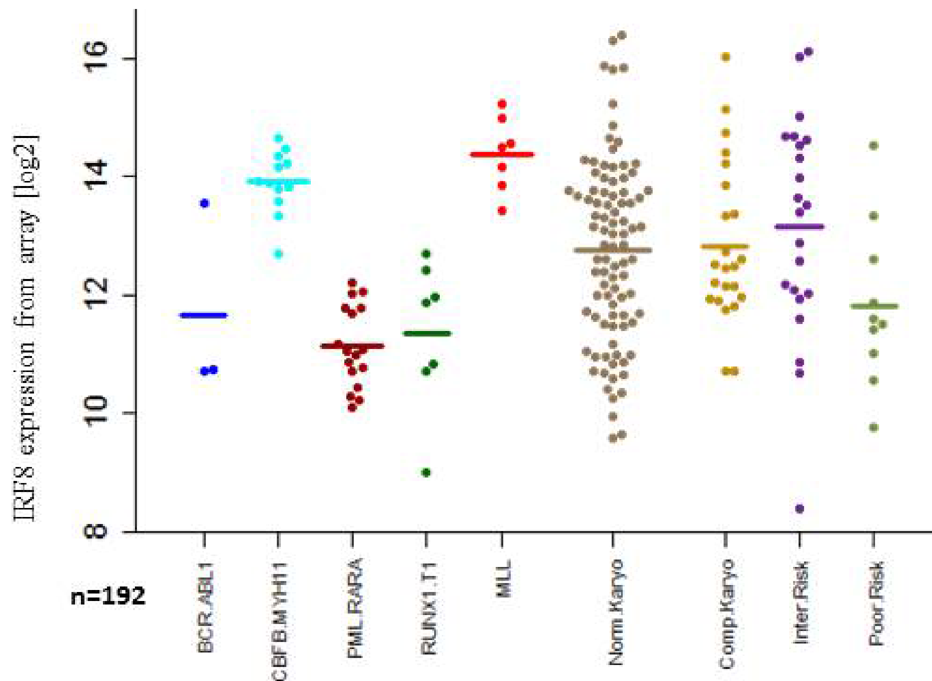

Figure S1: IRF8 expression is significantly lower in the PML-RARA subtype compared to most other subtypes of AML patient samples from TCGA. The log2 expression values of IRF8 from the Affymetrix Human Genome U133 Plus 2.0 Microarrays were shown as nine different AML subtypes: BCR-ABL1 (n=3); CBFB-MYH11 (n=12); PML/RARA (n=17); RUNX1-RUNX1T1 (n=7); MLL translocation (n=7); Normal Karyotype (n=91); Complex Cytogenetics (n=23); Intermediate Risk Cytogenetic Abnormality (n=22); Poor Risk Cytogenetic Abnormality (n=10). The AML patient microarray data were downloaded from TCGA website (https://tcga-data.nci.nih.gov/tcga/dataAccessMatrix.htm) and the patient annotation were downloaded from the cBioPortal website:

(http://www.cbioportal.org/study.do?cancer_study_id=laml_tcga_pub#clinical).

IRF8 expression in human APL is lower than in the CBFB-MYH11, MLL translocation, Normal Karyotype, Complex Cytogenetics, and Intermediate Risk Cytogenetic Abnormality subtypes.

($p<0.0001$ for APL in comparison to each of these groups). Similar data on low expression of IRF8 in M3 AMLs has been described elsewhere [16].

