

DISEÑO E IMPLEMENTACIÓN DE UN SISTEMA DE INFORMACIÓN EN β-LACTAMASAS



Luis M. Rodríguez R.

Trabajo de grado dirigido por
Emiliano Barreto Hernández, cPhD

Luis M. Rodríguez R.

AGENDA

Introducción

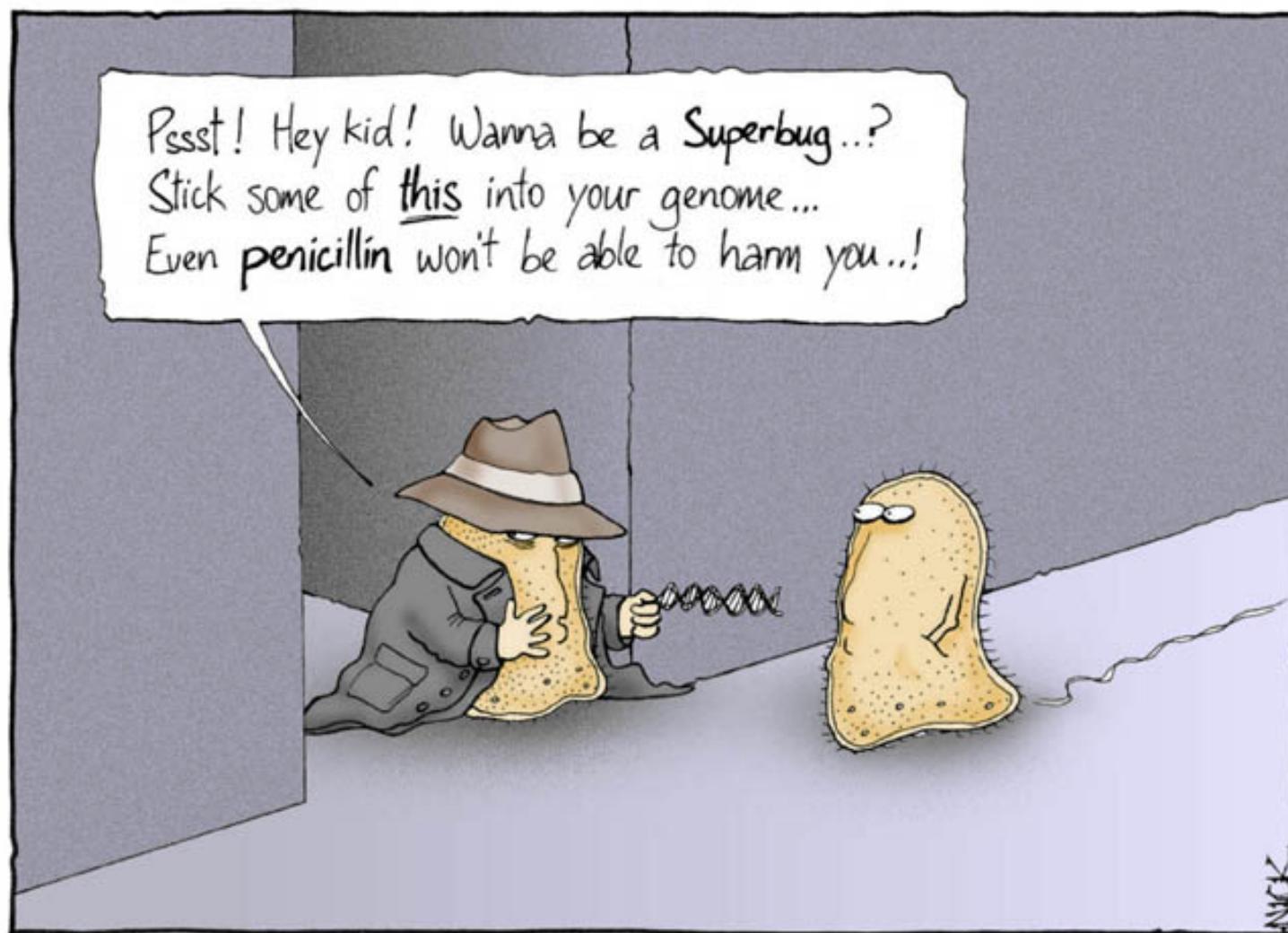
Métodos

Resultados

Conclusiones y perspectivas

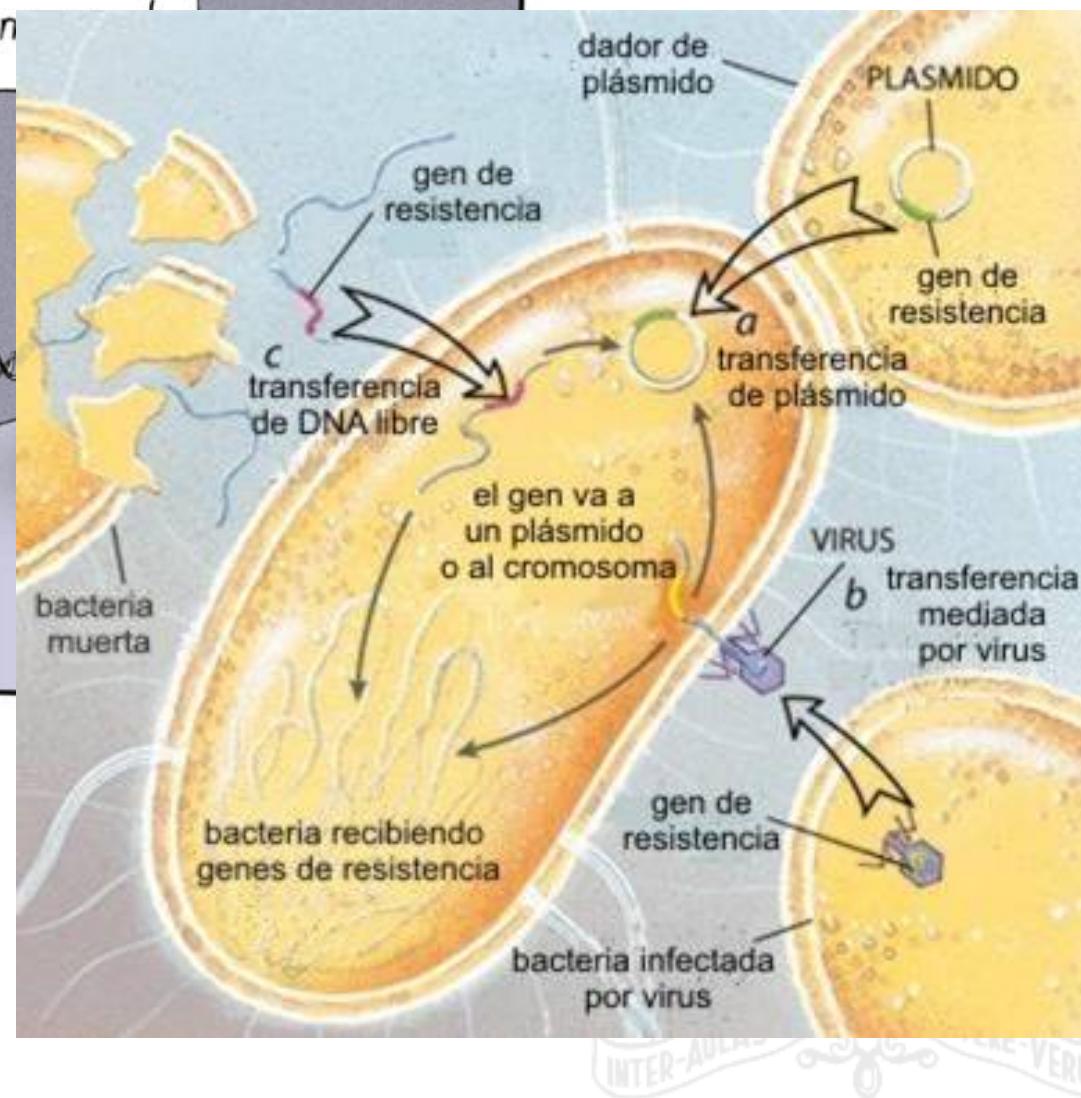
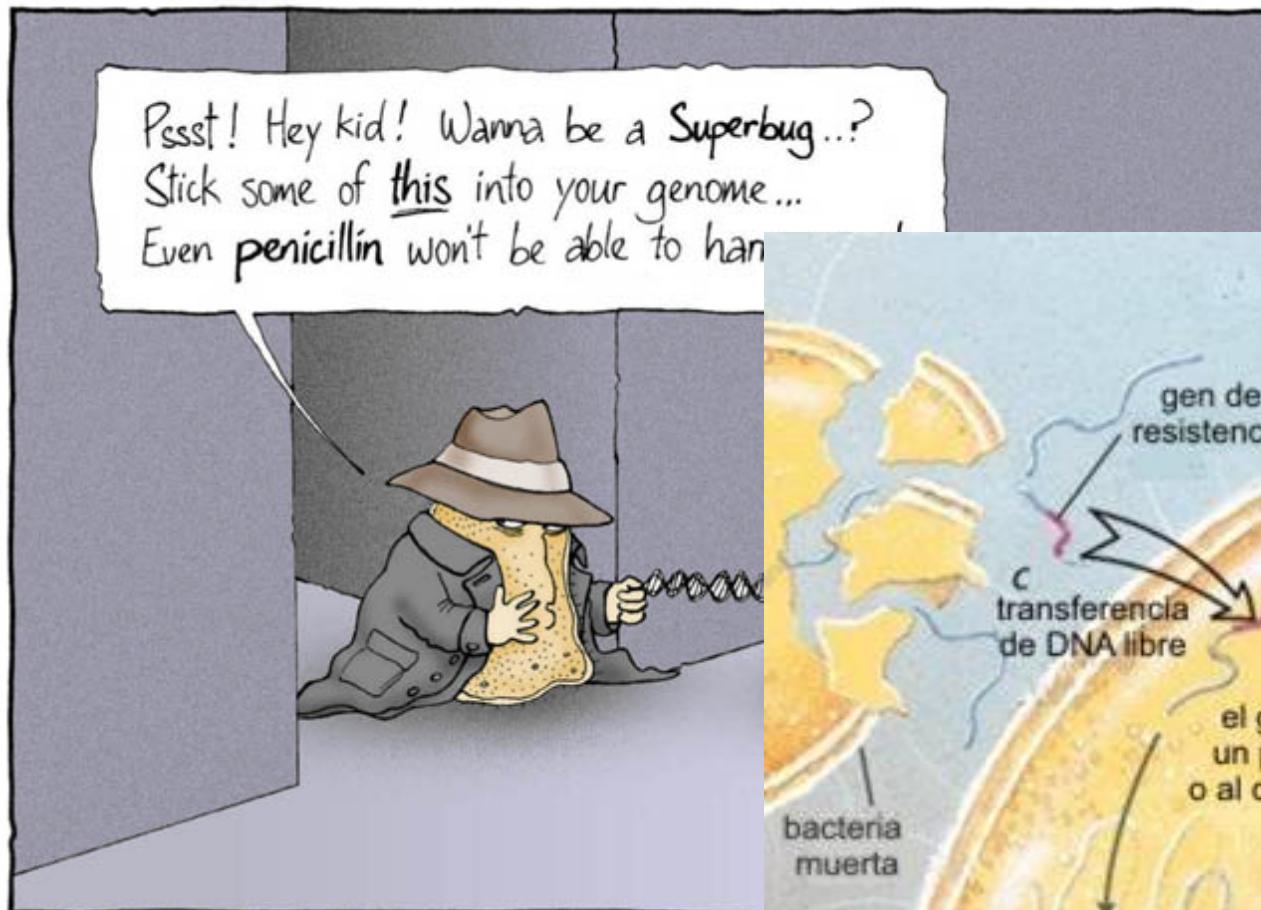


