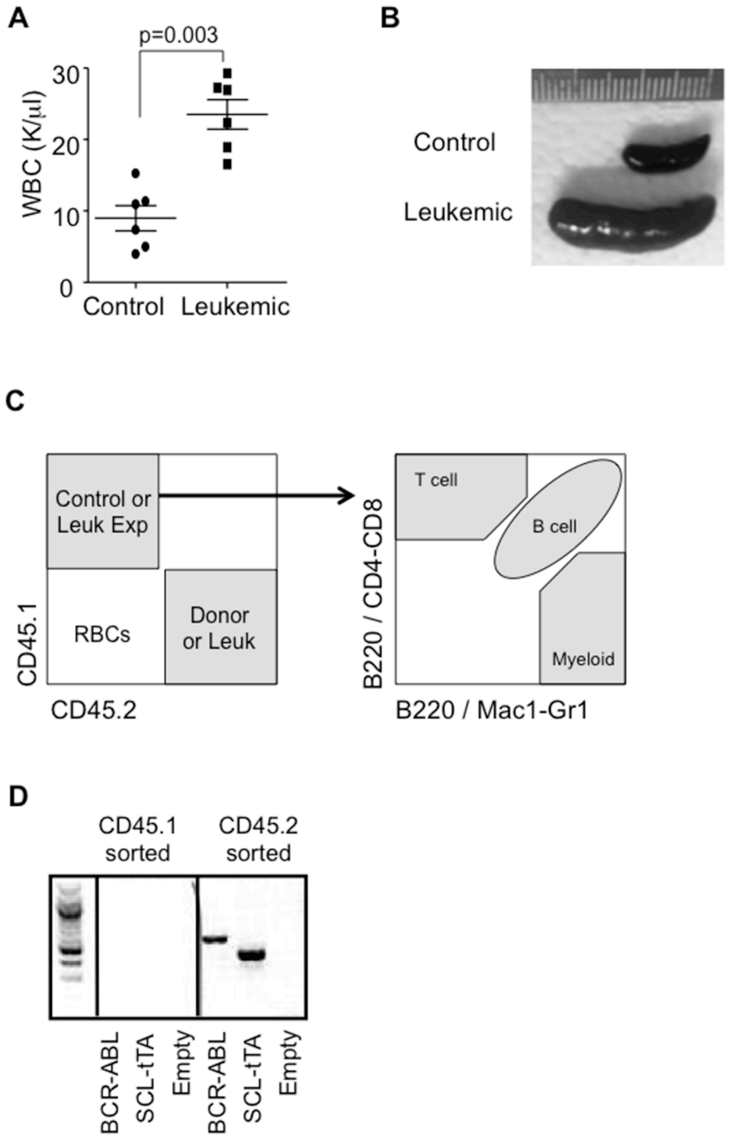


Figure S1, related to Figure 1: Establishing a model of chimeric CML

(A) Hemavet counts of white blood cells from peripheral blood were collected from either control or leukemic mice at 4 weeks post tetracycline withdrawal. Results represent the mean ± SEM of six mice per group.

(B) Splenic morphology from control or leukemic mice taken at 5 weeks post Tet withdrawal. Representative image of the splenomegaly observed in the transplanted chimeric mice is shown.

(C) Cartoon showing the analysis of peripheral blood. Red blood cells stain as the double negative population when using CD45.1 and CD45.2. When staining for B220/CD4-CD8 and Mac1-Gr1/B220,

the double positive population is $B220^{+}$ B lineage cells. CD4-CD8 only positive are T lineage cells, while Mac1-Gr1 only positive cells are from the myeloid lineage.

(D) BCR-ABL and SCL-tTa PCR profiling of peripheral blood cells from the leukemic mice was done for sorted CD45.1 (normal) and CD45.2 (leukemic) cells.

