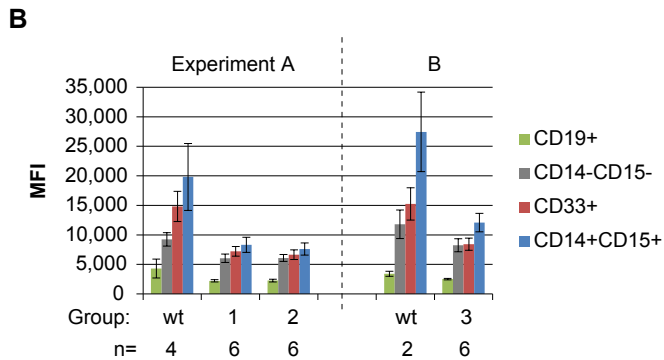
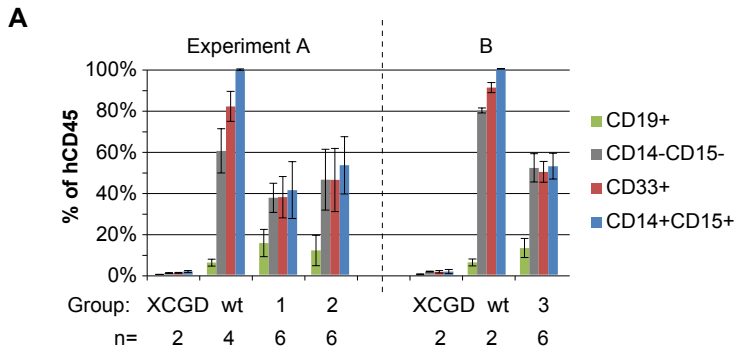
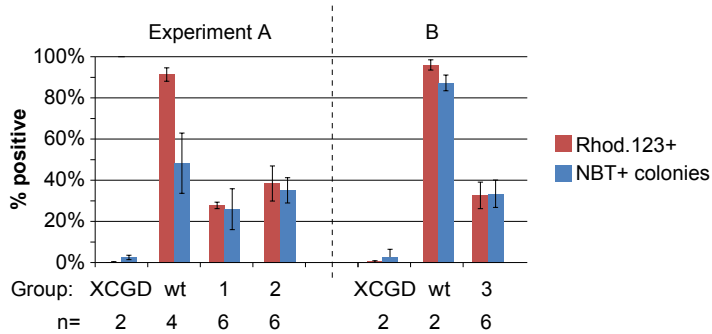


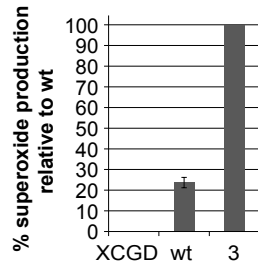
Supplementary Figure 1. Engraftment of human CD45+ cells in the bone marrow 12 weeks after transplantation, myeloid (CD33) vs. lymphoid (CD19) lineage distribution and fine mapping of myeloid maturation stages.



