Pharmacokinetics and Pharmacodynamics of Murepavadin (POL7080) in neutropenic lung infection models

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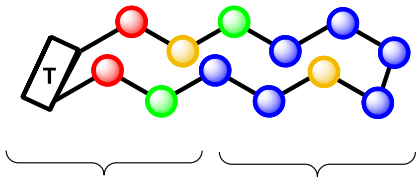
Murepavadin: Outer membrane protein targeting antibiotic

This novel class of antibiotic (OMPTA) contains two cooperative pharmacophores: Outer-membrane Protein targeting and LPS binding

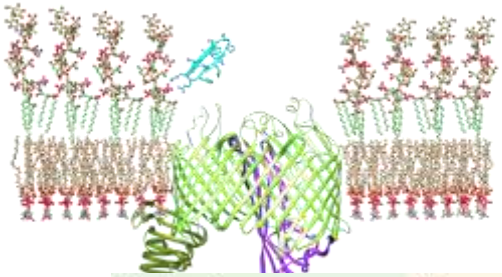
Murepavadin (POL7080)

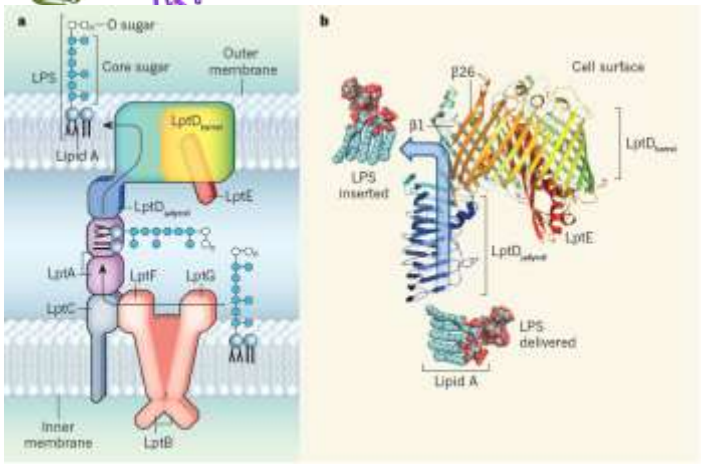


Pharmacophore 1
OMP binding

Pharmacophore 2
LPS binding

Target LptD





N. Srinivas et al. *Science* **2010**, *327*, 1010-1013; R. E. Bishop, *Nature* **2014**, *511*, 37-38; S. Qiao et al. *Nature* **2014**, *511*, 108-111; Dong et al. *Nature* **2014**, *511*, 52-56

LptD was identified as the Outer Membrane protein target for Murepavadin

Murepavadin: *In vitro* activity

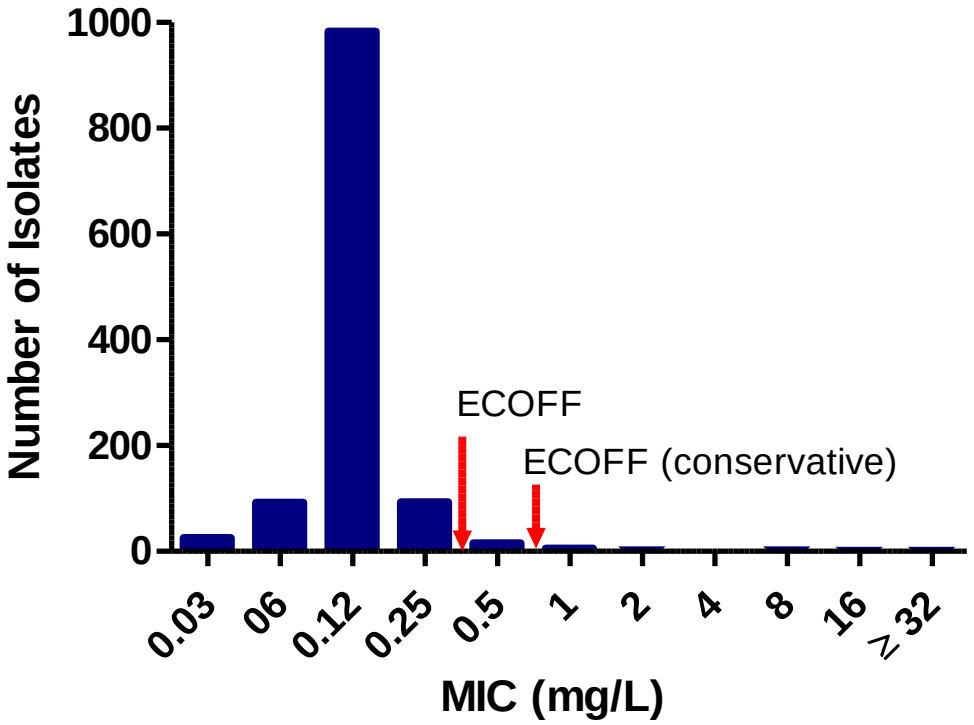
Summary of *in vitro* experiments

- Murepavadin displays potent anti-pseudomonal activity including MDR isolates
- Murepavadin displays potent activity on a large panel of CF isolates including mucoid strains
- Murepavadin demonstrates a potent and rapid bactericidal activity at 2-4 times the MIC
- Murepavadin is active across a broad range of pH values
- Human serum has only a moderate effect on the *in vitro* activity of Murepavadin
- Lung surfactant (Survanta®) has no effect on the *in vitro* activity of Murepavadin
- The inoculum size has only a minor effect on the *in vitro* activity of Murepavadin
- The *in vitro* activity of Murepavadin is not antagonized nor was synergy observed by the antibiotics tested to date

