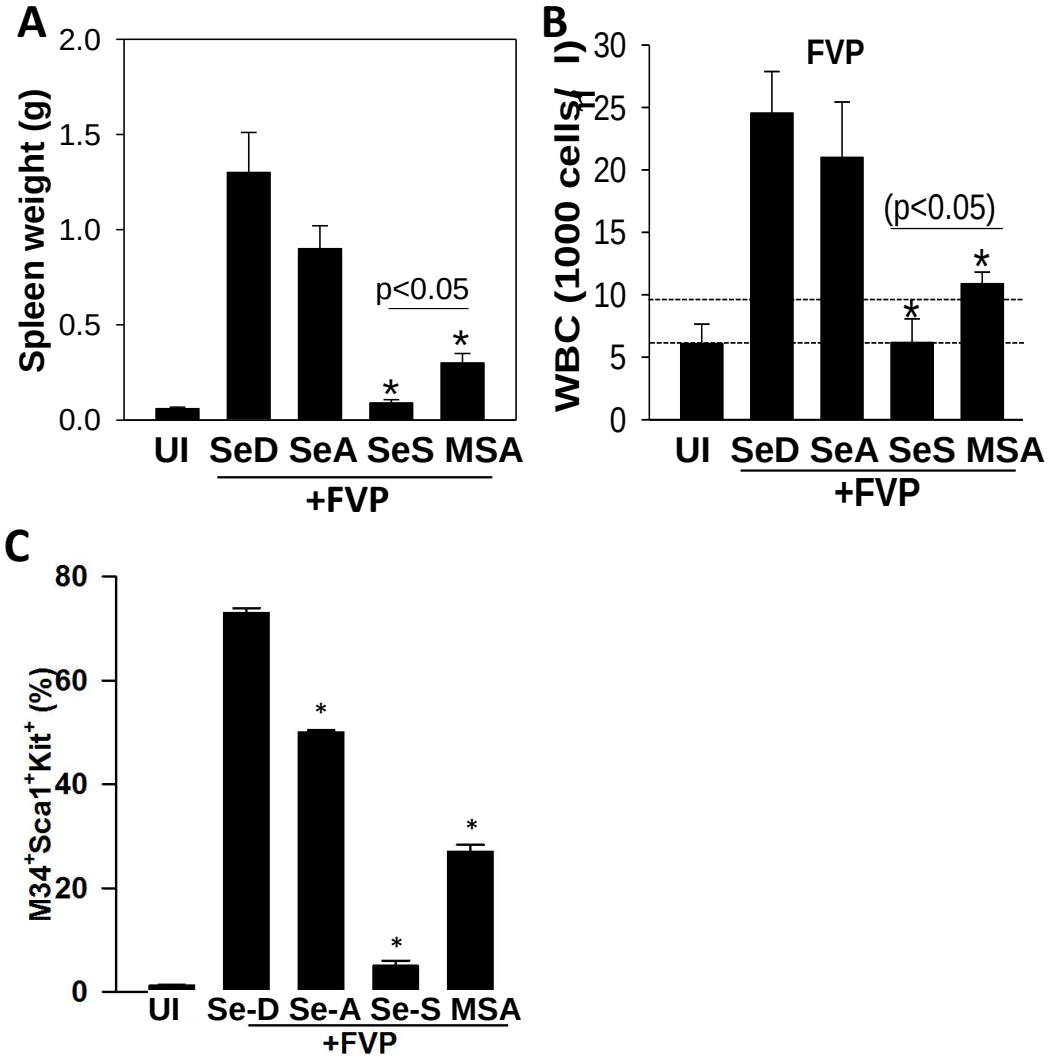
Supplementary Methods

Histology and TUNEL Staining: Histological analyses were also performed on the splenic sections from uninfected control and FV-infected mice from each of the diet groups. TUNEL assay was performed on splenic sections of BCR-ABL$^+$LSC transplanted or FV infected mice on Se-D, Se-A, and Se-S diet groups as per the manufacturer's protocol (Roche Diagnostics). TUNEL$^+$ cells were quantitated using Image J and are provided as total area of TUNEL$^+$ cells (in arbitrary units).

