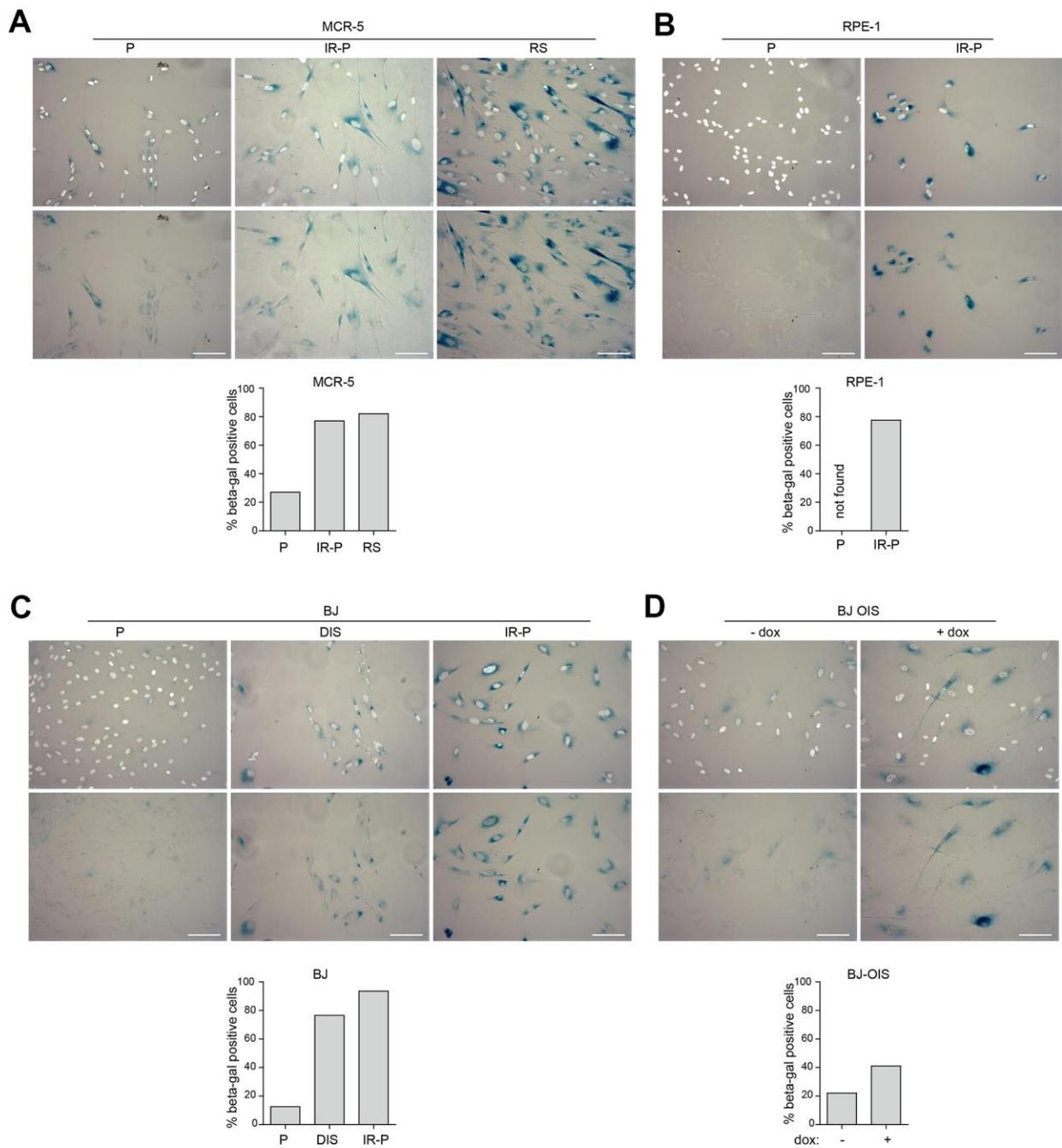
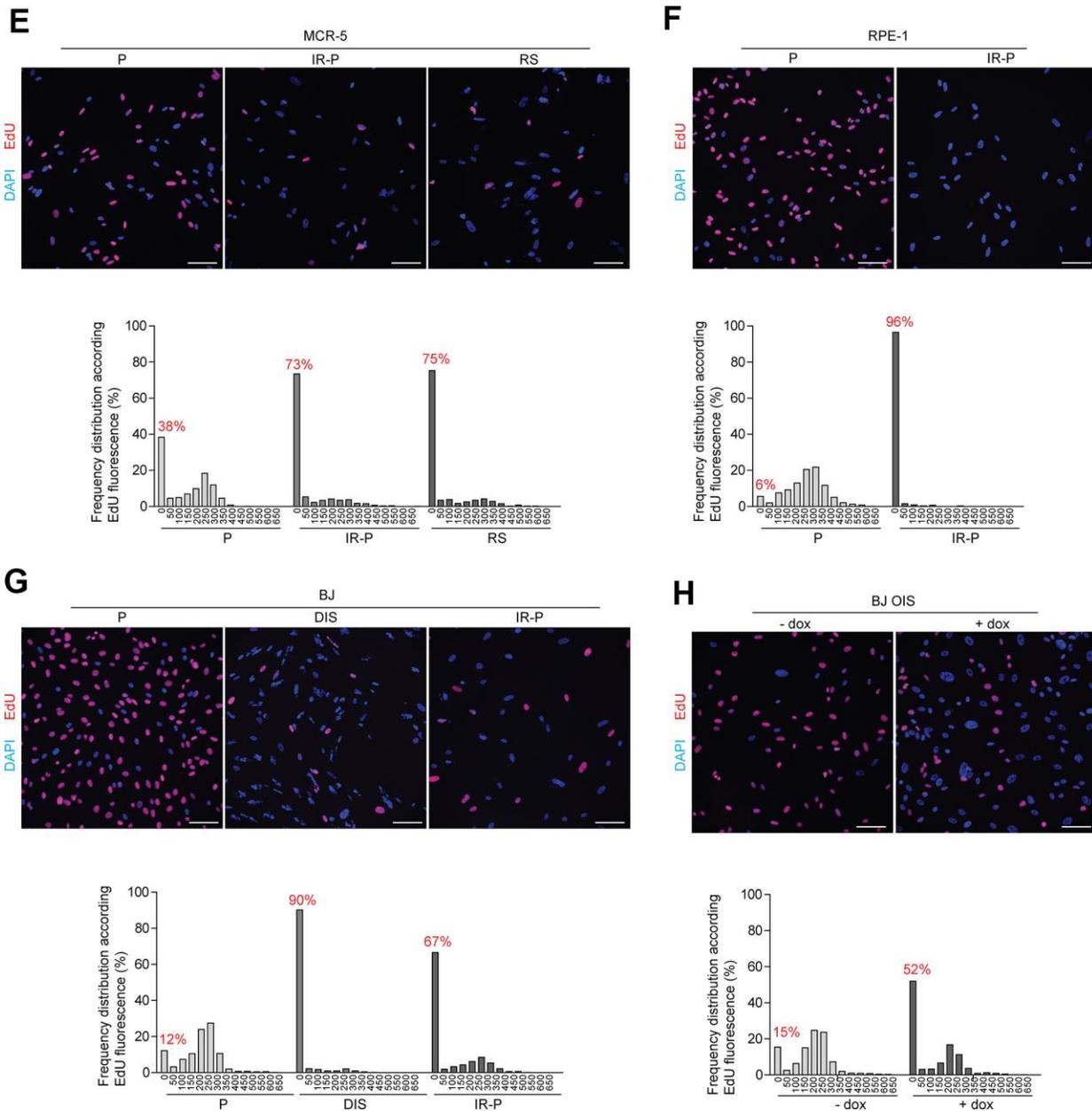
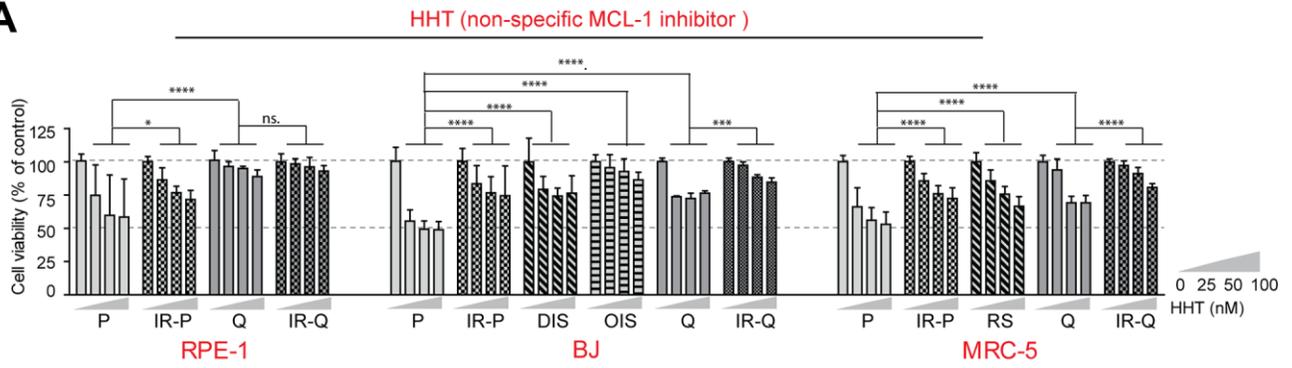
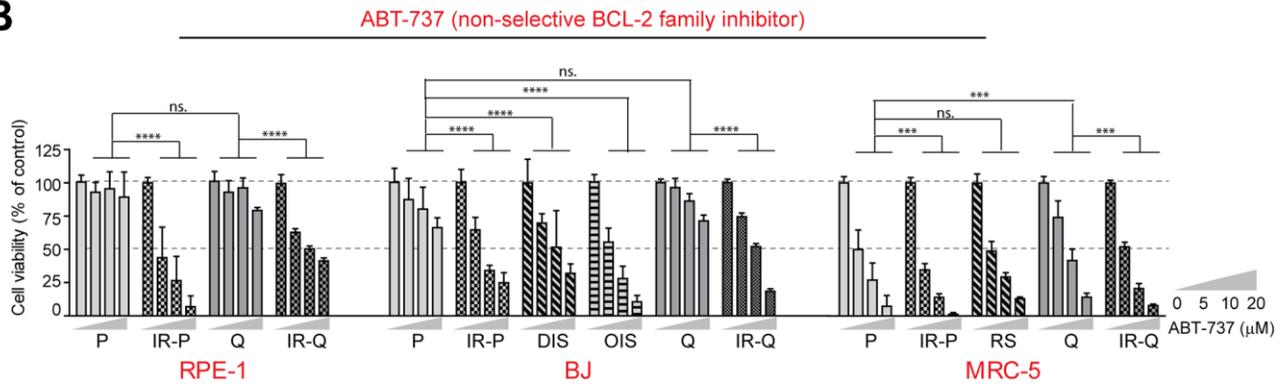
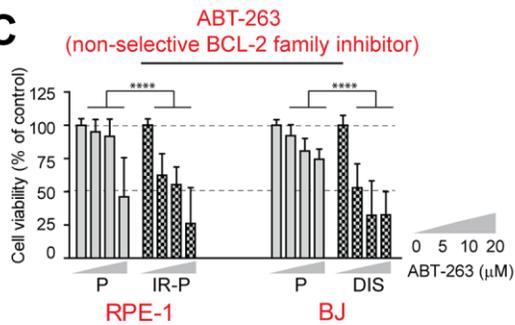


