FIG. 1A

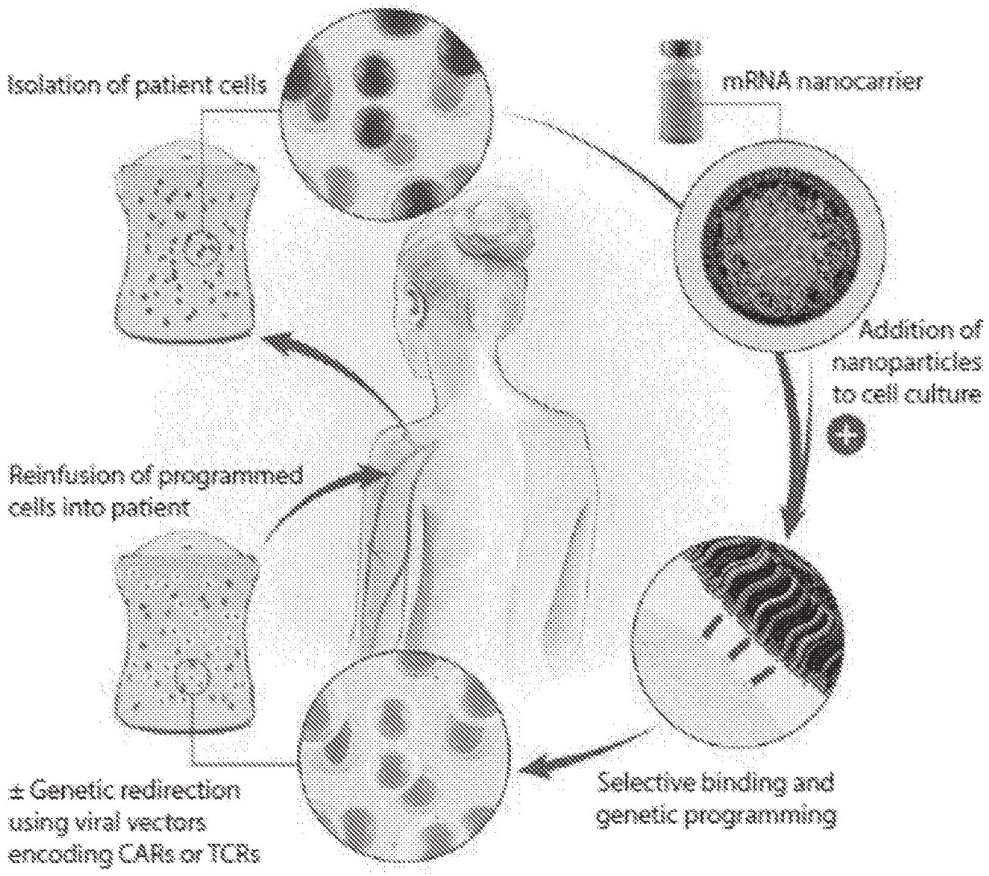

Isolation of patient cells
mRNA nanocarrier
Addition of nanoparticles to cell culture
Reinfusion of programmed cells into patient
± Genetic redirection using viral vectors encoding CARs or TCRs
Selective binding and genetic programming

FIG. 1B

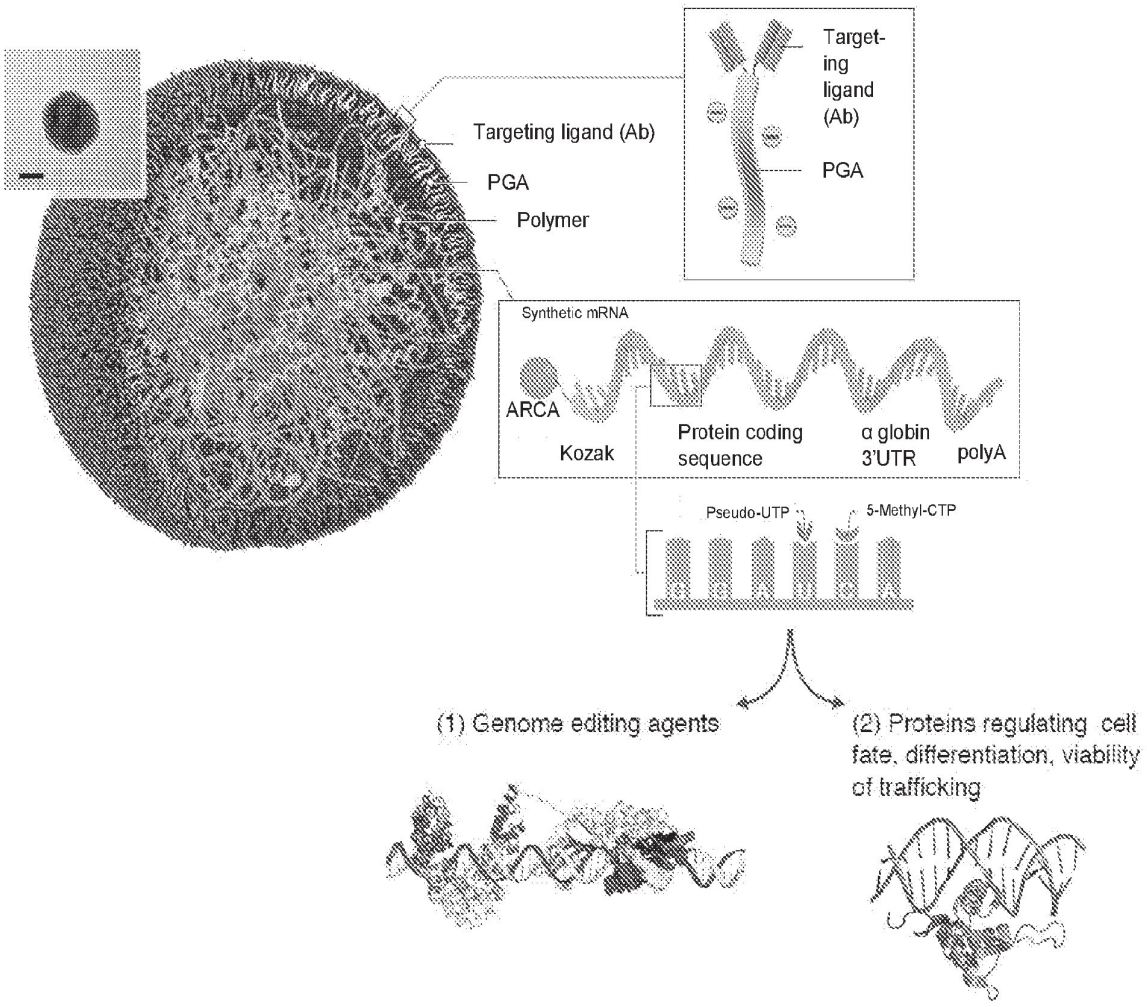
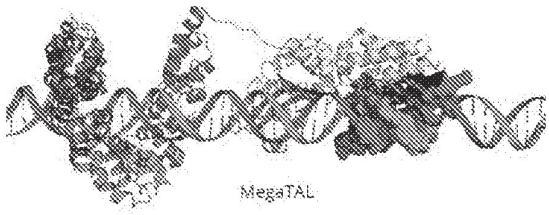

Nanoparticle with synthetic mRNA cargo
Targeting ligand (Ab)
PGA
Polymer
Target-ing ligand (Ab)
PGA
Synthetic mRNA
ARCA
Kozak
Protein coding sequence
α globin 3'UTR
polyA
Pseudo-UTP
5-Methyl-CTP
(1) Genome editing agents
(2) Proteins regulating cell fate, differentiation, viability of trafficking

FIG. 1C



Therapeutic area	Target gene
T cell Signaling	Shp1 phosphatase
Immune Checkpoint	PD1 receptor
Safety	endogenous TCRa
HIV resistance	CCR5 and or CXCR4



Therapeutic area	Target gene
T cell memory	**FOXO1, LKB1**
Cellular seescence	**TERT (prevents telomere shortening)**
Cell trafficking	Chemokine receptor CCR2b or CCR4

FIG. 2

Antibody Specificity	Dye	Clone	Supplier
CD34	BV421	561	Biolegend
CD90	APC	5E10	Biolegend
CD105	PE-Cy7	43A3	Biolegend
CD49F	PE	GOH3	Biolegend
CD28	BV 510	CD28-2	Biolegend
CD62L	APC-CY7	DERG56	Biolegend
CD62L	PE-CY5	DERG56	Biolegend
CD45RA	ALEXA 700	HI1000	Biolegend
CCR7	PE	G043H7	Biolegend
CD3	APC	HIT3A	Biolegend
CD3	BV421	HIT3A	Biolegend
CD45R0	PERCP-CY5.5	UCHL1	Biolegend
CD8	BV421	SK1	Biolegend
IL2	BV421	MQ1-17H12	Biolegend
IFN-G	PE	B27	Biolegend
CD19	PE	H1B19	Biolegend
CD133	PE-Vio615	AC133	Miltenyi
Foxo1	--	C29H4	Cell Signal
anti-Rabbit IG FAB2	Alexa 647	--	Cell Signal
StrepTag II	biotin	--	--
Streptavidin	APC	--	ebioscience
7AAD	--	--	ebioscience

