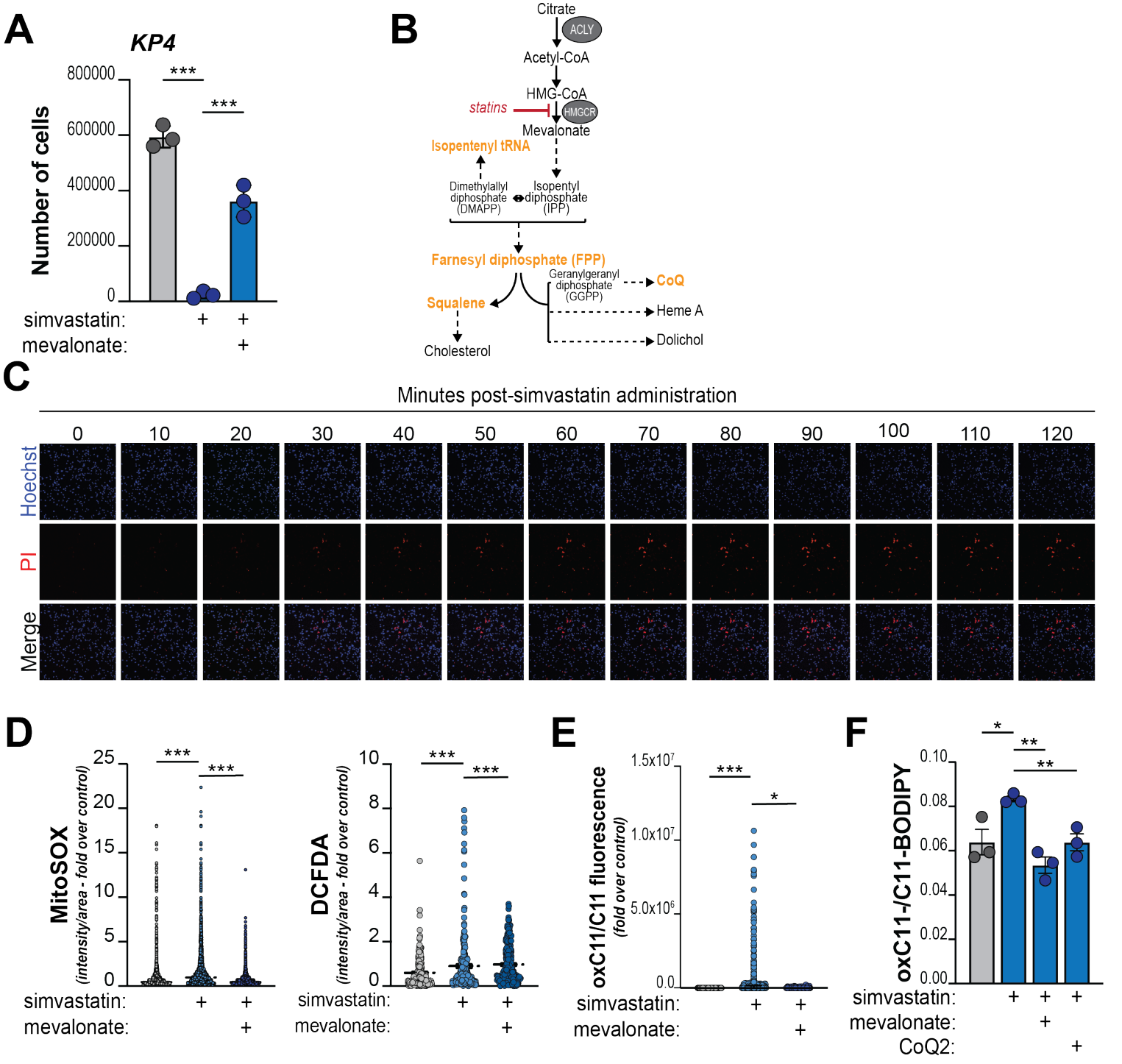
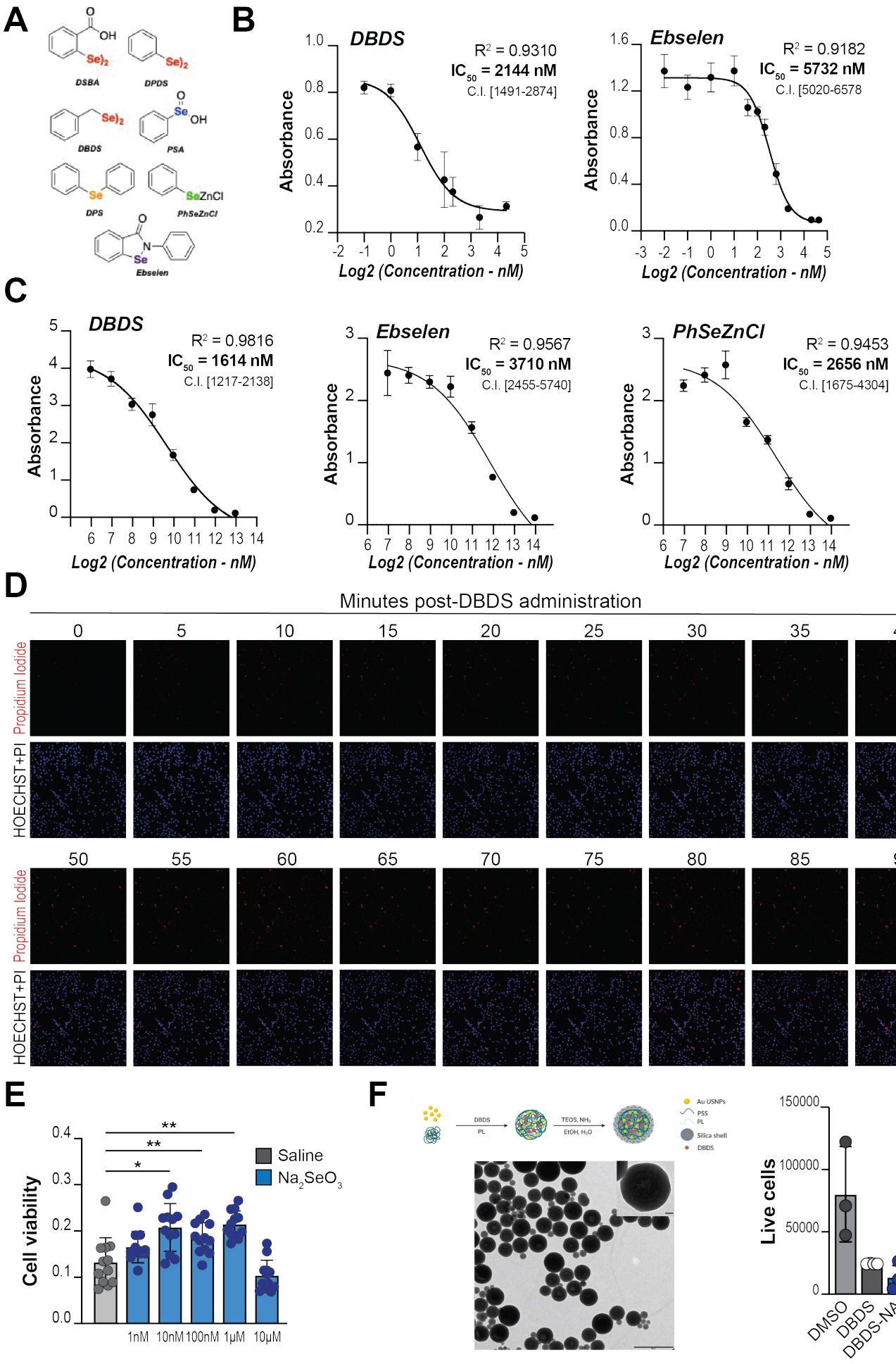
Suppl. Figure 1