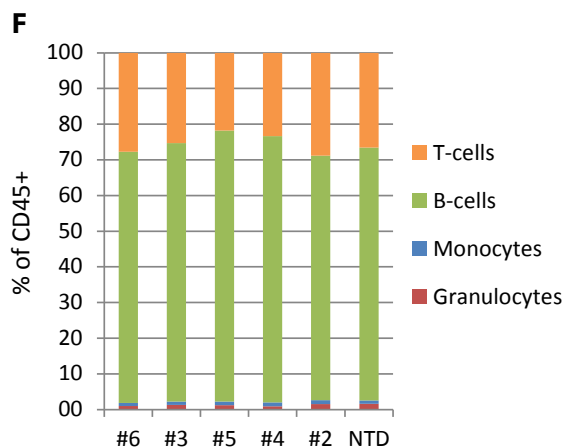
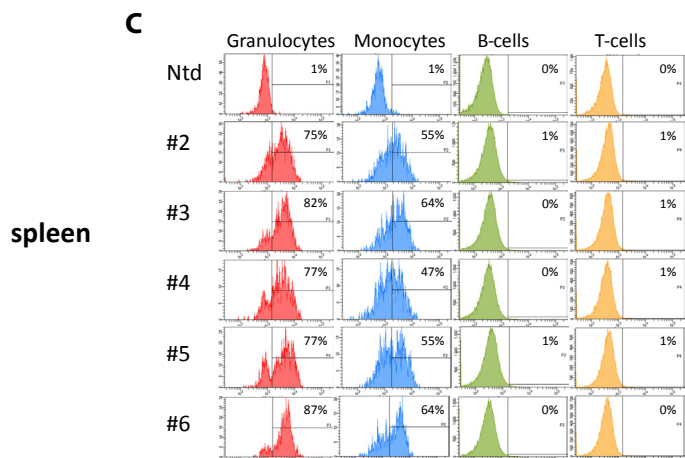
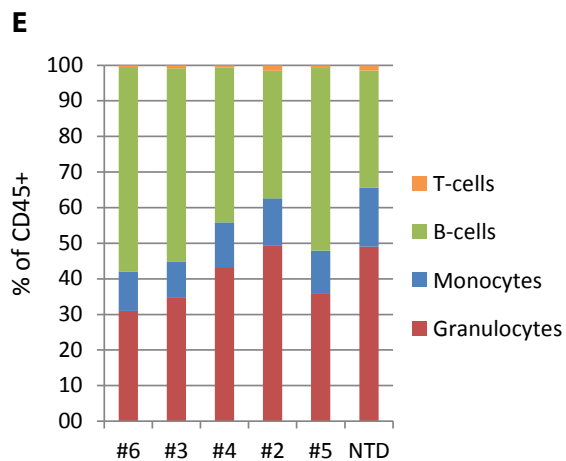
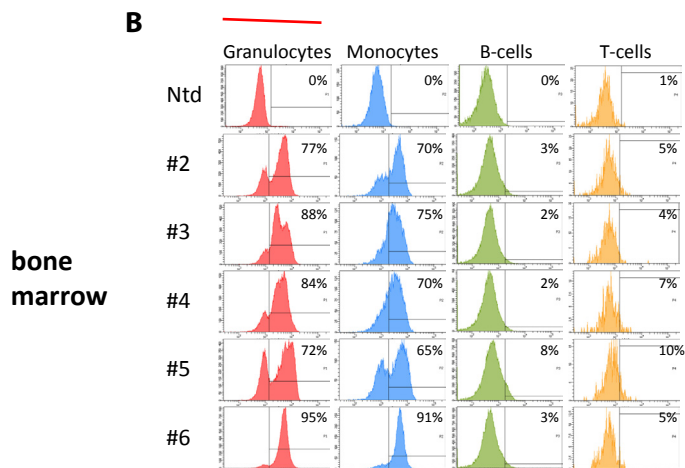
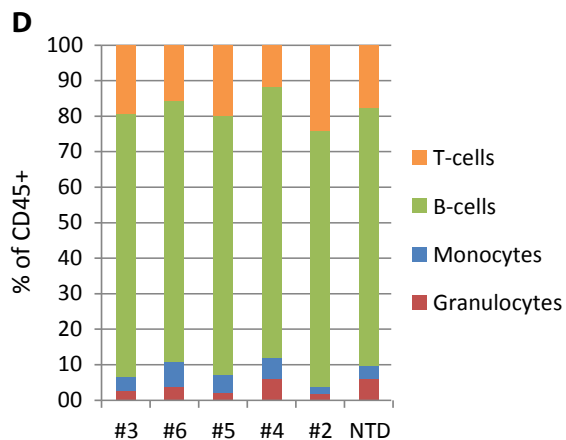
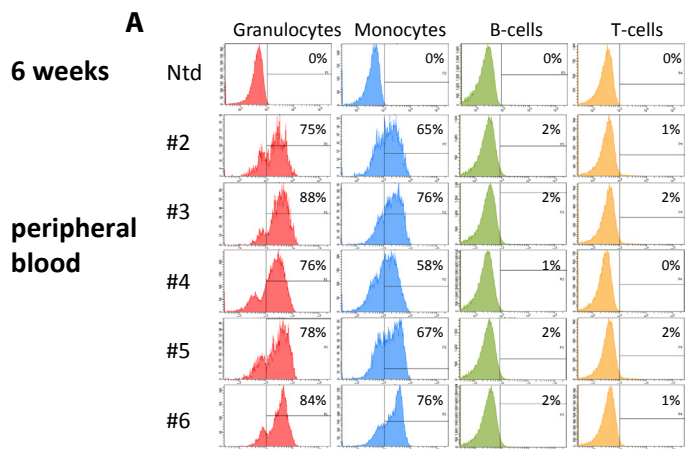
Supplementary Figure 2. Graphical summary of gp91phox expression *in vivo* in B-cells and different myeloid subpopulations (all gated on live hCD45+). A. Percentage of gp91phox expressing cells. B. Mean Fluorescence Intensity (MFI) of gp91phox expression in the respective cell populations. Vector copy numbers in bone marrow cells: Group 1:  $0.56 \pm 0.15$ , Group 2:  $1.69 \pm 0.43$ , Group 3:  $0.48 \pm 0.43$



