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(54) **COMPOSITIONS AND METHODS FOR REPROGRAMMING HEMATOPOIETIC STEM CELL LINEAGES**

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(57) **ABSTRACT**

Provided herein are compositions, methods, and kits for hematopoietic stem cell induction or for reprogramming cells to the multipotent state of hematopoietic stem cells. In some embodiments, the compositions comprise at least one HSC inducing factor. Such compositions, methods and kits can be used for inducing hematopoietic stem cells in vitro, ex vivo, or in vivo, as described herein, and these induced hematopoietic stem cells can be used in regenerative medicine applications and therapies.

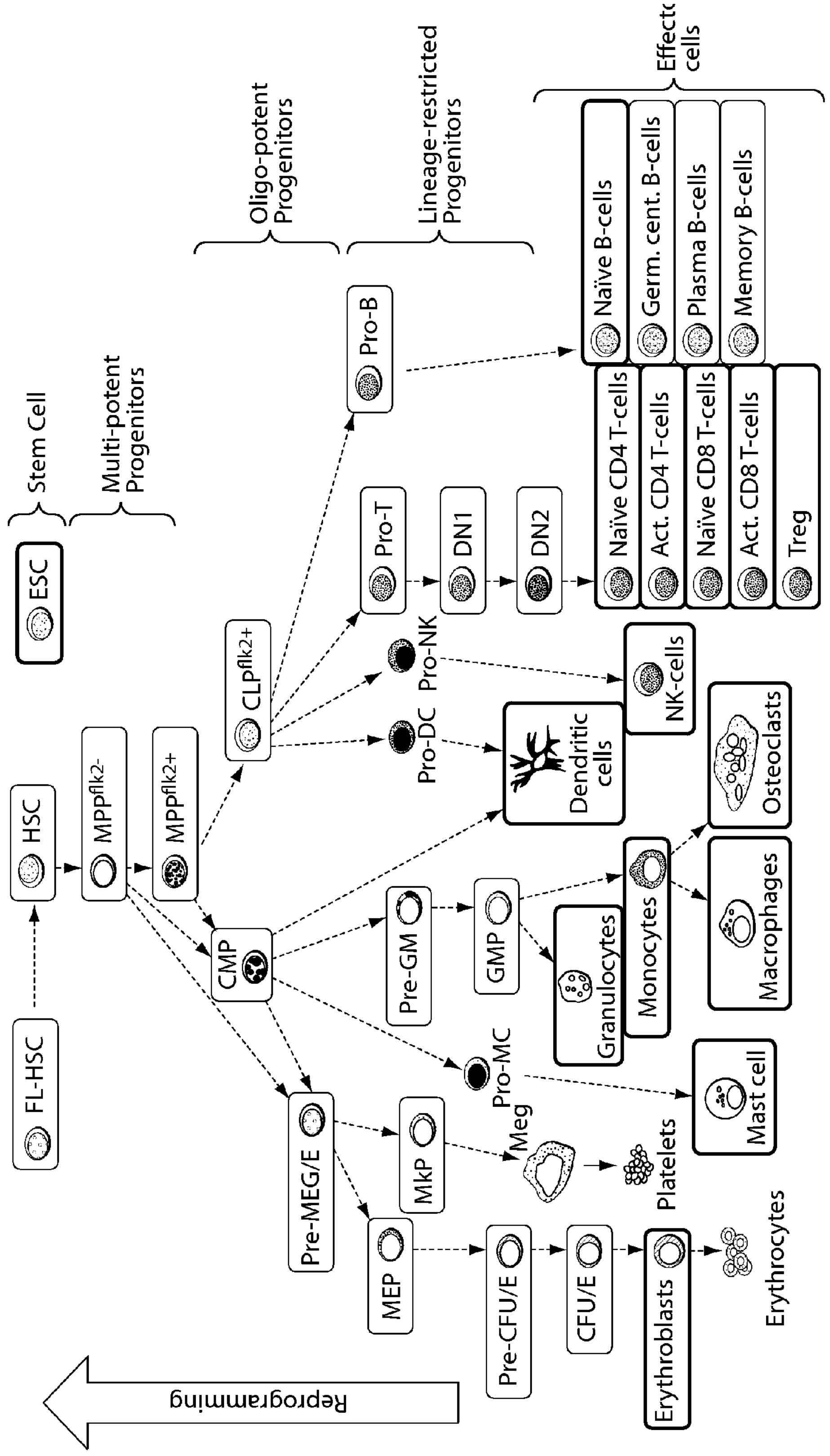

Stem Cell
Multi-potent Progenitors
Oligo-potent Progenitors
Lineage-restricted Progenitors
Effect
cells
ESC
FL-HSC
HSC
MPP^{flk2-}
MPP^{flk2+}
CLP^{flk2+}
CMP
Pre-MEG/E
MEP
MkP
Meg
Platelets
Pre-CFU/E
CFU/E
Erythroblasts
Erythrocytes
Pro-MC
Mast cell
Pre-GM
GMP
Granulocytes
Monocytes
Macrophages
Osteoclasts
Dendritic cells
Pro-DC
Pro-NK
NK-cells
Pro-T
DN1
DN2
Naïve CD4 T-cells
Act. CD4 T-cells
Naïve CD8 T-cells
Act. CD8 T-cells
Treg
Pro-B
Naïve B-cells
Germ. cent. B-cells
Plasma B-cells
Memory B-cells
Reprogramming

Fig. 1

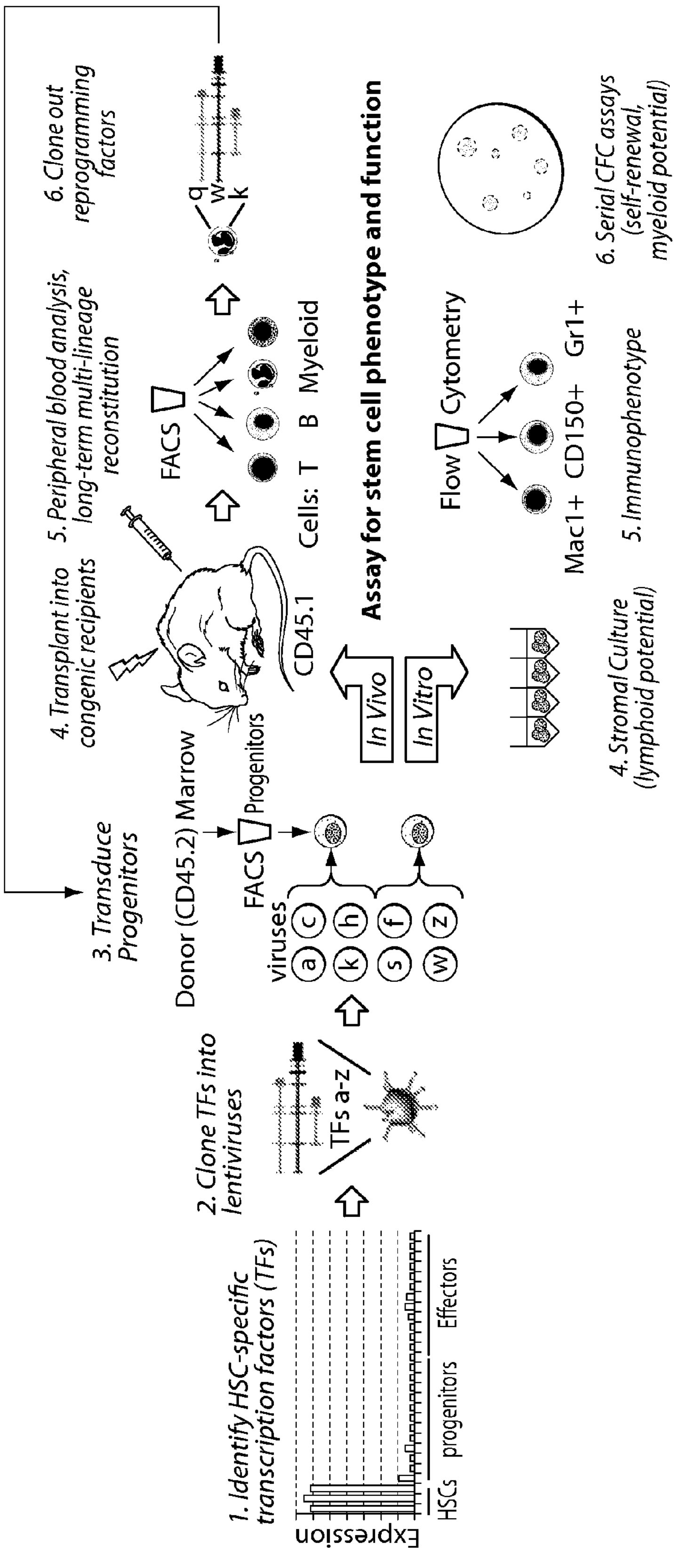

7. Validate, define minimal complement of reprogramming factors
1. Identify HSC-specific transcription factors (TFs)
Expression
HSCs
progenitors
Effectors
2. Clone TFs into lentiviruses
TFs a-z
viruses
a
c
k
h
s
f
w
z
3. Transduce Progenitors
Donor (CD45.2) Marrow
FACS
Progenitors
4. Transplant into congenic recipients
CD45.1
5. Peripheral blood analysis, long-term multi-lineage reconstitution
FACS
Cells: T B Myeloid
6. Clone out reprogramming factors
b
w
k
In Vivo
In Vitro
Assay for stem cell phenotype and function
4. Stromal Culture (lymphoid potential)
Flow Cytometry
Mac1+ CD150+ Gr1+
5. Immunophenotype
6. Serial CFC assays (self-renewal, myeloid potential)

Fig. 2

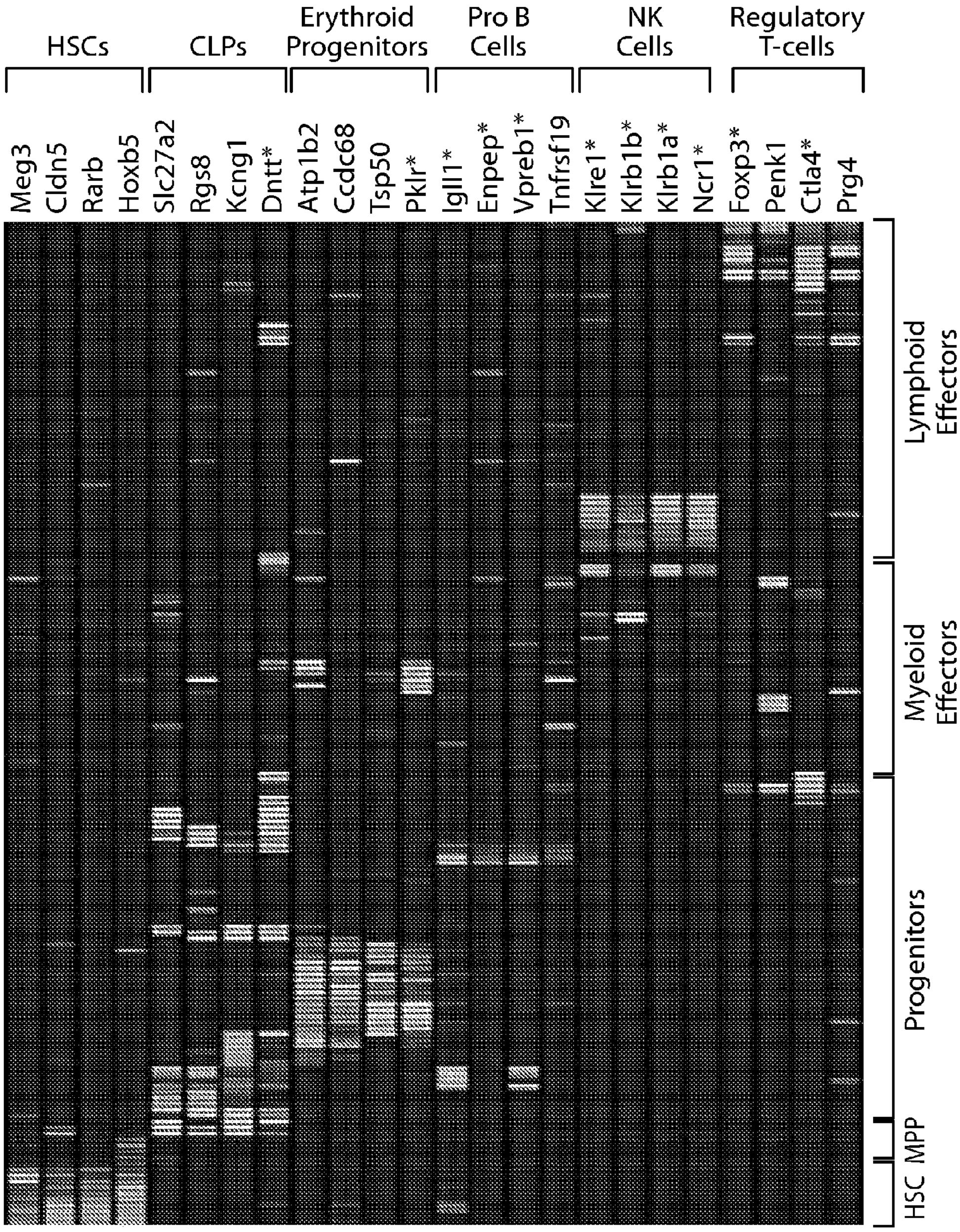

HSCs
CLPs
Erythroid Progenitors
Pro B Cells
NK Cells
Regulatory T-cells
Meg3
Cldn5
Rarb
Hoxb5
Slc27a2
Rgs8
Kcng1
Dntt*
Atp1b2
Ccdc68
Tsp50
Pklr*
Igll1*
Enpep*
Vpreb1*
Tnfrsf19
Klre1*
Klrb1b*
Klrb1a*
Ncr1*
Foxp3*
Penk1
Ctla4*
Prg4
Lymphoid Effectors
Myeloid Effectors
Progenitors
MPP
HSC

Fig. 3

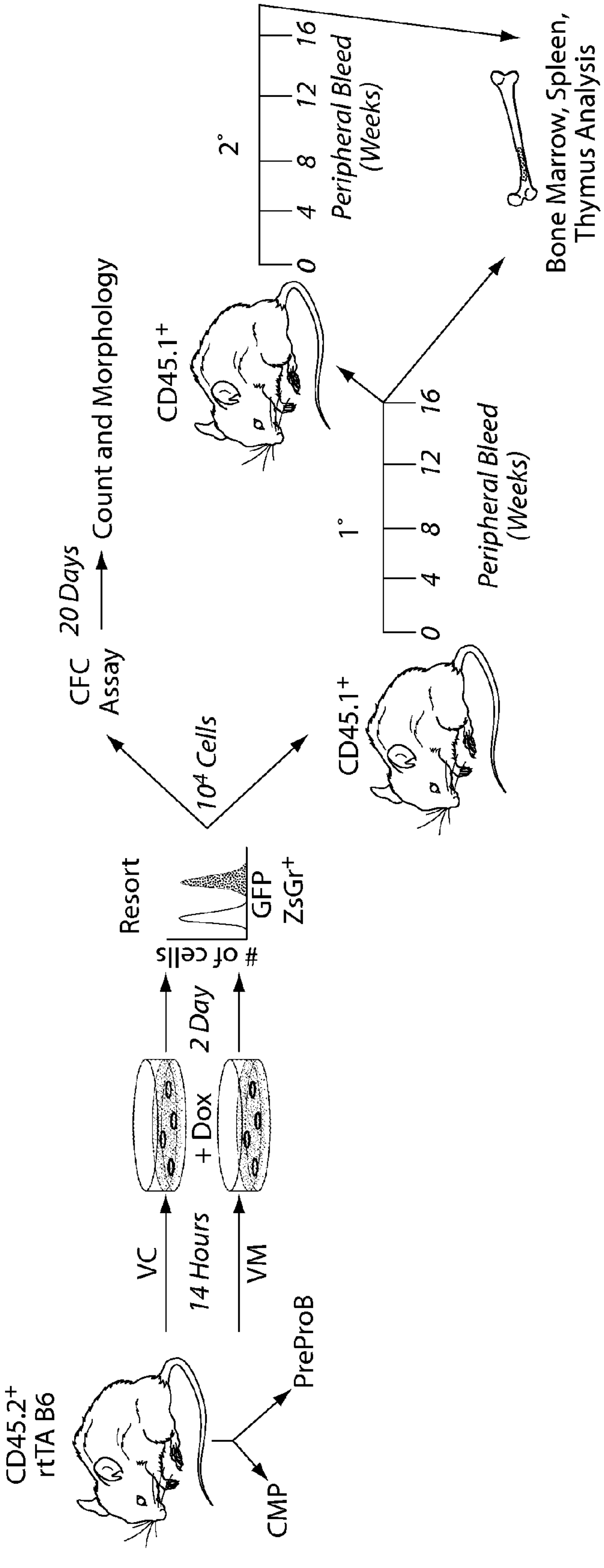
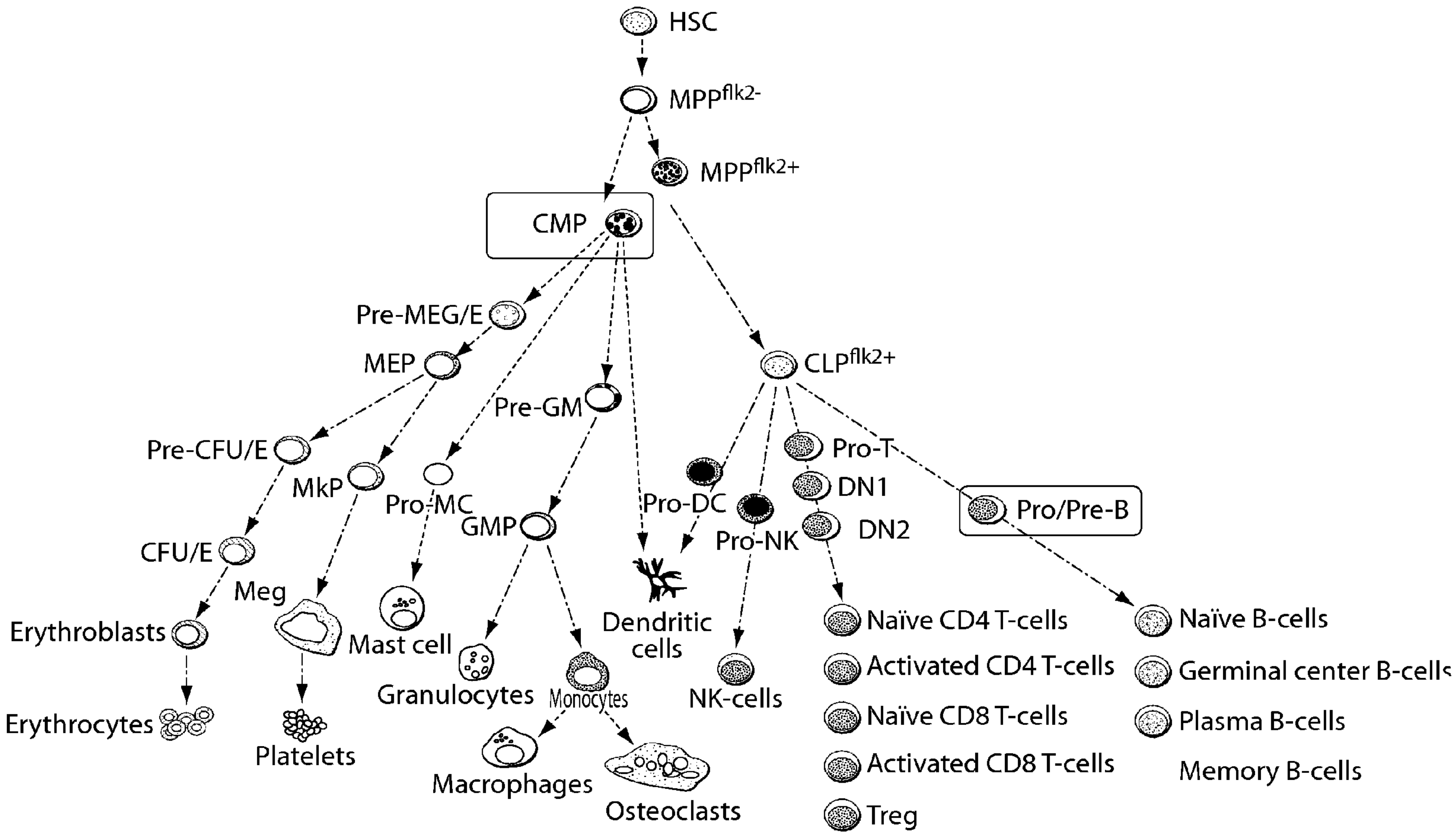

CD45.2+
rtTA B6
CMP
PreProB
VC
14 Hours
VM
+ Dox
2 Day
# of cells
Resort
GFP
ZsGr+
10^4 Cells
CFC
Assay
20 Days
Count and Morphology
CD45.1+
1°
0
4
8
12
16
Peripheral Bleed
(Weeks)
CD45.1+
2°
0
4
8
12
16
Peripheral Bleed
(Weeks)
Bone Marrow, Spleen,
Thymus Analysis

Fig. 4A



CMP: Lin^{-}, c-kit^{+}, Sca^{-}, CD34^{+}, FcγR^{low}

ProPreB Cell: B220^{+}, CD19^{+}, AA4.1^{+}, IgM^{low}, c-kit^{-}, CD25$^{+/-}$

Fig. 4B

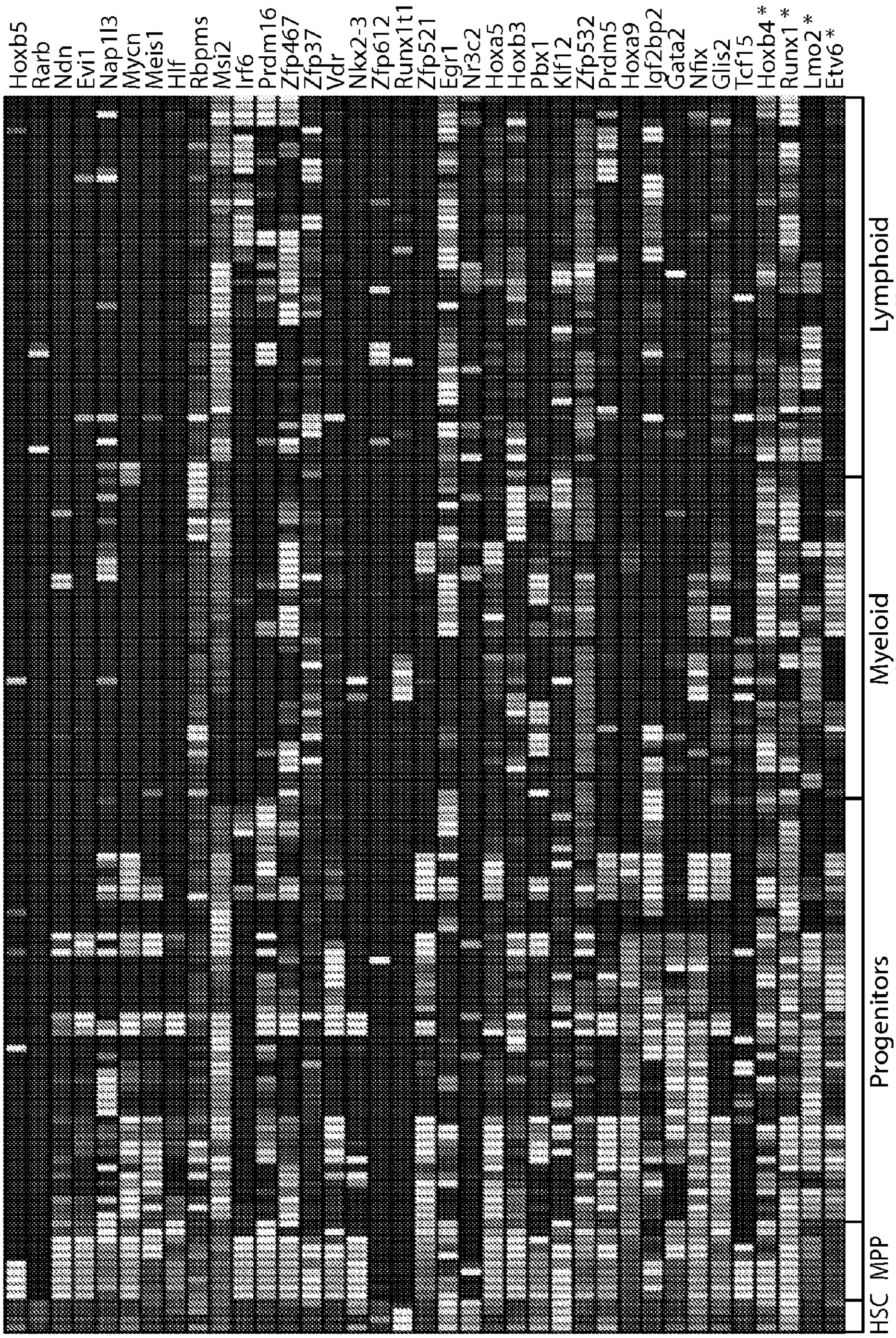

Hoxb5
Rarb
Ndn
Evi1
Nap1l3
Mycn
Meis1
Hlf
Rbpms
Msi2
Irf6
Prdm16
Zfp467
Zfp37
Vdr
Nkx2-3
Zfp612
Runx1t1
Zfp521
Egr1
Nr3c2
Hoxa5
Hoxb3
Pbx1
Klf12
Zfp532
Prdm5
Hoxa9
Igf2bp2
Gata2
Nfix
Glis2
Tcf15
Hoxb4 *
Runx1 *
Lmo2 *
Etv6 *
HSC
MPP
Progenitors
Myeloid Effectors
Lymphoid Effectors

Fig. 5A

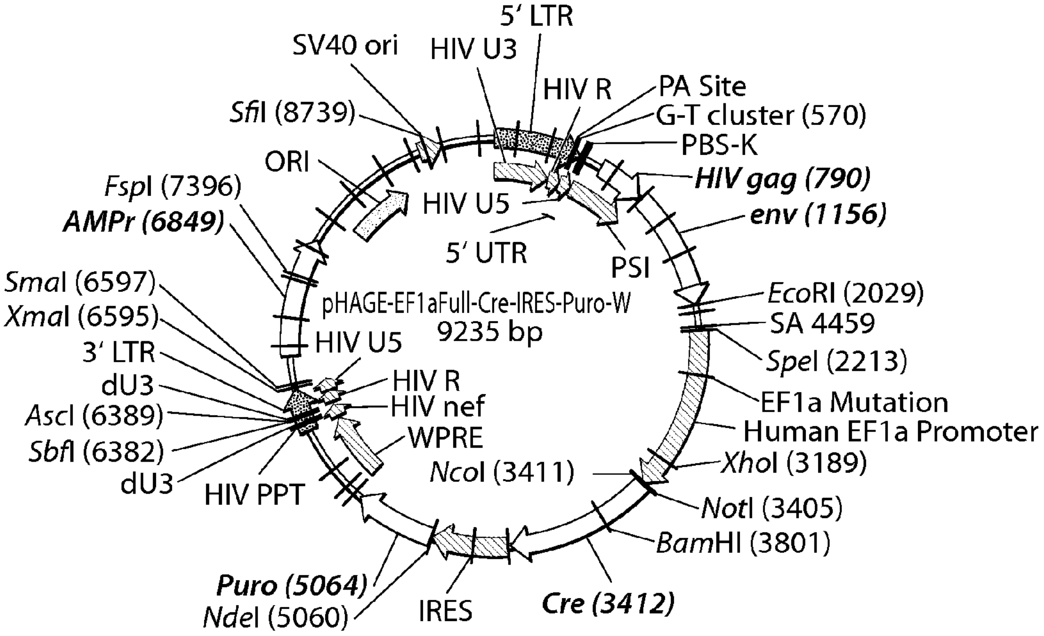

5′ LTR
SV40 ori
HIV U3
HIV R
PA Site
G-T cluster (570)
PBS-K
*Sfi*I (8739)
ORI
HIV gag (790)
*Fsp*I (7396)
HIV U5
AMPr (6849)
env (1156)
5′ UTR
PSI
*Sma*I (6597)
*Eco*RI (2029)
pHAGE-EF1aFull-Cre-IRES-Puro-W
9235 bp
*Xma*I (6595)
SA 4459
HIV U5
3′ LTR
*Spe*I (2213)
dU3
HIV R
EF1a Mutation
*Asc*I (6389)
HIV nef
Human EF1a Promoter
WPRE
*Sbf*I (6382)
*Xho*I (3189)
*Nco*I (3411)
dU3
HIV PPT
*Not*I (3405)
*Bam*HI (3801)
Puro (5064)
Cre (3412)
IRES
*Nde*I (5060)

Fig. 5B

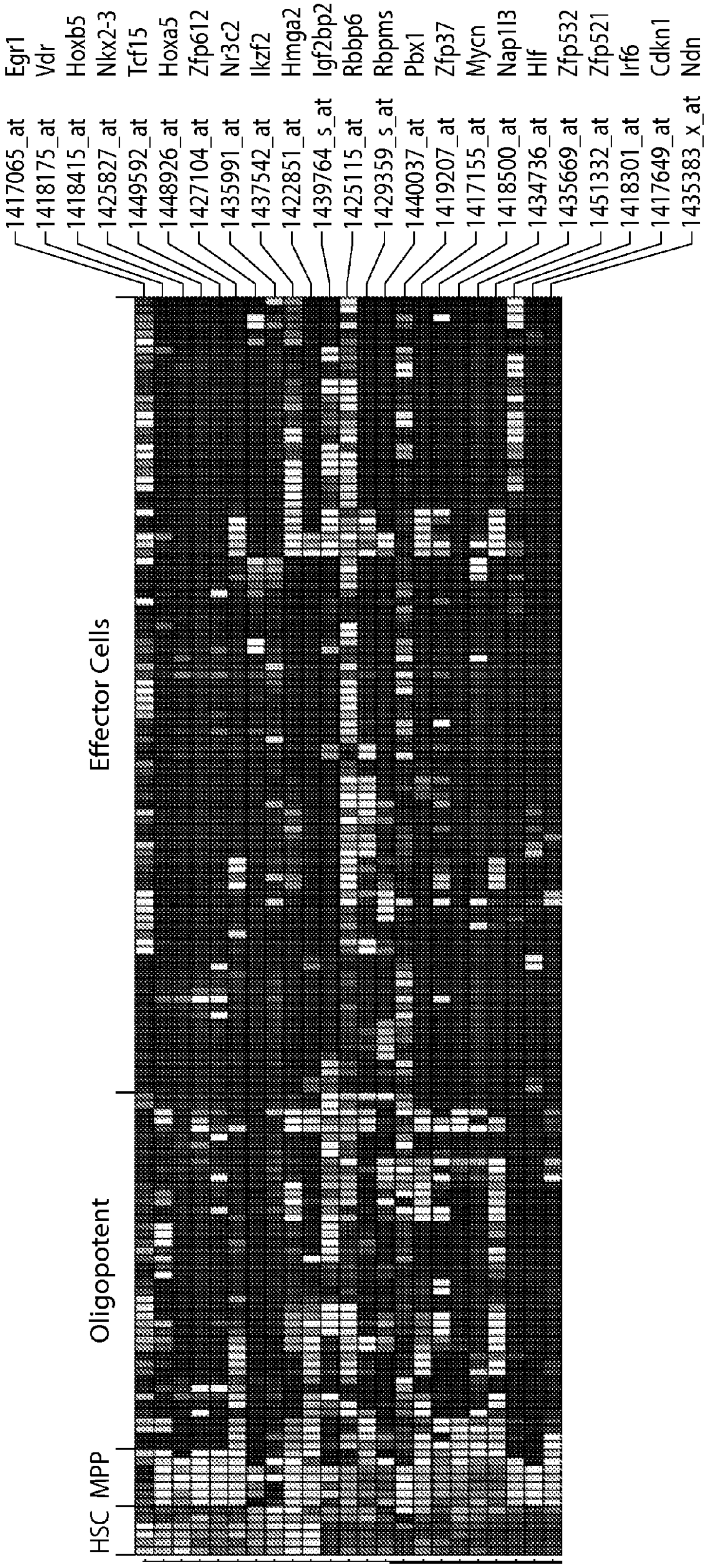

1417065_at Egr1
1418175_at Vdr
1418415_at Hoxb5
1425827_at Nkx2-3
1449592_at Tcf15
1448926_at Hoxa5
1427104_at Zfp612
1435991_at Nr3c2
1437542_at Ikzf2
1422851_at Hmga2
1439764_s_at Igf2bp2
1425115_at Rbbp6
1429359_s_at Rbpms
1440037_at Pbx1
1419207_at Zfp37
1417155_at Mycn
1418500_at Nap1l3
1434736_at Hlf
1435669_at Zfp532
1451332_at Zfp521
1418301_at Irf6
1417649_at Cdkn1
1435383_x_at Ndn
Effector Cells
Oligopotent
MPP
HSC

Fig. 5C-1

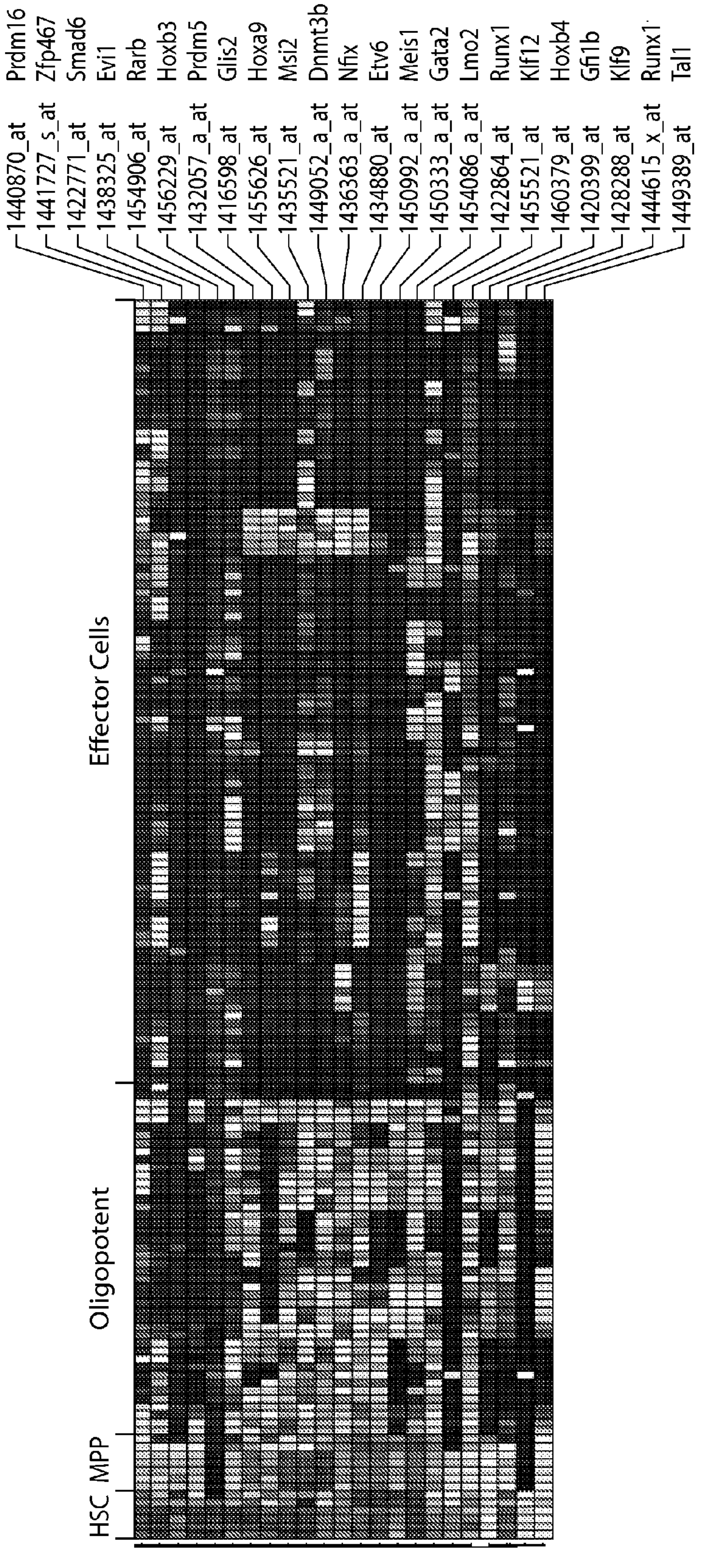

1440870_at Prdm16
1441727_s_at Zfp467
1422771_at Smad6
1438325_at Evi1
1454906_at Rarb
1456229_at Hoxb3
1432057_a_at Prdm5
1416598_at Glis2
1455626_at Hoxa9
1435521_at Msi2
1449052_a_at Dnmt3b
1436363_a_at Nfix
1434880_at Etv6
1450992_a_at Meis1
1450333_a_at Gata2
1454086_a_at Lmo2
1422864_at Runx1
1455521_at Klf12
1460379_at Hoxb4
1420399_at Gfi1b
1428288_at Klf9
1444615_x_at Runx1
1449389_at Tal1
Effector Cells
Oligopotent
HSC MPP

Fig. 5C-2

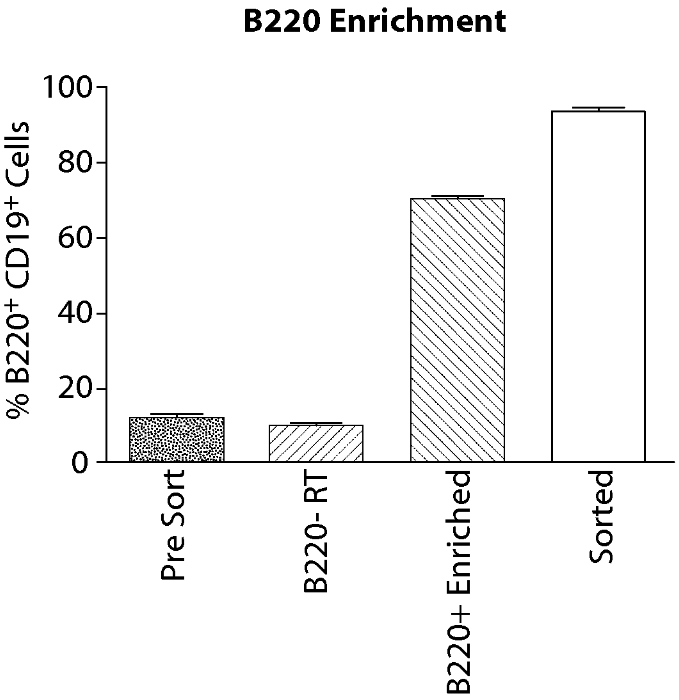

B220 Enrichment
% B220+ CD19+ Cells
100
80
60
40
20
0
Pre Sort
B220- RT
B220+ Enriched
Sorted

Fig. 6A

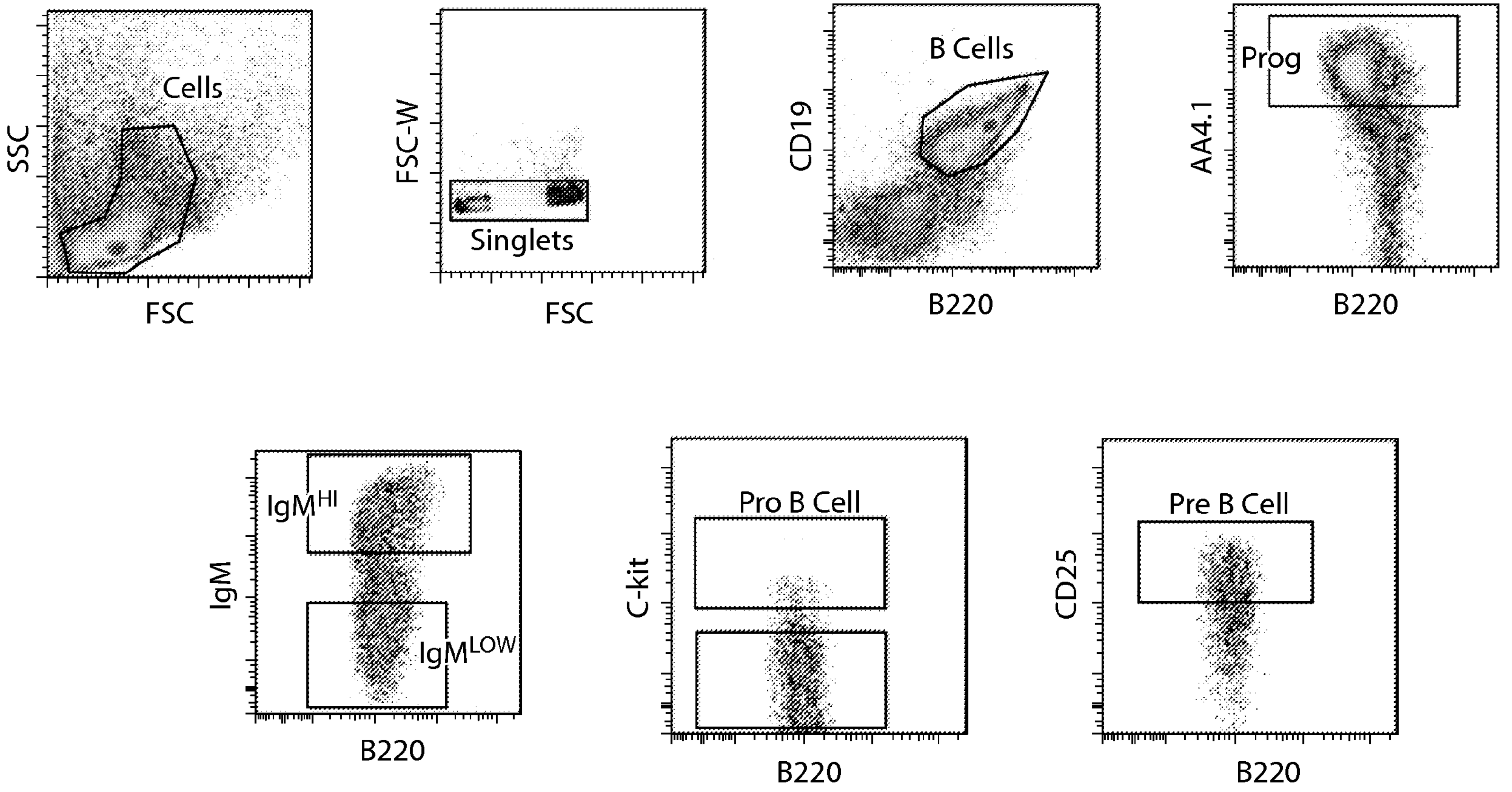

Cells
SSC
FSC
FSC-W
Singlets
FSC
B Cells
CD19
B220
Prog
AA4.1
B220
IgM^HI
IgM
IgM^LOW
B220
Pro B Cell
C-kit
B220
Pre B Cell
CD25
B220

Fig. 6B

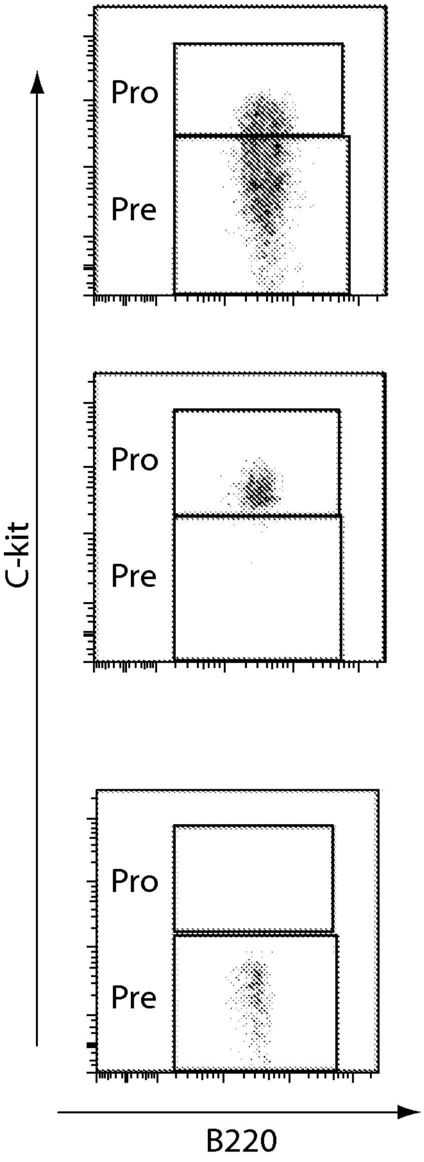


Fig. 6C

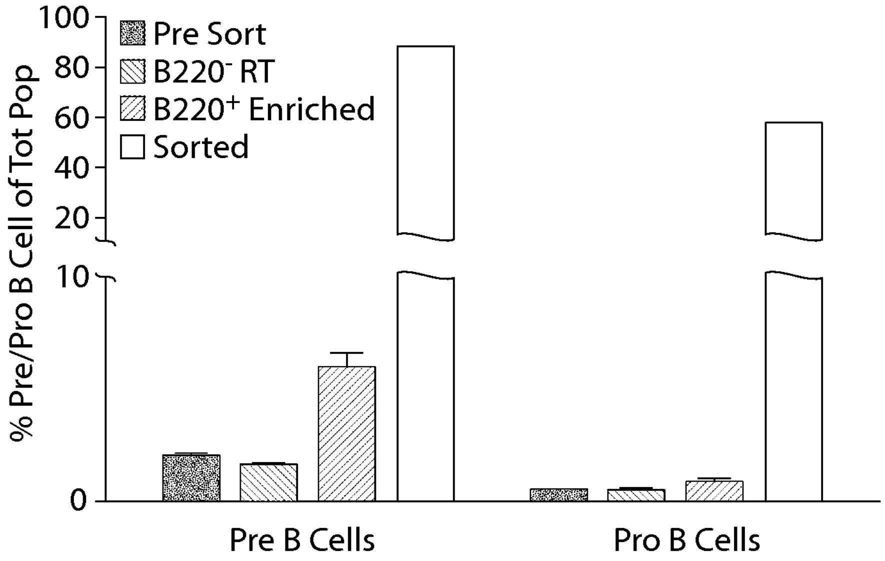

100
80
60
40
20
10
0
% Pre/Pro B Cell of Tot Pop
Pre Sort
B220⁻ RT
B220⁺ Enriched
Sorted
Pre B Cells
Pro B Cells

Fig. 6D

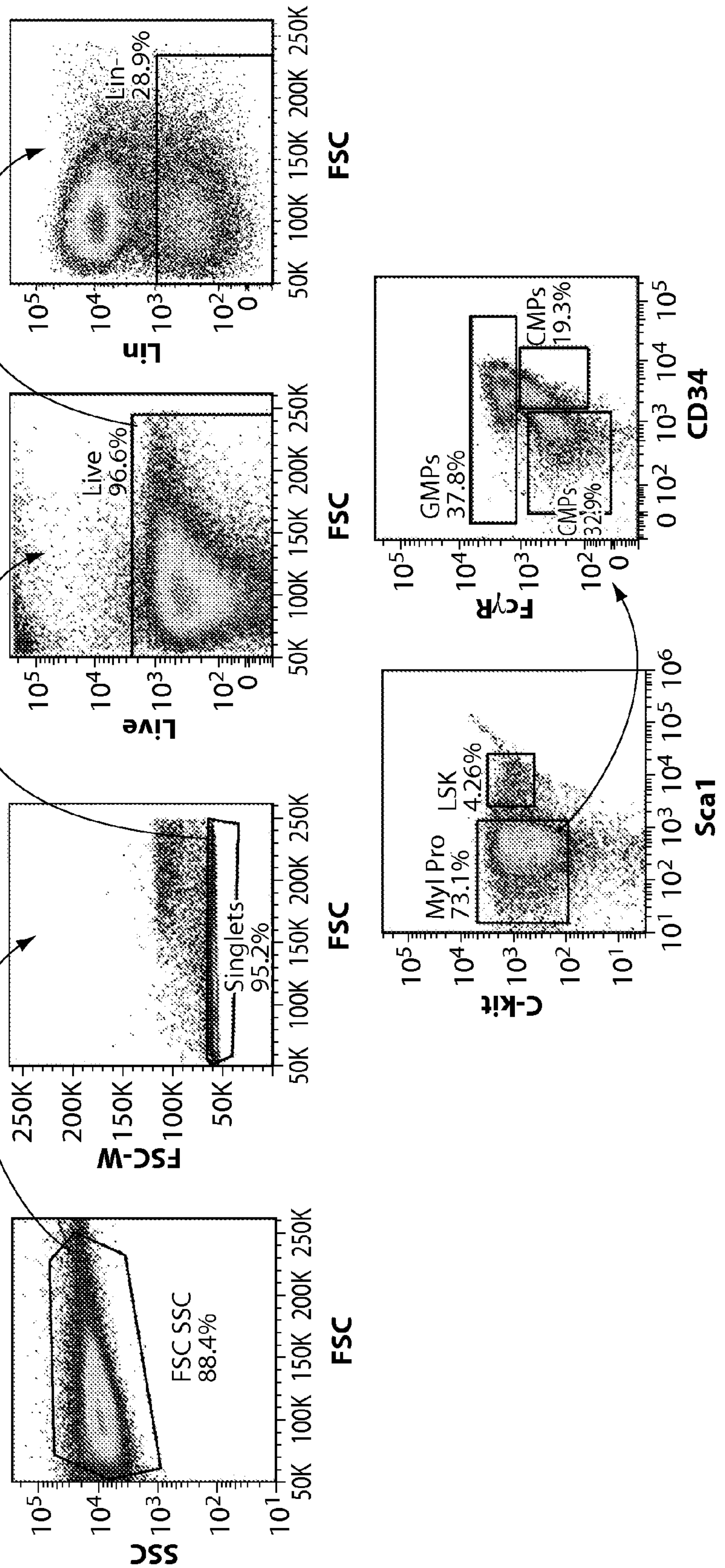

SSC
10^5
10^4
10^3
10^2
10^1
50K 100K 150K 200K 250K
FSC
FSC SSC
88.4%
FSC-W
250K
200K
150K
100K
50K
FSC
Singlets
95.2%
Live
96.6%
FSC
0
Lin
Lin-
28.9%
FSC
C-kit
Sca1
10^6
Myl Pro
73.1%
LSK
4.26%
FcγR
CD34
GMPs
37.8%
CMPs
19.3%
CMPs
32.9%

Fig. 7A

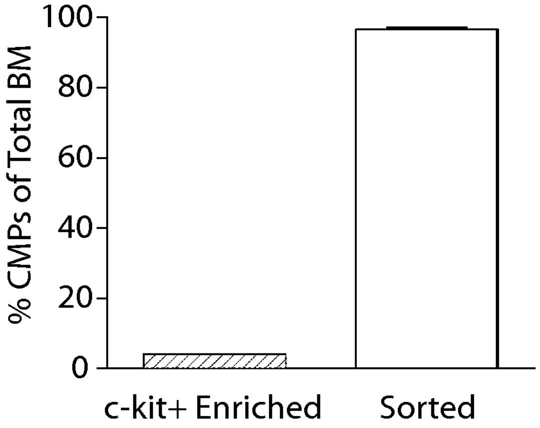


Fig. 7B

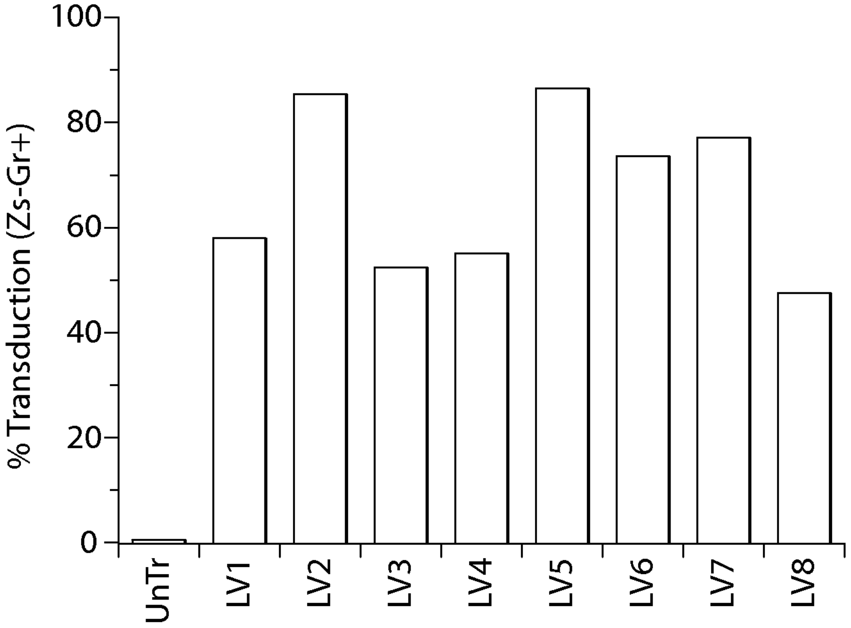

% Transduction (Zs-Gr+)
100
80
60
40
20
0
UnTr
LV1
LV2
LV3
LV4
LV5
LV6
LV7
LV8

Fig. 8A

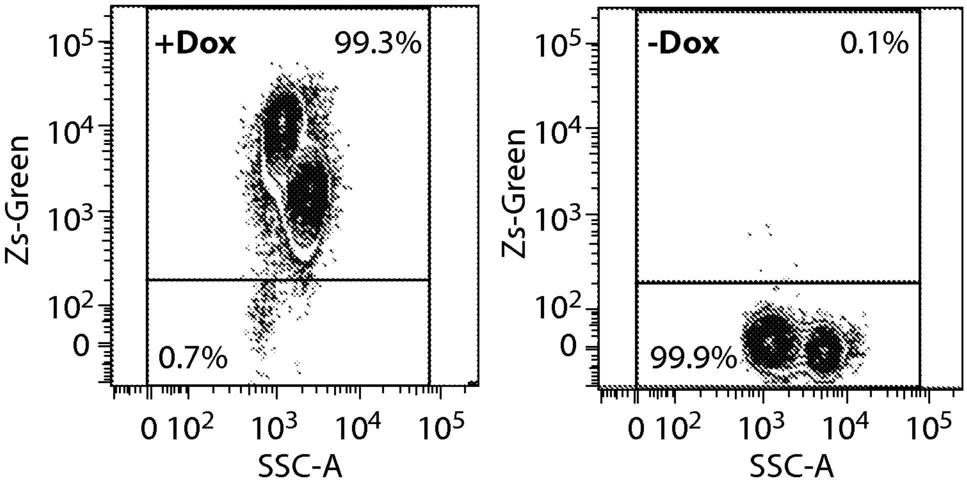
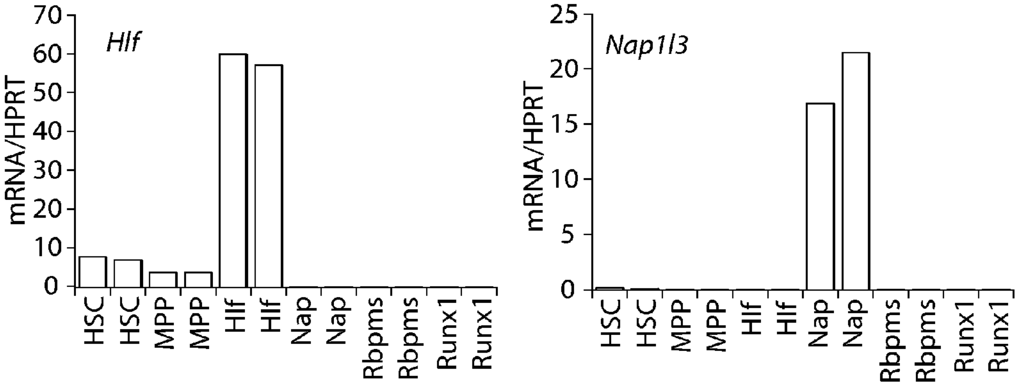
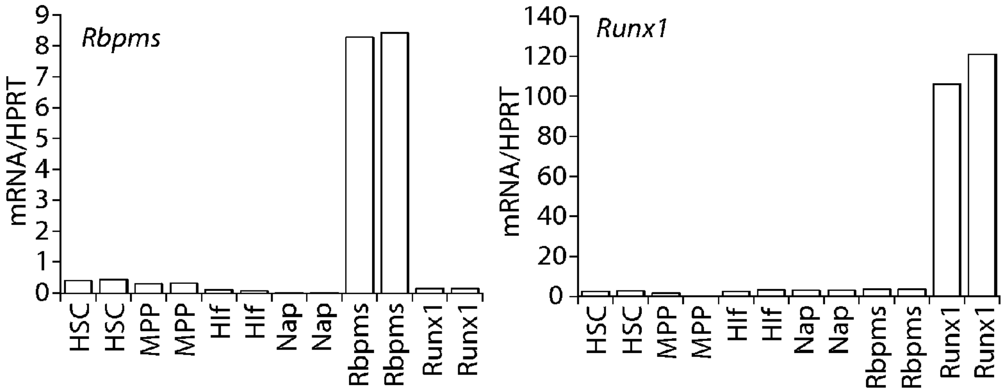

+Dox
99.3%
0.7%
-Dox
0.1%
99.9%
Zs-Green
10^5
10^4
10^3
10^2
0
SSC-A
0 10^2 10^3 10^4 10^5

Fig. 8B



Hlf Nap1l3



Rbpms Runx'

Fig. 8C

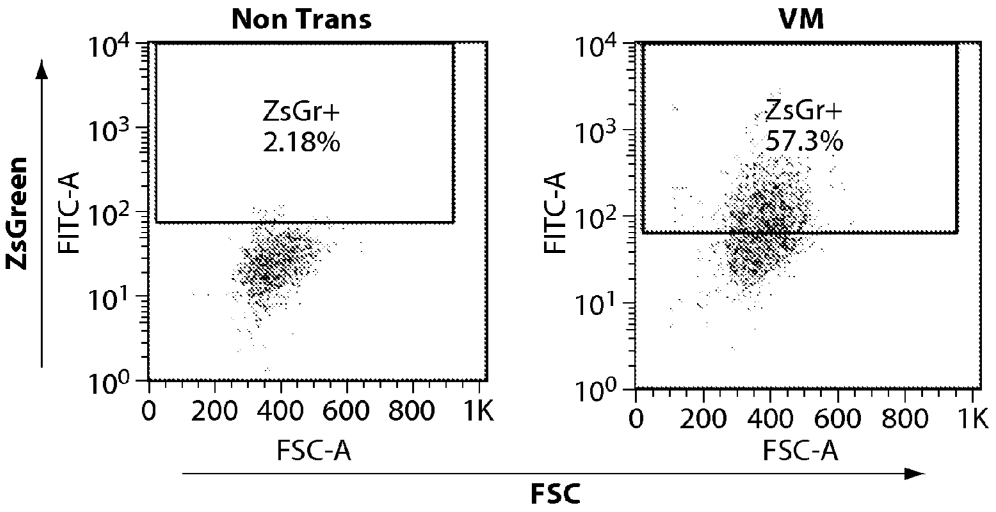


Fig. 9A

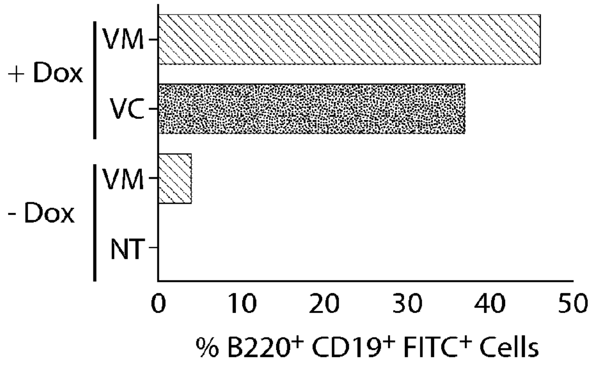


Fig. 9B

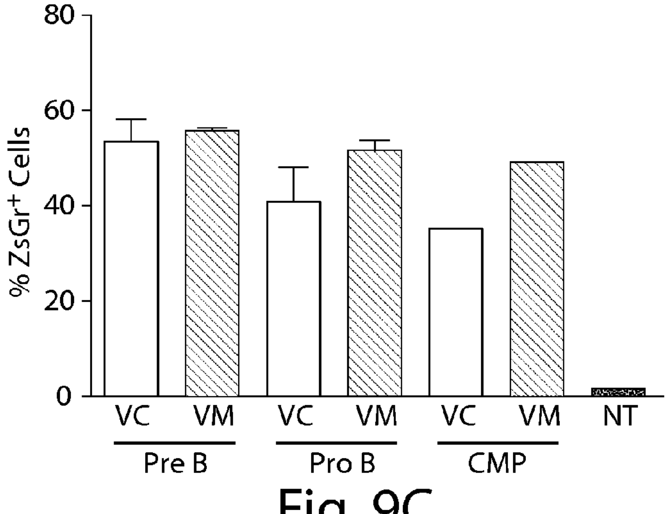


Fig. 9C

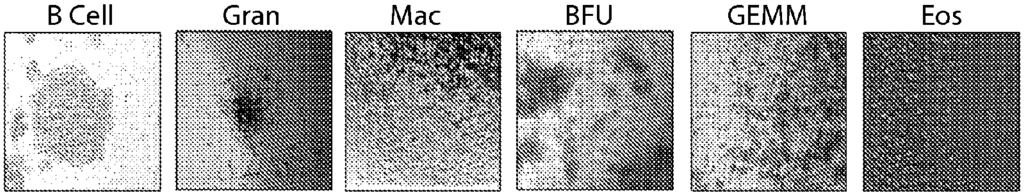


Fig. 10A

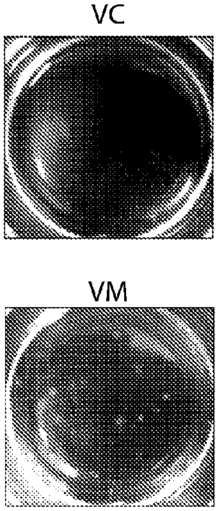


Fig. 10B

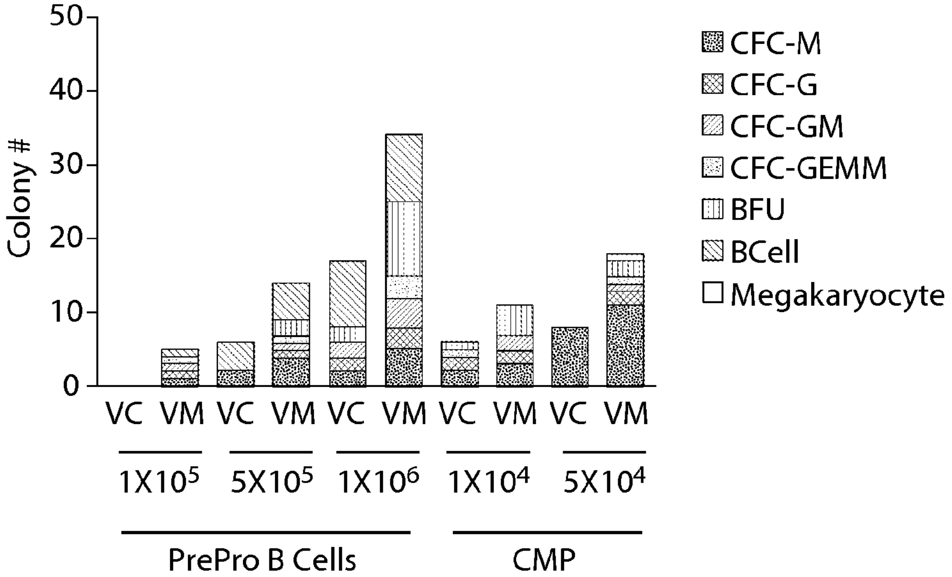


Fig. 10C

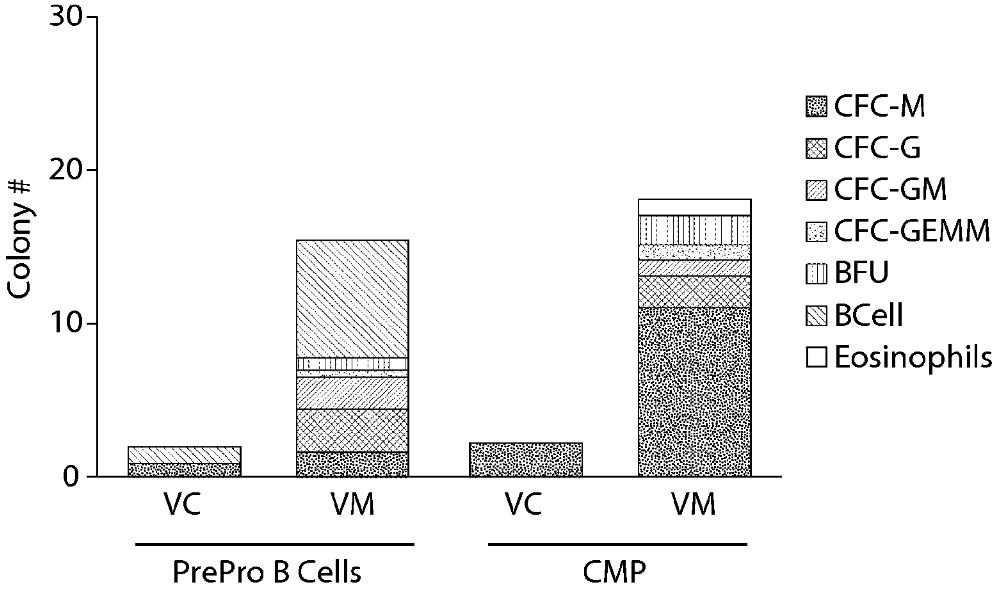


Fig. 10D

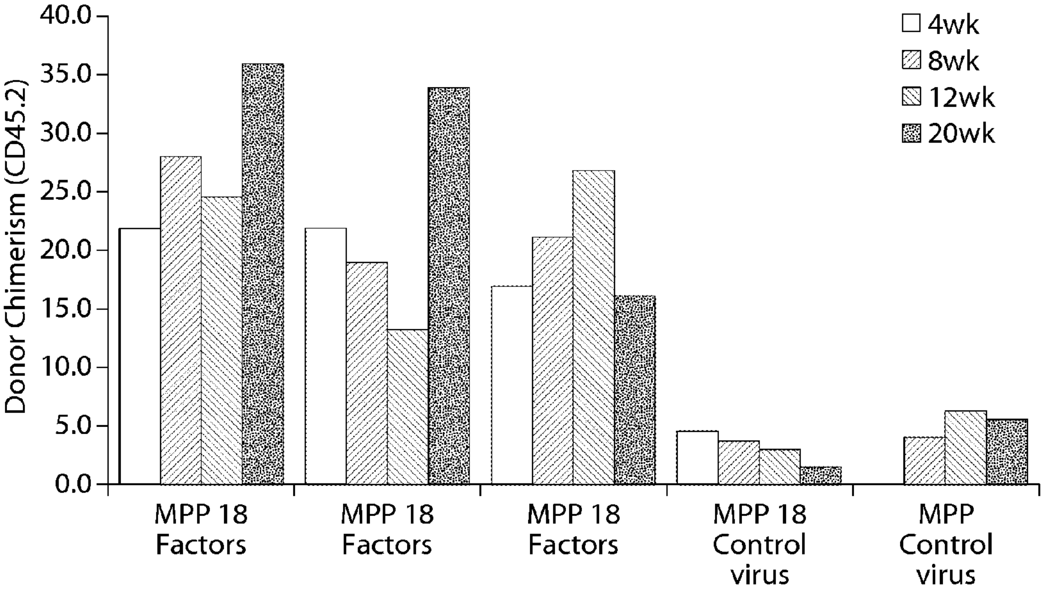

Donor Chimerism (CD45.2)
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
☐ 4wk
▨ 8wk
▧ 12wk
▩ 20wk
MPP 18 Factors
MPP 18 Factors
MPP 18 Factors
MPP 18 Control virus
MPP Control virus

Fig. 11

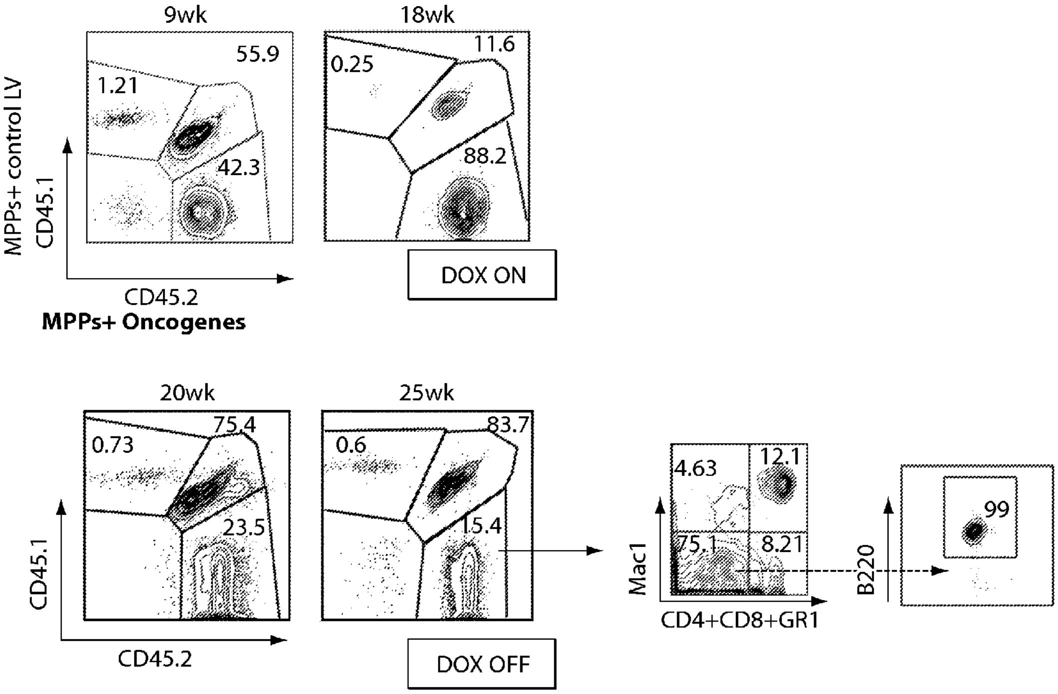

9wk
18wk
MPPs+ control LV
CD45.1
CD45.2
MPPs+ Oncogenes
1.21
55.9
42.3
0.25
11.6
88.2
DOX ON
20wk
25wk
CD45.1
CD45.2
0.73
75.4
23.5
0.6
83.7
15.4
DOX OFF
Mac1
CD4+CD8+GR1
4.63
12.1
75.1
8.21
B220
99

Fig. 12

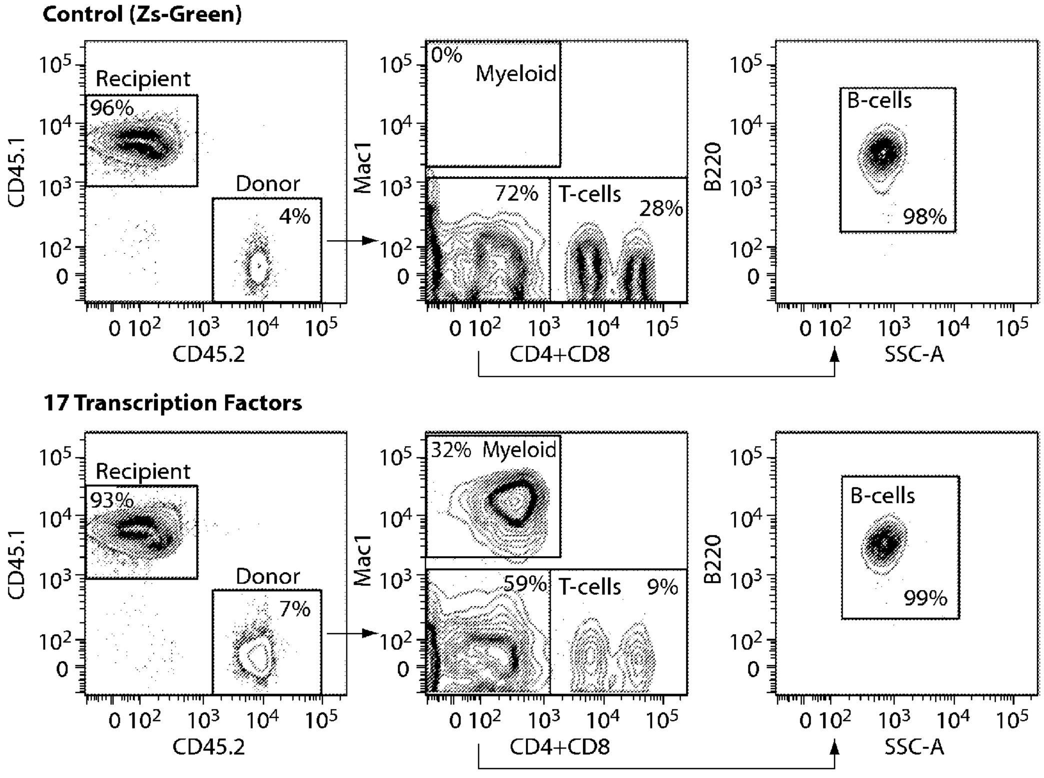

Control (Zs-Green)
CD45.1
Recipient
96%
Donor
4%
CD45.2
Mac1
0%
Myeloid
72%
T-cells
28%
CD4+CD8
B220
B-cells
98%
SSC-A
17 Transcription Factors
Recipient
93%
Donor
7%
32%
Myeloid
59%
T-cells
9%
B-cells
99%
10^5
10^4
10^3
10^2
0

Fig. 13A

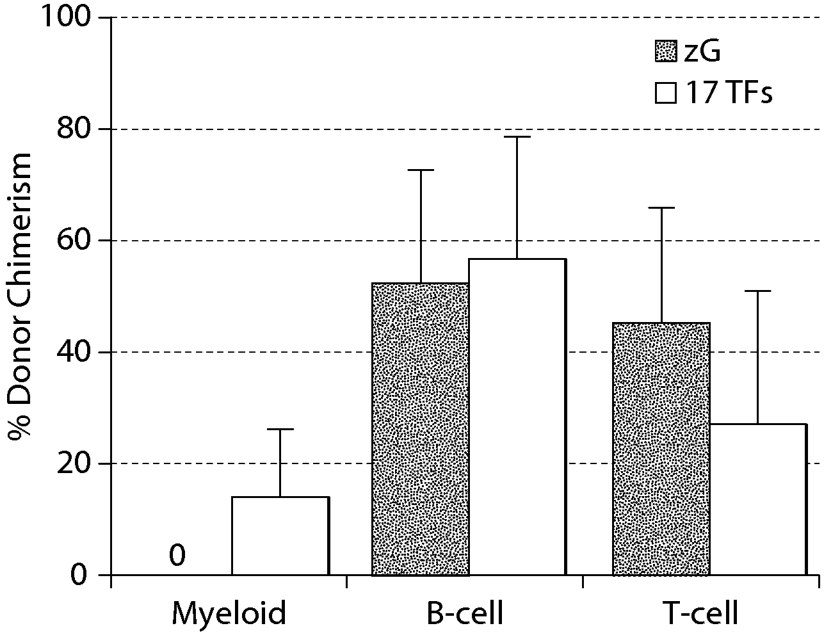

100
80
60
40
20
0
% Donor Chimerism
▨ zG
☐ 17 TFs
0
Myeloid
B-cell
T-cell

Fig. 13B

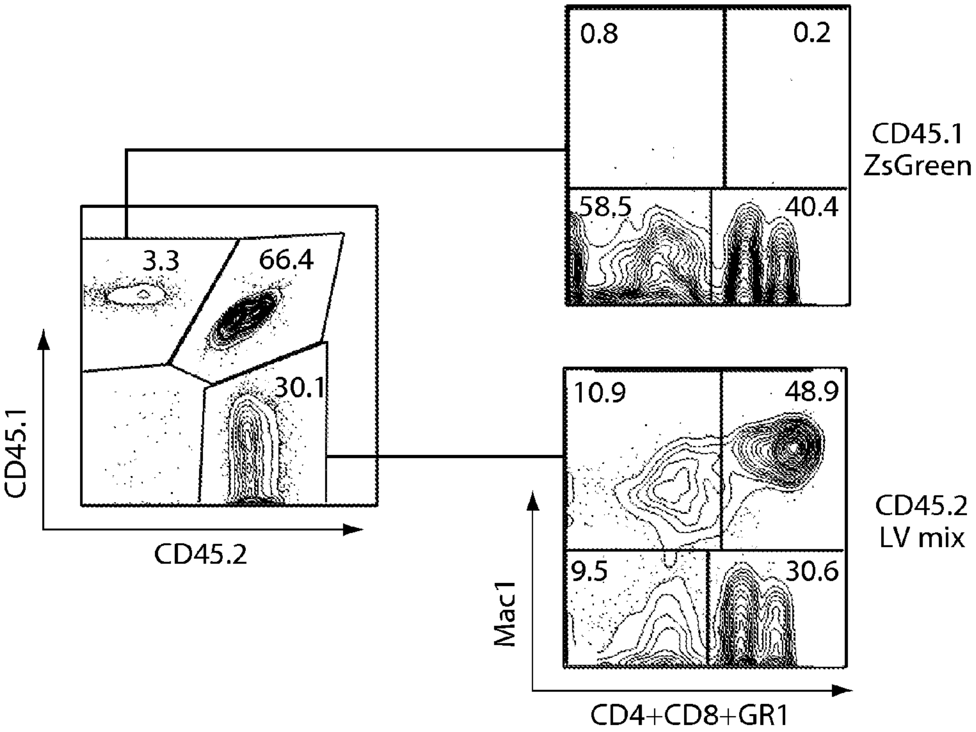

0.8
0.2
58.5
40.4
CD45.1
ZsGreen
3.3
66.4
30.1
CD45.1
CD45.2
10.9
48.9
9.5
30.6
CD45.2
LV mix
Mac1
CD4+CD8+GR1

Fig. 14

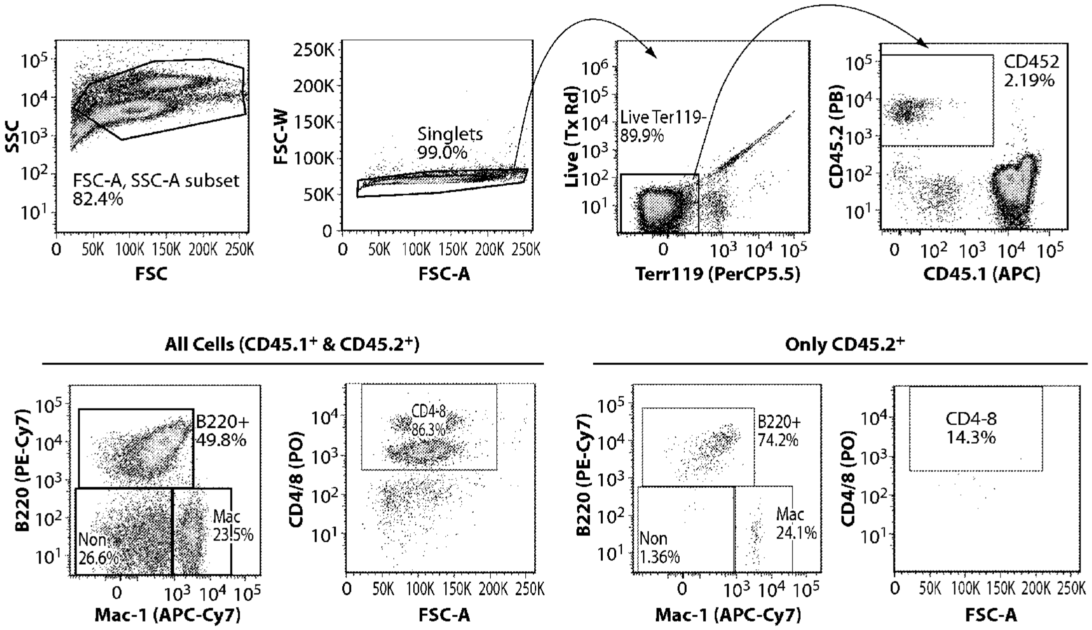

SSC
FSC
FSC-A, SSC-A subset
82.4%
FSC-W
FSC-A
Singlets
99.0%
Live (Tx Rd)
Terr119 (PerCP5.5)
Live Ter119-
89.9%
CD45.2 (PB)
CD45.1 (APC)
CD452
2.19%
All Cells (CD45.1+ & CD45.2+)
B220 (PE-Cy7)
Mac-1 (APC-Cy7)
B220+
49.8%
Non
26.6%
Mac
23.5%
CD4/8 (PO)
FSC-A
CD4-8
86.3%
Only CD45.2+
B220+
74.2%
Non
1.36%
Mac
24.1%
CD4-8
14.3%

Fig. 15

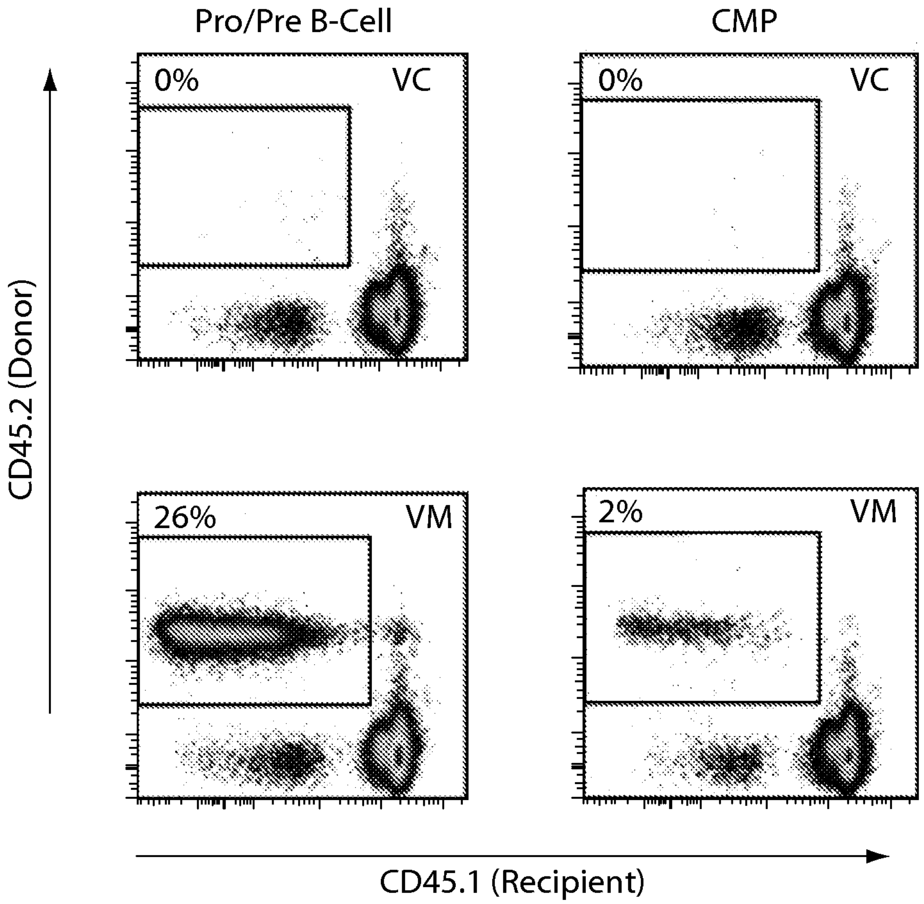

Pro/Pre B-Cell
CMP
0%
VC
0%
VC
26%
VM
2%
VM
CD45.2 (Donor)
CD45.1 (Recipient)

Fig. 16A

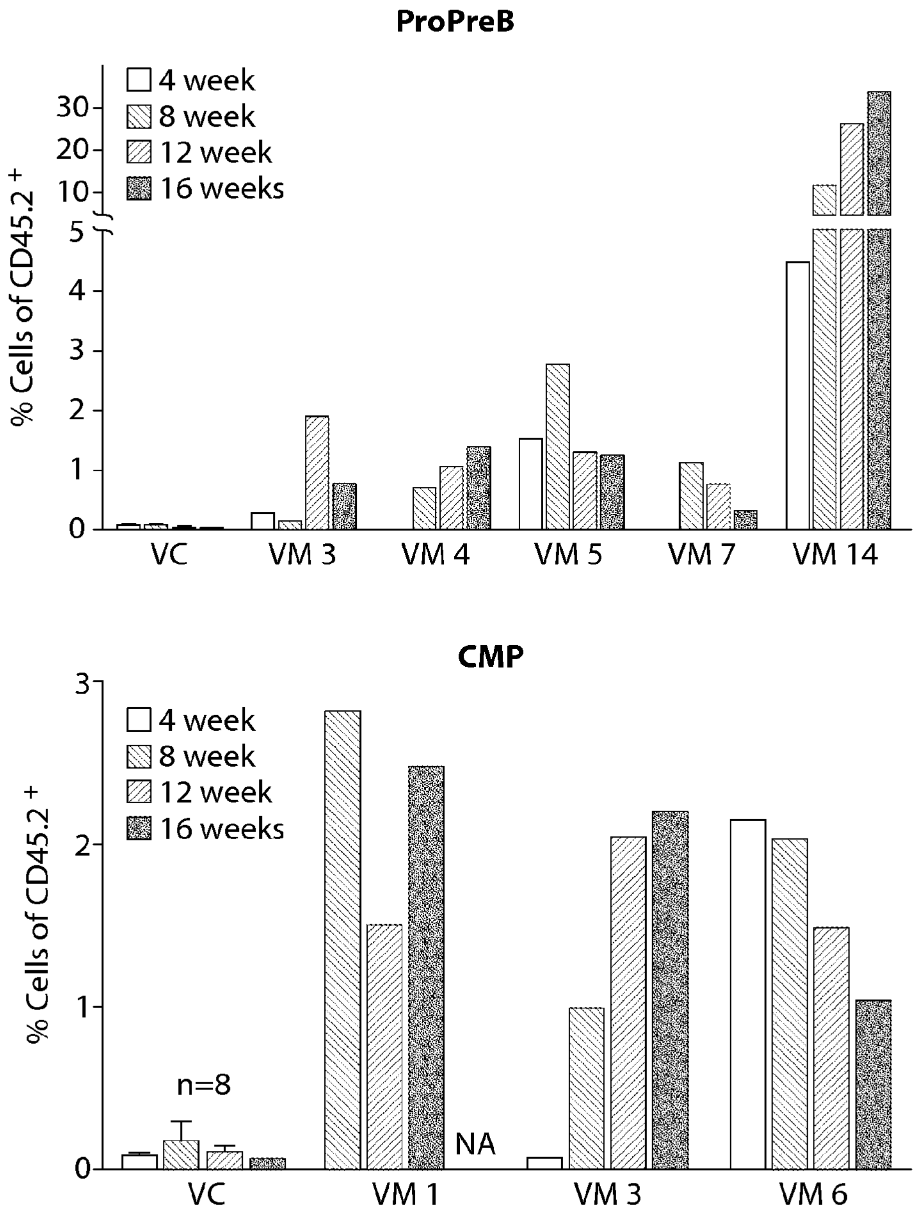

ProPreB
% Cells of CD45.2$^+$
30
20
10
5
4
3
2
1
0
4 week
8 week
12 week
16 weeks
VC
VM 3
VM 4
VM 5
VM 7
VM 14
CMP
% Cells of CD45.2$^+$
3
2
1
0
4 week
8 week
12 week
16 weeks
n=8
NA
VC
VM 1
VM 3
VM 6

Fig. 16B

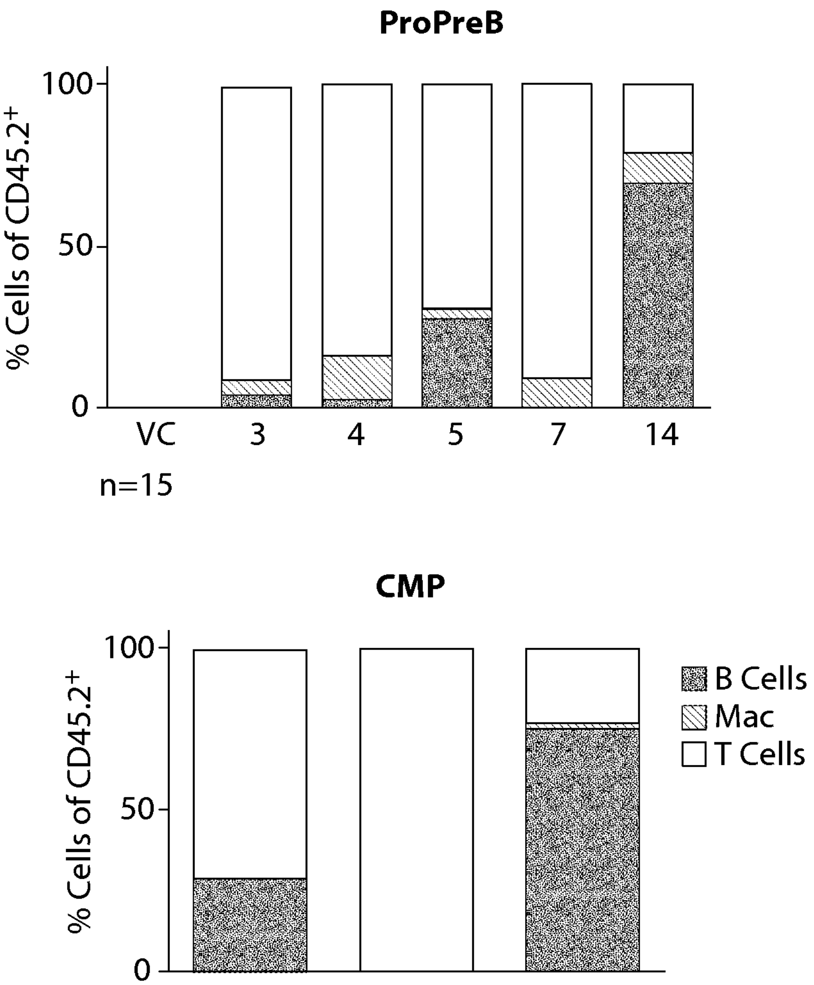

ProPreB
% Cells of CD45.2$^+$
100
50
0
VC
3
4
5
7
14
n=15
CMP
% Cells of CD45.2$^+$
100
50
0
1
3
6
▨ B Cells
▧ Mac
☐ T Cells

Fig. 16C

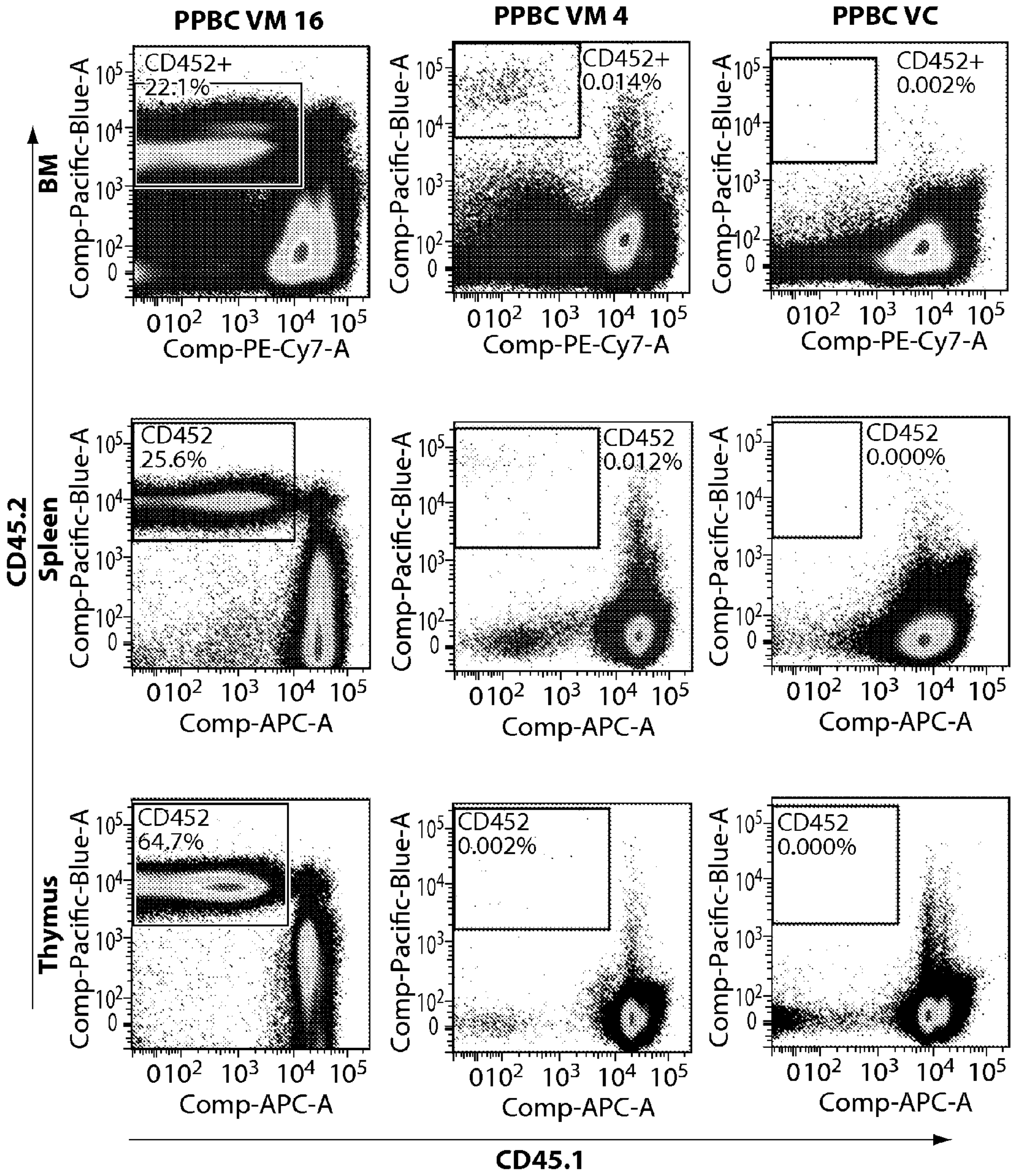

PPBC VM 16
PPBC VM 4
PPBC VC
BM
Spleen
Thymus
CD45.2
CD45.1
CD452+
22.1%
CD452+
0.014%
CD452+
0.002%
CD452
25.6%
CD452
0.012%
CD452
0.000%
CD452
64.7%
CD452
0.002%
CD452
0.000%
Comp-Pacific-Blue-A
Comp-PE-Cy7-A
Comp-APC-A
0
10^2
10^3
10^4
10^5

Fig. 17-1

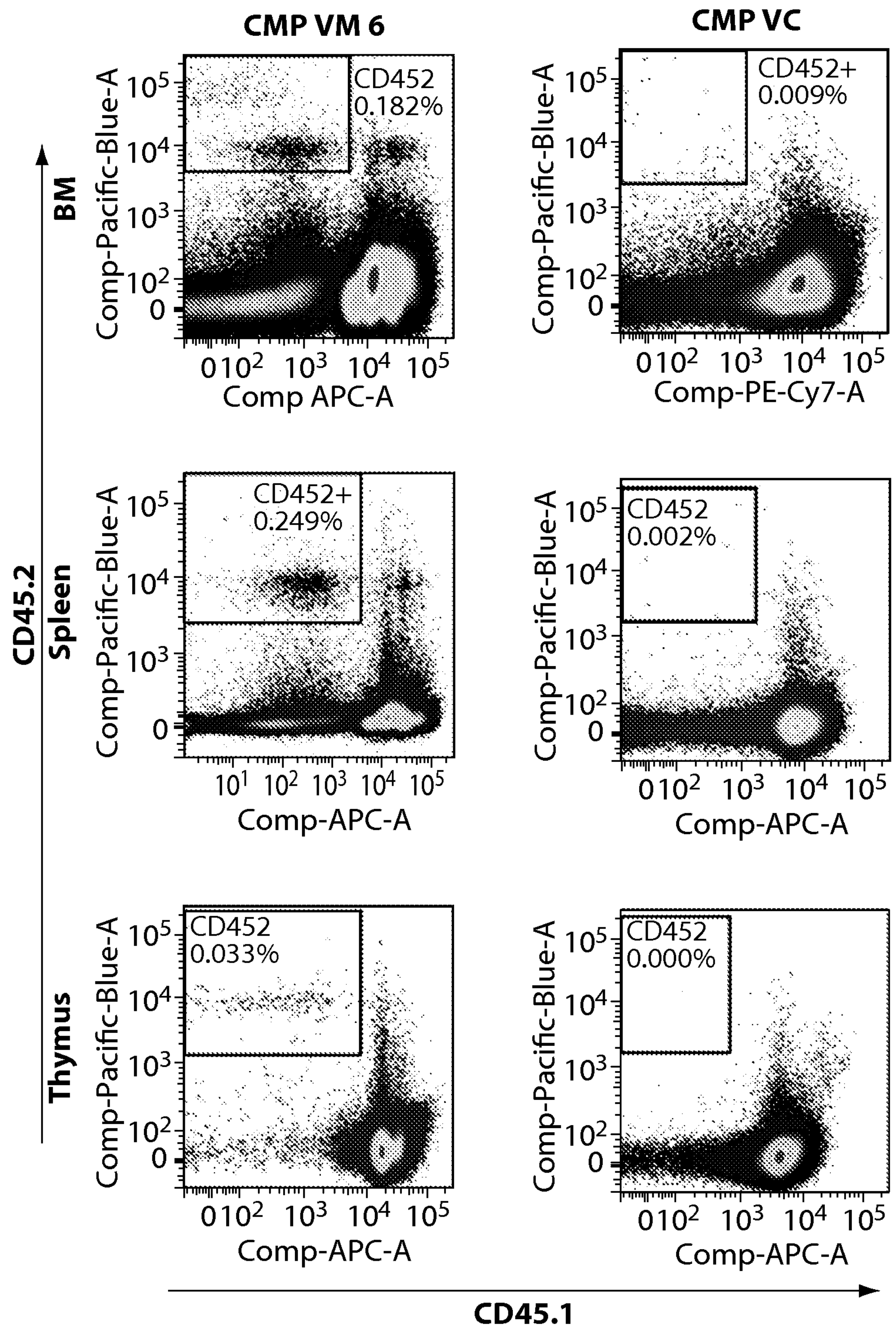

CMP VM 6
CMP VC
BM
Spleen
Thymus
CD45.2
CD45.1
Comp-Pacific-Blue-A
Comp APC-A
Comp-PE-Cy7-A
Comp-APC-A
CD452 0.182%
CD452+ 0.009%
CD452+ 0.249%
CD452 0.002%
CD452 0.033%
CD452 0.000%
0
10^1
10^2
10^3
10^4
10^5

Fig. 17-2

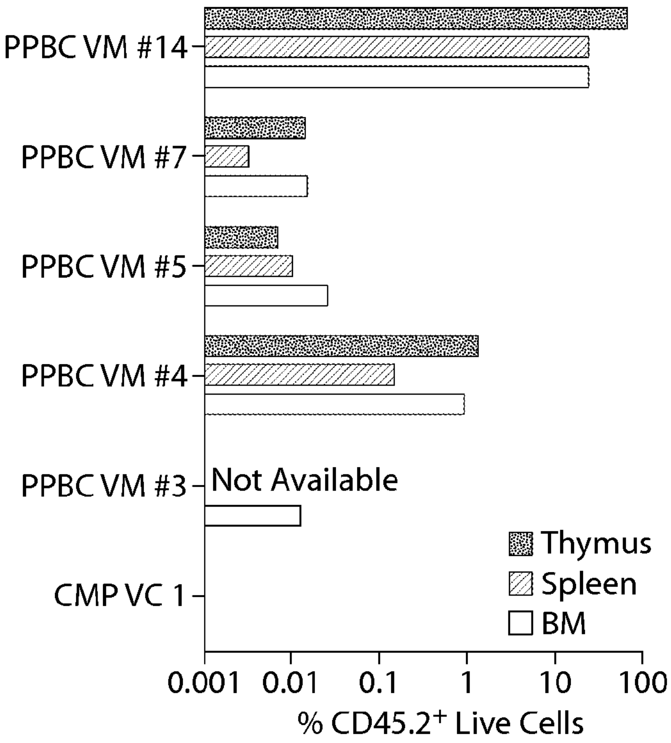


Fig. 18A

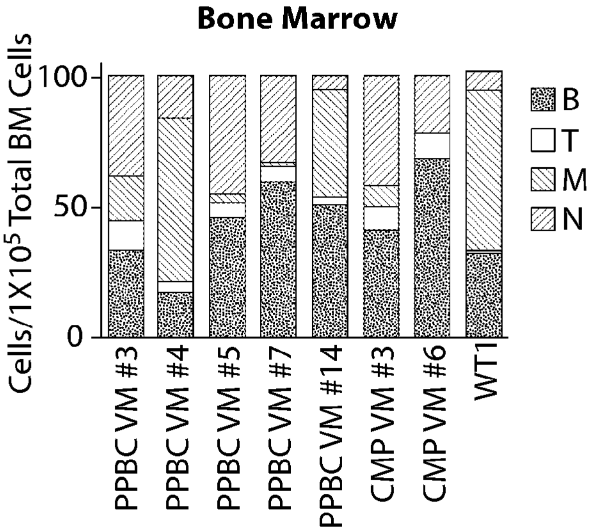


Fig. 18B

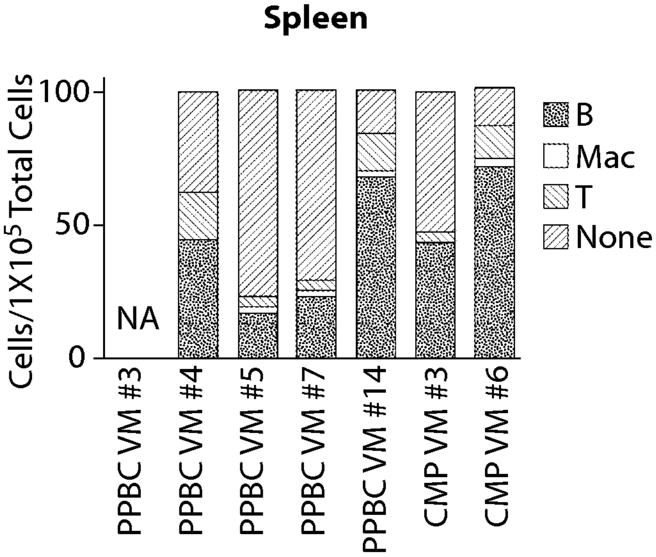


Fig. 18C

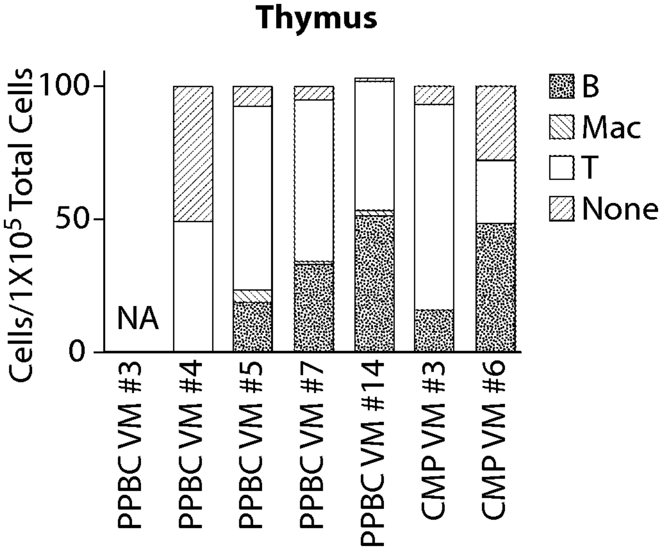


Fig. 18D

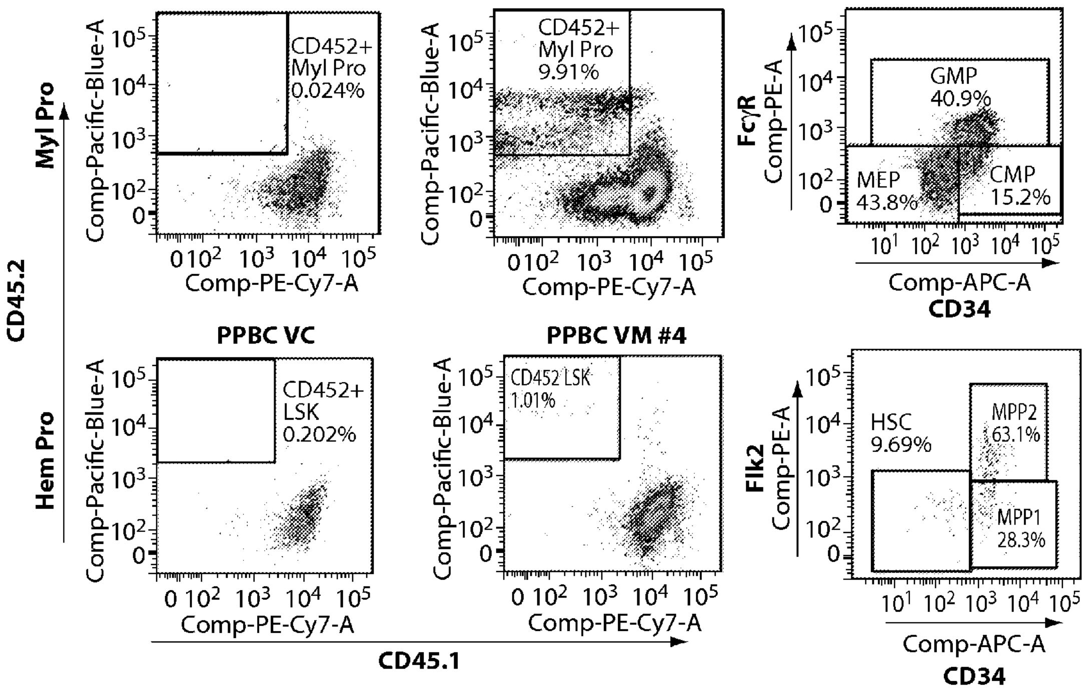

Myl Pro
Hem Pro
CD45.2
CD45.1
PPBC VC
PPBC VM #4
Comp-Pacific-Blue-A
Comp-PE-Cy7-A
CD452+ Myl Pro 0.024%
CD452+ Myl Pro 9.91%
CD452+ LSK 0.202%
CD452 LSK 1.01%
FcγR
Comp-PE-A
GMP 40.9%
MEP 43.8%
CMP 15.2%
Flk2
HSC 9.69%
MPP2 63.1%
MPP1 28.3%
Comp-APC-A
CD34
0
10^1
10^2
10^3
10^4
10^5

Fig. 19A

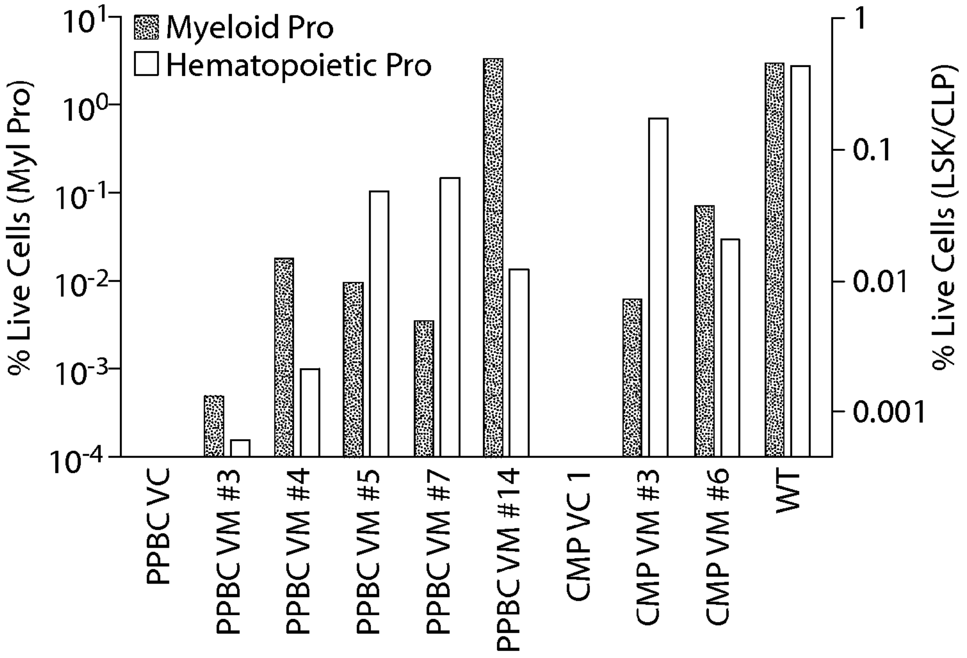


Fig. 19B

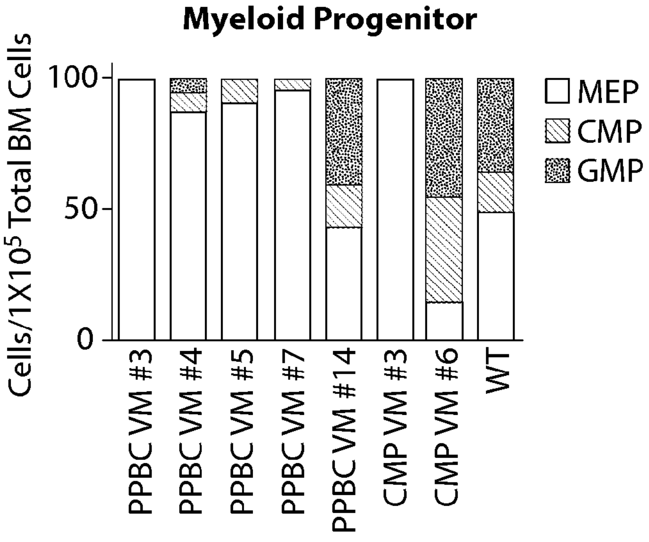


Fig. 19C

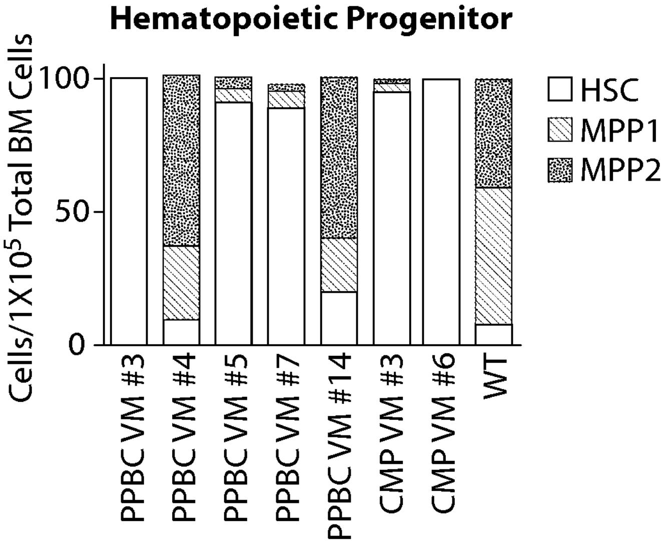

Hematopoietic Progenitor
Cells/1X10^5 Total BM Cells
100
50
0
HSC
MPP1
MPP2
PPBC VM #3
PPBC VM #4
PPBC VM #5
PPBC VM #7
PPBC VM #14
CMP VM #3
CMP VM #6
WT

Fig. 19D

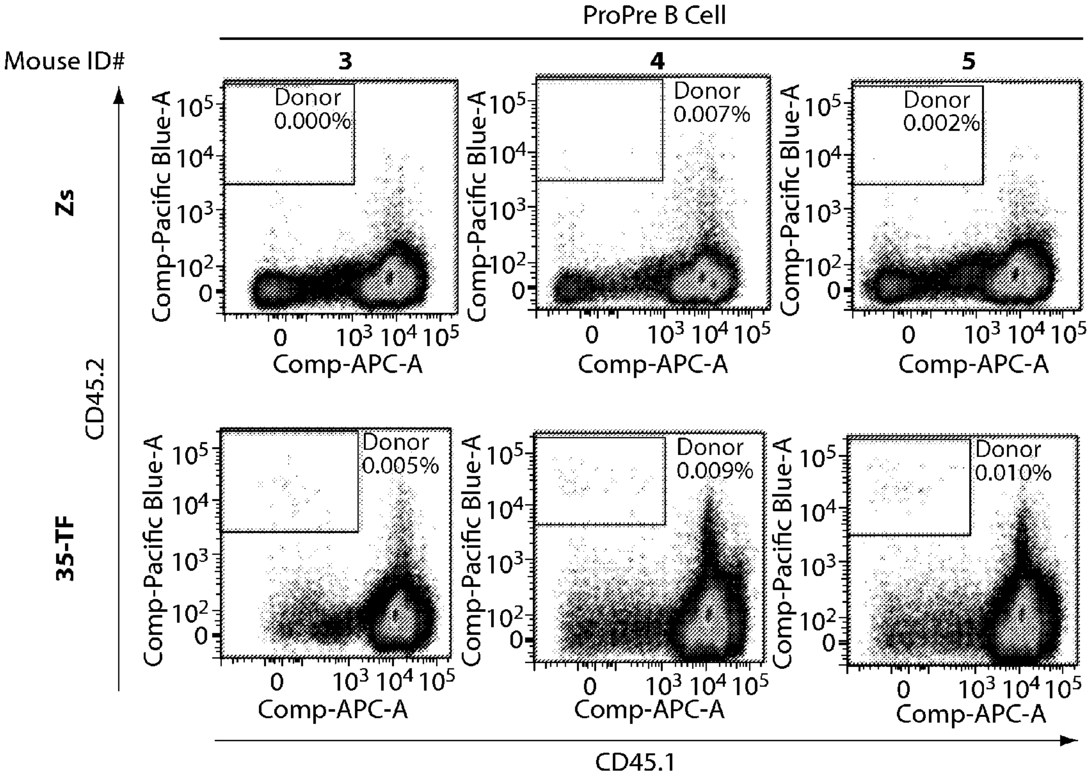

ProPre B Cell
Mouse ID#
3
4
5
Zs
35-TF
CD45.2
CD45.1
Comp-Pacific Blue-A
Comp-APC-A
0
10^2
10^3
10^4
10^5
Donor 0.000%
Donor 0.007%
Donor 0.002%
Donor 0.005%
Donor 0.009%
Donor 0.010%

Fig. 20A-1

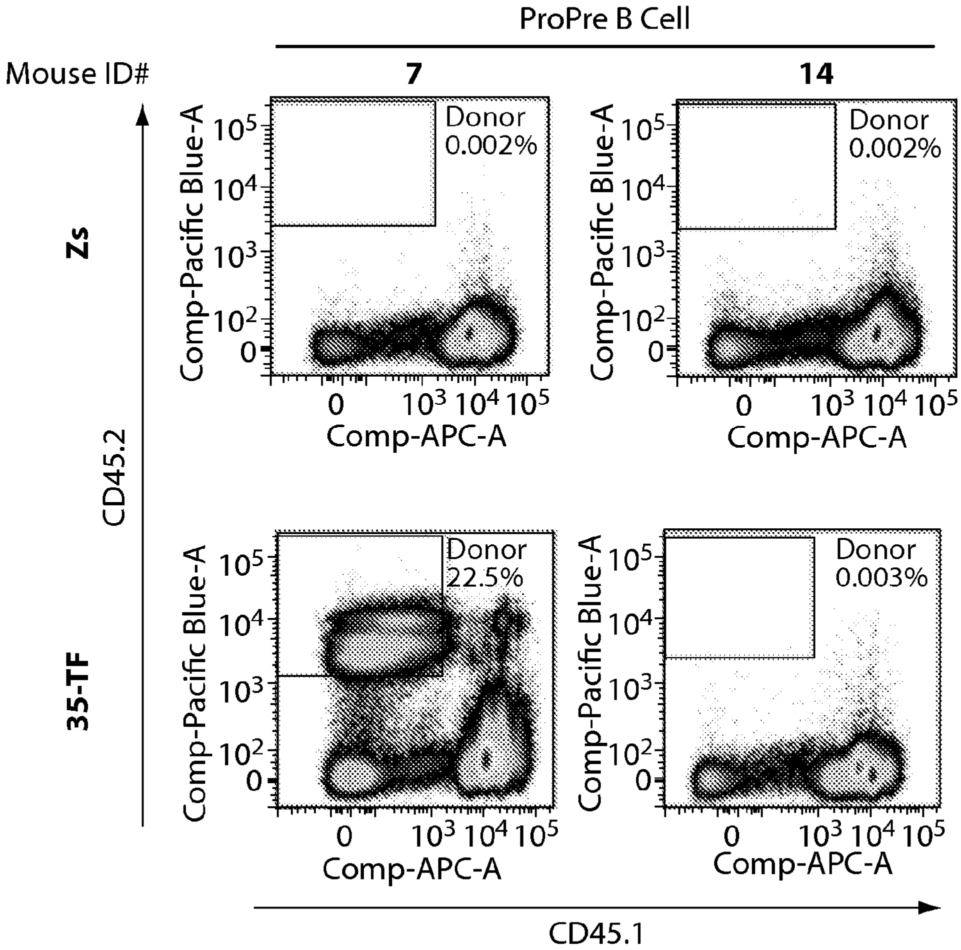

ProPre B Cell
Mouse ID#
7
14
Zs
35-TF
CD45.2
CD45.1
Comp-Pacific Blue-A
Comp-APC-A
10^5
10^4
10^3
10^2
0
Donor 0.002%
Donor 0.002%
Donor 22.5%
Donor 0.003%

Fig. 20A-2

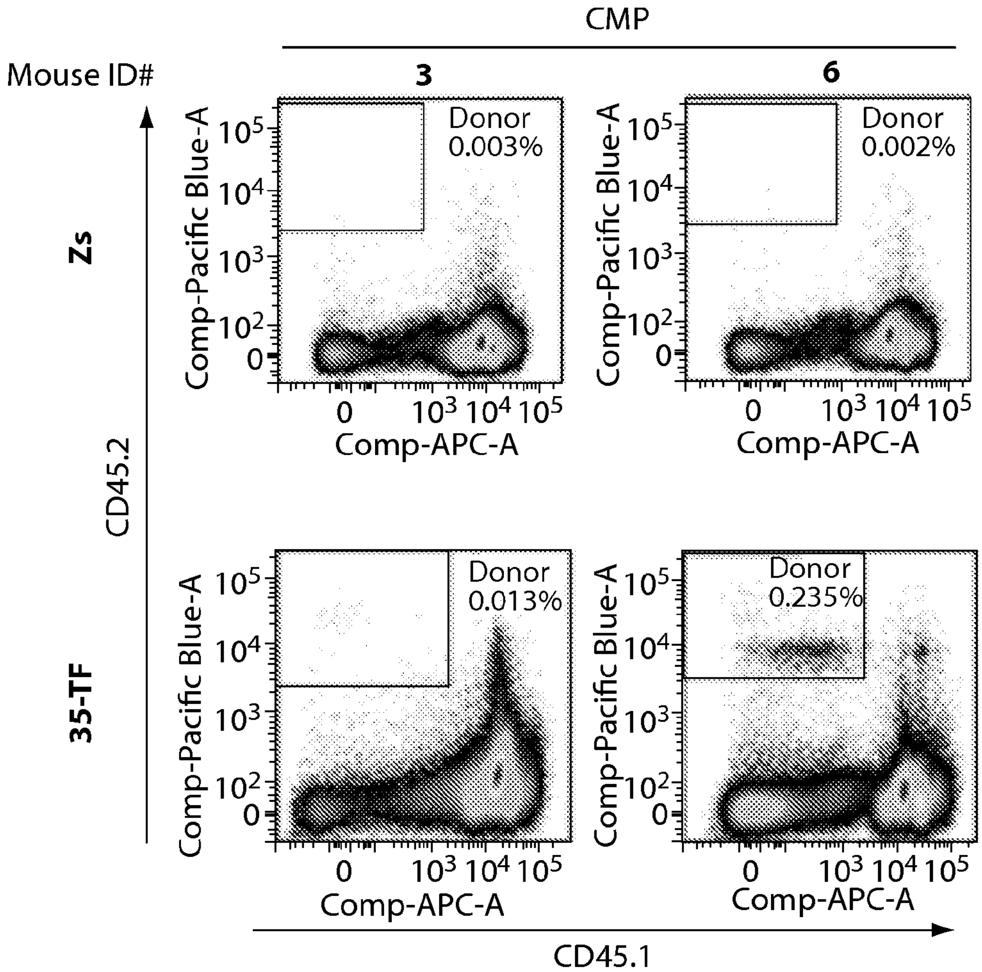

CMP
Mouse ID#
3
6
Zs
35-TF
CD45.2
CD45.1
Comp-Pacific Blue-A
Comp-APC-A
Donor 0.003%
Donor 0.002%
Donor 0.013%
Donor 0.235%
0
10^2
10^3
10^4
10^5

Fig. 20A-3

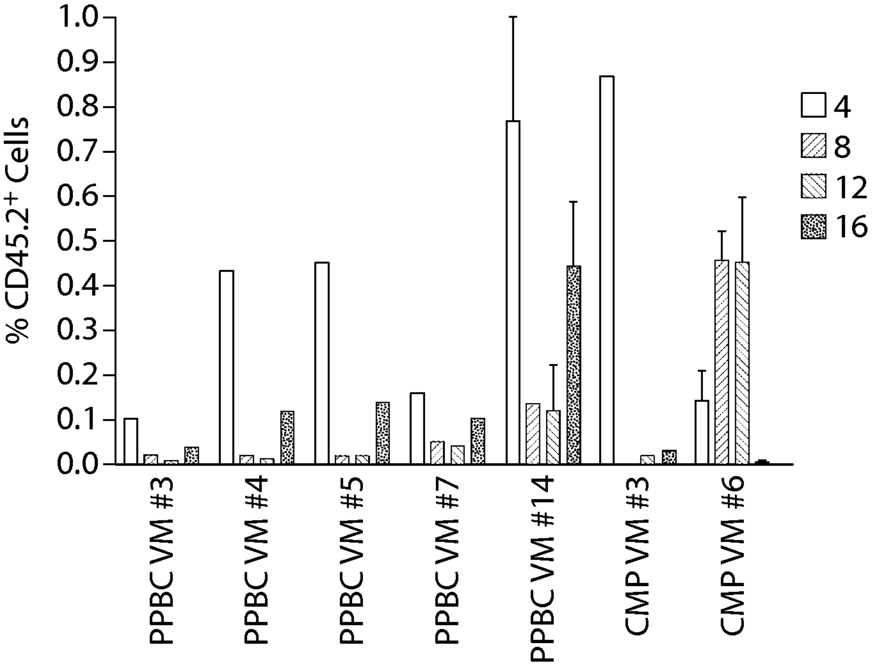


Fig. 20B

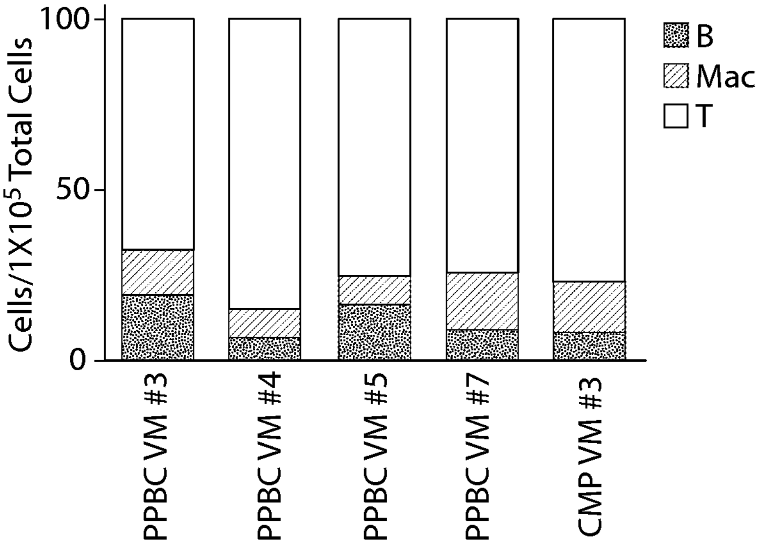


Fig. 20C

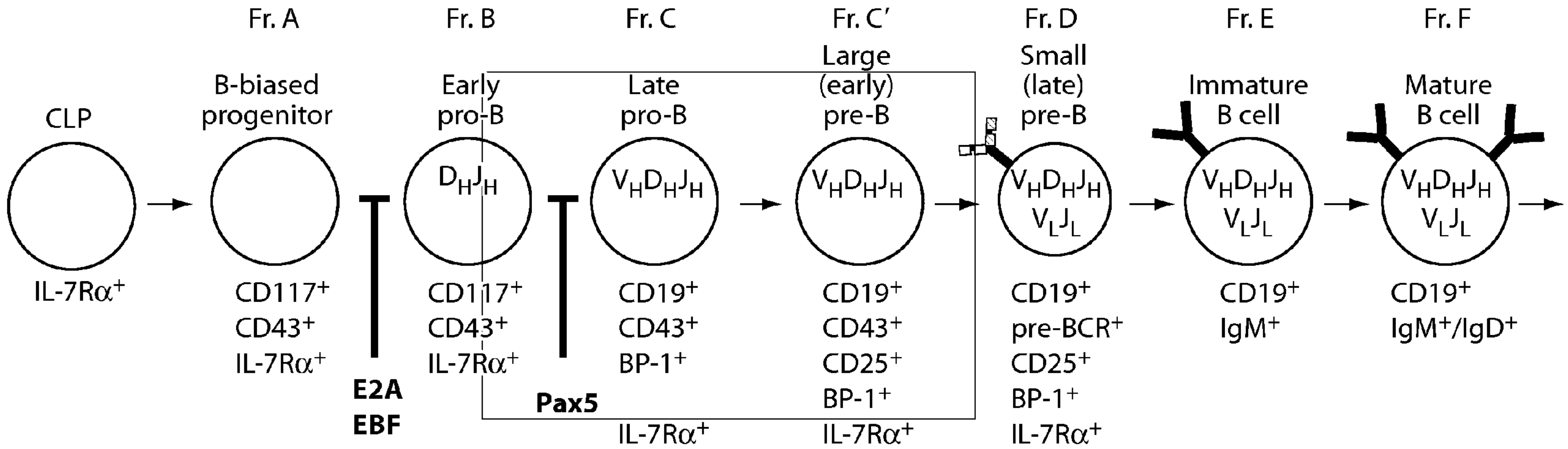

CLP
IL-7Rα+
Fr. A
B-biased progenitor
CD117+
CD43+
IL-7Rα+
E2A
EBF
Fr. B
Early pro-B
DHJH
CD117+
CD43+
IL-7Rα+
Pax5
Fr. C
Late pro-B
VHDHJH
CD19+
CD43+
BP-1+
IL-7Rα+
Fr. C′
Large (early) pre-B
VHDHJH
CD19+
CD43+
CD25+
BP-1+
IL-7Rα+
Fr. D
Small (late) pre-B
VHDHJH
VLJL
CD19+
pre-BCR+
CD25+
BP-1+
IL-7Rα+
Fr. E
Immature B cell
VHDHJH
VLJL
CD19+
IgM+
Fr. F
Mature B cell
VHDHJH
VLJL
CD19+
IgM+/IgD+

Fig. 21A

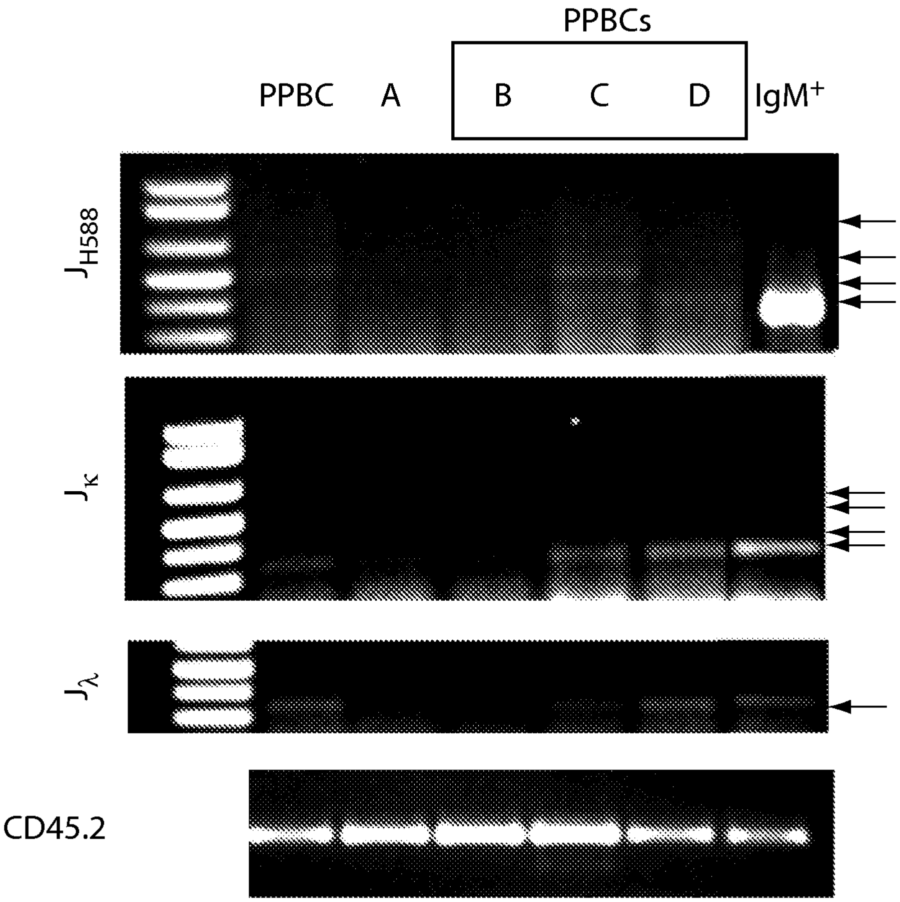


Fig. 21B

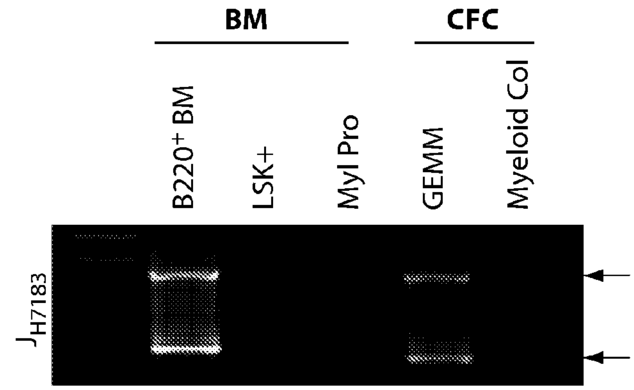


Fig. 22A

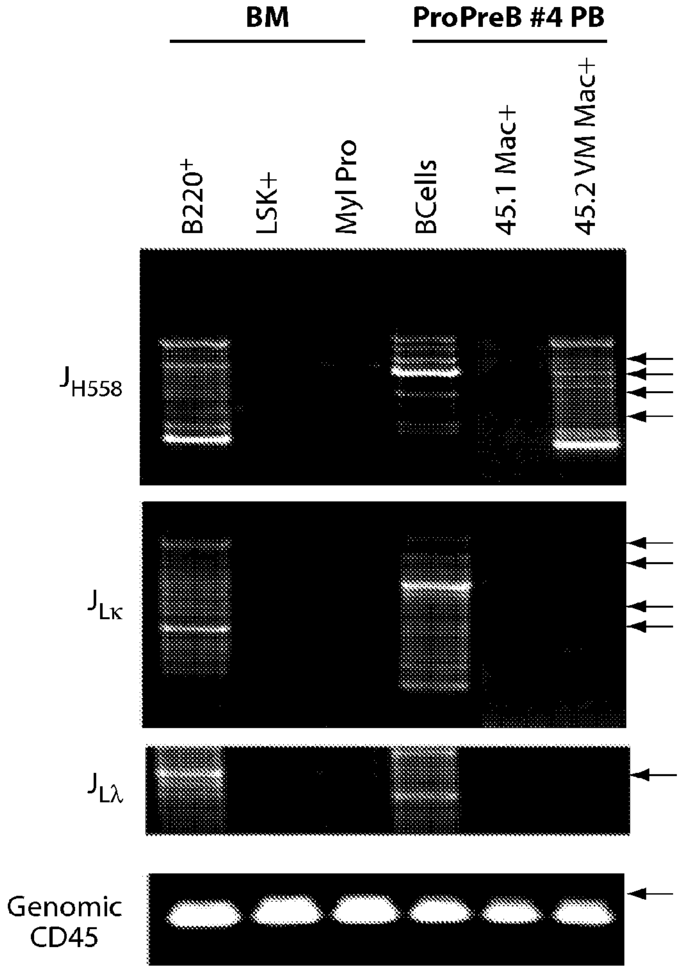


Fig. 22B

		V_{HJ558}	V_{κ}	V_{λ}
PPBC	3	Polyclonal	None	None
	4	Polyclonal	None	None
	5	Polyclonal	Polyclonal	None
	7	Polyclonal	Polyclonal	✓
	14	Polyclonal	Polyclonal	None

Fig. 22C

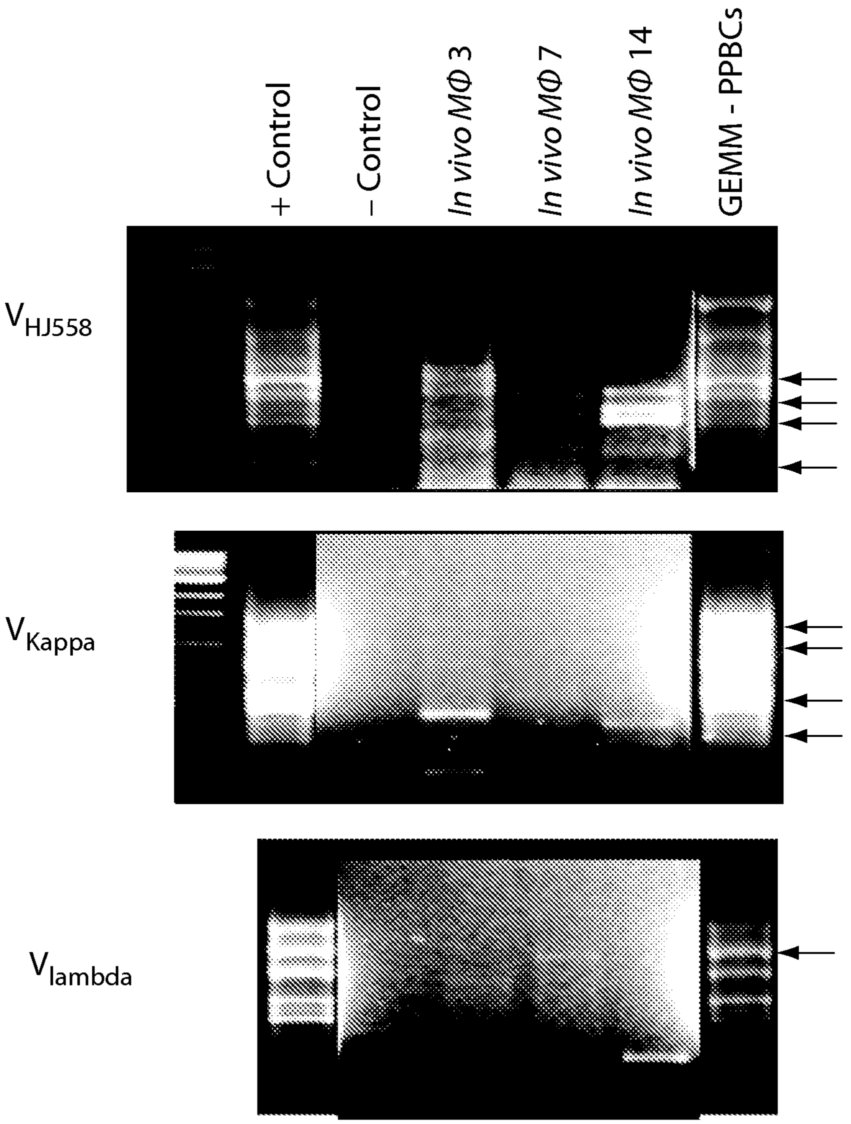

+ Control
− Control
In vivo MΦ 3
In vivo MΦ 7
In vivo MΦ 14
GEMM - PPBCs
V_{HJ558}
V_{Kappa}
V_{lambda}

Fig. 23A

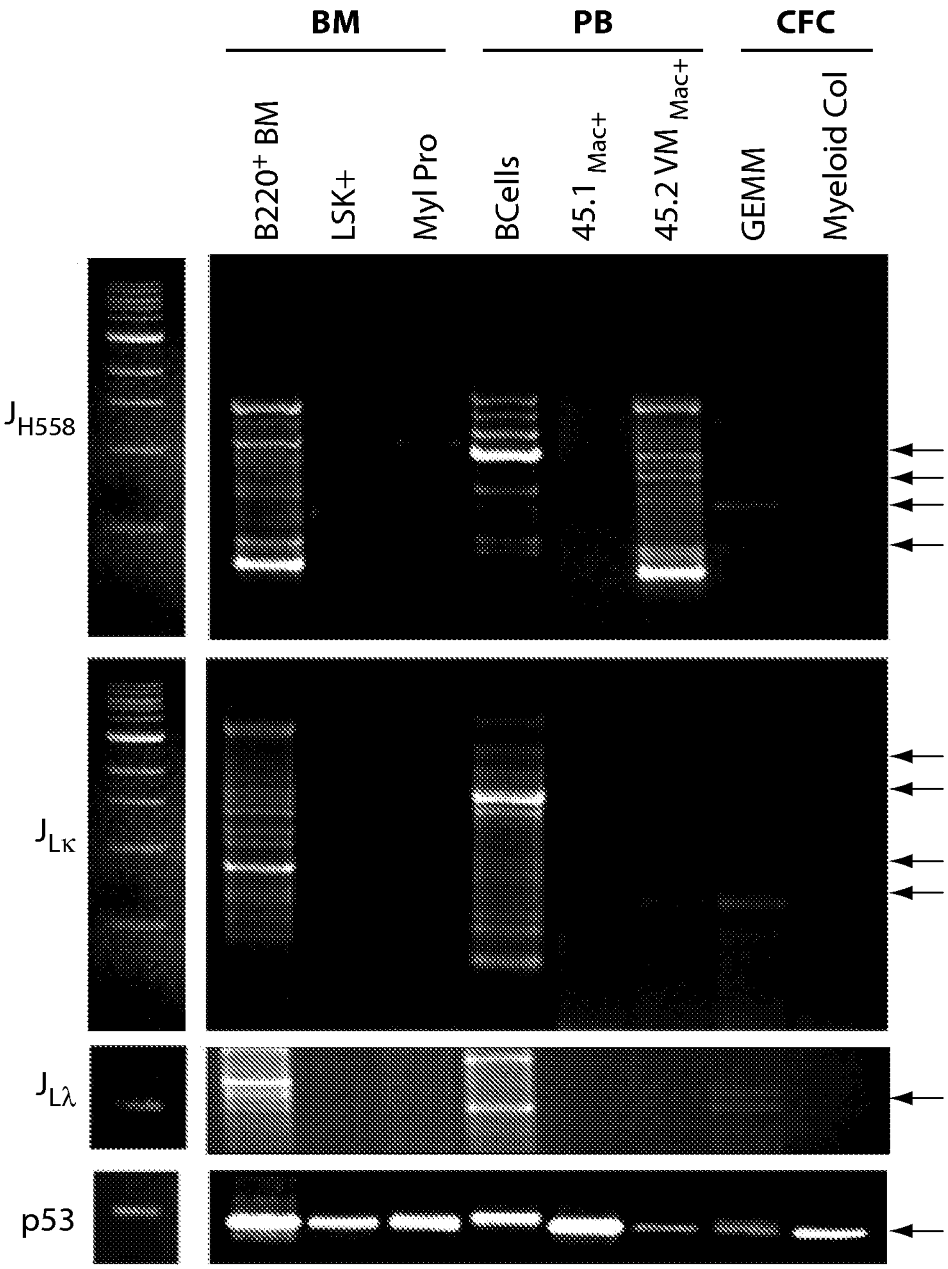

BM
PB
CFC
B220⁺ BM
LSK+
Myl Pro
BCells
45.1 Mac+
45.2 VM Mac+
GEMM
Myeloid Col
JH558
JLκ
JLλ
p53

Fig. 23B

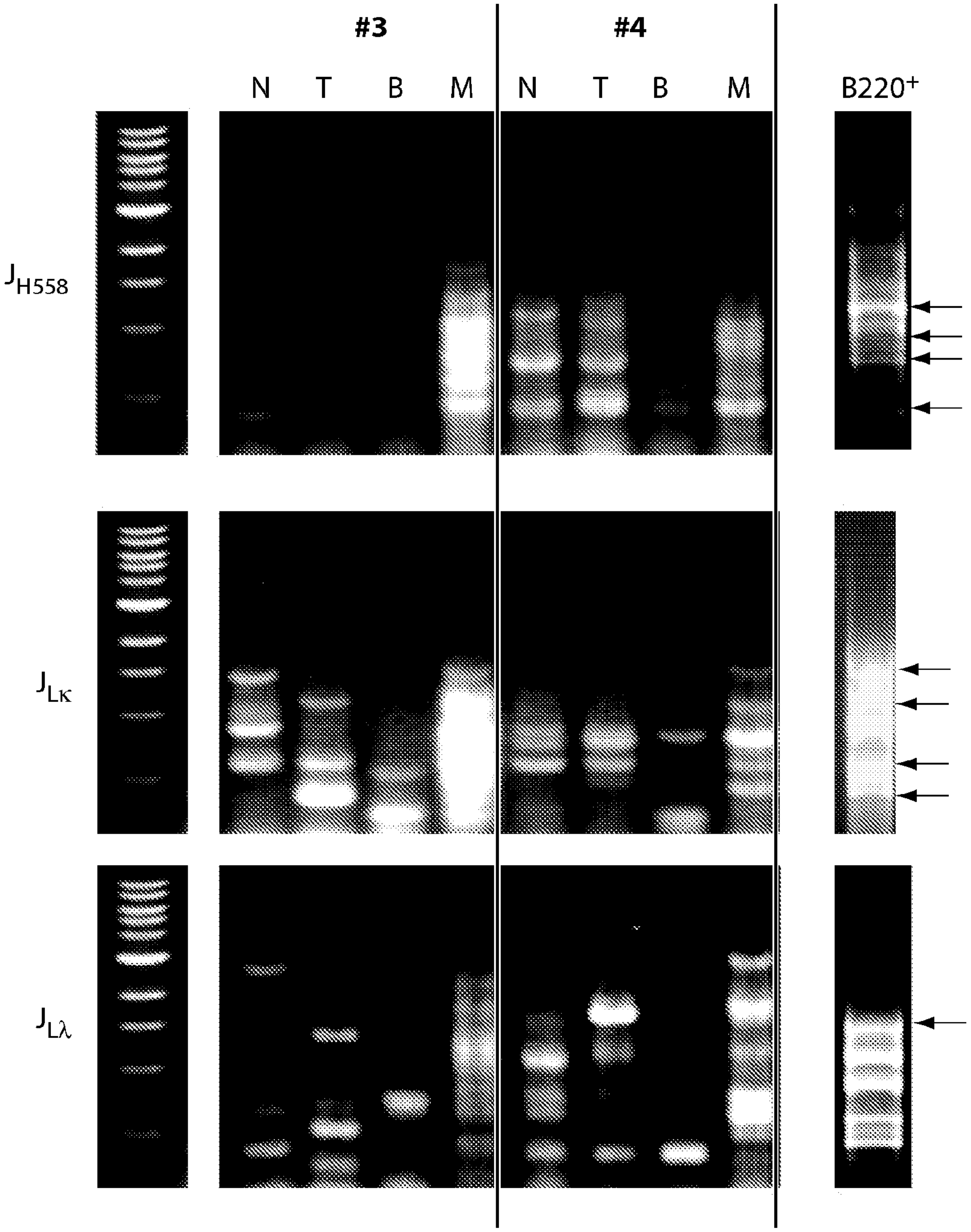


Fig. 24

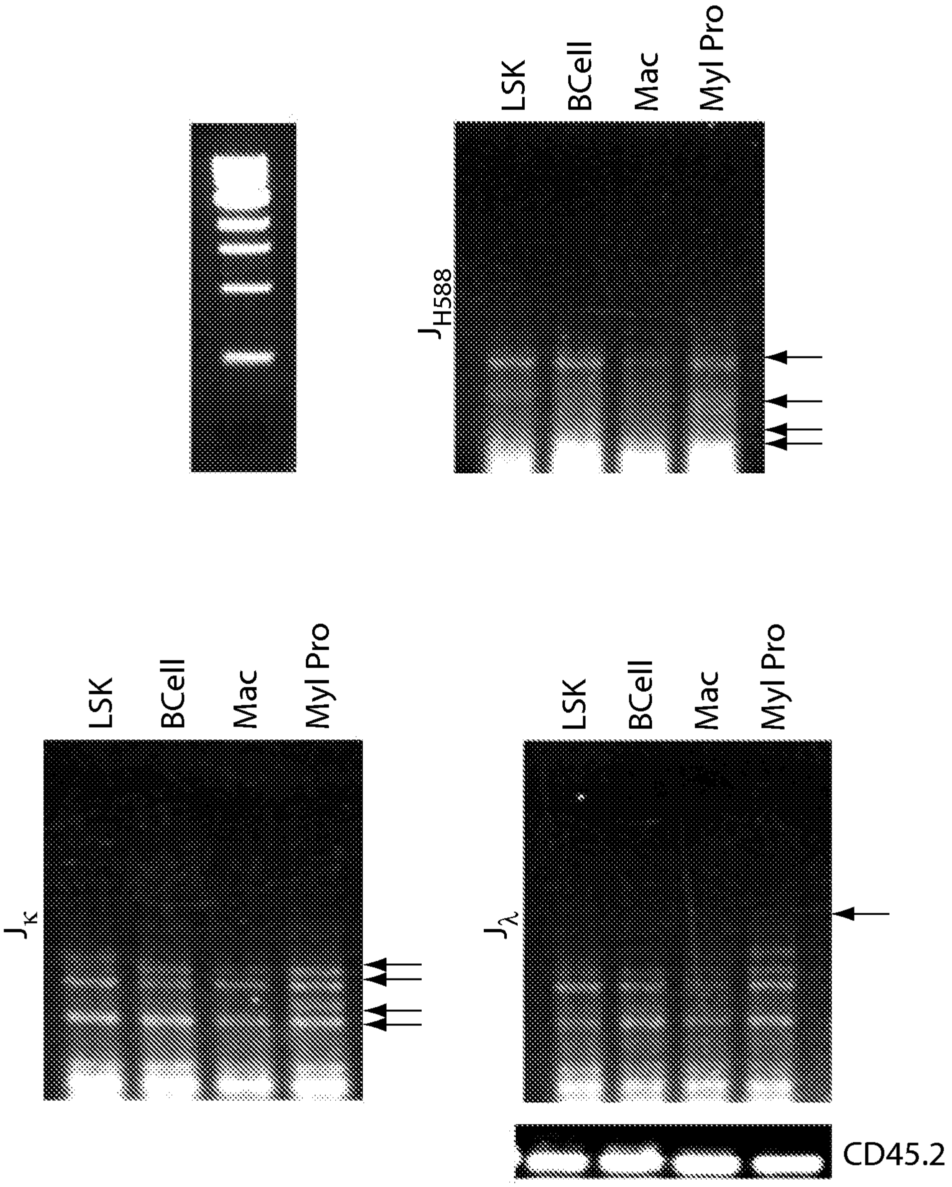

LSK
BCell
Mac
Myl Pro
J H588
LSK
BCell
Mac
Myl Pro
J κ
LSK
BCell
Mac
Myl Pro
J λ
CD45.2

