Cell Host & Microbe, Volume *24*

Supplemental Information

Bacterial Adaptation to the Host's Diet Is a Key Evolutionary Force Shaping *Drosophila-Lactobacillus* Symbiosis

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Supplemental figure titles and legends

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Bacterial adaptation to diet is a key evolutionary force shaping *Drosophila-Lactobacillus* symbiosis

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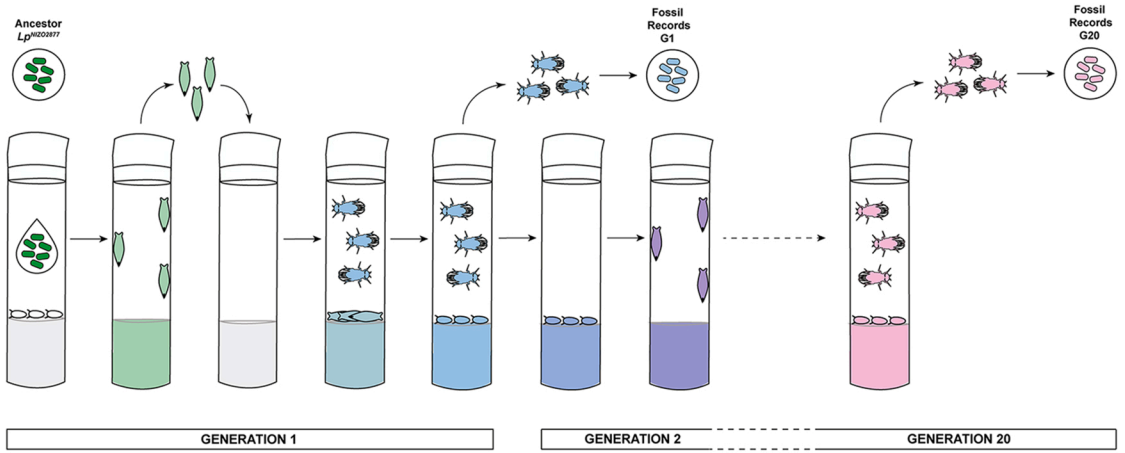
A


Ancestor
Lp NIZO2877
Fossil Records G1
Fossil Records G20
GENERATION 1
GENERATION 2
GENERATION 20

B

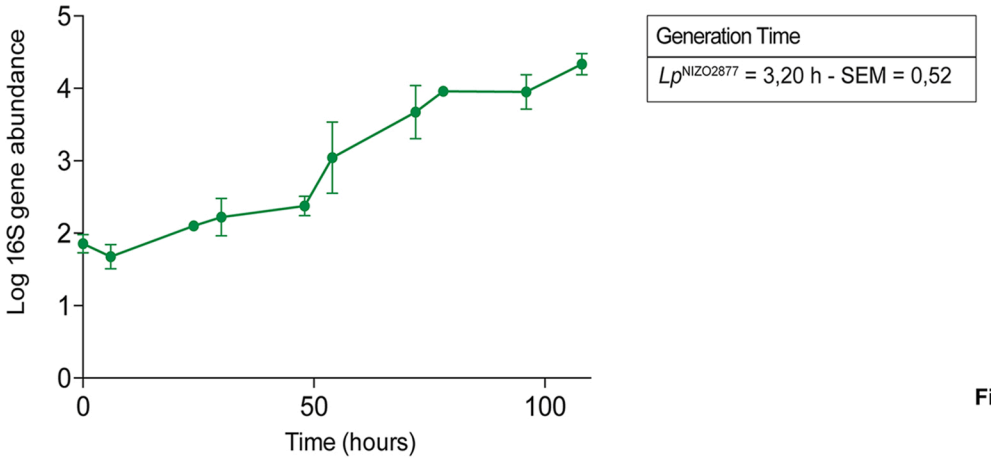

Log 16S gene abundance
Time (hours)
0
1
2
3
4
5
0
50
100
Generation Time
Lp NIZO2877 = 3,20 h - SEM = 0,52

Figure S1

Supplemental Figure 1 (related to Fig. 1): Rationale and schematic representation of the experimental setup for studying *L. plantarum* adaptive evolution (AE) with *Drosophila melanogaster*.

(A) The ancestor strain (*Lp*^{NIZO2877}) was added to 40 germ-free (GF) *Drosophila* embryos at the beginning of the first *Drosophila* generation (Generation 1). The first 15 emerging pupae were transferred to a new sterile poor nutrient diet. This allowed the bacteria associated with the pupae to propagate and colonize the new environment. The 15 adults emerged from the 15 transferred pupae, mated and females laid eggs that became the founders of the following fly generation (Generation 2). Once the eggs were laid, the adults were collected and homogenized to isolate the evolved bacteria they carry (fossil records from generation 1). Generation 2 followed the same experimental cycle as Generation 1, with the exception that no further inoculation of the ancestor strain *L. plantarum*^{NIZO2877} has been performed. Evolving bacteria were propagated through the transfer of the pupae during each generation. The experimental evolution lasted 20 *Drosophila* generations (313 days). Colour shading represents the evolution of the bacterial population during the experiment.

(B) 16S rRNA kinetics of *Lp*^{NIZO2877} in *Drosophila* Niche (*Drosophila* + Diet). The 16S rRNA gene quantification is shown in logarithmic scale. The mean generation time (h, hours) of *Lp*^{NIZO2877} in *Drosophila* niche ± the standard error of the mean (SEM) are reported on the graph (see Methods).

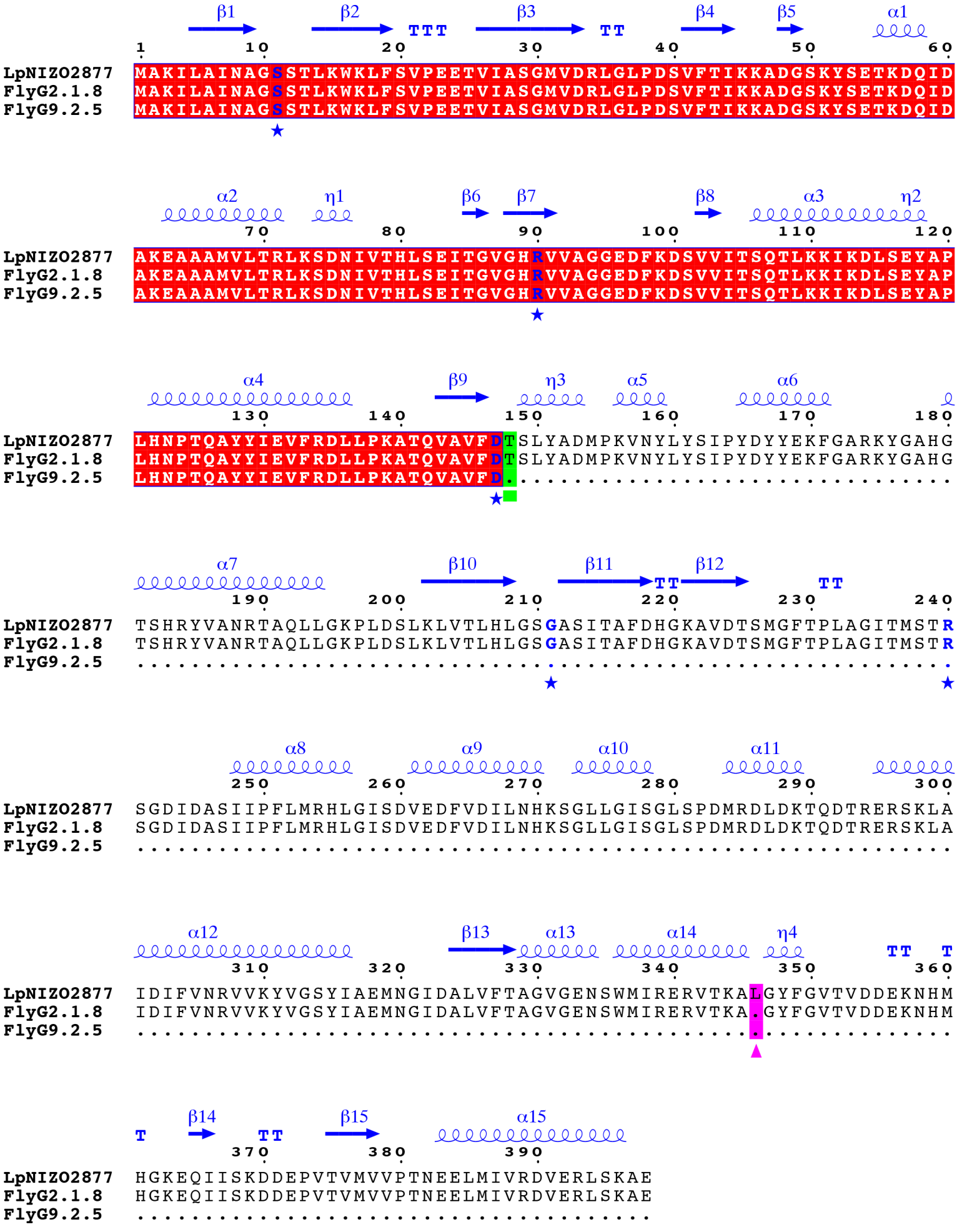

β1 β2 TTT β3 TT β4 β5 α1
1 10 20 30 40 50 60
LpNIZO2877 MAKILAINAGSSTLKWKLFSVPEETVIASGMVDRLGLPDSVFTIKKADGSKYSETKDQID
FlyG2.1.8 MAKILAINAGSSTLKWKLFSVPEETVIASGMVDRLGLPDSVFTIKKADGSKYSETKDQID
FlyG9.2.5 MAKILAINAGSSTLKWKLFSVPEETVIASGMVDRLGLPDSVFTIKKADGSKYSETKDQID
α2 η1 β6 β7 β8 α3 η2
70 80 90 100 110 120
LpNIZO2877 AKEAAAMVLTRLKSDNIVTHLSEITGVGHRVVAGGEDFKDSVVITSQTLKKIKDLSEYAP
FlyG2.1.8 AKEAAAMVLTRLKSDNIVTHLSEITGVGHRVVAGGEDFKDSVVITSQTLKKIKDLSEYAP
FlyG9.2.5 AKEAAAMVLTRLKSDNIVTHLSEITGVGHRVVAGGEDFKDSVVITSQTLKKIKDLSEYAP
α4 β9 η3 α5 α6
130 140 150 160 170 180
LpNIZO2877 LHNPTQAYYIEVFRDLLPKATQVAVFDTSLYADMPKVNYLYSIPYDYYEKFGARKYGAHG
FlyG2.1.8 LHNPTQAYYIEVFRDLLPKATQVAVFDTSLYADMPKVNYLYSIPYDYYEKFGARKYGAHG
FlyG9.2.5 LHNPTQAYYIEVFRDLLPKATQVAVFD.
α7 β10 β11 TT β12 TT
190 200 210 220 230 240
LpNIZO2877 TSHRYVANRTAQLLGKPLDSLKLVTLHLGSGASITAFDHGKAVDTSMGFTPLAGITMSTR
FlyG2.1.8 TSHRYVANRTAQLLGKPLDSLKLVTLHLGSGASITAFDHGKAVDTSMGFTPLAGITMSTR
FlyG9.2.5 .
α8 α9 α10 α11
250 260 270 280 290 300
LpNIZO2877 SGDIDASIIPFLMRHLGISDVEDFVDILNHKSGLLGISGLSPDMRDLDKTQDTRERSKLA
FlyG2.1.8 SGDIDASIIPFLMRHLGISDVEDFVDILNHKSGLLGISGLSPDMRDLDKTQDTRERSKLA
FlyG9.2.5 .
α12 β13 α13 α14 η4 TT T
310 320 330 340 350 360
LpNIZO2877 IDIFVNRVVKYVGSYIAEMNGIDALVFTAGVGENSWMIRERVTKALGYFGVTVDDEKNHM
FlyG2.1.8 IDIFVNRVVKYVGSYIAEMNGIDALVFTAGVGENSWMIRERVTKA.GYFGVTVDDEKNHM
FlyG9.2.5 .
T β14 TT β15 α15
370 380 390
LpNIZO2877 HGKEQIISKDDEPVTVMVVPTNEELMIVRDVERLSKAE
FlyG2.1.8 HGKEQIISKDDEPVTVMVVPTNEELMIVRDVERLSKAE
FlyG9.2.5 .

Figure S2

Supplemental Figure 2 (related to Fig. 2): Sequence/structural analysis of *Lp*^{NIZO2877} Acetate kinase A (AckA) protein aligned against the AckA of *Lp*^{NIZO2877}-derived strains (FlyG2.1.8, FlyG9.2.5) evolved in *Drosophila* niche. The secondary structure of the protein is indicated in blue above the sequence alignment. Catalytic residues of the predicted active site are shown in bold blue characters. The mutation sites are highlighted in pink and green for FlyG2.1.8 and FlyG9.2.5 strains respectively. The alignment was performed using Clustal Omega and drawn with ESPript.

