Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
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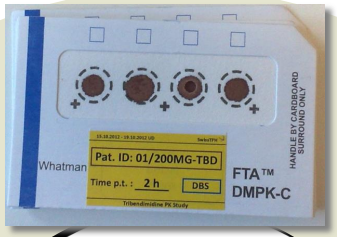
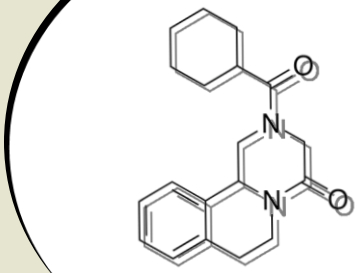
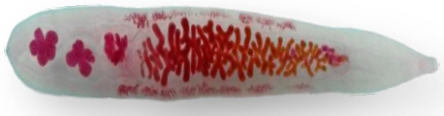
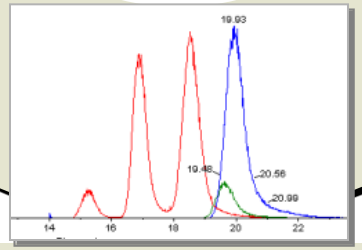
Unit of Helminth Drug Development

Praziquantel: novel insights from bench and field



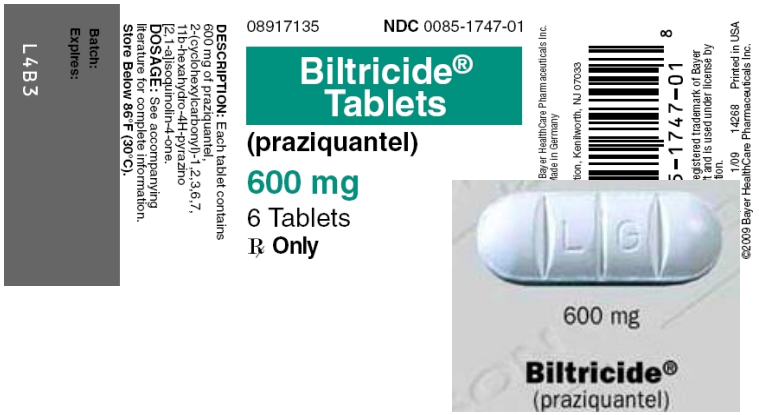


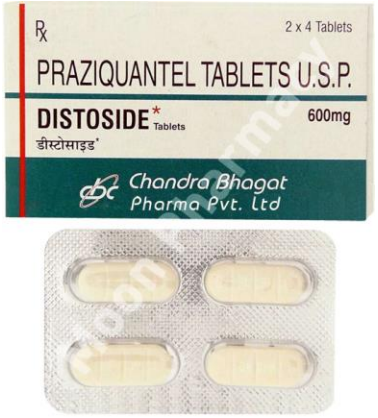




Praziquantel in short

-Developed by Merck and Bayer in 1977
-marketed by Bayer under the name of Biltricide
-dosage 40mg/kg (*Schistosoma mansoni*), 3x25mg/kg (*Opisthorchis viverrini*)
-various advantages as cost, application, broad spectrum, efficacy and low toxicity

