MATERIALS AND METHODS

Lentivirus infection of CD34$^+$ human cord blood (HCB) cells. Isolated hUCB CD34$^+$ cells were resuspended in IMDM supplemented with 10% FBS (Gibco), 50 ng/mL human SCF (PeproTech), 50 ng/mL human TPO (PeproTech), and 50 ng/mL human Flt3L (PeproTech) and pre-cultured at 37 °C in a humidified incubator. After 16 h, the cells were collected and washed with PBS. The cells were then resuspended in IMDM (Gibco) supplemented with 10% FBS (Gibco), 100 ng/mL human SCF (PeproTech), 100 ng/mL human TPO (PeproTech), and 100 ng/mL human Flt3L (PeproTech) at a concentration of 1×10^5 cells/mL. Next, cells were plated into RetroNectin precoated 24-well plates. Polybrene (at a final concentration of 5 μg/mL) and lentivirus (at a final concentration of 100 multiplicity of infection) were added to each well. After the plates were centrifuged at 1800 rpm at 33 °C for 90 min, the cells were cultured at 37 °C in a humidified incubator. After 48 h, the GFP$^+$ cells were sorted with a flow cytometer and were used for the following experiments.

Colony forming cell (CFC) assay. The GFP$^+$ cells were expanded for 7 d and then were harvested and mixed with MethoCult H4434 semi-solid medium (STEMCELL Technologies) at a density of cells equal to 1000 initiated CD34$^+$ cells per well. In the compound treatment assays, cells were cultured with 005A or vehicle for 7 days, and posterities equal to 1000 initiated CD34$^+$ cells were seeded per well. The cell mixtures were plated into 6-well plates at 1 mL per well and grown in a humidified incubator. After 14 d, the number of cell colonies that formed were counted based on their morphological features.

Cobblestone area forming cell (CAFC). M2-10B4 were used as feeder cells to support the growth of human hematopoietic stem cells in a long-term culture system. Briefly, M2-10B4 cells were irradiated with 80 Gy using ^{137}Cs as the source. The irradiated cells were then resuspended in human long-term culture medium (HLTM), MyeloCult H5100 (STEMCELL Technologies), and plated in collagen-precoated 96-well flat-bottom plates at 1.25×10^4 cells per well. To each well, 100 μl HLTM with 10-6 M hydrocortisone was added. The irradiated feeder cells were incubated for a minimum of 24 h before cultured cells were added to the upper wells in 0.1 mL HLTM containing 10^{-6} M hydrocortisone. CAFC cultures were incubated at 37 °C in a humidified incubator. One half

of the media was replaced with fresh HLTM supplemented with 10^{-6} M hydrocortisone weekly. After five weeks, cobblestone areas were scored as positive if one or more cobblestone areas were detected, or as negative if no cobblestone areas were observed. LTC-IC frequencies were computed using extreme limiting dilution analysis (ELDA) (http://bioinf.wehi.edu.au/software/elda/).

Apoptosis, and cell cycle analysis. 1×10^5 GFP^+ cells were expanded for 7 d (or 7 d compounds treated $CD34^+$ UCB cells) were used in apoptosis analysis. Annexin V apoptosis analysis kit (SUNGENE BIOTECH) was applied to detect the apoptosis status of cells by flow cytometry (LSR II, BD Biosciences). 1×10^6 GFP^+ cells expanded for 7 d (or 7 d compounds treated $CD34^+$ UCB cells) were used in cell cycle analysis. Cells were resuspended in PI/RNase staining buffer (BD Biosciences) for further cell cycle analysis.

Molecular Docking Studies of p18 and 005A. The structure of p18 was obtained from the ternary p18-CDK4/6-K-cyclin complex (PDB entry: 1G3N, resolution 2.90 Å) with SYBYL-X 1.2. Residual repair and energy minimization were subsequently performed. Detailed ligand-receptor interactions were predicted with Surflex-Dock GeomX (SFXC), a docking program in SYBYL. The Total Score was expressed as -log10 (Kd).

Molecular dynamics (MD) simulations. Representative complexes of p18-005A and p18-005A-CDK6 were selected to perform MD simulations. The simulation boxes included ~4525/~11782 water molecules and no sodium or chloride ions for a total of ~15973/~42261 atoms per periodic cell, respectively in each case. The box sizes were $68 \times 62 \times 43$ $Å^3$ and $71 \times 81 \times 73$ $Å^3$, respectively. The systems were first minimized for 50,000 steps with the proteins fixed. Then, the proteins were released and another 50,000 steps of minimization were performed. Starting from the last frame of the minimization, 100 nano-second (ns) were obtained for each system. Trajectory analysis was conducted with VMD and AMBER12 software.

Surface plasma resonance (SPR) array. A SPR system (Biacore T200, GE Healthcare Sciences, Pittsburgh, PA, USA) was used to measure binding of 005A to p18. Briefly, p18 proteins were dissolved in 10 mM sodium acetate buffer (pH 4.0) to a final concentration of 100 μg/ml and then were immobilized on a CM5 chip (GE Healthcare, Pittsburgh, PA, USA) using a standard amine

coupling procedure. The running buffer was PBS (pH 7.4) with 0.005% P20 surfactant. Various dilutions of 005A were used and binding of 005A to p18 was analyzed with Origin software to get the KD value (OriginLab Corp., Northampton, MA, USA).

