ENTASIS THERAPEUTICS

Addressing the evolving challenge of β-lactamase mediated antimicrobial resistance:

ETX2514, a next-generation BLI with potent broad-spectrum activity against Class A, C and D enzymes

Posters LB-024 & LB-117

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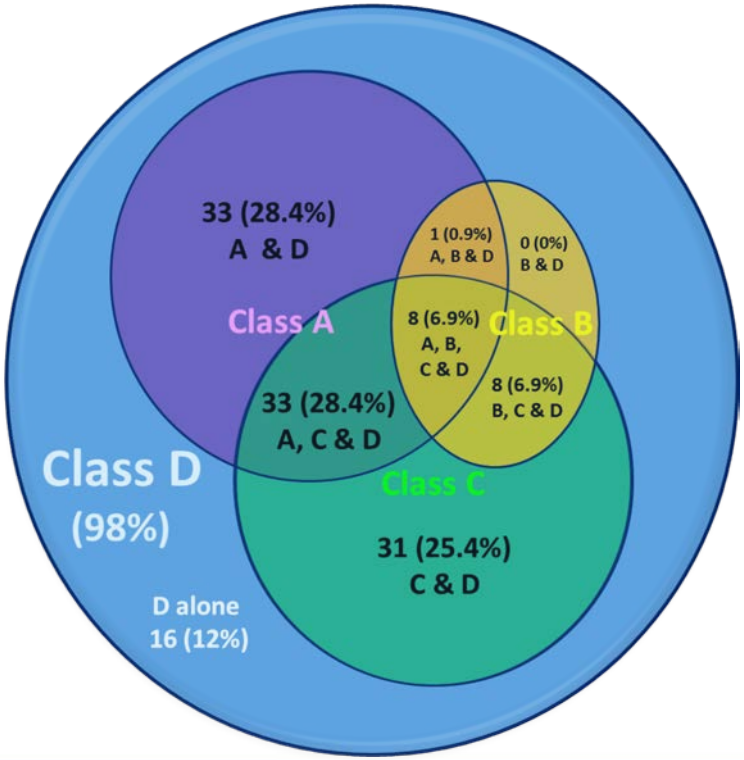
Inhibition of Class A, C and D Required for Robust *A. baumannii* Activity

LB-024

Whole-genome sequencing of 132 recent MDR *A. baumannii* strains provides insight into what is required for a successful next generation therapy.

➔ While nearly all the *A. baumannii* strains we have studied contain Class D enzymes, only 12% encode Class D only.

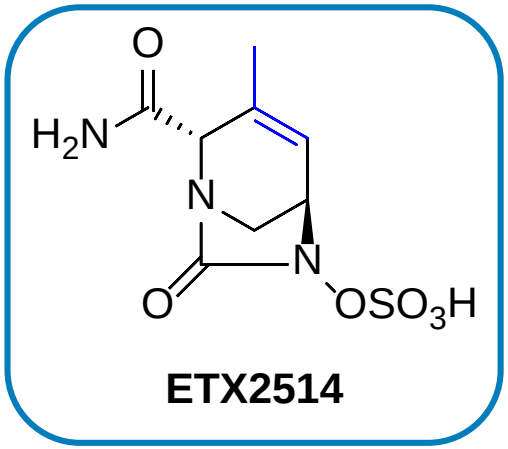


β-lactamase distribution (%)	
Class A (57.5%)	
TEM-1	80
SHV	9
KPC	0
Class C (62%)	
AmpC	100
Class D (98%)	
OXA-23	45
OXA-66	43
OXA-10	11
OXA-24/40	8
OXA-48	0

