asm microbe 2019

SPR206: Next Generation Polymyxin for the Treatment of Highly Resistant Gram-Negative Bacterial Infections

SPERO THERAPEUTICS

Troy Lister, PhD
VP Research & Early Development

Disclosures

Dr. Lister is a full-time employee of Spero Therapeutics

Spero Therapeutics gratefully acknowledges the support of NIAID and DoD in advancing SPR206 into clinical development

Award No. HHSN272201500014C

Contract No. HHSN272201500014C

Potentiator Platform: SPR206

SPR206 Poster Presentations at ASM Microbe 2019

Friday, June 21st, 11:00 am – 12:00 pm and 4:00 pm – 5:00 pm

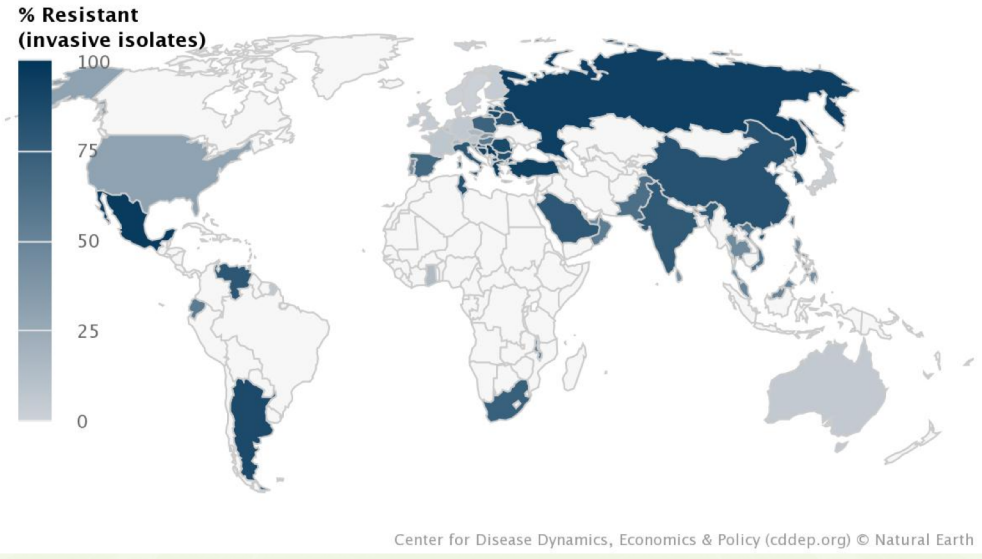
- **Optimization of Next-Generation Polymyxins Leading to SPR206 as a Development Candidate –** Poster 793
- **Mechanism of Action of SPR206, a Next-Generation Polymyxin Active Against Gram-Negative Pathogens –** Poster 794
- **The Impact of Varied Test Conditions on the *In Vitro* Activity of SPR206, a Next-Generation Polymyxin B Analog, against Drug-susceptible and Multidrug-resistant Gram-negative Pathogens –** Poster 795
- **Activity of Investigational Polymyxin-B-Like Compound (SPR206) against Set of *Enterobacteriaceae* Organisms Responsible for Human Infections –** Poster 796
- ***In Vitro* Bactericidal Activity of Next-Generation Polymyxin SPR206 against Susceptible and Multidrug-Resistant (MDR) *Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli*, and *Klebsiella pneumonia* as compared to Levofloxacin and Meropenem –** Poster 797
- ***In Vivo* Efficacy of Next-Generation Polymyxin SPR206 in an Immunocompetent Murine Ascending UTI Infection Model Caused by *Escherichia coli* –** Poster 798
- ***In Vivo* Efficacy of SPR206 in Murine Lung and Thigh Infection Models Caused by Multi-Drug Resistant Pathogens *Pseudomonas aeruginosa* and *Acinetobacter baumannii* –** Poster 799
- **A GLP 14-Day Repeat Dose Toxicology Study of SPR206 in Monkeys –** Poster 800