SUPPLEMENTARY FIGURES





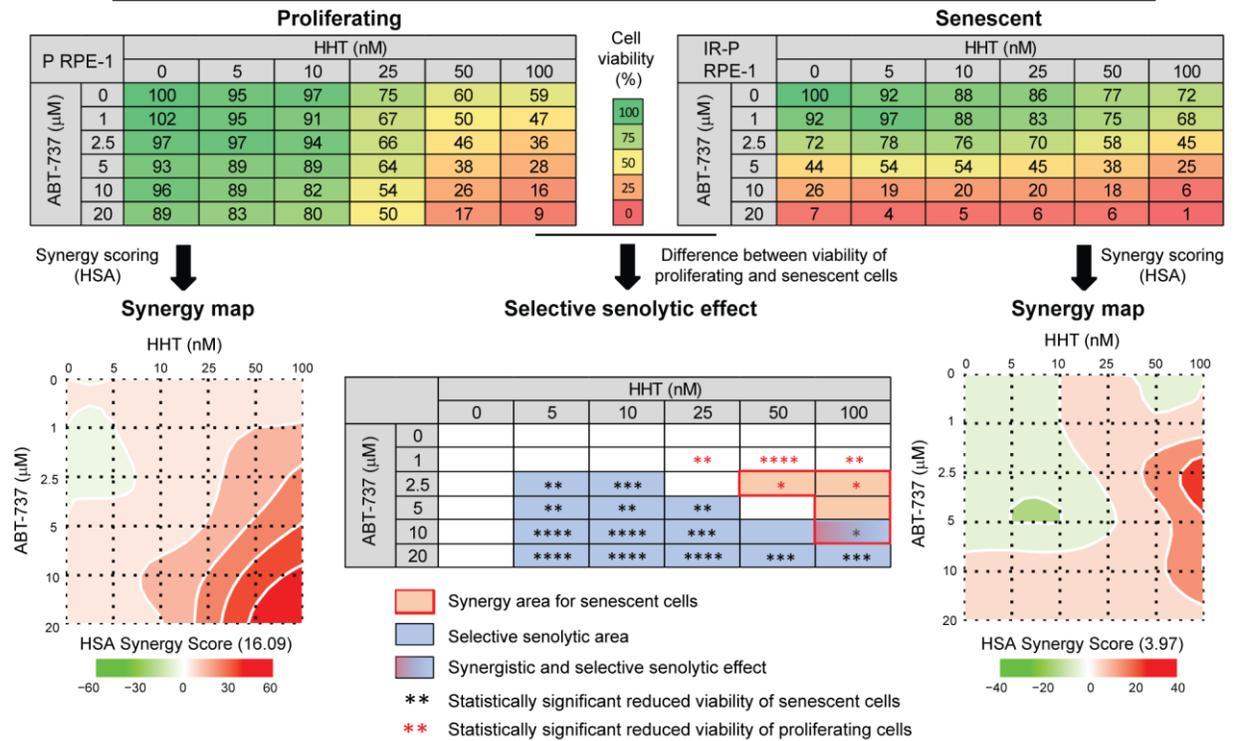
Supplementary Figure 1. Determination of cellular senescence markers in models of senescence. Senescence-associated β -galactosidase activity in (A) replicative (RS) and irradiated (10 Gy; IR-P) senescent MRC-5, (B) irradiated RPE-1 (20 Gy; IR-P), (C) docetaxel-induced BJ (BJ DIS), irradiated BJ (10 Gy; BJ IR-P), and (D) oncogenic Ras-induced BJ (BJ OIS; after induction with doxycycline, +dox) cells. Proliferating cells (-dox for BJ OIS) were used as controls. Cell nuclei were stained by DAPI (upper row; white color). The percentage of β -galactosidase-positive cells in proliferating and senescent populations was plotted ($n > 100$). DNA replication activity detected by EdU incorporation (red color) in (E) replicative (RS) and irradiated (10 Gy; IR-P) senescent MRC-5, (F) irradiated RPE-1 (20 Gy; IR-P), (G) docetaxel-induced BJ (BJ DIS), irradiated BJ (10 Gy; BJ IR-P), and (H) oncogenic Ras-induced BJ (BJ OIS; after induction with doxycycline, +dox) cells. Proliferating cells (-dox for BJ OIS) were used as controls. Cell nuclei were stained by DAPI (blue color). The percentage of EdU-positive cells was plotted ($n > 100$). Bar, 30 μ m.