Introducción: resistencia

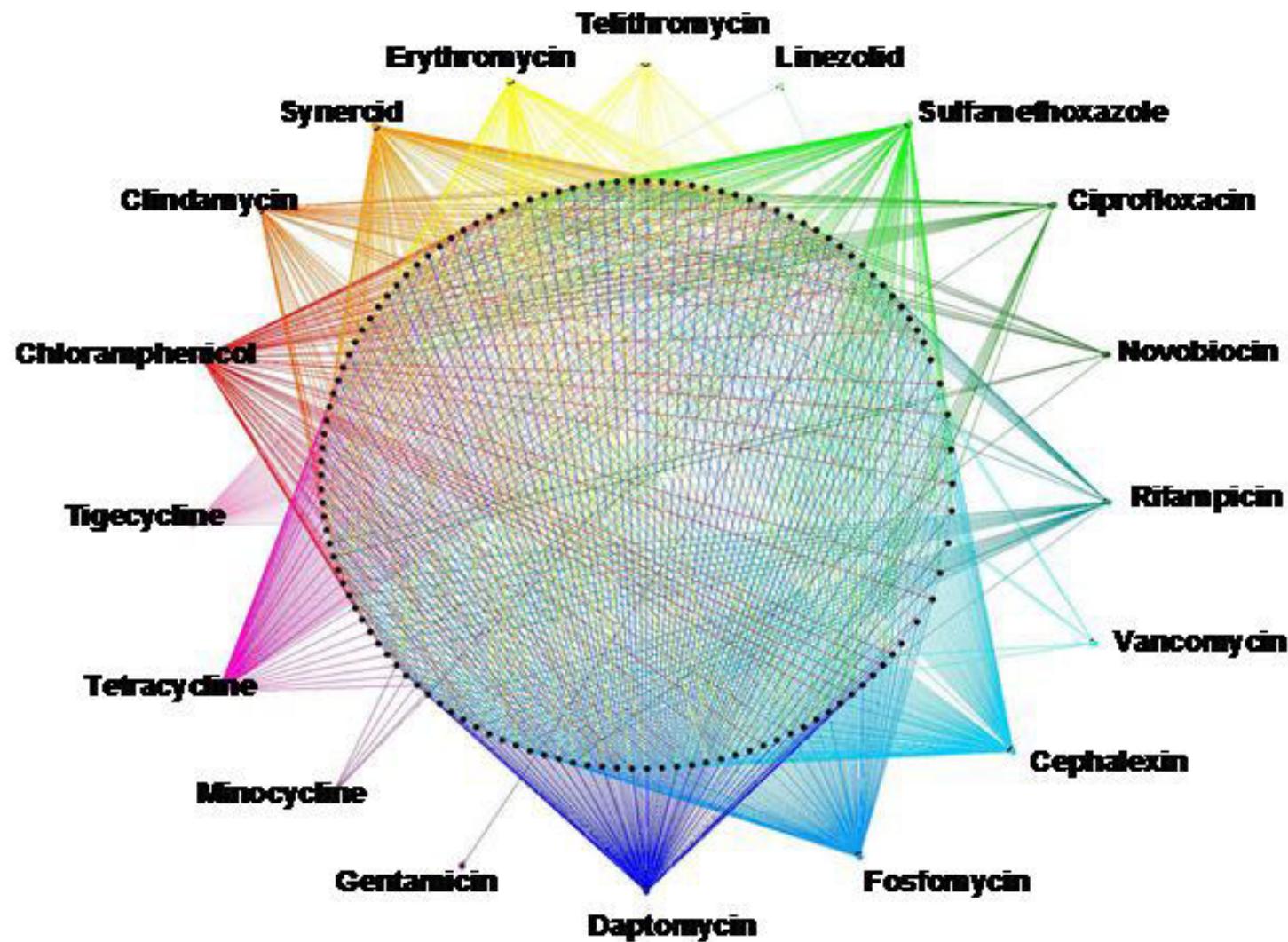


INTER-AULAS · DUÆRE-VERUM

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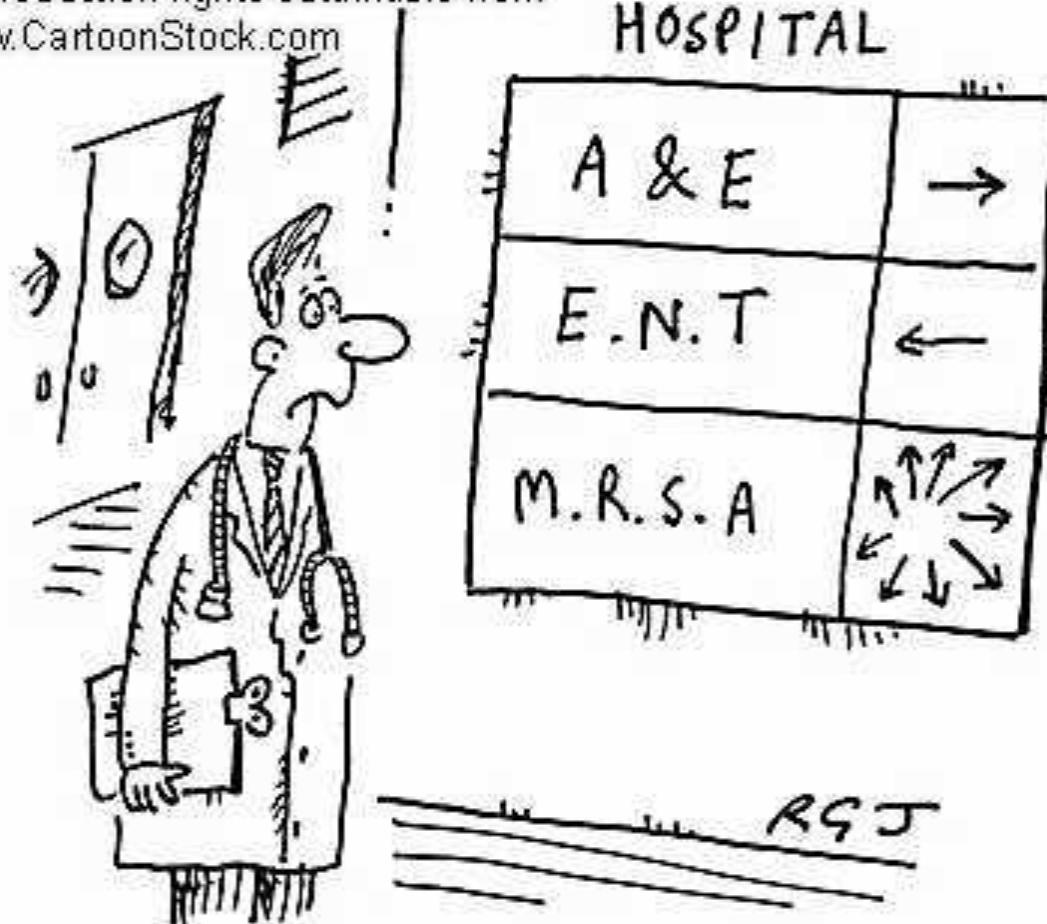
Sánchez de Rivas C. 2006. ¿Antibióticos, ayer, hoy y mañana...? QuímicaViva 5(2).

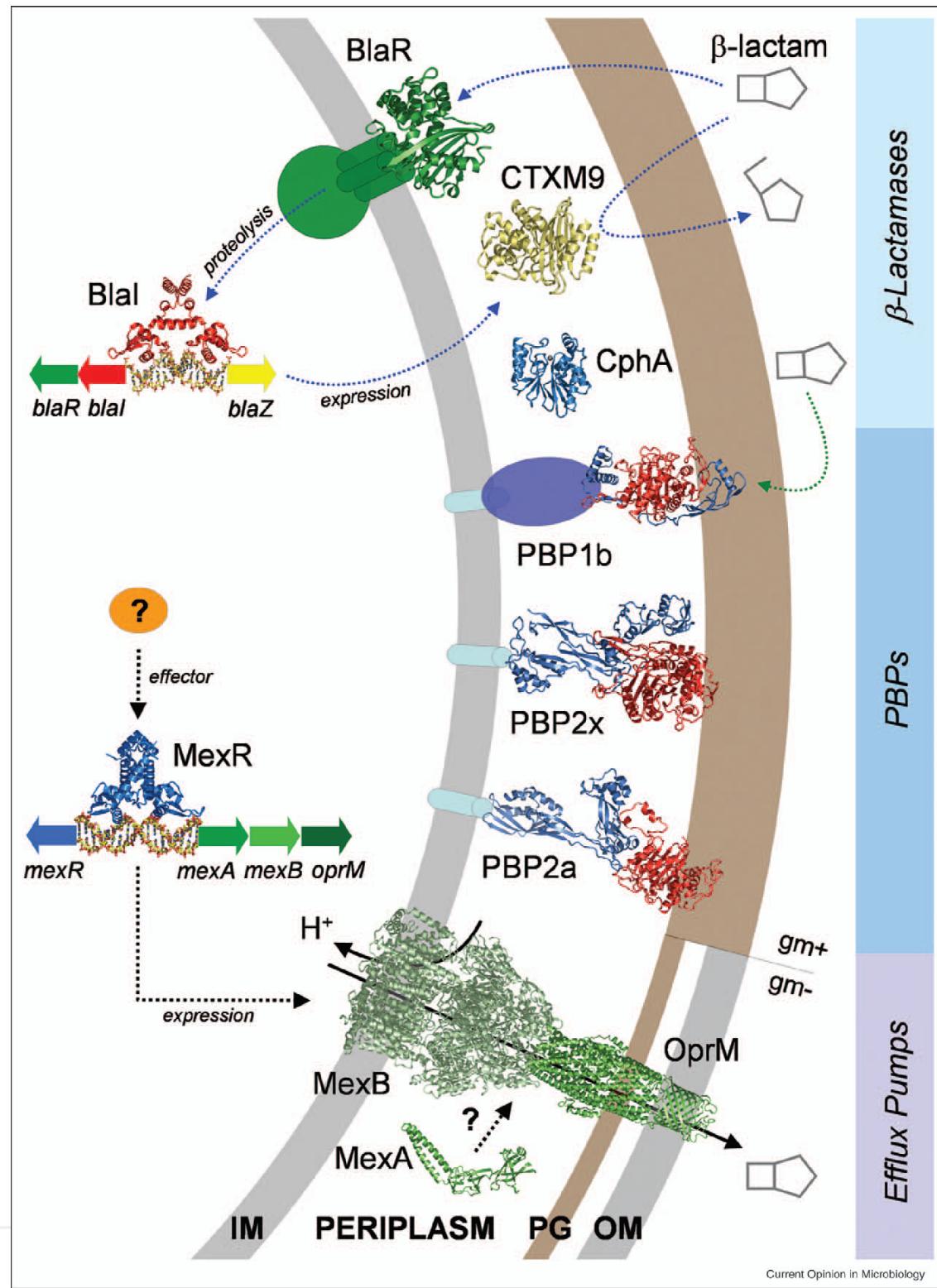


D'Costa VM, McGrann KM, Hughes DW, Wright GD.
2006. Science 311(5759):374-7.



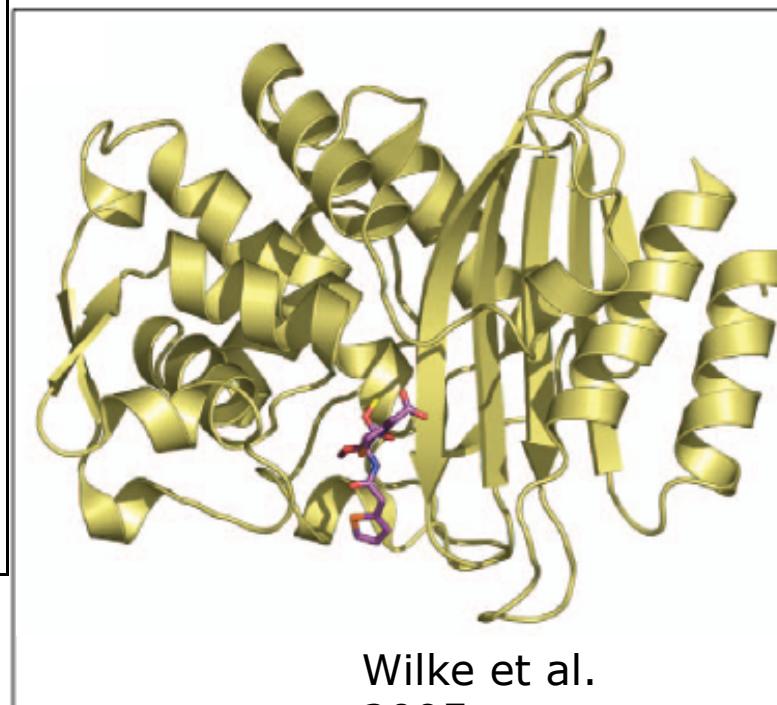
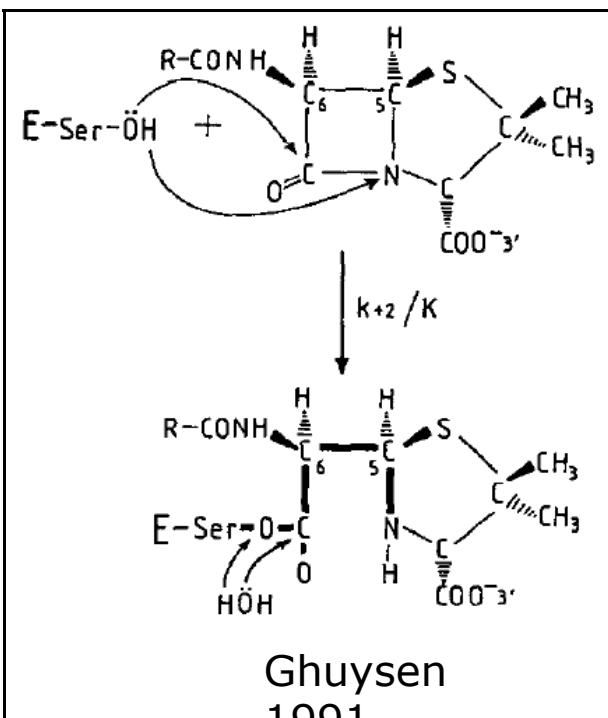
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Wilke MS, Lovering AL, Strynadka NCJ.
2005. β -lactam antibiotic resistance: a current structural perspective. Current Opinion in Microbiology 8:525-533.