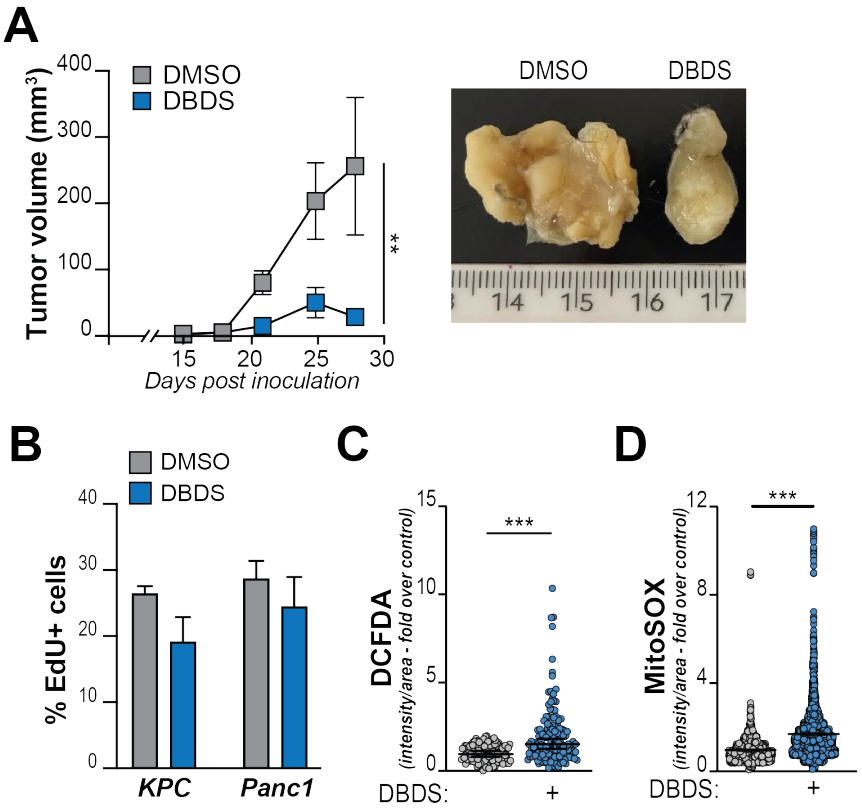
Supplementary Figure 1. **A,** KP4 cells were treated with simvastatin (20 μM) w/ or w/o supplementation with mevalonate (500 μM) and counted after 3 days. In **B,** schematic representation of the MVP. Redox-active intermediates are highlighted in orange. In red, statins inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR). **C,** Time course analysis of simvastatin-induced death. Before acquisition, cells were switched to propidium iodide (PI)-containing medium. Simvastatin was added at t=0, and images acquired at indicated time points. Pictures show same field over time (split channels and merge). **D,** Quantification of DCDFA and MitoSOX staining shown in Figure 1A. **E,** quantification of oxidized (green) and reduced (red) C11-BODIPY shown in Figure 1D. **F,** KP4 cells were treated with simvastatin (20 μM) w/ or w/o supplementation with mevalonate (500 μM), Coenzyme Q2 (15 μM) for 2 hours. Flow cytometry analysis was performed 50 minutes after the addition of C11-BODIPY. For **A**, **F**, bars show mean ± SD. For **D**, **E**, bars show mean, ± 95% CI. For all panels: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; calculated over vehicle-treated cells unless otherwise indicated.

