Supplementary Figure Legends:

Supplementary Figure 1. Doxycycline induces expression of Dnmt3a1 in mice carrying the TRE-Dnmt3a1 allele without altering levels of PML- RARα:

a) Expression of Dnmt3a1 in spleen cells determined by quantitative RT-PCR from three independent mice of each genotype maintained on doxycycline water. Beta-actin was used as loading control and data was normalized to WT bone marrow.

b) Expression of PML- RARα in spleen cells determined by quantitative RT-PCR from three independent mice of each genotype maintained on doxycycline water. Beta-actin was used as loading control and data was normalized to WT bone marrow.

c) Immunocytochemistry showing levels of Dnmt3a in skin and spleen sections from mice of the indicated genotypes. All mice were maintained on doxycycline-containing water.

Supplementary Figure 2. Flow cytometric immunophenotyping of mice expressing PML-RARα and Dnmt3a1:

Immunophenotypic analysis of bone marrow and spleen cells from Dnmt3a1, PRhom and PRhom + Dnmt3a1 mice stained with the indicated antibodies. Numbers represent the percentage of cells stained with indicated antibody combinations and gated with respect to the same population in control mice (Dnmt3a1). Based on the expression of specific cell surface markers, cells of the bone marrow and spleen were classified into the following populations: (1) hematopoietic stem and progenitors (KLS+) (c-kit+/Lin-/Sca1+); (2) hematopoietic stem cells (HSCs) (c-kit+/Lin-/Sca1+/Flk2-/CD34-); (3)

multipotent progenitors (MPPs) (c-kit+/Lin-/Sca1+/Flk2+/CD34+); (4) myeloid progenitors (MP) (c-kit+/Lin-/Sca1-); (5) granulocytes (Gr) (Gr1+/Mac1+); (6) immature myeloid cells (Mac1+/c-kit+); (7) B cells (B220+/CD19+) and (8) T cells (CD4+ or CD8+). MP cells were further sub-divided into common myeloid progenitors (CMP) (CD34+/FcγR-), granulocyte/macrophage progenitors (GMP) (CD34+/FcγR+) and megakaryocyte/erythrocyte progenitors (MEP) (CD34-/FcγR-). Flow cytometric plots of different populations in the bone marrow and spleen are shown for one representative experiment.

Supplementary Figure 3. PRhom and PRhom+Dnmt3a1 bone marrow cells differentiate similarly *in vitro*:

Graph shows the number of colonies obtained after plating 5000 bone marrow cells of each genotype on methylcellulose.

Supplementary Figure 4. Histological characterization of lungs:

Representative images of sections of lungs from mice showing the presence of eosiniphilic crystals or lymphoid infiltration. All sections are stained with hematoxylin and eosin and images are taken at 40X magnification. Lung sections with lymphoid infiltration (lymph) or presence of crystals (c) are shown. The degree of infiltration is represented as follows: + low; ++ intermediate, +++ extensive.

Supplementary Figure 5. Analysis of oxidative burst of myeloid cells in transgenic mice:

Representative histogram showing the percentage of dihydrorhodamine-positive (DHR) cells from the peritoneal cavity 72 hours post thioglycollate-induced inflammation after stimulation with PMA. DHR signal was collected on the FL-1 channel. Histograms to the left show the baseline fluorescence of unstimulated cells.

