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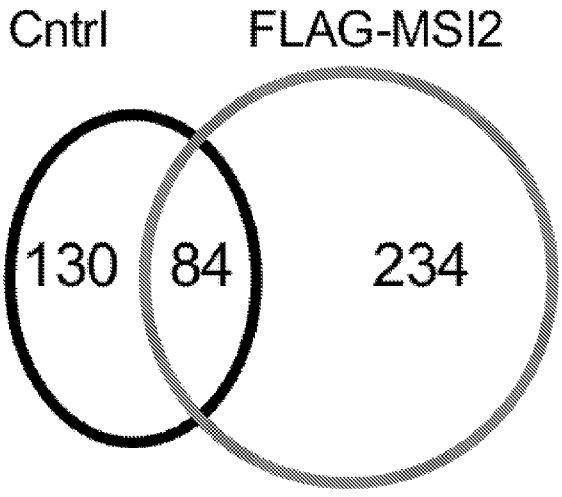


Figure 1(A)

(57) Abstract: The present disclosure relates generally to methods for preventing, ameliorating or treating leukemia. In particular, the present disclosure relates to administering a therapeutically effective amount of at least one agent to reduce the expression of synaptotagmin-binding, cytoplasmic RNA-interacting protein (SYNCRIP) to a subject diagnosed with, or at risk for acute myeloid leukemia (AML).

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METHODS FOR TREATMENT OR PREVENTION OF LEUKEMIA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to US Provisional Appl. No. 62/470,037, filed March 10, 2017, the disclosure of which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] The present technology relates generally to methods for treating, preventing, and/or ameliorating leukemia in a subject in need thereof. Also disclosed herein are methods for reducing the expression and/or activity of synaptotagmin-binding, cytoplasmic RNA-interacting protein (SYNCRIP; also known as NSAP1 or hnRNPQ1 in humans) to treat, prevent, and/or ameliorate leukemia.

BACKGROUND

[0003] The following description of the background of the present technology is provided simply as an aid in understanding the present technology and is not admitted to describe or constitute prior art to the present technology.

[0004] Acute myeloid leukemia (AML) is a genetically complex and heterogeneous set of diseases characterized by a diverse set of mutations (Lindsley, R.C. & Ebert, B.L., *Blood* 122, 3741–3748 (2013)). Overall survival of adult patients with AML has only improved modestly in the past 30 years (Maynadié, M. *et al.*, *Haematologica* 96, 55–61 (2011)). Leukemia stem cells (LSCs) are a subpopulation characterized by a self-renewal capacity and an ability to recapitulate the phenotypic heterogeneity of the disease. While somatic alterations in genetic and epigenetic mechanisms in leukemogenesis are intensively studied, how post-transcriptional and translational regulation of mRNA/protein expression influences leukemia progression and LSC function remains poorly defined.

SUMMARY OF THE PRESENT TECHNOLOGY

[0005] In one aspect, the present disclosure provides a method for treating or preventing AML in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one *SYNCRIP*-specific inhibitory nucleic acid that inhibits synaptotagmin-binding, cytoplasmic RNA-interacting protein (*SYNCRIP*) expression levels or activity in the subject. The AML may be T-cell acute lymphoblastic leukemia or B-cell acute lymphoblastic leukemia.

[0006] In some embodiments, the at least one *SYNCRIP*-specific inhibitory nucleic acid comprises a nucleic acid sequence selected from the group consisting of: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, and any complement thereof. The at least one *SYNCRIP*-specific inhibitory nucleic acid may be a siRNA, a shRNA, an antisense oligonucleotide, or a sgRNA.

[0007] Additionally or alternatively, in some embodiments of the methods of the present technology, the subject displays elevated expression levels of SYNCRIP protein in leukemic cells prior to treatment. In certain embodiments, treatment with the at least one *SYNCRIP*-specific inhibitory nucleic acid results in a decrease in SYNCRIP and/or HOXA9 levels in the subject compared to that observed prior to treatment.

[0008] In some embodiments of the methods of the present technology, the subject has been diagnosed as having AML. Signs or symptoms of AML may comprise one or more of leukemic cell proliferation, enlarged lymph nodes, anemia, neutropenia, leukopenia, leukostasis, chloroma, granulocytic sarcoma, myeloid sarcoma, fatigue, weakness, dizziness, chills, headaches, shortness of breath, thrombocytopenia, excess bruising and bleeding, frequent or severe nosebleeds, bleeding gums, gum pain and swelling, headache, weakness in one side of the body, slurred speech, confusion, sleepiness, blurry vision, vision loss, deep venous thrombosis (DVT), pulmonary embolism, bone or joint pain, swelling in the abdomen, seizures, vomiting, facial numbness, defects in balance, weight loss, fever, night sweats, and loss of appetite.

[0009] In any of the above embodiments of the methods disclosed herein, the subject may harbor one or more point mutations in *NRAS, DNMT3A, FLT3, KIT, IDH1, IDH2, CEBPA* and *NPM1* and/or one or more gene fusions selected from the group consisting of *CBFB-MYH11, DEK-NUP214, MLL-MLLT3, PML-RARA, RBM15-MKL1, RPN1-EVI1* and *RUNX1-RUNX1T1*. In certain embodiments, the subject is human.

[0010] Additionally or alternatively, in some embodiments of the methods of the present technology, the at least one *SYNCRIP*-specific inhibitory nucleic acid is administered orally, topically, intranasally, systemically, intravenously, subcutaneously, intraperitoneally, intradermally, intraocularly, iontophoretically, transmucosally, or intramuscularly. In some embodiments, the at least one *SYNCRIP*-specific inhibitory nucleic acid is administered daily for 6 weeks or more. In other embodiments, the at least one *SYNCRIP*-specific inhibitory nucleic acid is administered daily for 12 weeks or more.

[0011] Additionally or alternatively, in some embodiments, the methods further comprise separately, sequentially or simultaneously administering one or more additional therapeutic agents to the subject. Examples of additional therapeutic agents include cyclophosphamide, fluorouracil (or 5-fluorouracil or 5-FU), methotrexate, edatrexate (10-ethyl-10-deaza-aminopterin), thiotepa, carboplatin, cisplatin, taxanes, paclitaxel, protein-bound paclitaxel, docetaxel, vinorelbine, tamoxifen, raloxifene, toremifene, fulvestrant, gemcitabine, irinotecan, ixabepilone, temozolmide, topotecan, vincristine, vinblastine, eribulin, mutamycin, capecitabine, anastrozole, exemestane, letrozole, leuprolide, abarelix, buserlin, goserelin, megestrol acetate, risedronate, pamidronate, ibandronate, alendronate, denosumab, zoledronate, trastuzumab, tykerb, anthracyclines (*e.g.*, daunorubicin and doxorubicin), cladribine, midostaurin, bevacizumab, oxaliplatin, melphalan, etoposide, mechlorethamine, bleomycin, microtubule poisons, annonaceous acetogenins, chlorambucil, ifosfamide, streptozocin, carmustine, lomustine, busulfan, dacarbazine, temozolomide, altretamine, 6-mercaptopurine (6-MP), cytarabine, floxuridine, fludarabine, hydroxyurea, pemetrexed, epirubicin, idarubicin, SN-38, ARC, NPC, campothecin, 9-nitrocamptothecin, 9-aminocamptothecin, rubifen, gimatecan, diflomotecan, BN80927, DX-8951f, MAG-CPT, amsacnne, etoposide phosphate, teniposide, azacitidine (Vidaza), decitabine, accatin III, 10-deacetyltaxol, 7-xylosyl-10-deacetyltaxol, cephalomannine, 10-deacetyl-7-epitaxol, 7-epitaxol, 10-deacetylbaccatin III, 10-deacetyl cephalomannine, streptozotocin, nimustine, ranimustine, bendamustine, uramustine, estramustine, mannosulfan, camptothecin, exatecan, lurtotecan, lamellarin D9-aminocamptothecin, amsacrine, ellipticines, aurintricarboxylic acid, HU-331, or combinations thereof.

[0012] In another aspect, the present disclosure provides a method for inhibiting leukemic cell proliferation in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an *SYNCRIP*-specific inhibitory nucleic acid, wherein the subject suffers from a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP*.

[0013] Also disclosed herein are methods for monitoring the therapeutic efficacy of an *SYNCRIP*-specific inhibitory nucleic acid that targets *SYNCRIP* expression and/or activity in a subject diagnosed with AML comprising: (a) detecting SYNCRIP protein levels in a test sample obtained from the subject after the subject has been administered the *SYNCRIP*-specific inhibitory nucleic acid; and (b) determining that the *SYNCRIP*-specific inhibitory nucleic acid is effective when the SYNCRIP protein levels in the test sample are reduced

compared to that observed in a control sample obtained from the subject prior to administration of the *SYNCRIP*-specific inhibitory nucleic acid. The *SYNCRIP*-specific inhibitory nucleic acid may be a siRNA, a shRNA, an antisense oligonucleotide, or a sgRNA. The test sample may be tissues, cells or biological fluids (blood, plasma, saliva, urine, serum *etc.*) present within a subject. In certain embodiments, the method further comprises detecting HOXA9 levels in the subject. Additionally or alternatively, in some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid comprises a nucleic acid sequence selected from the group consisting of: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, and SEQ ID NO: 21, and any complement thereof.

[0014] Also provided herein are kits comprising one or more *SYNCRIP*-specific inhibitory nucleic acids comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-2, 18-21, and any complement thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1(A) shows a Venn diagram showing mass spectrometry analysis of Flag-MSI2 immunoprecipitation in K562 cells transduced with FLAG-MSI2 or empty vector.

[0016] Figure 1(B) shows a summary of the pooled shRNA screening strategy from primary leukemia cells.

[0017] Figure 1(C) shows a Waterfall plot depicting normalized depletion levels of all shRNAs in bone marrow (BM), generated from the data in Figure 15. Top candidate genes included SYNCRIP, Caprin1, Dyrk2, Hnrnpr, Cct3, Mybbp1a, and Hnrnpa3.

[0018] Figure 1(D) shows a Venn diagram showing score of 24 hits in bone marrow and spleen samples.

[0019] Figure 1(E) shows a heatmap depicting normalized depletion levels of all shRNAs targeting top 24 genes scored both in bone marrow (BM) and spleen (SP), generated from the data in Figure 15 and Figure 16.

[0020] Figure 1(F) shows a pie chart showing the scoring percentage of each screening pool in comparison to the predicted score based on pool representation.

[0021] Figure 1(G) shows Gene Ontology (GO) analysis of the top 24 genes scored in *in vivo* screen.

[0022] Figure 1(H) shows log_2fold depletion in the bone marrow (BM) and spleen (SP) of all the shRNAs against seven candidate genes in the pooled shRNA screen. error bars, s.e.m **p < 0.01 two tailed *t* test.

[0023] Figure 1(I) shows colony formation was impaired in KD leukemia cells. The number of colonies formed was normalized to that of control MLL-AF9 leukemia cells or control normal c-kit enriched bone marrow cells. n=4 independent experiments; error bars, s.e.m. P value calculated by two tailed *t* test.

[0024] Figure 2(A) shows the effects of SYNCRIP Knock Down (KD) in mouse MLL-AF9 leukemia cells.

[0025] Figure 2(B) shows that shRNA-mediated depletion of SYNCRIP promoted myeloid differentiation of leukemia cells. Representative FACS plot of control and SYNCRIP Knock Down (KD) leukemia cells.

[0026] Figure 2(C) shows the quantitative summary of FACS analysis of Gr-1 and Mac-1 expression in control and SYNCRIP Knock Down (KD) leukemia cells 3 days and 4 days post transduction, n=3 and n=5, respectively, independent experiments; error bars, s.e.m. ** p<0.01, * p<0.05 two sided *t* test.

[0027] Figure 2(D) shows Giemsa staining of control and SYNCRIP Knock Down (KD) leukemia cells at 4 days post transduction. Original magnification 63X, 1.4 NA Scale bars: 10 μM.

[0028] Figure 2(E) shows Annexin-V expression assessed by flow cytometry 5 days post transduction. n=3 independent experiments; error bars, s.e.m. ** p<0.01, * p<0.05 two tailed *t* test.

[0029] Figure 2(F) shows Kaplan Meier analysis of leukemia-free survival outcomes after injection of SYNCRIP depleted or control cells into sub-lethally irradiated mice. n=10 for each group, Mantel-Cox test *** p<0.001, **** p<0.0001.

[0030] Figure 2(G) shows the reduction of SYNCRIP expression in MLL-AF9 leukemia cells with mutant NRAS expressing a rtTA (RN2 cells) and transduced with tet(O)-inducible Cas9-GFP expressing guide RNAs specific for *SYNCRIP* (gRNA1 and gRNA3) or Cas9-GFP empty gRNA (Cas9-EV).

[0031] Figure 2(H) shows cells from Figure 2(g) plated and counted for cellular growth control and two gRNAs. n=3 independent experiments; error bars, s.e.m. * $p<0.05$ two tailed *t* test.

[0032] Figure 2(I) shows cells from 2(G) were plated into methylcellulose colony assay. n=4 independent experiments; error bars, s.e.m. * $p<0.05$ two tailed *t* test.

[0033] Figure 2(J) shows Kaplan Meier analysis of leukemia-free survival outcomes after injection of RN2 cells overexpressing SYNCRIP or carrying control- empty vector into sub-lethally irradiated mice n=10 for each group, Mantel-Cox test *** $p<0.001$.

[0034] Figure 2(K) shows that overexpression of SYNCRIP rescued colony forming ability of RN2 cells depleted of endogenous SYNCRIP. n=4 independent experiments; error bars, s.e.m. ** $p<0.01$ two tailed *t* test.

[0035] Figure 2(L) shows the quantitative summary of FACS analysis of Gr-1 and Mac-1 expression in Cas9-EV and *SYNCRIP*-gRNAs transduced leukemia cells in Figure 2(K), n=3 independent experiments; error bars, s.e.m. *$p<0.05$, ** $p<0.01$ two tailed *t* test.

[0036] Figure 3(A) shows the *Syncrip* locus and CRISPR/Cas9 targeting strategy for generation of *Syncrip*-CR-knockout (KO).

[0037] Figure 3(B) shows the experimental scheme for generation of hematopoietic *Syncrip*-CR-KO using CRISPR/Cas9 approach and bone marrow transplantation of fetal liver cells.

[0038] Figure 3(C) shows FACS analysis of hematopoietic stem and progenitor cells in WT and *Syncrip*-CR-KO fetal livers.

[0039] Figure 3(D) shows FACS histograms of SYNCRIP intracellular staining of CD45.2 positive bone marrow cells isolated from WT and *Syncrip*-CR-KO recipient mice.

[0040] Figure 3(E) shows immunoblot analysis of CD45.2 positive bone marrow cells isolated from WT and *Syncrip*-CR-KO recipient mice.

[0041] Figure 3(F) shows quantitative summary of FACS analysis of hematopoietic stem and progenitor compartments in WT and *Syncrip*-CR-KO recipient mice. LIVE: total bone marrow cells; LSK: $Lin^{-}Sca1^{+}Kit^{-}$ cells; PROG: Progenitor cells; GMP: Granulocyte Macrophage progenitor; CMP: Common Myeloid progenitor; MEP: Megakaryocyte-Erythrocyte progenitor. WT n=9; CR-KO n=5.

[0042] Figure 3(G) shows an experimental scheme for LSK-derived MLL-AF9 leukemia transplantation model and secondary bone marrow transplantation.

[0043] Figure 3(H) shows the quantitative summary of FACS analysis of hematopoietic stem and progenitor compartments in WT and *Syncrip*-CR-KO secondary recipient mice. WT n=6; CR-KO n=6, error bars, s.e.m. *p<0.05 two tailed *t* test.

[0044] Figure 3(I) shows the quantitative summary of relative median fluorescence intensity (MFI) analysis of SYNCRIP intracellular staining of engrafted CD45.2 cells in WT and *Syncrip*-CR-KO secondary recipient mice. WT n=4; CR-KO n=7 error bars, s.e.m. ***p<0.001 two tailed *t* test.

[0045] Figure 3(J) shows Kaplan Meier analysis of leukemia free survival outcomes after injection of MLL-AF9 transformed WT and *Syncrip*-CR-KO cells into lethally irradiated mice WT n=8, *Syncrip*-CR-KO n=12; Mantel-Cox test ** p<0.01.

[0046] Figure 3(K) shows the quantitative summary of relative MFI analysis of SYNCRIP intracellular staining of GFP positive and GFP positive c-kit high cells from mice succumbed to leukemia in WT vs. *Syncrip* -CR-KO. WT n=5; CR-KO n=5.

[0047] Figure 4(A) shows that *SYNCRIP* is upregulated in AML patient samples. The graph shows the $\log_2$ expression of *SYNCRIP* from transcriptional profiling of bone marrow cells from patients with various subtypes of AML and of the normal hematopoietic stem/progenitor cells (HSPCs) from healthy donors. AML n=142; AML inv(16)/t(16;16) n=27; AML t(11q23)/MLL n=38; AML ETO n=39; APL n=37; HSC n=8; HPC n=4; Prog n=9; B-cells n=5; Mono n=14; T cell CD4/CD8 n=10. error bars, s.e.m. **** p<0.0001 two tailed *t* test. (Hemaexplorer data of *SYNCRIP* probe 209024_s_at from the U133 Plus 2.0 array).

[0048] Figure 4(B) shows high expression levels of SYNCRIP in multiple human AML cell lines. Immunoblot of various myeloid leukemia cell lines are compared to cord blood derived $CD34^+$ cells.

[0049] Figure 4(C) shows SYNCRIP expression in primary AML patient samples. Actin serves as a loading control.

[0050] Figure 4(D) shows cell proliferation in MOLM13 cell line after transduction with lentivirus expressing control or *SYNCRIP*-specific shRNAs. n=3 independent experiments per cell line; error bars, s.e.m. ***p<0.001 two tailed *t* test.

[0051] Figure 4(E) shows cell proliferation in NOMO-1 cell line after transduction with lentivirus expressing control or *SYNCRIP*-specific shRNAs. n=3 independent experiments per cell line; error bars, s.e.m. ***p<0.001 two tailed *t* test.

[0052] Figure 4(F) shows cell proliferation in KASUMI-1 cell line after transduction with lentivirus expressing control or *SYNCRIP*-specific shRNAs. n=3 independent experiments per cell line; error bars, s.e.m. ***p<0.001 two tailed *t* test.

[0053] Figure 4(G) shows cell proliferation in NB4 cell line after transduction with lentivirus expressing control or *SYNCRIP*-specific shRNAs. n=3 independent experiments per cell line; error bars, s.e.m. ***p<0.001 two tailed *t* test.

[0054] Figure 4(H) shows Annexin-V expression assessed by flow cytometry 24 hours post puromycin selection. n=3 independent experiments per cell line; error bars, s.e.m. * p<0.05, **p<0.001 two tailed *t* test.

[0055] Figure 5(A) shows a gene expression heat map of the top 191 upregulated and downregulated genes from RNA-sequencing analysis of MLL-AF9 leukemia cells transduced with control and shRNAs against *SYNCRIP*. n=3 biological replicates.

[0056] Figure 5(B) shows Gene Set Enrichment Analysis (GSEA) results showing that the gene expression signature for genes enriched in hematopoietic stem cells was upregulated in *SYNCRIP*-KD cells.

[0057] Figure 5(C) shows GSEA results showing that the gene expression signature for genes enriched in leukemic stem cells was upregulated in *SYNCRIP*-KD cells.

[0058] Figure 5(D) shows GSEA results showing that the gene expression signature for genes enriched in myeloid development program was upregulated in *SYNCRIP*-KD cells.

[0059] Figure 5(E) shows GSEA results showing that the gene expression signature for MLL-AF9 directed target genes was downregulated in *SYNCRIP*-KD cells.

[0060] Figure 5(F) shows GSEA results showing that the gene expression signature for MLL-AF9 directed target genes was downregulated in *SYNCRIP*-KD cells.

[0061] Figure 5(G) shows GSEA results showing that the gene expression signature for HOXA9-MEIS1 target genes was downregulated in *SYNCRIP*-KD cells.

[0062] Figure 5(H) shows enrichment of MSI2 target genes among SYNCRIP regulated genes.

[0063] Figure 5(I) shows enrichment of MSI2 target genes among SYNCRIP regulated genes.

[0064] Figure 6(A) shows immunoprecipitation of endogenous MSI2 and SYNCRIP in human myeloid leukemia K562 cells overexpressing MSI2. Lysates of K562 cells overexpressing MSI2 were incubated with RNase and immunoprecipitated.

[0065] Figure 6(B) shows immunoprecipitation of SYNCRIP with IgG or SYNCRIP antibody in either wild-type (WT) mouse RN2 MLL-AF9 leukemia cells or human SYNCRIP overexpressing (OV) mouse RN2 MLL-AF9 leukemia cells. n=4 independent experiments; error bars, s.e.m. * $p<0.05$, ** $p<0.001$ two tailed *t* test.

[0066] Figure 6(C) shows downregulation of HOXA9, c-MYC and IKZF2 protein levels upon SYNCRIP knock down in RN2 cells 24 hours post induction with tetracycline with as assessed by immunoblot analysis.

[0067] Figure 6(D) shows expression levels of HOXA9 and c-MYC upon SYNCRIP-KD in human MOLM13 leukemia cells 3 and 4 days post transduction with viruses expressing control shRNA and SYNCRIP-shRNAs together with GFP as assessed by immunoblot analysis.

[0068] Figure 6(E) shows protein expression levels of SYNCRIP, HOXA9 and c-MYC in AHA-pull down fraction, input and flow through fraction as assessed by immunoblot analysis. AHA incorporation into newly synthesized HOXA9 (but not c-MYC) proteins was reduced in SYNCRIP-KD cells. Streptavidin-HRP, Ponceau staining and Actin serve as control for total protein input and loading control.

[0069] Figure 6(F) shows representative histogram analysis of OP-Puro incorporation in control and SYNCRIP-KD MOLM13 cells (shRNA#1 and shRNA#2) at 3 days post transduction with viruses expressing control shRNA and SYNCRIP-shRNAs.

[0070] Figure 6(G) shows quantitative summary of relative OP-Puro incorporation in cells described in Figure 6(F). CHX-treated cells were used as negative control (n=3). Cells without OP-Puro incorporation served as staining control. n=4 independent experiments; error bars, s.e.m. *$p<0.05$, **$p<0.001$, ***$p<0.0001$ two tailed *t* test.

[0071] Figure 7(A) shows colony formation was rescued in dsRed SYNCRIP-KD leukemia cells with MSI2 overexpression. n=3 independent experiments.

[0072] Figure 7(B) shows colony formation was rescued in dsRed SYNCRIP-KD leukemia cells with HOXA9-CDS overexpression. n=4 independent experiments.

[0073] Figure 7(C) shows depletion of SYNCRIP expression and expression of HOXA9 in dsRed SYNCRIP-KD leukemia cells that overexpress HOXA9-CDS as assessed by immunoblot analysis 4 days after transduction.

[0074] Figure 7(D) shows rescue of cell growth in SYNCRIP-KD human MOLM13 leukemia cells with HOXA9 overexpression. n=3 independent experiments.

[0075] Figure 7(E) shows depletion of SYNCRIP expression and expression of HOXA9 in SYNCRIP-KD human MOLM13 leukemia cells that overexpress HOXA9-CDS as assessed by immunoblot analysis 4 days after transduction.

[0076] Figure 7(F) shows quantitative summary of percentage of engrafted $hCD45^+$ GFP^+ cells in recipient mice transplanted with primary AML patient cells transduced with control shRNA or shRNAs against SYNCRIP (shRNA#1 and shRNA#2) at week 10 and week 16 post transplantation. n=5 for each group.

[0077] Figure 7(G) shows depletion of SYNCRIP expression in primary AML patient cells and downregulation of HOXA9 expression as assessed by immunoblots analysis. All data: error bars, s.e.m. ns:*$p<0.05$, **$p<0.001$, ***$p<0.0001$ two tailed *t* test.

[0078] Figure 7(H) shows a schematic depicting the dominant function of SYNCRIP when its expression is elevated in LSCs in comparison to normal HSCs. In LSCs, SYNCRIP and MSI2 binds and increases expression of the mRNA transcripts associated with the MLL self-renewal program, including *Hoxa9* thus driving the LSC program instead of normal hematopoietic development.

[0079] Figure 8(A) shows Coomassie blue staining of Flag-MSI2 immunoprecipitated complexes.

[0080] Figure 8(B) shows GO analysis of MSI2 interacting proteins.

[0081] Figure 8(C) shows the proportion of total read counts sequenced per pool. cntl=Control pool.

[0082] Figure 8(D) shows a scatterplot depicting concordance of shRNA abundance (log_2 normalized read counts) between each one of the replicates against their respective groups (median of log_2 normalized read counts).

[0083] Figure 8(E) shows number of control hairpins represented with a minimum arbitrary threshold (normalized counts>100).

[0084] Figure 8(F) shows a Waterfall plot depicting normalized depletion levels of all shRNAs in spleen (SP), generated from the data in Figure 16. Top candidate genes included SYNCRIP, Caprin1, Dyrk2, Hnrnpr, Cct3, Mybbp1a, and Hnrnpa3, and control shRNAs include RFP, lacZ and luciferase.

[0085] Figure 8(G) shows summary of seven candidate genes.

[0086] Figure 8(H) shows validation of efficient knockdown of target genes in mouse MLL-AF9 leukemia cells. Cells were selected under puromycin treatment for 48 hours prior to qRT-PCR assay. β-Actin serves as housekeeping gene control. All data represent the mean + s.e.m of at least three independent experiments. * $p < 0.05$, ** $p < 0.01$, *** $p<0.001$ by two tailed *t* test.

[0087] Figure 9(A) shows knockdown of SYNCRIP in mouse MLL-AF9 leukemia cells. MLL-AF9 cells were transduced with lentiviruses expressing control shRNA (shRNA against Luciferase) or shRNAs directed against *Syncrip* (shRNA-1 and shRNA-2). Cells were selected under puromycin treatment for 24 hours prior to immunoblotting. Cells were harvested and assayed 3 days post viral transduction. Actin serves as loading control.

[0088] Figure 9(B) shows shRNA depletion of SYNCRIP promoted myeloid differentiation of leukemia cells. Myeloid differentiation status was assayed by FACS analysis of F-480 and CD115 expression at 4 days post transduction. A representative FACS plot is shown for control and SYNCRIP-KD leukemia cells.

[0089] Figure 9(C) shows quantitative summary of FACS analysis of F-480 and CD115 expression in control and SYNCRIP-KD leukemia cells 3 days and 4 days post transduction.

[0090] Figure 9(D) shows quantitative summary of FACS analysis of percentage of c-kit^{high} cells in control and SYNCRIP-KD leukemia cells 4 days post transduction.

[0091] Figure 9(E) shows increased apoptosis was not observed in SYNCRIP-KD leukemia cells at 3 days and 4 days post transduction. Quantitative summary of Annexin-V assessed by flow cytometry.

[0092] Figure 9(F) shows Annexin-V expression assessed by flow cytometry 5 days post transduction of control and SYNCRIP-KD leukemia cells. A representative FACS analysis of Figure 2(E) is shown.

[0093] Figure 9(G) shows quantitative qPCR demonstrating KD of *SYNCRIP* in mouse AML1-ETO9a driven leukemia cells. Cells were selected under puromycin treatment for 48 hours prior to qRT-PCR. β-Actin serves as housekeeping gene control.

[0094] Figure 9(H) shows cells from Figure 9(G) were plated into methylcellulose and scored for number of colonies (average of three independent experiments).

[0095] Figure 9(I) shows the assessment of disease burden, including spleen weight and liver weight of recipient mice in Figure 2(F).

[0096] Figure 9(J) shows SYNCRIP protein expression in bone marrow (as assessed by immunoblot analysis) of mice succumbed to disease in Figure 2(F) and Figure 9(I). Mice injected with *SYNCRIP*-KD1 with reduced disease burden (group 1) maintained better *SYNCRIP* knockdown level compared to mice (group 2), which manifested similar disease to control group.

[0097] Figure 9(K) shows quantitative qPCR showing KD of *Syncrip* assayed by primers designed for specific gRNA targeting regions (gRNA specific primers) in RN2 cells that were transduced for 24 hours with CRISPR/Cas9 containing tet-inducible guide RNAs specific for *Syncrip* (gRNA1-3) in comparison to control- Cas9-EV 24 hours.

[0098] Figure 9(L) shows quantitative summary of FACS analysis of the percentage of Gr-1^+ and Mac-1^+ positive cells in Cas9-EV and *Syncrip*-gRNAs transduced leukemia cells shown in Figure 2(I).

[0099] Figure 9(M) shows the quantitative summary of FACS analysis of the percentage of c-kit^{high} cells in Cas9-EV and *SYNCRIP*-gRNAs transduced leukemia cells shown in Figure 2(I).

[00100] Figure 9(N) shows immunoblot analysis of RN2 cells overexpressing different isoforms of SYNCRIP corresponding to proteins of 527 amino acids (aa), 562 aa and 623 aa. The SYNCRIP 562-aa isoform was the predominantly expressed isoform in leukemia cells. Actin serves as loading control.

[00101] Figure 9(O) shows that SYNCRIP overexpression in RN2 cells promotes colony formation (average of three independent experiments).

[00102] Figure 9(P) shows mouse-*Syncrip* expression as assayed by qPCR using gRNA specific primers, and human-SYNCRIP expression for Figure 2(K).

[00103] Figure 9(Q) shows immunoblot analysis of RN2 cells overexpressing SYNCRIP or harboring control (empty vector (EV)) that were transduced for 24 hours with CRISPR/Cas9 containing tet-inducible gRNA1 and gRNA3 constructs or Cas9-EV in Figure 2(J). All data represent the mean + s.e.m of at least three independent experiments. * $p < 0.05$, ** $p < 0.01$, *** $p<0.001$ by two tailed *t* test.

[00104] Figure 10(A) shows representative PCR analysis for genotyping of *Syncrip* deletion in fetal liver cells.

[00105] Figure 10(B) shows a quantitative summary of FACS analysis of hematopoietic stem and progenitor cells in the WT and *Syncrip*-CR-KO fetal livers in Figure 3**(C)** (WT n=7; CR-KO n=7).

[00106] Figure 10(C) shows a quantitative summary of the number of all colony types formed by WT and *Syncrip*-CR-KO fetal liver cells (average of 6 biological samples). BFU-E: burst-forming unit-erythroid, M: macrophage, G: granulocyte, GM: granulocyte, macrophage, GEMM: granulocyte, erythroid, macrophage, megakaryocyte.

[00107] Figure 10(D) shows the assessment of disease burden, including spleen weight and liver weight of recipient mice shown in Figure 3(J)**.** * $p < 0.05$ by two tailed *t* test.

[00108] Figure 11(A) shows a graph of the $\log_2$ expression of SYNCRIP from transcript profiling of bone marrow cells from patients with various types of hematological malignancies including ALLs, B-ALLs, CLL, MDS, CML and subtypes of AML and of healthy donors. Hypodiploid B-ALL, $n = 40$; ALL with t(1;19), $n = 36$; ALL with t(12;21), $n = 58$; B-ALL with t(8;14), $n = 13$; c-/pre-B-ALL without t(9;22), $n = 237$; c-/pre-B-ALL with t(9;22), $n = 122$; pro-B-ALL with t(11q23)/*MLL*, $n = 70$; CLL, $n = 448$; T-ALL, $n = 174$; MDS, $n = 206$; CML, $n = 76$; complex AML, $n = 48$; AML with inv(16), $n = 28$; AML *MLL*, $n = 38$; AML with a normal karyotype, $n = 351$; AML with t(15;17), $n = 37$; AML with t(8;21), $n = 40$; healthy donors, $n = 73$. $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$, Student's *t* test. (Hemaexplorer data for *SYNCRIP* probe 209024_s_at from the U133 and U133 Plus 2.0 arrays).

[00109] Figure 11(B) shows qPCR of SYNCRIP mRNA levels in multiple human AML cell lines and normal cord blood derived $CD34^+$ cells (CB-$CD34^+$). β-actin served as a housekeeping gene control. Relative mRNA level was normalized to SYNCRIP mRNA in CB-$CD34^+$ cells.

[00110] Figure 11(C) shows SYNCRIP knockdown in MOLM13 AML cell line as assessed by immunoblot analysis.

[00111] Figure 11(D) shows SYNCRIP knockdown in NOMO-1 AML cell line as assessed by immunoblot analysis.

[00112] Figure 11(E) shows SYNCRIP knockdown in KASUMI AML cell line as assessed by immunoblot analysis.

[00113] Figure 11(F) shows SYNCRIP knockdown in NB4 AML cell line as assessed by immunoblot analysis.

[00114] Figure 11(G) shows a quantitative summary of $CD14^{high}$ and $CD13^{high}$ cells and CD14 and CD13 MFI in MOLM13, NB4 and NOMO-1 cells transduced with control shRNA or shRNAs against SYNCRIP (shRNA#1 and shRNA#2) 4 days post transduction.

[00115] Figure 11(H) shows representative FACS plots of cells in Figure 4(H). All data represent the mean + s.e.m of at least three independent experiments. * $p < 0.05$, ** $p < 0.01$, *** $p<0.001$ by two tailed *t* test.

[00116] Figure 12(A) shows plots representing the distribution of mean normalized counts of KD1 correlating with normalized mean counts of KD2 from RNA-sequencing data shown in Figure 5(A).

[00117] Figure 12(B) shows normalized read counts of *Syncrip*, *HoxA9, c-Myc, Ikzf2* and *Meis1* from RNA-sequencing data shown in Figure 5(A).

[00118] Figure 12(C) shows $\log_2$ mRNA expression levels of MSI2 in patients with high vs. low SYNCRIP mRNA expression in AML patients reported in Figure 4(A) (high SYNCRIP was defined as individuals with a value greater than the average + 1 s.d. while low SYNCRIP was defined as individuals with a value greater than the average – 1 s.d.). * $p < 0.05$, ** $p < 0.01$, *** $p<0.001$ by two tailed *t* test.

[00119] Figure 12(D) shows $\log_2$ mRNA expression levels of target genes upregulated by HOXA9-MEIS in patients with high vs. low SYNCRIP mRNA expression in AML patients reported in Figure 4(A) (high SYNCRIP was defined as individuals with a value greater than the average + 1 s.d. while low SYNCRIP was defined as individuals with a value greater than the average – 1 s.d.). * $p < 0.05$, ** $p < 0.01$, *** $p<0.001$ by two tailed *t* test.

[00120] Figure 12(E) shows $\log_2$ mRNA expression levels of target genes downregulated by HOXA9-MEIS in patients with high vs. low SYNCRIP mRNA expression in AML

patients reported in Figure 4(A) (high SYNCRIP was defined as individuals with a value greater than the average + 1 s.d. while low SYNCRIP was defined as individuals with a value greater than the average – 1 s.d.). * $p < 0.05$, ** $p < 0.01$, *** $p<0.001$ by two tailed *t* test.

[00121] Figure 12(F) shows $\log_2$ mRNA expression levels of *IZKF2* in patients with high vs. low SYNCRIP mRNA expression in AML patients reported in Figure 4(A) (high SYNCRIP was defined as individuals with a value greater than the average + 1 s.d. while low SYNCRIP was defined as individuals with a value greater than the average – 1 s.d.). * $p < 0.05$, ** $p < 0.01$, *** $p<0.001$ by two tailed *t* test.

[00122] Figure 12(G) shows $\log_2$ mRNA expression levels of c-MYC in patients with high vs. low SYNCRIP mRNA expression in AML patients reported in Figure 4(A) (high SYNCRIP was defined as individuals with a value greater than the average + 1 s.d. while low SYNCRIP was defined as individuals with a value greater than the average – 1 s.d.). * $p < 0.05$, ** $p < 0.01$, *** $p<0.001$ by two tailed *t* test.

[00123] Figure 13(A) shows MOLM13 human myeloid leukemia cells carrying the MLL-AF9 translocation overexpressing MSI2 were immunoprecipitated for endogenous MSI2 and SYNCRIP.

[00124] Figure 13(B) shows immunoblots showing protein expression of HOXA9, MYC and IKZF2 upon SYNCRIP knockdown in dsRed MLL-AF9 cells 3 and 4 days after transduction. Actin serves as a loading control.

[00125] Figure 13(C) shows immunoblots showing protein expression of HOXA9 and MYC upon SYNCRIP knockdown in MOLM13 cells after 2 days of puromycin selection (4 days after transduction).

[00126] Figure 13(D) shows qPCR measuring the mRNA expression of *Syncrip*, *Hoxa9*, *Myc* and *Ikzf2* in dsRed tertiary MLL-AF9 leukemia cells 3 days after transduction.

[00127] Figure 13(E) shows qPCR measuring the mRNA expression of *Syncrip*, *Hoxa9*, *Myc* and *Ikzf2* in dsRed tertiary MLL-AF9 leukemia cells 4 days after transduction.

[00128] Figure 13(F) shows immunoblots showing protein expression of HOXA9, MYC and SYNCRIP upon MSI2 knockdown in dsRed MLL-AF9 cells at 4 days after transduction.

[00129] Figure 13(G) shows qPCR measuring mRNA expression of *Syncrip*, *Hoxa9*, *Myc* and *Ikzf2* upon MSI2 knockdown in dsRed MLL-AF9 cells at 4 days after transduction.

[00130] Figure 13(H) shows qPCR measuring mRNA expression of *Syncrip*, *Hoxa9*, *Myc* and *Ikzf2* in RN2 cells 24 hours after induction.

[00131] Figure 13(I) shows qPCR measuring mRNA expression of *Syncrip*, *Hoxa9*, *Myc* and *Ikzf2* in human MOLM13 leukemia cells 3 days after transduction.

[00132] Figure 13(J) shows qPCR measuring mRNA expression of *Syncrip*, *Hoxa9*, *Myc* and *Ikzf2* in human MOLM13 leukemia cells 4 days after transduction.

[00133] Figure 13(K) shows normalized total RNA levels in dsRed MLL-AF9, RN2 and MOLM13 cells upon SYNCRIP depletion.

[00134] Figure 13(L) shows mRNA stability of *Syncrip*, *Hoxa9*, *Myc* and *Ikzf2* in dsRed cells transduced with control and SYNCRIP shRNAs 4 days after transduction.

[00135] Figure 13(M) shows mRNA stability of *Syncrip*, *Hoxa9*, *Myc* and *Ikzf2* in RN2 cells expressing Cas9-EV or gRNA1 and gRNA3 targeting *Syncrip* after 24 hours of doxycycline induction. Actin served as a loading control. β-actin served as a control housekeeping gene. All data represent the means + s.e.m. of at least three independent experiments. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, two-tailed *t* test.

[00136] Figure 14(A) shows qPCR measuring mRNA expression showing that MSI2 overexpression increased the mRNA levels of *Hoxa9*, *Myc* and *Ikzf2*. All data represent the means + s.e.m. of at least three independent replicates. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$, two-tailed *t* test.

[00137] Figure 14(B) shows immunoblots that show depletion of SYNCRIP, and protein expression of HOXA9 for the cells in Figure 14(A). Actin served as a loading control. β-actin served as a control housekeeping gene.

[00138] Figure 14(C) shows that colony formation was rescued in dsRed SYNCRIP-KD leukemia cells overexpressing full-length HOXA9. All data represent the means + s.e.m. of at least three independent replicates. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$, two-tailed *t* test.

[00139] Figure 14(D) shows immunoblots that show depletion of SYNCRIP, and protein expression of HOXA9 for the cells in Figure 14(C). Actin served as a loading control. β-actin served as a control housekeeping gene.

[00140] Figure 14(E) shows that colony formation was not rescued in dsRed SYNCRIP-KD leukemia cells overexpressing MYC. All data represent the means + s.e.m. of at least three independent replicates. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$, two-tailed *t* test.

[00141] Figure 14(F) shows immunoblots that show depletion of SYNCRIP, and protein expression of MYC for the cells in Figure 14(E). Actin served as a loading control. β-actin served as a control housekeeping gene.

[00142] Figure 14(G) shows that cell growth was not rescued in MOLM13 SYNCRIP-KD cells overexpressing MYC. All data represent the means + s.e.m. of at least three independent replicates. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$, two-tailed *t* test.

[00143] Figure 14(H) shows immunoblots that show depletion of SYNCRIP, and protein expression of MYC for the cells in Figure 14(G). Actin served as a loading control. β-actin served as a control housekeeping gene.

[00144] Figure 15 shows raw normalized read counts of all target sequences in the *in vivo* shRNA screen in bone marrow.

[00145] Figure 16 shows raw normalized read counts of all target sequences in the *in vivo* shRNA screen in spleen.

[00146] Figure 17 shows a list of differentially expressed genes in *Syncrip*-shRNA leukemia cells with $\log_2$(fold change) >1.5.

[00147] Figure 18 shows the nucleic acid sequence of *Homo sapiens* synaptotagmin binding cytoplasmic RNA interacting protein (*SYNCRIP*), transcript variant 7, mRNA (SEQ ID NO: 5).

[00148] Figure 19 shows the nucleic acid sequence of *Homo sapiens* synaptotagmin binding cytoplasmic RNA interacting protein (*SYNCRIP*), transcript variant 6, mRNA (SEQ ID NO: 6).

[00149] Figure 20 shows the nucleic acid sequence of *Homo sapiens* synaptotagmin binding cytoplasmic RNA interacting protein (*SYNCRIP*), transcript variant 2, mRNA (SEQ ID NO: 7).

[00150] Figure 21 shows the nucleic acid sequence of *Homo sapiens* synaptotagmin binding cytoplasmic RNA interacting protein (*SYNCRIP*), transcript variant 5, mRNA (SEQ ID NO: 8).

[00151] Figure 22 shows the nucleic acid sequence of *Homo sapiens* synaptotagmin binding cytoplasmic RNA interacting protein (*SYNCRIP*), transcript variant 1, mRNA (SEQ ID NO: 9).

[00152] Figure 23 shows the nucleic acid sequence of *Homo sapiens* synaptotagmin binding cytoplasmic RNA interacting protein (*SYNCRIP*), transcript variant 3, mRNA (SEQ ID NO: 10).

[00153] Figure 24 shows the nucleic acid sequence of *Homo sapiens* synaptotagmin binding cytoplasmic RNA interacting protein (*SYNCRIP*), transcript variant 4, mRNA (SEQ ID NO: 11).

[00154] Figure 25(A) shows the targeting scheme for SYNCRIP conditional knockout mice.

[00155] Figure 25(B) shows the experimental schemes for studying the effects of SYNCRIP depletion in normal hematopoiesis.

[00156] Figure 25(C) shows the experimental schemes for studying the effects of SYNCRIP depletion in leukemia.

DETAILED DESCRIPTION

[00157] It is to be appreciated that certain aspects, modes, embodiments, variations and features of the present methods are described below in various levels of detail in order to provide a substantial understanding of the present technology.

[00158] In practicing the present methods, many conventional techniques in molecular biology, protein biochemistry, cell biology, microbiology and recombinant DNA are used. *See, e.g.*, Sambrook and Russell eds. (2001) *Molecular Cloning: A Laboratory Manual*, 3rd edition; the series Ausubel *et al.* eds. (2007) *Current Protocols in Molecular Biology*; the series *Methods in Enzymology* (Academic Press, Inc., N.Y.); MacPherson *et al.* (1991) *PCR 1: A Practical Approach* (IRL Press at Oxford University Press); MacPherson *et al.* (1995)

PCR 2: A Practical Approach; Harlow and Lane eds. (1999) *Antibodies, A Laboratory Manual*; Freshney (2005) *Culture of Animal Cells: A Manual of Basic Technique*, 5th edition; Gait ed. (1984) *Oligonucleotide Synthesis*; U.S. Patent No. 4,683,195; Hames and Higgins eds. (1984) *Nucleic Acid Hybridization*; Anderson (1999) *Nucleic Acid Hybridization*; Hames and Higgins eds. (1984) *Transcription and Translation; Immobilized Cells and Enzymes* (IRL Press (1986)); Perbal (1984) *A Practical Guide to Molecular Cloning*; Miller and Calos eds. (1987) *Gene Transfer Vectors for Mammalian Cells* (Cold Spring Harbor Laboratory); Makrides ed. (2003) *Gene Transfer and Expression in Mammalian Cells*; Mayer and Walker eds. (1987) *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); and Herzenberg *et al.* eds (1996) *Weir's Handbook of Experimental Immunology*.

Definitions

[00159] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this technology belongs. As used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. For example, reference to "a cell" includes a combination of two or more cells, and the like. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, analytical chemistry and nucleic acid chemistry and hybridization described below are those well-known and commonly employed in the art.

[00160] As used herein, the term "about" in reference to a number is generally taken to include numbers that fall within a range of 1%, 5%, or 10% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would be less than 0% or exceed 100% of a possible value).

[00161] As used herein, the "administration" of an agent or drug to a subject includes any route of introducing or delivering to a subject a compound to perform its intended function. Administration can be carried out by any suitable route, including orally, intranasally, parenterally (intravenously, intramuscularly, intraperitoneally, or subcutaneously), or topically. Administration includes self-administration and the administration by another.

[00162] The terms "complementary" or "complementarity" as used herein with reference to polynucleotides (*i.e.*, a sequence of nucleotides such as an oligonucleotide or a target nucleic acid) refer to the base-pairing rules. The complement of a nucleic acid sequence as

used herein refers to an oligonucleotide which, when aligned with the nucleic acid sequence such that the 5' end of one sequence is paired with the 3' end of the other, is in "antiparallel association." For example, the sequence "5'-A-G-T-3'" is complementary to the sequence "3'-T-C-A-5." Certain bases not commonly found in naturally-occurring nucleic acids may be included in the nucleic acids described herein. These include, for example, inosine, 7-deazaguanine, Locked Nucleic Acids (LNA), and Peptide Nucleic Acids (PNA). Complementarity need not be perfect; stable duplexes may contain mismatched base pairs, degenerative, or unmatched bases. Those skilled in the art of nucleic acid technology can determine duplex stability empirically considering a number of variables including, for example, the length of the oligonucleotide, base composition and sequence of the oligonucleotide, ionic strength and incidence of mismatched base pairs. A complementary sequence can also be an RNA sequence complementary to the DNA sequence or its complementary sequence, and can also be a cDNA.

[00163] As used herein, a "control" is an alternative sample used in an experiment for comparison purpose. A control can be "positive" or "negative." For example, where the purpose of the experiment is to determine a correlation of the efficacy of a therapeutic agent for the treatment for a particular type of disease or condition, a positive control (a compound or composition known to exhibit the desired therapeutic effect) and a negative control (a subject or a sample that does not receive the therapy or receives a placebo) are typically employed.

[00164] As used herein, the term "effective amount" refers to a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, *e.g.*, an amount which results in the prevention of, or a decrease in a disease or condition described herein or one or more signs or symptoms associated with a disease or condition described herein. In the context of therapeutic or prophylactic applications, the amount of a composition administered to the subject will vary depending on the composition, the degree, type, and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. The compositions can also be administered in combination with one or more additional therapeutic compounds. In the methods described herein, the therapeutic compositions may be administered to a subject having one or more signs or symptoms of AML. As used herein, a "therapeutically effective amount" of a composition refers to composition levels in which the physiological effects of a disease or

condition are ameliorated or eliminated. A therapeutically effective amount can be given in one or more administrations.

[00165] As used herein, "expression" includes one or more of the following: transcription of the gene into precursor mRNA; splicing and other processing of the precursor mRNA to produce mature mRNA; mRNA stability; translation of the mature mRNA into protein (including codon usage and tRNA availability); and glycosylation and/or other modifications of the translation product, if required for proper expression and function.

[00166] As used herein, the term "gene" means a segment of DNA that contains all the information for the regulated biosynthesis of an RNA product, including promoters, exons, introns, and other untranslated regions that control expression.

[00167] "Homology" or "identity" or "similarity" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same nucleobase or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. A polynucleotide or polynucleotide region (or a polypeptide or polypeptide region) has a certain percentage (for example, at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99%) of "sequence identity" to another sequence means that, when aligned, that percentage of bases (or amino acids) are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art. In some embodiments, default parameters are used for alignment. One alignment program is BLAST, using default parameters. In particular, programs are BLASTN and BLASTP, using the following default parameters: Genetic code=standard; filter=none; strand=both; cutoff=60; expect=10; Matrix=BLOSUM62; Descriptions=50 sequences; sort by =HIGH SCORE; Databases=non-redundant, GenBank+EMBL+DDBJ+PDB+GenBank CDS translations+SwissProtein+SPupdate+PIR. Details of these programs can be found at the National Center for Biotechnology Information. Biologically equivalent polynucleotides are those having the specified percent homology and encoding a polypeptide having the same or similar biological activity. Two sequences are deemed "unrelated" or "non-homologous" if they share less than 40% identity, or less than 25% identity, with each other.

[00168] The term "hybridize" as used herein refers to a process where two substantially complementary nucleic acid strands (at least about 65% complementary over a stretch of at least 14 to 25 nucleotides, at least about 75%, or at least about 90% complementary) anneal to each other under appropriately stringent conditions to form a duplex or heteroduplex through formation of hydrogen bonds between complementary base pairs. Nucleic acid hybridization techniques are well known in the art. *See, e.g.*, Sambrook, *et al.*, 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Press, Plainview, N.Y. Hybridization and the strength of hybridization (*i.e.*, the strength of the association between the nucleic acids) is influenced by such factors as the degree of complementarity between the nucleic acids, stringency of the conditions involved, and the thermal melting point (T_m) of the formed hybrid. Those skilled in the art understand how to estimate and adjust the stringency of hybridization conditions such that sequences having at least a desired level of complementarity will stably hybridize, while those having lower complementarity will not. For examples of hybridization conditions and parameters, *see, e.g.*, Sambrook, *et al.*, 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Press, Plainview, N.Y.; Ausubel, F. M. *et al.* 1994, *Current Protocols in Molecular Biology*, John Wiley & Sons, Secaucus, N.J. In some embodiments, specific hybridization occurs under stringent hybridization conditions. An oligonucleotide or polynucleotide (*e.g.*, a probe or a primer) that is specific for a target nucleic acid will "hybridize" to the target nucleic acid under suitable conditions.

[00169] As used herein, "oligonucleotide" refers to a molecule that has a sequence of nucleic acid bases on a backbone comprised mainly of identical monomer units at defined intervals. The bases are arranged on the backbone in such a way that they can bind with a nucleic acid having a sequence of bases that are complementary to the bases of the oligonucleotide. The most common oligonucleotides have a backbone of sugar phosphate units. A distinction may be made between oligodeoxyribonucleotides that do not have a hydroxyl group at the 2' position and oligoribonucleotides that have a hydroxyl group at the 2' position. Oligonucleotides may also include derivatives, in which the hydrogen of the hydroxyl group is replaced with organic groups, *e.g.*, an allyl group. One or more bases of the oligonucleotide may also be modified to include a phosphorothioate bond (*e.g.*, one of the two oxygen atoms in the phosphate backbone which is not involved in the internucleotide bridge, is replaced by a sulfur atom) to increase resistance to nuclease degradation. The exact size of the oligonucleotide will depend on many factors, which in turn depend on the ultimate function or use of the oligonucleotide. The oligonucleotide may be generated in any manner,

including, for example, chemical synthesis, DNA replication, restriction endonuclease digestion of plasmids or phage DNA, reverse transcription, PCR, or a combination thereof. The oligonucleotide may be modified *e.g.*, by addition of a methyl group, a biotin or digoxigenin moiety, a fluorescent tag or by using radioactive nucleotides.

[00170] As used herein, the term "pharmaceutically-acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal compounds, isotonic and absorption delaying compounds, and the like, compatible with pharmaceutical administration. Pharmaceutically-acceptable carriers and their formulations are known to one skilled in the art and are described, for example, in Remington's Pharmaceutical Sciences (20^{th} edition, ed. A. Gennaro, 2000, Lippincott, Williams & Wilkins, Philadelphia, Pa.).

[00171] As used herein, the term "polynucleotide" or "nucleic acid" means any RNA or DNA, which may be unmodified or modified RNA or DNA. Polynucleotides include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, RNA that is mixture of single- and double-stranded regions, and hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, polynucleotide refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons.

[00172] As used herein, "prevention", "prevent", or "preventing" of a disorder or condition refers to one or more compounds that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset of one or more symptoms of the disorder or condition relative to the untreated control sample. As used herein, preventing AML, includes preventing or delaying the initiation of symptoms of AML. As used herein, prevention of AML also includes preventing a recurrence of one or more signs or symptoms of AML.

[00173] As used herein, the term "sample" refers to clinical samples obtained from a subject. Biological samples may include tissues, cells, protein or membrane extracts of cells, mucus, sputum, bone marrow, bronchial alveolar lavage (BAL), bronchial wash (BW), and biological fluids (*e.g.*, ascites fluid or cerebrospinal fluid (CSF)) isolated from a subject, as

well as tissues, cells and fluids (blood, plasma, saliva, urine, serum *etc.*) present within a subject.

[00174] As used herein, the term "separate" therapeutic use refers to an administration of at least two active ingredients at the same time or at substantially the same time by different routes.

[00175] As used herein, the term "sequential" therapeutic use refers to administration of at least two active ingredients at different times, the administration route being identical or different. More particularly, sequential use refers to the whole administration of one of the active ingredients before administration of the other or others commences. It is thus possible to administer one of the active ingredients over several minutes, hours, or days before administering the other active ingredient or ingredients. There is no simultaneous treatment in this case.

[00176] As used herein, the term "simultaneous" therapeutic use refers to the administration of at least two active ingredients by the same route and at the same time or at substantially the same time.

[00177] The term "specific" as used herein in reference to an oligonucleotide means that the nucleotide sequence of the oligonucleotide has at least 12 bases of sequence identity with a portion of a target nucleic acid when the oligonucleotide and the target nucleic acid are aligned. An oligonucleotide that is specific for a target nucleic acid is one that, under the stringent hybridization or washing conditions, is capable of hybridizing to the target nucleic acid of interest and not substantially hybridizing to nucleic acids which are not of interest. Higher levels of sequence identity are desirable and include at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity.

[00178] The term "stringent hybridization conditions" as used herein refers to hybridization conditions at least as stringent as the following: hybridization in 50% formamide, 5xSSC, 50 mM NaH_2PO_4, pH 6.8, 0.5% SDS, 0.1 mg/mL sonicated salmon sperm DNA, and 5x Denhart's solution at 42° C. overnight; washing with 2x SSC, 0.1% SDS at 45° C; and washing with 0.2x SSC, 0.1% SDS at 45° C. In another example, stringent hybridization conditions should not allow for hybridization of two nucleic acids which differ over a stretch of 20 contiguous nucleotides by more than two bases.

[00179] As used herein, the terms "subject," "individual," or "patient" are used interchangeably and refer to an individual organism, a vertebrate, a mammal, or a human. In certain embodiments, the individual, patient or subject is a human.

[00180] As used herein, the terms "target sequence" and "target nucleic acid sequence" refer to a specific nucleic acid sequence to be modulated (*e.g.*, inhibited or downregulated).

[00181] "Treating", "treat", or "treatment" as used herein covers the treatment of a disease or disorder described herein, in a subject, such as a human, and includes: (i) inhibiting a disease or disorder, *i.e.*, arresting its development; (ii) relieving a disease or disorder, *i.e.*, causing regression of the disorder; (iii) slowing progression of the disorder; and/or (iv) inhibiting, relieving, or slowing progression of one or more symptoms of the disease or disorder. In some embodiments, treatment means that the symptoms associated with the disease are, *e.g.*, alleviated, reduced, cured, or placed in a state of remission.

[00182] It is also to be appreciated that the various modes of treatment or prevention of medical diseases and conditions as described are intended to mean "substantial," which includes total but also less than total treatment or prevention, and wherein some biologically or medically relevant result is achieved. The treatment may be a continuous prolonged treatment for a chronic disease or a single, or few time administrations for the treatment of an acute condition.

SYNCRIP-specific Inhibitory Nucleic Acids of the Present Technology

[00183] Figures 18-24 show the nucleic acid sequences of seven human *SYNCRIP* transcript variants, represented by SEQ ID NOs: 5-11.

[00184] In one aspect, the present disclosure provides *SYNCRIP*-specific inhibitory nucleic acids comprising a nucleic acid molecule which is complementary to a portion of a *SYNCRIP* nucleic acid sequence selected from the group consisting of SEQ ID NOs: 5-11.

[00185] The present disclosure also provides an antisense nucleic acid comprising a nucleic acid sequence that is complementary to and specifically hybridizes with a portion of any one of SEQ ID NOs: 5-11 (*SYNCRIP* mRNA), thereby reducing or inhibiting *SYNCRIP* expression. The antisense nucleic acid may be antisense RNA, or antisense DNA. Antisense nucleic acids based on the known *SYNCRIP* gene sequence can be readily designed and engineered using methods known in the art. In some embodiments, the antisense nucleic acid comprises the nucleic acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, or a complement thereof.

[00186] Antisense nucleic acids are molecules which are complementary to a sense nucleic acid strand, *e.g.*, complementary to the coding strand of a double-stranded DNA molecule (or cDNA) or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can form hydrogen bonds with a sense nucleic acid. The antisense nucleic acid can be complementary to an entire *SYNCRIP* coding strand, or to a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). In some embodiments, the antisense nucleic acid is an oligonucleotide which is complementary to only a portion of the coding region of *SYNCRIP* mRNA. In certain embodiments, an antisense nucleic acid molecule can be complementary to a noncoding region of the *SYNCRIP* coding strand. In some embodiments, the noncoding region refers to the 5′ and 3′ untranslated regions that flank the coding region and are not translated into amino acids. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of *SYNCRIP*. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length.

[00187] An antisense nucleic acid can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-hodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl)uracil, 5-carboxymethylaminomethyl-2-thouridine, 5-carboxymethylaminometh-yluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-metnylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5′-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopenten-yladenine, uracil-5-oxyacetic acid (v), wybutosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thlouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-cxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced

biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest).

[00188] The antisense nucleic acid molecules may be administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding the protein of interest to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can occur *via* Watson-Crick base pairing to form a stable duplex, or in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix.

[00189] In some embodiments, the antisense nucleic acid molecules are modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. In some embodiments, the antisense nucleic acid molecule is an alpha-anomeric nucleic acid molecule. An alpha-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gaultier *et al.*, *Nucleic Acids. Res.* 15:6625-6641(1987)). The antisense nucleic acid molecule can also comprise a 2′-O -methylribonucleotide (Inoue *et al.*, *Nucleic Acids Res.* 15:6131-6148 (1987)) or a chimeric RNA-DNA analogue (Inoue *et al.*, *FEBS Lett.* 215:327-330 (1987)).

[00190] The present disclosure also provides a short hairpin RNA (shRNA) or small interfering RNA (siRNA) comprising a nucleic acid sequence that is complementary to and specifically hybridizes with a portion of any one of SEQ ID NOs: 5-11 (*SYNCRIP* mRNA), thereby reducing or inhibiting *SYNCRIP* expression. In some embodiments, the shRNA or siRNA is about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29 base pairs in length. Double-stranded RNA (dsRNA) can induce sequence-specific post-transcriptional gene silencing (*e.g.*, RNA interference (RNAi)) in many organisms such as *C. elegans*, *Drosophila*, plants, mammals, oocytes and early embryos. RNAi is a process that interferes with or significantly reduces the number of protein copies made by an mRNA. For example, a double-stranded siRNA or shRNA molecule is engineered to complement and hydridize to a mRNA of a target gene. Following intracellular delivery, the siRNA or shRNA molecule associates with an RNA-induced silencing complex (RISC), which then binds and degrades a complementary target mRNA (such as *SYNCRIP* mRNA). In some embodiments, the shRNA or siRNA

comprises the nucleic acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, or SEQ ID NO: 21.

[00191] The present disclosure also provides a ribozyme comprising a nucleic acid sequence that is complementary to and specifically hybridizes with a portion of any one of SEQ ID NOs: 5-11 (*SYNCRIP* mRNA), thereby reducing or inhibiting *SYNCRIP* expression. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a complementary single-stranded nucleic acid, such as an mRNA. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach, *Nature* 334:585-591 (1988))) can be used to catalytically cleave *SYNCRIP* transcripts, thereby inhibiting translation of *SYNCRIP*.

[00192] A ribozyme having specificity for a *SYNCRIP*-encoding nucleic acid can be designed based upon a *SYNCRIP* nucleic acid sequence disclosed herein. For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a *SYNCRIP*-encoding mRNA. See, *e.g.*, U.S. Pat. No. 4,987,071 and U.S. Pat. No. 5,116,742. Alternatively, *SYNCRIP* mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel and Szostak (1993) *Science* 261:1411-1418, incorporated herein by reference.

[00193] The present disclosure also provides a synthetic guide RNA (sgRNA) comprising a nucleic acid sequence that is complementary to and specifically hybridizes with a portion of any one of SEQ ID NOs: 5-11 (*SYNCRIP* mRNA). Guide RNAs for use in CRISPR-Cas systems are typically generated as a single guide RNA comprising a crRNA segment and a tracrRNA segment. The crRNA segment and a tracrRNA segment can also be generated as separate RNA molecules. The crRNA segment comprises the targeting sequence that binds to a portion of any one of SEQ ID NOs: 5-11, and a stem portion that hybridizes to a tracrRNA. The tracrRNA segment comprises a nucleotide sequence that is partially or completely complementary to the stem sequence of the crRNA and a nucleotide sequence that binds to the CRISPR enzyme. In some embodiments, the crRNA segment and the tracrRNA segment are provided as a single guide RNA. In some embodiments, the crRNA segment and the tracrRNA segment are provided as separate RNAs. The combination of the CRISPR enzyme with the crRNA and tracrRNA make up a functional CRISPR-Cas system. Exemplary CRISPR-Cas systems for targeting nucleic acids, are described, for example, in WO2015/089465.

[00194] In some embodiments, a synthetic guide RNA is a single RNA represented as comprising the following elements:

5′-X1-X2-Y-Z-3′

where X1 and X2 represent the crRNA segment, where X1 is the targeting sequence that binds to a portion of any one of SEQ ID NOs: 5-11, X2 is a stem sequence the hybridizes to a tracrRNA, Z represents a tracrRNA segment comprising a nucleotide sequence that is partially or completely complementary to X2, and Y represents a linker sequence. In some embodiments, the linker sequence comprises two or more nucleotides and links the crRNA and tracrRNA segments. In some embodiments, the linker sequence comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleotides. In some embodiments, the linker is the loop of the hairpin structure formed when the stem sequence hybridized with the tracrRNA.

[00195] In some embodiments, a synthetic guide RNA is provided as two separate RNAs where one RNA represents a crRNA segment: 5′-X1-X2-3′ where X1 is the targeting sequence that binds to a portion of any one of SEQ ID NOs: 5-11, X2 is a stem sequence the hybridizes to a tracrRNA, and one RNA represents a tracrRNA segment, Z, that is a separate RNA from the crRNA segment and comprises a nucleotide sequence that is partially or completely complementary to X2 of the crRNA.

[00196] Exemplary crRNA stem sequences and tracrRNA sequences are provided, for example, in WO/2015/089465, which is incorporated by reference herein. In general, a stem sequence includes any sequence that has sufficient complementarity with a complementary sequence in the tracrRNA to promote formation of a CRISPR complex at a target sequence, wherein the CRISPR complex comprises the stem sequence hybridized to the tracrRNA. In general, degree of complementarity is with reference to the optimal alignment of the stem and complementary sequence in the tracrRNA, along the length of the shorter of the two sequences. Optimal alignment may be determined by any suitable alignment algorithm, and may further account for secondary structures, such as self-complementarity within either the stem sequence or the complementary sequence in the tracrRNA. In some embodiments, the degree of complementarity between the stem sequence and the complementary sequence in the tracrRNA along the length of the shorter of the two when optimally aligned is about or more than about 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97.5%, 99%, or higher. In some embodiments, the stem sequence is about or more than about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 40, 50, or more nucleotides in length. In some

embodiments, the stem sequence and complementary sequence in the tracrRNA are contained within a single RNA, such that hybridization between the two produces a transcript having a secondary structure, such as a hairpin. In some embodiments, the tracrRNA has additional complementary sequences that form hairpins. In some embodiments, the tracrRNA has at least two or more hairpins. In some embodiments, the tracrRNA has two, three, four or five hairpins. In some embodiments, the tracrRNA has at most five hairpins.