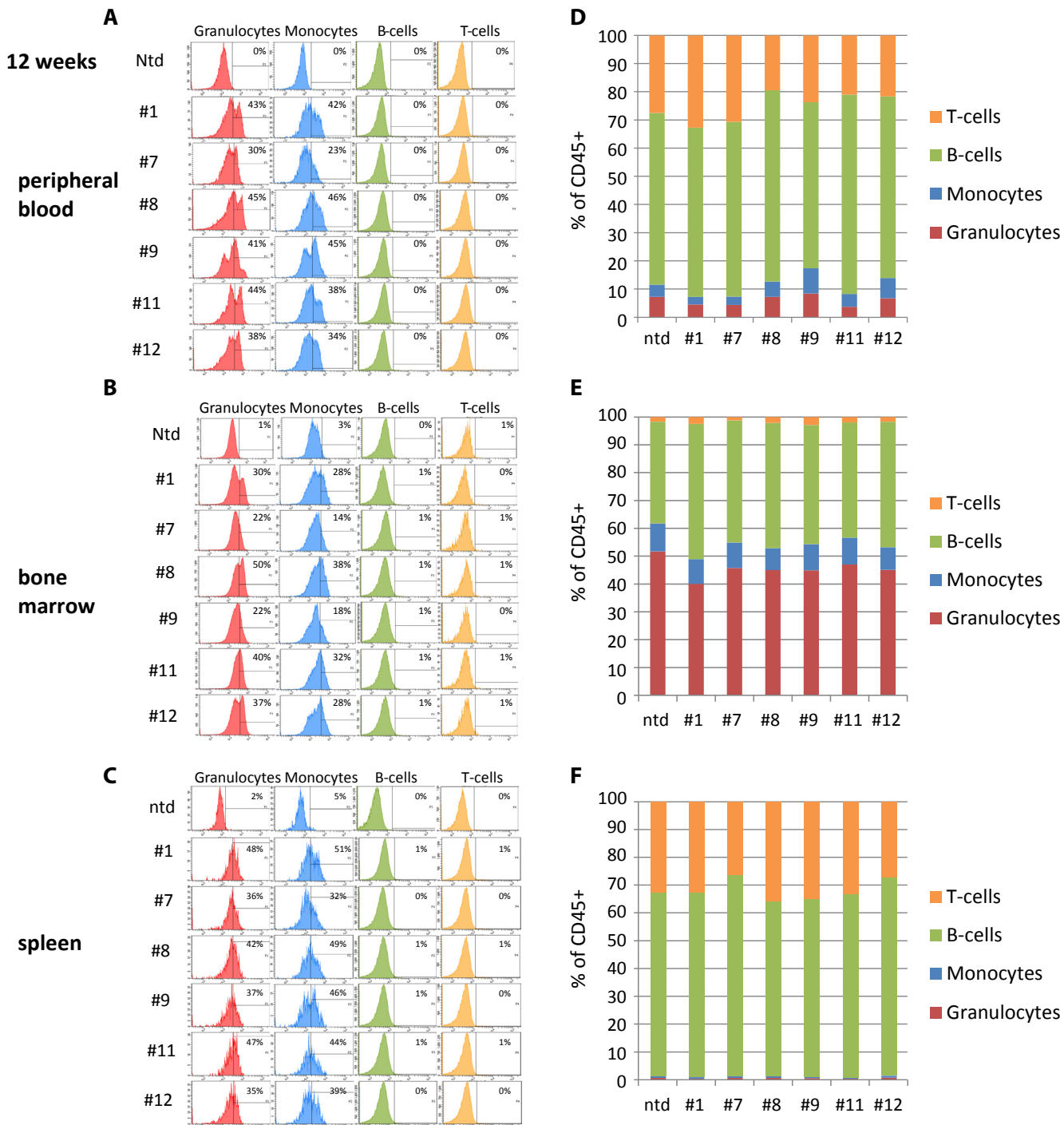
Supplementary Figure 3. NADPH-oxidase activity in in vitro differentiated hCD34+ purified from transplanted NSG animals as measured by DHR assay (red bars). The NBT-colony assays (blue bars) were performed after colony formation in semisolid media with hCD34+ purified from transplanted NSG animals. Number of independent experiments: DHR n=2 for XCGD and wt, (A and B); n=6, groups 1 and 2, n=8 group 3. NBT assays: n=4 plates per sample except for group 3 with n=16. Vector copy numbers: Group 1:  $0.34 \pm 0.08$ , Group 2:  $0.56 \pm 0.02$ , Group 3:  $0.39 \pm 0.06$



Supplementary Figure 4. Cytochrome C assay to assess superoxide production in bulk cultures of myeloid differentiated hCD34+ cells purified from the bone marrow of transplanted NSG-mice. Data is shown relative to healthy donor cells (wt) after 3 weeks of in vitro differentiation. Sample sizes: XCGD n=1, Group 3 n=6, wt n=1. VCN:  $0.39 \pm 0.06$