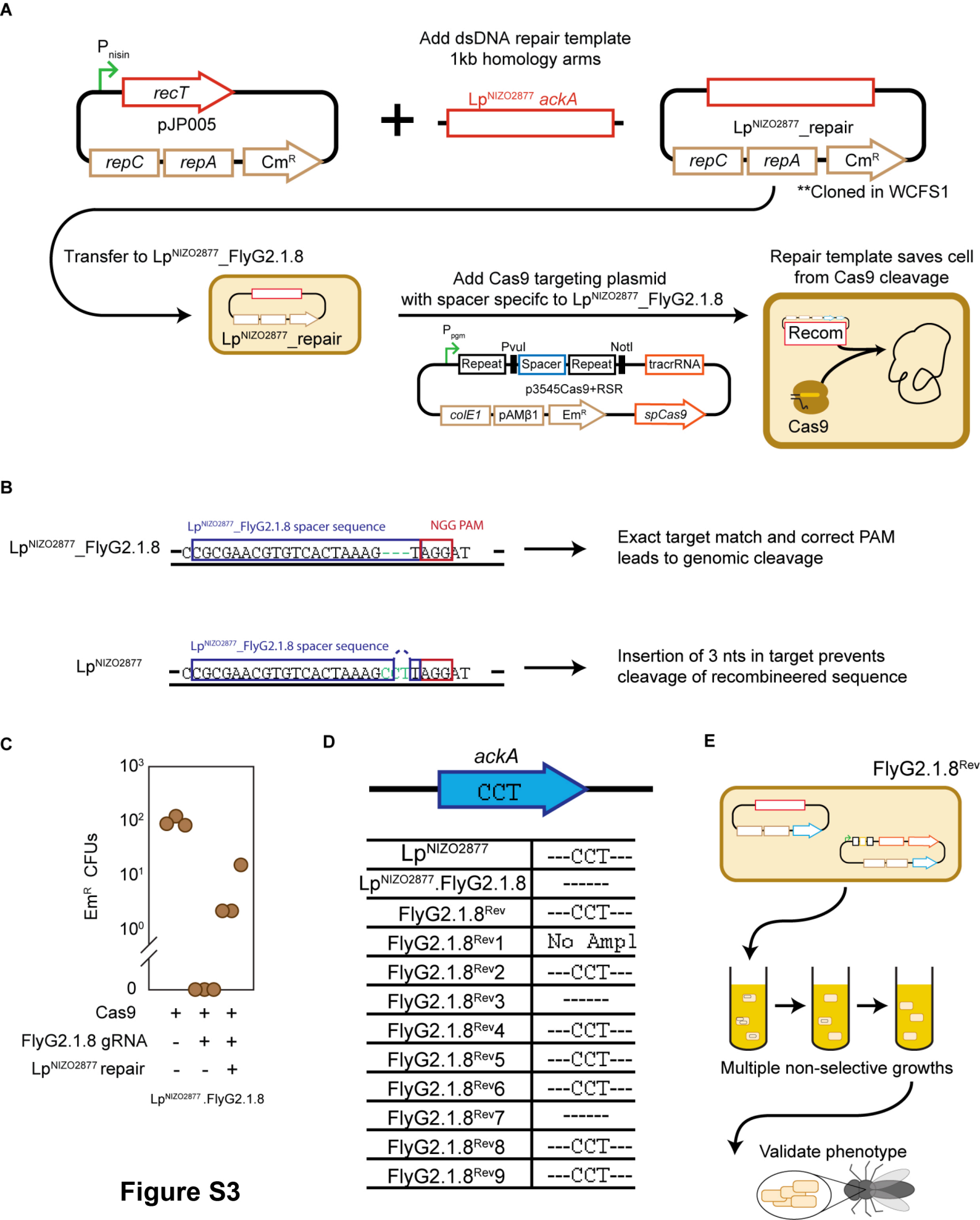

A
P nisin
recT
pJP005
repC
repA
Cm R
Add dsDNA repair template
1kb homology arms
Lp NIZO2877 ackA
Lp NIZO2877 _repair
repC
repA
Cm R
**Cloned in WCFS1
Transfer to Lp NIZO2877 _FlyG2.1.8
Lp NIZO2877 _repair
Add Cas9 targeting plasmid
with spacer specifc to Lp NIZO2877 _FlyG2.1.8
P pgm
PvuI
NotI
Repeat
Spacer
Repeat
tracrRNA
p3545Cas9+RSR
colE1
pAMβ1
Em R
spCas9
Repair template saves cell
from Cas9 cleavage
Recom
Cas9
B
Lp NIZO2877 _FlyG2.1.8
Lp NIZO2877 _FlyG2.1.8 spacer sequence
NGG PAM
CCGCGAACGTGTCACTAAAG---TAGGAT
Exact target match and correct PAM
leads to genomic cleavage
Lp NIZO2877
Lp NIZO2877 _FlyG2.1.8 spacer sequence
CCGCGAACGTGTCACTAAAGCCTTAGGAT
Insertion of 3 nts in target prevents
cleavage of recombineered sequence
C
Em R CFUs
10 3
10 2
10 1
10 0
0
Cas9 + + +
FlyG2.1.8 gRNA - + +
Lp NIZO2877 repair - - +
Lp NIZO2877 .FlyG2.1.8
D
ackA
CCT
Lp NIZO2877 ---CCT---
Lp NIZO2877 .FlyG2.1.8 ------
FlyG2.1.8 Rev ---CCT---
FlyG2.1.8 Rev 1 No Ampl
FlyG2.1.8 Rev 2 ---CCT---
FlyG2.1.8 Rev 3 ------
FlyG2.1.8 Rev 4 ---CCT---
FlyG2.1.8 Rev 5 ---CCT---
FlyG2.1.8 Rev 6 ---CCT---
FlyG2.1.8 Rev 7 ------
FlyG2.1.8 Rev 8 ---CCT---
FlyG2.1.8 Rev 9 ---CCT---
E
FlyG2.1.8 Rev
Multiple non-selective growths
Validate phenotype

Figure S3

Supplemental Figure 3 (related to Fig. 3): CRISPR/Cas9 genome editing in *Lactobacillus plantarum* with a dsDNA repair template.

(A) Construction of the repair template plasmid containing the dsDNA template. Following successful construct generation, cells containing the repair plasmid were transformed with the self-targeting Cas9 plasmid, thereby killing any cells that did not incorporate the repair template into the genome.

(B) Spacer design for targeting *ackA* in *Lp*^{NIZO2877}_FlyG2.1.8. The spacer will only successfully cleave *Lp*^{NIZO2877}_FlyG2.1.8, while allowing any edited survivors to evade cleavage due to a spacer mis-match and presence of a non-PAM.

(C) Transformation results after Cas9 self-targeting with the repair template plasmid. Presence of the repair template allowed for a total of 15 survivors clones to Cas9 killing.

(D) *ackA* locus sequencing results for 10 of the survivors. Two survivors contained the un-edited *ackA* gene in *Lp*^{NIZO2877}.FlyG2.1.8, and one did not yield a PCR product (No Ampl.). Seven colonies contained the edited *ackA* sequence.

(E) Plasmid removal after editing. Successfully edited cells were passaged multiple times through non-selective media to remove the genome editing plasmids. After validation of plasmid removal, strains had their genomes sequenced and were analyzed for *in vivo* validation.

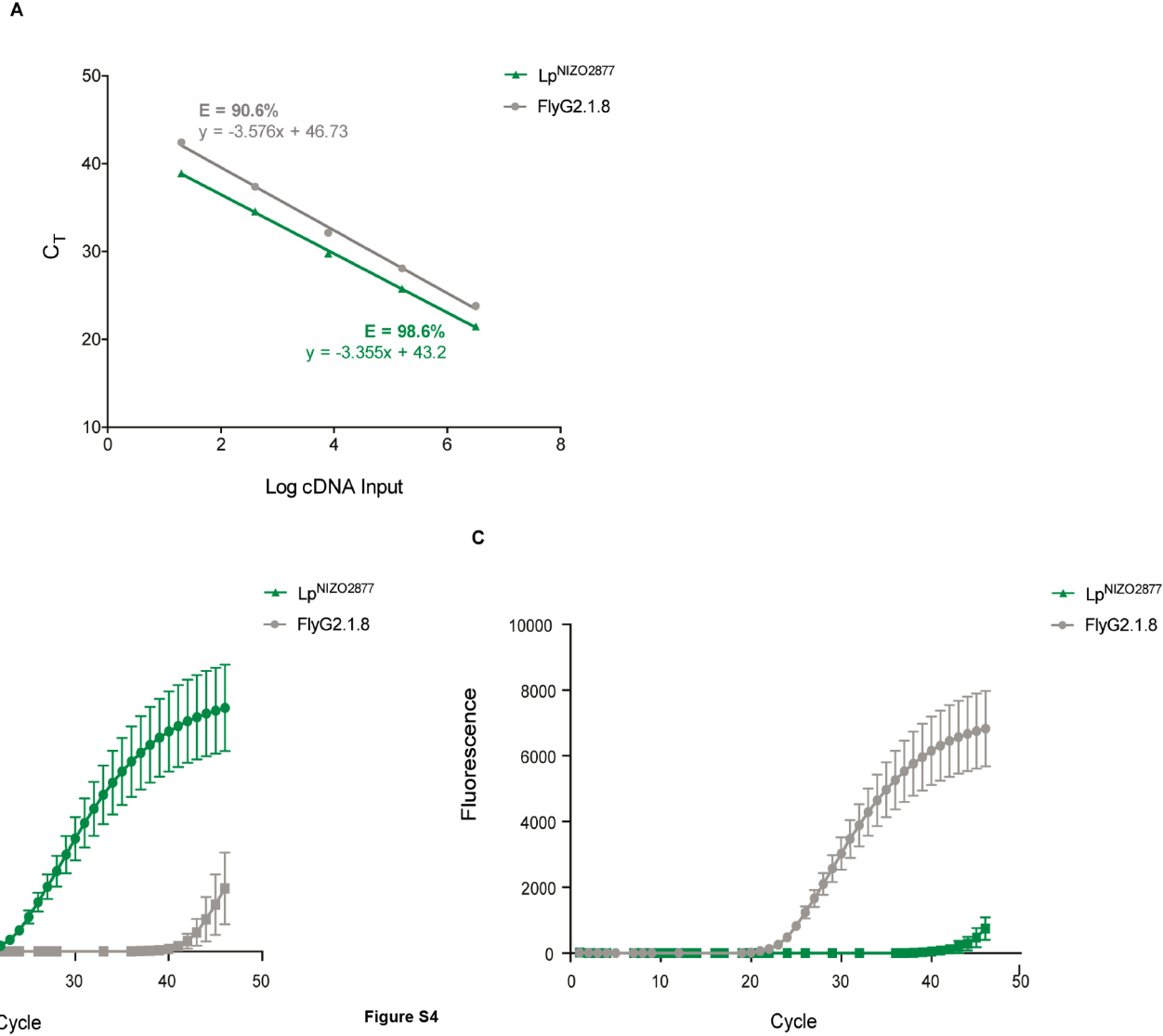

A
E = 90.6%
y = -3.576x + 46.73
E = 98.6%
y = -3.355x + 43.2
LpNIZO2877
FlyG2.1.8
CT
Log cDNA Input
B
Fluorescence
Cycle
C
Fluorescence
Cycle

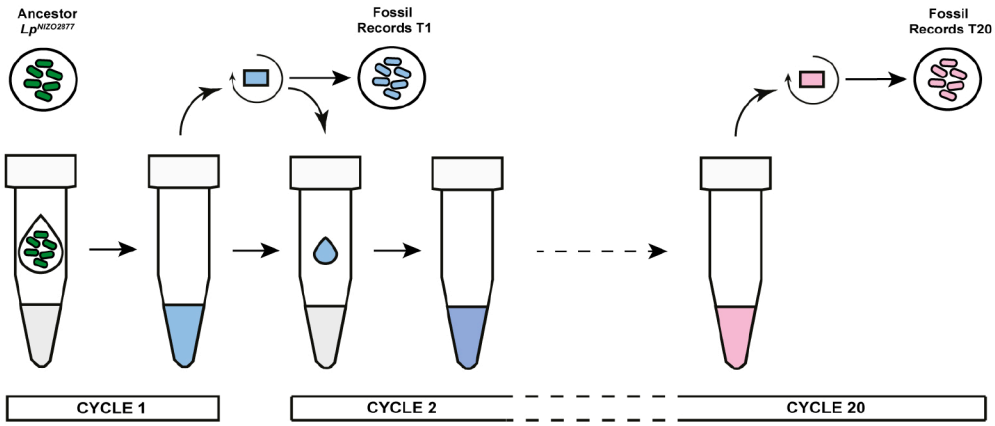
Figure S4

Supplemental Figure 4 (related to Fig. 4): Development of two Real-Time PCR assays for the discrimination and quantification of *Lp*^{NIZO2877} and *Lp*^{NIZO2877}–evolved strain FlyG2.1.8.

(A) Real-time PCR standard curves obtained from the amplification of *Lp*^{NIZO2877} (green) and FlyG2.1.8 (grey) strains. The graph shows the interpolated standard curves using determined threshold cycles (C_T) values and known template numbers for five standard samples. All points represent the mean of triplicate PCR amplifications. The respective efficiency values and curve equations are reported on the graph.

(B, C) Fluorescence amplification plots obtained from the amplification of *Lp*^{NIZO2877} and FlyG2.1.8 strains using *Lp*^{NIZO2877}-specific (B) and FlyG2.1.8 specific (C) Real-time assays.

A


Ancestor
Lp^NIZO2877
Fossil
Records T1
Fossil
Records T20
CYCLE 1
CYCLE 2
CYCLE 20

B

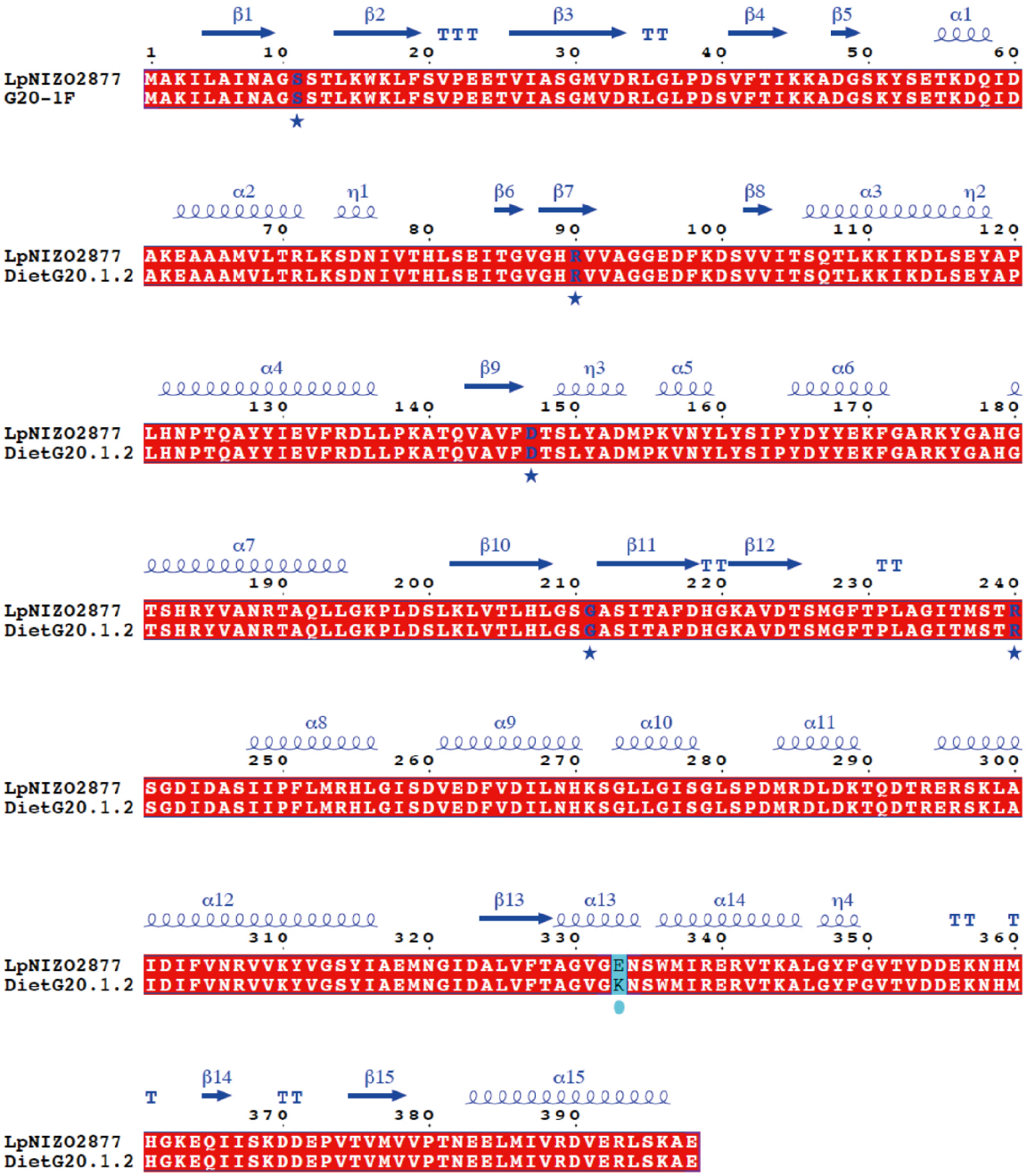

LpNIZO2877
G20-1F
LpNIZO2877
DietG20.1.2
LpNIZO2877
DietG20.1.2
LpNIZO2877
DietG20.1.2
LpNIZO2877
DietG20.1.2
LpNIZO2877
DietG20.1.2
LpNIZO2877
DietG20.1.2

Figure S5

Supplemental Figure 5 (related to Fig. 5): *L. plantarum* adaptive evolution (AE) in *Drosophila* diet without *Drosophila melanogaster*.

