samples of never senescent cells—initiated leukaemias in recipient mice ($P = 0.0275$, comparing previously senescent and never senescent groups); as expected, all Lin^- transplants gave rise to leukaemias ($P < 0.001$, comparing Lin^- and never senescent groups; Fig. 4b, c). Notably, and further adding to SAS in oncogene-induced senescent colon mucosa cells or melanocytes (compare with Fig. 1d), TIS reprogramming is not restricted to cells of lymphoid origin, as demonstrated for an acute myeloid leukaemia (AML) mouse model[24], culture-established human AML cells, and primary human leukaemic blast samples obtained at diagnosis from patients with AML (Extended Data Fig. 10e–l). Thus, cellular senescence is not only associated with additional stem-cell features in tumour cells with pre-existing self-renewal capability, but also catalyses the cell-autonomous reprogramming of non-stem bulk tumour cells of lymphoid and non-lymphoid origin into *de novo* cancer stem cells.

We present here an unexpected cell-intrinsic link between the senescence program and the acquisition of self-renewing properties, which we postulate serves as a physiological rescue mechanism in development and tissue homeostasis. We and others have observed that senescence not only occurs in critically stressed cells, but also may spread to adjacent cells via SASP components in a paracrine fashion (ref. 25; J.R.D. and C.A.S., unpublished observations). We propose that nature equipped normal cells with a latent SAS capacity (compare with Extended Data Fig. 1g) to counter the imminent loss of an entire tissue compartment due to pro-apoptotic and pro-senescent stresses: in rare cells spontaneously re-entering the cell cycle when threatening stresses no longer apply, SAS may become a tissue-replenishing principle. In a neoplastic context, cellular senescence—particularly in tumour cells with apoptotic defects—appears to be primarily a beneficial response by keeping tumour growth in check. However, post-senescent cells with 'hijacked' SAS exert their detrimental potential at relapse by driving a much more aggressive growth phenotype. Therefore, pharmacological strategies to specifically eliminate senescent cells before a fraction of them may implement their acquired stemness capacity become, as previously reported by us regarding cancer[9] and by others regarding ageing-related pathologies[26,27], a critical therapeutic need.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

Received 16 February 2014; accepted 24 November 2017.
Published online 20 December 2017.

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Supplementary Information is available in the online version of the paper.

Acknowledgements We thank G. Evan, the late A. Harris, T. Jacks and T. Jenuwein for mice, cells and materials; E. Berg, N. Burbach, A. Herrmann, H. Lammert, S. Mende, B. Teichmann and the Berlin-Brandenburg Center for Regenerative Therapies (BCRT) flow cytometry laboratory for technical assistance; and members of the Schmitt laboratory for discussions and editorial advice. This work was supported by a Ph.D. fellowship to J.R.D. from the Boehringer Ingelheim Foundation; by grants from the Deutsche Forschungsgemeinschaft to B.D., M.H. and C.A.S. (SFB/TRR 54) and to A.T. (SFB 873); by the Helmholtz Alliance 'Preclinical Comprehensive Cancer Center' grant (HA-305) from the Helmholtz Association to A.T. and C.A.S.; by the Dietmar Hopp Foundation to A.T.; and by the Deutsche Krebshilfe (grant 110678) to C.A.S. This interdisciplinary work was further made possible by the Berlin School of Integrative Oncology (BSIO) graduate program funded within the German Excellence Initiative, and the German Cancer Consortium (GCC).

Author Contributions M.Mi. performed mouse lymphoma and leukaemia work, stem-cell and senescence assays, and gene set enrichment analyses. J.H.M.D. and M.R. conducted analyses with human cancer cell lines and primary human material. D.N.Y.F. and D.B. carried out flow cytometric analyses. Z.Z. generated leukaemias in the p53-regulatable mouse T-ALL model, I.A.M.B. and J.Z. in the p53-regulatable mouse AML model. Y.Y. carried out biochemical analyses. J.R.D. provided transcriptome analyses and long-term outcome data from senescence-capable mouse lymphomas. L.D. and M.A.M.-P. performed chromatin immunoprecipitations and analysed related datasets. D.L. conducted Affymetrix gene expression profiling and analyses. T.K. and G.D. carried out proteome analyses. M.Me. generated β-catenin/TCF-reporter cancer cell lines and performed luciferase reporter assays. K.P. generated qPCR data. A.T., B.D., H.G. and S.L. contributed to study design, data interpretation and preparation of the manuscript. M.H. provided immunohistochemical analyses. C.A.S. designed experiments, analysed the data and wrote the manuscript.

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Reviewer Information *Nature* thanks J. P. Medema, J. Vormoor and the other anonymous reviewer(s) for their contribution to the peer review of this work.