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(54) **CHIMERIC ANTIGEN RECEPTORS (CARS), COMPOSITIONS AND METHODS THEREOF**

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(2) Date: **Dec. 21, 2018**

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A61P 35/02	(2006.01)

(52) **U.S. Cl.**

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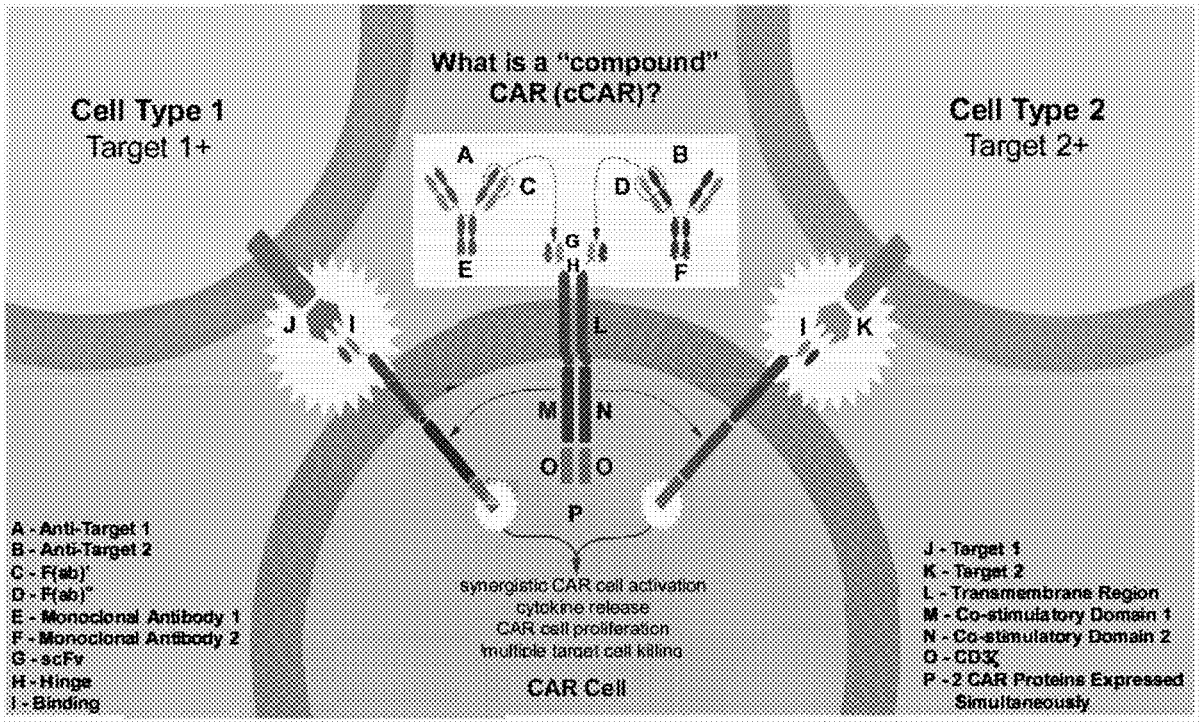
(57) **ABSTRACT**

The present disclosure relates to compositions and methods relating to chimeric antigen receptor (CAR) polypeptides and methods relating thereto. In one embodiment, the present disclosure relates to engineered cells having chimeric antigen receptor polypeptides directed to at least two targets. In another embodiment, the present disclosure relates to engineered cells having chimeric antigen receptor polypeptides and an enhancer moiety.

Specification includes a Sequence Listing.



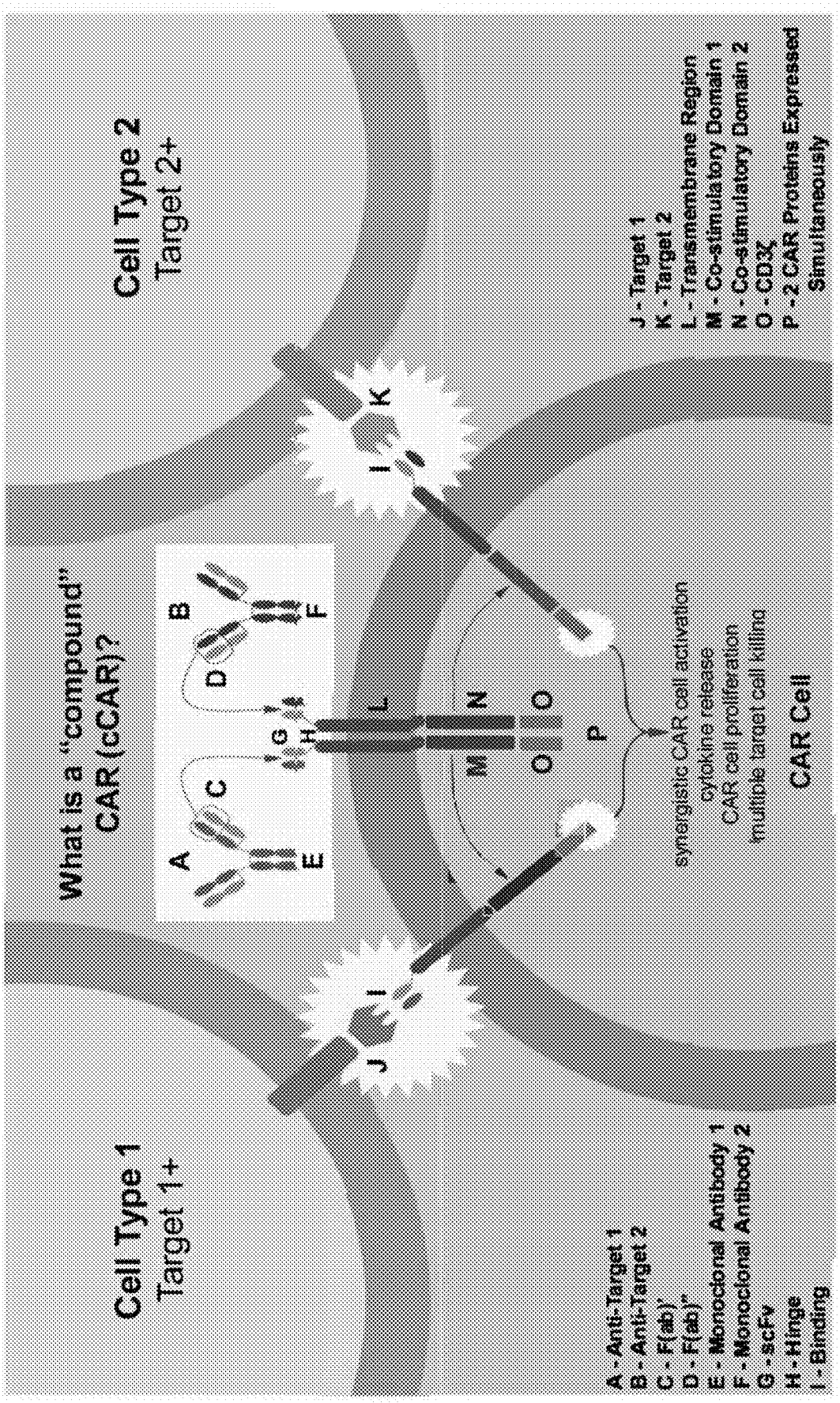

What is a "compound" CAR (cCAR)?
Cell Type 1
Target 1+
Cell Type 2
Target 2+
A
B
C
D
E
F
G
H
I
J
K
L
M
N
O
P
synergistic CAR cell activation
cytokine release
CAR cell proliferation
multiple target cell killing
CAR Cell
A - Anti-Target 1
B - Anti-Target 2
C - F(ab)'
D - F(ab)"
E - Monoclonal Antibody 1
F - Monoclonal Antibody 2
G - scFv
H - Hinge
I - Binding
J - Target 1
K - Target 2
L - Transmembrane Region
M - Co-stimulatory Domain 1
N - Co-stimulatory Domain 2
O - CD3ζ
P - 2 CAR Proteins Expressed Simultaneously

FIGURE 1

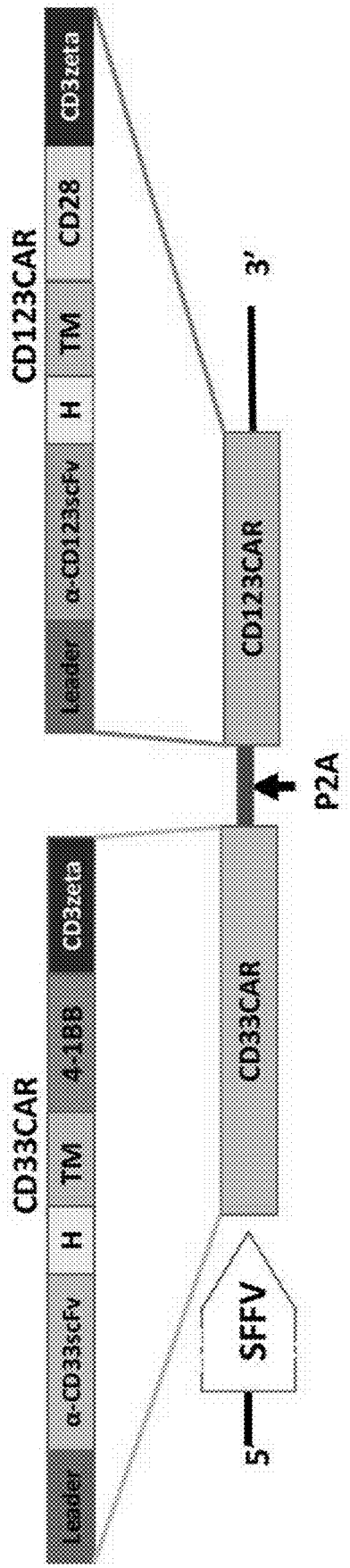

CD123CAR
Leader
α-CD123scFv
H
TM
CD28
CD3zeta
CD33CAR
Leader
α-CD33scFv
H
TM
4-1BB
CD3zeta
5'
SFFV
CD33CAR
P2A
CD123CAR
3'

FIGURE 2A

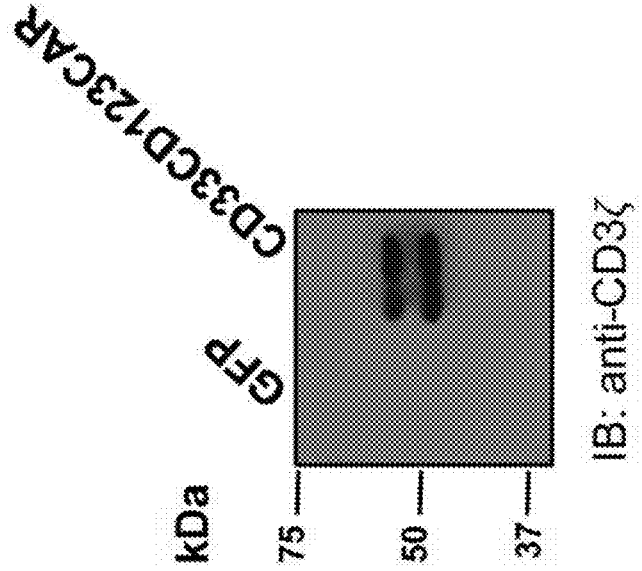
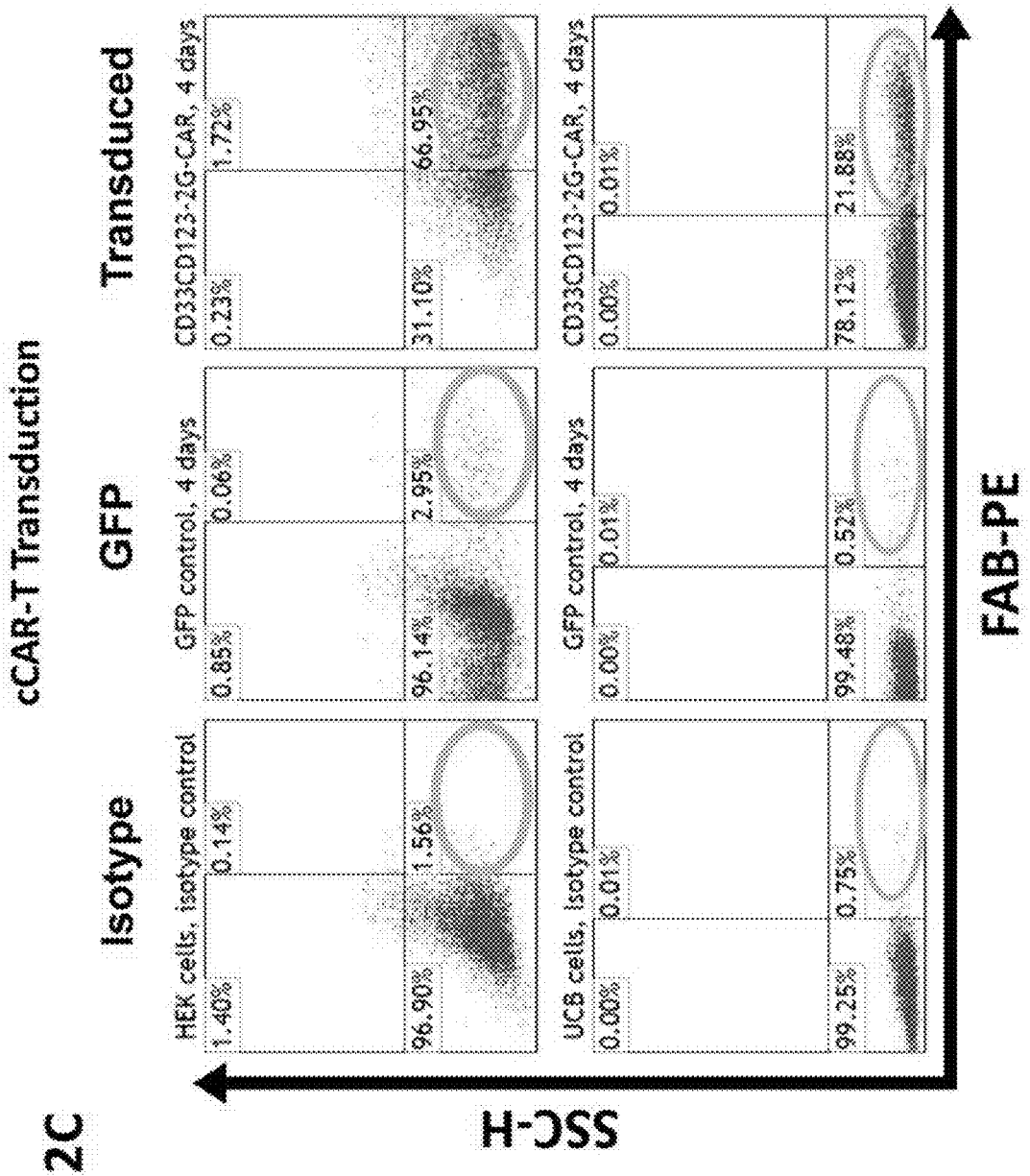


FIGURE 2B

FIGURE 2C


cCAR-T Transduction
Isotype
GFP
Transduced
HEK cells, isotype control
1.40%
0.14%
96.90%
1.56%
GFP control, 4 days
0.85%
0.06%
96.14%
2.95%
CD33CD123-2G-CAR, 4 days
0.23%
1.72%
31.10%
66.95%
UCB cells, isotype control
0.00%
0.01%
99.25%
0.75%
GFP control, 4 days
0.00%
0.01%
99.48%
0.52%
CD33CD123-2G-CAR, 4 days
0.00%
0.01%
78.12%
21.88%
SSC-H
FAB-PE

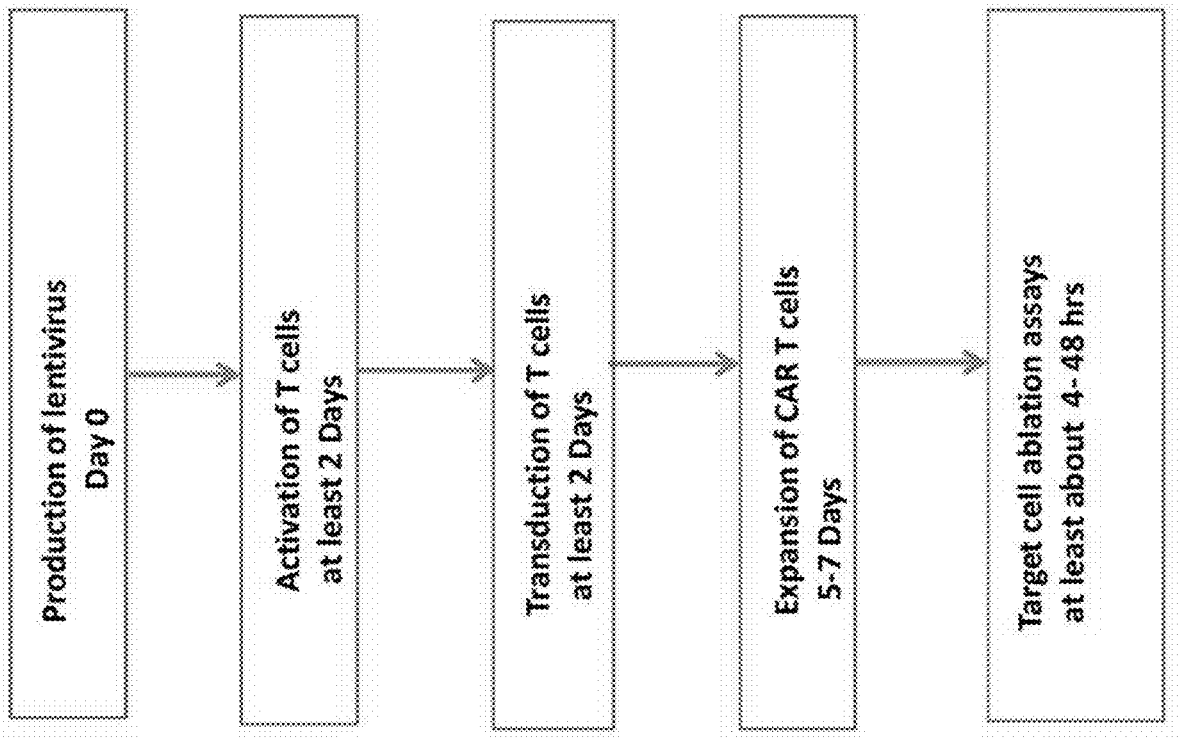

Production of lentivirus
Day 0
Activation of T cells
at least 2 Days
Transduction of T cells
at least 2 Days
Expansion of CAR T cells
5-7 Days
Target cell ablation assays
at least about 4- 48 hrs

FIGURE 3

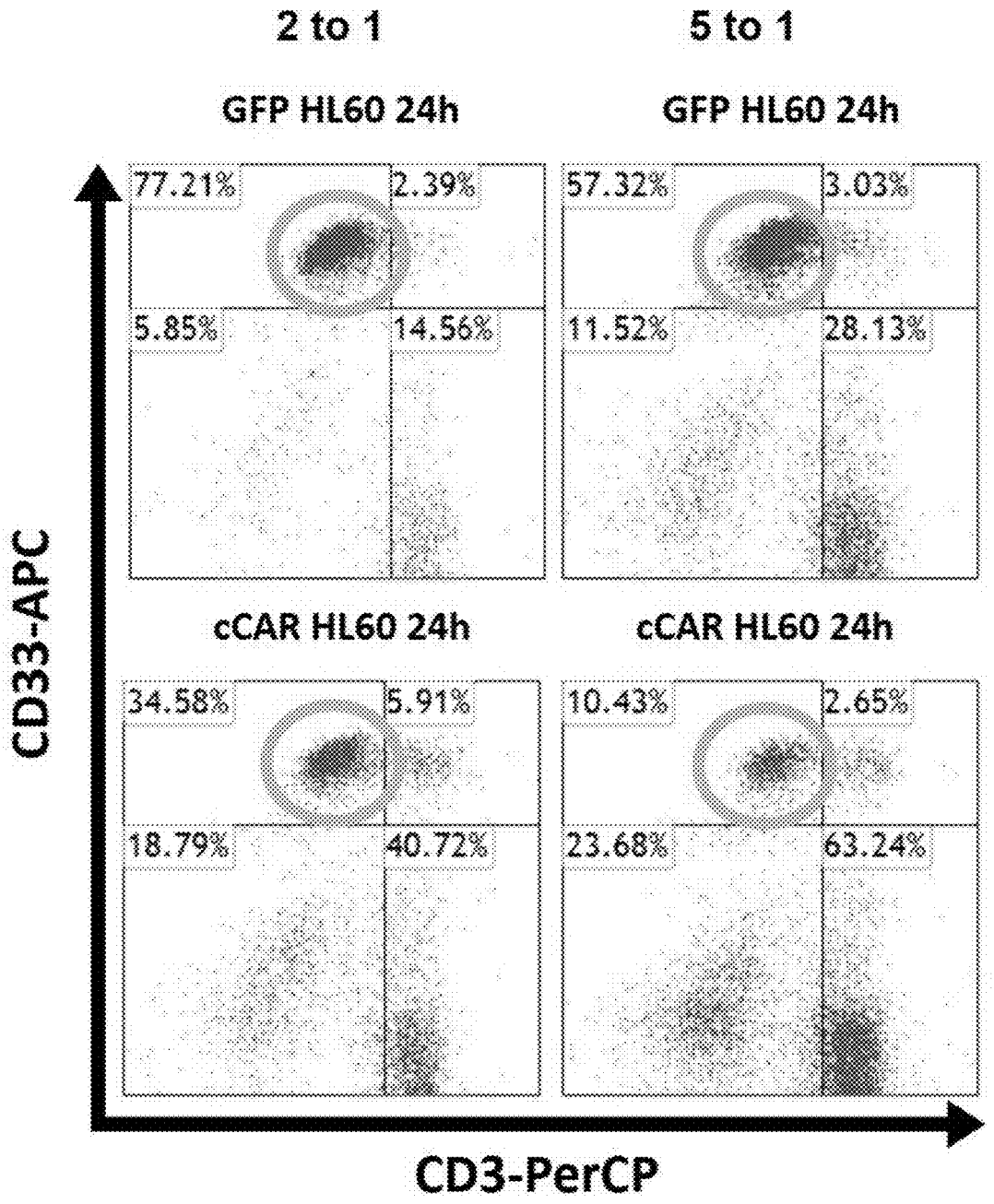

2 to 1
5 to 1
GFP HL60 24h
GFP HL60 24h
77.21%
2.39%
5.85%
14.56%
57.32%
3.03%
11.52%
28.13%
cCAR HL60 24h
cCAR HL60 24h
34.58%
5.91%
18.79%
40.72%
10.43%
2.65%
23.68%
63.24%
CD33-APC
CD3-PerCP

FIGURE 4

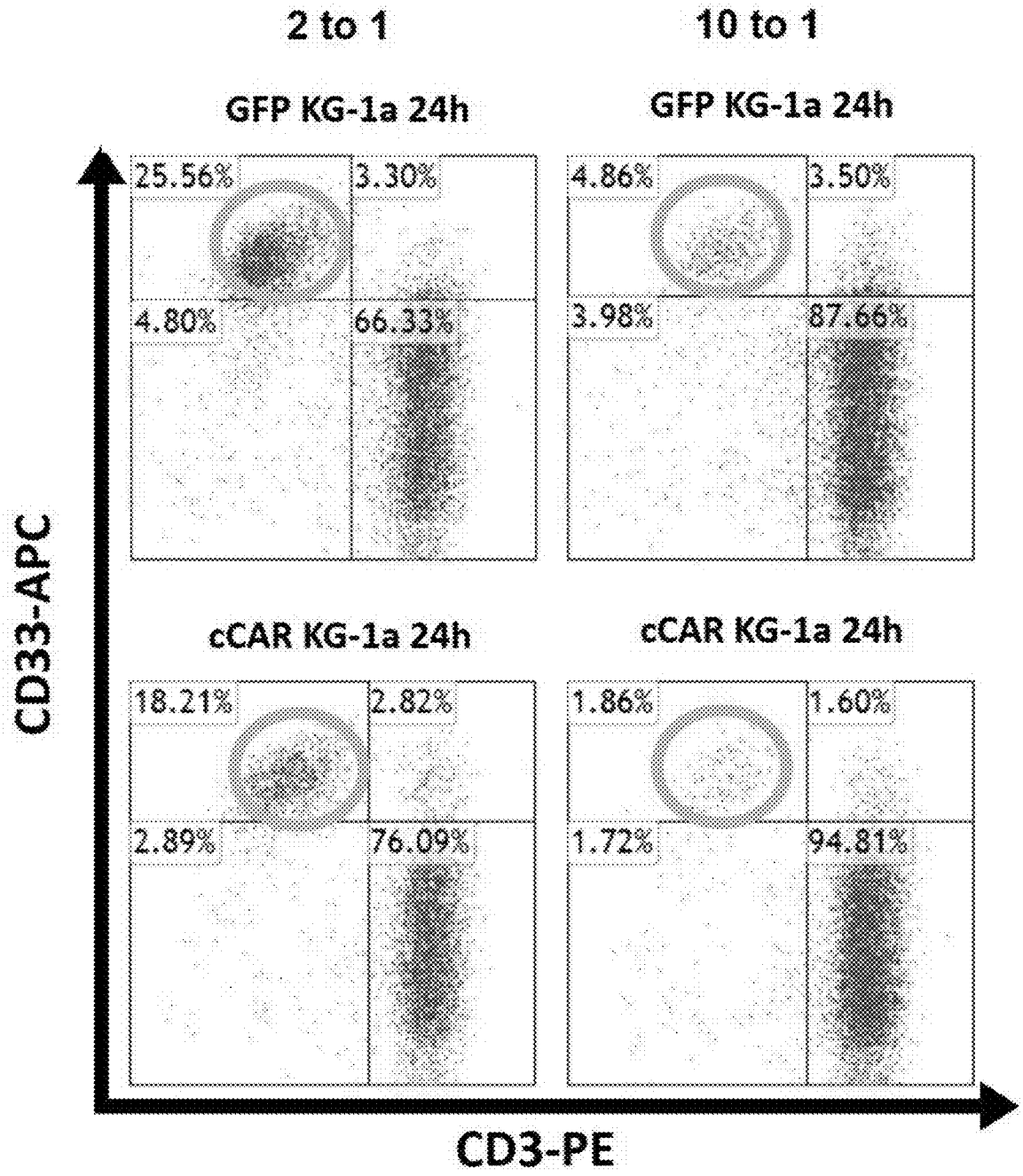

2 to 1
10 to 1
GFP KG-1a 24h
25.56%
3.30%
4.80%
66.33%
GFP KG-1a 24h
4.86%
3.50%
3.98%
87.66%
cCAR KG-1a 24h
18.21%
2.82%
2.89%
76.09%
cCAR KG-1a 24h
1.86%
1.60%
1.72%
94.81%
CD33-APC
CD3-PE

FIGURE 5

FIGURE 6

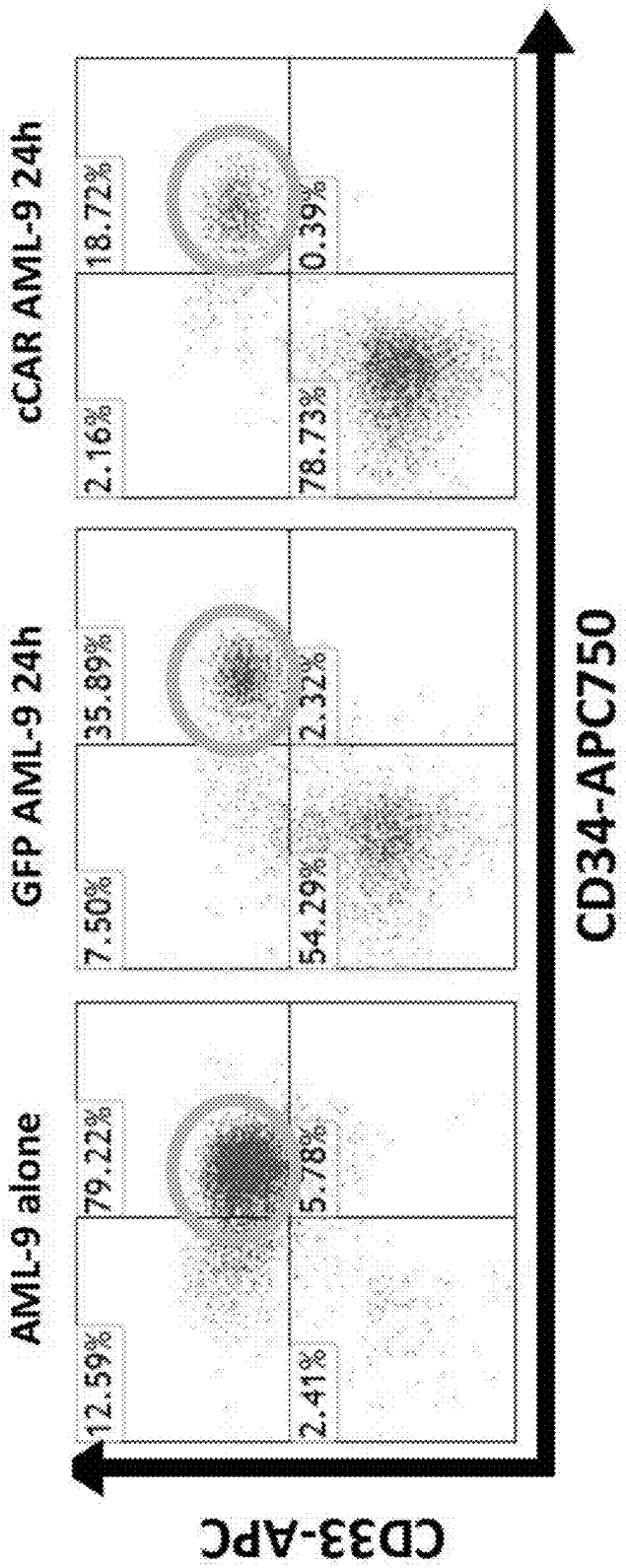

AML-9 alone
12.59%
79.22%
2.41%
5.78%
GFP AML-9 24h
7.50%
35.89%
54.29%
2.32%
cCAR AML-9 24h
2.16%
18.72%
78.73%
0.39%
CD34-APC750
CD33-APC

FIGURE 7

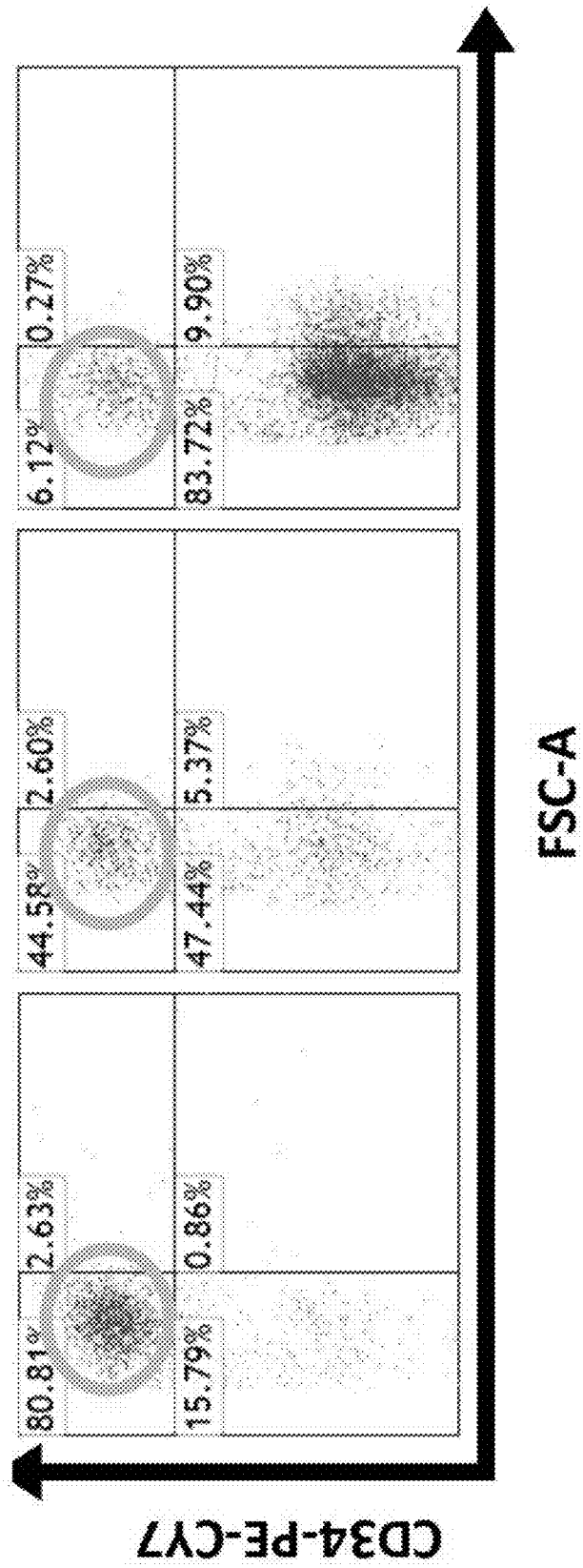

Sp-BM-B6 alone
80.81%
2.63%
15.79%
0.86%
GFP Sp-BM-B6 24h
44.58%
2.60%
47.44%
5.37%
cCAR Sp-BM-B6 24h
6.12%
0.27%
83.72%
9.90%
CD34-PE-CY7
FSC-A

FIGURE 8

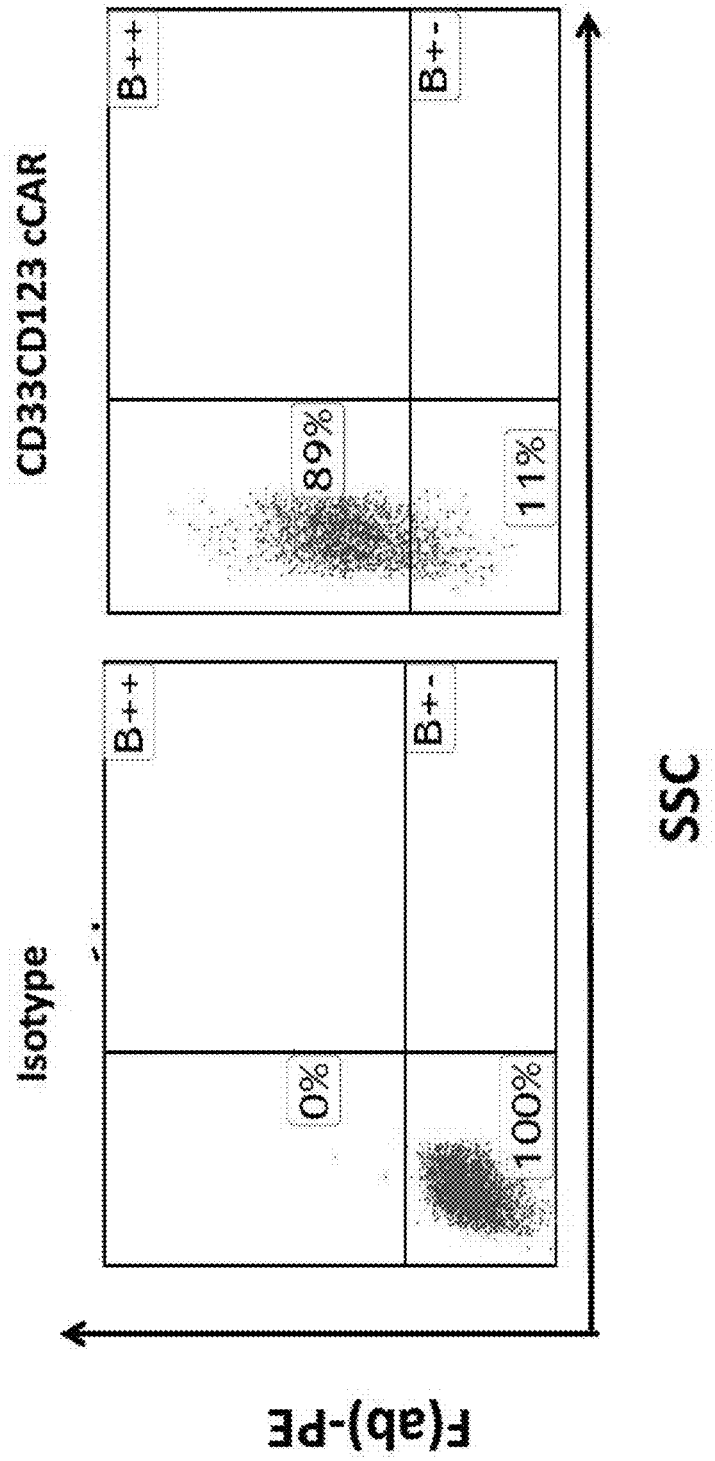


FIGURE 9

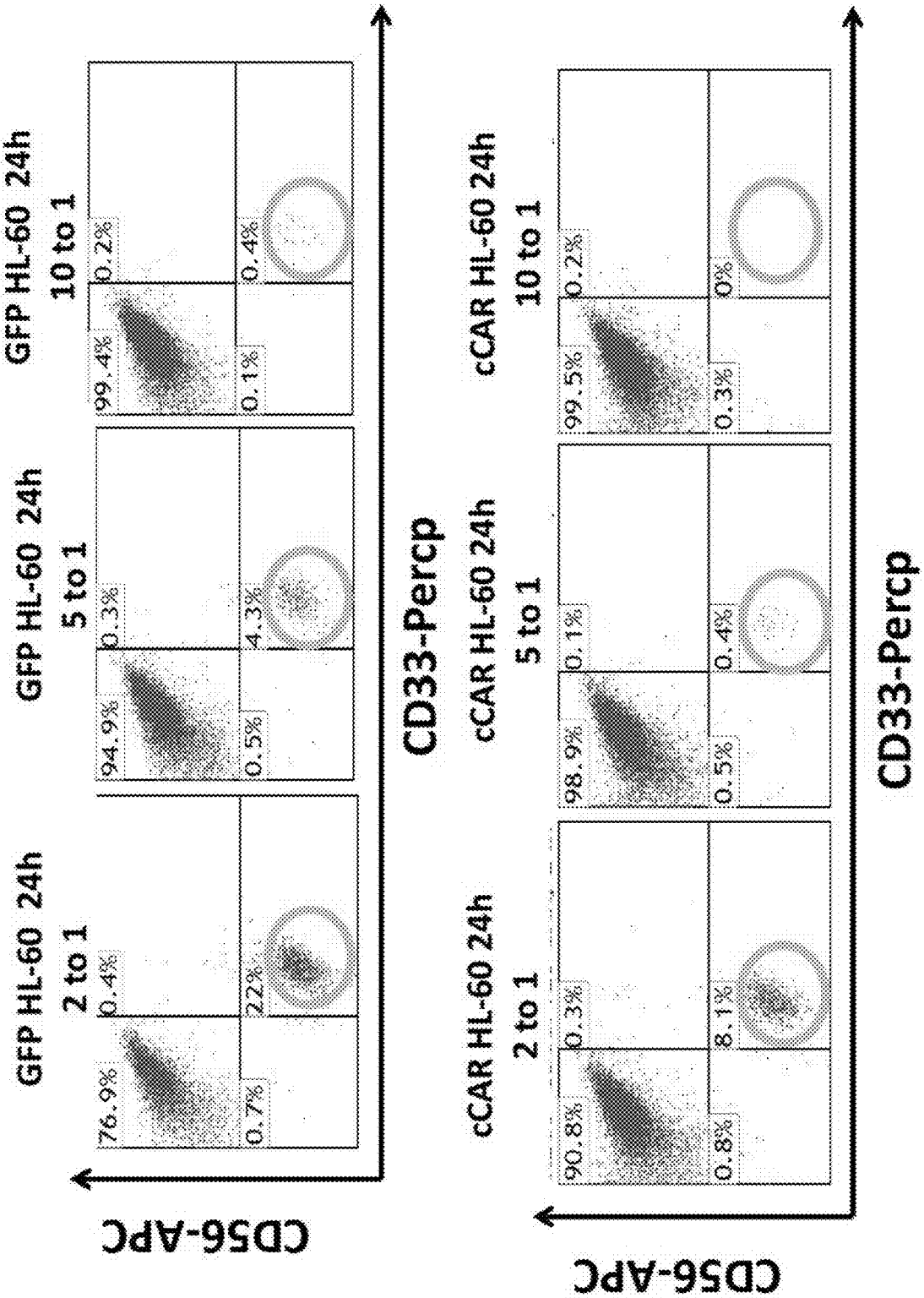

GFP HL-60 24h
2 to 1
76.9%
0.4%
0.7%
22%
GFP HL-60 24h
5 to 1
94.9%
0.3%
0.5%
4.3%
GFP HL-60 24h
10 to 1
99.4%
0.2%
0.1%
0.4%
cCAR HL-60 24h
2 to 1
90.8%
0.3%
0.8%
8.1%
cCAR HL-60 24h
5 to 1
98.9%
0.1%
0.5%
0.4%
cCAR HL-60 24h
10 to 1
99.5%
0.2%
0.3%
0%
CD56-APC
CD33-Percp
CD56-APC
CD33-Percp