[00197] In a hairpin structure, the portion of the sequence 5′ of the final "N" and upstream of the loop corresponds to the crRNA stem sequence, and the portion of the sequence 3′ of the loop corresponds to the tracrRNA sequence. Further non-limiting examples of single polynucleotides comprising a guide sequence, a stem sequence, and a tracr sequence are as follows (listed 5′ to 3′), where "N" represents a base of a guide sequence (*e.g.* a modified oligonucleotide provided herein), the first block of lower case letters represent stem sequence, and the second block of lower case letters represent the tracrRNA sequence, and the final poly-T sequence represents the transcription terminator: (a) NNNNNNNNNNNNNNNNNNNgtttttgtactctcaagatttaGAAAtaaatcttgcagaagctacaaagataa ggcttcatgccgaaatcaacaccctgtcattttatggcagggtgttttcgttatttaaTTTTTT (SEQ ID NO: 12); (b) NNNNNNNNNNNNNNNNNNNgtttttgtactctcaGAAAtgcagaagctacaaagataaggcttcatgccg aaatcaacaccctgtcattttatggcagggtgttttcgttatttaaTTTTTT (SEQ ID NO: 13); (c) NNNNNNNNNNNNNNNNNNNgtttttgtactctcaGAAAtgcagaagctacaaagataaggcttcatgccg aaatcaacaccctgtcattttatggcagggtgtTTTTTT (SEQ ID NO: 14); (d) NNNNNNNNNNNNNNNNNNNgttttagagctaGAAAtagcaagttaaaataaggctagtccgttatcaactt gaaaaagtggcaccgagtcggtgcTTTTTT (SEQ ID NO: 15); (e) NNNNNNNNNNNNNNNNNNNgttttagagctaGAAATAGcaagttaaaataaggctagtccgttatcaac ttgaaaaagtgTTTTTTT (SEQ ID NO: 16); and (f) NNNNNNNNNNNNNNNNNNNgttttagagctagAAATAGcaagttaaaataaggctagtccgttatcaTT TTTTTT (SEQ ID NO: 17).

[00198] Selection of suitable oligonucleotides for use in as a targeting sequence in a CRISPR Cas system depends on several factors including the particular CRISPR enzyme to be used and the presence of corresponding proto-spacer adjacent motifs (PAMs) downstream of the target sequence in the target nucleic acid. The PAM sequences direct the cleavage of the target nucleic acid by the CRISPR enzyme. In some embodiments, a suitable PAM is 5'-NRG or 5'-NNGRR (where N is any Nucleotide) for SpCas9 or SaCas9 enzymes (or derived enzymes), respectively. Generally the PAM sequences should be present between about 1 to

about 10 nucleotides of the target sequence to generate efficient cleavage of the target nucleic acid. Thus, when the guide RNA forms a complex with the CRISPR enzyme, the complex locates the target and PAM sequence, unwinds the DNA duplex, and the guide RNA anneals to the complementary sequence on the opposite strand. This enables the Cas9 nuclease to create a double-strand break. In some embodiments, the sgRNA comprises the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

[00199] A variety of CRISPR enzymes are available for use in conjunction with the disclosed guide RNAs of the present disclosure. In some embodiments, the CRISPR enzyme is a Type II CRISPR enzyme. In some embodiments, the CRISPR enzyme catalyzes DNA cleavage. In some embodiments, the CRISPR enzyme catalyzes RNA cleavage. In some embodiments, the CRISPR enzyme is any Cas9 protein, for instance any naturally-occurring bacterial Cas9 as well as any chimeras, mutants, homologs or orthologs. Non-limiting examples of Cas proteins include Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9 (also known as Csn1 and Csx12), Cas10, Csy1, Csy2, Csy3, Cse1, Cse2, Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, Csf4, homologues thereof, or modified variants thereof. In some embodiments, the CRISPR enzyme cleaves both strands of the target nucleic acid at the Protospacer Adjacent Motif (PAM) site. In some embodiments, the CRISPR enzyme is a nickase, which cleaves only one strand of the target nucleic acid.

Therapeutic Methods

[00200] The following discussion is presented by way of example only, and is not intended to be limiting.

[00201] One aspect of the present technology includes methods of treating a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP*. Additionally or alternatively, in some embodiments, the present technology includes methods of treating AML. In one aspect, the present disclosure provides a method for inhibiting leukemic cell proliferation in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one *SYNCRIP*-specific inhibitory nucleic acid, wherein the at least one *SYNCRIP*-specific inhibitory nucleic acid is selected from the group consisting of antisense oligonucleotide, sgRNA, shRNA, and siRNA, and wherein the subject suffers from a disease or condition characterized by elevated expression levels and/or

increased activity of *SYNCRIP*. The AML may be T-cell acute lymphoblastic leukemia or B-cell acute lymphoblastic leukemia.

[00202] In some embodiments, the subject is diagnosed as having, suspected as having, or at risk of having a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP*. Additionally or alternatively, in some embodiments, the subject is diagnosed as having AML.

[00203] In therapeutic applications, compositions or medicaments comprising an *SYNCRIP*-specific inhibitory nucleic acid disclosed herein are administered to a subject suspected of, or already suffering from such a disease or condition (such as, a subject diagnosed with a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP* and/or a subject diagnosed with AML), in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease, including its complications and intermediate pathological phenotypes in development of the disease.

[00204] Subjects suffering from a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP* and/or a subject diagnosed with AML can be identified by any or a combination of diagnostic or prognostic assays known in the art. For example, typical symptoms of AML include, but are not limited to, enlarged lymph nodes, anemia, neutropenia, leukopenia, leukostasis, chloroma, granulocytic sarcoma, myeloid sarcoma, fatigue, weakness, dizziness, chills, headaches, shortness of breath, thrombocytopenia, excess bruising and bleeding, frequent or severe nosebleeds, bleeding gums, gum pain and swelling, headache, weakness in one side of the body, slurred speech, confusion, sleepiness, blurry vision, vision loss, deep venous thrombosis (DVT), pulmonary embolism, bone or joint pain, swelling in the abdomen, seizures, vomiting, facial numbness, defects in balance, weight loss, fever, night sweats, and loss of appetite.

[00205] In some embodiments, the subject may exhibit one or more point mutations in *NRAS*, *DNMT3A*, *FLT3*, *KIT*, *IDH1*, *IDH2*, *CEBPA*, and *NPM1* and/or one or more chromosomal alterations (*e.g.*, an inversion, translocation, or gene fusion) such as *CBFB-MYH11*, *DEK-NUP214*, *MLL-MLLT3*, *PML-RARA*, *RBM15-MKL1*, *RPN1-EVI1* and *RUNX1-RUNX1T1*, and are detectable using techniques known in the art. See Naoe & Kiyoi, *Int J Hematol.* 97(2):165-74 (2013); Shih *et al.*, *Nat Rev Cancer.* 12(9):599-612 (2012).

[00206] In some embodiments, subjects with a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP*, and/or subjects suffering

from AML that are treated with the *SYNCRIP*-specific inhibitory nucleic acid will show amelioration or elimination of one or more of the following symptoms: enlarged lymph nodes, anemia, neutropenia, leukopenia, leukostasis, chloroma, granulocytic sarcoma, myeloid sarcoma, fatigue, weakness, dizziness, chills, headaches, shortness of breath, thrombocytopenia, excess bruising and bleeding, frequent or severe nosebleeds, bleeding gums, gum pain and swelling, headache, weakness in one side of the body, slurred speech, confusion, sleepiness, blurry vision, vision loss, deep venous thrombosis (DVT), pulmonary embolism, bone or joint pain, swelling in the abdomen, seizures, vomiting, facial numbness, defects in balance, weight loss, fever, night sweats, and loss of appetite.

[00207] In certain embodiments, subjects with a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP*, and/or subjects suffering from AML that are treated with the *SYNCRIP*-specific inhibitory nucleic acid will show reduced leukemic cell proliferation and/or increased survival compared to untreated AML subjects. In certain embodiments, subjects with a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP*, and/or subjects suffering from AML that are treated with the *SYNCRIP*-specific inhibitory nucleic acid will show reduced *SYNCRIP* and/or *HOXA9* expression levels compared to untreated AML subjects.

[00208] In one aspect, the present disclosure provides a method for monitoring the therapeutic efficacy of an *SYNCRIP*-specific inhibitory nucleic acid in a subject diagnosed with AML comprising: (a) detecting SYNCRIP protein levels in a test sample obtained from the subject after the subject has been administered the *SYNCRIP*-specific inhibitory nucleic acid; and (b) determining that the *SYNCRIP*-specific inhibitory nucleic acid is effective when the SYNCRIP protein levels in the test sample are reduced compared to that observed in a control sample obtained from the subject prior to administration of the *SYNCRIP*-specific inhibitory nucleic acid. The *SYNCRIP*-specific inhibitory nucleic acid may be an antisense oligonucleotide, a sgRNA, a shRNA, or a siRNA. The test sample may be tissues, cells or biological fluids (blood, plasma, saliva, urine, serum *etc.*) present within a subject. Alternatively, *HOXA9* expression levels may be used to determine efficacy of the *SYNCRIP*-specific inhibitory nucleic acid in the subject (see Example 9 described herein). Accordingly, in certain embodiments, the method further comprises detecting expression levels of *HOXA9* in the subject, wherein a decrease in *HOXA9* expression levels relative to those observed in the subject prior to treatment is indicative of the therapeutic efficacy of the *SYNCRIP*-specific inhibitory nucleic acid.

Prophylactic Methods

[00209] In one aspect, the present technology provides a method for preventing or delaying the onset of a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP*. Additionally or alternatively, in some aspects, the present technology provides a method for preventing or delaying the onset AML. The AML may be T-cell acute lymphoblastic leukemia or B-cell acute lymphoblastic leukemia.

[00210] Subjects at risk or susceptible to a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP*, and/or subjects at risk or susceptible to AML include those that exhibit one or more point mutations in *NRAS*, *DNMT3A, FLT3, KIT, IDH1, IDH2, CEBPA,* and *NPM1* and/or one or more chromosomal alterations (*e.g.*, an inversion, translocation, or gene fusion) such as *CBFB-MYH11, DEK-NUP214, MLL-MLLT3, PML-RARA, RBM15-MKL1, RPN1-EVI1* and *RUNX1-RUNX1T1*. Such subjects can be identified by, *e.g.*, any or a combination of diagnostic or prognostic assays known in the art.

[00211] In prophylactic applications, pharmaceutical compositions or medicaments comprising an *SYNCRIP*-specific inhibitory nucleic acid disclosed herein are administered to a subject susceptible to, or otherwise at risk of a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP*, and/or a subject susceptible to, or otherwise at risk of AML, in an amount sufficient to eliminate or reduce the risk, or delay the onset of the disease, including biochemical, histologic and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. Administration of a prophylactic *SYNCRIP*-specific inhibitory nucleic acid can occur prior to the manifestation of symptoms characteristic of the disease or disorder, such that the disease or disorder is prevented or, alternatively, delayed in its progression.

[00212] In some embodiments, treatment with the *SYNCRIP*-specific inhibitory nucleic acid will prevent or delay the onset of one or more of the following symptoms: leukemic cell proliferation, enlarged lymph nodes, anemia, neutropenia, leukopenia, leukostasis, chloroma, granulocytic sarcoma, myeloid sarcoma, fatigue, weakness, dizziness, chills, headaches, shortness of breath, thrombocytopenia, excess bruising and bleeding, frequent or severe nosebleeds, bleeding gums, gum pain and swelling, headache, weakness in one side of the body, slurred speech, confusion, sleepiness, blurry vision, vision loss, deep venous thrombosis (DVT), pulmonary embolism, bone or joint pain, swelling in the abdomen,

seizures, vomiting, facial numbness, defects in balance, weight loss, fever, night sweats, and loss of appetite. In certain embodiments, (a) subjects with a disease or condition characterized by elevated expression levels and/or increased activity of *SYNCRIP*, and/or (b) subjects with AML that are treated with the *SYNCRIP*-specific inhibitory nucleic acid will show *SYNCRIP* and/or *HOXA9* expression levels that resemble those observed in healthy control subjects.

[00213] For therapeutic and/or prophylactic applications, a composition comprising an *SYNCRIP*-specific inhibitory nucleic acid disclosed herein, is administered to the subject. In some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered one, two, three, four, or five times per day. In some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered more than five times per day. Additionally or alternatively, in some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered every day, every other day, every third day, every fourth day, every fifth day, or every sixth day. In some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered weekly, bi-weekly, tri-weekly, or monthly. In some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered for a period of one, two, three, four, or five weeks. In some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered for six weeks or more. In some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered for twelve weeks or more. In some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered for a period of less than one year. In some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered for a period of more than one year. In some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered throughout the subject's life.

[00214] In some embodiments of the methods of the present technology, the *SYNCRIP*-specific inhibitory nucleic acid is administered daily for 1 week or more. In some embodiments of the methods of the present technology, the *SYNCRIP*-specific inhibitory nucleic acid is administered daily for 2 weeks or more. In some embodiments of the methods of the present technology, the *SYNCRIP*-specific inhibitory nucleic acid is administered daily for 3 weeks or more. In some embodiments of the methods of the present technology, the *SYNCRIP*-specific inhibitory nucleic acid is administered daily for 4 weeks or more. In some embodiments of the methods of the present technology, the *SYNCRIP*-specific inhibitory nucleic acid is administered daily for 6 weeks or more. In some embodiments of the methods of the present technology, the *SYNCRIP*-specific inhibitory nucleic acid is administered daily

for 12 weeks or more. In some embodiments, the *SYNCRIP*-specific inhibitory nucleic acid is administered daily throughout the subject's life.

Determination of the Biological Effect of *SYNCRIP*-specific Inhibitory Nucleic acids

[00215] In various embodiments, suitable *in vitro* or *in vivo* assays are performed to determine the effect of a specific *SYNCRIP*-specific inhibitory nucleic acid and whether its administration is indicated for treatment. In various embodiments, *in vitro* assays can be performed with representative animal models, to determine if a given *SYNCRIP*-specific inhibitory nucleic acid exerts the desired effect on reducing or eliminating signs and/or symptoms of AML. Compounds for use in therapy can be tested in suitable animal model systems including, but not limited to rats, mice, chicken, cows, monkeys, rabbits, and the like, prior to testing in human subjects. Similarly, for *in vivo* testing, any of the animal model system known in the art can be used prior to administration to human subjects. In some embodiments, *in vitro* or *in vivo* testing is directed to the biological function of one or more *SYNCRIP*-specific inhibitory nucleic acids.

[00216] Animal models of AML may be generated using techniques known in the art. Such models may be used to demonstrate the biological effect of *SYNCRIP*-specific inhibitory nucleic acids in the prevention and treatment of conditions arising from disruption of a particular gene, and for determining what comprises a therapeutically effective amount of the one or more *SYNCRIP*-specific inhibitory nucleic acids disclosed herein in a given context.

Modes of Administration and Effective Dosages

[00217] Any method known to those in the art for contacting a cell, organ or tissue with one or more *SYNCRIP*-specific inhibitory nucleic acids disclosed herein may be employed. Suitable methods include *in vitro*, *ex vivo*, or *in vivo* methods. *In vivo* methods typically include the administration of one or more *SYNCRIP*-specific inhibitory nucleic acids to a mammal, suitably a human. When used *in vivo* for therapy, the one or more *SYNCRIP*-specific inhibitory nucleic acids described herein are administered to the subject in effective amounts (*i.e.*, amounts that have desired therapeutic effect). The dose and dosage regimen will depend upon the degree of the disease state of the subject, the characteristics of the particular *SYNCRIP*-specific inhibitory nucleic acid used, *e.g.*, its therapeutic index, and the subject's history.

[00218] The effective amount may be determined during pre-clinical trials and clinical trials by methods familiar to physicians and clinicians. An effective amount of one or more *SYNCRIP*-specific inhibitory nucleic acids useful in the methods may be administered to a mammal in need thereof by any of a number of well-known methods for administering pharmaceutical compounds. The *SYNCRIP*-specific inhibitory nucleic acids may be administered systemically or locally.

[00219] The one or more *SYNCRIP*-specific inhibitory nucleic acids described herein can be incorporated into pharmaceutical compositions for administration, singly or in combination, to a subject for the treatment or prevention of AML. Such compositions typically include the active agent and a pharmaceutically acceptable carrier. As used herein the term "pharmaceutically acceptable carrier" includes saline, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Supplementary active compounds can also be incorporated into the compositions.

[00220] Pharmaceutical compositions are typically formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral (*e.g.*, intravenous, intradermal, intraperitoneal or subcutaneous), oral, inhalation, transdermal (topical), intraocular, iontophoretic, and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. For convenience of the patient or treating physician, the dosing formulation can be provided in a kit containing all necessary equipment (*e.g.*, vials of drug, vials of diluent, syringes and needles) for a treatment course (*e.g.*, 7 days of treatment).

[00221] Pharmaceutical compositions suitable for injectable use can include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous

administration, suitable carriers include physiological saline, bacteriostatic water, CREMOPHOR EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, a composition for parenteral administration must be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi.

[00222] The pharmaceutical compositions having one or more *SYNCRIP*-specific inhibitory nucleic acids disclosed herein can include a carrier, which can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thiomerasol, and the like. Glutathione and other antioxidants can be included to prevent oxidation. In many cases, it will be advantageous to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate or gelatin.

[00223] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, typical methods of preparation include vacuum drying and freeze drying, which can yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00224] Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules, *e.g.*, gelatin capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as

part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00225] For administration by inhalation, the compounds can be delivered in the form of an aerosol spray from a pressurized container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer. Such methods include those described in U.S. Pat. No. 6,468,798.

[00226] Systemic administration of a therapeutic compound as described herein can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art. In one embodiment, transdermal administration may be performed by iontophoresis.

[00227] A therapeutic agent can be formulated in a carrier system. The carrier can be a colloidal system. The colloidal system can be a liposome, a phospholipid bilayer vehicle. In one embodiment, the therapeutic agent is encapsulated in a liposome while maintaining the agent's structural integrity. One skilled in the art would appreciate that there are a variety of methods to prepare liposomes. (See Lichtenberg, *et al.*, *Methods Biochem. Anal.*, 33:337-462 (1988); Anselem, *et al.*, *Liposome Technology*, CRC Press (1993)). Liposomal formulations can delay clearance and increase cellular uptake (See Reddy, *Ann. Pharmacother.*, 34(7-8):915-923 (2000)). An active agent can also be loaded into a particle prepared from pharmaceutically acceptable ingredients including, but not limited to, soluble, insoluble, permeable, impermeable, biodegradable or gastroretentive polymers or liposomes. Such particles include, but are not limited to, nanoparticles, biodegradable nanoparticles, microparticles, biodegradable microparticles, nanospheres, biodegradable nanospheres, microspheres, biodegradable microspheres, capsules, emulsions, liposomes, micelles and viral vector systems.

[00228] The carrier can also be a polymer, *e.g.*, a biodegradable, biocompatible polymer matrix. In one embodiment, the therapeutic agent can be embedded in the polymer matrix, while maintaining the agent's structural integrity. The polymer may be natural, such as polypeptides, proteins or polysaccharides, or synthetic, such as poly α-hydroxy acids. Examples include carriers made of, *e.g.*, collagen, fibronectin, elastin, cellulose acetate, cellulose nitrate, polysaccharide, fibrin, gelatin, and combinations thereof. In one embodiment, the polymer is poly-lactic acid (PLA) or copoly lactic/glycolic acid (PGLA). The polymeric matrices can be prepared and isolated in a variety of forms and sizes, including microspheres and nanospheres. Polymer formulations can lead to prolonged duration of therapeutic effect. (See Reddy, *Ann. Pharmacother.*, 34(7-8):915-923 (2000)). A polymer formulation for human growth hormone (hGH) has been used in clinical trials. (See Kozarich and Rich, *Chemical Biology*, 2:548-552 (1998)).

[00229] Examples of polymer microsphere sustained release formulations are described in PCT publication WO 99/15154 (Tracy, *et al.*), U.S. Pat. Nos. 5,674,534 and 5,716,644 (both to Zale, *et al.*), PCT publication WO 96/40073 (Zale, *et al.*), and PCT publication WO 00/38651 (Shah, *et al.*). U.S. Pat. Nos. 5,674,534 and 5,716,644 and PCT publication WO 96/40073 describe a polymeric matrix containing particles of erythropoietin that are stabilized against aggregation with a salt.

[00230] In some embodiments, the therapeutic compounds are prepared with carriers that will protect the therapeutic compounds against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Such formulations can be prepared using known techniques. The materials can also be obtained commercially, *e.g.*, from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to specific cells with monoclonal antibodies to cell-specific antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[00231] The therapeutic compounds can also be formulated to enhance intracellular delivery. For example, liposomal delivery systems are known in the art, see, *e.g.*, Chonn and Cullis, "Recent Advances in Liposome Drug Delivery Systems," *Current Opinion in Biotechnology* 6:698-708 (1995); Weiner, "Liposomes for Protein Delivery: Selecting

Manufacture and Development Processes," *Immunomethods*, 4(3):201-9 (1994); and Gregoriadis, "Engineering Liposomes for Drug Delivery: Progress and Problems," *Trends Biotechnol.*, 13(12):527-37 (1995). Mizguchi, *et al.*, *Cancer Lett.*, 100:63-69 (1996), describes the use of fusogenic liposomes to deliver a protein to cells both *in vivo* and *in vitro*.

[00232] Dosage, toxicity and therapeutic efficacy of any therapeutic agent can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds that exhibit high therapeutic indices are advantageous. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[00233] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds may be within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the methods, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to determine useful doses in humans accurately. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[00234] Typically, an effective amount of the one or more *SYNCRIP*-specific inhibitory nucleic acids disclosed herein sufficient for achieving a therapeutic or prophylactic effect, range from about 0.000001 mg per kilogram body weight per day to about 10,000 mg per kilogram body weight per day. Suitably, the dosage ranges are from about 0.0001 mg per kilogram body weight per day to about 100 mg per kilogram body weight per day. For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight every day, every two days or every three days or within the range of 1-10 mg/kg every week, every two weeks or every three weeks. In one embodiment, a single dosage of the therapeutic compound ranges from 0.001-10,000 micrograms per kg body weight. In one embodiment, one or more

SYNCRIP-specific inhibitory nucleic acid concentrations in a carrier range from 0.2 to 2000 micrograms per delivered milliliter. An exemplary treatment regime entails administration once per day or once a week. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, or until the subject shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

[00235] In some embodiments, a therapeutically effective amount of one or more *SYNCRIP*-specific inhibitory nucleic acids may be defined as a concentration of inhibitor at the target tissue of 10^{-32} to 10^{-6} molar, *e.g.*, approximately 10^{-7} molar. This concentration may be delivered by systemic doses of 0.001 to 100 mg/kg or equivalent dose by body surface area. The schedule of doses would be optimized to maintain the therapeutic concentration at the target tissue, such as by single daily or weekly administration, but also including continuous administration (*e.g.*, parenteral infusion or transdermal application).

[00236] The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to, the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of the therapeutic compositions described herein can include a single treatment or a series of treatments.

[00237] The mammal treated in accordance with the present methods can be any mammal, including, for example, farm animals, such as sheep, pigs, cows, and horses; pet animals, such as dogs and cats; laboratory animals, such as rats, mice and rabbits. In some embodiments, the mammal is a human.

Combination Therapy

[00238] In some embodiments, one or more of the *SYNCRIP*-specific inhibitory nucleic acids disclosed herein may be combined with one or more additional therapies for the prevention or treatment of AML. Additional therapeutic agents include, but are not limited to, chemotherapeutic agents, arsenic trioxide (Trisenox), all-trans retinoic acid (ATRA), and stem cell transplants.

[00239] In some embodiments, the one or more *SYNCRIP*-specific inhibitory nucleic acids disclosed herein may be separately, sequentially or simultaneously administered with at least one additional therapeutic agent selected from the group consisting of alkylating agents,

topoisomerase inhibitors, endoplasmic reticulum stress inducing agents, antimetabolites, mitotic inhibitors, nitrogen mustards, nitrosoureas, alkylsulfonates, platinum agents, taxanes, vinca agents, anti-estrogen drugs, aromatase inhibitors, ovarian suppression agents, VEGF/VEGFR inhibitors, EGF/EGFR inhibitors, PARP inhibitors, cytostatic alkaloids, cytotoxic antibiotics, antimetabolites, endocrine/hormonal agents, bisphosphonate therapy agents, phenphormin and targeted biological therapy agents (*e.g.*, therapeutic peptides described in US 6306832, WO 2012007137, WO 2005000889, WO 2010096603 *etc.*). In some embodiments, the at least one additional therapeutic agent is a chemotherapeutic agent.

[00240] Specific chemotherapeutic agents include, but are not limited to, cyclophosphamide, fluorouracil (or 5-fluorouracil or 5-FU), methotrexate, edatrexate (10-ethyl-10-deaza-aminopterin), thiotepa, carboplatin, cisplatin, taxanes, paclitaxel, protein-bound paclitaxel, docetaxel, vinorelbine, tamoxifen, raloxifene, toremifene, fulvestrant, gemcitabine, irinotecan, ixabepilone, temozolmide, topotecan, vincristine, vinblastine, eribulin, mutamycin, capecitabine, anastrozole, exemestane, letrozole, leuprolide, abarelix, buserlin, goserelin, megestrol acetate, risedronate, pamidronate, ibandronate, alendronate, denosumab, zoledronate, trastuzumab, tykerb, anthracyclines (*e.g.*, daunorubicin and doxorubicin), cladribine, midostaurin, bevacizumab, oxaliplatin, melphalan, etoposide, mechlorethamine, bleomycin, microtubule poisons, annonaceous acetogenins, chlorambucil, ifosfamide, streptozocin, carmustine, lomustine, busulfan, dacarbazine, temozolomide, altretamine, 6-mercaptopurine (6-MP), cytarabine, floxuridine, fludarabine, hydroxyurea, pemetrexed, epirubicin, idarubicin, SN-38, ARC, NPC, campothecin, 9-nitrocamptothecin, 9-aminocamptothecin, rubifen, gimatecan, diflomotecan, BN80927, DX-8951f, MAG-CPT, amsacnne, etoposide phosphate, teniposide, azacitidine (Vidaza), decitabine, accatin III, 10-deacetyltaxol, 7-xylosyl-10-deacetyltaxol, cephalomannine, 10-deacetyl-7-epitaxol, 7-epitaxol, 10-deacetylbaccatin III, 10-deacetyl cephalomannine, streptozotocin, nimustine, ranimustine, bendamustine, uramustine, estramustine, mannosulfan, camptothecin, exatecan, lurtotecan, lamellarin D9-aminocamptothecin, amsacrine, ellipticines, aurintricarboxylic acid, HU-331, or combinations thereof.

[00241] Examples of antimetabolites include 5-fluorouracil (5-FU), 6-mercaptopurine (6-MP), capecitabine, cytarabine, floxuridine, fludarabine, gemcitabine, hydroxyurea, methotrexate, pemetrexed, and mixtures thereof.

[00242] Examples of taxanes include accatin III, 10-deacetyltaxol, 7-xylosyl-10-deacetyltaxol, cephalomannine, 10-deacetyl-7-epitaxol, 7-epitaxol, 10-deacetylbaccatin III, 10-deacetyl cephalomannine, and mixtures thereof.

[00243] Examples of DNA alkylating agents include cyclophosphamide, chlorambucil, melphalan, bendamustine, uramustine, estramustine, carmustine, lomustine, nimustine, ranimustine, streptozotocin; busulfan, mannosulfan, and mixtures thereof.

[00244] Examples of topoisomerase I inhibitor include SN-38, ARC, NPC, camptothecin, topotecan, 9-nitrocamptothecin, exatecan, lurtotecan, lamellarin D9-aminocamptothecin, rubifen, gimatecan, diflomotecan, BN80927, DX-8951f, MAG-CPT, and mixtures thereof. Examples of topoisomerase II inhibitors include amsacrine, etoposide, etoposide phosphate, teniposide, daunorubicin, mitoxantrone, amsacrine, ellipticines, aurintricarboxylic acid, doxorubicin, and HU-331 and combinations thereof.

[00245] In certain embodiments, an additional therapeutic agent is administered to a subject in combination with the one or more *SYNCRIP*-specific inhibitory nucleic acids disclosed herein such that a synergistic therapeutic effect is produced. For example, administration of one or more *SYNCRIP*-specific inhibitory nucleic acids with one or more additional therapeutic agents for the prevention or treatment of AML will have greater than additive effects in the prevention or treatment of the disease. For example, lower doses of one or more of the therapeutic agents may be used in treating or preventing AML resulting in increased therapeutic efficacy and decreased side-effects. In some embodiments, the one or more *SYNCRIP*-specific inhibitory nucleic acids disclosed herein are administered in combination with any of the at least one additional therapeutic agents described above, such that a synergistic effect in the prevention or treatment of AML results.

[00246] In any case, the multiple therapeutic agents may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may vary from more than zero weeks to less than four weeks. In addition, the combination methods, compositions and formulations are not to be limited to the use of only two agents.

Kits

[00247] The present disclosure also provides kits for the prevention and/or treatment of AML comprising one or more *SYNCRIP*-specific inhibitory nucleic acids comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-2, 18-21 or any complement thereof. Optionally, the above described components of the kits of the present technology are packed in suitable containers and labeled for the prevention and/or treatment of AML.

[00248] The above-mentioned components may be stored in unit or multi-dose containers, for example, sealed ampoules, vials, bottles, syringes, and test tubes, as an aqueous, preferably sterile, solution or as a lyophilized, preferably sterile, formulation for reconstitution. The kit may further comprise a second container which holds a diluent suitable for diluting the pharmaceutical composition towards a higher volume. Suitable diluents include, but are not limited to, the pharmaceutically acceptable excipient of the pharmaceutical composition and a saline solution. Furthermore, the kit may comprise instructions for diluting the pharmaceutical composition and/or instructions for administering the pharmaceutical composition, whether diluted or not. The containers may be formed from a variety of materials such as glass or plastic and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper which may be pierced by a hypodermic injection needle). The kit may further comprise more containers comprising a pharmaceutically acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, culture medium for one or more of the suitable hosts. The kits may optionally include instructions customarily included in commercial packages of therapeutic or diagnostic products, that contain information about, for example, the indications, usage, dosage, manufacture, administration, contraindications and/or warnings concerning the use of such therapeutic or diagnostic products.

[00249] The kit can also comprise, *e.g.*, a buffering agent, a preservative or a stabilizing agent. The kit can also contain a control sample or a series of control samples, which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit. The kits of the present technology may contain a written product on or in the kit container. The written

product describes how to use the reagents contained in the kit. In certain embodiments, the use of the reagents can be according to the methods of the present technology.

EXAMPLES

[00250] The present technology is further illustrated by the following Examples, which should not be construed as limiting in any way. The following Examples demonstrate the preparation, characterization, and use of illustrative compositions of the present technology that inhibit SYNCRIP expression and/or activity.

Example 1: Experimental Materials and Methods

[00251] *Pool description for gene prioritization used for in vivo shRNA screen.* The number of genes used in the screen was determined based on previous studies that included approximately 100 genes (Cho S, *et al.*, *Mol Cell Biol.* 27:368–83 (2007)). Therefore, the genes in each pool were prioritized based on the following criteria. Pool 1 is made up of two sub-pools, 1a and 1b. Pool 1a was composed of differentially expressed genes prioritized based on Msi2 gene expression and other hematopoietic gene sets with a matrix score of 6 or more. Pool 1b was selected based on genes found in the leading edge taken from the GSEA with MSI2 overexpression in LSK cells overlapped with genes upregulated after shRNA depletion in CML/AML cell lines or leading edge genes in the rank list of Msi2 KO LSKs. Genes previously determined as canonical targets Numb, Numbl and CDKN1A, were added.

[00252] Pool 2 genes were chosen based on an intestinal CLIP-CHIP (UV-crosslinked mouse intestine) and immunoprecipitation for MSI1. MSI1 bound targets were ranked for the top 1000 genes, binding of the 3'UTR and their fold enrichment over the IgG control. These genes were ranked if they were MSI2-hematopoietic relevant genes. A combined score of 3 or more were included into the screen.

[00253] Pool 3 included MSI2 direct protein-protein interactors. A matrix score of 3 or more were chosen based on their ability to interact with MSI2 and was included in a MSI2 or hematopoietic relevant gene set.

[00254] *Intestinal MSI-1 CLIP-CHIP used for pool 2 gene prioritization.* UV-crosslinked mouse intestine was immunoprecipitated for MSI1. Similar CLIP protocol was performed as in Park *et al.*, *J Exp Med.* 211:71–87 (2014), with the exception that RNA was random primed and hybridized to Affymetric arrays 1.0ST array. Fold enrichment was ranked over IgG.

[00255] *Mass Spectrometry Methods and Analysis (used for Pool 3).* K562 cells were grown with either MSCV-IRES-GFP or with FLAG-MSI2 and immunoprecipitated with FLAG antibody as previously described in Park *et al.*, *J Clin Invest.* 125:1286–98 (2015). 150 million cells per experiment were then stained, and the gel was cut into nine slices. Control and MSI2 interacting proteins were considered to be represented if there were two or more peptides found and there was high confidence with a MASCOT score of either equal or greater than 20 or 77. Pairwise analysis was performed for two independent immunoprecipitation experiments and mass spectrometry analyses. TOPGENE was performed with 234 MSI2 direct binding targets.

[00256] *Lentiviral production, infection, and in vivo shRNA screen.* Lentiviruses expressing shRNAs in the pLKO.1 vectors were obtained from RNAi consortium at the Broad Institute (Boston, MA). Virus production and preparation of pooled and titered lentiviruses for screening was performed as described in Miller *et al.*, *Cancer Cell.* 24(1):45-58 (2013). Pooled titered virus was thawed and kept on ice. L-GMPs (c-kit high cells top 50% were sorted). Infection, 12 well dishes were re-suspended into 600 µL virus + 600 µL of cells ($2*10^6$ cells) per replicate (1.2mL/well). Cells were spinfected (2500 RPM, 90 minutes) and then cells were split for day 0 sequencing or injected into sub-lethally irradiated mice. Five pools representing a random set of ~100 shRNAs per pool with a total of titered 627 shRNA viruses were generated and used to transduce leukemia cells. Each transducing well was split: half was kept for sequencing and half was transplanted (1 million cells) into a sub-lethally irradiated recipient mice. There were five replicates per pool with five mice per pool with an experiment representing 25 total mice. After two weeks, cells were harvested from bone marrow and spleen and previously frozen cells for sequencing analysis. The sequences of the SYNCRIP shRNAs described herein are provided below:

Gene	shRNA ID	Sequence
Mouse SYNCRIP	KD-1	5’ GCAGCACAAGAGGCTGTTAAA 3’ (SEQ ID NO: 18)
Mouse SYNCRIP	KD-2	5’ GCAACCTTAAATATCTCGGAT 3’ (SEQ ID NO: 19)
Human SYNCRIP	shRNA#1	5’ GCACATAGTGATTTAGATGAA 3’ (SEQ ID NO: 20)
Human SYNCRIP	shRNA#2	5’ CCAAAGTAGCAGATTCTAGTA 3’ (SEQ ID NO: 21)

[00257] *Isolation, infection and selection of murine leukemia and normal cells.* Tibia and femurs, pelvis, and arm bones from leukemia or C57Bl/6 wild-type mice (6-8 weeks old) were harvested, crushed, filtered, and subjected to red blood cell lysis (QIAGEN, Hilden, Germany). To isolate c-kit positive cells, bone marrow cells were incubated with CD117 microbeads (Miltenyi Biotec, Somerville MA), according to manufacturer's instructions, and then subjected to positive selection using autoMACS Pro Separator. Cells were spinfected in RPMI with 10% FBS and cytokines: SCF (10 ng/ml), IL-3 (10 ng/ml), and IL-6 (10 ng/ml) and GM-CSF (10 ng/ml). 48 hours post-transduction, cells were treated with 2 μg/ml puromycin. Two days after puromycin selection, cells were harvested for further analysis.

[00258] *Colony forming assay.* 10,000 cells were plated on methocult GFM3434 (STEMCELL Technologies, Cambridge MA). Colonies were scored every five days for leukemia cells and every seven days for normal c-kit-enriched bone marrow cells.

[00259] *In vivo transplantation of leukemia cells.* MLL-AF9 tertiary mouse leukemia cells were transduced with lentiviruses expressing puromycin and shRNAs against *Syncrip* or a control shRNA. Transduced cells were selected by 2 μg/ml puromycin for 2 days. 50,000 selected cells were injected retro-orbitally into female C57Bl/6 (6-8 weeks old) recipient mice that had been sub-lethally irradiated with 475 cGy.

[00260] *CRISPR/Cas9 approach to create SYNCRIP-CRISPR-knock out (CR-KO).* The CRISPR gRNAs used for deleting exon 3 and 4 of the *Syncrip* gene were designed using the approach reported in Romanienko *et al.*, *PLoS One* 11(2):e0148362 (2016). The sequence for the 5'-gRNA is GTACCTGTATTACCCAATGC (SEQ ID NO: 1) and sequence for the 3'-gRNA is CAATTTGGAATTGACCGCAC (SEQ ID NO: 2). Both sgRNAs were produced by *in vitro* transcription using the pU6T7 promoter in the hybrid plasmid described in Romanienko *et al.*, *PLoS One* 11(2):e0148362 (2016). To initiate cleavage of the target locus in mice, gRNA (C67) and gRNA (C69) in conjunction with Cas9 mRNA were co-injected into the pronucleus of mouse zygotes at a concentration of 50 ng/μl each, using conventional techniques. Deleted samples were assayed using PCR primers: CAGTGTTCAGGACTACTTGGACAC (SYNCRIPA) (SEQ ID NO: 3) and GTCTATGCTTTCCATAGATGGTTGTAG (SYNCRIPD) (SEQ ID NO: 4), which are located outside of the gRNA cleavage sites (outside SYNCRIP exon 3-4) thereby revealing the size of the deletion based on the nucleotide length of the amplicon obtained (~ 900bp for wild-type vs. ~ 300 bp for deletion).

[00261] *Isolation of fetal liver cells, PCR genotyping and bone marrow transplantation.* Fetal liver cells were isolated and single cell suspended based on standard protocols (Hemann M. *Cold Spring Harb Protoc.* 2015(7):679-84 (2015). ~ 200,000 fetal liver cells after red blood cell lysis were used for DNA extracting using HotSHOT genomic DNA preparation methods. 2 µl supernatant containing DNA was used for PCR reactions with specific primers for detection of *Syncrip* exon 3-4. DNA was resolved in 1.5% agarose gel. 500,000 cells from confirmed wild-type and *Syncrip*-CR-KO fetal livers were retro-orbitally injected into lethally irradiated CD45.1 recipient mice. For secondary transplantation, 1 million bone marrow cells were retro-orbitally injected into lethally irradiated CD45.1 recipient mice.

[00262] *Generation of MLL-AF9 primary leukemia and transplantation.* Bone marrow cells from 6- to 10-week-old transplanted $WT^{fl/fl}$ or *CR-SYNCRIP KO* $^{\Delta/\Delta}$ mice were isolated and subsequently enriched for c-kit positive cells. c-kit enriched cells were stained with Lineage antibody cocktail (CD3, CD4, CD8, Gr1, B220, CD19, TER119 conjugated with PeCy5), Sca-Pac Blue, CD34-FITC, SLAM-APC, CD48-PE, and c-KIT-APC-Cy7. Lin-$Sca^{+}Kit^{+}$ cells were sorted using a BD FACS Aria. Sorted cells were grown overnight in SFEM medium with 10 ng/ml IL-3, 10 ng/ml IL-6, 50 ng/ml SCF, 10 ng/ml thrombopoietin (TPO), and 20 ng/ml FLT3L. Cells were transduced twice with supernatant containing retroviruses expressing MLL-AF9 and GFP on retronectin-coated 96 well flat-bottom plates. The cells were expanded for one week in GFM3434 methylcellulose (STEMCELL Technologies, Cambridge MA). MLL-AF9 transformed cells were sorted based on GFP positivity. 200,000 GFP^{+} sorted cells and 250,000 helper cells were injected retro-orbitally into each lethally irradiated 6-8 week-old C57Bl/6 mouse.

[00263] *Proliferation assay of human leukemia cells.* Human leukemia cells were infected with viruses expressing scramble and hairpins against SYNCRIP by spinfection of cells in RPMI with 10% FBS together with viral supernatant. After 48 hours of infection, cells were treated with 3 µg/ml puromycin. Two days after puromycin selection, cells were plated at 250,000 cells/ml for proliferation assay. Cells were counted everyday using MUSE cell analyzer (EMD Millipore, Billerica MA) after plating. Cell growth was calculated based on normalization of cell number to cell number at plating. All cell lines were purchased from ATCC (Manassas, VA), and tested negative for mycoplasma contamination.

[00264] *Intracellular staining and flow cytometry*. For intracellular staining, cells were fixed with 1.5% paraformaldehyde at room temperature for 15 minutes and permeabilized with ice-cold methanol. Cells were washed 3 times with PBS and incubated with SYNCRIP antibody (MAB11004, EMD Millipore, Billerica MA) in 2% FBS PBS for 1 hour at room

temperature. Cells were then washed twice with PBS and incubated with secondary antibody conjugated with Alexa Fluor 647 (Molecular Probes, Eugene OR) for 30 min at room temperature. Cells were washed with PBS and re-suspended prior to analysis using BD Fortessa instrument.

[00265] Cells were stained for Mac1-PB, Gr1-APC, F480-PE-Cy7, CD115-APC and c-Kit-APC-Cy7 and analyzed on a BD FACS LSR Fortessa instrument to assess differentiation status of wild-type and knockdown leukemia cells. For stem and progenitor cells analysis of fetal liver hematopoietic cells, 10^6 cells were stained with stem/progenitor cells' antibody panel including: lineage antibody cocktail (CD3, CD4, CD8, Gr1, B220, CD19, TER119 conjugated with PeCy5), Sca-Pac Blue, KIT-APC-Cy7, CD34-FITC, CD16/32-PE-CY7, CD48-PE and SLAM-CD150-APC. For analysis of engraftment in recipient mice, 10^6 bone marrow cells were stained with stem/progenitor cells' antibody panel and CD45.1-PE-Texas Red and CD45.2-A700.

[00266] To measure apoptosis, cells were washed with PBS and incubated with anti–ANNEXIN-V-PE (BD Biosciences, Franklin Lakes NJ) in the ANNEXIN-V binding buffer (10 mM HEPES, pH 7.4, 140 mM NaCl, 4 mM KCl, 0.75 mM $MgCl_2$, 1 mM $CaCl_2$) in a reaction volume of 100 µl for 15 minutes. DAPI was added prior to analysis using a BD Fortessa instrument.

[00267] *O-Propargyl-puromycin (OP-puro) flow analysis.* Cells were plated at 100,000 cells/ml density and treated with 50 µM OP-Puro (NU-931-05, Jena Bioscience, Jena, Germany). Control cells were treated with cyclohexamide (CHX) at 150 µg/ml for 15 minutes. Cells were washed twice prior to collection and processed using Click-iT® Flow Cytometry Assay Kit (C10418, Invitrogen, Carlsbad CA) following the manufacturer's instructions. Labelled cells were analyzed using BD Fortessa instrument.

[00268] *Immunoprecipitation and immunoblot analysis.* K562 cells were collected by spinning down at 1,500 rpm for five minutes at 4°C, washed twice with PBS, and then re-suspended thoroughly at $2x10^7$ per ml in 1× Ripa buffer (BP-115- Boston BioProducts, Ashland MA) with freshly added DTT (1mM) and proteinase inhibitor cocktail. The cells were incubated for 30 min on ice. Supernatant was then collected after the mix was spun at 14,000 rpm for 30 min at 4°C. For each immunoprecipitation assay, 250 µl of cell extract was mixed with 750 µl of 1x Ripa buffer 2 µg of anti-mouse/anti-SYNCRIP antibody or 2 µg anti-rabbit/anti-MSI2 and 50 µl agarose beads. For RNA independent assay, lysates were treated with RNase A (1µg/ml) for 30 min at 37°C prior to co-immunoprecipitation

reactions. After rotating at 4°C overnight, beads were washed 5 times with 1×Ripa buffer and boiled with 1× Lamine protein running buffer.

[00269] For immunoblot analysis, cells were counted and washed twice with cold PBS prior to collection. ~ 250,000 cells were re-suspended and lysed in 40 µl 1× Lamine protein running buffer and boiled for 5 minutes. Whole cell lysates were run on 4%–15% gradient SDS-PAGE and transferred to nitrocellulose membrane. Membranes were blotted for SYNCRIP (MAB11004 or 05-1517; EMD Millipore, Billerica MA), IKZF2 (sc-9864; Santa Cruz Biotechnology, Dallas TX), HOXA9 (07-178; EMD Millipore, Billerica MA and ab140631; Abcam, Cambridge, UK), MYC (5605S; Cell Signaling Technology, Danvers MA), MSI2 (ab76148; Abcam, Cambridge, UK), and Actin (A3854; Sigma-Aldrich, St. Louis MO).

[00270] *RNA immunoprecipitation.* $30x10^6$ RN2 leukemia cells were used for RNA-IP using the Magna RIP RNA-binding protein immunoprecipitation kit (03-115; EMD Millipore, Billerica MA). First, cells were washed with cold PBS and then lysed. Anti-rabbit antibody or anti-MSI2 antibody (EMD Millipore, Billerica MA); anti-mouse or anti-SYNCRIP (18E4; EMD Millipore, Billerica MA) incubated with magnetic beads was used to immunoprecipitate MSI2 and SYNCRIP. After washing, the immunoprecipitated complexes were treated with proteinase K. RNA extraction was performed by the phenol/chloroform method, and purified RNA was converted to cDNA using the Verso cDNA kit (Thermo Fisher Scientific, Waltham MA). Quantitative PCR was used for validating target mRNAs bound by MSI2 and SYNCRIP.

[00271] *mRNA stability analysis.* Control and SYNCRIP depleted cells were treated with 5 µg/ml of Actinomycin D and harvested at indicated time points. Total RNA was isolated using RNeasy RNA extraction kit. 200 ng of RNA was used for reverse transcription reaction and quantitative RT-PCR for *Syncrip, Hoxa9, Ikzf2, Myc* and β-actin was performed. β-actin served as a housekeeping gene control. Relative mRNA levels were normalized to the starting point of treatment.

[00272] *Metabolic labeling and capture of newly synthesized protein.* Newly synthesized proteins were labeled using the Click-iT Protein Labeling Kit (Invitrogen, Carlsbad CA). 48 hours after infection with corresponding shRNA-expressing plasmids, 1×10^7 MOLM13 selected cells were cultured at $1x10^6$ cells/mL in fresh media for 14 hours. After one wash with PBS, cells were re-suspended in methionine-free RPMI 1640 medium (Gibco, Thermo Fisher Scientific, Waltham MA) supplemented with 10% dialyzed FBS (Gibco, Thermo

Fisher Scientific, Waltham MA) for 30 min, at which point the methionine analog L-azidohomoalanine (AHA) was added (50 μM, 14 hours) to allow incorporation of AHA into nascent proteins. Cells were harvested and lysed in 50 mM Tris-HCl, pH 8.0, 1% SDS, with protease and phosphatase inhibitor mixes (complete and PhosSTOP, Roche, Basel, Switzerland). 150 μg of total protein (up to 50 μL of lysate) were used in the crosslinking of AHA-labeled nascent proteins to an alkyne-derivatized biotin in the Click-iT Protein Reaction Buffer (Invitrogen, Carlsbad CA) according to manufacturer's instructions. The resulting precipitated total protein pellet was re-solubilized in 100 μL of 1% SDS PBS with protease inhibitors by pipetting, vortexing and incubating at 70°C for 10 minutes. The SDS was then quenched with 100 μL of 6% NP-40 in PBS with protease inhibitors. After centrifuging at 15,000 ×g for 5 minutes at room temperature to remove any insoluble particles, biotin-crosslinked nascent proteins were then captured overnight with streptavidin-coated Dynabeads M-280 (Invitrogen, Carlsbad CA) and then eluted from the beads by boiling the samples for 5 min in 2% SDS loading buffer for Western Blotting. Beads were thoroughly washed with PBS with 0.1% bovine serum albumin and 2% NP-40, first, and finally with PBS. The whole volume of AHA-labeled, biotin-crosslinked, streptavidin-pulled down protein was separated by SDS-PAGE together with lysate depleted of nascent protein after streptavidin incubation and input lysates.

[00273] *RNA purification and quantitative Real time PCR (qRT-PCR).* Total RNA was isolated using TRIzol and the Qiagen RNeasy Plus® mini kit (QIAGEN, Hilden, Germany). cDNA was generated from RNA using iScript™ cDNA Synthesis (Biorad Kit #1708891, Biorad Laboratories, Hercules CA) with random hexamers according to the manufacturer's instructions. Real-time PCR reactions were performed using an ABI 7500 sequence detection system. Quantitative PCR for actin was performed to normalize for cDNA loading. Relative quantification of the genes was calculated using the method ($2^{-\Delta\Delta Ct}$) as described by the manufacturer.

[00274] *RNA sequencing.* Total RNA was isolated from 9 individually transduced and processed MLL-AF9 murine leukemia cells (n=3 for each group including shRNA against luciferase, two shRNAs against SYNCRIP) using TRIzol and the Qiagen RNeasy Plus® mini kit (QIAGEN, Hilden, Germany). RNA was denatured and the first chain of cDNA was synthesized using oligo-dT primer containing illumina-compatible linker sequence. After removal of RNA, the second cDNA chain was synthesized with random decamer containing

another illumina-compatible linker sequence. Illumina compatible annealing sequences and external barcodes were introduced during amplification of the libraries.

[00275] *Differential expression and pathway analysis.* Quality Control of raw reads was done using FastQC (v0.11.2) to make sure there were no major flaws in sequencing. The raw reads were then mapped to mm10 genome using STAR (v2.3.0e_r291) and default parameters. The mapped reads were counted using htseq-count (v0.6.0, parameters –t exon) and gene models from Ensembl (Mus_musculus.GRCm38.75.gtf). Differential expression was performed using DESeq2 (v1.2.10, default parameters).

[00276] *Statistical analysis.* Student's t test was used for significance testing in the bar graphs, except where stated otherwise. A two-sample equal variance with normal distribution was used. P values less than 0.05 were considered significant. Graphs and error bars reflect mean + s.e.m, except where stated otherwise.

[00277] For animal study, survival probabilities were estimated using the Kaplan-Meier method and compared with the log-rank test. Ten mice per group were chosen to have an estimated 80% power in detecting a greater than 1.50 s.d. difference in means at a significance level of $\alpha = 0.05$ using a two-sided test. All animals were randomly assigned to the experimental groups. All statistical analyses were carried out using GraphPad Prism 4.0 and the R statistical environment.

[00278] *Syncrip conditional knockout (cKO) mouse model.* A *Syncrip* cKO mouse was generated by targeting the *Syncrip* locus in embryonic stem cells with a construct containing loxP sites flanking *Syncrip* exons 3 and 4 (Figure 25(A)). The neomycin resistance selection cassette was removed and a *Syncrip*$^{flox/flox}$ mouse colony was established. The *Syncrip*$^{flox/flox}$ mice were crossed with *Mx-1 Cre* mice and an inducible *Syncrip* loss of function strain (*Syncrip*$^{flox/flox}$: *Mx1-Cre*) was generated.

Example 2: Identification of Novel Regulators of Leukemia Using Pooled In vivo shRNA Screening of the RNA-binding Protein Musashi2 (MSI2) Interactome

[00279] To identify which RBPs are required for the survival of myeloid leukemia, an *in vivo* pooled short hairpin (shRNAs) screen in MLL-AF9 driven leukemia cells enriched for LSCs was conducted. The mixed lineage leukemia (MLL) gene has been shown to be involved in chromosomal translocations in over 70% of childhood leukemia and 5-10% of leukemia in adult.

[00280] T(9;11) MLL-AF9 translocation is the most common translocation in acute myeloid leukemia (AML). Expression of the fusion protein MLL-AF9 in granulocyte-

monocyte progenitor cells (GMPs) results in an established, robust, and short latency leukemia model, where LSCs can be enriched after serial transplantations (Miller PG, *et al.*, *Cancer Cell* 24:45–58 (2013). MSI2 was used as a founding factor and mass spectrometry analysis was performed on FLAG-MSI2 immunoprecipitated complexes in a leukemia cell line (K562) (Figure 8(A)). A group of 234 proteins of multiple RBP classes were identified in association with MSI2 (Figure 1(A)). Functional GO term analysis linked these 234 proteins to RNA binding functions, including polyA binding and helicase activity (Figure 8(B)).

[00281] To obtain a comprehensive assessment of MSI2 functional networks, data generated from MSI2 associated genomic studies was used to prioritize genes in different candidate pools for functional screening. 51 genes with differential expression found in MSI2 depleted CML/AML cell lines, MSI2 overexpressing LSK cells, and MSI2 KO LSK cells were prioritized based on their associations with hematopoietic/leukemic gene sets, and Gene set enrichment analysis leading edge genes were included in Pool 1. Genes identified as MSI1 binding mRNA targets were ranked and evaluated for their relevance to MSI2 and hematopoietic system, and 19 genes were included in Pool 2. Similarly, 58 genes discovered from MSI2 protein-protein interactions and had relevance to hematopoietic/leukemic gene sets were selected for Pool 3.

[00282] A total of 128 genes were selected and 5-7 hairpins targeting each gene were obtained. Using a pooled library of titered shRNAs lentiviruses, LSC enriched cells (a tertiary transplant of c-kit enriched MLL-AF9-dsRed leukemia) were transduced sorted and subsequently transplanted into sub-lethally irradiated recipient mice (Figure 1(B)). The cells were allowed to engraft and then the relative representation of each shRNA in the leukemia cells was quantified from the bone marrow and spleen at day 0 and day 16 post transplantation. See Figure 15 and Figure 16. A pool of shRNAs with greater than 20 fold depletion was recovered, which indicated a strong selection against their expression during leukemia progression (Figure 1(C) and Figures 8(C)-8(F)).

[00283] The 24 top hits were prioritized; each hit had at least five hairpins that resulted in 20-fold depletion in both the bone marrow and spleen (Figures 1(D)-1(E), Figure 15 and Figure 16). GO analysis of the top genes revealed a significant enrichment for RBPs and mRNA binding proteins. The majority of the hits (20/24) were in the MSI2-protein-protein interaction group (Pool 3), demonstrating that these complexes were important for disease progression (Figures 1(F)-1(G)). Among the top 24 scored genes, seven genes were selected (of which four encode RBPs) for *in vitro* validation including: SYNCRIP, Caprin, Dyrk2,

Hnrnpr, Cct3, Mybbp1, and Hnrnpa3 (Figure 1(H) and Figure 8(G)). In all of the genes tested, knock down was confirmed and a reduction in colony formation was observed (Figure 1(I) and Figure 8(H)). Additionally, MLL-AF9 leukemia cells were generally more sensitive to shRNA depletion compared to normal cells (c-kit+ enriched from bone marrow), except for Dyrk2, which was equally depleted (Figure 1(I)). These data demonstrate that a dysregulated RBP network is differentially required for leukemia cell survival compared to normal cells.

[00284] Accordingly, the *SYNCRIP*-specific inhibitory nucleic acids disclosed herein are useful in methods for inhibiting leukemic cell proliferation and treating AML in a subject in need thereof.

Example 3: SYNCRIP is Required for Survival of Leukemia Cells

[00285] Of the *in vitro* validated genes from Example 2, SYNCRIP demonstrated the most differential effect (10-fold) in colony forming ability between leukemia cells and normal c-kit+ enriched cells. To further evaluate the effects of SYNCRIP depletion, it was first confirmed that shRNAs specific for SYNCRIP resulted in the reduction of SYNCRIP by immunoblot in MLL-AF9 transformed leukemia cells (Figure 2(A) and Figure 9(A)). SYNCRIP depletion in leukemic cells resulted in rapid increase in myeloid differentiation based on increased Gr-1 and Mac-1, F480 and CD115 surface staining (Figures 2(B)-2(C) and Figures 9(B)-9(C)), and cellular morphology (Figure 2(D)) at day 4 post transduction. Significant change in c-kit level was only observed for SYNCRIP-depleted cells with one hairpin shRNA (shRNA#2) but not the other shRNA (shRNA#1) (Figure 9(D)). SYNCRIP-KD also resulted in apoptosis of leukemia cells at 5 days post transduction (Figure 2(E) and Figures 9(E)-9(F)), demonstrating that differentiating cells subsequently underwent apoptosis. SYNCRIP function was not restricted to MLL-AF9 driven leukemia; a similar reduction in colony formation of AML-ETO9a driven leukemia cells depleted for SYNCRIP was also observed (Figures 9(G)-9(H)). shRNA mediated depletion in MLL-AF9 leukemia cells was performed, which demonstrated a requirement for leukemic disease *in vivo*, (Figure 2(F)) since diseased mice with SYNCRIP-shRNA expressing leukemia cells selected for attenuated SYNCRIP-knockdown (Figures 9(I)- 9(J)).

[00286] To rule out the potential for off-target effects from shRNA mediated knockdown and to test an additional leukemia cell line, SYNCRIP-guide RNAs (gRNAs) were developed for CRISPR/Cas9 mediated deletion. RN2- myeloid leukemia cells (MLL-AF9, NRASG12D and expressing rtTA-RN2 cells) were transduced with vectors expressing the inducible (tetO)

Cas9 and gRNAs specific for SYNCRIP or an empty vector (Cas9-EV) and sorted based on GFP positivity after induction by Doxycycline (Dox). A reduction in colony formation and proliferation with an increase in differentiation (Figures 2(G)-2(I) and Figures 9(K)-9(L)) in SYNCRIP depleted RN2 cells was observed. No significant change in percentage of c-kit high cells was observed upon SYNCRIP depletion (Figure 9(M)).

[00287] Multiple isoforms of SYNCRIP (UniProtKB - O60506 human SYNCRIP/HNRNP Q) are expressed in mammalian cells. To identify the SYNCRIP isoforms in leukemia, cDNAs encoding 3 different isoforms of SYNCRIP were overexpressed (hnRNP_Q1: 562 amino acids, Q3: 623 amino acids, and Q4: 527 amino acids) in RN2 cells. Immunoblot analysis demonstrated the existence of 2 SYNCRIP isoforms with the dominant isoform being Q1 (562 aa) and the alternative, larger isoform Q3 (623 aa) (Figure 9(N)). Despite the aggressiveness of the RN2 MLL-AF9 leukemia cells, SYNCRIP overexpression increased colony forming activity, demonstrating that SYNCRIP overexpression can potentiate leukemic cell growth (Figure 9(O)). Additionally, overexpression of SYNCRIP dominant isoform (562 aa) in RN2 cells drove a more rapid leukemia *in vivo* (Figure 2(J)).

[00288] Consistent with an on-target effect of CRISPR/Cas9 deletion for SYNCRIP, ectopic expression of non-target human SYNCRIP rescued the reduction in colony formation and reverse the increased differentiation from SYNCRIP depletion (Figures 2(K)-2(L) and Figures 9(P)-9(Q)). Therefore, the data shows that SYNCRIP is required for leukemic cell growth, cell survival, and maintenance of the undifferentiated state.

[00289] Accordingly, the *SYNCRIP*-specific inhibitory nucleic acids disclosed herein are useful in methods for inhibiting leukemic cell proliferation and treating AML in a subject in need thereof.

Example 4: CRIPSR/Cas9 Deletion of SYNCRIP Differentially Impairs Leukemogenesis but not Normal Hematopoiesis

[00290] To further assess SYNCRIP function in normal and malignant hematopoiesis *in vivo*, mice deficient for SYNCRIP were developed using CRISPR/Cas9 approach with co-injection of gRNAs and Cas9 mRNA into the pronucleus of mouse zygotes. Fetal liver cells were collected from developed embryos in pseudo moms at E14 and fetal liver genotypes were determined by PCR (Figures 3(A)-3(B) and Figure 10(A)). Confirmed wild type (WT) and CRIPSR-knockout samples (CR-KO) were analyzed, and an equivalent frequency of phenotypic HSCs in WTs versus CR-KOs was found (Figure 3(C) and Figure 10(B)) along

with a modest increase in colony forming units granulocyte-macrophage (CFU-GM) in the CR-KOs (Figure 10(C)).

[00291] Analysis of SYNCRIP functions during normal hematopoiesis *in vivo* was performed by monitoring the engraftment efficiency of WT vs. CR-KO cells in transplanted recipient mice. Reduction of SYNCRIP protein expression in engrafted bone marrow cells from CR-KO compared to WT recipient was confirmed (Figures 3(D)-3(E)). No defect in engraftment of CR-KO cells in primary transplant mice was observed (Figure 3(F)).

[00292] To determine whether SYNCRIP is required for development of leukemia *in vivo*, LSKs cells from bone marrow of SYNCRIP WT and CR-KO primary transplanted mice were isolated and transduced with MLL-AF9-GFP expressing viruses. MLL-AF9-GFP transformed cells were injected into recipient mice (Figure 3(G)). Additionally, a secondary bone marrow transplantation of SYNCRIP WT and CR-KO bone marrow cells into lethally irradiated mice was performed, which resulted in a mild reduction in engraftment (Figures 3(H)-3(I)). MLL-AF9-GFP transformed LSK cells derived from CR-KO recipients showed a delay in leukemogenesis *in vivo* when compared to WT cells (Figure 3(J)). It was determined that expression of SYNCRIP was maintained when the animals died of leukemia (Figure 3(K) and Figure 10(D)). This data shows that the CRISPR-driven KO fetal liver samples were mosaic for both WT and CR-KO SYNCRIP, resulting in the residual SYNCRIP-WT leukemia to grow out. Overall, this data show the requirement of SYNCRIP in the development of leukemia in a genetic mouse model.

[00293] Accordingly, the *SYNCRIP*-specific inhibitory nucleic acids disclosed herein are useful in methods for inhibiting leukemic cell proliferation and treating AML in a subject in need thereof.

Example 5: SYNCRIP is Highly Expressed and Essential for Human Leukemia Cells

[00294] To define SYNCRIP's role in human leukemia, a previously published expression dataset was surveyed (Bagger FO *et al.*, *Nucleic Acids Res.* 41:D1034-9 (2013)). SYNCRIP expression was elevated in AML patients with diverse genetic alterations compared to normal hematopoietic stem and progenitor cells (Figure 4(A)). Elevated expression of SYNCRIP in other hematological malignancies including T-ALL and B-ALLs with various genetic abnormalities was also determined (Figure 11(A)). High levels of SYNCRIP expression were also observed across multiple human myeloid leukemia cell lines compared to normal human CD34 enriched cord blood cells (CB-CD34+ cells)(Figure 11(B)). SYNCRIP was

highly expressed at the protein level in human myeloid leukemia cell lines (10/11) and primary patient samples (5 patients) compared to CB-CD34 cells (Figures 4(B)-4(C)).

[00295] To test the functional role of the increased SYNCRIP expression in leukemic cells, myeloid leukemia cells (MOLM13, NOMO-1, KASUMI-1 and NB4) were transduced with lentiviral shRNA vectors targeting SYNCRIP and knock down of SYNCRIP with 2 independent hairpins was obtained. Depletion of SYNCRIP resulted in reduced cell proliferation and increased apoptosis coupled with increased myeloid differentiation, depending on the particular marker, in the AML cell lines (Figures 4(D)-4(H) and Figures 11(C)-11(H)). This data shows that SYNCRIP plays a role in different types of human myeloid leukemia driven by various oncogenic drivers.

[00296] Accordingly, the *SYNCRIP*-specific inhibitory nucleic acids disclosed herein are useful in methods for inhibiting leukemic cell proliferation and treating AML in a subject in need thereof.

Example 6: SYNCRIP and MSI2 Co-regulate Leukemia Stem Cell Gene Expression Programs

[00297] To understand the molecular function of SYNCRIP in leukemia, RNA-sequencing was performed on MLL-AF9 leukemia cells transduced with shRNAs against SYNCRIP four days post-transduction. The transcriptional profile of SYNCRIP-shRNA transduced cells was significantly altered and the results obtained from two independent shRNA hairpins were highly correlated (Figure 12(A)). 282 genes were differentially expressed, where 57 were downregulated (SYNCRIP was ranked 9th most downregulated gene) and 225 were upregulated (Log_2 Fold change>1.5, FDR<0.01, Figures 5(A), and Figure 17). The RNA-sequencing analysis was functionally annotated by performing Gene Set Enrichment Analysis (GSEA) on all curated gene sets in the Molecular Signatures Database (MSigDB, Broad Institute, Cambridge MA; 3,256 gene sets) combined with an additional set of relevant gene sets (92 gene sets from experimentally derived or published hematopoietic self-renewal and differentiation signatures) using the ranked list of differentially expressed genes in SYNCRIP-shRNA samples (Cntrl/SYNCRIP-shRNA). Genes upregulated after SYNCRIP depletion were enriched in 236 gene sets and downregulated genes were enriched in 172 gene sets. Set of genes downregulated in HSCs (CD133+ vs CD133-), LSC related gene signature associated with a good prognosis in AML and the myeloid development program were significantly enriched for upregulated genes in SYNCRIP depleted cells (Figures 5(B)-5(D)).