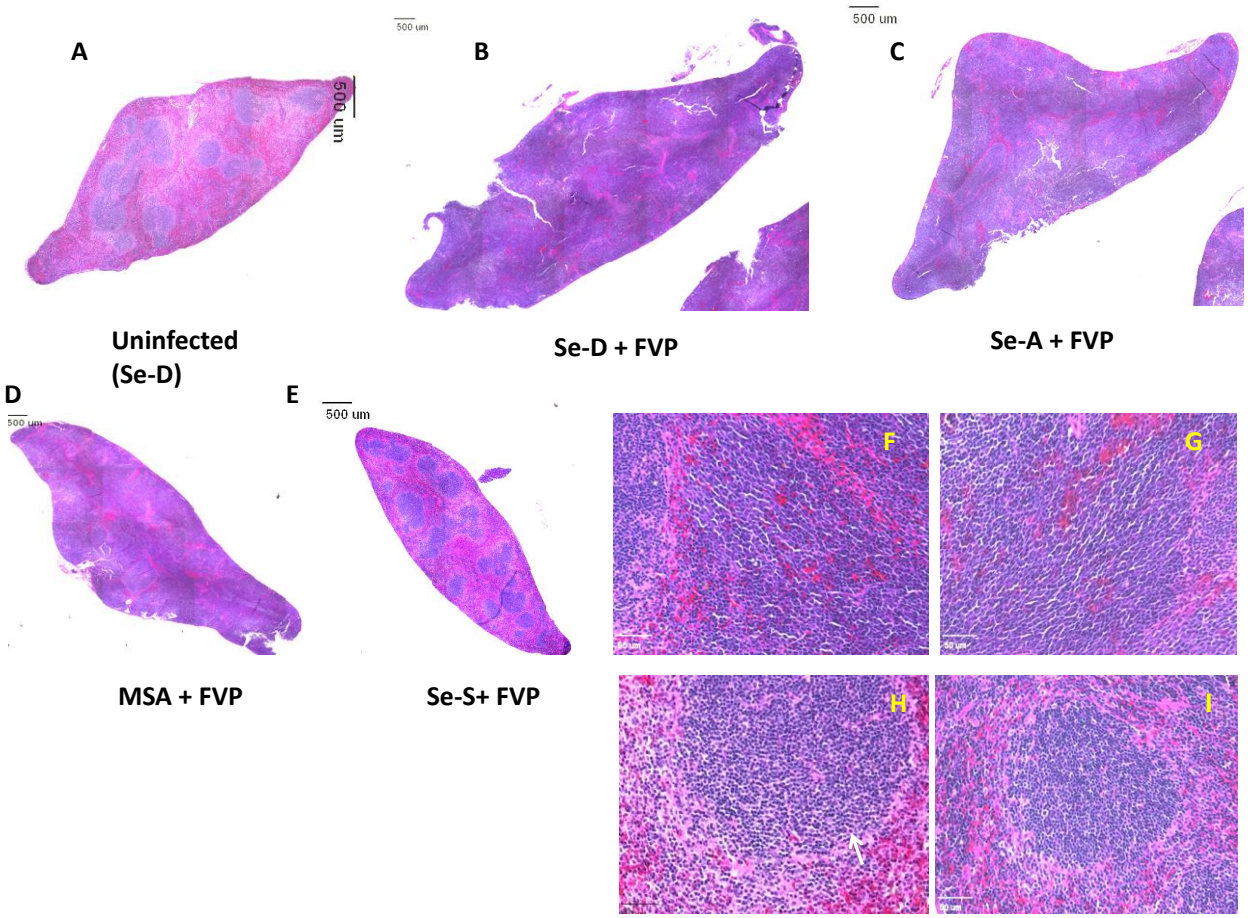
Gene Expression Studies: Quantitative RT-PCR (qPCR) with Taqman probes (from Life Technologies) was used in sorted sorted BCR-ABL$^+$LSCs and HSCs before and after treatment for 6 h with selenite or lipid extracts from selenite-treated macrophages as described in Supplementary Methods to examine the expression of *Nox1* (NADPH oxidase 1), *Nox2*, *Nox3*, *Gpx4* (glutathione peroxidase 4), *Sod2* (superoxide dismutase 2), *Cat* (catalase), *p21*, *Sesn1* (sestrin1), *Sesn2* (sestrin2), *Sco2*, *Tigar*, *Gls2* (glutamine synthase), and *Rm2b* in sorted BCR-ABL$^+$LSCs and HSCs before and after treatment for 6 h with selenite or lipid extracts from selenite-treated macrophages. Data was analyzed according to the method of Livak *et al* with normalization to 18S rRNA and were compared to untreated HSCs or LSCs to calculate fold changes.

