

Supplementary Information

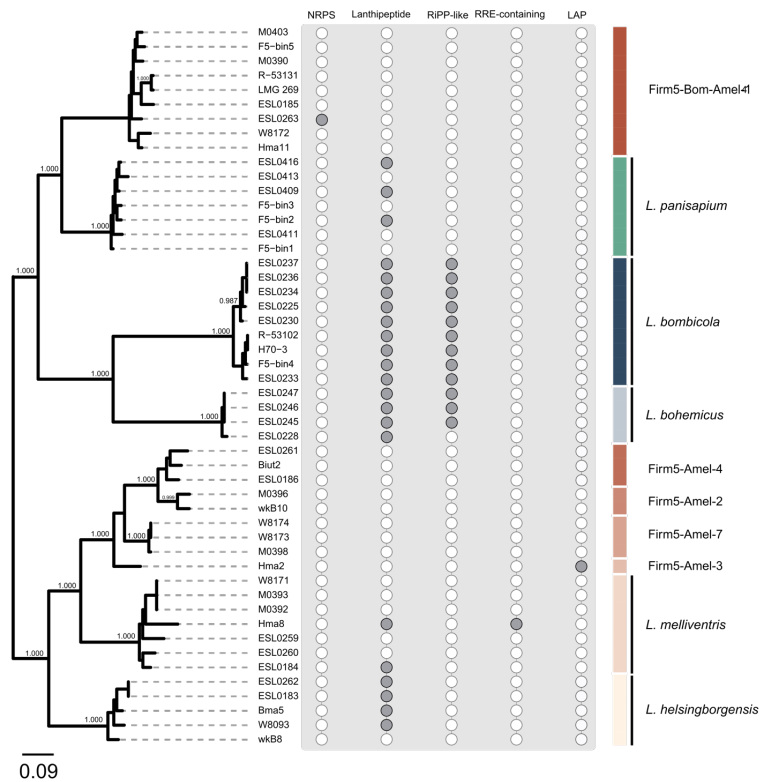
Identification of peptides from honeybee gut symbionts as potential antimicrobial agents against *Melissococcus plutonius*

Haoyu Lang¹, Yuwen Liu¹, Huijuan Duan¹, Wenhao Zhang¹, Xiaosong Hu¹,
Hao Zheng^{1,*}

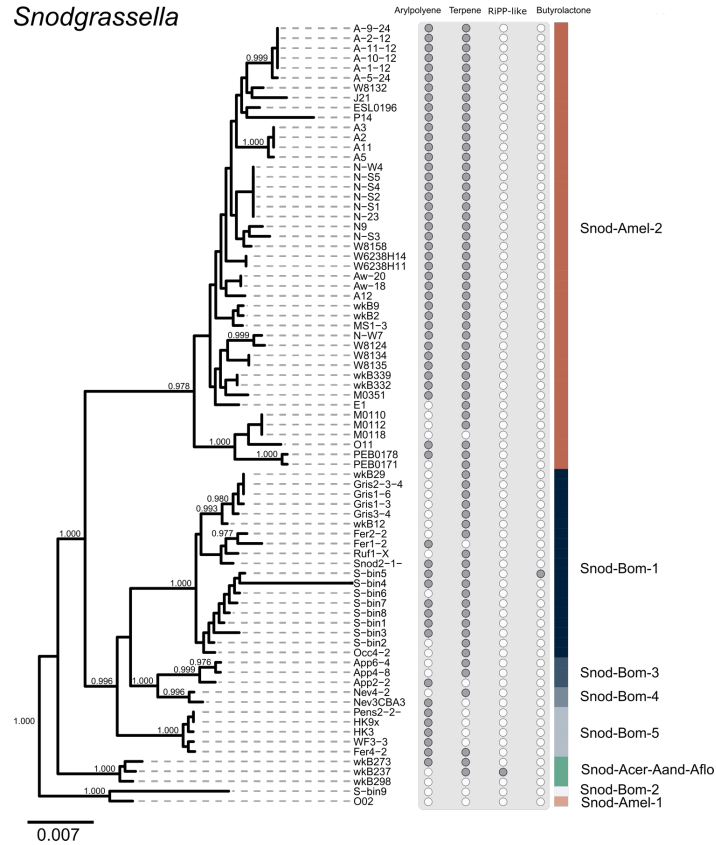
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Lactobacillus