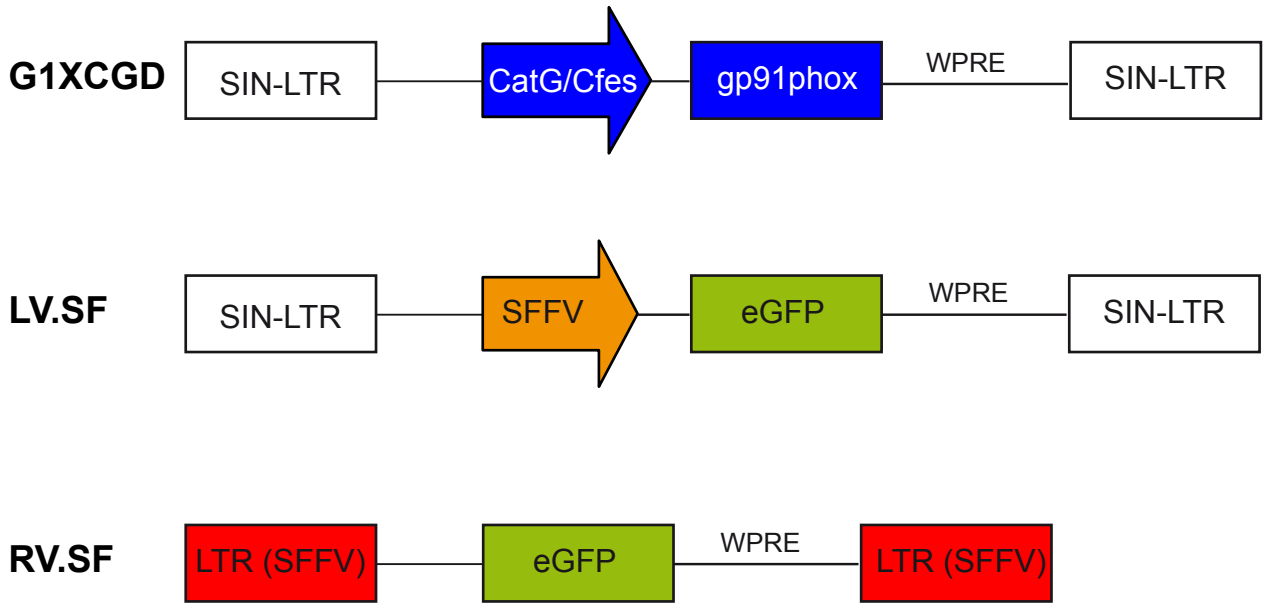


Supplementary Figure 5. Gp91phox expression (A-C) and lineage distribution (D-F) in peripheral blood (A, D), bone marrow (B, E) and spleen (C, F) of transplanted animals at week 6 post transplantation.



