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**

- IntelliCyt iQue Screener flow cytometer (Sartorius), LSRFortessa flow cytometer (BD Biosciences), Microplate reader (BioTek), EnVision Multilabel Reader (PerkinElmer), MesoScale Diagnostics QuickPlex SQ 120 (MSD), Biacore 8K SPR system (Cytiva).

**Data analysis**

- LSR Fortessa flow cytometry data was processed using FACSDiva v8 and v9.0 software (BD). Sartorius iQue flow cytometry data was processed using iQue ForeCyt v6.2 and v8.1 software (Sartorius). Flow cytometry data were analyzed using FlowJo V10 software (BD). Graphs were plotted and analyzed using GraphPad Prism 8.0 (DotMatics). EnVision data was processed using EnVision Workstation 1.13.3009.1401 software (Perkin Elmer). U-PLEX ProInflam data was processed using MesoScale Diagnostics Discovery Workbench v4.0. BioTek absorbance data was analyzed using BioTek GenS V1.04.5. BaGoL analysis was performed with the MATLAB implementation of BaGoL included with smite (https://github.com/LidkeLab/smite/) version 0.1.0 at the UNM Center for High Performance Computing (CARC) using MATLAB R2019b; post analysis of NN distance per ROI was computed with locally written MATLAB R2019b software using algorithm "knnsearch".

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.
Sequences of the variable domains and constant domains of recombinant antibodies tested herein were described in patent WO 2019/211472. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable 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 | All data shown are representative of at least three independent replicate experiments or three individual human donors tested. No sample size calculation was performed prior to execution of experiments; post-analysis of experiments demonstrated which group comparisons were sufficiently powered to draw statistically significant conclusions (see Supplementary Tables 3-7). For in vivo studies, group sizes were estimated based on previous experience with similar but not identical experimental settings. |
| Data exclusions | Whole blood donor samples from which insufficient target/effector cells could be recovered were excluded from analysis. All other samples were included. No mice were excluded from analysis, but lipid contamination of some samples precluded FACS analysis. |
| Replication | All data shown are representative of at least three independent replicate experiments or at least three individual human donors tested. All attempts at replication were successful. |
| Randomization | For in vivo studies, NSG mice were randomly assigned to experimental groups. NSG-HIS mice were randomized into different treatment groups based on the percentage of circulating B and T cells of the total hCD45+ population. For samples used in in vitro studies, randomization was not applicable, as sufficient donor material was available to test each treatment group on each donor sample. |
| Blinding | For in vivo studies, the investigators who directly performed the study were blinded to the group allocation during execution of the in vivo experiment and the ex vivo analysis. For in vitro studies, group allocation was not applicable, as cells from each donor were exposed to all test items. |

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

- Sequences of the variable domains and constant domains of recombinant antibodies tested herein were described in patent WO 2019/211472.

Commercially available antibodies used:
Validation

For antibodies expressed recombinantly in-house, the concentration of purified IgGs was determined by absorbance at 280 nm. Quality assessment of purified antibodies was performed by SDS/PAGE (>90% intact IgG, >95% HC + LC under reducing conditions), ESI-TOF MS (identity confirmation), HP-SEC (aggregate level <5%) and binding assays on target-expressing cells (specificity). For in vivo studies, endotoxin levels were below 0.5EU/mg. For validation statements of commercially available antibodies we refer to the manufacturer’s website.

