

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

Autodock Vina (1.1.2 and 1.2), Smina, QuickVina 2, FitDock, DOCK6, TankBind, EquiBind, PSOVina, MDock, Molegro, FRED, Glide, RLDock, SEED, AutoDock-GPU, RosettaLigand, GNINA, Light Dock, LeDock, PLANTS, GOLD, HDock, COOT, Topspin, NMRPipe, and CCPN. The platform AdaptiveFlow developed for this manuscript is freely available on GitHub at [https://github.com/QuantumAI4Bio/JChemAxon's JChem Package](https://github.com/QuantumAI4Bio/JChemAxon's-JChem-Package), Open Babel, and RDKit were used for ligand preparation. Biochemical and cellular-based assays were performed using a Cary 100 UV-Vis spectrophotometer and ClarioStar plate reader. X-ray diffraction data for protein crystallography were collected at the Swiss Light Source and European Synchrotron Radiation Facility in Grenoble (France). NMR of compounds: Bruker spectrometer equipped with a cryogenic probe and operating at a ^1H frequency of 400MHz. Data were acquired using TopSpin (Bruker, version 3.6.2)

Data analysis

Python; GraphPad Prism 9; For protein crystallography: data analysed and refined with CCP4 package, WinCoot CCP4 was used for electron density and model building

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 FSP1 ancestral sequence generated in this study has been submitted for deposition in the GenBank database. The accession code is PQ619396. FSP1 structures have been deposited with PDB under accession codes: 9IFZ 9IFT; 9IFY; 9IFU, 9IG9, 9QRT. The structure of PARP1-inhibitor complex has been deposited with PDB code 8VYH. The ready-to-dock Enamine REAL Space can be explored online via an interactive web interface available on the AdaptiveFlow homepage <http://adaptive-flow.ai/>.

Code Availability

The source code of AdaptiveFlow is released under the GNU GPL v2.0, a free and open-source license. The code can be accessed via GitHub. The Adaptive Flow GitHub repos can be found at <https://github.com/LigandUniverse>. The AFLP and AFVS modules of AdaptiveFlow can be found in AFLP (<https://github.com/LigandUniverse/AFLP>) and the AFVS (<https://github.com/LigandUniverse/VFVS>) GitHub repositories, respectively. The modules AdaptiveFlow Unity and Adaptive Flow Unity Parallelized can be found in the GitHub repo named AFU (<https://github.com/LigandUniverse/AFU>) and AFUpart (<https://github.com/LigandUniverse/AFUpart>), respectively

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

Reporting on race, ethnicity, or other socially relevant groupings

Population characteristics

Recruitment

Ethics oversight

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](https://www.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 exclusions

Replication

Randomization

Blinding

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

Antibodies

Antibodies used	Antibodies used: anti-AIFM2 antibody (clone 1115 1129 ZooMAb, rabbit monoclonal, Sigma-Aldrich): HRP-conjugated anti-rabbit secondary antibody(Millipore); Protein Strep-Tactin HRP-conjugate(BioRad). anti FSP1 antibody (HY-P80679 from MCE), a Rabbit-derived; HRP conjugated anti Rabbit secondly antibody (Jackson ImmnoResearch Laboratories, 711-035-152); anti GPX4 antibody (67763-1-1g from Proteintech), a mouse-derived; HRP conjugated anti Mouse secondly antibody (Jackson ImmnoResearch Laboratories 715-035-150); anti GapDH antibody (6C5) (AM4300 from Invitrogen), a mouse- derived; HRP conjugated anti Mouse secondly antibody (Jackson ImmnoResearch Laboratories 715-035-150); anti-BRCA1 (MilliporeSigma, 07-434, Rabbit polyclonal), anti-Alpha/beta-Tubulin (CST, 2148S, Rabbit polyclonal), HRP-linked anti-rabbit secondary antibody (Cytiva, NA9341ML)
Validation	anti-AIFM2 antibody dilution 1:1000 HRP-conjugated anti-rabbit secondary antibody dilution 1:10000; Protein Strep-Tactin HRP-conjugate antibody dilution 1:10000; Anti FSP1 antibody dilution 1:1000; HRP conjugated anti Rabbit secondary antibody 1:10000; Anti GPX4 antibody dilution 1:500; HRP conjugated anti Mouse secondary antibody 1:10000; Anti GapDH antibody dilution 1:2000; HRP conjugated anti Mouse secondary antibody 1:10000; anti-BRCA1 dilution 1:1000, anti-Alpha/beta-Tubulin 1:1000, HRP-linked anti-rabbit secondary antibody 1:5000

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	MDA-MB-436 were purchased from ATCC (HTB-130); Jurkat cells were purchased from ATCC; HEK293-EBNA1-6f cells were obtained from Yves Durocher (NRC-BRI, Montreal, Canada; patent number US8551774).
Authentication	For MDA-MB-436: The cell line was authenticated by STR profiling. For Jurkat and HEK293-EBNA1-6f: These cell lines were authenticated using morphology and functional assays
Mycoplasma contamination	For MDA-MB-436: The cell line was regularly tested for mycoplasma contamination using a PCR-based assay, For Jurkat and HEK293-EBNA1-6f: : The were not tested for Mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	N/A

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A