Murepavadin has favorable *in vitro* properties making it a potent antibiotic against *P. aeruginosa* including MDR isolates

Determining the ECOFF of Murepavadin

Surveillance data (n=1219) from Europe and USA (2014) and China (2012-2013) including 28% MDR pathogens

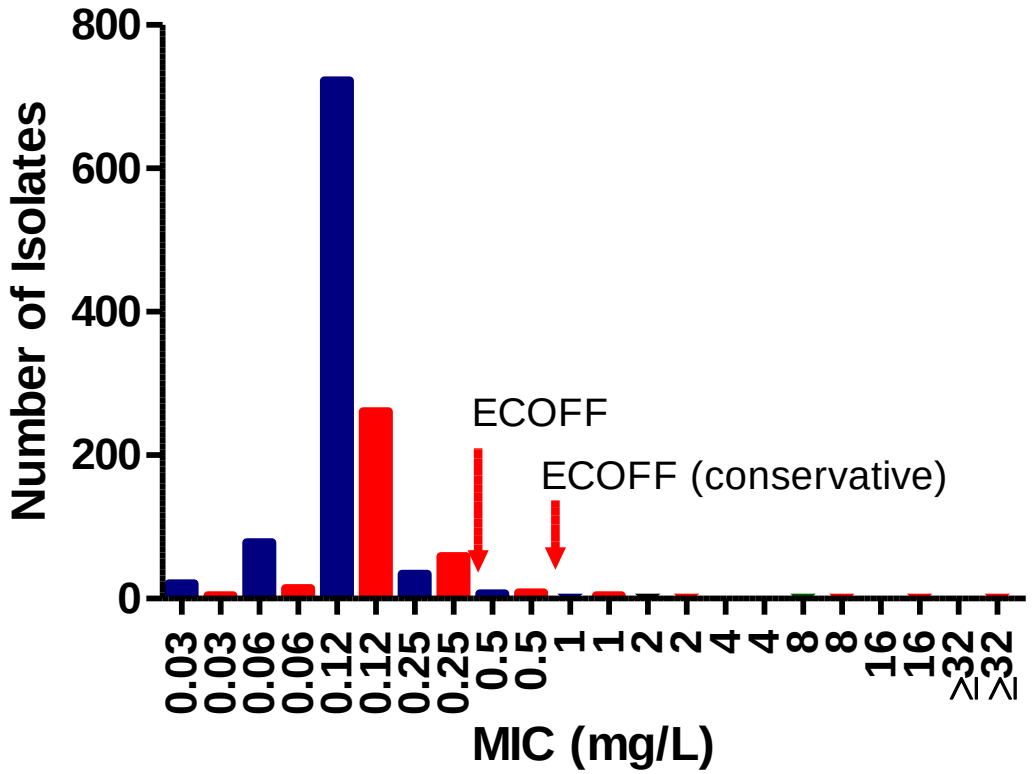


	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
n=1219	25	92	983	93	15	5	2	0	2	1	1
Cum %	2.1	9.6	90.2	97.9	99.1	99.5	99.7	99.7	99.8	99.9	100.0

The ECOFF would cover either 98 or 99% of the *P. aeruginosa* isolates

Comparison Non-MDR vs MDR

Surveillance data from Europe and USA (2014) and China (2012-2013) comparing non-MDR to MDR



n=1219	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	1	2	4	8	16	≥32
Non-MDR	**2.4**	**11.4**	**94.9**	**98.8**	**99.7**	99.8	99.9	99.9	100.0	100.0	100.0
MDR	**1.1**	**5.1**	**78.8**	**95.5**	**97.7**	98.9	99.2	99.2	99.4	99.7	100.0

*** MDR defined by Magiorakos *et al*, 2012. Susceptibility based on EUCAST break points**

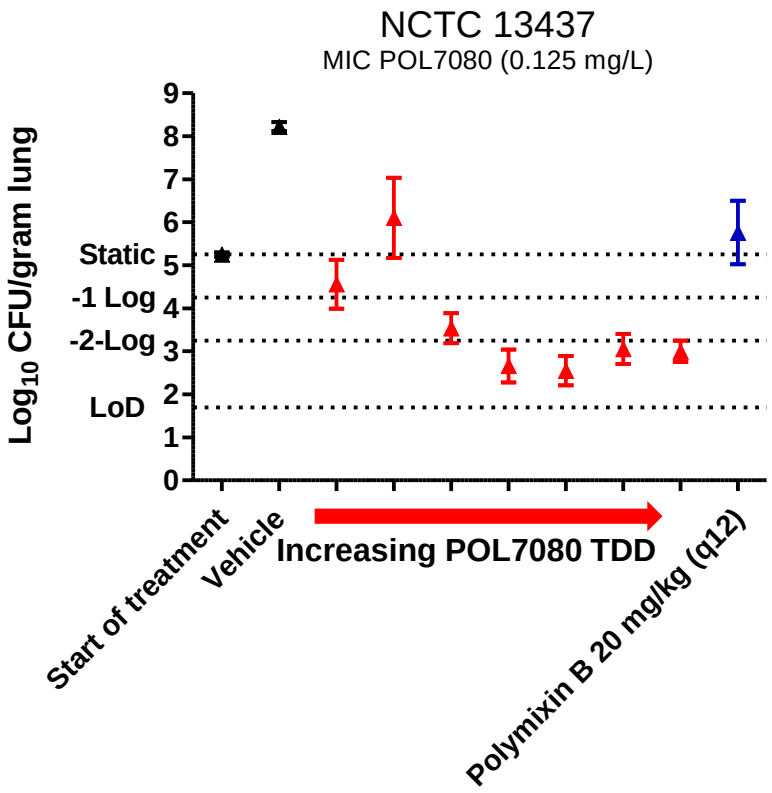
Surveillance study at Huashan Hospital China

