EBL-1463

a novel non β-lactam PBP inhibitor for the treatment of CRE infections

Mutabilis overview

MUTABILIS

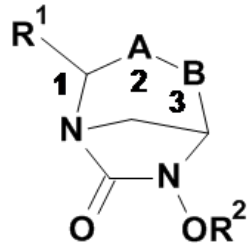
French biopharma. company

CEO	S. Huguet
COO	W. Ract-Madoux
CSO	F. Moreau
Dir. Chem.	S. Chasset

GOALS

Discovery of "Dabocins":

- Novel class antibacterials
- Multi-PBP inhibitors
- Non-β–lactams
- Stability to ABCD BLAs

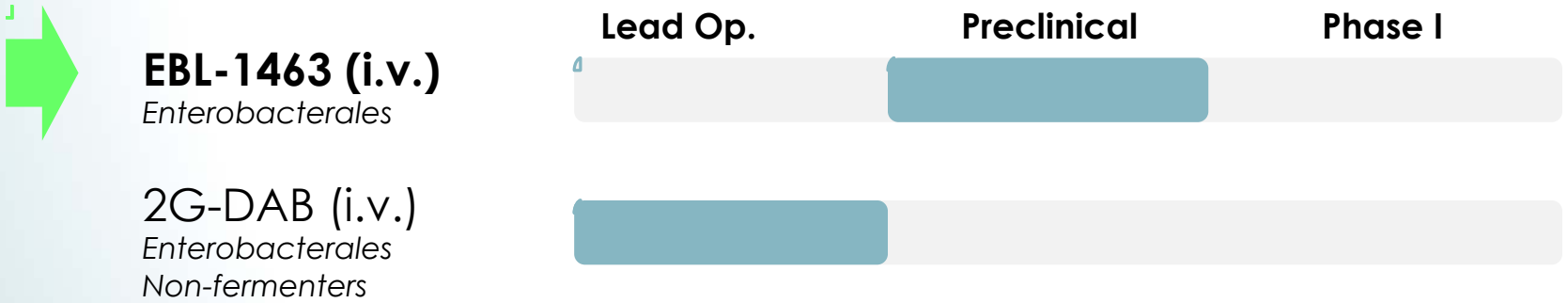


SAB

P. Ambrose
K. Bush
D. Livermore
P. Nordmann

PIPELINE

Stage



Support

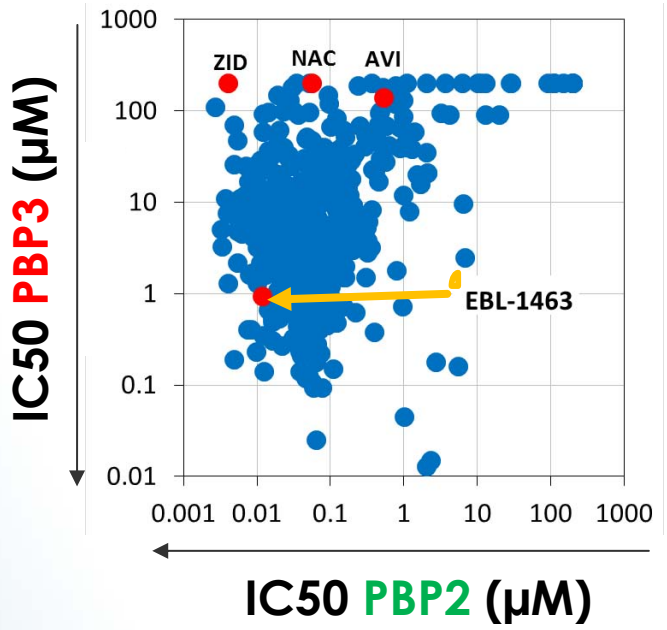
ND4BB ENABLE

repair impact fund

Discovery of EBL-1463

EBL-1463 is a small, highly soluble DBO impervious to efflux or porin- deletion in ***Enterobacteriaceae***