(A) Rationale and schematic representation of the experimental setup. The ancestor ($Lp^{NIZO2877}$) was added to sterile poor nutrient diet (Cycle 1). As soon as the microbial load reached the same value found on the 15 pupae used for propagating the bacterial population in the Niche adaptive evolution setup (10^7 CFU/mL of diet; Figure S1A), part of the medium was crushed and transferred to a new sterile poor nutrient diet. Fossil records were isolated from the crushed medium at the end of each cycle. Cycle 2 followed the same experimental course as Cycle 1. *L. plantarum* experimental evolution on *Drosophila* diet lasted 20 cycles. Colour shading represents the evolution of the bacterial population during the experiment.

(B) Sequence/structural analysis of $Lp^{NIZO2877}$ AckA protein aligned against AckA from $Lp^{NIZO2877}$-derived strain (DietG20.1.2) evolved in Drosophila diet. The secondary structure of the acetate kinase A protein is indicated in blue above the sequence alignment. The key catalytic residues of the predicted active sites are shown in bold blue characters. The mutation site is highlighted in cyan. The alignment was performed using Clustal Omega and drawn with ESPript.

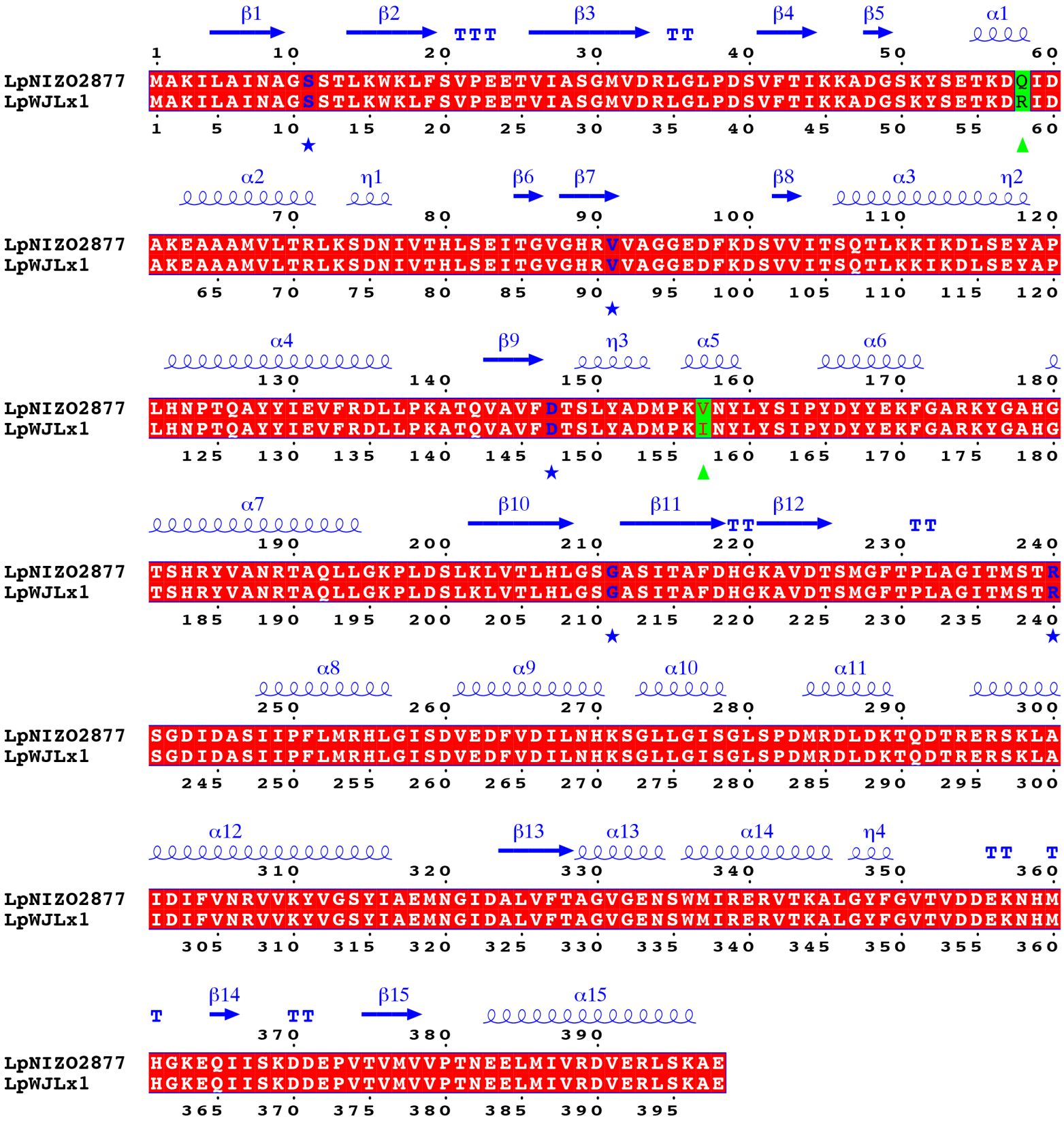

β1 β2 TTT β3 TT β4 β5 α1
1 10 20 30 40 50 60
LpNIZO2877 MAKILAINAGSSTLKWKLFSVPEETVIASGMVDRLGLPDSVFTIKKADGSKYSETKDQID
LpWJLx1 MAKILAINAGSSTLKWKLFSVPEETVIASGMVDRLGLPDSVFTIKKADGSKYSETKDRID
1 5 10 15 20 25 30 35 40 45 50 55 60
α2 η1 β6 β7 β8 α3 η2
70 80 90 100 110 120
LpNIZO2877 AKEAAAMVLTRLKSDNIVTHLSEITGVGHRVVAGGEDFKDSVVITSQTLKKIKDLSEYAP
LpWJLx1 AKEAAAMVLTRLKSDNIVTHLSEITGVGHRVVAGGEDFKDSVVITSQTLKKIKDLSEYAP
65 70 75 80 85 90 95 100 105 110 115 120
α4 β9 η3 α5 α6
130 140 150 160 170 180
LpNIZO2877 LHNPTQAYYIEVFRDLLPKATQVAVFDTSLYADMPKVNYLYSIPYDYYEKFGARKYGAHG
LpWJLx1 LHNPTQAYYIEVFRDLLPKATQVAVFDTSLYADMPKINYLYSIPYDYYEKFGARKYGAHG
125 130 135 140 145 150 155 160 165 170 175 180
α7 β10 β11 TT β12 TT
190 200 210 220 230 240
LpNIZO2877 TSHRYVANRTAQLLGKPLDSLKLVTLHLGSGASITAFDHGKAVDTSMGFTPLAGITMSTR
LpWJLx1 TSHRYVANRTAQLLGKPLDSLKLVTLHLGSGASITAFDHGKAVDTSMGFTPLAGITMSTR
185 190 195 200 205 210 215 220 225 230 235 240
α8 α9 α10 α11
250 260 270 280 290 300
LpNIZO2877 SGDIDASIIPFLMRHLGISDVEDFVDILNHKSGLLGISGLSPDMRDLDKTQDTRERSKLA
LpWJLx1 SGDIDASIIPFLMRHLGISDVEDFVDILNHKSGLLGISGLSPDMRDLDKTQDTRERSKLA
245 250 255 260 265 270 275 280 285 290 295 300
α12 β13 α13 α14 η4 TT T
310 320 330 340 350 360
LpNIZO2877 IDIFVNRVVKYVGSYIAEMNGIDALVFTAGVGENSWMIRERVTKALGYFGVTVDDEKNHM
LpWJLx1 IDIFVNRVVKYVGSYIAEMNGIDALVFTAGVGENSWMIRERVTKALGYFGVTVDDEKNHM
305 310 315 320 325 330 335 340 345 350 355 360
T β14 TT β15 α15
370 380 390
LpNIZO2877 HGKEQIISKDDEPVTVMVVPTNEELMIVRDVERLSKAE
LpWJLx1 HGKEQIISKDDEPVTVMVVPTNEELMIVRDVERLSKAE
365 370 375 380 385 390 395

Figure S6

Supplemental Figure 6 (related to Fig. 6): Sequence/structural analysis of *Lp*^{NIZO2877} AckA protein aligned against AckA from *Lp*^{WJL}. The secondary structure of the acetate kinase A protein is indicated in blue above the sequence alignment. The key catalytic residues of the predicted active sites are shown in bold blue characters. The mutation sites are highlighted in green. The alignment was performed using Clustal Omega and drawn with ESPript.

Supplemental tables Titles and Legends

Table S1. Bacterial strains, Related to Figures 1, 2, 3, 5. List of all *L. plantarum* strains used and sequenced in this study.

L. plantarum Strains	Description	Fly/Diet generation of isolation	Replicate	Accession Number	Reference
NIZO2877	Isolated from Vietnamese hotdog	-	-	LKHZ01000000	(Martino et al., 2015a)
WJL	Isolated from Drosophila melanogaster intestine	-	-	LKLZ00000000	(Martino et al., 2015b)
FlyG2.1.8	NIZO2877-evolved strain	2	1	PEBE00000000	This study
FlyG3.1.8	NIZO2877-evolved strain	3	1	PEGI00000000	This study
FlyG7.1.6	NIZO2877-evolved strain	7	1	PEGJ00000000	This study
FlyG8.1.1	NIZO2877-evolved strain	8	1	PEGK00000000	This study
FlyG8.1.2	NIZO2877-evolved strain	8	1	PEGL00000000	This study
FlyG9.1.4	NIZO2877-evolved strain	9	1	PEGM00000000	This study
FlyG10.1.5	NIZO2877-evolved strain	10	1	PEGN00000000	This study
FlyG10.1.9	NIZO2877-evolved strain	10	1	PEGO00000000	This study
FlyG11.1.2	NIZO2877-evolved strain	11	1	PEGP00000000	This study
FlyG11.1.6	NIZO2877-evolved strain	11	1	PEGQ00000000	This study
FlyG20.1.4	NIZO2877-evolved strain	20	1	PEGR00000000	This study
FlyG2.1.8Rev	NIZO2877-evolved strain	-	-	-	This study
FlyG9.2.5	NIZO2877-evolved strain	9	2	PEGS00000000	This study
FlyG11.2.6	NIZO2877-evolved strain	11	2	PEGT00000000	This study
FlyG20.2.6	NIZO2877-evolved strain	20	2	PEGU00000000	This study
DietG20.1.2	NIZO2877-evolved strain	20	1	PEGV00000000	This study
DietG20.2.2	NIZO2877-evolved strain	20	2	PEGW00000000	This study

Table S1

Table S2. Summary of mutations detected across the experimental evolution of *L. plantarum*, related to Figures 1, 2, 3, 5. List of all mutations detected in the *L. plantarum* experimental evolution replicates. §Locus tag refers to *L. plantarum* reference strain WCFS1 (Kleerebezem et al., 2003). nt: nucleotide; WGS: whole genome sequencing; SS: Sanger sequencing. Mutations identified by Sanger sequencing were confirmed from alignments of both forward and reverse reads.

Strain	Evolution Setup	Replicate	Generation/ Transfer	Detected mutation					
				Gene/ Region	Locus Tag[§]	Annotation	Mutation	Position in *Lp*^{NIZO2877}	Method
FlyG2.1.8	Niche	1	2	*ackA*	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS/SS
FlyG3.1.8	Niche	1	3	*ackA*	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS/SS
FlyG7.1.6	Niche	1	7	*int1*	-	*intergenic region*	1 nt substitution	504874	WGS/SS
				cheY	*lp_1544*	*two-component system response regulator*	1 nt substitution	1348923	WGS/SS
				ackA	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS
FlyG8.1.1	Niche	1	8	*int1*	-	*intergenic region*	1 nt substitution	504874	WGS
				cheY	*lp_1544*	*two-component system response regulator*	1 nt substitution	1348923	WGS
				ackA	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS
FlyG8.1.2	Niche	1	8	*int1*	-	*intergenic region*	1 nt substitution	504874	WGS
				cheY	*lp_1544*	*two-component system response regulator*	1 nt substitution	1348923	WGS
				ackA	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS
FlyG9.1.4	Niche	1	9	*int1*	-	*intergenic region*	1 nt substitution	504874	WGS
				cheY	*lp_1544*	*two-component system response regulator*	1 nt substitution	1348923	WGS
				adhE	*lp_3662*	*alcohol dehydrogenase/ acetaldehyde dehydrogenase*	1 nt substitution	2268660	WGS/SS
				int2	-	*intergenic region*	1 nt substitution	2456364	WGS/SS
				ackA	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS
FlyG10.1.5	Niche	1	10	*int1*	-	*intergenic region*	1 nt substitution	504874	WGS
				cheY	*lp_1544*	*two-component system response regulator*	1 nt substitution	1348923	WGS
				ackA	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS
FlyG10.1.9	Niche	1	10	*int1*	-	*intergenic region*	1 nt substitution	504874	WGS
				cheY	*lp_1544*	*two-component system response regulator*	1 nt substitution	1348923	WGS
				ackA	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS
FlyG11.1.2	Niche	1	11	*int1*	-	*intergenic region*	1 nt substitution	504874	WGS
				cheY	*lp_1544*	*two-component system response regulator*	1 nt substitution	1348923	WGS
				ackA	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS
FlyG11.1.6	Niche	1	11	*int1*	-	*intergenic region*	1 nt substitution	504874	WGS
				cheY	*lp_1544*	*two-component system response regulator*	1 nt substitution	1348923	WGS