Fig. 25A

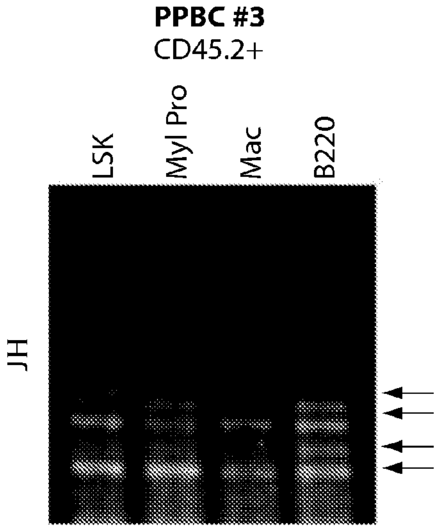


Fig. 25B

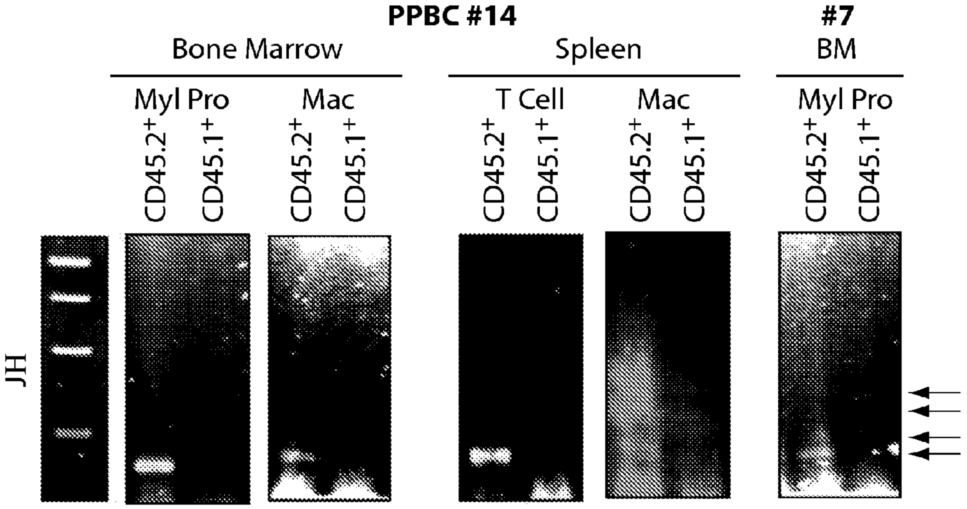


Fig. 25C

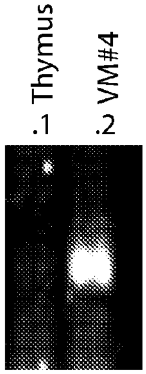


Fig. 25D

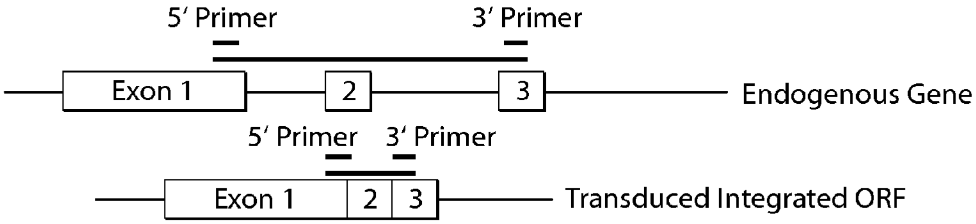

5′ Primer
3′ Primer
Exon 1
2
3
Endogenous Gene
5′ Primer
3′ Primer
Exon 1
2
3
Transduced Integrated ORF

Fig. 26

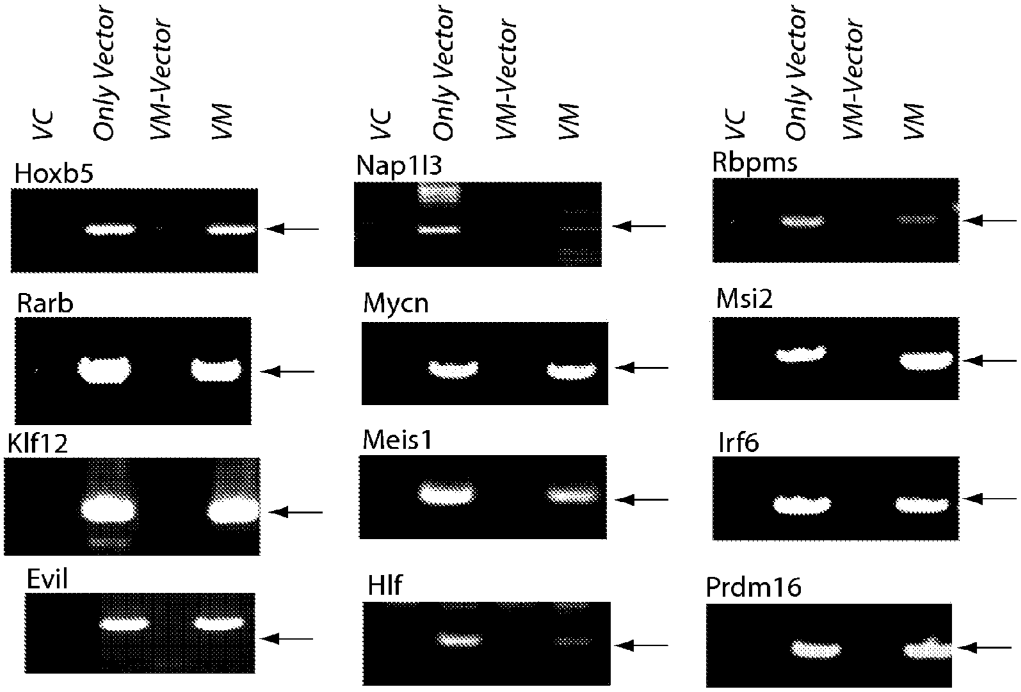

VC
Only Vector
VM-Vector
VM
Hoxb5
Rarb
Klf12
Evil
VC
Only Vector
VM-Vector
VM
Nap1l3
Mycn
Meis1
Hlf
VC
Only Vector
VM-Vector
VM
Rbpms
Msi2
Irf6
Prdm16

Fig. 27

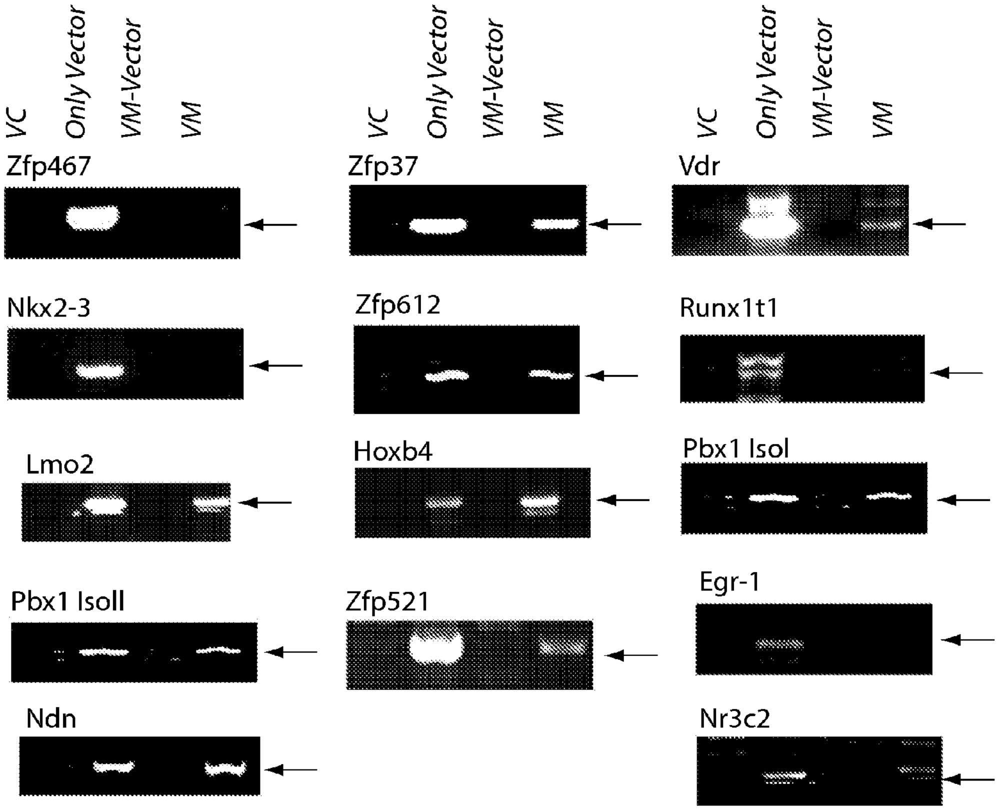
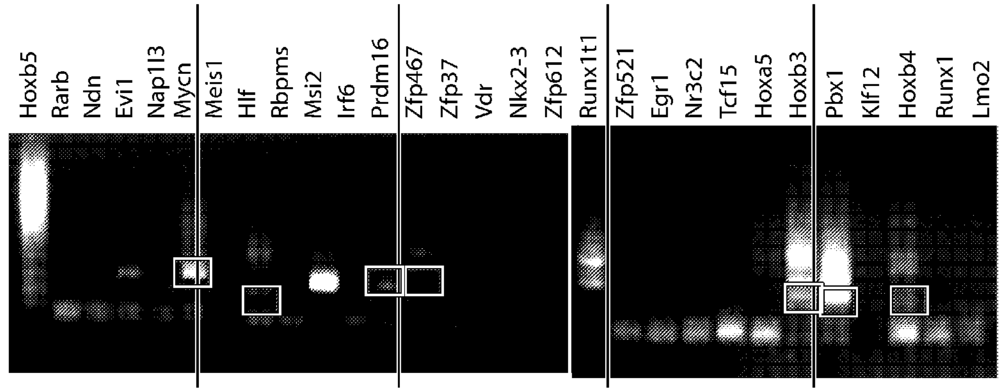

VC
Only Vector
VM-Vector
VM
Zfp467
Nkx2-3
Lmo2
Pbx1 IsoII
Ndn
Zfp37
Zfp612
Hoxb4
Zfp521
Vdr
Runx1t1
Pbx1 IsoI
Egr-1
Nr3c2

Fig. 28

Gran Colony: Hlf, Mycn, Prdm16, Zfp467, Hoxb3, Pbx1, Hoxb4



Mac Colony: Mycn, Vdr, Zfp521, Nr3c2, Pbx1, Lmo2

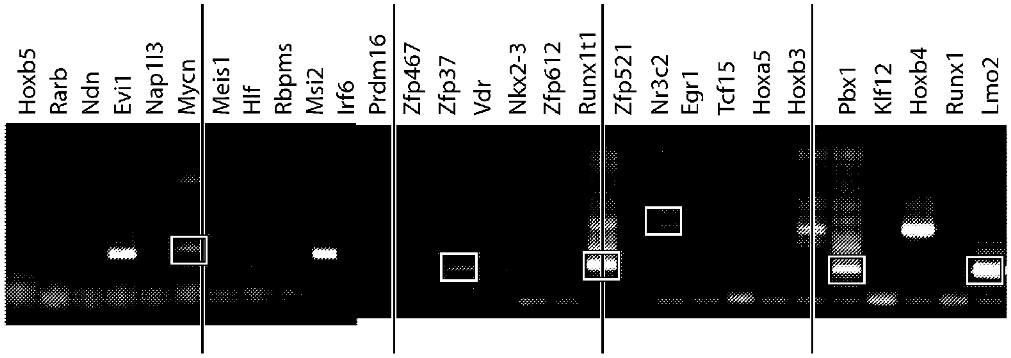
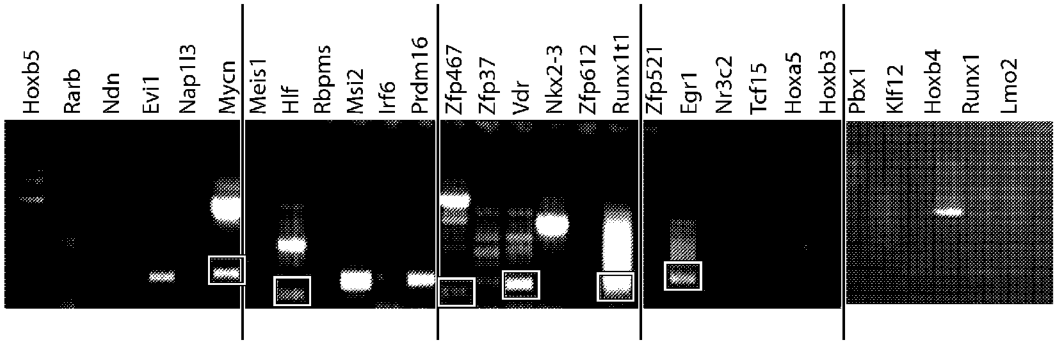


Fig. 29

GEMM: Mycn, Hlf, Zfp467, Vdr, Runx1t1, Egr1



B Cell Colony: Hoxb5, Hlf, Mycn, Zfp37, Runx1t, Zfp521, Pbx1, Lmo2

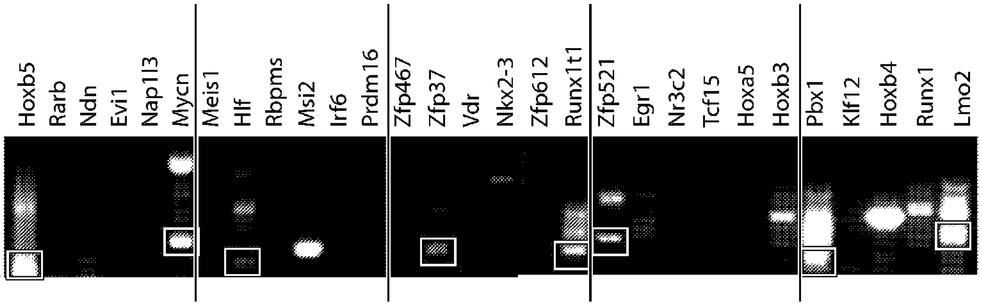
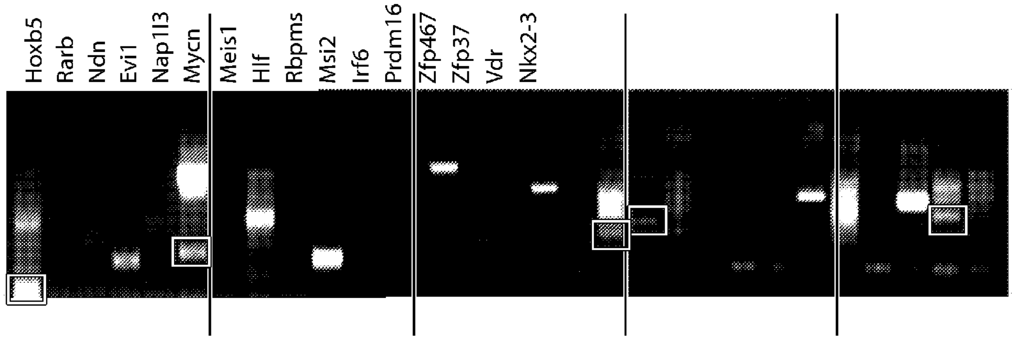


Fig. 30

BFU Colony 49: Hoxb5, Mycn, Zfp521, Runx1, Runx1t1



BFU Colony 46: Prdm16, Zfp467, Zfp37, Egr1, Runx1t1, Pbx1, Hoxb4

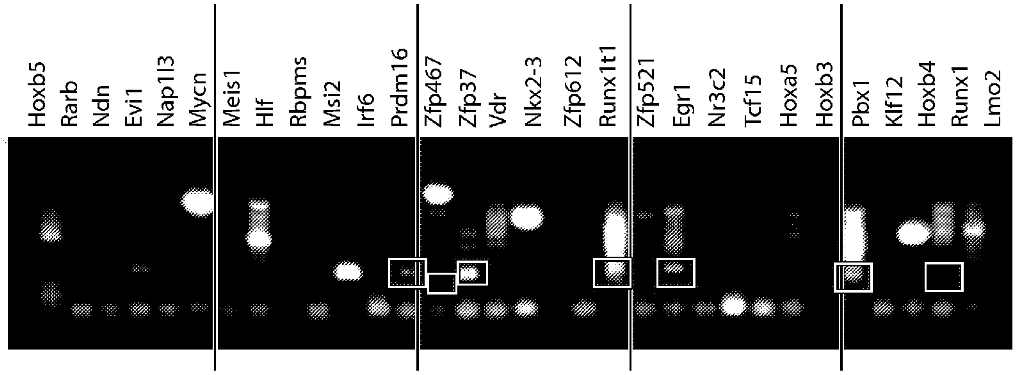


Fig. 31

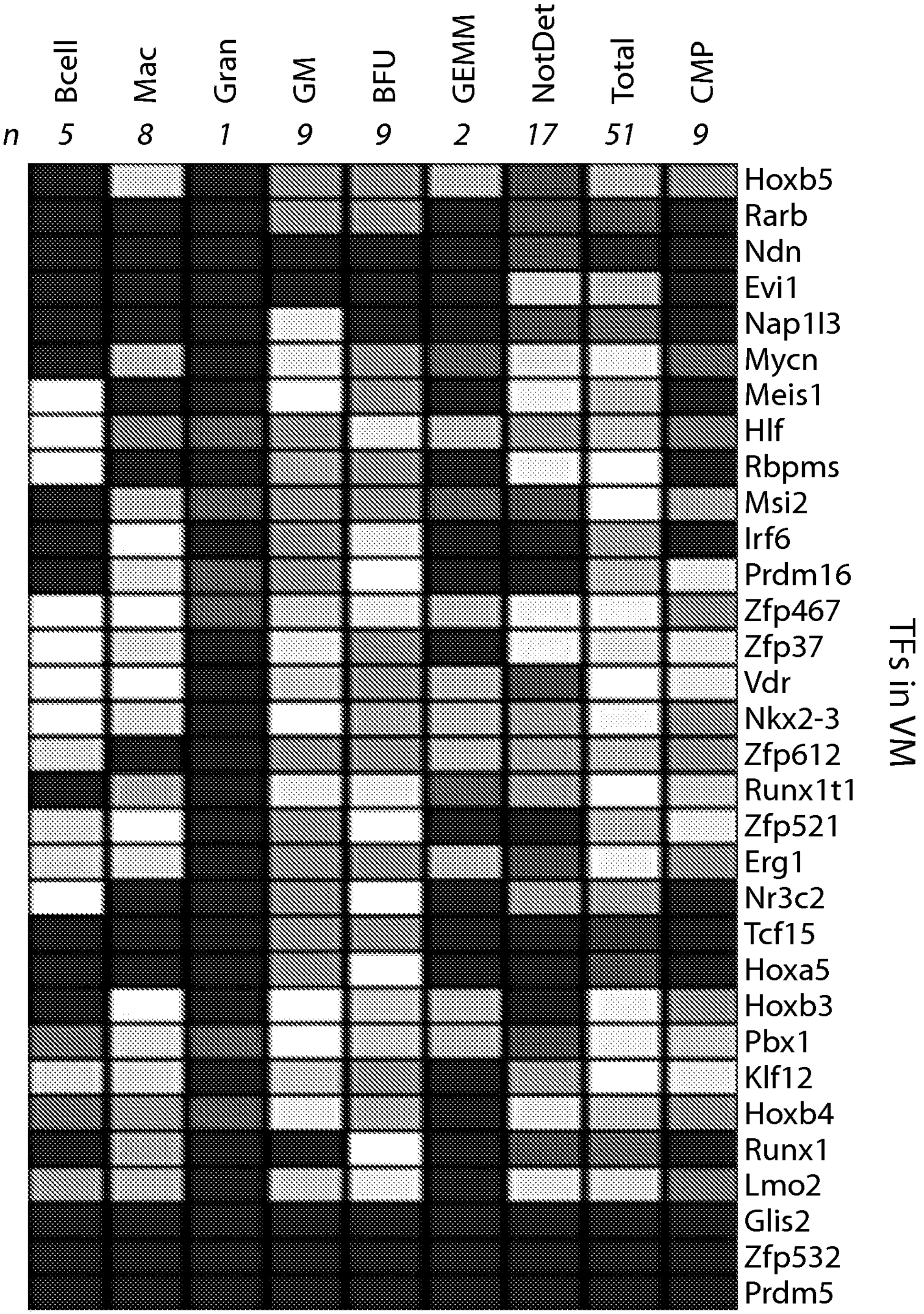

Bcell
Mac
Gran
GM
BFU
GEMM
NotDet
Total
CMP
n
5
8
1
9
9
2
17
51
9
Hoxb5
Rarb
Ndn
Evi1
Nap1l3
Mycn
Meis1
Hlf
Rbpms
Msi2
Irf6
Prdm16
Zfp467
Zfp37
Vdr
Nkx2-3
Zfp612
Runx1t1
Zfp521
Erg1
Nr3c2
Tcf15
Hoxa5
Hoxb3
Pbx1
Klf12
Hoxb4
Runx1
Lmo2
Glis2
Zfp532
Prdm5
TFs in VM

Fig. 32

ProPreB Cell VM #4: Hoxb5, Mycn, Hlf, Prdm16, Zfp37, Runx1t1, Pbx1, Lmo2, Prdm5

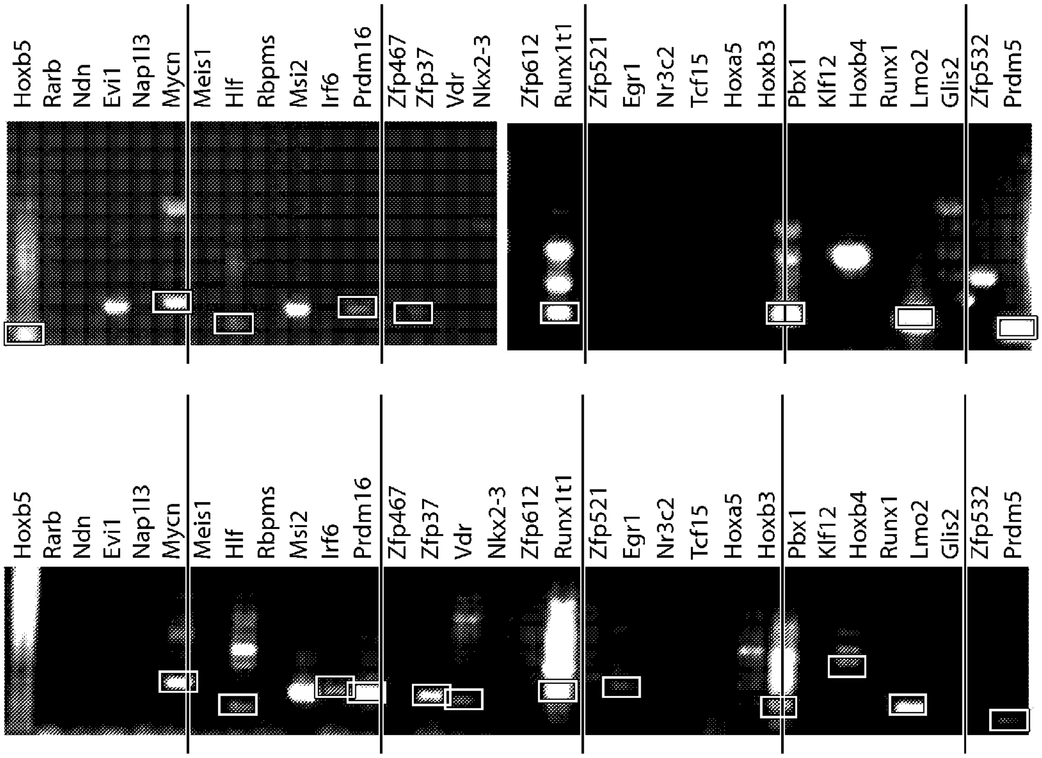


Fig. 33

Every Bleed contained : Hlf, Zfp37, Runx1t1, Pbx1 and Lmo2

Fig. 34A

Additional Factors:

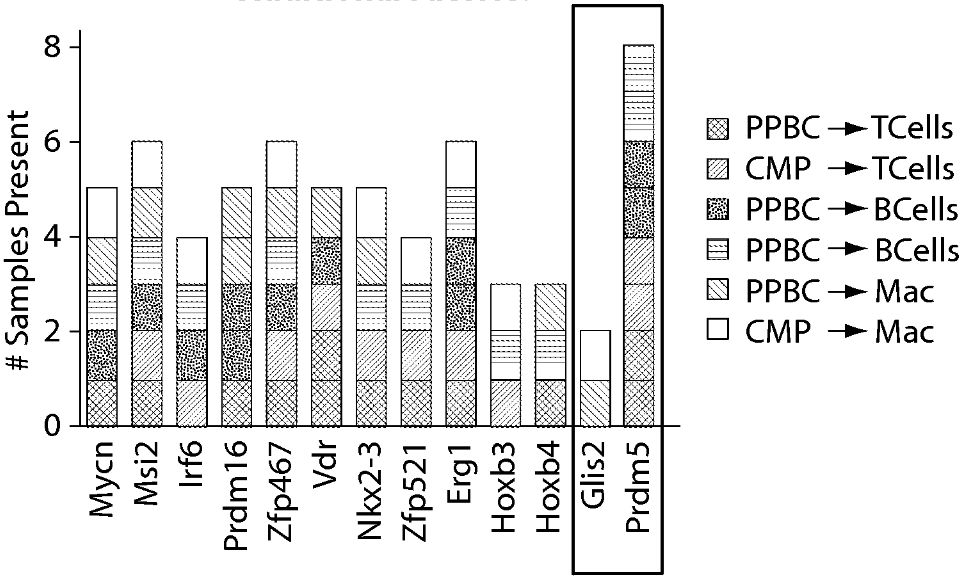


Fig. 34B

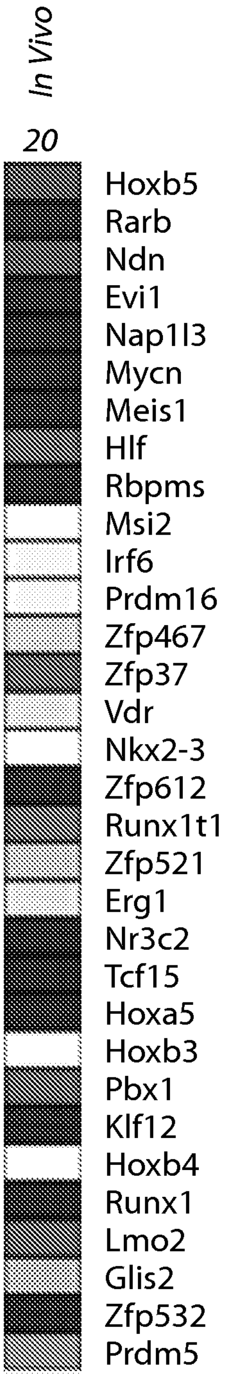

In Vivo
20
Hoxb5
Rarb
Ndn
Evi1
Nap1l3
Mycn
Meis1
Hlf
Rbpms
Msi2
Irf6
Prdm16
Zfp467
Zfp37
Vdr
Nkx2-3
Zfp612
Runx1t1
Zfp521
Erg1
Nr3c2
Tcf15
Hoxa5
Hoxb3
Pbx1
Klf12
Hoxb4
Runx1
Lmo2
Glis2
Zfp532
Prdm5

Fig. 34C

1. **Zfp467, Pbx1, Hoxb4, Msi2**
    - ± Hlf, Lmo2, Prdm16, Zfp37
    - PPBC → G/M/GM
2. **Mycn, Msi2, Nkx2-3, Runx1t1**
    - ± Hobx5, Hlf, Zfp37, Hoxb3, Lmo2, Pbx1, Zfp37, Zfp521
    - PPBC → BFU/GEMM
3. **Hoxb4, Pbx1, Lmo2, Zfp612, Zfp521**
    - ± Klf12, Hlf, Egr1
    - PPBC → B Cells
4. **Meis1, Rbpms, Zfp37, Runx1t1, Lmo2**
    - ± Klf12, Hlf
    - CMP → GEMM
5. **Zfp37, Hoxb4, Lmo2, Hlf**
    - ± Mycn, Zfp467, Nkx2-3, Pbx1, Klf12
    - *In Vitro* Overall Combination
6. **Hlf, Runx1t1, Pbx1, Lmo2, Prdm5**
    - ± Prdm16, Zfp37, Zfp467, Vdr
    - *In Vivo* Overall Combination
7. **Hlf, Runx1t1, Pbx1, Lmo2, Prdm5, Mycn, Msi2, Nkx2-3, Meis1, Rbpms**

Fig. 35

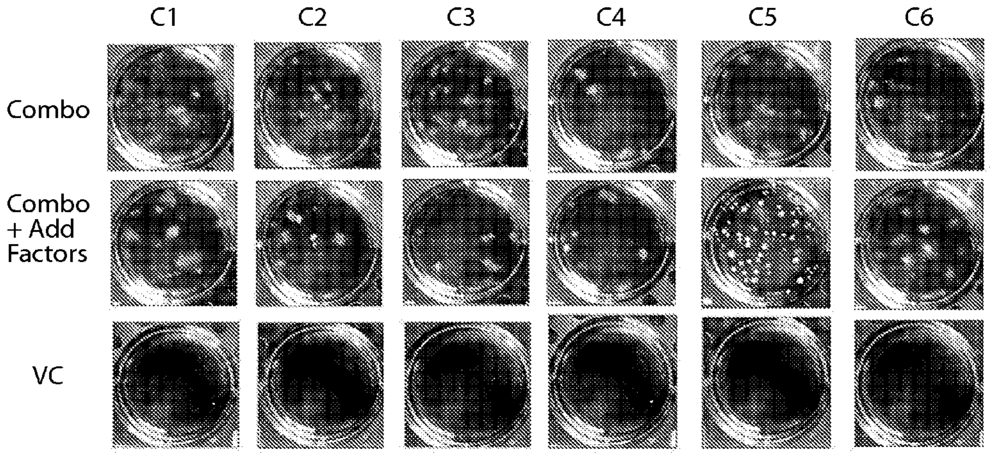


Fig. 36A

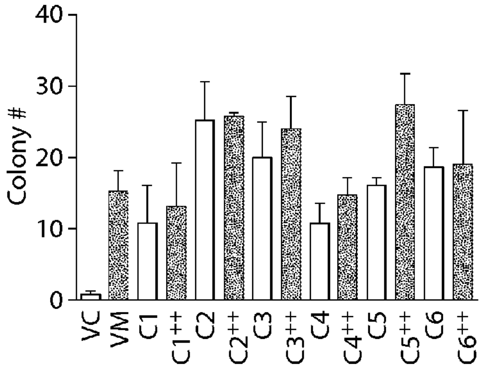


Fig. 36B

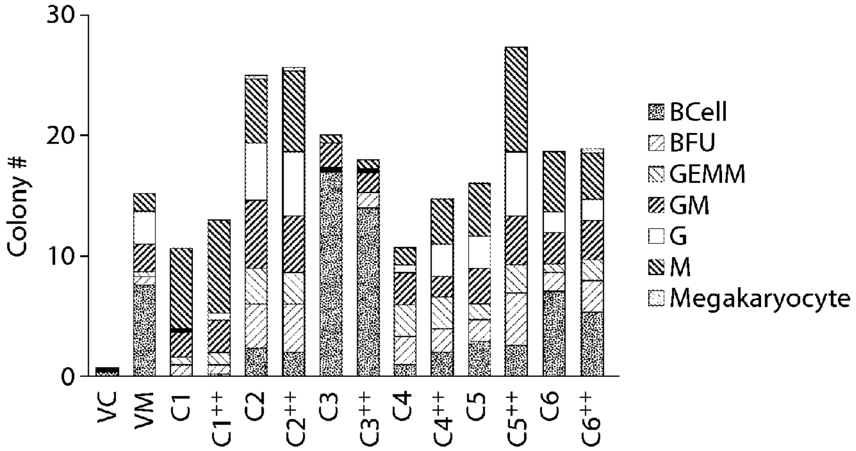


Fig. 37A

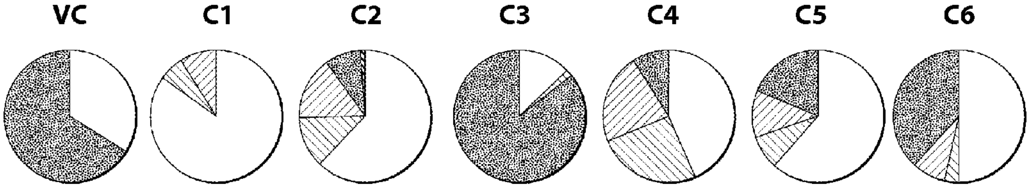


Fig. 37B

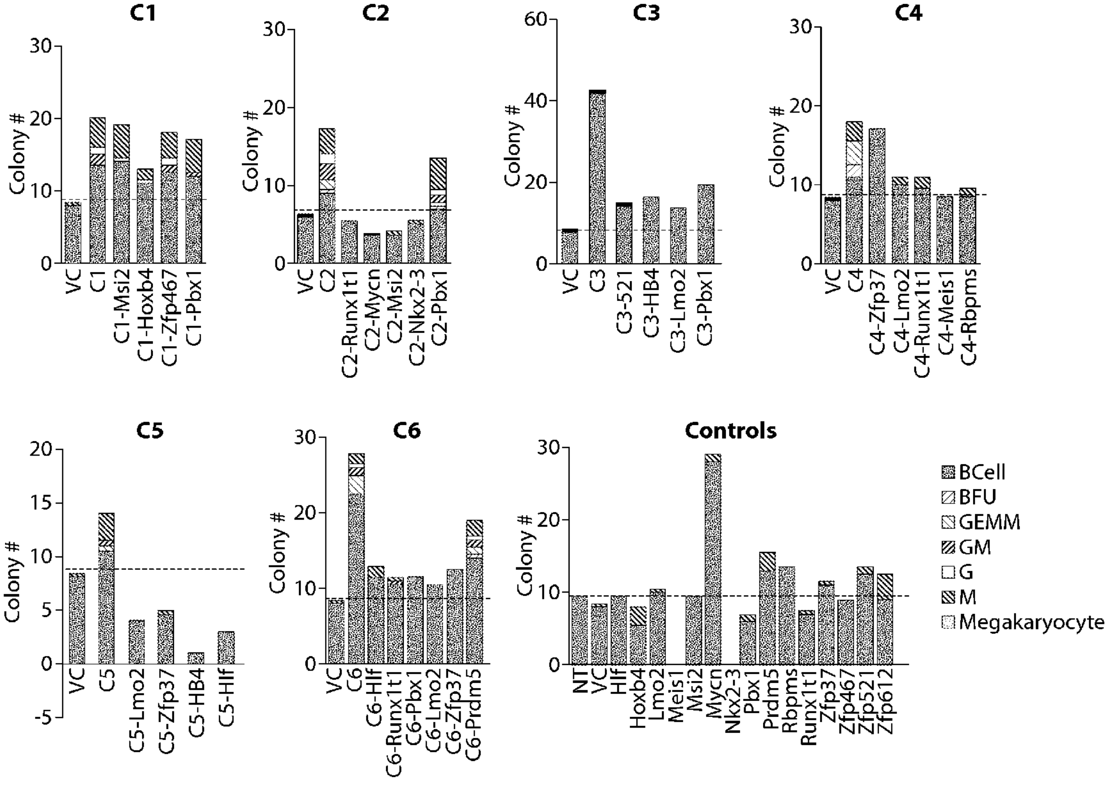

C1
Colony #
0
10
20
30
VC
C1
C1-Msi2
C1-Hoxb4
C1-Zfp467
C1-Pbx1
C2
Colony #
0
10
20
30
VC
C2
C2-Runx1t1
C2-Mycn
C2-Msi2
C2-Nkx2-3
C2-Pbx1
C3
Colony #
0
20
40
60
VC
C3
C3-521
C3-HB4
C3-Lmo2
C3-Pbx1
C4
Colony #
0
10
20
30
VC
C4
C4-Zfp37
C4-Lmo2
C4-Runx1t1
C4-Meis1
C4-Rbpms
C5
Colony #
-5
0
5
10
15
20
VC
C5
C5-Lmo2
C5-Zfp37
C5-HB4
C5-Hlf
C6
Colony #
0
10
20
30
VC
C6
C6-Hlf
C6-Runx1t1
C6-Pbx1
C6-Lmo2
C6-Zfp37
C6-Prdm5
Controls
Colony #
0
10
20
30
NT
VC
Hlf
Hoxb4
Lmo2
Meis1
Msi2
Mycn
Nkx2-3
Pbx1
Prdm5
Rbpms
Runx1t1
Zfp37
Zfp467
Zfp521
Zfp612
BCell
BFU
GEMM
GM
G
M
Megakaryocyte

Fig. 38

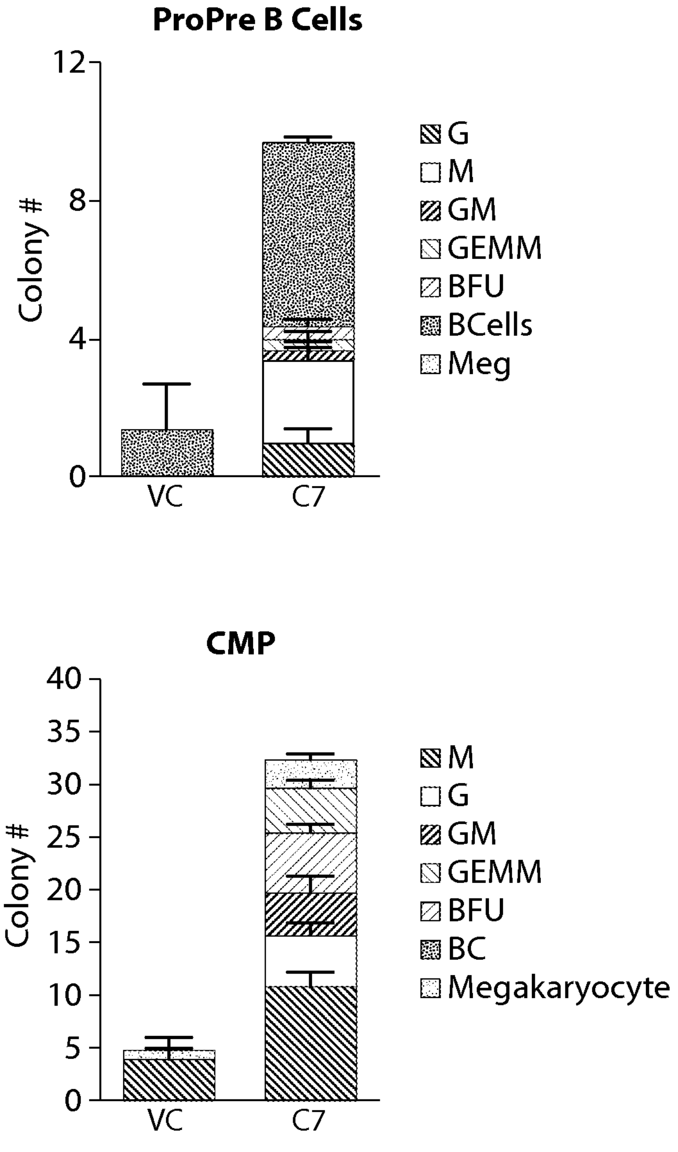

ProPre B Cells
Colony #
12
8
4
0
VC
C7
G
M
GM
GEMM
BFU
BCells
Meg
CMP
Colony #
40
35
30
25
20
15
10
5
0
VC
C7
M
G
GM
GEMM
BFU
BC
Megakaryocyte

Fig. 39

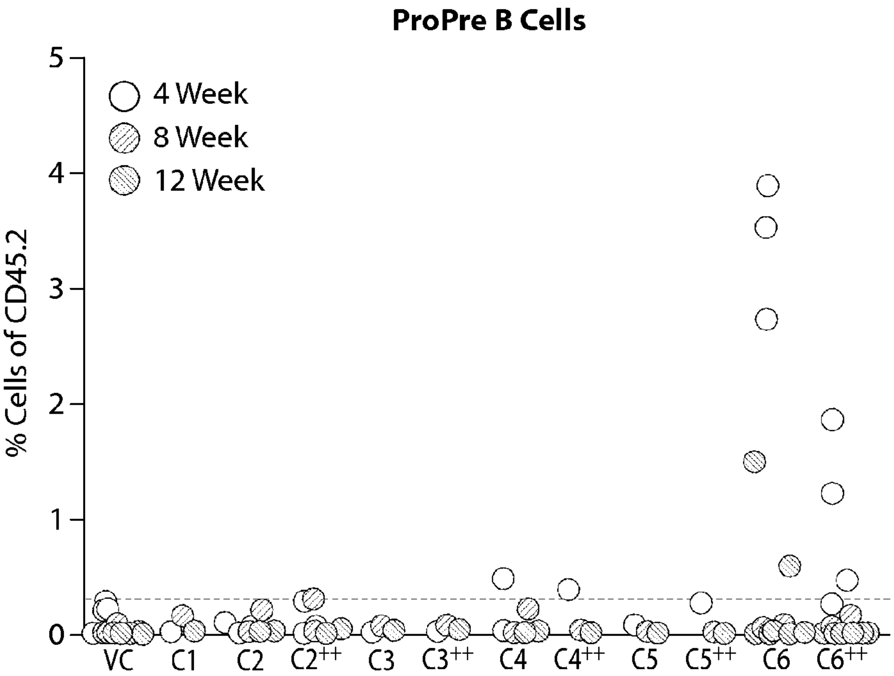


Fig. 40A

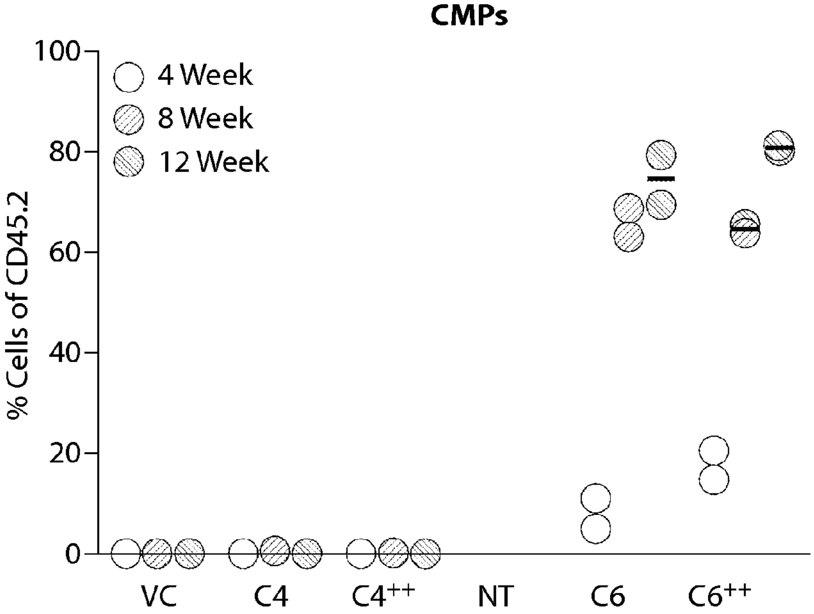


Fig. 40B

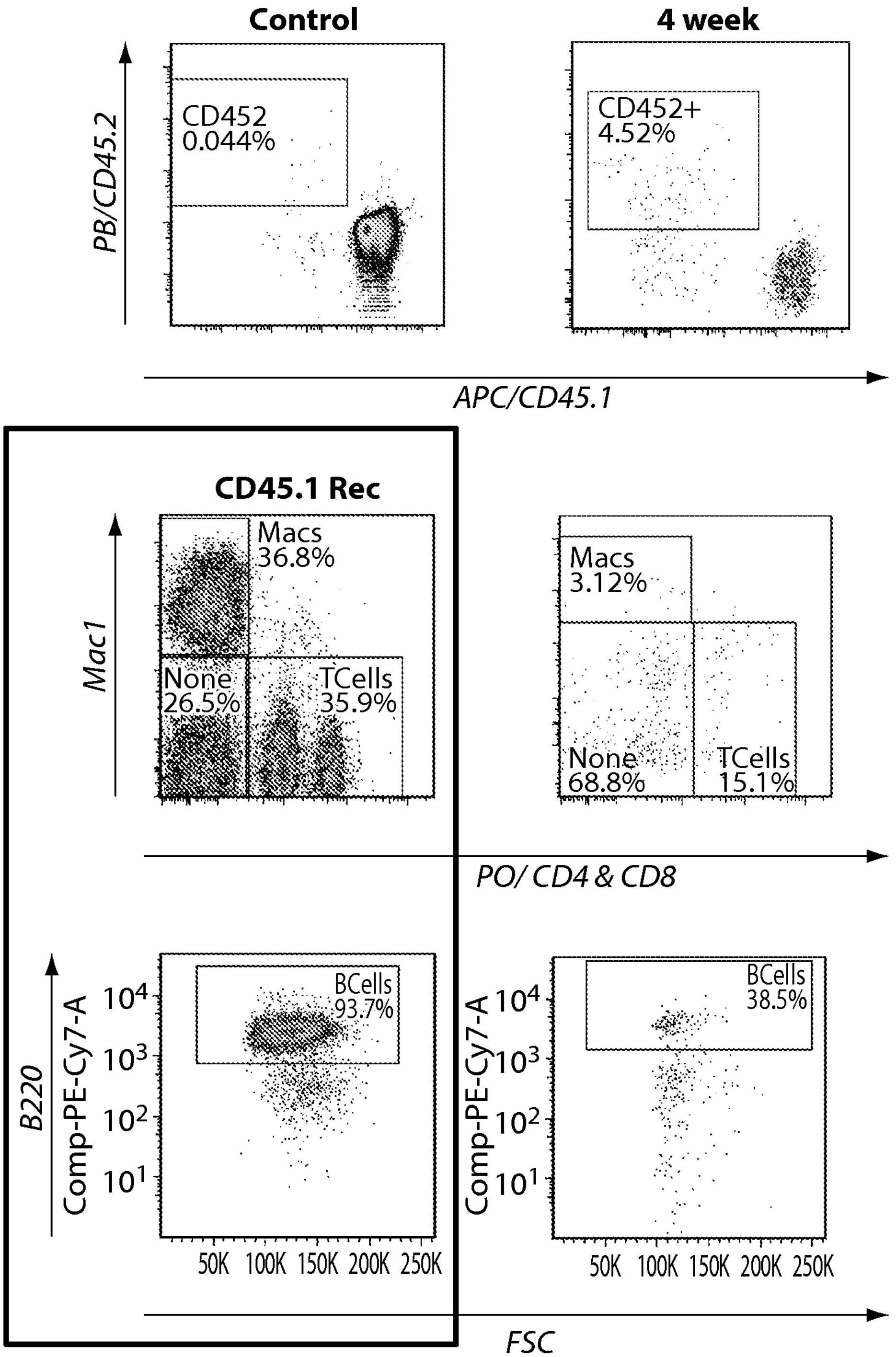

Control
4 week
PB/CD45.2
CD452
0.044%
CD452+
4.52%
APC/CD45.1
CD45.1 Rec
Mac1
Macs
36.8%
None
26.5%
TCells
35.9%
Macs
3.12%
None
68.8%
TCells
15.1%
PO/ CD4 & CD8
B220
Comp-PE-Cy7-A
10^4
10^3
10^2
10^1
BCells
93.7%
BCells
38.5%
50K 100K 150K 200K 250K
FSC

Fig. 41A-1

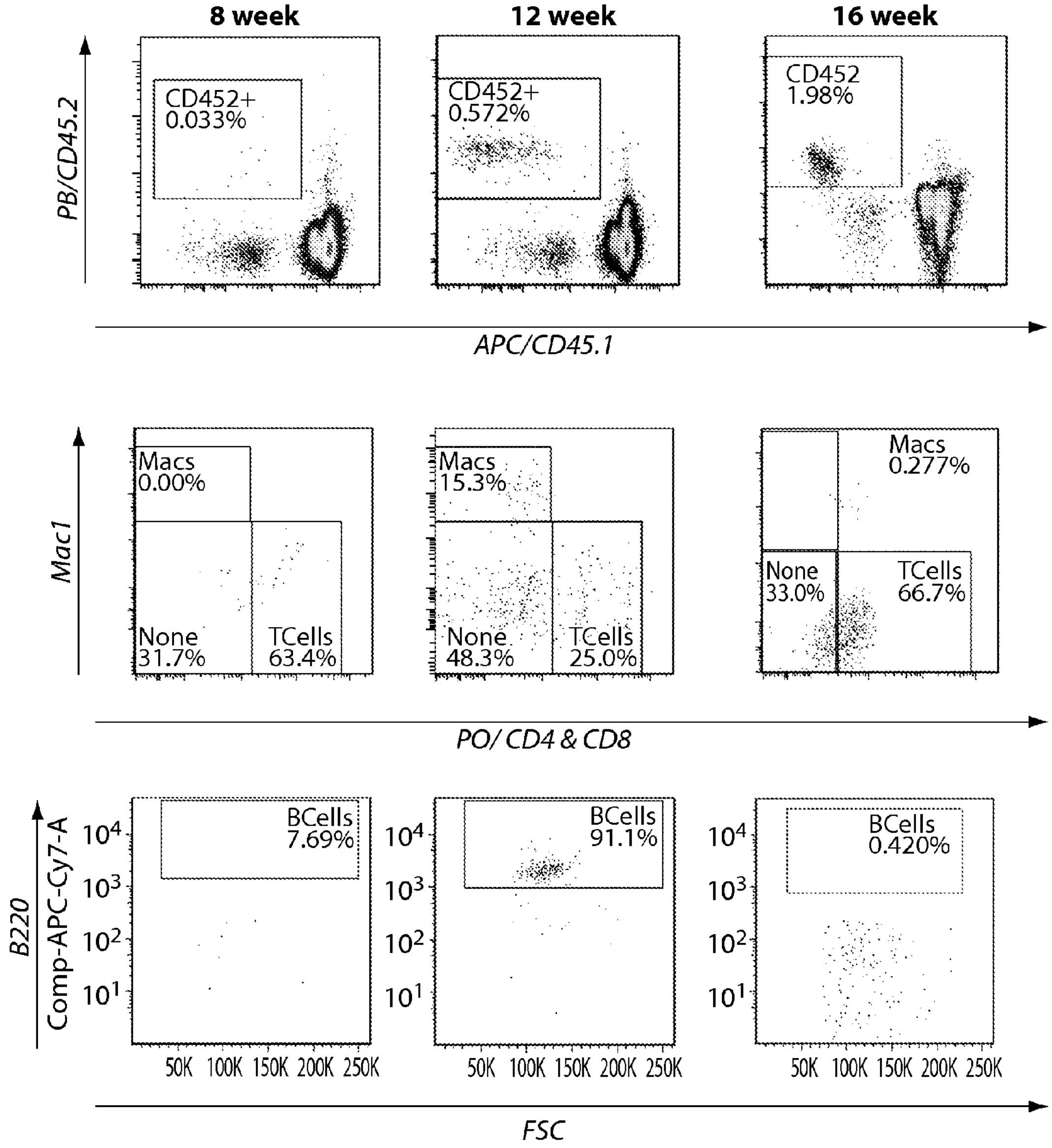

8 week
12 week
16 week
PB/CD45.2
CD452+
0.033%
CD452+
0.572%
CD452
1.98%
APC/CD45.1
Mac1
Macs
0.00%
None
31.7%
TCells
63.4%
Macs
15.3%
None
48.3%
TCells
25.0%
Macs
0.277%
None
33.0%
TCells
66.7%
PO/ CD4 & CD8
B220
Comp-APC-Cy7-A
10^4
10^3
10^2
10^1
BCells
7.69%
BCells
91.1%
BCells
0.420%
50K 100K 150K 200K 250K
FSC

Fig. 41A-2

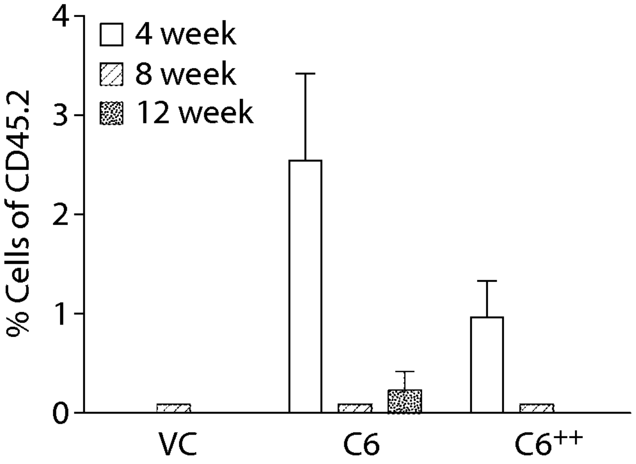


Fig. 41B

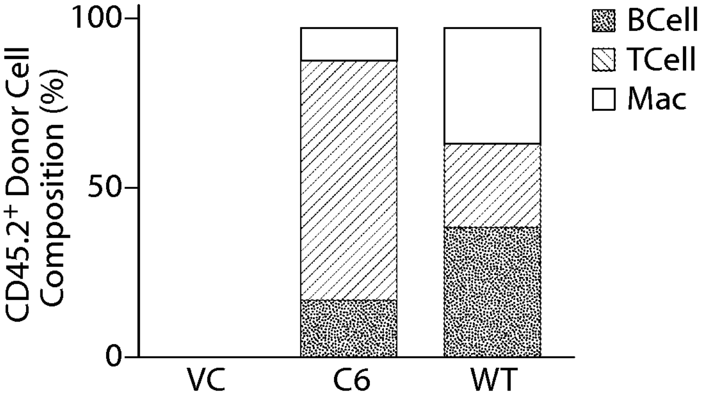


Fig. 41C

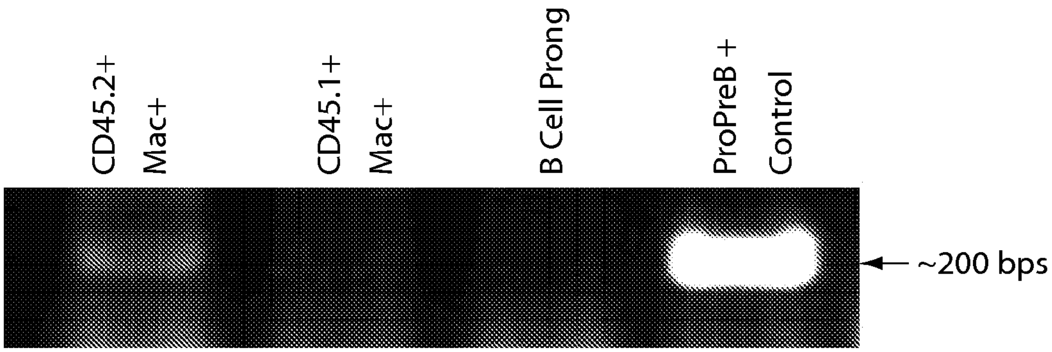

CD45.2+
Mac+
CD45.1+
Mac+
B Cell Prong
ProPreB +
Control
~200 bps

Fig. 42

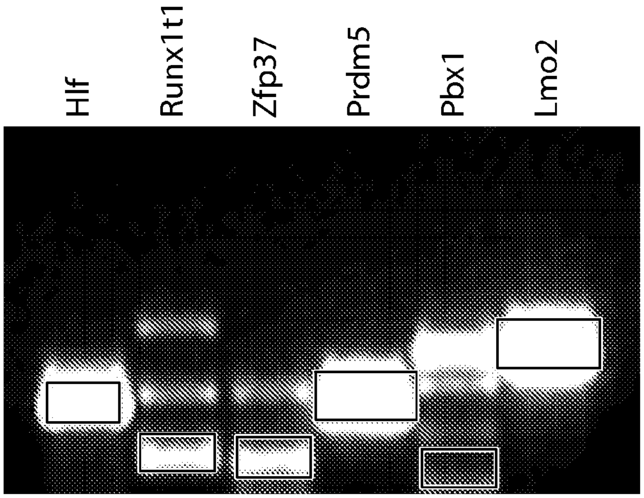

Hlf
Runx1t1
Zfp37
Prdm5
Pbx1
Lmo2

Fig. 43

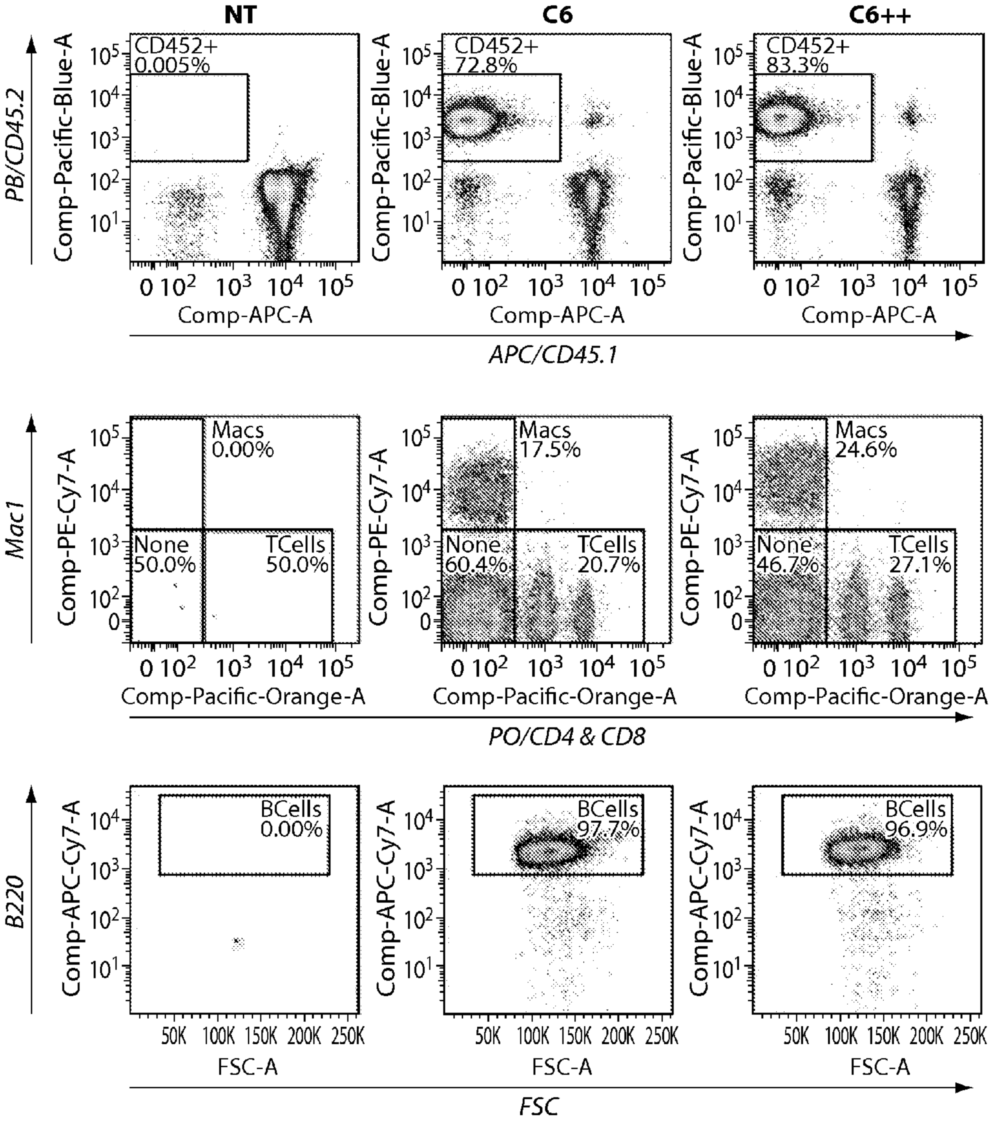

NT
C6
C6++
PB/CD45.2
Comp-Pacific-Blue-A
CD452+
0.005%
72.8%
83.3%
Comp-APC-A
APC/CD45.1
Mac1
Comp-PE-Cy7-A
Macs
0.00%
17.5%
24.6%
None
50.0%
60.4%
46.7%
TCells
50.0%
20.7%
27.1%
Comp-Pacific-Orange-A
PO/CD4 & CD8
B220
Comp-APC-Cy7-A
BCells
0.00%
97.7%
96.9%
FSC-A
FSC
50K 100K 150K 200K 250K
0 10^2 10^3 10^4 10^5

Fig. 44A

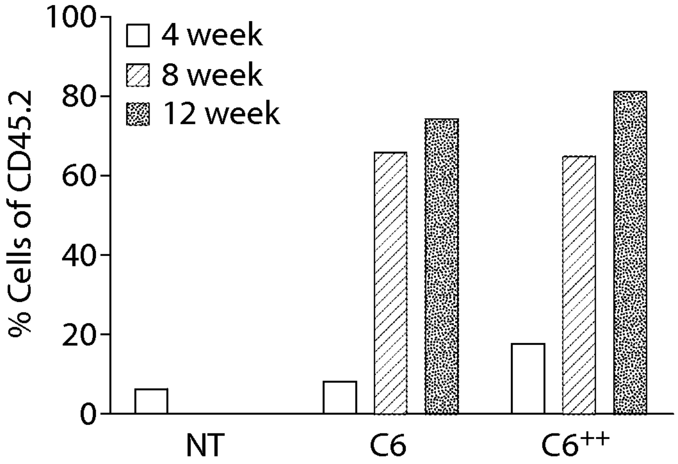


Fig. 44B

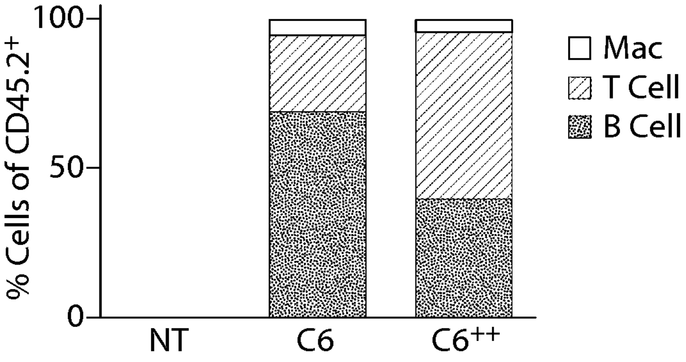


Fig. 44C

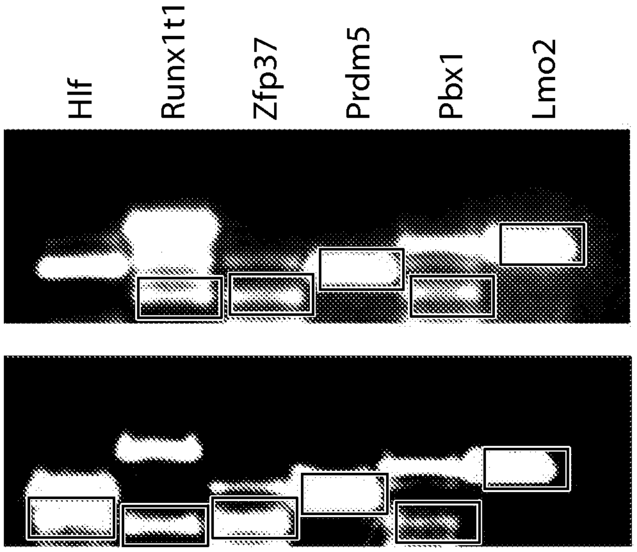


Fig. 45

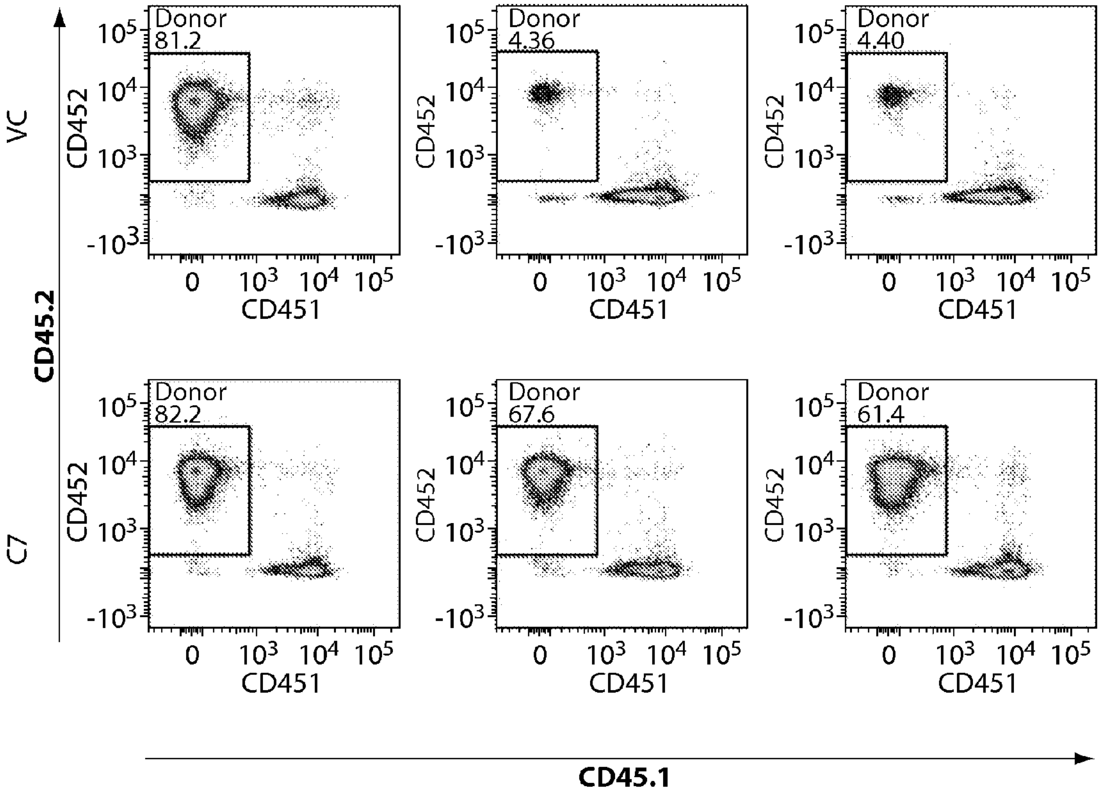

VC
C7
CD45.2
CD45.1
CD452
CD451
Donor
81.2
4.36
4.40
82.2
67.6
61.4
10^5
10^4
10^3
-10^3
0

Fig. 46A-1

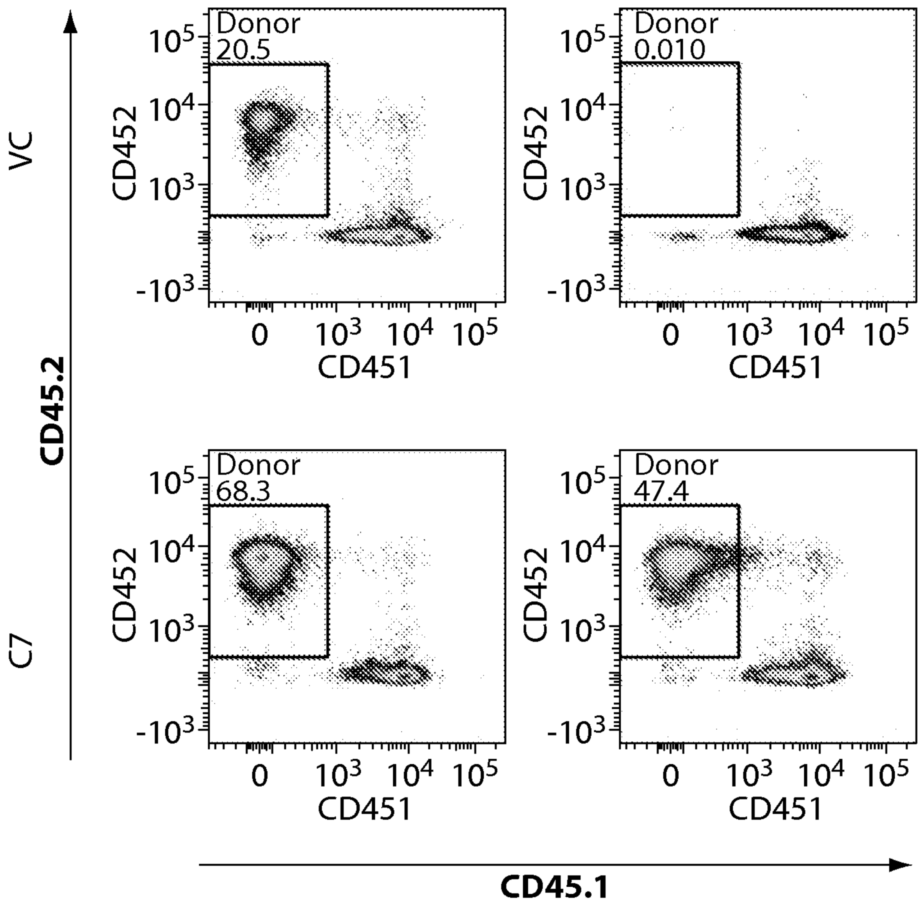

VC
C7
CD45.2
CD45.1
Donor
20.5
Donor
0.010
Donor
68.3
Donor
47.4
CD452
CD451
10^5
10^4
10^3
-10^3
0
10^3
10^4
10^5

Fig. 46A-2

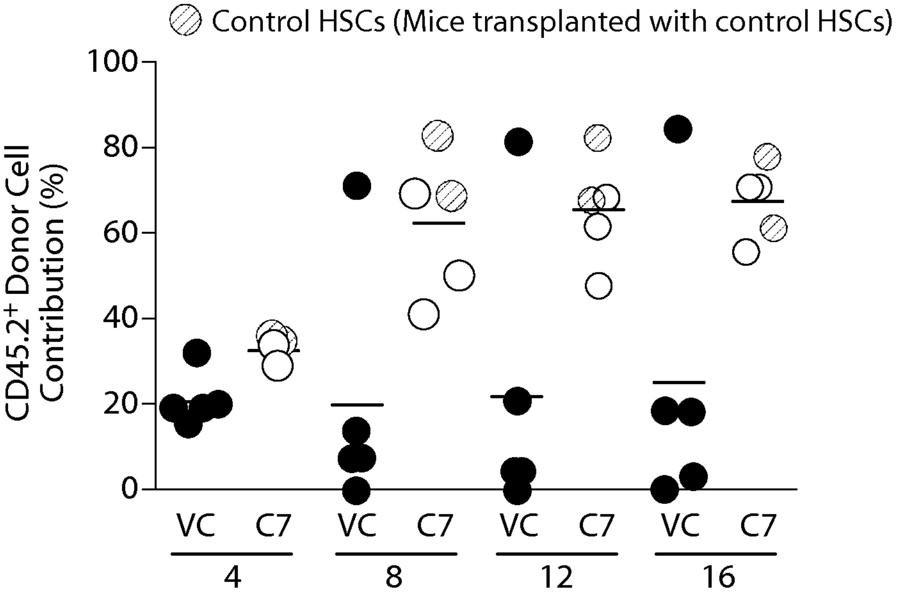


Fig. 46B

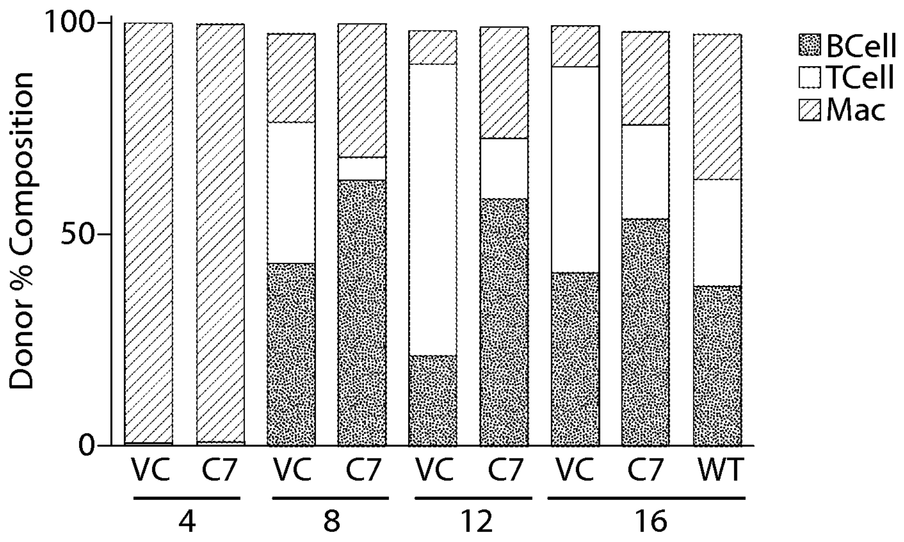


Fig. 46C

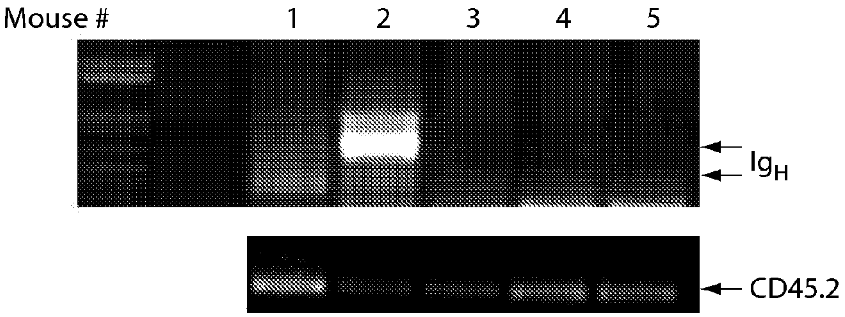

Mouse #
1
2
3
4
5
Ig_H
CD45.2

Fig. 47

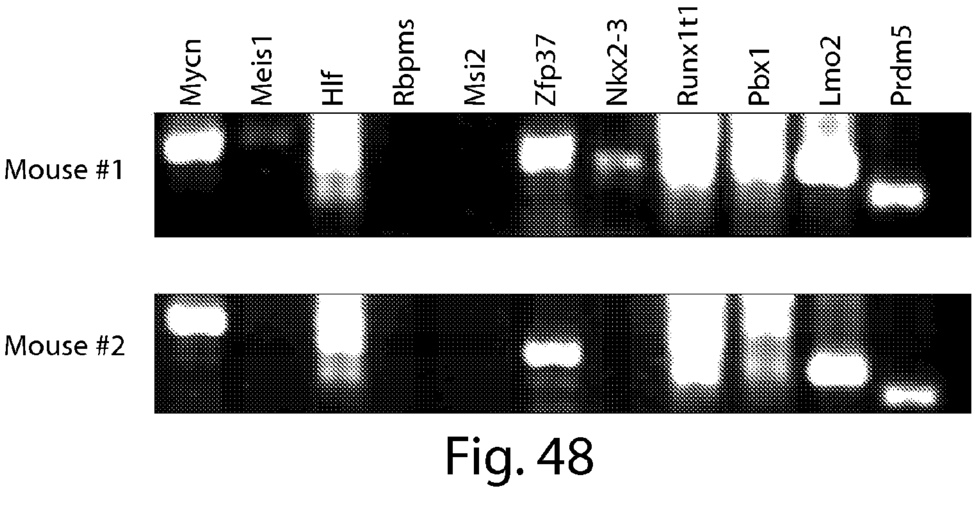

Mycn
Meis1
Hlf
Rbpms
Msi2
Zfp37
Nkx2-3
Runx1t1
Pbx1
Lmo2
Prdm5
Mouse #1
Mouse #2

Fig. 48

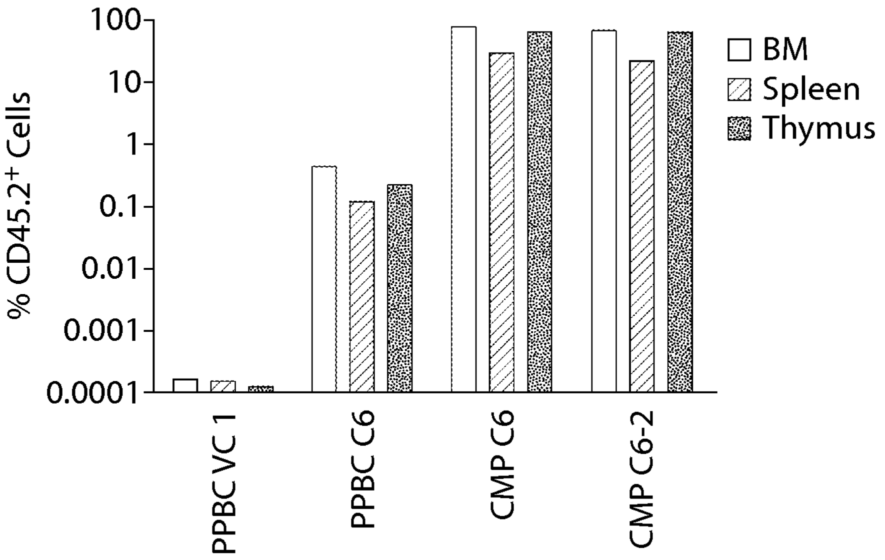


Fig. 49A

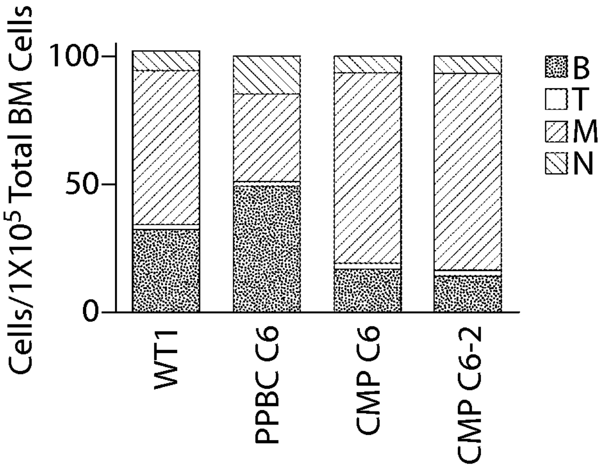


Fig. 49B

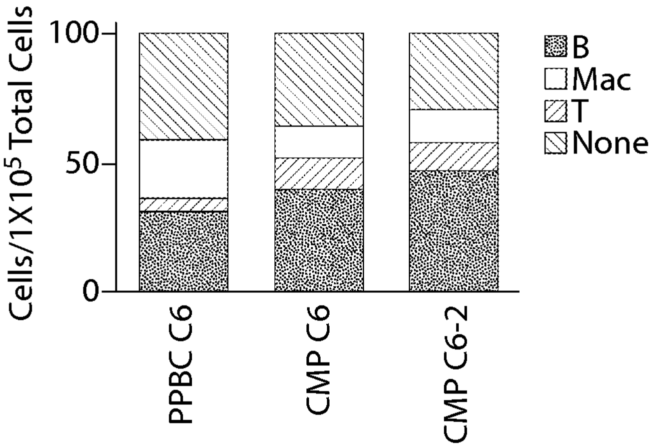


Fig. 49C

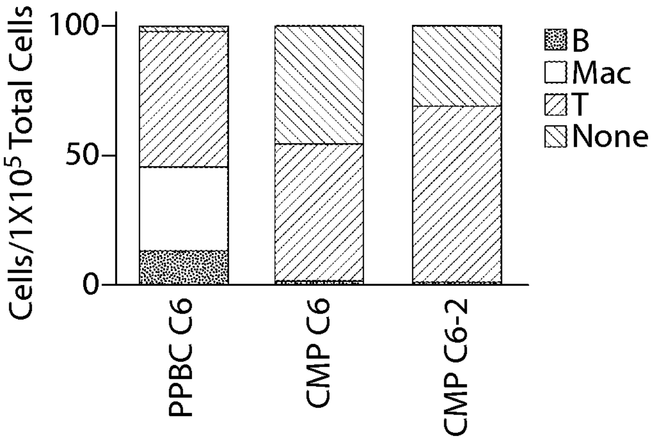


Fig. 49D

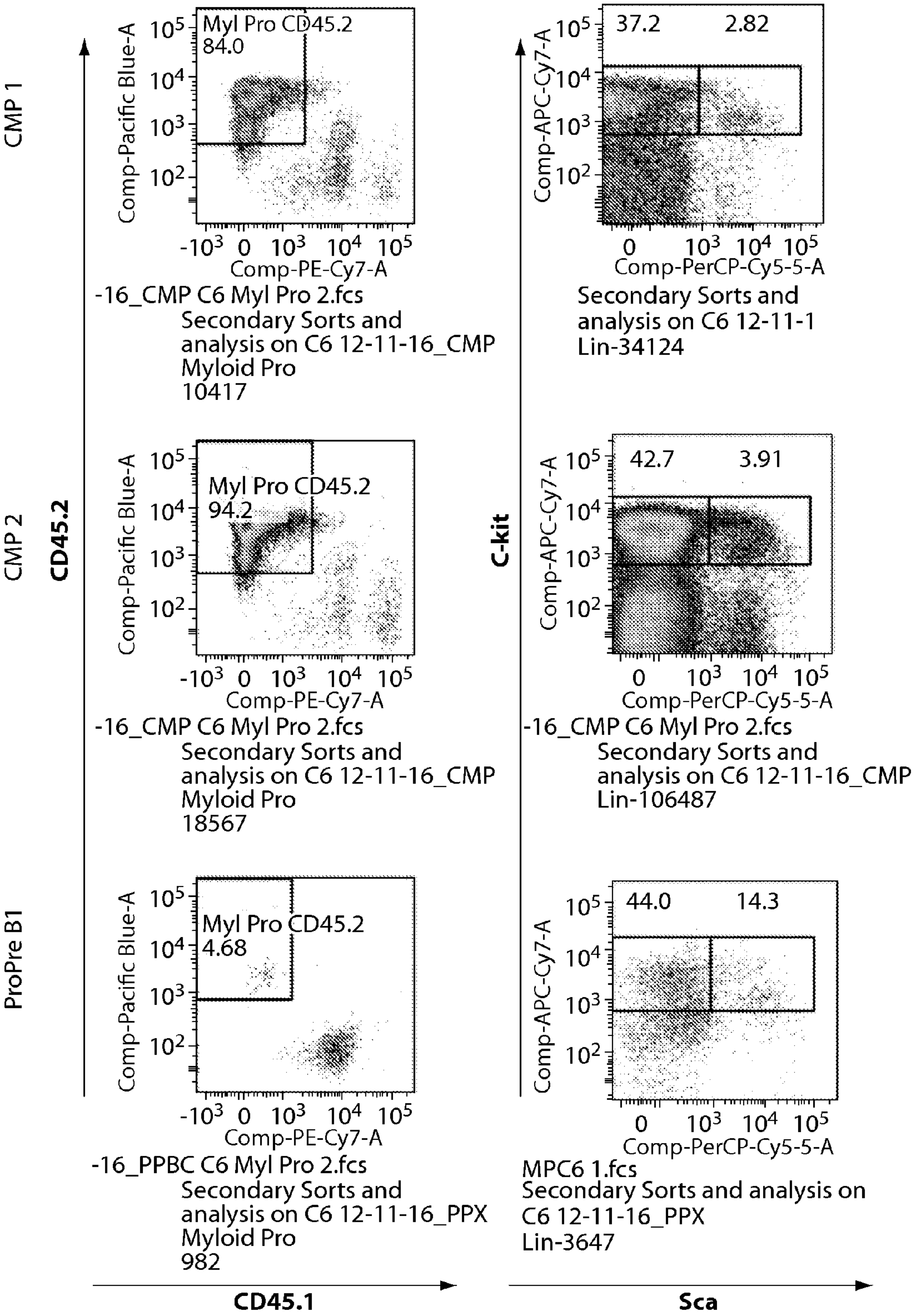

CMP 1
CMP 2
ProPre B1
CD45.2
C-kit
CD45.1
Sca
Comp-Pacific Blue-A
Comp-PE-Cy7-A
Comp-APC-Cy7-A
Comp-PerCP-Cy5-5-A
10^5
10^4
10^3
10^2
-10^3
0
Myl Pro CD45.2
84.0
37.2
2.82
-16_CMP C6 Myl Pro 2.fcs
Secondary Sorts and
analysis on C6 12-11-16_CMP
Myloid Pro
10417
Secondary Sorts and
analysis on C6 12-11-1
Lin-34124
Myl Pro CD45.2
94.2
42.7
3.91
-16_CMP C6 Myl Pro 2.fcs
Secondary Sorts and
analysis on C6 12-11-16_CMP
Myloid Pro
18567
-16_CMP C6 Myl Pro 2.fcs
Secondary Sorts and
analysis on C6 12-11-16_CMP
Lin-106487
Myl Pro CD45.2
4.68
44.0
14.3
-16_PPBC C6 Myl Pro 2.fcs
Secondary Sorts and
analysis on C6 12-11-16_PPX
Myloid Pro
982
MPC6 1.fcs
Secondary Sorts and analysis on
C6 12-11-16_PPX
Lin-3647

Fig. 50

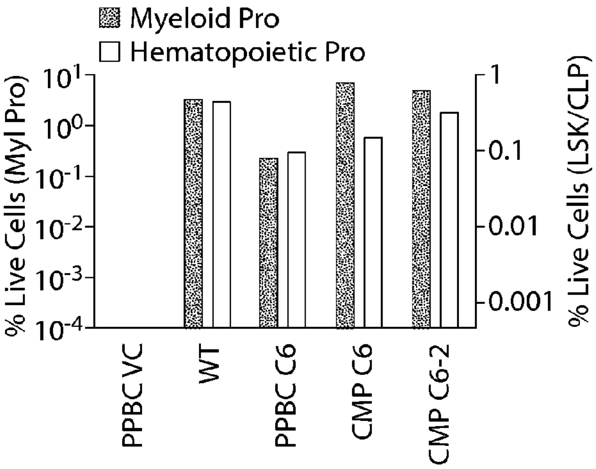


Fig. 51A

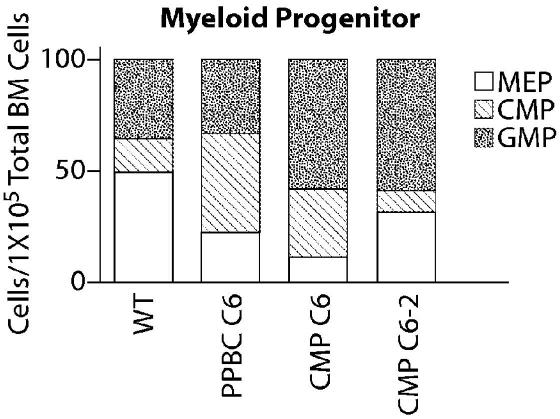


Fig. 51B

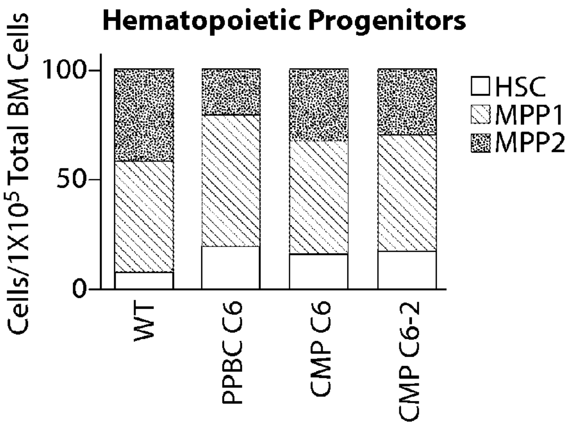


Fig. 51C

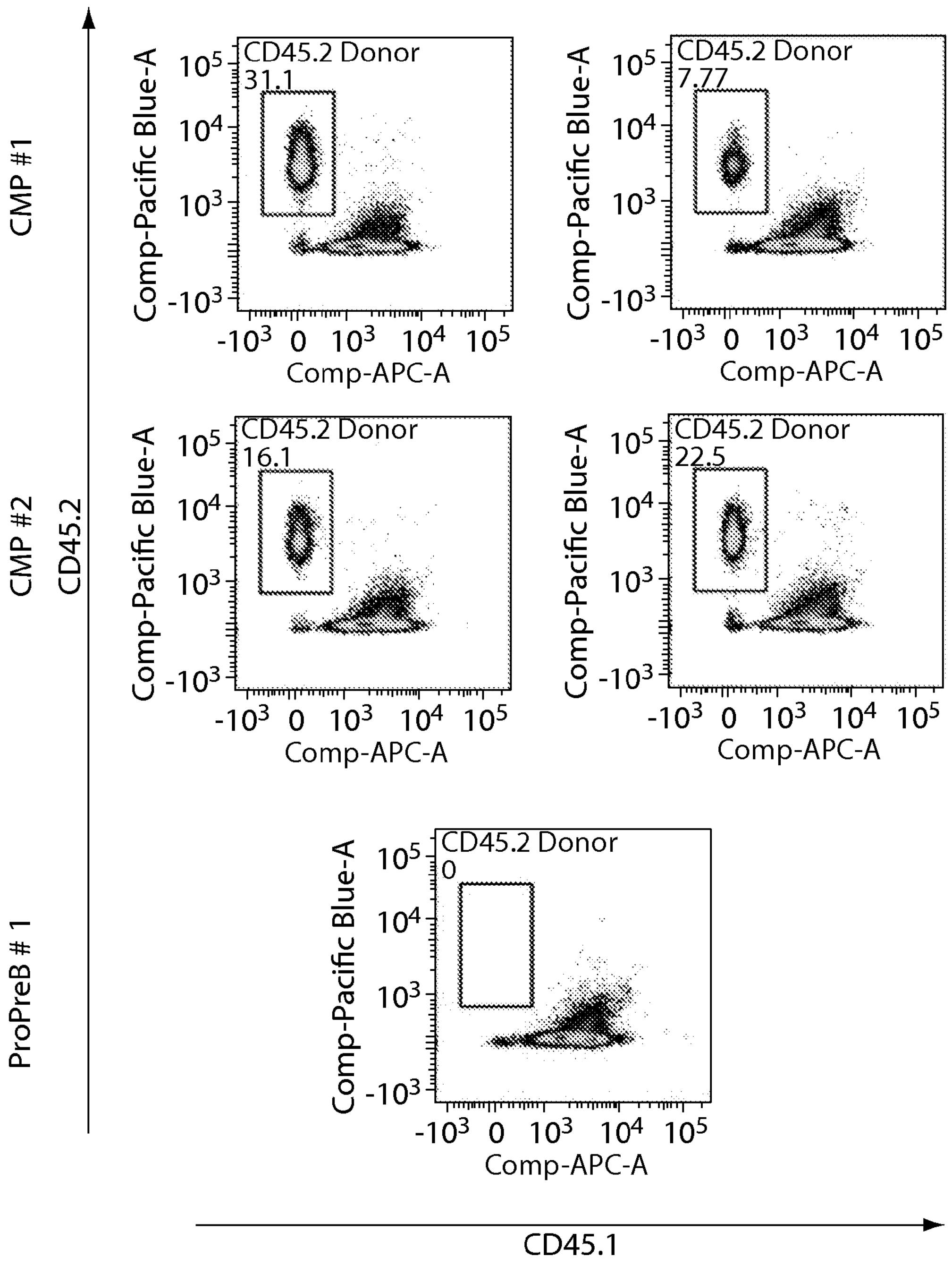

CMP #1
CMP #2
ProPreB # 1
CD45.2
CD45.1
CD45.2 Donor
31.1
7.77
16.1
22.5
0
Comp-Pacific Blue-A
Comp-APC-A
10^5
10^4
10^3
-10^3
0

Fig. 52-1

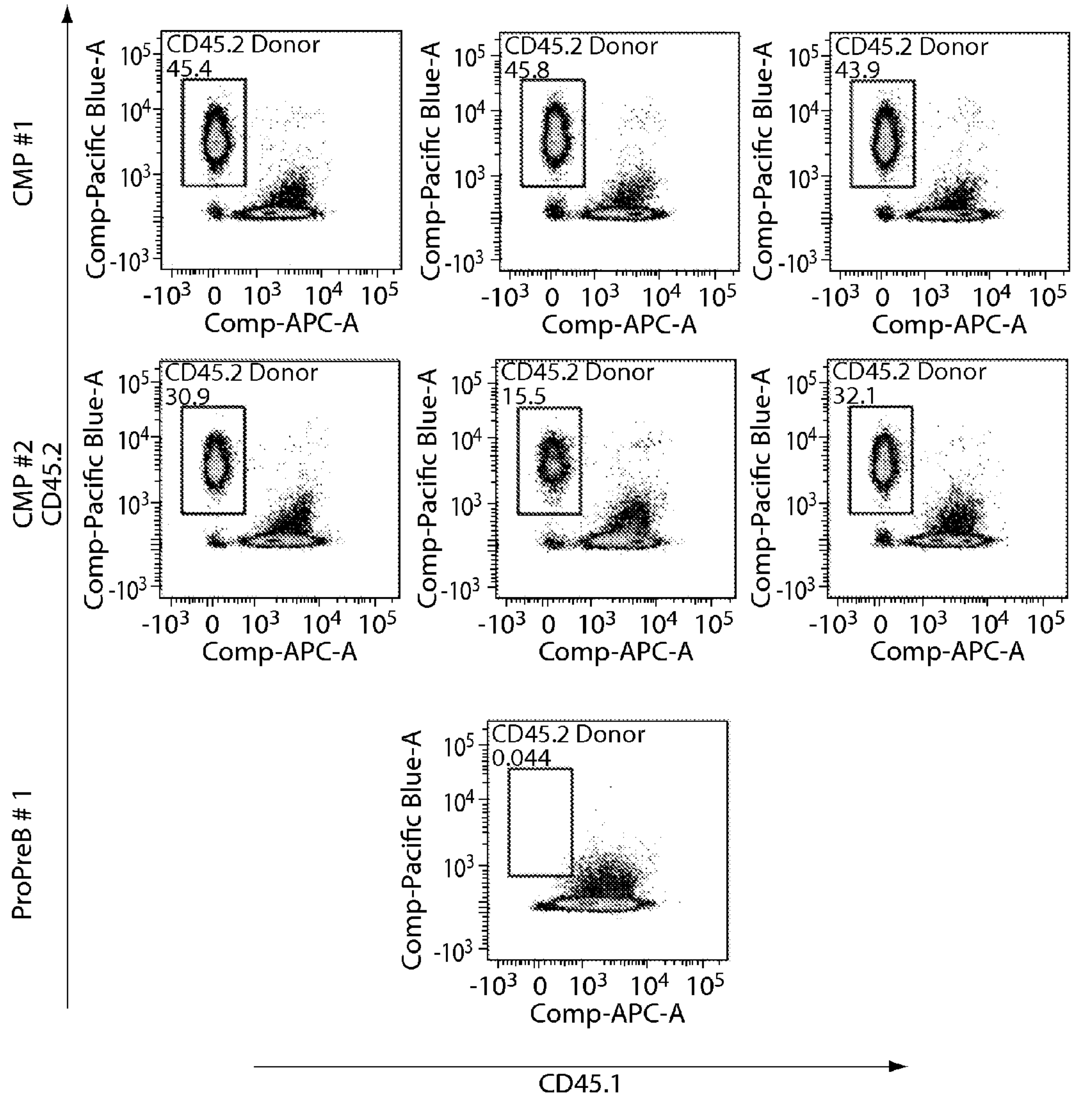

CMP #1
CMP #2
CD45.2
ProPreB # 1
CD45.2 Donor
45.4
45.8
43.9
30.9
15.5
32.1
0.044
Comp-Pacific Blue-A
Comp-APC-A
10^5
10^4
10^3
-10^3
0
CD45.1

Fig. 52-2

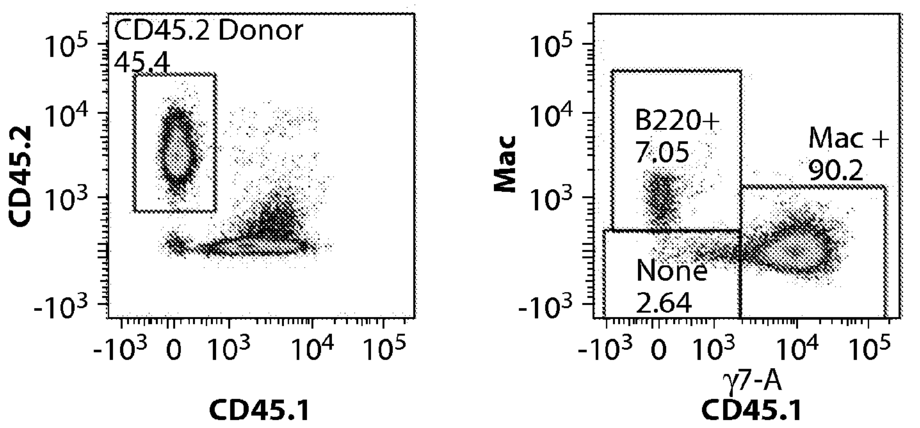


Fig. 53A

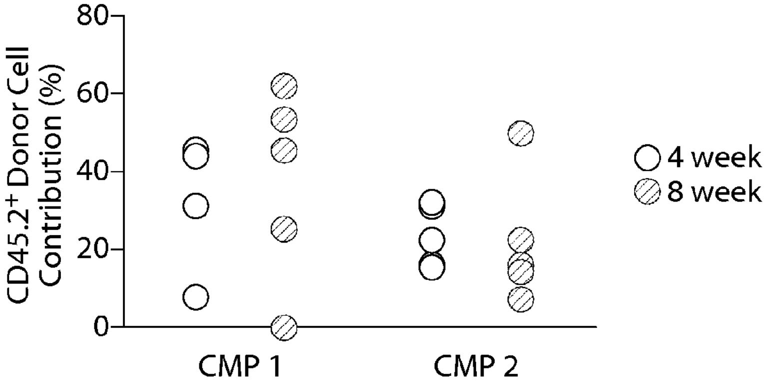


Fig. 53B

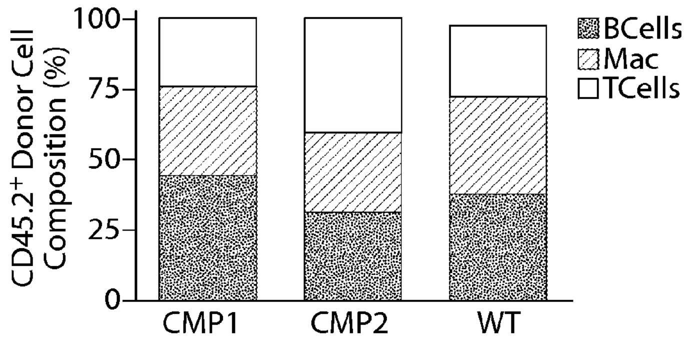


Fig. 53C

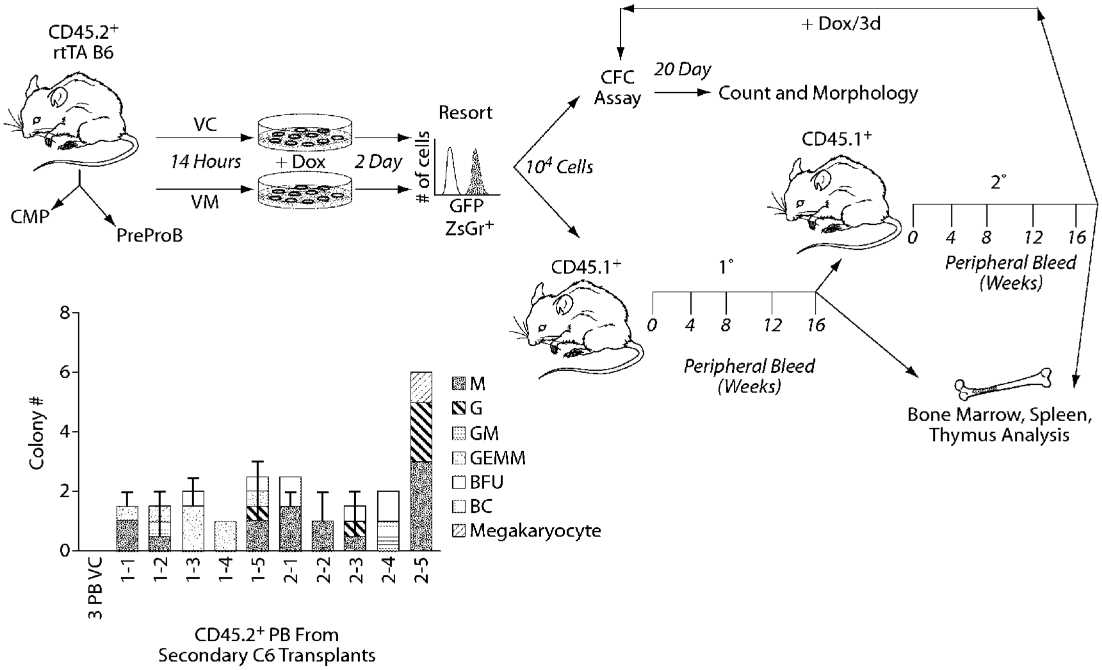

CD45.2+
rtTA B6
CMP
PreProB
VC
14 Hours
VM
+ Dox
2 Day
Resort
# of cells
GFP
ZsGr+
10⁴ Cells
CFC Assay
20 Day
Count and Morphology
+ Dox/3d
CD45.1+
CD45.1+
1°
0 4 8 12 16
Peripheral Bleed (Weeks)
2°
0 4 8 12 16
Peripheral Bleed (Weeks)
Bone Marrow, Spleen, Thymus Analysis
Colony #
0 2 4 6 8
M
G
GM
GEMM
BFU
BC
Megakaryocyte
3 PB VC
1-1
1-2
1-3
1-4
1-5
2-1
2-2
2-3
2-4
2-5
CD45.2+ PB From Secondary C6 Transplants

Fig. 54

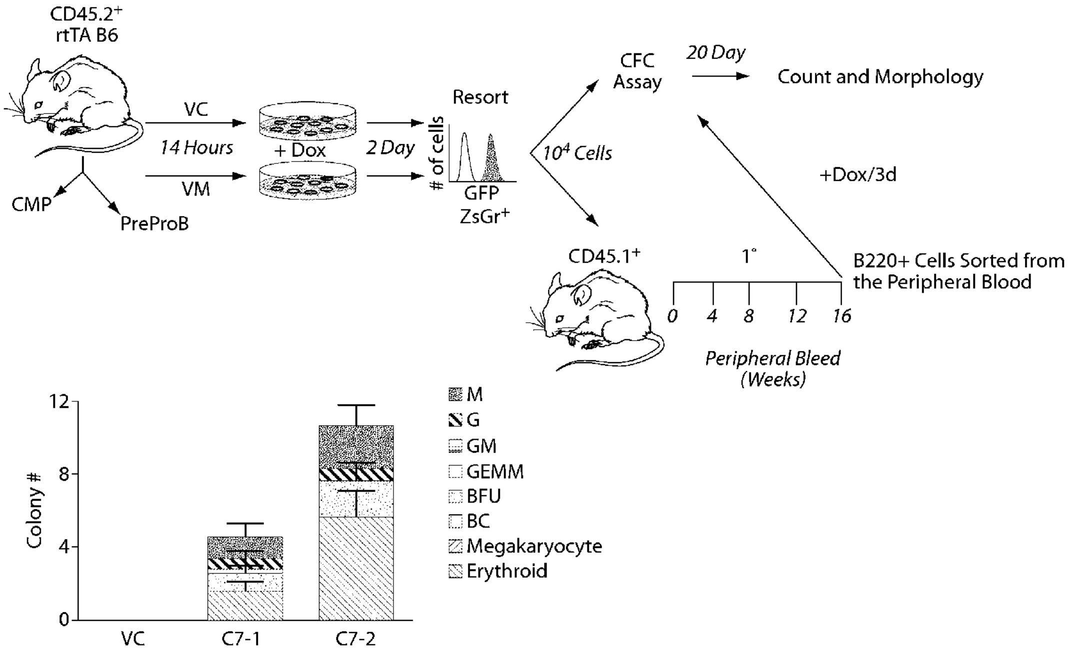

CD45.2+
rtTA B6
CMP
PreProB
VC
14 Hours
VM
+ Dox
2 Day
Resort
# of cells
GFP
ZsGr+
10⁴ Cells
CFC
Assay
20 Day
Count and Morphology
+Dox/3d
CD45.1+
1°
0
4
8
12
16
Peripheral Bleed
(Weeks)
B220+ Cells Sorted from
the Peripheral Blood
Colony #
0
4
8
12
VC
C7-1
C7-2
M
G
GM
GEMM
BFU
BC
Megakaryocyte
Erythroid

Fig. 55

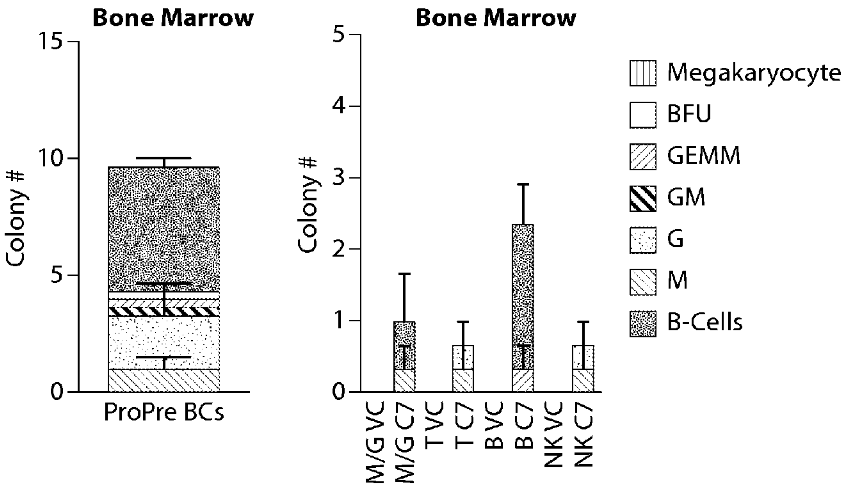


Fig. 56A

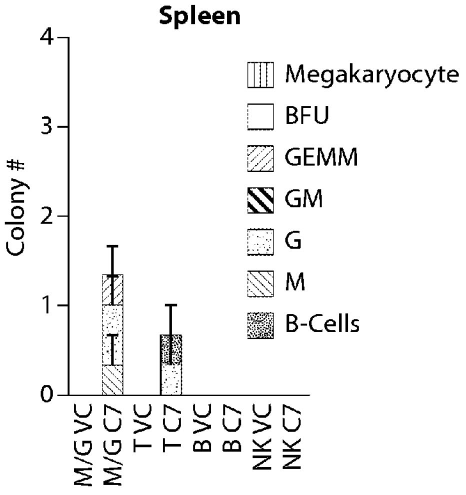


Fig. 56B

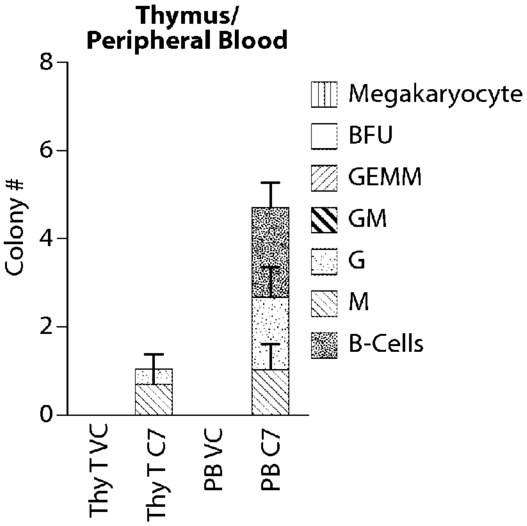


Fig. 56C

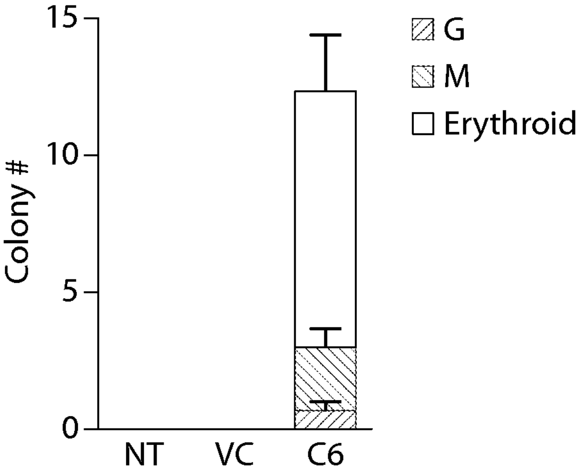


Fig. 57A

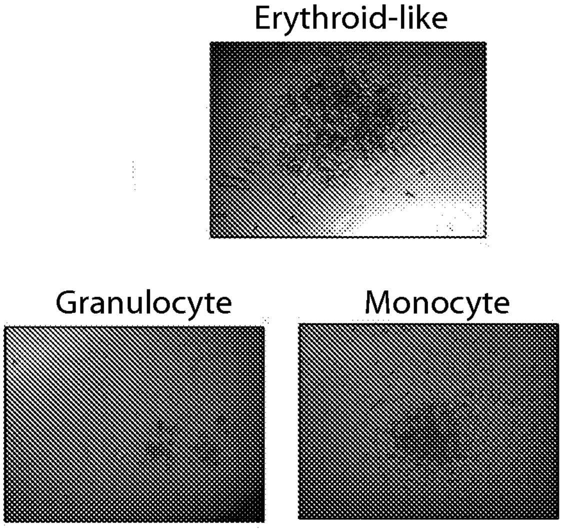


Fig. 57B

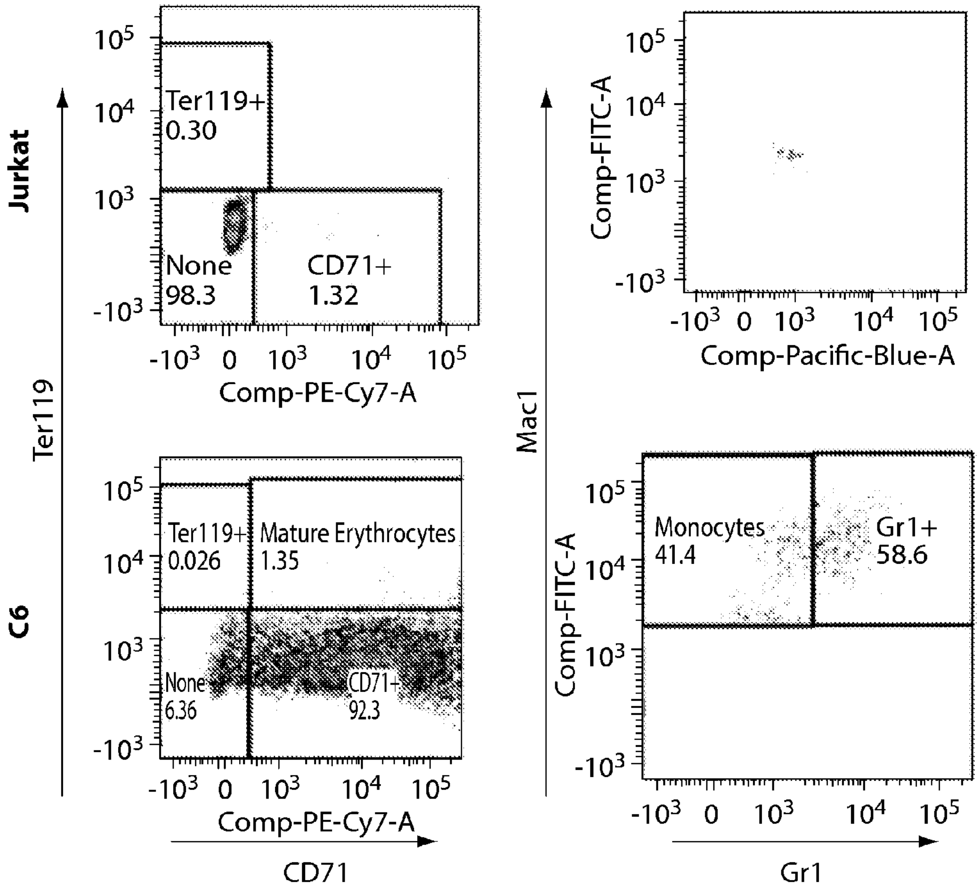

Jurkat
C6
Ter119
Mac1
CD71
Gr1
Ter119+
0.30
None
98.3
CD71+
1.32
Comp-PE-Cy7-A
Comp-FITC-A
Comp-Pacific-Blue-A
Ter119+
0.026
Mature Erythrocytes
1.35
None
6.36
CD71+
92.3
Monocytes
41.4
Gr1+
58.6
10^5
10^4
10^3
0
-10^3

Fig. 57C

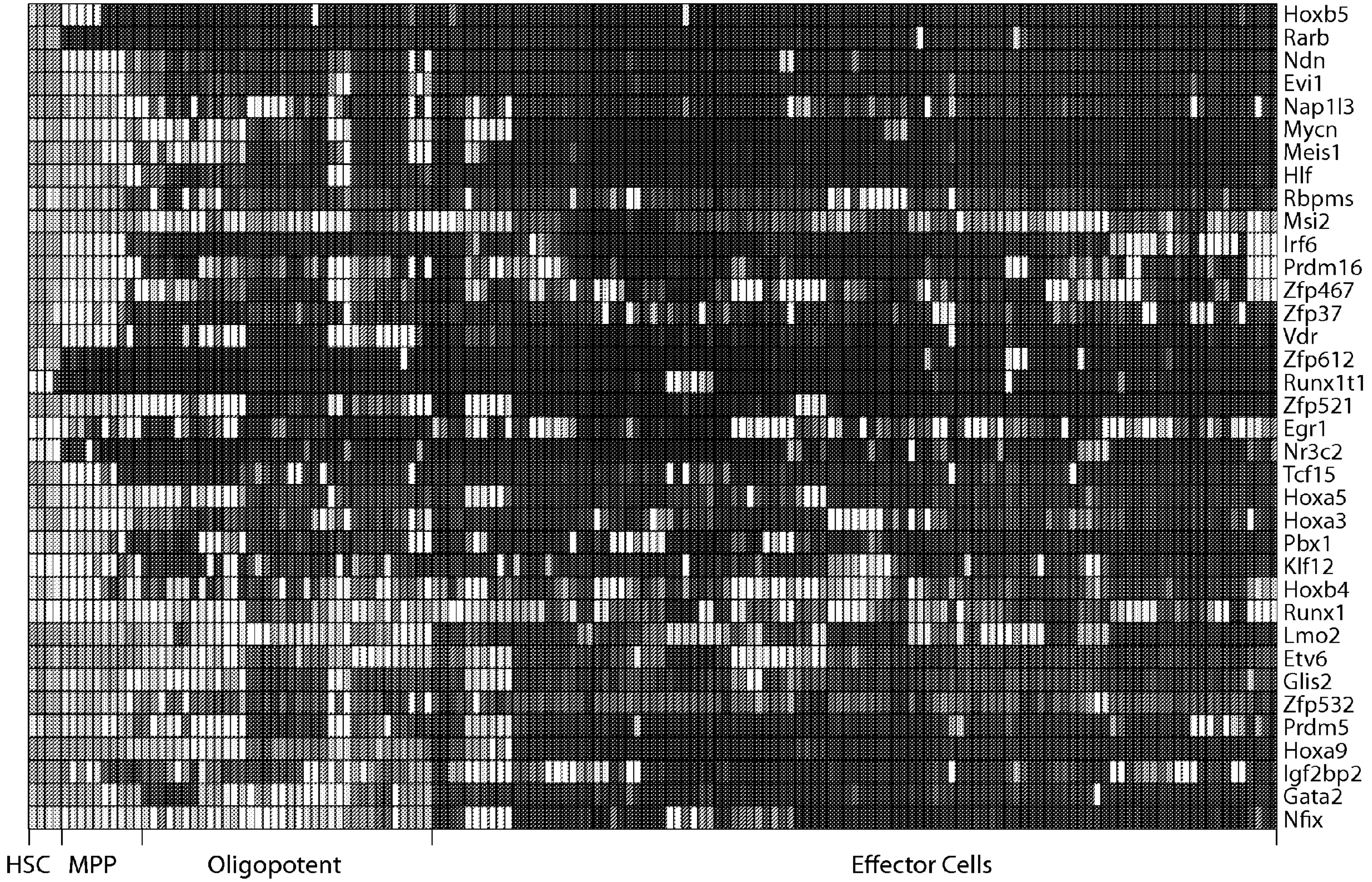

Hoxb5
Rarb
Ndn
Evi1
Nap1l3
Mycn
Meis1
Hlf
Rbpms
Msi2
Irf6
Prdm16
Zfp467
Zfp37
Vdr
Zfp612
Runx1t1
Zfp521
Egr1
Nr3c2
Tcf15
Hoxa5
Hoxa3
Pbx1
Klf12
Hoxb4
Runx1
Lmo2
Etv6
Glis2
Zfp532
Prdm5
Hoxa9
Igf2bp2
Gata2
Nfix
HSC
MPP
Oligopotent
Effector Cells

Fig. 58A

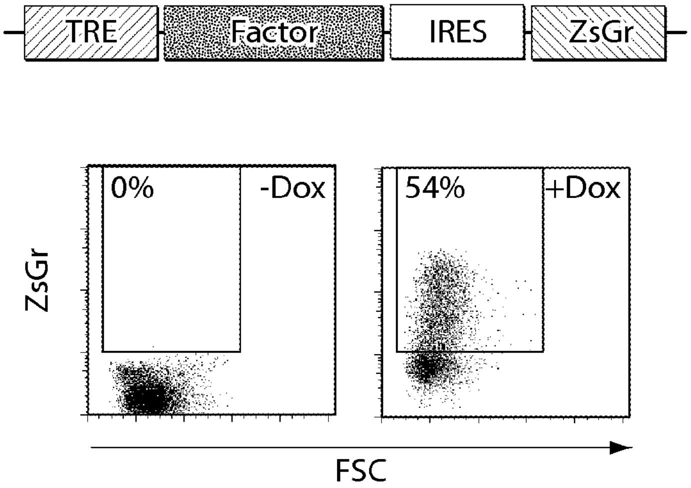


Fig. 58B

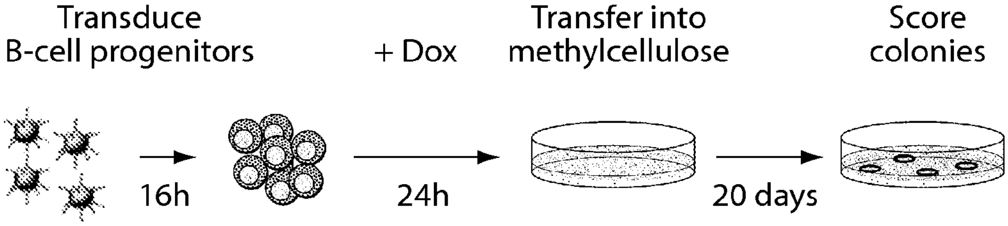


Fig. 58C

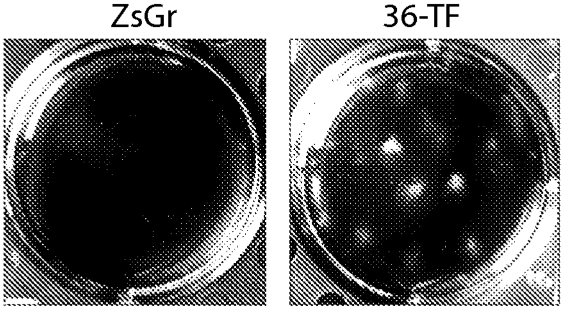


Fig. 58D

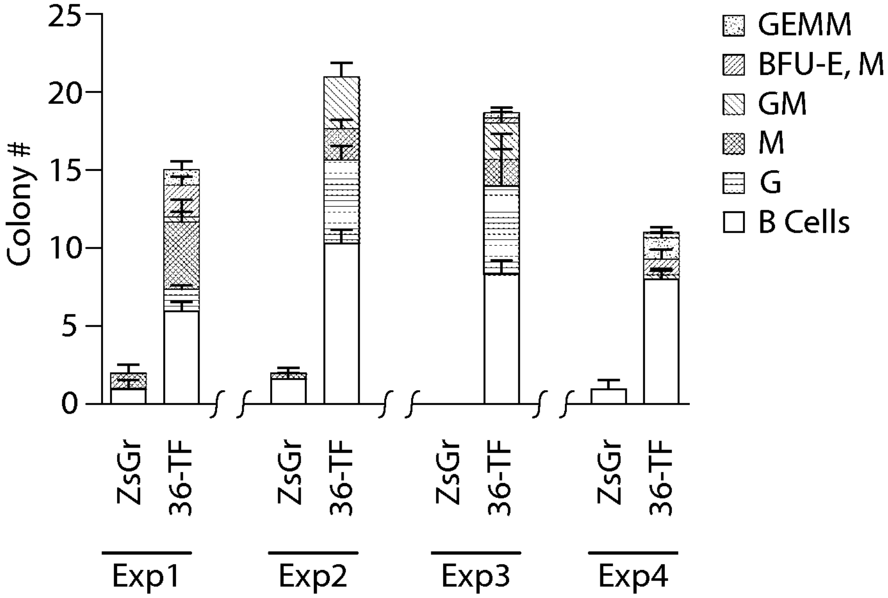


Fig. 58E

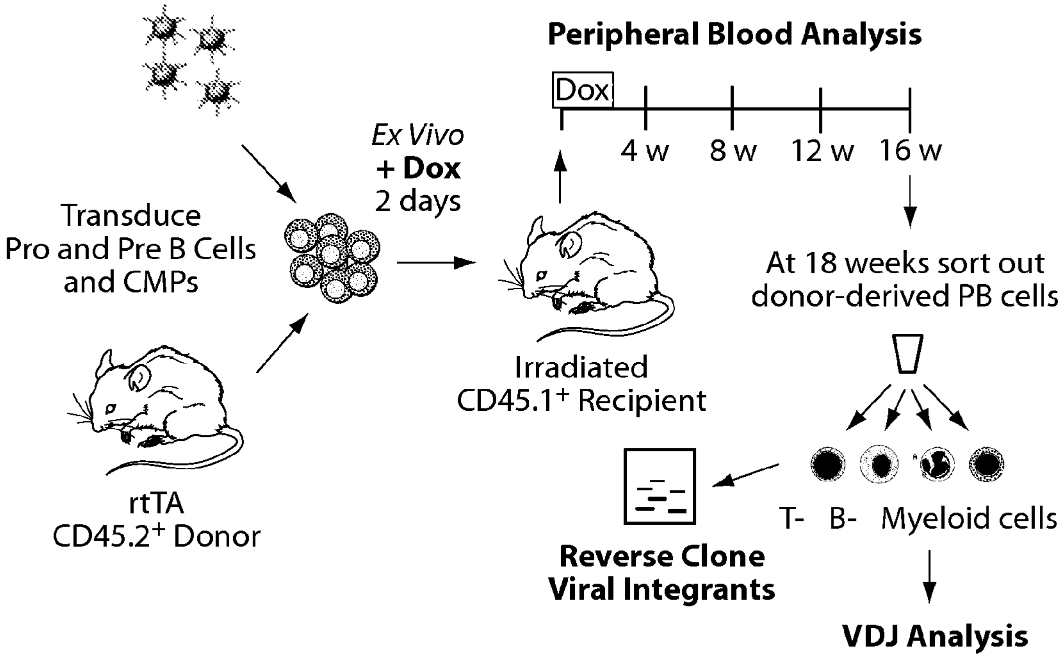

Transduce
Pro and Pre B Cells
and CMPs
rtTA
CD45.2⁺ Donor
Ex Vivo
+ Dox
2 days
Irradiated
CD45.1⁺ Recipient
Peripheral Blood Analysis
Dox
4 w
8 w
12 w
16 w
At 18 weeks sort out
donor-derived PB cells
T-
B-
Myeloid cells
Reverse Clone
Viral Integrants
VDJ Analysis

Fig. 59A

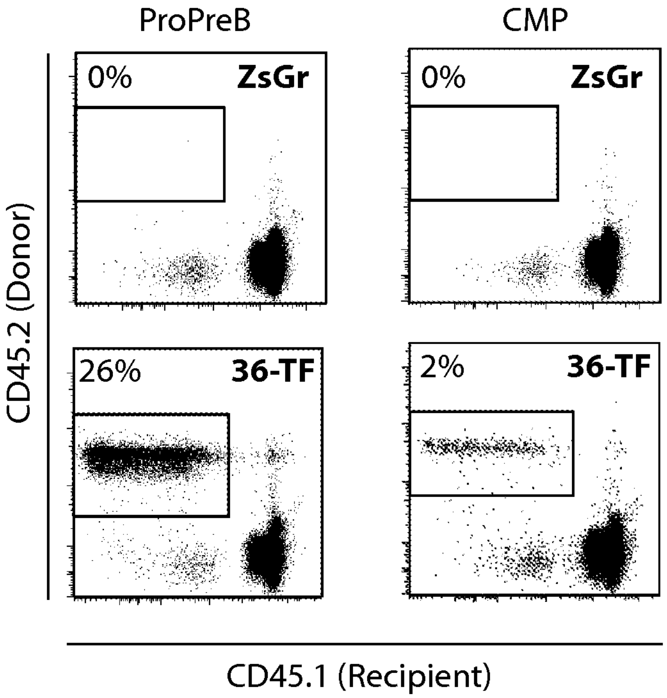

ProPreB
CMP
0%
ZsGr
0%
ZsGr
26%
36-TF
2%
36-TF
CD45.2 (Donor)
CD45.1 (Recipient)

Fig. 59B

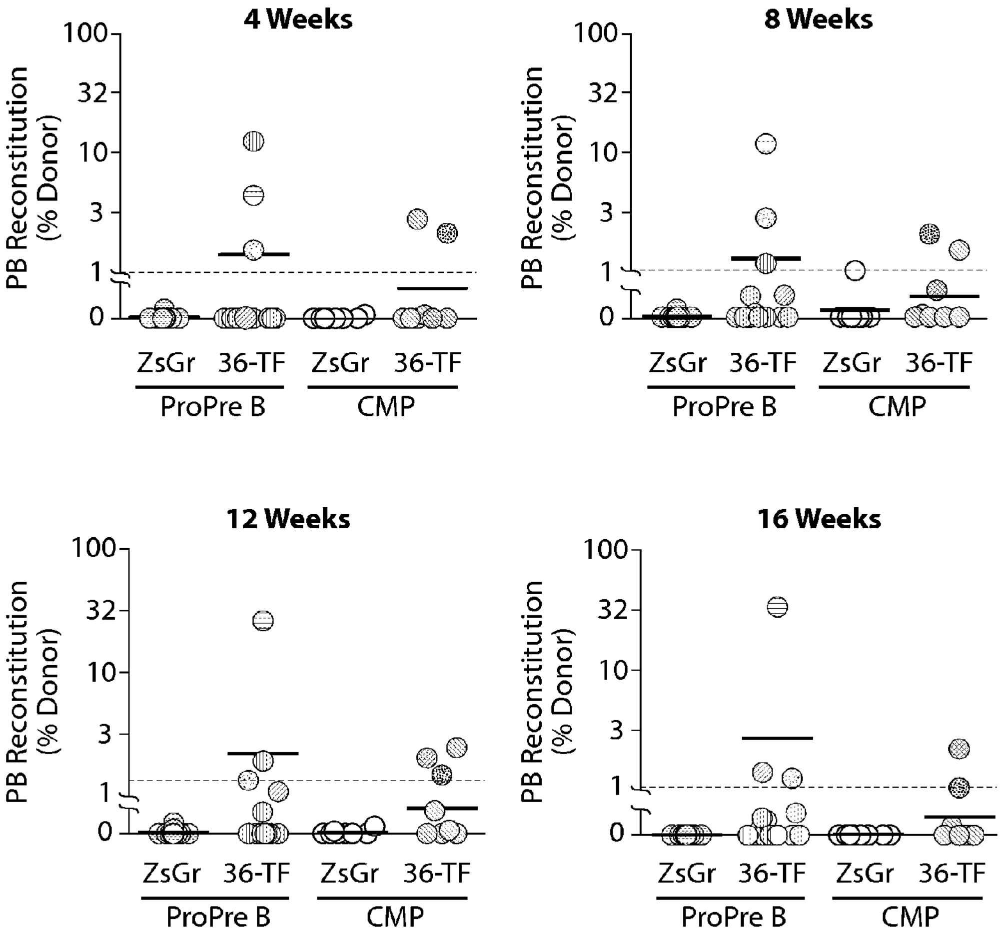

4 Weeks
8 Weeks
12 Weeks
16 Weeks
PB Reconstitution (% Donor)
100
32
10
3
1
0
ZsGr
36-TF
ZsGr
36-TF
ProPre B
CMP

Fig. 59C

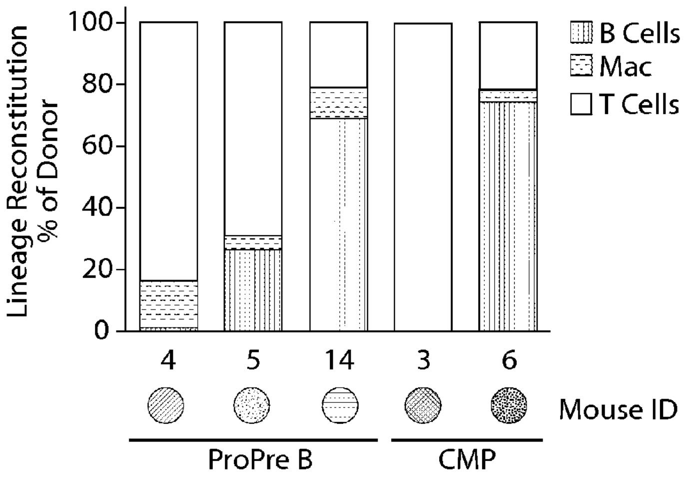


Fig. 59D

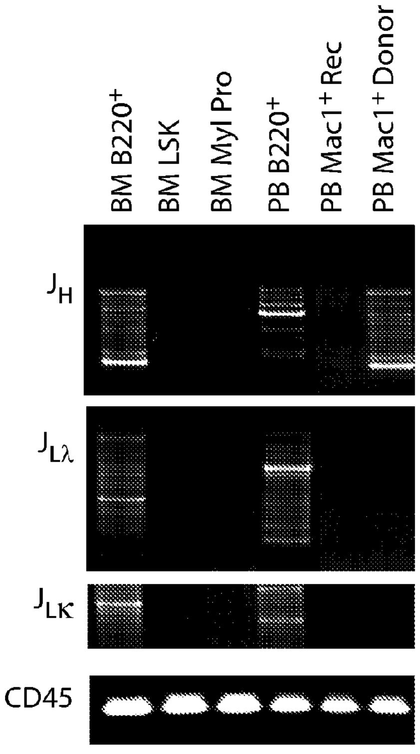


Fig. 59E

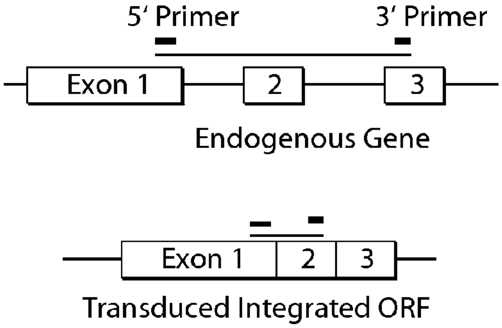


Fig. 59F

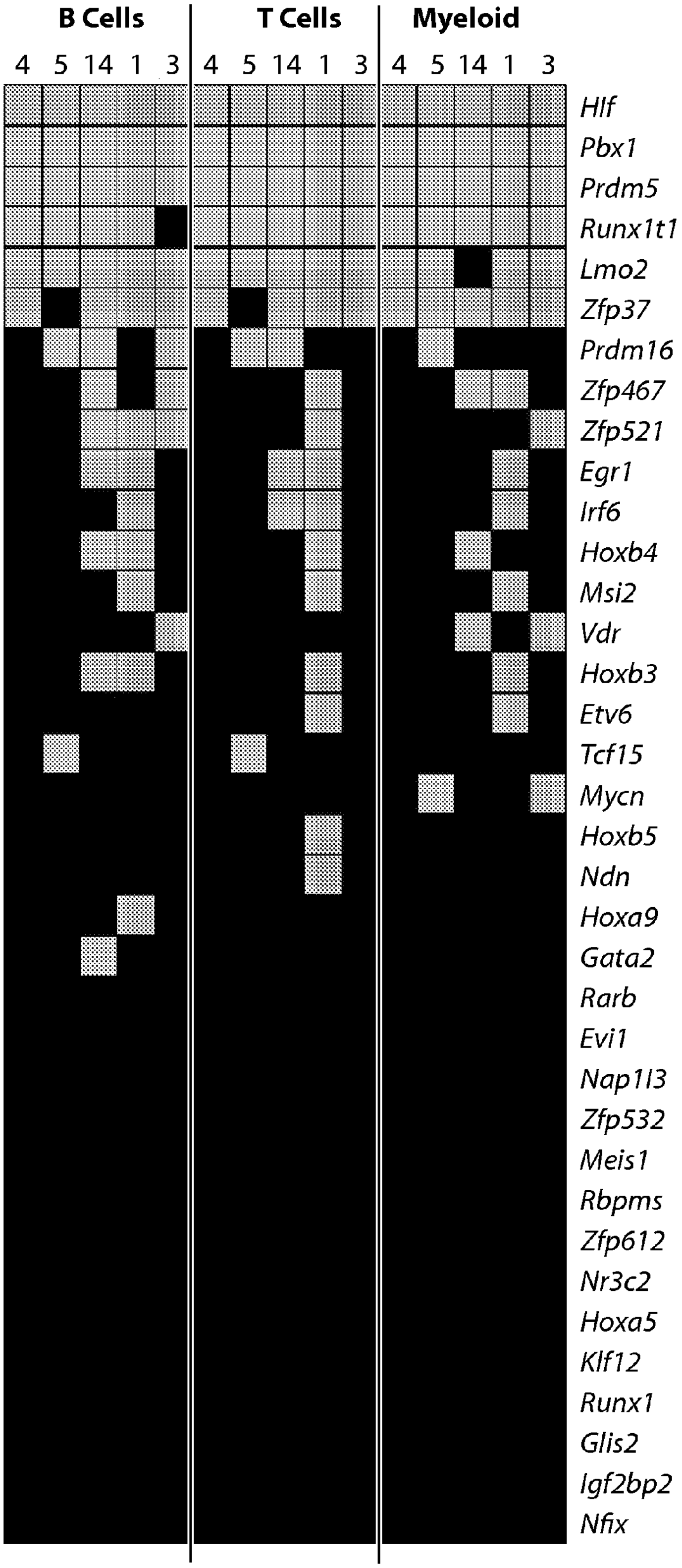

B Cells
T Cells
Myeloid
4 5 14 1 3
4 5 14 1 3
4 5 14 1 3
Hlf
Pbx1
Prdm5
Runx1t1
Lmo2
Zfp37
Prdm16
Zfp467
Zfp521
Egr1
Irf6
Hoxb4
Msi2
Vdr
Hoxb3
Etv6
Tcf15
Mycn
Hoxb5
Ndn
Hoxa9
Gata2
Rarb
Evi1
Nap1l3
Zfp532
Meis1
Rbpms
Zfp612
Nr3c2
Hoxa5
Klf12
Runx1
Glis2
Igf2bp2
Nfix

Fig. 59G

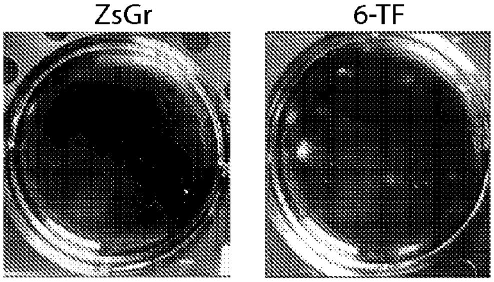


Fig. 60A

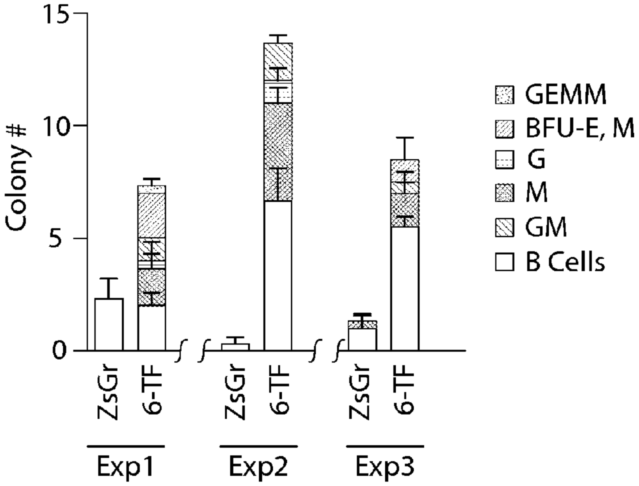


Fig. 60B

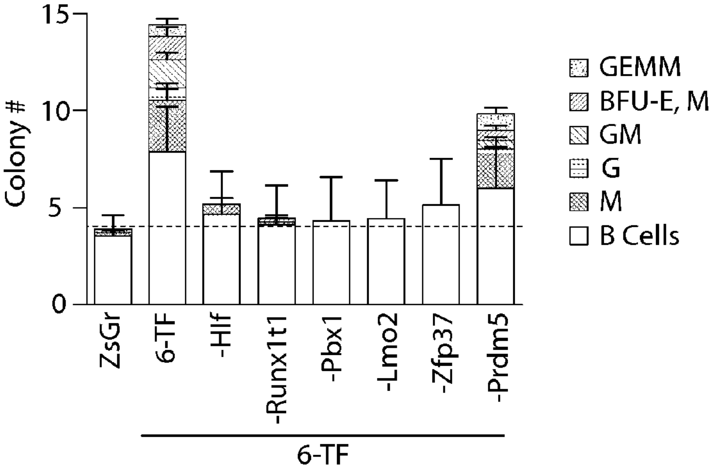


Fig. 60C

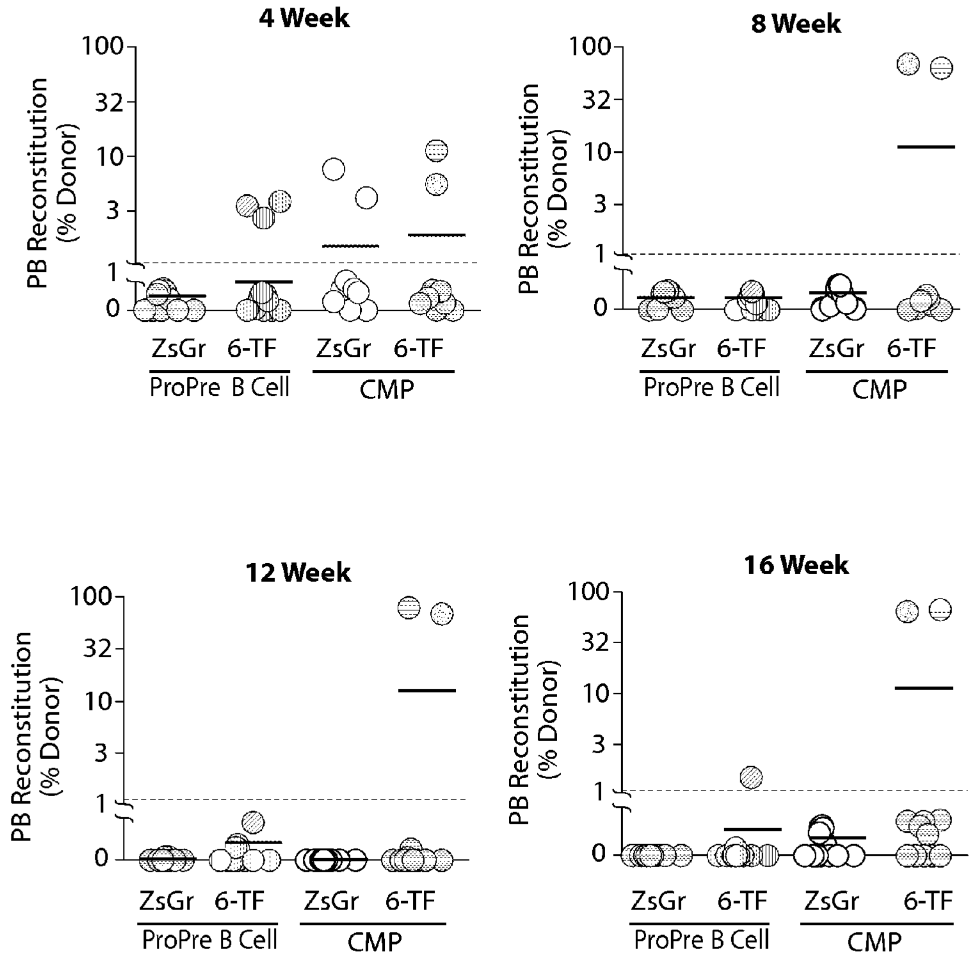

4 Week
8 Week
12 Week
16 Week
PB Reconstitution (% Donor)
100
32
10
3
1
0
ZsGr
6-TF
ProPre B Cell
CMP

Fig. 60D

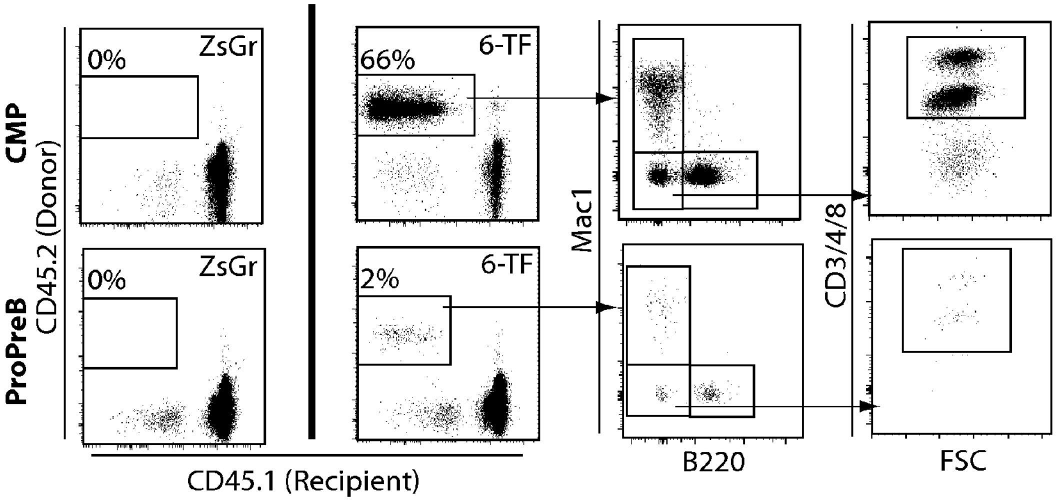


Fig. 60E

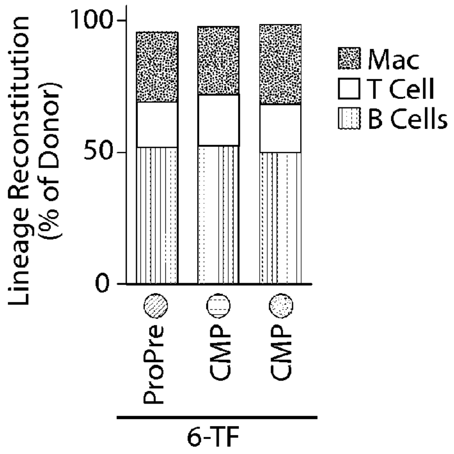


Fig. 60F

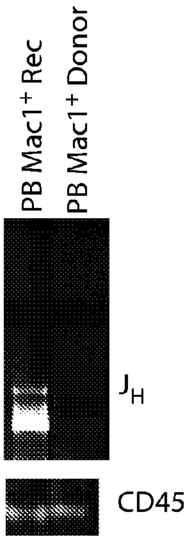


Fig. 60G

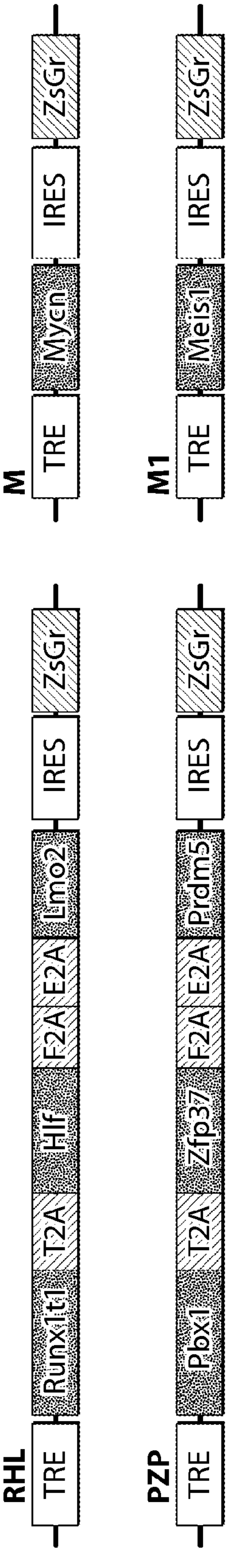

RHL
TRE
Runx1t1
T2A
Hlf
F2A
E2A
Lmo2
IRES
ZsGr
M
TRE
Mycn
IRES
ZsGr
PZP
TRE
Pbx1
T2A
Zfp37
F2A
E2A
Prdm5
IRES
ZsGr
M1
TRE
Meis1
IRES
ZsGr