Suppl. Figure 2



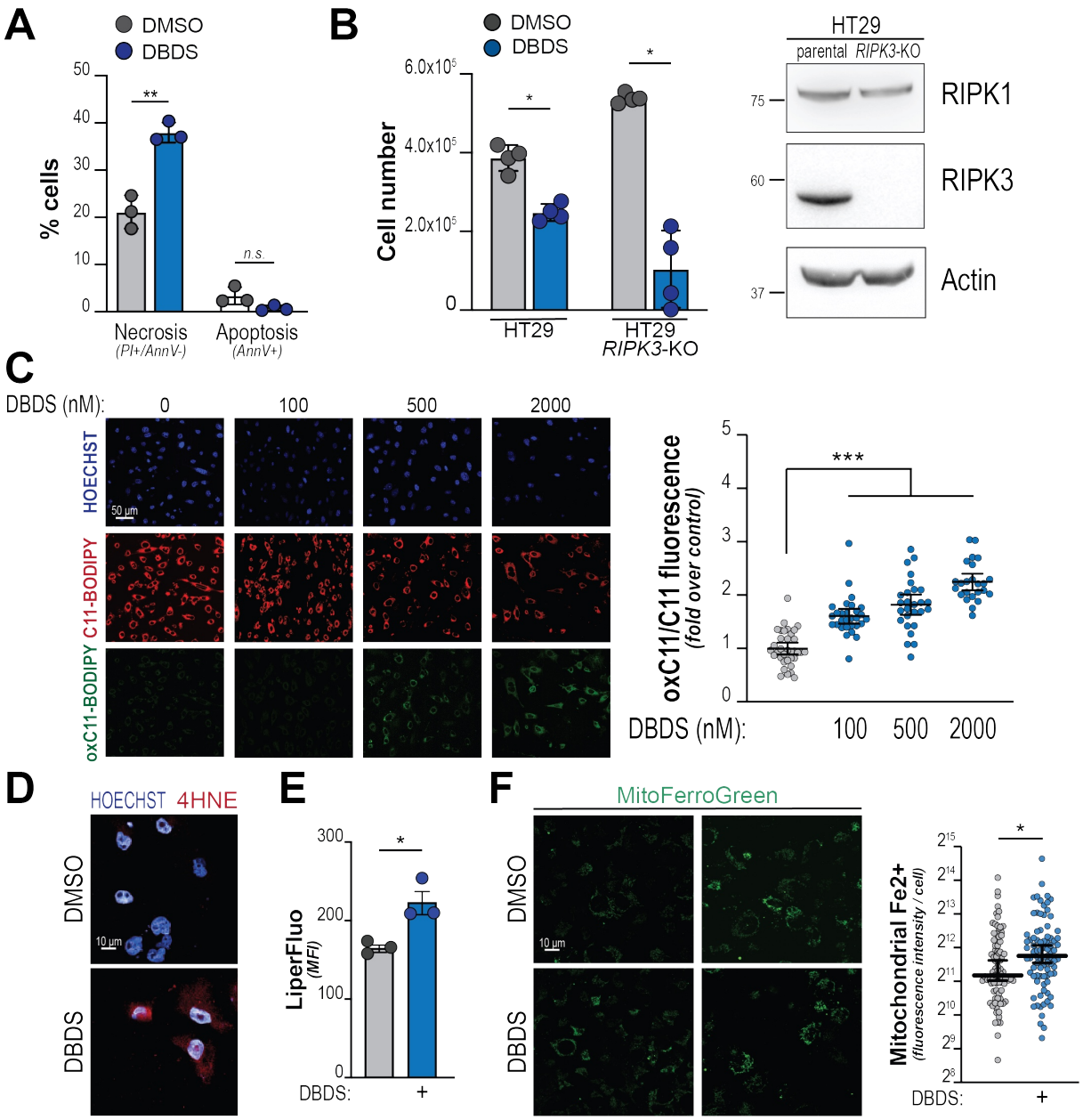
Supplementary Figure 2. **A,** structure of seleno compounds screened. **B-C,** KPC (**B**) or Panc1 (**C**) cells were treated with increasing concentrations of indicated compounds for 2 days and stained with Crystal Violet. Graphs show dose/response effect on cell viability (quantified by solubilization of Crystal Violet). Inhibitory concentration 50 (IC50), the coefficient of determination (R^2) and confidence interval (C.I.) are indicated in each plot. **D,** Time course analysis of DBDS-induced death. Before acquisition, cells were switched to propidium iodide (PI)-containing medium. DBDS was added at *t=0*, and images acquired at indicated time points. Pictures show same field over time (split channels and merge). **E,** Panc1 cells were administered increasing concentrations of sodium selenite and their viability quantified after 2 days. Dots denote experimental replicates. Bars show mean, ± SD (*, P < 0.05; **, P < 0.01; ***, P < 0.001). **F,** Schematic representation of DBDS-NAs synthetic protocol. Gold ultrasmall nanoparticles and DBDS are embedded in a polymeric matrix then surrounded by a silica shell. Magnified are transmission electron microscopy (TEM) images of DBDS-NAs. Scale bar: 500 nm. The inset zooms on a single DBDS-NA. Scale bar: 40 nm. On the far right, cell count of cells shown in Figure 2D.

