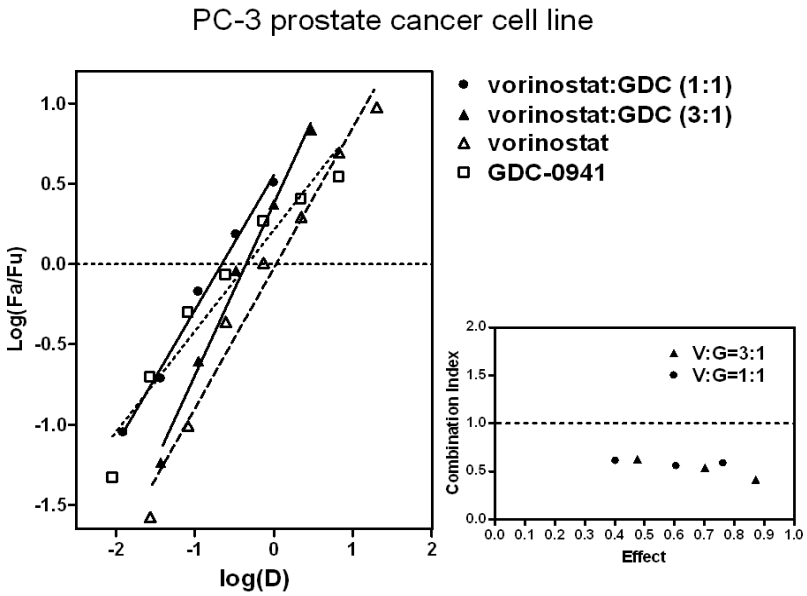
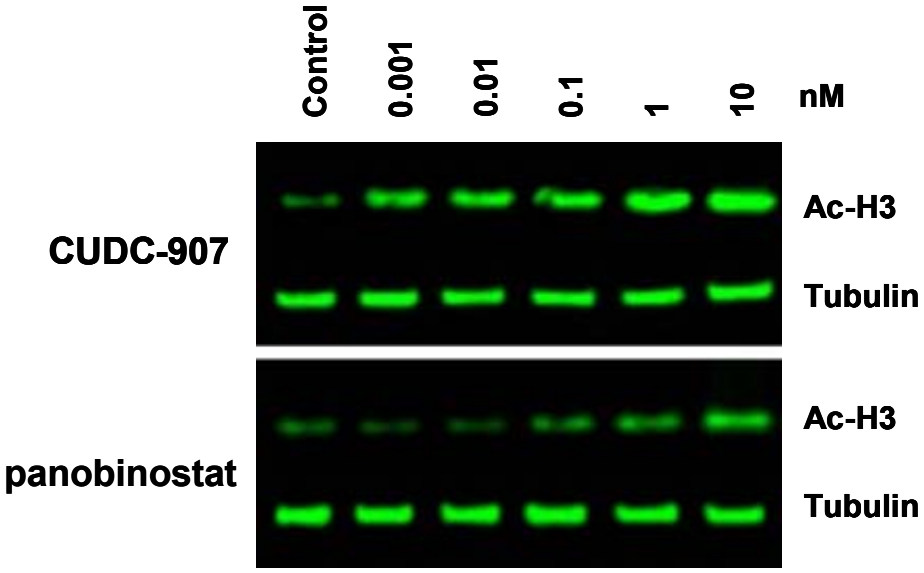
**Figure S1. Synergy between PI3K and HDAC pathway inhibition**