Co-immunoprecipitation assay (co-IP). The cells were harvested and lysed in an IP lysis buffer (50 mM Tris-HCl, pH8.0, 100 mM NaCl, 50 mM sodium fluoride, 1% Nonidet P-40, 1 mM dithiothreitol, 1 mM Na_3VO_4, 1 mM Microcystin-LR, 1 mM phenylmethylsulfonyl fluoride, 10 mg/ml leupeptin, 10 mg/ml aprotinin). The lysates were incubated with ANTI-FLAG M2 affinity gel beads (Sigma). The precipitates were washed six times with ice-cold lysis buffer, resuspended in PBS, followed by Western blot analysis.

***In vitro* CDK6 activity assay.** GST-p18 protein (100 ng, expressed and purified in our laboratory) was diluted in kinase dilution buffer (5 mM MOPS, 2.5 mM glycerol 2-phosphate, 5 mM $MgCl_2$, 1 mM EGTA, 0.4 mM EDTA, 0.05 mM DTT, and 50 ng/ml BSA), and pre-incubated with and without 005A compound (2 μM) at room temperature. After 30 min, 200 ng of CDK6/cyclinD1 complex (Life Technologies) and 2.0 μg of GST-Rb (Sigma) were added. The reaction was initiated when 2.0 μCi [γ-^{32}P] ATP was added, thereby bringing the final volume to 25 μl. Each mixture was incubated at 37 °C for 30 min before the reactions were terminated with spotting of the reaction mixtures onto individually pre-cut strips of polyvinylidene difluoride membrane. After the membranes were air-dried, they were washed three times in 1% phosphoric acid. Radioactivity of the ^{32}P-labeled GST-Rb was quantitatively measured with a LS6500 Scintillation Counter (Beckman Coulter).

Culturing of CD34$^+$ HCB and primary screening. HCB samples were collected from consenting donors according to ethically approved procedures at Tianjin Central Hospital of Gynecology Obstetrics (Tianjin, China). Human CD34$^+$ cord blood cells were isolated using a human CD34 MicroBead Kit (MiltenyiBiotec, San Diego, CA, USA) according to the manufacturer's protocol, which included the settling and lysis of red blood cells with HES and ACK Lysis Buffer, respectively.

Primary cell culture medium consisting of Iscove's Modified Dulbecco's Medium (IMDM; Gibco, Waltham, MA, USA), 10% fetal bovine serum (FBS, Gibco), 100 ng/mL human stem cell factor (SCF; PeproTech, Rocky Hill, NJ, USA), 50 ng/mL human thrombopoietin (TPO, PeproTech), and

100 ng/mL human FMS-like tyrosine kinase 3 ligand (Flt3L, PeproTech) was used. The serum-free culture medium consisted of StemSpan SFEM (STEMCELL Technologies, Vancouver, Canada), 100 ng/mL human SCF (PeproTech), 100 ng/mL human TPO, (PeproTech), and 100 ng/mL human Flt3L (PeproTech). Human $CD34^+$ cells were resuspended in expansion medium (5×10^4 cells/mL) before being aliquoted into 96-well plates (Costar, Corning Inc., Corning, NY, USA). Compounds were dissolved in DMSO and were added immediately to each well following plating. The final concentration of DMSO in the control group was the same as in the compound-treated group. Cells were cultured at 37 °C in a humidified incubator (> 95%) with 5% CO_2 in air (hereafter referred to as "a humidified incubator"). At day 7, cell counts and phenotypes were assessed using APC-conjugated anti-CD34 antibodies, PE-conjugated anti-CD49f antibodies (BD Biosciences), and a BD FACS Fortessa cell analyzer (Becton Dickinson Biosciences).

Xenotransplant assay. HSCs ($CD34^+CD38^-CD45RA^-CD90^+$) derived from 2-3 CB specimens from different persons were cultured for 4 days with vehicle or 005A, then a fraction of the final culture equivalent to 300 starting cells (300 $CD34^+CD38^-CD45RA^-CD90^+$ cells were immediately injected after sorting for transplantation in untreated group) were unilateral (Right) intrafemorally injected into sub-lethally irradiated (X-ray, 250 cGy), 6-week-old female NOG mice (Fig. 3F). Freshly sorted $CD34^+CD38^-CD45RA^-CD90^+$ cells were not cultured and directly injected into sub-lethally irradiated recipients as a blank control. The percentage of human $CD45^+$ cells in the peripheral blood at 12 weeks was measured. Engraftment was then performed within 12 h after irradiation. In serial transplantation experiments, bone marrow was harvested from primary recipients after 4 months, and 90% of the bone marrow cells was transplanted into each sub-lethally irradiated secondary recipient mouse. Engraftment was monitored by using a BD FACS LSR cell analyzer (Becton Dickinson Biosciences) to analyze bone marrow cells stained with FITC-labeled anti-human CD45 (BD; 555482). Multilineage reconstitution was analyzed in bone marrow using APC-Cy7-labeled anti-human CD33 (BioLegend; 366613), PerCP-Cy5.5-labeled anti-human CD19 (BD; 561295), PE-Cy7-labeled anti-human CD3 (BD; 557851), PerCP-Cy5.5-labeled anti-human CD56 (BD; 560842), and APC-labeled anti-human CD235a (BD; 561775).

