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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	Cryo-EM single particle data was automatically collected on the Titan Krios using serialEM 3.7.3. Crystal diffraction data was collected using automated data collection software package of Spring-8 beamline 41-XU.
Data analysis	XDS, SCALA, Phenix v-1.14, Buster, COOT-v0.8.9.2, Phaser, GraphPad Prism 8.1, Schrödinger Suite 2015-4, Glide 6.9, GROMACS 5.1.2, UCSF Chimera X0.9 package, Protein Preparation Wizard, Pymol 2.3.4, cryoSPARC v2.11, CHARMM-GUI, Gromacs, VMD.

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

The atomic coordinates for CXCR2-IL8 monomer-Gi-scFv16, CXCR2-IL8 dimer-Gi-scFv16 and CXCR2-00767013 have been deposited in the Protein Data Bank with the accession codes 6LFO, 6LFM and 6LFL. The EM maps for CXCR2-IL8 monomer-Gi-scFv16 and CXCR2-IL8 dimer-Gi-scFv16 have been deposited in EMDB with the codes EMD-0879 and EMD-0877, respectively. All other data are available upon request to the corresponding authors.

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	For all the functional assay, three independent experiments (n=3) were carried out.
Data exclusions	No data were excluded.
Replication	Cell-based signaling assays were independently replicated by two investigators and experimental results were reliably reproduced.
Randomization	Drug treatments were performed in dose-response studies on the same set of cells that also received control treatments and vehicle treatments on the same plates. All normalization to control and baseline/vehicle occurred within plate, then averaged among replicates. Drug treatment was randomized on the plate to avoid "plate effects." Wild-type controls were always run in parallel with mutant receptors.
Blinding	Blinding was not 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

Antibodies

Antibodies used	HA Epitope Tag Antibody, Alexa Fluor 488 conjugate (16B12), Catalog # A-21287, Thermo Fisher, 1:1000 dilution.
Validation	This antibody has been validated for use in flow cytometry and immunohistochemical staining previously (https://www.thermofisher.com/antibody/product/HA-Tag-Antibody-clone-16B12- Monoclonal/A-21287?pluginName=).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HTLA cells (an HEK293 cell line stably expressing a tTA-dependent luciferase reporter and a -arrestin2-TEV fusion gene) were generously provided by Richard Axel's lab
Authentication	HTLA cells expressing wild-type or mutant CXCR2 were authenticated by confocal microscopy and flow cytometry using the antibodies described above.
Mycoplasma contamination	HTLA cells have been tested as negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.