Fig. 61A

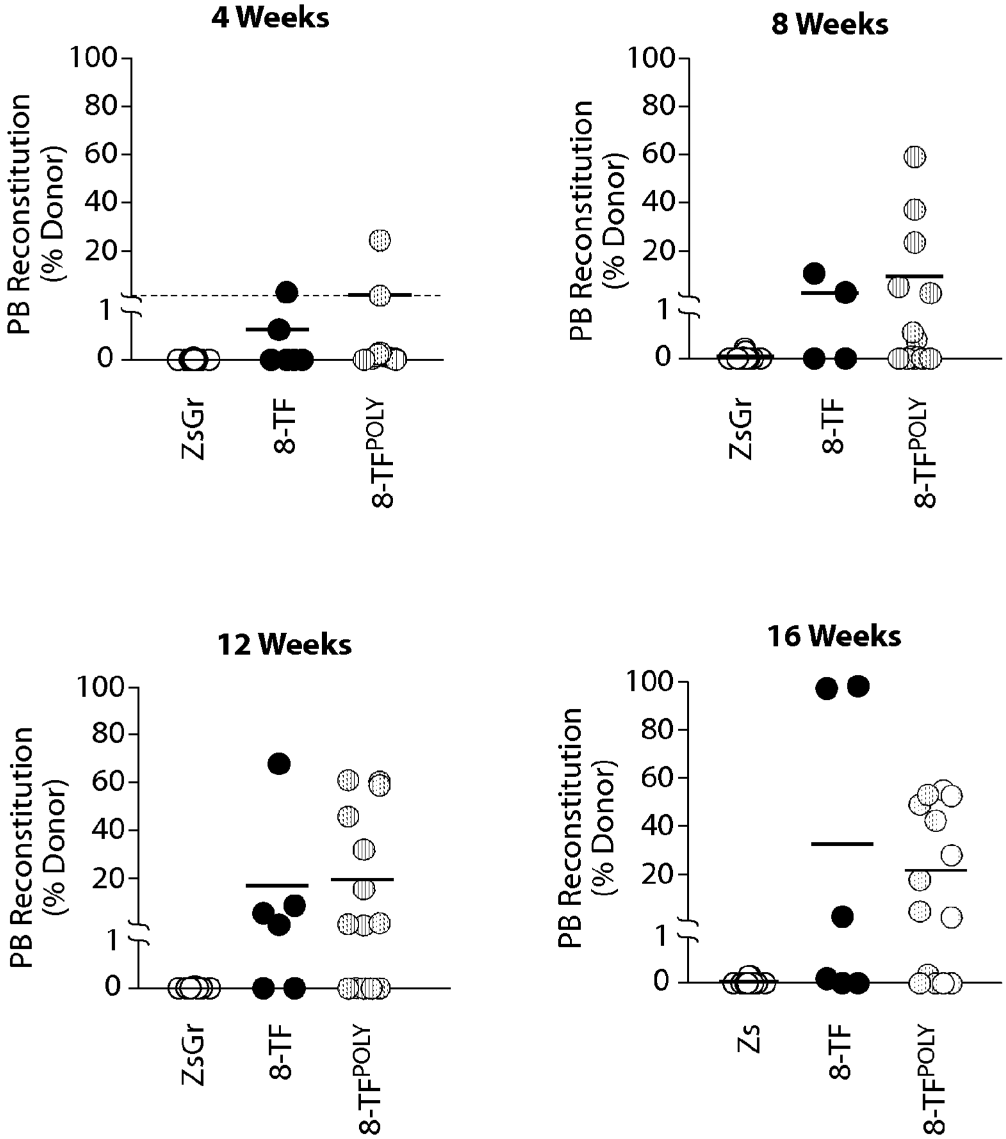

4 Weeks
8 Weeks
12 Weeks
16 Weeks
PB Reconstitution (% Donor)
100
80
60
40
20
1
0
ZsGr
8-TF
8-TF^{POLY}
Zs

Fig. 61B

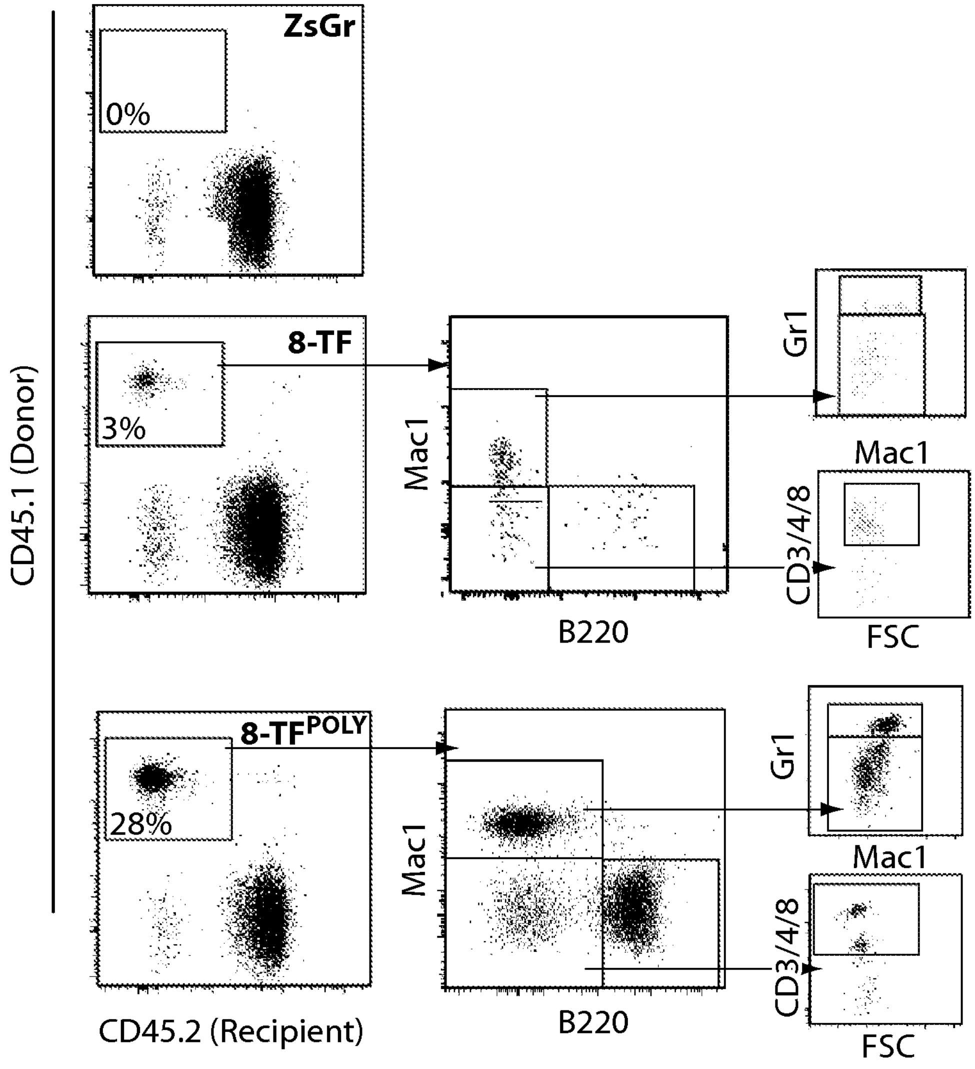

ZsGr
0%
8-TF
3%
$8\text{-}TF^{POLY}$
28%
CD45.1 (Donor)
CD45.2 (Recipient)
Mac1
B220
Mac1
B220
Gr1
Mac1
CD3/4/8
FSC
Gr1
Mac1
CD3/4/8
FSC

Fig. 61C

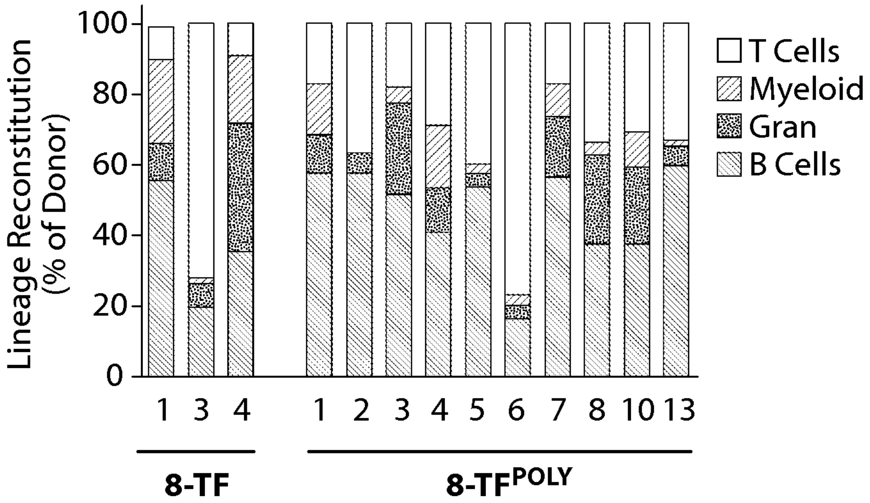


Fig. 61D

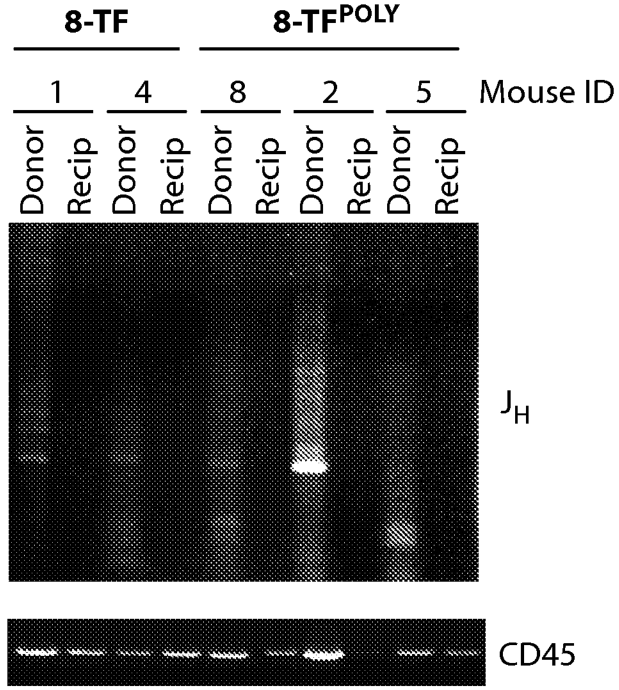


Fig. 61E

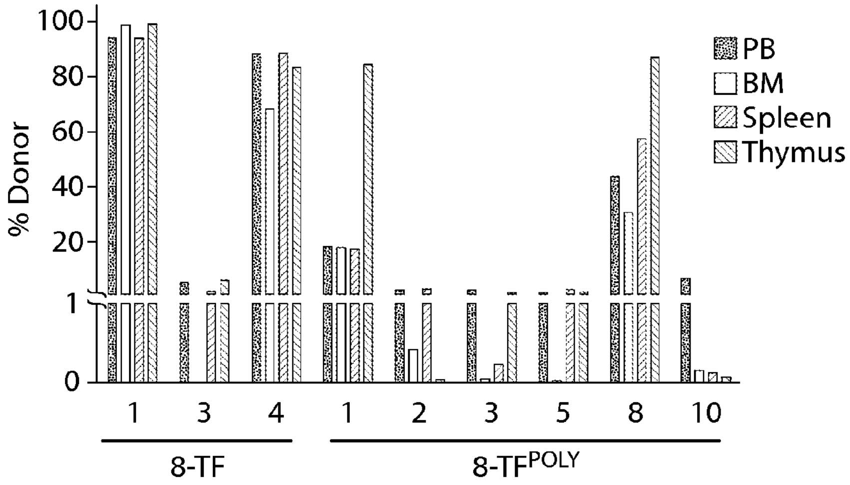


Fig. 62A

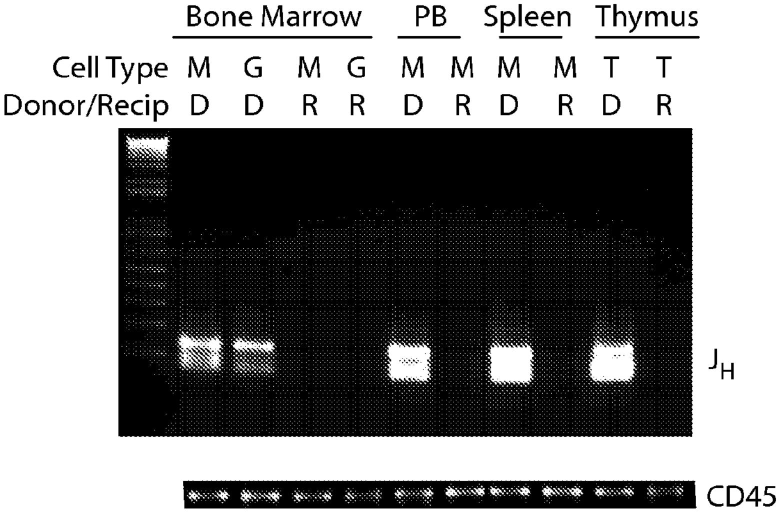


Fig. 62B

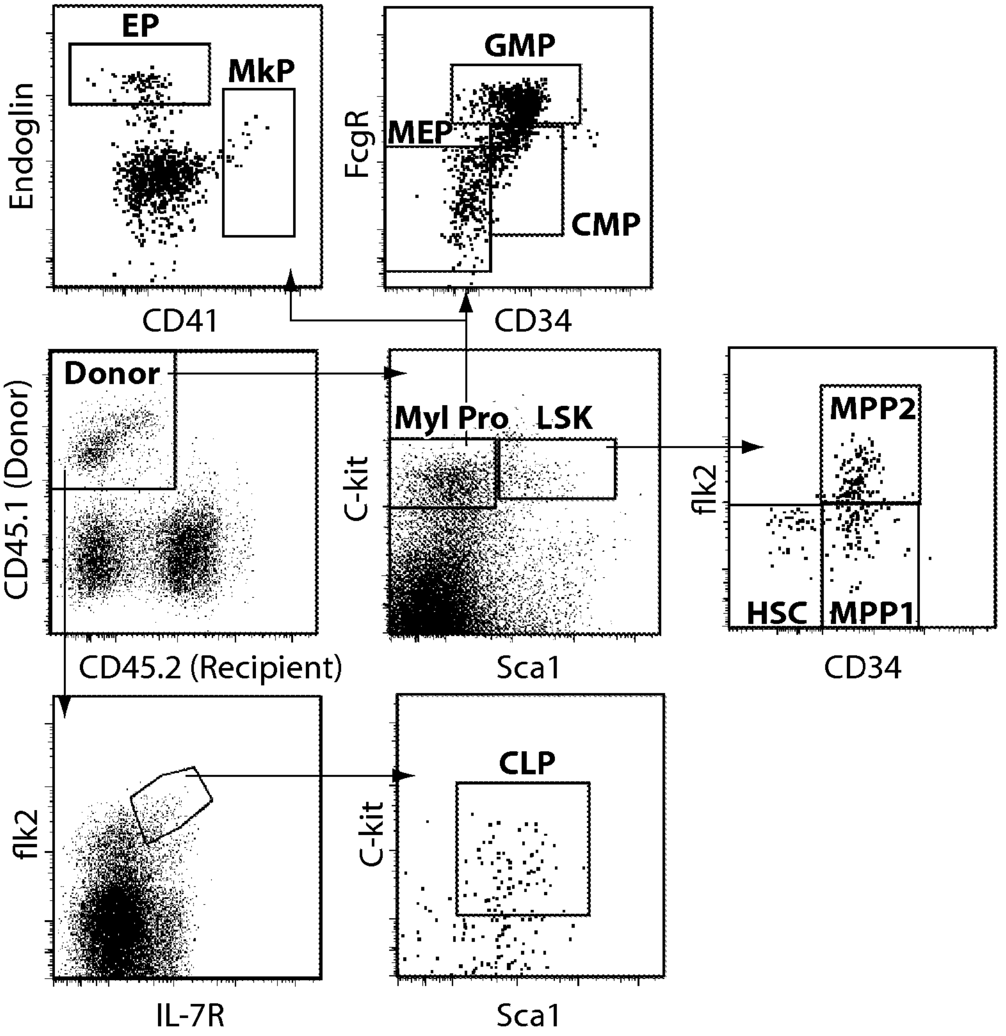

EP
MkP
Endoglin
CD41
GMP
MEP
CMP
FcgR
CD34
Donor
CD45.1 (Donor)
CD45.2 (Recipient)
Myl Pro
LSK
C-kit
Sca1
MPP2
flk2
HSC
MPP1
CD34
flk2
IL-7R
CLP
C-kit
Sca1

Fig. 62C

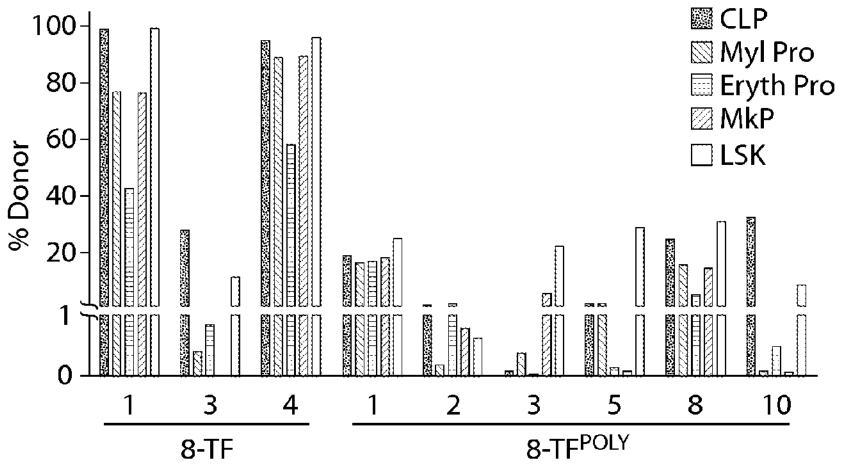


Fig. 62D

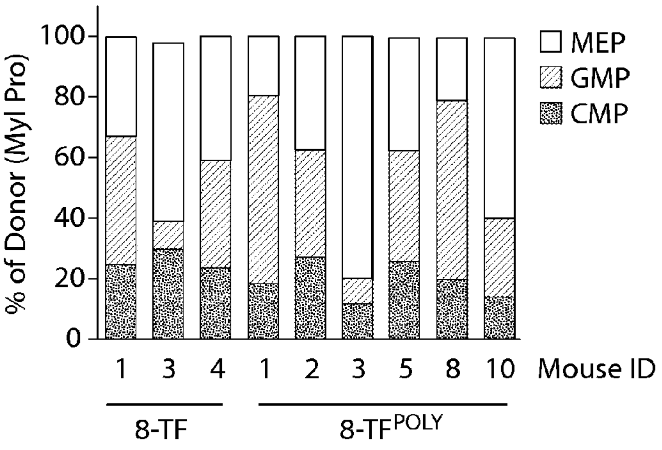


Fig. 62E

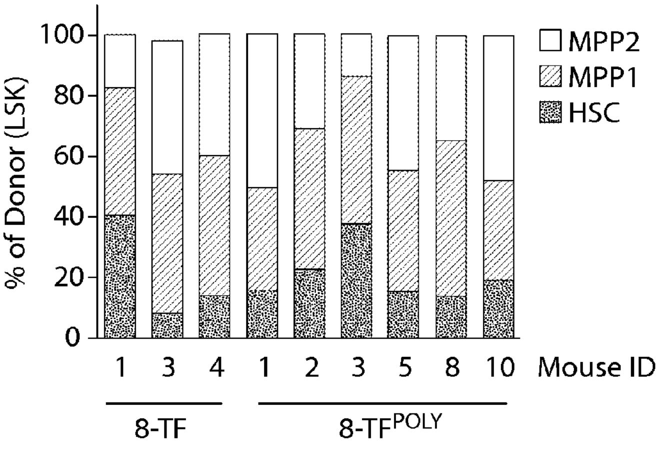


Fig. 62F

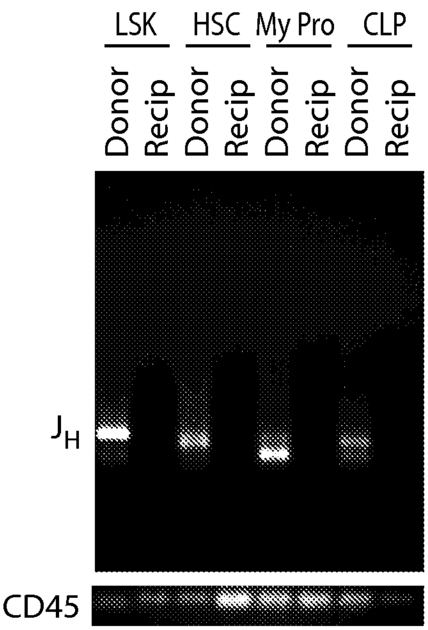


Fig. 62G

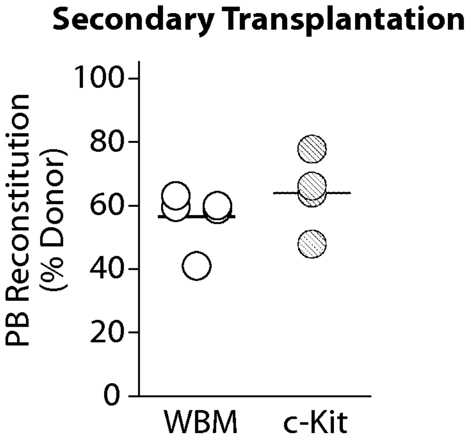


Fig. 62H

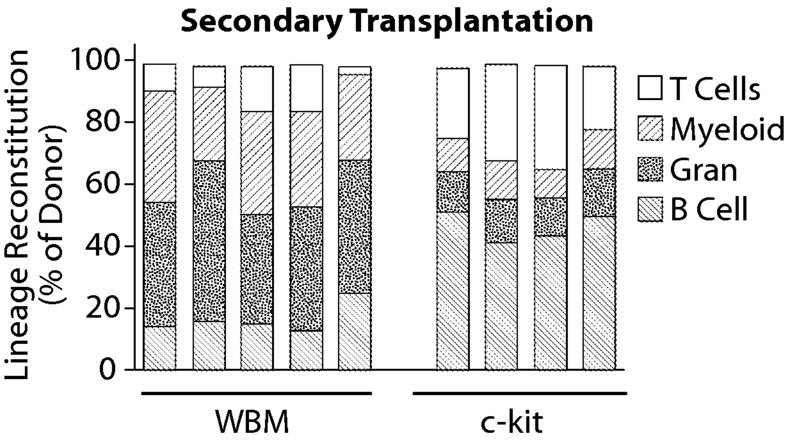


Fig. 62I

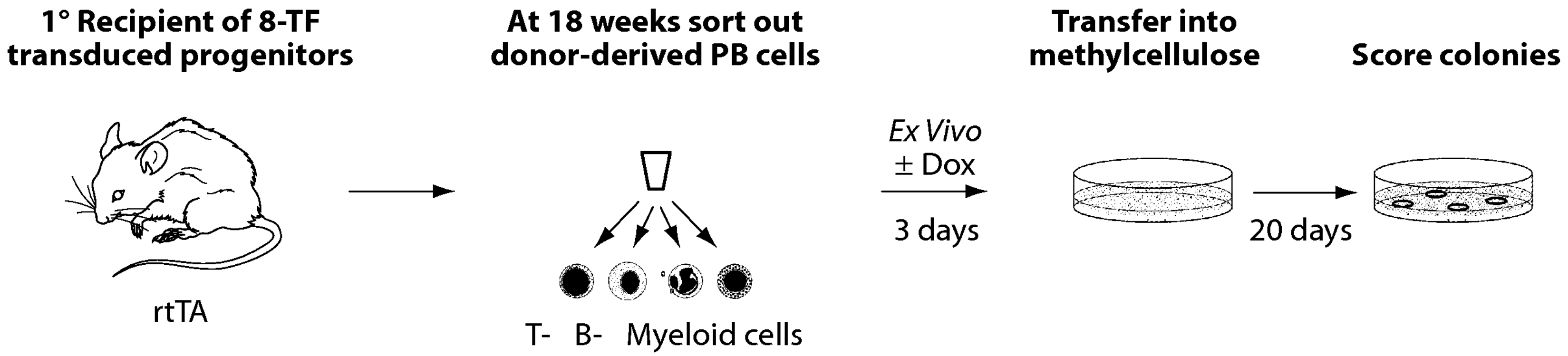

1° Recipient of 8-TF
transduced progenitors
rtTA
At 18 weeks sort out
donor-derived PB cells
T- B- Myeloid cells
Ex Vivo
± Dox
3 days
Transfer into
methylcellulose
20 days
Score colonies

Fig. 63A

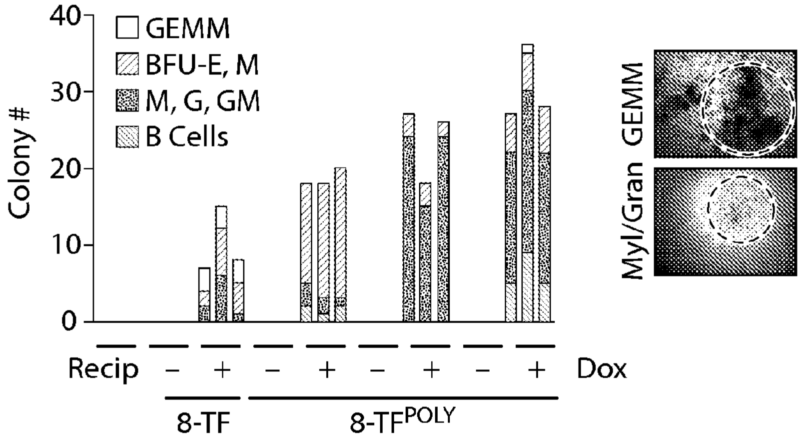


Fig. 63B

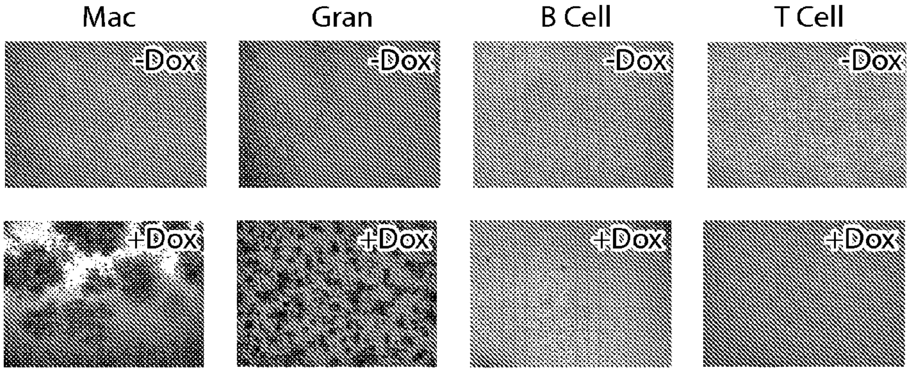


Fig. 63C

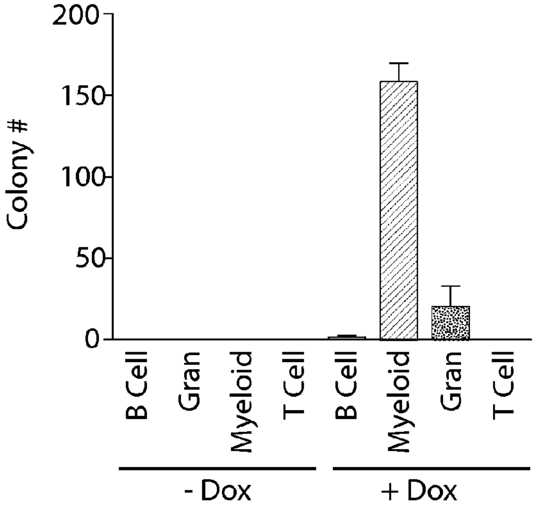


Fig. 63D

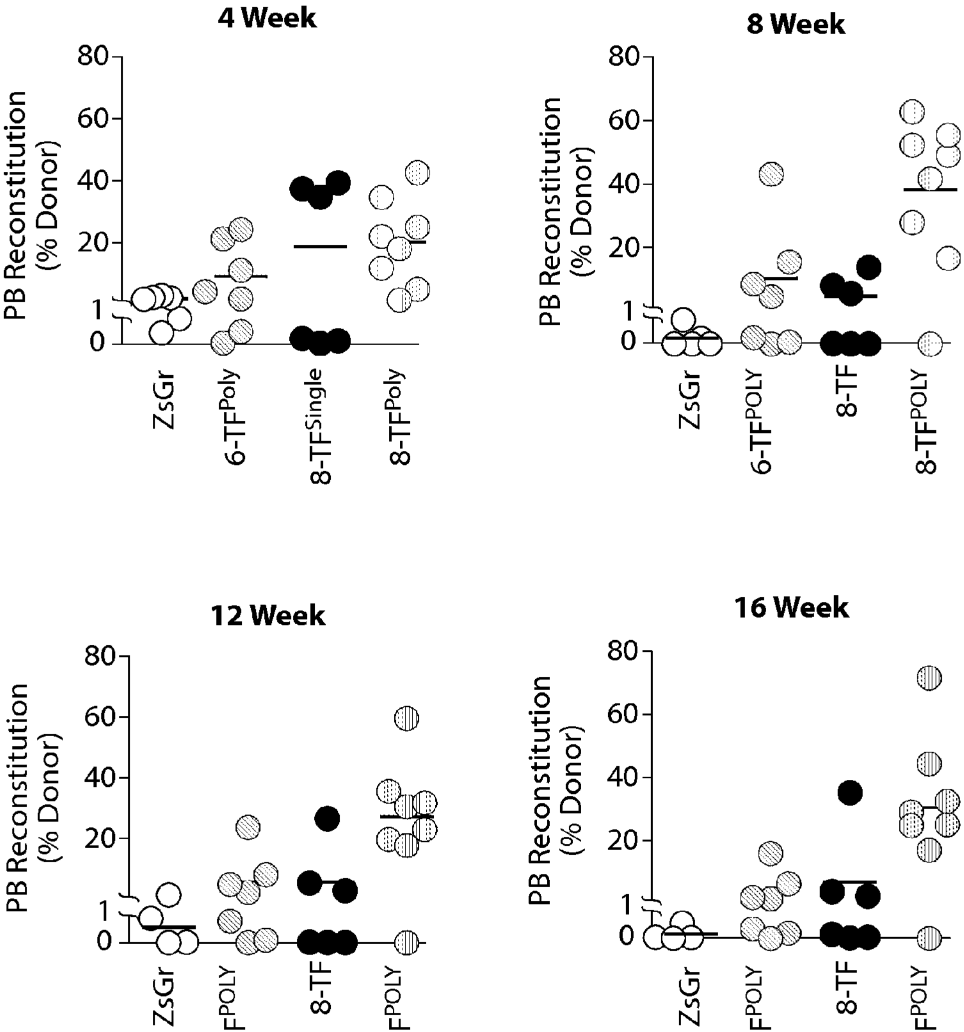

4 Week
8 Week
12 Week
16 Week
PB Reconstitution
(% Donor)
80
60
40
20
1
0
ZsGr
6-TF^{Poly}
8-TF^{Single}
8-TF^{Poly}
6-TF^{POLY}
8-TF
8-TF^{POLY}

Fig. 63E

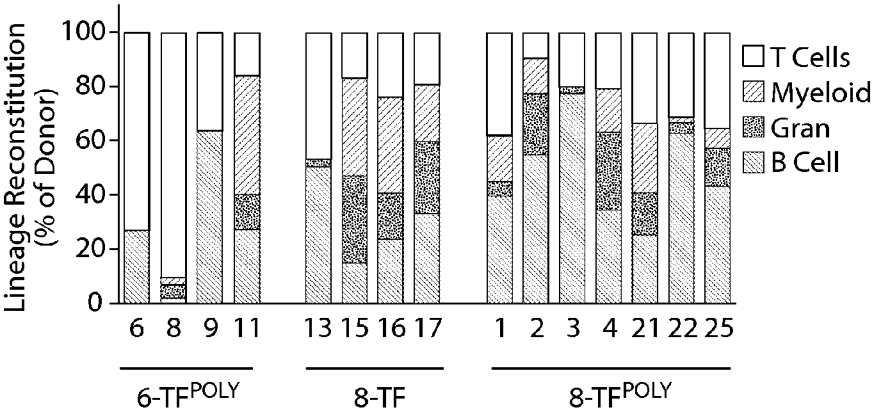


Fig. 63F

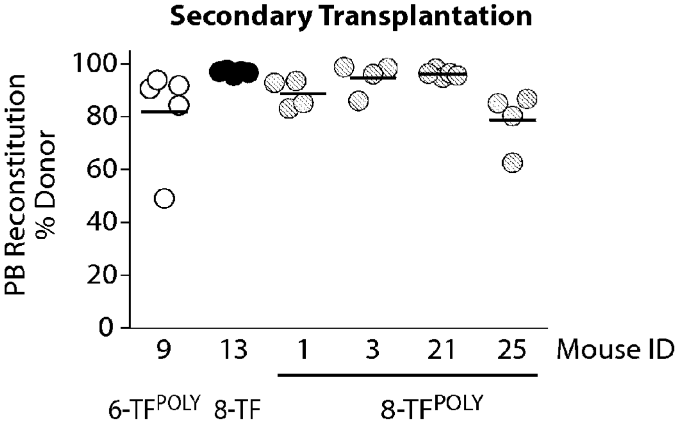


Fig. 63G

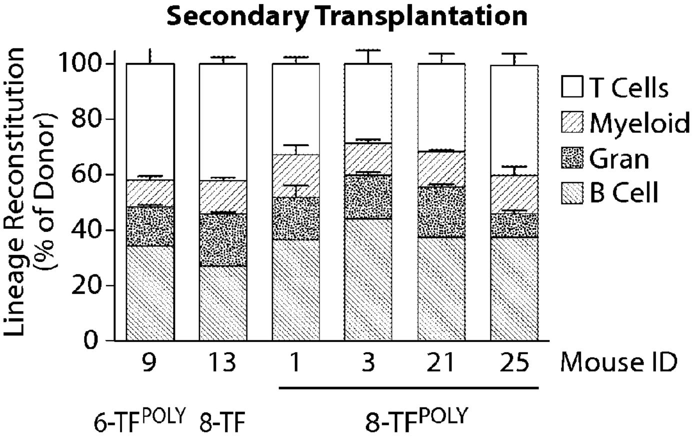


Fig. 63H

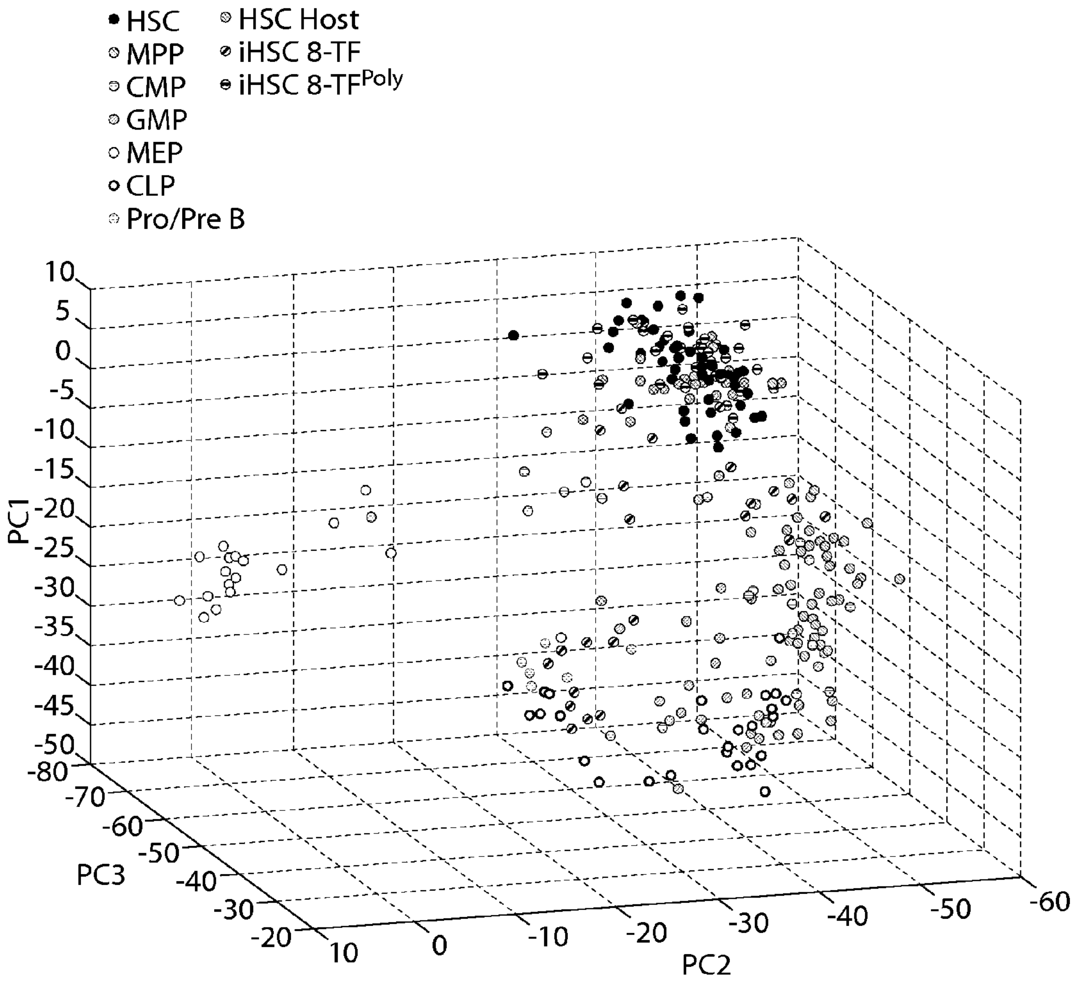

HSC
MPP
CMP
GMP
MEP
CLP
Pro/Pre B
HSC Host
iHSC 8-TF
iHSC 8-TF^{Poly}
PC1
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
PC3
-80
-70
-60
-50
-40
-30
-20
PC2
10
0
-10
-20
-30
-40
-50
-60

Fig. 64A

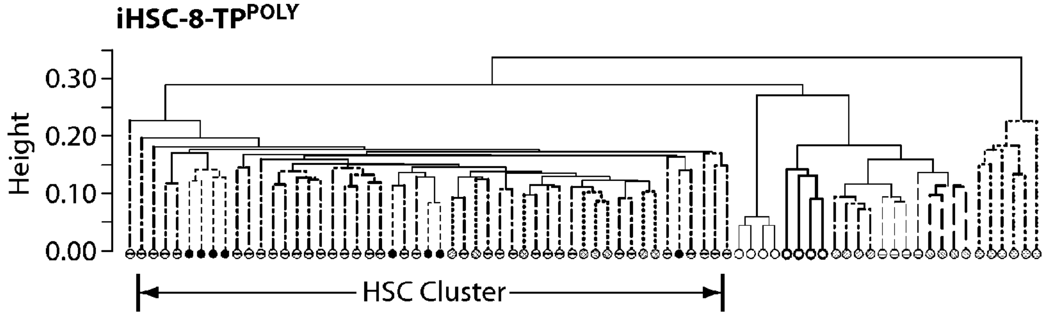


Fig. 64B

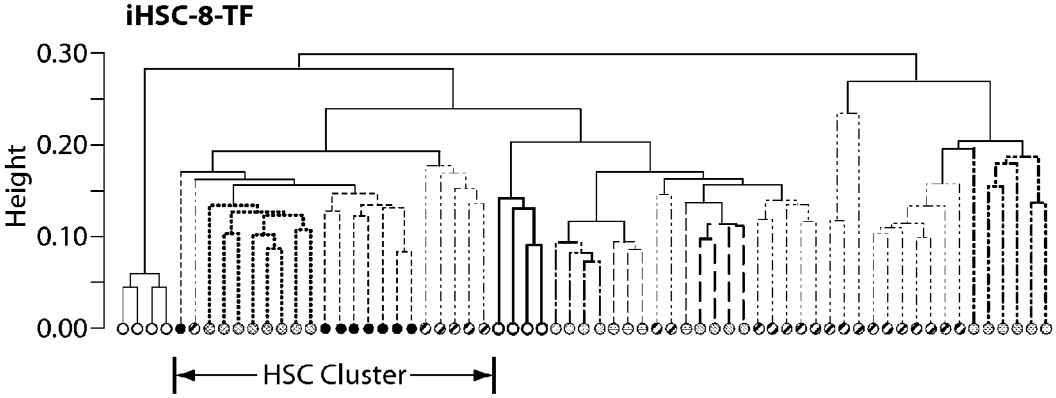


Fig. 64C

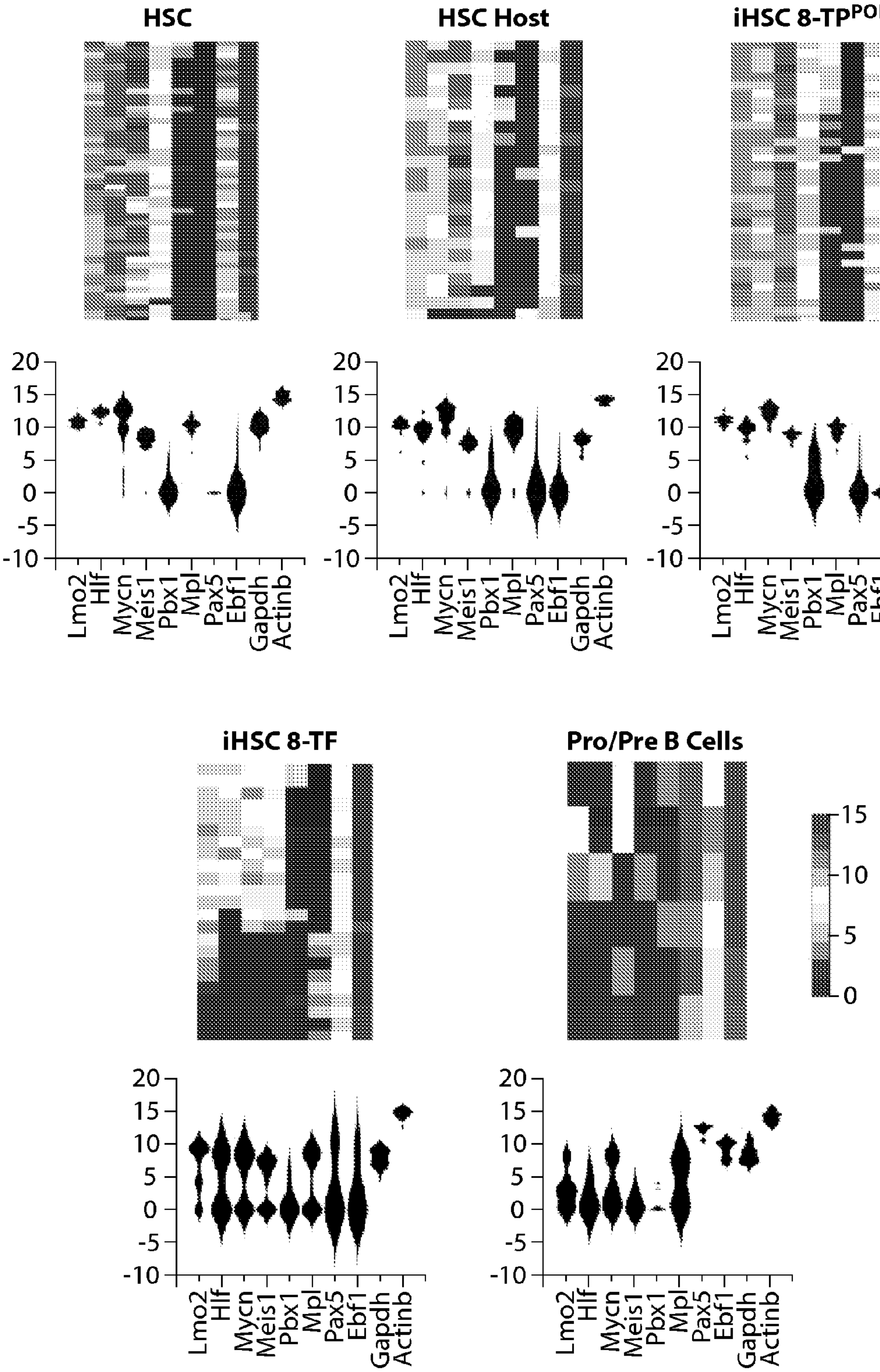

HSC
HSC Host
iHSC 8-TP^POLY
20
15
10
5
0
-5
-10
Lmo2
Hlf
Mycn
Meis1
Pbx1
Mpl
Pax5
Ebf1
Gapdh
Actinb
iHSC 8-TF
Pro/Pre B Cells
15
10
5
0

Fig. 64D

Pregated on doublet discriminated and PI Negative cells

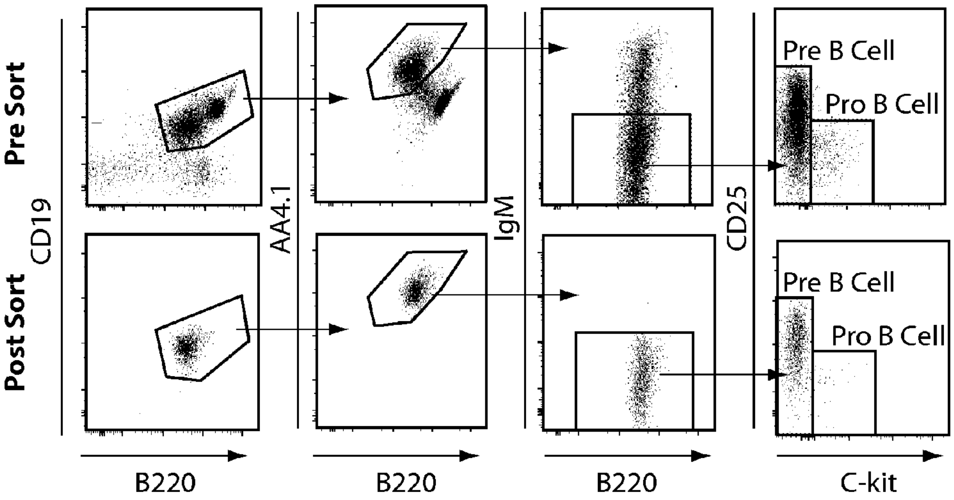


Fig. 65A

Pregated on doublet discriminated and PI Negative cells

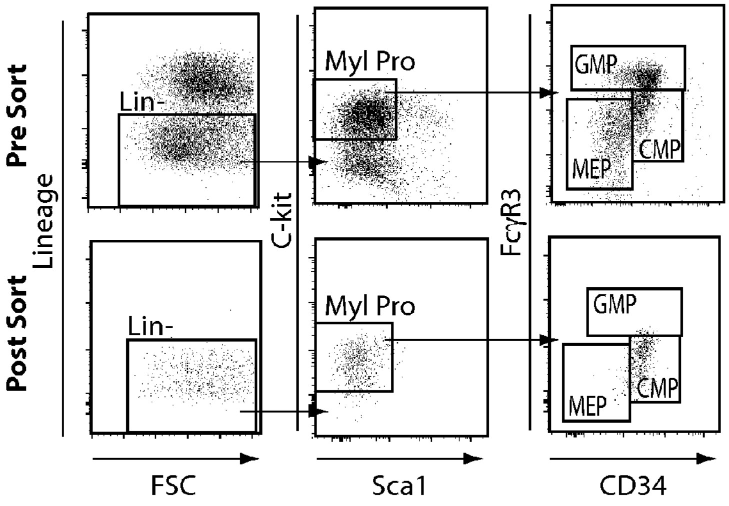


Fig. 65B

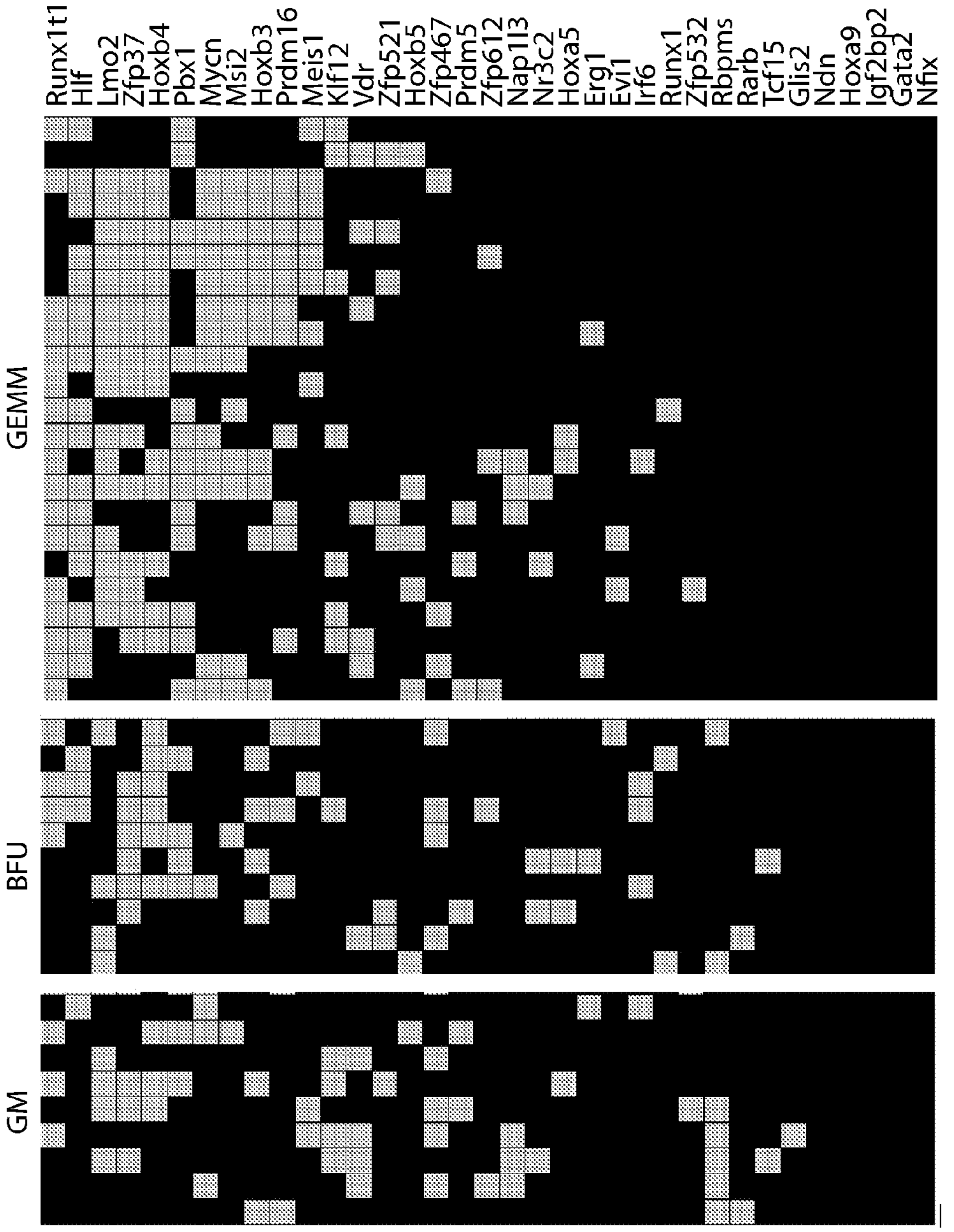

GEMM
BFU
GM
Runx1t1
Hlf
Lmo2
Zfp37
Hoxb4
Pbx1
Mycn
Msi2
Hoxb3
Prdm16
Meis1
Klf12
Vdr
Zfp521
Hoxb5
Zfp467
Prdm5
Zfp612
Nap1l3
Nr3c2
Hoxa5
Erg1
Evi1
Irf6
Runx1
Zfp532
Rbpms
Rarb
Tcf15
Glis2
Ndn
Hoxa9
Igf2bp2
Gata2
Nfix

Fig. 66

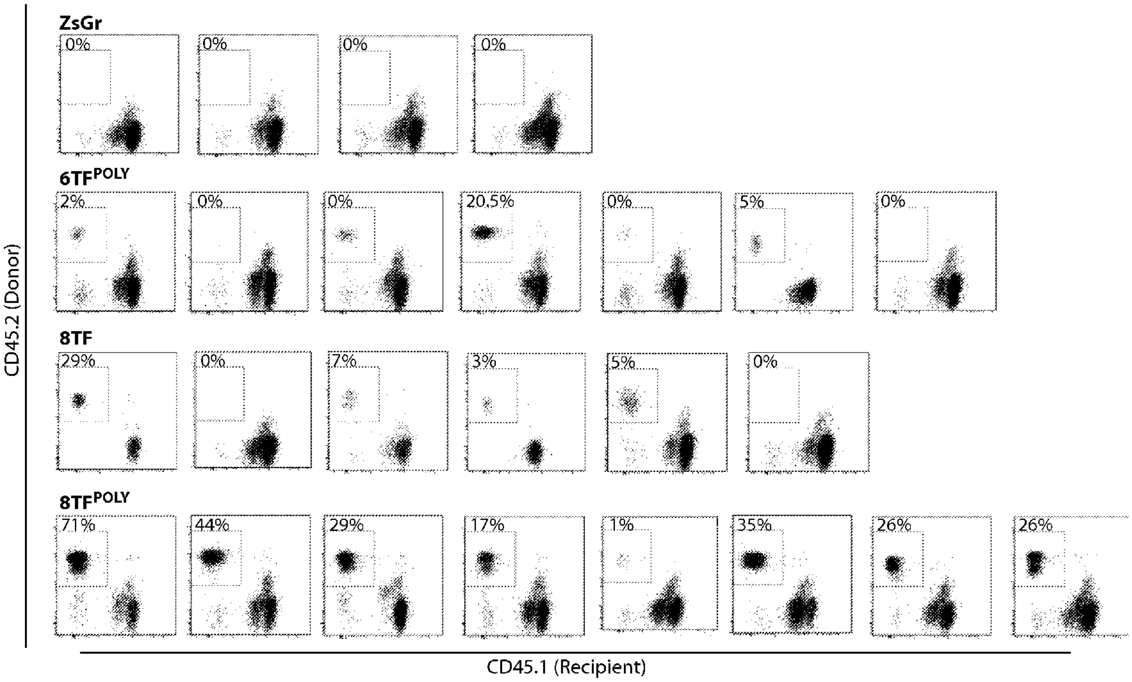

ZsGr
0%
0%
0%
0%
6TF^{POLY}
2%
0%
0%
20.5%
0%
5%
0%
8TF
29%
0%
7%
3%
5%
0%
8TF^{POLY}
71%
44%
29%
17%
1%
35%
26%
26%
CD45.2 (Donor)
CD45.1 (Recipient)

Fig. 67

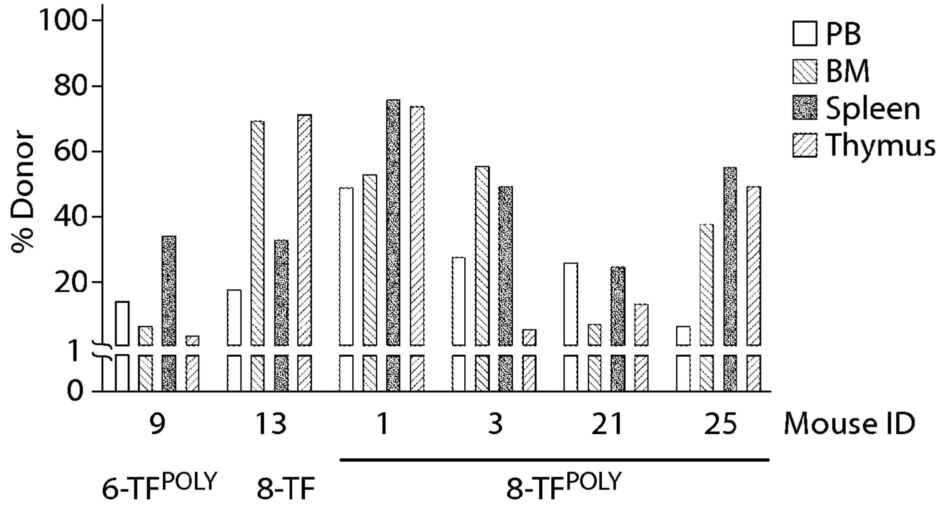


Fig. 68A

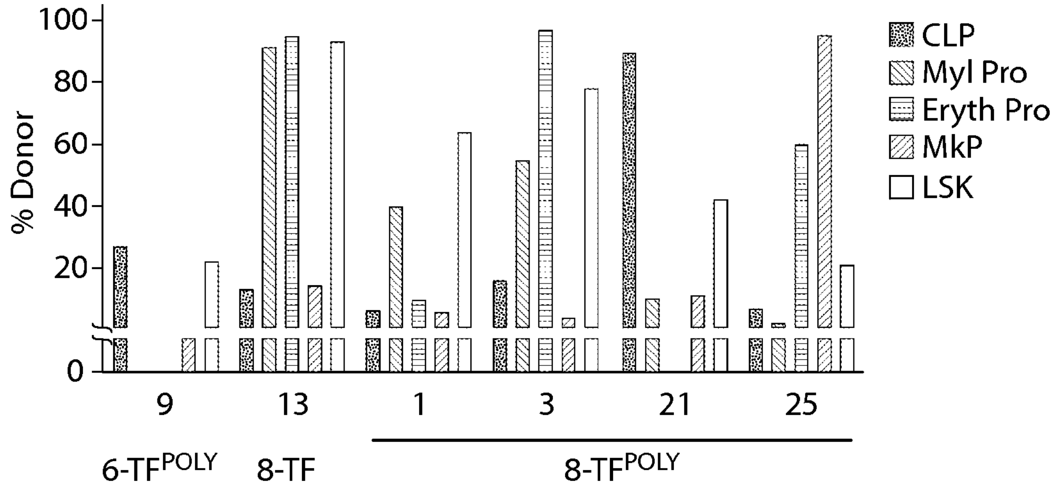


Fig. 68B

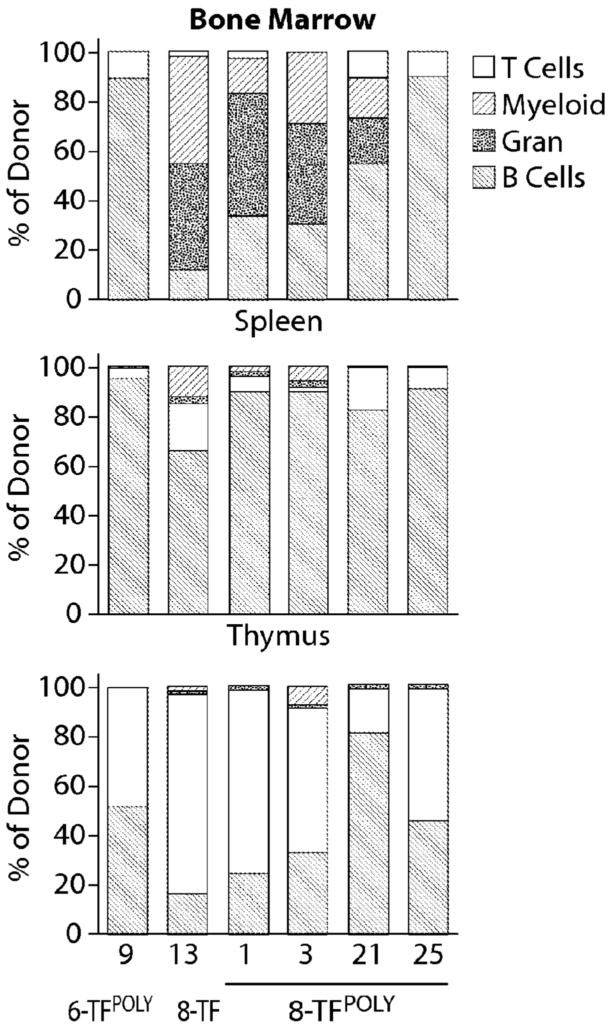


Fig. 68C

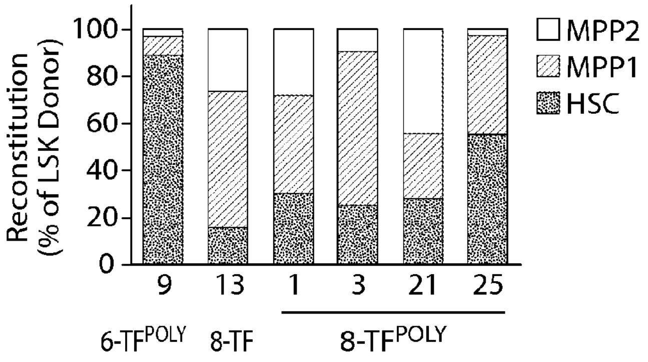


Fig. 68D

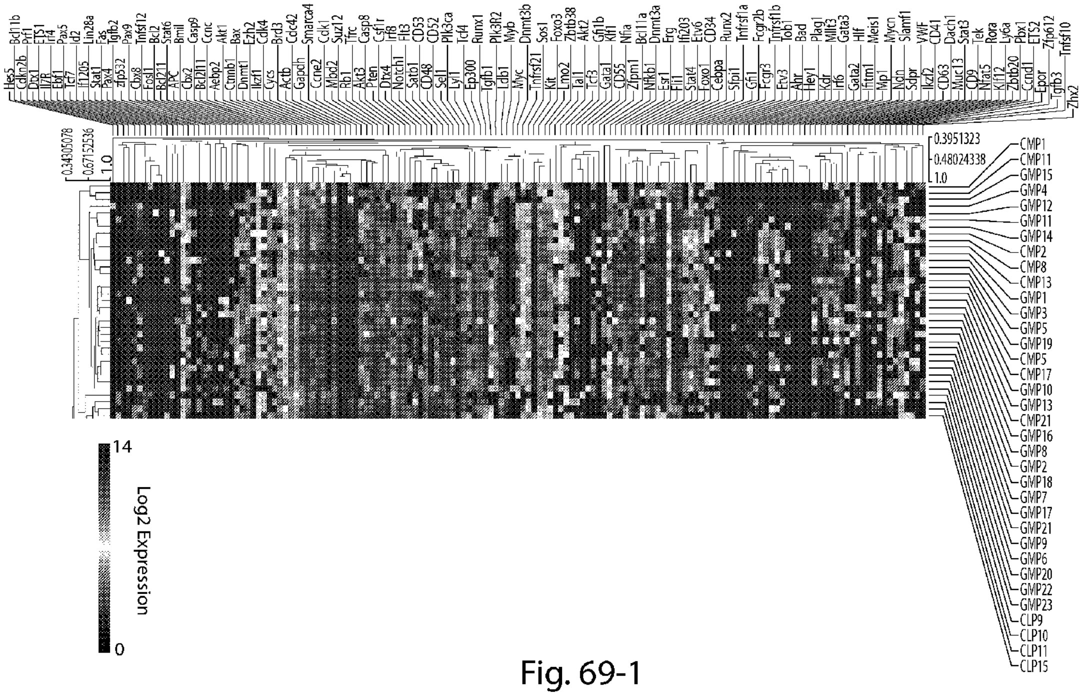
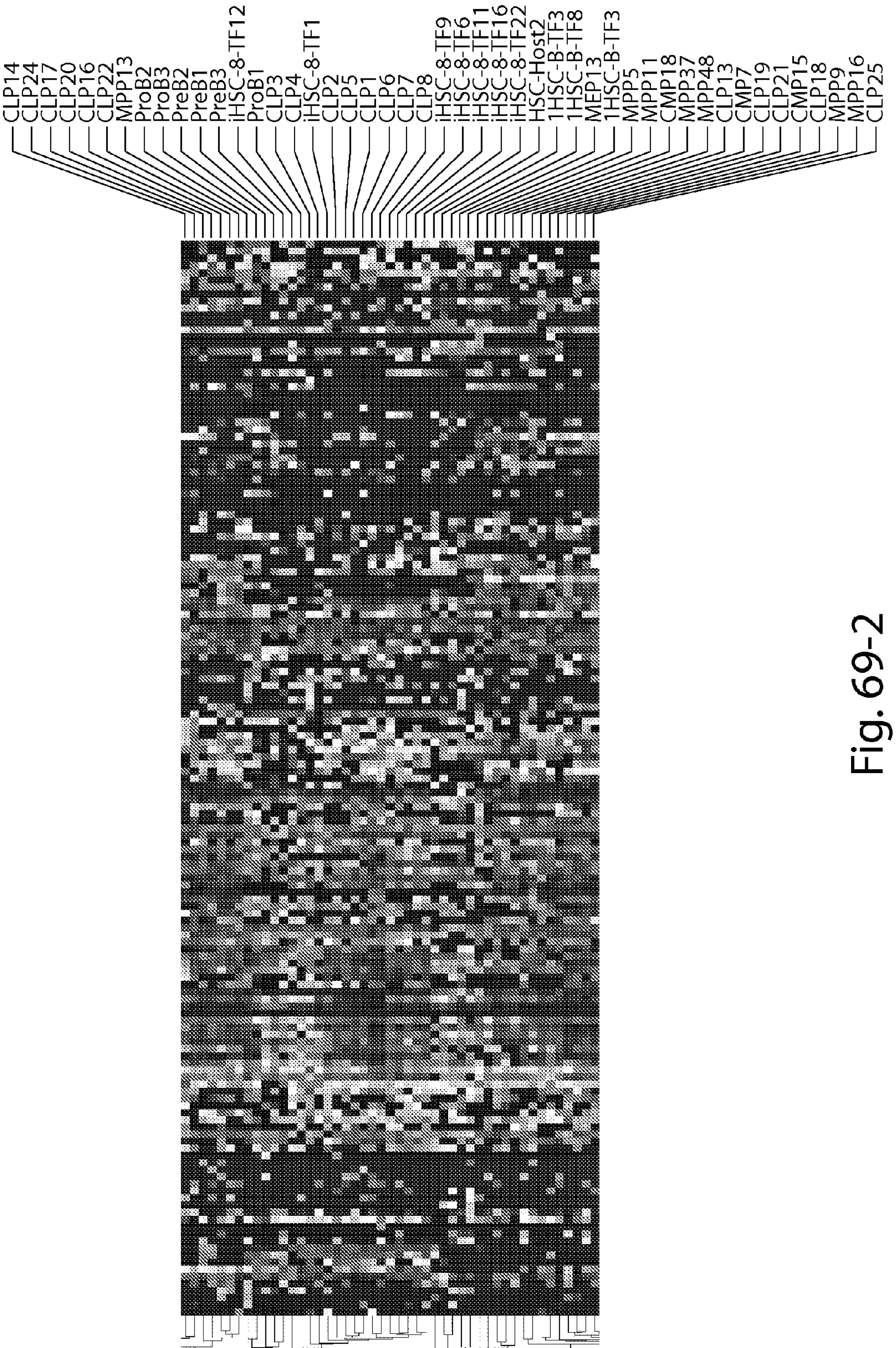

Hes5
Bcl11b
Cdkn2b
Prf1
Dtx1
ETS1
Il7R
Irf4
Ebf1
Pax5
Tcf7
Id2
If1205
Lin28a
Stat1
Fas
Pax4
Tgfb2
Zfp532
Pax9
Cbx8
Tnfsf12
Fosl1
Bcl2
Bcl2l1
Stat6
APC
Bmil
Cbx2
Casp9
Bcl2l11
Ccnc
Aebp2
Akt1
Ctnnb1
Bax
Dnmt1
Ezh2
Ikzf1
Cdk4
Cycs
Brd3
Actb
Cdc42
Gapdh
Smarca4
Ccne2
Cdk1
Mbd2
Suz12
Rb1
Tfrc
Akt3
Casp8
Pten
Csf1r
Dtx4
Irf8
Notch1
Flt3
Satb1
CD53
CD48
CD52
Sell
Pik3ca
Lyl1
Tcf4
Ep300
Runx1
Tgfb1
Pik3R2
Ldb1
Myb
Myc
Dnmt3b
Tnfrsf21
Sos1
Kit
Foxo3
Lmo2
Zbtb38
Tal1
Akt2
Tcf3
Gfi1b
Gata1
Klf1
CD55
Nfia
Zfpm1
Bcl11a
Nfkb1
Dnmt3a
Esr1
Erg
Fli1
Ifi203
Stat4
Etv6
Foxo1
CD34
Cebpa
Runx2
Sfpi1
Tnfrsf1a
Gfi1
Fcgr2b
Fcgr3
Tnfrsf1b
Etv3
Tob1
Ahr
Bad
Hey1
Plag1
Kdr
Mllt3
Irf6
Gata3
Gata2
Hlf
Ifitm1
Meis1
Mpl
Mycn
Ndn
Slamf1
Sdpr
VWF
Ikzf2
CD41
CD63
Dach1
Muc13
Stat3
CD9
Tek
Nfat5
Rora
Klf12
Ly6a
Zbtb20
Pbx1
Ccnd1
ETS2
Epor
Zfp612
Tgfb3
Tnfsf10
Zhx2
0.34305078
0.67152536
1.0
0.3951323
0.48024338
1.0
CMP1
CMP11
GMP15
GMP4
GMP12
GMP11
GMP14
CMP2
CMP8
CMP13
GMP1
GMP3
GMP5
GMP19
CMP5
CMP17
GMP10
GMP13
CMP21
GMP16
GMP8
GMP2
GMP18
GMP7
GMP17
GMP21
GMP9
GMP6
GMP20
GMP22
GMP23
CLP9
CLP10
CLP11
CLP15
14
Log2 Expression
0

Fig. 69-1


CLP14
CLP24
CLP17
CLP20
CLP16
CLP22
MPP13
ProB2
ProB3
PreB2
PreB1
PreB3
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ProB1
CLP3
CLP4
iHSC-8-TF1
CLP2
CLP5
CLP1
CLP6
CLP7
CLP8
iHSC-8-TF9
iHSC-8-TF6
iHSC-8-TF11
iHSC-8-TF16
iHSC-8-TF22
HSC-Host2
1HSC-B-TF3
1HSC-B-TF8
MEP13
1HSC-B-TF3
MPP5
MPP11
CMP18
MPP37
MPP48
CLP13
CMP7
CLP19
CLP21
CMP15
CLP18
MPP9
MPP16
CLP25

Fig. 69-2

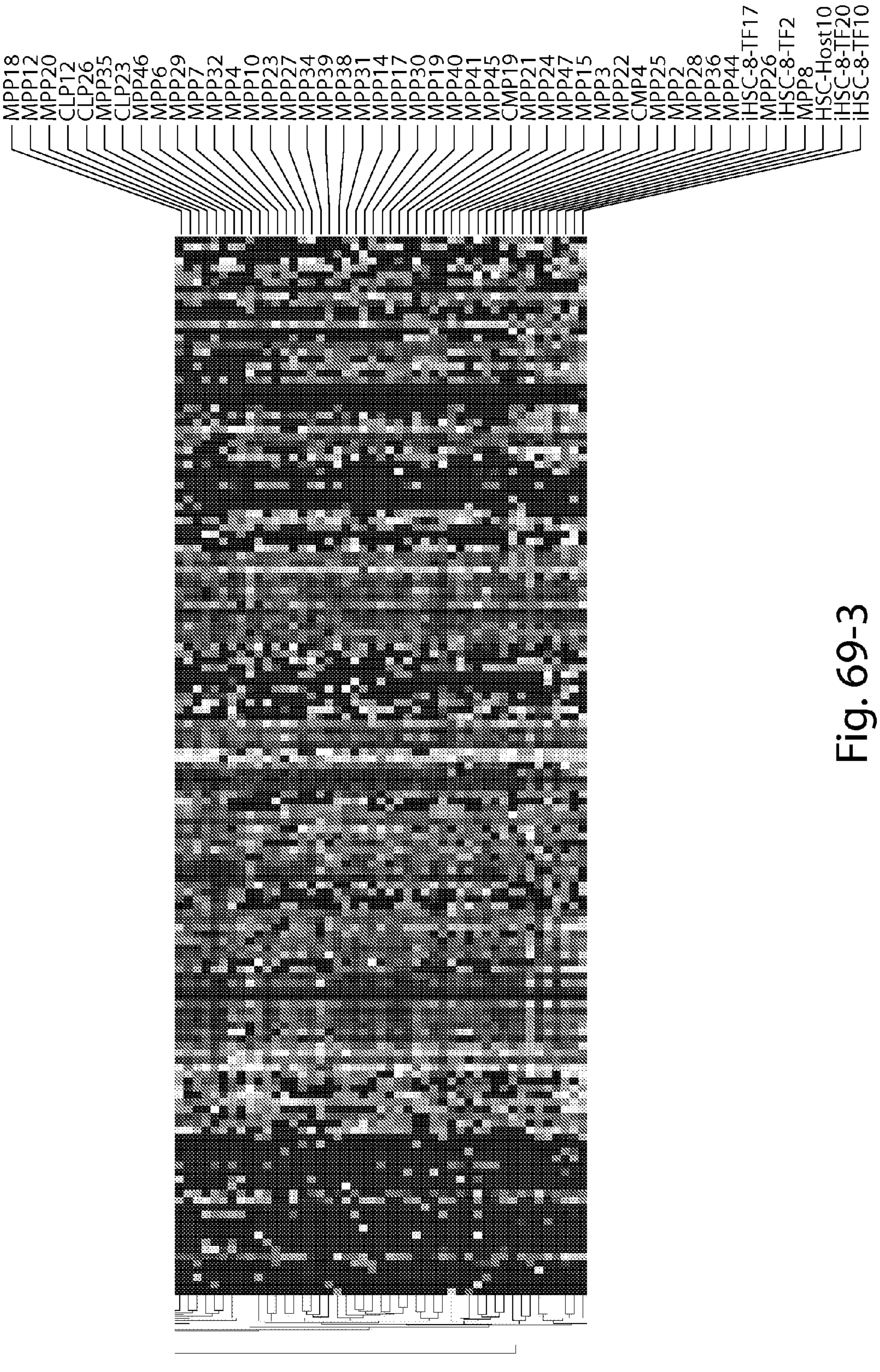
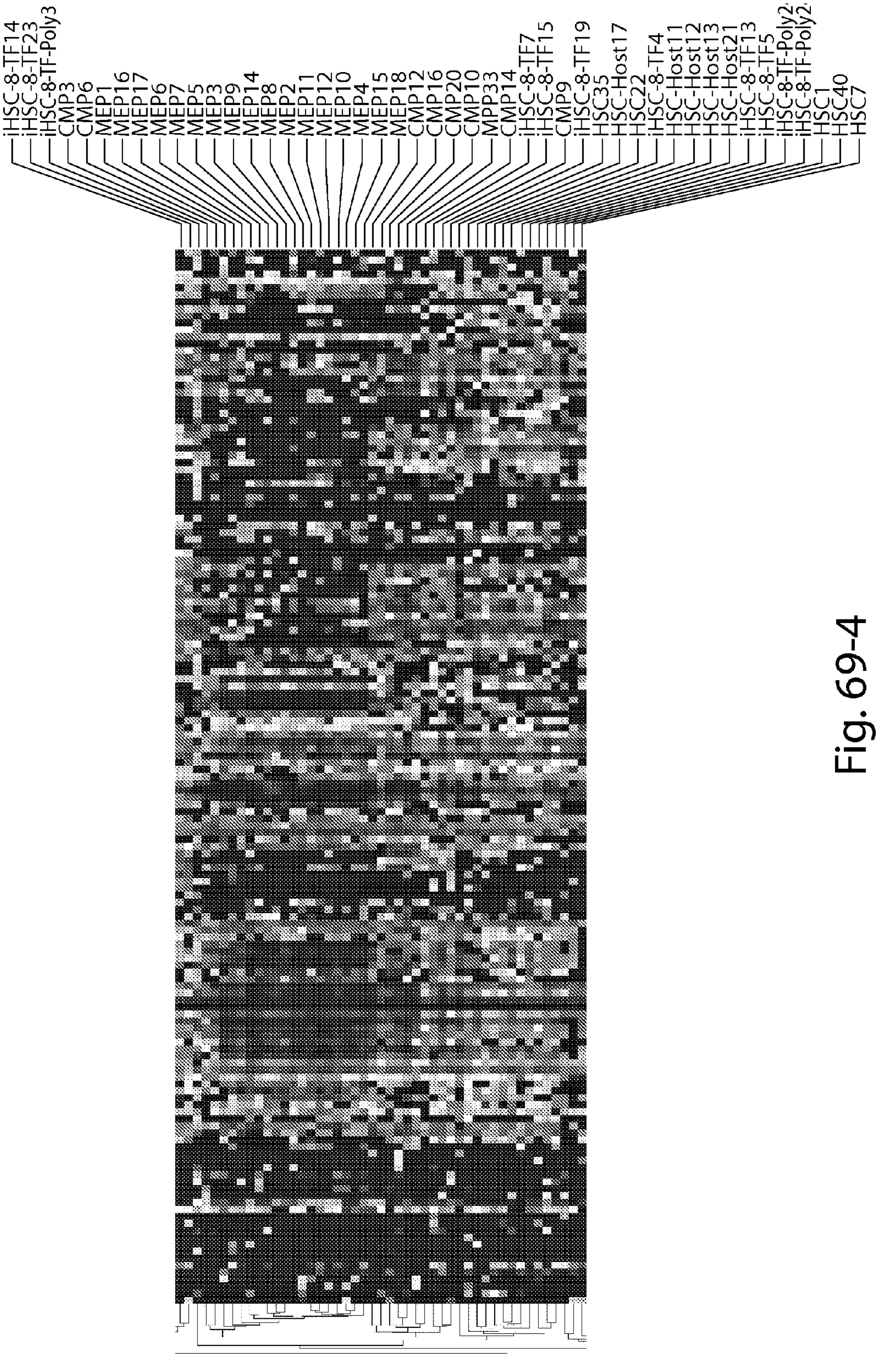

MPP18
MPP12
MPP20
CLP12
CLP26
MPP35
CLP23
MPP46
MPP6
MPP29
MPP7
MPP32
MPP4
MPP10
MPP23
MPP27
MPP34
MPP39
MPP38
MPP31
MPP14
MPP17
MPP30
MPP19
MPP40
MPP41
MPP45
CMP19
MPP21
MPP24
MPP47
MPP15
MPP3
MPP22
CMP4
MPP25
MPP2
MPP28
MPP36
MPP44
iHSC-8-TF17
MPP26
iHSC-8-TF2
MPP8
HSC-Host10
iHSC-8-TF20
iHSC-8-TF10

Fig. 69-3


iHSC-8-TF14
iHSC-8-TF23
iHSC-8-TF-Poly3
CMP3
CMP6
MEP1
MEP16
MEP17
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MEP7
MEP5
MEP3
MEP9
MEP14
MEP8
MEP2
MEP11
MEP12
MEP10
MEP4
MEP15
MEP18
CMP12
CMP16
CMP20
CMP10
MPP33
CMP14
iHSC-8-TF7
iHSC-8-TF15
CMP9
iHSC-8-TF19
HSC35
HSC-Host17
HSC22
iHSC-8-TF4
HSC-Host11
HSC-Host12
HSC-Host13
HSC-Host21
iHSC-8-TF13
iHSC-8-TF5
iHSC-8-TF-Poly2
iHSC-8-TF-Poly2
HSC1
HSC40
HSC7

Fig. 69-4

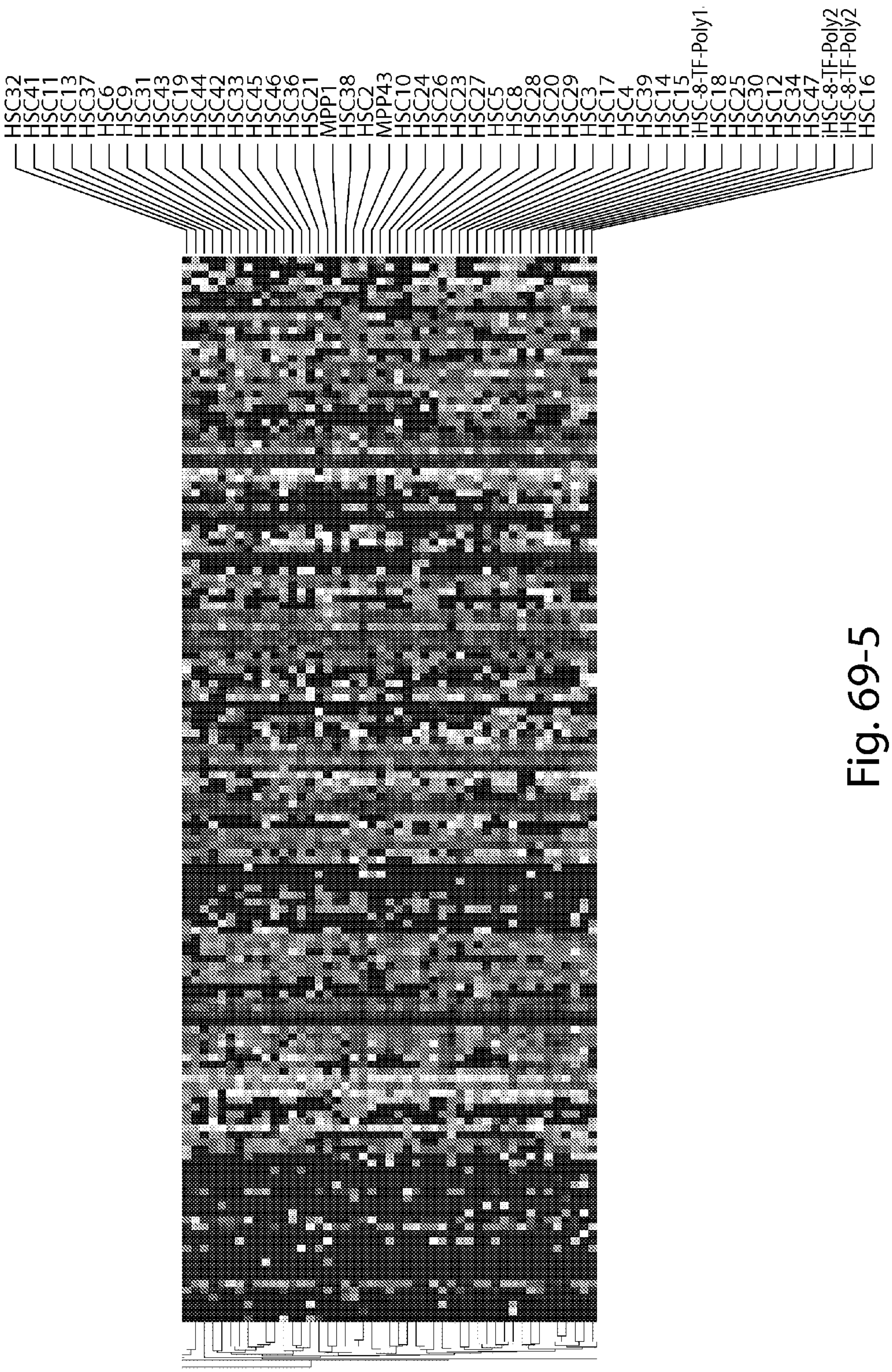
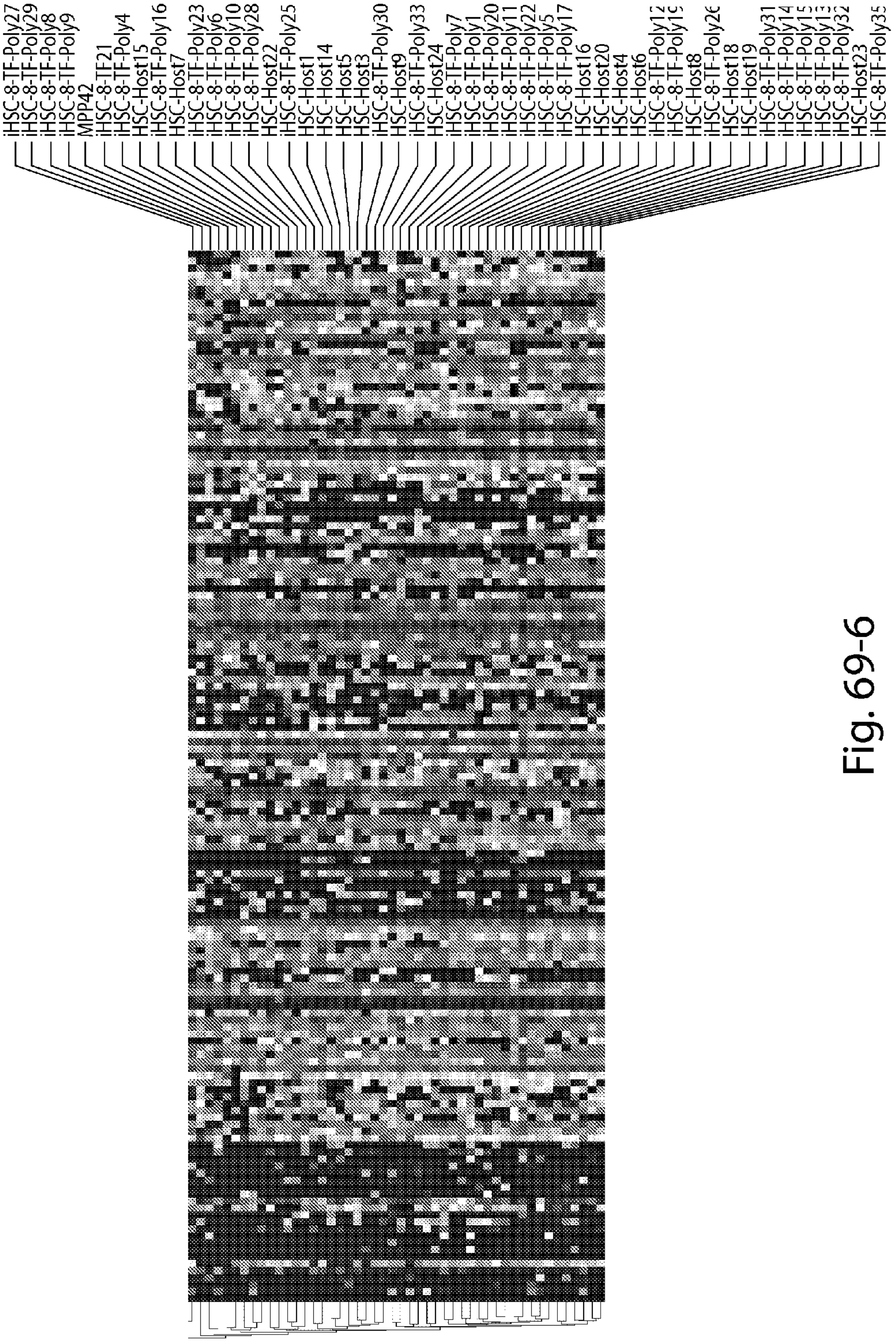

HSC32
HSC41
HSC11
HSC13
HSC37
HSC6
HSC9
HSC31
HSC43
HSC19
HSC44
HSC42
HSC33
HSC45
HSC46
HSC36
HSC21
MPP1
HSC38
HSC2
MPP43
HSC10
HSC24
HSC26
HSC23
HSC27
HSC5
HSC8
HSC28
HSC20
HSC29
HSC3
HSC17
HSC4
HSC39
HSC14
HSC15
iHSC-8-TF-Poly1
HSC18
HSC25
HSC30
HSC12
HSC34
HSC47
iHSC-8-TF-Poly2
iHSC-8-TF-Poly2
HSC16

Fig. 69-5


iHSC-8-TF-Poly27
iHSC-8-TF-Poly29
iHSC-8-TF-Poly8
iHSC-8-TF-Poly9
MPP42
iHSC-8-TF21
iHSC-8-TF-Poly4
HSC-Host15
iHSC-8-TF-Poly16
HSC-Host7
iHSC-8-TF-Poly23
iHSC-8-TF-Poly6
iHSC-8-TF-Poly10
iHSC-8-TF-Poly28
HSC-Host22
iHSC-8-TF-Poly25
HSC-Host1
HSC-Host14
HSC-Host5
HSC-Host3
iHSC-8-TF-Poly30
HSC-Host9
iHSC-8-TF-Poly33
HSC-Host24
iHSC-8-TF-Poly7
iHSC-8-TF-Poly1
iHSC-8-TF-Poly20
iHSC-8-TF-Poly11
iHSC-8-TF-Poly22
iHSC-8-TF-Poly5
iHSC-8-TF-Poly17
HSC-Host16
HSC-Host20
HSC-Host4
HSC-Host6
iHSC-8-TF-Poly12
iHSC-8-TF-Poly19
HSC-Host8
iHSC-8-TF-Poly26
HSC-Host18
HSC-Host19
iHSC-8-TF-Poly31
iHSC-8-TF-Poly14
iHSC-8-TF-Poly15
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iHSC-8-TF-Poly32
HSC-Host23
iHSC-8-TF-Poly35

Fig. 69-6

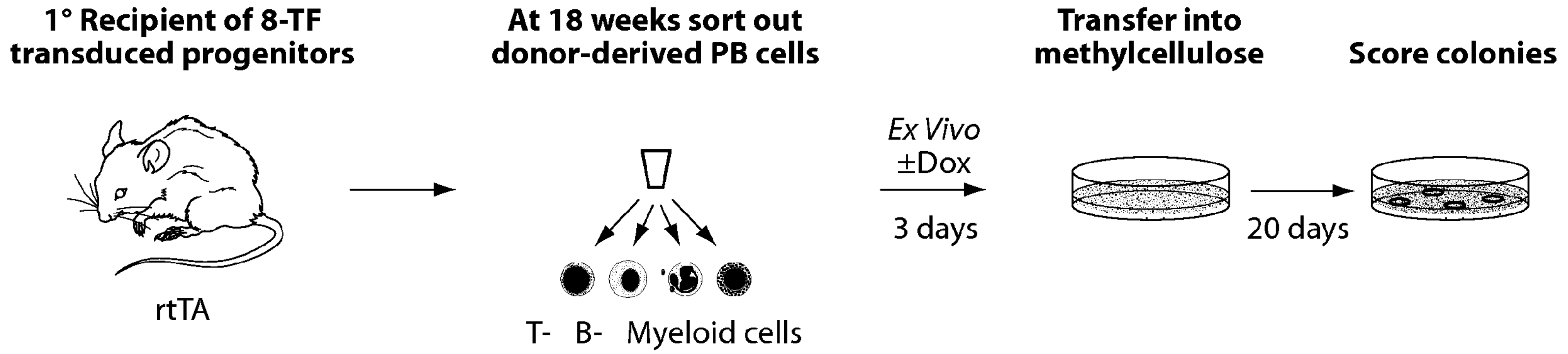
1° Recipient of 8-TF transduced progenitors
rtTA
At 18 weeks sort out donor-derived PB cells
T- B- Myeloid cells
Ex Vivo
±Dox
3 days
Transfer into methylcellulose
20 days
Score colonies

Fig. 70A

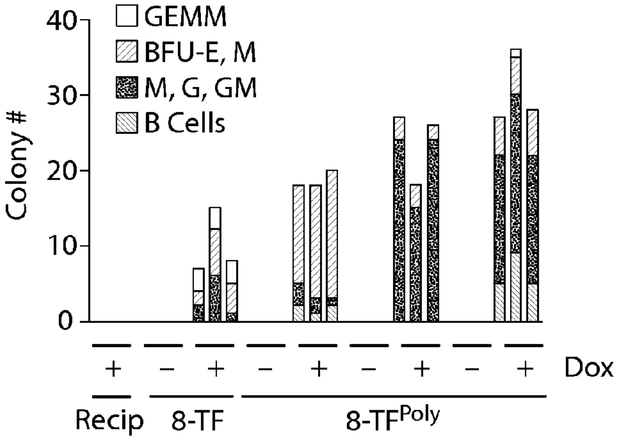

Fig. 70B

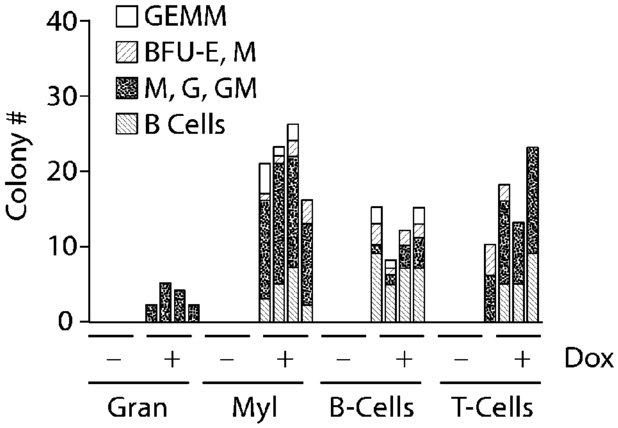

Fig. 70C

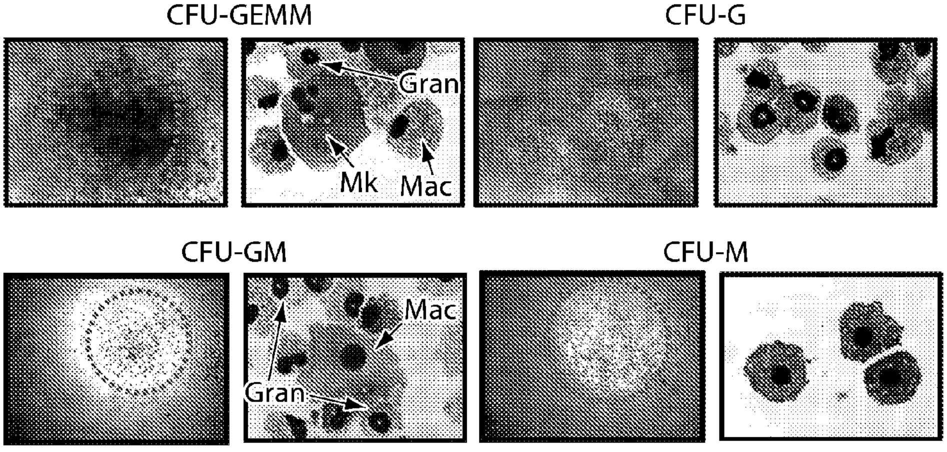

Fig. 70D

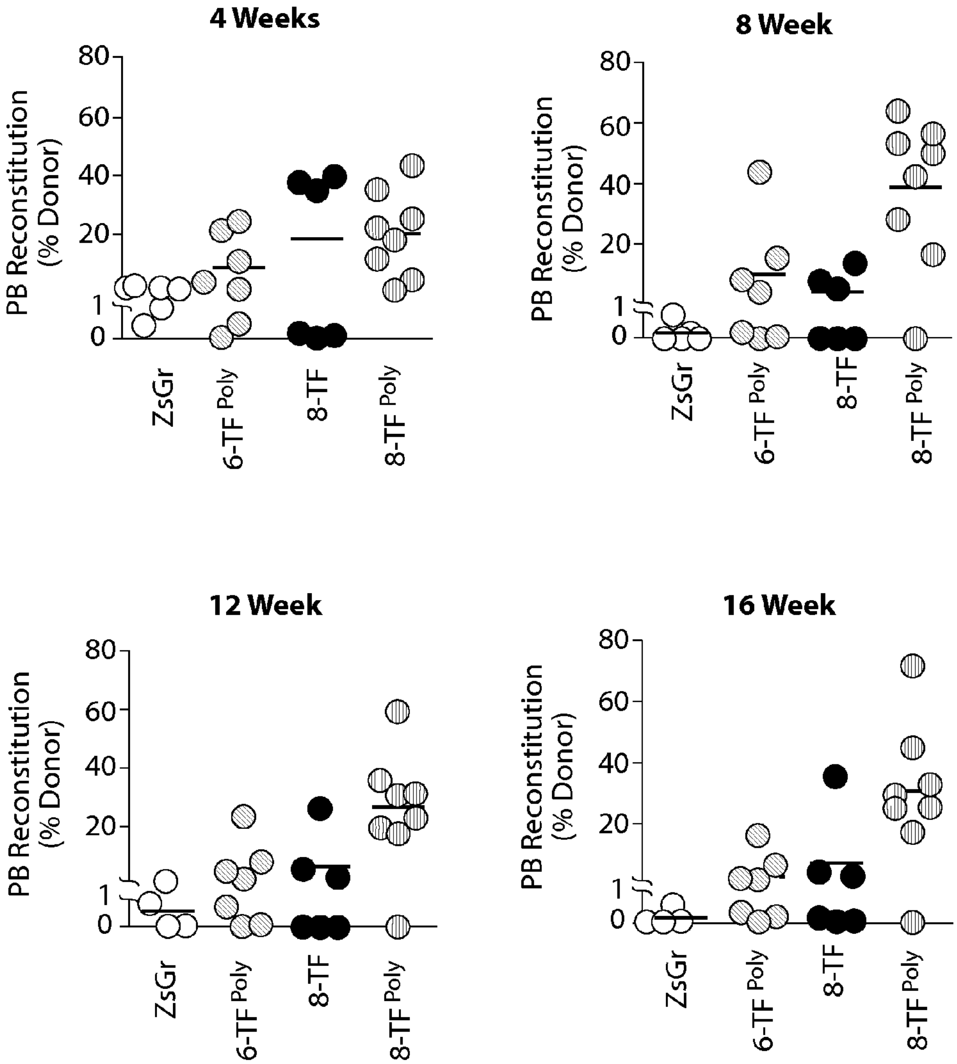
4 Weeks
8 Week
12 Week
16 Week
PB Reconstitution (% Donor)
80
60
40
20
1
0
ZsGr
6-TF Poly
8-TF
8-TF Poly

Fig. 70E

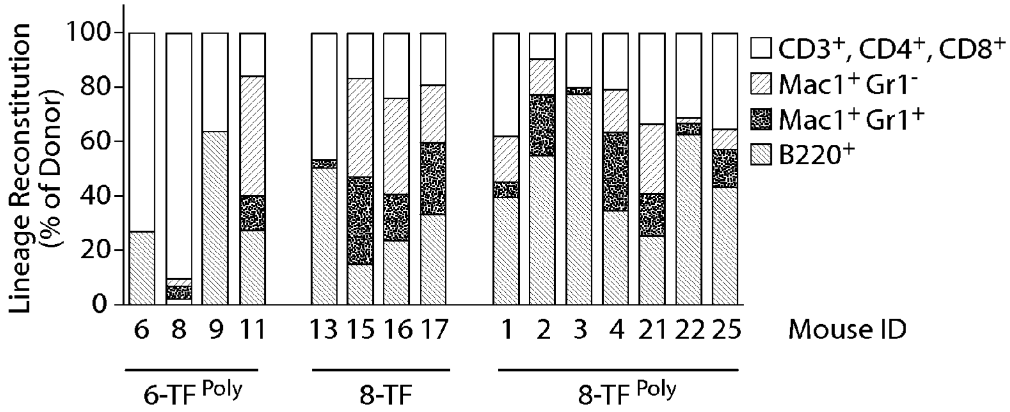

Fig. 70F

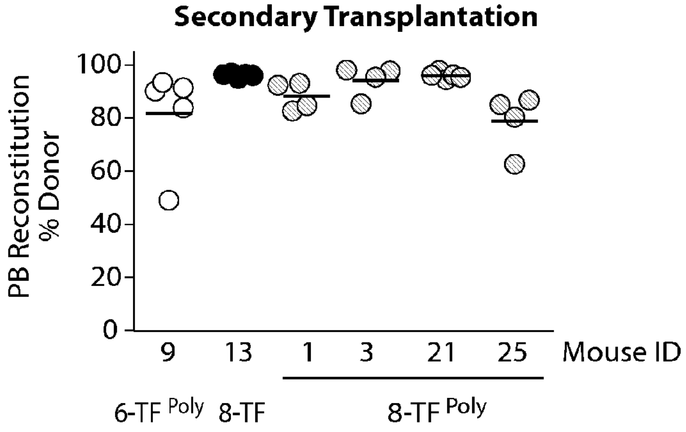

Fig. 70G

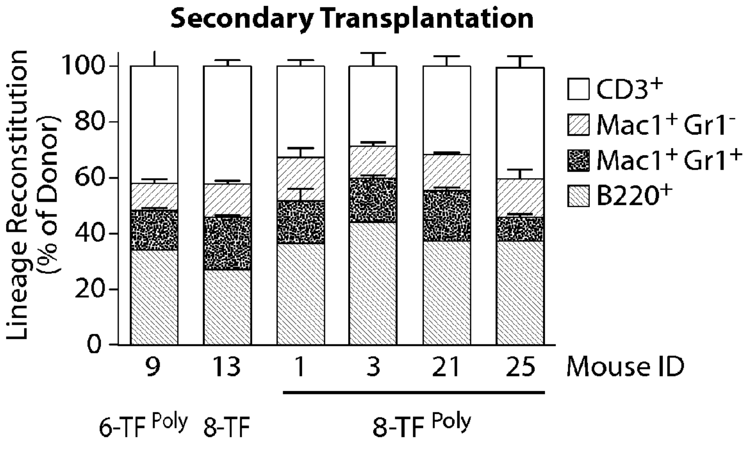

Fig. 70H

Donor	VDJ ID	Cell Type	V_H	D_H	J_H
1° - 1	V5-17/D2-3/J2-1	B-Cell	acacggccgtgtattactgtgcaagg	cc**tgatggtta**ggg	caaggcaccactct
		T-Cell	cacggccgtgtattactgtgcaagg	cc**tgatggtta**ggg	caaggcaccactct
		Myeloid	acacggccgtgtattactgtgcaagg	cc**tgatggtta**ggg	caaggcaccactct
		Gran	cacggccgtgtattactgtgcaagg	cc**tgatggtta**ggg	caaggcaccactct
1° - 8	V5-9/D1-1/J2-1	B-Cell	acacggccgtgtattactgt	gatag**tagctggct**tttctt	tctgcacattccaattct
		T-Cell	acacggccgtgtattactgt	gatag**tagctggct**tttctt	tctgcacattccaattct
		Myeloid	acacggccgtgtattactgt	gatag**tagctggct**tttctt	tctgcacattccaattct
		Gran	acacggccgtgtattactgt	gatag**tagctggct**tttctt	tctgcacattccaattct

Fig. 71A

Donor	VDJ ID	Cell Type	V_H	D_H	J_H
2° - 1	V5-17/D2-3/J2-1	B-Cell	acacggccgtgtattactgtgcaagg	cc**tgatggtta**ggg	caaggcaccactct
		T-Cell	acacggccgtgtattactgtgcaagg	cc**tgatggtta**ggg	caaggcaccactct
		Myeloid	acacggccgtgtattactgtgcaagg	cc**tgatggtta**ggg	caaggcaccactct
	V5-17/D2-3/ J1-1	B-Cell	actcggccgtgtttccctgtgcaagg	cc**tgatggtta**gggn	cc
		Myeloid	tacacggccgtgtattactgtgcaagg	cc**tgatggtta**gggc	cnngncccccttcac
	V1-54/D1-1/ J2-1	Myeloid	caaggaggcctta	ta**ctacggt**a	gtgactactttgactact
		Gran	aggaggcctta	ta**ctacggt**a	gtgactactttgactact
	V1-2/D4-11/ J4-03	Myeloid	gcaagacaggggctactat	a**gtaac**ct	ctttgactactggggcc
		Gran	ntan	a**gtaac**ct	ctttgactactggggcc

Fig. 71B

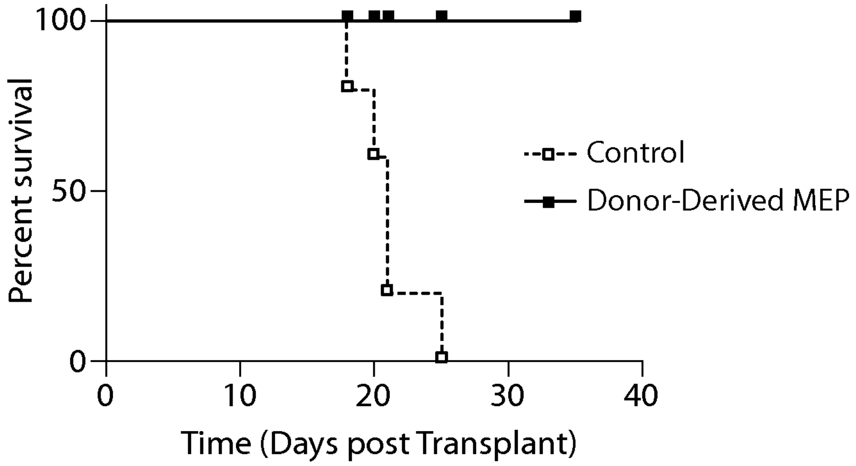

Fig. 72A

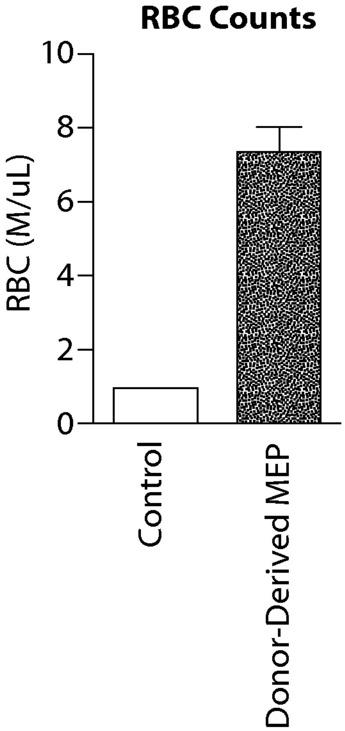

Fig. 72B

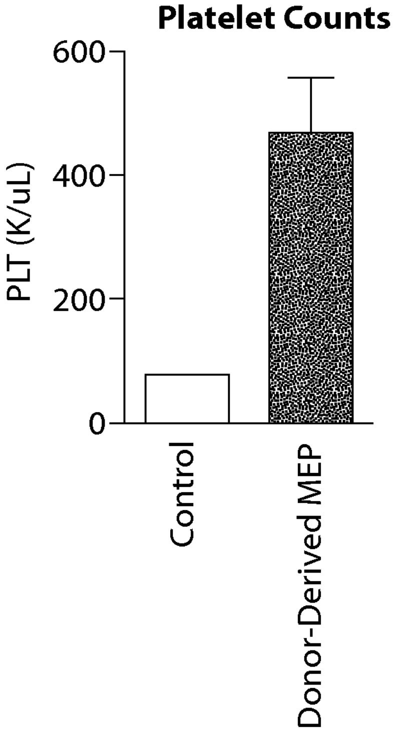

Fig. 72C

COMPOSITIONS AND METHODS FOR REPROGRAMMING HEMATOPOIETIC STEM CELL LINEAGES

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 61/782,037 filed Mar. 14, 2013, the content of which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Mar. 14, 2014, is named 701039-076171-PCT1_SL.txt and is 506,202 bytes in size.

FIELD OF THE INVENTION

[0003] The present invention relates to compositions, methods, and kits for reprogramming hematopoietic lineages and inducing hematopoietic stem cells.

BACKGROUND

[0004] Hematopoietic stem cells (HSCs) are a subset of multipotent stem cells that are responsible for the ability to sustain lifelong hematopoiesis, and continuously generate myriad and various blood cell types, while maintaining adequate number of stem cells in the bone marrow. Hematopoietic stem cells give rise to all the blood or immune cell types, including monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells, T-cells, B-cells, NKT-cells, and NK-cells. Hematopoietic tissues contain cells with long-term and short-term regeneration capacities, and committed multipotent, oligopotent, and unipotent progenitors.

[0005] Transplantation of hematopoietic stem cells (HSCT) has become the standard of care for many patients with defined congenital or acquired disorders of the hematopoietic system or with chemo- radio- or, immuno-sensitive malignancies. Over the last two decades, HSCT has seen rapid expansion and a constant evolution in technology use. (Gratwohl A, et al., (2010). Hematopoietic stem cell transplantation A Global Perspective. JAMA. 303(16):1617-24).

SUMMARY

[0006] The inventors have identified key transcription factors that can surprisingly reprogram committed cells and blood cells back into hematopoietic stem cells.

[0007] Hematopoietic stem cells (HSCs) are the best-characterized tissue-specific stem cells, yet the experimental study of HSCs remains challenging, due to the fact that they are exceedingly rare and methods to purify them are cumbersome, and vary between different laboratories. Moreover, genetic tools for specifically addressing issues related to HSC biology are lacking. In spite of wide clinical use, HSC transplantation remains a high-risk procedure, with the number of stem cells available for transplantation being the strongest predictor of transplantation success. One of the central clinical challenges of HSC transplantation arises from the fact that HSCs are exceedingly rare cells, occurring at a frequency of only 1/20,000 bone marrow cells and obtaining enough cells for transplant is challenging. Thus, an ability to expand HSC numbers prior to transplantation could overcome the problem of limited HSC numbers. Efforts to expand HSCs prior to transplant by ex vivo culturing have proven challenging and such efforts have not yet translated to the clinic. Thus, there remains a clinical need to find alternative strategies for either expanding the numbers of existing HSCs, or generating HSCs de novo from more abundant cell types.

[0008] The embodiments of the invention provide multiple applications, including kits for research use and methods for generation of cells useful for conducting small molecule screens for blood diseases. In addition, the invention provides commercially and medically useful methods to produce autologous hematopoietic stem cells and give them back to a patient in need, with or without genome editing. Transplant of hematopoietic stem cells is a critically important procedure that is currently limited for a variety of reasons.

[0009] Provided herein are compositions, methods, and kits for hematopoietic stem cell induction or for reprogramming cells to the multipotent state of hematopoietic stem cells, based, in part, on the discoveries described herein of novel combinations of transcription factors that permit dedifferentiation and reprogramming of more differentiated cells to the hematopoietic stem cell state. Such compositions, nucleic acid constructs, methods and kits can be used for inducing hematopoietic stem cells in vitro, ex vivo, or in vivo, as described herein, and these induced hematopoietic stem cells can be used in regenerative medicine applications and therapies.

[0010] For example, the methods described herein can be used to produce HSC cells for treat diseases including leukemia, lymphomas, solid tumors, aplastic anemia, congenital bone marrow failure syndromes, immune deficiencies, sickle cell disease, thalassemia and metabolic/storage diseases, such as amyloidosis.

[0011] Accordingly, provided herein, in some aspects are hematopoietic stem cell (HSC) inducing composition comprising one or more expression vectors encoding at least one, two, three, four, five, six, seven, eight, or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612.

[0012] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0013] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5.

[0014] Also provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0015] a. a nucleic acid sequence encoding HLF;

[0016] b. a nucleic acid sequence encoding RUNX1T1;

[0017] c. a nucleic acid sequence encoding ZFP37;

[0018] d. a nucleic acid sequence encoding PBX1;

[0019] e. a nucleic acid sequence encoding LMO2; and

[0020] f. a nucleic acid sequence encoding PRDM5.

[0021] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0022] a. a nucleic acid sequence encoding PRDM16;

[0023] b. a nucleic acid sequence encoding ZFP467; and

[0024] c. a nucleic acid sequence encoding VDR.

[0025] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0026] a. a nucleic acid sequence encoding HLF;

[0027] b. a nucleic acid sequence encoding RUNX1T1;

[0028] c. a nucleic acid sequence encoding PBX1;

[0029] d. a nucleic acid sequence encoding LMO2;

[0030] e. a nucleic acid sequence encoding PRDM5

[0031] f. a nucleic acid sequence encoding ZFP37;

[0032] g. a nucleic acid sequence encoding MYCN;

[0033] h. a nucleic acid sequence encoding MSI2;

[0034] i. a nucleic acid sequence encoding NKX2-3;

[0035] j. a nucleic acid sequence encoding MEIS1; and

[0036] k. a nucleic acid sequence encoding RBPMS.

[0037] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0038] a. a nucleic acid sequence encoding ZFP467;

[0039] b. a nucleic acid sequence encoding PBX1;

[0040] c. a nucleic acid sequence encoding HOXB4; and

[0041] d. a nucleic acid sequence encoding MSI2.

[0042] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0043] a. a nucleic acid sequence encoding HLF;

[0044] b. a nucleic acid sequence encoding LMO2;

[0045] c. a nucleic acid sequence encoding PRDM16; and

[0046] d. a nucleic acid sequence encoding ZFP37.

[0047] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0048] a. a nucleic acid sequence encoding MYCN;

[0049] b. a nucleic acid sequence encoding MSI2;

[0050] c. a nucleic acid sequence encoding NKX2-3; and

[0051] d. a nucleic acid sequence encoding RUNX1T1.

[0052] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0053] a. a nucleic acid sequence encoding HOXB5;

[0054] b. a nucleic acid sequence encoding HLF;

[0055] c. a nucleic acid sequence encoding ZFP467;

[0056] d. a nucleic acid sequence encoding HOXB3;

[0057] e. a nucleic acid sequence encoding LMO2;

[0058] f. a nucleic acid sequence encoding PBX1;

[0059] g. a nucleic acid sequence encoding ZFP37; and

[0060] h. a nucleic acid sequence encoding ZFP521.

[0061] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0062] a. a nucleic acid sequence encoding HOXB4;

[0063] b. a nucleic acid sequence encoding PBX1;

[0064] c. a nucleic acid sequence encoding LMO2;

[0065] d. a nucleic acid sequence encoding ZFP467; and

[0066] e. a nucleic acid sequence encoding ZFP521.

[0067] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0068] a. a nucleic acid sequence encoding KLF12;

[0069] b. a nucleic acid sequence encoding HLF; and

[0070] c. a nucleic acid sequence encoding EGR1.

[0071] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0072] a. a nucleic acid sequence encoding MEIS1;

[0073] b. a nucleic acid sequence encoding RBPMS;

[0074] c. a nucleic acid sequence encoding ZFP37;

[0075] d. a nucleic acid sequence encoding RUNX1T1; and

[0076] e. a nucleic acid sequence encoding LMO2.

[0077] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0078] a. a sequence encoding KLF12; and

[0079] b. a sequence encoding HLF;

[0080] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0081] a. a nucleic acid sequence encoding ZFP37;

[0082] b. a nucleic acid sequence encoding HOXB4;

[0083] c. a nucleic acid sequence encoding LMO2; and

[0084] d. a nucleic acid sequence encoding HLF.

[0085] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0086] a. a nucleic acid sequence encoding MYCN;

[0087] b. a nucleic acid sequence encoding ZFP467;

[0088] c. a nucleic acid sequence encoding NKX2-3

[0089] d. a nucleic acid sequence encoding PBX1; and

[0090] e. a nucleic acid sequence encoding KLF4.

[0091] In some embodiments of these aspects and all such aspects described herein, the one or more expression vectors are retroviral vectors.

[0092] In some embodiments of these aspects and all such aspects described herein, the one or more expression vectors are lentiviral vectors. In some embodiments, the lentiviral vectors are inducible lentiviral vectors.

[0093] Also provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising modified mRNA sequences encoding at least one, two, three, four, five, six, seven, eight, or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612, wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0094] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0095] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5.

[0096] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0097] a. a modified mRNA sequence encoding HLF;

[0098] b. a modified mRNA sequence encoding RUNX1T1;

[0099] c. a modified mRNA sequence encoding ZFP37;

[0100] d. a modified mRNA sequence encoding PBX1;

[0101] e. a modified mRNA sequence encoding LMO2; and

[0102] f. a modified mRNA sequence encoding PRDM5;

[0103] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0104] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0105] a. a modified mRNA sequence encoding PRDM16;

[0106] b. a modified mRNA sequence encoding ZFP467; and

[0107] c. a modified mRNA sequence encoding VDR;

[0108] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0109] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0110] a. a modified mRNA sequence encoding HLF;

[0111] b. a modified mRNA sequence encoding RUNX1T1;

[0112] c. a modified mRNA sequence encoding PBX1;

[0113] d. a modified mRNA sequence encoding LMO2;

[0114] e. a modified mRNA sequence encoding PRDM5

[0115] f. a modified mRNA sequence encoding ZFP37;

[0116] g. a modified mRNA sequence encoding MYCN;

[0117] h. a modified mRNA sequence encoding MSI2;

[0118] i. a modified mRNA sequence encoding NKX2-3;

[0119] j. a modified mRNA sequence encoding MEIS1; and

[0120] k. a modified mRNA sequence encoding RBPMS;

[0121] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0122] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0123] a. a modified mRNA sequence encoding ZFP467;

[0124] b. a modified mRNA sequence encoding PBX1;

[0125] c. a modified mRNA sequence encoding HOXB4; and

[0126] d. a modified mRNA sequence encoding MSI2;

[0127] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0128] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0129] a. a modified mRNA sequence encoding HLF;

[0130] b. a modified mRNA sequence encoding LMO2;

[0131] c. a modified mRNA sequence encoding PRDM16; and

[0132] d. a modified mRNA sequence encoding ZFP37.

[0133] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0134] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0135] a. a modified mRNA sequence encoding MYCN;

[0136] b. a modified mRNA sequence encoding MSI2;

[0137] c. a modified mRNA sequence encoding NKX2-3; and

[0138] d. a modified mRNA sequence encoding RUNX1T1;

[0139] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0140] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0141] a. a modified mRNA sequence encoding HOXB5;

[0142] b. a modified mRNA sequence encoding HLF;

[0143] c. a modified mRNA sequence encoding ZFP467;

[0144] d. a modified mRNA sequence encoding HOXB3;

[0145] e. a modified mRNA sequence encoding LMO2;

[0146] f. a modified mRNA sequence encoding PBX1;

[0147] g. a modified mRNA sequence encoding ZFP37; and

[0148] h. a modified mRNA sequence encoding ZFP521;

[0149] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0150] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0151] a. a modified mRNA sequence encoding HOXB4;

[0152] b. a modified mRNA sequence encoding PBX1;

[0153] c. a modified mRNA sequence encoding LMO2;

[0154] d. a modified mRNA sequence encoding ZFP467; and

[0155] e. a modified mRNA sequence encoding ZFP521;

[0156] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0157] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0158] a. a modified mRNA sequence encoding KLF12;

[0159] b. a modified mRNA sequence encoding HLF; and

[0160] c. a modified mRNA sequence encoding EGR;

[0161] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0162] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0163] a. a modified mRNA sequence encoding MEIS1;

[0164] b. a modified mRNA sequence encoding RBPMS;

[0165] c. a modified mRNA sequence encoding ZFP37;

[0166] d. a modified mRNA sequence encoding RUNX1T1; and

[0167] e. a modified mRNA sequence encoding LMO2.

[0168] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0169] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0170] a. a modified mRNA sequence encoding KLF12; and

[0171] b. a modified mRNA sequence encoding HLF;

[0172] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0173] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0174] a. a modified mRNA sequence encoding ZFP37;

[0175] b. a modified mRNA sequence encoding HOXB4;

[0176] c. a modified mRNA sequence encoding LMO2; and

[0177] d. a modified mRNA sequence encoding HLF;

[0178] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0179] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0180] a. a modified mRNA encoding MYCN;

[0181] b. a modified mRNA encoding ZFP467;

[0182] c. a modified mRNA encoding NKX2-3

[0183] d. a modified mRNA encoding PBX1; and

[0184] e. a modified mRNA encoding KLF4;

[0185] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0186] In some embodiments of these aspects and all such aspects described herein, the modified cytosine is 5-methylcytosine and the modified uracil is pseudouracil.

[0187] In some embodiments of these aspects and all such aspects described herein, the modified mRNA sequences comprise one or more nucleoside modifications selected from the group consisting of pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, 2-aminopurine, 2,6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine, inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine, and combinations thereof.

[0188] Also provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0189] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5, wherein each said nucleic acid sequence is operably linked to a promoter; and

[0190] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0191] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding PRDM16 a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding VDR.

[0192] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0193] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM5; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding MEIS1; and a nucleic acid sequence encoding RBPMS; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0194] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0195] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0196] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP467, a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding HOXB4; and a nucleic acid sequence encoding MSI2; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0197] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0198] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM16; and a nucleic acid sequence encoding ZFP37.

[0199] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0200] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2, a nucleic acid sequence encoding NKX2-3; and a nucleic acid sequence encoding RUNX1T1; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0201] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0202] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HOXB5; a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding HOXB3; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding ZFP37; and a nucleic acid sequence encoding ZFP521.

[0203] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0204] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding PBX1, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding ZFP521; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0205] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0206] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; a nucleic acid sequence encoding HLF; and a nucleic acid sequence encoding EGR1.

[0207] Provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0208] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding MEIS1; a nucleic acid sequence encoding RBPMS; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding RUNX1T1; and a nucleic acid sequence encoding LMO2; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0209] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0210] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; and a nucleic acid sequence encoding HLF.

[0211] Provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0212] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding HLF; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0213] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0214] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; and a nucleic acid sequence encoding HLF.

[0215] Provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0216] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding HLF; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0217] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0218] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding PBX1; and a nucleic acid sequence encoding KLF4.

[0219] In some embodiments of these aspects and all such aspects described herein, the somatic cell is a fibroblast cell.

[0220] In some embodiments of these aspects and all such aspects described herein, the somatic cell is a hematopoietic lineage cell.

[0221] In some embodiments of these aspects and all such aspects described herein, the hematopoietic lineage cell is selected from promyelocytes, neutrophils, eosinophils, basophils, reticulocytes, erythrocytes, mast cells, osteoclasts, megakaryoblasts, platelet producing megakaryocytes, platelets, monocytes, macrophages, dendritic cells, lymphocytes, NK cells, NKT cells, innate lymphocytes, multipotent hematopoietic progenitor cells, oligopotent hematopoietic progenitor cells, and lineage restricted hematopoietic progenitors.

[0222] In some embodiments of these aspects and all such aspects described herein, the hematopoietic lineage cell is selected from a multi-potent progenitor cell (MPP), common myeloid progenitor cell (CMP), granulocyte-monocyte progenitor cells (GMP), common lymphoid progenitor cell (CLP), and pre-megakaryocyte-erythrocyte progenitor cell.

[0223] In some embodiments of these aspects and all such aspects described herein, the hematopoietic lineage cell is selected from a megakaryocyte-erythrocyte progenitor cell (MEP), a ProB cell, a PreB cell, a PreProB cell, a ProT cell, a double-negative T cell, a pro-NK cell, a pro-dendritic cell (pro-DC), pre-granulocyte/macrophage cell, a granulocyte/macrophage progenitor (GMP) cell, and a pro-mast cell (ProMC).

[0224] Also provided herein, in some aspects, are methods of promoting transdifferentiation of a ProPreB cell to the myeloid lineage comprising:

[0225] a. transducing a ProPreB cell with one or more vectors comprising a nucleic acid sequence encoding ZFP467, a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding HOXB4; and a nucleic acid sequence encoding MSI2; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0226] b. culturing the transduced ProPreB cell in a cell media that supports growth of myeloid lineage cells, thereby transdifferentiating the ProPreB cell to the myeloid lineage.

[0227] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM16; and a nucleic acid sequence encoding ZFP37.

[0228] Also provided herein, in some aspects, are methods of increasing survival and/or proliferation of ProPreB cells, comprising:

[0229] a. transducing a ProPreB cell with one or more vectors comprising a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding PBX1, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding ZFP521; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0230] b. culturing the transduced ProPreB cell in a cell media that supports growth of ProPreB cells, thereby increasing survival and/or proliferation of ProPreB cells.

[0231] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; a nucleic acid sequence encoding HLF; and a nucleic acid sequence encoding EGR1.

[0232] Also provided herein, in some aspects, are isolated induced hematopoietic stem cells (iHSCs) produced using any of the HSC inducing compositions or methods described herein.

[0233] In some aspects, provided herein are cell clones comprising a plurality of the induced hematopoietic stem cells (iHSCs) produced using any of the HSC inducing compositions or methods described herein. In some embodiments of these aspects and all such aspects described herein, the cell clones further comprise a pharmaceutically acceptable carrier.

[0234] Also provided herein, in some aspects, are kits for making induced hematopoietic stem cells (iHSCs), the kits comprising any of the HSC inducing compositions comprising one or more expression vector components described herein.

[0235] Provided herein, in some aspects, are kits for making induced hematopoietic stem cells (iHSCs), the kits comprising any of the HSC inducing compositions comprising modified mRNA sequence components described herein.

[0236] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, and MEIS1

[0237] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, and LMO2.

[0238] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0239] a nucleic acid sequence encoding HLF;

[0240] a nucleic acid sequence encoding RUNX1T1;

[0241] a nucleic acid sequence encoding ZFP37;

[0242] a nucleic acid sequence encoding PBX1;

[0243] a nucleic acid sequence encoding LMO2;

[0244] a nucleic acid sequence encoding PRDM5;

[0245] a nucleic acid sequence encoding MYCN; and

[0246] a nucleic acid sequence encoding MEIS1.

[0247] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0248] a nucleic acid sequence encoding HLF;

[0249] a nucleic acid sequence encoding RUNX1T1;

[0250] a nucleic acid sequence encoding ZFP37;

[0251] a nucleic acid sequence encoding PBX1; and

[0252] a nucleic acid sequence encoding LMO2;

[0253] In some embodiments of these aspects and all such aspects described herein, the one or more expression vectors are lentiviral vectors. In some embodiments, the lentiviral vectors are inducible lentiviral vectors. In some embodiments, the lentiviral vectors are polycistronic inducible lentiviral vectors. In some embodiments, the polycistronic inducible lentiviral vectors express three or more nucleic acid sequences. In some embodiments, each of the nucleic acid sequences of the polycistronic inducible lentiviral vectors are separated by 2A peptide sequences.

[0254] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, and MEIS1.

[0255] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, and LMO2.

[0256] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising: a modified mRNA sequence encoding HLF; a modified mRNA sequence encoding RUNX1T1; a modified mRNA sequence encoding ZFP37; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding LMO2; a modified mRNA sequence encoding PRDM5; a modified mRNA sequence encoding MEIS1; and a modified mRNA sequence encoding MYCN; wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0257] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising a modified mRNA sequence encoding HLF; a modified mRNA sequence encoding RUNX1T1; a modified mRNA sequence encoding ZFP37; a modified mRNA sequence encoding PBX1; and a modified mRNA sequence encoding LMO2; wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0258] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising: transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5; a nucleic acid sequence encoding MEIS1; and a nucleic acid sequence encoding MYCN, wherein each said nucleic acid sequence is operably linked to a promoter; and

culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0259] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising: transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF; a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding PBX1; and a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5, wherein each said nucleic acid sequence is operably linked to a promoter; and culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0260] As demonstrated herein, the use of polycistronic viral expression systems can increase the in vivo reprogramming efficiency of somatic cells to iHSCs. Accordingly, in some embodiments of the aspects described herein, a polycistronic lentiviral vector is used. In such embodiments, sequences encoding two or more of the HSC inducing factors described herein, are expressed from a single promoter, as a polycistronic transcript. We used 2A peptide strategy to make polycistronic vectors (see, e.g., Expert Opin Biol Ther. 2005 May; 5(5):627-38). Polycistronic expression vector systems can also use internal ribosome entry sites (IRES) elements to create multigene, or polycistronic, messages. IRES elements are able to bypass the ribosome scanning model of 5'-methylated Cap dependent translation and begin translation at internal sites (Pelletier and Sonenberg, 1988). IRES elements can be linked to heterologous open reading frames. Multiple open reading frames can be transcribed together, each separated by an IRES, thus creating polycistronic messages. By virtue of the IRES element, each open reading frame is accessible to ribosomes for efficient translation. Multiple genes can be efficiently expressed using a single promoter/enhancer to transcribe a single message. See, for example, U.S. Pat. Nos. 4,980,285; 5,925,565; 5,631,150; 5,707,828; 5,759,828; 5,888,783; 5,919,670; and 5,935,819; and Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Press (1989).

DEFINITIONS

[0261] For convenience, certain terms employed herein, in the specification, examples and appended claims are collected here. Unless stated otherwise, or implicit from context, the following terms and phrases include the meanings provided below. Unless explicitly stated otherwise, or apparent from context, the terms and phrases below do not exclude the meaning that the term or phrase has acquired in the art to which it pertains. The definitions are provided to aid in describing particular embodiments, and are not intended to limit the claimed invention, because the scope of the invention is limited only by the claims. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0262] The term “HSC inducing factor,” as used herein, refers to a developmental potential altering factor, as that term is defined herein, such as a protein, RNA, or small molecule, the expression of which contributes to the reprogramming of a cell, e.g. a somatic cell, to the HSC state. An HSC inducing factor can be, for example, transcription factors that can reprogram cells to the HSC state, such as HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS, and the like, including any gene, protein, RNA or small molecule that can substitute for one or more of these factors in a method of making iHSCs in vitro. In some embodiments, exogenous expression of an HSC inducing factor induces endogenous expression of one or more HSC inducing factors, such that exogenous expression of the one or more HSC inducing factor is no longer required for stable maintenance of the cell in the iHSC state.

[0263] As used herein, the terms “developmental potential” or “developmental potency” refer to the total of all developmental cell fates or cell types that can be achieved by a given cell upon differentiation. Thus, a cell with greater or higher developmental potential can differentiate into a greater variety of different cell types than a cell having a lower or decreased developmental potential. The developmental potential of a cell can range from the highest developmental potential of a totipotent cell, which, in addition to being able to give rise to all the cells of an organism, can give rise to extra-embryonic tissues; to a “unipotent cell,” which has the capacity to differentiate into only one type of tissue or cell type, but has the property of self-renewal, as described herein; to a “terminally differentiated cell,” which has the lowest developmental potential. A cell with “parental developmental potential” refers to a cell having the developmental potential of the parent cell that gave rise to it.

[0264] The term “multipotent” when used in reference to a “multipotent cell” refers to a cell that has the developmental potential to differentiate into cells of one or more germ layers, but not all three. Thus, a multipotent cell can also be termed a “partially differentiated cell.” Multipotent cells are well known in the art, and examples of multipotent cells include adult stem cells, such as for example, hematopoietic stem cells and neural stem cells. “Multipotent” indicates that a cell may form many types of cells in a given lineage, but not cells of other lineages. For example, a multipotent hematopoietic cell can form all of the many different types of blood cells (red, white, platelets, etc. . . .), but it cannot form neurons.

Accordingly, the term "multipotency" refers to a state of a cell with a degree of developmental potential that is less than totipotent and pluripotent.

[0265] The terms "stem cell" or "undifferentiated cell" as used herein, refer to a cell in an undifferentiated or partially differentiated state that has the property of self-renewal and has the developmental potential to differentiate into multiple cell types, without a specific implied meaning regarding developmental potential (i.e., totipotent, pluripotent, multipotent, etc.). A stem cell is capable of proliferation and giving rise to more such stem cells while maintaining its developmental potential. In theory, self-renewal can occur by either of two major mechanisms. Stem cells can divide asymmetrically, which is known as obligatory asymmetrical differentiation, with one daughter cell retaining the developmental potential of the parent stem cell and the other daughter cell expressing some distinct other specific function, phenotype and/or developmental potential from the parent cell. The daughter cells themselves can be induced to proliferate and produce progeny that subsequently differentiate into one or more mature cell types, while also retaining one or more cells with parental developmental potential. A differentiated cell may derive from a multipotent cell, which itself is derived from a multipotent cell, and so on. While each of these multipotent cells can be considered stem cells, the range of cell types each such stem cell can give rise to, i.e., their developmental potential, can vary considerably. Alternatively, some of the stem cells in a population can divide symmetrically into two stem cells, known as stochastic differentiation, thus maintaining some stem cells in the population as a whole, while other cells in the population give rise to differentiated progeny only. Accordingly, the term "stem cell" refers to any subset of cells that have the developmental potential, under particular circumstances, to differentiate to a more specialized or differentiated phenotype, and which retain the capacity, under certain circumstances, to proliferate without substantially differentiating. In some embodiments, the term stem cell refers generally to a naturally occurring parent cell whose descendants (progeny cells) specialize, often in different directions, by differentiation, e.g., by acquiring completely individual characters, as occurs in progressive diversification of embryonic cells and tissues. Some differentiated cells also have the capacity to give rise to cells of greater developmental potential. Such capacity may be natural or may be induced artificially upon treatment with various factors. Cells that begin as stem cells might proceed toward a differentiated phenotype, but then can be induced to "reverse" and re-express the stem cell phenotype, a term often referred to as "dedifferentiation" or "reprogramming" or "retrodifferentiation" by persons of ordinary skill in the art, and as used herein.

[0266] In the context of cell ontogeny, the term "differentiate", or "differentiating" is a relative term that refers to a developmental process by which a cell has progressed further down a developmental pathway than its immediate precursor cell. Thus in some embodiments, a reprogrammed cell as the term is defined herein, can differentiate to a lineage-restricted precursor cell (such as a common lymphoid progenitor), which in turn can differentiate into other types of precursor cells further down the pathway (such as a ProBPreB cell, for example), and then to an end-stage differentiated cells, which play a characteristic role in a certain tissue type, and may or may not retain the capacity to proliferate further.

[0267] "Transdifferentiation," as used herein refers to a process by which the phenotype of a cell can be switched to that of another cell type, without the formation of a multipotent intermediate cell. Thus, when transdifferentiation methods are employed, it is not required that the cell first be de-differentiated (or reprogrammed) to a multipotent cell and then differentiated to another hematopoietic lineage cell; rather the cell type is merely "switched" from one cell type to another without first forming a multipotent iHSC phenotype, for example.

[0268] As used herein, the term "without the formation of a multipotent or pluripotent intermediate cell" refers to the transdifferentiation of one cell type to another cell type, preferably, in one step; thus a method that modifies the differentiated phenotype or developmental potential of a cell without the formation of a multipotent or pluripotent intermediate cell does not require that the cell be first dedifferentiated (or reprogrammed) to a multipotent state and then differentiated to another cell type.

[0269] The term "expression" refers to the cellular processes involved in producing RNA and proteins and as appropriate, secreting proteins, including where applicable, but not limited to, for example, transcription, translation, folding, modification and processing. "Expression products" include RNA transcribed from a gene, and polypeptides obtained by translation of mRNA transcribed from a gene. In some embodiments, an expression product is transcribed from a sequence that does not encode a polypeptide, such as a microRNA.

[0270] As used herein, the term "transcription factor" or "TF" refers to a protein that binds to specific parts of DNA using DNA binding domains and is part of the system that controls the transcription of genetic information from DNA to RNA.

[0271] As used herein, the term "small molecule" refers to a chemical agent which can include, but is not limited to, a peptide, a peptidomimetic, an amino acid, an amino acid analog, a polynucleotide, a polynucleotide analog, an aptamer, a nucleotide, a nucleotide analog, an organic or inorganic compound (e.g., including heterorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds.

[0272] The term "exogenous" as used herein refers to a nucleic acid (e.g., a synthetic, modified RNA encoding a transcription factor), or a protein (e.g., a transcription factor) that has been introduced by a process involving the hand of man into a biological system such as a cell or organism in which it is not normally found, or in which it is found in lower amounts. A factor (e.g. a synthetic, modified RNA encoding a transcription factor, or a protein, e.g., a polypeptide) is considered exogenous if it is introduced into an immediate precursor cell or a progeny cell that inherits the substance. In contrast, the term "endogenous" refers to a factor or expression product that is native to the biological system or cell (e.g., endogenous expression of a gene, such as, e.g., HLF refers to production of an HLF polypeptide by the endogenous gene in a cell).

[0273] The term "isolated" or "partially purified" as used herein refers, in the case of a nucleic acid or polypeptide, to a nucleic acid or polypeptide separated from at least one other component (e.g., nucleic acid or polypeptide) that is present with the nucleic acid or polypeptide as found in its natural source and/or that would be present with the nucleic acid or polypeptide when expressed by a cell, or secreted in the case of secreted polypeptides. A chemically synthesized nucleic acid or polypeptide or one synthesized using in vitro transcription/translation is considered "isolated".

[0274] The term "isolated cell" as used herein refers to a cell that has been removed from an organism in which it was originally found, or a descendant of such a cell. Optionally the cell has been cultured in vitro, e.g., in the presence of other cells. Optionally, the cell is later introduced into a second organism or re-introduced into the organism from which it (or the cell or population of cells from which it descended) was isolated.

[0275] The term "isolated population" with respect to an isolated population of cells as used herein refers to a population of cells that has been removed and separated from a mixed or heterogeneous population of cells. In some embodiments, an isolated population is a "substantially pure" population of cells as compared to the heterogeneous population from which the cells were isolated or enriched. In some embodiments, the isolated population is an isolated population of multipotent cells which comprise a substantially pure population of multipotent cells as compared to a heterogeneous population of somatic cells from which the multipotent cells were derived.

[0276] The term "immediate precursor cell" is used herein to refer to a parental cell from which a daughter cell has arisen by cell division.

[0277] The term "contacting" or "contact" as used herein in connection with contacting a cell with one or more constructs, viral vectors, or synthetic, modified RNAs, includes subjecting a cell to a culture medium which comprises one or more constructs, viral vectors, or synthetic, modified RNAs at least one time, or a plurality of times, or to a method whereby such constructs, viral vectors, or synthetic, modified RNAs are forced to contact a cell at least one time, or a plurality of times, i.e., a transduction or a transfection system. Where such a cell is in vivo, contacting the cell with a construct, viral vector, or synthetic, modified RNA includes administering the construct(s), viral vector(s), or synthetic, modified RNA(s) in a composition, such as a pharmaceutical composition, to a subject via an appropriate administration route, such that the compound contacts the cell in vivo.

[0278] The term "transfection" as used herein refers the use of methods, such as chemical methods, to introduce exogenous nucleic acids, such as synthetic, modified RNAs, into a cell, preferably a eukaryotic cell. As used herein, the term transfection does not encompass viral-based methods of introducing exogenous nucleic acids into a cell. Methods of transfection include physical treatments (electroporation, nanoparticles, magnetofection), and chemical-based transfection methods. Chemical-based transfection methods include, but are not limited to, cyclodextrin, polymers, liposomes, and nanoparticles. In some embodiments, cationic lipids or mixtures thereof can be used to transfect the synthetic, modified RNAs described herein, into a cell, such as DOPA, Lipofectamine and UptiFectin. In some embodiments, cationic polymers such as DEAE-dextran or polyethylenimine, can be used to transfect a synthetic, modified RNAs described herein.

[0279] The term "transduction" as used herein refers to the use of viral particles or viruses to introduce exogenous nucleic acids, such as nucleic acid sequences encoding HSC inducing factors, into a cell.

[0280] As used herein, the term "transfection reagent" refers to any agent that induces uptake of a nucleic acid into a host cell. Also encompassed are agents that enhance uptake e.g., by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%, at least 1-fold, at least 2-fold, at least 5-fold, at least 10-fold, at least 25-fold, at least 500-fold, at least 100-fold, at least 1000-fold, or more, compared to a nucleic acid sequence administered in the absence of such a reagent. In some embodiments, a cationic or non-cationic lipid molecule useful for preparing a composition or for co-administration with a synthetic, modified RNA is used as a transfection reagent. In other embodiments, the synthetic, modified RNA comprises a chemical linkage to attach e.g., a ligand, a peptide group, a lipophilic group, a targeting moiety etc. In other embodiments, the transfection reagent comprises a charged lipid, an emulsion, a liposome, a cationic or non-cationic lipid, an anionic lipid, or a penetration enhancer as known in the art or described herein.

[0281] As used herein, the term "repeated transfections" refers to repeated transfection of the same cell culture with a nucleic acid, such as a synthetic, modified RNA, a plurality of times (e.g., more than once or at least twice). In some embodiments, the cell culture is transfected at least twice, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, at least 10 times, at least 11 times, at least 12 times, at least 13 times, at least 14 times, at least 15 times, at least 16 times, at least 17 times at least 18 times, at least 19 times, at least 20 times, at least 25 times, at least 30 times, at least 35 times, at least 40 times, at least 45 times, at least 50 times or more. The transfections can be repeated until a desired phenotype of the cell is achieved.

[0282] The time between each repeated transfection is referred to herein as the "frequency of transfection." In some embodiments, the frequency of transfection occurs every 6 h, every 12 h, every 24 h, every 36 h, every 48 h, every 60 h, every 72 h, every 96 h, every 108 h, every 5 days, every 7 days, every 10 days, every 14 days, every 3 weeks, or more during a given time period in any developmental potential altering regimen. The frequency can also vary, such that the interval between each dose is different (e.g., first interval 36 h, second interval 48 h, third interval 72 h etc). It should be understood depending upon the schedule and duration of repeated transfections, it will often be necessary to split or passage cells or change or replace the media during the transfection regimen to prevent overgrowth and replace nutrients. For the purposes of the methods described herein, transfections of a culture resulting from passaging an earlier transfected culture is considered "repeated transfection," "repeated contacting" or "contacting a plurality of times," unless specifically indicated otherwise.