FIG. 3A

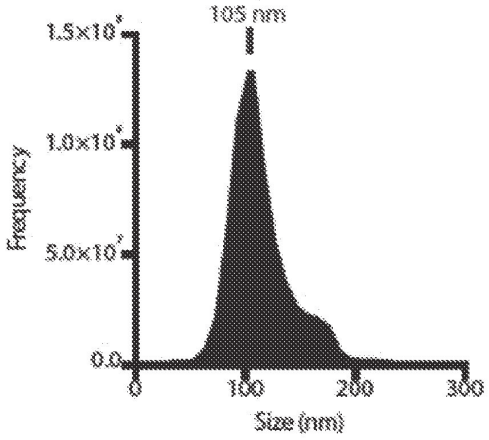


FIG. 3B

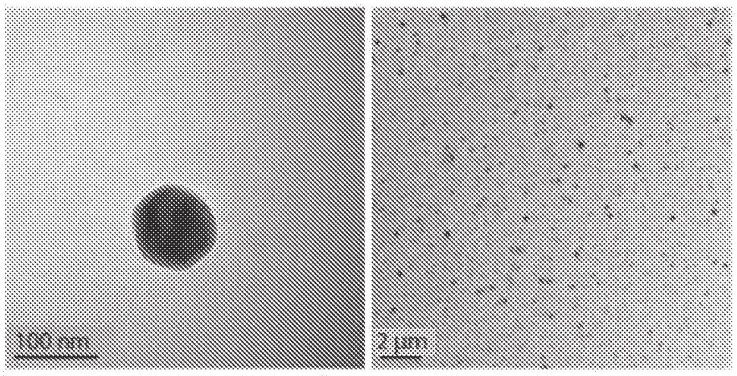


FIG. 3C

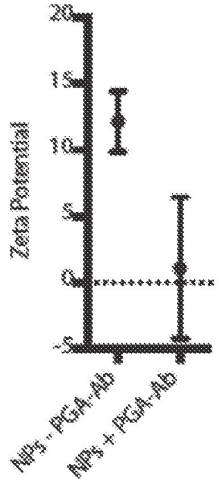


FIG. 4A

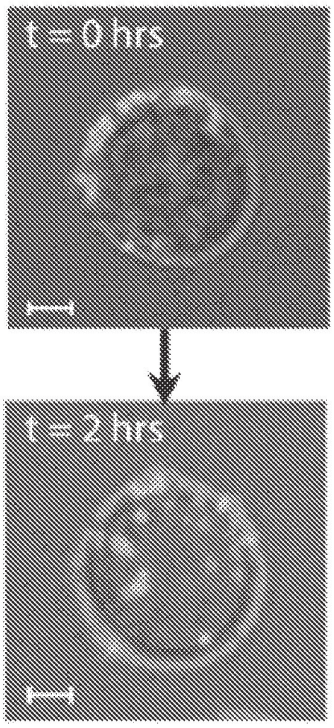

t = 0 hrs
t = 2 hrs

FIG. 4B

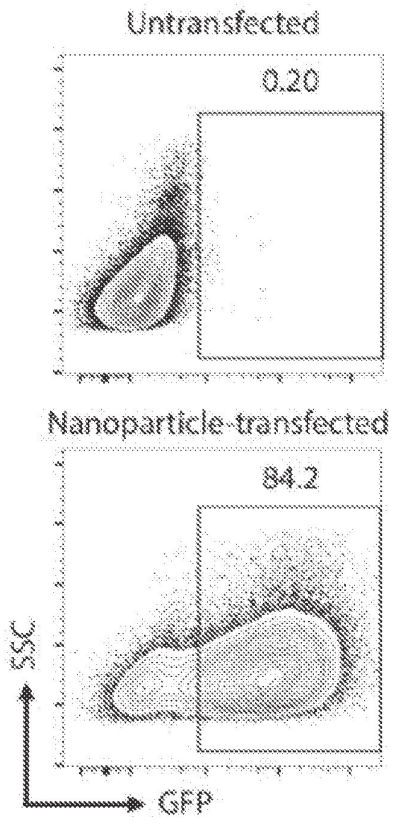

Untransfected
0.20
Nanoparticle-transfected
84.2
SSC
GFP

FIG. 4C

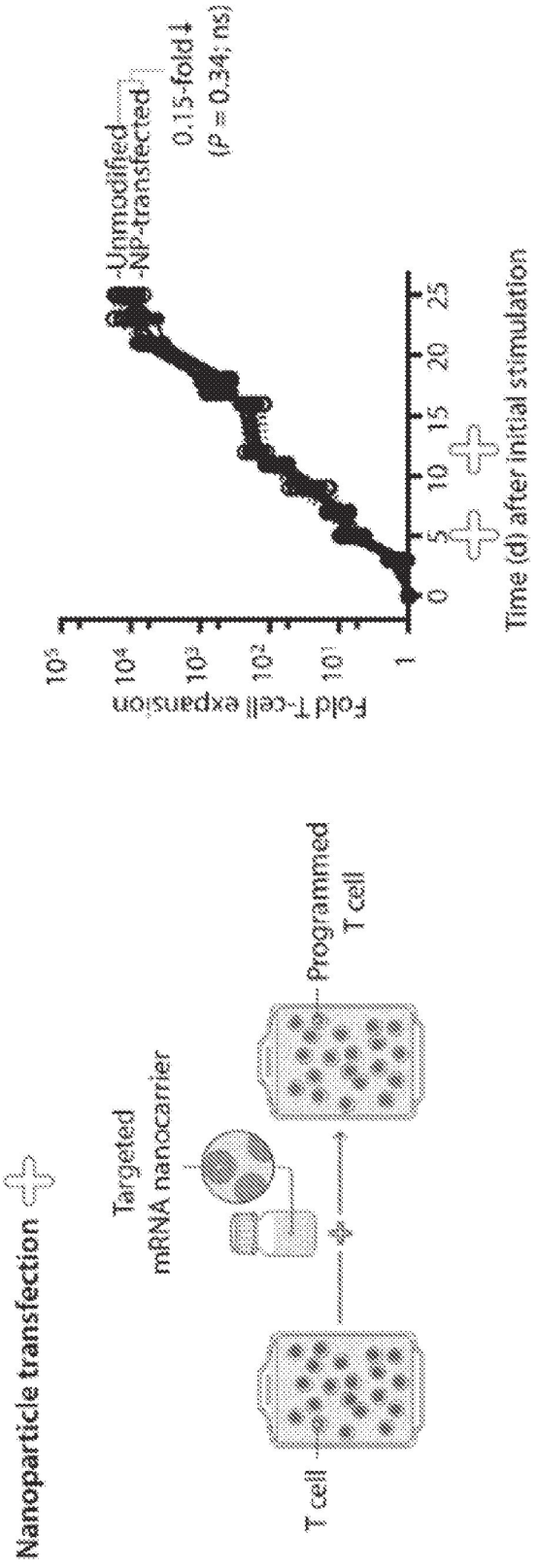

Nanoparticle transfection
T cell
Targeted
mRNA nanocarrier
Programmed
T cell
Unmodified
NP-transfected
0.15-fold ↓
(P = 0.34; ns)
Fold T-cell expansion
10⁵
10⁴
10³
10²
10¹
1
0
5
10
15
20
25
Time (d) after initial stimulation

FIG. 4D

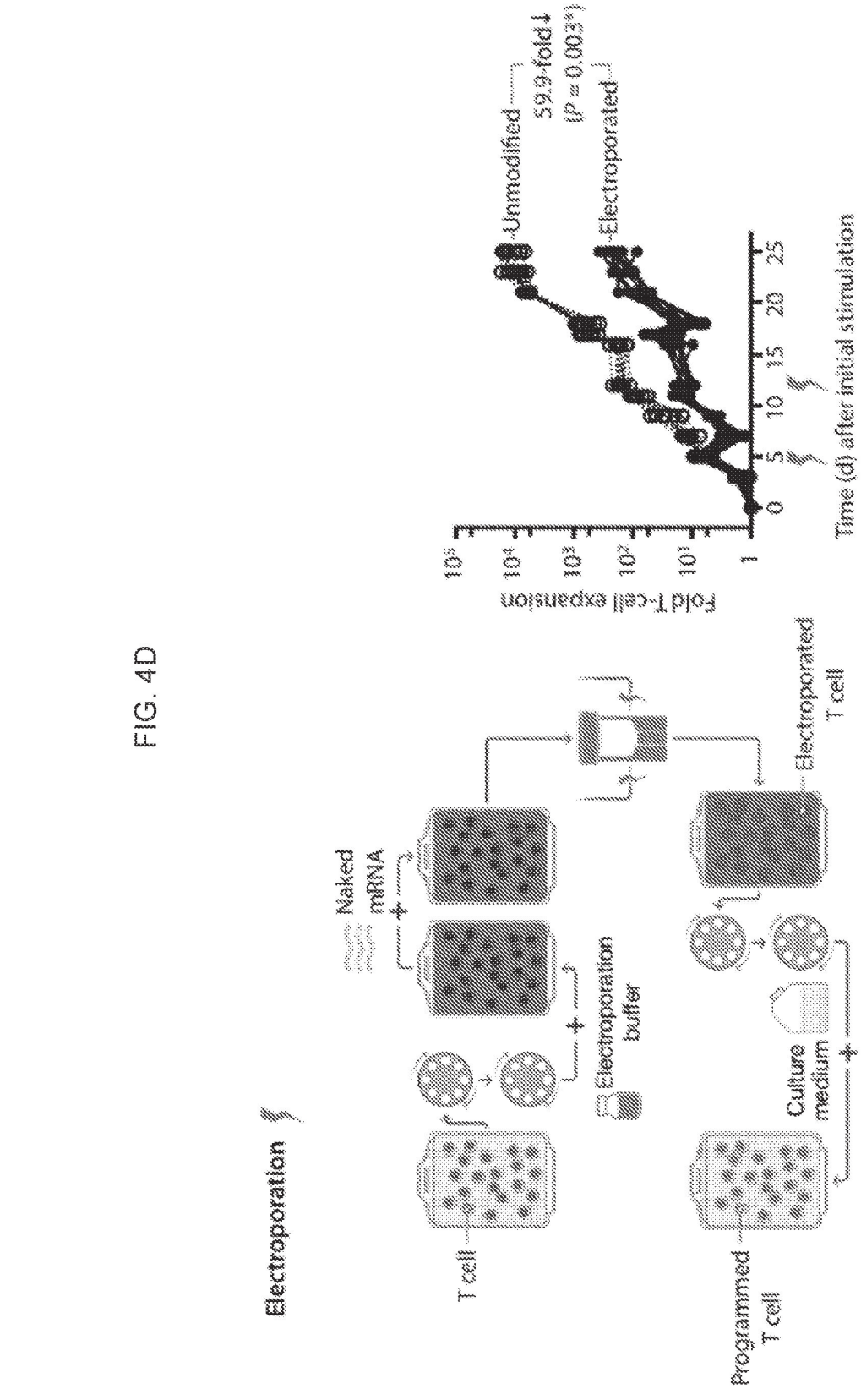

Electroporation
T cell
Naked mRNA
Electroporation buffer
Culture medium
Programmed T cell
Electroporated T cell
Fold T-cell expansion
Unmodified
59.9-fold↓
(P = 0.0023**)
Electroporated
Time (d) after initial stimulation

FIG. 5A

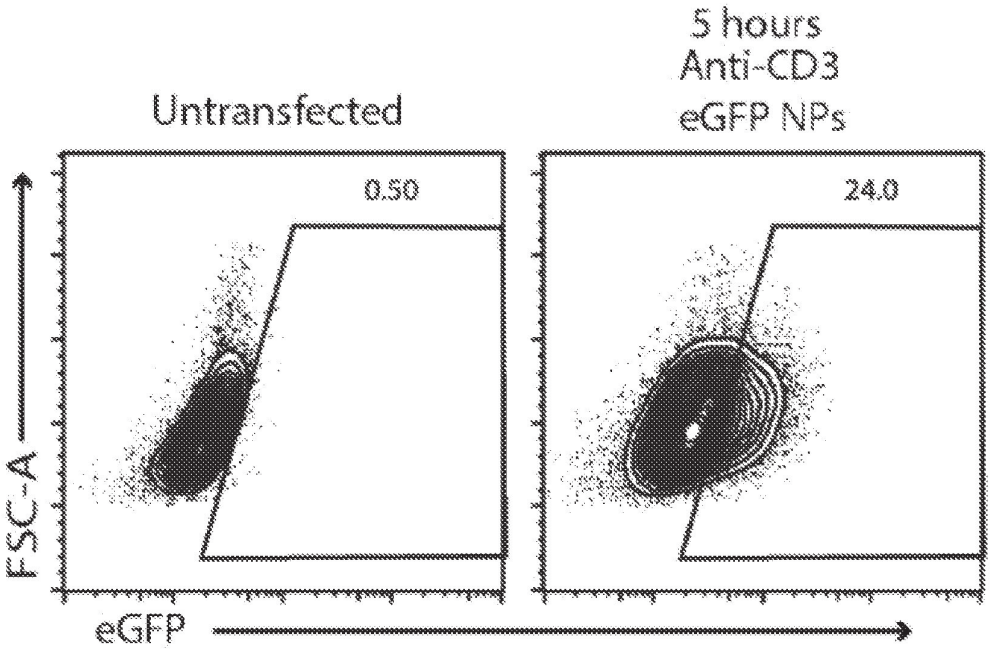


FIG. 5B

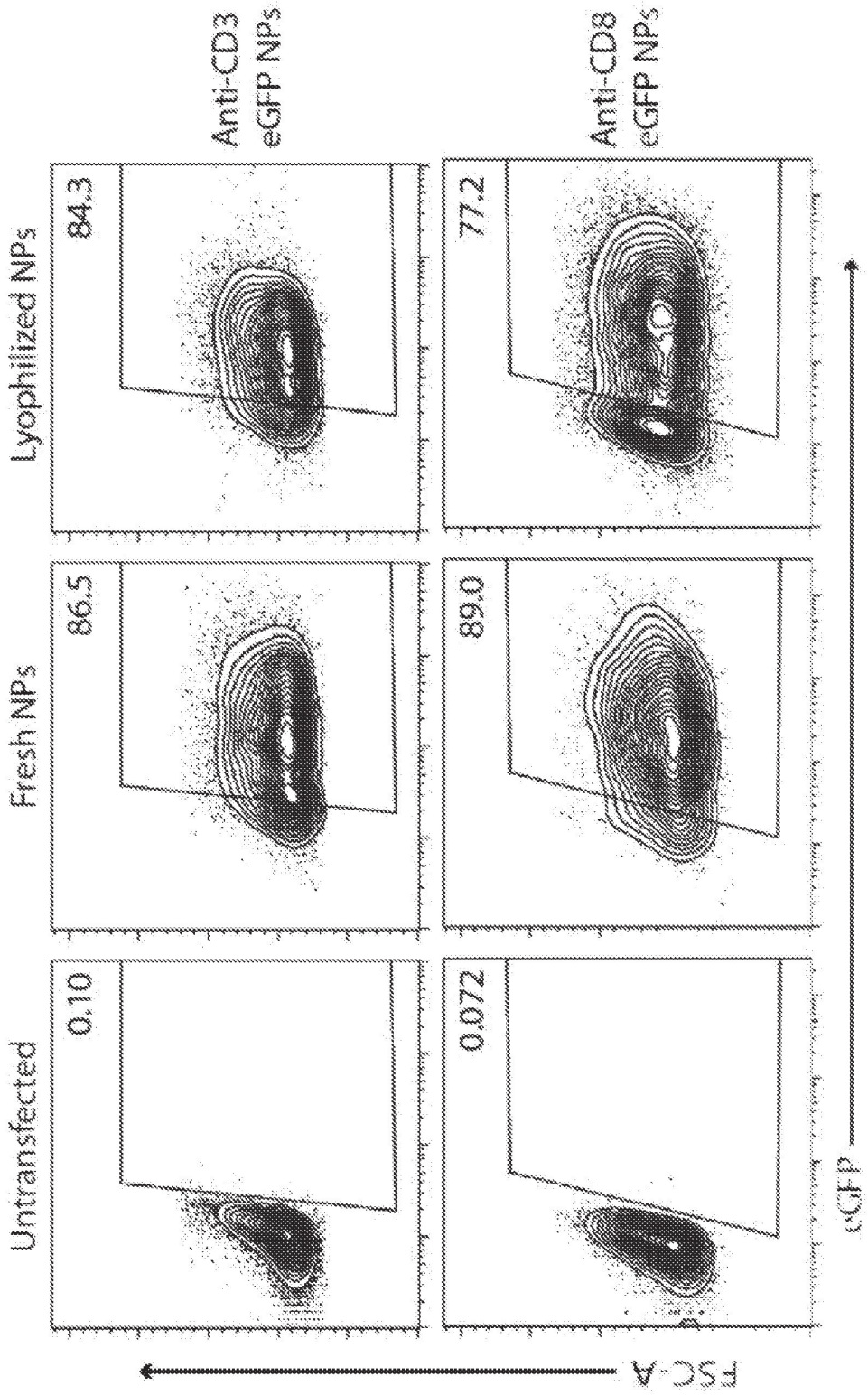

Untransfected
Fresh NPs
Lyophilized NPs
Anti-CD3 eGFP NPs
Anti-CD8 eGFP NPs
0.10
86.5
84.3
0.072
89.0
77.2
FSC-A
eGFP