Suppl. Figure 3



Supplementary Figure 3. **A,** Growth of KPCY-derived tumor cell clones (6419c5; *n=6 mice/group*) implanted subcutaneously into immune-competent C57BL/6J mice and treated with either DBDS (1 mg/kg) or vehicle (DMSO 1%), three times per week after tumors became palpable (day 15 after inoculation). On the right, representative images of tumor masses. **B,** Indicated cell lines were treated with DBDS (10 μM) or vehicle (DMSO 1%) for 24 hours and then pulsed with EdU for 1 hour. After staining, EdU-positive cells (% of DAPI-stained nuclei) were imaged and manually quantified. **C-D,** quantification of images in Figure 3D-E. Each dot denotes a cell; bars indicate mean, ± 95% CI. For all panels: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; calculated over vehicle-treated cells unless otherwise indicated.

Suppl. Figure 4



Supplementary Figure 4. **A,** KPC cells were treated with DBDS (5 μM) or DMSO for 24 hours and stained for flow cytometry analysis. Graph shows percentage of gated cells. Necrotic cells are defined as PI-positive, Annexin V-negative; apoptotic cells are defined as PI- and Annexin V-double positive events. **B,** RIPK3-proficient (HT29) or -deficient (HT29 RIPK3-KO) clones were treated with DBDS (5 μM) for 2 days and counted. Dots denote experimental replicates. Bars show mean, ± SD (*, $P < 0.05$). On the right, western blotting confirming efficient RIPK3 ablation. **C,** KPC cells were treated with increasing concentrations of DBDS for 1 hour and subsequently incubated with C11-BODIPY for 15 minutes. Left, representative images. Right, quantification of red-to-green (indicative of lipid peroxidation) fluorescence shift. **D,** immunostaining of 4HNE (red) in KP4 cells treated with DBDS (5 μM, for 24 hours). Nuclei were counterstained with HOECHST (blue). **E,** KP4 cells were treated with DBDS (10 μM) for 50 minutes and stained with MitoFerroGreen to detect mitochondrial iron. Live images were acquired and fluorescence intensity quantified. Graph shows replicates ± 95% CI. For all panels: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; calculated over vehicle-treated cells unless otherwise indicated.