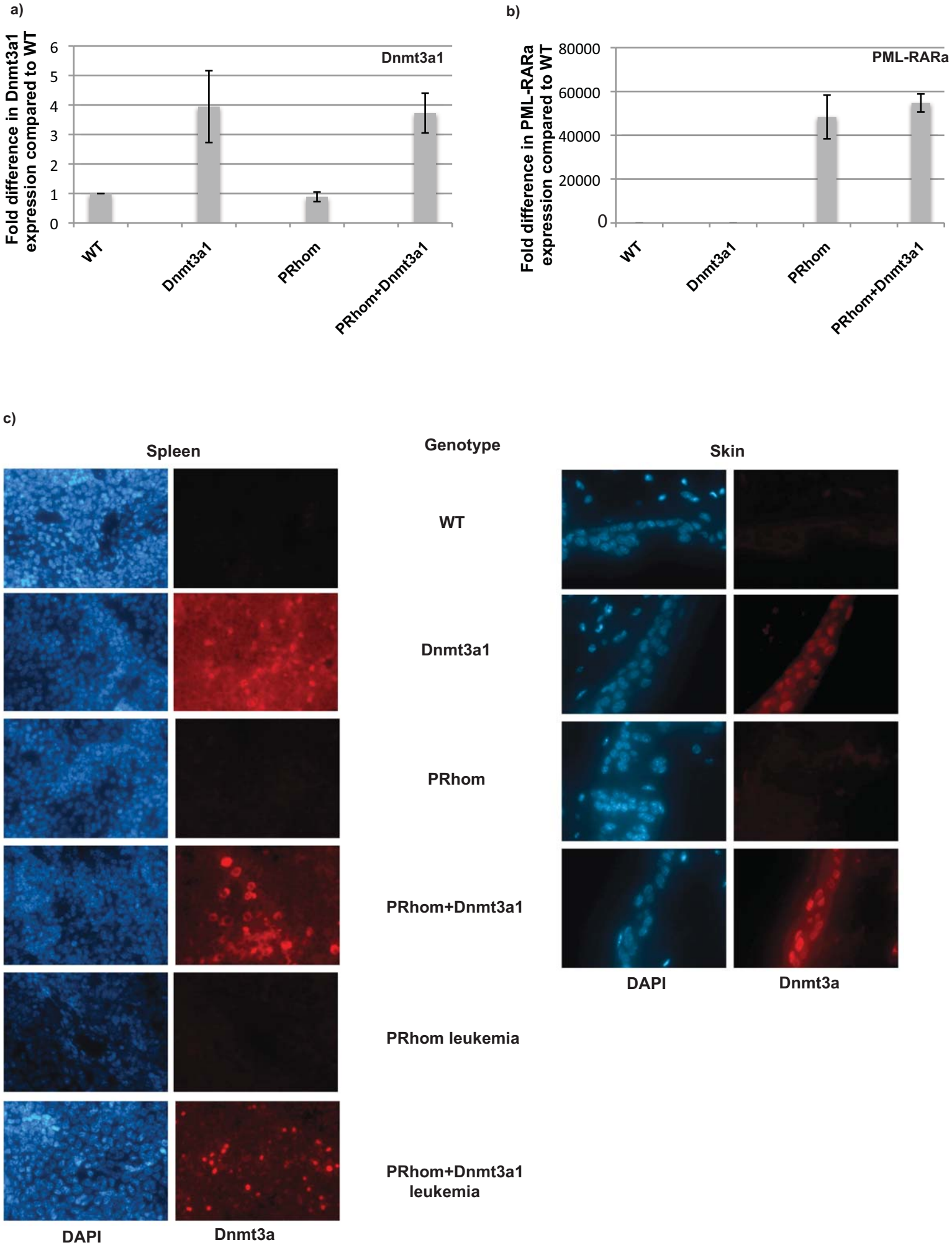
Supplementary Figure 6. Donor cells used for transplantation were obtained from pre-leukemic mice:

Cytospins of spleen cells showing the presence of mature myeloid cells in the spleen. A representative cytospin of a leukemic spleen is also shown for comparison.