FIGURE 10

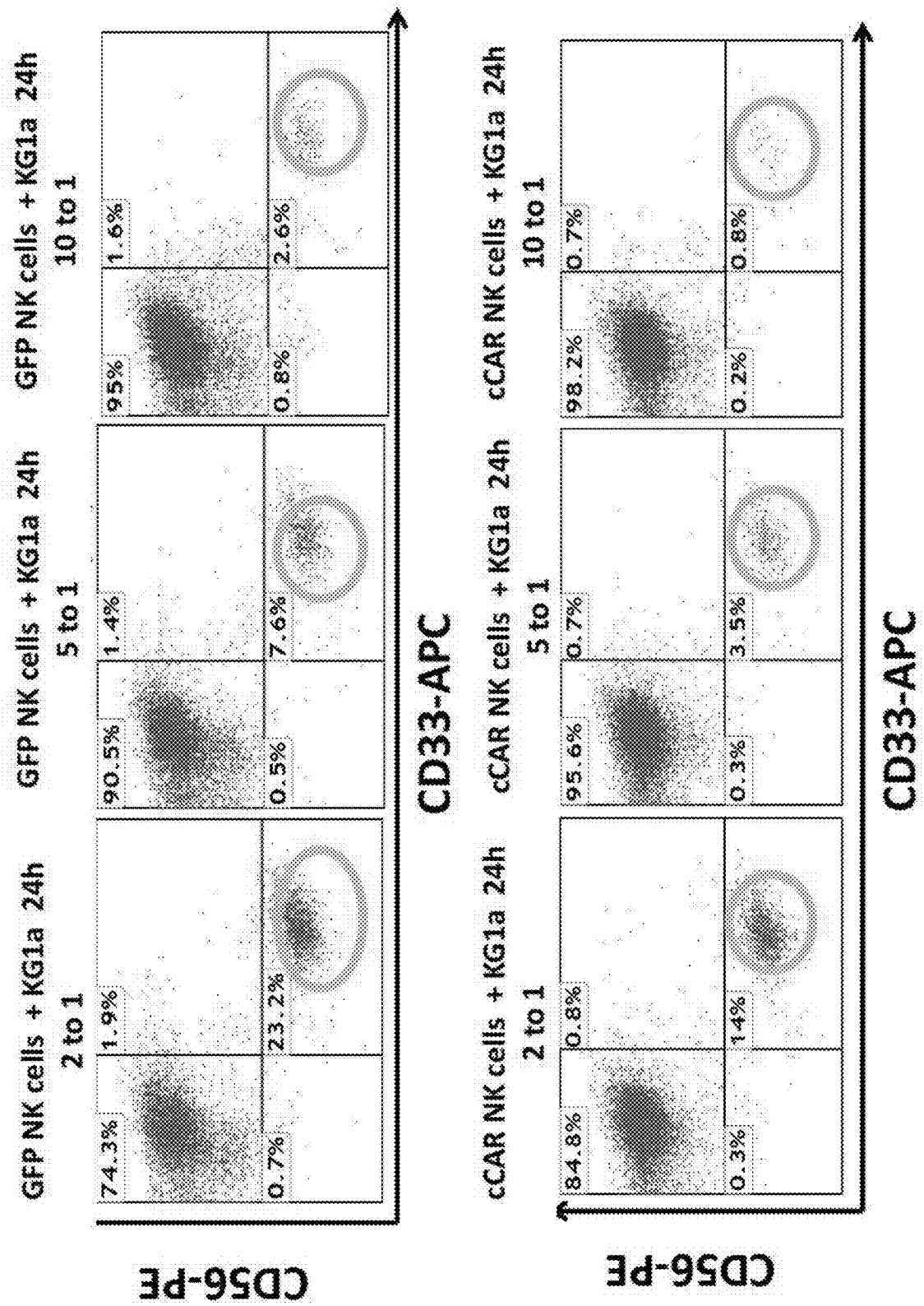

GFP NK cells + KG1a 24h
2 to 1
74.3%
1.9%
0.7%
23.2%
GFP NK cells + KG1a 24h
5 to 1
90.5%
1.4%
0.5%
7.6%
GFP NK cells + KG1a 24h
10 to 1
95%
1.6%
0.8%
2.6%
CD33-APC
CD56-PE
cCAR NK cells + KG1a 24h
2 to 1
84.8%
0.8%
0.3%
14%
cCAR NK cells + KG1a 24h
5 to 1
95.6%
0.7%
0.3%
3.5%
cCAR NK cells + KG1a 24h
10 to 1
98.2%
0.7%
0.2%
0.8%
CD33-APC
CD56-PE

FIGURE 11

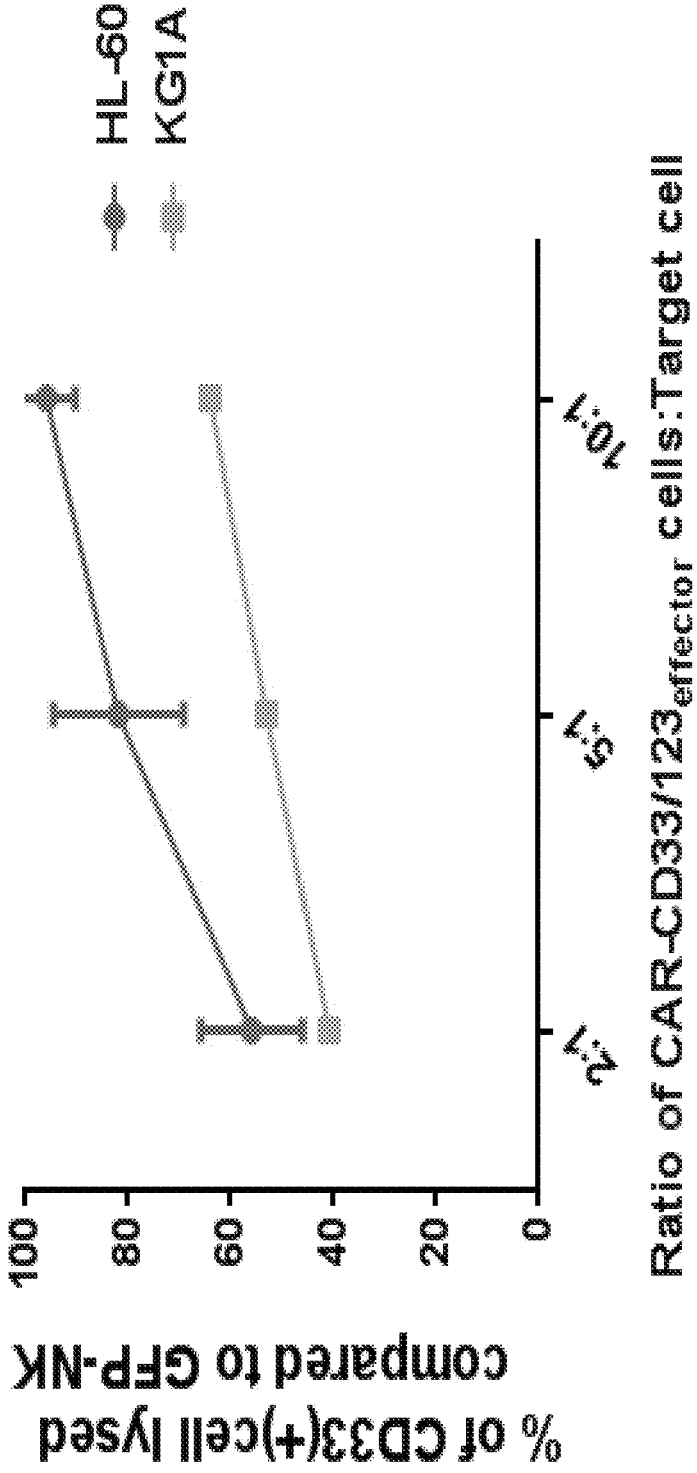
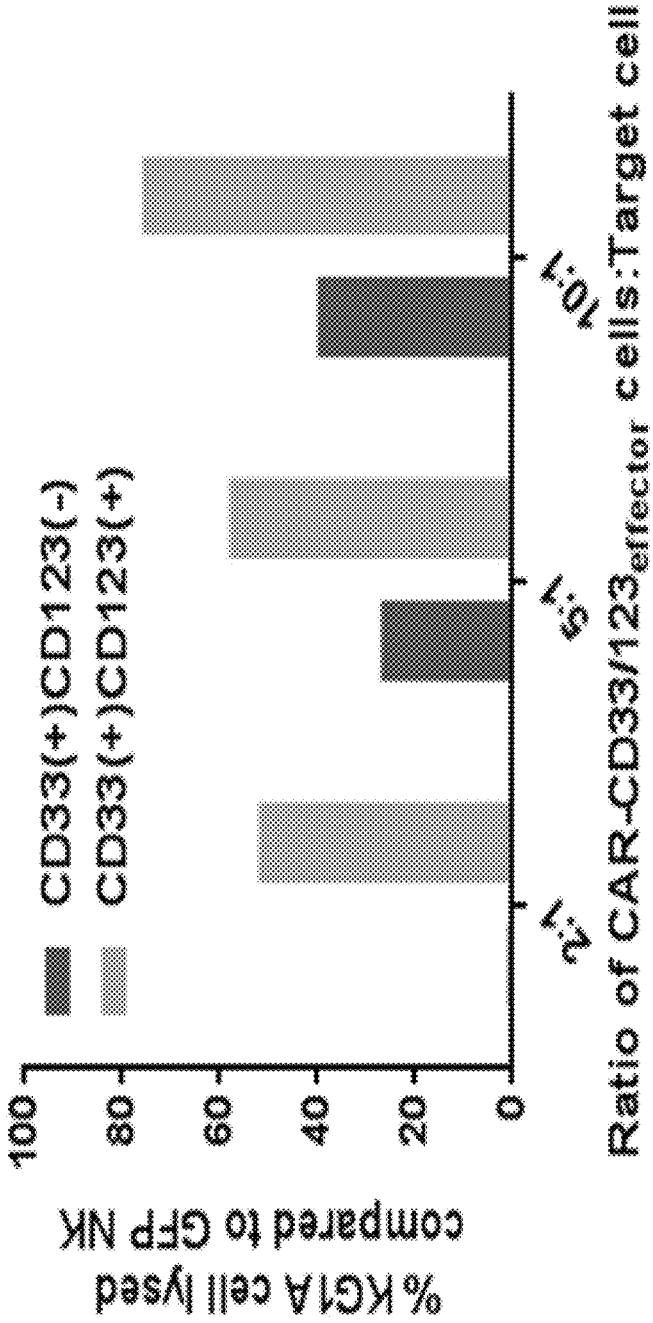

% of CD33(+)cell lysed compared to GFP-NK
100
80
60
40
20
0
10^{-2}
10^{-1}
10^{0}
10^{1}
Ratio of CAR-CD33/123$_{effector}$ cells:Target cell
HL-60
KG1A

FIGURE 12


CD33(+)CD123(-)
CD33(+)CD123(+)
100
80
60
40
20
0
% KG1A cell lysed compared to GFP NK
1:2
1:5
1:10
Ratio of CAR-CD33/123effector cells:Target cell

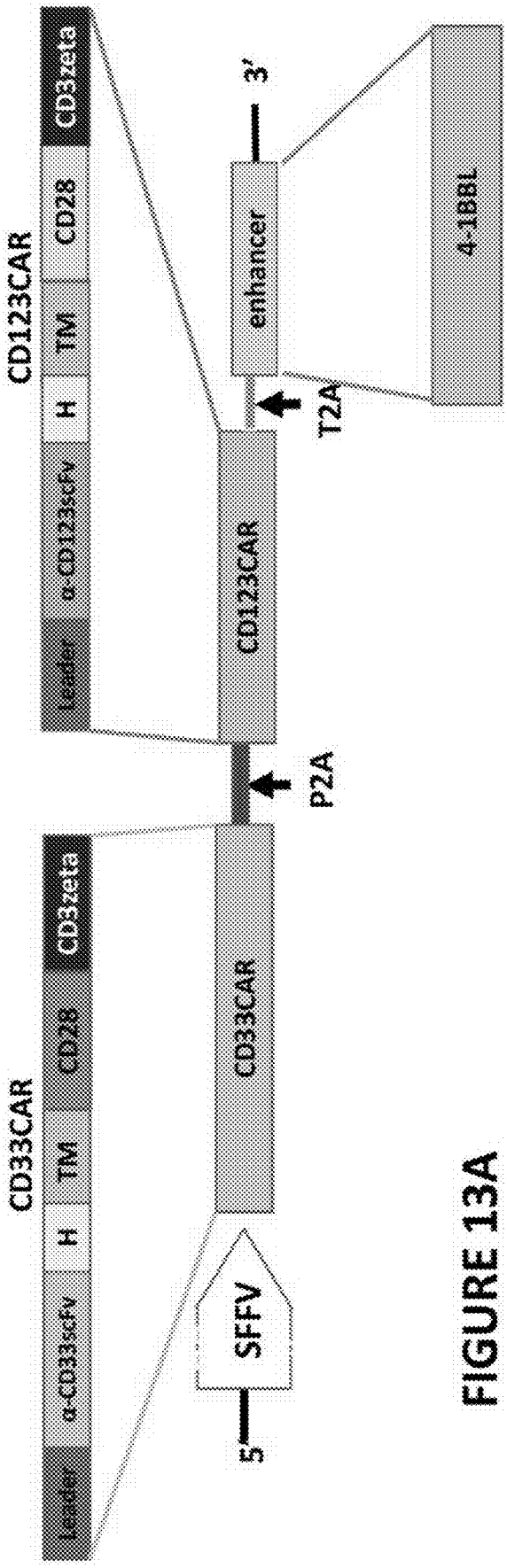

CD123CAR
Leader
α-CD123scFv
H
TM
CD28
CD3zeta
CD33CAR
Leader
α-CD33scFv
H
TM
CD28
CD3zeta
5'
SFFV
CD33CAR
P2A
CD123CAR
T2A
enhancer
3'
4-1BBL

FIGURE 13A

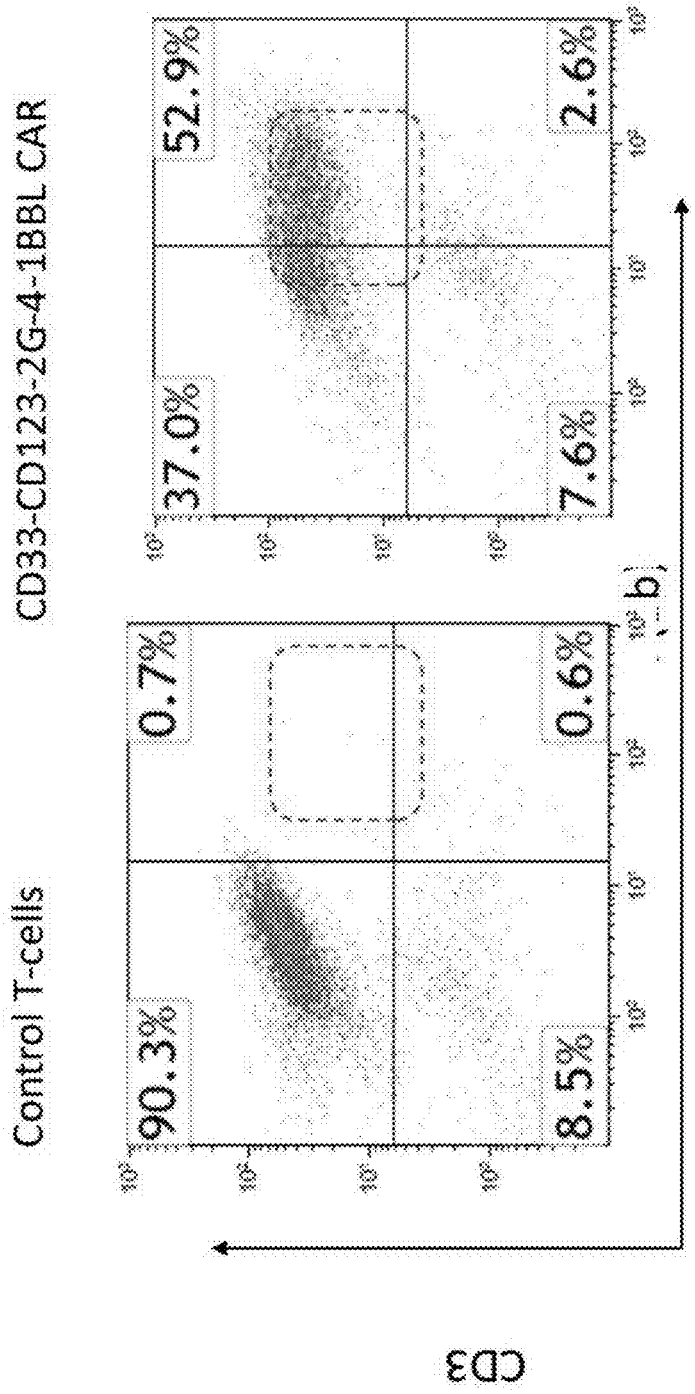

Control T-cells
CD33-CD123-2G-4-1BBL CAR
90.3%
0.7%
8.5%
0.6%
37.0%
52.9%
7.6%
2.6%
CD3

FIGURE 13B

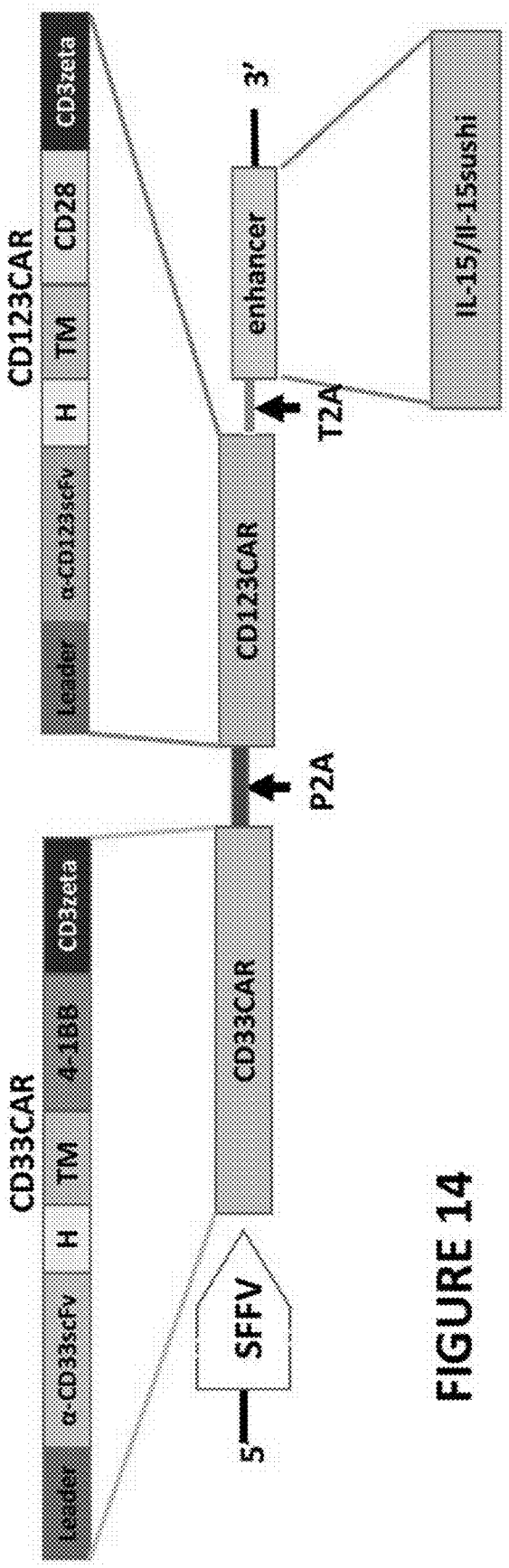

CD123CAR
Leader
α-CD123scFv
H
TM
CD28
CD3zeta
CD123CAR
P2A
CD33CAR
Leader
α-CD33scFv
H
TM
4-1BB
CD3zeta
CD33CAR
5'
SFFV
T2A
enhancer
3'
IL-15/Il-15sushi

FIGURE 14

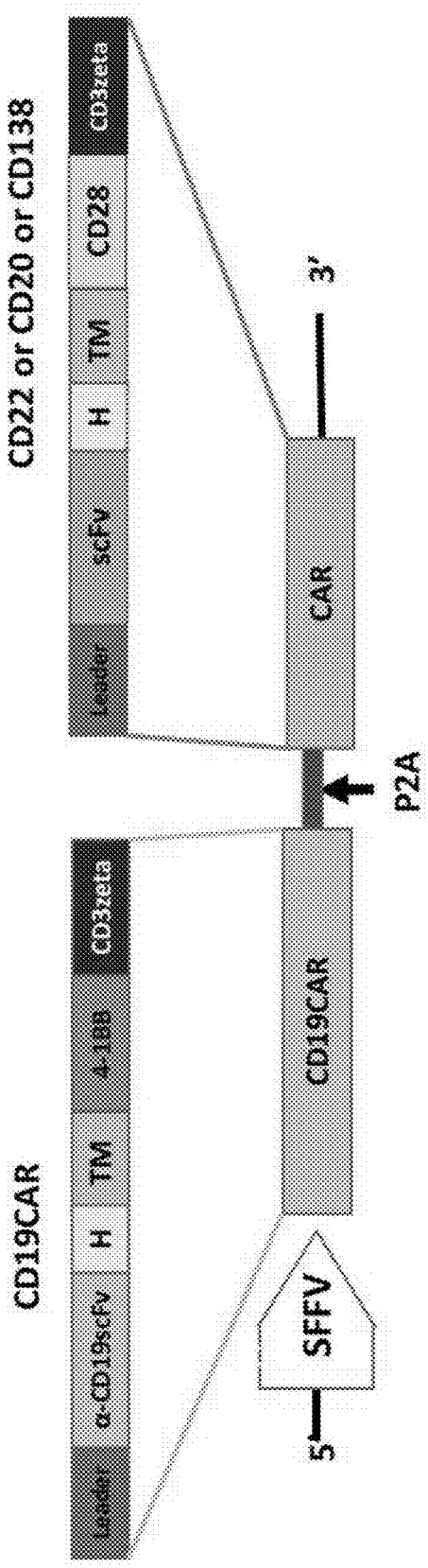
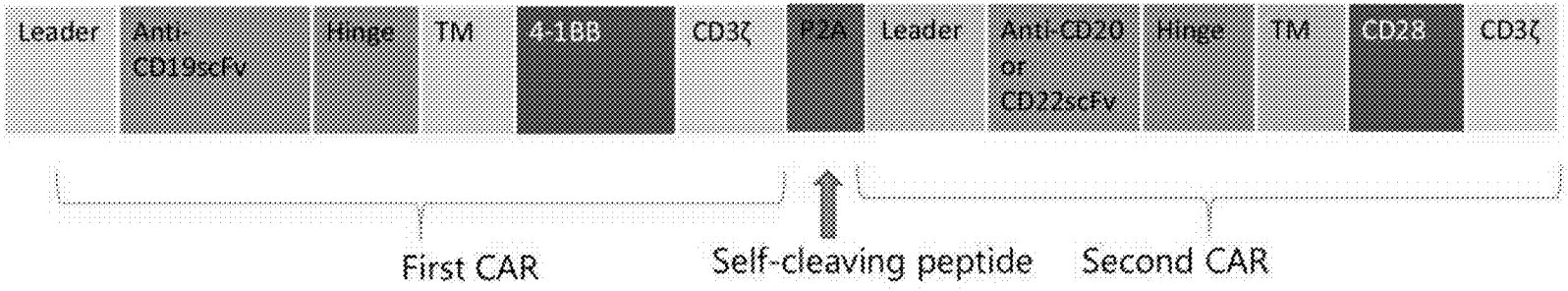
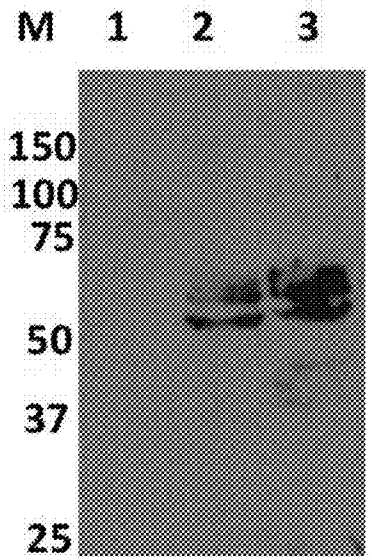

CD22 or CD20 or CD138
Leader
scFv
H
TM
CD28
CD3zeta
CD19CAR
Leader
α-CD19scFv
H
TM
4-1BB
CD3zeta
5'
SFFV
CD19CAR
P2A
CAR
3'

FIGURE 15

FIGURE 16A





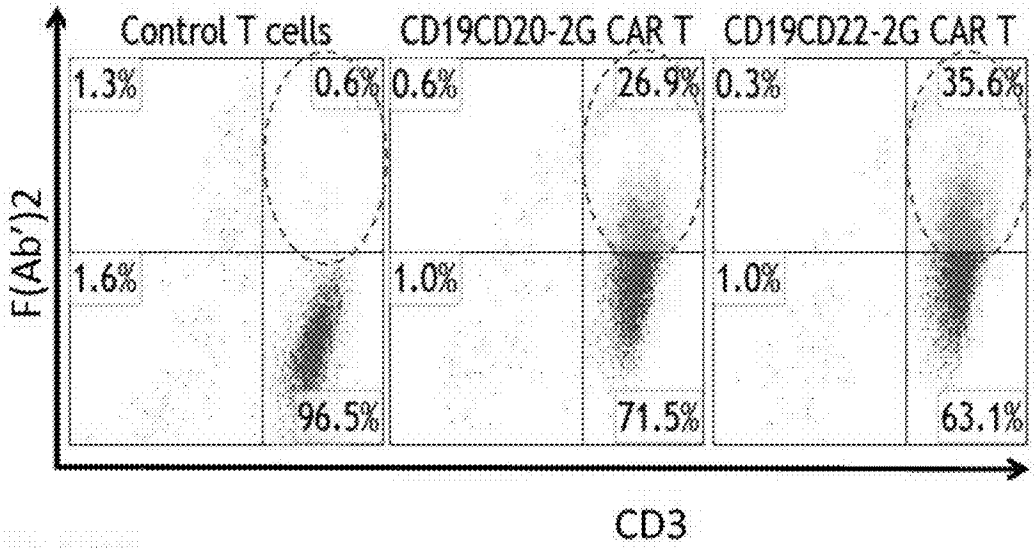


FIGURE 16B

FIGURE 17

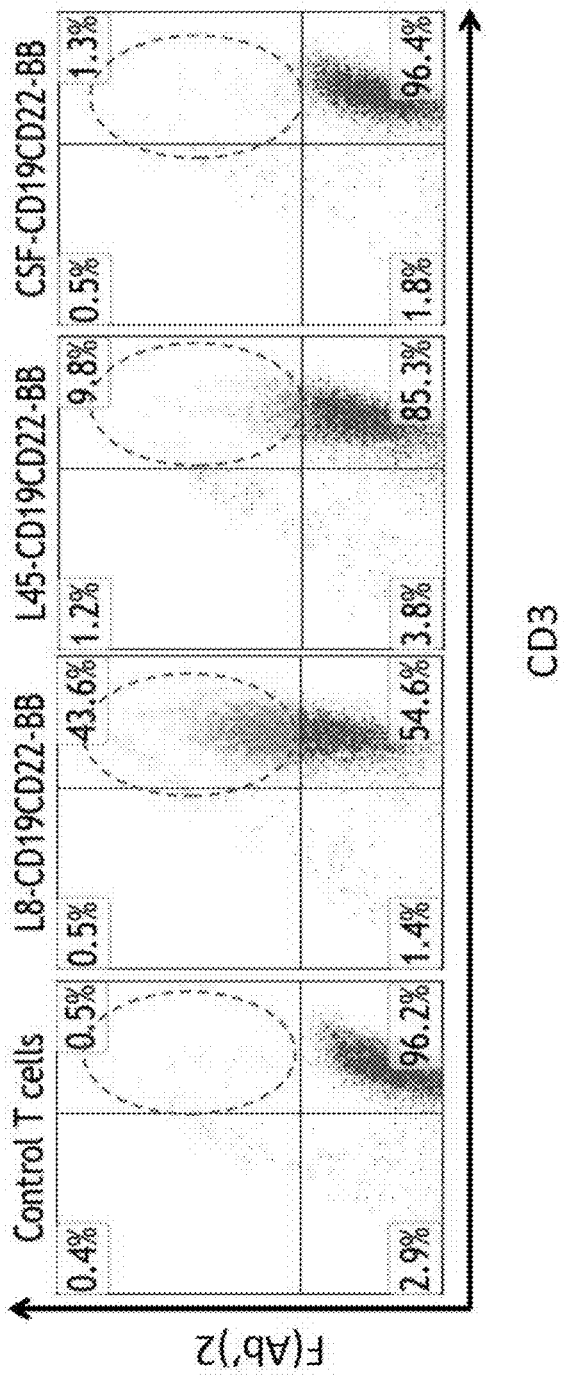
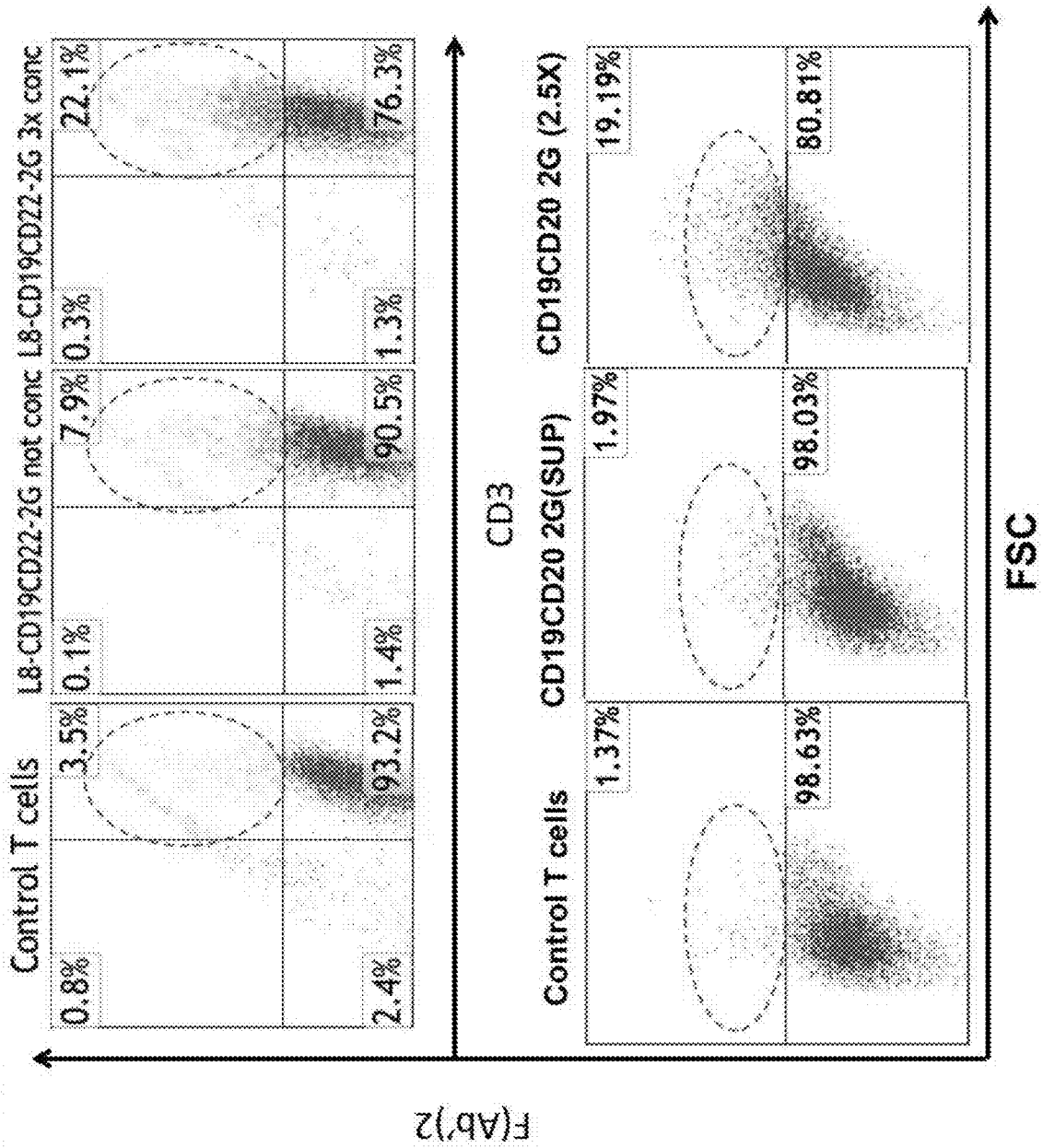

Control T cells
L8-CD19CD22-BB
L45-CD19CD22-BB
CSF-CD19CD22-BB
0.4%
0.5%
2.9%
96.2%
0.5%
43.6%
1.4%
54.6%
1.2%
9.8%
3.8%
85.3%
0.5%
1.3%
1.8%
96.4%
F(Ab')2
CD3

FIGURE 18


Control T cells
L8-CD19CD22-2G not conc
L8-CD19CD22-2G 3x conc
0.8%
3.5%
0.1%
7.9%
0.3%
22.1%
2.4%
93.2%
1.4%
90.5%
1.3%
76.3%
CD3
Control T cells
CD19CD20 2G(SUP)
CD19CD20 2G (2.5X)
1.37%
98.63%
1.97%
98.03%
19.19%
80.81%
FSC
F(Ab')2

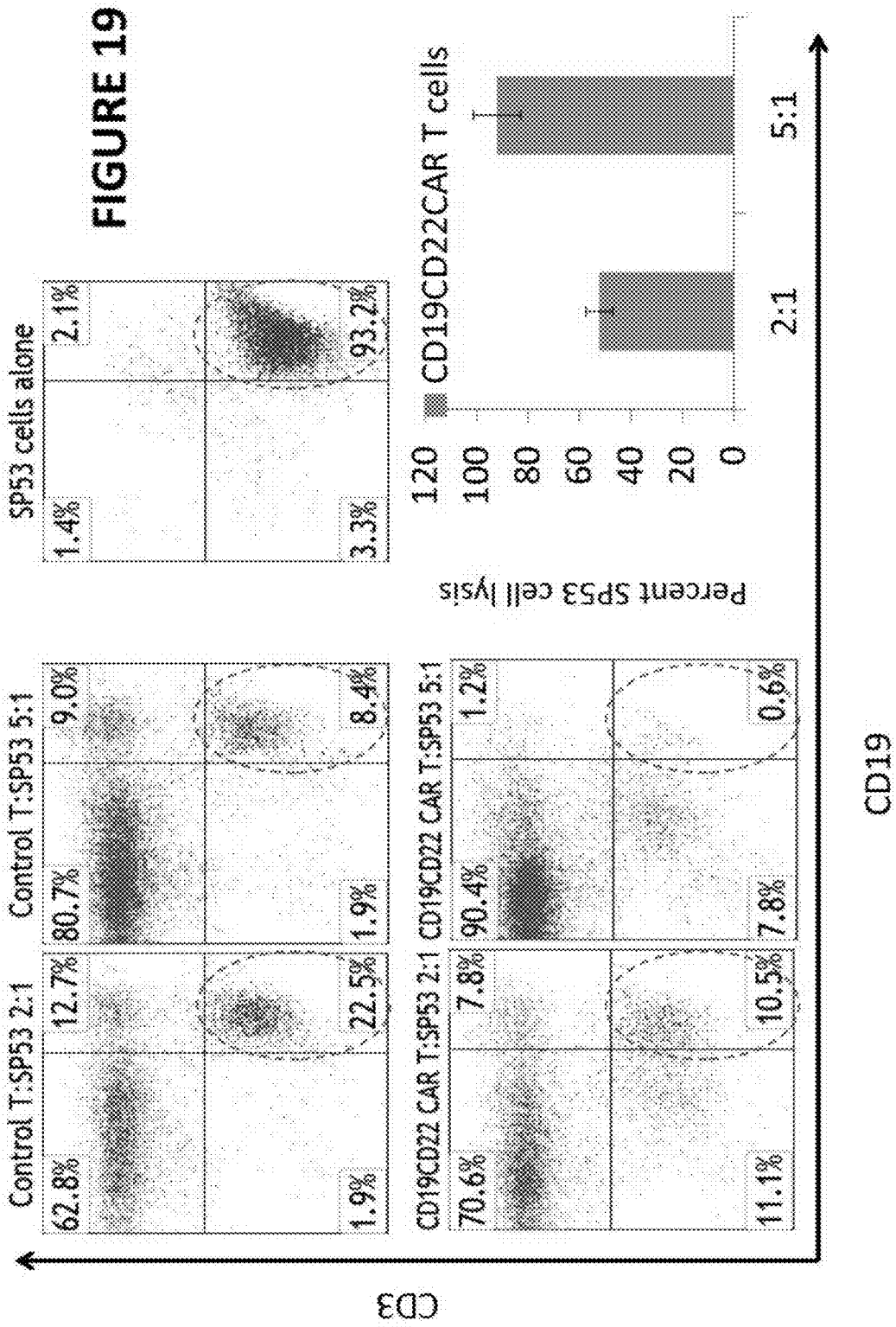


FIGURE 19
SP53 cells alone
1.4%
2.1%
3.3%
93.2%
Control T:SP53 2:1
62.8%
12.7%
1.9%
22.5%
Control T:SP53 5:1
80.7%
9.0%
1.9%
8.4%
CD19CD22 CAR T:SP53 2:1
70.6%
7.8%
11.1%
10.5%
CD19CD22 CAR T:SP53 5:1
90.4%
1.2%
7.8%
0.6%
CD3
CD19
Percent SP53 cell lysis
120
100
80
60
40
20
0
CD19CD22CAR T cells
2:1
5:1

