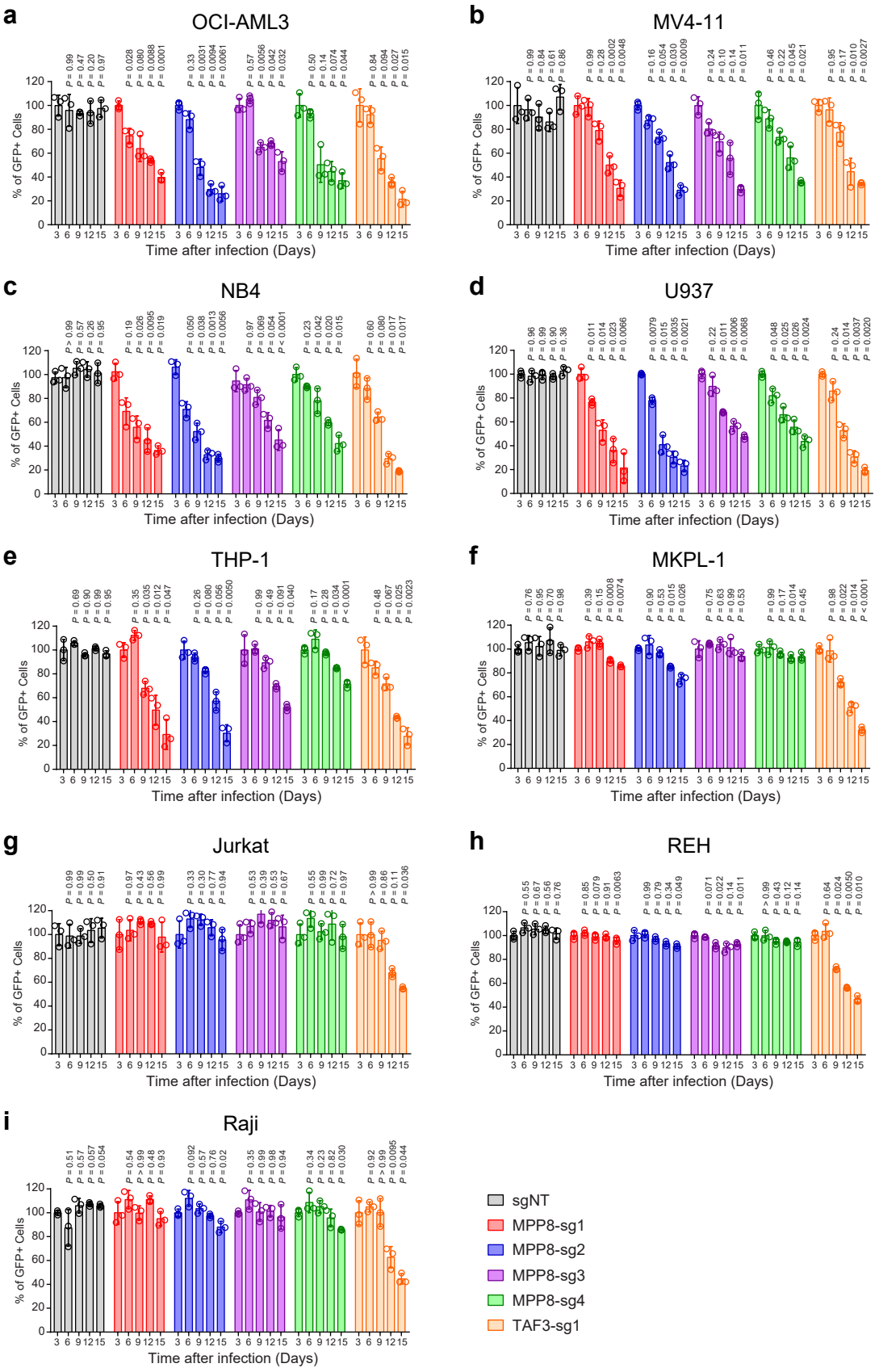