Obtained by convergent optimization of PBP2 and PBP3 inhibition + permeation

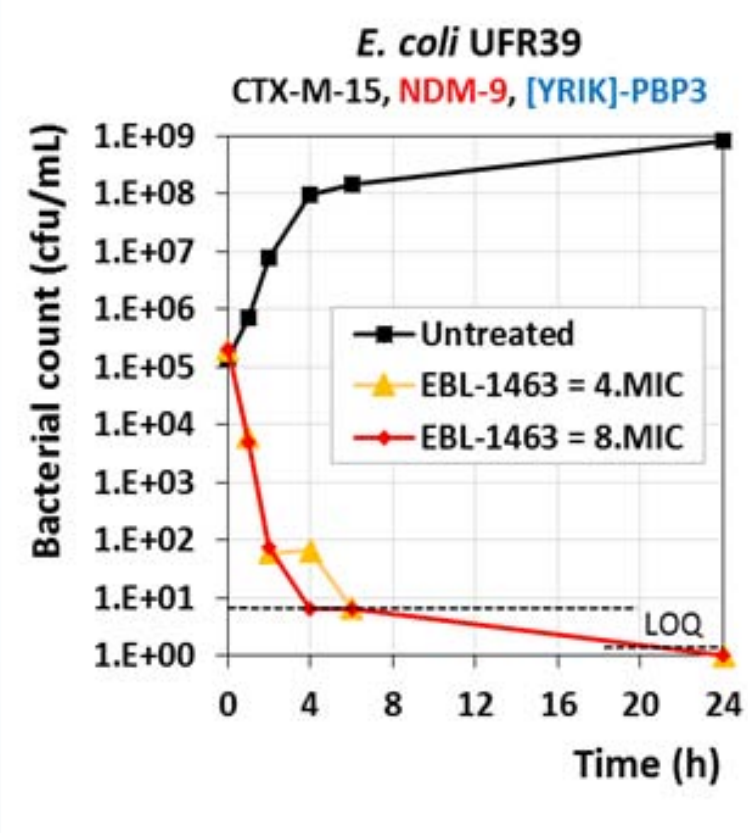


Like Meropenem, EBL-1463 is a strong **PBP2** inhibitor with collateral inhibition of **PBP1a/3**

	IC50 PBP of E. coli (µM)			
	PBP 1a	**PBP 1b**	**PBP 2**	**PBP 3**
AVIBACTAM	>200	>200	0.59	140
ZIDEBACTAM	>200	>200	**0.004**	>200
EBL-1463	**1.2**	**11**	**0.009**	**1.0**
MEROPENEM	1.0	0.36	**0.010**	0.20

EBL-1463 is bactericidal with low FoR

Thanks to multi-PBP inhibition
EBL-1463 is **bactericidal** @ 2-4xMIC



And shows very **low Frequency of resistance** at 4-8xMIC against *Enterobacterales,*

	ID	Main Resistance mechanism	FoR @ 4 MIC	FoR @ 8 MIC
E. coli	1	NDM-1	1.9E-09	<1.9E-09
	2	NDM-9, PBP3	4.2E-07	<2.6E-09
	3	NDM-5, PBP3	<6.7E-09	<6.7E-09
	4	NDM-1	<2.7E-09	<2.7E-09
K. pneumoniae	5	VIM-1	<4.4E-09	<4.4E-09
	6	KPC-3	<3.1E-09	<3.1E-09
C. freundii	7	KPC-2	<3.1E-09	<3.1E-09
E. cloacae	8	NDM-1	<2.5E-09	<2.5E-09
P. mirabilis	9	VEB-1	<2.3E-09	-
P. stuartii	10	VEB-1	<2.7E-09	<2.7E-09
P. rettgeri	11	NDM-1	<2.3E-09	<2.3E-09
S. marcescens	12	KPC-2	<4.0E-09	-
	13	ESAC	<2.8E-09	<2.8E-09

EBL-1463 has unique properties among latest β-lactams

Wide/outstanding stability to A,B,C,D β-lactamases:
To date, no serine or metallo-β-lactamase capable of hydrolyzing/deactivating EBL-1463 has been identified.

	MIC *E. coli* K12 ΔtolC (µg/mL)	MIC FOLD CHANGE [ECO+BLA] / [ECO WT]											
		SHV-12	CTX-M-15	KPC-2	GES-11	PER-1	VEB-1	AmpC P99	CMY-2	IMP-1	VIM-1	NDM-1	OXA-48
EBL-1463	1	1	1	1	1	1	1	1	1	1	1	2	1
Piperacillin	0.25	>1024	1024	512	>1024	512	512	1024	>1024	128	>1024	1024	512
Aztreonam	0.25	512	128	128	512	>512	>512	256	256	1	1	1	1
BOS-228	0.12	16	1	1	4	>256	256	8	8	1	1	1	1
Ceftazidime	0.25	>512	64	16	>512	>512	>512	512	>512	>512	>512	>512	1
Cefiderocol*	0.06	32	1	1	2	8	8	1	2	1	2	16	1
Meropenem	0.03	2	1	16	4	2	1	2	2	512	512	>1024	4