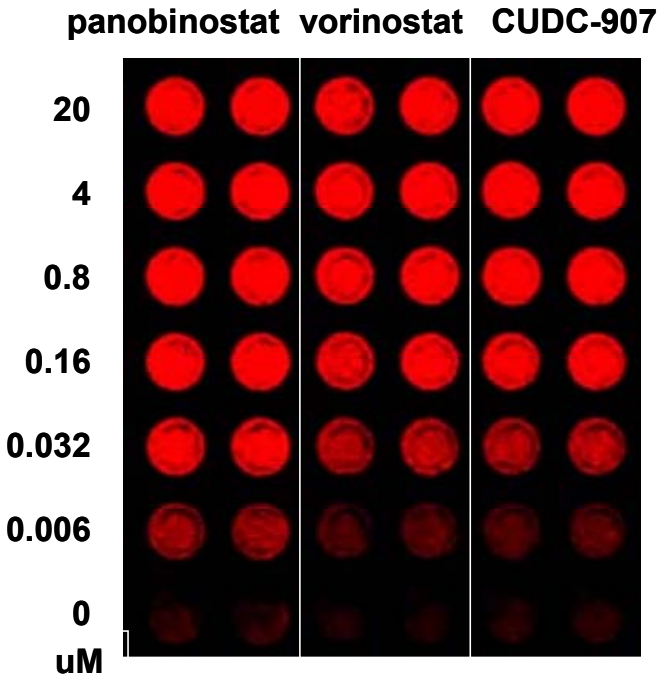

PC-3 prostate cancer cells were incubated with various concentrations of vorinostat and GDC-0941 for 72 h. Cell viability was accessed by ATP content assay. Synergism was detected by median effect analysis as described (18). A combination index (CI) lower than 1 indicates synergy.