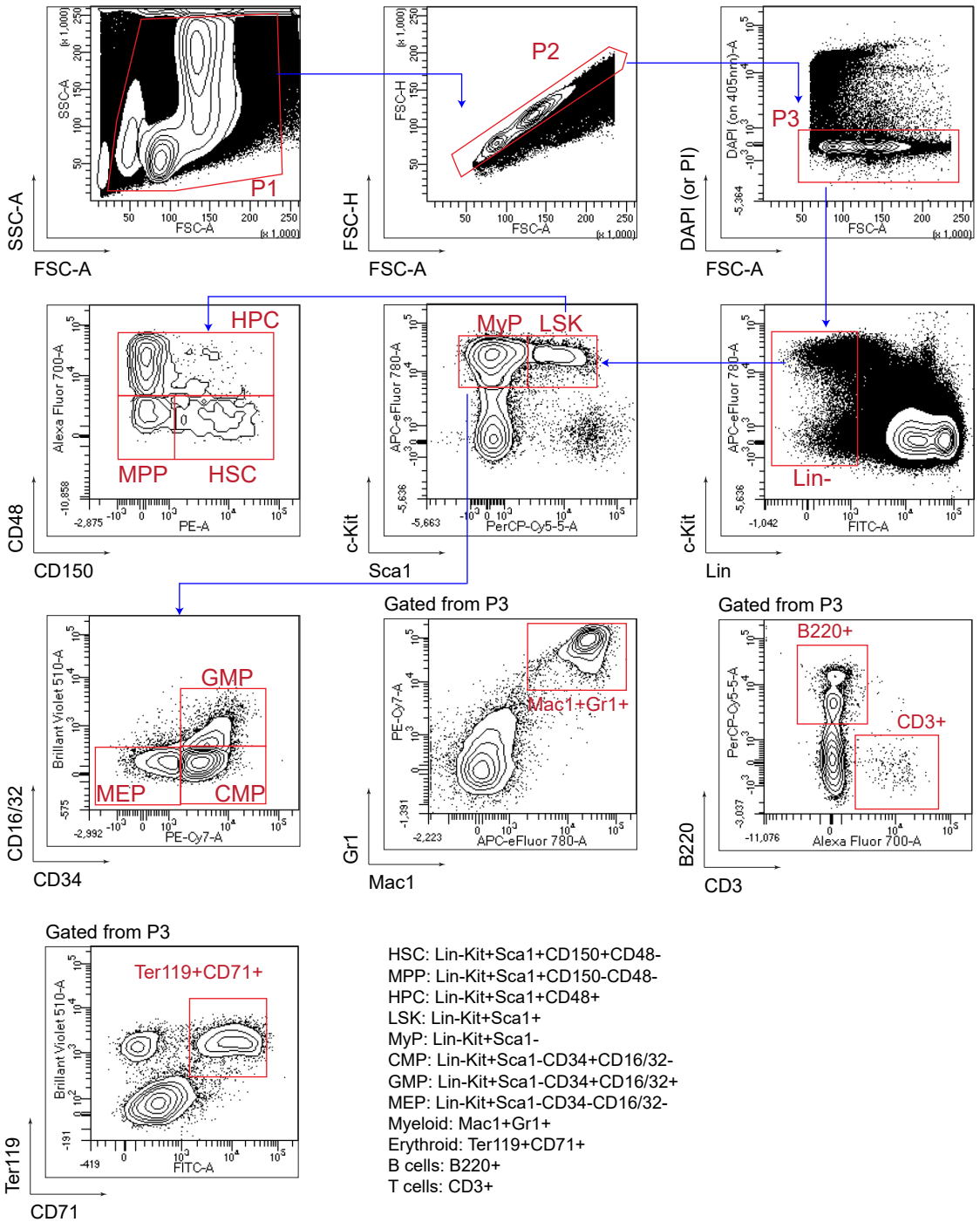
Supplementary Figure 1