[0283] As used herein, the terms "nucleic acid," "polynucleotide," and "oligonucleotide" generally refer to any polyribonucleotide or poly-deoxyribonucleotide, and includes unmodified RNA, unmodified DNA, modified RNA, and modified DNA. Polynucleotides include, without limitation, single- and double-stranded DNA and RNA polynucleotides. The term polynucleotide, as it is used herein, embraces chemically, enzymatically or metabolically modified forms of polynucleotides, as well as the naturally occurring chemical forms of DNA and RNA found in or characteristic of viruses and cells, including for example, simple (prokaryotic) and complex (eukaryotic) cells. A nucleic acid polynucleotide or oligonucleotide as described herein retains the ability to hybridize to its cognate complimentary strand.

[0284] Accordingly, as used herein, the terms "nucleic acid," "polynucleotide," and "oligonucleotide" also encompass primers and probes, as well as oligonucleotide fragments, and is generic to polydeoxyribonucleotides (containing 2-deoxy-D-ribose), to polyribonucleotides (containing D-ribose), and to any other type of polynucleotide which is an N-glycoside of a purine or pyrimidine base, or modified purine or pyrimidine bases (including, but not limited to, abasic sites). There is no intended distinction in length between the term "nucleic acid," "polynucleotide," and "oligonucleotide," and these terms are used interchangeably. These terms refer only to the primary structure of the molecule. An oligonucleotide is not necessarily physically derived from any existing or natural sequence, but can be generated in any manner, including chemical synthesis, DNA replication, DNA amplification, in vitro transcription, reverse transcription or any combination thereof

[0285] The terms "nucleotide" or "mononucleotide," as used herein, refer to a phosphate ester of a nucleoside, e.g., mono-, di-, tri-, and tetraphosphate esters, wherein the most common site of esterification is the hydroxyl group attached to the C-5 position of the pentose (or equivalent position of a non-pentose "sugar moiety"). The term "nucleotide" includes both a conventional nucleotide and a non-conventional nucleotide which includes, but is not limited to, phosphorothioate, phosphite, ring atom modified derivatives, and the like.

[0286] As used herein, the term "conventional nucleotide" refers to one of the "naturally occurring" deoxynucleotides (dNTPs), including dATP, dTTP (or TTP), dCTP, dGTP, dUTP, and dITP.

[0287] As used herein, the term "non-conventional nucleotide" refers to a nucleotide that is not a naturally occurring nucleotide. The term "naturally occurring" refers to a nucleotide that exists in nature without human intervention. In contradistinction, the term "non-conventional nucleotide" refers to a nucleotide that exists only with human intervention, i.e., an "artificial nucleotide." A "non-conventional nucleotide" can include a nucleotide in which the pentose sugar and/or one or more of the phosphate esters is replaced with a respective analog. Exemplary phosphate ester analogs include, but are not limited to, alkylphosphonates, methylphosphonates, phosphoramidates, phosphotriesters, phosphorothioates, phosphorodithioates, phosphoroselenoates, phosphorodiselenoates, phosphoroanilothioates, phosphoroanilidates, phosphoroamidates, boronophosphates, etc., including any associated counterions, if present. A non-conventional nucleotide can show a preference of base pairing with another non-conventional or "artificial" nucleotide over a conventional nucleotide (e.g., as described in Ohtsuki et al. 2001, Proc. Natl. Acad. Sci., 98: 4922-4925, hereby incorporated by reference). The base pairing ability may be measured by the T7 transcription assay as described in Ohtsuki et al. (supra). Other non-limiting examples of "non-conventional" or "artificial" nucleotides can be found in Lutz et al. (1998) Bioorg. Med. Chem. Lett., 8: 1149-1152); Voegel and Benner (1996) Helv. Chim Acta 76, 1863-1880; Horlacher et al. (1995) Proc. Natl. Acad. Sci., 92: 6329-6333; Switzer et al. (1993), Biochemistry 32:10489-10496; Tor and Dervan (1993) J. Am. Chem. Soc. 115: 4461-4467; Piccirilli et al. (1991) Biochemistry 30: 10350-10356; Switzer et al. (1989) J. Am. Chem. Soc. 111: 8322-8323, all of which are hereby incorporated by reference. A "non-conventional nucleotide" can also be a degenerate nucleotide or an intrinsically fluorescent nucleotide.

[0288] As used herein the term "modified ribonucleoside" refers to a ribonucleoside that encompasses modification(s) relative to the standard guanine (G), adenine (A), cytosine (C), and uracil (U) nucleosides. Such modifications can include, for example, modifications normally introduced post-transcriptionally to mammalian cell mRNA, and artificial chemical modifications, as known to one of skill in the art.

[0289] As used herein, the terms "synthetic, modified RNA" or "modified RNA" or "modified mRNA" refer to an RNA molecule produced in vitro which comprises at least one modified nucleoside as that term is defined herein below. The modified mRNAs do not encompass mRNAs that are isolated from natural sources such as cells, tissue, organs etc., having those modifications, but rather only synthetic, modified RNAs that are synthesized using in vitro techniques, as described herein. The term "composition," as applied to the terms "synthetic, modified RNA" or "modified RNA," encompasses a plurality of different synthetic, modified RNA molecules (e.g., at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, at least 40, at least 50, at least 75, at least 90, at least 100 synthetic, modified RNA molecules or more). In some embodiments, a synthetic, modified RNA composition can further comprise other agents (e.g., an inhibitor of interferon expression or activity, a transfection reagent, etc.). Such a plurality can include synthetic, modified RNA of different sequences (e.g., coding for different polypeptides), synthetic, modified RNAs of the same sequence with differing modifications, or any combination thereof.

[0290] As used herein the term "modified nucleoside" refers to a ribonucleoside that encompasses modification(s) relative to the standard guanine (G), adenine (A), cytidine (C), and uridine (U) nucleosides. Such modifications can include, for example, modifications normally introduced post-transcriptionally to mammalian cell mRNA, and artificial chemical modifications, as known to one of skill in the art.

[0291] As used herein, the term "polypeptide" refers to a polymer of amino acids comprising at least 2 amino acids (e.g., at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, at least 100, at least 125, at least 150, at least 175, at least 200, at least 225, at least 250, at least 275, at least 300, at least 350, at least 400, at least 450, at least 500, at least 600, at least 700, at least 800, at least 900, at least 1000, at least 2000, at least 3000, at least 4000, at least 5000, at least 6000, at least 7000, at least 8000, at least 9000, at least 10,000 amino acids or more). The terms "protein" and "polypeptide" are used interchangeably herein. As used herein, the term "peptide" refers to a relatively short polypeptide, typically between about 2 and 60 amino acids in length.

BRIEF DESCRIPTION OF THE DRAWINGS

[0292] FIG. **1** depicts a schematic of hematopoietic differentiation showing populations (boxes) for which microarray data has been generated. Data generated herein is shown in thin-line boxes, and by other groups in thick-line boxes. Whereas hematopoietic differentiation normally proceeds from HSCs to differentiated blood effector cells, the results described herein aim to utilize HSC-enriched transcription factors to reprogram committed hematopoietic cells back to HSCs (large arrow). Throughout this proposal HSCs are purified by stringent cell surface criteria (e.g., ckit^{+}Sca1^{+}lineage^{-} CD48^{-}flk2^{-}CD150^{+}CD34^{-}), as well as for fetal liver HSCs (e.g., ckit^{+}Sca1^{+}lineage–CD48^{-}CD150^{+}Mac1^{low}).

[0293] FIG. **2** depicts an overview of the approaches described herein for identifying factors capable of reprogramming committed hematopoietic cells back to HSCs.

[0294] FIG. **3** depicts gene discovery using the hematopoietic expression database. Heat map of expression of genes enriched in 6 different hematopoietic populations. Each column reflects microarray data from a hematopoietic subset (40 populations represented). Erythroid progenitors include MEP, pre-CFU-E and CFU-E. Expressed was visualized as red; Not expressed was visualized as blue. * Asterisk denotes genes with known roles in specifying the fate and/or function of the indicated cell type.

[0295] FIGS. **4**A-**4**B depict an overview of experimental approaches and experimental populations. FIG. **4**A depicts experimental approaches for screening induced HSCs (iHSCs) through expression of multiple critical HSC-enriched transcription factors by in vitro and in vivo methods. CD45.2 transgenic (rtTA) mice are used to identify congenic donor cells in transplant experiments using recipient CD45.1 host mice. Common myeloid progenitors (CMPs) and Pro/Pre B Cells were sorted out of the bone marrow of CD45.2 transgenic mice. Sorted cells were incubated for 14 hours with ZsGreen control (VC) or a viral cocktail of HSC-specific factors. ZsGr+ cells were resorted two days post doxycycline addition. Resorted ZsGr+ CMPs and ProPreB Cells were put into a CFC myeloid colony forming assays (scored for colony numbers and morphology 20 days later) or transplanted into conditioned IR CD45.1+ recipient mice. Peripheral bleeds were performed up to 16 weeks as to define the short and long term reconstitution potential of cells. Mice identified with adequate multi-lineage reconstitution were euthanized and donor derived cells sorted from the bone marrow to be transplanted into conditioned secondary CD45.1 recipients; also full analysis of the bone marrow, spleen and thymus was performed. FIG. **4**B depict CMPs and PrePro B cells that were predominately chosen as our starting populations so that we could demonstrate experimental reprogramming from the first defined committed blood cells in BOTH the B cell lineage and the myeloid lineage. These cell populations were identified using the phenotypic markers listed.

[0296] FIGS. **5**A-**5**C depict heat maps of HSC-enriched transcription factors. The Rossi Lab and others put together a detailed database including mRNA expression profiles for over 248 defined progenitor and effector sub populations. FIG. **5**A depicts an expression profile heat map for 37 HSC-enriched reprogramming factors. Columns represent microarray data for 40 distinct FACs sorted populations. * Denotes factors chosen because of their developmental importance. Expressed was visualized as red; Not expressed was visualized as blue. FIG. **5**B shows that all HSC-enriched factors were placed into a doxycycline inducible tet-on system based in the pHAGE2 lentiviral vector. Only exception to this vector map from addgene is that a CMV promoter is used in the systems described herein. Heat Map of expanded set of identified HSC-enriched Transcription Factors. FIG. **5**C depicts an expression profile heat map for 46 HSC-enriched putative reprogramming factors. Columns represent microarray data for 40 distinct FACs sorted populations. * Expressed was visualized as red; Not expressed was visualized as blue.

[0297] FIGS. **6**A-**6**D depict isolation strategies for Pro and Pre B cells. FIG. **6**A shows ProPre B cells that are sorted from the bone marrow by placing total bone marrow through a magnetic B220 enrichment column. Enrichment increases B220^{+}CD19^{+} B cells from 15% to 85% in their respective populations; through Aria cell sorting the purity of the sample increases further to 99-100%. (RT stands for the B220^{-} run through from the column) FIG. **6**B depicts a orting strategy to obtain ProPreB Cells that is demonstrated by flow histograms. FIG. **6**C shows overall purity for each of the following samples: overall B220 enriched (top panel), reanalyzed sorted Pro B cells (Middle panel) and reanalyzed sorted Pre B cells (Bottom Panel). By showing CD25 expression vs. B220 expression we demonstrate not only that Pro and Pre B cells can be effectively sorted but can also be distinguished via phenotypic markers and sorting. FIG. **6**D depicts overall sort purity of Pre B cells and Pro B Cells in each of the populations collected; indicating proficient sorting of ProPre B Cells (RT stands for the B220^{-} run through from the column).

[0298] FIGS. **7**A-**7**B depict an isolation strategy for CMPs. FIG. **7**A shows CMP cells that are sorted from the bone marrow by placing total bone marrow through a magnetic c-kit enrichment column. The indicated gating strategy isolated singlet, live, lineage negative, hematopoietic progenitors. FIG. **7**B shows that enrichment increases CMP levels and furthermore that using aria cell sorting, a purity of 99-100% is achieved.

[0299] FIGS. **8**A-**8**C demonstrate transduction and inducible expression of HSC-enriched transcription factors (TFs) in hematopoietic progenitors. FIG. **8**A shows transduction of multi-potent progenitors (MPPs) with lentiviruses bearing 8 different TFs (LV1-LV-8). Cells were cultured in the presence of doxycycline (Dox) for 5 days followed by flow cytometry. FIG. **8**B shows peripheral blood of a recipient transplanted with TF-transduced MPPs and maintained on Dox for 4 weeks (left panel), followed by 2 weeks Dox-off (right panel). FIG. **8**C shows viral mediated expression of putative reprogramming factors in vitro. Quantitative RT-PCR for the indicated genes showing their relative expression within primary hematopoietic stem cells (HSCs) or multi-potent progenitors (MPPs), and in primary cells that were transduced with LV encoding the indicated factor and cultured for 1 week. The mRNA levels in overexpressing cells was calculated by dividing to the expression levels in primary HSCs. Results show Hlf at 8-fold, Nap113 at 110-fold, Rbpms at 20-fold and Runx1' at 40-fold above endogenous levels.

[0300] FIGS. **9**A-**9**C demonstrate that Pro/Pre B Cells and CMPs can be transduced with doxycycline inducible viral cocktails. FIG. **9**A shows B220+ CD19+ B Cells that were sorted from the bone marrow; cells were incubated for 14 hours with nothing (non trans), control ZsGr Virus (VC) or a viral cocktail that express 28 HSC-enriched factors (VM). Doxycycline (dox) was added for 24 hours. An increase in ZsGr+ cells is observed when the VM is used on cells in comparison to non transduced cells. FIG. **9**B shows B220+ CD19+ B cells that were further analyzed in the presence and absence of dox in three independent trials. In the absence of Dox few ZsGr+ cells are observed however regardless of using VC or VM the addition of Dox increases ZsGr expression in the population. Addition of dox tightly regulates ZsGr expression and therein gene expression. FIG. **9**C shows pre B Cells, Pro B Cells, and CMPs that were sorted out of the bone marrow and incubated for 14 hours with VC or VM and left with Dox for two days before analysis. ProPreBCells and CMPs can be transduced with the viral cocktail to express HSC-enriched factors.

[0301] FIGS. **10**A-**10**D demonstrate that combinatorial TF expression increases ProPreB and CMP CFC colony number and alters lineage potential. ProPre B Cells and CMPs were sorted using phenotypic markers on the Aria Sorter. Cells were incubated with ZsGr control virus (VC) or a viral cocktail (VM) for 14 hours in S-clone media containing SCF, TPO and IL-12 (In the case of ProPreB Cells, IL-7 and Flk3). Dox was added for 24 hours and cells were resorted for ZsGr+ cells. ZsGr+ cells were placed into methylcellulose media in a 6 well plate format containing SCF, TPO and IL-12 (For ProPreB Cells IL-7 and Flk3). Colony forming potential was assayed on day 20. FIG. **10**A shows examples of types of cells observed during determination of colony morphology. FIG. **10**B depicts representative pictures that were taken of the Transduced ProPreB ZsGreen control (VC) and Viral mixture of 37 factors (VM) CFC plates. FIG. **10**C shows increasing number of cells that were plated to find an effective plating density of both ProPreBCells and CMPs. 2×10^5 ProPre B Cells and 1×10^4 CMPs were used in further experiments. Experiments were repeated in two individual trials. FIG. **10**D shows colony number and composition that were determined and noted for all colonies. Increased colony number is observed when ProPreB Cells and CMPs were transduced with the cocktail of 37 factors as compared to the ZsGreen control (VC). Experiments were done in duplicates for four trials.

[0302] FIG. **11** demonstrates that exposure to 18 putative reprogramming factors embues multi-potent progenitors with robust long-term multi-lineage engraftment potential in vivo. Multi-potent progenitors (MPP=Lineage$^-$Sca1$^+$ckit$^+$ CD150$^-$) were sorted and transduced with either control virus of a lentiviral mix containing Hlf, MycN, Meis1, Irf6, Cdkn1c, Nfix, Dnmt3b, Zfp612, Prdm5, HoxB4, Lmo2, Nkx2-3, RarB, Ndn, Nap113, Runx1t1, Zfp467, Zfp532. Transduced cells were transplanted into irradiated congenic recipients along with competitive WBM. Peripheral-blood chimerism is indicated at timepoints post-transplant showing that exposure to these factors greatly improved long-term donor engraftment.

[0303] FIG. **12** demonstrates that exposure to 9 putative reprogramming factors embues multi-potent progenitors with robust long-term multi-lineage engraftment potential in vivo. MPPs from CD45.2 or congenic CD45.1 donors were sorted as LSKCD34+flk2+ and equal numbers of cells were transduced with either control virus (into CD45.1 cells) of a lentiviral mix containing 9 factors, including Evi-1, Glis2, HoxB5, HoxA9, HLF, Meis1, MycN, Prdm16, Runx1 (CD45.2 cells). Cells were transplanted into irradiated CD45.1/CD45.2 F1 recipients along with CD45.1/CD45.2 competitor bone marrow (2e5 cells). Transgene-expression was sustained with doxycycline (dox-on) for 18 weeks (upper panel) followed by removal of Doxycycline for the remainder of the experiment (dox-off). Peripheral blood chimerism was measured at 20 and 25 weeks (lower panel) showing that in contrast to control transduced MPPs (CD45.1), 9-factor transduced MPPS retained rebust long-term repopulating activity. Panel on lower right: Engraftment from 9-factor transduction is multi-lineage. Donor-derived cells were stained for Mac1, Gr-1, CD3, CD8 and B220 revealing the presence of donor-derived, macrophage/monocytes, granulocytes, T-cells and B-cells.

[0304] FIGS. **13**A-**13**B demonstrate long-term multi-lineage reconstitution of multi-potent progenitors (MPPs) transduced with HSC-enriched transcription factors (TFs). FIG. **13**A. Flow cytometry of peripheral blood of a recipient transplanted with MPPs (ckit+Sca1+lineage−CD150−flk2+ CD34+) transduced with control virus (top panel), or a cocktail of 17 different TFs (lower panel), 20 weeks post-transplant. Equal numbers of MPPs from the same initial sort were transplanted. FIG. **13**B. Donor chimerism 20 weeks post-transplant of mice described in (FIG. **13**A). Results show that only the TF-transduced MPPs yielded long-term multi-lineage reconstitution of T-cells, B-cells and myeloid cells, whereas control cells only gave rise to lymphoid cells as expected. All recipients receiving TF-transduced cells were multi-lineage reconstituted suggesting that reprogramming was not a rare event. n=4 recipients for each control and 17-TF. 17 factors in this experiment included: Hlf, MycN, Meis1, Irf6, Nfix, Dnmt3b, Zfp612, Prdm5, HoxB4, Lmo2, Nkx2-3, RarB, Ndn, Nap113, Runx1t1, Zfp467, Zfp532.

[0305] FIG. **14** demonstrates that exposure to 8 putative reprogramming factors embues multi-potent progenitors with robust long-term multi-lineage engraftment potential in vivo. Multi-potent progenitors (MPP=Lineage$^-$Sca1$^+$ckit$^+$ CD150$^-$flk2$^+$CD34$^+$) were sorted and transduced with with either control virus of a lentiviral mix containing Runx1t1, HLF Zfp467 Rbpms hoxb5 nap113 msi2 Irf6. Transduced cells were transplanted into irradiated congenic recipients along with competitive WBM. Peripheral-blood chimerism is indicated at 16 weeks post-transplant showing that exposure to these factors led to long-term donor multi-lineage engraftment (bottom panel) in contrast to control transduced cells (top panel). Doxycline was maintained on for 2 weeks post-transplant followed by dox-removal.

[0306] FIG. **15** depicts using peripheral bleeds to test donor derived chimerism. Shown here is an example gating strategy on a peripheral bleeds done at 8 weeks on a transplanted mouse with ProPreB cells transduced with a cocktail of viruses that individually encode for expression of 37 transcription factors.

[0307] FIGS. **16**A-**16**C demonstrate that ProPreB Cell transplantation confers multi-lineage peripheral reconstitution when factors are expressed combinatorially. CD45.2+ ProPreB cells and CMPs transduced with control or VM were transplanted competitively into IR CD45.1+ recipients. Peripheral bleeds were performed at 4, 8, 12, and 16 weeks. FIG. **16**A. Flow histograms show 16 week peripheral bleeds for controls (VC—top panels) and cells expressing the mix of 37 factors (VM—bottom panels); demonstrated for ProPreB (Left) and CMP (Right). FIG. **16**B. Quantitative results for each of the peripheral bleeds are shown for ProPreB Cells and CMPs. Chimerism above 1.0% was observed in 5/14 mice transplanted with ProPreB and 3/8 mice transplanted with CMP. FIG. **16**C. Cellular composition of the peripheral bleeds of mice with chimerism over 1.0% is shown for mice transplanted with ProPreB Cells and CMPs.

[0308] FIG. **17** demonstrates that peripheral lymphoid organ and bone marrow reconstitution is observed from

CMPs and ProPreB Cells expressing combinatorial factors. The bone marrow, spleen, and thymus were harvested from mice transplanted with ProPreB Cells/CMPs transduced with control (VC) a viral cocktail (VM). Representative histograms of three ProPre B Cell transplanted mice (VC, VM4, VM14) and two CMP transplanted mice (VC and VM6)—VM#s are the same observed in FIG. **15**. Varying degrees of donor derived chimerism can be observed in each lymphoid compartment; consistently VM expressing cells had higher reconstitution in all lymphoid compartments in comparison to controls.

[0309] FIGS. **18**A-**18**D demonstrate that multi-lineage reconstitution is observed in peripheral lymphoid organs upon transplantation with combinatorial factor expression. FIG. **18**A. The bone marrow, spleen, and thymus were harvested from mice that were transplanted with transduced ProPre B cells and CMPs. Quantitation of the data is graphically summarized. In all ProPreB cells transplanted mice with >1.0% peripheral blood chimerism, donor derived chimerism above control levels were observed in all lymphoid compartments analyzed. FIGS. **18**B-**18**D. Composition of the bone marrow, spleen, and thymus for all control mice or experimental mice analyzed with >1% peripheral blood chimerism.

[0310] FIGS. **19**A-**19**D demonstrate that ProPreB Cells and CMPs expressing a cocktail of factors give rise to primitive hematopoietic progenitors. FIG. **19**A. Flow plots have been previously gated on myeloid progenitors (top panel) or primitive hematopoietic progenitors (LSK ($\text{Lin}^-\text{Sca}^+\text{c-kit}^+$) cells) (bottom panel). Only mice that received cells transduced with the viral cocktail give rise to donor (CD45.2+) derived cells hematopoietic progenitors or myeloid progenitors. Further break down of the myeloid progenitor gate (top panel) and hematopoietic progenitor (bottom panel) gates reveal a diversity of progenitor populations. FIG. **19**B. Quantitation of the overall numbers of myeloid progenitors and hematopoietic progenitor cells in each of the transplanted VC (average of five mice) and VM mice with peripheral chimerism above 1.0%. In all cases there is increased numbers of cells with respect to controls. FIGS. **19**C-**19**D. Composition of the compartments was analyzed and quantified. Each bar represents one mouse and the respective composition of the myeloid progenitor compartment (FIG. **19**C) or the hematopoietic progenitor compartment (FIG. **19**D).

[0311] FIGS. **20**A-**20**C demonstrate that ProPre B Cells and CMPs have serial transplant potential only when factors in combination are expressed. 1000 LSK CD45.2+ Cells were sorted and transplanted competitively with 2×105 CD45.1+ Competitors into competent CD45.1+ hosts. FIG. **20**A. At 4 weeks all the secondary transplants had distinguishable donor derived multi-lineage populations. Flow graphs representing each of those secondary transplants are shown. FIG. **20**B. Quantitation of these results was calculated and reported here as the % CD45.2+ of total peripheral blood. Only ProPre B Cell VM #14 had sustainable (>0.1%) long-term multi-lineage reconstitution even at 16 weeks. FIG. **20**C. The composition of the peripheral blood for all the mice referred to above at four weeks and at 16 weeks for PPBC#14. Multi-lineage reconstitution is observed for all bleeds.

[0312] FIGS. **21**A-**21**B. PCR based strategies can be used to identify VDJ rearrangements in B-cell progenitors. FIG. **21**A. B cells progenitors can be isolated based on the phenotypic markers shown in this schematic. FIG. **21**B. Fraction A, B, C and D and IgM positive mature B cells were sorted and subjected to PCR for V-D-J recombination of heavy and light chain. Heavy chain rearrangement begins as early as fraction B and continues to occur through Fraction C. Lambda and kappa light chain and rearrangement can occur as early as Fraction C and proceed through mature B cells. CD45.2 was used as a PCR loading control across all the samples. The experiments described herein demonstrate that we can effectively detect rearrangements in ProPreB Cells (Fractions B-D) in our system by PCR detection of rearrangement. Primers were adapted primers from Cobaleda et al. Nature 2007.

[0313] FIGS. **22**A-**22**C demonstrate VDJ rearrangement confirms the B-lineage origin of reprogrammed cells. To determine if cell populations and colonies originated from a VDJ recombined cell we assayed for recombinational events using PCR. FIG. **22**A. B cells (B220+), hematopoietic progenitor (Live, Lin−, c-kit+, Sca+), and myeloid progenitor (Live, Lin−, c-kit+, Sca−) bone marrow cells were FACs cell sorted and analyzed by PCR for heavy chain VDJ recombination. These populations provide a positive and two negative controls. Colonies arising from ProPreB cells expressing a mix of TFs were tested (GEMM colony); A myeloid colony taken from the control plate. FIG. **22**B. CD45.2+ donor and CD45.1+ recipient Mac1+ cells were FACs sorted. PCR was performed to test heavy chain (J_{H558}), kappa light chain (JLk), lambda light chain (JL1); genomic CD45 as a loading control. This demonstrates rearrangement in Mac+ cells isolated from a mouse transplanted with ProPreB Cells transduced with the viral cocktail (ProPreB #4). FIG. **22**C. Recombination analysis was performed and is summarized in table format for mice with CD45.2+ chimerism >1.0%. All mice with donor derived chimerism and transplanted with ProPre B Cells transduced with the viral cocktail had evidence of reprogramming on the heavy chain loci; a majority had either lambda or kappa light chain rearrangement. All recombinational events appear to be polyclonal and therefore reconstitution occurred from multiple clones.

[0314] FIGS. **23**A-**23**B demonstrate that VDJ Rearrangement confirms the origin of the reprogrammed cells. Although summarized in FIG. **22**C, further per testing of recombinational events in the peripheral blood of mice reconstituted by ProPreB Cells transduced with the viral cocktail. FIG. **23**A. Rearrangement PCR testing Mac1+ cells isolated from mice reconstituted with reprogrammed Pre/Pro B-cells (mice #'s 3, 7, 14) by a viral cocktail. B220+ cells are used as the positive control and primitive hematopoietic progenitors (unrearranged LSK cells) as the negative control. In the last lane is a mixed myeloid lineage CFC colony (GEMM) that was tested for both heavy and light chain rearrangement. FIG. **23**B. Rearrangement of Mac1+ cells sorted from the peripheral blood of a mouse reconstituted with reprogrammed Pre/Pro B-cells (VM#5). B220+ cells isolated from the bone marrow (BM) and peripheral blood (PB) are used as the positive control; primitive hematopoietic progenitors (unrearranged LSK+ cells) as the negative control. In the last lane is a mixed myeloid lineage CFC colony (GEMM) that was tested for both heavy and light chain rearrangement.

[0315] FIG. **24** demonstrates that VDJ Rearrangement confirms the origins of peripheral blood cells. Although rearrangement was observed in Mac+ positive cells from the peripheral blood, further analysis was performed on other populations from mice reconstituted from transplanted ProPre B cells transduced with the viral cocktail (#3 and #4). From these two mice the following donor (CD45.2+) populations were sorted: CD4/8+ T cells (T), B220+ B Cells (B), Mac1+ Myeloid cells (M), and all other cells with none of those markers (N). Each population displayed evidence of B cell recombinational events.

[0316] FIGS. **25**A-**25**D demonstrates that VDJ rearrangement confirms the origins of peripheral lymphoid cells and bone marrow populations. Tracking of VDJ B cell rearrangement in mice partially reconstituted by the proposed iHSC cells was taken one step further. When bone marrow of mice reconstituted from ProPreB cells transduced with the viral cocktail, aliquots of 50 cells were taken of donor derived hematopoietic progenitors [CD45.2+ LSK cells (LSK)], B cells [B220+ (B Cell)], myeloid cells [Mac1+ (Mac)], Myeloid progenitors [Lin−Sca−c-kit+=(MylPro)] and T cells [CD4+/8+/3+ T Cels (T cell)]. DNA was extracted from the samples and PCR performed to assay for recombination. FIG. **25**A. PCR recombination testing of mouse (#4) reconstituted from ProPreB Cells transduced with the viral mix. PCR testing was performed for heavy chain (J_{H588}), kappa light chain (J_k), and lambda light chain (J_l). FIG. **25**B. PCR recombination testing of mouse (#3) reconstituted from ProPreB Cells transduced with the viral mix. PCR testing was performed for heavy chain (J_{H588}). FIG. **25**C. PCR recombination testing of mouse (#14 and #7) reconstituted from ProPreB Cells transduced with the viral mix. PCR testing was performed for heavy chain (JH588). For mouse #14 that had high donor derived chimerism additional analysis was performed on the same populations from the spleen. Recipient CD45.1+ cells were included as a negative control. FIG. **25**D. PCR recombination testing of mouse (#7) reconstituted from ProPreB Cells transduced with the viral mix. PCR testing was performed for heavy chain (J_{H588}). Analysis of CD3/CD4/CD8+ T cells from the thymus. The left lane is CD45.1+ control T cells and the right is CD45.2+ donor cells. Only donor cells expressed B cell recombinational events.

[0317] FIG. **26** demonstrates a strategy for reverse cloning of reprogramming factors that allows for distinction between endogenous loci (top panel) and integrated reprogramming factors. Primers were designed to straddle intron/exon boundaries such that PCR identification of virally introduced transcription factors could readily be resolved from the endogenous genes—with the reprogramming factors yielding a smaller PCR product in all cases. See Table 5 for primer sequences used for reverse cloning of all reprogramming factors.

[0318] FIG. **27** demonstrates reverse cloning identification of transcription factors. ProPreB Cells were sorted and transduced for 14 hours with ZsGr control virus (VC), A single virus listed (Only Vector), a viral mix of 37 different factors minus that listed virus (VM-Vector) or the viral cocktail of 37 factors (VM). Doxycycline was added for 24 hours and then cells were harvested, DNA isolated, and PCR analysis performed using the indicated primers.

[0319] FIG. **28** shows reverse cloning identification of transcription factors. ProPreB Cells were sorted and transduced for 14 hours with ZsGr control virus (VC), A single virus listed (Only Vector), a viral mix of 37 different factors minus that listed virus (VM-Vector) or the viral cocktail of 37 factors (VM). Doxycycline was added for 24 hours and then cells were harvested, DNA isolated, and PCR analysis performed using the indicated primers.

[0320] FIG. **29** shows reverse cloning of reprogramming factors from myeloid (macrophage and granulocyte) colonies derived from reprogrammed pre/pro B cells. Examples of Gels run looking at 30 of the 37 different factors present in the cocktail. Notice that Evil, Msi2, Rux1t1, Hoxb3, and Pbx1 all have endogenous gene products present in every screen. White squares emphasize products that are at the correct size indicating integration of the factor listed.

[0321] FIG. **30** shows reverse cloning of reprogramming factors from myeloid (GEMM and B cell) colonies derived from reprogrammed pre/pro B cells. Examples of Gels run looking at 30 of the 37 different factors present in the cocktail. Notice that Evil, Msi2, Rux1t1, Hoxb3, and Pbx1 all have endogenous gene products present in every screen. White squares emphasize products that are at the correct size indicating integration of the factor listed.

[0322] FIG. **31** shows reverse cloning of reprogramming factors from myeloid (BFU) colonies derived from reprogrammed pre/pro B cells. Examples of Gels run looking at 30 of the 37 different factors present in the cocktail. Notice that Evil, Msi2, Rux1t1, Hoxb3, and Pbx1 all have endogenous gene products present in every screen. White squares emphasize products that are at the correct size indicating integration of the factor listed.

[0323] FIG. **32** shows frequency determination in which transcription factor combinations were reverse cloned in reprogrammed cells both intro (CFC colonies) and in vivo (donor-derived meyloid cells). To determine the individual factors contributing to the effects of the TF mix, integration primers were developed. ProPreB cells that gave rise to B cell (B cell), Macrophage (Mac), Granulocyte (Gran), Granulocyte-Macrophage (GM), Blast Forming Unit (BFU), GEMM, and those colonies not morphologically defined (Not Det) were collected and tested in the indicated n number. Similarly peripheral blood populations (B cell, macrophage, T cell, and other cells were tested for integration and grouped into the in vivo column. Results are summarized in a heat map. High prevalence in the population tested was visualized as red and low prevalence in the population was visualized as blue.

[0324] FIG. **33** shows reverse cloning of reprogramming factors from peripheral blood of mice reconstituted from ProPreB Cells expressing a combination of factors. Donor derived peripheral blood from the indicated mice (#4 and #5) reconstituted from ProPre B cells expressing a combination of factors was sorted and PCR analysis performed on the isolated DNA. Examples of two gels run looking at 30 of the 37 different factors present in the cocktail. Notice that Evil, Msi2, Rux1t1, Hoxb3, and Pbx1 all have endogenous gene products present in every screen. White squares emphasize products that are at the correct size indicating integration of the factor listed.

[0325] FIGS. **34**A-**34**C demonstrate identity of factor combinations that are integrated into peripheral blood populations from a mouse reconstituted with ProPre B cells and CMPs transduced with the viral cocktail. For three of the transplanted mice (two originating from a transformed ProPre B cell and one from a CMP) that had peripheral chimerism >1.0% the peripheral blood was further sorted into B220+ (B cells), Mac+ (Mac) and CD3+ (T cells). FIG. **34**A. Every peripheral bleed of donor derived cells originating from a reprogrammed ProPre B Cell or CMP contained Hlf, Zfp37, Runx1t1, Pbx1 and Lmo2. FIG. **34**B. Additional factors identified in those populations are listed here. Notice that Prdm5 is present in all samples except those collect from the Mac1+ cells. Glis2 on the other hand was only found in Mac+ populations. FIG. **34**C. Peripheral blood populations (B cell, macrophage, T cell, and other cells were tested for integration and grouped into the in vivo column for the n number of samples.

Results are summarized in a heat map. High prevalence in the population tested was visualized as red and low prevalence in the population was visualized as blue.

[0326] FIG. **35** shows transcription factor combination lists. Six combinations (C1-C6) of 4-6 factors were put together based on the integration testing (>75% prevalence). To each combination the additional factors that were 50%-75% prevalent in the samples were added as additional factors (++). Each combination was derived from a specific colony or population. C1: ProPreB to Mac/Gran/GM; C2: ProPreB to GEMM/BFU, C3: ProPreB to BCell; C4: CMP toGEMM; C5: Overall In vitro; C6: Overall In vivo.

[0327] FIGS. **36**A-**36**B show combinatorial expression of factors in ProPre B Cells increases colony formation. ProPre B Cells and CMPs were sorted using phenotypic markers on the Aria Sorter. Cells were incubated with ZsGr control virus (VC) or a viral cocktail for 14 hours in S-clone media containing SCF, TPO and IL-12 (In the case of ProPreB Cells, IL-7 and Flk3). Dox was added for 24 hours and cells were resorted for ZsGr+ cells. ZsGr+ cells were placed into methylcellulose media in a 6 well plate format containing SCF, TPO and IL-12 (For ProPreB Cells IL-7 and Flk3). Colony forming potential was assayed on day 20. FIG. **36**A. To ensure that all factors in the combinations were required; factors were singly subtracted out of the combination. Representative pictures of the wells are shown. FIG. **36**B. Quantitation of the data is demonstrated here. The ZsGreen control (VC) and the all the combination groups were performed in duplicates four independent experiments.

[0328] FIGS. **37**A-**37**B demonstrate defined combinations of transcription factors can reprogram cells to different fates. ProPre B Cells and CMPs were sorted using phenotypic markers on the Aria Sorter. Cells were incubated with ZsGr control virus (VC) or a viral cocktail for 14 hours in S-clone media containing SCF, TPO and IL-12 (In the case of ProPreB Cells, IL-7 and Flk3). Dox was added for 24 hours and cells were resorted for ZsGr+ cells. ZsGr+ cells were placed into methylcellulose media in a 6 well plate format containing SCF, TPO and IL-12 (For ProPreB Cells IL-7 and Flk3). Colony forming potential was assayed on day 20. FIG. **37**A. The morphology of each of the combinations is shown here. This again is an average of duplicate samples in four independent experiments. FIG. **37**B. Representative pictures of transduced ProPreB cell CFC wells for combinations and controls are shown with composition break downs in pie charts for each combination (average of four experiments). Notice that C1 a myeloid promoting combination gave rise to predominantly myeloid cells. Which a B Cell promoting combination (C3) promoted predominantly B cell colonies.

[0329] FIG. **38** shows factor combination minus one experiments to determine the requirement of individual factors for reprogramming ProPre B Cells and CMPs were sorted using phenotypic markers on the Aria Sorter. Cells were incubated with ZsGr control virus (VC) or a viral cocktail for 14 hours in S-clone media containing SCF, TPO and IL-12 (In the case of ProPreB Cells, IL-7 and Flk3). Dox was added for 24 hours and cells were resorted for ZsGr+ cells. ZsGr+ cells were placed into methylcellulose media in a 6 well plate format containing SCF, TPO and IL-12 (For ProPreB Cells IL-7 and Flk3). Colony forming potential was assayed on day 20. To ensure that all factors in the combinations were required; factors were singly subtracted out of the combination. For each combination listed in bold the factors were subtracted out singularly. As a control Pbx1 (a factor not in the required combination was included as a control, as expected this additional factor was not a required factor in C2). Consistently all other combinations appeared to have been narrowed down to only required factors. Singular factor controls are listed in the last Figure. Bars represent averages of double samples performed in duplicate experiments.

[0330] FIG. **39** demonstrates that a defined set of factors identified to give rise to in vivo reprogramming and GEMM formation in myeloid colony forming assays can increase colony formation and alter the lineage potential of both ProPre B cells and CMPs.ProPre B Cells and CMPs were sorted using phenotypic markers on the Aria Sorter. Cells were incubated with ZsGr control virus (VC) or the defined combination C7 (C7) for 14 hours in S-clone media containing SCF, TPO and IL-12 (In the case of ProPreB Cells, IL-7 and Flk3). Dox was added for 24 hours and cells were resorted for ZsGr+ cells. ZsGr+ cells were placed into methylcellulose media in a 6 well plate format containing SCF, TPO and IL-12 (For ProPreB Cells IL-7 and Flk3). Colony forming potential was assayed on day 20.

[0331] FIGS. **40**A-**40**B demonstrate that combination 6 leads to reprogramming of Pre-ProB cells into cells capable of giving rise to multi-lineage donor derived chimerism in vivo. ProPreB Cells and CMPs were sorted from CD45.2 rtTA transgenic bone marrow. Cells were then incubated with the indicated combination of factor expression viruses in equal concentrations. 10,000 Cells were then transplanted into congenic CD45.1+ mice. Mice were then bleed at 4, 8, 12, and 16 weeks. Only Combination 6 showed donor derived chimerism >1.0% in preliminary trials.

[0332] FIGS. **41**A-**41**C demonstrate donor derived multi-lineage reconstitution from ProPre B Cells expressing a defined set of factors. ProPreB cells were transduced to express C6, C6 and the additional factors identified, ZsGr Control (VC). Cells were transplanted competitively into mice and peripheral bleeds performed at 4, 8 and 12 weeks. FIG. **41**A. The gating strategy of mice transplanted with ProPre B Cells transduced with C6 and bleed at 4, 8, and 12 weeks. Donor-derived cells are observed over control level each bleed and are multi-lineage. FIG. **41**B. Quantitations for all the bleeds for ProPreB cells are demonstrated. No benefit of the additional factors was observed. FIG. **41**C. Cellular composition of the 12 week bleeds are shown in the graphs for ProPreB cells.

[0333] FIG. **42** demonstrates multi-lineage potential of reprogrammed B Cell progenitors by a defined set of factors (C6) is confirmed to have undergone recombination events and derived from B Cell origins. ProPreB cells were transduced to express C6, C6 and the additional factors identified, ZsGr Control (VC). Cells were transplanted competitively into mice and to demonstrate that the reconstitution was due to a cell that originated from a B cell, PCR analysis was performed on peripheral blood from the mouse that had long-term reconstitution in the peripheral blood. CD45.2+ donor Mac1+ cells had evidence of recombination events but recipient (CD45.1+) Mac1+ cells nor Fraction A B cells (B Cell Prog) had evidence of reprogramming.

[0334] FIG. **43** demonstrates a defined set of factors (C6) is expressed in peripheral blood derived from a reprogrammed ProPre B Cell. ProPreB cells were transduced to express C6, C6 and the additional factors identified, ZsGr Control (VC). Cells were transplanted competitively into mice and peripheral bleeds performed at 16 weeks. All the factors that were present in the viral mix were found to have integrated into the donor derived peripheral blood.

[0335] FIGS. **44**A-**44**C demonstrate donor derived multi-lineage reconstitution from CMPs expressing a defined set of factors. FIG. **44**A. CMP cells were transduced to express C6, C6 and the additional factors identified, ZsGr Control (VC). Cells were transplanted competitively into mice and peripheral bleeds performed at 4, 8 and 12 weeks. Lineage break down is shown by flow diagrams below for each mouse. FIG. **44**B. Quantitation for all the bleeds for both CMPs derived reconstituting mice are demonstrated. No benefit of the additional factors was observed. FIG. **44**C. Cellular composition of the 12 week bleeds are shown in the graphs for ProPreB cells.

[0336] FIG. **45** shows that reverse cloning confirms that donor derived peripheral blood originating from reprogrammed CMPs by C6 contains factors in Combination 6. CMP cells were transduced to express C6, C6 and the additional factors identified, ZsGr Control (VC). Cells were transplanted competitively into mice and a peripheral bleeds performed at 12 weeks. Peripheral blood was taken from both CMP originating iHSC reconstituting mice was taken and integration studies performed on the population. One mouse contained all factors used in the viral mix and the other was only missing Hlf.

[0337] FIGS. **46**A-**46**C demonstrate a defined set of factors give rise to multi-lineage reconstitution from reprogrammed B Cells. Five additional factors were added to C6 that gave rise to GEMM colonies from either ProPre B cells or CMPs. This combination was coined C7. B220 enriched cells were magnetically separated from the bone marrow of CD45.2 rtTA mice. Cells were transduced with ZsGr control (VC) or C7 for 14 hours, kept for 24 hours with doxycycline and then transplanted competitively with 1×10^5 whole bone marrow cells into CD45.1+ recipients. Bleeds were performed at 4, 8, 12, and 16 weeks. FIG. **46**A. Flow plots are shown for both VC and C7 transduced and transplanted recipients at 8 weeks. FIG. **46**B. Quantitation of peripheral bleeds for the B220 enriched cells transduced with ZsGr control (VC) or C7 at 4, 8, 12 and 16 weeks. Excluding one outlier all C7 transduced and transplanted mice are over VC transduced and transplanted cells. FIG. **46**C. The average composition of peripheral blood at 4, 8, 12, and 16 weeks.

[0338] FIG. **47** shows multi-lineage reconstitution by reprogrammed B220 enriched cells has evidence of B cell recombination in 2/5 mice. Five additional factors were added to C6 that gave rise to GEMM colonies from either ProPre B cells or CMPs. This combination was coined C7. B220 enriched cells were magnetically separated from the bone marrow of CD45.2 rtTA mice. Cells were transduced with ZsGr control (VC) or C7 for 14 hours, kept for 24 hours with doxycycline and then transplanted competitively with 1×10^5 whole bone marrow cells into CD45.1+ recipients. Bleed was performed at 16 weeks. To determine what reconstituted animals were derived from a B cell origin, peripheral blood was isolated, Mac1+ cells sorted, and tested by per analysis for B cell recombination. Two mice were found to have peripheral chimerism due to a transformed B cell. Those mice are shown in FIG. **40**A by highlighting them in orange.

[0339] FIG. **48** shows that reverse cloning confirms that donor derived peripheral blood originating from reprogrammed CMPs by C7 contains factors in combination 7. Five additional factors were added to C6 that gave rise to GEMM colonies from either ProPre B cells or CMPs. This combination was coined C7. B220 enriched cells were magnetically separated from the bone marrow of CD45.2 rtTA mice. Cells were transduced with ZsGr control (VC) or C7 for 14 hours, kept for 24 hours with doxycycline and then transplanted competitively with 1×10^5 whole bone marrow cells into CD45.1+ recipients. Bleed was performed at 16 weeks. Peripheral blood from the two B cell recombined mice was isolated and tested by per analysis for the integration of the factors in C7. Rbpms and Msi2 was missing from both analysis.

[0340] FIGS. **49**A-**49**D show that peripheral lymphoid organ and bone marrow reconstitution is observed from CMPs and ProPreB Cells expressing a defined set of factors, combination 6. FIG. **49**A. The bone marrow, spleen, and thymus were harvested from mice that were transplanted with C6 transduced ProPre B cells and CMPs. Quantitation of the data is graphically summarized. In all ProPreB cells transplanted mice with >1.0% peripheral blood chimerism, donor derived chimerism above control levels were observed in all lymphoid compartments analyzed. FIGS. **49**B-**49**D. Composition of the bone marrow, spleen, and thymus for all control mice or experimental mice analyzed with >1% peripheral blood chimerism.

[0341] FIG. **50** demonstrates bone marrow reconstitution of the hematopoietic progenitor and myeloid progenitor compartments is observed when CMPs and ProPreB Cells expressing a defined set of factors, combination 6, are transplanted. The bone marrow was harvested from mice transplanted with ProPreB Cells/CMPs transduced with control (VC) a defined viral cocktail (C6). Representative histograms are shown of populations reprogrammed with C6: two CMP transplanted mice (CMP1 and CMP2) and one ProPre B Cell transplanted mouse (ProPreB1). Cells have been previously gated for singlets, live, lineage negative cells. Varying degrees of donor derived chimerism can be observed. The c-kit and sca graphs show that there is donor derived hematopoietic progenitors (LSK; c-kit+Sca+) and myeloid progenitors (Myl Pro; c-kit+Sca−).

[0342] FIGS. **51**A-**51**C demonstrate that ProPreB Cells and CMPs expressing a defined set of factors (C6) give rise to primitive hematopoietic progenitors. The bone marrow was harvested from mice transplanted with ProPreB Cells/CMPs transduced with control (VC) a defined viral cocktail (C6). Representative histograms are shown of populations reprogrammed with C6: two CMP transplanted mice (CMP1 and CMP2) and one ProPre B Cell transplanted mouse (ProPreB1). Graphs represent donor (CD45.2+) derived hematopoietic progenitors (LSK; c-kit+Sca+) and myeloid progenitors (Myl Pro; c-kit+Sca−). FIG. **51**A. Quantitation of the overall numbers of myeloid progenitors and hematopoietic progenitor cells in each of the transplanted VC (average of five mice) and C6 mice with peripheral chimerism above 1.0%. In all cases there is increased numbers of cells with respect to controls. FIGS. **51**B-**51**C. Composition of the compartments was analyzed and quantified. Each bar represents one mouse and the respective composition of the myeloid progenitor compartment (FIG. **51**B) or the hematopoietic progenitor compartment (FIG. **51**C).

[0343] FIG. **52** demonstrates that reprogrammed CMPs by defined factors have serial transplantation potential. 16 weeks bone marrow analysis was performed and secondary transplants set up. The two CMP derived mice with donor derived chimerism underwent full bone marrow transplant of 5 million donor cells into five mice each. In the case of the mouse having donor derived chimerism originating from a ProPre B cell transduced with C6, 1 million whole donor bone marrow cells were competitively transplanted with 2×10^5 CD45.1+ whole bone marrow cells into two mice. Flow graphs of donor derived cells from each of these mice are shown. Donor cells are observed at 4 weeks.

[0344] FIGS. **53**A-**53**C demonstrate that reprogrammed CMPs by defined factors have serial long-term transplantation potential. 16 weeks bone marrow analysis was performed and secondary transplants set up. The two CMP derived mice with donor derived chimerism underwent full bone marrow transplant of 5 million donor cells into five mice each. In the case of the mouse having donor derived chimerism originating from a ProPre B cell transduced with C6, 1 million whole donor bone marrow cells were competitively transplanted with 2×10^5 CD45.1+ whole bone marrow cells into two mice. Flow graphs of donor derived cells from each of these mice are shown. Donor cells are observed at 4 weeks. FIG. **53**A. An example of multilineage donor chimerism at 4 weeks in the peripheral blood of secondary transplants. FIG. **53**B. Quantitation of CD45.2+ donor contributions in peripheral blood at 4 and 8 weeks. CMPs transduced with C6 gave rise to multilineage chimerism in primary recipients and in secondary transplants all the mice had donor cells. FIG. **53**C. Quantitation of the composition of peripheral blood cells in secondary recipients.

[0345] FIG. **54** demonstrates that peripheral blood derived from CMP C6 reconstituted mice can be reprogrammed to give rise to in vitro colony forming potential. Peripheral blood from serially transplanted C6 transduced CMP cells was collected. B220+ and CD3+ and Mac1+ cells were sorted and incubated for 48 hours with doxycycline. Cells were then put into methylcellulose media containing SCF, TPO, IL-12, Flk3, and IL-7. Colonies in the CFCs assays were counted and morphology characterized 20 days later. Control sorted cells from primary VC recipients were blank but colonies were observed when cells were derived from CMPs previously transduced with C6.

[0346] FIG. **55** demonstrates that peripheral blood derived from reconstituted mice having been transplanted with B220 enriched cells expressing C7 mice can undergo secondary reprogrammed to give rise to in vitro colony forming potential. Peripheral blood from mice transplanted with B220 enriched cells expressing combination C7 was collected at 16 weeks. B220+ and CD3+ and Mac1+ cells were sorted and incubated for 48 hours with doxycycline. Cells were then put into methylcellulose media containing SCF, TPO, IL-12, Flk3, and IL-7. Colonies in the CFCs assays were counted and morphology characterized 20 days later. Control sorted cells from primary VC recipients were blank but colonies were observed when cells were derived from the peripheral blood of either mouse reconstituted from reprogrammed B220 enriched cells expressing C7.

[0347] FIGS. **56**A-**56**C demonstrate that expression of defined factors in various populations can promote colony formation and altered lineage commitment in vitro. Various indicated populations were sorted from the bone marrow (FIG. **56**A), spleen (FIG. **56**B), thymus (FIG. **56**C), and peripheral blood (FIG. **56**C) of mice. Populations include: B220+ (B); Mac1+/Gr-1+ (M/G); CD3+/CD4+/CD8+ (T); NK1.1+ (NK); ProPreBCells as a control. In the case of peripheral blood (PB) B, T, and M/G was all sorted into one population. These populations were transduced with control (VC) or C7 viruses for 14 hours, dox added for 24 hours and then put into a CFC assay. Colonies were counted and morphology determined on day 20. Colony numbers with more than control levels in almost all cases. Indicating that transformation of committed blood cells into iHSC like cells could occur from multiple compartments and in multiple cell types.

[0348] FIGS. **57**A-**57**C demonstrate that expression of defined factors in human Jurkat cells can promote colony formation and altered lineage commitment in vitro. FIG. **57**A. Human Jurkat cells were cultured and left untransduced, transduced with ZsGr control virus (VC) or with C6 for 14 hours. Doxycycline was added for 24 hours and cells were put in CFC assays. Colonies were counted and morphology determined on day 20. Only Jurkat cells transduced with C6 gave rise to colonies. FIG. **57**B. Colonies that Jurkat cells transduced with C6 gave rise too are pictured. They included an erythroid like colony, granulocytes, and monocytes. FIG. **57**C. To further distinguish the transformed cells, flow analysis for phenotypic markers including Ter119, Mac1, CD71, and Gr1 was performed on freshly cultured Jurkat cells and the Jurkat cell colonies observed when transduced with C6. Jurkat colonies that were transduced with C6 had apparent increases in immature erythroid cells (CD71+Ter119−), Granulocyte (Gr1+Mac1+) and monocyte (Mac1+) populations.

[0349] FIGS. **58**A-**58**E show identification of factors capable of imparting alternative lineage potential in vitro. (FIG. **58**A) Heat map showing relative expression (green; high, to purple;low) of 36 regulatory genes identified as HSC-specific in the indicated cell types. (FIG. **58**B) Schematic representation of lentivirus transgene expression cassette (top), and flow cytometry plots showing reporter cassette (ZsGr) expression in Pro/Pre B-cells+/− doxycycline induction (48 hours post). (FIG. **58**C) Schematic representation of in vitro screening strategy for cell fate conversion. (FIG. **58**D) Representative images of wells showing colonies arising in methylcellulose from Pro/Pre B cells transduced with ZsGr or 36-factor cocktail. (FIG. **58**E) Colony number and type arising in methylcellulose from Pro/Pre B cells transduced with ZsGr or 36-factor cocktail. Four independent experiments are shown and each condition performed in triplicate.

[0350] FIGS. **59**A-**59**G show identification of factors capable of imparting multi-lineage engraftment potential onto committed progenitors in vivo. (FIG. **59**A) Schematic of experimental strategy to identify factors capable of imparting multi-lineage engraftment potential on committed progenitors in vivo. (FIG. **59**B) Representative flow cytometry plots showing donor (CD45.2) reconstitution of mice transplanted with control (ZsGr) or 36-factor transduced Pro/Pre B cells or CMPs 16-weeks post-transplant. (FIG. **59**C) Donor reconstitution of mice transplanted with ZsGr or 36-factor transduced Pro/Pre B cells or CMPs at indicated time points post-transplantation. Only mice with >1% donor chimerism (dotted line) were considered reconstituted. Recipients transplanted; Pro/PreB; ZsGr n=15, Pro/PreB; 36-factor n=15, CMP; ZsGr n=8, and CMP; 36-factor n=8. (FIG. **59**D) Reconstitution of indicated peripheral blood cell lineages of individual recipients showing >1% donor chimerism presented as % of donor. (FIG. **59**E) PCR analysis of immunoglobulin rearrangement showing heavy (J_H), and light chain ($J_{L\lambda}$, J_{LK}) in bone marrow (BM) cells including B-cells (B220+), stem/progenitor (LSK) cells, myeloid progenitors (Myl Pro), and peripheral blood (PB) cells including B-cells (B220+), recipient myeloid cells (Mac1+ Rec), and donor myeloid cells (Mac1+ Donor) originating from Pro/Pre B cell; 36-factor experiment. Loading control; genomic PCR for CD45. (FIG. **59**F) PCR-based strategy to identify virally integrated factors and discriminate from endogenous genes. (FIG. **59**G) Summary of data showing presence (gray) or absence (black) of each of the indicated factors in donor B−, T−, and myeloid cells in each of the reconstituted mice shown in (FIG. **59**C).

[0351] FIGS. **60**A-**60**G show transient ectopic expression of six transcription factors in committed progenitors is sufficient to alter lineage potential in vitro and impart long-term engraftment potential on committed progenitors in vivo. (FIG. **60**A) Representative images of wells showing colonies arising in methylcellulose from Pro/Pre B cells transduced with ZsGr or 6-TF cocktail. (FIG. **60**B) Colony number and indicated colony type arising in methylcellulose from Pro/Pre B cells transduced with ZsGr or 6-TF cocktail. 3 independent experiments are shown with each condition performed in triplicate. (FIG. **60**C) Colony number and type arising in methylcellulose from Pro/Pre B cells transduced with ZsGr, 6-TF cocktail, or 6-TF minus the indicated factor. Each condition performed in triplicate. (FIG. **60**D) Donor reconstitution of mice transplanted with ZsGr or 6-TF transduced Pro/Pre B cells or CMPs at indicated time points post-transplantation. Only mice with >1% donor chimerism (dotted line) were considered reconstituted. Recipients transplanted; Pro/PreB; ZsGr n=10, Pro/PreB; 6-TF n=12, CMP; ZsGr n=9, and CMP; 6-TF n=9. (FIG. **60**E) Representative flow cytometry plots showing donor reconstitution and lineage composition of mice transplanted with control (ZsGr) or 6-TF transduced Pro/Pre B cells or CMPs 16-weeks post-transplant. Lineage contribution to Mac1+ myeloid cells, B220+ B-cells, and CD3/4/8+ T-cells is shown. (FIG. **60**F) Reconstitution of indicated peripheral blood cell lineages of individual recipients showing >1% donor chimerism presented as % of donor. (FIG. **60**G) PCR analysis of immunoglobulin heavy (JH) chain rearrangement in recipient myeloid cells (Mac1+ Rec), and donor myeloid cells (Mac1+ Donor) originating from Pro/Pre B cell; 6-TF experiment. Loading control; genomic PCR for CD45.

[0352] FIGS. **61**A-**61**E show inclusion of Meis1 and Mycn and use of polycistronic viruses improves in vivo reprogramming efficiency. (FIG. **61**A) Schematic representation of RHL (Runxt1t1, Hlf, Lmo2) and PZP (Pbx1, Zfp37, Prdm5) polycistronic, and Meis1 and Mycn single factor viral constructs. (FIG. **61**B) Donor reconstitution of mice transplanted with ZsGr, 8-TF (8 single factor viruses), or 8-TFPoly (RHL, PZP polycistronic viruses plus Meis1 and Mycn viruses), transduced Pro/Pre B cells at indicated time points post-transplantation. Only mice with >1% donor chimerism were considered reconstituted. Recipients transplanted; ZsGr; n=12, 8-TF; n=6, 8TFPoly; n=14. (FIG. **61**C) Representative flow cytometry plots showing donor reconstitution and lineage contribution of mice transplanted with control (ZsGr), 8-TF, or 8TFPoly transduced Pro/Pre B cells 16-weeks post-transplant. Lineage contribution to Mac1+GR1− myeloid cells, Mac+GR1+ granulocytes, B220+ B-cells, and CD3/4/8+ T-cells is shown. (FIG. **61**D) Reconstitution of indicated peripheral blood cell lineages of individual recipients showing >1% donor chimerism presented as % of donor. (FIG. **61**E) PCR analysis of immunoglobulin heavy (JH) chain rearrangement in recipient (Recip), and donor (Donor) myeloid cells. Loading control; genomic PCR for CD45.

[0353] FIGS. **62**A-**62**I shows reprogrammed cells engraft secondary hematopoietic organs, bone marrow progenitor compartments and reconstitute secondary recipients. (FIG. **62**A) Donor reconstitution of peripheral blood (PB), bone marrow (BM), spleen, and thymus of mice transplanted with 8-TF, or 8-TFPoly transduced Pro/Pre B cells 18-20 weeks post-transplantation. (FIG. **62**B) PCR analysis of immunoglobulin heavy (J_H) chain rearrangement in recipient (R), and donor (D) cells. Cell types analyzed include Mac1+ myeloid cells (M), Mac1+GR1+ granulocytes (G), and T-cells (T). Loading control; genomic PCR for CD45. (FIG. **62**C) Representative bone marrow stem and progenitor analysis of a recipient transplanted with 8-TFPoly transduced Pro/Pre B cells 18-weeks post-transplantation showing donor-reconstitution of myeloid progenitors (Myl Pro), megarkaryocyte/erythrocyte progenitors (MEP), granulocyte/monocyte progenitors (GMP), common myeloid progenitors (CMP), megakaryocyte progenitors (MkP), erythroid progenitors (EP), common lymphoid progenitors (CLP), Lineage-negative Sca1+ckit+ multipotent progenitors (LSK), multipotent progenitors (MPP1, MPP2), and hematopoietic stem cells (HSC). All cells were pre-gated through doublet-discriminated, live (propidium iodide negative), and lineage negative cells. (FIG. **62**D) Total donor reconstitution of the indicated populations in mice analyzed in (FIG. **62**A). (FIGS. **62**E-**62**F) Reconstitution of the indicated myeloid progenitor (E) and primitive multi-potent and stem cell (F) populations in mice analyzed in (A) presented as percentage of donor. (FIG. **62**G) PCR analysis of immunoglobulin heavy (JH) chain rearrangement in the indicated recipient and donor populations. Loading control; genomic PCR for CD45. (FIG. **62**H) Donor reconstitution of secondary recipient mice transplanted with whole bone marrow (WBM) or c-Kit positive bone marrow cells derived from primary transplants of 8-TF transduced Pro/Pre B cells analyzed at 12 and 8 weeks respectively. Number of recipients transplanted; WBM; n=5, c-Kit+; n=4. (FIG. **62**I) Reconstitution of indicated peripheral blood cell lineages of individual recipients presented as % of donor.

[0354] FIGS. **63**A-**63**H show transient expression of defined transcription factors in myeloid effector cells is sufficient instill them with progenitor activity in vitro, and long-term multi-lineage transplantation potential in vivo. (FIG. **63**A) Schematic representation of experimental strategy for assaying the colony forming potential of 8-TF transduced peripheral blood cells. (FIG. **63**B) Colony number and type arising in methylcellulose from peripheral blood cells from recipient (left-most lanes) or donor cells derived from a recipient transplanted with Pro/Pre B cells transduced with 8-TF or 8-TFPoly cocktail, plus (+) or minus (−) exposure to doxycycline. Results from individual mouse performed in triplicate are shown. (FIG. **63**C) Colony number and type arising in methylcellulose from plated granulocytes, macrophages/monocytes (Myl), B-cells, and T-cells purified from the peripheral blood of cells pooled recipients transplanted with Pro/Pre B cells transduced with 8-TF^{Poly} cocktail plus (+) or minus (−) exposure to doxycycline. (FIG. **63**D) Representative colony types and cytospins stained with May Grunwald of colonies derived in (FIG. **63**C). (FIG. **63**E) Donor reconstitution of mice transplanted with ZsGr, 6-TF-^{Poly}, 8-TF or 8-TF^{Poly} transduced Mac1+cKit− myeloid effector cells at indicated time points post-transplantation. Only mice with >1% donor chimerism were considered reconstituted. Recipients transplanted; ZsGr; n=6, 6-TF^{Poly}; n=7, 8-TF; n=6, and 8-TFPoly; n=8. (FIG. **63**F) Reconstitution of indicated peripheral blood cell lineages of mice showing >1% donor chimerism presented as % of donor. (FIG. **63**G) Donor reconstitution 12 weeks post-transplant of secondary recipient mice transplanted non-competitively with 5×10^6 donor-derived (CD45.2+) bone marrow cells derived from primary recipients of 6-TF^{Poly}, 8-TF or 8-TF^{Poly} transduced Mac1+ cKit− myeloid effector cells. Cells from individual primary donor mice (indicated by ID) were transplanted into N=5 secondary recipients each. (FIG. **63**H) Average reconstitution of indicated peripheral blood cell lineages presented as % of donor. N=5 recipients per group.

[0355] FIGS. **64**A-**64**D shows iHSCs reprogrammed via 8 transcription factors closely resemble endogenous HSCs at the molecular level. FIG. **64**A shows phenotypic HSCs (doublet discriminated, live, lineage negative, c-kit+, Sca1+, CD34−, flk2− and CD150+) were FACS sorted from the bone marrow of mice reconstituted with Pro/Pre B cells transduced with 8-TF (Mouse #1) and 8-TF POLY (Mouse #10) viral cocktails. Cells were single cell sorted into 96 well plates and analyzed by qPCR for an array of transcription factors. Expression levels of individual cells were projected onto a three-dimensional space using principle component analysis. Recipient HSCs (HSC Host) and iHSCs derived from Pro/Pre B cells transduced with 8-TF (iHSC 8-TF) or 8-TF Poly (iHSC 8-TF Poly) were displayed with previously profiled and phenotypically characterized progenitor cells: HSC, MPP, CMP, GMP, MEP and CLP. Additionally, Pro/Pre B Cells were added as a control cell type. FIGS. **64**B-C shows phenotypic HSCs isolated from bone marrow reconstituted from Pro/Pre B cells transduced with 8-TF (iHSC 8-TF) and 8-TF^{Poly} (iHSC 8-TF^{Poly}) were then hierarchically clustered with respect to the qPCR transcription factor array. Each leaf of the dendrogram represents a single cell as indicated in the legend in panel A. FIG. **64**D shows analysis of indicated genes are shown for: phenotypic control HSCs (HSC), transplanted host HSCs (HSC host), iHSCs derived from Pro/Pre B Cells transduced with 8-TF (iHSC 8-TF) and 8-TF POLY (iHSC 8-TFPoly) and control Pro/Pre B Cells. Heat maps for expression levels in the indicated cell types are shown (high expression was visualized as red; low expression was visualized as blue). Violin plots show distribution patterns of each of the above transcription factors in one cell type. Expression level is on the y-axis.

[0356] FIGS. **65**A-**65**B show a sorting strategy for Pro/Pre B cells (FIG. **65**A) and CMPs (FIG. **65**B) from the bone marrow of rtTA transgenic mice. Doublet discriminated and PI negative cells were pre-gated and Pro/Pre B Cells were gated as indicated: B220+ CD19+, AA4.1+ and IgM−. FIG. **65**B shows doublet discriminated and PI negative cells were pre-gated and CMPs were gated as indicated: Lineage negative (Gr1−, Mac1−, B220−, CD3−, CD4−, CD8−, Ter119−), c-kit+, Sca1−, Fc□R3MID, and CD34+.

[0357] FIG. **66** shows Pro/Pre B cells and CMPs were transduced with the viral cocktail of 36-TFs. Dox is added after 16 hours for a period of 48 hours before cells were transferred to methylcellulose. 20 days later colonies were counted and characterized by morphology as indicated in FIGS. **59**A-**59**G. Colonies were collected and DNA isolated. Identification of plasmid integration was performed as indicated in FIGS. **60**A-**60**G for each of the 36 factors listed. Expression of the factors was clustered by the highest expression in GEMMs.

[0358] FIG. **67** shows Mac1+ bone marrow cells were isolated from transgenic rtTA mice. Cells were transduced for 16 hours with RHL+PZP (6-TF POLY), Runx1t1+Hlf+Lmo2+Pbx1+Zfp37+Prdm5+Mycn+Meis1 (8-TF) and RHL+PZP+Mycn+Meis1 (8-TF POLY). Dox was added in culture for 24 hours and 5.0×10^6 cells were transplanted into conditioned hosts with 1×10^5 Scat depleted support cells. Peripheral blood analysis was performed at 6 weeks. Representative flow demonstrating CD45.1+ (donor) gating from peripheral bleeds at 16 weeks is shown for each group.

[0359] FIGS. **68**A-**68**D show Mac1+ bone marrow cells were FACS sorted, transduced with ZsGr control, 6-TF, 8-TF, or 8-TF POLY viruses. (FIG. **68**A) Transplantation was done as indicated and 18 weeks post transplantation bone marrow, spleen, thymus, and peripheral blood was harvested from mice with peripheral blood reconstitution >5.0%. Donor contributions are shown graphically in the peripheral blood (PB), bone marrow (BM), spleen and thymus for a 6-TF POLY mouse, 8-TF mouse and four 8-TF POLY mice. The y-axis break marks 1.0% donor reconstitution. FIG. **68**B shows the composition break down for donor-derived cells in the bone marrow, spleen, and thymus. B cells (B), Granulocytes (G), Myeloid (M) and T Cells (T) were phenotypically defined as previously described. FIG. **68**C shows the % donor of each of the progenitor compartments was calculated by gating as previously shown but last through donor. Quantitation of these results is shown for mice reconstituted from Mac1+ bone marrow cells transduced with 6-TF POLY (1 mouse), 8-TF (1 mouse) and 8-TF POLY (4 mice). A break indicates a 1.0% donor composition. FIG. **68**D shows compositional breakdown of the Hematopoietic progenitor compartment for each mouse reconstituted from Mac1+ bone marrow cells transduced with 6-TF POLY (1 mouse), 8-TF (1 mouse) and 8-TF POLY (4 mice). Populations were gated first by donor and then by previously defined phenotypic markers.

[0360] FIG. **69** shows phenotypic HSCs (doublet discriminated, live, lineage negative, c-kit+, Sca1+, CD34−, flk2− and CD150+) were FACS sorted from the bone marrow of mice reconstituted with Pro/Pre B cells transduced with 8-TF and 8-TF POLY viral cocktails. Cells were single cell sorted into 96 well plates and analyzed by qPCR for an array of transcription factors. A heat map displays transcription factor expression (columns) for indicated cell types (rows), including: previously profiled and phenotypically sorted progenitor control cell types (HSC, MPP, MEP, CMP, GMP, CLP), control Pro/Pre B cells, recipient derived HSCs (Host HSC), and iHSC cells isolated from mice reconstituted from Pro/Pre B Cells transduced with viral mixtures of 8-TF (iHSC 8-TF) and 8-TF POLY (iHSC 8-TF POLY). High expression was visualized as red; Low Expression was visualized as blue.

[0361] FIGS. **70**A-**70**H shows reprogramming terminally differentiated myeloid cells to engraftable HSC-like cells. (FIG. **70**A) Schematic for secondary reprogramming experiments. Peripheral blood post 16 weeks from mice reconstituted from ProPre B Cells transduced with viral mixes of 8-TFs were isolated. Peripheral blood cells, FACS sorted CD45.1+ (donor) or further purified on magnetic columns for B220+ (B Cells), Mac1+ (Myl), Gran (Mac1+ Gr1+) and T cells (CD3+). Cells were then plated into F12 media in the presence or absence of dox. Three days post dox administration, cells are transferred into methylcellulose. Colonies are counted and scored 20 days later. (FIG. **70**B) Mice reconstituted with ProPre B Cells transduced with the viral cocktail 8-TF or 8-TF POLY were bled at 16-20 weeks and CD45.1+ (donor) and CD45.2+ (Recipient) cells were FACS sorted (8-TF) or unsorted (8-TF POLY), plated into F12 media in the presence/absence of dox for 3 days, transferred into methylcellulose, and counted/scored on day 20. Quantitation of the colony number and composition is shown for cells in the presence and absence of dox. Each column represents one or three replicates per mouse. A representative GEMM colony and GM (Granulocyte-Myeloid) colony are shown to the right for donor sorted cells in the presence of dox. (FIG. **70**C) Mice reconstituted with ProPre B Cells transduced with 8-TF POLY were bled at 16 weeks and CD45.1+ (donor) and CD45.2+ (recipient) cells were pooled, further enriched using magnetic columns for B220+ (B Cells), Mac1+ (Myl), Mac1+ Gr1+ (Gran) and CD3+ (T Cells). Cell populations were plated into F12 media in the presence/absence of dox for 3 days, transferred to methylcellulose, and counted/scored on day 20. Quantitation of the colony number and composition is shown for cells in the presence and absence of dox. (FIG. **70**D) Representative 10× views of colonies [GEMM, GM, Granulocyte (G) and Myeloid (M)] derived from donor cells are shown. Cytospins were performed on each colony and shown to the right with prominent cell types labeled. (FIG. **70**E) Mac1+ bone marrow cells were isolated from transgenic rtTA mice. Cells were transduced for 16 hours with RHL+PZP (6-TF POLY), Runx1t1+Hlf+Lmo2+Pbx1+Zfp37+Prdm5+Mycn+Meis1 (8-TF) and RHL+PZP+Mycn+Meis1 (8-TF POLY). Dox was added in culture for 24 hours and 5.0×106 cells were transplanted into conditioned hosts with 1×10^5 Sca1 depleted support cells. Peripheral blood analysis was performed at 4, 8, 12 and 16 weeks; donor contributions are summarized in the graph. Each circle represents a mouse and the 1% donor chimerism mark is represented by an axis break. (FIG. **70**F) Composition of mice reconstituted over 1% are shown and broken into B cell, myeloid, granulocyte, and T cell as previously defined. (FIG. **70**G) Secondary transplantation was performed by euthanizing and harvesting bone marrow from primary mice with donor reconstitutions over 5%. Five million FACS sorted donor (CD45.2+) whole bone marrow cells were transplanted non-competitively into five recipient pre-conditioned mice. Peripheral blood chimerism at 16 weeks is shown for each secondary recipient (each circle). (FIG. **70**H) The average composition of the donor-derived cells in the secondary transplant was calculated and graphically represented for 16 week bleed data.

[0362] FIGS. **71**A-**71**B show donor-derived bone marrow, originating from transformed Pro/Pre B-Cells, was isolated from two primary reconstituting animals and one secondary animal. B220+ (B-Cells), CD3+ (T-Cells), Mac1+Gr1− (Myeloid) and Mac1+Gr1+ (Gran) cells were FACS sorted. VDJ analysis was performed on each of the lineages, similar size bands were selected and individual VDJ amplicons were sequenced to obtain information on individual recombination events in each of the lineages. Sequence data is show for each of the indicated donors/cell types. Using IgBlast (http://www.ncbi.nlm.nih.gov/igblast/) VDJ recombinational events were identified (VDJ ID) and listed according to the VH, DH or JH segment to which the sequence corresponds. (FIG. **71**A) Sequences for Donor 1°-1 are disclosed as SEQ ID NOS 168-169, 168-169, 176, 176, 176, 176, 181, 181, 181 and 181 read from columns left to right. Sequences for Donor 1°-8 are disclosed as SEQ ID NOS 170, 170, 170, 170, 177, 177, 177, 177, 182, 182, 182 and 182 read from columns left to right. (FIG. **71**B) Sequences for Donor 2°-1 are disclosed as SEQ ID NOS 168, 168, 168, 171-175, 176, 176, 176, 178-180, 180, 183, 183, 183-185, 185-186 and 186 read from columns left to right.

[0363] FIGS. **72**A-**72**C Donor-derived MEP cells (Live, Lin−, c-kit+, Sca1−, CD34−, FcgR3−) were FACS sorted from the bone marrow of a primary recipient reconstituted from a transformed Pro/Pre B-Cell (Mouse ID 6). MEP cells were transplanted into three irradiated recipients (50,000 cells/recipient). Controls were irradiated but not transplanted. (FIG. **72**A) The survival of these mice is indicated graphically over time post transplant. At day 20 post transplant the peripheral blood of the remaining mice was tested for red blood cell counts (RBC Counts, FIG. **72**B) and platelet numbers (Platelet Counts, FIG. **72**C).

DETAILED DESCRIPTION

[0364] Provided herein are compositions, nucleic acid constructs, methods and kits thereof for hematopoietic stem cell induction or reprogramming cells to the hematopoietic stem cell multipotent state, based, in part, on the discoveries described herein of novel combinations of transcription factors that permit dedifferentiation and reprogramming of more differentiated cells the hematopoietic stem cell state. Such compositions, nucleic acid constructs, methods and kits can be used for inducing hematopoietic stem cells in vitro, ex vivo, or in vivo, and these induced hematopoietic stem cell can be used in regenerative medicine applications.

[0365] Hematopoietic stem cells (HSCs) are among the best-characterized and most experimentally tractable tissue-specific stem cells. HSCs reside at the top of hematopoietic hierarchy and give rise to a large repertoire of highly specialized effector cells by differentiating through a succession of increasingly committed downstream progenitor cells (FIG. **1**). HSCs are the only cells in the hematopoietic system that possess the ability to both differentiate to all blood lineages and to self-renew for life. These properties, along with the ability of HSCs to engraft conditioned recipients upon intravenous transplantation, have established the clinical paradigm for stem cell use in regenerative medicine. Allogeneic and autologous HSC transplantation are routinely used in the treatment of patients with a variety of life-threatening disorders. Despite wide clinical use, HSC transplantation remains a high-risk procedure, with the number of stem cells available for transplantation being the strongest predictor of transplantation success. Although stem cell mobilization with G-CSF alone, or in combination with other drugs, increases the yield of hematopoietic stem cells for transplantation, an ability to induce, expand, or generate patient-specific HSCs de novo, as described herein, could be useful in a number of clinical settings, or be used to model hematopoietic diseases ex vivo or in xenotransplantation models.

[0366] The developmental process by which differentiated cell types arise from more primitive progenitor cells is guided in part by progressive epigenetic changes. In general, lineage specification is unidirectional and irreversible with differentiated cell types, and even intermediate progenitors, being remarkably fixed with respect to their cellular identity and developmental potential. Studies by Gurdon and others have demonstrated that the process of differentiation can be reversed in experiments that showed that the nuclei of differentiated cell types could be reprogrammed to totipotency when exposed to the primitive cellular milieu of enucleated oocytes. This process, known as "somatic cell nuclear transfer," was subsequently shown to be capable of reprogramming nuclei from differentiated mammalian cells back to pluripotency. That ectopic expression of defined transcription factors was sufficient to convert cell fate was first shown in 1987 with the demonstration that enforced expression of MyoD could reprogram fibroblasts to the myogenic lineage. Enormous progress in this field has been made over the past

40 years culminating with the striking demonstration by Yamanaka and colleagues that ectopic expression of four transcription factors (c-Myc, Oct4, Klf4, Sox2, the so-called "Yamanaka factors") also described in e.g., U.S. Pat. No. 7,964,401; U.S. Pat. No. 8,048,999; U.S. Pat. No. 8,058,065; U.S. Pat. No. 8,129,187; U.S. Pat. No. 8,211,697, can reprogram adult fibroblasts from mice and man into cells, termed iPS (induced pluripotent stem) cells, that possess the developmental potential of embryonic stem (ES) cells. These discoveries opened the possibility of generating patient-specific pluripotent cells from abundant somatic cells that could be used to model disease, or for autologous cell replacement therapies.

[0367] However, these factors do not replicate this process if the starting cell is a cell from hematopoietic lineage.

[0368] Despite their enormous promise, significant hurdles must be overcome before iPS-based cell therapies enter the clinic. It must also be recognized that iPS cells cannot be directly used clinically, since—as is the case with ES cells—useful cell types must first be generated by directed differentiation.

[0369] Thus, alternative approaches, in which abundant cell types are directly reprogrammed to alternative fates without first returning to a pluripotent state, as described herein for making induced HSCs, can be a more direct and efficient way to generate clinically useful cell types. For example, a recent report using OCT4 in combination with hematopoietic cytokines also showed that it was possible to generate myeloid lineage hematopoietic cells (though not HSCs) from human fibroblasts.

[0370] Differentiation of HSCs to fully differentiated blood cells is believed to be an irreversible process under normal physiological conditions. Hematopoietic lineage specification takes place within the bounds of strict lineal relationships: for example, megakaryocyte progenitors give rise to megakaryocytes and ultimately platelets, but not to any other blood lineages. Some studies, however, have demonstrated that hematopoietic cells are amenable to reprogramming to alternative fates under experimental manipulation.

[0371] Within the hematopoietic system, the most clinically useful cell type to strive to generate by reprogramming are HSCs, as they are the only cells which possess the potential to generate all blood cell types over a lifetime, and transplantation protocols for their clinical use are already established. To date, no reports describing the generation of HSCs by reprogramming have been published because the factor(s) needed to reprogram to HSCs have not yet been determined. This point is central to the experimental rationale and strategies described herein, which were designed to first identify and clone transcriptional activators important for specifying HSC fate and function, and then utilize such factors to reprogram committed blood cells back to an induced HSC fate (FIG. **2**), as demonstrated herein.

[0372] Hematopoietic tissues contain cells with long-term and short-term regeneration capacities, and committed multipotent, oligopotent, and unipotent progenitors. Endogenous HSCs can be can be found in a variety of tissue sources, such as the bone marrow of adults, which includes femurs, hip, ribs, sternum, and other bones, as well as umbilical cord blood and placenta, and mobilized peripheral blood. Endogenous HSCs can be obtained directly by removal from, for example, the hip, using a needle and syringe, or from the blood following pre-treatment with cytokines, such as G-CSF (granulocyte colony-stimulating factors), that induce cells to be released from the bone marrow compartment. However, such methods yield varying amounts of HSCs, which are oftentimes not enough for use in treatment options.

[0373] Accordingly, "hematopoietic stem cells," or "HSCs," as the terms are used herein, encompass all multipotent cells capable of differentiating into all the blood or immune cell types of the hematopoietic system, including, but not limited to, myeloid cells (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells, NKT-cells, NK-cells), and which have multi-lineage hematopoietic differentiation potential and sustained self-renewal activity.

[0374] The term "stem cells," as used herein, refer to cells that retain the ability to renew themselves through mitotic cell division and can differentiate into a diverse range of specialized cell types. The two broad types of mammalian stem cells are: embryonic stem (ES) cells that are found in blastocysts, and adult stem cells that are found in adult tissues. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells, but also maintain the normal turnover of regenerative organs, such as blood, skin or intestinal tissues. Pluripotent stem cells can differentiate into cells derived from any of the three germ layers.

[0375] Stem cells are generally classified by their developmental potential as: (1) "totipotent," meaning able to give rise to all embryonic and extraembryonic cell types; (2) "pluripotent," meaning able to give rise to all embryonic cell types; (3) "multipotent," meaning able to give rise to a subset of cell lineages, but all within a particular tissue, organ, or physiological system (for example, hematopoietic stem cells (HSCs) can produce progeny that include HSCs (self-renewal), blood cell restricted oligopotent progenitors and the cell types and elements (e.g., platelets) that are normal components of the blood); (4) "oligopotent," meaning able to give rise to a more restricted subset of cell lineages than multipotent stem cells; and (5) "unipotent," meaning able to give rise to a single cell lineage (e.g., spermatogenic stem cells).

[0376] "Self-renewal" refers to the ability of a cell to divide and generate at least one daughter cell with the identical (e.g., self-renewing) characteristics of the parent cell. The second daughter cell may commit to a particular differentiation pathway. For example, a self-renewing hematopoietic stem cell divides and forms one daughter stem cell and another daughter cell committed to differentiation in the myeloid or lymphoid pathway. In contrast, a committed progenitor cell has typically lost the self-renewal capacity, and upon cell division produces two daughter cells that display a more differentiated (i.e., restricted) phenotype. True hematopoietic stem cells have the ability to regenerate long term multi-lineage hematopoiesis (e.g., "long-term engraftment") in individuals receiving a bone marrow or umbilical cord blood transplant, as described herein.

[0377] Hematopoietic stem cells are traditionally identified as being lineage marker negative, Sca1-positive, cKit-positive (or LSK cells), CD34-negative, Flk2-negative, CD48-negative, and CD150 positive. HSCs give rise to "multipotent progenitor cells" or "hematopoietic progenitor cells," which, as the terms are used herein, refer to a more differentiated subset of multipotent stem cells that while committed to the hematopoietic cell lineage generally do not self-renew. The terms "hematopoietic progenitor cells" or "multi-potent progenitor cells" (MPPs) encompass short term hematopoietic stem cells (also known as ST-HSCs, which are lineage marker negative, Sca1-positive, cKit-positive, CD34-positive, and Flk2-negative); common myeloid progenitor cells (CMPs); lymphoid-primed progenitor cells (LMPPs), granulocyte-monocyte progenitor cells (GMPs), and megakaryocyte-erythrocyte progenitor cells (MEPs). Hematopoietic stem cells subsets are sometimes also identified and discriminated on the basis of additional cell-surface marker phenotypes, such as by using combinations of members of the SLAM family, or the "SLAM phenotype," such as, long-term multi-lineage repopulating and self-renewing hematopoietic stem cells (HSCs): CD150^{+}CD48^{-}CD244^{-}; MPPs: CD150^{-}CD48^{-}CD244^{+}; lineage-restricted progenitor cells (LRPs): CD150^{-}CD48^{+}CD244^{+}; common myeloid progenitor cells (CMP): lin^{-}SCA-1^{-}c-kit^{+}CD34^{+}CD16/32^{mid}; granulocyte-macrophage progenitor (GMP): lin^{-}SCA-1^{-}c-kit^{+}CD34^{+} CD16/32^{hi}; and megakaryocyte-erythroid progenitor (MEP): lin^{-}SCA-1^{-}c-kit^{+}CD34^{+}CD16/32^{low}.

[0378] Accordingly, using the compositions, constructs, methods, and kits comprising the HSC reprogramming factors or HSC inducing factors described herein, induced hematopoietic stem cells or iHSCs can be generated that are multipotent and capable of differentiating into all the blood or immune cell types of the hematopoietic system, including, but not limited to, myeloid cells (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells, NKT-cells, NK-cells), and which have multi-lineage hematopoietic differentiation potential and sustained self-renewal activity. In some embodiments of the compositions, constructs, methods, and kits comprising the HSC reprogramming factors or HSC inducing factors described herein, cells are dedifferentiated into one or more other hematopoietic progenitor cells types, such as short term hematopoietic stem cells, common myeloid progenitor cells, common lymphoid progenitor cells, lymphoid-primed progenitor cells, granulocyte-monocyte progenitor cells, and megakaryocyte-erythrocyte progenitor cells.

[0379] The successful identification of HSC inducing factors capable of reprogramming committed blood cells to induced HSCs, as described herein, can advance our basic understanding of HSC biology in a number of ways. Despite the fact that HSCs are the most well characterized tissue-specific stem cells, surprisingly little is known about the molecular mechanisms involved in regulating their central properties of self-renewal and multi-potency. Identification of factors capable of imparting self-renewal and multi-lineage potential onto otherwise non-self-renewing, lineage-restricted cells, as described herein, provide important insights into the molecular basis of these fundamental attributes and provide strategies on how best to therapeutically manipulate HSCs. Further, mature blood cell production is an ongoing process requiring profound homeostatic control mechanisms—the primary level of which resides with HSCs. Since hematopoietic malignancies arise through deregulation of homeostatic control mechanisms, identification of regulators responsible for specifying HSC function, such as the HSC inducing factors described herein, can also provide important insights into how homeostasis is regulated by stem cells, and in turn, how deregulation of such processes manifest in disease. Functional conservation of reprogramming factors between species is well-documented indicating that it the methods and compositions described herein are applicable for reprogramming human blood cells to induced HSCs, using homologues of the murine reprogramming factors described herein. The ability to derive functional human induced HSCs in such a manner represents a new experimental paradigm for deriving these important cells that can be translated clinically, or used to model hematopoietic diseases. Because one mechanism in which lineage specification has been shown to occur is by the active suppression of alternative fates, by identifying factors involved in re-establishing core HSC properties, factors that function by suppressing differentiation programs can also be identified. If so, identification of such factors could provide fundamental insights into hematopoietic lineage specification. Transcription factors play a critical role in the specification of all cell types during development. The success of reprogramming strategies using transcription factor-mediated de-differentiation of cells indicates that it is equally plausible to direct the differentiation of pluripotent ES/iPS cells to specific fates using such factors. Accordingly, using the HSC inducing factors identified herein, directed differentiation of ES/iPS cells to a definitive HSC fate by expression of the HSC-enriched transcription factors can be achieved.

[0380] The combinatorial introduction of HSC-enriched TFs into downstream progenitors and screening for the introduction of stem cell properties onto these committed cells in vivo has identified a core set of TFs, referred to herein as "HSC inducing factors" or "HSC reprogramming factors" able to mediate the reprogramming of committed cells back to an induced hematopoietic stem cell (iHSC) state. With the approaches described herein, advantage can be taken of the fact that HSCs are the only cells in the hematopoietic system capable of giving rise to long-term (>4 months) multi-lineage reconstitution in transplantation assays, whereas committed progenitors reconstitute recipient mice only transiently with restricted lineage potential depending upon their stage of differentiation. Only progenitors that have been successfully reprogrammed to an induced hematopoietic stem cell state are able to give rise to long-term multi-lineage reconstitution in transplant recipients, using the compositions, methods, and kits described herein.

[0381] To realize the goal of identifying transcription factors specifically expressed in HSCs within the hematopoietic system, a comprehensive system-wide approach was undertaken in which expression profiles of 40 FACS purified hematopoietic cell types, representing the vast majority of hematopoietic stem, progenitor and effector cells, were generated and compiled (FIG. **1**). Since the success of the results described herein require a detailed knowledge of the molecular attributes of HSCs, the focus has been on defining these by expression profiling of purified HSCs from diverse settings ranging from steady state hematopoiesis through different stages of ontogeny (fetal development through to old age). Throughout the work described herein, HSCs are fluorescence activated cell sorted (FACS) purified by stringent cell surface phenotype, and defined through functional criteria (FIGS. **1**-**2**). In total, 46 expression profiles for HSCs were generated, which lends enormous statistical power to the analyses described herein. In total, 248 expression profiles of hematopoietic populations have been generated and normalized into a single database (referred to as the "hematopoietic expression database") (FIG. **3**).

[0382] Using the databases described herein, transcriptional factors (TFs) with HSC-enriched expression have been identified. In some embodiments of the aspects described herein, in addition to the factors with strict HSC-enriched expression, TFs involved in specifying hematopoietic fate during fetal development such as SCL/TAL1, RUNX1, HOXB4, and LMO2, can be used as HSC inducing factors, even though they do not exhibit particularly HSC-specific expression in the adult. In total, as described herein, over 40 TFs that can be used in various combinations as "HSC inducing factors," as the term is used herein, have been identified and the expression profiles of each have been confirmed by qRT-PCR.

[0383] The production of cells having an increased developmental potential (e.g., iHSCs) is generally achieved by the introduction of nucleic acid sequences encoding genes identified herein as "HSC inducing factors" into an adult, somatic cell, preferably, in some embodiments, a more differentiated cell of the hematopoietic lineage. Typically, nucleic acids encoding the HSC inducing factors, e.g., DNA or RNA, or constructs thereof, are introduced into a cell, using viral vectors or without viral vectors, via one or repeated transfections, and the expression of the gene products and/or translation of the RNA molecules result in cells that are morphologically, biochemically, and functionally similar to HSCs, as described herein. As used herein, "reprogramming" refers to a process of driving a cell to a state with higher developmental potential, i.e., backwards, to a less differentiated state. In some embodiments of the compositions, methods, and kits described herein, reprogramming encompasses a complete or partial reversion of the differentiation state to that of a cell having a multipotent state. In some embodiments of the compositions, methods, and kits described herein, reprogramming encompasses a complete or partial reversion of the differentiation state to that of a cell having the state of a hematopoietic progenitor cell, such as a CMP, a CLP, etc. The hematopoietic stem cells induced by the compositions, methods, and kits described herein are termed herein as "induced hematopoietic stem cells," "iHS cells," or "iHSCs." Compositions comprising amino acid or nucleic acid sequences or expression vectors thereof encoding these HSC inducing factors are referred to herein as "HSC inducing compositions."

[0384] As demonstrated herein, over 40 transcription factors were identified that can be introduced into a cell in various combinations as "HSC inducing factors" to generate induced hematopoietic stem cells or iHSCs that are multipotent and capable of differentiating into all or a majority the blood or immune cell types of the hematopoietic system, including, but not limited to, myeloid cells (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells, NKT-cells, NK-cells), and which have multi-lineage hematopoietic differentiation potential and sustained self-renewal activity. Thus, provided herein, in some aspects, are HSC inducing factors and combinations thereof comprising the genes listed in Table 1, which also provides exemplary sequences for making the identified proteins:

TABLE 1

HSC Inducing Factors

GENE NAME	Human mRNA REF SEQ	SEQ ID NOs:	Murine mRNA REF SEQ	SEQ ID NOs:
CDKN1C	NM_000076.2	SEQ ID NO: 1	NM_001161624.1	SEQ ID NO: 47
DNMT3B	NM_001207055.1	SEQ ID NO: 2	NM_001003960.4	SEQ ID NO: 48
EGR1	NM_001964.2	SEQ ID NO: 3	NM_133659.2	SEQ ID NO: 49
ETV6	NM_001987.4	SEQ ID NO: 4	NM_007961.3	SEQ ID NO: 50
EVI1	NM_001105078.3	SEQ ID NO: 5	NM_007963.2	SEQ ID NO: 51
GATA2	NM_032638.4	SEQ ID NO: 6	NM_008090.5	SEQ ID NO: 52
GFI1B	NM_001135031.1	SEQ ID NO: 7	NM_001160406.1	SEQ ID NO: 53
GLIS2	NM_032575.2	SEQ ID NO: 8	NM_031184.3	SEQ ID NO: 54
HLF	NM_002126.4	SEQ ID NO: 9	NM_172563.3	SEQ ID NO: 55
HMGA2	NM_003483.4	SEQ ID NO: 10	NM_010441.2	SEQ ID NO: 56
HOXA5	NM_019102.3	SEQ ID NO: 11	NM_010453.5	SEQ ID NO: 57
HOXA9	NM_152739.3	SEQ ID NO: 12	NM_010456.2	SEQ ID NO: 58
HOXB3	NM_002146.4	SEQ ID NO: 13	NM_001079869.1	SEQ ID NO: 59
HOXB4	NM_024015.4	SEQ ID NO: 14	NM_010459.7	SEQ ID NO: 60
HOXB5	NM_002147.3	SEQ ID NO: 15	NM_008268.2	SEQ ID NO: 61
IGF2BP2	NM_001007225.1	SEQ ID NO: 16	NM_183029.2	SEQ ID NO: 62
IKZF2	NM_001079526.1	SEQ ID NO: 17	NM_011770.4	SEQ ID NO: 63
KLF12	NM_007249.4	SEQ ID NO: 18	NM_010636.3	SEQ ID NO: 64
KLF4	NM_004235.4	SEQ ID NO: 19	NM_010637.3	SEQ ID NO: 65
KLF9	NM_001206.2	SEQ ID NO: 20	NM_010638.4	SEQ ID NO: 66
LMO2	NM_005574.3	SEQ ID NO: 21	NM_001142336.1	SEQ ID NO: 67
MEIS1	NM_002398.2	SEQ ID NO: 22	NM_00193271.1	SEQ ID NO: 68
MSI2	NM_138962.2	SEQ ID NO: 23	NM_054043.3	SEQ ID NO: 69
MYCN	NM_005378.4	SEQ ID NO: 24	NM_008709	SEQ ID NO: 70
NAP1L3	NM_004538.5	SEQ ID NO: 25	NM_138742.1	SEQ ID NO: 71
NDN	NM_004538.5	SEQ ID NO: 26	NM_010882.3	SEQ ID NO: 72
NFIX	NM_001271044.1	SEQ ID NO: 27	NM_001081981.1	SEQ ID NO: 73
NKX2-3	NM_145285.2	SEQ ID NO: 28	NM_008699.2	SEQ ID NO: 74
NR3C2	NM_000901.4	SEQ ID NO: 29	NM_001083906.1	SEQ ID NO: 75
PBX1	NM_001204961.1	SEQ ID NO: 30	NM_008783.2	SEQ ID NO: 76
PRDM16	NM_199454.2	SEQ ID NO: 31	NM_001177995.1	SEQ ID NO: 77
PRDM5	NM_018699.2	SEQ ID NO: 32	NM_027547.2	SEQ ID NO: 78
RARB	NM_000965.3	SEQ ID NO: 33	NM_011243.1	SEQ ID NO: 79
RBBP6	NM_006910.4	SEQ ID NO: 34	NM_011247.2	SEQ ID NO: 80
RBPMS	NM_001008712.1	SEQ ID NO: 35	NM_019733.2	SEQ ID NO: 81
RUNX1	NM_001001890.2	SEQ ID NO: 36	NM_001111021.1	SEQ ID NO: 82
RUNX1T1	NM_001198625.1	SEQ ID NO: 37	NM_009822.2	SEQ ID NO: 83

TABLE 1-continued

HSC Inducing Factors				
GENE NAME	Human mRNA REF SEQ	SEQ ID NOs:	Murine mRNA REF SEQ	SEQ ID NOs:
SMAD6	NM_001142861.2	SEQ ID NO: 38	NM_008542.3	SEQ ID NO: 84
TAL1	NM_003189.2	SEQ ID NO: 39	NM_011527.2	SEQ ID NO: 85
TCF15	NM_004609.3	SEQ ID NO: 40	NM_009328.2	SEQ ID NO: 86
VDR	NM_000376.2	SEQ ID NO: 41	NM_009504.4	SEQ ID NO: 87
ZFP37	NM_003408.1	SEQ ID NO: 42	NM_009554.3	SEQ ID NO: 88
ZFP467	NM_207336.1	SEQ ID NO: 43	NM_001085415.1	SEQ ID NO: 89
ZFP521	NM_015461.2	SEQ ID NO: 44	NM_145492.4	SEQ ID NO: 90
ZFP532	NM_018181.4	SEQ ID NO: 45	NM_207255.2	SEQ ID NO: 91
ZFP612	NM_145911.1	SEQ ID NO: 46	NM_175480.4	SEQ ID NO: 92

[0385] In some embodiments, polypeptide variants or family members having the same or a similar activity as the reference polypeptide encoded by the sequences provided in Table 1 can be used in the compositions, methods, and kits described herein. Generally, variants of a particular polypeptide encoding a HSC inducing factor for use in the compositions, methods, and kits described herein will have at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% or more sequence identity to that particular reference polynucleotide or polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art.

[0386] Accordingly, in some embodiments, the HSC inducing factors for use in the compositions, methods, and kits described herein, are selected from the group consisting of: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612 (SEQ ID NOs: 1-46).

[0387] As demonstrated herein, for example at FIG. **11**, exposure to 18 transcription factors from the genes listed in Table 1 provided MPP cells with robust long-term, multilineage engraftment properties, characteristic of HSCs, in vivo. Accordingly, in some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from: HLF, MYCN, MEIS1, IRF6, CDKN1C, NFIX, DNMT3B, ZFP612, PRDM5, HOXB4, LMO2, NKX2-3, RARB, NDN, NAP1L3, RUNX1T1, ZFP467, and ZFP532. Another grouping is a core 6 factors (Runx1t1, HLF, PRDM5, PBX1, LMO2, and ZFP37), and 8 factors (the 6 factors plus MEIS1, MYCN).

[0388] As demonstrated herein, for example at FIGS. **13**A-**13**B, exposure to 17 transcription factors from the genes listed in Table 1 provided MPP cells with robust long-term, multi-lineage engraftment properties, characteristic of HSCs, in vivo. Accordingly, in some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from: HLF, MYCN, MEIS1, IRF6, NFIX, DNMT3B, ZFP612, PRDM5, HOXB4, LMO2, NKX2-3, RARB, NDN, NAP1L3, RUNX1T1, ZFP467, and ZFP532.

[0389] As demonstrated herein, for example at FIG. **12**, exposure to 9 transcription factors from the genes listed in Table 1 provided MPP cells with robust long-term, multilineage engraftment properties, characteristic of HSCs, in vivo. Accordingly, in some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from: EVI-1, GLIS2, HOXB5, HOXA9, HLF, MEIS1, MYCN, PRDM16, and RUNX1.

[0390] As demonstrated herein, for example at FIG. **14**, exposure to 8 transcription factors from the genes listed in Table 1 provided MPP cells with robust long-term, multilineage engraftment properties, characteristic of HSCs, in vivo. In some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from: RUNX1T1, HLF, ZFP467, RBPMS, HOXB5, NAP1L3, MSI2, and IRF6.

[0391] In some embodiments of the aspects described herein, the HSC inducing factors for use with the compositions, methods, and kits comprise, consist essentially of, or consist of HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS. As demonstrated herein, the use of these 11 HSC inducing factors together, also referred to herein as "Combination 7" or "C7," resulted in increased colony formation, altered lineage potential, and multi-lineage reconstitution in vivo, from CMP cells or ProPreB cells. In addition, this combination was shown to have serial long-term transplantation potential in vivo. Accordingly, in some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0392] In some embodiments of the aspects described herein, the HSC inducing factors for use with the compositions, methods, and kits comprise, consist essentially of, or consist of HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5. As demonstrated herein, the use of these 6 HSC inducing factors together, also referred herein as "Combination 6" or "C6," was able to reprogram ProPreB or CMP cells into cells capable of giving rise to multi-lineage reconstitution in vivo. Accordingly, in some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from HLF, ZFP37, RUNX1T1, PBX1, LMO2, and PRDM5. In some embodiments, the compositions, methods, and kits described herein can further comprise one or more of the HSC inducing factors PRDM16, ZFP467, and VDR.

[0393] In some embodiments of the aspects described herein, the HSC inducing factors for use with the compositions, methods, and kits comprise, consist essentially of, or consist of ZFP467, PBX1, HOXB4, and MSI2. As demonstrated herein, the use of these HSC inducing factors together, also referred herein as "Combination 1" or "C1," was able to reprogram ProPreB cells to myeloid cells. Accordingly, in some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from ZFP467, PBX1, HOXB4, and MSI2. In some embodiments, the compositions, methods, and kits described herein can further comprise one or more of the HSC inducing factors HLF, LMO2, PRDM16, and ZFP37.

[0394] In some embodiments of the aspects described herein, the HSC inducing factors for use with the compositions, methods, and kits comprise, consist essentially of, or consist of MYCN, MSI2, NKX2-3, and RUNX1T1. As demonstrated herein, the use of these HSC inducing factors together, also referred herein as "Combination 2" or "C2," was able to reprogram ProPreB cells to iHSCs. Accordingly, in some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from MYCN, MSI2, NKX2-3, and RUNX1T1. In some embodiments, the compositions, methods, and kits described herein can further comprise one or more of the HSC inducing factors HOBX5, HLF, ZFP467, HOXB3, LMO2, PBX1, ZFP37, and ZFP521.

[0395] In some embodiments of the aspects described herein, the HSC inducing factors for use with the compositions, methods, and kits comprise, consist essentially of, or consist of HOXB4, PBX1, LMO2, ZFP612, and ZFP521. As demonstrated herein, the use of these HSC inducing factors together, also referred herein as "Combination 3" or "C3," was able to promote the proliferation and survival of ProPreB cells. Accordingly, in some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from HOXB4, PBX1, LMO2, ZFP612, and ZFP521. In some embodiments, the compositions, methods, and kits described herein can further comprise one or more of the HSC inducing factors KLF12, HLF, and EGR1.

[0396] In some embodiments of the aspects described herein, the HSC inducing factors for use with the compositions, methods, and kits comprise, consist essentially of, or consist of MEIS1, RBPMS, ZFP37, RUNX1T1, and LMO2. As demonstrated herein, the use of these HSC inducing factors together, also referred herein as "Combination 4" or "C4," was able to reprogram CMP cells to iHSCs. Accordingly, in some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from MEIS1, RBPMS, ZFP37, RUNX1T1, and LMO2. In some embodiments, the compositions, methods, and kits described herein can further comprise one or more of the HSC inducing factors KLF12 and HLF.

[0397] In some embodiments of the aspects described herein, the HSC inducing factors for use with the compositions, methods, and kits comprise, consist essentially of, or consist of ZFP37, HOXB4, LMO2, and HLF. As demonstrated herein, the use of these HSC inducing factors together, also referred herein as "Combination 5" or "C5," was able to reprogram the fates of CMP and ProPreB cells. Accordingly, in some embodiments of the compositions, methods, and kits described herein, the HSC inducing factors are selected from ZFP37, HOXB4, LMO2, and HLF. In some embodiments, the compositions, methods, and kits described herein can further comprise one or more of the HSC inducing factors MYCN, ZFP467, NKX2-3, PBX1, and KLF12ZFP37.

[0398] In some embodiments of the compositions, methods, and kids provided herein, the number of HSC inducing factors used or selected to generate iHSCs from a starting somatic cell, such as a fibroblast cell or hematopoietic lineage cell, is at least three. In some embodiments, the number of HSC inducing factors used or selected is at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, at least fifteen, at least sixteen, at least seventeen, at least eighteen, at least nineteen, at least twenty, or more.

[0399] Also provided herein, in various aspects of the compositions, methods, and kits, are isolated amino acid sequences, and isolated DNA or RNA nucleic acid sequences encoding one or more HSC inducing factors for use in making iHSCS.

[0400] In some embodiments of the compositions, methods, and kits described herein, the nucleic acid sequence or construct encoding the HSC inducing factor(s), such as HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS, is inserted or operably linked into a suitable expression vector for transfection of cells using standard molecular biology techniques. As used herein, a "vector" refers to a nucleic acid molecule, such as a dsDNA molecule that provides a useful biological or biochemical property to an inserted nucleotide sequence, such as the nucleic acid constructs or replacement cassettes described herein. Examples include plasmids, phages, autonomously replicating sequences (ARS), centromeres, and other sequences that are able to replicate or be replicated in vitro or in a host cell, or to convey a desired nucleic acid segment to a desired location within a host cell. A vector can have one or more restriction endonuclease recognition sites (whether type I, II or IIs) at which the sequences can be cut in a determinable fashion without loss of an essential biological function of the vector, and into which a nucleic acid fragment can be spliced or inserted in order to bring about its replication and cloning. Vectors can also comprise one or more recombination sites that permit exchange of nucleic acid sequences between two nucleic acid molecules. Vectors can further provide primer sites, e.g., for PCR, transcriptional and/or translational initiation and/or regulation sites, recombination signals, replicons, additional selectable markers, etc. A vector can further comprise one or more selectable markers suitable for use in the identification of cells transformed with the vector.

[0401] Accordingly, in some aspects, provided herein are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors encoding at least one, two, three, four, five, six, seven, eight or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612.

[0402] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0403] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5.

[0404] Also provided herein in some aspects are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising: a nucleic acid sequence encoding HLF; a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5.

[0405] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of: a nucleic acid sequence encoding PRDM16; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding VDR.

[0406] Also provided herein in some aspects are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising: a nucleic acid sequence encoding HLF; a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM5; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding MEIS1; and a nucleic acid sequence encoding RBPMS.

[0407] In some aspects, provided herein are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising: a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding HOXB4; and a nucleic acid sequence encoding MSI2.

[0408] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of: a nucleic acid sequence encoding HLF; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM16; and a nucleic acid sequence encoding ZFP37.

[0409] Also provided herein in some aspects are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising: a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2; a nucleic acid sequence encoding NKX2-3; and a nucleic acid sequence encoding RUNX1T1.

[0410] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises a nucleic acid sequence encoding HOXB5; a nucleic acid sequence encoding HLF; a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding HOXB3; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding ZFP37; and a nucleic acid sequence encoding ZFP521.

[0411] In other aspects, provided herein are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors composition comprising: a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding ZFP521.

[0412] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of: a nucleic acid sequence encoding KLF12; a nucleic acid sequence encoding HLF; and a nucleic acid sequence encoding EGR1.

[0413] Also provided herein in some aspects are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising: a nucleic acid sequence encoding MEIS1; a nucleic acid sequence encoding RBPMS; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding RUNX1T1; and a nucleic acid sequence encoding LMO2.

[0414] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of a sequence encoding KLF12; and a sequence encoding HLF.

[0415] Also provided herein in some aspects are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising: a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding HLF.

[0416] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of: a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding PBX1; and a nucleic acid sequence encoding KLF4.

[0417] In some embodiments of the compositions, methods, and kits described herein, the expression vector is a viral vector. Some viral-mediated expression methods employ retrovirus, adenovirus, lentivirus, herpes virus, pox virus, and adeno-associated virus (AAV) vectors, and such expression methods have been used in gene delivery and are well known in the art.

[0418] In some embodiments of the compositions, methods, and kits described herein, the viral vector is a retrovirus. Retroviruses provide a convenient platform for gene delivery. A selected gene can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to target cells of the subject either in vivo or ex vivo. A number of retroviral systems have been described. See, e.g., U.S. Pat. No. 5,219,740; Miller and Rosman (1989) BioTechniques 7:980-90; Miller, A. D. (1990) Human Gene Therapy 1:5-14; Scarpa et al. (1991) Virology 180:849-52; Burns et al. (1993) Proc. Natl. Acad. Sci. USA 90:8033-37; Boris-Lawrie and Temin (1993) Curr. Opin. Genet. Develop. 3:102-09. In some embodiments of the compositions, methods, and kits described herein, the retrovirus is replication deficient. Retroviral vector systems exploit the fact that a minimal vector containing the 5' and 3' LTRs and the packaging signal are sufficient to allow vector packaging, infection and integration into target cells, provided that the viral structural proteins are supplied in trans in the packaging cell line. Fundamental advantages of retroviral vectors for gene transfer include efficient infection and gene expression in most cell types, precise single copy vector integration into target cell chromosomal DNA and ease of manipulation of the retroviral genome.

[0419] In some embodiments of the compositions, methods, and kits described herein, the viral vector is an adenovirus-based expression vector. Unlike retroviruses, which integrate into the host genome, adenoviruses persist extrachromosomally, thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) J. Virol. 57:267-74; Bett et al. (1993) J. Virol. 67:5911-21; Mittereder et al. (1994) Human Gene Therapy 5:717-29; Seth et al. (1994) J. Virol. 68:933-40; Barr et al. (1994) Gene Therapy 1:51-58; Berkner, K. L. (1988) BioTechniques 6:616-29; and Rich et al. (1993) Human Gene Therapy 4:461-76). Adenoviral vectors infect a wide variety of cells, have a broad host-range, exhibit high efficiencies of infectivity, direct expression of heterologous genes at high levels, and achieve long-term expression of those genes in vivo. The virus is fully infective as a cell-free virion so injection of producer cell lines is not necessary. With regard to safety, adenovirus is not associated with severe human pathology, and the recombinant vectors derived from the virus can be rendered replication defective by deletions in the early-region 1 ("E1") of the viral genome. Adenovirus can also be produced in large quantities with relative ease. Adenoviral vectors for use in the compositions, methods, and kits described herein can be derived from any of the various adenoviral serotypes, including, without limitation, any of the over 40 serotype strains of adenovirus, such as serotypes 2, 5, 12, 40, and 41. The adenoviral vectors used herein are preferably replication-deficient and contain the HSC inducing factor of interest operably linked to a suitable promoter.

[0420] In some embodiments of the compositions, methods, and kits described herein, the nucleic acid sequences encoding the HSC inducing factor(s), such as HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS, are introduced or delivered using one or more inducible lentiviral vectors. Control of expression of HSC inducing factors delivered using one or more inducible lentiviral vectors can be achieved, in some embodiments, by contacting a cell having at least one HSC inducing factor in an expression vector under the control of or operably linked to an inducible promoter, with a regulatory agent (e.g., doxycycline) or other inducing agent. When using some types of inducible lentiviral vectors, contacting such a cell with an inducing agent induces expression of the HSC inducing factors, while withdrawal of the regulatory agent inhibits expression. When using other types of inducible lentiviral vectors, the presence of the regulatory agent inhibits expression, while removal of the regulatory agent permits expression. As used herein, the term "induction of expression" refers to the expression of a gene, such as an HSC inducing factor encoded by an inducible viral vector, in the presence of an inducing agent, for example, or in the presence of one or more agents or factors that cause endogenous expression of the gene in a cell.

[0421] In some embodiments of the aspects described herein, a doxycycline (Dox) inducible lentiviral system is used. Unlike retroviruses, lentiviruses are able to transduce quiescent cells making them amenable for transducing a wider variety of hematopoietic cell types. For example, the pHAGE2 lentivirus system has been shown to transduce primary hematopoietic progenitor cells with high efficiency. This vector also carries a reporter cassette (IRES Zs-Green) that enables evaluation of viral transduction efficiencies and purification of transduced cells by FACS. The ability to inducibly turn off introduced transcription factors, as demonstrated herein, is important since the HSC-enriched expression pattern of these TFs indicates their continued enforced expression in induced HSCs can impair differentiation to all lineages. Having an inducible system also allows ascertainment of the stability of the reprogrammed state and assess the establishment and fidelity of HSC transcriptional programs and epigenetic marks once enforced expression of reprogramming factors is lifted.

[0422] In some embodiments of the methods described herein, the nucleic acid sequences encoding the HSC inducing factor(s), such as HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS, are introduced or delivered using a non-integrating vector (e.g., adenovirus). While integrating vectors, such as retroviral vectors, incorporate into the host cell genome and can potentially disrupt normal gene function, non-integrating vectors control expression of a gene product by extra-chromosomal transcription. Since non-integrating vectors do not become part of the host genome, non-integrating vectors tend to express a nucleic acid transiently in a cell population. This is due in part to the fact that the non-integrating vectors are often rendered replication deficient. Thus, non-integrating vectors have several advantages over retroviral vectors including, but not limited to: (1) no disruption of the host genome, and (2) transient expression, and (3) no remaining viral integration products. Some non-limiting examples of non-integrating vectors for use with the methods described herein include adenovirus, baculovirus, alphavirus, picornavirus, and vaccinia virus. In some embodiments of the methods described herein, the non-integrating viral vector is an adenovirus. Other advantages of non-integrating viral vectors include the ability to produce them in high titers, their stability in vivo, and their efficient infection of host cells.

[0423] The phrases "operably linked," "operatively positioned," "operatively linked," "under control," and "under transcriptional control" indicate that a nucleic acid sequence, such as a sequence encoding an HSC inducing factor, is in a correct functional location and/or orientation in relation to a promoter and/or endogenous regulatory sequences, such that the promoter and/or endogenous regulatory sequences controls transcriptional initiation and/or expression of that sequence.

[0424] The terms "promoter" or "promoter sequence," as used herein, refer to a nucleic acid sequence that regulates the expression of another nucleic acid sequence by driving RNA polymerase-mediated transcription of the nucleic acid sequence, which can be a heterologous target gene, such as a sequence encoding an HSC inducing factor. A promoter is a control region of a nucleic acid sequence at which initiation and rate of transcription of the remainder of a nucleic acid sequence are controlled. A promoter can also contain one or more genetic elements at which regulatory proteins and molecules can bind. Such regulatory proteins include RNA polymerase and other transcription factors. Accordingly, a promoter can be said to "drive expression" or "drive transcription" of the nucleic acid sequence that it regulates, such as a sequence encoding an HSC inducing factor.

[0425] Nucleic acid constructs and vectors for use in generating iHSCs in the compositions, methods, and kits described herein can further comprise, in some embodiments, one or more sequences encoding selection markers for positive and negative selection of cells. Such selection marker sequences can typically provide properties of resistance or sensitivity to antibiotics that are not normally found in the cells in the absence of introduction of the nucleic acid construct. A selectable marker can be used in conjunction with a selection agent, such as an antibiotic, to select in culture for cells expressing the inserted nucleic acid construct. Sequences encoding positive selection markers typically provide antibiotic resistance, i.e., when the positive selection marker sequence is present in the genome of a cell, the cell is sensitive to the antibiotic or agent. Sequences encoding negative selection markers typically provide sensitivity to an antibiotic or agent, i.e., when the negative selection marker is present in the genome of a cell, the cell is sensitive to the antibiotic or agent.

[0426] Nucleic acid constructs and vectors for use in making iHSCs in the compositions, methods, and kits thereof described herein can further comprise, in some embodiments, other nucleic acid elements for the regulation, expression, stabilization of the construct or of other vector genetic elements, for example, promoters, enhancers, TATA-box, ribosome binding sites, IRES, as known to one of ordinary skill in the art.

[0427] In some embodiments of the compositions, methods, and kits described herein, the HSC inducing factor(s), such as HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS, are provided as synthetic, modified RNAs, or introduced or delivered into a cell as a synthetic, modified RNA, as described in US Patent Publication 2012-0046346-A1, the contents of which are herein incorporated by reference in their entireties. In those embodiments where synthetic, modified RNAs are used to reprogram cells to iHSCs according to the methods described herein, the methods can involve repeated contacting of the cells or involve repeated transfections of the synthetic, modified RNAs encoding HSC inducing factors, such as for example, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, or more transfections.

[0428] In addition to one or more modified nucleosides, the modified mRNAs for use in the compositions, methods, and kits described herein can comprise any additional modifications known to one of skill in the art and as described in US Patent Publications 2012-0046346-A1 and 20120251618A1, and PCT Publication WO 2012/019168. Such other components include, for example, a 5' cap (e.g., the Anti-Reverse Cap Analog (ARCA) cap, which contains a 5'-5'-triphosphate guanine-guanine linkage where one guanine contains an N7 methyl group as well as a 3'-O-methyl group; caps created using recombinant Vaccinia Virus Capping Enzyme and recombinant 2'-O-methyltransferase enzyme, which can create a canonical 5'-5'-triphosphate linkage between the 5'-most nucleotide of an mRNA and a guanine nucleotide where the guanine contains an N7 methylation and the ultimate 5'-nucleotide contains a 2'-O-methyl generating the Cap1 structure); a poly(A) tail (e.g., a poly-A tail greater than 30 nucleotides in length, greater than 35 nucleotides in length, at least 40 nucleotides, at least 45 nucleotides, at least 55 nucleotides, at least 60 nucleotide, at least 70 nucleotides, at least 80 nucleotides, at least 90 nucleotides, at least 100 nucleotides, at least 200 nucleotides, at least 300 nucleotides, at least 400 nucleotides, at least 500 nucleotides, at least 600 nucleotides, at least 700 nucleotides, at least 800 nucleotides, at least 900 nucleotides, at least 1000 nucleotides, or more) (SEQ ID NO: 93); a Kozak sequence; a 3' untranslated region (3' UTR); a 5' untranslated region (5' UTR); one or more intronic nucleotide sequences capable of being excised from the nucleic acid, or any combination thereof.

[0429] The modified mRNAs for use in the compositions, methods, and kits described herein can further comprise an internal ribosome entry site (IRES). An IRES can act as the sole ribosome binding site, or can serve as one of multiple ribosome binding sites of an mRNA. An mRNA containing more than one functional ribosome binding site can encode several peptides or polypeptides, such as the HSC inducing factors described herein, that are translated independently by the ribosomes ("multicistronic mRNA"). When nucleic acids are provided with an IRES, further optionally provided is a second translatable region. Examples of IRES sequences that can be used according to the invention include without limitation, those from picornaviruses (e.g. FMDV), pest viruses (CFFV), polio viruses (PV), encephalomyocarditis viruses (ECMV), foot-and-mouth disease viruses (FMDV), hepatitis C viruses (HCV), classical swine fever viruses (CSFV), murine leukemia virus (MLV), simian immune deficiency viruses (SW) or cricket paralysis viruses (CrPV).

[0430] In some embodiments of the compositions, methods, and kits described herein, the synthetic, modified RNA molecule comprises at least one modified nucleoside. In some embodiments of the compositions, methods, and kits described herein, the synthetic, modified RNA molecule comprises at least two modified nucleosides.

[0431] In some embodiments of the compositions, methods, and kits described herein, the modified nucleosides are selected from the group consisting of 5-methylcytosine (5mC), N6-methyladenosine (m6A), 3,2'-O-dimethyluridine (m4U), 2-thiouridine (s2U), 2' fluorouridine, pseudouridine, 2'-O-methyluridine (Um), 2'deoxy uridine (2' dU), 4-thiouridine (s4U), 5-methyluridine (m5U), 2'-O-methyladenosine (m6A), N6,2'-O-dimethyladenosine (m6Am), N6,N6,2'-O-trimethyladenosine (m62Am), 2'-O-methylcytidine (Cm), 7-methylguanosine (m7G), 2'-O-methylguanosine (Gm), N2,7-dimethylguanosine (m2,7G), N2,N2,7-trimethylguanosine (m2,2,7G), and inosine (I). In some embodiments, the modified nucleosides are 5-methylcytosine (5mC), pseudouracil, or a combination thereof.

[0432] Modified mRNAs need not be uniformly modified along the entire length of the molecule. Different nucleotide modifications and/or backbone structures can exist at various positions in the nucleic acid. One of ordinary skill in the art will appreciate that the nucleotide analogs or other modification(s) can be located at any position(s) of a nucleic acid such that the function of the nucleic acid is not substantially decreased. A modification can also be a 5' or 3' terminal modification. The nucleic acids can contain at a minimum one and at maximum 100% modified nucleotides, or any intervening percentage, such as at least 50% modified nucleotides, at least 80% modified nucleotides, or at least 90% modified nucleotides.

[0433] In some embodiments, it is preferred, but not absolutely necessary, that each occurrence of a given nucleoside in a molecule is modified (e.g., each cytosine is a modified cytosine e.g., 5-methylcytosine, each uracil is a modified uracil, e.g., pseudouracil, etc.). For example, the modified mRNAs can comprise a modified pyrimidine such as uracil or cytosine. In some embodiments, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the uracil in the nucleic acid are replaced with a modified uracil. It is also contemplated that different occurrences of the same nucleoside can be modified in a different way in a given synthetic, modified RNA molecule. The modified uracil can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures). In some embodiments, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the cytosine in the nucleic acid may be replaced with a modified cytosine. The modified cytosine can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures) (e.g., some cytosines modified as 5mC, others modified as 2'-O-methylcytosine or other cytosine analog). Such multi-modified synthetic RNA molecules can be produced by using a ribonucleoside blend or mixture comprising all the desired modified nucleosides, such that when the RNA molecules are being synthesized, only the desired modified nucleosides are incorporated into the resulting RNA molecule encoding the HSC inducing factor.

[0434] As used herein, "unmodified" or "natural" nucleosides or nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleosides include other synthetic and natural nucleobases such as inosine, xanthine, hypoxanthine, nubularine, isoguanisine, tubercidine, 2-(halo)adenine, 2-(alkyl)adenine, 2-(propyl)adenine, 2 (amino)adenine, 2-(aminoalkyll)adenine, 2 (aminopropyl) adenine, 2 (methylthio) N6 (isopentenyl)adenine, 6 (alkyl) adenine, 6 (methyl)adenine, 7 (deaza)adenine, 8 (alkenyl) adenine, 8-(alkyl)adenine, 8 (alkynyl)adenine, 8 (amino) adenine, 8-(halo)adenine, 8-(hydroxyl)adenine, 8 (thioalkyl) adenine, 8-(thiol)adenine, N6-(isopentyl)adenine, N6 (methyl)adenine, N6,N6 (dimethyl)adenine, 2-(alkyl)guanine, 2 (propyl)guanine, 6-(alkyl)guanine, 6 (methyl)guanine, 7 (alkyl)guanine, 7 (methyl)guanine, 7 (deaza)guanine, 8 (alkyl)guanine, 8-(alkenyl)guanine, 8 (alkynyl)guanine, 8-(amino)guanine, 8 (halo)guanine, 8-(hydroxyl)guanine, 8 (thioalkyl)guanine, 8-(thiol)guanine, N(methyl)guanine, 2-(thio)cytosine, 3 (deaza) 5 (aza)cytosine, 3-(alkyl)cytosine, 3 (methyl)cytosine, 5-(alkyl)cytosine, 5-(alkynyl)cytosine, 5 (halo)cytosine, 5 (methyl)cytosine, 5 (propynyl)cytosine, 5 (propynyl)cytosine, 5 (trifluoromethyl)cytosine, 6-(azo)cytosine, N4 (acetyl)cytosine, 3 (3 amino-3 carboxypropyl)uracil, 2-(thio)uracil, 5 (methyl) 2 (thio)uracil, 5 (methylaminomethyl)-2 (thio)uracil, 4-(thio)uracil, 5 (methyl) 4 (thio) uracil, 5 (methylaminomethyl)-4 (thio)uracil, 5 (methyl) 2,4 (dithio)uracil, 5 (methylaminomethyl)-2,4 (dithio)uracil, 5 (2-aminopropyl)uracil, 5-(alkyl)uracil, 5-(alkynyl)uracil, 5-(allylamino)uracil, 5 (aminoallyl)uracil, 5 (aminoalkyl)uracil, 5 (guanidiniumalkyl)uracil, 5 (1,3-diazole-1-alkyl) uracil, 5-(cyanoalkyl)uracil, 5-(dialkylaminoalkyl)uracil, 5 (dimethylaminoalkyl)uracil, 5-(halo)uracil, 5-(methoxy) uracil, uracil-5 oxyacetic acid, 5 (methoxycarbonylmethyl)-2-(thio)uracil, 5 (methoxycarbonyl-methyl)uracil, 5 (propynyl)uracil, 5 (propynyl)uracil, 5 (trifluoromethyl)uracil, 6 (azo)uracil, dihydrouracil, N3 (methyl)uracil, 5-uracil (i.e., pseudouracil), 2 (thio)pseudouracil, 4 (thio)pseudouracil, 2,4-(dithio)psuedouracil, 5-(alkyl)pseudouracil, 5-(methyl) pseudouracil, 5-(alkyl)-2-(thio)pseudouracil, 5-(methyl)-2-(thio)pseudouracil, 5-(alkyl)-4 (thio)pseudouracil, 5-(methyl)-4 (thio)pseudouracil, 5-(alkyl)-2,4 (dithio) pseudouracil, 5-(methyl)-2,4 (dithio)pseudouracil, 1 substituted pseudouracil, 1 substituted 2(thio)-pseudouracil, 1 substituted 4 (thio)pseudouracil, 1 substituted 2,4-(dithio) pseudouracil, 1 (aminocarbonylethylenyl)-pseudouracil, 1 (aminocarbonylethylenyl)-2(thio)-pseudouracil, 1 (aminocarbonylethylenyl)-4 (thio)pseudouracil, 1 (aminocarbonylethylenyl)-2,4-(dithio)pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-2(thio)-pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-4 (thio)pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-2,4-(dithio) pseudouracil, 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-substituted 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-substituted 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(guanidiniumalkyl-hydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 1,3,5-(triaza)-2,6-(dioxa)-naphthalene, inosine, xanthine, hypoxanthine, nubularine, tubercidine, isoguanisine, inosinyl, 2-aza-inosinyl, 7-deaza-inosinyl, nitroimidazolyl, nitropyrazolyl, nitrobenzimidazolyl, nitroindazolyl, aminoindolyl, pyrrolopyrimidinyl, 3-(methyl)isocarbostyrilyl, 5-(methyl)isocarbostyrilyl, 3-(methyl)-7-(propynyl)isocarbostyrilyl, 7-(aza)indolyl, 6-(methyl)-7-(aza)indolyl, imidizopyridinyl, 9-(methyl)-imidizopyridinyl, pyrrolopyrizinyl, isocarbostyrilyl, 7-(propynyl)isocarbostyrilyl, propynyl-7-(aza)indolyl, 2,4,5-(trimethyl)phenyl, 4-(methyl)indolyl, 4,6-(dimethyl)indolyl, phenyl, napthalenyl, anthracenyl, phenanthracenyl, pyrenyl, stilbenyl, tetracenyl, pentacenyl, difluorotolyl, 4-(fluoro)-6-(methyl)benzimidazole, 4-(methyl)benzimidazole, 6-(azo) thymine, 2-pyridinone, 5 nitroindole, 3 nitropyrrole, 6-(aza) pyrimidine, 2 (amino)purine, 2,6-(diamino)purine, 5 substituted pyrimidines, N2-substituted purines, N6-substituted purines, 06-substituted purines, substituted 1,2,4-triazoles, pyrrolo-pyrimidin-2-on-3-yl, 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl, 2-oxo-pyridopyrimidine-3-yl, or any O-alkylated or N-alkylated derivatives thereof.

[0435] In some embodiments of the compositions, methods, and kits described herein, modified nucleosides include 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, and 4-methoxy-1-methyl-pseudoisocytidine.

[0436] In other embodiments of the compositions, methods, and kits described herein, modified nucleosides include 2-aminopurine, 2,6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine.

[0437] In other embodiments of the compositions, methods, and kits described herein, modified nucleosides include inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, l-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine.

[0438] In certain embodiments it is desirable to intracellularly degrade a modified nucleic acid introduced into the cell, for example if precise timing of protein production is desired. Thus, in some embodiments of the compositions, methods, and kits described herein, provided herein are modified nucleic acids comprising a degradation domain, which is capable of being acted on in a directed manner within a cell.

[0439] Modified nucleosides also include natural bases that comprise conjugated moieties, e.g. a ligand. As discussed herein above, the RNA containing the modified nucleosides must be translatable in a host cell (i.e., does not prevent translation of the polypeptide encoded by the modified RNA). For example, transcripts containing s2U and m6A are translated poorly in rabbit reticulocyte lysates, while pseudouridine, m5U, and m5C are compatible with efficient translation. In addition, it is known in the art that 2'-fluoro-modified bases useful for increasing nuclease resistance of a transcript, leads to very inefficient translation. Translation can be assayed by one of ordinary skill in the art using e.g., a rabbit reticulocyte lysate translation assay.

[0440] Accordingly, provided herein, in some aspects are hematopoietic stem cell (HSC) inducing composition comprising modified mRNA sequences encoding at least one, two, three, four, five, six, seve, eight or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612, wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0441] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0442] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5

[0443] Also provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising: a modified mRNA sequence encoding HLF; a modified mRNA sequence encoding RUNX1T1; a modified mRNA sequence encoding ZFP37; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding LMO2; and a modified mRNA sequence encoding PRDM5; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0444] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of: a modified mRNA sequence encoding PRDM16; a modified mRNA sequence encoding ZFP467; and a modified mRNA sequence encoding VDR; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0445] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising: a modified mRNA sequence encoding HLF; a modified mRNA sequence encoding RUNX1T1; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding LMO2; a modified mRNA sequence encoding PRDM5; a modified mRNA sequence encoding ZFP37; a modified mRNA sequence encoding MYCN; a modified mRNA sequence encoding MSI2; a modified mRNA sequence encoding NKX2-3; a modified mRNA sequence encoding MEIS1; and a modified mRNA sequence encoding RBPMS; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0446] Also provided herein are hematopoietic stem cell (HSC) inducing compositions comprising: a modified mRNA sequence encoding ZFP467; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding HOXB4; and a modified mRNA sequence encoding MSI2; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0447] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of: a modified mRNA sequence encoding HLF; a modified mRNA sequence encoding LMO2; a modified mRNA sequence encoding PRDM16; and a modified mRNA sequence encoding ZFP37, wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0448] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising: a modified mRNA sequence encoding MYCN; a modified mRNA sequence encoding MSI2; a modified mRNA sequence encoding NKX2-3; and a modified mRNA sequence encoding RUNX1T1; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0449] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of: a modified mRNA sequence encoding HOXB5; a modified mRNA sequence encoding HLF; a modified mRNA sequence encoding ZFP467; a modified mRNA sequence encoding HOXB3; a modified mRNA sequence encoding LMO2; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding ZFP37; and a modified mRNA sequence encoding ZFP521; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0450] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising: a modified mRNA sequence encoding HOXB4; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding LMO2; a modified mRNA sequence encoding ZFP467; and a modified mRNA sequence encoding ZFP521; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0451] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of: a modified mRNA sequence encoding KLF12; a modified mRNA sequence encoding HLF; and a modified mRNA sequence encoding EGR; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0452] Also provided herein are hematopoietic stem cell (HSC) inducing compositions comprising: a modified mRNA sequence encoding MEIS1; a modified mRNA sequence encoding RBPMS; a modified mRNA sequence encoding ZFP37; a modified mRNA sequence encoding RUNX1T1; and a modified mRNA sequence encoding LMO2; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0453] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of: a modified mRNA sequence encoding KLF12; and a modified mRNA sequence encoding HLF; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0454] Also provided herein are hematopoietic stem cell (HSC) inducing compositions comprising: a modified mRNA sequence encoding ZFP37; a modified mRNA sequence encoding HOXB4; a modified mRNA sequence encoding LMO2; and a modified mRNA sequence encoding HLF; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0455] In some embodiments of these aspects and all such aspects described herein, the HSC inducing composition further comprises one or more of: a modified mRNA encoding MYCN; a modified mRNA encoding ZFP467; a modified mRNA encoding NKX2-3; a modified mRNA encoding PBX1; and a modified mRNA encoding KLF4; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0456] In some embodiments of these aspects and all such aspects described herein, the modified cytosine is 5-methylcytosine and the modified uracil is pseudouridine.

[0457] The modified mRNAs encoding HSC inducing factors described herein can be synthesized and/or modified by methods well established in the art, such as those described in "Current Protocols in Nucleic Acid Chemistry," Beaucage, S. L. et al. (Edrs.), John Wiley & Sons, Inc., New York, N.Y., USA, which is hereby incorporated herein by reference in its entirety. In some embodiments of the compositions, methods, and kits described herein, the modified mRNAs encoding the HSC inducing factor(s), such as HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS, are generated using the IVT templates and constructs, and methods thereof for rapidly and efficiently generating synthetic RNAs described in PCT Application No.: PCT/US12/64359, filed Nov. 9, 2012, and as described in US 20120251618 A1, the contents of each of which are herein incorporated by reference in their entireties. In some embodiments of the compositions, methods, and kits described herein, the synthetic, modified RNAs encoding the HSC inducing factor(s), such as HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS, are delivered and formulated as described in US 20120251618 A1.

[0458] One of skill in the art can easily monitor the expression level of the polypeptide encoded by a synthetic, modified RNA using e.g., Western blotting techniques or immunocytochemistry techniques. A synthetic, modified RNA can be administered at a frequency and dose that permit a desired level of expression of the polypeptide. Each different modified mRNA can be administered at its own dose and frequency to permit appropriate expression. In addition, since the modified RNAs administered to the cell are transient in nature (i.e., are degraded over time) one of skill in the art can easily remove or stop expression of a modified RNA by halting further transfections and permitting the cell to degrade the modified RNA over time. The modified RNAs will degrade in a manner similar to cellular mRNAs.

[0459] Accordingly, in some embodiments of the compositions, methods, and kits described herein, a plurality of synthetic, modified RNAs encoding HSC inducing factors can be contacted with, or introduced to, a cell, population of cells, or cell culture simultaneously. In other embodiments, the plurality of synthetic, modified RNAs encoding HSC inducing factors can be contacted with, or introduced to, a cell, population of cells, or cell culture separately. In addition, each modified RNA encoding an HSC inducing factor can be administered according to its own dosage regime.

[0460] In some embodiments of the compositions, methods, and kits described herein, a modified RNA encoding an HSC inducing factor can be introduced into target cells by transfection or lipofection. Suitable agents for transfection or lipofection include, for example, calcium phosphate, DEAE dextran, lipofectin, lipofectamine, DIMRIE C™, Superfect™, and Effectin™ (Qiagen™) Unifectin™, Maxifectin™, DOTMA, DOGS™ (Transfectam; dioctadecylamidoglycylspermine), DOPE (1,2-dioleoyl-sn-glycero-3-phosphoethanolamine), DOTAP (1,2-dioleoyl-3-trimethylammonium propane), DDAB (dimethyl dioctadecylammonium bromide), DHDEAB (N,N-di-n-hexadecyl-N,N-dihydroxyethyl ammonium bromide), HDEAB (N-n-hexadecyl-N,N-dihydroxyethylammonium bromide), polybrene, poly(ethylenimine) (PEI), and the like. (See, e.g., Banerjee et al., Med. Chem. 42:4292-99 (1999); Godbey et al., Gene Ther. 6:1380-88 (1999); Kichler et al., Gene Ther. 5:855-60 (1998); Birchaa et al., J. Pharm. 183: 195-207 (1999)).

[0461] In some embodiments, a modified RNA can be transfected into target cells as a complex with cationic lipid carriers (e.g., OLIGOFECTAMINE™) or non-cationic lipid-based carriers (e.g., Transit-TKOTM™, Mirus Bio LLC, Madison, Wis.).

[0462] In some embodiments of the aspects described herein, the synthetic, modified RNA is introduced into a cell using a transfection reagent. Some exemplary transfection reagents include, for example, cationic lipids, such as lipofectin (Junichi et al, U.S. Pat. No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (Lollo et al., PCT Application WO 97/30731). Examples of commercially available transfection reagents are known to those of ordinary skill in the art.

[0463] In other embodiments, highly branched organic compounds, termed "dendrimers," can be used to bind the exogenous nucleic acid, such as the synthetic, modified RNAs described herein, and introduce it into the cell.

[0464] In other embodiments of the aspects described herein, non-chemical methods of transfection are contemplated. Such methods include, but are not limited to, electroporation, sonoporation, the use of a gene gun, magnetofection, and impalefection, and others, as known to those of ordinary skill in the art. Other agents may be utilized to enhance the penetration of the administered nucleic acids, including glycols, such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes, such as limonene and menthone.

[0465] In some embodiments of the compositions, methods, and kits described herein, a modified RNA encoding an HSC inducing factor is formulated in conjunction with one or more penetration enhancers, surfactants and/or chelators. Suitable surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. In some embodiments, combinations of penetration enhancers are used, for example, fatty acids/salts in combination with bile acids/salts. One exemplary combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether.

[0466] In some embodiments of the compositions, methods, and kits described herein, a modified RNA encoding an HSC inducing factor is formulated into any of many possible administration forms, including a sustained release form. In some embodiments of the compositions, methods, and kits described herein, formulations comprising a plurality of different synthetic, modified RNAs encoding HSC inducing factors are prepared by first mixing all members of a plurality of different synthetic, modified RNAs, and then complexing the mixture comprising the plurality of different synthetic, modified RNAs with a desired ligand or targeting moiety, such as a lipid. The compositions can be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions can further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension can also contain stabilizers.

[0467] The compositions described herein can be prepared and formulated as emulsions for the delivery of synthetic, modified RNAs. Emulsions can contain further components in addition to the dispersed phases, and the active drug (i.e., synthetic, modified RNA) which can be present as a solution in either the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants can also be present in emulsions as needed. Emulsions can also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Emulsifiers can broadly be classified into four categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (see e.g., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, L V., Popovich N G., and Ansel H C., 2004, Lippincott Williams & Wilkins (8th ed.), New York, N.Y.; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

[0468] In some embodiments of the compositions, methods, and kits described herein, a modified RNA encoding an HSC inducing factor can be encapsulated in a nanoparticle. Methods for nanoparticle packaging are well known in the art, and are described, for example, in Bose S, et al (Role of Nucleolin in Human Parainfluenza Virus Type 3 Infection of Human Lung Epithelial Cells. J. Virol. 78:8146. 2004); Dong Y et al. Poly(d,l-lactide-co-glycolide)/montmorillonite nanoparticles for oral delivery of anticancer drugs. Biomaterials 26:6068. 2005); Lobenberg R. et al (Improved body distribution of 14C-labelled AZT bound to nanoparticles in rats determined by radioluminography. J Drug Target 5:171.1998); Sakuma S R et al (Mucoadhesion of polystyrene nanoparticles having surface hydrophilic polymeric chains in the gastrointestinal tract. Int J Pharm 177:161. 1999); Virovic L et al. Novel delivery methods for treatment of viral hepatitis: an update. Expert Opin Drug Deliv 2:707.2005); and Zimmermann E et al, Electrolyte- and pH-stabilities of aqueous solid lipid nanoparticle (SLN) dispersions in artificial gastrointestinal media. Eur J Pharm Biopharm 52:203. 2001), the contents of which are herein incorporated in their entireties by reference.

[0469] While it is understood that iHSCs can be generated by delivery of HSC inducing factors in the form of nucleic acid (DNA or RNA) or amino acid sequences, in some embodiments of the compositions, methods, and kits described herein, iHSC induction can be induced using other methods, such as, for example, by treatment of cells with an agent, such as a small molecule or cocktail of small molecules, that induce expression one or more of the HSC inducing factors.

[0470] The term "agent" as used herein means any compound or substance such as, but not limited to, a small molecule, nucleic acid, polypeptide, peptide, drug, ion, etc. An "agent" can be any chemical, entity or moiety, including without limitation synthetic and naturally-occurring proteinaceous and non-proteinaceous entities. In some embodiments, an agent is nucleic acid, nucleic acid analogues, proteins, antibodies, peptides, aptamers, oligomer of nucleic acids, amino acids, or carbohydrates including without limitation proteins, oligonucleotides, ribozymes, DNAzymes, glycoproteins, siRNAs, lipoproteins, aptamers, and modifications and combinations thereof etc. In some embodiments, the nucleic acid is DNA or RNA, and nucleic acid analogues, for example can be PNA, pcPNA and LNA. A nucleic acid may be single or double stranded, and can be selected from a group comprising; nucleic acid encoding a protein of interest, oligonucleotides, PNA, etc. Such nucleic acid sequences include, for example, but not limited to, nucleic acid sequence encoding proteins that act as transcriptional repressors, antisense molecules, ribozymes, small inhibitory nucleic acid sequences, for example but not limited to RNAi, shRNAi, siRNA, micro RNAi (mRNAi), antisense oligonucleotides etc. A protein and/or peptide agent or fragment thereof, can be any protein of interest, for example, but not limited to; mutated proteins; therapeutic proteins; truncated proteins, wherein the protein is normally absent or expressed at lower levels in the cell. Proteins of interest can be selected from a group comprising; mutated proteins, genetically engineered proteins, peptides, synthetic peptides, recombinant proteins, chimeric proteins, antibodies, humanized proteins, humanized antibodies, chimeric antibodies, modified proteins and fragments thereof.

[0471] Also provided herein, in some aspects, are methods of making, preparing, or generating induced hematopoietic stem cells using one or more expression vectors or one or more modified mRNA sequences encoding specific combinations of the HSC inducing factors described herein, such as at least one, two, three, four, five, six, seven, eight, or more of the HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612.

[0472] Accordingly, provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

> **[0473]** a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5, wherein each said nucleic acid sequence is operably linked to a promoter; and
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> **[0474]** b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0475] In some embodiments of these methods and all such method described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding PRDM16; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding VDR.

[0476] Also provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

> **[0477]** a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM5; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding MEIS1; and a nucleic acid sequence encoding RBPMS; wherein each said nucleic acid sequence is operably linked to a promoter; and
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> **[0478]** b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0479] Also provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

> **[0480]** a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP467, a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding HOXB4; and a nucleic acid sequence encoding MSI2; wherein each said nucleic acid sequence is operably linked to a promoter; and
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> **[0481]** b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0482] In some embodiments of these methods and all such method described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM16; and a nucleic acid sequence encoding ZFP37.

[0483] Also provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

> **[0484]** a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2, a nucleic acid sequence encoding NKX2-3; and a nucleic acid sequence encoding RUNX1T1; wherein each said nucleic acid sequence is operably linked to a promoter; and
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> **[0485]** b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0486] In some embodiments of these methods and all such method described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HOXB5; a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding HOXB3; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding ZFP37; and a nucleic acid sequence encoding ZFP521.

[0487] Also provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

> **[0488]** a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding PBX1, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding ZFP521; wherein each said nucleic acid sequence is operably linked to a promoter; and
>
> **[0489]** b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0490] In some embodiments of these methods and all such method described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; a nucleic acid sequence encoding HLF; and a nucleic acid sequence encoding EGR1.

[0491] Also provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0492] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding MEIS1; a nucleic acid sequence encoding RBPMS; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding RUNX1T1; and a nucleic acid sequence encoding LMO2; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0493] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0494] In some embodiments of these methods and all such method described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; and a nucleic acid sequence encoding HLF.

[0495] Provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0496] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding HLF; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0497] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0498] In some embodiments of these methods and all such method described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; and a nucleic acid sequence encoding HLF.

[0499] Also provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0500] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding HLF; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0501] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0502] In some embodiments of these methods and all such method described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding PBX1; and a nucleic acid sequence encoding KLF.

[0503] Also provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0504] a. repeatedly transfecting a somatic cell with one or more modified mRNA sequences encoding at least one, two, three, four, five, six, seve, eight, or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612, wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof

[0505] b. culturing the transfected somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0506] In some embodiments of these methods and all such methods described herein, the at least one, two, three, four, or more HSC inducing factors of step (a) are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0507] In some embodiments of these methods and all such methods described herein, the at least one, two, three, four, or more HSC inducing factors of step (a) are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5. In some such embodiments, the at least one, two, three, four, or more HSC inducing factors of step (a) further comprise one or more of: PRDM16; ZFP467; and VDR.

[0508] In some embodiments of these methods and all such methods described herein, the at least one, two, three, four, or more HSC inducing factors of step (a) are HLF; RUNX1T1; PBX1; LMO2; PRDM5; ZFP37; MYCN; MSI2; NKX2-3; MEIS1; and RBPMS.

[0509] In some embodiments of these methods and all such methods described herein, the at least one, two, three, four, or more HSC inducing factors of step (a) are ZFP467; PBX1; HOXB4; and MSI2. In some such embodiments, the at least one, two, three, four, or more HSC inducing factors of step (a) further comprise one or more of: HLF; LMO2; PRDM16; and ZFP37.

[0510] In some embodiments of these methods and all such methods described herein, the at least one, two, three, four, or more HSC inducing factors of step (a) are MYCN; MSI2; NKX2-3; and RUNX1T1. In some such embodiments, the at least one, two, three, four, or more HSC inducing factors of step (a) further comprise one or more of: HOXB5; HLF; ZFP467; HOXB3; LMO2; PBX1; ZFP37; and ZFP521.

[0511] In some embodiments of these methods and all such methods described herein, the at least one, two, three, four, or more HSC inducing factors of step (a) are HOXB4; PBX1; LMO2; ZFP467; and ZFP521. In some such embodiments, the at least one, two, three, four, or more HSC inducing factors of step (a) further comprise one or more of: KLF12; HLF; and EGR.

[0512] In some embodiments of these methods and all such methods described herein, the at least one, two, three, four, or more HSC inducing factors of step (a) are MEIS1; RBPMS; ZFP37; RUNX1T1; and LMO2. In some such embodiments, the at least one, two, three, four, or more HSC inducing factors of step (a) further comprise one or more of: KLF12; and HLF.