FIG. 6

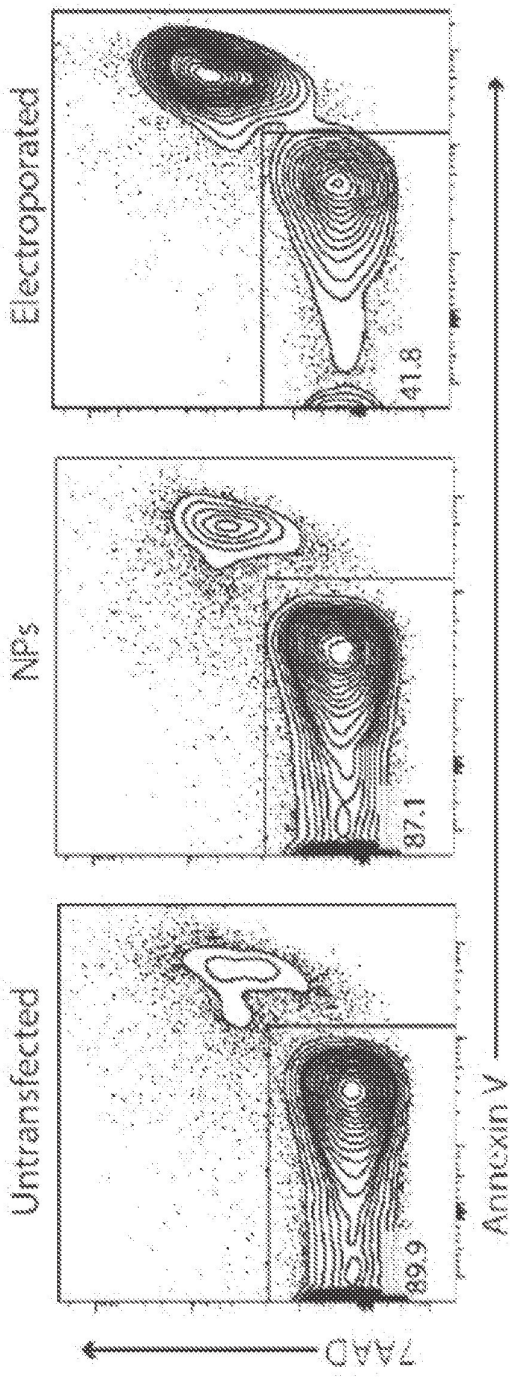

Untransfected
NPs
Electroporated
89.9
87.1
41.8
7AAD
Annexin V

FIG. 7A

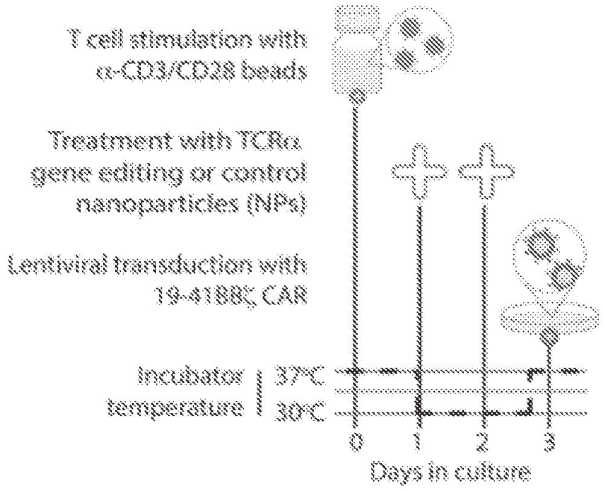

T cell stimulation with
α-CD3/CD28 beads
Treatment with TCRα
gene editing or control
nanoparticles (NPs)
Lentiviral transduction with
19-4188ζ CAR
Incubator
temperature
37°C
30°C
0
1
2
3
Days in culture

FIG. 7B

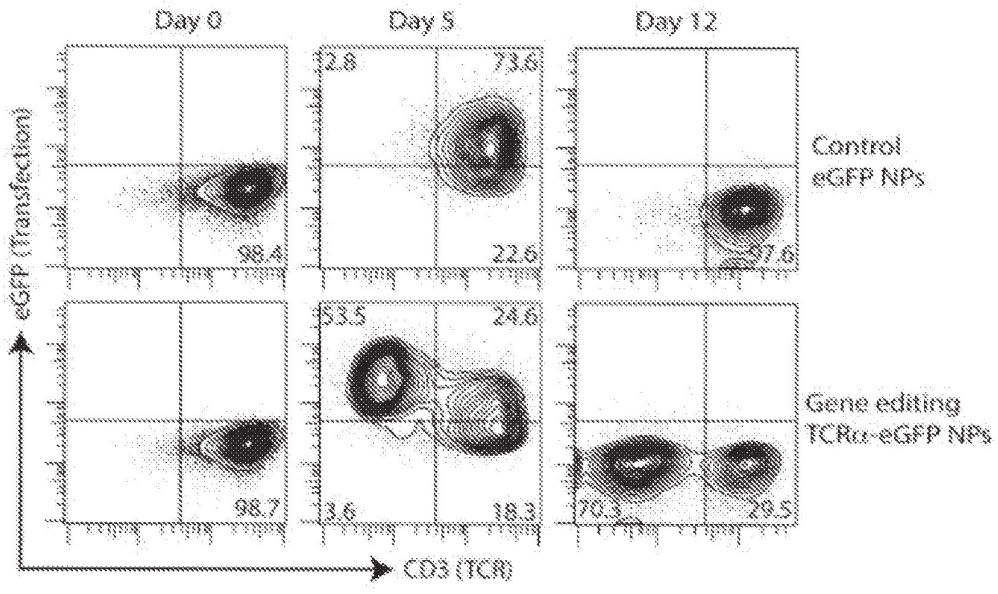

Day 0
Day 5
Day 12
2.8
73.6
98.4
22.6
37.6
Control
eGFP NPs
53.5
24.6
98.7
3.6
18.3
70.3
29.5
Gene editing
TCRα-eGFP NPs
eGFP (Transfection)
CD3 (TCR)

FIG. 7C

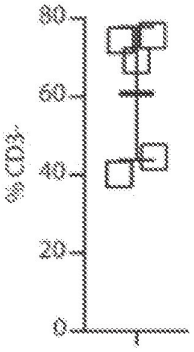


FIG. 7D

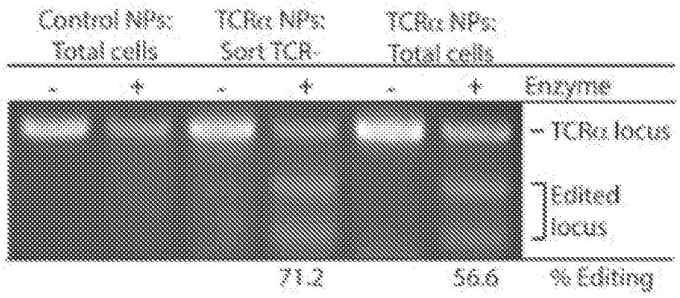


FIG. 7E

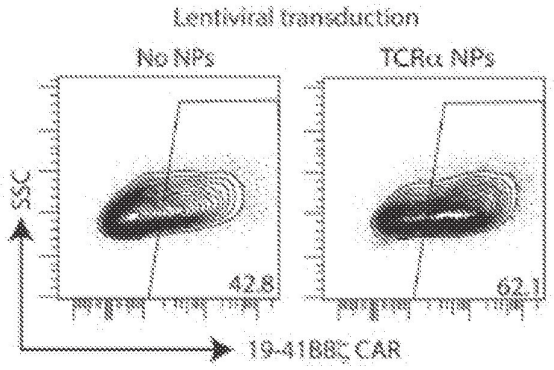


FIG. 7F

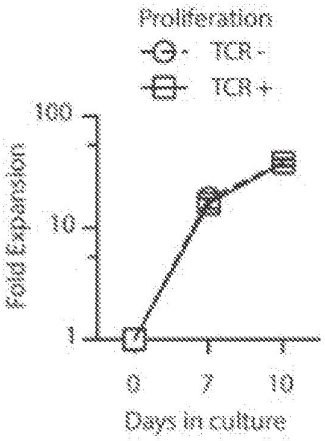


FIG. 7G

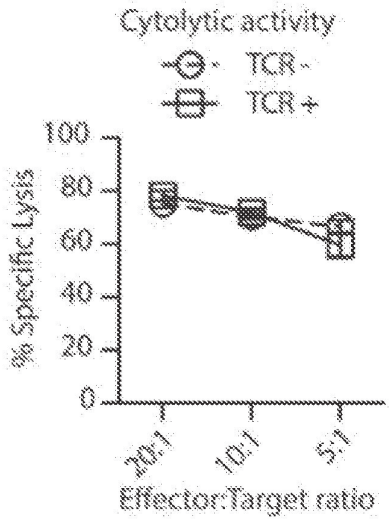

Cytolytic activity
TCR -
TCR +
100
80
60
40
20
0
% Specific Lysis
20:1
10:1
5:1
Effector:Target ratio

FIG. 7H

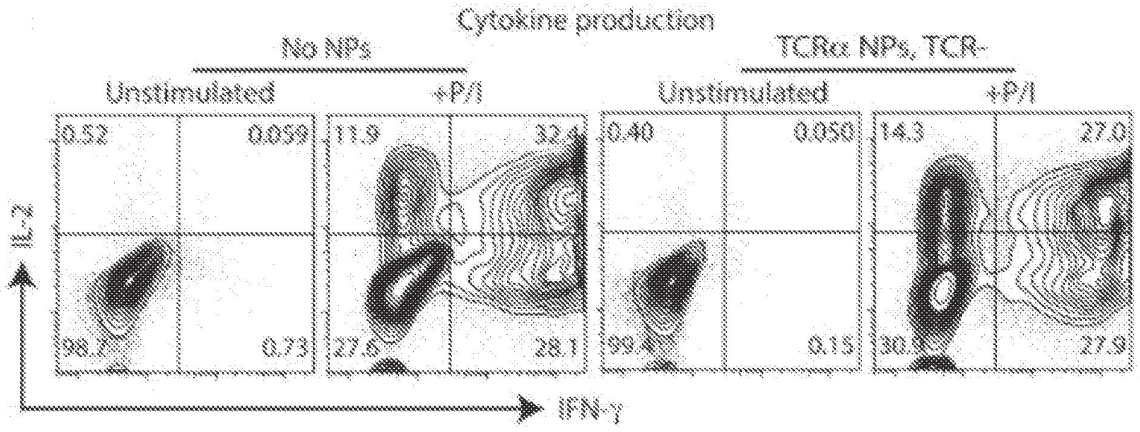

Cytokine production
No NPs
TCRα NPs, TCR-
Unstimulated
+P/I
Unstimulated
+P/I
0.52
0.059
11.9
32.4
0.40
0.050
14.3
27.0
98.7
0.73
27.6
28.1
99.4
0.15
30.5
27.9
IL-2
IFN-γ

FIG. 8A

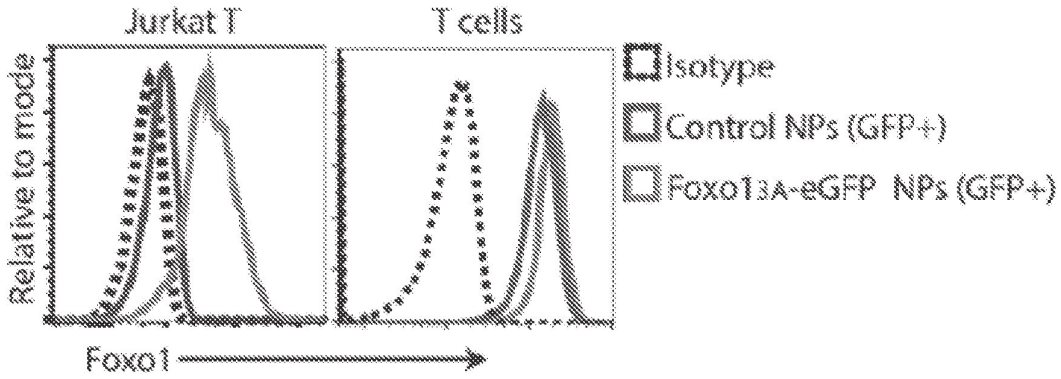

Jurkat T
T cells
Relative to mode
Isotype
Control NPs (GFP+)
Foxo13A-eGFP NPs (GFP+)
Foxo1

FIG. 8B

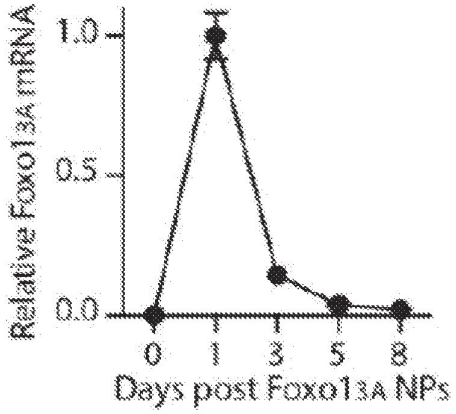

Relative Foxo13A mRNA
1.0
0.5
0.0
0
1
3
5
8
Days post Foxo13A NPs

FIG. 8C

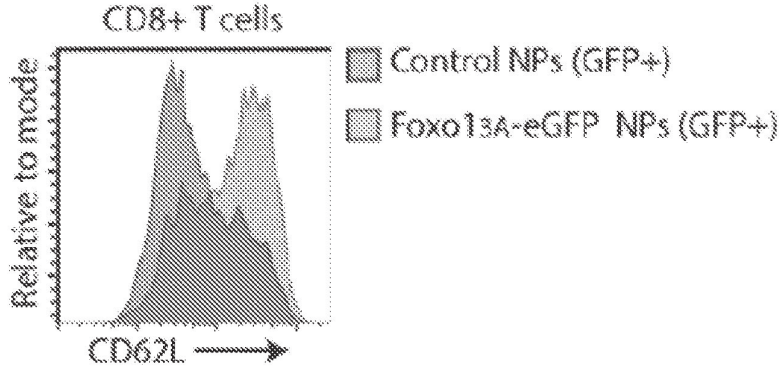

CD8+ T cells
Control NPs (GFP+)
Foxo1 3A-eGFP NPs (GFP+)
Relative to mode
CD62L

FIG. 8D

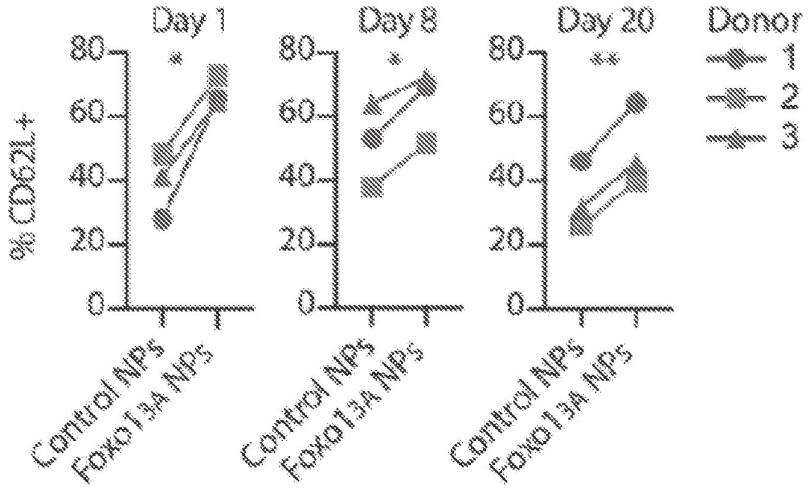

Day 1
Day 8
Day 20
Donor
1
2
3
% CD62L+
80
60
40
20
0
*
*
**
Control NPs
Foxo1 3A NPs