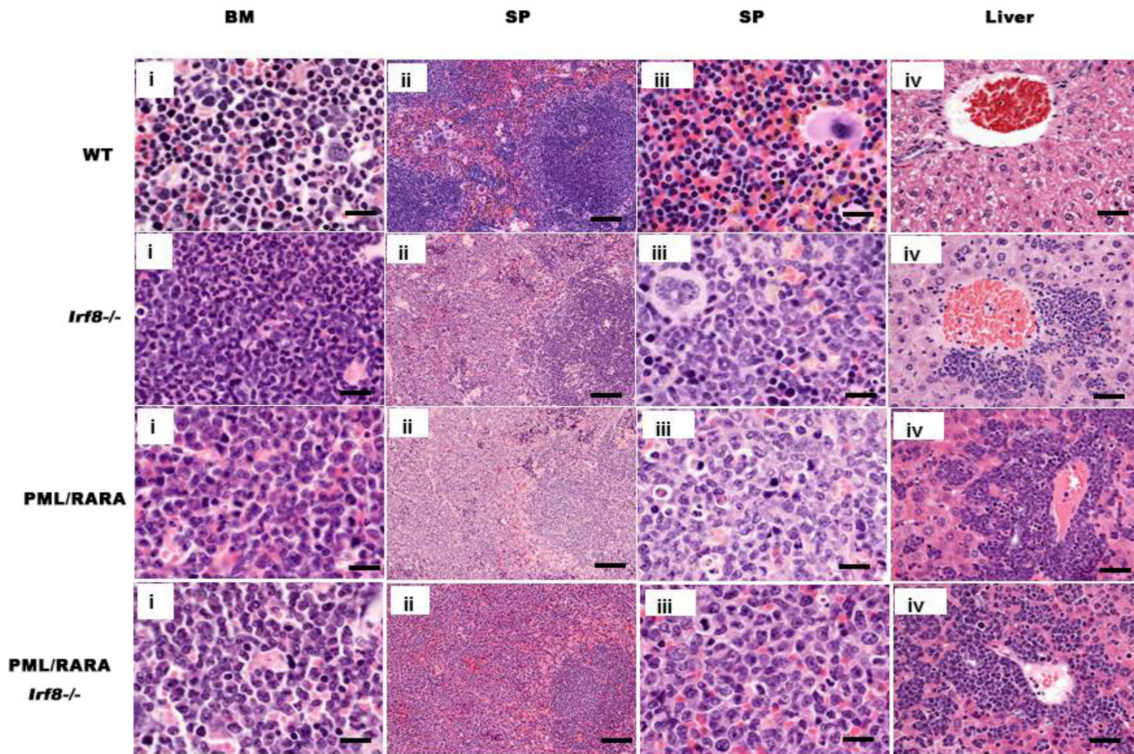

Figure S2: Representative pathology of diseased *PML/RARA, Irf8$^{-/-}$* and *PML/RARA Irf8$^{-/-}$* mice in comparison with healthy wild-type mice. (i) bone marrow, (ii and iii) spleen, (iv) liver; size bars: (i and iii) 12µm (ii) 60µm (iv) 30µm; hematoxylin & eosin stain. Note the well differentiated expansion of myeloid cells in the *Irf8$^{-/-}$* panels (MPN) in comparison to the numerous immature forms/blasts in the *PML/RARA* and *PML/RARA Irf8$^{-/-}$* panels (AML).

Supplemental Methods

Animal Protocol

Mice were bred and maintained at University of California, San Francisco under specific pathogen free conditions and in accordance with the Institutional Animal Care and Use Committee guidelines.

Western Blotting (methodological details)

Sorted cells were resuspended in 25µl of protease inhibitor cocktail-containing RIPA buffer, incubated on ice and spun. SDS was added to the supernatant, and the solution heated at 95°C. Samples were run and transferred to a nitrocellulose membrane (Biorad#160-0146) and blocked (Li-Cor#927-40100). Mouse anti-ICSBP (Invitrogen#39-8800-1/500) was added and incubated overnight in blocking buffer (0.1%Tween-20). Following a wash, membrane was incubated with goat anti-mouse IRDye (LI-COR#926-32210-1/5,000) for 1h. Following 3 washes, membrane was imaged on a LI-COR scanner. To detect ACTIN, the same membrane was incubated with rabbit anti-actin (Sigma#2066-1/7,000) for 1h. Following a wash, membrane was incubated with goat anti-rabbit IRDye (LI-COR#926-32211-1/15,000) for 1h, and imaged as above.