Western immunoblot analyses: Sorted murine CML LSCs and HSCs by FACS was performed and the cells were subjected to various doses of sodium selenite or lipid extracts from macrophages. Splenic samples from FVP-infected mice were used for Western immunoblot analysis. Briefly, cells or tissues were subjected to homogenized in M-PER or T-PER reagent from Thermo Fisher, respectively. Equal amount of protein was loaded on an SDS-PAGE gel followed by electroblotting onto PVDF membranes. The membranes were probed with

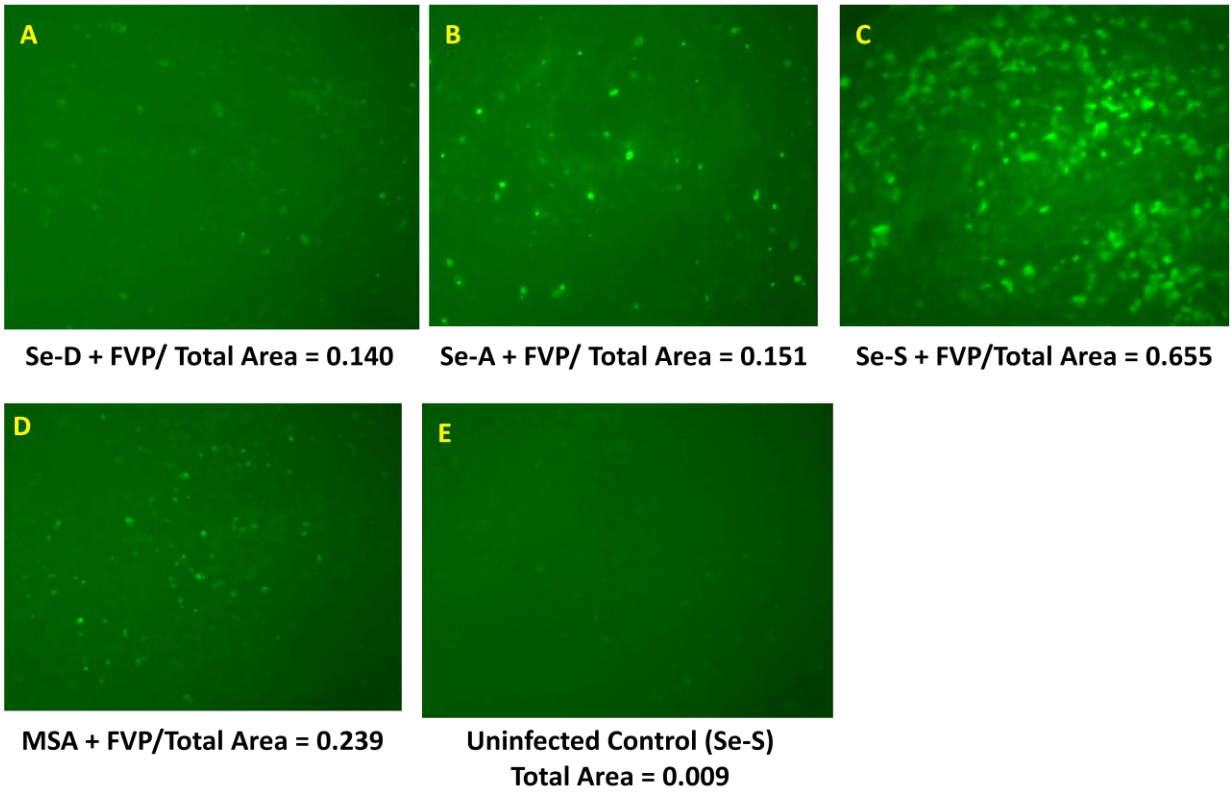
antibodies for pro-apoptotic proteins, p53, P-p53 (Ser13), pChk2, procaspase-3, caspase-3, and cleaved PARP and appropriate housekeeping controls (b-actin or GAPDH). The experiments were performed at least in triplicate and the autoradiographs were subjected to densitometric evaluation by Image J.