HSC division mode assay. Human UCB-derived $CD34^+CD38^-CD45RA^-CD90^+$ cells were cultured

in expansion medium supplemented with 1% bovine serum albumin (BSA; Sigma, St. Louis, MO, USA) as described above. After 72 h, the cells were harvested, washed at least 3 times in PBS, and then were fixed in 4% paraformaldehyde in PBS for 15 min at room temperature. After the cells were washed three more times in PBS, the cells were resuspended in α-minimum essential media (MEM) and were air-dried onto glass microscope slides (VWR, Radnor, PA, USA). For intracellular staining, cells were permeabilized with 0.25% Triton X (Sigma) in PBS for 15 min at room temperature. Non-specific sites were blocked with 3% BSA (Sigma) in PBS (blocking solution) for 1 h at room temperature. Centrosomes were stained with a goat anti-γ-tubulin antibody, and Numb was stained with a mouse anti-Numb antibody, (both from Abcam, Cambridge, MA, USA) in blocking solution overnight at 4 °C. After three washes in 1% BSA in PBS (wash solution), the cells were incubated with a chicken anti-goat AlexaFluor-488 labeled antibody (1 mg/mL) and a chicken anti-mouse AlexaFluor-647 labeled antibody (both from Life Technologies) in blocking solution in the dark. After 1 h, the slides were washed three times in wash solution and then were incubated with DAPI Nucleic Acid Stain (Invitrogen, Carlsbad, CA, USA). After being covered with a coverslip, each sample was analyzed using a Nikon ECLIPSE Ti-E confocal microscope (Nikon, Minato, Tokyo, Japan).

Single cell culture assay. Human UCB $CD34^+CD38^-CD45RA^-CD90^+$ cells were sorted with a BD Influx flow cytometer (Becton Dickinson Biosciences) into U-bottom 96-well plates with a single cell per well. Each well contained culture medium consisting of IMDM supplemented with 10% FBS (Gibco), 1% BSA (Sigma), 100 ng/mL human SCF (PeproTech), 100 ng/mL human TPO, (PeproTech), and 100 ng/mL human Flt3L (PeproTech). Cells were incubated at 37 °C in a humidified incubator. On day 14, cell counts and phenotypes were assessed using PE-conjugated anti-CD34 antibodies, FITC-conjugated anti-CD38 antibodies (BD Biosciences), and a BD FACS HTS-Fortessa cell analyzer (Becton Dickinson Biosciences).

Single Cells PCR. Human UCB-derived $CD34^+$ cells were cultured for 7 d and then were sorted into four populations: HSC cells ($CD34^+CD38^-CD45RA^-CD90^+$), HSPC cells ($CD34^+CD38^-$), MPP cells ($CD34^+CD38^-CD45RA^-CD90^+$), and progenitor cells ($CD34^+CD38^+$). Total RNA was extracted from each population using a CellsDirect™ One-Step qRT PCR Kit (Invitrogen) according

to the manufacturer's instructions. Briefly, 50 cells from each population were sorted directly into a mixture of CellsDirect 2x Reaction Mix, 0.2x TaqMan Assay Mix (Applied Biosystems), and SuperScript™ III RT/Platinum® Taq Mix (Invitrogen). Reverse transcription (RT) and specific target amplification (STA) were serially performed with the following parameters: 15 min at 50 °C, 2 min at 95 °C, and 18 cycles of 95 °C for 15 s and 60 °C for 4 min. Preamplified cDNA was then diluted with TE buffer (1:5) and subjected to real-time PCR. Briefly, a BioMark™ 48·48 Dynamic Array (Fluidigm) was used and the PCR parameters were: 10 min at 95 °C, followed by 40 cycles of 15 s at 95 °C and 60 s at 60 °C. Data were analyzed using BioMark™ Real-Time PCR Analysis Software (Fluidigm, San Francisco, CA, USA).

RNA sequencing assay. Human UCB cells were treated with or without 005A for 7 d. Each sample was performed in triplicate. The RNAs were purified with Trizol (Invitrogen). The sequencing assay was performed by Novogene (Beijing). The generated counts were normalized for mRNA abundance, and differential expression analysis was performed using DEseq2. GSEA was performed using the pre-ranked option in combination with log fold change values of each comparison calculated by edgeR. The geneset of "Genes up-regulated in human hematopoietic stem cell (HSC) enriched populations compared to committed progenitors and mature cells" was downloaded from http://software.broadinstitute.org/gsea/index.jsp (M19231).

Statistical Analysis. For all statistical analyses, an unpaired two-tailed Student's *t*-test was applied with the assumption that the experimental samples were of equal variance.

