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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Microsoft Excel Version 2311 was used to collect data.
Data analysis	Data was analyzed using Graphpad Prism 10.1.1, 10.1.2, or 10.5.0. Affinity Designer v2.6 was used for illustrations in Figure 6 and Supplementary Figure 1

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The sequencing data generated in this study from Mu208 grown in fosfomycin have been deposited in NCBI SRA: SAMN49513011 [https://www.ncbi.nlm.nih.gov/sra?LinkName=biosample_sra&from_uid=49513011]. Mu208 reference genome sequences are available at NCBI: GCF_048016555.1 [https://www.ncbi.nlm.nih.gov/datasets/genome/GCF_048016555.1/]. The copy number variation data associated with sequencing are provided in Supplementary Data 1. Source data are provided with this paper. Materials are available upon request to David S. Weiss.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	A priori sample size calculators were not used. Instead, preliminary data from this study other previous studies in our laboratory indicated that for most experiments using agar antibiotic selection, 2-3 independent experiments with 2-3 biological replicates is suitable for the magnitude of phenotypes and to ensure reproducibility. For experiments with antibiotic selection in broth, there is greater inherent variability because of subpopulations and occasionally the cultures fail to grow; thus these types of experiments generally require more biological replicates per experiment. Sample size for mice were based on previous infections with Enterobacter Mu208.
Data exclusions	No data was excluded from these studies
Replication	Certain key experimental findings (Mu208 HR, phenotypes of gene deletions, metabolite addition) were replicated by another 1-2 individuals to confirm reproducibility. Experiments with STZ and Lepob mice were completed by two individuals separately. In gerneral bacteriological experiments, independent experiments used independent streaks from bacterial glycerol stocks, independent antibiotic preparations, independent agar plate preparation, etc.
Randomization	For bacterial cultures, individual colonies from agar plates were selected randomly to inoculate broth. Otherwise, randomization does not apply to the bacteriological experiments in this study. Mice were selected randomly for infection strain, fosfomycin treatment or control groups.
Blinding	For certain replication experiments, individuals were blinded to bacterial genotype. Otherwise, blinding experimenters to conditions is not reasonable for bacterial culture experiments or murine treatment experiments.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	~8 week old Mus musculus strain C57BL/6J, ~10 week old Mus musculus strain C57BL/6J (for Streptozocin experiments), and ~8 week old Mus musculus strain C57BL/6JB6.Cg-Lepob/J heterozygous and homozygous were from Jackson Laboratory. Mice were housed under specific-pathogen-free conditions in filter-top cages at Emory National Primate Center, Emory University, and provided food and water ad libitum. The vivarium was maintained at 72°F at 30-70% (optimally 40-50%) relative humidity under 12 hour x 12 hour light/dark cycle.
Wild animals	N/A
Reporting on sex	Female mice were used for survival experiments, while male mice were used models of diabetes, as described in the methods and figure legend. "Male mice are the standard for STZ induced diabetes and only Jackson Laboratory data from male mice were available41", "Male mice were selected because they more reliably experience hyperglycemia42"
Field-collected samples	N/A
Ethics oversight	All experiments were conducted in compliance with approved protocols and guidelines of the Emory University Institutional Animal Care and Use Committee (IACUC) protocol #201700106.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*