				-	*lp_0055*	*fumarate reductase, flavoprotein subunit*	1 nt substitution	2347322	WGS/SS
				ackA	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS
FlyG20.1.4	Niche	1	20	*pstB*	*lp_0749*	*phosphate ABC transporter ATP-binding protein*	1 nt substitution	120791	WGS/SS
				-	*lp_0797*	*exoribonuclease II*	1 nt substitution	177140	WGS/SS
				int1	-	*intergenic region*	1 nt substitution	504874	WGS
				-	*lp_2499*	*ABC transporter ATP-binding protein/permease*	1 nt substitution	947607	WGS
				-	*lp_1258*	*LysR family transcriptional regulator*	1 nt substitution	1105664	WGS/SS
				cheY	*lp_1544*	*two-component system response regulator*	1 nt substitution	1348923	WGS
				int3	-	*intergenic region*	1 nt substitution	1736935	WGS/SS
				ackA	*lp_03010*	*acetate kinase*	deletion (Δ3)	2571613-5	WGS
FlyG9.2.5	Niche	2	9	*int4*	-	*intergenic region*	1 nt substitution	1982853	WGS/SS
				-	*lp_0197*	*cell surface protein precursor, LPXTG-motif cell wall anchor*	deletion (Δ6)	2471707-12	WGS/SS
				ackA	*lp_03010*	*acetate kinase*	1 nt substitution	2571025	WGS/SS
FlyG11.2.6	Niche	2	11	*int4*	-	*intergenic region*	1 nt substitution	1982853	WGS
				-	*lp_0197*	*cell surface protein precursor, LPXTG-motif cell wall anchor*	deletion (Δ6)	2471707-12	WGS
				ackA	*lp_03010*	*acetate kinase*	1 nt substitution	2571025	WGS
FlyG20.2.6	Niche	2	20	*cheY*	*lp_1544*	*two-component system response regulator*	1 nt substitution	1348886	WGS/SS
				-	*lp_2212*	*NADH-flavin reductase*	1 nt substitution	1937136	WGS
				int4	-	*intergenic region*	1 nt substitution	1982853	WGS
				-	*lp_0197*	*cell surface protein precursor, LPXTG-motif cell wall anchor*	deletion (Δ6)	2471707-12	WGS
				ackA	*lp_03010*	*acetate kinase*	1 nt substitution	2571025	WGS
DietG20.1.2	Diet	1	20	*ackA*	*lp_03010*	*acetate kinase*	1 nt substitution	2571576	WGS/SS
DietG20.2.2	Diet	2	20	*int5*	-	*intergenic region*	1 nt substitution	2313069	WGS/SS
				ackA	*lp_03010*	*acetate kinase*	1 nt substitution	2571576	WGS/SS
				int6	-	*intergenic region*	1 nt substitution	1736935	WGS/SS

Table S2

Table S3. Metabolomic dataset of *Drosophila* diet inoculated with *Lp*^{NIZO2877} and FlyG2.1.8 separately, Related to Figure 6. Table of metabolites resulted to be significantly different between Lp^{NIZO2877}- and FlyG2.1.8-associated *Drosophila* diets based on two-sided t-tests ($p<0.05$). Fold-changes (FC) are calculated with the ratio between means of Lp^{NIZO2877} and FlyG2.1.8 replicates for each metabolite. Metabolites with a positive FC are overrepresented in FlyG2.1.8-associated samples and those with a negative FC are underrepresented in FlyG2.1.8-associated samples. FC detail: If mean(FlyG2.1.8) > mean(Lp^{NIZO2877}), FC = mean(FlyG2.1.8)/mean(Lp^{NIZO2877}); If mean(Lp^{NIZO2877})>mean(FlyG2.1.8), FC = - mean(Lp^{NIZO2877})/mean(FlyG2.1.8)

Metabolite	Metabolite Class	$Lp^{NZO2877}$					FlyG2.1.8					Mean $Lp^{NZO2877}$	Mean FlyG2.1.8	FC	pvalue
		rep1	rep2	rep3	rep4	rep5	rep1	rep2	rep3	rep4	rep5				
2-aminoadipate	Amino Acid	1,1721	1,1259	0,7634	0,8569	1,0883	0,8108	1,1361	1,0611	1,0009	0,8761	1,00132	0,977	-1,0248925	0,81470234
2-hydroxy-3-methylvalerate	Amino Acid	1,4581	0,8634	1	0,9063	0,9814	1,1203	0,7945	0,925	1,243	0,7041	1,04184	0,95738	-1,0882199	0,57997116
3-(4-hydroxyphenyl) lactate	Amino Acid	1,1226	0,8179	1,1635	1,0026	0,976	0,9974	0,8097	0,8599	0,9336	0,7513	1,01652	0,87038	-1,1679037	0,09062559
4-guanidinobutanoate	Amino Acid	1,1821	1,0982	1,0856	0,9744	1,0666	0,9725	1,0347	0,9945	1,1894	1,0055	1,08138	1,03932	-1,0404688	0,43505117
4-hydroxyglutamate	Amino Acid	1,3091	0,6103	1,0206	1,1252	1,2235	0,6629	1,0585	1	1,0868	1,0593	1,05774	0,9735	-1,0865331	0,58024375
5-methylthioadenosine (MTA)	Amino Acid	1,0959	0,96	0,9639	0,8034	0,4754	0,4754	0,4754	0,4754	0,4754	0,6718	0,85972	0,51468	-1,6703971	0,02842545
5-oxoproline	Amino Acid	1,1954	1,1233	1,1947	1,195	1,1724	1,1093	0,9843	1,0254	1,1625	1,0666	1,17616	1,06962	-1,0996055	0,02291602
6-oxopiperidine-2-carboxylate	Amino Acid	1,7192	1,1342	0,993	1,0274	1,0631	1,2966	0,9756	0,9154	1,4487	1,0887	1,18738	1,145	-1,0370131	0,80769515
alpha-hydroxyisovalerate	Amino Acid	0,9352	1,0628	1,1737	1,0008	1,0235	1,028	0,8645	0,8496	0,9836	0,9314	1,0392	0,93142	-1,1157158	0,07337653
arginината*	Amino Acid	1,3557	1,1047	0,7951	0,6393	1	0,772	0,9297	0,6393	1,033	0,6393	0,97896	0,80266	-1,2196447	0,27003911
arginine	Amino Acid	1,0947	0,9995	1,0005	1,0144	1,0708	0,9955	1,0086	1,0046	1,0507	1,0452	1,03598	1,02092	-1,0147514	0,52933797
asparagine	Amino Acid	1,023	1,0109	1,0073	1,013	1,0218	0,9646	1,0003	0,9997	1,0675	1,0168	1,0152	1,00978	-1,0053675	0,76531216
beta-hydroxyisovalerate	Amino Acid	1,3585	1,3189	0,9354	0,6319	1,0873	1,3522	0,8014	1,1622	0,8728	1,0345	1,0664	1,04462	-1,0208497	0,89925383
betaine	Amino Acid	1,2	1,0632	1,1486	1,0452	1,0465	1,075	1,0252	1,0504	1,0965	1,1119	1,1007	1,0718	-1,026964	0,44066802
citrulline	Amino Acid	1,0994	1,0817	0,9968	1,0455	1,0638	0,9616	1,0032	0,8602	1,0719	0,9144	1,05744	0,96226	-1,098913	0,05809564
creatine	Amino Acid	1,607	1,1351	1,8726	1,2971	1,357	0,9386	1	0,898	0,997	0,9853	1,45376	0,96378	-1,508394	0,01843314
creatinine	Amino Acid	1,4011	1,2281	1,403	1,215	1,2862	0,9904	1,1115	0,997	0,9231	0,9789	1,30668	1,00018	-1,3064448	0,00042655
dimethylarginine	Amino Acid	1,1531	1,019	1,0559	1,0064	1,027	0,9517	1,0302	0,9957	1,052	1,1195	1,05228	1,02982	-1,0218096	0,57693576
gamma-aminobutyrate (GABA)	Amino Acid	1,4687	1,3374	1,3868	1,2807	1,3695	1,2188	1,2427	1,2288	1,3226	1,26	1,36862	1,25458	-1,0908989	0,01715585
gentisate	Amino Acid	1,4126	0,9723	1,3161	0,9425	1,3548	0,8668	0,99	0,9786	1,4068	1,181	1,19966	1,08464	-1,1060444	0,42919421
glutamine	Amino Acid	0,5846	0,362	0,0466	0,2916	0,16	0,128	0,1668	0,1731	0,1463	0,1323	0,28896	0,1493	-1,935432	0,20278362
histidine	Amino Acid	1,1493	0,7539	0,9959	0,7983	1,1392	0,8751	0,7085	0,7689	1,0211	1,015	0,96732	0,87772	-1,1020827	0,41691477
indole-3-carboxylic acid	Amino Acid	1,114	0,9486	1,2276	0,7704	1,2031	1,6359	0,5815	1,0634	0,5231	0,5231	1,05274	0,8654	-1,2164779	0,45830394
indoleacetate	Amino Acid	1,0697	1,052	0,967	1,0036	1,0486	0,9501	0,9964	0,9542	1,0818	1,0607	1,02818	1,00864	-1,0193726	0,57100065
indolelactate	Amino Acid	0,8525	0,841	1,0403	0,9854	1	0,8236	0,7344	0,8038	0,9121	0,9773	0,94384	0,85024	-1,1100866	0,15071114
leucine	Amino Acid	1,3723	1,2004	1,2288	1,2033	1,2548	1,2262	1,2101	1,1887	1,2538	1,2823	1,25192	1,23222	-1,0159874	0,6006747
lysine	Amino Acid	1,1143	0,9688	1,0113	0,9833	1,0953	0,9537	1,0109	1,0061	0,9906	1,0164	1,0346	0,99554	-1,039235	0,27123957
methionine sulfone	Amino Acid	1,0857	0,9206	0,8164	1,1381	1,0641	0,9823	1,2286	0,7304	0,7755	1,0756	1,00498	0,95848	-1,0485143	0,68625228
methionine sulfoxide	Amino Acid	1,1949	0,9476	1,0587	1,0264	1,0986	0,9607	0,9026	0,8874	1,0652	1,0445	1,06524	0,97208	-1,0958357	0,12619746
N-acetylglycine	Amino Acid	1,0657	0,5705	0,7542	0,9382	1,0038	0,6169	0,6166	0,6125	0,656	1,0228	0,86648	0,70496	-1,2291194	0,21821526
N-acetylhistamine	Amino Acid	0,2434	0,2434	0,2434	0,2434	0,2434	0,2434	0,2434	0,2434	0,2434	0,2434	0,2434	0,2434	-1	2
N-acetylserine	Amino Acid	1,238	1,2984	1,1698	1,1508	1,1555	1,1003	1,0157	1,1015	1,1172	1,0745	1,2025	1,08184	-1,1115322	0,00973102
N-acetyltaurine	Amino Acid	1,2099	0,9271	1,2037	0,9991	1,1427	1,1264	1,1501	0,8918	1,1832	0,8804	1,0965	1,04638	-1,0478985	0,58148706
N-formylmethionine	Amino Acid	1,1822	0,7999	1,1264	0,9315	1,0032	0,9266	0,9	0,8725	1,0437	0,7389	1,00864	0,89634	-1,1252873	0,22230373
N-formylphenylalanine	Amino Acid	1,7097	1,0462	1,4664	1,1893	1,0951	1,3092	0,7854	1	1,3644	0,7635	1,30134	1,0445	-1,2458976	0,18733804
N-methylproline	Amino Acid	0,916	1,416	1,248	2,0332	0,8394	0,9949	1,2046	0,9992	1,0587	1,3041	1,29052	1,1123	-1,1602266	0,46155114
N6,N6,N6-trimethyllysine	Amino Acid	1,1459	1,0173	0,965	1,0685	1,0693	0,9764	1,0009	1,017	1,0883	1,0979	1,0532	1,0361	-1,0165042	0,67037617