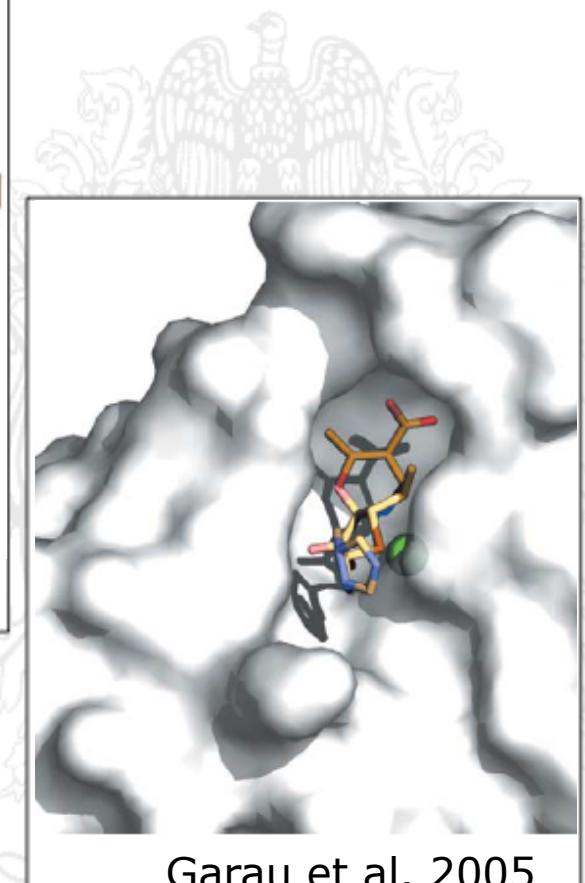
Introducción: las β -lactamasas



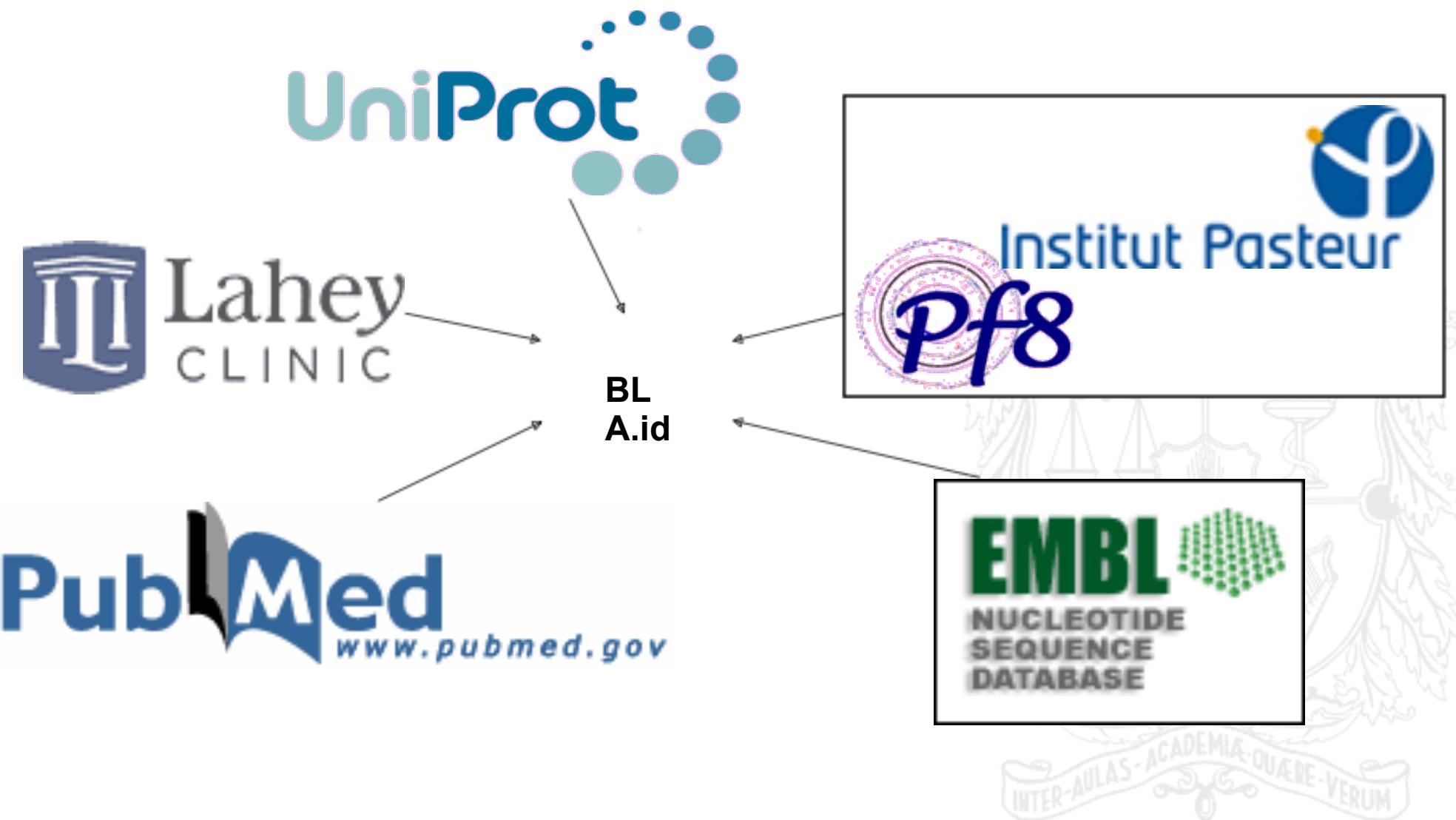
Ghysen J-M. 1991. Serin β -lactamases and penicillin-binding proteins. *Annual Review of Microbiology* 45:37-67.

Garau G.; Bebrone C.; Anne C.; Galleni M.; Frère J-M.; Dideberg O. 2005. A Metallo- β -lactamase Enzyme in Action: Crystal Structures of the Monozinc Carbapenemase CphA and its Complex with Biapenem. *Journal of Molecular Biology* 345:785-795.

Wilke M.S.; Lovering A.L.; Strynadka N.C. 2005. β -Lactam antibiotic resistance: a current structural perspective. *Current Opinion in Microbiology* 8:525-533.



Introducción: el reto computacional



AGENDA

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Métodos: obtención de datos

CTX-M-type β-Lactamases

β-Lactamase	Nucleotide	Reference	Enzyme	pl value	2	4	9	11	12	1	0	275	278	Reference(s)	Accession number(s)
CTX-M-1	X92506	AAC40:509, 1996	OXY-1-1	7.5	L	S	T	L	M			S	E	1	Z30177
CTX-M-2	X92507	AAC40:509	OXY-1-2	7.7	5	AJ871864, AJ871865
CTX-M-3	Y10278	AAC42:827	OXY-1-3	N. A.	2	AY077482
CTX-M-4	Y14156	AAC42:125	OXY-1-4	N. A.	2	AY077483
CTX-M-5	U95364	AAC42:198	OXY-1-5	N. A.	2	AY077486
CTX-M-6	AJ005044	FEMS Micr	OXY-1-6	5.25			K	.	3	Y17715
CTX-M-7	AJ005045	FEMS Micr	OXY-1-7	7.4	4	M27459
CTX-M-8	AF189721	AAC44:193	OXY-2-1	N. A.	I	.	I	M	L		N	.	.	5	AJ871866
CTX-M-9	AF174129	AAC44:197	OXY-2-2	N. A.	I	.	I	M	L		N	.	.	5	AJ871867
CTX-M-10	AF255298	AAC45:616	OXY-2-3	N. A.	I	.	I	M	L		N	.	.	2	AY077488
CTX-M-11	AY005110		OXY-2-4	N. A.	I	.	I	M	L		N	.	.	3	Y17714
CTX-M-12	AF305837	AAC45:214	OXY-2-5	N. A.	I	.	I	M	L		N	.	.	2	AY077487
CTX-M-13	AF252623	AAC 46:630	OXY-2-6	N. A.	I	.	I	M	L		N	.	.	2	AY077485
CTX-M-14	AF252622	AAC 46:630	OXY-2-7	N. A.	I	.	I	M	L		N	.	.	1	Z49084
CTX-M-15 (UOE-1)	AY044436	FEMS Micr	OXY-2-8	N. A.	I	.	I	M	L		N	.	.	6	AY055205
CTX-M-16	AY029068	AAC 45:220	OXY-3-1	6.7	I	T	S	.	I	L	.	D	.	2	
CTX-M-17	AY033516	AAC 46:121	OXY-4-1	7.7	.	.	S	2	
CTX-M-18	AF325133	AAC 45:339	OXY-5-1	7.2	5	
CTX-M-19	AF325134	AAC 45:339	OXY-5-2	7.7	5	
CTX-M-20	AJ416344	FEMS Micr													
CTX-M-21	AJ416346	FEMS Micr													
CTX-M-22	AY080894	J. Infect. 5:													
CTX-M-23	AF488377	JAC 54:40													
CTX-M-24	AY143430	JAC 57:14-													
CTX-M-25	AF518567	AAC 48:48													
CTX-M-26	AY157676	JAC 51:19													
CTX-M-27	AY156923	JAC 52:29													
CTX-M-28	AJ549244														
CTX-M-29	AY267213	J. Infect. 5:													
CTX-M-30	AY292654	AAC 48:44													
CTX-M-31	AJ567481	AAC 47:28													
CTX-M-32	AJ557142	AAC 48:23													
CTX-M-33	AY238472	Int. J. Antimicrob Agents 27:572, 2006													
CTX-M-34	AY515297	JAC 56:115													
CTX-M-35	Assigned														
CTX-M-36	AB177384														
CTX-M-37	AY649755														
CTX-M-38	^Y822595														
CTX-M-39	Y954516														
CTX-M-40	Y750914														

www.pasteur.f

AAC49:4745, 2005

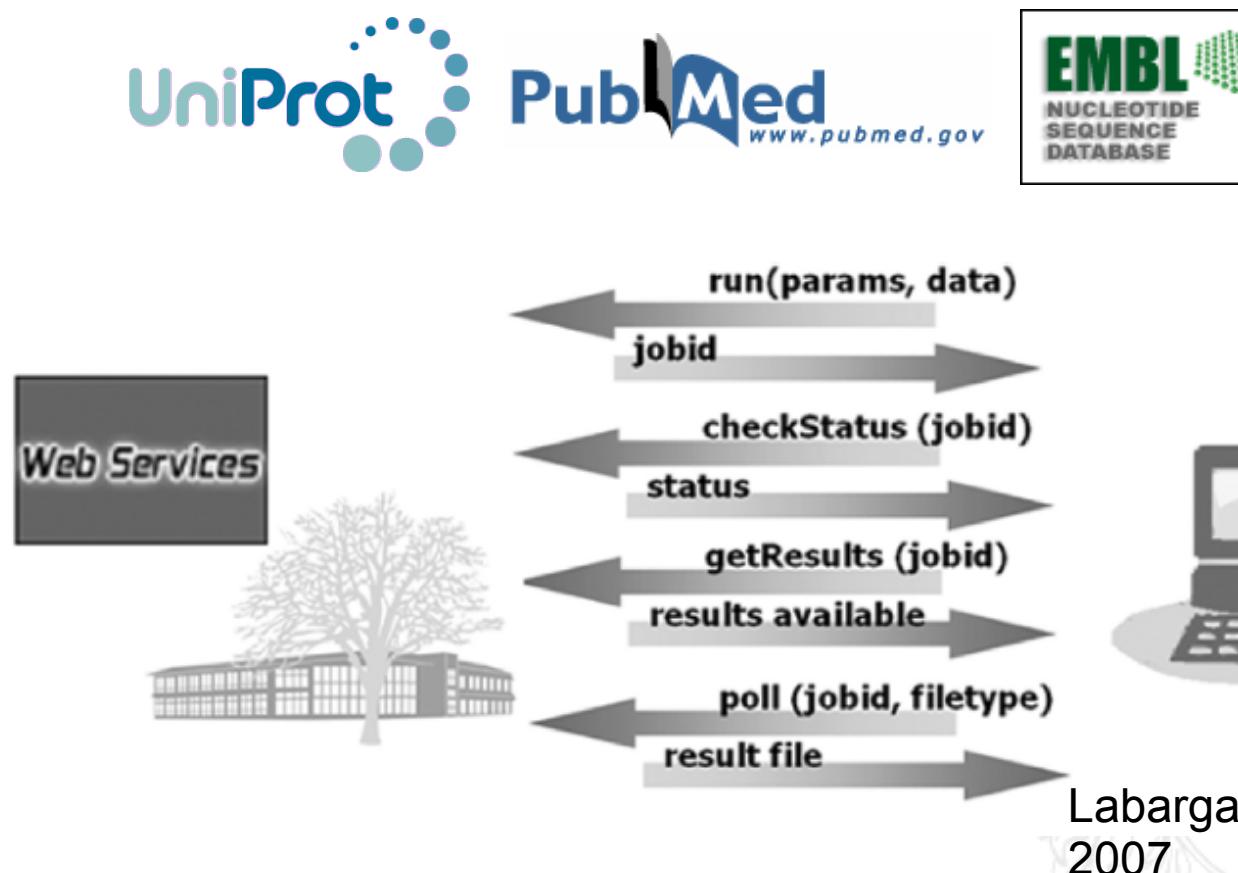
Int. J. Antimicrob Agents 27:572, 2006

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g Luis M. Rodríguez R.