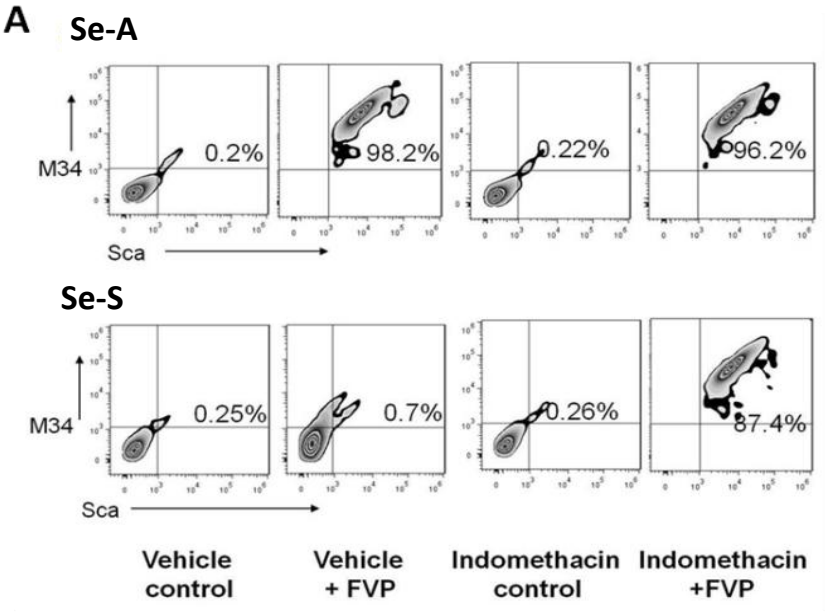
Supplementary Figure 1. Selenium supplementation abrogates leukemia in a Friend leukemia (FVP) model. Balb/c mice on Se-D, Se-A, Se-S, and Se-MSA diets were infected with FVP via retro-orbital injection and sacrificed two weeks post-infection. A, splenomegaly; mean ± s.e.m. of n= 6 per diet group. * $p<0.05$. B, WBC in the peripheral blood was assessed in these mice. mean ± s.e.m. of n= 6 per diet group. * $p<0.05$. **C,** presence of LSCs ($M34^+Sca1^+Kit^+$) in the spleen by flow cytometry. Mean ± s.e.m. of n= 6 per diet group. * $p<0.05$.



Supplementary Figure 2. Effect of selenium supplementation on the splenic histopathology in FVP-infected mice. Balb/c mice on Se-D, Se-A, Se-S, and Se-MSA diets were infected with FVP via retro-orbital injection and sacrificed two weeks post-infection. Splenic sections were stained with hematoxylin and eosin (H&E) for histological evaluation. A-E**,** spleen sections from uninfected (Se-D) control, Se-D+FVP, Se-A+FVP, Se-S+FVP, MSA+FVP, and Se-S+FVP, respectively. F-I, Higher magnification images of H&E sections from Se-D+FVP, Se-A+FVP, Se-S+FVP, and Se-D uninfected control. Scale bar, 50 μm. Representative sections from n= 4 mice per group are shown.