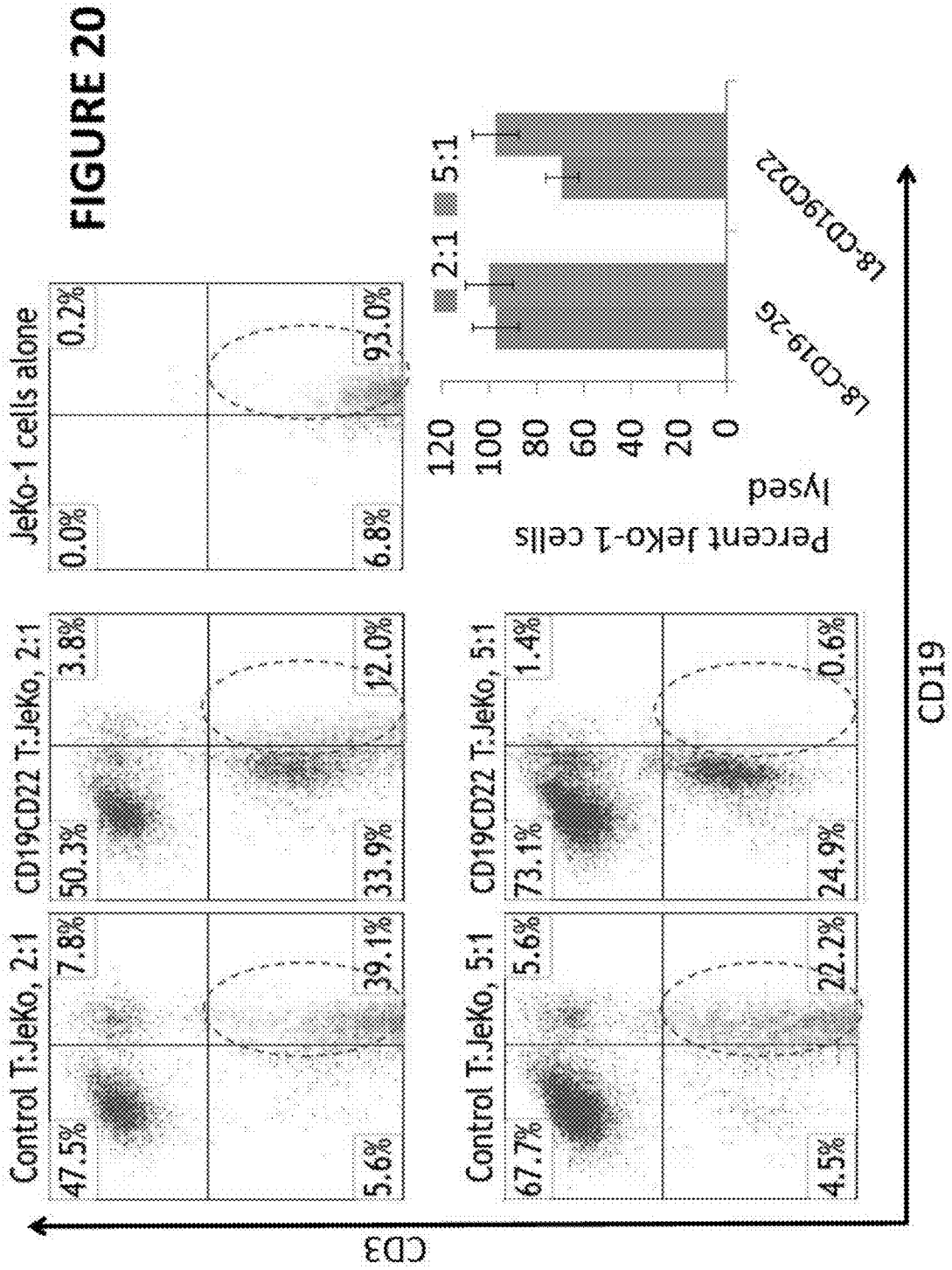

Control T:JeKo, 2:1
CD19CD22 T:JeKo, 2:1
JeKo-1 cells alone
47.5%
7.8%
50.3%
3.8%
0.0%
0.2%
5.6%
39.1%
33.9%
12.0%
6.8%
93.0%
Control T:JeKo, 5:1
CD19CD22 T:JeKo, 5:1
67.7%
5.6%
73.1%
1.4%
4.5%
22.2%
24.9%
0.6%
CD3
CD19
Percent JeKo-1 cells lysed
120
100
80
60
40
20
0
2:1
5:1
L8-CD19-2G
L8-CD19CD22

FIGURE 20

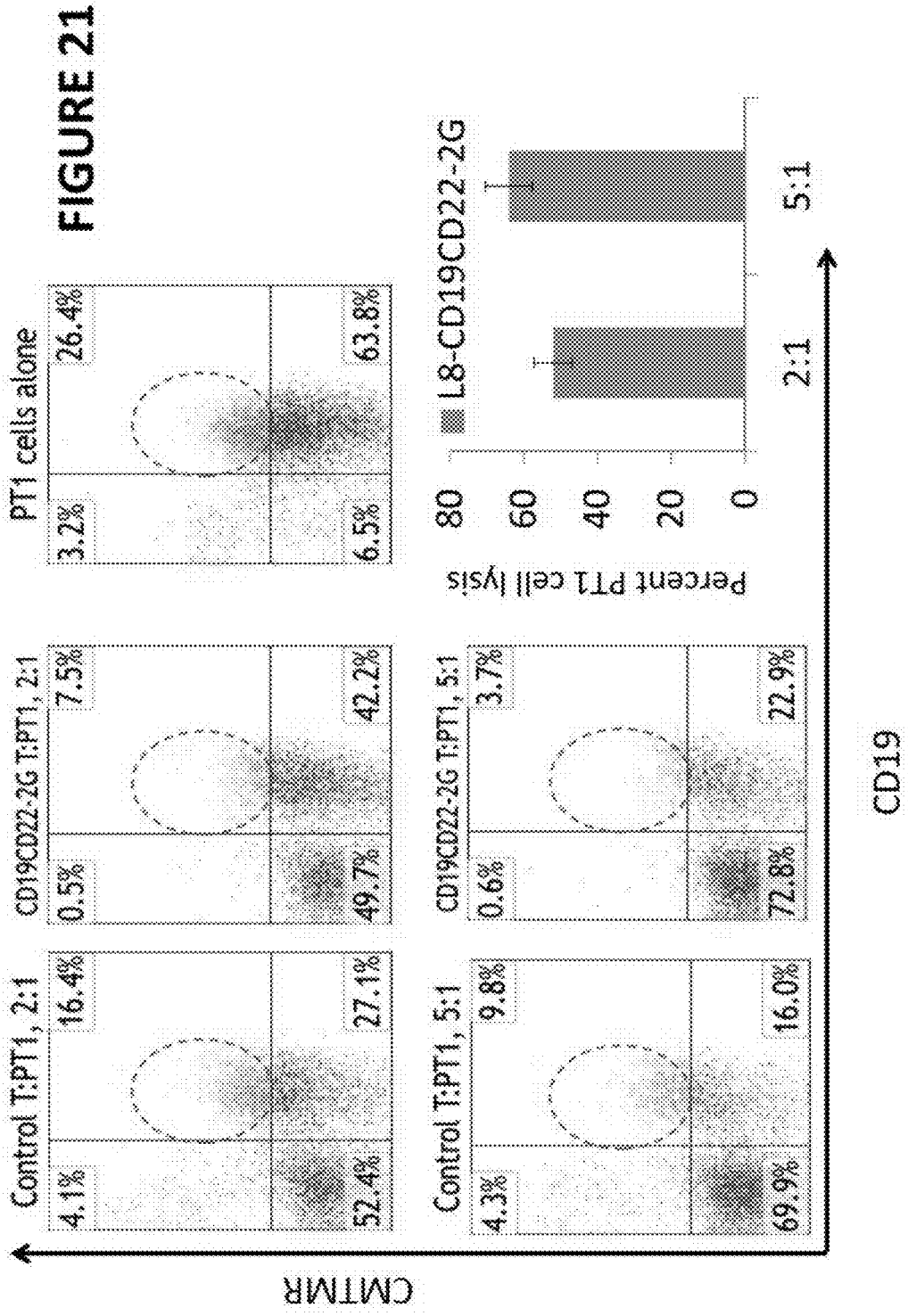

Control T:PT1, 2:1
4.1%
16.4%
52.4%
27.1%
CD19CD22-2G T:PT1, 2:1
0.5%
7.5%
49.7%
42.2%
PT1 cells alone
3.2%
26.4%
6.5%
63.8%
Control T:PT1, 5:1
4.3%
9.8%
69.9%
16.0%
CD19CD22-2G T:PT1, 5:1
0.6%
3.7%
72.8%
22.9%
CMTMR
CD19
L8-CD19CD22-2G
Percent PT1 cell lysis
80
60
40
20
0
2:1
5:1

FIGURE 21

FIGURE 22A

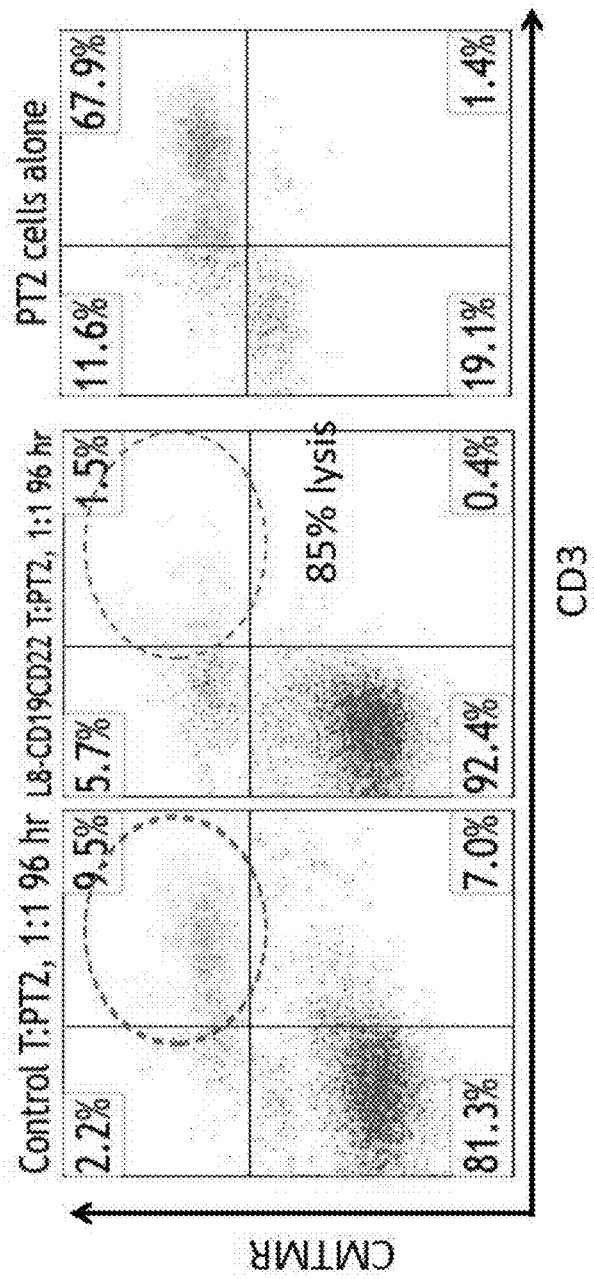
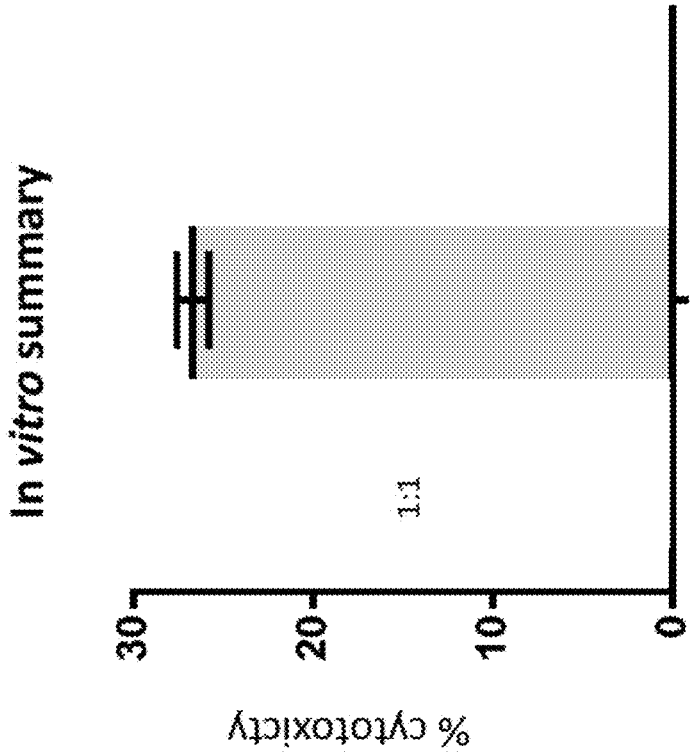

Control T:PT2, 1:1 96 hr
L8-CD19CD22 T:PT2, 1:1 96 hr
PT2 cells alone
2.2%
9.5%
5.7%
1.5%
11.6%
67.9%
81.3%
7.0%
92.4%
0.4%
19.1%
1.4%
85% lysis
CMTMR
CD3

FIGURE 22B



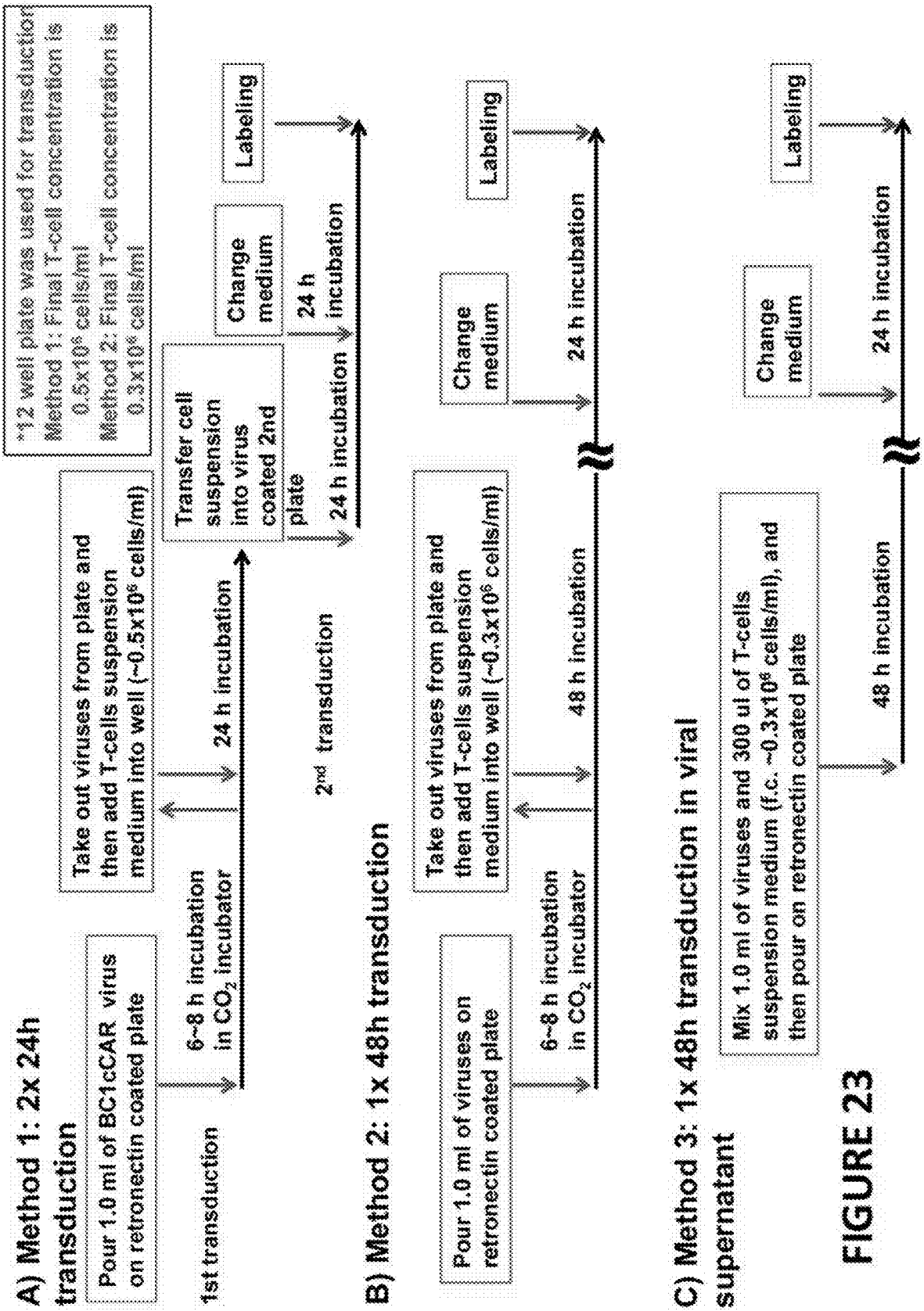

A) Method 1: 2x 24h transduction
Pour 1.0 ml of BC1cCAR virus on retronectin coated plate
1st transduction
6~8 h incubation in CO_2 incubator
Take out viruses from plate and then add T-cells suspension medium into well (~0.5x10^6 cells/ml)
24 h incubation
*12 well plate was used for transduction
Method 1: Final T-cell concentration is 0.5x10^6 cells/ml
Method 2: Final T-cell concentration is 0.3x10^6 cells/ml
2nd transduction
Transfer cell suspension into virus coated 2nd plate
24 h incubation
Change medium
24 h incubation
Labeling
B) Method 2: 1x 48h transduction
Pour 1.0 ml of viruses on retronectin coated plate
6~8 h incubation in CO_2 incubator
Take out viruses from plate and then add T-cells suspension medium into well (~0.3x10^6 cells/ml)
48 h incubation
Change medium
24 h incubation
Labeling
C) Method 3: 1x 48h transduction in viral supernatant
Mix 1.0 ml of viruses and 300 ul of T-cells suspension medium (f.c. ~0.3x10^6 cells/ml), and then pour on retronectin coated plate
48 h incubation
Change medium
24 h incubation
Labeling

FIGURE 23

FIGURE 24A

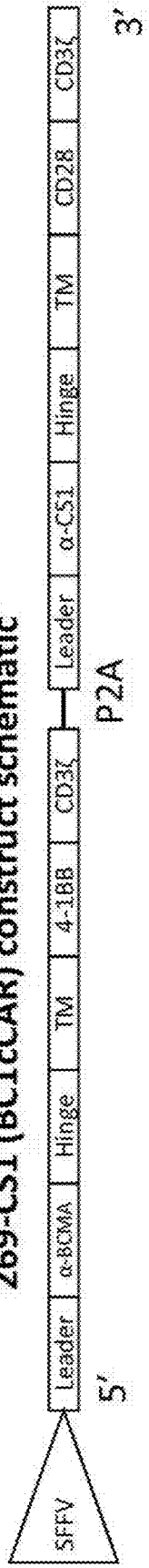
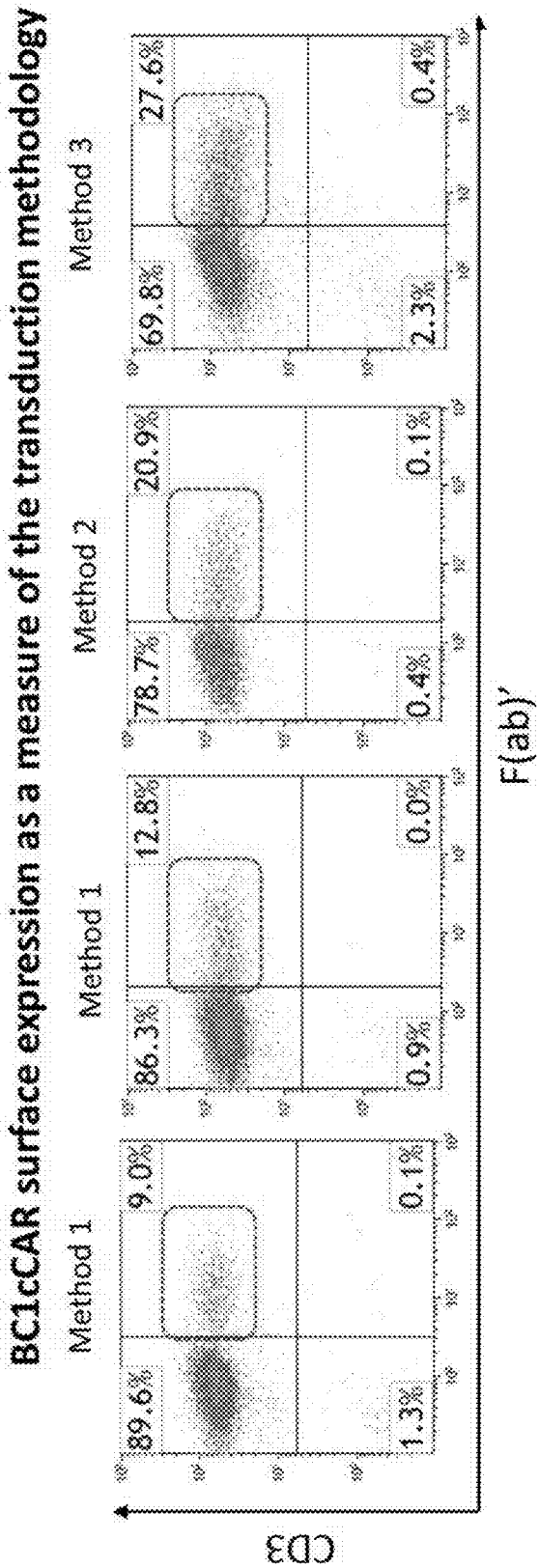


FIGURE 24B



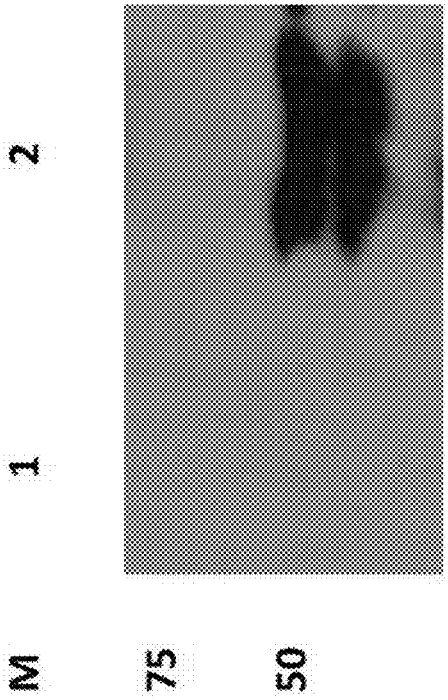


FIGURE 24D

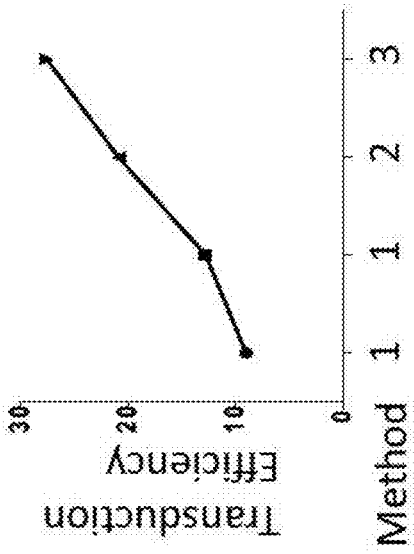


FIGURE 24C

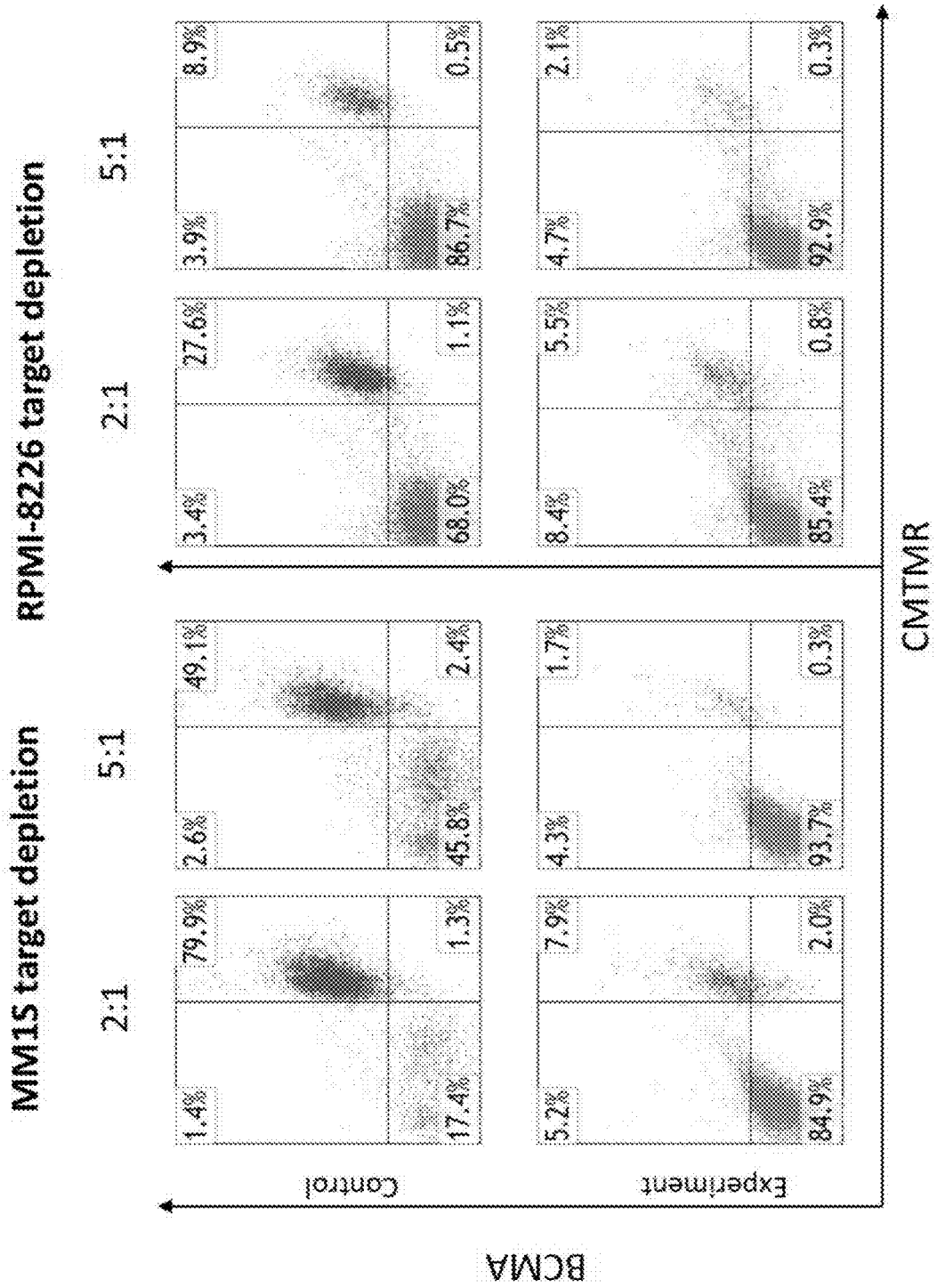

MM1S target depletion
RPMI-8226 target depletion
2:1
5:1
2:1
5:1
1.4%
79.9%
17.4%
1.3%
2.6%
49.1%
45.8%
2.4%
3.4%
27.6%
68.0%
1.1%
3.9%
8.9%
86.7%
0.5%
5.2%
7.9%
84.9%
2.0%
4.3%
1.7%
93.7%
0.3%
8.4%
5.5%
85.4%
0.8%
4.7%
2.1%
92.9%
0.3%
Control
Experiment
BCMA
CMTMR

FIGURE 25A

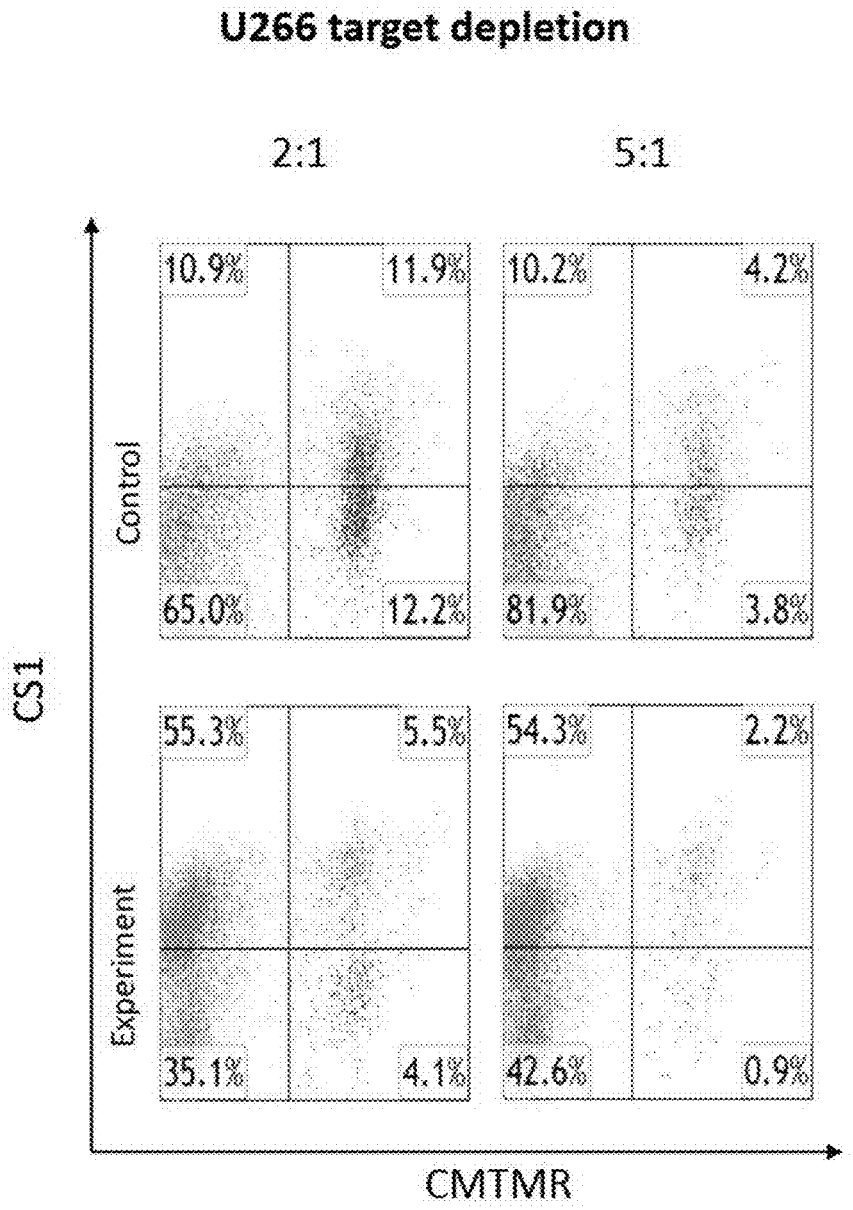

U266 target depletion
2:1
5:1
Control
Experiment
CS1
CMTMR
10.9%
11.9%
65.0%
12.2%
10.2%
4.2%
81.9%
3.8%
55.3%
5.5%
35.1%
4.1%
54.3%
2.2%
42.6%
0.9%

FIGURE 25B

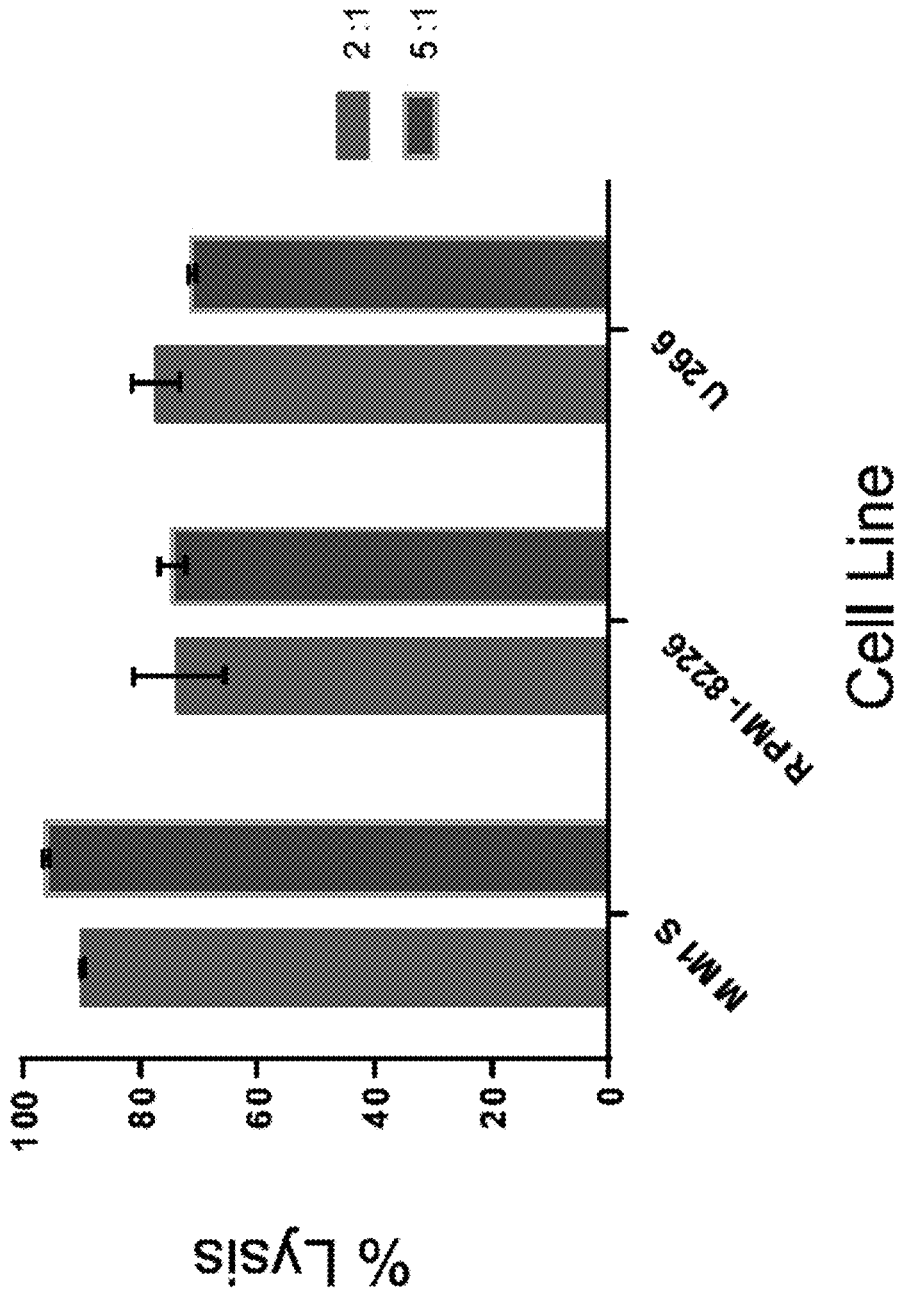
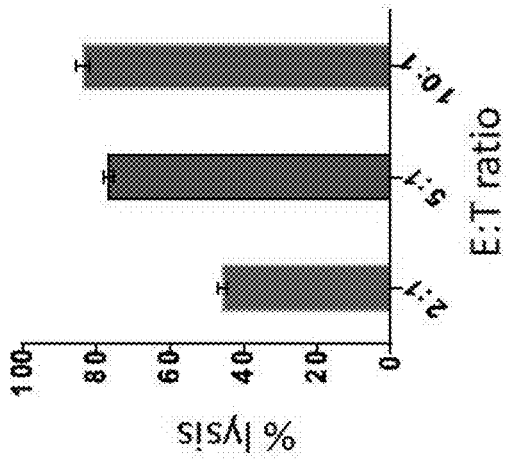


FIGURE 25C


% lysis
100
80
60
40
20
0
2:1
5:1
10:1
E:T ratio

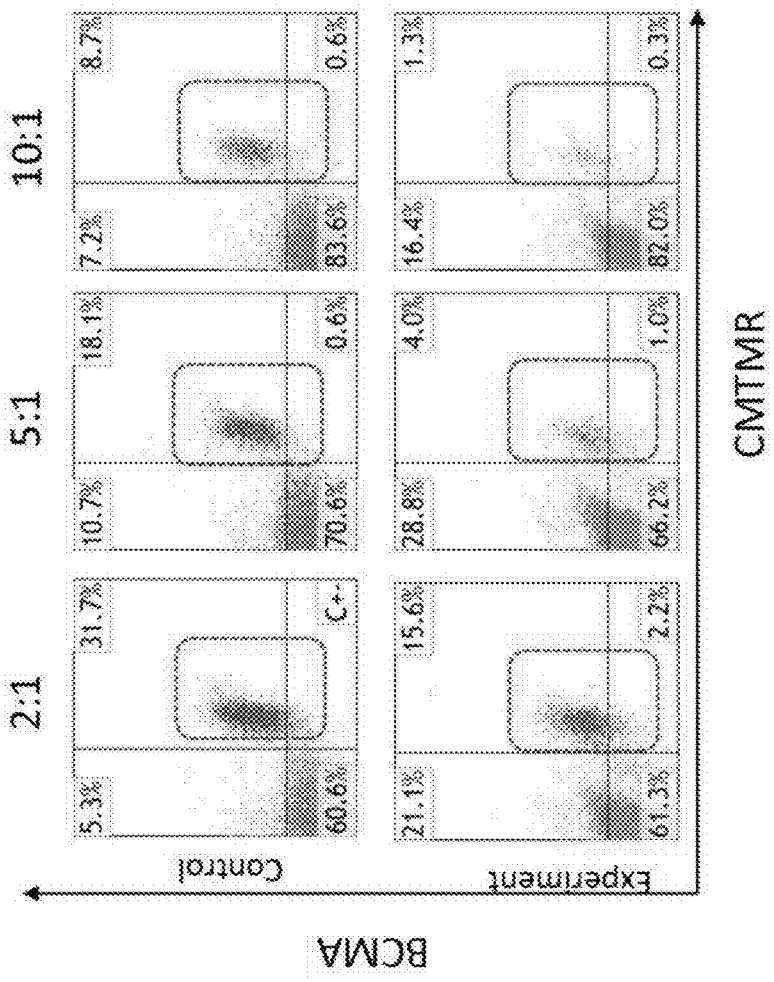

2:1
5:1
10:1
Control
Experiment
5.3%
31.7%
60.6%
C+-
10.7%
18.1%
70.6%
0.6%
7.2%
8.7%
83.6%
0.6%
21.1%
15.6%
61.3%
2.2%
28.8%
4.0%
66.2%
1.0%
16.4%
1.3%
82.0%
0.3%
BCMA
CMTMR

FIGURE 26A

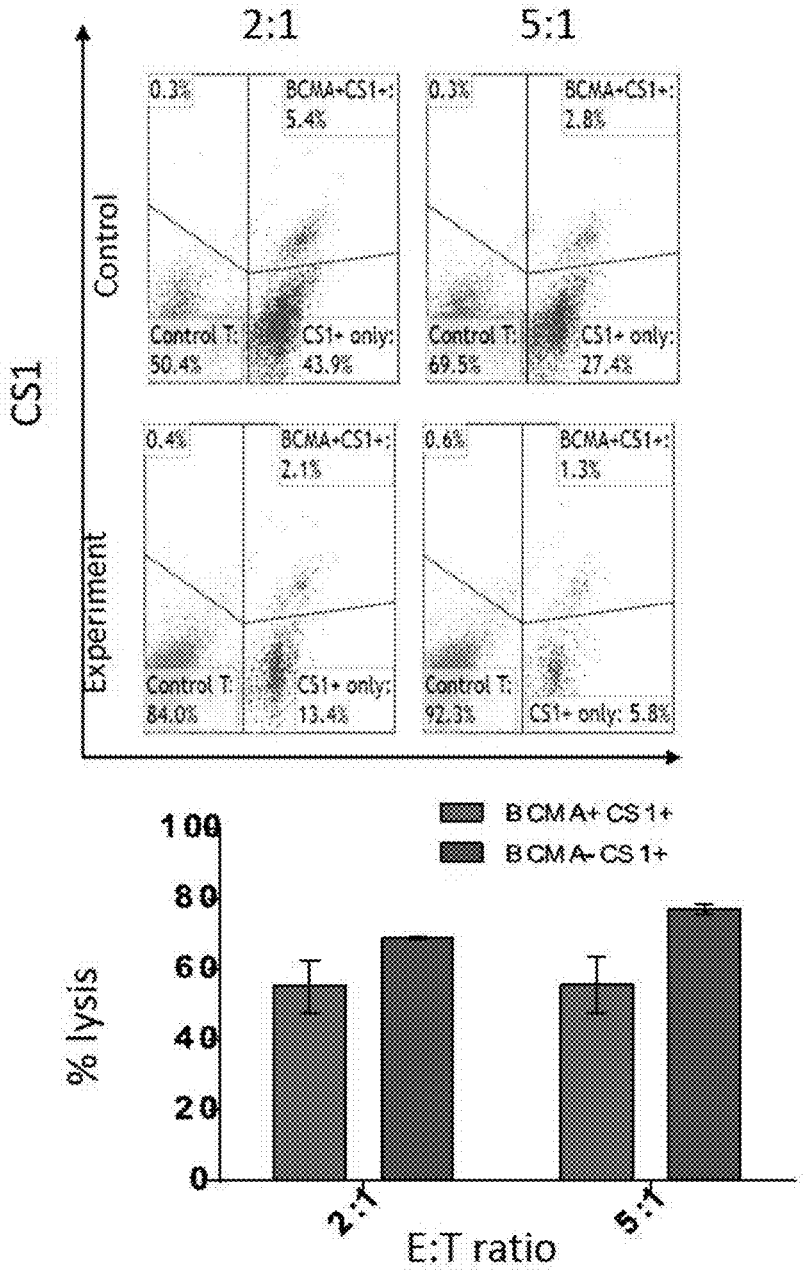

2:1
5:1
CS1
Control
Experiment
0.3%
BCMA+CS1+: 5.4%
Control T: 50.4%
CS1+ only: 43.9%
0.3%
BCMA+CS1+: 2.8%
Control T: 69.5%
CS1+ only: 27.4%
0.4%
BCMA+CS1+: 2.1%
Control T: 84.0%
CS1+ only: 13.4%
0.6%
BCMA+CS1+: 1.3%
Control T: 92.3%
CS1+ only: 5.8%
BCMA+ CS1+
BCMA- CS1+
% lysis
100
80
60
40
20
0
2:1
5:1
E:T ratio