SPR206: Why? There Remains Great Need for Better Tolerated Antibiotics for Problematic Gram-Negative Pathogens

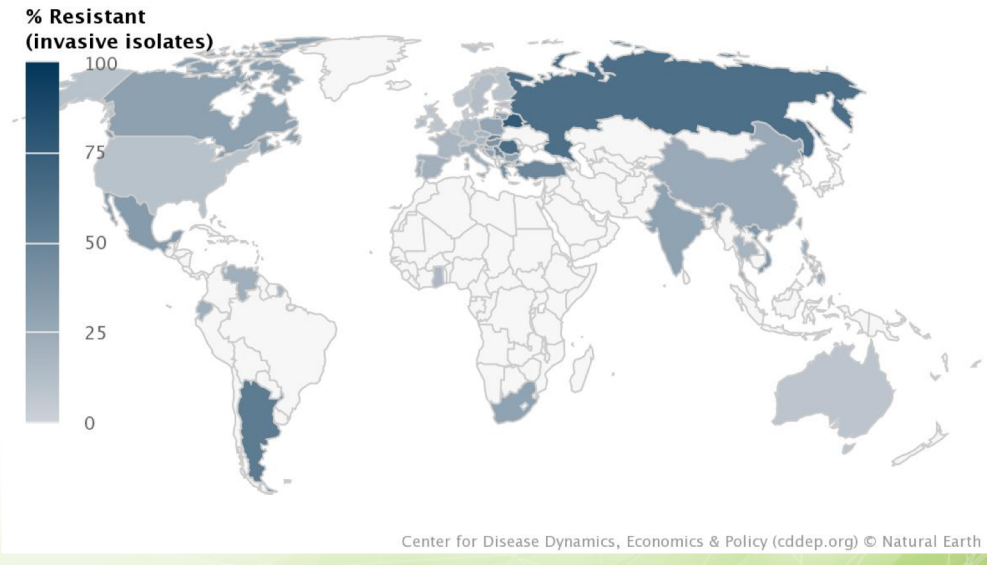
Carbapenem-Resistant *Acinetobacter* in US exceeding 50%

Carbapenem-Resistant *Pseudomonas* in US reaching 20%

Resistance of *Acinetobacter baumannii* to Carbapenems



Resistance of *Pseudomonas aeruginosa* to Carbapenems



SPR206 Overview

Potent, Broad Spectrum Gram-Negative Activity

- Potent *in vitro* and *in vivo* activity across a wide variety of MDR Gram-negative bacteria, including serine-CRE, metallo-CRE, carbapenem-resistant *P. aeruginosa*, *Acinetobacter* spp.

Well Tolerated

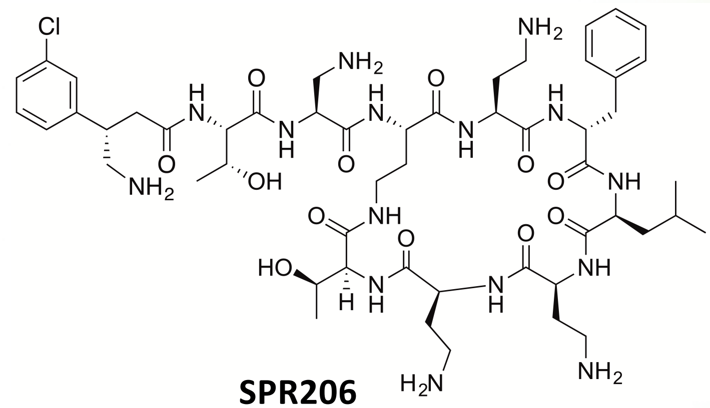
- Pre-clinical safety profile supported progression into Phase 1