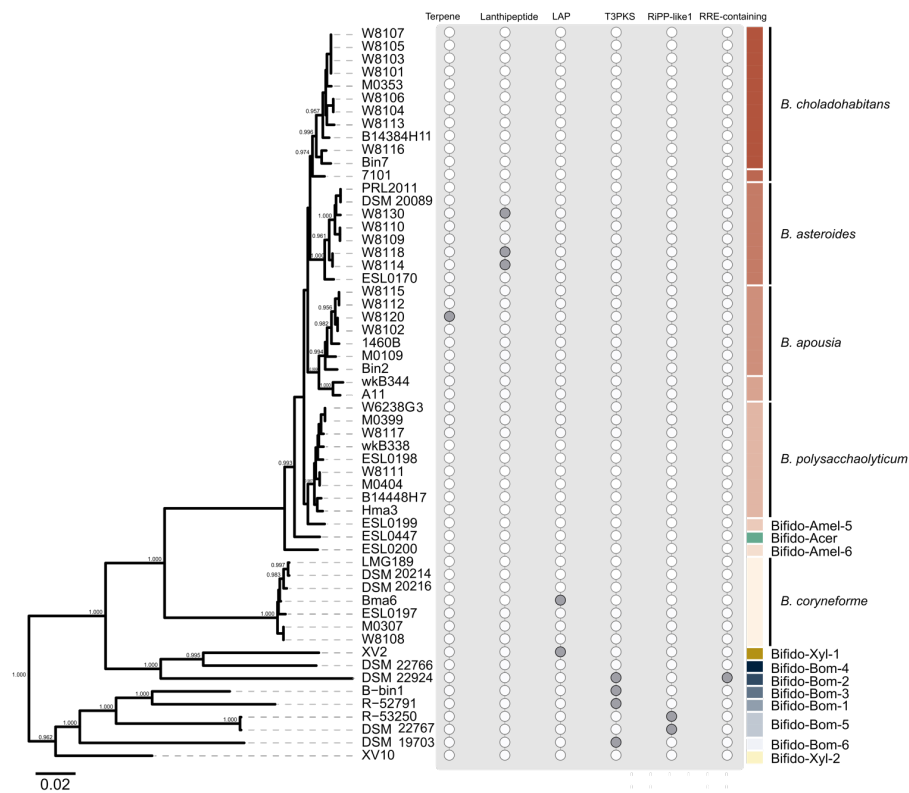


Supplementary Fig. 1. Genome phylogenies and species cluster classification of the *Lactobacillus* genus from honey and bumble bee guts. Cladograms on the left of each panel are maximum-likelihood trees inferred by GTDB-tk based on the amino acid sequences of bacterial marker genes. The presence of BGCs is indicated by grey circles.