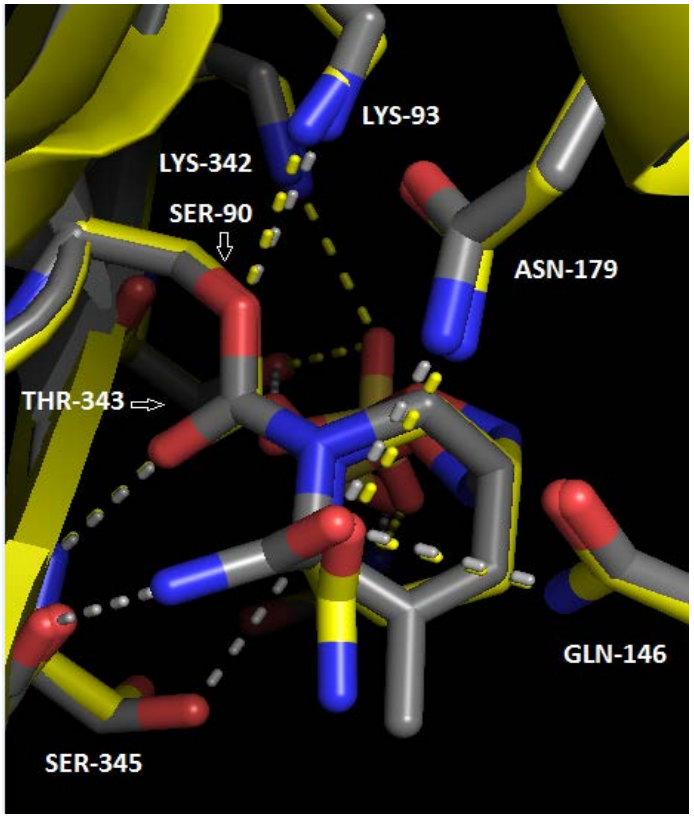
Discovery of ETX2514, a Novel Broad-spectrum Serine BLI

LB-024

A combination of innovative chemistry, structure-based design, and quantum mechanics calculations culminated in the discovery of ETX2514.



ETX2514



Overlay of ETX2514 and avibactam AmpC co-crystal structures

ETX2514 Exhibits Excellent β-lactamase Inhibition across Class A, C and D

LB-024

	β-lactamase acylation rate - k_{inact}/K_i in $M^{-1}s^{-1}$								
	Class A			Class C		Class D			
	CTX-M-15	TEM-1	KPC-2	AmpC	P99	OXA-10	OXA-23	OXA-24	OXA-48
ETX2514	7,400,000	14,000,000	940,000	920,000	2,300,000	8,600	5,100	9,300	830,000
Relebactam MK-7655	11,000	53,000	2,000	1,900	11,000	44	6	17	39

Exceptional enzymatic spectrum translates into excellent activity across an isogenic panel of *P. aeruginosa* strains.

	Piperacillin MIC in mg/L (+/- ETX2514 at 4 mg/L)										
	PAO1 *ampC-poxB-*	Class A			Class B	Class C		Class D			
		CTX-M-15	TEM-1	KPC-2	VIM-2	AmpC	P99	OXA-10	OXA-23	OXA-24	OXA-48
No BLI	4	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
+ ETX2514	4	4	4	8	>64	4	4	16	8	8	8

ETX2514 Restores β-lactam Activity vs Multiple Gram-negative Pathogens

LB-024

- Excellent activity vs *E. coli* & *K. pneumoniae* with all β-lactams tested
- Restores imipenem to MIC_{90} of 2 mg/L vs *P. aeruginosa*
- Restores sulbactam to MIC_{90} of 4 mg/L vs *A. baumannii*

Compound (MIC_{90}, mg/L)		***E. coli*** n = 202	***K. pneumoniae*** n = 198	***P. aeruginosa*** n = 202	***A. baumannii*** n = 195
Imipenem	alone	0.25	1	16	>64
	+ ETX2514	**≤0.06**	**0.12**	**2**	**16**
Meropenem	alone	≤0.06	≤0.06	16	>64
	+ ETX2514	**≤0.06**	**≤0.06**	**8**	**16**
Aztreonam	alone	32	32	64	>64
	+ ETX2514	**≤0.06**	**≤0.06**	**32**	**>64**
Ceftazidime	alone	16	>64	>64	>64
	+ ETX2514	**≤0.06**	**≤0.06**	**8**	**32**
Sulbactam	alone	64*	>64¥	>64	64
	+ ETX2514	**≤0.06***	**0.12¥**	**>64**	**4**
ETX2514 alone		1	8	>64	>64