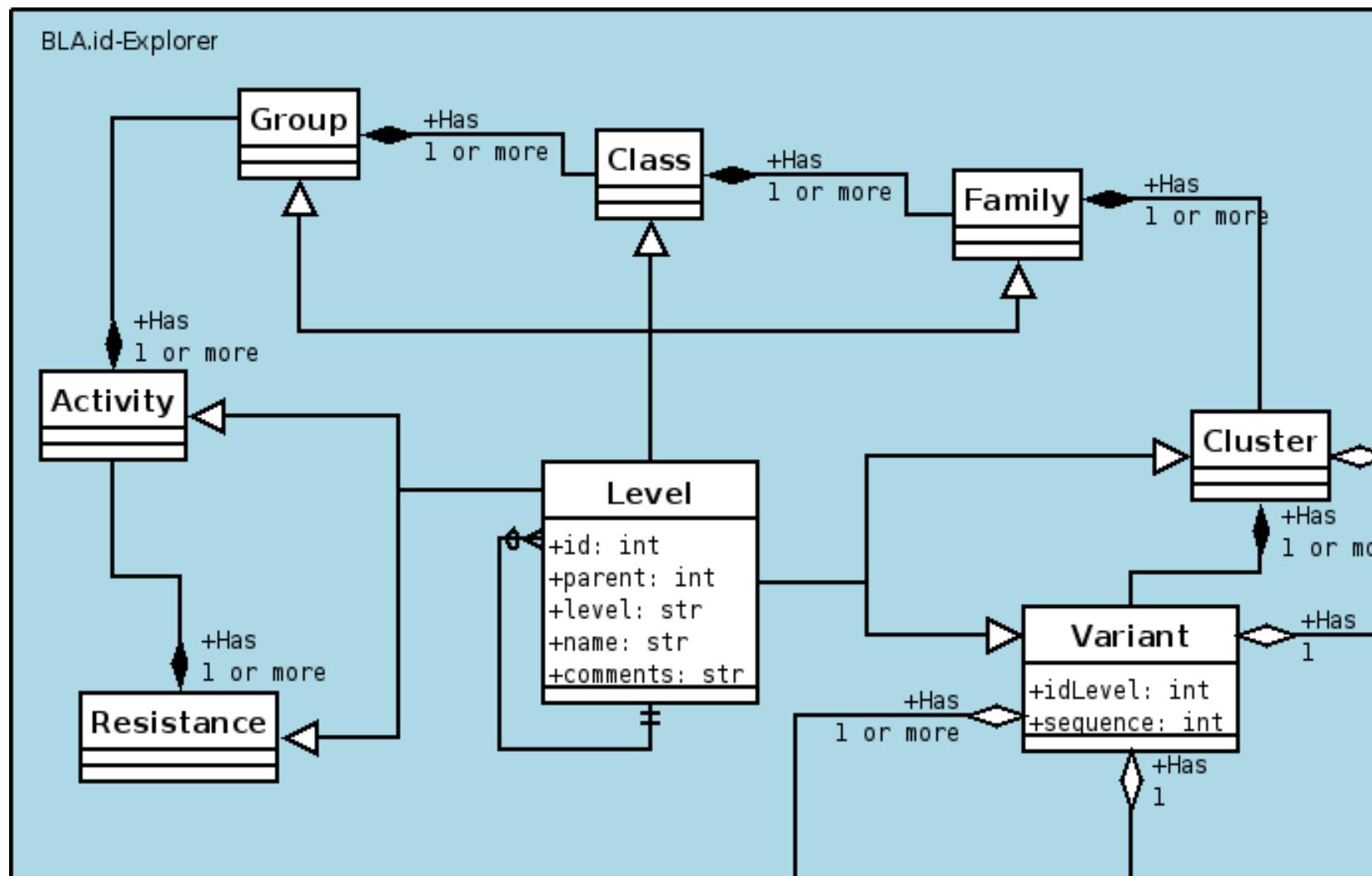


Métodos: obtención de datos

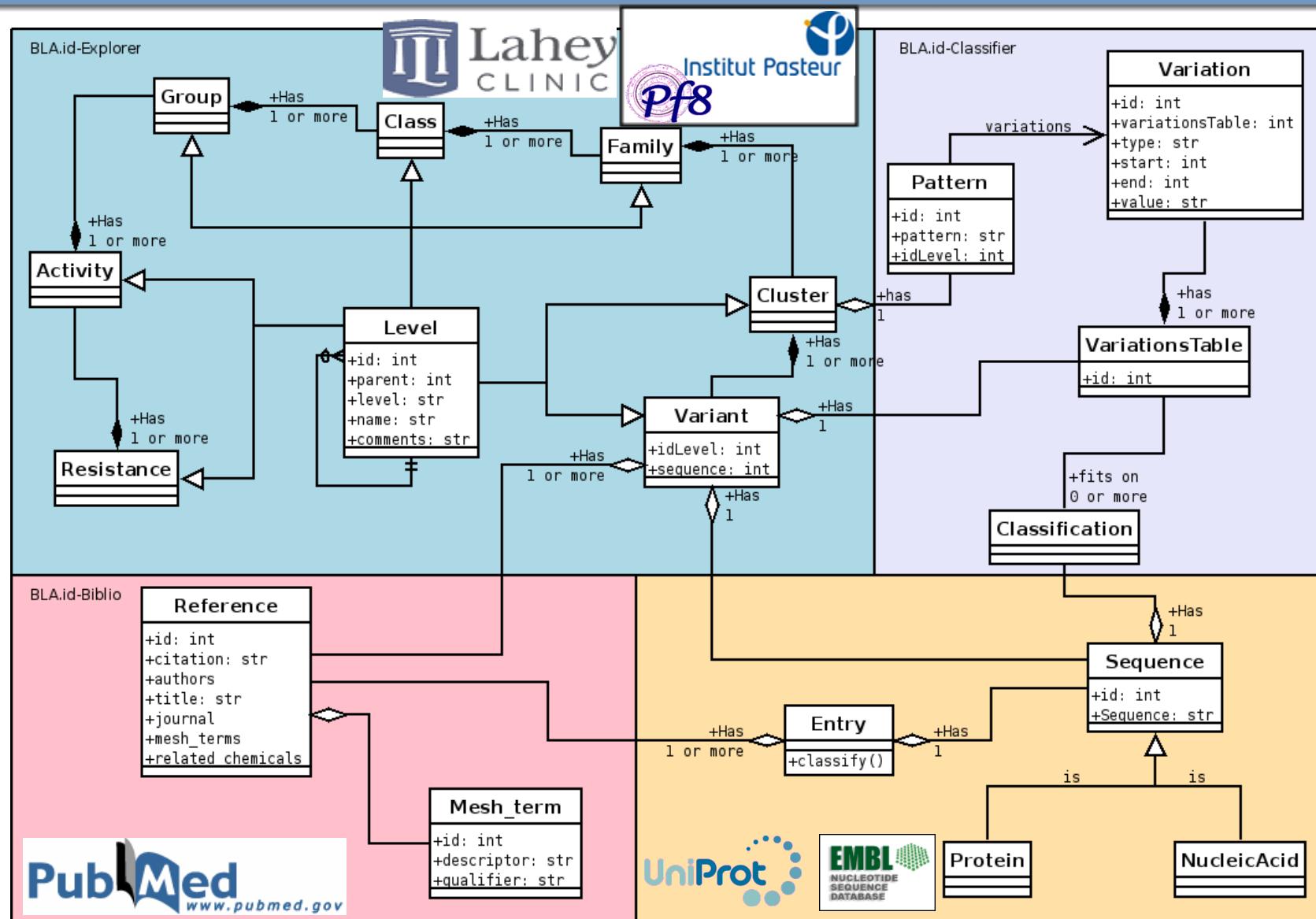


Labarga, A.; Valentin, F.; Andersson, M.; López, R. 2007. Web services at the European Bioinformatics Institute. *Nucleic Acids Research* 35:W6-W11.

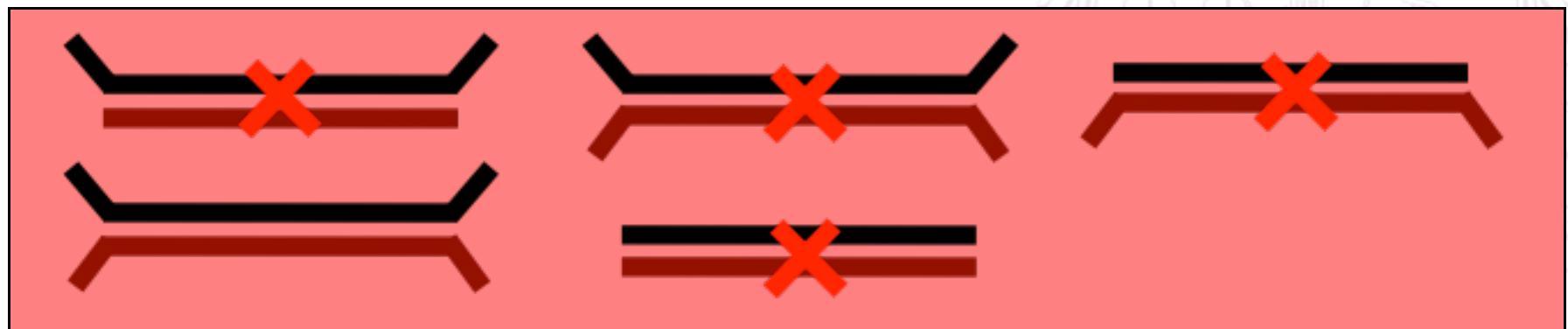
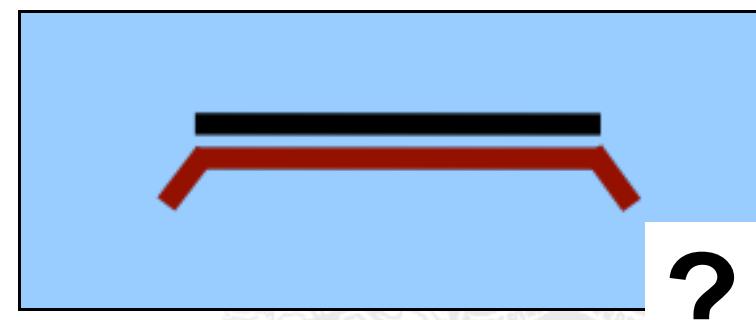
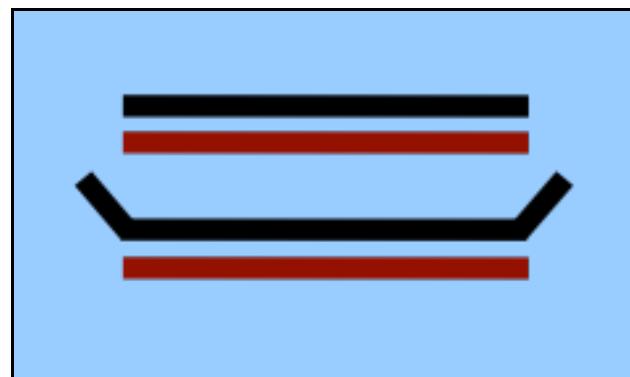
Métodos: estructura y organización



Métodos: estructura y organización

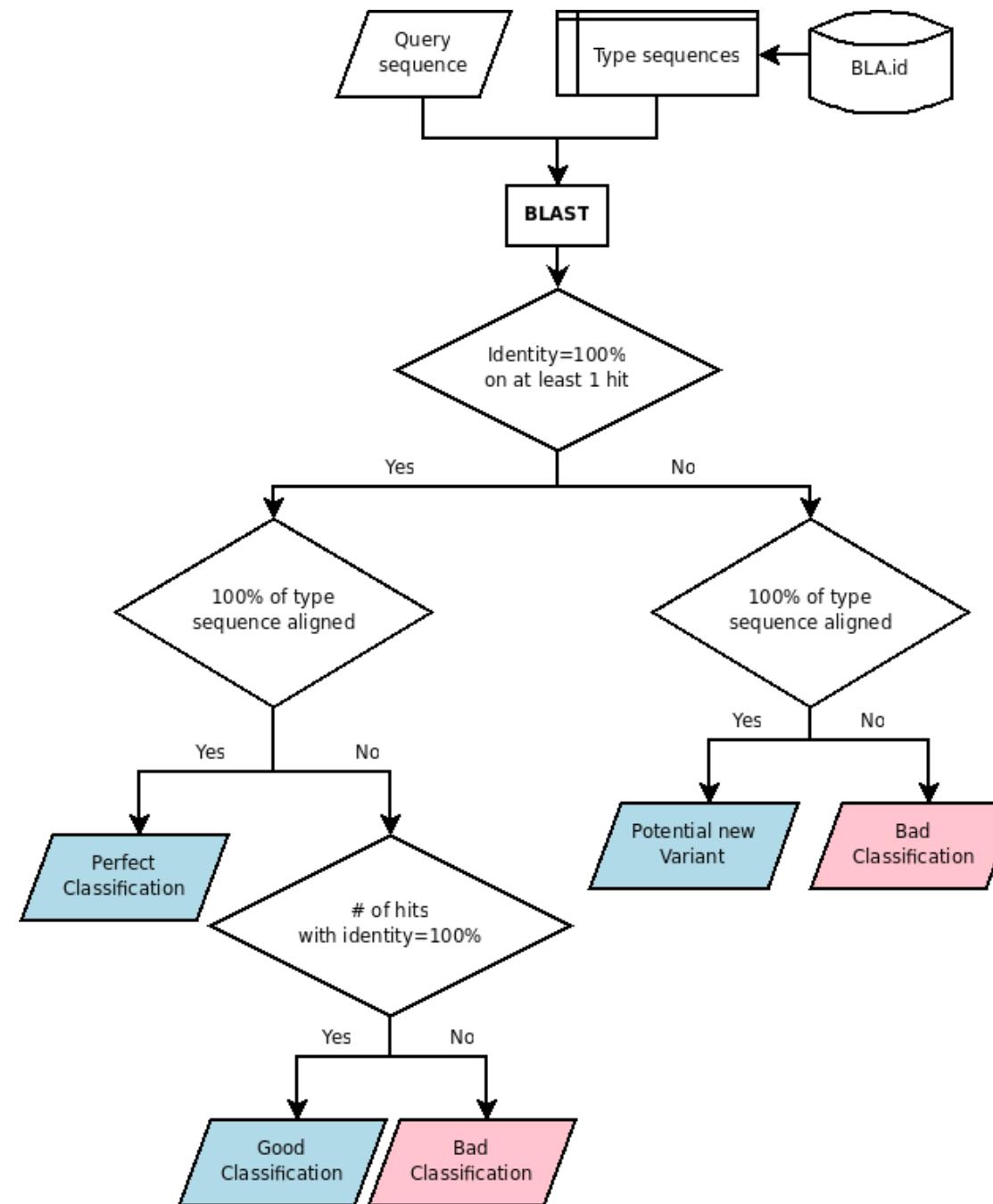


Métodos: clasificación



INTER-AULAS-ACADEMIA-QUÆRE-VERUM

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Métodos: implementación

PHP
JavaScri
pt
C / C++
(bio)Perl
R
XML
MySQL
Apache
Linux
SOAP
AJAX



<xml />



AGENDA

Introducción

Métodos

Resultados

Conclusiones y perspectivas



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Resultados: Web-GUI

Acción

Clasificar Buscar Proteínas Buscar Ácidos Nucléicos

Tipo de secuencia

Proteína Ácido nucléico

Introduzca su secuencia

```
>lcl|2|CME-2: CME_2 extended spectrum
beta-lactamase.
MKKIIILLFILSQLVLAQHTSILNDINAVTKDKKKATVAVSVLGIENDFQF
SNANGNLKMPMLSVFKFHIALAVLNQVDKGNLTLQKILIKKSDLLENTW
SPLREKYPDGNVELPLSEIITYTVAQSDNNNGCDILLRLIGGTKTQKLMD
VNGVKNFQIKYNEEEMHKNDVKTLHYANYTTASMVKTLKAFYKGMFLSKR
STIFLMDIMTKNTGMSKLPGLLPKVRMARKTGSSGKMKNGLTIAENDSG
IVTLANGKHYAIAVFKDSMEEVNCGIIAQVSKIWDALNKKNP
```

o desde un archivo

Examinar...



