

Supplementary Information for

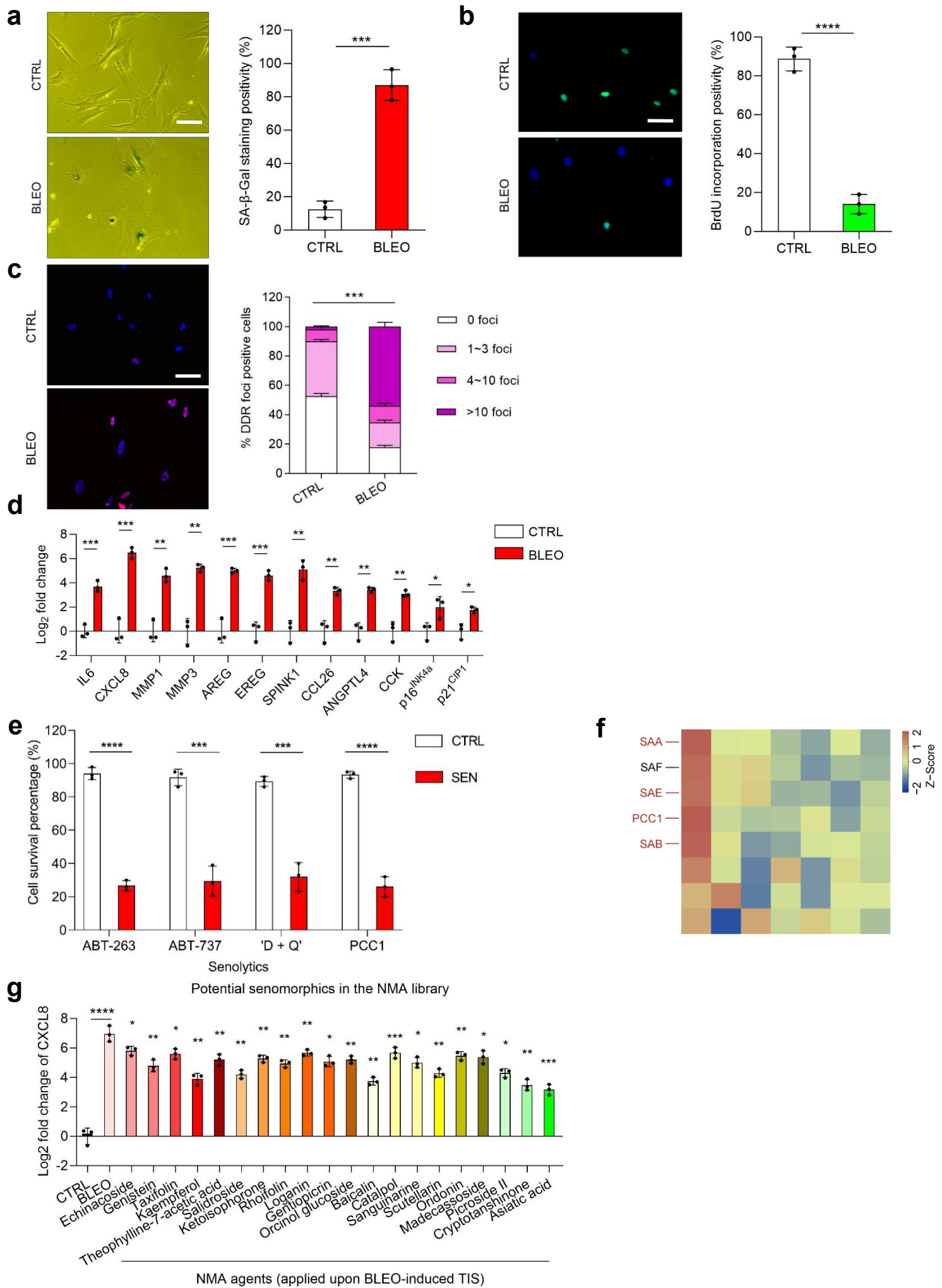
Salvianolic acids are natural senolytics and increase lifespan in old age

Hongwei Zhang, Zhirui Jiang, Qiang Fu, Qixia Xu, Halidan Wufuer, Shuangbai Zhou,
Qingfeng Li, Larissa Langhi Prata, Guilong Zhang, James L. Kirkland and Yu Sun

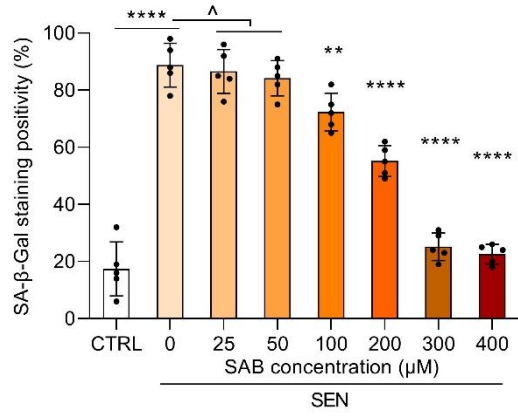
Supplementary Figures 1-27

Supplementary Tables 1-6

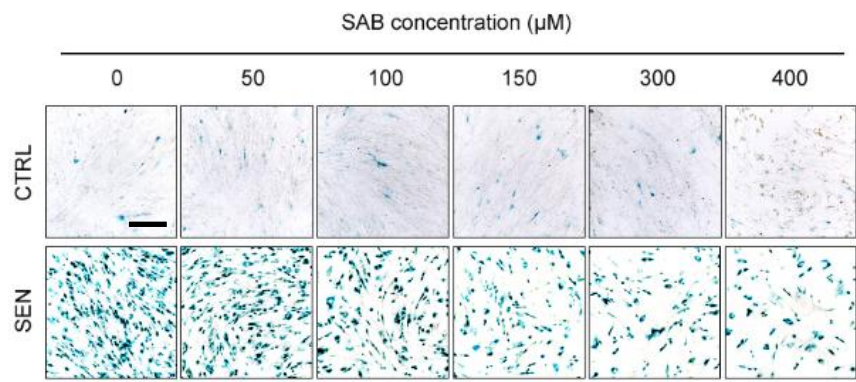
Supplementary Fig. 1



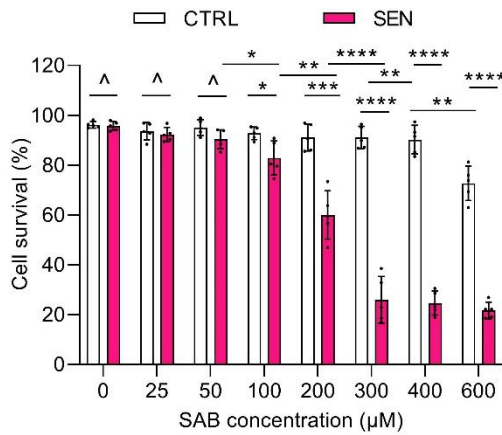
a



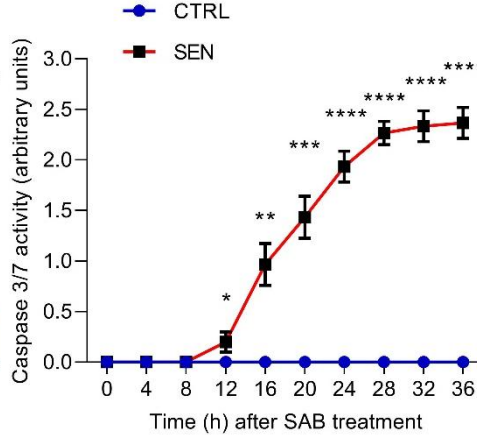
b



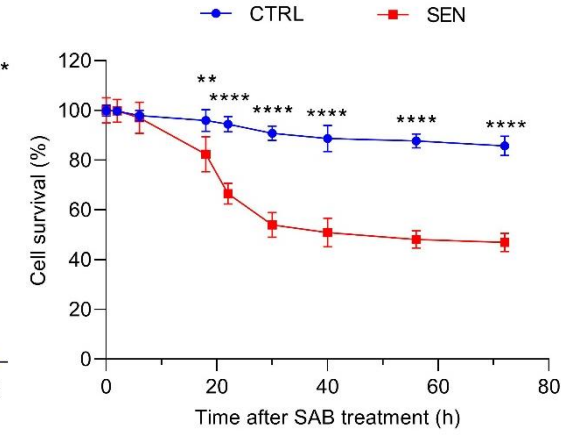
c



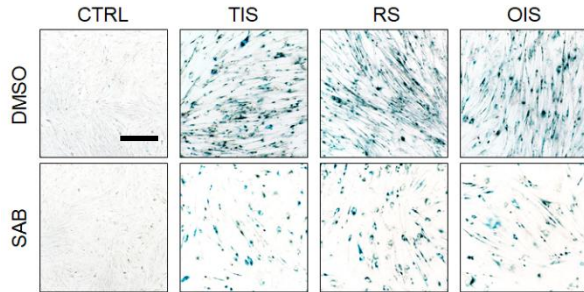
d



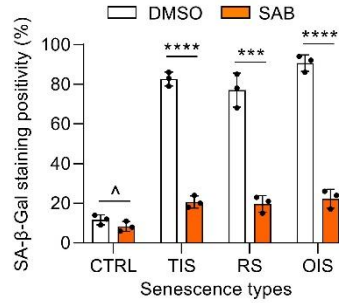
e



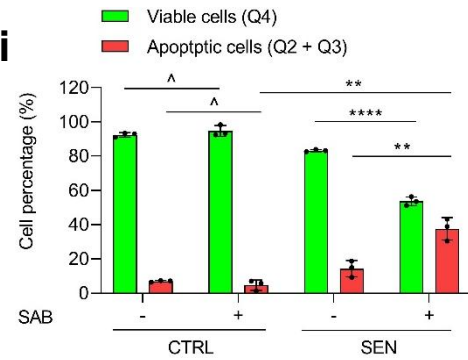
f



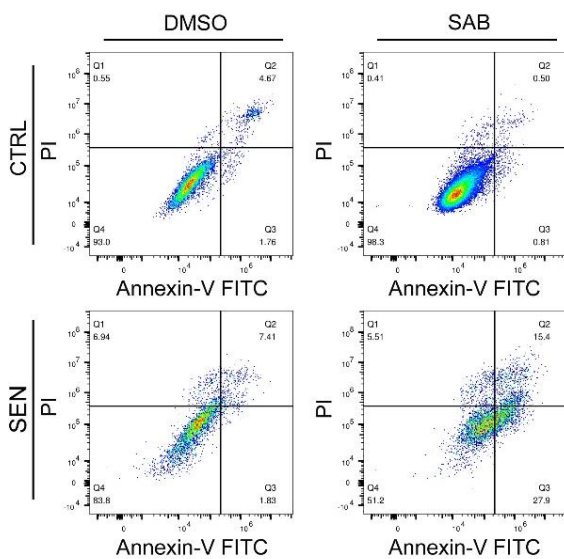
g



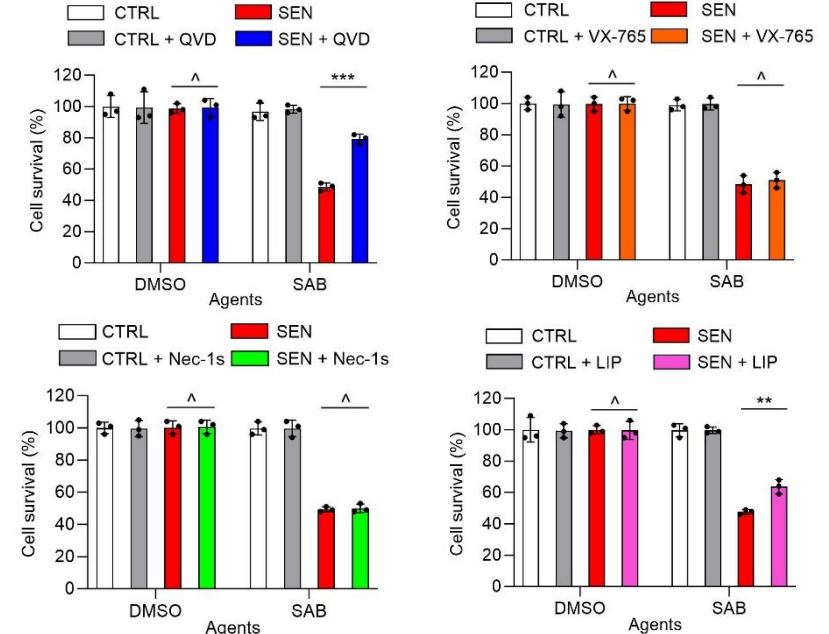
i

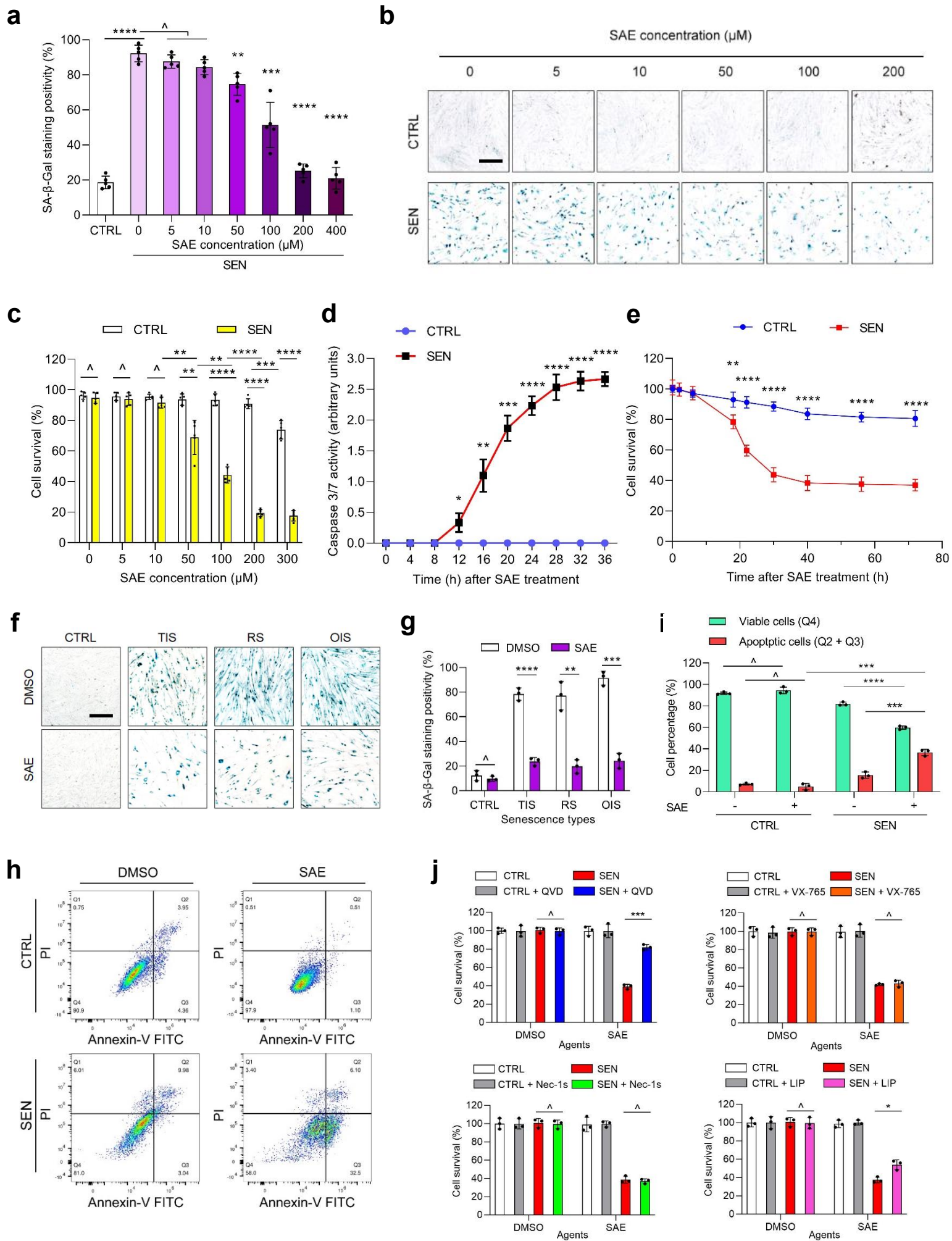


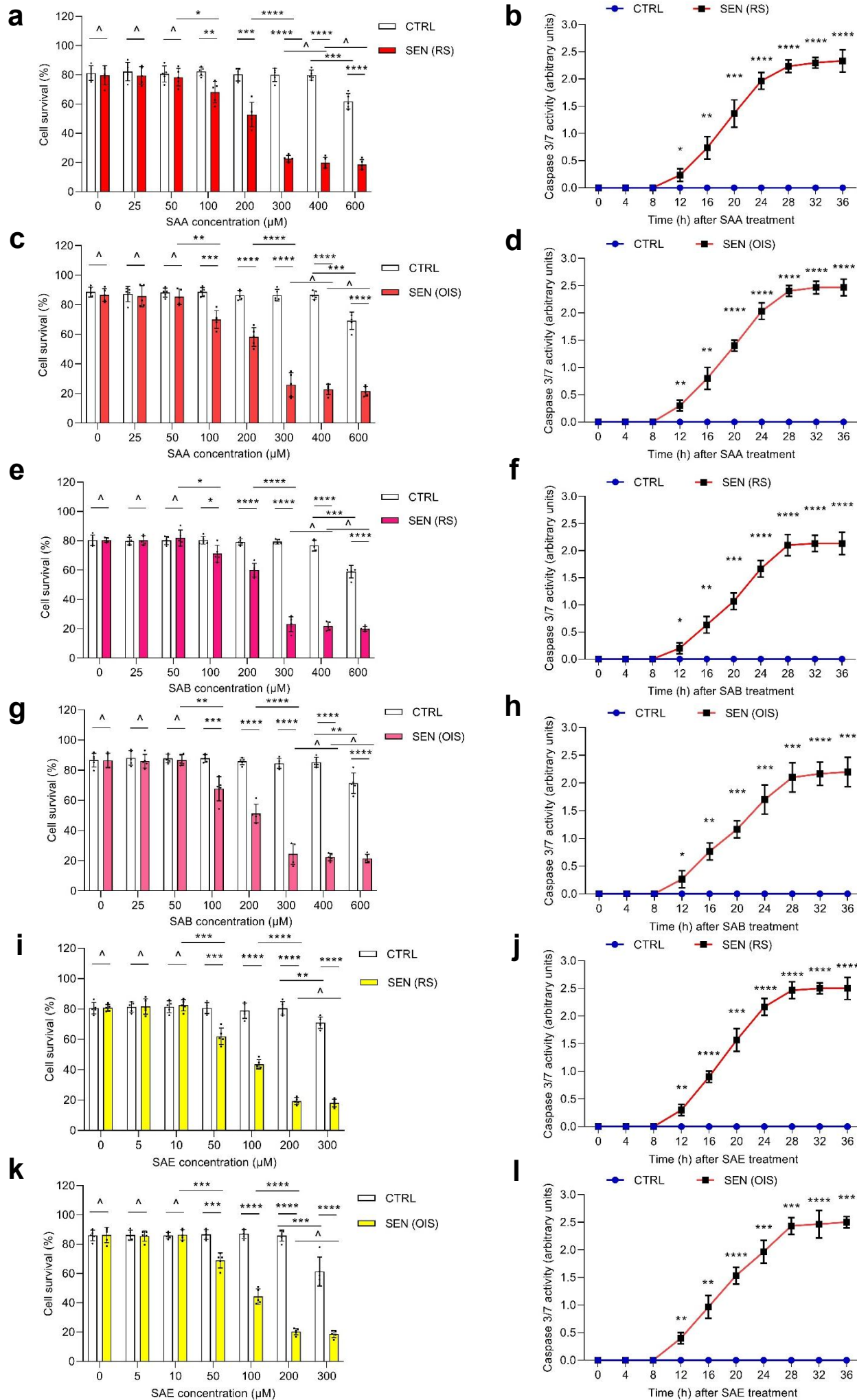
h

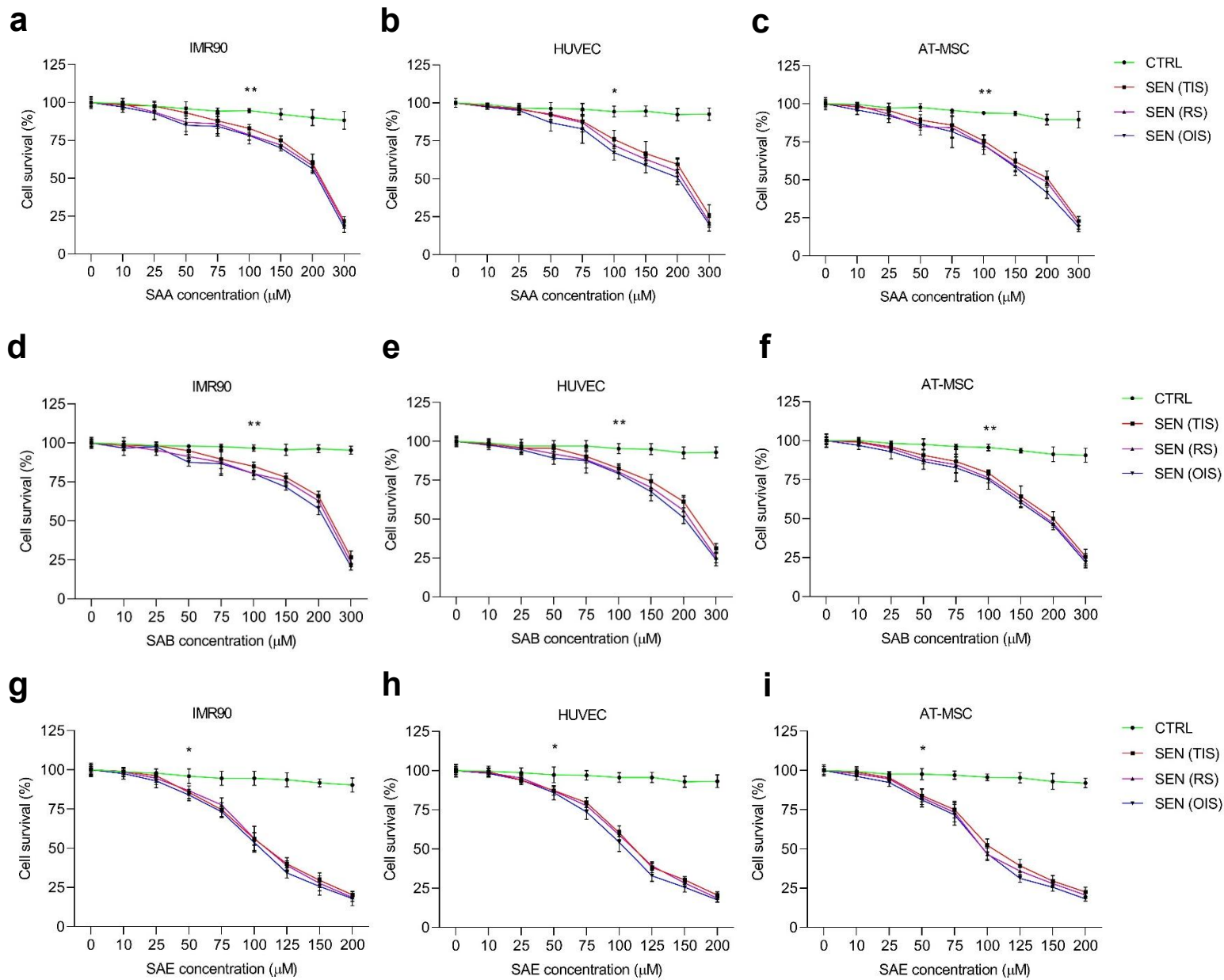


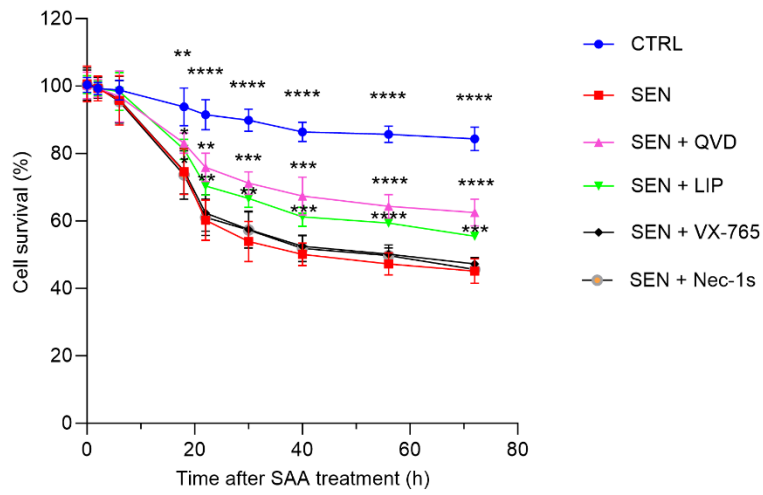
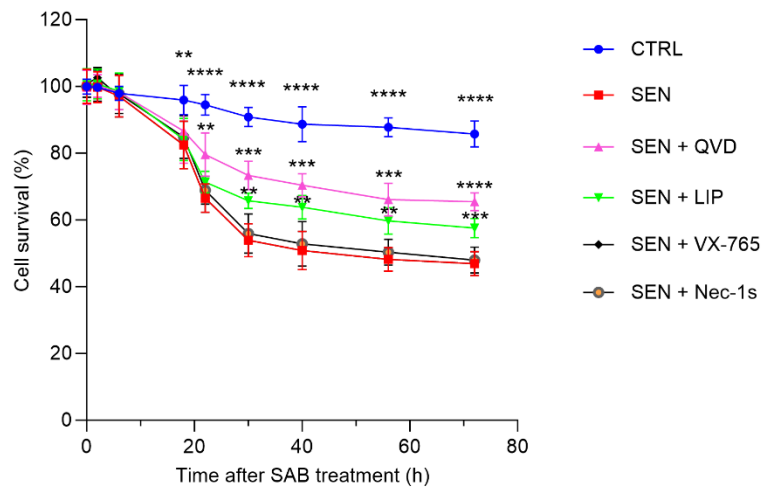
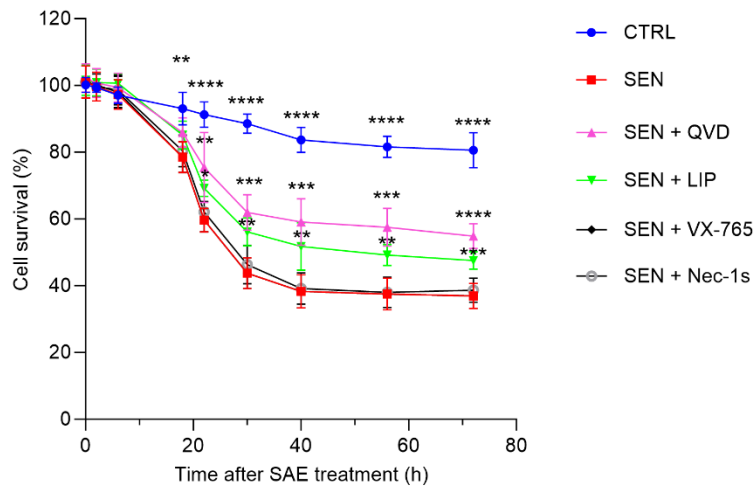
j