A**B****C**

D

RPE-1: IR-induced senescence (from proliferation)

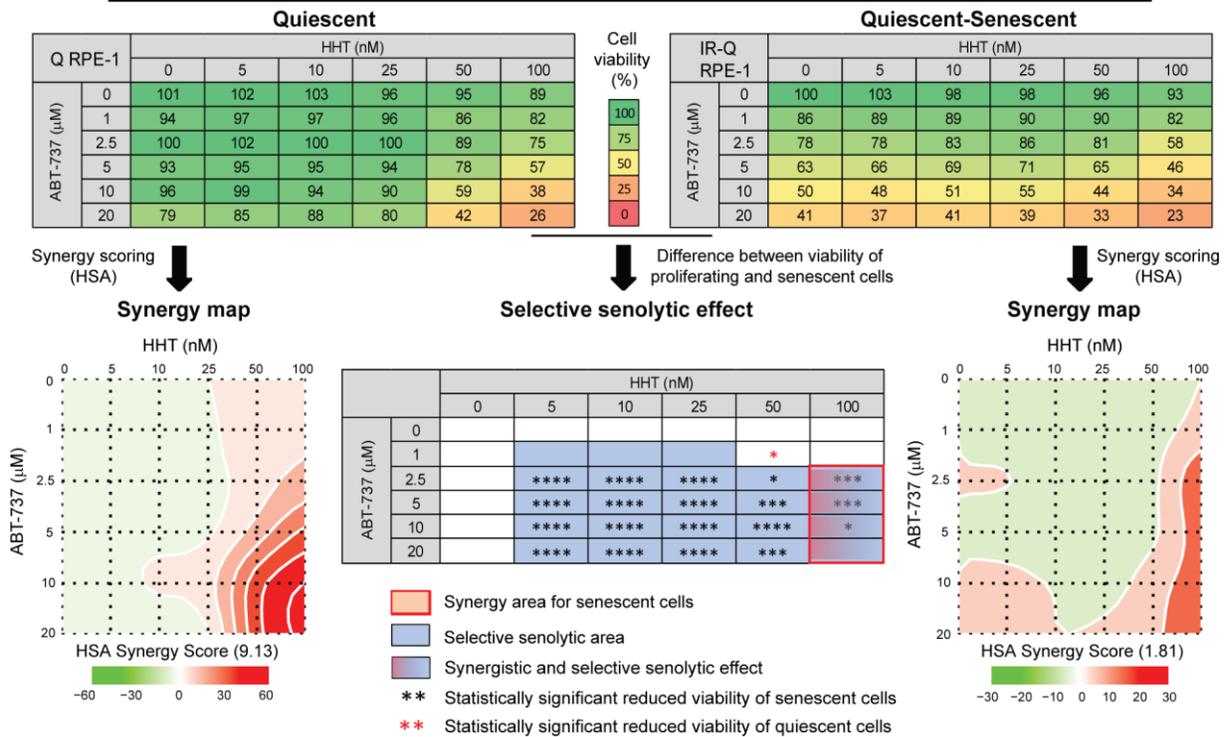
Compound combination: ABT-737 and HHT



E

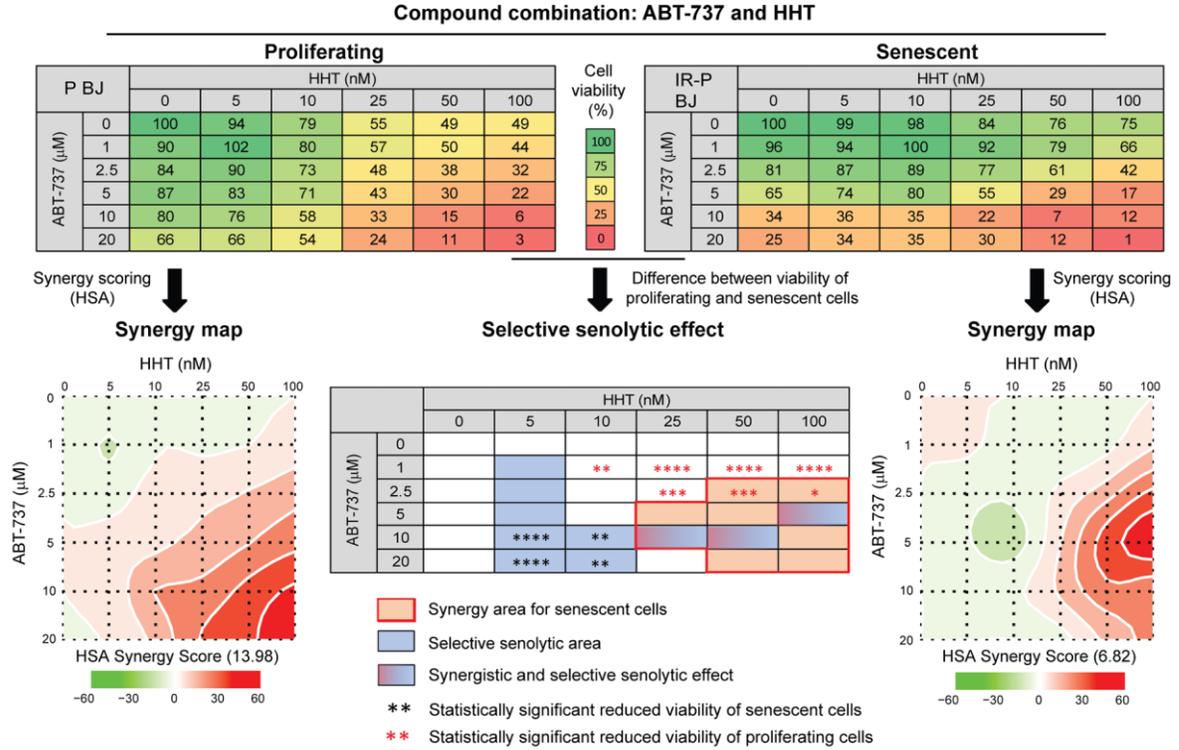
RPE-1: IR-induced senescence (from quiescence)

Compound combination: ABT-737 and HHT



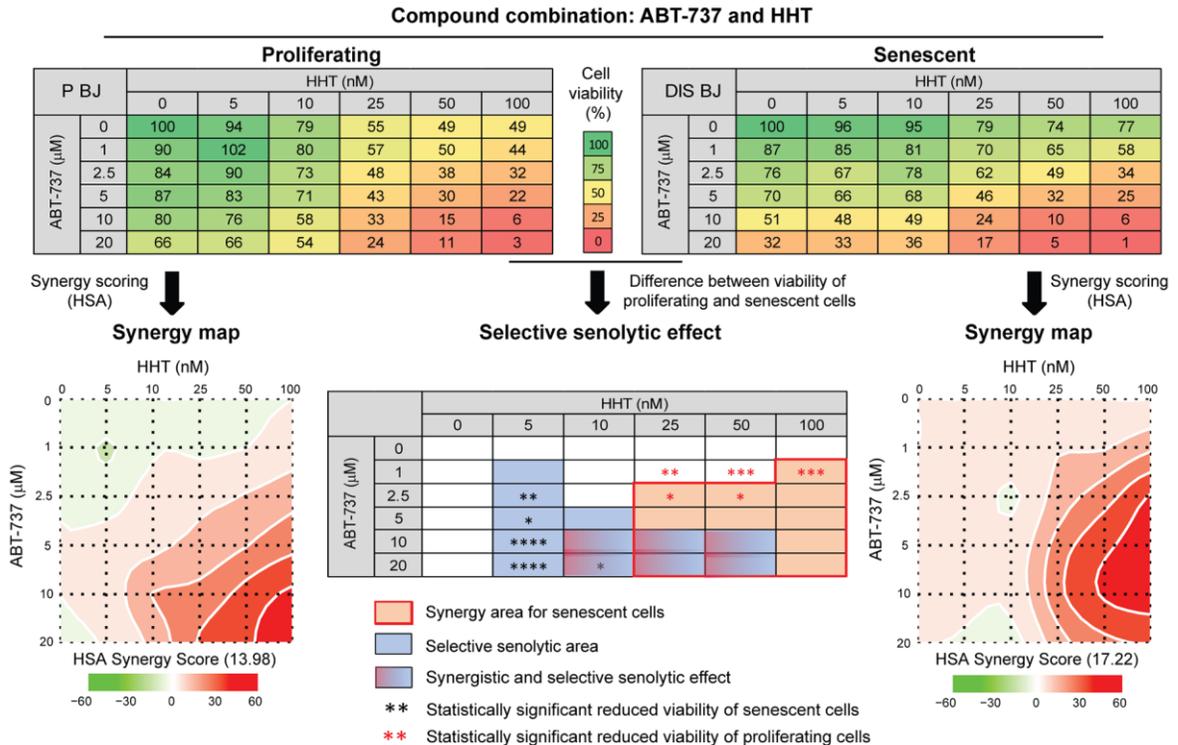
BJ: IR-induced senescence (from proliferation)

