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Beta-lactamase database (BLDB) – structure and function

Thierry Naas^a , Saoussen Oueslati^a, Rémy A. Bonnin^a , Maria Laura Dabos^{a,b}, Agustin Zavala^{a,b}, Laurent Dortet^a , Pascal Retailleau^b  and Bogdan I. Iorga^b 

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ABSTRACT

Beta-Lactamase Database (BLDB) is a comprehensive, manually curated public resource providing up-to-date structural and functional information focused on this superfamily of enzymes with a great impact on antibiotic resistance. All the enzymes reported and characterised in the literature are presented according to the class (A, B, C and D), family and subfamily to which they belong. All three-dimensional structures of β -lactamases present in the Protein Data Bank are also shown. The characterisation of representative mutants and hydrolytic profiles (kinetics) completes the picture and altogether these four elements constitute the essential foundation for a better understanding of the structure-function relationship within this enzymes family. BLDB can be queried using different protein- and nucleotide-based BLAST searches, which represents a key feature of particular importance in the context of the surveillance of the evolution of the antibiotic resistance. BLDB is available online at <http://blldb.eu> without any registration and supports all modern browsers.

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Database; beta-lactamase; antibiotic resistance; hydrolytic profile; mutant

Introduction

β -Lactams, due to their safety, reliable killing properties and clinical efficacy, are among the most frequently prescribed antibiotics used to treat bacterial infections. However, their utility is being threatened by the worldwide proliferation of β -lactamases (BLs) with broad hydrolytic capabilities, especially in multi-drug-resistant gram-negative bacteria. These BLs are divided into four classes based on their sequence identities¹. While a handful of BLs were known in the early 1970s, their number has ever since been growing rapidly, especially with the description in clinical isolates of novel enzymes being capable of hydrolysing carbapenems, last resort antibiotics². A representative example is the class A KPC-2 that in a few years became one of the most menacing BL currently spreading worldwide³.

Historically, the principal resource of BLs was maintained from 2001 at the Lahey Clinic (<http://www.lahey.org/Studies/>) by George Jacoby and Karen Bush, by assigning new enzyme numbers for a number of representative BL families. From July 2015, this resource was transferred into the Bacterial Antimicrobial Resistance Reference Gene Database (<https://www.ncbi.nlm.nih.gov/bioproject/313047/>) maintained at the NCBI. Other resources are the Institute Pasteur MLST Database (<http://bigsdbs.pasteur.fr/klebsiella/klebsiella.html>), the Antibiotic Resistance Genes Database⁴, the Lactamase Engineering Database^{5,6}, the Metallo- β -Lactamase Engineering Database⁷, the Comprehensive Antibiotic Resistance Database⁸, the β -Lactamase Database⁹, the Comprehensive β -Lactamase Molecular Annotation Resource¹⁰. However, most of these databases are either not maintained

anymore, have a very broad scope or are focused on a few BL families.

The aim of our *Beta-Lactamase Database (BLDB)* is to compile sequence information as well as biochemical and structural data on all the currently known BLs. This comprehensive web-based database, which is updated on a weekly basis, may provide at a glance useful insights in the structure-function relationships of BLs, allowing a better understanding of substrate specificities and key residues involved in substrate recognition and hydrolysis. Altogether, the information provided by BLDB may help to foresee the impact of future mutations on the evolution of BLs.





Implementation details


The database is hosted on a dedicated virtual server in the cloud, which allows easy adjustments and evolution of computing resources according to the needs.

The core pages are implemented in PHP on a Linux Server under the CentOS 7.2 operating system, whereas the raw data is stored as tabulated files in order to facilitate the updates.

The interactive images showing the list of BL families that are present in the BLDB are generated dynamically in SVG format from the raw data, thus ensuring an updated display at any time. The corresponding URL links are directly embedded in the SVG images.

Multiple sequence alignments are automatically generated with Clustal Omega¹¹ using the default parameters. Phylogenetic trees are processed using Phylip version 3.695

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 Supplemental data for this article can be accessed [here](#).

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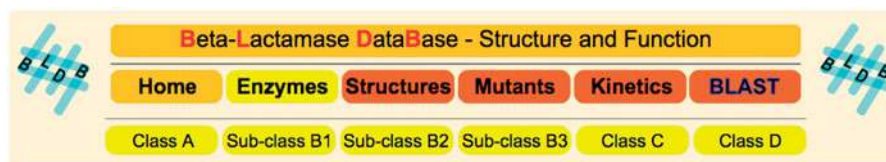


Figure 1. Global architecture of the Beta-Lactamase Database. In addition to the *Home page*, there are five main sections, dedicated to *Enzymes* (classified into the four classes A, B, C and D, and further into the three sub-classes of class B), three-dimensional *Structures* available in the Protein Data Bank, synthetic *Mutants* and hydrolytic profiles (*Kinetics*) described in the literature, and a graphical interface for *BLAST* queries.

(<http://evolution.genetics.washington.edu/phylip/>) using Clustal Omega's *DND* output files and represented as *SVG* images to provide the best quality and minimal file size.

The radar charts representing hydrolytic profiles are dynamically built using a modified and personalised version of the *D3.js* JavaScript library (<https://gist.github.com/nbremer/6506614>).

The *BLAST* interface is provided by *SequenceServer*¹² and the *BLAST* + binaries are downloaded from *NCBI*¹³.

Input data is downloaded from *NCBI* using the "Entrez Direct: E-utilities on the UNIX Command Line"¹³ and from the *PDB* with personalised scripts.