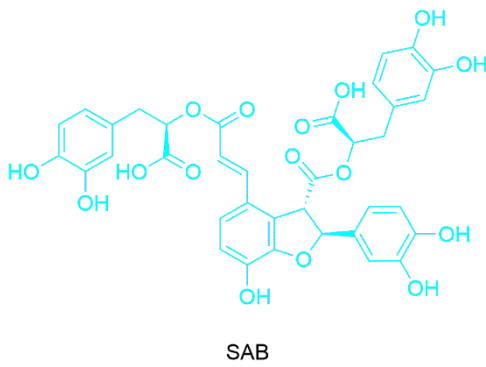




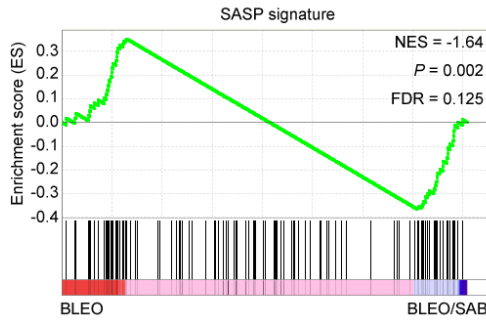
Supplementary Fig. 5

a**b****c**

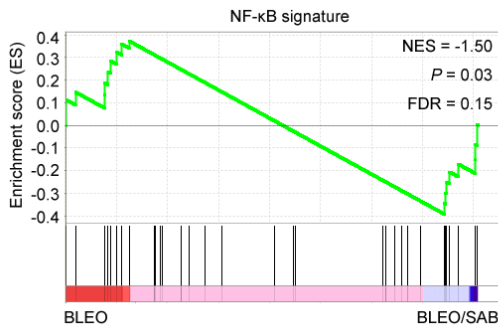
a



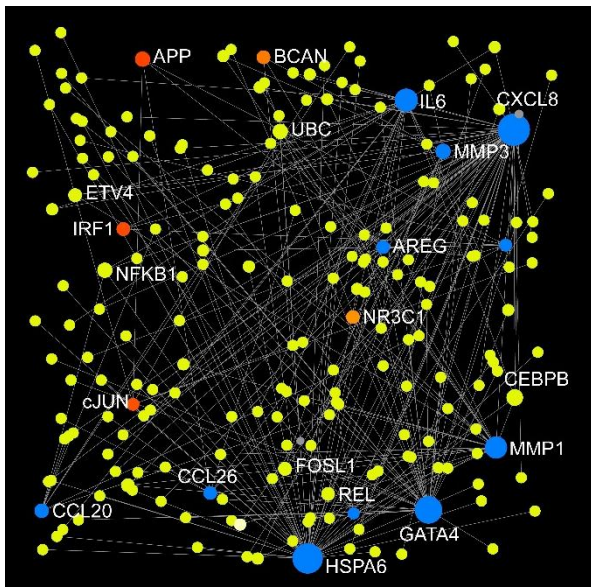
c



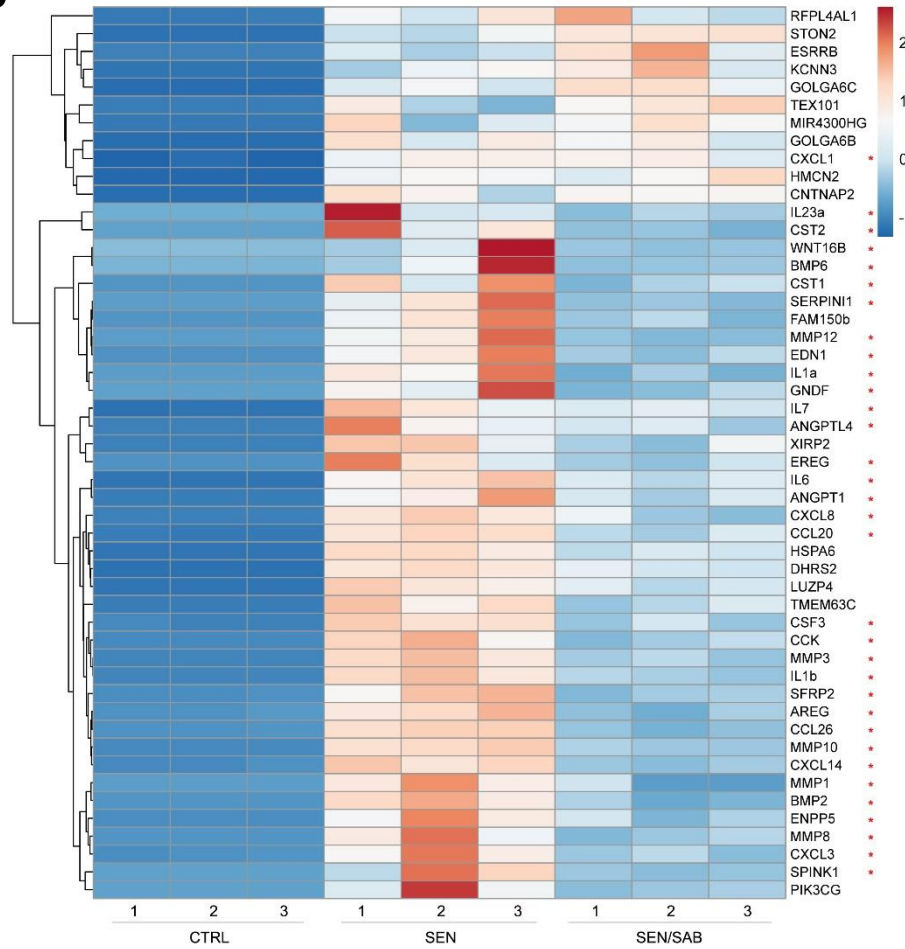
d



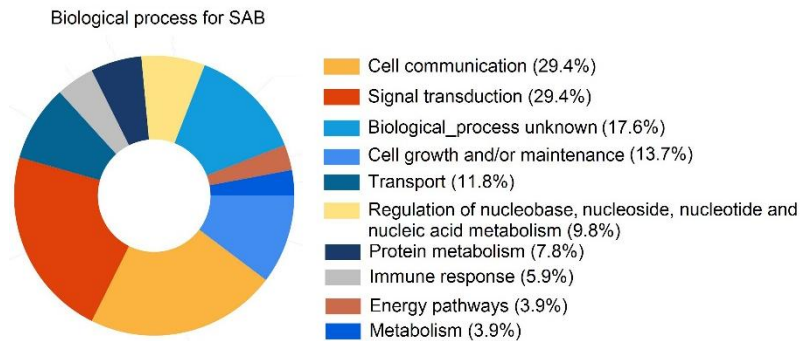
e



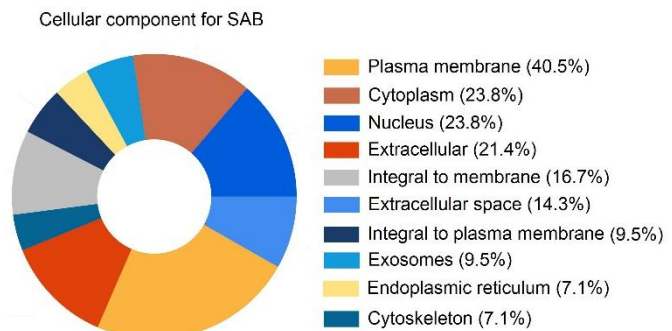
b



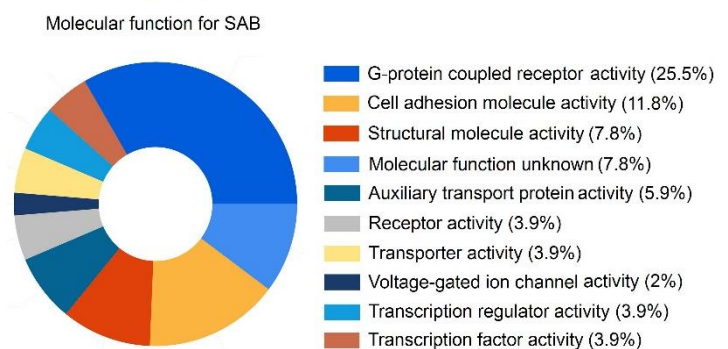
f



g

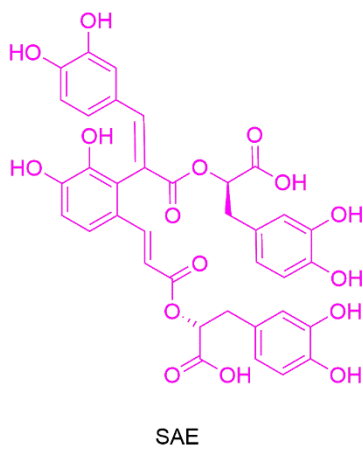


h

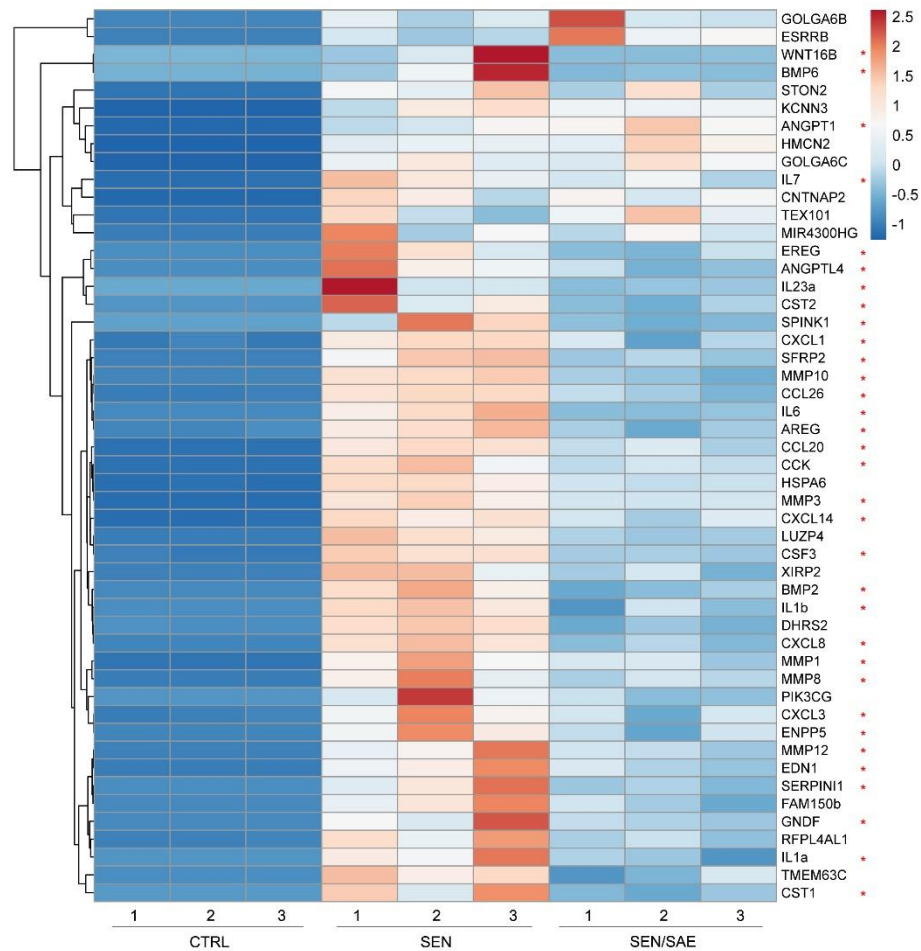


Supplementary Fig. 8

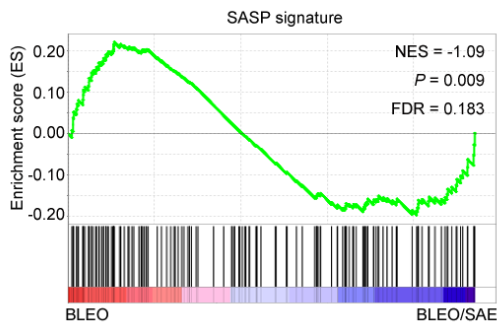
a



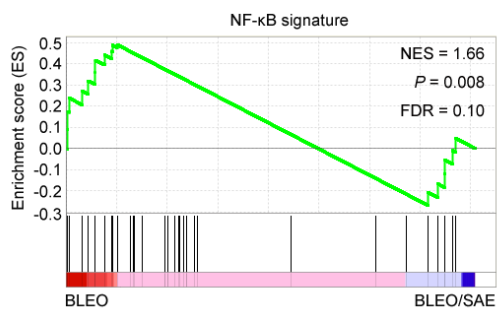
b



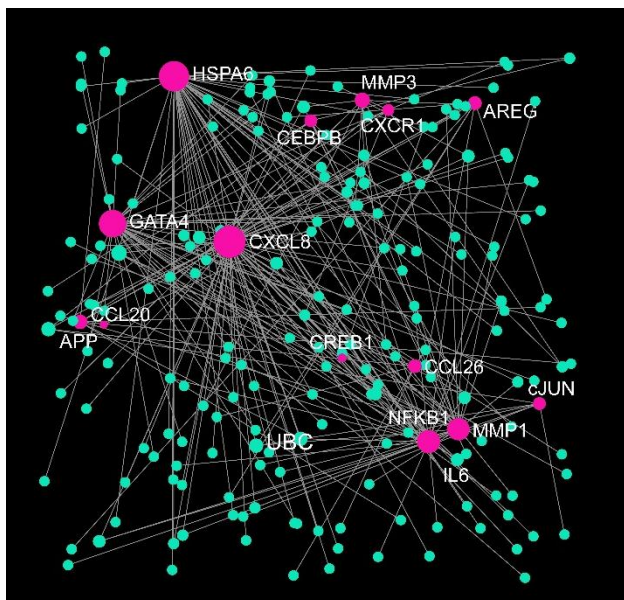
c



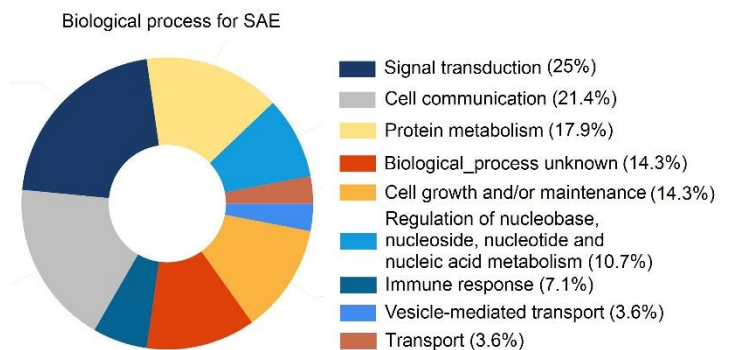
d



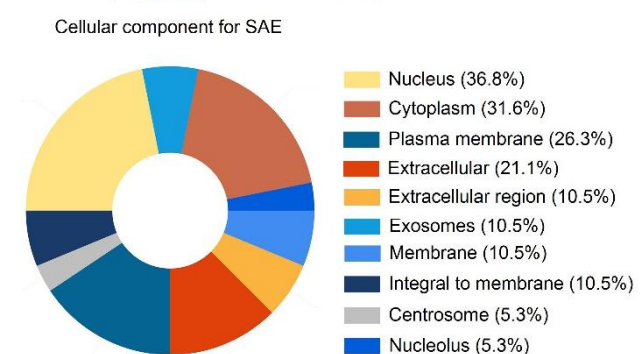
e



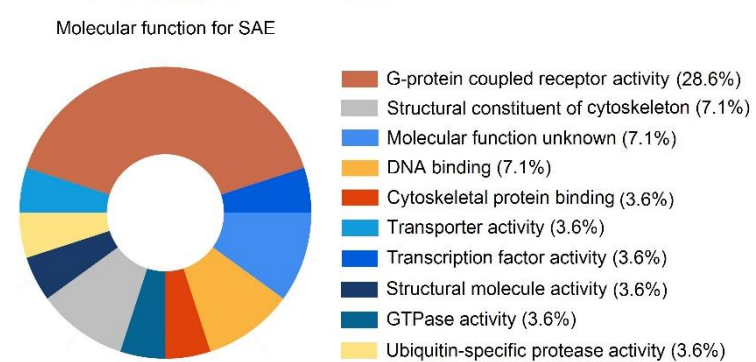
f

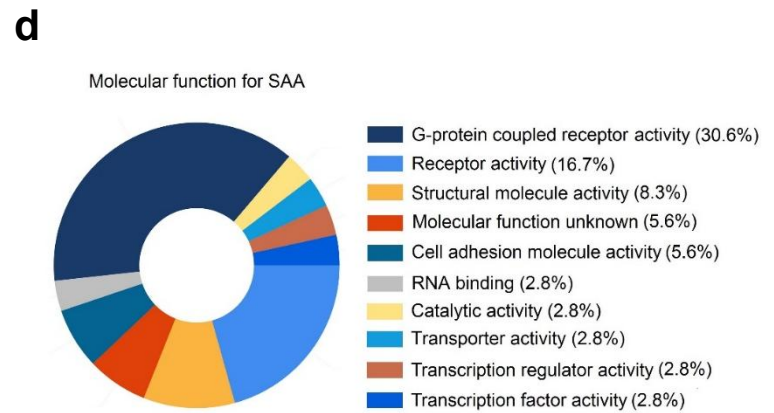
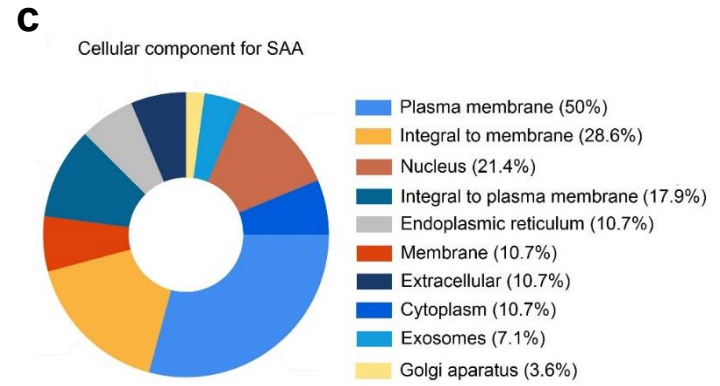
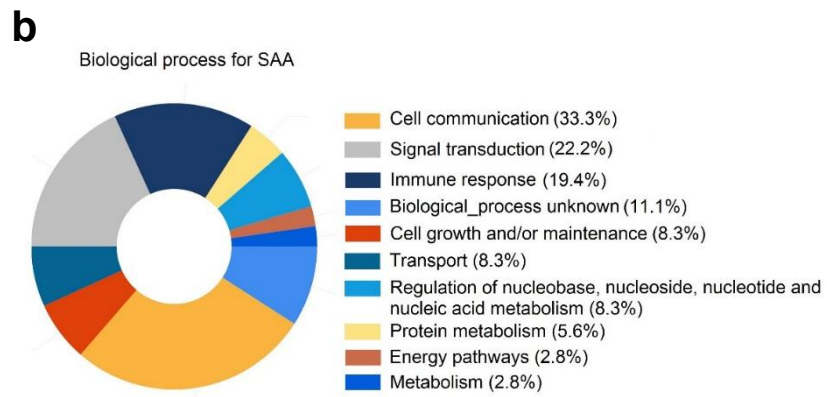
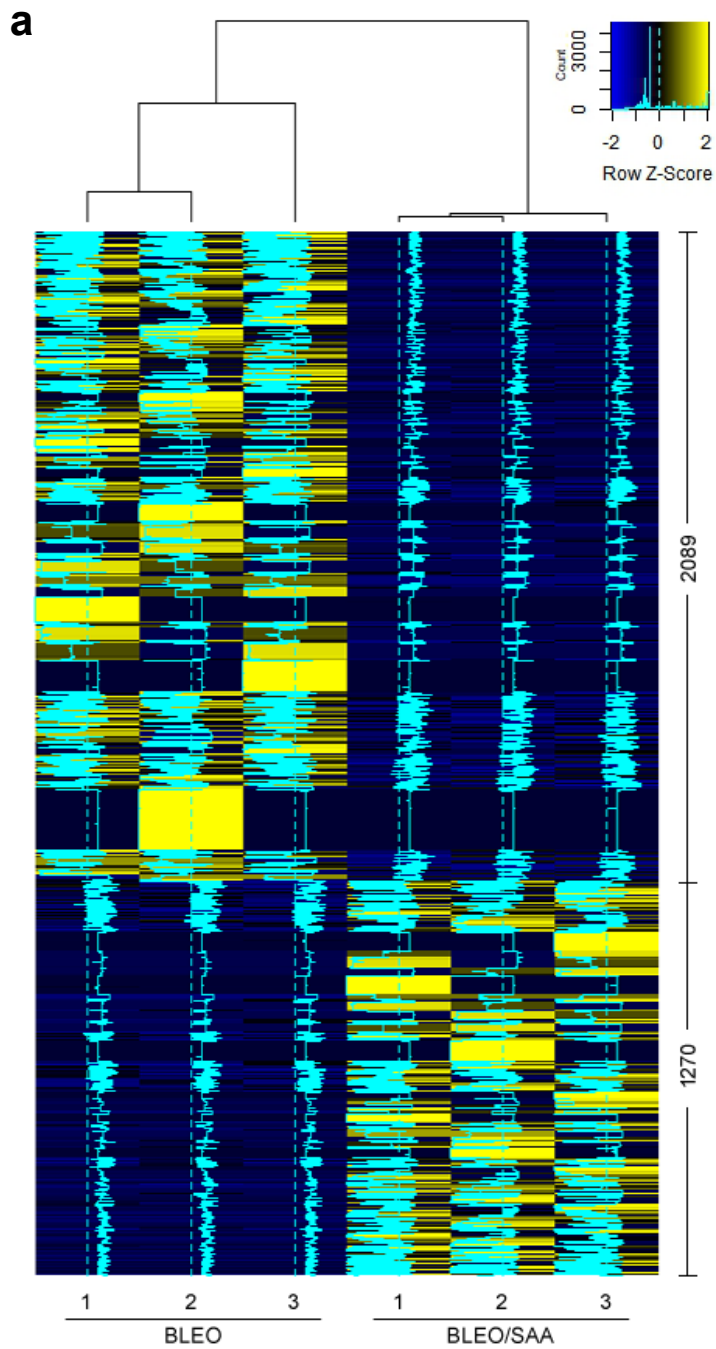


g

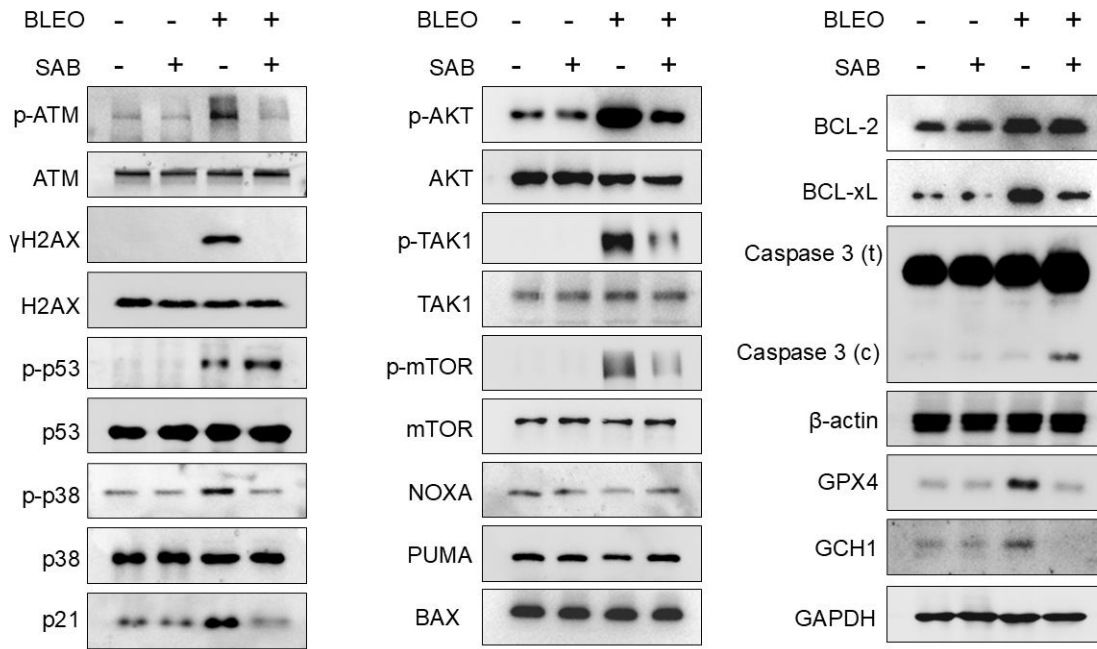


h

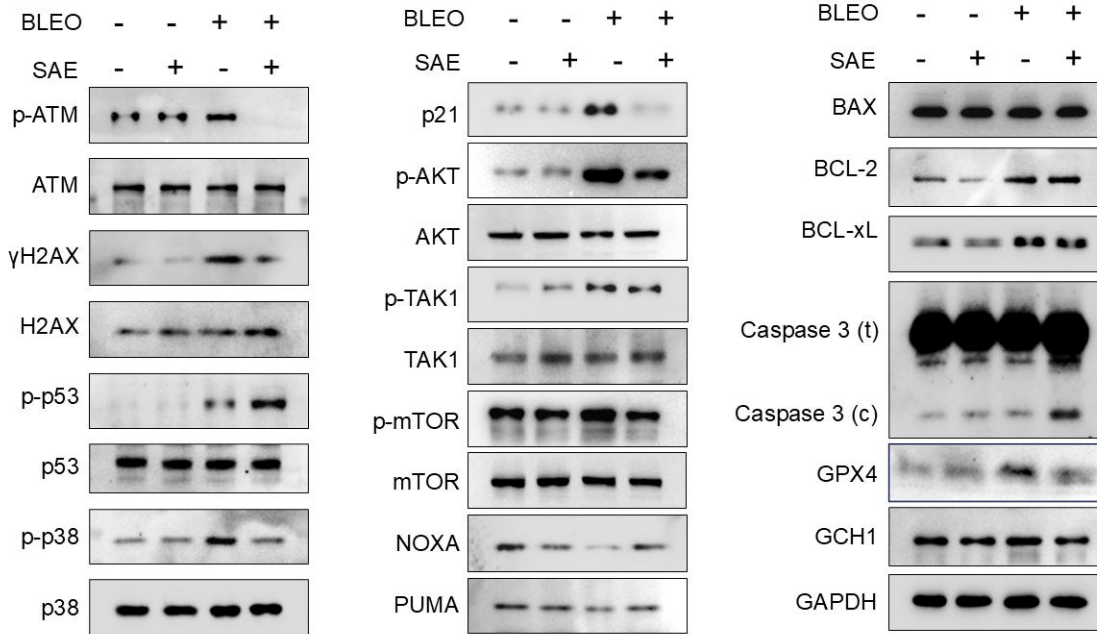


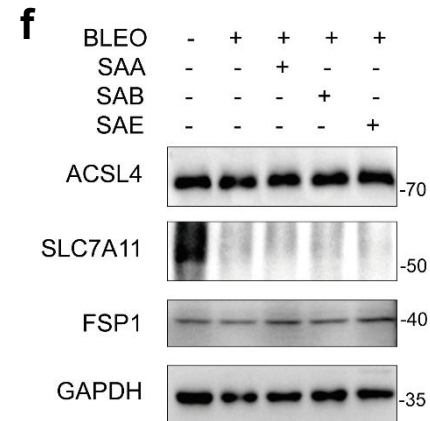
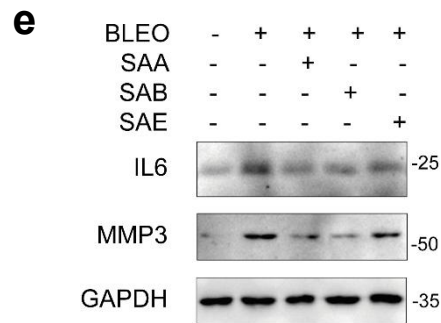
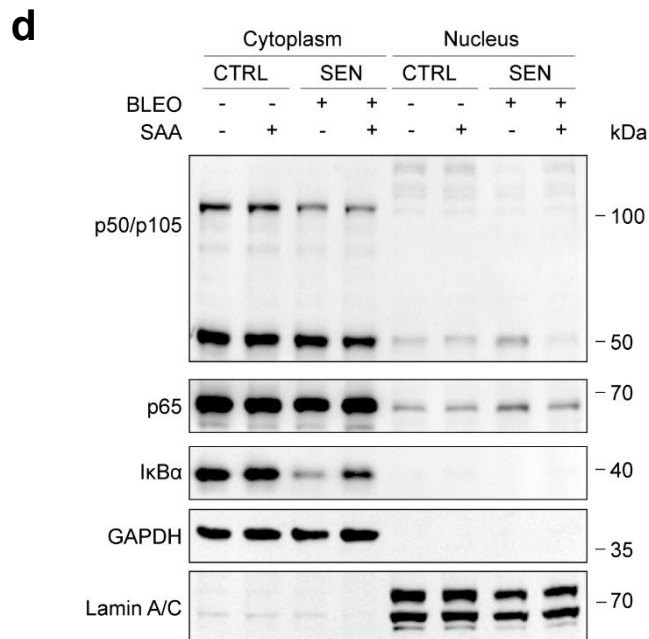
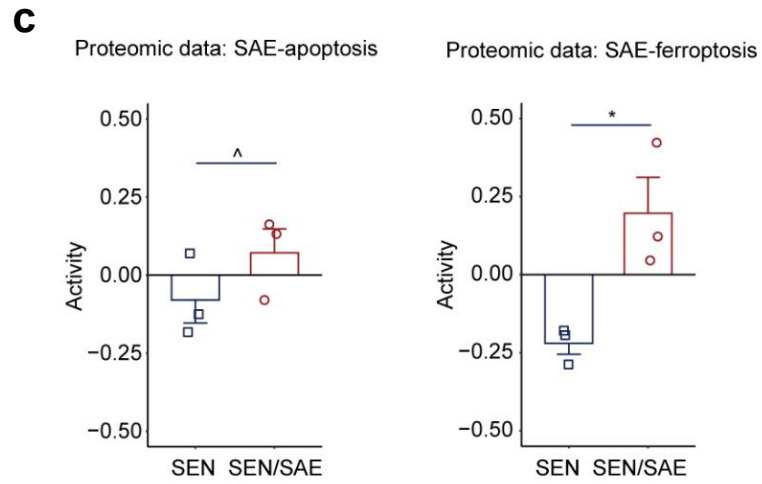
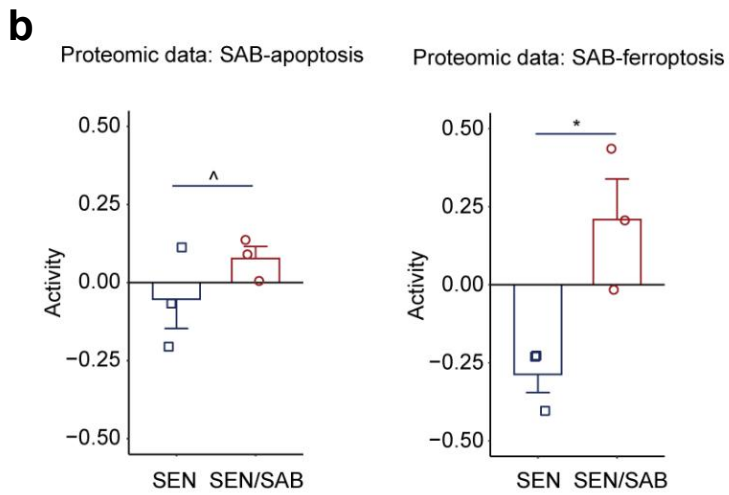
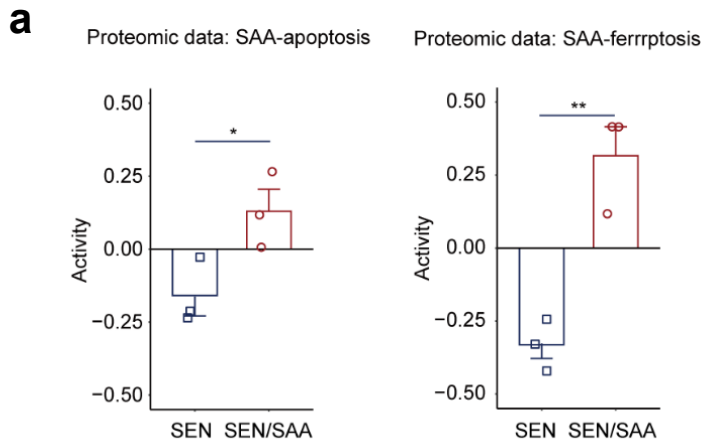


