**Supplemental Figure Legends**

**Supplemental Figure 1. Chemical structures for the molecules utilized in these studies. A.** Auranofin. **B**. BSO. **C**. Zn-BG. **D**. carfilzomib

**Supplemental Table 1. Characteristics of the 50 primary CLL samples that were utilized in this study.**

**Note:** The gender of the patients, the IgHV mutational status (U=unmutated, M= mutated) if known, ZAP70 status (+= positive for ZAP70 expression ; - = negative for ZAP70 expression) if known, CD38 expression, the cytogenetic alterations observed, and the IC50 concentration of AF for each patient sample is shown. \* indicates that the status of a specific characteristic for a patient is unknown.

**Supplemental Figure 2. Co-treatment with NAC significantly inhibits AF-induced apoptosis of cultured CLL cells.** MEC-1 cells were treated with the indicated concentrations of AF with or without 2.5 mM NAC for 48 hours. At the end of treatment, cells were washed with 1X PBS and stained with annexin V and TO-PRO-3 iodide. The % of annexin-V-positive, apoptotic cells were determined by flow cytometry. Columns, mean of three independent experiments; Bars, SEM.

**Supplemental Figure 3. Treatment with AF does not induce loss of viability of nurse-like cells (NLCs). A.** Fresh PBMCs from 5 patients with CLL were cultured in 6 well-plates for 2 weeks to allow NLC differentiation. Each sample was split into 4 wells to allow duplicate analysis (control x 2, AF x 2). AF 1.0 µM (or equivalent volume of DMSO) was added to the appropriate well, and cells were incubated for 24 hours. At the end of the incubation period, non-adherent cells were removed, washed, re-suspended in PBS, and re-plated in their original wells. Cell viability was quantified using the LIVE/DEAD Viability/Cytotoxicity Kit (Life Technologies) following the manufacturer protocol. Viability was quantified using a fluorescence microscope. Live (green) and dead (red) CLL and NLCs were quantified by visually counting the cells in 2-4 random fields at 20x magnification. Shown are representative fluorescent micrographs obtained from control and AF-treated samples of 2 different CLL patients, reduced from magnification 20x. **B**. Cell viability of CLL and NLC from 5 patients following 24 hours of treatment with 1.0 µM of AF. **C**. Box plot demonstrating the relative change in viability of CLL (n=5) and NLC (n=5) following 24 hours of treatment with 1.0 µM AF.

**Supplemental Table 2. Leukemia cell burden for the individual TCL-1 mice pre-and post-treatment with 2 weeks of auranofin.**

**Supplemental Table 3. Gene expression changes of the 39 most up and downregulated genes in primary CLL cells following treatment with 1.0 µM of AF for 8 hours.**

**Supplemental Table 4. Ingenuity Pathway Analysis of the top 5 perturbed networks in Primary CLL cells treated with 1 µM of AF.**  Note: The score assigned by IPA for the associated network functions (i.e. a score of 41) indicates that there is a 1 in 1041 chance that the focus genes in the dataset are together in a network due to random chance alone.

**Supplemental Figure 4. Ingenuity Pathway Analysis identifies multiple connected biologic networks that are significantly perturbed in primary CLL cells following treatment with AF.** Ingenuity Pathway Analysis and representation of significantly perturbed genes, and their associated biological networks from primary CLL cells following 8 hours of treatment with 1.0 µM of AF are shown. Individual gene products are represented as nodes. Upregulated gene products are colored red and downregulated gene products are colored green. Interactions between two gene products are represented by a line. A solid line represents a direct interaction between two gene products whereas a dashed line represents an indirect interaction. In addition, the connectivity of each of the individual networks (by their key components or intermediary components) to the other networks in the gene set is also shown.

**Supplemental Figure 5. Co-treatment with AF and ZnBG or BSO synergistically induces apoptosis of cultured and primary CLL cells. A-B.** MEC-1 and primary CLL cells were treated with the indicated concentrations of AF and ZnBG for 48 hours. Isobologram analyses were performed. Shown are the doses of AF and ZnBG, the % of cells affected, and the corresponding combination index value for each drug combination as calculated by the Calcusyn software. All values are less than 1.0 indicating a synergistic interaction between the two drugs. **C-D**. MEC-1 and primary CLL cells were treated with the indicated concentrations of AF and BSO for 48 hours. Isobologram analyses were performed. Shown are the doses of AF and BSO, the % of cells affected, and the corresponding combination index value for each drug combination. All values are less than 1.0 indicating a synergistic interaction between the two drugs.

**Supplemental Figure 6. Treatment with hydrogen peroxide induces markers of oxidative stress, ER-stress and apoptosis in CLL cells.** MEC-1 cells were treated with the indicated concentrations of hydrogen peroxide and/or NAC for 8 hours. Then, cells were harvested and total cell lysates were prepared. Immunoblot analyses were conducted for the expression levels of Nrf2, CHOP, GRP78, cleaved Caspase 3 and β-actin in the cell lysates.