nature research

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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	LCMS: Agilent Technologies 6130 LCMS HRMS: HP 1100 MSD Next Generation Sequencing: Illumina NextSeq500 and BaseSpace™ Sequence Hub NMR: Agilent/Varian VNMRS two-channel 500 MHz , Agilent VNMRS four-channel, dual receiver 700 MHz spectrometer ITC: Microcal VP-Isothermal Calorimeter GE healthcare (serial no:05.00.144)
Data analysis	LCMS: Agilent MassHunter Analytica Studio Reveiwer, MassHunter Qualitative Analsysis Previously published MatLab Scripts for determining reaction rate k based on LCMS results R v3.5.2, edgeR v3.24.0, limma v3.38.0 for plotting and statistical analysis of deep sequencing data. BaseSpace™ Sequence Hub and previously published MatLab / Python scripts for parsing of deep-sequencing data ITC curves: Origin 5,using single binding site curve fitting method

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Provide your data availability statement here.

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	Sample sizes were not determined in advance. Sample sizes were chosen to sufficiently show the variation in the data.
Data exclusions	NGS Reads that could not be mapped to specific DNA-barcodes or their neighbors (Hamming distance = 1) were excluded from all of the the analyses. DNA barcodes that exhibited only singleton and zero copies in all test and reference sets were excluded from the differential enrichment analysis.
Replication	Number of replicates for each plotted data is provided in the figure legend.
Randomization	No randomization was used since it was not relevant for the types of studies performed.
Blinding	No blinding was used during the data collection/analysis. Blinding was not relevant for the types of studies performed.

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
☐	☒	Animals and other organisms
☒	☐	Human research participants
☒	☐	Clinical data

Methods

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

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Species: Mouse, Strain: C57BL/6J, Host strain:Naive mice of above strain, Donor strain: Do not apply as naive mice were used in this study Sex: female Age: 6-12 weeks
Wild animals	n/a
Field-collected samples	n/a
Ethics oversight	All the procedures and experiments using a protocol approved by the Health Sciences Laboratory Animal Services (HSLAS),

Ethics oversight	University of Alberta and according to Canadian Council on Animal Care (CCAC) guidelines.

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