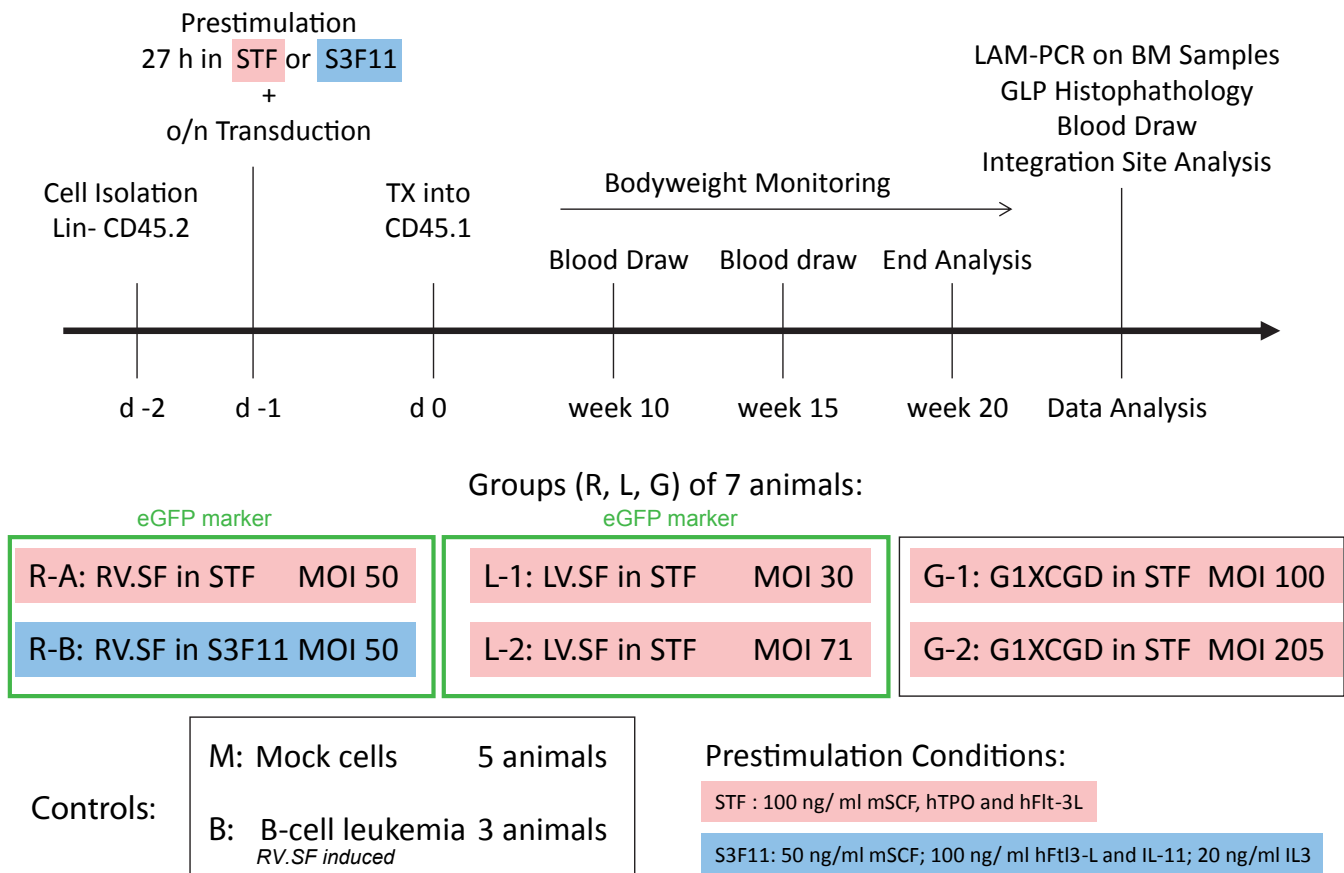
Supplementary Figure 6. Gp91phox expression (A-C) and lineage distribution (D-F) in peripheral blood (A, D), bone marrow (B, E) and spleen (C, F) of transplanted animals at week 12 post transplantation.

**Suppl. Figure 7**



**Suppl. Figure 7.** Schematic architecture of the vectors used in the genotoxicity studies. SIN = self-inactivating; CatG = Cathepsin G; Cfes = c-Fes (Promoter described in Sanitilli et al., Mol Ther.2011). WPRE = posttranscriptional regulatory element of woodchuck hepatitis virus; LTR = long-terminal repeat; eGFP = enhance green fluorescent protein; LV.SF = lentiviral vector with internal SFFV promoter; RV.SF = gammaretroviral vector with intact LTRs containing the SFFV promoter.