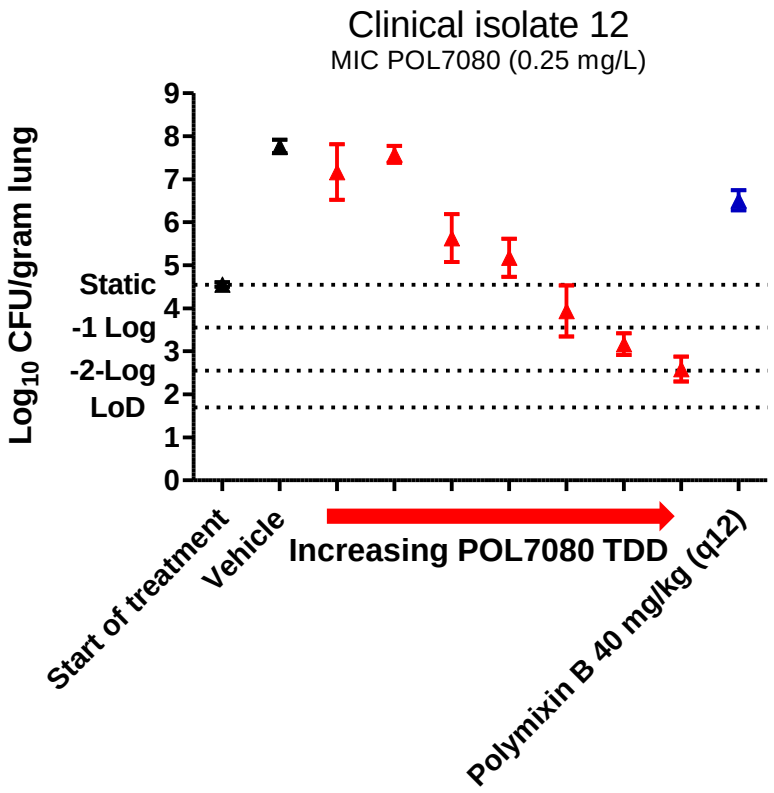
Huashan hospital, China. *In vitro* activities of POL7080 and comparative antimicrobial agents against *Pseudomonas aeruginosa* (MIC mg/L)

Organisms	Antimicrobial agents	Breakpoint S	Breakpoint R	MIC Range	MIC_{50}	MIC_{90}	R%	S%
P. aeruginosa	**POL7080**			**0.06 - 2**	**0.25**	**0.5**		
(510)*	Colistin	≤2	≥8	≤0.12 - 32	1	4	6.5	82.7
	Meropenem	≤2	≥8	≤0.06 - >128	0.5	64	31.2	59.8
	Ceftazidime	≤8	≥32	0.5 - >128	8	>128	29.8	59.2
	Piperacillin- tazobactam	≤16/4	≥128/4	0.25 - >128	32	>128	30.2	48.6
	Ceftolozane-tazobactam	≤4	≥16	0.25 - >32	2	>32	20.6	72
	Tobramycin	≤4	≥16	0.12 - >16	2	>16	20.8	77.6
	Ciprofloxacin	≤1	≥4	0.12 - >32	2	>32	40.8	49
Colistin-R (33)	**POL7080**			**0.06 - 2**	**0.25**	**0.5**		
	Colistin	≤2	≥8	8 - 32	8	16	100	0
	Meropenem	≤2	≥8	≤0.06 - 128	0.25	16	18.2	72.7
	Ceftazidime	≤8	≥32	2 - >128	4	32	12.1	75.8
	Piperacillin- tazobactam	≤16/4	≥128/4	8 - >128	16	128	12.1	57.6
	Ceftolozane-tazobactam	≤4	≥16	1 - >32-	2	16	15.2	78.8
	Tobramycin	≤4	≥16	1 - >16	2	>16	18.2	75.8
	Ciprofloxacin	≤1	≥4	0.25 - >32	1	32	24.2	66.7
XDR* (43)	**POL7080**			**0.06 - 1**	**0.25**	**0.5**		
	Colistin	≤2	≥8	≤0.12 - 8	1	2	4.7	93
	Meropenem	≤2	≥8	8 – >128	64	>128	100	0
	Ceftazidime	≤8	≥32	32 - >128	>128	>128	100	0
	Piperacillin- tazobactam	≤16/4	≥128/4	128 - >128	>128	>128	100	0
	Ceftolozane-tazobactam	≤4	≥16	2 –>32	>32	>32	88.4	4.7
	Tobramycin	≤4	≥16	>16	>16	>16	100	0
	Ciprofloxacin	≤1	≥4	4 –>32	>32	>32	100	0