FIG. 8E

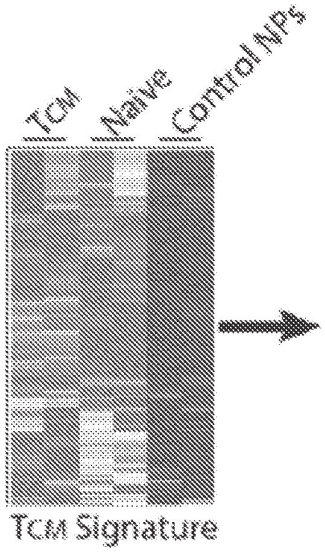

TCM
Naive
Control NPs
TCM Signature

FIG. 8F

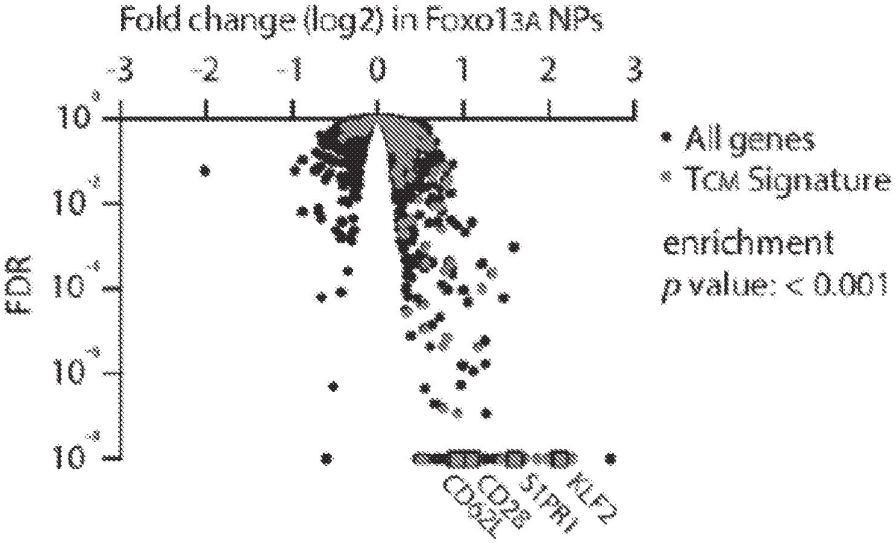

Fold change (log2) in Foxo1 3A NPs
-3
-2
-1
0
1
2
3
FDR
• All genes
• TCM Signature
enrichment
p value: < 0.001
CD62L
CD28
S1PR1
KLF2

FIG. 9A

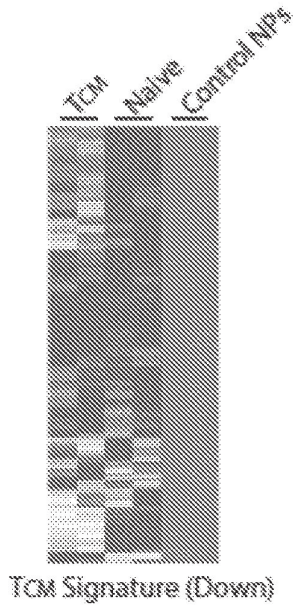

TCM
Naïve
Control NPs
TCM Signature (Down)

FIG. 9B

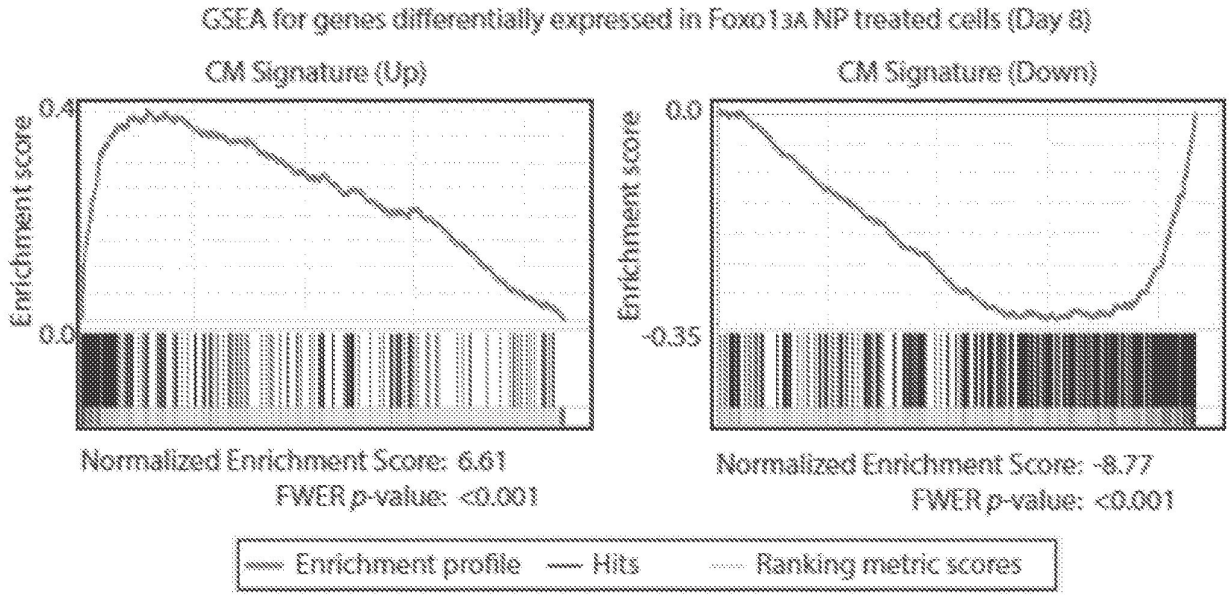

GSEA for genes differentially expressed in Foxo13A NP treated cells (Day 8)
CM Signature (Up)
CM Signature (Down)
Enrichment score
0.4
0.0
-0.35
Normalized Enrichment Score: 6.61
FWER p-value: <0.001
Normalized Enrichment Score: -8.77
FWER p-value: <0.001
Enrichment profile
Hits
Ranking metric scores

FIG. 10A

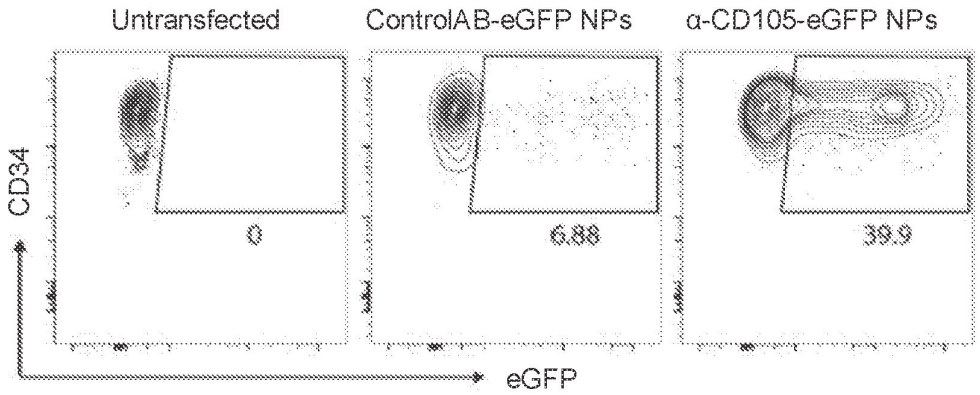


FIG. 10B

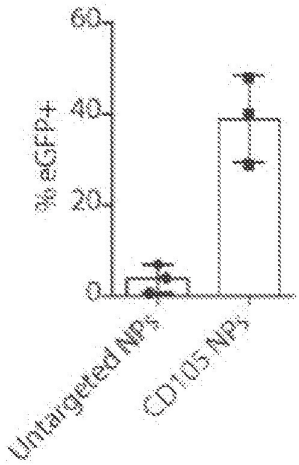


FIG. 10C

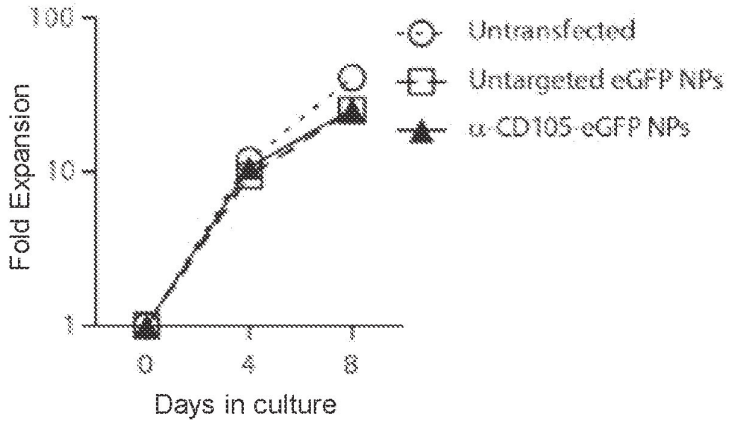


FIG. 10D

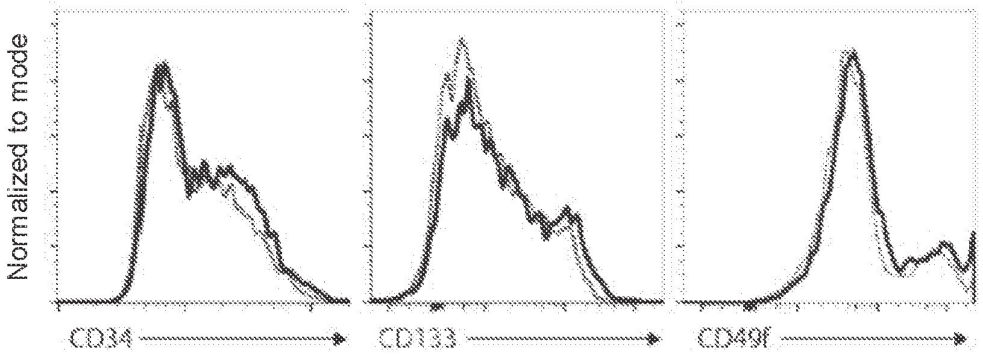


FIG. 11

Exemplary megaTAL Specific for TCRα

MGSCRYPYDVPDYAPPKKKRKVVDLRTLGYSQQQQEKIKPKVRSTVAQHHEALVGHGFT
HAHIVALSQHPAALGTVAVTYQHIITALPEATHEDIVGVGKQWSGARALEALLTDAGELRGP
PLQLDTGQLVKIAKRGGVTAMEAVHASRNALTGAPLNLTPDQVVAIASNIGGKQALETVQR
LLPVLCQDHGLTPDQVVAIASNIGGKQALETVQRLLPVLCQDHGLTPDQVVAIASNIGGKQA
LETVQRLLPVLCQDHGLTPDQVVAIASNGGGKQALETVQRLLPVLCQDHGLTPDQVVAIAS
HDGGKQALETVQRLLPVLCQDHGLTPDQVVAIASHDGGKQALETVQRLLPVLCQDHGLTP
DQVVAIASNIGGKQALETVQRLLPVLCQDHGLTPDQVVAIASNNGGKQALETVQRLLPVLC
QDHGLTPDQVVAIASNGGGKQALETVQRLLPVLCQDHGLTPDQVVAIASNNGGKQALETV
QRLLPVLCQDHGLTPDQVVAIASNIGGKQALESIVAQLSRPDPALAALTNDHLVALACLGGR
PAMDAVKKGLPHAPELIRRVNRRIGERTSHRVAISRVGGSSRRESINPWILTGFADAEGSFI
LDIRNRNNESNRYRTSLRFQITLHNKDKSILENIQSTWKVGKITNSGDRAVMLRVTRFEDLK
VIIDHFEKYPLITQKLGDYKLFKQAFSVMENKEHLKENGIKELVRIKAKMNWGLTDELKKAFP
ENISKERPLINKNIPNFKWLAGFTSGDGYFGVNLKKVKGNAKVYVGLRFSISQHIRDKNLMN
SLITYLGCGSIWEKNKSEFSWLEFVVTKFSDINDKIIPVFQENTLIGVKLEDFEDWCKVAKLIE
EKKHLTESGLDEIKKIKLNMNKGRVF* (SEQ ID NO: 1)

FIG. 11 (cont'd)