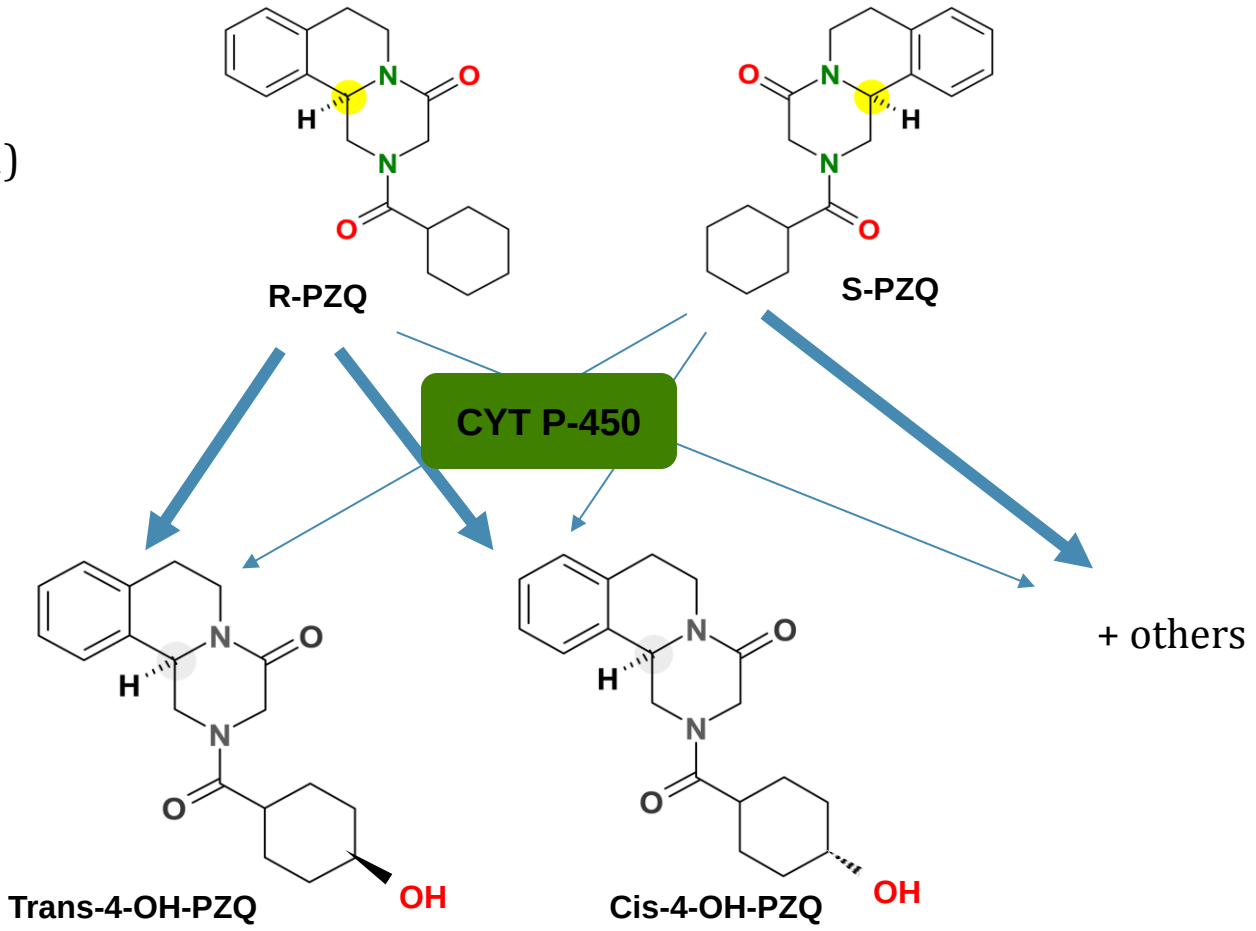




Drawbacks:
-resistance
-only active in adult schistos (not in juvenile stages)
-huge tablets
-bitter taste
-adverse effects

Metabolism

Praziquantel (1:1)



Activity in Schistosomes: background

Praziquantel

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 0022–1899/89/5903–0035$01.00

Comparative in Vitro and in Vivo Activity of Racemic Praziquantel and Its Levorotated Isomer on *Schistosoma mansoni*

⌫ *In vitro*: minimum effective concentration of R-PZQ half of rac PZQ
⌫ *In vivo*: similar outcome (activity resides in R-PZQ enantiomere)

Trans-4-OH

Light and scanning electron microscopy studies on the effects of the enantiomers of praziquantel and its main metabolite on *Schistosoma mansoni* in vitro

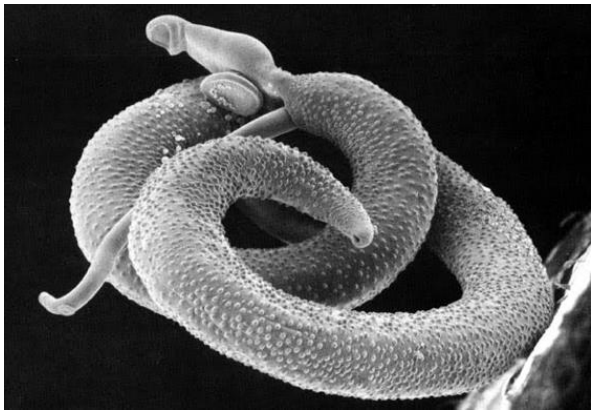
Ute Staudt[1], Günter Schmahl[2], Gottfried Blaschke[1], and Heinz Mehlhorn[2]