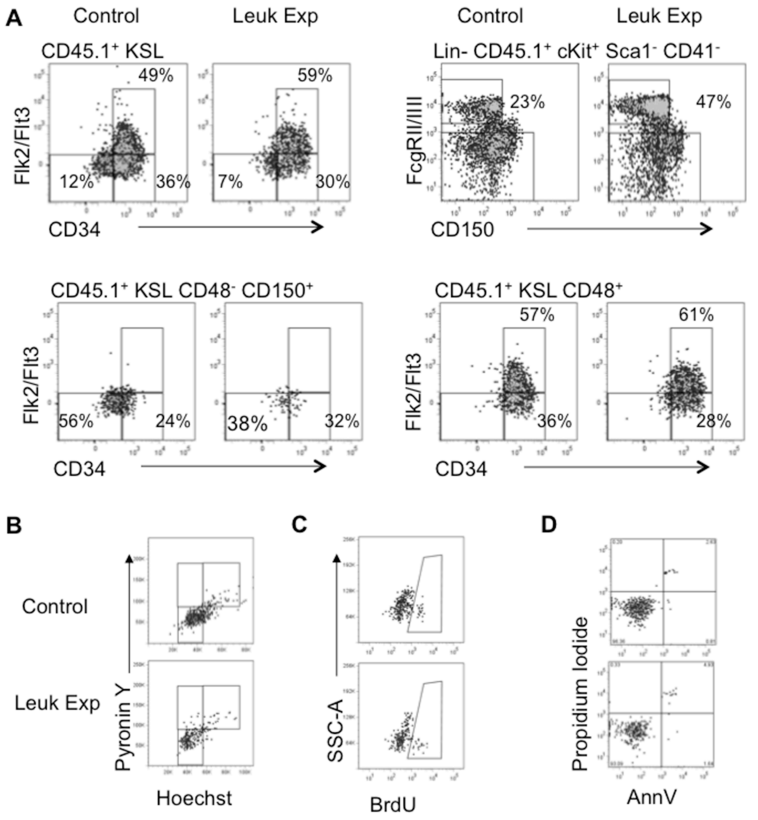


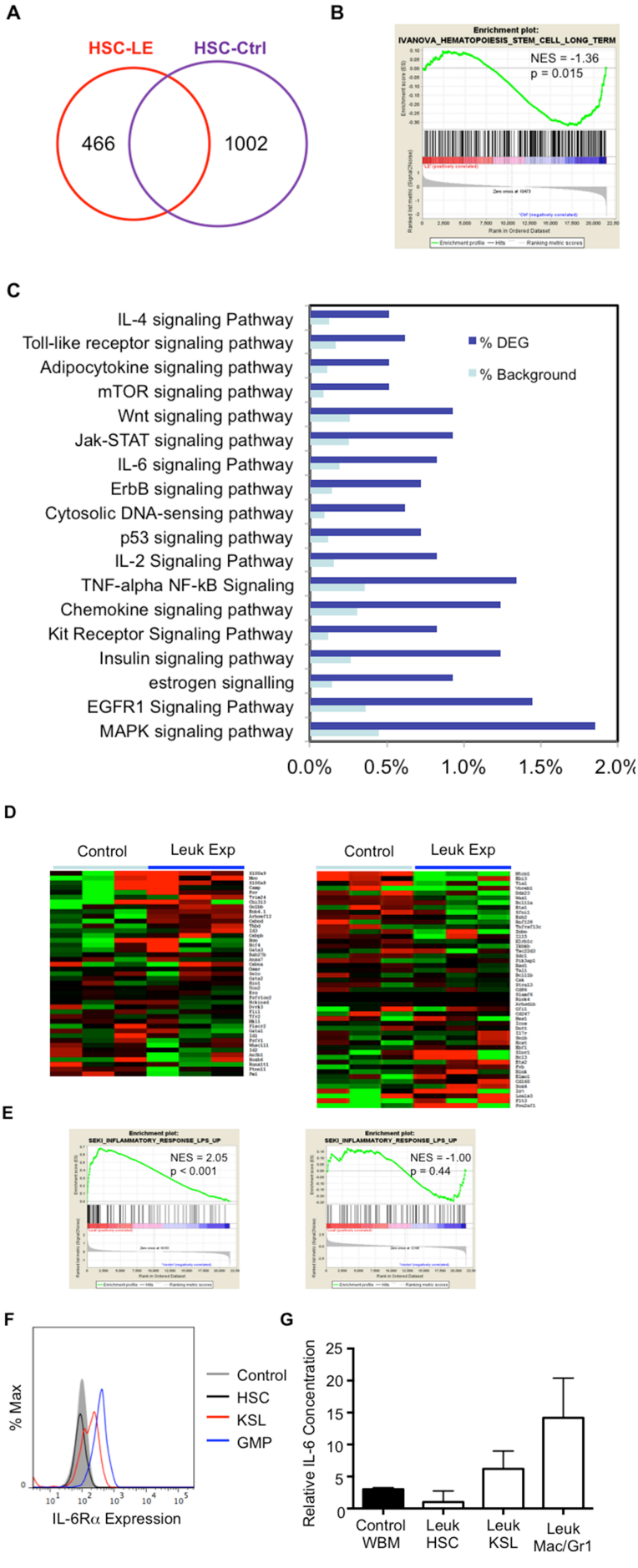
Figure S2, Related to Figure 2: Pertubation of normal stem and progenitor cells by chronic CML