FIGURE 26B

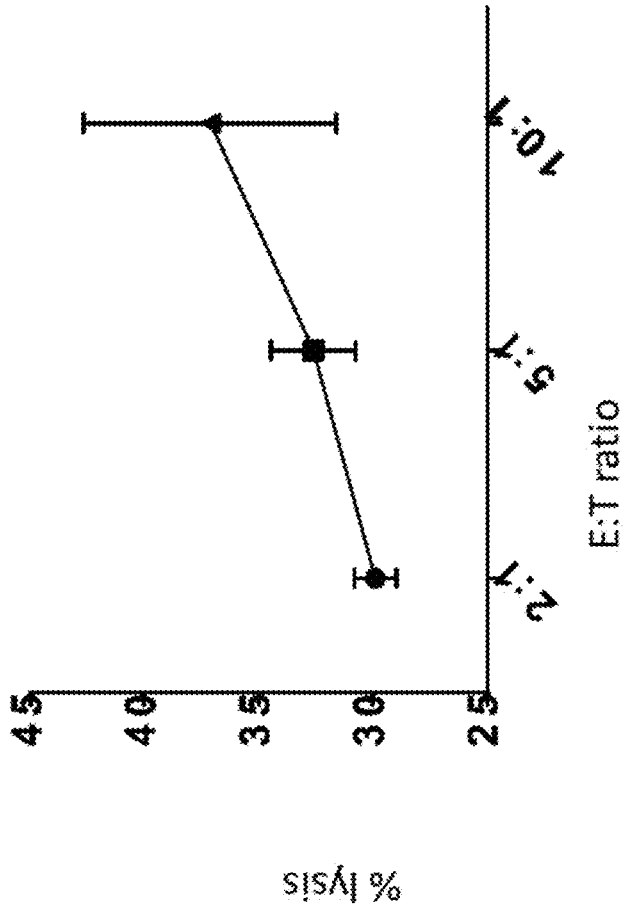


FIGURE 26C

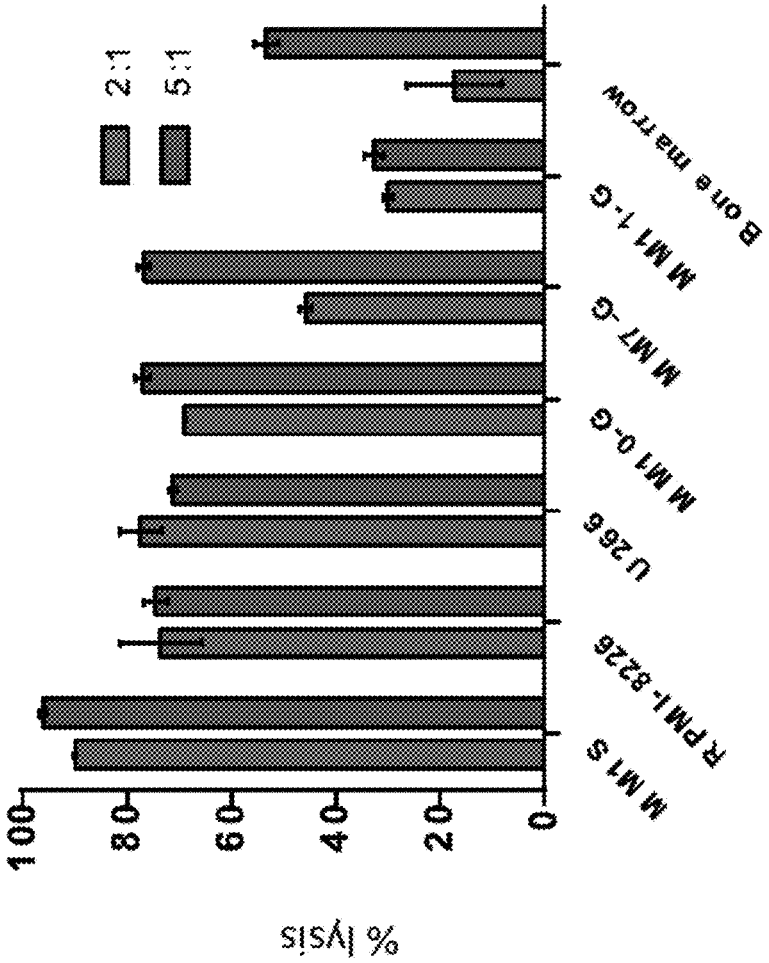

% lysis
100
80
60
40
20
0
2:1
5:1
M M1 S
RPMI-8226
U266
M M1 0-G
M MT -G
M M1 1-G
Bone marrow

FIGURE 26D

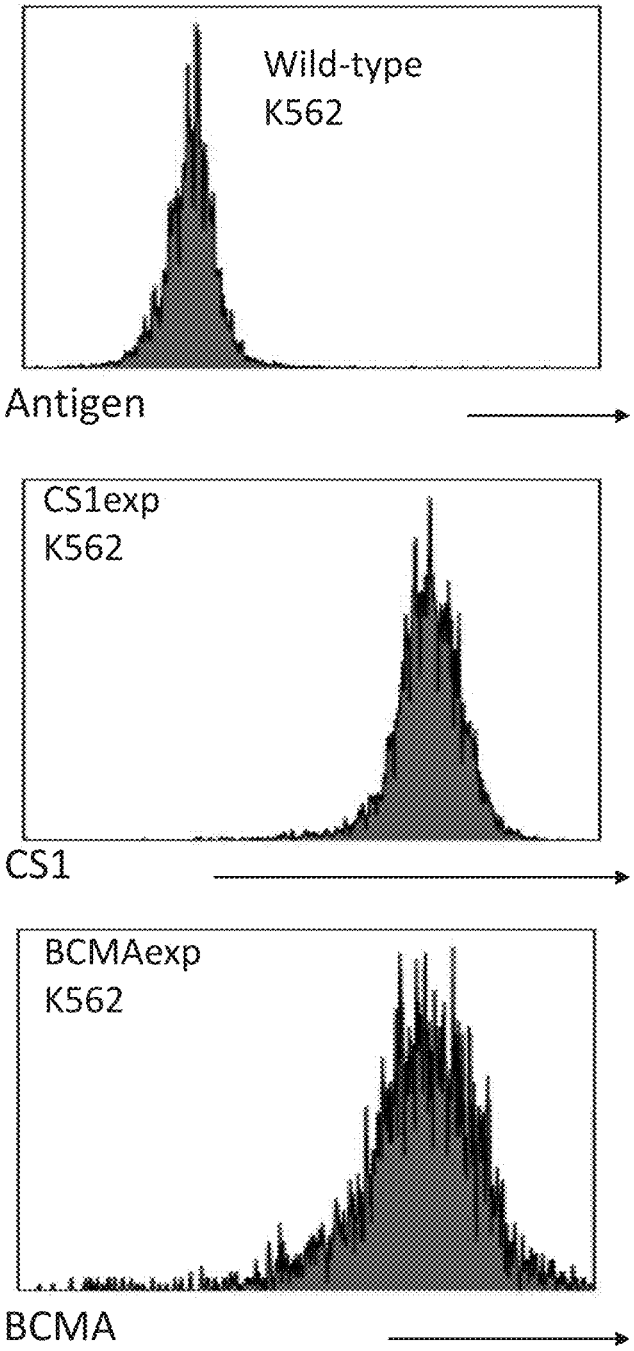
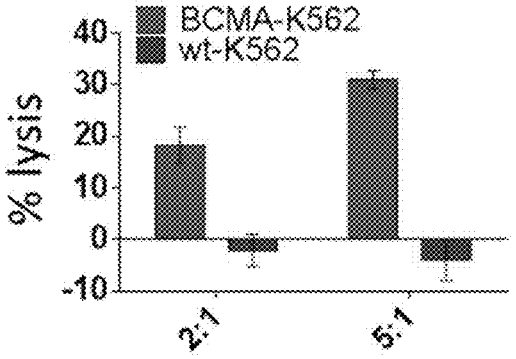
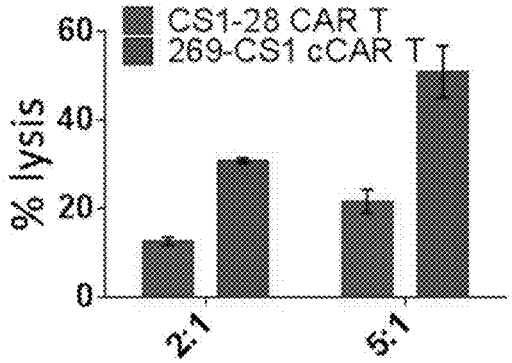


FIGURE 27A

Short-term BCMA depletion by BC1cCAR T-cells



Short-term CS1 depletion by BC1cCAR T vs. CS1 CAR T



Anti-CS1 activity of BC1cCAR T against CS1^{dim} NK-92 cells

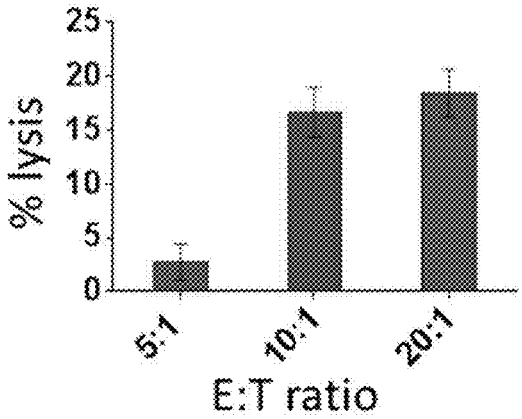


FIGURE 27B

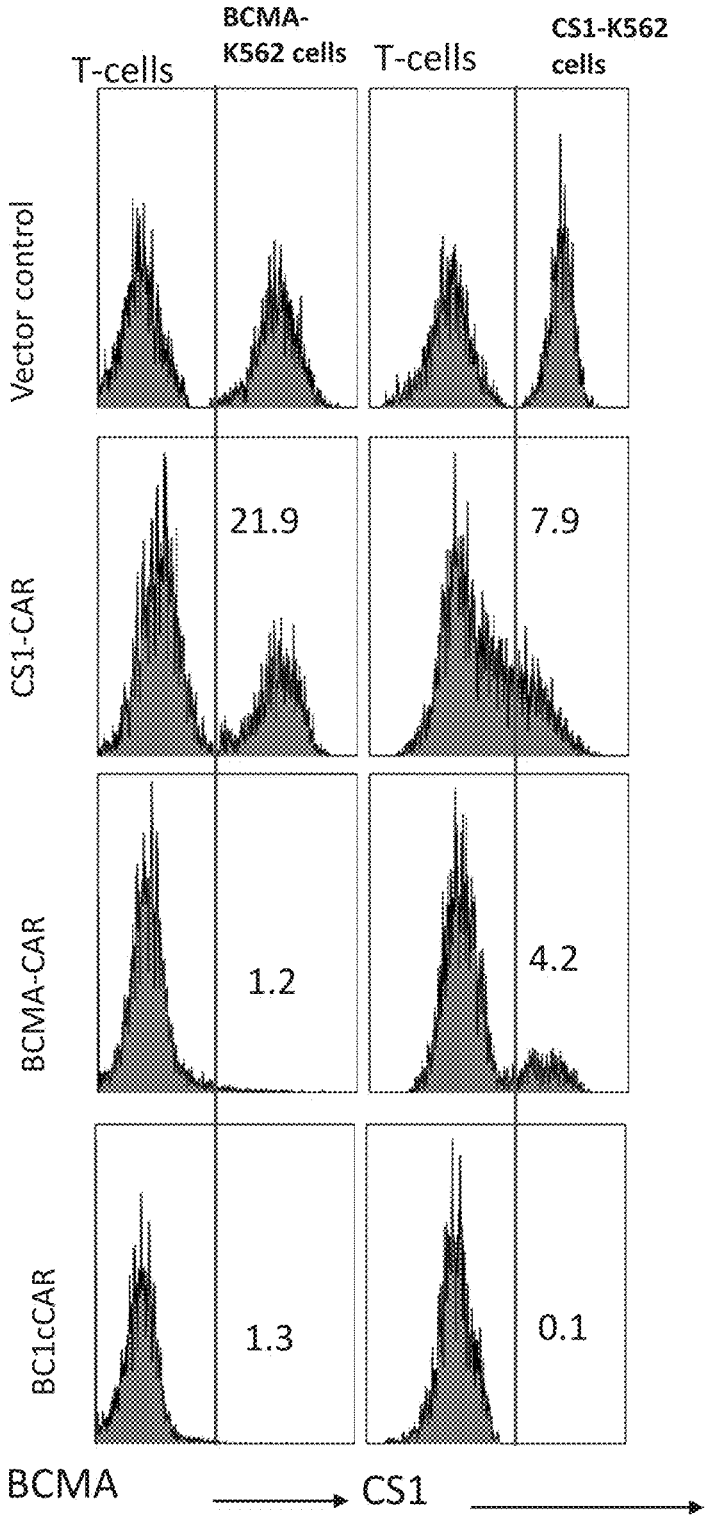
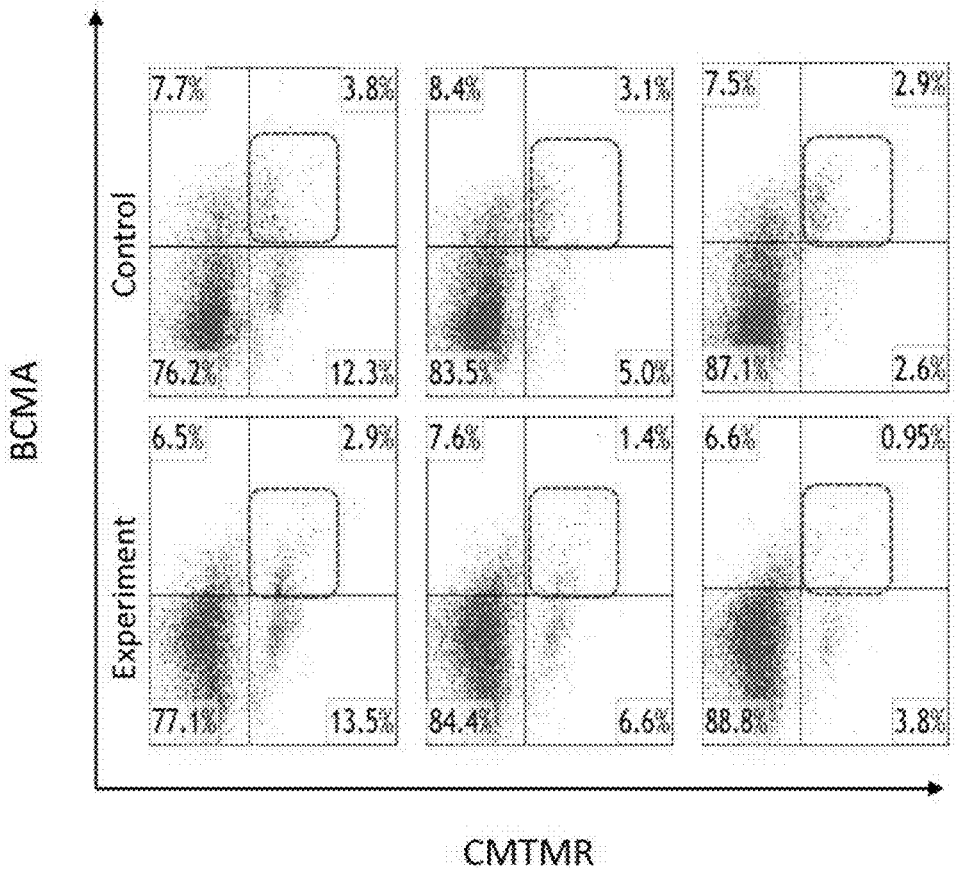

T-cells
BCMA-K562 cells
T-cells
CS1-K562 cells
Vector control
CS1-CAR
21.9
7.9
BCMA-CAR
1.2
4.2
BC1cCAR
1.3
0.1
BCMA
CS1

FIGURE 27C


BCMA
Control
Experiment
7.7%
3.8%
76.2%
12.3%
8.4%
3.1%
83.5%
5.0%
7.5%
2.9%
87.1%
2.6%
6.5%
2.9%
77.1%
13.5%
7.6%
1.4%
84.4%
6.6%
6.6%
0.95%
88.8%
3.8%
CMTMR

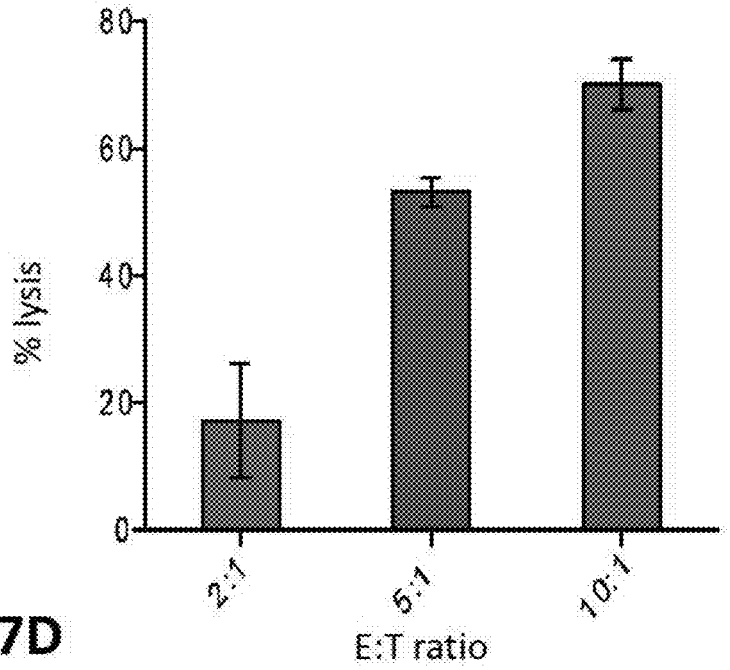

% lysis
80
60
40
20
0
2:1
5:1
10:1
E:T ratio

FIGURE 27D

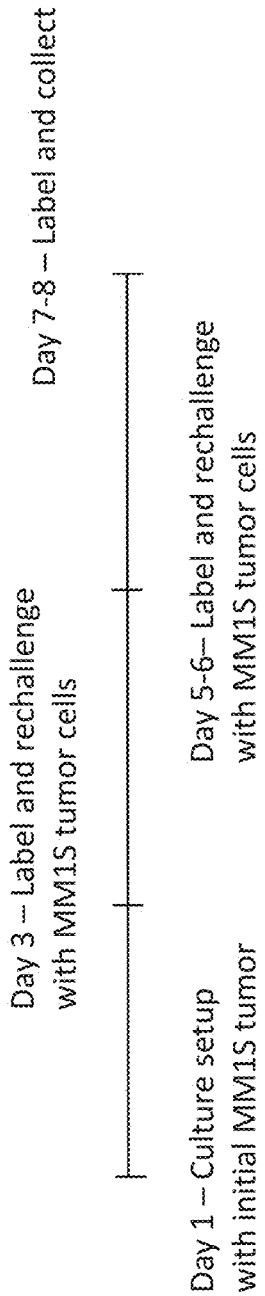

Day 1 – Culture setup
with initial MM1S tumor
Day 3 – Label and rechallenge
with MM1S tumor cells
Day 5-6– Label and rechallenge
with MM1S tumor cells
Day 7-8 – Label and collect

FIGURE 28A

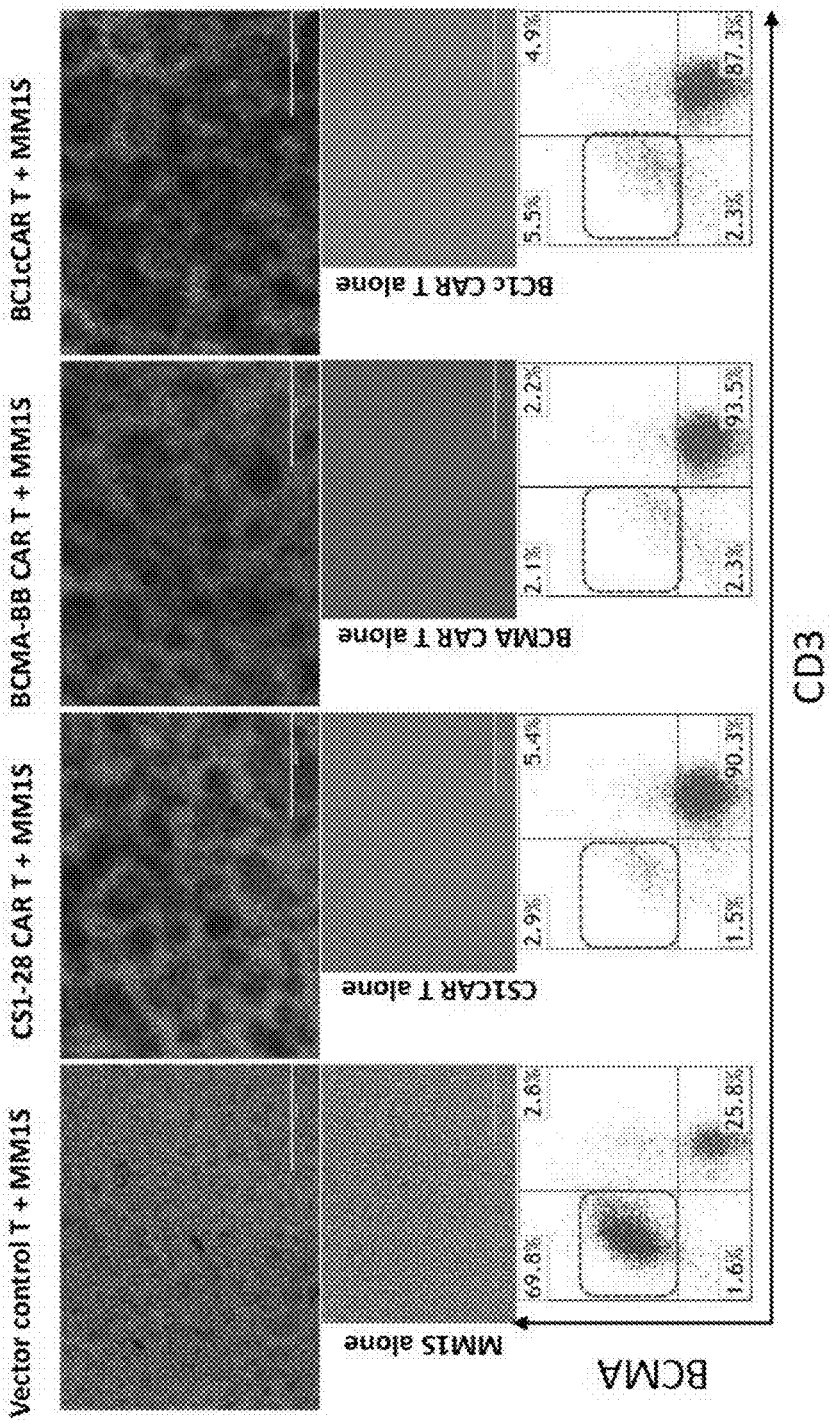

Vector control T + MM1S
CS1-28 CAR T + MM1S
BCMA-BB CAR T + MM1S
BC1cCAR T + MM1S
MM1S alone
CS1CAR T alone
BCMA CAR T alone
BC1c CAR T alone
69.8%
2.6%
1.6%
25.8%
2.9%
5.4%
1.5%
90.3%
2.1%
2.2%
2.3%
93.5%
5.5%
4.9%
2.3%
87.3%
BCMA
CD3

FIGURE 28B

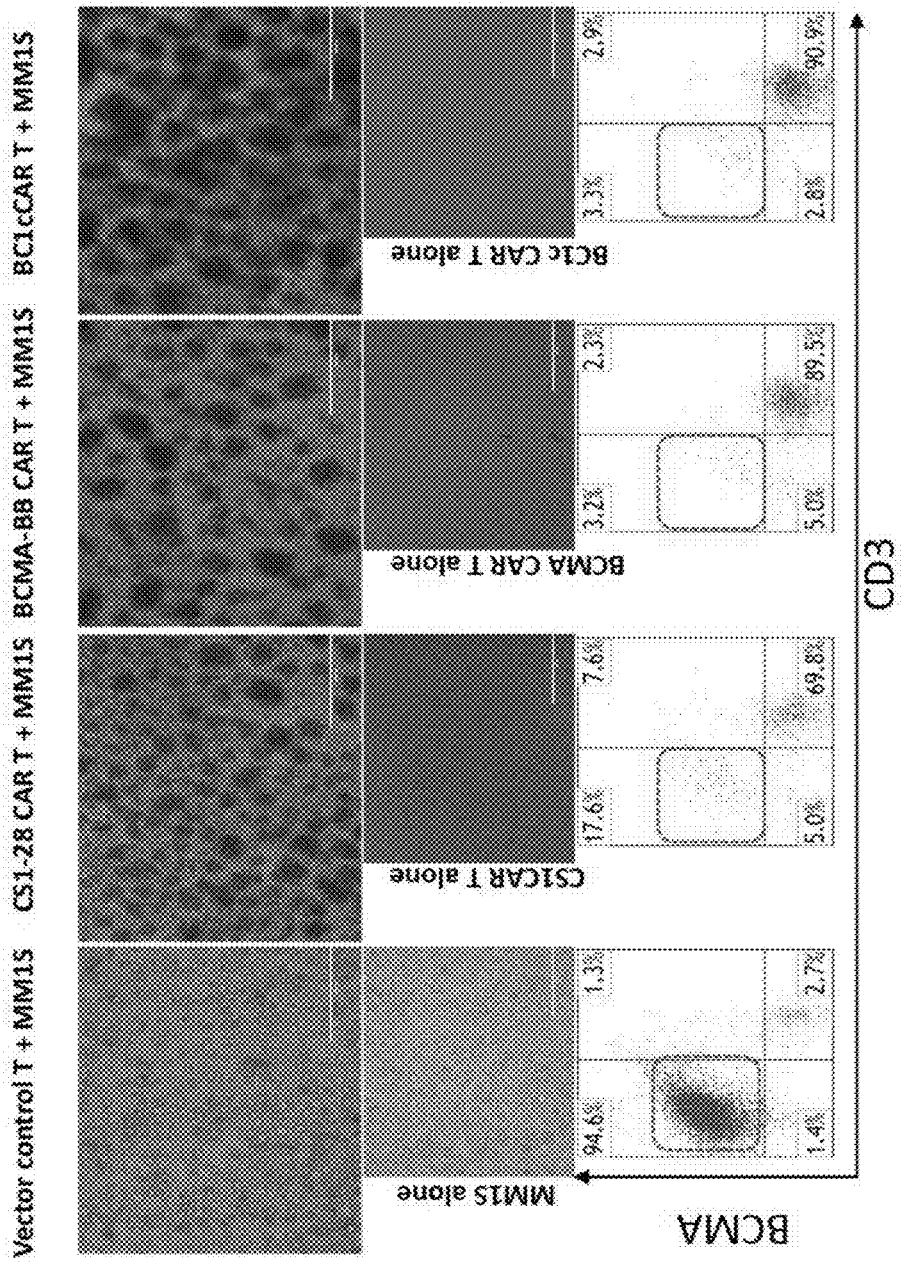

Vector control T + MM1S
CS1-28 CAR T + MM1S
BCMA-BB CAR T + MM1S
BC1cCAR T + MM1S
MM1S alone
CS1CAR T alone
BCMA CAR T alone
BC1c CAR T alone
94.6%
1.3%
1.4%
2.7%
17.6%
7.6%
5.0%
69.8%
3.2%
2.3%
5.0%
89.5%
3.3%
2.9%
2.8%
90.9%
BCMA
CD3

FIGURE 28C

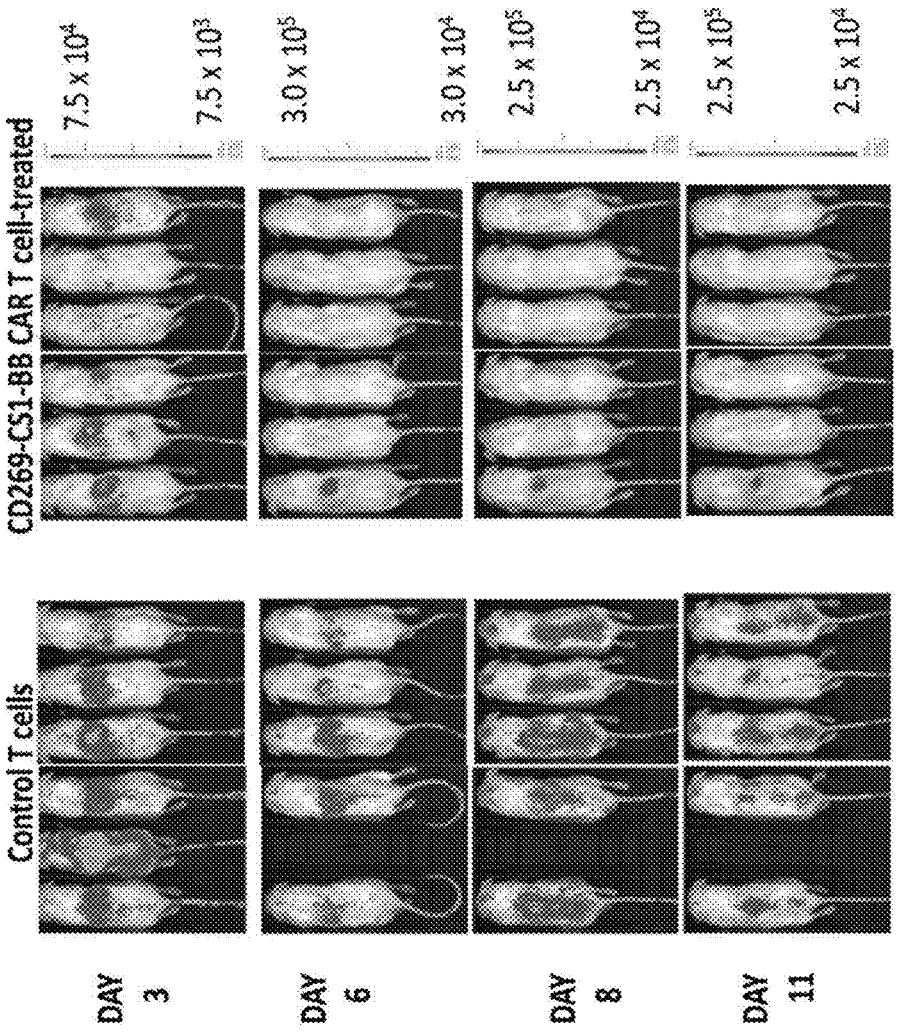

Control T cells
CD269-CS1-BB CAR T cell-treated
DAY 3
DAY 6
DAY 8
DAY 11
7.5 x 10^4
7.5 x 10^3
3.0 x 10^5
3.0 x 10^4
2.5 x 10^5
2.5 x 10^4
2.5 x 10^5
2.5 x 10^4

FIGURE 29A

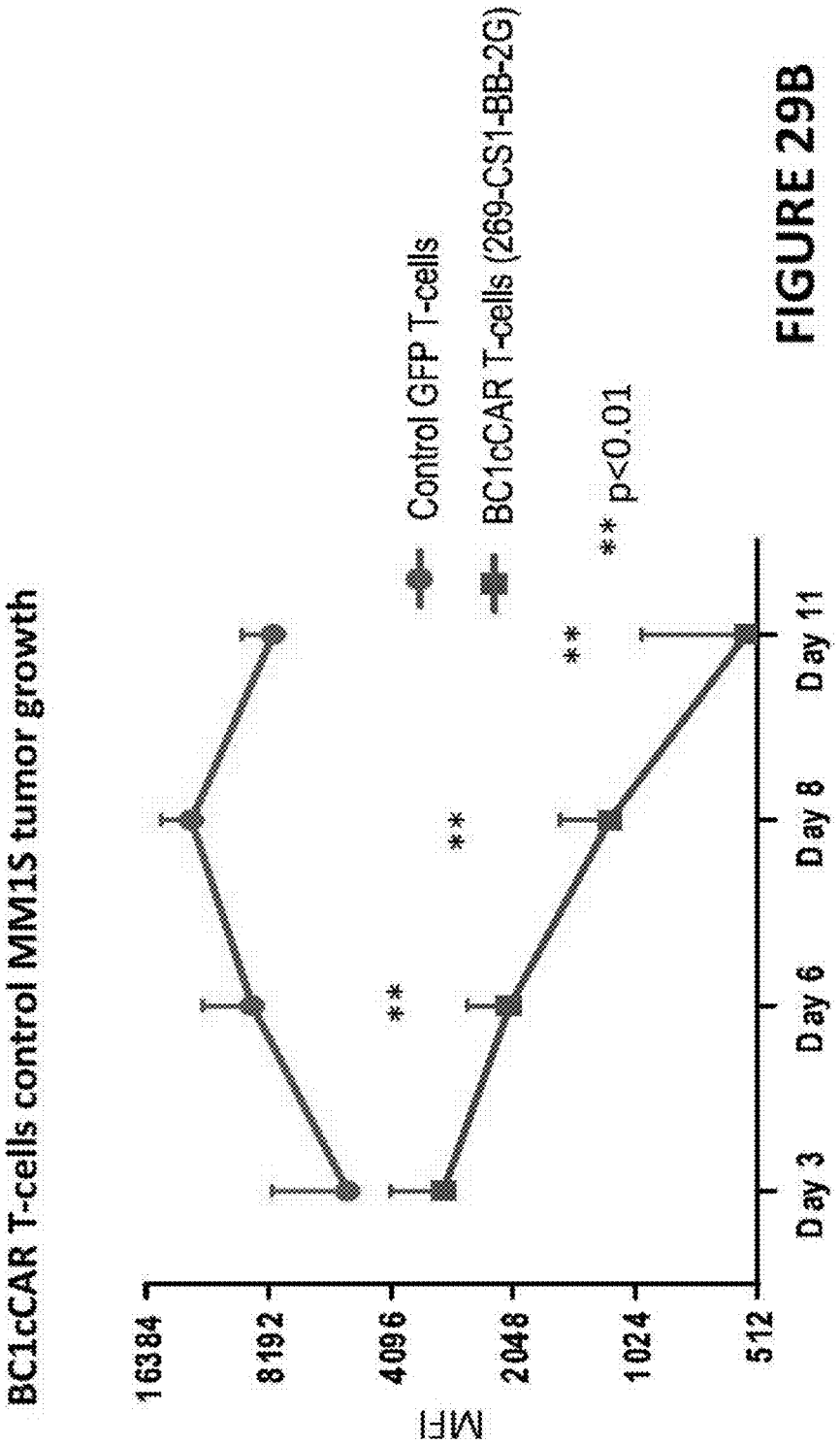

BC1cCAR T-cells control MM1S tumor growth
MFI
16384
8192
4096
2048
1024
512
Day 3
Day 6
Day 8
Day 11
**
**
**
Control GFP T-cells
BC1cCAR T-cells (269-CS1-BB-2G)
** p<0.01

FIGURE 29B

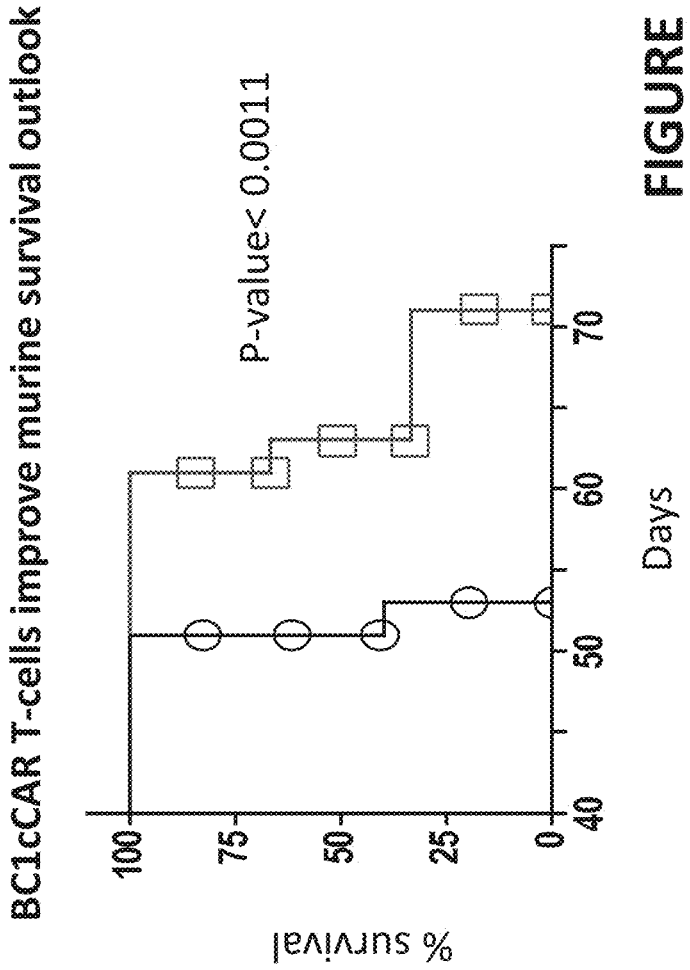

BC1cCAR T-cells improve murine survival outlook
% survival
100
75
50
25
0
40
50
60
70
Days
P-value< 0.0011

FIGURE 29C

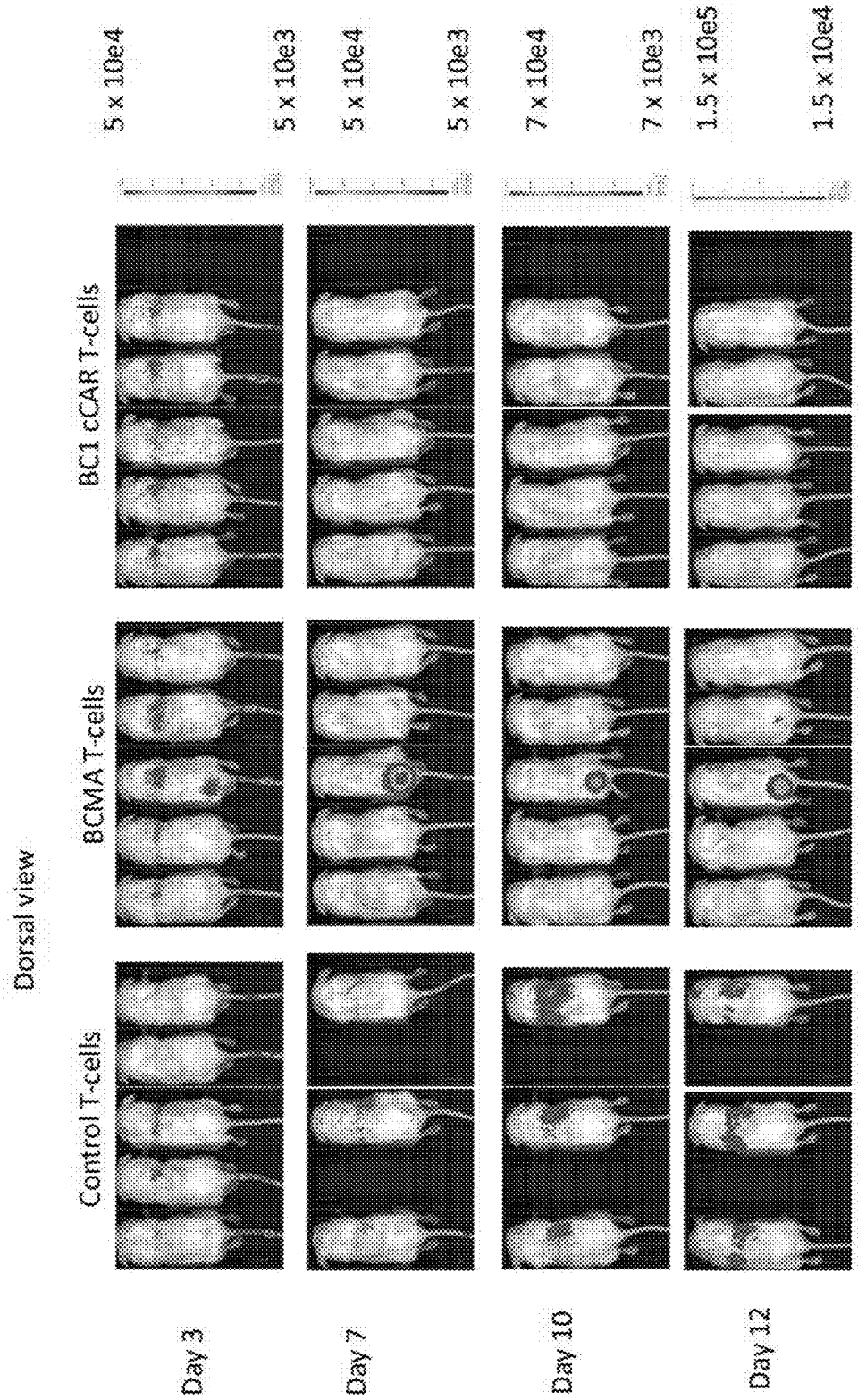

Dorsal view
Control T-cells
BCMA T-cells
BC1 cCAR T-cells
Day 3
Day 7
Day 10
Day 12
5 x 10e4
5 x 10e3
5 x 10e4
5 x 10e3
7 x 10e4
7 x 10e3
1.5 x 10e5
1.5 x 10e4