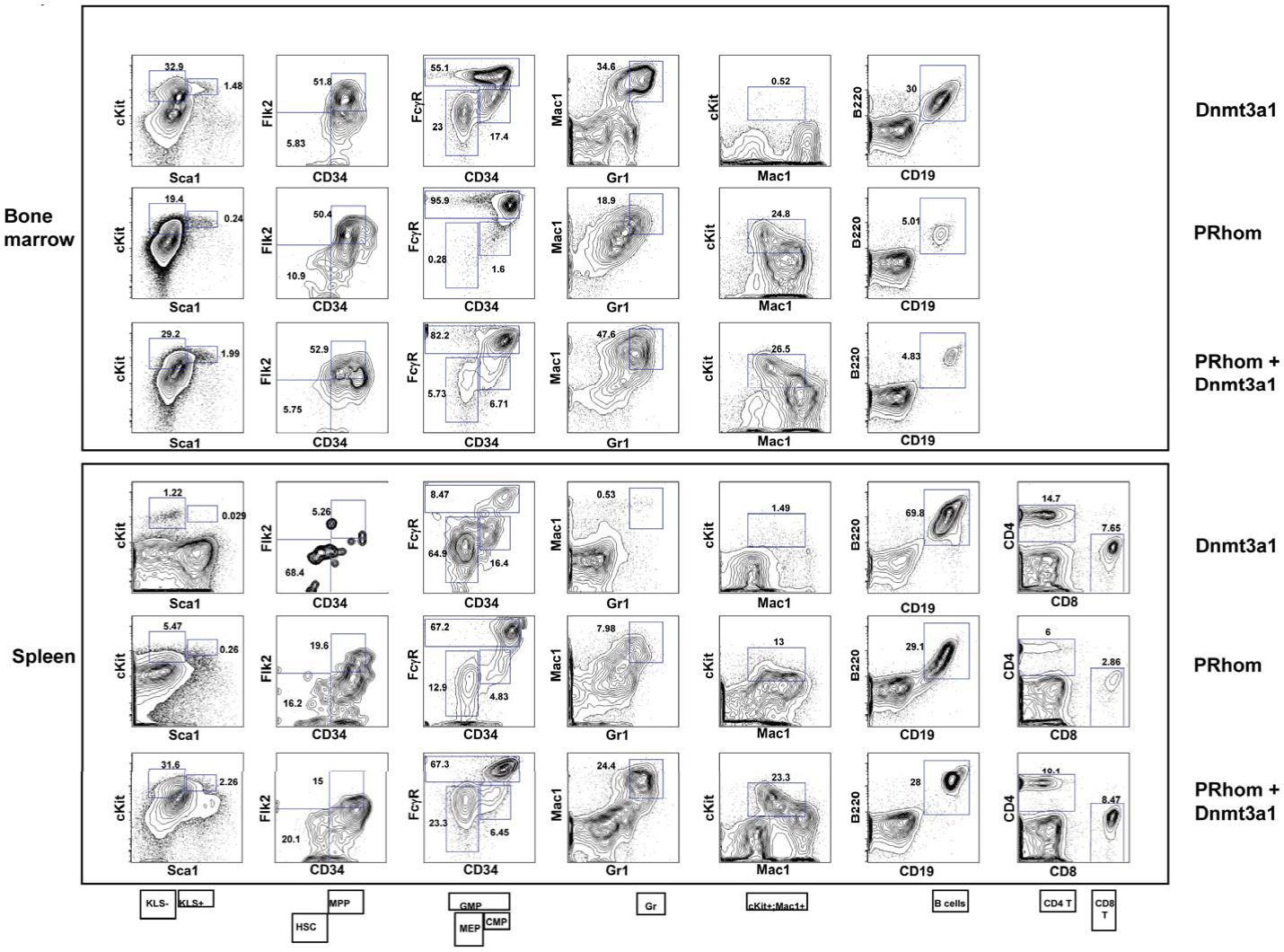
Supplementary Figure 7. Overexpression of PML-RARα and Dnmt3a1 cooperates to induce death in transplant recipients:

Graph showing survival percentage of transplanted mice receiving either PRhom or PRhom+Dnmt3a1 bone marrow transplants. Mice were monitored over a period of 200 days after transplantation. 3 donors were used for each genotype. Numbers in parenthesis indicate the number of recipients injected per donor, with the first number representing round 1 and the second number round 2. Single numbers indicate the number of recipients used in round 2.