F



BJ: Drug-induced senescence

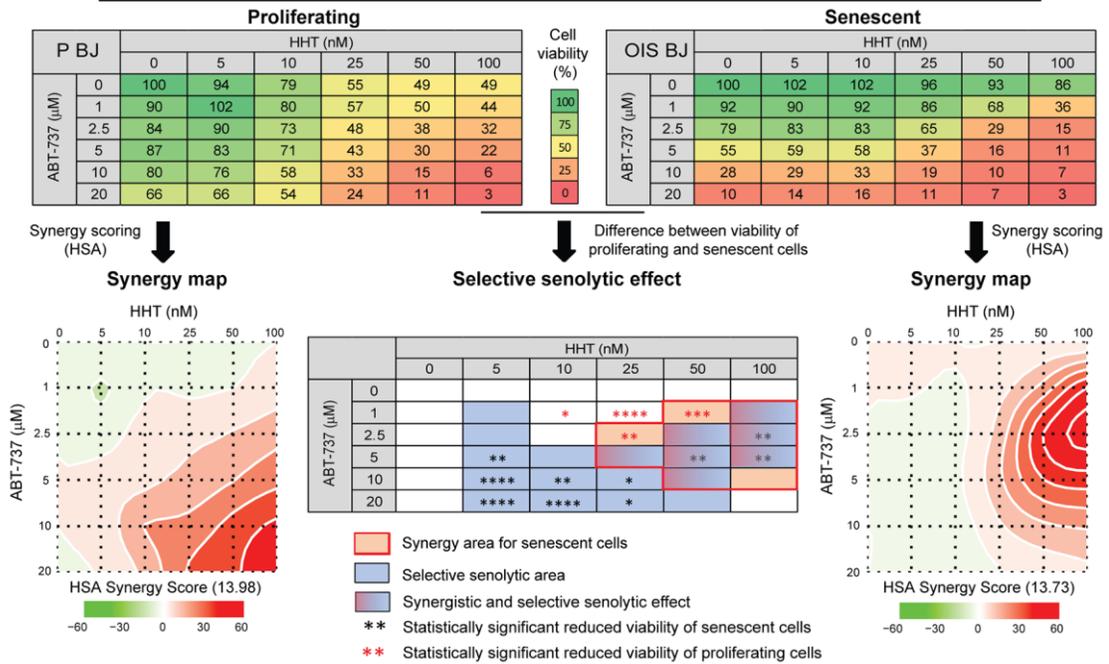
G



H

BJ: Oncogene-induced senescence

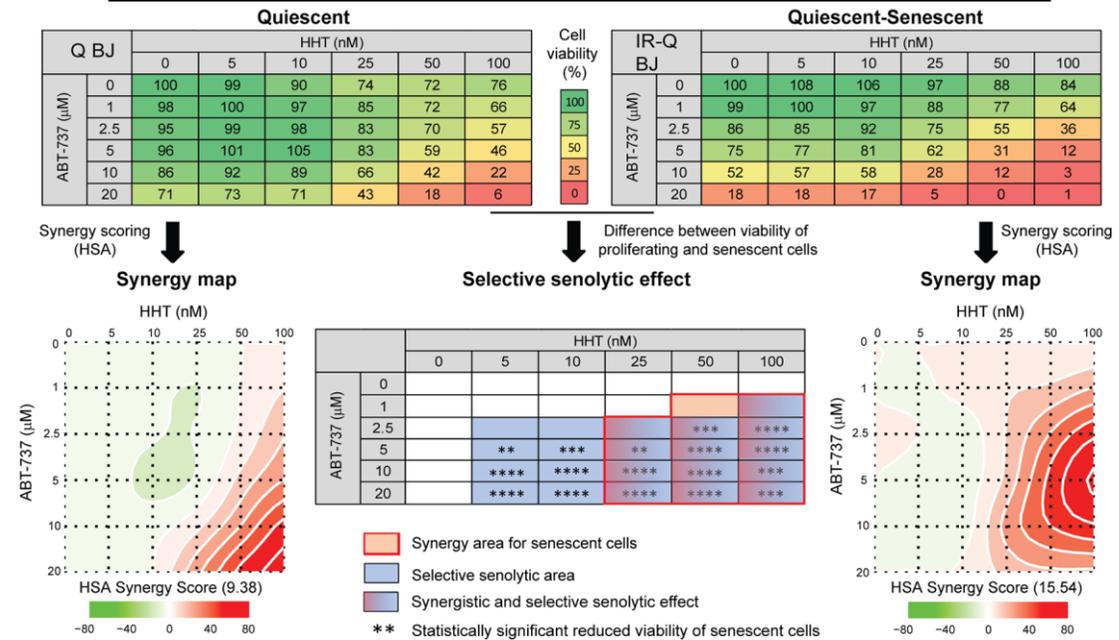
Compound combination: ABT-737 and HHT



I

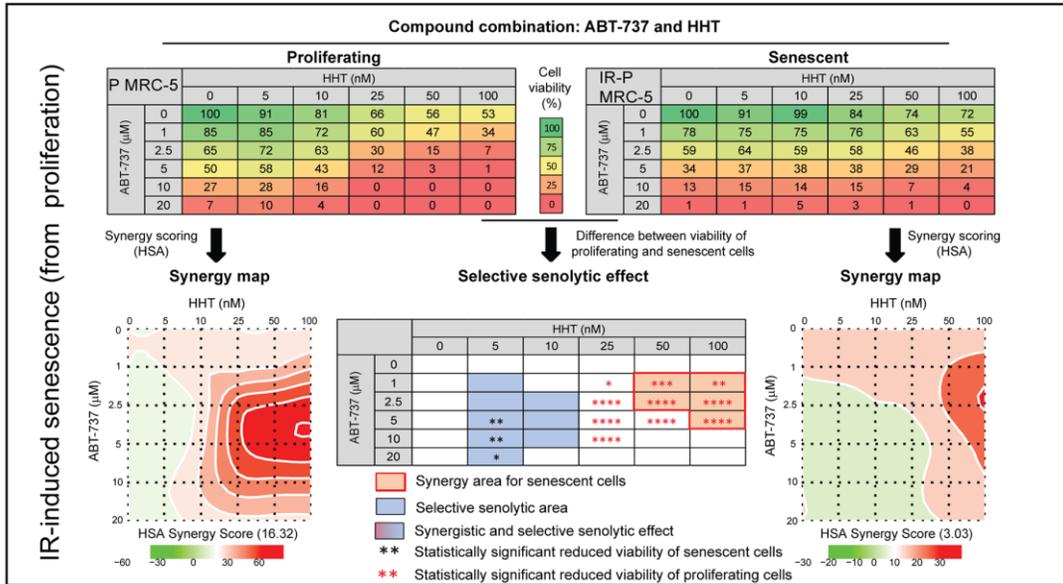
BJ: IR-induced senescence (from quiescent cells)