Murepavadin is active against XDR isolates

Neutropenic mouse lung infection model



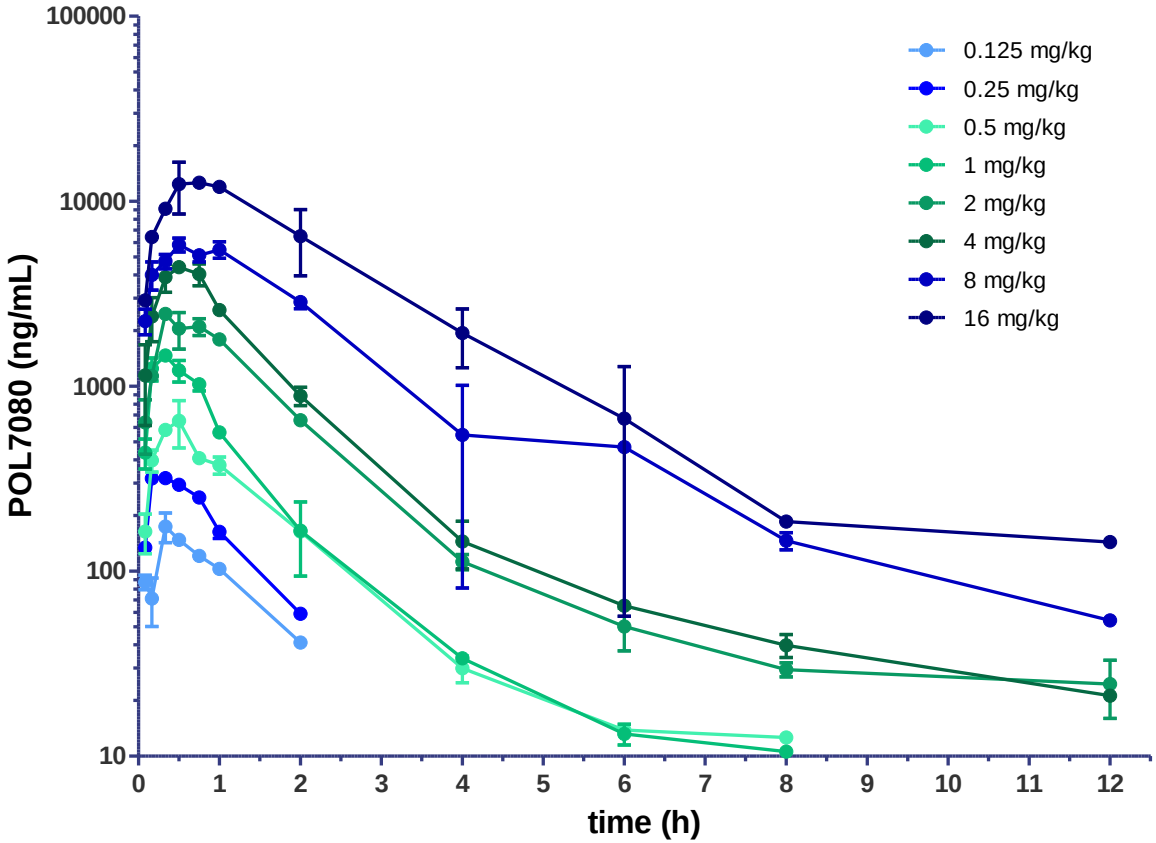


Murepavadin is effective against XDR* isolates whereas Polymyxin B shows little activity

*** XDR defined by Magiorakos *et al*, 2012. Susceptibility based on EUCAST break points**

Pharmacokinetics in the neutropenic mouse

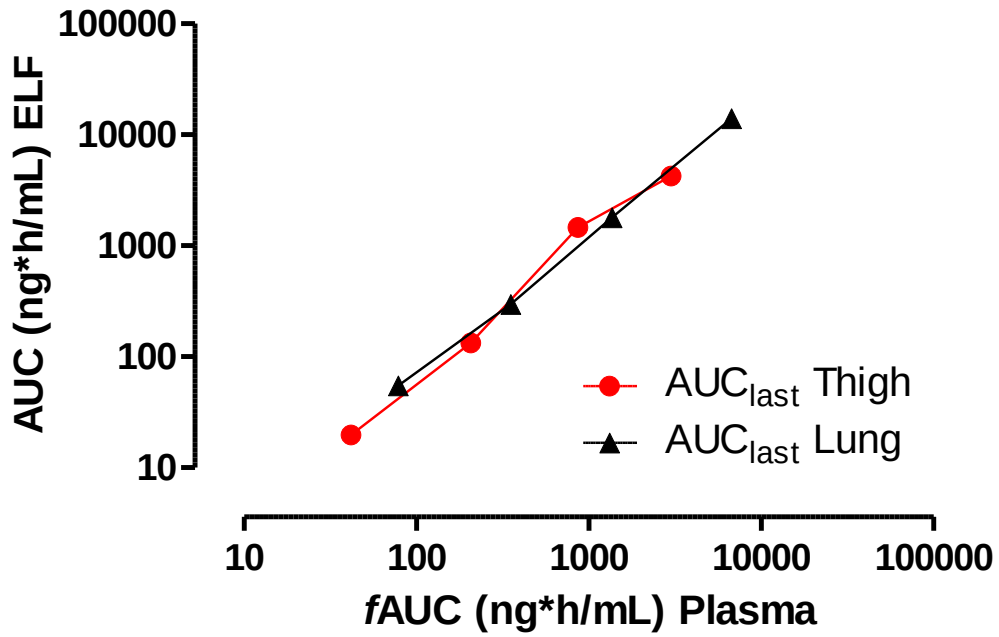
POL7080 plasma concentration (mean ± SD)