phenyllactate (PLA)	Amino Acid	1,1256	0,7493	1,1427	0,9547	0,8822	0,8226	0,8967	0,825	0,9543	0,6518	0,9709	0,83008	-1,1696463	0,1616931
pipecolate	Amino Acid	1,0504	1,0393	1	1,0618	1,0165	0,9434	0,97	0,8951	1,0813	1,0548	1,0336	0,98892	-1,0451806	0,27717606
pyroglutamine*	Amino Acid	1,1314	0,9956	1,0133	1,015	1,0256	0,9036	1,0185	0,9924	1,1726	0,9552	1,03618	1,00846	-1,0274875	0,60902803
S-adenosylhomocysteine (SAH)	Amino Acid	1,8301	1,0978	1,0552	1,2031	1,1273	1,3721	0,8572	0,9161	1,1742	0,9334	1,2627	1,0506	-1,2018846	0,26099616
taurine	Amino Acid	0,0893	0,0893	0,0893	0,0893	0,0893	0,0893	0,0893	0,0893	0,0893	0,0893	0,0893	0,0893	-1	2
threonine	Amino Acid	1,3126	1,2661	1,1474	1,2233	1,2764	1,094	1,1903	1,1534	1,2544	1,1367	1,24516	1,16576	-1,0681101	0,07695586
trans-4-hydroxyproline	Amino Acid	0,9686	0,9201	1,0077	1,0258	0,975	0,8219	0,8974	0,8724	0,9923	1,0896	0,97944	0,93472	-1,0478432	0,4191927
valine	Amino Acid	1,2502	1,9833	1,1377	1,1379	1,1671	1,0592	1,1019	1,0696	1,1327	1,2006	1,33524	1,1128	-1,1998922	0,24652702
xanthurenate	Amino Acid	1,0011	0,7499	0,9823	0,7477	0,6868	0,8383	0,8728	0,7067	0,7431	0,7816	0,83356	0,7885	-1,0571465	0,55739379
4-imidazoleacetate	Amino Acid	1,0122	0,9682	0,8716	0,9881	0,9737	1,0564	1,0432	0,905	1,1204	0,9533	0,96276	1,01566	1,0549462	0,28283795
alanine	Amino Acid	1,033	1,0419	0,9645	0,9371	1,0272	1,034	1,0226	1,0404	1,0608	1,1352	1,00074	1,0586	1,05781722	0,08180066
alpha-hydroxyisocaproate	Amino Acid	1,4456	0,9708	0,8753	0,8119	0,871	1,2138	0,8471	1,0014	1,1525	0,9961	0,99492	1,04218	1,04750131	0,73272191
aspartate	Amino Acid	1,0586	0,9894	0,9506	0,9624	1,0115	1,0297	1,0841	1,0106	1,1181	1,0749	0,9945	1,06348	1,06936149	0,03521152
ethylmalonate	Amino Acid	0,7807	0,7392	0,8047	0,7392	1,3356	0,8859	0,7392	0,7398	1,1967	0,9705	0,87988	0,90642	1,0301632	0,8574675
glutamate	Amino Acid	0,9563	0,9885	0,7233	1,0058	0,9942	1,1712	1,247	1,1943	1,4677	1,3506	0,93362	1,28616	1,37760545	0,00173601
glycine	Amino Acid	1,3081	1,127	1,2494	1,2628	1,1822	1,1231	1,2027	1,1427	1,4415	1,2703	1,2259	1,23606	1,00828779	0,8819727
guanidinoacetate	Amino Acid	1,0972	0,6146	1,0934	1,3844	0,6831	1,1046	1	0,9058	0,7254	1,3776	0,97454	1,02268	1,04939766	0,79621322
isoleucine	Amino Acid	1,2648	1,1238	1,1452	1,0742	1,202	1,2208	1,1671	1,1304	1,2382	1,1821	1,162	1,18772	1,02213425	0,52289333
kynurenate	Amino Acid	0,8664	0,6308	0,8748	0,7749	0,7909	0,8555	0,8988	0,81	1,0272	0,7934	0,78756	0,87698	1,11354056	0,17864716
methionine	Amino Acid	1,0182	0,9693	0,9272	0,9818	1,0621	1,1629	1,0982	1,0992	1,1786	1,2042	0,99172	1,14862	1,15820998	0,00104888
N-acetylalanine	Amino Acid	0,9658	1,1091	0,9235	0,94	1,0957	1,0572	1,0562	1,3974	1,2363	1,2544	1,00682	1,2003	1,1921694	0,04033587
N-acetylarginine	Amino Acid	0,3485	0,2798	0,2798	0,2798	0,2798	0,4054	0,6587	0,5008	0,7395	0,5657	0,29354	0,57402	1,95550862	0,00738758
N-acetylasparagine	Amino Acid	1,0085	1,0644	1,0962	0,9287	1,2155	1,1956	1,2274	1,1242	1,253	0,9377	1,06266	1,14758	1,07991267	0,2857394
N-acetylaspartate (NAA)	Amino Acid	0,3949	0,3998	0,467	0,4612	0,4146	7,3352	8,2812	12,3127	12,0894	10,5231	0,4275	10,10832	23,645193	0,000635
N-acetylglutamate	Amino Acid	0,8785	0,7962	0,7353	0,8743	0,816	1,4849	1,585	1,7843	2,1916	1,6108	0,82006	1,73132	2,11121137	0,00145244
N-acetylglutamine	Amino Acid	0,2742	0,3003	0,3644	0,4042	0,3024	1,6617	1,9639	2,7624	2,2177	1,7411	0,3291	2,06936	6,2879368	0,00084106
N-acetylhistidine	Amino Acid	0,5149	0,3183	0,5836	0,3183	0,3183	1,1369	1,1205	1,3972	1,2086	1,0886	0,41068	1,19036	2,89850979	1,03E-05
N-acetylleucine	Amino Acid	1,1655	0,8828	1,2131	0,8811	1,0749	1,367	1,3074	1,0511	1,5741	0,9287	1,04348	1,24566	1,19375551	0,17904377
N-acetylmethionine	Amino Acid	0,8415	0,5484	0,825	0,7222	0,7306	1,2018	1,2086	1,1557	1,4926	0,9947	0,73354	1,21068	1,65046214	0,00169883
N-acetylmethionine sulfoxide	Amino Acid	0,8126	0,6495	0,8693	0,7369	0,6781	1,404	1,3291	1,2726	1,4526	1,3576	0,74928	1,36318	1,81931988	4,02E-06
N-acetylphenylalanine	Amino Acid	1,0778	0,7442	0,9095	0,829	0,9385	1,1166	1,2441	1,1609	1,1314	1,0727	0,8998	1,14514	1,27266059	0,00802764
N-acetylproline	Amino Acid	1,1479	1,1241	0,9511	0,9948	1,003	1,0197	1,0381	1,0346	1,2274	1,0652	1,04418	1,077	1,03143136	0,56336781
N-acetylputrescine	Amino Acid	0,9809	0,7866	0,9323	0,9213	1,1367	0,9437	0,9476	0,9347	1,0191	0,9573	0,95156	0,96048	1,00937408	0,885101
N-acetylthreonine	Amino Acid	0,4678	0,4678	0,4678	0,648	0,4678	1,0007	0,8654	1,1921	1,0541	0,9993	0,50384	1,02232	2,02905684	7,80E-05
N-acetyltyrosine	Amino Acid	0,8873	0,3601	0,654	0,457	0,4815	1,5428	1,5231	1,4744	1,8088	1,2527	0,56798	1,52036	2,67678439	7,58E-05
N-acetylvaline	Amino Acid	0,9961	0,7003	0,8994	0,9644	0,9749	1,4683	1,0339	0,9663	1,3429	0,9807	0,90702	1,15842	1,2771714	0,07450521
N-delta-acetylornithine	Amino Acid	1,1848	0,6875	0,8556	1,2311	1,1832	0,8897	1,2133	0,6378	1,0483	1,5393	1,02844	1,06568	1,03621018	0,84726539
N-formylanthranilic acid	Amino Acid	0,983	1,1072	1,0148	0,924	1,0293	1,1139	0,9942	0,8559	1,0893	1,1716	1,01166	1,04498	1,03293597	0,61461533
N-monomethylarginine	Amino Acid	1,1686	1,0081	0,9461	1,0118	1,0534	0,9883	0,9919	1,0337	1,1198	1,1	1,0376	1,04674	1,00880879	0,84747212
N6-acetyllysine	Amino Acid	0,184	0,184	0,184	0,184	0,184	0,8411	0,8439	0,8888	1,0152	0,79	0,184	0,8758	4,75978261	5,47E-05
phenylalanine	Amino Acid	1,124	1,0201	1,0432	1,0384	1,0589	1,0193	1,0431	1,031	1,088	1,1161	1,05692	1,0595	1,00244106	0,92219507
proline	Amino Acid	1,0615	1,0505	1,0001	1,0158	0,9949	0,9927	0,9999	1,0063	1,0716	1,0944	1,02456	1,03298	1,00821816	0,74427001
S-methylmethionine	Amino Acid	1,0005	1,0085	0,8215	0,9995	1,4104	1,2299	1,1038	0,9911	1,1847	1,2055	1,04808	1,143	1,09056561	0,40959418
saccharopine	Amino Acid	1,0321	0,9788	1,0154	0,9846	1,0822	1,0672	1,1009	0,9571	1,1848	1,0465	1,01862	1,0713	1,05171703	0,25176614
serine	Amino Acid	1,0959	0,9533	0,9828	1,0125	0,9961	1,0287	1,0537	0,9981	1,1644	1,1113	1,00812	1,07124	1,06261159	0,13924948
tryptophan	Amino Acid	1,0552	0,9964	0,9678	0,9698	1,053	1,0055	1,0108	1,0087	1,0702	1,1418	1,00844	1,0474	1,03863393	0,27171396
tyramine	Amino Acid	0,7952	0,8528	0,6251	0,9176	0,842	0,6562	0,9307	0,6472	0,9732	0,8582	0,80654	0,8131	1,00813351	0,94013007
tyrosine	Amino Acid	1,2294	1,026	1,001	0,999	0,9302	1,1007	1,1563	1,0081	1,3702	1,1222	1,03712	1,1515	1,11028618	0,18406264
arabonate/xylonate	Carbohydrate	1,1729	0,8812	1,0507	1,0245	1,0817	0,7683	0,9928	1,0072	0,9207	1,1181	1,0422	0,96142	-1,0840216	0,3120413
erythronate*	Carbohydrate	1,1881	1,0539	1,0952	1,115	1,1419	0,9559	1,017	1,0002	1,1275	1,1078	1,11882	1,04168	-1,0740535	0,09268504
fructose	Carbohydrate	0,1146	1,7312	0,0257	1,2054	0,0257	0,2468	0,2192	0,1921	0,1343	0,3085	0,62052	0,22018	-2,8182396	0,3247124
galactitol (dulcitol)	Carbohydrate	1,4706	0,0325	1	1,2755	1,0425	0,6709	1,1254	1,3727	0,0325	1,2692	0,96422	0,89414	-1,078377	0,84612051
galactonate	Carbohydrate	1,1779	0,8372	1,105	1,0001	1,1789	0,6414	0,8904	0,9952	0,8707	1,0157	1,05982	0,88268	-1,2006843	0,09259813
glucose	Carbohydrate	0,1298	1,1057	0,1075	0,7517	0,1075	0,1075	0,1457	0,2443	0,1493	0,3803	0,44044	0,20542	-2,144095	0,32560781
lactate	Carbohydrate	1,1775	1,0848	1,2105	1,1281	1,1801	0,9122	0,9262	1,0074	1,07	0,9872	1,1562	0,9806	-1,179074	0,00151445
maltopentaose	Carbohydrate	0,0119	0,0119	0,0119	0,0123	0,0119	0,0119	0,0119	0,0119	0,0119	0,0119	0,01198	0,0119	-1,0067227	0,37390097
maltotriose	Carbohydrate	0,2632	0,2632	0,2632	0,2632	0,2632	0,2632	0,2632	0,2632	0,2632	0,2632	0,2632	0,2632	-1	2
pyruvate	Carbohydrate	1,1706	1,2522	1,3282	1,0995	1,2212	1,2048	1,1487	1,0007	1,1219	1,0506	1,21434	1,10534	-1,0986122	0,07254645
arabitol/xylitol	Carbohydrate	1,228	0,6427	0,9701	0,6427	0,9222	0,9658	0,9058	1,2533	1	1,3077	0,88114	1,08652	1,23308441	0,17539072