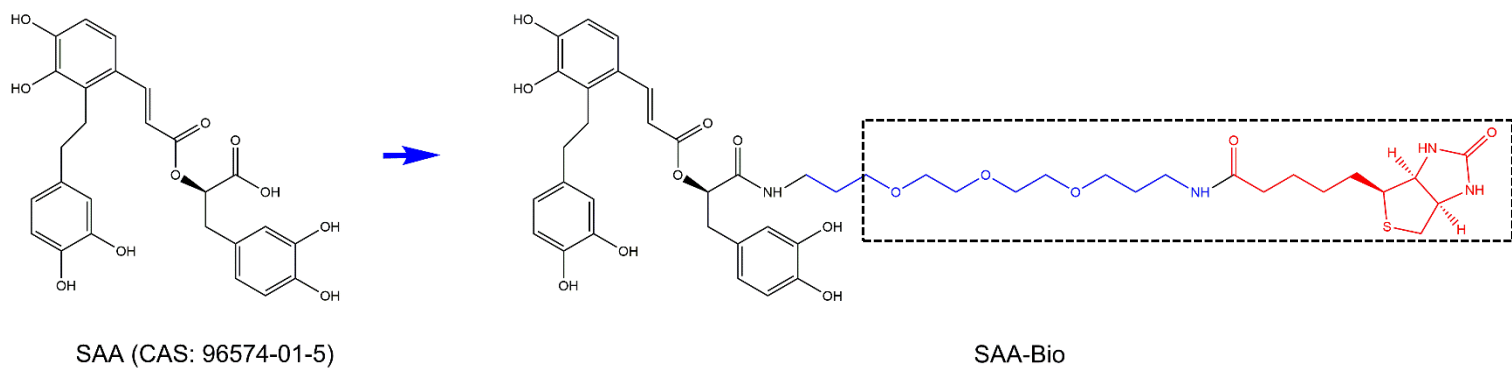
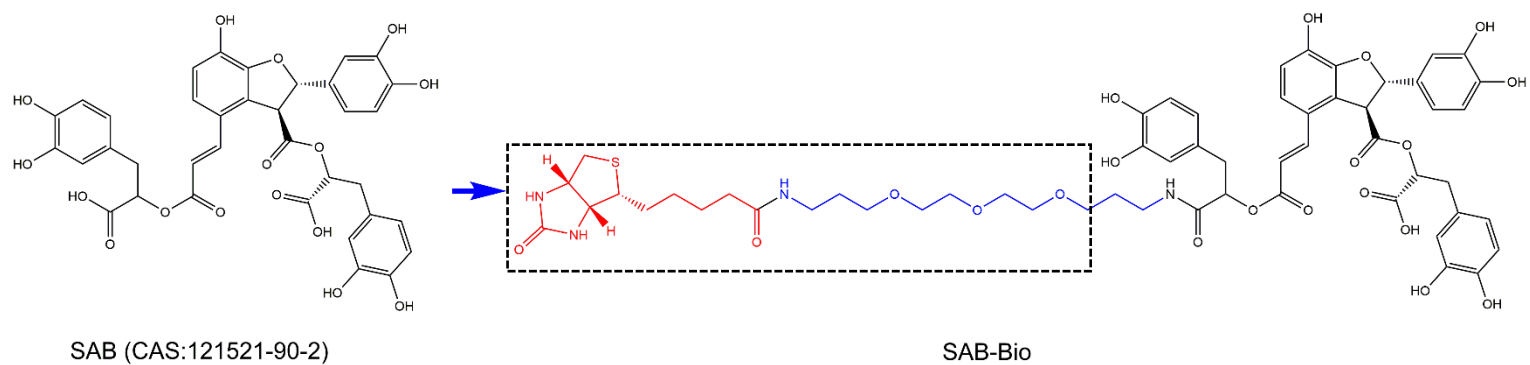
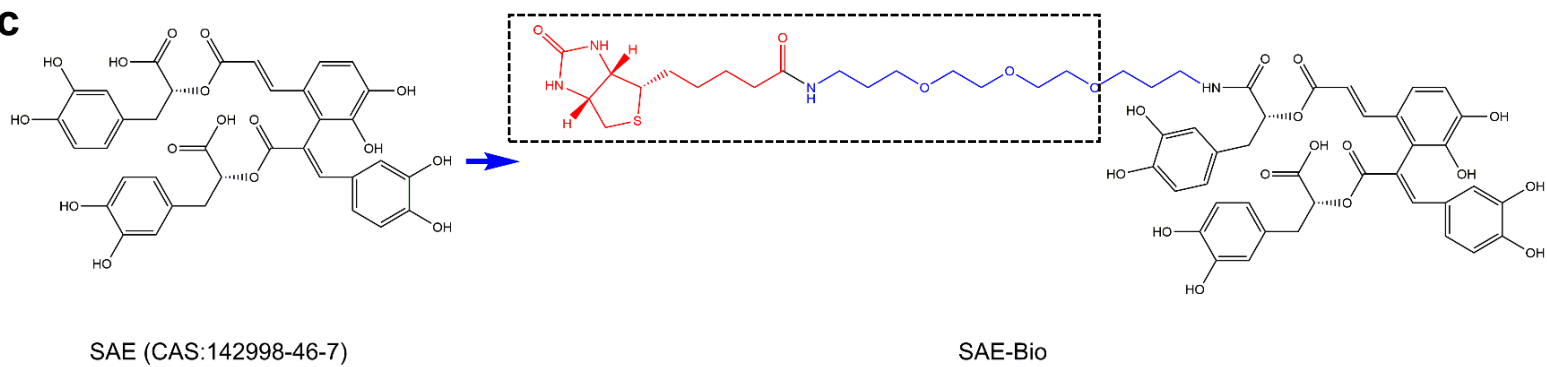
a

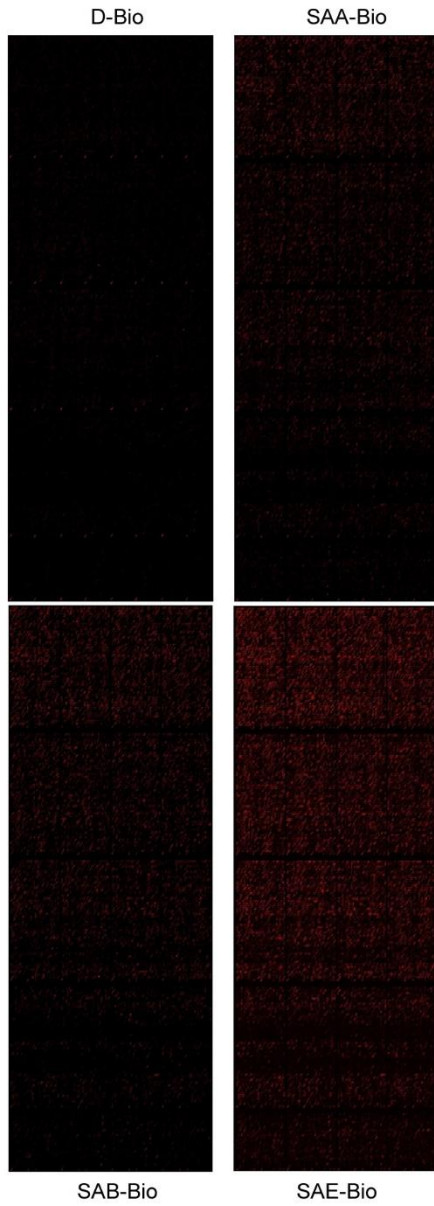
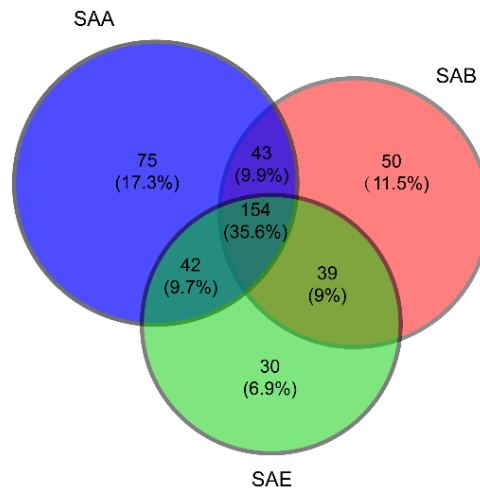
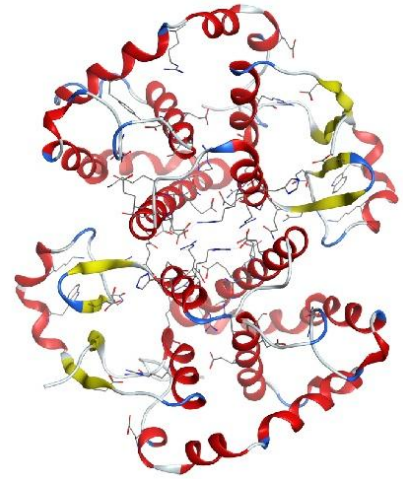
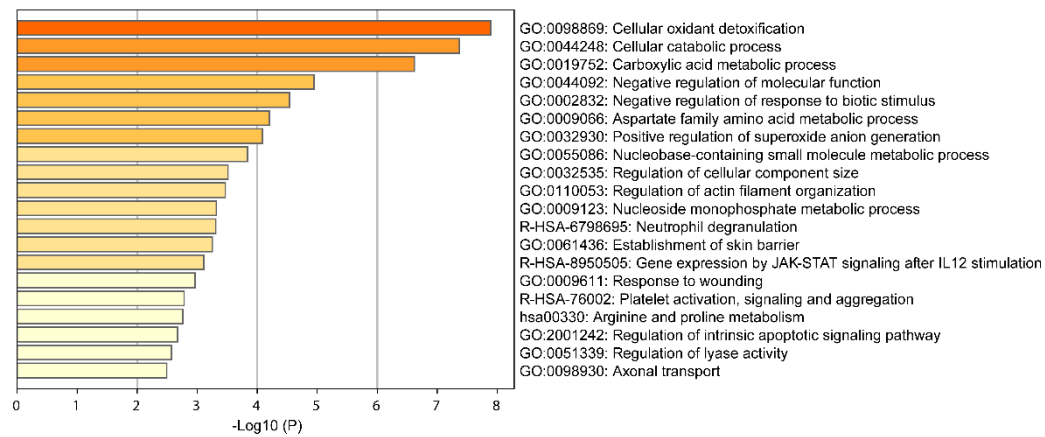
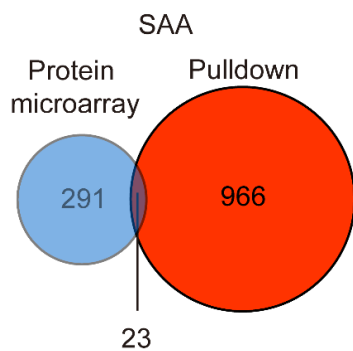
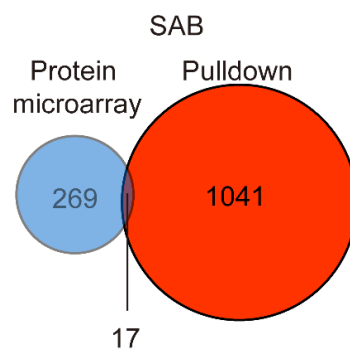
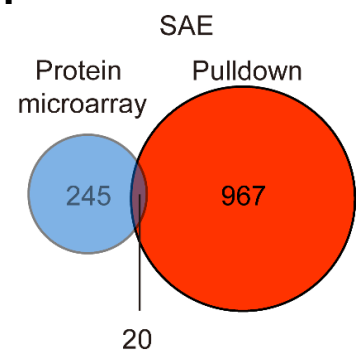


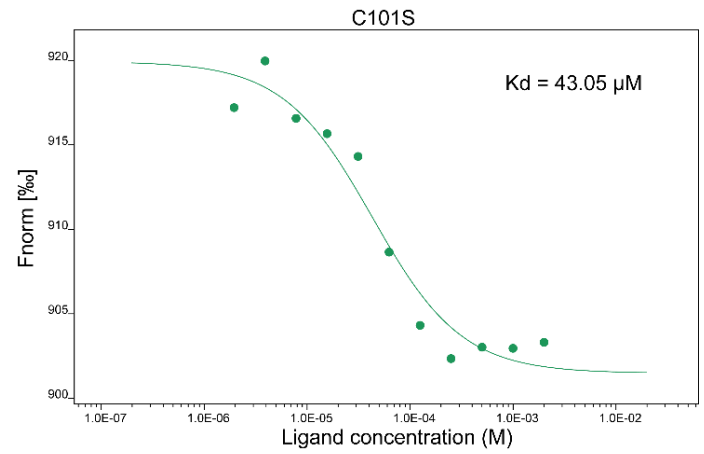
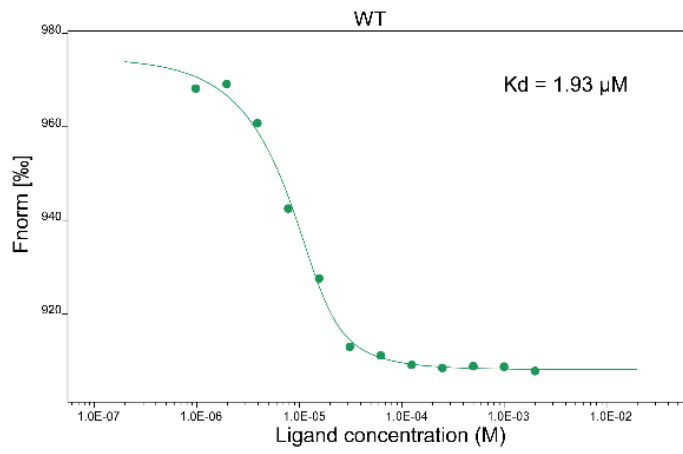
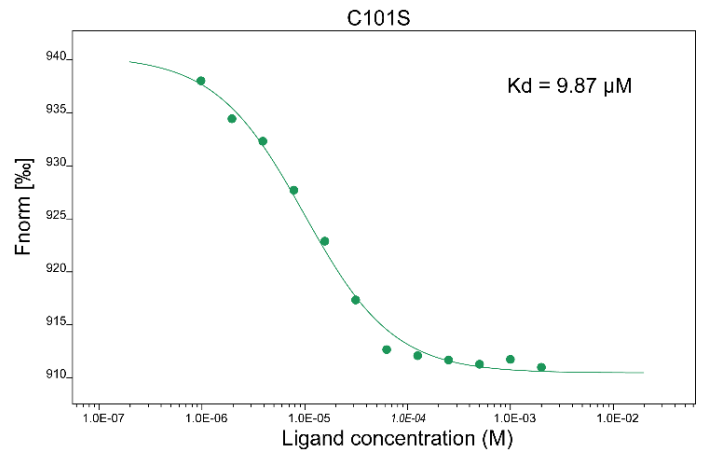
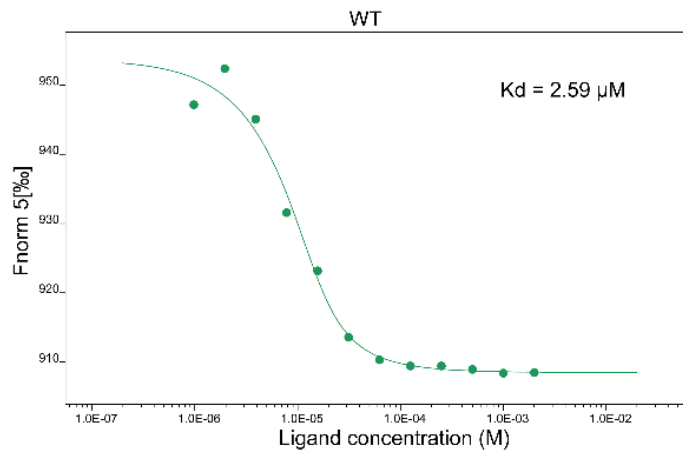
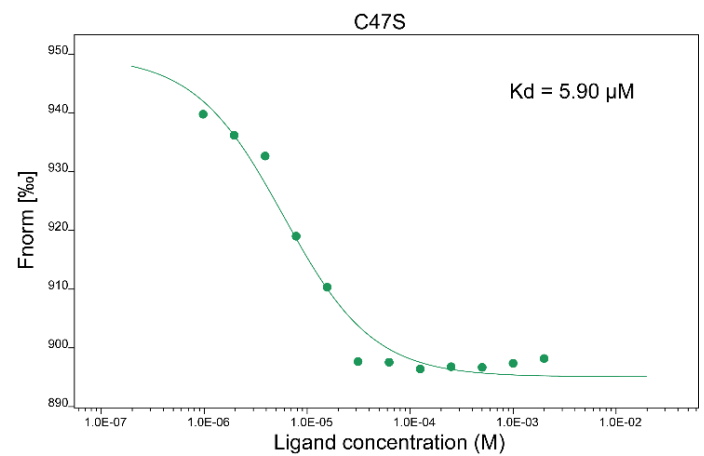
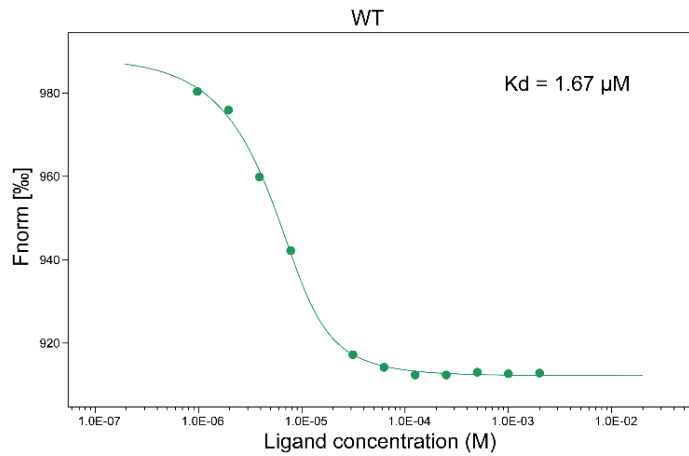
b