Supplemental figure legends

Figure S1. **(A)** Representative flow cytometry data for sorting the infected $CD34^+$ cells. **(B)** Fold change of p18 mRNA levels in p18 knockdown ($p18^{KD}$) by three different shRNAs and negative control in hUCB $CD34^+$ cells at 48h after infection (n=3). Data were normalized to the expression levels in control group. **(C)**. Representative flow image (left panel) and absolute numbers (right panel) of the flow cytometry data of human $CD34^+CD49f^+$ cell populations of hUCB $CD34^+$ cells

following infection of lentivirus carrying $p18^{KD2}$ and $p18^{KD3}$ were measured at 7 d (n = 3). 1×10^4 $CD34^+GFP^+$ human UCB cells were seeded at the beginning. **(D)** Number of total cells in the $p18^{KD}$ group and in the control group (n = 3) were matured after 7d culture. (n = 4). 1×10^4 $CD34^+GFP^+$ human UCB cells were seeded at the beginning. **(E)** Typical images of representative morphologies of various type of colonies as indicated. **(F)** Total CFC contents of control and $p18^{KD2}$ and $p18^{KD3}$ grouped human $CD34^+$ cells at 2 weeks (n=3). GEMM, colony-forming unit-granulocyte, erythroid, macrophage, megakaryocyte; CFU-GM, colony-forming unit-granulocyte, macrophage; BFU-E, Burst-forming unit-erythroid; CFU-E, colony-forming unit-erythroid. **(F, H)** Cell cycle distribution and percentage of viable cells were detected for p18 knockdown cells ($p18^{KD}$) and negative control cells (n=3). All data represent the means ± SD. Compared with control unless specified, *$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ by two-tailed unpaired *t*-test.

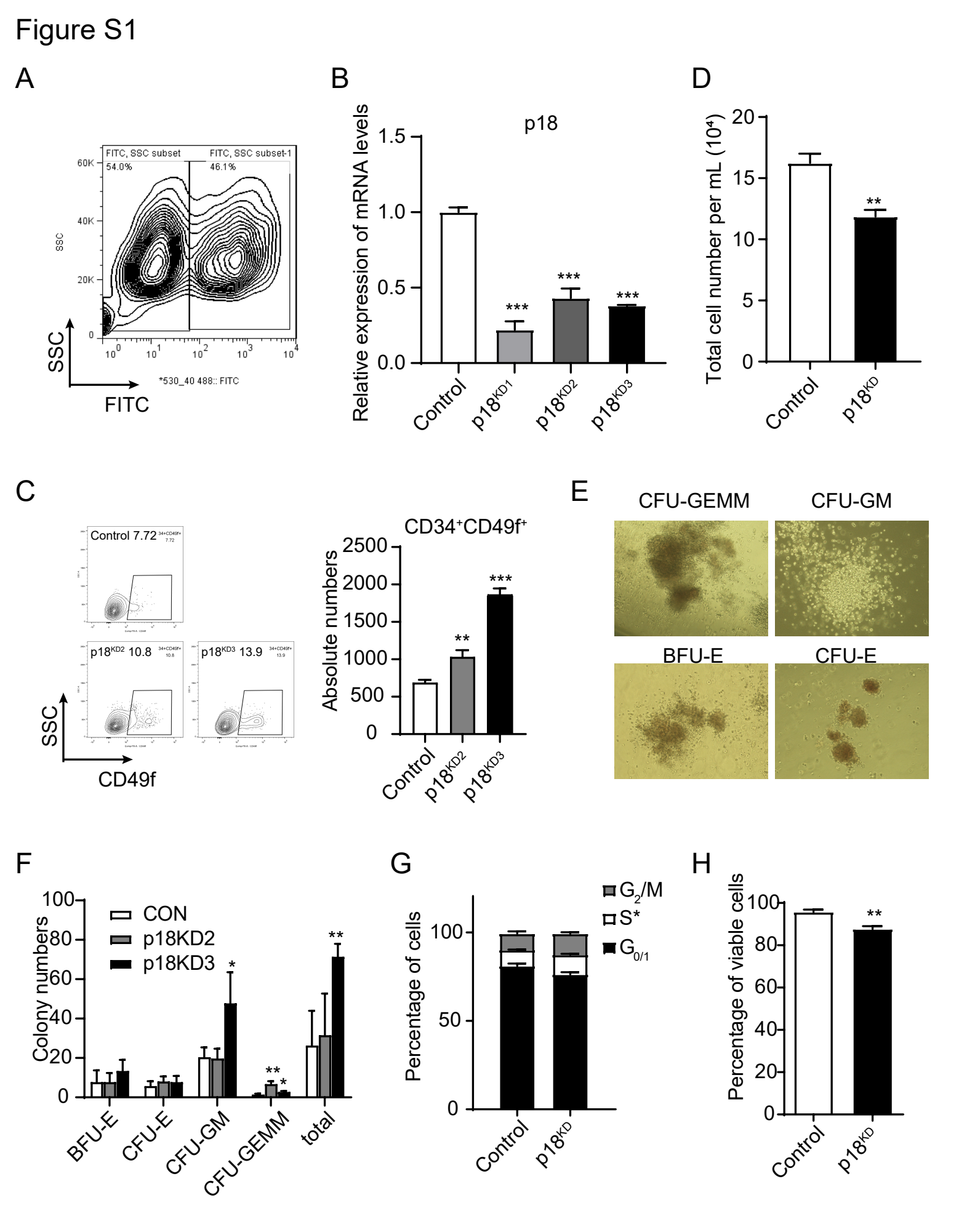
Figure S2. Changes in binding distance predicted for p18 and CDK6 in the presence of 005A before **(A)** and after **(B)** molecular dynamics simulations were performed. The dotted lines indicated potential molecular interactions. **(C)** SPR results of the binding activity of p16 (left) and p19 (right) at various concentrations of compound 005A. **(D)** Co-IP assay using Flag taged CDK4 and Myc taged p18. HEK293T cells were treated with 005A for 24 h after 48 h transient transfection. **(E)** Co-IP assay using Flag taged CDK6 and Myc taged p18. HEK293T cells were treated with 005A for various days after 48 h transient transfection.