Clinical Stage Therapy

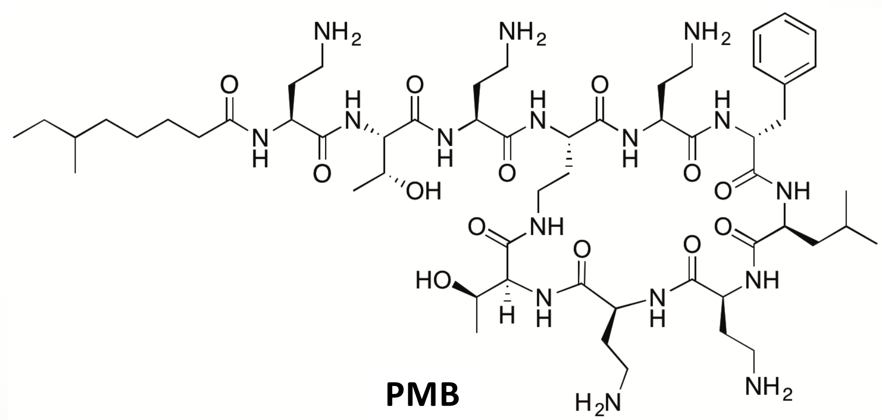
- Phase 1 SAD/MAD trial ongoing

Well Positioned for Combination Therapy

- Replacement for aminoglycosides and original polymyxins



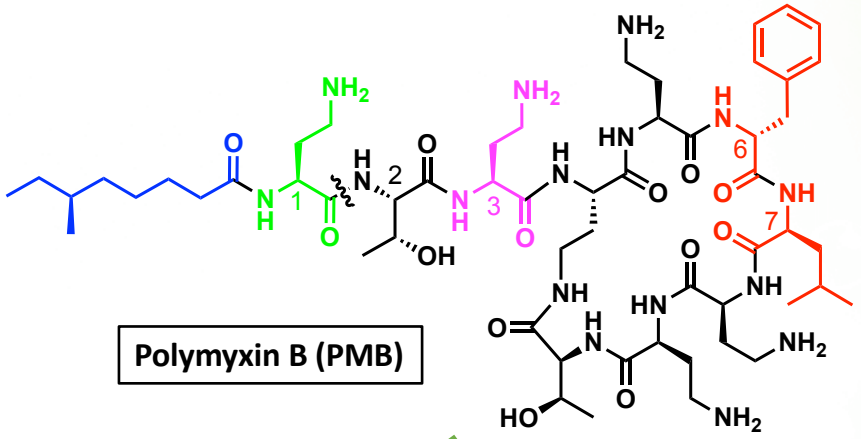
SPR206



PMB

SPR206 Discovery Chemistry

Aminoacyl polymyxin nonapeptides

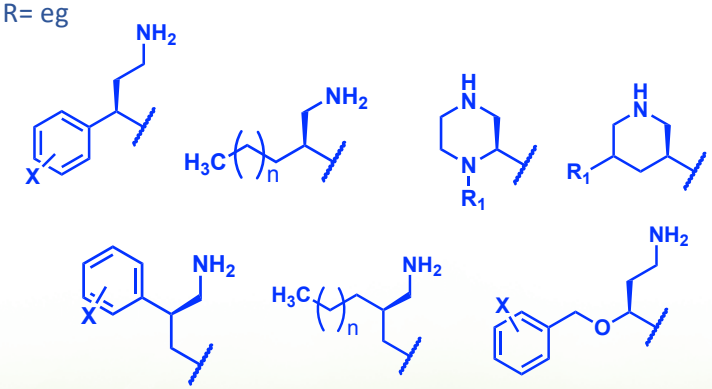


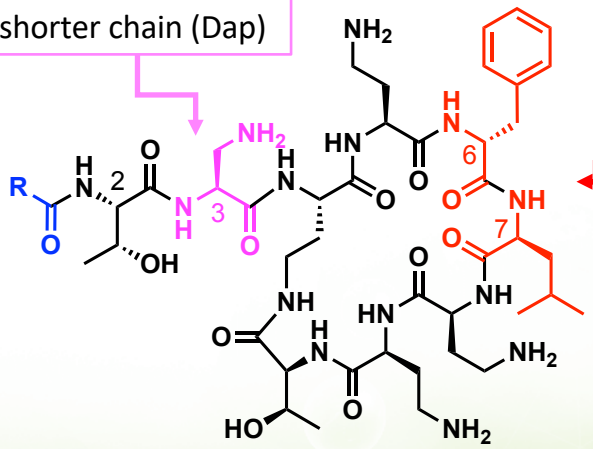
Polymyxin B (PMB)

