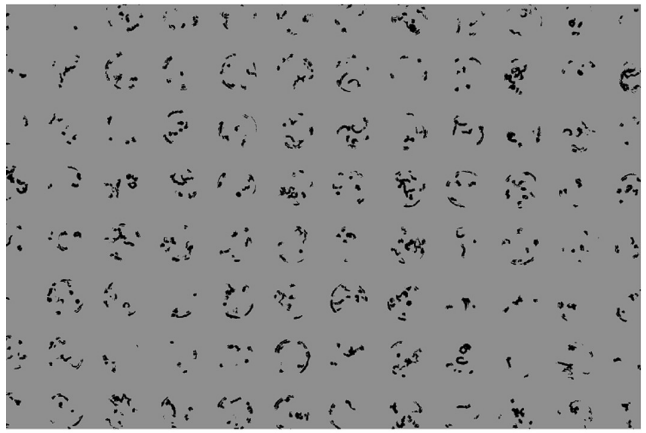
Need : establish a revised lead compound which has an improved safety profile.

TranslationManchester
Projects 4 Translation

INVAPP/Paragon movement index algorithm high-throughput system







The INVAPP setup: worms cultured in 96 well plates and movies captured

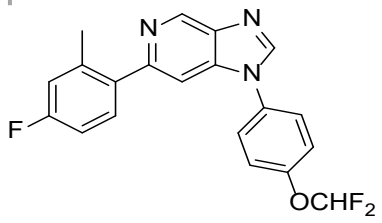
Principle of the algorithm: thresholding pixel variance analysis

96-well plate processed image determining motile regions of the image

Partridge, F. A. et al. An automated high-throughput screening system for phenotypic screening of chemical libraries on *C. elegans* and parasitic nematodes, Int J Parasitol Drugs Drug Resist 8, 8 (2018)

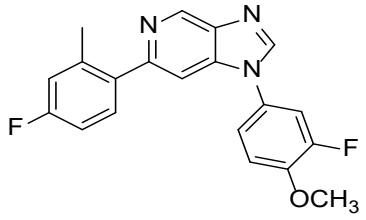
(3) Advanced compounds have EC_{50} against *ex vivo T. muris* in low micromolar range and reduced hERG activity

IMPs



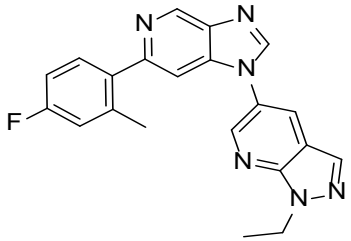
OXS007417

EC_{50} (worm) 22 µM
IC (hERG) 700 nM
GI_{50} (HepG2) < 50% @ 10 µM
Caco-2 Papp / EfR = 14 / 1.5
MLM (t1/2): 43 min
ST solubility >100 µM



OXS007373

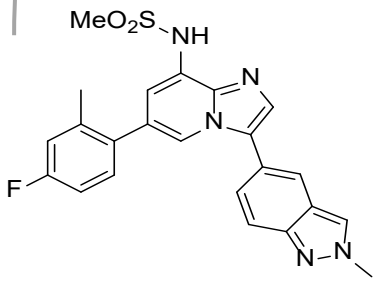
EC_{50} (worm) 8 µM
hERG 97% @ 10 µM
EC_{50} (CMT93) > 100 µM
Caco-2 Papp / EfR tbd
MLM (t1/2): 6 min
ST solubility 50 µM



OXS008553

EC_{50} (worm) 23 µM
hERG) 55% @ 10 µM
EC_{50} (CMT93) tbd
Caco-2 Papp / EfR tbd
MLM (t1/2): 17 min
ST solubility 51 µM

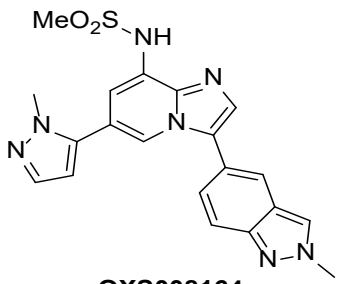
IMPAs



OXS007883

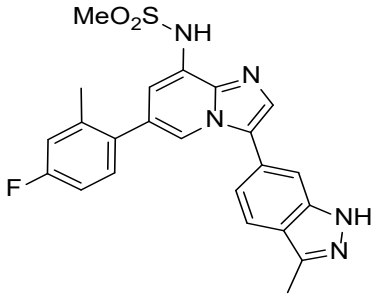
EC_{50} (worm) 10 µM
hERG 55% @ 10 µM
EC_{50} (CMT93) > 100 µM
Caco-2 Papp / EfR = 27 / 0.9
MLM (t1/2): 166 min
ST solubility 28 µM