Supplementary Figure 3. Selenium supplementation increases apoptosis in the spleen of FVP-infected mice. TUNEL assays were performed on the sections from the spleen of mice on indicated diets that were infected with FVP. A-D, TUNEL assay of the splenic sections from BCR-ABL^{+}LSC transplanted mice on Se-D, Se-A, or Se-S diets. E, uninfected splenic section from Se-S mice is shown as a control. Total area of TUNEL^{+} staining is shown below each panel. Data shown is representative of n=3 independent experiments.



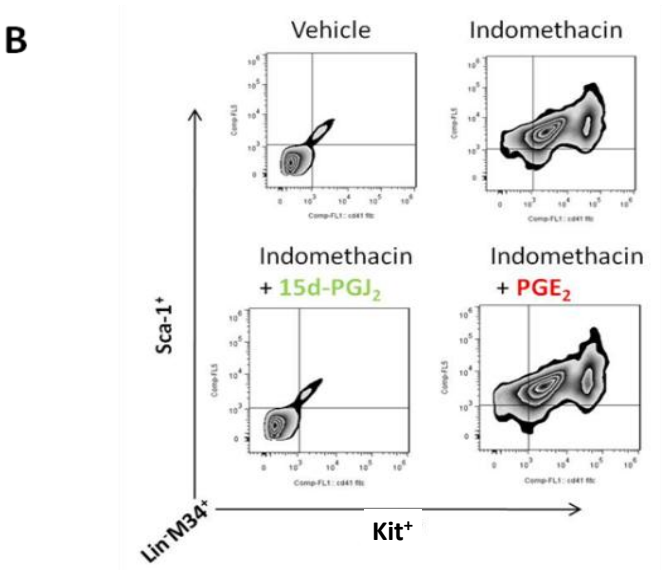
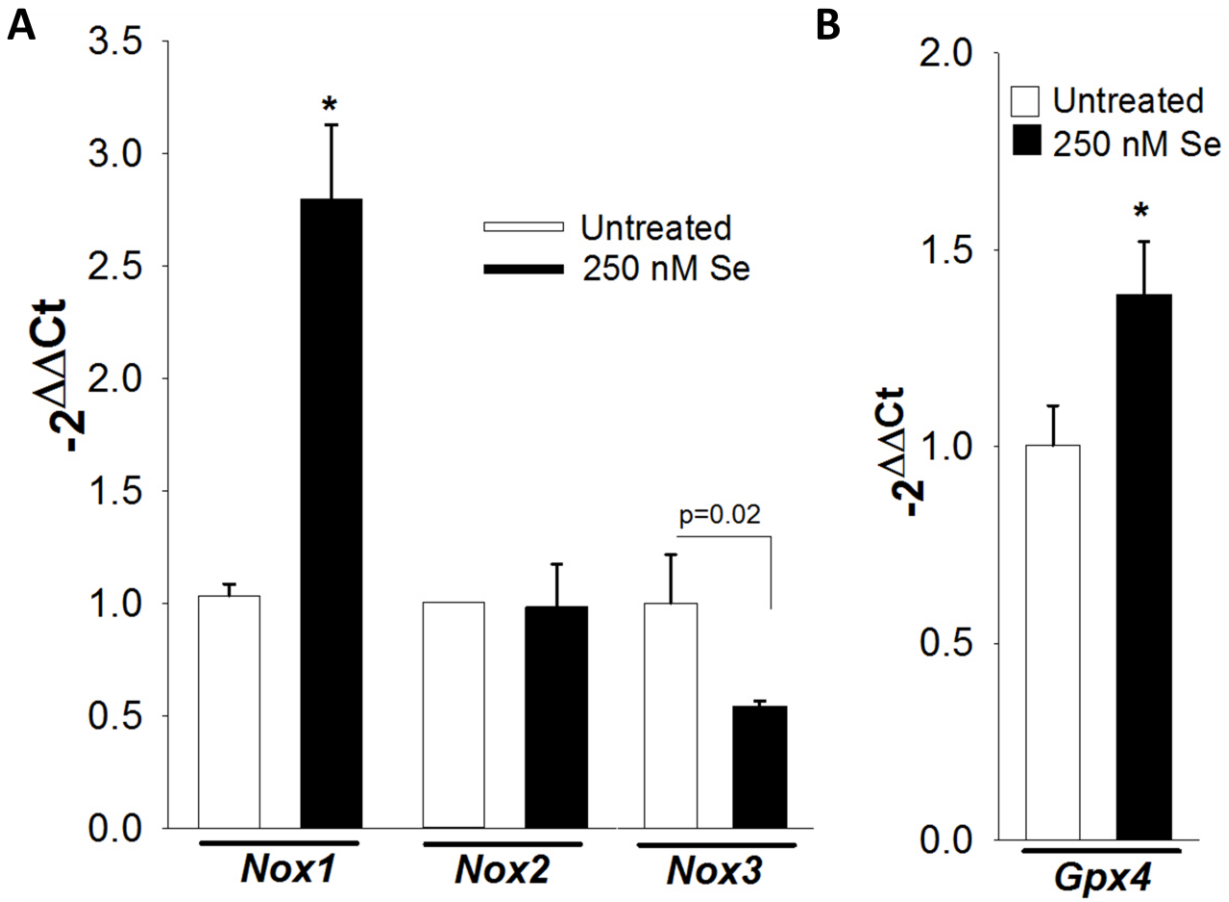
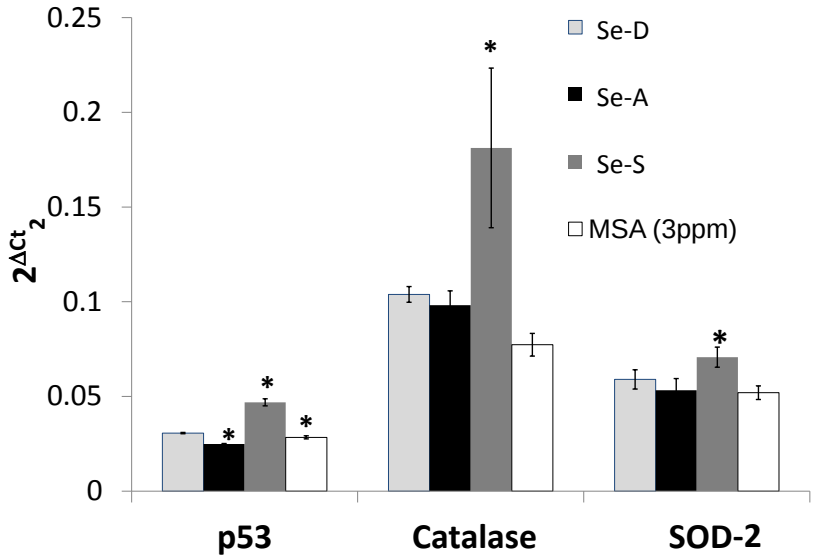


Figure S4

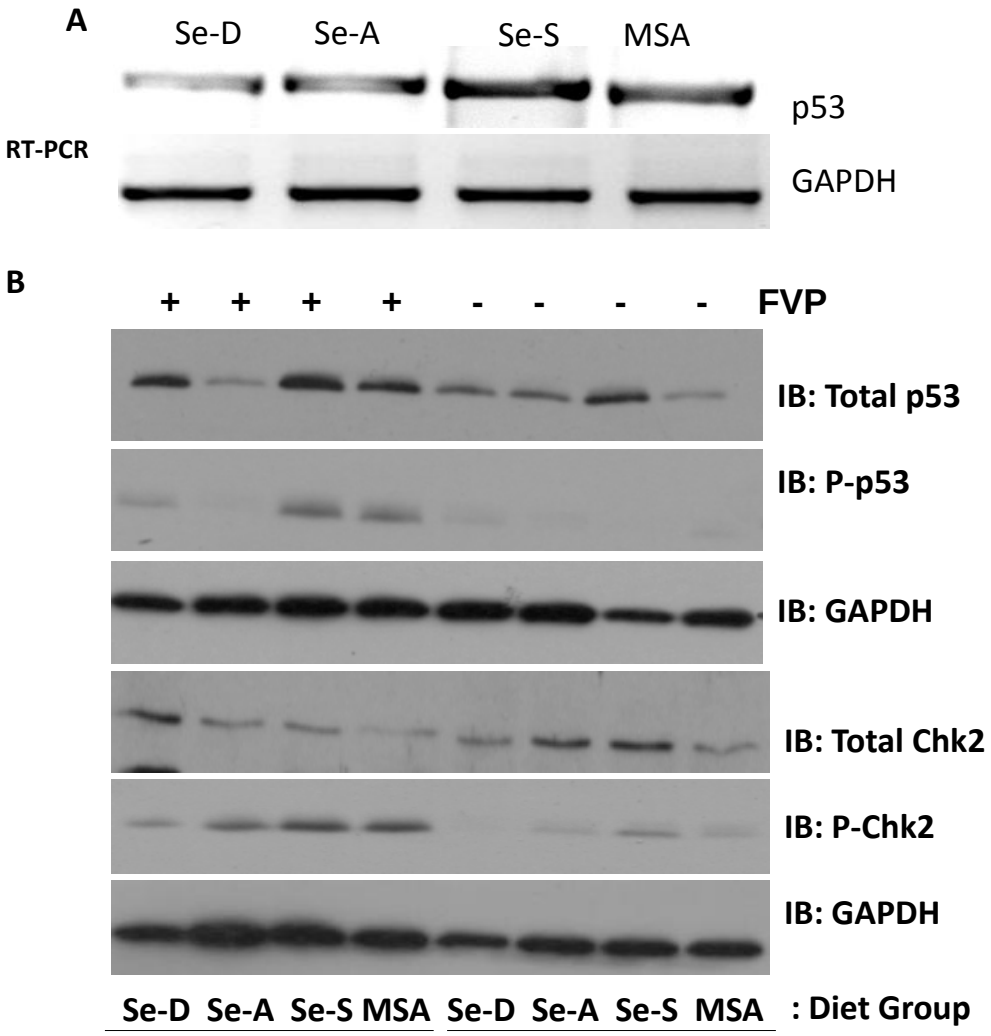
Supplementary Figure 4. Essential role of the COX/eicosanoid pathway in the ablation of LSCs in FVP-infected Se-S mice. Se-A or Se-S mice weaned on the respective diets for 8 weeks were treated with or without indomethacin (0.00325 % w/v) for two weeks prior to FVP infection. Indomethacin was continued for two additional weeks post FVP infection. A, LSCs ($M34^+c\text{-}Kit^+Sca1^+Lin^-$) in the spleen were examined by flow cytometry in the vehicle-treated and indomethacin-treated groups. Representative of n= 4 mice in each group. B, indomethacin- or vehicle-treated FVP-mice on Se-S diet were exogenously treated with 15d-PGJ_2 (0.025 mg/kg/d) or 16,16-dimethyl-PGE_2 (0.025 mg/kg/d) for 1 week post FVP infection. All mice were sacrificed on day 14 post FVP infection and the splenic LSCs were examined by flow cytometry. Data shown are representative of n= 4 mice in each group.