** MIC determined in ID-caMHB according to CLSI protocol*

Same results obtained with:
DHA-1, **KPC**-3, **OXA**-23,40,58,64,
VIM-2, 4, **NDM**-2,4,5,6, 7, 9

EBL-1463 is not impacted by YRI-PBP3 mutations
New mechanism of resistance to β-lactams in *E. coli with* possible high prevalence in India (*Periasamy, 2020*)

Monobactams/cephalosporins strongly impacted

MIC FOLD CHANGE	*E. coli* 25922 WT / [YRIK]-PBP3
EBL-1463	2
Meropenem	2
Aztreonam	32
BOS-228	16
Ceftazidime	16
Cefepime	16
Cefiderocol*	8

** MIC determined in ID-caMHB according to CLSI protocol*

EBL-1463 is unsurpassed against highly challenging MBL-producing *Enterobacterales* from LMICs

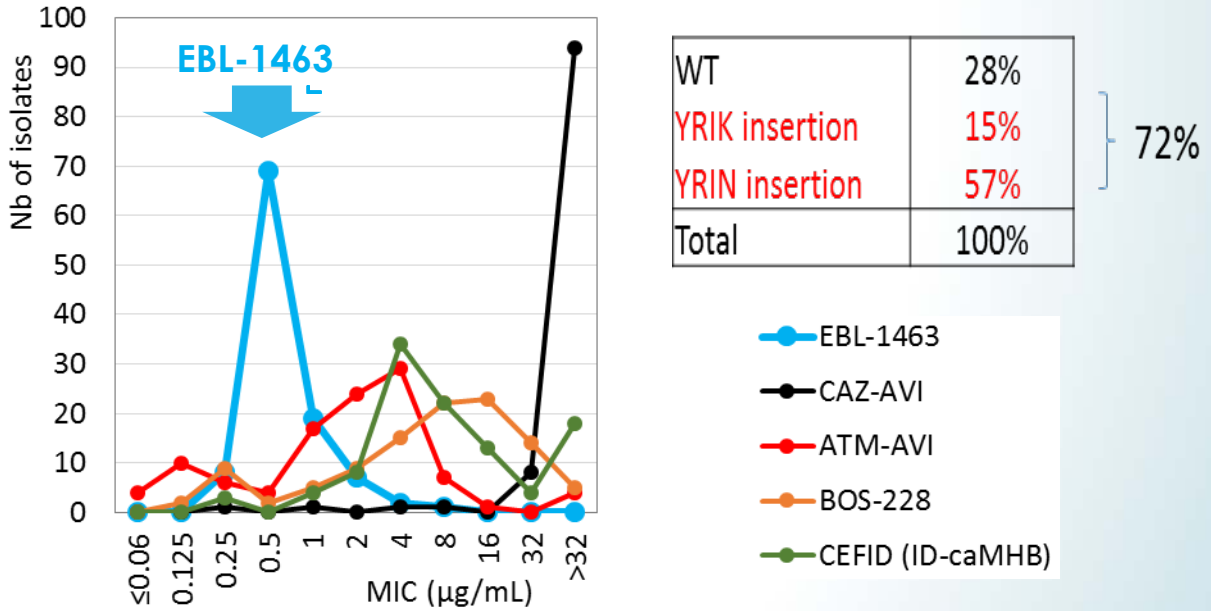
T. Walsh *et al*, Cardiff University:

Against 468 MBL-producing *Enterobacterales* 100% resistant to carbapenems and CAZ/AVI, EBL-1463 was the most potent antibacterial

Against *E. coli*, EBL-1463 was **>8 fold more potent** than MBL-targeted comparators (ATM/AVI, BOS-228, Cefiderocol) due to surprisingly high prevalence (72%) of PBP3 mutations in *E. coli* (YRI insertions)

		MIC90 (mg/L)				
		EBL-1463	ATM-AVI	BOS-228	CEFID	CAZ-AVI
E. coli	**(n=106)**	**1**	**8**	**32**	**>32**	**>32**
K. pneumoniae	(n=278)	**2**	0.5	2	16	>32
Enterobacter spp.	(n=43)	**2**	0.25	2	>32	>32
Citrobacter spp.	(n=20)	**1**	0.25	4	8	>32
Providencia spp.	(n=14)	**4**	≤0.06	0.5	1	>32
Total	**(n=468)**	**2**	2	16	32	>32
NDM	(n=420)	**2**	4	16	32	>32
VIM	(n=47)	**1**	1	2	8	>32