⌫R trans-4-OH more active than S enantiomere
⌫R-PZQ and R-trans nearly same activity

Objectives

- assess the *in vitro* activities of : R- and S-PZQ
  R- and S-*trans*-4-OH-PZQ
  R- and S-*cis*-4-OH-PZQ

- characterize the hepatic shift *in vivo*: R- and S-PZQ



Aim

identify the active molecule to optimize the treatment

Methods

In vitro assays:
- adult *S. mansoni*
- concentrations from 0.01 to 100µg/ml PZQ and metabolites
- viability assessment (motility scale) at 4 and 72 h
- calculate IC_{50}
- microcalorimetry

In vivo R/S-PZQ:
- mice infected with adult *S. mansoni*
- 400 mg/kg rac PZQ and S-PZQ; 200mg/kg R-PZQ
- dissection at 30min, 1, 4 and 24h post-treatment
- worm counts in veins and liver (dead/alive)

Results

In vitro (adults):

	IC_{50} at 4 h (µg/mL)	IC_{50} at 72 h (µg/mL)	IC_{90} at 72 h (µg/mL)	Eudysmic ratio
Rac-PZQ	0.1	0.05	0.4	
R-PZQ	0.04	0.02	0.04	293
S-PZQ	5.7	5.9	17.9	
Rac-*trans*-4-OH-PZQ	16.7	7.9	3694.1[a)]	
R-trans-4-OH-PZQ	13.4	4.1	58.4	
S-trans-4-OH-PZQ	Not active at 100	Not active at 100	Not active at 100	
Rac-*cis*-4-OH-PZQ	15.8	4.8	81.4	
R-cis-4-OH-PZQ	4.5	2.4	48.7	
S-cis-4-OH-PZQ	Not active at 100	Not active at 100	Not active at 100	

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S-cis-4-OH-PZQ	Not active at 100	Not active at 100	Not active at 100	

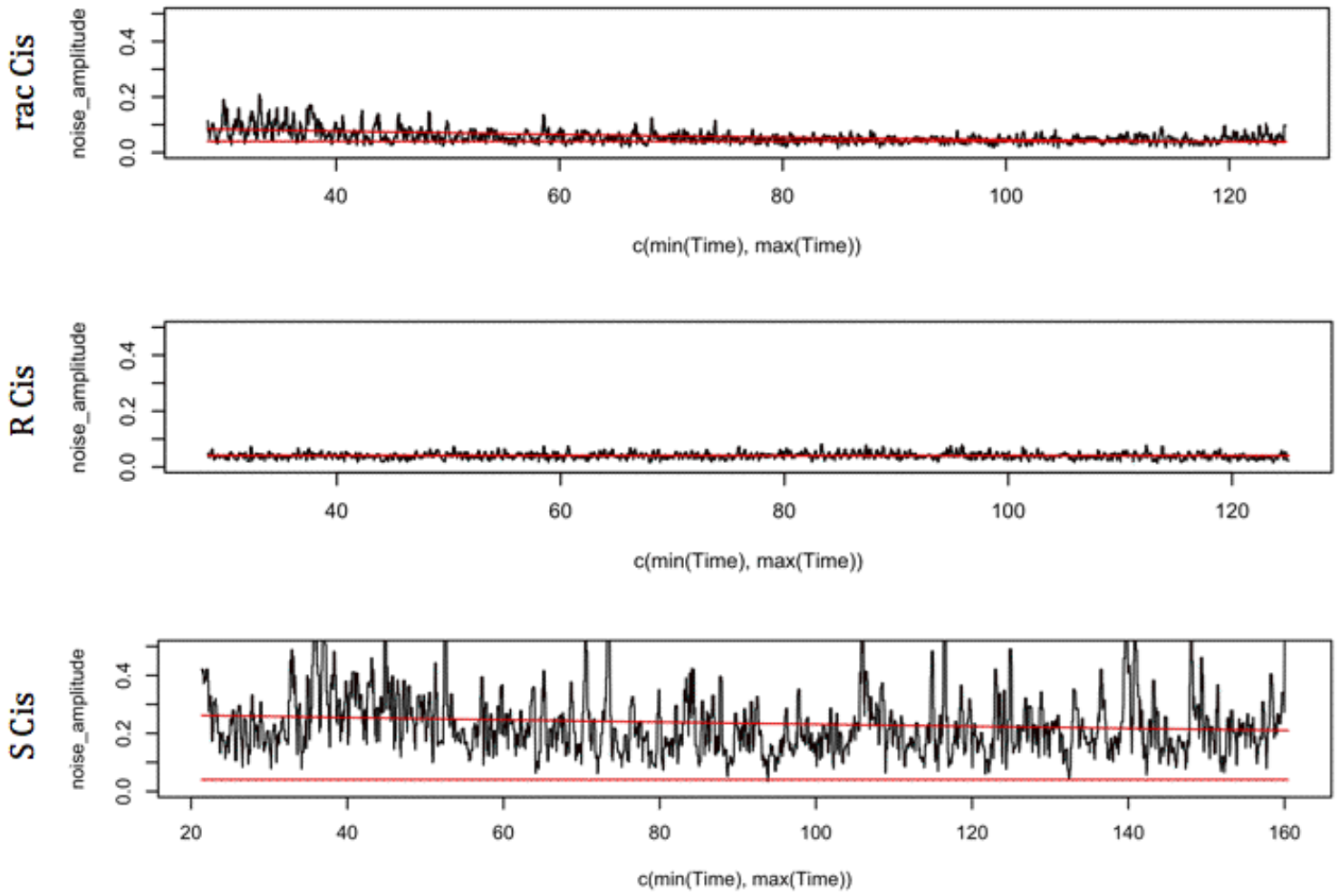
PK data:

	C_{max} (µg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (µg ml^{-1} h)	AUC/IC_{50}
R-PZQ	0.16	2.67	1.55	0.87	43.5
S-PZQ	0.52	2.55	1.46	2.99	0.5
R-trans-4-OH-PZQ	1.31	2.72	1.70	8.80	2.1
S-trans-4-OH-PZQ	0.78	3.05	1.91	5.60	No IC_{50}

Results

Swiss TPH

Microcalorimetry:



Results

Swiss TPH

Microcalorimetry (hours):

	0.04 µg/mL	0.2 µg/mL	1 µg/mL
Rac-PZQ	> 120	< 3	< 3
R-PZQ	< 3	< 3	< 3
S-PZQ	> 120	> 120	> 120
	1 µg/mL	5 µg/mL	50 µg/mL
Rac-*trans*-4-OH-PZQ	> 120	> 120	< 3
R-trans-4-OH-PZQ	> 120	75 (5)	< 3
S-trans-4-OH-PZQ	> 120	> 120	> 120
Rac-*cis*-4-OH-PZQ	> 120	96.7 (16.1)	< 3
R-cis-4-OH-PZQ	> 120	< 3	< 3
S-cis-4-OH-PZQ	Not tested	Not tested	> 120

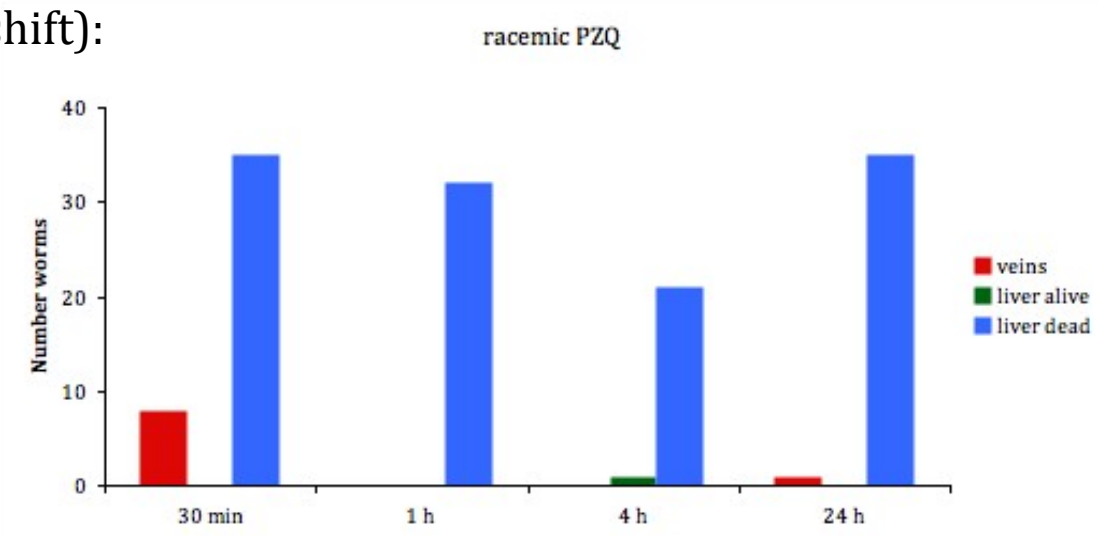
Results

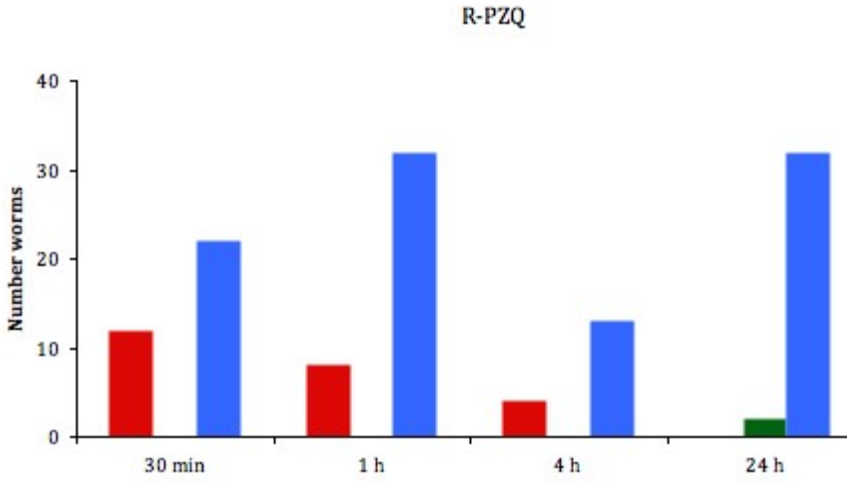
In vivo:

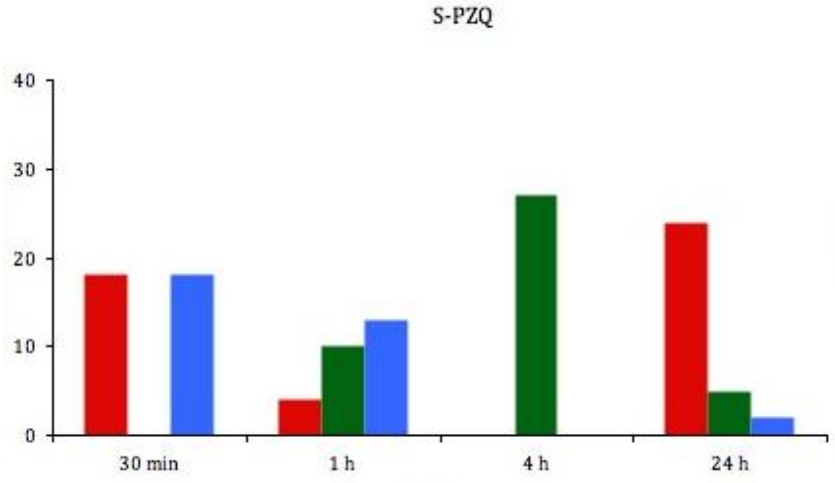
Rac PZQ	Number mice	WBR [%] (SD)	ED_{50} (mg/kg)	
400 mg/kg	4	94.1 (8.6)	246.5	
100 mg/kg[b)]	6	15 (9.5)		
R-PZQ			ED_{50} (mg/kg)	
400 mg/kg	3	100.0 (0)	95.4	
200 mg/kg	6	98.1 (2.3)		
100 mg/kg	6	52.0 (30.8)		
S-PZQ			ED_{50} (mg/kg)	Eudysmic ratio
800 mg/kg	6	19.6 (22.2)	3066777[a)]	32136
400 mg/kg	4	18.0 (21.4)		

Results

In vivo (hepatic shift):