Structures are updated semi-automatically on a weekly basis, after each *PDB* update. New enzymes are added following every update of the *Bacterial Antimicrobial Resistance Reference Gene Database*. Constant literature survey also provides newly described *BLs* and synthetic mutants, as well as their hydrolytic profiles. The long-term maintenance of the *BLDB* is ensured by the collaboration between two academic teams with active interest and experience in the field of *BL*-mediated antibiotic resistance.

Database architecture

BLDB is designed around five main sections, which are strongly interconnected and gathered around the main home page (Figure 1). All pages contain (i) a header showing the overall structure of the *BLDB*, with links for an easy access to all sections at any moment, and (ii) a footer with acknowledgments to funding bodies that have contributed to this project and with contact details.

Home page

A short introduction to the present challenges associated with the antibiotic resistance is presented, highlighting the important contribution provided by the *BLDB* in this field.

Real-time statistics with the number of entries for each type of data present in the *BLDB* (*Enzymes*, *Structures*, *Mutants* and *Kinetics*) and for each one of the four classes of *BL* are also provided. The entries corresponding to the subclasses B1, B2 and B3 of class B are further detailed, for a better presentation of their similarities and differences (Figure S1).

Enzymes

The *Enzymes* tab of the main menu gives access to a list of classes and sub-classes of *BLs*, together with their corresponding *BL* families (Figure S3). This is represented as an *SVG* image that is dynamically generated from the raw data, which always ensures up-to-date information.

Each entry of a given *BL* family contains the class, protein name and eventually alternative names. When the family features several clearly defined sub-families, this information is also present. *GenPeptID* and *GenBankID* (with a *RefSeq* number when provided by *NCBI*) are also provided, with the corresponding links on the *NCBI*'s website for more detailed information. Bibliographic

data (*PubMedID*, *DOI*), functional (phenotype, hydrolytic profile) and genetic (natural or acquired type) information and links to the other sections are also provided (Figure S2).

Sequence alignments are provided for each class, subclass, family and subfamily (Figure S4), together with the corresponding phylogenetic tree (Figure S5).

Structures

The *Structures* tab gives access to a table containing all three-dimensional structures of *BLs* reported in the *Protein Data Bank*¹⁴. Each entry contains the name of *BL*, together with the class or sub-class to which it belongs, followed by the *PDB* code and resolution (if applicable). The protein sequence is linked to the corresponding *UniProt* entry and, if appropriate, the existing mutations (extracted from the *PDB* file content) are shown. Bibliographic data (*PubMedID*, *DOI*) allows an easy retrieval of the original articles associated with the structure through links to *PubMed* and to the journal website. All ligands, buffer molecules and ions present in the structures are highlighted, together with their interaction mode with the protein (non-covalent, covalent, metal coordination). For all these molecules, links to their corresponding dedicated page on the *PDB* website are provided. Crystallographic details (space group, unit cell parameters, *Z*-value) are also presented, in order to facilitate the resolution of new structures and to allow an easy comparison of the existing ones (Figure S6).

Mutants

The synthetic mutants that were described for each enzyme in the literature are presented, together with bibliographical information (*PubMedID*, *DOI*) and links to *PDB* structures and hydrolytic profiles when appropriate (Figure S7). Given the very important number of synthetic mutants described to date, the present version of the *BLDB* is not complete. More mutants will be added in the near future.

Kinetics (hydrolytic profiles)

This section is organised in two parts: (i) a table containing the hydrolytic profiles on different β -lactam antibiotics, with values for the turnover number (k_{cat}), the Michaelis constant (K_m) and the catalytic efficiency (k_{cat}/K_m) (Figure S8); (ii) a radar chart representing a superposition of hydrolytic profiles selected for easier comparison (Figure S9). The number of hydrolytic profiles currently available in the *BLDB* is relatively modest, and more entries are scheduled to be added in the near future.

BLAST

Protein- and nucleotide-based *BLAST* search capabilities of *BLDB* are implemented using a personalised version of the *SequenceServer* graphical interface¹². The input sequence type (protein or nucleotide) is automatically detected, and the *BLAST* search type is adapted accordingly. Advanced parameters can be

used for the BLAST search in order to obtain more refined results (Figure S10).

The BLAST search is executed using the default parameters and the results are shown using a personalised interface, with the name of BL highlighted in red and links to the corresponding entries on the NCBI's website. The number of identical residues between the query and each sequence producing a significant alignment is provided, together with the percentage of identity (Figure S11). Together with the E-value, this represents useful information for a quick assessment of the BLAST results. A percentage of 100.00% means that the input sequence is already present in the BLDB, whereas a high sequence identity points out towards the BL class and/or family to which the input sequence might belong.

In the lower part of the results page, the alignments between the query and sequences producing significant alignments are provided (Figure S12).

Initial content

As of 25 April 2017, BLDB contains 2666 unique enzymes from all four classes of BLs, as well as 810 three-dimensional structures of BLs that are currently available in the Protein Data Bank (PDB)¹⁴. BLDB also contains 167 mutants and 47 hydrolytic profiles.

Conclusion

BLDB is developed and maintained by two well-established research groups that are active in the field of BL-mediated antibiotic resistance. This resource is designed to provide appropriate answers to the needs of the research and clinical communities working on antimicrobial resistance.

