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Reporting Summary

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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	BD CSampler Plus or FACS Diva (v 8.0) were used for flow cytometry data acquisition. Wyatt ASTRA software package (v 7.0.1.24) was used for GPC data acquisition. Image Studio Software (v 5.2) was used for Western blot scanning. NIS Elements (v 5.11.00) was used for fluorescence microscopy image acquisition. Excalibur (v 4.2) was used for MS data acquisition.
Data analysis	MaxQuant (1.6.3.4) and the Andromeda search algorithm along with Perseus (1.6.22) were used for MS data analysis. MestReNova (v 12.0.3) was used for all chemical NMR analysis. The Wyatt ASTRA software package (v 7.0.1.24) was used for analysis of aqueous GPC data. Microsoft Excel (v 16.23) and Graphpad Prism (v 5.0) were used for data analysis. FlowJo (v 10.0) was used for flow cytometry data analysis. ImageJ (v 1.0) was used for fluorescence microscopy image analysis. Image Studio Software (v 5.2) was used for Western blot quantification.

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

All data relevant to the manuscript are included, including full data sets from CRISPRi screens and proteomics and source data. Further details and information are available from the corresponding author upon request.

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	No statistical method was used to determine sample size. Sample size choice was based on our experience with variability in these assays and our ability to detect meaningful differences between treatments. Variability was low based on our experience with western blot analysis and flow cytometry quantification experiments of protein uptake, degradation experiments, and surface measurement experiments. The sample size for mouse experiments was chosen based on previous experience with respect to the observed variability differences among groups when using western blot analysis of mouse serum to detect meaningful differences between treatments.
Data exclusions	There were no data exclusions except those resulting from technical errors making data interpretation impossible (torn gels, blots, poor gel transfers).
Replication	All data were successfully replicated with multiple biological replicates as indicated in the Figure legends. Experiments in Extended Data Fig. 6c were performed once with two experimental replicates. After two passages post-selection of dCas9-CRISPRi with EXOC1 sgRNA, K562 cells lost the EXOC1 phenotype. Data in Fig. 2 were obtained within one passage of one another.
Randomization	Initial choice of mouse for injection of antibody or conjugate was random. The order of analysis in flow cytometry experiments was randomized. No further formal randomization was employed as internal controls were employed for quantitative comparisons.
Blinding	Sample treatments and subsequent MS sample processing and MS analysis were blinded from one another. No additional blinding was employed for western blot analysis or flow cytometry analysis in order to make comparisons between specific treatments.

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

Atezolizumab (A1305, Biovision, lot 4K23A13050, usage varied)

Rabbit anti-pAKT (S473) (9271, Cell Signaling Technologies, lot 14, 1:1000)

Rabbit anti-pEGFR (Y1068) (2234, Cell Signaling Technologies, lot 21, 1:1000)

Rabbit anti-p44/42 MAPK (4376, Clone 20G11, lot 18, Cell Signaling Technologies, 1:1000)

Rabbit anti-EGFR (4267, Clone D38B1, lot 19, Cell Signaling Technologies, 1:1000)

Goat anti-EGFR (AF231, R&D Systems, lot AUC1217071, 1 µg/mL)

Mouse anti-sCD71 (VMA00037, Bio-Rad, lot 09071, 1:1000)

Rabbit anti-PD-L1 (13684, Clone E1L3N, Cell Signaling Technologies, lot 7, 1:500)

Mouse anti-Vinculin (MCA465GA,Clone V284, Bio-Rad, lot 1806, 1:1000)

Mouse anti-alpha-Tubulin (T5168, Clone B-5-1-2, Millipore Sigma, 1:5000)

Rabbit anti-EXOC1 (ab118798, Abcam, 1:2500)

Rabbit anti-CIM6PR (14364, Clone D3V8C, Cell Signaling Technologies, lot 1, 1:1000)

Mouse anti-CD71 (BE0023, Clone OKT-9, BioXCell, usage varied)