Compound combination: ABT-737 and HHT

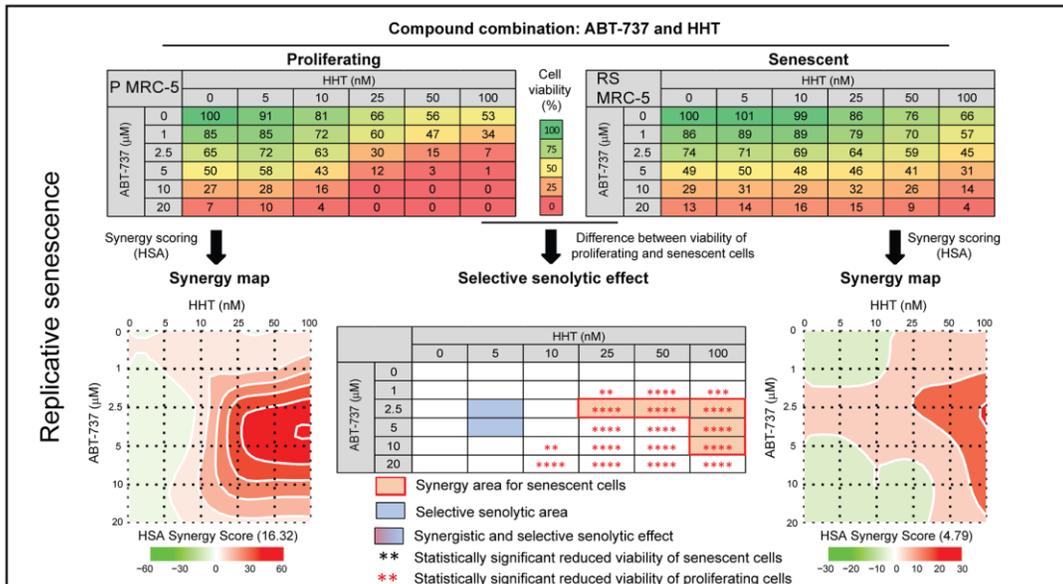


MRC-5

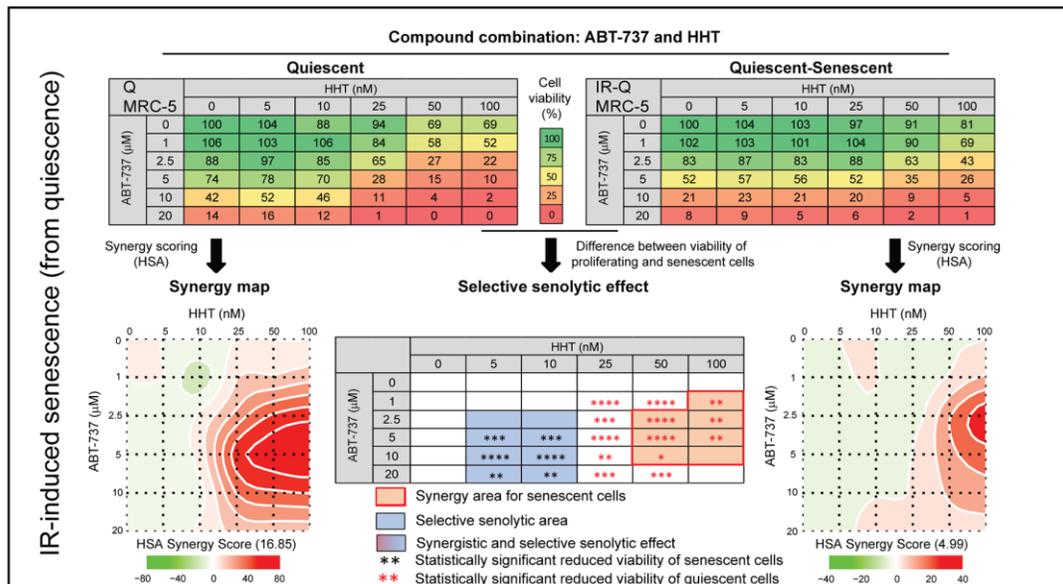
J



K



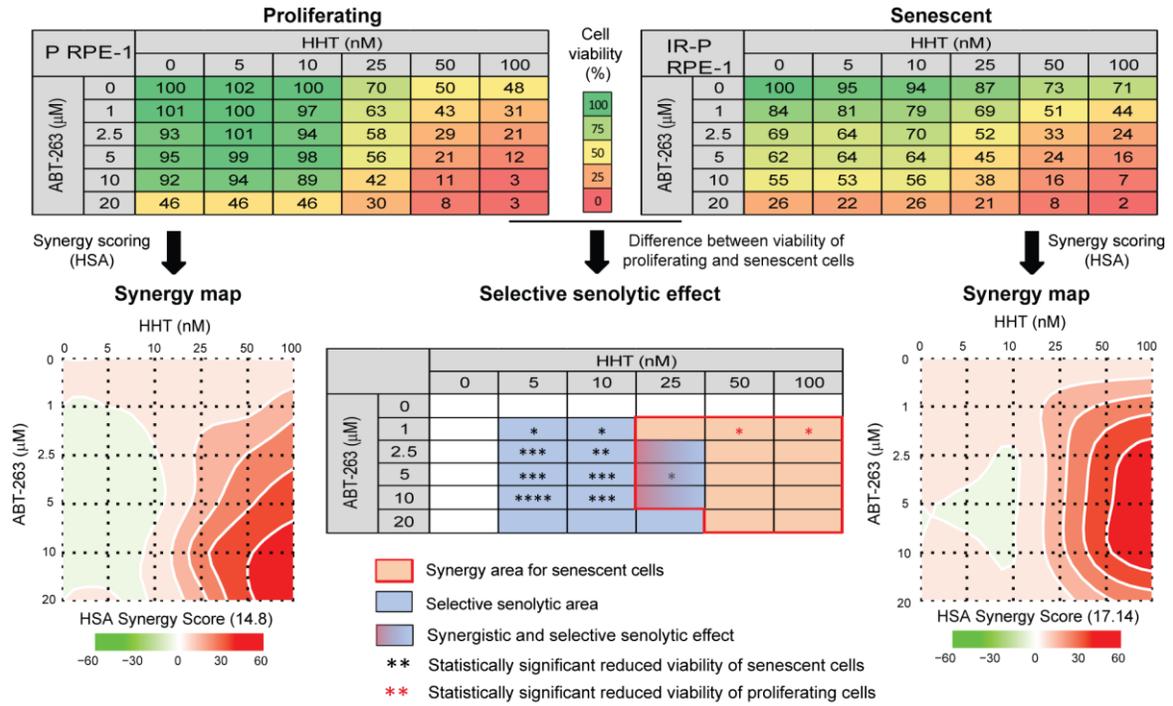
L



M

RPE-1: IR-induced senescence (from proliferation)

