

BIO 2016 Global Workshop for Novel Anti-Infectives

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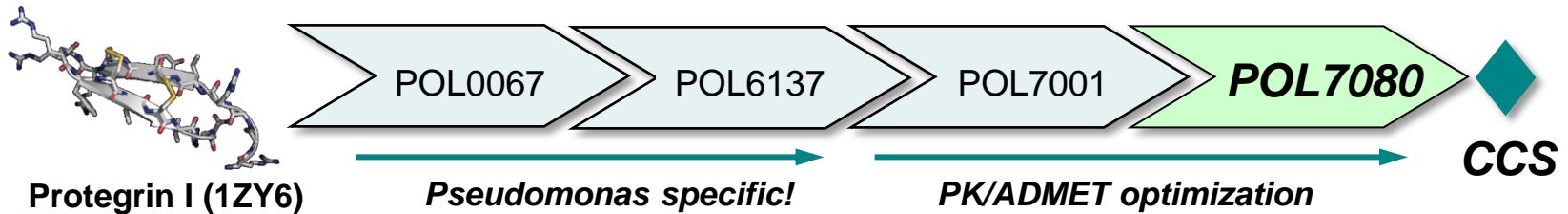


Discovery and Development of Novel Macrocycle Antibiotics

Murepavadin (POL7080)

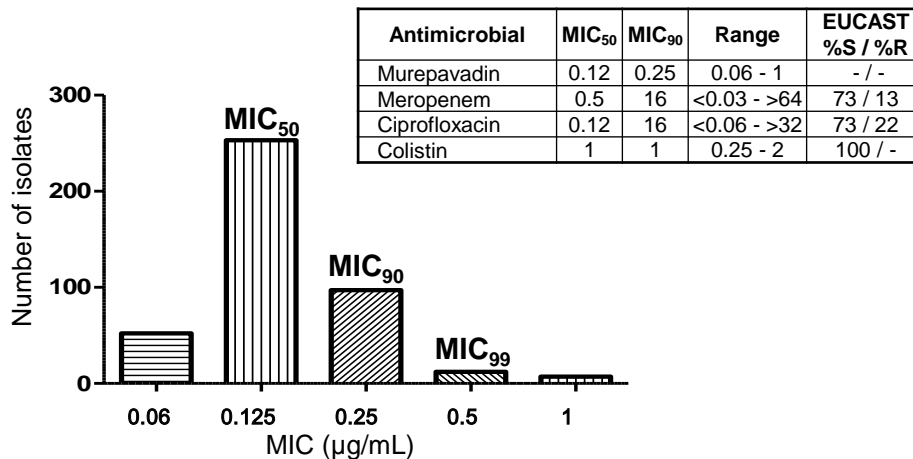
A once in a generation discovery

POL7080, antibiotic against *Pseudomonas* with a new mode of action

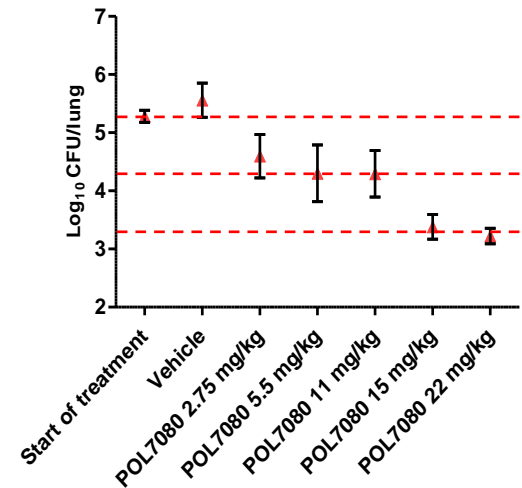


Srinivas, S., et al. (2010) *Science*, 327: 1010 – 1012

**Very potent and narrow MIC distribution
(400 recent *Pseudomonas* strains)**



Efficacy of POL7080 in a murine pneumonia model against *Pseudomonas aeruginosa* (clinical isolate PAX11045, MIC = 0.125 mg/mL)



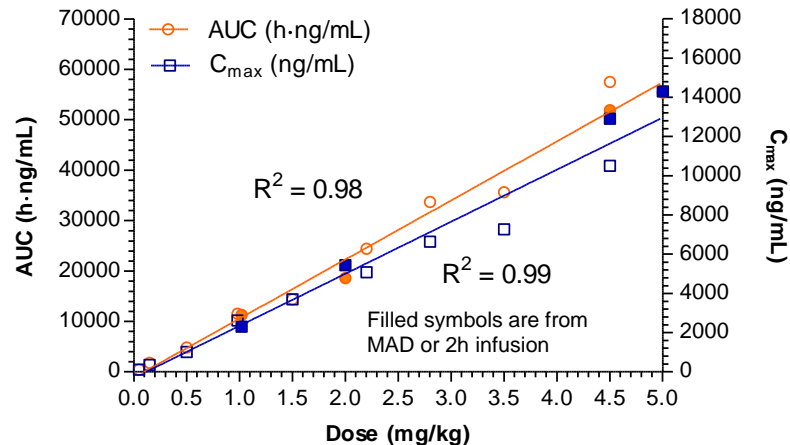
Very potent anti-*Pseudomonas* activity, rapidly bactericidal at 2-4 times the MIC, with a narrow WT distribution. Excellent *in vivo* efficacy and safety in broad range of systemic infection models, allowed for FIM studies

