Corresponding author(s): Gudmundur Vignir Helgason (Vignir.Helgason@Glasgow.ac.uk) and Eyal Gottlieb (e.gottlieb@technion.ac.il)

☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

Describe how sample size was determined.

No statistical method was used to predetermine sample size. For in vivo work the number of animals used in each experiment was carefully estimated based on our preliminary experiments and previous experience. For in vitro experiments, a minimum of 3 patient samples were chosen as a sample size to ensure adequate power, unless stated otherwise. Data obtained from each patient sample represents an independent experiment.

2. Data exclusions

Describe any data exclusions.

For in vitro LTC-IC experiments, 2 patients were excluded from the analysis as no visible colonies were present in the vehicle-treated condition following 5-week in vitro culture.
For in vivo experiments, no animal was excluded from the analysis.

3. Replication

Describe whether the experimental findings were reliably reproduced.

Each experiment was reproduced at least 3 times independently (unless otherwise stated) and were reproducible.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

Primary human samples or animals were not randomized. For in vitro work primary samples were selected by disease stage (i.e. CML chronic phase). For in vivo work, primary samples were selected by transplantability into NSG mice. Prior to drug treatment, mice were allocated based on their pre-treatment engraftment levels.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

The investigators were not blinded to allocation during experiments.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ A statement indicating how many times each experiment was replicated
☐	☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	Statistic analysis: GraphPad Prism 5.03

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	CML and normal samples required informed consent in accordance with the Declaration of Helsinki and approval of the National Health Service (NHS) Greater Glasgow Institutional Review Board. Ethical approval has been given to the research tissue bank (REC 15/WS/0077) and for using surplus human tissue in research (REC 10/S0704/60).

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Total OXPHOS cocktail (Abcam, ab110413) and MT-CO2 (Thermo Fisher Scientific, A-6404) were both validated to react with human by the suppliers.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	N/A
b. Describe the method of cell line authentication used.	N/A
c. Report whether the cell lines were tested for mycoplasma contamination.	N/A
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	N/A

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

8 week-old sub-lethally irradiated (2.5Gy) female NOD.Cg-PrkdcscidIl2rgtm1Wjl/SzJ NSG mice (The Jackson Laboratory) were used.
Animal work was carried out with ethical approval from the University of Glasgow under the Animal (Scientific Procedures) Act 1986.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

Patient sample: age/gender/disease and state/BCR-ABL status
CML 1: 63/M/CML Chronic Phase (CP)/BCR-ABL positive
CML 4: 56/M/CML-CP/BCR-ABL positive
CML 5: 56/F/CML-CP/BCR-ABL positive
CML 6: 48/F/CML-CP/BCR-ABL positive
CML 7: 58/M/CML-CP/BCR-ABL positive
CML 8: 46/M/CML-CP/BCR-ABL positive
CML 9: 30/M/CML-CP/BCR-ABL positive
CML 10: 33/M/CML-CP/BCR-ABL positive
CML 12: 62/M/CML-CP/BCR-ABL positive
CML 14: 43/M/CML-CP/BCR-ABL positive
CML 15: 69/M/CML-CP/BCR-ABL positive
nonCML 020: 60/M/mantle cell lymphoma/BCR-ABL negative
nonCML 026: 69/M/mantle cell lymphoma/BCR-ABL negative
nonCML 029: 66/M/Diffuse Large B-Cell lymphoma/BCR-ABL negative
nonCML 031: 60/M/Diffuse Large B-Cell lymphoma/BCR-ABL negative

Corresponding author(s): Gudmundur Vignir Helgason (Vignir.Helgason@Glasgow.ac.uk) and Eyal Gottlieb (e.gottlieb@technion.ac.il)

☐ Initial submission ☐ Revised version ☒ Final submission

Flow Cytometry Reporting Summary

Form fields will expand as needed. Please do not leave fields blank.

Data presentation

For all flow cytometry data, confirm that:

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

☒ 2. 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).

☒ 3. All plots are contour plots with outliers or pseudocolor plots.

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

Methodological details

5. Describe the sample preparation.	CML samples were leukapheresis products from patients in chronic phase CML at the time of diagnosis. Normal samples were; i) bone marrow products from healthy donors, ii) surplus cells collected from femoral head bone marrow, surgically removed from patients undergoing hip replacement or iii) leukapheresis products from patients with non-myeloid Ph-negative haematological disorders. CD34+ cells were isolated using CD34 MicroBead Kit or CliniMACS (both Miltenyi Biotec); the flow through consisting of CD34- cells. For isolation of the CD34+38- population, CD34+ samples were stained with anti-human CD34 (APC; BD Biosciences) and anti-human CD38 (PerCP; Biolegend) and sorted using a FACSAriaTM Fusion Cell sorter (BD Biosciences). For the mouse engraftment experiments, total bone marrow cells were collected from femurs and tibias and stained with antibodies as described in methods.
6. Identify the instrument used for data collection.	BD FacsVerse
7. Describe the software used to collect and analyze the flow cytometry data.	Flow Jo
8. Describe the abundance of the relevant cell populations within post-sort fractions.	The expression of human CD34 and human CD38 was verified post-sort by flow cytometry. Enrichment of the cells of interest within the post-sort fraction was confirmed to be above 90% in all samples tested.
9. Describe the gating strategy used.	The gating strategy is explained as a Supplementary Information . Human CD34, CD45, CD38 were gated based on the fluorescence of unstained, single colours and fluorescence minus one (FMO) samples.

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