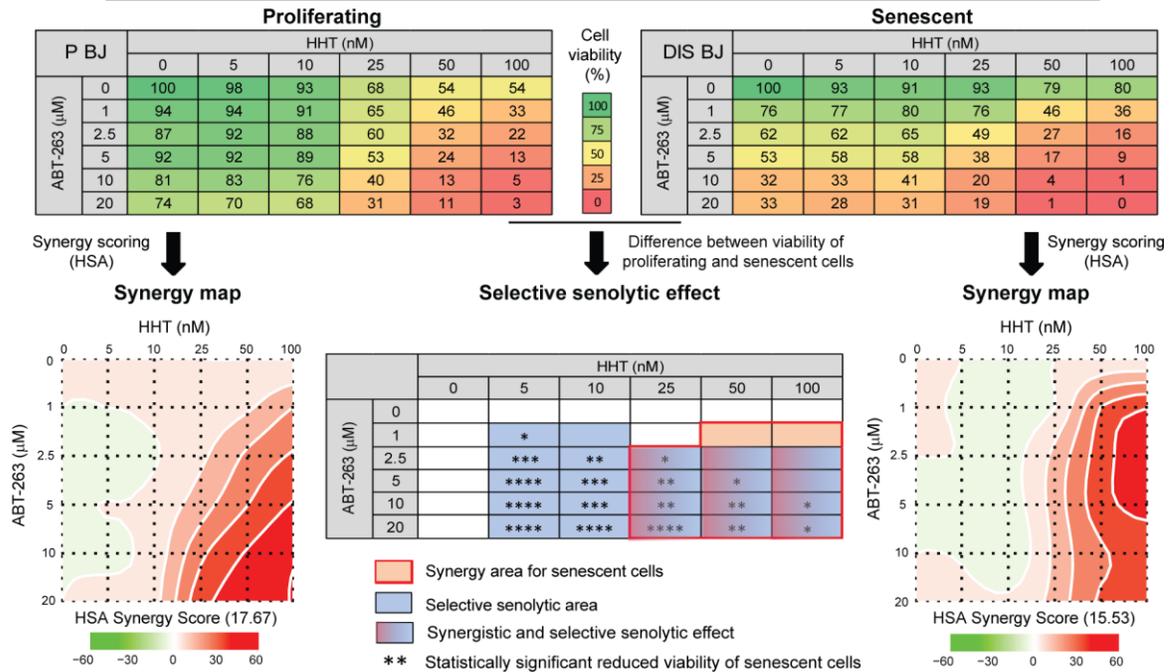
Compound combination: ABT-263 and HHT



N

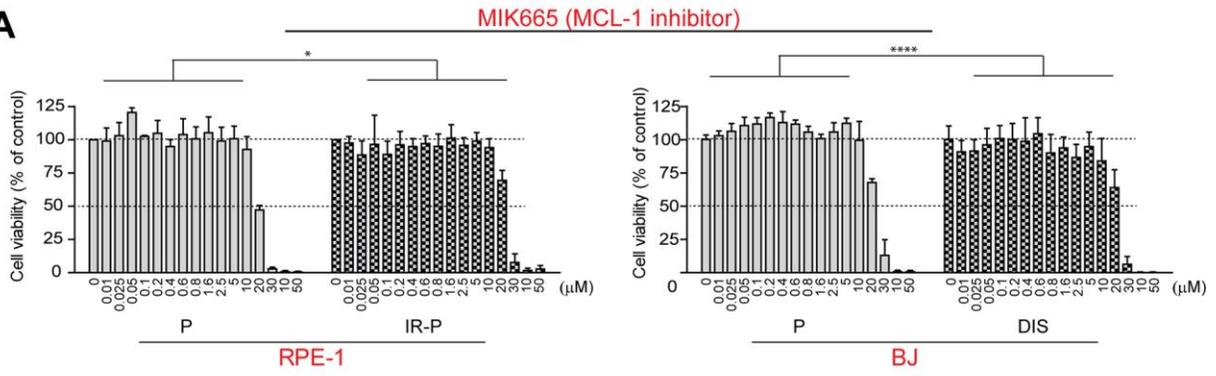
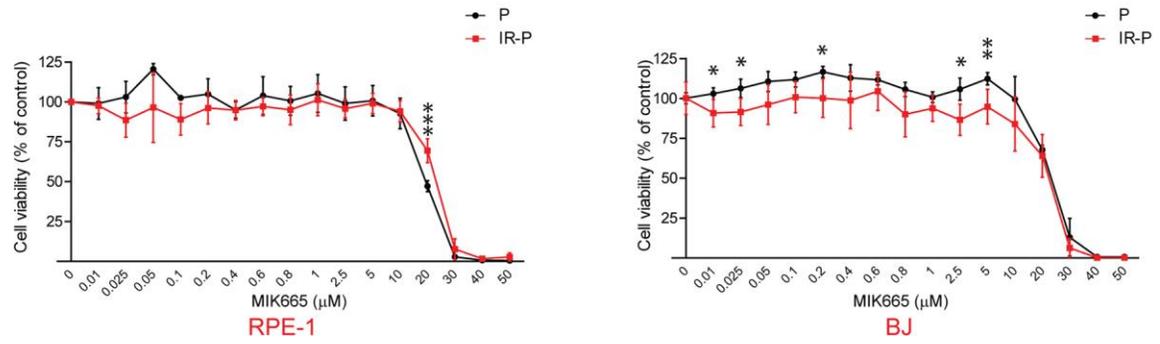
BJ: Drug-induced senescence

Compound combination: ABT-263 and HHT



Supplementary Figure 2. The effect of homoharringtonine, ABT-737, ABT-263, and their combinations on the viability of senescent, quiescent, and proliferating cells. Senescent cells and their appropriate controls were treated for 24 hours either with a

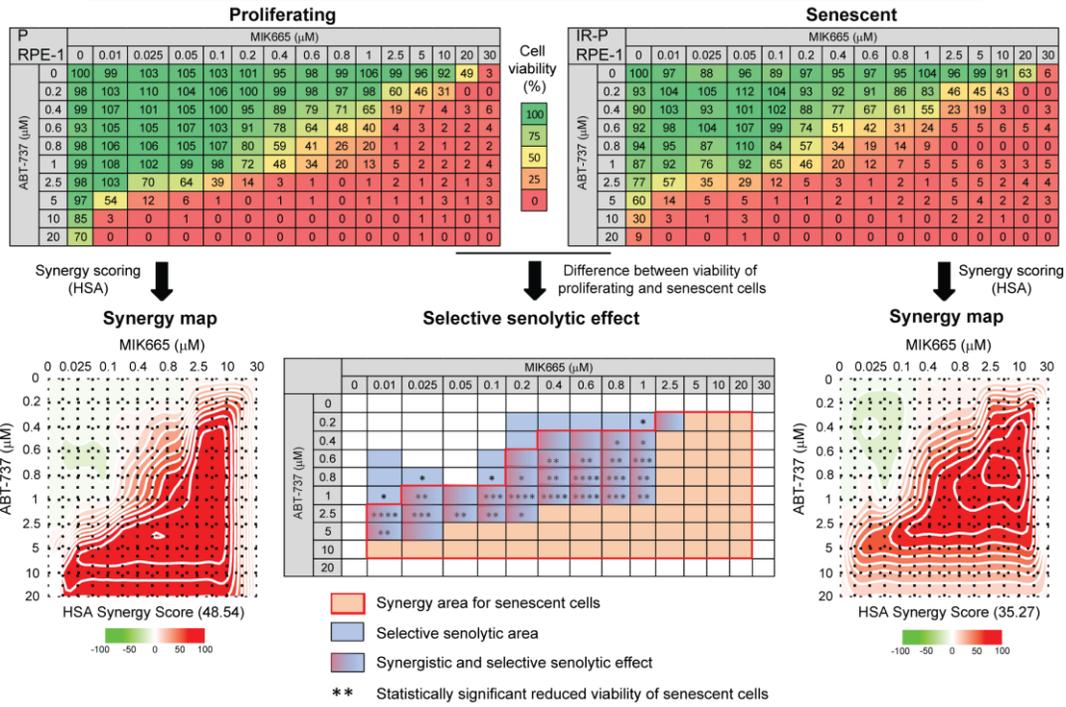
single compound (**A–C**) or with their combinations (**D–N**). The residual viability was assessed by staining with crystal violet and presented as a percentage of untreated control. For treatment with HHT (**A**), ABT-737 (**B**), and ABT-263 (**C**), the viability was expressed as the mean \pm S.D. from at least three independent experiments and plotted in histograms. The statistical analysis in panels A – C was carried out using two way ANOVA; ns. = no significant difference, $P > 0.05$; **, $P < 0.01$; ***, $P < 0.001$. The results for treatment with a combination of two compounds are expressed as matrices of viabilities with color scales inside (dark green, 100% viability; orange, 50% viability; dark red, 0% viability) and the diagram of the synergy score (SC; $SC < -10$: the interaction between two drugs is likely to be antagonistic; $-10 < SC < 10$: the interaction between two drugs is likely to be additive; $SC > 10$: the interaction between two drugs is likely to be synergistic) both for control and senescent models. Next, the matrix showing the region with synergistic and selective senolytic effect and its statistical significance (two-tailed Student's t-test; *, $P > 0.05$; **, $P < 0.01$; ***, $P < 0.001$) is shown. This scheme presents the cytotoxic and senolytic effect of ABT-737 and HHT on IR-induced senescence from proliferation (IR-P) in RPE-1 (**D**), IR-induced senescence from quiescence (IR-Q) in RPE-1 (**E**), IR-P BJ (**F**), drug-induced senescence (DIS) in BJ (**G**), oncogene-induced senescence (OIS) in BJ (**H**), IR-Q BJ (**I**), IR-P MRC-5 (**J**), replicative senescence (RS) in MRC-5 (**K**), and IR-Q MRC-5 (**L**). The same scheme was also used to present the senolytic effect of ABT-263 and HHT on IR-P RPE-1 (**M**) and DIS BJ (**N**) cells.

A**B**

C

RPE: IR-induced senescence (from proliferation)

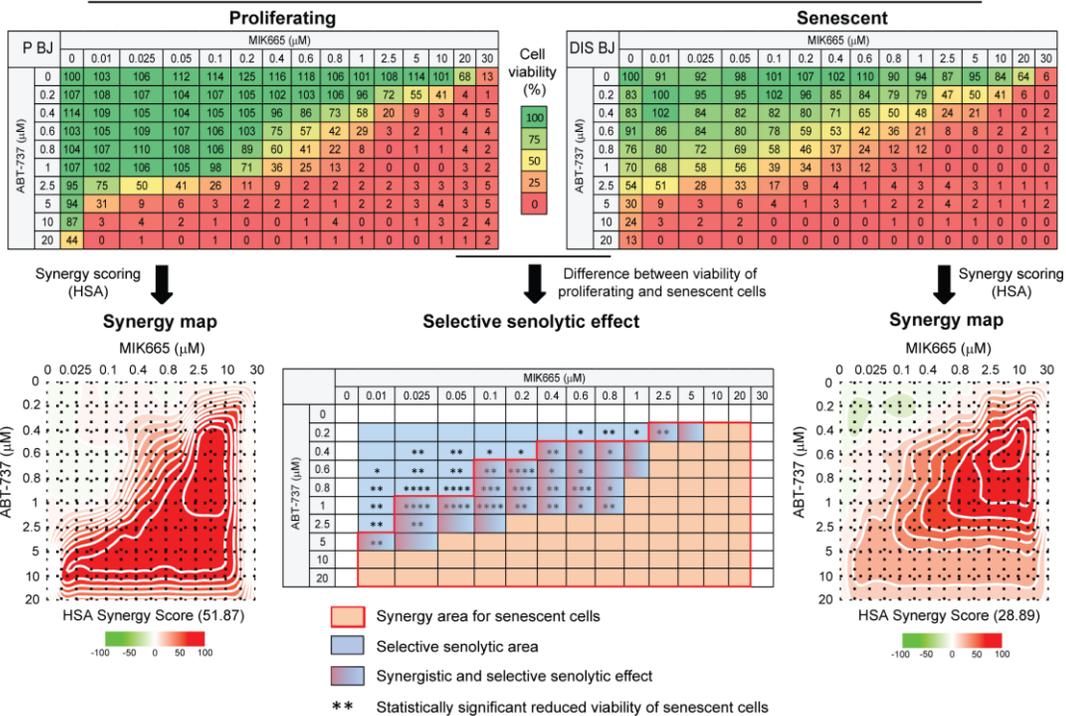
Compound combination: ABT-737 and MIK665