*n = 21 strains ¥n = 20 strains

MIC_{90} across recent clinical isolates (+/- ETX2514 at 4 mg/L)

Sulbactam/ETX2514: A Novel Combination Against MDR *A. baumannii*

LB-024

- Sulbactam/ETX2514 maintains excellent activity over time

MIC (mg/L)		≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>64
2011 N=195	Cumul %	1	3.1	13.8	41.5	65.6	89.7	**96.9**	97.9	99.5	100	100
2012 N=209	Cumul %	0	0.5	2.9	20.1	46.9	79	**98.6**	100	100	100	100
2013 N=207	Cumul %	0	0	4.3	15.9	43.4	73.8	**96.5**	97.5	99	99	100
2014 N=1131	Cumul %	1	1.6	7.8	27.9	63.7	88.9	**99.6**	99.6	99.7	100	100

MIC distributions for globally diverse *A. baumannii* clinical strains

- Sulbactam/ETX2514 activity remains unchanged in carbapenem-resistant, colistin-resistant and multidrug resistant strains (see details on poster)

Sulbactam/ETX2514 Exhibits Excellent *In Vivo* Activity

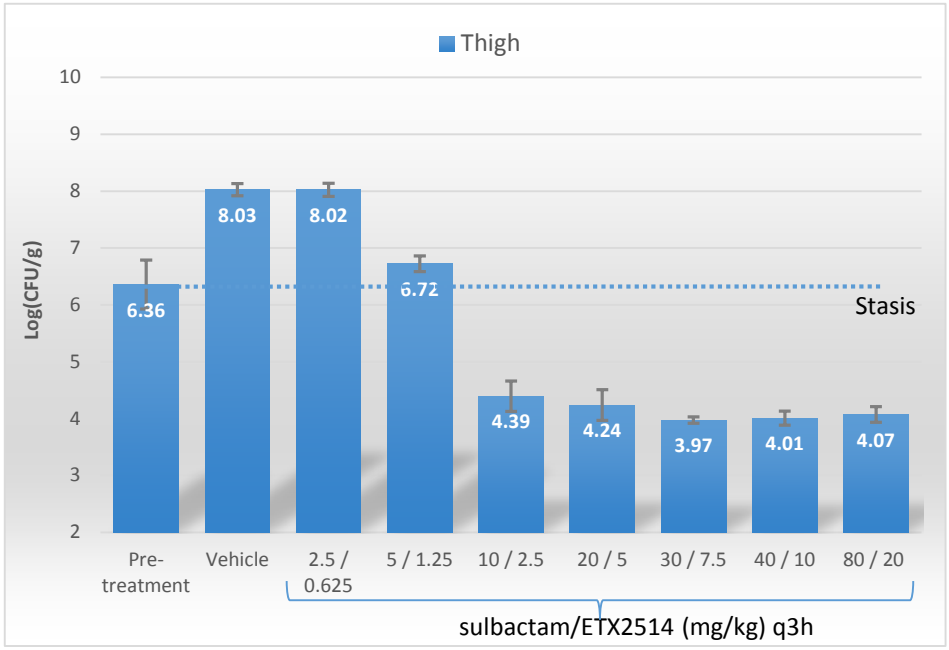
LB-117

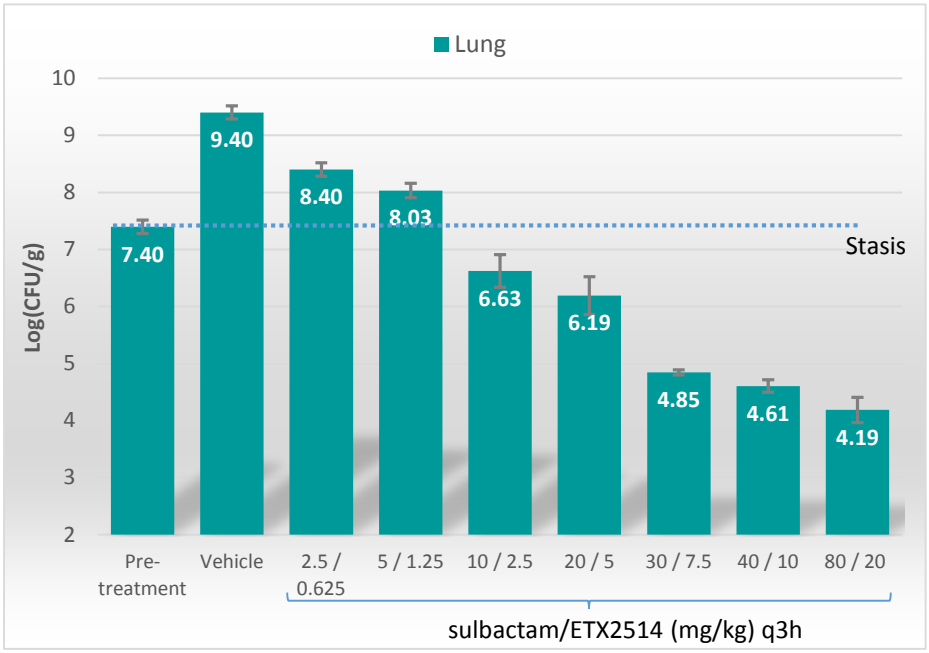
- Greater than 2-log kill achieved in both neutropenic mouse thigh and lung models of *A. baumannii* infections

Sulbactam/ETX2514 dose response (IV, 4/1 ratio)

MDR *A. baumannii* ARC3486 (OXA-72, OXA-66, TEM-1, AmpC)

MIC(sulbactam) ≥ 32 mg/L, MIC(sulbactam/ETX2514) = 0.5 mg/L

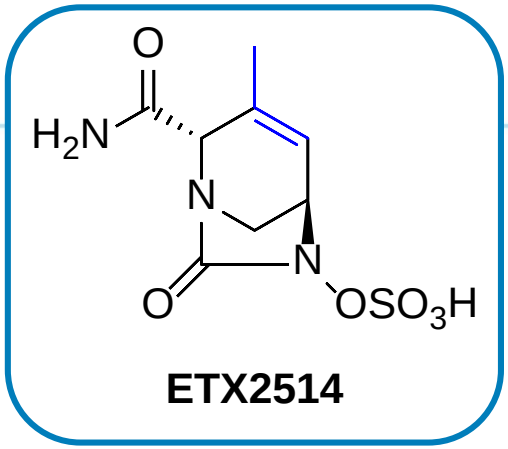