fructose 1,6-diphosphate/glucose 1,6-diphosphate/myo-inositol diphosphates	Carbohydrate	1	0,1986	0,6404	0,4824	0,9056	0,4214	1,2822	1,5068	0,9927	1,3021	0,6454	1,10104	1,70598079	0,09413044
glucuronate	Carbohydrate	1,0083	0,9586	1,0626	0,9994	1,0006	0,9902	0,9733	1,0118	1,054	1,0378	1,0059	1,01342	1,00747589	0,7444315
glycerate	Carbohydrate	1,1554	0,8964	1,011	1,0019	0,9733	1,1051	1,2756	1,1966	1,1782	1,1625	1,0076	1,1836	1,17467249	0,0102688
maltose	Carbohydrate	0,424	0,4707	0,2404	0,5574	0,2891	0,4465	0,3341	0,3768	0,5675	0,3597	0,39632	0,41692	1,0519782	0,78243403
maltotetraose	Carbohydrate	0,6031	0,3501	0,386	0,522	0,3543	0,6664	0,3571	0,1609	0,9833	0,3809	0,4431	0,50972	1,15034981	0,67947593
mannitol/sorbitol	Carbohydrate	1,0454	0,9449	1,0109	1,0218	1,0368	1,0776	0,9846	0,983	1,2238	1,0544	1,01196	1,06468	1,05209692	0,31448366
raffinose	Carbohydrate	1,787	1,0459	0,9251	0,9623	0,9895	1,4937	1,0067	0,9487	1,5413	1,0487	1,14196	1,20782	1,05767277	0,75850796
ribitol	Carbohydrate	1,0072	0,7497	0,981	0,7497	0,9604	0,9928	1,0928	1,3484	1,1192	1,268	0,8896	1,16424	1,30872302	0,01282779
ribonate	Carbohydrate	1,0111	0,8465	0,9566	0,963	1,0209	0,945	0,9169	0,9668	1,0529	1,1199	0,95962	1,0003	1,04239178	0,42859886
ribose	Carbohydrate	1,0794	0,96	1,04	0,7772	0,852	1,1784	1,0733	1,1743	1,0844	1,3415	0,94172	1,17038	1,24281103	0,01560515
sedoheptulose	Carbohydrate	1,066	0,7179	0,4877	0,6589	0,8642	1,1795	1,3365	1,1112	0,9764	1,69	0,75894	1,25872	1,65852373	0,01360922
sucrose	Carbohydrate	2,0338	0,9788	0,0253	0,6534	0,0434	6,5318	5,8872	4,5691	5,181	6,1905	0,74694	5,67192	7,59354165	1,15E-05
gamma-tocotrienol	ofactors and Vitami	1,6364	1,1621	1,1783	1,0528	1,1718	0,8595	0,9642	0,8903	1,1714	0,9676	1,24028	0,9706	-1,2778488	0,05711716
gulonate*	ofactors and Vitami	1,0381	0,8561	0,9255	0,9128	1,0744	0,6496	0,6301	0,9934	0,9178	1,0366	0,96138	0,8455	-1,137055	0,2720135
nicotinamide	ofactors and Vitami	1,1212	1,1445	1,398	0,8727	0,8451	0,8313	1,0781	0,7317	0,9554	0,9534	1,0763	0,90998	-1,1827732	0,20271386
nicotinamide ribonucleotide (NMN)	ofactors and Vitami	0,327	0,327	0,327	0,327	0,327	0,327	0,327	0,327	0,327	0,327	0,327	0,327	-1	2
nicotinamide riboside	ofactors and Vitami	0,4988	0,4988	0,4988	0,4988	0,4988	0,4988	0,4988	0,4988	0,4988	0,4988	0,4988	0,4988	-1	2
nicotinate ribonucleoside	ofactors and Vitami	1,0806	1,0296	0,9746	1,0193	1,0786	1,0081	0,9919	0,8783	1,122	1,0515	1,03654	1,01036	-1,0259116	0,57932692
pyridoxamine	ofactors and Vitami	1,2385	1,0785	0,9965	0,8538	1,0035	0,7849	1,0713	0,7742	0,8701	1,1494	1,03416	0,92998	-1,1120239	0,3240835
pyridoxate	ofactors and Vitami	1,1611	0,9077	1,0767	1,0462	1,0544	0,9773	1,1042	1,0398	0,9996	1,0004	1,04922	1,02426	-1,0243688	0,61054433
pyridoxine (Vitamin B6)	ofactors and Vitami	1,4825	0,7224	1,1405	0,9329	1,0664	1,0607	0,9502	0,3911	0,9809	1,1891	1,06894	0,9144	-1,169007	0,43009484
quinolinate	ofactors and Vitami	1,2692	1,1077	1,264	0,8951	1,2154	0,8772	0,8958	0,9653	0,9502	1,221	1,15028	0,9819	-1,1714839	0,11016278
trigonelline (N'-methylnicotinate)	ofactors and Vitami	1,095	1	0,9826	1,0263	1,0209	0,9804	1,0179	1	1,0647	1,0573	1,02496	1,02406	-1,0008789	0,97232082
gamma-tocopherol/beta-tocopherol	ofactors and Vitami	1,3028	0,8128	1,0116	0,6261	0,9317	0,5552	1,0277	1,2233	1,1538	0,8501	0,937	0,96202	1,02670224	0,88264191
nicotinamide adenine dinucleotide (NAD+)	ofactors and Vitami	2,2908	0,9508	1,4376	1	1,1665	2,6687	1,463	1,3185	1,617	1,2599	1,36914	1,66542	1,21639862	0,43003351
nicotinate	ofactors and Vitami	0,9089	1,0053	0,8693	0,8467	0,9217	0,9639	0,9947	0,8521	0,9866	1,1259	0,91038	0,98464	1,08157033	0,19390318
oxalate (ethanedioate)	ofactors and Vitami	1,2328	0,8164	0,9956	0,7418	1,0428	0,8049	1,1148	1,0233	1,0259	0,9478	0,96588	0,98334	1,01807678	0,86810468
pantothenate	ofactors and Vitami	1,1371	1,0358	1,0629	0,8487	0,9318	1,1225	1,1015	0,9423	1,002	1,1028	1,00326	1,05422	1,05079441	0,43540455
pyridoxal	ofactors and Vitami	1,0105	0,9965	0,9611	1,0433	1,1131	0,9854	0,9832	0,9928	1,1269	1,0662	1,0249	1,0309	1,00585423	0,87968752
thiamin (Vitamin B1)	ofactors and Vitami	1,1079	0,9583	1,0133	1,055	1,0055	0,9943	0,9946	1,0558	1,0054	1,1185	1,028	1,03372	1,0055642	0,8736155
threonate	ofactors and Vitami	1,036	0,964	1,0485	1,0798	1,0259	0,6945	1,1149	0,9218	1,171	1,2703	1,03084	1,0345	1,0035505	0,97350284
alpha-ketoglutarate	Energy	0,8859	1,0048	0,813	0,998	1,002	0,8518	0,842	0,8028	0,9086	1,0898	0,94074	0,899	-1,0464294	0,53315182
phosphate	Energy	1,1785	0,7914	1,0379	0,729	0,9406	0,8382	1,0097	0,9379	0,9381	0,9272	0,93548	0,93022	-1,0056546	0,95364638
succinate	Energy	1,1276	1,0151	0,9707	0,9776	0,9698	1,0037	0,9811	0,9338	1,0233	1,0467	1,01216	0,99772	-1,014473	0,69826066
aconitate [cis or trans]	Energy	1,2215	0,7849	0,7948	0,7857	0,8235	1,1791	0,8497	0,818	1,1082	0,8432	0,88208	0,95964	1,08792853	0,51650657
citrate	Energy	1,4244	0,248	0,4935	0,3962	1,4821	0,2859	1,4428	1,2766	0,5082	0,8862	0,80884	0,87994	1,08790366	0,84209122
fumarate	Energy	1,0156	0,9991	0,9225	0,9732	0,8461	0,9073	1,0009	0,9689	1,0738	1,1249	0,9513	1,01516	1,06712919	0,2314736
malate	Energy	0,8309	0,4631	0,6008	0,6554	0,8684	0,4335	1,0588	1,1074	0,7883	1,1289	0,68372	0,90338	1,32127187	0,19641065
1-linoleoyl-GPC (18:2)	Lipid	1,0154	1,2285	1,0796	1,1615	0,7716	0,8374	0,81	0,9132	1,1372	1,0171	1,05132	0,94298	-1,1148911	0,3086021
1-linoleoyl-GPE (18:2)*	Lipid	1,0057	1,185	1,0825	1,0351	0,7924	0,8042	0,8301	0,9027	1,079	0,9943	1,02014	0,92206	-1,1063705	0,26996727
1-linoleoyl-GPG (18:2)*	Lipid	1,4088	1,1435	0,7473	1,0282	0,7066	0,9763	0,7889	0,8927	1,3475	0,8691	1,00688	0,9749	-1,0328034	0,84946594
1-linoleoyl-GPI (18:2)*	Lipid	1,3583	1,1308	0,7971	0,9983	0,8062	0,9311	0,6984	0,927	1,2655	0,8817	1,01814	0,94074	-1,0822757	0,59508047
1-oleoyl-2-linoleoyl-GPC (18:1/18:2)*	Lipid	1,0404	0,9694	1,2703	0,9786	0,9883	0,7482	0,9043	0,8795	1,0347	1,0474	1,0494	0,92282	-1,1371665	0,14772059
1-oleoyl-GPC (18:1)	Lipid	1,0355	1,1452	1,0706	1,0398	0,7256	0,7797	0,8152	0,8982	1,1176	0,9597	1,00334	0,91408	-1,0976501	0,36979093
1-palmitoleoyl-GPC (16:1)*	Lipid	0,9708	1,197	1,0876	1,2011	0,6817	0,7398	0,811	0,8293	1,089	0,8675	1,02764	0,86732	-1,1848453	0,20105339
1-palmitoyl-2-linoleoyl-GPE (16:0/18:2)	Lipid	0,9685	0,9412	1,2939	0,9146	0,7912	0,8706	0,7081	0,9006	0,8837	1,025	0,98188	0,8776	-1,1188241	0,32371488
1-palmitoyl-2-oleoyl-GPC (16:0/18:1)	Lipid	1,0166	1,0403	1,1046	0,9773	0,9766	0,6886	0,8423	0,9591	1,1415	1,0928	1,02308	0,94486	-1,0827848	0,40810552
1-palmitoyl-2-oleoyl-GPE (16:0/18:1)	Lipid	0,336	0,336	0,336	0,336	0,336	0,336	0,336	0,336	0,336	0,336	0,336	0,336	-1	2
1-palmitoyl-GPC (16:0)	Lipid	1,005	1,192	1,0421	1,0404	0,7365	0,796	0,8137	0,8809	1,1352	0,999	1,0032	0,92496	-1,0845874	0,44620244
1-palmitoyl-GPE (16:0)	Lipid	1,0648	1,1267	1,041	1,05	0,8109	0,8069	0,8909	0,9034	1,1083	0,9727	1,01868	0,93644	-1,087822	0,29828253
1-stearoyl-GPC (18:0)	Lipid	1,0489	1,2245	1,0876	1,0037	0,7223	0,8561	0,7821	0,9109	1,1798	1,0682	1,0174	0,95942	-1,0604323	0,611907
1,2-dilinoleoyl-GPC (18:2/18:2)	Lipid	1,061	0,997	1,1533	0,9876	0,8246	0,7763	0,8738	0,8332	1,0876	1,0043	1,0047	0,91504	-1,0979848	0,28686595
1,2-dioleoyl-GPC (18:1/18:1)	Lipid	1,1354	0,9967	1,3872	0,8983	1,0645	0,8356	0,9151	1,0764	1,2334	1,0792	1,09642	1,02794	-1,0666187	0,54416015
2-hydroxyadipate	Lipid	0,884	0,9057	0,9847	1,0961	1,1187	0,8467	1,1178	0,8698	1,1503	0,9731	0,99784	0,99154	-1,0063538	0,93811244
2-hydroxyglutarate	Lipid	1,0464	0,9113	1,0105	0,9752	0,9732	0,8337	0,8955	0,8713	0,9454	0,9895	0,98332	0,90708	-1,0840499	0,06503983
2-hydroxypalmitate	Lipid	0,8529	1,1518	0,6102	1,1902	1,0422	0,8352	0,8306	1,1008	0,8353	1,1156	0,96946	0,9435	-1,0275146	0,84357342
2-linoleoylglycerol (18:2)	Lipid	0,8877	1,7588	0,6084	0,7073	0,748	0,9437	0,3418	0,8456	0,9936	0,7643	0,94204	0,7778	-1,2111597	0,51675818
3-hydroxy-3-methylglutarate	Lipid	1,2583	0,9048	0,8378	0,9161	0,9768	0,887	0,8894	0,9365	0,9915	0,9365	0,97876	0,92818	-1,0544937	0,53670202
9,10-DiHOME	Lipid	0,9963	1,0057	1,0164	1,0495	1,0037	0,9372	1,0553	0,8305	0,9557	1,0475	1,01432	0,96524	-1,0508475	0,30410442
caprate (10:0)	Lipid	0,635	1,803	0,771	1,8676	1,2245	0,6859	1,8517	0,3524	1,0551	1,0494	1,26022	0,9989	-1,2616078	0,48465203
choline	Lipid	1,085	1,0048	1,0101	1,0352	1,0086	0,9541	0,9915	0,9807	1,0665	1,0447	1,02874	1,0075	-1,0210819	0,43502174
choline phosphate	Lipid	0,8083	0,761	0,7817	0,8776	0,8726	0,7827	0,7773	0,7939	0,8005	0,8848	0,82024	0,80784	-1,0153496	0,69761704
dihomo-linoleate (20:2n6)	Lipid	1,1897	1,1242	1,319	0,9152	0,8411	0,9366	0,893	0,9727	1,2744	0,9824	1,07784	1,01182	-1,0652488	0,56953
glutarate (pentanedioate)	Lipid	1,0092	1,1987	1,4373	1,398	1,1073	0,8737	1,0195	1,1352	1,1699	1,1742	1,2301	1,0745	-1,1448115	0,16467306
glycerol 3-phosphate	Lipid	1,0894	1,1119	1,0508	1,1241	1,2032	0,9252	1,007	1,1496	1,1673	0,993	1,11588	1,04842	-1,0643444	0,25237566
glycerophosphoethanolamine	Lipid	1,3415	1,1455	1,3653	1,1018	1,4908	1,4485	1,1876	1,2484	0,951	1,0091	1,28898	1,16892	-1,1027102	0,3267353
glycerophosphoglycerol	Lipid	1,1182	0,9434	1,1166	1,0049	1,0437	1,0561	0,9976	1,0141	1,0095	1,0068	1,04536	1,01682	-1,0280679	0,45379637
glycerophosphorylcholine (GPC)	Lipid	1,2288	1,1294	1,2289	1,07	1,2458	1,2494	1,1373	1,207	1,0933	1,133	1,18058	1,164	-1,014244	0,71941729
glycosyl ceramide (d18:2/24:1, d18:1/24:2)*	Lipid	0,8749	1,7386	1,2833	1,2808	0,9389	1,3177	0,7717	0,9207	1,4415	0,7903	1,2233	1,04838	-1,1668479	0,42399987
hexadecadienoate (16:2n6)	Lipid	1,0346	0,9168	0,7534	0,9589	0,8337	0,7532	0,8002	0,8545	0,9774	0,9087	0,89948	0,8588	-1,0473684	0,53615184
linoleoyl-linolenoyl-glycerol (18:2/18:3) [1]*	Lipid	1,2222	0,9996	1,0321	0,8965	0,9298	0,8511	0,8053	0,8665	1,3175	0,9867	1,01604	0,96542	-1,0524331	0,65725471
linoleoyl-linolenoyl-glycerol (18:2/18:3) [2]*	Lipid	1,1421	1,0108	1,0157	0,8615	0,9076	0,7377	0,7606	0,8125	1,1851	0,95	0,98754	0,88918	-1,1106188	0,34203418
linoleoyl-linoleoyl-glycerol (18:2/18:2) [1]*	Lipid	1,2995	1,0001	1,0869	0,9526	0,9999	0,916	0,8976	0,8833	1,3108	0,9594	1,0678	0,99342	-1,0748727	0,48557195
malonate	Lipid	1,0256	0,8002	1,0547	0,7537	0,8158	0,7667	0,8458	0,8289	0,9611	0,8679	0,89	0,85408	-1,042057	0,625782
methylmalonate (MMA)	Lipid	0,9369	0,714	0,7216	0,3709	0,5458	0,3709	1,0074	0,3709	0,3709	0,9682	0,65784	0,61766	-1,065052	0,82861291
myo-inositol	Lipid	1,0677	0,9805	1,0605	1,0333	1,0217	0,9901	0,9653	1,028	1,0748	1,0589	1,03274	1,02342	-1,0091067	0,72734005
N-palmitoyl-sphinganine (d18:0/16:0)	Lipid	1,0407	0,9752	1,4975	0,5457	0,9524	0,7878	0,8401	0,9904	1,4934	0,8946	1,0023	1,00126	-1,0010387	0,99594022
oleoyl-linolenoyl-glycerol (18:1/18:3) [2]*	Lipid	1,3351	1,2157	1,1812	0,8611	0,8442	0,8096	0,7462	0,8527	1,6093	1,0798	1,08746	1,01952	-1,0666392	0,7266958
oleoyl-linoleoyl-glycerol (18:1/18:2) [1]	Lipid	1,2511	1,0023	1,0888	0,9302	0,9977	0,9179	0,8714	0,8485	1,3279	0,9932	1,05402	0,99178	-1,0627559	0,56762049
oleoyl-linoleoyl-glycerol (18:1/18:2) [2]	Lipid	1,1919	1,0402	1,0572	0,8643	0,9494	0,8276	0,8803	0,8482	1,2367	0,9718	1,0206	0,95292	-1,0710238	0,48985713
oleoyl-oleoyl-glycerol (18:1/18:1) [1]*	Lipid	1,2874	0,9775	1,1538	1,0007	1,0861	0,9993	0,8741	0,8428	1,4572	0,612	1,1011	0,95708	-1,1504785	0,38098034
oleoyl-oleoyl-glycerol (18:1/18:1) [2]*	Lipid	1,1551	1,0481	1,4351	0,8664	0,9229	0,9178	0,9655	0,8657	1,2908	0,7629	1,08552	0,96054	-1,1301143	0,38039732
oleoyl ethanolamide	Lipid	1,0158	1,1971	0,9984	1,1052	0,8448	0,9519	0,8822	0,8846	1,2616	1,0016	1,03226	0,99638	-1,0360104	0,70507124
palmitoyl-linoleoyl-glycerol (16:0/18:2) [1]*	Lipid	1,2098	0,9661	1,0819	0,91	1,0207	0,9035	0,8827	0,8517	1,2838	0,9793	1,0377	0,9802	-1,0586615	0,56103911
palmitoyl-linoleoyl-glycerol (16:0/18:2) [2]*	Lipid	1,1462	1,0383	1,0669	0,8903	0,9308	0,8328	0,866	0,8642	1,1903	0,965	1,0145	0,94366	-1,0750694	0,40622207
palmitoyl-oleoyl-glycerol (16:0/18:1) [1]*	Lipid	1,2036	0,9529	1,0714	0,9531	1,0897	0,9435	0,9076	0,8343	1,3906	0,9267	1,05414	1,00054	-1,0535711	0,64384692
palmitoyl-oleoyl-glycerol (16:0/18:1) [2]*	Lipid	1,1378	1,0717	1,1185	0,9298	0,9852	0,8848	0,9679	0,8469	1,2859	0,9934	1,0486	0,99578	-1,0530438	0,56556983
palmitoyl-palmitoyl-glycerol (16:0/16:0) [2]*	Lipid	1,0503	1,076	1,1684	0,8574	0,8434	0,838	1,158	0,9257	0,933	0,951	0,9991	0,96114	-1,0394948	0,65976985
phytosphingosine	Lipid	1,142	1,6092	1,1178	1,2147	0,8373	0,8272	0,8667	0,8661	1,3171	1,0576	1,1842	0,98694	-1,1998703	0,24011356
sphingadienine*	Lipid	1,0348	1,1066	1,0353	1,096	0,8346	0,8677	0,8582	0,9684	1,0537	1,0337	1,02146	0,95634	-1,0680929	0,33764096
sphinganine	Lipid	1,0914	1,1646	1,0625	1,0007	0,8239	0,8489	0,8476	0,9163	1,1611	0,9705	1,02862	0,94888	-1,0840359	0,35694886
sphingosine	Lipid	1,0333	1,0752	1,0686	1,0295	0,8002	0,7534	0,8614	0,9051	1,0147	0,8922	1,00136	0,88536	-1,1310201	0,11882471
tetradecanedioate	Lipid	1,1139	1,1155	1,3669	0,5802	1,3302	1,0942	0,9287	1,2659	0,5802	0,5802	1,10134	0,88984	-1,2376832	0,31289956
linolenate [alpha or gamma; (18:3n3 or 6)]	Lipid	1,2186	0,9955	0,8318	0,9744	0,8486	0,9892	0,8792	0,9623	1,0418	1,028	0,97378	0,9801	1,00649017	0,93602846
1-linoleoylglycerol (18:2)	Lipid	1,5419	0,9281	0,7158	0,8987	0,8996	1,0043	0,8036	0,7122	1,7251	0,7906	0,99682	1,00716	1,01037299	0,96584347
1-oleoyl-GPE (18:1)	Lipid	1,5217	1,2579	0,5207	0,8298	0,9921	0,7543	1,1124	0,9067	1,6794	0,9414	1,02444	1,07884	1,05310218	0,82321335
1-oleoyl-GPG (18:1)*	Lipid	1,6638	1,4181	0,7546	0,8868	0,759	1,2409	1	1,1178	1,9856	0,9363	1,09646	1,25612	1,14561407	0,56554719

