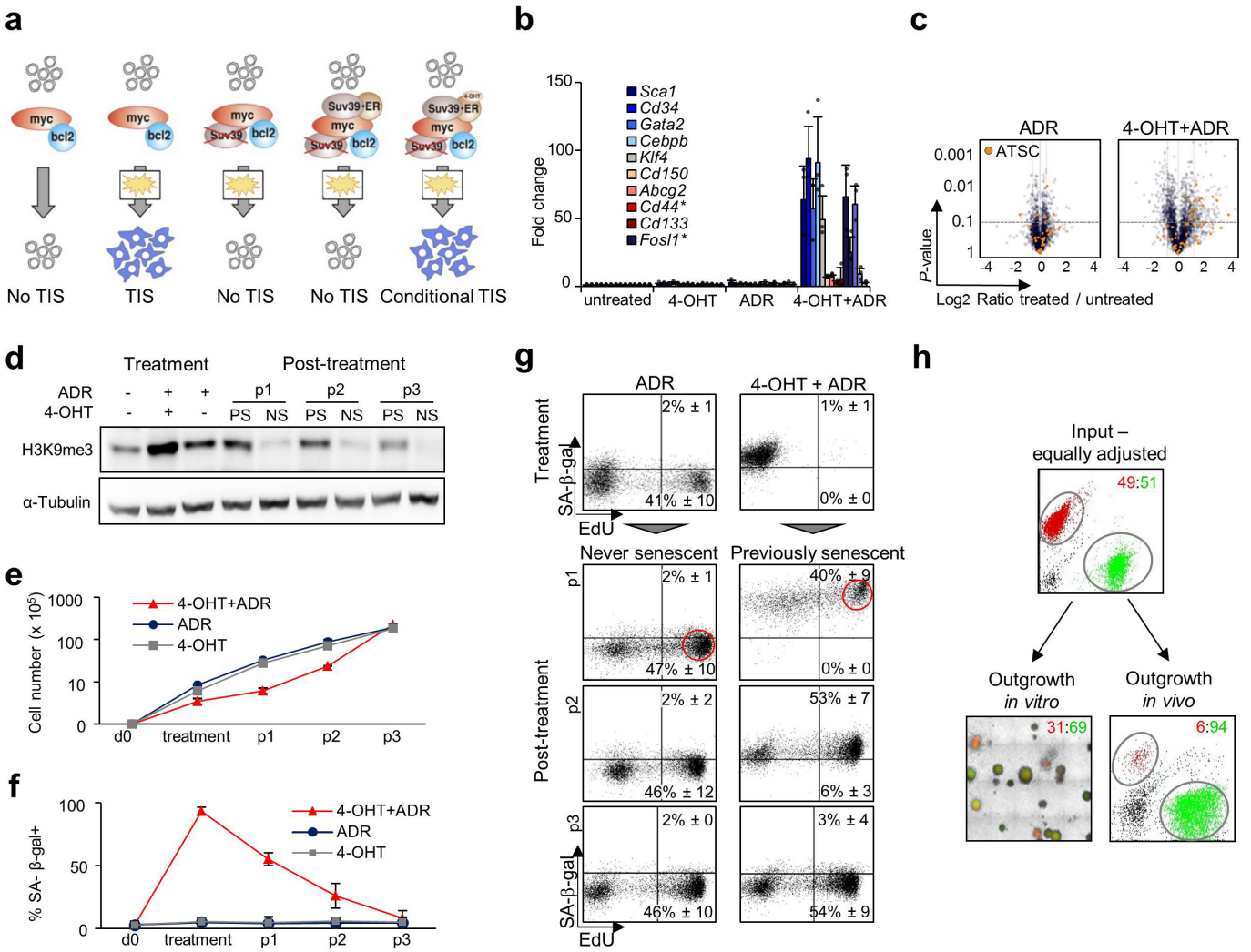

Extended Data Figure 2 | Genetic, biochemical and functional properties of regulatable senescence models. a, Graphic illustration of the model system engineered to stably express a regulatable senescence-essential gene moiety, such as *Suv39h1*$^{-}$ proficient and -deficient Eμ-*Myc* transgenic and *Bcl2*-infected lymphoma variants of which only *Suv39h1*$^{-}$;*Bcl2*;*Suv39h1*-ER^{T2} cells regain conditional TIS capability if exposed to 4-OHT. **b**, Relative transcript levels of the indicated stem-cell-related and Wnt target (asterisk) genes by qPCR in *Suv39h1*$^{-}$;*Bcl2*;*Suv39h1*-ER^{T2} lymphoma cells exposed to the indicated treatments for five days. Results represent mean fold induction relative to the untreated condition ± s.d. ($n = 3$ biologically independent samples). **c**, Global proteome analysis of total *Suv39h1*$^{-}$;*Bcl2*;*Suv39h1*-ER^{T2} cell lysates after five days of ADR ± 4-OHT treatment, showing mean protein expression changes relative to untreated condition (*x* axis) and their statistical significance (*y* axis), $n = 3$ biologically independent samples analysed by Wilcoxon test. All identifications with a $-\log_{10}$ transformed *P* value greater than 1 were considered significant. Dots representing ATSC factors are highlighted in orange. **d**, Immunoblot of H3K9me3 expression in *Suv39h1*$^{-}$;*Bcl2*;*Suv39h1*-ER^{T2} lymphoma cells treated as in **b** ('treatment'), and monitored at the indicated passages in 4-OHT/ADR-free medium ('post-treatment'; p1–3, each passage reflects 7 days in culture). Never senescent, ADR-only- and previously senescent ADR+4-OHT-pretreated lymphoma cells are analysed, α-tubulin is used as a loading control. One out of two independent experiments shown. For gel source data, see Supplementary Fig. 1. **e**, **f**, Growth curve analysis (**e**) and SA-β-gal reactivity time course (**f**) of cells treated as in **d**. Results represent mean cell numbers or percentages of positive cells, respectively ± s.d., from three biologically independent samples. **g**, Kinetics of the proliferation marker EdU and the fluorescent SA-β-gal marker in *Suv39h1*$^{-}$;*Bcl2*;*Suv39h1*-ER^{T2} lymphoma cells after five days of ADR ± 4-OHT treatment ('treatment'), and subsequent passages in 4-OHT/ADR-free medium ('post-treatment', p1–3, each passage reflecting seven days in culture), demonstrating outgrowth of senescent (SA-β-gal^{+}) cells after terminating the 4-OHT/ADR treatment. Mean percentages of EdU^{+}/SA-β-gal^{+} and EdU^{+}/SA-β-gal^{-} cells ± s.d., $n = 4$ biologically independent samples. Representative photomicrographs from cell populations marked by red circles are shown in Fig. 2a. **h**, Competition assays of matched passage 2 previously senescent (GFP-labelled) and never senescent (DsRed-labelled) lymphomas plated at an equal ratio (top) and evaluated by fluorescence microscopy-scored colony formation *in vitro* (bottom left), and by flow cytometric analysis of lymphoma cells isolated from manifest tumours after transplantation (bottom right). Numbers reflect the ratio of red- to green-fluorescent colonies or cells, respectively. One representative out of four independent experiments shown, including colour reversal.