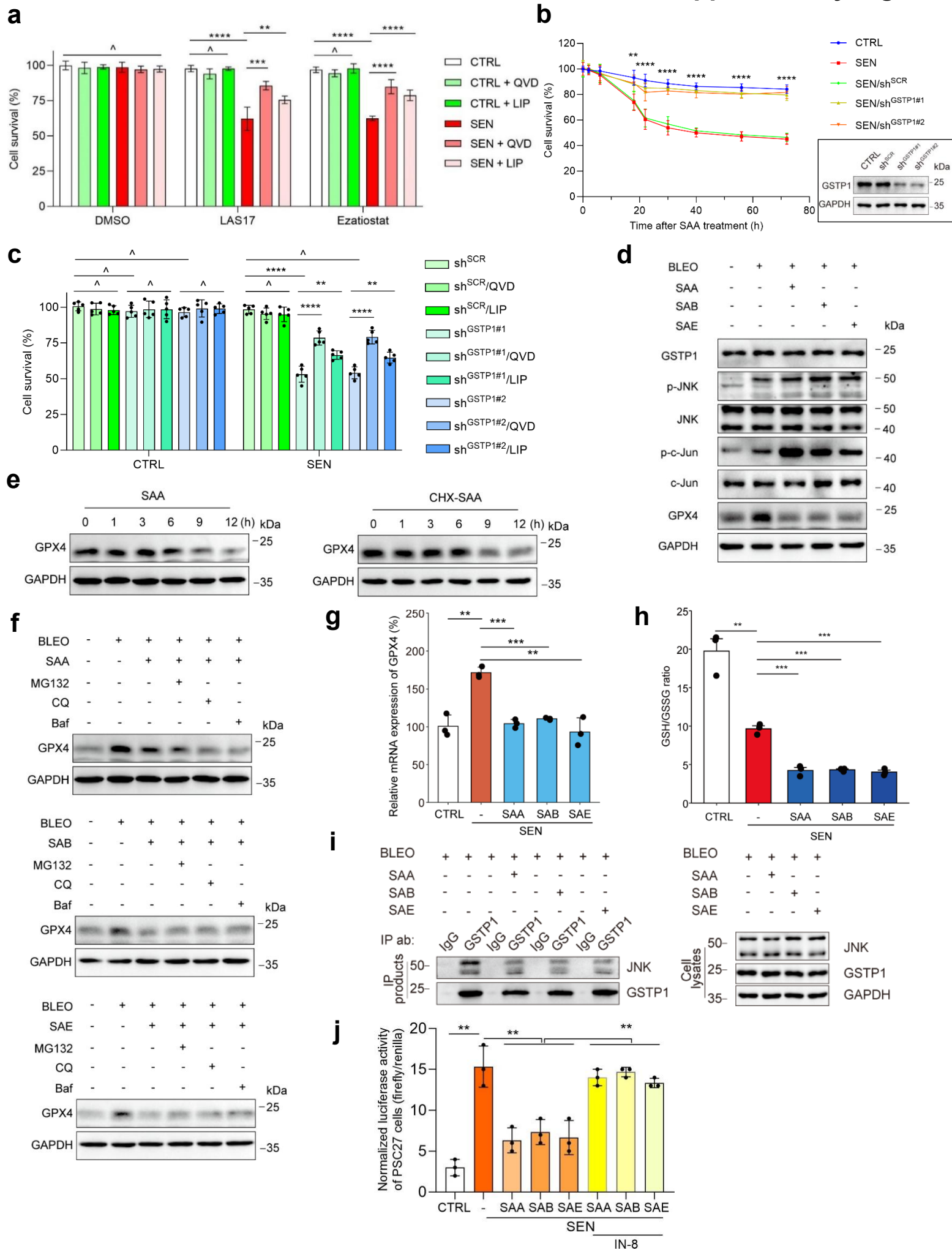




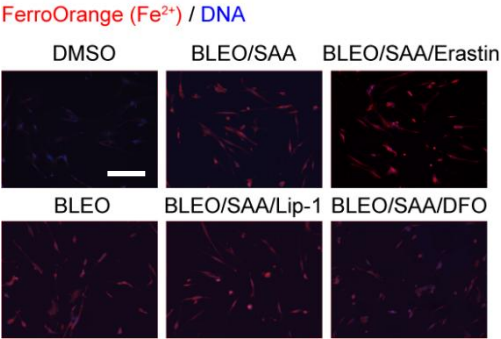
a**b****c**

a**b****g****c****d****e****f**

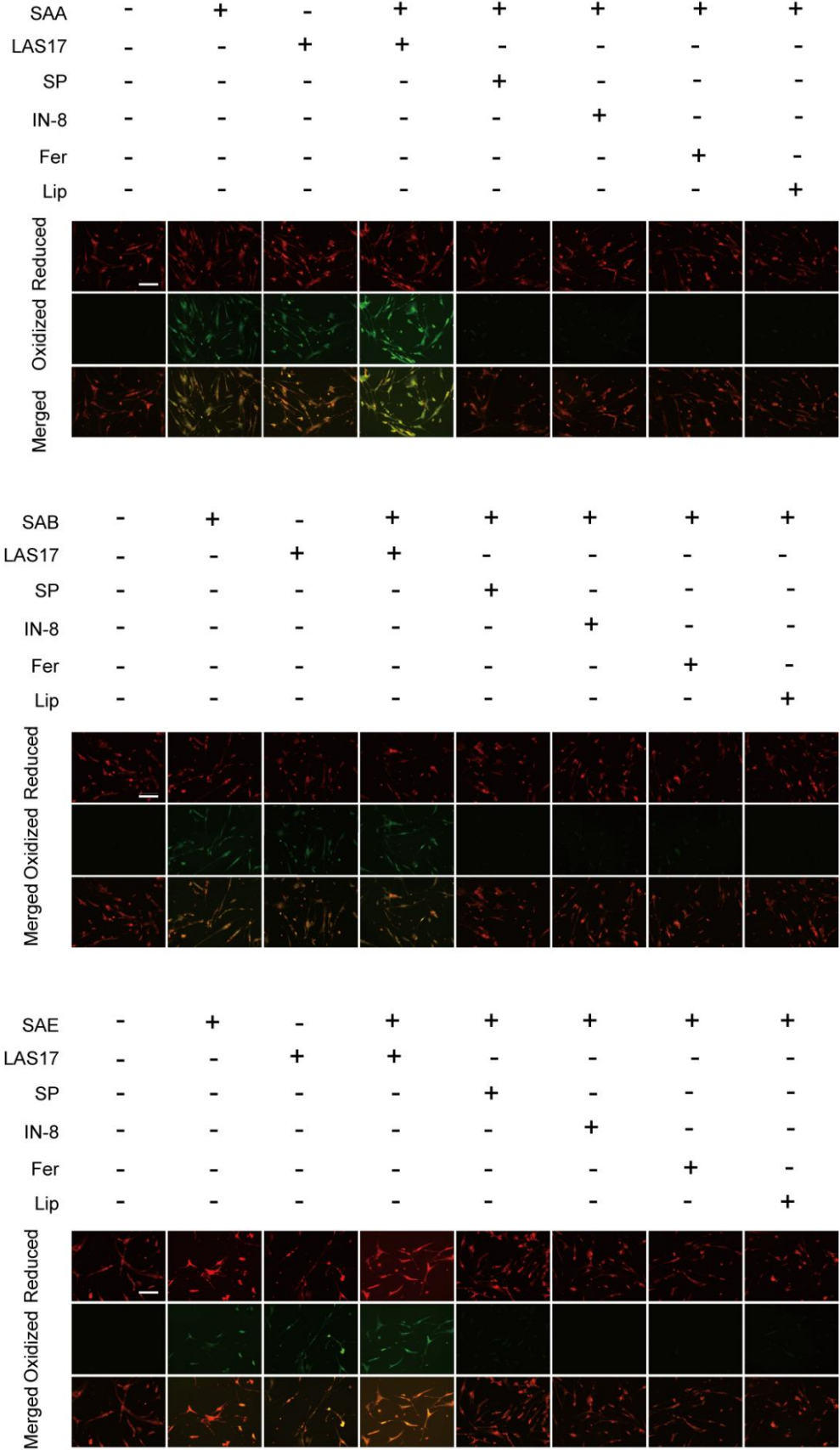
a**b****c**

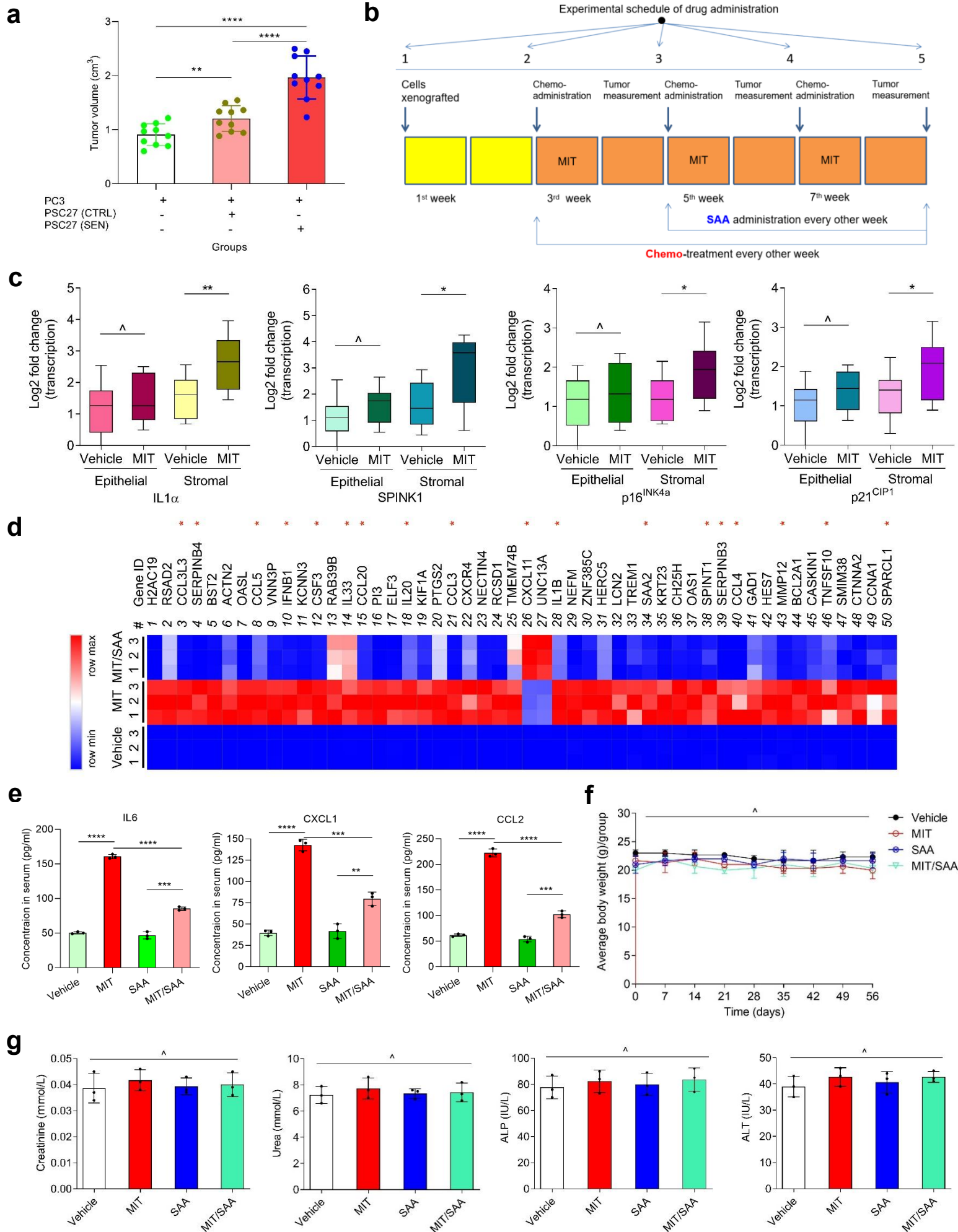


a

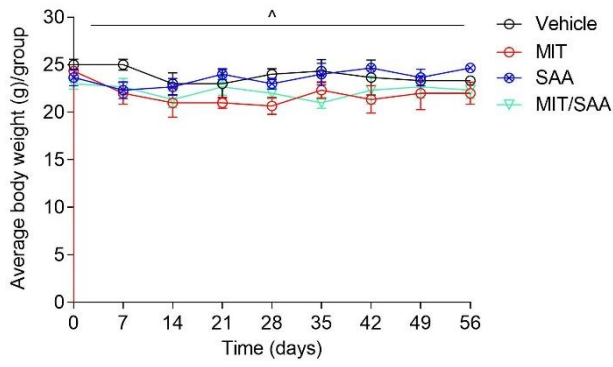


b

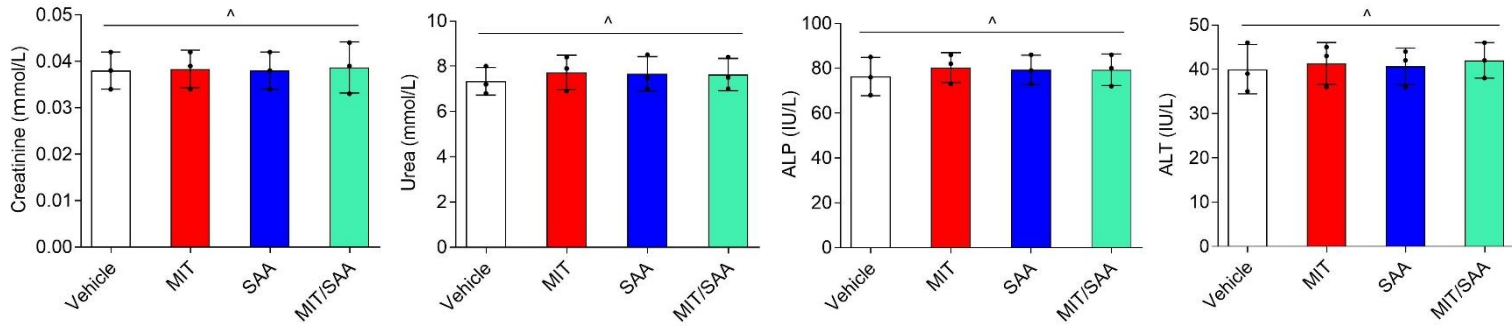




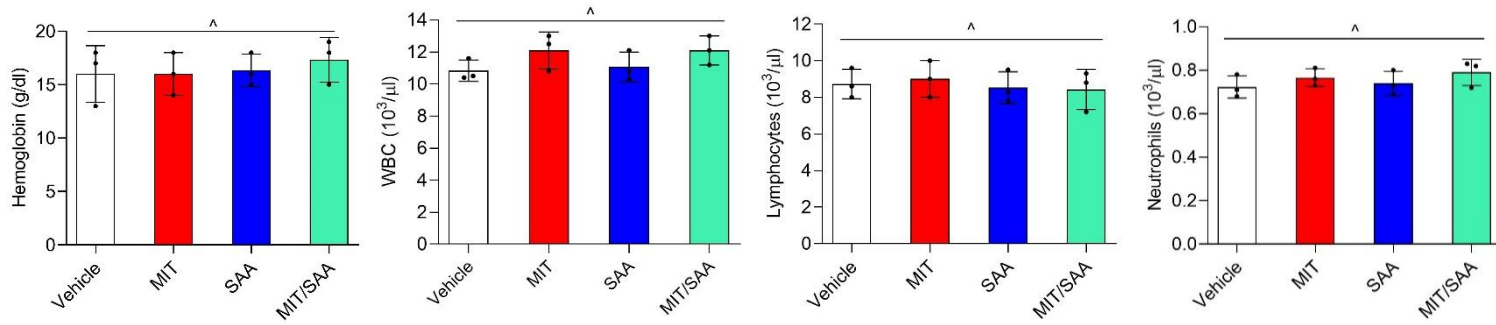
a

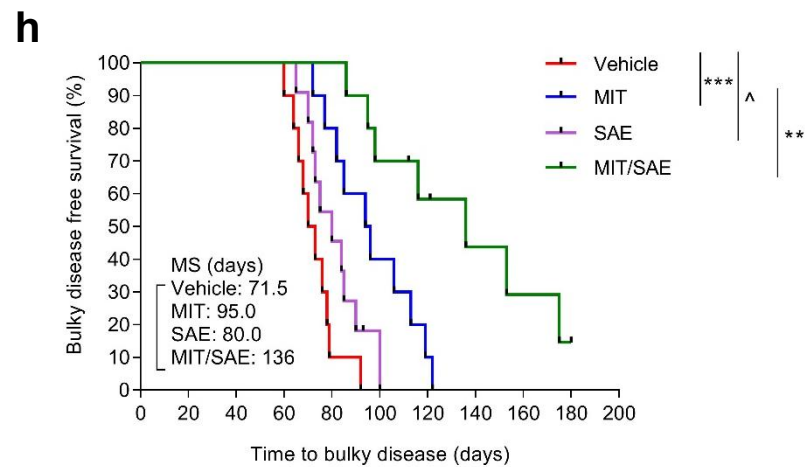
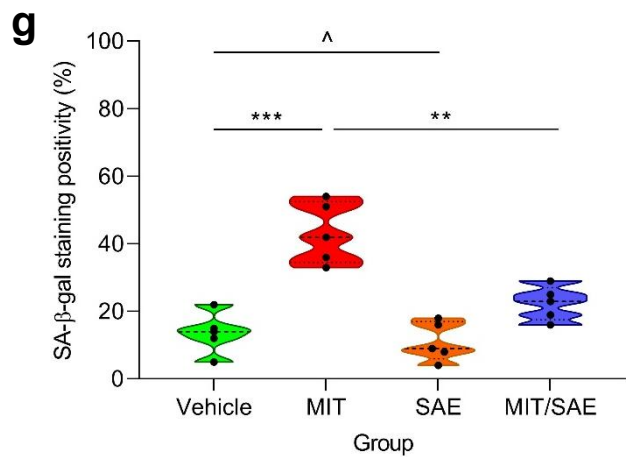
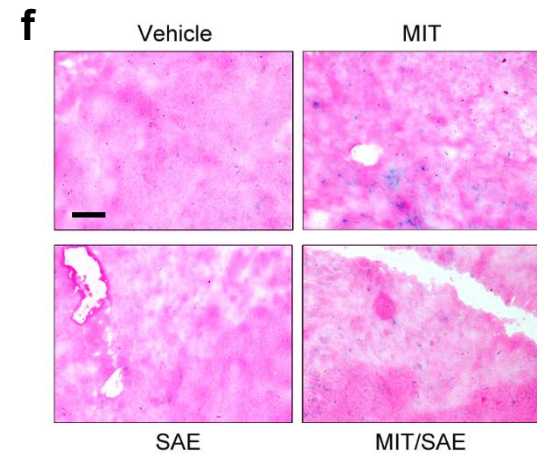
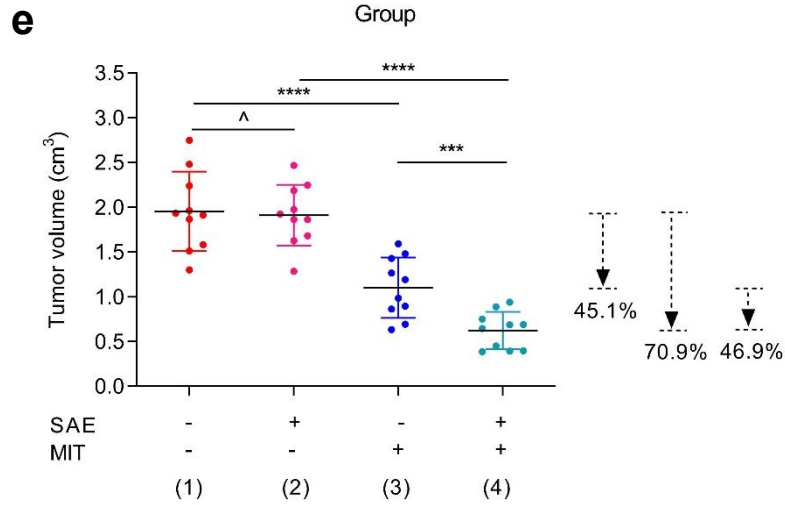
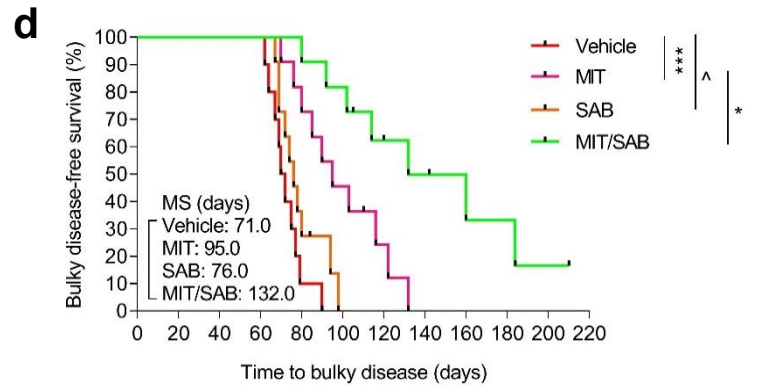
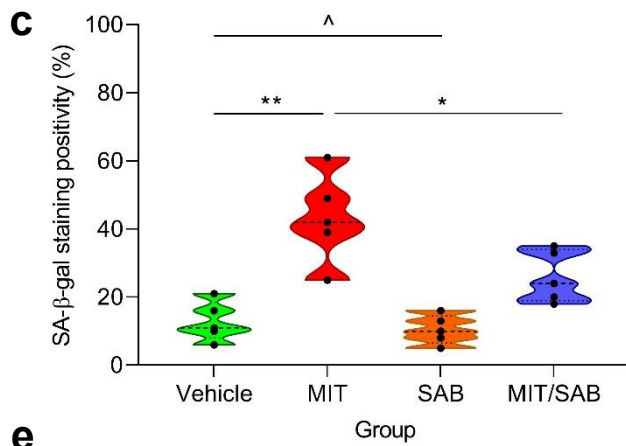
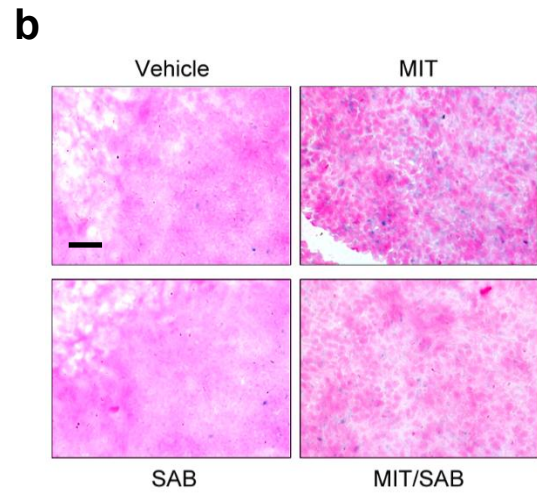
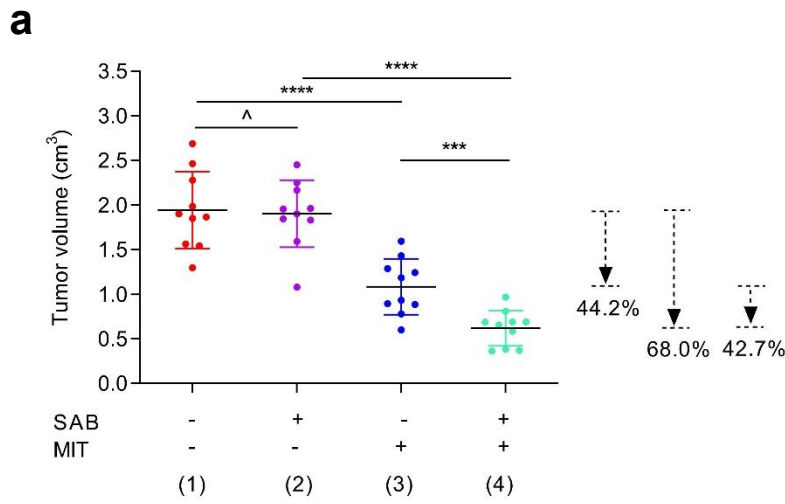


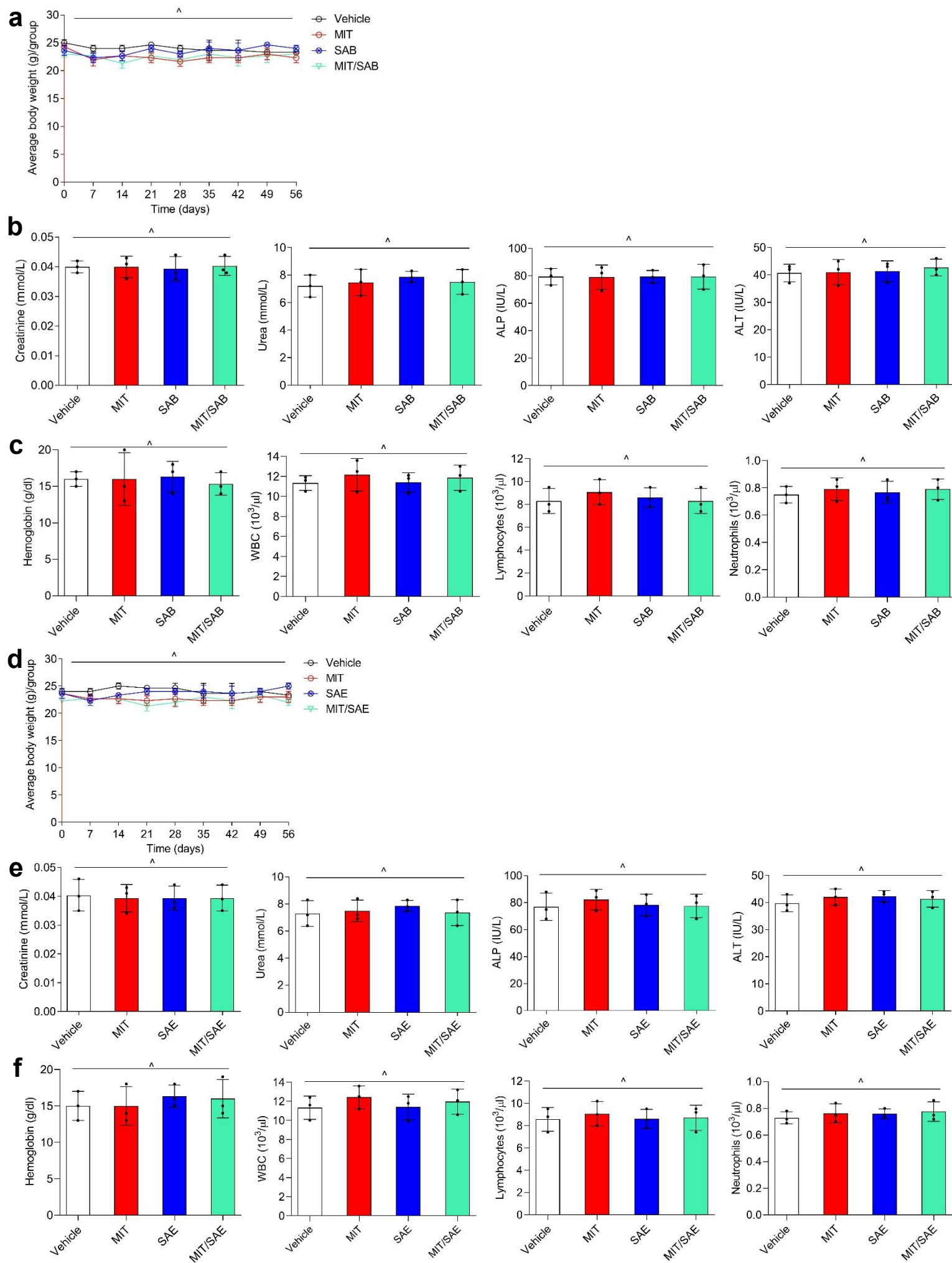
b



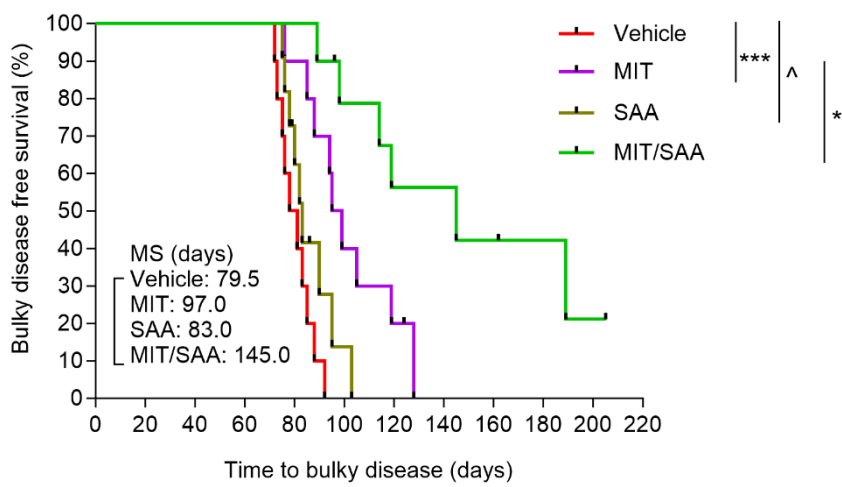
c



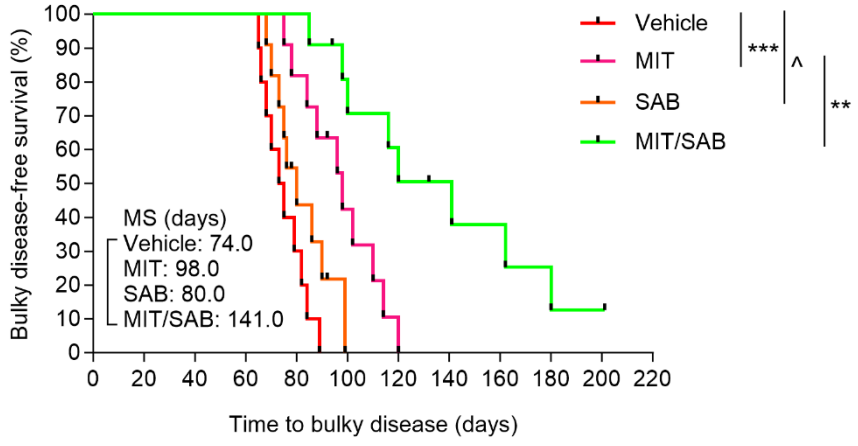




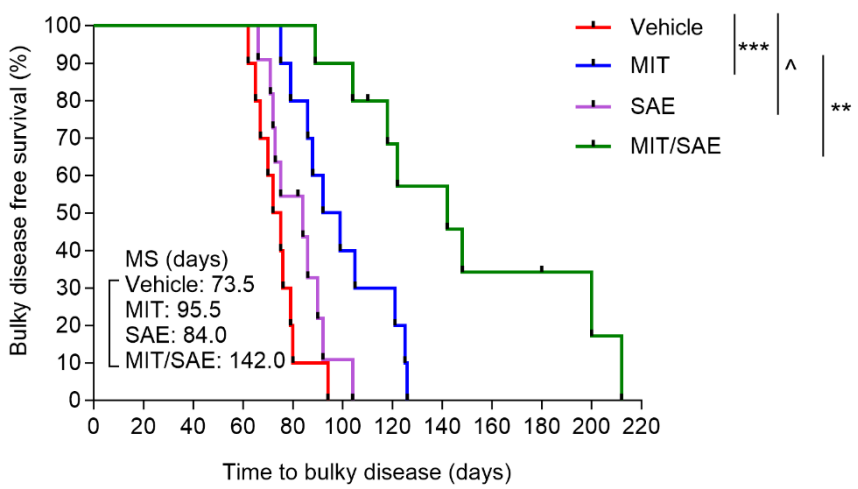
a

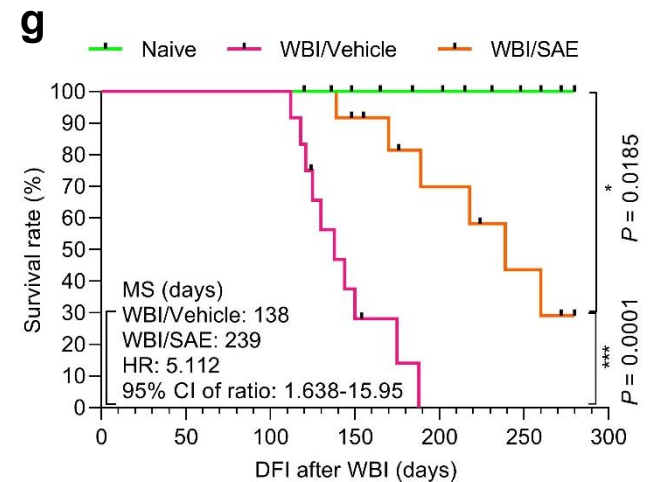
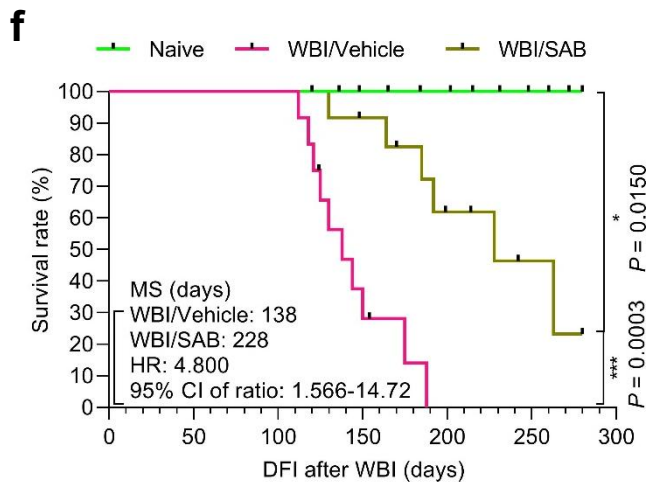
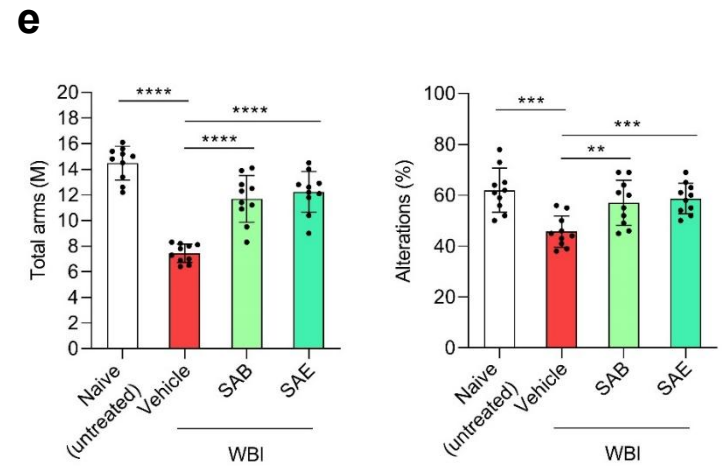
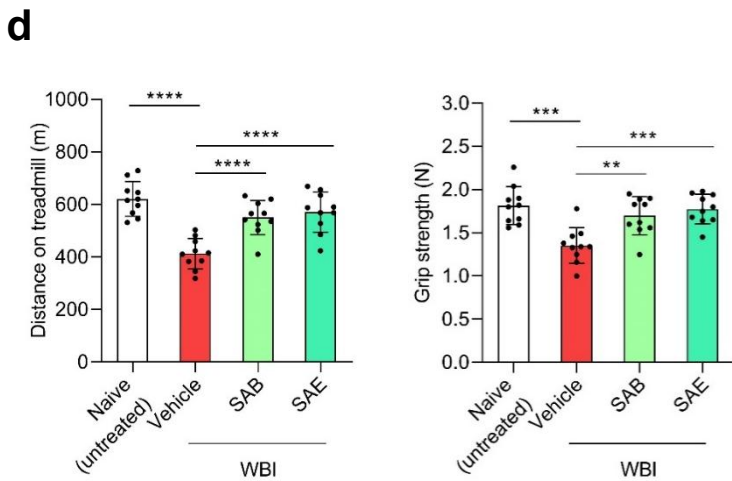
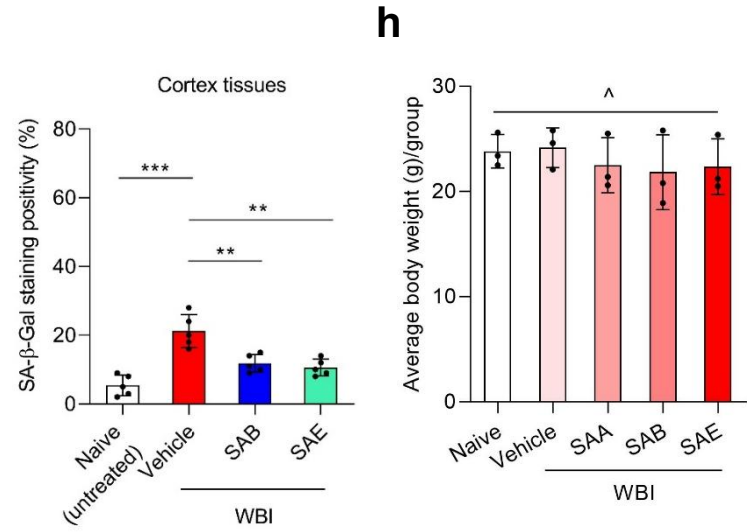
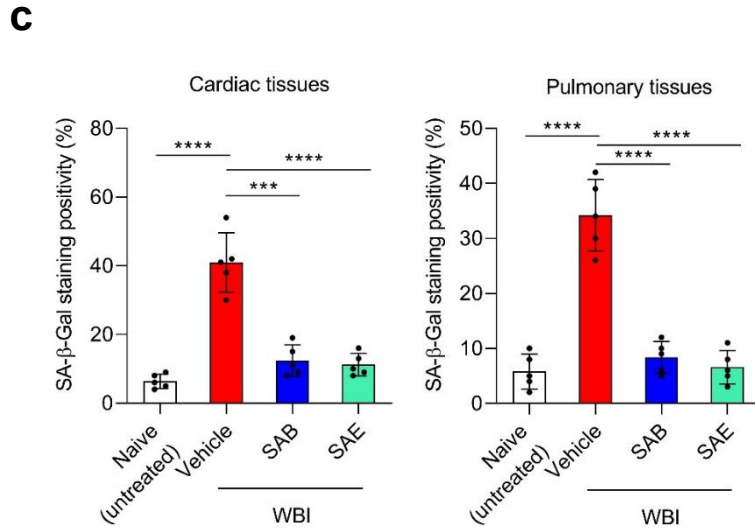
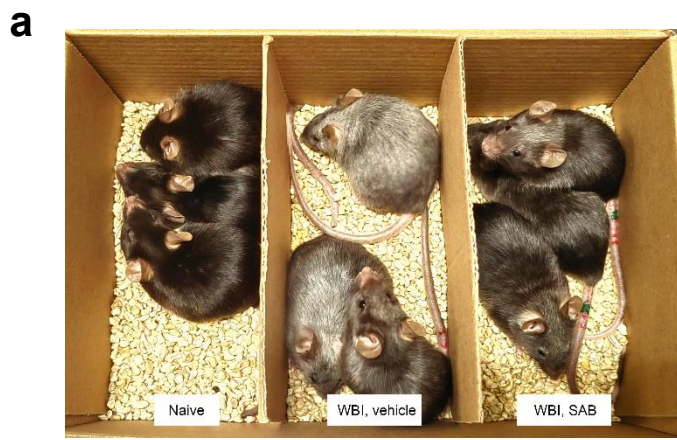