FIGURE 29D

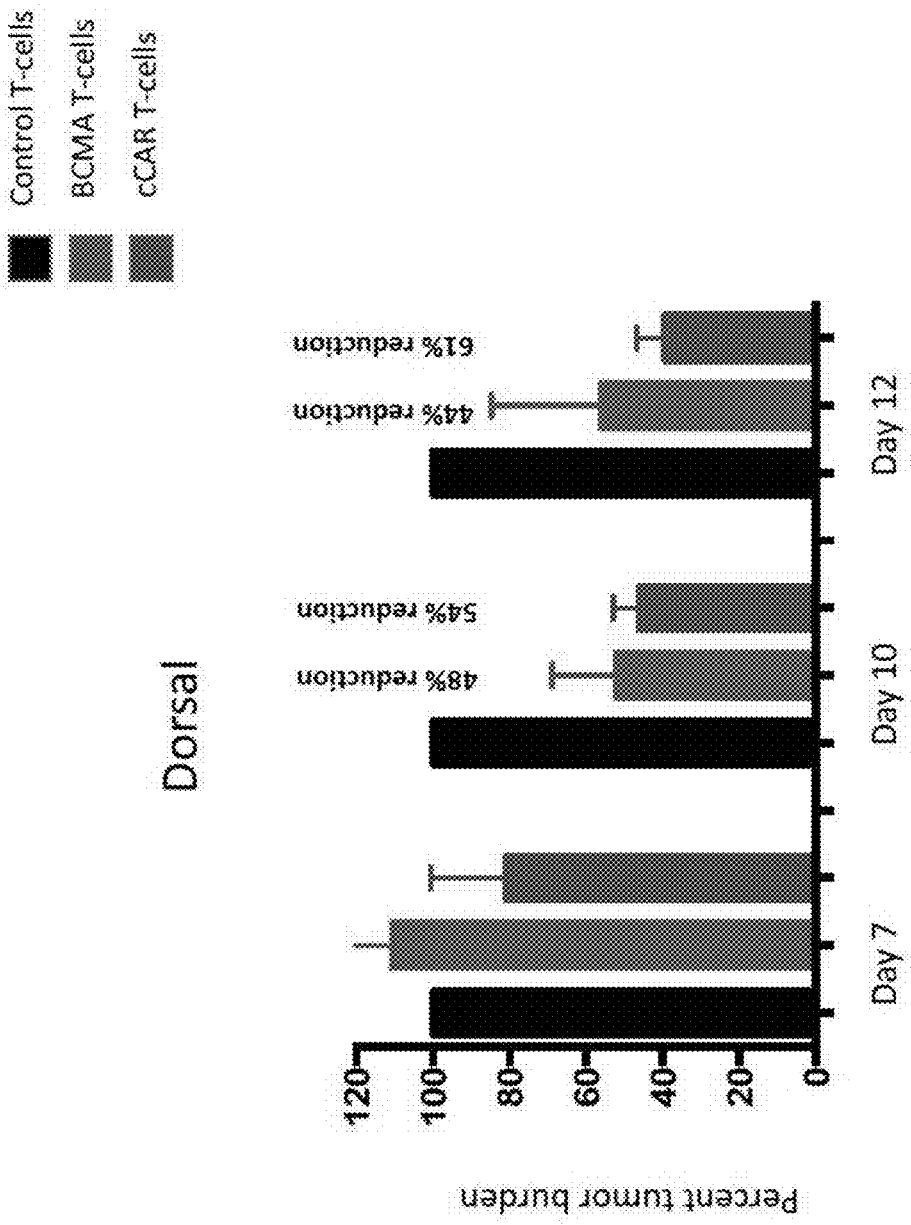

Control T-cells
BCMA T-cells
cCAR T-cells
Dorsal
Percent tumor burden
120
100
80
60
40
20
0
Day 7
Day 10
Day 12
48% reduction
54% reduction
44% reduction
61% reduction

FIGURE 29E

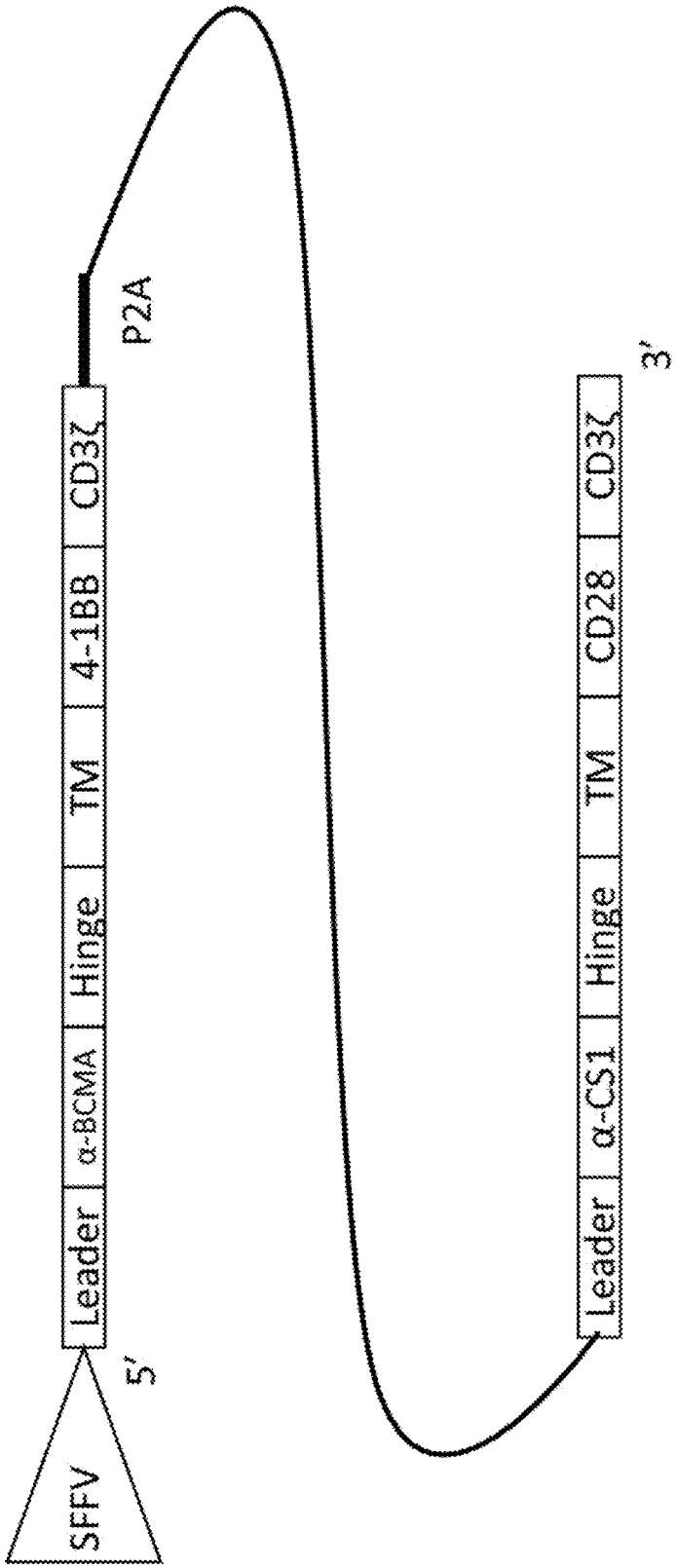
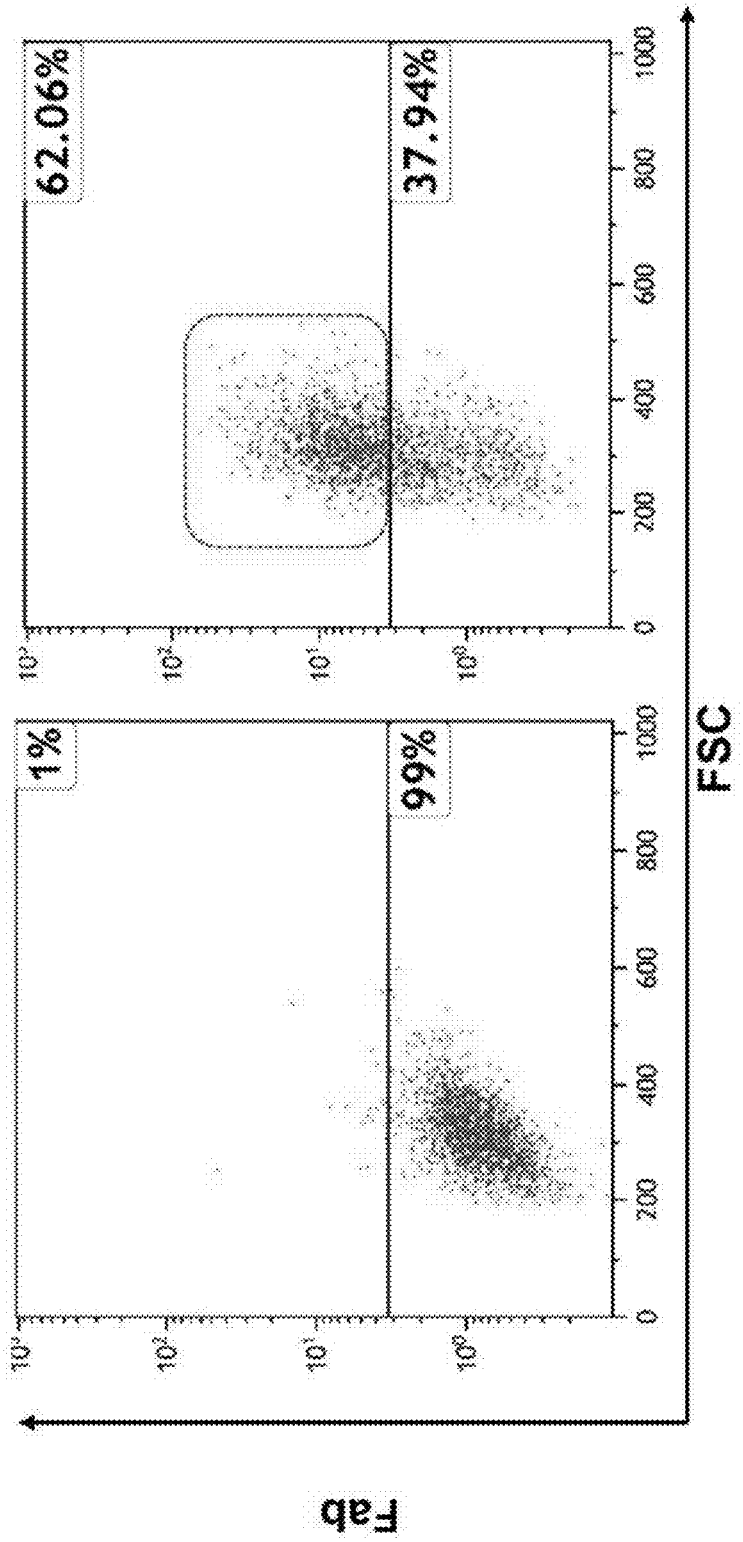

SFFV
5'
Leader
α-BCMA
Hinge
TM
4-1BB
CD3ζ
P2A
Leader
α-CS1
Hinge
TM
CD28
CD3ζ
3'

FIGURE 30A

FIGURE 30B



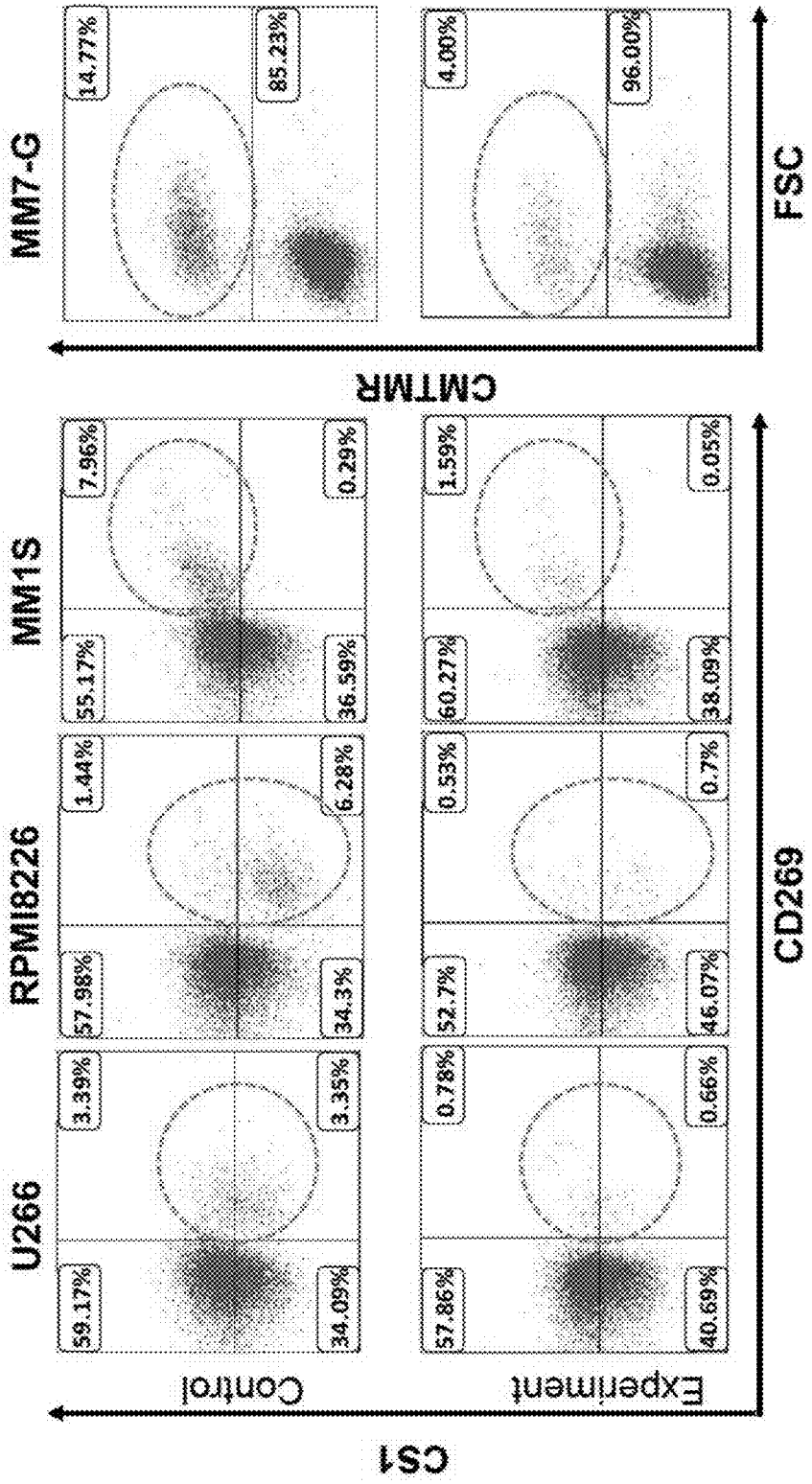

U266
RPMI8226
MM1S
MM7-G
Control
Experiment
CS1
CD269
CMTMR
FSC
59.17%
3.39%
57.98%
1.44%
55.17%
7.96%
14.77%
34.09%
3.35%
34.3%
6.28%
36.59%
0.29%
85.23%
57.86%
0.78%
52.7%
0.53%
60.27%
1.59%
4.00%
40.69%
0.66%
46.07%
0.7%
38.09%
0.05%
96.00%

FIGURE 31A

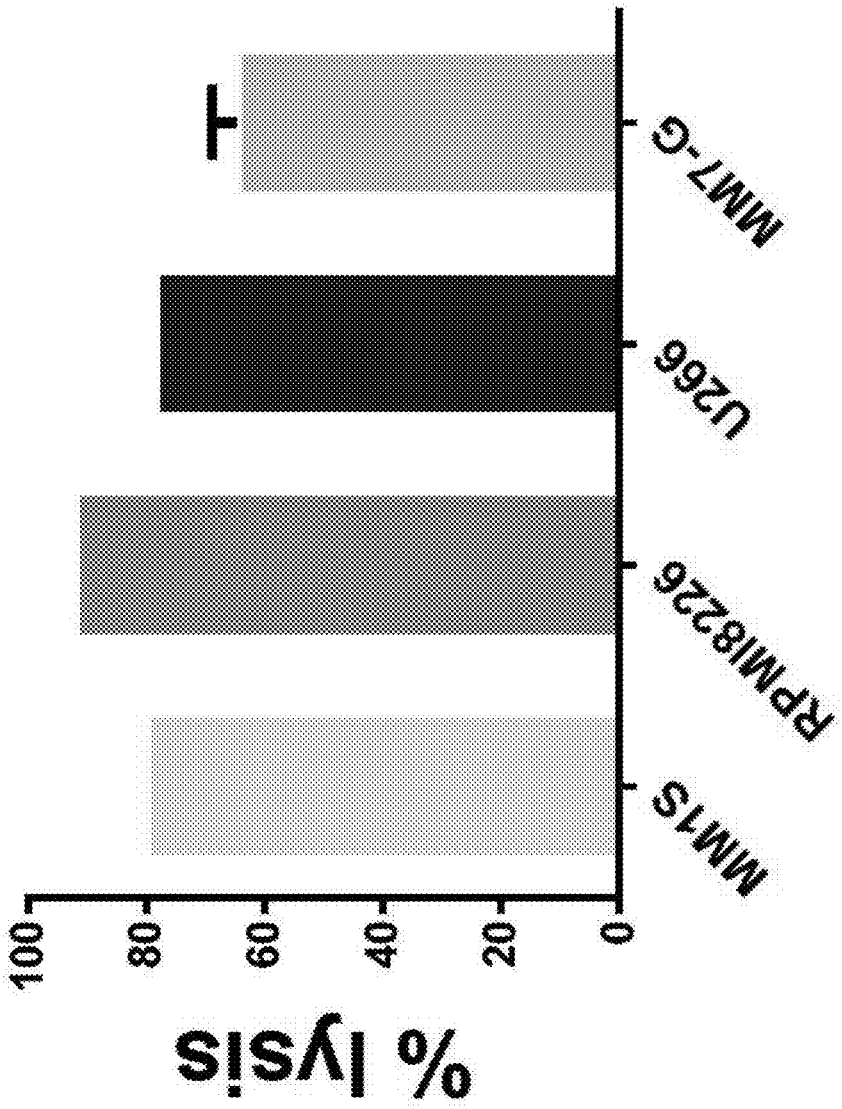
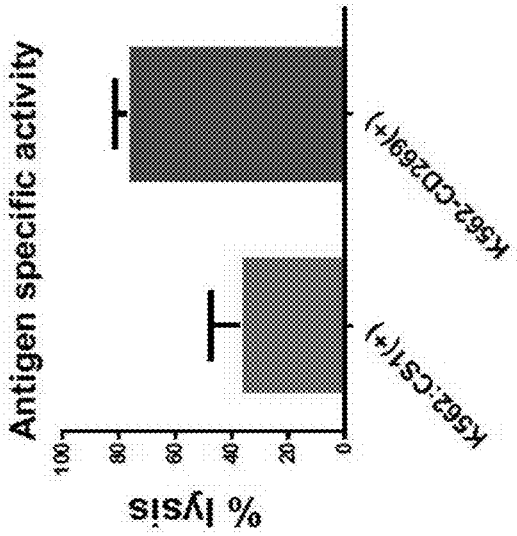


FIGURE 31B


Antigen specific activity
% lysis
100
80
60
40
20
0
K562-CS1(+)
K562-CD269(+)

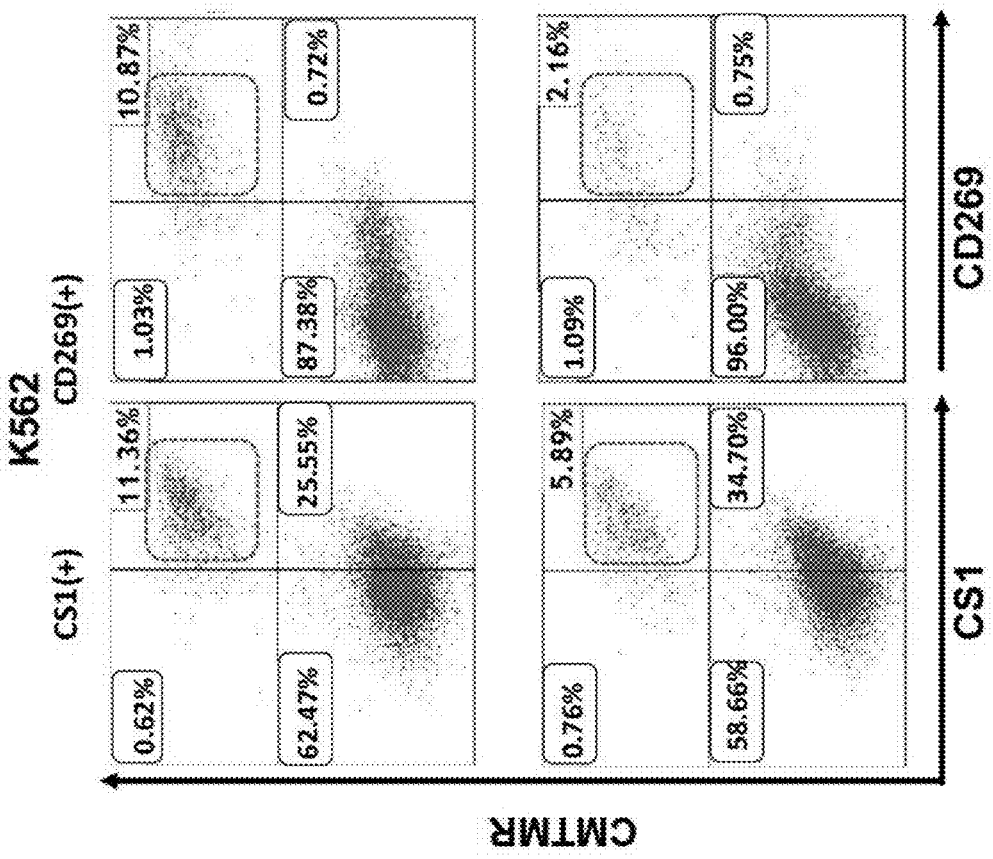

K562
CS1(+)
CD269(+)
0.62%
11.36%
1.03%
10.87%
62.47%
25.55%
87.38%
0.72%
0.76%
5.89%
1.09%
2.16%
58.66%
34.70%
96.00%
0.75%
CS1
CD269
CMTMR

FIGURE 31C

FIGURE 32A

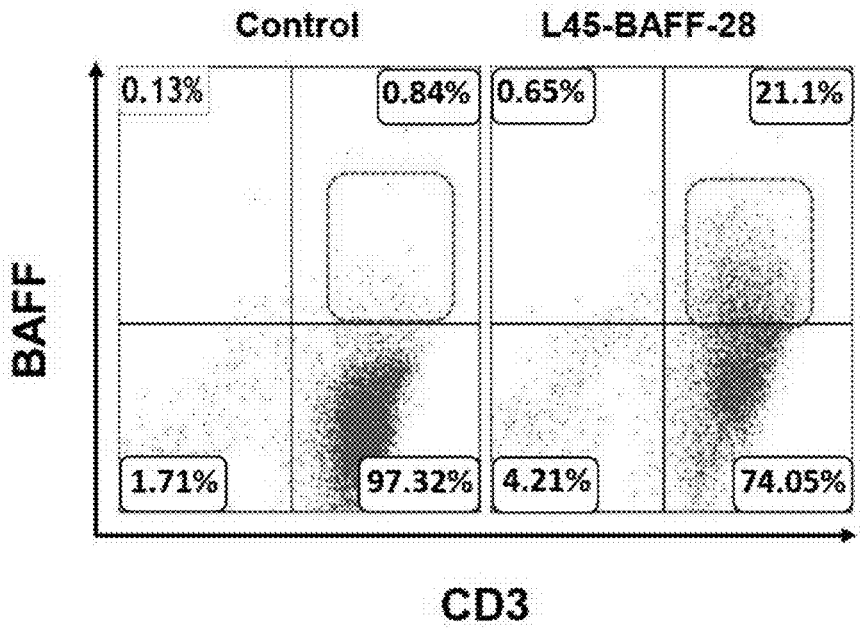
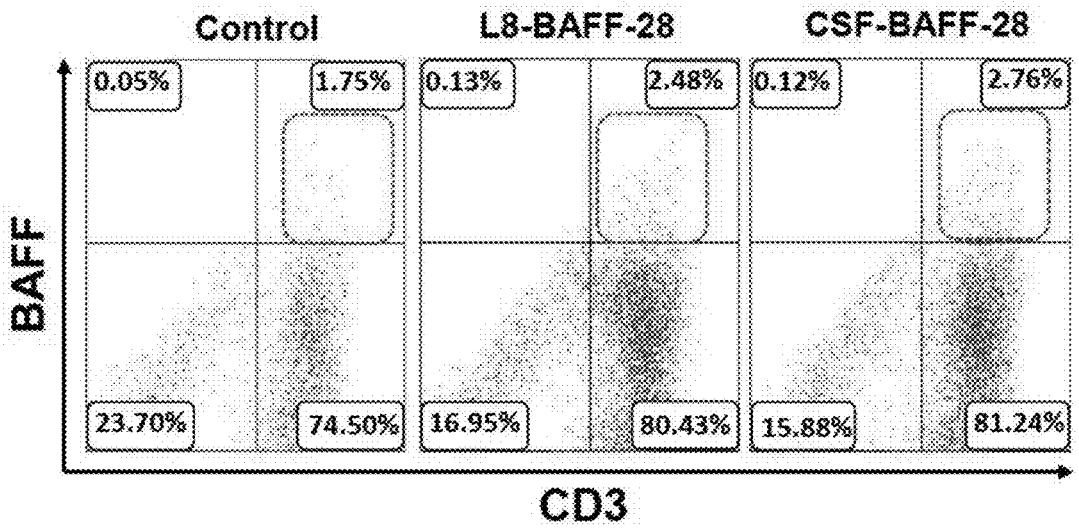


FIGURE 32B



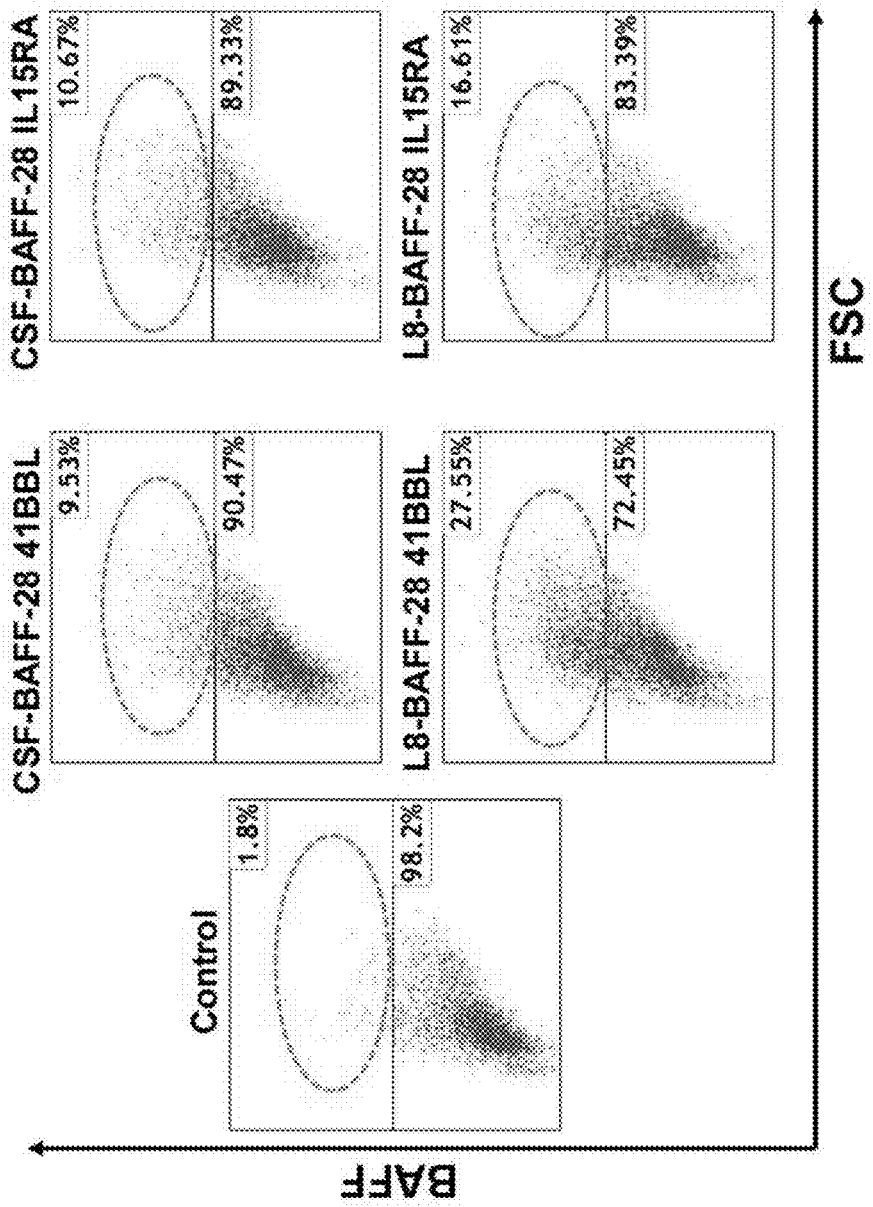

Control
1.8%
98.2%
CSF-BAFF-28 41BBL
9.53%
90.47%
L8-BAFF-28 41BBL
27.55%
72.45%
CSF-BAFF-28 IL15RA
10.67%
89.33%
L8-BAFF-28 IL15RA
16.61%
83.39%
BAFF
FSC

FIGURE 32C

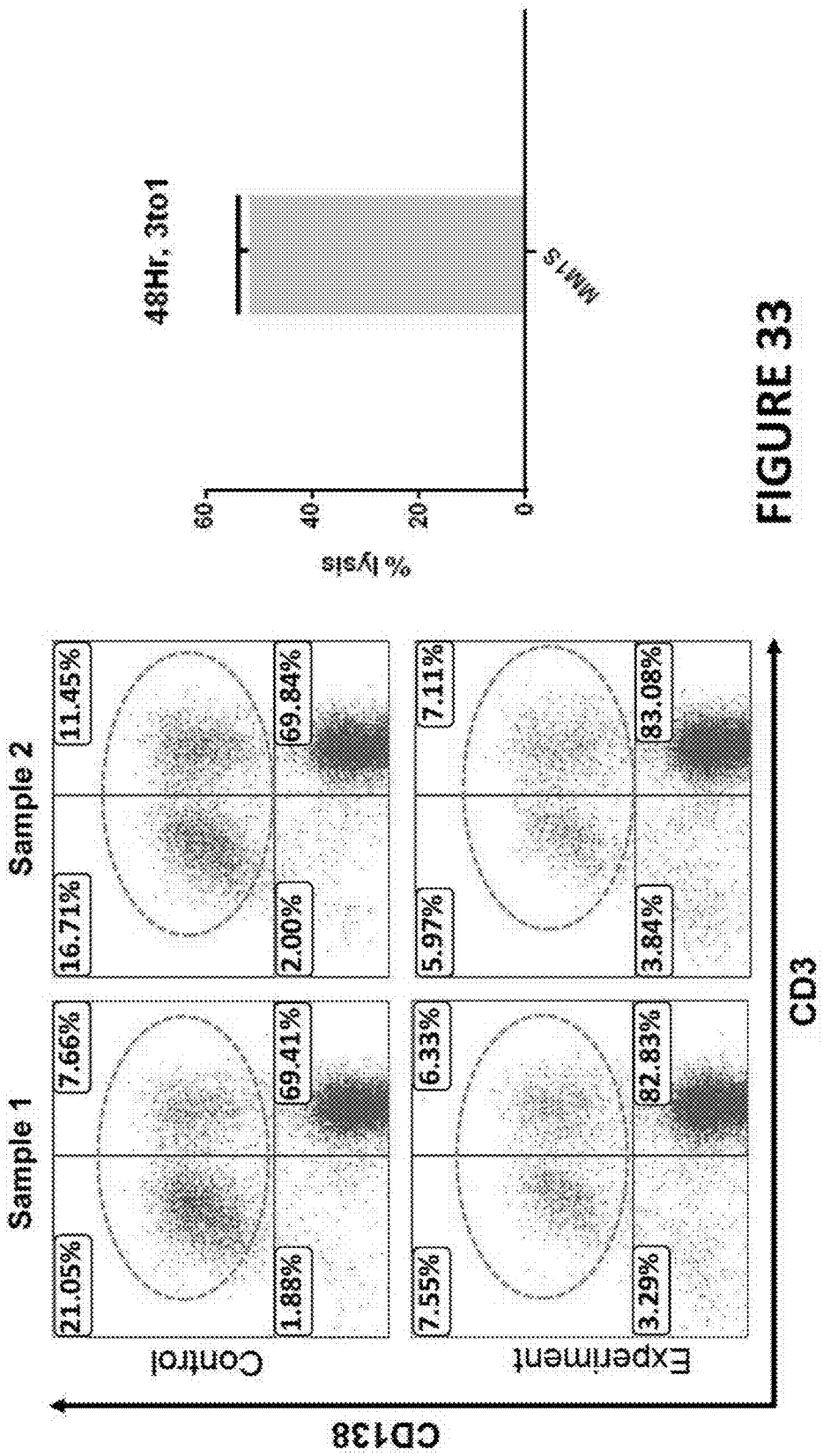

48Hr, 3to1
% lysis
60
40
20
0
MM1S
Sample 1
Sample 2
Control
Experiment
21.05%
7.66%
1.88%
69.41%
16.71%
11.45%
2.00%
69.84%
7.55%
6.33%
3.29%
82.83%
5.97%
7.11%
3.84%
83.08%
CD138
CD3

FIGURE 33

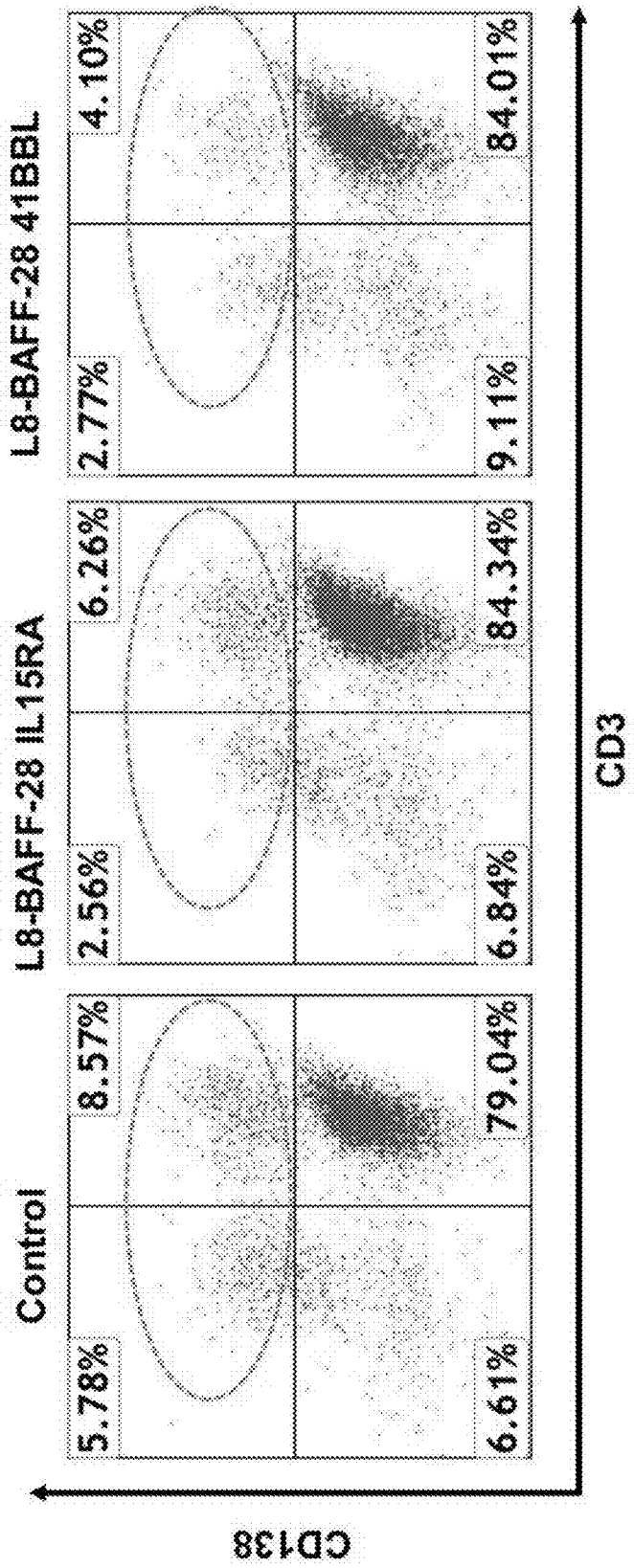
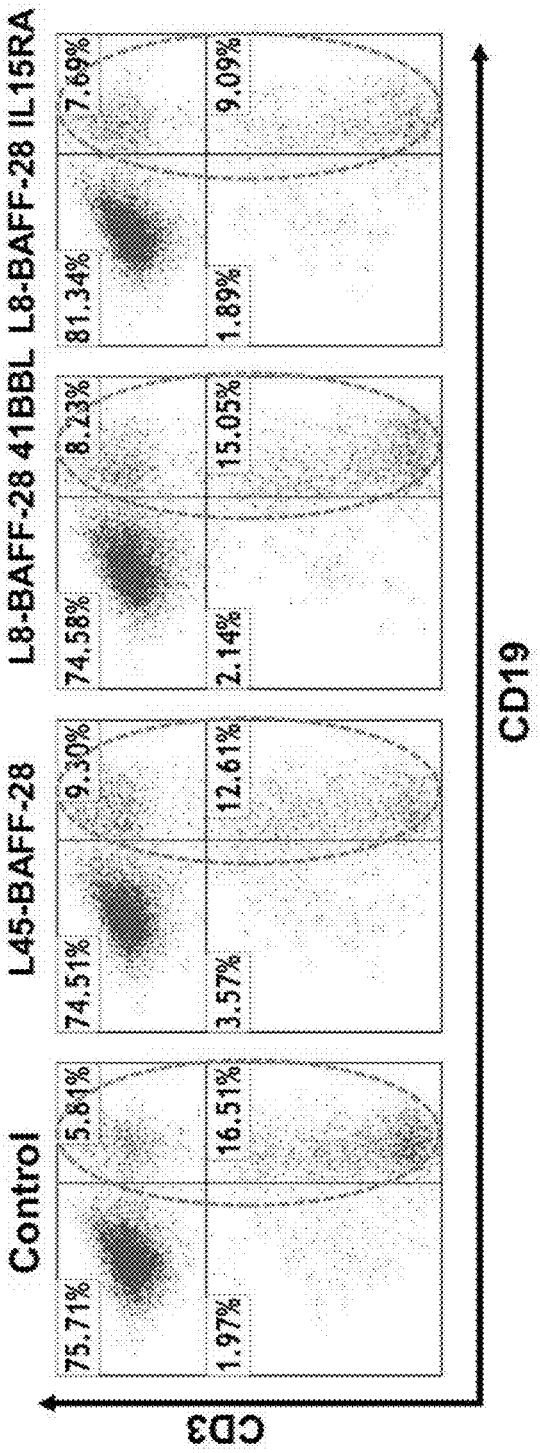

Control
L8-BAFF-28 IL15RA
L8-BAFF-28 41BBL
5.78%
8.57%
6.61%
79.04%
2.56%
6.26%
6.84%
84.34%
2.77%
4.10%
9.11%
84.01%
CD3
CD138

