

## 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                                                                                                                                                                                                                                                                                      |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> A description of all covariates tested                                                                                                                                                                                                                                |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                                   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                                      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                                |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> 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 | Mass spectrometers used for data acquisition were operated using Thermo Scientific Xcalibur v4.2.4.7 (HF-X devices) or v 4.4.16.14 (Exploris devices)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Data analysis   | For Data analysis the following tools were used: MeroX standalone/ v 2.0.1.4; MS Annika in PD 2.5, v 1.2.17259; XlinkX integrated to PD 2.5; pLink standalone/ v2.3.9; xiSearch/xiFDR standalone xi1.7.6.5/xiFDR2.1.5.5; MaxLynx integrated to MaxQuant v 2.0.2.0. Post processing was done via IMP-X-FDR that using the following modules: Biopython 1.79 (using the submodules Bio package, Bio.SeqUtils subpackage and Bio.SeqUtils.ProtParam), matplotlib_venn 0.11.6, openpyxl 3.0.9, toolz 0.11.2, venn 0.1.3, xlrd 1.2.0, XlsxWriter 3.0.3 and seqlogo 5.29.843. Custom code for IMP-X-FDR is available on github ( <a href="https://github.com/fstane/imp-x-fdr">https://github.com/fstane/imp-x-fdr</a> ) |

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](#)

Raw data and result files are accessible via the PRIDE repository using the identifier PXD029252

## 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](https://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     | Data was recorded in triplicates measured on different days using the same settings by mass spectrometry. For the main library we used 20 groups of 6-10 synthetic peptides from which the theoretical maximum number of crosslinks that can be formed is 1018. For the enrichable library we used 16 groups of 7-8 synthetic peptides from which the theoretical maximum number of crosslinks that can be formed is 512. For the acidic library we used 13 groups of 6-7 synthetic peptides from which the theoretical maximum number of crosslinks that can be formed is 280.<br>Besides that, no calculations for sample size have been done as no biological variation is to be expected in this synthetic peptide library set. |
| Data exclusions | No data were excluded from the analysis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Replication     | Reproducibility by means of ID numbers was estimated by calculation of standard deviations. Reproducibility by means of Id type was visualized by creating Venn diagrams, visualized in the manuscript figures.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Randomization   | Not applicable to the study, as this is a synthetic peptide library and we do not investigate any biological effects in this study. The same library was used for the whole study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Blinding        | As this is not a clinical study, blinding is not applicable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

## 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                                     |
|-------------------------------------|-----------------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Antibodies                       |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Eukaryotic cell lines |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Human research participants      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern     |

### Methods

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Eukaryotic cell lines

Policy information about [cell lines](#)

|                                                                   |                                                                                                                                                                                                                           |
|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cell line source(s)                                               | HEK293T Lenti-X cells (TaKaRa) were used only as to mimick a complex matrix in samples of crosslinked peptide library.                                                                                                    |
| Authentication                                                    | Cell line was purchased directly from provider (TaKaRa bio, Cat# 632180), expanded and frozen at passage 4. Early passages of this stock collection were used for all experiments. Cell line was not further authenticate |
| Mycoplasma contamination                                          | Cell lines were not regularly tested for mycoplasma status.                                                                                                                                                               |
| Commonly misidentified lines (See <a href="#">ICLAC</a> register) | No commonly misidentified cell lines were used in the study.                                                                                                                                                              |