+



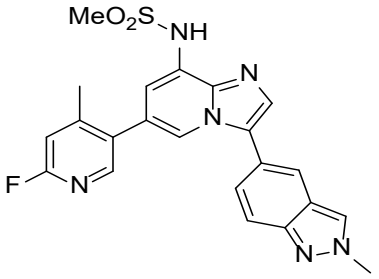
OXS008164

EC_{50} (worm) 17 µM
hERG 22% @ 10 µM
EC_{50} (CMT93) > 100 µM
Caco-2 Papp / EfR tbd
MLM (t1/2): 307 min
ST solubility >200 µM



OXS007867

EC_{50} (worm) 15 µM
hERG 47% @ 10 µM
EC_{50} (CMT93) tbd
Caco-2 Papp / EfR = 6.7/ 1.9
MLM (t1/2): 237 min
ST solubility 39 µM

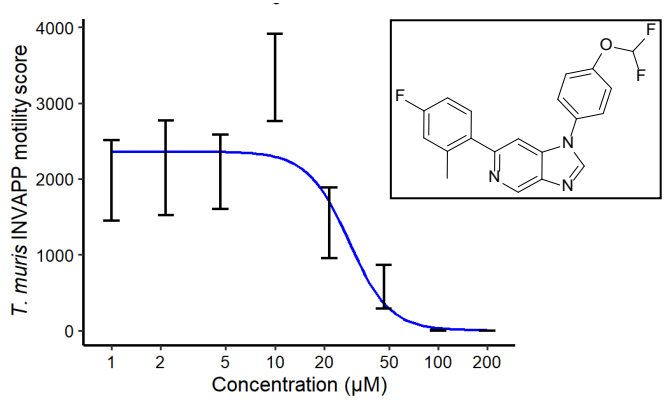


OXS008163

EC_{50} (worm) 34 µM
hERG 45% @ 10 µM
EC_{50} (CMT93) > 100 µM
Caco-2 Papp / EfR = 29 / 0.8
MLM (t1/2): 338 min
ST solubility 120 µM

New screen, new hit series: a newly-identified anthelmintic compound series

OXS007417 (IMP)



Worm EC_{50} = 28μM

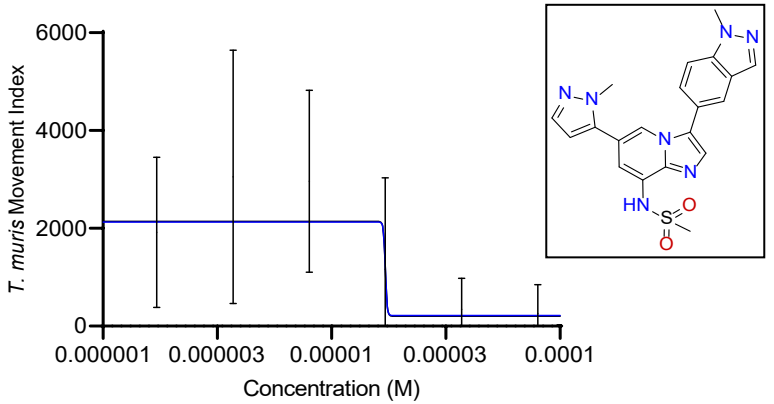
hERG IC_{50} = 700nM

CMT93 cytotoxicity EC50 = 27μM

MLM (t1/2): 43 min

ST solubility > 100μM

OXS008164 (IMPA)



Worm EC_{50} = 17.2μM

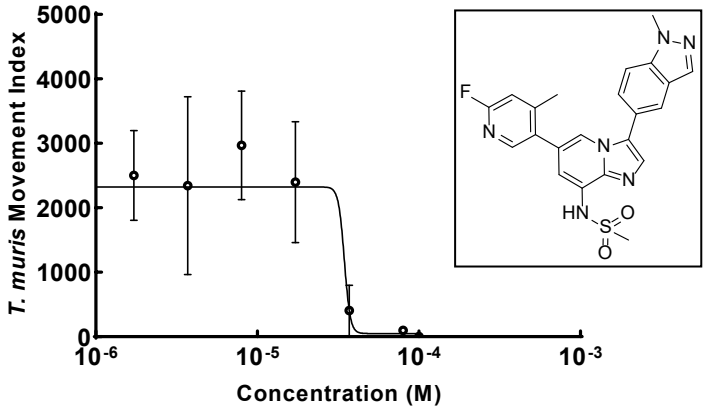
hERG = 22% inhib @10μM

CMT93 cytotoxicity EC50 > 100μM

MLM (t1/2): 307 min

ST solubility = >200μM

OXS008163 (IMPA)