Acknowledgements

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supplementary Information

Beta-Lactamase DataBase (BLDB) – Structure and Function

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Beta-Lactamase DataBase - Structure and Function

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[Structures](#)
[Mutants](#)
[Kinetics](#)
[BLAST](#)

BLDB Presentation

Multidrug resistant (MDR) gram-negative pathogens, especially *Enterobacteriaceae*, are emerging worldwide. The MDR pattern is relatively common with resistance appearing to all major classes of anti-gram-negative agents (e.g. β -lactams, fluoroquinolones, and aminoglycosides), and in some cases, resistance to all available drugs. This is particularly worrisome in view of the current dearth of new compounds active against MDR gram-negatives in the pipeline.

β -Lactams, due to their safety, reliable killing properties and clinical efficacy, are among the most frequently prescribed antibiotics used to treat bacterial infections. However, their utility is being threatened by the worldwide proliferation of β -lactamases (BLs) with broad hydrolytic capabilities, especially in MDR gram-negative bacteria. These BLs are divided into 4 classes based on their sequence identities. Classes A, C and D contain active-site serine enzymes whose reaction pathways involve acylenzyme adducts while class B represents metallo- β -lactamases (MBLs) which do not form such intermediates (require zinc ion (s) for their function). Currently, BL-mediated resistance does not spare even the newest and most powerful β -lactams (i.e. carbapenems), whose activity is challenged by the MBLs (IMP, VIM, NDM, ...) as well as classes A and D serine-carbapenemases (KPC, IMI, GES, OXA-48, OXA-23, OXA-40, ...).

While a handful of β -lactamases were known in the early 1970's, the number of β -lactamases has ever since been growing rapidly, especially with novel enzymes described, and the current dissemination of some enzymes in clinical isolates that undergo changes in their amino-acid sequence, yielding novel hydrolytic properties. The substrate specificities may be relatively narrow or broad including the extended-spectrum cephalosporins and the carbapenems. The class A enzymes (known primarily as penicillinases) tend to hydrolyze penicillins over cephalosporins as substrates although many variants may hydrolyze significantly broad-spectrum cephalosporins and carbapenems. The class B enzymes (metallo- β -lactamases) typically have an extremely broad-spectrum substrate specificity including all β -lactams except monobactams (aztreonam). The class C enzymes (cephalosporinases) tend to prefer cephalosporins as substrates whereas class D enzymes (oxacillinases) have an unusually high substrate preference for oxacillin and related penicillins. None of the marketed β -lactam molecules may resist to the hydrolysis by β -lactamases.

The aim of the Beta-Lactamase DataBase (BLDB) is to compile sequence information as well as biochemical and structural informations on all the currently known β -lactamases. BLDB offers in addition tools to analyze β -lactamases and provides important links to the related web resources (NCBI, PDB, etc.). This comprehensive web-based database may provide at a glance useful insights in the structure-function relationships of β -lactamases, and thus allowing a better understanding of substrate specificities, determine key residues involved in substrate recognition and hydrolysis, and to foresee the impact of mutations in the hydrolysis profile.

Statistics

Enzymes:
Overall (2666); class A (1111); subclass B1 (202); subclass B2 (18); subclass B3 (60); class C (628); class D (564).

Structures:
Overall (810); class A (340); subclass B1 (161); subclass B2 (14); subclass B3 (45); class C (154); class D (96).

Mutants:
Overall (167); class A (81); subclass B1 (35); subclass B2 (3); subclass B3 (6); class C (19); class D (13).

Kinetics:
Overall (47); class A (21); subclass B1 (3); subclass B2 (0); subclass B3 (4); class C (0); class D (19).

Last updated: April 25, 2017.

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Contact: contact@bldb.eu

Fig. S1. Global overview of the Home page.

Enzymes

Ambler sub-class B1 beta-lactamases

Sequence alignment for sub-class B1

Ambler class	Protein name	Alternative protein names	Subfamily	GenPeptID	GenBankID	PubMedID (DOI)	Sequence	Number of PDB structures	Mutants	Phenotype	Functional information	Natural (N) or Acquired (A)
NDM												
The official nomenclature for NDM family is maintained at NCBI .												
B1	NDM-1			AHM26723	KJ018857	19770275 (DOI)	view	32	2	3a	Carbapenemase	A
B1	NDM-2			AE441876	JF703135	21427107 (DOI)	view			3a	Carbapenemase	A
B1	NDM-3			AFK80349	JQ734687	23330550 (DOI)	view	1		3a	Carbapenemase	A
B1	NDM-4			AFB82585	JQ348841	22252797 (DOI)	view	1		3a	Carbapenemase	A
B1	NDM-5			ANE23847	KX062216	21930874 (DOI)	view	1		3a	Carbapenemase	A
B1	NDM-6			AEX08599	JN967644	23731823 (DOI)	view	1		3a	Carbapenemase	A
B1	NDM-7			AKN33289	KP826705	23557929 (DOI)	view			3a	Carbapenemase	A
B1	NDM-8			AJES1442	KP265938	23459485 (DOI)	view	1		3a	Carbapenemase	A
B1	NDM-9			ASL91756	KC999080	24913967 (DOI)	view			3a	Carbapenemase	A
B1	NDM-10			AGT37351	KF361506		view			3a	Carbapenemase	A
B1	NDM-11			AJEG1443	KP265939		view			3a	Carbapenemase	A
B1	NDM-12			BAQ79439	AB926431	25092693 (DOI)	view			3a	Carbapenemase	A
B1	NDM-13			BAQ23218	LCB12596	26169399 (DOI)	view			3a	Carbapenemase	A
B1	NDM-14			AJPI3054	KM210086	25645836 (DOI)	view			3a	Carbapenemase	A
B1	NDM-15			AKF43458	KP735848		view			3a	Carbapenemase	A
B1	NDM-16			AKZ20823	KP862821		view			3a	Carbapenemase	A
B1	NDM-17			AQT73359	KX812714		view			3a	Carbapenemase	A
B1	NDM-18			APZ75411	KY503030		view			3a	Carbapenemase	A
PEDO												
B1	PEDO-3			AJPT7076	KP109679	26482314 (DOI)	view					N (Pedobacter sp. Stok-3)
SFB												