Figure S3. **(A and B)** Dose response assay for 005A. Human $CD34^+$ cells were cultured with various concentrations or without 005A for 7d, and the increased percentage relative to vehicle group of $CD34^+$ (A) and $CD34^+$ $CD49f^+$ (B) cells were measured by flow cytometry (n=3). **(C)** Increase of human $CD34^+$ $CD49f^+$ cells compared to the vehicle group in serum free medium with 20 nM 005A after 4 d and 7 d (n=3). **(D)** The total cell number per well were matured (n=4). 1×10^5 $CD34^+$ UBCs were planted in 24-well plate, and cell populations were analyzed by flow cytometry after 7 d treatment with vehicle, SR1(1 μmol/L), UM171 (35 nmol/L) or 005A (20 nmol/mL) in (D-G). **(E)** Up panel: The percentage of live cells and absolute numbers per well of human $CD34^+$ cells were measured (n=4). Down panel: Percentage and representative images of the flow cytometry data of CD34 cell population. (F) Up panel: The percentage of live cells and absolute numbers per

well of human $CD34^+CD38^-$ cells were measured (n=4). Down panel: Percentage and representative images of the flow cytometry data of $CD34^+CD38^-CD45RA^-CD90^+$ cell population. **(G)** Up panel: The percentage of live cells and absolute numbers per well of human $CD34^+CD38^-CD201^+$ cells were measured (n=4). Down panel: Representative images of the flow cytometry data of $CD34^+CD38^-CD201^+$ cell population and percentage in $CD34^+CD38^-$ cells. **(H)** Levels of human cell engraftment in peripheral blood (PB) of NOG mice transplanted with uncultured or cultured human $CD34^+CD38^-CD45RA^-CD90^+$ cells with or without 005A at 12 weeks (n = 4 for uncultured group, n = 6 for control group and 005A group). Each symbol represents the results from an individual mouse. **(I)** Representative images of the flow cytometry data collected for detection of progenitors ($CD34^+CD38^-$) at 16 weeks after interfemoral injection of human $CD34^+CD38^-CD45RA^-CD90^+$ cells that were directly transplanted (uncultured) or cultured with vehicle (Control), or 005A. **(J, K)** Multi-lineage contribution of human cells in bone marrow of engrafted mice. Intrafemoral injected (R, right) or none injected (L, left) bone marrow was harvested 4 months after transplantation and analyzed by FCM to detect T and B lymphocytes ($CD3^+$ and $CD19^+$), myeloid cells ($CD33^+$), NK cells ($CD56^+$), and erythroid cells ($CD235a^+$) derived from human $CD34^+CD38^-CD45RA^-CD90^+$ cells that were directly transplanted (uncultured) or cultured in 005A for 4 d before transplantation (n = 4 for uncultured group, n = 6 for control group and 005A group). The representative FACS profiles were shown in **(K)**. **(L)** Levels of human engraftment ($CD45^+$) in bone marrow from primary recipients of human $CD34^+CD38^-CD45RA^-CD90^+$ cells that were directly transplanted cultured with 005A, SR1 or 005A+SR1.

Figure S4. **(A, B)** Expression of Notch signaling genes in $p18^{KD}$ HSCs and HSPCs cell relative to that in control cells (n=3). **(C)** Representative flow images of $CD34^+CD38^-CD45RA^-CD90^+$ (up panel) and $CD34^+CD38^-CD45RA^-CD90^+CD49f^+$ (down panel) cells. 1×10^5 $CD34^+$ UBCs were planted in 24-well plate, and cell populations were analyzed by flow cytometry after 7 d treatment with vehicle, 005A (20 nmol/mL), or 005A (20 nmol/mL) + DBZ (10 μmol/L). **(D)** Heat map analysis of RNA sequencing data showing hierarchical clustering of differentially expressed genes between 005A or vehicle cultured $CD34^+$ UCB cells. ** $p < 0.01$, *** $p < 0.001$ by two-tailed unpaired *t*-test.