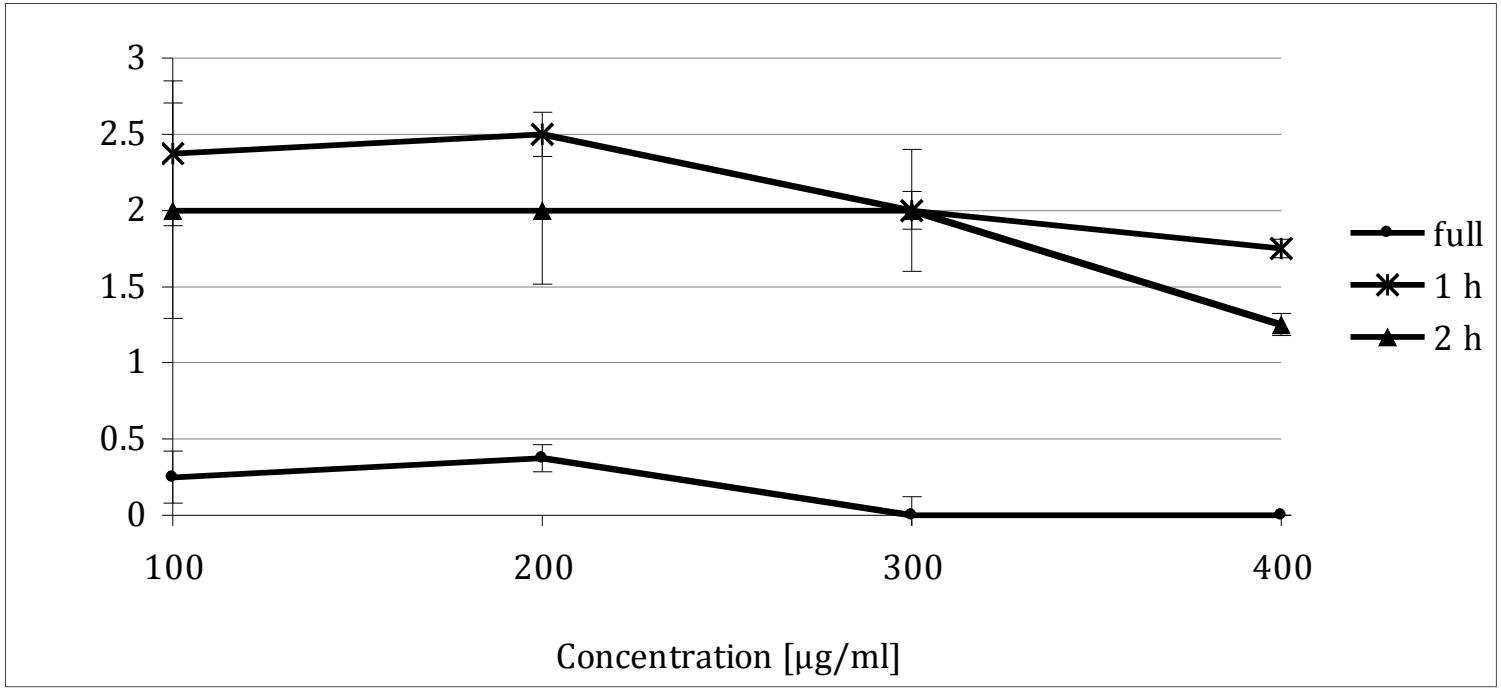






Results

In vitro incubation with S-PZQ (adults):



What we take from the bench

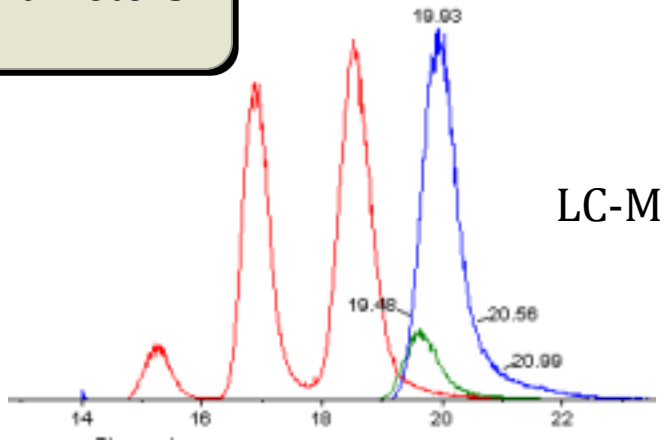
- R-PZQ treatment could effectively replace actual racemic treatment
  - ⌫ tablet volume reduced by 1/2
  - ⌫ S-PZQ might be source of adverse effects and bitter taste