**Figure S2. CUDC-907 increases acetylation of histone H3 in cultured cancer cells**



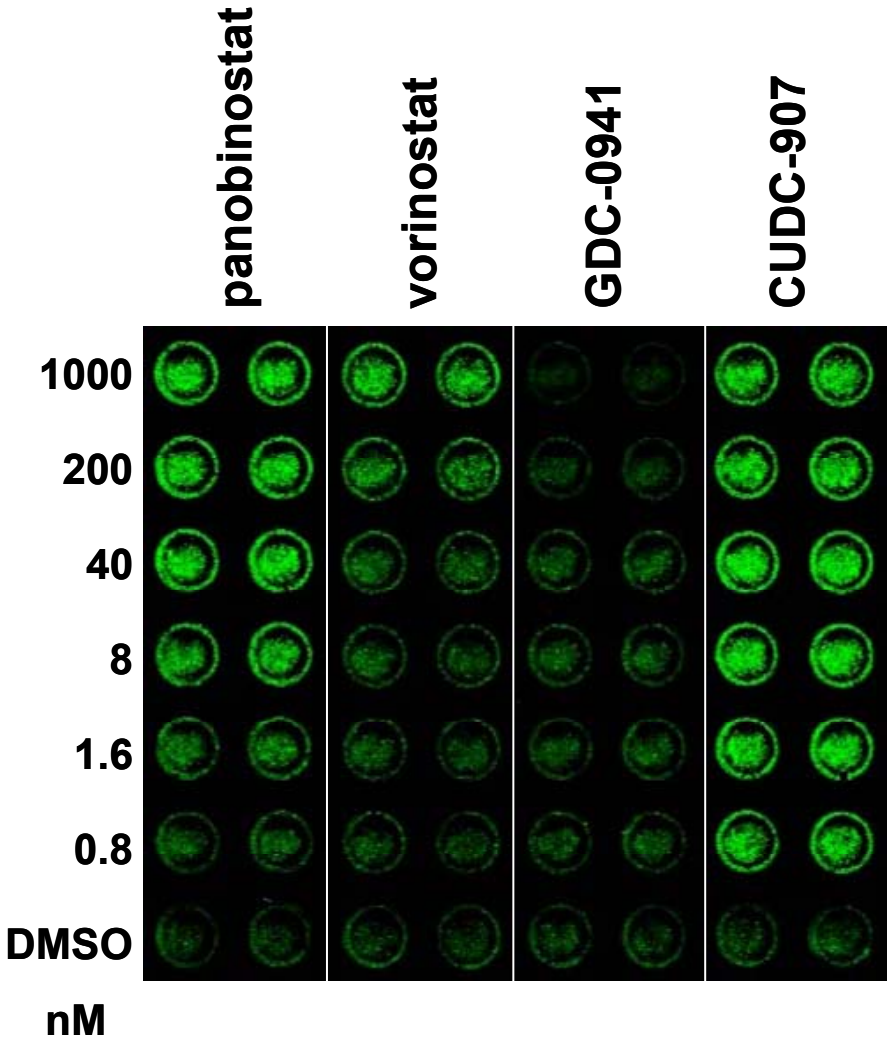

H460 NSCLC cells were treated with various concentrations of CUDC-907 or panobinostat for 1 h as indicated. Western analysis reveals that CUDC-907 induces the accumulation of acetylated histone H3 and is more potent than panobinostat.

**Figure S3. CUDC-907 increases tubulin acetylation in cultured cancer cells**



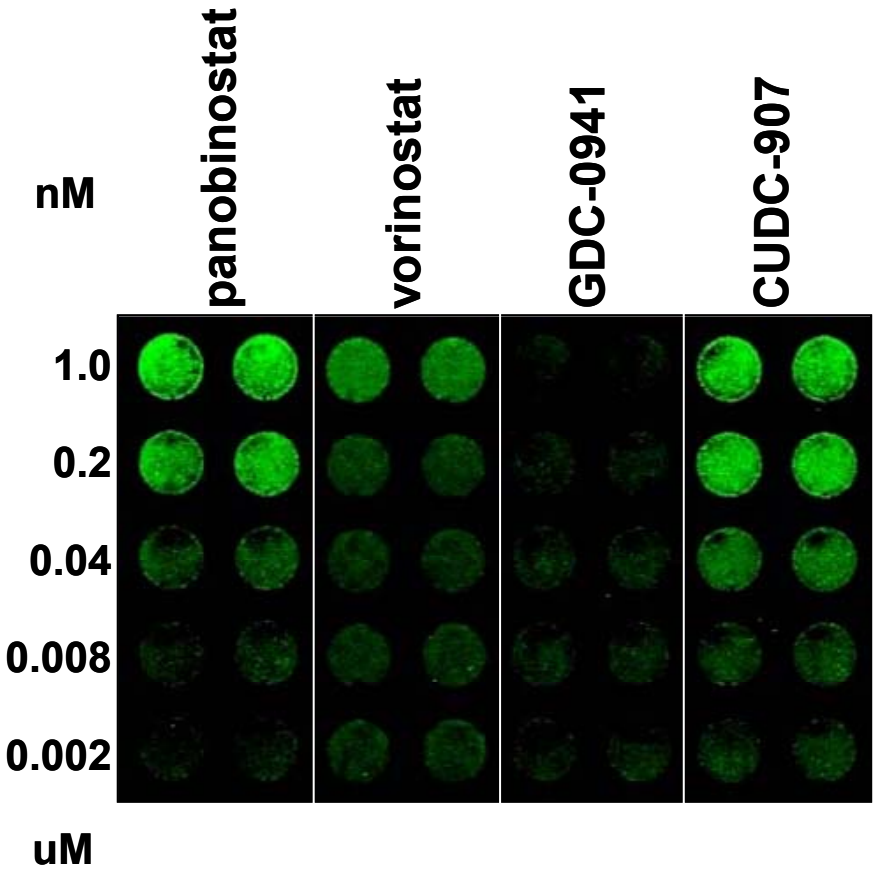

H460 NSCLC cells were cultured in 96-well plates and treated with various concentrations of CUDC-907, vorinostat, or panobinostat for 1 h as indicated. Immunocytochemical analysis reveals that CUDC-907 induces the accumulation of acetylated tubulin with a similar potency as vorinostat.