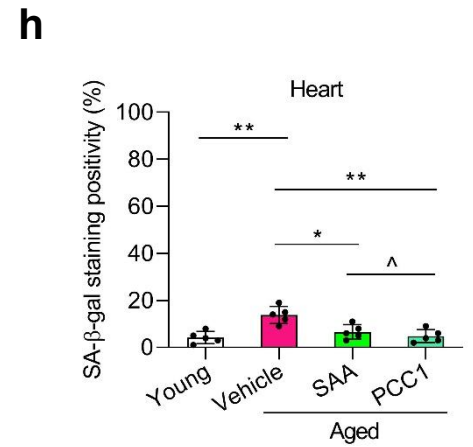
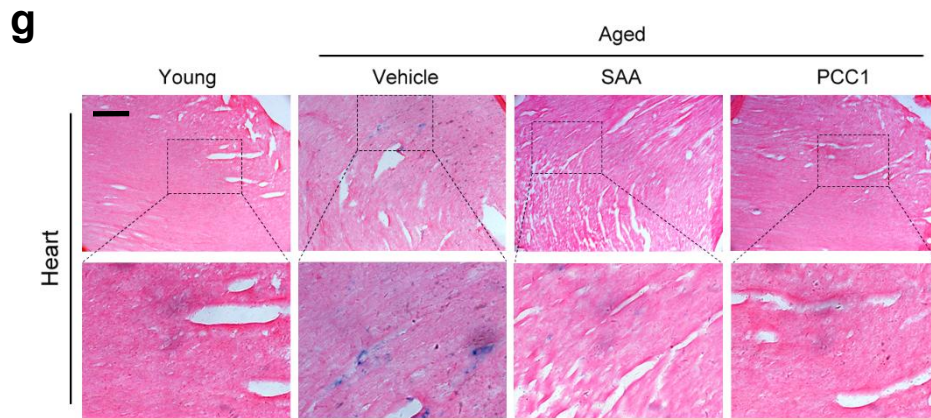
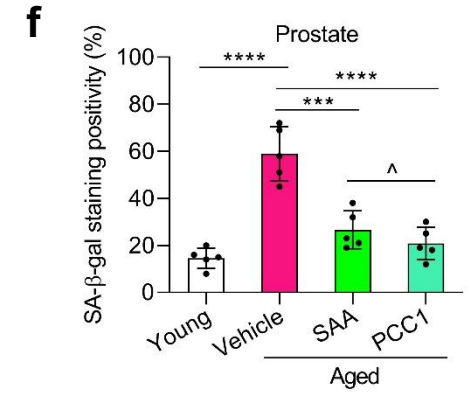
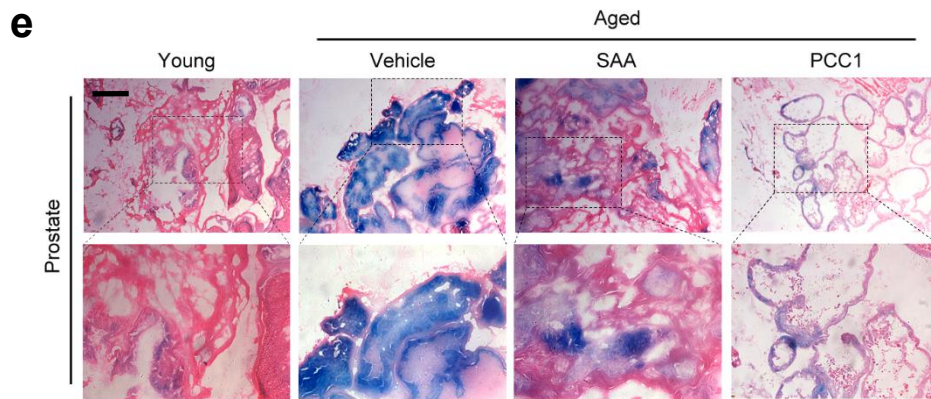
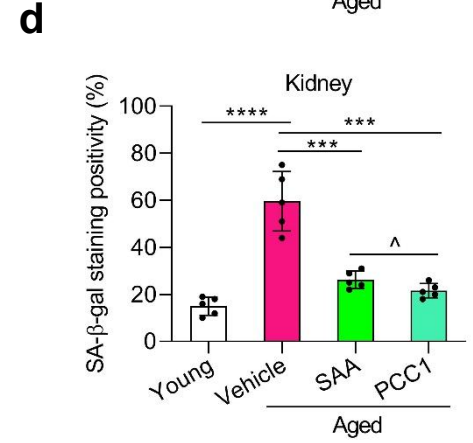
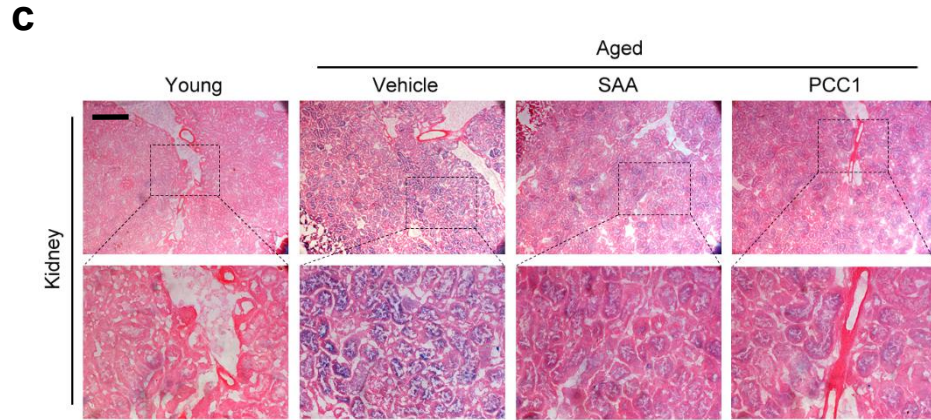
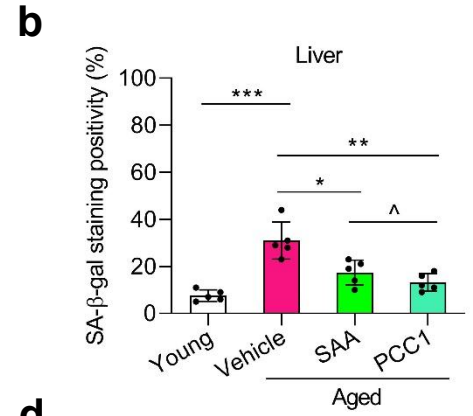
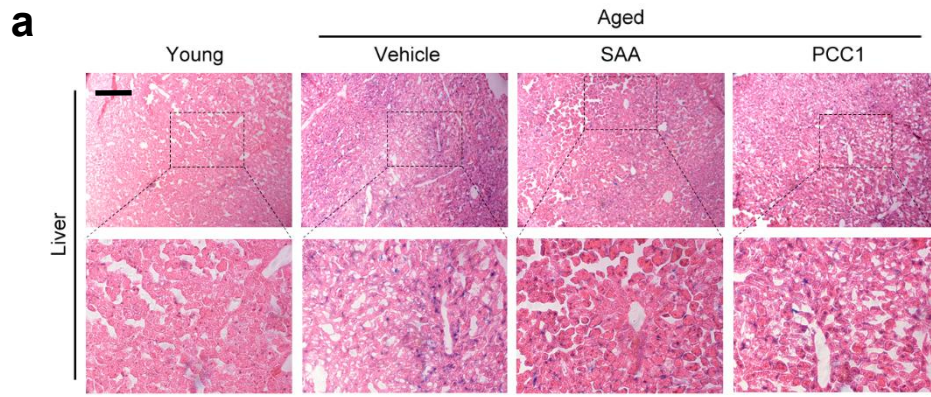
b



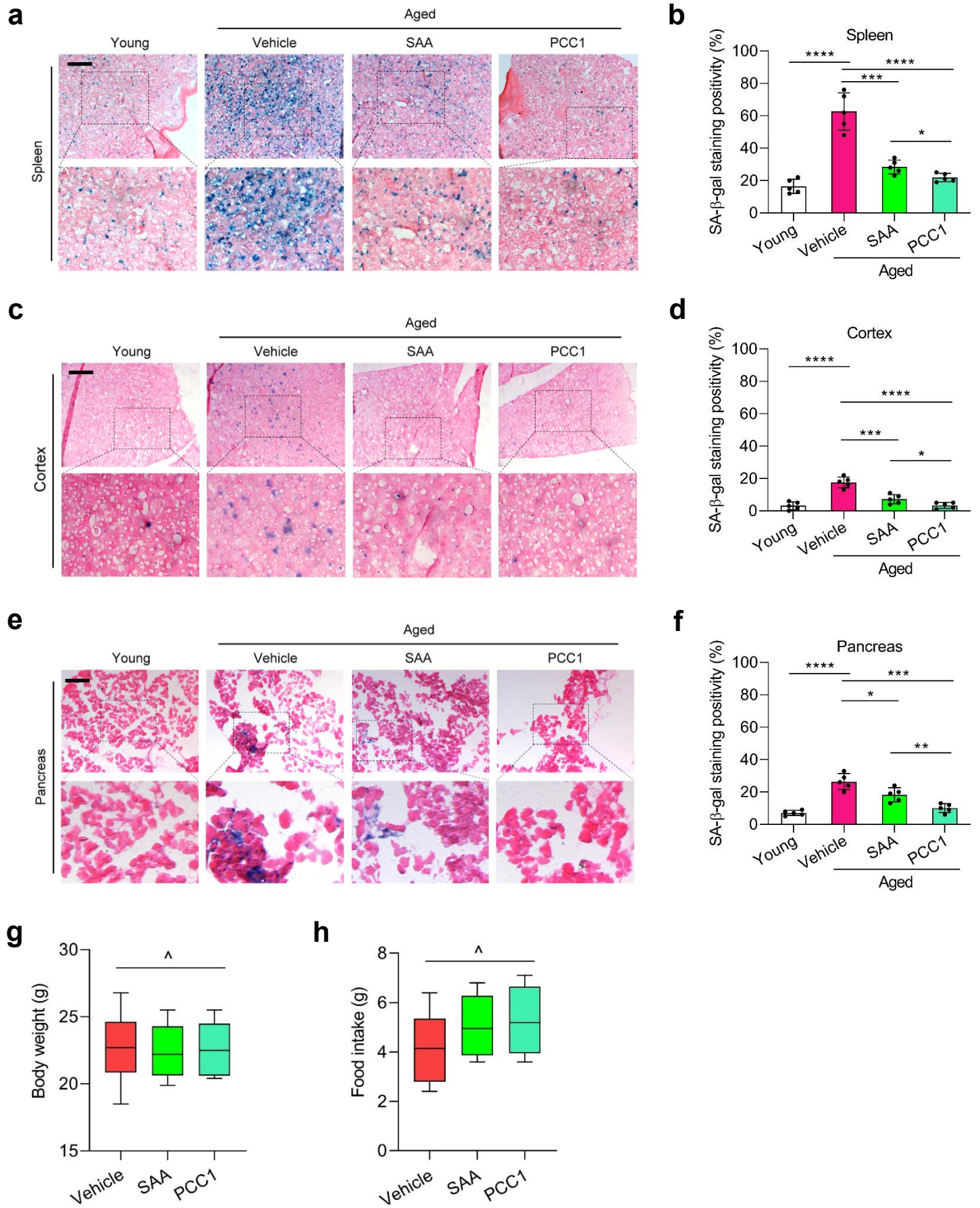
c



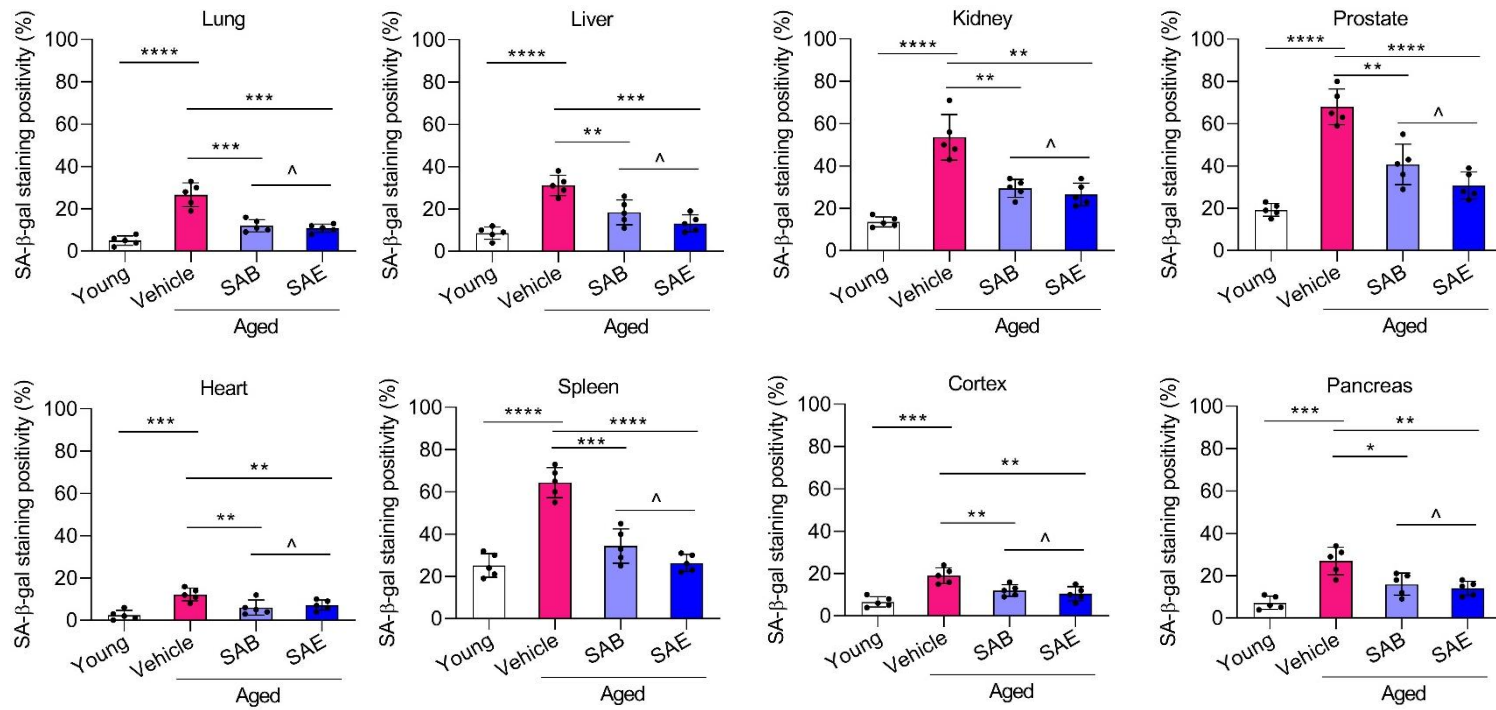




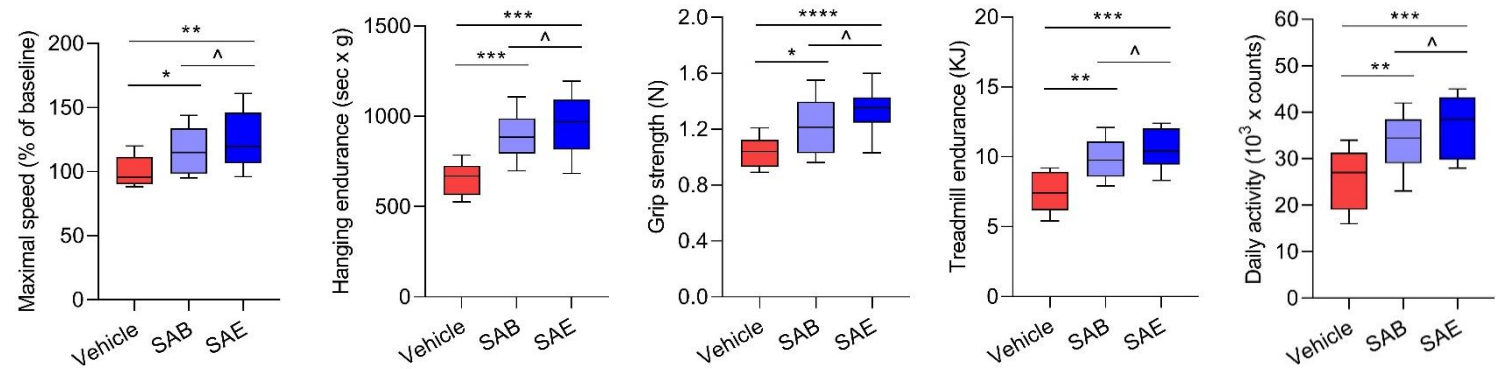
Supplementary Fig. 24



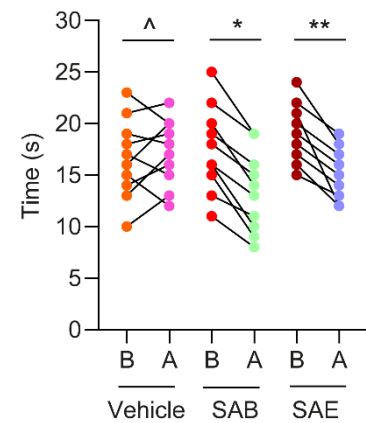
a



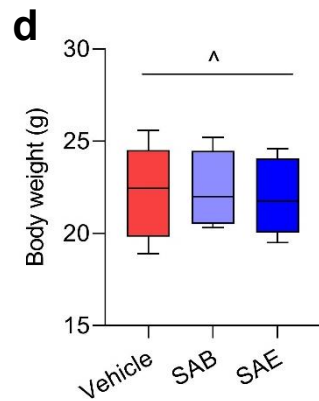
b



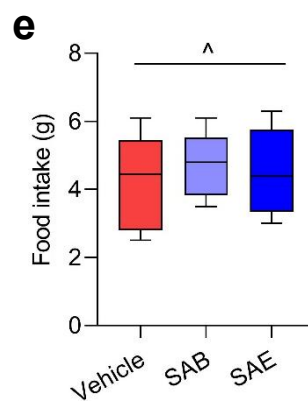
c



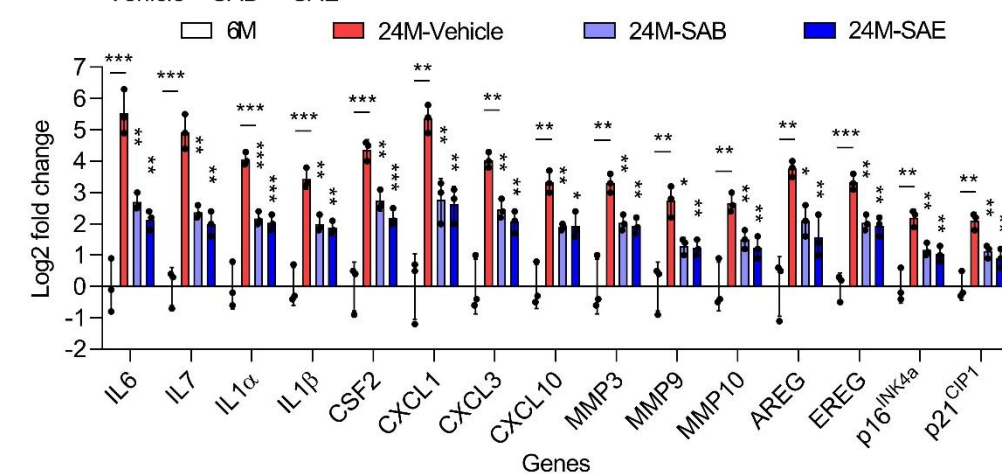
d

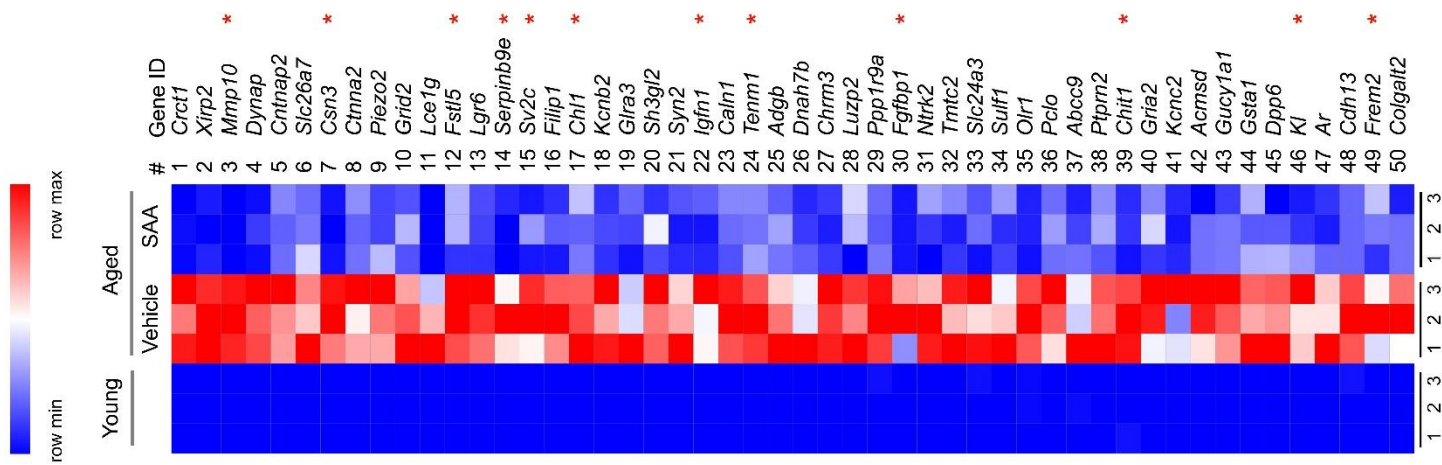
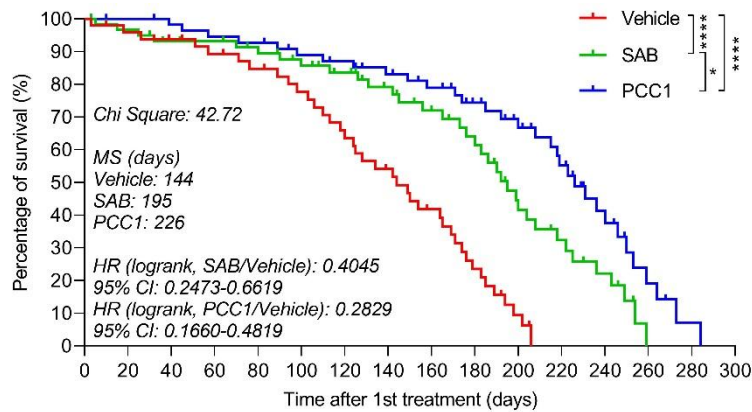
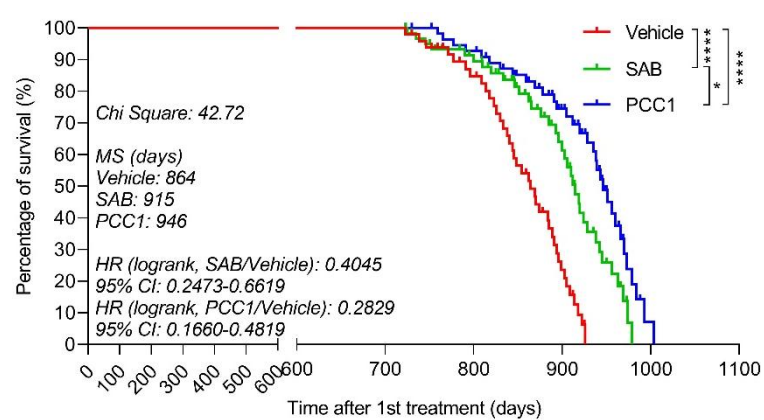
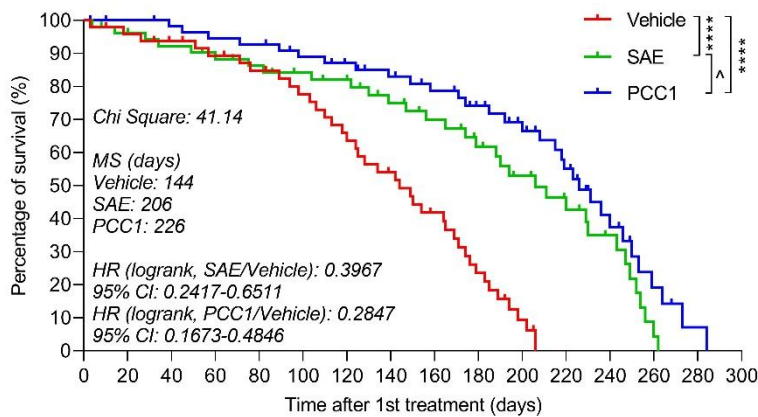
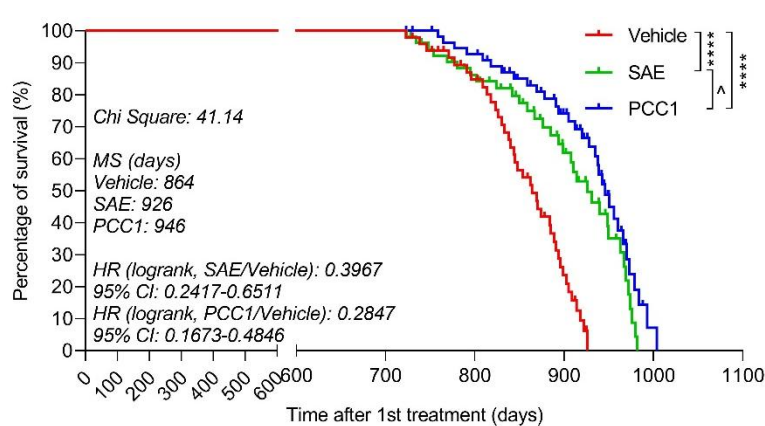
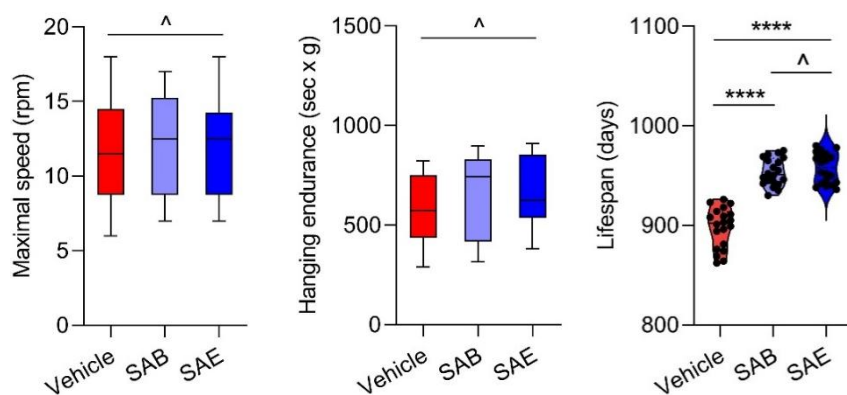
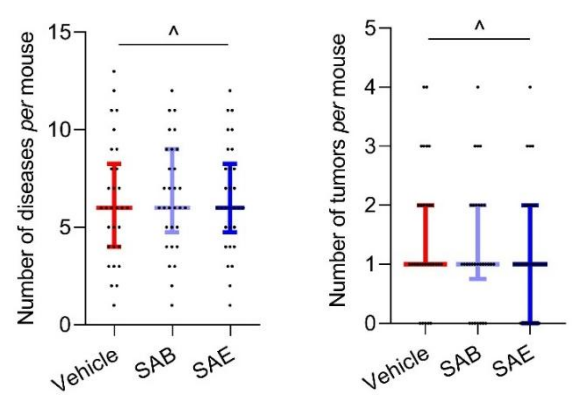


