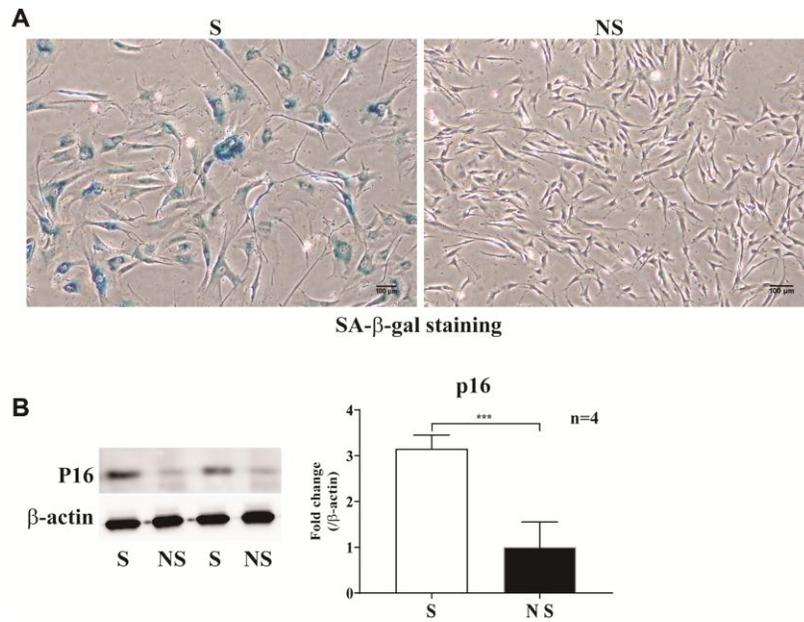
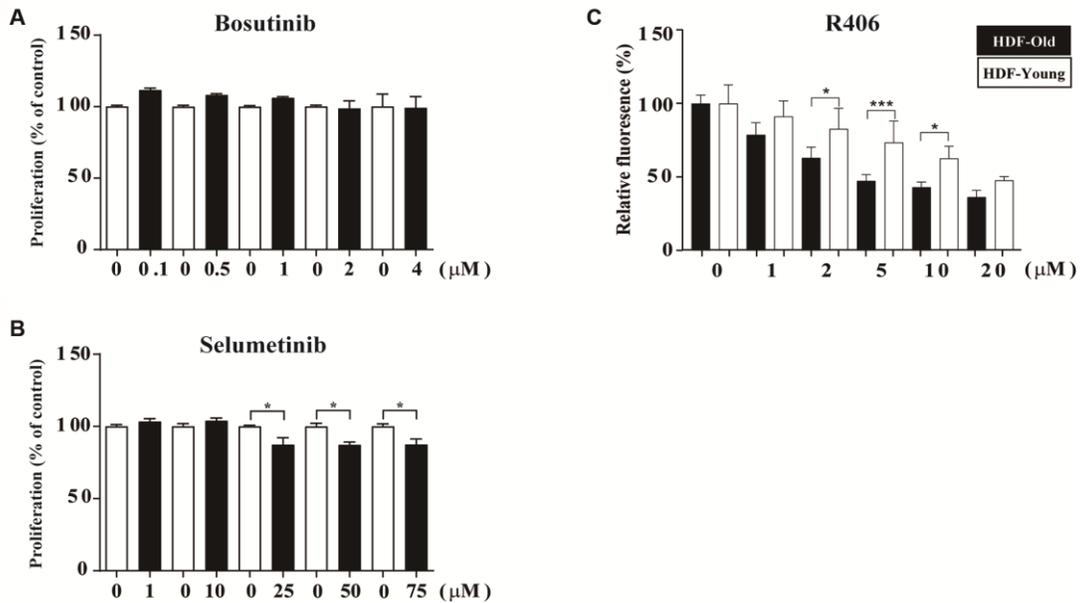