**Figure S4. CUDC-907 increases p53 acetylation in cultured cancer cells**



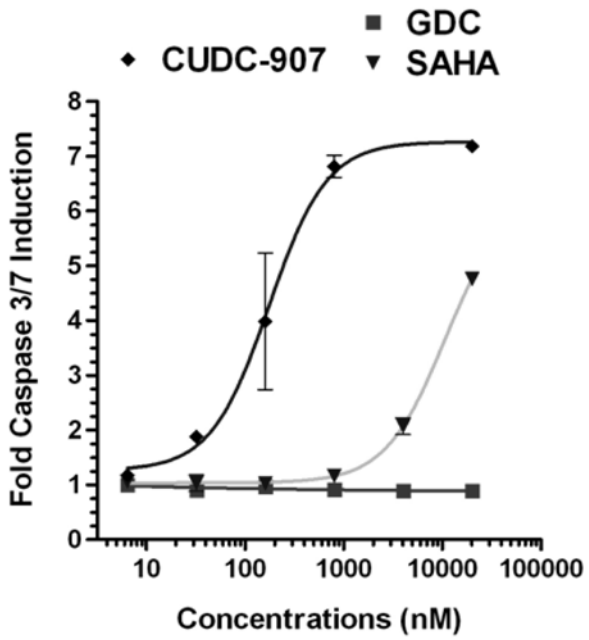

H460 NSCLC cells were cultured in 96-well plates and treated with various concentrations of CUDC-907, vorinostat, panobinostat, or GDC-0941 for 1 h as indicated. Immunocytochemical analysis reveals that CUDC-907 induces the accumulation of acetylated p53 with a higher potency than panobinostat and vorinostat.

**Figure S5. CUDC-907 increases p21 levels in cultured cancer cells**



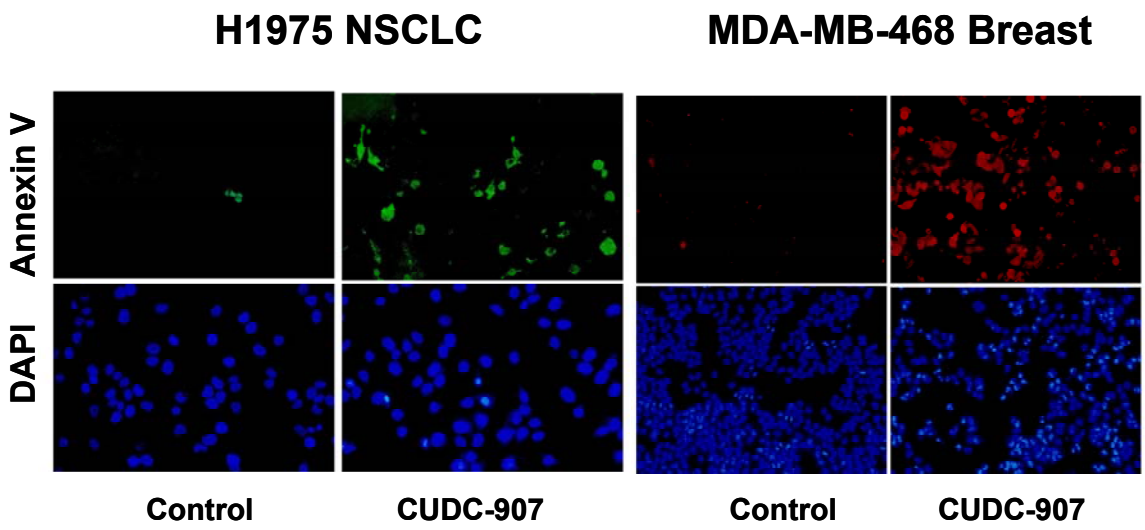

**H460 NSCLC cells were cultured in 96-well plates and treated with various concentrations of CUDC-907, vorinostat, panobinostat, or GDC-0941 for 16 h as indicated. Immunocytochemical analysis reveals that CUDC-907 induces the accumulation of the CDK inhibitor p21.**