[00298] Additionally, it was found that MLL-AF9 direct targets were enriched for genes downregulated after SYNCRIP depletion (Figures 5(E)-5(F)). Consistent with the MLL

program being reversed upon SYNCRIP knockdown, genes negatively regulated by HOXA9/MEIS1 were enriched for genes suppressed by SYNCRIP (Figure 5(G)). Overall, these data demonstrate that SYNCRIP depletion results in a loss of the HSC/LSC program and the MLL-AF9 gene expression program. The studies show that SYNCRIP and MSI2 coregulate the LSC/MLL epigenetic program. Consistent with this observation, genes downregulated after SYNCRIP depletion were significantly enriched for MSI2's direct mRNA binding targets (Top HITS-CLIP; Cross-linking immunoprecipitation followed by high throughput RNA-sequencing targets) (Figure 5(H)). Furthermore, genes upregulated in SYNCRIP depleted cells were enriched for genes that were also upregulated in *Msi2* deleted LSCs (Figure 5(I)). Genes regulated by MSI2 including Hoxa9, c-Myc, Ikzf2, and Meis1 were found to be downregulated upon loss of SYNCRIP (Figure 12(B)).

[00299] A human expression dataset was examined (Figure 4(A)) and it was found that elevated SYNCRIP expression corresponded to an increase in HOXA9/MEIS1 target genes, IKZF2 and c-MYC, but without corresponding to altered MSI2 levels (Figures 12(C)-12(G)). Taken together, these data show that SYNCRIP and MSI2 coregulate a gene expression program that is essential for myeloid leukemia cells.

[00300] Accordingly, the *SYNCRIP*-specific inhibitory nucleic acids disclosed herein are useful in methods for inhibiting leukemic cell proliferation and treating AML in a subject in need thereof.

Example 7: SYNCRIP and MSI2 Interact Through Shared Common mRNA Targets

[00301] To investigate the interaction between SYNCRIP and MSI2, reciprocal immunoprecipitations were performed in MSI2 overexpressing leukemia cell line (K562) to confirm SYNCRIP as an identified protein-protein interacting partner of MSI2 from the mass-spectrometry data. The interaction was detected by reciprocal immunoprecipitation using antibodies against either MSI2 or SYNCRIP. It was found that the interaction is RNA-dependent, as treatment of the lysate with RNase diminished the interaction between the two proteins (Figure 6(A)).

[00302] A similar interaction was observed in MOLM13, a myeloid leukemia cell line carrying MLL-AF9 fusion protein (Figure 13(A)). This data shows that SYNCRIP and MSI2 bind to a common set of mRNA targets. To test if SYNCRIP and MSI2 share MSI2's previously validated targets in MLL-AF9 driven leukemia, RNA-IP was performed. AS shown in Figure 6(B), SYNCRIP also binds Myc, Hoxa9, and Ikzf2 mRNA.

Example 8: SYNCRIP Post-transcriptionally Regulates HOXA9 Expression

[00303] Targeted depletion of SYNCRIP with CRISPR/Cas9 or shRNA hairpins in multiple myeloid leukemia cells (RN2 cells, mouse dsRed MLL-AF9 cells and MOLM13 cells) significantly reduced HOXA9 (Figures 6(C)-6(D) and Figures 13(B)-13(C)). A decrease in c-MYC and IKZF2 was observed with CRISPR/Cas9 depletion of SYNCRIP in RN2 cells (Figure 6(C)), while reduction in c-MYC was observed at 4 days post transduction compared to 3 days post transduction in both dsRed MLL-AF9 cells and MOLM13 cells (Figure 6(D) and Figures 13(B)-13(C)). While these changes occurred at the protein level, variable reductions were also observed in mRNA levels of *HoxA9, c-Myc*, and *Ikzf2* (Figures 13(D)-13(E), 13(H)-13(J)). MSI2 depletion reduced HOXA9 and c-MYC protein expression and downregulated *HoxA9, c-Myc*, and *Ikzf2* mRNA levels at 4 days post transduction, similar to the phenotype observed in SYNCRIP knockdown cells (Figures 13(F)-13(G)).

[00304] To further understand the mechanism for SYNCRIP regulation of HOXA9 expression, the effects of SYNCRIP depletion on total RNA was examined. There was no change in SYNCRIP depleted cells compared to control cells (Figure 13(K)). Additionally, reduced HOXA9, c-MYC, and IKZF2 protein levels in SYCNRIP depleted cells were not due to an effect on mRNA stability, since mRNA levels of these genes were equivalent after the addition of actinomycin D to block transcription (Figures 13(L)-13(M)). Moreover, measurement of newly synthesized proteins based on AHA incorporation revealed a significant decrease in AHA labeled HOXA9 protein in SYNCRIP depleted cells. Despite its short half-life, c-MYC labeling at day 3 remained unchanged (Figure 6(E)), and global peptide synthesis was modestly increased by quantifying total OP-Puro incorporation (Figures 6(F)-6(G)). This data shows that SYNCRIP, in part, controls translation of specific targets including HOXA9.

[00305] Accordingly, the *SYNCRIP*-specific inhibitory nucleic acids disclosed herein are useful in methods for inhibiting leukemic cell proliferation and treating AML in a subject in need thereof.

Example 9: HOXA9 is a functional downstream target of SYNCRIP in leukemia cells

[00306] In support of SYNCRIP and MSI2 co-regulating the MLL-associated transcriptional program, MSI2 overexpression rescued the reduced colony formation and reversed the reduction of HOXA9 after *shRNA-SYNCRIP* depletion (Figure 7(A) and Figures 14(A)-14(B)). Verifying the functional relationship between SYNCRIP and HOXA9, retroviral HOXA9 overexpression partially reversed the reduction in colony formation of

dsRed MLL-AF9 cells after SYNCRIP depletion (Figures 7(B)-7(C) and Figures 14(C)-14(D)). Similarly, overexpression of HOXA9 also rescued the cell growth in SYNCRIP-KD MOLM13 cells (Figures 7(D)-7(E)). In contrast, forced MYC expression failed to rescue the effects of SYNCRIP depletion (Figures 14(E)-14(H)). MYC protein levels were also reduced after SYNCRIP depletion but remained higher than the controls after shRNA depletion. This data shows that SYNCRIP maintains translation of the MLL and LSC program in part through its control of HOXA9 expression.

[00307] To directly demonstrate the relevance of SYNCRIP function in human leukemia, SYNCRIP expression was knocked down in leukemia cells derived from a primary AML patient by transducing cells with control shRNA or SYNCRIP-shRNAs. Engraftment of the cells *in vivo* was monitored after transplantation of sorted GFP positive transduced cells into recipient mice. Depletion of SYNCRIP protein expression resulted in a marked reduction in engraftment of human CD45 GFP positive leukemia cells at week 10 (for shRNA#1) and week 16 (for both shRNA#1 and #2) (Figure 7(F)). HOXA9 expression in the primary AML patient cells correlated with extent of SYNCRIP shRNA depletion (Figure 7(G)). This data shows that SYNCRIP regulates myeloid leukemia cell survival at least in part through regulating expression of HOXA9, a critical target in leukemia. Figure 7(H) shows a schematic depicting the dominant function of SYNCRIP when its expression is elevated in LSCs in comparison to normal HSCs. In LSCs, SYNCRIP and MSI2 binds and increases expression of the mRNA transcripts associated with the MLL self-renewal program, including *Hoxa9* thus driving the LSC program instead of normal hematopoietic development.

[00308] Accordingly, the *SYNCRIP*-specific inhibitory nucleic acids disclosed herein are useful in methods for inhibiting leukemic cell proliferation and treating AML in a subject in need thereof.

Example 10: Effects of SYNCRIP Depletion on Normal Hematopoietic Stem Cells Function and Leukemia Stem Cell Function Using SYNCRIP Conditional Knockout (cKO) Mouse Model

[00309] Using the *Syncrip* cKO mouse model described herein, the Cre transgene will be activated by injecting the mice with polyinositol-polycytosine (pIpC) three times. Deletion of *Syncrip* will be determined by PCR, quantitative real time PCR (qPCR) and western blot analysis within the hematopoietic stem and progenitor cells (HSPCs; LSK: Lineage^{lo} c-kit^{+} Sca^{+}). Cohorts of 10 animals of *Syncrip* deleted mice *Syncrip*$^{\Delta/\Delta}$ and control *Syncrip*$^{flox/flox}$

mice will be sacrificed and assessed for hematopoietic phenotypes. Complete analysis will include peripheral blood counts, histopathology, flow cytometry for terminally differentiated cells using Mac1, Gr1, B220, CD3, CD4 and CD8; multiparametric flow cytometry analysis to characterize the size and distribution of the stem and progenitor compartments; cell cycle analysis of stem and progenitor compartments using Hoechst and pyronin Y staining, and apoptosis analysis using Annexin V staining.

[00310] Stem cell function will be assayed using *in vitro* colony forming assays in methylcellulose, and *in vivo* long-term repopulating potential in non-competitive and competitive repopulation and serial transplantation assays (primary, secondary and tertiary). See Figure 25(B). It is anticipated that SYNCRIP depletion will not adversely impact hematopoietic homeostasis in normal hematopoietic stem cells.

[00311] As demonstrated herein, depletion of SYNCRIP with shRNAs and CRIPSR-sgRNAs resulted in apoptosis and growth inhibition of leukemia cells. To determine if *SYNCRIP* is required for LSC function and leukemia initiation and maintenance, retroviral transductions of MLL-AF9 oncogene to LSK cells isolated from 3 SYNCRIP deficient $Syncrip^{\Delta/\Delta}$ and 3 control mice will be performed. Transformed cells from each donor will be injected into 6 recipients mice. Survival of recipient mice will be monitored and a complete analysis will be performed at the time of sacrifice. Complete analysis will include peripheral blood counts, histopathology, flow cytometry for terminally differentiated cells using Mac1, Gr1, B220, CD3, CD4 and CD8; multiparametric flow cytometry analysis to characterize the size and distribution of the stem and progenitor compartments; cell cycle analysis of stem and progenitor compartments using Hoechst and pyronin Y staining, and apoptosis analysis using Annexin V staining.

[00312] To evaluate requirement of SYNCRIP for maintenance of leukemia *in vivo*, LSK isolated from $Syncrip^{flox/flox}$: *Mx1-Cre* and control $Syncrip^{flox/flox}$ mice will be transformed with MLL-AF9 oncogene and the cells will be transplanted into recipient mice. Prior to onset of leukemia, pIpC injection will be initiated at week 12 and the animals will be evaluated as described above to determine whether loss of SYNCRIP will attenuate disease penetrance and/or latency or alter the disease phenotype. Frequency and number of LSCs will be determined by frequency of c-kit^{high} cells and limiting-dilution transplantation of leukemia formed in recipient mice (Figure 25(C)). It is anticipated that SYNCRIP depletion will adversely impact LSC function and leukemia initiation and maintenance.

[00313] Accordingly, the *SYNCRIP*-specific inhibitory nucleic acids disclosed herein are useful in methods for inhibiting leukemic cell proliferation and treating AML in a subject in need thereof.

EQUIVALENTS

[00314] The present technology is not to be limited in terms of the particular embodiments described in this application, which are intended as single illustrations of individual aspects of the present technology. Many modifications and variations of this present technology can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and apparatuses within the scope of the present technology, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the present technology. It is to be understood that this present technology is not limited to particular methods, reagents, compounds compositions or biological systems, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[00315] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[00316] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, *etc.* As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, *etc.* As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 cells refers to groups having 1, 2, or 3 cells. Similarly, a group having 1-5 cells refers to groups having 1, 2, 3, 4, or 5 cells, and so forth.

[00317] All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

CLAIMS

1. A method for treating or preventing AML in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one *SYNCRIP*-specific inhibitory nucleic acid that inhibits synaptotagmin-binding, cytoplasmic RNA-interacting protein (*SYNCRIP*) expression levels or activity in the subject.

2. The method of claim 1, wherein the at least one *SYNCRIP*-specific inhibitory nucleic acid comprises a nucleic acid sequence selected from the group consisting of: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, and any complement thereof.

3. The method of claim 1 or claim 2, wherein the at least one *SYNCRIP*-specific inhibitory nucleic acid is a siRNA, a shRNA, an antisense oligonucleotide, or a sgRNA.

4. The method of any one of claims 1-3, wherein the subject displays elevated expression levels of SYNCRIP protein in leukemic cells prior to treatment.

5. The method of any one of claims 1-4, wherein treatment with the at least one *SYNCRIP*-specific inhibitory nucleic acid results in a decrease in SYNCRIP and/or HOXA9 levels in the subject compared to that observed prior to treatment.

6. The method of any one of claims 1-5, wherein the subject has been diagnosed as having AML.

7. The method of claim 6, wherein the signs or symptoms of AML comprise one or more of leukemic cell proliferation, enlarged lymph nodes, anemia, neutropenia, leukopenia, leukostasis, chloroma, granulocytic sarcoma, myeloid sarcoma, fatigue, weakness, dizziness, chills, headaches, shortness of breath, thrombocytopenia, excess bruising and bleeding, frequent or severe nosebleeds, bleeding gums, gum pain and swelling, headache, weakness in one side of the body, slurred speech, confusion, sleepiness, blurry vision, vision loss, deep venous thrombosis (DVT), pulmonary embolism, bone or joint pain, swelling in the abdomen, seizures, vomiting, facial numbness, defects in balance, weight loss, fever, night sweats, and loss of appetite.

8. The method of any one of claims 1-7, wherein the subject harbors one or more point mutations in *NRAS*, *DNMT3A*, *FLT3*, *KIT*, *IDH1*, *IDH2*, *CEBPA* and *NPM1*.

9. The method of any one of claims 1-8, wherein the subject harbors one or more gene fusions selected from the group consisting of *CBFB-MYH11, DEK-NUP214, MLL-MLLT3, PML-RARA, RBM15-MKL1, RPN1-EVI1* and *RUNX1-RUNX1T1.*

10. The method of any one of claims 1-9, wherein the subject is human.

11. The method of any one of claims 1-10, wherein the at least one *SYNCRIP*-specific inhibitory nucleic acid is administered orally, topically, intranasally, systemically, intravenously, subcutaneously, intraperitoneally, intradermally, intraocularly, iontophoretically, transmucosally, or intramuscularly.

12. The method of any one of claims 1-11, further comprising separately, sequentially or simultaneously administering one or more additional therapeutic agents to the subject.

13. The method of claim 12, wherein the additional therapeutic agents are selected from the group consisting of cyclophosphamide, fluorouracil (or 5-fluorouracil or 5-FU), methotrexate, edatrexate (10-ethyl-10-deaza-aminopterin), thiotepa, carboplatin, cisplatin, taxanes, paclitaxel, protein-bound paclitaxel, docetaxel, vinorelbine, tamoxifen, raloxifene, toremifene, fulvestrant, gemcitabine, irinotecan, ixabepilone, temozolmide, topotecan, vincristine, vinblastine, eribulin, mutamycin, capecitabine, anastrozole, exemestane, letrozole, leuprolide, abarelix, buserlin, goserelin, megestrol acetate, risedronate, pamidronate, ibandronate, alendronate, denosumab, zoledronate, trastuzumab, tykerb, anthracyclines (*e.g.*, daunorubicin and doxorubicin), cladribine, midostaurin, bevacizumab, oxaliplatin, melphalan, etoposide, mechlorethamine, bleomycin, microtubule poisons, annonaceous acetogenins, chlorambucil, ifosfamide, streptozocin, carmustine, lomustine, busulfan, dacarbazine, temozolomide, altretamine, 6-mercaptopurine (6-MP), cytarabine, floxuridine, fludarabine, hydroxyurea, pemetrexed, epirubicin, idarubicin, SN-38, ARC, NPC, campothecin, 9-nitrocamptothecin, 9-aminocamptothecin, rubifen, gimatecan, diflomotecan, BN80927, DX-8951f, MAG-CPT, amsacnne, etoposide phosphate, teniposide, azacitidine (Vidaza), decitabine, accatin III, 10-deacetyltaxol, 7-xylosyl-10-deacetyltaxol, cephalomannine, 10-deacetyl-7-epitaxol, 7-epitaxol, 10-deacetylbaccatin III, 10-deacetyl cephalomannine, streptozotocin, nimustine, ranimustine, bendamustine, uramustine, estramustine, mannosulfan, camptothecin, exatecan, lurtotecan, lamellarin D9-aminocamptothecin, amsacrine, ellipticines, aurintricarboxylic acid, HU-331, or combinations thereof.

14. The method of any one of claims 1-13, wherein the AML is T-cell acute lymphoblastic leukemia or B-cell acute lymphoblastic leukemia.

15. The method of any one of claims 1-14, wherein the at least one *SYNCRIP*-specific inhibitory nucleic acid is administered daily for 6 weeks or more.

16. The method of any one of claims 1-15, wherein the at least one *SYNCRIP*-specific inhibitory nucleic acid is administered daily for 12 weeks or more.

17. A method for monitoring the therapeutic efficacy of an *SYNCRIP*-specific inhibitory nucleic acid that targets *SYNCRIP* expression and/or activity in a subject diagnosed with AML comprising:

(a) detecting SYNCRIP protein levels in a test sample obtained from the subject after the subject has been administered the *SYNCRIP*-specific inhibitory nucleic acid; and

(b) determining that the *SYNCRIP*-specific inhibitory nucleic acid is effective when the SYNCRIP protein levels in the test sample are reduced compared to that observed in a control sample obtained from the subject prior to administration of the *SYNCRIP*-specific inhibitory nucleic acid.

18. The methods of claim 17, wherein the *SYNCRIP*-specific inhibitory nucleic acid is a siRNA, a shRNA, an antisense oligonucleotide, or a sgRNA.

19. The method of claim 17 or claim 18, further comprising detecting HOXA9 levels in the subject.

20. A method for inhibiting leukemic cell proliferation in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an *SYNCRIP*-specific inhibitory nucleic acid.

21. The method of any one of claims 17-20, wherein the *SYNCRIP*-specific inhibitory nucleic acid comprises a nucleic acid sequence selected from the group consisting of: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21 and any complement thereof.

22. A kit comprising one or more *SYNCRIP*-specific inhibitory nucleic acids comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-2, 18-21 and any complement thereof.

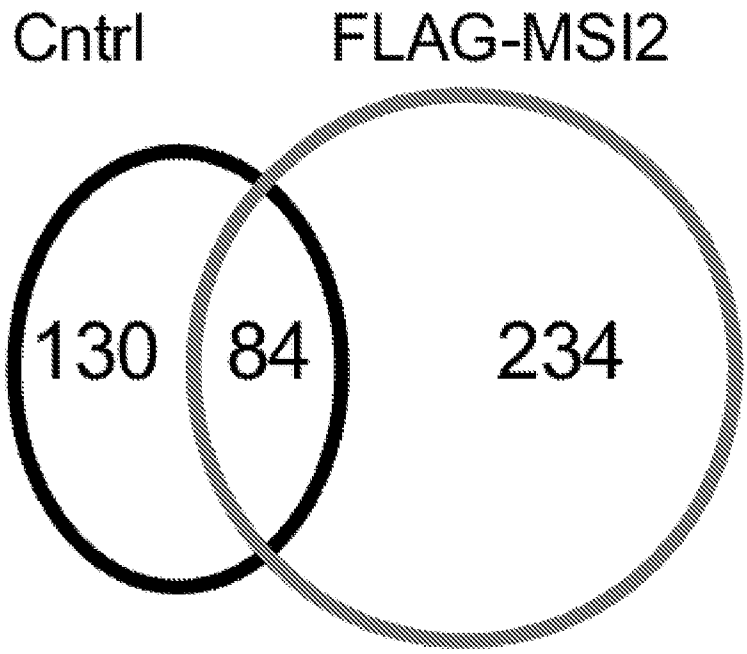


Figure 1(A)

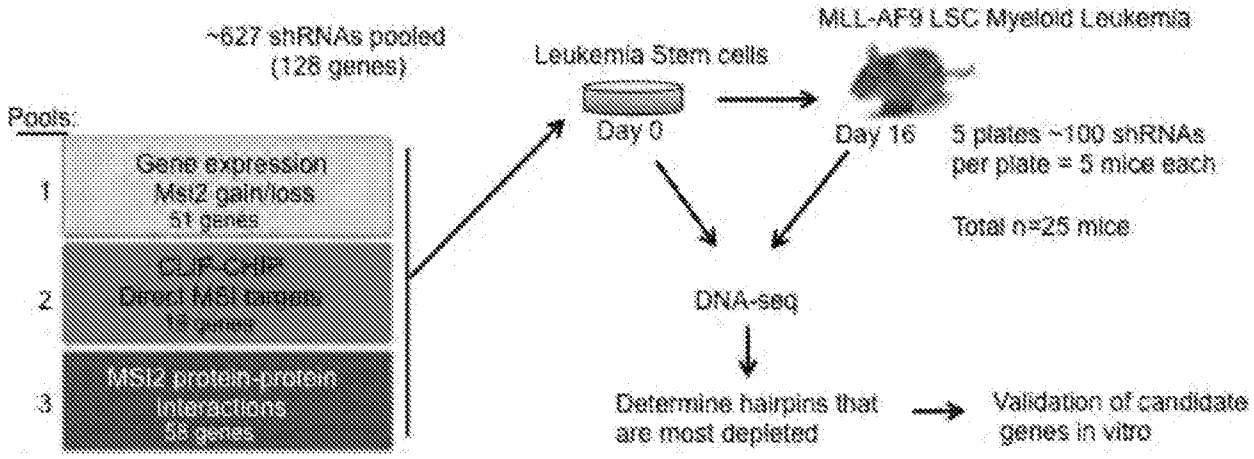


Figure 1(B)

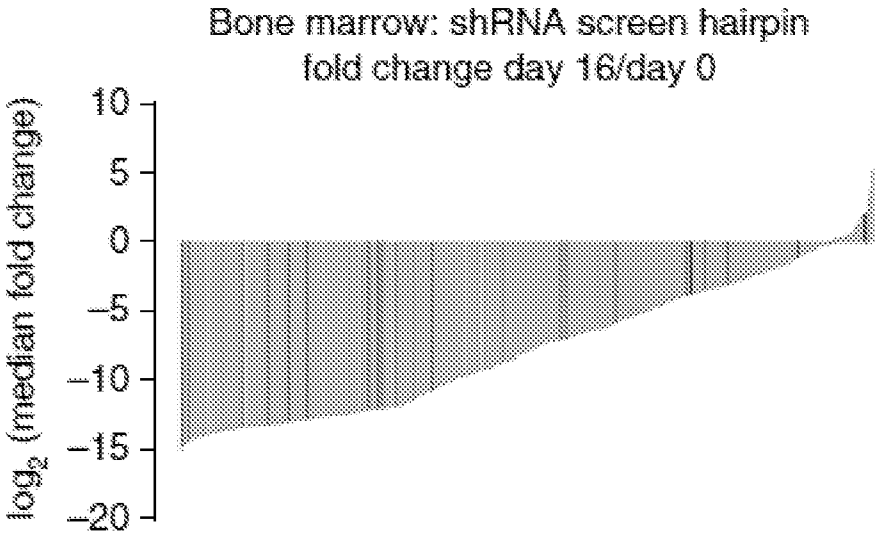


Figure 1(C)

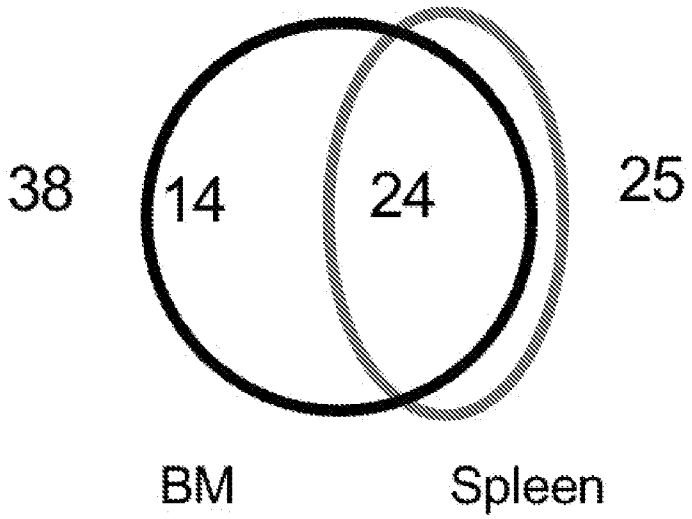


Figure 1(D)

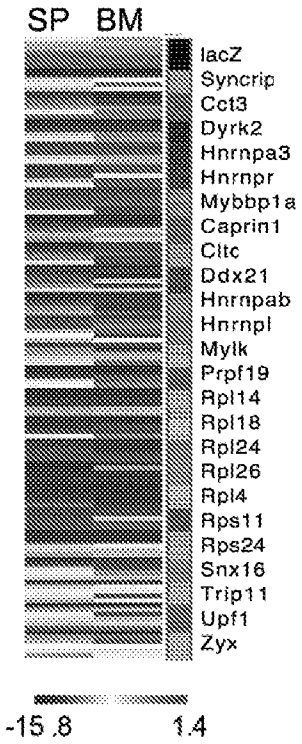


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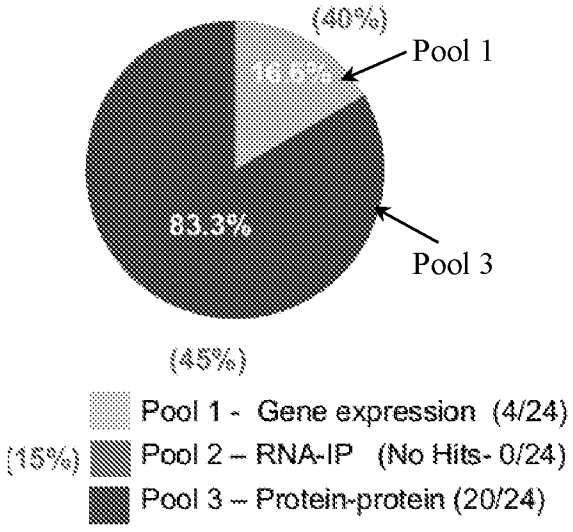


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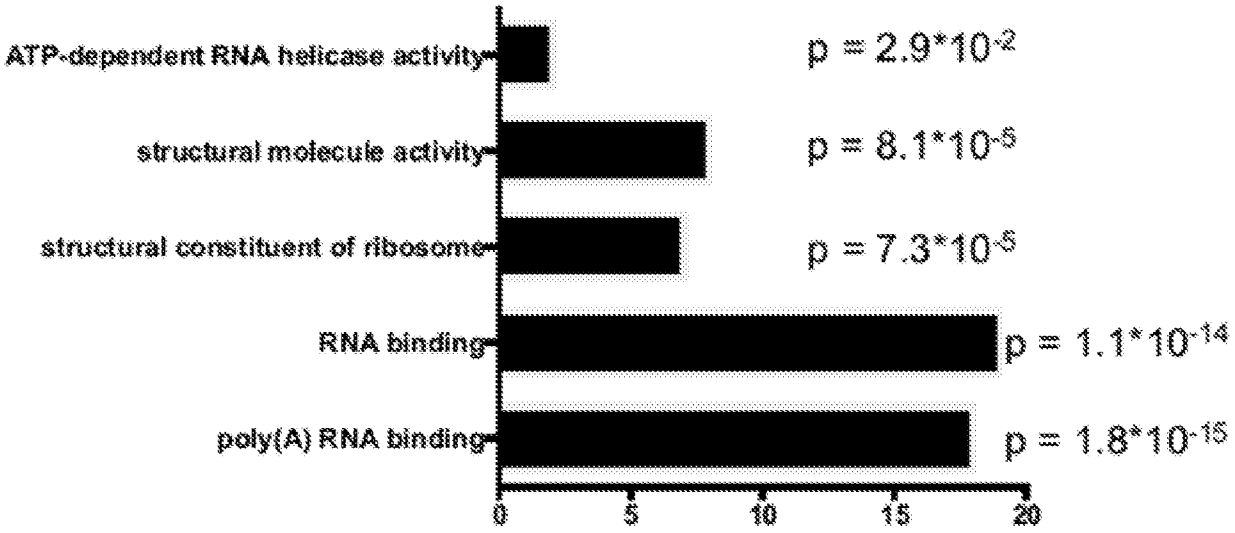


Figure 1(G)

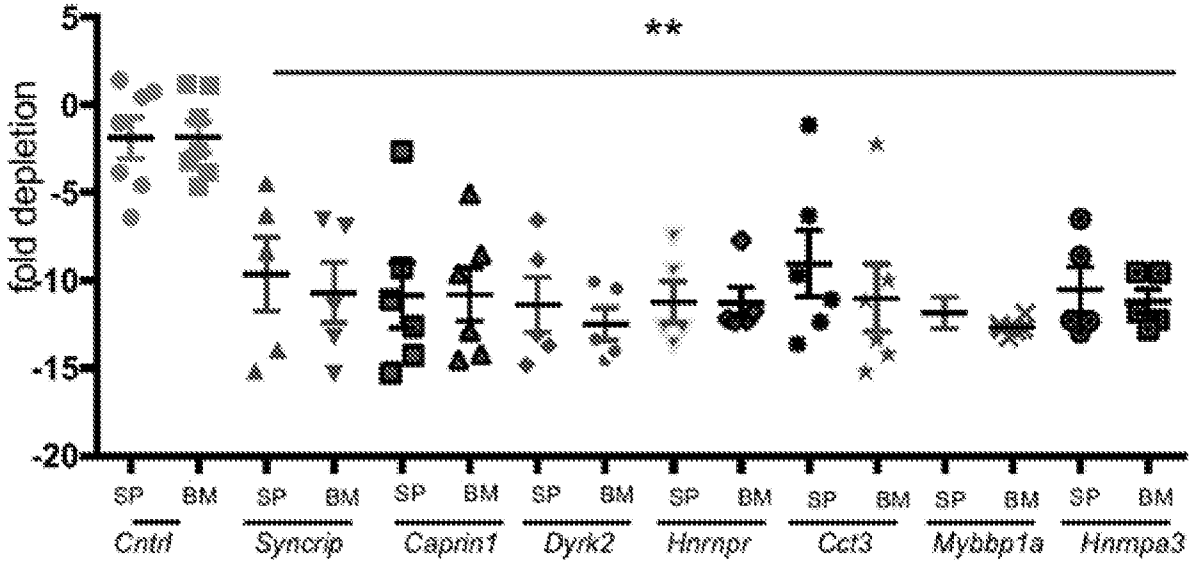


Figure 1(H)

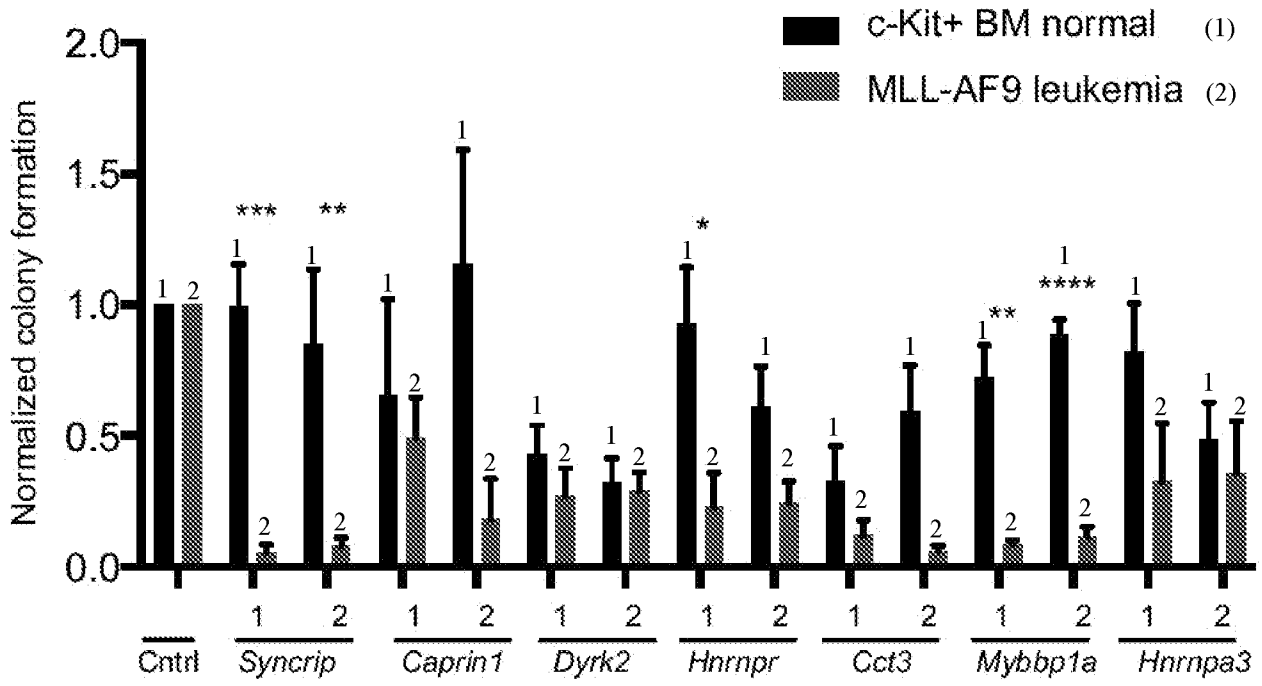

c-Kit+ BM normal (1)
MLL-AF9 leukemia (2)
Normalized colony formation
2.0
1.5
1.0
0.5
0.0
Cntrl
Syncrip
Caprin1
Dyrk2
Hnrnpr
Cct3
Mybbp1a
Hnrnpa3

Figure 1(I)

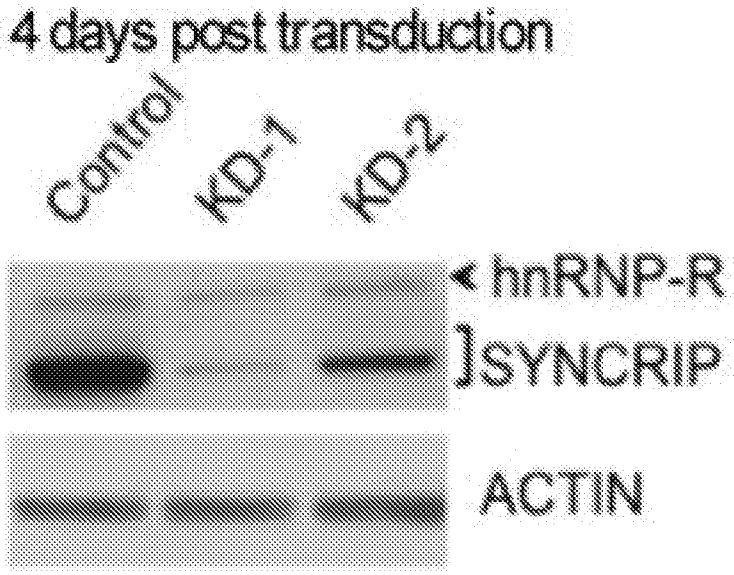


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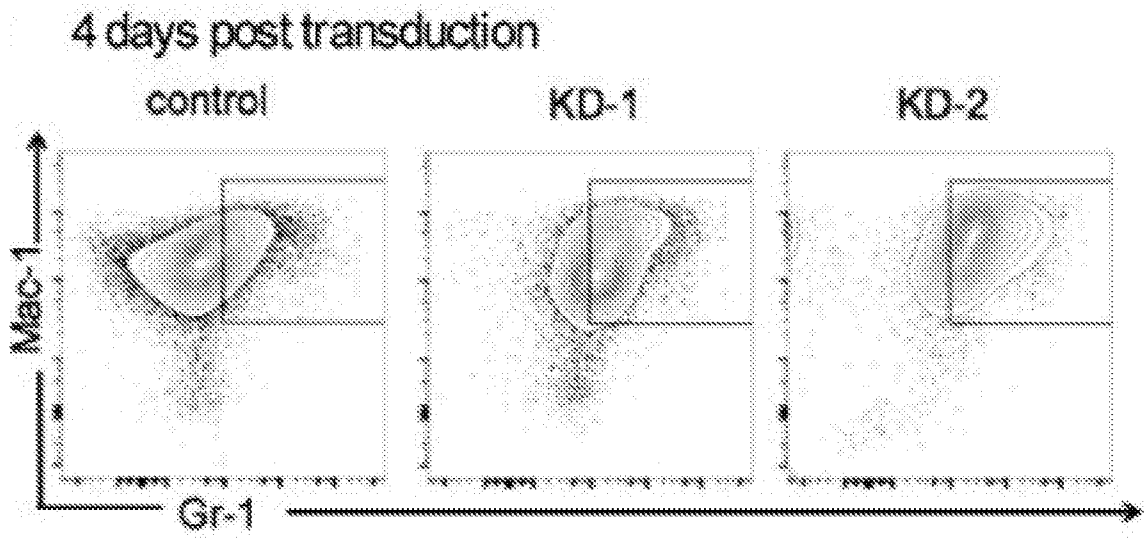


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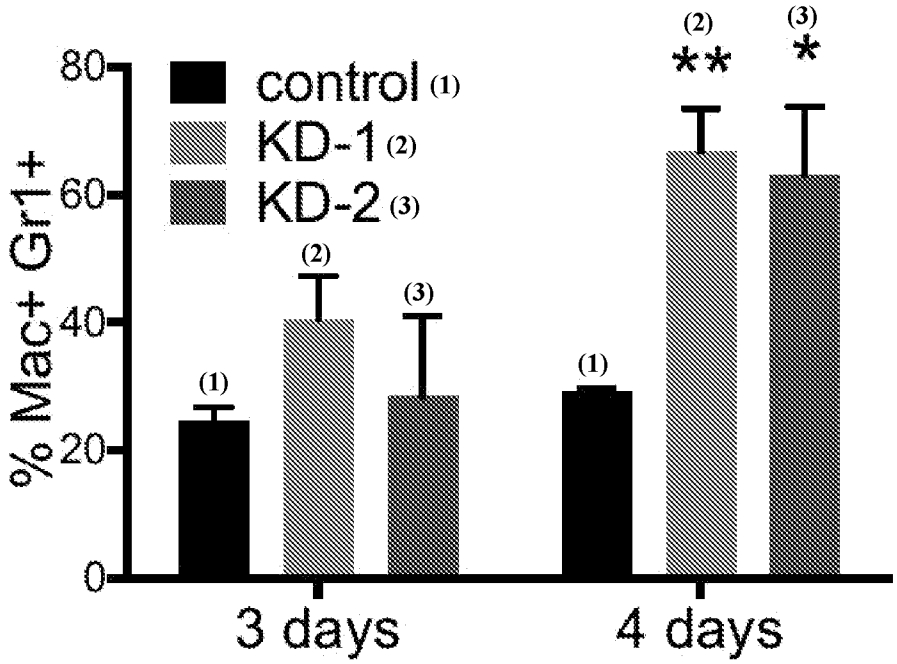


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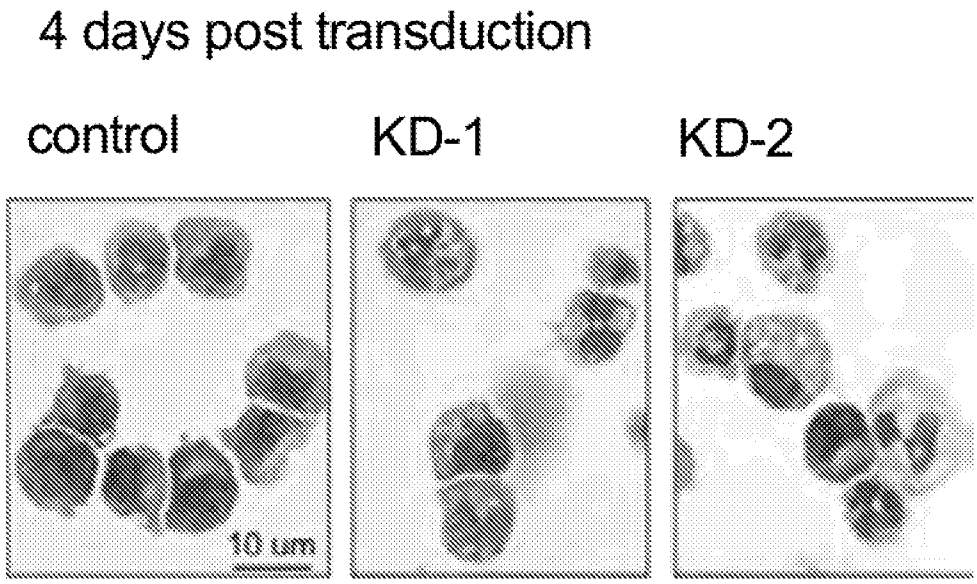


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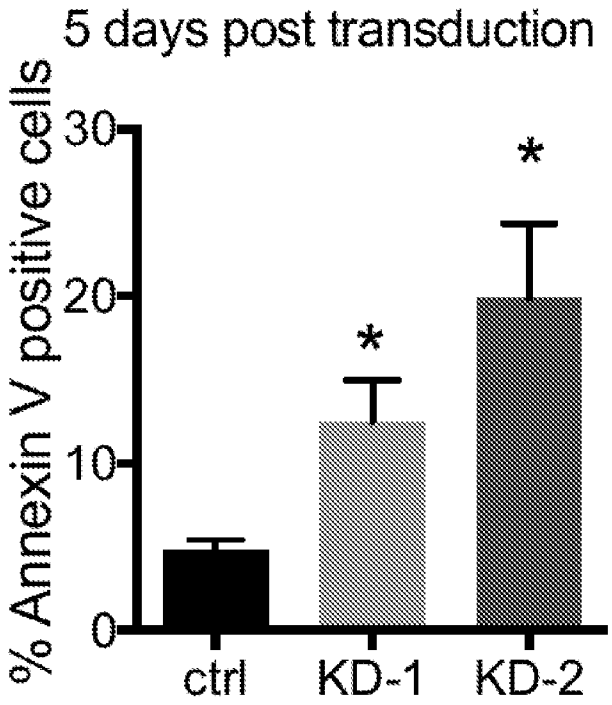


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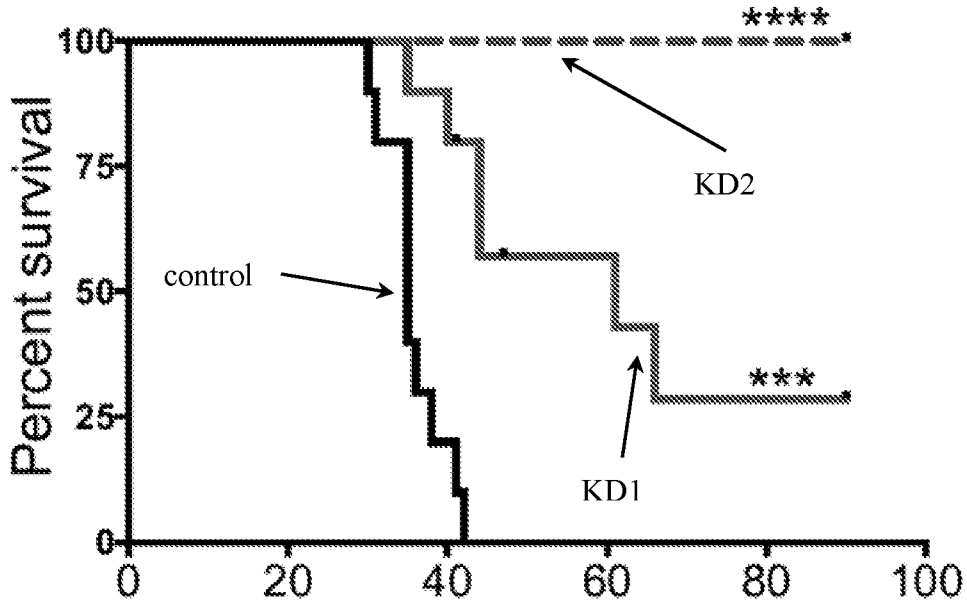


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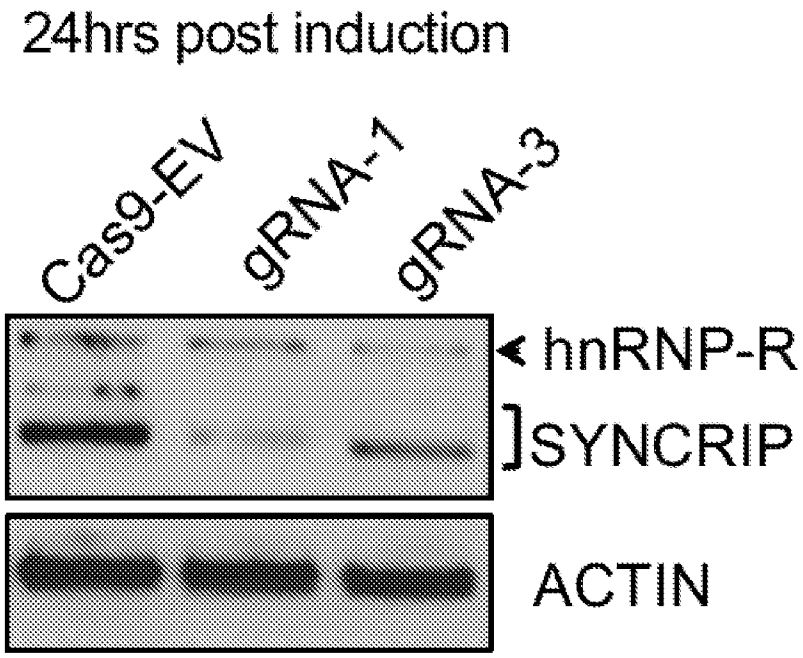


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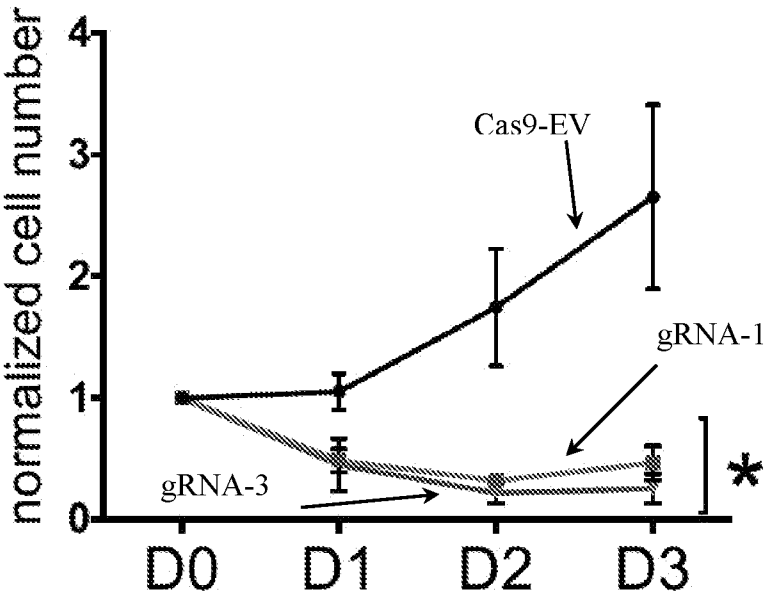


Figure 2(H)

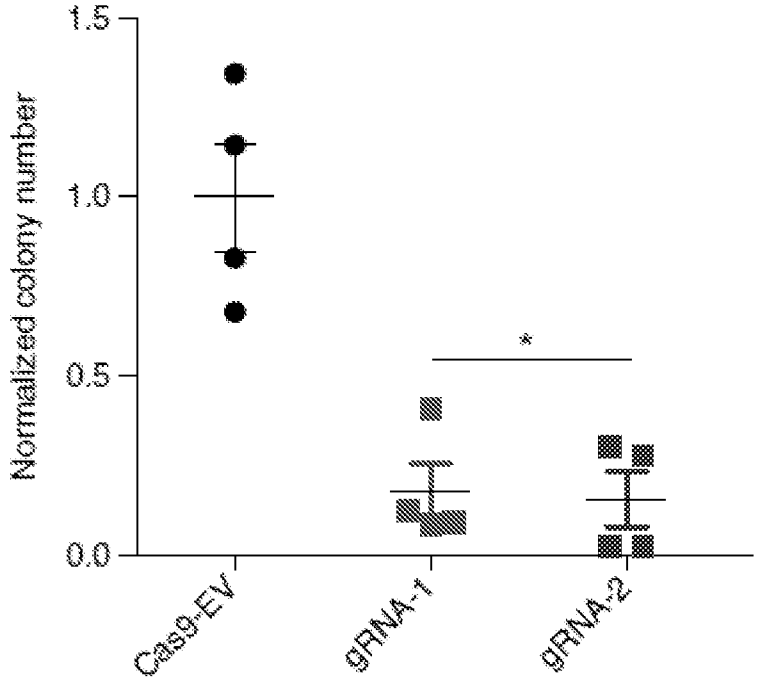


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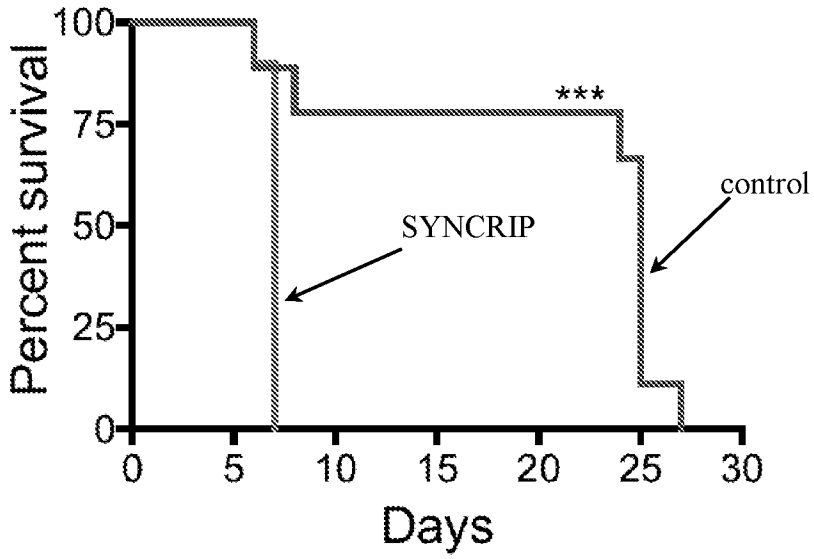


Figure 2(J)

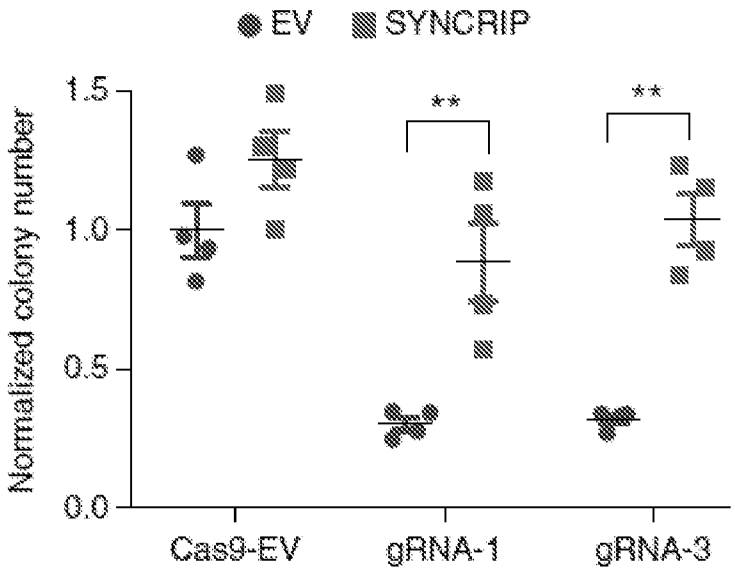


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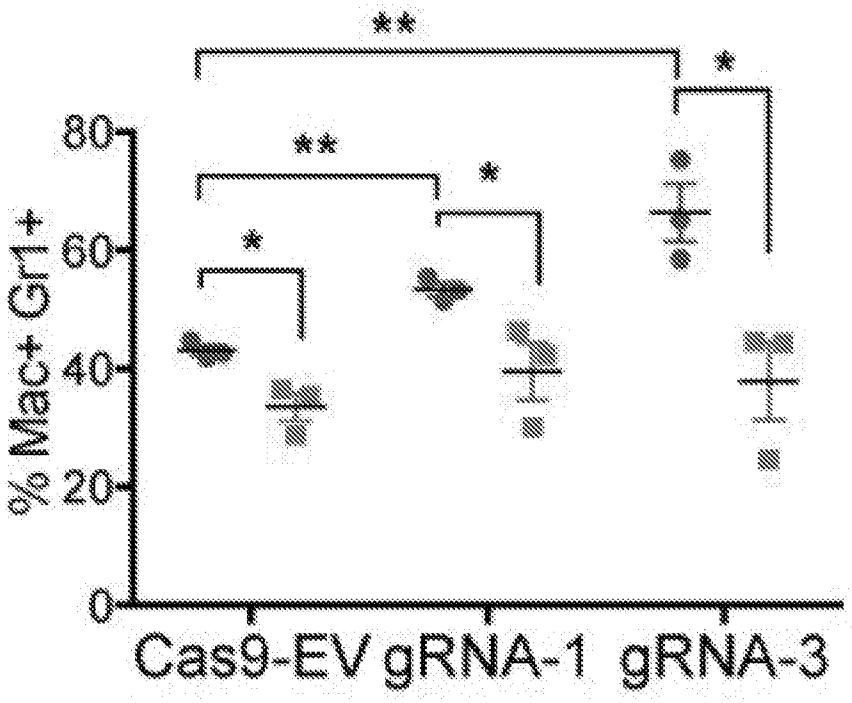


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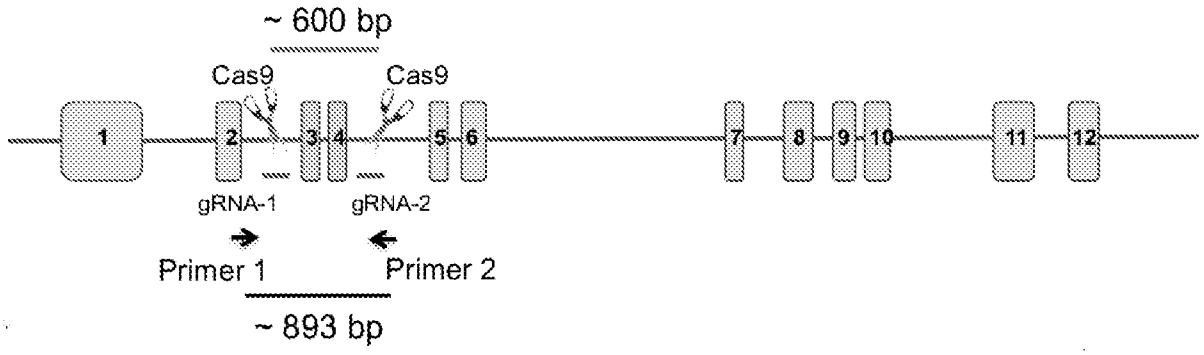


Figure 3(A)

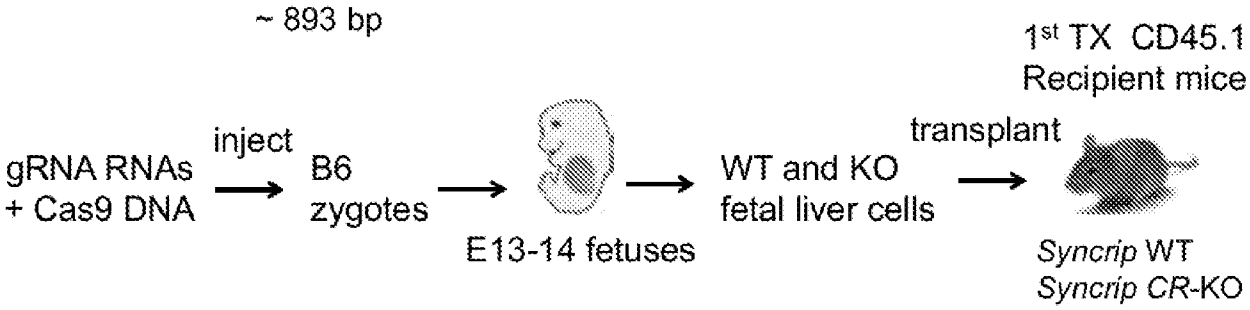


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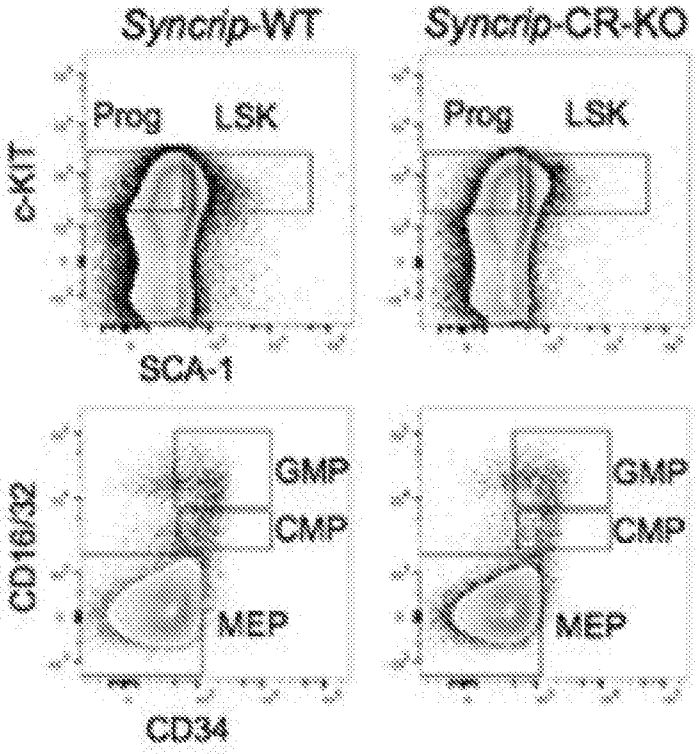


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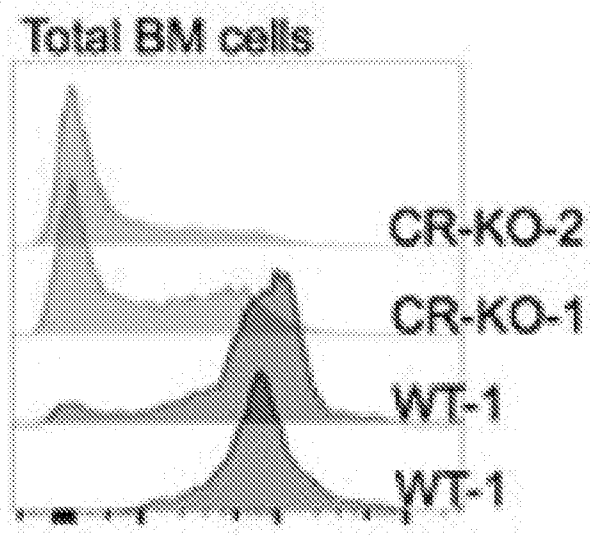


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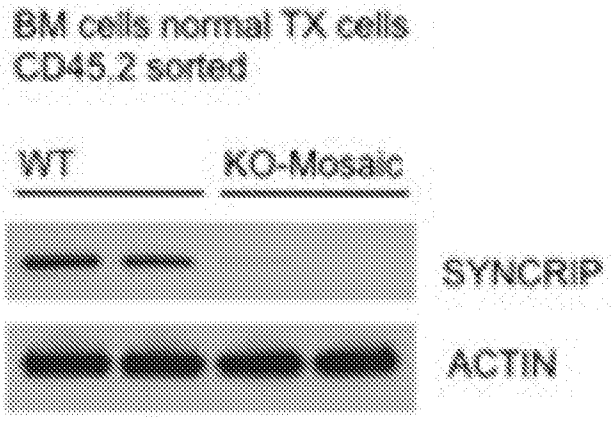


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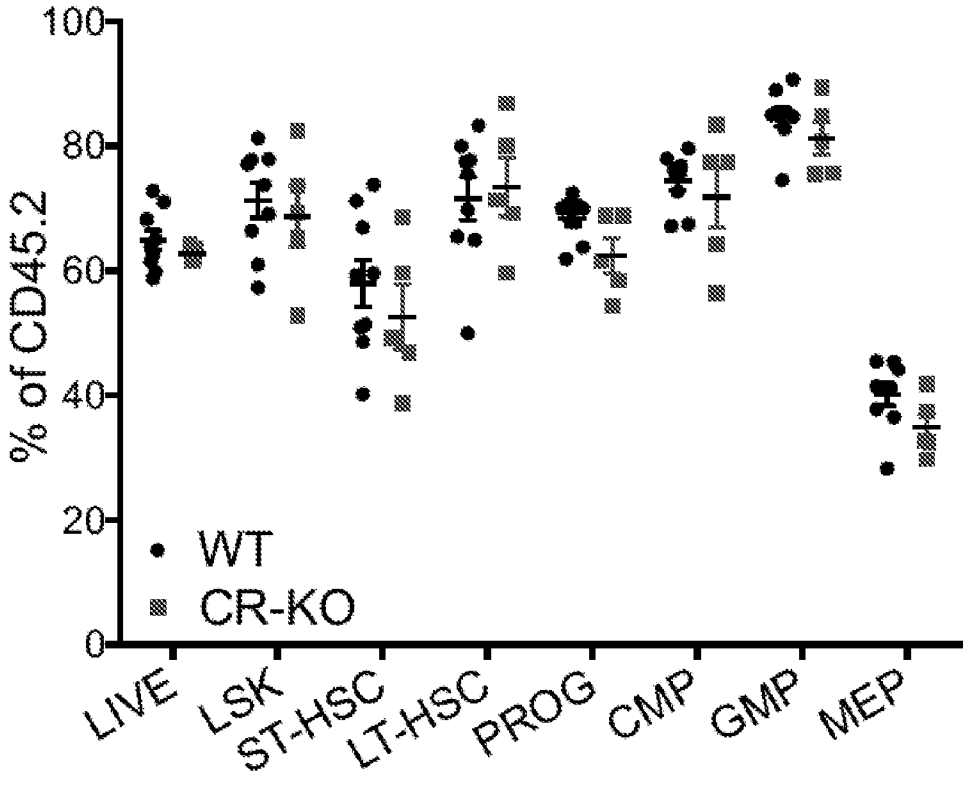


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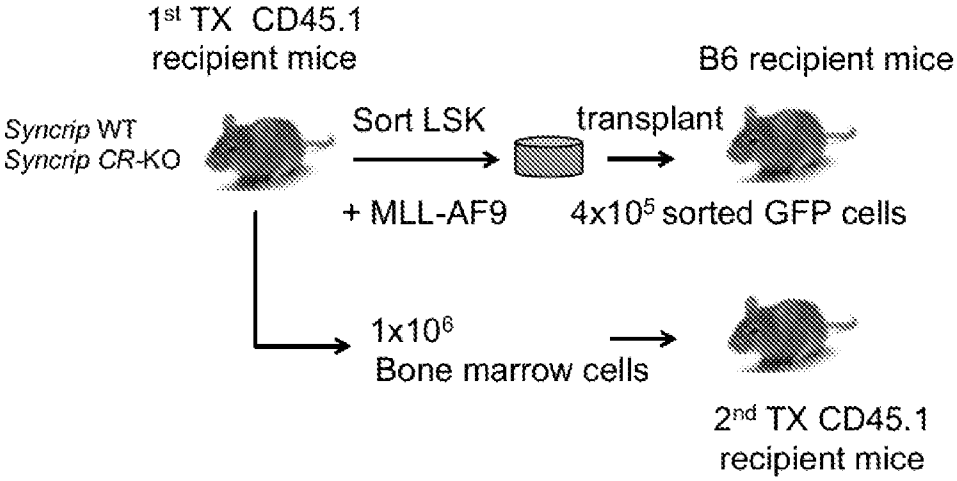