Exemplary Shp-1 phosphatase gene

ACCESSION NM_080549: Human

actctaaaacgagaagtacaagtgagttcccccaaggggtcggccgcgcctcttcctgtccccgccctgccggctgccccaggccagtgg
agtggcagccccagaactgggaccaccgggggtggtgaggcggcccggcactgggagctgcatctgaggcttagtccctgagctctctg
cctgcccagactagctgcacctcctcattccctgcgccccccttcctctccggaagcccccaggatggtgaggtggtttcaccgagacctcagt
gggctggatgcagagaccctgctcaagggccgaggtgtccacggtagcttcctggctcggcccagtcgcaagaaccagggtgacttctcg
ctctccgtcagggtgggggatcaggtgacccatattcggatccagaactcaggggatttctatgacctgtatggaggggagaagtttgcgact
ctgacagagctggtggagtactacactcagcagcagggtgtcctgcaggaccgcgacggcaccatcatccacctcaagtacccgctgaa
ctgctccgatcccactagtgagaggtggtaccatggccacatgtctggcgggcaggcagagacgctgctgcaggccaagggcgagccct
ggacgtttcttgtgcgtgagagcctcagccagcctggagacttcgtgctttctgtgctcagtgaccagcccaaggctggcccaggctccccgc
tcagggtcacccacatcaaggtcatgtgcgagggtggacgctacacagtgggtggtttggagaccttcgacagcctcacggacctggtgga
gcatttcaagaagacggggattgaggaggcctcaggcgcctttgtctacctgcggcagccgtactatgccacgagggtgaatgcggctgac
attgagaaccgagtgttggaactgaacaagaagcaggagtccgaggatacagccaaggctggcttctgggaggagtttgagagtttgcag
aagcaggaggtgaagaacttgcaccagcgtctggaagggcagcggccagagaacaagggcaagaaccgctacaagaacattctccc
ctttgaccacagccgagtgatcctgcagggacgggacagtaacatccccgggtccgactacatcaatgccaactacatcaagaaccagct
gctaggccctgatgagaacgctaagacctacatcgccagccagggctgtctggaggccacggtcaatgacttctggcagatggcgtggca
ggagaacagccgtgtcatcgtcatgaccacccgagaggtggagaaaggccggaacaaatgcgtcccatactggcccgaggtgggcat
gcagcgtgcttatgggccctactctgtgaccaactgcggggagcatgacacaaccgaatacaaactccgtaccttacaggtctccccgctg
gacaatggagacctgattcgggagatctggcattaccagtacctgagctggcccgaccatggggtccccagtgagcctgggggtgtcctca
gcttcctggaccagatcaaccagcggcaggaaagtctgcctcacgcagggcccatcatcgtgcactgcagcgccggcatcggccgcac
aggcaccatcattgtcatcgacatgctcatggagaacatctccaccaagggcctggactgtgacattgacatccagaagaccatccagatg
gtgcgggcgcagcgctcgggcatggtgcagacggaggcgcagtacaagttcatctacgtggccatcgcccagttcattgaaaccactaag
aagaagctggaggtcctgcagtcgcagaagggccaggagtcggagtacgggaacatcacctatcccccagccatgaagaatgcccatg
ccaaggcctcccgcacctcgtccaagagcttggagtctagtgcagggaccgtggctgcgtcacctgtgagacggggtggccagagggga
ctgccagtgccgggtccccctgtgctgtctcctgacctgcaccaactgcctgtacttgccccctgcacccggctgcagacacaaggaggat
gtgtatgagaacctgcacactaagaacaagagggaggagaaagtgaagaagcagcggtcagcagacaaggagaagagcaagggtt
ccctcaagaggaagtgagcggtgctgtcctcaggtggccatgcctcagccctgaccctgtggaagcatttcgcgatggacagactcacaac
ctgaacctaggagtgccccattcttttgtaatttaaatggctgcatcccccccacctctccctgaccctgtatatagcccagccaggccccagg
cagggccaacccttctcctcttgtaaataaagccctgggatcactgtgaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa (SEQ ID NO: 2)

Exemplary PD1 Receptor (PDCD1 gene)

ACCESSION AY238517: Human

atgcagatcccacaggcgccctggccagtcgtctgggcggtgctacaactgggctggcggccaggatggttcttagactccccagaca
ggccctggaaccccccccaccttctccccagccctgctcgtggtgaccgaaggggacaacgccaccttcacctgcagcttctccaacac
atcggagagcttcgtgctaaactggtaccgcatgagccccagcaaccagacggacaagctggccgccttccccgaggaccgcagc
cagcccggccaggactgccgcttccgtgtcacacaactgcccaacgggcgtgacttccacatgagcgtggtcagggcccggcgcaat
gacagcggcacctacctctgtggggccatctccctggcccccaaggcgcagatcaaagagagcctgcgggcagagctcagggtga
cagagagaagggcagaagtgcccacagcccaccccagcccctcacccaggccagccggccagttccaaaccctggtggttggtgt
cgtgggcggcctgctgggcagcctggtgctgctagtctgggtcctggccgtcatctgctcccgggccgcacgagggacaataggagcc
aggcgcaccggccagcccctgaaggaggacccctcagccgtgcctgtgttctctgtggactatggggagctggatttccagtggcgag
agaagaccccggagccccccgtgccctgtgtccctgagcagacggagtatgccaccattgtctttcctagcggaatgggcacctcatcc
cccgcccgcaggggctcagctgacggccctcggagtgcccagccactgaggcctgaggatggacactgctcttggcccctctga
(SEQ ID NO: 3)

FIG. 11 (cont'd)

Exemplary TCRα gene

ACCESSION X04954: Human
atgacatccattcgagctgtatttatattcctgtggctgcagctggacttggtgaatggagagaatgtggagcagcatccttcaaccctgagtgtc
caggagggagacagcgctgttatcaagtgtacttattcagacagtgcctcaaactacttcccttggtataagcaagaacttggaaaaagacct
cagcttattatagacattcgttcaaatgtgggcgaaaagaaagaccaacgaattgctgttacattgaacaagacagccaaacatttctccctgc
acatcacagagacccaacctgaagactcggctgtctacttctgtgcagcaagtaggaaggactctgggggttaccagaaagttacctttgga
actggaacaaagctccaagtcatcccaaatatccagaaccctgac (SEQ ID NO: 4)

Exemplary CCR5 gene

ACCESSION U66285: Human
ttggattatcaagtgtcaagtccaatctatgacatcaattattatacatcggagccctgccaaaaaatcaatgtgaagcaaatcgcagcccgcc
tcctgcctccgctctactcactggtgttcatctttggttttgtgggcaacatgctggtcatcctcatcctgataaactgcaaaaggctgaagagcatg
actgacatctacctgctcaacctggccatctctgacctgtttttccttcttactgtccccttctgggctcactatgctgccgcccagtgggactttgga
aatacaatgtgtcaactcttgacagggctctattttataggcttcttctctggaatcttcttcatcatcctcctgacaatcgataggtacctggctgtcg
tccatgctgtgtttgctttaaaagccaggacggtcacctttggggtggtgacaagtgtgatcacttgggtggtggctgtgtttgcgtctctcccagg
aatcatctttaccagatctcaaaaagaaggtcttcattacacctgcagctctcatttttccatacattaaagatagtcatcttggggctggtcctgcc
gctgcttgtcatggtcatctgctactcgggaatcctaaaaactctgcttcggtgtcgaaatgagaagaagaggcacagggctgtgaggcttatc
ttcaccatcatgattgtttatttttctcttctgggctccctacaacattgtccttctcctgaacaccttccaggaattctttggcctgaataattgcagtagc
tctaacaggttggaccaagctatgcaggtgacagagactcttgggatgacgcactgctgcatcaaccccatcatctatgcctttgtcggggag
aagttcagaaactacctcttagtcttcttccaaaagcacattgccaaacgcttctgcaaatgctgttctatttttccagcaagaggctcccgagcga
gcaagctcagtttacacccgatccactggggagcaggaaatatctgtgggcttgtga (SEQ ID NO: 5)

Exemplary CXCR4 gene

ACCESSION NM_001008540: Human
ttttttttcttccctctagtgggcggggcagaggagttagccaagatgtgactttgaaaccctcagcgtctcagtgccctttgttctaaacaaagaa
ttttgtaattggttctaccaaagaaggatataatgaagtcactatgggaaaagatggggaggagagttgtaggattctacattaattctcttgtgc
ccttagcccactacttcagaatttcctgaagaaagcaagcctgaattggtttttaaattgctttaaaaatttttttttaactgggttaatgcttgctgaatt
ggaagtgaatgtccattcctttgcctcttttgcagatatacacttcagataactacaccgaggaaatgggctcaggggactatgactccatgaa
ggaaccctgtttccgtgaagaaaatgctaatttcaataaaatcttcctgcccaccatctactccatcatcttcttaactggcattgtgggcaatgga
ttggtcatcctggtcatgggttaccagaagaaactgagaagcatgacggacaagtacaggctgcacctgtcagtggccgacctcctctttgtc
atcacgcttcccttctgggcagttgatgccgtggcaaactggtactttgggaacttcctatgcaaggcagtccatgtcatctacacagtcaacctc
tacagcagtgtcctcatcctggccttcatcagtctggaccgctacctggccatcgtccacgccaccaacagtcagaggccaaggaagctgttg
gctgaaaaggtggtctatgttggcgtctggatccctgccctcctgctgactattcccgacttcatctttgccaacgtcagtgaggcagatgacag
atatatctgtgaccgcttctaccccaatgacttgtgggtggttgtgttccagtttcagcacatcatggttggccttatcctgcctggtattgtcatcctgt
cctgctattgcattatcatctccaagctgtcacactccaagggccaccagaagcgcaaggccctcaagaccacagtcatcctcatcctggcttt
cttcgcctgttggctgccttactacattgggatcagcatcgactccttcatcctcctggaaatcatcaagcaagggtgtgagtttgagaacactgt
gcacaagtggatttccatcaccgaggccctagctttcttccactgttgtctgaaccccatcctctatgctttccttggagccaaatttaaaacctctg
cccagcacgcactcacctctgtgagcagagggtccagcctcaagatcctctccaaaggaaagcgaggtggacattcatctgtttccactgag
tctgagtcttcaagttttcactccagctaacacagatgtaaaagacttttttttatacgataaataacttttttttaagttacacatttttcagatataaaa
gactgaccaatattgtacagtttttattgcttgttggatttttgtcttgtgtttctttagtttttgtgaagtttaattgacttatttatataaatttttttttgtttcatattg
atgtgtgtctaggcaggacctgtggccaagttcttagttgctgtatgtctcgtggtaggactgtagaaaagggaactgaacattccagagcgtgt
agtgaatcacgtaaagctagaaatgatccccagctgtttatgcatagataatctctccattcccgtggaacgtttttcctgttcttaagacgtgatttt
gctgtagaagatggcacttataaccaaagcccaaagtggtatagaaatgctggtttttcagtttcaggagtgggttgatttcagcacctacagt
gtacagtcttgtattaagttgttaataaaagtacatgttaaacttaaaaaaaaaaaaaaaaaaa (SEQ ID NO: 6)

FIG. 11 (cont'd)

Exemplary FOXO1 gene

ACCESSION BC021981: Human

ttccgtccttccgtccgcggccctgtcagctggagcgcggcgcaggctctgccccggcccggcggctctggccggccgtccagtccgtgcgg
cggaccccgaggagcctcgatgtggatggccccgcgaagttaagttctgggctcgcgcttccactccgccgcgccttcctcccagtttccgtcc
gctcgccgcaccggcttcgttccccaaatctcggaccgtcccttcgcgcccctccccgtccgcccccagtgctgcgttctccccctcttggctc
tcctgcggctgggggaggggcgggggtcaccatggccgaggcgcctcaggtggtggagatcgacccggacttcgagccgctgccccggc
cgcgctcgtgcacctggccgctgcccaggccggagtttagccagtccaactcggccacctccagcccggcgccgtcgggcagcgcggctg
ccaaccccgacgccgcggcgggcctgccctcggcctcggctgccgctgtcagcgccgacttcatgagcaacctgagcttgctggaggaga
gcgaggacttcccgcaggcgcccggctccgtggcggcggcggtggcggcggcggccgccgcggccgccaccgggggggctgtgcgggg
acttccagggcccggaggcgggctgcctgcacccagcgccaccgcagcccccgccgcccgggccgctgtcgcagcacccgccggtgcc
ccccgccgccgctgggccgctcgcggggcagccgcgcaagagcagctcgtcccgccgcaacgcgtggggcaacctgtcctacgccgac
ctcatcaccaaggccatcgagagctcggcggagaagcggctcacgctgtcgcagatctacgagtggatggtcaagagcgtgccctacttca
aggataagggtgacagcaacagctcggcgggctggaagaattcaattcgtcataatctgtccctacacagcaagttcattcgtgtgcagaat
gaaggaactggaaaaagttcttggtggatgctcaatccagagggtggcaagagcgggaaatctcctaggagaagagctgcatccatgga
caacaacagtaaatttgctaagagccgaagccgagctgccaagaagaaagcatctctccagtctggccaggagggtgctggggacagcc
ctggatcacagttttccaaatggcctgcaagccctggctctcacagcaatgatgactttgataactggagtacatttcgccctcgaactagctca
aatgctagtactattagtgggagactctcacccattatgaccgaacaggatgatcttggagaaggggatgtgcattctatggtgtacccgccat
ctgccgcaaagatggcctctactttacccagtctgtctgagataagcaatcccgaaaacatggaaaatcttttggataatctcaaccttctctcat
caccaacatcattaactgtttcgacccagtcctcacctggcaccatgatgcagcagacgccgtgctactcgtttgcgccaccaaacaccagttt
gaattcacccagcccaaactaccaaaaatatacatatggccaatccagcatgagccctttgccccagatgcctatacaaacacttcaggac
aataagtcgagttatggaggtatgagtcagtataactgtgcgcctggactcttgaaggagttgctgacttctgactctcctccccataatgacatta
tgacaccagttgatcctggggtagcccagcccaacagccgggttctgggccagaacgtcatgatgggccctaattcggtcatgtcaacctatg
gcagccaggcatctcataacaaaatgatgaatcccagctcccatacccaccctggacatgctcagcagacatctgcagttaacgggcgtcc
cctgccccacacggtaagcaccatgccccacacctcgggtatgaaccgcctgacccaagtgaagacacctgtacaagtgcctctgcccca
ccccatgcagatgagtgccctgggggctactcctccgtgagcagctgcaatggctatggcagaatgggccttctccaccaggagaagctc
ccaagtgacttggatggcatgttcattgagcgcttagactgtgacatggaatccatcattcggaatgacctcatggatggagatacattggatttt
aactttgacaatgtgttgcccaaccaaagcttcccacacagtgtcaagacaacgacacatagctgggtgtcaggctgagggttagtgagcag
gttacacttaaaagtacttcagattgtctgacagcaggaactgagagaagcagtccaaagatgtctttcaccaactccctttagttttctcggtta
aaaaaaaaaaaaaaaaaaaaa (SEQ ID NO: 7)