- PK/PD driver identification and analysis highlighted on poster

Conclusions

Posters:
LB-024 (Friday)
LB-117 (Monday)



ETX2514

- ETX2514 is a potent inhibitor of a broad-spectrum of Class D β-lactamases while maintaining exquisite potency on Class A and C enzymes.
- ETX2514 potently restores the activity of multiple β-lactams in Gram-negative MDR pathogens.
- Sulbactam/ETX2514 is a novel BL/BLI combination to treat MDR *A. baumannii* infections, with an MIC_{90} = 4 mg/L (N = 1742 clinical isolates) and excellent *in vivo* activity.

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Poster Times and Locations

Title: ETX2514, a Novel, Rationally Designed Inhibitor of Class A, C & D β-lactamases, for the Treatment of Gram-negative Infections

Presenter: **Adam Shapiro**

Session: 033 - Friday Late-Breaker Poster Presentations

Date: June 17, 2016

Time: 12:30 - 2:30 pm ET

Poster Number: LB-024

Title: *In Vitro* and *In Vivo* Efficacy of the Novel β-lactamase Inhibitor ETX2514 Combined with Sulbactam Against Multidrug Resistant *Acinetobacter baumannii*

Presenter: **John O'Donnell**

Session: 393 - Monday Late-Breaker Poster Presentations

Date: June 20, 2016

Time: 12:30 - 2:30 pm ET

Poster Number: LB-117