D

BJ: Drug-induced senescence

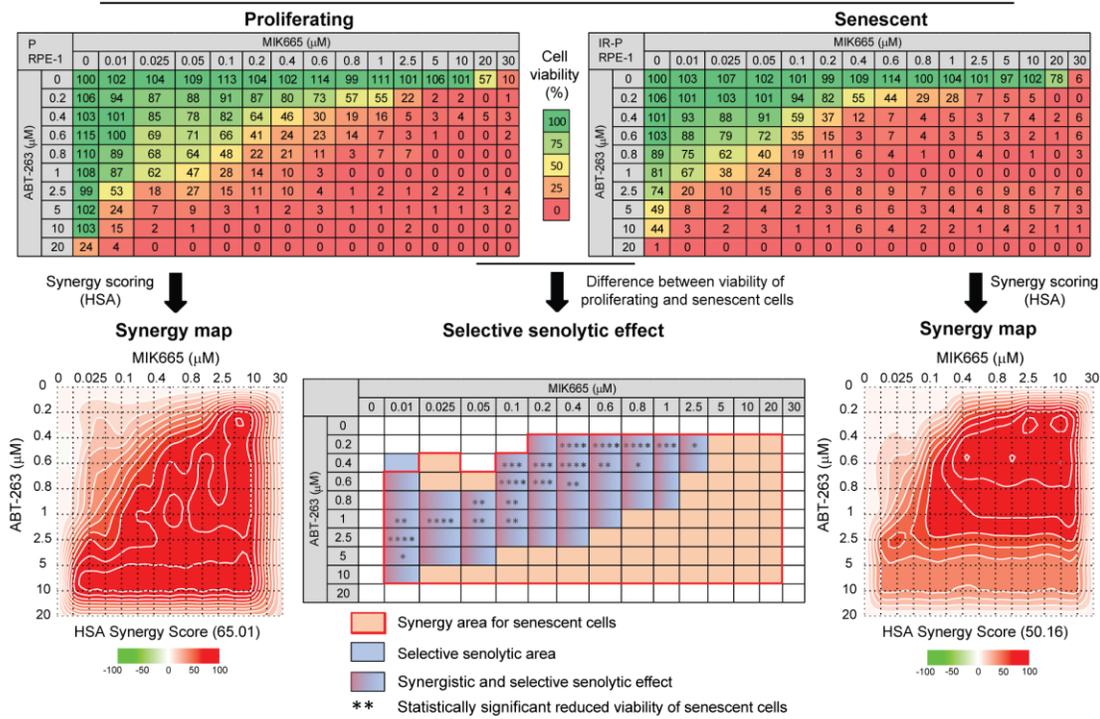
Compound combination: ABT-737 and MIK665



E

RPE-1: IR-induced senescence (proliferating cells)

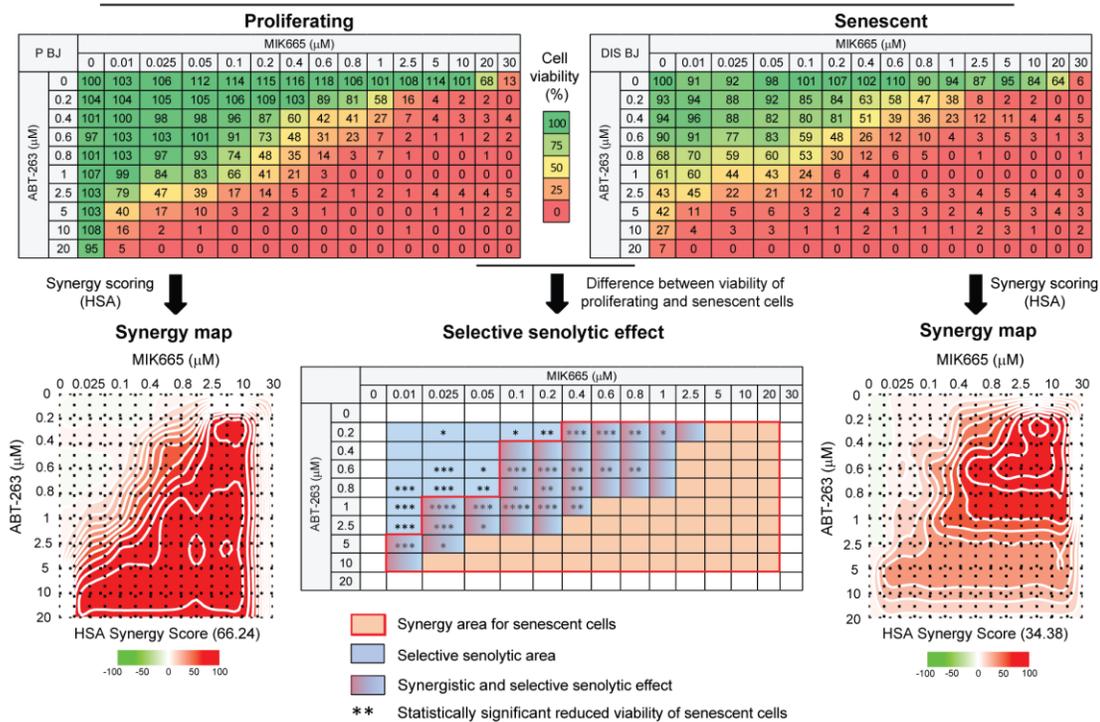
Compound combination: ABT-263 and MIK665



F

BJ: Drug-induced senescence

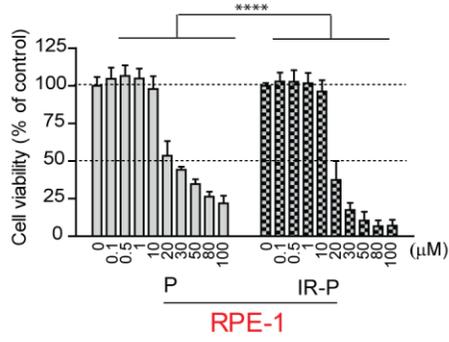
Compound combination: ABT-263 and MIK665



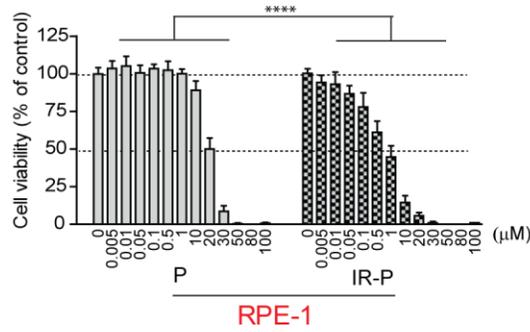
Supplementary Figure 3. The effect of MIK665 and its combinations with ABT-737 and ABT-263 on the viability of senescent and proliferating cells. Senescent cells and their appropriate controls were treated for 24 hours either with MIK665 (A, B) or in

combination with ABT-737 (**C, D**) or ABT-263 (**E, F**). The residual viability was assessed by staining with crystal violet and presented as a percentage of untreated control. For treatment with MIK665 alone, the viability was expressed as the mean \pm S.D. from at least three independent experiments and plotted in histograms (**A**) or line graph (**B**). The statistical analysis in panel A was carried out using two way ANOVA, in panel B using t-test; $P > 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$. The results for treatment with a combination of two compounds are expressed as matrices of viabilities with color scales inside (dark green, 100% viability; orange, 50% viability; dark red, 0% viability) and the diagram of the synergy score (SC; $SC < -10$: the interaction between two drugs is likely to be antagonistic; $-10 < SC < 10$: the interaction between two drugs is likely to be additive; $SC > 10$: the interaction between two drugs is likely to be synergistic) both for control and senescent models. Next, the matrix showing the region with synergistic and selective senolytic effect and its statistical significance (two-tailed Student's t-test; *, $P > 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$) is shown. This scheme presents the cytotoxic and senolytic effect of ABT-737 and MIK665 on IR-induced senescence from proliferation (IR-P) in RPE-1 (**C**), and drug-induced senescence (DIS) in BJ (**D**). The same scheme was also used for the presentation of the senolytic effect of ABT-263 and MIK665 on IR-P RPE-1 (**E**) and DIS BJ (**F**) cells.