FIG. 11 (cont'd)

Exemplary LKB1 gene

ACCESSION NM_000455: Human

gcgtgtcgggcgcggaaggggaggcggcccggggcgcccgcgagtgaggcgcggggcggcgaagggagcgcgggtggcg
gcacttgctgccgcggccttggatgggctgggccccctcgccgctccgcctcctccacacgcgcggcggccgcggcgagggggga
cgcgccgcccggggcccggcaccttcgggaacccccccggcccggagcctgcggcctgcgccgcctcggccgccgggagccccg
tggagcccccgccgccgcgccgccccgcggaccggacgctgagggcactcggggcggggcgcgcgctcgggcagacgtttgcg
gggaggggggcgcctgccgggccccggcgaccaccttgggggtcgcgggccggctcgggggggcgcccagtgcgggccctcgc
gggcgccgggcagcgaccagccctgagcggagctgttggccgcggcgggaggcctcccggacgcccccagcccccgaacgc
tcgcccgggccggcgggagtcggcgcccccgggaggtccgctcggtcgtccgcggcggagcgtttgctcctgggacaggcggtg
ggaccggggcgtcgccggagacgcccccagcgaagttgggctctccaggtgtgggggtcccgggggggtagcgacgtcgcggacc
cggcctgtgggatgggcggcccggagaagactgcgctcggccgtgttcatacttgtccgtgggcctgaggtccccggaggatgacct
agcactgaaaagccccggccggcctccccagggtccccgaggacgaagttgaccctgaccgggccgtctcccagttctgaggccc
gggtcccactggaactcgcgtctgagccgccgtcccggaccccccggtgcccgccggtccgcagaccctgcaccgggcttggactcg
cagccgggactgacgtgtagaacaatcgtttctgttggaagaagggtttttccccttcctttttggggtttttgttgccttttttttttctttttttctttgtaa
aattttggagaagggaagtcggaacacaaggaaggaccgctcacccgcggactcagggctggcggcgggactccaggaccctg
ggtccagcatggaggtggtggacccgcagcagctgggcatgttcacggagggcgagctgatgtcggtgggtatggacacgttcatcc
accgcatcgactccaccgaggtcatctaccagccgcgccgcaagcgggccaagctcatcggcaagtacctgatgggggacctgct
gggggaaggctcttacggcaaggtgaaggaggtgctggactcggagacgctgtgcaggagggccgtcaagatcctcaagaagaa
gaagttgcgaaggatccccaacggggaggccaacgtgaagaaggaaattcaactactgaggaggttacggcacaaaaatgtcat
ccagctggtggatgtgttatacaacgaagagaagcagaaaatgtatatggtgatggagtactgcgtgtgtggcatgcaggaaatgctg
gacagcgtgccggagaagcgtttcccagtgtgccaggcccacgggtacttctgtcagctgattgacggcctggagtacctgcatagcc
agggcattgtgcacaaggacatcaagccggggaacctgctgctcaccaccggtggcaccctcaaaatctccgacctgggcgtggc
cgaggcactgcacccgttcgcggcggacgacacctgccggaccagccagggctccccggctttccagccgcccgagattgccaac
ggcctggacaccttctccggcttcaaggtggacatctggtcggctggggtcaccctctacaacatcaccacgggtctgtacccttcga
aggggacaacatctacaagttgtttgagaacatcgggaaggggagctacgccatcccgggcgactgtggcccccgctctctgacct
gctgaaagggatgcttgagtacgaaccggccaagaggttctccatccggcagatccggcagcacagctggttccggaagaaacat
cctccggctgaagcaccagtgcccatcccaccgagcccagacaccaaggaccggtggcgcagcatgactgtggtgccgtacttgg
aggacctgcacggcgcggacgaggacgaggacctcttcgacatcgaggatgacatcatctacactcaggacttcacggtgcccgg
acaggtcccagaagaggaggccagtcacaatggacagcgccgggggcctccccaaggccgtgtgtatgaacggcacagaggcg
gcgcagctgagcaccaaatccagggcggagggccgggccccccaaccctgcccgcaaggcctgctccgccagcagcaagatcc
gccggctgtcggcctgcaagcagcagtgaggctggccgcctgcagcccgtgtccaggagccccgccaggtgcccgcgccaggcc
ctcagtcttcctgccggttccgcccgccctcccggagaggtggccgccatgcttctgtgccgaccacgccccaggacctccggagcg
ccctgcagggccgggcaggggacagcagggaccgggcgcagccctccccctcggccgcccggcagtgcacgcggcttgttg
acttcgcagccccgggcggagccttcccgggcgggcgtgggaggagggaggcggcctccatgcactttatgtggagactactggcc
ccgcccgtggcctcgtgctccgcagggcgcccagcgccgtccggcggccccgccgcagaccagctggcgggtgtggagaccag
gctcctgaccccgccatgcatgcagcgccacctggaagccgcgcggccgctttggttttttgtttggttggttccatttttcttttttttcttttttttttt
aagaaaaaaataaaaggtggatttgagctgtggctgtgaggggtgtttgggagctgctgggtggcaggggggctgtggggtcgggctc
acgtcgcggccgcctttgcgctctcgggtcaccctgctttggcggcccggccggagggcaggaccctcacctctccccaaggccac
tgcgctcttgggaccccagagaaaaccccggagcaagcaggagtgtgcggtcaatatttatatcatccagaaaagaaaaacacgag
aaacgccatcgcgggatggtgcagacgcggcggggactcggagggtgccgtgcgggcgaggccgcccaaatttggcaataaata
aagcttgggaagcttggacctgaaaaaaaaaa (SEQ ID NO: 8)

FIG. 11 (cont'd)

Exemplary EOMES gene

NCBI Reference Sequence: NC_000003.12 Human

aagtttccaagtggtcaacttgaccgatgctttggcaattgaaaaagggcagaaaggcgcgggctagtgggtggatggggacaaagat
ctaagtcaccttcttccagcgtgtgagcctgggaggagggtgggggtcctgaggagcaagaggtacgaggaaggaaaaggagaggg
cttctgggttagtttccacctcctgctttccaactcacggcgctttccttccggaaaggacgctggattcagggcgcgccagtacgcgcagta
gcggcccgcgagtcggcaggtgggtagccccggcgcgggaggaaggggaagttaccttcccctcggaagagggcgctggctccccc
atcctgcctttataataaggccaccggaggagaggaagcagccagctgccgtctgcgctttgcaaagcatgcagttaggggagcagctc
ttggtgagctcagtgaacctgcctggcgcgcacttctacccgctggagagtgcgcgaggcggcagcggcgggagcgctggccacctcc
ccagcgcggcccccctctcctcagaagttggacttagacaaagcgtccaagaagttttccggcagtctctcctgcgaggcggtgagcggg
gagcccgcagccgccagcgcaggggcccccgcggccatgcttagtgacaccgacgccggggacgcatttgccagcgctgcggcagt
ggccaagccggggcccccggacggccgcaagggctccccctgcggggaggaggagctgccctccgccgctgcagccgccgccgc
cgccgccgccgcggctgcggccactgcgcgctactccatggacagcctgagctccgagcggtactacctccagtcccccggtcctcag
gggtcggagctggctgcgccctgctcactcttcccgtaccaggcggcggctggggcgcccacggacctgtgtacccggctcctaacgg
ggcgcgctacccctacggctccatgctgccccccggcggcttccccgcggctgtgtgcccacccgggagggcgcagttcggcccagga
gccggtgcgggcagtggcgcgggcggtagcagcggcgggggcggcggcccgggcacctatcagtacagccaggggctccgctct
acgggccgtaccctggagccgcagcggcgggatcttgcggaggactgggggcctgggggttccaggttctggcttccgtgcccacgtc
tacctgtgcaaccggcctctgtggctcaaattccaccgccaccaaactgagatgatcattacgaaacagggcaggtgagcgcagcgtg
gaggggcccctgggttcggggataaagggtgacgtgtggtcctggggaaggtccgggatgagggagctgaacccagttgttccgcgcg
gtgcttagagtgtttcaccgcgcgcaataaatctccgtagacaccgcatctccaatgcggtgtccctctgtgtcagtgccccggcggctcttg
cagggtgccaatgttacggctgtacaccgcttttcctcccatcatcctcacctgaacagacctggaggaggcggaaatggaaattaggg
catgtccacaagctggattcgttagatcctcctgctcggcggtatgcttgtgcatgcctgcatgccggcaaggagccacggatagggaag
gctcaagagctggccacctgagcgcagtagatgggctcccgcagttttaggcgccagggtctccacggggcgtctccgggaggtgggc
atgaaggctagagcgccggcctcggaagctcggtcggagtaggtggttagatctgccctggagccagacctggctcgggttcggtgcgc
gagaaagttctgatatacatccaactgctaacactggctacttctggggaaagggaggggtgggtgctgagagaggggcactcaaagg
ggacttttagcctaaagttttaatatatatttttaacaagaataacctaatattgttctctggtacttttcaaaatggtgcatttaaaaattagtagtttt
taacattctaggagaaaaattttaagagcgtctgaaagggccgagaatatgagccttcggaagcacgcgcgaatttggaatataccgat
gttggggcaagctttttttttttttttttttttttttttttttttttttttttttttgaaaagacggaaaggttccaagagttgccaactcaaaaatattttacatagtttc
agaccacttgatctaccagcattctgttcactgcaaacttttaaatgtgttccgaccctatcccaggtgtctggggaacccgctggggcctgg
gcctgttctaggacatcccaattaaaatcgatttttctgattctattcccttgcacaggcgcatgtttccttttcttgagcttcaacataaacggactc
aatcccactgcccactacaatgtgttcgtagaggtggtgctggcggaccccaaccactggcgcttccaggggggcaaatgggtgacctgt
ggcaaagccgacaataacatgcagggtgagcagagaagaggctcgggccgggggaggaacgggcgggaagaaatcgtaaccctc
gactcacacaactcacatttaaatgtagcacttttttttttccccttccattctgaggcctagaggtgttagtatgagtgtctttgagttgcttgtttgac
ggagaggagagtttgctaagtcagatttcttgtctgccaatatgtagatatttagaaccttaactaagacatcaccccaccccccaatccct
acgtttaacaaatcagtagtcataagctctccaggtgggaagggctcctgggattctaatgttcacttgagaaagcccagccaaagtttagt
tcacccataaatatccaactgtcttccatcggatgttgcccttacagctttagaaggccccaaattgaccttcaagagtcatctcttgttagctc
cgtttctaaattctgaaatgccattcaggggagtccctagtgcaaggaaggttggaagcacaggggcctgggagggatatggatgtagtc
ctgctggtctccactggcctctttaagcaacttttactgggagaccaactgtaagtctagctcttatatcttgctcatagctaagagacatccctc
cgctttctccatttgtaaacagccctatatgcttgggttttgtgttttgtttcattttctcttaggcaacaaaatgtatgttcacccagagtctcctaata
ctggttcccactggatgagacaggagatttcattcgggaaattaaaactcaccaataacaaaggcgcaaataacaacaacacccaggt
agagtgacagagcaggaggggatatcttctggctttgactataaggctttttttctaataagagtccctactcttttcactgtatttataatatttgca
tttgtgacctgtttgctcgcctatttctaaccatttttgttcttttgaccttctcatcttcacttttcttattggatttcgataacagtgagttgactattaaga
acagaaatagcgaagtattttgggaatttaggaaaccaagaggaaagcatatctatcacaaccacatacccagctatgatttaaatttcaa
aaaaaaagTgggggggcaataatgagacctttaaacttgcaataaacaaagctgttagtgaggagcatttagaagtccaataccaaa
atacataatttgtcaaaatctaattttgttgaaccactaagaggctttttagatttagcaatttttttctgtactctttccagatgatagtcttacaatcc
ttacacaaataccaaccccgactgcatattgttgaagttacagaggatggcgtggaggacttgaatgagccctcaaagacccagacttttta
ccttctcagaaacgcaattcattgcagtgactgcctaccaaaacaccgatgtgagtgtcccagacatctcaagaatctctaaagctaaggt
ccagcatgataaatcactcaatgactgtttttctcccctatctagattactcaactaaagattgatcataacccctttgcaaaaggcttcagag
acaactatgattc