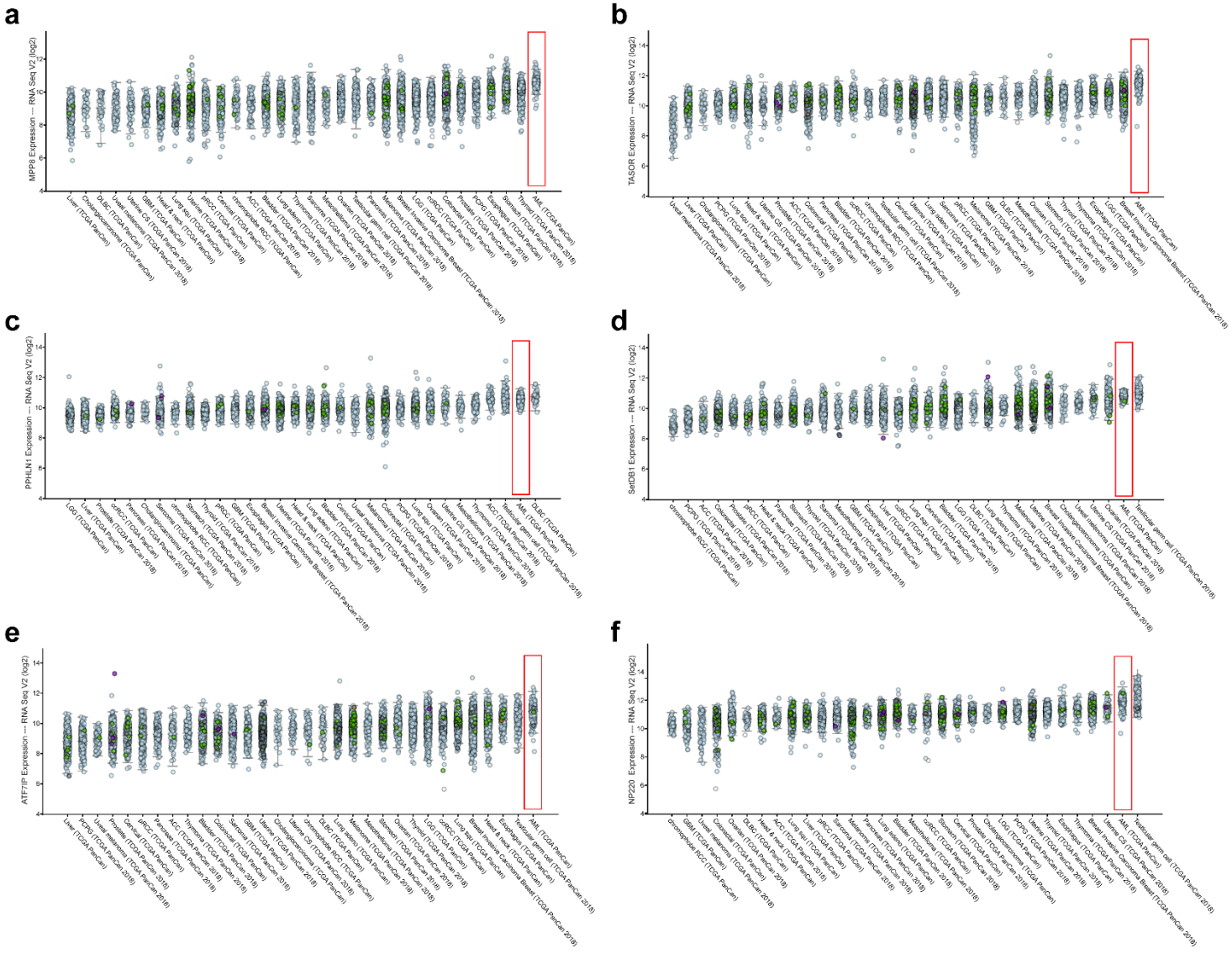


Supplementary Fig 2



HSC: Lin-Kit+Sca1+CD150+CD48-
MPP: Lin-Kit+Sca1+CD150-CD48-
HPC: Lin-Kit+Sca1+CD48+
LSK: Lin-Kit+Sca1+
MyP: Lin-Kit+Sca1-
CMP: Lin-Kit+Sca1-CD34+CD16/32-
GMP: Lin-Kit+Sca1-CD34+CD16/32+
MEP: Lin-Kit+Sca1-CD34-CD16/32-
Myeloid: Mac1+Gr1+
Erythroid: Ter119+CD71+
B cells: B220+
T cells: CD3+

Supplementary Figure 3



Supplementary Figure 1 | Validation of MPP8 as the myeloid leukemia-specific dependency. **a-i,** MPP8 depletion by 4 independent sgRNAs impaired the growth of myeloid but not lymphoid leukemia cells relative to the control sgRNA (sgNT) by the negative-selection competition assays. Six myeloid leukemia cell lines (OCI-AML3, MV4-11, NB4, U937, THP-1 and MKPL-1) and three lymphoid leukemia cell lines (Jurkat, REH and Raji) were used. The known essential gene TAF3 was used as a positive control. Results are mean ± SD (N = 3 independent experiments) and analyzed by a two-way ANOVA with Dunnett's test.

Supplementary Figure 2 | Representative flow cytometry gating strategy. Representative flow cytometry gates are shown for the analysis of various hematopoietic stem/progenitor cells and mature lineages in mouse bone marrow.

Supplementary Figure 3 | Expression of L1 regulators in human cancers. Expression of **(a)** MPP8 **(b)** TASOR **(c)** PPHLN1 **(d)** SETDB1 **(e)** ATF7IP **(f)** NP220 is shown across the TCGA panel of cancers from CBioPortal, sorted by the expression level from low to high. AML samples are indicated by the *red* boxes.

Supplementary Table 1. sgRNAs for CRISPR screening of human chromatin regulators.
The gene symbols and sgRNA sequences are shown for human chromatin regulators, positive and negative control genes. For non-targeting negative controls, the sgRNA numbers (CTRL00001 to CTRL00265) are shown.

Supplementary Table 2. Sequences of primers and sgRNAs.
The name and sequence of each primer or sgRNA are shown.

Supplementary Table 3. sgRNA enrichment or depletion by CRISPR screens in MOLM-13 and REH cells.
The gene symbol, sgRNA sequences, and mean sgRNA log2 fold changes in day 14 relative to day 0 from two independent CRISPR screens in MOLM13 and REH cells are shown.

Supplementary Table 4. List of genomic datasets used in this study.
The name, data type, cell type, GEO accession number and citation are shown.

Supplementary Table 5. Differentially expressed genes in MPP8 KO MOLM-13 cells.
The significantly upregulated or downregulated genes or annotated repetitive elements in MPP8 KO relative to WT MOLM-13 cells are shown. Differentially expressed genes or repetitive elements were identified by DESeq2 using fold change ≥ 2 and FDR-adjusted P value ≤ 1e-30.

Supplementary Table 6. List of key reagents and resources.

Supplementary Table 7. Statistical analysis of Figure 3h.