Acción

Clasificar Buscar Proteínas Buscar Ácidos Nucléicos

Tipo de secuencia

Proteína Ácido nucléico

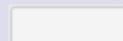
Introduzca su secuencia

```
>lcl|2|CME-2: CME_2 extended spectrum  
beta-lactamase.  
MKKIILLFILTSQQLVLAQHTSILNDINAVTKDKKATVAWSVLGIENDFQF  
SNANGNLKMPMPLSVFKFHIALAVLNQVDKGNLTLDDQKILIKKSDLLENTW  
SPLREKYPDGNVELPLSEIITYTVAQSDNNNGCDILLRLIGGTVQKLMD  
VNGVKNFQ:  
STIFLMDII  
IVTLANGKII
```



Su secuencia ha sido clasificada con éxito.

o desde un archivo



RESULTADO

Su secuencia se ha clasificado exitosamente como

CME-2 (297 aa)

Identidad: 100%

E-value: 3e-168

Longitud del alineamiento: 297

ARCHIVOS ORIGINALES

[Ver la secuencia original](#)

[Ver el resultado en xml](#)

[Ver el resultado en html](#)

REFERENCIA (BLAST)

Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schäffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402.

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Actividad β -lactamase



Grupo Serin-protease



Clase A



Familia CME



Familia CTX-M



Familia GES



Familia OXY



Familia KPC



Clado KPC-2



Variante KPC-1



Variante KPC-2



Variante KPC-3



Variante KPC-4



Variante KPC-5

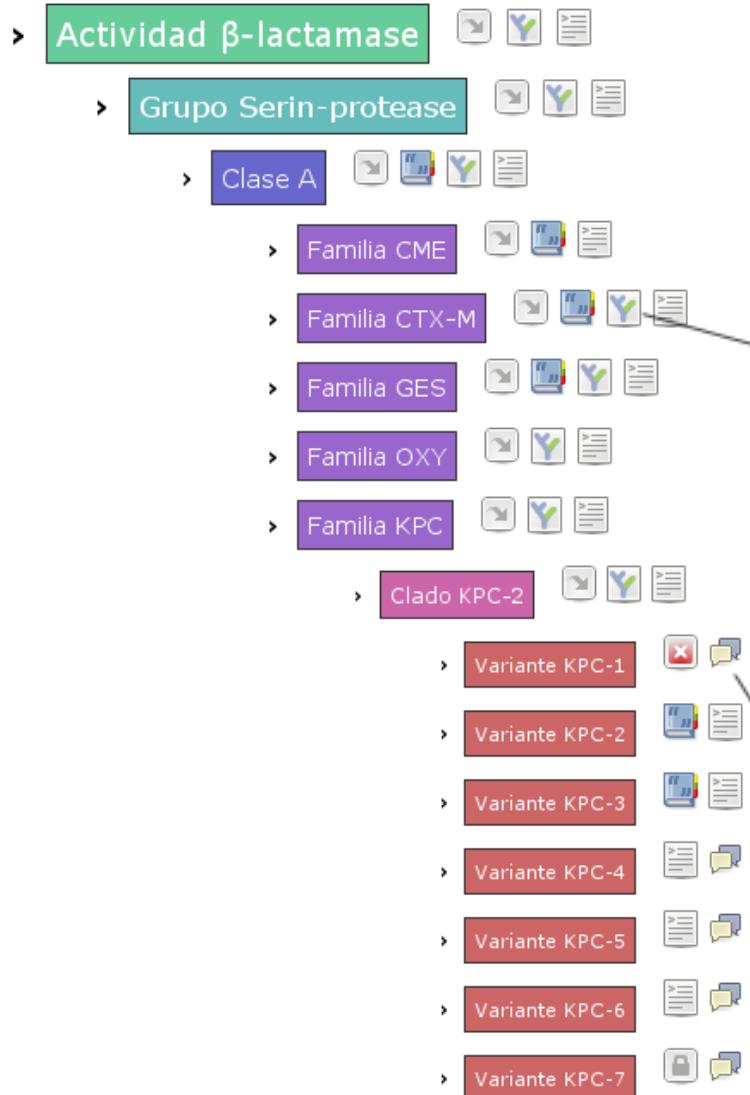


Variante KPC-6

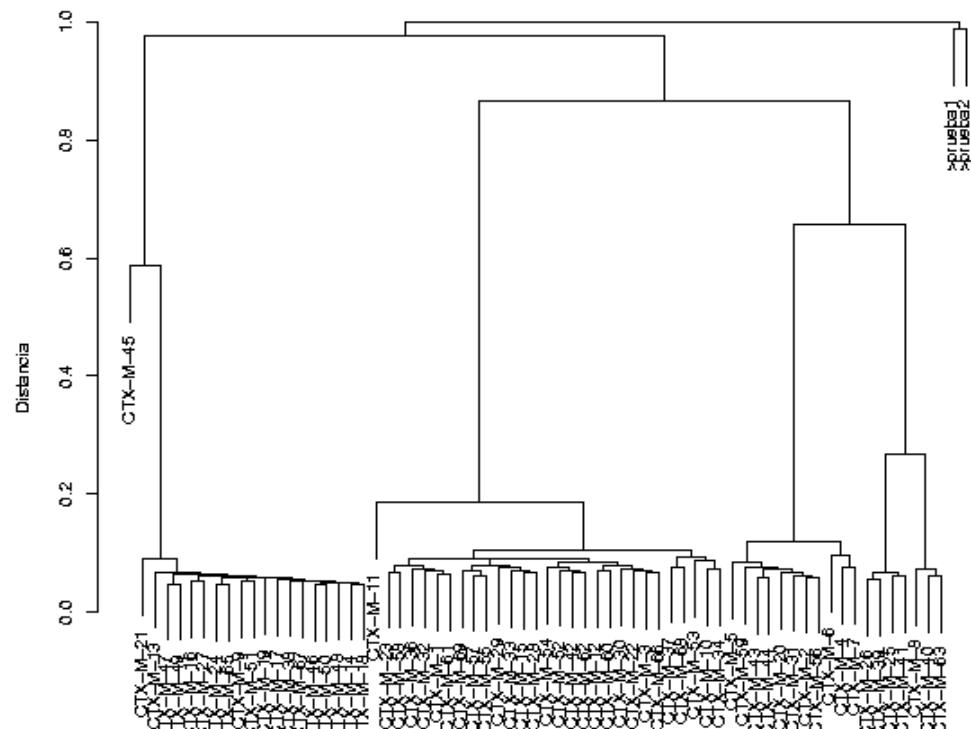


Variante KPC-7





Dendrograma de Familia CTX-M y 2 ramas extra.



Hecho con BLA.id: <http://bioinf.ibun.unal.edu.co/BLA.id/0.3/> 13 Jul 2008.

This denomination was deprecated after the publication of erratum from Yigit H et al (2001) on February 2008. The sequence reported on 2001 had an erroneous codon, and corrected sequence is identical to that of Variante KPC-2.

Aceptar



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DE COLOMBIA

Bioinformática
Centro de Bioinformática
Instituto de Biotecnología

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..:: Biblio

BLA.ID-BIBLIO

Colección de referencias bibliográficas relacionadas con β-lactamasas, con información adicional obtenida de Medline.

INFORMACIÓN GENERAL

Título	The structure of beta-lactamases.
Autores	Ambler RP .
Revista	Philosophical transactions of the Royal Society of London. Series B, Biological sciences .
Referencia cruzada	PubMed:6109327 dP .
Cita	Ambler RP. The structure of beta-lactamases. Philos Trans R Soc Lond B Biol Sci. 1980 May 16;289(1036):321-31.

RESUMEN

The beta-lactamases are widely distributed in both Gram-positive and Gram-negative bacteria. They all inactivate penicillins and cephalosporins by opening the beta-lactam ring. Many varieties of the enzyme can be distinguished on the basis of their catalytic and molecular properties, but only amino acid sequence determination gives information upon which a molecular phylogeny can be based. The present evidence suggests that the beta-lactamases have a polyphyletic origin. All the beta-lactamases of currently known amino acid sequence belong to one homology group, here called class A enzymes. Class B consists of the mechanistically distinct *Bacillus cereus* beta-lactamase II, which preliminary partial sequence analysis suggests to be structurally unrelated to the class A enzymes. It is predicted that sequence analysis will show that further classes will need to be created to account for particular beta-lactamases of distinctive molecular and mechanistic properties.

ADMINISTRATION TASKS

SUBMIT A SEQUENCE TO THE DATABASE

Node to link sequence (may be blank)

- KPC-7 (variant)
- KPC-6 (variant)
- KPC-5 (variant)
- KPC-4 (variant)
- KPC-3 (variant)
- KPC-2 (variant)
- KPC-1 (variant)
- OXY-6-4 (variant)
- OXY-6-3 (variant)

Database in which sequence is stored (may be blank)
 UniProt EMBL

Entryname on the database (may be blank)

Sequence (this must be filled only if database or entryname are blank)

Comments

[Back to the main menu.](#)



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Resultados: anotación y curaduría