POL7080 has a linear pharmacokinetic in the neutropenic mouse

Pharmacokinetics in the neutropenic mouse

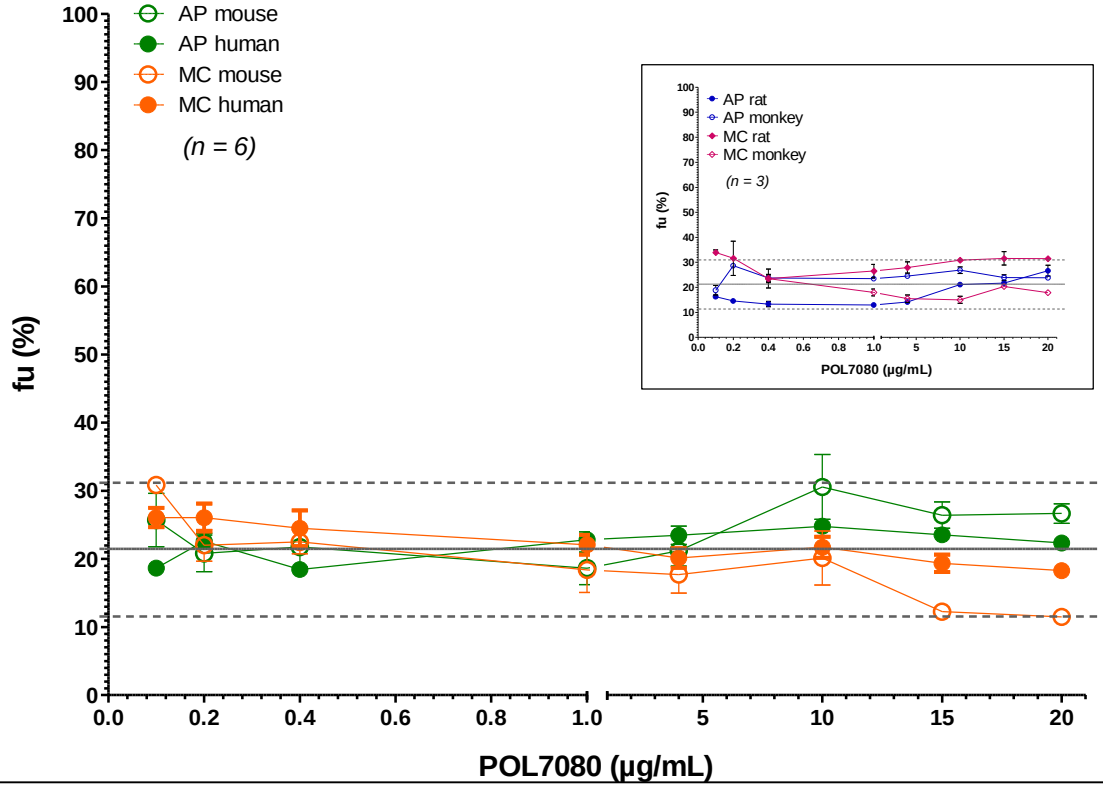
Comparison of POL7080 ELF and free plasma concentrations



POL7080 has a linear, nearly 1:1 relationship of total ELF concentration and unbound plasma concentration