FIGURE 34A

FIGURE 34B


Control
L45-BAFF-28
L8-BAFF-28 41BBL
L8-BAFF-28 IL15RA
75.71%
5.81%
1.97%
16.51%
74.51%
9.30%
3.57%
12.61%
74.58%
8.23%
2.14%
15.05%
81.34%
7.69%
1.89%
9.09%
CD3
CD19

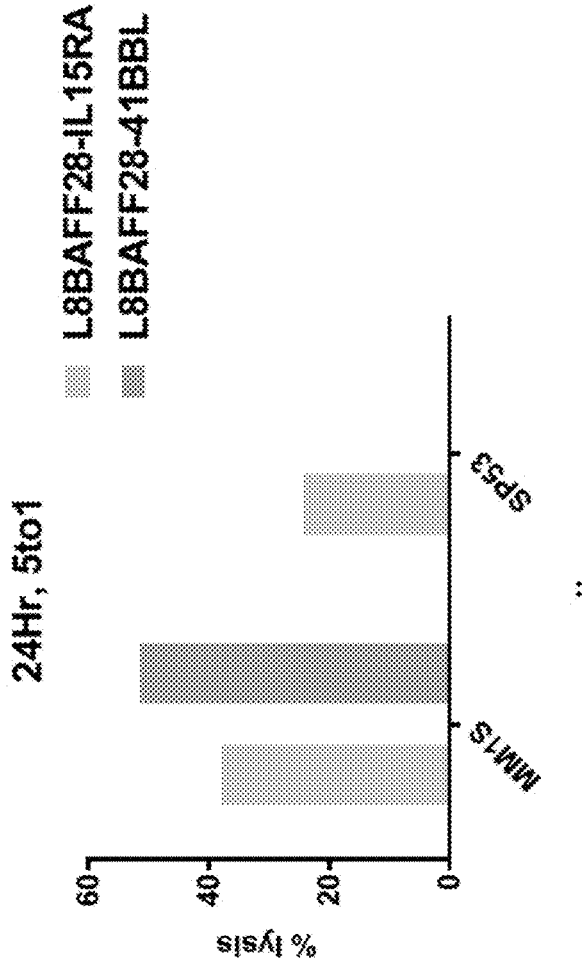
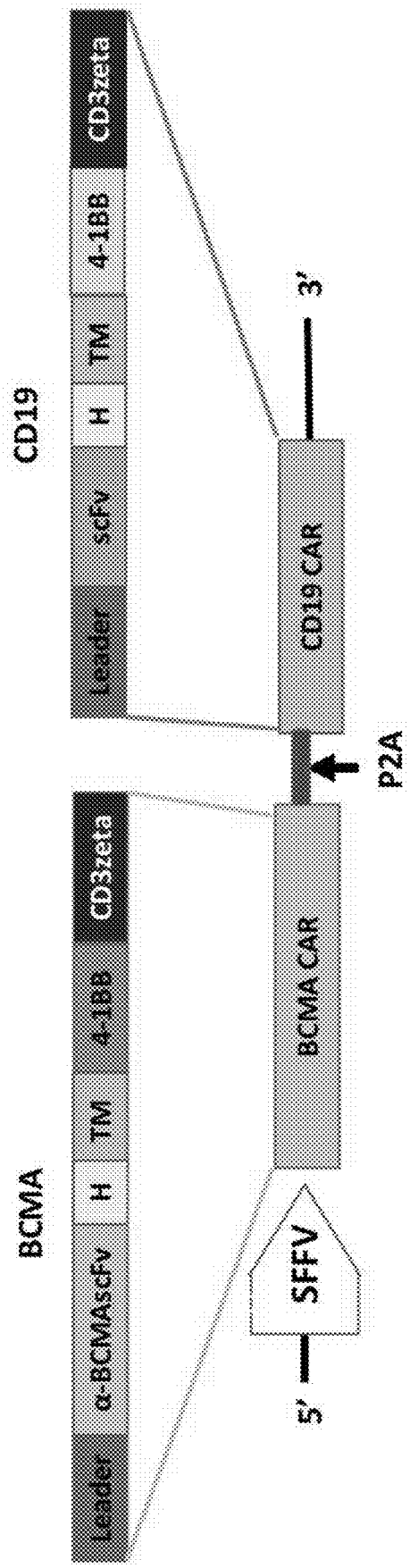
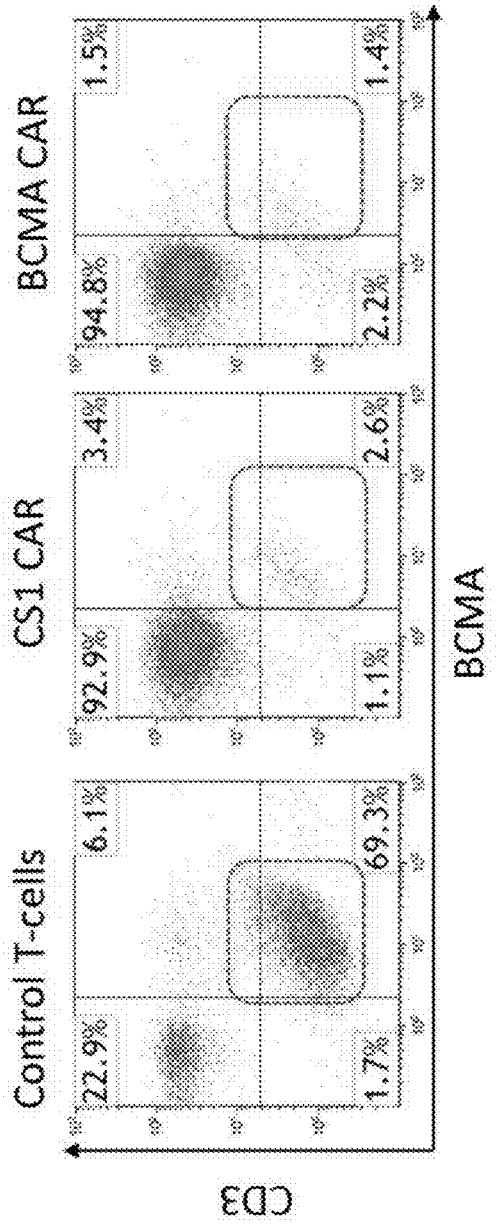
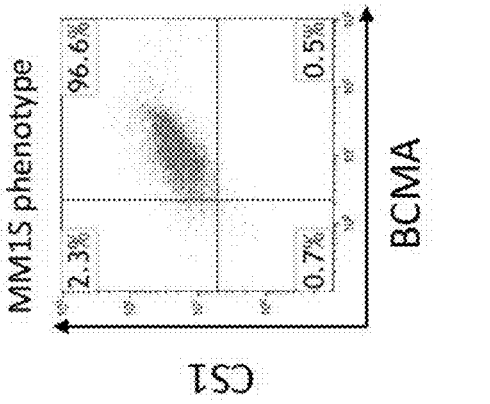

24Hr, 5to1
L8BAFF28-IL15RA
L8BAFF28-41BBL
% lysis
60
40
20
0
MM1S
SP53

FIGURE 34C

FIGURE 35


CD19
Leader
scFv
H
TM
4-1BB
CD3zeta
3'
CD19 CAR
P2A
BCMA
Leader
α-BCMAscFv
H
TM
4-1BB
CD3zeta
BCMA CAR
SFFV
5'


Control T-cells
CS1 CAR
BCMA CAR
22.9%
6.1%
1.7%
69.3%
92.9%
3.4%
1.1%
2.6%
94.8%
1.5%
2.2%
1.4%
CD3
BCMA


CARs + MM1S summary
%lysis
100
75
50
25
0
CS1 CAR
BCMA CAR

MM1S phenotype
2.3%
96.6%
0.7%
0.5%
CS1
BCMA

FIGURE 36A

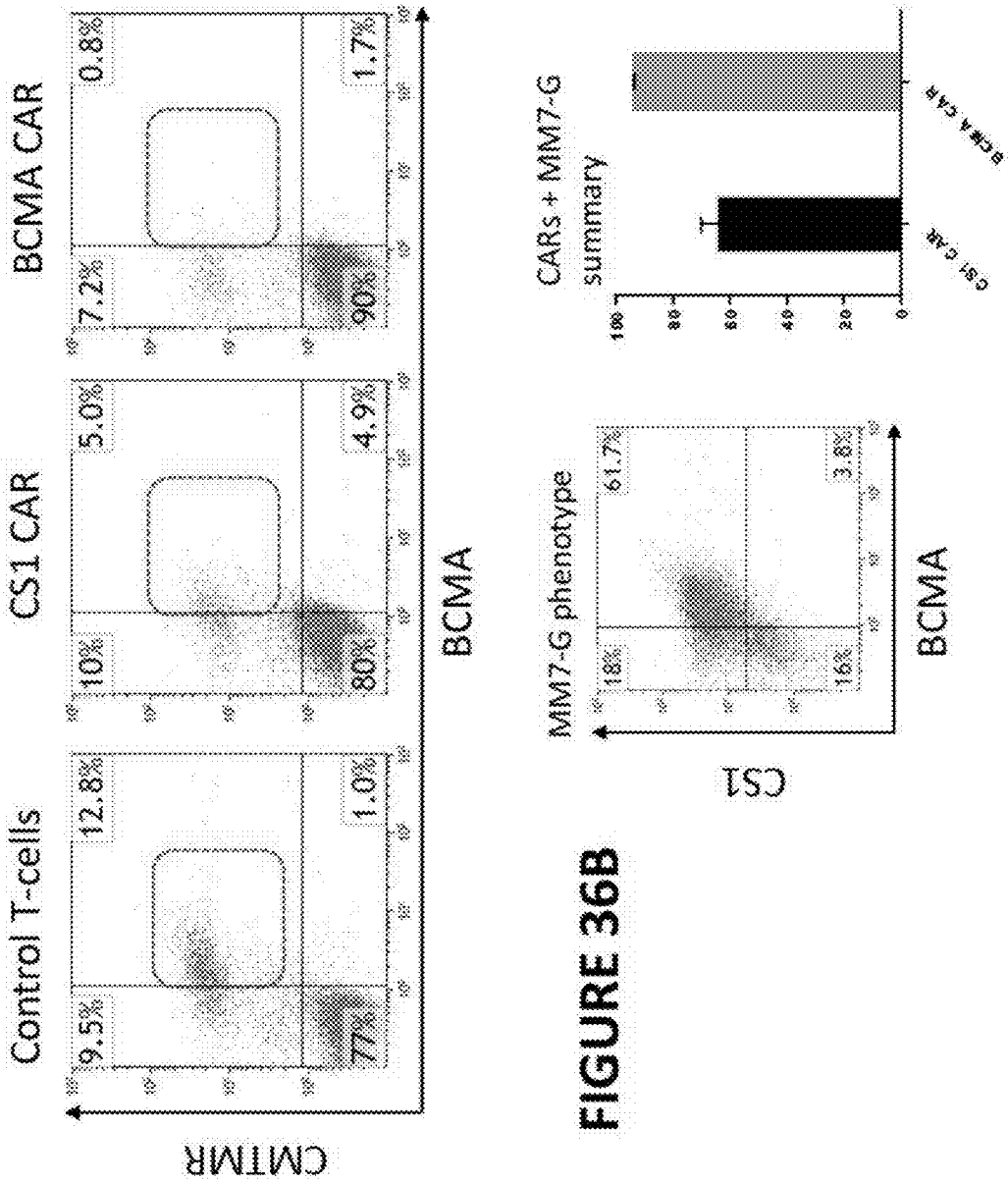

Control T-cells
CS1 CAR
BCMA CAR
9.5%
12.8%
77%
1.0%
10%
5.0%
80%
4.9%
7.2%
0.8%
90%
1.7%
BCMA
CMTMR
MM7-G phenotype
18%
61.7%
16%
3.8%
BCMA
CS1
CARs + MM7-G summary
CS1 CAR
BCMA CAR

FIGURE 36B

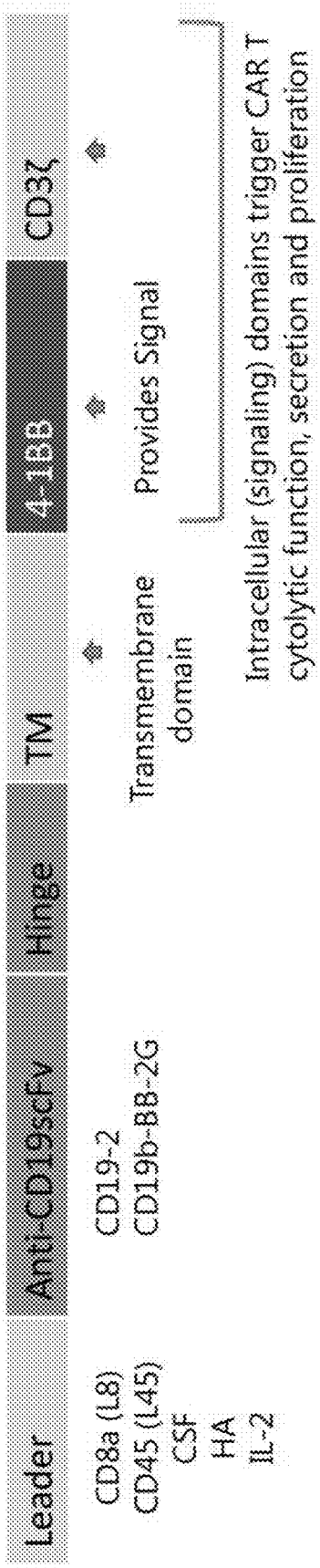

Leader
CD8a (L8)
CD45 (L45)
CSF
HA
IL-2
Anti-CD19scFv
CD19-2
CD19b-BB-2G
Hinge
TM
Transmembrane domain
4-1BB
Provides Signal
CD3ζ
Intracellular (signaling) domains trigger CAR T cytolytic function, secretion and proliferation

FIGURE 37A

FIGURE 37B

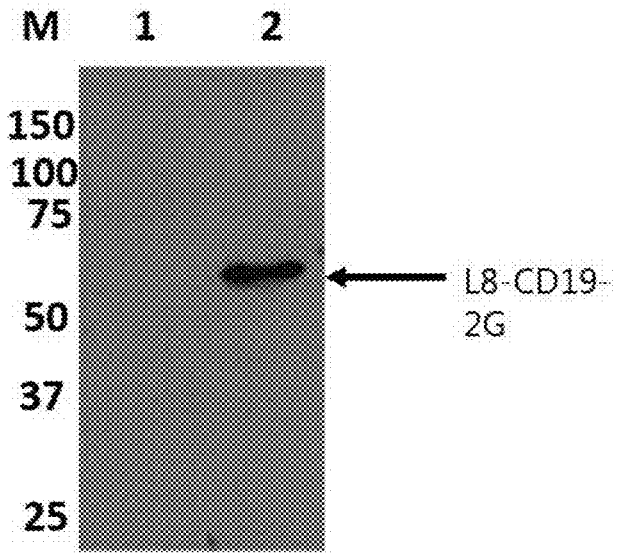


FIGURE 37C

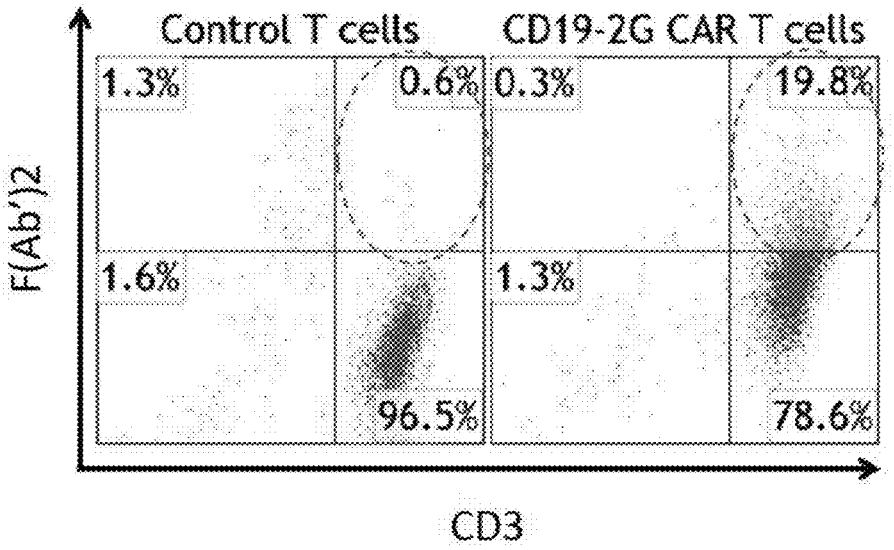


FIGURE 38A

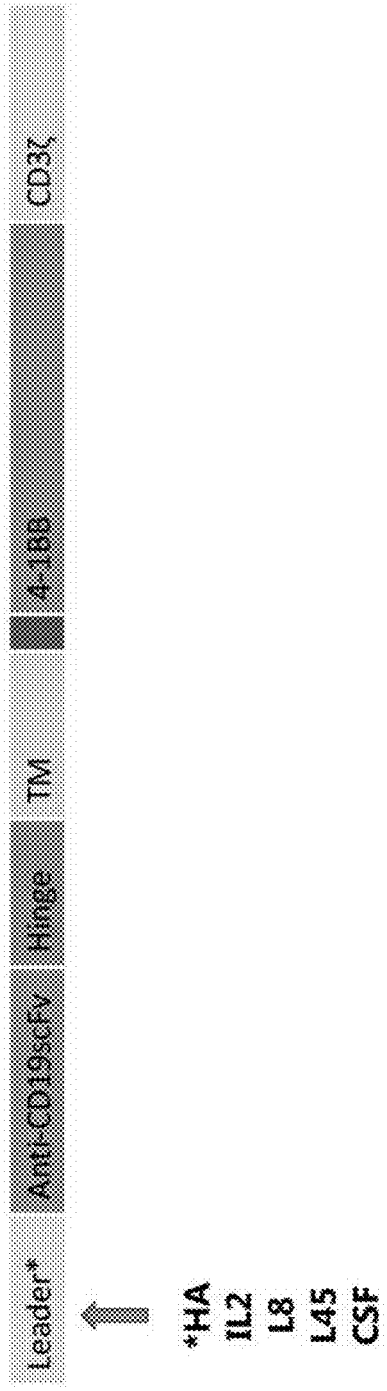


FIGURE 38B

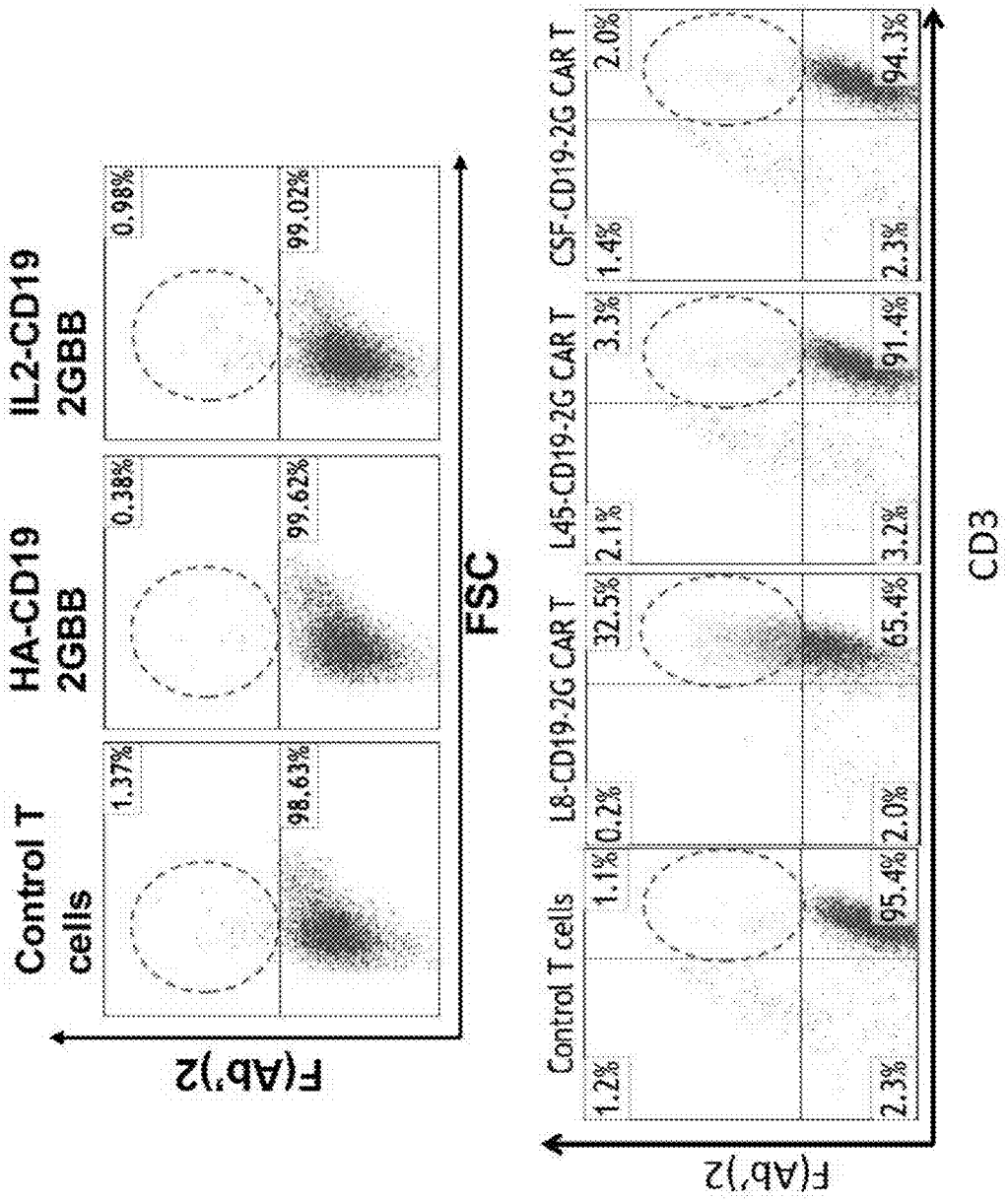

Control T cells
HA-CD19 2GBB
IL2-CD19 2GBB
1.37%
98.63%
0.38%
99.62%
0.98%
99.02%
F(Ab')2
FSC
Control T cells
L8-CD19-2G CAR T
L45-CD19-2G CAR T
CSF-CD19-2G CAR T
1.2%
2.3%
1.1%
95.4%
0.2%
2.0%
32.5%
65.4%
2.1%
3.2%
3.3%
91.4%
1.4%
2.3%
2.0%
94.3%
F(Ab')2
CD3

FIGURE 39A

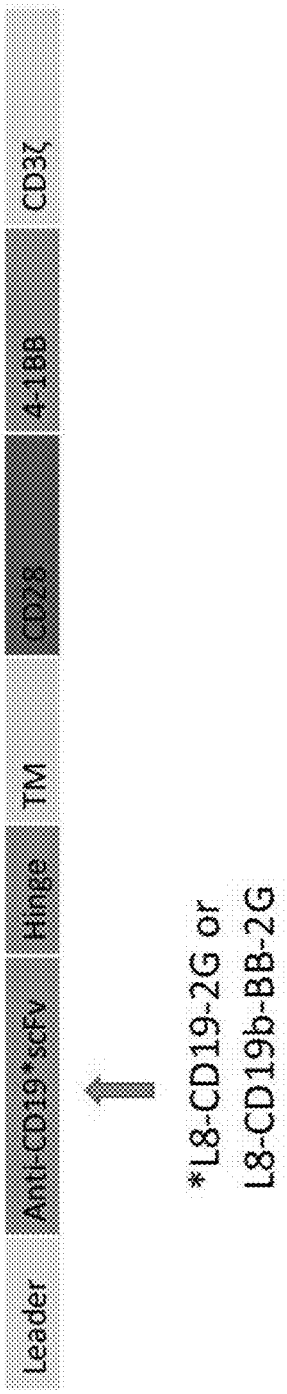


FIGURE 39B

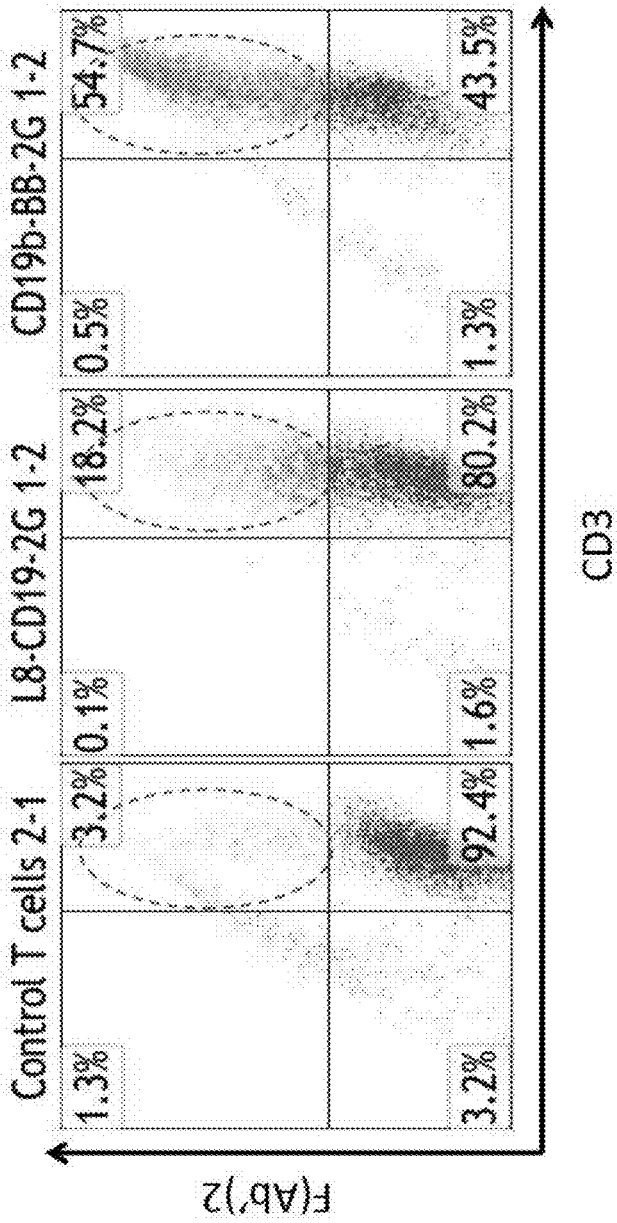
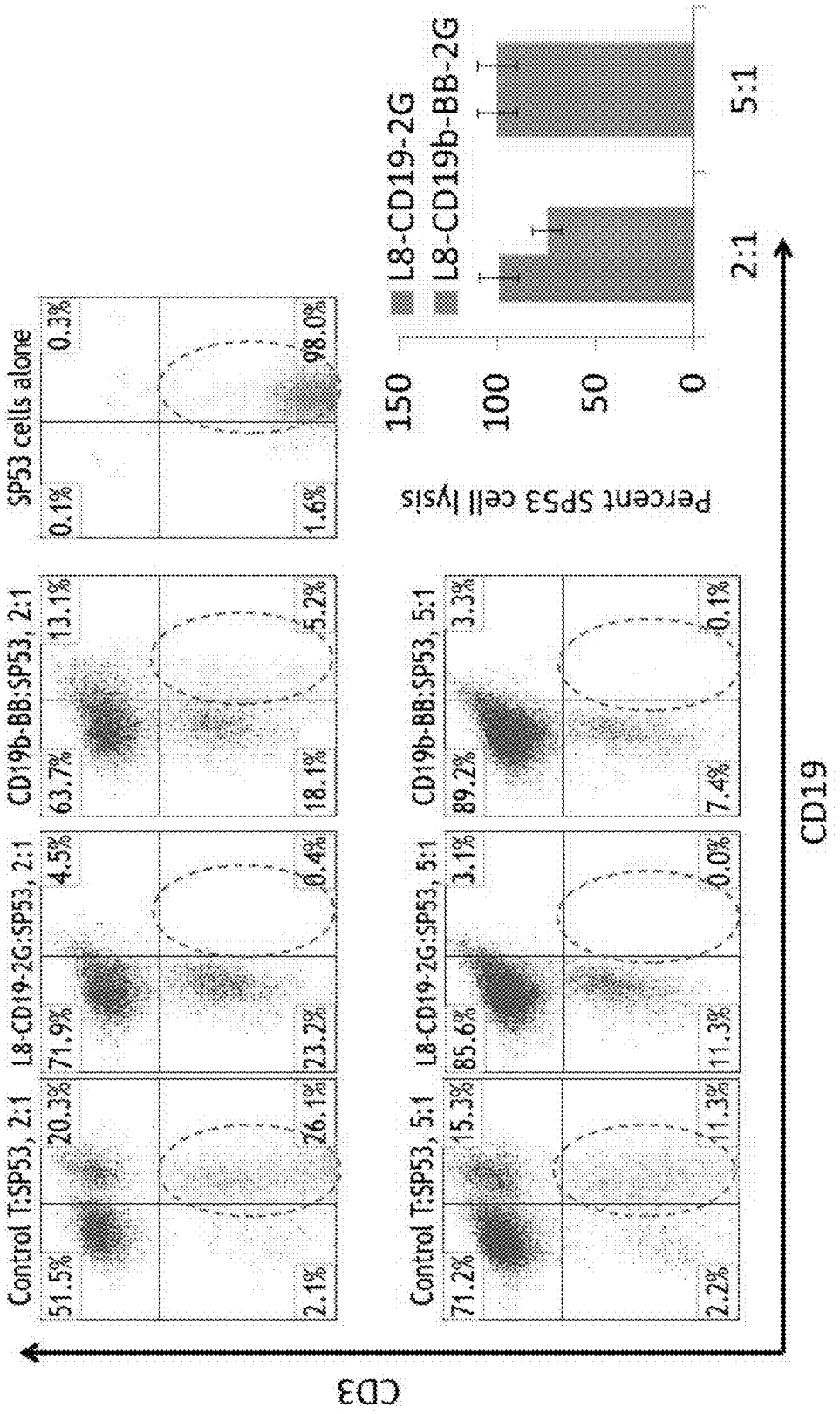


FIGURE 40


Control T:SP53, 2:1
L8-CD19-2G:SP53, 2:1
CD19b-BB:SP53, 2:1
SP53 cells alone
51.5%
20.3%
71.9%
4.5%
63.7%
13.1%
0.1%
0.3%
2.1%
26.1%
23.2%
0.4%
18.1%
5.2%
1.6%
98.0%
Control T:SP53, 5:1
L8-CD19-2G:SP53, 5:1
CD19b-BB:SP53, 5:1
71.2%
15.3%
85.6%
3.1%
89.2%
3.3%
2.2%
11.3%
11.3%
0.0%
7.4%
0.1%
CD3
CD19
Percent SP53 cell lysis
150
100
50
0
L8-CD19-2G
L8-CD19b-BB-2G
2:1
5:1

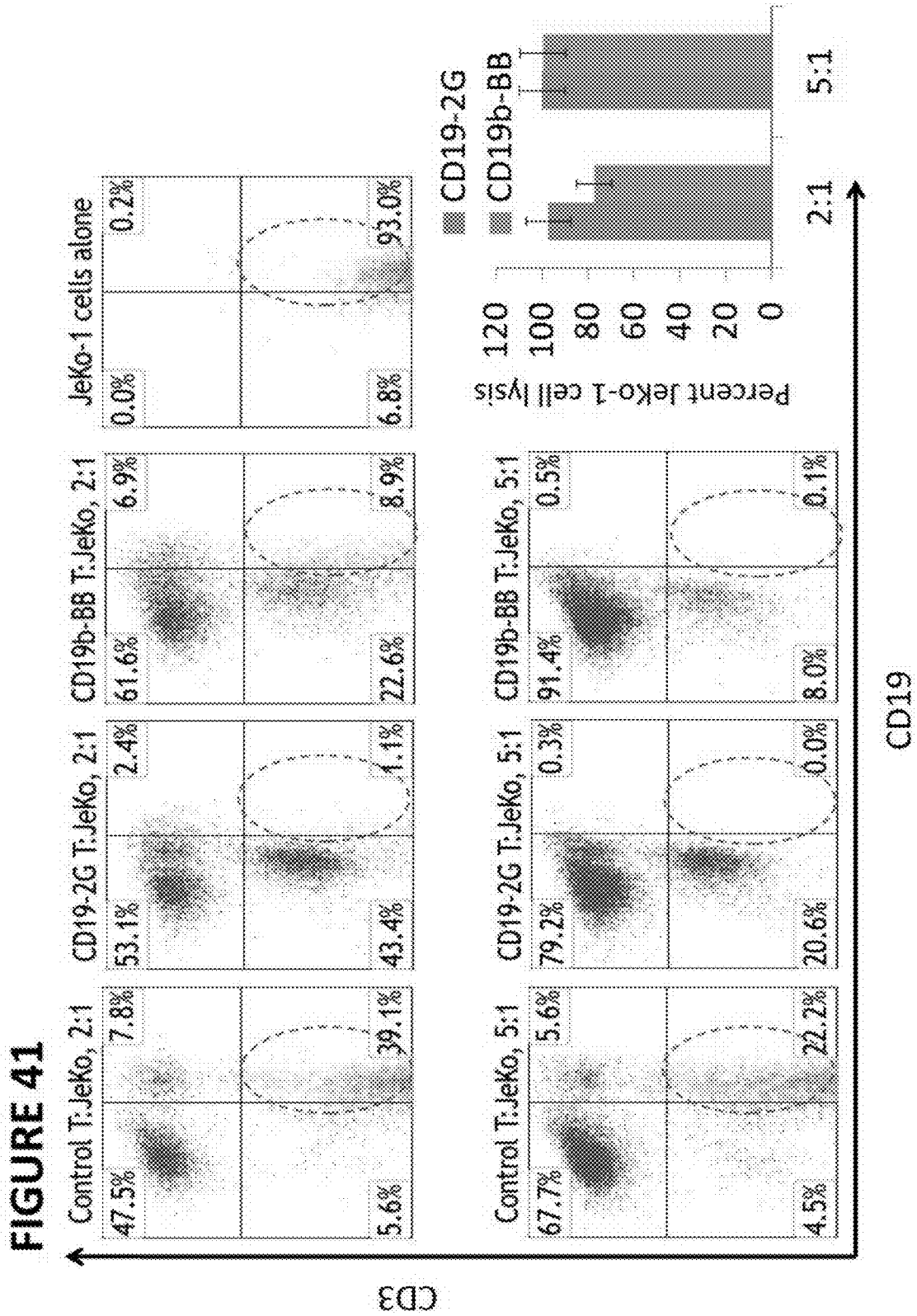


FIGURE 41
Control T:JeKo, 2:1
CD19-2G T:JeKo, 2:1
CD19b-BB T:JeKo, 2:1
JeKo-1 cells alone
47.5%
7.8%
53.1%
2.4%
61.6%
6.9%
0.0%
0.2%
5.6%
39.1%
43.4%
1.1%
22.6%
8.9%
6.8%
93.0%
Control T:JeKo, 5:1
CD19-2G T:JeKo, 5:1
CD19b-BB T:JeKo, 5:1
67.7%
5.6%
79.2%
0.3%
91.4%
0.5%
4.5%
22.2%
20.6%
0.0%
8.0%
0.1%
CD3
CD19
CD19-2G
CD19b-BB
Percent JeKo-1 cell lysis
120
100
80
60
40
20
0
2:1
5:1

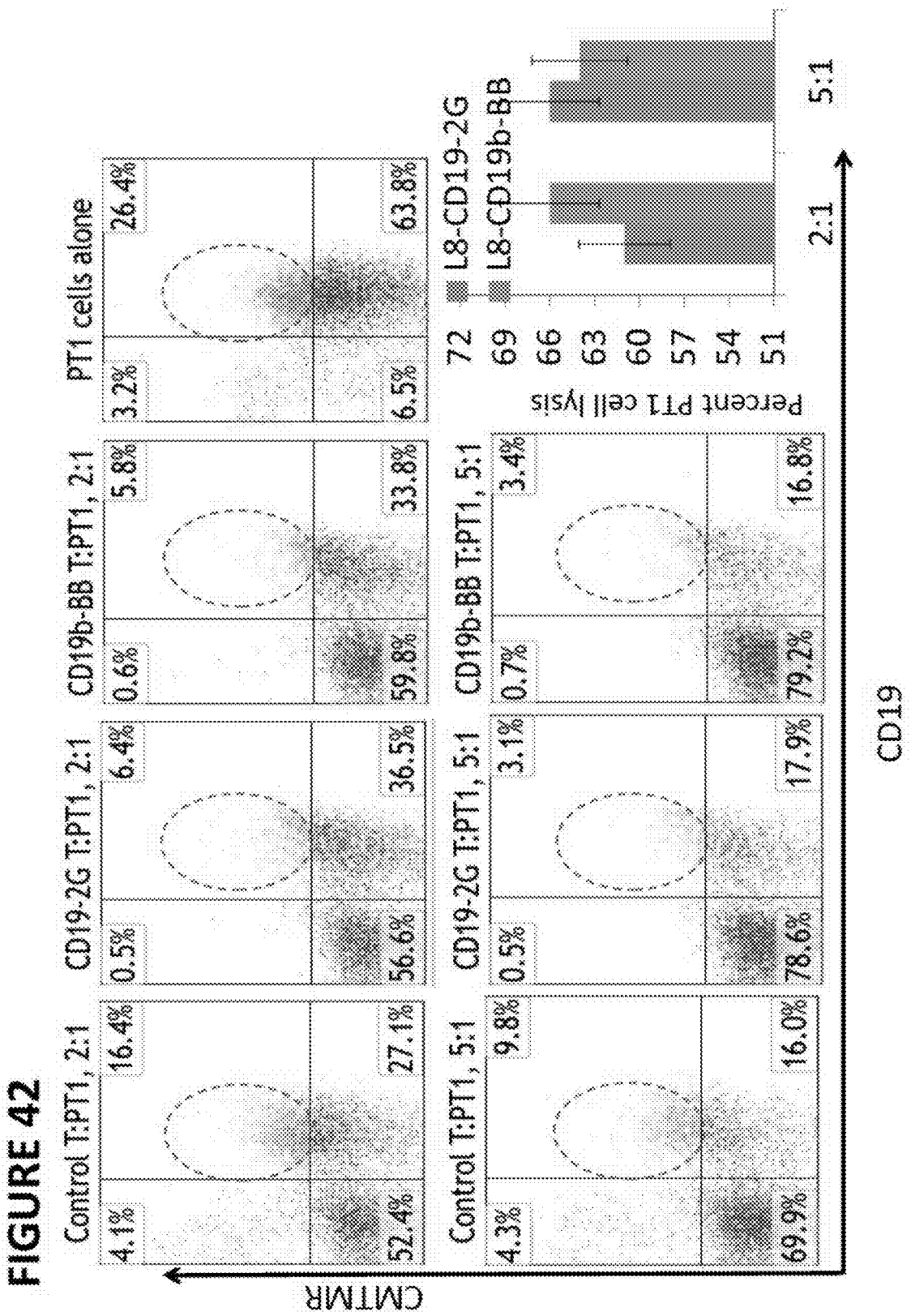


FIGURE 42
Control T:PT1, 2:1
CD19-2G T:PT1, 2:1
CD19b-BB T:PT1, 2:1
PT1 cells alone
Control T:PT1, 5:1
CD19-2G T:PT1, 5:1
CD19b-BB T:PT1, 5:1
4.1%
16.4%
52.4%
27.1%
0.5%
6.4%
56.6%
36.5%
0.6%
5.8%
59.8%
33.8%
3.2%
26.4%
6.5%
63.8%
4.3%
9.8%
69.9%
16.0%
0.5%
3.1%
78.6%
17.9%
0.7%
3.4%
79.2%
16.8%
CMTMR
CD19
Percent PT1 cell lysis
72
69
66
63
60
57
54
51
L8-CD19-2G
L8-CD19b-BB
2:1
5:1