Murepavadin (POL7080)

New class of anti-Pseudomonal antibiotics with novel mode of action

PK snapshot and summary of clinical studies ongoing or completed

AUC and C_{max} increase linearly with dose, $t_{1/2}$ is approx. 5.0 - 5.5 h



- In FIM study, Murepavadin has been given as 2 hour and 3 hour infusions, from once daily to three times daily, with doses up to of 10 mg/kg/day
- Murepavadin was safe and well tolerated. Adverse events were mild to moderate
- Pharmacokinetic analyses showed C_{max} and AUC to be linear with dose
- No accumulation with repeated applications

Multiple clinical studies are ongoing or completed

- Phase I: SAD and MAD in healthy volunteers
- Phase I: Study in patients with renal impairment
- Phase I: BAL/ELF study in healthy volunteers → *ELF AUC / free Plasma AUC ratio ~1*
- Phase I: Drug-drug interaction study (POL7080 and colistin)
- Phase I: Thorough QT study in healthy volunteers
- Phase II: Treatment of patients with acute exacerbation of Non-Cystic Fibrosis Bronchiectasis (NCFB) due to *Pseudomonas* infection
- Phase II: PK, safety and efficacy of POL7080 co-administered with SoC in patients with VAP due to suspected or documented *Pseudomonas aeruginosa* infection

Polyphor is now preparing the ground for the pivotal trial

Broad-spectrum Gram-negative activity

PEM compounds with potent activity against MDR G-ve pathogens

Most relevant nosocomial Gram-negative pathogens

Pseudomonas aeruginosa *Acinetobacter baumannii* *Escherichia coli* *Klebsiella pneumoniae* *Enterobacter cloacae*

Murepavadin

Extended spectrum - including MDR strains

Broad spectrum against Gram-negative pathogens - including MDR strains

MIC ($\mu\text{g/mL}$) against recent clinical isolates

	Example 1	Example 2	Example 3	Example 4	Colistin	Gentamicin	Tobramycin	Ciprofloxacin	Ceftazidime	Ceftriaxone	Imipenem	Meropenem
<i>K. pneumoniae</i> SSI8010	0.25	0.125	0.125	0.125	0.125	0.5	0.25	0.25	0.25	≤ 0.06	0.5	≤ 0.06
<i>K. pneumoniae</i> 400455	0.25	0.25	0.125	0.25	0.125	64	64	64	64	64	64	64
<i>K. pneumoniae</i> 501326	0.125	0.25	0.25	0.125	0.25	64	64	16	16	64	8	16
<i>K. pneumoniae</i> 402006	2	4	>8	2	>64	4	16	>64	>64	>64	64	>64
<i>P. aeruginosa</i> 403000	4	8	1	1	1	64	16	0.25	>64	>64	16	4
<i>P. aeruginosa</i> 504871	4	4	0.5	0.5	0.5	8	1	8	8	32	32	16
<i>P. aeruginosa</i> 401190	0.5	1	0.25	0.5	1	64	64	32	64	64	64	64
<i>E. coli</i> 401808	0.5	0.5	0.25	0.125	64	>64	>64	64	>64	>64	64	64
<i>E. coli</i> 926415	0.25	0.125	0.125	0.25	8	>64	32	64	32	>64	0.5	≤ 0.06
<i>A. baumannii</i> 431941	1	0.5	0.125	0.06	64	64	64	64	64	64	64	64
<i>A. baumannii</i> 919656	1	1	0.25	1	16	>64	>64	64	>64	>64	16	32
<i>E. cloacae</i> 950265	0.5	0.5	0.5	0.25	8	>64	>64	64	64	>64	1	0.125
<i>E. cloacae</i> 952508	0.25	0.25	0.25	1	8	0.5	0.25	≤ 0.06	0.5	2	2	≤ 0.06

Green = Sensitive, Yellow = Intermediate, Red = Resistant

EUCAST clinical breakpoints

- In vitro* activity improved to a level of SoC antibiotics, including coverage of multi-drug resistant pathogens, including Col^R isolates of *E. coli*, *A. baumannii*, *P. aeruginosa*, *E. cloacae* and *K. pneumoniae*
- Potent *in vivo* activity also confirmed
- Anticipated selection of pre-clinical candidate in 12-18 months