Murepavadin plasma protein binding

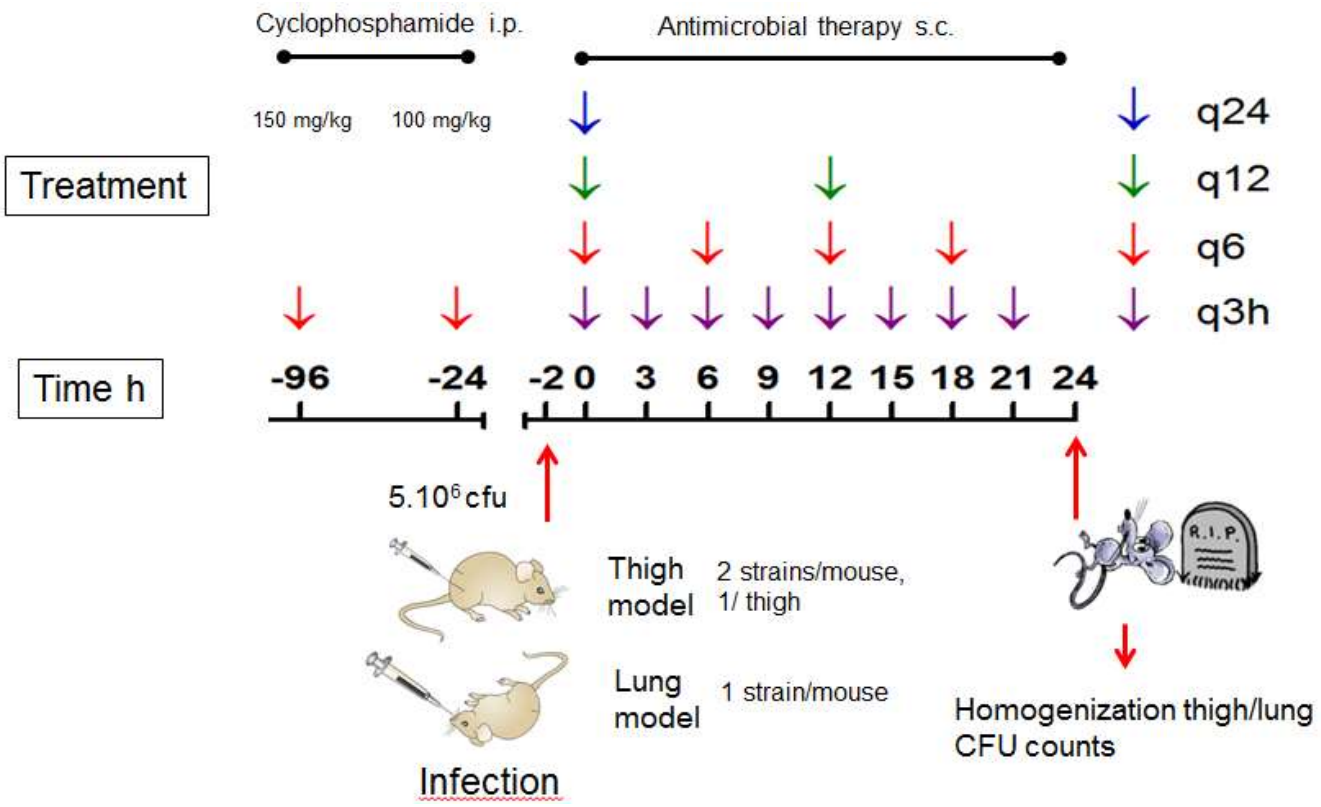
POL7080 f_u as a function of compound concentration (mean±SD) in plasma from mouse and human (inset: rat and monkey)



An overall cross-species mean of the % f_u factor of 22.4 is likely sufficient to calculate the free compound fraction over the concentration range from 0.1-20 µg/mL for human, monkey, rat, and mouse

Neutropenic Lung/thigh infection models

The assays were conducted at three seperate facilities (Evotec UK Ltd., Staten Serum Institue, Radboudumc)