Mouse anti-PD-L1 (BE0285, Clone 29E.2A3, BioXCell, usage varied)

Mouse anti-mCherry (orb66657, Clone 5A12A7H10, Biorbyt, usage varied)

Mouse anti-ApoE4 (NBP1-49529, Clone 4E4, Novus Biologicals, lot E-2, usage varied)

Goat anti-Mouse IgG (115-005-062, Jackson ImmunoResearch, usage varied)

Mouse anti-biotin-Alexa Fluor 488 (200-542-211, Jackson ImmunoResearch, lot 119967, usage varied)

Cetuximab, obtained from Eli Lilly (usage varied, 0.1 µM when used for flow cytometry staining, batch IMF406)

Mouse anti-CIM6PR Abcam (ab2733, Clone 2G11, Abcam, lot GR310738-6, 1:500)

Goat anti-mouse IgG-Alexa Fluor 488 (115-545-008, Jackson ImmunoResearch, 1:375)

Goat anti-mouse IgG-Alexa Fluor 647 (115-605-071, Jackson ImmunoResearch, 1:375)

Goat anti-human IgG-Alexa Fluor 647 (109-605-003, Jackson ImmunoResearch, 1:375)

Goat anti-Rabbit IgG 800CW (926-32211, LI-COR, 1:10000)

Goat anti-Mouse IgG 800CW (926-32210, LI-COR, 1:10000)

Donkey anti-Goat IgG 800CW (926-32214, LI-COR, 1:10000)

Goat anti-Rabbit IgG 680LT (926-68021, LI-COR, 1:10000)

Goat anti-Mouse IgG 680LT (926-68020, LI-COR, 1:10000)

Goat anti-Human IgG 800CW (926-32232, LI-COR, 1:1000)

Validation

All antibodies were used for applications validated by antibody suppliers per quality assurance provided by each supplier.

Atezolizumab (A1305, Biovision): https://www.biovision.com/anti-pd-l1-atezolizumab-humanized-antibody.html. Tecentriq is the United States FDA-approved antibody against PD-L1. Binding to PD-L1 verified by knockdown measured by blot with E1L3N (Cell Signaling Technologies) in Fig.4.

anti-pAKT (S473) (9271, Cell Signaling Technologies): https://www.cellsignal.com/products/primary-antibodies/phospho-akt-ser473-antibody/9271. Validated from manufacturer's website and citations therein, validation included stimulation with AKT activating ligands (i.e. PDGF) as well transfection with phospho-inactive AKT mutants.

anti-pEGFR (Y1068) (2234, Cell Signaling Technologies): https://www.cellsignal.com/products/primary-antibodies/phospho-egf-receptor-tyr1068-antibody/2234. Validated from manufacturer's website and citations therein, validation included stimulation with EGF.

anti-p44/42 MAPK (4376, Clone 20G11, Cell Signaling Technologies): https://www.cellsignal.com/products/primary-antibodies/phospho-p44-42-mapk-erk1-2-thr202-tyr204-20g11-rabbit-mab/4376. Validated from manufacturer's website and citations therein. Validation included comparison with p38 and protein levels in the presence and absence of MAPK activating ligands.

anti-EGFR (4267, Clone D38B1, Cell Signaling Technologies): https://www.cellsignal.com/products/primary-antibodies/egf-receptor-d38b1-xp-rabbit-mab/4267. Validated from manufacturer's website and citations therein, validation included EGFR knock-out.

anti-EGFR (AF231, R&D Systems): https://www.rndsystems.com/products/human-egfr-antibody_af231#product-details. Validated from manufacturer's website and citations therein, results cross-validated with anti-EGFR D38B1 (Cell Signaling Technologies) by comparison with Extended Data Fig. 5.

anti-sCD71 (VMA00037, Bio-Rad): https://www.bio-rad-antibodies.com/monoclonal/human-cd71-soluble-antibody-vma00037.html?f=antibody%20only&thirdPartyCookieEnabled=false. Validated from manufacturer's website. Manufacturer's statement: "The PrecisionAb label is reserved for antibodies that meet the defined performance criteria within Bio-Rad's ongoing antibody validation programme."