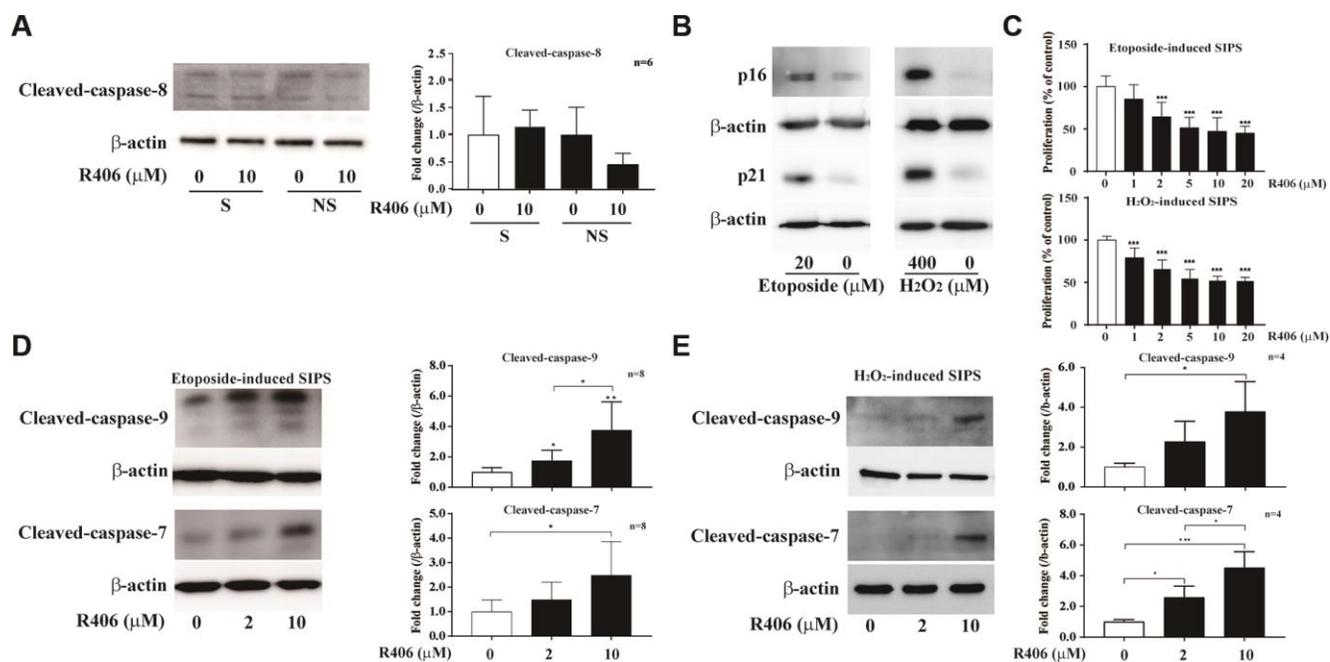
SUPPLEMENTARY FIGURES



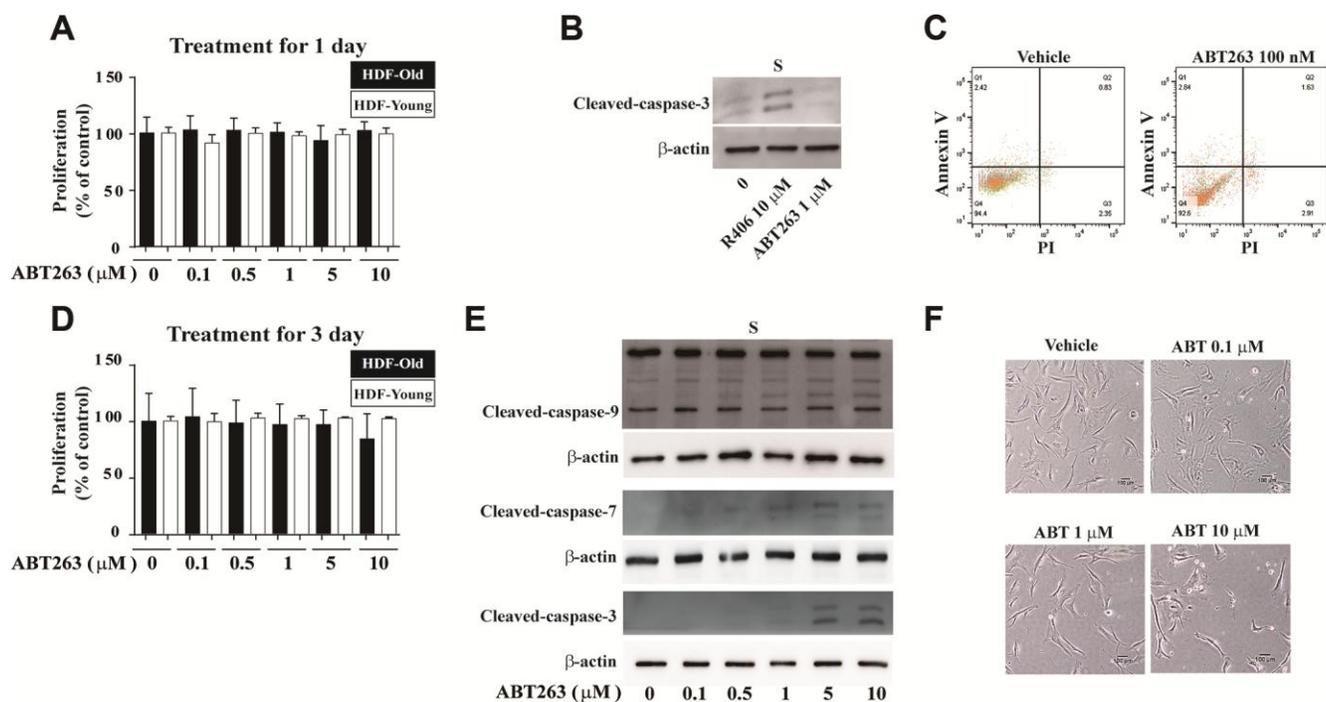
Supplementary Figure 1. Characterizing senescent and non-senescent HDFs. (A) Senescent cells increase SA-β-gal activity. Representative photomicrographs of SA-β-gal staining for non-senescent cells (NS) or senescent cells (S) are presented (scale bar: 100 μm). (B) Increasing p16 in senescent HDFs was determined by western blot analysis. * $p < 0.05$, ** $p < 0.01$, *** $P < 0.001$ compared to senescent HDFs.



