**Supplementary Figure and Table Legends**

**Supplementary Table S1. Data obtained from the HT-screen for all 94 hits.**

**Supplementary Fig. S1. SUM149PT cell line meets the screening criteria.** **(A) Adenovirus infectivity.** Cells were seeded in 24-well plates and allowed to cycle for 24 hours. Cells were then infected with media (mock), adenovirus-null (ad-NULL), or adenovirus-GFP (ad-GFP). Infection was carried out in regular growth media at 50pfu/cell for 4 hours. After 24 hours, cells were examined for GFP expression by fluorescent microscopy under 10X objective. GFP expression indicates adenovirus infectivity. Brightfield images obtained for mock (data not shown) and ad-NULL (inset) infections confirmed the presence of cells. **(B) DNA repair activity.** SUM149PT and MCF7 cell lines were infected with ad-GFP subjected to photodynamic treatment (PDT) for 0, 1, or 2 minutes and analyzed by host-cell-reactivation (HCR) for GFP expression at 24 hours using flow cytometry. Imaging confirmed these data (not shown). MCF7 cells showed a 6 and 30% decrease in GFP expression relative to the undamaged control when infected with ad-GFP subjected to PDT for 1 and 2 minutes, respectively, whereas SUM149PT cells showed a 52 and 82% decrease in GFP expression relative to the undamaged control when infected with ad-GFP subjected to PDT for 1 and 2 minutes, respectively. Therefore, SUM149PT cell line exhibits deficient repair of oxidative DNA damage (ODD), and MCF7 control cell line shows functional repair.

**Supplementary Fig. S2. A preliminary screen identified BrdU as a small-molecule positive control.** **(A) BrdU in a preliminary screen.** Using our HT-protocol, we screened a subset of compounds from LOPAC (Sigma-Aldrich) using SUM149PTcells infected with undamaged adGFP (PDT=0 mins) as the positive control and SUM149PT cells infected with damaged ad-GFP (PDT=2 mins) as the negative control. The molecule that produced the greatest GFP signal was defined as the small-molecule positive control. A montage of the images obtained from the 384-well plate at the highest concentration tested (18uM) is shown. BrdU (red box) produced a visible signal similar to that of SUM149PTcells infected with undamaged adGFP. **(B) Signal detection by imaging.** BrdU produced a dose-response increase in the percentage of GFP-positive cells (normalized to the number of Hoechst 33342-positive cells). **(C) Signal detection by plate reading.** BrdU produced a dose-response increase in GFP intensity (normalized to Hoechst 33342-intensity).

**Supplementary Fig. S3. Optimization of conditions for HT-screening**. **(A) Seeding density.** Cells were plated in black-wall, clear-bottom, 384-well plates at 4000cells/well followed by 1:1 serial dilutions. Seeding density was defined to produce logarithmically growing cells after 4 days, which is consistent with the timing for the HT-screen, and was determined to be 750 cells/well. **(B) Determination of MOI.** SUM149PT cells were seeded as described in (A) and subjected to the screening protocol using mock reagents, but were infected with ad-GFP at M.O.I. = 100pfu/cell followed by 2-fold serial dilutions. Infections were carried out in duplicate. Optimal MOI was defined as the lowest amount of virus that delivered the greatest fluorescent signal by high-content imaging, and was determined to be 50pfu/ml, which is within the range specified by the manufacturer (i.e. 10-100pfu/ml). **(C) Optimization of Hoechst 33342 concentration**. SUM149PT cells were seeded as described in (a) and subjected to the screening protocol using mock reagents, but were stained using 5μg/ml followed by 1:1 serial dilutions of Hoechst 33342. Optimal Hoechst 33342 concentration was defined to produce a significant signal above background for the complete population of cells and was determined to be 2µg/ml.

Supplementary Fig. S4. Validation of the HT screening protocol. (a) Signal calculations. On day 0, cells were seeded in 384-well black-wall/clear bottom plates. On day 1, cells were treated with 18uM BrdU (small-molecule positive control) or DMSO (vehicle, negative control), alternating every 4 columns. On day 2, cells were infected with ad-GFP subjected to PDT for 2 minutes. On day 3, fluorescence was measured using MetaXpress software (Molecular Devices). GFP expression was calculated as % GFP-positive cells (GFP-positive cells/Hoechst 33342-positive cells x 100) to determine CV, S/B, and Z’-factor. (B) Spatial uniformity assessment. Scatter plots reveal the number of GFP-positive cells for each positive control well (i.e. max signal; green) and negative control well (i.e. min signal; black) arranged by row, then column (top) or by column, then row (bottom). No drift or edge effects were observed as evidenced by the lack of a significant trend in signal from left-to-right and top-to-bottom. Percent drift was calculated from the max signal. (C) Summary of acceptance criteria. Observed values for each validation parameter were compared to the accepted criteria as defined by the NIH Assay Guidance Manual for high-throughput screening. All values were within acceptable range.

Supplementary Fig. S5. DNA repair-activating agents exhibit minimal cytotoxicity at concentrations that enhance BER of ODD. DNA repair-activating agents exhibit minimal cytotoxicity at concentrations that enhance BER of ODD. (A) Dose-response effect of acetohexamide on cell number. The percentage of live SUM149 cells treated with increasing concentrations of acetohexamide for 48 hours was determined by Hoechst 33342 staining. (B) Dose-response effect of benserazide on cell number. The percentage of live SUM149 cells treated with increasing concentrations of benserazide for 48 hours was determined by Hoechst 33342 staining. (C) Dose-response effect of acetohexamide on cell viability. The cell viability of SUM149 cells treated with increasing concentrations of acetohexamide for 72 hours was determined by MTT assay. (D) Dose-response effect of benserazide on cell viability. The cell viability of SUM149 cells treated with increasing concentrations of benserazide for 72 hours was determined by MTT assay. (E) Effect of acetohexamide on cell number in mutant *BRCA1* cell lines. The effect of 20µM acetohexamide on the percentage of live cells relative to the vehicle control in cell lines with mutant *BRCA1* was determined by Hoechst 33342 staining. Error bars represent the s.e.m. of at least four independent experiments. (F) Effect of benserazide on cell number in mutant *BRCA1* cell lines. The effect of 20µM benserazide on the percentage of live cells relative to the vehicle control in cell lines with mutant *BRCA1* was determined by Hoechst 33342 staining. (G) Effect of acetohexamide and benserazide on cell viability in breast cell lines. The effect of 20µM acetohexamide or benserazide on cell viability relative to the vehicle control in SUM149 breast cancer cells (mutant *BRCA1*) and MCF10a normal-like breast cells (wild-type *BRCA1*) was determined by the MTT assay. Unless otherwise indicated, all data are representative means ± s.d.