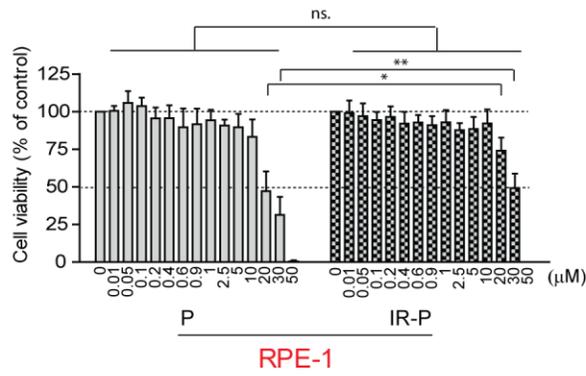
A ABT-199 (BCL-2 selective inhibitor)



B A1331852 (BCL-XL selective inhibitor)

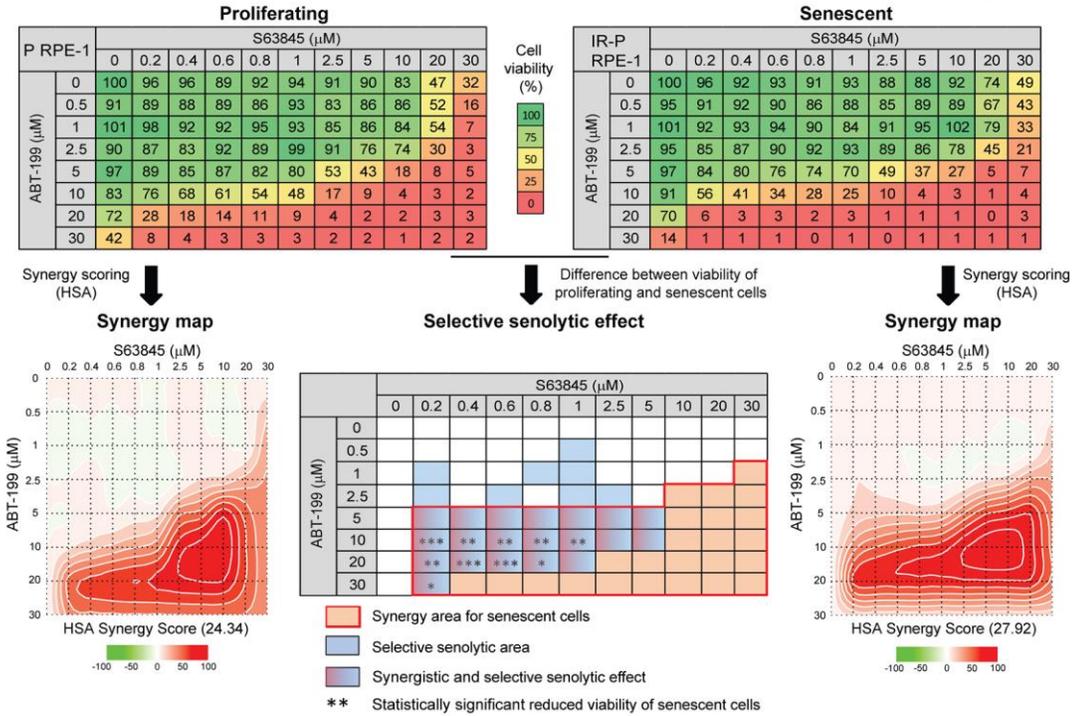


C S63845 (MCL-1 selective inhibitor)



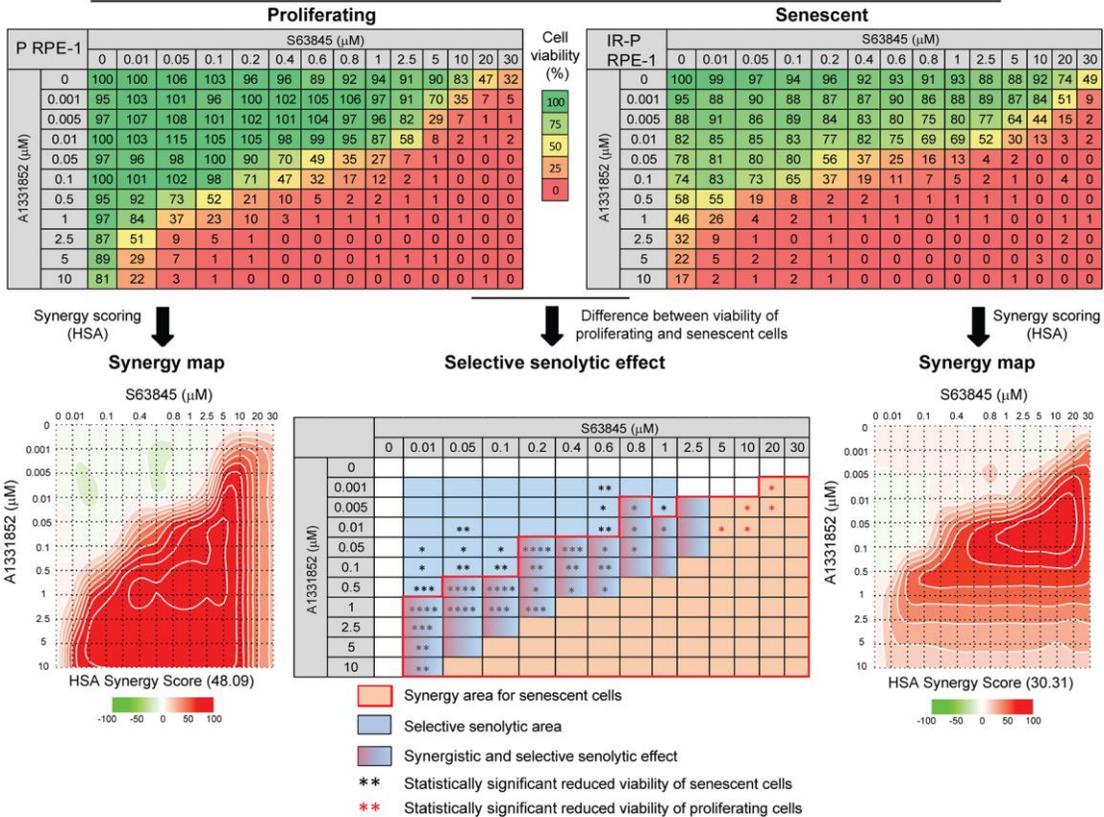
Compound combination: ABT-199 and S63845

D



E

Compound combination: A1331852 and S63845



Supplementary Figure 4. The effect of ABT-199, A1331852, S63845, and their combinations on the viability of senescent, quiescent, and proliferating cells. Senescent cells and their appropriate controls were treated for 24 hours either with a single compound

(A–C) or with their combinations (D, E). The residual viability was assessed by staining with crystal violet and presented as a percentage of untreated control. The residual viability was assessed by staining with crystal violet and presented as a percentage of untreated control. For treatment with ABT199 (A), A1331852 (B), and S63845 (C), the viability was expressed as the mean \pm S.D. from at least three independent experiments and plotted in histograms. The statistical analysis in panels A – C was carried out using two way ANOVA and two-tailed Student's t-test (C); ns. = no significant difference, $P > 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$. The results for treatment with a combination of two compounds are expressed as matrices of viabilities with color scales inside (dark green, 100% viability; orange, 50% viability; dark red, 0% viability) and the diagram of the synergy score (SC; $SC < -10$: the interaction between two drugs is likely to be antagonistic; $-10 < SC < 10$: the interaction between two drugs is likely to be additive; $SC > 10$: the interaction between two drugs is likely to be synergistic) both for control and senescent models. Next, the matrix showing the region with synergistic and selective senolytic effect and its statistical significance (two-tailed Student's t-test; *, $P > 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$) is shown. This scheme presents the cytotoxic and senolytic effect of ABT-199 and S63845 (C) or A1331852 and S63845 (D) on IR-induced senescence from proliferation (IR-P) in RPE-1 cells.