**SUPPLEMENTARY LEGENDS**

**Supplemental Figure 1.  Selection of Plumbagin dose for optimal drug synergy.**Cells were treated with 3, 4 and 5 µmol/L of Plumbagin alone or in combination with Celecoxib (30 to 50 µmol/L) for 72 hours **(S1A to SIC)**. Cell viability was measured by MTS assay. Plumbagin 5 µmol/L with Celecoxib 30 to 50 µmol/L led to maximal killing of UACC 903 cells.

**Supplemental Figure 2.  Thermal stability of Celecoxib and Plumbagin.**The thermal stability of Celecoxib (37.5, 75 and 150 µmol/L) **(S1A)** and Plumbagin (5, 10 and 15 µmol/L) **(S1B)** in DMSO solution was measured following exposure to 60oC over time. Samples were analyzed for UACC 903 killing efficacy by MTS assay.

**Supplemental Figure 3. Selection of the optimal ratio of Plumbagin and Celecoxib for synergistic killing of melanoma cells.** Plumbagin or Celecoxib drugs at ratios of 1:10 or 1:20 were identified to cause maximal killing of UACC 903 cells.

**Supplemental Figure 4. CelePlum-777 led to synergistic killing of melanoma cell lines lacking (V600E)-BRAF.** CelePlum-777 inhibited the viability of C8161.Cl9 and MelJuSo cells in a cooperative manner compared with liposomes containing Plumbagin or Celecoxib alone. Data represent averages of at least 3 independent experiments; bars, S.E.M.

**Supplemental Figure 5.  H&E Stained sections of organs from mice treated with CelePlum-777.** Analysis of H&E stained tissue sections comparing control or CelePlum-777 (Celecoxib 15 mg/kg and Plumbagin 1.5 mg/kg) treated mice showed no changes in cellular morphology or tissue architecture of spleen, heart, kidney, or liver.

**Supplemental Figure 6. Tumor inhibition of Celeplum-777 compared to combined nanoliposomes containing each agent alone.**  UACC 903 xenograft tumor inhibition when treating with CelePlum-777 was similar to that occurring with nanoparticles containing each individual agent individually but combined at the synergizing 10:1 drug ratio. Empty liposome was the vehicle control. Agents were delivered on alternate days for 3 to 4 weeks. Line graph represents tumor volume (mm3); insert represents body weight (g). Data was obtained from duplicate experiments with four mice per group; bars, S.E.M.

**Supplemental Figure 7. No significant change in TUNEL positive apoptotic cells occurred in CelePlum-777 treated tumors compared to controls.** Size and time matched xenograft tumors were treated with liposomes containing Celecoxib (15 mg/kg body weight), Plumbagin (1.5 mg/kg body weight), or CelePlum-777 (Celecoxib 15 mg/kg + Plumbagin 0.75 mg/kg body weight) starting day 6 until day 15. Empty liposome in saline was used as a vehicle control. Tumors were removed from mice on days 13 and 15, and immunostained for TUNEL positive cells to assess apoptotic cells. Fold difference in TUNEL positive cells compared to controls was plotted. Data was obtained from three to four tumors, with four to five fields averaged per tumor; bars, S.E.M.

**Supplemental Figure 8. Caspase-3/7 activity in cell lysates following 24 hour CelePlum-777 treatment.** Caspase-3/7 activity in the cell lysates collected for Western blot analysis was used to determine the Apo-ONE homogenous caspase-3/7 activity (Promega Corporation). Bar graph represents fold increase over CelePlum-777 compared to Celecoxib or Plumbagin liposomes.

**Supplemental Table 1. Biochemical and stability characterization of** **CelePlum-777 containing varying drug ratios.** Plumbagin and Celecoxib loaded at ratios of 1:10 or 1:20 into nanoliposomes was stable in terms of size and charge over time.

**Supplemental Table 2.**  **CelePlum-777 caused negligible systemic toxicity.** Levels of ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), ALKP (Alkaline phosphatase), TPR (Total Protein), GLB (Globulin), TBIL (Total bilirubin), BUN (Blood urea nitrogen), CHOL (Total cholesterol), TRIG (Total triglyceride), GLU (Glucose), PHOS (Phosphate), CAL (Calicium), and AMY (Amylase) were analyzed in blood collected from animals treated on alternate days for 26 days with liposomes containing Celecoxib at 15 mg/kg body weight, Plumbagin at 1.5 mg/kg body weight, or CelePlum-777 containing Celecoxib at 15 mg/kg body weight + Plumbagin 1.5 mg/kg body weight indicate no significant changes in these blood indicators of major organ stress. Values in brackets represent the normal range of the parameters for nude mice.

**Supplemental Table 3. CelePlum-777 did not act through AKT or cPLA2 signaling.** Western blotting of UACC 903 or 1205 Lu melanoma cells treated with empty liposome, Celecoxib liposome (100 µmol/L), Plumbagin liposome (5 µmol/L), or CelePlum-777 (100 µmol/L Celecoxib, 5 µmol/L Plumbagin). Values represent the change in protein levels compared to untreated cells at 24 hours. CL = Celecoxib liposome, PL = Plumbagin liposome, CP-777 = CelePlum-777.