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A standard numbering scheme for the Class A β-lactamases

β-Lactamases catalyse the hydrolysis of the β-lactam ring of penicillins, cephalosporins and related compounds, and thereby protect the bacteria which elaborate the enzymes against the action of these antibiotics. A recent review of the molecular properties of the proteins is given by Coulson (1985).

The proteins have been classified on the basis of their sequences; the largest group is called 'Class A' (Ambler, 1980). Enzymes of this class are found in Gram-negative and Gram-positive organisms, cell-bound, periplasmic or secreted, and derived from plasmid or chromosomal genes. For a recent survey of this and the other sequence classes, and of the relation of β-lactamases to other proteins such as the cell-wall synthesis enzymes, see Joris *et al.* (1988). Mechanistic and structural studies (including X-ray crystallography) are in progress with at least half-a-dozen of the Class A enzymes. There is no doubt that the proteins are homologous, and it is to be expected that molecular studies of any of the Class A enzymes can be extended to other members of the class. However, the known sequences vary considerably in length. The leader peptides are not in general homologous, and have a wide range of lengths. Some sequences are known only from the protein (lacking the leader sequence), and some proteins show different processing for the cell-bound and secreted forms, etc. In addition, it is clear that there are differences in length internal to the processed forms of the proteins, and these are presumably associated with surface loops of different lengths connecting conserved internal structures.

For these reasons, homologous residues from different Class A sequences generally differ in their 'natural' or 'sequential' numbers. In order to avoid the confusion and inconvenience that arises in the comparison of molecular studies of different Class A enzymes, we propose here a standard numbering scheme for this group of proteins. The scheme (Fig. 1) has been generated by aligning 20 Class A sequences, and attaching numbers to the alignment in order to preserve as much as possible of the numbering used by Ambler (1980) for the first four members of the class.

It is not intended that the present schemes will replace the natural or sequential scheme for individual proteins. The scheme will be used in the context of comparison of homologous residues, and the standard numbers will be indicated by the label 'ABL' (for Class **A** **b**eta **l**actamase). Thus 'Val-77 (ABL80)' of the R-TEM enzyme will indicate a residue homologous to Leu-75 of PSE-4, with the same ABL number.

Alignment of protein sequences is most reliable when it is based on X-ray crystal structures of all the proteins concerned, and it cannot be ruled out that X-ray crystallography will suggest changes in the detail of the alignment in Fig. 1. However, there is no doubt the alignment is mostly correct. Fragments of sequence have been omitted in several places (particularly with the more recently added sequences) where homology is uncertain. It is a virtue of the scheme we propose that future corrections and adjustments to individual residues will not alter the overall numbering and no changes will be made to accommodate new, longer sequences. Nor should the alignment of Fig. 1 be regarded as a definitive statement of the homology relations which exist amongst these proteins. For example, any worker who does not regard the DI (ABL 116–117) of the *Staphylococcus aureus* protein as equivalent to the GM sequence which is generally found here will simply not use the ABL numbers to refer to the *S. aureus* residues.

In order to give the active site serine residue the ABL number 70, it was necessary to start the numbering within some of the leader sequences. Expressed sequences start about ABL31, and though an alignment is shown for earlier residues, numbers 1–30 are unlikely to be used in practice since the leader sequences are not homologous.

A network of sequence relations has been recognized amongst many of the proteins which interact with β-lactams. It is possible, especially as X-ray crystal structures become available, that the current scheme can be extended to, for example, the Class C proteins.