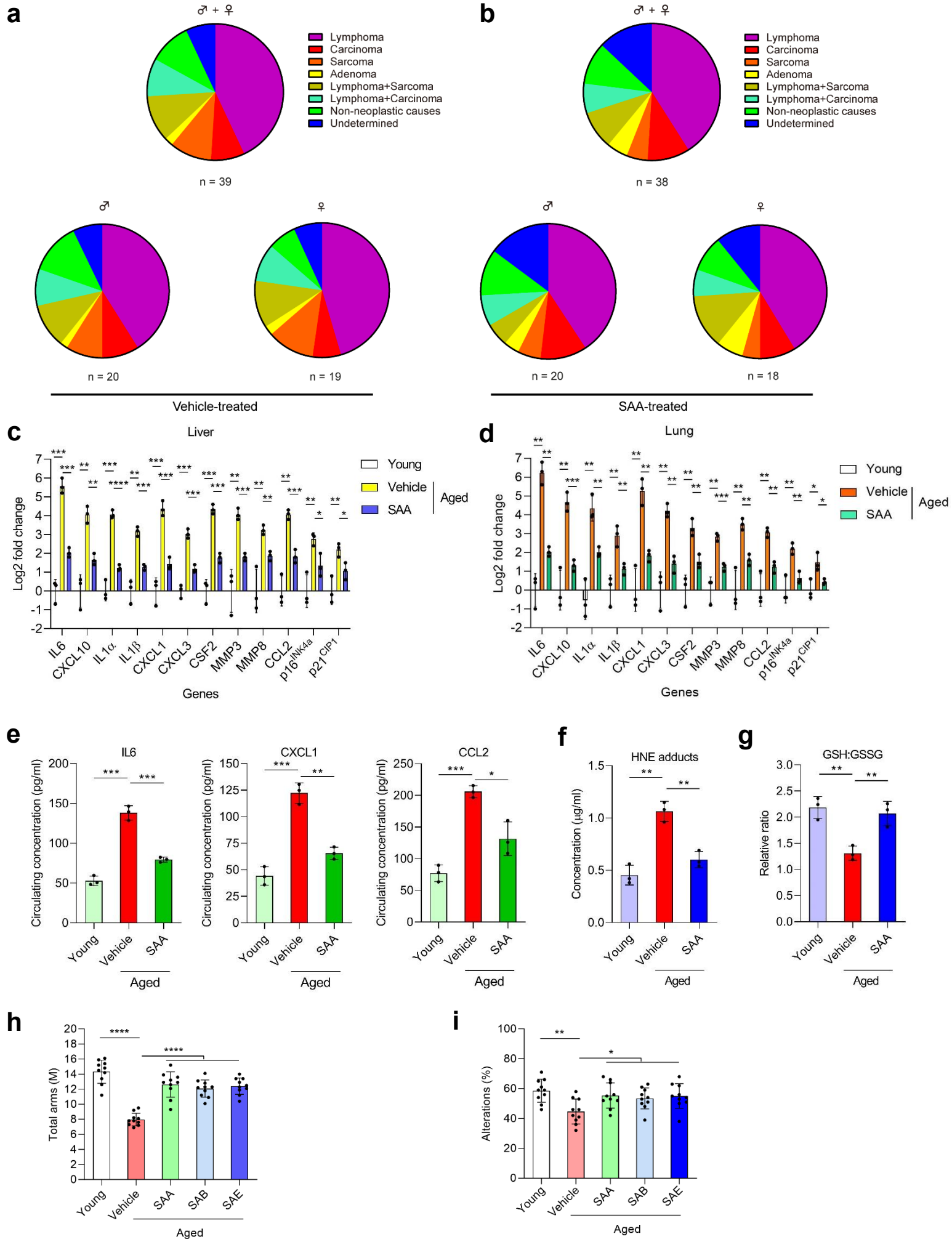
e



f



a**b****c****d****e****f****g**



Supplementary Figure Legends

Supplementary Fig. 1 Characterization of PSC27 as a cell-based model for senescence studies. (a) Senescence assessment by SA- β -gal staining of PSC27 cells. Left, representative images. Scale bar, 10 μ m. Right, statistics. (b) DNA synthesis appraisal by BrdU incorporation. Left, representative images, Scale bar, 10 μ m. Right, statistics. (c) DNA damage response (DDR) profiling of cells. Left, representative images. Scale bar, 5 μ m. Right, statistics. Immunofluorescence staining of γ H2AX was performed with PSC27 cells, with the DDR profile categorized into 4 subgroups including 0 foci, 1-3 foci, 4-10 foci and >10 foci *per* cell. (d) Analysis of the senolytic potential of several agents, including ABT-263, ABT-737, 'D+Q' and PCC1. 'D+Q', dasatinib and quercetin. (e) Representative results from assessment of the senomorphic efficacy of natural compounds by analyzing the expression of a canonical SASP soluble factor CXCL8. (f) The efficacy of 56 compounds in the NMA library in killing senescent cells. Note, SAA, SAB, SAE, SAF and PCC1 showed the highest capacity as senolytics. However, SAF was subsequently excluded mainly due to its cytotoxicity to proliferating cells. (g) Expression of CXCL8 at transcription level in PSC27 cells after treatment by various agents that showed senomorphic potential. For all datasets, samples were examined after treatment with individual agents in culture for 3 days. Data in **a-e** are shown as mean $\pm$ SD and representative of 3 independent biological replicates with *P* values calculated by Student's *t*-tests. [^], *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001; ****, *P* < 0.0001.

Supplementary Fig. 2 Characterization of the senolytic potential of SAB. (a) Measurement of senescent PSC27 survival by SA- β -gal staining. SAB was applied at increasing concentrations as indicated. CTRL, control. SEN, senescent. (b) Representative images from SA- β -gal staining to profile survival of cells including CTRL and their SEN counterparts induced by BLEO and treated by increasing concentrations of SAB. Scale bar, 50 μ m. (c) Cell counting-based survival assay of CTRL cells and their SEN counterparts induced by BLEO and subsequently

exposed to increasing concentrations of SAB. **(d)** Cell apoptosis examination by caspase 3/7 activity measurement. **(e)** Cell viability assay in the time course to assess survival after treatment by SAB. **(f)** Representative images after SA- β -gal staining. TIS, therapy-induced senescence (by BLEO). RS, replicative senescence (by exhaustive passaging). OIS, oncogene-induced senescence (by oncogenic *HRas*^{G12V}). Scale bar, 50 μ m. **(g)** Comparative statistics of SA- β -gal staining assays as described in **(f)**. **(h)** FACS measurement upon sorting with an annexin V-FITC/PI kit and DAPI staining to determine apoptosis. **(i)** Quantitative profiling of individual percentages of viable (Q4: PI⁻/annexin V⁻) and apoptotic (Q2 and Q3: PI⁺/annexin V⁺ and PI⁻/annexin V⁺, respectively) cells after treatment with vehicle or SAB for 3 days. **(j)** Cell counting-based survival evaluation of CTRL and SEN cells after exposure to various agents targeting apoptosis, pyroptosis, necroptosis and ferroptosis. QVD, VX-765, Nec-1s and LIP, chemical inhibitors against apoptosis, pyroptosis, necroptosis and ferroptosis, respectively. Data in **a**, **c**, **d**, **e**, **g**, **i** and **j** are shown as mean $\pm$ SD and representative of 3 independent biological replicates with *P* values calculated by Student's *t*-tests. [^], *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001; ****, *P* < 0.0001.

Supplementary Fig. 3 Characterization of the senolytic potential of SAE. **(a)** Measurement of senescent PSC27 survival by SA- β -gal staining. SAE was applied at increasing concentrations as indicated. CTRL, control. SEN, senescent. **(b)** Representative images after SA- β -gal staining to profile survival of PSC27 including CTRL cells and their SEN counterparts induced by BLEO and treated by increasing concentrations of SAE. Scale bar, 50 μ m. **(c)** Cell counting-based survival appraisal of CTRL cells and their SEN counterparts generated by BLEO induction and subsequently exposed to increasing concentrations of SAE. **(d)** Cell apoptosis examination by caspase 3/7 activity measurement. **(e)** Cell viability assay in the time course to assess survival after SAE treatment. **(f)** Representative images after SA- β -gal staining. TIS, therapy-induced senescence (by BLEO). RS, replicative senescence (by exhaustive passaging). OIS, oncogene-induced senescence (by

oncogenic *HRas*^{G12V}). Scale bar, 50 μ m. **(g)** Statistical comparison of SA- β -gal staining assays as described in **(f)**. **(h)** FACS measurement upon sorting with an annexin V-FITC/PI kit and DAPI staining to determine apoptosis. **(i)** Quantitative profiling of individual percentages of viable (Q4: PI⁻/annexin V⁻) and apoptotic (Q2 and Q3: PI⁺/annexin V⁺ and PI⁻/annexin V⁺, respectively) cells after treatment with vehicle or SAE for 3 days. **(j)** Cell counting-based survival analysis of CTRL and SEN cells after exposure to various agents targeting apoptosis, pyroptosis, necroptosis and ferroptosis. QVD, VX-765, Nec-1s and LIP, chemical inhibitors against apoptosis, pyroptosis, necroptosis and ferroptosis, respectively. Data in **a**, **c**, **d**, **e**, **g**, **i** and **j** are shown as mean $\pm$ SD and representative of 3 independent biological replicates with *P* values calculated by Student's *t*-tests. ^, *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001; ****, *P* < 0.0001.

Supplementary Fig. 4 Characterization of the senolytic potential of SA compounds against different types of senescence. **(a)** Cell counting-based survival evaluation of control (CTRL) cells and their senescent (SEN) counterparts generated by consecutive passaging, or subsequently exposed to increasing concentrations of SAA. **(b)** Cellular apoptosis examination by caspase 3/7 activity measurement upon exposure of SEN cells to SAA at 100 μ M as described in **(a)**. **(c)** Cell counting-based survival appraisal of CTRL cells and their SEN counterparts generated by overexpression of oncogenic *HRAS*^{G12V}, or subsequently exposed to increasing concentrations of SAA. **(d)** Cellular apoptosis appraisal by caspase 3/7 activity measurement upon exposure of senescent cells to SAA at 100 μ M as described in **(c)**. **(e)** Cell counting-based survival appraisal of CTRL cells and their SEN counterparts generated by consecutive passaging and subsequently exposed to increasing concentrations of SAB. **(f)** Cellular apoptosis examination by caspase 3/7 activity measurement upon exposure of senescent cells to SAB at 100 μ M as described in **(e)**. **(g)** Cell counting-based survival appraisal of CTRL cells and their SEN counterparts generated by overexpression of oncogenic *HRAS*^{G12V} and subsequently exposed to increasing concentrations of SAB. **(h)** Cellular apoptosis

appraisal by caspase 3/7 activity measurement upon exposure of senescent cells to SAB at 100 μ M as described in (g). (i) Cell counting-based survival appraisal of CTRL cells and their SEN counterparts generated by consecutive passaging and subsequently exposed to increasing concentrations of SAE. (j) Cellular apoptosis examination by caspase 3/7 activity measurement upon exposure of senescent cells to SAE at 50 μ M as described in (i). (k) Cell counting-based survival appraisal of CTRL cells and their SEN counterparts generated by overexpression of oncogenic *HRAS*^{G12V} and subsequently exposed to increasing concentrations of SAE. (l) Cellular apoptosis appraisal by caspase 3/7 activity measurement upon exposure of senescent cells to SAE at 50 μ M as described in (k). Data in a-l are shown as mean $\pm$ SD and representative of 3 independent biological replicates with *P* values calculated by Student's *t*-tests. ^, *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001; ****, *P* < 0.0001.

Supplementary Fig. 5 Stromal cell-based *in vitro* assays identify SA compounds as broad-spectrum senolytics. (a-c) Quantitative measurements of the viability of IMR90 (a), HUVEC (b) and AT-MSC (c) cells examined in CTRL, TIS, RS and OIS groups treated by 100 μ M SAA for 3 d. (d-f) Quantitative measurements of the viability of IMR90 (d), HUVEC (e) and AT-MSC (f) cells examined in CTRL, TIS, RS and OIS groups treated by 100 μ M SAB for 3 d. (g-i) Quantitative measurements of the viability of IMR90 (g), HUVEC (h) and AT-MSC (i) cells examined in CTRL, TIS, RS and OIS groups treated by 50 μ M SAE for 3 d. CTRL, control. TIS, therapy-induced senescence. RS, replicative senescence. OIS, oncogene-induced senescence. Data in a-i are shown as mean $\pm$ SD and representative of 3 independent biological replicates with *P* values calculated by Student's *t*-tests. ^, *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01.

Supplementary Fig. 6 Comparative cell viability in a time course to assess *in vitro* survival after treatment with SA agents and/or chemical inhibitors. (a) Proliferating or senescent PSC27 cells were treated with SAA alone or together with QVD, LIP,

VX765 or Nec-1s. Cell viability was measured at a series of timepoints within 80 h. (b) Cell viability measurement of PSC27 cells similar as that of (a), except that SAB was applied instead of SAA. (c) Cell viability measurement of PSC27 cells similar as that of (a), except that SAE was applied instead of SAA. [^], $P > 0.05$; ^{*}, $P < 0.05$; ^{**}, $P < 0.01$; ^{***}, $P < 0.001$; ^{****}, $P < 0.0001$.

Supplementary Fig. 7 Bioinformatics profiling of SAB-induced expression change in senescent cells. (a) Chemical structure of SAB (CAS no. 121521-90-2). (b) Heatmap depicting top genes (50, according to fold change) significantly upregulated in senescent PSC27 cells but downregulated upon SAB treatment (50 μ M). Red stars, SASP components. (c) GSEA plot analysis of a significant gene set of the SASP spectrum upon treatment by BLEO vs. BLEO/SAB. (d) GSEA plot assessment of a significant gene set associated with NF- κ B-mediated signaling upon treatment by BLEO vs. BLEO/SAB. (e) NetworkAnalyst map profiling protein-protein interactions of typical SASP-associated factors significantly upregulated in senescent cells but downregulated by SAB. (f-h) Pie charts depicting the biological process (BP) (f), cellular component (CC) (g) and molecular function (MF) (h) associated with transcripts upregulated by BLEO but downregulated by SAB as disclosed by GO analysis.

Supplementary Fig. 8 Bioinformatics profiling of SAE-induced expression change in senescent cells. (a) Chemical structure of SAE (CAS no. 142998-46-7). (b) Heatmap depicting top genes (50, according to fold change) significantly upregulated in senescent PSC27 cells but downregulated upon SAE treatment (25 μ M). Red stars, SASP components. (c) GSEA plot analysis of a significant gene set of the SASP spectrum upon treatment by BLEO vs. BLEO/SAE. (d) GSEA plot assessment of a significant gene set associated with NF- κ B-mediated signaling upon treatment by BLEO vs. BLEO/SAE. (e) NetworkAnalyst map profiling protein-protein interactions of typical SASP-associated factors significantly upregulated in senescent cells but downregulated by SAE. (f-h) Pie charts depicting the biological

process (BP) (f), cellular component (CC) (g) and molecular function (MF) (h) associated with transcripts upregulated by BLEO but downregulated by SAE as indicated by GO analysis.

Supplementary Fig. 9 Bioinformatics profiling the expression pattern of senescent cells exposed to a sublethal dose of SAA. (a) Heatmap showing the expression of human genes, which were significantly upregulated (1270) or downregulated (2089) upon treatment of senescent PSC27 cells by SAA (50 μ M). Data derived from triplicate samples *per* group. (b-d) Pie charts depicting the biological process (BP) (b), cellular component (CC) (c) and molecular function (MF) (d) associated with transcripts upregulated by BLEO but downregulated by SAA as disclosed by GO analysis.

Supplementary Fig. 10 Immunoblot analysis of PSC27 cells treated under different conditions involving BLEO and/or SAB (or SAE). Expression of DDR signaling molecules, SASP regulatory factors, pro-apoptotic and anti-apoptotic proteins, and anti-ferroptotic factors was examined. Caspase 3 (t), total caspase 3; caspase 3 (c), cleaved caspase 3; p, phosphorylated. GAPDH, loading control.

Supplementary Fig. 11 GSVA profiling of proteomic data and immunoblot analysis of NF- κ B nuclear translocation, SASP expression and ferroptosis-related factors. (a) GSVA profiling of proteomic data indicating SAA-induced apoptosis and ferroptosis. Left, apoptosis. Right, ferroptosis. (b) GSVA profiling of proteomic data indicating SAB-induced apoptosis and ferroptosis. Left, apoptosis. Right, ferroptosis. (c) GSVA profiling of proteomic data indicating SAE-induced apoptosis and ferroptosis. Left, apoptosis. Right, ferroptosis. (d) Immunoblot of NF- κ B subunit nuclear translocation upon SAA treatment. (e) Immunoblot of the expression of SASP factors IL6 and MMP3 upon cell treatment by SA agents. (f) Immunoblot of the expression of ferroptosis-related factors.

Supplementary Fig. 12 Illustration of chemical synthesis to conjugate biotin with SA compounds and venn diagram profiling potential targets of these SA compounds. (a-c) A schematic workflow of chemical synthesis for SAA-Biotin (a), SAB-Biotin (b) and SAC-Biotin (c), respectively. The chemical structure of biotin is highlighted by the dashed black rectangle in a-c.

Supplementary Fig. 13 Generation of biotin-conjugated complexes to probe potential targets of SA compounds and illustration of target-specific GO profiling. (a) Representative presentation of human protein microarrays (20K) applied to probe the potential targets of SA compounds, with DMSO-treated biotin (D-Biotin) employed as negative control. (b) Venn diagram outlining all the potential co-targets (154) of SAA, SAB and SAE compounds as identified by pulldown assays. (c) GO profiling of the top 100 molecules out of the 154 co-targets of SA compounds identified by protein microarrays, with all relevant GO items presented for a quick view. (d-f) Venn diagrams showing the potential targets of SAA (d), SAB (e) and SAE (f), respectively, as co-identified by protein microarrays and pulldown assays. (g) Crystal structure of human dimeric GSTP1 showing experimentally-determined 3D architectures derived from the Protein Data Bank (PDB) (ID: 2A2R) archive (method, X-Ray diffraction; resolution, 1.40 Å)¹. The asymmetric unit of the crystal contains 2 GSTP1 monomers. Red, α -helix; yellow, β -pleated sheets; blue, β -bend; grey, random coil.

Supplementary Fig. 14 MST-based profiling of the interaction between SA compounds and GSTP1 or its functionally disruptive mutants and performance of cell death assessment. (a) Interaction between SAA and GSTP1 overexpressed in cells with a GFP tag was assessed by the cellular microscale thermophoresis analysis (MST). Left, WT. Right, the C101S mutant. (b) Interaction between SAB and GSTP1 overexpressed in cells with a GFP tag was assessed by the cellular MST. Left, WT. Right, the C101S mutant. (c) Interaction between SAE and GSTP1 overexpressed in cells with a GFP tag was assessed by the cellular

MST. Left, WT. Right, the C47S mutant.

Supplementary Fig. 15 Characterization of a dual death mechanism of senescent cells mediated by GSTP1.

(a) Survival measurement of CTRL and SEN cells after exposure to GSTP1 inhibitors LAS17 or Ezatiostat, each applied at 10 μ M. Cells were treated by the apoptosis inhibitor QVD (10 μ M), with DMSO as a solvent control. (b) Cell viability assay of CTRL and SEN cells upon SAA treatment. GSTP1 knockdown cell lines were generated by gene-specific shRNAs. Inlet, immunoblot of cell lysates to confirm target protein knockdown. (c) Survival measurement of CTRL and SEN cells after GSTP1 knockdown. Cells were exposed to QVD or LIP, individually. (d) Immunoblot of protein expression of a set of key factors including GSTP1, JNK/c-Jun pathway and GPX4. GAPDH, loading control. (e) Immunoblot of GPX4 expression in senescent cells treated by SAA in the absence or presence of CHX. GAPDH, loading control. CHX, cycloheximide. (f) Immunoblot of GPX4 expression in cells treated by BLEO alone or together with SAA(B/E), MG-132, CQ or Baf. CQ, chloroquine. Baf, bafilomycin. (g) Measurement of GPX4 expression at transcription level. (h) Determination of the ratio of reduced (GSH) to oxidized (GSSG) glutathione measured as an index of oxidative stress in PSC27 cells as indicated. (i) Immunoprecipitation followed by immunoblot analysis of cells treated as indicated. (j) Luciferase reporter assay of cells transfected with vectors of a Reporter Assay System. IN-8, JNK-IN-8, a JNK inhibitor.

Supplementary Fig. 16 Determination of the potential of SA compounds in inducing ferroptosis in senescent cells.

(a) PSC27 cells were induced to senesce for 7days and stained with FerroOrange to quantify intracellular Fe^{2+} . Scale bar, 10 μ m. (b) SAA, SAB or SAE was added to cell culture media, either alone or together with LAS17, SP, IN-8, Fer, Lip. The chemical agent 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY-C11), was used to assess the levels of ferroptosis in cells. Note, BODIPY-C11 is a BODIPY-based, red fluorescent dye with a fatty acid modification. Upon oxidation by free radicals, its emission fluorescence shifts

towards shorter wavelengths, resulting in green fluorescence. LAS17, L-buthionine sulfoximine analogue 17. SP, SP600125. IN-8, JNK-IN-8. Fer, Ferrostatin-1. Lip, Liproxstatin-1. SP and IN-8 are chemical inhibitors of JNK. Fer and Lip are chemical inhibitors of ferroptosis. Scale bar, 10 μ m.

Supplementary Fig. 17 Schematic design of preclinical trial, SASP expression assessment and therapeutic side-effect appraisal.

(a) Statistics of tumor end volumes. PC3 cells were xenografted alone or together with PSC27 to the hind flank of animals, with tumor volumes measured at the end of an 8-week period. **(b)** Cancer cells (PC3) alone or alongside stromal cells (PSC27) were inoculated subcutaneously to NOD/SCID males 2 weeks before chemotherapy. MIT was delivered *via* intravenous injection on the 1st day of each week starting from the 3rd week, then given every other week, totally 3 doses. SAA administered *via* i.p. starting from beginning of the 5th week, then once *per* 2 weeks (biweekly). At the end of 8 weeks mice were sacrificed, tumor volume measured and tissues assessed. **(c)** Transcript analysis of canonical SASP factors (IL1 α /SPINK1) and senescence markers (p16^{INK4a}/p21^{CIP1}) expressed in epithelial and stromal cells, respectively. Individual cell types were isolated from tumor tissues *via* LCM. Data are representative of 3 biological replicates ($n = 10$ animals *per* group). Datasets are displayed as box-and-whisker plots, where a box extends from the 25th to 75th percentile with the median shown as a line in the middle, with whiskers indicating smallest and largest values. **(d)** Heatmap depicting top genes (50) significantly upregulated in stromal cells xenografted subcutaneously to mice and induced senescent by MIT. Gene expression in animals experiencing MIT/SAA co-treatment also profiled, with transcript signals normalized to vehicle-treated group. Red stars, SASP factors. **(e)** Comparative measurement of IL6, CXCL1 and CCL2 in mouse serum with ELISA. **(f)** Body weight determination performed weekly for immunodeficient mice. **(g)** Serum measurement of creatinine, urea, alkaline phosphatase (ALP) and alanine aminotransferase (ALT) with terminal bleeds (cardiac punctures) taken at the end of therapeutic regimens. For **a** and **c**, P values

were calculated by Student's *t*-tests. For **f-g**, *P* values were calculated by one-way ANOVA with Tukey's multiple-comparison test. Data in **a**, **f** and **g** are shown as mean $\pm$ SD and representative of 3 independent experiments. MIT, mitoxantrone. LCM, laser capture microdissection. For each dataset, *n* = 10 (**a**, **c**) or 3 (**f**, **g**) *per* treatment arm. [^], *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001; ****, *P* < 0.0001.

Supplementary Fig. 18 Pathophysiological assessment of SAA treatment effects on immunocompetent mice (males). (a) Animal body weight determination performed on a weekly basis for immunocompetent C57BL/6J mice. (b) Serum measurement of creatinine, urea, alkaline phosphatase (ALP), and alanine aminotransferase (ALT) with terminal bleeds (cardiac punctures) taken at the end of therapeutic regimens. (c) Routine analysis of peripheral blood. The circulating levels of hemoglobin, white blood cells, lymphocytes and platelets at the end of each therapeutic regimen were assessed. Data are shown as mean $\pm$ SD and representative of 3 independent experiments. MIT, mitoxantrone. WBC, white blood count. For all datasets, *n* = 3 *per* treatment arm. For all datasets, *P* values were calculated by one-way ANOVA with Tukey's multiple-comparison test. [^], *P* > 0.05.

Supplementary Fig. 19 Senolysis by SAB/SAE in the treatment-damaged tumor microenvironment restrains SASP-conferred cancer resistance. (a) Comparative statistics of tumor end volumes. PC3 cancer cells were inoculated either alone or combined with PSC27 stromal cells before implanted subcutaneously to the hind flank of NOD/SCID animals. The mice were then administered with MIT and SAB, either alone or in combination. (b) Representative images of *in vivo* senescence in tumors by SA- β -gal staining. Scale bar, 50 μ m. (c) Comparative statistics of tumor senescence as described in (b). (d) Comparative survival of animals (MIT/SAB) sacrificed upon development of advanced bulky diseases. (e) Comparative statistics of tumor end volumes. PC3 cancer cells were inoculated either alone or combined with PSC27 stromal cells before implanted subcutaneously

to the hind flank of NOD/SCID animals, which were administered with MIT and SAE, either alone or in combination. **(f)** Representative images of *in vivo* senescence in tumors by SA- β -gal staining. Scale bar, 50 μ m. **(g)** Comparative statistics of tumor senescence as described in **(f)**. **(h)** Comparative survival of animals (MIT/SAE) sacrificed upon development of advanced bulky diseases. Data in **a**, **c**, **e** and **g** are shown as mean $\pm$ SD and representative of 3 independent experiments. In **d** and **h**, survival duration was calculated from tissue recombinant injection until death. *P* values were calculated by a two-sided log-rank (Mantel-Cox) test. MIT, mitoxantrone. For each dataset, *n* = 10 *per* treatment arm. [^], *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001; ****, *P* < 0.0001.

Supplementary Fig. 20 Pathophysiological assessment of SAB/SAE treatment effects on immunocompetent mice (males). **(a)** Animal body weight determination performed on a weekly basis for immunocompetent C57BL/6J mice treated with MIT/SAB. **(b)** Serum measurement of creatinine, urea, ALP and ALT with terminal bleeds (cardiac punctures) taken at the end of therapeutic regimens of animals treated with MIT/SAB. **(c)** Routine analysis of peripheral blood from animals treated with MIT/SAB. The circulating levels of hemoglobin, white blood cells, lymphocytes and platelets at the end of each therapeutic regimen were assessed. **(d)** Animal body weight determination performed on a weekly basis for immunocompetent C57BL/6J mice treated with MIT/SAE. **(e)** Serum measurement of creatinine, urea, ALP and ALT with terminal bleeds (cardiac punctures) taken at the end of therapeutic regimens of animals treated with MIT/SAE. **(f)** Routine analysis of peripheral blood from animals treated with MIT/SAE. The circulating levels of hemoglobin, white blood cells, lymphocytes and platelets at the end of each therapeutic regimen were assessed. Data are shown as mean $\pm$ SD and representative of 3 independent experiments. MIT, mitoxantrone. ALP, alkaline phosphatase. ALT, alanine aminotransferase. WBC, white blood count. For all datasets, *n* = 3 *per* treatment arm. For all datasets, *P* values were calculated by one-way ANOVA with Tukey's multiple-comparison test. [^], *P* > 0.05.

Supplementary Fig. 21 Comparative survival of wildtype mice that have an intact immune system. B16-F10 melanoma cells and mouse embryonic fibroblasts (both of a C57/BL6 background) were transplanted into C57/BL6 mice to make a syngeneic tumor model. (a) Comparative survival of mice that received vehicle, MIT and/or SAA treatment. (b) Comparative survival of mice that received vehicle, MIT and/or SAA treatment. (c) Comparative survival of mice that received vehicle, MIT and/or SAA treatment. *P* values were calculated by a two-sided log-rank (Mantel-Cox) test. ^, *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001.

Supplementary Fig. 22 SAB/SAE treatment mitigates physical dysfunction of animals exposed to WBI. (a) Whole body snapshot comparison of C57BL/6J males that were naïve, WBI-exposed followed by vehicle-treatment or WBI-exposed followed by SAB (a) or SAE (b) treatment, respectively. (c) Comparative statistics of SA-β-gal staining positivity of cardiac (left), pulmonary (middle) and cortex (right) tissues of animals either naïve, WBI followed by treatment with SAB or SAE, respectively. (d) Measurement of running distance on treadmill (left) and grip strength (right) for animals in each group as described in (c). (e) Y-maze test for experimental mice. Left, comparative total arms. Right, comparative alterations. (f, g) Comparative survival of naïve, WBI mice followed by treatment with either SAB (f) or SAE (g). (h) Quantitative comparison of body weight of animals treated as indicated. *P* values were calculated by a two-sided log-rank (Mantel-Cox) test. Data in c-e are shown as mean ± SD and representative of 3 independent biological replicates, with *P* values calculated by Student's *t*-tests. ^, *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001; ****, *P* < 0.0001.

Supplementary Fig. 23 Intermittent SAA treatment depletes senescent cells in multiple organs. (a) Representative images of SA-β-gal staining of liver tissues from young and aged mice treated with vehicle or SAA. Scale bar, 100 μm. As a positive control of natural senolytic agent, PCC1 was administered in a parallel group. (b) Comparative statistics of SA-β-gal staining positivity in liver tissues. (c)

Representative images of SA- β -gal staining of kidney tissues from young and aged mice treated with vehicle or SAA. Scale bar, 100 μ m. **(d)** Comparative statistics of SA- β -gal staining positivity in kidney tissues. **(e)** Representative images of SA- β -gal staining of prostate tissues from young and aged mice treated with vehicle or SAA. Scale bar, 100 μ m. **(f)** Comparative statistics of SA- β -gal staining positivity in prostate tissues. **(g)** Representative images of SA- β -gal staining of heart tissues from young and aged mice treated with vehicle or SAA. Scale bar, 100 μ m. **(h)** Comparative statistics of SA- β -gal staining positivity in heart tissues. Data in **c**, **d**, **f** and **h** are shown as mean $\pm$ SD and representative of 3 independent biological replicates. *P* values were calculated by Student's *t*-tests. [^], *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001; ****, *P* < 0.0001.