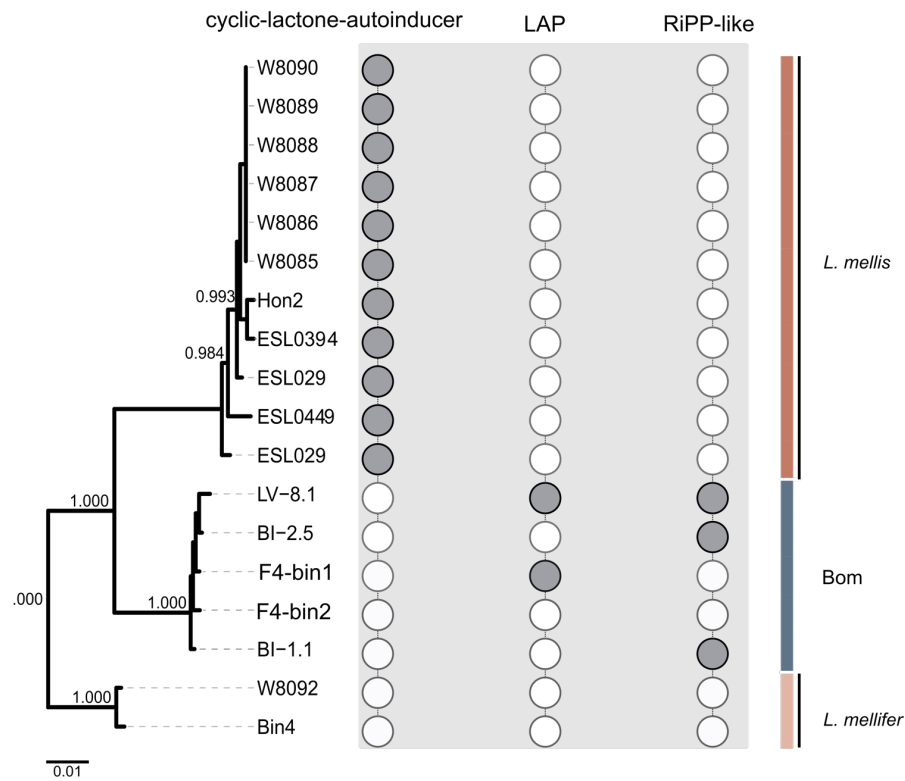
Supplementary Fig. 2. Genome phylogenies and species cluster classification of the *Snodgrassella* genus from honey and bumble bee guts. Cladograms on the left of each panel are maximum-likelihood trees inferred by GTDB-tk based on the amino acid sequences of bacterial marker genes. The presence of BGCs is indicated by grey circles.

Bifidobacterium



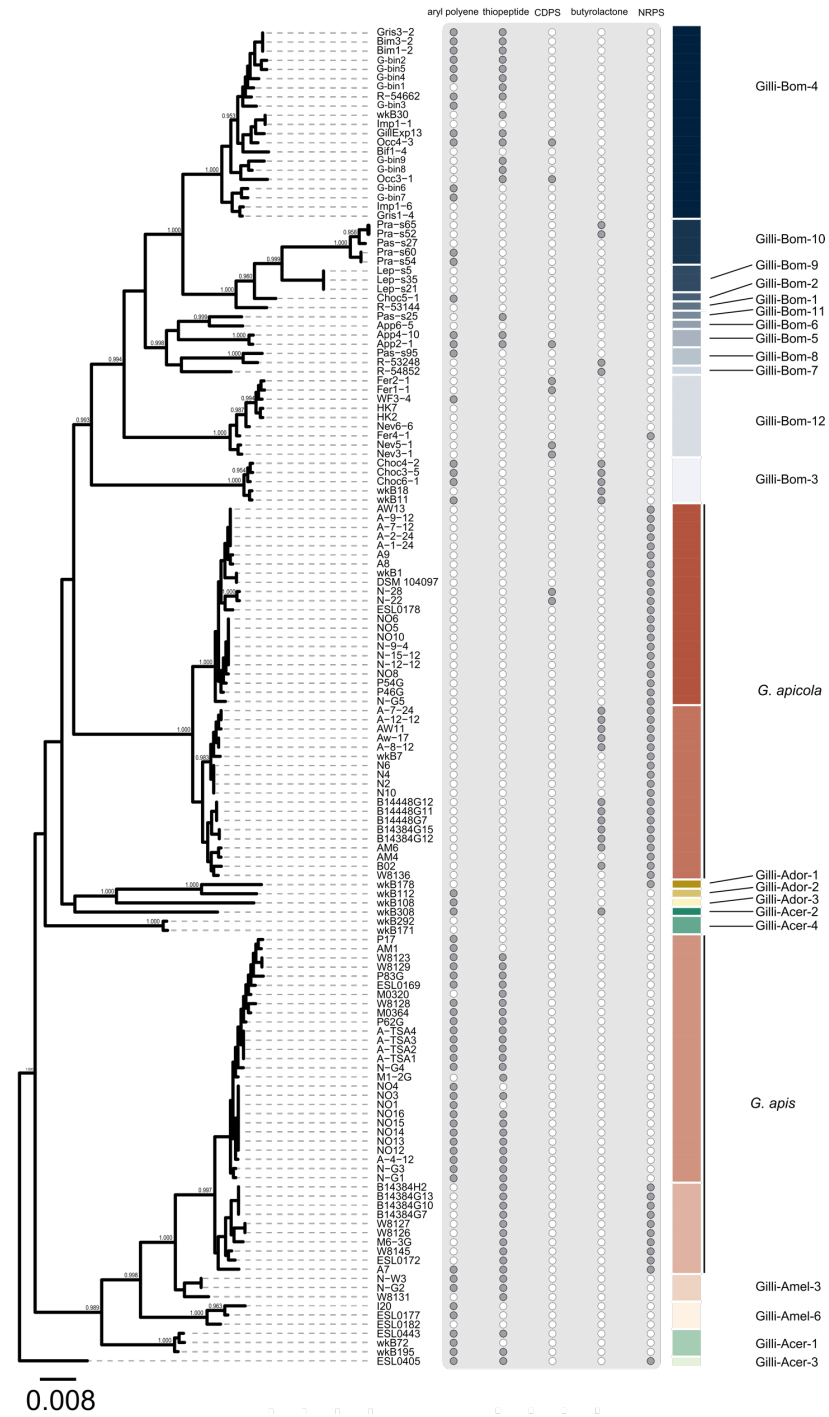
Supplementary Fig. 3. Genome phylogenies and species cluster classification of the *Bifidobacterium* genus from honey and bumble bee guts. Cladograms on the left of each panel are maximum-likelihood trees inferred by GTDB-tk based on the amino acid sequences of bacterial marker genes. The presence of BGCs is indicated by grey circles.

