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Corresponding author(s): Andrew Sewell

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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	FACSDiva v. software for flow cytometry acquisition; MiSeq control software by Illumina for DNA sequencing; Perkin Elmer Microbeta Workstation Software.
Data analysis	MAGeCK analysis of whole genome CRISPR data, as outlined in Li, W. et al. Genome Biol. 15, 554 (2014); FlowJo V10 for flow cytometry analysis; Prism v6 for graph production; Microsoft Excel. The logrank p-value and Hazard Ratio (HR) were calculated using the MatSurv survival analysis function in Matlab, available at https://www.github.com/aebergl/MatSurv.

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

Overall: all raw data can be provided if needed. Figure 1: A, raw data displayed. B, raw absorbance available. C, some raw data in supplementary to show the methodology, other can be provided. D, flow data can be provided. E flow data can be provided. Figure 2: B, raw absorbance available. C, MAGeCK data available. Figure 3: A, B, and D, raw absorbance available. B and C, raw Cr51 data available. Figure 4: A, C and E, flow data displayed. B and D, raw absorbance available. E, raw flow data available. Figure 5: A and B, raw absorbance available. C, raw flow data available. Figure 6: A, flow data available. B and C, flow data displayed. B, raw flow available. Figure 7: A, representative flow data displayed in the supplementary figures; all other available. B, raw data displayed. Body weights can be provided. Figure 8: A, raw data displayed. B, raw flow data available.

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	We based our approach on our previous studies of duplicate or triplicate samples within an in vitro assay. In vivo design was based on our previous work to give group sizes amenable to statistical testing.
Data exclusions	Data exclusion was not pre-established: confirmation of CD1a restriction of clone 40E.22 not shown due to future publication of data. Data exclusion was pre-established: whole genome sequencing data where hits were <2 were not included due to lack of relevance regarding enrichment.
Replication	All experiments were performed in either duplicates or triplicates. Experiments were repeated multiple times as indicated in the legends as requested. All data was repeatable. Not possible to repeat whole genome sequencing due to high cost, robustness provided by high throughput design.
Randomization	Mice were allocated randomly into treatment groups.
Blinding	No blinding was performed as only one author performed the experiments.

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	Pan-αβTCR PE (clone IP26, BioLegend, Catalogue number 306708, 1:50), pan-γδ TCR-FITC (clone REA591, Miltenyi Biotec, cat 130-113-511 , 1:50), CD3 PerCP (clone UCHT1, BioLegend, cat 300428, 1:100), CD4 APC (clone VIT4, Miltenyi Biotec, cat 130-113-210, 1:50), CD8 PE (clone BW135/80, Miltenyi Biotec, cat 130-113-158, 1:100), rat CD2 PE (clone OX-34, Biolegend, cat 201305 1:200) and MR1 (clone 26.5, Biolegend, PE cat 361106: 1:25 for staining, cat 361109: blocking details in the methods section), CD69 APC (clone FN50, BioLegend, cat 310910, 1:50), pan HLA class I (clone W6/32, BioLegend, APC cat 311410: 1:50 for staining, cat 311427: blocking details in the methods section), HLA DR DP DQ antibody (clone Tu39, cat 361702: blocking details in the methods section), CD45 APC-Cy7 (clone HI30, BioLegend, cat 304014, 1:50); TNF PE-Vio770 (clone cA2/ Miltenyi Biotec, cat 130-120-492, 1:66), CD107a PE (clone H4A3, Miltenyi Biotec, cat 130-119-872, 1:83); IFNy APC (clone 45-15, Miltenyi Biotec, cat 130-113-490, 1:50); and CD11b PE-Cy7 (clone M1/70, BD Biosciences, cat 552850, 1:100).
Validation	All antibodies were validated by manufacturers for flow cytometry, with positive and negative staining provided in appropriate data sheets available at the following links: IP26 (https://www.biolegend.com/en-gb/products/pe-anti-human-alpha-beta-t-cell-receptor-antibody-773); REA591 (https://www.miltenyibiotec.com/GB-en/products/macs-flow-cytometry/antibodies/primary-antibodies/anti-tcrg-d-antibodies-human-rea591-1-50.html#fitc:for-100-tests); UCHT1 (https://www.biolegend.com/en-gb/products/percp-anti-human-cd3-antibody-4213); VIT4 (https://www.miltenyibiotec.com/GB-en/products/macs-flow-cytometry/antibodies/primary-antibodies/cd4-antibodies-human-vit4-1-50.html#apc:for-100-tests); BW135/80 (https://www.miltenyibiotec.com/GB-en/products/macs-flow-cytometry/antibodies/primary-antibodies/cd8-antibodies-human-bw135-80-1-50.html#pe:for-100-tests); OX-34 (https://www.biolegend.com/en-gb/products/pe-anti-rat-cd2-antibody-2379); 26.5 (staining: https://www.biolegend.com/en-gb/products/pe-anti-human-mouse-rat-mr1-antibody-9281. blocking: https://www.biolegend.com/en-gb/products/ultra-leaf-purified-anti-humanmouserat-mr1-antibody-17174; PMID 28632133); FN50 (https://www.biolegend.com/en-gb/products/apc-anti-human-cd69-antibody-1674); W6/32 (staining: https://