**Figure. S6. CUDC-907 induces the accumulation of activated caspases-3 and -7**



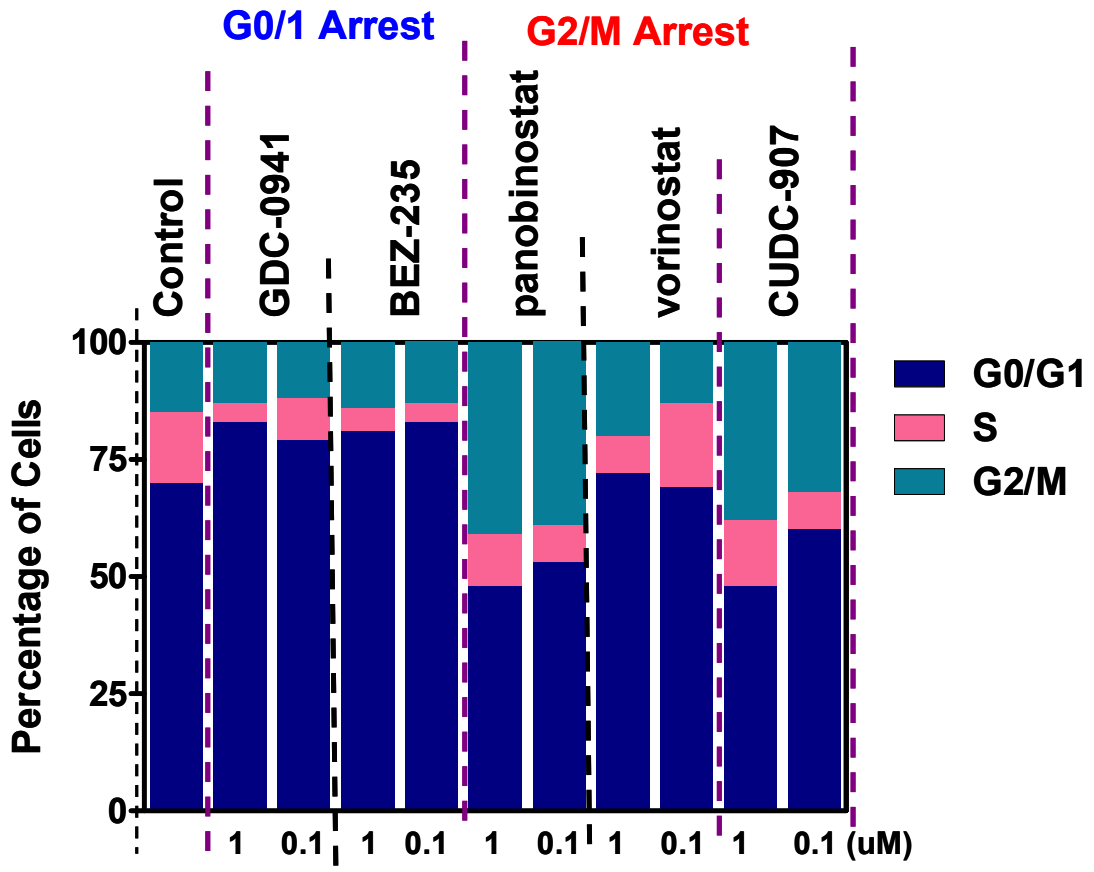

HCT116 colon cancer cells were treated with various concentrations of CUDC-907, GDC-0941, or vorinostat. Apoptosis was assessed by measuring caspase-3 and -7 activity using the profluorescent caspase substrate Z-DEVD-Rhodamine 110 (Apo-ONE Homogeneous Assay Kit from Promega). Upon sequential cleavage and removal of DEVD peptides by caspase 3/7 activity and excitation at 499 nm, the remaining rhodamine 110 groups become intensely fluorescent. The amount of fluorescent product generated is proportional to the amount of caspase 3/7 cleavage activity present in the sample.

