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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 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	Crystallography data were collected at APS/NE-CAT or APS/GMCA. Binding data were collected on ForteBio Octet RED96e. Western blotting data were collected on ChemiDoc MP Imaging System. Cell imaging was carried out on TIRF/SOTRM Nikon Ti2-microscope. HDX-MS data were collected using a HDX-2 PAL platform (LEAP Technologies) interfaced with an Acquity UPLC-M class (Waters) and a Synapt G2-Si (Waters) mass spectrometer
Data analysis	Crystallography data were analyzed with PHENIX software (version 1.11.1-2575 & version 1.19.1-4122) and CCP4 7.1 (Coot in this package). Images were analyzed with Fiji 20190218. Statistical analysis were performed with GraphPad Prism 8.1.1 & 9.1. HDX-MS data were analyzed with ProteinLynx Global Server 3.0.3 (PLGS, Waters) and Waters DynamX 3.0.

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 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

The refined structural protein models and corresponding structure–factor amplitudes have been deposited under PDB accession codes 7LS0 (human ALK-ALKAL complex), 7LRZ (human ALK), 7LIR (nematode ALK), and 7MK7 (ALKAL-MBP).

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.
All data generated or analysed during this study are included in this published article (and its supplementary information files).

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	Prior sample size determination was not done. Independent replicates of experiments were performed. If replicates gave similar results, the experiments were considered reproducible and complete. In vitro binding studies (HDX-MS and BLI) were repeated with different batches of protein.
Data exclusions	No data was excluded.
Replication	HDX-MS ligand-receptor experiments were repeated independently with different preparations of protein, n=2. Each preparation repeat has 3 technical repeats done by the robot. HDX-MS for antibody complexes were carried out with the same preparation of Celldex antibody, which included three technical repeats. HDX-MS followed guide lines for statistics (Masson, G. R. et al. Recommendations for performing, interpreting and reporting hydrogen deuterium exchange mass spectrometry (HDX-MS) experiments. Nat Methods 16, 595-602, doi:10.1038/s41592-019-0459-y (2019)). Binding assays were repeated by different batches of proteins when possible to help account for errors in protein concentration determination. Each experiment was performed with at least 3 biological repeats, with the exception of difficult to express mutants (E974R, R123E, R133E and R140E) which had 2 independent repeats . Western blotting and imaging have at least three biologic replicates. All the reported results are from experiments in which every repeat gave similar results.
Randomization	Cells for imaging were randomly selected. Other experiments did not involve randomization.
Blinding	Blinding was not applicable to this study because this type of study does not use group allocation.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	p44/42 MAPK (Erk1/2) (137F5) Rabbit mAb antibody, Cell Signaling Technology, Cat# 4695, 1:1000 Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) antibody, Cell Signaling Technology, Cat# 4370, 1:1000 ALK (C26G7) Rabbit mAb antibody, Cell Signaling Technology ,Cat# 3333, 1:1000 ALK (D5F3®) XP® Rabbit mAb, Cell Signaling Technology, Cat# 3633, 1:1000 ALK (phospho Y1604) antibody, Abcam, Cat# ab62185, 1:500 Anti-Phosphotyrosine Antibody, clone 4G10, Millipore, Cat# 05-321, 1:1000 Goat Anti-Rabbit IgG - H&L Polyclonal antibody, HRP Conjugated, Abcam, Cat# ab6721, 1:5000 Rabbit Anti-Mouse IgG H&L (HRP), Abcam, Cat# ab97046, 1:5000 Celldex®-mAb123 and Celldex®-mAb125 (Celldex Therapeutics, Inc.). These two antibodies were used for binding assay. They were diluted to 20 ug/mL. For testing the inhibition of receptor dimerization, Celldex®-mAb123 was treated with papain to generate Fab123.
Validation	p44/42 MAP Kinase (137F5) Rabbit mAb detects endogenous levels of total p44/42 MAP kinase (Erk1/Erk2) protein. The antibody does not cross-react with JNK/SAPK or p38 MAP kinase. Species reactive with Human, Mouse, Rat, Hamster, Monkey, Mink, D.

melanogaster, Zebrafish, Bovine, Dog, Pig, C. elegans.
Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (D13.14.4E) XP® Rabbit mAb detects endogenous levels of p44 and p42 MAP Kinase (Erk1 and Erk2) when dually phosphorylated at Thr202 and Tyr204 of Erk1 (Thr185 and Tyr187 of Erk2), and singly phosphorylated at Thr202. This antibody does not cross-react with the corresponding phosphorylated residues of either JNK/SAPK or p38 MAP kinases. Species reactive with Human, Mouse, Rat, Hamster, Monkey, Mink, D. melanogaster, Zebrafish, Bovine, Dog, Pig, S. cerevisiae
ALK (C26G7) Rabbit mAb detects endogenous levels of total ALK protein. This antibody does not cross-react with other family members. Species reactive with Human.
ALK (D5F3®) XP® Rabbit mAb detects endogenous levels of total ALK protein as well as ALK fusion proteins, such as EML4-ALK variants and NPM-ALK, even at low levels. This antibody does not cross-react with other family members. Species reactive with Human.
ALK (phospho Y1604) antibody, ab62185 detects endogenous levels of ALK only when phosphorylated at tyrosine 1604. Species reactive with Human.
Anti-Phosphotyrosine Antibody, clone 4G10 detects tyrosine phosphorylated proteins in all species. This unique monoclonal antibody is validated for use in IC, IH, IP, WB. All the commercial antibodies above are backed by hundreds of publications
Celldex®-mAb123 and Celldex®-mAb125 were validated by several publications such as Sano, R. et al. An antibody-drug conjugate directed to the ALK receptor demonstrates efficacy in preclinical models of neuroblastoma. Sci Transl Med 11, doi:10.1126/scitranslmed.aau9732 (2019).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	NIH/3T3 was purchased from ATCC (Cat# CRL-1658). IMR-32 was purchased from ATCC (Cat# CCL-127). All the ALK or ALK mutant stable cell lines were generated in this work.
Authentication	Cells were not further authenticated.
Mycoplasma contamination	The cell lines were not tested for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.