Worm EC_{50} = 34.6μM

hERG = 45% inhib @10μM

CMT93 cytotoxicity EC50 > 100μM

MLM (t1/2): 338 min

ST solubility = 120μM

OUTCOMES of P4T fund

- Armed with the newly-identified anthelmintic compound series: IMPAs
- MRC DPFS preproposal 2021 - success!
- Invited to full proposal in 2022

- New collaboration with Katie Moore (Material Sciences) and Nick Lockyer (Chemistry) – NanoSIMS and ToFSIMs -determine the localisation of drugs in tissues

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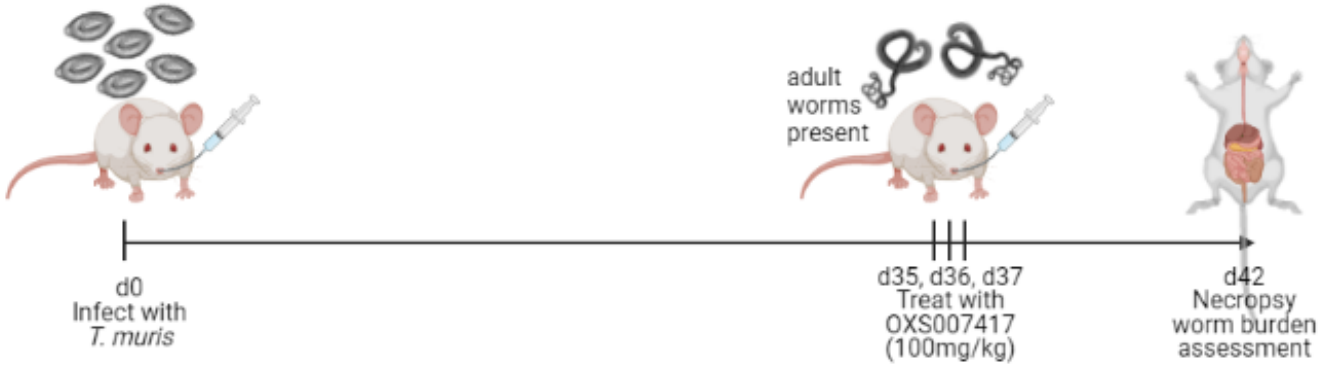
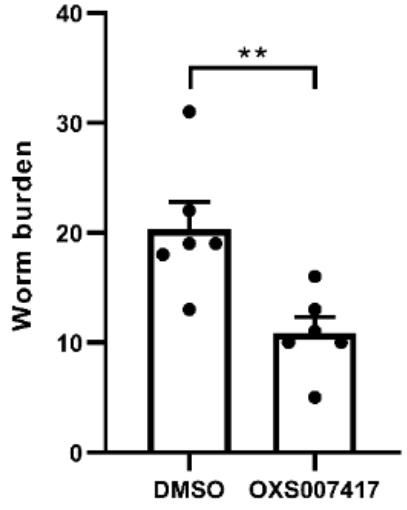
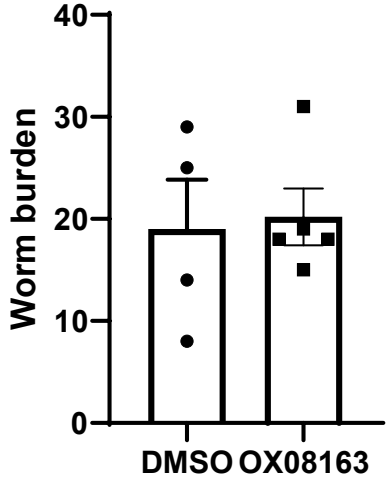
Thank you

New screen, new hit series: a newly-identified anthelmintic compound series







Caco-2 Papp / EfR = 14/1.5

Caco-2 Papp / EfR: 29/0.81