[0513] In some embodiments of these methods and all such methods described herein, the at least one, two, three, four, or more HSC inducing factors of step (a) are ZFP37; HOXB4; LMO2; and HLF. In some such embodiments, the at least one, two, three, four, or more HSC inducing factors of step (a) further comprise one or more of: MYCN; ZFP467; NKX2-3; PBX1; and KLF4.

[0514] Detection of expression of HSC inducing factors introduced into cells or induced in a cell population using the compositions, methods, and kits described herein, can be achieved by any of several techniques known to those of skill in the art including, for example, Western blot analysis, immunocytochemistry, and fluorescence-mediated detection.

[0515] In order to distinguish whether a given combination of HSC inducing factors has generated iHSCs or other committed progenitors, one or more HSC activities or parameters can be measured, such as, in some embodiments, differential expression of surface antigens. The generation of induced HSCs using the compositions, methods, and kits described herein preferably causes the appearance of the cell surface phenotype characteristic of endogenous HSCs, such as lineage marker negative, Sca1-positive, cKit-positive (or LSK cells), CD34-negative, Flk2-negative, CD48-negative, and CD150-positive or as CD150+CD48−CD244−, for example.

[0516] HSCs are most reliably distinguished from committed progenitors by their functional behavior. Functional aspects of HSC phenotypes, or hematopoietic stem cell activities, such as the ability of an HSC to give rise to long-term, multi-lineage reconstitution in a recipient, can be easily determined by one of skill in the art using routine methods known in the art, and as described herein, for example, in the Examples and the Drawings, i.e., FIGS. **1-57**C. In some embodiments of the aspects described herein, functional assays to identify reprogramming factors can be used. For example, in some embodiments, Colony forming cell (CFC) activity in methylcellulose can be used to confirm multi-lineage (granulocytes, macrophages, megakaryocytes and erythrocytes) potential of iHSCs generated using the compositions, methods, and kits thereof. Serial plating can be used to confirm self-renewal potential of iHSCs generated using the compositions, methods, and kits described herein. Lymphoid potential of iHSCs generated using the compositions, methods, and kits described herein can be evaluated by culturing transduced cells on OP9 and OP9delta stromal cells, followed by immunostaining on day 14 for B- and T-cells, respectively.

[0517] As used herein, "cellular parameter," "HSC parameter," or "hematopoietic stem cell activity" refer to measureable components or qualities of endogenous or natural HSCs, particularly components that can be accurately measured. A cellular parameter can be any measurable parameter related to a phenotype, function, or behavior of a cell. Such cellular parameters include, changes in characteristics and markers of an HSC or HSC population, including but not limited to changes in viability, cell growth, expression of one or more or a combination of markers, such as cell surface determinants, such as receptors, proteins, including conformational or post-translational modification thereof, lipids, carbohydrates, organic or inorganic molecules, nucleic acids, e.g. mRNA, DNA, global gene expression patterns, etc. Such cellular parameters can be measured using any of a variety of assays known to one of skill in the art. For example, viability and cell growth can be measured by assays such as Trypan blue exclusion, CFSE dilution, and ^{3}H incorporation. Expression of protein or polypeptide markers can be measured, for example, using flow cytometric assays, Western blot techniques, or microscopy methods. Gene expression profiles can be assayed, for example, using microarray methodologies and quantitative or semi-quantitative real-time PCR assays. A cellular parameter can also refer to a functional parameter or functional activity. While most cellular parameters will provide a quantitative readout, in some instances a semi-quantitative or qualitative result can be acceptable. Readouts can include a single determined value, or can include mean, median value or the variance, etc. Characteristically a range of parameter readout values can be obtained for each parameter from a multiplicity of the same assays. Variability is expected and a range of values for each of the set of test parameters will be obtained using standard statistical methods with a common statistical method used to provide single values.

[0518] In some embodiments of the compositions, methods, and kits described herein, additional factors can be used to enhance HSC reprogramming. For example, agents that modify epigenetic pathways can be used to facilitate reprogramming into iHSCs.

[0519] Essentially any primary somatic cell type can be used for producing iHSCs or reprogramming somatic cells to iHSCs according to the presently described compositions, methods, and kits. Such primary somatic cell types also include other stem cell types, including pluripotent stem cells, such as induced pluripotent stem cells (iPS cells); other multipotent stem cells; oligopotent stem cells; and (5) unipotent stem cells. Some non-limiting examples of primary somatic cells useful in the various aspects and embodiments of the methods described herein include, but are not limited to, fibroblast, epithelial, endothelial, neuronal, adipose, cardiac, skeletal muscle, hematopoietic or immune cells, hepatic, splenic, lung, circulating blood cells, gastrointestinal, renal, bone marrow, and pancreatic cells, as well as stem cells from which those cells are derived. The cell can be a primary cell isolated from any somatic tissue including, but not limited to, spleen, bone marrow, blood, brain, liver, lung, gut, stomach, intestine, fat, muscle, uterus, skin, spleen, endocrine organ, bone, etc. The term "somatic cell" further encompasses, in some embodiments, primary cells grown in culture, provided that the somatic cells are not immortalized. Where the cell is maintained under in vitro conditions, conventional tissue culture conditions and methods can be used, and are known to those of skill in the art. Isolation and culture methods for various primary somatic cells are well within the abilities of one skilled in the art.

[0520] In some embodiments of the compositions, methods, and kits described herein, a somatic cell to be reprogrammed or made into an iHSC cell is a cell of hematopoietic origin. As used herein, the terms "hematopoietic-derived cell," "hematopoietic-derived differentiated cell," "hematopoietic lineage cell," and "cell of hematopoietic origin" refer to cells derived or differentiated from a multipotent hematopoietic stem cell (HSC). Accordingly, hematopoietic lineage cells for use with the compositions, methods, and kits described herein include multipotent, oligopotent, and lineage-restricted hematopoietic progenitor cells, granulocytes (e.g., promyelocytes, neutrophils, eosinophils, basophils), erythrocytes (e.g., reticulocytes, erythrocytes), thrombocytes (e.g., megakaryoblasts, platelet producing megakaryocytes, platelets), monocytes (e.g., monocytes, macrophages), dendritic cells, and lymphocytes (e.g., T-lymphocytes, which carry T-cell receptors (TCRs), B-lymphocytes or B cells, which express immunoglobulin and produce antibodies, NK cells, NKT cells, and innate lymphocytes). As used herein, the term "hematopoietic progenitor cells" refer to multipotent, oligopotent, and lineage-restricted hematopoietic cells capable of differentiating into two or more cell types of the hematopoietic system, including, but not limited to, granulocytes, monocytes, erythrocytes, megakaryocytes, and lymphocytes B-cells and T-cells. Hematopoietic progenitor cells encompass multi-potent progenitor cells (MPPs), common myeloid progenitor cells (CMPs), common lymphoid progenitor cells (CLPs), granulocyte-monocyte progenitor cells (GMPs), and pre-megakaryocyte-erythrocyte progenitor cell. Lineage-restricted hematopoieticprogenitor cells include megakaryocyte-erythrocyte progenitor cells (MEP), roB cells, PreB cells, PreProB cells, ProT cells, double-negative T cells, pro-NK cells, pro-dendritic cells (pro-DCs), pre-granulocyte/macrophage cells, granulocyte/macrophage progenitor (GMP) cells, and pro-mast cells (ProMCs). A differentiation chart of the hematopoietic lineage is provided at FIG. **1**

[0521] Cells of hematopoietic origin for use in the compositions, methods, and kits described herein can be obtained from any source known to comprise these cells, such as fetal tissues, umbilical cord blood, bone marrow, peripheral blood, mobilized peripheral blood, spleen, liver, thymus, lymph, etc. Cells obtained from these sources can be expanded ex vivo using any method acceptable to those skilled in the art prior to use in with the compositions, methods, and kits for making iHCSs described herein. For example, cells can be sorted, fractionated, treated to remove specific cell types, or otherwise manipulated to obtain a population of cells for use in the methods described herein using any procedure acceptable to those skilled in the art. Mononuclear lymphocytes may be collected, for example, by repeated lymphocytophereses using a continuous flow cell separator as described in U.S. Pat. No. 4,690,915, or isolated using an affinity purification step of common lymphoid progenitor cell (CLP)r method, such as flow-cytometry using a cytometer, magnetic separation, using antibody or protein coated beads, affinity chromatography, or solid-support affinity separation where cells are retained on a substrate according to their expression or lack of expression of a specific protein or type of protein, or batch purification using one or more antibodies against one or more surface antigens specifically expressed by the cell type of interest. Cells of hematopoietic origin can also be obtained from peripheral blood. Prior to harvest of the cells from peripheral blood, the subject can be treated with a cytokine, such as e.g., granulocyte-colony stimulating factor, to promote cell migration from the bone marrow to the blood compartment and/or promote activation and/or proliferation of the population of interest. Any method suitable for identifying surface proteins, for example, can be employed to isolate cells of hematopoietic origin from a heterogenous population. In some embodiments, a clonal population of cells of hematopoietic origin, such as lymphocytes, is obtained. In some embodiments, the cells of hematopoietic origin are not a clonal population.

[0522] Further, in regard to the various aspects and embodiments of the compositions, methods, and kits described herein, a somatic cell can be obtained from any mammalian species, with non-limiting examples including a murine, bovine, simian, porcine, equine, ovine, or human cell. In some embodiments, the somatic cell is a human cell. In some embodiments, the cell is from a non-human organism, such as a non-human mammal.

[0523] In general, the methods for making iHSCs described herein involve culturing or expanding somatic cells, such as cells of hematopoietic origin, in any culture medium that is available and well-known to one of ordinary skill in the art. Such media include, but are not limited to, Dulbecco's Modified Eagle's Medium® (DMEM), DMEM F12 Medium®, Eagle's Minimum Essential Medium®, F-12K Medium®, Iscove's Modified Dulbecco's Medium®, RPMI-1640 Medium®, and serum-free medium for culture and expansion of progenitor cells SFEM®. Many media are also available as low-glucose formulations, with or without sodium. The medium used with the methods described herein can, in some embodiments, be supplemented with one or more growth factors. Commonly used growth factors include, but are not limited to, bone morphogenic protein, basic fibroblast growth factor, platelet-derived growth factor and epidermal growth factor, Stem cell factor, and thrombopoietin. See, for example, U.S. Pat. Nos. 7,169,610; 7,109,032; 7,037,721; 6,617,161; 6,617,159; 6,372,210; 6,224,860; 6,037,174; 5,908,782; 5,766,951; 5,397,706; and 4,657,866; all incorporated by reference herein in their entireties for teaching growing cells in serum-free medium.

[0524] For example, as described herein, primary cultures of mouse hematopoietic cells were kept a total of three days ex vivo during the transduction process. Cells were maintained in minimal growth S-clone media supplemented with 20 ng/μL IL-12, TPO, SCF, 5 ng/μL IL-7, 2 ng/μL FLK-3, and 100 ng/ml Penicillin/streptomycin in a 5% CO_2 37° C. incubator. Transduction with concentrated and titered viruses was performed for 16 hours, in some embodiments, and then a24 hour incubation with doxycycline, in some embodiments. At this time ZsGr+ cells were re-sorted and put into CFCs assays or in vivo transplantation. Doxycycline induction can be maintained for 2 weeks post-transplant, in some embodiments. In some embodiments, when using an inducible expression vector, the inducing agent, such as doxycycline, can be maintained for at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days or a week, at least 10 days, at least 2 weeks, or more, following transplantation of a induced iHSC population into a subject.

[0525] Cells in culture can be maintained either in suspension or attached to a solid support, such as extracellular matrix components or plating on feeder cells, for example. Cells being used in the methods described herein can require additional factors that encourage their attachment to a solid support, in some embodiments, such as type I and type II collagen, chondroitin sulfate, fibronectin, "superfibronectin" and fibronectin-like polymers, gelatin, poly-D and poly-L-lysine, thrombospondin and vitronectin. In some embodiments, the cells are suitable for growth in suspension cultures. Suspension-competent host cells are generally monodisperse or grow in loose aggregates without substantial aggregation. Suspension-competent host cells include cells that are suitable for suspension culture without adaptation or manipulation (e.g., cells of hematopoietic origin, such as lymphoid cells) and cells that have been made suspension-competent by modification or adaptation of attachment-dependent cells (e.g., epithelial cells, fibroblasts).

[0526] Also provided herein, in some aspects, are isolated induced hematopoietic stem cells (iHSCs) produced using any of the HSC inducing compositions or methods of preparing iHSCs described herein.

[0527] Also provided herein, in some aspects, are cell clones comprising a plurality of the induced hematopoietic stem cell (iHSCs) produced using any of the HSC inducing compositions or methods of preparing iHSCs described herein.

[0528] In some embodiments of these aspects and all such aspects described herein, the isolated induced hematopoietic stem cells (iHSCs) or cell clones thereof further comprise a pharmaceutically acceptable carrier for administration to a subject in need.

[0529] Also provided herein, in some aspects, are methods of treating a subject in need of treatment for a disease or disorder in which one or more hematopoietic cell lineages are deficient or defective using the HSC inducing compositions and methods of preparing iHSCs described herein, or using the isolated induced hematopoietic stem cells (iHSCs) and cell clones thereof produced using any of the combinations of HSC inducing factors, HSC inducing compositions, or methods of preparing iHSCs described herein. In such methods of treatment, somatic cells, such as fibroblast cells or hematopoietic lineage cells, can first be isolated from the subject, and the isolated cells transduced or transfected, as described herein with an HSC inducing composition comprising expression vectors or synthetic mRNAs, respectively. The isolated induced hematopoietic stem cells (iHSCs) and cell clones thereof produced using any of the combinations of HSC inducing factors, HSC inducing compositions, or methods of preparing iHSCs described herein, can then be administered to the subject, such as via systemic injection of the iHSCs to the subject.

[0530] The reprogrammed iHSCs generated using the compositions, methods, and kits described herein can, in some embodiments of the methods of treatment described herein, be used directly or administered to subjects in need of cellular therapies or regenerative medicine applications or, in other embodiments, redifferentiated to other hematopoietic cell types for use in or administration to subjects in need of cellular therapies or regenerative medicine applications. Accordingly, various embodiments of the methods described herein involve administration of an effective amount of an iHSC or a population of iHSCs, generated using any of the compositions, methods, and kits described herein, to an individual or subject in need of a cellular therapy. The cell or population of cells being administered can be an autologous population, or be derived from one or more heterologous sources. Further, such iHSCs or differentiated cells from iHSCs can be administered in a manner that permits them to graft to the intended tissue site and reconstitute or regenerate the functionally deficient area. In some such embodiments, iHSCs can be introduced to a scaffold or other structure to generate, for example, a tissue ex vivo, that can then be introduced to a patient.

[0531] A variety of means for administering cells to subjects are known to those of skill in the art. Such methods can include systemic injection, for example, i.v. injection, or implantation of cells into a target site in a subject. Cells may be inserted into a delivery device which facilitates introduction by injection or implantation into the subject. Such delivery devices can include tubes, e.g., catheters, for injecting cells and fluids into the body of a recipient subject. In one preferred embodiment, the tubes additionally have a needle, e.g., through which the cells can be introduced into the subject at a desired location. The cells can be prepared for delivery in a variety of different forms. For example, the cells can be suspended in a solution or gel or embedded in a support matrix when contained in such a delivery device. Cells can be mixed with a pharmaceutically acceptable carrier or diluent in which the cells remain viable.

[0532] Accordingly, the cells produced by the methods described herein can be used to prepare cells to treat or alleviate at least the following diseases and conditions wherein hematopoietic stem cell transplants have proven to be one effective method of treatment: leukemia such as acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic/myeloproliferative syndromes, chronic myeloid leukemia, chronic lymphocytic leukemia, and other leukemia; lymphoproliferative disorders such as plasma cell disorders, Hodgkin disease, non-Hodgkin lymphoma, and other lymphoma; solid tumors such as neuroblastoma, germinal cancer, breast cancer, and Ewing sarcoma; Nonmalignant disorders such as bone marrow failures, hemoglobinopathies, immune deficiencies, inherited diseases of metabolism, and autoimmune disorders.

[0533] In addition to the above, the methods of the invention can be used for the treatment of the following diseases and conditions: Angiogenic Myeloid Metaplasia (Myelofibrosis); Aplastic Anemia; Acquired Pure Red Cell Aplasia; Aspartylglucosaminuria; Ataxia Telangiectasia; Choriocarcinoma; Chronic Lymphocytic Leukemia (CLL); Chronic Myelogenous Leukemia (CML); Common Variable Immunodeficiency; Chronic Pulmonary Obstructive Disease; Desmoplastic small round cell tumor; Diamond-Blackfan anemia; DiGeorge syndrome; Essential Thrombocythemia; Haematologica Ewing's Sarcoma; Fucosidosis; Gaucher disease; Griscelli syndrome; Hemophagocytic lymphohistiocytosis (HLH); Hodgkin's Disease; Human Immunodeficiency Virus (HIV); Human T-lymphotropic Virus (HTLV); Hunter syndrome (MPS II, iduronidase sulfate deficiency); Hurler syndrome (MPS I H, α-L-iduronidase deficiency); Infantile neuronal ceroid lipofuscinosis (INCL, Santavuori disease); Jansky-Bielschowsky disease (late infantile neuronal ceroid lipofuscinosis); Juvenile Myelomonocytic Leukemia (JMML); Kostmann syndrome; Krabbe disease (globoid cell leukodystrophy); Maroteaux-Lamy syndrome (MPS VI); Metachromatic leukodystrophy; Morquio syndrome (MPS IV); Mucolipidosis II (I-cell disease); Multiple Myeloma; Myelodysplasia; Neuroblastoma; NF-Kappa-B Essential Modulator (NEMO) deficiency; Niemann-Pick disease; Non-Hodgkin's Lymphoma; paroxysmal nocturnal hemoglobinuria (PNH); Plasma Cell Leukemia; Polycythemia Vera; Radiation Poisoning; Sanfilippo syndrome (MPS III); Severe combined immunodeficiency (SCID), all types; Shwachman-Diamond syndrome; Sickle cell disease; Sly syndrome (MPS VII); Thalassemia; Wilm's tumors; Wiskott-Aldrich syndrome; Wolman disease (acid lipase deficiency); and X-linked lymphoproliferative disorder

[0534] Pharmaceutically acceptable carriers and diluents include saline, aqueous buffer solutions, solvents and/or dispersion media. The use of such carriers and diluents is well known in the art. The solution is preferably sterile and fluid. Preferably, prior to the introduction of cells, the solution is stable under the conditions of manufacture and storage and preserved against the contaminating action of microorganisms such as bacteria and fungi through the use of, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like.

[0535] It is preferred that the mode of cell administration is relatively non-invasive, for example by intravenous injection, pulmonary delivery through inhalation, topical, or intranasal administration. However, the route of cell administration will depend on the tissue to be treated and may include implantation. Methods for cell delivery are known to those of skill in the art and can be extrapolated by one skilled in the art of medicine for use with the methods and compositions described herein.

[0536] Direct injection techniques for cellular administration of iHSCs can also be used to stimulate transmigration of cells through the entire vasculature, or to the vasculature of a particular organ. This includes non-specific targeting of the vasculature. One can target any organ by selecting a specific injection site, e.g., a liver portal vein. Alternatively, the injection can be performed systemically into any vein in the body. This method is useful for enhancing stem cell numbers in aging patients. In addition, the cells can function to populate vacant stem cell niches or create new stem cells to replenish those lost through, for example, chemotherapy or radiation treatments, for example. If so desired, a mammal or subject can be pre-treated with an agent, for example an agent is administered to enhance cell targeting to a tissue (e.g., a homing factor) and can be placed at that site to encourage cells to target the desired tissue. For example, direct injection of homing factors into a tissue can be performed prior to systemic delivery of ligand-targeted cells.

[0537] A wide range of diseases in which one or more blood cell populations are deficient or defective are recognized as being treatable with HSCs Accordingly, also provided herein are compositions and methods comprising iHSCs for use in cellular therapies, such as stem cell therapies. Non-limiting examples of conditions or disorders that can be treated using the compositions and methods described herein include aplastic anemia, Fanconi anemia, paroxysmal nocturnal hemoglobinuria (PNH); acute leukemias, including acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute biphenotypic leukemia and acute undifferentiated leukemia; chronic leukemias, including chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), juvenile chronic myelogenous leukemia (JCML) and juvenile myelomonocytic leukemia (JMML); myeloproliferative disorders, including acute myelofibrosis, angiogenic myeloid metaplasia (myelofibrosis), polycythemia vera and essential thrombocythemia; inherited platelet abnormalities, including amegakaryocytosis/congenital thrombocytopenia; plasma cell disorders, including multiple myeloma, plasma cell leukemia, and Waldenstrom's macroglobulinemia; lung disorders, including COPD and bronchial asthma; congenital immune disorders, including ataxia-telangiectasia, Kostmann syndrome, leukocyte adhesion deficiency, DiGeorge syndrome, bare lymphocyte syndrome, Omenn's syndrome, severe combined immunodeficiency (SCID), SCID with adenosine deaminase deficiency, absence of T & B cells SCID, absence of T cells, normal B cell SCID, common variable immunodeficiency and X-linked lymphoproliferative disorder, and HIV (human immunodeficiency virus) and AIDS (acquired immune deficiency syndrome).

[0538] Efficacy of treatment is determined by a statistically significant change in one or more indicia of the targeted disease or disorder, as known to one of ordinary skill in the art. For example, whole blood of a subject being treated with iHSCs generated using the compositions, methods, and kits described herein can be analyzed using a complete blood count (CBC). A CBC test can comprise one or more of the following:

a. White blood cell (WBC) count: A count of the actual number of white blood cells per volume of blood.

b. White blood cell differential: A count of the types of white blood cells present in the blood: neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

c. Red blood cell (RBC) count: A count of the actual number of red blood cells per volume of blood.

d. Hemoglobin level: A measure of the amount of oxygen-carrying protein in the blood.

e. Hematocrit level: A measures of the percentage of red blood cells in a given volume of whole blood.

f. Platelet count: A count of the number of platelets in a given volume of blood.

g. Mean platelet volume (MPV): A measurement of the average size of platelets. Newly produced platelets are larger and an increased MPV occurs when increased numbers of platelets are being produced in the bone marrow.

h. Mean corpuscular volume (MCV): A measurement of the average size of RBCs (e.g. whether RBCs are larger than normal (macrocytic) or RBCs are smaller than normal (microcytic)).

i. Mean corpuscular hemoglobin (MCH): A calculation of the average amount of oxygen-carrying hemoglobin inside a red blood cell.

j. Mean corpuscular hemoglobin concentration (MCHC): A calculation of the average concentration of hemoglobin inside a red cell (e.g. decreased MCHC values (hypochromia) or increased MCHC values (hyperchromia)),

k. Red cell distribution width (RDW): A calculation of the variation in the size of RBCs {e.g. amount of variation (anisocytosis) in RBC size and/or variation in shape (poikilocytosis) may cause an increase in the RDW).

[0539] In some embodiments of the compositions, methods, and kits described herein, additional factors can be used to enhance treatment methods using the iHSCs described herein, such as G-CSF, e.g. as described in U.S. Pat. No. 5,582,823; AMD3100 (1,1[1,4-phenylene-bis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane), granulocyte-macrophage colony stimulating factor (GM-CSF), Interleukin-1 (IL-I), Interleukin-3 (IL-3), Interleukin-8 (IL-8), PIXY-321 (GM-CSF/IL-3 fusion protein), macrophage inflammatory protein, stem cell factor (SCF), thrombopoietin, flt3, myelopoietin, anti-VLA-4 antibody, anti-VCAM-1 and growth related oncogene (GRO).

[0540] Provided herein, in some aspects are hematopoietic stem cell (HSC) inducing composition comprising one or more expression vectors encoding at least one, two, three, four, five, six, seven, eight, or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612.

[0541] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0542] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, and MEIS1.

[0543] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5.

[0544] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, and LMO2.

[0545] Also provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0546] a nucleic acid sequence encoding HLF;

[0547] a nucleic acid sequence encoding RUNX1T1;

[0548] a nucleic acid sequence encoding ZFP37;

[0549] a nucleic acid sequence encoding PBX1;

[0550] a nucleic acid sequence encoding LMO2; and

[0551] a nucleic acid sequence encoding PRDM5.

[0552] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0553] a nucleic acid sequence encoding HLF;

[0554] a nucleic acid sequence encoding RUNX1T1;

[0555] a nucleic acid sequence encoding ZFP37;

[0556] a nucleic acid sequence encoding PBX1;

[0557] a nucleic acid sequence encoding LMO2;

[0558] a nucleic acid sequence encoding PRDM5;

[0559] a nucleic acid sequence encoding MYCN; and

[0560] a nucleic acid sequence encoding MEIS1.

[0561] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0562] a nucleic acid sequence encoding HLF;

[0563] a nucleic acid sequence encoding RUNX1T1;

[0564] a nucleic acid sequence encoding ZFP37;

[0565] a nucleic acid sequence encoding PBX1; and

[0566] a nucleic acid sequence encoding LMO2;

[0567] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0568] a nucleic acid sequence encoding PRDM16;

[0569] a nucleic acid sequence encoding ZFP467; and

[0570] a nucleic acid sequence encoding VDR.

[0571] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0572] a nucleic acid sequence encoding HLF;

[0573] a nucleic acid sequence encoding RUNX1T1;

[0574] a nucleic acid sequence encoding PBX1;

[0575] a nucleic acid sequence encoding LMO2;

[0576] a nucleic acid sequence encoding PRDM5

[0577] a nucleic acid sequence encoding ZFP37;

[0578] a nucleic acid sequence encoding MYCN;

[0579] a nucleic acid sequence encoding MSI2;

[0580] a nucleic acid sequence encoding NKX2-3;

[0581] a nucleic acid sequence encoding MEIS1; and

[0582] a nucleic acid sequence encoding RBPMS.

[0583] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0584] a nucleic acid sequence encoding ZFP467;

[0585] a nucleic acid sequence encoding PBX1;

[0586] a nucleic acid sequence encoding HOXB4; and

[0587] a nucleic acid sequence encoding MSI2.

[0588] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0589] a nucleic acid sequence encoding HLF;

[0590] a nucleic acid sequence encoding LMO2;

[0591] a nucleic acid sequence encoding PRDM16; and

[0592] a nucleic acid sequence encoding ZFP37.

[0593] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0594] a nucleic acid sequence encoding MYCN;

[0595] a nucleic acid sequence encoding MSI2;

[0596] a nucleic acid sequence encoding NKX2-3; and

[0597] a nucleic acid sequence encoding RUNX1T1.

[0598] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0599] a nucleic acid sequence encoding HOXB5;

[0600] a nucleic acid sequence encoding HLF;

[0601] a nucleic acid sequence encoding ZFP467;

[0602] a nucleic acid sequence encoding HOXB3;

[0603] a nucleic acid sequence encoding LMO2;

[0604] a nucleic acid sequence encoding PBX1;

[0605] a nucleic acid sequence encoding ZFP37; and

[0606] a nucleic acid sequence encoding ZFP521.

[0607] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0608] a nucleic acid sequence encoding HOXB4;

[0609] a nucleic acid sequence encoding PBX1;

[0610] a nucleic acid sequence encoding LMO2;

[0611] a nucleic acid sequence encoding ZFP467; and

[0612] a nucleic acid sequence encoding ZFP521.

[0613] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0614] a nucleic acid sequence encoding KLF12;

[0615] a nucleic acid sequence encoding HLF; and

[0616] a nucleic acid sequence encoding EGR1.

[0617] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0618] a nucleic acid sequence encoding MEIS1;

[0619] a nucleic acid sequence encoding RBPMS;

[0620] a nucleic acid sequence encoding ZFP37;

[0621] a nucleic acid sequence encoding RUNX1T1; and

[0622] a nucleic acid sequence encoding LMO2.

[0623] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0624] a sequence encoding KLF12; and

[0625] a sequence encoding HLF;

[0626] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising one or more expression vectors comprising:

[0627] a nucleic acid sequence encoding ZFP37;

[0628] a nucleic acid sequence encoding HOXB4;

[0629] a nucleic acid sequence encoding LMO2; and

[0630] a nucleic acid sequence encoding HLF.

[0631] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more expression vectors comprising:

[0632] a nucleic acid sequence encoding MYCN;

[0633] a nucleic acid sequence encoding ZFP467;

[0634] a nucleic acid sequence encoding NKX2-3

[0635] a nucleic acid sequence encoding PBX1; and

[0636] a nucleic acid sequence encoding KLF4.

[0637] In some embodiments of these aspects and all such aspects described herein, the one or more expression vectors are retroviral vectors.

[0638] In some embodiments of these aspects and all such aspects described herein, the one or more expression vectors are lentiviral vectors. In some embodiments, the lentiviral vectors are inducible lentiviral vectors. In some embodiments, the lentiviral vectors are polycistronic inducible lentiviral vectors. In some embodiments, the polycistronic inducible lentiviral vectors express three or more nucleic acid sequences. In some embodiments, each of the nucleic acid sequences of the polycistronic inducible lentiviral vectors are separated by 2A peptide sequences.

[0639] Also provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising modified mRNA sequences encoding at least one, two, three, four, five, six, seven, eight, or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, ZFP612, and ZFP467, wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0640] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0641] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, and MEIS1.

[0642] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5.

[0643] In some embodiments of these aspects and all such aspects described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, and LMO2.

[0644] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0645] a modified mRNA sequence encoding HLF;

[0646] a modified mRNA sequence encoding RUNX1T1;

[0647] a modified mRNA sequence encoding ZFP37;

[0648] a modified mRNA sequence encoding PBX1;

[0649] a modified mRNA sequence encoding LMO2; and

[0650] a modified mRNA sequence encoding PRDM5;

[0651] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0652] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0653] a modified mRNA sequence encoding HLF;

[0654] a modified mRNA sequence encoding RUNX1T1;

[0655] a modified mRNA sequence encoding ZFP37;

[0656] a modified mRNA sequence encoding PBX1;

[0657] a modified mRNA sequence encoding LMO2;

[0658] a modified mRNA sequence encoding PRDM5;

[0659] a modified mRNA sequence encoding MEIS1; and

[0660] a modified mRNA sequence encoding MYCN;

[0661] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0662] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0663] a modified mRNA sequence encoding HLF;

[0664] a modified mRNA sequence encoding RUNX1T1;

[0665] a modified mRNA sequence encoding ZFP37;

[0666] a modified mRNA sequence encoding PBX1; and

[0667] a modified mRNA sequence encoding LMO2;

[0668] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0669] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0670] a modified mRNA sequence encoding PRDM16;

[0671] a modified mRNA sequence encoding ZFP467; and

[0672] a modified mRNA sequence encoding VDR;

[0673] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0674] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0675] a modified mRNA sequence encoding HLF;

[0676] a modified mRNA sequence encoding RUNX1T1;

[0677] a modified mRNA sequence encoding PBX1;

[0678] a modified mRNA sequence encoding LMO2;

[0679] a modified mRNA sequence encoding PRDM5

[0680] a modified mRNA sequence encoding ZFP37;

[0681] a modified mRNA sequence encoding MYCN;

[0682] a modified mRNA sequence encoding MSI2;

[0683] a modified mRNA sequence encoding NKX2-3;

[0684] a modified mRNA sequence encoding MEIS1; and

[0685] a modified mRNA sequence encoding RBPMS;

[0686] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0687] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0688] a modified mRNA sequence encoding ZFP467;

[0689] a modified mRNA sequence encoding PBX1;

[0690] a modified mRNA sequence encoding HOXB4; and

[0691] a modified mRNA sequence encoding MSI2;

[0692] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0693] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0694] a modified mRNA sequence encoding HLF;

[0695] a modified mRNA sequence encoding LMO2;

[0696] a modified mRNA sequence encoding PRDM16; and

[0697] a modified mRNA sequence encoding ZFP37.

[0698] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0699] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0700] a modified mRNA sequence encoding MYCN;

[0701] a modified mRNA sequence encoding MSI2;

[0702] a modified mRNA sequence encoding NKX2-3; and

[0703] a modified mRNA sequence encoding RUNX1T1;

[0704] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0705] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0706] a modified mRNA sequence encoding HOXB5;

[0707] a modified mRNA sequence encoding HLF;

[0708] a modified mRNA sequence encoding ZFP467;

[0709] a modified mRNA sequence encoding HOXB3;

[0710] a modified mRNA sequence encoding LMO2;

[0711] a modified mRNA sequence encoding PBX1;

[0712] a modified mRNA sequence encoding ZFP37; and

[0713] a modified mRNA sequence encoding ZFP521;

[0714] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0715] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0716] a modified mRNA sequence encoding HOXB4;

[0717] a modified mRNA sequence encoding PBX1;

[0718] a modified mRNA sequence encoding LMO2;

[0719] a modified mRNA sequence encoding ZFP467; and

[0720] a modified mRNA sequence encoding ZFP521;

[0721] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0722] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0723] a modified mRNA sequence encoding KLF12;

[0724] a modified mRNA sequence encoding HLF; and

[0725] a modified mRNA sequence encoding EGR;

[0726] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0727] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0728] a modified mRNA sequence encoding MEIS1;

[0729] a modified mRNA sequence encoding RBPMS;

[0730] a modified mRNA sequence encoding ZFP37;

[0731] a modified mRNA sequence encoding RUNX1T1; and

[0732] a modified mRNA sequence encoding LMO2.

[0733] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0734] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0735] a modified mRNA sequence encoding KLF12; and

[0736] a modified mRNA sequence encoding HLF;

[0737] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0738] Provided herein, in some aspects, are hematopoietic stem cell (HSC) inducing compositions comprising

[0739] a modified mRNA sequence encoding ZFP37;

[0740] a modified mRNA sequence encoding HOXB4;

[0741] a modified mRNA sequence encoding LMO2; and

[0742] a modified mRNA sequence encoding HLF;

[0743] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0744] In some embodiments of these aspects and all such aspects described herein, the composition further comprises one or more of:

[0745] a modified mRNA encoding MYCN;

[0746] a modified mRNA encoding ZFP467;

[0747] a modified mRNA encoding NKX2-3

[0748] a modified mRNA encoding PBX1; and

[0749] a modified mRNA encoding KLF4;

[0750] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof.

[0751] In some embodiments of these aspects and all such aspects described herein, the modified cytosine is 5-methylcytosine and the modified uracil is pseudouracil.

[0752] In some embodiments of these aspects and all such aspects described herein, the modified mRNA sequences comprise one or more nucleoside modifications selected from the group consisting of pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, 2-aminopurine, 2,6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine, inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine, and combinations thereof.

[0753] Also provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0754] transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5, wherein each said nucleic acid sequence is operably linked to a promoter; and

[0755] culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0756] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0757] transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5; a nucleic acid sequence encoding MEIS1; and a nucleic acid sequence encoding MYCN, wherein each said nucleic acid sequence is operably linked to a promoter; and

[0758] culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0759] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0760] transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF; a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding PBX1; and a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5, wherein each said nucleic acid sequence is operably linked to a promoter; and

[0761] culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0762] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding PRDM16 a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding VDR.

[0763] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0764] transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM5; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding MEIS1; and a nucleic acid sequence encoding RBPMS; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0765] culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0766] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0767] transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP467, a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding HOXB4; and a nucleic acid sequence encoding MSI2; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0768] culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0769] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM16; and a nucleic acid sequence encoding ZFP37.

[0770] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0771] transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2, a nucleic acid sequence encoding NKX2-3; and a nucleic acid sequence encoding RUNX1T1; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0772] culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0773] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HOXB5; a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding HOXB3; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding ZFP37; and a nucleic acid sequence encoding ZFP521.

[0774] Provided herein in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0775] transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding PBX1, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding ZFP521; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0776] culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0777] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; a nucleic acid sequence encoding HLF; and a nucleic acid sequence encoding EGR1.

[0778] Provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0779] transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding MEIS1; a nucleic acid sequence encoding RBPMS; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding RUNX1T1; and a nucleic acid sequence encoding LMO2; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0780] culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0781] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; and a nucleic acid sequence encoding HLF.

[0782] Provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0783] transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding HLF; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0784] culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0785] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; and a nucleic acid sequence encoding HLF.

[0786] Provided herein, in some aspects, are methods for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0787] transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding HLF; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0788] culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0789] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding PBX1; and a nucleic acid sequence encoding KLF4.

[0790] In some embodiments of these aspects and all such aspects described herein, the somatic cell is a fibroblast cell.

[0791] In some embodiments of these aspects and all such aspects described herein, the somatic cell is a hematopoietic lineage cell.

[0792] In some embodiments of these aspects and all such aspects described herein, the hematopoietic lineage cell is selected from promyelocytes, neutrophils, eosinophils, basophils, reticulocytes, erythrocytes, mast cells, osteoclasts, megakaryoblasts, platelet producing megakaryocytes, platelets, monocytes, macrophages, dendritic cells, lymphocytes, NK cells, NKT cells, innate lymphocytes, multipotent hematopoietic progenitor cells, oligopotent hematopoietic progenitor cells, and lineage restricted hematopoietic progenitors.

[0793] In some embodiments of these aspects and all such aspects described herein, the hematopoietic lineage cell is selected from a multi-potent progenitor cell (MPP), common myeloid progenitor cell (CMP), granulocyte-monocyte progenitor cells (GMP), common lymphoid progenitor cell (CLP), and pre-megakaryocyte-erythrocyte progenitor cell.

[0794] In some embodiments of these aspects and all such aspects described herein, the hematopoietic lineage cell is selected from a megakaryocyte-erythrocyte progenitor cell (MEP), a ProB cell, a PreB cell, a PreProB cell, a ProT cell, a double-negative T cell, a pro-NK cell, a pro-dendritic cell (pro-DC), pre-granulocyte/macrophage cell, a granulocyte/macrophage progenitor (GMP) cell, and a pro-mast cell (ProMC).

[0795] Also provided herein, in some aspects, are methods of promoting transdifferentiation of a ProPreB cell to the myeloid lineage comprising:

[0796] transducing a ProPreB cell with one or more vectors comprising a nucleic acid sequence encoding ZFP467, a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding HOXB4; and a nucleic acid sequence encoding MSI2; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0797] culturing the transduced ProPreB cell in a cell media that supports growth of myeloid lineage cells, thereby transdifferentiating the ProPreB cell to the myeloid lineage.

[0798] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM16; and a nucleic acid sequence encoding ZFP37.

[0799] Also provided herein, in some aspects, are methods of increasing survival and/or proliferation of ProPreB cells, comprising:

[0800] transducing a ProPreB cell with one or more vectors comprising a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding PBX1, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding ZFP521; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0801] culturing the transduced ProPreB cell in a cell media that supports growth of ProPreB cells, thereby increasing survival and/or proliferation of ProPreB cells.

[0802] In some embodiments of these aspects and all such aspects described herein, the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; a nucleic acid sequence encoding HLF; and a nucleic acid sequence encoding EGR1.

[0803] Also provided herein, in some aspects, are isolated induced hematopoietic stem cells (iHSCs) produced using any of the HSC inducing compositions or methods described herein.

[0804] In some aspects, provided herein are cell clones comprising a plurality of the induced hematopoietic stem cells (iHSCs) produced using any of the HSC inducing compositions or methods described herein. In some embodiments of these aspects and all such aspects described herein, the cell clones further comprise a pharmaceutically acceptable carrier.

[0805] Also provided herein, in some aspects, are kits for making induced hematopoietic stem cells (iHSCs), the kits comprising any of the HSC inducing compositions comprising one or more expression vector components described herein.

[0806] Provided herein, in some aspects, are kits for making induced hematopoietic stem cells (iHSCs), the kits comprising any of the HSC inducing compositions comprising modified mRNA sequence components described herein.

[0807] Also provided herein, in some aspects, are kits comprising one or more of the HSC inducing factors described herein as components for the methods of making the induced hematopoietic stem cells described herein.

[0808] Accordingly, in some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) one or more expression vectors encoding at least one, two, three, four, five, six, seven, eight, or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, ZFP612, and ZFP467; and (b) packaging and instructions therefor.

[0809] In some embodiments of these kits and all such kits described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0810] In some embodiments of these kits and all such kits described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5.

[0811] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) one or more expression vectors comprising: a nucleic acid sequence encoding HLF; a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5; and (b) packaging and instructions therefor.

[0812] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of: a nucleic acid sequence encoding PRDM16; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding VDR.

[0813] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) one or more expression vectors comprising: a nucleic acid sequence encoding HLF; a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM5; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding MEIS1; and a nucleic acid sequence encoding RBPMS; and (b) packaging and instructions therefor.

[0814] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) one or more expression vectors comprising: a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding HOXB4; and a nucleic acid sequence encoding MSI2; and (b) packaging and instructions therefor.

[0815] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of: a nucleic acid sequence encoding HLF; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM16; and a nucleic acid sequence encoding ZFP37.

[0816] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) one or more expression vectors comprising: a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2; a nucleic acid sequence encoding NKX2-3; and a nucleic acid sequence encoding RUNX1T1; and (b) packaging and instructions therefor.

[0817] In some embodiments of these kits and all such kits described herein, the kit further comprises a nucleic acid sequence encoding HOXB5; a nucleic acid sequence encoding HLF; a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding HOXB3; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding ZFP37; and a nucleic acid sequence encoding ZFP521.

[0818] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) one or more expression vectors composition comprising: a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding ZFP521; and (b) packaging and instructions therefor.

[0819] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of: a nucleic acid sequence encoding KLF12; a nucleic acid sequence encoding HLF; and a nucleic acid sequence encoding EGR1.

[0820] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) one or more expression vectors comprising: a nucleic acid sequence encoding MEIS1; a nucleic acid sequence encoding RBPMS; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding RUNX1T1; and a nucleic acid sequence encoding LMO2; and (b) packaging and instructions therefor.

[0821] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of a sequence encoding KLF12; and a sequence encoding HLF.

[0822] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) one or more expression vectors comprising: a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding HLF; and (b) packaging and instructions therefor.

[0823] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of: a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding PBX1; and a nucleic acid sequence encoding KLF4.

[0824] In some embodiments of these kits, the expression vector is a viral vector. In some embodiments of these kits, the viral vector is a retroviral vector, adenoviral vector, lentiviral vector, herpes virus vector, pox virus vector, or an adeno-associated virus (AAV) vector. In some embodiments, the expression vector is inducible.

[0825] Also provided herein, in some aspects, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) modified mRNA sequences encoding at least one, two, three, four, five, six, seven, eight, or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612, wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0826] In some embodiments of these kits and all such kits described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0827] In some embodiments of these kits and all such kits described herein, the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5

[0828] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) a modified mRNA sequence encoding HLF; a modified mRNA sequence encoding RUNX1T1; a modified mRNA sequence encoding ZFP37; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding LMO2; and a modified mRNA sequence encoding PRDM5; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof and (b) packaging and instructions therefor.

[0829] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of: a modified mRNA sequence encoding PRDM16; a modified mRNA sequence encoding ZFP467; and a modified mRNA sequence encoding VDR; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0830] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) a modified mRNA sequence encoding HLF; a modified mRNA sequence encoding RUNX1T1; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding LMO2; a modified mRNA sequence encoding PRDM5; a modified mRNA sequence encoding ZFP37; a modified mRNA sequence encoding MYCN; a modified mRNA sequence encoding MSI2; a modified mRNA sequence encoding NKX2-3; a modified mRNA sequence encoding MEIS1; and a modified mRNA sequence encoding RBPMS; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof and (b) packaging and instructions therefor.

[0831] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) a modified mRNA sequence encoding ZFP467; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding HOXB4; and a modified mRNA sequence encoding MSI2; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof; and (b) packaging and instructions therefor.

[0832] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of: a modified mRNA sequence encoding HLF; a modified mRNA sequence encoding LMO2; a modified mRNA sequence encoding PRDM16; and a modified mRNA sequence encoding ZFP37, wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0833] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) a modified mRNA sequence encoding MYCN; a modified mRNA sequence encoding MSI2; a modified mRNA sequence encoding NKX2-3; and a modified mRNA sequence encoding RUNX1T1; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof; and (b) packaging and instructions therefor.

[0834] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of: a modified mRNA sequence encoding HOXB5; a modified mRNA sequence encoding HLF; a modified mRNA sequence encoding ZFP467; a modified mRNA sequence encoding HOXB3; a modified mRNA sequence encoding LMO2; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding ZFP37; and a modified mRNA sequence encoding ZFP521; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0835] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) a modified mRNA sequence encoding HOXB4; a modified mRNA sequence encoding PBX1; a modified mRNA sequence encoding LMO2; a modified mRNA sequence encoding ZFP467; and a modified mRNA sequence encoding ZFP521; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof; and (b) packaging and instructions therefor.

[0836] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of: a modified mRNA sequence encoding KLF12; a modified mRNA sequence encoding HLF; and a modified mRNA sequence encoding EGR; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0837] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) a modified mRNA sequence encoding MEIS1; a modified mRNA sequence encoding RBPMS; a modified mRNA sequence encoding ZFP37; a modified mRNA sequence encoding RUNX1T1; and a modified mRNA sequence encoding LMO2; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof; and (b) packaging and instructions therefor.

[0838] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of: a modified mRNA sequence encoding KLF12; and a modified mRNA sequence encoding HLF; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0839] In some aspects, provided herein, are kits for preparing induced hematopoietic stem cells comprising the following components: (a) a modified mRNA sequence encoding ZFP37; a modified mRNA sequence encoding HOXB4; a modified mRNA sequence encoding LMO2; and a modified mRNA sequence encoding HLF; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof; and (b) packaging and instructions therefor.

[0840] In some embodiments of these kits and all such kits described herein, the kit further comprises one or more of: a modified mRNA encoding MYCN; a modified mRNA encoding ZFP467; a modified mRNA encoding NKX2-3; a modified mRNA encoding PBX1; and a modified mRNA encoding KLF4; wherein each cytosine of each of the modified mRNA sequences is a modified cytosine, each uracil of each of the modified mRNA sequences is a modified uracil, or a combination thereof.

[0841] In some embodiments of these kits and all such kits described herein, the modified cytosine is 5-methylcytosine and the modified uracil is pseudouridine.

[0842] In some embodiments of these kits and all such kits described herein, one or more of the synthetic, modified mRNAs can further comprise one or more of a poly(A) tail, a Kozak sequence, a 3' untranslated region, a 5' untranslated regions, and a 5' cap, such as 5' cap analog, such as e.g., a 5' diguanosine cap, tetraphosphate cap analogs having a methylene-bis(phosphonate) moiety, cap analogs having a sulfur substitution for a non-bridging oxygen, N7-benzylated dinucleoside tetraphosphate analogs, or anti-reverse cap analogs. The kits can also comprise a 5' cap analog. The kit can also comprise a phosphatase enzyme (e.g., Calf intestinal phosphatase) to remove the 5' triphosphate during the RNA modification procedure. Optionally, the kit can comprise one or more control synthetic mRNAs, such as a synthetic, modified RNA encoding green fluorescent protein (GFP) or other marker molecule.

[0843] In other embodiments, the kit can further comprise materials for further reducing the innate immune response of a cell. For example, the kit can further comprise a soluble interferon receptor, such as B18R. In some embodiments, the kit can comprise a plurality of different synthetic, modified RNA molecules.

[0844] The kits described herein can also comprise, in some aspects, one or more linear DNA templates for the generation of synthetic mRNAs encoding the HSC inducing factors described herein.

[0845] The kits described herein, in some embodiments, can further provide the synthetic mRNAs or the one or more expression vectors encoding HSC inducing factors in an admixture or as separate aliquots.

[0846] In some embodiments, the kits can further comprise an agent to enhance efficiency of reprogramming. In some embodiments, the kits can further comprise one or more antibodies or primer reagents to detect a cell-type specific marker to identify cells induced to the hematopoietic stem cell state.

[0847] In some embodiments, the kits can further comprise a buffer. In some such embodiments, the buffer is RNase-free TE buffer at pH 7.0. In some embodiments, the kit further comprises a container with cell culture medium.

[0848] All kits described herein can further comprise a buffer, a cell culture medium, a transduction or transfection medium and/or a media supplement. In preferred embodiments, the buffers, cell culture mediums, transfection mediums, and/or media supplements are DNAse and RNase-free. In some embodiments, the synthetic, modified RNAs provided in the kits can be in a non-solution form of specific quantity or mass, e.g., 20 μg, such as a lyophilized powder form, such that the end-user adds a suitable amount of buffer or medium to bring the components to a desired concentration, e.g., 100 ng/μl.

[0849] All kits described herein can further comprise devices to facilitate single-administration or repeated or frequent infusions of the cells generated using the kits components described herein, such as a non-implantable delivery device, e.g., needle, syringe, pen device, or an implantatable delivery device, e.g., a pump, semi-permanent stent (e.g., intravenous, intraperitoneal, intracisternal or intracapsular), or reservoir. In some such embodiments, the delivery device can include a mechanism to dispense a unit dose of a pharmaceutical composition comprising the iHSC clone. In some embodiments, the device releases the composition continuously, e.g., by diffusion. In some embodiments, the device can include a sensor that monitors a parameter within a subject. For example, the device can include pump, e.g., and, optionally, associated electronics.

[0850] The induced hematopoietic stem cells in some aspects of all the embodiments of the invention, while similar in functional characteristics, differ significantly in their gene expression or methylation pattern from the naturally occurring endogenous hematopoietic stem cells. For example, compared to the endogenous HSC gene expression pattern, exemplary genes of which are shown in Tables 2 and 3, the induced hematopoietic stem cells differ by showing about 1-5%, 5-10%, 5-15%, or 5-20% increased expression of about 1-5%, 2-5%, 3-5%, up to 50%, up to 40%, up to 30%, up to 25%, up to 20%, up to 15%, or up to 10% of the genes in endogenous HSCs, for example, those set forth in Tables 2 and 3. Specifically, the expression in the iHSCs of genes the expression of which is reduced or insignificant in the naturally occurring HSCs (see, selected examples in Table 2), is increased or the expression of the genes the expression of which is significant in the naturally occurring HSCs (see, selected examples of highly expressed genes in isolated HSCs in Table 3) is decreased in iHSCs.

[0851] In some aspects of all the embodiments of the invention, while similar in functional characteristics, the induced pluripotent stem cells differ significantly in their methylation pattern from the naturally occurring or endogenous HSCs. For example, compared to the endogenous methylation pattern of genes as exemplified in Table 4, the iHSCs differ by showing about 1-5%, in some aspects 1-10%, in some aspects 5-10% difference in the methylation of at about 1-5%, 1-10%, 5-10%, up to 50%, up to 40%, up to 30%, up to 25%, up to 20%, up to 15%, or up to 10% of the methylation sites of naturally occurring HSCs, which are exemplified in Table 4. The difference may be increased or decreased methylation compared to endogenous HSCs. In some aspects, some methylation sites are methylated and some unmethylated in iHSCs compared to the endogenous HSCs methylation sites as exemplified in Table 4.

[0852] Table 4 includes 35 exemplary profiles from each chromosome (1-19, x and y) as profiled in naturally occurring or endogenous HSCs. The screening was done by randomizing the most and least methylated sites (i.e. the top/bottom 20%) where 100 were taken from each group (except the Y chromosome which had a very small number of sites and only 35 random sites were selected). Of the mid (20-80%) percentiles, 3000 methylation sites were randomly selected. From this pool of 3000 sites, 35 methylation sites were randomly selected. These examples were selected to represent the methylation status of the entire chromosome but enrich for those mid-range sites of methylation which, without wishing to be bound by theory, may be more characteristic of the naturally occurring HSC.

HSC Expression Analysis

[0853] Genome-wide gene expression analysis was performed on purified LSKCD34-Flk2-using the Affymetrix GeneChip Mouse Genome 430 2.0 Array platform. RNA was isolated using TRIzol (Life Technologies) and purified RNA was amplified, labeled, hybridized, and scanned according to Affymetrix's. Raw data was normalized using gcRMA together with 383 other hematopoietic cell types. These data were log transformed and average of the four biological replicates of are presented as expression levels.

DNA Methylation Analysis of HSCs

[0854] RRBS libraries for DNA methylation analysis were prepared from 30 ng input DNA per biological replicate of LSKCD34-FLk2-HSCs following a published protocol (Gu et al Nat. Protoc, 6 (2011), pp. 468-481) and sequenced by the Broad Institute's Genome Sequencing Platform on Illumina Genome Analyzer II or HiSeq 2000 machines. Bioinformatic data processing and quality control were performed as described in Bock et al (Cell, 144 (2011), pp. 439-452). The raw sequencing reads were aligned using Maq's bisulfite alignment mode and DNA methylation calling was performed using custom software (Gu et al, Nat Methods 7(2010) 133-136). DNA methylation levels were calculated for 1-kilobase tiling regions throughout the genome as coverage-weighted means of the DNA methylation levels of individual CpGs. Only regions with at least two CpGs with at least 5 independent DNA methylation measurements per CpG were retained, giving rise to a list of genomic regions with high-confidence DNA methylation measurements. In the initial filtering step, all 1-kb tiles of DNA methylation were excluded for which the two biological replicates were not sufficiently consistent with each other. Any measurement was excluded if the absolute divergence between biological replicates exceeded 0.2 and if the relative divergence between biological replicates exceeded 0.05. These absolute thresholds were selected based on our previous experience with RRBS data analysis, and the relative thresholds were calculated such that the absolute and relative thresholds became equivalent for values close to the center of the spectrum, i.e. around 0.5. Identification of significant differentially methylated regions were based on the average DNA methylation difference between the biological replicates of two cell types, requiring a minimum absolute difference of 0.1 for 1-kb tiles, and a more stringent threshold of 0.2 for single CpGs. The relative difference thresholds were calculated from the absolute difference thresholds as described above. The combined use of relative and absolute difference thresholds resulted in robust identification of relevant differences across the spectrum of genes and genomic regions with high, medium and low DNA methylation.

TABLE 2

Examples of transcripts showing reduced/insignificant expression in endogenous HSCs

Probeset	Expression (Average of 4 datasets of purified HSCs)	Gene Symbol
1425771_at	4.65	Akr1d1
1425772_at	4.65	Col4a4
1425773_s_at	4.65	Nmnat1
1425774_at	4.65	Srrm4
1425775_at	4.65	Zfp820
1425776_a_at	4.65	C87436
1425777_at	4.65	Cacnb1
1425778_at	4.65	Ido2
1425779_a_at	4.65	Tbx1
1425780_a_at	4.65	Tmem167
1425781_a_at	4.65	Plcb1
1425782_at	4.65	Plcb1
1425783_at	4.65	Tc2n
1425784_a_at	4.65	Olfm1
1425785_a_at	4.65	Txk
1425786_a_at	4.65	Hsf4
1425787_a_at	4.65	Sytl3
1425788_a_at	4.65	Echdc2
1425789_s_at	4.65	Anxa8
1425790_a_at	4.65	Grik2
1425791_at	4.65	Pon2
1425792_a_at	4.65	Rorc
1425793_a_at	4.65	Rorc
1425794_at	4.65	Pola2
1425795_a_at	4.65	Map3k7
1425796_a_at	4.65	Fgfr3
1425797_a_at	4.65	Syk
1425808_a_at	4.65	Myocd
1425798_a_at	4.65	Recql
1425800_at	4.65	Rad9b
1425801_x_at	4.65	Cotl1
1425802_a_at	4.65	Fcrla
1425803_a_at	4.65	Mbd2
1425804_at	4.65	Hmx2
1425806_a_at	4.65	Med21
1425807_at	4.65	BC021891
1425809_at	4.65	Fabp4
1425810_a_at	4.65	Csrp1

TABLE 2-continued

Examples of transcripts showing reduced/insignificant expression in endogenous HSCs

Probeset	Expression (Average of 4 datasets of purified HSCs)	Gene Symbol
1425811_a_at	4.65	Csrp1
1425812_a_at	4.65	Cacna1b
1425813_at	4.65	Pign
1425814_a_at	4.65	Calcrl
1425815_a_at	4.65	Hmmr
1425816_at	4.65	Zfp287
1425817_a_at	4.65	Slc8a1
1425818_at	4.65	4930520O04Rik
1425819_at	4.65	Zbtb7c
1425820_x_at	4.65	Gpatch4
1425821_at	4.65	Clcn7
1425822_a_at	4.65	Dtx1
1426032_at	4.65	Nfatc2
1425823_at	4.65	Cfhr2
1425825_at	4.65	Eml6
1425826_a_at	4.65	Sorbs1
1425827_at	4.65	Nkx2-3
1425828_at	4.65	Nkx6-1
1425829_a_at	4.65	Steap4
1425830_a_at	4.65	Cinp /// LOC640972
1425831_at	4.65	Zfp101
1425832_a_at	4.65	Cxcr6
1425833_a_at	4.65	Hpca
1425834_a_at	4.65	Gpam
1425835_a_at	4.65	Bbx
1425836_a_at	4.65	Limk1
1425837_a_at	4.65	Ccrn4l
1425838_at	4.65	Atp9a
1425839_at	4.65	Fkbp11
1425840_a_at	4.65	Sema3f
1425842_at	4.65	Edil3
1425843_at	4.65	Mrpl33
1425845_a_at	4.65	Shoc2
1425846_a_at	4.65	Caln1
1425848_a_at	4.65	Dusp26
1425849_at	4.65	Chrnb4
1425850_a_at	4.65	Nek6
1425851_a_at	4.65	Amigo1
1425852_at	4.65	Catsperg1
1425855_a_at	4.65	Crk
1425857_at	4.65	Fbxw9
1425858_at	4.65	Ube2m
1425859_a_at	4.65	Psmd4
1425861_x_at	4.65	Cacna2d1
1425863_a_at	4.65	Ptpro
1425864_a_at	4.65	Sorcs1
1425865_a_at	4.65	Lig3
1425866_a_at	4.65	Plekha4
1425867_at	4.65	Plekha4
1425868_at	4.65	Hist2h2bb
1425869_a_at	4.65	Psen2
1425870_a_at	4.65	Kcnip2
1425871_a_at	4.65	Igk-V28
1425874_at	4.65	Hoxc13
1425875_a_at	4.65	Lepr
1425876_a_at	4.65	Glce
1425877_at	4.65	Hyal3
1425878_at	4.65	Cabp4
1425879_at	4.65	Zfp352
1425880_x_at	4.65	Zfp352
1425881_at	4.65	Psg28
1425882_at	4.65	Gdf2
1425883_at	4.65	Smg6
1425884_at	4.65	Rpf2
1425885_a_at	4.65	Kcnab2
1425888_at	4.65	Klra17
1425889_at	4.65	Wnt9a
1425890_at	4.65	Ly6i
1425891_a_at	4.65	Grtp1
1425893_a_at	4.65	Fhit
1425895_a_at	4.65	Id1
1425897_at	4.65	—
1425898_x_at	4.65	Olfm3
1425899_a_at	4.65	Itsn1
1425901_at	4.65	Nfatc2
1425903_at	4.65	Sema6a
1425904_at	4.65	Satb2
1425905_at	4.65	—
1425906_a_at	4.65	Sema3e
1425907_s_at	4.65	Amot
1425908_at	4.65	Gnb1
1425910_at	4.65	Dnajc2
1425911_a_at	4.65	Fgfr1
1425912_at	4.65	Cep164
1425913_a_at	4.65	Spats2l
1425914_a_at	4.65	Armcx1
1425915_at	4.65	Slc26a8
1425916_at	4.65	Capn8
1425917_at	4.65	H28
1425918_at	4.65	—
1425919_at	4.65	Ndufa12
1425920_at	4.65	Cuedc1
1425921_a_at	4.65	1810055G02Rik
1425922_a_at	4.65	Mycn
1425923_at	4.65	Mycn
1425925_at	4.65	Fcamr
1425926_a_at	4.65	Otx2
1425927_a_at	4.65	Atf5
1425928_at	4.65	Xkr6
1425929_a_at	4.65	Rnf14
1425931_a_at	4.65	Arntl2
1425932_a_at	4.65	Celf1
1425934_a_at	4.65	B4galt4
1425935_at	4.65	Hspb11
1425936_a_at	4.65	Ankmy2
1425937_a_at	4.65	Hexim1
1425939_at	4.65	Rad50
1425940_a_at	4.65	Ssbp3
1425941_a_at	4.65	Fanci
1425942_a_at	4.65	Gpm6b
1425943_at	4.65	Nmur2
1425944_a_at	4.65	Rad51l3
1425945_at	4.65	Zfp626
1425946_at	4.65	Gstm7
1425947_at	4.65	Ifng
1425949_at	4.65	Slc25a30
1425950_at	4.65	Slc17a9
1425951_a_at	4.65	Clec4n
1425952_a_at	4.65	Gcg
1425953_at	4.65	—
1425954_a_at	4.65	Apex2
1425955_at	4.65	Cav2
1425958_at	4.65	Il1f9
1425959_x_at	4.65	Klra16
1425960_s_at	4.65	Pax6
1425962_at	4.65	Klrb1f
1425963_at	4.65	Cabp7
1425964_x_at	4.65	Hspb1
1425965_at	4.65	Ubc
1425966_x_at	4.65	Ubc
1425967_a_at	4.65	Mcpt4
1425968_s_at	4.65	Speg
1425969_a_at	4.65	Htt
1425970_a_at	4.65	Ros1
1425971_at	4.65	Naip3
1425972_a_at	4.65	Zfx
1425973_at	4.65	Lyst
1425975_a_at	4.65	Mapk8ip3

TABLE 2-continued

Examples of transcripts showing reduced/ insignificant expression in endogenous HSCs

Probeset	Expression (Average of 4 datasets of purified HSCs)	Gene Symbol
1426023_a_at	4.65	Rabep1
1426024_a_at	4.65	Dbn1
1426025_s_at	4.65	Laptm5
1425976_x_at	4.65	Zfp353
1425977_a_at	4.65	Slk
1425979_a_at	4.65	Fbf1
1425980_at	4.65	Wdr54
1425981_a_at	4.65	Rbl2
1425983_x_at	4.65	Hipk2
1425985_s_at	4.65	Masp1
1425986_a_at	4.65	Dcun1d1
1425987_a_at	4.65	Kcnma1
1425988_a_at	4.65	Hipk1
1425989_a_at	4.65	Eya3
1425990_a_at	4.65	Nfatc2
1425991_a_at	4.65	Kank2
1425992_at	4.65	Slc6a5
1425994_a_at	4.65	Asah2
1425995_s_at	4.65	Wt1
1425996_a_at	4.65	Hltf
1425997_a_at	4.65	Pign
1425998_at	4.65	Sytl4
1426001_at	4.65	Eomes
1426004_a_at	4.65	Tgm2
1426005_at	4.65	Dmp1
1426006_at	4.65	Kcnq2
1426008_a_at	4.65	Slc7a2
1426009_a_at	4.65	Pip5k1a
1426010_a_at	4.65	Epb4.1l3
1426011_a_at	4.65	Ggnbp2
1426012_a_at	4.65	2610301G19Rik
1426013_s_at	4.65	Plekha4
1426014_a_at	4.65	Cdhr5
1426017_a_at	4.65	0610011L14Rik
1426018_a_at	4.65	Sox6
1426019_at	4.65	Plaa
1426021_a_at	4.65	Cdc7
1426022_a_at	4.65	Vill
1426026_at	4.65	Prpf6
1426027_a_at	4.65	Arhgap10
1426028_a_at	4.65	Cit

TABLE 3

Examples of transcripts showing expression/ significant expression in endogenous HSCs

Probeset	Expression (Average of 4 datasets of purified HSCs)	Gene Symbol
1424256_at	100879.78	Rdh12
1424539_at	79795.71	Ubl4
1420954_a_at	76447.45	Add1
1421742_at	75395.99	—
1424295_at	72899.90	Dppa3
1423567_a_at	72869.27	Psma7
1423106_at	70905.48	Ube2b
1424391_at	69677.87	Nrd1
1424069_at	69512.25	Napg
1424721_at	67140.32	Mfap3
1422960_at	65644.79	Srd5a2
1421948_a_at	64085.44	Ccdc123
1423089_at	62549.13	Tmod3
1424335_at	62005.99	Ppcdc
1423792_a_at	60183.19	Cmtm6
1422398_at	58720.84	Hist1h1e
1421896_at	58579.47	Elk1
1423355_at	57569.64	Snap29
1420529_at	57554.85	Dpf1
1423240_at	57379.26	Src
1421410_a_at	56489.03	Pstpip2
1421584_at	54335.88	Opn4
1420202_at	54182.06	—
1422376_at	54014.33	Vmn1r50
1423848_at	53959.70	Mphosph6
1422416_s_at	53943.95	Vpreb1///Vpreb2
1423907_a_at	53750.78	Ndufs8
1419015_at	52526.85	Wisp2
1422702_at	52048.42	Azin1
1423817_s_at	51920.82	Use1
1422664_at	51789.77	Rab10
1421988_at	51730.79	Papss2
1420092_at	51443.43	Morc3
1419919_at	50903.42	—
1423493_a_at	50864.75	Nfix
1420517_at	49770.55	Chmp4c
1422490_at	49492.67	Bnip2
1423805_at	49225.38	Dab2
1421893_a_at	49082.98	Tpp2
1422607_at	48373.32	Etv1
1422808_s_at	48260.89	Dock2
1423728_at	47793.86	Eif3l
1422634_a_at	47057.45	Vsig2
1423415_at	46829.97	Gpr83
1423774_a_at	46597.55	Prc1
1421205_at	46410.24	Atm
1422725_at	46373.82	Mak
1422876_at	46000.03	Capn9
1420030_at	45773.96	Slu7
1423082_at	45717.01	Derl1
1424369_at	45609.09	Psmf1
1424432_at	45430.90	Ubtd1
1421578_at	45382.12	Ccl4
1422729_at	45325.62	Pcdhb10
1424004_x_at	45166.17	4930444A02Rik
1419676_at	45159.39	Mx2
1422946_a_at	45067.84	Dnmt1
1420200_at	44965.21	—
1421868_a_at	44891.20	Pnlip
1420217_x_at	44808.32	—
1419864_x_at	44771.30	Tnpo1
1432675_at	44721.78	Mdn1
1423206_s_at	44538.34	2310003F16Rik/// Serf2
1423402_at	44427.28	Creb1
1420539_a_at	43572.89	Chrdl2
1423072_at	43569.21	6720475J19Rik
1423348_at	43334.95	Fzd8
1422152_at	43301.54	Hmx1
1420955_at	42958.08	Vsnl1
1422534_at	42719.81	Cyp51
1421514_a_at	42690.03	Scml2
1420573_at	42424.32	Hoxd1
1422139_at	42321.56	Plau
1423193_at	42255.15	Pspc1
1422949_at	41969.65	Nos1
1422585_at	41579.30	Odf1
1421685_at	41540.59	Clec4b1
1421144_at	41368.55	Rpgrip1
1422038_a_at	41364.86	Tnfrsf22
1425165_at	41318.16	Gzmn
1425101_a_at	41263.26	Fkbp6
1421858_at	40782.82	Adam17
1424361_at	40305.18	Tti2
1432026_a_at	39842.37	Herc6
1421877_at	39450.73	Mapk9
1424168_a_at	39344.00	Capzb

TABLE 3-continued

Examples of transcripts showing expression/significant expression in endogenous HSCs

Probeset	Expression (Average of 4 datasets of purified HSCs)	Gene Symbol
1423746_at	39125.86	Txndc5
1421784_a_at	39087.91	Efna4
1422216_at	38969.12	Mid2
1437495_at	38891.23	Mbtps2///Yy2
1422193_at	38621.58	Gucy2e
1424209_at	38397.04	Rars2
1421734_at	38265.53	Cxcr2
1422764_at	38046.45	Mapre1
1422461_at	37752.66	Atad3a
1422319_at	37656.70	—
1421828_at	37384.32	Kpna3
1422947_at	37379.83	Hist1h4a
1417187_at	37147.52	Ube2k
1420237_at	37138.69	—
1421111_at	37129.17	Rybp
1421762_at	36844.59	Kcnj5
1425001_at	36814.72	Rnf146
1422763_at	36738.09	Gipc1
1421198_at	36633.80	Itgav
1423022_at	36619.85	Adra2a
1425460_at	36318.33	Mtmr2
1423718_at	35541.24	Ak3
1424746_at	35456.02	Kif1c
1422791_at	35371.28	Pafah1b2
1443492_at	35208.55	—
1422154_at	35197.92	Gpr27
1423232_at	35156.06	Etv4
1434987_at	34983.28	Aldh2
1421928_at	34894.19	Epha4
1421276_a_at	34783.78	Dst
1418807_at	34723.24	3110070M22Rik
1421357_at	34509.96	Gtf2a1
1420450_at	33787.26	Mmp10
1425562_s_at	33760.26	Trnt1
1422137_at	33732.68	Duoxa2
1420882_a_at	33268.28	Acd
1420792_at	32727.55	4930433N12Rik
1428618_at	32608.49	Hcfc2
1423324_at	32498.13	Pnn
1421066_at	32380.36	Jak2
1421767_at	32357.95	Adk
1423465_at	32223.80	Frrs1
1420412_at	32006.60	Tnfsf10
1422403_at	31627.13	Gm12597
1420644_a_at	31555.81	Sec61a2
1424157_at	31355.35	Ehd2
1425678_a_at	31211.98	Snrk
1419171_at	30993.36	Fam174a
1424059_at	30975.22	Suv420h2
1423390_at	30941.65	Siah1a
1430244_at	30636.46	4921509J17Rik
1424356_a_at	30596.60	Metrnl
1422035_at	30526.30	Serpinb9c
1424763_at	30455.13	Rsph9
1420242_at	30259.70	—
1423292_a_at	30255.63	Prx
1425719_a_at	30011.99	Nmi
1422891_at	29811.27	H2-Ea-ps
1433073_at	29755.02	4933425E08Rik
1424874_a_at	29586.89	Ptbp1
1421795_s_at	29485.47	Klrc2///Klrc3
1424781_at	29441.10	Reep3
1420106_at	29316.87	Siah1a
1423735_a_at	29115.24	Wdr36
1421132_at	28979.38	Pvrl3
1423440_at	28884.32	Fam33a
1424619_at	28807.35	Sf3b4
1420359_at	28678.72	Sva
1422121_at	28666.64	Oprd1
1424773_at	28663.97	Fam125a
1422217_a_at	28522.13	Cyp1a1
1419908_at	28487.43	Fcrla
1416576_at	27695.03	Socs3
1422574_at	27639.56	Mxd4
1433622 at	27471.80	Gemin4///Glod4///Gm6330
1438263_at	27434.33	9430020K01Rik
1425220_x_at	27306.78	LOC100038937
1422454_at	27268.17	Krt13
1422240_s_at	26926.68	Sprr2h
1433942_at	26894.49	Myo6
1437613_s_at	26870.76	Ptpdc1
1418969_at	26582.64	Skp2
1421818_at	26510.49	Bcl6
1422017_s_at	26492.47	4833439L19Rik
1422088_at	26321.36	Mycl1
1424911_a_at	26252.42	Lyzl4
1415812_at	26042.95	Gsn
1422592_at	25974.74	Ctnnd2
1421422_at	25602.36	5033411D12Rik
1422511_a_at	25483.54	Ogfr
1432823_at	25438.68	Sypl2
1421211_a_at	25380.22	Ciita
1416578_at	25267.25	Gm9840///Rbx1
1425535_at	25144.30	Repin1
1420466_at	25061.79	Mucl1
1437720_at	24921.64	Eif2d
1422435_at	24867.70	2210010C04Rik
1420648_at	24760.09	Trim12a
1421382_at	24658.48	Prlr
1416404_s_at	24652.70	Rps16
1424118_a_at	24646.84	Spc25
1425180_at	24391.49	Sgip1
1422621_at	24276.19	Ranbp2
1421265_a_at	24108.68	Rbm38
1423590_at	23955.37	Napsa
1431842_at	23948.99	4930422C21Rik
1428567_at	23851.44	Hspbap1
1424928_at	23715.06	2210018M11Rik
1421894_a_at	23697.49	Tpp2
1420489_at	23628.96	Mrps14
1425406_at	23574.24	Clec4a2
1419907_s_at	23407.93	Fcrla
1421139_a_at	23222.94	Zfp386
1420219_at	23098.02	Dnajc21
1420714_at	23021.11	Lbx2
1419571_at	23014.90	Slc28a3
1424501_at	22942.41	Utp6
1423777_at	22813.47	Usp20
1424712_at	22776.38	Ahctf1
1421693_a_at	22651.12	Gpr98
1437991_x_at	22601.85	Rusc1
1418666_at	22593.56	Ptx3
1420348_at	22525.87	Lhx5
1422735_at	22457.19	Foxq1
1424455_at	22297.49	Gprasp1
1420446_at	22176.11	Odf3
1420207_at	22023.74	—
1421363_at	21974.00	Cyp2c39

TABLE 4

Exemplary methylation sites in isolated/endogenous HSCs

Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chr1	38475000	38476000	35378	Rev1	ENSMUSG00000026082	0.971
chr1	174135000	174136000	168890	Dcaf8	ENSMUSG00000026554	0.663
chr1	187516000	187517000	181864	Slc30a10	ENSMUSG00000026614	0.540
chr1	190087000	190088000	184435	Ush2a	ENSMUSG00000026609	0.974
chr1	38011000	38012000	34914	Lyg2	ENSMUSG00000061584	0.612
chr1	36290000	36291000	33193	Hs6st1	ENSMUSG00000045216	0.522
chr1	91946000	91947000	86834	Asb18	ENSMUSG00000067081	0.576
chr1	91825000	91826000	86713	Agap1	ENSMUSG00000055013	0.365
chr1	12966000	12967000	9967	Sulf1	ENSMUSG00000016918	0.596
chr1	191714000	191715000	186062	Ptpn14	ENSMUSG00000026604	0.994
chr1	94962000	94963000	89850	Aqp12	ENSMUSG00000045091	0.604
chr1	36355000	36356000	33258	Neurl3	ENSMUSG00000047180	0.539
chr1	34593000	34594000	31496	Cfc1	ENSMUSG00000026124	0.211
chr1	185803000	185804000	180151	Tlr5	ENSMUSG00000079164	0.213
chr1	74195000	74196000	71098	Rufy4	ENSMUSG00000061815	0.610
chr1	90736000	90737000	85624	Arl4c	ENSMUSG00000049866	0.653
chr1	191658000	191659000	186006	Ptpn14	ENSMUSG00000026604	0.974
chr1	191661000	191662000	186009	Ptpn14	ENSMUSG00000026604	0.968
chr1	38579000	38580000	35482	Rev1	ENSMUSG00000026082	0.969
chr1	127809000	127810000	122697	Lypd1	ENSMUSG00000026344	0.213
chr1	25234000	25235000	22137	Lmbrd1	ENSMUSG00000073725	0.550
chr1	191952000	191953000	186300	Smyd2	ENSMUSG00000026603	0.658
chr1	91954000	91955000	86842	Asb18	ENSMUSG00000067081	0.980
chr1	188658000	188659000	183006	Rrp15	ENSMUSG00000001305	0.000
chr1	34308000	34309000	31211	Dst	ENSMUSG00000026131	0.365
chr1	137815000	137816000	132703	Pkp1	ENSMUSG00000026413	0.035
chr1	191583000	191584000	185931	Ptpn14	ENSMUSG00000026604	0.979
chr1	14812000	14813000	11813	Msc	ENSMUSG00000025930	0.587
chr1	94547000	94548000	89435	Otos	ENSMUSG00000044055	0.795
chr1	36327000	36328000	33230	Uggt1	ENSMUSG00000037470	0.150
chr1	90701000	90702000	85589	Ar14c	ENSMUSG00000049866	0.893
chr1	40212000	40213000	37115	Il1r2	ENSMUSG00000026073	0.970
chr1	140473000	140474000	135361	Atp6v1g3	ENSMUSG00000026394	0.599
chr1	90565000	90566000	85453	Glrp1	ENSMUSG00000062310	0.564
chr1	51516000	51517000	48419	Sdpr	ENSMUSG00000045954	0.707
chr2	163597000	163598000	351938	Ada	ENSMUSG00000017697	0.588
chr2	29297000	29298000	217736	Med27	ENSMUSG00000026799	0.969
chr2	170120000	170121000	358461		ENSMUSG00000084013	0.640
chr2	170332000	170333000	358673	Cyp24a1	ENSMUSG00000038567	0.553
chr2	63809000	63810000	252199		ENSMUSG00000065837	0.612
chr2	143610000	143611000	331951	Pcsk2	ENSMUSG00000027419	0.894
chr2	163321000	163322000	351662	R3hdml	ENSMUSG00000078949	0.795
chr2	147874000	147875000	336215	Foxa2	ENSMUSG00000037025	0.030
chr2	151719000	151720000	340060	Rspo4	ENSMUSG00000032852	0.482
chr2	170107000	170108000	358448	Zfp217	ENSMUSG00000052056	0.650
chr2	101484000	101485000	289874		ENSMUSG00000027165	0.969
chr2	157964000	157965000	346305	Rprd1b	ENSMUSG00000027651	0.974
chr2	162773000	162774000	351114	L3mbtl	ENSMUSG00000035576	0.573
chr2	82981000	82982000	271371		ENSMUSG00000075248	0.640
chr2	165999000	166000000	354340	Sulf2	ENSMUSG00000006800	0.795
chr2	29061000	29062000	217500	Setx	ENSMUSG00000043535	0.622
chr2	173161000	173162000	361500	Pmepa1	ENSMUSG00000038400	0.036
chr2	92582000	92583000	280972	Chst1	ENSMUSG00000027221	0.381
chr2	160803000	160804000	349144	Emilin3	ENSMUSG00000050700	0.976
chr2	57034000	57035000	245473	Nr4a2	ENSMUSG00000026826	0.002
chr2	153116000	153117000	341457	Pofut1	ENSMUSG00000046020	0.510
chr2	37898000	37899000	226337	Crb2	ENSMUSG00000035403	0.971
chr2	78788000	78789000	267178	Ube2e3	ENSMUSG00000027011	0.640
chr2	152737000	152738000	341078	Mylk2	ENSMUSG00000027470	0.465
chr2	127978000	127979000	316319	Bcl2l11	ENSMUSG00000027381	0.532
chr2	34060000	34061000	222499	Fam125b	ENSMUSG00000038740	0.990
chr2	38079000	38080000	226518	Crb2	ENSMUSG00000035403	0.621
chr2	152831000	152832000	341172	Ttll9	ENSMUSG00000074673	0.971
chr2	151272000	151273000	339613		ENSMUSG00000083391	0.645
chr2	32730000	32731000	221169	Stxbp1	ENSMUSG00000026797	0.115
chr2	35302000	35303000	223741	Ggta1	ENSMUSG00000035778	0.402
chr2	173251000	173252000	361590	Pmepa1	ENSMUSG00000038400	0.643
chr2	26338000	26339000	214777	Sec16a	ENSMUSG00000026924	0.530
chr2	131778000	131779000	320119	Prnd	ENSMUSG00000027338	0.131
chr2	26436000	26437000	214875	Egfl7	ENSMUSG00000026921	0.641
chr3	102264000	102265000	469052	Vangl1	ENSMUSG00000027860	0.600
chr3	149018000	149019000	515708	Gm5149	ENSMUSG00000069803	0.894
chr3	98205000	98206000	464993	Zfp697	ENSMUSG00000050064	0.830

TABLE 4-continued

Exemplary methylation sites in isolated/endogenous HSCs

Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chr3	130829000	130830000	497568	Lef1	ENSMUSG00000027985	0.973
chr3	99341000	99342000	466129	M6pr-ps	ENSMUSG00000078549, ENSMUSG00000080832	0.648
chr3	154140000	154141000	520830	Lhx8	ENSMUSG00000028201	0.489
chr3	68330000	68331000	435118	Schip1	ENSMUSG00000027777	0.540
chr3	50817000	50818000	417605	Slc7a11	ENSMUSG00000027737	0.973
chr3	152572000	152573000	519262	Pigk	ENSMUSG00000039047	0.655
chr3	159417000	159418000	526107	Rpe65	ENSMUSG00000028174	0.887
chr3	96723000	96724000	463511	Gpr89	ENSMUSG00000028096	0.780
chr3	97116000	97117000	463904	Bcl9	ENSMUSG00000038256	0.519
chr3	38101000	38102000	404942		ENSMUSG00000064315	0.211
chr3	149189000	149190000	515879	Gm5149	ENSMUSG00000069803	0.979
chr3	45185000	45186000	412022	Pcdh10	ENSMUSG00000049100	0.035
chr3	102460000	102461000	469248	Ngf	ENSMUSG00000027859	0.781
chr3	51629000	51630000	418417	Maml3	ENSMUSG00000061143	0.978
chr3	96493000	96494000	463281	Ankrd35	ENSMUSG00000038354	0.385
chr3	129255000	129256000	495994	Elovl6	ENSMUSG00000041220	0.201
chr3	44165000	44166000	411002	D3Ertd751e	A,ENSMUSG00000025766	0.990
chr3	130507000	130508000	497246	Rpl34	ENSMUSG00000062006	0.366
chr3	130921000	130922000	497660	Lef1	ENSMUSG00000027985	0.380
chr3	153483000	153484000	520173		ENSMUSG00000062046	0.968
chr3	96332000	96333000	463120	Hfe2	ENSMUSG00000038403	0.566
chr3	41372000	41373000	408209	Phf17	ENSMUSG00000025764	0.980
chr3	68780000	68781000	435568		ENSMUSG00000046999	0.969
chr3	63843000	63844000	430631	Gmps	ENSMUSG00000027823	0.061
chr3	41391000	41392000	408228	Phf17	ENSMUSG00000025764	0.096
chr3	68524000	68525000	435312	Il12a	ENSMUSG00000027776	0.614
chr3	8717000	8718000	375607	Hey1	ENSMUSG00000040289	0.114
chr3	43890000	43891000	410727	D3Ertd751e	A,ENSMUSG00000025766	0.975
chr3	53171000	53172000	419959	Lhfp	ENSMUSG00000048332	0.781
chr3	51163000	51164000	417951	Elf2	ENSMUSG00000037174	0.124
chr3	51001000	51002000	417789	Slc7a11	ENSMUSG00000027737	0.578
chr3	102264000	102265000	469052	Vangl1	ENSMUSG00000027860	0.600
chr4	109103000	109104000	632057	Ttc39a	ENSMUSG00000028555	0.531
chr4	71043000	71044000	594086		ENSMUSG00000061903, ENSMUSG00000083914	1.000
chr4	62267000	62268000	585310	Rgs3	ENSMUSG00000059810	0.536
chr4	116947000	116948000	639901	Tmem53	ENSMUSG00000048772	0.968
chr4	82154000	82155000	605197	Nfib	ENSMUSG00000008575	0.614
chr4	47445000	47446000	570636	Tgfbr1	ENSMUSG00000007613	0.968
chr4	116828000	116829000	639782	Rps8	ENSMUSG00000047675, ENSMUSG00000064457	0.077
chr4	113690000	113691000	636644	Skint5	ENSMUSG00000078598	0.655
chr4	138656000	138657000	661461	Nbl1	ENSMUSG00000041120	0.982
chr4	137949000	137950000	660754	Cda	ENSMUSG00000028755	0.707
chr4	47398000	47399000	570589	Tgfbr1	ENSMUSG00000007613	0.977
chr4	106926000	106927000	629880	Hspb11	ENSMUSG00000028617, ENSMUSG00000063172	0.031
chr4	154374000	154375000	676931	Pank4	ENSMUSG00000029056	0.640
chr4	116976000	116977000	639930	Rnf220	ENSMUSG00000028677	0.473
chr4	137307000	137308000	660112	Rap1gap	ENSMUSG00000041351	0.347
chr4	116951000	116952000	639905	Tmem53	ENSMUSG00000048772	0.893
chr4	138649000	138650000	661454	Nbl1	ENSMUSG00000041120	0.474
chr4	115825000	115826000	638779	Pomgnt1	ENSMUSG00000028700	0.984
chr4	149287000	149288000	671844	Spsb1	ENSMUSG00000039911	0.584
chr4	47014000	47015000	570205	Gabbr2	ENSMUSG00000039809	0.492
chr4	153893000	153894000	676450	Arhgef16	ENSMUSG00000029032	0.043
chr4	116985000	116986000	639939	Rnf220	ENSMUSG00000028677	0.602
chr4	62847000	62848000	585890	Kif12	ENSMUSG00000028357	0.105
chr4	141376000	141377000	664181	Casp9	ENSMUSG00000028914	0.976
chr4	119963000	119964000	642917	Foxo6	ENSMUSG00000052135	0.492
chr4	52456000	52457000	575647	Smc2	ENSMUSG00000028312	0.971
chr4	137218000	137219000	660023	Usp48	ENSMUSG00000043411	0.593
chr4	46837000	46838000	570028	Gabbr2	ENSMUSG00000039809	0.344
chr4	140221000	140222000	663026	Arhgef101	ENSMUSG00000040964	0.582
chr4	150263000	150264000	672820	Errfi1	ENSMUSG00000028967	0.589
chr4	46606000	46607000	569797	Coro2a	ENSMUSG00000028337	0.654
chr4	138060000	138061000	660865	Camk2n1	ENSMUSG00000046447	0.536
chr4	155029000	155030000	677586	Mmp23	ENSMUSG00000029061	0.178
chr4	107243000	107244000	630197	Glis1	ENSMUSG00000034762	0.548
chr4	150514000	150515000	673071	Camta1	ENSMUSG00000014592	0.114
chr5	44595000	44596000	718679	Prom1	ENSMUSG00000029086	0.606
chr5	66887000	66888000	740971	Apbb2	ENSMUSG00000029207	0.972

TABLE 4-continued

Exemplary methylation sites in isolated/endogenous HSCs

Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chr5	122493000	122494000	796432		ENSMUSG00000072641	0.994
chr5	116454000	116455000	790393	Cit	ENSMUSG00000029516	0.706
chr5	116427000	116428000	790366	Cit	ENSMUSG00000029516	0.614
chr5	110977000	110978000	784951	Galnt9	ENSMUSG00000033316	0.519
chr5	110987000	110988000	784961	Galnt9	ENSMUSG00000033316	0.106
chr5	146283000	146284000	819726	Cyp3a16	ENSMUSG00000038656	0.781
chr5	140407000	140408000	814100	Elfn1	ENSMUSG00000048988	0.517
chr5	151234000	151235000	824622	Fry	ENSMUSG00000056602	0.975
chr5	66886000	66887000	740970	Apbb2	ENSMUSG00000029207	0.613
chr5	24096000	24097000	699235	Chpf2	ENSMUSG00000038181	0.538
chr5	140986000	140987000	814679	Chst12	ENSMUSG00000036599	0.516
chr5	140449000	140450000	814142	Elfn1	ENSMUSG00000048988	0.514
chr5	74283000	74284000	748367	Spata18	ENSMUSG00000029155	0.598
chr5	38746000	38747000	712830	Drd5	ENSMUSG00000039358	0.975
chr5	125772000	125773000	799620	Ncor2	ENSMUSG00000029478	0.968
chr5	75642000	75643000	749715	Pdgfra	ENSMUSG00000029231	0.974
chr5	75356000	75357000	749429	Gm6116	ENSMUSG00000072874	0.380
chr5	66444000	66445000	740528		ENSMUSG00000054598	0.975
chr5	66141000	66142000	740225	Pds5a	ENSMUSG00000029202	0.968
chr5	128822000	128823000	802670	Glt1d1	ENSMUSG00000049971	0.707
chr5	75544000	75545000	749617	Gsx2	ENSMUSG00000035946	0.089
chr5	29591000	29592000	703830	Rnf32	ENSMUSG00000029130	0.968
chr5	148458000	148459000	821851	Pan3	ENSMUSG00000029647	0.117
chr5	135031000	135032000	808854	Clip2	ENSMUSG00000063146	0.027
chr5	147572000	147573000	820965	Gpr12	ENSMUSG00000041468	0.971
chr5	125751000	125752000	799599	Ncor2	ENSMUSG00000029478	0.592
chr5	112852000	112853000	786826	Asphd2	ENSMUSG00000029348	0.516
chr5	116048000	116049000	789987	Gcn1l1	ENSMUSG00000041638	0.980
chr5	71808000	71809000	745892	Gabra2	ENSMUSG00000000560	0.894
chr5	129288000	129289000	803130	Piwil1	ENSMUSG00000029423	0.657
chr5	74256000	74257000	748340	Spata18	ENSMUSG00000029155	0.571
chr5	8930000	8931000	684118	Abcb4	ENSMUSG00000042476	0.970
chr5	36741000	36742000	710905	Sorcs2	ENSMUSG00000029093	0.129
chr6	113592000	113593000	936418	Irak2	ENSMUSG00000060477	0.612
chr6	35312000	35313000	858188	Fam180a	ENSMUSG00000047420	0.645
chr6	113622000	113623000	936448	Irak2	ENSMUSG00000060477	0.646
chr6	93644000	93645000	916470		ENSMUSG00000077180	0.984
chr6	71485000	71486000	894311	Rnf103	ENSMUSG00000052656	0.976
chr6	56967000	56968000	879793	V1rc20	ENSMUSG00000058923	0.646
chr6	114459000	114460000	93728	5Hrh1	ENSMUSG00000053004	0.606
chr6	52152000	52153000	874978	Hoxa3	ENSMUSG00000079560	0.894
chr6	114167000	114168000	936993	Slc6a11	ENSMUSG00000030307	0.506
chr6	52140000	52141000	874966	Hoxa3	ENSMUSG00000079560	0.575
chr6	120083000	120084000	942909	Ninj2	ENSMUSG00000041377	0.981
chr6	114576000	114577000	937402	Hrh1	ENSMUSG00000053004	0.655
chr6	91642000	91643000	914468	S1c6a6	ENSMUSG00000030096	0.974
chr6	113892000	113893000	936718	Atp2b2	ENSMUSG00000030302	0.619
chr6	115569000	115570000	938395	Mkrn2	ENSMUSG00000000439	0.147
chr6	88868000	88869000	911694	Tpra1	ENSMUSG00000002871	0.538
chr6	121007000	121008000	943833		ENSMUSG00000052437	0.984
chr6	93016000	93017000	915842	Adamts9	ENSMUSG00000030022	0.184
chr6	55531000	55532000	878357	Adcyap1r1	ENSMUSG00000029778	0.659
chr6	120015000	120016000	942841	Wnk1	ENSMUSG00000045962	0.612
chr6	121857000	121858000	944683	Mug1	ENSMUSG00000059908	0.641
chr6	120062000	120063000	942888	Ninj2	ENSMUSG00000041377	0.089
chr6	71930000	71931000	894756	Polr1a	ENSMUSG00000049553	0.581
chr6	113233000	113234000	936059	Cpne9	ENSMUSG00000030270	0.055
chr6	119270000	119271000	942096	Cacna2d4	ENSMUSG00000041460	0.509
chr6	95698000	95699000	918524	Suc1g2	ENSMUSG00000061838	0.968
chr6	119076000	119077000	941902	Cacna1c	ENSMUSG00000051331	0.980
chr6	114478000	114479000	937304	Hrh1	ENSMUSG00000053004	0.595
chr6	120922000	120923000	943748	Bid	ENSMUSG00000004446	0.970
chr6	90569000	90570000	913395	S1c41a3	ENSMUSG00000030089	0.536
chr6	37476000	37477000	860352	Creb312	ENSMUSG00000038648	0.567
chr6	92560000	92561000	915386	Prickle2	ENSMUSG00000030020	0.622
chr6	133994000	133995000	956820	Etv6	ENSMUSG00000030199	0.275
chr6	97236000	97237000	920062	Lmod3	ENSMUSG00000044086	0.970
chr6	114568000	114569000	937394	Hrh1	ENSMUSG00000053004	0.587
chr7	63706000	63707000	1025546	Oca2	ENSMUSG00000030450	0.578
chr7	148203000	148204000	1109860	Ifitm6	ENSMUSG00000059108	0.255
chr7	80664000	80665000	1042454	Chd2	ENSMUSG00000025788	0.973
chr7	29529000	29530000	998369	Sars2	ENSMUSG00000070699	0.977
chr7	150661000	150662000	1112279	Slc22a18	ENSMUSG00000000154	0.559

TABLE 4-continued

Exemplary methylation sites in isolated/endogenous HSCs

Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chr7	28261000	28262000	997101	Sertad3	ENSMUSG00000055200	0.978
chr7	138081000	138082000	1099817	Htra1	ENSMUSG00000006205	0.487
chr7	86133000	86134000	1047923	Isg20	ENSMUSG00000039236	0.977
chr7	25919000	25920000	994759	Pou2f2	ENSMUSG00000008496	0.512
chr7	135532000	135533000	1097268	BC017158	ENSMUSG00000030780	0.575
chr7	139909000	139910000	1101595	Lhpp	ENSMUSG00000030946	0.566
chr7	64394000	64395000	1026234	Gabrg3	ENSMUSG00000055026	0.653
chr7	31251000	31252000	1000091	Nphs1	ENSMUSG00000006649	0.115
chr7	137155000	137156000	1098891	Brwd2	ENSMUSG00000042055	0.564
chr7	30000000	30001000	998840	Catsperg1	ENSMUSG00000049676	0.539
chr7	30010000	30011000	998850	Catsperg1	ENSMUSG00000049676	0.579
chr7	52120000	52121000	1013960	Pnkp	ENSMUSG00000002963	0.510
chr7	134528000	134529000	1096264	Zfp747	ENSMUSG00000054381	0.968
chr7	29957000	29958000	998797	Ggn	ENSMUSG00000031493	0.652
chr7	118165000	118166000	1079901	Mrvi1	ENSMUSG00000005611	0.556
chr7	80522000	80523000	1042312	Rgma	ENSMUSG00000070509	0.541
chr7	142677000	142678000	1104363	Foxi2	ENSMUSG00000048377	0.104
chr7	26388000	26389000	995228	Ceacam2	ENSMUSG00000054385	0.968
chr7	53048000	53049000	1014888	Lmtk3	ENSMUSG00000062044	0.658
chr7	52679000	52680000	1014519	Lhb	ENSMUSG00000038194	0.968
chr7	25941000	25942000	994781		ENSMUSG00000074274	0.489
chr7	127450000	127451000	1089186	Abca14	ENSMUSG00000062017	0.969
chr7	148124000	148125000	1109781	Nlrp6	ENSMUSG00000038745	0.579
chr7	148031000	148032000	1109688	Scgb1c1	ENSMUSG00000038801	0.362
chr7	72838000	72839000	1034628	Tm2d3	ENSMUSG00000078681	0.031
chr7	36472000	36473000	1005312	Pdcd5	ENSMUSG00000030417	0.213
chr7	52615000	52616000	1014455	Ppfia3	ENSMUSG00000003863	0.525
chr7	30719000	30720000	999559	Zfp27	ENSMUSG00000062040	0.981
chr7	52128000	52129000	1013968	Ptov1	ENSMUSG00000038502	0.585
chr7	92172000	92173000	1053957	Vmn2r66	ENSMUSG00000072241	0.893
chr8	119062000	119063000	1226266	Dynlrb2	ENSMUSG00000034467	0.591
chr8	24265000	24266000	1133309	Nkx6-3	ENSMUSG00000063672	0.582
chr8	119147000	119148000	1226351	Cdyl2	ENSMUSG00000031758	0.969
chr8	18034000	18035000	1129177	Csmd1	ENSMUSG00000060924	0.781
chr8	116490000	116491000	1223694	Adamts18	ENSMUSG00000053399	0.609
chr8	119154000	119155000	1226358	Cdyl2	ENSMUSG00000031758	0.496
chr8	107998000	107999000	1215202	Tppp3	ENSMUSG00000014846	0.554
chr8	25462000	25463000	1134506		ENSMUSG00000053979	0.186
chr8	11605000	11606000	1122748	Ing1	ENSMUSG00000045969	0.969
chr8	109135000	109136000	1216339	Cdh1	ENSMUSG00000000303	0.596
chr8	117689000	117690000	1224893	Wwox	ENSMUSG00000004637	0.077
chr8	109576000	109577000	1216780	Pdf	ENSMUSG00000078931	0.971
chr8	11476000	11477000	1122619	Col4a2	ENSMUSG00000031503	0.048
chr8	28267000	28268000	1137311	Brf2	ENSMUSG00000031487	0.969
chr8	8319000	8320000	1119462		ENSMUSG00000077378	0.979
chr8	109363000	109364000	1216567	Tmco7	ENSMUSG00000041949	0.581
chr8	117268000	117269000	1224472	Wwox	ENSMUSG00000004637	0.496
chr8	16794000	16795000	1127937	Csmd1	ENSMUSG00000060924	0.980
chr8	109034000	109035000	1216238	Cdh3	ENSMUSG00000061048	0.036
chr8	26081000	26082000	1135125	Adam32	ENSMUSG00000037437	0.974
chr8	117123000	117124000	1224327	Wwox	ENSMUSG00000004637	0.645
chr8	124847000	124848000	1232051	Zfpm1	ENSMUSG00000049577	0.641
chr8	117231000	117232000	1224435	Wwox	ENSMUSG00000004637	0.344
chr8	109202000	109203000	1216406	Cdh1	ENSMUSG00000000303	0.106
chr8	15029000	15030000	1126172	Kbtbd11	ENSMUSG00000055675	0.510
chr8	18751000	18752000	1129894	Angpt2	ENSMUSG00000031465	0.978
chr8	11464000	11465000	1122607	Col4a2	ENSMUSG00000031503	0.591
chr8	11421000	11422000	1122564	Col4a2	ENSMUSG00000031503	0.646
chr8	114534000	114535000	1221738	Kars	ENSMUSG00000031948	0.000
chr8	119606000	119607000	1226810	Pkd1l2	ENSMUSG00000034416	0.647
chr8	19090000	19091000	1130233	Defb39	ENSMUSG00000061847	0.795
chr8	12467000	12468000	1123610	Gm5607	ENSMUSG00000047935	0.532
chr8	108693000	108694000	1215897	Slc7a6	ENSMUSG00000031904	0.043
chr8	124579000	124580000	1231783	Banp	ENSMUSG00000025316	0.662
chr8	125039000	125040000	1232243	Fam38a	ENSMUSG00000014444	0.973
chr9	64478000	64479000	1300320	Megf11	ENSMUSG00000036466	0.780
chr9	5029000	5030000	1240972	Gria4	ENSMUSG00000025892	0.993
chr9	30371000	30372000	1266263	Snx19	ENSMUSG00000031993	0.616
chr9	14477000	14478000	1250369	Amotl1	ENSMUSG00000013076	0.830
chr9	20712000	20713000	1256604	Eif3g	ENSMUSG00000070319	0.969
chr9	20548000	20549000	1256440	Olfm2	ENSMUSG00000032172	0.183
chr9	78369000	78370000	1314211	Eef1a1	ENSMUSG00000037742	0.060
chr9	71465000	71466000	1307307	Gcom1	ENSMUSG00000041361	0.588

TABLE 4-continued

Exemplary methylation sites in isolated/endogenous HSCs

Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chr9	98765000	98766000	1334495		ENSMUSG00000032460	0.488
chr9	54281000	54282000	1290123	Dmxl2	ENSMUSG00000041268	0.697
chr9	119542000	119543000	1355198	Scn5a	ENSMUSG00000032511	0.533
chr9	26749000	26750000	1262641	Gm1110	ENSMUSG00000079644	0.548
chr9	27108000	27109000	1263000	Igsf9b	ENSMUSG00000034275	0.037
chr9	100740000	100741000	1336470	Stag1	ENSMUSG00000037286	0.648
chr9	3199000	3200000	1239142		ENSMUSG00000042360	0.337
chr9	87134000	87135000	1322886		ENSMUSG00000056919	0.970
chr9	46251000	46252000	1282142		ENSMUSG00000056617	0.035
chr9	107803000	107804000	1343525	Mon1a	ENSMUSG00000032583	0.242
chr9	119441000	119442000	1355097	Exog	ENSMUSG00000042787	0.659
chr9	23786000	23787000	1259678	Bmper	ENSMUSG00000031963	0.780
chr9	99010000	99011000	1334740	Gm1123	ENSMUSG00000044860	0.602
chr9	119469000	119470000	1355125	Exog	ENSMUSG00000042787	0.610
chr9	63818000	63819000	1299660	Smad3	ENSMUSG00000032402	0.546
chr9	21905000	21906000	1257797	Cnn1	ENSMUSG00000001349	0.547
chr9	86648000	86649000	1322401	Prss35	ENSMUSG00000033491	0.968
chr9	60719000	60720000	1296561		ENSMUSG00000052143	0.980
chr9	59450000	59451000	1295292	Brunol6	ENSMUSG00000032297	0.365
chr9	57505000	57506000	1293347	Cyp1a1	ENSMUSG00000032315	0.661
chr9	121210000	121211000	1356866	Trak1	ENSMUSG00000032536	0.662
chr9	11634000	11635000	1247577		ENSMUSG00000077550	0.975
chr9	49014000	49015000	1284905	Tmprss5	ENSMUSG00000032268	0.391
chr9	17002000	17003000	1252894	Fat3	ENSMUSG00000074505	0.602
chr9	119508000	119509000	1355164	Scn5a	ENSMUSG00000032511	0.411
chr9	99371000	99372000	1335101		ENSMUSG00000046242	0.581
chr9	76105000	76106000	1311947	Gfral	ENSMUSG00000059383	0.556
chr10	85249000	85250000	1441793	Btbd11	ENSMUSG00000020042	0.655
chr10	75416000	75417000	1431960	Vpreb3	ENSMUSG00000000903	0.616
chr10	51662000	51663000	1408296		ENSMUSG00000062224	0.894
chr10	115215000	115216000	1471759	LgrS	ENSMUSG00000020140	0.363
chr10	83855000	83856000	1440399	Appl2	ENSMUSG00000020263	0.254
chr10	90735000	90736000	1447279	Tmpo	ENSMUSG00000019961	0.548
chr10	117325000	117326000	1473869	Rap1b	ENSMUSG00000052681	0.573
chr10	75345000	75346000	1431889	Mif	ENSMUSG00000033307	0.549
chr10	85194000	85195000	1441738	Btbd11	ENSMUSG00000020042	0.619
chr10	44176000	44177000	1400810	Atg5	ENSMUSG00000038160	0.476
chr10	76133000	76134000	1432677	Col6a2	ENSMUSG00000020241	0.588
chr10	92841000	92842000	1449385	Elk3	ENSMUSG00000008398	0.975
chr10	94048000	94049000	1450592	Tmcc3	ENSMUSG00000020023	0.970
chr10	84220000	84221000	1440764	Rfx4	ENSMUSG00000020037	0.211
chr10	118113000	118114000	1474657	Ifng	ENSMUSG00000055170	0.600
chr10	45400000	45401000	1402034	Hace1	ENSMUSG00000038822	0.977
chr10	111079000	111080000	1467623	Phlda1	ENSMUSG00000020205	0.973
chr10	92739000	92740000	1449283	Cdk17	ENSMUSG00000020015	0.385
chr10	82467000	82468000	1439011	Chst11	ENSMUSG00000034612	0.107
chr10	93294000	93295000	1449838	Usp44	ENSMUSG00000020020	0.341
chr10	80415000	80416000	1436959	Gadd45b	ENSMUSG00000015312	0.644
chr10	92997000	92998000	1449541	Hal	ENSMUSG00000020017	0.055
chr10	83995000	83996000	1440539		ENSMUSG00000020033	0.337
chr10	42742000	42743000	1399376	Scml4	ENSMUSG00000044770	0.181
chr10	76421000	76422000	1432965	Col6a1	ENSMUSG00000001119, ENSMUSG00000078445	0.975
chr10	70862000	70863000	1427406	Ipmk	ENSMUSG00000060733	0.404
chr10	44149000	44150000	1400783	Atg5	ENSMUSG00000038160	0.187
chr10	6199000	6200000	1362882	Akap12	ENSMUSG00000038587	0.973
chr10	115629000	115630000	1472173	Ptprr	ENSMUSG00000020151	0.604
chr10	80291000	80292000	1436835	Oaz1	ENSMUSG00000035242	0.547
chr10	42639000	42640000	1399273	Scml4	ENSMUSG00000044770	0.972
chr10	83854000	83855000	1440398	Appl2	ENSMUSG00000020263	0.366
chr10	93508000	93509000	1450052	Fgd6	ENSMUSG00000020021	0.969
chr10	59002000	59003000	1415551	Ccdc109a	ENSMUSG00000009647	0.574
chr10	58540000	58541000	1415089	Sh3rf3	ENSMUSG00000037990	0.572
chr11	4029000	4030000	1487567	Sec1412	ENSMUSG00000003585	0.968
chr11	45926000	45927000	1529414	Adam19	ENSMUSG00000011256	0.981
chr11	106891000	106892000	1590329		ENSMUSG00000078607	0.494
chr11	117984000	117985000	1601422	Dnahc17	ENSMUSG00000033987	0.649
chr11	48650000	48651000	1532138	Trim7	ENSMUSG00000040350	0.502
chr11	66988000	66989000	1550476	Myh2	ENSMUSG00000033196	0.986
chr11	75765000	75766000	1559253	Rph3al	ENSMUSG00000020847	0.969
chr11	75450000	75451000	1558938	Inpp5k	ENSMUSG00000006127	0.214
chr11	69666000	69667000	1553154	Plscr3	ENSMUSG00000019461	0.780
chr11	65271000	65272000	1548759	Myocd	ENSMUSG00000020542	0.978

TABLE 4-continued

Exemplary methylation sites in isolated/endogenous HSCs						
Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chr11	61115000	61116000	1544603	Aldh3a2	ENSMUSG00000010025	0.524
chr11	67489000	67490000	1550977	Gas7	ENSMUSG00000033066	0.278
chr11	68767000	68768000	1552255	Arhgef15	ENSMUSG00000052921	0.201
chr11	3404000	3405000	1486942	Inpp5j	ENSMUSG00000034570	0.591
chr11	69218000	69219000	1552706	Tmem88	ENSMUSG00000045377	0.968
chr11	45870000	45871000	1529358	Adam19	ENSMUSG00000011256	0.043
chr11	48982000	48983000	1532470	Olfr1394	ENSMUSG00000048378	0.088
chr11	61166000	61167000	1544654	Slc47a2	ENSMUSG00000069855	0.650
chr11	3578000	3579000	1487116	Morc2a	ENSMUSG00000034543	0.977
chr11	96207000	96208000	1579645	Hoxb3	ENSMUSG00000048763	0.655
chr11	121247000	121248000	1604685	Wdr451	ENSMUSG00000025173	0.591
chr11	32129000	32130000	1515667	Mpg	ENSMUSG00000020287	0.985
chr11	70029000	70030000	1553517	Slc16a11	ENSMUSG00000040938	0.473
chr11	69831000	69832000	1553319	Dlg4	ENSMUSG00000020886	0.516
chr11	67611000	67612000	1551099	Dhrs7c	ENSMUSG00000033044	0.707
chr11	61891000	61892000	1545379	Cytsb	ENSMUSG00000042331	0.027
chr11	65240000	65241000	1548728	Myocd	ENSMUSG00000020542	0.983
chr11	115195000	115196000	1598633	Otop2	ENSMUSG00000050201	0.143
chr11	73078000	73079000	1556566	Trpv1	ENSMUSG00000005952	0.655
chr11	77698000	77699000	1561186	Myo18a	ENSMUSG00000000631	0.615
chr11	17184000	17185000	1500722	C1d	ENSMUSG00000000581	0.561
chr11	85104000	85105000	1568592	Appbp2	ENSMUSG00000018481	0.970
chr11	58948000	58949000	1542436	Obscn	ENSMUSG00000061462	0.043
chr11	32168000	32169000	1515706	Mare	ENSMUSG00000020289	0.610
chr11	117062000	117063000	1600500	Sept9	ENSMUSG00000059248	0.546
chr12	110498000	110499000	1711988	Begain	ENSMUSG00000040867	0.970
chr12	110272000	110273000	1711762	Wdr25	ENSMUSG00000040877	0.616
chr12	29768000	29769000	1631742	Tssc1	ENSMUSG00000036613	0.577
chr12	32516000	32517000	1634490	Gpr22	ENSMUSG00000044067	0.983
chr12	27219000	27220000	1629193	Cmpk2	ENSMUSG00000020638	0.510
chr12	106915000	106916000	1708405	Bdkrb1	ENSMUSG00000041347	0.985
chr12	109577000	109578000	1711067	Cyp46a1	ENSMUSG00000021259	0.554
chr12	71553000	71554000	1673143	Trim9	ENSMUSG00000021071	0.002
chr12	109209000	109210000	1710699		ENSMUSG00000060375	0.565
chr12	77414000	77415000	1679004	Mthfd1	ENSMUSG00000021048	0.984
chr12	3366000	3367000	1605648	Kif3c	ENSMUSG00000020668	0.362
chr12	16075000	16076000	1618348	Trib2	ENSMUSG00000020601	0.973
chr12	70859000	70860000	1672449	Atp5s	ENSMUSG00000054894	0.105
chr12	77317000	77318000	1678907	Esr2	ENSMUSG00000021055	0.516
chr12	106372000	106373000	1707862	Glrx5	ENSMUSG00000021102	0.211
chr12	111900000	111901000	1713390	Dync1h1	ENSMUSG00000018707	0.987
chr12	120161000	120162000	1721651	Sp8	ENSMUSG00000048562	0.612
chr12	12558000	12559000	1614831	Fam49a	ENSMUSG00000020589	0.554
chr12	110309000	110310000	1711799	Begain	ENSMUSG00000040867	0.132
chr12	29483000	29484000	1631457	Tssc1	ENSMUSG00000036613	0.610
chr12	25412000	25413000	1627386	Rrm2	ENSMUSG00000020649	0.585
chr12	25595000	25596000	1627569	Mboat2	ENSMUSG00000020646	0.984
chr12	22990000	22991000	1625063		ENSMUSG00000073164	0.117
chr12	41126000	41127000	1643097	Ifrd1	ENSMUSG00000001627	0.979
chr12	105456000	105457000	1706946	Serpina3f	ENSMUSG00000066363	0.795
chr12	70858000	70859000	1672448	Atp5s	ENSMUSG00000054894	0.160
chr12	109189000	109190000	1710679		ENSMUSG00000060375	0.527
chr12	53846000	53847000	1655436	Akap6	ENSMUSG00000061603	0.521
chr12	4880000	4881000	1607153		ENSMUSG00000051721	0.539
chr12	72398000	72399000	1673988		ENSMUSG00000034601	0.609
chr12	109856000	109857000	1711346	Evl	ENSMUSG00000021262	0.551
chr12	71368000	71369000	1672958	Pygl	ENSMUSG00000021069	0.477
chr12	74638000	74639000	1676228		ENSMUSG00000056359	0.588
chr12	35345000	35346000	1637319	Hdac9	ENSMUSG00000004698	0.510
chr12	59370000	59371000	1660960	Clec14a	ENSMUSG00000045930	0.575
chr13	59765000	59766000	1779334	Naa35	ENSMUSG00000021555	0.979
chr13	76000000	76001000	1795520	Glrx	ENSMUSG00000021591	0.781
chr13	38751000	38752000	1758369	Eef1e1	ENSMUSG00000001707	0.343
chr13	40990000	40991000	1760572	Gcnt2	ENSMUSG00000021360	0.658
chr13	77139000	77140000	1796659	Mctp1	ENSMUSG00000021596	0.604
chr13	49415000	49416000	1768997	Fgd3	ENSMUSG00000037946	0.346
chr13	56077000	56078000	1775646	Pitx1	ENSMUSG00000021506	0.830
chr13	82225000	82226000	1801745	Cetn3	ENSMUSG00000021537	0.599
chr13	55020000	55021000	1774589	Tspan17	ENSMUSG00000025875	0.510
chr13	43483000	43484000	1763065	Sirt5	ENSMUSG00000054021	0.969
chr13	54894000	54895000	1774463	Tspan17	ENSMUSG00000025875	0.131
chr13	95993000	95994000	1814860	Pde8b	ENSMUSG00000021684	0.061
chr13	56101000	56102000	1775670	Pitx1	ENSMUSG00000021506	0.664

TABLE 4-continued

Exemplary methylation sites in isolated/endogenous HSCs						
Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chr13	86771000	86772000	1806291	Cox7c	A,ENSMUSG00000017778	0.920
chr13	53330000	53331000	1772912	Nfil3	ENSMUSG00000056749	0.489
chr13	48812000	48813000	1768394	Barx1	ENSMUSG00000021381	0.697
chr13	73397000	73398000	1792917	Irx4	ENSMUSG00000021604	0.036
chr13	96324000	96325000	1815191	F2rl1	ENSMUSG00000021678	0.550
chr13	54940000	54941000	1774509	Tspan17	ENSMUSG00000025875	0.279
chr13	86554000	86555000	1806074	Cox7c	A,ENSMUSG00000017778	0.920
chr13	54925000	54926000	1774494	Tspan17	ENSMUSG00000025875	0.116
chr13	55274000	55275000	1774843	Fgfr4	ENSMUSG00000005320	0.576
chr13	55709000	55710000	1775278	B4galt7	ENSMUSG00000021504	0.980
chr13	100412000	100413000	1819279	Mtap1b	ENSMUSG00000052727	0.485
chr13	73653000	73654000	1793173	Lpcat1	ENSMUSG00000021608	0.970
chr13	52665000	52666000	1772247	Diras2	ENSMUSG00000047842	0.978
chr13	117104000	117105000	1835951	Isl1	ENSMUSG00000042258	0.030
chr13	24788000	24789000	1744406	Fam65b	ENSMUSG00000036006	0.657
chr13	47211000	47212000	1766793	Dek	ENSMUSG00000021377	0.977
chr13	108636000	108637000	1827483	Zswim6	ENSMUSG00000032846	0.178
chr13	61026000	61027000	1780595	Tpbpb	ENSMUSG00000062705	0.830
chr13	102732000	102733000	1821599	Pik3r1	ENSMUSG00000041417	0.968
chr13	24954000	24955000	1744572		ENSMUSG00000006711	0.619
chr13	114100000	114101000	1832947	Gzmk	ENSMUSG00000042385	0.971
chr13	51526000	51527000	1771108	S1pr3	ENSMUSG00000067586	0.550
chr14	57183000	57184000	1892761	Rnf17	ENSMUSG00000000365	0.978
chr14	106319000	106320000	1941897	Spry2	ENSMUSG00000022114	0.123
chr14	105999000	106000000	1941577		ENSMUSG00000022116	0.981
chr14	56719000	56720000	1892297	Mcpt8	ENSMUSG00000022157	0.795
chr14	60590000	60591000	1896168	Shisa2	ENSMUSG00000044461	0.974
chr14	111264000	111265000	1946842	Slitrk6	ENSMUSG00000045871	0.580
chr14	81960000	81961000	1917538	Olfm4	A,ENSMUSG00000022026	0.620
chr14	70216000	70217000	1905794	Rhobtb2	ENSMUSG00000022075	0.583
chr14	57752000	57753000	1893330	Gjb6	ENSMUSG00000040055	0.035
chr14	32114000	32115000	1867841	Bap1	ENSMUSG00000021901	0.968
chr14	122033000	122034000	1957611	S1c15a1	ENSMUSG00000025557	0.603
chr14	121197000	121198000	1956775	Rap2a	ENSMUSG00000051615	0.618
chr14	33421000	33422000	1869148	Prrxl1	ENSMUSG00000041730	0.662
chr14	81245000	81246000	1916823	Olfm4	A,ENSMUSG00000022026	0.620
chr14	120198000	120199000	1955776	Hs6st3	ENSMUSG00000053465	0.974
chr14	73245000	73246000	1908823	Fndc3a	ENSMUSG00000033487	0.489
chr14	119647000	119648000	1955225	Hs6st3	ENSMUSG00000053465	0.657
chr14	49199000	49200000	1884777		ENSMUSG00000036339	0.663
chr14	70567000	70568000	1906145		ENSMUSG00000044551	0.492
chr14	32461000	32462000	1868188	Btd	ENSMUSG00000021900	0.969
chr14	121311000	121312000	1956889	IpoS	ENSMUSG00000030662	0.000
chr14	32930000	32931000	1868657	Oxnad1	ENSMUSG00000021906	0.254
chr14	56445000	56446000	1892023	Nfatc4	ENSMUSG00000023411	0.650
chr14	80124000	80125000	1915702	Lect1	ENSMUSG00000022025	0.545
chr14	122785000	122786000	1958363	Clybl	ENSMUSG00000025545	0.970
chr14	84828000	84829000	1920406	Olfm4	ENSMUSG00000022026	0.781
chr14	58417000	58418000	1893995	Sap18	ENSMUSG00000021963	0.097
chr14	47600000	47601000	1883178	Samd4	ENSMUSG00000021838	0.566
chr14	47833000	47834000	1883411	Gch1	ENSMUSG00000037580	0.646
chr14	121037000	121038000	1956615	Rap2a	ENSMUSG00000051615	0.507
chr14	104872000	104873000	1940450	Pou4f1	ENSMUSG00000048349	0.035
chr14	121905000	121906000	1957483	Slc15a1	ENSMUSG00000025557	0.357
chr14	57183000	57184000	1892761	Rnf17	ENSMUSG00000000365	0.978
chr14	106319000	106320000	1941897	Spry2	ENSMUSG00000022114	0.123
chr14	105999000	106000000	1941577		ENSMUSG00000022116	0.981
chr14	56719000	56720000	1892297	Mcpt8	ENSMUSG00000022157	0.795
chr15	8666000	8667000	1966439	Slc1a3	ENSMUSG00000005360	0.031
chr15	5586000	5587000	1963359	Ptger4	ENSMUSG00000039942	0.985
chr15	89152000	89153000	2046871	Sbf1	ENSMUSG00000036529	0.617
chr15	93058000	93059000	2050777	Pdzrn4	ENSMUSG00000036218	0.612
chr15	12613000	12614000	1970382	Pdzd2	ENSMUSG00000022197	0.894
chr15	11848000	11849000	1969617	Npr3	ENSMUSG00000022206	0.706
chr15	92836000	92837000	2050555	Pdzrn4	ENSMUSG00000036218	0.591
chr15	93229000	93230000	2050948	Pphln1	ENSMUSG00000036167	0.077
chr15	84494000	84495000	2042213	Ldoc1l	ENSMUSG00000055745	0.391
chr15	64125000	64126000	2021844		ENSMUSG00000078299	0.979
chr15	10965000	10966000	1968734	Slc45a2	ENSMUSG00000022243	0.620
chr15	100962000	100963000	2058681	Acyrl1	ENSMUSG00000000530	0.567
chr15	89231000	89232000	2046950	Odf3b	ENSMUSG00000047394	0.480
chr15	62051000	62052000	2019770	H2afy3	ENSMUSG00000056590	0.535
chr15	76363000	76364000	2034082	Scrt1	ENSMUSG00000048385	0.585

TABLE 4-continued

Exemplary methylation sites in isolated/endogenous HSCs

Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chr15	89194000	89195000	2046913	Ncaph2	ENSMUSG00000008690	0.975
chr15	35232000	35233000	1993001	Osr2	ENSMUSG00000022330	0.097
chr15	55228000	55229000	2012947	Col14a1	ENSMUSG00000022371	0.781
chr15	12305000	12306000	1970074	Golph3	ENSMUSG00000022200	0.150
chr15	103014000	103015000	2060733	Smug1	ENSMUSG00000036061	0.147
chr15	92920000	92921000	2050639	Pdzrn4	ENSMUSG00000036218	0.214
chr15	102996000	102997000	2060715	Smug1	ENSMUSG00000036061	0.000
chr15	76468000	76469000	2034187	Vps28	ENSMUSG00000062381	0.970
chr15	96238000	96239000	2053957	Arid2	ENSMUSG00000033237	0.970
chr15	103145000	103146000	2060864	Gpr84	ENSMUSG00000063234	0.578
chr15	81531000	81532000	2039250	Chadl	ENSMUSG00000063765	0.794
chr15	80282000	80283000	2038001	Cacna1i	ENSMUSG00000022416	0.502
chr15	100304000	100305000	2058023	Letmd1	ENSMUSG00000037353	0.969
chr15	60989000	60990000	2018708	A1bg	ENSMUSG00000022347	0.574
chr15	62397000	62398000	2020116	H2afy3	ENSMUSG00000056590	0.500
chr15	86070000	86071000	2043789	Tbc1d22a	ENSMUSG00000051864	0.610
chr15	35317000	35318000	1993086	Vps136	ENSMUSG00000037646	0.972
chr15	84189000	84190000	2041908	Parvg	ENSMUSG00000022439	0.340
chr15	98957000	98958000	2056676	Spats2	ENSMUSG00000051934	0.036
chr15	96201000	96202000	2053920	Arid2	ENSMUSG00000033237	0.972
chr16	72990000	72991000	2131115	Robo1	ENSMUSG00000022883	0.970
chr16	46495000	46496000	2104660	Pvrl3	ENSMUSG00000022656	0.069
chr16	44680000	44681000	2102845	Boc	ENSMUSG00000022687	0.646
chr16	69797000	69798000	2127922	Cadm2	ENSMUSG00000064115	0.580
chr16	70668000	70669000	2128793		ENSMUSG00000062087	0.894
chr16	44795000	44796000	2102960	Cd200r1	ENSMUSG00000022667	0.569
chr16	37957000	37958000	2096122	Gpr156	ENSMUSG00000046961	0.657
chr16	70376000	70377000	2128501	Gbe1	ENSMUSG00000022707	0.973
chr16	35185000	35186000	2093350	Adcy5	ENSMUSG00000022840	0.969
chr16	69612000	69613000	2127737	Cadm2	ENSMUSG00000064115	0.980
chr16	48993000	48994000	2107158	Dzip3	ENSMUSG00000064061	0.037
chr16	28517000	28518000	2086682	Fgf12	ENSMUSG00000022523	0.557
chr16	94552000	94553000	2152456	Ripply3	ENSMUSG00000022941	0.980
chr16	88506000	88507000	2146631	Grik1	ENSMUSG00000022935	0.970
chr16	37078000	37079000	2095243	Polq	ENSMUSG00000034206	0.971
chr16	38432000	38433000	2096597	Popdc2	ENSMUSG00000022803	0.650
chr16	44632000	44633000	2102797	Boc	ENSMUSG00000022687	0.060
chr16	37684000	37685000	2095849	Ndufb4	ENSMUSG00000022820	0.185
chr16	93116000	93117000	2151241	Runx1	ENSMUSG00000022952	0.971
chr16	77115000	77116000	2135240	Usp25	ENSMUSG00000022867	0.980
chr16	36199000	36200000	2094364	Gm5483	ENSMUSG00000079597	0.390
chr16	35230000	35231000	2093395	Adcy5	ENSMUSG00000022840	0.574
chr16	65629000	65630000	2123754	Chmp2b	ENSMUSG00000004843	0.516
chr16	95680000	95681000	2153584	Erg	ENSMUSG00000040732	0.000
chr16	44099000	44100000	2102264	Gramd1c	ENSMUSG00000036292	0.969
chr16	91321000	91322000	2149446	Olig1	ENSMUSG00000046160	0.780
chr16	94342000	94343000	2152246	Sim2	ENSMUSG00000062713	0.642
chr16	96621000	96622000	2154525	Pcp4	ENSMUSG00000000159	0.608
chr16	87843000	87844000	2145968		ENSMUSG00000055972	0.393
chr16	91248000	91249000	2149373	Olig2	ENSMUSG00000039830	0.656
chr16	44308000	44309000	2102473	Gm608	ENSMUSG00000068284	0.482
chr16	35156000	35157000	2093321	Adcy5	ENSMUSG00000022840	0.043
chr16	95822000	95823000	2153726	Erg	ENSMUSG00000040732	0.655
chr16	77077000	77078000	2135202	Usp25	ENSMUSG00000022867	0.972
chr16	48449000	48450000	2106614	Morc1	ENSMUSG00000022652	0.970
chr17	87535000	87536000	2240396	Socs5	ENSMUSG00000037104	0.982
chr17	14106000	14107000	2167126	Gm7168	ENSMUSG00000067941	0.894
chr17	73266000	73267000	2226176	Ypel5	ENSMUSG00000039770	0.001
chr17	25014000	25015000	2178031	Hagh	ENSMUSG00000024158	0.589
chr17	49153000	49154000	2202162	Lrfn2	ENSMUSG00000040490	0.654
chr17	24950000	24951000	2177967	Hs3st6	ENSMUSG00000039628	0.524
chr17	64898000	64899000	2217808	Pja2	ENSMUSG00000024083	0.519
chr17	27336000	27337000	2180353	Ip6k3	ENSMUSG00000024210	0.522
chr17	56616000	56617000	2209625	Ptprs	ENSMUSG00000013236	0.588
chr17	87778000	87779000	2240639	Ttc7	ENSMUSG00000036918	0.621
chr17	8201000	8202000	2161321	Rsph3a	ENSMUSG00000073471	0.658
chr17	29571000	29572000	2182588	Fgd2	ENSMUSG00000024013	0.985
chr17	71600000	71601000	2224510	Lpin2	ENSMUSG00000024052	0.215
chr17	25366000	25367000	2178383	Unkl	ENSMUSG00000015127	0.655
chr17	40678000	40679000	2193695	Crisp1	ENSMUSG00000025431	0.781
chr17	76215000	76216000	2229076	Fam98a	ENSMUSG00000002017	0.595
chr17	32967000	32968000	2185984	Zfp799	ENSMUSG00000059000	0.000
chr17	86656000	86657000	2239517	Prkce	ENSMUSG00000045038	0.660

TABLE 4-continued

Exemplary methylation sites in isolated/endogenous HSCs

Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chr17	68263000	68264000	2221173	Lama1	ENSMUSG00000032796	0.587
chr17	32541000	32542000	2185558	Rasal3	ENSMUSG00000052142	0.968
chr17	86148000	86149000	2239009	Six2	ENSMUSG00000024134	0.645
chr17	86663000	86664000	2239524	Prkce	ENSMUSG00000045038	0.986
chr17	27338000	27339000	2180355	Ip6k3	ENSMUSG00000024210	0.531
chr17	86702000	86703000	2239563	Prkce	ENSMUSG00000045038	0.507
chr17	31418000	31419000	2184435	Rsph1	ENSMUSG00000024033	0.607
chr17	88122000	88123000	2240983	Msh2	ENSMUSG00000024151	0.968
chr17	69736000	69737000	2222646	Zfp161	ENSMUSG00000049672	0.970
chr17	86358000	86359000	2239219	Six2	ENSMUSG00000024134	0.361
chr17	87846000	87847000	2240707	Calm2	ENSMUSG00000036438	0.002
chr17	29497000	29498000	2182514	Fgd2	ENSMUSG00000024013	0.035
chr17	28669000	28670000	2181686		ENSMUSG00000024223	0.601
chr17	8453000	8454000	2161573	Ccr6	ENSMUSG00000040899	0.530
chr17	15929000	15930000	2168949	Chd1	ENSMUSG00000023852	0.893
chr17	43106000	43107000	2196123	Cd2ap	ENSMUSG00000061665	0.659
chr17	6988000	6989000	2160163	Ezr	ENSMUSG00000052397	0.510
chr18	6345000	6346000	2251479		ENSMUSG00000073640	0.981
chr18	64653000	64654000	2309787	Fech	ENSMUSG00000024588	0.592
chr18	7719000	7720000	2252853	Mpp7	ENSMUSG00000057440	0.493
chr18	82658000	82659000	2327623	Mbp	ENSMUSG00000041607	0.608
chr18	56728000	56729000	2301862	Aldh7a1	ENSMUSG00000053644	0.184
chr18	57189000	57190000	2302323		ENSMUSG00000024592	0.498
chr18	66564000	66565000	2311698	Ccbe1	ENSMUSG00000046318	0.132
chr18	81827000	81828000	2326824	Sall3	ENSMUSG00000024565	0.989
chr18	24166000	24167000	2269300	Zfp35	ENSMUSG00000063281	0.992
chr18	37646000	37647000	2282780	Pcdhb17	ENSMUSG00000046387	0.620
chr18	53553000	53554000	2298687	Snx24	ENSMUSG00000024535	0.968
chr18	67296000	67297000	2312430	Gnal	ENSMUSG00000024524	0.657
chr18	39029000	39030000	2284163	Fgf1	ENSMUSG00000036585	0.781
chr18	11424000	11425000	2256558	Gata6	ENSMUSG00000005836	0.795
chr18	46970000	46971000	2292104	Ap3s1	ENSMUSG00000024480	0.969
chr18	62149000	62150000	2307283	Sh3tc2	ENSMUSG00000045629	0.980
chr18	56754000	56755000	2301888		ENSMUSG00000032900	0.642
chr18	78134000	78135000	2323131	Pstpip2	ENSMUSG00000025429	0.178
chr18	36124000	36125000	2281258	Psd2	ENSMUSG00000024347	0.035
chr18	9472000	9473000	2254606	Ccny	ENSMUSG00000024286	0.972
chr18	11169000	11170000	2256303	Gata6	ENSMUSG00000005836	0.558
chr18	77108000	77109000	2322112	Smad2	ENSMUSG00000024563	0.660
chr18	56618000	56619000	2301752	Gramd3	ENSMUSG00000001700	0.384
chr18	66627000	66628000	2311761	Pmaip1	ENSMUSG00000024521	0.603
chr18	12706000	12707000	2257840	Lama3	ENSMUSG00000024421	0.887
chr18	11905000	11906000	2257039	Rbbp8	ENSMUSG00000041238	0.969
chr18	67438000	67439000	2312572	Mppe1	ENSMUSG00000062526	0.202
chr18	10324000	10325000	2255458	Rock1	ENSMUSG00000024290	0.487
chr18	70663000	70664000	2315797	Stard6	ENSMUSG00000079608	0.582
chr18	13223000	13224000	2258357	Hrh4	ENSMUSG00000037346	0.490
chr18	80559000	80560000	2325556	Kcng2	ENSMUSG00000059852	0.036
chr18	57380000	57381000	2302514	Megf10	ENSMUSG00000024593	0.978
chr18	37424000	37425000	2282558	Pcdhb1	ENSMUSG00000051663	0.132
chr18	12631000	12632000	2257765	Lama3	ENSMUSG00000024421	0.664
chr18	61534000	61535000	2306668		ENSMUSG00000069367	0.992
chr19	32517000	32518000	2365055	Sgms1	ENSMUSG00000040451	0.978
chr19	19316000	19317000	2351854	Rorb	ENSMUSG00000036192	0.780
chr19	28813000	28814000	2361351	Glis3	ENSMUSG00000052942	0.780
chr19	26228000	26229000	2358766	Dmrt2	ENSMUSG00000048138	0.609
chr19	53632000	53633000	2386170	Dusp5	ENSMUSG00000034765	0.255
chr19	53728000	53729000	2386266	Smc3	ENSMUSG00000024974	0.593
chr19	53403000	53404000	2385941	Mxi1	ENSMUSG00000025025	0.001
chr19	30525000	30526000	2363063	Mbl2	ENSMUSG00000024863	0.659
chr19	47520000	47521000	2380058	Gm5098	ENSMUSG00000078104	0.551
chr19	53067000	53068000	2385605	Ins1	ENSMUSG00000035804	0.522
chr19	53914000	53915000	2386452	Rbm20	ENSMUSG00000043639	0.974
chr19	18952000	18953000	2351490	Trpm6	ENSMUSG00000024727	0.642
chr19	8912000	89130002	341450	Hnmpul2	ENSMUSG00000071659	0.061
chr19	45107000	45108000	2377645	Pdzd7	ENSMUSG00000074818	0.652
chr19	41372000	41373000	2373910	Tm9sf3	ENSMUSG00000025016	1.000
chr19	25488000	25489000	2358026	Kank1	ENSMUSG00000032702	0.571
chr19	58750000	58751000	2391288	Pnlip	ENSMUSG00000046008	0.974
chr19	53756000	53757000	2386294	Rbm20	ENSMUSG00000043639	0.339
chr19	46835000	46836000	2379373	As3mt	ENSMUSG00000003559	0.000
chr19	55585000	55586000	2388123	Vti1a	ENSMUSG00000024983	0.974
chr19	17507000	17508000	2350045	Rfk	ENSMUSG00000024712	0.978

TABLE 4-continued

Exemplary methylation sites in isolated/endogenous HSCs

Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chr19	10366000	10367000	2342904	Gm98	ENSMUSG00000036098	0.482
chr19	55149000	55150000	2387687	Adra2a	ENSMUSG00000033717	0.970
chr19	47857000	47858000	2380395		ENSMUSG00000044948	0.593
chr19	36132000	36133000	2368670	Htr7	ENSMUSG00000024798	0.130
chr19	41675000	41676000	2374213	AI606181	ENSMUSG00000074873	0.570
chr19	30565000	30566000	2363103	Mbl2	ENSMUSG00000024863	0.211
chr19	9018000	9019000	2341556		ENSMUSG00000072030	0.089
chr19	45891000	45892000	2378429	Kcnip2	ENSMUSG00000025221	0.565
chr19	16673000	16674000	2349211	Gna14	ENSMUSG00000024697	0.403
chr19	53895000	53896000	2386433	Rbm20	ENSMUSG00000043639	0.617
chr19	46545000	46546000	2379083	Sufu	ENSMUSG00000025231	0.664
chr19	37765000	37766000	2370303	Cyp26c1	ENSMUSG00000062432	0.535
chr19	46399000	46400000	2378937	Psd	ENSMUSG00000037126	0.600
chr19	33836000	33837000	2366374	AI747699	ENSMUSG00000024766	0.077
chrX	49967000	49968000	2439805	Gpc3	ENSMUSG00000055653	0.030
chrX	78812000	78813000	2468491		ENSMUSG00000060673	0.590
chrX	6577000	6578000	2397159	Dgkk	ENSMUSG00000062393	0.893
chrX	35994000	35995000	2425832	C1galt1c1	ENSMUSG00000048970	0.584
chrX	87250000	87251000	2476929		ENSMUSG00000035387	0.660
chrX	72445000	72446000	2462124		ENSMUSG00000073094	0.893
chrX	96789000	96790000	2486468	Pja1	ENSMUSG00000034403	0.104
chrX	73119000	73120000	2462798	Pls3	ENSMUSG00000016382	0.160
chrX	46065000	46066000	2435903	Rbmx2	ENSMUSG00000031107	0.971
chrX	83469000	83470000	2473148	Nr0b1	ENSMUSG00000025056	0.920
chrX	153966000	153967000	2543397	Sms	ENSMUSG00000071708	0.617
chrX	7721000	7722000	2398303	Wdr13	ENSMUSG00000031166	0.420
chrX	45948000	45949000	2435786	Zfp280c	ENSMUSG00000036916	0.571
chrX	71527000	71528000	2461206	Dnase111	ENSMUSG00000019088	0.000
chrX	50266000	50267000	2440104	Phf6	ENSMUSG00000025626	0.000
chrX	35838000	35839000	2425676	Lamp2	ENSMUSG00000016534	0.561
chrX	159421000	159422000	2548852	Ctps2	ENSMUSG00000031360	0.972
chrX	35953000	35954000	2425791	Mcts1	ENSMUSG00000000355	0.001
chrX	39260000	39261000	2429098		ENSMUSG00000081918	0.980
chrX	7650000	7651000	2398232		ENSMUSG00000082572	0.000
chrX	37253000	37254000	2427091	Cypt14	ENSMUSG00000079618	0.780
chrX	49033000	49034000	2438871		ENSMUSG00000082968	0.031
chrX	11069000	11070000	2401651	Gm4906	ENSMUSG00000069038	0.185
chrX	48194000	48195000	2438032		ENSMUSG00000031112	0.002
chrX	54306000	54307000	2443994	Htatsf1	ENSMUSG00000067873	0.002
chrX	7459000	7460000	2398041	Pim2	ENSMUSG00000031155	0.972
chrX	68810000	68811000	2458489	Hmgb3	ENSMUSG00000015217	0.043
chrX	6356000	6357000	2396988	Dgkk	ENSMUSG00000062393	0.043
chrX	136406000	136407000	2525887	Morc4	ENSMUSG00000031434	0.037
chrX	133634000	133635000	2523115		ENSMUSG00000080718	0.083
chrX	12410000	12411000	2402992	Med14	ENSMUSG00000064127	0.344
chrX	91367000	91368000	2481046		ENSMUSG00000081055	0.117
chrX	97016000	97017000	2486695	Tmem28	ENSMUSG00000071719	0.069
chrX	46847000	46848000	2436685		ENSMUSG00000036198	0.069
chrX	39421000	39422000	2429259	Xiap	ENSMUSG00000025860	0.031
chrY	293000	294000	2556276	Kdm5d	ENSMUSG00000056673	0.826
chrY	325000	326000	2556308	Kdm5d	ENSMUSG00000056673	0.784
chrY	334000	335000	2556317		ENSMUSG00000075874	0.851
chrY	335000	336000	2556318		ENSMUSG00000075874	0.778
chrY	456000	457000	2556439	Eif2s3y	ENSMUSG00000069049	0.818
chrY	699000	700000	2556682		ENSMUSG00000077793	0.959
chrY	817000	818000	2556800	Usp9y	ENSMUSG00000069044	0.767
chrY	818000	819000	2556801	Usp9y	ENSMUSG00000069044	0.878
chrY	917000	918000	2556900	Usp9y	ENSMUSG00000069044	0.626
chrY	936000	937000	2556919	Usp9y	ENSMUSG00000069044	0.940
chrY	948000	949000	2556931	Usp9y	ENSMUSG00000069044	0.820
chrY	956000	957000	2556939	Usp9y	ENSMUSG00000069044	0.870
chrY	961000	962000	2556944	Usp9y	ENSMUSG00000069044	0.859
chrY	1109000	1110000	2557092	Usp9y	ENSMUSG00000069044	0.870
chrY	1126000	1127000	2557109	Usp9y	ENSMUSG00000069044	0.915
chrY	1146000	1147000	2557129	Usp9y	ENSMUSG00000069044	0.925
chrY	1156000	1157000	2557139	Usp9y	ENSMUSG00000069044	0.725
chrY	1310000	1311000	2557293	Usp9y	ENSMUSG00000069044	0.910
chrY	1420000	1421000	2557403	Usp9y	ENSMUSG00000069044	0.910
chrY	1454000	1455000	2557437	Zfy2	ENSMUSG00000000103	0.945
chrY	1460000	1461000	2557443	Zfy2	ENSMUSG00000000103	0.785
chrY	1464000	1465000	2557447	Zfy2	ENSMUSG00000000103	0.865
chrY	1537000	1538000	2557520	Zfy2	ENSMUSG00000000103	0.850
chrY	1617000	1618000	2557600	Zfy2	ENSMUSG00000000103	0.905

TABLE 4-continued

Exemplary methylation sites in isolated/endogenous HSCs						
Chr.	Chr. Start	Chr. End	Name	Gene Name	EnsemblId	HSC
chrY	1618000	1619000	2557601	Zfy2	ENSMUSG00000000103	0.870
chrY	1664000	1665000	2557647	Zfy2	ENSMUSG00000000103	0.830
chrY	1779000	1780000	2557762	Zfy2	ENSMUSG00000000103	0.865
chrY	1801000	1802000	2557784	Zfy2	ENSMUSG00000000103	0.945
chrY	1839000	1840000	2557822	Zfy2	ENSMUSG00000000103	0.900
chrY	1840000	1841000	2557823	Zfy2	ENSMUSG00000000103	0.910
chrY	1858000	1859000	2557841	Zfy2	ENSMUSG00000000103	0.920
chrY	1875000	1876000	2557858	Zfy2	ENSMUSG00000000103	0.875
chrY	1973000	1974000	2557956	Sry	ENSMUSG00000069036	0.915
chrY	2016000	2017000	2557999	Sry	ENSMUSG00000069036	0.835
chrY	2035000	2036000	2558018	Sry	ENSMUSG00000069036	0.935

[0855] Induced hematopoietic stem cells are made by the hand of man by, e.g., modifying the gene expression of at least one of the factors disclosed herein of a somatic cell, a pluripotent cell, a progenitor cell or a stem cell, or by exposing any one of these cell types to at least one protein or RNA that produces at least one protein as disclosed herein. The cells can further be made by exposing them to small molecules that turn on at least one of the factors disclosed herein. In some aspects at least two, three, four, five, six, seven, or eight factors are used to make the induced hematopoietic stem cells.

[0856] The induced hematopoietic stem cells as described herein differ from naturally occurring hematopoietic stem cells by both their posttranslational modification signatures and their gene expression signatures. These differences are passed along to their progeny. Therefore, also their progeny, whether clonal or differentiated, differs from the naturally occurring differentiated cells.

[0857] Induced hematopoietic stem cell as it is defined in some aspects of all the embodiments of the invention comprise, consist essentially of or consist of cells that are functionally capable of copying themselves as well as differentiating into various cells of hematopoietic lineage. In other words, they can be defined as having multilineage potential.

[0858] Induced hematopoietic stem cell is also defined as comprising a gene expression signature that differs from naturally occurring hematopoietic stem cells. One can experimentally show the difference by comparing the gene expression pattern of a naturally occurring hematopoietic stem cell to that of the induced hematopoietic stem cells. For example, the gene expression signature can differ in regard to the genes as shown in Tables 2 or 3. Therefore, in some aspects of all the embodiments of the invention, the induced hematopoietic stem cells comprise an expression signature that is about 1-5%, 5-10%, 5-15%, or 5-20% different from the expression signature of about 1-5%, 2-5%, 3-5%, up to 50%, up to 40%, up to 30%, up to 25%, up to 20%, up to 15%, or up to 10% of the genes of Tables 2 or 3.

[0859] Induced hematopoietic stem cell is further defined as comprising a posttranslational modification signature that differs from naturally occurring hematopoietic stem cells. In some embodiments, the posttranslational modification is methylation. For example, the methylation pattern of the induced hematopoietic stem cells is in some aspects about 1-5%, in some aspects 1-10%, in some aspects 5-10% different from the methylation pattern at about 1-5%, 1-10%, 5-10%, up to 50%, up to 40%, up to 30%, up to 25%, up to 20%, up to 15%, or up to 10% of the methylation sites shown in Table 4. In some aspects, the amount of methylation in the iHSC differs from the isolated or endogenous HSCs by no more than 1%, 2%, 3%, 4% or no more than 5%, for example as compared to the amount of methylation in the example loci listed in Table 4. Other methylation sites can naturally be used as well in any comparison for differentiating the iHSCs from HSCs.

[0860] It should be understood that this invention is not limited to the particular methodology, protocols, and reagents, etc., described herein and as such may vary. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which is defined solely by the claims.

[0861] As used herein and in the claims, the singular forms include the plural reference and vice versa unless the context clearly indicates otherwise. The term "or" is inclusive unless modified, for example, by "either." Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about."

[0862] All patents and other publications identified are expressly incorporated herein by reference for the purpose of describing and disclosing, for example, the methodologies described in such publications that might be used in connection with the present invention. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

[0863] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as those commonly understood to one of ordinary skill in the art to which this invention pertains. Although any known methods, devices, and materials may be used in the practice or testing of the invention, the methods, devices, and materials in this regard are described herein.

[0864] Some embodiments of the invention are listed in the following paragraphs:

[0865] 1. A hematopoietic stem cell (HSC) inducing composition comprising one or more expression vectors encoding at least one, two, three, four, five, six, seven, eight, or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612.

[0866] 2. The HSC inducing composition of paragraph 1, wherein the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0867] 3. The HSC inducing composition of paragraph 1, wherein the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5.

[0868] 4. A hematopoietic stem cell (HSC) inducing composition comprising one or more expression vectors comprising:

[0869] a. a nucleic acid sequence encoding HLF;

[0870] b. a nucleic acid sequence encoding RUNX1T1;

[0871] c. a nucleic acid sequence encoding ZFP37;

[0872] d. a nucleic acid sequence encoding PBX1;

[0873] e. a nucleic acid sequence encoding LMO2; and

[0874] f. a nucleic acid sequence encoding PRDM5.

[0875] 5. The HSC inducing composition of paragraph 4, further comprising one or more of:

[0876] a. a nucleic acid sequence encoding PRDM16;

[0877] b. a nucleic acid sequence encoding ZFP467; and

[0878] c. a nucleic acid sequence encoding VDR.

[0879] 6. A hematopoietic stem cell (HSC) inducing composition comprising one or more expression vectors comprising:

[0880] a. a nucleic acid sequence encoding HLF;

[0881] b. a nucleic acid sequence encoding RUNX1T1;

[0882] c. a nucleic acid sequence encoding PBX1;

[0883] d. a nucleic acid sequence encoding LMO2;

[0884] e. a nucleic acid sequence encoding PRDM5

[0885] f. a nucleic acid sequence encoding ZFP37;

[0886] g. a nucleic acid sequence encoding MYCN;

[0887] h. a nucleic acid sequence encoding MSI2;

[0888] i. a nucleic acid sequence encoding NKX2-3;

[0889] j. a nucleic acid sequence encoding MEIS1; and

[0890] k. a nucleic acid sequence encoding RBPMS.