* after the protein name denotes a temporary name in BLDB, while waiting for a definitive assignment by NCBI. GeneBankIDs represented in bold face correspond to entries for which NCBI has assigned a RefSeq.

Fig. S2. Global overview of the Enzymes section.

Beta-Lactamase DataBase - Structure and Function												
Home		Enzymes		Structures		Mutants		Kinetics		BLAST		
Class A			Sub-class B1		Sub-class B2		Sub-class B3		Class C		Class D	
ACI	AER	BclI	BlaB	CphA	SFH	AIM	BJP	ACC	ACT	AmpH	BAC	
AFA	AST	CGB	CfiA			CAR	CAU	ADC	AQU	BAD	BAT	
Bcl	BCL	DIM	EBR			CPS	EAM	AsbA1	CepS	BED	BEN	
BEL	BES	FIM	GIM			ECM	EFM	BUT	CAV	BOC	BPU	
BIC	BKC	HMB	IMP			ELM	ESP	CepH	CFE	BSU	LCR	
BlaS	BOR	IND	JOHN			EVM	FEZ	CHR	CMH	NPS	OXA	
BPS	BRO	KHM	MOC			GOB	L1	CMY	DHA			
CAD	CARB	MUS	NDM			MSI	PEDO	Ear	EDC			
CblA	CBP	PEDO	SFB			POM	RM3	ERH	ESC			
CdiA	CepA	SIM	SLB			SMB	SPG	FOX	LHK			
CfxA	CGA	SPM	TMB			SPR	THIN	LYL	MIR			
CIA	CKO	TUS	VIM					MOR	MOX			
CME	CRH							OCH	PDC			
CRP	CRS							PLY	SEC			
CTX-M	DES							TRU	UCB			
ERP	FAR							XAN	YEC			
FEC	FONA							YER				
FPH	FRI											
FTU	GES											
GIL	GPA											
HugA	IMI											
KLUA	KLUC											
KLUG	KLUY											
KPC	L2											
LAP	LEN											
LUT	MAL											
MIN	OHIO											
OIH	OKP											
ORN	OXY											
PC1	PC2											
PER	PLA											
PME	PenA											
PenB	PenC											
PenD	PenE											
PenP	PSV											
RAHN	RCAP											
ROB	RUB											
SCA	SCO											
SED	SFC											
SFR	SFO											
SGM	SHV											
SME	TEM											
TER	TLA											
VCC	VEB											
VHH	VHW											
YENT												

Fig. S3. Global overview of the β -lactamase families that are present in the BLDB.

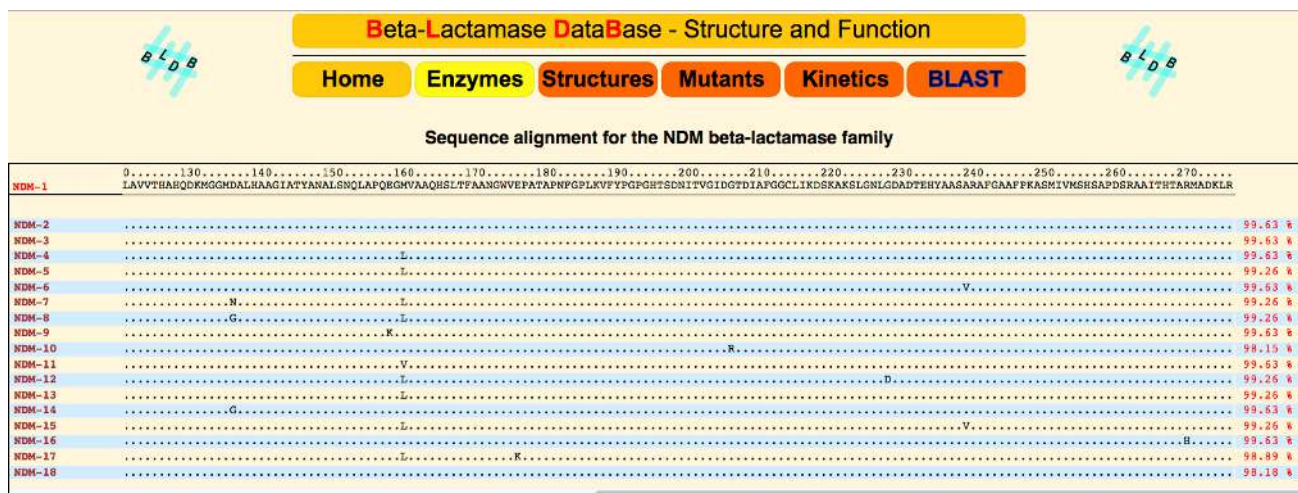


Fig. S4. Sequence alignment.