anti-PD-L1 (13684, Clone E1L3N, Cell Signaling Technologies): https://www.cellsignal.com/products/primary-antibodies/pd-l1-

e1l3n-xp-rabbit-mab/13684. Validated from manufacturer's website and citations therein, validation included demonstration of PD-L1 increases in the presence of absence of IFN-γ.

anti-Vinculin (MCA465GA,Clone V284, Bio-Rad): https://www.bio-rad-antibodies.com/monoclonal/human-vinculin-antibody-v284-mca465.html?f=purified&thirdPartyCookieEnabled=false. Validated from manufacturer's website and citations therein.

anti-alpha-Tubulin (T5168, Clone B-5-1-2, Millipore Sigma): https://www.sigmaaldrich.com/catalog/product/sigma/t5168?lang=en&region=US. Validated from manufacturer's website and citations therein.

anti-EXOC1 (ab118798, Abcam): https://www.abcam.com/exoc1-antibody-ab118798.html. Validated from manufacturer's website and citations therein, validated with CRISPRi knockdown in Fig. 2 of this work.

anti-CIM6PR (14364, Clone D3V8C, Cell Signaling Technologies): https://www.cellsignal.com/products/primary-antibodies/igf-ii-receptor-ci-m6pr-d3v8c-rabbit-mab/14364. Validated from manufacturer's website and citations therein, validated with CRISPRi knockdown in Fig. 2 of this work.

anti-CD71 (BE0023, Clone OKT-9, BioXCell): https://bxcell.com/product/h-cd71/. Validated from manufacturer's website and citations therein.

anti-PD-L1 (BE0285, Clone 29E.2A3, BioXCell): https://bxcell.com/product/invivomab-anti-human-pd-l1-b7-h1/. Validated from manufacturer's website and citations therein.

anti-mCherry (orb66657, Clone 5A12A7H10, Biorbyt): https://www.biorbyt.com/mcherry-antibody-orb66657.html. Validated from manufacturer's website and citations therein. Validated by uptake of recombinant mCherry in Fig. 3.

anti-ApoE4 (NBP1-49529, Clone 4E4, Novus Biologicals): https://www.novusbio.com/products/apoe4-antibody-4e4_nbp1-49529. Validated from manufacturer's website and citations therein.

goat anti-Mouse IgG (115-005-062, Jackson ImmunoResearch): https://www.jacksonimmuno.com/catalog/products/115-005-062. Validated from manufacturer's website and citations therein.

mouse anti-biotin-Alexa Fluor 488 (200-542-211, Jackson ImmunoResearch): https://www.jacksonimmuno.com/catalog/products/200-542-211. Validated from manufacturer's website and citations therein, validated by investigators performing uptake experiments with anti-mouse IgG (Extended Data Fig. 4).

Cetuximab (anti-EGFR) is an United States FDA-approved antibody against EGFR.

anti-CIM6PR (ab2733, Clone 2G11, Abcam): https://www.abcam.com/m6pr-cation-independent-antibody-2g11-ab2733.html. Validated from manufacturer's website and citations therein, validated in Fig. 2 by CRISPRi knockdown.

Goat anti-mouse IgG-Alexa Fluor 488 (115-545-008, Jackson ImmunoResearch): https://www.jacksonimmuno.com/catalog/products/115-545-008. Validated from manufacturer's website and citations therein.

Goat anti-mouse IgG-Alexa Fluor 647 (115-605-071, Jackson ImmunoResearch): https://www.jacksonimmuno.com/catalog/products/115-605-071. Validated from manufacturer's website and citations therein.

Goat anti-human IgG-Alexa Fluor 647 (109-605-003, Jackson ImmunoResearch): https://www.jacksonimmuno.com/catalog/products/109-605-003. Validated from manufacturer's website and citations therein.