Bombilactobacillus



Supplementary Fig. 4. Genome phylogenies and species cluster classification of the *Bombilactobacillus* genus from honey and bumble bee guts. Cladograms on the left of each panel are maximum-likelihood trees inferred by GTDB-tk based on the amino acid sequences of bacterial marker genes. The presence of BGCs is indicated by grey circles.

Gilliamella

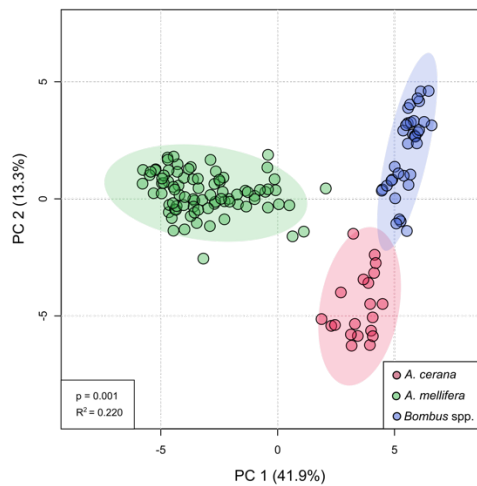
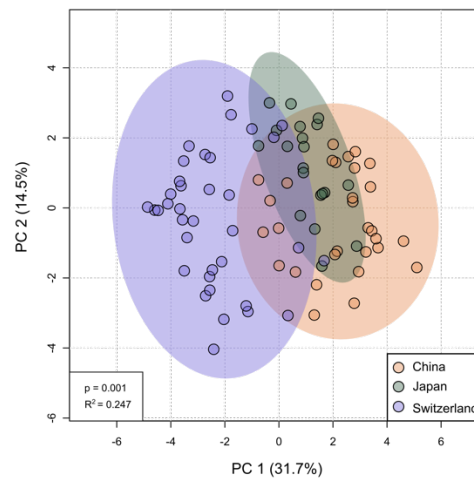


Supplementary Fig. 5. Genome phylogenies and species cluster

classification of the *Gilliamella* genus from honey and bumble bee guts.

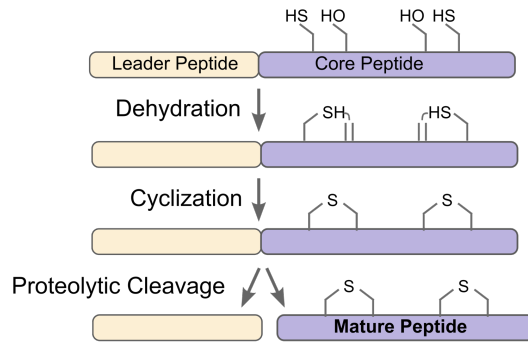
Cladograms on the left of each panel are maximum-likelihood trees inferred by GTDB-tk based on the amino acid sequences of bacterial marker genes.