Figure S1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p18KD1
p18KD2
p18KD3
D
Total cell number per mL (10⁴)
Control
p18KD
C
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p18KD2 10.8
p18KD3 13.9
SSC
CD49f
CD34⁺CD49f⁺
Absolute numbers
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CFU-GEMM
CFU-GM
BFU-E
CFU-E
F
CON
p18KD2
p18KD3
Colony numbers
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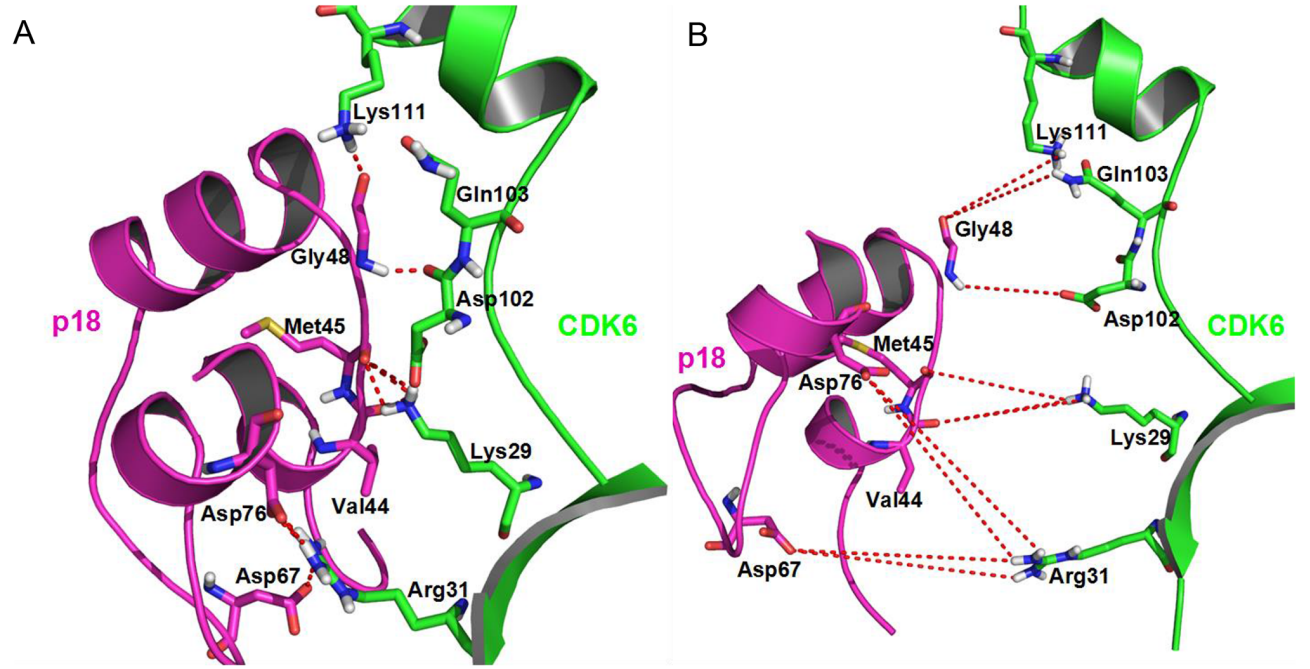
G2/M
S*
G0/1
Percentage of cells
H
Percentage of viable cells

Figure S2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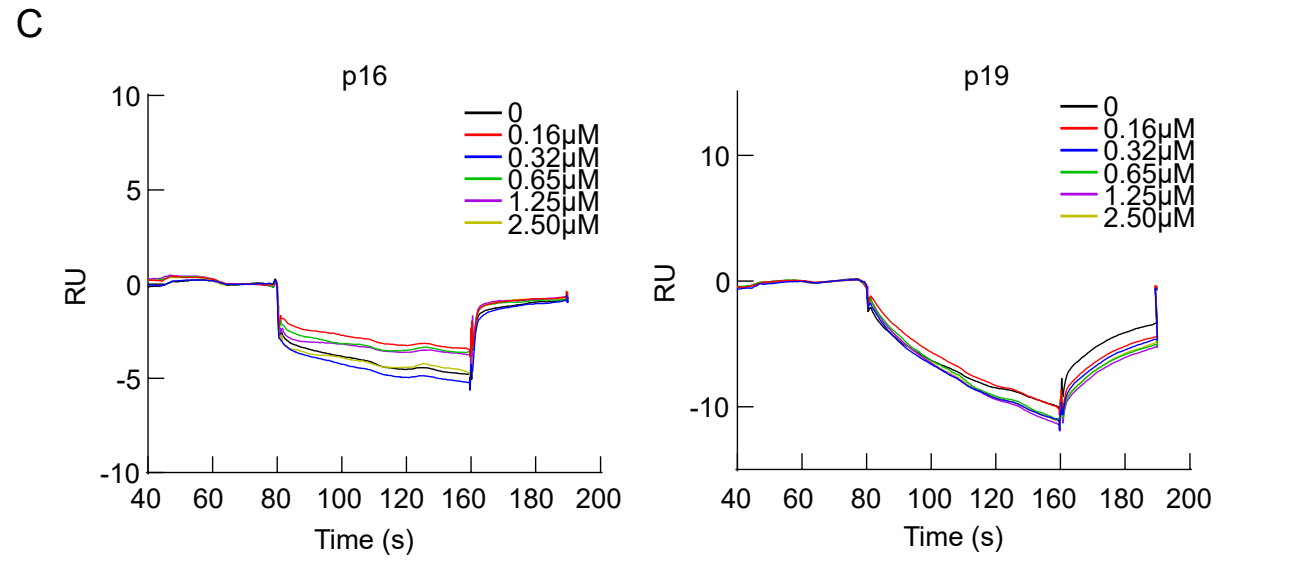
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Time (s)