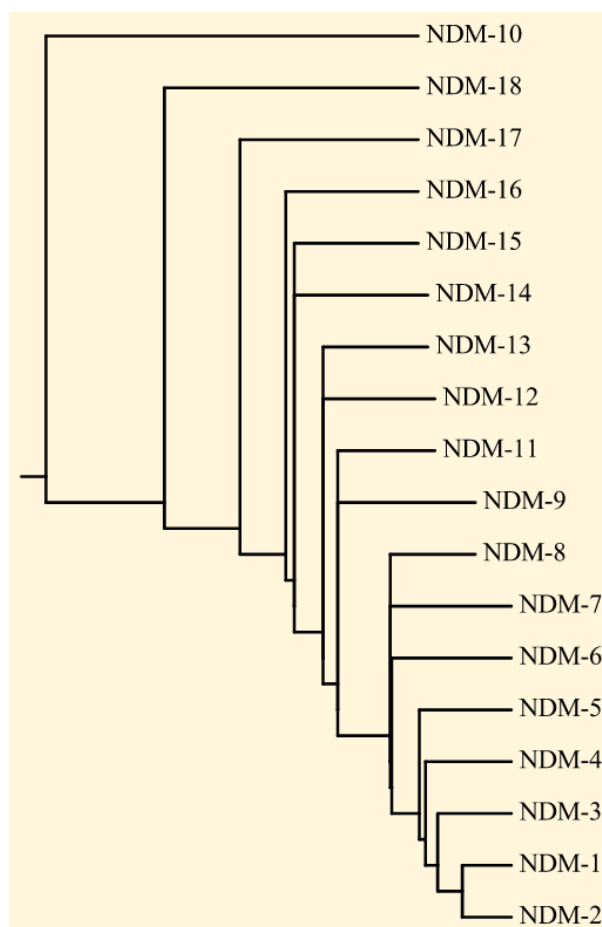


Fig. S5. Rooted phylogenetic tree corresponding to the sequence alignment.

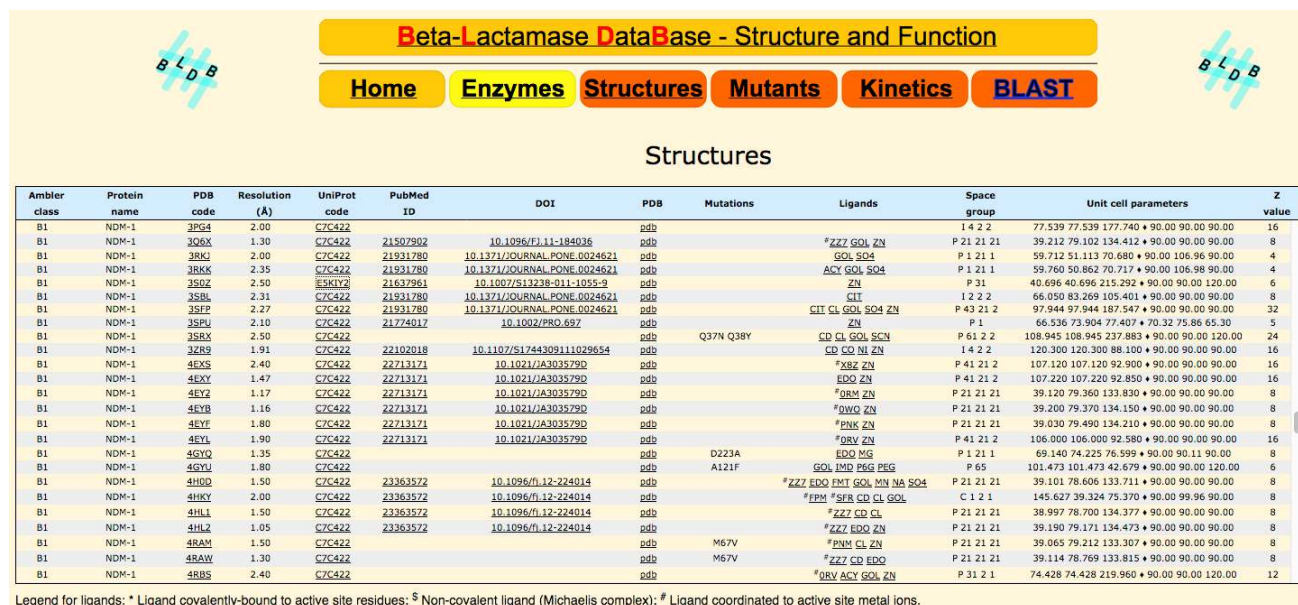


Fig. S6. Global overview of the Structures section.

