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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	The design of protein mimics was performed using custom code programmed in python and ipython, in combination with the scientific/ high-performance modules: pyrosetta, numpy and scipy, matplotlib, sklearn, cython and pandas. Protein sequence design was performed using Rosetta and RosettaScripts. The computer code and examples are provided along with SI.
Data analysis	Data analysis was performed using custom code programmed in python and ipython and Rosetta, in combination with the scientific/high-performance modules: pyrosetta, numpy and scipy, matplotlib, sklearn, cython and pandas. Protein visualization was performed using PyMOL (PyMOL | pymol.org).

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 upon request. 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

PDBs for Neoleukin-2/15 monomer and for its ternary complex with mIL-2Rβgc have been deposited in the RCSB protein data bank (PDB IDs: 6DG6 and 6DG5, respectively), diffraction images have been deposited in the SBGrid Data Bank (IDs: 587 and 588, respectively) and validation reports for each of the PDBs are part of the supplementary information. The databases of clustered fragments and the algorithms used for designing de novo protein mimetics (programmed as python/ pyrosetta scripts) as described in this manuscript are available in the online repository Zenodo (ID: "to be provided with the final manuscript") .Other data and materials related to this manuscript are available upon request to the corresponding authors.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Yeast display: Sample size was based on historical data which revealed statistical significance in previous experiments. In vitro Stat5 experiments: Sample size was based on historical data which revealed statistical significance in previous experiments. Ex vivo Stat5 experiments: Sample size was based on historical data which revealed statistical significance in previous experiments. In vivo Airway inflammation experiments: Sample size was based on historical data which revealed statistical significance in previous experiments. Colorectal carcinoma in vivo experiments: Sample size was based on historical data for similar colorectal cancer experiments, .no statistical methods were used to pre-determine sample size. Melanoma in vivo experiments: The minimum group size was determined using G*Power for an expected large effect size (Cohen's d = 1.75). Car-T cells in vivo experiments: Sample size was based on historical data for similar CAR-T cell experiment which revealed statistical significance in previous experiments.
Data exclusions	Yeast display: No data were excluded from the analyses. In vitro Stat5 experiments: No data were excluded from the analyses for STAT5 phosphorylation studies and surface plasmon resonance studies. Cell populations were identified based on forward/side scatter profiles and singlets were discriminated using forward scatter area versus height plots. Ex vivo Stat5 experiments: No data were excluded from the analyses. In vivo Airway inflammation experiments: Two samples were excluded from analysis of % lung resident CD8+ T cells in Figure 4b due to failure of intravascular labeling (Thy1.2-BUV395) prior to sacrifice, as determined by the absence of Thy1.2+ cells in the collected sample. Colorectal carcinoma in vivo experiments: No data were excluded from the analysis Melanoma in vivo experiments: For melanoma tumor model experiments, no data points were excluded from analysis. Car-T cells in vivo experiments: No data were excluded from the analysis
Replication	Yeast display: All experiments were repeated at least once and all attempts of replication were successful. In vitro Stat5 experiments: All STAT5 phosphorylation studies were performed in triplicate and iterated at least 3 times to ensure reproducibility. Surface plasmon resonance studies were performed at least twice to ensure reproducibility. Ex vivo Stat5 experiments: All experiments were repeated and all attempts of replication were successful.

In vivo Airway inflammation experiments: All experiments were repeated and all attempts of replication were successful.

Colorectal carcinoma in vivo experiments: Experiments were repeated with similar results that are included in the extended information.

Melanoma in vivo experiments: Findings were conserved across a minimum of two experiments.

Car-T cells in vivo experiments: Experiments were not repeated, but multiple subjects were included in each experimental group.

Randomization

Yeast display: Not used.

In vitro Stat5 experiments: Not used.

Ex vivo Stat5 experiments: Not used. Mice used in the in vivo experiments were purchased from The Jackson Laboratory and randomly allocated into experimental groups upon receipt.

In vivo Airway inflammation experiments: Mice used in the in vivo experiments were purchased from The Jackson Laboratory and randomly allocated into experimental groups upon receipt.

Colorectal carcinoma in vivo experiments: Mice were randomly assigned into each experimental group according to their tumor volumes and in order to attain an even tumor volume average across experimental groups.