FIG. 11 (cont'd)

gtaagtgcagcttttatccacacttgcctgatcatctctgagcaggacatacatcaacaggcactttgctgataatgtattttaggaagagctt
ttacctttgggatttttacatatttttctttttccaaaatttttttcctttactaatcttgctttagatttttctcagaaaggttgtgttaatttctgaagaaatgtt
aaggacttaaaaatgaagaggtttttttagcatttgagtgaagatttgaaatttaagaatctgcatttatatataccttttcttttcatttgatccatttt
tttatcctcccaagagcagatattattactctcccccacccccacttttttttttaacataagaaaaaactgaaactaagaggatgtaatttcac
aacacgaaatagcaaggccctgctctttttaaaatctgagttttctaccgccacagccagtgtttttttccatcacattgacaaaggaggtttga
tctgagtttttcgtgttctaggactagtaaaggtagattttctatagtttaaatacttgatgcctaggaggaaacttttttcttgcatggtgggaaattt
ttcccaataagccaagagtccagctaaaatgggccagtgcatctcctgcctctgttctttcagcccaacagaccagcactttcggtgtagat
aaccaacacaagccttttttcatttctgggaggtggtttgtttggggacaacattagggttttttttttttttttaagtgtttctctttatattgtagcatgtac
accgcttcagaaaatgacaggttaactccatctcccacggattctcctagatcccatcagattgtccctggaggtcggtacggcgttcaatc
cttcttcccggagcccttttgtcaacactttacctcaagcccgctattataatggcgagagaaccgtgccacagaccaacggcctcctttcac
cccaacagagcgaagaggtggccaaccctccccagcggtggcttgtcacgcctgtccagcaacctgggaccaacaaactagacatc
agttcctatgaatctgaatatacttctagcacattgctcccatatggcattaaatccttgccccttcagacatcccatgccctggggtattaccc
agacccaacctttcctgcaatggcagggtggggaggtcgaggttcttaccagaggaagatggcagctggactaccatggacctccaga
acaagccccactgtgttctctgaagatcagctctccaaggagaaagtgaaagaggaaattggctcttcttggatagagacacccccttcc
atcaaatctctagattccaatgattcaggagtatacaccagtgcttgtaagcgaaggcggctgtctcctagcaactccagtaatgaaaatt
caccctccataaagtgtgaggacattaatgctgaagagtatagtaaagacacctcaaaaggcatgggagggtattatgctttttacacaa
ctccctaaagagttattttaacctcaaaaattagctaacttttttgcagatggacttggtggtgtttttttgttgtcttctttgcctaggttgccaaaaag
atgtttgccttccaccttgatgcatcctgttttgtgcaattctctaaaagaaggtgccaaagctttttgattgctgcaggtaactgaaacaaacct
agcatttttaaaaaataagattaatggaagactttaaggtattttaaaattcgaagggtatccaaggttctgtatttatttattggggagacact
aacccttcaaagaagcaggctgtgaacattgggtgcccagtgctatcagatgagttaaaaccctttgattctcatttctatttgtaaattcttaag
caaatagaagccgagtgttaaggtgttttgcttctgaaagagggctgtgccttccgtttcagaaggagacattttgctgttacattctgccagg
ggcaaaagatactaggcccaggagtcaagaaaagcttttgtgaaagtgatagtttcacctgactttgattccttaacccccggcttttggaa
caagccatgtttgccctagtccaggattgcctcacttgagacttgctaggcctctgctgtgtgctggggtggccagtgggactcaggagag
agcaagctaaggagtcaccaaaaaaaaaaaaaaaaaaaaggggagaatttaaaagtgtacagttgtgtgtttagatacactatagaat
aatgtggtatatattgtacaaatagtctacataggtgtctgggataatgtaaaactggtgctttggctttgtaaagaatttgcaaatcacttaac
agctgcaggggcaaggggagagtttcatcatccccatgatatttgggaatattctgtttacttcttagatagttaagaatgtattcagctactat
gtactaacttgaaccgtgtttaaggaaaactcctatttcatcctcttcttgcgccatcccctctccctaacttggtaatgtgaagaaactaaaac
ctgataccacagctcctataggcattttagagatcttggatttttatgtacagtcttagtcatttttaataaatgtggttcagtaagggaacgga
(SEQ ID NO: 9)

FIG. 11 (cont'd)

Exemplary ID2 gene

NCBI Reference Sequence: NC 000002.12 Human
ggggacgaagggaagctccagcgtgtggccccggcgagtgcggataaaagccgccccgccgggctcgggcttcattctgagccgag
cccggtgccaagcgcagctagctcagcaggcggcagcggcggcctgagcttcagggcagccagctccctcccggtctcgccttccctc
gcggtcagcatgaaagccttcagtcccgtgaggtccgttaggaaaaacagcctgtcggaccacagcctgggcatctcccggagcaaaa
cccctgtggacgacccgatgagcctgctatacaacatgaacgactgctactccaagctcaaggagctggtgcccagcatcccccagaa
caagaaggtgagcaagatggaaatcctgcagcacgtcatcgactacatcttggacctgcagatcgccctggactcgcatcccactattgt
cagcctgcatcaccagagacccgggcagaaccaggcgtccaggacgccgctgaccaccctcaacacggatatcagcatcctgtcctt
gcaggtaagacctgctccggggtccccgccccgccgccgcacactcccgcggtcgtctgggctgtcactaggagatccgtagcccaga
cggtgactttcgtatgagctatttaactttatttttcttcagaatctgctgtagattgagctgtgcgtgaaattgctagtaagttctgacatgttaatgc
gtctgtctttaaatctgaattgttaccataaacgtgtttaatggaacttgctggtctgtggactacaaaaaaaaaaaaaaaaaaaaaaaaac
cctttctacttaacattgtcttaacctcgtactctttatcctctttctttccaggcttctgaattcccttctgagttaatgtcaaatgacagcaaagcac
tgtgtggctgaataagcggtgagtgtttgcttgtgccacccgtgggtaaactgcccctcggtgtgtgtgcgcgcgcgcgcatgtgtttttgcttgt
gtatctataaaatgtctgatttggtaaatgcatgcttacttcgcggtgttacccgtactacattgtctcactagacatgaaggagcttgtagctttg
ggtgctcgagatcacagaacattttccttttaaaaggaaatgatgccaataacttactacgaaggcggccgaggaacgtgtgtattggctttg
tagcaaatgtaatgccctggatcttcctacgagtcctctggtactatgaggtactaacctccactgtaattaatcttaccgccacaaattccata
gtgatcctccttccctaaaactatagtcctctgggattctctgggctagttgaggattgctaccctgtgccttcaaccctgtgatgtgggatccca
gacttccctatctgttaactaaagggctgttttcaatcaaataattgttacgagaagcagactggcgcctgtagcactgctgttggagatccaa
ataggagattgggttgggaagtttttcccttgagtctctgctattttaatgtttaatttgcgctgtcgaggcgagtgtgtgtgttgcatctggacgcc
agggtttgcccaatctttgagtgtttggttaaatgttcaaactgtggcttcctcccggcgccagtcgcccgcctctgcccttaggttacattctctt
aaacatgcctttctcccccactctttcgcaggtgttcatgatttcttttattctttgcacaacaacaacaacaacaaattcacggaatcttttaagt
gctgaacttatttttcaaccatttcacaaggaggacaagttgaatggacctttttaaaaagaaaaaaaaaatggaaggaaaactaagaat
gatcatcttcccagggtgttctcttacttggactgtgatattcgttatttatgaaaaagacttttaaatgccctttctgcagttggaaggttttctttata
tactattcccaccatggggagcgaaaacgttaaaatcacaaggaattgcccaatctaagcagactttgccttttttcaaaggtggagcgtga
ataccagaaggatccagtattcagtcacttaaatgaagtcttttggtcagaaattacctttttgacacaagcctactgaatgctgtgtatatatttt
atatataaatatatctatttgagtgaaaccttgtgaactctttaattagagttttcttgtatagtggcagagatgtctatttctgcattcaaaagtgta
atgatgtacttattcatgctaaactttttataaaagtttagttgtaaacttaacccttttatacaaaataaatcaagtgtgtttattgaatggtgattgc
ctgctttatttcagaggaccagtgctttgatttttattatgctatgttataactgaacccaaataaatacaagttcaaatttatgtagactgtataag
attataataaaacatgtctgaagtcaa (SEQ ID NO: 10)

FIG. 11 (cont'd)

Exemplary TERT gene

ACCESSION NM_198253: Human
caggcagcgctgcgtcctgctgcgcacgtgggaagccctggccccggccaccccccgcgatgccgcgcgctccccgctgccgagccgt
gcgctccctgctgcgcagccactaccgcgaggtgctgccgctggccacgttcgtgcggcgcctggggccccagggctggcggctggtgc
agcgcggggacccggcggctttccgcgcgctggtggcccagtgcctggtgtgcgtgccctgggacgcacggccgccccccgccgcccc
ctccttccgccaggtgtcctgcctgaaggagctggtggcccgagtgctgcagaggctgtgcgagcgcggcgcgaagaacgtgctggcctt
cggcttcgcgctgctggacggggcccgcgggggccccccccgaggccttcaccaccagcgtgcgcagctacctgcccaacacggtgac
cgacgcactgcgggggagcggggcgtgggggctgctgctgcgccgcgtgggcgacgacgtgctggttcacctgctggcacgctgcgcg
ctctttgtgctggtggctcccagctgcgcctaccaggtgtgcgggccgccgctgtaccagctcggcgctgccactcaggcccggccccgc
cacacgctagtggaccccgaaggcgtctgggatgcgaacgggcctggaaccatagcgtcagggaggccggggtcccctgggcctgc
cagccccgggtgcgaggaggcgcgggggcagtgccagccgaagtctgccgttgcccaagaggcccaggcgtggcgctgccctgag
ccggagcggacgcccgttgggcaggggtcctgggcccacccgggcaggacgcgtggaccgagtgaccgtggtttctgtgtggtgtcacc
tgccagacccgccgaagaagccacctctttggagggtgcgctctctggcacgcgccactcccacccatccgtgggccgccagcaccac
gcgggccccccatccacatcgcggccaccacgtccctgggacacgccttgtcccccggtgtacgccgagaccaagcacttcctctactcc
tcaggcgacaaggagcagctgcggccctccttcctactcagctctctgaggcccagcctgactggcgctcggaggctcgtggagaccatc
tttctgggttccaggccctggatgccagggactccccgcaggttgccccgcctgccccagcgctactggcaaatgcggcccctgtttctgga
gctgcttgggaaccacgcgcagtgcccctacggggtgctcctcaagacgcactgcccgctgcgagctgcggtcaccccagcagccggt
gtctgtgcccgggagaagccccagggctctgtggcggcccccgaggaggaggacacagacccccgtcgcctggtgcagctgctccgc
cagcacagcagcccctggcaggtgtacggcttcgtgcgggcctgcctgcgccggctggtgcccccaggcctctggggctccaggcaca
acgaacgccgcttcctcaggaacaccaagaagttcatctccctggggaagcatgccaagctctcgctgcaggagctgacgtggaagatg
agcgtgcgggactgcgcttggctgcgcaggagcccaggggttggctgtgttccggccgcagagcaccgtctgcgtgaggagatcctggc
caagttcctgcactggctgatgagtgtgtacgtcgtcgagctgctcaggtctttcttttatgtcacggagaccacgtttcaaaagaacaggctct
ttttctaccggaagagtgtctggagcaagttgcaaagcattggaatcagacagcacttgaagagggtgcagctgcgggagctgtcggaag
cagaggtcaggcagcatcgggaagccaggcccgccctgctgacgtccagactccgcttcatccccaagcctgacgggctgcggccgat
tgtgaacatggactacgtcgtgggagccagaacgttccgcagagaaaagagggccgagcgtctcacctcgagggtgaaggcactgttc
agcgtgctcaactacgagcgggcgcggcgccccggcctcctgggcgcctctgtgctgggcctggacgatatccacagggcctggcgca
ccttcgtgctgcgtgtgcgggcccaggacccgccgcctgagctgtactttgtcaaggtggatgtgacgggcgcgtacgacaccatccccca
ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcgtcggtatgccgtggtccagaaggccgcc
catgggcacgtccgcaaggccttcaagagccacgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcag
gagaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccagcagtggcctcttcgacgtcttcctacgct
tcatgtgccaccacgccgtgcgcatcaggggcaagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctct
gcagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggctgctcctgcgtttggtggatgatttcttgttgg
tgacacctcacctcacccacgcgaaaaccttcctcaggaccctggtccgaggtgtccctgagtatggctgcgtggtgaacttgcggaaga
cagtggtgaacttcccctgtagaagacgaggccctgggtggcacggcttttgttcagatgccggcccacggcctattcccctggtgcggcctg
ctgctggatacccggaccctggaggtgcagagcgactactccagctatgcccggacctccatcagagccagtctcaccttcaaccgcgg
cttcaaggctgggaggaacatgcgtcgcaaactctttggggtcttgcggctgaagtgtcacagcctgtttctggatttgcaggtgaacagcct
ccagacggtgtgcaccaacatctacaagatcctcctgctgcaggcgtacaggtttcacgcatgtgtgctgcagctcccatttcatcagcaag
tttggaagaaccccacatttttcctgcgcgtcatctctgacacggcctccctctgctactccatcctgaaagccaagaacgcagggatgtcgc
tgggggccaagggcgccgccggccctctgccctccgaggccgtgcagtggctgtgccaccaagcattcctgctcaagctgactcgacac
cgtgtcacctacgtgccactcctggggtcactcaggacagcccagacgcagctgagtcggaagctcccggggacgacgctgactgccct
ggaggccgcagccaacccggcactgccctcagacttcaagaccatcctggactgatggccacccgcccacagccaggccgagagca
gacaccagcagccctgtcacgccgggctctacgtcccagggagggaggggcggcccacacccaggcccgcaccgctgggagtctga
ggcctgagtgagtgtttggccgaggcctgcatgtccggctgaaggctgagtgtccggctgaggcctgagcgagtgtccagccaagggctg
agtgtccagcacacctgccgtcttcacttccccacaggctggcgctcggctccaccccagggccagcttttcctcaccaggagcccggctt
ccactccccacataggaatagtccatccccagattcgccattgttcacccctcgccctgccctcctttgccttccaccccccaccatccaggtg
gagaccctgagaaggaccctgggagctctgggaatttggagtgaccaaaggtgtgccctgtacacaggcgaggaccctgcacctggat
gggggtccctgtgggtcaaattgggggggaggtgctgtgggagtaaaatactgaatatatgagtttttcagttttgaaaaaaa (SEQ ID
NO: 11)