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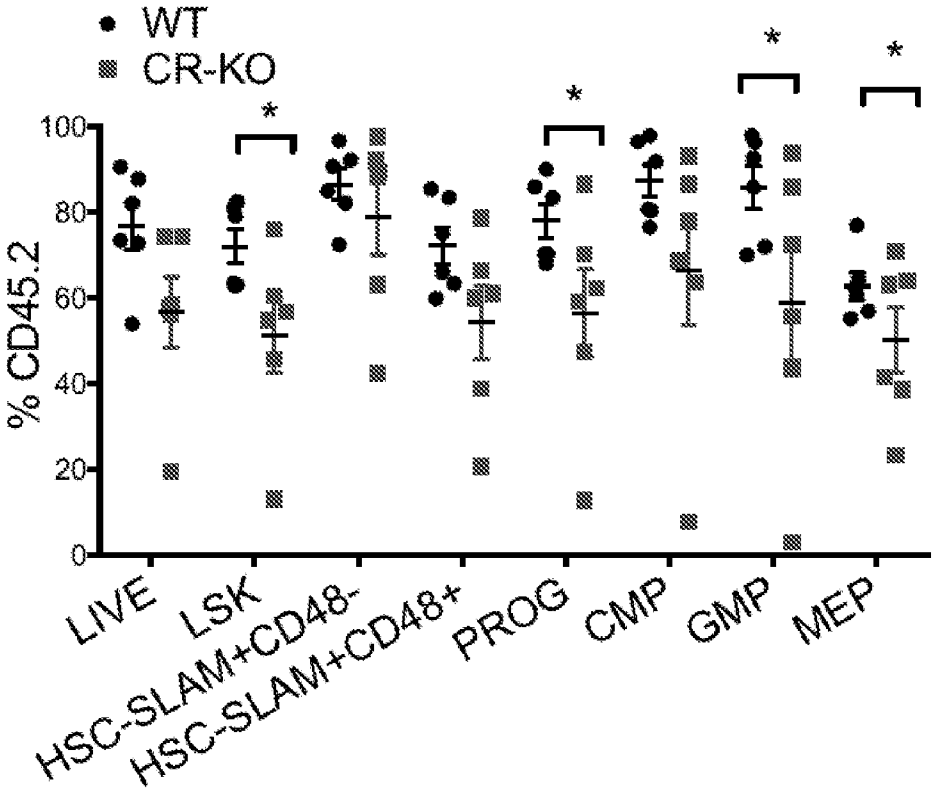


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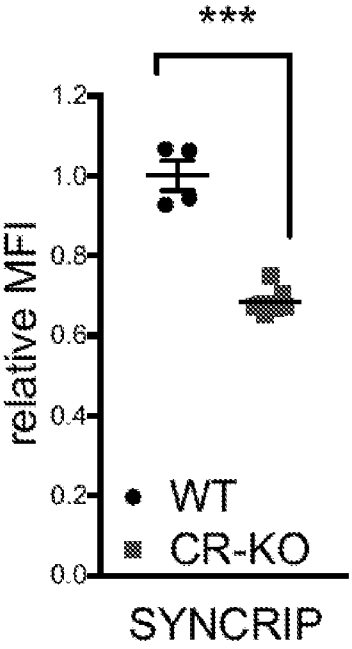


Figure 3(I)

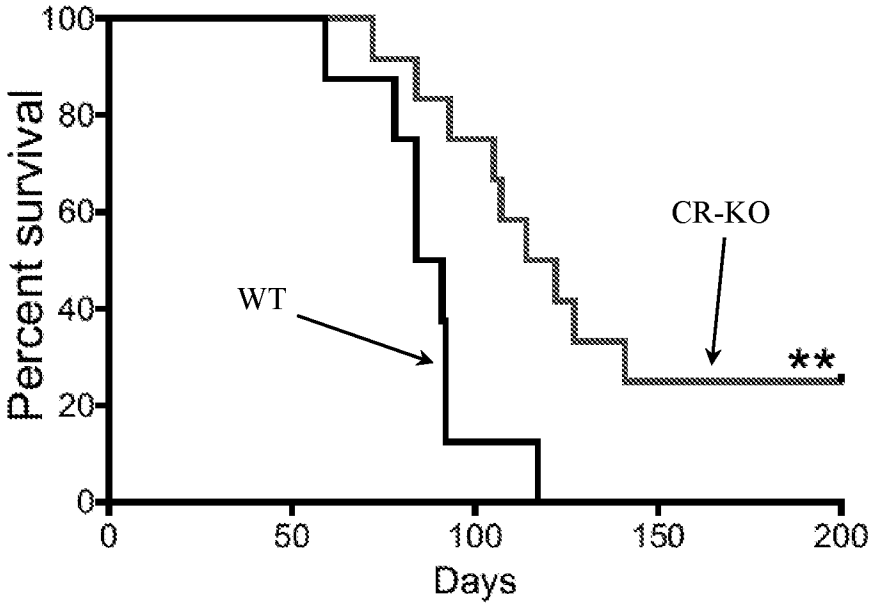


Figure 3(J)

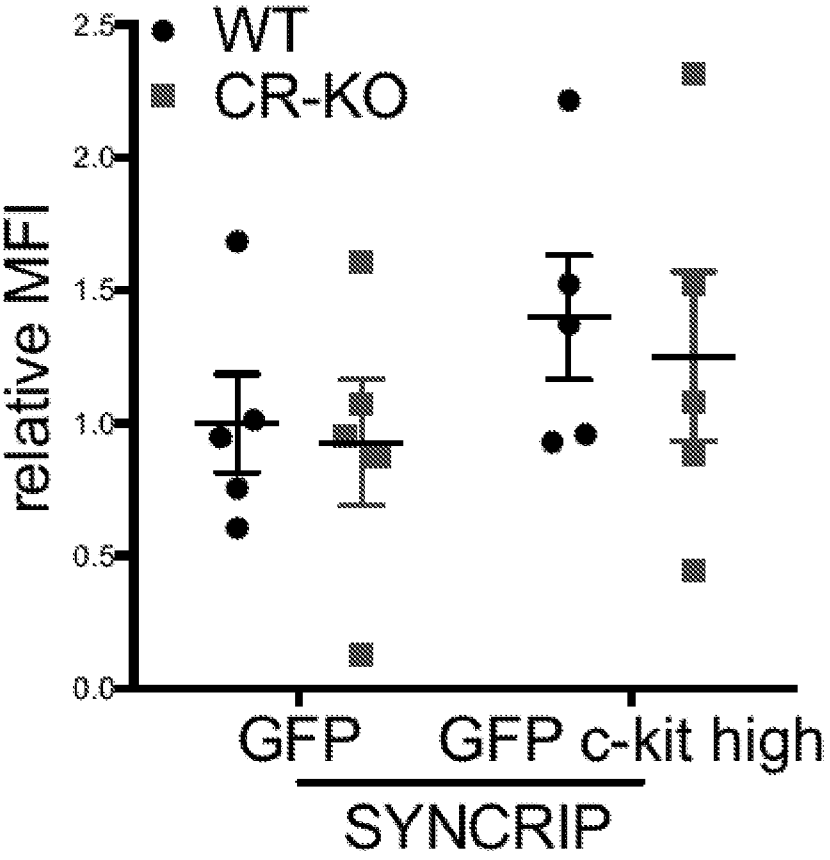

WT
CR-KO
relative MFI
2.5
2.0
1.5
1.0
0.5
0.0
GFP
GFP c-kit high
SYNCRIP

Figure 3(K)

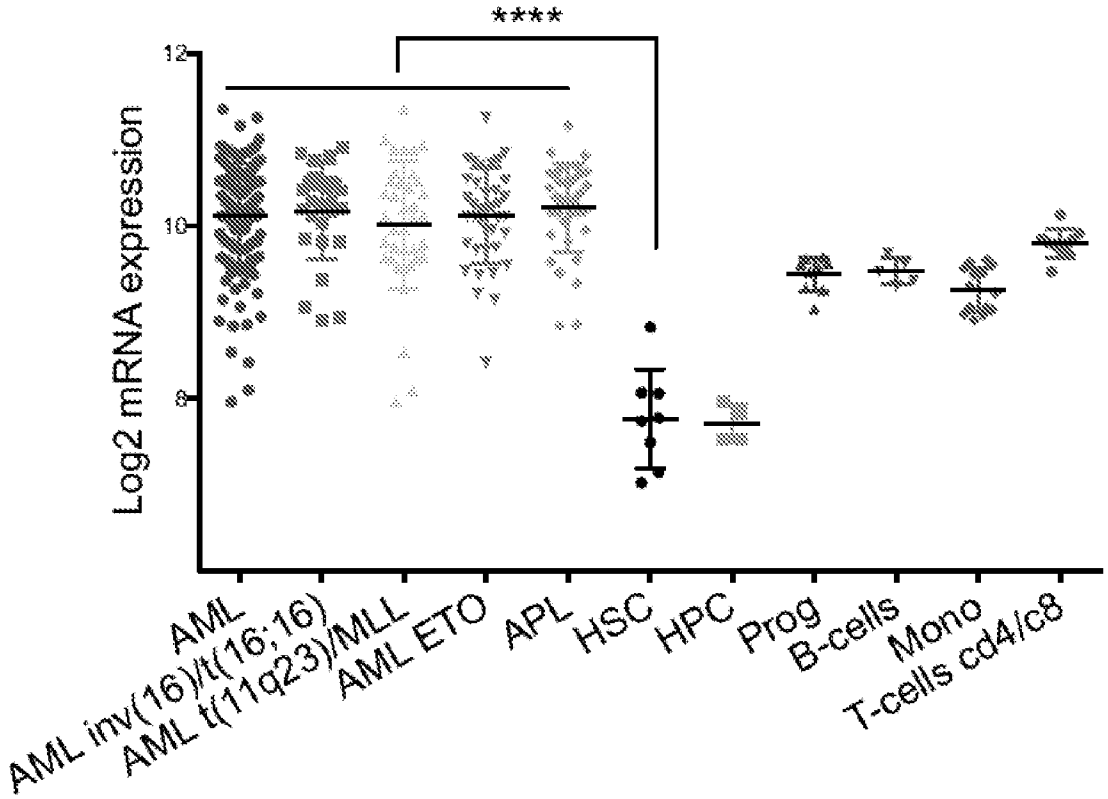


Figure 4(A)

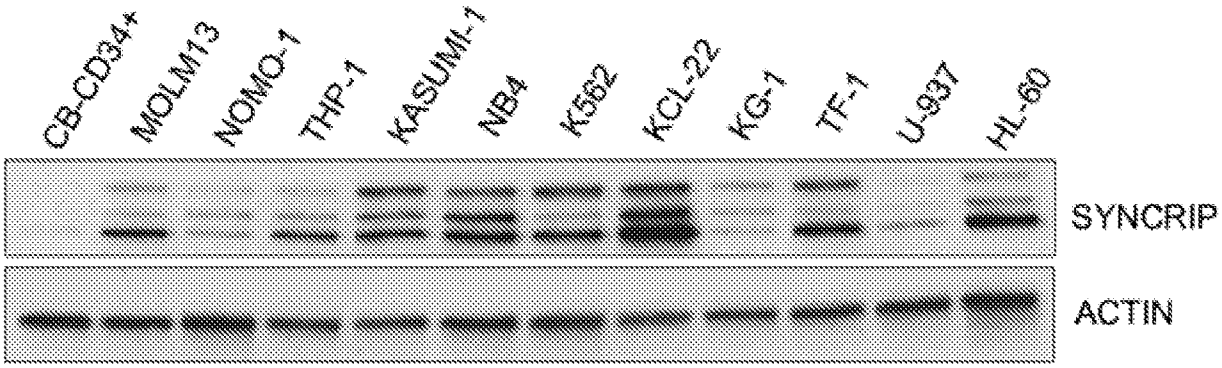


Figure 4(B)

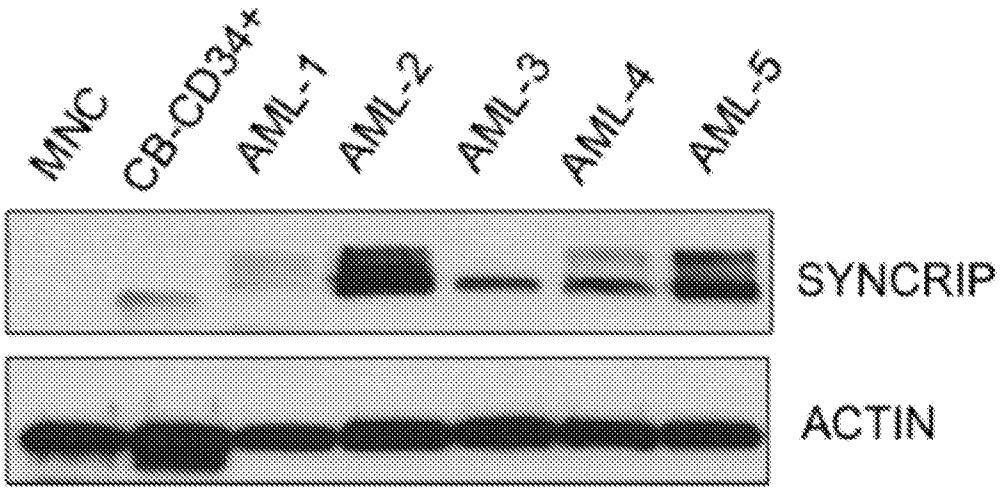


Figure 4(C)

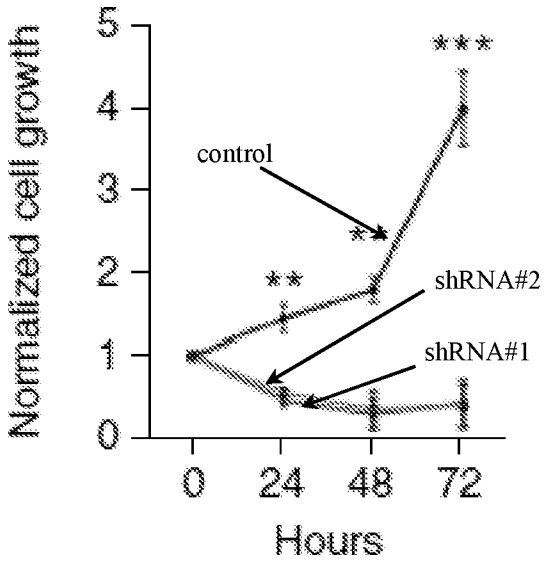


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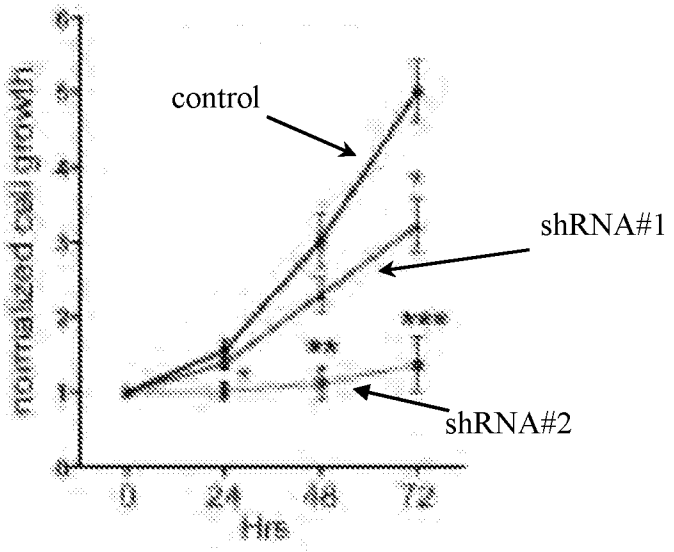


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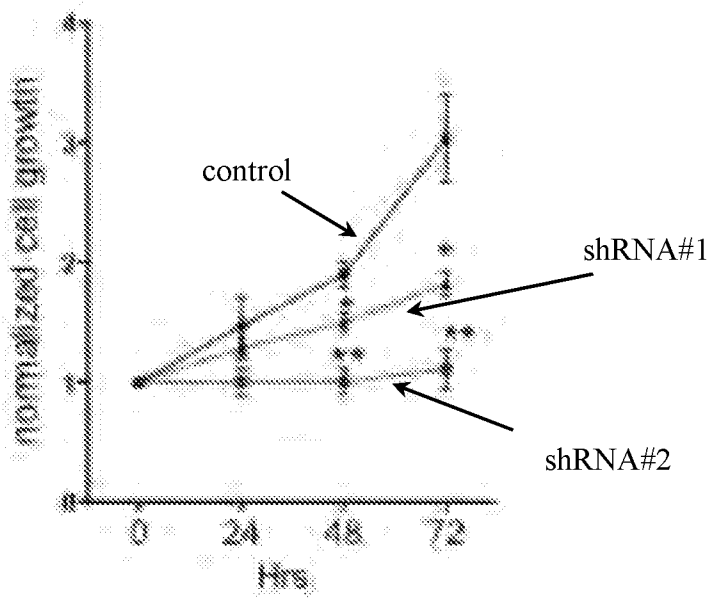


Figure 4(F)

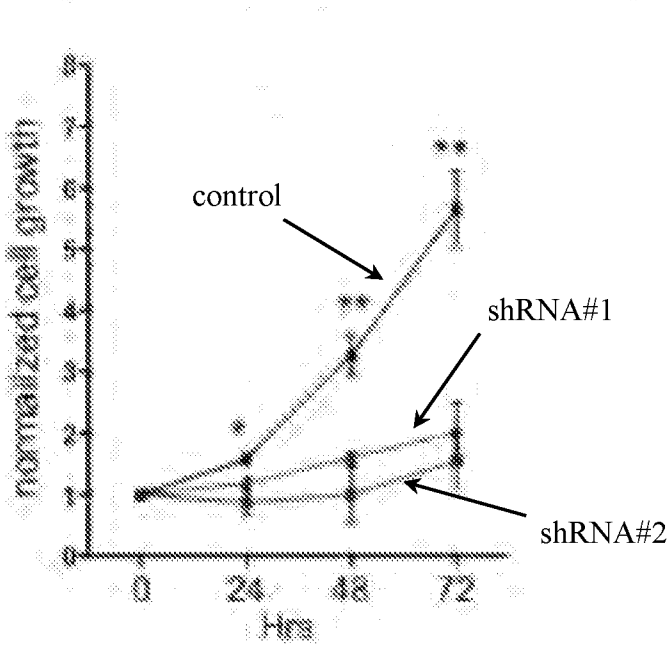


Figure 4(G)

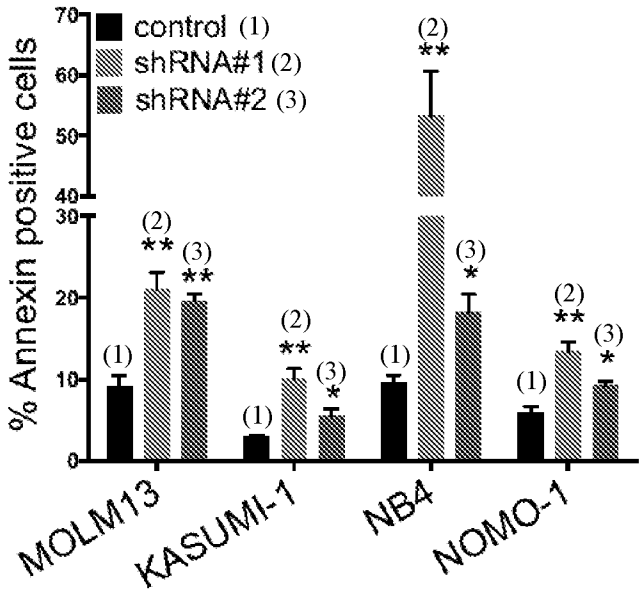


Figure 4(H)

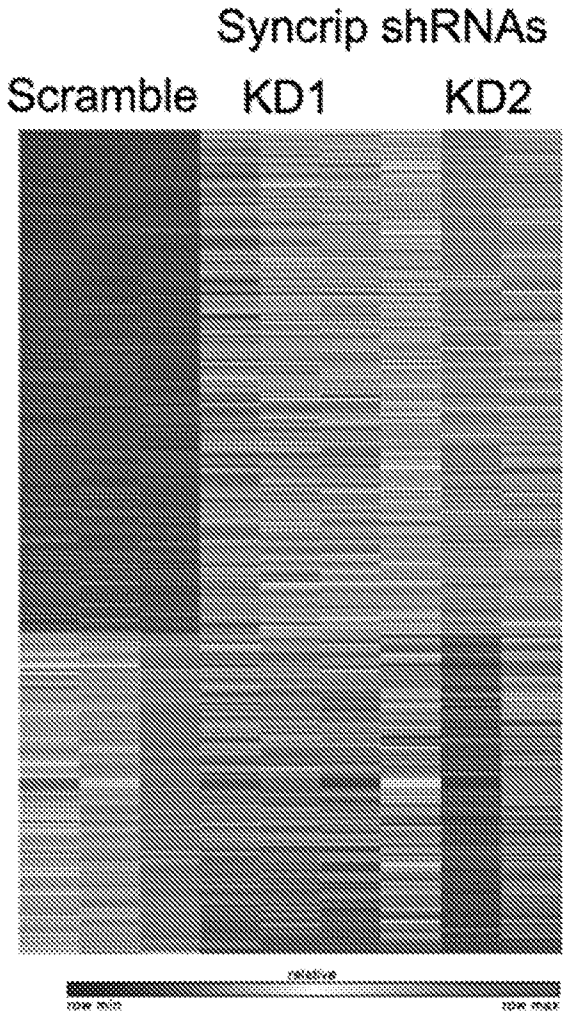


Figure 5(A)

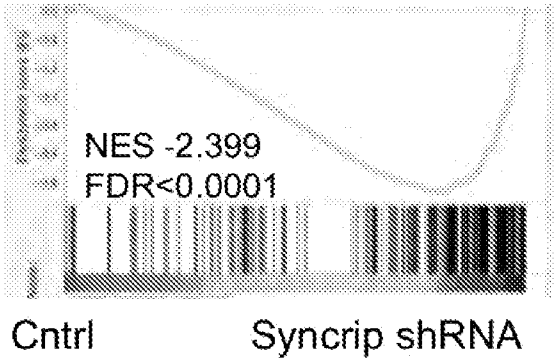


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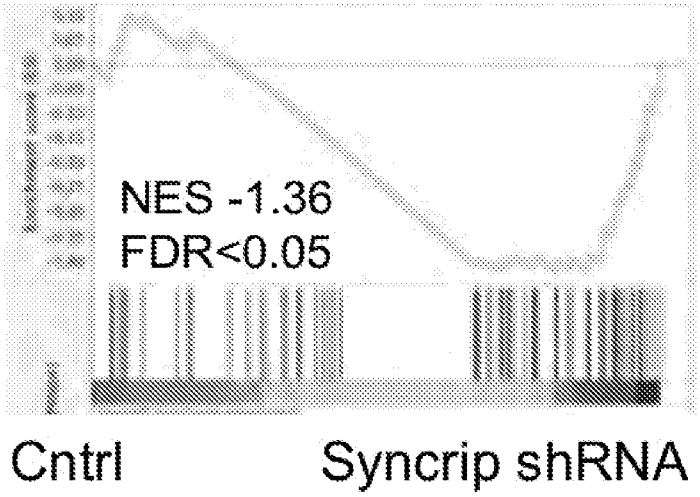


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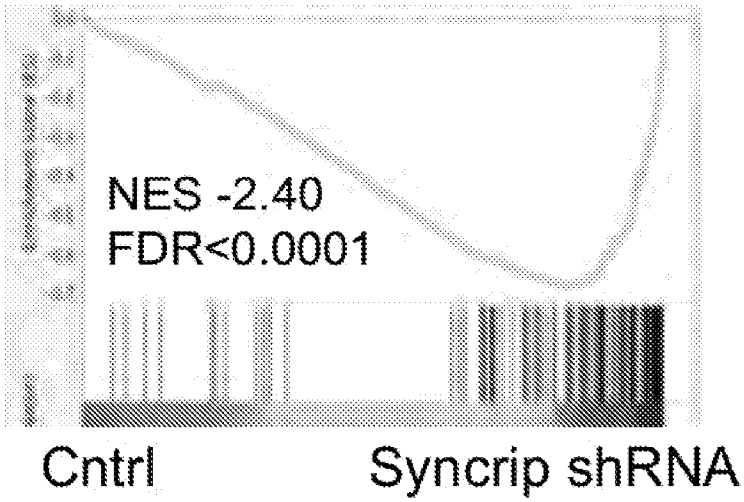


Figure 5(D)

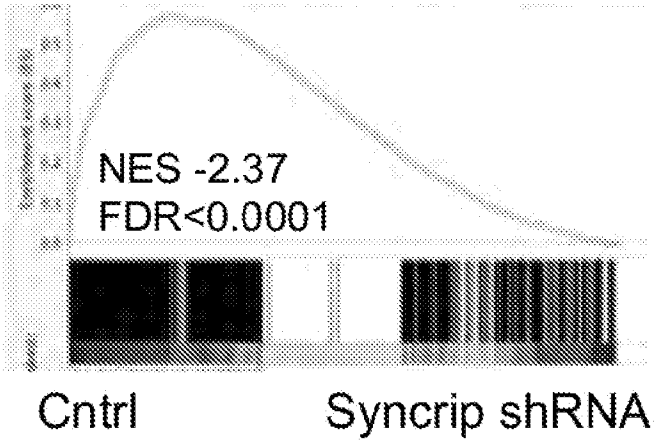


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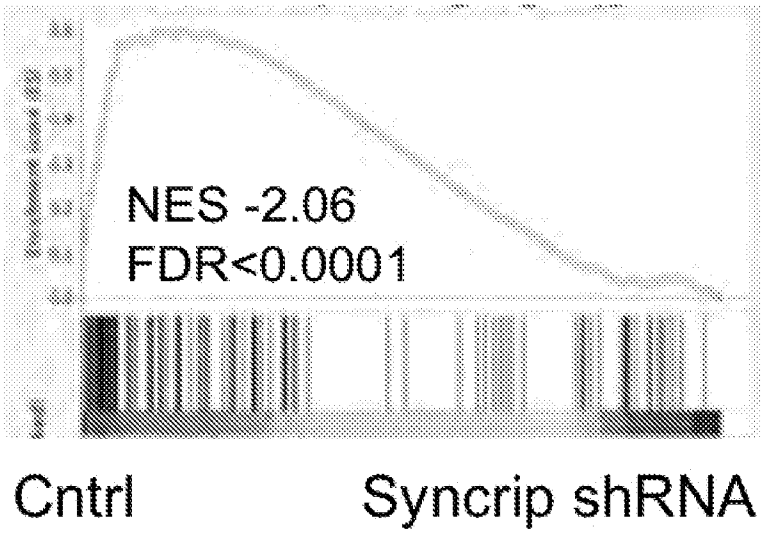


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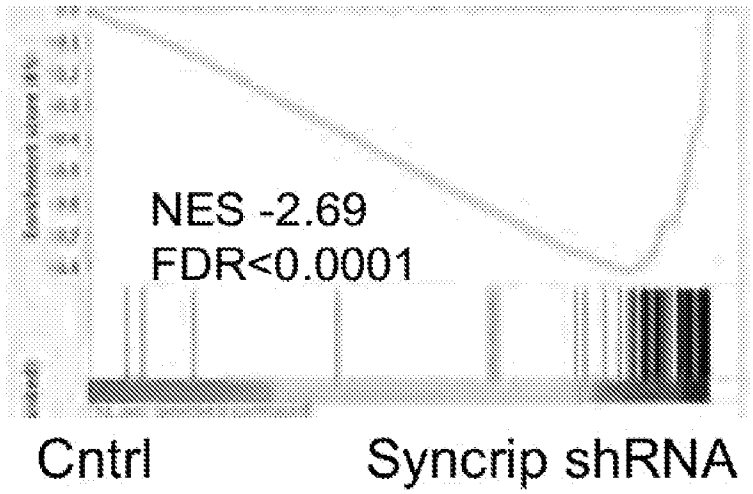


Figure 5(G)

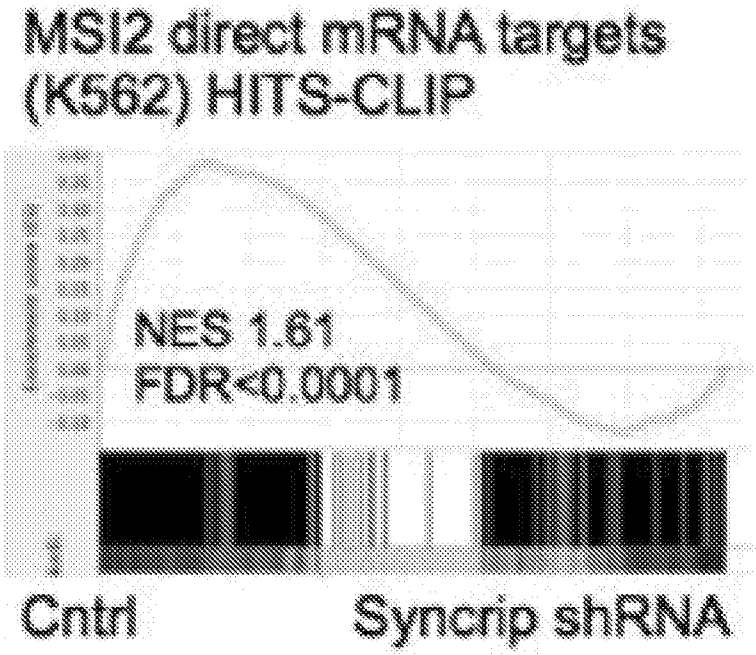


Figure 5(H)

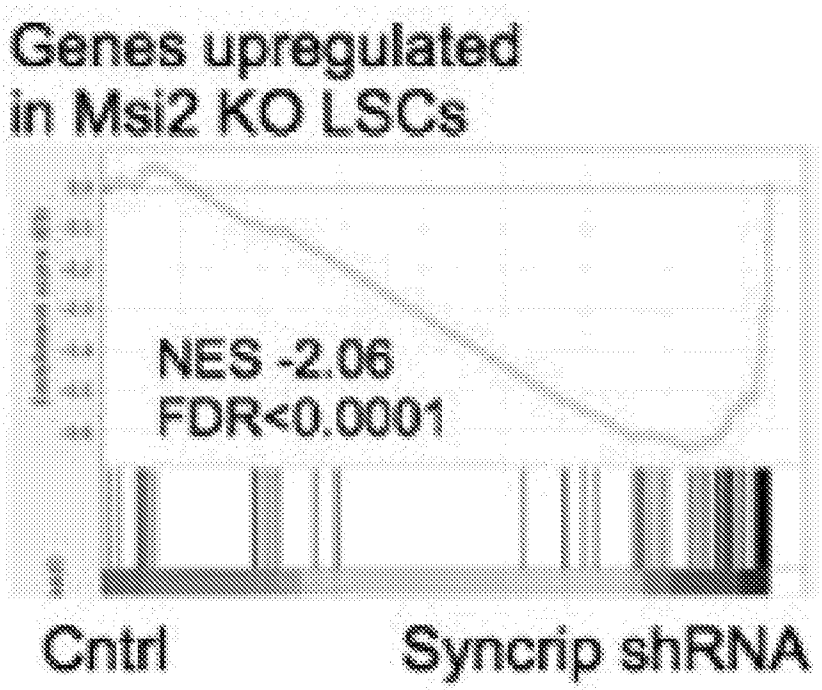

Genes upregulated
in Msi2 KO LSCs
NES -2.06
FDR<0.0001
Cntrl
Syncrip shRNA

Figure 5(I)

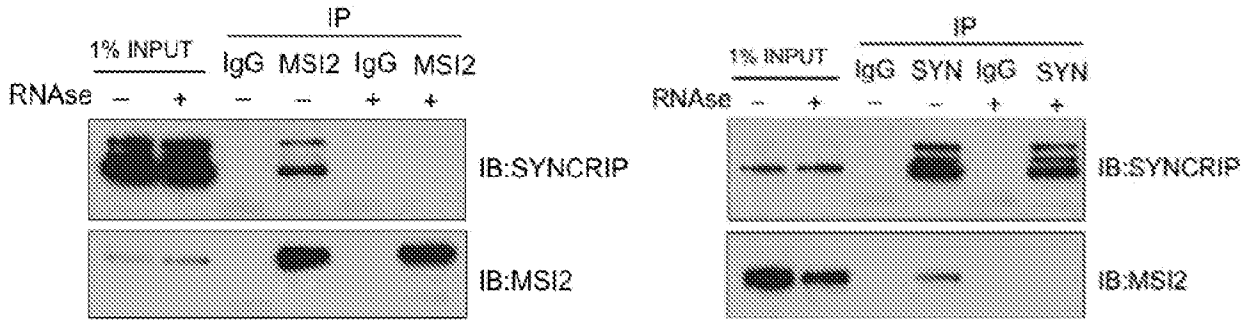


Figure 6(A)

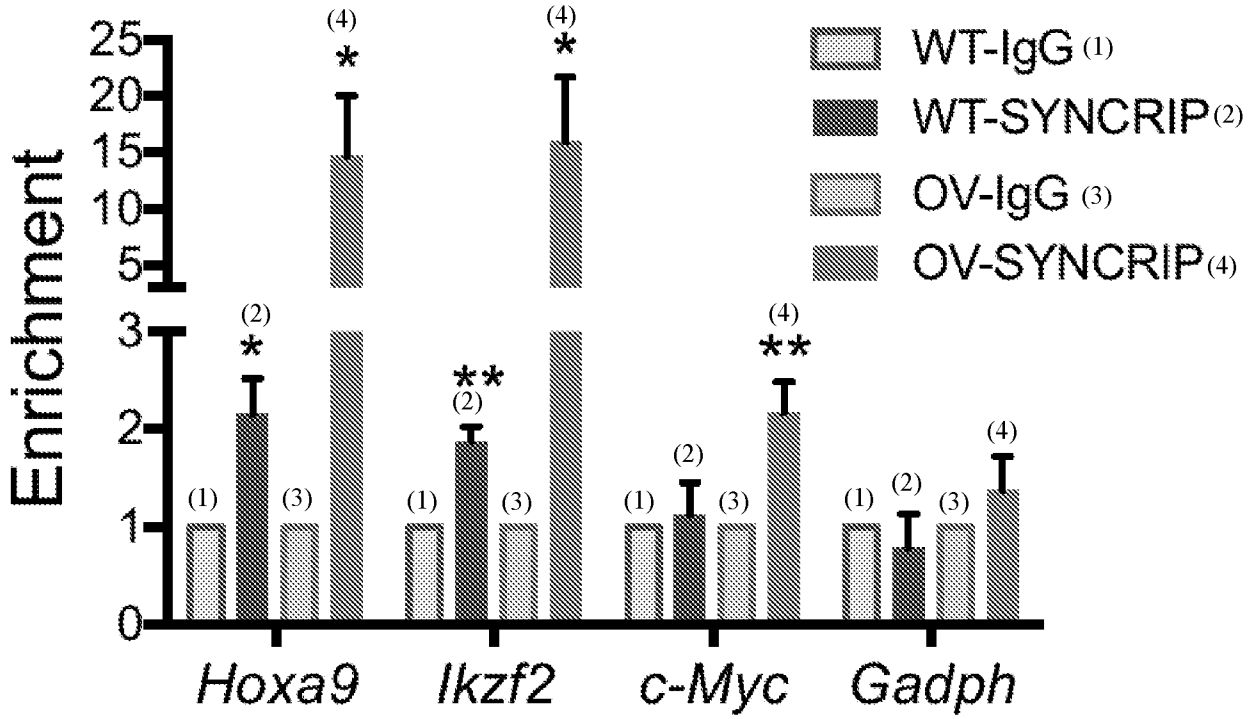


Figure 6(B)

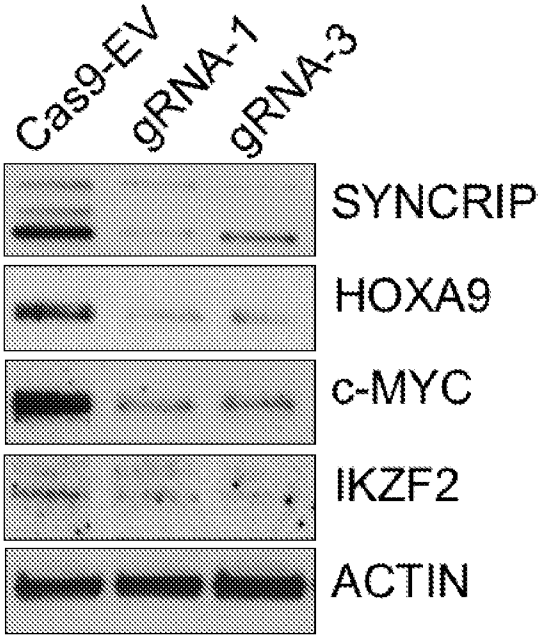


Figure 6(C)

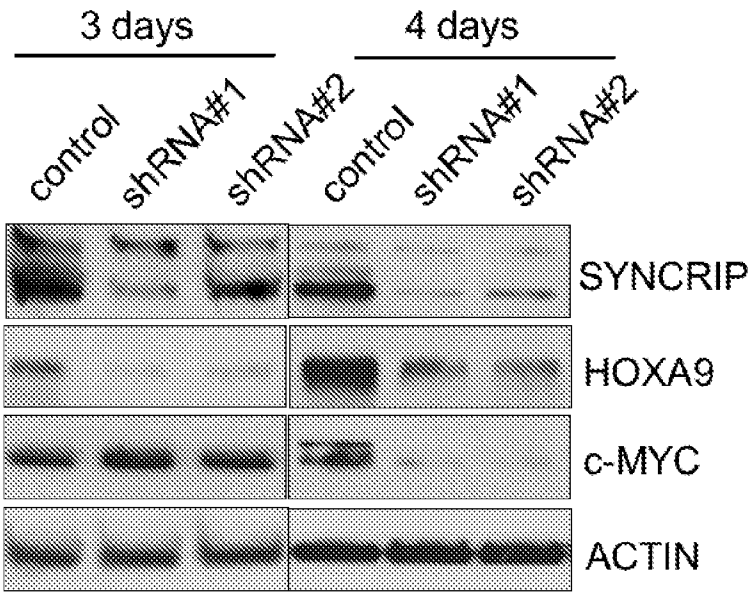


Figure 6(D)

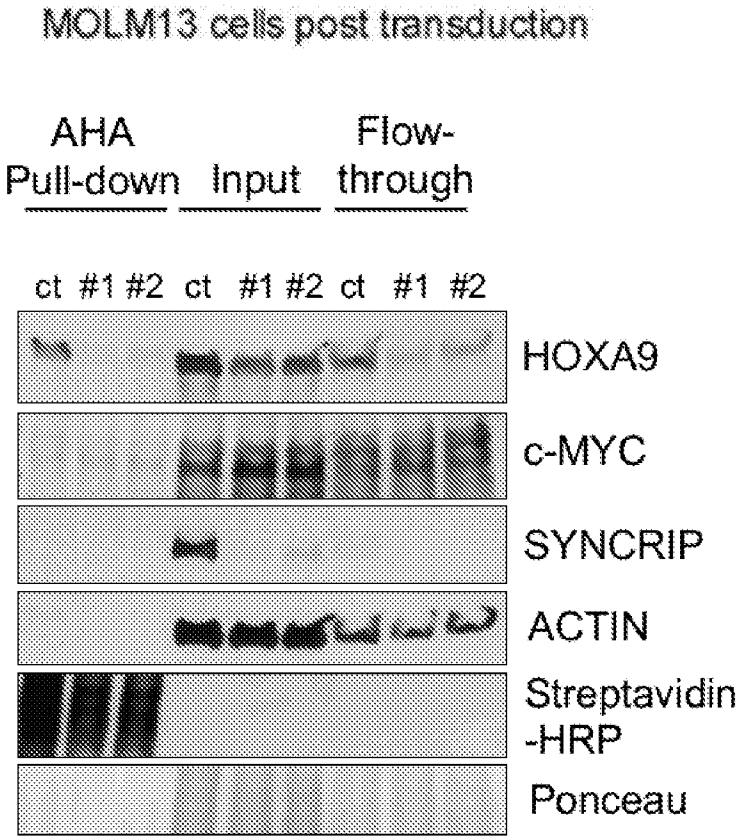


Figure 6(E)

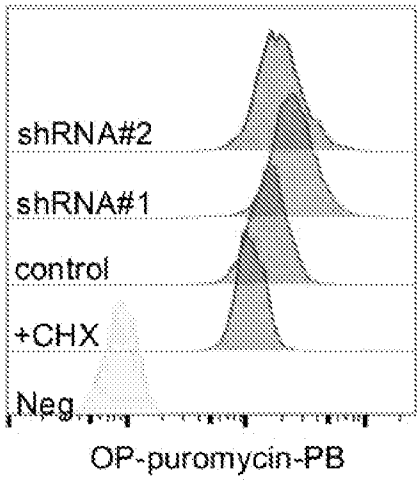


Figure 6(F)

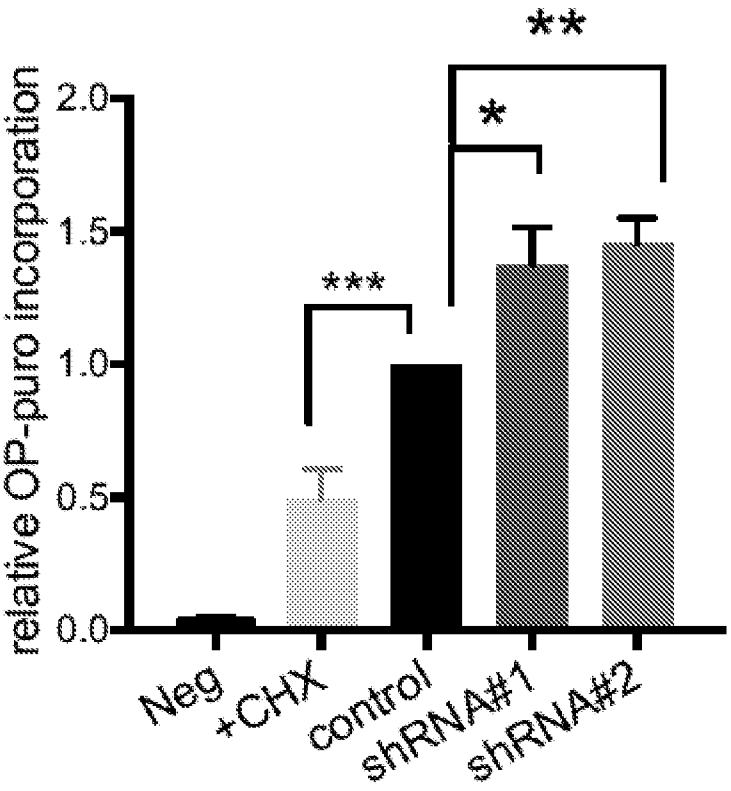

relative OP-puro incorporation
2.0
1.5
1.0
0.5
0.0
***
*
**
Neg
+CHX
control
shRNA#1
shRNA#2

Figure 6(G)

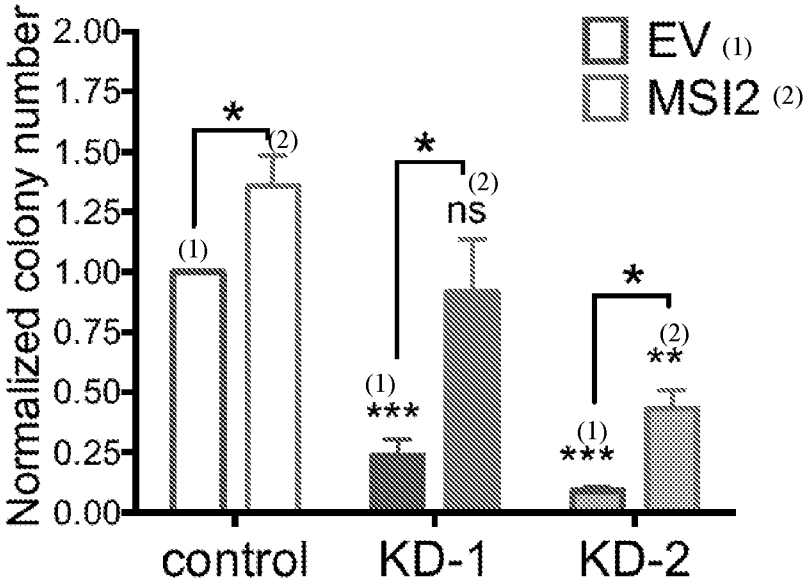


Figure 7(A)

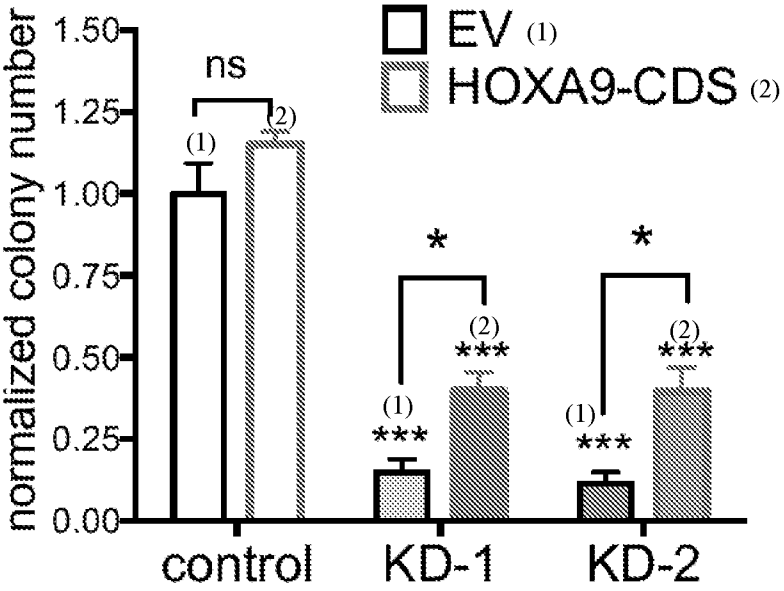


Figure 7(B)

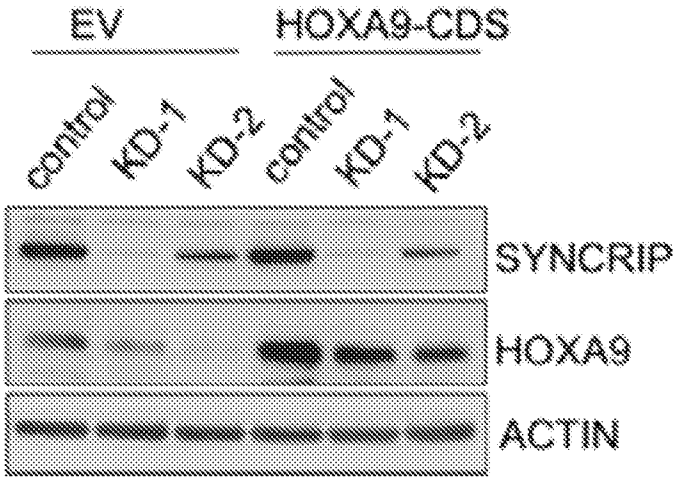


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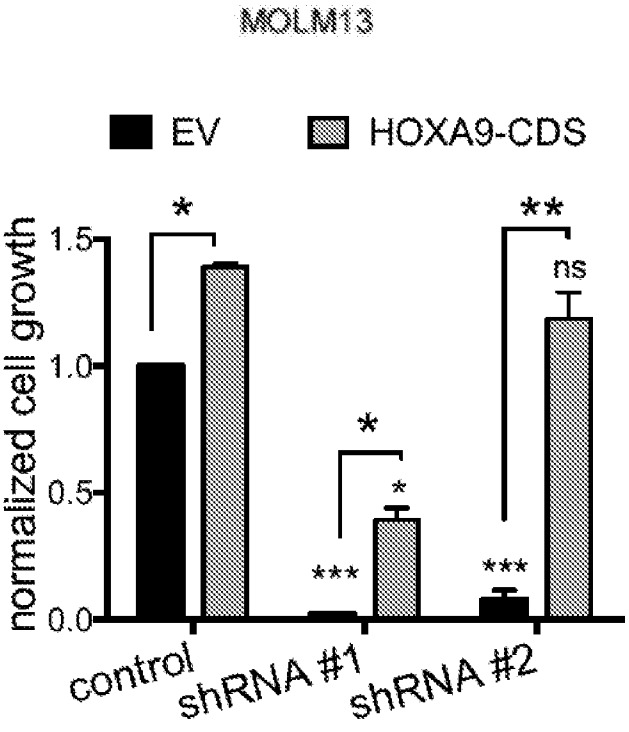


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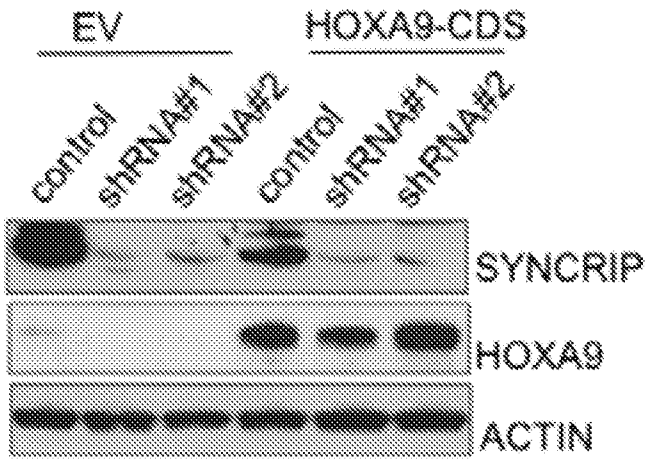


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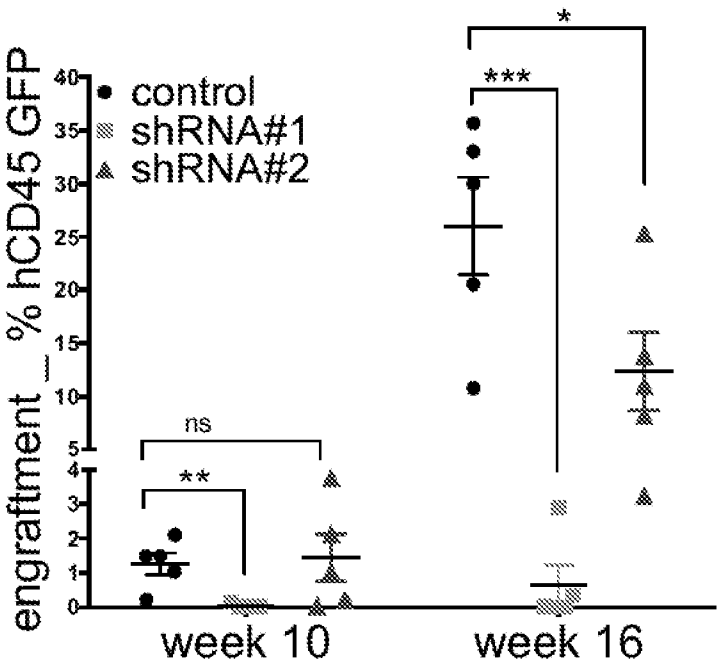


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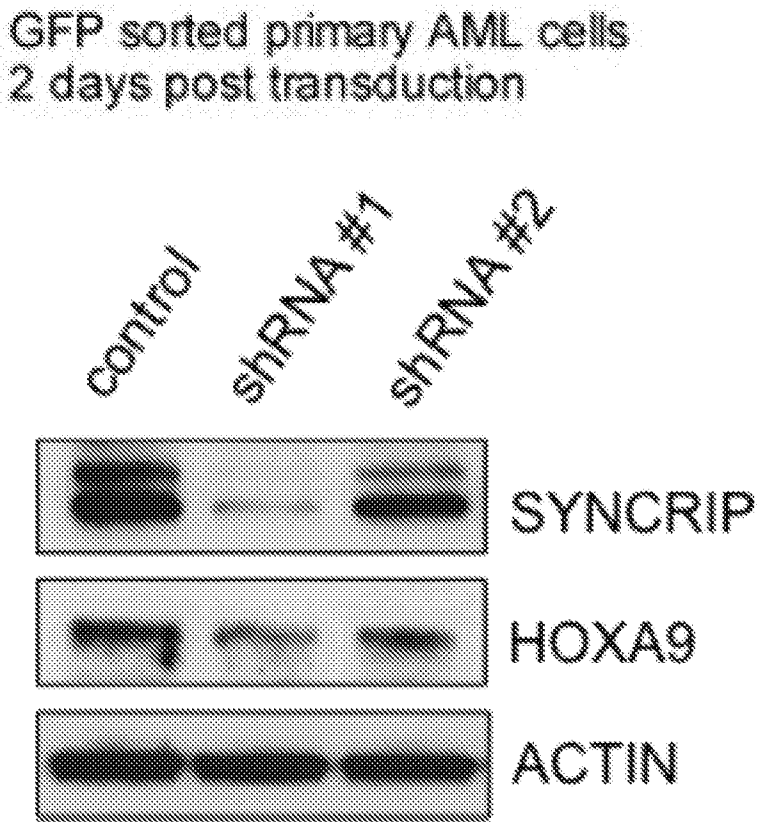


Figure 7(G)

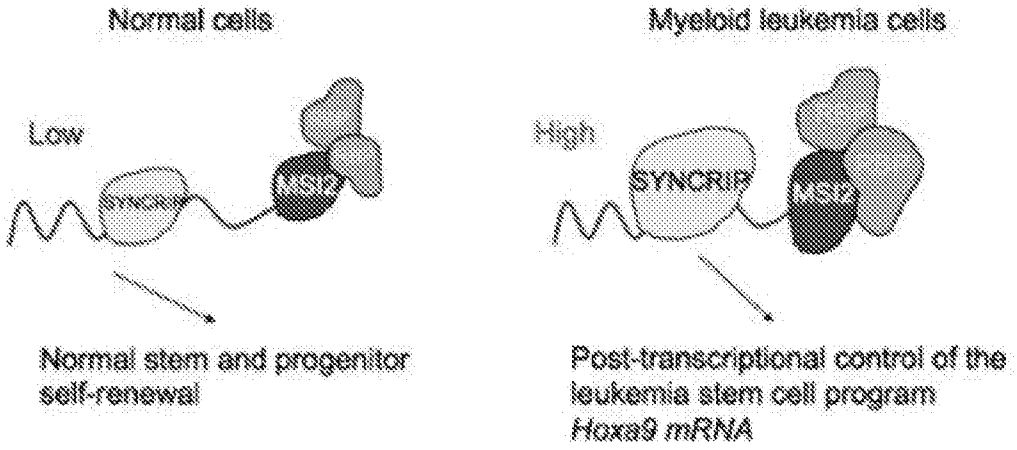


Figure 7(H)

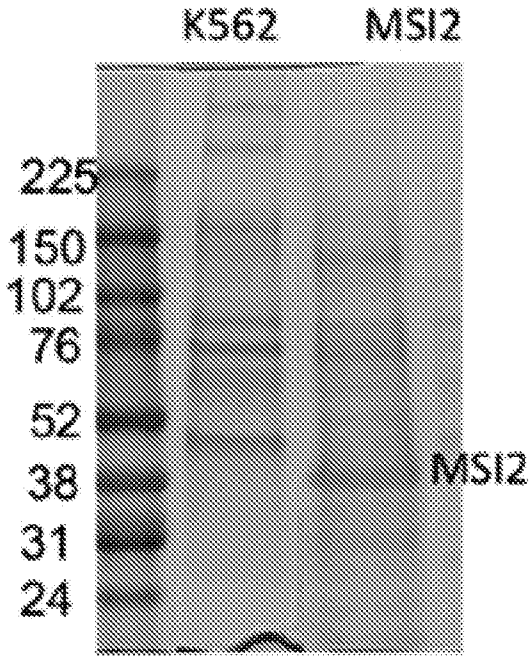


Figure 8(A)

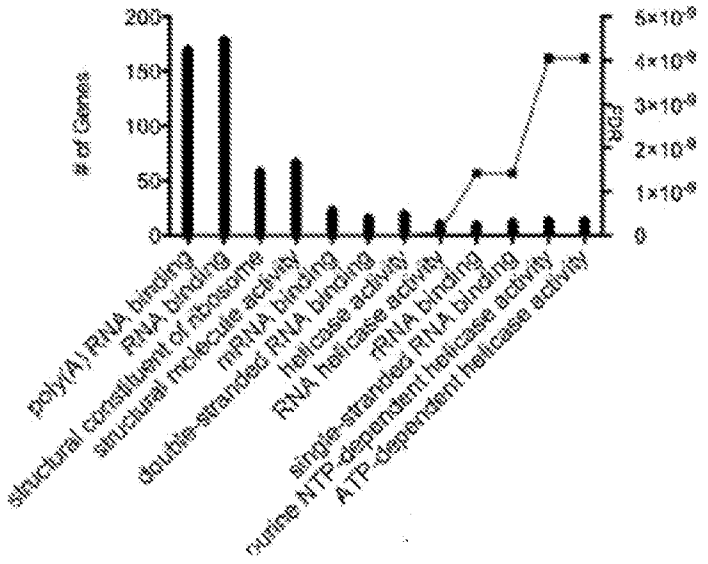


Figure 8(B)

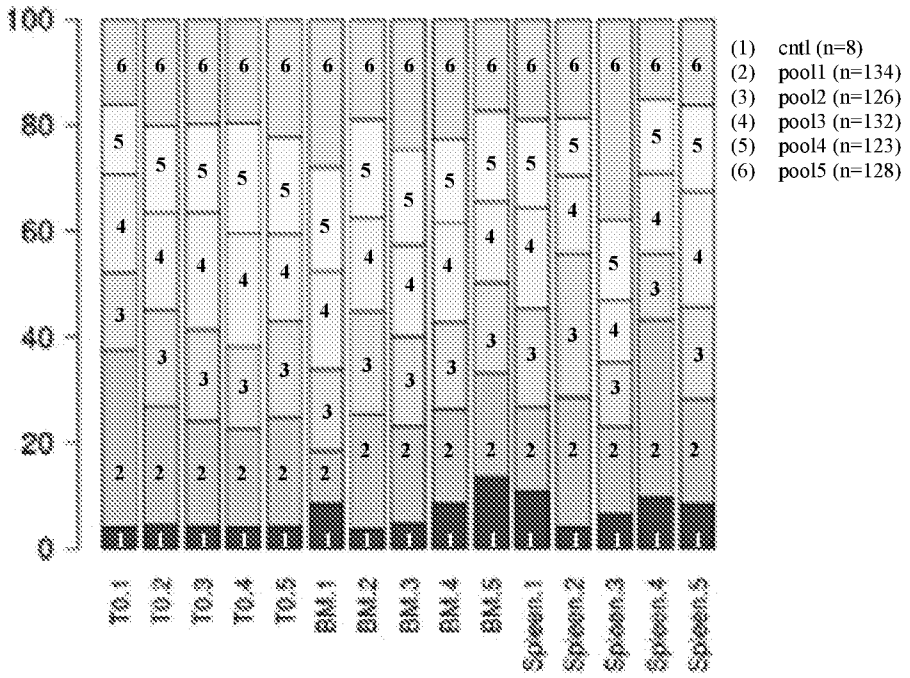


Figure 8(C)

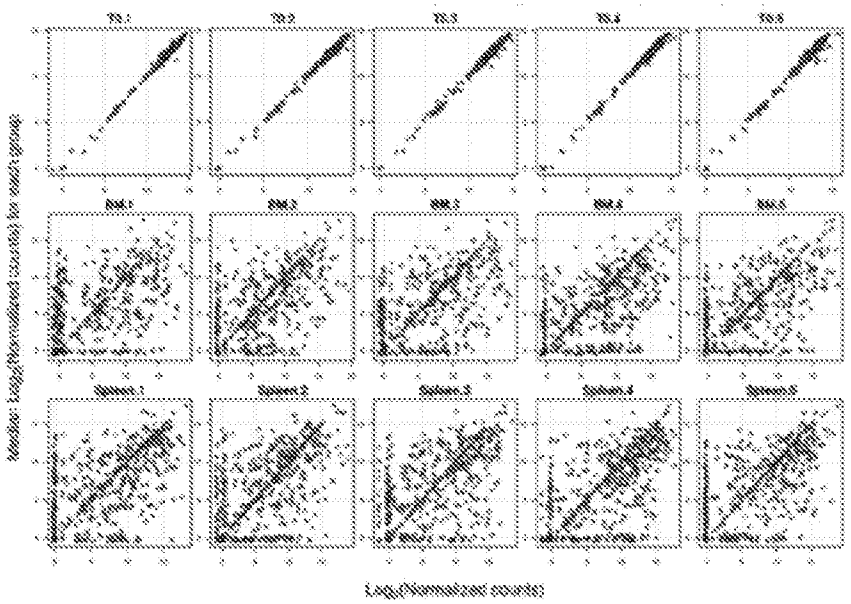


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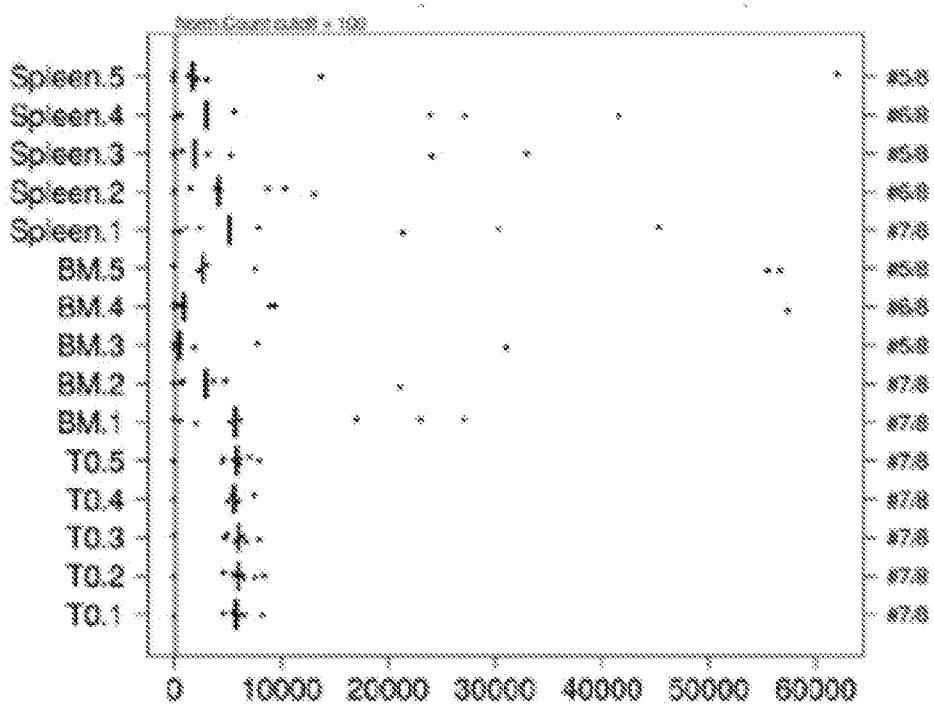


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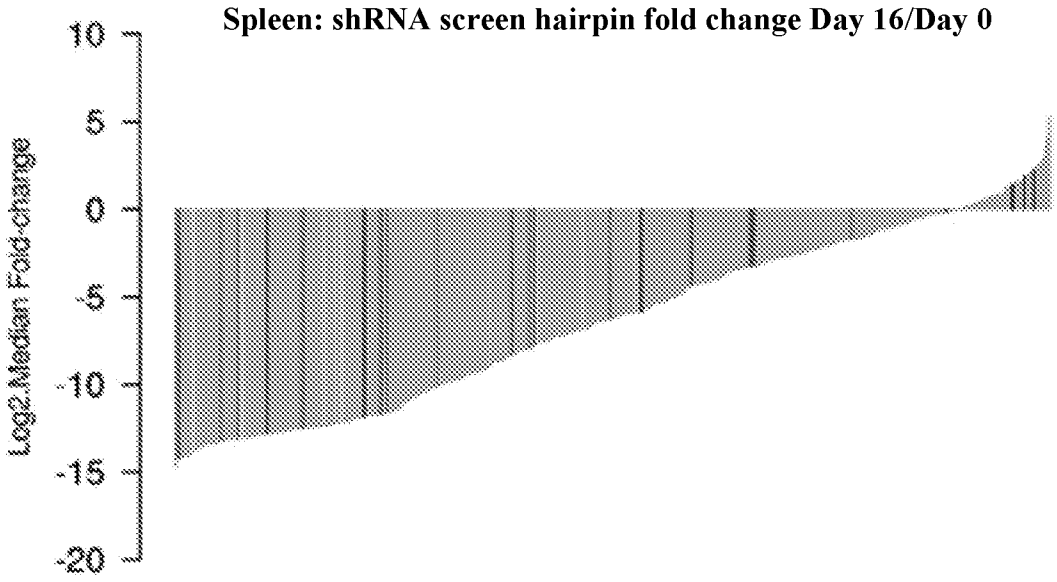


Figure 8(F)