(A) FACS profiles for CD45.1^{+} Lin^{-} ckit^{Hi} Sca1^{+} CD48^{+} CD34$^{+/-}$, Flt3$^{+/-}$ (MPP subsets) and Lin^{-} CD45.1^{+} cKit^{+} Sca1^{-} CD41^{-} FcgRII/III^{+} (GMP) in both control and leukemic-exposed marrow at 4 weeks post Tet withdrawal, n=5.

(B) CD45.1^{+} HSCs (Lin^{-} ckit^{Hi} Sca1^{+} CD150^{+} CD48^{-}) were sorted from either control or leukemic-exposed environments, and then cell cycle status was determined using pyroninY and Hoescht, n=4.

(C) BrdU incorporation by CD45.1^{+} HSCs (KSL CD150^{+} CD48^{-}) from control or leukemic exposed mice was quantified, n=4.

(D) Cell viability by AnnexinV staining was on control or leukemic exposed CD45.1^{+} HSCs to determine the apoptosis within this subset of progenitors, n=4.


A
HSC-LE
HSC-Ctrl
466
1002
B
Enrichment plot:
IVANOVA_HEMATOPOIESIS_STEM_CELL_LONG_TERM
NES = -1.36
p = 0.015
C
IL-4 signaling Pathway
Toll-like receptor signaling pathway
Adipocytokine signaling pathway
mTOR signaling pathway
Wnt signaling pathway
Jak-STAT signaling pathway
IL-6 signaling Pathway
ErbB signaling pathway
Cytosolic DNA-sensing pathway
p53 signaling pathway
IL-2 Signaling Pathway
TNF-alpha NF-kB Signaling
Chemokine signaling pathway
Kit Receptor Signaling Pathway
Insulin signaling pathway
estrogen signalling
EGFR1 Signaling Pathway
MAPK signaling pathway
% DEG
% Background
0.0%
0.5%
1.0%
1.5%
2.0%
D
Control
Leuk Exp
Control
Leuk Exp
E
Enrichment plot:
SEKI_INFLAMMATORY_RESPONSE_LPS_UP
NES = 2.05
p < 0.001
Enrichment plot:
SEKI_INFLAMMATORY_RESPONSE_LPS_UP
NES = -1.00
p = 0.44
F
% Max
Control
HSC
KSL
GMP
IL-6Rα Expression
G
Relative IL-6 Concentration
25
20
15
10
5
0
Control WBM
Leuk HSC
Leuk KSL
Leuk Mac/Gr1