FIG. 11 (cont'd)

Exemplary CCR2b gene

ACCESSION NM_001123396: Human
gttattctctggaacatgaaacattctgttgtgctcatatcatgcaaattatcactagtaggagagcagagagtggaaatgttccaggtataa
agacccacaagataaagaagctcagagtcgttagaaacaggagcagatgtacagggtttgcctgactcacactcaaggttgcataag
caagatttcaaaattaatcctattctggagacctcaacccaatgtacaatgttcctgactggaaaagaagaactatatttttctgatttttttttc
aaatctttaccattagttgccctgtatctccgccttcactttctgcaggaaactttatttcctacttctgcatgccaagtttctacctctagatctgttt
ggttcagttgctgagaagcctgacataccaggactgcctgagacaagccacaagctgaacagagaaagtggattgaacaaggacgc
atttccccagtacatccacaacatgctgtccacatctcgttctcggtttatcagaaataccaacgagagcggtgaagaagtcaccacctttttt
tgattatgattacggtgctccctgtcataaatttgacgtgaagcaaattggggcccaactcctgcctccgctctactcgctggtgttcatctttg
gttttgtgggcaacatgctggtcgtcctcatcttaataaactgcaaaaagctgaagtgcttgactgacatttacctgctcaacctggccatctc
tgatctgctttttcttattactctcccattgtgggctcactctgctgcaaatgagtgggtctttgggaatgcaatgtgcaaattattcacagggctgt
atcacatcggttattttggcggaatcttcttcatcatcctcctgacaatcgatagatacctggctattgtccatgctgtgtttgctttaaaagccag
gacggtcacctttggggtggtgacaagtgtgatcacctggttggtggctgtgtttgcttctgtcccaggaatcatctttactaaatgccagaaa
gaagattctgtttatgtctgtggcccttattttccacgaggatggaataatttccacacaataatgaggaacattttggggctggtcctgccgct
gctcatcatggtcatctgctactcgggaatcctgaaaaccctgcttcggtgtcgaaacgagaagaagaggcatagggcagtgagagtc
atcttcaccatcatgattgtttactttctcttctggactccctataatattgtcattctcctgaacaccttccaggaattcttcggcctgagtaactgt
gaaagcaccagtcaactggaccaagccacgcaggtgacagagactcttgggatgactcactgctgcatcaatcccatcatctatgccttt
cgttggggagaagttcagaaggtatctctcggtgttcttccgaaagcacatcaccaagcgcttctgcaaacaatgtccagttttctacaggg
agacagtggatggagtgacttcaacaaacacgccttccactggggagcaggaagtctcggctggtttataaaacgaggagcagtttgat
tgttgtttataaagggagataacaatctgtatataacaacaaacttcaagggtttgttgaacaatagaaacctgtaaagcaggtgcccagg
aacctcagggctgtgtgtactaatacagactatgtcacccaatgcatatccaacatgtgctcagggaataatccagaaaaactgtgggta
gagactttgactctccagaaagctcatctcagctcctgaaaaatgcctcattaccttgtgctaatcctctttttctagtcttcataatttcttcactc
aatctctgattctgtcaatgtcttgaaatcaagggccagctggaggtgaagaagagaatgtgacaggcacagatgaatgggagtgagg
gatagtggggtcagggctgagaggagaaggagggagacatgagcatggctgagcctggacaaagacaaaggtgagcaaagggc
tcacgcattcagccaggagatgatactggtccttagccccatctgccacgtgtatttaaccttgaagggttcaccaggtcagggagagtttg
ggaactgcaataacctgggagttttggtggagtccgatgattctcttttgcataagtgcatgacatatttttgctttattacagtttatctatggcac
ccatgcaccttacatttgaaatctatgaaatatcatgctccattgttcagatgcttcttaggccacatccccctgtctaaaaattcagaaaatttt
tgtttataaaaga (SEQ ID NO: 12)

FIG. 11 (cont'd)

Exemplary CCR4 gene

ACCESSION NM_005508: Human
tctcacaggaagccacgcacccttgaaaggcaccgggtccttcttagcatcgtgcttcctgagcaagcctggcattgcctcacagaccttcctc
agagccgctttcagaaaagcaagctgcttctggttgggcccagacctgccttgaggagcctgtagagttaaaaaatgaaccccacggatata
gcagacaccaccctcgatgaaagcatatacagcaattactatctgtatgaaagtatccccaagccttgcaccaaagaaggcatcaaggcatt
tggggagctcttcctgcccccactgtattccttggtttttgtatttggtctgcttggaaattctgtggtggttctggtcctgttcaaatacaagcggctcag
gtccatgactgatgtgtacctgctcaaccttgccatctcggatctgctcttcgtgttttccctccctttttggggctactatgcagcagaccagtgggtttt
tgggctaggtctgtgcaagatgatttcctggatgtacttggtgggcttttacagtggcatattctttgtcatgctcatgagcattgatagatacctggca
attgtgcacgcggtgttttccttgagggcaaggaccttgacttatggggtcatcaccagtttggctacatggtcagtggctgtgttcgcctcccttcct
ggctttctgttcagcacttgttatactgagcgcaaccatacctactgcaaaaccaagtactctctcaactccacgacgtggaaggttctcagctcc
ctggaaatcaacattctcggattggtgatcccccttagggatcatgctgttttgctactccatgatcatcaggaccttgcagcattgtaaaaatgaga
agaagaacaaggcggtgaagatgatctttgccgtggtggtcctcttccttgggttctggacaccttacaacatagtgctcttcctagagaccctgg
tggagctagaagtccttcaggactgcacctttgaaagatacttggactatgccatccaggccacagaaactctggcttttgttcactgctgccttaa
tcccatcatctacttttttctgggggagaaatttcgcaagtacatcctacagctcttcaaaacctgcaggggccttttgtgctctgccaatactgtgg
gctcctccaaatttactctgctgacacccccagctcatcttacacgcagtccaccatggatcatgatctccatgatgctctgtagaaaaatgaaat
ggtgaaatgcagagtcaatgaactttccacattcagagcttacttaaaattgtattttagtaagagattcctgagccagtgtcaggaggaaggctt
acacccacagtggaaagacagcttctcatcctgcaggcagctttttctctcccactagacaagtccagcctggcaagggttcacctgggctga
ggcatccttcctcacaccaggcttgcctgcaggcatgagtcagtctgatgagaactctgagcagtgcttgaatgaagttgtaggtaatattgcaa
ggcaaagactattcccttctaacctgaactgatgggtttctccagagggaattgcagagtactggctgatggagtaaatcgctacctttttgctgtgg
caaatgggccctct (SEQ ID NO: 13)

FIG. 11 (cont'd)

anti-CD19 scFv (VH-VL) FMC63

Cacatccagatgacccagaccacctccagcctgagcgccagcctgggcgaccgggtgaccatcagctgccgggccagccaggacat
cagcaagtacctgaactggtatcagcagaagcccgacggcaccgtcaagctgctgatctaccacaccagccggctgcacagcggcgt
gcccagccggtttagcggcagcggctccggcaccgactacagcctgaccatctccaacctggaacaggaagatatcgccacctacttttt
gccagcagggcaacacactgccctacacctttggcggcggaacaaagctggaaatcaccggcagcacctccggcagcggcaagcct
ggcagcggcgagggcagcaccaagggcgaggtgaagctgcaggaaagcggccctggcctggtggcccccagccagagcctgagc
gtgacctgcaccgtgagcggcgtgagcctgcccgactacggcgtgagctggatccggcagccccccaggaagggcctggaatggctg
ggcgtgatctggggcagcgagaccacctactacaacagcgccctgaagagccggctgaccatcatcaaggacaacagcaagagcc
aggtgttcctgaagatgaacagcctgcagaccgacgacaccgccatctactactgcgccaagcactactactacggcggcagctacgc
catggactactggggccagggcaccagcgtgaccgtgagcag (SEQ ID NO: 28)

anti-CD19 scFv (VH-VL) FMC63

DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRLHSGVPSRFSGS
GSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQ
ESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIK
DNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS (SEQ ID NO: 29)

CD28 effector domain

cggagcaagcggagcagaggcggccacagcgactacatgaacatgacccccagacggcctggccccacccggaagcactacc
agccctacgccccacccagggactttgccgcctacagaagc (SEQ ID NO: 36)

FIG. 11 (cont'd)

P28z CAR

Gtggcctcaccgttgacccgctttctgtcgctgaacctgctgctgctgggtgagtcgattatcctggggagtggagaagctgaggtgcag
ctgcagcagtcaggacctgaactggtgaagcctgggacttcagtgaggatatcctgcaagacttctggatacacattcactgaatatacc
atacactgggtgaagcagagccatggaaagagccttgagtggattggaaacatcaatcctaacaatggtggtaccacctacaatcag
aagttcgaggacaaggccacattgactgtagacaagtcctccagtacagcctacatggagctccgcagcctaacatctgaggattctg
cagtctattattgtgcagctggttggaactttgactactggggccaagggaccacggtcaccgtctcctcaggtggaggtggatcaggtg
gaggtggatctggtggaggtggatctgacattgtgatgacccagtctcacaaattcatgtccacatcagtaggagacagggtcagcatc
atctgtaaggccagtcaagatgtgggtactgctgtagactggtatcaacagaaaccaggacaatctcctaaactactgatttattgggcat
ccactcggcacactggagtccctgatcgcttcacaggcagtggatctgggacagacttcactctcaccattactaatgttcagtctgaaga
cttggcagattatttctgtcagcaatataacagctatcccctcacgttcggtgctgggaccatgctggacctgaaacgggcggccgcatct
actactaccaagccagtgctgcgaactccctcacctgtgcaccctaccgggacatctcagccccagagaccagaagattgtcggccc
cgtggctcagtgaaggggaccggattggacttcgcctgtgatatttacatctgggcacccttggccggaatctgcgtggcccttctgctgtc
cttgatcatcactctcatctgctacaatagtagaaggaacagactccttcaaagtgactacatgaacatgactccccggaggcctgggct
cactcgaaagccttaccagccctacgcccctgccagagactttgcagcgtaccgccccagagcaaaattcagcaggagtgcagaga
ctgctgccaacctgcaggaccccaaccagctctacaatgagctcaatctagggcgaagagaggaatatgacgtcttggagaagaag
cgggctcgggatccagagatgggaggcaaacagcagaggaggaggaaccccccaggaaggcgtatacaatgcactgcagaaag
acaagatggcagaagcctacagtgagatcggcacaaaaggcgagaggcggagaggcaaggggcacgatggcctttaccagggt
ctcagcactgccaccaaggacacctatgatgccctgcatatgcagaccctggcccctcgctaa (SEQ ID NO: 37)

FIG. 11 (cont'd)

IgG4-Fc
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 39)

Hinge-CH2-CH3
ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 40)

Hinge-CH3
ESKYGPPCPPCPGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
(SEQ ID NO: 41)

Hinge only
ESKYGPPCPPCP (SEQ ID NO: 42)

CD28 Transmembrane domain
MFWVLVVVGGVLACYSLLVTVAFIIFWV (SEQ ID NO: 43)

CD28 Cytoplasmic domain (LL to GG)
RSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS (SEQ ID NO: 44)

4-1BB Cytoplasmic domain
KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL (SEQ ID NO: 45)

CD3-ζ Cytoplasmic domain
RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE
LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO:
46)

FIG. 11 (cont'd)

T2A
LEGGGEGRGSLLTCGDVEENPGPR (SEQ ID NO: 47)

tEGFR
MLLLVTSLLLCELPHPAFLLIPRKVCNGIGIGEFKDSLSINATNIKHFKNCTSISGDLHILPVAFRGD
SFTHTPPLDPQELDILKTVKEITGFLLIQAWPENRTDLHAFENLEIIRGRTQHGQFSLAVVSLNITS
LGLRSLKEISDGDVIISGNKNLCYANTINWKKLFGTSGQKTKIISNRGENSCKATGQVCHALCSP
EGCWGPEPRDCVSCRNVSRGRECVDKCNLLEGEPREFVENSECIQCHPECLPQAMNITCTGR
GPDNCIQCAHYIDGPHCVKTCPAGVMGENNTLVWKYADAGHVCHLCHPNCTYGCTGPGLEGC
PTNGPKIPSIATGMVGALLLLLVVALGIGLFM (SEQ ID NO: 48)

Strep tag II
WSHPQFEK (SEQ ID NO: 49)

Myc tag
EQKLISEEDL (SEQ ID NO: 50)

V5 tag
GKPIPNPLLGLDST (SEQ ID NO: 51)

FLAG tag
DYKDDDDK (SEQ ID NO: 52)