[0891] 7. A hematopoietic stem cell (HSC) inducing composition comprising one or more expression vectors comprising:

[0892] a. a nucleic acid sequence encoding ZFP467;

[0893] b. a nucleic acid sequence encoding PBX1;

[0894] c. a nucleic acid sequence encoding HOXB4; and

[0895] d. a nucleic acid sequence encoding MSI2.

[0896] 8. The HSC inducing composition of paragraph 7, further comprising one or more of:

[0897] a. a nucleic acid sequence encoding HLF;

[0898] b. a nucleic acid sequence encoding LMO2;

[0899] c. a nucleic acid sequence encoding PRDM16; and

[0900] d. a nucleic acid sequence encoding ZFP37.

[0901] 9. A hematopoietic stem cell (HSC) inducing composition comprising one or more expression vectors comprising:

[0902] a. a nucleic acid sequence encoding MYCN;

[0903] b. a nucleic acid sequence encoding MSI2;

[0904] c. a nucleic acid sequence encoding NKX2-3; and

[0905] d. a nucleic acid sequence encoding RUNX1T1.

[0906] 10. The HSC inducing composition of paragraph 9, further comprising one or more of:

[0907] a. a nucleic acid sequence encoding HOXB5;

[0908] b. a nucleic acid sequence encoding HLF;

[0909] c. a nucleic acid sequence encoding ZFP467;

[0910] d. a nucleic acid sequence encoding HOXB3;

[0911] e. a nucleic acid sequence encoding LMO2;

[0912] f. a nucleic acid sequence encoding PBX1;

[0913] g. a nucleic acid sequence encoding ZFP37; and

[0914] h. a nucleic acid sequence encoding ZFP521.

[0915] 11. A hematopoietic stem cell (HSC) inducing composition comprising one or more expression vectors composition comprising:

[0916] a. a nucleic acid sequence encoding HOXB4;

[0917] b. a nucleic acid sequence encoding PBX1;

[0918] c. a nucleic acid sequence encoding LMO2;

[0919] d. a nucleic acid sequence encoding ZFP467; and

[0920] e. a nucleic acid sequence encoding ZFP521.

[0921] 12. The HSC inducing composition of paragraph 11, further comprising one or more of:

[0922] a. a nucleic acid sequence encoding KLF12;

[0923] b. a nucleic acid sequence encoding HLF; and

[0924] c. a nucleic acid sequence encoding EGR1.

[0925] 13. A hematopoietic stem cell (HSC) inducing composition comprising one or more expression vectors comprising:

[0926] a. a nucleic acid sequence encoding MEIS1;

[0927] b. a nucleic acid sequence encoding RBPMS;

[0928] c. a nucleic acid sequence encoding ZFP37;

[0929] d. a nucleic acid sequence encoding RUNX1T1; and

[0930] e. a nucleic acid sequence encoding LMO2.

[0931] 14. The HSC inducing composition of paragraph 13, further comprising one or more of:

[0932] a. a sequence encoding KLF12; and

[0933] b. a sequence encoding HLF;

[0934] 15. A hematopoietic stem cell (HSC) inducing composition comprising one or more expression vectors comprising:

[0935] a. a nucleic acid sequence encoding ZFP37;

[0936] b. a nucleic acid sequence encoding HOXB4;

[0937] c. a nucleic acid sequence encoding LMO2; and

[0938] d. a nucleic acid sequence encoding HLF.

[0939] 16. The HSC inducing composition of paragraph 15, further comprising one or more of:

[0940] a. a nucleic acid sequence encoding MYCN;

[0941] b. a nucleic acid sequence encoding ZFP467;

[0942] c. a nucleic acid sequence encoding NKX2-3

[0943] d. a nucleic acid sequence encoding PBX1; and

[0944] e. a nucleic acid sequence encoding KLF4.

[0945] 17. The HSC inducing compositions of any one of paragraphs 4-16, wherein the one or more expression vectors are retroviral vectors.

[0946] 18. The HSC inducing compositions of any one of paragraphs 4-16, wherein the one or more expression vectors are lentiviral vectors.

[0947] 19. The HSC inducing composition of paragraph 18, wherein the lentiviral vectors are inducible lentiviral vectors.

[0948] 20. A method for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0949] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5, wherein each said nucleic acid sequence is operably linked to a promoter; and

[0950] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0951] 21. The method of paragraph 20, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding PRDM16 a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding VDR.

[0952] 22. A method for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0953] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM5; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding MEIS1; and a nucleic acid sequence encoding RBPMS; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0954] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0955] 23. A method for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0956] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP467, a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding HOXB4; and a nucleic acid sequence encoding MSI2; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0957] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0958] 24. The method of paragraph 23, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM16; and a nucleic acid sequence encoding ZFP37.

[0959] 25. A method for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0960] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding MSI2, a nucleic acid sequence encoding NKX2-3; and a nucleic acid sequence encoding RUNX1T1; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0961] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0962] 26. The method of paragraph 25, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HOXB5; a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding HOXB3; a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding ZFP37; and a nucleic acid sequence encoding ZFP521.

[0963] 27. A method for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0964] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding PBX1, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding ZFP521; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0965] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0966] 28. The method of paragraph 27, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; a nucleic acid sequence encoding HLF; and a nucleic acid sequence encoding EGR1.

[0967] 29. A method for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0968] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding MEIS1; a nucleic acid sequence encoding RBPMS; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding RUNX1T1; and a nucleic acid sequence encoding LMO2; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0969] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0970] 30. The method of paragraph 29, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; and a nucleic acid sequence encoding HLF.

[0971] 31. A method for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0972] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding HLF; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0973] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0974] 32. The method of paragraph 31, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; and a nucleic acid sequence encoding HLF.

[0975] 33. A method for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

[0976] a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding HLF; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0977] b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

[0978] 34. The method of paragraph 33, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding ZFP467; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding PBX1; and a nucleic acid sequence encoding KLF4.

[0979] 35. The method of any one of paragraphs 20-34, wherein the somatic cell is a fibroblast cell.

[0980] 36. The method of any one of paragraphs 20-34, wherein the somatic cell is a hematopoietic lineage cell.

[0981] 37. The method of paragraph 36, wherein the hematopoietic lineage cell is selected from promyelocytes, neutrophils, eosinophils, basophils, reticulocytes, erythrocytes, mast cells, osteoclasts, megakaryoblasts, platelet producing megakaryocytes, platelets, monocytes, macrophages, dendritic cells, lymphocytes, NK cells, NKT cells, innate lymphocytes, multipotent hematopoietic progenitor cells, oligopotent hematopoietic progenitor cells, and lineage restricted hematopoietic progenitors.

[0982] 38. The method of paragraph 36, wherein the hematopoietic lineage cell is selected from a multi-potent progenitor cell (MPP), common myeloid progenitor cell (CMP), granulocyte-monocyte progenitor cells (GMP), common lymphoid progenitor cell (CLP), and pre-megakaryocyte-erythrocyte progenitor cell.

[0983] 39. The method of paragraph 36, wherein the hematopoietic lineage cell is selected from a megakaryocyte-erythrocyte progenitor cell (MEP), a ProB cell, a PreB cell, a PreProB cell, a ProT cell, a double-negative T cell, a pro-NK cell, a pro-dendritic cell (pro-DC), pre-granulocyte/macrophage cell, a granulocyte/macrophage progenitor (GMP) cell, and a pro-mast cell (ProMC).

[0984] 40. A method of promoting transdifferentiation of a ProPreB cell to the myeloid lineage comprising:

[0985] a. transducing a ProPreB cell with one or more vectors comprising a nucleic acid sequence encoding ZFP467, a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding HOXB4; and a nucleic acid sequence encoding MSI2; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0986] b. culturing the transduced ProPreB cell in a cell media that supports growth of myeloid lineage cells, thereby transdifferentiating the ProPreB cell to the myeloid lineage.

[0987] 41. The method of paragraph 40, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM16; and a nucleic acid sequence encoding ZFP37.

[0988] 42. A method of increasing survival and/or proliferation of ProPreB cells, comprising:

[0989] a. transducing a ProPreB cell with one or more vectors comprising a nucleic acid sequence encoding HOXB4; a nucleic acid sequence encoding PBX1, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding ZFP521; wherein each said nucleic acid sequence is operably linked to a promoter; and

[0990] b. culturing the transduced ProPreB cell in a cell media that supports growth of ProPreB cells, thereby increasing survival and/or proliferation of ProPreB cells.

[0991] 43. The method of paragraph 42, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding KLF12; a nucleic acid sequence encoding HLF; and a nucleic acid sequence encoding EGR1.

[0992] 44. An isolated induced hematopoietic stem cell (iHSC) produced by the method of any one of paragraphs 20-39.

[0993] 45. A cell clone comprising a plurality of the induced hematopoietic stem cells (iHSCs) of paragraph 44.

[0994] 46. The cell clone of paragraph 45, further comprising a pharmaceutically acceptable carrier.

[0995] 47. A kit for making induced hematopoietic stem cells (iHSCs) comprising the HSC inducing compositions comprising one or more expression vector components of any one of paragraphs 1-19.

[0996] 48. An induced pluripotent stem cell.

[0997] 49. An induced hematopoietic stem cell induced by contacting a somatic cell, a pluripotent cell, a progenitor cell or a stem cell with at least one of the factors selected from the group consisting of nucleic acid encoding a gene encoding CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612 or a protein encoded by such gene.

[0998] 50. The induced hematopoietic stem cell of paragraph 49, wherein the at least one factor is selected from the group consisting of HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[0999] 51. The induced hematopoietic stem cell of paragraph 49, wherein the at least one factor is selected from the group consisting of HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5.

[1000] 52. The induced hematopoietic stem cell of any of paragraphs 49-51, wherein the somatic cell, the pluripotent cell, the progenitor cell or the stem cell is contacted with at least two of the factors.

[1001] 53. The induced hematopoietic stem cell of any of paragraphs 49-51, wherein the somatic cell, the pluripotent cell, the progenitor cell or the stem cell is contacted with at least three of the factors.

[1002] 54. The induced hematopoietic stem cell of any of paragraphs 49-51, wherein the somatic cell, the pluripotent cell, the progenitor cell or the stem cell is contacted with at least three of the factors.

[1003] 55. The induced hematopoietic stem cell of any of paragraphs 49-51, wherein the somatic cell, the pluripotent cell, the progenitor cell or the stem cell is contacted with at least four of the factors.

[1004] 56. The induced hematopoietic stem cell of any of paragraphs 49-51, wherein the somatic cell, the pluripotent cell, the progenitor cell or the stem cell is contacted with at least five of the factors.

[1005] 57. The induced hematopoietic stem cell of any of paragraphs 49-51, wherein the somatic cell, the pluripotent cell, the progenitor cell or the stem cell is contacted with at least six of the factors.

[1006] 58. The induced hematopoietic stem cell of any of paragraphs 49-51, wherein the somatic cell, the pluripotent cell, the progenitor cell or the stem cell is contacted with at least seven of the factors.

[1007] 59. The induced hematopoietic stem cell of any of paragraphs 49-51, wherein the somatic cell, the pluripotent cell, the progenitor cell or the stem cell is contacted with at least eight of the factors.

[1008] 60. The induced hematopoietic stem cell of any of paragraphs 49-59, comprising at least one vector.

[1009] 61. The induced hematopoietic stem cell of paragraph 60, wherein the vector is integrated in the genome of the stem cell.

[1010] 62. The induced hematopoietic stem cell of any of paragraphs 49-61, wherein the somatic cell is a fibroblast cell.

[1011] 63. The induced hematopoietic stem cell of any of paragraphs 49-61, wherein the somatic cell is a hematopoietic lineage cell.

[1012] 64. The induced hematopoietic stem cell of paragraph 63, wherein the hematopoietic lineage cell is selected from promyelocytes, neutrophils, eosinophils, basophils, reticulocytes, erythrocytes, mast cells, osteoclasts, megakaryoblasts, platelet producing megakaryocytes, platelets, monocytes, macrophages, dendritic cells, lymphocytes, NK cells, NKT cells, innate lymphocytes, multipotent hematopoietic progenitor cells, oligopotent hematopoietic progenitor cells, and lineage restricted hematopoietic progenitors.

[1013] 65. The induced hematopoietic stem cell of paragraph 63, wherein the hematopoietic lineage cell is selected from a multi-potent progenitor cell (MPP), common myeloid progenitor cell (CMP), granulocyte-monocyte progenitor cells (GMP), common lymphoid progenitor cell (CLP), and pre-megakaryocyte-erythrocyte progenitor cell.

[1014] 66. The induced hematopoietic stem cell of paragraph 63, wherein the hematopoietic lineage cell is selected from a megakaryocyte-erythrocyte progenitor cell (MEP), a ProB cell, a PreB cell, a PreProB cell, a ProT cell, a double-negative T cell, a pro-NK cell, a pro-dendritic cell (pro-DC), pre-granulocyte/macrophage cell, a granulocyte/macrophage progenitor (GMP) cell, and a pro-mast cell (ProMC).

[1015] 67. The induced hematopoietic cell of any of paragraphs 49-61, wherein the stem cell is an embryonic stem cell or a progeny thereof

[1016] 68. The induced hematopoietic cell of any of paragraphs 49-61, wherein the stem cell is an induced pluripotent stem cell or a progeny thereof

[1017] 69. An induced hematopoietic stem cell induced by increasing or inducing in a somatic cell, a pluripotent cell, a progenitor cell or a stem cell the expression of at least one of the factors selected from the group consisting of nucleic acid encoding a gene encoding CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612.

[1018] 70. The induced hematopoietic stem cell of paragraph 69, wherein the increasing or inducing is performed by contacting the somatic cell, the pluripotent cell, the progenitor cell or the stem cell with at least one small molecule capable of increasing or inducing the expression of at least one of the factors of paragraph 69.

[1019] 71. An induced hematopoietic stem cell made by any one of the methods of paragraphs 20-43.

[1020] 72. A clone or progeny of any of the induced hematopoietic stem cells of paragraphs 48-71.

[1021] 73. A differentiated progeny cell differentiated from any of the induced hematopoietic stem cells of paragraphs 48-72.

[1022] 74. A hematopoietic stem cell (HSC) inducing composition comprising modified mRNA sequences encoding at least one, two, three, four, five, six, seven, eight, or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, and ZFP612, wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1023] 75. The HSC inducing composition of paragraph 74, wherein the at least one, two, three, four, or more

HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

[1024] 76. The HSC inducing composition of paragraph 74, wherein the at least one, two, three, four, or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5

[1025] 77. A hematopoietic stem cell (HSC) inducing composition comprising:

[1026] a. a modified mRNA sequence encoding HLF;

[1027] b. a modified mRNA sequence encoding RUNX1T1;

[1028] c. a modified mRNA sequence encoding ZFP37;

[1029] d. a modified mRNA sequence encoding PBX1;

[1030] e. a modified mRNA sequence encoding LMO2; and

[1031] f. a modified mRNA sequence encoding PRDM5;

[1032] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1033] 78. The HSC inducing composition of paragraph 77, further comprising one or more of:

[1034] a. a modified mRNA sequence encoding PRDM16;

[1035] b. a modified mRNA sequence encoding ZFP467; and

[1036] c. a modified mRNA sequence encoding VDR;

[1037] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1038] 79. A hematopoietic stem cell (HSC) inducing composition comprising:

[1039] a. a modified mRNA sequence encoding HLF;

[1040] b. a modified mRNA sequence encoding RUNX1T1;

[1041] c. a modified mRNA sequence encoding PBX1;

[1042] d. a modified mRNA sequence encoding LMO2;

[1043] e. a modified mRNA sequence encoding PRDM5

[1044] f. a modified mRNA sequence encoding ZFP37;

[1045] g. a modified mRNA sequence encoding MYCN;

[1046] h. a modified mRNA sequence encoding MSI2;

[1047] i. a modified mRNA sequence encoding NKX2-3;

[1048] j. a modified mRNA sequence encoding MEIS1; and

[1049] k. a modified mRNA sequence encoding RBPMS;

[1050] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1051] 80. A hematopoietic stem cell (HSC) inducing composition comprising:

[1052] a. a modified mRNA sequence encoding ZFP467;

[1053] b. a modified mRNA sequence encoding PBX1;

[1054] c. a modified mRNA sequence encoding HOXB4; and

[1055] d. a modified mRNA sequence encoding MSI2;

[1056] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1057] 81. The HSC inducing composition of paragraph 80, further comprising one or more of:

[1058] a. a modified mRNA sequence encoding HLF;

[1059] b. a modified mRNA sequence encoding LMO2;

[1060] c. a modified mRNA sequence encoding PRDM16; and

[1061] d. a modified mRNA sequence encoding ZFP37.

[1062] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1063] 82. A hematopoietic stem cell (HSC) inducing composition comprising:

[1064] a. a modified mRNA sequence encoding MYCN;

[1065] b. a modified mRNA sequence encoding MSI2;

[1066] c. a modified mRNA sequence encoding NKX2-3; and

[1067] d. a modified mRNA sequence encoding RUNX1T1;

[1068] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1069] 83. The HSC inducing composition of paragraph 82, further comprising one or more of:

[1070] a. a modified mRNA sequence encoding HOXB5;

[1071] b. a modified mRNA sequence encoding HLF;

[1072] c. a modified mRNA sequence encoding ZFP467;

[1073] d. a modified mRNA sequence encoding HOXB3;

[1074] e. a modified mRNA sequence encoding LMO2;

[1075] f. a modified mRNA sequence encoding PBX1;

[1076] g. a modified mRNA sequence encoding ZFP37; and

[1077] h. a modified mRNA sequence encoding ZFP521;

[1078] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1079] 84. A hematopoietic stem cell (HSC) inducing composition comprising:

[1080] a. a modified mRNA sequence encoding HOXB4;

[1081] b. a modified mRNA sequence encoding PBX1;

[1082] c. a modified mRNA sequence encoding LMO2;

[1083] d. a modified mRNA sequence encoding ZFP467; and

[1084] e. a modified mRNA sequence encoding ZFP521;

[1085] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1086] 85. The HSC inducing composition of paragraph 84, further comprising one or more of:

[1087] a. a modified mRNA sequence encoding KLF12;

[1088] b. a modified mRNA sequence encoding HLF; and

[1089] c. a modified mRNA sequence encoding EGR;

[1090] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1091] 86. A hematopoietic stem cell (HSC) inducing composition comprising:

[1092] a. a modified mRNA sequence encoding MEIS1;

[1093] b. a modified mRNA sequence encoding RBPMS;

[1094] c. a modified mRNA sequence encoding ZFP37;

[1095] d. a modified mRNA sequence encoding RUNX1T1; and

[1096] e. a modified mRNA sequence encoding LMO2.

[1097] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1098] 87. The HSC inducing composition of paragraph 86, further comprising one or more of:

[1099] a. a modified mRNA sequence encoding KLF12; and

[1100] b. a modified mRNA sequence encoding HLF;

[1101] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1102] 88. A hematopoietic stem cell (HSC) inducing composition comprising:

[1103] a. a modified mRNA sequence encoding ZFP37;

[1104] b. a modified mRNA sequence encoding HOXB4;

[1105] c. a modified mRNA sequence encoding LMO2; and

[1106] d. a modified mRNA sequence encoding HLF;

[1107] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1108] 89. The HSC inducing composition of paragraph 88, further comprising one or more of:

[1109] a. a modified mRNA encoding MYCN;

[1110] b. a modified mRNA encoding ZFP467;

[1111] c. a modified mRNA encoding NKX2-3

[1112] d. a modified mRNA encoding PBX1; and

[1113] e. a modified mRNA encoding KLF4;

[1114] wherein each cytosine of each said modified mRNA sequence is a modified cytosine, each uracil of each said modified mRNA sequence is a modified uracil, or a combination thereof

[1115] 90. The HSC inducing compositions of any one of paragraphs 74-89, wherein the modified cytosine is 5-methylcytosine and the modified uracil is pseudouracil.

[1116] 91. The HSC inducing compositions of any one of paragraphs 74-90, wherein the modified mRNA sequences comprise one or more nucleoside modifications selected from the group consisting of pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, 2-aminopurine, 2,6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine, inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine, and combinations thereof

[1117] 92. A kit for making induced hematopoietic stem cells (iHSCs) comprising the HSC inducing compositions comprising modified mRNA sequence components of any one of paragraphs 74-91.

EXAMPLES

[1118] HSC reprogramming necessitates imparting both self-renewal potential and multi-lineage capacity onto otherwise non-self-renewing, lineage-restricted cells. Induced HSCs must also be able to interact with the stem cell niche in order to sustain productive hematopoiesis, and be able to regulate long periods of dormancy (quiescence) and yet retain the capacity to generate downstream progenitors when called into cycle. The approaches described herein permit transducing committed cells with cocktails of lentiviruses bearing multiple transcriptional factors and permit efficient combinatorial screening of thousands of combinations of these factors. Moreover, the in vivo transplantation approaches described herein, in which stem cell functional potential to be imparted onto downstream progenitors is screened, allows even rare reprogramming events to be identified due to the inherent self-selecting nature of the assay system: only cells reprogrammed to functional HSCs will be able to contribute to long-term multi-lineage reconstitution, whereas cells that are not reprogrammed will only contribute to transient reconstitution of specific lineages upon transplantation (depending upon which progenitor is used). It has been recognized that one of the challenges to reprogramming mature cells is that they are inherently stable. This is, however, not necessarily true of the populations we will first attempt to reprogram which include multi-potent, oligo-potent, and lineage-restricted progenitors in the process of differentiation. Moreover, progenitors that are developmentally proximal to HSCs are likely to be more epigenetically related and therefore more permissive to reprogramming to an induced stem cell fate. At the same time clinical translation of blood cell reprogramming to HSCs may benefit most from an ability to reprogram differentiated cell types that can be readily obtained from the peripheral blood of patients.

[1119] Identification of candidate genes that mediate HSC reprogramming necessitates a detailed knowledge not only of the gene expression profile of HSCs, but also of all downstream hematopoietic progenitor and effector cells. Towards this, we have undertaken a microarray expression profiling approach in which we compared expression profiles of highly purified HSCs to the majority of downstream cell types involved in hematopoietic differentiation (FIG. **1**). Microarray analysis was performed as previously described. In total, 248 expression profiles from 40 populations were generated and compiled including unpublished and published data, in addition to datasets carefully curated from available databases (FIG. **1**). All datasets were subjected to stringent quality control using the ArrayQualityMetrics package of R/Bioconductor, and data not meeting these standards were discarded. Unsupervised hierarchical clustering analysis of normalized data showed that lineal relationships and the hierarchical structure of the hematopoietic hierarchy could be recapitulated confirming the biological robustness of the data.

[1120] Although expression datasets of selected hematopoietic populations have been published, the dataset we have generated, and described herein, represents the most comprehensive database of the molecular attributes of hematopoiesis from stem cells through to effector cells available. Using this database we are readily able to identify genes specifically expressed in any hematopoietic cell type (FIG. **3**). Analysis of such cell type-specific gene lists indicates that functionally important genes can be identified.

[1121] To clone HSC-enriched TFs, a cDNA library we generated from FACS purified HSCs is used, which allow cloning of splice variants that uniquely operate in HSCs. Consistent with this we have cloned splice variants for Nkx2-3, Msi2, Runx1, and Prdm16 and Zfp467 that are either minor variants, or have not been previously reported. To date, we have successfully cloned these TFs and confirmed their integrity by sequencing.

[1122] To test the viability of the approaches described herein for identifying HSC reprogramming factors, experiments were conducted in which progenitors were transduced with 22 individual TFs and evaluated by the phenotypic and functional assays detailed above. To show one example, enforced expression of HLF in MPPs (ckit$^+$Sca1$^+$lin$^-$flk2$^+$ CD34$^+$CD150$^-$CD48$^+$) or myeloid progenitors (ckit$^+$Sca1$^-$ lin$^-$CD150$^-$CD48$^+$) was able to endow a significant fraction of the transduced cells with a primitive CD150$^+$lin$^-$ surface phenotype (consistent with primitive stem/progenitor cells) over a time course of ex vivo culturing. After 30 days in culture in the presence of Dox, the cells were cytospun and stained, which revealed that the HLF-transduced cultures contained multiple cell types including megakaryocytes, macrophages, granulocytes and progenitor cells, whereas control cultures contained only macrophages. Functional evaluation in serial CFC assays showed that HLF conferred extensive self-renewal potential onto all progenitors tested. Examination of colony composition at each successive plating revealed that HLF expression led to diverse colony types including primitive CFU-GEMM. Importantly, withdrawal of Dox led to loss of both self-renewal and multi-lineage potential indicating that HLF (not insertional mutagenesis) was responsible for functional activity. Multiple independent experiments have confirmed these results. In vivo assays were then performed that demonstrated that HLF was able to endow long-term multi-lineage potential onto otherwise short-term reconstituting MPPs in transplantation assays.

[1123] FACS sorted progenitors from Rosa26-rtTA donors are transduced with cocktails of TF-bearing lentiviruses at multiplicities of infection intended to deliver multiple different viruses to individual cells. Assuming equivalence of viral titers, independence of infection, and viral titers sufficient for infecting 20% of the cells by each virus, we have calculated that to be reasonably confident of transducing each cell with at least 3 different viruses (3,276 permutations for 28 factor transductions) requires transduction of 4×10^4 cells. This calculation does not take into account cells that are infected with more than 3 viruses, although cells transduced with more viruses can occur and may be required for reprogramming Since tens or even hundreds of thousands of downstream hematopoietic progenitors can readily be sorted from a single donor mouse, high numbers of cells can be transduced in order to maximize the chance that one or more cells is transduced with a combination of factors capable of re-establishing the stem cell state.

[1124] Different progenitor populations can be more or less amenable to reprogramming depending upon their epigenetic state and developmental proximity to HSCs. To account for this and to maximize our chances of success, FACS purified multi-potent, oligo-potent and lineage-restricted progenitors from all branches of the hematopoietic hierarchy including MPPflk2$^-$, MPPflk2$^+$, CLPs, Pro-B cells, Pro-T cells, CMPs, MEPs, and GMPs have been used in different experiments. Transduced progenitors (CD45.2) are transplanted into irradiated congenic (CD45.1) recipients along with a radio-protective dose of CD45.1 marrow cells to ensure survival of recipients. As noted, the lentiviral system being used is Dox-inducible, and doxycycline is administered to transplanted mice for a period of 1-4 weeks post-transplant as this should be long enough to reprogram even the most distal blood cells to HSCs. In contrast, reprogramming of blood cells to induced pluripotency takes 3 to 4 weeks.

[1125] Transplant recipients were evaluated at 4-week intervals for 24 weeks by peripheral blood analysis staining for donor-derived B-cells, T-cells and granulocytes/monocytes. Control transduced or unsuccessfully reprogrammed progenitor cells are expected to transiently reconstitute specific lineages, whereas cells successfully reprogrammed to an induced stem cell state are identified by their ability to support long-term multi-lineage reconstitution in primary recipients. In this way, the approaches described herein have a strong selection criteria for identifying reprogramming factors. Importantly, if the induced HSCs generated using the compositions and methods described herein function as endogenous HSCs do, then even the presence of a small number of induced HSCs should read out in this assay system as single HSCs can read out and be detected in transplantation assays. Thus, even if the efficiency of reprogramming is low, induced HSCs can still be identified.

[1126] To control for unintentional transplantation of contaminating HSCs from our progenitor sorts being identified as false positives, sorted progenitors were transduced with control virus and transplanted alongside test recipients. Definitive demonstration that downstream cells can be reprogrammed to HSCs can achieved when progenitors that have undergone V(D)J recombination such as Pro-B cells are used as the starting cell type, as described herein, since all blood cells derived from such induced HSCs will have, and can be screened for the recombined locus, and this can serve as a "bar code" for identifying iHSCs.

[1127] The in vivo strategies described herein are designed to screen the potential of thousands of combinations of TFs for the ability to affect reprogramming. However, since cells transfected with multiple viruses are being screened, additional steps are necessary to determine which TFs mediated activity in successful reprogramming experiments. To achieve this, donor-derived granulocytes from recipients exhibiting stable long-term multi-lineage reconstitution can be FACS sorted, DNA extracted, and TFs cloned out by factor specific PCR, as demonstrated herein. Granulocytes are used since they are short-lived and their continued production results from ongoing stem cell activity. Primer pairs for each TF have been designed and tested, as described herein.

[1128] Experiments were performed to determine the minimum complement of TFs required for reprogramming, as described herein. Removing individual TFs from subsequent transduction/transplantation experiments and then assaying for loss of reprogramming ability achieves this, as shown herein. Once a minimal set of TFs capable of reprogramming a given progenitor was determined, whether the same set of factors is also able to mediate reprogramming of different blood lineages can be tested, as described herein. Experiments have been carried out using different oligo-potent progenitor cells, and depending upon the success of these experiments, terminal effector blood cells including B-cells, T-cells, and monocyte/macrophages are tested.

[1129] A key issue related to all reprogramming studies is the efficiency with which reprogramming can be affected. To determine this, limited dilution transplantation experiments were performed with blood cells transduced with validated reprogramming factors. To do this effectively, a polycistronic lentivirus containing the core complement of reprogramming factors is constructed. Use of such a polycistronic virus is important to ensure that all cells are transduced with all factors thereby allowing an accurate determination of limit dilution frequency, and by extension, reprogramming efficiency. Primary purified HSCs are used as a control in these experiments.

[1130] In some embodiments of the compositions, methods, and kits described herein, the nucleic acid sequences encoding the HSC inducing factor(s), such as HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS, are introduced or delivered using one or more inducible lentiviral vectors. Control of expression of HSC inducing factors delivered using one or more inducible lentiviral vectors can be achieved, in some embodiments, by contacting a cell having at least one HSC inducing factor in an expression vector under the control of or operably linked to an inducible promoter, with a regulatory agent (e.g., doxycycline) or other inducing agent. When using some types of inducible lentiviral vectors, contacting such a cell with an inducing agent induces expression of the HSC inducing factors, while withdrawal of the regulatory agent inhibits expression. When using other types of inducible lentiviral vectors, the presence of the regulatory agent inhibits expression, while removal of the regulatory agent permits expression. As used herein, the term "induction of expression" refers to the expression of a gene, such as an HSC inducing factor encoded by an inducible viral vector, in the presence of an inducing agent, for example, or in the presence of one or more agents or factors that cause endogenous expression of the gene in a cell.

[1131] In some embodiments of the aspects described herein, a doxycycline (Dox) inducible lentiviral system is used. Unlike retroviruses, lentiviruses are able to transduce quiescent cells making them amenable for transducing a wider variety of hematopoietic cell types. For example, the pHAGE2 lentivirus system has been shown to transduce primary hematopoietic progenitor cells with high efficiency. This vector also carries a reporter cassette (IRES Zs-Green) that enables evaluation of viral transduction efficiencies and purification of transduced cells by FACS. The ability to inducibly turn off introduced transcription factors, as demonstrated herein, is important since the HSC-enriched expression pattern of these TFs indicates their continued enforced expression in induced HSCs can impair differentiation to all lineages. Having an inducible system also allows ascertainment of the stability of the reprogrammed state and assess the establishment and fidelity of HSC transcriptional programs and epigenetic marks once enforced expression of reprogramming factors is lifted.

[1132] As demonstrated herein, the use of polycistronic viral expression systems can increase the in vivo reprogramming efficiency of somatic cells to iHSCs. Accordingly, in some embodiments of the aspects described herein, a polycistronic lentiviral vector is used. In such embodiments, sequences encoding two or more of the HSC inducing factors described herein, are expressed from a single promoter, as a polycistronic transcript. Polycistronic expression vector systems use internal ribosome entry sites (IRES) elements to create multigene, or polycistronic, messages. IRES elements are able to bypass the ribosome scanning model of 5'-methylated Cap dependent translation and begin translation at internal sites (Pelletier and Sonenberg, 1988). IRES elements can be linked to heterologous open reading frames. Multiple open reading frames can be transcribed together, each separated by an IRES, thus creating polycistronic messages. By virtue of the IRES element, each open reading frame is accessible to ribosomes for efficient translation. Multiple genes can be efficiently expressed using a single promoter/enhancer to transcribe a single message. See, for example, U.S. Pat. Nos. 4,980,285; 5,925,565; 5,631,150; 5,707,828; 5,759,828; 5,888,783; 5,919,670; and 5,935,819; and Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Press (1989).

[1133] The experiments described herein indicate that the approaches described herein are a viable approach to affect HSC reprogramming. As described herein, purified MPPs (ckit+Sca1+lin−flk2+CD34+CD150−) transduced with control, or a pool of 17 different TF viruses were transplanted into irradiated congenic recipients. As expected, MPPs transduced with control virus gave rise to long-lived B- and T-cells but their myeloid lineage potential was quickly extinguished by 8 weeks post-transplant consistent with the fact that MPPs do not self-renew. MPPs transduced with the 17-factor cocktail however gave rise to long-term myeloid, B- and T-cell reconstitution in recipient mice, indicating successful reprogramming of these progenitors to an induced HSC fate. The fact that all transplant recipients in this experiment were multi-lineage reconstituted indicates that reprogramming was not a rare event.

[1134] To rigorously test multi-potency and self-renewal, induced HSCs are FACS purified from the bone marrow (BM) of primary transplant recipients 4 months post-transplant by stringent cell surface criteria, as described herein. These cells are serially transplanted at varying doses (10, 50, 250 cells) into secondary (2°) recipients (along with radio-protective BM cells), to gauge their functional potential in comparison to endogenous, unmanipulated HSCs. Peripheral blood analysis of recipients is performed at monthly intervals for 4 months to evaluate multi-potency and long-term-self renewal. In addition, 3° and 4° transplants can be performed to establish the absolute replicative capacity of induced HSCs. BM analysis 4 months post-transplant of 1° and 2° recipients is done to determine the extent to which induced HSCs reconstitute the primitive stem cell compartment. At the same time, donor-derived myeloid, thrombo-erythroid, and lymphoid progenitor compartments are quantified to evaluate the ability of induced HSCs to give rise to different progenitor compartments.

[1135] Single HSCs that are rigorously purified are able to reconstitute irradiated recipients at a frequency of about 40% of transplant recipients. To clonally evaluate induced HSCs, single reprogrammed HSCs are sorted from the BM of primary recipients and transplanted into irradiated secondary recipients along with radio-protective BM cells, as described herein. Peripheral blood analysis of donor-chimerism is done as described above to evaluate the functional capacity of individual clones. CFC activity in methylcellulose is also used to assess clonal ability of induced HSCs. Purified unmanipulated HSCs are used as controls in these assays.

[1136] To examine the fidelity of reprogramming at the molecular level, donor-derived induced HSCs can be FACS purified from the BM of recipient mice 4 months post-transplant, as described herein, and RNA extracted, and microarray analysis performed as described. Resulting data is normalized to our hematopoietic expression database and unsupervised hierarchical clustering analysis is performed to determine the extent to which induced HSCs recapitulate the molecular signature of endogenous HSCs, as described herein. qRT-PCR analysis is performed to confirm the integrity of the microarray data as described.

[1137] Finally, stringent evaluation of reprogramming at the molecular level is best achieved by determining how faithfully epigenetic marks are re-established. To examine this, sorted induced HSCs and endogenous HSCs are subjected to genome-wide methylation analysis using reduced representation bi-sulfite deep sequencing, which provides nucleotide level resolution of CpG methylation status at genome scale.

[1138] As described herein, we have employed doxycycline to achieve relatively high levels of expression of individual TFs as measured by qRT-PCR, and reporter activity. However, successful reprogramming can require expression levels to be within a certain range. In consideration of this, doxycycline can be titered to achieve different levels of expression. Lentiviral integration can inadvertently activate genes contributing to reprogramming and in such a way confound interpretations regarding the reprogramming activity of introduced TFs. Subsequent validation experiments however can be designed to control for this.

[1139] An important consideration for the compositions and methods described herein is that induced HSCs must be capable of homing to and occupying a suitable niche to mediate long-term multi-lineage reconstitution. Transplanting transduced progenitors cells into lethally irradiated recipients can enable this homing, since irradiation acts, at least in part, to clear endogenous HSCs from their bone marrow niche facilitating occupancy by transplanted HSCs. Further, since HSCs have the ability to exit their niches, circulate, and then re-home to niches in the normal course of their biology, induced HSCs should be capable of homing to, and establishing residency in a productive niche. However, should induced HSCs fail to properly engraft within the bone marrow, alternative strategies of direct intra-femoral injection can be applied to directly deposit transduced progenitors into the bone marrow of irradiated recipients. Alternatively, co-transduction with Cxcr4, a critical HSC homing receptor can be used to facilitate proper homing of induced HSCs.

[1140] The inducible TF expression in the systems described herein require the presence of doxycycline (Dox) and the tet-transactivator, rtTA. Towards this, an rtTA lentivirus has been cloned that can be co-transduced with the TF containing viruses. We have also obtained a transgenic strain in which rtTA is constitutively expressed from the Rosa26 locus. Using cells isolated from these mice obviates the need for rtTA co-transduction. All viruses are titered using Jurkat cells. Experiments show that high titer viruses can be generated that routinely transduce purified hematopoietic progenitors with high efficiency (50-90%), and that the system is tightly Dox-inducible in vivo.

[1141] HSC inducing factors capable of reprogramming progenitors to an HSC state can be capable of introducing phenotypic properties of HSCs onto transduced progenitors through continued enforced expression. To evaluate this, TF-transduced progenitors were monitored for markers associated with HSCs by flow cytometry during ex vivo culturing. Experiments can first be conducted using single TF-transductions, followed by experiments in which TFs are co-transduced. For these experiments FACS purified progenitors are transduced for 2 days with virus followed by resorting the transduced cells (Zs-Green positive). 200-500 cells are seeded into wells for culturing in an HSC supportive media. Flow cytometry is performed at weekly intervals for a month Immunostaining of cells can be performed with antibodies for CD150, and lineage markers (cocktail of antibodies against differentiated cells) since these have been shown to be reliable for HSC identification under diverse conditions. Transcription factors scoring positively with these markers can be examined using additional HSC markers including Sca1, CD48, CD105 and CD20127. On day 30, cultures are cytospinned, stained (May-Grunwald), and cell types scored.

[1142] Depending upon which starting cell is being reprogrammed, in some embodiments, it can be required to knock-down lineage specific factors to convert downstream progenitors back to an induced HSC fate, such as, for example when using B-lineage committed cells.

TABLE 5

Primer Sequences Used For Reverse Cloning of HSC Inducing Factors

Factor	5' Primer	SEQ ID NO:	3' Primer	SEQ ID NO:	Size
Hoxb5	CCTGTCCTCGCCCGAGTCCCTGCC	94	CGTCGCCGCCGGGTCAGGTAGCGATTG	131	465
Rarb	CTCGTCCCGAGCCCACCATCTCCACTTCCTCC	95	GCAAAGGTGAACACAAGGTCAGTCAGAGG	132	696
Ndn	CAACAACCGTATGCCCATGACAGG	96	CATCCTCTTCTGGTCCTTCACCAAC	133	275
Evi1	GGAGGTGGGATGGAGGGAATCCTTG	97	CAATTTCATCGGGAACAGCAACCATG	134	313
Napll3	GGGAAATTGAAGTCCAGCCAAGAGTG	98	CTGCACCCGATTTCTTACGGCTTG	135	1000
Mycn	CCCGGTGAACAAGCGAGAGTCGGCGTC	99	GTTGACGCTCCAGGATGTTGTGGTTG	136	385
Meis1	GCATGGGTTCCTCGGTCAATGACG	100	GTCCTTATCAGGGTCATCATCGTC	137	622
Hlf	GCGCCCTCGGTCATGGATCTCAGC	101	CCATGTTGTTCTTTCTGCGCCTCGCCC	138	354
Rbpms	GACCCTATTTGTCAGCGGTCTGCCTC	102	GAAAGCGGCAGGAGGAGGAAGAGC	139	432
Msi2	CTCCAGAGGCTTCGGTTTCGTCAC	103	CTGCCATAGGTTGCCACAAAGTTG	140	503
Irf6	GTGGAGACCGGAAAGTACCAGGAAGG	104	GTTTGCCCATACTCCTTCCCACGATAC	141	535
Prdm16	GGAGGCCGACTTTGGATGGGAGCAG	105	CTTCTCGTTGGTGATATGCTCTGGACCTG	142	510
Zfp467	GGATGGGTTCAGTAATGCCCAGGAGAAG	106	CCACCCGGACAGCGCGATTCCACC	143	375
Zfp37	CAGGTTTAGATGGAGTACGGCAGTGTG	107	GCAAGGCCCAAGACAGCAGGAACAAG	144	506
Vdr	CATCACCAAGGACAACCGGCGACAC	108	CAGCATGGAGAGCGGAGACAGGTC	145	465
Nkx2-3	CGAGGAAGAAGAGGGAGAGAAACTGTC	109	CTGCCGCTGTCTCTTGCACTTGTACC	146	432
Zfp612	GGTGACCTTTGAGGACGTGGCTGTG	110	GACTAAACAAACACCCTTCCACAGAGC	147	433

TABLE 5-continued

Primer Sequences Used For Reverse Cloning of HSC Inducing Factors

Factor	5' Primer	SEQ ID NO:	3' Primer	SEQ ID NO:	Size
Runx1t1	CAACGGGCCTTCTTCTTCCTCTTCCTC	111	CATTATTTGGACTGTACCGCTGGCCTGG	148	533
Runx1	CTGCTCCGTGCTACCCACTCACTG	112	GAGGCTGAGGGTTAAAGGCAGTGGAG	149	496
Hoxb4	CGATTACCTACCCAGCGACCACTC	113	CGTCAGGTAGCGATTGTAGTGAAACTCC	150	483
Nr3c2	CCAACACTTGAGTTCCTTTCCGCCTGTC	114	GCAGGACAGTTCTTTCTCCGAATC	151	405
Tcf15	CCGAAAGCTGTCTAAGATCGAGACG	115	CTGCCCCCCAGGTCACGACGGCTGC	152	331
Hoxa5	GGCAGCACCCACATCAGCAGCAGAG	116	CGCCGAAGAAGGATCGAAATAGCTC	153	291
Hoxb3	CTGGATGAAAGAGTCGAGGCAAAC	117	GGTAGTTGGAAGGCAGCGCGTAGGC	154	318
Pbx1	GAGTTTGGATGAAGCGCAGGCCAG	118	GATGCCGCACTTCTTGGCTAACTC	155	433
Klf2	CAAGGGTCTCCAAACGTCCACAAC	119	GTCACATTTGGCAGGTCATCATCG	156	605
Lmo2	GCCATCGAAAGGAAGAGCCTGGAC	120	CCACTCGTAGATGTCTTGTTCACACAC	157	443
Etv6	GAGCAGAGATGACGTAGCCCAGTG	121	GTGGTTGTTCTCCTGCTGTAGCCTGG	158	507
Hoxa9	CGCTCTCCTTCGCGGGCTTACCCTCC	122	GTGGAGCGAGCATGTAGCCAGTTGG	159	239
Igf2BP2	GAACTGGGCCATCCGCGCCATCGAGAC	123	CTTCAGGTTTCTGCCTTCTTTGCCAATC	160	703
Gata2	GTCTTCTTCAACCATCTCGACTCGCAGG	124	GGTATCGGGTGGTGTGTTGCAGGCTGGG	161	574
Zfp521	GGGTTTCGTTGTGTGGTGTGTATGCAG	125	GAACAAACACTGTGAAACAGACGGG	162	406
Glis2	CGGCAGCGGGAAGGTGAACGGGAGCTAC	126	GCACAGGGTGAGGAGGAGGCTGAAGAG	163	488
Zfp532	CGGTCCCGGCAGACCAGATGATAGTTC	127	CTCCTCCTCCTCATCGTTGGTAACATC	164	518
Nfix	GCACGAGAAGCGGATGTCAAAGGACGAG	128	CACATCATCTACTGGACTCTCCATCTC	165	723
Prdm5	CTGATGTGGGAGGTACGTGGGAGCAAG	129	CAGGCAAAGTCCTCTTCACAGCCAAGG	166	314
Egr1	GAGCGAGGACCAGTCACTATTTGAG	130	CCATATTCTTTCACCGCCCACTCC	167	416

[1143] *Homo sapiens* hepatic leukemia factor (HLF), mRNA (SEQ ID NO: 9) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

[1144] *Homo sapiens* LIM domain only 2 (rhombotin-like 1) (LMO2), transcript variant 1, mRNA (SEQ ID NO: 21) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

[1145] *Homo sapiens* Meis homeobox 1 (MEIS1), mRNA (SEQ ID NO: 22) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

[1146] *Homo sapiens* musashi RNA-binding protein 2 (MSI2), transcript variant 1, mRNA (SEQ ID NO: 23) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

[1147] *Homo sapiens* v-myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian) (MYCN), mRNA (SEQ ID NO: 24) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

[1148] *Homo sapiens* NK2 homeobox 3 (NKX2-3), mRNA (SEQ ID NO: 28) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

[1149] *Homo sapiens* pre-B-cell leukemia homeobox 1 (PBX1), transcript variant 2, mRNA (SEQ ID NO: 30) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

[1150] *Homo sapiens* PR domain containing 5 (PRDM5), mRNA (SEQ ID NO: 32) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

[1151] *Homo sapiens* RNA binding protein with multiple splicing (RBPMS), transcript variant 3, mRNA (SEQ ID NO: 35) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

[1152] *Homo sapiens* runt-related transcription factor 1; translocated to, 1 (cyclin D-related) (RUNX1T1), transcript variant 5, mRNA (SEQ ID NO: 37) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

[1153] *Homo sapiens* ZFP37 zinc finger protein (ZFP37), mRNA (SEQ ID NO: 42) and a codon optimized, or different codons encoding the same amino acids, are naturally also contemplated to be covered by the reference to the nucleic acid as set forth herein.

Example 2

Identification of Factors Capable of Imparting Alternative Lineage Potential In Vitro and Multi-Lineage Engraftment Potential on Committed Progenitors In Vivo

[1154] Experimental strategies for reprogramming diverse cell types generally rely on the action of one or more genes able to impart the cellular and molecular properties of one cell type onto a different cell type. We hypothesized that regulatory factors with relatively restricted expression in HSCs in relation to their downstream hematopoietic progeny are likely to be involved in defining the functional identity of HSCs through regulation of the gene networks underlying their fundamental properties which include self-renewal and multi-lineage differentiation potential. We reasoned that transient ectopic expression of such factors in committed blood cells might therefore instill them with the functional properties of HSCs and potentially stably reprogram them back to an HSC-like state. To identify such factors we analyzed microarray data of 40 different purified hematopoietic cell types that we and others have generated that comprise the vast majority of hematopoietic progenitor and effector cells in addition to HSCs. These datasets (142 arrays in total) were normalized together into a single database providing a comprehensive molecular overview of hematopoiesis from stem cells through to effector cells. Using this database we identified 36 regulatory factors with relatively restricted expression in HSCs in relation to their downstream progeny. These included 33 genes encoding transcription factors, and 3 genes encoding translational regulators (FIG. **58**A). Consistent with our hypothesis, multiple genes with known roles in regulating the core properties of HSCs were identified which included Ndn (Kubota et al., 2009), Evil (Yuasa et al., 2005), Meis1 (Hisa et al., 2004), HLF (Gazit et al.), Egrl (Min et al., 2008) and others. We also identified multiple regulatory proteins that remain unstudied in HSC biology. Each of the 36 factors was then cloned into doxycycline-inducible lentiviruses bearing a reporter cassette (Zs-Green) (Mostoslaysky et al., 2005) and high-titer viruses were produced (FIG. **58**B).

[1155] It has been recognized that one of the challenges to reprogramming mature cells is that they are inherently stable (Zhou and Melton, 2008). This is not necessarily true of oligo-potent and lineage-committed hematopoietic progenitors, which are transient cell types in the process of differentiation. Moreover, since progenitor cells proximal to HSCs are more epigenetically related to HSCs (Bock et al., 2012), we reasoned that these might be more amenable to reprogramming back to an HSC-like state. Thus we first sought to determine if we could impart alternative lineage potentials onto lineage-restricted progenitors by assaying the ability of the 36 factors to instill myeloid lineage potential onto otherwise B-cell restricted progenitors in colony forming assays. We purified Pro/Pre B-cells (CD19+B220+AA4.1+IgM−) from mice expressing the reverse tetracycline-controlled transactivator (rtTA) from the Rosa26 locus (Rosa26rtTA) (FIG. **65**), and transduced them with control virus (Zs-green), or the 36-factor viral cocktail. Transduced cells were then exposed to doxycycline followed by plating into methylcellulose in the presence of myeloid promoting cytokines (FIG. **58**C). These experiments showed that whereas control-transduced Pro/Pre B-cells were unable to form myeloid colonies as expected, cells transduced with the 36-factor cocktail readily gave rise to colonies bearing diverse myeloid lineages including granulocytes, erythrocytes, megakaryocytes and macrophages (FIG. **58**D-E).

[1156] We next determined if transient ectopic expression of the 36-factor cocktail imparted HSC-like potential onto lineage-restricted lymphoid or myeloid progenitors in vivo. We took advantage of the fact that HSCs are the only hematopoietic cells capable of long-term multi-lineage reconstitution in myeloablated recipients upon transplantation, whereas downstream progenitors only transiently reconstitute recipient mice with restricted lineage potential depending upon their stage of differentiation (FIG. **59**A). Moreover, we reasoned that the sensitivity of the transplantation assay, in which even a single HSC can give rise to detectable multi-lineage engraftment, would permit detection of even rare reprogramming events. Thus, only progenitors transduced with a combination of factors capable of instilling them with long-term reconstitution potential would be read out in this assay. Towards this we purified Pro/Pre B-cells or common myeloid progenitors (CMPs: lin−c-kit+Sca1−Fc□rlowCD34+) from Rosa26rtTA mice (CD45.2) and following a 2-day transduction protocol with control (Zs-green) or viruses bearing the 36-factors in the presence of doxycycline, we transplanted them into lethally irradiated congenic recipients (CD45.1) along with radio-protective bone marrow cells (CD45.1) (FIG. **59**A). Doxycycline was maintained in the drinking water for 2 weeks post-transplant to maintain ectopic expression of the introduced factors, followed by doxycycline withdrawal. Peripheral blood analysis of the reconstituted mice over the 16-week course of the experiment revealed that, as expected, control-transduced Pro/Pre B-cells or CMPs did not give rise to donor-derived long-term engraftment (FIG. **59**B-C). By contrast, a few of the recipients transplanted with the 36-factor transduced B-cell progenitors (3/15) or CMPs (2/8) exhibited long-term donor-derived reconstitution (FIG. **59**B-C). All but one of the reconstituted mice showed multi-lineage engraftment of B-, T- and myeloid cells though the degree of engraftment of each lineage varied amongst the different recipients (FIG. **59**D). Analysis of V(D)J recombination of sorted donor-derived myeloid cells from the Pro/Pre B-cell arm of the experiment confirmed the B-lineage origin of the reconstituting cells as evidenced by recombination of the heavy chain of the IG locus (FIG. **59**E). The observation of multiple heavy chain bands in the gel indicated that the reconstituting cells were polyclonal.

[1157] These experiments indicated that one or more factors from the 36-factor cocktail could imbue long-term multi-lineage reconstituting potential onto otherwise committed lymphoid and myeloid progenitors. To determine which factors might be involved in conferring this potential, we sorted donor-derived myeloid, B-cells and T-cells to test for the presence of each of the 36 factors using a PCR-based strategy (FIG. **59**F, Table 5). This analysis revealed that whereas multiple factors could be identified in the donor-derived cells from each of the reconstituted mice, 6 transcription factors, Hlf, Runx1t1, Pbx1, Lmo2, Zfp37, and Prdm5 were consistently detected in all of the reconstituted recipients in multiple lineages (FIG. **59**G).

[1158] Six transcription factors (Hlf, Runx1t1, Pbx1, Lmo2, Zfp37, and Prdm5) are sufficient to reprogram progenitor potential in vitro and impart long-term multi-lineage engraftment potential in vivo.

[1159] We next assessed if the 6 transcription factors we had identified in our in vivo screen were sufficient to confer myeloid colony forming potential onto Pro/Pre B-cells in methylcellulose. As we had observed with the 36-factor cocktail (FIG. **58**D-E), transduction with the viral combination of Hlf, Runx1t1, Pbx1, Lmo2, Zfp37, and Prdm5 was able to imbue lineage-restricted B-cell progenitors with myeloid lineage potential in these assays (FIG. **60**A-B). To test the requirement for each of the 6 transcription factors (6-TF) we employed "N minus 1" experiments in which each of the factors was sequentially omitted from the transduction cocktail (FIG. **60**C). These experiments revealed that whereas Hlf, Runx1t1, Pbx1, Lmo2, and Zfp37 were all required for instilling myeloid colony forming potential onto Pro/Pre B-cells in vitro, the 5-factor cocktail minus Prdm5 still gave rise to myeloid colonies albeit at lower numbers than the 6-TF combination (FIG. **60**C).

[1160] We next tested whether the 6-TF cocktail was sufficient to impart long-term multi-lineage reconstituting potential onto committed myeloid or B-cell progenitors in transplantation assays. Purified Pro/Pre B-cells (CD45.2) were transduced with control (Zs-green) virus or the 6-TF cocktail followed by transplantation into congenic recipients (CD45.1). In contrast to control-transduced cells, long-term multi-lineage reconstitution was observed in 1/13 and 2/12 recipients transplanted with 6-TF transduced Pro/Pre cells or CMPs cells, respectively (FIG. **60**D). Peripheral blood analysis of recipient mice throughout the course of the experiment revealed that in all cases, donor-derived cells from the reconstituted recipients showed multi-lineage engraftment (FIG. **60**D-F). Heavy chain rearrangement was observed in donor-derived myeloid cells sorted from the Pro/Pre B-cell reconstituted mouse confirming the B-cell origin of the reconstituting cells (FIG. **60**G). These results indicate that transient ectopic expression of Hlf, Runx1t1, Pbx1, Lmo2, and Zfp37, and Prdm5 is sufficient to impart long-term, multi-lineage transplantation potential onto otherwise committed myeloid and lymphoid progenitors.

[1161] Inclusion of Meis1 and Mycn and use of polycistronic viruses improves in vivo reprogramming efficiency.

[1162] The absence of donor-derived reconstitution in many of the recipient mice in our 6-TF transplantation experiments (FIG. **60**D) suggested that the efficiency of imparting this long-term multi-lineage potential onto committed progenitors was low. To try to improve this we developed polycistronic doxycycline-inducible lentiviruses bearing three transcription factors each separated by 2A peptide sequences (Runx1T1.Hlf.Lmo2 (RHL), Pbx1.Zfp37.Prdm5 (PZP)). We also included two additional transcription factors (Mycn and Meis1) that we had repeatedly identified from primitive colonies generated in in vitro colony forming experiments (FIGS. **61**A, **66**, and data not shown). To test the utility of these strategies we transduced purified Pro/Pre B-cells with control virus, or the 8-transcription factor cocktail as individual viruses (8-TF), or using the RHL and PZP polycistronic viruses along with viruses bearing Mycn, and Meis1 (8-TF-Poly), and transplanted them into irradiated congenic recipients at greater numbers than in previous experiments. Peripheral blood analysis of transplanted mice over the course of 16 weeks revealed that in contrast to the control-transduced cells that showed no donor-derived chimerism (0/12), multiple recipients transplanted with either the 8-TF (3/6) or the 8-TF-Poly (9/14) transduced cells exhibited donor-derived chimerism (FIG. **61**B). All recipients showed multi-lineage reconstitution 18-22 weeks post-transplant though again the degree of B-cell, T-cell and myeloid chimerism varied amongst recipients (FIG. **61**C-D). The B-cell origin of the reconstituting cells was confirmed through evidence of IG heavy chain rearrangement in donor-derived myeloid cells, with the presence of many bands indicating that the reconstituting cells were polyclonal (FIG. **61**E).

[1163] Reprogrammed cells engraft bone marrow progenitor compartments and can reconstitute secondary recipients.

[1164] In addition to reconstituting the peripheral blood, HSCs efficiently engraft secondary hematopoietic organs and bone marrow progenitor cell compartments upon transplantation. To determine if the B-cell progenitors transduced with the 8-TF or 8-TFPoly cocktails possessed this ability, reconstituted mice were sacrificed and analyzed 18-20 weeks post-transplant, which showed that all the mice had donor-derived chimerism of the bone marrow, spleen and thymus though the level of varied between recipients as we had observed in the periphery (FIG. **62**A). The Pro/Pre B-cell origin of the engrafting cells was confirmed through analysis of IG rearrangement from DNA isolated from granulocytes and myeloid cells purified from the bone marrow and spleen, and T-cells derived from the thymus (FIG. **62**B) Immunophenotyping of bone marrow cells revealed donor contribution to common lymphoid progenitors (CLPs: lin−Flk2+IL7R□+ ckitlowSca1low), CMPs, granulocyte/monocyte progenitors

(GMPs: lin−ckit+Sca1−Fc□rhighCD34+), megarkaryocyte/erythrocyte progenitors (MEPs: lin−ckit+Sca1−Fc□r−CD34−), and primitive LSK progenitors (lin−Sca1+ckit+) (FIGS. **62**C-F). Importantly, we also observed donor contribution to megakaryocyte progenitors (MkPs: lin−c-kit+Sca1−CD41+), and erythroid progenitors (EPs: lin−ckit+Sca1−Endoglin+) suggesting that the reconstituting cells were able of give rise to precursor cells of platelets and erythrocytes, lineages which we could not track in the peripheral blood in the congenic CD45-based transplantation system we used. Subfractionation of the LSK compartment revealed donor-derived reconstitution of the multi-potent progenitor (MPP1: lin−ckit+Sca1+CD34+Flk2−, MPP2: lin−c-kit+Sca1+CD34+Flk2+) and HSC (lin−c-kit+Sca1+CD34−Flk2−) compartments (FIGS. **62**C-**62**F). Donor-marked progenitors and HSCs were found to be heavy chain rearranged confirming their B-cell origin (FIG. **62**G).

[1165] A defining property of HSCs is their ability to self-renewal, a potential that can be evidenced by an ability to reconstitute secondary recipients upon serial transplantation. To test if the cells generated in our experiments possessed this potential we sacrificed primary recipient mice 18 weeks post-transplant and transplanted whole bone marrow or donor-derived c-kit+ cells into irradiated secondary congenic recipients. Peripheral blood analysis at 4, 8 and 12 weeks post-transplant reveled robust donor reconstitution of B-, T- and myeloid cells in all secondary recipient mice (FIGS. **62**H-I). Taken together, these results indicate that transient ectopic expression of 8 transcription factors imparts multi-lineage reconstituting potential, reconstitutes bone marrow progenitor compartments, and enables long-term self-renewal potential—the functional hallmarks of HSCs—onto lineage-restricted B-cell progenitors.

Reprogramming Terminally Differentiated Myeloid Cells to Transplantable HSC-Like Cells.

[1166] Eventual clinical translation of blood cell reprogramming to derive HSCs would likely benefit from an ability to reprogram cell types that can be readily and non-invasively obtained from the peripheral blood. We therefore sought to determine if multi-lineage progenitor activity could be conferred onto terminally differentiated blood cells using the transcription factors we identified. Recipient and donor-derived peripheral blood was sorted from mice engrafted with Pro/Pre B-cells transduced with the 8-factor cocktail (8-TF or 8TFPoly) 16-22 weeks post-transplant (ie. 14-20 weeks post-doxycycline induction). Sorted cells were then cultured in the absence or presence of doxycycline—with the latter condition intended to lead to re-expression of the transduced factors—followed by plating the cells in methylcellulose (FIG. **63**A). As expected, neither the recipient-marked cells, nor the donor-derived cells cultured and plated in the absence of doxycycline gave rise to colonies, consistent with low-level progenitor activity in the peripheral blood of mice (FIG. **63**B). By contrast, plates seeded with donor cells that had seen reactivation of the 8 transcription factors by exposure to doxycycline gave rise to mixed myeloid lineage colonies that included primitive GEMM colonies (FIG. **63**B). To determine which lineage(s) in the peripheral blood had the potential to give rise to these colonies upon re-expression of the transcription factors, we sorted donor-derived B-cells, T-cells, myeloid cells and granulocytes from the 8-TF reconstituted mice, and tested their colony forming potential following culturing and plating in the absence or presence of doxycycline. These experiments revealed that essentially all colony-forming potential originated from the myeloid and granulocyte cell fractions (FIG. **63**C-**63**D). Interestingly, the colonies generated from the sorted myeloid cells were much larger than those derived from granulocytes though a greater number of colonies arose from the latter.

[1167] Encouraged by these results we next determined if the transcription factors we identified impart multi-lineage reconstituting potential onto terminally differentiated myeloid cells in transplantation assays. We sorted Mac1+c-kit− myeloid effector cells from Rosa26rtTA mice and transduced them with either 6-factor (6-TFPoly), or 8-factor cocktails (8-TF and 8-TFPoly) and transplanted them into irradiated congenic recipients. Peripheral blood analysis at monthly intervals revealed that, whereas none of mice transplanted with cells transduced with control virus were reconstituted, multiple recipients transplanted with cells transduced with 6-TFPoly (4/7), 8-TF (3/6), and 8-TFPoly (7/8) exhibited long-term donor-derived engraftment (FIG. **63**F, **66**). Lineage analysis of the reconstituted mice revealed donor-derived contribution to B-cell, T-cell, myeloid, and granulocyte lineages with the contribution to each lineage varying between recipients (FIG. **63**F). Donor-derived contribution to secondary hematopoietic organs, and bone marrow progenitor cell compartments was observed in mice sacrificed and analyzed 20 weeks post-transplant (FIGS. **68**A-D). Serial transplantation of donor-derived bone marrow cells demonstrated that the 6-TF or 8-TF transduced myeloid effectors could engraft secondary recipients in all lineages to 12 weeks post-transplant (FIG. **63**G-**63**H).

[1168] Based on the functional data presented in FIGS. **58**-**63**, we conclude that transient ectopic expression of 6 (Hlf, Runx1t1, Pbx1, Lmo2, Zfp37, and Prdm5) or 8 (Hlf, Runx1t1, Pbx1, Lmo2, and Zfp37, Prdm5, Mycn, and Meis1) transcription factors reprograms differentiated hematopoietic progenitors and effector cells to cells that possess the functional properties of HSCs. We term these reprogrammed cells induced-HSCs (iHSCs).

[1169] Single cell expression profiling of iHSCs reveals evidence of partial and full reprogramming.

[1170] To assess the extent to which reprogrammed iHSCs recapitulate the molecular properties of endogenous HSCs, we employed a recently developed single cell gene expression profiling methodology that accurately defines hematopoietic stem and progenitor identity through the simultaneous quantification of expression of 152 lineage-specific transcription factors, epigenetic modifiers, cell surface molecules, and cell-cycle regulators (Guo et al., 2013). We sorted and analyzed donor-derived iHSCs by immunophenotype (CD45.2+lineage−ckit+Sca1+Fk2−CD34−/lowCD150+) from two different experiments in which Pro/Pre B cells had been transduced with the 8-TF cocktail as single viruses (8-TF), or with polycistronic viruses (8-TFPoly) (FIG. **61**). In both settings mice exhibiting long-term multi-lineage donor-derived reconstitution were sacrificed at 18 weeks post-transplantation. We also sorted and analyzed host-derived HSCs (CD45.1+lineage−ckit+Sca1+Fk2−CD34−/lowCD150+) from the same mice to serve as controls. Single cell expression data generated from iHSCs and host HSCs was then analyzed in comparison to data generated from Pro/Pre B-cells (the starting cell type), and also to data previously generated from HSCs, MPPs, CLPs, CMPs, GMPs, and MEPs purified at steady-state (Guo et al., 2013). Analysis of the raw data revealed high correlation between gene expression for the vast majority of the control and test cell types (FIG. **69**, Tables 6-8). To further interrogate the transcriptional relationships amongst all the cell types analyzed, we performed principal component analysis (PCA) to define the transcriptional distances between the cells. As expected, steady-state HSCs and progenitor cells were largely positioned in agreement with established lineal relationships where HSCs forming a clearly defined cluster, with MPPs positioned proximal, and oligopotent progenitors (MEPs, GMPs, CLPs) positioned more distal to HSCs (FIG. **64**A). Pro/Pre B-cells positioned closely to CLPs consistent with the lineal relationship between these cell types, while the host-derived HSCs were positioned within the steady-state HSC cluster as expected (FIG. **64**A). Interestingly, iHSCs derived from the two experiments (8-TF or 8-TFPoly) exhibited very distinct patterns of expression with the iHSCs derived from the 8-TF single virus experiment being more heterogeneous than the iHSCs derived from the 8-TFPoly transduced cells (FIGS. **64**A, **69**, Tables 6-8). As a result, PCA analysis of these cells showed that whereas some of the iHSCs 8-TF positioned closely or within the HSC cluster, others mapped closer to MPPs while others yet positioned closely to the Pro/Pre B cluster (FIG. **64**A). By contrast, all of the iHSCs derived using the polycistronic viruses (iHSC 8-TFPoly) homogenously clustered within the HSC node (FIG. **64**A). Unsupervised hierarchical clustering analysis confirmed that whereas approximately equal numbers of iHSCs derived using single viruses mapped closely to HSCs (7/23), others mapped closely to MPPs (7/23), while the remainder mapped more closely to Pro/Pre B cells (10/23) (FIG. **64**B). In contrast, all of the iHSCs derived using the polycistronic approach showed very high similarity to host and control HSCs (35/35).

[1171] The inclusion of five (Mycn, Hlf, Lmo2, Meis1 and Pbx1) of the eight reprogramming factors amongst the 152 genes analyzed in these experiments allowed us to address how endogenous levels of these factors was reestablished in iHSCs post-reprogramming Consistent with their known roles in regulating HSCs, high levels of each of MycN, Hlf, Lmo2, and Meis1 were observed in steady-state HSCs, which contrasted the low levels observed in Pro/Pre B cells (FIG. **64**D). Pbx1 expression was lower in the majority of HSCs and absent in Pro/Pre B cells. Conversely, Ebf1 and Pax5, which are critical transcription factors for B-cell development were expressed at high levels in Pro/Pre B cells and negligible levels in HSCs. Analysis of the expression of these genes in iHSCs again revealed distinct differences depending upon whether or not single or polycistronic viruses were used for their derivation. Whereas high levels of endogenous MycN, Hlf, Lmo2, Meis1 and moderate levels of Pbx1 was reestablished in many of the iHSCs derived using single viruses, low levels of these genes and high levels of Ebf1 and Pax5 were still observed in a significant fraction of the cells (FIG. **64**D). By contrast, the expression of each of these genes in iHSCs derived using the polycistronic viruses fully recapitulated the expression patterns observed in the control HSCs (FIG. **64**D), as was the expression of all other genes analyzed known to be critical for HSCs function including the transcription factors Gfi1b, Gata2, and Ndn, and the cytokine receptors Mpl, and c-kit (FIG. **64**D, Tables 6-8). Taken together, these results demonstrate that 8-TF reprogramming of Pro/Pre B using single viruses generates iHSCs with transcriptional properties consistent with either full or partial reprogramming, whereas iHSCs derived under optimal polycistronic viral conditions exhibit an expression profile synonymous with HSCs.

Discussion

[1172] Within the hematopoietic system, HSCs are the only cells with the functional capacity to differentiate to all blood lineages, and to self-renew for life. These properties, in combination with the ability of HSCs to engraft conditioned recipients upon transplantation, have established the paradigm for stem cell use in regenerative medicine. Allogeneic and autologous HSC transplantation is used in the treatment of ~50,000 patients/year for congenital and acquired hematopoietic diseases and other malignancies (Gratwohl et al., 2010). Current challenges to transplantation therapies include the availability of histocompatible donor cells and associated graft versus host disease. De novo generation of isogenic HSCs from patient derived cells would obviate these issues, and extend transplantation to all patients as opposed to those for whom a histocompatible donor can be identified. Deriving HSCs from alternative cell types has thus has been a long sought after goal in regenerative medicine. Here we report the generation of induced-HSCs via reprogramming from committed hematopoietic progenitor and effector cells. Through identification and functional screening of 36 HSC-enriched factors, we identified 6 transcription factors Hlf, Runx1t1, Pbx1, Lmo2, Zfp37, and Prdm5 whose transient ectopic expression was sufficient to impart HSC functional potential onto committed blood cells. Inclusion of two additional transcription factors, Mycn, and Meis1, and the use of polycistronic viruses increased reprogramming efficacy. These findings demonstrate that ectopic expression of a small number of defined transcription factors in committed blood cells is sufficient to activate the gene regulatory networks governing HSC functional identity. The derivation of iHSCs therefore represents a novel cell-based system for exploring the mechanisms underlying the establishment and maintenance of fundamental HSC properties such as self-renewal and multi-lineage differentiation potential. Moreover, our results demonstrate that blood cell reprogramming is a viable strategy for the derivation of transplantable stem cells that could serve as a paradigm for eventual clinical application.

[1173] Despite the fact that HSCs are the most well characterized tissue-specific stem cells, surprisingly little is known about the molecular mechanisms involved in regulating their central properties. The identification of a defined set of transcription factors capable of stably imparting self-renewal and multi-lineage differentiation potential onto otherwise non-self-renewing, lineage-restricted cells, demonstrates that these factors are critically involved in regulating the transcriptional networks underlying HSC functional identity. Consistent with this, several of the factors that we identified have previously been shown to be important for regulating diverse aspects of HSC biology. For example, PBX1 and MEIS1, which interact and can form heterodimeric and heterotrimeric complexes with HOX proteins, have both been shown to regulate HSC self-renewal by maintaining HSC quiescence (Ficara et al., 2008; Kocabas et al., 2012; Unnisa et al., 2012). LMO2 is required for hematopoiesis and in its absence, neither primitive or definitive blood cells form (Warren et al., 1994; Yamada et al., 1998). And while MYCN is dispensable for HSC activity due to the functional redundancy of MYC, combined ablation of both Myc and MycN severely disrupts HSC self-renewal and differentiation potential (Laurenti et al., 2008). In contrast to these well-characterized genes, Prdm5 and Zfp37 remain unstudied in HSC biology, and though the role of RUNX1T1 (as known as ETO) as a fusion partner with RUNX1 in acute myeloid leukemia is well established, its role in normal hematopoiesis remains unclear. Defining the roles that each of the reprogramming factors play in normal HSC biology will be critical for understanding their function in blood cell reprogramming.

[1174] Going forward it will also be important to elucidate how the reprogramming factors activate and maintain the transcriptional networks underlying HSC functional identity in other cell types during reprogramming Given that 6 of the 8 factors we identified, Hlf (Inaba et al., 1992), Meis1 (Moskow et al., 1995), Lmo2 (Boehm et al., 1991), Mycn (Brodeur et al., 1984; Marx, 1984), Pbx1 (Kamps et al., 1991), and Runx1t1 (Erickson et al., 1992) are proto-oncogenes, suggests that blood cell reprogramming to iHSC likely involves the activation and/or repression of gene networks that are common to stem cells and transformed cells. This is also consistent with the finding that virtually all the transcription factors required for HSC formation, maintenance, or lineage commitment are targeted by somatic mutation or translocation in heme malignancy {Orkin, 2008 #5327}. Some insights into how the individual reprogramming factors mediate their activity has been provided by recent studies. For example, LMO2 overexpression in committed T-cell progenitors led to a preleukemic state characterized by sustained self-renewal activity yet without blocking T-cell differentiation potential, and this was associated with upregulation of a cadre of genes normally expressed by primitive hematopoietic stem and progenitor cells (HSPCs) (McCormack et al., 2010). Similarly, ectopic expression of HLF in downstream multi-potent and oligo-potent myeloid progenitors imbued them with potent self-renewal activity ex vivo without blocking their differentiation potential, which was associated with expression of CD150, and sustained repression of lineage commitment markers, phenotypes consistent with HSCs (Gazit et al.). HLF expression alone was nonetheless insufficient to impart HSC transplantation potential onto downstream progenitors (RG, BG, DJR unpublished). These studies show that while ectopic expression of HLF or LMO2 can instill at least some of the functional and molecular properties of HSCs onto committed blood cells, alone they cannot access the full repertoire of transcriptional programs needed to establish and maintain HSC function. In these regards, it is interesting that whereas iHSCs generated using polycistronic viruses all exhibited expression profiles that were indistinguishable from control HSCs, iHSCs generated using monocistronic viruses were heterogeneous at the molecular level with many of the cells analyzed showing clear evidence of partial reprogramming That some of these partially reprogrammed cells clustered closely to the Pro/Pre B cells from which they were derived suggests that these cells retained an epigenetic memory of their cell of origin despite being purified by an immunophenotype consistent with HSCs. It is likely that the partially reprogrammed iHSCs in the 8-TF single virus experiments did not receive the full complement of reprogramming factors. If so, further study of fully reprogrammed versus partially reprogrammed cells may provide mechanistic insights into how the reprogramming factors collaborate to activate the gene regulatory networks underlying HSC functional identity.

[1175] Although the transcriptional properties of iHSCs derived under optimal 8-TF polycistronic conditions were indistinguishable from endogenous HSCs, further analysis will be required to determine if the epigenetic landscape of these cells is fully reset to that of HSCs. In this regard, it was interesting that the lineage potential observed in our experiments in mice reconstituted with iHSCs sometimes, though not always, evolved over time post-transplantation, with donor-derived chimerism showing lineage skewing at early time points post-transplant, and more balanced output at later time points. These results suggest that iHSCs may need time to fully reset their epigenetic landscape to achieve balanced HSC potential, in a manner similar to the erasure of epigenetic memory observed with continued passage of iPS cells (Polo et al., 2010). Whether or not cell passage influences epigenetic resetting during iHSC derivation is at this point unclear. It is plausible that iHSCs may require a period of "maturation" in the stem cell niche to achieve full HSC potential. It is notable that some of the partially reprogrammed iHSCs we analyzed had not appropriately upregulated the MPL or KIT receptors suggesting an inability to transduce signals in response to TPO or SCF emanating from the niche.

[1176] Transcription factors play a critical role in the specification of different lineages during development, and as such the discovery of a set of transcription factors capable of activating the gene regulatory networks underlying HSC functional identity suggests that it may be possible to use these factors on cells derived from pluripotent stem cells to facilitate the generation of definitive HSCs. Along these lines, a recent study showed that expression of 5 transcription factors HOXA9, RORA, ERG, SOX4, and MYB was able to impart transient myeloerythroid engraftment potential onto iPS-derived blood cell progenitors, though these factors were unable to instill HSC potential onto the cells (Doulatov et al., 2013). It will also be important to test if the reprogramming factors we identified can be used to convert cell types outside of the hematopoietic system to an iHSC fate in a manner similar to the ability of the Yamanaka factors to bestow pluripotency onto cells of diverse lineages, though it remains possible that iHSCs derivation using the factors we defined will be limited to the blood system. Nonetheless, the generation of iHSCs via blood cell reprogramming represents a powerful new experimental paradigm for studying the fundamental mechanisms underlying HSC identity that might eventually be lead to the derivation of transplantable stem cells with clinical potential.

Materials and Methods

[1177] Microarray: Microarray data was generated on the Affymetrix 430 2.0 platform and included previously published data generated in our lab in addition to datasets that were curated from GEO. Overall the database consists of 142 expression profiles from 40 FACs purified hematopoietic cell populations based on known cell surface phenotypes. All datasets were subjected to quality control (QC) measures provided in the ArrayQualityMetrics package of R/Bioconductor (http://www.bioconductor.org). Datasets were normalized (gcRMA) using R bioconductor. To identify potential regulators of HSCs, we applied a filter in which the ratio of expression in HSCs to all others had to be greater than 2.5-fold. The list of potential regulators was finalized by cross-referencing the literature to identify factors with known transcriptional/translation regulatory roles.

[1178] Mice: B6.SJL-Ptprca/BoyAiTac1 (Taconic Farms; Hudson, N.Y.) and C57BL/6N (Charles River Laboratories; Cambridge, Mass.) recipient mice and B6.CgGt(ROSA) 26Sortm1(rtTA*M2)Jae/J donor mice (Jackson, Bar Harbor, Me.) were used. For some experiments, B6.CgGt(ROSA) 26Sortm1(rtTA*M2)Jae/J mice crossed to the CD45.1 background were used. All mice were maintained according to protocols approved by Harvard Medical School Animal Facility and all procedures were performed with consent from the local ethics committees.

[1179] Pro/pre B-cell, CMP and HSC purification: Antibodies used in FACs purification included: CD34, Sca1, c-kit, AA4.1 from eBioscience (San Diego, Calif.); Fc□R from BD Bioscience (San Jose, Calif.); IgM Sigma Aldrich (St. Louis, Mo.); IL-7R□, Ter119, CD45.1, CD45.2, Mac1, CD3, CD4, CD8, Gr1, CD150, CD19, CD25 and B220 from BioLegend (San Diego, Calif.). 6-12 week old B6 CD45.2+rtTA heterozygous mice were sacrificed and the bone marrow harvested as previously described (Rossi et al. PNAS 2005). To obtain Pro/Pre B cells, a B220 enrichment was performed using biotin B220 (BD Bioscience), streptavidin magnetic beads and a magnetic column (Milteny Biotec). Enrichment was performed according to published protocols. To obtain CMPs, a c-kit enrichment using directly conjugated magnetic beads (BD Bioscience) was performed on whole bone marrow cells. Cells were sorted directly into sample media containing 2% FBS. All cells were sorted on a FACS Aria II (Becton Dickinson).

[1180] Virus Production: Factors were cloned into the pHage2 dox inducible system under the TRE reporter using restriction site directional (Not1 and BamH1) cloning as previously described (Gazit et al. 2013). Importantly, a number of these constructs were cloned out of a cDNA library created from FACS sorted HSCs. All constructs were checked by restriction diagnostics and fully sequenced. Constructs (FIG. **58**B) include an IRES that enables ZsGr reporter expression. Polycistronics (FIG. **61**A) combined individual viruses to create RHL and PZP. Individual factors (RUNX1T1, HLF and LMO2) and (PBX1, ZFP37 and PRDM5) were linked using non directional cloning and stepwise insertion into the respective restriction sites Sal1, Spe1, BamH1 separated by 2A sequences. All constructs were checked by restriction digest diagnostics and sequenced. Viruses for all the 36 factors were produced according to a previously established protocol (Mostoslayský et al., 2005). All viruses are titered on Jurkat cells to an approximated working MOI ~5.0.

[1181] Pro/PreB and CMP CFC assays: Sorted Pro/Pre B cells and CMPs were isolated from rtTA transgenic CD45.2+ and when indicated CD45.1+ donors. 60,000 cells/200 uL media are incubated with the indicated viruses for 16 hours. Media used is Sclone supplemented with 10 ng/mL SCF, 10 ng/ml IL-12, 10 ng/ml TPO, 5 ng/mL Flk-3, and 5 ng/mL IL-7. After transduction, 1.0 mg/ml Doxacycline is added for 48 hours and then transferred to methylcellulose or transplanted. In the case of FIGS. **4**-**6**, a 24 hour ex vivo dox induction was implemented because more cells appeared viable at this time point.

[1182] In CFC assays, 10,000 Pro/PreB or 1,000 CMP cells were transferred from the dox containing media to be diluted and mixed with 1.75 mL per well of M3630 methylcellulose (Stem Cell Technology) and plated into a 6 well dish. 20 days later the colonies were counted and characterized by morphology.

[1183] CFC secondary reprogramming ex vivo was accomplished by plating 60,000 donor-derived FACS sorted cells into a 12 well plate with 500 uL of F12 media supplemented with 10 ng/mL SCF, 10 ng/ml IL-12, 10 ng/ml TPO, 5 ng/mL Flk-3, and 5 ng/mL IL-7. When indicated 1.0 mg/ml dox was added for 72 hours. 10,000 cells were then directly transferred to 1.0 mL of methylcellulose in a 12 well format. 20 days later colonies were counted and characterized by classically defined morphologies.

[1184] Pro/Pre B cell Transplantation: Transplants were performed by combining 10,000 ZsGr+ resorted cells or 2.0×10^6 unsorted Pro/Pre B/CMP cells with 2×105 B6 CD45.1+ competitor cells and transplanted intravenously into IR B6 CD45.1+ recipients. Alternatively, sorted and transduced Pro/Pre B cells and CMPs were injected non competitively with 2×10^5 Sca1 depleted bone marrow cells (depletion performed with the Macs magnetic depletion columns previously described according to manufactures instructions). Peripheral bleeds were performed at 4, 8, 12, and 16 weeks. Post 16 weeks, the same analysis as peripheral blood was performed on the bone marrow, spleen, and thymus.

[1185] Serial transplantation was performed by isolating bone marrow from primary mice with reconstitution from either CD45.1+ Pro/Pre B cells (>1.0%) or CD45.2+ Mac1+ bone marrow cells (>5.0%). In the case of Pro/Pre B cells, whole bone marrow was counted and 107 cells were noncompetitively transplanted into CD45.2+ recipients. Alternatively (c-kit secondary), 10,000 FACS sorted doublet discriminated, live, lineage negative, c-kit+ donor CD45.1+ cells were transplanted non-competitively with 2×10^5 Sca1 depleted cells into IR and conditioned recipients. Mac1+ bone marrow reconstituted whole bone marrow cells were FACS sorted on donor (CD45.2+). Generally, 5.0×10^6 donor-derived FACs sorted cells were transplanted noncompetitively into conditioned and IR recipients. Peripheral bleeds were performed at 4, 8 and 12 weeks.

[1186] Peripheral Blood Analysis and Bone Marrow Analysis: Flk2, CD34, c-kit and Sca1 antibodies were purchased from eBioscience (San Diego, Calif.). FcgR3 (CD16) was purchased from BD Bioscience (San Jose, Calif.). IL-7R□, SLAM (CD150), Ter119, CD45.1, CD45.2, B220, Mac1, CD3, CD4, CD8, Gr1 (Ly-6G/Ly-6C) were purchased from Biolegend (San Diego, Calif.)

[1187] Staining for both the peripheral blood and the progenitor compartments was done as previously described (Beerman, Rossi, Bryder). Examples of cell stains and gating strategies are described for peripheral blood (FIGS. **59**B, **60**E, **61**C and **63**G) and bone marrow analysis (FIGS. **62**A-**62**I and **67**). In general, peripheral blood populations include: B cells (B220+), Myeloid cells (Mac1+ and Gr1−), Granulocyte (Mac1+ and Gr1+), T Cells (CD3+/CD4+/CD8+).

[1188] Progenitor populations are defined as such: All are doublet discriminated, live (PI negative) and lineage negative (Gr1−, Mac1−, B220−, CD3−, CD4−, CD8−, Ter119−−). Hematopoietic progenitors (HSC, MPP1, and MPP2) were gated c-kit+Sca1+ then defined by flk2 and CD34 expression. Common lymphoid progenitors (CLPs) were gated flk2+ IL-7R+ then defined by c-kit and Sca1 status. Myeloid Progenitors (GMP, CMP, and MEP) were gated c-kit+Sca1− and defined by Fc□R3 and CD34 expression. Erythroid progenitors (EP) and Megakaryocyte Precursors (MkP) were both gated c-kit+Sca1− but defined respectively by Endoglin and CD41 expression.

[1189] VDJ Rearrangement—Heavy and light chain (kappa and lambda) recombinational events were tested using a PCR based assay established by Brisco et al. (British Journal of Hematology 1990; 75:163-167) and Busslinger et al. (Nature 2007; 449:473-481). In overview, the strategy spans the region from VH2 to JH4, Therefore, covering the predominant recombinational events of heavy chain rearrangement. All PCR based strategies were confirmed on both bone marrow and peripheral blood positive and negative controls.

[1190] Transcription Factor Integration—To test for viral integration of the factor to be expressed primers were designed to generate products over intron-exon barriers (FIG. **59**F). Endogenous products are eliminated by their larger size or that the primers will not extend over the intron. Rigorous controls were performed to ensure that false positives would not be detected. All primers proved negative when they singly were subtracted from the 36 factor mix and when ZsGr control virus is used, only when the factor is present does the band appear. Primers are listed in the Supplementary Table 1. PCR conditions were performed according to manufactures instructions (Kappa Biosystems).

[1191] High throughput single cell qPCR and computational analysis: Individual primer sets were pooled to a final concentration of 0.1 μM for each primer. Individual cells were sorted directly into 96 well PCR plates loaded with 5 μL RT-PCR master mix (2.5 μL CellsDirect reaction mix, Invitrogen; 0.5 μL primer pool; 0.1 μL RT/Taq enzyme, Invitrogen; 1.9 μL nuclease free water) in each well. Sorted plates were immediately frozen on dry ice. After brief centrifugation at 4° C., the plates were immediately placed on PCR machine. Cell lyses and sequence-specific reverse transcription were performed at 50° C. for 60 minutes. Then reverse transcriptase inactivation and Taq polymerase activation was achieved by heating to 95° C. for 3 min. Subsequently, in the same tube, cDNA went through 20 cycles of sequence-specific amplification by denaturing at 95° C. for 15 sec, annealing and elongation at 60° C. for 15 min After preamplification, PCR plates were stored at −80° C. to avoid evaporation. Pre-amplified products were diluted 5-fold prior to analysis. Amplified single cell samples were analyzed with Universal PCR Master Mix (Applied Biosystems), EvaGreen Binding Dye (Biotium) and individual qPCR primers using 96.96 Dynamic Arrays on a BioMark System (Fluidigm). Ct values were calculated using the BioMark Real-Time PCR Analysis software (Fluidigm).

[1192] Gene expression levels were estimated by subtracting the background level of 28 by the Ct level, which approximately represent the Log 2 gene expression levels. Principal component analysis (PCA) was performed in Matlab to project all the control and experimental cells onto a three dimensional space to aid visualization. An unsupervised hierarchical clustering was used to cluster representative control cells and all the iHSC 8-TF or iHSC 8-TFPoly cells. The analysis was done with R using the average linkage method and a correlation-based distance. The representative control cells were selected as those whose expression levels were closest to the median based on Euclidean distance. Eight HSC cells, eight HSC Host cells, all six Pro/Pre B-cells, and four from each of the remaining control cell types were selected. The dendrogram branches were color-coded by cell type, as in the PCA analysis. Violin plots and the correlation heatmaps were generated with Matlab. The master heatmap of all the raw data (Supplement to FIGS. **64**A-**64**D) was generated with MultiExperiment Viewer (MeV) program (http://www.tm4.org/mev.html) using the default setting.

TABLE 6-1

Single cell expression data (reduced list)---Control

Factor	HSC-Host1	HSC-Host2	HSC-Host3	HSC-Host4	HSC-Host5	HSC-Host6
Actb	13.2775869	14.168841	13.9178852	14.0751018	14.3746391	14.7443427
Aebp2	6.28419787	6.32255813	7.19444936	5.65953541	6.95783404	7.26360494
Ahr	0	7.57209355	0	0	0	0
Akt1	9.4500759	0	10.0765631	9.94327921	10.6548673	10.0745346
Akt2	6.22818312	0	6.70532413	0.8889789	6.47748177	5.95383663
Akt3	7.51547845	0	6.07943514	6.17938762	6.4222982	7.17078745
APC	7.79584916	0	6.19688147	0	0	0
Bad	0	0	0	0	0	0
Bax	8.2648093	9.18808438	6.51775922	9.27759397	6.43362681	9.23990229
Bel11a	0	3.15885611	0	5.12533276	4.04738876	0
Bcl11b	0	0	0	0	0	0
Bcl2	6.98611579	5.59253753	5.86437743	5.82350133	5.38565841	6.25071983
Bcl2l1	6.3386176	7.46201946	5.95513383	7.54053745	8.78325414	9.89410694
Bcl2l11	0	0	6.94600503	6.87358216	4.32552584	7.85341182
Bmi1	6.84030124	7.45817288	8.3898639	8.30544124	8.55457965	9.47756119
Brd3	7.90377097	0	7.95461448	5.59030834	9.00631299	9.052141
Casp8	7.51030052	8.02616926	4.9493906	8.5494905	8.91073923	7.93953605
Casp9	0	0	8.5609996	1.67117364	4.0331817	9.80298865
Cbx2	2.56416415	5.63988167	5.00035293	0	7.4548439	5.99738299
Cbx8	0	0	0	0	0	0
Ccnc	0	7.05018411	6.61535219	7.14719604	0	0
Ccnd1	9.03626766	0	10.6728171	9.38229874	9.65405424	11.2577639
Ccne2	6.17995523	0	0	7.11543157	3.58571536	6.20681303
CD34	9.47324504	4.55399303	0	6.67982887	8.80998961	8.42129488
CD41	6.83783924	0	0	7.46208028	5.97956704	7.65198306
CD48	0	5.56947557	0	0	0	0
CD52	3.35679477	11.0232754	4.14631098	2.71474755	0	0
CD53	8.20861996	9.55294311	10.642603	0	10.0045947	8.2383003
CD55	5.73982206	7.34724526	0	8.36090066	0	6.70252191
CD63	7.99968851	3.87874565	8.90775134	6.61989086	7.62771038	8.83849433
CD9	7.44138139	6.21616714	6.50446133	8.246429	7.64906334	8.63028596
Cdc42	12.1710731	11.0591526	12.4549519	11.9800985	12.2018552	11.6731426
Cdk1	0	0	0	6.25722026	8.10356032	0
Cdk4	7.18574541	0	8.80614599	8.60901532	8.72742091	8.91034066
Cdkn2b	0	3.88923712	0	0	3.6614691	0

TABLE 6-1-continued

Single cell expression data (reduced list)---Control

Factor	HSC-Host1	HSC-Host2	HSC-Host3	HSC-Host4	HSC-Host5	HSC-Host6
Cebpa	0	0	0	0	2.11474663	0
Csf1r	0	0	0	0	0	0
Ctnnb1	6.77574215	5.35561197	8.53644908	6.17550579	8.17135019	8.90801971
Cycs	9.45352333	8.28562581	9.69867329	9.15788233	8.5747268	11.0355392
Dach1	10.8615494	0	9.31769339	9.02821771	8.02501106	10.7915469
Dnmt1	7.9760193	7.79001706	9.59934161	9.46537455	10.1834542	9.73235565
Dnmt3a	9.17213793	6.74216981	10.3864007	8.88588303	10.0903643	9.57095471
Dnmt3b	7.6743627	0	8.58221524	8.13192866	6.41659753	10.5256969
Dtx1	0	3.41522411	2.46078468	0	0	0
Dtx4	0	0	8.6835801	0	2.66840805	0
Ebf1	0	6.662193	0	0	0	0
Ep300	9.71487536	9.16729643	9.43974794	9.62406494	8.10311513	8.26149733
Epor	8.68447169	7.68763276	7.25429274	7.04722818	8.24346493	6.54478382
Erg	9.20284562	0	8.87410211	11.3197691	11.1784466	10.0567225
Esr1	8.43503126	0	9.11129812	10.8937654	8.57545747	8.3892723
ETS1	0	7.93156712	8.24336392	8.54381125	0	7.97895885
ETS2	7.69340598	10.4359154	7.88475206	9.15565609	9.36749687	9.44827774
Etv3	0	4.64796195	0	4.71186206	6.09191076	4.93626547
Etv6	10.9918334	8.3432591	12.062043	10.4969697	11.0891387	10.5930954
Ezh2	0	0	6.2199413	0	7.2175748	0
Fas	0	0	0	0	0	6.34199177
Fcgr2b	7.06819715	6.31957073	0	0	6.89220045	0
Fcgr3	3.08395665	0	5.1508941	0	5.42301679	4.43817889
Fli1	10.9830573	8.55863827	11.2140047	10.3178185	11.6619233	12.1483502
Flt3	6.20637493	0	0	0	0	0
Fosl1	4.69007508	0	0	0	0	0
Foxo1	10.3454599	7.31474333	10.967598	9.8657691	10.5194737	10.0861124
Foxo3	9.0799276	0	9.7189551	7.47165548	8.73488596	7.96186755
Gapdh	8.55078967	5.52545622	9.00242399	8.73312904	8.52812774	9.39231339
Gata1	5.60159574	0.06279515	5.86590598	7.1439751	0	0
Gata2	5.74244502	0	7.41208662	7.07920109	7.70789061	8.00674346
Gata3	8.00418853	7.18159892	8.43773446	5.50080971	8.12295844	8.25560613
Gfi1	0	6.18652121	10.6772443	7.54787108	7.83956553	0
Gfi1b	0	0	0	5.51370457	0	0
Hes5	0	0	0	0	0	0
Hey1	0	0	0	0	0	0
Hlf	10.44305	0	10.7025095	9.93038235	10.4823111	12.2258256
Id2	5.87344248	0	7.19031139	5.96142885	0	6.51341399
Ifi203	11.7852987	9.71801159	11.3716491	11.0104458	12.6373979	11.6777944
Ifi205	4.67282232	0	7.24586334	0	0	0
Ifitm1	12.1471017	4.92118909	13.4884472	12.662214	12.5615878	13.0294612
Ikzf1	8.64469135	7.79726997	7.85685442	8.12528579	9.68635073	8.48962708
Ikzf2	7.81120077	0	9.37252819	8.30677295	7.26836862	0
I17R	0	0	0	0	0	0
Irf4	0	0	0	0	0	0
Irf6	0	0	0	4.20551755	4.88594856	3.08177568
Irf8	0	8.68822939	0	0	0	6.53060321
Kdr	0	0	0	0	0	0
Kit	11.2070686	0	11.6440993	11.4804292	12.2611324	12.206451
Klf1	6.92350949	1.98980206	0	4.56789131	0.13589585	0
Klf12	7.06267367	0	4.57402202	6.08382143	7.94374986	3.9594648
Ldb1	10.4073068	7.3896168	10.1500409	10.0911962	10.7267532	11.0127515
Lin28a	7.17248465	0	5.58873198	6.56573609	6.38615843	3.82188034
Lmo2	10.9902154	6.18088066	10.6616656	10.3550894	11.1327095	10.9913151
Ly6a	9.77053874	11.2332276	11.7270289	8.28647953	12.6717193	10.3350604
Lyl1	0	2.97626088	1.79806679	7.18080529	6.9416814	6.73671636
Mbd2	8.49739572	8.19189415	8.04081234	9.76536757	9.15455462	8.59064535
Meis1	8.29093013	0	7.29725525	7.26528892	8.67247017	9.42229127
Mllt3	5.89848994	0	0	6.69623752	4.4179384	3.79041107
Mpl	11.2861484	0	11.0645033	10.5099396	9.03000686	11.3155121
Muc13	8.25899032	0	8.64152378	9.29492519	10.7390115	9.98391777
Myb	12.4569362	0	12.2263569	12.4668319	11.4934181	12.0411759
Myc	7.58661569	6.21232154	9.20695093	8.73071418	9.41854475	10.7856834
Mycn	12.9947643	0	13.0918794	13.9626228	12.9338862	12.4445334
Ndn	8.80844917	6.48582533	0	10.4252572	8.84853759	9.65347239
Nfat5	10.4466948	9.45749742	10.690876	10.0164749	10.9448261	10.5579754
Nfia	9.61905092	0	7.82309617	10.1397415	0	10.3055652
Nfkb1	0	0	0	0	0	2.96900953
Notch1	0	0	9.29999671	0	7.33702794	0
Pax4	0	0	0	3.25862559	0	0
Pax5	0	8.92648494	0	0	0	0
Pax9	2.08863054	0	0	0	0	5.05619592
Pbx1	1.42391331	0	0	0	0	0

TABLE 6-1-continued

Single cell expression data (reduced list)---Control

Factor	HSC-Host1	HSC-Host2	HSC-Host3	HSC-Host4	HSC-Host5	HSC-Host6
PIk3ca	8.96748889	6.64436068	9.27732513	8.90571616	7.62247587	8.4100092
PIk3R2	9.65824684	0	9.22847732	7.39263343	0	4.40944775
Plag1	0	0	7.01820576	7.02904616	3.5641265	0
Prf1	0	0	0	0	1.57408799	0
Pten	10.9497819	0	10.2918594	8.92771496	10.4641876	10.3191806
Rb1	8.96820297	10.0038452	9.14142412	9.85888737	8.18977625	9.89607842
Rora	5.35194121	4.24098601	5.85010593	4.61334456	5.97348017	8.17380426
Runx1	0	7.58178739	8.9334852	0	7.0497458	0
Runx2	4.95241455	0	0	0	5.41048102	5.81273837
Satb1	0	0	0	0	7.86361531	0
Sdpr	0	0	0	0	2.58354882	3.26451236
Sell	0	0	2.34457587	0	0	0
Sfpi1	9.71796118	7.47768178	8.88184673	7.30312418	8.77086956	10.3270219
Slamf1	8.97990603	0	3.04564598	8.47261051	7.18152704	8.21009783
Smarca4	10.4765281	3.61354971	10.1872564	10.8633232	8.60015526	10.9354338
Sos1	4.33343207	0	3.63532361	0	5.53536226	6.14254392
Stat1	3.23775129	0.21307953	7.58861399	3.02927896	8.80721388	3.51485392
Stat3	10.6966168	7.76941207	10.6364369	10.0799192	10.5294486	11.2164717
Stat4	9.20300453	0	7.8248698	9.2674567	8.94657563	9.64694998
Stat6	9.03894911	8.52947719	9.97364377	9.05233066	9.64957237	11.0757572
Suz12	6.16330105	5.48666925	9.32289767	8.71099601	7.89367605	8.06855486
Tal1	8.36403791	0	2.33394532	0	1.38047772	0
Tcf3	10.4218407	9.72305906	0	0	8.61448405	0
Tcf4	9.16127496	9.85224012	11.534616	11.3598757	5.53155003	8.0963221
Tcf7	0	0	0	0	0	1.57791407
Tek	0	0	0	7.32114021	0	6.95981526
Tfrc	9.28718925	7.02384574	0	8.22631353	0	9.43880717
Tgfb1	5.88177291	0	0	0	0	0
Tgfb2	0	0	0	0	0	0
Tgfb3	0	0	7.27300183	0	0	7.34148597
Tnfrsf1a	8.90379373	7.13050062	8.48751907	8.869291	10.08512	9.56614844
Tnfrsf1b	8.00152361	6.49040287	9.95513535	9.15449888	2.53578357	6.5261916
Tnfrsf21	4.84351147	0	4.60229475	4.67842921	5.52125012	6.58500292
Tnfsf10	5.57895478	0	0	6.17029357	8.11110849	3.52628697
Tnfsf12	0	0	0	5.66296916	5.15470027	2.81029519
Tob1	6.60883404	4.71028925	6.61940548	0	7.53391259	0
vWF	6.42109411	0	7.67992352	6.67113351	6.93148562	7.2346756
Zbtb20	9.18932471	11.395783	9.15649836	8.61284336	8.06915897	9.60060809
Zbtb38	7.24785674	4.49081527	7.78800121	7.85959557	7.66905166	8.13608089
Zfp532	0	0	0	0	0	0
Zfp612	9.06730892	6.8781252	7.30966311	9.19853084	2.55278286	8.83891365
Zfpm1	0	0	7.6939382	5.55204554	0	8.02880897
Zhx2	0	6.41697281	7.21040835	0	5.66262749	9.35665478

TABLE 6-2

Single cell expression data (reduced list)-Control

Factor	HSC-Host7	HSC-Host8	HSC-Host9	HSC-Host10	CLP1	CLP2
Actb	14.6718473	13.3708842	14.0765648	14.5363732	15.5720296	15.6020418
Aebp2	6.934218	5.38858023	6.92870369	6.83990914	6.91310458	6.13397519
Ahr	6.67106288	0	0	0	0	0
Akt1	8.78938258	10.6910195	9.8127768	10.8956807	10.5882487	9.71594698
Akt2	6.75253581	3.62756205	0	6.81240671	0	5.50111064
Akt3	8.32305076	5.46246892	6.80790868	6.46650561	8.93439362	7.9618537
APC	0	6.36004551	0	6.14208966	3.44926722	0
Bad	0	0	0	0	0	0
Bax	0	8.20505106	7.76032108	10.25022	10.2921476	8.60030468
Bcl11a	7.92077667	3.60167833	0	0	0	0
Bcl11b	0	0	0	0	0	0
Bcl2	4.96817114	5.18391882	5.86834513	4.77451604	0	0
Bcl211	10.2036955	9.4735452	9.29507619	9.23047931	10.060975	7.87502531
Bcl2111	0	0	0	8.25557161	0	0
Bmi1	9.60604305	6.56999362	7.5702476	8.14038399	7.42571732	7.00110773
Brd3	2.43074124	7.93247983	5.487038	7.62759044	11.1411249	9.66763681
Casp8	8.13383235	8.73409	8.17193114	9.06003622	9.92872956	9.74113972
Casp9	8.4257186	7.57293558	7.8464349	7.80792483	8.37487536	0
Cbx2	7.07511053	4.48424451	5.84700109	6.23176944	0	6.13244563

TABLE 6-2-continued

Single cell expression data (reduced list)-Control

Factor	HSC-Host7	HSC-Host8	HSC-Host9	HSC-Host10	CLP1	CLP2
Cbx8	0	0	0	4.43331023	2.09486638	0
Ccnc	0	6.2797398	0	6.38691873	6.07677146	7.90773679
Ccnd1	10.0212014	0	9.34071635	0	8.62709974	0
Ccne2	0	6.53512964	6.54945811	6.0438482	7.34684561	6.25723346
CD34	0.01674269	7.67391972	0	10.7870089	0	0
CD41	0	0	0	8.09312343	0	0
CD48	0	0	0	8.10107986	10.5431066	4.18270305
CD52	0	3.64518416	0	0	5.65535037	8.4769989
CD53	8.91469588	0	10.1863121	10.1806135	11.1188968	10.5349358
CD55	7.2980864	7.31878302	0	6.29391433	1.43412606	6.99636364
CD63	8.51246386	6.54126666	7.37134704	6.37418902	0	0
CD9	8.74271831	0	8.72127967	8.8170788	0	0
Cdc42	11.9094394	11.5894082	11.1126665	12.1006451	13.0861829	12.2864927
Cdk1	2.68752057	0	0	11.8397661	11.3123555	0
Cdk4	8.12335302	7.87079584	7.5720236	9.24576955	10.3762179	10.4600518
Cdkn2b	0	0	0	0.35740427	0	0
Cebpa	0	0	5.63552878	0	0	0
Csf1r	0	0	0	0	6.27133994	5.26584779
Ctnnb1	6.79339335	7.40629301	6.87918414	8.36101904	5.95935578	8.05082722
Cycs	10.0442638	7.54030732	9.0344585	10.6654921	11.2529958	11.2582352
Dach1	0	9.84505342	7.97799952	11.9672696	0	0
Dnmt1	8.50686835	7.570001	3.23481103	10.5464652	12.6178625	12.0559888
Dnmt3a	10.0573123	9.34977288	8.47634202	10.5147996	8.06454655	9.25761414
Dnmt3b	8.08236706	7.77693525	7.43902731	6.35981456	8.61270517	0
Dtx1	0	1.20990211	0	2.35858319	0	0
Dtx4	0	0.84530668	0	8.42626641	0	0
Ebf1	0	0	0	0	10.5975489	11.2372886
Ep300	8.67464583	9.2042527	8.90097872	9.29742804	8.73799831	8.9933198
Epor	7.4651798	7.99907556	7.67252065	7.98170347	0.10277376	4.78402129
Erg	11.1082009	7.23780514	10.3502921	10.2615194	12.9408351	11.0993994
Esr1	8.54768834	7.99110915	6.24818597	9.62048384	10.4231044	0
ETS1	6.86365699	4.84774761	8.3168225	6.6480974	13.8494997	11.6438204
ETS2	7.64755071	7.54891501	0	8.17449216	0	0
Etv3	5.78507161	0	5.75634937	3.75032653	4.76128972	2.70875229
Etv6	8.82488989	10.4027054	10.0840126	12.226941	10.5939014	9.97978593
Ezh2	6.34735252	4.06993896	5.66118811	8.83156708	11.5011279	10.4172165
Fas	0	0	5.0587006	0	0	0
Fcgr2b	5.48237699	1.56950279	6.50908621	6.14234211	3.36211875	0
Fcgr3	0	0	0	0	0	0
Fli1	10.6505478	9.64542823	11.1441998	11.6211551	10.9483997	10.3713463
Flt3	0	0	0	9.55475223	0	0
Fosl1	0	0	0	1.86707308	0	8.47337507
Foxo1	7.87606422	9.05152117	9.80912191	11.1420747	11.6728318	10.918137
Foxo3	8.4243012	7.7040044	9.07363846	9.75726551	6.51553987	6.92529651
Gapdh	7.84932494	8.15466782	8.21027854	8.00493653	12.3780006	11.3641618
Gata1	0	0	1.32627298	4.99268331	0	0
Gata2	7.1358369	7.84253879	7.5357683	4.15447711	0	0
Gata3	9.23864702	7.08926856	7.70423652	9.1691048	6.33257429	0
Gfi1	8.4722437	0	2.45881453	8.01637799	0	6.71345188
Gfi1b	9.78145684	0	0	7.14731375	0	0
Hes5	0	0	0	0	0	0
Hey1	0	0	0	0.50104001	0	0
Hlf	10.4196373	7.93837692	9.25512238	9.64501202	0	0
Id2	0	0	0	0.37307203	0	0
Ifi203	11.2385326	10.675148	11.1293957	11.5993821	13.2875382	10.2274453
Ifi205	0	0	0	0	0	0
Ifitm1	11.8294232	11.1006374	12.8299047	11.7081516	0	0
Ikzf1	10.4603278	7.9081258	8.39039117	9.30500104	11.2708394	10.4757841
Ikzf2	8.66069698	0	8.07815335	9.24251035	0	0
Il7R	0	0	0	0	3.86371591	4.80700829
Irf4	0	0	0	0	9.2290601	10.2309003
Irf6	2.64609076	0	4.55767937	4.22209488	0	0
Irf8	0	1.57386134	0	8.84149401	0	8.81600274
Kdr	0	0	0	0	0	0
Kit	12.2681758	11.1853776	11.5755541	11.3487544	10.3091102	9.16742564
Klf1	0	0	5.19001782	2.69496283	0	0
Klf12	8.99195223	6.89401764	0	0	4.77266959	7.98400431
Ldb1	10.7730297	9.4520141	9.55889768	9.47012092	8.99931122	10.47084
Lin28a	6.21043595	5.10100157	8.34850576	7.64045938	7.50871774	9.03894646
Lmo2	11.5565524	9.01389959	10.9404097	10.1650659	4.46826015	6.2900714
Ly6a	10.274331	8.62489906	10.9730888	0.67547765	0	0
Lyl1	3.44144381	7.53639677	6.92249445	8.41401114	7.99916677	8.4577076

TABLE 6-2-continued

Single cell expression data (reduced list)-Control						
Factor	HSC-Host7	HSC-Host8	HSC-Host9	HSC-Host10	CLP1	CLP2
Mbd2	7.07180263	8.80305911	9.83435118	7.32171913	11.0889587	11.1378285
Meis1	7.80771805	6.57260088	8.3801574	6.64771096	0	5.32655256
Mllt3	5.27987488	4.98216842	0	4.98006428	0	0.43104733
Mpl	9.95026098	9.29878047	10.5382189	8.92503515	0	0
Muc13	9.58693895	5.98850625	10.5817646	10.34105	0	0
Myb	11.9113929	11.3263068	9.38747922	12.0083232	13.2716596	13.3551636
Myc	0	7.55865639	5.71326556	9.60742235	0	7.03978632
Mycn	9.2475789	11.2225067	12.0059366	9.17037192	0	0
Ndn	9.34022589	8.94700354	8.72830108	7.25627641	0	0
Nfat5	10.9266838	10.3886042	10.2456748	9.51279929	3.18257792	0
Nfia	9.8356555	8.60236457	8.92289712	10.0014286	8.2885559	0
Nfkb1	0	0	4.48890776	0	3.74973604	0
Notch1	7.66102275	0	6.91201627	8.32291131	7.91814495	7.36965349
Pax4	0	0	0	0	0	0
Pax5	0	0	0	0	9.67689902	11.6203933
Pax9	0	0	0	0.57036927	4.48973549	0
Pbx1	5.69269047	0	5.43069763	0	0	0
PIk3ca	0	7.18092062	7.27208139	9.05710063	9.40185149	9.55052543
PIk3R2	0	0	7.5160141	8.56807024	9.73539407	0
Plag1	7.73898932	7.96365738	8.07352148	0	0	0
Prf1	0	0	0	0	0	0
Pten	10.1342741	9.78469549	9.33811703	11.1785408	10.1894192	10.4359312
Rb1	9.29604621	9.27765839	7.51678183	8.27880038	11.9054276	10.9424567
Rora	6.10890584	7.3877893	8.15836998	5.4939429	0	0
Runx1	0	7.76888704	8.78603048	7.67062362	8.305547	0
Runx2	0	3.79386494	3.6008219	5.35557258	0	0
Satb1	0	0	0	8.99400379	10.1837922	8.39346313
Sdpr	5.78136407	4.21076733	0	0.82691288	0	0
Sell	0	0	1.61946707	0	0	0
Sfpi1	10.0042663	9.37371199	9.15518065	9.65832452	0	9.26882608
Slamf1	7.81411202	6.8594725	7.95128279	0	0	0
Smarca4	10.3380905	7.42905599	9.2510329	11.5218685	14.4938783	13.4081997
Sos1	0	0	6.5261554	6.79179662	0	5.43289492
Stat1	1.71494059	0	0	3.42562416	5.64062199	0
Stat3	10.7412032	8.92068828	8.96113036	10.4989945	8.68504508	8.21020662
Stat4	9.21395012	9.36252836	9.57705104	8.5317536	0	0.65364229
Stat6	8.27498229	8.51520973	8.34381559	8.60680209	10.1139186	9.61023286
Suz12	8.36186765	7.85222591	8.01568165	9.19083991	12.1912291	10.7847116
Tal1	1.22646608	0	0	0.85919234	8.29002547	0
Tcf3	0	10.0641005	0	0	10.2329064	9.57044442
Tcf4	10.3945958	8.86390901	9.93214915	10.6432336	11.5584564	11.0576929
Tcf7	1.59196764	0	0.92915579	0	0	5.45500333
Tek	0	0	0	7.77878275	0	0
Tfrc	4.90970417	8.02894875	7.93433882	7.81882114	10.1158882	10.2735536
Tgfb1	0	3.32919416	5.90260252	3.25808206	3.7705399	0
Tgfb2	0	0	0	3.22432655	0	3.37538454
Tgfb3	0	6.69135338	1.40782238	3.95650619	0	0
Tnfrsf1a	9.92981833	7.3738534	8.64338251	8.24251812	0	0
Tnfrsf1b	8.93673702	9.48765082	9.5506678	6.21083423	3.78885776	3.73572941
Tnfrsf2l	4.89969433	0	6.93921933	7.10963898	0	0
Tnfsf10	7.10728827	0	0	1.58582089	7.14613579	8.05630727
Tnfsf12	3.38261217	0	2.19082075	0	0	0
Tob1	0	5.20593174	0	0	0	0
vWF	4.95948597	6.28053967	5.43694051	0	0	0
Zbtb20	9.61893778	9.81916761	9.00655347	7.72955135	0	0
Zbtb38	9.10026874	6.185996	7.56423848	6.82663886	7.73312626	3.84361329
Zfp532	0	0	0	0	0.10416971	0
Zfp612	5.28324577	6.48139199	8.74136356	5.56744079	0	6.50143494
Zfpm1	8.58664951	6.0911617	8.1830324	0	6.44606012	5.62364305
Zhx2	7.56629134	7.63051187	0	5.24483627	0	0

TABLE 6-3

Single cell expression data (reduced list)-Control						
Factor	CLP3	CLP4	CLP5	CLP6	CLP7	CLP8
Actb	13.4721085	15.2351724	15.2719547	16.31177	16.919695	17.0516789
Aebp2	4.45141147	4.38441532	7.10616819	6.49378333	7.1531144	5.6116867

TABLE 6-3-continued

Single cell expression data (reduced list)-Control						
Factor	CLP3	CLP4	CLP5	CLP6	CLP7	CLP8
Ahr	0	0	7.00481198	0	0	0
Akt1	7.3884758	9.17609503	9.55146467	10.0057847	10.2031478	11.1623017
Akt2	1.87065597	0	0	0	7.27787365	0
Akt3	7.14641592	0	0	8.91809255	8.53101085	8.95553865
APC	0	0	7.27741159	0	9.72461612	0
Bad	0	0	0	0	0	0
Bax	5.64368167	7.7793443	7.96170511	9.7217077	11.9875259	11.9783765
Bcl11a	0	0	0	0	8.6331668	9.1297033
Bcl11b	0	0	0	8.64946621	0	0
Bcl2	0	0	0	4.47644651	4.63608396	0
Bcl211	4.6189348	0	10.2286999	10.9686351	10.604158	11.3030776
Bcl2111	4.8989012	0	8.32168555	0	0	0
Bmi1	3.17094341	6.36759845	5.13831255	6.9969786	8.36369633	7.04410175
Brd3	6.59116273	8.85891039	10.3417165	10.3202288	11.5288449	11.1568732
Casp8	9.02211423	8.05947856	9.77788318	10.1196359	11.9218075	10.3568659
Casp9	5.06149028	0	0	0	8.30557433	9.75192608
Cbx2	4.42759599	7.57182896	2.65329776	8.35205791	6.1484868	7.77479327
Cbx8	0	0	0	7.10684953	0	0
Ccnc	3.70061852	7.15959988	8.92627786	8.61131431	9.6072497	9.48325249
Ccnd1	0	2.93758213	0	0	10.6400803	0
Ccne2	5.21666008	7.17885114	11.5186474	0	9.77794018	10.5222899
CD34	0	0	0	0	0	0
CD41	6.34043371	0	0	0	0	0
CD48	0	7.57200005	9.20489806	9.11301325	12.225357	9.60365514
CD52	7.65018871	7.48017023	7.43352856	0	12.104936	12.1008653
CD53	10.1411695	7.84826499	9.96783218	10.4527685	10.929522	11.4800078
CD55	7.0314255	0	0	0	0	0
CD63	0	0	0	0	0	0
CD9	0	0	0	0	0	7.60428115
Cdc42	11.4392736	12.714625	12.1761207	13.5034801	13.8493379	13.7053792
Cdk1	6.69762232	0	9.85122167	11.4158803	12.1196679	12.4467872
Cdk4	5.98607517	6.97494046	9.31645941	10.220209	12.7159863	12.2210916
Cdkn2b	0	0	0	0	0	0
Cebpa	0	3.58268727	0	0	0	0
Csf1r	0	0	1.65538427	3.97435095	8.52442108	0
Ctnnb1	3.62240099	6.62276734	7.86637465	7.51682333	9.83553487	10.0053905
Cycs	9.02261009	11.2219931	12.0781554	10.7960042	14.1072249	14.0649415
Dach1	0	0	0	0	0	0
Dnmt1	9.22693253	9.45595878	12.0119534	12.2094736	13.5638023	13.6951805
Dnmt3a	10.1899327	10.0717063	9.85756039	6.45117101	8.59850296	10.3104357
Dnmt3b	0	0	0	8.47080648	9.14187427	5.69957905
Dtx1	1.994687	4.40399225	3.53694035	1.04383263	0.47312172	3.02752053
Dtx4	3.40004889	0	2.47750396	0	9.02141488	8.78305504
Ebf1	9.85337813	10.0549087	10.0192028	10.3755802	10.3006671	10.0964241
Ep300	8.7177225	7.49266991	9.85202509	10.4082795	9.68961902	9.97406922
Epor	2.12061309	0	3.84685187	4.15570632	3.80975151	5.26571959
Erg	9.92070322	10.2435688	11.5232616	11.7222598	12.279183	12.5339555
Esr1	8.69677383	10.4600212	10.205356	8.31154408	7.71734777	0
ETS1	11.3057093	12.1559856	12.6586051	12.5933092	12.1381441	12.9889476
ETS2	0	0	9.6997688	8.36290987	8.2095168	0.73462164
Etv3	0	3.38933838	0	3.43657627	6.61600906	2.44247804
Etv6	0	0	8.65286731	10.7013694	10.9628988	10.3361814
Ezh2	8.02471927	8.50978683	12.1912021	10.8533753	11.493762	11.5119798
Fas	0	0	0	0	0	0
Fcgr2b	7.6797349	0	0	0	0	0
Fcgr3	0	0	0	6.10259634	0	0
Fli1	9.93711884	10.9464019	11.1285519	9.54487089	10.8365241	11.5533691
Flt3	0	0	0	0	9.56640355	10.3432711
Fosl1	0	0	0	0	0	0
Foxo1	11.0966868	8.79275995	11.8050162	12.7164993	12.8446053	12.3408678
Foxo3	3.57817888	6.51216426	0	6.58016006	7.771922	8.46989317
Gapdh	5.85168672	10.6505893	12.1850341	12.4040061	13.3572594	13.192243
Gata1	6.47274743	0	0	2.62704169	3.52126724	0
Gata2	0	0	0.36206896	0	0	0
Gata3	0	0	0	0	0	0
Gfi1	5.89645562	0	8.17908872	0	4.89958389	2.83324318
Gfi1b	7.35569282	0	0	0	0	0
Hes5	2.85354691	0	0	0	6.33604471	0
Hey1	0	0	0	0	0	0
Hlf	0	0	0	0	0	0
Id2	0	0	0	0	0	0
Ifi203	11.7954894	10.973362	11.001131	11.4270334	12.5609017	10.7759677
Ifi205	0	0	0	0	0	8.09318704

TABLE 6-3-continued

Single cell expression data (reduced list)-Control

Factor	CLP3	CLP4	CLP5	CLP6	CLP7	CLP8
Ifitm1	0	0	0	2.84027402	0	0
Ikzf1	9.73388122	8.31161283	9.89390965	8.89596541	11.5318373	11.7353046
Ikzf2	7.68319581	0	0	0	0	0
Il7R	3.50218592	3.36711209	5.2921046	4.8044562	5.550561	6.76651483
Irf4	9.79482653	0	9.58168074	8.08809386	7.5643288	2.25516181
Irf6	0	4.76893306	4.55078055	0	2.82795862	2.04839193
Irf8	7.95992816	10.1806094	7.75876351	8.80670344	11.7480118	9.73229364
Kdr	0	0	0	0	0	0
Kit	0.53419079	0	9.96379129	10.7375717	10.2201977	9.16826777
Klf1	6.82013214	0	0	1.0024718	0	0
Klf12	0	0	0	0	0	0
Ldb1	9.90431329	9.96028836	11.2260518	9.83927772	11.895041	11.7935625
Lin28a	5.35085436	7.33632529	6.44890786	6.34118404	6.36516284	9.37400697
Lmo2	6.46868712	4.61214257	5.14599266	5.60258194	6.56246105	3.9775212
Ly6a	0	3.53194881	0	0.37013501	7.4460115	10.5913393
Lyl1	9.3983485	8.54480739	7.34706955	9.10668449	11.3876375	7.64786048
Mbd2	8.94182953	9.36449253	10.2060984	9.52243477	11.5407023	12.2595821
Meis1	0	0	5.21224582	5.79085752	5.40464488	0
Mllt3	0	0	0	2.11014429	0	2.59630677
Mpl	0	0	0	4.02311498	0	0
Muc13	0	2.57260911	0	0	0	0
Myb	12.3033699	12.488897	12.3730793	12.3171025	13.0048416	12.7052775
Myc	5.93099913	11.6265583	0	0	14.0060868	10.9410236
Mycn	0	0	0	0	0	0
Ndn	0	0	0	0	0	0
Nfat5	7.24590475	5.59931195	10.8263667	6.57678171	8.07891887	6.14435558
Nfia	8.37013642	8.26157976	10.2847505	8.23082089	0	8.96451019
Nfkb1	0	0	4.99179474	0	3.6973326	6.1512888
Notch1	8.10251427	0	0	0	8.45173916	8.82084626
Pax4	0	0	0	4.36397603	3.43221858	0
Pax5	9.34367693	9.92404452	9.77304	11.0122144	10.3872408	10.8331107
Pax9	0	0	5.18709971	0	3.29966428	0
Pbx1	0	0	0	0	0	0
PIk3ca	9.63937118	6.79728215	11.3857624	10.7462144	9.15262138	10.9538129
PIk3R2	7.90901728	7.26209506	8.54304817	8.37704722	9.50572232	9.62140977
Plag1	0	0	0	5.97796547	0	0
Prf1	0	0	0	0	0	0
Pten	9.72285323	11.0091543	10.636038	10.0259098	11.7798461	10.8939695
Rb1	9.00979222	8.85052189	11.0074341	12.0368206	11.2827	12.2052216
Rora	0	0	0	0	0	0
Runx1	3.35520365	8.41018156	0	7.20098788	10.3169336	7.21605593
Runx2	0	0	0	0	0	0
Satb1	10.3474498	0	10.4087951	10.4125548	11.5917762	10.8352979
Sdpr	0	0	0	0	0	0
Sell	0	0	0	9.4220848	11.0820261	0
Sfpi1	0	6.01015121	9.2965798	0	9.91399926	8.59032855
Slamf1	0	0	0	5.98712463	0	0
Smarca4	13.439393	12.5294897	14.6724616	15.0680818	14.5786721	13.7911882
Sos1	0.97380716	6.19138786	0	5.38334215	7.45674234	7.50591767
Stat1	0.7689796	6.50704145	0	0.30611506	2.57411315	0
Stat3	0	8.93991247	0	6.7379161	10.502702	0
Stat4	6.56531371	6.26156325	7.27133959	8.37209933	7.78457398	6.6457098
Stat6	7.7239777	8.43459593	9.892434	9.03877839	10.1786368	3.86022053
Suz12	9.22489651	0	10.0290041	12.3349832	12.611291	13.0733851
Tal1	0	0	6.67626014	6.82238434	7.45135976	3.68581347
Tcf3	3.3752031	0	7.69136582	8.65824457	9.6940747	8.57311453
Tcf4	11.1561631	9.47548756	10.1792855	11.8284673	11.6158594	10.8851719
Tcf7	0	0	1.68581989	0	1.46116868	6.50226768
Tek	0	0	0	0	0	0
Tfrc	8.384231	8.62609735	8.72228476	9.79712611	12.2298851	12.6617066
Tgfb1	0	1.30714129	0	0	8.57409133	4.42951853
Tgfb2	0	0	0	0	0	0
Tgfb3	0	0	0	5.906968	6.8247631	0
Tnfrsf1a	0	0	8.13776036	0	6.6654212	0
Tnfrsf1b	5.48788691	0	0	0	8.83222639	0
Tnfrsf21	0	3.83171313	4.44763219	5.66301599	6.31162299	5.70640904
Tnfsf10	0	0	7.49803338	0	7.18042827	0
Tnfsf12	0	0	0	0	0	0
Tob1	0	4.40571001	0	0	0	0
vWF	0	0	0	0	0	0
Zbtb20	8.29135619	0	8.47708838	0	0	8.27839243
Zbtb38	8.58554038	0.99042294	8.02102069	0	0	7.24565903
Zfp532	0	3.87621119	2.9154077	0	4.19402652	3.24319594

TABLE 6-3-continued

Single cell expression data (reduced list)-Control						
Factor	CLP3	CLP4	CLP5	CLP6	CLP7	CLP8
Zfp612	1.03716649	0	2.11894576	6.50227904	7.64231508	7.61374585
Zfpm1	6.66189343	0	3.0682001	0	0	0
Zhx2	8.44133547	0	0	0	0	9.15911003

TABLE 6-4

Single cell expression data (reduced list)-Control						
Factor	CLP9	CLP10	CMP1	CMP2	CMP3	CMP4
Actb	16.7472085	16.8352612	16.8602626	16.1110931	14.4827986	15.0603357
Aebp2	5.10557045	3.3120632	5.90217636	5.99828664	4.16296449	5.95408203
Ahr	7.89043699	0	0	0	0	0
Akt1	8.18148335	8.76665238	9.82206378	10.7068971	8.0750109	9.71182542
Akt2	0	0	4.73623383	5.90460679	0	5.31671466
Akt3	7.62109377	8.60100117	10.3161486	9.89323892	7.25420238	7.89506854
APC	0	0	0	6.42364613	0	1.66166347
Bad	0	0	0	0	0	0
Bax	9.29238441	8.3822507	9.02204677	9.89324281	0	8.05690985
Bcl11a	10.3227685	0	0	0	0	0
Bcl11b	4.17625304	3.92709271	0	0	0	6.87178744
Bcl2	5.16525658	0	0	0	0	7.99225602
Bcl211	8.3489033	9.55544552	0	8.39669119	0	0
Bcl2111	0	4.95609125	9.99775747	9.90050891	8.99255245	2.85336974
Bmi1	7.02747752	7.05328898	6.44377861	6.35815343	0	5.61256235
Brd3	10.4902324	10.3566216	9.01263098	11.3736884	9.51822117	10.0173723
Casp8	10.3220679	10.7369556	9.56591918	12.353426	10.3690709	10.4324467
Casp9	0	0	0	8.91438552	0	9.50719509
Cbx2	5.63357469	5.32126348	0	6.26420923	0	4.88635048
Cbx8	0	4.8985443	0	0	0	0
Ccnc	9.44462333	10.6012883	8.71922383	8.09587133	7.39164169	7.88535554
Ccnd1	13.1309938	8.71442109	10.4720419	7.63908907	0	7.37626749
Ccne2	0	8.35161245	0	7.74541722	0	0
CD34	0	0	0	11.0938464	0	10.9563356
CD41	0	0	0	10.8578571	10.6626378	0
CD48	10.1531953	9.61840884	11.7599349	12.6456392	7.70003657	10.4526615
CD52	11.7226951	10.1559179	12.0658796	10.3906592	0	7.66859187
CD53	12.8012579	11.5337875	11.257362	13.1982289	0	11.0963127
CD55	0	0	0	0	8.8819203	0
CD63	0	0	6.94398394	9.24084619	0	6.92519888
CD9	7.17538049	0	8.11834259	0	0	7.63859446
Cdc42	12.9539909	13.4145126	14.1395004	13.5734692	12.5791339	12.8894502
Cdk1	11.2702793	11.3939722	0.20875207	11.1428913	0	0
Cdk4	8.41570405	11.076971	6.87263164	10.9598136	9.6088668	10.5827767
Cdkn2b	0	0	0	0	0	0
Cebpa	0.89723358	0	10.2311173	13.4808053	8.18762349	11.6632459
Csf1r	0.68220487	0	8.91048376	8.52043829	7.87011519	9.68797102
Ctnnb1	6.632855	7.60076967	4.83416648	8.15260001	5.67395641	6.9102424
Cycs	10.3257774	11.5926	11.9196287	13.2793334	7.61714986	10.435771
Dach1	0	0	0	11.8661392	9.79500635	0
Dnmt1	10.9639197	10.9779133	9.7927147	13.2742978	6.43285115	11.5344213
Dnmt3a	10.1312258	10.6116941	0.01680684	11.2120611	10.1685075	9.93533932
Dnmt3b	6.02587145	0	0.28023125	10.9143614	8.14598611	11.5847104
Dtx1	0	0	1.92305529	0	0	2.30151059
Dtx4	9.68534196	5.647952	0	4.77885166	0	0
Ebf1	0	0	0	0	0	6.27167952
Ep300	10.430224	10.5649677	10.9844624	11.2861422	10.0900532	10.0078637
Epor	6.0607173	5.65375289	6.31948929	5.15194981	4.40969335	2.82619662
Erg	0	0	0	12.0363518	10.0931312	10.5218299
Esr1	10.9412325	8.69857347	0	8.23822017	0	8.23908889
ETS1	12.3373625	12.1142197	0	0	0	0
ETS2	6.29583632	0	0	0.68650314	0	6.35073519
Etv3	4.3355231	4.42802306	5.32393809	5.87942342	0	3.92981296
Etv6	8.83941501	0	8.61360798	12.0360378	10.3250242	10.9028847
Ezh2	8.85028888	10.0605202	7.27389146	9.32121342	7.38296829	10.0425905
Fas	0	0	0	4.30798527	7.17965527	0
Fcgr2b	0	0	7.77302706	7.68233416	0	0
Fcgr3	0	0	2.16280252	7.43345552	0	0
Fli1	10.3126762	11.0853737	8.11430154	9.84452071	11.0778188	10.5409282
Flt3	10.8733788	11.8851759	10.4953795	8.72900327	0	11.9407693

TABLE 6-4-continued

Single cell expression data (reduced list)-Control						
Factor	CLP9	CLP10	CMP1	CMP2	CMP3	CMP4
Fosl1	0	0	0	0	0	0
Foxo1	12.9862277	0	9.12833227	10.3210046	8.57814146	10.4483982
Foxo3	9.35939781	9.17812532	7.75264584	8.79843273	7.38358954	9.91435082
Gapdh	12.0414546	10.6649131	8.59496634	13.2322627	9.24678558	10.5425893
Gata1	2.47237968	5.18777488	0	0	9.92586716	0
Gata2	0	1.70095059	0	5.59893348	5.27123302	2.16028386
Gata3	0	5.17595033	0	0	0	6.05524501
Gfi1	3.35012985	0	0	5.30002147	3.26363882	6.13120183
Gfi1b	0	8.53467602	0	10.0611223	11.6926351	8.75372639
Hes5	0	0	0	0	0	0
Hey1	0	1.04367745	0	0	0	0
Hlf	0	0	0	7.97611682	7.82618822	9.46609084
Id2	8.21405404	0	9.70225491	5.84854144	0	4.38699582
Ifi203	13.121305	11.7715254	13.5766403	10.4527001	10.3475725	11.3925667
Ifi205	0	0	12.6181685	0	0	0
Ifitm1	9.57706163	0	0	9.63434379	11.5761744	11.1838971
Ikzf1	12.4531104	12.1544134	10.0753763	10.6241986	9.99327753	10.5079787
Ikzf2	0	0	0	11.2294386	10.0871853	10.8948866
Il7R	2.6756414	3.11340227	0	0	0	0
Irf4	10.9460654	0	7.83866655	0	0	0
Irf6	3.75002159	0	0	0	0	0
Irf8	0	14.7096031	14.2888668	0	0	8.8628089
Kdr	0	0	0	0	0	0
Kit	0.24445292	0.50621599	11.0295653	12.5726203	12.3791378	12.0919625
Klf1	5.84397562	0	0	0	8.46482083	0
Klf12	8.05086964	0	0	0	0	0
Ldb1	11.2686965	8.12945947	8.68054007	11.6527152	12.2469401	11.316521
Lin28a	1.96158082	6.99342123	5.60046956	8.55574345	6.63350297	8.68718725
Lmo2	3.89774451	8.38732066	8.20469078	10.3169241	5.11243451	9.84586404
Ly6a	8.85142518	0	0	0	4.09411947	0
Lyl1	0	9.75810271	0	0	0	9.50789901
Mbd2	11.5068886	11.2014367	11.5257283	11.0058202	9.54315445	10.0659452
Meis1	8.51879687	0	0	4.87021647	0	0
Mllt3	1.72128743	0	0	0	0	1.98967093
Mpl	0	5.37493792	0	0	4.57579908	8.42884537
Muc13	0	0	7.94365244	12.3910631	9.66287501	9.27532572
Myb	8.92481613	11.9021578	7.74778663	13.4608829	13.6082862	12.5062084
Myc	0	0	9.66579628	13.1468373	11.1237836	12.2368797
Mycn	0	0	0	0	4.71550783	0
Ndn	0	0	0	0	0	0
Nfat5	1.68337396	6.42382445	8.11771068	8.50241858	8.29542914	6.81510443
Nfia	11.1966351	0.51538312	8.76871243	10.4414063	8.37541044	0
Nfkb1	6.28053175	4.20047424	7.24237126	3.02501649	0	0
Notch1	9.23968393	9.80621601	0	0	0	9.04276389
Pax4	0	4.30341437	0	0	4.67280508	3.18275178
Pax5	0	0	0	0	0	0
Pax9	0	5.11348672	0	0	0	0
Pbx1	0	0	0	0	0	2.85814132
PIk3ca	10.7501901	10.4597043	8.71137418	8.63082063	10.2150339	9.12110399
PIk3R2	0	0	0	8.41565889	0	8.86044462
Plag1	0	0	0	5.73253318	0	0
Prf1	0	0	0	0	0	0
Pten	10.402978	10.7323361	8.45327824	9.15804062	8.02557223	9.55214218
Rb1	11.5095723	10.3228048	11.0518462	8.80830469	10.975973	10.2070756
Rora	0	0	0	10.3525123	0	0
Runx1	0	10.5448042	8.49404453	9.79896396	8.32589216	0
Runx2	9.55408881	8.83337957	8.58263825	5.6671043	0	6.59981576
Satb1	10.6618569	10.6425259	11.0333257	10.4623762	5.50666657	11.6829394
Sdpr	0	0	0	0	0	0
Sell	13.3986811	12.636786	11.8418847	12.1758077	8.32310492	10.6231619
Sfpi1	10.755918	10.840172	10.234157	11.6285965	4.19803029	10.180779
Slamf1	0	0	0	0	0	0
Smarca4	12.4059967	12.3958203	10.7430601	12.6426923	9.78305678	11.6074547
Sos1	1.96984274	7.60327488	8.55093991	7.00950203	7.97175828	7.25923732
Stat1	0.57217994	4.66285063	8.17622822	7.02260834	5.60396427	6.85302887
Stat3	12.1553826	10.5962174	10.1047053	10.4043949	10.6890265	11.1026336
Stat4	11.2376366	0	0	8.1182282	0	6.31665833
Stat6	10.4721199	9.57987162	0	10.8577127	8.31312981	8.9859846
Suz12	8.50068008	11.8114564	10.0842116	11.4415014	8.88768825	10.3591033
Tal1	0	0	7.35199805	7.41118762	0	3.34846603
Tcf3	6.0690736	6.37460317	0	0	7.14327082	10.0950413
Tcf4	13.9829509	13.2477205	11.1633078	10.5566707	10.2373849	11.9154368
Tcf7	12.5483718	0	0	0	0	0

TABLE 6-4-continued

Single cell expression data (reduced list)-Control

Factor	CLP9	CLP10	CMP1	CMP2	CMP3	CMP4
Tek	0	0	0	0	0	0
Tfrc	11.5310872	13.6794866	8.69647395	10.1124605	9.94594668	8.66198046
Tgfb1	0	0	0	8.39098114	0	0
Tgfb2	2.54299473	0	0	0	0	0
Tgfb3	1.83073988	0	0	0	0	0
Tnfrsf1a	0	0	10.5575923	10.2288397	5.8586183	10.085531
Tnfrsf1b	5.27266462	0	0	10.3201112	0.95315427	0.80836534
Tnfrsf21	0.70732573	0	6.05902828	7.64675137	0	7.86021375
Tnfsf10	4.81322759	0	3.8552827	7.3711495	0	0
Tnfsf12	0	0	4.39444523	0	0	0
Tob1	3.38203155	0	7.3702815	8.22337837	0	5.83579043
vWF	0	0	0	0	0	0
Zbtb20	6.49874585	8.98366904	7.76355827	7.5019406	9.51185133	9.03587558
Zbtb38	6.31337663	0	8.66735889	8.88619321	8.85030113	7.99157356
Zfp532	0	0	4.28968013	0	2.01705667	3.84180886
Zfp612	5.14316607	0	1.45139554	6.82565849	0	4.40273428
Zfpm1	0	0	0	0	0	0
Zhx2	0	1.36199848	9.44707427	0	0	6.34007356

TABLE 6-5

Single cell expression data (reduced list)-Control

Factor	CMP5	CMP6	CMP7	CMP8	CMP9	CMP10
Actb	17.3394053	14.6706888	15.3006859	15.6706136	16.2161296	16.2031528
Aebp2	7.48010576	4.52217501	4.85718391	6.22489648	6.15542349	6.65750054
Ahr	0	0	0	0	8.48248567	0
Akt1	11.0295746	9.13888127	8.50202567	9.48522978	9.83325343	10.1423732
Akt2	5.6982268	6.43649925	0	6.54782485	5.67097403	6.91885001
Akt3	10.7535896	5.05597233	8.96329552	9.39938997	8.41514892	8.63112027
APC	0	0	5.85738488	0	0	8.00067699
Bad	0	0	0	0	0	0
Bax	10.7709938	7.60268797	9.74661453	9.46994606	10.0956302	9.66835081
Bcl11a	7.25102747	0	3.44256113	0	0	0
Bcl11b	0	0	0	0	0	0
Bcl2	0	0	5.71221572	8.46600782	4.51709175	7.63420792
Bcl211	0	0	8.642915	9.8449129	9.83242806	11.727409
Bcl2111	4.94361446	6.96342995	0	8.82547082	7.49063229	0
Bmi1	8.04079881	6.47044397	6.99413119	7.02301797	5.66629178	7.29852135
Brd3	11.7497296	9.48652042	10.2279983	10.7336706	9.99622743	10.5589239
Casp8	11.4458868	9.37414266	10.730553	11.5737089	10.042092	11.3341723
Casp9	8.60157869	0.43486175	8.11116214	8.49830047	8.46979801	0
Cbx2	8.14298572	5.42369511	0	2.02852747	6.14976979	0
Cbx8	0	0	0	0	0	6.5352377
Ccnc	9.337732	0	0	0	8.74862406	8.05461177
Ccnd1	12.3424395	0	0	5.08950715	10.3980334	9.67251383
Ccne2	10.6836164	0	0	8.88454106	7.76036683	0
CD34	13.0466336	0	10.0606452	11.7867314	8.70281995	11.9349176
CD41	7.22234749	9.88958898	0	8.74031169	13.4959806	11.1372918
CD48	12.0992452	10.568177	7.88392396	10.8210925	8.89620358	11.2734612
CD52	11.0838001	0	5.49447739	8.00130213	7.2008291	7.95395412
CD53	12.7670824	0	10.9959227	11.3777197	0	0
CD55	0	8.42133148	0	0	9.29531826	0
CD63	9.14519387	0	7.74259128	9.32290779	9.53162102	7.281967
CD9	0	0	0	0	9.68777068	0
Cdc42	14.6585333	12.6841565	13.4268211	13.5192656	13.4441459	13.1256535
Cdk1	10.9097239	6.60224216	0	9.60826336	9.2659687	11.8683968
Cdk4	12.2911932	9.86090165	7.8025631	11.0577815	11.3768742	11.0385295
Cdkn2b	0	0	0	0	0	0
Cebpa	12.8418824	0	10.2324455	13.6075773	8.81482957	11.9755884
Csf1r	11.0511238	0	0	10.585565	7.27360003	3.88021025
Ctnnb1	8.35670072	4.81362741	5.97188813	5.22508782	8.07136491	8.28703889
Cycs	14.5377046	11.2691463	10.1789357	13.0405966	12.4297442	13.3283287
Dach1	4.97803655	4.14474045	10.5451334	8.59226416	11.9267309	13.5465833
Dnmt1	12.8726368	10.4919004	0	12.5203344	12.4834927	12.7064491
Dnmt3a	11.0265538	11.1062288	10.9186344	5.45624458	10.3948879	8.98758434
Dnmt3b	10.5790239	0	8.38337161	9.97828774	10.4507647	10.9212224
Dtx1	4.3790403	0	0	0.78348056	4.24129098	0
Dtx4	11.1502546	0	10.8469873	8.96806057	8.43544431	0

TABLE 6-5-continued

Single cell expression data (reduced list)-Control

Factor	CMP5	CMP6	CMP7	CMP8	CMP9	CMP10
Ebf1	0	0	0	0	0	0
Ep300	10.4632229	10.6518923	9.84642833	10.2654483	11.2467128	10.6061578
Epor	3.12221538	5.0756706	5.30043509	0.65533034	5.10260705	2.33815245
Erg	10.3534511	0	10.8266427	10.3592454	10.8159451	10.2449054
Esr1	10.4969031	0	7.69419665	9.81964633	0	10.7394097
ETS1	0	0	0	0	8.4833129	0
ETS2	4.07083276	8.45916169	8.45527663	0	7.1341973	0.7101611
Etv3	4.43481527	0	0	6.56778632	4.52654183	4.69321163
Etv6	11.1448929	9.69394925	11.1261285	10.0656969	11.7161763	11.8183036
Ezh2	10.8670738	7.48291356	6.20161136	8.65707232	9.49516932	9.8783733
Fas	0	0	0	0	6.62884488	0
Fcgr2b	9.85267441	0	0	8.23013247	0	0
Fcgr3	0	0	8.119839	6.61788198	0	0
Fli1	11.1890149	7.33814185	10.2757687	12.4967795	12.0912236	10.2473636
Flt3	12.6574132	0	8.78397217	8.19832375	0	0
Fosl1	8.40640045	0	0	0	0	0
Foxo1	10.3981463	8.56491822	10.2557995	8.32166089	10.0603533	10.0759643
Foxo3	9.39347931	8.64471911	10.6380669	10.7062816	10.0359107	9.78384345
Gapdh	13.8965059	9.81728739	8.9549559	10.5129808	11.6006197	11.7863478
Gata1	0	11.2237171	8.02113847	0	9.99443513	10.5689067
Gata2	2.95452348	2.89363096	3.76227155	4.70253038	7.1084613	7.11132825
Gata3	0	0	7.93855591	0	5.10350469	2.65446248
Gfi1	0	0	0	6.53413949	0	0
Gfi1b	0	9.24282738	8.39289491	9.64648209	0	0
Hes5	0	1.45446472	0	0	0	0
Hey1	0	0	0	0	0	0
Hlf	10.1384281	0	12.7210851	9.7255738	0	7.72908307
Id2	0	0	0	0	0	0
Ifi203	12.0764195	0	11.9267051	9.88952822	9.82976425	11.7604599
Ifi205	0	0	0	0	0	0
Ifitm1	10.026959	13.4455145	10.1142515	9.62949447	7.52584164	9.35647384
Ikzf1	11.1162893	10.1776721	9.8444204	9.56063417	9.76312629	10.2802226
Ikzf2	9.29677615	9.26597898	10.0113973	10.6548835	0	11.7095844
Il7R	0	0	0	0	0	0
Irf4	0	0	0	0	0	0
Irf6	0	4.07511467	4.21960052	0	3.38207598	1.77623393
Irf8	11.496976	0.64529505	8.3919475	9.72740536	0	5.4029575
Kdr	0	0	0	0	0	0
Kit	12.5171017	12.5279914	12.8127026	13.3103212	12.0370385	12.3472302
Klf1	0	10.8766523	0	0	7.07393535	0
Klf12	0	0	0	0	0	0
Ldb1	12.6976636	12.9835097	12.2468903	12.365463	12.0631399	10.863801
Lin28a	6.74728963	7.35105581	6.84975068	6.51455602	4.68753784	6.94552367
Lmo2	10.5379436	9.34407841	10.2403324	11.0343922	11.009923	9.20928647
Ly6a	0	0	0	0	0	0
Lyl1	8.51165848	0	7.37416084	9.52238028	0	8.2113635
Mbd2	10.784295	10.4108785	10.1955821	10.6851427	10.63494	9.7729213
Meis1	1.70692163	0	8.17244297	7.73150896	9.6859662	9.65905238
Mllt3	0	0	0	0	0	0
Mpl	0	0	8.32138383	9.02983537	10.6949276	9.03531377
Muc13	10.0268838	10.6859087	10.408149	10.9764924	10.4182397	10.4076086
Myb	13.3352034	13.5300503	12.2422918	13.8875021	12.5291358	12.9438126
Myc	14.3568801	13.271873	11.7486234	13.7517564	13.3585202	13.2342566
Mycn	0	3.51516181	8.22715916	0	12.5856289	9.69546069
Ndn	0	0	0	0	0	0
Nfat5	6.28186815	5.14468333	9.22002325	8.30051998	6.00790584	7.26449937
Nfia	7.45568183	8.69437239	0	9.99729448	0	0
Nfkb1	4.00335392	1.98855259	4.45405858	4.48909452	5.48703027	4.4024728
Notch1	8.69453625	0	7.51819143	9.54735802	0	0
Pax4	0	0.4697586	0	0	1.82857332	0
Pax5	0	0	0	0	0	0
Pax9	1.81855969	0	0	0	0	6.9598383
Pbx1	0	4.33008847	0	0	0	0
PIk3ca	11.4126663	7.92679365	10.1322248	10.2563679	10.571161	10.2438679
PIk3R2	10.1509326	7.23727926	10.6194334	0	10.0876344	8.17463706
Plag1	0	8.268993	0	0	8.61635192	8.90930204
Prf1	0	0	0	0	0	0
Pten	10.0980102	8.44584924	10.8389704	10.0450831	9.96600275	9.11441299
Rb1	10.5049014	11.035184	10.2686739	8.28260838	11.2325685	0
Rora	0	0	9.40803685	0	0	0
Runx1	9.80351196	9.89394529	11.2310772	10.8511201	9.61241397	11.260184
Runx2	7.14600662	0	6.60312795	6.31525159	5.12629061	5.98996282
Satb1	11.6190523	0	10.5185268	9.31688989	0	0

