**Supplemental Methods**

**Reagents and antibodies.** Heme oxygenase inhibitor Zn (II) Deuteroporphyrin IX 2,4, bis ethylene glycol (ZnBG) was obtained from Echelon Biosciences. Glutathione synthesis inhibitor, Buthionine-sulfoximine (BSO); antioxidant, N-acetyl cysteine (NAC), phalloidin for immunostaining and lentiviral shRNAs targeting HMOX-1 and GADD153/CHOP were obtained from Sigma-Aldrich. Chemical structures for the molecules utilized in these studies are provided in Supplemental Figure 1. The following antibodies were used in the studies: NRF2, HMOX1, GRP78, CHOP/GADD153, HDAC6 (Santa Cruz Biotechnologies), TxNIP (Abcam), GCLM (Millipore), cleaved Caspase 3, AKT and ZAP70 (Cell Signaling), polyubiquitin (Covance; clone Ubi-1; MMS-264R), P97/VCP (BD Biosciences; clone 18/VCP), c-RAF (BD Biosciences; clone 53/c-RAF-1; #610151), HSF-1 (Enzo; SPA-901), hsp90 (Enzo; SPA-835 or SPA-830), hsp40 (Enzo; SPA-450), hsp27 (Enzo; SPA-800), hsp70 (Enzo; SPA-810) and β-actin (Sigma-Aldrich; clone AC-74).

**Gene expression analysis.** Separate gene analysis was performed in different labs with different primary CLL patients. Total RNA from primary CLL PBMCs treated with AF for 4, 8, or 10 hours or left untreated for 10 hours was extracted using the RNeasy Mini Kit (Qiagen, Louisville, KY). One microgram of RNA was used for the generation of labeled cRNA according to the manufacturer’s instructions (Affymetrix, Santa Clara, CA). Hybridization of the labeled cRNA fragments, washing, staining and scanning of the arrays were performed according to the manufacturer’s instructions. Labeled cRNA were profiled using the Affymetrix Human Genome-U133-Plus 2.0 platform. Array data were imported into Affymetrix Expression Console (Affymetrix, CA), and normalized with RMA method. For the 4 and 10 hour AF treated samples, a two-way ANOVA with patient effect (2 patients) and time effect (0, 4, and 10hours) was carried out for each gene. Genes were selected for p <.01 for time effect and 2 fold-changes of treated versus untreated. One-way heatmap for the selected genes was generated from JMP 8 (SAS Inc., NC). For the 8 hour AF-treated CLL samples, relative fold change analysis was calculated utilizing Partek Genomic Suite. Comparison of the up- and down-regulated genes from the individual AF-treated CLL cells (0, 4, 8 and 10 hours) identified significant overlap in the expression signatures. Genes that were commonly up and down regulated in the gene expression datasets from both analyses were chosen for further study.

**Ingenuity pathway analysis (IPA)**. Significantly perturbed gene lists acquired from the microarray analysis of AF-treated primary CLL cells were imported into the Ingenuity Pathway Analysis Tool (IPA Tool, Ingenuity Systems Inc., Redwood City, CA, USA; <http://www.ingenuity.com>) for assignment of biologic function and identification of differentially altered genetic networks. Up and down regulated identifiers were defined as value parameters for the analysis. Within the IPA software, a Core Analysis was performed to identify the signaling and metabolic pathways as well as the molecular networks and biological processes that were significantly perturbed in the differentially expressed gene (DEG) dataset. The DEGs were mapped to genetic networks in the database and ranked by score. The significance of the molecular and cellular functions over-represented in the gene set, as well as the signaling pathways and biological networks to which they belong was tested by Fisher’s exact test p-value. The created biological networks were ranked according to the number of significantly differentially expressed genes that they contained. Individual gene products are represented as nodes and the biologic interaction between individual gene products is represented by a line. Direct interactions are presented by a solid line whereas; indirect interactions are represented by a dashed line. In addition, the connectivity of each individual network to the other networks in the gene set by their key components or intermediary components was also determined.

**Immunoblot analyses**.Seventy five micrograms of total cell lysates from MEC-1 or primary CD19+ CLL cells were used for SDS-PAGE and immunoblot analyses. Immunoblot analyses were performed using monoclonal antibodies or specific anti-sera. Blots were washed with 1X PBST, then incubated in IRDye 680 goat anti-mouse or IRDye 800 goat anti-rabbit secondary antibodies (LI-COR, Lincoln, NE) for 1 hour, washed 3 times in 1X PBST and scanned with an Odyssey Infrared Imaging System (LI-COR, Lincoln, NE).The expression level of β-actin in the cell lysates was used as the loading control. Immunoblots were performed at least twice and representative images are shown. Densitometry was performed on representative immunoblots utilizing ImageQuant version 5.2 (GE Healthcare). For HDAC6 expression following AF treatment, the mean % decline from 10 primary CD19+ CLL cells was calculated and graphed.