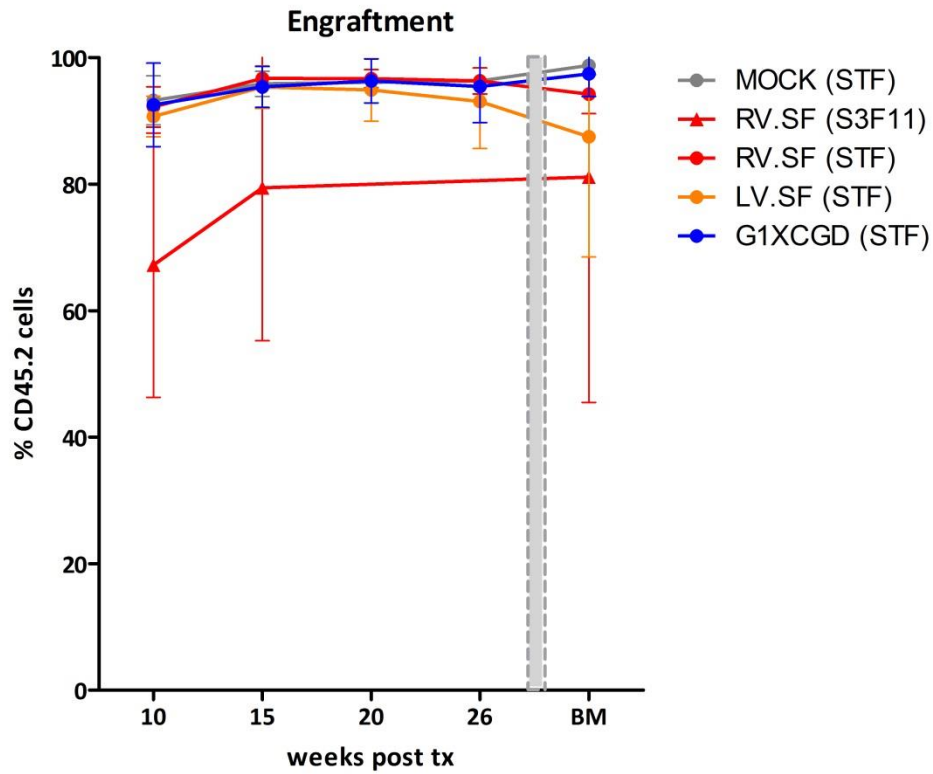
## Supplementary Figure 8



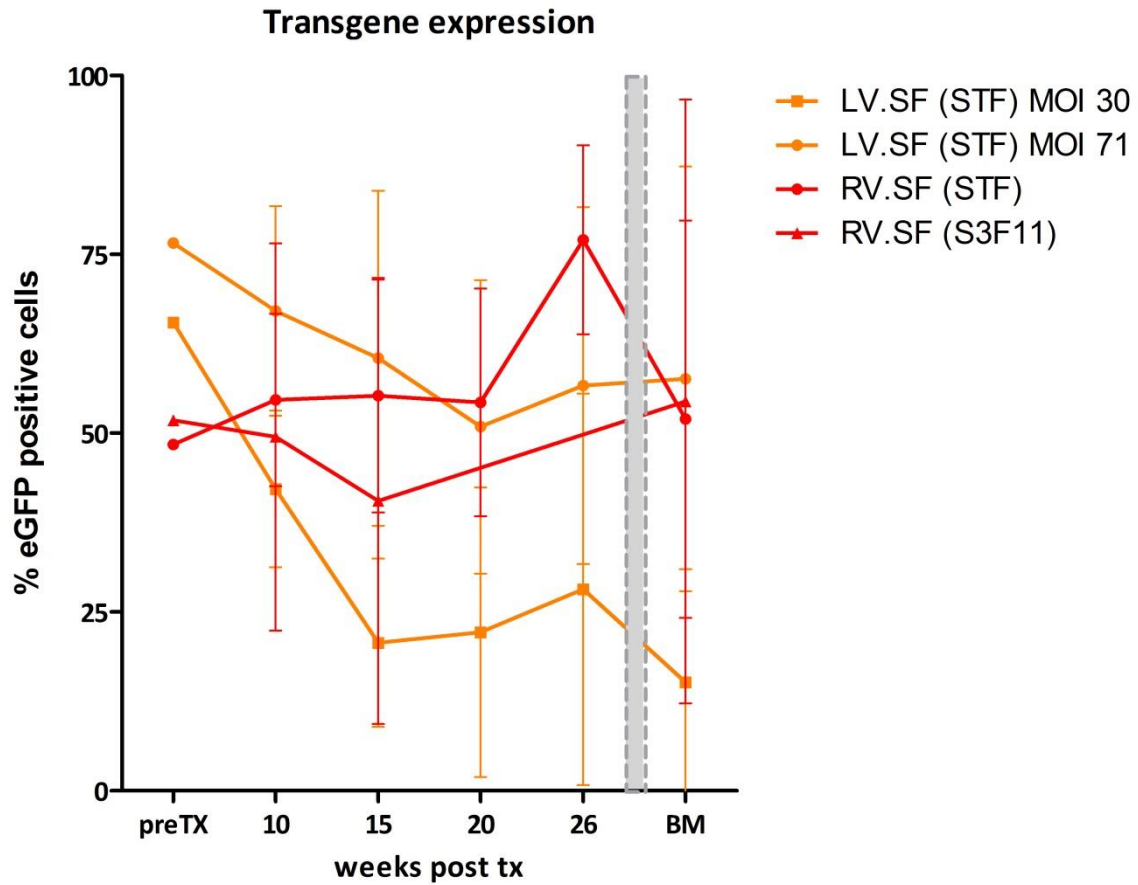
### Supplementary Figure 8. Experimental outline and summary of animal groups.

GLP = good laboratory practise; BM = bone marrow; LAM-PCR = linear amplification mediated PCR; o/n = over night; Lin- = lineage negative bone marrow cells; TX = transplantation; d = day; MOI = multiplicity of infection.