Amino acid -1 and N-terminal chain replaced by group R

Amino acid -3 with shorter chain (Dap)

R= eg





Amino acids 6 and 7 can be modified

SPR206 Structure Activity/Structure Toxicity Relationship

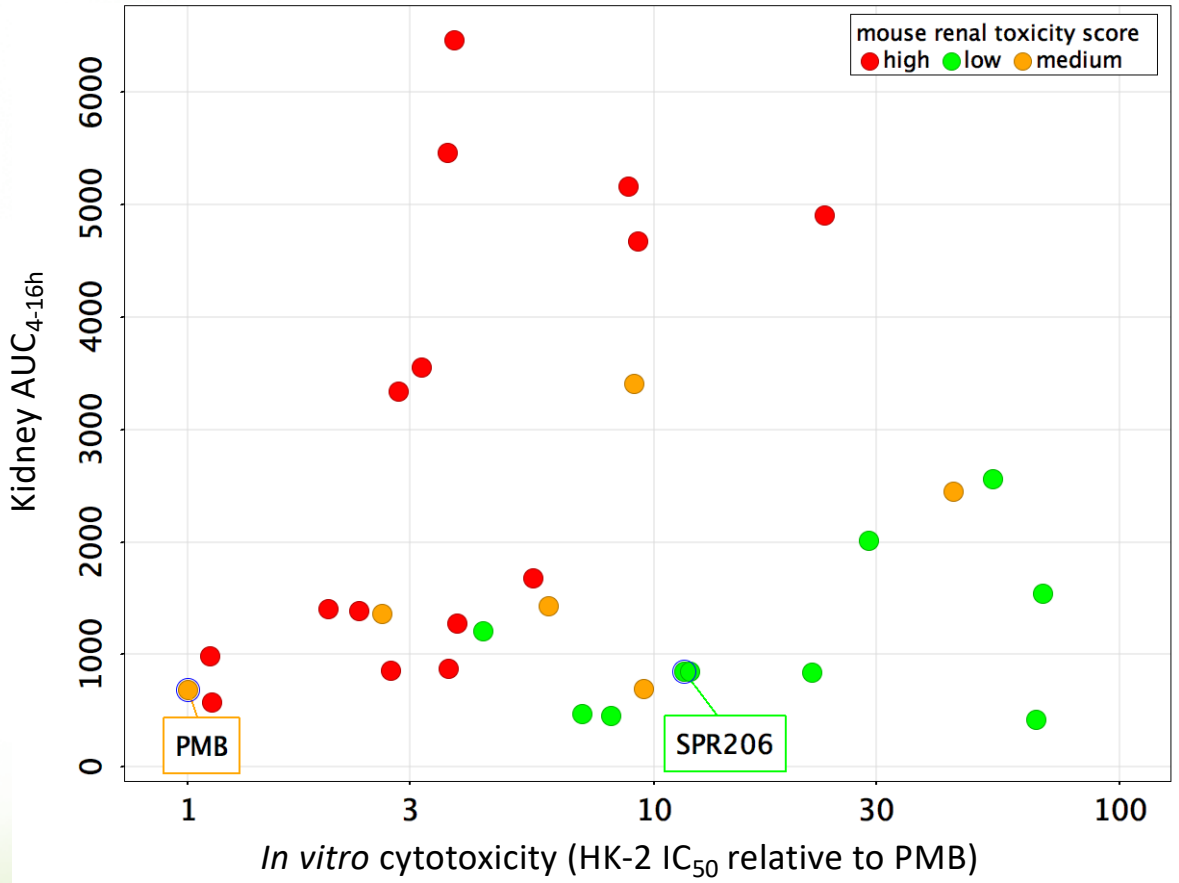
- Three pronged approach to understanding SAR/STR in lead optimization
- Triangulation of antibacterial activity, kidney cell cytotoxicity and kidney accumulation

