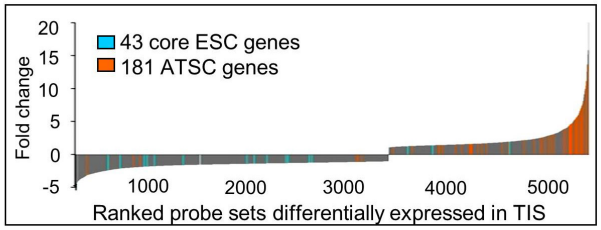
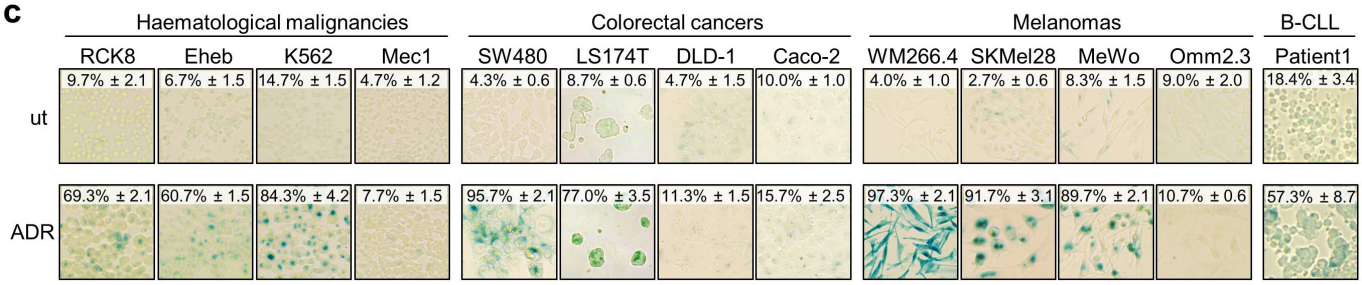
a



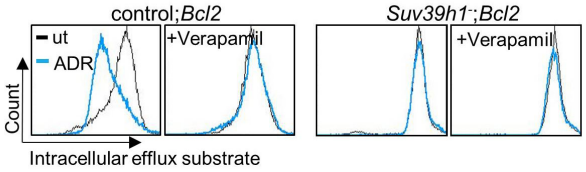
b

Gene set	Reference	ctrl;*Bcl2*		*Suv39h1*$^{-}$;*Bcl2*	
		NES	*P*	NES	*P*
Cell cycle process	GO:0022402	-2.235	< 0.001	-1.827	< 0.001
Proliferation cluster	Ref. 58	-2.931	< 0.001	-1.858	< 0.001
Cycling genes	Ref. 59	-2.680	< 0.001	-1.692	< 0.001
ATSC	Ref. 17	2.511	< 0.001	**0.915**	0.790
core ESC	Ref. 49	**1.012**	0.435	**1.105**	0.284
HSC signature	Ref. 56	1.618	0.001	**0.988**	0.503
LT-HSC signature	Ref. 60	1.513	0.001	**0.788**	0.922

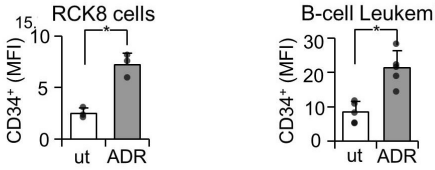
c



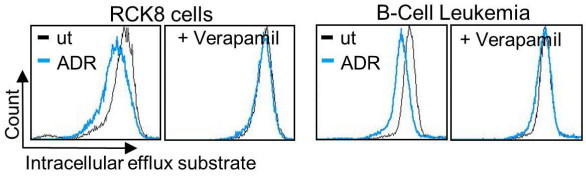
d



e



f



g

Replicative stressor		Aging		Aging		Stasis, p16-dependent		Agonescence, telomere shortening	
Cell type		Mesenchymal stem cells		BJ - skin fibroblasts		Mammary epithelial cells		Mammary epithelial cells	
Gene set	Reference	NES	*P*	NES	*P*	NES	*P*	NES	*P*
Cell Cycle	GO:0022402	-4.154	<0.001	-1.282	0.032	-2.308	<0.001	-1.778	<0.001
ATSC	Ref.17	1.889	0.014	1.215	0.024	1.294	<0.001	1.847	<0.001

Extended Data Figure 1 | Senescent cells of mouse and human origin present with enhanced stem-cell markers and functionalities. **a**, 5,401 probe sets (corresponding to 3,867 genes) differentially expressed in TIS were determined from the transcriptome data comparing untreated and ADR-senescent primary control;*Bcl2* lymphomas by two-way ANOVA adjusted for multiple testing (cut-off $q < 0.05$, $n = 12$ biologically independent samples). 181 out of 737 genes belonging to an ATSC[17] or 43 out of 337 genes of core embryonic stem-cell (ESC) signature[49] were detected and marked orange and blue, respectively, in the fold-change-ranked gene list. Whereas the expression of core embryonic stem-cell genes was not correlated with senescence, ATSC transcripts exhibit a strong association with TIS. **b**, Senescence-selective gene set enrichment pattern of proliferation- and stem-cell-related gene modules (including haematopoietic stem cell (HSC) and long-term HSC (LT-HSC) signatures)[56,58–60] in control;*Bcl2* and *Suv39h*$^{-}$;*Bcl2* lymphoma cells as in Fig. 1a. GSEA based on the Kolmogorov–Smirnov test, with negative NES indicating enrichment in untreated lymphomas, and positive NES reflecting enrichment in TIS. $n = 12$ biologically independent control;*Bcl2* samples and $n = 5$ *Suv39h*$^{-}$;*Bcl2* samples. NES of $P < 0.05$ are considered statistically significant and are shown in red. **c**, Senescence induction by ADR treatment in various human cell lines consisting of haematological malignancies, colorectal cancers, melanomas, or in primary samples from patients with B-CLL as determined by SA-β-gal staining (mean percentage of positive cells ± s.d., $n = 3$ independent experiments for cell lines; $n = 4$ individual B-CLL samples). TIS-competent cells are defined by a greater than fourfold induction of SA-β-gal-positive cells (with the exception of B-CLL samples, in which SA-β-gal-positive cells were at least threefold induced), and depicted as a blue box symbol in Fig. 1c. **d**, ABC transporter activity in cells as in Fig. 1a, measured by the efflux of a fluorescent substrate with and without the ABC transporter inhibitor verapamil. Representative plots of four independent lymphomas tested per genotype. **e**, Enhanced expression of the stem-cell marker CD34 in the RCK8 cell line or primary human B-cell leukaemia samples exposed to ADR treatment *in vitro*. Mean fluorescence intensity ± s.d. from three independent experiments (RCK8 cells) and five individual leukaemia cases determined by flow cytometry. Two-tailed, unpaired *t*-test with Welch's correction, $^{*}P < 0.05$. **f**, TIS-mediated increase and verapamil-dependent blockage of ABC transporter activity in ADR-senescent RCK8 cells and primary human B-cell leukaemia samples as in **e**. One representative out of three independent experiments shown. **g**, SAS occurring in non-malignant senescence scenarios: GSEA of proliferation- or stem-cell-related gene sets (as in **b**) in publicly available transcriptome data representing different models of replicative senescence: primary human mammary epithelial cells in stasis or agonescence (GSE16058, 12 prestasis, 9 stasis and 4 agonescence individual biological samples), high-passage BJ human skin fibroblasts (GSE13330, $n = 6$ pairs of proliferating/senescent cells from individual donors) or high-passage primary human mesenchymal stem cells (GSE9593, $n = 3$ pairs of proliferating/senescent cells from individual donors).