# Identification of the Biosynthetic Gene Cluster of the Lipopeptide Antibiotic Plusbacin

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Lipopeptide antibiotics form a compound class that comprises a number of clinically relevant antibiotics, such as daptomycin or polymyxins. Within this class the guanidine-containing cyclic lipopeptides, which are represented by the naturally occurring empedopeptin, tripropeptins and plusbacins, exhibit potent antibacterial activity against a variety of gram-positive pathogens. Although the exact mode of action is not completely understood previous findings suggest interference with the membrane-bound steps of peptidoglycan biosynthesis. Despite the quite significant difference in the potency of the main representatives of this group, the structural similarity within the guanidine-containing cyclic lipopeptides is striking. The common scaffold consists of a cyclic depsi-octapeptide core structure which is acylated with a fatty acid tail. While the amino acid composition of the southern hemisphere of the macrocycle is identical, variations occur in the northern hemisphere, as well as the fatty acid tail, that is variable in length and can occur branched or unbranched [1].

In order to pinpoint the biosynthetic locus, which is responsible for the production of plusbacins, the whole genome of the plusbacin producer *Lysobacter firmicutimachus* PB-6250$^T$ [2] was sequenced. Based on these data a putative gene cluster, consisting of nonribosomal peptid synthetase (NRPS) structural genes, and adjacent accessory genes coding for dioxygenases were identified. To verify these findings, and to gain further insights into the biosynthesis of plusbacins, knock out studies were conducted.

[1] Hashizume H, Nishimura Y. Cyclic Lipopeptide Antibiotics, p. 693-751. *In* R. Atta ur (ed.), Studies in Natural Products Chemistry, vol. 35. Elsevier (2008).
[2] Miess H *et al.*, *Int. J. Syst. Evol. Microbiol.* 66: 4162-4166 (2016).