Compound	cLogP	MIC (relative to PMB)				Resistant Strains (relative to PMB)	HK-2 IC_{50} (relative to PMB)	4hr Kidney Level (µg/g)	Kidney $AUC_{4\text{-}16hr}$ (µg*hr/g)
		E. coli	*K. pneumonia*	*P. aeruginosa*	*A. baumannii*				
PMB	-6.3	0	0	0	0	0	1.0	128	688
SPR206	-6.3	1.5	0.8	0.8	1.7	-0.7	11.6	170	850
CA1338	-6.8	0.3	0.7	1.1	1.9	-1.0	>68	330	1,545
CA1405	-6.8	1.4	0.9	1.9	2.6	-0.6	8.1	110	453
CA1406	-7.8	0.1	0	0.1	-0.3	-1.9	>66	91	419
CA1408	-6.5	1.0	0.9	1.3	2.2	-0.5	21.8	203	841

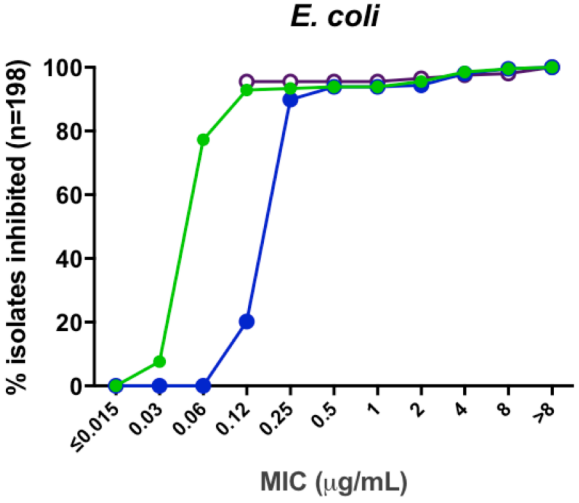
- Antibacterial activity is based on MIC values and refers to average number of dilutions better than PMB when tested across 8 strains per species, or 15 strains of all four species with reduced susceptibility to polymyxins (resistant strains)
- 4hr kidney level and 4 – 16hr AUC were measured after a single 17.2 mg/kg dose to mice