FIGURE 43

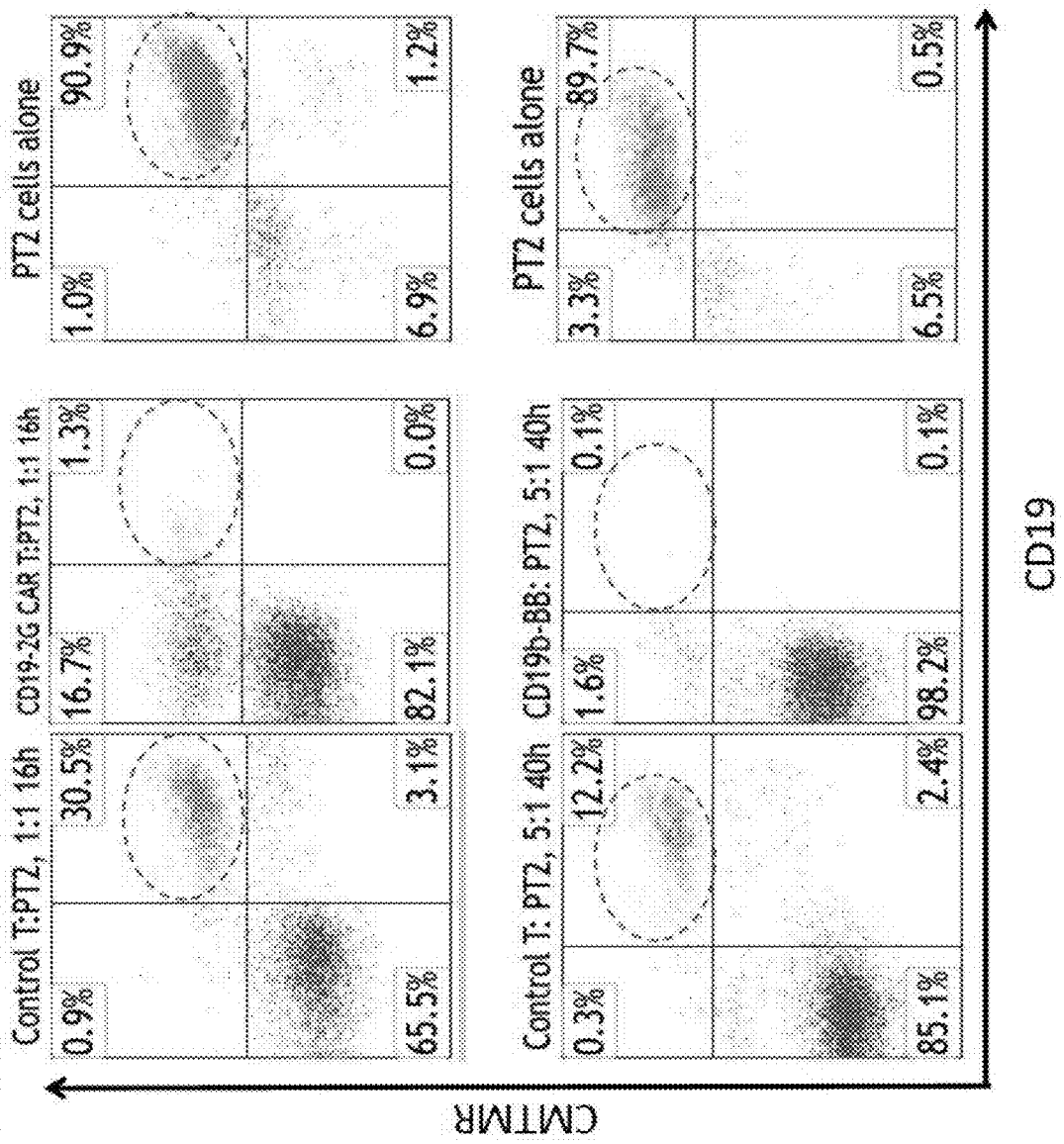

Control T:PTZ, 1:1 16h
0.9%
30.5%
65.5%
3.1%
CD19-2G CAR T:PTZ, 1:1 16h
16.7%
1.3%
82.1%
0.0%
PTZ cells alone
1.0%
90.9%
6.9%
1.2%
Control T: PTZ, 5:1 40h
0.3%
12.2%
85.1%
2.4%
CD19b-BB: PTZ, 5:1 40h
1.6%
0.1%
98.2%
0.1%
PTZ cells alone
3.3%
89.7%
6.5%
0.5%
CMTMR
CD19

FIGURE 44

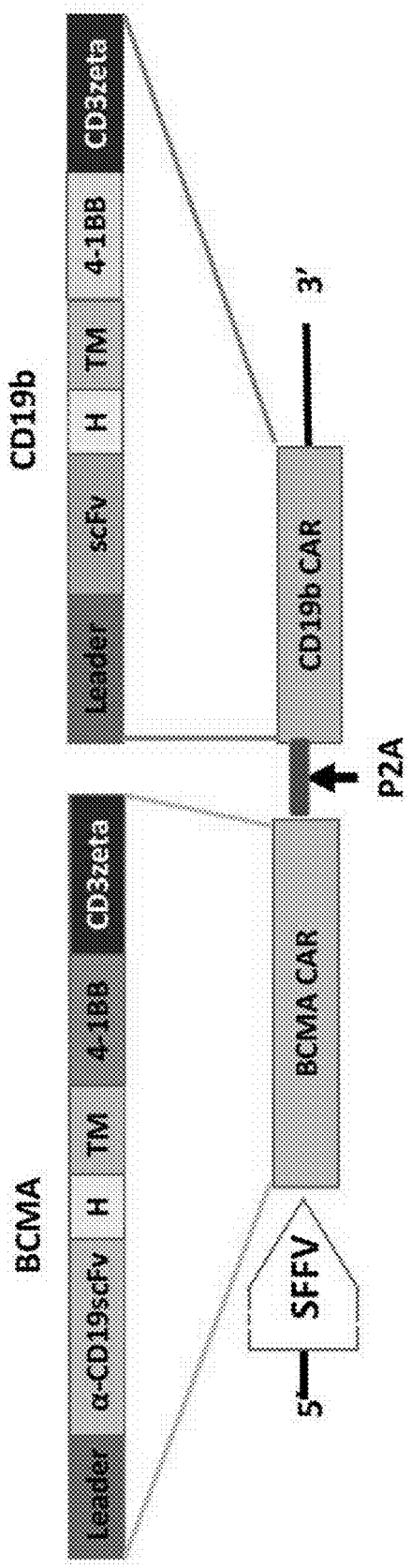

BCMA
Leader
α-CD19scFv
H
TM
4-1BB
CD3zeta
CD19b
Leader
scFv
H
TM
4-1BB
CD3zeta
5'
SFFV
BCMA CAR
P2A
CD19b CAR
3'

FIGURE 45A

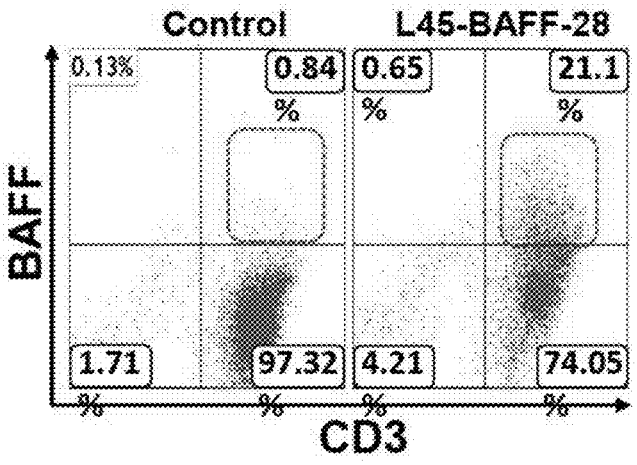


FIGURE 45B

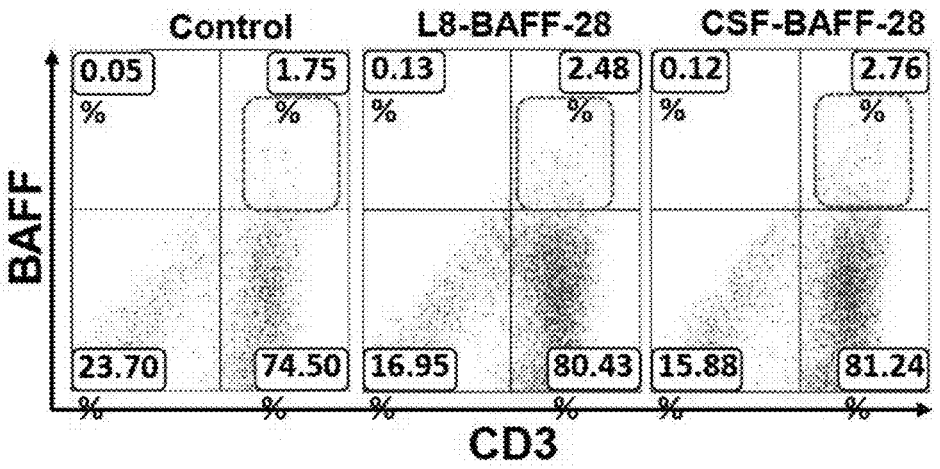


FIGURE 45C

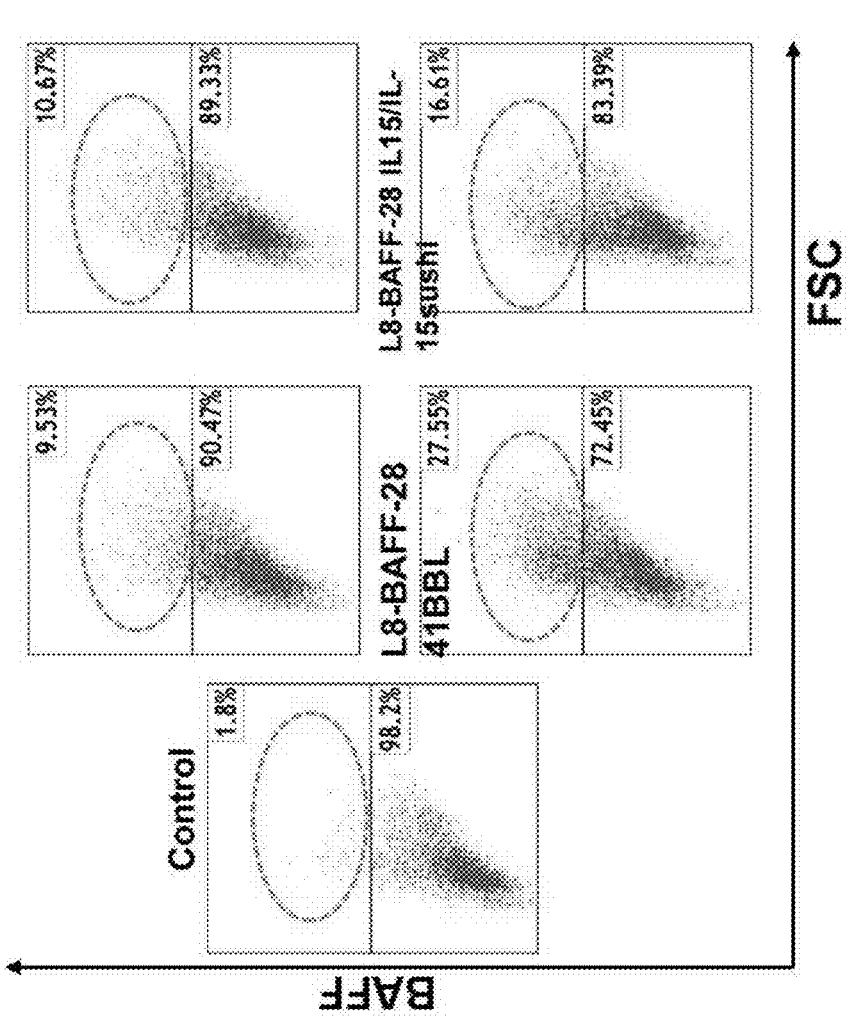

CSF-BAFF-28
41BBL
CSF-BAFF-28
IL15/IL-15sushi
Control
1.8%
98.2%
9.53%
90.47%
10.67%
89.33%
L8-BAFF-28
41BBL
27.55%
72.45%
L8-BAFF-28 IL15/IL-15sushi
16.61%
83.39%
BAFF
FSC

FIGURE 46A

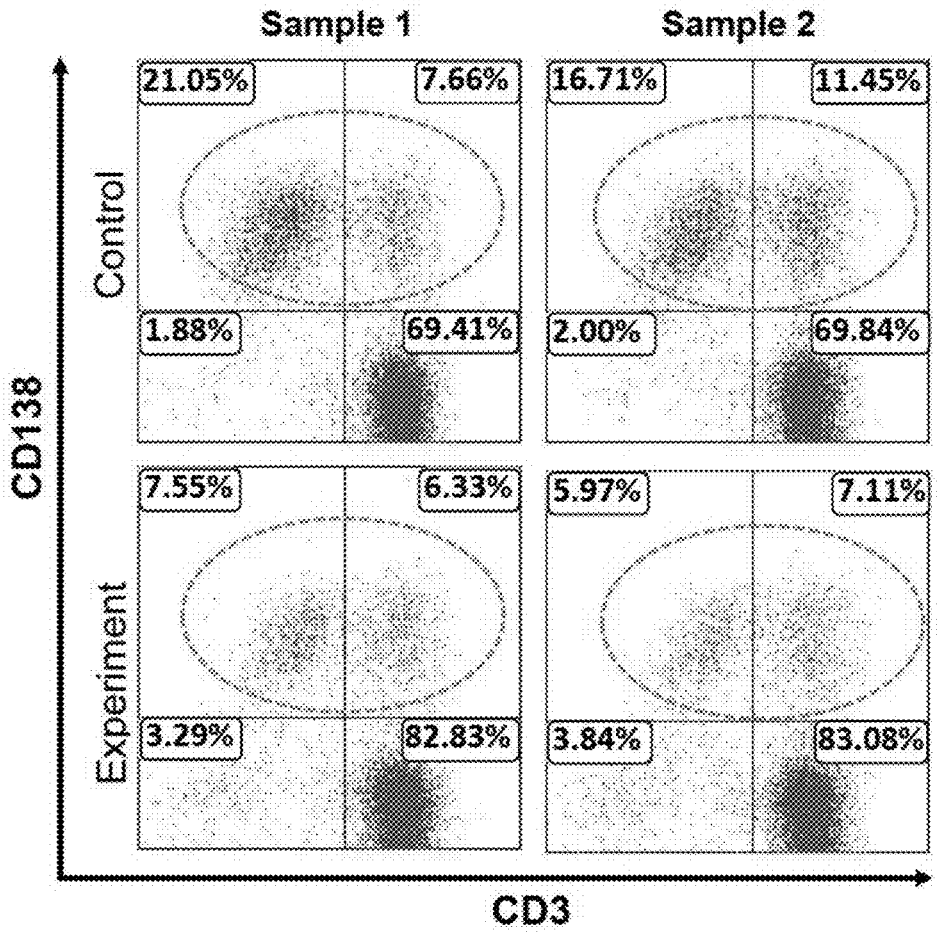


FIGURE 46B

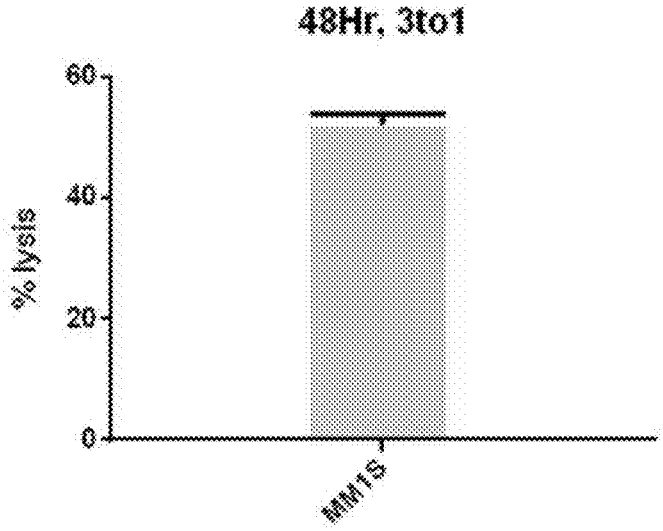


FIGURE 47A

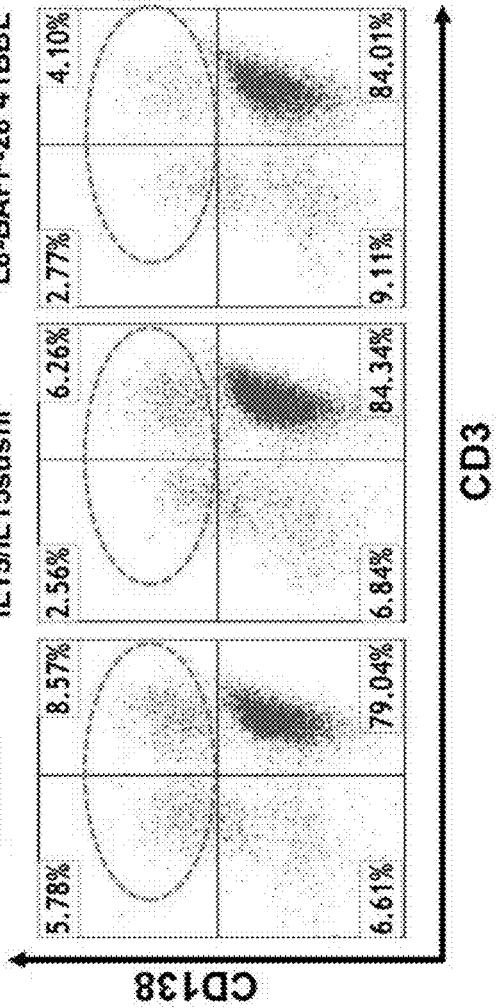


FIGURE 47B

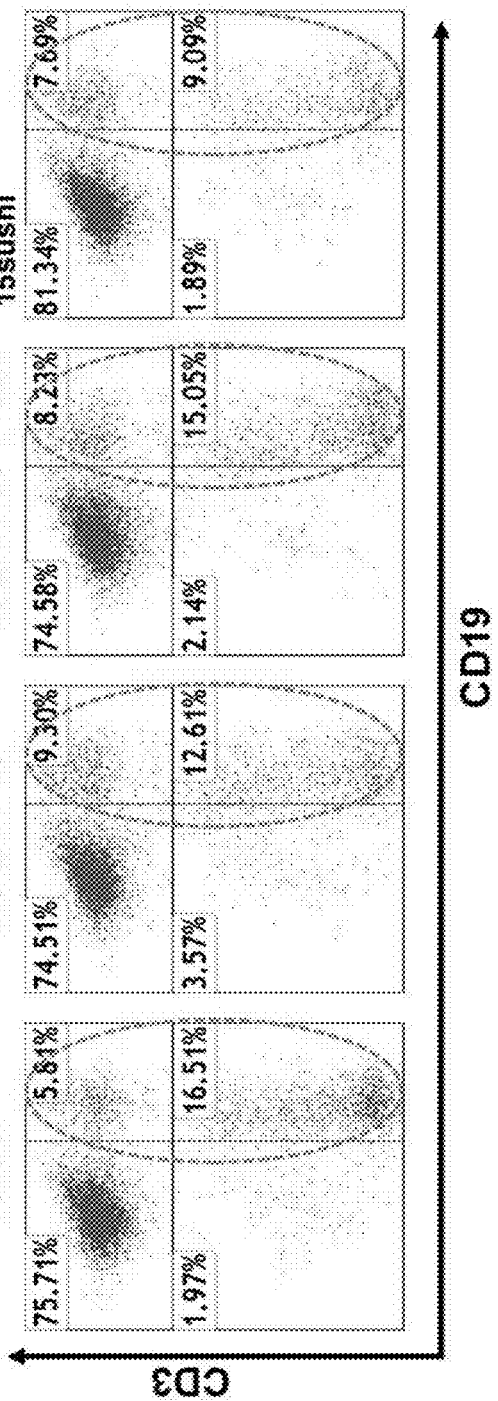


FIGURE 48

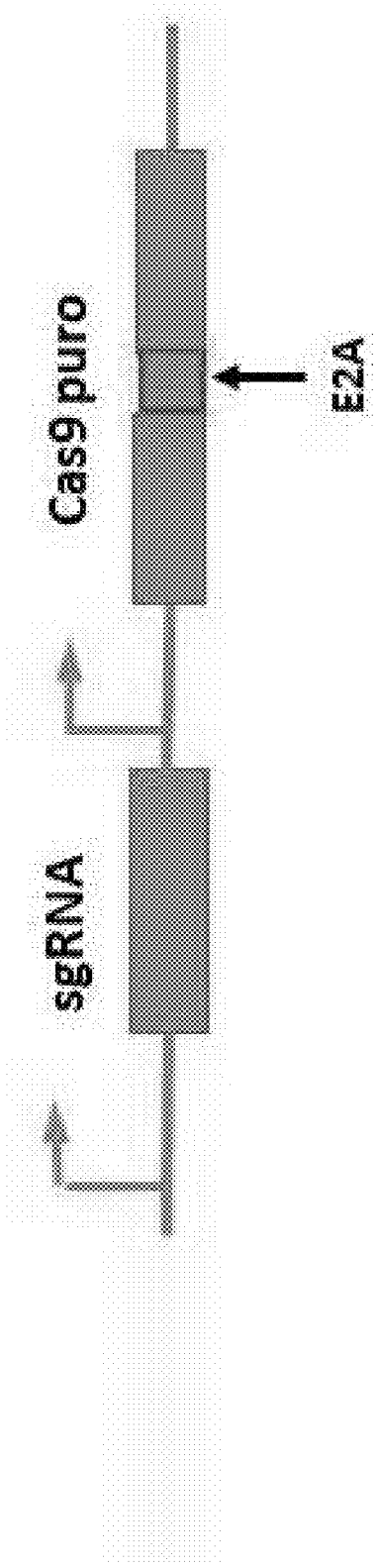
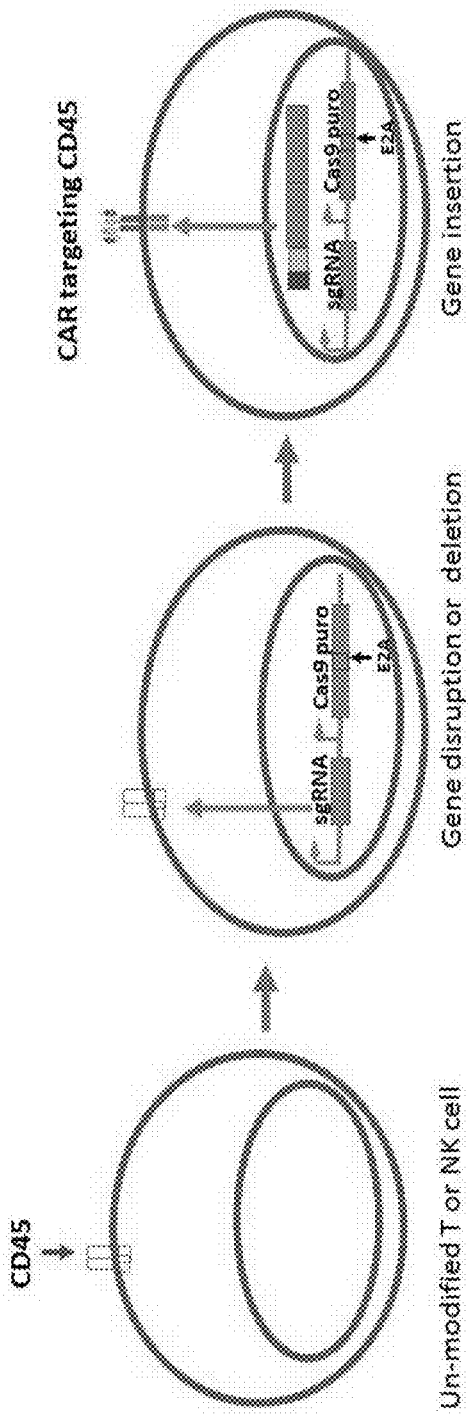


FIGURE 49A



Steps: T or NK cells armed with CARs targeting hematologic malignancies

1. Donor T cells or NK cells
2. Gene disruption or deletion of CD45
3. Insert of scFv CAR targeting CD45

FIGURE 49B

B.

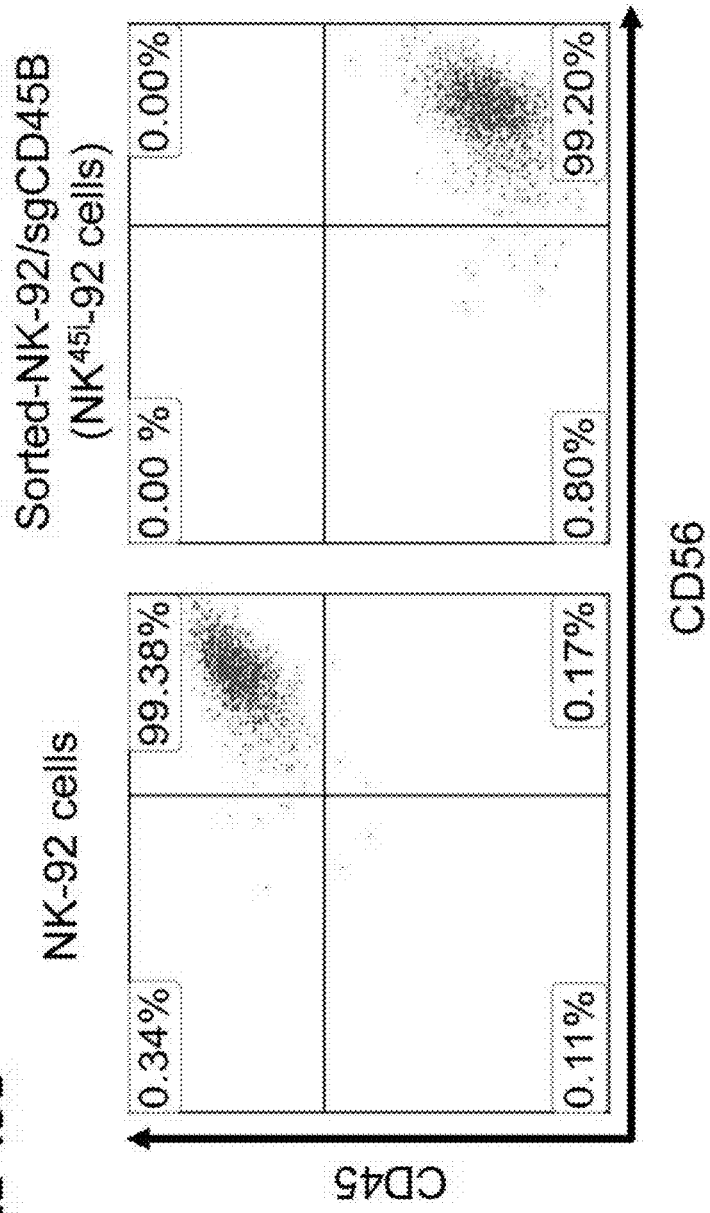

NK-92 cells
Sorted-NK-92/sgCD45B
(NK45L-92 cells)
0.34%
99.38%
0.11%
0.17%
0.00 %
0.00%
0.80%
99.20%
CD45
CD56

FIGURE 50

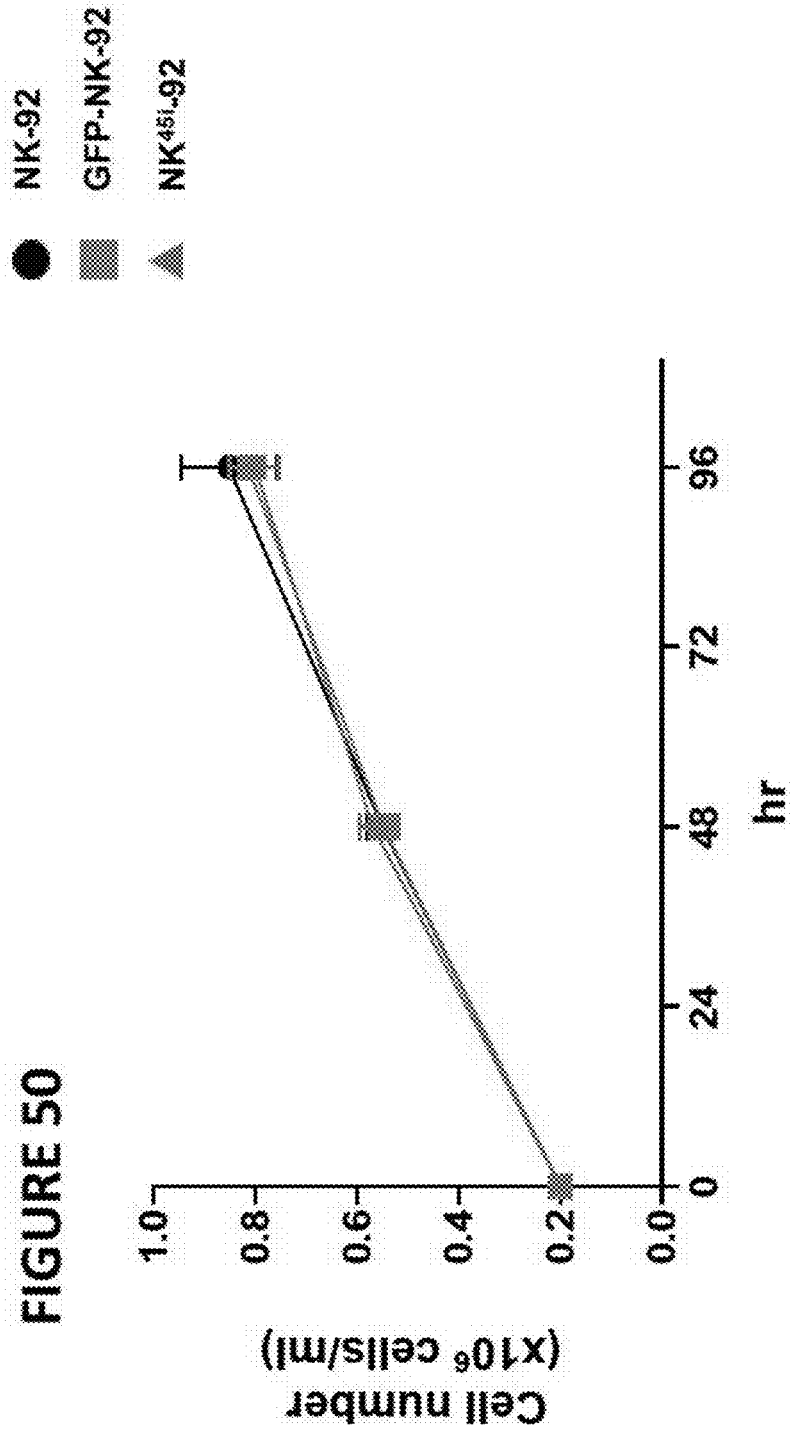

NK-92
GFP-NK-92
NK451-92
Cell number
(x10^6 cells/ml)
1.0
0.8
0.6
0.4
0.2
0.0
0
24
48
72
96
hr

FIGURE 51A

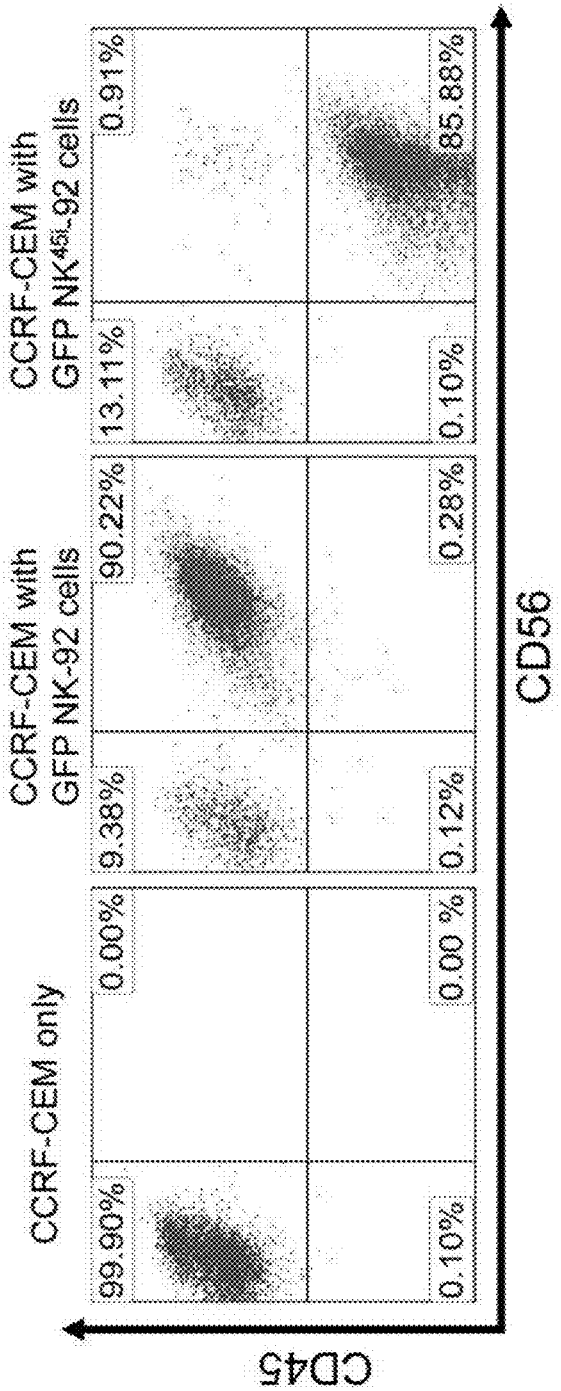
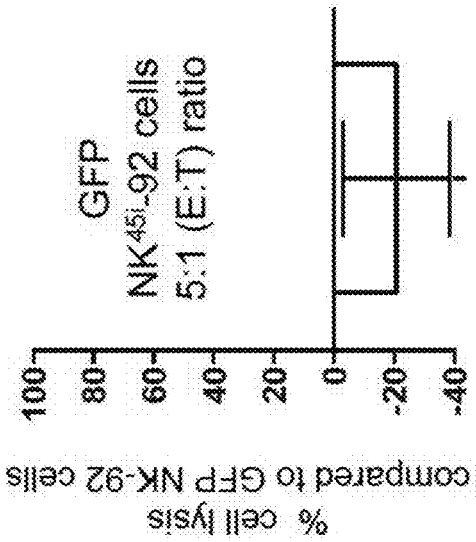


FIGURE 51B



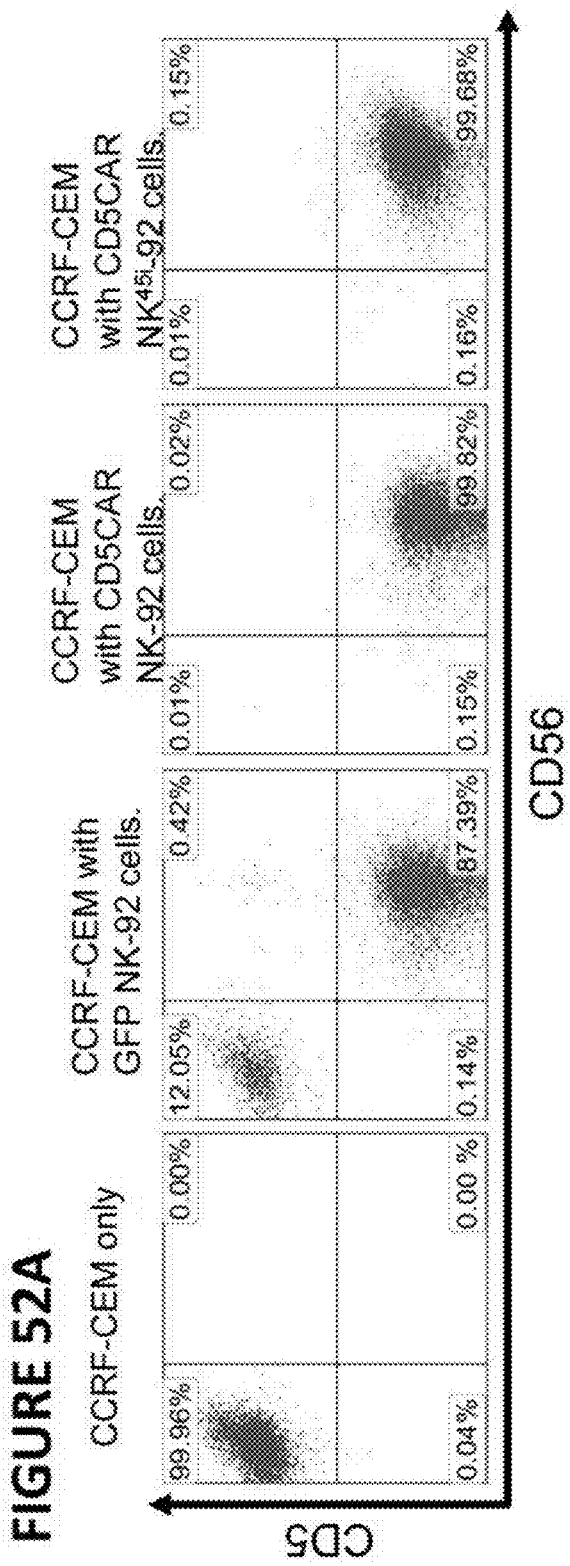


FIGURE 52A
CCRF-CEM only
CCRF-CEM with GFP NK-92 cells.
CCRF-CEM with CD5CAR NK-92 cells.
CCRF-CEM with CD5CAR NK45i-92 cells.
99.96%
0.00%
12.05%
0.42%
0.01%
0.02%
0.01%
0.15%
0.04%
0.00 %
0.14%
87.39%
0.15%
99.82%
0.16%
99.68%
CD5
CD56

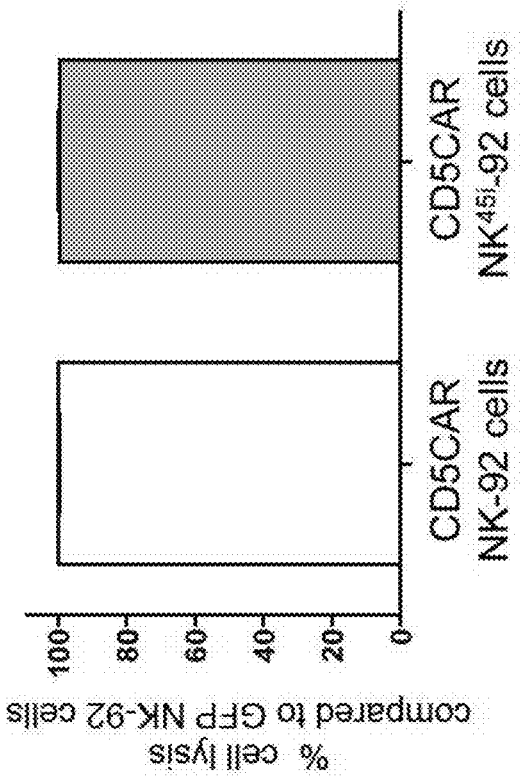


FIGURE 52B
% cell lysis compared to GFP NK-92 cells
100
80
60
40
20
0
CD5CAR NK-92 cells
CD5CAR NK45i-92 cells