5 casos típicos de anotación y curaduría: nodos problemáticos

Clase C

Familia LEN

Clado OKP-B

Variante IBC-1

Familia FONA / SFO

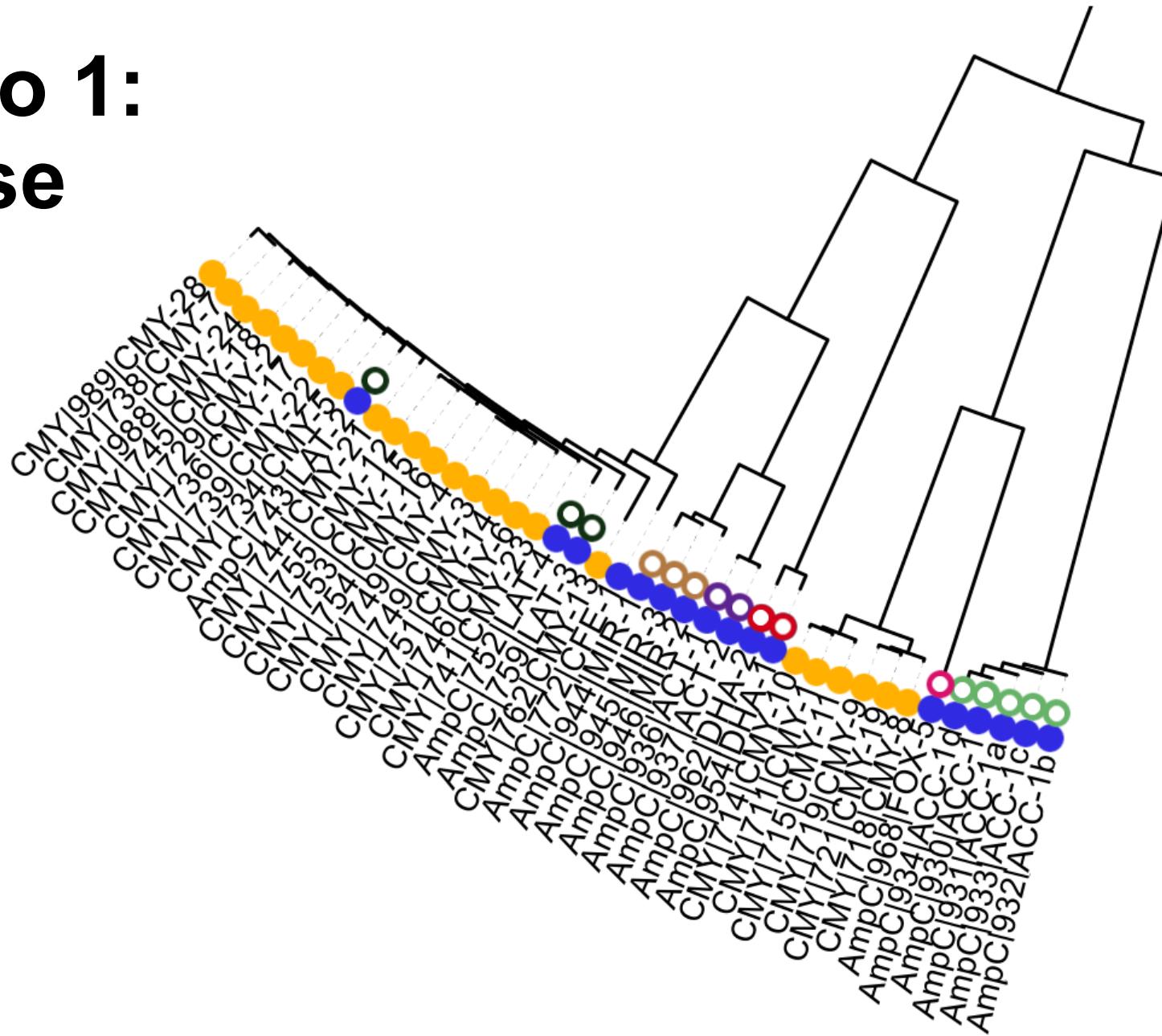


Caso 1: Clase C



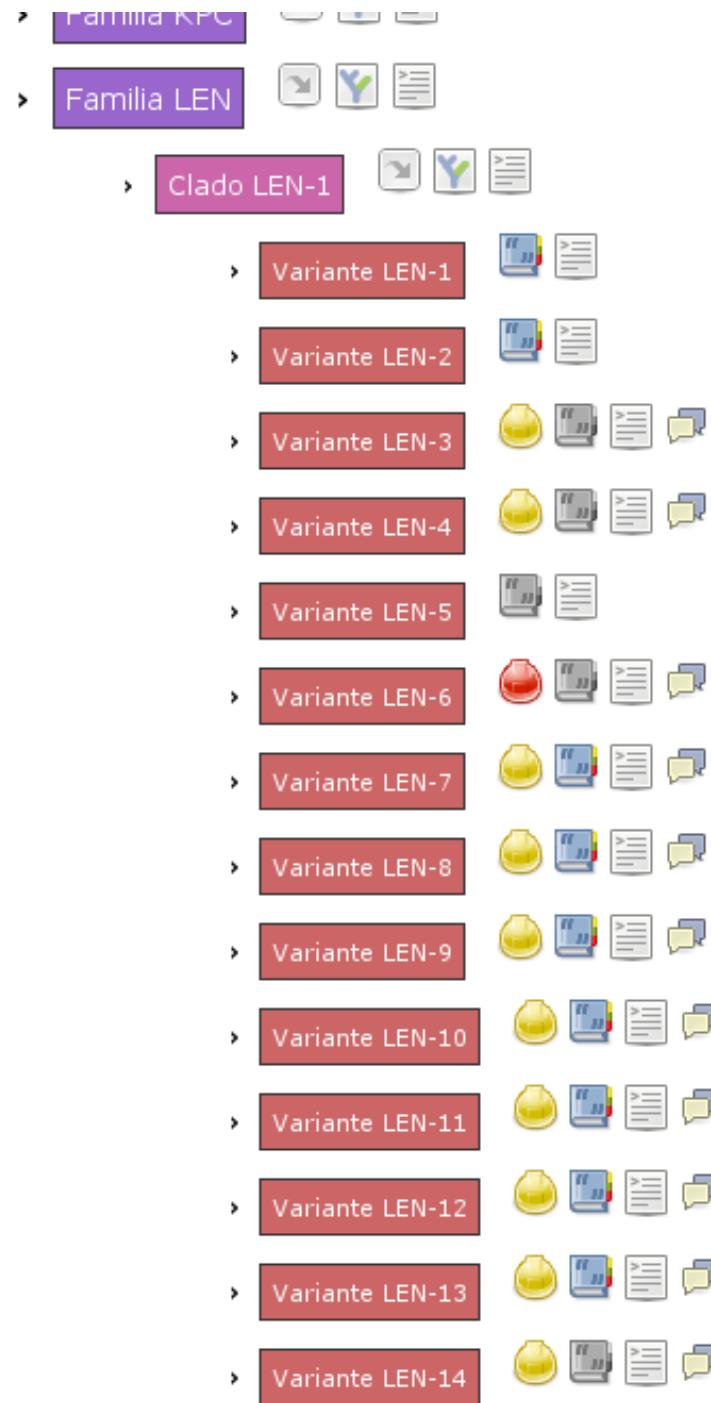
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Caso 1: Clase C



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Caso 2: Familia LEN



Caso 3: Clado OKP-B

- Variante OKP-B-8  
- Variante OKP-B-9  
- Variante OKP-B-10  
- Variante OKP-B-11  
- Variante OKP-B-12    
- Variante OKP-B-13  
- Variante OKP-B-14    
- Variante OKP-B-15  
- Variante OKP-B-16  
- Variante OKP-B-17  
- Variante OKP-B-18  
- Variante OKP-B-19  
- Variante OKP-B-20  



Caso 4: Variante IBC-1

Download:



CLASSIFICATION

Group	Serin-proteasa
Class	A
Family	GES
Variant	GES-7

VARIANT DATA

BLA.id entry	PR885
Registered entries	PR885 PR886 PR1143
Reference	Giakkoupi P; Tzouvelekis LS; Tsakris A; Loukova V; Sofianou D; Tzelepi E. 2000. IBC-1, a novel integron-associated class A beta-lactamase with extended-spectrum properties produced by an <i>Enterobacter cloacae</i> clinical strain. <i>Antimicrob. Agents Chemother.</i> , 44, 2247-2253.

ENTRY DATA

Description	Class A beta-lactamase.
Organism	<i>Enterobacter cloacae</i> . [DSMZ] [Taxonomy]
xRef	Uniprot:Q9L8E3_ENTCL
Bibliographic reference	PubMed:10952563
Sequence	Isoelectric Point: 7.6222 (Calculated on the basis of sequence) Length: 287 Update: 01-JUN-2003 Sequence >

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Caso 5: Familia FONA / SFO

FONA-type	Identity	Similarity
FONA-1	95.3%	98.0%
FONA-2	95.6%	97.3%
FONA-3	96.3%	97.3%
FONA-4	95.6%	98.0%
FONA-5	95.9%	96.6%
FONA-6	96.6%	97.6%

Comparación de las secuencias de SFO-1 con las
6
variantes FONA



Sinónimos

Family	Synonyms on variants
CTX-M	4
GES	2
OXA	1
OXY	1
SFO	6
SHV	5
TEM	57
Total	76



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Referencias geográficas

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 8, pp. 3737–3741, August 1978
Biochemistry

Nucleotide sequence of the ampicillin resistance gene of *Escherichia coli* plasmid pBR322

(protein sequence/secretion signal/ β -lactamase/DNA chemistry)

J. GREGOR SUTCLIFFE*

The Biological Laboratories, Harvard University, Cambridge, Massachusetts 02138

Communicated by Walter Gilbert, June 14, 1978



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Referencias geográficas

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 8, pp. 3737-3741, August 1978
Biochemistry

Nucleotide of *Escherich.*

(protein sequence)

J. GREGOR SUTCLIFFE

The Biological Laboratories

Communicated by Walter

JOURNAL OF BACTERIOLOGY, Jan. 1974, p. 56-62
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Vol. 117, No. 1
Printed in U.S.A.

Molecular Specificities of R Factor-Determined Beta-Lactamases: Correlation with Plasmid Compatibility

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Department of Bacteriology, Clinic of Therapeutics, University of Athens, Athens, Greece; and

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Received for publication 19 September 1973



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Referencias geográficas

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 8, pp. 3737-3741, August 1978
Biochemistry

Nucleotide
of *Escheric*.

JOURNAL OF BACTERIOLOGY, Jan. 1974, p. 56-62
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Vol. 117, No. 1
Printed in U.S.A.

Molecular Specification of R Factor Determined

Vol. 104, No. 1
Printed in U.S.A.

Incompatibility

J.
T.
C.
Circular R-Factor Molecules Controlling Penicillinase
Synthesis, Replicating in *Escherichia coli* Under
Either Relaxed or Stringent Control

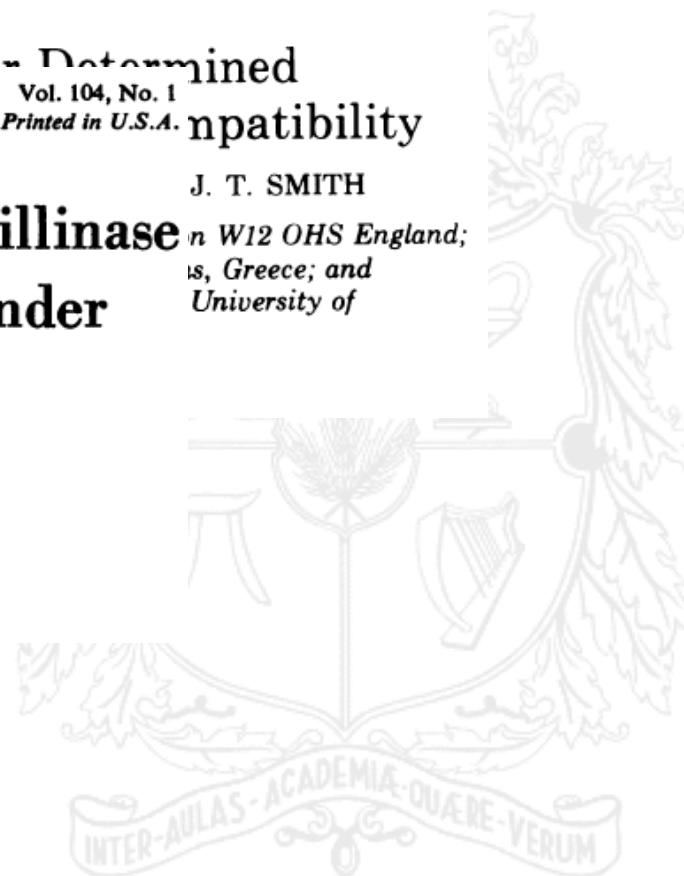
J. T. SMITH

in W12 OHS England;
is, Greece; and
University of

POLYXENI KONTOMICHALOU,¹ MICHIKO MITANI,² AND
ROYSTON C. CLOWES

Division of Biology, The University of Texas at Dallas, Dallas, Texas 75230

Received for publication 20 April 1970



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Referencias geográficas

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 8, pp. 3737-3741, August 1978
Biochemistry

Nucleotide of *Escherichia*

JOURNAL OF BACTERIOLOGY, Jan. 1974, p. 56-62
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Vol. 117, No. 1
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Molecular Specification of R Factor Determined

Vol. 104, No. 1
Printed in U.S.A.

J.

Circular R-Factor Molecules Controlling Penicillinase

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is, Greece; and
University of*

Synthesis Replicating in *Escherichia coli* Under

Vol. 122, No. 1
Printed in U.S.A.

JOURNAL OF BACTERIOLOGY, Apr. 1975, p. 250-256
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Origin of the TEM Beta-Lactamase Gene Found on Plasmids

FRED HEFFRON,* R. SUBLETT,¹ R. W. HEDGES, ALAN JACOB, AND STANLEY FALKOW

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Bacteriology, Royal Postgraduate Medical School, London, England*

Received for publication 4 November 1974



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Resultados: datos almacenados

484 variantes, 2254 secuencias, 606 entradas bibliográficas con más de 1000 términos MeSH con calificadores, 63 comentarios y 67 referencias geográficas revisadas de 24 países.

Acceso libre desde <http://bioinf.ibun.unal.edu.co/BLA.id/>.

genetics of beta-Lactamases



AGENDA

Introducción

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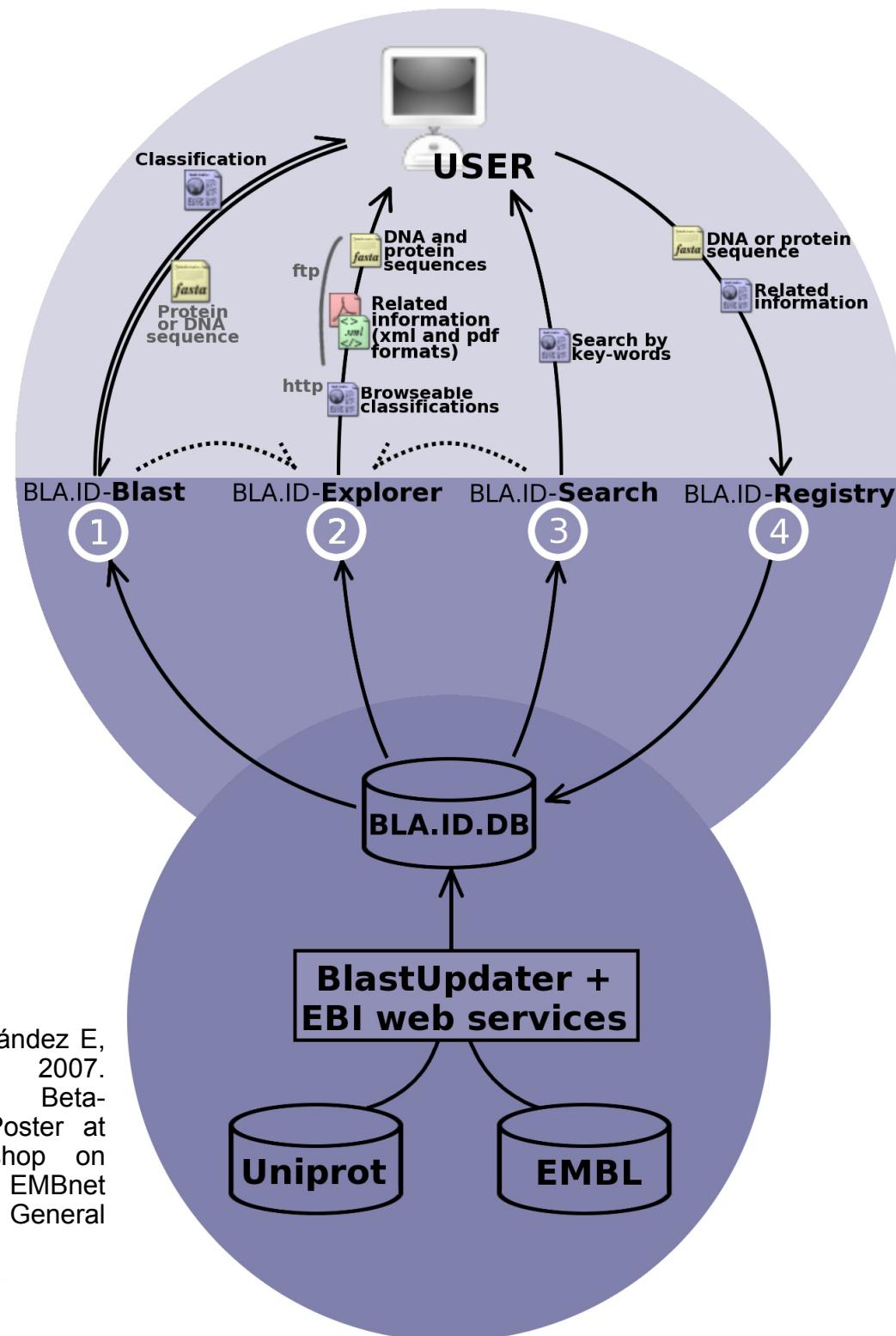
Conclusiones y perspectivas



Conclusiones

- ¿Qué puede hacer un usuario?
 - Clasificar secuencias.
 - Buscar secuencias similares reportadas.
 - Encontrar información relacionada centralizada:
 - Bibliografía.
 - Anotación manual.
 - Referencias geográficas
 - ...
 - Generar dendrogramas de secuencias reportadas y/o provistas por el usuario.
- ¿Qué hemos encontrado?