Melanoma in vivo experiments: The mice were given tumors and then randomized after tumor injection to specific treatments. In some instances, mice were further randomized if a treatment was started later in the experiments. This is specifically stated in the methods or figure legend when that was the case.

Car-T cells in vivo experiments: Mice were randomly allocated into experimental groups.

Blinding

Yeast display: Investigators were not blinded to the treatment groups.

In vitro Stat5 experiments: Investigators were not blinded to the treatment groups.

Ex vivo Stat5 experiments: Investigators were not blinded to the treatment groups.

In vivo Airway inflammation experiments: Investigators were not blinded to the treatment groups. Blinding was not relevant as mice were not scored throughout treatment.

Colorectal carcinoma in vivo experiments: Investigators were not blinded to the treatment groups.

Melanoma in vivo experiments: Investigators were not blinded to the treatment groups.

Car-T cells in vivo experiments: Investigators were not blinded to the treatment groups.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials

Materials related to this manuscript are available upon request to the corresponding authors.

Antibodies

Antibodies used

Yeast display: FITC-conjugated anti-c-Myc antibody

In vitro Stat5 experiments:
- Alexa Fluor® 647-conjugated mouse anti-STAT5 pY694 (BD Biosciences, 612599, Clone 47/Stat5(pY694))
- AlexaFluor 700 anti-CD44, clone IM7

Ex vivo Stat5 experiments:
- PE anti-pSTAT5 (pY694), clone 47
- PE-Cy7 anti-CD25, clone PC61
- PerCP anti-CD4, clone RM4-5
- AF700 anti-CD44, clone IM7

In vivo Airway inflammation experiments:
- FITC anti-Ki67, clone SolA15
- PerCP-Cy5.5 anti-CD25, clone PC61
- eFluor 450 anti-Foxp3, clone FJK-16S
- BV510 anti-CD8, clone 53-6.7
- BV605 anti-PD-1, clone J43
- BV711 anti-CD4, clone RM4-5
- BV786 anti-CD62L, clone MEL-14
- PE anti-CD69, clone H1.2F3
- PE-CF594 anti-B220, clone RA3-6B2
- PE-Cy7 anti-CXCR5, clone 2G8
- BUV395 anti-Thy1.2, clone 53-2.1

Colorectal carcinoma in vivo experiments: (BioLegend antibodies):
Brilliant Violet 510™ anti-mouse CD45 Antibody, 103138, 30-F11, B235434;
Brilliant Violet 711™ anti-mouse CD3 Antibody, 100241, 17A2, B245637;
FITC anti-mouse CD49b (pan-NK cells) Antibody, 108906, DX5, B159570;
Brilliant Violet 605™ anti-mouse CD4 Antibody , 100548, RM4-5, B244808;
PE/Cy7 anti-mouse CD8a Antibody, 100721, 53-6.7, B239089;
FOXP3 Monoclonal Antibody (FJK-16s), APC, eBioscience™, 17-5773-82, FJK-16s, 4303649.

Melanoma in vivo experiments: (BioLegend antibodies):
- CD45-BV711 (clone 30-F11, catalog 103147, lot number B243834),
- CD8-BV650 (53-6.7, 100742, B249326),
- CD4-BV421 (GK1.5, 100443, B244726),
- TCRβ-BV510 (H57-597, 109233, B245719),
- CD25-AF488 (PC61, 102017, B220118),
- FoxP3-PE (MF-14, 126404, B254089).

Validation

Yeast display: Positive and negative controls of specific-binding (for each of the florescent labeled targets) were included in each experiment.

In vitro Stat5 experiments: Antibodies were used at the dilutions recommended by the manufacturer and validated using appropriate positive (cytokine-stimulated cells) and negative (unstimulated cells) controls.

Ex vivo Stat5 experiments: Positive controls of specific-binding (for each of the florescent labeled targets) were included in each experiment.

In vivo Airway inflammation experiments: N/A

Colorectal carcinoma in vivo experiments: Every antibody was previously validated by the manufacturer. All antibody stainings were previously titrated and tested by single-staining. Numerous references were cited in the product's web-page.