Next steps:

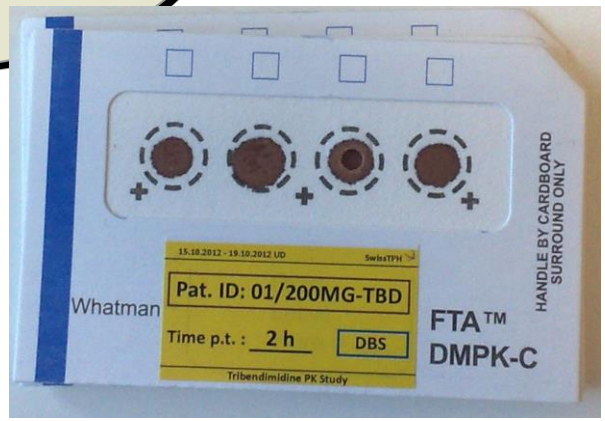
-more PK data (chiral separation)
-test recovery of worms after *in vitro* treatment with metabolites
-CYT P-450 inhibition studies

Field insights: dried blood spots (DBS)

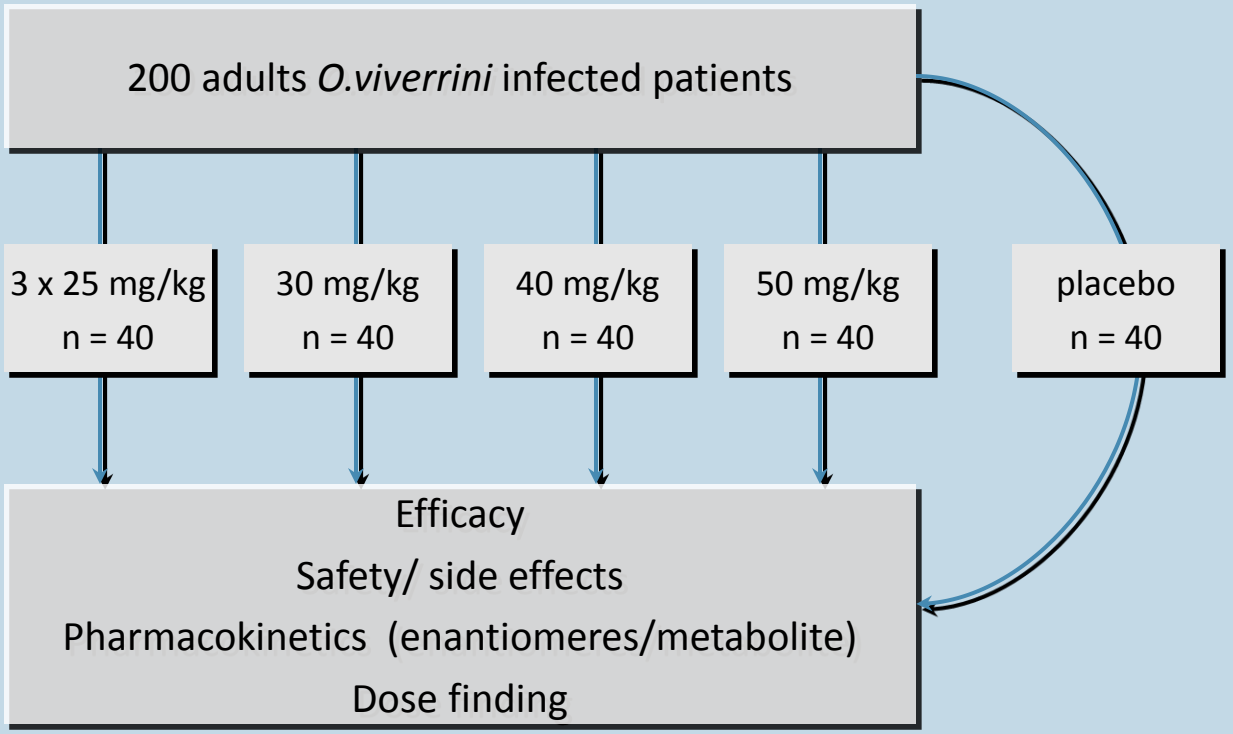
PK parameters



LC-MS/MS



Study settings



DBS sampling: 0.5, 1, 1.5, 2, 2.5, 3, 6, 8, 12, 24 h

Analytical method