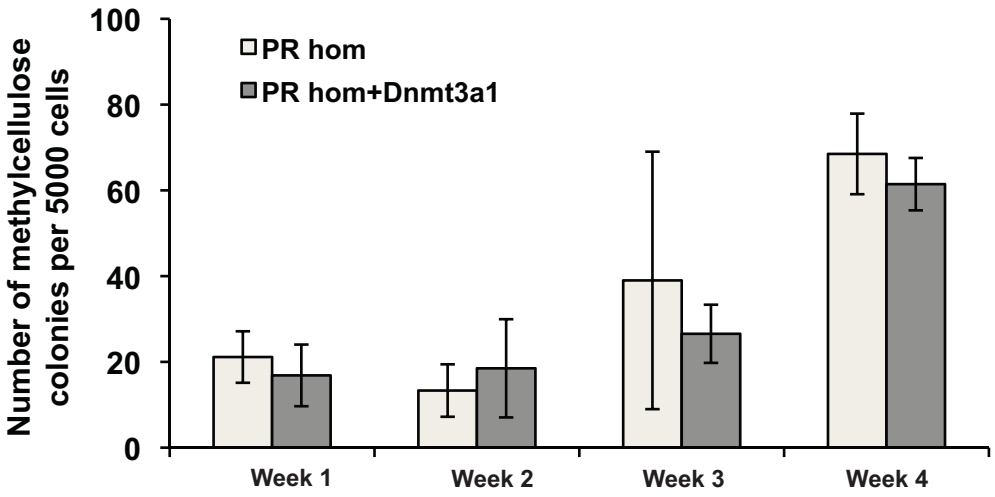
Supplementary Figure 1



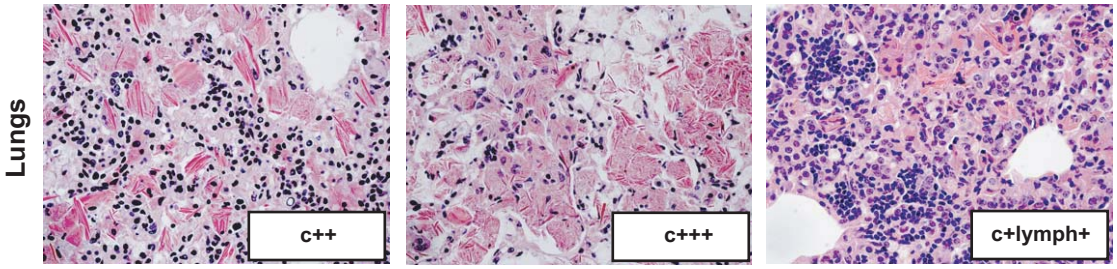
Supplementary Figure 2



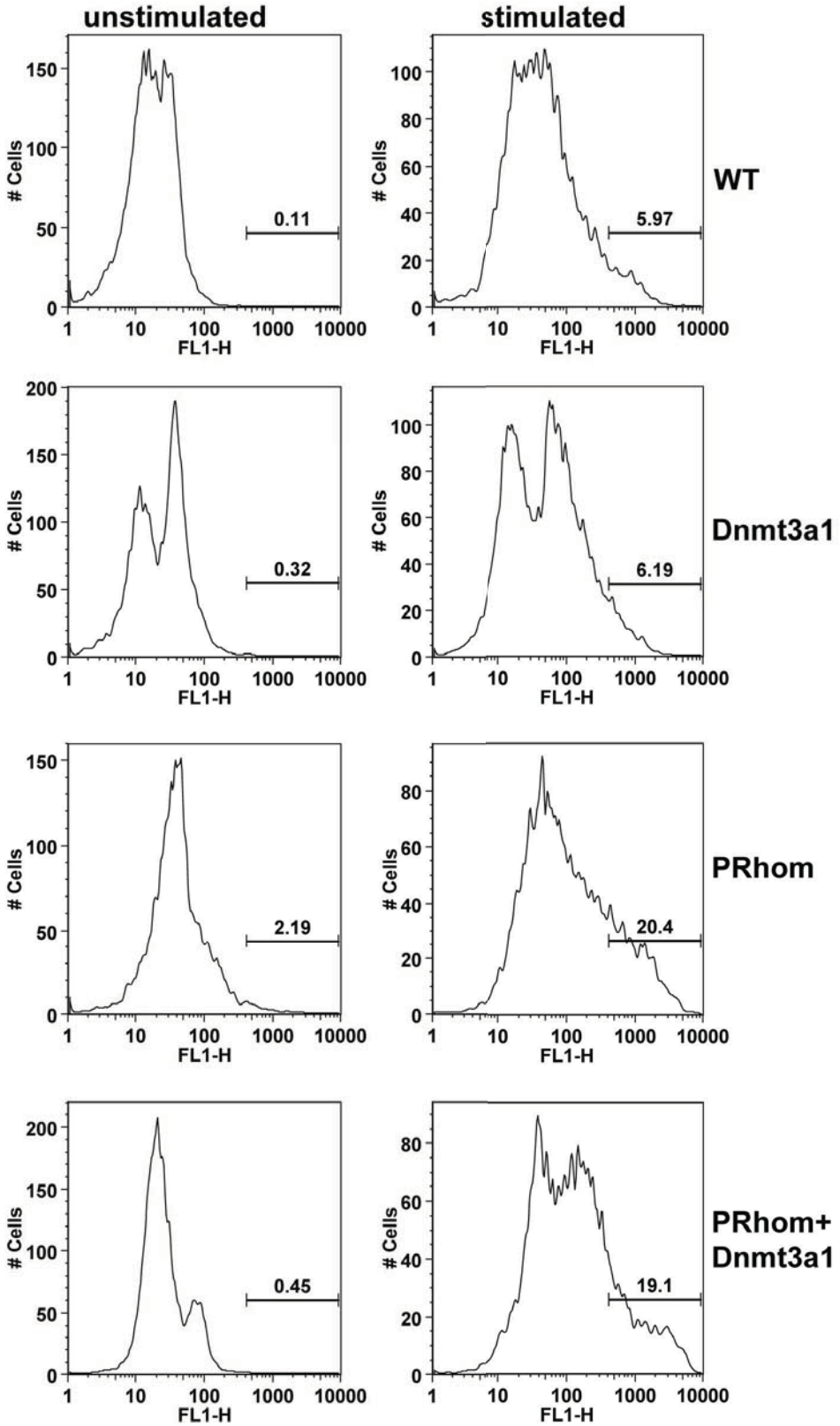
Supplementary Figure 3



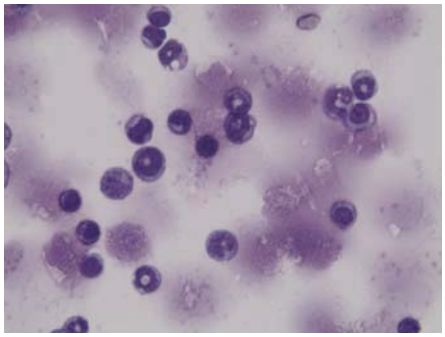
Supplementary Figure 4



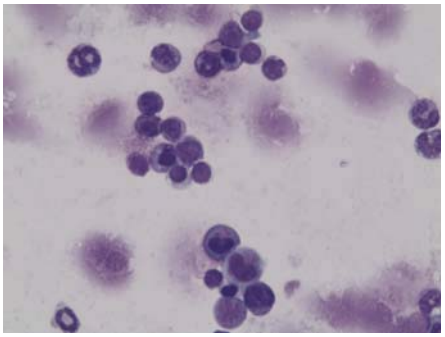
Supplementary Figure 5



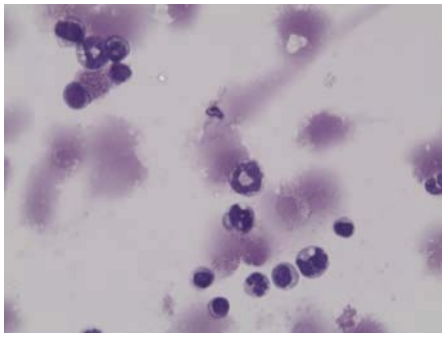
Supplementary Figure 6