Goat anti-Rabbit IgG 800CW (926-32211, LI-COR): https://www.licor.com/bio/reagents/irdye-800cw-goat-anti-rabbit-igg-secondary-antibody. Validated from manufacturer's website.

Goat anti-Mouse IgG 800CW (926-32210, LI-COR): https://www.licor.com/bio/reagents/irdye-800cw-goat-anti-mouse-igg-secondary-antibody. Validated from manufacturer's website.

Donkey anti-Goat IgG 800CW (926-32214, LI-COR, 1:10000): https://www.licor.com/bio/reagents/irdye-800cw-donkey-anti-goat-igg-secondary-antibody. Validated from manufacturer's website.

Goat anti-Rabbit IgG 680LT (926-68021, LI-COR, 1:10000): https://www.licor.com/bio/reagents/irdye-680lt-goat-anti-rabbit-igg-secondary-antibody. Validated from manufacturer's website.

Goat anti-Mouse IgG 680LT (926-68020, LI-COR, 1:10000): https://www.licor.com/bio/reagents/irdye-680lt-goat-anti-mouse-igg-secondary-antibody. Validated from manufacturer's website.

Goat anti-Human IgG 800CW (926-32232, LI-COR, 1:1000): https://www.licor.com/bio/reagents/irdye-800cw-goat-anti-human-igg-secondary-antibody. Validated from manufacturer's website.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Jurkat, HeLa, MDA-MB-361, MDA-MB-231, THP-1, K562, HEK293, Hep3B, HepG2 and BT474 were obtained from the American Tissue Culture Collection (ATCC), HDLM-2 were obtained from the laboratory of Dr. Thomas Waldmann (NIH), CRISPRi cell lines were obtained from Dr. Michael Bassik's laboratory (Stanford University)

Authentication	Cell lines were authenticated by the supplier, HDLM-2 and CRISPRi lines were not subjected to additional authentication.
Mycoplasma contamination	Cell lines were verified to be mycoplasma negative by Lonza MycoAlert Mycoplasma Detection Assay.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	BALB/c mice, female, 6-8 weeks old
Wild animals	No wild animals were involved in this study.
Field-collected samples	This study did not involve collecting samples from the field.
Ethics oversight	IACUC and Stanford APLAC approval# 31511

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	For protein uptake experiments in suspension cell lines, cells were incubated for the indicated time with proteins and conjugates, then washed three times with PBS at 4 °C. Cells were then incubated with either Sytox Green or Sytox Red according to the manufacturer's specifications for 15 minutes on ice. For protein uptake experiments in adherent cell lines, cells were incubated for the indicated time with proteins and conjugates, then washed two times quickly with PBS and lifted with trypsin. Cells were transferred to a 96-well V-bottom plate and washed three times with PBS, then incubated with either Sytox Green or Sytox Red according to the manufacturer's specifications for 15 minutes on ice. For surface staining experiments, adherent cells were lifted with non-enzymatic cell dissociation buffer (Gibco) and transferred to a 96-well V-bottom plate, and suspension cells were transferred to a 96-well V-bottom plate. After washing three times with 0.5% BSA in PBS, cells were incubated with primary antibody for 30 minutes on ice. Cells were subsequently washed three times with 0.5% BSA in PBS, then incubated with secondary antibodies for 30 minutes on ice. After incubation, cells were washed three times with 0.5% BSA in PBS and incubated with either Sytox Green or Sytox Red according to the manufacturer's specifications for 15 minutes on ice.
Instrument	BD-Accuri C6 Plus and DxP FACScan for analysis, BD Aria II for sorthing
Software	BD CSampler Plus or FACS Diva were used for data collection, data analysis was performed using the FlowJo software package.
Cell population abundance	N/A
Gating strategy	Gating was based on FSC and SSC area, followed by dead cell removal using a Sytox stain, and doublet removal using FSC-H vs FSC-A.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.