Melanoma in vivo experiments: antibodies were validated by BioLegend; citations are available on the manufacturer's website.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

In vitro Stat5 experiments: CTLL-2 cells were purchased from ATCC.
Colorectal carcinoma in vivo experiments: CT26.WT (ATCC® CRL-2638™) .
Melanoma in vivo experiments: B16 cells were obtained from the ATCC.

Authentication

In vitro Stat5 experiments: ATCC provided authentication for cell lines.
Colorectal carcinoma in vivo experiments: no authentication was performed.

Melanoma in vivo experiments: no authentication was performed.

Mycoplasma contamination

In vitro Stat5 experiments: All cells tested negative for mycoplasma contamination via PCR assay.
Colorectal carcinoma in vivo experiments: Cell line was tested negative for mycoplasma using the MycoAlert™ Mycoplasma Detection Kit from Lonza.
Melanoma in vivo experiments: testing for mycoplasma was done every 3-6 months.

Commonly misidentified lines
(See ICLAC register)

None.

Animals and other organisms

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

Laboratory animals

Ex vivo Stat5 experiments: Female wild-type C57BL/6J and CD25KO mice aged 6-8 weeks were purchased from The Jackson Laboratory and used in the experiments.

In vivo Airway inflammation experiments: Female wild-type C57BL/6J and CD25KO mice aged 6-8 weeks were purchased from The Jackson Laboratory and used in the experiments.

Colorectal carcinoma in vivo experiments: Mus musculus, BALB/c, female and male, age between 10-12 weeks of age.

Melanoma in vivo experiments: Female C57BL/6 mice between 6 and 8 weeks old were used.

Car-T cells in vivo experiments: NSG mice were obtained from the Jackson Laboratory

Wild animals

None

Field-collected samples

None

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

Yeast display: Yeast were grown in C-Trp-Ura media prior to induction in SGCAA media as previously described. 12-18 hours after induction, cells were washed in chilled display buffer (50mM NaPO4 pH 8, 20mM NaCl, 0.5% BSA) and incubated with varying concentrations of biotinylated receptor (either human or murine IL-2Rα or IL-2Rβ, ɣc) while being agitated at 4°C. After approximately 30 minutes, cells were washed again in chilled buffer, and then incubated on ice for 5 minutes with FITC-conjugated anti-c-Myc antibody (1 uL per 3x106 cells) and streptavidin-phycoerythrin (1 uL per 100 uL volume of yeast). Yeast were then washed and counted by flow cytometry (Accuri C6) or sorted by FACS (Sony SH800).

In-vitro Stat5 experiments: Cells were stimulated for 15 min at 37ºC and immediately fixed by addition of formaldehyde to 1.5% and 10 min incubation at room temperature. Permeabilization of cells was achieved by resuspension in ice-cold 100% methanol for 30 min at 4ºC. Fixed and permeabilized cells were washed twice with FACS buffer (phosphate-buffered saline [PBS] pH 7.2 containing 0.1% bovine serum albumin) and incubated with Alexa Fluor® 647-conjugated anti-STAT5 pY694 (BD Biosciences) diluted 1:50 in FACS buffer for 2 hr at room temperature. Cells were then washed twice in FACS buffer and MFI was determined on a CytoFLEX flow cytometer (Beckman-Coulter).

Ex vivo Stat5 experiments: Spleens and lymph nodes were harvested from wild-type C57BL/6J or B6;129S4-Il2ratm1Dw (CD25KO) mice purchased from The Jackson Laboratory and made into a single cell suspension in sort buffer (2% Fetal Calf Serum in pH 7.2 phosphate-buffered saline). CD4+ T cells were enriched through negative selection by staining the cell suspension with biotin-conjugated anti-B220, CD8, NK1.1, CD11b, CD11c, Ter119, and CD19 antibodies at 1:100 for 30 min on ice. Following a wash with sort buffer, anti-biotin MicroBeads (Miltenyi Biotec) were added to the cell suspension at 20 µL per 107 total cells and incubated on ice for 20 minutes. Cells were washed, resuspended and negative selection was then performed using EasySep Magnets (STEMCELL Technologies). Approximately 1 x105 enriched cells were added to each well of a 96-well plate in RPMI complete medium with 5% FCS with 10-fold serial dilutions of mIL-2, Super-2, or Neoleukin-2/15. Cells were stimulated for 20 min at 37ºC in 5% CO2, fixed with 4% PFA and incubated for 30 minutes at 4ºC. Following fixation, cells were harvested and washed twice with sort buffer and again fixed in 500 µL 90% ice-cold methanol in dH2O for 30 min on ice for permeabilization. Cells were washed twice with Perm/Wash Buffer (BD Biosciences) and stained with anti-CD4-PerCP in Perm/Wash buffer (1:300), anti-CD44-Alexa Fluor 700 (1:200), anti-CD25-PE-Cy7 (1:200), and 5 µL per sample of anti-pSTAT5-PE pY694 for 45 min at room temperature in the dark. Cells were washed with Perm/Wash and re-suspended in sort buffer for analysis on a BD LSR II flow cytometer (BD Biosciences).

