

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

The code for building helical backbone structures has been implemented into Rosetta at https://github.com/RosettaCommons/main/tree/koga/all-alpha_design. The demo for building helical structures will be available at https://github.com/kogalab21/all-alpha_design. Rosetta software suite 3 was used for protein design and folding calculations. JASCO SpectraManager software v2 was used for CD.

Data analysis

Analyses on helical backbone structures were carried out with Rosetta. The code for analyzing helical structures has been implemented into Rosetta at https://github.com/RosettaCommons/main/tree/koga/all-alpha_design. Thermal denaturation data by CD were fit using nls function in R programming 3.3.1. SEC-MALS data were analyzed by the ASTRA software 6.1.2. HSQC data were analyzed by the Delta 5.0.4 NMR softwares. All NMR structure analyses were done as described in the methods section with the following programs: MagRO-NMRViewJ (updated version of Kujira), Filt_Robot, TALOS+ 2017, FLYA 3.98.5, CYANA 3.98.5, Amber 12, and PALES 2.1. The X-ray structure analysis was done as described in the methods section with the following programs: XDS VERSION Jan 26, 2018 BUILT=20180126, CCP4 7.0.052, Coot 0.8.1, Phenix Refine 1.12, and RAMPAGE (CCP4: 7.0.053).

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 solution NMR structures have been deposited in the wwPDB as PDB 7BQM (H5_fold-0_Chantal), 7BQN (H6_fold-C_Rei), 7BQQ (H6_fold-Z_Gogy), 7BQS (H6_fold-U_Nomur), and 7BQR (H7_fold-K_Mussoc). The NMR data were deposited in the BMRB under the accession numbers 36335 (H5_fold-0_Chantal), 36336 (H6_fold-C_Rei), 36337 (H6_fold-Z_Gogy), 36339 (H6_fold-U_Nomur), and 36338 (H7_fold-K_Mussoc). The crystal structure of H5_fold-0_Elsa has been deposited in the wwPDB as 7DNS. The computational design models are presented as Supplementary Data 1. The generated compact and steric-clash-free five-helix (1,899,355) and six-helix (380,869) structures are available at https://github.com/kogalab21/all-alpha_design. The plasmids encoding the designed sequences are available through Addgene under the accession numbers 201825 (H5_fold-0_Elsa), 201826 (H5_fold-0_Chantal), 201827 (H6_fold-C_Rei), 201828 (H6_fold-Z_Gogy), 201829 (H6_fold-U_Nomur), and 201830 (H7_fold-K_Mussoc). Source Data are available at https://github.com/kogalab21/all-alpha_design.

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 | Computational designs that passed selection criteria were experimentally tested. Based on the previously reported success rate of de novo designed proteins (N. Koga et al. Nature, 2012; Y.-R. Lin et al., PNAS, 2015), we estimated the number of designs we should test in order to be successful. |
| Data exclusions | No data were excluded |
| Replication | The representative designs for NMR structure determination were purified, verified by SDS-PAGE, mass spectrometry, and HSQC measurements twice independently. All attempts at replication were successful. |
| Randomization | Randomization is not relevant to our study. This is an observational study, which does not involve evaluation of conditional effects. |
| Blinding | Blinding is not relevant to our study. Keeping track of the identity of each designed protein was necessary for characterizing biophysical properties and solving the structure. |

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 checked="" type="checkbox"/> | <input 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 |