Validation statements available for commercially accessible antibodies:
1. According to statements provided by the manufacturer, antibody M5E2-PE-Cy7 was reactive to human CD14 and validated for use in flow cytometry.
2. According to statements provided by the manufacturer, antibody ICRF44-PE was reactive to human CD11b and validated for use in flow cytometry.
3. According to statements provided by the manufacturer, antibody 10.1-FITC was reactive to human CD64 and validated for use in flow cytometry.
4. According to statements provided by the manufacturer, antibody 2010-APC was reactive to human CD80 and validated for use in flow cytometry.
5. According to statements provided by the manufacturer, antibody GHI/61-BV421 was reactive to human CD163 and validated for use in flow cytometry.
6. According to statements provided by the manufacturer, antibody 15-2-BV711 was reactive to human CD206 and validated for use in flow cytometry.
7. According to statements provided by the manufacturer, antibody OKT3-eFluor450 was reactive to human CD3 and validated for use in flow cytometry by relative expression to ensure that the antibody binds to the antigen stated.
8. According to statements provided by the manufacturer, antibody HI189-BV711 was reactive to human CD19 and validated for use in flow cytometry.
9. According to statements provided by the manufacturer, antibody 4E3-PE was reactive to human CD25 and validated for use in flow cytometry by cell treatment to ensure that the antibody binds to the antigen stated.
10. According to statements provided by the manufacturer, antibody 2D1-PerCP was reactive to human CD45 and validated for use in flow cytometry.
11. According to statements provided by the manufacturer, antibody NCAM16.2-BV711 was reactive to human CD163 and validated for use in flow cytometry.
12. According to statements provided by the manufacturer, antibody G10FS-PE-Cy7 was reactive to human CD66b and validated for use in flow cytometry.
13. According to statements provided by the manufacturer, antibody FN50-FITC was reactive to human CD69 and validated for use in flow cytometry.
14. According to statements provided by the manufacturer, antibody RPA-T8-Alexa Fluor 700 was reactive to human CD8a and validated for use in flow cytometry.
15. According to statements provided by the manufacturer, antibody OKT4-APC-eFluor780 was reactive to human CD4 and validated for use in flow cytometry.
16. According to statements provided by the manufacturer, antibody 3G8-BV650 was reactive to human CD16 and validated for use in flow cytometry.
17. No validation statement available from the manufacturer.
19. According to statements provided by the manufacturer, antibody S-HCL-1-PE was reactive to human CD22 and validated for use in flow cytometry.
20. According to statements provided by the manufacturer, antibody HIB19-PE-CF594 was reactive to human CD19 and validated for use in flow cytometry.
21. According to statements provided by the manufacturer, antibody RPA-2.10-APC was reactive to human CD2 and validated for use in flow cytometry.
22. According to statements provided by the manufacturer, antibody RmC11H9-FITC was reactive to mouse C3 and validated for use in flow cytometry.
23. According to statements provided by the manufacturer, antibody 2.4G2 was reactive to mouse Fc and validated for use in flow cytometry.
24. According to statements provided by the manufacturer, antibody Fc1.3216 was reactive to human Fc and validated for use in flow cytometry.
25. According to statements provided by the manufacturer, antibody MφP-9-FITC was reactive to human CD14 and validated for use in flow cytometry.
26. According to statements provided by the manufacturer, antibody J3-119-PE was reactive to human CD19 and validated for use in flow cytometry.
27. According to statements provided by the manufacturer, antibody Bu15-PE-Cy7 was reactive to human CD11c and validated for use in flow cytometry.
28. According to statements provided by the manufacturer, antibody WM53-APC was reactive to human CD33 and validated for use in flow cytometry.
29. According to statements provided by the manufacturer, antibody CMSSB-PerCP-eFluor710 was reactive to human CD56 and validated for use in flow cytometry.
30. According to statements provided by the manufacturer, antibody 30-F11-APC-eFluor780 was reactive to mouse CD45 and validated for use in flow cytometry.
31. According to statements provided by the manufacturer, antibody NB600-363AF647 was reactive to the HA tag and validated for use in immunofluorescence.
Population characteristics

Population characteristics of blood samples or derivatives from healthy human donors were blinded to the authors in accordance with GDPR policy. Population characteristics of PBMCs derived from CLL patients are described in Supplementary Table 9. Importantly, this study did not involve any diagnostics specific to age, gender, or race, or draw any conclusions based on these patient characteristics.

Recruitment

PBMCs derived from CLL patients were commercially obtained from Discovery Life Sciences (Huntsville, AL, USA). Buffy coats from healthy human donors and complement-competent, pooled normal human serum (NHS; AB positive) were obtained from Sanquin (Amsterdam, The Netherlands). Whole blood samples from healthy human volunteers were freshly obtained from the University Medical Center Utrecht (Netherlands).

Ethics oversight

Commercially available patient-derived PBMCs and healthy donor blood-derived samples were collected at the site of the vendor after patient written and informed consent in accordance with the declaration of Helsinki. All vendors maintained strict ethical compliance, including fully de-identified materials and stringent Institutional Review Board (IRB) and Ethics Committee compliance.

Flow Cytometry

Plots

- 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 an in-depth description of sample preparation, we refer to the individual assay sections within the online methods: cells and reagents, whole blood cytotoxicity, C1q binding, CDC, ADCP, FRET, and In Vivo POC studies.

Instrument

IntelliCyt iQue Screener flow cytometer (Sartorius) and LSRFortessa flow cytometer (BD Biosciences).

Software

FlowJo software v10.

Cell population abundance

N.A., as no cell sorting was performed.

Gating strategy

After gating of forward scatter (FSC) vs. side scatter (SSC), doublets were excluded by FSC-A vs. FSC-H. For whole blood assays, leukocytes were selected by CD45+ staining. Dead cells were excluded by fixable viability stain (FVS). Lymphocytes and granulocytes were separated based on CD66b staining. B- and T cells within the lymphocyte (CD66b-) cell population were identified as CD19+ and CD3+/CD4+, respectively. More details are supplied in supplementary table 1 and supplementary figure 7.

For ADCP assays, target cells were distinguished from hMDM by CD11b, CalceinAM and CD19 staining as described in the ‘ADCP’ paragraph in the methods section. For binding assays, binding was quantified as the geometric mean fluorescent intensity (gMFI) of a directly-labeled antibody, or fluorochrome-conjugated secondary antibody respectively. More details are supplied in supplementary table 2 and supplementary figure 7.

For analysis of murine samples, gating and analysis are detailed in the relevant Methods Sections, documented in detail in supplementary table 8 and illustrated in supplementary figure 7.

For cytotoxicity assays, dead cells were distinguished by propidium iodide (PI) or fixable viability stain (FVS) as indicated.

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