In vivo Airway inflammation experiments: Circulating T cells were intravascularly labeled and tetramer positive cells were enriched from lymph nodes and spleen or lung as previously described (Hondowicz et al., Immunity, 2016). Both the column flow-trhough and bound fractions were saved for flow cytometry analysis. Cells were surface stained and fixed/permeabilized (eBioscience) according to manufacturer's directions prior to intracellular staining for Foxp3 or Ki67. Samples were then analyzed on a BD LSR II.

Colorectal carcinoma in vivo experiments: Mice tumours were minced, digested using a mix of collagenase I, collagenase IV and DNase I for 20 minutes at 37ºC. After digestion the samples were passed through a 100uM cell strainer, and resuspended in cold complete DMEM medium. The cell suspensions from the spleens and the inguinal lymph nodes were obtained trough the smashing of the tissues against the filter of a 100uM cell strainer.

Melanoma in vivo experiments: Cell suspensions from spleens, tumors, and tumor-draining lymph nodes were washed once with PBS, and the cell pellet was resuspended in 2% inactivated fetal calf serum then stained.

Instrument

Yeast display: Sony SH800, Accuri C6

In-vitro Stat5 experiments: CytoFLEX, Accuri C6

Ex vivo Stat5 experiments: BD LSR II

In vivo Airway inflammation experiments: BD LSR II

Colorectal carcinoma in vivo experiments: BD LSRFortessa™

Melanoma in vivo experiments: special order BD Biosciences LSRFortessa.

Software

Yeast display: CytExpert Software for CytoFLEX and Flowjo

In-vitro Stat5 experiments: CytExpert Software for CytoFLEX and Flowjo

Ex vivo Stat5 experiments: BD FACSDiva was used for flow cytometry sample collection, and FlowJo 9.9.4 was used for analysis of the flow samples.

In vivo Airway inflammation experiments: BD FACSDiva was used for flow cytometry sample collection, and FlowJo 9.9.4 was used for analysis of the flow samples.

Colorectal carcinoma in vivo experiments: BD FACSDiva software™ for data collection, parameterization and compensation; FlowJo, LCC for data analysis

Melanoma in vivo experiments: analysis was performed on FlowJo 10.4.2.

Cell population abundance

Yeast display: No cell sorting was performed for binding screening assays.

In-vitro Stat5 experiments: No cell sorting was performed.

Ex vivo Stat5 experiments: No cell sorting was performed.

In vivo Airway inflammation experiments: No cell sorting was performed.

Colorectal carcinoma in vivo experiments: No cell sorting was performed.

Melanoma in vivo experiments: No cell sorting was performed.

Gating strategy

In-vitro Stat5 experiments: Cell populations were identified based on forward/side scatter profiles and singlets were discriminated using forward scatter area versus height plots. Gating examples are shown in the supplementary information figures.

Ex vivo Stat5 experiments: Gating strategies are shown in the supplementary information figures.

In vivo Airway inflammation experiments: Gating strategies are shown in the supplementary information figures.

Colorectal carcinoma in vivo experiments: FSC and SSC gating was performed in order to specifically select lymphocytes, according to what is defined as the gating strategy for lymphocytes in lymphoid organs (small size, low complexity). Boundaries between positive and negative were defined according to the unstained sample, single stainings and fluorescence minus one controls in order to prevent the selection of unspecific signal, autofluorescence or parasitic fluorescence from other fluorophores. Gating strategies are shown in the supplementary information figures.

Melanoma in vivo experiments: Gating strategies are shown in the supplementary information figures.

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