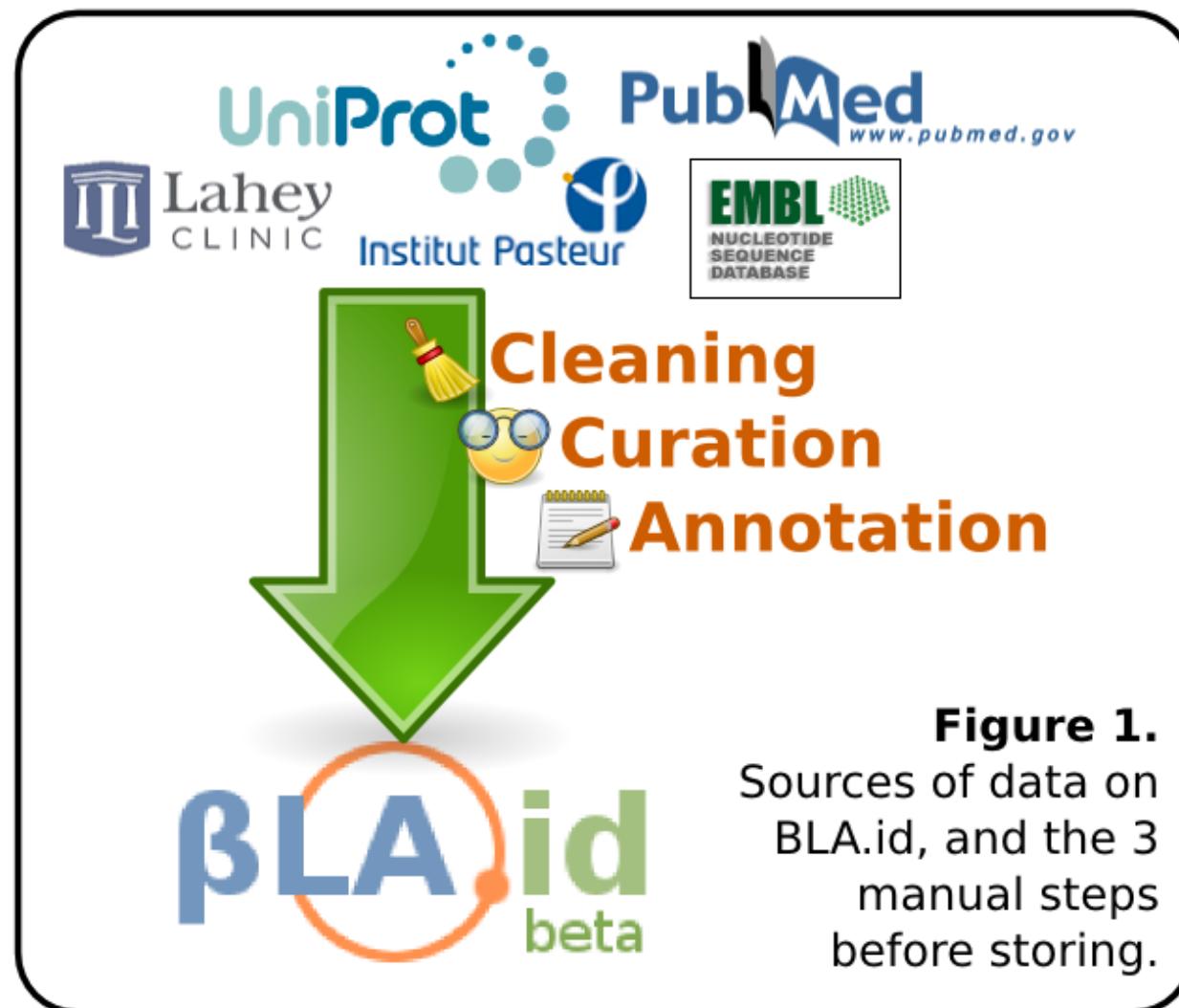
Rodríguez RLM, Barreto-Hernández E, Reguero Reza MT. 2007. BLA.ID.CLINIC: A new Beta-lactamases web resource. Poster at Bioinformatics 2007: Workshop on Collaborative Bioinformatics, EMBnet Annual Meeting, RIB Annual General Meeting. Torremolinos, Spain.



Conclusiones

- ¿Qué puede hacer un usuario?
- ¿Qué hemos encontrado?
 - Nodos problemáticos.
 - Sinónimos.
 - Secuencias no reportadas como tipo.
 - Problemas en la referenciación geográfica.





Rodriguez L, Mantilla R, Falquet L, Reguero MT, Barreto E. 2008. Storage, classification and molecular patterns detection of beta-lactamases sequences. Abstract 70. Poster at EMNet Conference 2008: 20th Anniversary Celebration: Leading applications and technologies in bioinformatics. Martina Franca, Taranto, Italy.

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Perspectivas

- Herramientas de web 2.0 para mejorar el flujo de información.
- Perfiles AMSA (HMM-like).
- Antibióticos.
- No solo β -lactamasas.
- Minería de textos.



Final

. Agradecimientos

- Familia, amigos, compañeros, profesores.
- Emiliano Barreto Hernández, María Teresa Reguero, Ramón Mantilla, Laurent Falquet.
- Usuarios tempranos.

Colciencias.

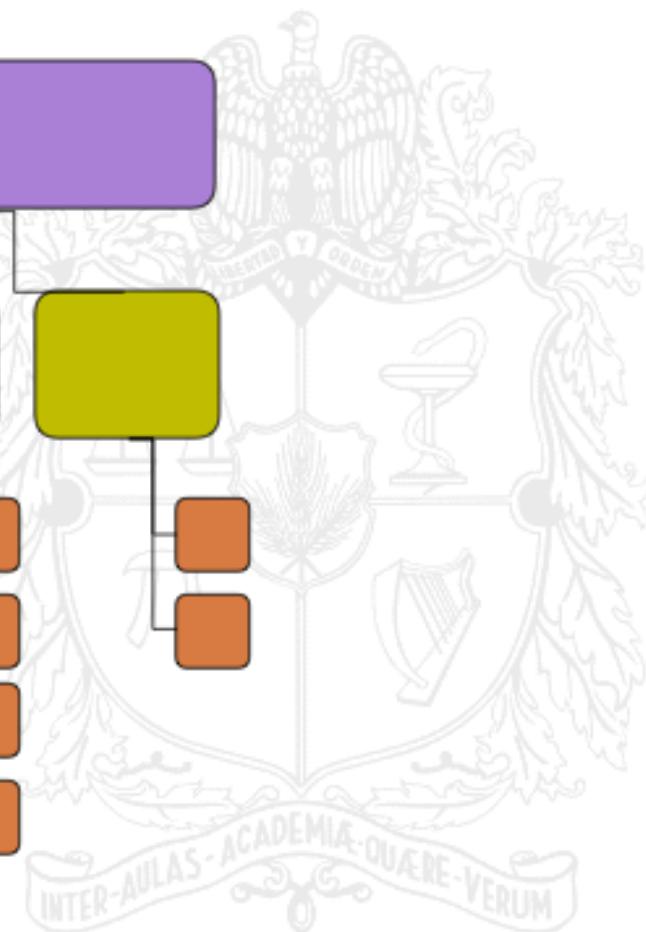
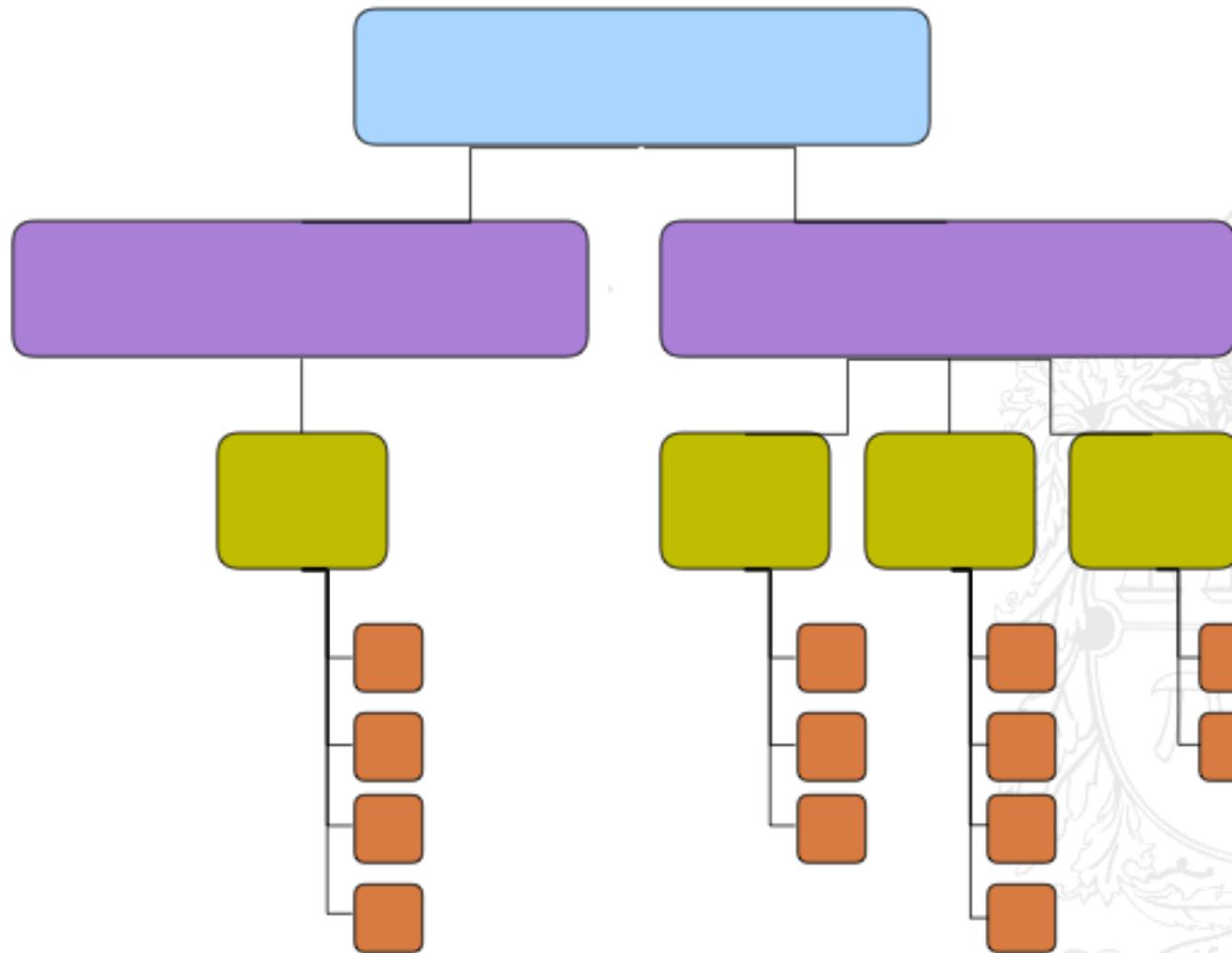
Universidad Nacional
de Colombia

Instituto de
Biotecnología

Departamento de
Biología

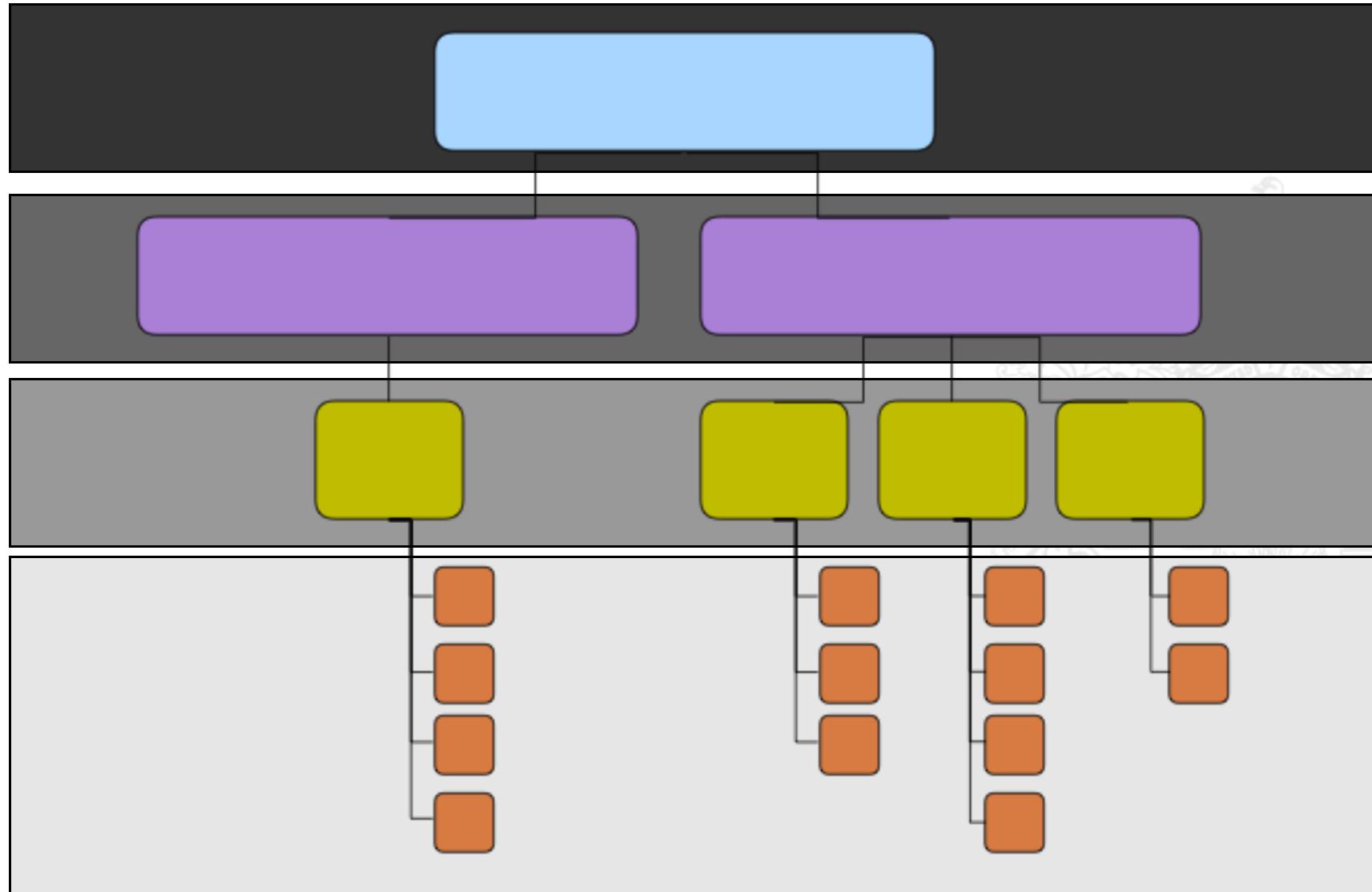
Dirección de
Investigación Sede
Bogotá, Universidad
Nacional de Colombia