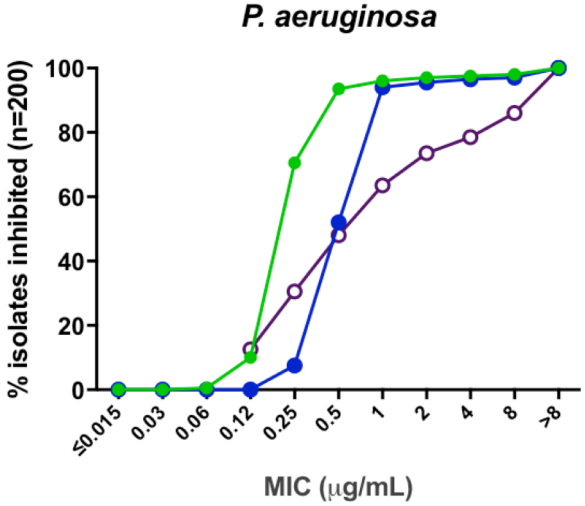
SPR206 Structure Toxicity Relationship

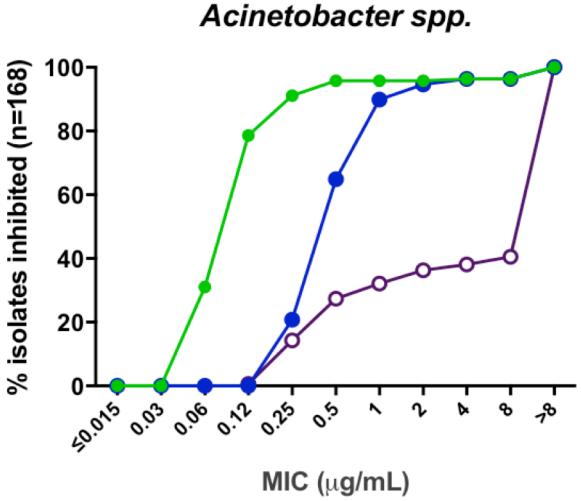
- Relationship between intrinsic kidney cytotoxicity (HK-2 IC_{50}) and kidney levels of molecule are predictive *in vivo* murine nephrotoxicity

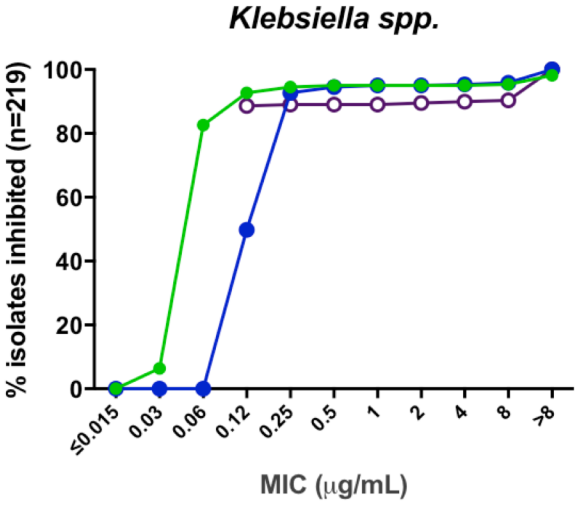


SPR206 Potency Against Gram-Negative Pathogens









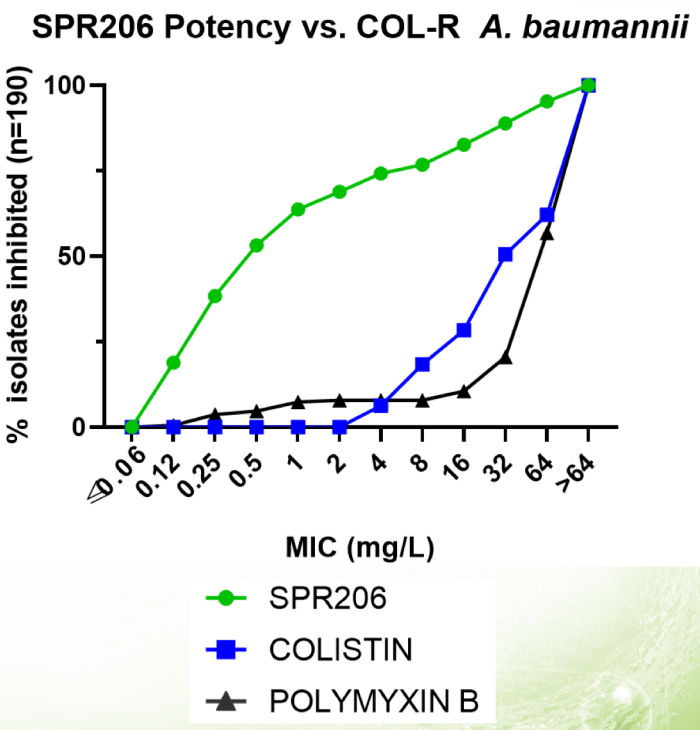
SPR206
Colistin
Meropenem

Organism	N	MIC_{90} (μg/mL)		
		SPR206	Colistin	Meropenem
Acinetobacter spp.	168	0.25	2	>8
E. coli	198	0.12	0.5	≤0.12
Klebsiella spp.	219	0.12	0.25	8
P. aeruginosa	200	0.5	1	>8