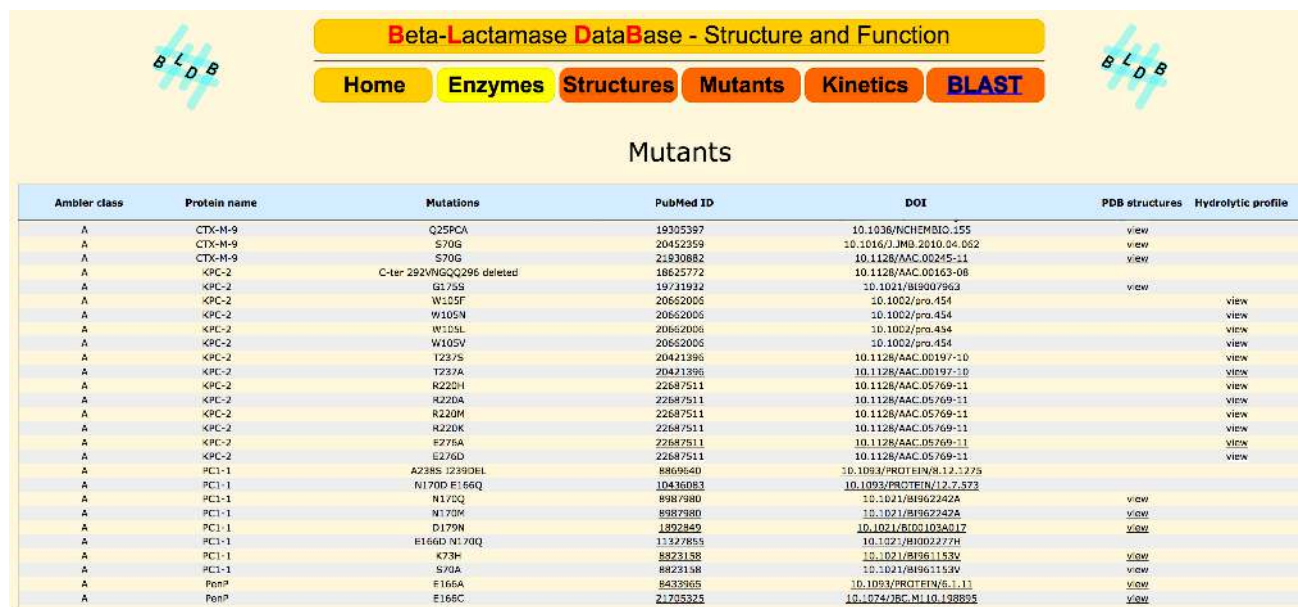


Fig. S7. Global overview of the Mutants section.

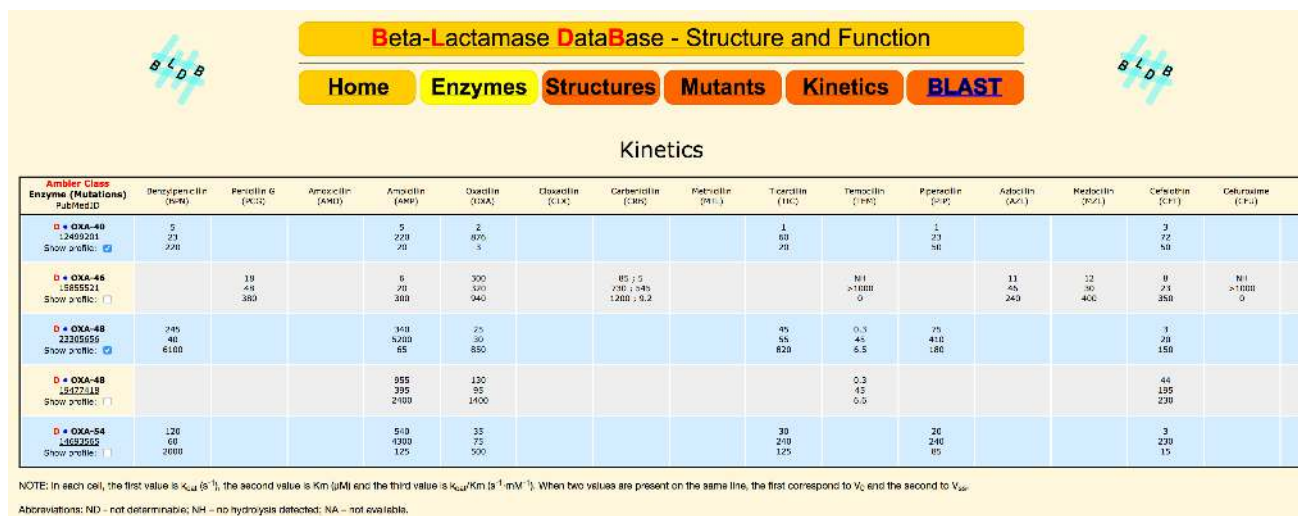


Fig. S8. Global overview of the Kinetics section, showing the hydrolytic profiles.