Supplementary Fig. 24 Intermittent SAA delivery eliminates senescent cells in various organs. **(a)** Representative images of SA- β -gal staining of spleen tissues from young and aged mice treated with vehicle or SAA. Scale bar, 100 μ m. As a positive control for senolytics, PCC1 was administered in a parallel group. **(b)** Comparative statistics of SA- β -gal staining positivity in spleen tissues. **(c)** Representative images of SA- β -gal staining of cortex tissues from young and aged mice treated with vehicle or SAA. Scale bar, 100 μ m. **(d)** Comparative statistics of SA- β -gal staining positivity in cortex tissues. **(e)** Representative images of SA- β -gal staining of pancreas tissues from young and aged mice treated with vehicle or SAA. Scale bar, 100 μ m. **(f)** Comparative statistics of SA- β -gal staining positivity in pancreas tissues. **(g)** Quantification of body weight of animals as described in Fig. 8a. **(h)** Measurement of food intake of animals as described in Fig. 8a. Data in **b**, **d**, **f**, **g** and **h** are shown as mean $\pm$ SD and representative of 3 independent biological replicates. *P* values were calculated by Student's *t*-tests. [^], *P* > 0.05; *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001; ****, *P* < 0.0001.

Supplementary Fig. 25 SAB/SAE treatment eliminates senescent cells in multiple organs. **(a)** Comparative statistics of SA- β -gal staining positivity in the lung,

liver, kidney, prostate, heart, spleen, cortex and pancreas tissues of young, aged mice treated with vehicle, SAB or SAE. **(b)** Quantification of maximal walking speed (relative to baseline), hanging endurance, grip strength, treadmill endurance and daily activity of 20-month-old C57BL/6J males after 4-month intervention with SAB or SAE. **(c)** Quantification of the time to cross the balance beam. Data before and after treatment of each animal are connected to allow direct comparison of treatment effects. **(d)** Comparison of body weight of animals as described in Fig. 8a. **(e)** Measurement of food intake of animals as described in Fig. 8a. **(f)** Quantitative transcript profiling of SASP expression in lung tissues collected from 6-month-old untreated (6M), 24-month-old vehicle-treated (24M-Vehicle), 24-month-old SAB-treated mice (24M-SAB) and 24-month-old SAE-treated mice (24M-SAE), respectively. Data are shown as mean $\pm$ SD and derive from 3 biological replicates ($n = 3$ independent assays). P values were calculated by Student's t -tests. $^{\wedge}$, $P > 0.05$; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$.

Supplementary Fig. 26 SAA suppresses the SASP expression *in vivo* and intervention with SAB/SAE prolongs survival of aged mice. **(a)** Heatmap depicting top genes (50) significantly upregulated in lung tissues of mice but subject to reversal by SAA intervention. **(b-e)** Post-treatment survival **(b,d)** and whole-life survival **(c,e)** curves of C57BL/6J animals treated biweekly with SAB ($n = 35$; 18 males, 17 females) or SAE ($n = 33$; 18 males, 15 females), or vehicle ($n = 39$; 20 males, 19 females) starting at 24-27 months of age. PCC1 was administered as a positive control ($n = 32$; 17 males, 15 females). **(f)** Maximal walking speed and hanging endurance averaged over the last 2 months of life for mice treated with SAB/SAE ($n = 10$ /group), and lifespan for the longest living mice (top 20) in both groups. **(g)** Disease burden and tumor burden at death of mice treated with SAB/SAE. For both sexes, n (animal number) = 30 *per arm* in each case. Cox proportional hazard regression model **(b-e)** and one-way ANOVA with Tukey's multiple-comparison test **(f-g)**. $^{\wedge}$, $P > 0.05$; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$.

Supplementary Fig. 27 Late life intervention with SAA does not alter the cause of death, but restrains the SASP and reduces oxidative stress. (a-b) Pie charts depicting the ultimate causes of death of C57BL/6J mice (males and females) that had undergone vehicle (a) or SAA (b) biweekly treatment starting from 24-27 months of age. Note, there was no significant difference between vehicle- and SAA-treated animals upon analysis using either Chi-square or Fisher's exact tests. (c-d) Transcript profiling of the SASP and senescence marker expression in tissues of solid organs, including liver (c) and lung (d) collected from young (6-month-old, untreated), aged (24-27-month-old) vehicle-treated and aged (24-27-month-old) SAA-treated animals, respectively. (e) Measurement of circulating levels of hallmark SASP factors IL6, CXCL1 and CCL2 in mouse blood by ELISA assays. (f) Examination of 4-hydroxynonenal (HNE) adducts, a marker of lipid peroxidation and oxidative stress by ELISA measurement with tissue lysates of the liver. (g) Determination of the ratio of reduced (GSH) to oxidized (GSSG) glutathione measured as an index of oxidative stress. (h-i) Data from mouse Y-maze tests. h, comparative total arms. i, comparative alterations. Data in c-i are shown as mean $\pm$ SD and derive from 3 biological replicates. *P* values were calculated by Student's *t*-tests. [^], *P* > 0.05. *, *P* < 0.05. **, *P* < 0.01. ***, *P* < 0.001. ****, *P* < 0.0001.

Supplementary Table 1. A list of naturally derived agents in the NMA library

No.	ID	Name	Synonyms	CAS	SMILES	Formula	Molecular weight
1	Flavin	Flavin mononucleotide	Riboflavin 5'-phosphate sodium; Vitamin B2 Phosphate Sodium Salt; FMN-Na; Riboflavin phosphate sodium; riboflavin-5'-phosphate; FMN	130-40-5	<chem>[Na+].c12c(nc3c(n1C[C@@H]([C@@H]([C@@H](COP(=O)([O-])O)O)O)cc(c(C)c3)C)c(=O)[nH]c(=O)n2</chem>	C ₁₇ H ₂₀ N ₄ NaO ₉ P	478.33
2	Teniposide	Teniposide	VM26; NSC 122819	29767-20-2	<chem>O1COc2c1cc1[C@H]([C@@H]3[C@@H]([C@@H](c1c2)c1cc(c(c1)OC)O)OC)C(=O)OC3O[C@H]1[C@@H]([C@H]([C@@H]2O[C@@H](OC[C@H]2O1)c1cccs1)O)O</chem>	C ₃₂ H ₃₂ O ₁₃ S	656.66
3	7-Hydroxycoumarin	7-Hydroxycoumarin	Hydrangin; Hydrangine; NSC 19790; Skimmetine; Umbelliferone	93-35-6	<chem>Oc1cc2c(cc1)ccc(=O)o2</chem>	C ₉ H ₆ O ₃	162.14
4	Methyl protocatechuate	Methyl protocatechuate	Methyl 3,4-dihydroxybenzoate; Protocatechuic acid methyl ester; 3,4-Dihydroxybenzoic acid methyl ester	2150-43-8	<chem>COC(=O)c1cc(O)c(O)cc1</chem>	C ₈ H ₈ O ₄	168.15

5	Echinacoside	Echinacoside		82854-37-3	<chem>c1(ccc(cc1O)/C=C/C(=O)O[C@H]1[C@@H]([C@H]([C@@H](O[C@@H]1CO[C@@H]1O[C@@H]([C@H]([C@@H]([C@H]1O)O)O)CO)OCCc1ccc(c(c1)O)O)O)[C@@H]1O[C@H]([C@@H]([C@H]([C@H]1O)O)O)C)O</chem>	C35H46O20	786.73
6	Genistein	Genistein	NPI 031L	446-72-0	<chem>c12c(c(=O)c(cc1)c1ccc(cc1)O)c(cc(c2)O)O</chem>	C15H10O5	270.24
7	Taxifolin	Taxifolin	(+)-Taxifolin;(+)-Dihydroquercetin;Dihydroquercetin	480-18-2	<chem>Oc1ccc(cc1O)[C@@H]1[C@@H](O)C(=O)c2c(O)cc(O)cc2O1</chem>	C15H12O7	304.25
8	Kaempferol	Kaempferol	Kempferol;Robigenin	520-18-3	<chem>Oc1ccc(cc1)c1c(O)c(=O)c2c(O)cc(O)cc2o1</chem>	C15H10O6	286.23
9	Theophylline-7-acetic acid	Theophylline-7-acetic acid	Acefylline;Theophyllineacetic acid;acetyloxytheophylline;Carboxymethyltheophylline	652-37-9	<chem>Cn1c2c(c(=O)n(c1=O)C)n(cn2)CC(=O)O</chem>	C9H10N4O4	238.2
10	Salidroside	Salidroside	Rhodioloside	10338-51-9	<chem>c1cc(ccc1CCO[C@H]1[C@@H]([C@H]([C@@H]([C@H]([C@H](O1)CO)O)O)O)O</chem>	C14H20O7	300.3
11	Ketoisophorone	Ketoisophorone	4-Oxoisophorone;2,6,6-Trimethyl-2-cyclohexene-1,4-dione	1125-21-9	<chem>CC1=CC(=O)CC(C)(C)C1=O</chem>	C9H12O2	152.19

12	Rhoifolin	Rhoifolin	Rhoifoloside;Apigenin 7-O-neohesperidoside;Apigenin-7-O-rhamnoglucoside	17306-46-6	<chem>c1(cc(=O)c2c(cc(cc2o1)O[C@H]1[C@@H]([C@H]([C@@H]([C@H](O1)CO)O)O)[C@H]1[C@@H]([C@@H]([C@H]([C@@H](O1)C)O)O)O)c1ccc(cc1)O</chem>	C27H30O14	578.53
13	Swertiamarin	Swertiamarin	Swertiamaroside	17388-39-5	<chem>OC[C@H]1O[C@@H](O[C@@H]2OC=C3C(=O)OCC[C@@]3(O)[C@H]2C=C)[C@H](O)[C@@H](O)[C@@H]1O</chem>	C16H22O10	374.34
14	Loganin	Loganin	Loganoside	18524-94-2	<chem>C[C@H]1[C@H](C[C@H]2[C@@H]1[C@@H](OC=C2C(=O)OC)[C@H]1[C@@H]([C@H]([C@@H]([C@H](O1)CO)O)O)O</chem>	C17H26O10	390.38
15	10-Hydroxycamptothecin	10-Hydroxycamptothecin	(S)-10-Hydroxycamptothecin;10-HCPT	19685-09-7	<chem>CC[C@@]1(O)C(=O)OCc2c1cc1-c3nc4ccc(O)cc4cc3Cn1c2=O</chem>	C20H16N2O5	364.36
16	Neohesperidin Dihydrochalcone	Neohesperidin Dihydrochalcone	NHDC;Neohesperidin DC;NCI-c60764	20702-77-6	<chem>C[C@H]1[C@@H]([C@H]([C@H]([C@@H](O1)O[C@@H]1[C@H]([C@@H]([C@H](O[C@H]1O)c1cc(c(c1)O)C(=O)CCc1cc(c(cc1)OC)O)O)CO)O)O)O</chem>	C28H36O15	612.58

17	Gentiopicroin	Gentiopicroin	Gentiopicroside	20831-76-9	<chem>C=C[C@H]1[C@@H](OC=C2C1=CCOC2=O)O[C@H]1[C@@H]([C@H]([C@@H]([C@H](O1)CO)O)O)O</chem>	C16H20O9	356.33
18	Orcinol glucoside	Orcinol glucoside	Sakakin	21082-33-7	<chem>Cc1cc(O)cc(O[C@@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2O)c1</chem>	C13H18O7	286.28
19	Baicalin	Baicalin	Baicalein 7-O-β-D-glucuronide	21967-41-9	<chem>c1ccc(cc1)c1cc(=O)c2c(c(c(cc2o1)O)[C@H]1[C@@H]([C@H]([C@@H]([C@H](O1)C(=O)O)O)O)O)O</chem>	C21H18O11	446.37
20	Catalpol	Catalpol	Catalpinoside; Digitalis purpurea L	2415-24-9	<chem>OC[C@H]1O[C@@H](O[C@@H]2OC=C[C@H]3[C@H](O)[C@@H]4O[C@@]4(CO)[C@@H]23)[C@H](O)[C@@H](O)[C@@H]1O</chem>	C15H22O10	362.33
21	Sanguinarine	Sanguinarine	Sanguinarin; Pseudocheleythrine	2447-54-3	<chem>C[n+]1c2c(c3ccc4c(c3c1)OCO4)ccc1cc3c(cc21)OCO3</chem>	C20H14NO4	332.33
22	Picroside I	Picroside I	6'-Cinnamoylcatalpol	27409-30-9	<chem>OC[C@]12O[C@H]1[C@@H](O)[C@@H]1C=CO[C@@H](O[C@@H]3O[C@H](COC(=O)\C=C\c4ccccc4)[C@@H](O)[C@H](O)[C@H]3O)[C@H]21</chem>	C24H28O11	492.47
23	Scutellarin	Scutellarin	Breviscapinun; Breviscapine; Scutellarein-7-glucuronide; Breviscapin	27740-01-8	<chem>c1cc(ccc1c1cc(=O)c2c(c(c(cc2o1)O)[C@H]1[C@@H]([C@H]([C@@H]([C@H](O1)C(=O)O)O)O)O)O)O</chem>	C21H18O12	462.37

24	Oridonin	Oridonin	Isodonol; NSC-250682; Rubescenin; Rubescensin A	28957-04-2	<chem>CC1(C)CC[C@H](O)[C@@]23CO[C@](O)([C@@H](O)[C@H]12)[C@@]12[C@H](O)[C@@H](CC[C@@H]31)C(=C)C2=O</chem>	C ₂₀ H ₂₈ O ₆	364.44
25	Pectolarin	Pectolarin		28978-02-1	<chem>COc1ccc(cc1)-c1cc(=O)c2c(O)c(OC)c([C@@H]3O[C@H](CO[C@@H]4O[C@H](C)[C@H](O)[C@H](O)[C@H]4O)[C@@H](O)[C@H](O)[C@H]3O)cc2o1</chem>	C ₂₉ H ₃₄ O ₁₅	622.59
26	Caffeic acid	Caffeic Acid Phenethyl Ester	CAPE; Phenylethyl Caffeate	104594-70-9	<chem>c1ccc(cc1)CCOC(=O)/C=C/c1ccc(c(c1)O)O</chem>	C ₁₇ H ₁₆ O ₄	284.31
27	Madecassoside	Madecassoside	Asiaticoside A	34540-22-2	<chem>C[C@@H]1CC[C@@]2(CC[C@]3(C)C(=CC[C@@H]4[C@@]5(C)C[C@@H](O)[C@H](O)[C@@](C)(CO)[C@H]5[C@H](O)C[C@@]34C)[C@@H]2[C@H]1C)C(=O)O[C@@H]1O[C@H](CO[C@@H]2O[C@H](CO)[C@@H](O)[C@@H]3O[C@@H](C)[C@H](O)[C@@H](O)[C@H]3O)[C@H](O)[C@H]2O)[C@@H](O)[C@H]1O</chem>	C ₄₈ H ₇₈ O ₂₀	975.12

28	Picroside II	Picroside II	6-Vanilloylcatalpol;Vanilloyl catalpol	39012-20-9	<chem>[C@@H]1(OC(=O)c2cc(c(cc2)O)OC)[C@H]2[C@@](O2)(CO)[C@H]2[C@H]1C=CO[C@H]2O[C@H]1[C@@H]([C@H]([C@@H]([C@H](O1)CO)O)O)O</chem>	C23H28O13	512.46
29	Methyl Vanillate	Methyl Vanillate		3943-74-6	<chem>COC(=O)c1cc(OC)c(O)c1</chem>	C9H10O4	182.17
30	Cryptotanshinone	Cryptotanshinone	Tanshinone c;Cryptotanshinon	35825-57-1	<chem>c12c(C(CCC1)(C)C)ccc1c2C(=O)C(=O)C2=C1OC[C@@H]2C</chem>	C19H20O3	296.37
31	7,8-Dihydroxyflavone	7,8-Dihydroxyflavone	7,8-Dihydroxyflavone;7,8-DHF	38183-03-8	<chem>c1ccc(cc1)c1cc(=O)c2c(o1)c(c(cc2)O)O</chem>	C15H10O4	254.24
32	Ethyl ferulate	Ethyl ferulate	Ferulic acid ethyl ester;Ethyl 4'-hydroxy-3'-methoxycinnamate;Ethyl 3-(4-hydroxy-3-methoxyphenyl)acrylate	4046-02-0	<chem>CCOC(=O)/C=C/c1cc(c(cc1)O)OC</chem>	C12H14O4	222.24
33	Asiatic acid	Asiatic acid	Dammarolic acid;Asiantic acid	464-92-6	<chem>C[C@@H]1CC[C@@]2(CC[C@@]3(C(=CC[C@H]4[C@]3(CC[C@@H]3[C@@]4(C[C@H]([C@@H]([C@@]3(C)CO)O)O)C)C)[C@@H]2[C@H]1C)C(=O)O</chem>	C30H48O5	488.7
34	Betulinic acid	Betulinic acid	Betulic acid;Lupatic acid;ALS-357	472-15-1	<chem>[C@H]12[C@@](CC[C@@]3([C@@]4(CC[C@H]5C([C@H](CC[C@@]5([C@H]4CC[C@H]13)C)O)(C)C)C)(CC[C@H]2C(=C)C)C(=O)O</chem>	C30H48O3	456.71
35	Dehydrocostus Lactone	Dehydrocostus Lactone	Epiligulyl oxide;(-)-Dehydrocostus lactone	477-43-0	<chem>C=C1CC[C@@H]2[C@H]1[C@H]1OC(=O)C(=C)[C@@H]1CCC2=C</chem>	C15H18O2	230.3

36	Nobiletin	Nobiletin	Hexamethoxyflavone	478-01-3	<chem>COc1c(cc(cc1)c1cc(=O)c2c(o1)c(c(c(c2OC)OC)OC)OC)OC</chem>	C21H22O8	402.4
37	Morin	Morin	Al-Morin;Aurantica;Calico Yellow;Toxylon pomiferum	480-16-0	<chem>Oc1cc(O)c2c(=O)c(O)c(c3c(O)cc(O)cc3)oc2c1</chem>	C15H10O7	302.23
38	Chrysin	Chrysin	5,7-Dihydroxyflavone;NSC 407436;5, 7-Dihydroxyflavone	480-40-0	<chem>Oc1cc(O)c2c(=O)cc(oc2c1)cccc1</chem>	C15H10O4	254.24
39	Naringenin	Naringenin	NSC 34875;S-Dihydrogenistein;NSC 11855;Salipurool;Naringetol;Pelargidanon	480-41-1	<chem>C1[C@H](Oc2cc(cc(c2C1=O)O)O)c1ccc(cc1)O</chem>	C15H12O5	272.26
40	Tangeretin	Tangeretin	NSC53909;NSC618905;Tangeritin	481-53-8	<chem>COC1=CC=C(C=C1)C1=CC(=O)C2=C(O1)C(OC)=C(OC)C(OC)=C2OC</chem>	C20H20O7	372.38
41	Hyperoside	Hyperoside	Hyperin;Quercetin 3-galactoside	482-36-0	<chem>c1cc(c(cc1c1c(c(=O)c2c(cc(cc2o1)O)O)O[C@H]1[C@@H]([C@H]([C@H]([C@H]([C@H](O1)CO)O)O)O)O)O</chem>	C21H20O12	464.38
42	Isoimperatorin	Isoimperatorin		482-45-1	<chem>CC(=CCOc1c2ccc(=O)oc2cc2c1cco2)C</chem>	C16H14O4	270.28
43	Daphnetin	Daphnetin	7,8-Dihydroxycoumarin;Daphnetol	486-35-1	<chem>c1cc(c(c2c1ccc(=O)o2)O)O</chem>	C9H6O4	178.14
44	Curcumol	Curcumol	(-)-Curcumol	4871-97-0	<chem>C1C[C@@H]([C@@]23C[C@H]([C@@](CC(=C)[C@H]12)(O3)O)C(C)C)C</chem>	C15H24O2	236.35

45	Forsythin	Forsythin	Phillyrin	487-41-2	<chem>[C@@H]1([C@@H]([C@H]([C@@H]([C@@H]([C@H](O1)CO)O)O)Oc1c(cc(cc1)[C@H]1OC[C@H]2[C@@H]1CO[C@H]2c1cc(c(cc1)OC)OC)OC</chem>	C27H34O11	534.56
46	Icariin	Icariin	Icariline	489-32-7	<chem>COc1ccc(cc1)-c1oc2c(C\C=C(\C)C)c(O[C@@H]3O[C@H](CO)[C@@H](O)[C@H](O)[C@H]3O)cc(O)c2c(=O)c1O[C@@H]1O[C@@H](C)[C@H](O)[C@@H](O)[C@H]1O</chem>	C33H40O15	676.68
47	Epicatechin	Epicatechin	(-)-Epicatechin;(-)-Epicatechol;L-Epicatechin	490-46-0	<chem>C1[C@H]([C@H](Oc2cc(cc(c12)O)O)c1cc(c(cc1)O)O)O</chem>	C15H14O6	290.28
48	Gentisic acid	Gentisic acid	2,5-Dihydroxybenzoic acid;Phloretate;5-Hydroxysalicylic acid;Gentianic acid;Carboxyhydroquinone;Hydroquinonecarboxylic acid	490-79-9	<chem>c1cc(c(cc1O)C(=O)O)O</chem>	C7H6O4	154.12
49	Salvianolic acid A	Salvianolic acid A	Dan Phenolic Acid A	96574-01-5	<chem>OC(=O)[C@@H](Cc1ccc(O)c(O)c1)OC(=O)\C=C\c1ccc(O)c(O)c1C=C\c1ccc(O)c(O)c1</chem>	C26H22O10	494.45

50	Salvianolic acid B	Salvianolic acid B	Dan Phenolic Acid B	115939-25-8	<chem>OC(=O)[C@@H](Cc1ccc(O)c(O)c1)OC(=O)\C=C\c1ccc(O)c2O[C@@H]([C@@H](C(=O)O[C@H](Cc3ccc(O)c(O)c3)C(O)=O)c12)c1ccc(O)c(O)c1</chem>	C36H30O16	718.59
51	Salvianolic acid C	Salvianolic Acid C	Dan Phenolic Acid C	115841-09-3	<chem>OC(=O)[C@@H](Cc1ccc</chem>	C26H20O10	492.43
52	Salvianolic acid D	Salvianolic acid D	Dan Phenolic Acid D	142998-47-8	<chem>OC(=O)Cc1c(O)c(O)ccc1</chem>	C20H18O10	418.35
53	Salvianolic acid E	Salvianolic acid E	Dan Phenolic Acid E	142998-46-7	<chem>OC(=O)Cc1c(O)c(O)ccc1\C=C\C(=O)O[C@H](Cc1ccc(O)c(O)c1)C(O)=O1OC(=O)Cc1c(O)c(O)cc1\C=C\C(=O)O[C@H](Cc1ccc(O)c(O)c1)C(O)=O</chem>	C36H30O16	718.61
54	Salvianolic acid F	Salvianolic acid F	Dan Phenolic Acid F	158732-59-3	<chem>OC1=C(C=CC(/C=C/C(O</chem>	C17H14O6	314.29

**Supplementary Table 2. Significance analysis related to data in Fig. 2c,
Supplementary Fig. 2c, 3c, 4a, 4c, 4e, 4g, 4i, 4k.**

SAA-related dataset

Student's <i>t</i> -test (unpaired two-tailed)	Summary	Adjusted <i>P</i> Value
SAA - 0 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	$\wedge$	0.3218
CTRL vs. Replication-induced senescence (RS)	$\wedge$	0.6873
CTRL vs. Oncogene-induced senescence (OIS)	$\wedge$	0.4380
SAA - 25 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	$\wedge$	0.1345
CTRL vs. Replication-induced senescence (RS)	$\wedge$	0.5195
CTRL vs. Oncogene-induced senescence (OIS)	$\wedge$	0.7290
SAA - 50 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	$\wedge$	0.0522
CTRL vs. Replication-induced senescence (RS)	$\wedge$	0.5631
CTRL vs. Oncogene-induced senescence (OIS)	$\wedge$	0.3560
SAA - 100 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	*	0.0121
CTRL vs. Replication-induced senescence (RS)	**	0.0041
CTRL vs. Oncogene-induced senescence (OIS)	***	0.0003
SAA - 200 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	***	0.0004
CTRL vs. Replication-induced senescence (RS)	***	0.0002
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001
SAA - 300 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	****	< 0.0001
CTRL vs. Replication-induced senescence (RS)	****	< 0.0001
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001
SAA - 400 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	****	< 0.0001
CTRL vs. Replication-induced senescence (RS)	****	< 0.0001
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001
SAA - 600 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	****	< 0.0001
CTRL vs. Replication-induced senescence (RS)	****	< 0.0001
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001

SAB-related dataset

Student's <i>t</i> -test (unpaired two-tailed)	Summary	Adjusted <i>P</i> Value
SAB - 0 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	$\wedge$	0.6559
CTRL vs. Replication-induced senescence (RS)	$\wedge$	0.9375
CTRL vs. Oncogene-induced senescence (OIS)	$\wedge$	0.9529
SAB - 25 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	$\wedge$	0.5313
CTRL vs. Replication-induced senescence (RS)	$\wedge$	0.7679
CTRL vs. Oncogene-induced senescence (OIS)	$\wedge$	0.4971
SAB - 50 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	$\wedge$	0.0621
CTRL vs. Replication-induced senescence (RS)	$\wedge$	0.5432
CTRL vs. Oncogene-induced senescence (OIS)	$\wedge$	0.6250
SAB - 100 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	*	0.0157
CTRL vs. Replication-induced senescence (RS)	*	0.0116
CTRL vs. Oncogene-induced senescence (OIS)	***	0.0007
SAB - 200 μ M		
CTRL vs. Bleomycin-induced senescence (TIS)	***	0.0002

CTRL vs. Replication-induced senescence (RS)	****	< 0.0001
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001
SAB - 300 µM		
CTRL vs. Bleomycin-induced senescence (TIS)	****	< 0.0001
CTRL vs. Replication-induced senescence (RS)	****	< 0.0001
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001
SAB - 400 µM		
CTRL vs. Bleomycin-induced senescence (TIS)	****	< 0.0001
CTRL vs. Replication-induced senescence (RS)	****	< 0.0001
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001
SAB - 600 µM		
CTRL vs. Bleomycin-induced senescence (TIS)	****	< 0.0001
CTRL vs. Replication-induced senescence (RS)	****	< 0.0001
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001

SAE-related dataset

Student's <i>t</i> -test (unpaired two-tailed)	Summary	Adjusted <i>P</i> Value
SAE - 0 µM		
CTRL vs. Bleomycin-induced senescence (TIS)	Λ	0.3874
CTRL vs. Replication-induced senescence (RS)	Λ	0.9141
CTRL vs. Oncogene-induced senescence (OIS)	Λ	0.9182
SAE - 5 µM		
CTRL vs. Bleomycin-induced senescence (TIS)	Λ	0.4587
CTRL vs. Replication-induced senescence (RS)	Λ	0.9036
CTRL vs. Oncogene-induced senescence (OIS)	Λ	0.7831
SAE - 10 µM		
CTRL vs. Bleomycin-induced senescence (TIS)	Λ	0.0723
CTRL vs. Replication-induced senescence (RS)	Λ	0.7073
CTRL vs. Oncogene-induced senescence (OIS)	Λ	0.7607
SAE - 50 µM		
CTRL vs. Bleomycin-induced senescence (TIS)	**	0.0016
CTRL vs. Replication-induced senescence (RS)	***	0.0002
CTRL vs. Oncogene-induced senescence (OIS)	***	0.0002
SAE - 100 µM		
CTRL vs. Bleomycin-induced senescence (TIS)	****	< 0.0001
CTRL vs. Replication-induced senescence (RS)	****	< 0.0001
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001
SAE - 200 µM		
CTRL vs. Bleomycin-induced senescence (TIS)	****	< 0.0001
CTRL vs. Replication-induced senescence (RS)	****	< 0.0001
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001
SAE - 300 µM		
CTRL vs. Bleomycin-induced senescence (TIS)	****	< 0.0001
CTRL vs. Replication-induced senescence (RS)	****	< 0.0001
CTRL vs. Oncogene-induced senescence (OIS)	****	< 0.0001