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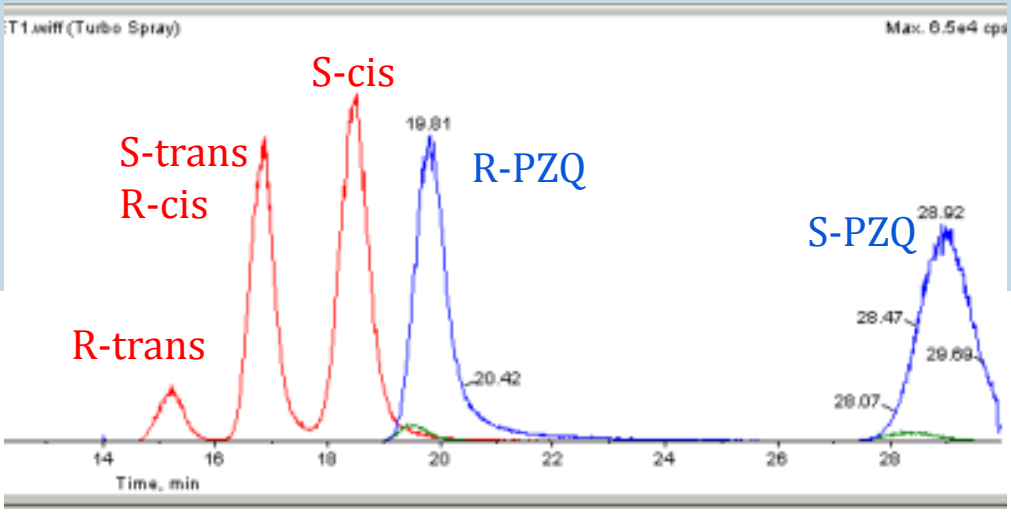
Detection of R and S praziquantel, and R-trans metabolite

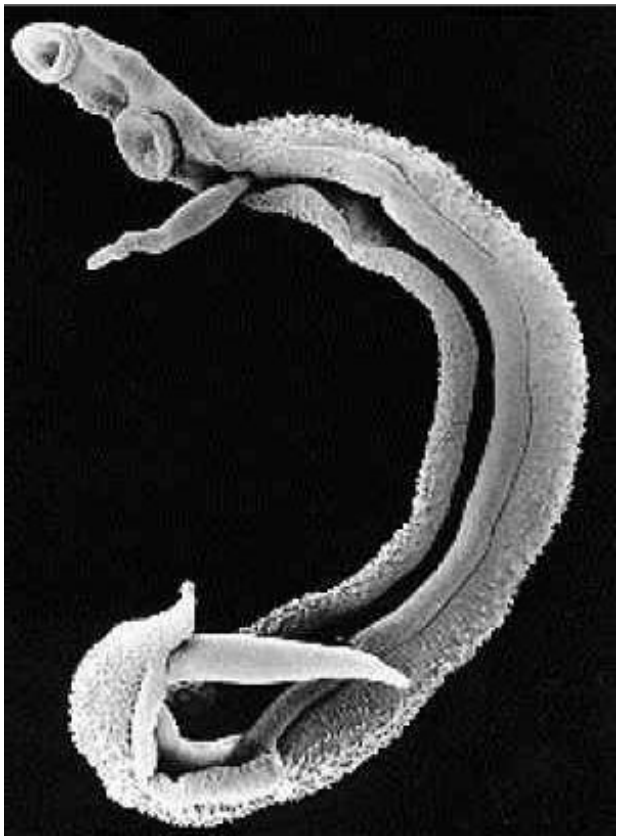
Sensitivity of 10-2500 ng/mL for PZQ (extraction ca. 15µl blood spot)

Sensitivity of 20-5000 ng/mL for the metabolite



Acknowledgements

Prof. Jennifer Keiser and all the team…



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