MBL-*E. coli*: MIC distribution



WT	28%
YRIK insertion	15%
YRIN insertion	57%
Total	100%

72%

PK/PD and human dose prediction of EBL-1463

EBL-1463 shows good PK properties consistent with UTI indication
Potential for other indications

CL (L/h/kg)	
Mouse	6.4
Rat	2.0
Dog	0.55
NHP	0.55
Human (pred.)	**0.19**

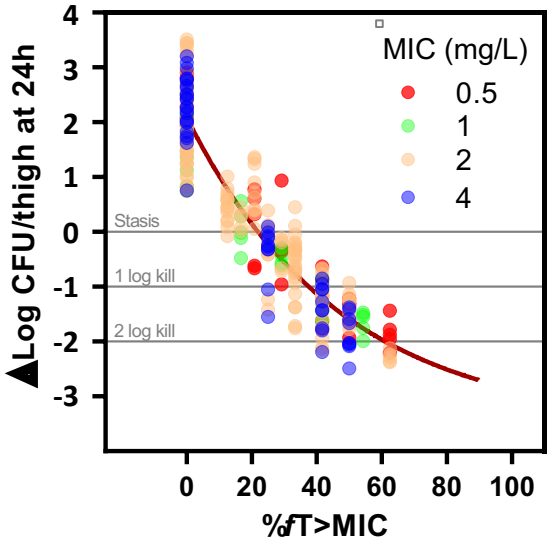
Urinary excretion (unchanged)	
Mouse	**44%**
Rat	**90%**

ELF exposure	
Mouse	**98%**
(/ free plasma)	

PK/PD typical of β-lactams': % *f*T>MIC

Low Human Efficacious Dose (HED) predicted: <1g q8h with 2 or 3h infusion for 1log kill

Δ-Log in mouse thigh infection model / %*f*T>MIC



EBL-1463 - Competition (PBP targeting compounds)

	β-lactam included ?	Single-agent pharmacology	Carbapenem sparing	Resistance : ABCD BLA covered	Resistance: PBP3 insertion covered
EBL-1463	**NO**	**YES**	**YES**	**YES**	**YES**
ATM/AVI	YES	NO	**YES**	**YES**	NO
BOS-228	YES	**YES**	**YES**	**YES**	NO
CEFIDEROCOL	YES	**YES**	**YES**	**YES**	NO
MEM/VAB	YES	NO	NO	A,C	**YES**
MEM/NAC	YES	NO	NO	A,C	**YES**
IMI/CIL/REL	YES	NO	NO	A,C	**YES**
MEM/QPX7728	YES	NO	NO	**YES**	**YES**
CAZ/AVI	YES	NO	**YES**	A,C	NO
FEP/TAZ,NMTAZ	YES	NO	**YES**	A,C	NO
FEP/ZID	YES	NO	**YES**	A,C	NO
FEP/TANIB.	YES	NO	**YES**	**YES**	NO

EBL-1463 has **unique characteristics** compared to drugs marketed or in development
Potential to be **the first novel class PBP inhibitor** clearly differentiated from β-lactam-base regimen
And **without class toxicity** as with Aminoglycosides, Polymyxins, Fluoroquinolones, Cyclines.

Summary

EBL-1463 is a novel-class PBP inhibitor which transcends the β-lactam family

- Unsurpassed stability to ABCD β-lactamases
- Unaffected by worrying PBP3 mutations showing up in LMICs
- Single-acting, bactericidal with low frequency of resistance
- Carbapenem-sparing
- No class-toxicity, no safety alert
- Small, highly soluble, easy to formulate

Vision:

- First develop **EBL-1463 as IV single-agent for empirical treatment of cUTI**
- Tackling newest worrisome resistance pathways in LMICs (MBL, PBP3)
- Ideally extend to all CRE infections

Status:

- Candidate selection scheduled by 2020 end (ENABLE)
- IND-enabling studies scheduled in 2021

Acknowledgments

ENABLE public/private partnership, an *ad hoc* structure for novel antibacterials discovery, providing an efficient mix of **expertise, resources and guidance** in microbiology, chemistry and drug development

EFPIA (GSK, EVOTEC)

Latvian Institute of Organic Synthesis

Uppsala University (IMBIM, UDOPP, Pharmacometrics)

Cardiff University School of Medicine

Copenhagen Statens Serum Institut

Research Institutes of Sweden

Asclepia