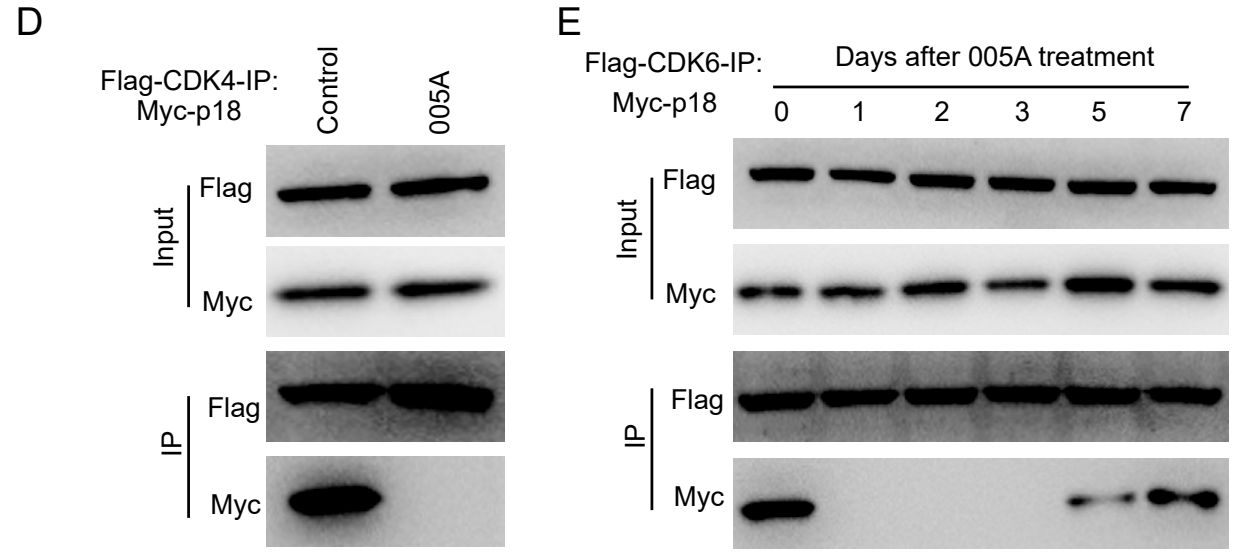
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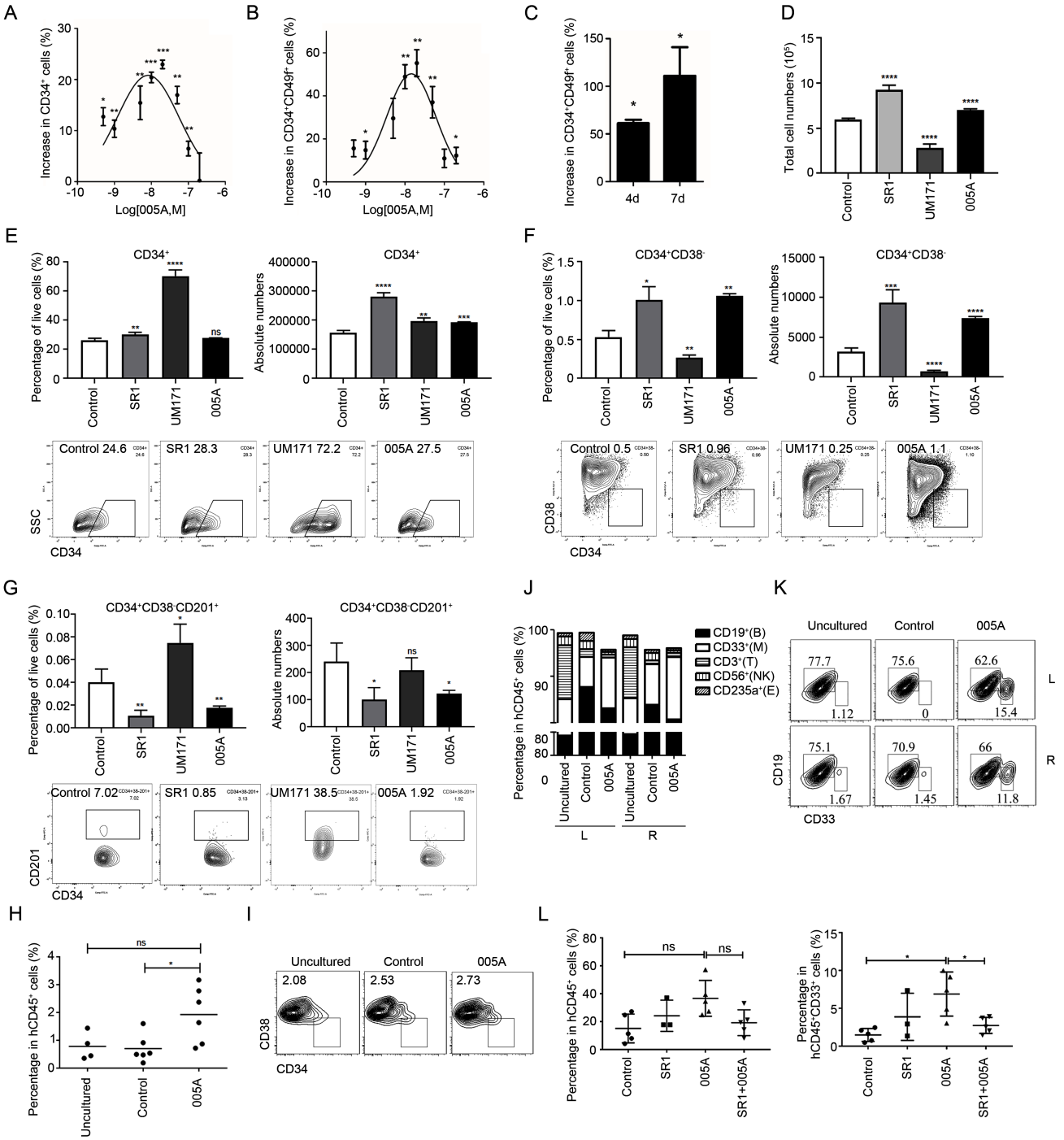
Figure S3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Increase in CD34+CD49f- cells (%)
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4d
7d
D
Total cell numbers (10^5)
Control
SR1
UM171
005A
E
CD34+
Percentage of live cells (%)
Absolute numbers
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SR1 28.3
UM171 72.2
005A 27.5
SSC
CD34
F
CD34+CD38-
Percentage of live cells (%)
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UM171 0.25
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CD38
CD34
G
CD34+CD38-CD201+
Percentage of live cells (%)
Absolute numbers
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CD201
CD34
J
Percentage in hCD45+ cells (%)
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CD33+(M)