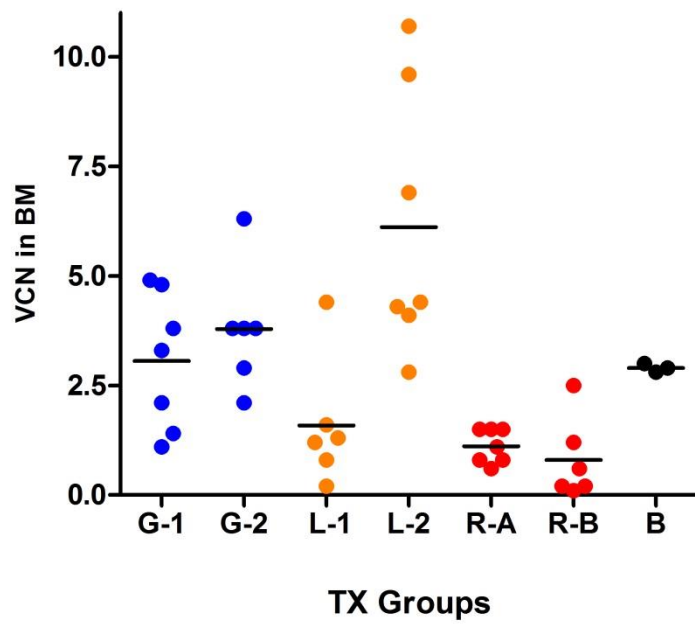




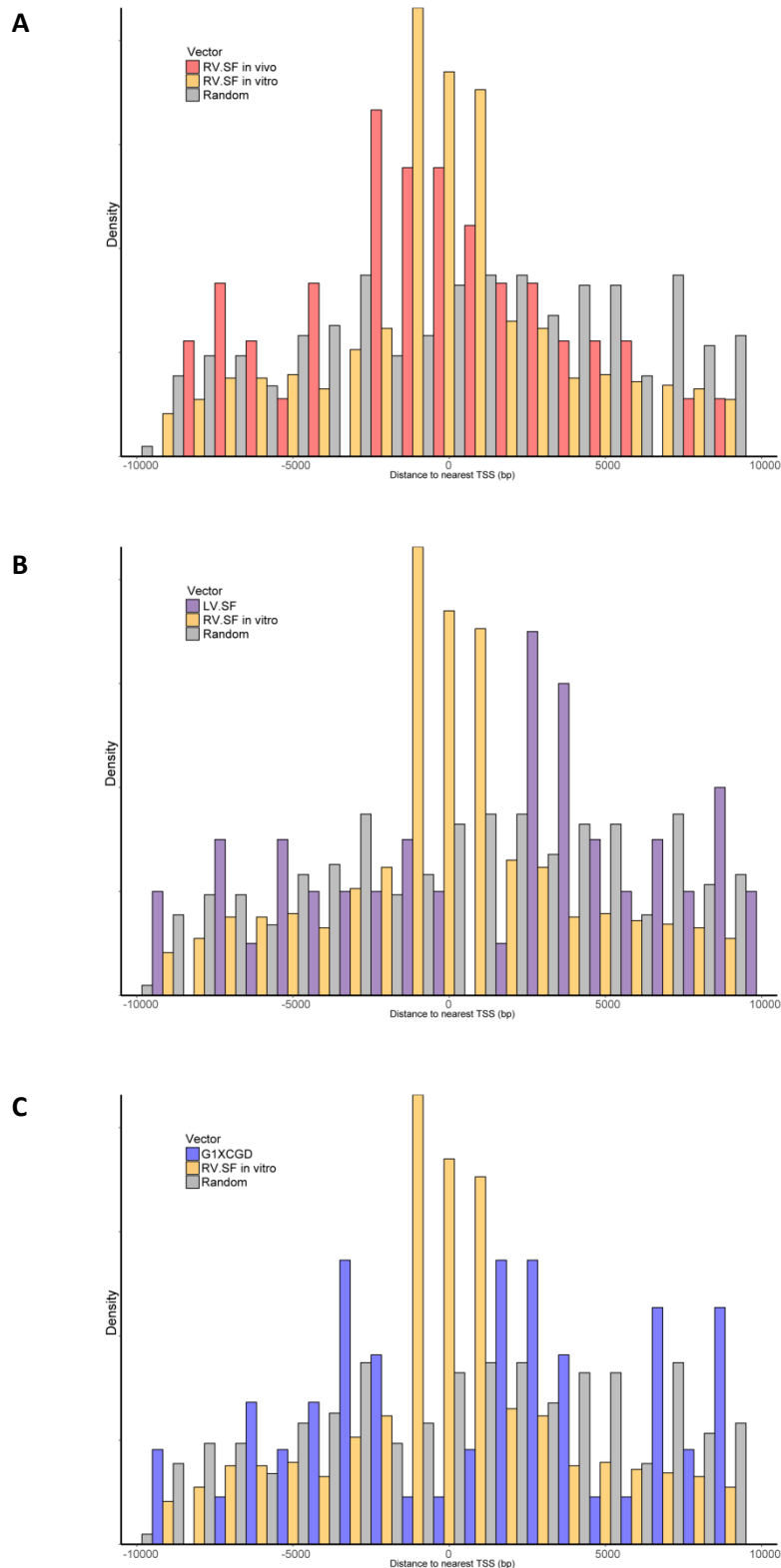
**Supplementary Figure 9a. Chimerism.** The relative amount of CD45.2 expressing donor derived leukocytes in percent of all CD45 positive cells. Values for the different bleeding time points in peripheral blood as well as bone marrow (BM) are shown per group with error bars indicating standard deviation. tx = transplantation. STF and S3F11 refer to the different medium conditions as shown in Supplementary Figure 8.