SPR206 Activity Against PMX Resistant *A. baumannii*

- Evaluation of larger collection of mostly COL^{R} *A. baumannii* uncovered differentiated activity profile for SPR206
- 148 of 190 have SPR206 MIC <2 mg/L, Colistin MIC >2 mg/L. All have >8-fold lower MIC for SPR206

SPR206 MIC (mg/L) \ Colistin MIC (mg/L)	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
>64													9
64												1	11
32									1	6	3		2
16										5	3		3
8									1	2			3
4								1			2	3	4
2						1		1	1	1		5	2
1					2	2	2	2	1	3	2	6	4
0.5				3	6	3		2	5	7	4	5	5
0.25				1	10	9	3	7	8	9	4	5	1
0.12			3	9	10	8	7	10	2	9	4	4	
≤0.06			1	6	3	3							

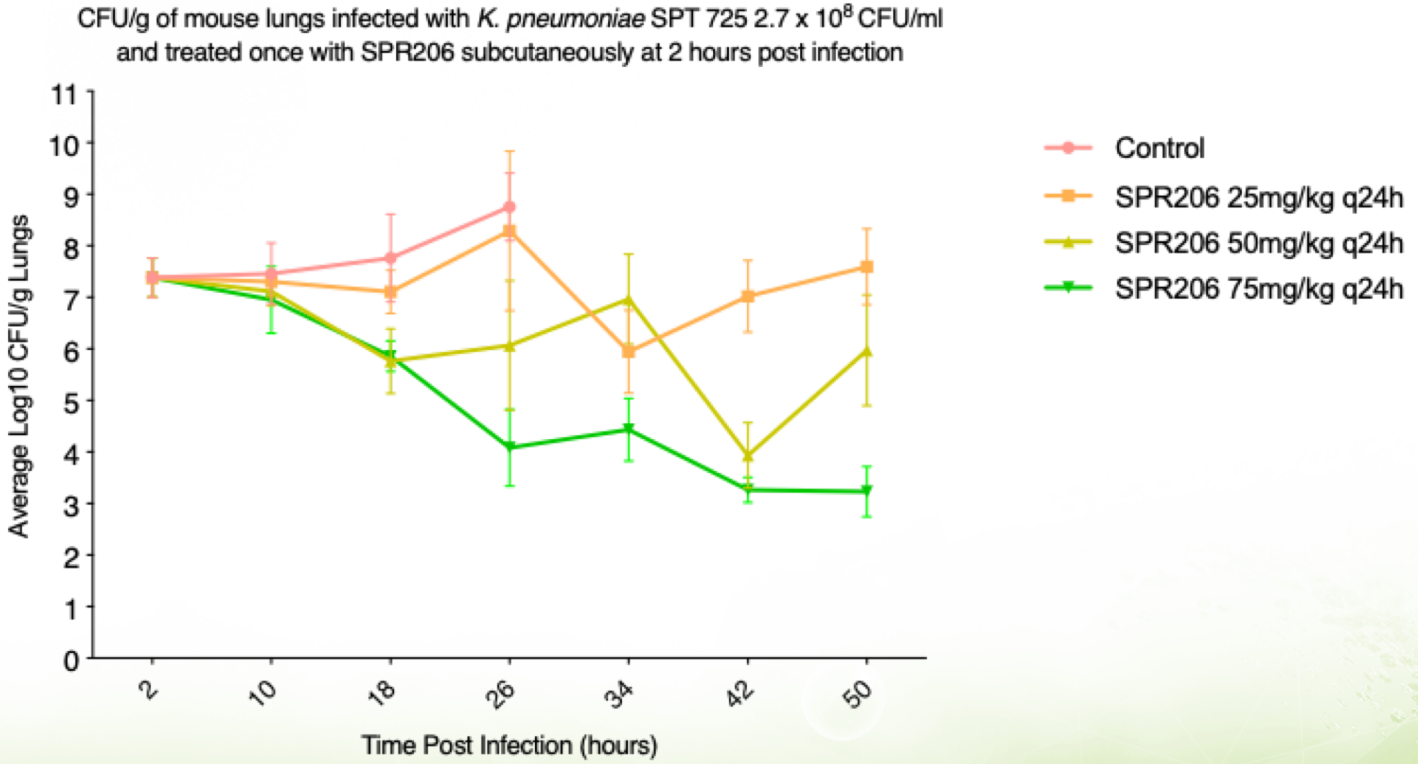


SPR206 *In Vivo* Efficacy Summary

Infecting Organism/Site	Efficacy Endpoint	Dose Required (mg/kg/dose; 3 doses)	
		SPR206	PMB
E. coli thigh (IV dosing)	Stasis	0.71	0.40
	-1 log	2.56	2.37
	-2 log	N/A	N/A
K. pneumonia thigh (IV dosing)	Stasis	0.37	0.35
	-1 log	0.43	0.42
	-2 log	N/A	N/A
A. baumannii thigh (IV dosing)	Stasis	0.42	0.33
	-1 log	0.54	0.42
	-2 log	0.66	0.66
P. aeruginosa lung (SC dosing)	Stasis	14.5	N/A
	-1 log	N/A	N/A
	-2 log	N/A	N/A
A. baumannii lung (SC dosing)	Stasis	11.5	N/A
	-1 log	14.9	N/A
	-2 log	19.1	N/A

SPR206 Exhibits Persistent Efficacy in Lung Infection

- Immunocompromised *K. pneumoniae* murine lung infection model
- Single dose of SPR206 2 h post infection
- Robust dose response, with persistent efficacy at all dose levels, despite rapid clearance from plasma



SPR206 Has Favorable Profile for Clinical Evaluation