Gene ID	Pool	Prognostic correlation	Cellular function(s)
Syncrip	Protein-protein	Poor prognosis	RNA binding protein
Caprin1	Protein-Protein	Poor prognosis	Cell cycle associated protein 1
Hnrnpa3	Protein-Protein	Poor prognosis	RNA binding protein
Cct3	Protein-protein	Poor prognosis	Chaperon containing TCP1, subunit3
Hnrnpr	Protein-protein	Poor prognosis	RNA binding protein
Mybbp1a	Protein-protein	Poor prognosis	Myb binding protein 1
Dyrk2	Target gene	Poor Prognosis	Dual Specificity Tyrosine-Phosphorylation-Regulated Kinase 2

Figure 8(G)

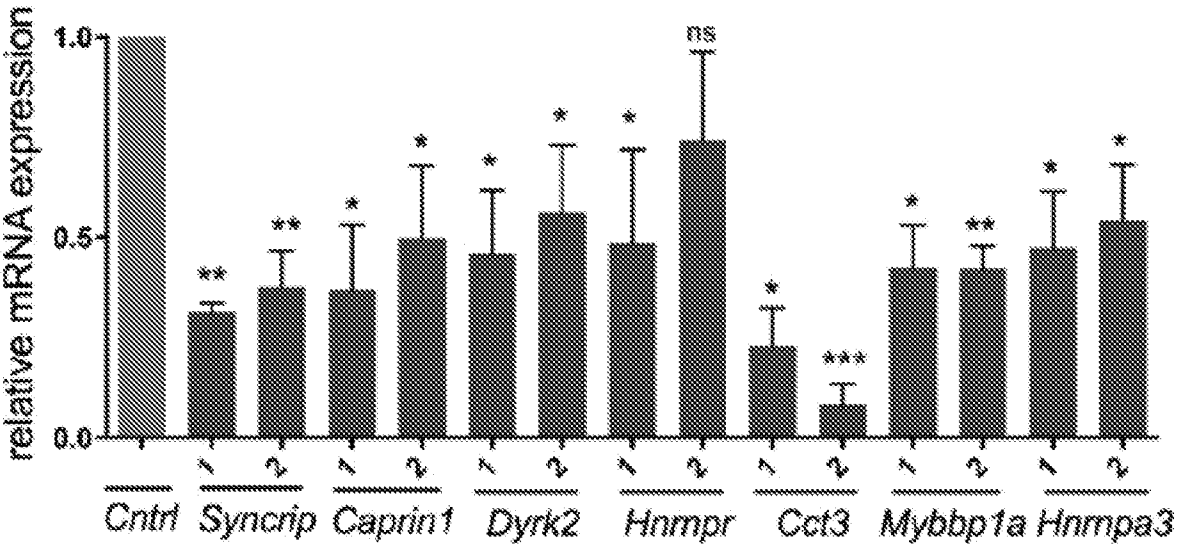


Figure 8(H)

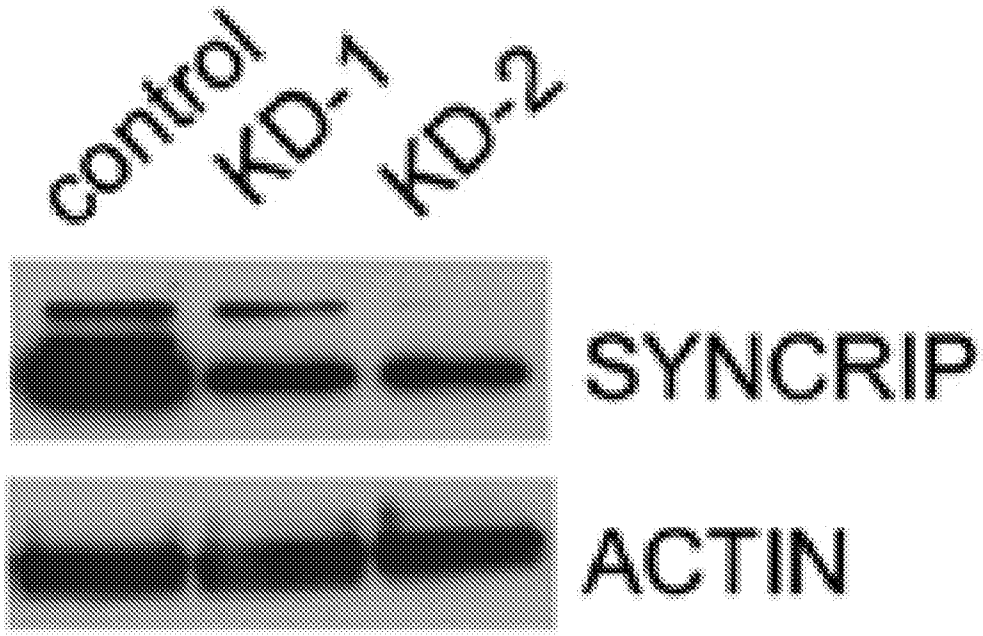


Figure 9(A)

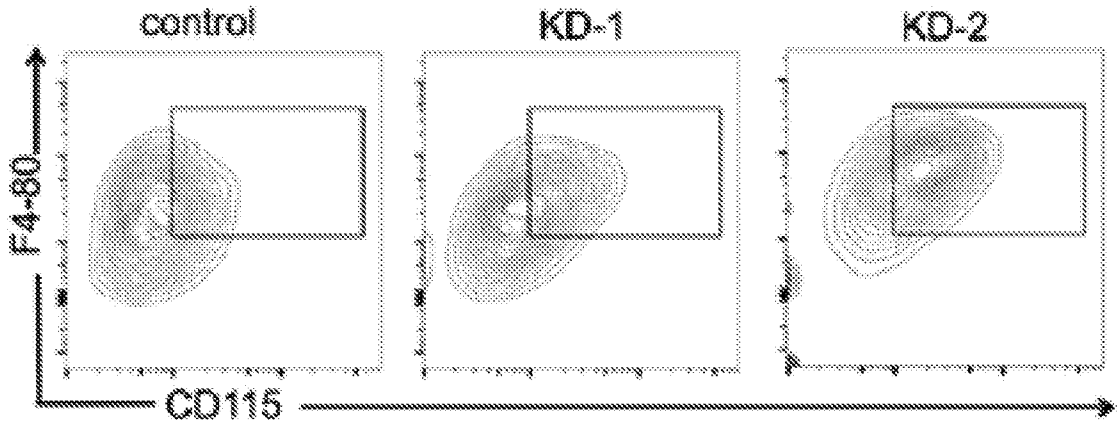


Figure 9(B)

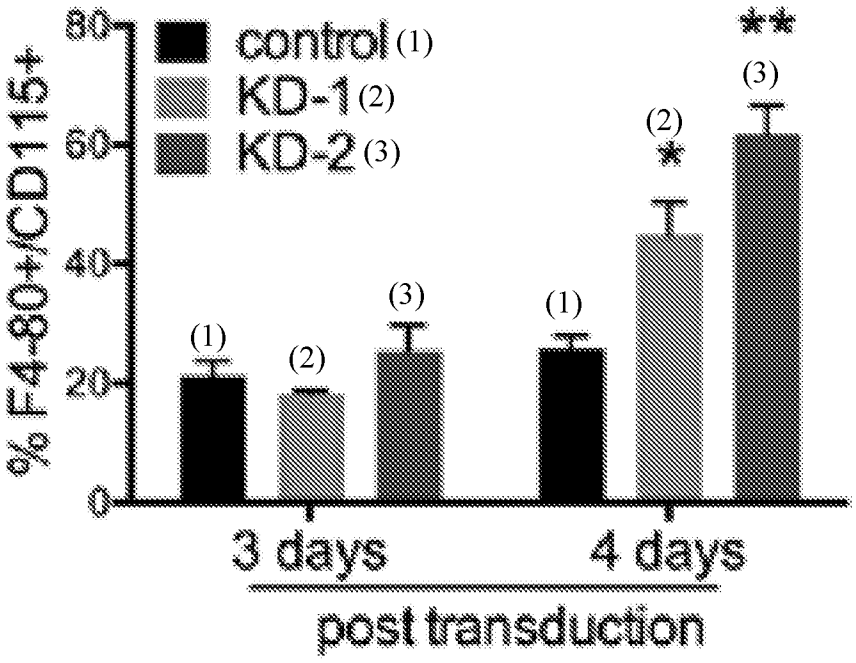


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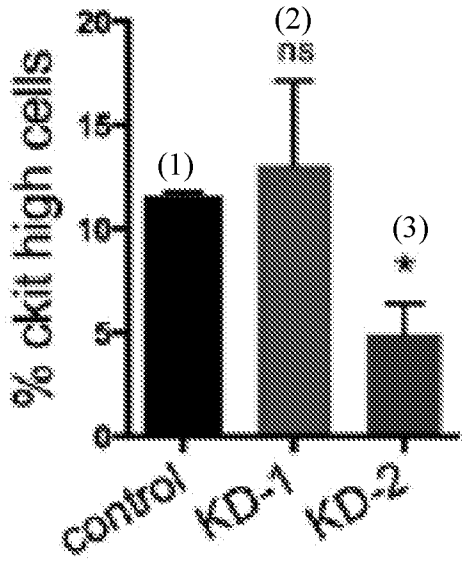


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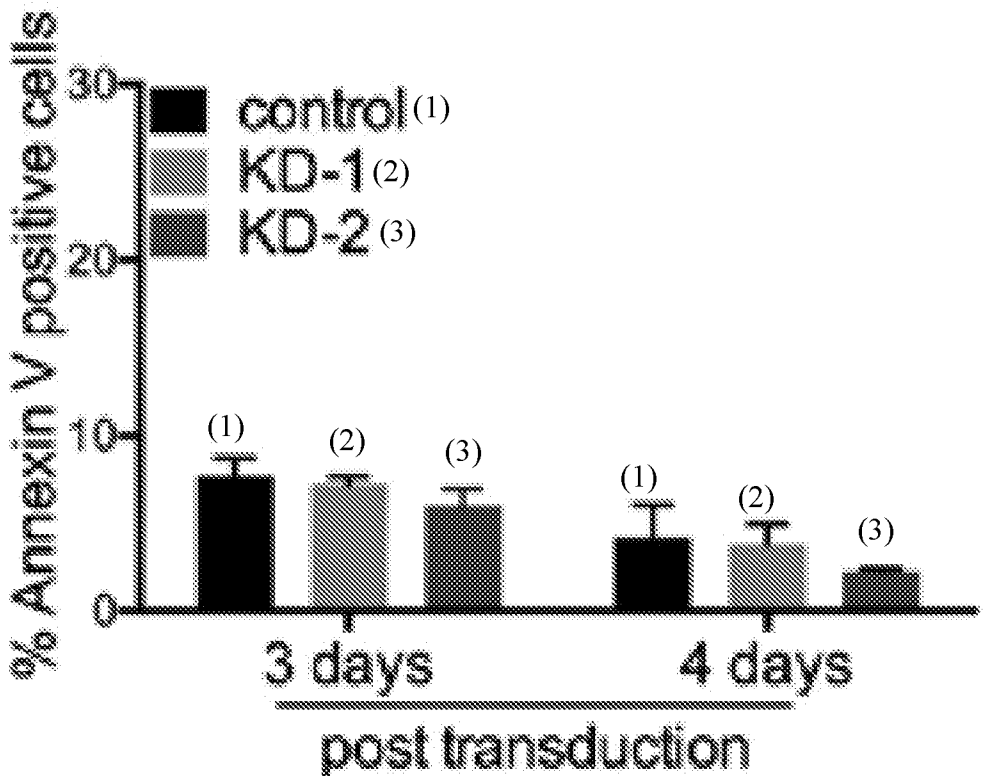


Figure 9(E)

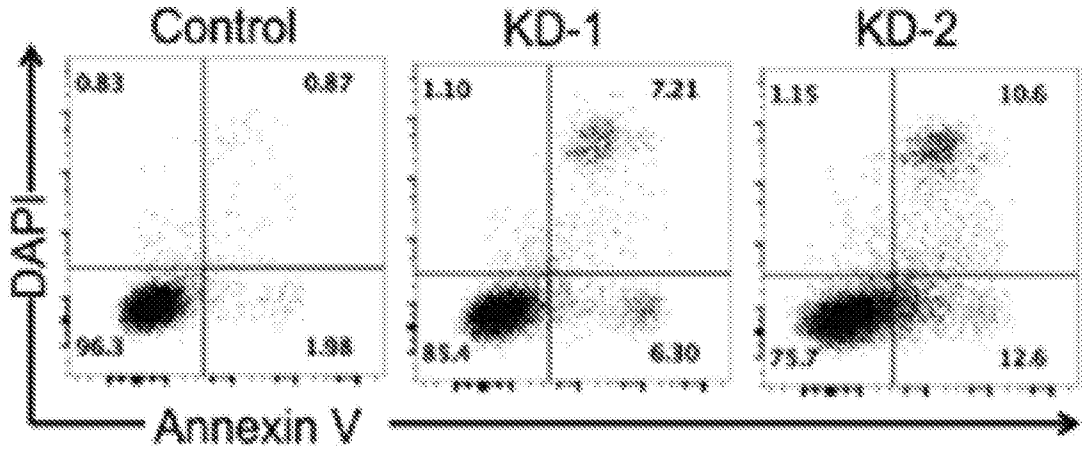


Figure 9(F)

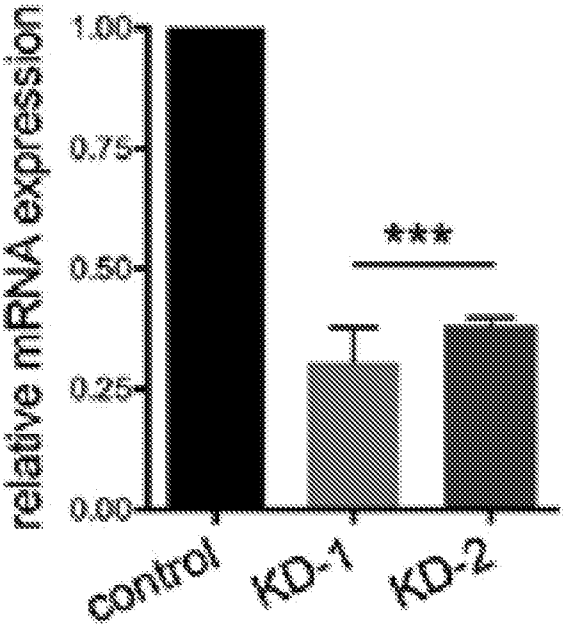


Figure 9(G)

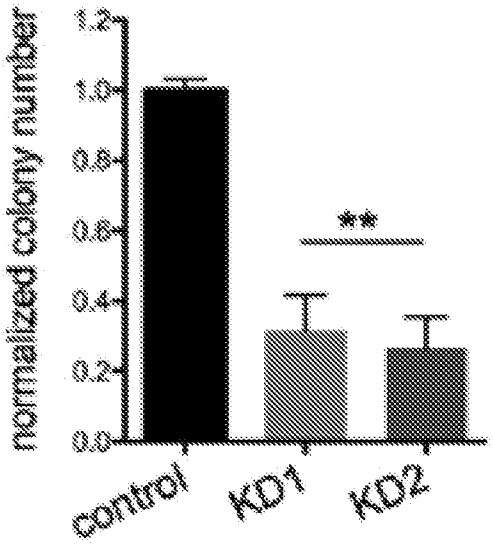


Figure 9(H)

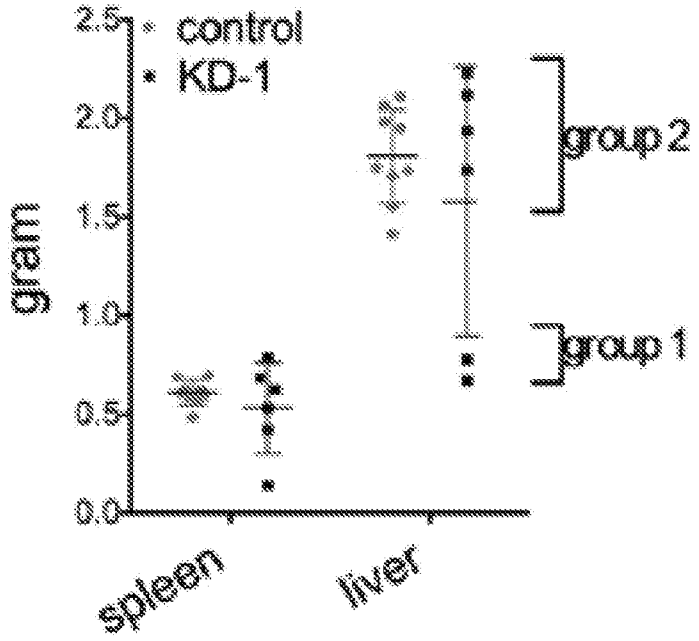


Figure 9(I)

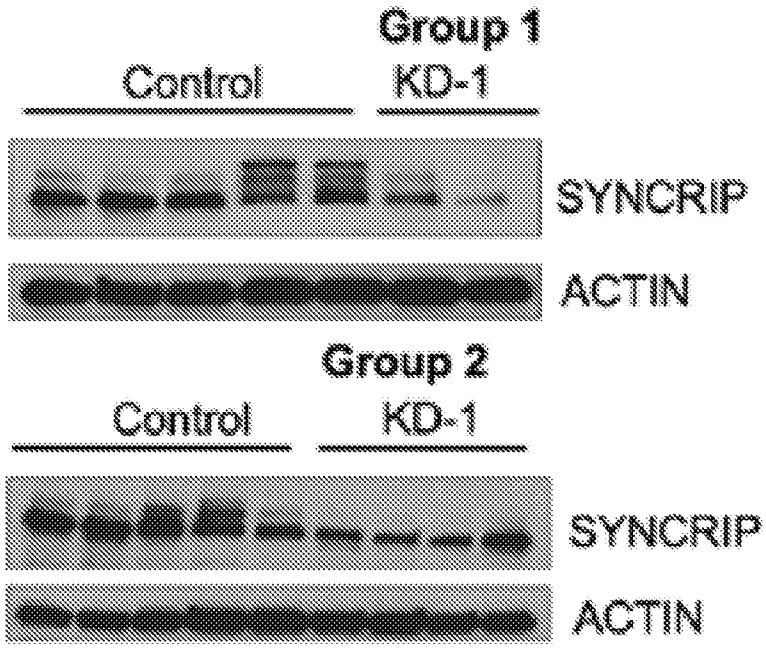


Figure 9(J)

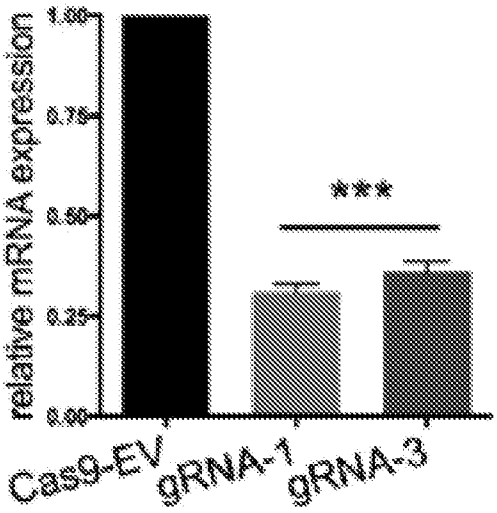


Figure 9(K)

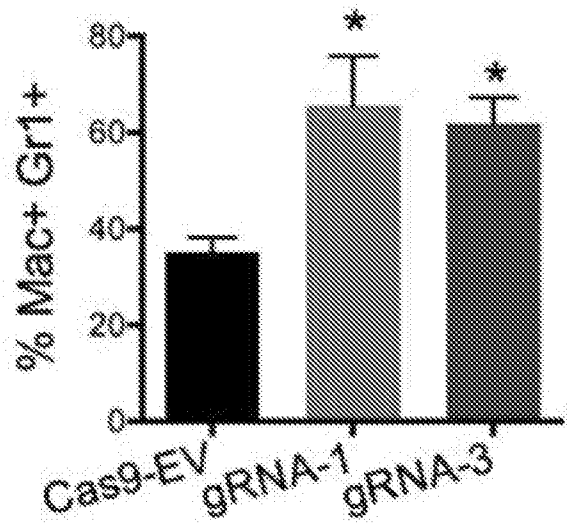


Figure 9(L)

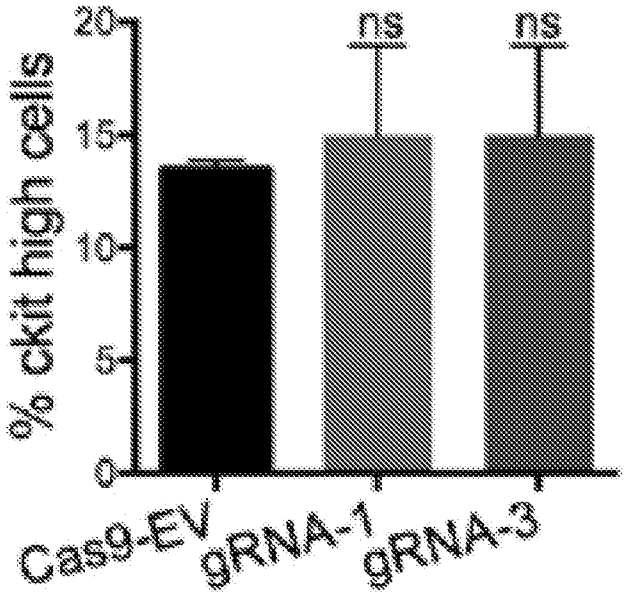


Figure 9(M)

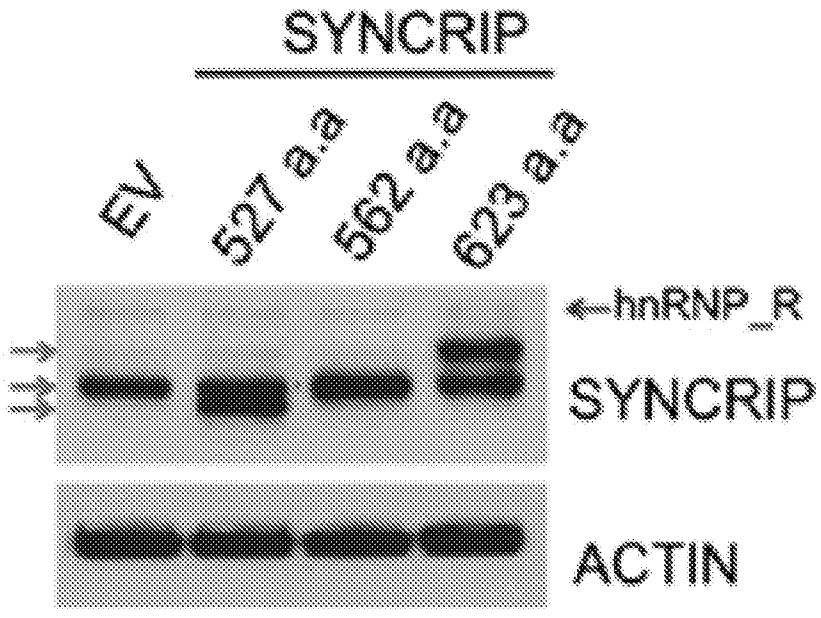


Figure 9(N)

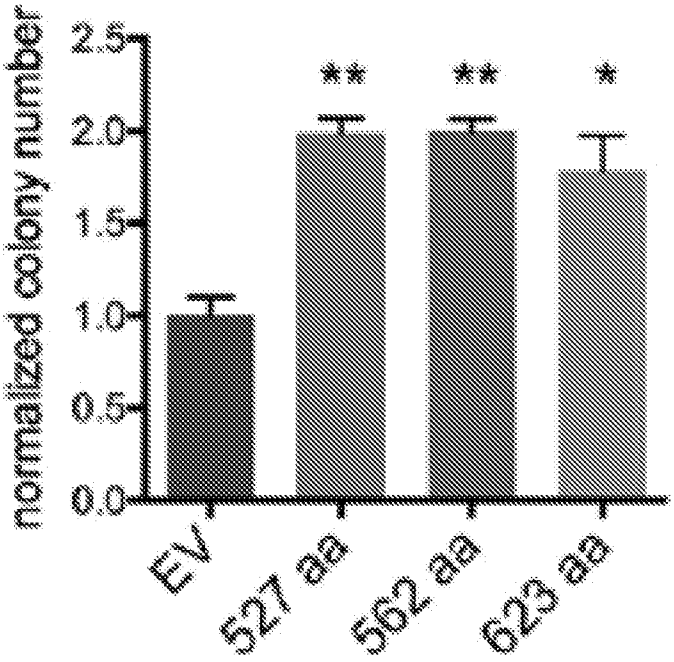


Figure 9(O)

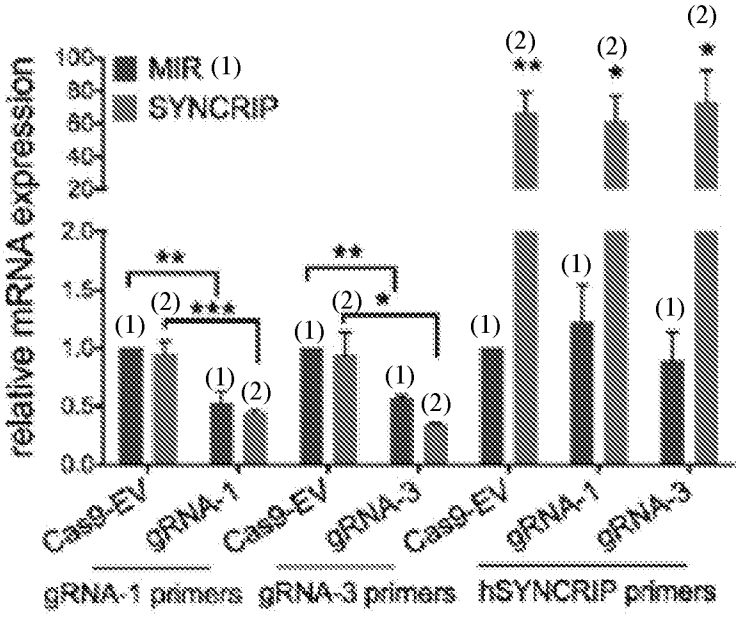


Figure 9(P)

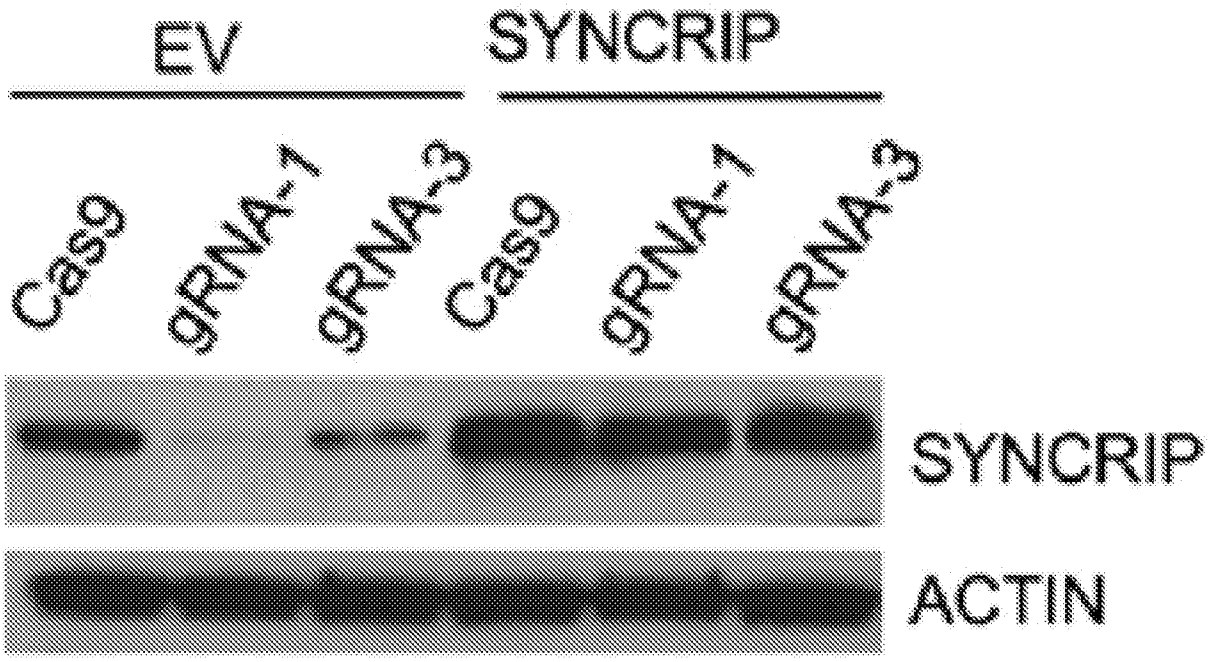


Figure 9(Q)

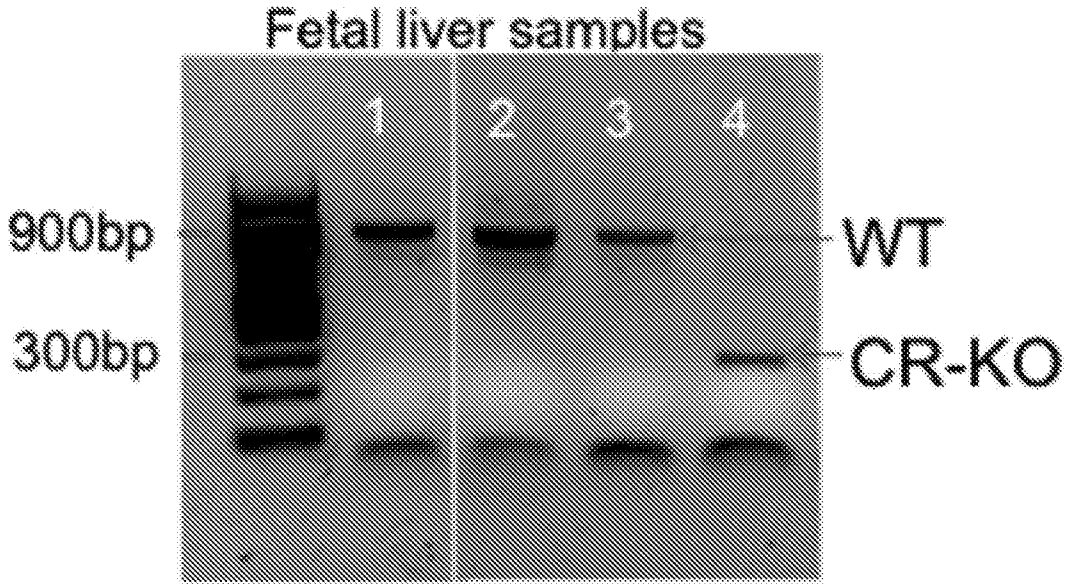


Figure 10(A)

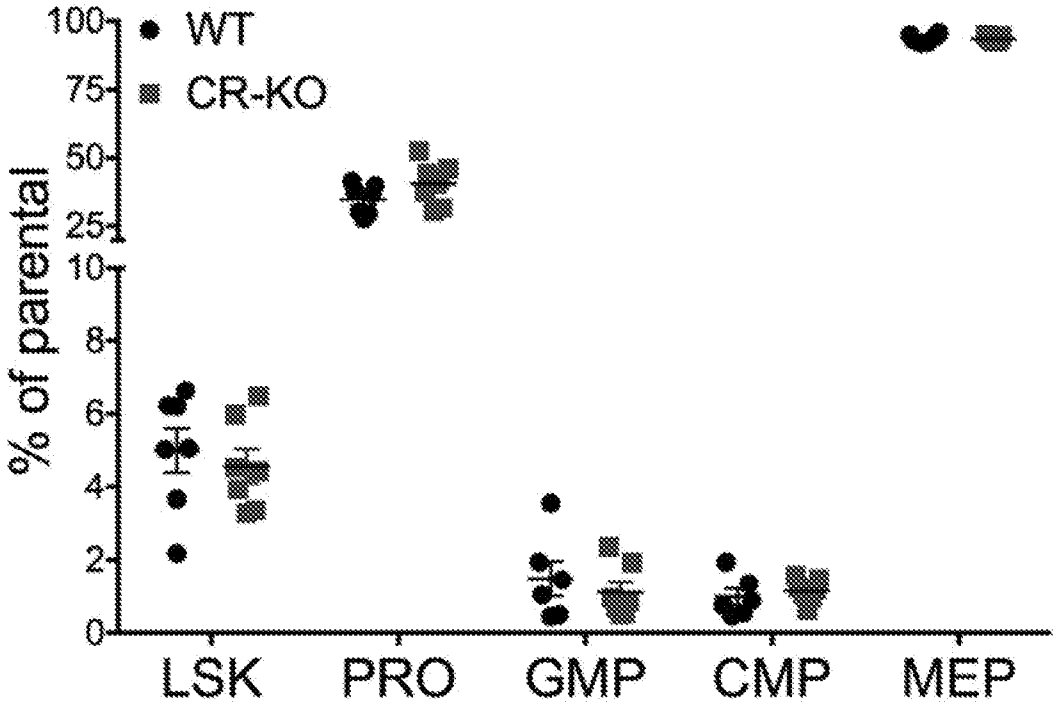


Figure 10(B)

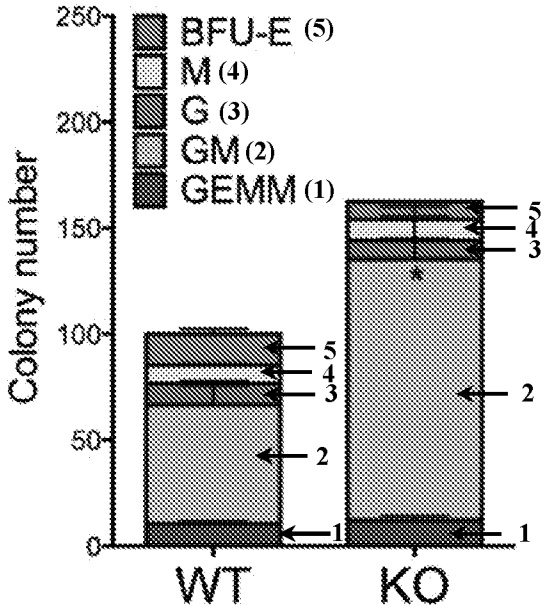


Figure 10(C)

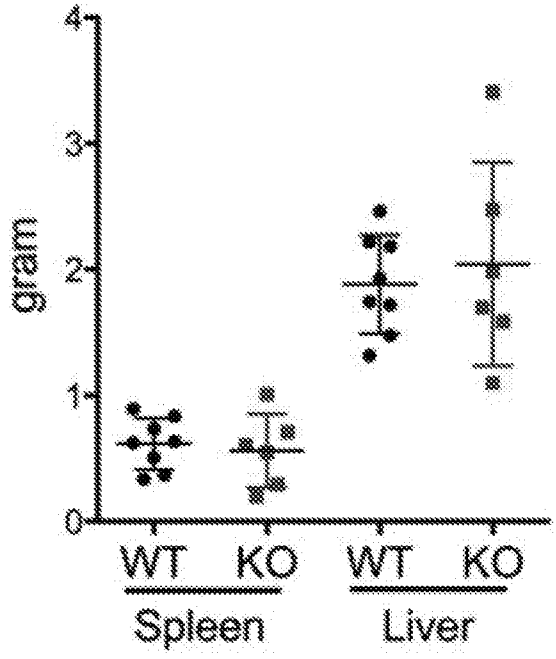


Figure 10(D)

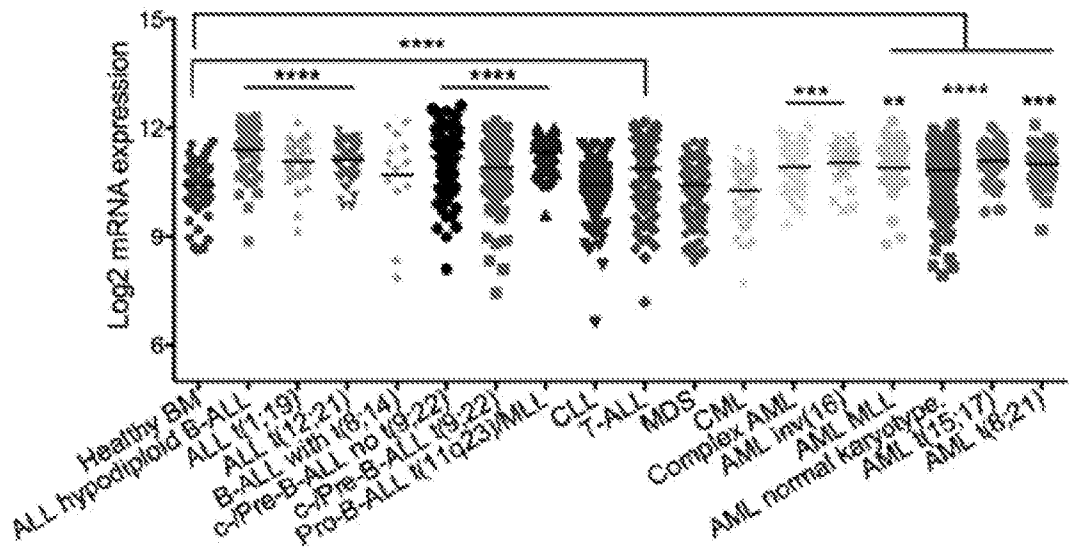


Figure 11(A)

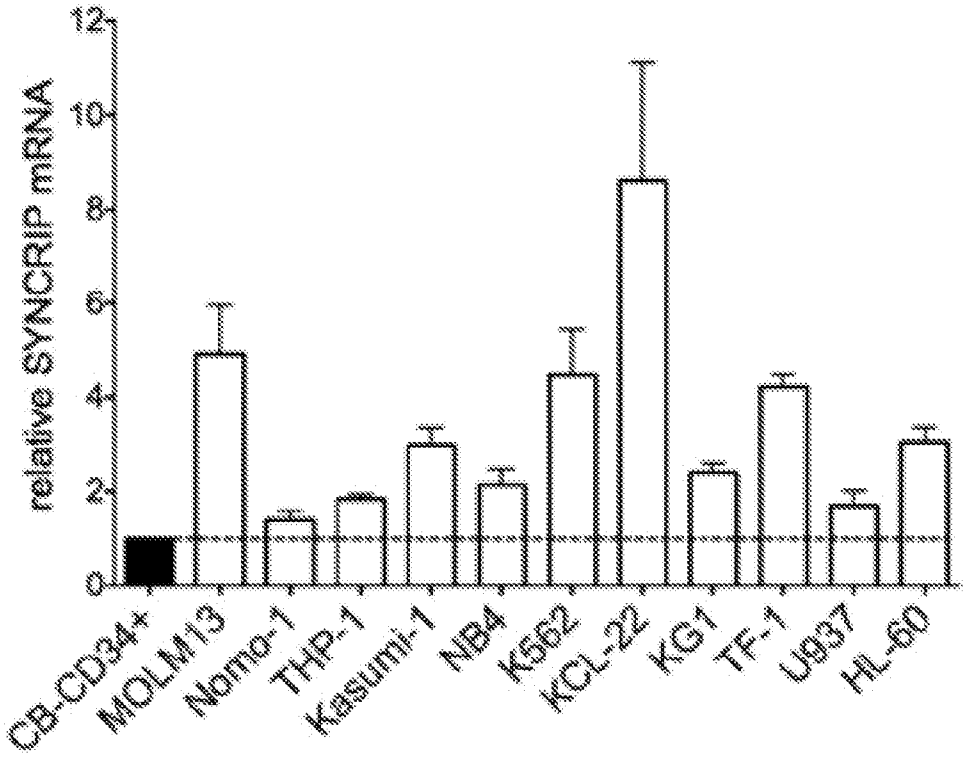


Figure 11(B)

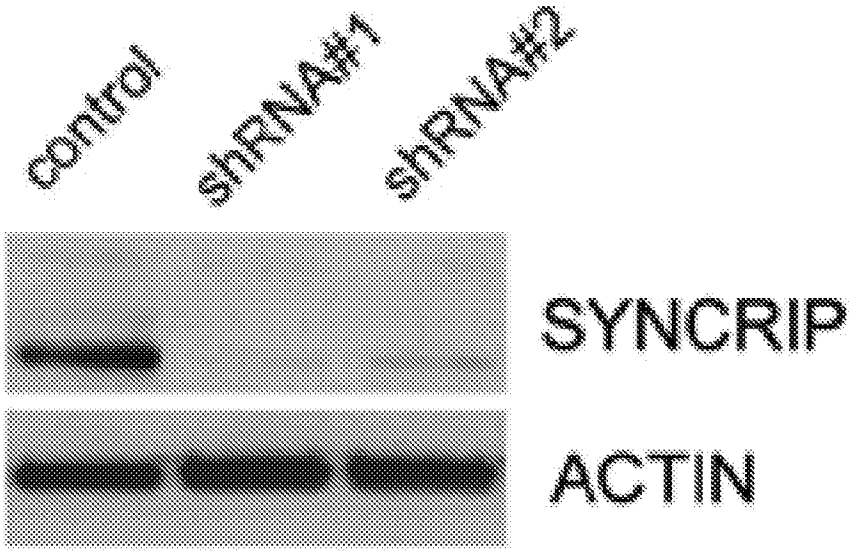


Figure 11(C)

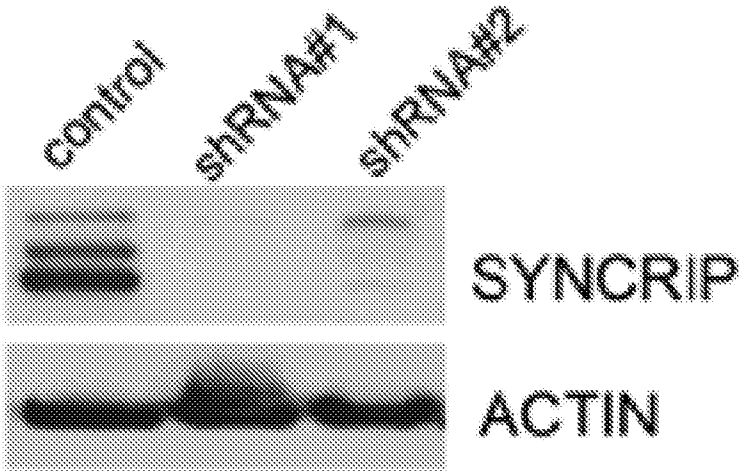


Figure 11(D)

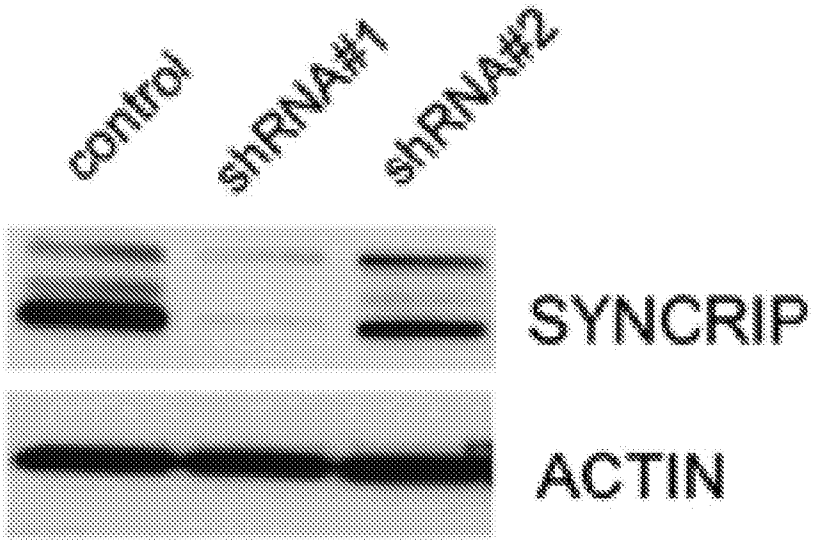


Figure 11(E)

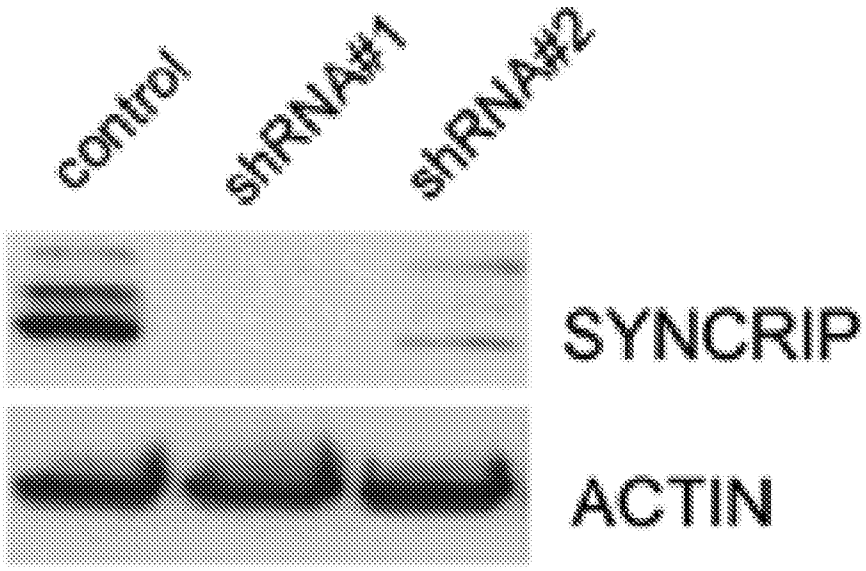


Figure 11(F)

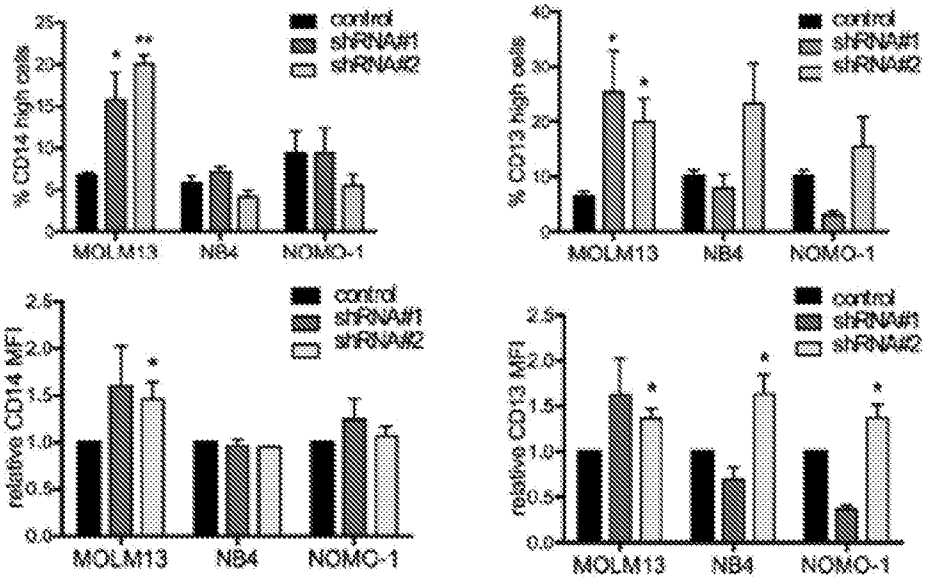


Figure 11(G)

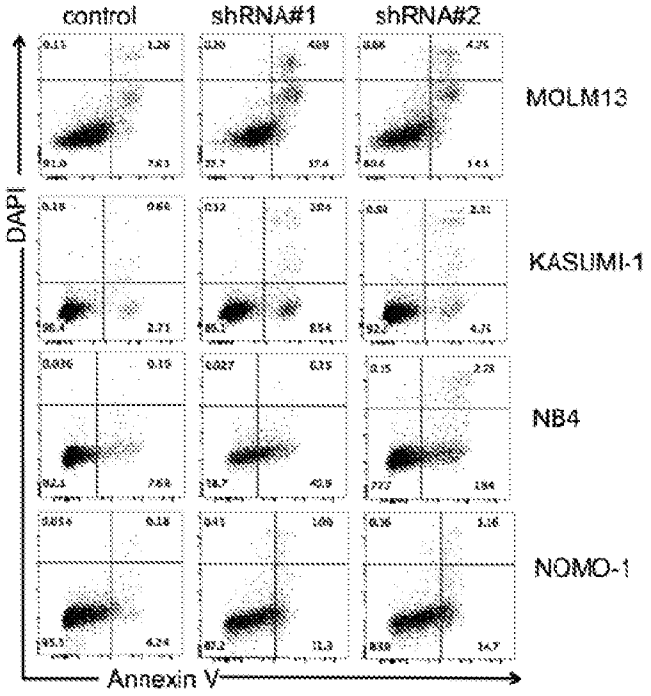


Figure 11(H)

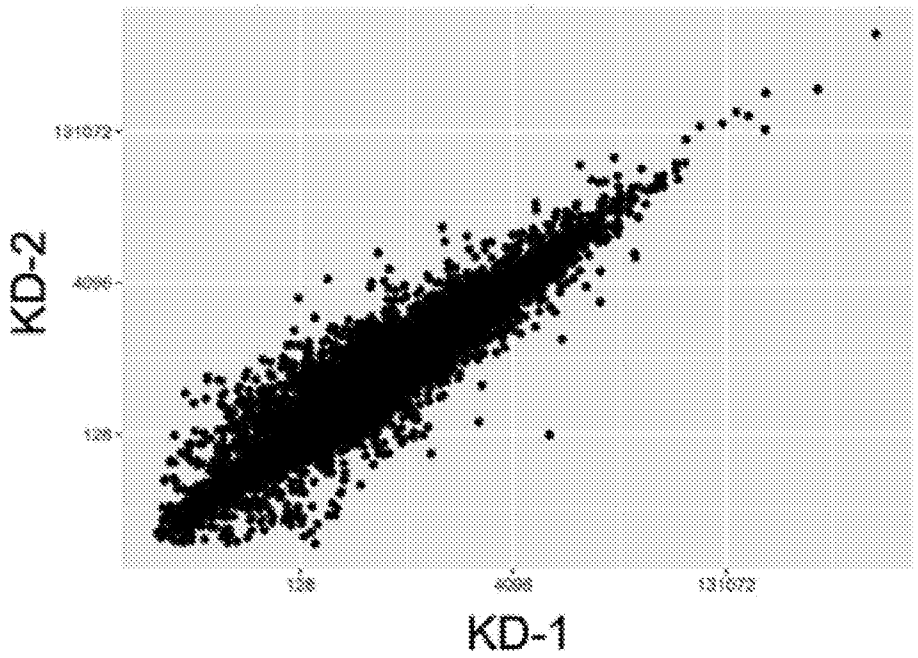


Figure 12(A)

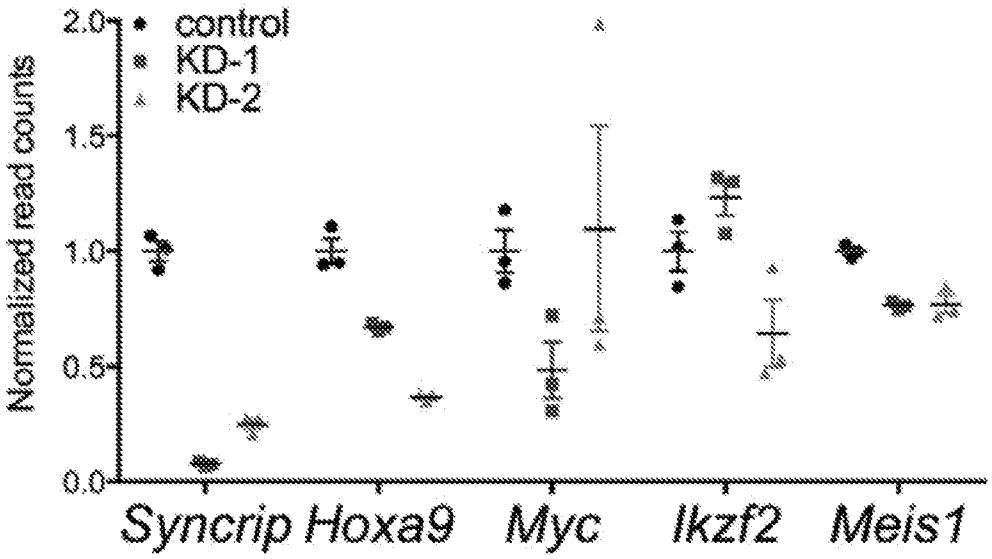


Figure 12(B)

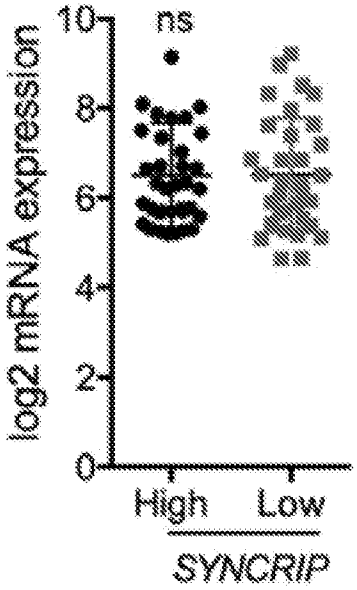


Figure 12(C)

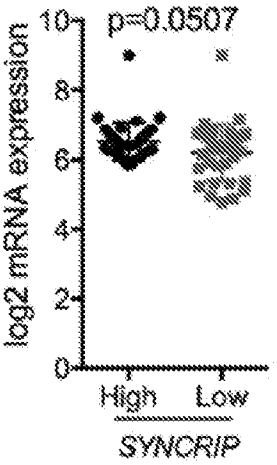


Figure 12(D)

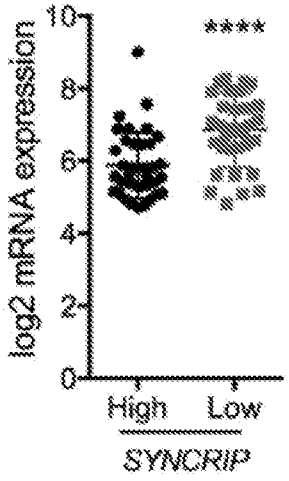


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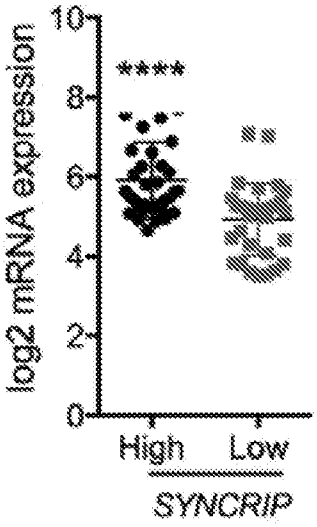


Figure 12(F)

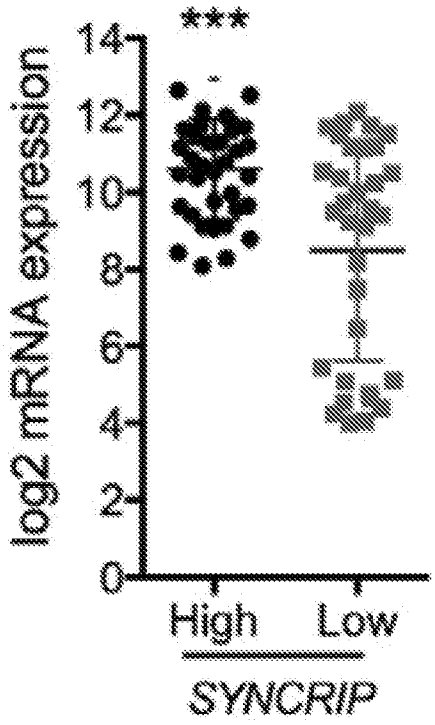


Figure 12(G)

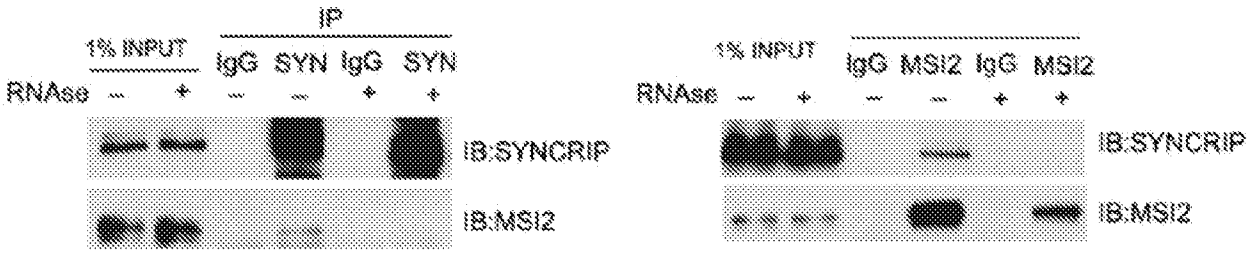


Figure 13(A)

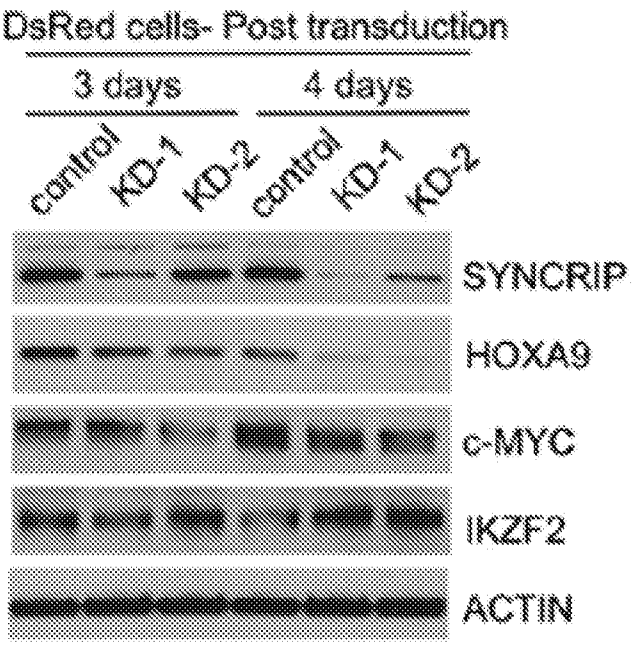


Figure 13(B)

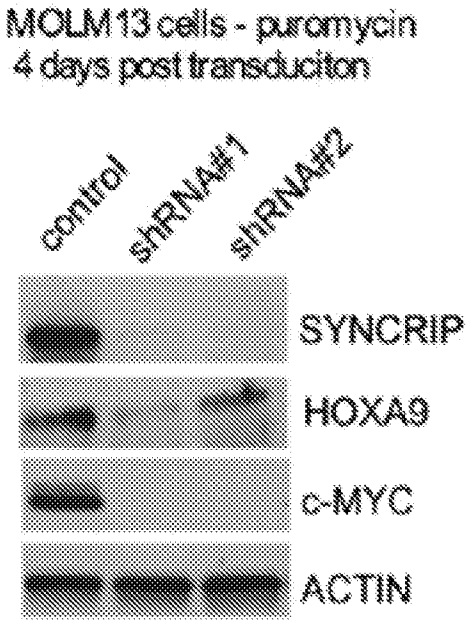


Figure 13(C)

c

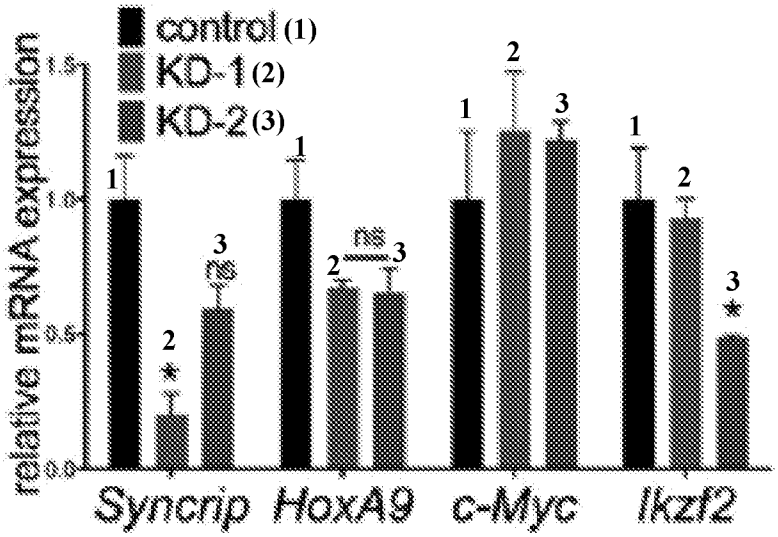


Figure 13(D)

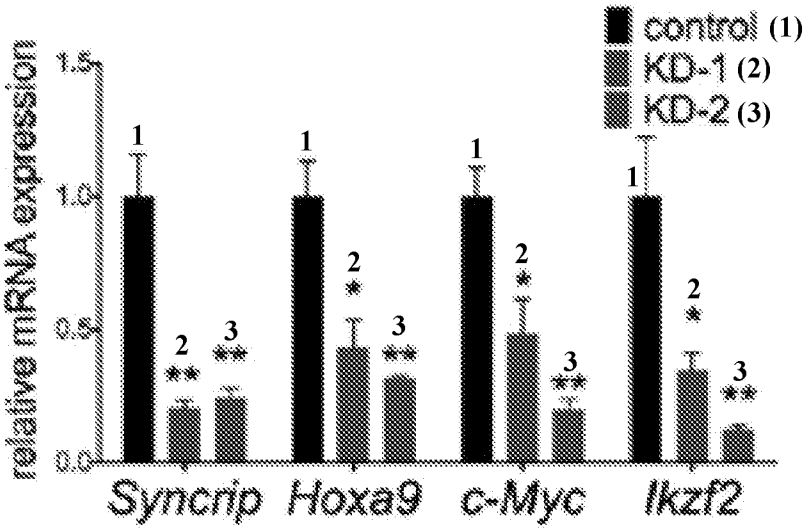


Figure 13(E)

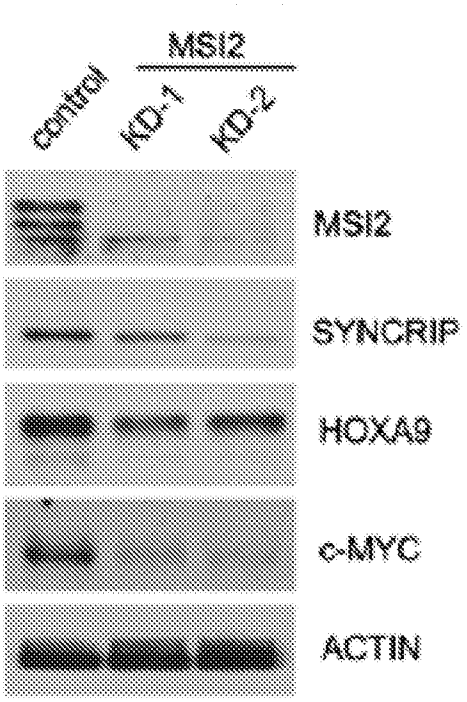


Figure 13(F)

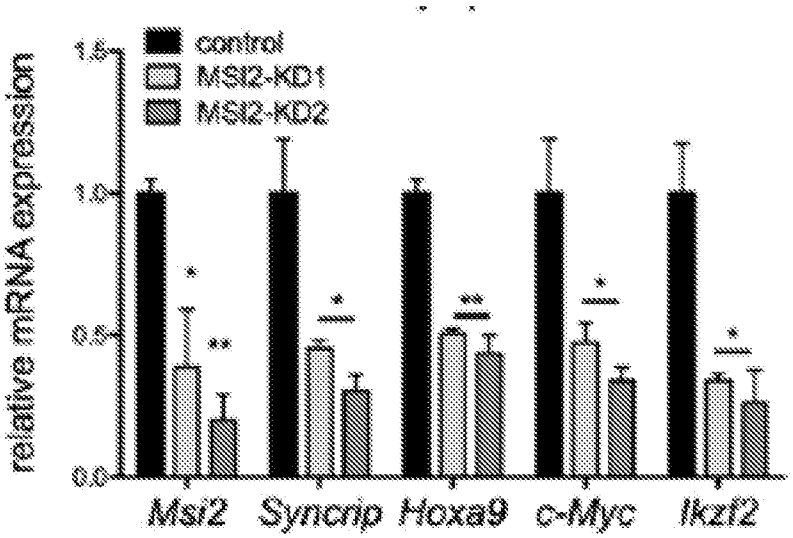


Figure 13(G)