The presence of BGCs is indicated by grey circles.

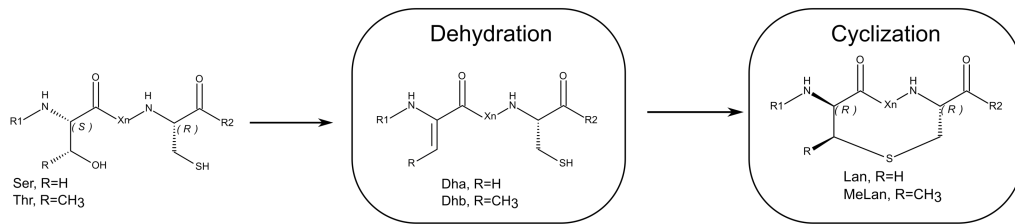
a**b**

Supplementary Fig. 6. a PCA analysis shows RiPPs distribution in the gut microbiomes of *A. cerana*, *A. mellifera*, and *B. terrestris* individuals. **b** RiPPs of the honeybee gut microbiota are distinguishable between China, Japan, and Switzerland. PCA analysis shows RiPPs distribution in the honeybee gut microbiomes of China, Japan, and Switzerland country individuals. Group differences were tested by one-way permutational multivariate ANOVA (PERMANOVA).

a



b



Supplementary Fig. 7. a Processing order of the precursor peptide by the lanthipeptide processing enzyme. **b** Underlying principles of Lanthipeptide II biosynthesis. Dha = Dehydroalanine. Dhb = Dehydrobutyrin

Lyase domain

LysE domain		K104	H106	K136	R148	Y158		D201	R213
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OspF		MPIKKPCCLKNLNLSLNVRSR-IPQMLSANERKLKNFNILYQIQPAYVYFKVASN-----VPTSDICO-SFSVYMQCFQIVNH-----SGDVFTHACRENPSQSGKDFGDKFHISIAREQVPLAFQILSGLFLSEDSFSDPKWIKV-----TDMNRXVSQSRVIGIAQFTLYKFP--DQECQYSALLHNLHTRQPIECLESRLSRKIAQPEYPSDVPDQEDKPNKWLYSVYRNLRSGR--							
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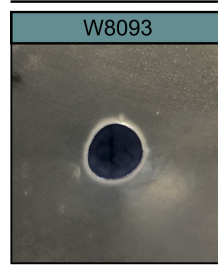
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Kinase domain