TABLE 6-5-continued

Single cell expression data (reduced list)-Control

Factor	CMP5	CMP6	CMP7	CMP8	CMP9	CMP10
Sdpr	0	0	0	0	3.41819471	0
Sell	13.4721541	2.89807481	11.2017393	12.147405	7.52145725	11.8940425
Sfpi1	12.1814824	0	10.3051236	11.135862	10.6759176	8.61401742
Slamf1	0	0	0	0	8.27576355	0
Smarca4	13.4159099	12.6986337	11.0603738	12.4208763	11.5131011	13.1672711
Sos1	7.05920683	6.93067259	7.46342294	7.99375888	8.94290202	8.2090476
Stat1	6.96525561	3.0714838	3.32406997	6.73484676	2.55117066	1.90884457
Stat3	10.2805664	7.3966824	11.052227	11.4922447	9.33437336	11.3081762
Stat4	7.45961139	0	8.01611823	6.16856977	7.27293514	9.2165467
Stat6	9.84695626	7.3258474	10.0351652	9.04651696	9.68468703	9.93759651
Suz12	12.160067	9.36880984	10.4227735	11.2065549	11.719744	11.4025496
Tal1	4.01061915	6.6880475	7.39995658	0	0	0
Tcf3	9.28106881	8.46463489	10.0783131	6.78607403	8.04893309	7.02457762
Tcf4	11.9822362	10.7280242	10.8947009	10.4060663	9.61927383	10.7021269
Tcf7	5.23267198	1.68626678	0	0	2.66766182	2.23952747
Tek	0	0	0	0	0	8.15055552
Tfrc	11.5315055	10.3078535	8.70556098	0	10.6282683	10.1053058
Tgfb1	8.61614955	5.35612843	0	0	6.65768412	6.16568389
Tgfb2	0	0	0	0	0	0
Tgfb3	8.18570265	0	6.23265555	6.9879955	0	6.47320472
Tnfrsf1a	11.3960482	9.71137069	10.5553381	10.0882949	8.80578171	9.01361307
Tnfrsf1b	9.21806977	0	9.61506083	8.80892599	9.64596728	4.62484099
Tnfrsf21	7.08978321	5.63889855	3.52361608	5.13475364	7.18706943	6.49011462
Tnfsf10	0	0	0	7.44776059	0	4.80467952
Tnfsf12	0	0	4.92147767	0	0	6.45276939
Tob1	0	0	4.87096526	0	0	0
vWF	0	0	0	0	0.92959921	0
Zbtb20	8.91468776	7.47378037	8.65801097	6.07085525	7.77205018	9.83080899
Zbtb38	7.61532556	8.16188767	7.21002151	9.37139278	9.52940602	7.19300308
Zfp532	0	4.20413936	0	0	0	2.33025492
Zfp612	6.36251023	0	0	5.89338537	5.72389563	0
Zfpm1	0	7.38814478	0	6.75057183	4.81492174	0
Zhx2	0	10.0153129	0	10.0672844	0	0

TABLE 6-6

Single cell expression data (reduced list)-Control

Factor	GMP1	GMP2	GMP3	GMP4	GMP5	GMP6
Actb	17.1489215	17.1987952	17.0261935	17.386841	16.8304269	16.7489209
Aebp2	7.38412472	7.37000886	7.67068492	8.3165713	5.4136843	7.57713129
Ahr	0	0	0	0	8.2586416	2.48178389
Akt1	11.235626	11.370018	11.2228314	11.4580108	9.35433585	11.3917982
Akt2	0	5.65369871	6.60168541	7.30834154	7.09194507	7.27954511
Akt3	9.2040554	6.42589774	7.76683642	10.3335	0	0
APC	0	0	10.3835517	0	8.371236	0
Bad	0	0	0	0	0	0
Bax	12.3982935	11.548933	11.7457261	12.5304908	9.63819013	9.58757022
Bcl11a	0	4.8496745	5.5277101	0	0	0
Bcl11b	2.47388586	0	0	3.3676317	4.51519907	0
Bcl2	8.67205883	4.74052395	7.4793676	9.81638057	0	0
Bcl211	11.2985207	10.9107736	8.31831953	10.0601684	7.45200039	0
Bcl2111	9.91590871	8.18472841	7.91574582	8.84722554	10.1748095	6.43500489
Bmi1	7.65085777	4.83187475	9.02271832	6.18509638	7.09454308	7.56761362
Brd3	12.2200241	8.5222524	12.5897181	12.3613327	12.0766338	11.4340477
Casp8	11.9935864	12.4728177	11.2081299	11.7931878	10.6330727	9.95275872
Casp9	9.85784236	9.2795417	10.4608042	9.30079864	8.68972348	8.67710004
Cbx2	8.13468181	6.26338723	4.15904155	2.80402938	0	4.90815454
Cbx8	0	0	0	0	0	0
Ccnc	6.54457096	7.80869339	10.2612515	10.5944974	9.89068237	8.39273481
Ccnd1	8.58525018	9.07320206	0.44602581	11.6985658	0	8.4714389
Ccne2	10.2847235	10.3613222	10.2263111	7.68162663	7.00126105	7.38398862
CD34	9.76737788	11.3493653	12.3762338	12.665751	0.7308249	0
CD41	0	0	9.92285908	10.1379171	0	0
CD48	11.1755703	12.3720324	11.2216769	13.1172131	8.98467946	11.1712268
CD52	12.214887	11.4843836	6.92750614	10.055469	9.88050006	9.66769309
CD53	13.734581	12.9470142	11.5566919	12.0795346	11.4796107	11.6332867
CD55	0	0	0	0	0	1.98400237
CD63	5.83669083	10.6791061	11.1660619	9.5002936	11.8417986	11.5674632

TABLE 6-6-continued

Single cell expression data (reduced list)-Control

Factor	GMP1	GMP2	GMP3	GMP4	GMP5	GMP6
CD9	7.33502006	0	10.0478265	0	9.8535396	9.37192294
Cdc42	15.071603	14.9063997	14.4251672	15.2700451	14.1058059	14.2812027
Cdk1	11.1089539	12.565398	10.0640308	12.9451584	8.92252913	10.3979323
Cdk4	12.1492532	12.2049096	11.3481552	12.5805625	10.3340466	10.1996484
Cdkn2b	0	1.8448054	0	0	0	0
Cebpa	13.5582841	13.0751849	14.1307094	14.8662046	13.3279428	12.940603
Csf1r	13.2965977	9.82859309	9.7227165	12.1147466	7.15970464	7.14539069
Ctnnb1	9.16188305	7.52545352	8.60919966	9.20385918	8.67653144	9.17983079
Cycs	14.5117323	15.5509006	14.3926146	14.8500674	13.3320521	13.6650347
Dach1	10.9910945	8.44938041	12.3883714	8.79080043	10.4536266	10.6691965
Dnmt1	12.9020312	12.4369612	12.7558873	12.902768	11.6602754	11.0715158
Dnmt3a	10.7289813	6.56627584	10.702069	11.2807594	10.0406974	10.0659832
Dnmt3b	9.58857441	6.44688601	10.7118482	10.5910128	8.18039351	7.21703334
Dtx1	3.0913916	0	3.91641931	0	0	0
Dtx4	10.1882254	11.1715529	12.6766112	13.3330567	12.3246264	12.2398755
Ebf1	0	0	0	0	0	6.35563108
Ep300	11.0646985	5.51844512	10.4585713	10.8818586	10.7818993	10.2687707
Epor	4.1948605	5.82587694	4.04624715	4.16263046	4.31309197	5.7777581
Erg	10.0476497	10.8998172	8.31856172	10.7787749	8.41282235	8.00315491
Esr1	0	9.61295568	7.43332756	11.6298664	9.26139595	0
ETS1	0	8.49664543	0	0	11.774333	10.8678821
ETS2	0	7.04070704	8.18875575	0.30773145	9.76422043	0
Etv3	0	5.70625189	4.29581374	5.43089153	4.8703617	1.40350183
Etv6	12.0523052	11.0382089	9.74143581	13.0923382	0	9.61119192
Ezh2	11.652838	11.5860694	11.1993861	11.4872376	10.1109725	10.4391363
Fas	0	0	0	0	0	8.72358173
Fcgr2b	9.19136771	8.72106918	9.14865833	8.70635442	10.0101786	7.27372444
Fcgr3	10.5154928	11.1483415	9.97180324	10.3691572	10.0558965	10.006567
Fli1	12.1113098	10.2964886	11.1111683	13.0309888	12.5529343	13.2435265
Flt3	0	0	0	8.20154666	0	0
Fosl1	9.14818795	0	0	0	0	8.95584384
Foxo1	10.6678286	7.11027738	10.5639142	11.4065349	7.68627588	8.03189028
Foxo3	8.6581534	8.83051249	9.05928824	10.1872797	8.17891127	9.65874783
Gapdh	14.5697489	14.8364814	14.4841585	15.2948511	12.4951942	11.7288864
Gata1	2.68117413	5.3286228	2.40405255	0	6.20074437	0
Gata2	0	0	1.18893452	5.03280609	0	0
Gata3	0	0	0	0	0	0
Gfi1	0	9.95120128	10.4607555	10.4250456	10.2403166	9.63774464
Gfi1b	0	0	0	0	0	0
Hes5	0	0	0	0	0	0
Hey1	0	0	0	0	0	0
Hlf	0	0	0	8.36237805	0	0
Id2	0	0	0	0	8.92503527	6.47603665
Ifi203	12.4820599	10.2059101	9.66114357	10.9751352	0	8.43723516
Ifi205	0	4.02559453	0	0	0	0
Ifitm1	0	7.59695531	9.85532823	0	7.57013634	0
Ikzf1	12.0462915	11.0027006	10.1806326	12.6066347	10.1787075	9.1812643
Ikzf2	8.42131399	6.66467431	9.37167983	0	0	0
Il7R	0	0	0	0	0	0
Irf4	0	0	0	0	0	0
Irf6	0	2.58748455	0	0	3.59687181	0
Irf8	13.8990229	12.7012696	0.47691932	14.1636759	1.98646599	0
Kdr	0	0	0	0	0	0
Kit	11.4828646	10.9088944	12.3859747	13.5844173	11.2619077	12.5333324
Klf1	0	0	1.53786674	0	1.35001333	0
Klf12	0	0	0	0	0	0
Ldb1	11.6022208	12.5920203	10.6653308	12.5336097	11.495488	12.3066988
Lin28a	7.90392609	3.12320396	6.33237234	1.79305028	6.59839184	7.06652167
Lmo2	9.87792981	9.91993508	11.2848458	11.9924048	10.0290151	10.1483392
Ly6a	7.86019166	0	0	7.73891186	7.84163194	0
Lyl1	0	8.217674	9.1254904	9.44826214	8.82368626	8.22225726
Mbd2	12.0598914	12.2588426	11.112991	11.5901371	9.15035566	11.3382915
Meis1	0	0	4.25525076	7.0666261	0	0
Mllt3	0	0	0	0	0	0
Mpl	0	0	0	0	0	0
Muc13	6.21902111	6.09924564	10.3554653	9.73058449	0	9.36857432
Myb	12.6635861	11.8365941	14.2028029	14.5090875	13.301967	14.4078534
Myc	9.1352006	14.8322048	14.0818035	15.1689656	10.5951842	12.5380787
Mycn	5.64989123	0	0	0	0	0
Ndn	0	0	0	0	0	0
Nfat5	10.8366496	3.68452734	8.92920727	10.0449498	9.57236112	7.70240307
Nfia	8.66284129	9.64290212	8.28353384	0	0	0
Nfkb1	4.1409895	1.10789555	6.0665323	2.33679964	4.16758728	3.4944722

TABLE 6-6-continued

Single cell expression data (reduced list)-Control

Factor	GMP1	GMP2	GMP3	GMP4	GMP5	GMP6
Notch1	9.67689195	7.78055521	10.5333446	10.0774827	10.2196335	10.5378767
Pax4	0	2.69956228	4.5651786	0	0	0
Pax5	0	0	0	0	0	0
Pax9	0	0	0	0	0	0
Pbx1	0	0	0	1.84774739	0	0
PIk3ca	11.6583177	9.35235227	10.3476041	11.0004673	9.86525632	11.9782697
PIk3R2	10.3431352	9.62249368	9.03318404	11.2354698	0	9.21073238
Plag1	2.1446229	0	0	0	0	0
Prf1	0	0	0	0	0	0
Pten	11.4197765	9.13702301	10.7392588	12.0713175	10.7961825	11.0569877
Rb1	12.3671936	9.29319202	10.4219806	10.1129328	11.381463	10.889451
Rora	0	0	0	0	0	7.95341913
Runx1	13.783041	11.1039612	11.2727924	14.2307475	10.5352512	12.0416809
Runx2	5.65817302	5.03497789	4.41480127	5.28240362	5.90471616	6.86059385
Satb1	9.63218514	0	9.35749111	10.3868222	10.9890151	9.27731882
Sdpr	0	0	0	0	0	0
Sell	13.346662	14.2717617	11.4404307	12.6975062	10.7600258	10.916911
Sfpi1	12.9675055	11.9210703	12.4452889	13.2408628	11.6645721	12.6354578
Slamf1	0	0	0	0	0	0
Smarca4	12.6576943	11.1882941	13.3524008	13.9464355	12.5556067	12.548269
Sos1	8.75240526	4.47302434	9.76938074	9.21626024	5.77526698	8.46060551
Stat1	7.83159291	5.19471875	1.94245366	3.19107626	3.69538692	4.99541136
Stat3	9.94864616	8.03134798	12.2126573	12.2361408	12.6530163	11.4027843
Stat4	7.30783486	6.44025276	8.04438756	6.41767238	7.74175516	9.24847993
Stat6	11.4183952	7.63189419	11.402629	11.427093	11.1296225	11.0864028
Suz12	12.0645852	9.97123248	12.3070014	12.586926	11.1205885	11.9182639
Tal1	0	0	3.6852286	7.53257554	7.0164346	6.40585349
Tcf3	8.17529451	8.44265648	0.46728578	7.69609118	0.32105529	7.98262856
Tcf4	10.7240061	10.8374419	11.2234939	12.5413021	9.18774076	9.58716005
Tcf7	0	0	0	0	0	0
Tek	0	0	0	0	0	0
Tfrc	11.0749821	12.561574	12.1280736	13.583871	11.1008997	11.8397881
Tgfb1	6.27914163	9.26600463	9.08857843	9.47356083	4.49109661	0
Tgfb2	3.56183374	0	0	0	0	0
Tgfb3	0	0	5.7011227	0.46458839	8.34339661	0
Tnfrsf1a	12.297425	11.7846035	11.7957289	13.0383546	11.8629069	12.0139251
Tnfrsf1b	12.4247113	8.90867624	12.1885403	11.8433223	10.5206013	10.2570003
Tnfrsf21	7.44931949	6.46752449	7.14549464	7.31352162	7.9695614	7.76578158
Tnfsf10	0	1.68498558	6.44830699	5.74757111	6.17892222	0
Tnfsf12	0	0	0	0	0	0
Tob1	0	0	0	6.10049513	0	0
vWF	0	0	0	0	0	0
Zbtb20	0	0	0	8.30629918	0	0
Zbtb38	8.27537196	8.75347218	10.5074098	10.1488632	9.05482607	10.0593391
Zfp532	0	1.56494117	0	0	0	2.30677569
Zfp612	0	3.91554231	1.00265837	6.21466929	7.67481421	0.57219649
Zfpm1	0	0	0	5.38371259	0	0
Zhx2	0	6.85838682	0	3.16109771	8.51542476	0

TABLE 6-7

Single cell expression data (reduced list)-Control

Factor	GMP7	GMP8	GMP9	GMP10	HSC1	HSC2
Actb	16.9514796	17.399739	17.2637454	16.9850638	14.2167236	14.6194148
Aebp2	7.35505455	4.38592355	5.1807596	7.51562781	2.42975426	4.97605754
Ahr	0	8.88485487	10.3510122	0	0	0
Akt1	12.2492506	10.7788814	9.09878888	11.5407814	8.96092519	8.92881088
Akt2	7.07125847	6.57841965	5.05613909	8.09120983	0	5.44823903
Akt3	9.84112573	10.6234887	8.79800603	10.3335926	0	9.31021549
APC	0	0	8.16762557	8.43918267	0	0
Bad	0	0	0	0	0	0
Bax	11.0109809	11.0453066	9.34116544	11.9634436	7.34390449	8.34746535
Bcl11a	0	9.41212409	0	0	8.75277008	0
Bcl11b	0	0	0	1.88740222	0	0
Bcl2	0	0	0	8.52796043	5.87135064	0
Bcl211	9.44244435	10.1472452	0	11.1322976	8.66094346	9.94832245
Bcl2111	10.1673298	0	0	0	0	8.69198824
Bmi1	8.07353481	7.72482902	4.98516188	8.47434036	6.82657462	7.46085956

TABLE 6-7-continued

Single cell expression data (reduced list)-Control

Factor	GMP7	GMP8	GMP9	GMP10	HSC1	HSC2
Brd3	12.6394847	11.2028078	7.11480939	11.8951694	9.33404025	8.63333449
Casp8	11.8613695	9.99564976	9.21248114	11.5898934	0	8.6154989
Casp9	8.59054116	8.91150088	8.46508701	8.65641125	8.2106278	0
Cbx2	4.51981855	0	0	0	0	0
Cbx8	7.59923933	0	0	5.95563266	4.01892229	0
Ccnc	5.81056153	1.75012419	6.70114967	7.82322872	0	7.8085882
Ccnd1	11.5505776	0	10.1157016	9.71290948	0	8.62150748
Ccne2	11.303028	9.04842269	0	9.50031357	0	4.39863781
CD34	12.2237971	0	8.89631259	13.6407341	9.50379181	9.06540049
CD41	0	0	0	0	0	0
CD48	11.4659003	9.71355517	10.4133748	11.4910927	0	0
CD52	9.60985547	9.93196311	12.5022437	10.7028269	0	0
CD53	12.1131339	12.7875274	11.5957042	12.2029543	0	0
CD55	0	0	0	0	6.89471557	7.36408685
CD63	8.93841954	12.146554	0	5.48306679	9.19375582	7.65368115
CD9	0	10.1324772	7.67704046	0	7.8387743	0
Cdc42	14.4664142	14.2907989	14.0122499	15.0649621	11.9634665	12.0459978
Cdk1	11.3777802	8.11959637	0	12.7269855	0	0
Cdk4	12.784903	10.8753402	6.80400834	12.6121689	9.62020787	8.49447754
Cdkn2b	0	0.00701553	0	0	0	0
Cebpa	13.8746339	13.8824666	0	14.641417	0	8.06551113
Csf1r	11.5330216	3.88795501	7.38801037	12.5028245	0.17278247	0
Ctnnb1	8.77284547	8.15585683	7.63240721	9.49085314	7.84991528	6.63261919
Cycs	14.9720652	13.8929845	11.7488184	14.6315404	9.69074953	9.01652869
Dach1	10.0139282	11.094158	0	0	0	9.34452255
Dnmt1	13.8203577	13.062377	8.93180003	12.6151647	8.13040287	8.73259462
Dnmt3a	11.5907989	10.5082482	8.16704073	12.2259286	0	9.03600947
Dnmt3b	10.3460639	8.40852444	0	11.6532099	8.08118305	9.0180945
Dtx1	0	0	0	0	0	0
Dtx4	12.3828586	12.8400604	9.87791515	12.95339	0	0
Ebf1	0	0	0	0	0	0
Ep300	9.94498424	10.2010752	9.23583811	10.6282941	10.4403515	8.59444295
Epor	5.16793546	5.09166176	6.07340251	5.10546348	0	2.7151266
Erg	11.0543498	8.41211355	0	12.089156	10.1146713	11.7537883
Esr1	11.6199962	10.7508391	0	10.3804934	10.0633516	0
ETS1	0	11.8060427	0	2.87560829	10.507867	0
ETS2	0	8.07791161	2.28329408	0.76338635	0	8.47008891
Etv3	5.74740043	7.36604372	0	5.34860303	4.23394023	5.05619729
Etv6	12.9684077	11.0021541	9.73755797	13.9096409	3.98851235	10.7091763
Ezh2	11.2994093	9.96948763	8.77091516	11.243305	0	9.25661058
Fas	0	0	0	0	0	0
Fcgr2b	9.44038194	9.26444191	8.49671511	0	0	7.5507537
Fcgr3	8.9878976	11.2705376	0	7.10105394	0	2.57719687
Fli1	12.3237708	12.3248589	9.73909286	12.1105145	10.3593911	9.96450923
Flt3	12.2416095	0	12.2385762	12.4225757	0	7.96248373
Fosl1	0	0	0	8.07129215	0	0
Foxo1	11.0340434	9.06969139	10.1546488	12.3061817	9.40775249	10.5472402
Foxo3	9.90987077	7.70047424	0	11.2129013	10.4052826	9.57989143
Gapdh	14.3410656	13.3216214	6.17605235	13.0958987	9.71964182	8.2639086
Gata1	0	1.6059749	0	0	0	0
Gata2	4.56581362	0	0	3.24897579	5.55356347	6.52542185
Gata3	8.22656643	0	0	0	8.13700583	7.25082557
Gfi1	9.06056316	11.6538294	0	9.16221659	4.02040206	0
Gfi1b	0	0	0	0	0.25126544	0
Hes5	0	0	0	0	5.25748063	0
Hey1	0	0	0	0	0	0
Hlf	8.11935658	7.41139148	0	0	11.998899	13.3665089
Id2	0	9.73284535	11.8927611	0	0	0
Ifi203	10.9125767	1.56076385	10.965723	10.6623233	11.8059937	12.2738519
Ifi205	0	7.49013979	11.8971931	0	0	0
Ifitm1	9.61917406	0	0	11.9413193	13.1252834	12.4718304
Ikzf1	11.9046539	11.2671835	10.14486	12.5650158	8.82268993	9.28321375
Ikzf2	8.46869314	0	0	8.47986869	8.78289078	10.6878177
Il7R	0	0	0	0	0	0
Irf4	0	0	0	0	0	0
Irf6	4.12909642	2.27592361	0	0	5.77682646	0
Irf8	12.9456699	0	13.624962	13.7405608	0	0
Kdr	0	0	0	0	0	0
Kit	14.0868279	13.592776	11.2221993	14.0164883	12.0391773	12.8744425
Klf1	0	0	0	0	0	0
Klf12	2.66660298	0	0	6.20104085	0	7.38482289
Ldb1	12.285869	11.2819471	10.3063821	12.5631382	10.866794	10.6556867
Lin28a	5.33704681	6.88472231	6.51112264	2.23418642	0.05736793	4.0435655

TABLE 6-7-continued

Single cell expression data (reduced list)-Control

Factor	GMP7	GMP8	GMP9	GMP10	HSC1	HSC2
Lmo2	10.4881207	9.5635547	7.59010325	11.8118436	10.8803219	11.4475084
Ly6a	0	0	0	0	11.3195152	10.5870103
Lyl1	8.61035099	7.73468542	0	10.6447346	0	7.65003858
Mbd2	11.2505579	10.5919527	10.3145503	11.3020134	0	10.1428358
Meis1	4.34410862	0	0	7.55516029	8.67866413	9.02711955
Mllt3	0	0	0	0	7.12963107	2.87940553
Mpl	8.28694489	0	0	0	10.2778907	10.3627362
Muc13	8.74153092	9.29662392	0	11.121408	5.14911074	8.76580934
Myb	13.9147396	14.2812014	0	14.2295701	10.5024756	11.003359
Myc	13.6235281	13.0901273	9.58950863	15.1619084	10.3020722	9.29939524
Mycn	0	7.0328665	0	0	7.93226454	8.80500295
Ndn	0	0	0	0	9.24126109	0
Nfat5	9.56450436	10.5541109	5.24115849	7.8400374	7.82456966	9.32565577
Nfia	10.4800163	0	0	8.6877674	8.3554248	9.44711328
Nfkb1	4.11854617	4.55346432	4.3546122	6.00282408	5.32088492	4.27063216
Notch1	11.0427965	7.69294924	7.4684003	9.6813143	0	9.14014597
Pax4	0	0	0	0	0	0
Pax5	0	0	0	0	0	0
Pax9	0	0	0	0	0	0
Pbx1	0	2.41999393	0	4.60427348	0	0
PIk3ca	10.5133138	10.9351105	8.30194999	11.8682584	8.19933736	7.15189306
PIk3R2	10.800657	9.31109965	8.14508176	9.89144953	0	8.29464733
Plag1	0	0	0	0	8.62119125	8.41624245
Prf1	6.25999009	0	0	0	0	0
Pten	9.85373481	10.1046387	8.4375715	11.8662431	8.3775621	9.78100476
Rb1	11.4058642	10.524729	9.64537306	10.6398779	0	0
Rora	0	0	0	9.2194702	0	9.92254216
Runx1	12.5823583	11.612649	0	13.1810639	8.13980404	0
Runx2	6.07520491	4.62008078	3.85299235	8.15725883	5.48807374	4.3288158
Satb1	10.3473077	10.4586335	0	12.8507889	0	0
Sdpr	0	0	0	0	0	0
Sell	13.1615763	11.0919349	8.27837081	12.9352801	0	0
Sfpi1	12.2685432	12.3834981	11.8275651	12.5999867	9.7600535	0
Slamf1	0	0	0	0	0	0
Smarca4	13.9278719	12.4252093	11.4331679	14.0406109	10.7650413	10.4302513
Sos1	7.08440665	9.19453302	0	8.82410076	0	7.80818117
Stat1	7.33456058	8.62844753	3.26903654	4.37970726	2.44310501	2.24193334
Stat3	11.6046184	12.0058285	10.4937808	10.7199143	10.1332837	11.4837559
Stat4	9.89970671	8.7484529	0	10.0534291	7.14597799	8.52079622
Stat6	10.0340055	7.76884318	9.26899604	8.52011684	0	0
Suz12	12.1917303	10.6415578	0	11.4192066	0	10.1796014
Tal1	3.27202494	2.33635462	5.43421365	1.99510515	3.23551253	7.24054415
Tcf3	8.95886195	9.27584441	7.18949224	7.95247356	0	5.94183007
Tcf4	11.7535018	10.7218079	5.87396176	13.0570735	10.2194603	10.2598245
Tcf7	0	0	0	0	0	0
Tek	0	0	0	0	8.12191874	0
Tfrc	11.1276806	11.6773601	0	9.99135979	0	2.48510433
Tgfb1	8.59999451	7.86082222	0	7.41061996	0	0
Tgfb2	0	0	0	5.61040412	0	0
Tgfb3	0	1.64625868	0	0	8.66536386	0
Tnfrsf1a	12.1075835	11.7893286	10.2883436	12.9872996	9.70789834	10.0685048
Tnfrsf1b	11.1644655	10.6687255	0	10.8829595	0	8.01385336
Tnfrsf21	7.9588553	8.25912716	0	6.93837391	5.31291687	0
Tnfsf10	7.2217542	0	0	6.57504105	0	6.42935948
Tnfsf12	6.10886882	0	0	5.7030187	0	0
Tob1	4.89785115	0	4.30862997	1.32359285	1.07788382	0
vWF	0	0	0	0	0	6.1655458
Zbtb20	7.51328071	0	8.49995327	7.62054695	8.85871267	9.72768241
Zbtb38	9.44025595	10.3426011	7.11037442	10.7447144	8.87190914	8.84029249
Zfp532	0	0	0	0	0	0
Zfp612	0	5.18701551	7.05359804	3.11635926	0	5.7890343
Zfpm1	0	0	0	0	0	0
Zhx2	0	5.27170259	0	0	0	0

TABLE 6-8

Single cell expression data (reduced list)—Control

Factor	HSC3	HSC4	HSC5	HSC6	HSC7	HSC8
Actb	13.577974	14.0296483	14.1103469	15.5819895	15.4017467	14.5186085
Aebp2	6.10559528	5.88912085	4.6132596	6.72522268	6.54183737	6.53821191
Ahr	0	8.48413666	0	8.64794663	0	0
Akt1	5.7101674	8.39335711	8.11021366	10.2087847	8.77360611	9.23696389
Akt2	0	0	0	5.73394549	4.95527812	5.5482851
Akt3	8.79551486	1.55468933	8.24574153	9.13533117	9.22444783	8.23443739
APC	0	0	0	9.1544444	8.26372086	0
Bad	0	0	0	0	0	0
Bax	10.4587872	7.84637341	8.21704944	10.5910972	9.05419378	8.1433208
Bcl11a	0	0	0	0	0	8.71685996
Bcl11b	0	0	0	0	0	0
Bcl2	0	0	0	6.60286713	0	0
Bcl2l1	0	8.15463837	0	8.81750986	9.51798174	9.26348136
Bcl2l11	0	7.08014318	0	0	8.80771493	0
Bmi1	6.37303271	6.75760763	6.40723471	8.78539598	6.73467101	0
Brd3	8.10648223	9.12195615	0	10.313197	9.04032119	8.4172914
Casp8	8.60911844	8.67718647	8.08973581	8.8351678	8.29348209	10.4887846
Casp9	8.50198655	0	0	8.0906086	8.93408591	0
Cbx2	2.12580066	0	1.37858473	0	6.38626502	3.95391221
Cbx8	0	0	0	0	0	0
Ccnc	8.0612119	7.75585225	0	8.0425277	7.97210372	4.50082307
Ccnd1	0	9.44185728	0	10.806783	0	9.84865359
Ccne2	0	0	0	0	0	0
CD34	8.17751775	5.00363076	7.74656357	7.72536834	7.31850948	0
CD41	0	0	0	10.2838042	0	10.3942665
CD48	0	0	0	0	0	0
CD52	0	8.30090194	0	0	0	0
CD53	0	0	0	0	0	0
CD55	7.69179367	4.79347239	6.9936477	9.05205329	0	8.21658095
CD63	8.84869188	9.80818054	8.85251987	10.377284	8.91902336	8.99037439
CD9	7.96692234	7.15928214	7.1345801	8.5320473	3.5188154	8.2765401
Cdc42	11.8342425	11.274525	11.5477464	12.9667945	11.216272	12.9992851
Cdk1	0	0	1.70469042	9.19399937	0	8.58515514
Cdk4	6.80715808	7.17264944	2.02643408	11.1452163	9.41268282	6.45109978
Cdkn2b	0	0	0	0	0	0
Cebpa	8.66392034	0	8.58072977	6.63194812	0	0
Csf1r	0	0	8.74066681	1.70542256	7.47370204	0
Ctnnb1	6.45093961	6.80576451	7.03105301	8.66585445	4.63621377	6.42492055
Cycs	7.76931122	8.17385953	9.1062029	11.5938916	10.2963567	10.5610571
Dach1	8.32689948	9.6993744	0	10.5160163	11.5555411	12.1784951
Dnmt1	0	0	0	11.5088913	0	10.870094
Dnmt3a	10.0217648	11.1560578	9.24043447	10.2575566	10.2648603	12.1222467
Dnmt3b	0	0	0	8.90491552	0	9.12251996
Dtx1	3.63908589	0.2314944	3.28281301	0	0	1.84006193
Dtx4	0	0	0	0	1.19632544	0
Ebfl	0	0	0	0	0	0
Ep300	11.0845039	8.98243523	10.7104073	9.62872537	9.96024059	9.41340549
Epor	4.04169265	5.05457514	6.15980606	4.89038806	5.63286624	5.89050554
Erg	11.8077154	11.2396194	11.3083977	11.0154674	10.8697562	10.0863194
Esr1	8.38535842	0	9.45876416	0	8.20146951	9.59278249
ETS1	7.78767496	8.3813926	8.32316912	0	0	0
ETS2	0	5.54640271	0	9.236687	0	10.2058893
Etv3	1.54998505	6.21266641	4.23572008	6.55515366	0	3.67608709
Etv6	10.2492298	11.658684	11.1884801	12.4484167	10.2573908	11.513336
Ezh2	0	6.45902485	8.45850492	9.86622345	6.62197678	0
Fas	0	0	0	0	0	0
Fcgr2b	0	0	0	3.00096067	0	0
Fcgr3	0	0	0	0	0	0
Fli1	10.825293	10.3056342	10.1656639	12.7030871	9.81370266	10.7815026
Flt3	0	0	0	0	8.83959351	0
Fosl1	0	5.63779061	0	9.84241504	0	0
Foxo1	11.1098742	10.8687068	10.3544835	11.2304826	9.6589649	11.609313
Foxo3	8.96881644	9.34207286	0	10.574468	7.95875599	10.5612825
Gapdh	10.3938142	10.020788	9.78199569	11.7324163	11.2583198	10.2840324
Gata1	3.66598041	1.2604332	0	0	0	8.0389608
Gata2	4.10700961	5.22811433	6.14699434	5.75841883	6.0549266	5.76445634
Gata3	6.39172576	0	8.61417098	7.96956347	7.63953107	8.62787032
Gfi1	0	0	0	0	0	0
Gfi1b	10.6982479	8.35858247	0	9.76814181	0	9.06455865
Hes5	0	0	0	0	0	0
Hey1	2.14957956	0	0	5.41172737	3.30247516	0
Hlf	12.2869167	12.3244122	12.7023562	11.4515454	12.4604982	12.6666107
Id2	7.39149179	0	0	0	0	7.98972755

TABLE 6-8-continued

Single cell expression data (reduced list)—Control

Factor	HSC3	HSC4	HSC5	HSC6	HSC7	HSC8
Ifi203	12.5769615	12.1345502	12.0725801	11.3590361	12.2927044	11.1325428
Ifi205	0	0	0	0	0	0
Ifitm1	13.1901123	12.7092713	11.5835195	13.4449774	11.4136686	13.2554104
Ikzf1	9.7363741	9.85625177	0	10.250229	9.90890256	8.72152915
Ikzf2	10.2835862	9.22641485	0	8.77854263	0	7.21339614
Il7R	0	0	0	0	0	0
Irf4	0	0	0	0	0	0
Irf6	3.19293607	0	3.18045922	3.89301413	3.20245453	4.43165432
Irf8	0	7.94066203	0	0	7.94125807	2.2099363
Kdr	0	0	0	0	0	10.4341118
Kit	11.6075917	11.3831769	13.0210319	12.1707632	12.6193513	11.9124539
Klf1	0	0	0	0	0	0
K1f12	0	8.1606124	0	8.75728664	2.77952504	8.68882167
Ldb1	10.7018656	10.5501009	10.3395739	11.8108028	11.1819378	11.9298611
Lin28a	0	0.65022055	8.32375974	0	0	8.92276223
Lmo2	11.1260842	11.2055555	11.2304278	11.1718854	10.0919978	9.95604882
Ly6a	11.6807743	13.0059956	0	11.8972718	9.8150555	8.15846371
Lyl1	7.71114163	0	9.39299973	5.87215945	0	7.14723677
Mbd2	4.92840001	0	9.40592756	8.95643535	8.35525208	10.4778257
Meis1	9.33744894	7.24719639	8.11655673	9.24808657	9.02869584	8.20607406
Mllt3	4.39596095	0	0	4.84582581	2.28189221	1.22539492
Mpl	8.37937771	11.6344232	10.240321	9.1484092	9.92137235	11.7759292
Muc13	5.85943592	8.69171484	5.79478348	8.86606586	8.08439421	5.87402461
Myb	11.4543645	11.6634674	11.813638	12.4301573	11.6054666	10.9746986
Myc	0	9.07187777	10.4973302	12.1156989	11.1821332	0
Mycn	10.0040447	1.76067461	8.7209187	11.9081484	9.172818	13.4121675
Ndn	11.413717	0	0	11.1011159	8.47770715	0
Nfat5	8.80140323	8.27575413	8.94488444	10.4915077	7.87669831	8.9488905
Nfia	9.26039859	8.37576634	8.54427003	9.80432597	10.4688522	9.95162743
Nfkb1	4.28180114	1.0386031	0	4.30632205	4.27397363	0
Notch1	0	0	7.85740045	0	0	0
Pax4	0	0	0	0	0	0
Pax5	0	0	0	0.34067989	0	0
Pax9	0	0	0	0	0	0
Pbx1	0	0	0	0	0	0
PIk3ca	9.48126253	8.2821557	10.3094662	8.07275737	0	8.54082063
PIk3R2	0	0	9.46846214	8.95184962	0	0
Plag1	8.44717703	0	8.62974666	6.40451656	10.2884491	9.70437763
Prf1	0	0	0	0	3.42401778	0
Pten	9.35030834	5.62716649	8.59897884	8.41844617	9.21702967	8.85833533
Rb1	9.73808815	0	9.45856621	10.3613325	5.17427811	4.88975979
Rora	0	8.26236355	10.2950769	9.73645132	0	0
Runx1	9.69584379	8.40584267	10.6007548	0	10.9238866	8.69978638
Runx2	4.75896314	5.38267048	0	6.2671313	7.04999695	0
Satb1	9.80742018	0	0	8.57255153	0	0
Sdpr	0	0	0	0	0	3.04221011
Sell	0	0	0	0	0	0
Sfpi1	10.1339723	10.3780048	10.4866679	0	10.0355372	9.31766744
Slamf1	7.9591016	0	0	0	0	9.42150329
Smarca4	9.57780054	9.85977591	10.4104054	11.7238705	9.46298092	11.1339334
Sos1	0	8.2843901	0	7.22160003	7.53838311	7.29089291
Sta1	2.50659523	6.02858174	2.36927337	3.71643375	2.2740799	12.52689091
Stat3	8.29378181	10.7345608	9.55246631	10.8963074	10.3681668	8.97518786
Stat4	8.4227657	7.83127215	8.8192144	10.1874616	9.68055604	7.69477544
Stat6	0	10.5487746	9.40667371	9.72923693	9.87383314	9.84674959
Suz12	9.05894393	0	8.44467624	10.0115616	8.21144523	9.0031541
Tal1	0	3.75390852	0	7.11083842	5.49903472	3.85114596
Tcf3	0	0	0	0	3.17986266	4.49147102
Tcf4	10.6387202	9.81058079	10.1324014	10.7265873	9.19540096	11.280981
Tcf7	0	0	4.14707011	0	0	0
Tek	8.14772158	0	7.22964189	6.69314683	7.21296798	0
Tfrc	5.69240635	8.85266347	0	8.37463351	0	0
Tgfb1	0	0	0	0	7.01325075	0
Tgfb2	0	0	0	0	0	0
Tgfb3	0	0	0	0	5.62887852	0
Tnfrsf1a	9.20893254	7.99674932	8.49210484	9.09094768	8.72598965	8.95788173
Tnfrsf1b	10.4438284	0	8.3857973	3.73738697	8.30125396	0
Tnfrsf2l	4.92370115	6.91456141	5.18164833	6.87061679	0	5.73392501
Tnfsf10	0	0	7.01737198	4.03273131	0	5.00807925
Tnfsf12	0	0	0	0	0	0
Tob1	5.71122498	7.95080155	0	6.10121099	7.42164007	0
vWF	3.86680517	0	0	0	4.46829427	8.91506154
Zbtb20	8.16491305	7.28441527	7.64424277	3.60015575	8.29513002	8.35006537

TABLE 6-8-continued

Single cell expression data (reduced list)—Control

Factor	HSC3	HSC4	HSC5	HSC6	HSC7	HSC8
Zbtb38	0	7.67871493	9.19649825	8.51227823	9.98861231	7.66701854
Zfp532	0	4.08592807	3.77146991	4.36860224	0	2.64992417
Zfp612	5.04540623	1.29781735	6.43562895	1.81941986	0	5.71057878
Zfpm1	0	0	0	0	7.43302501	0
Zhx2	0	3.17433055	0	0	0	10.2241584

TABLE 6-9

Single cell expression data (reduced list)—Control

Factor	HSC9	HSC10	MEP1	MEP2	MEP3	MEP4
Actb	14.9725561	15.5430056	16.6739018	17.1798405	16.7754755	16.9120965
Aebp2	5.34272666	2.46759537	7.60291615	5.68775766	8.40647947	8.15032471
Ahr	0	0	0	0	0	0
Akt1	8.71552396	9.04361278	10.8964237	10.6593665	10.5554637	10.4625715
Akt2	1.6860339	0	5.40370098	7.79517803	7.18806974	6.57237902
Akt3	9.27378957	9.16410517	0	7.90778801	7.25351311	8.6899408
APC	0	0	0	0	0	8.92917564
Bad	0	0	0	0	0	0
Bax	9.57334173	9.01870701	13.1654553	12.6147597	11.6763189	11.8499785
Bcl11a	0	6.38030957	8.61622865	0	0	6.50601386
Bcl11b	0	0	0	3.99048372	0	0
Bcl2	6.53694296	5.97214969	0	0	0	0
Bcl2l1	10.5706275	2.81256542	0	9.90189687	7.93964747	0
Bcl2l11	0	0	11.4930521	9.68858479	11.1719166	11.744598
Bmi1	8.0356025	5.71483882	8.52931514	8.55595556	10.0673986	8.43810889
Brd3	11.4628865	8.46832128	11.0280089	11.2582907	10.1577315	11.3931352
Casp8	9.80815784	10.7239994	8.89508957	6.21772996	7.84127145	10.4709266
Casp9	0	0	5.82312549	10.5005325	10.3674251	10.8167842
Cbx2	2.20378454	5.19558249	5.96803494	4.9871259	0	1.36472366
Cbx8	0	0	0	0	0	0
Ccnc	7.14555417	9.54460991	9.10840098	7.7775943	9.69822219	10.7463612
Ccnd1	10.3147623	8.43483043	12.5806504	10.1616065	0	9.50499479
Ccne2	2.11634283	0	12.3632828	11.5458361	7.65370744	11.8196672
CD34	8.7300738	7.56097552	0	0	0	0
CD41	9.90770066	10.2820486	0	0	0	0
CD48	0	0	8.8519551	0	0	10.2839816
CD52	0	0	0	0	0	0
CD53	0	0	0	0	0	0
CD55	0	0	9.35100587	9.53334636	6.17916642	8.52837797
CD63	9.95525539	9.13287496	0	0	0	0
CD9	8.19006868	8.93484354	0	0	0	0
Cdc42	12.8484097	12.3557558	14.0139592	14.5300457	13.7188884	14.3827631
Cdk1	8.40315409	0	10.2066902	12.0503625	11.856245	10.4737341
Cdk4	9.36174345	9.55697505	12.4311347	12.9555662	12.0600059	13.2462207
Cdkn2b	0	0	0	7.13192772	0	0
Cebpa	0	0	4.83137386	0	6.06861889	0
Csf1r	0.78905294	5.76347829	7.35935898	0	0	0.43693507
Ctnnb1	6.91786038	7.30835446	9.09223561	9.17717471	8.27674053	9.66975154
Cycs	9.20845458	9.97537598	14.4833117	14.8868575	14.3632329	14.6822205
Dach1	11.8391027	11.4620792	0	8.08586478	0	8.85421269
Dnmt1	0	0	13.0436858	12.9585708	12.173667	12.6846992
Dnmt3a	10.6627832	10.9853226	0	0	8.14594383	11.3793103
Dnmt3b	8.4439035	7.87008545	9.13349446	10.0430891	0	8.58078692
Dtx1	0	0	0	0	0	0
Dtx4	0	8.77381733	0	3.59988975	0	0
Ebf1	0	0	0	0	0	0
Ep300	10.2826339	9.35773902	9.97912263	9.64315597	7.04223723	9.25408444
Epor	5.62014836	3.32438848	6.0772899	6.71011031	7.0106626	6.12830238
Erg	11.4258262	11.2053622	0	0	0	0
Esr1	9.13193309	9.35521874	0	0	0	0
ETS1	8.08986929	4.00036102	0	0	0	3.28475493
ETS2	8.93566794	8.12463187	8.26008629	7.11961974	8.01954074	9.00778633
Etv3	4.73179257	6.37769317	0	0	0	0
Etv6	10.868184	11.7795506	0	0	0	9.64836021
Ezh2	0	2.07633721	11.8577244	11.7699702	9.0854248	11.235091
Fas	0	0	0	0	0	0
Fcgr2b	0	0	0	0	0	0
Fcgr3	0	0	0	0	0	0

TABLE 6-9-continued

Single cell expression data (reduced list)—Control

Factor	HSC9	HSC10	MEP1	MEP2	MEP3	MEP4
Fli1	12.2531926	10.9251156	0	0	0	1.16488259
Flt3	0	0	0	0	0	0
Fosl1	0	0	0.29931482	9.04736396	0	0
Foxo1	9.01385813	10.4459955	5.73742257	0	0	9.36919814
Foxo3	8.79125674	8.68822067	9.68364766	10.649167	11.0869714	10.3601155
Gapdh	11.7285693	11.1757682	13.63523	13.4830598	13.1943802	11.9720384
Gata1	5.94283713	0	12.3245112	13.7649949	12.797531	13.2227802
Gata2	6.83304794	6.87340412	2.25249885	0	0	3.77741299
Gata3	9.24060916	9.14520142	0	0	0	0
Gfi1	3.34268315	0	0	0	0	4.24919213
Gfi1b	9.56101095	9.49767669	13.5283046	14.1818634	13.7733661	14.9174041
Hes5	0	0	0	2.29471695	0	0
Hey1	0	0	0	1.95932422	0	0
Hlf	12.1074683	11.9161928	0	0	0	0
Id2	0	0	0	0	0	0
Ifi203	12.278004	11.192533	0	0	0	0
Ifi205	0	0	0	0	0	0
Ifitm1	13.0046432	12.4025715	0.31225789	0	0	0
Ikzf1	9.53642019	0	12.6360198	12.9519677	12.6541472	12.6965722
Ikzf2	0	8.56779353	5.40027468	0	0	0
Il7R	0	0	0	0	0	0
Irf4	0	0	0	0	0	0
Irf6	4.10562562	0	0	0	0	0
Irf8	0	0	6.12370867	8.41676829	0	0
Kdr	0	0	0	0	0	0
Kit	12.3160333	9.89526777	12.0150326	9.98117872	11.4951247	12.8352736
Klf1	0	0	13.1692563	13.8873887	13.1692722	13.1308469
Klf12	9.72448024	0	0	0	0	7.34581981
Ldb1	12.4178652	11.01075	13.0390188	13.7874605	13.1564759	13.2168482
Lin28a	3.82329997	6.81496961	7.33729444	6.61281699	0	6.08888311
Lmo2	11.5637423	9.92019304	11.5030529	11.9384772	12.6434079	10.6947974
Ly6a	7.06884075	8.44508253	0	0	0	0
Lyl1	8.88014622	8.35784347	6.95117372	9.77435583	0	9.20859202
Mbd2	9.13439987	8.56907105	13.0509809	13.9543519	12.6665248	13.1243311
Meis1	9.80331618	8.1571184	0	0	0	0
Mllt3	4.15938546	0	4.12160509	7.79510244	0	4.48253793
Mpl	10.996255	9.44406546	0	0	0	0
Muc13	6.82422246	7.13195827	0	0	5.01336678	1.81337571
Myb	11.5244445	12.4461891	13.2111197	12.8071283	12.9764179	13.9759288
Myc	0	10.9160751	11.9866355	11.2429304	12.3999539	13.9029694
Mycn	14.4756491	11.6026038	0	0	0	0
Ndn	11.2837686	10.4369415	0	0	0	0
Nfat5	9.61855366	6.82014528	6.59682409	7.27479713	0	8.74499807
Nfia	9.41329393	10.6171397	13.5009826	14.0902354	12.9714138	13.0254549
Nfkb1	0	2.2519501	3.25804287	2.4908206	0	5.47964873
Notch1	8.12991025	0	0	0	0	0
Pax4	6.1516811	0	4.85665083	0	0	3.3619616
Pax5	0	0	0	0	0	0
Pax9	0	0	0	0	0	0
Pbx1	0	0	0	0	0	0
Plk3ca	9.25738741	8.96174345	10.7256565	10.8683249	9.65150968	11.2464339
PIk3R2	9.30544358	0	12.2128948	12.2784314	11.0187609	12.287832
Plagl	8.64324095	0	9.06569451	0	0	0
Prf1	0	0	0	6.84326582	0	0
Pten	9.60478178	9.6731031	10.2929626	10.3569939	10.4823987	9.95159857
Rb1	10.2970029	8.60735432	12.6978008	13.4211639	10.6504251	12.7561166
Rora	0	0	0	0	0	0
Runx1	10.1584718	9.33038616	10.7805682	8.07026179	0	9.37272993
Runx2	4.28423467	4.26402635	0	0	0	0
Satb1	0	0	0	0	0	0
Sdpr	4.32744503	1.7057899	0	0	0	0
Sell	0	0	0	0	0	0
Sfpi1	6.83682861	11.0545418	0	5.45218154	2.04252139	0
Slamf1	9.49023226	0	0	0	0	0
Smarca4	12.2973535	11.2507486	13.5426414	13.619892	12.1620756	12.8704926
Sos1	8.06475892	6.27720781	9.19936975	7.36566754	6.8048466	9.35683189
Stat1	4.52662558	0.99719233	2.64761229	4.45186216	3.7746722	7.81972053
Stat3	11.0439439	11.5366037	8.88331309	0	9.64846927	9.55859823
Stat4	9.34715798	6.79032745	6.31260327	0	0	0
Stat6	11.0298664	7.72102603	11.0611639	8.69939135	9.35073565	2.30375272
Suz12	9.21902863	9.76884858	13.4162816	13.3069763	12.1189393	12.8721225
Tal1	3.5749488	2.63840682	5.48831658	5.90135703	5.14302435	6.08051416
Tcf3	8.19970314	7.80579899	10.3443653	9.82695879	7.84599927	11.004031

TABLE 6-9-continued

Single cell expression data (reduced list)—Control

Factor	HSC9	HSC10	MEP1	MEP2	MEP3	MEP4
Tcf4	11.8040378	9.82961636	10.260851	11.3188496	11.2508544	11.653967
Tcf7	0	4.73697982	1.43010499	0	0	0
Tek	9.36503436	0	0	0	0	0
Tfrc	0	8.8168966	13.9704118	14.578062	12.3681007	13.856442
Tgfb1	0	5.44659661	0	6.89639764	0	7.19033201
Tgfb2	0	0	5.36997264	0	0	0
Tgfb3	8.5895152	11.83410769	0	0	0	0
Tnfrsf1a	11.0327854	10.3930716	0	0	0	9.18248017
Tnfrsf1b	8.64142351	8.04393607	0	0	0	0
Tnfrsf21	6.97043206	6.09809349	0	5.3555269	0	4.45599329
Tnfsf10	6.74936749	5.83080275	6.33722942	0	0	6.31492348
Tnfsf12	0	0	0	0	0	0
Tob1	5.23114212	0	7.58798007	0	8.41045357	8.34798458
vWF	8.26879091	5.5354592	3.98254277	0	0	0
Zbtb20	6.7194969	9.77047876	0	6.66889471	0	0
Zbtb38	9.66819933	8.29751972	10.3083101	9.74280335	8.68702379	10.8279681
Zfp532	0	0	3.7690821	2.38462111	0	4.07815427
Zfp612	6.99532728	0	0	0	0	6.43937583
Zfpm1	6.81923051	6.31482951	8.84469315	0	7.30319601	10.1270265
Zhx2	8.4994904	0	0	1.62381423	0	0

TABLE 6-10

Single cell expression data (reduced list)—Control

Factor	MEP5	MEP6	MEP7	MEP8	MEP9	MEP10
Actb	17.2576396	17.1978808	15.5072422	17.1016623	17.0883469	16.1373068
Aebp2	8.8914175	8.24109539	5.927731	8.12926334	6.58436041	7.2192823
Ahr	0	0	0	0	0	7.10578696
Akt1	11.6018488	11.5146864	4.42998334	11.601648	10.7522773	10.3129742
Akt2	7.900821	1.74602406	4.64739684	7.50740455	6.69059007	7.16770014
Akt3	0	7.96018226	0	7.35315614	2.17729258	7.80192128
APC	8.39335253	8.06797773	0	1.75142305	1.8927044	0
Bad	0	0	0	0	0	0
Bax	13.6760247	13.3176728	10.1228648	12.4537506	12.065459	11.730697
Bcl11a	0	0	0	0	2.71314006	0
Bcl11b	0	0	0	0	0	0
Bc12	0	0	0	5.96566948	0	0
Bcl2l1	8.42050716	8.5397273	8.24768464	7.86215744	7.9016606	7.95497919
Bcl2l11	12.229686	10.1662961	8.73177655	9.85270326	8.51815048	10.7405021
Bmi1	10.2387084	9.31396694	6.36310467	6.09634272	7.60876135	5.56419831
Brd3	12.1884423	11.3821336	9.16931971	11.5847665	10.3403875	11.440292
Casp8	9.45558864	9.60183486	0	8.96045034	9.60483639	9.81855927
Casp9	10.983114	11.2997749	4.1377792	3.19674834	10.6397827	5.83890378
Cbx2	3.91898214	6.93850275	2.68444976	5.77648185	4.81078818	5.84443483
Cbx8	0	0	0	0	0	0
Ccnc	10.1627738	9.76965727	1.35355046	10.8327556	10.2251453	8.87207477
Ccnd1	9.06711014	9.78697864	3.39014804	7.92433606	3.63100877	1.61547934
Ccne2	10.0835116	11.319821	3.31015618	11.1288883	10.1332622	10.1575498
CD34	0	0	0	0	2.43527288	0
CD41	0	0	0	0	0	0
CD48	7.9867099	4.18399936	9.74423407	0	4.67729616	10.3311682
CD52	0	0	11.240447	0	0	0
CD53	0	0	10.718297	0	0	3.47755329
CD55	8.72944056	7.02423588	0.47752312	7.30323746	8.24842184	6.71445599
CD63	0	0	0	0	0	8.48127545
CD9	0	0	9.11541164	0	0	0
Cdc42	14.5293724	14.6486438	12.7027151	14.5111753	13.888067	13.4366617
Cdk1	13.1448472	11.9598095	4.7963663	12.1075135	9.74103341	9.76908148
Cdk4	13.7494226	13.5258502	5.39347158	13.2132059	11.559049	12.3004943
Cdkn2b	0	7.45318318	2.03311382	0	0	0
Cebpa	0	0	1.93783554	4.65819114	0	5.14048555
Csf1r	0	0	1.18696511	7.77368454	0	4.57700679
Ctnnb1	9.37096958	9.83654035	7.40506371	9.20900353	8.84284741	8.21343097
Cycs	15.3928254	15.4217364	9.00426594	14.9998511	14.3770315	13.6916743
Dach1	10.0101828	8.37636957	1.87676967	8.46157503	8.37438306	10.2033785
Dnmt1	13.5752055	13.5629832	0	13.1496695	12.9313015	12.2958028
Dnmt3a	10.9466601	8.51255715	2.35640024	11.4731999	8.29952651	10.4041202
Dnmt3b	8.48193549	10.1968081	0	0	8.25040799	9.82871253

TABLE 6-10-continued

Single cell expression data (reduced list)—Control

Factor	MEP5	MEP6	MEP7	MEP8	MEP9	MEP10
Dtx1	2.92606728	0	0	0	0	0
Dtx4	0	7.82554643	4.92304422	0	0	0
Ebf1	0	0	0	0	0	4.67430018
Ep300	10.0634333	9.34942163	8.21967146	10.5762593	10.121413	8.87201287
Epor	7.16021518	6.62083976	4.26609394	6.51806867	5.52700029	6.09748073
Erg	0	0	0	0	0	5.68555987
Esr1	0	0	0	0	0	2.51533896
ETS1	3.76571695	0	13.1369479	0	0	6.54848086
ETS2	5.16493701	9.76053928	3.59712435	8.2969717	8.32663081	0
Etv3	5.60165087	4.73300606	0	3.87270615	3.64676519	5.18534646
Etv6	10.2693757	10.3333581	3.69074449	10.0372574	8.50609787	9.04344531
Ezh2	11.9461386	11.3539663	3.95203132	11.7590423	11.3908077	10.6007943
Fas	0	0	0	0	0	0
Fcgr2b	0	0	0	0	0	0.23425105
Fcgr3	0	0	8.07918835	1.52130196	0	0
Fli1	0	3.18894624	9.44502726	5.01815175	3.11865062	10.9846923
Flt3	0	0	0	0	0	0
Fosl1	3.90147912	9.28797126	0	8.52770733	0	8.71529532
Foxo1	10.1059327	9.46825613	9.87277386	9.5068882	6.79088829	9.52716774
Foxo3	11.880669	10.5592031	7.72876079	11.0684154	9.43154757	9.25402338
Gapdh	13.9931627	13.3857099	10.5346589	14.1082473	12.92779	11.113379
Gata1	13.6190358	13.9835206	5.62359022	13.9713491	12.5041093	12.511952
Gata2	3.92449227	2.84914463	0	1.01456852	0	6.83641959
Gata3	0	2.25413244	7.84794279	0	0	0
Gfi1	0	0	3.85434754	6.19324658	0.26378938	0
Gfi1b	13.6114909	13.5975417	5.17245225	13.9889482	13.039689	12.8606179
Hes5	0	0	0	0	0	0
Hey1	0	5.28516598	0	1.81677056	0	0
Hlf	0	0	0	0	0	9.91303577
Id2	0	0	11.4964505	0	0	0
Ifi203	0	0	11.6357055	0	7.02168865	6.48869747
Ifi205	0	0.48785466	0	0	0	0.04446014
Ifitm1	0	0	0	3.39877768	0	0
Ikzf1	14.3275555	14.0316022	9.42911846	13.1119643	12.6313804	12.3162902
Ikzf2	5.2858744	0	0	0	4.28650806	10.7927559
Il7R	0	0	0	0	0	0
Irf4	0	0	0	0	0	3.75675557
Irf6	4.47123029	3.22821179	4.339607	1.36832553	0	0
Irf8	3.37099886	2.31508294	0	6.44379002	0	0
Kdr	0	0	0	0	0	0
Kit	13.3537238	12.8580221	11.7556361	11.3366407	12.6638144	13.3561223
Klf1	14.2979136	13.6308232	5.96653235	13.5935874	12.7713044	12.127983
Klf12	3.98365645	0	0	0	0	0
Ldb1	14.5635445	14.0908295	8.35195984	14.3971418	13.093488	13.9731006
Lin28a	4.24471852	6.991793	0	6.53901741	3.59537839	7.3031128
Lmo2	12.9830675	12.5177653	4.67072022	12.0390668	11.5425664	10.1528281
Ly6a	0	0	0	0	0	0
Lyl1	8.76148245	9.87461972	0	8.97801904	1.61425898	0
Mbd2	14.3088686	14.1788793	10.6850909	13.7604538	13.6786771	12.4484023
Meis1	0	0	0	0	0	0
Mllt3	6.75437066	4.87929073	0.36628079	7.04238465	1.04227285	0
Mpl	0	0	0	0	7.82872486	0
Muc13	6.50258482	9.17003155	2.94436572	6.93025842	0	8.96811757
Myb	14.5775089	14.3566219	6.22959734	13.1602938	13.678872	15.059386
Myc	14.0547532	13.3673906	5.6369054	14.4815067	12.1006266	13.6012191
Mycn	0	0	5.97826269	0	0	0
Ndn	0	0	0	3.30758821	0	4.50321309
Nfat5	6.8997464	8.60819523	8.05163374	9.06664427	5.40897018	6.6641746
Nfia	14.4761658	14.140814	5.89547833	14.0665307	13.4354033	12.1410189
Nfkb1	5.0181859	2.309416	3.98387116	4.10351957	4.95579258	0
Notch1	0	0	0	0	0	0
Pax4	0	0	0	0	0	0
Pax5	0	0	0	0	0	0.97924165
Pax9	0	0	0	5.83889268	0	0
Pbx1	0	0	0	0	0	0
PIk3ca	11.0496351	11.3740226	8.25771166	9.9484021	8.3447194	0
PIk3R2	13.0336384	11.9086806	4.45143877	12.6406896	12.5663171	10.6748968
Plag1	0	0	0	8.62527154	8.27129457	0
Prf1	0	0	7.95861297	0	5.64429588	0
Pten	10.8777303	10.2906901	8.05284894	10.7251068	10.0886075	10.5809166
Rb1	13.3531695	12.8920186	8.68520402	12.4552038	12.5020608	11.9804354
Rora	0	0	0	0	0	0
Runx1	10.3327309	10.1695965	2.15987744	8.22784853	8.33584994	8.47230462

TABLE 6-10-continued

Single cell expression data (reduced list)—Control

Factor	MEP5	MEP6	MEP7	MEP8	MEP9	MEP10
Runx2	4.49773995	0	0	3.58458245	0	0
Satb1	0	0	8.06753085	0	0	2.71209422
Sdpr	0	0.18954202	0	0	0	0
Sell	0	7.67225672	9.98123205	0	0	0
Sfpi1	0	0	0	0.46212458	0	8.14790234
Slamf1	0	0	0	0	0	0
Smarca4	14.0639422	13.68311	5.6018656	13.0990363	13.3134848	12.9739128
Sos1	9.61043591	9.24302377	0.84637826	9.30907613	8.92422084	9.07163316
Stat1	5.06501781	7.57488158	2.81371618	2.88085862	1.86966235	1.68793237
Stat3	6.91429151	7.407193	8.67732684	7.75419499	8.30889661	10.0828057
Stat4	0	0	8.79727168	0	1.92039891	0
Stat6	10.7036377	10.9195918	7.52472475	9.55035514	8.28177793	10.9191881
Suz12	13.538197	13.0876648	8.23876575	13.2750979	12.6890707	11.8669775
Tal1	5.4291009	6.69589556	0	7.56623027	4.77147026	4.69263937
Tcf3	10.9470082	10.4293296	0	10.598365	9.91291781	2.59346866
Tcf4	11.9008105	11.8187116	7.59295834	11.3626835	10.2619576	10.2854661
Tcf7	0	0.93440846	6.96284694	0	0	0
Tek	5.48770868	0	0	7.34302092	0.55382256	0
Tfrc	15.1003637	14.1185956	6.68189103	13.6781033	14.0561821	11.5817117
Tgfb1	0	5.9321715	3.29941964	6.77315808	8.10258704	0
Tgfb2	0	0	0	0	0	0
Tgfb3	0	0	0	8.05286418	2.7676147	0
Tnfrsf1a	0	0	9.44208849	0	0	7.52151547
Tnfrsf1b	0	7.33777528	8.96218157	0	4.27782113	0
Tnfrsf21	0	5.97030087	1.15224807	4.81031941	3.82725759	5.22821771
Tnfsf10	0	0	7.50776293	6.28059236	0	0.19985742
Tnfsf12	0	0	0	0	0	0
Tob1	7.49341793	9.775516	4.53888952	7.30658141	5.12736672	0
vWF	4.76480777	5.8950733	0	0	0	0
Zbtb20	7.31711148	6.7543605	6.09700763	0	0	3.99093784
Zbtb38	10.5208922	8.98561327	8.24763973	10.833188	9.72578991	9.49544458
Zfp532	0	0	0	0	0	0
Zfp612	2.66699095	0	5.65730748	3.15028498	0	0
Zfpm1	9.91367246	8.38424838	0	7.63005335	5.88946627	8.04762332
Zhx2	8.58545196	0	6.98674013	9.3468461	5.30923464	9.33665392

TABLE 6-11

Single cell expression data (reduced list)—Control

Factor	MPP1	MPP2	MPP3	MPP4	MPP5	MPP6
Actb	15.9338457	15.4232208	16.2711873	14.6823	14.2918152	15.8659118
Aebp2	7.21100476	5.2867401	6.93025793	5.90925673	5.25462477	9.18427092
Ahr	0	0	8.34801326	0	0	0
Akt1	10.720231	9.40876898	11.0220046	9.04411511	9.0996424	11.2217446
Akt2	2.21487307	5.4868309	0	0	5.35510644	0
Akt3	8.87303458	8.64995993	8.90809022	8.03436457	0	10.0275887
APC	9.11114608	0	8.0871966	1.98598274	8.73132197	4.78295182
Bad	0	0	0	0	0	8.89131665
Bax	8.98329445	10.498022	9.02157645	9.45119586	0	9.14566934
Bcl11a	0	0	0	8.89978638	0	8.82676654
Bcl11b	0	0	0	0	0	0
Bcl2	5.4456877	6.76850037	8.56326925	0	0	6.41872246
Bcl2l1	8.77442328	9.4903021	8.32482213	8.37825811	0	9.68984903
Bcl2l11	8.65261883	0	8.55329576	0	0	0
Bmi1	7.92005647	8.96348283	7.6988806	5.99607904	8.09101102	10.2547476
Brd3	11.0992941	10.6513546	9.61291134	9.43861553	6.3757271	10.8237539
Casp8	11.3348993	11.0515753	10.9825524	9.29875931	8.5871616	10.8985747
Casp9	8.73428375	10.0497654	0	0	0	2.43946663
Cbx2	7.57992406	6.71714066	0	0	0	0.6708544
Cbx8	0	0	0	0	0	0
Ccnc	8.35164492	0	6.07511496	9.13555725	0	7.33770601
Ccnd1	8.60823223	0	9.93021361	0	9.80132789	8.95924036
Ccne2	7.6057764	10.4324496	10.1697513	7.75985448	0	10.6399418
CD34	11.1537947	12.1750274	11.4199898	10.0501247	10.5540352	11.3151543
CD41	0	5.28178356	0	0	0	0
CD48	9.48857003	11.0978106	11.3892976	8.80517983	0	9.56184962
CD52	9.67070973	9.66597181	10.8936843	7.05264794	7.44343937	10.2105126
CD53	11.1467937	11.241697	10.1035022	11.4194355	0	11.4433546

TABLE 6-11-continued

Single cell expression data (reduced list)—Control						
Factor	MPP1	MPP2	MPP3	MPP4	MPP5	MPP6
CD55	0	0	0	0	0	0
CD63	6.93667918	10.6830361	7.91059718	7.48471238	4.0814483	0
CD9	0	0	0	9.13917551	0	0
Cdc42	13.4222253	12.5348596	13.56969	12.3378718	11.7636509	12.8887671
Cdk1	10.9643801	11.4007291	9.70754751	0	0	10.4661432
Cdk4	11.8074379	10.3164272	12.5018024	9.48804452	6.81583478	11.7800185
Cdkn2b	0	0	2.77346992	0	0	0
Cebpa	9.22772932	10.0275028	11.2952199	11.0642013	9.09418965	10.4493234
Csf1r	0	8.45310432	8.99182682	7.91613811	10.0723015	0
Ctnnb1	8.32067527	5.00574303	8.39061689	8.19898063	4.79592084	8.46222031
Cycs	13.0347923	12.4656213	14.3162078	9.98439188	9.65986044	12.6497946
Dach1	0	13.3892767	0	7.3947807	9.10470453	0
Dnmt1	12.8259216	12.6055461	12.7124172	10.1043631	0	12.0574902
Dnmt3a	11.5381376	7.80820219	11.1160495	10.4359516	9.17576912	10.796858
Dnmt3b	10.7508563	11.1492963	9.71848489	10.1049899	8.03011401	10.8681675
Dtx1	0	0	0.31107154	0	0	0
Dtx4	11.1069971	7.43011153	12.4091038	0	0	0
Ebf1	0	0	0	0	0	0
Ep300	8.75076257	8.59075653	9.62468843	9.68032474	9.58816102	8.39625294
Epor	4.91252317	3.1681373	2.6614969	0	3.60216649	0
Erg	9.15107944	12.1140199	10.0602319	8.05974652	9.1838276	7.70552462
Esr1	11.9774405	8.93512079	9.30574164	10.8765411	0	10.0872926
ETS1	10.5968066	10.5087649	0	8.1786786	0	10.9157853
ETS2	8.80623923	5.91625835	6.07444663	8.44682963	1.07952469	8.81372256
Etv3	5.042175	0	6.17334389	5.48927278	0	4.47456273
Etv6	11.2690271	11.8468993	10.1410346	10.3082532	10.7932873	11.5654449
Ezh2	10.9805883	10.1182621	9.56833692	8.93691074	5.75295828	11.0075626
Fas	0	0	0	0	0	0
Fcgr2b	0	0	7.59523747	0	0	0
Fcgr3	0	0	0	0	0	0
Fli1	10.0608425	11.8155209	11.4638535	11.1403327	11.1245373	11.1412932
Flt3	13.4713208	10.9848512	12.2344582	12.3865902	11.8521808	13.8892265
Fosl1	9.53355426	0	0	0	0	0
Foxo1	10.3135469	10.291036	8.38726315	8.71085607	9.18316568	10.070319
Foxo3	8.99316696	10.5108484	7.44733165	8.87606497	8.84685185	10.0201581
Gapdh	11.6345343	12.8310252	11.770259	9.91293629	9.88727626	10.8114969
Gata1	0	0	0	5.30872103	0	0
Gata2	0	6.25587723	0	0	0	5.46348074
Gata3	8.22743301	6.73112619	0	7.17096276	7.71368531	0
Gfi1	7.2915492	8.85268611	0	0	8.61482142	8.29984645
Gfi1b	0	10.9458698	7.94961583	0	0	9.2539235
Hes5	0	0	0	0	0	0
Hey1	0	0	0	0	0	0
Hlf	11.6107089	11.3506889	8.23973525	11.1220263	12.3616717	9.67605941
Id2	0	0	0	3.01634284	0	0
Ifi203	12.2933836	13.4311987	12.3810812	11.2387169	11.1057026	13.854702
Ifi205	1.46825299	0	0	0	0	0
Ifitm1	10.3158671	12.2548019	1.80612474	9.53491036	11.6097006	10.8254147
Ikzf1	12.2449774	10.9137692	11.8885062	9.44640906	10.0772827	11.7883861
Ikzf2	8.72612533	10.5247685	0	9.54996851	9.19777951	0
Il7R	0	0	0	0	0	0
Irf4	8.88932449	0	0	0	0	0
Irf6	0	2.28451212	3.12345728	0	2.94453997	7.03646954
Irf8	10.1140031	9.69303494	12.6201361	0	0	7.96421851
Kdr	0	0	0	0	0	0
Kit	10.3323157	13.290097	10.3759975	11.6752403	11.4546255	9.73802765
Klf1	0	0	0	0	0	0
K1f12	0	7.5771355	0	0	0	0
Ldb1	11.7920145	11.5152136	11.7984669	10.9682206	10.6778344	11.0742708
Lin28a	7.77696226	2.72948667	3.67493945	7.0652472	9.08749361	0
Lmo2	10.6837852	10.8046961	10.6266379	10.9303176	10.719542	11.3314271
Ly6a	11.5474621	10.2394989	7.73593565	8.32586298	10.6491694	9.60404877
Lyl1	8.11242278	0	10.1020158	0	0	8.83335686
Mbd2	10.0753161	10.3506985	11.4298385	9.11525309	10.5529714	10.6747769
Meis1	8.19052316	9.67159559	6.53658539	0	9.3704605	8.58771639
Mllt3	0	7.01032363	0	0	0	0
Mpl	0	11.6188289	0	0	0	0
Muc13	9.18176099	10.7974567	0	10.159424	0	0
Myb	13.8600806	13.3102917	13.8966992	11.8930023	12.3157054	12.0374473
Myc	12.4572692	12.7756443	13.0591357	10.6719002	0	11.658761
Mycn	4.48759571	12.0648986	7.88422472	10.1149438	10.4601304	12.3658929
Ndn	0	8.73723256	0	0	0	9.05565846
Nfat5	9.23389178	8.43831408	5.08317626	7.08881328	7.14783983	9.11031201

TABLE 6-11-continued

Single cell expression data (reduced list)—Control

Factor	MPP1	MPP2	MPP3	MPP4	MPP5	MPP6
Nfia	8.22536613	10.3181464	0	0	0	0
Nfkb1	0	4.25773876	6.36053701	6.28335202	0	0
Notch1	10.5411213	0	10.0596251	9.15986762	7.79669562	10.5613034
Pax4	0	0	0	0	0	0
Pax5	0	0	0	0	0	0
Pax9	0	4.39855399	0	0	7.47812976	0
Pbx1	0	0	3.98886737	0	0	0
PIk3ca	9.98779925	8.66693277	8.36771159	8.07241137	8.11823529	10.7576739
PIk3R2	0	8.41914228	11.2909208	9.22643964	0	10.8038558
Plag1	8.91111651	0	0	0	0	0
Prf1	0	0	0	0	0	0
Pten	9.73746823	8.52844961	10.3610336	9.7554549	8.9576986	9.39466925
Rb1	10.56726	11.135636	10.6281849	9.77464462	9.64300093	8.52928352
Rora	0	0	0	0	8.95379549	0
Runx1	0	7.57506234	11.3878361	9.64485117	0	8.01381659
Runx2	8.01374944	6.92871391	8.2119077	5.88438904	6.41322446	7.86904824
Satb1	12.19321	9.07418197	12.4338909	11.4331637	8.41406481	11.7354143
Sdpr	0	0	0	0	0	0
Sell	0	11.4107566	11.5576376	0	0	9.39436203
Sfpi1	10.4751592	10.2858722	10.7956608	10.7612319	8.28792429	9.65907002
Slamf1	0	0	0	0	0	0
Smarca4	13.0055606	11.8353641	12.3437472	11.4881732	11.951662	11.9434175
Sos1	2.66805577	7.04399519	7.54270055	7.21891711	7.15270243	6.4810902
Stat1	3.79515281	3.7506045	2.42604397	7.25585273	2.19651358	5.20779754
Stat3	0	7.35454462	0	11.4070872	9.90639954	0
Stat4	8.61934296	8.48689909	0	7.19354193	6.92208828	8.11912795
Stat6	8.38514449	9.97948225	10.91246	10.0950254	10.3501987	11.7262422
Suz12	12.1314037	11.5904284	12.2840569	10.4055215	6.87697186	12.3236445
Tal1	0	5.08496506	2.73114378	0	7.48698209	0
Tcf3	6.67565349	8.31215232	2.15386392	0	0	8.29747218
Tcf4	11.1250971	9.46376933	11.7038871	11.1179238	9.78786393	11.7491444
Tcf7	0	0	0	0	0	0
Tek	0	9.20065767	0	0	0	0
Tfrc	11.1514151	9.64401783	12.0859674	9.26164167	0	10.1615771
Tgfb1	0	0	7.66944594	0	0	7.04752663
Tgfb2	0	0	0	0	0	0
Tgfb3	0	0	0	0	0	0
Tnfrsf1a	10.4658528	3.19243814	1.74940044	9.34788925	9.69155039	8.79792759
Tnfrsf1b	9.13020949	8.49093408	9.13944664	0	5.57625399	0
Tnfrsf2l	6.50412724	7.08061356	6.13813065	6.59804131	5.91417667	6.16646549
Tnfsf10	0.19476122	0	0	0	6.29693535	7.28794504
Tnfsf12	0	0	0	0	0	0
Tob1	0	0	0	5.53534788	6.34080934	0
vWF	0	0	0	0	0	0
Zbtb20	7.26349348	7.01562217	0	0	7.96980448	9.33850376
Zbtb38	6.57611355	10.1472497	8.96566992	7.6851333	8.72294732	7.63005742
Zfp532	3.74373752	0	0	0	0	0
Zfp612	0	7.24390911	0	0	5.76142983	0
Zfpm1	4.4433929	4.77658905	4.37031599	6.57885334	4.4872645	5.50679362
Zhx2	0	0	0	0	0	0

TABLE 6-12

Single cell expression data (reduced list)-Control

Factor	MPP7	MPP8	MPP9	MPP10
Actb	15.5799561	16.4231342	14.9413529	16.4806567
Aebp2	4.74041619	5.79768478	4.60544211	5.70833163
Ahr	0	0	0	0
Akt1	8.28402993	10.5440223	8.94826142	10.0634546
Akt2	0	0	0	5.73559526
Akt3	9.55466835	7.76861222	7.22498152	9.10794373
APC	0	0	3.09166097	7.5684068
Bad	0	0	0	0
Bax	7.56956863	10.0339298	9.18437556	10.0584079
Bcl11a	0	8.73822897	0	0
Bcl11b	0	0	0	0
Bcl2	0	6.49304714	0	0
Bcl2l1	0	9.34594529	0	9.25723428

TABLE 6-12-continued

Single cell expression data (reduced list)-Control				
Factor	MPP7	MPP8	MPP9	MPP10
Bcl2l11	0	8.61453833	8.08425995	9.37832844
Bmi1	0	8.32976055	8.25021212	7.88080894
Brd3	9.25530682	11.2819662	8.12620738	10.4587875
Casp8	10.6378139	11.1806726	10.2895215	11.39495
Casp9	0	0	0	0.01340377
Cbx2	6.79558984	8.59803667	7.0009243	8.51339363
Cbx8	0	0	0	0
Ccnc	0	9.44435886	0	9.60093989
Ccnd1	0	9.91482334	8.70488465	9.74960081
Ccne2	8.92637293	10.6434763	0	11.3631899
CD34	10.913548	11.4119115	10.4402497	11.0324695
CD41	0	8.7488255	0	0
CD48	9.32813788	11.6576097	3.44806841	10.543773
CD52	9.61936432	8.73437329	8.14742149	10.7452684
CD53	11.2776098	11.1779516	9.29476445	11.5298596
CD55	0	0	0	0
CD63	0	7.40996888	7.37062015	0
CD9	0	0	0	0
Cdc42	13.2349309	13.2478421	11.8304766	13.479261
Cdk1	3.55141534	10.9443851	7.01908412	0
Cdk4	10.9902569	12.2074899	10.5113998	11.5285061
Cdkn2b	0	0	0	0
Cebpa	9.95273834	9.17238843	9.49773051	10.1225975
Csf1r	9.04324667	0.80192533	7.08749126	10.0144786
Ctnnb1	5.98292685	8.32930377	7.13625717	8.62467592
Cycs	11.4299521	13.7723272	10.3832219	13.3171266
Dach1	0	0	0	0
Dnmt1	11.4993032	13.0255564	11.8407164	12.2146515
Dnmt3a	10.7606522	10.2684942	8.39313135	11.1114075
Dnmt3b	7.92873762	10.0182754	10.504402	10.6600185
Dtx1	0	4.7728077	0	0
Dtx4	11.6922822	0	0	10.7071
Ebf1	0	0	0	0
Ep300	9.37108183	9.81215211	7.97358115	9.71578584
Epor	4.28849905	5.02706212	5.93378806	2.52024536
Erg	11.0872096	10.9417369	12.2901755	10.555884
Esr1	11.6554563	8.57331038	9.75278719	10.1047334
ETS1	11.9723848	3.46036603	3.47419373	11.9193271
ETS2	8.55484649	0	0	1.48502139
Etv3	6.2991095	3.863445	5.31929463	3.86067028
Etv6	9.37003784	11.6844245	12.2546514	11.8922382
Ezh2	8.86828602	10.9599669	8.96305659	10.2990075
Fas	0	0	0	0
Fcgr2b	0	6.76599483	0	5.22192452
Fcgr3	0	0	0	0
Fli1	11.8629795	11.3479034	10.9761779	11.4859541
Flt3	13.2221419	13.2364137	12.1561632	13.2561177
Fosl1	0	0	0	0
Foxo1	10.1123954	10.2137253	10.6020045	10.7842805
Foxo3	5.59015224	9.10555731	11.3588563	10.8953427
Gapdh	11.0477044	13.1655109	11.4008552	13.1404894
Gata1	0.94564173	0	0	0
Gata2	3.65013785	3.51256127	5.2315933	0
Gata3	1.39088214	6.3891916	0	0
Gfi1	8.84634557	6.27872603	6.48893372	0
Gfi1b	0	8.82811597	10.2832164	9.20982917
Hes5	4.64107681	0	6.957973	0
Hey1	0	0	0	0
Hlf	0	9.33667569	11.9867391	9.23572861
Id2	0	8.21997193	0	4.79088829
Ifi203	13.6649212	12.9454442	12.6378994	13.2045669
Ifi205	0	0	0	0
Ifitm1	0	11.8326933	9.99492608	8.92490776
Ikzf1	12.3564729	11.2597407	11.3032006	10.227332
Ikzf2	10.0349533	9.92808204	8.40270492	0
Il7R	8.47052626	0	0	4.98728556
Irf4	0	0	0	0
Irf6	0	0	0	0
Irf8	8.35824062	10.9054686	0	11.9512698
Kdr	0	0	0	0
Kit	10.6608131	11.4159407	11.8825308	10.6648273
Klf1	0	6.3799233	0	0
Klf12	0	0	0	0

TABLE 6-12-continued

Single cell expression data (reduced list)-Control

Factor	MPP7	MPP8	MPP9	MPP10
Ldb1	11.0037537	10.768767	11.3221586	11.5395242
Lin28a	0	0	8.71671372	8.10538829
Lmo2	9.8811249	11.1975103	11.572644	10.6241439
Ly6a	10.5512136	8.03714344	10.4350633	10.3456629
Lyl1	9.23026917	7.59193214	0	9.49619226
Mbd2	11.6682738	11.3388742	10.0098962	10.6943395
Meis1	6.79368245	8.42564079	8.98994745	7.80483069
Mllt3	0	0	0	0
Mpl	0	0	9.17845367	0
Muc13	0	9.30164297	7.01923521	0
Myb	13.4971968	13.3599043	12.082765	13.8765431
Myc	11.6030817	12.0932166	8.10743215	11.4606205
Mycn	8.2487794	0	10.0709306	0
Ndn	0	0	10.0775359	0
Nfat5	7.09690528	8.60254985	7.31614621	7.43938448
Nfia	0	0	10.937255	0
Nfkb1	3.83053939	4.11240597	5.24127431	3.64341386
Notch1	11.1593775	8.27953256	7.48014451	9.14338513
Pax4	0	0	0	0
Pax5	0	0	0	0
Pax9	0	0	0	0
Pbx1	0	4.9309508	0	0
PIk3ca	8.96893649	10.6627449	8.54724566	9.22944916
PIk3R2	8.65643169	11.8510785	10.1724212	0
Plag1	0	0	0	0
Prf1	0	0	0	0
Pten	8.25469691	9.67626184	6.97446432	9.5307241
Rb1	9.59233164	11.5007352	9.77688089	11.1455471
Rora	0	0	8.65726707	0
Runx1	0	10.0522268	8.31416339	9.56394879
Runx2	7.48955293	5.94137868	5.7987657	7.28443718
Satb1	12.4017526	9.90535075	7.60722496	12.7657794
Sdpr	0	0	0	0
Sell	11.5341189	11.4001825	9.51107337	9.17958828
Sfpi1	9.55284835	10.8357053	8.89491205	10.3685731
Slamf1	0	0	0	0
Smarca4	12.3428509	13.5642625	10.6464189	11.9223443
Sos1	8.19189077	0	7.3490338	8.77541216
Stat1	4.94305767	3.60841055	0	6.83329035
Stat3	9.23352711	10.6650348	11.2676229	0
Stat4	9.73904725	9.11900076	8.47015672	7.05959532
Stat6	9.78343857	10.2042159	9.87121731	10.0443104
Suz12	10.3249963	12.0359278	10.0398783	11.7614625
Tal1	0	0	8.600419	7.76085711
Tcf3	8.03699653	5.45181491	9.06930734	0
Tcf4	11.8413493	11.1111843	9.69541167	12.2817037
Tcf7	0	0	0	6.54941349
Tek	0	0	0	0
Tfrc	10.6830	9029.59395121	0	10.8582641
Tgfb1	0	8.23296021	0	0
Tgfb2	0	0	0	0
Tgfb3	0	0	0	0
Tnfrsf1a	8.68589512	10.7994818	0	9.35978037
Tnfrsf1b	7.9316098	8.07814768	0	2.48402645
Tnfrsf21	5.70122301	7.82568809	6.38571982	6.05359643
Tnfsf10	4.37639922	6.48140769	0	0
Tnfsf12	0	0	0	0
Tob1	9.18275412	0	5.06745741	5.90038553
vWF	0	0	0	0
Zbtb20	10.0142217	8.86759709	9.14684532	6.41102139
Zbtb38	8.26590238	9.71780996	10.6136333	8.51332267
Zfp532	3.78349621	0	4.01404165	4.28805397
Zfp612	6.67634499	0	0	0
Zfpm1	0	6.52079531	0	0
Zhx2	0	8.45764455	7.05698459	0

TABLE 7-1

Single cell expression data (reduced list)—iHSC-8-TF

Factor	iHSC-8-TF1	iHSC-8-TF2	iHSC-8-TF3	iHSC-8-TF4	iHSC-8-TF5	iHSC-8-TF6
Actb	15.3406135	15.3198955	12.6214841	13.9265913	14.907027	15.0828458
Aebp2	5.851253	6.91015329	6.18045816	6.13677942	6.31619136	6.55729075
Ahr	0	0	0	0	0	0
Akt1	10.3432926	10.2118447	8.44749976	8.43295768	11.0465135	11.5937761
Akt2	3.80481193	4.13073296	3.84759163	4.37730874	4.24877633	0
Akt3	6.26062374	5.80767709	0	6.66877618	0	7.28666292
APC	7.75143555	0	0	0	6.70926589	6.91997434
Bad	0	0	0	0	0	0
Bax	10.0841523	8.99852595	8.53670881	7.1491247	9.41403376	10.0713208
Bcl11a	0	3.57733258	0	0	0	0
Bcl11b	0	0	0	5.03025421	0	0
Bc12	3.78836066	7.35286615	6.11642851	5.60720562	0	4.75013415
Bcl2l1	6.11017227	0	0	8.25842512	8.41053397	10.5350727
Bcl2l11	7.53158421	0	0	5.97717038	6.54979563	7.23702656
Bmi1	8.99154721	8.57213633	1.00536134	7.1259908	7.77630502	9.13913696
Brd3	9.63555762	6.68960269	5.68713764	7.26905043	7.53751543	8.54151772
Casp8	8.69580853	7.82250438	7.27391311	7.12647247	8.13689545	8.33966066
Casp9	7.50634956	7.89665585	8.78122572	8.22640477	0	0
Cbx2	7.63597293	0	0	2.88451144	6.55755634	7.70632981
Cbx8	0	0	0	0	6.58332722	1.23705272
Ccnc	7.07744906	7.39096581	7.05379006	0	8.19654082	8.46919791
Ccnd1	7.17456113	0	3.67561661	9.15556129	0	0
Ccne2	8.84703835	6.74398849	0	0	0	0
CD34	7.76800322	10.2510414	2.42976374	6.94679739	7.33591375	0
CD41	0	7.75482846	0	0	8.70769069	0
CD48	0	7.17814996	8.01816633	0	0	9.55567614
CD52	10.0135314	0	11.8982735	8.81778186	7.57773901	11.0136116
CD53	10.0270236	10.1725729	10.2462871	7.3567463	0	10.7604721
CD55	4.54836488	6.25337777	0	6.26516647	4.55684724	5.44238382
CD63	5.17005936	7.47563153	3.07832198	6.44407765	5.26499364	5.17350267
CD9	0	9.46828366	8.37563384	6.77430086	9.39342697	0
Cdc42	11.4639526	11.5821246	9.83848584	11.2577485	10.7756615	12.9047404
Cdk1	10.9656852	10.4158817	0	2.26172673	7.6531999	12.2460627
Cdk4	8.77324798	9.12698531	5.45837872	7.85877388	6.28997376	9.83593049
Cdkn2b	0	0.21758523	0	0	0	0
Cebpa	0	4.87998831	0	0	0.53841585	0
Csf1r	8.20143195	0	0	3.50945636	0	0
Ctnnb1	8.29419721	8.94929575	5.66620169	7.85504317	8.48239691	9.80654905
Cycs	11.9286577	10.5773877	9.78151272	9.24318367	10.6036621	13.1484729
Dach1	0	11.8938366	0	7.85242012	0	0
Dnmt1	12.431398	10.6797953	5.10859902	8.60332571	8.90303261	11.5573084
Dnmt3a	9.31238906	0.66595298	9.50580001	9.36857301	8.96311662	9.41823059
Dnmt3b	0	0	6.81942467	4.98217548	7.49626958	7.95317289
Dtx1	0	0	5.32869997	0	1.98980211	0
Dtx4	0	0	8.14939517	0	2.92777138	8.31531242
Ebf1	10.1697266	0	0	0	0	10.6720985
Ep300	9.00180094	9.44219254	8.29306018	8.55233656	8.84559399	7.94463523
Epor	7.5372094	7.39704832	8.33400054	7.37800353	7.68712078	7.35168775
Erg	10.1327499	9.75516364	0	7.70627287	8.62033362	12.0140747
Esr1	8.88296212	9.04098261	0	6.92108807	0	8.4763699
ETS1	9.58515675	7.76396965	6.09305906	0	5.02126265	10.27795
ETS2	0	0	0	8.15364762	0	0
Etv3	0	5.70016295	0	4.23406152	2.35483367	0
Etv6	7.93361831	11.1215646	0	7.27988804	7.89445014	8.88475474
Ezh2	8.77165156	7.66705207	4.30929244	0	0	9.57003012
Fas	0	0	5.64848062	0	0	0
Fcgr2b	0.30420554	0.45440292	5.15394181	0	0	6.8494956
Fcgr3	0	0	4.41247907	0	1.24977442	4.25323357
Fli1	10.6596619	11.3769697	9.56699345	9.82489406	11.1881229	9.43156848
Flt3	0	8.59953308	0	0	0	0
Fosl1	0	7.74223892	0	0	0	0
Foxo1	10.5153363	9.99673903	9.6360569	8.19670491	6.62389626	11.7131359
Foxo3	6.94925231	8.89744564	8.17471245	8.28738773	8.1441656	7.11214992
Gapdh	8.94923539	7.63885103	6.1114181	6.39966913	8.06887865	9.83613157
Gata1	6.93311607	1.95105225	4.1024026	6.71747066	9.80051859	7.32322012
Gata2	0	6.84778411	0	6.48936067	7.0603346	3.31930144
Gata3	0	8.07886909	0	6.09390185	6.13467871	0
Gfi1	0	1.65773111	0	0	0	6.42475488
Gfi1b	0	0	0	8.76265343	10.5244821	0
Hes5	6.16742566	0	0	0	0	0
Hey1	0	0	0	0	0	0
Hlf	0	10.1536689	0	8.17012499	8.27321734	0

TABLE 7-1-continued

Single cell expression data (reduced list)—iHSC-8-TF

Factor	iHSC-8-TF1	iHSC-8-TF2	iHSC-8-TF3	iHSC-8-TF4	iHSC-8-TF5	iHSC-8-TF6
Id2	0	0	0	0	4.45263385	4.84341023
Ifi203	11.7002151	11.6173765	10.7830968	11.2037766	8.89825585	10.7833025
Ifi205	0	0	0	0	0	0
Ifitm1	8.79797577	9.30388568	0	9.61640866	9.63355399	0
Ikzf1	9.06085707	9.97570248	9.51200603	8.72018894	8.01748442	10.3459707
Ikzf2	0	9.19579333	0	8.34323416	0	0
Il7R	0	0	0	0	0	2.82350147
Irf4	6.24028863	0	11.2249245	0	0	0
Irf6	3.86697265	4.68374949	0	0	2.8135202	0
Irf8	8.6858537	4.6101286	8.99498491	0	4.89636707	9.36420702
Kdr	0	0	0	0	0	0
Kit	8.06121617	11.9083565	7.88520732	10.3475565	11.5383331	7.96739286
Klf1	1.36227074	7.02627962	0	0	0	0
Klf12	0	3.7799555	3.59391415	6.64529932	0	0
Ldb1	8.95380125	8.26779513	6.67202901	7.76543805	8.512649	10.3751947
Lin28a	5.97666173	0	0	7.2842936	4.1303577	4.23775192
Lmo2	0	9.90783707	4.1601552	8.76750141	9.49745795	6.40470448
Ly6a	6.49157656	9.20829801	11.7720222	8.78675489	6.61460984	8.7967369
Lyl1	3.47100366	8.3783465	0	0	0	0
Mbd2	10.1353897	9.91842346	7.76162024	8.01621694	8.98629969	11.7384075
Meis1	0	7.58467677	4.18043129	6.15361674	7.3922156	0
Mllt3	0	0	0	0	0	0
Mpl	0	7.78365781	0	7.84750206	9.14807149	0
Muc13	1.28725247	10.3687609	0	8.47827528	8.95782857	6.65183597
Myb	11.2938204	11.7723867	0	10.7012638	10.0192772	12.3107218
Myc	6.57202892	9.18538633	0	8.83016864	9.14318076	10.0463899
Mycn	0	7.76977355	5.06288392	6.8514822	10.8400837	0
Ndn	8.3289328	7.37671042	0	5.16705845	7.20854243	7.11546949
Nfat5	9.5189948	10.536889	9.07919517	9.36357896	8.84740478	8.99109512
Nfia	7.94744233	7.71267144	0	8.18008257	5.13480173	8.01727058
Nfkb1	4.49309052	0	0	3.48186805	0.74786804	0
Notch1	0	7.53698774	7.22766077	0	0	0
Pax4	0	0	0	0.90906537	0	0
Pax5	10.5019087	0	0	0	0	10.127363
Pax9	0	0	0	0	0	0
Pbx1	0	0	0	0	0	0
PIk3ca	8.87496334	9.59446253	8.38080955	7.92496672	7.19725366	8.34649914
PIk3R2	0	9.01075671	7.65058108	0	0	8.8251932
Plag1	6.21437664	0	0	0	0	0
Prf1	5.13052494	0	0	5.10255205	1.86255408	0
Pten	10.4209011	9.40062124	8.96322075	9.10909358	9.71271677	11.3745533
Rb1	11.498329	7.96524059	9.94840657	8.51800071	8.72633492	10.2612969
Rora	4.6565537	4.45455454	4.29766187	0	6.78445169	0
Runx1	0	3.59548673	0	0	8.70903268	8.69444499
Runx2	0	4.8737639	0	2.43317885	2.69308191	0
Satb1	9.58445099	0	0	0	0	10.0568223
Sdpr	0	0	0	3.31280029	5.62934476	0
Sell	0	9.75709978	0	6.9298617	0	8.38589128
Sfpi1	7.63770596	10.0783626	7.41813664	9.49550468	7.19133526	0
Slamf1	0	0	0	6.06097964	6.25642952	0
Smarca4	13.0953186	10.9600388	9.46765173	9.90759459	9.19212961	12.8606875
Sos1	5.40387814	5.43895529	0	2.67690483	5.14978146	4.18611634
Stat1	0	2.91513401	0.07241094	0	2.60150676	0.29458547
Stat3	8.81593264	10.0143888	8.51673559	5.70612457	9.26273642	8.62967589
Stat4	7.59462882	7.57005869	4.91836386	6.5553935	7.72874787	8.74767888
Stat6	0	9.26322869	9.00041636	9.18130068	9.26639055	10.2390779
Suz12	10.8674987	9.11262594	8.17970692	0	7.7627513	10.4085025
Tal1	0	1.8367319	0	5.71521273	1.96056078	0
Tcf3	10.5687751	0	9.21497368	0	0	10.0481927
Tcf4	8.34840792	10.2104083	9.82698659	10.0410063	8.76568475	11.7542786
Tcf7	0	3.71590064	0	0	0	3.04107777
Tek	0	7.63031049	0	0	8.79573534	0
Tfrc	10.7744689	9.18072216	0	6.62621094	7.8677122	12.4601279
Tgfb1	0	5.93085307	0	5.17968196	6.39280849	0
Tgfb2	0	0	0	0	0	0
Tgfb3	0	4.2326363	0	0	0	0
Tnfrsf1a	0	10.0793196	7.131272	8.00451161	8.93391961	6.97464589
Tnfrsf1b	0	7.84101337	0	6.33601316	7.87941437	0
Tnfrsf21	5.0514495	5.18842864	0	5.90203138	3.76922431	5.16498449
Tnfsf10	5.74118369	4.73595896	0	0	0	0
Tnfsf12	0	0	0	0	0	0
Tob1	0	0	0	0	0	0

TABLE 7-1-continued

Single cell expression data (reduced list)—iHSC-8-TF

Factor	iHSC-8-TF1	iHSC-8-TF2	iHSC-8-TF3	iHSC-8-TF4	iHSC-8-TF5	iHSC-8-TF6
vWF	0	0	0	0	0	0
Zbtb20	0	8.54271536	10.2199855	6.6588198	6.37611928	0
Zbtb38	6.56462732	6.67014526	8.73007335	7.61868645	7.62865123	0
Zfp532	0	0	0	0	0	4.60375818
Zfp612	0	0	0	0	0	7.16346579
Zfpm1	5.66600566	0	0	0	0	0
Zhx2	0	7.63580107	9.72406195	1.95086519	0	7.13427169

TABLE 7-2

Single cell expression data (reduced list)—iHSC-8-TF

Factor	iHSC-8-TF7	iHSC-8-TF8	iHSC-8-TF9	iHSC-8-TF10	iHSC-8-TF11	iHSC-8-TF12
Actb	14.1168122	14.2687572	15.8641756	14.4381106	14.3257382	14.6272225
Aebp2	6.58743305	5.66417136	5.22379812	5.95905614	7.01711608	6.02218741
Ahr	0	0	0	0	0	0
Akt1	10.4975255	8.19356615	10.0511812	9.94944796	10.0904307	9.78983507
Akt2	0	5.90204274	5.55935143	0	0	0
Akt3	4.44707058	0	5.01641454	5.89301145	6.31601984	2.88783769
APC	0	0	6.72226741	7.01362759	0	0
Bad	0	0	0	0	0	0
Bax	9.21290548	10.3301544	9.28539174	6.90668957	8.43007045	7.04487576
Bcl11a	0	0	7.05226632	6.95413316	0	0
Bcl11b	0	6.70827939	0	0	2.52118042	0
Bcl2	0	6.16765619	5.32242768	3.97203709	4.00080172	6.6941012
Bcl2l1	8.66402847	0	9.00530066	8.98651494	9.26985486	0
Bcl2l11	0	0	3.75189301	7.10582142	6.50890906	7.33360294
Bmi1	0	6.89348049	7.29668045	5.02457691	7.99433734	5.36245978
Brd3	7.71511488	6.04924659	9.23743083	7.95074744	8.60723746	6.91699201
Casp8	7.12754238	0	8.13700313	7.47959123	7.47348015	7.66051539
Casp9	9.29896423	7.90126543	0	8.30432388	5.33319179	6.17992512
Cbx2	0	6.43063067	0	6.62363681	7.67267315	3.20105562
Cbx8	0	0	0	0	0	0
Ccnc	0	6.40890962	7.63555762	6.20647804	0	6.24921005
Ccnd1	0	0	0	8.82298676	3.76604926	7.56671747
Ccne2	0	0	1.01221314	6.17859245	9.00851145	0
CD34	9.13922982	0	0	10.584104	0	0
CD41	7.61145278	0	0	7.90679374	0	0
CD48	7.21190179	8.92159518	8.98615136	10.0247552	6.7930497	8.02173906
CD52	9.13495653	13.2787307	10.360447	10.8185364	10.295746	10.2005651
CD53	0	10.4873969	10.0471444	10.0930693	10.8734016	10.6865731
CD55	5.57901574	4.03055026	4.3185467	0	2.08180138	6.99084057
CD63	5.12554231	0	4.77761362	7.17726095	5.43373369	4.70694381
CD9	0	5.59346873	0	6.80671919	0	6.82472844
Cdc42	10.5111244	11.2158271	11.7756836	11.2231375	11.759242	11.3052155
Cdk1	0	6.83989229	11.7557885	8.64473028	11.1023897	7.79953619
Cdk4	6.35473944	6.496508	8.83507662	8.83931041	9.36294383	5.64163688
Cdkn2b	0	0	0	0	0	0
Cebpa	9.04823476	0	2.69352882	9.40045224	0	0
Csf1r	0	1.30677937	6.92694177	0	0	5.59152648
Ctnnb1	6.57811297	7.88039783	9.34406389	9.25901152	7.83045263	7.02810979
Cycs	9.94917515	11.6037181	10.8649283	11.5428262	10.6576893	10.8861042
Dach1	9.69728721	0	0	8.33375194	0	0
Dnmt1	8.82661641	8.89078551	11.301271	10.5172729	11.1892253	8.83847491
Dnmt3a	7.83006841	7.52705094	9.67344982	11.0465423	6.51186067	9.32316712
Dnmt3b	0	0	0	8.62689966	4.86534252	6.40167463
Dtx1	0	0	0	0.59861137	0	0
Dtx4	0	8.83830171	8.41636566	0	0	0
Ebfl	0	0	9.22197094	0	6.9679956	0
Ep300	8.5523291	8.04374842	8.98301466	10.1771185	10.3582779	9.66613489
Epor	6.61213076	6.94262834	7.09878512	8.50640442	7.91438576	6.14148414
Erg	8.01216895	0	10.904728	10.0129949	10.7400648	9.32820082
Esr1	0	7.15035885	7.57306955	8.35236198	9.77947514	0
ETS1	0	3.60473663	11.2257118	7.54149304	10.6508588	8.51473144
ETS2	0	0	0	2.44626873	0	0
Etv3	0	3.45927904	4.8894594	4.37811575	0	0
Etv6	9.45530062	5.9105115	7.89766842	9.28460759	9.35002095	0

TABLE 7-2-continued

Single cell expression data (reduced list)—iHSC-8-TF

Factor	iHSC-8-TF7	iHSC-8-TF8	iHSC-8-TF9	iHSC-8-TF10	iHSC-8-TF11	iHSC-8-TF12
Ezh2	4.35380876	0	9.27707588	6.82488745	9.39229357	7.36394339
Fas	0	6.29945666	0	0	0	0
Fcgr2b	0	6.38732146	0	0	2.46788098	0
Fcgr3	0	0	0	0	0	0
Fli1	10.1576383	10.8206693	11.9187865	11.2788817	10.703534	7.93882312
Flt3	0	0	0	0	0	0
Fosl1	0	0	0	7.6654807	0	0
Foxo1	8.18173307	7.60923615	11.1745002	8.28381064	10.4449586	7.15153855
Foxo3	8.0408479	5.81741644	6.93021419	8.73445684	6.05213918	7.63571997
Gapdh	6.89740048	4.87578711	8.93535347	8.19662939	8.71071609	6.0484422
Gata1	9.61468987	0	5.9071982	2.11048309	5.4250803	6.89996511
Gata2	6.95268834	1.92704567	0	0	0	4.03544209
Gata3	6.51624104	0	5.81915409	7.20652789	0	6.15745412
Gfi1	0	0	8.24022584	8.33162082	8.54743017	0
Gfi1b	0	0	0	0	0	0
Hes5	0	0	0	0	0	0
Hey1	0	0	0	0	0	0
Hlf	0	0	0	9.32403067	0	0
Id2	0	8.47672002	0	0	0	0
Ifi203	8.71443714	9.91898509	11.2916134	12.2525286	11.6968592	10.2006689
Ifi205	0	0	0	0	0	0
Ifitm1	8.45511146	0	3.69283421	12.5234623	0	7.9891841
Ikzf1	9.34781477	8.16468581	10.0890344	8.27576881	5.59828783	9.92149712
Ikzf2	6.24292039	0	0	8.36452991	0	6.57569221
I17R	0	0	4.10352619	0	3.7996169	4.54349931
Irf4	0	0	6.02386675	0	0	0
Irf6	2.86463898	0	0	2.12737397	0	1.02930007
Irf8	6.58557808	8.00355731	7.93428618	7.19297404	3.05664681	7.37397995
Kdr	0	0	0	0	0	0
Kit	10.2589067	7.85501741	7.73411021	11.0726033	6.84977833	3.48477947
Klf1	0	0	0	0	0	0
Klf12	0	0	0	0	0	5.38786195
Ldb1	8.48024052	7.15652923	8.13838568	9.97532882	8.59067702	7.61339925
Lin28a	4.37557978	7.54315374	6.6611673	8.6930828	5.55717398	6.52150568
Lmo2	8.85722605	0	3.81100563	9.91085057	2.29006541	0
Ly6a	7.16972478	12.3655436	0	10.1051955	0	0
Lyl1	6.96600063	0	7.38272032	0	7.10726678	0
Mbd2	7.44236082	8.00969676	10.7184582	7.17557655	10.2817993	6.91322033
Meis1	6.6721765	0	0	7.89126204	0	0
Mllt3	2.76806472	3.87482965	3.75675909	0	0	0
Mpl	0	3.70133444	0	7.96516188	0	0
Muc13	9.22434143	2.95206595	0	9.00435575	4.86915097	6.41388415
Myb	11.2843335	0	11.8407814	11.6847567	10.6838134	9.98616175
Myc	7.93764864	0	0	6.9817147	0	0
Mycn	8.50979223	0	0	8.87104756	0	0
Ndn	0	2.31950644	6.46122501	0	8.52326206	0
Nfat5	9.67674286	9.22514461	9.53936508	10.725362	10.3961199	9.48647076
Nfia	0	0	0	7.88567867	0	0
Nfkb1	0	4.11255372	3.3186588	4.06803019	3.53872344	0
Notch1	0	0	0	7.4117428	0	0
Pax4	0	0	0	0	0	0
Pax5	0	0	10.6232231	0	10.2526594	9.85425333
Pax9	0	0	0	0	0	0
Pbx1	4.77796595	0	0	5.89394817	0	0
PIk3ca	7.06910008	7.7317113	9.10120998	7.88352097	7.35188556	7.24036714
PIk3R2	0	7.20794908	0	7.60310033	0	0
Plag1	0	0	0	0	0	0
Prf1	0	6.93683892	0	0	0	7.53304996
Pten	9.40099595	7.481518	10.9944646	10.6633747	9.16883013	10.6424771
Rb1	7.82300867	10.1428432	10.6672492	8.80739047	10.7566543	7.64031183
Rora	5.26511699	4.55919881	3.56025341	0	0	0
Runx1	9.23271499	0	3.36917166	8.86537555	9.39215951	7.72407872
Runx2	0.81275604	0	0	5.00576119	0	0
Satb1	0	0	8.24704373	0	8.23134552	9.39921429
Sdpr	0	0	0	3.18733123	0	0
Sell	8.88207346	0	9.44019649	0	7.16166271	0
Sfpi1	7.84155525	7.29077483	8.68860268	7.60080318	0	7.23304962
Slamf1	6.22492877	0	0	0	0	0
Smarca4	8.02041815	8.75617101	13.1046438	11.1511994	13.0182874	12.8133987
Sos1	0	0	5.69285508	5.55998031	2.30626703	3.42009457
Stat1	1.97314588	1.73607307	0	3.86647267	2.39385509	0
Stat3	9.12583565	8.80346971	8.32489816	9.58777265	7.04362269	8.57493998

TABLE 7-2-continued

Single cell expression data (reduced list)—iHSC-8-TF

Factor	iHSC-8-TF7	iHSC-8-TF8	iHSC-8-TF9	iHSC-8-TF10	iHSC-8-TF11	iHSC-8-TF12
Stat4	0	0	7.10054367	6.547509	9.30748517	9.01247436
Stat6	7.61361468	7.70780272	9.10788213	10.06886	8.46082693	7.60385028
Suz12	8.66924158	7.78426963	9.89026714	9.23254249	10.4123574	0
Tal1	2.37117102	0	6.30535461	6.58054019	0	7.16548188
Tcf3	0	9.80006797	10.7038707	0	10.1748615	9.50402931
Tcf4	10.6046337	10.677077	11.3483408	2.06873405	10.6701323	10.3793339
Tcf7	0	2.81355742	0	0	0	0
Tek	0	0	0	0	0	0
Tfrc	7.64318103	0	8.74634259	10.161451	9.22544138	9.23442125
Tgfb1	0	0	5.68279082	0	0	5.63076967
Tgfb2	0	6.35582439	0	0	3.41038781	0
Tgfb3	0	0	6.50340017	6.4796621	0	3.14159544
Tnfrsf1a	9.13753474	8.30559171	6.21261252	8.77734771	0	0
Tnfrsf1b	6.8202573	0	0	8.45197156	7.39481301	2.16712637
Tnfrsf21	4.9636023	0	3.88334514	7.04685483	5.86000083	1.87974929
Tnfsf10	5.83655197	0	5.38524996	5.6592177	0	6.87832602
Tnfsf12	0	0	0	0	0	0
Tob1	0	5.42079899	0	0	5.55304429	0
vWF	0	0	0	0	0	0
Zbtb20	0	11.116707	0	7.47693235	7.16188955	0
Zbtb38	6.05752543	7.56440082	7.45865121	7.69697887	7.27478686	2.68202784
Zfp532	0	0	0	0	0	0
Zfp612	0	0	0	7.66883285	0.41563857	6.98993492
Zfpm1	0	0	0	0	0	0
Zhx2	0	7.97860435	7.16760698	0	0	2.5744204

TABLE 7-3

Single cell expression data (reduced list)---iHSC-8-TF

Factor	iHSC-8-TF13	iHSC-8-TF14	iHSC-8-TF15	iHSC-8-TF16	iHSC-8-TF17	iHSC-8-TF18
Actb	15.4534796	15.0457213	14.7547847	15.7050081	14.3181958	15.2330791
Aebp2	6.93704471	4.91542799	7.05506882	6.86348616	6.24968398	5.62877356
Ahr	0	6.43180668	0	0	0	0
Akt1	9.16365108	9.30008467	10.763603	10.9936127	9.4294317	0
Akt2	6.73569225	0	6.4766602	0	4.80553304	0
Akt3	6.11863003	6.64875353	5.17305023	0	0	0
APC	0	0	0	0	0	0
Bad	0	0	0	0	0	0
Bax	10.2213052	9.11498692	0	9.44119327	7.49341326	8.82070706
Bcl11a	0	0	6.11771712	0	0	0
Bcl11b	0	0	0	0	0	0
Bcl2	7.93705313	5.59605449	6.02070196	4.81608191	6.50918987	6.69771435
Bcl2l1	9.7231417	8.58128508	10.0362848	10.2067064	0	11.066282
Bcl2l11	7.37172881	7.69830505	7.17734172	9.34606481	0	6.72034529
Bmi1	7.34695691	7.21167775	6.05530861	8.46478884	8.08106641	7.75522788
Brd3	8.02785515	5.00010534	8.51144277	9.52747453	6.80545653	0
Casp8	8.37321188	7.75230575	8.13985014	8.57969582	8.23333205	8.00637905
Casp9	7.68090941	2.32375499	0	6.320208	8.96183861	0
Cbx2	6.504426	1.54049084	7.04621731	7.72437829	2.30499009	0.11481278
Cbx8	0	0	0	0	0	0
Ccnc	0	0	7.36621375	6.70170152	6.00327617	6.24461652
Ccnd1	6.62265505	7.4467213	7.52700713	6.9456186	9.35651788	0
Ccne2	8.90201474	0	9.03686227	8.45653951	4.11742928	0
CD34	8.79163706	9.8829815	0	0	7.5325444	0.57823047
CD41	10.2235313	0	10.1703794	0	0	0
CD48	7.97202788	8.9224792	8.76089598	9.39765892	0	8.03809749
CD52	0	9.99964113	10.2992003	9.8539851	8.86491007	12.4913694
CD53	0	10.8351065	0	10.056315	9.14134727	10.1859346
CD55	5.74807313	0	6.03533722	4.24146883	0	0
CD63	7.74519483	7.00827947	6.94140733	5.72566979	7.10413036	4.56443151
CD9	8.90957851	7.49731749	8.92034488	0	8.64862026	5.6361667
Cdc42	10.9823548	11.4094614	11.4173435	12.0104029	10.8763938	12.158319
Cdk1	10.1932253	0	10.4913805	0	0	0
Cdk4	8.9755164	8.35943257	8.53085097	8.9627628	8.36068234	5.6036139
Cdkn2b	0	0	1.36381366	0	0	0
Cebpa	5.893276	9.70964699	8.88909053	0	8.03529285	0

TABLE 7-3-continued

Single cell expression data (reduced list)---iHSC-8-TF

Factor	iHSC-8-TF13	iHSC-8-TF14	iHSC-8-TF15	iHSC-8-TF16	iHSC-8-TF17	iHSC-8-TF18
Csf1r	0	0	0	1.44879467	3.67785521	0
Ctnnb1	7.48981199	8.1336946	9.20156778	8.61320717	7.43105241	7.17682577
Cycs	10.8157891	10.720996	11.7664034	12.1637591	8.54219495	10.5592201
Dach1	8.37404548	11.5809914	10.0147913	0	0	0
Dnmt1	12.1405773	8.76320326	11.4721676	10.43018	8.16086858	8.31332046
Dnmt3a	8.03355106	10.3047393	10.4905211	7.34945749	9.69684484	8.09559308
Dnmt3b	7.76598102	7.12399038	7.7635638	5.62611906	0	0
Dtx1	0	0	0	3.00328203	3.57731956	0
Dtx4	0	0	3.31637812	0	2.0047145	0
Ebf1	0	0	0	7.91519142	0	0
Ep300	8.3902995	8.72299654	7.98001879	8.27110318	8.43022421	8.55383003
Epor	3.5885028	6.89489217	8.24303376	7.15203704	8.10722751	8.67458521
Erg	8.06240346	8.91508586	8.37991482	10.1830057	9.48944314	0
Esr1	7.72434085	8.96175574	0	0	8.66618842	0
ETS1	0	3.98233032	6.85509411	10.3680088	3.46823602	10.4743299
ETS2	0	0	0	0	7.34802596	0
Etv3	4.37702979	3.36062871	4.09342768	4.95938064	5.16369302	0
Etv6	10.5013427	9.98804513	10.0093729	8.59292994	10.687523	2.49925909
Ezh2	7.69398439	5.90756213	7.75922202	8.50519978	5.14578313	0
Fas	0	0	0	0	0	5.59986323
Fcgr2b	5.67144377	6.33265476	0	3.2724894	6.59136946	0
Fcgr3	1.78683374	0	0	0	0	0
Fli1	12.6094269	10.2126474	11.3348213	5.58078903	10.5075133	10.1080811
Flt3	0	8.58695173	6.08980954	0	8.01264279	0
Fosl1	0	0	0	0	0	0
Foxo1	9.24339118	9.00386695	9.38862847	11.2318159	9.69497736	8.21951707
Foxo3	8.23726385	8.41088091	8.38255114	5.96599129	7.30821346	7.64232189
Gapdh	8.1689278	7.39978258	9.08120856	9.85054865	7.02681009	7.07904214
Gata1	9.82252363	2.06392862	8.7659977	0	0	1.37647648
Gata2	7.82083798	0	5.11254203	0	6.83205962	3.78221217
Gata3	7.8976454	7.41211086	6.99172072	0	6.53375566	7.34314284
Gfi1	0	8.55495398	0	0	9.00701704	7.3926737
Gfi1b	9.48743661	8.40675043	8.43006036	0	0	0
Hes5	0	0	0	0	0	0
Hey1	0	0	0	0	0	0
Hlf	7.97486047	5.83601979	7.98213905	0	10.5637188	0
Id2	0	0	7.30919327	0	0	11.4618755
Ifi203	8.94723689	10.879845	10.187699	11.3297255	11.4247052	11.6820609
Ifi205	0	0	4.25940374	0	0	0
Ifitm1	9.9243259	12.4987853	9.54492255	0	12.3039462	0
Ikzf1	8.1181871	9.10399583	8.67459587	10.7026464	8.28318113	8.02649557
Ikzf2	7.07471442	9.59931945	8.68627507	0	6.74038185	7.10072297
Il7R	0	0	0	3.30157767	0	0
Irf4	0	0	0	6.54858531	0	0
Irf6	4.17514012	0	1.48026891	0	0.90882603	0
Irf8	0	7.73738742	0	7.77087801	0	8.75705818
Kdr	0	0	0	0	0	0
Kit	10.468969	10.2388187	11.4153206	10.0405697	10.0963359	10.0173351
Klf1	0	0	0	0	0	0
Klf12	2.45882665	0	0	0	0.45168356	0
Ldb1	9.26322757	8.316956	9.33639067	9.61680777	9.26471492	8.37672695
Lin28a	3.6669966	6.33329084	6.0896607	6.57376149	0	7.17664498
Lmo2	8.01911171	9.39935871	8.30261571	4.75634564	10.0755277	4.24162405
Ly6a	9.3661827	9.11566635	0	5.99007554	10.942034	11.0081547
Lyl1	8.42712124	0	0	7.18926092	5.77433467	1.48922057
Mbd2	9.41810563	8.88421488	9.50400444	9.47109869	6.09034145	8.48104688
Meis1	7.83156174	6.93022589	8.37207046	0	5.60921016	0
Mllt3	2.67198941	0	2.16275894	0	0	0
Mpl	9.75089216	7.35694857	9.44891837	0	8.66269181	0
Muc13	9.13568741	8.32054225	7.72893994	0	7.20741875	0
Myb	10.2082629	11.5128574	11.7486723	12.2596713	11.0720251	0
Myc	7.83057978	9.42868399	9.41309135	0	9.98070807	4.55264807
Mycn	8.6004619	6.86525583	9.28449734	0	7.96551367	0
Ndn	7.1716298	2.63847367	0	0	0	2.27428691
Nfat5	10.104519	9.08807257	8.54046796	8.4835257	9.84582546	9.01999895
Nfia	9.95835509	7.45899512	7.64708656	0	9.2845695	7.85053506
Nfkb1	0	4.7667181	1.41310845	0	4.77499935	0
Notch1	8.1980529	0	0	6.53133175	0	5.39606879
Pax4	0	0	0	0	0	6.14490349
Pax5	0	0	0	10.708211	0	0
Pax9	0	0	2.19025952	0	0	0
Pbx1	5.99597205	0	0	0	0	0

TABLE 7-3-continued

Single cell expression data (reduced list)---iHSC-8-TF

Factor	iHSC-8-TF13	iHSC-8-TF14	iHSC-8-TF15	iHSC-8-TF16	iHSC-8-TF17	iHSC-8-TF18
PIk3ca	7.88230828	7.47696985	7.5500399	9.55020565	6.23869048	0
PIk3R2	0	8.24510008	5.82312994	8.02116203	8.93406942	0
Plag1	0	0	4.73744613	0	0	0
Prf1	0	0	0	0	0	8.73382677
Pten	9.55201959	9.3026472	9.49894524	11.3146776	9.82256436	9.31971728
Rb1	9.83548418	7.73051188	10.3125708	10.4278048	7.92474575	8.22490833
Rora	4.4155683	6.32539597	0	0	7.55184114	7.19241896
Runx1	0	5.18013526	0	9.10402185	7.60847018	0
Runx2	0	5.23198449	4.54870316	0	4.71944112	3.96352253
Satb1	0	8.30286654	5.48340999	9.87087431	8.3878369	8.22536909
Sdpr	3.37708308	0	2.17164004	0	0	0
Sell	0	9.64179428	7.32622835	8.59354275	8.72934132	0
Sfpi1	9.45330676	9.91279299	8.0266668	8.88627935	8.00223079	0
Slamf1	6.39337217	0	0	0	0	0
Smarca4	8.7128158	8.97012069	10.9947025	12.3094648	9.47484623	10.0915303
Sos1	4.95670739	0	4.42734538	4.56448493	4.86048311	0
Stat1	2.59737419	0.92027174	2.88493807	0.05319102	3.02184606	6.8812924
Stat3	8.06315119	9.21638478	9.06430179	0	8.13669425	8.30721918
Stat4	7.76112821	8.49004979	8.31123322	8.314415	9.29957534	9.64865985
Stat6	9.09210898	9.16948618	9.52175835	7.90699543	8.80158849	6.97978077
Suz12	10.3161732	7.41216521	10.0021849	9.25973518	7.31107544	7.00993321
Tal1	6.27023033	4.03587018	1.91607573	4.92820293	0	6.45443658
Tcf3	0	9.72331909	0	9.28003491	0	0
Tcf4	9.95842877	8.92609345	10.0138544	9.69802767	9.51627828	0
Tcf7	0	0	3.75075381	0	0	6.71655185
Tek	0	0	8.51364933	0	6.50570444	0
Tfrc	9.36631796	7.95001878	9.55542439	10.7476449	8.42531067	6.36552267
Tgfb1	0	0	0	0	0	0
Tgfb2	0	0	0	0	0	6.33693857
Tgfb3	0	0	0	0	0	4.26158858
Tnfrsf1a	8.85163318	8.0786507	8.1845794	7.00521923	8.5460922	8.06973511
Tnfrsf1b	7.55637493	0	7.74358799	0	5.00485983	10.174932
Tnfrs21	6.24363175	5.64683619	5.81156194	2.03622926	5.64009919	0
Tnfsf10	0	0	4.63222478	2.26191299	6.65398125	6.60294222
Tnfsf12	0	0	0	0	0	3.81293855
Tob1	5.67117711	5.63664714	0	0	0	0
vWF	0	0	0	0	0	0
Zbtb20	5.79959989	8.65423374	6.14739537	0	8.35748709	4.4844404
Zbtb38	8.10033265	8.58157099	6.34336723	7.98028306	7.8341961	0.56648659
Zfp532	0	0	0	0	0	0
Zfp612	5.9361768	6.93547371	7.20224287	6.60794851	1.35609575	2.25216372
Zfpm1	0	0	6.47136166	0	7.35425474	6.44185159
Zhx2	0	0	7.18849248	6.69019455	8.13323938	8.15233325

TABLE 7-4

Single cell expression data (reduced list)-iHSC-8-TF

Factor	iHSC-8-TF19	iHSC-8-TF20	iHSC-8-TF21	iHSC-8-TF22	iHSC-8-TF23
Actb	15.5949722	14.7271674	14.9192297	14.8524722	13.742072
Aebp2	6.02657711	6.46555858	0	6.77047	5.81780576
Ahr	0	0	0	0	0
Akt1	11.1358482	10.4380466	1.18490888	10.7142832	7.65650276
Akt2	3.53699864	6.27657983	0	0	4.99455434
Akt3	4.67734217	6.17450015	4.49098184	7.31178082	1.69186959
APC	0	6.39404584	0	8.12096298	0
Bad	0	7.94551754	0	0	0
Bax	9.7269672	9.53189139	9.22347188	8.98116411	8.92650111
Bcl11a	2.68677282	0	7.45791631	4.52048937	0
Bcl11b	0	0	0	5.10896278	0
Bcl2	6.32982374	5.73745116	6.26778953	4.96019175	4.06183255
Bcl2l1	8.58581684	8.25950033	0	8.61267991	8.15193143
Bcl2l11	4.23328455	0	0	8.33934299	6.38428587
Bmi1	8.09215612	6.82056434	7.88053812	9.25859235	7.3067493
Brd3	6.26049404	8.40584215	7.39130082	8.74987977	6.56313183
Casp8	8.55881676	9.01946362	8.89797827	7.89925135	7.36966954
Casp9	5.69785323	6.80005229	0	0	0

TABLE 7-4-continued

Single cell expression data (reduced list)-iHSC-8-TF					
Factor	iHSC-8-TF19	iHSC-8-TF20	iHSC-8-TF21	iHSC-8-TF22	iHSC-8-TF23
Cbx2	4.25975897	4.50344312	0	7.05085087	7.3652097
Cbx8	0	3.10519482	0	0	0
Ccnc	5.68144375	7.04800476	0	7.33402583	6.47052476
Ccnd1	7.32501662	0	9.14379317	7.80790367	8.06188774
Ccne2	6.81736138	6.12179616	4.01589047	9.60114654	7.32828462
CD34	9.10085124	10.8245974	8.030799	0	9.90933084
CD41	9.18976923	8.06311742	6.29822743	0	8.58124579
CD48	9.66357797	8.92273252	0	8.22498968	9.97655942
CD52	9.55607491	9.32703404	0	11.1238367	10.7706642
CD53	7.4753101	10.9421001	5.62923652	10.1462312	9.7742959
CD55	6.60757077	5.77529023	3.89364423	0	0
CD63	7.54605205	8.20511072	7.4468906	4.45819758	6.43605916
CD9	7.39378017	8.69852575	0	0	6.48705589
Cdc42	11.6616377	11.8297355	11.3272877	12.0401101	11.7498088
Cdk1	8.93880406	11.8672804	0	10.8047988	6.7710175
Cdk4	9.02876243	9.33369417	7.80946054	9.48909263	8.12248444
Cdkn2b	0	0	0	0	0
Cebpa	9.51613005	7.67127586	0	0	7.89753488
Csf1r	2.62576601	8.12277306	0	8.02931482	6.8366434
Ctnnb1	8.87487327	8.44525294	5.35747893	8.09503157	8.19325132
Cycs	12.2270781	12.1725171	10.077783	12.1894717	10.1903946
Dach1	8.9706084	9.54223727	7.78677331	0	11.0376368
Dnmt1	11.4798219	11.2665469	7.84049793	11.501541	9.05733118
Dnmt3a	10.0508273	9.21718083	8.22085764	10.709976	7.9890194
Dnmt3b	8.3035469	8.51151681	0	7.95017678	7.02438034
Dtx1	0	0	0	5.24802196	0
Dtx4	8.40755097	0	0	0	0
Ebf1	0	0	0	10.4583774	0
Ep300	8.46322899	8.98779971	7.79215349	9.02871727	8.54713076
Epor	7.74276166	7.5739171	7.09149108	7.66734299	7.34316306
Erg	9.42302499	10.0003759	9.88764997	11.1477312	10.1170711
Esr1	6.07339556	7.67273366	7.53899738	8.109266	7.19142983
ETS1	0	5.65065592	4.26833184	11.1615476	5.0938395
ETS2	7.99052669	9.33508118	7.04822799	5.98729189	7.4612499
Etv3	2.614744	3.42408061	0	2.0997937	3.65980713
Etv6	8.97419088	10.9666148	8.76350897	0	8.62985794
Ezh2	6.16548689	8.22342442	4.15641592	9.95784542	0
Fas	0	0	0	0	0
Fcgr2b	0	6.31986343	0	2.15906025	5.75272607
Fcgr3	0	6.13773377	0	0	0
Fli1	10.3284821	11.6513954	11.2427712	11.0210733	9.6653856
Flt3	7.14138117	9.90006307	8.60740057	0	9.49158073
Fosl1	0	2.54124545	0	0	0
Foxo1	8.68988455	10.7307691	8.78369362	10.3774981	7.14678055
Foxo3	8.43953086	9.53817626	7.34342736	7.20503849	9.38714958
Gapdh	9.35145628	8.81107493	7.38188726	9.49765691	6.77752673
Gata1	6.60958193	6.00088041	0	6.68660622	0
Gata2	5.15938223	6.18940099	6.94627744	1.11995453	0
Gata3	3.13442163	5.1062862	0	0	6.86901394
Gfi1	7.080742	9.20777369	10.2560592	0	8.52865693
Gfi1b	0	0	6.30300041	0	0
Hes5	3.28111377	0	0	0	5.84689612
Hey1	0	0	0	0	0
Hlf	8.16750889	9.01107414	9.44716816	0	6.3367949
Id2	0	1.59283696	0	0	6.89130613
Ifi203	10.5868051	11.9050857	11.7792822	11.263719	10.6719015
Ifi205	0	0	0.57526313	0	0
Ifitm1	12.8767036	12.1154443	12.6189753	0	12.8492636
Ikzf1	8.97220393	10.0637995	5.78319283	10.2519422	9.26900298
Ikzf2	9.22178598	8.10492715	8.78007149	0	7.86617002
Il7R	0	0	0	4.64255927	0
Irf4	0	0	0	6.71439284	0
Irf6	4.29929913	4.17383383	4.16212746	5.11342417	2.29092324
Irf8	0	0	0	9.04754663	0
Kdr	0	0	0	0	0
Kit	10.8452909	11.46819	10.6310949	8.0844973	10.702966
Klf1	0	0	0	0	0
Klf12	0	6.98159901	0	6.91529257	0
Ldb1	9.6599478	9.52797416	8.80192696	9.71715245	9.66305984
Lin28a	7.69345152	5.72024396	7.45549962	3.50792444	6.18530259
Lmo2	9.1278825	10.7135692	9.55065494	0	9.24867161
Ly6a	8.52775889	9.24169784	10.4450327	10.1506563	9.23981383

TABLE 7-4-continued

Single cell expression data (reduced list)-iHSC-8-TF

Factor	iHSC-8-TF19	iHSC-8-TF20	iHSC-8-TF21	iHSC-8-TF22	iHSC-8-TF23
Lyl1	0	9.23687977	6.01993559	1.85529048	0.14133291
Mbd2	9.00365197	9.32705014	7.01222795	10.2980675	0
Meis1	7.35816194	7.96386677	7.8940322	0	5.75544333
Mllt3	0	0	1.20748749	3.26279787	0
Mpl	7.07285751	8.83332562	9.28099881	0	9.71165465
Muc13	8.910028	10.4501608	9.66072897	5.93439112	9.95951444
Myb	12.1660716	12.3866801	10.9652485	11.4963858	11.9435595
Myc	10.5226652	8.50048408	6.80094773	0	8.29035189
Mycn	10.2559863	7.33715811	8.69237062	0	10.7681053
Ndn	0	6.24114931	0	0	0
Nfat5	0	9.94482313	9.4521204	9.25617131	9.31963903
Nfia	0	7.75199021	8.40775952	0	7.32732142
Nfkb1	5.05715116	3.70671963	5.59515553	0	3.68175399
Notch1	0	0	0	7.42247038	7.51617552
Pax4	1.35750393	0	0	0	0
Pax5	0	0	0	10.7836978	0
Pax9	0	4.82495586	0	0	0
Pbx1	0	0	0	2.22267062	0
PIk3ca	7.79947633	9.12079212	5.33285433	8.74513804	6.2959762
PIk3R2	9.94903409	0	7.55937679	4.93743794	8.18553433
Plag1	6.97544118	0	6.53760217	0	0
Prf1	0	0	0	0	0
Pten	10.0437172	11.1348822	9.70193974	10.5813312	10.666182
Rb1	7.83303543	9.28805228	8.58914181	11.1046418	9.02986546
Rora	5.99045132	4.57639061	4.8566497	0	6.30205008
Runx1	0	0	7.72374854	9.29351398	9.35240374
Runx2	3.63268457	5.76424475	6.13835151	0	3.93338711
Satb1	7.27713223	8.13179502	0	9.00538844	9.07324987
Sdpr	0	0	0	0	0
Sell	7.51974568	0	0	7.51639506	8.23065964
Sfpi1	10.3537335	10.3438079	9.35308484	7.34210532	10.1166949
Slamf1	0	0	0	0	0
Smarca4	10.6216587	11.4880312	7.91879599	12.7228124	10.1231921
Sos1	4.77662362	5.70044036	6.6446615	5.15475115	4.08108678
Stat1	3.68097567	3.18143788	2.33007484	0	1.70796503
Stat3	9.6835973	10.9736276	9.82324679	8.88395426	10.1030436
Stat4	8.89602699	8.66526465	8.61546176	9.97092626	9.15162945
Stat6	8.03975516	9.68534085	7.65197427	8.88963802	8.72505432
Suz12	9.2920734	9.9317102	5.55351096	11.0088039	6.92957444
Tal1	0	0.5321352	0	0	0
Tcf3	0	0	0	10.0357268	0
Tcf4	8.55403838	11.1342293	9.5053365	11.1326587	9.23590743
Tcf7	0	0	0	2.09395859	0
Tek	0	0	0	0	0
Tfrc	8.92977574	10.3347741	0	11.2959377	0
Tgfb1	4.99360374	0	0	0	0
Tgfb2	6.02165975	0	0	0	0
Tgfb3	0	3.95433485	6.38152066	7.26386529	0
Tnfrsf1a	8.32699141	9.38371569	8.98684403	0	9.01007344
Tnfrsf1b	7.71407597	7.24025508	0	7.84690402	7.6973118
Tnfrsf21	5.10082829	5.74389161	5.35986658	0	5.6231703
Tnfsf10	0	5.61139944	3.95505967	0	0
Tnfsf12	0	0	0	0	0
Tob1	0	0	6.45804508	0	5.48264167
vWF	0	0	3.92489179	0	0
Zbtb20	6.89389913	7.17608138	0	6.53831854	6.98907536
Zbtb38	6.02485068	8.58071957	7.5954863	5.38002324	7.47434598
Zfp532	5.25185019	0	0	0	0
Zfp612	6.35234454	2.37453437	6.42837344	3.48387397	6.69808578
Zfpm1	0	0	0	0	0
Zhx2	0	0	0	5.58795878	5.46898073

TABLE 8-1

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly1	iHSC-8-TF-Poly2	iHSC-8-TF-Poly3	iHSC-8-TF-Poly4	iHSC-8-TF-Poly5	iHSC-8-TF-Poly6
Actb	14.4017745	14.2732193	15.1526286	13.8643652	13.9815065	14.3047991
Aebp2	5.95955683	6.89726869	6.24332431	6.30280532	6.9095424	7.47978946
Ahr	9.54980521	8.51756005	7.1706196	0	0	0
Akt1	9.2199823	10.5771332	10.3125839	10.115699	8.64780047	8.65031952
Akt2	5.38910968	4.02386518	4.9461932	0	5.38465875	0
Akt3	7.03433438	6.15943216	7.67195681	7.81890549	9.32598867	7.96268327
APC	0	6.92782146	6.85867754	0	0	7.94220629
Bad	0	0	0	0	0	0
Bax	9.05413463	10.0987868	10.8354331	9.74710118	7.76338529	8.52100861
Bcl11a	7.41102372	0	7.15076275	8.58322415	8.20030062	0
Bcl11b	7.64367926	0	3.66716509	0	1.93636742	0
Bcl2	3.57531389	5.85403867	0	3.16043824	5.61646233	5.76077245
Bcl2l1	9.07993883	8.03643261	9.87966794	0.83585263	8.58326585	8.40210943
Bcl2l11	0	0	7.06374493	8.39612427	0	8.4773465
Bmi1	9.07560792	8.22518209	8.42569938	0	9.40851644	7.96975432
Brd3	6.95890888	6.24785555	7.56579491	6.62403459	6.88629365	7.85394619
Casp8	7.8559411	8.60926927	8.8582654	6.01680512	9.44420835	8.42884993
Casp9	0	8.33784339	7.33820605	8.25717213	8.44629053	8.27100862
Cbx2	5.65213624	0	0	2.18365236	7.0766812	3.66755176
Cbx8	0	0	0	0	0	0
Ccnc	7.23528126	7.86231075	0	7.38487279	8.84791023	0
Ccnd1	0	9.72602652	7.48420059	8.30654599	11.8053072	11.1237592
Ccne2	0	4.88759578	7.32135738	6.93922401	0	6.77972753
CD34	0	8.05101797	3.40774581	8.23829804	0	0
CD41	5.41030089	9.39327537	7.15100623	8.76650086	7.87007098	8.71774229
CD48	0	0	0	0	0	0
CD52	0	0	0	0	0	0
CD53	9.89133699	0	0	8.96185069	0	0
CD55	8.79899388	7.63015791	5.88277643	7.59780097	7.37088799	7.76280542
CD63	8.65376387	8.79228248	9.15870494	6.99196008	7.38940631	9.44747605
CD9	8.16707472	7.77311627	9.13626418	7.43428177	6.47201397	6.79388862
Cdc42	10.6693066	12.1804797	11.8620482	10.497805	11.8021081	11.9762404
Cdk1	0	8.11620358	7.60561917	0	0	2.42017354
Cdk4	8.95820807	9.15744736	11.0338829	8.57125161	9.69513549	10.0356562
Cdkn2b	0.46087622	0	0	0	0	0
Cebpa	0	0	0	0	0	0
Csf1r	0	0	0	6.04286637	0	0
Ctnnb1	8.44935695	10.0514987	0	9.05018407	7.94648144	9.18714944
Cycs	6.68979802	10.8213383	10.6404742	9.78073283	10.3505161	9.81337298
Dach1	9.47386037	8.81206403	7.5999307	6.57582267	6.70986766	7.32706794
Dnmt1	10.1960231	7.65655217	8.31004681	8.92673119	9.2261255	9.71151883
Dnmt3a	4.24750121	7.63469215	9.34742168	10.0524941	10.4262419	9.47291437
Dnmt3b	9.14843642	7.69961419	7.21411913	0	8.70429266	0
Dtx1	0	0	0	5.01837469	4.02137797	0
Dtx4	2.30088686	7.91425669	4.17934489	7.92978791	0	7.80407419
Ebf1	0	0	0	0	0	0
Ep300	8.42978448	8.16009533	8.11371035	8.59805316	7.6395129	8.21791669
Epor	6.2878854	6.64044771	6.75920564	8.02055392	7.93934358	6.20584516
Erg	8.62942227	10.521998	10.168764	9.83912345	9.13177011	8.6111314
Esr1	9.06471078	9.18829675	6.19515636	11.4378777	9.44975997	10.8199014
ETS1	0	8.87124698	0	8.10142716	7.23106564	6.79930712
ETS2	5.11680482	8.0568843	8.65044922	9.01833153	8.46467898	7.94602145
Etv3	0	0	0	0	4.82743292	0
Etv6	9.79251329	9.35978258	0	10.0075324	11.5885534	10.1921514
Ezh2	5.41817556	7.64667858	6.75543645	0	6.4159182	6.97011891
Fas	0	0	0	6.6771592	0	0
Fcgr2b	0	0	0	0	0	1.9110038
Fcgr3	0	0	2.86176005	0	0	2.44845107
Fli1	10.5336811	12.3667862	11.7858238	12.4608812	10.493611	12.4773028
Flt3	0	0	0	0	0	0
Fosl1	1.44076501	0	0	0	3.94928081	0
Foxo1	8.43424564	8.28876873	8.26229198	9.69686347	10.3959606	9.55451527
Foxo3	7.99528032	8.67713907	8.99464508	8.9062438	9.10399053	8.60034284
Gapdh	9.3099242	9.15763066	10.6029147	9.65043692	9.00857274	9.93076521
Gata1	0.63672388	0	10.3113521	7.1250339	4.80520903	8.55590577
Gata2	6.28005196	7.16819061	7.23533947	7.77620156	8.04600994	5.86169735
Gata3	10.2558503	8.50826002	6.98895568	9.32797131	8.9982892	8.78943303
Gfi1	8.68722923	0	3.61351347	8.08251783	9.37851925	7.53665623
Gfi1b	0	7.82299121	10.8795811	9.55418491	0	10.141432
Hes5	0	0	0	0	0	0
Hey1	0	0	0	0	0	0
Hlf	10.7996121	7.80302654	8.07339235	10.3328103	10.1642256	10.9369893

TABLE 8-1-continued

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly1	iHSC-8-TF-Poly2	iHSC-8-TF-Poly3	iHSC-8-TF-Poly4	iHSC-8-TF-Poly5	iHSC-8-TF-Poly6
Id2	0	7.19510114	0	0	7.34117982	6.73327638
Ifi203	11.2049311	11.7941593	10.6750846	11.8592034	11.3822198	11.0667002
Ifi205	0	0	0	0	5.12094266	0
Ifitm1	13.6239128	12.8211493	12.5380217	13.5860342	12.7310037	12.7572775
Ikzf1	8.02126587	9.04043972	7.72357321	9.05398182	9.50868305	7.99342233
Ikzf2	0	7.54783051	6.77079194	7.44755496	8.52813905	8.80116026
Il7R	0	0	0	0	0	0
Irf4	0	0	5.95460689	0	0	0
Irf6	5.93922618	6.29386942	6.10533594	5.63670862	6.21974252	6.69067944
Irf8	6.34567669	6.763163	0	0	0	0
Kdr	0	7.90283794	6.7399962	6.04306679	7.693852	0
Kit	11.5010613	10.5293391	7.24957866	12.1134045	11.2585393	10.0523104
Klf1	0	0	0	0	5.80555786	5.1540702
Klf12	7.55975795	7.04089627	7.935156	0	8.409808	3.6068298
Ldb1	10.8094981	10.8874078	10.0963676	10.4803974	10.0508605	10.1714957
Lin28a	0	2.05211875	7.65136108	8.44983026	4.23628819	0
Lmo2	11.5045036	11.4654604	12.7062374	11.6099483	11.790659	11.6996282
Ly6a	11.0781952	10.7918825	0	9.61026549	10.6187689	9.77041941
Lyl1	6.9228556	7.88957298	7.41124593	7.57483786	0	0.11188596
Mbd2	8.86366453	9.83898085	11.2188215	9.25784881	10.0178474	10.0634688
Meis1	8.59070238	10.0819024	8.56901622	8.96918024	9.55460124	8.92762134
Mllt3	0	5.19972913	6.98132487	4.33487907	3.43331896	4.72749687
Mpl	10.6098091	10.2976387	9.44740225	9.50399788	10.1164058	10.0146934
Muc13	8.22110323	10.3149031	10.5075791	10.121513	6.38829389	9.90926088
Myb	11.3740645	11.6070815	0	11.252238	11.1854878	11.6427141
Myc	7.58773767	6.92502957	11.0745262	0	10.1593651	7.81411074
Mycn	12.3961119	13.821477	11.2941091	13.4141112	13.2655937	13.4922153
Ndn	7.95802745	10.8486792	9.89395444	9.10341388	9.93546083	10.1963811
Nfat5	10.2193279	10.6492324	8.61806674	10.6812757	9.9915593	9.75117783
Nfia	8.65330763	7.06341868	7.38701122	9.59475644	9.95424844	8.85076252
Nfkb1	4.446709	0	6.6481504	0	2.89270377	3.94764604
Notch1	0	0	8.69218776	9.10479408	0	6.95197356
Pax4	0	0	0	1.44235065	0	0
Pax5	0	0	0	0	6.66633311	0
Pax9	0	5.03638998	3.19142852	0	0	0
Pbx1	5.79433853	2.40166484	0	6.25602965	0	0
PIk3ca	0	8.94646056	8.24915927	9.68680408	8.07553724	9.42366483
PIk3R2	7.86660372	7.73972411	7.38377942	8.09713775	8.00818253	8.75992262
Plag1	0	7.49123813	5.82502843	7.76160342	1.23953556	9.47539828
Prf1	2.80996555	0	0	1.55094842	0	0
Pten	10.4165886	9.60432119	10.2437146	9.90287857	10.8245223	9.89550714
Rb1	9.09620227	10.2509564	7.03917768	10.0166256	9.88895181	10.011227
Rora	5.67210945	8.16786484	8.22163059	8.40806013	8.20332033	4.82153142
Runx1	10.0392064	9.36216612	0	10.0169963	7.55675639	1.95995368
Runx2	3.02975474	0	0	4.00168042	4.49363883	3.39036905
Satb1	0	0	6.72850441	0	0	0
Sdpr	6.47855527	7.37567768	5.18752317	5.78827462	4.5789996	7.14989941
Sell	0	0	0	0	0	0
Sfpi1	7.93492701	1.16071284	8.97426329	9.01058427	8.8542142	8.64133779
Slamf1	7.5910261	8.53583734	7.18007615	8.00938404	7.5562505	8.6742552
Smarca4	9.2280708	10.369666	8.2235885	10.7058201	10.261829	10.5475105
Sos1	2.79113487	5.88655824	7.60011468	6.41704302	6.34226658	5.65496301
Stat1	2.30720619	2.35055788	6.29759725	3.85091293	5.28729455	2.53753709
Stat3	10.5102227	11.654284	7.98961351	9.69221977	10.9831963	9.46455273
Stat4	9.73148085	9.19610287	8.40332968	9.9249724	8.15997772	9.14000192
Stat6	8.08137592	8.26948638	7.50391096	0	10.2215169	8.55245944
Suz12	9.3961376	9.96724283	7.37908318	9.47883474	9.42011558	8.32573094
Tal1	1.72237282	0	6.69073047	3.11164048	1.32936699	0.00662202
Tcf3	8.96333241	9.31481932	0	0	9.07224108	10.1220054
Tcf4	8.80005664	9.41908139	10.3132992	8.69843764	8.97235944	9.3667886
Tcf7	0	0	2.25026637	0	3.89585347	4.39562419
Tek	4.43072212	0	0	0	0	8.57224426
Tfrc	0	8.54731767	6.89401888	9.74317989	5.81615029	0
Tgfb1	0	0	0	0	0	0
Tgfb2	0	0	6.42618862	0	0	8.02240011
Tgfb3	7.17263032	0	6.69764691	8.16263704	7.62575941	3.60618469
Tnfrsf1a	9.12239254	9.94871547	10.5626763	8.3415255	8.80960043	8.44697988
Tnfrsf1b	7.57265388	2.1044987	5.61187541	9.91624698	7.9098197	8.62491508
Tnfrsf21	4.87454812	3.46004955	0	4.70959999	4.73578778	4.96266939
Tnfsf10	0	6.11608237	7.18551286	8.23570855	7.29990668	6.85883769
Tnfsf12	0	0	0	0	0	0
Tob1	0	0	0	7.63203105	5.15771067	0