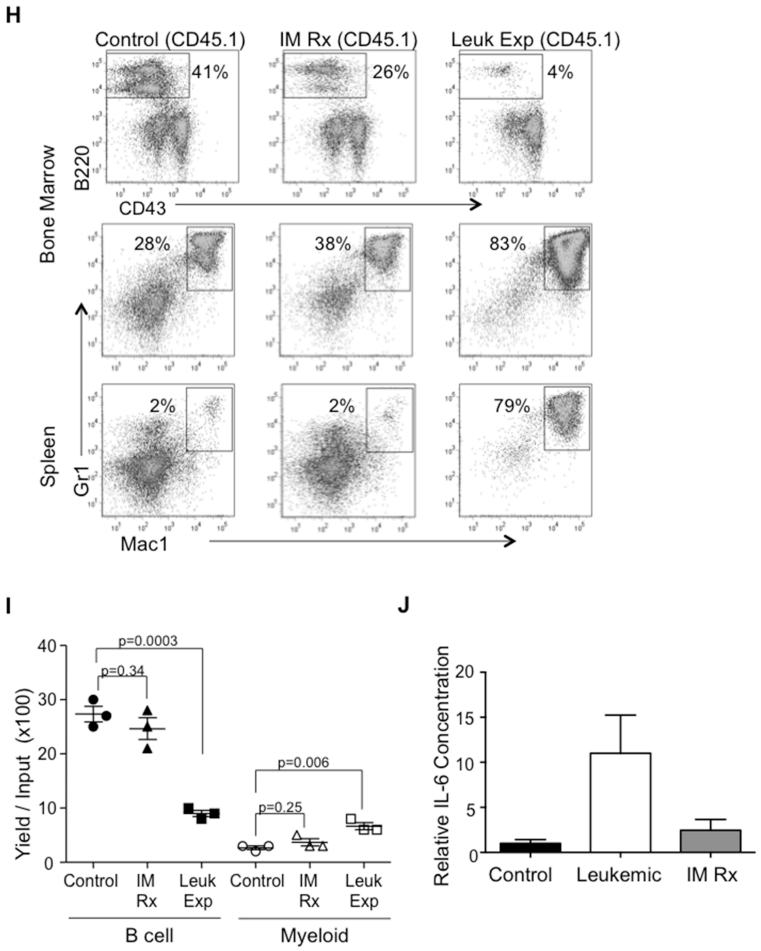


Figure S3, Related to Figure 4: Pro-inflammatory environment of CML leads to changes in normal stem and progenitor cells

(A) Venn diagram showing the differences in gene expression between control HSC and leukemic-exposed HSC.

(B) Enrichment plots of GSEA analysis using both control and leukemic-exposed HSCs expression data against a list of hematopoietic stem cell related genes.

(C) List of the most dyregulated pathways in leukemic-exposed progenitors differentially expressed genes as compared to control progenitors.

(D) Hierarchical clustering with average linkage was used to generate the heatmap of myeloid (left) or lymphoid (right) lineage specific transcription factors from the control and leukemic-exposed HSCs.

(E) Enrichment plots of GSEA analysis using both leukemic (left) and leukemic-exposed (right) KSL for inflammatory signatures.

(F) HSC, KSL, and myeloid progenitors were stained for surface expression of IL-6Rα as compared to an Ig isotype control.

(G) Cell populations from leukemic mice were sorted for expression of IL-6. RT-PCR results show the cells ability to make IL-6 RNA. Error bars represent ± SD.

(H) FACS profiles for normal ($CD45.1^+$) B lineage cells ($B220^+$ $CD43^{+/-}$) from the bone marrow of control, imatinib treated (IM) or leukemic mice after 3 weeks Tet withdrawal with an additional 5 weeks of IM treatment. Similarly, bone marrow or spleens from the control, imatinib (IM) and leukemic mice were analyzed for the normal ($CD45.1^+$) myeloid lineage cells ($Mac1^+$ $Gr1^+$), n=4.