- GLP 14 day repeat dose studies in monkey established near identical safety profile between SPR206 and SPR741

Species	NOAEL (mg/kg)	Cmax (μg/mL)	AUC (μg*hr/mL)
Rat	10	6.4	6.8
Monkey	30	47	345

Compound	Dose (mg/kg/day)	Cmax (μg/mL)	$AUC_{(0\text{-}24)}$ (μg*hr/mL)	AUC/dose
SPR206	30	**42**	**345**	11.5
SPR741	40	**47**	**363**	9.1

✓ Non-genotoxic

✓ No inhibition or metabolism in ADME studies – low risk for DDI. Very low PPB: human (10%), monkey (8%), rat (14%), mouse (20%)

✓ Clean in all safety pharmacology studies

✓ No hemolysis, flocculation or local irritation

Efficacy Target Exposure			*f*AUC Margin	
Species	Efficacy Target (mg/kg)	*f*AUC (μg*hr/mL)	Rat	Monkey
Mouse	<50	<48	>0.12	**>6**

SPR206 Phase 1 SAD/MAD Study

A Two-part, Randomized, Double-blind, Placebo-controlled, Phase I Study of the Safety, Tolerability and Pharmacokinetics of SPR206 Following Administration of Single and Multiple Ascending IV Doses in Healthy Volunteers

- Objectives: Safety, Tolerability, PK, QT-monitoring
- Single Center (Scientia, Australia)
- Healthy volunteers, male and female (non-childbearing): 18-55 yo
- 8 Single Ascending Dose (SAD) Cohorts
- 4 Multiple Ascending Dose (MAD) Cohorts (14-days duration)
- 108 subjects (planned); 3:1 randomization

Acknowledgements

- Mike Dawson, Pam Brown, Cantab Team
- Nicole Cotroneo, Lisa Morelli, Evan Hecker, Nick Clayton, Tom Parr, Jon Bruss, David Melnick, Spero Team
- Michael Bleavins, University of Liverpool, ICPD, JMI, and collaborators