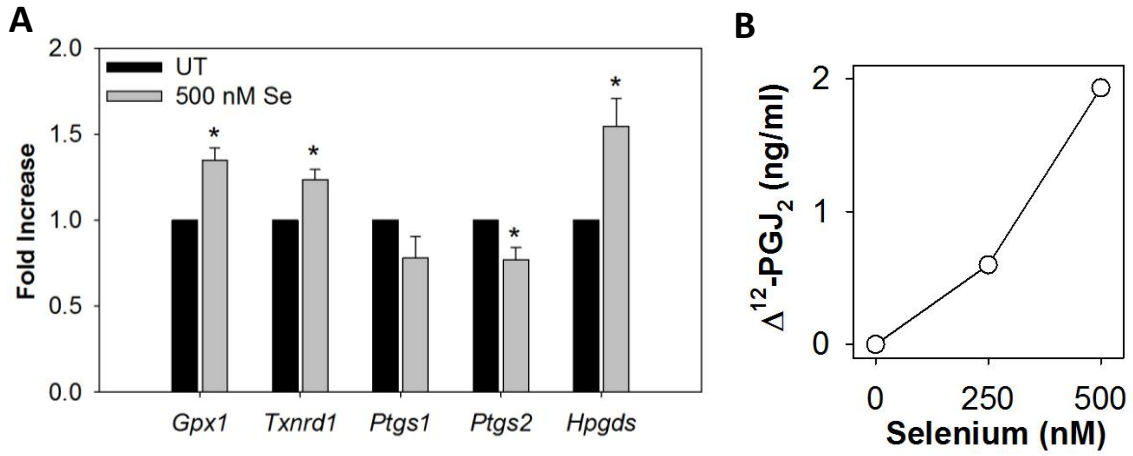
Supplementary Figure 5. Modulation of expression of NADPH oxidases (A) and Gpx4 (B) by selenium-treatment of BCR-ABL^{+}LSCs. LSCs were sorted for cKit^{+}Sca1^{+}Lin^{-}CD45.1^{+}GFP^{+} markers and cultured in IMDM media as described earlier. Selenium (as sodium selenite) was added at 250 nM to these sorted LSCs for 6 h and total RNA was isolated for qPCR analyses. A, mRNA expression of NADPH oxidases, *Nox1* (Gp91phox subunit), *Nox2*, and *Nox3*. B, LSCs were also examined for the expression of phospholipid glutathione peroxidase (*Gpx4*) upon treatment with selenium. Data shown is representative of n=2 independent experiments performed in triplicate. * $p<0.01$compared to the untreated group.



Supplementary Figure 6. Expression of *Tp53*, *Cat* and *Sod2* in the spleen of FVP-infected mice. Spleen samples from FVP-infected mice weaned on Se-D, Se-A, Se-S, and MSA diets were used to examine transcript levels of p53 and two antioxidant enzymes, catalase and SOD-2. All data shown are mean ± s.e.m. of n= 5 per diet group. * $p<0.05$ compared to the Se-D group.



Supplementary Figure 7. Activation of p53 in FVP-infected Se-S and MSA mice. A, *Tp53* expression by semi-quantitative RT-PCR in the spleen on FVP-infected mice weaned on Se-D, Se-A, Se-S, and MSA diets. B, splenic tissue lysates from FVP infected and uninfected controls were examined for the activation of p53 and ChK2 by Western immunoblot analysis. Data shown are representative of n= 3 independent experiments.



Supplementary Figure 8. Selenium-dependent expression of selenoproteins and CyPG synthesis machinery and endogenous production of Δ^{12}-PGJ_2 by LC-MS/MS in BCR-ABL$^+$LSCs. LSCs were sorted for cKit$^+$Sca1$^+$Lin$^-$CD45.1$^+$GFP$^+$ markers and cultured in IMDM supplemented with 15 % FBS (ATCC), 1 % v/v BSA (Sigma), insulin (Sigma; 10 μg/ml), transferrin (Sigma; 200 μg/ml), L-glutamine (Cellgro; 2 mM), SHH (Peprotech; 25 ng/ml), SCF (Peprotech; 50 ng/ml), GDF15 (Peprotech; 4.5 ng/ml), and IL-3 (Peprotech; 1 ng/ml) and treated for 24 h at 37 °C in 5% CO_2. Selenium (as sodium selenite) was added to these sorted LSCs at indicated concentrations for 24 h. A, expression of *Gpx1*, *Txnrd1*, *Ptgs1*, *Ptgs2*, and *Hpgds* were measured in LSCs by qPCR. Mean ± s.e.m of n=2 independent experiments performed in triplicate. * $p<0.05$ compared to corresponding untreated controls. B, endogenous production of Δ^{12}-PGJ_2 was measured in the cell culture media supernatant by LC-MS/MS using MRM method. Data shown is representative of samples pooled from n=2 independent experiments.