All sites followed the same methodology

MICs of isolates tested

MICs were determined at JMI Labs, 5 repeats, modal value used for analysis

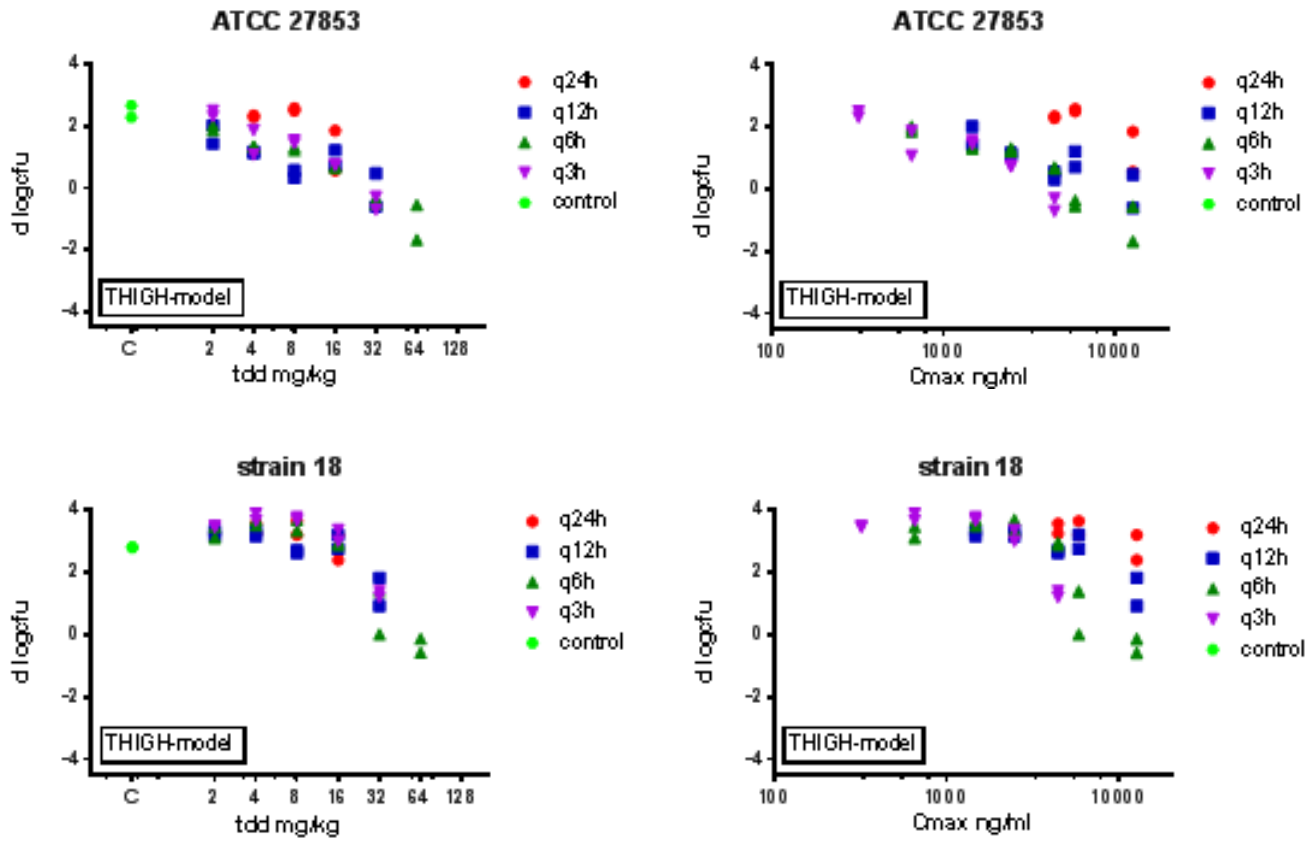
Isolate ID	POL7080	CST	PMB	ATM	CAZ	FEP	IPM	MER	DOR	TZP	CIP	LVX	GEN	TOB	AKN
5 (MDR)	0.75	2	2	>16	>32	16	>8	8	>4	>64	2	4	8	2	32
6	0.38	1	1	8	8	4	8	8	4	32	0.12	0.5	2	0.5	4
9	0.19	1	1	4	1	4	0.5	0.25	0.25	4	0.25	0.5	2	0.5	4
11 (MDR)	0.5	2	2	>16	>32	16	>8	16	>4	>64	>4	>4	>8	>8	16
12 (MDR)	0.19	1	2	16	16	8	8	4	4	64	>4	>4	>8	>8	4
15 (MDR)	0.19	1	1	>16	32	8	8	4	4	>64	>4	>4	>8	>8	4
16 (MDR)	0.19	1	1	16	4	4	8	8	>4	32	>4	>4	≤0.5	≤0.12	0.5
18 (MDR)	0.25	1	1	>16	32	16	8	4	4	>64	>4	>4	2	0.5	4
19 (MDR)	0.25	1	1	>16	32	16	8	4	4	64	>4	>4	2	0.5	4
21 (MDR)	0.25	1	1	8	>32	16	8	4	2	32	>4	>4	>8	>8	>32
22 (MDR)	0.25	1	1	8	32	16	4	4	4	16	>4	>4	>8	>8	>32
X11045	0.19	2	1	2	1	2	2	1	0.25	2	0.25	0.5	4	1	16
ATCC BAA 2113	0.125	1	2	16	4	4	0.5	0.5	0.25	16	0.12	0.5	1	0.5	2
NCTC 13437 (MDR)	0.19	1	1	>16	>32	>16	>8	32	>4	32	>4	>4	>8	>8	32
ATCC27853	0.125	1	1		2	2	4	0.5			0.5			0.5	8

CST: colistin, PMB: polymixin B, ATM: aztreonam, CAZ: ceftazidime, FEP: cefepime, IPM: imipenem, MER: meropenem, DOR: doripenem, TZP: pipericillin/tazobactam, CIP: ciprofloxacin, LVX: levofloxacin, GEN: gentamicin, TOB: tobramycin, AKN: amikacin
Susceptibility was based upon EUCAST breakpoints

10 of 15 isolates are MDR, all isolates are ≥ MIC_{90} (0.125 mg/L) Murepavadin

Pharmacodynamics of murepavadin

Exposure response curves for ATCC 27853 and clinical isolate 18 in the thigh infection model

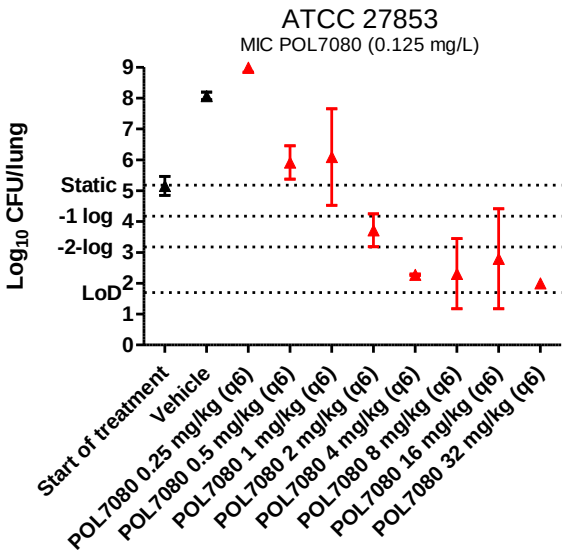


AUC is the main pharmacodynamic driver for efficacy

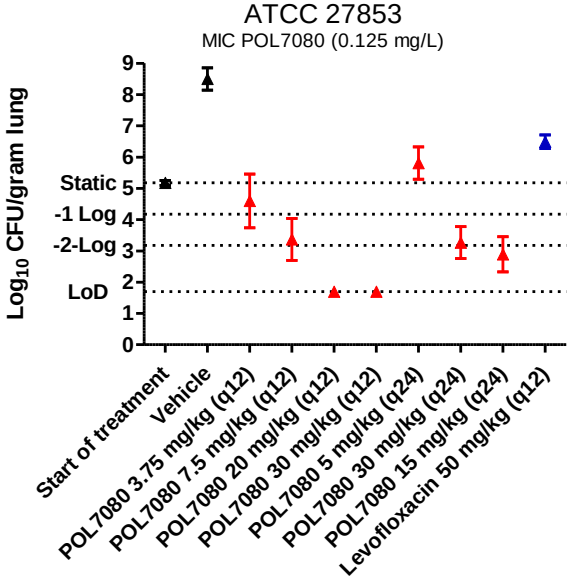
Murepavadin shows potent and reproducible in vivo activity