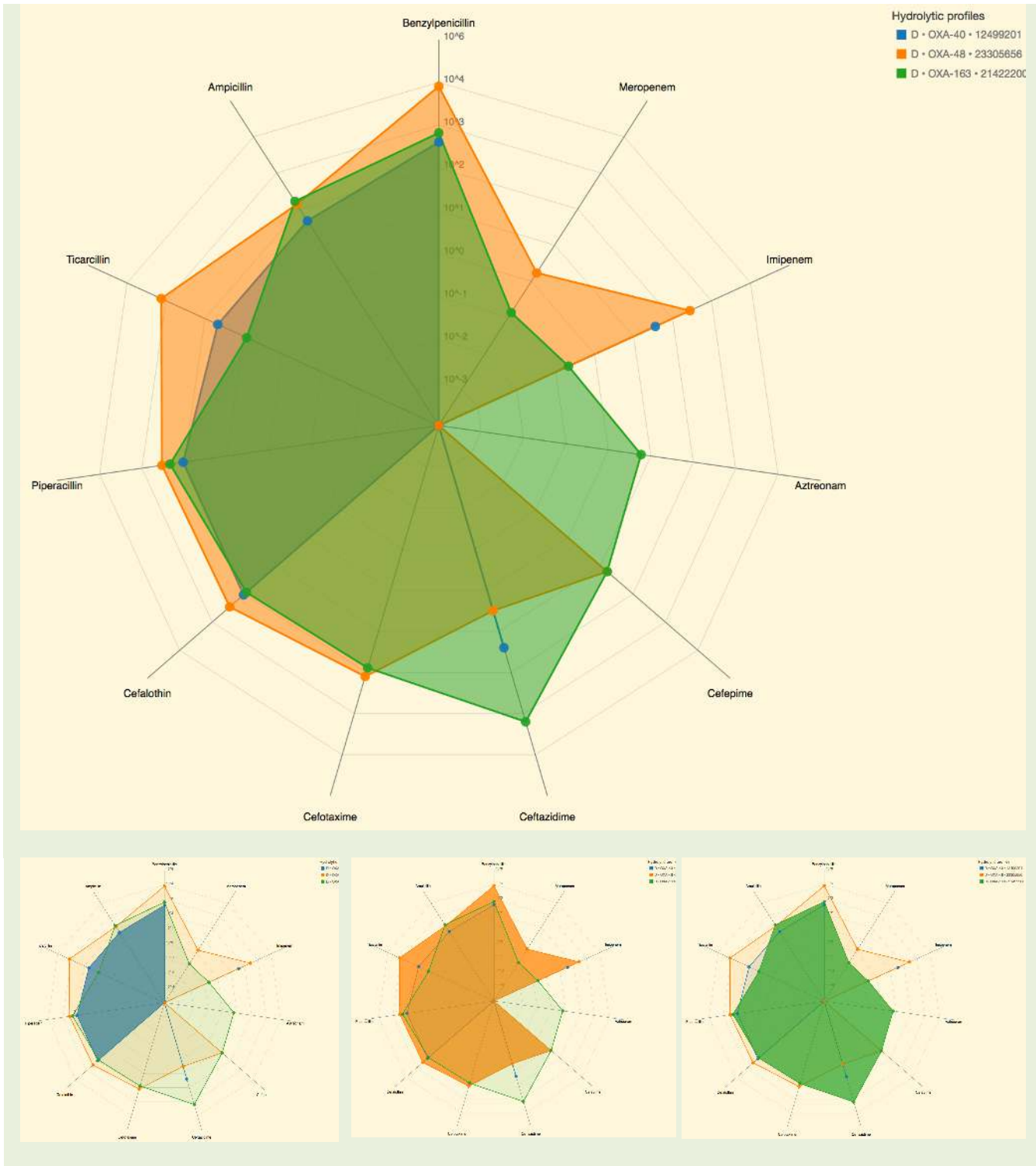


Fig. S9. Radar chart showing the superposition of hydrolytic profiles for OXA-40 (blue), OXA-48 (orange) and OXA-163 (green).

```
>gi|595266892|gb|AHM26723.1|NDM-1| beta-lactamase NDM-1 [Achromobacter sp. NF518]
MELPNIMHPVAKLSTALAAALMLSGCMPGEIRPTIGQQMETGDQRFGLVFRQLAPNVWQHTSYLDMPGF
GAVASNGLIVRDGGRVLVVDTAWTDDQTAQILNWIKQEIINLPVALAVVTHAQDKMGGMDALHAAGIATY
ANALSNQLAPQEGMVAAQHSLTFAANGWVEPATAPNFGPLKVFYPPGHTSDNITVIGIDGTDIAFGGCLI
KDSKAKSLGNLGDADTEHYAASARAFGAAPKASMIVMHSAPDSRAAITHTARMADKLR
```

Detected: protein sequence(s).

Nucleotide databases

beta-lactamases-all-nucleotide

Protein databases

beta-lactamases-all-protein

Advanced Parameters:

eg: -evalue 1.0e-5 -num_alignments 100

?

BLASTP

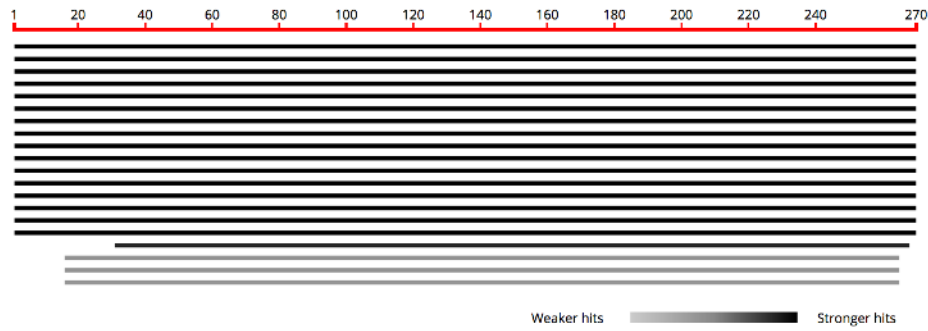
Fig. S10. SequenceServer graphical interface for the nucleotide- and protein-based BLAST queries.