**Figure S7. CUDC-907 induces the accumulation of annexin V binding sites**



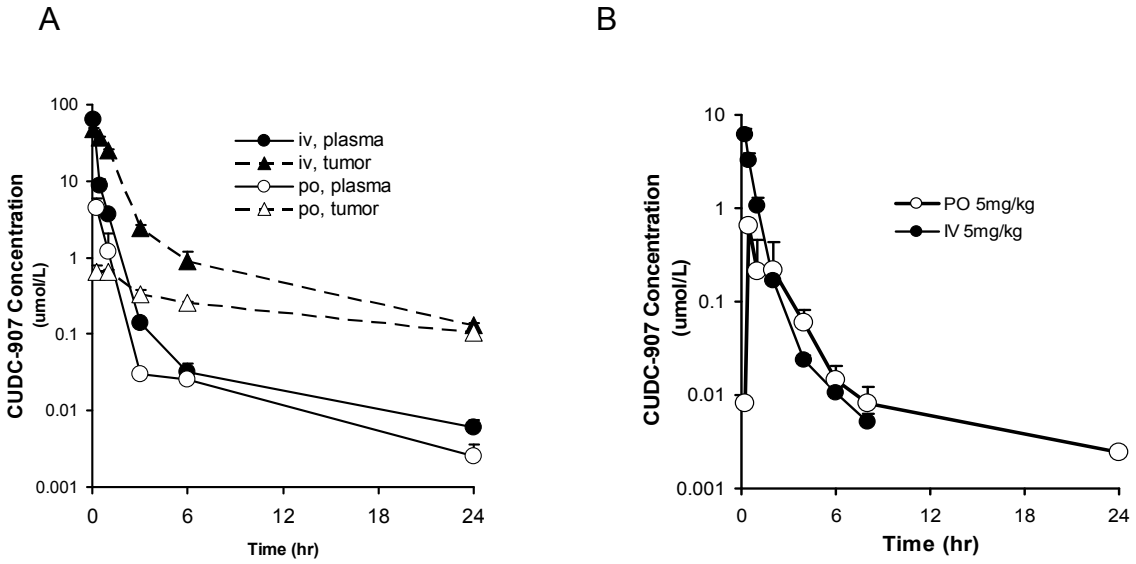

H1975 NSCLC and MDA-MB-468 breast cancer cells were treated with 1 μmol/L of CUDC-907 for 30 h. Cells were fixed and stained with PE-conjugated annexin V (H1975) or anti-annexin V antibody (MDA-MB-468).

**Figure S8. CUDC-907 induces a G2/M cell cycle arrest**




H460 NSCLC cells were treated with 0.1 or 1 µmol/L of GDC-0941, BEZ-235, panobinostat, vorinostat, or CUDC-907 for 16 h as indicated. Cell cycle analysis was performed using flow cytometry (Accuri Cytometers Inc, Ann Arbor, MI) to distinguish cells in different phases of the cell cycle. After treatment, cells were permeabilized and stained with propidium iodide.

**Figure S9. CUDC-907 is orally bioavailable and shows intratumoral accumulation**




Pharmacokinetic (PK) study of CUDC-907 in tumor-bearing mice and dogs. A, CUDC-907 was administered at 100 mg/kg intravenously (iv) or orally (PO) in a Daudi NHL xenograft mouse model. CUDC-907 concentrations in plasma and tumor tissues were determined at various time points. The values represent mean ± SE of three mice at each time point. Data indicate that CUDC907 is orally bioavailable with a half-life of 7.7 h in plasma and 12.6 h in tumor tissue, and that it is highly distributed in tumor tissues following either IV or PO administration. B, CUDC-907 was administered at 5 mg/kg iv or PO to dogs and then plasma samples were collected at various time points to determine compound concentration. The results are mean values ± SE of three dogs at each time point. CUDC-907 has relatively shorter half-life in dogs, but similar oral bioavailability in the two species.