Exposure response curves for ATCC 27853 in the neutropenic lung infection model

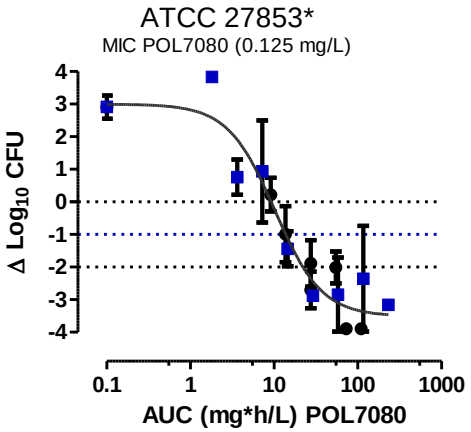
Radboudumc



Evotec (UK) Ltd



Pooled Analysis



The potent *in vivo* activity of Murepavadin is reproducible at various sites

Summary table of PD targets

Emax model parameter estimates for AUC and fAUC. PD target is 1-log[10] drop

Parameter	ATCC 27853	ATCC BAA2113	NCTC 13437	Clinical Isolate 9	6	11	12	15	16	18	19	21	22	X11045	Mean	n/14
MIC (mg/L)	0.13	0.13	0.19	0.19	0.38	0.50	0.19	0.19	0.19	0.25	0.25	0.25	0.25	0.19		
Minimum	-3.89	= -3.78	-3.55	-4.02	-2.93	= -2.78	-2.86	-4.63	-3.41	= -4.37	= -4.18	-3.29	= -2.70	-3.29		
Maximum	2.91	2.3	2.97	3.65	3.41	1.64	3.21	2.06	2.40	2.81	3.16	2.94	3.99	1.32		
R2	0.81	0.59	0.70	0.78	0.60	0.44	0.67	0.56	0.89	0.61	0.78	0.93	0.58	0.63		
Static tAUC	9.08	3.40	9.97	34.67	11.22	16.22	41.68	28.18	3.73	27.54	97.72	30.90	60.25	63.09	31.26	14
1-$\log_{10}$ tAUC	13.80	20.89	16.21	57.54	22.38	34.67	66.06	29.51	5.14	50.11	104.00	31.60	93.32	70.79	44.00	14
2-$\log_{10}$ tAUC	21.87	N	35.48	N	66.07	85.11	N	N	7.85	89.12	N	41.69	N	N	49.60	7
Static tAUC/MIC	72.64	27.20	52.47	182.47	29.53	32.44	219.37	148.32	19.63	110.16	390.88	123.60	241.00	332.05	141.55	14
1-$\log_{10}$ tAUC/MIC	**110.40**	**167.12**	**85.32**	**302.84**	**58.89**	**69.34**	**347.68**	**155.32**	**27.05**	**200.44**	**416.00**	**126.40**	**373.28**	**372.58**	**200.90**	**14**
2-$\log_{10}$ tAUC/MIC	174.96	N	186.74	N	173.87	170.22	N	N	41.32	356.48	N	166.76	N	N	181.48	7
Static *f*AUC/MIC	16.27	6.09	11.75	40.87	6.61	7.27	49.14	33.22	4.40	24.68	63.40	27.69	53.98	74.38	29.98	14
1-$\log_{10}$ *f*AUC/MIC	24.73	37.43	19.11	67.84	13.19	15.53	77.88	34.79	6.06	44.90	93.18	28.31	83.61	83.46	**45.00**	14
2-$\log_{10}$ *f*AUC/MIC	39.19	N	41.83	N	38.95	38.13	N	N	9.25	79.85	N	37.35	N	N	40.65	7

- PD target was reached for 14 of the evaluated isolates. 2-log drop reached for 7 of 14 isolates
- Isolate 5 did not reach a 1-log decrease, however it also did not reach a 1-log decrease when with 160 mg gentamicin b.i.d.

PD target established as AUC/MIC = 200 or *f*AUC/MIC = 45

Summary

In conclusion

- Murepavadin is the first in class of the Outer membrane protein targeting antibiotics
- Murepavadin showed linear pharmacokinetics for total drug and was dose proportional.
- Protein binding is not concentration dependent and is 77.6 % bound across species
- Murepavadin had good penetration in ELF with a mean penetration (AUC) ratio of 25.6% for total drug and 114.5% for free drug
- Efficacy was primarily dependent of total daily dose and therefore AUC
- 15 P. aeruginosa isolates were tested in the lung infection model, 10 isolates were MDR and all isolates had a MIC ≥ 0.125 mg/L
- 14 isolates were evaluated in the lung model, 1 strain (clinical isolate 5) could not be evaluated
- The mean 1-log drop was 200 for AUC/MIC and 45 for *f*AUC/MIC for 14/14 the evaluable strains.

Murepavadin has the potential to address an important unmet medical need in patients with nosocomial pneumonia due to *P. aeruginosa*