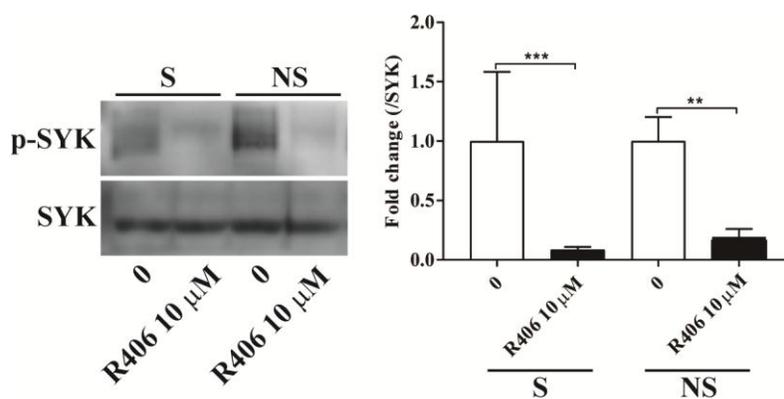
Supplementary Figure 2. Bosutinib and Selumetinib did not show senolytic effects in senescent cells. Senescent HDFs were respectively treated with DMSO (white bar), (A) Bosutinib (0.1, 0.5, 1, 2, 4 μM; black bar), and (B) Selumetinib (1, 10, 25, 50, 75 μM; black bar) for one day and then CCK-1 assays were conducted to investigate cell viability. (C) Senescent HDFs (HDF-Old) and non-senescent HDFs (HDF-Young) were treated with R406 (1, 2, 5, 10, 20 μM), and then, cell number was detected with Hoechst 33342 staining. $n = 12$, * $p < 0.05$, ** $p < 0.01$, *** $P < 0.001$.



Supplementary Figure 3. R406 was not affect caspase-8 activity in senescent HDFs. (A) Senescent (S) and non-senescent (NS) HDFs were treated with DMSO and/or R406 (10 μM) for one day and then western blot assays were conducted with anti-cleaved caspase-8. (B) Non-senescent HDFs were treated with 20 μM etoposide for two days (left panel), and non-senescent HDFs were treated with 400 μM H₂O₂ for six days (right panel) and then western blot assays were conducted with anti-p16 and anti-p21. (C) 20 μM etoposide induced HDFs for two days were treated with DMSO and/or R406 (1, 2, 5, 10, 20 μM) for one day (upper panel), and 400 μM H₂O₂ induced HDFs for six days were treated with DMSO and/or R406 (1, 2, 5, 10, 20 μM) for one day (lower panel) and then CCK-1 assays were conducted to investigate cell viability. (D) Etoposide-induced SIPS were treated with DMSO and/or R406 (2, 10 μM) for one day and then western blot assays were conducted with anti-cleaved caspase-9, and -7. (E) H₂O₂-induced SIPS were treated with DMSO and/or R406 (2, 10 μM) for one day and then western blot assays were conducted with anti-cleaved caspase-9, and -7. **p*<0.05, ***p*<0.01, ****p*<0.001.



Supplementary Figure 4. ABT263 for one day treatment did not exhibit senolytic effect in the RS model. (A) Senescent HDFs (HDF-old) and non-senescent HDFs (HDF-young) were treated with DMSO or ABT263 (0.1, 0.5, 1, 5, 10 μM) for one day, and then CCK-1 assays were conducted to investigate cell viability. (B) Senescent HDFs were treated with DMSO or R406 (10 μM) or ABT263 100 nM for one day and then western blot assay (anti-caspase-3 antibody) was conducted. (C) Senescent HDF cell were treated with DMSO or ABT263 (100 nM) for one day and flow cytometry was conducted after Annexin V/PI staining. (D, E) HDF-old and HDF-young were treated with DMSO or ABT263 (0.1, 0.5, 1, 5, 10 μM) for three days. Then, (D) CCK-1 assays and (E) western blot assays (anti-caspase-9, anti-caspase-7, and anti-caspase-3 antibodies) were conducted. (F) Cell morphological change. Senescent HDFs were treated with DMSO or ABT263 (0.1, 1, 10 μM) for one day. Images were randomly captured by inverted microscopy (scale bar: 100 μm).



Supplementary Figure 5. R406 inhibited phosphorylation of SYK in both senescent and non-senescent HDFs. Senescent (S) and non-senescent (NS) HDFs were treated with DMSO or R406 (10 μM) for 1 h and then western blot assays with anti-SYK antibodies were conducted. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.