Supplementary Information: Beta-Lactamase DataBase (BLDB)

Query= gi|595266892|gb|AHM26723.1|NDM-1| beta-lactamase NDM-1 [Achromobacter sp. NF518] 1/1

BLASTP: 1 query, 1 database

Query= gi|595266892|gb|AHM26723.1|NDM-1|



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FASTA of all hits

FASTA of selected hit(s)

Standard tabular report

Full tabular report

Full XML report

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Number	Sequences producing significant alignments	Total score	E value	Identities
1.	gi 595266892 gb AHM26723.1 NDM-1 beta-lactamase NDM-1 [Achromobacter sp. NF518]	555.83	0.00	270/270 (100.00)
2.	gi 378405411 gb AFB82585.1 NDM-4 metallo-beta-lactamase NDM-4 [Escherichia coli]	555.06	0.00	269/270 (99.63)
3.	gi 537849610 gb AGU91756.1 NDM-9 New Delhi metallo-beta-lactamase [Klebsiella pneumoniae subsp. pneumoniae]	554.29	0.00	269/270 (99.63)
4.	gi 366085573 gb AEX08599.1 NDM-6 NDM carbapenemase [Escherichia coli]	554.29	0.00	269/270 (99.63)
5.	gi 388890593 gb AFK80349.1 NDM-3 NDM-3 metallo-beta-lactamase [Escherichia coli]	554.29	0.00	269/270 (99.63)
6.	gi 748762923 gb AJE61443.1 NDM-11 metallo-beta-lactamase NDM-11 [Escherichia coli]	554.29	0.00	269/270 (99.63)
7.	gi 916370098 gb AKZ20823.1 NDM-16 class B beta-lactamase [Klebsiella pneumoniae]	553.52	0.00	269/270 (99.63)
8.	gi 848612134 gb AKN35289.1 NDM-7 NDM-7 (plasmid) [Enterobacter cloacae]	553.13	0.00	268/270 (99.26)

Fig. S11. SequenceServer formatted results of a protein BLAST query.

Supplementary Information: Beta-Lactamase DataBase (BLDB)

▼ [gij595266892|gb|AHM26723.1](#) | #NDM-1# beta-lactamase NDM-1 [Achromobacter sp. NF518] 1 / 259 BLASTP: 1 query, 1 database

Query= [gij595266892|gb|AHM26723.1...](#)

Hit length: 270 Select | Sequence | [FASTA](#) | [NCBI](#)

1. Positives	Score	Identities	Gaps	E value
270/270 (100.00)	555.83 (1431)	270/270 (100.00)	0/270 (0.00)	0.00 × 10 ⁺⁰⁰
Query 1	MELPNIMHPVAKLSTALAAALMLSGCMPGEIRPTIGQQMETGDRFGDLVFRQLAPNVWQ			60
Subject 1	MELPNIMHPVAKLSTALAAALMLSGCMPGEIRPTIGQQMETGDRFGDLVFRQLAPNVWQ			60
Query 61	HTSYLDMPGFGAVASNGLIVRDGGRVLVVDTAWTDDQTAQLLNWIKQEIINLPVALAVVTH			120
Subject 61	HTSYLDMPGFGAVASNGLIVRDGGRVLVVDTAWTDDQTAQLLNWIKQEIINLPVALAVVTH			120
Query 121	AHQDKMGGMDALHAAGIATYANALSNQLAPQEGMVAHQHSLTFAANGWVEPATAPNFGPL			180
Subject 121	AHQDKMGGMDALHAAGIATYANALSNQLAPQEGMVAHQHSLTFAANGWVEPATAPNFGPL			180
Query 181	KVFYPPGGHTSDNITVIGIDGTDIAFGGCLIKDSKAKSLGNLGDADTEHYAASARAFGAAF			240
Subject 181	KVFYPPGGHTSDNITVIGIDGTDIAFGGCLIKDSKAKSLGNLGDADTEHYAASARAFGAAF			240
Query 241	PKASMIVMHSAPDSRAAITHTARMADKLR	270		
Subject 241	PKASMIVMHSAPDSRAAITHTARMADKLR	270		

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▼ [gij378405411|gb|AFB82585.1](#) | #NDM-4# metallo-beta-lactamase NDM-4 [Escherichia coli] 2 / 299

Hit length: 270 Select | Sequence | [FASTA](#) | [NCBI](#)

1. Positives	Score	Identities	Gaps	E value
270/270 (100.00)	555.06 (1429)	269/270 (99.63)	0/270 (0.00)	0.00 × 10 ⁺⁰⁰
Query 1	MELPNIMHPVAKLSTALAAALMLSGCMPGEIRPTIGQQMETGDRFGDLVFRQLAPNVWQ			60
Subject 1	MELPNIMHPVAKLSTALAAALMLSGCMPGEIRPTIGQQMETGDRFGDLVFRQLAPNVWQ			60
Query 61	HTSYLDMPGFGAVASNGLIVRDGGRVLVVDTAWTDDQTAQLLNWIKQEIINLPVALAVVTH			120
Subject 61	HTSYLDMPGFGAVASNGLIVRDGGRVLVVDTAWTDDQTAQLLNWIKQEIINLPVALAVVTH			120
Query 121	AHQDKMGGMDALHAAGIATYANALSNQLAPQEGMVAHQHSLTFAANGWVEPATAPNFGPL			180
Subject 121	AHQDKMGGMDALHAAGIATYANALSNQLAPQEGMVAHQHSLTFAANGWVEPATAPNFGPL			180
Query 181	KVFYPPGGHTSDNITVIGIDGTDIAFGGCLIKDSKAKSLGNLGDADTEHYAASARAFGAAF			240
Subject 181	KVFYPPGGHTSDNITVIGIDGTDIAFGGCLIKDSKAKSLGNLGDADTEHYAASARAFGAAF			240
Query 241	PKASMIVMHSAPDSRAAITHTARMADKLR	270		
Subject 241	PKASMIVMHSAPDSRAAITHTARMADKLR	270		

Fig. S12. Sequence alignment of protein BLAST results with the initial query.