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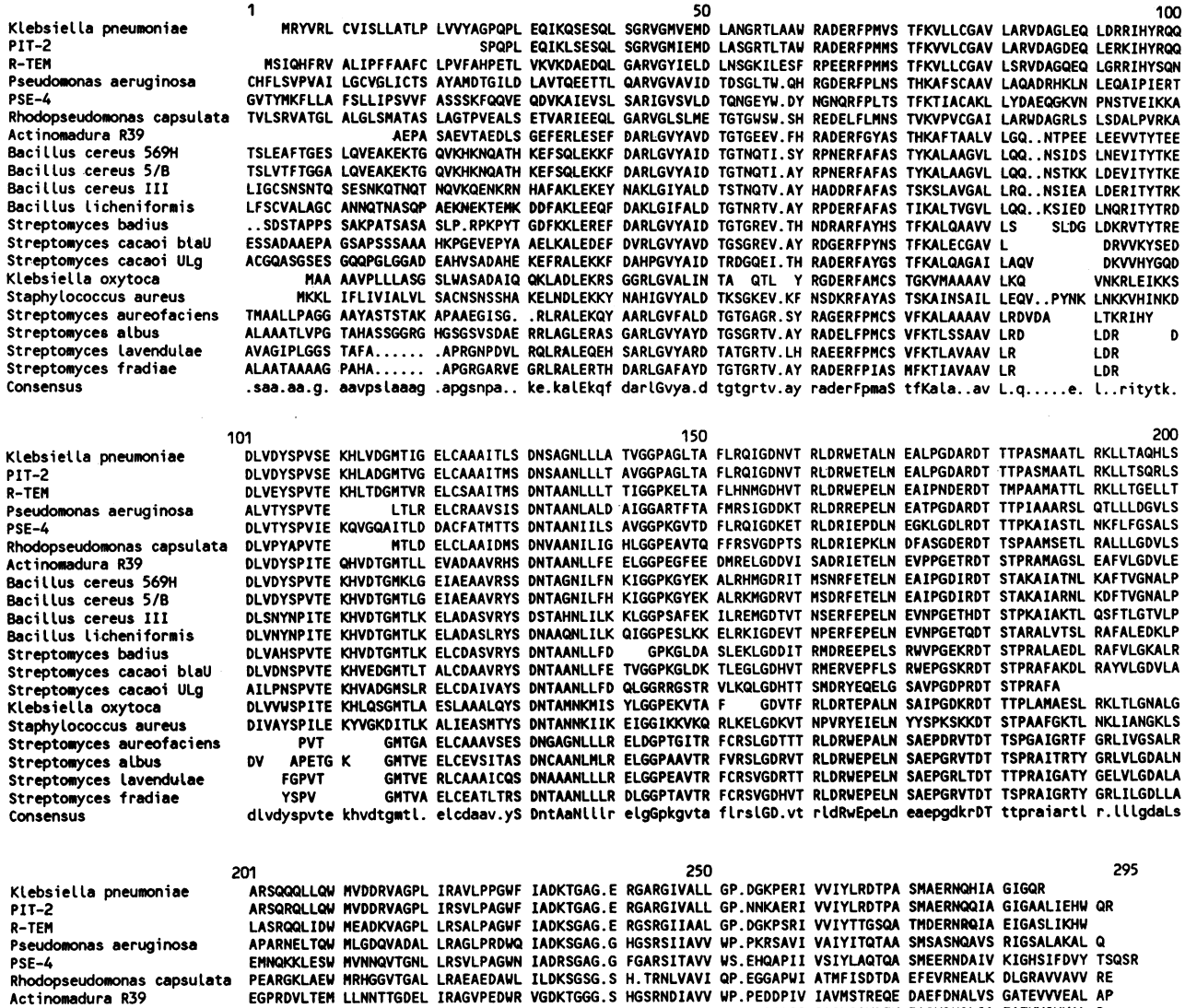

Fig. 1. Alignment of 20 Class A β-lactamases numbered according to the ABL scheme

The sequences are referred to by their most familiar names. '.' indicates a postulated deletion; blank spaces indicate one or more residues omitted from the alignment. Leader sequences before position 1 are omitted. Note that single tyrosine residues have been omitted from the *Streptomyces badius* and *Streptomyces cacaoi* sequences at position 241. Publication references are as follows: *Klebsiella pneumoniae*: Arakawa, Y., Ohta, M., Kido, N., Fujii, Y., Komatsu, T. & Kato, N. (1986) FEBS Lett. **207**, 69–74; PIT-2: Barthelemy, M., Peduzzi, J. & Labia, R. (1988) Biochem. J. **251**, 73–79; R-TEM: Sutcliffe, J. G. (1978) Proc. Natl. Acad. Sci. U.S.A. **75**, 3737–3741; *Pseudomonas aeruginosa* and *Rhodopseudomonas capsulata*: Campbell, J. I. A., Scahill, S. A., Gibson, T. & Ambler, R. P. (1989) Biochem. J. **260**, 803–812; PSE-4: Boissinot, M. & Levesque, R. C. (1990) J. Biol. Chem. **265**, 1225–1230; *Actinomadura* R39: Houba, S., Molitor, C., Willem, S., Ghuysen, J.-M., Frère, J.-M., Duez, C. & Dusart, J. (1989) FEMS Microbiol. Lett. **65**, 241–246; *Bacillus cereus* 569H and 5/B; Madgwick, P. J. & Waley, S. G. (1987) Biochem. J. **248**, 657–662 and Madonna, M. J., Zhu, Y. F. & Lampen, J. O. (1987) Nucleic Acids Res. **15**, 1877; *Bacillus cereus* III: Husain, M., Pastor, F. I. J. & Lampen, J. O. (1987) J. Bacteriol. **169**, 579–586; *Bacillus licheniformis*: Neugebauer, K., Sprengel, R. & Schaller, H. (1981) Nucleic Acids Res. **9**, 2577–2588; *Streptomyces badius, cacaoi* blaU, *lavendulae* and *fradiae*: Forsman, M., Haggstrom, B., Lindgren, L. & Jaurin, B. (1990) J. Gen. Microbiol. **136**, 589–598; *Streptomyces cacaoi* ULg: Lenzini, M. V., Ishihara, H., Dusart, J., Ogawara, H., Joris, B., Van Beeumen, J., Frère, J.-M. & Ghuysen, J.-M. (1988) FEMS Microbiol. Lett. **49**, 371–376; *Klebsiella oxytoca*: Arakawa, Y., Ohta, M., Kido, N., Mori, M., Ito, H., Komatsu, T., Fujii, Y. & Kato, N. (1989) Antimicrob. Agents Chemother. **33**, 63–70; *Staphylococcus aureus*: Ambler, R. P. (1975) Biochem. J. **151**, 197–218 and McLaughlin, J. R., Murray, C. J. & Rabinowitz, J. C. (1981) J. Biol. Chem. **256**, 11273–11282; *Streptomyces aureofaciens*: G. Tiraby, unpublished work; *Streptomyces albus* G: Dehottay, P., Dusart, J., De Meester, F., Joris, B., Van Beeumen, J., Erpicum, T., Frère, J.-M. & Ghuysen, J.-M. (1987) Eur. J. Biochem. **166**, 345.