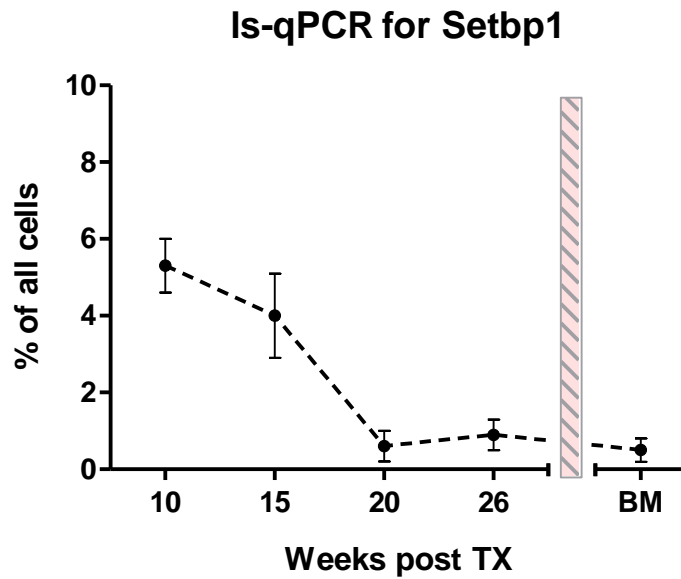
**Supplementary Figure 9b** Transgene expression for the groups carrying an eGFP marker gene. Flow cytometry results for the pre-transplantation (preTX) sample, the different bleeding time points in peripheral blood as well as bone marrow (BM) are shown per group with error bars indicating standard deviation.



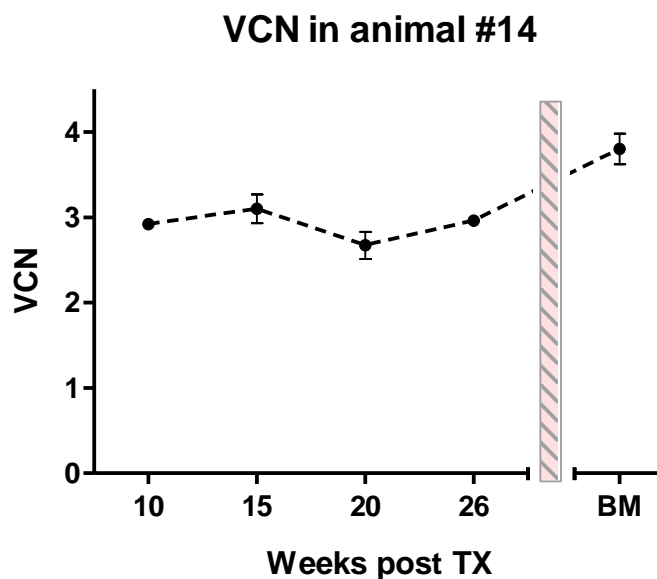
**Supplementary Figure 9c** VCN in bone marrow (BM). The mean vector copy number in the bone marrow samples of the different transplantation (TX) groups is shown. The groups and animals are explained in Supplementary Figure 8 and Table 3 of the Supplementary Information file.



**Supplementary Figure 10a-c. Insertion site distribution around the transcriptional start site (TSS).** Density plots representing frequencies of insertions in a 10-kb window around the TSS for animals transplanted with gene modified cells using RV.SF (A), LV.SF (B) or G1XCGD (C). Results are shown in comparison to *in vitro* data of RV-SF or a random *in silico* control. The RV-SF animals show a typical gammaretroviral insertion profile with integrations close to and preferentially upstream of the TSS. In contrast, the lentiviral vectors integrate rather downstream of the TSS.



**Supplementary Figure 11a. Result of Is-qPCR for Setbp1 in animal #14.** We observed a very low contribution of this insertion over time (% of all cells). On the x-axis the peripheral blood samples (10, 15, 20 and 26 weeks) are shown, which were separated (red bar) from the value measured in the bone marrow. The efficiency of a plasmid standard was used as the genomic dilutions of the BM sample did not allow for a target specific quantification.



**Supplementary Figure 11b. Vector copy number (VCN) development in animal #14.** We saw a stable VCN of  $3.1 \pm 0.5$  over the whole course of the experiment. On the x-axis the peripheral blood samples (10, 15, 20 and 26 weeks) are shown, which were separated (red bar) from the value measured in the bone marrow.

The parallel observation of stable VCN, decreasing Is-qPCR contributions and unaltered gene expression for Setbp1 (data not shown), does not suggest the development of a vector induced clonal dominance in animal#14.