(I) $CD45.1^+$ KSLs from control, IM treated or leukemic mice were sort purified and cultured on OP9 stromal cells. Quantification of $CD45.1^+$ B lineage cells ($CD19^+$) or myeloid cells ($Mac1^+$) from the OP9 co-cultures were plotted as yield per input, n=4. Results represent the mean ± SEM.

(J) We used an antibody based protein array to measure cytokine changes in the sera from our both control, transgenic or IM treated mice. Results are shown based on the normalization of the control sera. Error bars represent ± SD.

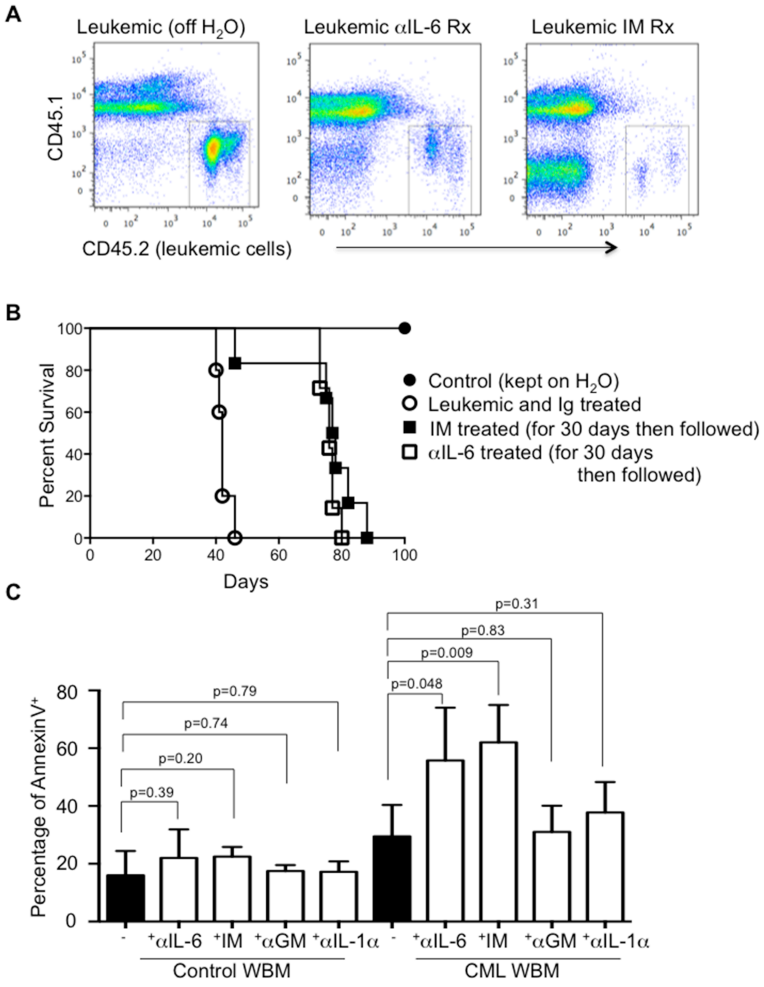


Figure S4, Related to Figure 5: Inflammatory cytokine IL-6 is responsible for most of the changes observed in normal hematopoiesis

(A) Dot plots of CD45.2 (leukemic) and CD45.1 (control) from leukemic mice, anti-IL-6 or imatinib (IM) treated mice 2 weeks after initiation of therapy.

(B) Survival curves of control and transgenic chimeric mice after tetracycline withdrawal and then treated for 30 days with either anti-IL-6 or imatinib (IM). After 30 days, treatment was stopped to show that minimal residual disease cells remain with these therapies.

(C) Whole bone marrow or CML marrow was cultured for one-week alone, with anti-IL-6, imatinib (IM), anti-GM-CSF, or anti-IL-1α. Cells were then stained and flow cytometry was performed for $CD45.2^+$ $AnnexinV^+$ cells. The percent of $AnnexinV^+$ cells is plotted for each condition, n=3. Error bars represent ± SD.