1-oleoylglycerol (18:1)	Lipid	0,8558	1,0093	0,7619	0,6636	0,7992	0,8443	1,1191	0,7637	0,9907	1,9098	0,81796	1,12552	1,37600861	0,21329515
1-palmitoyl-GPG (16:0)*	Lipid	1,5448	1,2734	0,7997	1,0023	0,8391	1,243	0,8587	0,9223	1,5908	0,8957	1,09186	1,1021	1,00937849	0,96012739
1-palmitoyl-GPI (16:0)	Lipid	1,4135	1,1587	0,7175	0,8409	0,9174	1,3177	0,8671	0,6537	1,5915	0,9055	1,0096	1,0671	1,05695325	0,7918413
1-palmitoylglycerol (16:0)	Lipid	0,9799	0,986	0,6992	0,6751	0,6734	0,7747	1,014	0,7512	0,9139	1,551	0,80272	1,00096	1,24696033	0,27061432
12,13-DiHOME	Lipid	0,9855	1,0015	0,9985	1,1403	1,0438	1,0674	1,0964	0,8646	1,0108	1,1927	1,03392	1,04638	1,01205122	0,84517444
13-HODE + 9-HODE	Lipid	1,006	1,034	0,9699	1,0326	1,0039	0,9719	1,0555	0,982	0,9961	1,1162	1,00928	1,02434	1,01492153	0,63059816
13-HpODE/9-HpODE	Lipid	1,1845	1,1682	0,9436	0,9157	1,0243	1,1942	1,1651	1,0174	1,1823	1,0752	1,04726	1,12684	1,07598877	0,26553353
2-hydroxybehenate	Lipid	1,3927	0,7421	0,8439	0,699	0,8355	0,9946	0,8537	0,8771	1,3826	1,0002	0,90264	1,02164	1,1318355	0,47304379
2-hydroxystearate	Lipid	1,0463	1,0205	0,8631	0,8446	0,9165	1,1219	0,9651	0,9337	1,2183	0,8366	0,9382	1,01512	1,08198678	0,36882708
2-oleoylglycerol (18:1)	Lipid	0,7083	0,5907	0,2939	0,2939	0,2939	0,3591	1,6547	0,5691	0,4182	1,7945	0,43614	0,95912	2,19911038	0,17573925
2-palmitoyl-GPC (16:0)*	Lipid	1,5046	1,005	0,824	0,92	0,8154	1,3793	0,995	0,8918	1,529	0,8624	1,0138	1,1315	1,11609785	0,54491521
3-hydroxyoctanoate	Lipid	1,3034	0,9157	0,9882	1,0106	0,9237	1,1223	0,8845	0,7486	1,4643	0,9894	1,02832	1,04182	1,01312821	0,92682386
3-methylglutarate/2-methylglutarate	Lipid	0,9745	1,0181	0,9483	0,9819	1,1196	1,1173	0,7955	1,1108	1,6087	1,2672	1,00848	1,1799	1,16997858	0,26779498
acetylcholine	Lipid	0,9264	0,8267	0,9682	0,8299	0,8382	0,9528	1,0038	1	1,0587	0,9569	0,87788	0,99444	1,13277441	0,0126683
azelate (nonanedioate)	Lipid	1,0589	0,9931	0,9872	1,0688	1,1152	1,2421	0,9041	0,9805	1,0726	1,0612	1,04464	1,0521	1,00714122	0,90764289
carnitine	Lipid	0,9137	0,8481	1,0407	0,9578	0,9207	0,9584	1,0269	0,8946	1,0618	0,9148	0,9362	0,9713	1,03749199	0,45741064
deoxycarnitine	Lipid	1,0946	0,9204	0,8229	1,3453	1,0687	1,116	1,1937	1,0345	1,3059	1,478	1,05038	1,22562	1,16683486	0,1759277
diacylglycerol (16:1/18:2 [2], 16:0/18:3 [1])*	Lipid	1,1867	0,9282	1,1258	0,8913	0,8623	0,8322	0,9318	0,8848	1,3677	1,0771	0,99886	1,01872	1,01988267	0,8695684
eicosenoate (20:1)	Lipid	1,4003	1,0386	0,678	0,9253	0,923	1,1652	0,871	0,991	1,2617	0,8612	0,99304	1,03002	1,03723918	0,80215158
glycerol	Lipid	0,9733	0,5898	0,6015	0,4697	0,5649	1,9144	1,1819	1,1781	1,5947	1,644	0,63984	1,50262	2,34843086	0,00154734
glycerophosphoinositol*	Lipid	1,1017	1,1008	1,0822	0,8944	0,9838	1,0508	1,024	1,1099	1,0514	1,0162	1,03258	1,05046	1,01731585	0,70067249
linoleate (18:2n6)	Lipid	1,123	1,0108	0,8061	1,002	0,8409	0,942	0,8765	0,9751	1,1166	0,993	0,95656	0,98064	1,02517354	0,74311042
linoleoyl ethanolamide	Lipid	1,1593	0,9716	0,7752	0,9237	0,8979	1,0785	1,0641	0,7966	1,1905	1,021	0,94554	1,03014	1,08947268	0,374715
maleate	Lipid	1,0717	1,1405	1,0578	0,907	0,9363	0,9864	0,8725	1,1304	1,1901	1,377	1,02266	1,11128	1,08665637	0,39656363
myristoleate (14:1n5)	Lipid	1,1114	0,7568	0,9059	0,8108	0,5958	0,7364	0,656	1,0086	0,7502	1,3115	0,83614	0,89254	1,06745282	0,71314868
oleate/vaccenate (18:1)	Lipid	1,2396	1,0098	0,8351	0,9649	0,8306	0,9611	0,8938	0,9722	1,2921	0,9132	0,976	1,00648	1,03122951	0,77773876
palmitate (16:0)	Lipid	1,0067	0,9854	0,8655	0,9933	0,8952	1,0572	0,8954	0,894	1,138	0,9295	0,94922	0,98282	1,03539748	0,57410771
palmitoleate (16:1n7)	Lipid	1,065	1,0493	0,9028	0,9932	0,8567	0,979	0,9213	0,9451	1,0903	0,9646	0,9734	0,98006	1,006842	0,89787184
palmitoyl ethanolamide	Lipid	0,3116	0,5534	0,8068	1,4032	0,7873	1,2936	0,3116	0,3116	1,7916	0,5093	0,77246	0,84354	1,09201771	0,84482406
pelargonate (9:0)	Lipid	0,9774	0,6742	1,4341	0,6742	1,273	1,0699	1,4521	1,737	0,9742	1	1,00658	1,24664	1,23849073	0,29662346
stearoyl-linoleoyl-glycerol (18:0/18:2) [2]*	Lipid	1,2779	0,9843	0,4587	0,8684	1,0157	0,8325	0,779	0,8214	1,1742	1,0332	0,921	0,92806	1,00766558	0,96473201
trans-nonadecenoate (tr 19:1)*	Lipid	0,8166	0,5832	0,7147	0,6037	0,4538	0,8168	0,8087	0,6045	1	0,5993	0,6344	0,76586	1,20721942	0,21448365
2'-deoxyadenosine	Nucleotide	1,1888	1,259	0,9446	1,226	0,9806	1,0766	0,8486	0,8545	1,0905	1,0931	1,1198	0,99266	-1,1280801	0,18346321
2'-deoxyguanosine	Nucleotide	1,0057	0,4119	0,7496	0,8819	0,7655	0,8498	0,6086	0,5465	0,5033	0,5971	0,76292	0,62106	-1,2284159	0,26311952
2'-deoxyinosine	Nucleotide	0,426	0,426	0,426	0,426	0,426	0,426	0,426	0,426	0,426	0,426	0,426	0,426	-1	2
2'-O-methyluridine	Nucleotide	1,4288	0,9251	1,0831	1,1242	1,0399	0,6919	1,006	0,7004	1,0615	0,8311	1,12022	0,85818	-1,3053439	0,05006147
3-ureidopropionate	Nucleotide	0,0335	0,0335	0,0335	0,0335	0,0335	0,0335	0,0335	0,0335	0,0335	0,0335	0,0335	0,0335	-1	2
7-methylguanine	Nucleotide	1,0708	0,9734	0,9151	1,0928	1,0213	1,0171	0,9275	0,9543	1,019	1,1388	1,01468	1,01134	-1,0033025	0,94708572
adenosine	Nucleotide	0,729	1,0861	0,5689	0,7963	0,4846	0,3474	0,3408	0,3308	0,4293	0,3871	0,73298	0,36708	-1,9967854	0,02352945
adenosine 5'-monophosphate (AMP)	Nucleotide	1,6924	1,4091	1,4674	1,7111	1,4112	1,1274	1,2557	1,301	1,3956	1,337	1,53824	1,28334	-1,1986223	0,01659363
allantoin	Nucleotide	0,8591	1,0072	1,0246	1,0654	0,9746	0,7077	0,7021	1,224	0,9964	1,2169	0,98618	0,96942	-1,0172887	0,89525564
cytidine	Nucleotide	1,2768	0,8204	1,0522	1,1129	0,8845	0,4527	0,7507	0,9049	0,9283	0,8741	1,02936	0,78214	-1,3160815	0,07343996
cytidine 2',3'-cyclic monophosphate	Nucleotide	1,3462	1,1368	1,2724	1,287	1,2023	1,5157	1,0746	1,0478	1,1324	1,0567	1,24894	1,16544	-1,0716468	0,42159462
cytosine	Nucleotide	1,1013	0,9714	1,0704	0,9148	0,9865	0,9183	0,9336	0,9772	1,0135	0,9211	1,00888	0,95274	-1,0589248	0,1954908
dihydroorotate	Nucleotide	1,4386	1,0584	1,599	1,4373	0,9977	1,0974	1	0,9263	0,9718	1,0367	1,3062	1,00644	-1,2978419	0,06199096
guanine	Nucleotide	1,3007	1,2677	1,2661	1,1753	1,3389	1,3579	1,2204	1,1808	1,3449	1,2415	1,26974	1,2691	-1,0005043	0,98884766
guanosine	Nucleotide	1,4825	0,8601	1,1353	1,181	0,9165	0,8598	0,9506	0,9266	1,02	1,0203	1,11508	0,95546	-1,1670609	0,22717968
guanosine-2',3'-cyclic monophosphate	Nucleotide	1,792	0,8475	1,1433	1,1097	0,9655	1,5631	1,1603	0,9581	1,2053	0,9568	1,1716	1,16872	-1,0024642	0,98879313
guanosine 3'-monophosphate (3'-GMP)	Nucleotide	1,5843	1,079	0,9463	1,3672	1,1226	1,082	1,1693	0,9497	1,2366	1,1951	1,21988	1,12654	-1,0828555	0,48438683
hypoxanthine	Nucleotide	1,0822	0,9441	1,0027	1,0128	0,9973	0,886	0,831	0,8386	0,9263	0,9412	1,00782	0,88462	-1,1392688	0,00437762
inosine	Nucleotide	0,5806	0,44	0,6309	0,7353	0,5952	0,2299	0,4311	0,4983	0,5639	0,4126	0,5964	0,42716	-1,3961981	0,05115105
N6-succinyladenosine	Nucleotide	1,5519	0,9477	1,0411	1,1632	1,1617	1,3104	1,0443	1,1572	1,3457	0,9517	1,17312	1,16186	-1,0096914	0,93206237
orotate	Nucleotide	1,1181	0,9612	0,9846	1,0384	1,0248	1,037	0,9845	0,9535	1,0801	0,9727	1,02542	1,00556	-1,0197502	0,59238686
uridine	Nucleotide	1,2536	1,0676	0,9312	0,8632	0,7015	0,3801	0,7278	0,7004	0,8253	0,7542	0,96342	0,67756	-1,4218962	0,04720149
uridine 5'-monophosphate (UMP)	Nucleotide	1,3452	0,7887	1,32	1,0956	1,1044	1,3893	1	0,7359	0,8617	0,6192	1,13078	0,92122	-1,2274809	0,24653935
1-methyladenine	Nucleotide	1,1726	0,9715	1,0172	1,0067	0,8681	1,0241	0,9933	0,9482	1,0649	1,0478	1,00722	1,01566	1,0083795	0,87978715
adenine	Nucleotide	1,3283	1,2368	1,2068	1,2303	1,2428	1,2373	1,2693	1,2141	1,3179	1,2911	1,249	1,26594	1,01356285	0,5594228
adenosine-2',3'-cyclic monophosphate	Nucleotide	1,359	0,6233	1,0425	1,1309	0,8835	1,8886	1,0687	0,9501	1,1333	0,8328	1,00784	1,1747	1,16556199	0,47852441
adenosine 3'-monophosphate (3'-AMP)	Nucleotide	1,516	1,085	0,8319	0,9582	0,912	1,1165	1,1324	1,2053	1,2002	1,0517	1,06062	1,14122	1,07599329	0,54878757
allantoic acid	Nucleotide	1,0487	0,8603	0,6053	1,1138	1,0383	0,9078	0,8062	1,1091	1	1,1039	0,93328	0,9854	1,05584605	0,64756305
beta-alanine	Nucleotide	0,982	0,917	0,9523	0,8903	0,9077	0,8508	0,9137	0,9306	1,018	0,9427	0,92986	0,93116	1,00139806	0,96832251
pseudouridine	Nucleotide	1,1112	1,1262	1,0027	0,9192	0,9536	0,8999	1,4777	1,2734	0,9973	1,1733	1,02258	1,16432	1,13861018	0,25141284
uracil	Nucleotide	2,9752	2,9363	2,5617	2,5172	2,9212	3,272	3,1914	2,7828	3,1426	2,8939	2,78232	3,05654	1,09855804	0,07955209
urate	Nucleotide	0,8974	0,8549	0,6849	0,7435	0,7148	0,5169	0,8376	0,7877	0,9582	1,0418	0,7791	0,82844	1,06332948	0,63641045
uridine-2',3'-cyclic monophosphate	Nucleotide	1,5094	0,9842	1,0309	1,1329	1,0158	1,1845	1,2681	1,2447	1,1143	1,1006	1,13464	1,18244	1,0421279	0,66108158
xanthine	Nucleotide	0,9085	0,9223	0,9667	0,9931	0,9054	0,9911	0,9807	0,941	1,0408	1,043	0,9392	0,99932	1,06401193	0,04956226
gamma-glutamylleucine	Peptide	1,2246	0,8274	1,1882	1,0318	1,0783	1,0921	1,0018	1,128	1,0512	0,9895	1,07006	1,05252	-1,0166648	0,82384899
gamma-glutamylphenylalanine	Peptide	1,5524	0,7864	1,0201	0,9629	1,1383	0,9556	1,0213	1,0661	1,1322	0,9056	1,09202	1,01616	-1,0746536	0,59795099
gamma-glutamylalanine	Peptide	1,0801	1,0689	0,9283	0,9862	1,126	0,9595	1,0586	1,0439	1,1365	1,0451	1,0379	1,04872	1,0104249	0,8174162
gamma-glutamyltyrosine	Peptide	1,7456	0,8704	0,8446	0,6599	0,9662	1,0892	1,1463	1,0338	1,1885	1,2191	1,01734	1,13538	1,11602807	0,5694003
gamma-glutamylvaline	Peptide	1,0354	1,1092	0,8446	1,098	1,3462	0,9694	1,0245	0,7986	1,4257	1,4036	1,08668	1,12436	1,03467442	0,8065167
4-hydroxyhippurate	Xenobiotics	0,1977	0,1977	0,1977	0,1977	0,1977	0,1977	0,1977	0,1977	0,1977	0,1977	0,1977	0,1977	-1	2
carotene diol (1)	Xenobiotics	0,9326	1,1278	1,0847	0,9745	0,9002	0,7413	0,8974	0,892	1,0436	1,0044	1,00396	0,91574	-1,0963374	0,23553706
carotene diol (3)	Xenobiotics	0,9277	1,0283	1,0858	0,9901	0,8052	0,6156	0,9256	1,0191	0,8315	1,022	0,96742	0,88276	-1,0959038	0,3762776
diaminopimelate	Xenobiotics	0,9301	1,0576	0,9163	1,0399	1,4326	0,7743	0,6763	0,8273	1	1,0556	1,0753	0,8667	-1,2406831	0,11618712
N-propionylmethionine	Xenobiotics	1,3064	0,9681	1,4861	1,1378	1,1758	0,1405	0,0826	0,1324	0,1066	0,1427	1,21484	0,12096	-10,04332	0,00019124
O-sulfo-L-tyrosine	Xenobiotics	1,1441	1	1,1127	1,0722	1,0199	0,8702	1,0021	1,0644	1,2075	0,9741	1,06978	1,02366	-1,045054	0,48537384
stachydrine	Xenobiotics	1,1315	1,0429	0,9871	1,0339	1,0385	0,9986	0,9929	0,963	1,191	1,0353	1,04678	1,03616	-1,0102494	0,82713955
theanine	Xenobiotics	1,0519	0,9977	0,9517	1,0328	1,0023	0,9314	1,017	0,9299	1,1012	1,0451	1,00728	1,00492	-1,0023484	0,9516864
thioproline	Xenobiotics	1,1296	0,9181	0,8971	1,0819	1,0503	0,9733	0,9949	1,0051	1,0481	1,0541	1,0154	1,0151	-1,0002955	0,99530625
2-oxindole-3-acetate	Xenobiotics	0,9988	1,065	0,9255	1,003	1,0207	0,9707	1,028	1,0012	1,1225	1,0898	1,0026	1,04244	1,03973668	0,30174442
2,3-dihydroxyisovalerate	Xenobiotics	0,9842	0,7748	0,9836	1,1137	0,9129	0,8611	0,725	0,9919	1,1598	1,0946	0,95384	0,96648	1,0132517	0,89903467
3-deoxyoctulosonate	Xenobiotics	1,0296	1,0415	0,9484	0,8506	0,9819	1,0596	0,9972	0,9257	1,0028	1,0117	0,9704	0,9994	1,02988458	0,49774824
4-hydroxybenzoate	Xenobiotics	1,2845	0,9506	0,8983	0,9184	0,9567	1,2211	0,9564	0,9473	1,2668	1,0153	1,0017	1,08138	1,07954477	0,44208154
4-hydroxycinnamate	Xenobiotics	1,6693	1,1014	1,033	0,9174	0,9854	1,3734	1,1651	1,0146	1,2822	0,9589	1,1413	1,15884	1,01536844	0,91408933
beta-cryptoxanthin	Xenobiotics	1,0212	0,8316	0,4959	0,4549	0,838	0,5463	1,3002	1,2362	0,7314	0,9788	0,72832	0,95858	1,31615224	0,24089934
beta-guanidinopropanoate	Xenobiotics	1,5519	0,9748	0,9454	1,1276	0,5911	0,6596	1,0988	0,9166	1,3572	1,2439	1,03816	1,05522	1,01643292	0,93376308
carotene diol (2)	Xenobiotics	0,8213	1,0121	0,9476	0,8309	0,8961	0,6405	1,007	0,9062	0,9991	1,0521	0,9016	0,92098	1,02149512	0,82189823
epsilon-caprolactam	Xenobiotics	1,2192	0,9169	0,8828	1,0815	0,8137	0,9153	1,0274	0,9048	0,8008	1,4264	0,98282	1,01494	1,03268147	0,81403352
ergothioneine	Xenobiotics	1,107	1,1005	0,7356	0,8685	0,948	0,9522	1,1173	1,0183	0,7472	0,9796	0,95192	0,96292	1,01155559	0,90902045
erythritol	Xenobiotics	1,0344	1,059	1,0619	1,1411	1,1086	0,9839	1,1072	1,1069	1,0161	1,3049	1,081	1,1038	1,02109158	0,71585995
gluconate	Xenobiotics	1,0658	0,2772	0,3517	0,7111	0,3998	0,9342	1,1957	1,2488	1,0699	1,8398	0,56112	1,25768	2,24137439	0,01150106
methyl-4-hydroxybenzoate	Xenobiotics	1,0434	1,0441	0,9735	1,0005	0,9749	1,0311	0,9995	0,9781	1,0281	1,0924	1,00728	1,02584	1,01842586	0,47706856
quinate	Xenobiotics	1,0048	0,9867	1,018	1,0545	1,0213	0,944	0,9952	0,9403	1,15	1,0647	1,01706	1,01884	1,00175014	0,96742627
salicylate	Xenobiotics	1,1754	0,5037	1,0116	0,3088	0,6482	1,1692	0,9695	1,024	1,1379	0,6339	0,72954	0,9869	1,35277024	0,21293494
sulfate*	Xenobiotics	1,0906	0,9854	0,9877	0,8575	0,8698	1,0922	0,9944	0,9068	1,0555	0,8764	0,9582	0,98506	1,02803173	0,66532104