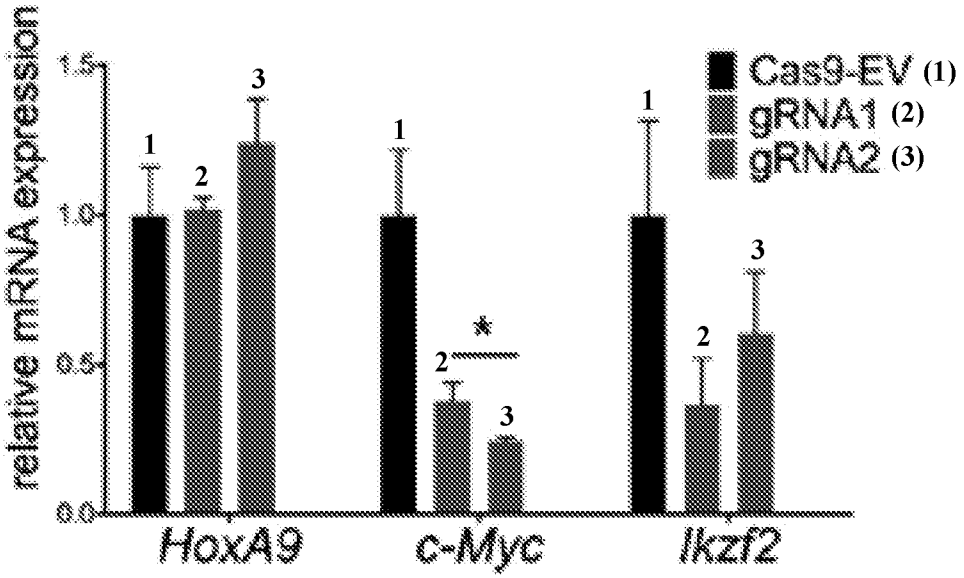


Figure 13(H)

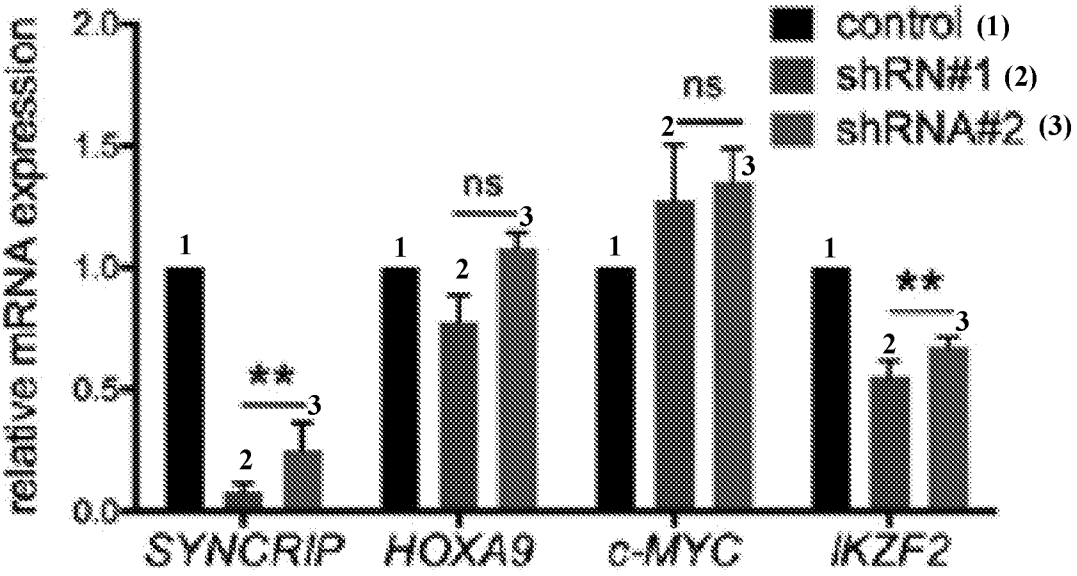


Figure 13(I)

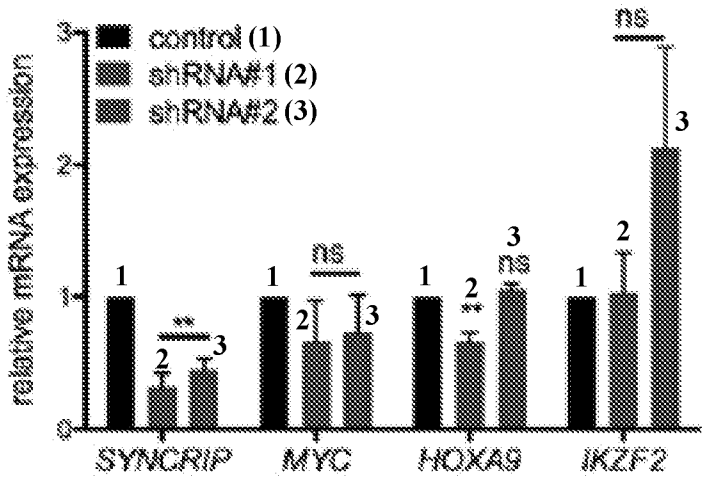


Figure 13(J)

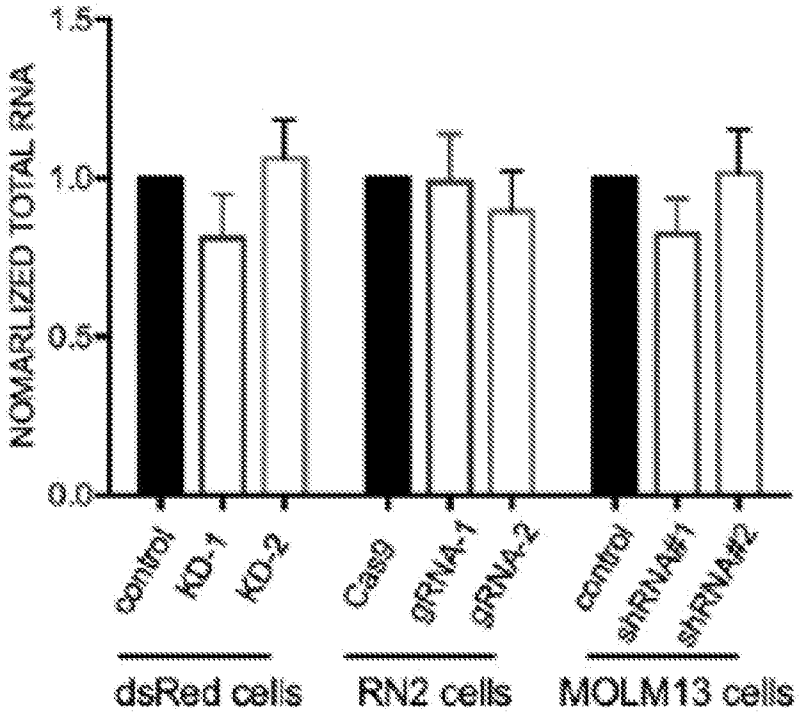


Figure 13(K)

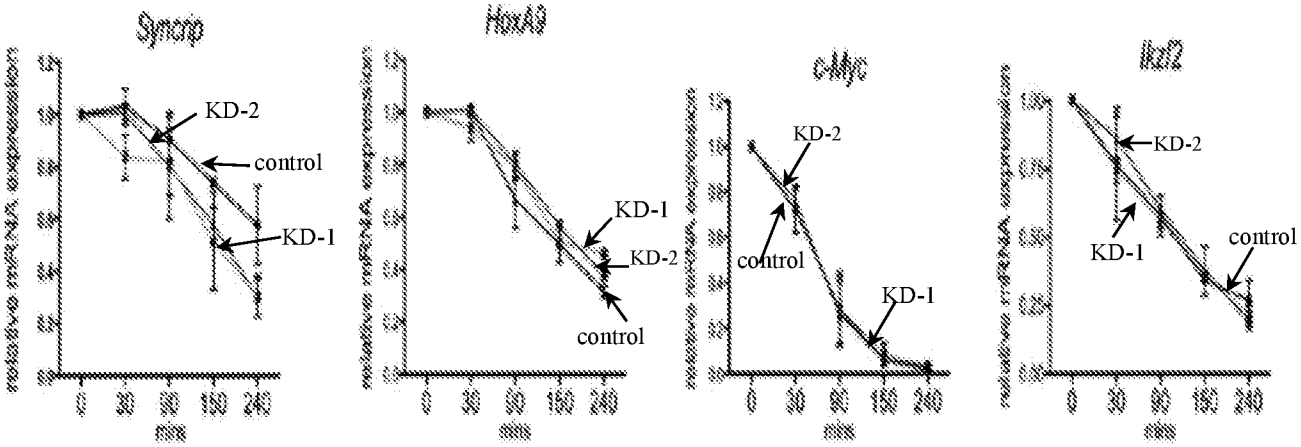


Figure 13(L)

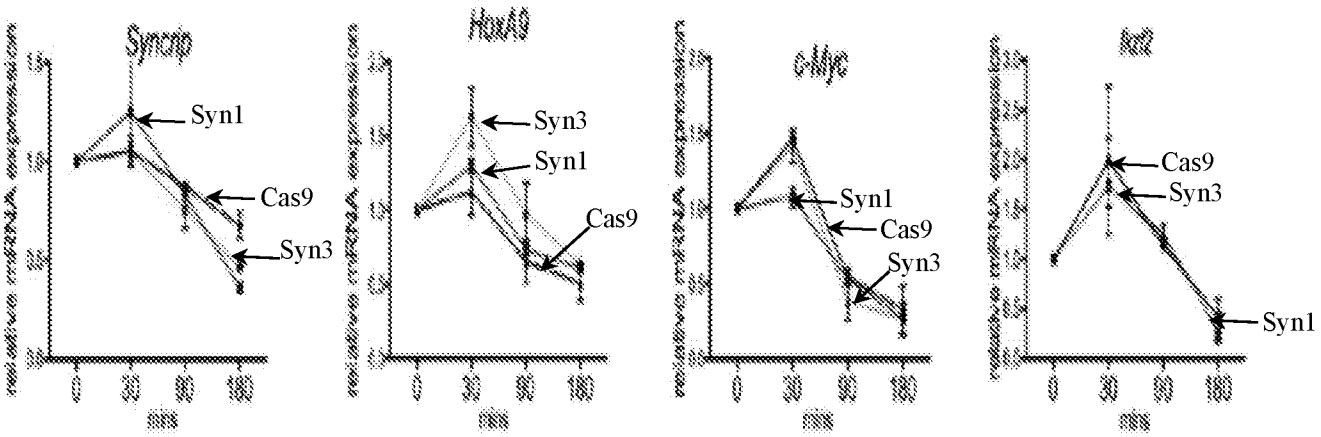


Figure 13(M)

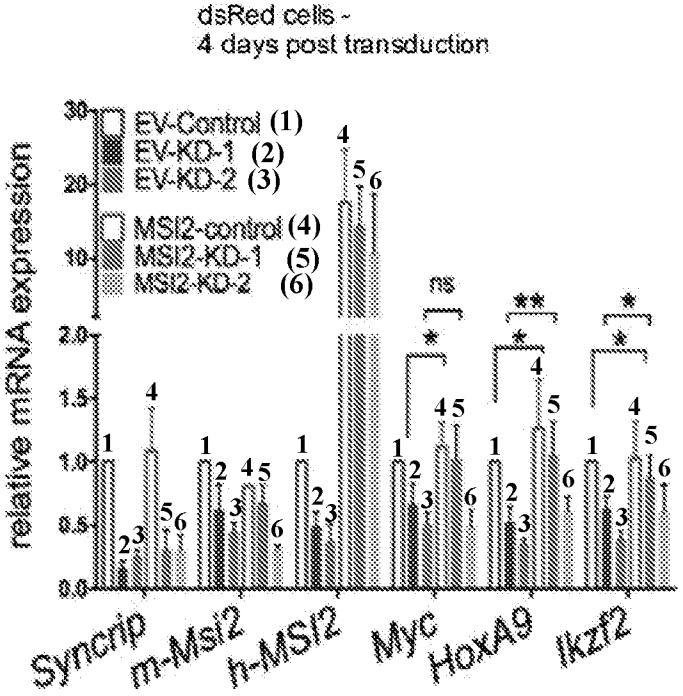


Figure 14(A)

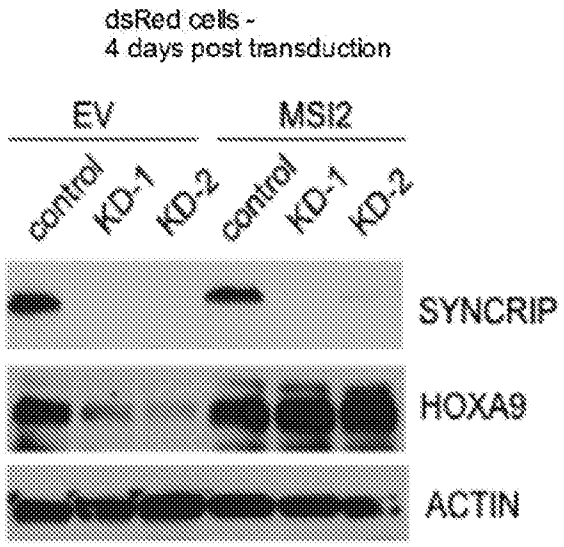


Figure 14(B)

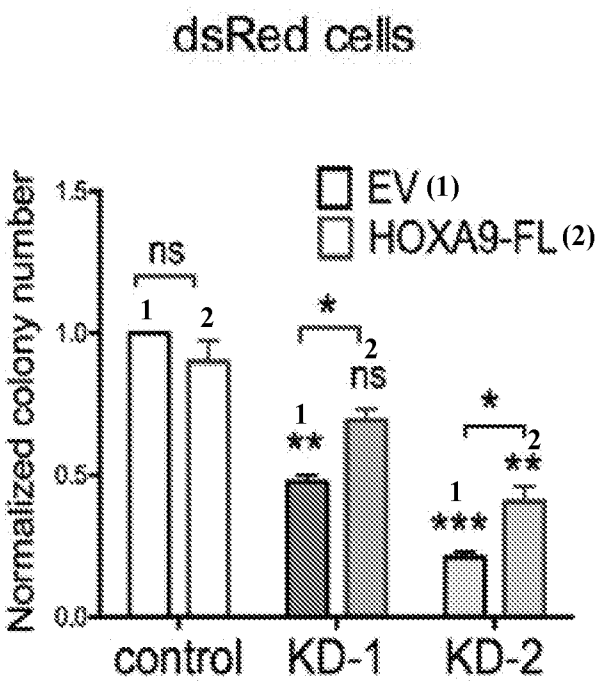


Figure 14(C)

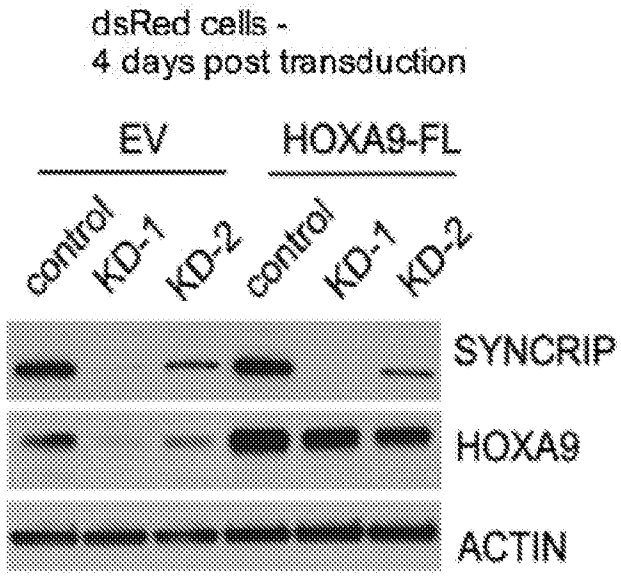


Figure 14(D)

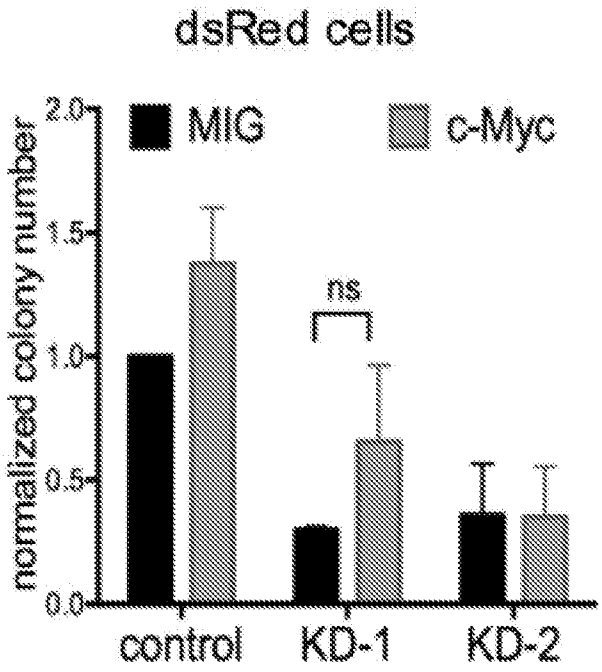


Figure 14(E)

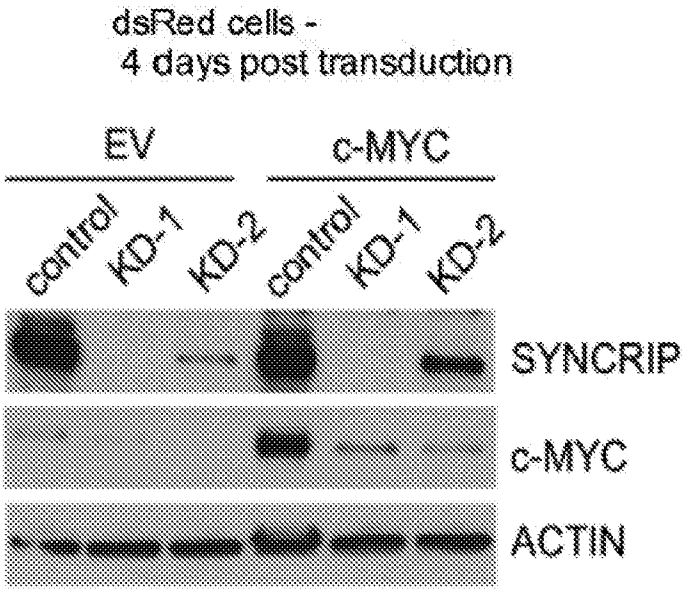


Figure 14(F)

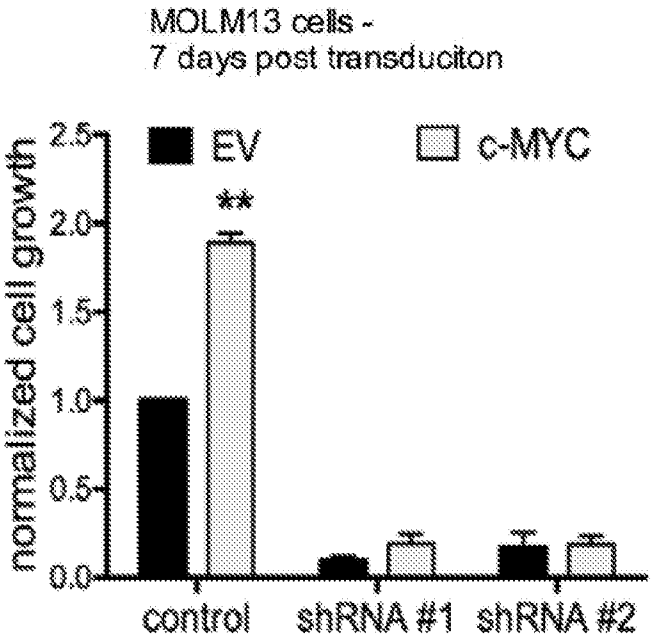


Figure 14(G)

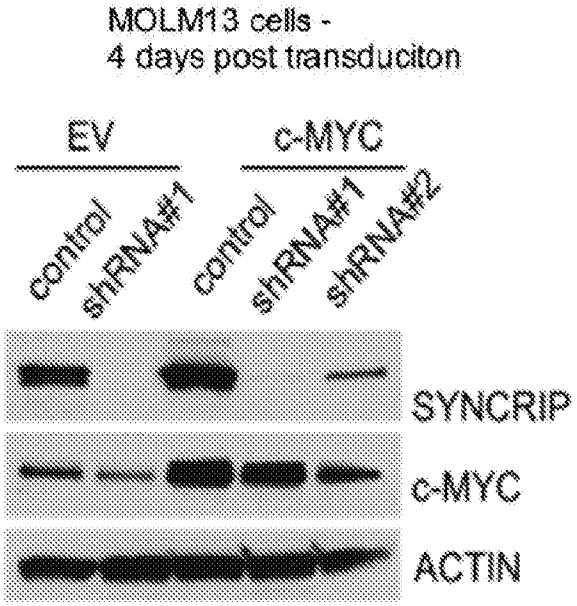


Figure 14(H)

Figure 15

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Upf1	846.1513	13176.4116	100.3417	1108.5996	2406.2984
Upf1	0.6657	0.9252	0.9122	64.3215	0.6821
Bnip3l	120.4583	76912.9716	218.357	21683.3832	186.2719
Bnip3l	149.3683	47031.1781	11406.3614	2273.1985	145307.197
Bnip3l	84230.8817	236.6392	138.1235	71162.0771	53.4752
Bnip3l	1.4455	62.6398	0.9141	0.8293	0.8913
Bnip3l	1.6061	391.4987	81.2491	36.8577	16.0426
Spcs1	1461.7888	1521.1152	7025.4269	6902.1075	85062.2821
Spcs1	0.865	0.9018	0.9956	0.8334	1.1102
Cdk6	404.9639	906.1425	22524.9518	452.0843	64.2147
Cdk6	41.0511	44.1531	0.921	15.1009	10.8532
Cdk6	203.0367	699.4256	635.5002	214.2445	2226.7142
Cdk6	0.9985	0.9031	0.921	0.8494	0.814
Cdk6	1034.0447	1.0035	273.2344	0.8494	103.1054
Mapk6	2309.5875	13.92	6334.3848	700.2962	0.8021
Mapk6	88.3361	0.783	9.1405	0.8293	0.8021
Atr	0.9611	36.0739	51649.222	1634.3198	148805.4266
Atr	0.865	49.1006	1.1062	860.217	5.551
Atr	0.865	0.9018	0.9956	3093.6331	66.6119
Atr	0.865	3598.3695	7.7433	0.926	2904.2787
Atr	0.865	9.0185	338.4948	2.7779	0.9992
Mylk	1535.442	0.783	0.9141	596.1732	6.2388
Mylk	4248.1634	204.4493	4.0625	0.8293	1.7825
Mylk	12707.5497	20.0099	17.2654	0.8293	7.13
Mylk	1.6061	15.6599	1.0156	836.6697	0.8021
Stk17b	20123.93	12827.4857	823.7966	931.539	509.1958
Stk17b	0.9985	0.9031	0.921	3805.4358	28.0374
Stk17b	924.2052	138.4802	6.1401	790.9115	0.814
Stk17b	6484.9692	308166.7222	35812.1253	345852.9528	233866.4966
Stk17b	0.9985	1.0035	0.921	0.8494	0.9044
Gpsm2	24.0917	112.2296	1.0156	47408.2128	16262.6914
Gpsm2	1.6061	0.783	1515.2962	1.8429	0.8021
Gpsm2	8586.269	4472.6556	19.2967	111.4945	1032.9621
Gpsm2	49.7894	254.0392	0.9141	2.7643	0.8021
Frmd6	25243.2455	2857.9408	1744.8249	18515.4641	201.4232
Frmd6	1027.911	28.7099	84846.429	1705.5899	1036.5271
Npepps	0.9985	4.0139	21.4903	1606.362	10.8532
Zcchc3	1.1095	0.9031	0.921	0.8494	0.9044
Rrm2	1.4455	0.783	0.9141	0.8293	195.1844
Rrm2	2908.6669	198.3594	1737.7156	70.0296	1174.6713
Mycn	17853.5291	381.9288	834.8347	316.0548	92550.3736
Mycn	79520.1583	1875.7139	22911.2374	6318.3307	1929.5625
Mycn	11380.9021	13678.9658	3644.0232	717.8036	935.8155
Mycn	1.6061	6.96	4631.2001	16839.3603	1697.8368
Cdkn1a	0.865	0.9018	0.9956	0.8334	0.9992
Cdkn1a	12338.2277	146584.2045	101.7697	6.4817	13.3224
Cdkn1a	0.865	0.9018	0.9956	0.8334	0.9992

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Rrm2	1.4455	9395.0997	0.9141	3505.167	4.4563
Rrm2	46.5772	58.2898	0.9141	26.7218	0.8021
Rrm2	1.4455	180.0894	1.0156	9842.848	0.8021
Rpl14	0.5408	1.0117	0.6237	0.6211	0.7143
Rpl14	0.5408	0.9105	0.6237	0.6211	0.7143
Rpl14	0.5408	72.8406	0.6237	0.6211	0.7143
Rpl14	0.5408	1.0117	0.693	16.5623	0.7143
Cdkn1a	0.865	270.5541	7.7433	0.8334	0.9992
Cdkn1a	0.9611	2467.0525	163.7165	0.926	1.1102
Hnrnpa1	1784.5641	100510.8957	636.1839	234432.6768	218054.1776
Ilf2	513.7381	0.9105	0.6237	0.6211	0.7143
Ilf3	144.97	36711.592	8285.7893	1360.5885	5327.9614
Ilf3	0.6657	0.9252	1.0136	381.3885	0.6821
Ilf3	14.7929	4.1118	37.5014	21.1883	0.7579
Ltb	9039.8325	679.3914	217.9199	0.926	4057.7747
Ltb	0.865	680.3934	1678.0936	120.3748	203.1663
Ltb	1489.6598	40119.164	4167.0262	32141.9312	10994.2936
Slc25a24	0.865	1012.0727	0.9956	6797.474	1784.0886
Slc25a24	0.865	17.0349	0.9956	5.5558	8.8816
Slc25a24	0.9611	4860.9552	13201.2982	23435.1272	46864.8001
Slc25a24	0.865	0.9018	0.9956	0.8334	0.9992
Slc25a24	13720.2476	209489.0335	14.3805	323.1601	6763.3279
Clcn3	0.865	1370.8074	2202.4288	0.8334	1942.847
Clcn3	0.9611	714.4632	346.2382	0.8334	0.9992
Csda	0.6657	1.028	38.515	509.2748	0.7579
Csda	42405.9396	461.5548	22568.767	2437.4057	4739.8394
Csda	656.0631	1497.74	912.197	0.6811	862.478
Csda	0.6657	0.9252	0.9122	0.6811	0.6821
Csda	1.4793	0.9252	1750.4047	236.0977	0.6821
Hnrnpa2b1	33570.9066	380.3458	245.2796	10.5941	42910.1735
Hnrnpa2b1	0.6657	321.752	0.9122	8716.6957	19.7051
Hnrnpa2b1	6189.3308	42.1464	132.7753	6501.0098	616.9218
Ssb	523.352	0.9105	0.6237	0.6211	0.7143
Ssb	1476.922	3.035	0.6237	155.9613	93.656
Ssb	407.3853	2.0233	13455.4973	1134.5153	1.5874
Msi2	0.7396	292.9691	145.9515	612.9459	297.8505
Msi2	1.4793	103.8241	291.903	267.1233	1473.3367
Msi2	1883.1305	547.9035	0.9122	58128.4568	13.642
RFP	0.9031	0.8847	0.8733	0.7628	0.9984
RFP	0.9031	0.8847	0.8733	0.7628	0.9984
RFP	0.9031	0.8847	0.8733	0.7628	0.9984
RFP	0.9031	0.8847	0.8733	0.7628	0.9984
RFP	0.9031	0.8847	0.8733	0.7628	0.9984
RFP	0.9031	0.8847	0.8733	0.7628	0.9984
lacZ	2004.9536	569.2191	1882.8936	44.0129	1.9216
lacZ	2004.9536	569.2191	1882.8936	44.0129	1.9216
lacZ	2004.9536	569.2191	1882.8936	44.0129	1.9216
lacZ	2004.9536	569.2191	1882.8936	44.0129	1.9216
lacZ	2004.9536	569.2191	1882.8936	44.0129	1.9216

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
lacZ	2004.9536	569.2191	1882.8936	44.0129	1.9216
lacZ	5163.4602	2999.7031	513.5229	949.1465	3058.8926
lacZ	5163.4602	2999.7031	513.5229	949.1465	3058.8926
lacZ	5163.4602	2999.7031	513.5229	949.1465	3058.8926
lacZ	5163.4602	2999.7031	513.5229	949.1465	3058.8926
lacZ	5163.4602	2999.7031	513.5229	949.1465	3058.8926
lacZ	5163.4602	2999.7031	513.5229	949.1465	3058.8926
LUCIFERASE	6149.914	749.7539	10.9873	343.6663	1.1509
LUCIFERASE	6149.914	749.7539	10.9873	343.6663	1.1509
LUCIFERASE	6149.914	749.7539	10.9873	343.6663	1.1509
LUCIFERASE	6149.914	749.7539	10.9873	343.6663	1.1509
LUCIFERASE	6149.914	749.7539	10.9873	343.6663	1.1509
LUCIFERASE	6149.914	749.7539	10.9873	343.6663	1.1509
LUCIFERASE	23013.5536	21168.921	373.2051	9377.7272	56693.9323
LUCIFERASE	23013.5536	21168.921	373.2051	9377.7272	56693.9323
LUCIFERASE	23013.5536	21168.921	373.2051	9377.7272	56693.9323
LUCIFERASE	23013.5536	21168.921	373.2051	9377.7272	56693.9323
LUCIFERASE	23013.5536	21168.921	373.2051	9377.7272	56693.9323
LUCIFERASE	23013.5536	21168.921	373.2051	9377.7272	56693.9323
LUCIFERASE	16987.9402	3632.376	31050.8723	8936.2058	7518.0908
LUCIFERASE	16987.9402	3632.376	31050.8723	8936.2058	7518.0908
LUCIFERASE	16987.9402	3632.376	31050.8723	8936.2058	7518.0908
LUCIFERASE	16987.9402	3632.376	31050.8723	8936.2058	7518.0908
LUCIFERASE	16987.9402	3632.376	31050.8723	8936.2058	7518.0908
LUCIFERASE	16987.9402	3632.376	31050.8723	8936.2058	7518.0908
LUCIFERASE	493.3644	2942.9214	67.5411	696.0734	2292.8136
LUCIFERASE	493.3644	2942.9214	67.5411	696.0734	2292.8136
LUCIFERASE	493.3644	2942.9214	67.5411	696.0734	2292.8136
LUCIFERASE	493.3644	2942.9214	67.5411	696.0734	2292.8136
LUCIFERASE	493.3644	2942.9214	67.5411	696.0734	2292.8136
LUCIFERASE	493.3644	2942.9214	67.5411	696.0734	2292.8136
LUCIFERASE	27109.0901	4769.9831	7796.2666	57389.3186	55493.3215
LUCIFERASE	27109.0901	4769.9831	7796.2666	57389.3186	55493.3215
LUCIFERASE	27109.0901	4769.9831	7796.2666	57389.3186	55493.3215
LUCIFERASE	27109.0901	4769.9831	7796.2666	57389.3186	55493.3215
LUCIFERASE	27109.0901	4769.9831	7796.2666	57389.3186	55493.3215
LUCIFERASE	27109.0901	4769.9831	7796.2666	57389.3186	55493.3215
Zyx	7.2104	0.9105	0.6237	4.8307	8032.1923
Zyx	105.7519	8.0934	1838.5576	63335.4887	119.8479
Zyx	97.9407	35.4086	0.6237	4063.9662	38.0974
Atp5a1	516.2707	0.9252	8.1084	3.7836	48.5049
Atp5a1	0.7396	225.1236	23.3117	56.7542	1.5158
Atp5a1	0.6657	0.9252	31.4201	401.0633	138.6937
Atp5a1	0.6657	17.4753	0.9122	0.6811	0.6821
Acox1	1875.9376	43691.2589	78.2023	518.7721	1415.3096
Acox1	342.1016	0.783	33989.5554	0.8293	4.4563
Acox1	9.6367	14.79	9.1405	125.3162	8.0213
Acox1	1.6061	50871.3457	6267.3543	2.7643	2403.709
Acox1	1376.4371	9381.1797	127.9674	1407.964	6310.0704

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Ybx1	75.7088	12.1401	0.6237	701.136	0.7143
Ybx1	28167.8716	6149.9707	81349.7632	2070.2834	77.7821
Peli1	0.9985	0.9031	0.921	0.8494	0.814
Dyrk2	0.9985	0.9031	0.921	0.8494	0.814
Dyrk2	616.8765	0.9031	20.467	11.3257	0.9044
Dyrk2	0.9985	0.9031	0.921	0.8494	0.814
Dyrk2	0.9985	0.9031	0.921	0.8494	0.814
Dyrk2	0.9985	0.9031	185.2263	12.2695	42.5084
Slc19a2	27.8711	50.1026	9.9557	10.1856	0.9992
Slc19a2	1441.6063	4646.5161	0.9956	0.8334	114.3504
Slc19a2	0.9611	0.9018	0.9956	0.8334	1.1102
Slc40a1	1.6061	249.6892	0.9141	1653.9892	0.8021
Ppp2r5c	0.9985	714.4778	61.401	0.8494	0.9044
Ppp2r5c	23891.7582	40496.4417	433.9003	317.1196	2103.7113
Ppp2r5c	1006.3075	11.0383	223512.8937	253.8845	215.2551
Ppp2r5c	22.1898	53.1844	4.0934	0.8494	188.1221
Mtmr9	1.1095	1268.3988	38.8873	569.1165	42754.3605
E2f7	14.4234	80.2784	383.7562	0.8494	9897.2112
E2f7	17.7518	0.9031	10.2335	0.8494	1709.3785
E2f7	79.8833	0.9031	382.7328	48.1342	18.9931
E2f7	130.9198	8123.1712	796.1661	25437.526	2760.3298
E2f7	0.9985	308.0684	17.3969	0.9438	0.814
Dst	65.4599	0.9031	66.5177	271.8168	3505.5826
Dst	3381.7256	1.0035	2433.5258	19590.6325	20113.6872
Krt6b	3444.7494	0.9105	0.6237	0.6211	0.7143
Krt6b	1047.3048	0.9105	0.6237	26.9137	0.7143
Krt6b	11.4164	2.0233	0.6237	5.5208	0.7937
Krt6b	35.4509	132.5294	0.6237	383.0024	0.7143
Krt6b	285.4101	228.6385	0.693	12365.8025	472.2485
Anln	17800.5274	339.2989	10.1561	472.7	18.7163
Anln	11279.7171	3411.259	1710.2941	9664.0882	73580.0559
Anln	75.4872	5413.1225	1.0156	1688.0825	21053.1757
Tubb2c	0.5408	0.9105	0.6237	104.8944	11.9054
Tubb2c	0.5408	1936.3454	0.693	2685.1575	61.9082
Tubb2c	0.6009	224.5918	0.693	15.8722	373.8303
Tubb2c	0.5408	0.9105	0.6237	27.6038	0.7143
Tubb2c	0.5408	0.9105	0.6237	0.6211	0.7143
Tjp1	0.865	39.08	65.2653	234.2679	979.1949
Tjp1	0.865	1.0021	0.9956	0.8334	12.2122
Tjp1	0.9611	20.041	0.9956	0.8334	0.9992
Eps8	1.4455	0.783	0.9141	0.8293	0.8913
Mybbp1a	17181.0638	0.9018	402.654	0.926	0.9992
Mybbp1a	0.865	0.9018	0.9956	0.8334	153.2074
Mybbp1a	0.865	0.9018	0.9956	6817.8451	22.204
Igf2bp3	0.865	0.9018	0.9956	0.8334	0.9992
Igf2bp3	0.865	0.9018	0.9956	0.8334	0.9992
Igf2bp3	0.865	1208.475	2642.6933	23.149	0.9992
Igf2bp3	0.9611	1524.1214	542.0342	1.8519	8960.4103
Igf2bp3	0.865	13.0267	721.2373	94.4479	13067.0338

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Mov10	16331.3126	0.9252	126309.8895	158366.2949	178.8619
Mov10	1125.7363	0.9252	138.8567	2.2702	3196.019
Mov10	0.6657	0.9252	0.9122	0.6811	0.6821
Ube2k	1.4455	0.783	0.9141	114.2589	0.8021
Ube2k	94.7605	0.87	2525.8321	15404.6745	2607.8059
Ablim1	1988.3653	999.6268	26.406	387.0058	4184.4323
Ablim1	53.0017	66560.875	2003.8065	151.1166	191.6194
Ablim1	64.2444	7008.6974	10329.8105	11.0573	163.9905
Ablim1	5202.1933	1142.3063	40571.7501	1104.8095	8427.6873
Ablim1	9949.8572	325.3789	11.1718	1280.805	587.3357
Mrpl22	0.6009	1.0117	586.9801	0.6211	0.7143
Mrpl22	2949.0372	4932.926	5.5441	4443.5182	16.6676
Atp10d	464.1972	0.9018	23332.913	51.8538	0.9992
Atp10d	0.865	453.9296	19.9115	7432.6827	10716.744
Atp10d	86254.1879	8691.8008	71774.1775	21035.0383	19539.4898
Atp10d	0.865	961.9701	4361.716	4170.5248	0.9992
Atp10d	0.865	23.0472	21780.9253	108151.2278	3378.3334
Caprin1	33335.7002	25.699	439.8817	354.9032	462.3124
Caprin1	0.7396	0.9252	1.0136	8882.4181	29.5577
Caprin1	0.6657	0.9252	0.9122	0.6811	0.6821
Stau1	0.6657	1497.74	35.4743	0.7567	15.9157
Stau1	6798.0568	402.9609	29.393	103.6711	0.6821
Stau2	828.3999	1.028	1849.7328	2801.3896	39535.2926
Stau2	188833.0212	22.6152	1.0136	3368.1754	0.7579
Stau2	1653.1016	0.9252	6299.227	416.9545	2744.317
Prpf19	0.6657	391.6534	1.0136	20.4315	18.1893
Prpf19	0.6657	2.0559	0.9122	4575.1491	13.642
Prpf19	0.7396	1.028	1.0136	0.7567	0.7579
Prpf19	0.7396	0.9252	0.9122	0.6811	0.7579
Prpf19	102.0707	0.9252	7.0949	10.5941	0.7579
Pura	14969.3079	26.3035	1486.5081	0.6211	0.7143
Pura	54.6786	1.0117	977.1452	621.7751	0.7143
Pura	0.5408	39.4553	2.772	4.1406	0.7937
Pura	97131.3583	502444.2061	502.4328	320.2038	196.0426
Pura	649.5332	22414.6652	443.5269	6824.344	49.2091
Hnrnpab	1105.2315	0.9018	0.9956	0.8334	0.9992
Hnrnpab	0.865	0.9018	0.9956	0.8334	7.7714
Hnrnpab	0.865	1.0021	0.9956	0.8334	0.9992
Hnrnpab	0.865	0.9018	0.9956	0.8334	333.0595
Hnrnpab	1.9221	0.9018	0.9956	0.8334	18943.3133
Ddx56	0.6657	41.1185	0.9122	0.6811	0.6821
Ddx21	213.0171	1.028	112548.8912	21.1883	0.6821
Ddx21	0.6657	0.9252	35.4743	0.7567	0.6821
Ddx21	245.5614	1034.1294	1776.757	9.0807	0.6821
Rbmx	24.6354	0.9105	81.0823	4.8307	4328.8119
Rbmx	2038.1284	31.3619	28.4134	136273.6418	749.248
Rbmx	21.0302	0.9105	180.1828	13.1118	61.1145
Rbmx	0.5408	2.0233	1.386	676.9827	0.7143
Rbmx	95.5373	929.7291	0.6237	10740.6301	688.1335

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Rps24	147.8124	304.5141	2.079	41517.4625	21758.3517
Rps24	0.6009	0.9105	0.6237	0.6901	0.7143
Rps24	0.5408	1.0117	0.6237	0.6211	0.7937
Rpl24	0.6657	0.9252	0.9122	1.5134	0.6821
Rpl24	0.7396	1.028	7919.8969	2.2702	0.6821
Rpl24	0.6657	1.028	0.9122	0.6811	0.6821
Rpl24	0.6657	0.9252	0.9122	0.6811	0.6821
Rpl24	0.6657	0.9252	1.0136	0.6811	0.6821
Mrpl4	0.865	0.9018	0.9956	393.5331	51.0691
Mrpl4	0.865	449.9214	0.9956	0.8334	0.9992
Mrpl4	861.1195	24.0493	0.9956	12.0375	11633.7678
Rpl26	0.5408	0.9105	0.6237	0.6211	0.7143
Rpl26	0.5408	2.0233	0.6237	0.6211	1134.9837
Rpl26	0.5408	0.9105	0.6237	0.6211	0.7937
Rpl26	0.5408	0.9105	0.6237	0.6211	0.7143
Rpl26	19.2276	55690.6703	54.7479	0.6901	9.5243
Rps11	0.865	0.9018	0.9956	0.8334	0.9992
Mrpl39	1.2017	322.7242	0.6237	162.8623	59.5271
Mrpl39	0.6009	0.9105	0.6237	0.6211	7.9369
Mrpl39	240483.5267	200.3116	39.5016	15.8722	48.4154
Mrpl39	329.874	835.6433	2365.2458	19989.2759	38137.8331
Rpl4	0.6009	0.9105	0.693	0.6211	0.7143
Rpl4	0.5408	0.9105	0.693	0.6211	0.7143
Rpl4	0.5408	0.9105	1.386	0.6211	0.7143
Rpl4	0.5408	1.0117	0.6237	0.6211	0.7143
Rpl4	0.5408	0.9105	0.6237	0.6211	0.7143
Mrps9	476.33	2196.7539	99338.2518	1282.646	30223.8653
Mrps9	1379.4338	791.5304	501.7083	1334.1032	3968.3081
Rpl18	242.6028	13.3635	6351.9317	11.3508	0.6821
Rpl18	0.6657	1.028	0.9122	0.6811	0.7579
Rpl18	0.6657	0.9252	0.9122	0.6811	29.5577
Rpl18	0.6657	0.9252	0.9122	0.6811	3226.3345
Numb	65404.0493	4226.4463	108.6707	0.9214	262.9196
Numb	72.275	8.7	0.9141	387.0058	298.5697
Numb	1.6061	64.3798	0.9141	0.8293	0.8021
Snx14	1.1095	731.537	1602.5657	249.1654	101.2965
Snx14	0.9985	0.9031	0.921	11.3257	47.0305
Snx14	38.8322	145.5046	14.3269	66.0666	1931.8691
Snx14	0.9985	0.9031	412.41	6.6067	15.3754
Numbl	6905.2942	17202.2302	13283.1565	16005.2224	2844.328
Smc4	0.9985	30.1044	2449.8994	17.9324	927.0439
Smc4	138969.1728	363334.0425	43102.469	793.7429	5337.964
Ptbp1	5724.8351	1649.8783	4062.3172	8035.6447	517.6384
Ptbp1	37.7218	52.426	24.3253	0.6811	253.135
Crot	4.8183	20.0099	2.0312	0.8293	838.669
Crot	14.455	26.0999	2354.1934	3.6858	0.8913
Abcc5	63706.3901	47660.1861	269.1377	5391.3596	6842.1484
Abcc5	25429.5544	852.5972	52188.3436	1771.0123	687.156
Abcc5	1.4455	5.22	126.9518	19862.6129	141.7092

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Pdia6	94.9364	105218.2182	428.2807	89.7123	34.9226
Pdia6	116491.7754	1245.3716	2791.4474	10289.3083	73137.3965
Pdia6	0.5408	51255.4883	410.2624	89.7123	4558.9834
Pdia6	0.6009	0.9105	0.6237	0.6211	0.7937
Hnrnpl	35.5596	89.1826	5.531	298801.8075	3497.1246
Syncrip	6.6095	0.9105	3217.649	4.1406	0.7143
Syncrip	0.5408	0.9105	0.6237	0.6211	0.7143
Hnrnpc	1425.2478	1992.9992	0.693	193.9165	483.3602
Hnrnpc	0.5408	149.7279	177.4108	364.3699	0.7143
Hnrnpc	0.6009	0.9105	0.6237	129.7378	0.7937
Hnrnpc	58.8846	51.5954	0.6237	140.0892	0.7143
Hnrnpr	0.865	0.9018	0.9956	99.0777	281.9904
Hnrnpr	0.865	0.9018	0.9956	89.8181	0.9992
Hnrnpa3	7992.6839	32.3736	0.6237	0.6901	0.7937
Hnrnpa3	14.4207	217.5101	0.6237	0.6211	20.6361
Hnrnpa3	3231.4429	3.035	6.9301	24.1533	0.7143
Hnrnpa3	0.5408	21.2452	0.6237	35.1948	0.7143
Hnrnpa3	1530.9997	0.9105	0.6237	0.6211	9.5243
Asph	1.4455	111.3596	0.9141	2.7643	0.8021
Asph	611.9283	0.783	0.9141	0.8293	0.8021
Kif21a	893.1395	0.9031	0.921	1.8876	4.5222
Kif21a	2.219	0.9031	1.0233	993.8303	0.814
Cltc	0.9985	2.007	6.1401	544.5775	1.8089
Ap3s1	7006.2066	911.8675	0.9956	272.2323	583.9643
Ap3s1	0.865	1705.4928	4.4248	0.8334	81.0445
Crbn	3461.1691	6344.0195	94.4521	9715.6889	60.6052
Crbn	1.4455	0.783	0.9141	0.8293	3.565
Crbn	1084.1249	802.1374	1734.6688	214.6961	57.9314
Abca1	28867.8209	950.2956	17.3969	1277.9167	5519.7551
Abca1	1471.1838	9.0313	129.9654	1.8876	12.6621
Mrpl38	1279.1853	13137.9064	2225.6588	10029.0752	2950.907
Mrpl38	4616.9844	2335.7837	0.9956	226.8603	48002.7533
Mrpl38	0.865	10.0205	0.9956	0.8334	0.9992
Cct3	0.7396	0.9252	0.9122	0.6811	0.6821
Cct3	1974.8462	2401.3183	202.7104	511.5449	30882.4711
Cct3	0.6657	0.9252	653.7412	0.7567	0.6821
Sepp1	8371.1022	7.0244	0.921	6.6067	3219.7818
Sepp1	210.8031	69493.0017	530.0952	51951.9375	774.1947
Sepp1	13914.1144	40.1392	5175.0798	47405.6121	151.0403
Sepp1	55.4745	1.0035	3219.4584	0.8494	165.5113
Tmem50b	0.9985	2.007	101.3116	5.6629	0.9044
Tmem50b	280.701	0.9031	140.1989	0.8494	0.814
Aqp11	146030.8181	450.6585	159.4514	15589.8844	75195.0061
Mrpl37	0.7396	89.4327	165.209	490.3567	4.5473
Lst1	4531.1573	0.9031	0.921	22.6514	186.3132
Lst1	24.4088	27.094	21.4903	18.8762	87.73
Aqp11	1318.6171	21.7499	183.8261	23.0361	43.6714
Mrpl37	81.3607	0.9252	0.9122	55.2408	0.6821
Fastkd2	0.865	35.0718	178.097	13210.6745	43.2977

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Fastkd2	0.865	13.0267	124378.0434	366.6802	345.2717
Fastkd2	0.865	0.9018	0.9956	0.8334	0.9992
Cyb5	1.4455	165.2995	0.9141	281.0399	0.8021
Mrpl37	0.7396	78.1251	1.0136	32340.0836	139.4516
Cyb5	73903.5884	14347.1237	2770.5951	283.8043	74.8652
Ptcd3	15.0216	3401.2504	384065.1874	167.693	8884.6206
Ptcd3	84.7217	0.9105	10033.41	13941.2881	0.7143
Snx16	3.2122	3.48	2.0312	217776.4673	123.8842
Snx16	19.2733	31444.3084	10.1561	0.8293	137.2529
Tax1bp1	1.4455	0.783	0.9141	0.8293	0.8021
Tax1bp1	1.4455	0.783	43.6714	1705.5899	0.8913
Tax1bp1	16.0611	809.0974	222.4195	4607.2121	84.669
Mrps27	0.5408	10.1167	0.6237	4828.5909	60.3208
Snx16	1.4455	58.2898	0.9141	2.7643	0.8021
Mrps27	101.5459	9699.9373	67568.5509	353.3284	20.6361
Mrps27	0.5408	0.9105	0.6237	0.6211	188.8994
Rabep1	163.095	0.9031	0.921	8.4943	35.2729
Mrps28	85.0589	2.0559	116756.1464	1136.5984	39511.0402
Fcho2	0.865	0.9018	1695.7927	2.7779	0.9992
Baz2b	1.1095	102622.8962	157.5959	59049.3772	134.7605
Fcho2	1428.1513	598.2252	528.7599	15182.9697	3952.3059
Fcho2	0.865	338.6936	32.0796	429.6455	2001.6875
Rabep1	369.4602	6.0209	60685.6648	13407.7432	330932.9679
Paip1	2538.1882	54962.5633	18785.3567	1013.0005	14861.1142
Ttc3	781.081	36.1253	753.1854	46.2466	2753.9987
Mrps28	250.7389	6.1678	14.1897	504.7344	21.2209
Fcho2	0.865	0.9018	0.9956	0.8334	0.9992
Baz2b	45851.8942	60.2088	43058.465	18.8762	17161.6177
Fcho2	48775.3074	72469.4174	90.7078	176.8584	17480.0719
Baz2b	4756.3837	1144.9708	45311.8812	9061.5052	35281.03
Ict1	183692.5039	71868.9061	218579.6282	169138.2511	123635.9888
Ict1	727.0689	0.9252	0.9122	0.6811	0.6821
Sertad2	5037.9335	79.1621	1.1062	0.8334	0.9992
Ict1	72.485	10126.4496	39.5285	14598.7059	29.5577
Fastkd2	0.865	79.1621	613.9367	154.6354	54.3997
Mrpl37	0.6657	2.0559	51.6912	241.3947	13.642
Ptcd3	0.5408	27.3152	8.3161	86.2618	0.7143
Aqp11	3170.463	16241.1075	13812.3511	7421.2973	434.9314
Aqp11	70.6689	0.783	353.4337	5.5287	48.1277
Mrps27	0.5408	0.9105	0.6237	0.6211	0.7143
Mrps27	69.7001	64.7472	17.3253	17.9425	184.9309
Tax1bp1	112.4278	956.1269	10167.3123	7612.9573	36.5414
Ttc3	58.803	19.0661	1.0233	1.8876	126.6206
Paip1	20177.6828	35152.9933	38162.5262	7134.5235	63564.4026
Baz2b	1264.8186	2.007	2.0467	64.179	33.464
Mrps28	20780.264	133.635	531.1014	122382.5887	1211.107
Mrpl37	75648.4448	8196.9657	37522.7162	67727.4918	105123.0282
Cyb5	1.4455	25.2299	0.9141	0.8293	0.8021
Sertad2	25594.2782	39466.8281	16.5929	1008.3707	567.3113

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Sertad2	0.865	0.9018	8.8495	0.8334	11.102
Tax1bp1	1068.0638	4318.6661	11.1718	104.123	1028.5058
Ybx1	1.2017	2.0233	10.3952	2.7604	13285.6587
Trip11	28.8467	0.9031	0.921	209.5255	0.814
Trip11	93.1972	0.9031	0.921	25009.9808	53.3616
Trip11	24520.839	119.4141	0.921	0.8494	117.5763
Trip11	0.9985	61.2123	612.9865	0.8494	0.814
Trip11	158.6571	1.0035	107.4517	619.1384	132.0472
Sertad2	794.8056	0.9018	0.9956	93.522	0.9992
Sertad2	0.865	1265.5919	6662.5959	1483.3883	2523.4807
Mybbp1a	0.865	0.9018	0.9956	0.8334	1.1102
Mybbp1a	0.9611	0.9018	0.9956	0.8334	0.9992
Mybbp1a	0.865	0.9018	0.9956	0.8334	8.8816
Gpr65	1.4455	0.783	0.9141	66.3439	5.3475
Gpr65	1.4455	0.783	425.5423	0.8293	1.7825
Gpr65	6355.381	8259.7533	42.6558	15727.1793	230.8345
Gpr65	6601.1159	8303.2532	62.9681	13809.6576	31.1939
Gpr65	72997.7418	85.2597	6629.9285	48.8364	0.8913
Mll3	0.9985	0.9031	0.921	0.8494	0.814
Mll3	34.3942	0.9031	0.921	0.8494	0.814
Mll3	0.9985	0.9031	480.9744	0.8494	2.7133
Mll3	0.9985	0.9031	0.921	0.8494	0.814
Mll3	0.9985	0.9031	0.921	0.8494	0.814
Cenpf	12.8489	221.8493	12802.8307	16.586	4480.3283
Cenpf	3734.2079	817.7974	4.0625	33.1719	5.3475
Cenpf	1.6061	0.783	0.9141	0.8293	0.8021
Cenpf	101.185	2434.2521	4.0625	382.3986	2.6738
Cenpf	1.6061	21.7499	558.5877	0.8293	1.7825
Mns1	0.865	0.9018	0.9956	0.8334	0.9992
Mns1	0.865	42.0862	47.5663	187.044	198.7255
Mns1	0.865	0.9018	0.9956	666.6914	0.9992
Mrps22	26641.6788	23242.2152	22749.4648	89169.1746	1320.7083
Mrps22	0.5408	20.2335	155.2344	0.6901	0.7143
Mrps22	11412.7979	111.2842	100528.1435	4102.6115	296.0482
Mrps22	0.5408	0.9105	0.6237	0.6211	0.7143
Mrps22	0.5408	0.9105	0.6237	0.6211	56.3523
Mrps23	27740.3025	356.7027	4985.6633	6.0538	0.6821
Mrps23	3170.109	0.9252	0.9122	0.6811	0.6821
Mrps23	0.6657	0.9252	0.9122	0.6811	0.7579
Mrps23	0.6657	1071.136	334.4722	4259.5954	0.6821
Mrps23	0.6657	3509.4608	0.9122	0.6811	0.6821
Cep70	530.0166	63.5098	1503.1088	53697.0574	37.4326
Cep70	1.4455	0.783	10.1561	891.9563	44.5626
Cep70	72.275	46.1099	223.4351	406.3561	263.8109
Cep70	1.4455	11.31	19324.0885	372.2627	0.8021
Cep70	443.2866	1206.6861	1001.3955	0.8293	21.3901
Rwdd4a	1821.3298	2751.8011	75.1554	849.5699	476.8203
Rwdd4a	9390.9306	11.31	0.9141	269.0612	6.2388
Rwdd4a	518.7738	109676.1957	85.3116	2439.0581	25374.861

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Rwdd4a	21467.2787	10420.8263	2021.072	2279.6486	5032.0138
Rwdd4a	2846.0286	0.87	4734.7927	3428.6873	0.8021
Bex1	1.4455	0.783	3918.239	3.6858	0.8021
Bex1	29223.1884	1820.0341	17.2654	4040.525	1376.0945
Mrpl44	15.6224	1.0117	100757.5301	1794.2456	446.0565
Mrpl44	828.5905	203.3466	0.6237	42.0958	0.7143
Mrpl44	0.5408	119.3776	0.6237	24.1533	0.7143
Mrpl44	0.5408	0.9105	0.6237	0.6211	0.7143
Mrpl44	1051.5108	2668.7979	15763.2232	10042.9446	13.4928
Lst1	346920.8878	707.4534	2479.5765	11746.6403	2801.0292
Lst1	1.1095	0.9031	61.401	0.8494	0.814
Lst1	0.9985	0.9031	3875.4256	324.6701	6.331
Tnrc6a	0.9985	2.007	1.0233	0.9438	0.9044
Tnrc6a	3624.7039	61980.9499	70998.9838	32465.1239	2096.4759
Tnrc6a	55.4745	0.9031	0.921	0.8494	66.0236
Tnrc6a	0.9985	4.0139	1.0233	0.8494	1.8089
Iqgap2	0.9985	6.0209	1508.4176	13.2133	3.6177
Iqgap2	7.7664	12.0418	3.07	0.8494	0.814
Iqgap2	928.6431	0.9031	14.3269	2.8314	403.3772
Iqgap2	365.0222	5.0174	0.921	0.8494	0.814
Iqgap2	0.9985	36.1253	12.2802	0.8494	1466.086
Mns1	0.865	1.0021	0.9956	1383.3846	1990.5855
Mns1	39.4039	4061.3176	344560.0784	4240.8978	18417.0793
Bex1	1.4455	0.783	0.9141	0.9214	1.7825
Bex1	1.4455	0.783	2.0312	0.8293	0.8021
Bex1	1.4455	14.79	0.9141	102.2801	0.8021
Asph	9707.3345	55.6798	1251.2365	2.7643	122.9929
Asph	70.6689	118.3196	16.2498	35.0148	0.8021
Asph	70.6689	0.783	0.9141	11.0573	41.8889
Tnrc6a	717.84	331.1484	86.9847	3.7752	8.1399
Abca1	84432.1907	17.0592	401.1531	16.9886	538.1377
Abca1	0.9985	11.0383	0.921	1123.1321	9.9488
Abca1	0.9985	0.9031	0.921	31.1457	33058.8379
Upf1	0.6657	0.9252	1.0136	0.6811	0.6821
Upf1	2562.1226	1993.2175	13581.5996	0.6811	7338.6416
Upf1	0.6657	0.9252	281.7675	0.6811	6.0631
Upf1	0.6657	0.9252	57.7725	99.8875	1687.0615
Snx16	81.9117	0.783	0.9141	2.7643	1516.0212
Snx16	12.8489	0.783	0.9141	0.8293	0.8021
Paip1	4320.0135	0.9018	69167.9886	2867.6988	3.3306
Paip1	1.9221	898.8408	36661.4233	26.8528	19437.3515
Paip1	1.9221	9870.2142	1710.1732	49.0759	11093.1012
Spcs1	0.9611	0.9018	3482.2932	334.2716	44.4079
Spcs1	41.326	1.0021	6.6372	0.8334	39.9671
Ptbp1	273.6678	0.9252	4305.5698	50.7005	18.9472
Ptbp1	30013.2248	146.9985	9501.0384	10221.0616	418.3549
Hnrnpl	0.865	0.9018	0.9956	0.8334	44.4079
Hnrnpl	46608.0926	24.0493	0.9956	0.8334	1.1102
Hnrnpl	64314.8622	326.669	2.2124	2.7779	12.2122

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Ddx56	0.7396	0.9252	1266.9403	314.7969	120282.3289
Ddx56	20475.5311	5049.3473	61.8267	9167.7027	914.7723
Rps24	0.6009	0.9105	0.6237	0.6211	0.7143
Rps11	0.865	0.9018	0.9956	0.8334	0.9992
Rps11	0.865	0.9018	0.9956	0.926	0.9992
Rps11	0.865	0.9018	0.9956	0.8334	0.9992
Cyb5	1288.101	9641.3089	42.6558	0.9214	2630.0873
Gpsm2	4400.744	36.5399	0.9141	0.8293	3099.7775
Cyb5	379.0422	43237.9903	32.4996	363.9698	3.565
Ptbp1	360.206	784303.849	187.5072	289.0683	124.2938
Hnrnpl	0.865	0.9018	3882.7348	1.8519	317.5167
Hnrnpl	0.865	0.9018	0.9956	0.8334	5.551
Ptbp1	122.7807	0.9252	260.4829	612.9459	25.7682
Rps24	24.6354	19.2218	15398.6995	359.5392	0.7143
Rps24	0.5408	24.2802	0.6237	1837.0314	10738.6918
Rps11	0.865	1.0021	14.3805	0.8334	0.9992
Rps11	0.865	4275.7567	12.1681	29.6307	0.9992
Spcs1	0.865	0.9018	115.044	197.2295	76.6037
Ilf2	1606.7085	5124.1325	2.079	3.4505	244134.1979
Ilf2	4.8069	96.1091	0.6237	11.7316	0.7143
Ssb	1.8026	0.9105	0.6237	0.6211	0.7143
Ssb	0.5408	0.9105	0.6237	8.2811	0.7143
Tjp1	0.865	55.1129	0.9956	0.8334	0.9992
Tjp1	0.9611	354.7265	61.9468	371.31	1.1102
Mrps9	0.6657	0.9252	0.9122	31.0257	0.7579
Mrps9	2699.6962	0.9252	31.4201	638.6745	0.7579
Mrps9	0.6657	0.9252	3485.606	499.4374	130.357
Hnrnpa2b1	992.6006	187.089	1173.6935	2306.4926	0.7579
Hnrnpa2b1	136.0943	386.5136	0.9122	0.6811	31.8313
Ilf3	117.6032	70.9293	121.6263	3921.3401	210.6932
Ilf2	0.6009	1210.9746	483.0285	76.6005	0.7143
Ilf2	0.5408	0.9105	0.6237	0.6901	0.7143
Ilf2	0.5408	0.9105	0.6237	0.6901	0.7143
Kif21a	7.7664	42.1462	0.921	4897.4222	8.1399
Mrpl22	10.8155	0.9105	0.693	0.6211	0.7937
Abcc5	1.4455	2043.6234	132902.239	476.3857	2649.6948
Abcc5	6175.4965	20.0099	4.0625	2094.4386	0.8021
Ddx56	0.6657	1.028	0.9122	0.6811	236.4614
Ddx56	0.6657	13.3635	1.0136	0.6811	114.4413
Ddx56	0.6657	0.9252	0.9122	0.6811	0.6821
Kif21a	4744.1793	2673.2709	526.0018	475.6795	3973.1745
Stau2	0.6657	2.0559	204.7375	0.6811	264.5033
Stau2	0.6657	189.1449	0.9122	0.6811	0.6821
Syncrip	209335.9739	256.9654	63.064	6.9009	3.1748
Syncrip	20030.3796	2050.6647	0.6237	86.2618	0.7143
Syncrip	0.5408	40.467	0.6237	26.2236	0.7143
Hnrnpr	0.9611	133.2729	0.9956	8759.5837	66.6119
Hnrnpr	0.865	2117.3363	1.1062	0.8334	9878.5443
Hnrnpr	0.865	0.9018	86.283	236.1199	0.9992

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Cltc	0.9985	0.9031	8.1868	7.5505	0.814
Ap3s1	0.865	0.9018	0.9956	0.8334	0.9992
Ap3s1	1.9221	647.3257	1327.4307	602.8001	131920.421
Ap3s1	583688.1287	1496.0639	1837.3853	467.6099	25.5346
Anln	1.4455	1.74	0.9141	52.5222	0.8021
Ube2k	1443.8937	21.7499	0.9141	7357.7178	0.8021
Peli1	4.438	367.2737	1.0233	18.8762	27.133
Peli1	0.9985	0.9031	0.921	7.5505	0.814
Mrpl11	0.6657	14.3915	8.1084	289.0683	23.4946
Mrpl11	0.6657	0.9252	0.9122	0.6811	483.5333
Mrpl11	1568.7823	0.9252	0.9122	7.5672	0.6821
Peli1	16.6424	241.8387	1655.7799	2475.6096	14.4709
Peli1	60975.3527	5.0174	826.8666	131.1894	2280.9802
Caprin1	22.1893	0.9252	0.9122	132.4266	43.1997
Caprin1	53.2543	81.209	0.9122	1.5134	43.1997
Npepps	4937.2306	4.0139	2.0467	1.8876	8133.5667
Hnrnpa1	0.5408	1.0117	0.6237	0.6211	0.7143
Npepps	0.9985	0.9031	0.921	0.8494	2.7133
Npepps	0.9985	15.0522	14.3269	2.8314	3047.035
Npepps	813.2562	2036.0611	1545.2582	9305.0078	0.814
Hnrnpa1	48.6699	273.1522	0.6237	0.6211	0.7143
Hnrnpa1	2.4035	0.9105	49.8968	0.6211	0.7143
Hnrnpa1	0.5408	0.9105	0.6237	0.6211	0.7143
Ddx21	0.6657	1019.7379	12.1626	0.6811	0.6821
Ddx21	0.6657	0.9252	0.9122	0.6811	1630.2198
Stau1	26474.0341	142.8867	900.0344	1311.4015	0.6821
Stau1	0.6657	16.4474	0.9122	3.0269	1808.3237
Stau1	0.6657	0.9252	0.9122	0.6811	0.6821
Zyx	88.9278	1305.0604	0.6237	69.6995	0.7143
Zyx	0.5408	0.9105	0.6237	0.6211	0.7143
Kif21a	319.5331	135.4698	0.921	1507.2621	0.814
Ilf3	50.2957	1.028	4.0542	8.324	922.3512
Crbn	1.4455	0.783	223.4351	0.8293	0.8021
Crbn	5844.6377	28689.8973	10.1561	0.8293	3.565
Dap3	15500.4711	868.0169	0.6237	111.7953	14.2865
Dap3	11870.6558	4630.4352	921.0113	5465.5481	5778.8925
Dap3	0.5408	0.9105	0.6237	0.6211	0.7937
Dap3	0.5408	0.9105	34812.7034	431.9991	7.9369
Dap3	0.5408	17247.0307	19.4043	2255.9188	8.7306
Ddx21	0.6657	0.9252	1413.9053	0.6811	0.7579
Stau1	0.6657	1.028	1.0136	0.7567	0.6821
Zyx	0.5408	57.6655	382.5419	3.4505	0.7143
Hnrnpa1	97354.8795	68.7939	122.6629	407.8458	116522.3465
Eps8	1.6061	0.783	307.7311	4585.0975	25.8463
Slc40a1	1.4455	0.783	0.9141	0.8293	2749.5152
Rpl18	0.6657	0.9252	706.4459	0.6811	0.6821
Eps8	1.6061	340.1689	5.0781	0.8293	0.8021
Eps8	1.6061	0.783	109116.558	5149.0203	18.7163
Eps8	1.4455	7338.4263	0.9141	23.9575	0.8021