Supplementary Table 3. Protein targets identified by 20K arrays

SAA-Bio	SAB-Bio	SAE-Bio	Co-identified targets
CKS2	COL4A3BP	GAP43	GAP43
GAP43	GAP43	GUK1	AK6
GTF2I	GTF2I	NME2	TK1
GUK1	PICK1	AK6	GKAP1
KHK	PRMT2	TK1	PIP4K2C
NME1	AK6	CMPK1	ULK2
PICK1	TK1	GKAP1	CLIC2
SGK1	GKAP1	MAPK12	GNAI2
SYTL2	PIP4K2C	PIP4K2C	PRPSAP1
AK6	ULK2	ULK2	RAB14
TK1	ARL2	ATP6V1C1	RAB3B
CMPK1	CLIC2	CLIC2	PLEKHJ1
GKAP1	GNAI2	GNAI2	RTN4
MAPK12	PRPSAP1	PRPSAP1	SAT1
PIP4K2C	RAB14	RAB14	SFN
ULK2	RAB18	RAB3B	SOD1
ARL2	RAB3B	EMC9	GGCT
ATP6V1C1	RAB9A	NTMT1	GLOD4
CLIC2	RCVRN	PLEKHJ1	NDUFA8
GNAI2	SAR1B	RTN4	RPLP1
PRPSAP1	HN1	SAT1	ARL5B
RAB14	PLEKHJ1	SFN	CRABP2
RAB18	RTN4	SOD1	PHPT1
RAB3B	SAT1	GGCT	CDC34
RAB9A	SOD1	GLOD4	EMCN
RRAS2	GGCT	NDUFA8	USP15
SAR1B	GLOD4	RPLP1	NEIL2
EMC9	NDUFA8	ARL5B	HPGDS
NTMT1	RPLP1	CDC37L1	DTNBP1
HN1	ARL5B	CRABP2	AZIN1
IFIT3	CRABP2	PHPT1	C11orf49
IP6K1	PHPT1	SAAL1	GSTP1
PANK3	S100A6	CALB1	MB
PHF23	SAAL1	CDC34	SCG3
PLEKHJ1	ARL2BP	EMCN	AP1AR
RTN4	CALB1	CYTH4 frag	METTTL21B
S100A11	CDC34	SELENBP1	FAM131C
SAT1	EMCN	USP15	LYPLA2
SFN	USP15	NEIL2	RBBP9
SOD1	BHMT2	HPGDS	TSPAN1
GGCT	NEIL2	GTF3C6	WIPI2
DYNLT3	HPGDS	DTNBP1	APIP
GAPDH	GTF3C6	PPCDC	ASNS
GLOD4	DTNBP1	AZIN1	BLVRA
LGALS1	AZIN1	GSTP1	BTF3
NDUFA8	BBOX1	MB	SMAP
RPLP1	DCPS	SCG3	MAD2L1
ARL5B	GSTP1	AP1AR	PRDX3
CDC37L1	MB	CMBL	TBCB
CRABP2	SCG3	METTTL21B	ETS1
PHPT1	AP1AR	FAM131C	TSR2
S100A6	METTTL21B	OLA1	EIF4EBP3
CDC34	FAM131C	MAGEA4	HBG1
EMCN	OLA1	LYPLA2	HBG2
CYTH4 frag	HNRNPA0	GLO1	HRSP12

USP15	MAGEA4	NOSIP	ISG15
NEIL2	ECE2	RBBP9	CA1
HPGDS	LYPLA2	TSPAN1	GRAP2
DTNBP1	RBBP9	WIPI2	NOTCH2NL
PPCDC	TSPAN1	ZG16B	ARG1
AZIN1	WIPI2	APIP	GIMAP7
BBOX1	ZG16B	ASNS	45353
C11orf49	APIP	BLVRA	COTL1
DCPS	ASNS	BTF3	HSPBAP1
GSTP1	BCL2L13	SMAP	PLEK
MB	BLVRA	MAD2L1	SNAPC5
MRPL44	BTF3	PBLD	DEF6 frag
SCG3	SMAP	PRDX3	TGM4
AP1AR	FXYD5	TBCB	ARPC1B
METTL21B	MAD2L1	GDPD5	SHD
FAM131C	PRDX3	PIM1	AAR2
HNRNPA0	TBCB	ETS1	ECHDC1
ECE2	ETS1	TSR2	HM13
LYPLA2	HAUS8	EIF4EBP3	ANXA8
GLO1	TSR2	HBG1	HACL1
NOSIP	AIF1	HBG2	ID3
RBBP9	C1orf21	HRSP12	METTL9
TSPAN1	EIF4EBP3	ISG15	NUDT2
WIPI2	HBG1	MCM7	PGM3
APIP	HBG2	CA1	ARRB1
ASNS	HRSP12	GRAP2	C6orf106
BLVRA	IL32	NOTCH2NL	C9orf16
BTF3	ISG15	ARG1	TRIAP1
SMAP	SKP1	DYDC1	XM 002816682.3 frag
CMSS1	CA1	GIMAP7	GINS2
FXYD5	GRAP2	MAGEB2	GPBP1 frag
MAD2L1	IDO1	2-Mar	RAD1
PBLD	NOTCH2NL	COTL1	SPG21
PRDX3	ARG1	HSPBAP1	MYL6
SNX3	GIMAP7	PLEK	KXD1
TBCB	2-Mar	SNAPC5	HSBP1
GDPD5	NDUFA3	CRYAB	UBQLN4 frag
ETS1	SMCP	DEF6 frag	ILF2
HPGD	COTL1	PDCD2L	PSMD4
HAUS8	HSPBAP1	TGM4	S100A8
RAB24	PLEK	ARPC1B	OLA1
TSR2	SNAPC5	CCT3	KJ903456 frag
EIF4EBP3	CRYAB	SHD	DACT3
HBG1	DEF6 frag	AAR2	PVRL3 frag
HBG2	PDCD2L	CALCOCO2	NUDCD2
HRSP12	TGM4	ECHDC1	SCGB3A2
IL32	ANP32A	HM13	LYPLAL1
ISG15	ARPC1B	ANXA8	ANAPC15
MCM7	CAPRIN2 frag	HACL1	S100B
SETMAR	CCT3	ID3	TMSB10
C11orf16	PNMA6A	METTL9	LRAT
CA1	SHD	CPTP frag	NME5
GRAP2	TUBB2B	NUDT2	ARL1
IDO1	AAR2	PGM3	ZNF471 frag
NOTCH2NL	ECHDC1	TSTA3	ATG4C
ARG1	HM13	ARRB1	BC047307 frag
DYDC1	LCP1	C11orf49	COMT
GIMAP7	ANXA8	C6orf106	DAPP1

MAGEB2	ADIRF	C9orf16	CCDC53
2-Mar	HACL1	TRIAP1	C3orf52
SMCP	ID3	XM 002816682.3 frag	NANP
COTL1	METTL9	GINS2	TXNDC17
HSPBAP1	NUDT2	GPBP1 frag	ATG12
PLEK	PGM3	RAD1	CSTA
SNAPC5	ARRB1	SPG21	FNDC3B
DEF6 frag	C11orf49	MYL6	S100P
FABP4	C6orf106	KXD1	BC033035.2 frag
TGM4	C9orf16	HSBP1	URM1
ARPC1B	CA3	UBQLN4 frag	C15orf41
CAPRIN2 frag	DHFR	ILF2	DEPP
MAN1B1	PLP1	PSMD4	CBX1
NABP2	THAP4	S100A8	GUCA1A
PNMA6A	TRIAP1	ZCCHC7	NDUFAF2
SHD	UBE2R2	TRMT12	SDSL
AAR2	XM 002816682.3 frag	IFIT5	C4orf19
ECHDC1	GINS2	KJ903456 frag	FTSJ1
HM13	GPBP1 frag	DACT3	CD53
LCP1	NASP	KLHL3 frag	REEP6
ZCCHC17	RAD1	PVRL3 frag	GDA
ANXA8	RUVBL2	C1QTNF7	UBE2H
ADIRF	SERPINB6	NUDCD2	THOC1
HACL1	SPG21	SCGB3A2	ABTB1
ID3	DBNDD1	TTR	IGFBP6
METTL9	MYL6	DPY30	STARD7
CPTP frag	PEX19	LYPLAL1	XAGE3
MPST	KXD1	ANAPC15	BMF
NUDT2	HSBP1	S100B	THEM4
PGM3	SNRPF	TMSB10	EXOSC7
PSAT1	SNX1	GID8	DMRTC1
SNCB	UBQLN4 frag	FAM131A	FAM84A
ARRB1	ILF2	LRAT	RNH1
C6orf106	PSMD4	NME5	L3HYPDH
C9orf16	S100A8	BCL2A1	CYP4F11
CA3	ZCCHC7	TEX2 frag	MIEN1
IFT20	NFKBIB	ARL1	PITPNA
RNF181	KJ903456 frag	LGALS2	TPM1
DHFR	DACT3	THRSP	ALOXE3
THAP4	KLHL3 frag	LSM8	IL18
TRIAP1	PLEK2	SHFM1	CREG1
XM 002816682.3 frag	PVRL3 frag	ZNF471 frag	
DCXR	NUDCD2	ATG4C	
GINS2	SCGB3A2	BC047307 frag	
GPBP1 frag	TTR	PAPSS1	
NXT1	CFP	FGFR1OP	
RAD1	LYPLAL1	COMT	
SERPINB6	ANAPC15	DAPP1	
SPG21	FANCI frag	CCDC53	
DBNDD1	S100B	HMGB2	
IST1	TMSB10	PPP1R2	
MYL6	CLDN3	UCHL1	
KXD1	FAM131A	C3orf52	
HSBP1	LRAT	NANP	
UBQLN4 frag	NME5	PHLDA3	
ILF2	SERPINA1	TXNDC17	
ODAM frag	BCL2A1	ATG12	
PSMD4	ARHGDI	CSTA	

RPLP2	ARL1	FNDC3B
S100A8	SENP8	S100P
OLA1	THRSP	TIMM13
TRMT12	SHFM1	BC033035.2 frag
IFIT5	ZNF471 frag	URM1
KJ903456 frag	ATG4C	PAGE4
DACT3	BC047307 frag	C15orf41
STAM	COMT	RABGGTB
PVRL3 frag	DAPP1	DEPP
S100A3	HAO2	CBX1
NUDCD2	ANXA5	EFCAB1
SCGB3A2	CCDC53	EIF3K
CFP	HDGFRP3	SPAG7
GAGE2D	PPP1R2	MTUS2
LYPLAL1	C3orf52	WDR61
ANAPC15	CALM1	GUCA1A
PSMG3	DNAL1	NDUFAF2
FANCI frag	NANP	BHMT
S100B	TXNDC17	SCIN
TMSB10	ATG12	SDSL
ATF2	CSTA	TDO2
CLDN3	FNDC3B	UROD
LRAT	S100P	C4orf19
NME5	TIMM13	PRKAR1A
TEX2 frag	ARRB2	IFIH1
ARL1	BC033035.2 frag	FTSJ1
C12orf10	INPP1	MAGEC2
LGALS2	SDCCAG3	PKIB
MMP28	URM1	CD53
SENP8	SP140L	REEP6
CRABP1	ANXA10	AAGAB
LSM8	C15orf41	SART3
ZNF471 frag	NUDC	STK16
ATG4C	RABGGTB	NDUFAB1
TPD52L1	DEPP	RABEPK
BC047307 frag	CBX1	RMI1 frag
PAPSS1	KIAA0513	GDA
FGFR10P	MTUS2	CNOT7
COMT	CALML5	GRB2
DAPP1	PMP2	UBE2H
CCDC53	SFN	ADSS
EIF2S1	GUCA1A	KJ902886
HDGFRP3	NDUFAF2	CMIP
HMGB2	RAB37	THOC1
C3orf52	TPT1	GSKIP
NANP	BHMT	ABTB1
TXNDC17	SDSL	IGFBP6
ATG12	C4orf19	DRICH1
CSTA	PRKAR1A	STARD7
FNDC3B	IFIH1	CHCHD4
S100P	ALOX15B	EXTL3
TPRKB	FTSJ1	CCNDBP1
ARRB2	MAGEC2	PTGES3
BC033035.2 frag	PKIB	XAGE3
SDCCAG3	CD53	BMF
URM1	REEP6	THEM4
SP140L	AAGAB	PCP2
PAGE4	SART3	BSND

POP7	RMI1 frag	C1orf174
ANXA10	GDA	PMAIP1
C15orf41	PAGE2	EXOSC7
NUDC	VCY	KRT18P55
2-Sep	TNIK frag	ATG4A
DEPP	SESTD1	PTMS
CBX1	UBE2H	UBA3
IL6	S100A1	DMRTC1
MARVELD2	ADSS	HBM
GUCA1A	SYAP1	S100A2
NDUFAF2	KJ902886	FAM84A
RAB37	CMIP	TMSB4X
SDSL	UBALD1	TRAPPC3
TDO2	FBXO2	N6AMT2
UROD	SERPINB4	RNH1
C4orf19	RGS10	TRIM13
CROCCP2	THOC1	L3HYPDH
ALOX15B	GSKIP	CYP4F11
FTSJ1	ABTB1	MIEN1
CD53	IGFBP6	MAPK8
REEP6	PRUNE	PITPNA
STK16	DRICH1	TCL6
NDUFAB1	STARD7	TPM1
GDA	CHCHD4	SET
DCUN1D2	EXTL3	THOC7
HTATIP2	GAB1	MGEA5
RAB1B	XAGE3	TYW3
UBE2H	BMF	LETM2
AIPL1	THEM4	ALOXE3
SAR1A	OCM	HNRNPC
SYAP1	ALOX12B	PVALB
DRAP1	EXOSC7	ATXN10
SERPINB4	IFNA6	POLR3H
THOC1	NACA	IL18
ABTB1	ANKRD26P1	CREG1
ACTN1	DMRTC1	PRMT3
IGFBP6	SH3BGR	
STARD7	FAM84A	
RLBP1	MRI1	
PTGES3	RNH1	
RBP2	GLMN	
XAGE3	L3HYPDH	
BMF	CYP4F11	
THEM4	MIEN1	
PCP2	PITPNA	
C1orf174	TCL6	
PMAIP1	TPM1	
EXOSC7	SET	
ATG4A	THOC7	
CSK	MUM1L1	
PTMS	ALOXE3	
TSR1	ATXN10	
ANKRD26P1	POLR3H	
DMRTC1	ENDOU	
HBM	IL18	
S100A2	GCSH	
FAM84A	CREG1	
G6PD		

MRI1			
RNH1			
PDE9A			
TRIM13			
L3HYPDH			
CYP4F11			
MIEN1			
MAPK8			
PITPNA			
RMND5B			
TPM1			
PDE6D			
GPN1			
ZCRB1			
NUDT10			
TYW3			
LETM2			
IFNA14			
IFNA4			
ALOXE3			
ME3			
DEFA1			
ENDOU			
IL18			
C14orf166			
CREG1			
TUBGCP4			

Note: GSTP1 is hypothesized to be a putative co-target that mediates the senolytic activity of SA-compounds.

Supplementary Table 4. Pathway and process enrichment analysis outputs

GO	Category	Description	Count	Percentage (%)	Log10(P)	Log10(q)
GO:0098869	GO Biological Processes	Cellular oxidant detoxification	8	5.56	-7.89	-3.55
GO:0044248	GO Biological Processes	Cellular catabolic process	18	12.5	-7.37	-3.33
GO:0019752	GO Biological Processes	Carboxylic acid metabolic process	17	11.81	-6.62	-2.97
GO:0044092	GO Biological Processes	Negative regulation of molecular function	14	9.72	-4.95	-1.56
GO:0002832	GO Biological Processes	Negative regulation of response to biotic stimulus	6	4.17	-4.54	-1.31
GO:0009066	GO Biological Processes	Aspartate family amino acid metabolic process	4	2.78	-4.21	-1.16
GO:0032930	GO Biological Processes	Positive regulation of superoxide anion generation	3	2.08	-4.09	-1.15
GO:0055086	GO Biological Processes	Nucleobase-containing small molecule metabolic process	11	7.64	-3.84	-0.96
GO:0032535	GO Biological Processes	Regulation of cellular component size	8	5.56	-3.51	-0.78
GO:0110053	GO Biological Processes	Regulation of actin filament organization	7	4.86	-3.47	-0.75
GO:0009123	GO Biological Processes	Nucleoside monophosphate metabolic process	4	2.78	-3.32	-0.66
R-HSA-6798695	Reactome Gene Sets	Neutrophil degranulation	9	6.25	-3.31	-0.66
GO:0061436	GO Biological Processes	Establishment of skin barrier	3	2.08	-3.25	-0.63
R-HSA-8950505	Reactome Gene Sets	Gene and protein expression by JAK-STAT signaling after interleukin-12 stimulation	3	2.08	-3.11	-0.53
GO:0009611	GO Biological Processes	Response to wounding	8	5.56	-2.96	-0.44
R-HSA-76002	Reactome Gene Sets	Platelet activation, signaling and aggregation	6	4.17	-2.78	-0.32
hsa00330	KEGG Pathway	Arginine and proline metabolism	3	2.08	-2.76	-0.31
GO:2001242	GO Biological Processes	Regulation of intrinsic apoptotic signaling pathway	5	3.47	-2.67	-0.25
GO:0051339	GO Biological Processes	Regulation of lyase activity	3	2.08	-2.57	-0.21
GO:0098930	GO Biological Processes	Axonal transport	3	2.08	-2.49	-0.16

Note: Above are top 20 clusters with their representative enriched terms (one *per* cluster).
"Count" is the number of genes in the user-provided lists with membership in the given ontology term.
"%" is the percentage of all of the user-provided genes that are found in the given ontology term (only input genes with at least one ontology term annotation are included in the calculation).
"Log10(P)" is the p-value in log base 10. "Log10(q)" is the multi-test adjusted p-value in log base 10.

Supplementary Table 5. Protein targets co-identified by pulldown assays

No.	<i>Gene Symbol</i>
1	TRIO
2	FILIP1L
3	ANXA2
4	APEX1
5	HNRNPUL1
6	ACO2
7	TJP1
8	NIBAN2
9	EIF2S3
10	PPA2
11	TXNRD1
12	PABPC1
13	CAST
14	FUBP1
15	SF3B1
16	TWF1
17	PAICS
18	CDC37
19	LRPAP1
20	ARHGAP17
21	DNM1L
22	HSPA2
23	MAPK1
24	NT5C2
25	SELENBP1
26	MAP1A
27	ERC1
28	DDX46
29	CAPZA2
30	UBE2L3
31	KHDRBS1
32	FUBP3
33	SNX27
34	HSPH1
35	KYNU
36	TXLNA
37	GSTP1
38	HDGF
39	BAG3
40	SF3A3
41	EIF4B
42	DNAJB1
43	PCYT1A
44	NPLOC4
45	VASP
46	PARP14
47	SEC24D
48	TRIOBP

49	ECHS1
50	SVIL
51	DBNL
52	INPPL1
53	TBK1
54	GLRX3
55	SPTBN1
56	STXBP3
57	HNRNPH3
58	CKAP5
59	TLN2
60	TWF2
61	TIPRL
62	MTPN
63	TACO1
64	MCTS1
65	SF1
66	GSR
67	SRRT
68	HNRNPDL
69	GPX4
70	SNRNP70
71	DDX42
72	AKR7A2
73	STAMBPL1
74	RANGAP1
75	SF3B2
76	CHORDC1
77	ECPAS
78	NOMO2
79	CCDC50
80	COLGALT1
81	IGFBP5
82	GATD3B
83	SNRPD1
84	PSPC1
85	PRPF8
86	DAZAP1
87	NIT1
88	FAM98B
89	UBE2I
90	BLVRA
91	CSK
92	CARS1
93	GSTO1
94	SH3GL1
95	MAPKAPK2
96	ABCF2
97	CRKL
98	CTTNBP2NL
99	GRHPR

100	HK2
101	SCRIB
102	XRN2
103	ST13P4
104	PDAP1
105	SELENOH
106	AK2
107	ATG7
108	SEC24A
109	ACSF2
110	AKT1
111	SCLY
112	RNF214
113	HMGCL
114	LAP3
115	CHID1
116	H2BC21
117	AMPD2
118	SCP2
119	GSK3B
120	PHLDB1
121	COA3
122	RBM25
123	PPP5C
124	CIRBP
125	RBPM5
126	NMT1
127	HNRNPAB
128	SF3A2
129	DENR
130	PIP4K2B
131	VPS11
132	PPP1R12C
133	EGLN1
134	TSN
135	TRIM3
136	PLCD1
137	MT2A
138	NCKIPSD
139	ASAP1
140	RRAGA
141	TXNDC12
142	FYCO1
143	CPSF7
144	RCC2
145	SEH1L
146	CAMSAP2
147	THYN1
148	ELAVL1
149	BTF3
150	EWSR1

151	RASA1
152	EIF4H
153	EFTUD2
154	SF3B4
155	SF3B3
156	RAB11FIP5
157	STK24
158	HBS1L
159	DRG1
160	MINK1
161	CLASP1
162	ATXN2
163	DDX23
164	HOOK3
165	EIF2S2
166	ACTR10
167	OLA1
168	BPNT1
169	PLPBP
170	CMPK1
171	EXOC6B
172	C3
173	SMAP
174	IVD
175	NDUFS5
176	CHMP1B
177	ARIH1
178	PRPF6
179	ATXN2L
180	ATAD3A
181	HSPB8
182	EEFSEC
183	CDC42BPA
184	RNF213
185	CCDC6
186	MAP2K1
187	SEC23B
188	GLRX
189	RBM3
190	TIMP1
191	PAFAH1B2
192	H2AZ2
193	MXRA8
194	CARS2
195	FAM98A
196	IGFBP7
197	HPCAL1
198	MTSS2
199	FUS
200	STC1
201	RPL26

202	NUMB
203	ATP5IF1
204	TMEM132A
205	MAPRE2
206	AIDA
207	PDLIM2
208	TBCD
209	IRF2BP2
210	ABHD12
211	HOMER3
212	EIF1
213	NUBP2
214	USP28
215	IGFBP4
216	VBP1
217	ZFP36L1
218	WDR26
219	OGFR
220	SBF1
221	IKBKG
222	ADAM10
223	PPP1R18
224	FAM91A1
225	WNK1
226	MPRIP
227	ECM1
228	DLD
229	USP39
230	PRKRA
231	PRPF31
232	ALDH3A2
233	SWAP70
234	AAK1
235	FAM98C
236	RELA
237	ARFGAP1
238	UAP1L1
239	SNRPG
240	CC2D1A
241	SLC9A3R2
242	PFDN5
243	PTK2
244	TRIM21
245	NCBP1
246	ARIH2
247	PANX1
248	SRRM1
249	DAPK3
250	HNRNPLL
251	SNRPC
252	HDAC2

253	GTPBP1
254	VPS45
255	NADK2
256	APOOL
257	GBF1
258	GIPC1
259	ATE1
260	TBC1D2
261	RAF1
262	EXOC5
263	VPS39
264	MBNL2
265	DNAJC10
266	TIGAR
267	SNTB2
268	WDR82
269	CYRIB
270	PTPN14
271	STX5
272	LSM12
273	ATP6V1G1
274	CAMK2G
275	EIF4G3
276	PCBP3
277	TCEAL3
278	COL8A1
279	KRAS
280	TUBAL3
281	CPAMD8
282	KPNA4
283	GIT2
284	DCTN6
285	PRKAB1
286	EML3
287	RPS28
288	ACOT1
289	SRGAP1
290	RPP30
291	MYD88
292	SERPINB7
293	VPS4A
294	C1orf198
295	LPAR1
296	RPS21
297	GNA13
298	HSPA14
299	HDHD5
300	ABRA1
301	GOPC
302	CEP120
303	NDUFAB1

304	CACYBP
305	SH3PXD2B
306	MIA3
307	XAGE1A
308	USP15
309	EDEM3
310	OSBPL8
311	CSNK1A1
312	SRSF2
313	RIPK2
314	CIAO2B
315	COMMD2
316	CCDC22
317	MRPL37
318	PRPF40A
319	QKI
320	ATP5F1D
321	LARS2
322	YARS2
323	GHDC
324	GAK
325	PCYT2
326	GIT1
327	CTSA
328	LANCL1
329	PATL1
330	CSNK2A2
331	LSM4
332	MRPS35
333	NUP133
334	GNE
335	NRP2
336	ACSF3
337	SELENOM
338	ASCC3
339	C11orf68
340	PAIP1
341	PDP1
342	PUF60
343	NDUFA8
344	PGLS
345	PFDN2
346	PRRC2C
347	SV2A
348	FHL3
349	MAPKAP1
350	DHRS4
351	PRUNE1
352	ARHGEF17
353	MRPL55
354	UTRN

355	PELO
356	SART3
357	PCDH18
358	FKBP3
359	NUFIP2
360	YLPM1
361	RBBP7
362	UBLCP1
363	WIP1
364	TJP2
365	UBE2D3
366	PTPN12
367	SLC16A6
368	MTIF2
369	POLR2B
370	EDC3
371	CLPP
372	SRP14
373	TP53RK
374	MIPEP
375	TMPO
376	MYO10
377	LUZP1
378	SCO2
379	CNOT3
380	NRDC
381	VPS33B
382	FRMD8P1
383	SKP1
384	SRM
385	TAGLN
386	TBL1XR1
387	MMS19
388	DDX49
389	NDUFS7
390	TSNAX
391	SCAF4
392	CDK2
393	FADS3
394	XRN1
395	RBM26
396	PPP2R5D
397	CASZ1
398	GALT
399	GSDMD
400	TRIM32
401	PQBP1
402	ABI1
403	ECI2
404	INPP4B
405	DRG2

406	FBXL18
407	CHRM5
408	ZC3H15
409	PRPF4
410	SHFL
411	MTMR1
412	ZNF207
413	METTL13
414	EIF2AK4
415	LRCH4
416	ANGPTL4
417	NRBP1
418	GOLGA2
419	NOM1
420	NEB
421	UBE3C
422	STAMBP
423	MRPL2
424	DCAKD
425	RIC8A
426	ARL6IP1
427	TBL2
428	SUMF1
429	TTN
430	COG1
431	DECR2
432	EIF2B2
433	MRPL48
434	PPFIA1
435	DAGLB
436	ZNF827

Supplementary Table 6. Pharmacokinetics of SAA and SAB in mouse serum in the time course after intraperitoneal administration

SAA							SAB						
Time (h)	1	2	3	Average	(ng/ml)	or (µg/l)	Time (h)	1	2	3	Average	(ng/ml)	or (µg/l)
0.083	16151	21320	11410	16294			0.083	16990	9982	12820	13264		
0.25	6982	6691	7211	6961			0.25	9866	4537	7786	7396		
0.5	2986	3245	3543	3258			0.5	4722	6546	5527	5598		
1	1151	1299	1188	1213			1	877.6	715.9	838.7	811		
2	128.4	67.05	71.3	89			2	35.94	59.68	47.79	48		
4	56.56	49.41	64.43	57			4						
8													
Statistical Moment Parameters							Statistical Moment Parameters						
Param.	Unit	No1	No2	No3	Mean	SD	Param.	Unit	No1	No2	No3	Mean	SD
AUC(0-t)	ug/L*h	4092.78	4114.68	4324.615	4177.358	127.997	AUC(0-t)	ug/L*h	4950.36	4216.445	4720.835	4629.213	375.438
AUC(0-∞)	ug/L*h	4093.775	4115.606	4325.636	4178.339	128.029	AUC(0-∞)	ug/L*h	4950.378	4216.616	4720.883	4629.292	375.358
AUMC(0-t)		2939.42	2810.945	3009.06	2919.808	100.503	AUMC(0-t)		2272.02	2230.903	2299.333	2267.419	34.446
AUMC(0-∞)		2948.35	2819.735	3017.931	2928.672	100.553	AUMC(0-∞)		2273.364	2232.682	2300.826	2268.957	34.285
MRT(0-t)	h	0.718	0.683	0.696	0.699	0.018	MRT(0-t)	h	0.459	0.529	0.487	0.492	0.035
MRT(0-∞)	h	0.72	0.685	0.698	0.701	0.018	MRT(0-∞)	h	0.459	0.529	0.487	0.492	0.035
VRT(0-t)	h^2	0.673	0.575	0.668	0.639	0.055	VRT(0-t)	h^2	0.09	0.098	0.096	0.095	0.004
VRT(0-∞)	h^2	0.69	0.591	0.684	0.655	0.056	VRT(0-∞)	h^2	0.091	0.1	0.097	0.096	0.005
Tmax	h	0.25	0.25	0.25	0.25	0	Tmax	h	0.25	0.5	0.25	0.333	0.144
CLz/F	L/h/kg	4.885	4.86	4.624	4.79	0.144	CLz/F	L/h/kg	4.04	4.743	4.236	4.34	0.363
Vz/F	L/kg	4.851	4.757	4.564	4.724	0.146	Vz/F	L/kg	1.259	1.916	1.457	1.544	0.337
Zeta		1.007	1.022	1.013	1.014	0.008	Zeta		3.208	2.475	2.908	2.864	0.369
Zeta(terminal log-line)		124	124	124	--	--	Zeta(terminal log-line)		235	235	235	--	--
Cz (predicted)	ug/L	1.002	0.946	1.035	0.994	0.045	Cz (predicted)	ug/L	0.059	0.424	0.141	0.208	0.192
Cmax	ug/L	6982	6691	7211	6961.333	260.615	Cmax	ug/L	9866	6546	7786	8066	1677.617

Note: following intraperitoneal administration, both SAA and SAB reached peak plasma concentrations within 5 min, indicating rapid systemic absorption. Plasma concentrations declined sharply thereafter, demonstrating rapid elimination. The Cmax values were 6.96 and 8.07 mg/l for SAA and SAB, respectively, while the corresponding AUC_{0-t} values were 4.18 and 4.63 mg·h/l.