CD3+(T)
CD56+(NK)
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0
62.6
15.4
75.1
1.67
70.9
1.45
66
11.8
CD19
CD33
H
Percentage in hCD45+ cells (%)
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Control
005A
I
Uncultured
Control
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2.53
2.73
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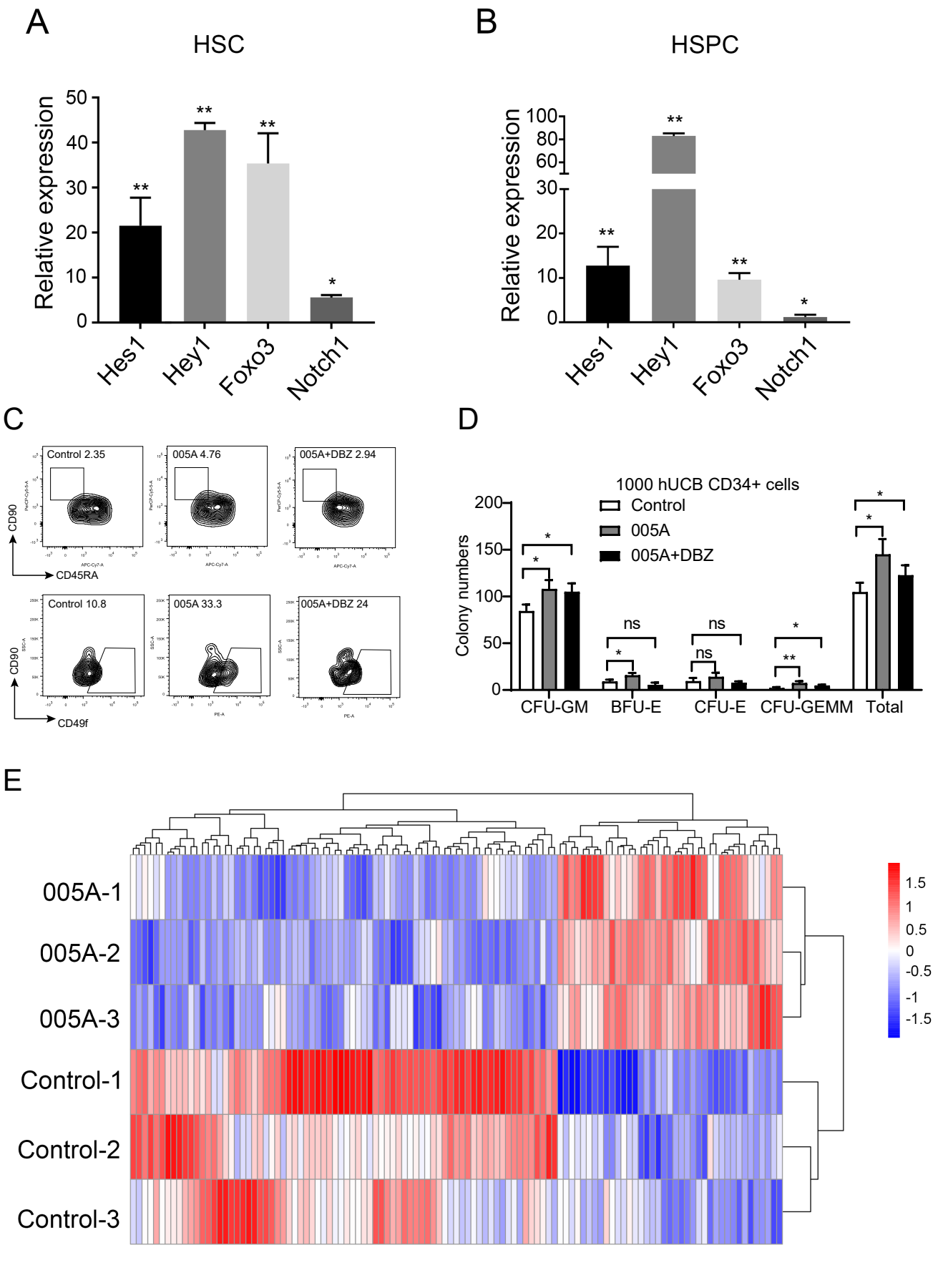
SR1+005A

Figure S4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HSPC
Relative expression
100
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30
20
10
0
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Hey1
Foxo3
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CD45RA
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CD49f
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Colony numbers
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