Table S3

Table S4. Primers, Related to Figures 1, 2, 4, 5. List of DNA oligonucleotide primers used in this study.

Name	DNA sequence (5'-3')	Annealing t°	Reference
ackA_F	TAAGACGCAAGATACCCGTG	62	This study
acka_R	ACGCACAATCATCAGCTCTT	62	This study
int1_F	TTTAAAACATCGGCTACGGAAG	63	This study
int1_R	TTATTTATCGCCCGCCAAGA	62	This study
cheY_F	CTCGCTCGTGATGTCTTACT	59	This study
cheY_R	TAACAGCACTAGCCACGTTC	60	This study
adhE_F	GGCTCCCTTAATTCACAAAGG	62	This study
adhE_R	ATCCTTGAAAGCTAACCGGG	63	This study
int2_F	AGCGATATCCTCCTGTGAAC	60	This study
int2_R	CGCGTTGTGCTAGCTAATTT	61	This study
lp_0055_F	GCCATGTGTGTAAACGTGTC	61	This study
lp_0055_R	GTGATCCAAGGGGTCCAAAT	62	This study
pstB_F	AAGACAATTAAGGACGGTTCAC	60	This study
pstB_R	TGGTCGATAAGCCACATTCTT	62	This study
lp_0797_F	ATTTTCCAAAGTGTGATTCGGT	63	This study
lp_0797_R	ACTTTCGATCATTCGTTCAGC	63	This study
lp_1258_F	GGCGTTAACGGATGAATCTAA	62	This study
lp_1258_R	GACCTTGTTCTCCGCAGT	60	This study
int3_F	TTCTTCACACTTGGTTTTTCGT	62	This study
int3_R	GCGAATGTCATAGTCGGAGA	62	This study
int4_F	GACGATTAGACTAGTCGCGG	61	This study
int4_R	CATTCAAGCTGATATTGTCGGT	62	This study
lp_0197_F	CCGCCATGTTGACATTGATT	63	This study
lp_0197_R	CGTTGTGCTAGATGATTGGG	63	This study
ackA2_F	GTGAAATCACTGGGGTTGGT	63	This study
ackA2_R	ACCATGATCAAAAGCCGTGA	65	This study
int5_F	CAACGCAGAAGTTACATGCT	60	This study
int5_R	GCAATCCTGCGTTCATCATC	62	This study
int6_F	GTTCGACGTTATTTCACGGAT	62	This study
int6_R	CATCACGAATAGGTGCCAAA	63	This study
16S_UniF	GTGSTGCAYGGYTGTCGTCA	70	(Packey et al., 2013)
16S_UniR	ACGTCRTCCMCACCTTCCTC	68	(Packey et al., 2013)
ackA_NIZO	CGAACGTGTCACTAAAGCCTT	63	This study
ackA_FlyG2	GCGAACGTGTCACTAAAGTAGG	62	This study
ackA_R_RT	CACGCACAATCATCAGCTCT	63	This study

Table S4

Table S5. Plasmids used in this work, Related to Figure 3. List of plasmids used to engineer *Lp*^{NIZO2877}with CRISPR-Cas9.

Plasmid	Description	Resistance	Source	Stock
pJP005	RecT protein under a nisin-inducible promoter, without nisR and nisK genes	Cm	(Van Pijkeren and Britton, 2012)	CB651
pMSP3545	Gram-positive bacterial shuttle vector for nisin-controlled inducible expression	EmR	Addgene CN#46888	pCB574
pCas9	Plasmid containing Streptococcus pyogenes Cas9 and its tracrRNA	Amp	Addgene CN# 42876	pCB339
p3545Cas9	Shuttle vector containing S. pyogenes Cas9 and its tracrRNA	EmR	This work	pCB577
p3545Cas9+RSR	Shuttle vector containing S. pyogenes Cas9, tracrRNA, and a repeat-spacer-repeat array for targeting	EmR	This work	pCB578
p3545Cas9+ackA_G2 target	Cas9 shuttle vector targeting the acetate kinase gene in NIZO.G2	EmR	This work	pCB579
PJP005_NIZO ackA	pJP005 vector with repair template for the ackA target	Cm	This work	CB711

Table S5

Table S6. Oligonucleotides used to engineer *Lp*^{NIZO2877} with CRISPR-Cas9, Related to Figure 3.

Shorthand	Name	Sequence
oRL1	pCas9.Gibson.fwd	GATGATAAGCTGTCCAAACATGAGAATTCCTTACGAAATCATCCTGTGGAGCTTAG
oRL2	pCas9.Gibson.rev	ATTTTTAGGATAACTTCTGCCCCACCTTTTTCAGTCACCTCCTAGCTGACTC
oRL3	pMSP3545.Gibson.fwd	ATTGATTTGAGTCAGCTAGGAGGTGACTGAAAAAGGTGGGGCAGAAGTTATCCTAA
oRL4	pMSP3545.Gibson.rev	CCTACTAAGCTCCACAGGATGATTTCGTAAGGAATTCTCATGTTTGGACAGCTTATCATCG
oRL5	gBlockRSR.Gibson.fwd	TTGGTTCAAAGAAAGCTTGAGCTCTCGAGTCAGGGGTACCGATCA
oRL6	gBlockRSR.Gibson.rev	GGAGGCACTCACCATGGGTACTGCAAATGTCTGCAATGAGTTGATCGC
oRL7	Acet.Kin.pJP005.f	ATTTACTAGTGTTTTTTTCATCATGATCGCCTC
oRL8	Acet.Kin.pJP005.r	TCGCGAGCTCACAACGCATCTATCAGGAAG
oRL9	pJP005.seq.rev	TGATTGTTCTATCGAAAGCGAA
oRL10	pJP005.seq.fwd	AATTGCTAGAAGGATTTCAAAAGTC
oRL11	AcetKin.Outer.fwd	GGAGGAGGACAGCAAAGCC
oRL12	AcetKin.Outer.rev	TGCGCGTCAAAACGTTTGTTGTT
oRL13	G2.Reversion.sgRNA.fwd	CCACCGCGAACGTGTCACTAAAGTGTTTTAGAGCTATGCTGTTTTGAATGGTCCCAAAACATCGATCGAAGC
oRL14	G2.Reversion.sgRNA.rev	GGCCGCTTCGATCGATGTTTTGGGACCATTCAAAACAGCATAGCTCTAAAACACTTTAGTGACACGTTCGCGGTGGAT

Table S6