Métodos: estructura y organización



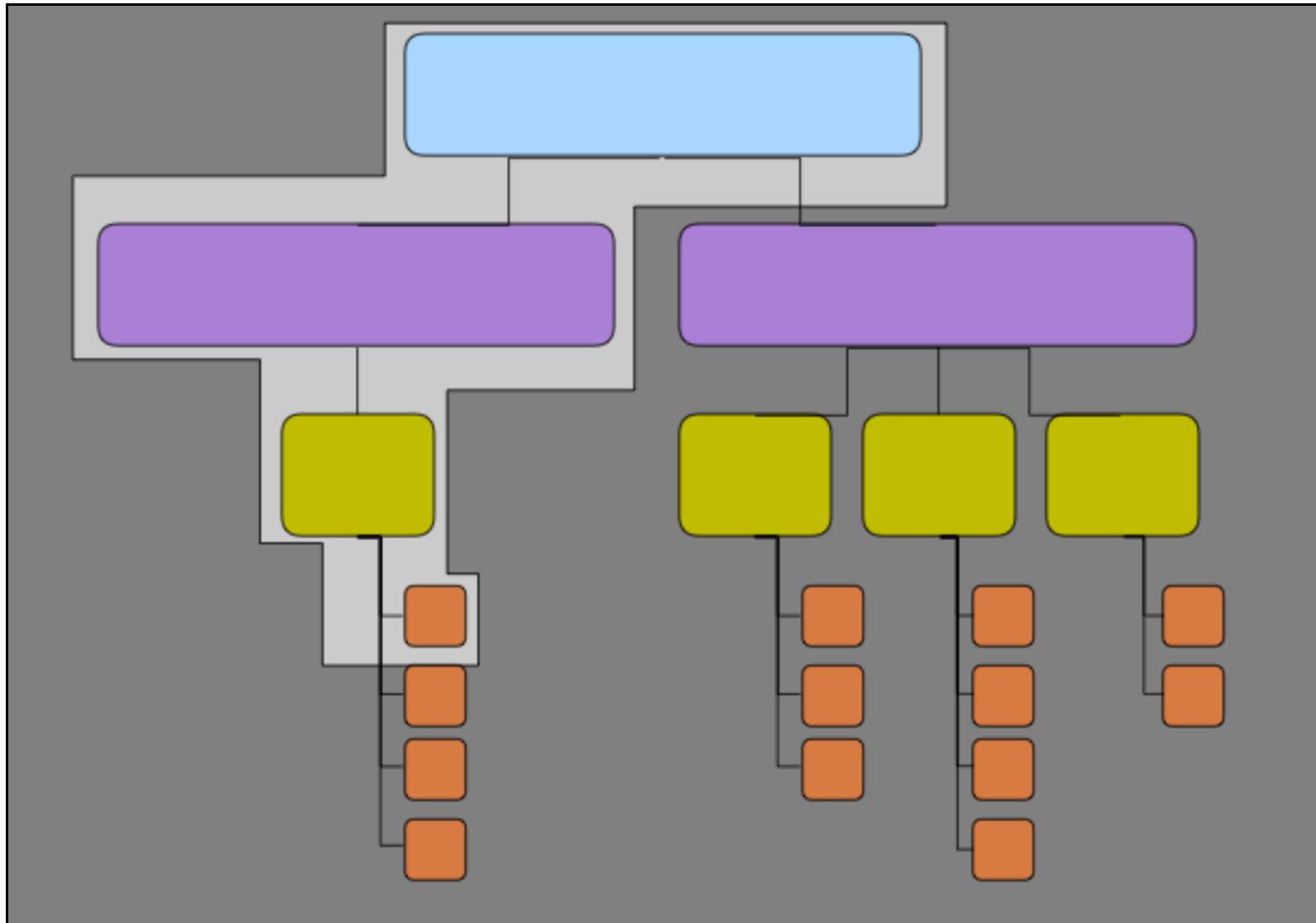
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Métodos: estructura y organización



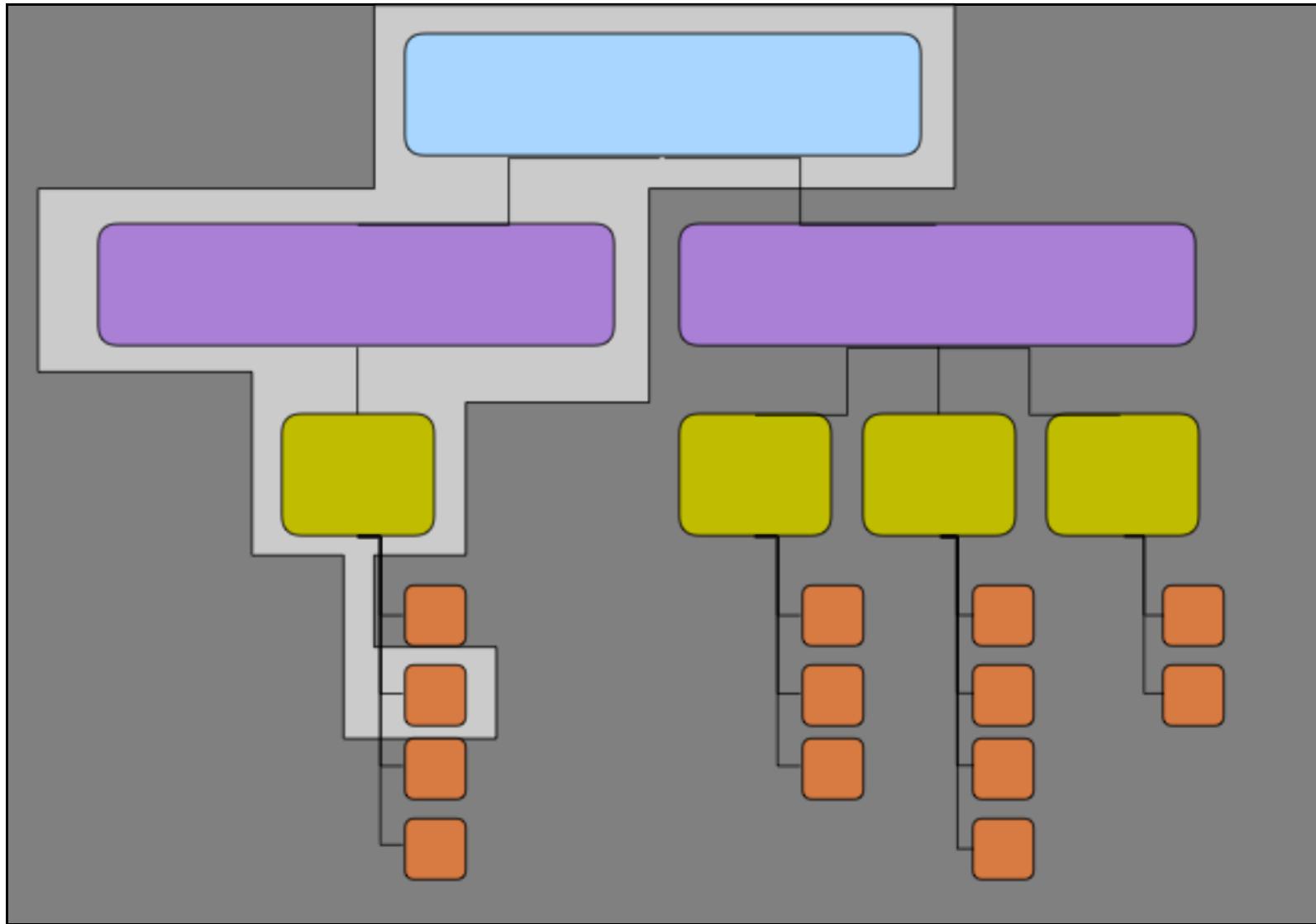
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Métodos: estructura y organización



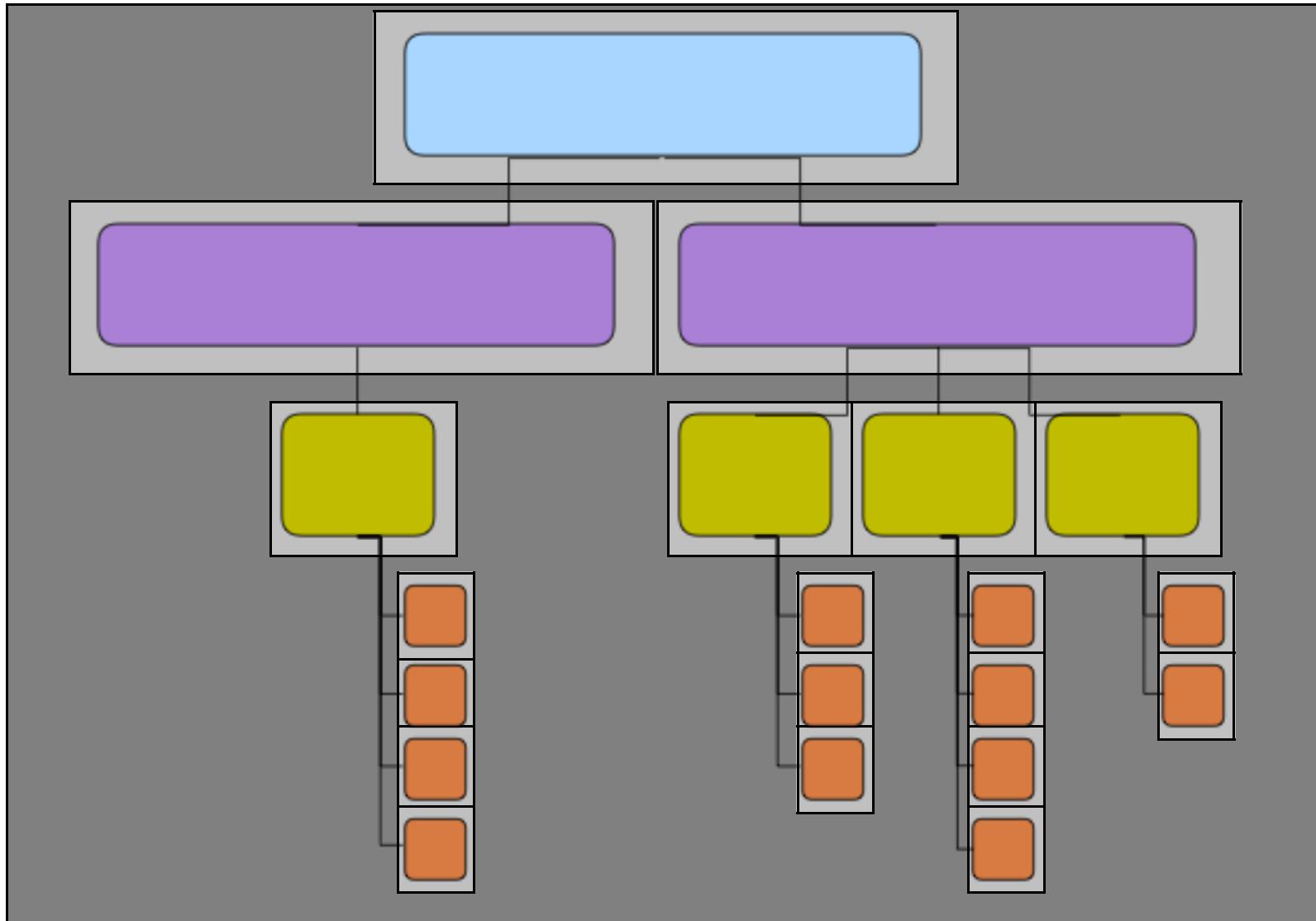
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Métodos: estructura y organización



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Métodos: estructura y organización



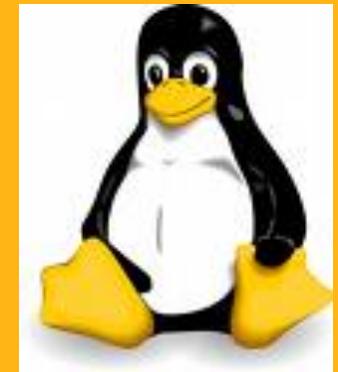
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Métodos: implementación

Recopilación de datos



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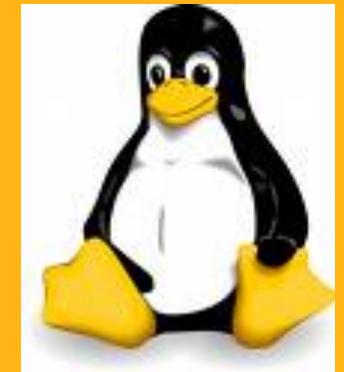
Métodos: implementación

Almacenamiento de datos



Métodos: implementación

GUI / Web



Métodos: implementación

PHP
JavaScri
pt
C / C++
(bio)Perl
R
XML
MySQL
Apache
Linux
SOAP
AJAX



<xml />