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Slc40a1	73.8811	3084.14	85.3116	12.9002	0.8021
Slc40a1	1829.3604	284.4891	191.9511	89.3799	90.0165
Slc40a1	1.4455	0.783	32.4996	0.8293	0.8021
Mrpl37	4.4379	121.2995	0.9122	31.0257	0.6821
Ict1	16.2721	1601.5641	5.0678	82.4828	647.2374
Irf6	0.865	0.9018	0.9956	585.2069	0.9992
Irf6	1.9221	264.5418	929.2015	176896.3665	3922.3305
Irf6	0.865	0.9018	11636.0362	12.0375	9.9918
Irf6	0.865	20413.8075	691.3702	9384.6068	31108.866
Mrps28	3392.7414	0.9252	49.6641	43.89	27655.3787
Mrps28	0.6657	0.9252	0.9122	5.2971	0.6821
Mrpl4	1.9221	136635.8302	6129.4112	19098.8555	438.5283
Mrpl38	3233.0424	0.9018	67.4777	6.4817	34.4161
Mrpl38	0.865	281.5767	0.9956	0.8334	0.9992
Msi2	61055.2927	116.1597	1913.5866	1204.7035	132134.201
Msi2	3277.3572	0.9252	0.9122	247.4485	0.6821
Slc19a2	98.9903	13894.4558	95799.5668	2545.4646	11577.1477
Numbl	114.3674	505.0343	2.2124	4.6298	1182.3612
Numbl	0.865	1.0021	0.9956	12091.1886	118.7912
Numbl	0.865	0.9018	100.6635	0.926	0.9992
Numbl	0.865	0.9018	0.9956	7.4077	0.9992
Crot	1.4455	0.783	0.9141	0.8293	0.8021
Crot	19.2733	49.5898	503.7446	405.4347	82164.6037
Crot	486.6516	52.1998	2.0312	18707.1241	379259.2976
Tmem50b	9189.9059	14.0487	169.8761	0.8494	121.194
Mov10	20.71	4528.1708	408.4615	2090.8265	419.8706
Ube2k	99.5789	28.7099	0.9141	0.8293	0.8021
Numb	19930.2305	554.1882	575.8532	997.0007	67.7352
Numb	1.6061	173.9994	302079.1651	2699.8263	17.8251
Ltb	0.865	41.0841	4365.0346	9.2596	0.9992
Ltb	27592.3445	3753.6876	2.2124	8491.9812	1713.0359
Zcchc3	0.9985	0.9031	0.921	0.8494	0.814
Zcchc3	13.3139	0.9031	0.921	0.8494	0.814
Zcchc3	7.2104	0.9105	0.6237	97.3033	0.7143
Zcchc3	0.9985	0.9031	0.921	0.8494	0.814
Zcchc3	0.5408	1387.006	0.6237	3802.4204	10.318
Cltc	0.9985	0.9031	0.921	0.8494	268.6166
Anln	3.2122	227519.9251	166.5607	8644.0514	581.9881
Mrpl39	76.9105	501.7907	12.4742	153.8911	0.7143
Ybx1	23.4337	76.8873	0.6237	16.5623	0.7143
Ybx1	3.6052	0.9105	0.6237	4625.7031	0.7937
Mycn	1.4455	0.783	0.9141	0.8293	0.8913
Mtmr9	2.219	96.3341	1.0233	8245.1108	1830.5726
Mtmr9	955.2709	257.8944	1.0233	42350.5739	8186.0238
Mtmr9	3886.5436	22.0766	2.0467	17.9324	84.1123
Mrpl22	1768.9416	0.9105	0.6237	14663.1269	101.5929
Atp5a1	499.2589	2.0559	151899.0421	709.0497	77.3047
Rabep1	49817.2115	1252.3431	184.203	12.2695	12.6621
Rabep1	0.9985	6287.8061	2074.33	32461.3487	123.9073

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Rabep1	142.0147	0.9031	145.3157	0.8494	72.3546
Frmd6	1.4455	2273.3027	873.4281	4359.3441	141.7092
Frmd6	1.4455	0.783	0.9141	0.8293	0.8021
Ttc3	0.9985	0.9031	0.921	0.8494	0.814
Ttc3	0.9985	0.9031	0.921	0.8494	0.814
Cct3	0.6657	0.9252	4.0542	0.6811	0.6821
Cct3	0.6657	0.9252	18.2439	0.6811	15.1578
Frmd6	1.4455	0.783	0.9141	0.8293	0.8021
Ttc3	0.9985	0.9031	0.921	0.8494	0.814
4932438A13Rik	0.865	0.9018	996.6792	1175.0435	255.3456
4932438A13Rik	0.865	2629.385	278.7604	47.224	26804.6273
4932438A13Rik	0.9611	8540.4909	82.9644	2488.9811	9.9918
4932438A13Rik	0.865	0.9018	587.3881	4.6298	2444.6566
4932438A13Rik	26.91	0.9018	0.9956	0.8334	0.9992
Ptcd3	49.8717	1986.9292	169.0946	2.0703	153.9768
Ptcd3	444.6389	40883.799	79.6962	65568.6344	1373.8859
Sepp1	0.9985	0.9031	816.6331	1604.4744	636.7209
Mapk6	1.4455	0.783	0.9141	482.8358	762.9125
Mapk6	2365.8014	11376.0833	60953.0928	293368.8396	4015.9855
Mapk6	77.0933	0.783	334.137	2967.0446	2056.1204
Baz2b	32007.6777	4.0139	8456.9625	142815.2108	61457.1321
Ybx1	10474.2494	980.3128	0.6237	757.7237	3498.6071
Mtmr9	1259.2712	513.7818	346.9156	465.2976	1163.1009
Hnrnpc	0.6009	2017.2794	72.0731	0.6211	0.7143
Hnrnpc	0.5408	58.6771	6.9301	4.1406	1.5874
Pdia6	551.5925	950.9742	37030.3379	2733.4641	20.6361
Snx14	823.2416	6854.7724	3908.1728	8196.0328	756.1061
Mrpl11	0.6657	0.9252	0.9122	0.6811	0.6821
Mrpl11	0.6657	0.9252	3.0407	1320.4822	0.6821
Caprin1	0.6657	0.9252	1.0136	0.6811	0.7579
Cct3	0.6657	0.9252	0.9122	0.6811	0.6821
Ptcd3	0.5408	0.9105	0.6237	0.6211	0.7143
Mrpl22	0.5408	0.9105	0.6237	133.8783	0.7143
Ppp2r5c	13.3139	46.1601	156.5725	1989.5483	4645.1683
Mrpl4	0.865	0.9018	0.9956	0.8334	0.9992
Mov10	0.6657	0.9252	0.9122	6.8105	32.5892
Tmem50b	0.9985	18.0626	9209.1246	12.2695	0.814
Tmem50b	1.1095	13.0452	1.0233	0.9438	0.814
Ube2k	1.4455	8.7	0.9141	13.8216	378.7825
Irf6	41.326	3385.9344	1.1062	0.926	233.1416
Clcn3	0.865	1.0021	0.9956	0.8334	103.2484
Clcn3	0.865	2.0041	0.9956	0.8334	0.9992
Dst	0.9985	22.0766	4723.7825	0.8494	7.2355
Smc4	409.4018	221.7691	282.4445	6857.7124	4558.3427
Ilf3	86.5382	13571.1488	130.7482	3.0269	87.9152
Slc19a2	0.865	0.9018	1.1062	0.8334	1.1102
Clcn3	20.1825	17216.2589	25.4424	147949.9241	143482.0259
Smc4	0.9985	0.9031	0.921	0.8494	0.814
Smc4	0.9985	1.0035	7.1634	0.8494	0.814

Figure 15(cont'd)

Symbol	BM.1	BM.2	BM.3	BM.4	BM.5
Dst	1.1095	1.0035	232813.0964	72.6733	189.0265
Dst	1.1095	14.0487	63542.8574	201.975	987.6409
Cltc	305.1098	0.9031	6.1401	0.8494	0.814
Cltc	127.5914	1.0035	1.0233	0.8494	11566.7946
Rpl14	77.5114	11.1284	8.3161	0.6211	0.7937
Mylk	1.4455	0.783	6.0937	0.8293	32.9764
Rpl14	112.3614	5.0584	1194.0576	159702.3485	1096.8863

Figure 16

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Upf1	975.9612	115.5126	559.1414	339.572	27596.1232
Upf1	0.9236	1.316	0.7863	771.0722	0.9541
Bnip3l	1580.9733	1011.1836	3182.5908	17205.2588	7164.8995
Bnip3l	1518.4018	9721.5662	35809.7226	4037.3829	26113.8497
Bnip3l	14410.2167	111.4126	2197.5669	22953.3292	625.8369
Bnip3l	1.0429	257.3567	0.803	0.3614	0.7632
Bnip3l	0.9386	2612.0072	1215.2197	585.0872	110.2423
Spcs1	4564.7549	16306.4351	52785.1947	65201.2748	19521.3716
Spcs1	0.9789	1.0226	1.1188	0.8861	0.7323
Cdk6	69427.385	14269.8448	3998.4344	36.8822	949.7391
Cdk6	199.8426	59.3179	1.0123	239.7341	435.8392
Cdk6	1868.3396	1180.3659	1827.695	7895.5497	3833.3403
Cdk6	0.8484	0.5393	1.0123	0.8298	0.8364
Cdk6	2772.3444	0.5393	1547.6359	0.9221	1743.3567
Mapk6	8465.9241	13.6823	1511.4406	18.0706	0.7632
Mapk6	840.5438	13.0307	124.0202	2.0078	14.4163
Atr	1.0876	306.7896	7863.5819	12598.1957	37967.8962
Atr	0.9789	1497.5877	1.1188	560.2042	0.7323
Atr	0.9789	1.1363	1.2431	955.0055	14.6459
Atr	0.9789	14581.5958	68.3682	0.8861	5323.7885
Atr	0.9789	56.8129	4501.1113	12.799	0.7323
Mylk	9454.5538	19.5461	1.7845	4704.792	0.7632
Mylk	193.9717	272.9935	7.1379	16.8659	0.7632
Mylk	10506.7979	15.6369	20.5213	0.3614	68.6894
Mylk	1633.1162	18.243	0.8922	27.7083	0.7632
Stk17b	56945.7079	26903.9542	2090.8831	4169.5289	5639.889
Stk17b	0.9427	0.5393	48.3636	13474.8994	2.7879
Stk17b	14663.9204	708.8187	106.8499	18264.9707	6.5051
Stk17b	7329.1322	269980.2394	118352.5326	88483.0826	54117.4721
Stk17b	0.8484	14.3801	5.6237	22.1293	0.8364
Gpsm2	35.4572	129.6556	0.803	1844.8117	6386.4195
Gpsm2	0.9386	3.9092	11028.8771	169.0609	0.7632
Gpsm2	932.3154	1925.9399	166.8473	1712.2937	29239.6421
Gpsm2	544.3721	1430.7727	0.8922	38.5507	0.7632
Frmd6	27639.9177	7710.9266	12534.9643	7368.003	2194.6692
Frmd6	134.5287	461.9389	5646.0427	860.1625	1068.502
Npepps	0.8484	400.2459	482.5115	261.8634	32.5253
Zcchc3	0.8484	0.5393	1.0123	0.8298	0.9293
Rrm2	0.9386	0.6515	0.803	0.4016	410.4405
Rrm2	1842.7307	554.457	6177.8129	186.73	8596.353
Mycn	10434.8406	2294.0577	8819.7112	6331.1497	68519.811
Mycn	32430.809	6903.6737	77868.6367	29116.2211	18431.6595
Mycn	25901.4728	26115.5108	11900.5875	386.3102	3878.8319
Mycn	16.6857	23.4553	131.1581	918.7917	3829.6469
Cdkn1a	0.9789	1.0226	1.1188	0.8861	0.7323
Cdkn1a	18331.8904	43535.716	100.6877	0.8861	0.8137
Cdkn1a	0.9789	1.0226	1.1188	0.8861	0.7323

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Rrm2	8.3429	16440.8552	0.803	31075.0787	0.848
Rrm2	353.529	61.2444	0.803	1112.75	0.7632
Rrm2	0.9386	59.2898	7.1379	12612.9064	0.7632
Rpl14	0.8465	0.8563	0.3383	0.6498	0.7439
Rpl14	0.9406	0.7706	0.3383	0.722	0.7439
Rpl14	0.8465	18.8381	0.3383	0.6498	0.7439
Rpl14	0.8465	0.7706	0.3383	12.2744	0.7439
Cdkn1a	0.9789	205.6627	266.0143	17.7218	0.7323
Cdkn1a	0.9789	19801.5639	2154.2187	0.8861	63.4656
Hnrnpa1	7469.9233	17581.0701	1147.8825	44044.2659	43320.0613
Ilf2	2350.4581	0.7706	0.3383	0.722	0.7439
Ilf3	1441.8775	9701.5973	46474.2638	1089.0692	18.1284
Ilf3	0.9236	1.316	0.7863	529.0569	0.8587
Ilf3	109.8085	1.316	10.4839	69.4153	3.8165
Ltb	52712.75	6417.5838	1859.6141	0.8861	10861.5701
Ltb	0.9789	1664.6176	26825.1814	5313.5716	902.3508
Ltb	1648.8369	50002.1589	11175.0871	7822.1839	178213.0687
Slc25a24	0.9789	7198.1929	1.2431	1882.4438	8049.5553
Slc25a24	0.9789	443.1405	1.1188	6.8918	43.1241
Slc25a24	140.3034	18148.3089	110673.1405	4370.3807	184730.499
Slc25a24	0.9789	1.1363	1.1188	2.9536	0.7323
Slc25a24	88664.1376	50736.1814	1.2431	916.6083	4680.1821
Clcn3	51.1183	4439.3591	99.4446	0.9845	107479.8293
Clcn3	34.8039	5227.9219	5512.9601	24.6135	46.3787
Csda	27.7087	1.316	469.1546	6.5663	0.8587
Csda	50770.5065	9956.0175	607.1927	21923.9659	23084.0717
Csda	9037.1337	1146.353	1185.5546	8.4424	9550.7794
Csda	2.0525	1.316	0.7863	0.8442	0.8587
Csda	31.8137	1.316	73.3873	40.3359	0.8587
Hnrnpa2b1	1242.7855	462126.4848	4360.4296	15.0087	6878.2786
Hnrnpa2b1	4.105	4244.723	45.4302	6145.1267	20.9907
Hnrnpa2b1	13323.7687	1.316	164.2478	4482.9126	1834.7801
Ssb	166.479	2.5688	0.3383	0.6498	0.7439
Ssb	6497.3848	0.8563	0.7517	984.1205	576.124
Ssb	5533.3113	58.2268	83098.9521	8091.0156	0.7439
Msi2	9.2362	5097.1768	1375.1385	6877.7391	3218.2596
Msi2	0.9236	500.0673	1223.9956	450.2612	2803.2158
Msi2	0.9236	1.316	0.8737	7830.7919	0.8587
RFP	11.0872	4.9106	3.3565	3.4665	2.6076
RFP	11.0872	4.9106	3.3565	3.4665	2.6076
RFP	11.0872	4.9106	3.3565	3.4665	2.6076
RFP	11.0872	4.9106	3.3565	3.4665	2.6076
RFP	11.0872	4.9106	3.3565	3.4665	2.6076
RFP	11.0872	4.9106	3.3565	3.4665	2.6076
lacZ	2362.3175	1520.956	676.2075	376.6063	10.3411
lacZ	2362.3175	1520.956	676.2075	376.6063	10.3411
lacZ	2362.3175	1520.956	676.2075	376.6063	10.3411
lacZ	2362.3175	1520.956	676.2075	376.6063	10.3411
lacZ	2362.3175	1520.956	676.2075	376.6063	10.3411

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
lacZ	2362.3175	1520.956	676.2075	376.6063	10.3411
lacZ	7899.9864	10308.6634	5254.3744	5571.0108	2094.6508
lacZ	7899.9864	10308.6634	5254.3744	5571.0108	2094.6508
lacZ	7899.9864	10308.6634	5254.3744	5571.0108	2094.6508
lacZ	7899.9864	10308.6634	5254.3744	5571.0108	2094.6508
lacZ	7899.9864	10308.6634	5254.3744	5571.0108	2094.6508
lacZ	7899.9864	10308.6634	5254.3744	5571.0108	2094.6508
LUCIFERASE	499.8757	4356.6762	92.9703	540.2586	20.7619
LUCIFERASE	499.8757	4356.6762	92.9703	540.2586	20.7619
LUCIFERASE	499.8757	4356.6762	92.9703	540.2586	20.7619
LUCIFERASE	499.8757	4356.6762	92.9703	540.2586	20.7619
LUCIFERASE	499.8757	4356.6762	92.9703	540.2586	20.7619
LUCIFERASE	499.8757	4356.6762	92.9703	540.2586	20.7619
LUCIFERASE	30365.8995	3839.4901	3151.3043	23921.2133	13668.3973
LUCIFERASE	30365.8995	3839.4901	3151.3043	23921.2133	13668.3973
LUCIFERASE	30365.8995	3839.4901	3151.3043	23921.2133	13668.3973
LUCIFERASE	30365.8995	3839.4901	3151.3043	23921.2133	13668.3973
LUCIFERASE	30365.8995	3839.4901	3151.3043	23921.2133	13668.3973
LUCIFERASE	30365.8995	3839.4901	3151.3043	23921.2133	13668.3973
LUCIFERASE	21372.1362	13092.5802	24120.3636	41498.4173	1315.4021
LUCIFERASE	21372.1362	13092.5802	24120.3636	41498.4173	1315.4021
LUCIFERASE	21372.1362	13092.5802	24120.3636	41498.4173	1315.4021
LUCIFERASE	21372.1362	13092.5802	24120.3636	41498.4173	1315.4021
LUCIFERASE	21372.1362	13092.5802	24120.3636	41498.4173	1315.4021
LUCIFERASE	21372.1362	13092.5802	24120.3636	41498.4173	1315.4021
LUCIFERASE	1119.1982	64.3461	40.3416	98.8824	3075.036
LUCIFERASE	1119.1982	64.3461	40.3416	98.8824	3075.036
LUCIFERASE	1119.1982	64.3461	40.3416	98.8824	3075.036
LUCIFERASE	1119.1982	64.3461	40.3416	98.8824	3075.036
LUCIFERASE	1119.1982	64.3461	40.3416	98.8824	3075.036
LUCIFERASE	1119.1982	64.3461	40.3416	98.8824	3075.036
LUCIFERASE	45329.1986	8677.3381	32901.4396	27171.2966	61989.5924
LUCIFERASE	45329.1986	8677.3381	32901.4396	27171.2966	61989.5924
LUCIFERASE	45329.1986	8677.3381	32901.4396	27171.2966	61989.5924
LUCIFERASE	45329.1986	8677.3381	32901.4396	27171.2966	61989.5924
LUCIFERASE	45329.1986	8677.3381	32901.4396	27171.2966	61989.5924
LUCIFERASE	45329.1986	8677.3381	32901.4396	27171.2966	61989.5924
Zyx	12.2273	0.7706	0.3383	322.7453	16871.2582
Zyx	3029.542	144.7107	9767.9015	6366.8192	176.8874
Zyx	362.1154	1581.5428	3.7586	1600.7301	95.0563
Atp5a1	275.0343	1.316	67.2717	7.5044	1595.295
Atp5a1	76.9685	902.1681	137.1644	795.4614	8.5871
Atp5a1	0.9236	1.4622	179.9737	1833.8761	429.3557
Atp5a1	0.9236	4.3866	0.7863	2.8141	0.9541
Acox1	722.7008	704.9618	8.0301	4196.4046	1964.0084
Acox1	357.7004	1.9546	29184.9017	3.6141	0.7632
Acox1	738.3437	99.685	60.6718	155.0059	162.8194
Acox1	93.8573	61278.2482	1589.957	0.3614	3221.6183
Acox1	6972.5509	1257.4642	2463.452	1870.5122	25789.9071

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Ybx1	1225.549	42.8138	0.7517	4585.5827	2.4797
Ybx1	28065.3538	12478.5182	1524.8721	22183.5056	77.6982
Peli1	1.8853	4.7934	1.0123	0.8298	1.8586
Dyrk2	0.8484	1.1983	4.4989	0.8298	0.8364
Dyrk2	3411.4636	0.5393	199.0782	44.2586	0.8364
Dyrk2	1.8853	0.5393	1.0123	10.1426	0.8364
Dyrk2	0.8484	0.5393	1.0123	7.3764	3.7172
Dyrk2	1884.3647	3.595	120.3467	121.7111	388.4452
Slc19a2	30.4535	539.7224	2021.2115	568.0806	65.0929
Slc19a2	16938.645	14.7714	2.4861	0.8861	790.8792
Slc19a2	0.9789	11.3626	1.1188	0.8861	0.7323
Slc40a1	11.4714	459.9843	14.2757	37499.7942	468.9537
Ppp2r5c	0.8484	7.7892	73.1078	0.8298	0.8364
Ppp2r5c	16489.8406	24185.5176	1904.177	4687.7233	541.7788
Ppp2r5c	1552.5506	633.9224	19268.967	1629.2697	8.3637
Ppp2r5c	98.9786	911.9375	1.0123	0.8298	2074.1856
Mtmr9	22.6237	12137.397	37.1163	17342.9165	38620.5551
E2f7	277.1402	4315.226	719.8307	0.8298	384.728
E2f7	295.9933	8.3884	169.835	0.9221	17.6566
E2f7	214.925	0.5393	846.9258	0.8298	181.2125
E2f7	3120.1836	4036.0125	6827.1439	4866.6018	10005.7152
E2f7	0.8484	9151.7303	70.8583	0.8298	0.8364
Dst	140.4554	32.3552	163.0866	3904.8993	2929.1366
Dst	4640.684	37.7477	19109.2545	4043.2075	82155.2201
Krt6b	402.5595	0.8563	0.3759	2.8881	0.7439
Krt6b	10738.3674	8.5628	0.3383	1781.9585	19.8378
Krt6b	106.2832	5.9939	54.1241	9.3863	0.7439
Krt6b	5681.9197	3835.2627	0.3383	5241.1817	0.8266
Krt6b	109324.9887	606.2438	0.7517	459.9301	2372.2753
Anln	2121.1739	117.928	28.5514	2900.1372	360.4074
Anln	44444.5371	8985.9822	7864.1309	36618.3484	37335.6648
Anln	584.0007	15765.2125	12.4912	1835.9772	4426.6512
Tubb2c	2.8217	0.7706	21.8	345.1281	0.8266
Tubb2c	69.6014	29812.1244	0.3759	2532.8648	1057.1917
Tubb2c	0.9406	216.638	0.7517	176.1742	1596.1197
Tubb2c	0.8465	11.1316	0.3383	14.4405	0.7439
Tubb2c	0.8465	0.7706	0.3383	71.4805	0.7439
Tjp1	2.1752	431.7779	1189.6061	1356.6985	5466.993
Tjp1	0.9789	1.0226	1.1188	0.9845	43.1241
Tjp1	0.9789	698.7985	1.1188	0.8861	8.1366
Eps8	0.9386	0.5864	0.803	0.4016	0.7632
Mybbp1a	89333.0259	35.224	10304.9469	0.8861	0.8137
Mybbp1a	0.9789	1.0226	300.8199	0.8861	1659.0562
Mybbp1a	0.9789	1.1363	1.1188	152.604	0.7323
Igf2bp3	0.9789	1.0226	1.1188	0.8861	0.8137
Igf2bp3	0.9789	1.0226	1.1188	0.8861	0.7323
Igf2bp3	0.9789	6516.4382	1177.1755	3334.6428	30.9191
Igf2bp3	1.0876	104835.6858	12234.1721	0.8861	177.3783
Igf2bp3	2.1752	209.0714	448.7438	259.919	908.0465

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Mov10	3022.2983	10.2353	37424.0354	151606.6819	107.816
Mov10	53.3649	17.5462	54.1668	0.8442	289.0995
Mov10	0.9236	1.316	0.7863	0.8442	0.8587
Ube2k	0.9386	0.5864	0.803	1401.4787	1.696
Ube2k	7423.0657	44.956	20723.8676	58650.4764	126268.1041
Ablim1	18659.8644	320.5556	275.6996	62775.4016	6050.6046
Ablim1	19314.7795	14258.2102	14766.436	1217.5597	5036.3757
Ablim1	2714.5603	540.1232	12888.2881	311.6182	8638.7539
Ablim1	9989.5401	5832.5488	5283.7966	11784.4678	22977.0331
Ablim1	3199.4894	165.4901	0.8922	2998.9234	14434.9532
Mrpl22	1.8811	5.9939	1445.1894	3.6101	0.7439
Mrpl22	32130.4518	4089.5768	70.6621	15178.4161	23.9707
Atp10d	5956.9127	379.5101	19503.5725	1866.6911	0.7323
Atp10d	1.0876	1462.3637	432.584	2207.3425	4312.407
Atp10d	515.5334	40657.5751	4478.7363	1014.078	10919.3401
Atp10d	0.9789	7464.0772	8884.1321	1468.9362	21.9689
Atp10d	35.8916	119.3071	22198.5213	75825.4644	1120.4122
Caprin1	55566.1601	1.316	9654.8001	750.4353	1970.2657
Caprin1	1.0262	1.316	0.7863	32474.1475	0.8587
Caprin1	0.9236	1.316	0.7863	0.8442	0.8587
Stau1	0.9236	242.7227	7.8629	0.938	143.1186
Stau1	33240.1501	3608.6725	124.9332	88.1761	0.9541
Stau2	778.9217	1.316	1379.5068	18409.1148	51395.7877
Stau2	5678.2263	36.5546	1.7473	24015.8042	1.9082
Stau2	98.5197	1.316	39289.2963	983.0702	1551.4053
Prpf19	34.8924	440.1177	7.8629	553.446	170.7882
Prpf19	1.0262	1.316	0.7863	1249.4747	51.5227
Prpf19	0.9236	1.316	0.7863	0.938	0.8587
Prpf19	0.9236	1.316	0.7863	0.8442	5.7247
Prpf19	1560.9221	1.316	149.3956	319.873	0.8587
Pura	3172.5071	0.7706	62.3931	0.6498	0.7439
Pura	1485.1434	39.3887	1097.517	568.2339	0.7439
Pura	17.8706	10.2753	10.9	574.7321	0.7439
Pura	123973.2618	575989.8343	18.0414	1368.238	19.0113
Pura	4207.1225	14767.3454	4593.4094	42019.707	64.473
Hnrnpab	3694.6563	7.9538	8.7014	0.8861	0.7323
Hnrnpab	1.0876	2.2725	74.5835	0.8861	17.0869
Hnrnpab	0.9789	1.0226	1.1188	0.8861	0.8137
Hnrnpab	2.1752	1.0226	1.1188	0.8861	158.664
Hnrnpab	0.9789	44.3141	12.4306	0.8861	9462.072
Ddx56	0.9236	1.316	0.8737	0.8442	0.8587
Ddx21	241.1681	1.316	113901.4793	3.7522	0.8587
Ddx21	99.546	1.4622	709.4107	9.3804	0.8587
Ddx21	11.2887	1555.7648	1403.0955	57.2207	21.9448
Rbmx	348.9476	0.7706	12.4034	2.1661	12838.3902
Rbmx	34425.4169	215.7817	457.424	26686.0555	3185.6268
Rbmx	442.0629	0.8563	4.1345	15.1625	273.5969
Rbmx	19.7517	0.7706	3.7586	11872.2622	11.5721
Rbmx	1222.7273	1259.5828	0.3383	298.9185	3890.6968

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Rps24	1869.8322	3.4251	24.0552	7117.0035	54478.0209
Rps24	0.8465	3.4251	27.4379	0.722	0.7439
Rps24	0.8465	163.5488	0.3383	0.722	0.7439
Rpl24	0.9236	43.8655	3.4946	5.6283	0.8587
Rpl24	10.2625	1.316	1349.8024	0.8442	0.8587
Rpl24	0.9236	1.316	0.7863	0.8442	0.8587
Rpl24	1.0262	1.316	4.3683	0.8442	0.9541
Rpl24	18.4725	1.316	0.7863	0.8442	0.8587
Mrpl4	0.9789	6.8175	24.8612	1635.3238	0.7323
Mrpl4	0.9789	874.9185	3.7292	0.8861	0.7323
Mrpl4	0.9789	267.0206	113.1182	171.3103	2362.0599
Rpl26	0.9406	0.7706	0.3383	0.6498	0.7439
Rpl26	0.8465	0.8563	0.3759	0.6498	860.4664
Rpl26	0.9406	0.7706	0.3383	0.6498	7.4392
Rpl26	0.8465	0.7706	0.3383	0.6498	14.0518
Rpl26	39.5035	2693.846	0.7517	0.722	0.7439
Rps11	0.9789	1.0226	8.7014	0.8861	0.7323
Mrpl39	7.5245	81.3463	0.3759	3610.8486	210.7771
Mrpl39	15.049	18.8381	0.3383	0.6498	25.6239
Mrpl39	35927.4904	90.7653	1.5034	425.9949	70.259
Mrpl39	4782.7449	1585.8242	18.4172	83814.864	46244.4898
Rpl4	0.8465	13.7004	13.1552	0.722	0.7439
Rpl4	0.8465	0.7706	4.5103	7.2203	0.7439
Rpl4	0.8465	0.7706	0.3383	0.6498	0.7439
Rpl4	2.8217	101.8969	0.3383	10.1084	0.7439
Rpl4	0.8465	0.7706	0.3383	1.4441	0.7439
Mrps9	35.9187	2137.7144	73971.7913	2984.8562	6878.2786
Mrps9	1998.1035	5493.4289	418.4824	15498.3641	9743.5124
Rpl18	1303.3341	190.084	5933.0149	0.8442	0.8587
Rpl18	0.9236	1.4622	0.7863	8.4424	0.8587
Rpl18	18.4725	1.4622	0.7863	0.8442	41.0273
Rpl18	0.9236	1.316	0.7863	0.938	1392.0667
Numb	6802.565	17489.1764	70.4863	1.6063	20438.0689
Numb	2179.574	41.0468	5.3534	4463.4485	563.9316
Numb	8.3429	18.8945	0.803	0.3614	0.7632
Snx14	0.8484	841.8346	27956.4233	3928.8727	1666.2253
Snx14	0.8484	65.3096	1.1247	130.0096	877.2541
Snx14	469.4415	19.7726	662.4692	24.8955	5607.3637
Snx14	0.8484	0.5393	10515.1513	8.2985	326.1824
Numbl	11384.1529	29364.3092	8432.9022	29297.9922	4021.9298
Smc4	6.5986	364.8948	41.6152	218.5268	2036.0845
Smc4	87418.8729	346005.3901	192814.5154	3247.4747	17328.5568
Ptbp1	8808.2806	7695.4795	18959.2631	29668.4577	4251.5757
Ptbp1	346.8716	766.1849	99.5971	0.8442	1592.4327
Crot	107.4144	9.773	74.0552	1.6063	131.4427
Crot	589.215	135.5195	1.7845	118.8647	36.4648
Abcc5	33260.9242	174946.4926	215.9201	12277.9971	18307.849
Abcc5	33219.2099	6425.4464	41060.5067	6745.5698	21477.7383
Abcc5	76.1287	60.5928	1329.4254	2021.904	29884.1354

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Pdia6	610.4231	15835.9785	658.1343	559.5696	161.1825
Pdia6	70195.8339	9782.1033	2352.5202	35748.1951	26451.2828
Pdia6	0.9406	40147.3823	10.9	569.678	5867.8684
Pdia6	0.8465	5.1377	0.3759	0.722	0.7439
Hnrnpl	90.2727	724.9324	718.4872	208006.0963	0.7323
Syncrip	484.3881	80.49	258.5931	0.722	0.8266
Syncrip	0.8465	0.7706	0.3759	9.3863	0.7439
Hnrnpc	1013.9231	8336.7085	0.3759	1989.1797	55.3806
Hnrnpc	2.8217	245.7514	918.6067	1888.0962	18.1847
Hnrnpc	31.979	7.7065	0.3383	1273.6526	0.7439
Hnrnpc	647.1049	1179.0928	4.1345	1266.4324	0.7439
Hnrnpr	15.2267	1.0226	31.0764	4388.1024	2044.7319
Hnrnpr	0.9789	1.1363	1.1188	153.5885	0.7323
Hnrnpa3	75958.6417	0.8563	0.3759	7.9423	0.7439
Hnrnpa3	34.8007	746.6732	1.5034	2.1661	75.2185
Hnrnpa3	2361.7448	17.9818	90.5827	659.9311	0.8266
Hnrnpa3	0.8465	104.4657	0.3383	1313.364	0.7439
Hnrnpa3	864.3741	0.7706	0.3383	8.6643	0.8266
Asph	0.9386	4.5608	0.803	34.535	0.7632
Asph	259.6717	0.6515	0.803	0.3614	0.848
Kif21a	2742.1795	0.5393	1.0123	0.8298	4.6465
Kif21a	0.9427	0.5393	1.1247	23.0514	0.8364
Cltc	0.8484	0.5393	23.6194	2472.9492	0.8364
Ap3s1	9648.3061	6203.9674	36.0487	7560.2958	1294.5358
Ap3s1	1.0876	6035.8012	218.7781	0.8861	665.5753
Crbn	15973.4613	8633.5013	0.803	22418.4382	2840.0105
Crbn	0.9386	0.6515	0.803	0.3614	132.2907
Crbn	3922.1903	2420.4556	6815.7586	740.4947	3245.3628
Abca1	1314.0592	1897.573	194.5792	27355.5026	477.6574
Abca1	223.4089	44.9378	711.9575	46.1027	154.2629
Mrpl38	3754.4756	45216.2412	3942.9785	147.6813	4027.6254
Mrpl38	17895.7535	48.8591	1.1188	5154.0759	1811.211
Mrpl38	0.9789	17.0439	1.1188	0.8861	0.7323
Cct3	0.9236	1.316	1.7473	0.8442	27.6696
Cct3	8507.5901	5709.8323	512.8375	5043.8629	3126.6638
Cct3	12.315	1.316	243.7507	4.6902	0.8587
Sepp1	11433.4463	3.595	1.1247	7.3764	1504.528
Sepp1	4216.4898	63750.5437	1520.6423	24516.4979	9576.381
Sepp1	9100.3785	63.5121	31813.141	26954.409	418.1826
Sepp1	783.3452	52.1278	1576.879	0.9221	646.7891
Tmem50b	1892.8486	0.5393	97.852	98.6598	15.798
Tmem50b	22.6237	0.5393	39.3657	1.8441	1.8586
Aqp11	151623.2612	497.1218	2436.685	58168.1911	10126.1765
Mrpl37	13.3412	767.6471	1143.619	4480.0985	19.0825
Lst1	147.9966	0.5393	1.0123	189.0211	4.6465
Lst1	473.2121	6.5909	557.8688	1021.636	2210.7919
Aqp11	331.629	123.1403	689.6952	491.5215	1963.1604
Mrpl37	104.6772	1.316	0.8737	226.0686	48.6603
Fastkd2	1.0876	251.113	4120.7357	652.7512	29.2918

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Fastkd2	2.1752	32.9515	3505.4222	810.2778	2520.724
Fastkd2	0.9789	1.0226	1.1188	0.8861	0.7323
Cyb5	1.0429	115.9734	0.803	37.346	0.7632
Mrpl37	0.9236	339.2269	3.4946	4671.4594	20.0366
Cyb5	11846.8709	12738.8286	14701.3031	4.0157	9545.2846
Ptcd3	68026.9038	2244.3008	373926.6791	275.0916	41771.883
Ptcd3	79.9476	0.8563	49006.0142	28891.8428	76.8716
Snx16	125.143	121.8372	26.767	13632.8937	10.1762
Snx16	301.3861	286.6758	29.4436	15.2597	680.11
Tax1bp1	0.9386	26.0614	4.4612	0.3614	0.7632
Tax1bp1	0.9386	1.3031	48929.0988	8625.7197	0.7632
Tax1bp1	946.9154	1678.3563	2617.8081	31983.0281	3481.9597
Mrps27	21.6329	1414.5689	0.3759	6719.1675	13.2252
Snx16	0.9386	190.2485	0.803	0.3614	0.7632
Mrps27	1409.8986	3737.6471	115765.1178	4807.9665	15.705
Mrps27	0.8465	0.7706	0.3383	0.6498	951.3898
Rabep1	727.7286	0.5393	4.4989	1169.1647	227.6772
Mrps28	127.2547	1.4622	16812.6841	12654.2144	49555.2829
Fcho2	159.8806	1.1363	78.3126	0.8861	0.7323
Baz2b	4.7133	50173.9392	35.9915	7315.5776	13.0101
Fcho2	27.1906	426.0967	2798.1225	17042.417	9835.5427
Fcho2	0.9789	361.33	1485.4537	877.2267	846.2082
Rabep1	2586.6417	2.9959	12875.9709	64310.511	317051.1623
Paip1	23914.6607	16623.451	14694.183	13136.74	17984.3647
Ttc3	4827.3294	665.6784	1615.12	822.4723	4875.0796
Mrps28	193.9607	40.9412	127.5541	1202.5725	9.5412
Fcho2	0.9789	1.0226	1.1188	0.8861	0.7323
Baz2b	44513.9913	6.5909	3557.5381	7.3764	473.9403
Fcho2	923.3922	162789.3764	1971.4892	3995.2703	24713.347
Baz2b	12519.3833	1966.4776	73824.2578	72444.8727	106095.7081
Ict1	294552.4741	118460.3777	175860.4663	120909.1898	469576.8079
Ict1	6406.8619	4.3866	0.7863	64.725	0.9541
Sertad2	168.5816	471.547	53.4515	13.7836	0.7323
Ict1	297.6117	5880.908	371.3049	1352.6595	49.6144
Fastkd2	1.0876	1401.0058	19015.0509	2838.4338	286.4089
Mrpl37	2.0525	49.7143	189.5839	46.9022	45.7979
Ptcd3	0.8465	48.8078	0.7517	101.0835	0.7439
Aqp11	5981.8355	25852.9418	87026.5037	37074.5318	9793.7537
Aqp11	1271.2443	26.0614	3857.118	148.5808	1511.1671
Mrps27	0.8465	0.7706	0.3383	0.6498	0.7439
Mrps27	612.3042	122.4475	8.269	108.3038	605.8808
Tax1bp1	2931.4748	838.5266	84696.8866	20629.8462	1545.9358
Ttc3	1002.0408	395.4525	5.6237	346.6924	44.6061
Paip1	1037.5926	1525.9942	7046.8931	8302.6402	42419.4394
Baz2b	3686.7185	7.19	5.6237	919.288	468.3645
Mrps28	16513.3453	678.4538	11204.6702	206652.9837	1042.8573
Mrpl37	16073.0852	12279.4294	52571.5264	40307.7535	9404.7985
Cyb5	1.0429	1.3031	0.803	1.6063	0.848
Sertad2	144368.9392	8385.5823	207.5906	28724.0044	407.6445

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Sertad2	1.0876	14.7714	364.2159	39.3817	13.0186
Tax1bp1	6879.7365	1058.7457	137.4037	1189.0482	29910.4239
Ybx1	0.8465	0.8563	14.6586	34.6572	18262.3869
Trip11	679.6533	4.1942	186.7061	993.0523	0.9293
Trip11	87.6668	0.5393	22.4947	10291.9684	11.1515
Trip11	861.5854	16.7768	14.6216	0.8298	2187.5595
Trip11	0.8484	1479.9512	571.3656	0.8298	0.8364
Trip11	579.732	54.5245	644.4734	9029.6763	936.729
Sertad2	4414.6629	11.3626	1.1188	73.8406	0.7323
Sertad2	0.9789	5661.9724	87834.4446	34220.7008	10817.6324
Mybbp1a	0.9789	1.1363	1.1188	0.8861	0.7323
Mybbp1a	0.9789	1.0226	3.7292	41.3508	0.7323
Mybbp1a	0.9789	1.0226	1.1188	0.8861	78.9252
Gpr65	0.9386	0.5864	0.803	534.4894	80.5617
Gpr65	0.9386	0.5864	1307.1196	1.6063	5.9361
Gpr65	30201.1778	12770.1023	163.2784	31.724	5743.6223
Gpr65	450.5148	10248.0071	1231.2799	29487.2716	322.2466
Gpr65	2984.6606	28.6676	2874.7708	543.324	14.4163
Mll3	0.8484	0.5393	1.0123	0.8298	3.7172
Mll3	222.4663	0.5393	1.0123	0.8298	3.7172
Mll3	0.8484	2.9959	6035.3302	14.7529	0.8364
Mll3	0.8484	0.5393	1.0123	0.8298	0.9293
Mll3	0.8484	0.5393	1.0123	0.8298	0.8364
Cenpf	538.1149	1289.3894	97387.9915	116.0537	21950.932
Cenpf	21011.51	4798.5614	0.803	367.0348	0.848
Cenpf	0.9386	25.4099	0.803	0.3614	0.848
Cenpf	282.6146	1136.93	0.803	4712.8234	230.6607
Cenpf	47.9715	151.8078	4772.5478	0.3614	54.2731
Mns1	0.9789	1.0226	1.1188	0.8861	0.8137
Mns1	23.9277	106.8082	1587.3845	1972.037	877.1273
Mns1	106.5871	1.0226	2.4861	38.3971	13.0186
Mrps22	11989.3115	202.9375	151374.6589	163979.1681	18021.853
Mrps22	12.2273	17.1255	324.3689	0.6498	19.0113
Mrps22	31747.6441	1603.806	2043.5617	4132.8729	6.6126
Mrps22	0.8465	5.9939	0.3383	0.6498	0.7439
Mrps22	0.8465	0.7706	5.6379	5.0542	405.8492
Mrps23	7035.9515	4158.4541	70356.5925	2207.2177	0.8587
Mrps23	329.4254	1.316	3.4946	0.938	0.8587
Mrps23	12.315	1.316	0.8737	0.8442	0.8587
Mrps23	0.9236	1003.0589	480.5122	623.7993	21.9448
Mrps23	0.9236	12981.2782	2.621	3.7522	0.8587
Cep70	4210.0192	187.6423	6648.9113	9923.9949	8.4802
Cep70	2.0857	0.5864	137.4037	10435.9964	59.3612
Cep70	160.6002	517.3195	3748.2657	9741.2806	1844.438
Cep70	0.9386	602.0191	26559.9557	3754.2762	35.6167
Cep70	167.9002	331.6317	4958.132	5.2204	708.0946
Rwdd4a	5681.4923	319362.0161	41.9349	820.4071	524.0748
Rwdd4a	1863.5879	9.773	0.8922	313.626	161.1233
Rwdd4a	1317.1301	2849.1662	36.5815	76194.6602	19125.3378

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Rwdd4a	18128.0067	22246.0395	1852.2732	7073.6523	20543.223
Rwdd4a	7.3	34.5314	24970.8909	28690.9587	0.7632
Bex1	0.9386	0.5864	662.036	0.4016	0.7632
Bex1	33680.1533	1908.3485	34.797	17006.8833	2324.4159
Mrpl44	524.8322	5.9939	16880.3379	14166.1366	1595.2931
Mrpl44	6180.4162	48.8078	0.3383	352.3484	0.7439
Mrpl44	0.8465	750.9545	0.3383	490.2552	0.7439
Mrpl44	0.8465	0.7706	0.3383	0.722	0.7439
Mrpl44	3382.2518	17.1255	12047.8803	35426.8939	32.2365
Lst1	68154.8026	16899.6042	20731.123	1785.0968	32509.5137
Lst1	10.3692	0.5992	2189.8598	0.8298	0.8364
Lst1	19.7957	0.5393	7782.0443	7872.4984	107.7982
Tnrc6a	0.8484	7.7892	1065.1244	0.8298	7.4344
Tnrc6a	45833.7065	37312.7442	18282.574	45935.8158	13961.7224
Tnrc6a	40.5341	0.5393	43.8647	0.8298	1028.7291
Tnrc6a	0.8484	41.3428	2.2495	330.0954	0.8364
Iqgap2	16.0251	225.8873	5326.7469	302.4338	0.8364
Iqgap2	0.8484	0.5992	3.3742	0.9221	3.7172
Iqgap2	4140.1349	45.537	122.5962	0.8298	3154.9552
Iqgap2	426.0795	90.4747	1.0123	0.8298	0.8364
Iqgap2	0.8484	1062.9285	1.0123	0.8298	11298.364
Mns1	0.9789	1.0226	1.1188	77.7788	12139.8326
Mns1	2.1752	10875.123	66465.0427	12300.8641	48731.8269
Bex1	7.3	0.5864	0.803	0.3614	83.9537
Bex1	0.9386	0.5864	4.4612	0.3614	0.7632
Bex1	0.9386	385.7092	0.803	96.3768	0.7632
Asph	22260.8543	652.1874	16665.9975	20.4801	5097.433
Asph	79.2572	65.8051	42.8271	33.3303	29.6806
Asph	118.8859	0.5864	15.1679	257.4063	5151.7061
Tnrc6a	2646.0288	5418.8981	7.8731	210.2283	97.5759
Abca1	11258.1127	170.1644	4890.3495	82.9849	6847.0428
Abca1	9.4265	187.5404	76.482	16472.4974	0.8364
Abca1	0.8484	10.1859	1.0123	20.2852	3318.5111
Upf1	0.9236	1.316	6.9893	0.8442	0.8587
Upf1	16768.8809	519.0757	13458.7092	0.938	7845.7602
Upf1	98.5197	23.395	2458.475	0.8442	67.7428
Upf1	0.9236	1.316	133.6698	589.0917	326.3103
Snx16	838.4581	24.1068	0.803	28.913	21214.0048
Snx16	587.1293	0.5864	1.7845	5.2204	0.7632
Paip1	39394.8029	1.0226	19220.1554	31690.4286	24.4099
Paip1	133.7777	321.5609	33543.9073	6.8918	14017.7639
Paip1	0.9789	3636.0248	125.5488	252.0427	1130.9898
Spcs1	0.9789	1.0226	1146.099	436.152	65.9066
Spcs1	0.9789	1.0226	211.3198	0.8861	668.8299
Ptbp1	6865.5944	57.0252	426.3453	0.8442	131.6691
Ptbp1	50297.4065	1469.4959	7111.5802	53933.7816	3181.0488
Hnrnpl	0.9789	1.0226	1.1188	0.8861	0.7323
Hnrnpl	692.816	334.0598	1.1188	0.8861	0.7323
Hnrnpl	198204.1164	84.0831	1.2431	41.3508	0.7323

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Ddx56	0.9236	23.395	13524.2335	4628.3094	14289.9124
Ddx56	41244.879	450.353	551.2785	48812.061	2708.7575
Rps24	0.8465	0.7706	0.3759	0.6498	14.8784
Rps11	0.9789	1.0226	1.1188	0.8861	0.7323
Rps11	0.9789	1.0226	1.1188	0.8861	0.7323
Rps11	0.9789	1.0226	1.1188	0.8861	0.7323
Cyb5	2248.4026	31559.7442	543.3692	30.9209	22087.4628
Gpsm2	133.4859	0.6515	0.803	8.8345	42520.4436
Cyb5	1421.4159	10560.7443	0.803	2252.4051	2.5441
Ptbp1	367.3965	236388.5201	2489.0531	466.2079	2045.6415
Hnrnpl	0.9789	1.0226	96110.7216	174.2639	2007.3034
Hnrnpl	0.9789	1.0226	1.1188	0.8861	69.9749
Ptbp1	496.7037	2.9244	942.6775	5157.3663	0.8587
Rps24	56.4336	88.1965	185.6758	10844.0981	9.0923
Rps24	0.8465	451.2577	0.3383	12514.8647	14991.6226
Rps11	0.9789	1.0226	1.1188	0.8861	0.8137
Rps11	0.9789	52151.9586	1.2431	871.3194	0.7323
Spcs1	1.0876	1.0226	780.6401	5204.2875	371.0297
Ilf2	27.2762	375.9054	28.1896	23.8268	267373.6102
Ilf2	3.7622	498.353	0.3383	508.3058	0.7439
Ssb	17.8706	0.7706	0.3383	0.6498	0.7439
Ssb	0.8465	0.7706	19.9207	12.9965	0.7439
Tjp1	0.9789	299.972	1.1188	0.8861	0.7323
Tjp1	0.9789	2517.9472	989.4738	22.6445	0.7323
Mrps9	0.9236	1.316	0.7863	313.3067	6.6789
Mrps9	8285.9207	1.316	481.3858	3436.0554	166.9717
Mrps9	0.9236	1.316	49623.8027	5013.8455	1728.8724
Hnrnpa2b1	27402.8554	3387.8826	1807.5994	363.0231	11.4495
Hnrnpa2b1	2205.4054	2849.7985	5.242	0.938	94.4583
Ilf3	1439.825	947.4959	678.8327	36534.9403	1652.5425
Ilf2	0.8465	414.4379	1190.7308	18.7727	0.7439
Ilf2	0.8465	5.9939	0.3383	0.6498	0.7439
Ilf2	0.8465	0.7706	0.3383	1.4441	0.7439
Kif21a	17.9104	220.4947	6.7484	2913.6911	0.8364
Mrpl22	1.8811	0.7706	1.1276	0.6498	3.3063
Abcc5	20.8572	2620.4771	735.199	4321.2928	416.3766
Abcc5	80104.0355	609.186	0.803	1072.1914	262.0374
Ddx56	0.9236	1.316	34.9463	2.8141	62.9722
Ddx56	16.42	1.316	219.2883	18.7609	144.0727
Ddx56	0.9236	1.316	0.7863	0.8442	0.8587
Kif21a	13920.1667	12663.4687	2577.8936	678.6319	7304.2557
Stau2	26.6824	36.5546	6676.4982	3.7522	644.0336
Stau2	30.7874	2779.6136	16.5995	0.8442	0.8587
Syncrip	30284.1336	26.5446	37.5862	0.722	0.7439
Syncrip	1266.9336	226.057	0.3383	465.7063	19.0113
Syncrip	0.8465	263.7332	0.3383	251.2648	0.7439
Hnrnpr	0.9789	495.4084	1.1188	1719.0098	0.7323
Hnrnpr	0.9789	5723.3303	12.4306	0.9845	51172.812
Hnrnpr	0.9789	1.0226	2060.9894	0.8861	0.7323

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Cltc	7.5412	1.1983	7.8731	0.8298	0.8364
Ap3s1	0.9789	1.0226	1.2431	0.8861	0.7323
Ap3s1	1.0876	5074.5271	42895.429	19902.5107	12270.8322
Ap3s1	68403.8911	4851.8206	233.6948	4176.4259	54.5153
Anln	0.9386	0.5864	0.8922	500.356	13.5683
Ube2k	665.3436	17.5915	0.803	1505.8868	0.7632
Peli1	6.5986	46.1361	1.0123	287.6809	102.2224
Peli1	0.8484	10.7851	1.0123	93.1275	0.8364
Mrpl11	1.0262	42.4034	18.3468	209.1838	105.9077
Mrpl11	0.9236	1.316	13.9785	0.8442	1165.9393
Mrpl11	1479.8486	71.6471	0.7863	15.0087	0.8587
Peli1	32.0502	1062.3293	2387.8133	4958.8072	33.4546
Peli1	242491.9992	0.5992	4935.339	2496.0006	6869.3458
Caprin1	37.9712	43.8655	0.7863	2.8141	119.2655
Caprin1	28.7349	1.316	0.7863	8.4424	4.7706
Npepps	562.7642	0.5992	50.6131	59.0115	30999.4099
Hnrnpa1	9.4056	0.7706	0.3759	0.722	0.7439
Npepps	0.8484	0.5393	39.3657	24.8955	22.3031
Npepps	0.8484	26.9627	1.0123	1.8441	2259.1152
Npepps	2704.4734	198.3254	1096.617	4076.4014	0.8364
Hnrnpa1	189.993	2907.9152	11.6517	6.4982	0.7439
Hnrnpa1	7.5245	3.4251	83.4414	0.6498	0.7439
Hnrnpa1	0.8465	12.8441	0.3383	0.6498	0.7439
Ddx21	0.9236	1914.0001	13.9785	4.6902	0.8587
Ddx21	0.9236	1.316	0.8737	0.938	2108.6136
Stau1	54236.1436	2108.4707	5100.4183	16983.2878	65.8345
Stau1	0.9236	73.1092	0.7863	25.3272	7129.2132
Stau1	0.9236	1.316	0.7863	0.8442	0.8587
Zyx	1830.3287	210.644	8.269	85.921	0.7439
Zyx	1127.7308	17.1255	0.3383	0.6498	0.7439
Kif21a	7170.7664	6236.7658	202.4524	121866.0532	0.8364
Ilf3	70.8111	1.316	1065.8634	101.3088	7643.4859
Crbn	0.9386	0.5864	4292.5271	0.3614	0.7632
Crbn	1544.4732	13511.5501	0.8922	36.9444	52.5771
Dap3	25126.1055	1604.6623	18.0414	85.199	36.3694
Dap3	38898.7177	1131.9976	14021.9075	9620.9873	1540.7391
Dap3	0.8465	0.7706	0.3383	0.6498	0.7439
Dap3	0.8465	2.5688	1598.1652	197.1129	0.7439
Dap3	4.7028	7039.4495	0.3759	1042.6045	0.7439
Ddx21	0.9236	1.316	18913.8328	0.8442	0.8587
Stau1	48.2336	1.316	6.1156	31.8935	0.8587
Zyx	0.9406	381.8993	2974.5718	25.9929	0.8266
Hnrnpa1	60574.8511	19.6944	790.0619	265.7053	15162.724
Eps8	9.3857	4.5608	1872.7945	2674.0534	796.2884
Slc40a1	136.6144	5.8638	0.803	0.3614	4786.2106
Rpl18	1.0262	1.316	0.7863	3.7522	0.8587
Eps8	0.9386	731.6747	0.803	3.6141	5.0881
Eps8	9.3857	3.9092	8339.6905	20800.9149	0.848
Eps8	0.9386	846.345	17.8446	720.8178	29.6806

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Slc40a1	960.4725	719.2956	1597.0949	331.6967	0.7632
Slc40a1	181.4574	895.8618	1771.9723	1647.2394	3156.321
Slc40a1	0.9386	0.5864	820.8532	0.3614	6.7841
Mrpl37	26.6824	1634.7228	1.7473	838.6114	0.8587
Ict1	61.5748	5285.7987	37.5673	423.0579	775.7027
Irf6	0.9789	31.8152	1.1188	13307.0658	0.7323
Irf6	5.4381	649.9394	12840.7842	98672.7393	2014.6264
Irf6	0.9789	1.1363	7788.9984	0.8861	54.5153
Irf6	0.9789	69159.4647	2406.5594	441.0747	12396.1361
Mrps28	2549.1983	1.316	220.1619	250.4578	9091.8459
Mrps28	0.9236	1.316	0.8737	90.0522	0.8587
Mrpl4	1.0876	8975.3	944.7237	49119.7705	1205.033
Mrpl38	26072.5053	1.0226	476.091	79.7479	298.6138
Mrpl38	0.9789	3324.6902	1.1188	0.8861	19.5279
Msi2	5017.3231	928.4875	15442.7876	240.1393	112343.309
Msi2	550.0686	1.316	0.7863	2151.8731	0.8587
Slc19a2	746.1096	4083.7104	28845.1498	17069.9842	17560.4469
Numbl	30.4535	55.6766	124.3058	72.8561	85.4345
Numbl	26.103	1.0226	1.1188	3306.0911	0.7323
Numbl	0.9789	1.0226	2721.0529	5.9073	0.7323
Numbl	0.9789	47.7228	41.0209	190.0166	1.6273
Crot	0.9386	0.5864	0.803	0.3614	0.7632
Crot	15806.604	404.6038	613.8555	409.1996	62097.7747
Crot	4516.6195	291.8881	12.4912	95292.9191	20647.5292
Tmem50b	43576.0509	207.9122	2178.6125	30.4278	1088.204
Mov10	5.1312	780.8068	6502.6402	1536.5162	1392.0667
Ube2k	531.8578	171.3539	8.9223	20.8816	0.7632
Numb	3024.2892	5.8638	75.8397	7196.9343	2377.841
Numb	107.4144	7392.3256	94294.6239	227.2885	2050.5062
Ltb	0.9789	44.3141	34445.124	0.8861	11.3913
Ltb	164300.7235	6794.8214	63.3959	19803.072	2814.4558
Zcchc3	0.9427	156.3835	1.0123	0.8298	0.8364
Zcchc3	0.8484	0.5393	1.0123	0.8298	0.8364
Zcchc3	264.2972	0.7706	0.3383	3050.5569	0.7439
Zcchc3	0.8484	0.5393	1.0123	0.8298	0.8364
Zcchc3	0.8465	26.5446	0.3759	3387.7428	0.7439
Cltc	0.8484	7.19	1.0123	11.0646	1990.5491
Anln	214.8288	19474.406	939.5201	2318.2626	16309.0718
Mrpl39	796.6539	12.8441	252.9551	938.6329	0.7439
Ybx1	65.8392	3.4251	0.3383	192.7808	3.3063
Ybx1	17.8706	1.7126	25.5586	7570.4354	0.8266
Mycn	0.9386	0.5864	0.803	0.3614	0.7632
Mtmr9	26.3943	1940.7133	8.9979	4881.3547	8009.5903
Mtmr9	399.6852	2388.8928	28.1184	9402.1862	41083.1858
Mtmr9	17411.7558	0.5393	39.3657	504.3636	5277.4641
Mrpl22	251.1294	0.8563	0.3383	2137.1949	0.7439
Atp5a1	2053.5208	1.316	42101.603	8753.8272	25222.2631
Rabep1	2145.4797	898.7558	1741.0904	486.8446	205.3741
Rabep1	16.9678	6654.3877	39101.4264	11827.1886	30.6667

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Rabep1	773.9187	0.5393	2379.9401	0.9221	795.4762
Frmd6	105.3287	1894.6662	9353.2658	123.6835	3228.4025
Frmd6	0.9386	0.5864	0.803	0.3614	0.7632
Ttc3	0.8484	0.5393	1.0123	0.8298	22.3031
Ttc3	0.8484	0.5393	1.0123	0.8298	0.9293
Cct3	0.9236	1.316	11.3576	0.8442	0.8587
Cct3	0.9236	29.2437	137.1644	0.8442	442.7135
Frmd6	0.9386	0.5864	0.803	0.3614	0.7632
Ttc3	0.8484	0.5393	1.0123	0.8298	0.8364
4932438A13Rik	0.9789	1.1363	33153.5872	26396.5478	5.6956
4932438A13Rik	22.8401	7093.6572	7439.6993	128.975	47850.6312
4932438A13Rik	2.1752	257.9305	191.4309	17898.9683	14.6459
4932438A13Rik	0.9789	10.2263	64271.0462	145.7122	16822.4558
4932438A13Rik	0.9789	2.2725	1.1188	0.8861	11.3913
Ptcd3	463.6958	1775.0613	16.1621	33.9352	847.2412
Ptcd3	4625.6714	169570.1577	1100.5239	100020.0001	166817.2414
Sepp1	22.6237	0.5393	10327.3205	2746.7993	266.7076
Mapk6	129.3144	0.5864	0.803	1529.5794	13670.0415
Mapk6	15191.3176	31871.1783	84373.0064	18152.562	51269.4397
Mapk6	3.1286	0.5864	2976.4852	148.5808	2166.6846
Baz2b	1068.0266	1.1983	35778.958	42490.0994	7227.1243
Ybx1	12002.4793	126.7289	0.3383	8259.2475	961.3088
Mtmr9	9601.8702	18797.1772	4006.3075	3878.1598	8138.7623
Hnrnpc	32.9196	5856.0753	429.6103	1.4441	0.7439
Hnrnpc	3.7622	531.7477	6.3897	6.4982	0.8266
Pdia6	6148.4372	3658.0134	82458.1074	1711.922	2.4797
Snx14	21599.0234	8579.5225	1464.4055	5985.9756	9510.4011
Mrpl11	0.9236	2.9244	0.7863	0.8442	0.8587
Mrpl11	0.9236	13.1597	27.9571	187.6088	0.9541
Caprin1	0.9236	1.4622	5.242	0.8442	0.8587
Cct3	69.7848	1.316	5.242	0.8442	0.8587
Ptcd3	0.8465	0.7706	0.3383	10.8304	0.8266
Mrpl22	0.8465	0.7706	0.3759	3908.323	12.3987
Ppp2r5c	137.6274	1433.2159	906.5367	297.8235	7063.5684
Mrpl4	0.9789	1.0226	3.7292	7.8763	0.7323
Mov10	0.9236	1.316	3.4946	17.8228	345.3928
Tmem50b	0.8484	631.5257	8302.7968	274.7721	0.8364
Tmem50b	0.8484	214.503	1.0123	0.8298	63.192
Ube2k	0.9386	184.3846	366.7073	461.4037	10645.1632
Irf6	28.2782	23062.6237	1.1188	0.8861	1209.915
Clcn3	0.9789	1.0226	1162.2588	5.9073	480.8741
Clcn3	0.9789	65.9029	1.2431	0.8861	0.8137
Dst	0.8484	0.5393	871.6699	0.8298	8.3637
Smc4	6503.3676	538.6543	108270.4044	82947.9915	1419.9622
Ilf3	812.7879	593.6471	3134.6867	4.6902	3015.0313
Slc19a2	85.9222	1.1363	1.1188	0.8861	0.8137
Clcn3	329.5499	80456.1393	1.1188	91021.8657	11855.8647
Smc4	0.8484	3.595	1.0123	0.8298	0.9293
Smc4	31.1076	0.5393	121.4714	0.9221	5.5758

Figure 16 (cont'd)

Symbol	Spleen.1	Spleen.2	Spleen.3	Spleen.4	Spleen.5
Dst	0.9427	6.5909	18500.7727	3.6882	227.6772
Dst	22.6237	0.5393	62748.9883	1653.2431	3161.4603
Cltc	582.56	0.5393	1.0123	0.8298	0.8364
Cltc	82.0109	95.8673	1.0123	15.6749	38938.3738
Rpl14	34.8007	333.9479	0.3383	13.7185	3.3063
Mylk	1.0429	0.5864	35.6893	0.3614	2179.4049
Rpl14	1417.4231	103.6095	7231.2089	13488.1548	1028.2615

Figure 17

Differentially Expressed Upregulated Genes (n=225)	Differentially Expressed Downregulated Genes (n=57)
Anxa1	Slc25a23
Clec4a3	4922501C03Rik
Ppbp	Ccar1
3110043O21Rik	Kif15
Clec4n	Nefh
Klra2	Cbs
Cmklr1	Rock1
Trim30b	Brca2
Slfn1	Uaca
Slfn1	Chd5
Thbs1	Cenpf
Clec4b2	Sned1
S100a6	Slc22a3
Chi3l3	Bod1l
Arg2	Tmem86b
Slc19a2	Sp9
Ifitm6	Ccdc176
Fam214b	Leprel4
Il18	Ccdc102a
Jag1	Slc7a3
Cd38	Arhgdig
C5ar1	Tespa1
Clec4a1	Eltd1
Socs1	Hirip3
P2ry13	Golga4
Abcg3	Gata2
Naaa	Purb
Mgst1	Cyp26a1
Ptplad2	Zfp820
I830012O16Rik	Kcnip3
Lgmn	Soat2
Id3	Ptprf
Serpinb10	Myo6
Derl3	Prpf40b
Mpeg1	Chdh

Figure 17 (cont'd)