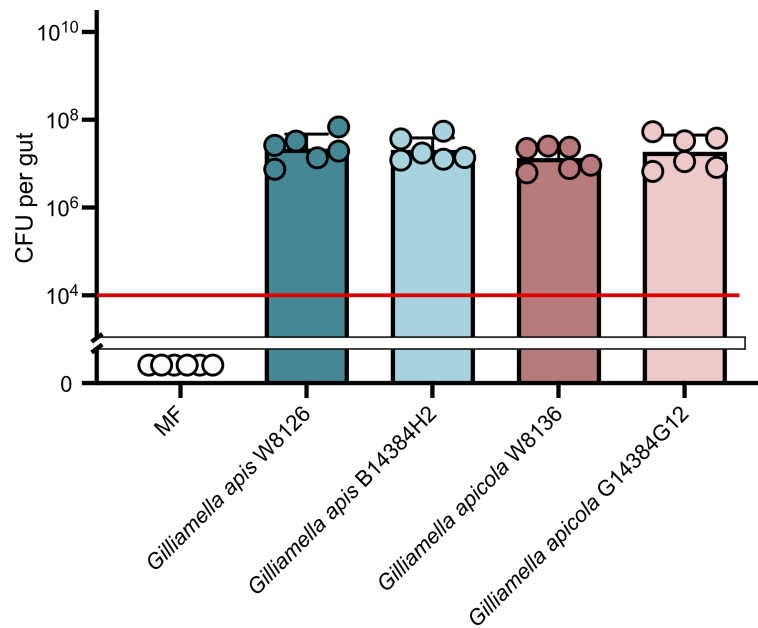
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 F5-bin2_3 DPSGKLIPDKRVYYLPEFVKPEMKIQENN-----KAVPISYEKLKYLKIVNA--ISFS DAGGVYKAS--IN--NRTCLIKEGRAPGLSDGDTGYRVLHREYVLDSLKDNPFPVNV--NNYTFAMKHNYLEENFI--GMNLDLFIATKFPFNIAKFSKELQKMTNIKFISEL LKAISIHAEGVAVGLOPNSVIFSEKE--QKITLIDFEEAQNPNPTYKE--P--GIMT
 ESI0416_3 DPSGKLIPDKRVYYLPEFVKPEMKIQENN-----KAVPISYEKLKYLKIVNA--ISFS DAGGVYKAS--IN--NRTCLIKEGRAPGLSDGDTGYRVLHREYVLDSLKDNPFPVNV--NNYTFAMKHNYLEENFI--GMNLDLFIATKFPFNIAKFSKELQKMTNIKFISEL LKAISIHAEGVAVGLOPNSVIFSEKE--QKITLIDFEEAQNPNPTYKE--P--GIMT
 ESI0228_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--SK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 ESI0245_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--SK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 ESI0246_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--SK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 ESI0247_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--SK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 ESI0233_3 DNKHDLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--FK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 F5-bin4_3 DNKHDLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--FK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 ESI0225_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--FK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 ESI0234_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--FK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 ESI0237_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--FK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 ESI0236_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--FK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 H70-3_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--FK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 R-53102_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--FK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOPDNVILD--T--DKKILDFENAKQTSAAYN--P--GLAT
 ESI0230_3 DNKHNLEDKRLPYYPQDFIPEPEQLKNV-----QHYDQNEFFKMLNINVDFS--LHYS NAGGVYHAV--FK--GKEWLVKEGRFAPGLDANGDGNFRIKHEYKILKQLAETPTVNV-----YESFKAMKHVLYVEEYLQ--GDTLADFVDSQYPTTANKQK-----NEYLTKVKI IITAL LNTINGIQHKGIAVGLOP

Supplementary Fig. 8. a Excerpt of an alignment of OspF from *Shigella dysenteriae* and SpvC from *Salmonella paratyphi* with the lyase domains of exemplary Lanthipeptide III and IV synthetases. Above the alignment, the numbering of the catalytic residues of SpvC is shown. **b** The kinase domains of *Lactobacillus* Firm5 shared the conserved residues with exemplary Lanthipeptide III (AciKC, AplKC, LabKC, CruKC, AviKC, EryKC)/IV (StcL) and the mycobacterial protein kinases (PknB, PknG) enzymes¹. Conserved catalytic residues are shown in grey and structural features important for activity are highlighted.

Lactobacillus Firm5



Supplementary Fig. 9. The cell-free supernatant of W8093 does not inhibit the growth of *M. plutonius in vitro*.



Supplementary Fig. 10. The graph showing the total CFU per gut estimated by bacteria culture for MF honeybees and *G. apis* strains (B14384H2, W8126) and *G. apicola* strains (W8136, G14384G12). Error bars represent mean SD. n=6 biologically independent replicates. Source data are provided as a Source Data file.

Supplementary Table 1. List of peptide sequence. P-Values of the peptide-spectrum matches are computed using MS-Direct Probability Redistribution for estimating Peptide Spectrum Matches based on rare event probability estimation by multilevel splitting².

ID	Fragment Sequence	Modified Sequence	Score	P-Value	PeptideMass	SpectrumMass	Charge	FDR
1	KATTSNTISA	KATTSNT-18ISA	6	8.10E-11	974.503	488.253	2	0
2	IFMILTRN	IFMILTRN	6	8.90E-12	1006.56	504.293	2	25
3	MILPI	MILPI	5	2.40E-11	585.356	586.363	1	50
4	YTLF	YT-20LF	5	3.80E-11	522.248	523.244	1	33.33
5	PIYP	PIYP	5	3.90E-11	488.263	489.275	1	25

Supplementary information references

1. Hegemann JD, Sussmuth RD. Matters of class: coming of age of class III and IV lanthipeptides. *RSC Chem Biol* **1**, 110-127 (2020).
2. Mohimani H, Kim S, Pevzner PA. A new approach to evaluating statistical significance of spectral identifications. *J Proteome Res* **12**, 1560-1568 (2013).