www.biolegend.com/en-gb/products/apc-anti-human-hla-a-b-c-antibody-1870. Blocking: https://www.biolegend.com/en-gb/products/ultra-leaf-purified-anti-human-hla-a-b-c-antibody-8095); Tu39 (blocking: https://www.biolegend.com/en-gb/products/purified-anti-human-hla-dr--dp--dq-antibody-9337); HI30 (https://www.biolegend.com/en-us/products/apc-cyanine7-anti-human-cd45-antibody-1914); cA2 (https://www.miltenyibiotec.com/GB-en/products/macs-flow-cytometry/antibodies/primary-antibodies/anti-tnf-a-antibodies-human-ca2-1-50.html); 45-15 (https://www.miltenyibiotec.com/GB-en/products/macs-flow-cytometry/antibodies/primary-antibodies/anti-ifn-g-antibodies-human-45-15-1-50.html); H4A3 (https://www.miltenyibiotec.com/GB-en/products/macs-flow-cytometry/antibodies/primary-antibodies/cd107a-lamp-1-antibodies-human-h4a3-1-50.html) and M1/70 (https://www.bdbiosciences.com/us/applications/research/stem-cell-research/mesenchymal-stem-cell-markers-bone-marrow/mouse/negative-markers/pe-cy7-rat-anti-cd11b-m170/p/552850). Antibodies were titrated in-house to confirm required concentration. Isotype Abs were sourced as recommended from the corresponding manufacturer. The Abs used for mouse experiments was based on our Nature Medicine publication (PMID: 29131157). We had previously used the MR1 26.5 Ab and relevant isotype controls for characterization of wild-type and MR1 knockout cells (PMID: 27307560).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Breast adenocarcinomas MCF-7 (HTB-22); prostate adenocarcinoma LnCAP (CRL-1740); cervical adenocarcinomas HeLa (CCL-2) and SiHa (HTB-36); acute lymphoblastic leukaemia MOLT3 (CRL-1552); chronic myeloid leukaemia K562 (CRL-3344); myeloma/plasmacytoma U266 (TIB-196); osteosarcoma U-2 OS (HTB-96); immortalized embryonic kidney cell HEK293T (CRL-1573); acute monocytic leukaemia THP-1 (TIB-202); lung carcinoma A549 (CCL-185); acute T-cell leukaemia Jurkat (TIB-152); colorectal adenocarcinoma COLO 205 (CCL-222); ovarian carcinoma A2780 (ECACC 93112519 for culture guidelines). Melanomas FM-45, MM909.11 and MM909.24, renal cell carcinoma RCC17, MM909.20 and MM909.21 were sourced from the CCIT, and MEL 624 from in-house. CIR and lymphoblastoid cell line (LCL) SAR26 were sourced or generated in-house. Epithelial ovarian cancer cell line EOC031 was generated from ascites. SMC3 (colonic smooth muscle); CIL-1 (non-pigmented bronchial ciliary epithelium); HH (hepatocyte); pulmonary alveolar epithelia; melanocytes; renal epithelia; and pancreatic stellate cells were all sourced from Sciencell (Carlsbad, CA, USA). MRC5s (fibroblast) were sourced locally. Intestinal epithelia were sourced from Lonza (Basel, Switzerland). Dendritic cells and Langerhans were generated from CD14+ cells purified from PBMCs from the Welsh Blood Service, as were healthy T- and B-cells.
Authentication	Normal/healthy cells from Sceincell (via Caltag) or Lonza were purchased for the purpose of this study and came with validation certification. The normal cell lines undergo senescence if kept in culture. Melanomas and renal cell carcinomas from the CCIT in Copenhagen and ovarian primary cancer cell line EOC031 were generated using established methods as described in previous publications. This includes removal of fibroblasts, other non-cancer cell subsets (such as T-cells) and passaged to ensure immortalisation. EOC031 was used as a primary cancer cell line, but a passaged cancer cell has been established, which divides as avidly as other cancer cell lines and could be used for further validation if required. HLA-typing confirmed patient origin after the cancer cells were generated as lines. Lymphoblastoid made in-house cell lines undergo repeated division and stain for CD19 (CD3- CD8- CD4-) and activate EBV specific T-cells. Langerhans and dendritic cells were phenotyped for standard markers of differentiation and maturation (CD14 CD209 CD86 CD80 CD83). Purified T-cells and B-cells stained with CD3 or CD19 respectively. All other cell lines are checked regularly for morphology based on imagery, and growth habit descriptions, according to information available from the ATCC. Additionally, surface Ab staining and functional testing was performed for ongoing validation of cell lines: of MCF-7 (HLA A1- A2+ A24- A3-), LnCAP (HLA A1+ A2+ A3- A24-), HeLa (HLA A1- A2- A3- A24-), SiHa (HLA A1- A2- A3- A24+), MOLT3 (HLA A1+ A2- A3- A24- BST2+ CD4+), K562 (HLA null), U266 (HLA A1- A2+ A3+ A24-), U-2 OS (HLA A1- A2+ A3- A24-), HEK293T (able to produce lentivirus), THP-1 (HLA A1- A2+ A3- A24-), A549 (able to take up bacterium and activate MAITs), Jurkat (CD3+ alpha beta TCR+ CD4+, and able to express transduced T-cell receptors), COLO205 (HLA A1+ A2+ A3- A24-), C1R (HLA null, and able to activate EBV specific T-cells when transduced with HLA A2), MEL624 (HLA A1- A2+ A3+ A24-, and able to activate Melan A specific T-cells through HLA A2) and A2780 (HLA A1- A2- A3- A24-).
Mycoplasma contamination	All cell lines tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used (according to ICLAC).