PRhom Donor 2



PRhom + Dnmt3a1 Donor 1



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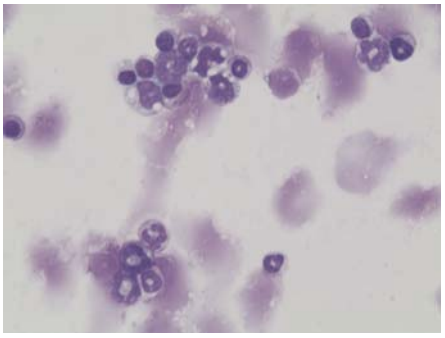
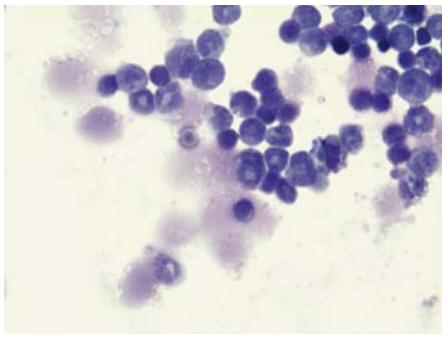
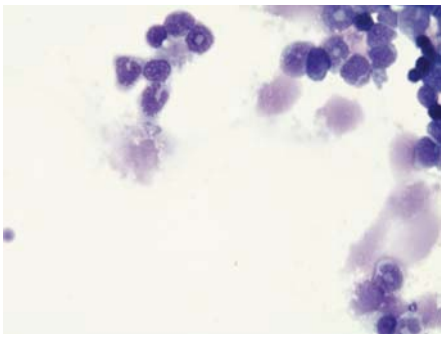


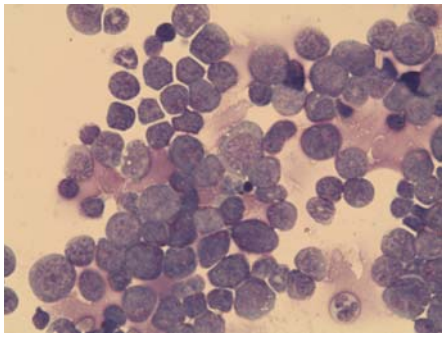
PRhom + Dnmt3a1 Donor 7



PRhom Donor 11



PRhom + Dnmt3a1 Donor 10



Leukemic recipient (Donor 1)

Supplementary Figure 7