TABLE 8-1-continued

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly1	iHSC-8-TF-Poly2	iHSC-8-TF-Poly3	iHSC-8-TF-Poly4	iHSC-8-TF-Poly5	iHSC-8-TF-Poly6
vWF	7.28131553	7.6135713	8.13113957	7.42453844	8.00520062	8.84927559
Zbtb20	9.1393088	8.47880681	7.90821765	8.9457529	8.12571437	10.22509
Zbtb38	7.37904176	9.35075276	7.06713579	8.59650634	6.5271098	7.65089916
Zfp532	0	0	7.67157289	0	0	0
Zfp612	3.43885333	8.66672996	0	6.73462534	0	5.03501087
Zfpm1	0	0	7.24131733	0	0	0
Zhx2	1.94879631	0	7.81335591	8.46235816	8.2166298	0

TABLE 8-2

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly7	iHSC-8-TF-Poly8	iHSC-8-TF-Poly9	iHSC-8-TF-Poly10	iHSC-8-TF-Poly11	iHSC-8-TF-Poly12
Actb	14.5566982	13.615687	13.2557353	13.9045548	13.625207	13.6632976
Aebp2	7.46754461	6.09082663	7.88599221	3.70216827	6.20483355	6.71566468
Ahr	7.777933	8.74434412	8.10667368	7.49909044	7.20337973	0
Akt1	10.2515898	10.0377805	10.6829232	9.27077113	10.266825	10.5734114
Akt2	5.61051736	0	5.3893609	5.11237848	5.46400025	5.08512838
Akt3	6.93473018	6.61452163	7.44026837	7.77588506	7.14760449	5.28506516
APC	8.24864591	7.30804883	6.70709773	0	0	2.08510464
Bad	0	7.83220622	0	0	0	0
Bax	9.48202132	8.9969831	10.9826718	9.37331185	9.48416241	8.8896616
Bcl11a	5.55206094	0	9.30842622	0	0	8.16251064
Bcl11b	0	0	4.04933387	0	6.56686767	0
Bcl2	5.48513078	5.01756113	7.17323639	4.60865583	6.53959776	6.15098683
Bcl2l1	8.40580553	2.85422793	8.83253241	9.37360231	8.97631666	7.51350228
Bcl2l11	7.06672118	0	0	7.28322794	6.13979045	2.83394681
Bmi1	10.1062229	8.64380505	8.99015684	7.21992126	8.87436353	0
Brd3	7.25721075	0	7.0965374	0	7.48140966	7.08332896
Casp8	7.10606382	7.11213334	9.13994663	8.261719	7.95659871	4.65164926
Casp9	0	8.75571495	0	1.70805493	0	2.58327705
Cbx2	2.75579197	0	4.17954883	2.44741358	4.393594	5.87793163
Cbx8	0	0	0	0	0	0
Ccnc	7.23061803	9.11473694	7.78622312	2.54536069	6.92719273	6.83659195
Ccnd1	10.6653784	8.89949686	9.37926846	9.10837155	10.9590543	9.95508055
Ccne2	0	0	6.67129745	0	6.26507974	7.44075399
CD34	7.84002032	6.14401226	2.96413812	0	0	7.08263627
CD41	0	0	0	6.79226229	1.8891056	7.90833057
CD48	0	0	0	0	0	0
CD52	0	0	0	0	0	0
CD53	10.2116886	10.7187208	7.08173192	0	7.86597872	9.01398982
CD55	6.98771698	2.38132592	7.08507818	7.89992021	7.15246355	6.12899081
CD63	9.35889467	8.34609702	7.4525258	8.40948734	8.52745636	9.28338595
CD9	0	0	0	0	0	7.73063553
Cdc42	11.5785879	10.5894656	10.8671101	11.1168037	11.7063764	11.8716066
Cdk1	0	7.59230634	4.57373649	8.26530963	0	2.79902594
Cdk4	10.4501041	9.38183794	9.45444547	9.17523295	8.69628583	10.0283801
Cdkn2b	0	0	0	0	0	2.20414523
Cebpa	7.67068515	0	0	3.00431304	0	0
Csf1r	0	0	0	0	0	0
Ctnnb1	8.98595118	8.61438975	8.0072686	8.55085327	8.3102969	8.76868574
Cycs	10.5867211	9.35280265	9.4126619	8.77371577	8.18994032	9.55716753
Dach1	7.9702221	8.18463035	10.0236829	9.42554937	8.13824416	10.359611
Dnmt1	7.80846616	7.40084034	8.85990662	4.70802589	7.27623299	9.44760185
Dnmt3a	8.89119048	9.27747566	10.2871952	9.54112251	9.5508204	10.4670722
Dnmt3b	7.3240984	7.49715046	0	7.22284209	8.54691735	5.83497538
Dtx1	0	0	4.9945392	0	0	0
Dtx4	4.11683447	0	0	4.01331301	0	2.68856134
Ebf1	0	0	0	0	0	0
Ep300	8.75880732	8.22004845	7.22949951	6.94738149	8.43564543	7.87430334
Epor	0	7.59352322	7.74083769	7.95447845	6.07198618	8.08667718
Erg	10.8478089	10.1398615	9.1558768	9.52550271	9.47527555	9.24391502
Esr1	9.72073813	7.43499017	3.58070546	9.16795158	11.0351211	7.34656788
ETS1	8.67731549	0	0	8.84936082	5.14149904	6.25528985
ETS2	0	8.91107552	7.23512522	7.43400303	2.1535625	8.78478124
Etv3	3.30675555	5.24405155	3.81620636	6.12231898	4.75328706	5.44221188
Etv6	10.8163092	9.32897355	10.6859753	11.9313243	10.2425034	11.6285131

TABLE 8-2-continued

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly7	iHSC-8-TF-Poly8	iHSC-8-TF-Poly9	iHSC-8-TF-Poly10	iHSC-8-TF-Poly11	iHSC-8-TF-Poly12
Ezh2	0	0	2.21554199	0	5.32363089	0
Fas	0	0	0	0	2.16604599	0
Fcgr2b	3.47793	0	1.71970146	2.23921869	0	5.04737267
Fcgr3	0	0	0	0	0	2.18806711
Fli1	10.8345473	11.5409772	10.5318652	10.662109	11.4388002	10.1671415
Flt3	0	0	0	0	0	0
Fosl1	0	0	5.8347835	0	7.70592608	7.84850811
Foxo1	9.4405956	8.63244642	9.95832224	11.215797	9.9252048	10.7941741
Foxo3	9.38655913	8.08321966	8.07438022	8.8867453	7.74085669	8.93178924
Gapdh	8.63027458	8.73797671	8.14527812	9.4866405	7.33039136	9.67482926
Gata1	0	0	1.55162308	0	0	0
Gata2	5.47644994	6.97088567	8.20284665	8.01626434	5.91147422	6.88724501
Gata3	9.08511237	9.31182071	0	9.62706291	9.32930381	6.65922323
Gfi1	0	7.22139719	6.85380432	8.35817389	7.00712317	0
Gfi1b	0	0	7.2469058	7.45722502	6.87129889	6.92216504
Hes5	0	0	0	0	0	0
Hey1	0	0.67601338	0	0	1.09702737	0
Hlf	10.4853838	10.1092492	9.53028437	9.80884657	9.89274135	11.105232
Id2	7.46080895	0	0	0	7.18836307	4.4396478
Ifi203	11.1510789	10.5179013	12.3149838	11.1576976	10.6080303	11.3037035
Ifi205	0	0	0	5.11004436	0	0
Ifitm1	13.4850079	14.3779702	11.310825	12.3177214	13.3652001	12.6945896
Ikzf1	8.54385455	6.97196539	8.4861291	6.77958196	8.19579315	6.83946026
Ikzf2	8.26817651	1.0114979	0	8.04160023	8.17715371	7.37397864
Il7R	0	0	0	0	0	0
Irf4	0	0	0	0	0	0
Irf6	6.51071164	5.62197926	1.33986609	3.6512894	5.74729803	6.27874544
Irf8	7.35064711	0	5.67817332	0	0	0
Kdr	0	7.43990645	0	0	7.74287744	0
Kit	9.44396168	9.99654642	9.05604605	10.7370375	11.1484528	9.48452903
Klf1	0	0	0	0	0	2.66895857
Klf12	7.83284751	1.79551807	8.02838739	8.41667992	7.31689315	8.22947494
Ldb1	10.8649416	11.0311014	10.2531103	9.96867512	9.44479733	10.237399
Lin28a	0.07648021	5.44206338	2.28808923	0	4.26911442	7.49478468
Lmo2	10.3300198	11.4044966	10.8122837	12.0024401	10.8122958	11.5354295
Ly6a	11.0261252	9.19365169	0	11.2822375	10.9680129	10.2245897
Lyl1	0	0	0	0	8.1627394	6.9405754
Mbd2	9.778048	7.88381457	9.85411747	8.93004612	9.84729194	9.50047741
Meis1	9.79079972	9.26553519	9.47724048	9.11875429	7.83230069	9.28003396
Mllt3	4.95820732	6.82834374	3.31729194	4.78671361	5.72656509	5.03058026
Mpl	10.5885966	10.2036925	10.3769602	9.29493118	10.1733655	10.194539
Muc13	6.47555273	4.0744404	0.74602045	9.11384586	9.74461615	9.05918759
Myb	10.7442288	9.96147288	10.993789	10.1482872	11.1603183	11.6769893
Myc	7.89827193	9.71889144	8.37756333	6.2345676	8.71491271	9.57514794
Mycn	13.0888737	11.9671485	14.0143762	12.1914809	11.9099683	12.4213923
Ndn	8.94858448	10.4219509	7.73679165	7.97014772	9.18715689	9.75918486
Nfat5	10.3527976	9.84044429	9.78500077	9.69671217	9.49142498	10.0570506
Nfia	8.77963768	9.1388192	9.92274441	7.88222414	8.46281343	10.5459452
Nfkb1	4.42634987	0	4.92034792	4.79418239	5.49712885	5.77034407
Notch1	7.75076794	0	0	0	9.00866938	7.22412965
Pax4	0	0	0	0	0	0
Pax5	0	5.51060272	0	0	0	0
Pax9	0	0	0	0	0	0
Pbx1	0	0	5.27140189	0	5.62172032	6.67462266
PIk3ca	9.62050132	9.28712078	9.2982715	8.72600436	8.2306778	6.59758348
PIk3R2	6.02135145	0	0	0	0	7.90960372
Plag1	0	6.72260382	7.03486336	7.18387794	4.17261924	6.64273979
Prf1	0	3.90415649	0	0	0.63556078	0
Pten	9.26090346	10.2405116	10.3794127	9.50933483	10.4712953	8.8938414
Rb1	9.66749617	7.6292368	8.71116734	8.9432676	4.68235943	9.80937685
Rora	0	4.97514677	7.9587669	7.68976191	4.34907105	5.02881742
Runx1	10.1268518	0	7.85747808	5.75506403	9.96928817	8.24404878
Runx2	5.5286143	0	3.79093014	4.65939933	4.88754632	0
Satb1	0	8.4748954	0	0	0	0
Sdpr	5.27902633	6.32635852	6.5332166	0	7.17059601	4.59848613
Sell	0	0	0	0	0	0
Sfpi1	9.46010411	7.75399359	7.72602312	9.76515629	9.72539923	7.02277564
Slamf1	8.20190825	8.19833438	0	5.55930467	0	0
Smarca4	9.4413014	10.1563545	8.79018319	8.8549291	10.3361654	11.228265
Sos1	4.54939546	6.56343031	5.6282784	3.49839747	6.033343	7.34548491
Stat1	1.6954329	2.46606654	4.59411276	3.22835285	3.56380291	2.65186982
Stat3	9.7980754	9.90644603	10.0618227	10.0057991	9.46974309	11.2477057

TABLE 8-2-continued

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly7	iHSC-8-TF-Poly8	iHSC-8-TF-Poly9	iHSC-8-TF-Poly10	iHSC-8-TF-Poly11	iHSC-8-TF-Poly12
Stat4	10.1144294	8.47352328	8.70582293	8.52494598	8.72233963	8.2171884
Stat6	7.86406378	0	0	8.26236445	9.0629236	7.69535411
Suz12	8.39719356	7.93784732	8.38043045	8.85608556	9.42803983	9.28167431
Tal1	0	0.681281	0	2.08441416	0	1.70076747
Tcf3	0	0	9.9455106	9.29810349	9.8282128	9.54784562
Tcf4	0	8.51908255	9.24863486	10.5880166	7.28528289	7.66941102
Tcf7	4.32833396	0	0	0	6.36792384	2.47636179
Tek	7.42071469	0	7.43721036	0	0	7.67578104
Tfrc	8.06611575	7.71886079	8.5698818	0	0	8.80876058
Tgfb1	0	5.94187127	4.16958245	1.7066482	0	7.44368223
Tgfb2	0	3.64491004	0	8.61953374	0	4.82967208
Tgfb3	7.96037916	2.36951015	3.0455015	0	8.1575853	0
Tnfrsf1a	9.58272277	8.66151272	9.23558302	8.67592568	9.37894037	9.03022699
Tnfrsf1b	8.90229636	7.93923169	5.29156723	7.81247487	8.26692579	8.39371317
Tnfrs21	0	0	0	5.44213484	4.19136877	5.44890931
Tnfsf10	0	0	0	5.44208502	6.0556815	5.34683032
Tnfsf12	0	0	4.3913846	0	0	0
Tob1	0	0	6.16399931	0	0	6.29096864
vWF	6.35040864	6.82666845	7.07089703	5.30969082	6.82119478	7.28636659
Zbtb20	8.54677311	8.62567076	8.34955811	8.95833222	8.46048893	10.0348575
Zbtb38	8.6859832	6.69172463	7.38375805	6.45223583	8.91459553	8.06672637
Zfp532	0	0	0	0	0	0
Zfp612	8.55308069	8.49590308	7.30051048	0	8.54459297	8.15113011
Zfpm1	0	0	7.83370461	0	7.67338465	0
Zhx2	0	0	4.36096658	9.52701148	7.8156659	7.69538745

TABLE 8-3

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly13	iHSC-8-TF-Poly14	iHSC-8-TF-Poly15	iHSC-8-TF-Poly16	iHSC-8-TF-Poly17	iHSC-8-TF-Poly18
Actb	14.2727767	12.7280483	14.0956291	13.7082256	13.0574175	13.8899065
Aebp2	6.11070016	7.67413704	5.4199737	5.67517041	6.12979862	6.39309702
Ahr	0	7.60162142	8.68953508	7.22521443	0	7.80170326
Akt1	10.5537808	10.2359843	10.1876416	10.2045296	9.32528266	11.2037137
Akt2	6.04771205	5.46968411	4.61114177	0.36361906	5.15470193	6.76905664
Akt3	7.46685201	8.87527885	6.41367312	6.57064203	7.42714251	8.82945036
APC	5.47404929	0	0	3.30240815	0	0
Bad	0	0	0	8.25308495	0	0
Bax	9.58600628	7.72059484	8.90118521	9.0595556	8.89711711	10.2420317
Bcl11a	0	7.2152692	0	9.99754542	8.21413322	8.37765853
Bcl11b	0	0	0	0	0	5.9803208
Bcl2	6.3930411	6.07276828	6.16216896	7.49388797	5.68656739	0
Bcl2l1	8.95652025	7.10261013	9.81018845	5.27192178	8.28376117	7.94107304
Bcl2l11	6.33813274	0	0	5.92621331	0	0
Bmi1	8.66147977	8.96414419	8.75077682	8.37533133	8.69114053	9.23230416
Brd3	8.28803382	6.3971659	6.25298854	7.15381467	7.6478676	8.17779551
Casp8	8.45968253	8.1712985	7.71775573	7.76600997	8.57602393	7.87394894
Casp9	4.45260333	0	0	0	4.29714485	0
Cbx2	2.07247445	4.80091864	2.61905814	0	1.54064757	4.53169391
Cbx8	0	0	0	0	0	0.67434266
Ccnc	0	8.28176951	8.20203458	0.20286217	7.36331044	7.27287576
Ccnd1	11.3129135	10.4797236	8.88976756	7.2170424	8.33377627	9.15479719
Ccne2	0	0	1.50040192	0	0	0
CD34	8.22979468	0	0	6.91091458	8.44625303	7.87973307
CD41	0	7.16278626	0	7.18437958	0	0
CD48	0	0	0	0	0	0
CD52	0	0	0	0	0	0
CD53	0	8.91427674	8.44378297	9.13656802	0	9.74428678
CD55	6.01147624	5.07787524	7.69978384	2.8938614	7.50395162	8.09488889
CD63	9.97144686	8.71949217	8.16499862	8.98186831	6.4416781	9.43079454
CD9	9.65832099	5.7460499	8.59279056	7.41372418	8.48726798	7.98386084
Cdc42	12.0879567	10.9317607	11.4005236	11.0823193	10.9521574	11.5405133
Cdk1	0	2.72753967	0	2.05216916	0	0
Cdk4	8.5419578	8.78105981	9.25298713	7.52696871	8.30059711	9.43641662
Cdkn2b	0	0	0	0	0	5.12306489
Cebpa	0	0	0	0	8.64186061	0

TABLE 8-3-continued

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly13	iHSC-8-TF-Poly14	iHSC-8-TF-Poly15	iHSC-8-TF-Poly16	iHSC-8-TF-Poly17	iHSC-8-TF-Poly18
Csf1r	0	0	0	0	0	0
Ctnnb1	8.20473117	8.50969794	8.69357555	9.73103801	5.608402	9.62623328
Cycs	10.355627	8.70346871	9.62459322	8.44123772	8.67759939	9.25455509
Dach1	9.82088619	7.86150494	9.96350332	8.99831455	0	10.570503
Dnmt1	8.77747907	7.53562918	0	7.44505386	8.60952809	10.0209151
Dnmt3a	10.9895968	8.80508017	9.0263749	9.03931586	9.52116455	9.94330249
Dnmt3b	9.0938017	1.17472267	3.10327969	0	2.84001275	8.34532121
Dtx1	0	0	0	0	0	0
Dtx4	4.43088049	3.87028229	4.43041562	7.35767066	0	5.6117422
Ebf1	0	0	0	0	0	0
Ep300	9.017599	6.78903265	7.43151301	7.60373336	8.45575033	7.95781099
Epor	5.61905305	6.57651712	6.697122	7.72336468	7.6721107	7.16092395
Erg	11.2267843	11.2338502	8.98943025	8.67311388	10.5300473	10.3920801
Esr1	9.88779417	9.5988785	10.7077127	9.32817858	9.04585226	0
ETS1	7.00604522	8.10866426	8.03570905	7.99879785	4.90118407	7.96807866
ETS2	9.43655065	7.58250039	8.78658622	7.59607589	7.77738844	8.52035769
Etv3	6.23826064	3.83649683	5.71839126	3.62372678	5.97641387	4.51702701
Etv6	11.5745983	9.67915008	11.1480528	9.02130654	10.2698644	11.1857554
Ezh2	5.31268746	0	4.20179525	6.18588773	0	6.62582331
Fas	0	0	0	0	1.51519502	0
Fcgr2b	6.48856047	4.94876599	0	0	0	0
Fcgr3	3.61683637	0.44366131	0	0	0	0
Fli1	11.8751419	11.3361252	12.1903114	11.2030884	11.240247	11.2863366
Flt3	0	0	0	0	0	0
Fosl1	9.57090972	0	7.58226569	0	0	7.82360513
Foxo1	10.3871499	9.3667248	10.4078656	9.09496896	10.2176456	10.0456512
Foxo3	8.47876623	9.50744661	9.2592793	7.51365588	7.19553746	9.10509162
Gapdh	9.38324817	7.33400257	8.80742103	7.06433381	7.70747783	9.59697776
Gata1	5.31073843	0	0	0	1.26264701	7.26109145
Gata2	6.68669869	6.50786707	7.6104304	3.89707824	6.63102054	8.2588868
Gata3	7.04848734	8.94414597	8.45487627	9.75563278	9.27170655	10.8195073
Gfi1	9.73235707	9.86036822	8.40070436	4.05484467	5.30647504	8.60826828
Gfi1b	0	0	0	0	0	7.65342243
Hes5	0	0	0	0	0	0
Hey1	0	0	0	7.33170389	0	0
Hlf	9.04765144	10.6533675	10.5269011	9.04230199	9.56488914	9.70383891
Id2	7.62991754	0	4.23111706	0	0	0
Ifi203	11.2501676	11.914907	11.8653931	11.1350751	12.3322589	11.9786983
Ifi205	0	0	0	0	0	0
Ifitm1	13.6024841	13.2671579	13.1559778	14.6147998	12.3940005	13.0506359
Ikzf1	8.99227257	0	6.59952389	4.22155675	8.51392841	8.28888823
Ikzf2	7.97202071	9.3328216	8.73462182	7.32657718	7.08686654	9.84110991
Il7R	0	0	0	0	0	0
Irf4	4.70292121	0	0	0	0	0
Irf6	5.54666139	6.23688513	0	5.97785483	5.02049373	4.96109854
Irf8	7.86823205	8.15367383	2.63621427	6.83354507	0	0
Kdr	5.53840288	0	8.15341571	7.01205599	7.4642774	7.1326176
Kit	11.2607047	10.3606009	8.79628445	11.5915902	10.481916	11.5872617
Klf1	0	3.25860663	7.84616118	0	0	0
Klf12	8.51276514	0	7.11967734	0	6.76070903	7.21735901
Ldb1	10.1909279	10.4320215	9.54439153	10.2617076	9.04575239	10.805799
Lin28a	5.62179949	3.31473014	1.92780466	0	6.68984894	3.16561904
Lmo2	11.3839154	11.4034046	11.3907002	10.8211784	10.7792744	11.5849622
Ly6a	10.4770569	8.56680086	10.4469799	10.6032693	9.78976088	10.5262032
Lyl1	7.72600868	7.4205871	7.75834476	0	2.04943398	5.36599153
Mbd2	7.18160941	0	8.37079723	8.40944262	7.72922325	9.44956043
Meis1	8.38029564	9.48751454	8.92807614	9.17214844	9.24061666	9.66150816
Mllt3	5.70832826	4.43853888	6.41671792	3.9945214	3.62889877	5.44463465
Mpl	9.80451345	10.0432958	9.24266526	8.79519105	8.10182066	11.1002171
Muc13	8.98196707	5.59560036	5.88707405	8.6485199	9.85981222	8.758467
Myb	12.229057	11.105609	10.5930915	11.6502743	11.2030698	12.0392037
Myc	5.94054515	8.26431355	0	0	9.23698786	0
Mycn	12.9133833	12.0386919	12.9135442	11.3734877	12.9094945	13.2019114
Ndn	10.1539124	10.0168565	10.2371109	10.6363452	9.55015746	10.2823756
Nfat5	10.0281421	9.33420441	9.33337438	9.24446933	9.36691113	10.2854003
Nfia	9.50780688	9.55882506	9.20366745	10.0443654	8.63527972	8.37856563
Nfkb1	4.40547181	0	6.72539404	5.68195326	3.69104625	2.61534874
Notch1	7.92730103	0	0	0	1.91842901	7.254093
Pax4	0	0	2.75717363	0	0	0
Pax5	0	0	0	0	0	0
Pax9	0	0	0	0	7.51446706	0
Pbx1	0	0	0	0	7.35355438	0

TABLE 8-3-continued

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly13	iHSC-8-TF-Poly14	iHSC-8-TF-Poly15	iHSC-8-TF-Poly16	iHSC-8-TF-Poly17	iHSC-8-TF-Poly18
PIk3ca	9.36193609	10.1573699	8.69135241	7.22797069	9.350244	9.7945183
PIk3R2	9.08458317	7.31464789	0	7.23501761	0	8.77459895
Plag1	9.35742205	9.87687278	6.76687433	9.21256194	7.60654426	9.96667624
Prf1	0	0	8.2323039	0	0	0
Pten	10.0306742	10.2227214	9.46793062	8.97227711	10.0315494	10.1169538
Rb1	9.14716883	8.05715458	9.38141621	7.77964535	8.78223278	9.78773033
Rora	7.18374293	8.46056013	5.83820968	8.93757151	4.90427489	0
Runx1	10.9790323	6.4366202	7.3434187	9.02591347	7.456308	8.6424525
Runx2	5.06108884	4.73894347	3.57947524	0	4.71767067	4.01213338
Satb1	0	0	6.988754	0	0	0
Sdpr	7.25321831	1.49255939	5.03703907	7.36858199	5.63016034	4.99059297
Sell	0	0	0	0	0	0
Sfpi1	8.23548593	9.30951305	8.23896762	9.70211776	9.06710973	9.02501417
Slamf1	8.97871652	7.69050245	8.12971792	8.19661263	6.49955824	9.49238402
Smarca4	9.16368267	8.86000678	7.42507799	10.3635361	8.42813404	9.89775871
Sos1	6.95641434	6.76871668	5.24577661	4.77916419	5.28495752	5.60242229
Stat1	2.55560167	1.57984978	2.47684151	3.53475743	5.10154814	2.60129708
Stat3	10.050798	10.319077	10.6594607	10.4305246	8.82047476	11.132745
Stat4	9.33292587	6.1179188	9.39461735	8.20558579	8.85019502	10.5591988
Stat6	9.12089244	9.48439599	8.23719382	8.55868133	9.07236102	8.98821013
Suz12	9.38104801	6.98601382	9.13046142	8.52416999	7.65310844	8.32511917
Tal1	0	0	3.47169406	0	2.67263762	7.4198786
Tcf3	10.5584	9.01499115	9.3657276	0	9.47219667	9.8412718
Tcf4	9.215939	9.39183959	7.54261135	9.26545368	9.99166629	10.0227825
Tcf7	0	0	0	3.59122317	0	0
Tek	0	0	9.1484583	3.17123575	7.42337143	5.89012912
Tfrc	8.51963706	8.20530652	8.13700044	0	8.25042927	0
Tgfb1	2.78186927	6.42869806	5.89270974	0	1.05785152	6.22071528
Tgfb2	0	0	0	0	0	0
Tgfb3	3.34813	0	7.79588299	7.42980658	7.51930126	8.10294994
Tnfrsf1a	8.97610513	9.40934119	9.51740906	8.73586007	7.77034164	8.68220529
Tnfrsf1b	7.7581593	7.64845624	8.38084662	0	9.10235665	9.03749186
Tnfrsf21	2.71798644	0	1.74571738	2.68827623	3.04822159	5.61552431
Tnfsf10	6.81258092	7.05606832	4.88500889	6.08129458	4.45443159	7.17866012
Tnfsf12	0	0	0	0	3.42201447	3.17042749
Tob1	6.08956479	0	1.0254279	0	4.07499239	0
vWF	8.69641471	7.83148927	5.7541953	7.51750945	6.84122876	8.68209545
Zbtb20	10.7465428	8.11584272	10.0666657	8.72759216	8.97604308	9.84825138
Zbtb38	7.4776121	7.71700408	8.82991017	6.57384818	2.72358522	8.69891554
Zfp532	0	0	0	0	0	0
Zfp612	5.94153564	6.7720852	7.52351011	7.44920631	6.39354799	7.81847435
Zfpm1	7.42741579	6.64520623	8.37192116	0	0	6.62040347
Zhx2	0	0	2.08517851	8.18192171	8.6593969	7.86530332

TABLE 8-4

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly19	iHSC-8-TF-Poly20	iHSC-8-TF-Poly21	iHSC-8-TF-Poly22	iHSC-8-TF-Poly23	iHSC-8-TF-Poly24
Actb	14.0222957	14.9852165	14.7231936	13.0780412	13.1822769	14.7520851
Aebp2	6.09276785	5.91339645	7.15748106	7.15006465	6.44734708	7.56825651
Ahr	0	7.35656431	0	0	7.39042048	0
Akt1	10.1537514	9.0396397	10.8518586	10.0130998	9.0677075	10.2965742
Akt2	5.37628872	5.62239369	4.54633859	4.9627968	0	6.55702093
Akt3	6.43567703	0	8.32809947	7.77517295	7.00340875	6.69568826
APC	0	6.02993274	7.1076109	0	0	7.41151949
Bad	0	7.95577502	0	0	0	0
Bax	9.62042258	10.1007541	9.93762446	10.5704358	8.58778402	9.82062487
Bcl11a	8.25024263	0	6.13142565	8.06182977	0	0
Bcl11b	0	0	0	0	0	0
Bcl2	5.80097299	6.96327952	5.50955358	6.14344881	6.33146119	8.64834323
Bcl2l1	7.19137797	9.09460414	8.68585536	8.37559007	7.91961022	9.1222599
Bcl2l11	7.10099787	0	0	8.66530941	7.92945207	7.29055975
Bmi1	0	8.89333432	8.82500517	8.04845917	7.27905634	7.66241462
Brd3	7.81963512	6.53346079	8.46718639	6.63970649	3.58678146	8.79527153
Casp8	8.16002179	7.41674663	9.68556501	8.98596978	7.82524756	8.16507587
Casp9	8.12191839	0	0	8.20184923	6.86433721	0

TABLE 8-4-continued

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly19	iHSC-8-TF-Poly20	iHSC-8-TF-Poly21	iHSC-8-TF-Poly22	iHSC-8-TF-Poly23	iHSC-8-TF-Poly24
Cbx2	5.83990951	7.17824899	1.13974563	0	1.69623499	5.47697139
Cbx8	0	0.94186577	4.35885212	0.62378639	0	0
Ccnc	6.44758404	7.56469246	7.28657546	0	3.55530815	7.0627638
Ccnd1	10.2579337	10.3894912	10.1044493	9.85934264	7.70190072	10.2600958
Ccne2	4.05061191	7.82199556	0	0	0	0
CD34	5.35839334	1.30106581	7.35425184	6.61374857	6.44471518	1.61234414
CD41	5.77643219	0	10.4393533	0	0	10.3495091
CD48	0	0	0	0	0	0
CD52	0	0	0	3.01619125	0	0
CD53	8.03999469	0	0	7.50341317	10.1028594	0
CD55	7.33579923	5.27016862	7.79008222	7.56180434	6.90429703	7.62824401
CD63	8.37023042	8.80391232	9.66493806	8.10475976	6.51700946	8.24520437
CD9	7.12446184	0	7.78614293	0	8.48314556	7.50038252
Cdc42	11.193945	11.5997344	12.2211899	11.14451	9.02347781	11.8346973
Cdk1	3.82114993	0	0	0	0	8.8707332
Cdk4	8.72490443	9.2366055	9.21810563	8.92536239	7.92269766	9.0715251
Cdkn2b	0	0	0	0	0	0
Cebpa	0	0.92340397	0	0	1.00115542	3.07355052
Csf1r	0	0	0	0	0	4.67306388
Ctnnb1	9.02013289	8.1995723	8.88842654	7.35118018	7.79633098	9.06433317
Cycs	4.40114607	10.7395371	9.31670975	9.50564127	8.73967132	10.179991
Dach1	9.36485262	8.82201919	0	8.05339981	0	10.8270759
Dnmt1	0	9.58140407	10.0497632	8.2793687	6.63806785	8.17811462
Dnmt3a	10.9905048	9.19877847	7.56408268	9.58520501	8.76598997	11.0073815
Dnmt3b	6.12321822	5.91369116	6.74621053	8.79572673	0	8.46193889
Dtx1	0	0	4.45860491	0	4.40787301	2.92452083
Dtx4	0	0	0	0	0	4.65526374
Ebf1	0	0	0	0	0	0
Ep300	8.31116148	9.22743592	7.7293946	8.80009368	7.48345043	9.03015668
Epor	6.59886102	8.36411013	6.46843364	7.45226452	6.61055385	8.51394952
Erg	9.78578531	7.35912985	11.1497111	10.1003655	10.2588034	10.1895405
Esr1	10.7256327	11.2332794	8.62974835	10.714868	9.12800318	7.71830109
ETS1	9.50337181	9.15865955	8.17116294	8.01408055	7.45017515	0
ETS2	7.42626021	9.43167027	7.78315302	9.20343927	9.3179479	8.01612975
Etv3	1.3458142	5.98695328	4.79867027	2.51010934	4.92346803	3.7511546
Etv6	10.6179622	10.4118422	10.2187025	9.96156985	10.038584	9.91374759
Ezh2	0	7.4963002	5.11451697	0	4.27019431	5.00451192
Fas	0	0	6.38955508	0	0	6.53357255
Fcgr2b	0	0	0	0	0	0
Fcgr3	0	0	0	0	0	4.03293964
Fli1	11.3359409	10.6665214	12.2098328	11.3839786	12.0700831	12.5969288
Flt3	0	0	5.17872234	0	0	0
Fosl1	0	0	0	7.88407638	0	0
Foxo1	10.6157657	10.0233787	10.3312339	8.69958676	10.0863135	8.75473743
Foxo3	8.75455393	8.2202859	9.4323668	8.96146302	8.37704731	9.54868349
Gapdh	9.39063578	9.6332912	9.01611712	8.48869618	7.45420386	9.51346889
Gata1	2.29550385	0	2.19508312	0	0	7.81928617
Gata2	7.90701459	6.57337507	7.74249758	7.39810444	5.78754669	7.21810544
Gata3	9.25625641	9.59194441	7.96562707	9.02739686	9.24201171	5.54111636
Gfi1	8.16247965	9.05106935	1.53883386	9.20704112	8.86848623	1.74671367
Gfi1b	7.48261818	0	9.01407569	7.92225525	0	10.4544307
Hes5	0	0	0	0	0	0
Hey1	0	0	0.23980869	0	3.99694016	0
Hlf	10.0172951	8.57271376	9.52837203	9.19521494	10.1704945	8.00758435
Id2	3.69016431	6.66309649	0	8.09079275	0	0
Ifi203	10.7615272	11.4665288	9.34620527	12.029167	12.0276813	12.3753844
Ifi205	0	0	6.21186981	0	0	0
Ifitm1	12.52963	14.056977	12.1062642	14.4446358	13.0043214	11.5613877
Ikzf1	9.49333946	8.39564132	6.74977708	7.60909535	7.65040476	9.02382942
Ikzf2	8.34635213	6.9536272	8.61475235	6.86277574	6.23476562	7.53972582
Il7R	0	0	0	0	0	0
Irf4	0	0	0	5.32286189	0	0
Irf6	4.23055125	6.62986325	5.38490108	4.90732154	1.6439306	3.52949201
Irf8	0	7.03460532	0	2.07699694	0	6.38053878
Kdr	0	0	0	8.31606549	0	1.78210879
Kit	10.3885328	6.36619186	9.89600505	10.6754558	10.6599878	12.0390472
Klf1	0	5.96327424	0	0	3.13498357	0
Klf12	0	5.07853345	0	0	5.94120823	7.42134808
Ldb1	10.1606712	9.4851491	10.5743575	10.1071175	9.70318406	9.85749521
Lin28a	7.17967747	5.7551298	0	6.67444585	0	7.1800316
Lmo2	11.3790886	10.9990795	11.1248884	10.5434856	10.8867459	11.3916155
Ly6a	9.90063146	10.425202	9.30350233	10.6994618	9.83374053	7.67564131

TABLE 8-4-continued

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly19	iHSC-8-TF-Poly20	iHSC-8-TF-Poly21	iHSC-8-TF-Poly22	iHSC-8-TF-Poly23	iHSC-8-TF-Poly24
Lyl1	7.14647222	8.82469566	7.29100041	7.01495401	8.09680593	0
Mbd2	10.0576916	9.28619721	9.17962218	9.39666712	0	8.99242891
Meis1	9.19612035	7.20888322	9.3457055	8.41585689	8.18293381	9.0030273
Mllt3	6.32843166	0.74266874	4.39498203	3.39205835	6.23365027	3.44437544
Mpl	8.94809398	10.5780332	10.4781264	10.277185	8.87490577	9.39242946
Muc13	8.27790617	0	10.4076758	6.76806625	5.00295934	10.3973791
Myb	11.7453163	11.8586016	11.7506552	11.1696323	10.9979778	11.7377404
Myc	9.36837161	7.05635853	8.52793183	9.28427723	0	11.6017931
Mycn	13.2729086	13.0027169	11.5828444	12.1822321	11.3420486	10.4739711
Ndn	10.1608893	0	9.76813472	10.8699711	6.85887785	7.86045035
Nfat5	9.33700148	9.37171439	9.61477453	10.0347254	9.16012698	11.0068399
Nfia	9.19929579	8.60111942	9.05469309	8.45114924	7.63071837	10.4493102
Nfkb1	5.80357529	3.19392376	5.18644292	2.62506816	4.67722842	4.73163984
Notch1	0	0	7.11863629	0	0	0
Pax4	5.85834965	0	0	0	0	0
Pax5	0	0	0	0	0	0
Pax9	1.49067007	1.89512232	6.48812116	0	4.05075553	0
Pbx1	0	6.44666705	1.43020832	5.65796056	0	5.75884417
PIk3ca	8.51982982	7.20799174	6.37633123	0	0	6.46020226
PIk3R2	8.38136327	8.97464344	9.98572262	0	7.61404741	8.48818785
Plag1	0	0	6.4230689	7.11287226	0	0
Prf1	0	0	0	0	0	0
Pten	10.540168	9.73816633	10.8896648	9.24580983	9.87665899	10.9693546
Rb1	7.31833258	9.22662137	9.69069735	10.0839906	8.40316967	8.99999716
Rora	6.73484556	0	0	0	9.2605019	9.02226435
Runx1	0	10.6851969	8.05120975	9.13766939	0	7.96523554
Runx2	4.65669851	4.87793717	0	4.53994772	5.95340157	5.22261949
Satb1	0	0	0	7.42656655	7.19081992	0
Sdpr	4.8919743	5.24630781	5.31896107	5.91836204	4.45600583	6.97989467
Sell	1.98131911	0	0	0	0	0
Sfpi1	7.85387748	7.69052148	0	0	6.83763769	0
Slamf1	0	8.49168885	0	8.17041428	8.03774087	8.97604844
Smarca4	10.9295084	10.7537022	10.631709	7.01755625	0	11.2935237
Sos1	6.74790018	4.84633913	6.25614779	5.08932828	5.99132703	7.55749624
Stat1	4.09438953	3.12874153	0.0136088	7.49778073	3.08878778	4.41941405
Stat3	10.6461698	10.1970393	11.6374187	10.6737607	10.7089761	10.407426
Stat4	7.94643022	7.77936924	7.15328942	9.69556223	8.59968281	10.8890815
Stat6	10.6283289	9.39699663	7.46878642	10.3247299	8.10965668	9.61146029
Suz12	8.47536799	7.00434943	7.22403444	9.07440769	6.61891321	9.26075033
Tal1	0	0.78562075	0.32304358	0	1.05194194	3.12802446
Tcf3	8.71121837	8.47702552	9.5832776	9.51241599	0	0
Tcf4	8.74989108	10.019422	9.67827255	9.15887745	9.0850838	11.1528985
Tcf7	0	1.52995296	0	0	0	5.98283478
Tek	8.29344896	0	0	0	7.0599381	6.9286127
Tfrc	8.98222729	0	8.46857397	0	0	9.30593475
Tgfb1	5.18251178	0	1.45806631	6.10276766	6.19575758	4.43408052
Tgfb2	0	0	0	0	0	6.69513523
Tgfb3	4.31080402	7.71403034	0	0	8.43808726	7.6392649
Tnfrsf1a	8.37097875	9.75633627	9.2929424	8.88457116	9.33603379	9.21302132
Tnfrsf1b	8.69059649	8.23787663	9.40938599	8.83717215	8.39065647	10.0362648
Tnfrsf21	3.20614275	6.19102698	5.06049798	3.05259086	3.46771395	6.05459577
Tnfsf10	0	0	5.97171916	0	7.59819331	7.31664485
Tnfsf12	0	0	0	0	0	0
Tob1	6.69079448	6.00223918	0	3.73540562	0	5.02457741
vWF	7.03390478	7.00183766	6.76991781	7.90167655	7.3503261	8.19082768
Zbtb20	8.75751032	8.56608423	7.87546645	9.54728999	9.08834794	8.98417896
Zbtb38	8.42709931	6.65368752	8.31325825	7.64612461	5.85086359	7.6993122
Zfp532	0	2.57549982	0	0	0	0
Zfp612	7.39496006	9.86263779	8.6174037	6.07547603	7.44714339	7.42549287
Zfpm1	0	0	7.32419209	0	0	7.09081266
Zhx2	5.14338261	7.9453336	7.54993366	7.52150615	0	0

TABLE 8-5

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly25	iHSC-8-TF-Poly26	iHSC-8-TF-Poly27	iHSC-8-TF-Poly28	iHSC-8-TF-Poly29	iHSC-8-TF-Poly30
Actb	15.1467264	15.0603057	14.7898411	13.7224541	13.1728469	12.9889544
Aebp2	7.22454633	8.054577	6.2934136	5.40380392	6.94511987	6.23324236
Ahr	0	0	0	8.0387708	6.82981017	0
Akt1	10.4393078	11.2053361	10.3315581	9.52591131	8.93069445	9.8447304
Akt2	5.46798025	4.36096146	0	0	6.22509388	5.58121685
Akt3	8.54577868	9.10928289	6.11061488	5.23070804	7.20403999	7.48254296
APC	7.54219167	8.23602617	0	3.26916842	7.12783167	7.33873364
Bad	0	0	0	0	0	0
Bax	9.50825239	10.7263374	10.1709333	8.9480305	7.02132481	9.08482722
Bcl11a	0	0	0	0	5.41177469	5.64855342
Bcl11b	0	0	4.08334085	0	0	0
Bcl2	3.68995409	7.32318474	7.06144794	6.58939055	3.18869428	4.94548147
Bcl2l1	6.81430281	9.83800287	9.83067128	9.33405878	1.18529944	0
Bcl2l11	9.18689234	4.87995875	2.32073334	7.05754987	7.15679605	0
Bmi1	9.41703263	10.590967	8.13517912	8.21207019	7.89416001	8.36530966
Brd3	7.40062986	8.45229557	7.37805192	6.73549941	6.38937753	0
Casp8	9.06859401	9.89552232	7.64299925	9.08071818	6.57464487	8.31311348
Casp9	3.44991217	6.93448309	0	9.05103431	7.48305696	8.79567172
Cbx2	5.65665485	4.81978051	5.01321494	7.38009168	6.31186522	7.25681223
Cbx8	7.51395854	5.26741788	0	0	0	0
Ccnc	3.40126563	7.17806544	7.78283799	8.63152446	8.813967	6.58765669
Ccnd1	10.8599552	11.4320536	11.3331975	7.53991341	0	9.29046471
Ccne2	7.83759047	8.65858417	0	0	3.32687121	0
CD34	6.63187034	9.7565564	7.40591115	8.39371742	6.77659879	5.99841538
CD41	2.14023125	8.47542727	6.69580828	4.98782898	0	0
CD48	0	0	0	0	0	0
CD52	7.91998753	8.98451985	0	4.94138545	0	5.93717087
CD53	6.94204489	10.5301752	0	7.40829181	6.96255155	9.16158967
CD55	2.67695364	7.24868997	0	6.8723678	6.65669014	0
CD63	7.9251335	9.70346434	8.76574443	8.18049221	7.4946542	8.16601991
CD9	5.82915993	0	7.99497783	0	0	7.22604682
Cdc42	12.2364611	12.3344896	12.0159112	11.7559163	10.3539974	9.97336176
Cdk1	0	0	0	6.53350976	4.26316228	0
Cdk4	9.99908798	10.1349512	9.51946578	8.41035443	8.08864468	8.77958527
Cdkn2b	0	0	0	0	0	0
Cebpa	0	0	0	0	2.49157455	0
Csf1r	0	0	0	7.64542858	0	0
Ctnnb1	8.99986283	10.3367688	8.5457773	7.874021	8.83840174	7.30650645
Cycs	10.4684479	10.2719616	11.6179928	8.6873144	8.85811424	9.08493865
Dach1	10.2351588	10.5375086	5.28114978	7.94289632	9.06367016	8.61751831
Dnmt1	10.4609244	10.9431578	9.49692678	8.00548457	4.47880176	8.89034639
Dnmt3a	10.1900028	10.2175853	10.5489199	10.1873262	8.0649379	8.61671847
Dnmt3b	10.4287559	7.64484667	7.66846002	7.47190296	7.46314199	0
Dtx1	2.87373766	0	4.45487641	0	3.39237286	0
Dtx4	8.30188881	0	3.76809623	8.90387752	7.33254088	0
Ebf1	0	0	0	0	0	0
Ep300	9.27663432	10.1042304	9.68113841	8.5374249	8.21206612	9.24606331
Epor	7.85270065	8.04294538	9.16962943	8.54759033	7.35632339	6.14561167
Erg	8.55265099	10.2669084	10.2169225	7.63186499	8.95845922	10.2164651
Esr1	9.38768526	9.97524679	0	10.8874494	7.8990261	7.59868432
ETS1	6.6308345	8.37613488	6.37681253	7.42772803	0	0
ETS2	8.17680732	10.0653554	3.38470303	8.81529422	0	7.77351284
Etv3	6.11040493	0	3.98584882	3.26053429	4.70577394	4.48214929
Etv6	9.8608361	11.5277743	11.4810765	8.43992379	9.20838366	11.0463499
Ezh2	7.709826	6.54832	0	4.52144944	0	0
Fas	0	0	0	0	0	0
Fcgr2b	1.90741417	0	0	0	4.85415356	1.74014502
Fcgr3	0	0	1.08750014	0	3.68471648	0
Fli1	11.0534143	13.0298511	11.2583348	10.8538562	11.3158563	10.8772294
Flt3	0	4.16157253	0	0	8.03117137	0
Fosl1	0	0	0	8.2455383	0	0
Foxo1	9.70714029	10.6720909	10.3788241	9.80708641	8.26507304	10.6496396
Foxo3	9.48634989	9.86647621	7.51118011	8.70034889	7.37972878	8.55743355
Gapdh	8.86227153	8.45555869	8.72625477	8.41917922	8.02370137	6.10600952
Gata1	0	3.80535399	0	0	6.75158933	0
Gata2	5.91383797	8.18298805	7.06534352	6.42930963	4.69341126	5.21404746
Gata3	9.11573842	10.3308833	8.31030094	9.17077025	8.17912775	9.3094042
Gfi1	0	0	1.23659601	6.90153413	8.4360923	6.0672508
Gfi1b	0	7.73951118	0	8.27925976	2.60027956	0
Hes5	0	0	0	0	0	0
Hey1	0	4.03507957	0	0	0	0
Hlf	11.6008005	10.3681868	8.12581134	9.33949169	9.74960861	9.90445603

TABLE 8-5-continued

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly25	iHSC-8-TF-Poly26	iHSC-8-TF-Poly27	iHSC-8-TF-Poly28	iHSC-8-TF-Poly29	iHSC-8-TF-Poly30
Id2	0	0	0	0	7.98559854	0
Ifi203	13.7479568	12.7438712	11.8807423	11.6897407	8.68436391	11.1266634
Ifi205	0	4.09293031	0	6.42758045	0	0
Ifitml	13.859925	14.1799111	12.4645038	13.3616994	12.6048996	13.2905626
Ikzf1	9.27873989	10.4587279	5.91103149	7.22522005	7.63638395	7.21841248
Ikzf2	8.55691698	9.00296885	0	10.0127515	7.05646755	7.55750237
Il7R	0	0	0	0	0	0
Irf4	0	0	0	0	0	3.13466963
Irf6	0	4.45135084	2.0970079	4.45935177	2.34298554	3.11901816
Irf8	8.36267886	0	8.28087448	0	0	0
Kdr	0	0	0	7.11467704	0	0
Kit	7.33440621	11.676319	12.0482852	10.3613984	10.8447689	9.71837065
Klf1	4.6113579	0	0	7.07231232	0	0
Klf12	7.16079482	7.39809865	7.38280606	7.94577018	8.65600956	7.11655703
Ldb1	11.0650833	10.7394902	9.391079	9.69631695	9.34063818	8.23556142
Lin28a	8.59487815	7.9674739	8.97421223	4.11702404	8.12470644	8.71804793
Lmo2	10.8175242	11.0371363	9.96662941	10.9024038	10.303006	9.67048273
Ly6a	11.3320064	10.8896747	11.6269362	10.7750255	8.734268	8.94138397
Lyl1	0	8.45036073	8.31542245	7.1453941	6.78867557	0
Mbd2	9.82815303	7.77519918	9.72316715	8.71004644	0	8.71389867
Meis1	8.72386921	9.27416327	7.7021466	8.50453784	8.4108095	7.11187223
Mllt3	1.20911588	2.90532993	3.24157892	6.04227027	3.56250704	3.41569762
Mpl	8.16713987	11.1382076	8.84138738	9.51523532	6.45757591	9.14051092
Muc13	3.84864206	10.6660629	10.1548311	7.8264378	7.56339286	8.44043237
Myb	11.9506659	12.679687	12.354001	11.6763394	11.1472311	10.8315677
Myc	0	10.0093188	8.34807296	9.25839322	7.84577514	7.52780084
Mycn	10.870635	12.9395207	12.3151591	12.053502	12.6255533	9.68590773
Ndn	6.69958267	11.2092172	8.79795885	10.1009021	4.07328976	8.99463446
Nfat5	10.4275502	11.0533765	9.97984923	10.6782945	9.95523149	10.2518547
Nfia	8.76693228	11.1506945	10.3677089	9.02919232	7.97805043	7.23689606
Nfkb1	4.92161927	7.85783734	0	5.31107579	0	5.41888462
Notch1	0	6.97371909	6.50677693	8.20930046	7.14314591	8.77749162
Pax4	0	0.41579145	0	0	1.78594162	0
Pax5	0	0	0	0	0	0
Pax9	0	1.29709712	5.34825344	0	0	0
Pbx1	0	0	4.99498393	0	4.3948675	0
PIk3ca	7.29512319	5.10151123	9.26701666	8.77108696	7.8137764	8.06874559
PIk3R2	0	9.54668408	0	4.03560663	7.63724867	8.09289398
Plag1	4.05714178	7.17110365	7.47615183	6.78269553	6.68706596	8.11285307
Prf1	0	0	0	0	1.76277593	0
Pten	9.67233193	10.8750291	11.2752335	9.07906849	9.619202	9.54758043
Rb1	2.4815274	9.83858258	9.93875591	8.12503051	0	9.56415776
Rora	6.2784063	7.96217943	8.97191919	5.69747967	6.69619858	0
Runx1	7.72158429	11.5617806	8.0209297	0	7.34188594	9.3066077
Runx2	6.44168173	6.47921853	4.05939813	0	4.52343132	0
Satb1	0	0	0	0	0	0
Sdpr	3.14060766	4.67747404	0	5.13849374	4.35123979	0
Sell	0	7.82142452	0	0	0	0
Sfpi1	9.44004137	10.6112564	9.57177198	9.73952896	7.67485892	9.1636508
Slamf1	0	9.8509578	0	7.94976735	0	0
Smarca4	9.67242674	11.3679625	10.9120144	8.33633778	9.38747622	8.96597469
Sos1	6.73189286	7.18014773	6.17729215	2.57292994	0	5.02443057
Stat1	5.68555984	3.02264624	7.3271143	5.35339745	0.83073004	3.29153215
Stat3	11.3131951	9.57939384	9.0893893	9.5064832	8.66288619	9.76664759
Stat4	8.57556847	8.81788595	7.9582273	8.78864361	9.09957433	8.97134532
Stat6	10.8376145	10.2010288	8.49312223	9.35277641	7.40643256	8.90732864
Suz12	9.41780703	9.04550097	8.43918141	6.8443864	8.23939832	7.20948647
Tal1	0.36745858	3.76022412	1.90443062	1.20031735	0	1.80499304
Tcf3	0	11.0694031	10.6447268	0	0	0
Tcf4	10.6969499	10.046866	9.90816861	9.69613559	10.4609901	8.34637629
Tcf7	0	0	4.47895555	0	0	0.42028063
Tek	0	0	6.45746287	7.3858809	0	0
Tfrc	10.1334859	10.3260932	9.35672673	8.44227518	4.80666561	0
Tgfb1	0	6.89665934	5.8186116	6.7222637	0.76900814	0
Tgfb2	4.82881658	0	0	0	0	0
Tgfb3	7.47747614	8.54176509	0	0	8.79652611	0
Tnfrsf1a	9.39147825	10.7935619	9.25501158	9.89472761	8.6880689	8.31560598
Tnfrsf1b	9.23838068	9.80031527	8.22142743	0	7.28814434	7.90865273
Tnfrsf21	6.28949914	5.97728009	5.19350171	5.57452029	4.50016048	0
Tnfsf10	7.22789618	7.36848679	6.75517567	7.16478253	0	7.06007861
Tnfsf12	0	4.3060738	0	4.85239643	0	2.04680563
Tob1	1.76727829	0	0	1.31719975	0	5.22971098

TABLE 8-5-continued

Single cell expression data (reduced list)---iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly25	iHSC-8-TF-Poly26	iHSC-8-TF-Poly27	iHSC-8-TF-Poly28	iHSC-8-TF-Poly29	iHSC-8-TF-Poly30
vWF	4.32082285	6.06693197	0	5.71670619	6.04694734	5.12273794
Zbtb20	8.1961861	9.72922487	8.03051751	9.40713548	7.57941477	7.38691184
Zbtb38	7.5702152	9.54076295	6.6697548	7.46445387	6.53307434	7.23318321
Zfp532	0	0	0	0	5.04108384	5.18050424
Zfp612	5.72138328	8.03852538	5.85275553	5.51442076	5.97875939	8.22421158
Zfpm1	0	6.44875688	6.30023725	0	1.71015037	0
Zhx2	9.12067496	8.78641727	0	8.48763196	0	0

TABLE 8-6

Single cell expression data (reduced list)-iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly31	iHSC-8-TF-Poly32	iHSC-8-TF-Poly33	iHSC-8-TF-Poly34	iHSC-8-TF-Poly35
Actb	14.2069371	13.8470594	13.8401959	13.917789	15.1280325
Aebp2	5.98889731	6.37700771	7.03385188	7.32807418	5.967507558
Ahr	0	7.35587653	7.14024783	0	7.726173885
Ala1	9.63022936	9.79043235	8.92541514	10.255464	10.06829133
Akt2	4.7739806	6.20050837	0	6.6173956	6.266455938
Akt3	7.83294768	7.93223254	7.33454157	7.96075903	7.609211364
APC	7.03824303	2.01225823	7.3738631	6.86740225	0
Bad	0	0	0	0	0
Bax	7.92377163	9.35241369	8.79541456	10.1556033	9.298454044
Bcl11a	6.79087658	9.42268001	0	5.94056	9.650354382
Bcl11b	0	7.91342229	0	0	0
Bcl2	7.71843033	4.37394315	3.67661636	6.48782736	6.12384282
Bcl2l1	7.32275084	8.01987482	8.88727066	10.3391458	5.482050078
Bcl2l11	5.79196834	7.61927617	0	0	7.954405054
Bmi1	8.81392639	9.20924156	9.08236893	0	8.889304656
Brd3	7.23409493	7.45401462	5.51991989	8.04268652	7.389789509
Casp8	7.67563079	8.20820007	6.55654411	7.54337459	8.32215887
Casp9	0	0	8.99779312	4.59384186	5.848587768
Cbx2	1.44235903	5.10087886	3.11514136	4.33721335	7.198562206
Cbx8	0	0	0	0	0
Ccnc	6.39235909	2.98958517	6.90788079	8.33600559	0
Ccnd1	9.85365523	9.35220323	10.3423931	10.596546	10.3258133
Ccne2	0	0	0	0	0
CD34	8.18588751	7.74906415	7.26970785	0	7.499624637
CD41	9.13809414	0	2.48229859	9.03163232	2.624405589
CD48	0	0	0	0	0
CD52	0	0	0	0	0
CD53	9.41977885	9.65013579	7.29556871	0	7.157577428
CD55	8.06965354	6.20993378	0	0	8.314622092
CD63	8.2891293	8.70844929	8.28276973	7.95614666	7.974507291
CD9	5.61055111	8.76259165	7.38090105	9.05799841	7.984779418
Cdc42	11.6414373	11.5413516	11.8105407	12.0218361	12.15037822
Cdk1	0	0	5.92738978	6.4822881	0
Cdk4	9.11192333	8.53731642	7.38211559	9.25948872	8.7744804
Cdkn2b	0	2.02544167	0	0	0
Cebpa	0	0	0	1.76275336	0
Csf1r	0	0	0	0	0
Ctnnb1	8.53778061	8.99449917	8.50354705	8.54550946	8.150621469
Cycs	8.74992664	9.3211739	7.56416714	11.6306877	9.73444361
Dach1	10.2255054	8.13381132	9.01635767	9.67564058	9.403674066
Dnmt1	7.06488647	8.20709121	5.48806315	10.7511069	9.291062883
Dnmt3a	9.34089662	10.5431275	9.68146699	9.67721509	9.574078858
Dnmt3b	7.10396864	7.14264453	0	8.67608269	8.398086808
Dtx1	0	3.92664652	0	0	1.079050232
Dtx4	0	0	6.49224019	0	7.288080256
Ebf1	0	0	0	0	0
Ep300	8.96510963	9.64835081	9.30091348	8.39112866	8.866505918
Epor	7.23361451	8.89683938	8.61954912	7.62063998	8.194140038
Erg	9.8355606	10.6000491	9.47258834	9.6821144	10.01801557
Esr1	6.30347997	5.64608692	9.59441989	0	7.287947864
ETS1	6.09111489	6.98717296	7.45969571	6.50362082	5.966052941
ETS2	8.21354447	9.19096881	1.88892339	8.82189923	7.475011402
Etv3	2.96178532	5.48992927	4.14441284	0	2.046570736
Etv6	10.858902	10.7925323	9.17798475	10.4215528	8.441479121

TABLE 8-6-continued

Single cell expression data (reduced list)-iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly31	iHSC-8-TF-Poly32	iHSC-8-TF-Poly33	iHSC-8-TF-Poly34	iHSC-8-TF-Poly35
Ezh2	0	0	0	5.45401289	5.720754812
Fas	0	0	0	0	0
Fcgr2b	6.88075674	5.54617113	7.14891342	0	5.207646663
Fcgr3	0	7.00826514	2.35530291	0	0
Fli1	10.4691328	10.6639924	10.8692473	10.8916346	11.73795664
Flt3	7.70280609	0	0	0	0
Fosl1	0	0	0	7.93834953	0
Foxo1	9.88312231	9.91869001	9.41788508	9.980959	9.032259159
Foxo3	8.9575813	9.11938907	5.14307614	6.31778497	8.269683905
Gapdh	7.77415605	8.26157075	7.66942984	7.99106849	8.407711578
Gata1	0	0	0	9.41402438	0
Gata2	7.15464892	7.34496127	8.49543986	7.32606855	6.666698464
Gata3	8.87820207	6.20110618	8.30533556	6.87821567	10.13942411
Gfi1	3.66002454	10.3420315	3.3332712	0	9.13521169
Gfi1b	9.7202357	0	7.68331245	7.60509615	0
Hes5	0	0	0	0	0
Hey1	0	0	0	0.16937746	0
Hlf	9.6974979	11.3333543	10.0480033	5.45401024	10.71087925
Id2	0	1.73028986	2.9821102	0	0
Ifi203	11.0839141	12.322849	11.1353627	0	11.36781538
Ifi205	0	0.60415365	0	0	0
Ifitm1	11.7471245	14.7096222	13.8201159	10.3244566	12.69088657
Ikzf1	4.65390199	9.36172059	8.32379103	9.23805477	9.117655761
Ikzf2	8.1800366	9.34772631	8.67384155	7.5997184	7.633862356
Il7R	0	0	0	0	0
Irf4	0	0	0	0	0
Irf6	4.55947022	0	6.20746303	1.90705149	0
Irf8	4.17972502	5.19690275	0	0	1.168908887
Kdr	0	6.4546143	0	0	0
Kit	10.568118	10.7326629	9.66035824	10.235182	10.49875083
Klf1	0	0	0	0	0
Klf12	7.90580132	8.82046599	6.9604333	0	4.799978797
Ldb1	10.1435572	10.8500431	9.02813399	10.0262901	10.57537202
Lin28a	2.01835712	0	7.60463245	7.26719796	7.0567702
Lmo2	10.2921708	10.7989969	10.2263373	10.2137336	10.88135035
Ly6a	9.83101715	10.8834217	10.9471589	7.0165923	8.632926147
Lyl1	5.64299125	8.39061157	8.05543657	0	6.93753767
Mbd2	7.43457425	9.26608484	9.03952586	9.2082395	8.436864241
Meis1	7.17124275	8.43708101	8.22260057	9.10089289	9.11887556
Mllt3	4.68195721	7.14795197	0	0	0
Mpl	8.08112178	11.2655793	8.31206648	8.38505498	10.42540532
Muc13	7.69684641	8.740324	7.23849573	9.18630096	9.032771705
Myb	10.8533459	12.0368698	11.2785518	11.5385888	11.07370836
Myc	10.6275942	0	7.98150016	10.2477795	0
Mycn	11.5919441	13.7950767	13.0318118	11.572173	9.884323219
Ndn	7.40457998	10.7183908	8.75991643	0	9.66450548
Nfat5	9.91314435	11.3027566	10.3793203	9.5179896	9.779535652
Nfia	7.79221189	10.051871	9.80645605	8.5847577	9.825414289
Nfkb1	5.30418245	4.7738356	0	2.24245044	0
Notch1	0	0	8.15000269	0	7.573067604
Pax4	0	0	0	0	0
Pax5	6.27471676	0	0	0	0
Pax9	0	0	0	0	0
Pbx1	2.98370939	0	5.09401103	0	4.388365504
PIk3ca	8.75259112	8.2331466	9.04017873	8.40060398	8.480971265
PIk3R2	5.26485409	8.45942473	7.82585643	7.39316382	9.393048953
Plag1	0	7.30362382	0	7.34771911	9.10689314
Prf1	0	1.7040015	1.56236886	0	0
Pten	8.31345133	10.2695925	9.97217513	9.13715083	10.61329076
Rb1	9.95763649	9.79666893	7.99445736	9.2214006	9.482724273
Rora	0	6.56427305	5.64107699	4.56057422	6.331115465
Runx1	0	8.14608613	8.71941715	8.19287364	7.870521822
Runx2	5.34834113	4.59771607	3.47214128	0	5.551463025
Satb1	0	0	0	0	0
Sdpr	3.37648888	5.96772223	4.92952477	6.2586625	0.440922771
Sell	0	0	0	0	0
Sfpi1	8.60729629	8.1629534	8.63327996	0	9.702906322
Slamf1	8.18217953	8.5258681	9.31528985	0	0
Smarca4	9.34699951	9.96472508	9.88851572	10.4282604	9.608738237
Sos1	5.09407549	6.03558245	5.61700797	6.34922122	5.074256436
Stat1	1.59542643	3.04779271	4.03139248	2.14901292	1.713356031
Stat3	9.68231911	10.8000054	9.77728389	8.12814266	9.356540529

TABLE 8-6-continued

Single cell expression data (reduced list)-iHSC-8-TF-Poly

Factor	iHSC-8-TF-Poly31	iHSC-8-TF-Poly32	iHSC-8-TF-Poly33	iHSC-8-TF-Poly34	iHSC-8-TF-Poly35
Stat4	9.03078852	8.81875947	9.7628284	9.23753873	9.345223627
Stat6	8.80712329	10.4891182	8.86298599	9.36542993	9.506915587
Suz12	9.14292326	7.20766953	7.75046294	8.75372748	8.5960251
Tal1	2.01130091	0.68276644	6.73023432	2.3305105	3.375132509
Tcf3	10.2607205	0	10.2753363	0	9.495266453
Tcf4	9.35302065	9.01808097	10.5037967	9.43819789	10.19593089
Tcf7	0	0	0	0	2.167615009
Tek	0	7.96828571	0	0	0
Tfrc	10.289075	9.33491809	0	8.98476872	8.421750863
Tgfb1	0	0	1.58449749	3.70605263	0
Tgfb2	0	6.77707617	0	3.27306737	0
Tgfb3	7.58607476	0	0	0	0
Tnfrsf1a	10.1591524	9.83805082	9.98992194	8.08094003	9.174520259
Tnfrsf1b	9.13727	7.96181671	7.64996091	8.33642919	8.933678342
Tnfrsf21	5.11707811	5.6723159	2.99946137	5.63253583	4.286614066
Tnfsf10	4.56651794	7.36235451	6.96023501	0	0
Tnfsf12	0	0	0	0	0
Tob1	0	7.90731485	0	5.34587986	6.280356776
vWF	5.50820839	7.20387901	7.86788155	7.34146511	6.367927725
Zbtb20	9.56374662	9.76898114	9.31718552	6.40168708	9.092322576
Zbtb38	7.131271	8.33887914	7.67573354	5.98684877	7.925976084
Zfp532	0	0	0	0	0
Zfp612	7.37417759	7.21875833	8.50575865	7.70407891	7.488313843
Zfpm1	0	0	0	0	0
Zhx2	8.5972312	0	8.15875098	0	7.312382961

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Example 3

[1256] Radioprotection transplantation assays performed using donor-derived MEPs (Na Nakorn, J Clin Invest. 2002, 109(12), 1579-85) confirmed a robust ability to give rise to platelets and red blood cells in vivo (FIGS. **72**B-C).

[1257] In addition to sustained self-renewal potential, a hallmark property of HSCs is their ability to give rise to multi-lineage differentiation at the clonal level. Although we had observed clonal multi-lineage differentiation potential in vitro after induction of our factors (FIGS. **60**B-C), our in vivo transplantation experiments, which were done at the population level, precluded us from concluding clonal differentiation potential in vivo. We reasoned that Ig heavy chain rearrangements arising in Pro/Pre B-cells could be used as a lineage-tracing tool, and that the presence of common V(D)J rearrangements in different donor-derived lineages in our transplantation experiments could provide evidence of clonal multi-lineage differentiation potential. We therefore isolated

DNA from sorted donor-derived B- and T-cells, granulocytes, and macrophage/monocytes from primary recipients exhibiting long-term multi-lineage reconstitution derived from Pro/Pre B-cells transduced with the 8-TF^{Poly} viral cocktail. Ig heavy chain-specific PCR spanning the V(D)J junction was then performed and selected products common in size to all lineages were gel purified, cloned and sequenced. This analysis revealed the presence of V(D)J rearrangements common to all of the donor-derived lineages we analyzed from two independent experiments, indicating multi-lineage differentiation potential from clonal reprogrammed Pro/Pre B-cells (FIG. **71**A). That single reprogrammed cells possessed multi-lineage differentiation potential in vivo was further confirmed using a LAM-PCR-based approach, which revealed common viral integration sites in sorted donor-derived B-, T-, and myeloid cells (not shown). To test if reprogrammed cells sustained multi-lineage differentiation capacity during serial transplantation, we analyzed V(D)J junctions and viral integration via LAM-PCR on sorted donor-derived B-, T- and myeloid cells from secondary recipients transplanted with reprogrammed cells from mice that had been analyzed by these approaches during primary transplantation. These experiments revealed that both shared V(D)J rearrangements and common viral integration sites could be identified in multiple lineages in both primary and secondary recipients (FIGS. **71**B-**71**C), indicating that single reprogrammed cells possessed both multi-lineage differentiation, and long-term self-renewal potential.

[1258] To determine which lineage(s) in the peripheral blood had the potential to give rise to these colonies upon re-expression of the transcription factors, we purified B-cells, T-cells, myeloid cells and granulocytes from the 8-TF^{Poly} reconstituted mice, and tested their colony forming potential following culturing and plating in the absence or presence of doxycycline. These experiments revealed that cells from each of these lineages were imbued with progenitor activity upon factor re-induction. Of these, granulocytes gave rise to the fewest colonies whereas Mac1+ macrophages/monocytes yielded the largest number of colonies and the greatest number of primitive GEMM colonies (FIGS. **70**C-D).

[1259] We focused on differentiated myeloid cells because unlike differentiated lymphoid cells that have rearranged TCR (T-cells) or IG (B-cells) loci, multi-lineage reconstituting cells derived via reprogramming of myeloid cells would be expected to have the potential to give rise to full repertoires of lymphoid effector cells upon differentiation.

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<213> ORGANISM: Homo sapiens

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ggtccgctga acaccatgcg gccgctcggc gtgccgccca ggctctgctg gtgagcgccg    180

ccaccccgcg cccaggtccc gcgagcccgc ctgccgcgca cctcgccctg ctcccagctc    240

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

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<210> SEQ ID NO 8
<211> LENGTH: 3705
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

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<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<210> SEQ ID NO 15
<211> LENGTH: 1830
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<211> LENGTH: 3547
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

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catcgagacc ctctcgggta aagtggaatt gcatgggaaa atcatggaag ttgattactc    300

agtctctaaa aagctaagga gcaggaaaat tcagattcga aacatccctc ctcacctgca    360

gtgggaggtg ttggatggac ttttggctca atatgggaca gtggagaatg tggaacaagt    420

caacacagac acagaaaccg ccgttgtcaa cgtcacatat gcaacaagag aagaagcaaa    480

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<211> LENGTH: 9512
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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ccacagccca tccatagtaa ctgacatgat tagcagaaga aaggaacatt taggggcaag 1800

caggcgctgt gctatcatga tggaatttca tatctacaga tagagagttg ttgtgtacag 1860

acttgttgtg actttgacgc ttgcgaacta gagatgtgca attgatttct tttcttcctg 1920

gctttttaac tcccctgttt caatcactgt cctccacaca agggaaggac agaaaggaga 1980

gtggccattc tttttttctt ggccccccttc ccaaggcctt aagctttgga cccaaggaaa 2040

actgcatgga gacgcatttc ggttgagaat ggaaaccaca acttttaacc aaacaattat 2100

ttaaagcaat gctgatgaat cactgttttt agacaccttc attttgaggg gaggagttcc 2160

acagattgtt tctatacaaa tataaatctt aaaaagttgt tcaactattt tattatccta 2220

gattatatca aagtatttgt cgtgtgtaga aaaaaaaaca gctctgcagg cttaataaaa 2280

atgacagact gaaaaaaaaa aaa 2303

<210> SEQ ID NO 22
<211> LENGTH: 3198
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

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aacctcgcct gtgattgaca gctggagtgg cagaaagcca tgagatttgg tagttgggtc 120

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tgaggggcgc tcttttttt cctttctttt ctttctttct tttttttttt ttaaactgat 180

ttttggggga gagaagatct gcttttttt gcccccgctg ctgtcttgga aacggagcgc 240

ttttatgctc agtgactcgg gcgctttgct tcaggtcccg tagaccgaag atctgggacc 300

agtagctcac gttgctggag acgttaaggg atttttcgtc gtgctttttt tttttttttt 360

ttttttttcc gggggagttt gaatatttgt ttcttttcac actggcctta aagaggatat 420

attagaagtt gaagtaggaa gggagccaga gaggccgatg gcgcaaaggt acgacgatct 480

accccattac gggggcatgg atggagtagg catcccctcc acgatgtatg gggacccgca 540

tgcagccagg tccatgcagc cggtccacca cctgaaccac gggcctcctc tgcactcgca 600

tcagtacccg cacacagctc ataccaacgc catggccccc agcatgggct cctctgtcaa 660

tgacgcttta aagagagata aagatgccat ttatggacac cccctcttcc ctctcttagc 720

actgattttt gagaaatgtg aattagctac ttgtaccccc cgcgagccgg gggtggcggg 780

cggggacgtc tgctcgtcag agtcattcaa tgaagatata gccgtgttcg ccaaacagat 840

tcgcgcagaa aaacctctat tttcttctaa tccagaactg gataacttga tgattcaagc 900

catacaagta ttaaggtttc atctattgga attagagaag gtacacgaat tatgtgacaa 960

tttctgccac cggtatatta gctgtttgaa agggaaaatg cctatcgatt tggtgataga 1020

cgatagagaa ggaggatcaa aatcagacag tgaagatata acaagatcag caaatctaac 1080

tgaccagccc tcttggaaca gagatcatga tgacacggca tctactcgtt caggaggaac 1140

cccaggccct tccagcggtg gccacacgtc acacagtggg gacaacagca gtgagcaagg 1200

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ggacaaaaag cgtcacaaaa agcgtggcat ctttcccaaa gtagccacaa atatcatgag 1320

ggcgtggctg ttccagcatc taacacaccc ttacccttct gaagaacaga aaaagcagtt 1380

ggcacaagac acgggactca ccatccttca agtgaacaat tggtttatta atgcccggag 1440

aagaatagtg cagcccatga tagaccagtc caaccgagca gtaagtcaag gaacacctta 1500

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ctacatgtaa ccttcatcta gttaaccaat cgcaaagcaa gggggaaggc tgcaaagtat 1680

gccaggggag tatgtagccc ggggtggtcc aatgggtgtg agtatgggac agccaagtta 1740

tacccaaccc cagatgcccc cccatcctgc tcagctgcgt catgggcccc ccatgcatac 1800

gtacattcct ggacaccctc accacccaac agtgatgatg catggaggac cgccccaccc 1860

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ctctggacca aggagcatcc ctaattcttc atagggacct ttaaaaagca ggaaatacca 2100

actgaagtca atttggggga catgctaaat aactatataa gacattaaga gaacaaagag 2160

tgaaatattg taaatgctat tatactgtta tccatattac gttgtttctt atagattttt 2220

taaaaaaaat gtgaaatttt tccacactat gtgtgttgtt tccatagctc ttcacttcct 2280

ccagaagcct ccttacatta aaaagcctta cagttatcct gcaagggaca ggaaggtctg 2340

atttgcagga tttttagagc attaaaataa ctatcaggca gaagaatctt tcttctcgcc 2400

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ctgaacagat gtaaatcggg aaggatggga aaaactgcag tcatcaacaa tgattaatca 2580

gctgttgcag gcagtgtctt aaggagactg gtaggaggag gcatggaaac caaaaggccg 2640

tgtgtttaga agcctaattg tcacatcaag catcattgtc cccatgcaac aaccaccacc 2700

ttatacatca cttcctgttt taagcagctc taaaacatag actgaagatt tatttttaat 2760

atgttgactt tatttctgag caaagcatcg gtcatgtgtg tatttttttca tagtcccacc 2820

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ctgtattatt gcaatttttt tttgtaaaag tagcagtttg gtatgagttg gcatgcatac 2940

aagatttact aagtgggata agctaattat actttttgtt gtggataaac aaatgcttgt 3000

tgatagcctt tttctatcaa gaaaccaagg agctaattat taataacaat cattgcacac 3060

tgagtcttag cgtttctgat ggaaacagtt tggattgtat aataacgcca agcccagttg 3120

tagtcgtttg agtgcagtaa tgaaatctga atctaaaata aaaacaagat tatttttgtc 3180

aaaaaaaaaa aaaaaaa 3198

<210> SEQ ID NO 23
<211> LENGTH: 1581
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

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aggaggaggg ggaggaggga gcggagatct cggggctcgg agccggccgc cgctccgctc 120

cgatcgctgt ggggcttggt tttttggggg tgggggggcg ggggggctca gatatggagg 180

caaatgggag ccaaggcacc tcgggcagcg ccaacgactc ccagcacgac cccggtaaaa 240

tgtttatcgg tggactgagc tggcagacct caccagatag ccttagagac tattttagca 300

aatttggaga aattagagaa tgtatggtca tgagagatcc cactacgaaa cgctccagag 360

gcttcggttt cgtcacgttc gcagacccag caagtgtaga taaagtatta ggtcagcccc 420

accatgagtt agattccaag acgattgacc ccaaagttgc atttcctcgt cgagcgcaac 480

ccaagatggt cacaagaaca aagaaaatat ttgtaggcgg gttatctgcg aacacagtag 540

tggaagatgt aaagcaatat ttcgagcagt ttggcaaggt ggaagatgca atgctgatgt 600

ttgataaaac taccaacagg cacagagggt ttggctttgt cacttttgag aatgaagatg 660

ttgtggagaa agtctgtgag attcatttcc atgaaatcaa taataaaatg gtagaatgta 720

agaaagctca gccgaaagaa gtcatgttcc cacctgggac aagaggccgg gcccggggac 780

tgccttacac catggacgcg ttcatgcttg gcatggggat gctgggatat cccaacttcg 840

tggcgaccta tggccgtggc taccccggat ttgctccaag ctatggctat cagttcccag 900

gcttcccagc agcggcttat ggaccagtgg cagcagcggc ggtggcggca gcaagaggat 960

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gcccacagcc gggctcgggc ttcggccacg gcatagctgg acctttgatt gcaacggcct 1140

ttacaaatgg ataccattga gcaggtgctt tcgttgccat ctcactctga gagcatacct 1200

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ggatgtccag gcaagactgg gcgaagtttc tgagtggccc tttgtttagg tgatgtcctc   1260

agacctggac ccccaccagc ctcactcccc atcccaacca gagatggctc acttcggatc   1320

gagggttgac tacatctcat catctcacga atctgctgta atataagaca acagctttta   1380

aatgtgtata taacccatga tttcggtttt gttttgtttt gtttttcttg atggtttccc   1440

tctccctccc tctcttccca ttctcctttt aaatctcttt gaatcacatt tggtagtgat   1500

tttgacttag tccagtagtc acatagcttt aatatctagt tcaaagctaa ccatagtata   1560

attgttatat taaggagtta t                                              1581


<210> SEQ ID NO 24
<211> LENGTH: 2613
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

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cccccggccc acccggagac acccgcgcag aatcgcctcc ggatcccctg cagtcggcgg    180

gagtgttgga ggtcggcgcc ggcccccgcc ttccgcgccc cccacgggaa ggaagcaccc    240

ccggtattaa aacgaacggg gcggaaagaa gccctcagtc gccggccggg aggcgagccg    300

atgccgagct gctccacgtc caccatgccg ggcatgatct gcaagaaccc agacctcgag    360

tttgactcgc tacagccctg cttctacccg gacgaagatg acttctactt cggcggcccc    420

gactcgaccc ccccggggga ggacatctgg aagaagtttg agctgctgcc cacgcccccg    480

ctgtcgccca gccgtggctt cgcggagcac agctccgagc ccccgagctg ggtcacggag    540

atgctgcttg agaacgagct gtggggcagc ccggccgagg aggacgcgtt cggcctgggg    600

ggactgggtg gcctcacccc caacccggtc atcctccagg actgcatgtg gagcggcttc    660

tccgcccgcg agaagctgga gcgcgccgtg agcgagaagc tgcagcacgg ccgcgggccg    720

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cacccggccg ccgagtgcgt ggatcccgcc gtggtcttcc cctttcccgt gaacaagcgc    900

gagccagcgc ccgtgcccgc agccccggcc agtgccccgg cggcgggccc tgcggtcgcc    960

tcgggggcgg gtattgccgc cccagccggg gccccggggg tcgcccctcc gcgcccaggc   1020

ggccgccaga ccagcggcgg cgaccacaag gccctcagta cctccggaga ggacaccctg   1080

agcgattcag atgatgaaga tgatgaagag gaagatgaag aggaagaaat cgacgtggtc   1140

actgtggaga agcggcgttc ctcctccaac accaaggctg tcaccacatt caccatcact   1200

gtgcgtccca agaacgcagc cctgggtccc gggagggctc agtccagcga gctgatcctc   1260

aaacgatgcc ttcccatcca ccagcagcac aactatgccg ccccctctcc ctacgtggag   1320

agtgaggatg cacccccaca gaagaagata aagagcgagg cgtccccacg tccgctcaag   1380

agtgtcatcc ccccaaaggc taagagcttg agcccccgaa actctgactc ggaggacagt   1440

gagcgtcgca gaaaccacaa catcctggag cgccagcgcc gcaacgacct tcggtccagc   1500

tttctcacgc tcagggacca cgtgccggag ttggtaaaga atgagaaggc cgccaaggtg   1560

gtcattttga aaaaggccac tgagtatgtc cactccctcc aggccgagga gcaccagctt   1620
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ttgctggaaa aggaaaaatt gcaggcaaga cagcagcagt tgctaaagaa aattgaacac   1680

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ttttttttt aaacaaacat tgtgttgaca ttaagaatgt tggtttactt tcaaatcggt   1800

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catgacagcg ctaaacgttg gtgacggttg ggagcctctg gggctgttga agtcaccttg   1980

tgtgttccaa gtttccaaac aacagaaagt cattccttct ttttaaaatg gtgcttaagt   2040

tccagcagat gccacataag ggtttgcca tttgataccc ctggggaaca tttctgtaaa   2100

taccattgac acatccgcct tttgtataca tcctgggtaa tgagaggtgg cttttgcggc   2160

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atgttttgta tacaaatata ttgttaatct ctgttatgta ctgtactaat tcttacactg   2280

cctgtatact ttagtatgac gctgatacat aactaaattt gatacttata ttttcgtatg   2340

aaaatgagtt gtgaaagttt tgagtagata ttactttatc actttttgaa ctaagaaact   2400

tttgtaaaga aatttactat atatatatgc ctttttccta gcctgtttct tcctgttaat   2460

gtatttgttc atgtttggtg catagaactg ggtaaatgca aagttctgtg tttaatttct   2520

tcaaaatgta tatatttagt gctgcatctt atagcacttt gaaatacctc atgtttatga   2580

aaataaatag cttaaaatta aatgaaaaaa aaa                                2613
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<210> SEQ ID NO 25
<211> LENGTH: 2761
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

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gctgcggtac atctcggcac tctagctgca gccgggagag gccttgccgc caccgctgtc    180

gcccaagcct ccactgccgc tgccacctca gcgccggcct ctgcatcccc agctccagct    240

ccgctctgcg ccgctgctgc catcgccgct gccacctccg cagcccgggc ctccgccgcc    300

gccactcaag catccgtgag tcattttctg cccatctctg gtcgcgcggt ctccctggta    360

gagtttgtag gcttgcaaga tggcagaagc agattttaaa atggtctcgg aacctgtcgc    420

ccatggggtt gccgaagagg agatggctag ctcgactagt gattctgggg aagaatctga    480

cagcagtagc tctagcagca gcactagtga cagcagcagc agcagcagca ctagtggcag    540

cagcagcggc agcggcagca gcagcagcag cagcggcagc actagcagcc gcagccgctt    600

gtatagaaag aagagggtac ctgagccttc cagaagggcg cggcgggccc cgttgggaac    660

aaatttcgtg gataggctgc ctcaggcagt tagaaatcgt gtgcaagcgc ttagaaacat    720

tcaagatgaa tgtgacaagg tagataccct gttcttaaaa gcaattcatg atcttgaaag    780

aaaatatgct gaactcaaca agcctctgta tgataggcgg tttcaaatca tcaatgcaga    840

atacgagcct acagaagaag aatgtgaatg gaattcagag gatgaggagt tcagcagtga    900

tgaggaggtg caggataaca cccctagtga aatgcctccc ttagagggtg aggaagaaga    960

aaaccctaaa gaaaacccag aggtgaaagc tgaagagaag gaagttccta aagaaattcc   1020
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tgaggtgaag gatgaagaaa aggaagttcc taaagaaatt cctgaggtaa aggctgaaga   1080

aaaagcagat tctaaagact gtatggaggc aacccctgaa gtaaaagaag atcctaaaga   1140

agtcccccag gtaaaggcag atgataaaga acagcctaaa gcaacagagg ctaaggcaag   1200

ggctgcagta agagagactc ataaaagagt tcctgaggaa aggcttcagg acagtgtaga   1260

tcttaaaaga gctaggaagg gaaagcctaa aagagaagac cctaaaggca ttcctgacta   1320

ttggctgatt gttttaaaga atgttgacaa gctcgggcct atgattcaga agtatgatga   1380

gcccattctg aagttcttgt cggatgttag cctgaagttc tcaaaacctg gccagcctgt   1440

aagttacacc tttgaatttc attttctacc caacccatac ttcagaaatg aggtgctggt   1500

gaagacatat ataataaagg caaaaccaga tcacaatgat cccttctttt cttggggatg   1560

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atttggcaaa cattatggaa acaagaaata cagaaaataa gtcaatctga aagatttttc   1920

aagaatctta aaatctcaag aagtgaagca gattcataca gccttgaaaa aagtaaaacc   1980

ctgacctgta acctgaacac tattattcct tatagtcaag tttttgtggt ttcttggtag   2040

tctatatttt aaaaatagtc ctaaaaagtg tctaagtgcc agtttattct atctaggctg   2100

ttgtagtata atattcttca aaatatgtaa gctgttgtca attatctaaa gcatgttagt   2160

ttggtgctac acagtgttga tttttgtgat gtcctttggt catgtttctg ttagactgta   2220

gctgtgaaac tgtcagaatt gttaactgaa acaaatattt gcttgaaaaa aaaagttcat   2280

gaagtaccaa tgcaagtgtt ttattttttt ctttttttcca gcccataaga ctaagggttt   2340

aaatctgctt gcactagctg tgccttcatt agtttgctat agaaatccag tacttatagt   2400

aaataaaaca gtgtattttg aagtttgact gcttgaaaaa gattagcata catctaatgt   2460

gaaaagacca catttgattc aactgagacc ttgtgtatgt gacatatagt ggcctataaa   2520

tttaatcata atgatgttat tgtttaccac tgaggtgtta atataacata gtatttttga   2580

aaaagtttct tcatcttata ttgtgtaatt gtaaactaaa gataccgtgt tttctttgta   2640

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tcttgtattg caacctaaaa taaataaata ttaaagtgtg ttatactata aaaatctaaa   2760

a                                                                   2761


<210> SEQ ID NO 26
<211> LENGTH: 2761
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

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gctgcggtac atctcggcac tctagctgca gccgggagag gccttgccgc caccgctgtc    180

gcccaagcct ccactgccgc tgccacctca gcgccggcct ctgcatcccc agctccagct    240
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ccgctctgcg ccgctgctgc catcgccgct gccacctccg cagcccgggc ctccgccgcc 300

gccactcaag catccgtgag tcattttctg cccatctctg gtcgcgcggt ctccctggta 360

gagtttgtag gcttgcaaga tggcagaagc agattttaaa atggtctcgg aacctgtcgc 420

ccatggggtt gccgaagagg agatggctag ctcgactagt gattctgggg aagaatctga 480

cagcagtagc tctagcagca gcactagtga cagcagcagc agcagcagca ctagtggcag 540

cagcagcggc agcggcagca gcagcagcag cagcggcagc actagcagcc gcagccgctt 600

gtatagaaag aagagggtac ctgagccttc cagaagggcg cggcgggccc cgttgggaac 660

aaatttcgtg gataggctgc ctcaggcagt tagaaatcgt gtgcaagcgc ttagaaacat 720

tcaagatgaa tgtgacaagg tagataccct gttcttaaaa gcaattcatg atcttgaaag 780

aaaatatgct gaactcaaca agcctctgta tgataggcgg tttcaaatca tcaatgcaga 840

atacgagcct acagaagaag aatgtgaatg gaattcagag gatgaggagt tcagcagtga 900

tgaggaggtg caggataaca cccctagtga aatgcctccc ttagagggtg aggaagaaga 960

aaaccctaaa gaaaacccag aggtgaaagc tgaagagaag gaagttccta aagaaattcc 1020

tgaggtgaag gatgaagaaa aggaagttcc taaagaaatt cctgaggtaa aggctgaaga 1080

aaaagcagat tctaaagact gtatggaggc aacccctgaa gtaaaagaag atcctaaaga 1140

agtcccccag gtaaaggcag atgataaaga acagcctaaa gcaacagagg ctaaggcaag 1200

ggctgcagta agagagactc ataaaagagt tcctgaggaa aggcttcagg acagtgtaga 1260

tcttaaaaga gctaggaagg gaaagcctaa aagagaagac cctaaaggca ttcctgacta 1320

ttggctgatt gttttaaaga atgttgacaa gctcgggcct atgattcaga agtatgatga 1380

gcccattctg aagttcttgt cggatgttag cctgaagttc tcaaaacctg gccagcctgt 1440

aagttacacc tttgaatttc attttctacc caacccatac ttcagaaatg aggtgctggt 1500

gaagacatat ataataaagg caaaaccaga tcacaatgat cccttctttt cttggggatg 1560

ggaaattgaa gattgcaaag gctgcaagat agactggaga agaggaaaag atgttactgt 1620

gacaactacc cagagtcgca caactgctac tggagaaatt gaaatccagc caagagtggt 1680

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atttggcaaa cattatggaa acaagaaata cagaaaataa gtcaatctga aagatttttc 1920

aagaatctta aaatctcaag aagtgaagca gattcataca gccttgaaaa aagtaaaacc 1980

ctgacctgta acctgaacac tattattcct tatagtcaag tttttgtggt ttcttggtag 2040

tctatatttt aaaaatagtc ctaaaaagtg tctaagtgcc agtttattct atctaggctg 2100

ttgtagtata atattcttca aaatatgtaa gctgttgtca attatctaaa gcatgttagt 2160

ttggtgctac acagtgttga tttttgtgat gtcctttggt catgtttctg ttagactgta 2220

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<211> LENGTH: 2492
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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gaggaaaact ccatttcctc cttccctgcc ggtttctccc ctctaccctg gcaccccaaa 180

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<210> SEQ ID NO 33
<211> LENGTH: 3142
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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aaggagaact tgggatcttt ctgggaaccc cccgccccgg ctggattggc cgagcaagcc 180

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<210> SEQ ID NO 34
<211> LENGTH: 6853
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

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ctccgacttc tgccagttcc ggcctccagt tcgtgtgaat gatggtggag ggagccatcc 660

ttccaggccc aactccagac acactcccag cttctctggg gactcctcct cctcctgctc 720

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<210> SEQ ID NO 42
<211> LENGTH: 2752
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

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gttggggaag gggaaaagac ccagtcaagg ttgtccaagt aaaatagcaa gacccaagca 360

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gaaaaggctt cttaaatttg agtcatgtgg aaaaattttg aaacagaatt tagatttacc 600

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<211> LENGTH: 2295
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

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aaaaaaaaaa aaaaa 2295

<210> SEQ ID NO 44
<211> LENGTH: 4985
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

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ccatggacaa gaagacaaga tctatgactg tacacaatgt ccacagaagt tttcttcca 4140

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gttgcacatg tattatgtcg tctgatacta aaatggtctt ataaagacaa gtggacttgg 4440

gccctattca ggcaagatta aaaaaaaaaa aagactatga ccaaaatggc ttaagataaa 4500

gtatttttaa ggaagaaaga ttaaaaacaa ctgttataca tgagactatg gttggacttc 4560

cttttcttta cacttaagcc tagaatttct ctttaggtat atcagcgctt aaatccaaga 4620

ctatttttta ttgctgaaga ttcttgcaaa ccatgaagag atgttctcac agaacagaac 4680

cccacagctg gataaggccc gtatatatat atttgtaagc cttgcaatgt gacaggtagc 4740

atcactatat atgcaatagt tgttatgtag actgtcaaag aatttttttt tccctggata 4800

catttgaagc tttgagtgtt caaggttttc cttaatgatt tcacgcagcc aaattcttga 4860

atcagttgaa ctaacctgta tgttactgtt attaatgttt actctgcagt ctgaacctgg 4920

agattactgg aattgttttc caagaggaaa taaattcagt ttaccattag gaaaaaaaaa 4980

aaaaa 4985

<210> SEQ ID NO 45
<211> LENGTH: 6493
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

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ccagggcttt ctccccaccc caggggggtgt cttccatcct tttgtggctc agttgaaggc 120

gaaaagggct ccaaaccact aactaaccag aggagagccc cttcttccac ctccagggag 180

aatttcagat ttaatttgtc cgaagatagc gtgctctctt cttactcatt tgccatcatt 240

acgaggaaaa caaaccacca ccttggcttc aagatcctgg gtagaggctc acggtctttt 300

caaccatctt tggcgaggcc ttgcttcctt ccactcgagg tatgttctgt cttgtgcttt 360

ttcttttaga agctactaaa gggtgttggg gatgcttctg actattatga aggccaaaag 420

gcctgttgac tggggctgct tttaaccctt tcctatttgc tgagaatgca gccgtgtgac 480

agtaactgaa cattggtcta aagtctttcc aaaaggtcaa ggttcacaag aacatctgct 540

caaattaatg accatggggg atatgaagac cccagacttt gatgacctcc tggcagcatt 600

tgacatccca gatatggtcg atcctaaagc agctattgag tctggacacg atgaccatga 660

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tgtgggtgtc agcgttatcg tcaagaatgt tcggaacatt gactcttccg agggcgggga 780

gaaagacggc cacaacccca ctggcaatgg cttacataat gggtttctca cagcatcctc 840

ccttgacagt tacagtaaag atggagcaaa gtccttgaaa ggagatgtgc ctgcctctga 900

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actcggaggg gaaaactcca gcaaaactgg actctctacg tcaggcaatg tggagaaaaa 1140

caaagctgtt aagagagaaa cagaagccag ttctataaac ctgagtgttt atgaaccttt 1200

taaagtcaga aaagcagagg ataaattgaa ggaaagctct gacaaggtgc tggaaaacag 1260

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cccgttacca aaagaagtaa atgacagtcc gagagccgct gacaagtctc ctgaatccca 1500

gaatctcatc gacgggacca aaaaaccatc cctgaagcaa ccggatagtc ccagaagcat 1560

ctcaagtgag aacagcagca aaggatcccc gtcctctccc gcagggtcca caccagcaat 1620

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cacccccaaa caggtcacaa tcaagcctgt ggctactgct ttcctcccag tgtctgctgt 1920

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gtgtaatgaa gtcttccagg acgagacatc actggctaca catttccagc aggctgcaga 2880

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catctgcagg tcggtgcact tccagaccca cgtcaccaag aactgtctgc actacacgag 3060

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gtttaagtct gccccaagca cacattccca cgcctacaca cagcatcctg gcatcaagat 3240

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tccagactgt tctcttttat atgcacagaa gcaacttatg atggaccata tcaagtctat 3420

gcatggaaca ttgaaaagta ttgaagggcc tccaaacttg ggtataaact tgcctttgag 3480

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tgggaaagag aaattggaaa agaaatctcc atctcctgtg aaaaaatcaa tggaaaccaa 3600

gaaagtggcc agtcctgggt ggacgtgttg ggagtgtgac tgcctgttca tgcagagaga 3660

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tcagttgact taaccctttg ctgtcaaaag agttggcgtt tcctgttctg ggtgctactg 5460

ccaaacgtta tggtacttag agtcgggatg cacaacttca accaccgact tatcaatgca 5520

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ggtacaatcc gagggtgtga atttcagctt gaaattccat tgctgttcct tgttttgttt 6180

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aataagcctg tgtggtaggc cacataggtc cgaataacct agttttacag ttgagggagc 6300

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aaaaaaaaaa aaa 6493

<210> SEQ ID NO 46
<211> LENGTH: 3271
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

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actccagctt tggtctttgt ggctcaatag cttgcgccca ttggaagggg aaacgcacgt 240

tgctgtccca gccacgaggc cctgagcatt tagcacttgg tcgacggggg aagatgtgtc 300

ggtgcagcta aaagatggaa tatttgcggg cgtgaagcgg cccgaggtga taccacaagt 360

cttttgacat gctgaggtct ggcaggaaca ttaacctatg tgcatcccga gtatggaccg 420

tgtgctccca ggctcctgac atagggtcat gaattagggc cgagtgggag cgcagagccc 480

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gtgtcagtcc caaaagctcc agcccttctc tgagacgggg accaggggat ggcagccatg 600

cacctgacag cctggcccca gggacttcac ggatcccctg aagctcatcc atggacttcc 660

atggactaca gggcctgagc tatggaattg gccctagggc agcaggaacc tattgtttca 720

gaagtcggtg acctttgagg acgtggctgt gtacttcacc caggcggaat gggatggcct 780

gtcccctgca cagaggaccc tgtacaggga tgtgatgctg gagaattatg ggaatgtggc 840

ctccctggga tttccacttc tcaaacctgc tgtgatctca caactggagg gaggaagtga 900

gctgggggc tcatctccac tggctgcagg aacaggcctc cagggcctcc agactgatat 960

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tcagtgtcat accatcactg gagagcagcc ctctgggtgt acaggattgg ggaaatccat   1260

cagctttgat acaaaaactcg tgaagcatga aataattaat tctgaggaaa gacctttcaa   1320

atgtgaagaa ttagtagagc cctttaggtg tgactctcaa cttattcaac atcaagagaa   1380

caacactgag gaaaagcctt atcagtgttc ggagtgtggc aaagctttca gcattaatga   1440

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gaagccctat cagtgtaaga tgtgtgggaa ggccttcagt gttaatggaa gcctaagtag   1620

gcatcagaga atccatacgg gagagaagcc ctatcagtgc aaggaatgtg gaaatggctt   1680

cagctgtagt tctgcatata ttacacatca gagagtccac actggagaga aaccttacga   1740

gtgtaatgac tgtgggaaag cgttcaatgt taatgcaaaa ttaattcaac atcagagaat   1800

ccatactgga gagaaacctt atgaatgtaa tgaatgtgga aaaggcttca ggtgcagctc   1860

ccagcttagg cagcatcaga gcatccacac aggagaaaag ccctatcagt gtaaagagtg   1920

tggaaaaggc ttcaataata atacaaaact cattcagcat cagagaatcc acacaggtga   1980

gaaaccctat gaatgcactg aatgtggaaa agccttcagt gtcaaaggga agttaatcca   2040

acaccagaga attcacacag gcgagaaacc ctatgagtgt aatgaatgcg ggaaagcctt   2100

cagatgtaac tcccaatttc ggcagcatct gagaattcac actggggaga agccctatga   2160

gtgtaatgag tgtggaaagg ccttcagcgt taatgggaaa ctaatgcggc atcagagaat   2220

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tgggaaagcc ttcagtatca atgccaaact aactaggcat cagaggatac atactgggga   2400

gaaacctttc aaatgtatgg aatgtgagaa agcattcagc tgtagttcta actatattgt   2460

gcaccagaga atccatacag gagagaaacc ctttcagtgt aaggagtgtg gaaaagcctt   2520

ccatgttaat gcccatttaa ttcggcatca gagaagccac actggggaga aacccttcag   2580

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tgtaccaaca ggaattagaa aatataatga aaagatttcg ttcccagcag catcaagaaa   3000

agtagatttt ctagaaataa acagttatgg aggacttgta tggagaaatt taagtcttca   3060

ctgagggcca ctttacaaag gaaatttgaa taaatggaga gagagagaag ccttgttgtt   3120

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<210> SEQ ID NO 47
<211> LENGTH: 1952
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 47

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ccatcaccaa tcagccagcc ttcgaccatg ggcatgtccg acgtgtacct ccgcagcaga 240

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gacgagaatc aagagcagcg cggccaggag ctgaaggacc agcctctctc ggggattcca 1080

ggacgtcctg cacccgggac tgctgcggcc aatgcgaacg acttcttcgc caagcgcaag 1140

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gtggctcctg ggtgggcgc ggtggagcag accccgcgca aacgtctgag atgagttagt 1260

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aatctctact cgctctcagt gcaaaacaaa aagagaaact agaaaatgta gaacgaagga 1560

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ttagcttaca gtgtccccca cttcattaga ttgctcttaa acttggtgac cagacagtcg 1860

aaatggttcc tgtactgccc ataccaactg cccagggctc ctcgtccgcc aggttctaaa 1920

taaagaggcc caacaaaaat caaaaaaaaa aa 1952

<210> SEQ ID NO 48

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<211> LENGTH: 4281
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 48

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gagacagcag acatctgaat gaagaagagg gtgccagcgg gtatgaggag tgcattatcg 480

ttaatgggaa cttcagtgac cagtcctcag acacgaagga tgctccctca cccccagtct 540

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<212> TYPE: DNA
<213> ORGANISM: Mus musculus

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gcatttaaag tctggtgacc ttaaactgaa tgagtaaaga aagagagaga aaaaggaagc   3180

tatttattct caatattttg ttttgcacag ccaaggcagc tgctgacttc tggaggatca   3240

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cagatggaag tagtcagaag aaatgcacaa tgattatagg aagtgatagc aggatttttt   3540

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acataactgt ttatcaccac tgtaccacta atacaatgtt tgccaaatcc ttgtaatgac   3720

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taaaaagaga gaagtaaata acagacatta ttcagttatt ttgtccttta tcgaaaaacc   4260

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<211> LENGTH: 3258
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 52

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ccctggaacg cgctgtcgct gggcccgccg tacccgggct ctcctggtgt ctcttactct    180

ctactgctga gccctcccct tcccgcgccg ctgcgagtgg ccgccccacc ttcgcctggt    240

tcccaagaca cagtagtgga ccatggaggt ggcgcctgag cagcctcgct ggatggcgca    300

ccccgccgta ttgaatgcgc agcaccccga ctcgcaccat ccgggcctgg cgcataacta    360

catggagcca gcacagctgc tgcctcccga cgaggtggat gtcttcttca accatctcga    420

ctcgcagggc aacccttact acgccaaccc ggcccacgcg cgcgcgcgcg tttcctacag    480

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caagcccaag cggaggctgt ctgctgccag aagagcgggc acctgttgtg caaattgtca   1320

gacgacaacc accaccttat ggcgccggaa cgccaacggg gaccctgtgt gcaacgcctg   1380

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gcagggtagc ccctgccctg acgcagccct agagggcaga gacaattgca ggcggtcctg   2340

cgcagattcc caggccaggg ctgggtcaca ggaaggaaac attctctgga aaggggaaac   2400

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aaaccctcgg ccccctcccc ctctaagata aataagaaaa tactcaaagc gaaaaccaaa   2580

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gcataagaga agaatcggca gtattttctg tttttatgtt ttgggcttgt tttattttga 3120

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gaaaaaaaaa aaaaaaaa 3258

<210> SEQ ID NO 53
<211> LENGTH: 1823
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 53

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<210> SEQ ID NO 54
<211> LENGTH: 3619
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 54

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<210> SEQ ID NO 55
<211> LENGTH: 5665
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 55

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gtaatttttt ttttagcacc tcaccagaca taacaattag gtattatcct ttcgacaaca 5520

ccacaaagat tgcatctgtc aaacaggctc aagttaacaa gaggttagtg taattgtata 5580

ccatgatatt gctggtattt atgctgtcaa gtccaaaact tcatttgttc ttctaaatgt 5640

ttaataaact aatttttttc ctttt 5665

<210> SEQ ID NO 56
<211> LENGTH: 4226
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 56

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gggcgccgac attcaatttc tacctcagca tcagttggat cttttgaagg gagaagacac 1260

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ggcggggctg ggcgaggggc ggggccgggg tgggcgaaat cgcataacct tgagaaggac 1380

tatattaatc actttgtaat cccttcacag tcccaggttt agtgaaaaac tgctgtaaac 1440

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tacacagcca aaagccactt agccataaat gacacttgtc agccttgaag catcggagat 2040

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tgatttgcaa ggaactacct ccacacttcc aaaggaacga acttgcagcc tatatcactc 2940

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agaatatgct tgaccgatat tttttcatgt attttacaca atgtgatttt tgtaaaaaaa 3240

tgtctcaagc agatttgttt tggacgcttc ttgtgtagag tttctatgcc tttctctcct 3300

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ttccagctgt tttcagggag gttacttcaa aggccacgtg ccgctctgag actggcagat   3480

ggctcactgt tgtgagtcgc caaaggagct atggagagat taaaattcaa catgactgtt   3540

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tcttcggatg ggccttacag aaacctcatt ttggccagct cataaaaact gaagcagctt   3660

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gctgtctgtg attgtacttg gacggcttgc ttgtggcaat accttctcta gtggattatc   4140

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aaaaaaaaaa aaaaaaaaaa aaaaaa                                         4226


<210> SEQ ID NO 57
<211> LENGTH: 1877
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 57

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ggagggaacc gagtacatgt cccagtcatt tccataattc atcataaatt gtgcaagggt    180

gctatagacg cacaaacgac cgcgagccac aaatcaagca cacatatcaa aaaacaaatg    240

agctcttatt ttgtaaactc attttgcggt cgctatccaa atggcccgga ctaccagttg    300

cataattatg gagatcatag ttccgtgagc gaacaattca gggactcggc gagcatgcac    360

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tacactcgct accagaccct ggagctggag aaagaattcc acttcaaccg ctacctgacc    900

cgccgaagaa ggatcgaaat agctcatgcc ctttgcctct ccgagagaca aattaaaatc    960

tggttccaaa acaggaggat gaagtggaaa aaagataata agctgaaaag catgagtatg   1020

gccgcggcag ggggggcttt ccgcccctga gcatctgagc ggccaaagta ctgagcagta   1080
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tacttgaagt aactaaaaca aaaaaaaaaa aaaaagaaaa gagaaaaaaa aactacacac   1380

acaaaaagcc cccccacctc gtttagtgcc aatgttgtgt gttgcacttg agttctttaa   1440

tgtgcatgta cgtggaagtg ttcctgtctc aatagctcca agctgttaaa gatattttta   1500

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caaattaact tgttcaacgt gtagtggcta gtggctctgt gacgaaaact gtgactccaa   1620

gcggtgtgtc cctgcgtgcc tttgtaggac cctttgcacg aactctggaa gtggctctta   1680

taagcgcagc ttcagtgatg tatgtttttg tgaaaaagtt acaaatattg tccaagtctg   1740

gctgtttaag caaactgtga tcagcttttt tttttttttg tatttgtttt taaggaaaaa   1800

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tatgccaaat agcaagc                                                 1877
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<210> SEQ ID NO 58
<211> LENGTH: 2272
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 58

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gtctggggag cgggactagg catacagatg atggagctta gaacccgctg gctagggaat    180

aaaattcgct gggcagtttg tgctcaaaga agtgggccag ggcgcttgtg acacaatcag    240

ggcgtttgtg acacaaaccc ttgagggttg gcagttctct ccttggcggt tgctctggtt    300

gctctgtggg gccttccctg tggagcaagg gtgatctggc cgatgtgcaa gcgcctggct    360

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ctaggccggc cctgggggcg cgcgcgggcg gggggctcac atctctgagg actgcaagga    540

ttatttacag ggtattcacc aaccaaacac aacagtctaa tttaaccttt ccaagtcctc    600

ataaattttt acagggagcc acagcgaggc aaacgaatct gttggtcgct cctgactttc    660

caccagcctg tgtggcttcc gaaacaataa ctccttatga aatatcataa atatagattt    720

aaatacagta gagtgagaat gcgatttggc tgcttttta tggcttcaat tattgtctaa    780

ttttatgtga ggggctctgc tggccgtgct cacacgcggg acccgcgcct tcctgatggc    840

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tgttgggggg gtggcaaggg agagtacaga ggcaaggcca gatttgatct tttaatcttc    960

gttggccaca attaaaacaa accagatcgt ggagctgcgc gatccctttg cataaaaaca   1020

tatggctttt gctataaaaa ttatgactgc aaaacaccgg gccattaata gcgtgcggag   1080

tgatttacgc gttattgttc tgccgggcgg acacgtgacg cgcgtggcca atgggggcgc   1140

gggcgccggc aacttattag gtgactgtac ttcacccccc cctggtgcca ccaagttgtt   1200
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gccgacgctg ctgatgagct gggtgcggga cgctacgctc cagggaccct gggtcaaccc 1380

ccaaggcagg cggcagctct ggccgaacac cccgacttca gtccttgcag cttccagtcc 1440

aaggcggcgg tgtttggtgc ctcgtggaac ccagtgcacg cggcgggcgc caatgcggtg 1500

cctgctgcag tgtatcatca ccaccaccac ccctacgtgc atccccaggc gcccgtggcg 1560

gcggcggcgc cggacggcag gtatatgcgc tcctggctgg aacccacgcc cggtgcgctc 1620

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ggttctcctc cagttgatag agaaaaacaa cccagcgaag gcgccttctc cgaaaacaat 1800

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aaaatgaaga aaatcaacaa ggaccgagca aaagacgagt gagcctttta ggggctcatt 2100

taaaaagaga gcaagctaga aagaaaaaga aaggactgtc cgtctccctc tgtctcctct 2160

cccccaaacc cagcctccac ccgcacaaag gggctctaaa tcccaggcct catctcccca 2220

ctggcagtcc gtgctcaggc tggctcttag gcctgcggct ttgatggagg ag 2272

<210> SEQ ID NO 59
<211> LENGTH: 3390
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 59

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cgtctctccg gatcggcaag gggaaaaaat tttggagcca taaagttgaa aacttttttc 240

tctcagtttt ggaagaagcc ttcctttcgt catgaacggg accagaggag ctcaggcgag 300

agcgggcaag aggctcagag gaggggagat ttctcgcctg ccgctcgcgc tggggctcga 360

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ggccaggcct ggccccagag cccctgcccg cacctccggg ctcacccccca cccagcgccg 840

cacctaccag taccactagc aacagcaata acgggggtgg gcccagcaaa agcggccccc 900

ccaagtgcgg tgccggctcc aactccaccc tcaccaaaca gatattcccc tggatgaaag 960

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<211> LENGTH: 2566
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 60

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gtgggaagac tgctcactcc cttccaccat agacttagaa gggggaacag aagggaattg 2040

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<210> SEQ ID NO 61
<211> LENGTH: 1912
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 61

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<210> SEQ ID NO 62
<211> LENGTH: 3902
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 62

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gagaacgtgg agcaagtcaa cacagataca gaaactgccg ttgtcaacgt cacctatatg    720

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<210> SEQ ID NO 63
<211> LENGTH: 9457
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 63

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agcttgcagc agtaacaacc cggccctcct agcccggagg gagaccgagg agttcaacga 900

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cagcagccct tcggtcatca gtgttagcaa aggaagccca gacggcagcc accccgtggt 1380

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caacggccac cggcccaaca cacacgactt ccccctgggg cggcagctcc ccaccaggac 1560

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gccagaggag cccaagccaa agaggggaag aaggtcgtgg ccccggaaaa gaacagccac 1800

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acacctgcga actcacacag gcgagaaacc ttaccactgt gactgggacg gctgtgggtg 1920

gaaattcgcc cgctccgatg aactgaccag gcactaccgc aaacacacag ggcaccggcc 1980

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aagcgctaca atcatggtca agttcccagc aagtcagctt gtgaatggat aatcaggaga   2220

aaggaagagt tcaagagaca aaacagaaat actaaaaaca aacaaacaaa aaaacaaaca   2280

aaaaaaacaa gaaaaaaaaa tcacagaaca gatggggtct gatactggat ggatcttcta   2340

tcattccaat accaaatcca acttgaacat gcccggactt acaaaatgcc aaggggtgac   2400

tggaagtttg tggatatcag ggtatacact aaatcagtga gcttgggggg agggaagacc   2460

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gttttgtctt ccgatctaca ttgatgacct aagccaggta aataagcctg gtttatttct   2760

gtaacatttt tatgcagaca gtctgttatg cactgtggtt tcagatgtgc aataatttgt   2820

acaatggttt attcccaagt atgcctttaa gcagaacaaa tgtgtttttc tatatagttc   2880

cttgccttaa taaatatgta atataaattt aagcaaactt ctattttgta tatttgtaaa   2940

ctacaaagta aaaaaaaatg aacattttgt ggagtttgta ttttgcatac tcaaggtgag   3000

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<210> SEQ ID NO 66
<211> LENGTH: 3263
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 66

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tgccccgggg cgtcagctcg gcggagaggc ggtcgaggac gtgcgcctgg ctcgcagttg    180

gctttctctg ggactccgac acgtttgcag tcgaataaac ttgcgaccgc cacgtgtggc    240

atctctccga ggagggcgcg cccatcgtgg gatcgcgcgg ggcgccgggc agggcggcgg    300

cgacagcggc ggagccggcc gcggctgctg cgtgcggagg cgctgccggt tacgtaaaga    360

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tcggccgcgc cgcaccgcgc tcgtcgtccg aggccagggc agggctagcc gaagctccgc    480

agccaccttc aagtttggcc gcaccgcccg ggctgccgtc gcccgcacca tgtccgcggc    540

cgcctacatg gacttcgtgg ctgcccagtg tctggtttcc atctccaacc gcgccgccgt    600

gccggagcac gggggcgctc cggaagccga gcggctgcga ctacctgagc gcgaggtgac    660

caaggaacac ggtgacccgg gggacacctg gaaggattat tgcacgctgg tcactatcgc    720

caagagcttg ttggacctca acaaataccg acccatccag accccctcgg tgtgcagcga    780

cagtctggag agtcccgatg aggatatagg atccgacagc gacgtgacca ccgaatctgg    840

gtcgagtcct tcccacagcc cggaggagag acaggattct ggcagcgcgc ccagcccact    900

ctccctcctc cactctggag tggcttcgaa ggggaaacac gcctccgaaa agaggcacaa    960

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gaaacagact gacacatgga aatctgccac agcagaggcg cgctggccac aggaggtcac 1380

tgcttctttg gccaatattc tgatatctcc ctgcactgtt tccaaaaagc acatggtagc 1440

cctaaggtca aagtcaacat ttggtcccct tgcagaggca actctgaacc gtctctgact 1500

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gagggggcaa ggccaagacg aggggtagga ttctgaagat tcagactggt ggtgtacata 1620

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caagagcaca cctactccag catgatttgt catctaaaga cttgaaaaca aaacaacaac 1920

aacaaaaagt tacttatagt caatggataa gcagagtccg aatttacact aatcaagaca 1980

gaccttcgag ggtcacgat aagtccggaa ctttcaaacc ttgcttcgta tgaattgtac 2040

tatctgaaca taaactgcac ttttattttc taataccgag ggtgaatacg gtaaatacat 2100

gctttgaggg tagaagccga cggtctgttt ggcaccacgt tataatctgc ttattttaac 2160

agtatacaca tttccctgag aacctatggc aaagatggga gggcagaaca tatgaaacac 2220

atgctgacga gggggaggag gaggggagtg cttttaaaga taacaaaaaa tgagcaaaca 2280

attttaactt catgaatttg tttgaattcc cccatgcttt ctgataacgc cgtctcgttc 2340

cacgctcggg actaggacag agcgagagcg gtcggctggc tctctgtagc gttggttgat 2400

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gttaaaaaac aaaaaaagaa aacaacaaaa aaaaagaaaa caaaaacctc atttgagggg 2880

agtcagcagt gatcatgggg aaatgtttac atttttcct tcagaaatac cactttctga 2940

tgattttatc tgatatttaa aacagggagc tatggtgcac tctagtttgc acatggtgtg 3000

taaactcggg gttcccacct gcagtgagct ccacatttca cccagcgcat gctcaccccc 3060

atctcagcgt ggttgctcct gcagtgggca cagggcacag ctgactccga cttccaatac 3120

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ttctcatgag aaaacatgtc agg 3263

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<210> SEQ ID NO 67
<211> LENGTH: 1605
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 67

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cgagcgcgcg ctagccagcc attagcaacg cttgcatttc tgcagggagc gcggtgactg 180

tccttgagcg tggaggggcg agctcgccag cggagcgacc gagcaagagg aggcgcagga 240

gcggcggcgc ccgagcaccc gagggggtcc gagtccaggc agctagccag ccacgcgcca 300

caaagggagc gcccccgccg cccggcacgc cgcccccctc cccaatgtcc tcggccatcg 360

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ccctgctgac atgtggtggc tgccagcaga acataggga ccgctacttc ctgaaagcca 480

tcgaccagta ctggcatgag gattgcctca gctgtgacct ctgtgggtgt cggctgggag 540

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agaagcattt ctgtgtaggt gacagatacc ttctcatcaa ctccgacata gtgtgtgaac 780

aagacatcta cgagtggacc aagatcaatg ggatcatcta ggccagagtc ccaggcacct 840

gtggggaggt gttcagtgaa gacgccgtct cggtgtggtc ttcactctta ggctctttgg 900

gaacctgagg gtgggtgagg catttcttag gagattatgg actcttcctg ggcactaacg 960

acatagcaat cacatgacat aatgcaaagg ctgagacttc agtgacaaaa aggaccagcc 1020

cttagagaga atttatggtc acaggctagc catagtaact gacaagatta gtggaggaaa 1080

tatttgggga ccagcatgca ctgtgccatc ctgataggct tccccaggta actatcgatt 1140

agatgtgacc ttggtgttca tggactagag ttgtgcaatt aatttttttcc tggctttggt 1200

aactaccctg ttctagtcac agtccttcac actaggaaag gaaagagaga agaaatagtc 1260

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gccaagggaa actgcatgga ggtacatttc agttgggaat gaaatccaca tctttcaacc 1380

agacaaatat ttatagcgat gttgatgaat cactgttttt agacaccttc attttgaggt 1440

gaggcgcccc acagattgtt tctatacaaa tgtaaatctt aaaaaaaaaa ggtcaaagtt 1500

gttcaactat tttattatct tagattatat caaagtattt gttgtgtgtc attaaaaaaa 1560

aaactcgatt ctgaagactt aataaaaatg acaagctgaa atgca 1605

<210> SEQ ID NO 68
<211> LENGTH: 3441
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 68

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gactgcaagc gggcagcatc gatcgtggct cctttaagac aaactcagac agacattttt 120

ttaaccctcc tctctaatct cccttcagtg cagcagttgc aaagagggag agagaaagag 180

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aaagagagcg agagaagaga gaaactgatt aggaattagg actgattcaa ggaaagcggg    240

cgctagggct ttgtgcattt gaatattaac atttgaggtg ttctgaccag aagaagacag    300

aacggacgat cattcattca ccacgttgac aacctcgcct gtgattgaca gctggagtgg    360

cagaaagcca tgagatttgg tagttgggtc tgaggggcgc tctttttttt ttttcttttt    420

cttttctttt ctttcttttt ttttaaactg atttttttgg gggggagaga agatctgctt    480

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agacgcaaag ggattttttt ttgttattgt tgtgctttat ttttttttcc gggggagttt    660

gcatatttgt ttcttttcac actggcctta aagaggatat attagaagtt gaagtaggaa    720

gggagccaga gaggccgatg gcgcaaaggt acgacgacct accccattat gggggtatgg    780

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aagatgccat ttatggacac cccctcttcc ctctcttagc actgattttt gagaaatgtg   1020

aattagctac ttgtaccccc cgcgagccgg gggtggcggg cggggacgtc tgctcgtcag   1080

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ttgtgcaaaa aggactggaa agatgaactg tattattgca tttattttgt tttttttttt 3240

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taattatact ttttgttgtg gataaaaaat gcttgtcaat agcctttttc tatcaagaaa 3360

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gtatgcaaac tccaggtcca g 3441

<210> SEQ ID NO 69
<211> LENGTH: 6505
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 69

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ctttgtcacc tttgagaatg aagacgttgt ggagaaagtc tgtgagattc atttccatga 660

aatcaataat aaaatggtag aatgtaagaa agctcagccg aaagaagtca tgttcccacc 720

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ggggatgctg ggctacccca actttgtggc aacctatggc agaggctacc ccggatttgc 840

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<211> LENGTH: 2596
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 70

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<210> SEQ ID NO 71
<211> LENGTH: 2861
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 71

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<210> SEQ ID NO 72
<211> LENGTH: 1652
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 72

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<210> SEQ ID NO 73
<211> LENGTH: 3565
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 73

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ttctgaacat cccacagcag tctcagtcct ggttcctctg attaagatca acaaagaaac   2520

aactaaattt aaaaaaggaa aaaaaaaaaa gaggttcctc aaaatggggg agaagaaatt   2580

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ggaacagctc gtaacaatag tagacattcg agctcccctc cggacttcgt ctctttccct   3000

caccccaccc cccactcccc aacctctctt gcccttcctg ggagcctctg ctcaggcttc   3060

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caaggcagcc tccacctgcg ctaggtaggc gtcctgctct cgagactttg agttcctgtg   3540

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<211> LENGTH: 2145
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 74

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tccccgcccc cgccgggatt tattgagtat ttggactgga caattaagtg gccctgatga    180

tgttaccaag cccggtcacc tccacccctt tctcagtcaa agacattttg aatctggagc    240

agcagcggca cttccacgga gctcacttgc aggcggaatt ggagcagcac ttccactcgg    300

caccctgcat gctggccacg gctgaaggga cgcagttttc cgatgcaggg gaggaggacg    360

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cgcggagccg ccggaagccc cgggtgctct tctcgcaagc tcaggtcttt gagctggagc    660

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gcgtggcagt gccggtgctc gtgcgggacg gcaagccgtg cgtcacgccc agcgcacaaa 900

cctacggctc gccctacggc gtgggcgccg gcgcctactc ctacaacagc ttccccgcct 960

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cggcttacag cggcagctac ggctgcgcct atccgaccgg tggcggcggt ggtggtggcg 1080

gcacggcctc cgcggcgacc accgccatgc aacccgcctg cagcgccacc ggcggtggat 1140

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gccaggttgg tttcctttct gttttgtatt ctgtattccg cacattatct ctctataact 2040

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caatatttct gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa 2145

<210> SEQ ID NO 75
<211> LENGTH: 4087
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 75

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cttctcttgg acctgcagag aggaccaatg agaacagcta catggagatt gtcaacgtca 180

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aaactgagct ggaatccaag gaactttcag ccacggtggc tgagtccatg ggtttataca 360

tggattctgt gagagatgcc gagtacactt atgatcagca aaaccaacaa ggaagcctga 420

gcccggcaaa gatttatcaa aacatggagc agctggtgaa gttttacaaa gagaatggtc 480

acaggtcctc cacactgagt gctataagca ggcctttgag gtcattcatg cctgactctg 540

ggacctccat gaatggtggg gccttgcgtg ccatcgttaa gagcccaatc atctgtcatg 600

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tcactcaagg aacctcactg acatgctccc ccagtgttga aaatagaggc tcaaggtcac    780

acagccccgt acatgcgagc aatgtgggct ctcctctttc aagtccatta agcagcatga    840

aatccccaat ttccagccct ccaagtcact gcagtgtaaa atctccagta tccagtccaa    900

acaatgtccc tctgcgctcc tctgtgtcaa gcccggcaaa tcttaacaat tcaaggtgct    960

ctgtttccag cccttccaac accaacaata gatctacact ctccagcccg acagctagca   1020

cagtggggtc cattggcagc cccatcagca atgccttcag ctataccact tcaggcgctt   1080

cggctggagc cggtgccatc caggatatgg ttcccagtcc agacacccac gagaaaggtg   1140

ctcacgacgt tcctttccct aagacagagg aagtcgagaa ggccatttcc aatggtgtga   1200

ctggtcagct caacattgtc cagtacataa aaccagaacc agatggggct ttcagcagtt   1260

cctgcctagg aggaaacaac aaaatcaacc ccagttctcc gttctctgta ccaataaagc   1320

aagagtcaag caagcactca tgttcaggcg cctcttttaa agggaacccc acagtcaacc   1380

catttccatt catggatggc tcgtactttt cttttatgga tgataaagac tattattccc   1440

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catcatctgc catcattggt gtgaattcag gtggacagtc ctttcactac cggattggtg   1620

ctcaaggtac aatatcttta tcacggtcac ctagagacca atctttccaa cacttgagtt   1680

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aggcttctgg gtgtcactat ggggtagtga cctgcggcag ctgcaaagtc ttcttcaaaa   1920

gagccgtgga aggacaacac aactatctgt gtgctggaag aaatgactgc attattgata   1980

agattcggag aaagaactgt cctgcctgca ggctccagaa atgcctccaa gccggcatga   2040

acttaggagc tcgaaagtca aagaagctgg ggaagttaaa aggccttcac gaggagcagc   2100

cacagcagcc cccaccgcca ccaccccaga gcccagaaga ggggaccaca tacattgctc   2160

ctaccaagga gccatcagtg aactctgcgc tggtcccgca gctcgcctcg atcacgcgtg   2220

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gctacgacaa ttccaagcct gacaccgccg agagcctgct ctccacgctc aaccgcctgg   2340

cgggcaagca gatgatccaa gtcgtgaagt gggccaaggt acttccagga tttaaaaact   2400

tgcctcttga ggaccaaatt accctcatcc agtattcttg gatgtgtcta tcatcgtttg   2460

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actttgcctt aagtttcccc acgttgttct acaactacga aggacccaag aaatcacatt 3060

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ctggctt 4087

<210> SEQ ID NO 76
<211> LENGTH: 3978
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 76

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gaggctgacg gggctgctgg agtttgcaga gacacggagg aggaaagagc ttgggctttg 180

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ggcggctctg atttcttttc gccaagtggg aaggtggttt atttttcttg ctttttttgga 480

gtcaacaccc ttccccacca gcccttatcc ccaccctcac cccgcaaccc cttcacgccc 540

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gaagacagct tgaaggataa aaagcctcgg tgcttcccag gcgccgatcc gaggagccga 720

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tgagatcaat ggagatggct agtaaaatgt ggcatcccta ggaaacaaga caaatgggta 3900

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aaaaaaaaaa aaaaaaaa 3978

<210> SEQ ID NO 77
<211> LENGTH: 8433
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 77

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gaacctgacc cggacctgct ggccggccag agtgccgagg aggagaccga agacggcatc 240

ctgtccccca tccccatggg gccaccgtcc cccttcccca ccagcgagga cttcactccc 300

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aacctcgcca tgtgtcagat caacgaacag atttactata aagtcattaa ggacatcgag 720

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<212> TYPE: DNA
<213> ORGANISM: Mus musculus

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<211> LENGTH: 2789
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 79

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<211> LENGTH: 6199
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 80

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<213> ORGANISM: Mus musculus

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<212> TYPE: DNA
<213> ORGANISM: Mus musculus

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gatgaacctg gatccctggt tttctccaag aaggactcca gagaaagagg ccatgagcca 660

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gaccggagga caatggcctg ggcacagggc tcaccctgga gagccacaag gacccatcta 780

gccatccagg cctagctggc cagggacaag gcagaaattt tagaaaacca aagactattt 840

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<211> LENGTH: 4354
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 87

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<210> SEQ ID NO 88
<211> LENGTH: 3579
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 88

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gaaatcaaga tcccaaacaa gacatagtct ccgtgttgga agaagaagag ccatcatcgg 360

gaaaggggaa aaaagccagc ccaagtagtc tgaaaaaaat agcaaggccc aagacagcag 420

gaacaagtgc aaaactccaa caagatgatg agcataggga ggaaaagcag aagtcccaaa 480

gcaaacttac taaggaagtg acactcagga agaaaagttc caacagcaag aaaagcagtg 540

agtatggttt gttggagaac aaaagtctcc actcaaaaca cactccttcc gagaaaaaac 600

tgcttaagtc cagttcccgt gggaagaact cgaatcagaa ttcagactct ctgaaaaaga 660

aacctgacac agctaatgac cacaggaaat cactcagcca ttctgcatct gatgtgaaca 720

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aaggtgacaa aaaccaaacc agcaaaaaat gtgagaaagt atgccgtcat agtgcatccc 840

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tgctccttta tgaacaatga atttaagaca tatggcattg aaccttgata ttgaattcac 3480

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<210> SEQ ID NO 89
<211> LENGTH: 3276
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 89

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<210> SEQ ID NO 90
<211> LENGTH: 6152
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 90

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tgcagccctc agtgaatgta gatgctgtat ttgctatcga tgcctgccat acaagcatac 3480

actatattaa cagcatgtta gagttcctac tttgtattga ctgaactctt caaacatagc 3540

tacgccctga aggaaggtat cctgctttga ttttgatgct ttgtgaattg ggctccatga 3600

agatgttgga attcttgaga taccctttga aatctcttac cccctttaag aaaaatgtaa 3660

gccattagta agagcacttg agctgcccag aagctgagaa acagctgttg tttctctgtt 3720

gtcaactggt aatagttaag aaaagttttc ttacttaaaa cacctctagt accaaatatt 3780

catgtttcca caccagttca attgtttgaa gacaccaact ggatgtcctc caatctatat 3840

caatttagtc tctacccata atatcctgct agtgagatgg gcttagtctg agaagactgt 3900

ctctccccac cctccccaca ttcagacatt aatgaggagt cctacattac tgatttggct 3960

acagattgaa ccctctgggt tcagtaattt gctatggtaa ctcaccaaac ataaattgtt 4020

taaagttacc atttactcta tattgtgaat gtcacaggag cagccagatg aagagatgga 4080

acaagatcca aagggttccc acgtgaaggt gtgtttgtct ttatagagtt ggagtgcctt 4140

accctattga gccttgttta gtgcttttat ggagattaca ctgtgtgccc atgattgatg 4200

aagtccttgg ctgttacata agtttcccct gccagaagtc aacaggggtt gctgaaagtt 4260

ccaactctgt tagcacatag ttggctcctt tgacaatcag ccctaatcct ggagttagtg 4320

acactgagtc tagcaacaag tcactttagc ataaacagat ggctgtaaga gaccttagga 4380

gtaacaaaag gctttataat atttttctgc tggaaacaag agagaccaaa catacttaag 4440

tcacagacag aaacccattt acttggttca catcccctta tgtctgtctg ggcaatttgg 4500

ggatttgttt gtctttggtt cagtagttaa gtgggataaa atgaaaatgc agcactctgg 4560

aagctgtcaa tctaggaaca cacacgaaca ttagacagtg cagaatatta gtgtttttcc 4620

ataaagcagt tctttccaaa atgtcttcat ttaaaagtat gtaatggcta gtgacatggc 4680

tcagcaggta aaggcgaagc ccaacctgag tttcaacctc tagagcccac atggtgggaa 4740

ggacagactg acacacagtt gtcctctggt ctctgtgcat gcatgaaaac aatgtcattc 4800

ttaaaaacta aaatacctat actgaaatta agcattttga tcatcttgaa gtgtgcaact 4860

tgtctattca aataaatcta ataaaactgc agaattgctg ag 4902

<210> SEQ ID NO 93
<211> LENGTH: 1000
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1000)
<223> OTHER INFORMATION: This sequence may be 30-1000 bases in length

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<220> FEATURE:
<223> OTHER INFORMATION: See specification as filed for detailed
description of substitutions and preferred embodiments

<400> SEQUENCE: 93

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 600

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 720

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 840

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 960

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1000

<210> SEQ ID NO 94
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 94

cctgtcctcg cccgagtccc tgcc 24

<210> SEQ ID NO 95
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 95

ctcgtcccga gcccaccatc tccacttcct cc 32

<210> SEQ ID NO 96
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 96

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caacaaccgt atgcccatga cagg                                       24


<210> SEQ ID NO 97
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 97

ggaggtggga tggagggaat ccttg                                      25


<210> SEQ ID NO 98
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 98

gggaaattga agtccagcca agagtg                                     26


<210> SEQ ID NO 99
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 99

cccggtgaac aagcgagagt cggcgtc                                    27


<210> SEQ ID NO 100
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 100

gcatgggttc ctcggtcaat gacg                                       24


<210> SEQ ID NO 101
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 101

gcgccctcgg tcatggatct cagc                                       24


<210> SEQ ID NO 102
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
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<400> SEQUENCE: 102

gaccctattt gtcagcggtc tgcctc                                          26


<210> SEQ ID NO 103
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 103

ctccagaggc ttcggtttcg tcac                                            24


<210> SEQ ID NO 104
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 104

gtggagaccg gaaagtacca ggaagg                                          26


<210> SEQ ID NO 105
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 105

ggaggccgac tttggatggg agcag                                           25


<210> SEQ ID NO 106
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 106

ggatgggttc agtaatgccc aggagaag                                        28


<210> SEQ ID NO 107
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 107

caggtttaga tggagtacgg cagtgtg                                         27


<210> SEQ ID NO 108
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 108

catcaccaag gacaaccggc gacac                                            25


<210> SEQ ID NO 109
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 109

cgaggaagaa gagggagaga aactgtc                                          27


<210> SEQ ID NO 110
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 110

ggtgaccttt gaggacgtgg ctgtg                                            25


<210> SEQ ID NO 111
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 111

caacgggcct tcttcttcct cttcctc                                          27


<210> SEQ ID NO 112
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 112

ctgctccgtg ctacccactc actg                                             24


<210> SEQ ID NO 113
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 113

cgattaccta cccagcgacc actc                                             24


<210> SEQ ID NO 114
<211> LENGTH: 28
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 114

ccaacacttg agttcctttc cgcctgtc                                          28


<210> SEQ ID NO 115
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 115

ccgaaagctg tctaagatcg agacg                                             25


<210> SEQ ID NO 116
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 116

ggcagcaccc acatcagcag cagag                                             25


<210> SEQ ID NO 117
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 117

ctggatgaaa gagtcgaggc aaac                                              24


<210> SEQ ID NO 118
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 118

gagtttggat gaagcgcagg ccag                                              24


<210> SEQ ID NO 119
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 119

caagggtctc caaacgtcca caac                                              24


<210> SEQ ID NO 120
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<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 120

gccatcgaaa ggaagagcct ggac                                        24


<210> SEQ ID NO 121
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 121

gagcagagat gacgtagccc agtg                                        24


<210> SEQ ID NO 122
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 122

cgctctcctt cgcgggctta ccctcc                                      26


<210> SEQ ID NO 123
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 123

gaactgggcc atccgcgcca tcgagac                                     27


<210> SEQ ID NO 124
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 124

gtcttcttca accatctcga ctcgcagg                                    28


<210> SEQ ID NO 125
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 125

gggtttcgtt gtgtggtgtg tatgcag                                     27
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<210> SEQ ID NO 126
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 126

cggcagcggg aaggtgaacg ggagctac                                        28


<210> SEQ ID NO 127
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 127

cggtcccggc agaccagatg atagttc                                         27


<210> SEQ ID NO 128
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 128

gcacgagaag cggatgtcaa aggacgag                                        28


<210> SEQ ID NO 129
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 129

ctgatgtggg aggtacgtgg gagcaag                                         27


<210> SEQ ID NO 130
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 130

gagcgaggac cagtcactat ttgag                                           25


<210> SEQ ID NO 131
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 131
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cgtcgccgcc gggtcaggta gcgattg 27

<210> SEQ ID NO 132
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 132

gcaaaggtga acacaaggtc agtcagagg 29

<210> SEQ ID NO 133
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 133

catcctcttc tggtccttca ccaac 25

<210> SEQ ID NO 134
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 134

caatttcatc gggaacagca accatg 26

<210> SEQ ID NO 135
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 135

ctgcacccga tttcttacgg cttg 24

<210> SEQ ID NO 136
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 136

gttgacgctc caggatgttg tggttg 26

<210> SEQ ID NO 137
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

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<400> SEQUENCE: 137

gtccttatca gggtcatcat cgtc                                        24


<210> SEQ ID NO 138
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 138

ccatgttgtt ctttctgcgc ctcgccc                                     27


<210> SEQ ID NO 139
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 139

gaaagcggca ggaggaggaa gagc                                        24


<210> SEQ ID NO 140
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 140

ctgccatagg ttgccacaaa gttg                                        24


<210> SEQ ID NO 141
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 141

gtttgcccat actccttccc acgatac                                     27


<210> SEQ ID NO 142
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 142

cttctcgttg gtgatatgct ctggacctg                                   29


<210> SEQ ID NO 143
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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      primer

<400> SEQUENCE: 143

ccacccggac agcgcgattc cacc                                            24


<210> SEQ ID NO 144
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 144

gcaaggccca agacagcagg aacaag                                          26


<210> SEQ ID NO 145
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 145

cagcatggag agcggagaca ggtc                                            24


<210> SEQ ID NO 146
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 146

ctgccgctgt ctcttgcact tgtacc                                          26


<210> SEQ ID NO 147
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 147

gactaaacaa acacccttcc acagagc                                         27


<210> SEQ ID NO 148
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 148

cattatttgg actgtaccgc tggcctgg                                        28


<210> SEQ ID NO 149
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 149

gaggctgagg gttaaaggca gtggag   26

<210> SEQ ID NO 150
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 150

cgtcaggtag cgattgtagt gaaactcc   28

<210> SEQ ID NO 151
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 151

gcaggacagt tctttctccg aatc   24

<210> SEQ ID NO 152
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 152

ctgcccccca ggtcacgacg gctgc   25

<210> SEQ ID NO 153
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 153

cgccgaagaa ggatcgaaat agctc   25

<210> SEQ ID NO 154
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 154

ggtagttgga aggcagcgcg taggc   25

<210> SEQ ID NO 155
<211> LENGTH: 24

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 155

gatgccgcac ttcttggcta actc 24

<210> SEQ ID NO 156
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 156

gtcacatttg gcaggtcatc atcg 24

<210> SEQ ID NO 157
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 157

ccactcgtag atgtcttgtt cacacac 27

<210> SEQ ID NO 158
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 158

gtggttgttc tcctgctgta gcctgg 26

<210> SEQ ID NO 159
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 159

gtggagcgag catgtagcca gttgg 25

<210> SEQ ID NO 160
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 160

cttcaggttt ctgccttctt tgccaatc 28

<210> SEQ ID NO 161
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 161

ggtatcgggt ggtgtgttgc aggctggg 28

<210> SEQ ID NO 162
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 162

gaacaaacac tgtgaaacag acggg 25

<210> SEQ ID NO 163
<211> LENGTH: 27
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 163

gcacagggtg aggaggaggc tgaagag 27

<210> SEQ ID NO 164
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 164

ctcctcctcc tcatcgttgg taacatc 27

<210> SEQ ID NO 165
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 165

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<210> SEQ ID NO 166
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 166

caggcaaagt cctcttcaca gccaagg 27

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<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 167

ccatattctt tcaccgccca ctcc                                          24


<210> SEQ ID NO 168
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 168

acacggccgt gtattactgt gcaagg                                        26


<210> SEQ ID NO 169
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 169

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<210> SEQ ID NO 170
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 170

acacggccgt gtattactgt                                               20


<210> SEQ ID NO 171
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 171

actcggccgt gtttccctgt gcaagg                                        26


<210> SEQ ID NO 172
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 172
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<210> SEQ ID NO 173
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<400> SEQUENCE: 173

caaggaggcc tta                                                       13


<210> SEQ ID NO 174
<211> LENGTH: 11
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 174

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<211> LENGTH: 19
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 175

gcaagacagg ggctactat                                                 19


<210> SEQ ID NO 176
<211> LENGTH: 14
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 176

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<210> SEQ ID NO 177
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 177

gatagtagct ggctttttct t                                              21


<210> SEQ ID NO 178
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<221> NAME/KEY: modified_base
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: a, c, t, g, unknown or other

<400> SEQUENCE: 178

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<210> SEQ ID NO 179
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 179

cctgatggtt agggc                                                   15


<210> SEQ ID NO 180
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 180

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<210> SEQ ID NO 181
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 181

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<210> SEQ ID NO 182
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 182

tctgcacatt ccaattct                                                18


<210> SEQ ID NO 183
<211> LENGTH: 14
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 183

caaggcacca ctct                                                    14


<210> SEQ ID NO 184
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<211> LENGTH: 16
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (2)..(3)
<223> OTHER INFORMATION: a, c, t, g, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: a, c, t, g, unknown or other

<400> SEQUENCE: 184

cnngnccccc tttcac                                                   16


<210> SEQ ID NO 185
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 185

gtgactactt tgactact                                                 18


<210> SEQ ID NO 186
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 186

ctttgactac tggggcc                                                  17
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1. A hematopoietic stem cell (HSC) inducing composition comprising one or more expression vector encoding four or more HSC inducing factors selected from: CDKN1C, DNMT3B, EGR1, ETV6, EVI1, GATA2, GFI1B, GLIS2, HLF, HMGA2, HOXA5, HOXA9, HOXB3, HOXB4, HOXB5, IGF2BP2, IKZF2, KLF12, KLF4, KLF9, LMO2, MEIS1, MSI2, MYCN, NAP1L3, NDN, NFIX, NKX2-3, NR3C2, PBX1, PRDM16, PRDM5, RARB, RBBP6, RBPMS, RUNX1, RUNX1T1, SMAD6, TAL1, TCF15, VDR, ZFP37, ZFP467, ZFP521, ZFP532, ZFP612, and ZPF467.

2-**47**. (canceled)

48. The HSC inducing composition of claim **1**, wherein the four or more HSC inducing factors are HLF, RUNX1T1, PBX1, LMO2, PRDM5, ZFP37, MYCN, MSI2, NKX2-3, MEIS1, and RBPMS.

49. The HSC inducing composition of claim **1**, wherein the four or more HSC inducing factors are HLF, RUNX1T1, ZFP37, PBX1, LMO2, and PRDM5.

50. The HSC inducing compositions of claim **1**, wherein the expression vector is a retroviral vector.

51. The HSC inducing compositions of claim **1**, wherein the expression vector is a lentiviral vector.

52. The HSC inducing composition of claim **51**, wherein the lentiviral vector is an inducible lentiviral vector.

53. A method for preparing an induced hematopoietic stem cell (iHSC) from a somatic cell comprising:

a. transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding RUNX1T1; a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding LMO2; and a nucleic acid sequence encoding PRDM5, wherein each said nucleic acid sequence is operably linked to a promoter; and

b. culturing the transduced somatic cell in a cell media that supports growth of hematopoietic stem cells, thereby preparing an iHSC.

54. The method of claim **53**, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding PRDM16 a nucleic acid sequence encoding ZFP467; and a nucleic acid sequence encoding VDR wherein each said nucleic acid sequence is operably linked to a promoter.

55. The method of claim **53** further comprising transducing the somatic cell with one or more vectors comprising a nucleic acid sequence encoding ZFP37; a nucleic acid sequence encoding MYCN; a nucleic acid sequence encoding

MSI2; a nucleic acid sequence encoding NKX2-3; a nucleic acid sequence encoding MEIS1; and a nucleic acid sequence encoding RBPMS; wherein each said nucleic acid sequence is operably linked to a promoter.

56. The method of claim **53**, wherein the expression vector is a retroviral vector.

57. The method of claim **53**, wherein the expression vector is a lentiviral vector.

58. The method of claim **57**, wherein the lentiviral vector is an inducible lentiviral vector.

59. The method of claim **53**, wherein the somatic cell is a fibroblast cell.

60. The method of claim **53**, wherein the somatic cell is a hematopoietic lineage cell.

61. The method of claim **60**, wherein the hematopoietic lineage cell is selected from promyelocytes, neutrophils, eosinophils, basophils, reticulocytes, erythrocytes, mast cells, osteoclasts, megakaryoblasts, platelet producing megakaryocytes, platelets, monocytes, macrophages, dendritic cells, lymphocytes, NK cells, NKT cells, innate lymphocytes, multipotent hematopoietic progenitor cells, oligopotent hematopoietic progenitor cells, and lineage restricted hematopoietic progenitors.

62. The method of claim **60**, wherein the hematopoietic lineage cell is selected from a multi-potent progenitor cell (MPP), common myeloid progenitor cell (CMP), granulocyte-monocyte progenitor cells (GMP), common lymphoid progenitor cell (CLP), and pre-megakaryocyte-erythrocyte progenitor cell.

63. The method of claim **60**, wherein the hematopoietic lineage cell is selected from a megakaryocyte-erythrocyte progenitor cell (MEP), a ProB cell, a PreB cell, a PreProB cell, a ProT cell, a double-negative T cell, a pro-NK cell, a pro-dendritic cell (pro-DC), pre-granulocyte/macrophage cell, a granulocyte/macrophage progenitor (GMP) cell, and a pro-mast cell (ProMC).

64. A method of promoting transdifferentiation of a ProPreB cell to the myeloid lineage comprising:

a. transducing a ProPreB cell with one or more vectors comprising a nucleic acid sequence encoding ZFP467, a nucleic acid sequence encoding PBX1; a nucleic acid sequence encoding HOXB4; and a nucleic acid sequence encoding MSI2; wherein each said nucleic acid sequence is operably linked to a promoter; and

b. culturing the transduced ProPreB cell in a cell media that supports growth of myeloid lineage cells, thereby transdifferentiating the ProPreB cell to the myeloid lineage.

65. The method of claim **64**, wherein the transducing of step (a) further comprises one or more vectors comprising one or more of: a nucleic acid sequence encoding HLF, a nucleic acid sequence encoding LMO2; a nucleic acid sequence encoding PRDM16; and a nucleic acid sequence encoding ZFP37.

66. The method of claim **63**, wherein the expression vector is a retroviral vector.

67. The method of claim **63**, wherein the expression vector is a lentiviral vector.

68. A kit for making induced hematopoietic stem cells (iHSCs) comprising the HSC inducing compositions of claim **1**.

* * * * *