Animals and other organisms

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

Laboratory animals	Female JAX NOD scid gamma (NSG®) were purchased from Charles Rivers (Wilmington, MA, US) at 6-7 weeks of age, housed under specific pathogen free conditions and experiments initiated within one week of arrival.
Wild animals	Study did not involve wild animals.
Field-collected samples	Study did not involve field collected samples.
Ethics oversight	United Kingdom Home Office approved projects 30/3188 and P2FB675AB.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Metatastic melanoma patients prior to immunotherapy: age (MM909.11 41 years, MM909.24 56 years), gender (MM909.11 and MM909.24 male) and genotypic profile not critical for the study. Ovarian cancer patient with active disease: age, gender and genotypic profile not critical for the study. Healthy donors: age (18-65 year donation criteria for the Welsh Blood Service), gender (unknown) and genotypic profile not critical for the study.
Recruitment	Melanoma patients: selected due to the availability of PBMCs collected prior to immunotherapy, and because an autologous melanoma line was available. Patients MM909.11 and MM909.24 were selected from a cohort of banked samples at the CCIT in Copenhagen. Ovarian cancer patient: selected due to the local availability of ascites fluid, removed from the patient as part of palliative care, and that a primary cancer line could be generated from the ascites. Healthy donors: selected due to the availability of donated blood, as purchased from the Welsh Blood Service from donations not needed for hospital use.
Ethics oversight	Ethical agreement to cover the work performed in Cardiff with human samples: School of Medicine Research Ethics Committee (reference 18/56). Melanoma patients: ethics reference EudraCT no. 2008-008141-20. Ovarian patient: Wales Cancer Bank ethics reference WCB14/004.

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	Cells were harvested and washed in PBS before fixable live/dead staining. Antibodies were added and incubated at 4 degrees celcius for 20 minutes, cells were washed in PBS and resuspended in appropiate volume for analysis. Cells were either from PBMCs or cancer cell lines as described in 'Eukaryotic Cell Lines' described above.
Instrument	BD FACS Canto II 8 colour, BD Biosciences Cat No.:338962; BD FACS Aria (https://www.cardiff.ac.uk/central-biotechnology-services).
Software	BD FACS DIVA v6.0.
Cell population abundance	Cell numbers were provided by FACS DIVA sorting software. Confirmation not possible as cells were immediately placed into T-cell expansion conditions with irradiated feeder cells.
Gating strategy	Cells were gated on FSC/SSC for lymphocytes, followed by single cell gating on FSC-A/FSC-H, followed by alive gating using a fixable live/dead stain. Positive and negative gating based on FMO staining.

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