Differentially Expressed Upregulated Genes (n=225)	Differentially Expressed Downregulated Genes (n=57)
Mgl2	Mss51
Dusp6	Slc6a9
6430548M08Rik	Eml5
Gpr34	Cenpe
Lrg1	Gm16586
Ly6a	Pdgfrb
Clec4a2	Gm13776
P2ry12	Hoxa3
Gm19705	Armcx4
Acvrl1	Sltm
1-Mar	9430002A10Rik
Rgag4	Kmt2a
Cxcl3	Cep290
1100001G20Rik	Syncrip
Sirpb1c	Nkx6-1
Sirpb1c	Gm6484
Sirpb1c	Dlk1
Sirpb1c	Ccdc40
Mmp8	Epx
Gm13986	Angpt1
P2ry6	Hspa2
Ltc4s	Prg3
Serpinb2	
Abcg1	
Msr1	
Camk1d	
Adrb2	
Rnase4	
AA467197	
Clec4d	
Adtrp	
Hs3st3b1	
Hs3st3b1	
Dse	
Crispld2	
Ptafr	
Tgfbi	

Figure 17 (cont'd)

Differentially Expressed Upregulated Genes (n=225)	Differentially Expressed Downregulated Genes (n=57)
4933430I17Rik	
Cyp4v3	
Ifit3	
Ms4a7	
Tmem243	
Ifi202b	
Kmo	
Pgap1	
Sdcbp	
Raet1e	
Tbc1d9	
D630023F18Rik	
Tlr4	
Mgst2	
Slc40a1	
Xdh	
Irf5	
9030619P08Rik	
Ms4a4c	
Slc11a1	
Rbpms	
Dlg2	
Cd274	
Hsd11b1	
Fbxo8	
C920021L13Rik	
Mapre3	
Mylip	
Cxcr2	
C3ar1	
KCTD12	
Abcc3	
Oasl2	
Il1f9	
Gm7676	
Gm7676	
Gm7676	

Figure 17 (cont'd)

Differentially Expressed Upregulated Genes (n=225)	Differentially Expressed Downregulated Genes (n=57)
Hspb11	
Fcgrt	
S100a10	
S100a8	
Fcnb	
Fcnb	
Gsap	
Gm1673	
Trp53inp1	
Ifi204	
Kcnn3	
Sez6	
Ly96	
Creb5	
Klf6	
Agpat9	
Gm7665	
Sell	
Gm11965	
Lrrc57	
Ifi27l2a	
Ifi27l2a	
Cd200r4	
Cd200r4	
Pnpla1	
Ankrd22	
Gm15830	
2210408F21Rik	
Smox	
Fcgr4	
Fcgr4	
Fcgr1	
Fcgr1	
Tlr3	
Ces2g	
Ube2l6	
Rab32	

Figure 17 (cont'd)

Differentially Expressed Upregulated Genes (n=225)	Differentially Expressed Downregulated Genes (n=57)
Cd52	
Lyz2	
Spint1	
Gm6977	
Tmem86a	
Rnase6	
Rbm47	
Gbp9	
Gm12164	
Tarm1	
Pde8b	
Ccl2	
Tlr8	
Plxdc1	
Fn1	
Ctss	
Gm22767	
Gm13392	
2010012P19Rik	
Ear6	
Ear6	
Bst1	
Itm2c	
Ceacam10	
Oas1g	
H2-T23	
Clec7a	
Tnfrsf11a	
Gm5548	
Lyz1	
Irf4	
Ifit2	
Kcnk13	
Mctp1	
Lpar6	
Zfp36l1	
5031414D18Rik	

Figure 17 (cont'd)

Differentially Expressed Upregulated Genes (n=225)	Differentially Expressed Downregulated Genes (n=57)
Smug1	
Tlr7	
9530053A07Rik	
St3gal5	
Zc3h12d	
Gad1-ps	
Dfna5	
Prickle1	
Ccdc109b	
Fpr2	
Kcnj2	
A530064D06Rik	
Ednrb	
Pglyrp1	
Calcrl	
Ccr1	
Gbp2	
Rcbtb2	
Fam89a	
Adora2b	
Sirpb1b	
Sirpb1b	
Sirpb1b	
Sirpb1b	
Gm25820	
Gm25820	
Adam8	
Pfn1	
Ahrr	
Stard3nl	
Cib2	
Slc7a8	
Lsp1	
Lsp1	
Samd5	
Ptplb	
Cxcl16	

Figure 17 (cont'd)

Differentially Expressed Upregulated Genes (n=225)	Differentially Expressed Downregulated Genes (n=57)
Ptprj	
Slc9a9	
Rdh12	
Ctsl	
2310058D17Rik	

Figure 18

Homo sapiens synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP), transcript variant 7, mRNA

NCBI Reference Sequence: NM_001253771.1 (SEQ ID NO: 5)

```
   1 ctccactcgc gccggacaca gggagcagcg agcacgcgtt tcccgcaacc cgataccatc
  61 ggacaggatt tctccgcctc agcccaacgg ggagggctag ttgcacatag tgatttagat
 121 gaaagagcta ttgaagcttt aaaagaattc aatgaagacg gtgcattggc agttcttcaa
 181 cagtttaaag acagtgatct ctctcatgtt cagaacaaaa gtgccttttt atgtggagtc
 241 atgaagactt acaggcagag agaaaaacaa gggaccaaag tagcagattc tagtaaagga
 301 ccagatgagg caaaaattaa ggcactcttg gaaagaacag gctacacact tgatgtgacc
 361 actggacaga ggaagtatgg aggaccacct ccagattccg tttattcaga tatttgtggg
 421 aaagatccca agagatctat ttgaggatga acttgttcca ttatttgaga aagctggacc
 481 tatatgggat cttcgtctaa tgatggatcc actcactggt ctcaatagag gttatgcgtt
 541 tgtcactttt tgtacaaaag aagcagctca ggaggctgtt aaactgtata ataatcatga
 601 aattcgttct ggaaaacata ttggtgtctg catctcagtt gccaacaata ggctttttgt
 661 gggctctatt cctaagagta aaaccaagga acagattctt gaagaattta gcaaagtaac
 721 agagggtctt acagacgtca ttttatacca ccaaccggat gacaagaaaa aaaacagagg
 781 cttttgcttt cttgaatatg aagatcacaa aacagctgcc caggcaaggc gtaggttaat
 841 gagtggtaaa gtcaaggtct gggggaatgt tggaactgtt gaatgggctg atcctataga
 901 agatcctgat cctgaggtta tggcaaaggt aaaagtgctg tttgtacgca accttgccaa
 961 tactgtaaca gaagagattt tagaaaaggc atttagtcag tttgggaaac tggaacgagt
1021 gaagaagtta aaagattatg cgttcattca ttttgatgag cgagatggtg ctgtcaaggc
1081 tatggaagaa atgaatggca aagacttgga gggagaaaat attgaaattg tttttgccaa
1141 gccaccagat cagaaaagga aagaaagaaa agctcagagg caagcagcaa aaaatcaaat
1201 gtatgacgat tactactatt atggtccacc tcatatgccc cctccaacaa gaggtcgagg
1261 gcgtggaggt agaggtggtt atggatatcc tccagattat tatggatatg aagattatta
1321 tgattattat ggttatgatt accataacta tcgtggtgga tatgaagatc catactatgg
1381 ttatgaagat tttcaagttg gagctagagg aaggggtggt agaggagcaa ggggtgctgc
1441 tccatccaga ggtcgtgggg ctgctcctcc ccgcggtaga gccggttatt cacagagagg
1501 aggtcctgga tcagcaagag gcgttcgagg tgcgagagga ggtgcccaac aacaaagagg
1561 ccgcgggcag ggaaaagggg tcgaggccgg tcctgacctg ttacaatgaa gactgacttg
1621 ctatgtggga ttacaccaga agcttgcagt ggagtaatgg taaggaaatc aagcaacctt
1681 aaatatgtcg gctgtatagg agcatattct attgcagaag accttcctat gaagatcatg
1741 gaatcaaata cgggacattg aactaatact tggactttga tatgaatttc tttaacaatt
1801 ttctctgcag tgcaagttat taaactaaag ctactctatt ttcaaaatgt gttccaacag
1861 aaatccttca taactcctag catggtatct taataaagaa taaagttctt ttaaaaatct
1921 gctctaagta gatttttccc ctttttttaaa ttaaggatcc caacagtggt attttgaaat
1981 attctcttga atttgtgcat ttaaatttta ttgcagtggt atagatgaat gccactgatg
2041 gtatccttaa attttatttc tgctcaccaa ggttaatcat gattgtctat atctttttta
2101 tagtgatcac ttttgaattg tgttcagata tgcagtttca ggtgtaatca tcagagctgg
2161 ttagtcaggc attccagata gtggttcttt tcagaacctt tttaaaaggg ttggttaact
2221 acctcagtag cagaggattg aactataccc tgtctgtact gtacatagaa aatctttgta
2281 gataaaagca aggcttgtta aatatgatat gagggtaaga ttttaatata ccaaatgtaa
2341 cattcttagt tgcctttagt ttcagaggct tgtaagactt cctcatgacc atcataacag
2401 gccttgcttt tgtcgtattt tgtggctgaa aaagcagcct tgcttcttca gatattgtag
2461 ttatttggat gtataatagt ttagcaagat gttacttttg taagacatca gatgttcaaa
2521 aaagtgcatc cgaacttgta ctaaatactg cagtgtccct ttataaaaag tcagactaaa
2581 actgacaatt gtacagcgaa gcctgacatt tggatatttt gaagtttttt cataaatcat
2641 agaaattagt atatggctgt agtttagctt tttaggtaaa aggtatgttt cattagtgca
2701 tttcttcctg ctgatcactg taaacatgtg aatcagcttt ccatttctta tgcaggtcat
2761 gataacttgt agagtagagt acaatcattt gtgctatgtt tttaattttc taaagcacct
2821 tgatgacagt gagtgtccag tggtgaagca tcctctattg aaccaccctc aaaaatttttt
2881 ttgccaagtc ctaagttgat agcttaaagt aaaaagtgaa aattatagtt tcattaggac
```

Figure 18 (cont'd)

```
2941 ttggtgtaaa gaaatcccct ccccccttcc ccaaagggat actgcagtta tatcacatac
3001 ccaataggca ccacgatgaa gatcagagct tatacttaat taaggtttta tacacaccag
3061 ttccccagta aatgcaaatt taacaagaaa atcagacatg tcatatgttc aaaatgctca
3121 tggcaaacaa tcattttgca ttcctgcaaa taaaattgtt ttatactgta agctggaggc
3181 gagtgtaact tatttttgta ataaagtttt tatttttttt atgtgtcatt aatataaatg
3241 tgtgttagtg tagaaatctt ctggtttaaa aacttagaat tgcacacatt tcagtatgtt
3301 tatttgtact tacataattt tagaatagtg gttgccaata gcctgtatgt ttcacattaa
3361 ttggtttttt gttatctaaa taaatcattt tagtatgttg tatgtcagtt actgggatag
3421 ctgggacata gagtgtaatt taaaatttgt caataagtat tcattggaat atatgtaaat
3481 gtgccttgcc ggttattgaa acttatctac aaaatgagta tggggtgaca aaaattagtt
3541 cctggtgctt aatgaaactt tctgccactg attttatata ttaccccgtg ctttttaaa
3601 gtacatctct ctcaaaactt agtgtaagtt tgagggctac acaaaacatt tacatttcat
3661 tctaacataa tgaatataat aggttgtgga aagtgggtaa actaaatgta gccttcagta
3721 aaattgaatc tcagtgtaat ccttggtgct ggcatttctc agttccgagg agttaaatga
3781 tcccatctaa gaggtcattg ccatgcctat tggcacttta ctgtcatagc atttttaagg
3841 gacactgtca aggtgtttaa gttctcagaa ttacttgttg ggattttagg acaggtttgt
3901 ttacttaaag taagaactgc attgtcaaag ttgaaagagg aacacttttg tgagttcaca
3961 aatgtgttct taagaaaaca ttaaaatatg gagctctggg ttttcaagac tatttggcat
4021 tcttaatttg gggacttggg agggaaactg ataaaaagaa attgaagaat tgatggttat
4081 acttaaagaa gggtaatgta aacagtggtg atgaaatata tacacatcaa gtgaaattac
4141 ttgacagtgt tcatttgaat gactttgaat tcaagccatt ataattactt ttaaaattaa
4201 atatcatttg cactgttctg ataatgggtg cagtttttga gcaatataat cagagctaaa
4261 tatgcatgta gtgattagtg atgtgaacaa ttaacgttct gagaagaaat actaactgtg
4321 gtattttcaa acttaaattt ctgtagtaaa atcagtatca aagtcttatc agatcaagga
4381 aaaacaggca atgcatataa acatactttt gaatgttgtg tggcctataa agcaataatg
4441 caatttatat ggaatgtcat gggatatgag aaatggaaat gcaaaaataa ctaatccttt
4501 agtaaaaatg tcaacatgtt aaaggggaa tgttaactaa tgtaggttat tgctatttgt
4561 gatttgttta tgggttcttg gctttgacag cttcaaagaa tggacagtga taagttaaaa
4621 gaaattttgt atattgtcaa ggaaagggtc ttaaatccga gtcaagtccc ttccttgggg
4681 taaaaaatgt attcttaaag cattctgatg ttaaaaagaa aacttaagtt atctaaccaa
4741 aacagacgca agattttgtt tctgcagact acttggcaat caaaagtgat cataaattta
4801 ggttatcagt tttcagaaag ttgctttgtg agaaaatttt gttagatata ttctcccaag
4861 catgcttttt gtggaaggtt ttcagccatt gccactgaat cagatgttaa aaatgaaggg
4921 aaaattgagt gtgcacacac acaactgttg tacactcatg attgcagttt ttagcttaag
4981 aaacttttct accagttact gtgaatctga cttaaaatgt aaagtttcct catgataaaa
5041 taggaacaac atagaaatgg attgatgggg tgatctgagt tattgtatat aaaagttttt
5101 aaagaataga atgaacatca agctagatag gcaaaaattg acacattcag aacagctttt
5161 ttgactgcga agccaaaagt tgtcagaaac agcaaaagat cccttattat tacagagtat
5221 tttacgtagt ctctatttta aggagagaaa ttaaatagaa gggcttcatg catttagggg
5281 agggtgctaa aacttctcaa gttcgtcaaa cttacaggaa tacccaccat gatcattttc
5341 tctctaatta tgtataccac aaaattttca tctggccata ggaattcact ggtgggtgta
5401 aaattaatga ctaaagaaat taagtgacaa atacataaaa gaaacagact tgtggggata
5461 ttgttttaag gtgtattaat tactcagtga tgataccact caatagggca tgccactact
5521 tttcttaaga tgctaattat gaagcagtgc tcacaggcat tttttaacta gcaaattagt
5581 agatggactt ttggggtctg tcacttttta aaagtattta agacttaaat tctattagca
5641 ccacagtctg ccttcagtaa tacacctaaa atatttttca ggaccagaag cattcagttt
5701 gaaaatttgc agatgcaaac cagtattatt actaacgctc tgggtcaaag attaggtttt
5761 taatattaac agtagtctgg taaatattta gaagtctggc attgagaaac aaaagcttgt
5821 acctgactag tatttttatt taaaaaaatt agttctgtta gcttatttaa attgtgtttt
5881 atttatccgt agaatttata tttatttcat tcctttcatc tcactgaaaa ctgtctgcag
5941 gccctttgat ttggattaga tgtgtgaagt actgtctttt gccaaaaacc tcaaattacc
6001 tgttcttttc aacgtagtgg gtttgtgctt gtttggagat cagttcaaaa actatctgta
6061 ctatctgtac tgcctctgat gttaagattt tatgtatagc ataaggaagc tagctctgac
6121 tatattttcc taagaataaa gacctatttt tgtagcatgt cttaggatct ccaggagtcc
6181 aagaattatt gtgggtgtcc tccaattcat cactcttcac ttaacagctt ttaagtagac
6241 acttggaatc tttagaggtc tgtcgccctt tgattatcca tacattcgaa gtaactagcc
6301 aatggtgaaa aattcctcaa gatatcctca gttgcaatca cattactgga agatgaatag
```

Figure 18 (cont'd)

```
6361 aataaatgta ttaggctggt cttaattttt gatggaaata ttctgttgtc ccgtacttgc
6421 cattggattt gataaagtta gtggtaattt ggaaagaatc ggggacttgc caatatattt
6481 gtgggtttta gcttataccc ctaggatttc ttggttgcgg gacgagcagt tttggccact
6541 tccatcagga caagactttt taggtcactt agtgcaggtt ttagtttcta ttttggatta
6601 acaacattta tattgattat cgaaaagaag ctttcatcat ttcagaacag tcctggaagt
6661 ttgactttga gtgtgggaga agtcctaata aaccattttg gaaattaaaa aaaaaa
```

Figure 19

Homo sapiens synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP), transcript variant 6, mRNA

NCBI Reference Sequence: NM_001159677.1 (SEQ ID NO: 6)

```
   1 agcgcgggag agagaaagag aggagccgac tcggcaggga ctgggggacc gggccgagag
  61 tgcgagcgag cgagggaggg agtgagggag cgtgcgagcc agaaggggaa aggcggccac
 121 tcgtgcctga gcgaccgcag aggggagtgg gagcagtggg gtaaaggagc gggggggcggg
 181 aataagaaag gccgagagaa ggcggacaga ggctagtggt ggtggtggtg gtagggggag
 241 aaggaggagc tggaggaggg caggggctga gggagtgagt gaagcggacg cgcgagggag
 301 gggagggaag ggaagggaag ggaaggggggg gtcacgcggg ggcgcgcgcg cgcaccggga
 361 gcgcgctcgg aggcgagtgg aactggatcg ggtttgctgc cagcggcgtg agcttcggcc
 421 gccattttac aacagctcca ctcgcgccgg acacagggag cagcgagcac gcgtttcccg
 481 caacccgata ccatcggaca ggatttctcc gcctcagccc aacggggaga tctctggaaa
 541 catggctaca gaacatgtta atggaaatgg tactgaagag cccatggata ctacttctgc
 601 agttatccat tcagaaaatt ttcagacatt gcttgatgct ggtttaccac agaaagttgc
 661 tgaaaaacta gatgaaattt acgttgcagg gctagttgca catagtgatt tagatgaaag
 721 agctattgaa gctttaaaag aattcaatga agacggtgca ttggcagttc ttcaacagtt
 781 taaagacagt gatctctctc atgttcagaa caaaagtgcc tttttatgtg gagtcatgaa
 841 gacttacagg cagagagaaa aacaagggac caaagtagca gattctagta aaggaccaga
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 961 acagaggaag tatggaggac cacctccaga ttccgtttat tcaggtcagc agccttctgt
1021 tggcactgag atatttgtgg gaaagatccc aagagatcta tttgaggatg aacttgttcc
1081 attatttgag aaagctggac ctatatggga tcttcgtcta atgatggatc cactcactgg
1141 tctcaataga ggttatgcgt ttgtcacttt ttgtacaaaa gaagcagctc aggaggctgt
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1621 gtttgggaaa ctggaacgag tgaagaagtt aaaagattat gcgttcattc attttgatga
1681 gcgagatggt gctgtcaagg ctatggaaga aatgaatggc aaagacttgg agggagaaaa
1741 tattgaaatt gtttttgcca agccaccaga tcagaaaagg aaagaaagaa aagctcagag
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2101 agccggttat tcacagagag gaggtcctgg atcagcaaga ggcgttcgag gtgcgagagg
2161 aggtgcccaa caacaaagag gccgcgggca gggaaaaggg gtcgaggccg gtcctgacct
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2581 ccaacagtgg tattttgaaa tattctcttg aatttgtgca tttaaatttt attgcagtgg
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2761 aggtgtaatc atcagagctg gttagtcagg cattccagat agtggttctt ttcagaacct
2821 ttttaaaagg gttggttaac tacctcagta gcagaggatt gaactatacc ctgtctgtac
2881 tgtacataga aaatctttgt agataaaagc aaggcttgtt aaatatgata tgagggtaag
```

Figure 19 (cont'd)

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2941 attttaatat accaaatgta acattcttag ttgcctttag tttcagaggc ttgtaagact
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3061 ttgcttcttc agatattgta gttatttgga tgtataatag tttagcaaga tgttactttt
3121 gtaagacatc agatgttcaa aaaagtgcat ccgaacttgt actaaatact gcagtgtccc
3181 tttataaaaa gtcagactaa aactgacaat tgtacagcga agcctgacat ttggatattt
3241 tgaagttttt tcataaatca tagaaattag tatatggctg tagtttagct ttttaggtaa
3301 aaggtatgtt tcattagtgc atttcttcct gctgatcact gtaaacatgt gaatcagctt
3361 tccatttctt atgcaggtca tgataacttg tagagtagag tacaatcatt tgtgctatgt
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3481 gaaccaccct caaaaatttt tttgccaagt cctaagttga tagcttaaag taaaaagtga
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3601 tactgcagtt atatcacata cccaataggc accacgatga agatcagagc ttatacttaa
3661 ttaaggtttt atacacacca gttccccagt aaatgcaaat ttaacaagaa aatcagacat
3721 gtcatatgtt caaaatgctc atggcaaaca atcattttgc attcctgcaa ataaaattgt
3781 tttatactgt aagctggagg cgagtgtaac ttatttttgt aataaagttt ttatttttt
3841 tatgtgtcat taatataaat gtgtgttagt gtagaaatct tctggtttaa aaacttagaa
3901 ttgcacacat ttcagtatgt ttatttgtac ttacataatt ttagaatagt ggttgccaat
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4021 gtatgtcagt tactgggata gctgggacat agagtgtaat ttaaaatttg tcaataagta
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4261 cacaaaacat ttacatttca ttctaacata atgaatataa taggttgtgg aaagtgggta
4321 aactaaatgt agccttcagt aaaattgaat ctcagtgtaa tccttggtgc tggcatttct
4381 cagttccgag gagttaaatg atcccatcta agaggtcatt gccatgccta ttggcacttt
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5641 taaagtttcc tcatgataaa ataggaacaa catagaaatg gattgatggg gtgatctgag
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5941 atacccacca tgatcatttt ctctctaatt atgtatacca caaaattttc atctggccat
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6061 agaaacagac ttgtggggat attgttttaa ggtgtattaa ttactcagtg atgataccac
6121 tcaatagggc atgccactac ttttcttaag atgctaatta tgaagcagtg ctcacaggca
6181 ttttttaact agcaaattag tagatggact tttggggtct gtcacttttt aaaagtattt
6241 aagacttaaa ttctattagc accacagtct gccttcagta atacacctaa aatatttttc
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Figure 19 (cont'd)

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6481 agcttattta aattgtgttt tatttatccg tagaatttat atttatttca ttcctttcat
6541 ctcactgaaa actgtctgca ggcccctttga tttggattag atgtgtgaag tactgtcttt
6601 tgccaaaaac ctcaaattac ctgttctttt caacgtagtg ggtttgtgct tgtttggaga
6661 tcagttcaaa aactatctgt actatctgta ctgcctctga tgttaagatt ttatgtatag
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6781 tcttaggatc tccaggagtc caagaattat tgtgggtgtc ctccaattca tcactcttca
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6901 atacattcga agtaactagc caatggtgaa aaattcctca agatatcctc agttgcaatc
6961 acattactgg aagatgaata gaataaatgt attaggctgg tcttaatttt tgatggaaat
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7141 ggacgagcag ttttggccac ttccatcagg acaagacttt ttaggtcact tagtgcaggt
7201 tttagtttct attttggatt aacaacattt atattgatta tcgaaaagaa gctttcatca
7261 tttcagaaca gtcctggaag tttgactttg agtgtgggag aagtcctaat aaaccatttt
7321 ggaaattaaa aaaaaaa
```

Figure 20

Homo sapiens synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP), transcript variant 2, mRNA

NCBI Reference Sequence: NM_001159673.1 (SEQ ID NO: 7)

```
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  61 cgagcacgcg tttcccgcaa cccgatacca tcggacagga tttctccgcc tcagcccaac
 121 ggggagggct agttgcacat agtgatttag atgaaagagc tattgaagct ttaaaagaat
 181 tcaatgaaga cggtgcattg gcagttcttc aacagtttaa agacagtgat ctctctcatg
 241 ttcagaacaa aagtgccttt ttatgtggag tcatgaagac ttacaggcag agagaaaaac
 301 aagggaccaa agtagcagat tctagtaaag gaccagatga ggcaaaaatt aaggcactct
 361 tggaaagaac aggctacaca cttgatgtga ccactggaca gaggaagtat ggaggaccac
 421 ctccagattc cgtttattca ggtcagcagc cttctgttgg cactgagata tttgtgggaa
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 541 tatgggatct tcgtctaatg atggatccac tcactggtct caatagaggt tatgcgtttg
 601 tcacttttg tacaaaagaa gcagctcagg aggctgttaa actgtataat aatcatgaaa
 661 ttcgttctgg aaaacatatt ggtgtctgca tctcagttgc caacaatagg ctttttgtgg
 721 gctctattcc taagagtaaa accaaggaac agattcttga agaatttagc aaagtaacag
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2701 aaattagtat atggctgtag tttagctttt taggtaaaag gtatgtttca ttagtgcatt
2761 tcttcctgct gatcactgta aacatgtgaa tcagctttcc atttcttatg caggtcatga
2821 taacttgtag agtagagtac aatcatttgt gctatgtttt taattttcta aagcaccttg
2881 atgacagtga gtgtccagtg gtgaagcatc ctctattgaa ccaccctcaa aaatttttt
```

Figure 20 (cont'd)

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3061 aataggcacc acgatgaaga tcagagctta tacttaatta aggttttata cacaccagtt
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3361 tttgtactta cataatttta gaatagtggt tgccaatagc ctgtatgttt cacattaatt
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Figure 20 (cont'd)

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6661 aacatttata ttgattatcg aaaagaagct ttcatcattt cagaacagtc ctggaagttt
6721 gactttgagt gtgggagaag tcctaataaa ccattttgga aattaaaaaa aaaa
```

Figure 21

Homo sapiens synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP), transcript variant 5, mRNA

NCBI Reference Sequence: NM_001159676.1 (SEQ ID NO: 8)

```
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 121 cagaaagttg ctgaaaaact agatgaaatt tacgttgcag ggctagttgc acatagtgat
 181 ttagatgaaa gagctattga agctttaaaa gaattcaatg aagacggtgc attggcagtt
 241 cttcaacagt ttaaagacag tgatctctct catgttcaga acaaaagtgc ctttttatgt
 301 ggagtcatga agacttacag gcagagagaa aaacaaggga ccaaagtagc agattctagt
 361 aaaggaccag atgaggcaaa aattaaggca ctcttggaaa gaacaggcta cacacttgat
 421 gtgaccactg gacagaggaa gtatggagga ccacctccag attccgttta ttcaggtcag
 481 cagccttctg ttggcactga gatatttgtg ggaaagatcc caagagatct atttgaggat
 541 gaacttgttc cattatttga gaaagctgga cctatatggg atcttcgtct aatgatggat
 601 ccactcactg gtctcaatag aggttatgcg tttgtcactt tttgtacaaa agaagcagct
 661 caggaggctg ttaaactgta taataatcat gaaattcgtt ctggaaaaca tattggtgtc
 721 tgcatctcag ttgccaacaa taggcttttt gtgggctcta ttcctaagag taaaaccaag
 781 gaacagattc ttgaagaatt tagcaaagta acagagggtc ttacagacgt cattttatac
 841 caccaaccgg atgacaagaa aaaaaacaga ggcttttgct ttcttgaata tgaagatcac
 901 aaaacagctg cccaggcaag gcgtaggtta atgagtggta aagtcaaggt ctgggggaat
 961 gttggaactg ttgaatgggc tgatcctata gaagatcctg atcctgaggt tatggcaaag
1021 gtaaaagtgc tgtttgtacg caaccttgcc aatactgtaa cagaagagat tttagaaaag
1081 gcatttagtc agtttgggaa actggaacga gtgaagaagt taaaagatta tgcgttcatt
1141 cattttgatg agcgagatgg tgctgtcaag gctatggaag aaatgaatgg caaagacttg
1201 gagggagaaa atattgaaat tgtttttgcc aagccaccag atcagaaaag gaaagaaaga
1261 aaagctcaga ggcaagcagc aaaaaatcaa atgtatgacg attactacta ttatggtcca
1321 cctcatatgc cccctccaac aagaggtcga gggcgtggag gtagaggtgg ttatggatat
1381 cctccagatt attatggata tgaagattat tatgattatt atggttatga ttaccataac
1441 tatcgtggtg gatatgaaga tccatactat ggttatgaag attttcaagt tggagctaga
1501 ggaaggggtg gtagaggagc aaggggtgct gctccatcca gaggtcgtgg ggctgctcct
1561 ccccgcggta gagccggtta ttcacagaga ggaggtcctg gatcagcaag aggcgttcga
1621 ggtgcgagag gaggtgccca acaacaaaga ggccgcgggg gaaaaggggt cgaggccggt
1681 cctgacctgt tacaatgaag actgacttgc tatgtgggat tacaccagaa gcttgcagtg
1741 gagtaatggt aaggaaatca agcaacctta aatatgtcgg ctgtatagga gcatattcta
1801 ttgcagaaga ccttcctatg aagatcatgg aatcaaatac gggacattga actaatactt
1861 ggactttgat atgaatttct ttaacaattt tctctgcagt gcaagttatt aaactaaagc
1921 tactctattt tcaaaatgtg ttccaacaga aatccttcat aactcctagc atggtatctt
1981 aataaagaat aaagttcttt taaaaatctg ctctaagtag atttttcccc ttttttaaat
2041 taaggatccc aacagtggta ttttgaaata ttctcttgaa tttgtgcatt taaattttat
2101 tgcagtggta tagatgaatg ccactgatgg tatccttaaa ttttatttct gctcaccaag
2161 gttaatcatg attgtctata tctttttttat agtgatcact tttgaattgt gttcagatat
2221 gcagtttcag gtgtaatcat cagagctggt tagtcaggca ttccagatag tggttctttt
2281 cagaaccttt ttaaaagggt tggttaacta cctcagtagc agaggattga actataccct
2341 gtctgtactg tacatagaaa atctttgtag ataaaagcaa ggcttgttaa atatgatatg
2401 agggtaagat tttaatatac caaatgtaac attcttagtt gcctttagtt tcagaggctt
2461 gtaagacttc ctcatgacca tcataacagg ccttgctttt gtcgtatttt gtggctgaaa
2521 aagcagcctt gcttcttcag atattgtagt tatttggatg tataatagtt tagcaagatg
2581 ttacttttgt aagacatcag atgttcaaaa aagtgcatcc gaacttgtac taaatactgc
2641 agtgtccctt tataaaaagt cagactaaaa ctgacaattg tacagcgaag cctgacattt
2701 ggatattttg aagtttttc ataaatcata gaaattagta tatggctgta gtttagcttt
2761 ttaggtaaaa ggtatgtttc attagtgcat ttcttcctgc tgatcactgt aaacatgtga
2821 atcagctttc catttcttat gcaggtcatg ataacttgta gagtagagta caatcatttg
2881 tgctatgttt ttaatttttct aaagcacctt gatgacagtg agtgtccagt ggtgaagcat
```

Figure 21 (cont'd)

```
2941 cctctattga accaccctca aaaatttttt tgccaagtcc taagttgata gcttaaagta
3001 aaaagtgaaa attatagttt cattaggact tggtgtaaag aaatcccctc ccccttccc
3061 caaagggata ctgcagttat atcacatacc caataggcac cacgatgaag atcagagctt
3121 atacttaatt aaggttttat acacaccagt tccccagtaa atgcaaattt aacaagaaaa
3181 tcagacatgt catatgttca aaatgctcat ggcaaacaat cattttgcat tcctgcaaat
3241 aaaattgttt tatactgtaa gctggaggcg agtgtaactt atttttgtaa taaagttttt
3301 atttttttta tgtgtcatta atataaatgt gtgttagtgt agaaatcttc tggtttaaaa
3361 acttagaatt gcacacattt cagtatgttt atttgtactt acataatttt agaatagtgg
3421 ttgccaatag cctgtatgtt tcacattaat tggtttttg ttatctaaat aaatcatttt
3481 agtatgttgt atgtcagtta ctgggatagc tgggacatag agtgtaattt aaaatttgtc
3541 aataagtatt cattggaata tatgtaaatg tgccttgccg gttattgaaa cttatctaca
3601 aaatgagtat ggggtgacaa aaattagttc ctggtgctta atgaaacttt ctgccactga
3661 ttttatatat taccccgtgc ttttttaaag tacatctctc tcaaaactta gtgtaagttt
3721 gagggctaca caaaacattt acatttcatt ctaacataat gaatataata ggttgtggaa
3781 agtgggtaaa ctaaatgtag ccttcagtaa aattgaatct cagtgtaatc cttggtgctg
3841 gcatttctca gttccgagga gttaaatgat cccatctaag aggtcattgc catgcctatt
3901 ggcactttac tgtcatagca tttttaaggg acactgtcaa ggtgtttaag ttctcagaat
3961 tacttgttgg gattttagga caggtttgtt tacttaaagt aagaactgca ttgtcaaagt
4021 tgaaagagga acacttttgt gagttcacaa atgtgttctt aagaaaacat taaaatatgg
4081 agctctgggt tttcaagact atttggcatt cttaatttgg ggacttggga gggaaactga
4141 taaaaagaaa ttgaagaatt gatggttata cttaaagaag ggtaatgtaa acagtggtga
4201 tgaaatatat acacatcaag tgaaattact tgacagtgtt catttgaatg actttgaatt
4261 caagccatta taattacttt taaaattaaa tatcatttgc actgttctga taatgggtgc
4321 agtttttgag caatataatc agagctaaat atgcatgtag tgattagtga tgtgaacaat
4381 taacgttctg agaagaaata ctaactgtgg tattttcaaa cttaaatttc tgtagtaaaa
4441 tcagtatcaa agtcttatca gatcaaggaa aaacaggcaa tgcatataaa catacttttg
4501 aatgttgtgt ggcctataaa gcaataatgc aatttatatg gaatgtcatg ggatatgaga
4561 aatggaaatg caaaaataac taatccttta gtaaaaatgt caacatgtta aaggggaat
4621 gttaactaat gtaggttatt gctatttgtg atttgtttat gggttcttgg ctttgacagc
4681 ttcaaagaat ggacagtgat aagttaaaag aaattttgta tattgtcaag gaaagggtct
4741 taaatccgag tcaagtccct tccttggggt aaaaaatgta ttcttaaagc attctgatgt
4801 taaaaagaaa acttaagtta tctaaccaaa acagacgcaa gattttgttt ctgcagacta
4861 cttggcaatc aaaagtgatc ataaatttag gttatcagtt ttcagaaagt tgctttgtga
4921 gaaaattttg ttagatatat tctcccaagc atgcttttg tggaaggttt tcagccattg
4981 ccactgaatc agatgttaaa aatgaaggga aaattgagtg tgcacacaca caactgttgt
5041 acactcatga ttgcagtttt tagcttaaga aacttttcta ccagttactg tgaatctgac
5101 ttaaaatgta aagtttcctc atgataaaat aggaacaaca tagaaatgga ttgatggggt
5161 gatctgagtt attgtatata aaagttttta aagaatagaa tgaacatcaa gctagatagg
5221 caaaaattga cacattcaga acagcttttt tgactgcgaa gccaaaagtt gtcagaaaca
5281 gcaaaagatc ccttattatt acagagtatt ttacgtagtc tctattttaa ggagagaaat
5341 taaatagaag ggcttcatgc atttagggga gggtgctaaa acttctcaag ttcgtcaaac
5401 ttacaggaat acccaccatg atcattttct ctctaattat gtataccaca aaattttcat
5461 ctggccatag gaattcactg gtgggtgtaa aattaatgac taaagaaatt aagtgacaaa
5521 tacataaaag aaacagactt gtggggatat tgttttaagg tgtattaatt actcagtgat
5581 gataccactc aatagggcat gccactactt ttcttaagat gctaattatg aagcagtgct
5641 cacaggcatt ttttaactag caaattagta gatggacttt tggggtctgt cacttttaa
5701 aagtatttaa gacttaaatt ctattagcac cacagtctgc cttcagtaat acacctaaaa
5761 tatttttcag gaccagaagc attcagtttg aaaatttgca gatgcaaacc agtattatta
5821 ctaacgctct gggtcaaaga ttaggttttt aatattaaca gtagtctggt aaatatttag
5881 aagtctggca ttgagaaaca aaagcttgta cctgactagt atttttattt aaaaaaatta
5941 gttctgttag cttatttaaa ttgtgtttta tttatccgta gaatttatat ttatttcatt
6001 cctttcatct cactgaaaac tgtctgcagg ccctttgatt tggattagat gtgtgaagta
6061 ctgtcttttg ccaaaaacct caaattacct gttcttttca acgtagtggg tttgtgcttg
6121 tttggagatc agttcaaaaa ctatctgtac tatctgtact gcctctgatg ttaagatttt
6181 atgtatagca taaggaagct agctctgact atattttcct aagaataaag acctattttt
6241 gtagcatgtc ttaggatctc caggagtcca agaattattg tgggtgtcct ccaattcatc
6301 actcttcact taacagcttt taagtagaca cttggaatct ttagaggtct gtcgcccttt
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Figure 21 (cont'd)

```
6361 gattatccat acattcgaag taactagcca atggtgaaaa attcctcaag atatcctcag
6421 ttgcaatcac attactggaa gatgaataga ataaatgtat taggctggtc ttaatttttg
6481 atggaaatat tctgttgtcc cgtacttgcc attggatttg ataaagttag tggtaatttg
6541 gaaagaatcg gggacttgcc aatatatttg tgggttttag cttatacccc taggatttct
6601 tggttgcggg acgagcagtt ttggccactt ccatcaggac aagacttttt aggtcactta
6661 gtgcaggttt tagtttctat tttggattaa caacatttat attgattatc gaaaagaagc
6721 tttcatcatt tcagaacagt cctggaagtt tgactttgag tgtgggagaa gtcctaataa
6781 accattttgg aaattaaaaa aaaaa
```

Figure 22

Homo sapiens synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP), transcript variant 1, mRNA

NCBI Reference Sequence: NM_006372.4 (SEQ ID NO: 9)

```
   1 agcgcgggag agagaaagag aggagccgac tcggcaggga ctgggggacc gggccgagag
  61 tgcgagcgag cgagggaggg agtgagggag cgtgcgagcc agaaggggaa aggcggccac
 121 tcgtgcctga gcgaccgcag aggggagtgg gagcagtggg gtaaaggagc gggggggcggg
 181 aataagaaag gccgagagaa ggcggacaga ggctagtggt ggtggtggtg gtagggggag
 241 aaggaggagc tggaggaggg caggggctga gggagtgagt gaagcggacg cgcgagggag
 301 gggagggaag ggaagggaag ggaaggggggg gtcacgcggg ggcgcgcgcg cgcaccggga
 361 gcgcgctcgg aggcgagtgg aactggatcg ggtttgctgc cagcggcgtg agcttcggcc
 421 gccattttac aacagctcca ctcgcgccgg acacagggag cagcgagcac gcgtttcccg
 481 caacccgata ccatcggaca ggatttctcc gcctcagccc aacggggaga tctctggaaa
 541 catggctaca gaacatgtta atggaaatgg tactgaagag cccatggata ctacttctgc
 601 agttatccat tcagaaaatt ttcagacatt gcttgatgct ggtttaccac agaaagttgc
 661 tgaaaaacta gatgaaattt acgttgcagg gctagttgca catagtgatt tagatgaaag
 721 agctattgaa gctttaaaag aattcaatga agacggtgca ttggcagttc ttcaacagtt
 781 taaagacagt gatctctctc atgttcagaa caaaagtgcc tttttatgtg gagtcatgaa
 841 gacttacagg cagagagaaa aacaagggac caaagtagca gattctagta aaggaccaga
 901 tgaggcaaaa attaaggcac tcttggaaag aacaggctac acacttgatg tgaccactgg
 961 acagaggaag tatggaggac cacctccaga ttccgtttat tcaggtcagc agccttctgt
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1321 tgaagaattt agcaaagtaa cagagggtct tacagacgtc attttatacc accaaccgga
1381 tgacaagaaa aaaaacagag gcttttgctt tcttgaatat gaagatcaca aaacagctgc
1441 ccaggcaagg cgtaggttaa tgagtggtaa agtcaaggtc tgggggaatg ttggaactgt
1501 tgaatgggct gatcctatag aagatcctga tcctgaggtt atggcaaagg taaaagtgct
1561 gtttgtacgc aaccttgcca atactgtaac agaagagatt ttagaaaagg catttagtca
1621 gtttgggaaa ctggaacgag tgaagaagtt aaaagattat gcgttcattc attttgatga
1681 gcgagatggt gctgtcaagg ctatggaaga aatgaatggc aaagacttgg agggagaaaa
1741 tattgaaatt gtttttgcca agccaccaga tcagaaaagg aaagaaagaa aagctcagag
1801 gcaagcagca aaaaatcaaa tgtatgacga ttactactat tatggtccac ctcatatgcc
1861 ccctccaaca agaggtcgag ggcgtggagg tagaggtggt tatggatatc ctccagatta
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2101 agccggttat tcacagagag gaggtcctgg atcagcaaga ggcgttcgag gtgcgagagg
2161 aggtgcccaa caacaaagag gccgcggggt acgtggtgcg aggggtggcc gcggtggaaa
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2461 actcacccta aatctgaacg ggtgccgcta taatttgtga catctggcaa gatttccctt
2521 tatgtatata ttttaacaat ccgcttggac acgaacaaag ccacacttct aactgcttct
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2641 tagttaatga gtttgcattt gtgcttgaga aaatttggct caagtccatt tggctgtagt
2701 gtcaacgatg tttccagtag tgtttagatt tggtgtcttc aaaggtagtt gattaaaacc
2761 aagtgtgtct ttaatatctt gtatcagaat aactttgtat gttaccaact taaattgcta
2821 gaataaggta aattgataca caactgctat ttttaattta gaactttgac ctaatttggg
2881 ttttcaaaac cattttggct acttgtattc tttatgctgt tgtttatttc aataaaaaat
```

Figure 22 (cont'd)

```
2941 tcacacctaa atgtatactt actaaaattg tgtttacaat tcgtttttca caaaatttcc
3001 tgcaaatttg gttcaaattg tatagcatgt caaggccaat taaagggttt tgtgccttgt
3061 taattcttgt gtggaatatg tctgcacatt acacaacact gatttattgc agttttctgc
3121 ttctggttta aagtgctatt ttacaacaga cttcatgttc ccatcaaaaa taaaaagata
3181 atacatgtag taag
```

Figure 23

Homo sapiens synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP), transcript variant 3, mRNA

NCBI Reference Sequence: NM_001159674.1 (SEQ ID NO: 10)

```
   1 ctccactcgc gccggacaca gggagcagcg agcacgcgtt tcccgcaacc cgataccatc
  61 ggacaggatt tctccgcctc agcccaacgg ggagatctct ggaaacatgg ctacagaaca
 121 tgttaatgga aatggtactg aagagcccat ggatactact tctgcagtta tccattcaga
 181 aaattttcag acattgcttg atgctggttt accacagaaa gttgctgaaa aactagatga
 241 aatttacgtt gcagggctag ttgcacatag tgatttagat gaaagagcta ttgaagcttt
 301 aaaagaattc aatgaagacg gtgcattggc agttcttcaa cagtttaaag acagtgatct
 361 ctctcatgtt cagaacaaaa gtgccttttt atgtggagtc atgaagactt acaggcagag
 421 agaaaaacaa gggaccaaag tagcagattc tagtaaagga ccagatgagg caaaaattaa
 481 ggcactcttg gaaagaacag gctacacact tgatgtgacc actggacaga ggaagtatgg
 541 aggaccacct ccagattccg tttattcagg tcagcagcct tctgttggca ctgagatatt
 601 tgtgggaaag atcccaagag atctatttga ggatgaactt gttccattat ttgagaaagc
 661 tggacctata tgggatcttc gtctaatgat ggatccactc actggtctca atagaggtta
 721 tgcgtttgtc acttttgta caaaagaagc agctcaggag gctgttaaac tgtataataa
 781 tcatgaaatt cgttctggaa aacatattgg tgtctgcatc tcagttgcca acaataggct
 841 ttttgtgggc tctattccta agagtaaaac caaggaacag attcttgaag aatttagcaa
 901 agtaacagag ggtcttacag acgtcatttt ataccaccaa ccggatgaca agaaaaaaaa
 961 cagaggcttt tgctttcttg aatatgaaga tcacaaaaca gctgcccagg taaaagtgct
1021 gtttgtacgc aaccttgcca atactgtaac agaagagatt ttagaaaagg catttagtca
1081 gtttgggaaa ctggaacgag tgaagaagtt aaaagattat gcgttcattc attttgatga
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1381 ttatggatat gaagattatt atgattatta tggttatgat taccataact atcgtggtgg
1441 atatgaagat ccatactatg gttatgaaga ttttcaagtt ggagctagag gaaggggtgg
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1861 atatgaattt ctttaacaat tttctctgca gtgcaagtta ttaaactaaa gctactctat
1921 tttcaaaatg tgttccaaca gaaatccttc ataactccta gcatggtatc ttaataaaga
1981 ataaagttct tttaaaaatc tgctctaagt agatttttcc ccttttttaa attaaggatc
2041 ccaacagtgg tattttgaaa tattctcttg aatttgtgca tttaaatttt attgcagtgg
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2521 ttgcttcttc agatattgta gttatttgga tgtataatag tttagcaaga tgttactttt
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2701 tgaagttttt tcataaatca tagaaattag tatatggctg tagtttagct ttttaggtaa
2761 aaggtatgtt tcattagtgc atttcttcct gctgatcact gtaaacatgt gaatcagctt
2821 tccatttctt atgcaggtca tgataacttg tagagtagag tacaatcatt tgtgctatgt
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Figure 23 (cont'd)

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2941 gaaccaccct caaaaatttt tttgccaagt cctaagttga tagcttaaag taaaaagtga
3001 aaattatagt ttcattagga cttggtgtaa agaaatcccc tccccccttc cccaaaggga
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3181 gtcatatgtt caaaatgctc atggcaaaca atcattttgc attcctgcaa ataaaattgt
3241 tttatactgt aagctggagg cgagtgtaac ttatttttgt aataaagttt ttatttttt
3301 tatgtgtcat taatataaat gtgtgttagt gtagaaatct tctggtttaa aaacttagaa
3361 ttgcacacat ttcagtatgt ttatttgtac ttacataatt ttagaatagt ggttgccaat
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3481 gtatgtcagt tactgggata gctgggacat agagtgtaat ttaaaatttg tcaataagta
3541 ttcattggaa tatatgtaaa tgtgccttgc cggttattga aacttatcta caaaatgagt
3601 atggggtgac aaaaattagt tcctggtgct taatgaaact ttctgccact gattttatat
3661 attaccccgt gctttttaa agtacatctc tctcaaaact tagtgtaagt ttgagggcta
3721 cacaaaacat ttacatttca ttctaacata atgaatataa taggttgtgg aaagtgggta
3781 aactaaatgt agccttcagt aaaattgaat ctcagtgtaa tccttggtgc tggcatttct
3841 cagttccgag gagttaaatg atcccatcta agaggtcatt gccatgccta ttggcacttt
3901 actgtcatag catttttaag ggacactgtc aaggtgttta agttctcaga attacttgtt
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4021 gaacactttt gtgagttcac aaatgtgttc ttaagaaaac attaaaatat ggagctctgg
4081 gttttcaaga ctatttggca ttcttaattt ggggacttgg gagggaaact gataaaaaga
4141 aattgaagaa ttgatggtta tacttaaaga agggtaatgt aaacagtggt gatgaaatat
4201 atacacatca agtgaaatta cttgacagtg ttcatttgaa tgactttgaa ttcaagccat
4261 tataattact tttaaaatta aatatcattt gcactgttct gataatgggt gcagtttttg
4321 agcaatataa tcagagctaa atatgcatgt agtgattagt gatgtgaaca attaacgttc
4381 tgagaagaaa tactaactgt ggtattttca aacttaaatt tctgtagtaa aatcagtatc
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4621 atgtaggtta ttgctatttg tgatttgttt atgggttctt ggctttgaca gcttcaaaga
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4741 agtcaagtcc cttccttggg gtaaaaaatg tattcttaaa gcattctgat gttaaaaaga
4801 aaacttaagt tatctaacca aaacagacgc aagattttgt ttctgcagac tacttggcaa
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6241 tcttaggatc tccaggagtc caagaattat tgtgggtgtc ctccaattca tcactcttca
6301 cttaacagct tttaagtaga cacttggaat ctttagaggt ctgtcgccct ttgattatcc
```

Figure 23 (cont'd)

```
6361 atacattcga agtaactagc caatggtgaa aaattcctca agatatcctc agttgcaatc
6421 acattactgg aagatgaata gaataaatgt attaggctgg tcttaatttt tgatggaaat
6481 attctgttgt cccgtacttg ccattggatt tgataaagtt agtggtaatt tggaaagaat
6541 cggggacttg ccaatatatt tgtgggtttt agcttatacc cctaggattt cttggttgcg
6601 ggacgagcag ttttggccac ttccatcagg acaagacttt ttaggtcact tagtgcaggt
6661 tttagtttct attttggatt aacaacattt atattgatta tcgaaaagaa gctttcatca
6721 tttcagaaca gtcctggaag tttgactttg agtgtgggag aagtcctaat aaaccatttt
6781 ggaaattaaa aaaaaaa
```

Figure 24

Homo sapiens synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP), transcript variant 4, mRNA

NCBI Reference Sequence: NM_001159675.1 (SEQ ID NO: 11)

```
   1 atctctggaa acatggctac agaacatgtt aatggaaatg gtactgaaga gcccatggat
  61 actacttctg cagttatcca ttcagaaaat tttcagacat tgcttgatgc tggtttacca
 121 cagaaagttg ctgaaaaact agatgaaatt tacgttgcag ggctagttgc acatagtgat
 181 ttagatgaaa gagctattga agctttaaaa gaattcaatg aagacggtgc attggcagtt
 241 cttcaacagt ttaaagacag tgatctctct catgttcaga acaaaagtgc ctttttatgt
 301 ggagtcatga agacttacag gcagagagaa aaacaaggga ccaaagtagc agattctagt
 361 aaaggaccag atgaggcaaa aattaaggca ctcttggaaa gaacaggcta cacacttgat
 421 gtgaccactg gacagaggaa gtatggagga ccacctccag attccgttta ttcaggtcag
 481 cagccttctg ttggcactga gatatttgtg ggaaagatcc caagagatct atttgaggat
 541 gaacttgttc cattatttga gaaagctgga cctatatggg atcttcgtct aatgatggat
 601 ccactcactg gtctcaatag aggttatgcg tttgtcactt tttgtacaaa agaagcagct
 661 caggaggctg ttaaactgta taataatcat gaaattcgtt ctggaaaaca tattggtgtc
 721 tgcatctcag ttgccaacaa taggcttttt gtgggctcta ttcctaagag taaaaccaag
 781 gaacagattc ttgaagaatt tagcaaagta acagagggtc ttacagacgt cattttatac
 841 caccaaccgg atgacaagaa aaaaaacaga ggcttttgct ttcttgaata tgaagatcac
 901 aaaacagctg cccaggtaaa agtgctgttt gtacgcaacc ttgccaatac tgtaacagaa
 961 gagattttag aaaaggcatt tagtcagttt gggaaactgg aacgagtgaa gaagttaaaa
1021 gattatgcgt tcattcattt tgatgagcga gatggtgctg tcaaggctat ggaagaaatg
1081 aatggcaaag acttggaggg agaaaatatt gaaattgttt ttgccaagcc accagatcag
1141 aaaaggaaag aaagaaaagc tcagaggcaa gcagcaaaaa atcaaatgta tgacgattac
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1261 ggtggttatg gatatcctcc agattattat ggatatgaag attattatga ttattatggt
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1381 caagttggag ctagaggaag gggtggtaga ggagcaaggg gtgctgctcc atccagaggt
1441 cgtggggctg ctcctccccg cggtagagcc ggttattcac agagaggagg tcctggatca
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1561 ggtgcgaggg gtggccgcgg tggaaatgta ggaggaaagc gcaaagctga tgggtacaac
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1681 cagcaaccgc tccaaggtgg tgatcattct ggtaactatg gttacaaatc tgaaaaccag
1741 gagttttatc aggatacttt tgggcaacag tggaagtaga aacagtaggg cctctgtaaa
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1981 aagatattct tagatactga aagaaatagt taatgagttt gcatttgtgc ttgagaaaat
2041 ttggctcaag tccatttggc tgtagtgtca acgatgtttc cagtagtgtt tagatttggt
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2521 atgttcccat caaaaataaa aagataatac atgtagtaag
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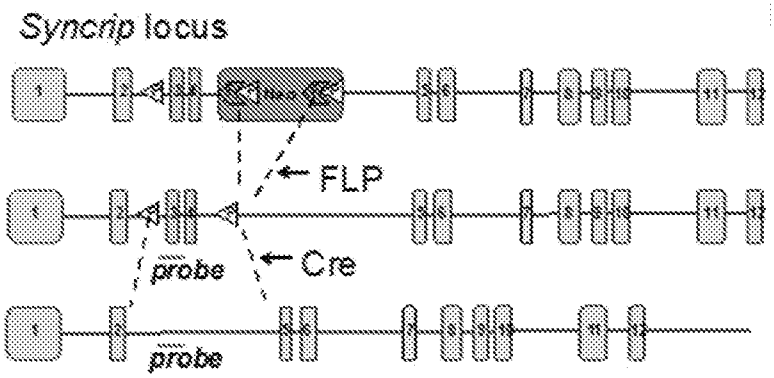


Figure 25(A)

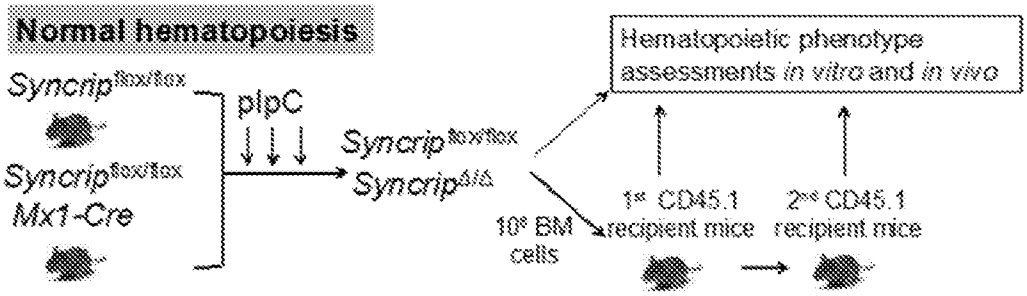


Figure 25(B)

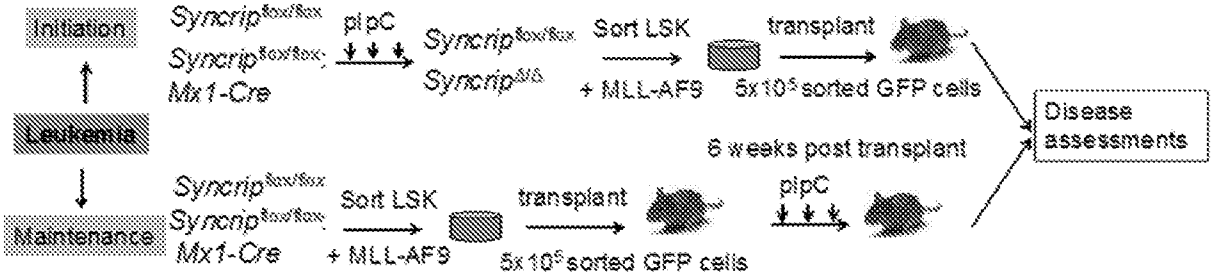

Initiation
Leukemia
Maintenance
Syncrip fl/fl
Syncrip fl/fl; Mx1-Cre
pIpC
Syncrip fl/fl
Syncrip Δ/Δ
Sort LSK
+ MLL-AF9
transplant
5x10^5 sorted GFP cells
6 weeks post transplant
pipC
Disease assessments

Figure 25(C)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/21626

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/21626

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-16, 21
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
-***-Please See Within the Next Supplemental Box-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 17-20, 22; SEQ ID NO: 1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/21626

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/7088, 31/7105, 31/7115; G01N 33/50, 33/58; C21Q 1/68 (2018.01)

CPC - A61K 31/7088, 31/7105, 31/7115, 31/712, 31/7125; G01N 33/6863, 33/6866; C12Q 1/6886, 1/6883, 1/6809

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2016/0313300 A1 (CELGENE CORPORATION) October 27, 2016; paragraphs [0002], [0053], [0054], [0058], [0071], [0091], [0096], [0102], [0110], [0167], [0175], [0349], [0390], [0460], [0686], [0710]	1, 3/1, 17, 18, 19/17-18, 20
Y	CHEN, H-H et al., hnRNP Q Regulates Cdc42-Mediated Neuronal Morphogenesis. 9 April 2012; Vol. 32, No. 12, pages 2224-2238; abstract; page 2226, second column, fourth paragraph; page 2231, first column, second paragraph; Fig 6	1, 3/1, 17, 18, 19/17-18, 20
Y	US 2016/0298195 A1 (MEMORIAL SLOAN-KETTERING CANCER CENTER) October 13, 2016; paragraphs [0005], [0025], [0043], [0331]; Fig. 9	19/17-18
A	US 2014/0010861 A1 (MODERNA THERAPEUTICS) January 9, 2014; paragraph [0058]; SEQ ID NO: 115,471	2, 3/2, 22
A	US 2014/0161721 A1 (THE HOSPITAL FOR SICK CHILDERN et al.) June 12, 2014; paragraph [0253]; SEQ ID NO: 633	2, 3/2, 22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2018 (25.07.2018)	07 AUG 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US18/21626

-***-Continued from Box III: Lack of Unity of Invention -***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-3, 17-20, 22 and SEQ ID NO: 1 are directed toward methods and kits for treating or preventing AML by administering at least one SYNCRIP-specific inhibitory nucleic acid that inhibits synaptotagmin-binding, cytoplasmic RNA-interacting protein (SYNCRIP) expression levels or activity in a subject and for monitoring the efficacy of said administration.

The methods will be searched to the extent that they encompass a nucleic acid sequence encompassing SEQ ID NO: 1 (first exemplary SYNCRIP-specific inhibitory nucleic acid). Applicant is invited to elect additional nucleic acid(s), with specified SEQ ID NO: for each, such that the sequence of each elected species is fully specified (i.e. no optional or variable residues or substituents), to be searched. Additional nucleic acid sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1, 2 (in-part), 3 (in-part), 17-20 and 22 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 1 (SYNCRIP-specific inhibitory nucleic acid). Applicants must specify the claims that encompass any additionally elected nucleic acid sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a nucleic acid encompassing SEQ ID NO: 2 (SYNCRIP-specific inhibitory nucleic acid).

No technical features are shared between the nucleic acid sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of: a method for treating or preventing AML in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of at least one SYNCRIP-specific inhibitory nucleic acid that inhibits synaptotagmin-binding, cytoplasmic RNA-interacting protein (SYNCRIP) expression levels or activity in the subject; a method for monitoring the therapeutic efficacy of a SYNCRIP-specific inhibitory nucleic acid that targets SYNCRIP expression and/or activity in a subject diagnosed with AML comprising: (a) detecting SYNCRIP protein levels in a test sample obtained from the subject after the subject has been administered the SYNCRIP-specific inhibitory nucleic acid; and (b) determining that the SYNCRIP-specific inhibitory nucleic acid is effective when the SYNCRIP protein levels in the test sample are reduced compared to that observed in a control sample obtained from the subject prior to administration of the SYNCRIP-specific inhibitory nucleic acid; a method for inhibiting leukemic cell proliferation in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a SYNCRIP-specific inhibitory nucleic acid; and a kit comprising one or more SYNCRIP-specific inhibitory nucleic acids comprising a nucleic acid sequence of any defined sequence and any complement thereof; however, these shared technical features are previously disclosed by US 2016/0313300 A1 to Cellgene Corporation (hereinafter 'Celgene') in view of the publication entitled, "hnRNP Q Regulates Cdc42-Mediated Neuronal Morphogenesis," by Chen et al. (hereianfter 'Chen').

Celgene discloses a method for treating or preventing AML (treating cancers including AML; paragraphs [0053], [0058]) in a subject in need thereof (administering treatment to an AML patient; paragraphs [0107], [0110]), comprising administering to the subject a therapeutically effective amount (paragraph [0054]) of at least one inhibitory nucleic acid (gene silencing with shRNA; paragraphs [0709], [0710]) that inhibits expression levels or activity in the subject (for down-regulation of expression of biomarkers including SYNCRIP; paragraph [0390]); a method for monitoring the therapeutic efficacy (paragraphs [0002], [0071]) of an inhibitory nucleic acid (gene silencing with shRNA; paragraphs [0709], [0710]) that targets biomarker expression and/or activity (for down-regulation of expression of biomarkers including SYNCRIP; paragraph [0390]) in a subject diagnosed with AML (paragraph [0054]) comprising: (a) detecting biomarker protein levels (determining levels of a protein biomarker; paragraph [0349]) in a test sample obtained from the subject (paragraph [0091]) after the subject has been administered the inhibitory nucleic acid (measuring biomarker expression levels before and after administration of therapeutic agents; paragraphs [0098], [0101]); and (b) determining that the inhibitory nucleic acid is effective when the biomarker protein levels in the test sample are reduced (expression levels lowered compared to control; paragraph [0102]) compared to that observed in a control sample obtained from the subject prior to administration of the inhibitory nucleic acid (marker levels compared from samples obtained before and after therapeutic administration; paragraphs [0098], [0101]); a method for inhibiting leukemic cell proliferation (reducing tumor cell growth or proliferation with shRNA; paragraphs [0175], [0460], [0686]) in a subject in need thereof (administering treatment to an AML patient; paragraphs [0107], [0110]), comprising administering to the subject a therapeutically effective amount (paragraph [0054]) of an inhibitory nucleic acid (gene silencing with shRNA; paragraphs [0709], [0710]); and a kit (paragraphs [0002], [0167]) comprising one or more inhibitory nucleic acids (shRNA for gene silencing paragraphs [0709], [0710]) comprising a nucleic acid sequence of any defined sequence (paragraph [0675]) and any complement thereof. Celgene discloses does not disclose wherein the inhibitory nucleic acid is at least one SYNCRIP-specific inhibitory nucleic acid that inhibits synaptotagmin-binding, cytoplasmic RNA-interacting protein (SYNCRIP) expression levels or activity in the subject or detecting SYNCRIP protein levels in a test sample obtained from the subject after the subject has been administered the SYNCRIP-specific inhibitory nucleic acid; and determining that the SYNCRIP-specific inhibitory nucleic acid is effective when the SYNCRIP protein levels in the test sample are reduced compared to that observed in a control sample obtained from the subject prior to administration of the SYNCRIP-specific inhibitory nucleic acid.

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from Previous Supplemental Box-***-

Chen discloses targeting the mRNA of hnRNAPQ1 (abstract; wherein hnRNPQ1 is an equivalent term for SYNCRIP, as evidenced in the instant specification at paragraph [0002]) with a SYNCRIP-specific inhibitory nucleic acid (siRNAs specific for hnRNPQ1; page 2226, second column, fourth paragraph) or antisense oligonucleotide selective for hnRNPQ1; (page 2231, first column, Figure 6) wherein the hnRNPQ1 inhibitory nucleic acid blocks expression of hnRNPQ1 (siRNA specific to hnRNPQ1 knockdown of all Q isoforms; page 2226, second column, fourth paragraph; Figure 8c-d). It would have been obvious to one of ordinary skill in the art at the time of the invention to have modified the disclosure of Celgene to provide wherein the inhibitory nucleic acid is at least one SYNCRIP-specific inhibitory nucleic acid that inhibits synaptotagmin-binding, cytoplasmic RNA-interacting protein (SYNCRIP) expression levels or activity in the subject and the method steps of (a) detecting SYNCRIP protein levels in a test sample obtained from the subject after the subject has been administered the SYNCRIP-specific inhibitory nucleic acid; and (b) determining that the SYNCRIP-specific inhibitory nucleic acid is effective when the SYNCRIP protein levels in the test sample are reduced compared to that observed in a control sample obtained from the subject prior to administration of the SYNCRIP-specific inhibitory nucleic acid, because the ability of inhibitory nucleic acids, such as siRNA or antisense oligonucleotides specific for hnRNPQ1 (SYNCRIP) to block the expression of SYNCRIP as disclosed by Chen would have motivated the skilled artisan to employ said SYNCRIP-inhibitory nucleic acids to treating or preventing AML with their administration; to monitor the efficacy of SYNCRIP-inhibitory nucleic acids treatment on expression levels of SYNCRIP; to decrease proliferation of leukemic cell proliferation and to provide a kit comprising said SYNCRIP-inhibitory nucleic acids as previously disclosed by Celgene.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the combination of the Celgene and Chen references, unity of invention is lacking.