FIGURE 53A

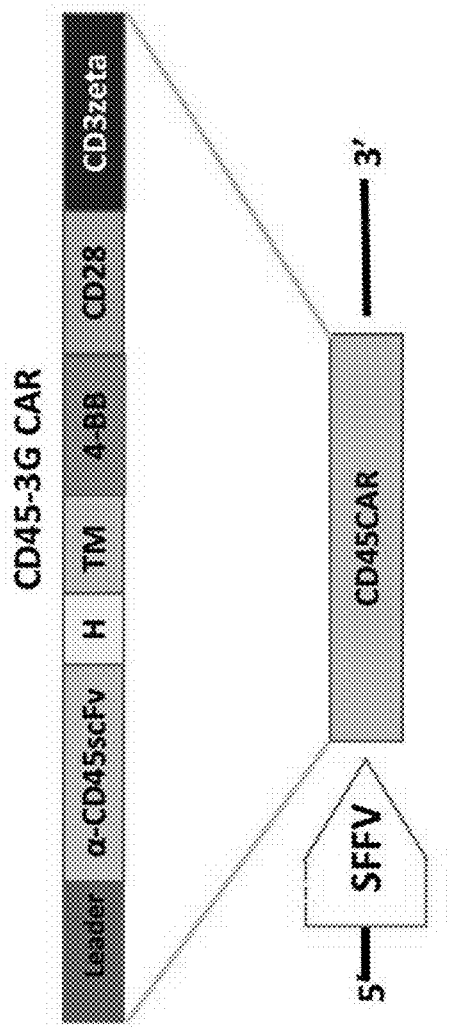


FIGURE 53B

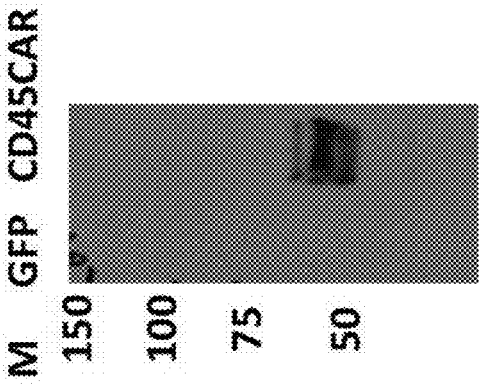


FIGURE 54

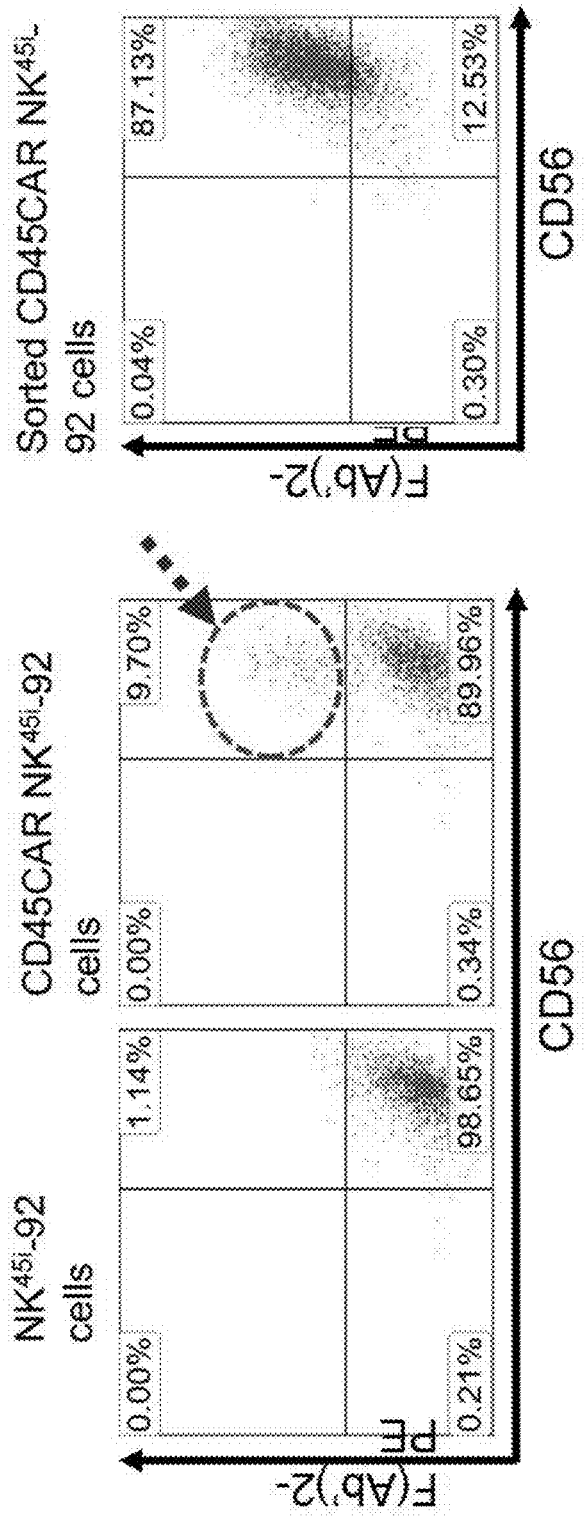

NK45L-92 cells
0.00%
1.14%
0.21%
98.65%
CD45CAR NK45L-92 cells
0.00%
9.70%
0.34%
89.96%
Sorted CD45CAR NK45L-92 cells
0.04%
87.13%
0.30%
12.53%
F(Ab')2-PE
CD56

FIGURE 55A

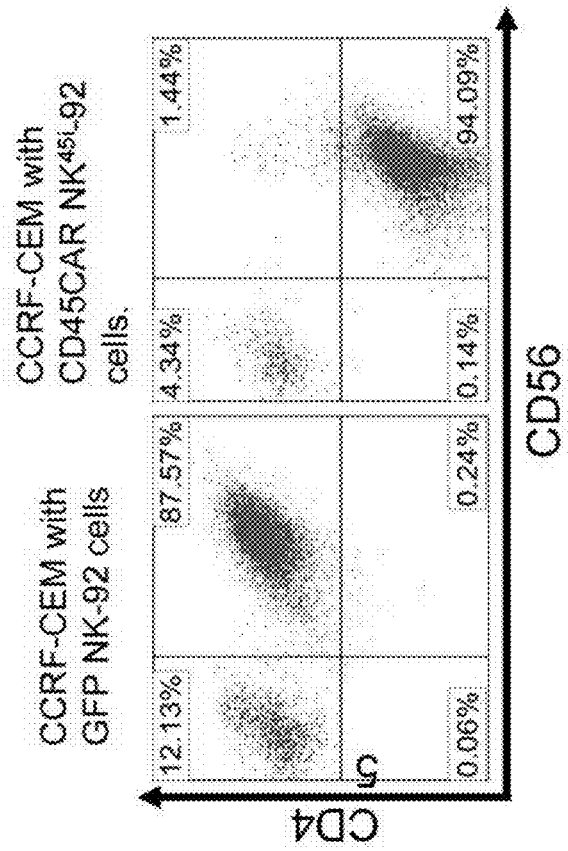
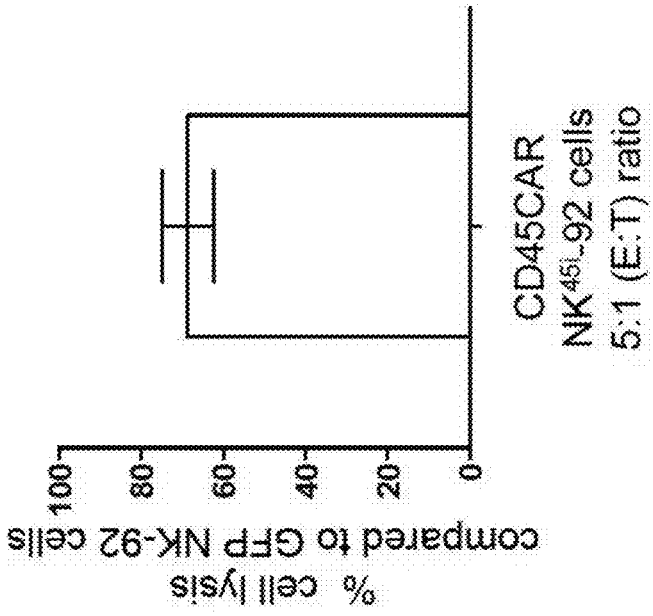


FIGURE 55B



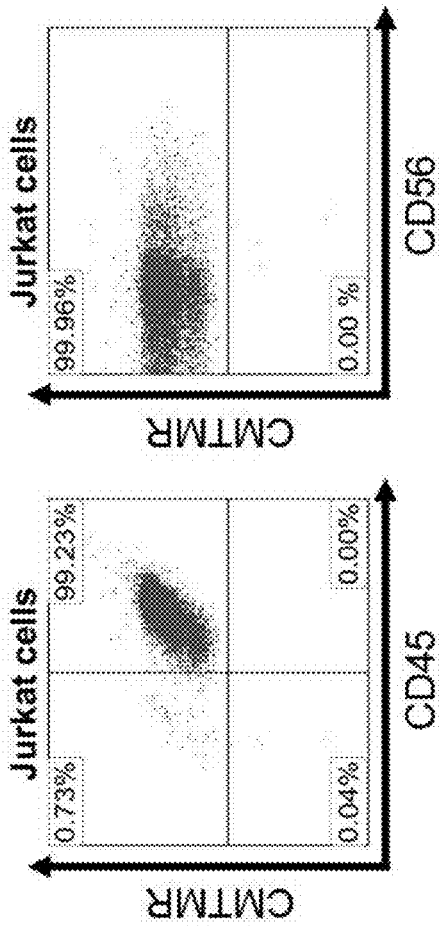


FIGURE 56A

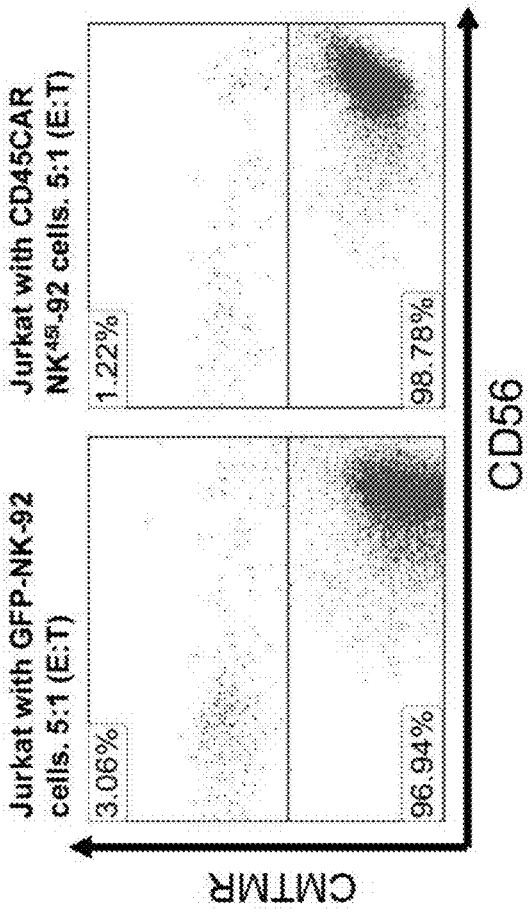


FIGURE 56B

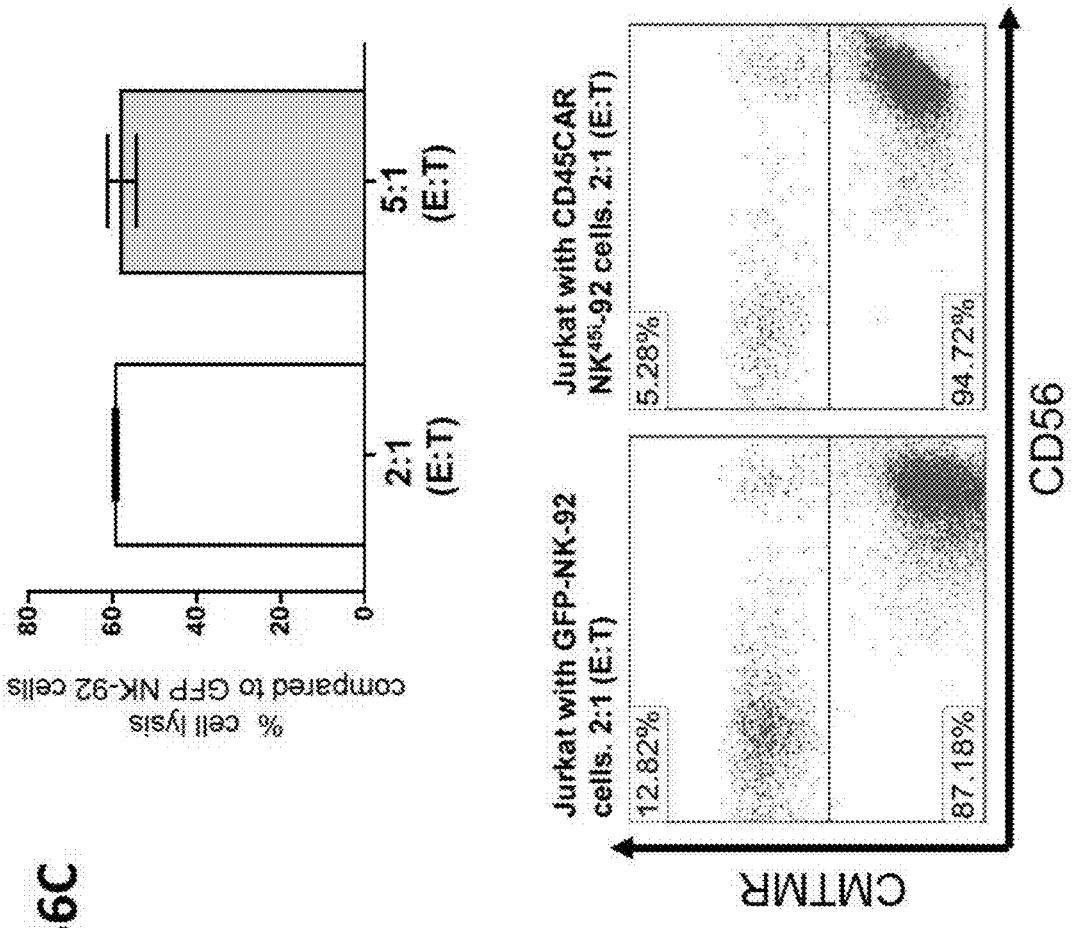

% cell lysis
compared to GFP NK-92 cells
80
60
40
20
0
2:1
(E:T)
5:1
(E:T)
Jurkat with GFP-NK-92
cells. 2:1 (E:T)
12.82%
87.18%
Jurkat with CD45CAR
NK45-92 cells. 2:1 (E:T)
5.28%
94.72%
CMTMR
CD56

FIGURE 56C

FIGURE 57A

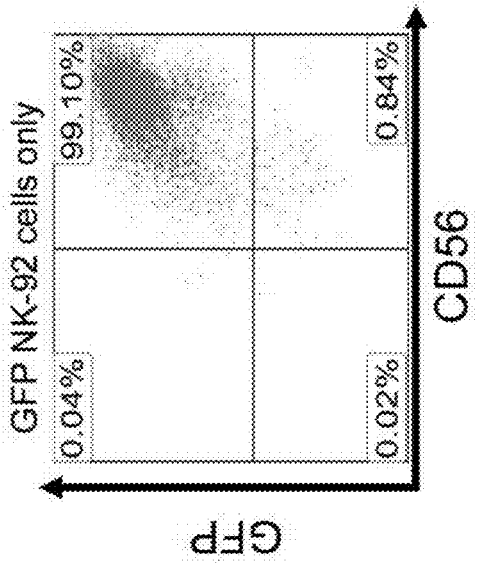


FIGURE 57B

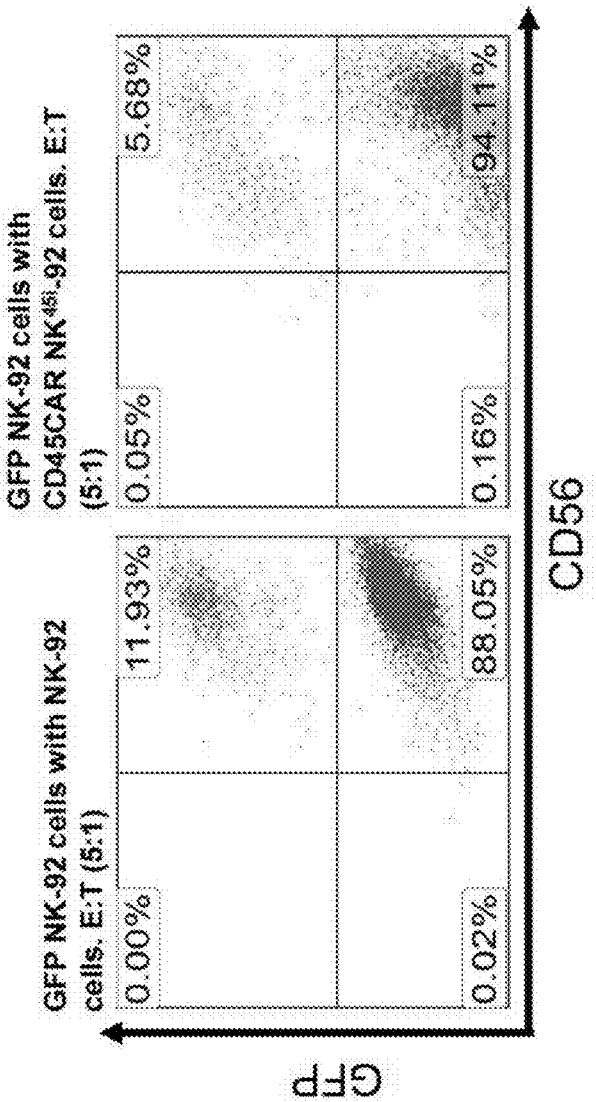


FIGURE 57C

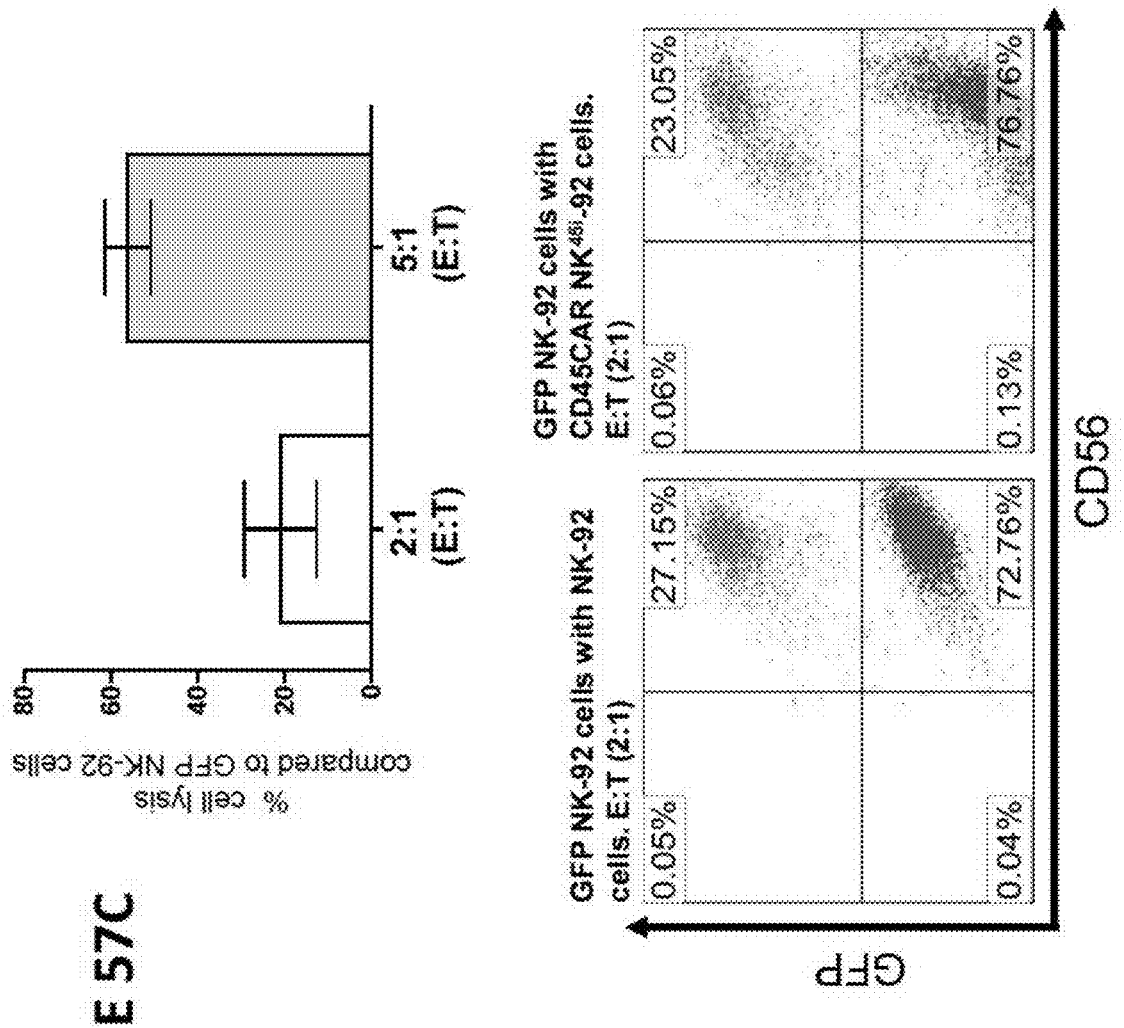

% cell lysis
compared to GFP NK-92 cells
80
60
40
20
0
2:1
(E:T)
5:1
(E:T)
GFP NK-92 cells with NK-92
cells. E:T (2:1)
0.05%
27.15%
0.04%
72.76%
GFP NK-92 cells with
CD45CAR NK^{48i}-92 cells.
E:T (2:1)
0.06%
23.05%
0.13%
76.76%
GFP
CD56

FIGURE 57D

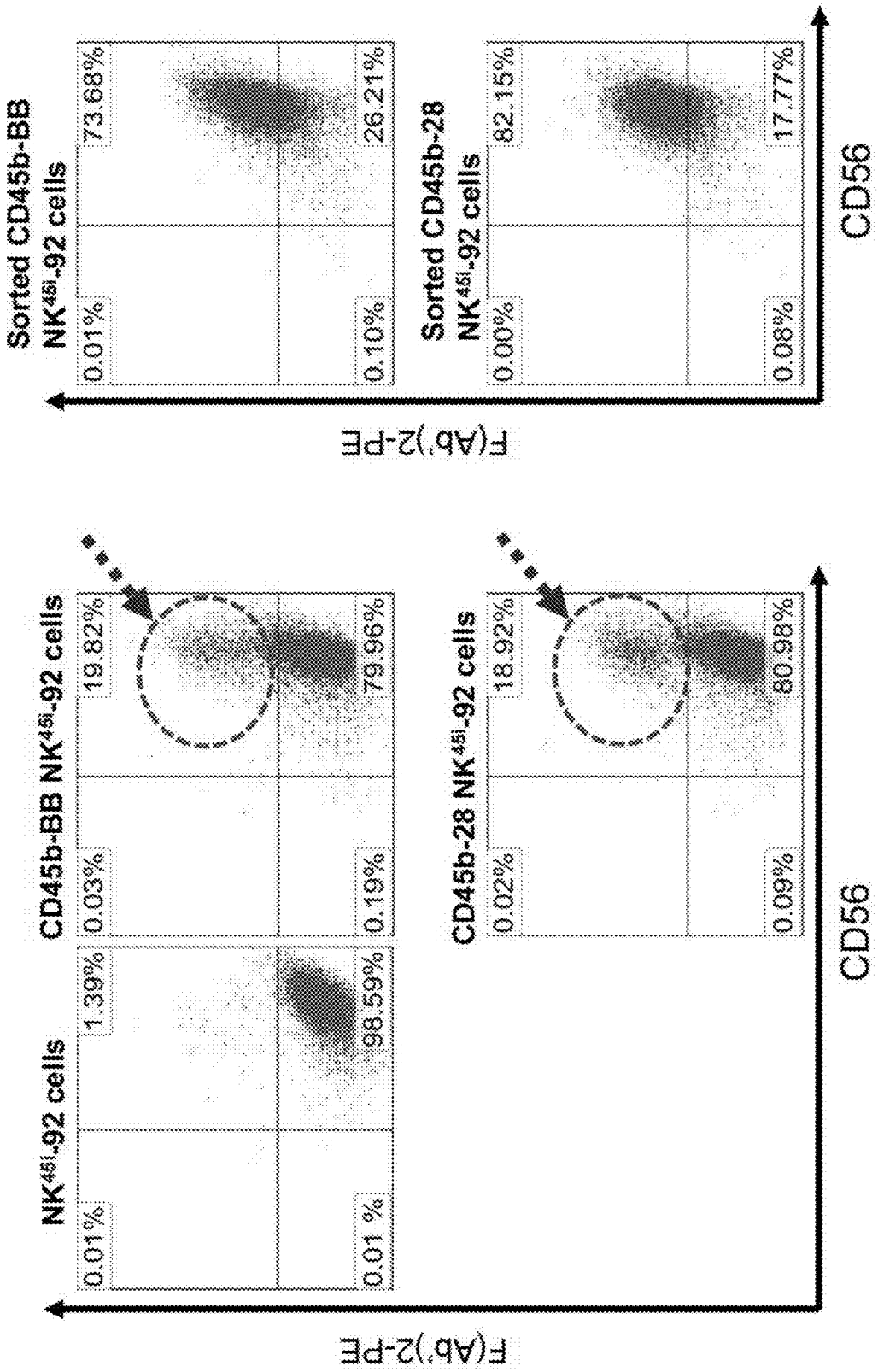

NK45i-92 cells
0.01%
1.39%
0.01 %
98.59%
CD45b-BB NK45i-92 cells
0.03%
19.82%
0.19%
79.96%
CD45b-28 NK45i-92 cells
0.02%
18.92%
0.09%
80.98%
Sorted CD45b-BB NK45i-92 cells
0.01%
73.68%
0.10%
26.21%
Sorted CD45b-28 NK45i-92 cells
0.00%
82.15%
0.08%
17.77%
F(Ab')2-PE
CD56

FIGURE 57E

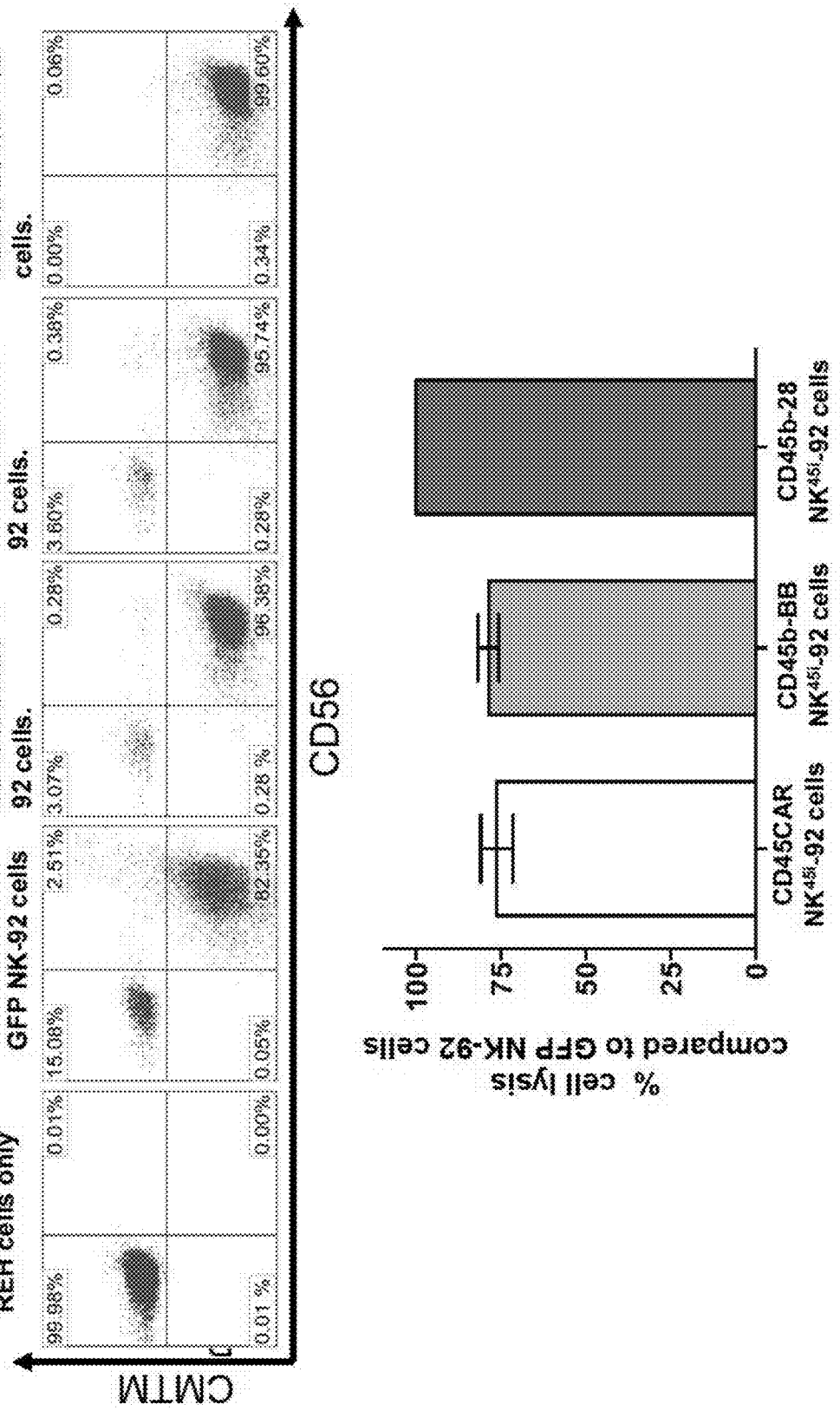

REH cells only
REH cells with GFP NK-92 cells
REH cells with CD45CAR NK45L-92 cells.
REH cells with CD45b-1BB NK45L-92 cells.
REH cells with CD45b-28 NK45L-92 cells.
99.98%
0.01%
0.01 %
0.00%
15.08%
2.51%
0.05%
82.35%
3.07%
0.28%
0.28 %
96.38%
3.60%
0.38%
0.28%
95.74%
0.00%
0.06%
0.34%
99.60%
CM1TM
CD56
% cell lysis compared to GFP NK-92 cells
100
75
50
25
0
CD45CAR NK45L-92 cells
CD45b-BB NK45L-92 cells
CD45b-28 NK45L-92 cells

FIGURE 57FA

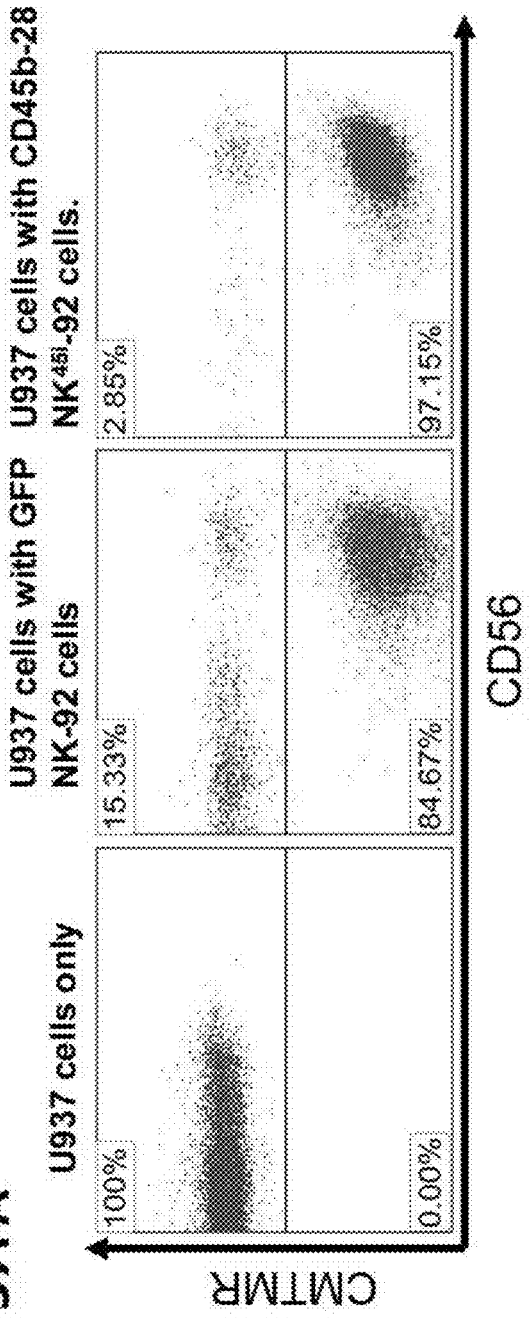


FIGURE 57FB

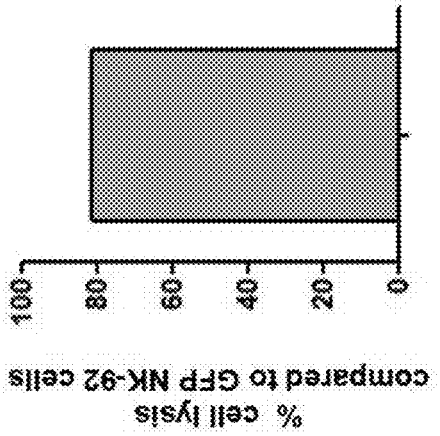


FIGURE 57GA

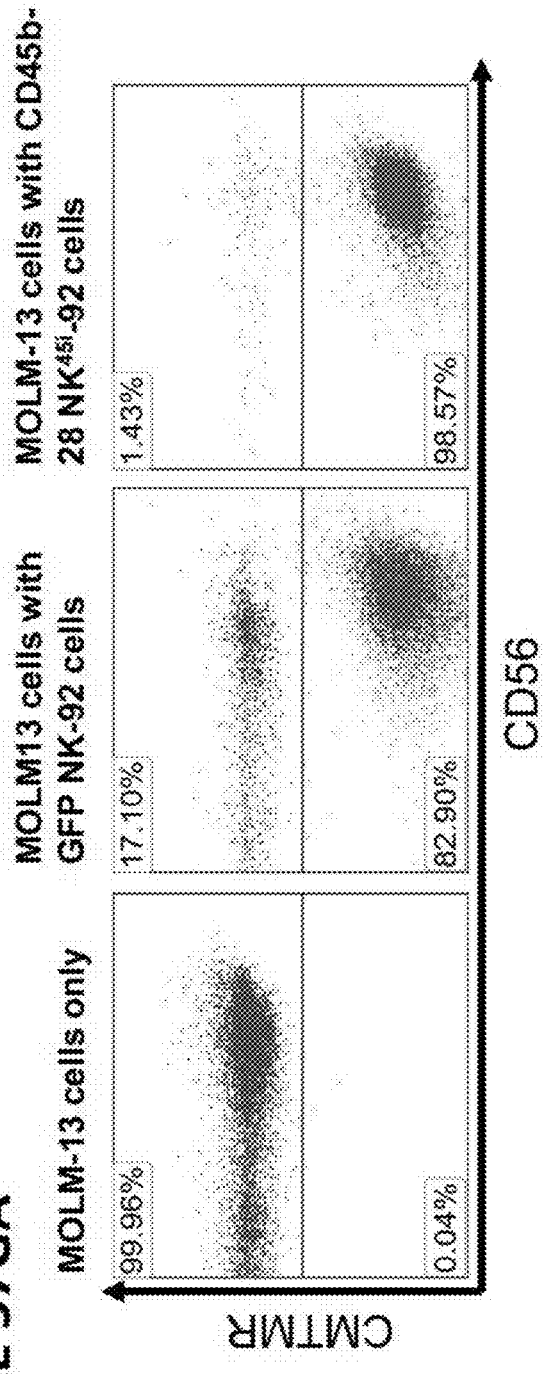
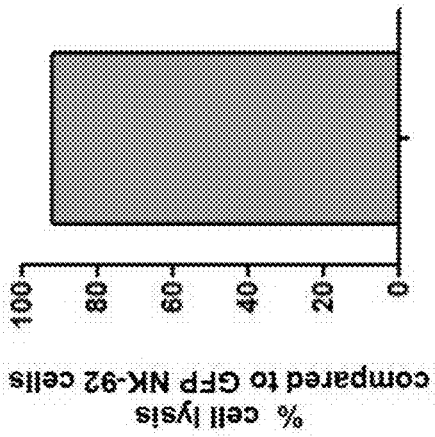


FIGURE 57GB



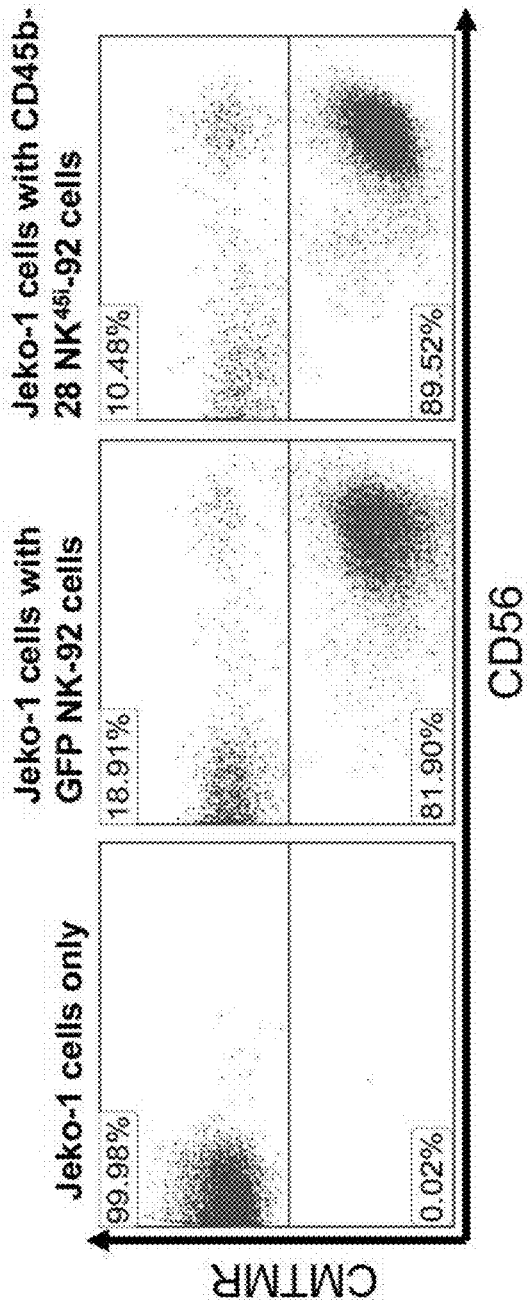


FIGURE 57HA

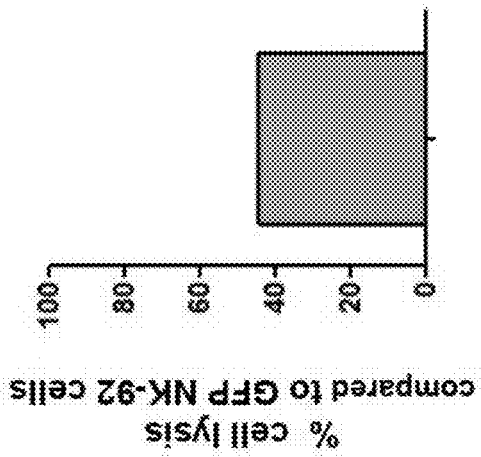


FIGURE 57HB

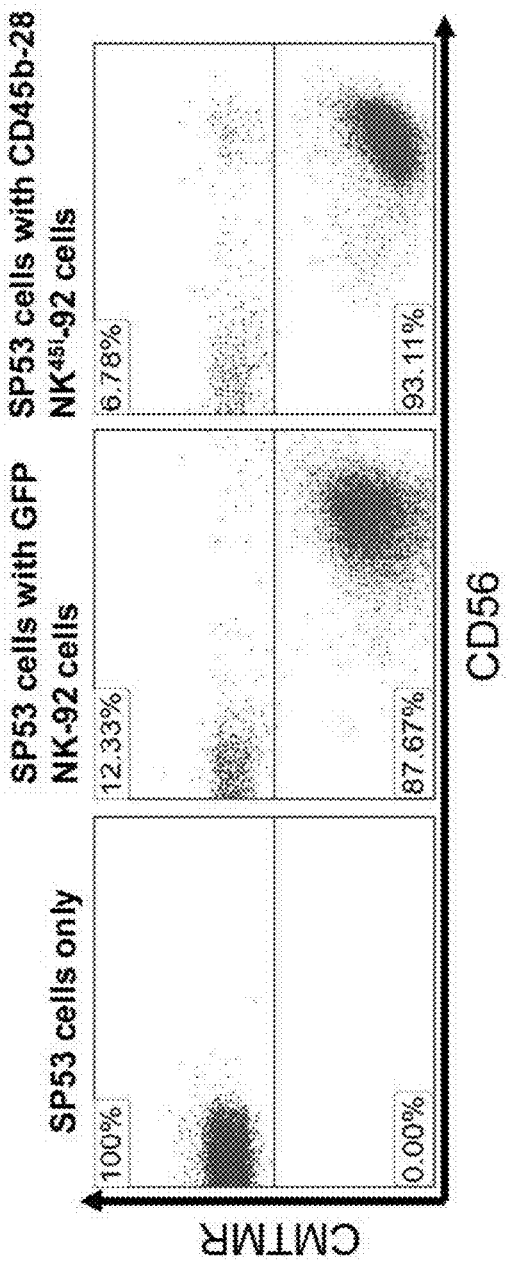


FIGURE 57IA

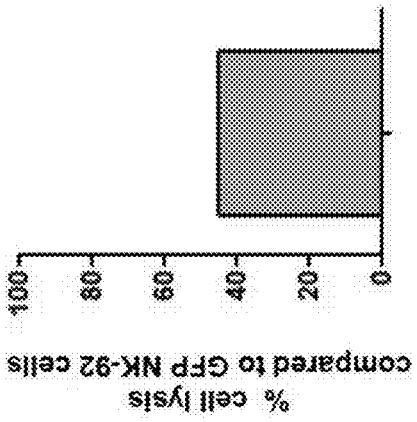


FIGURE 57IB

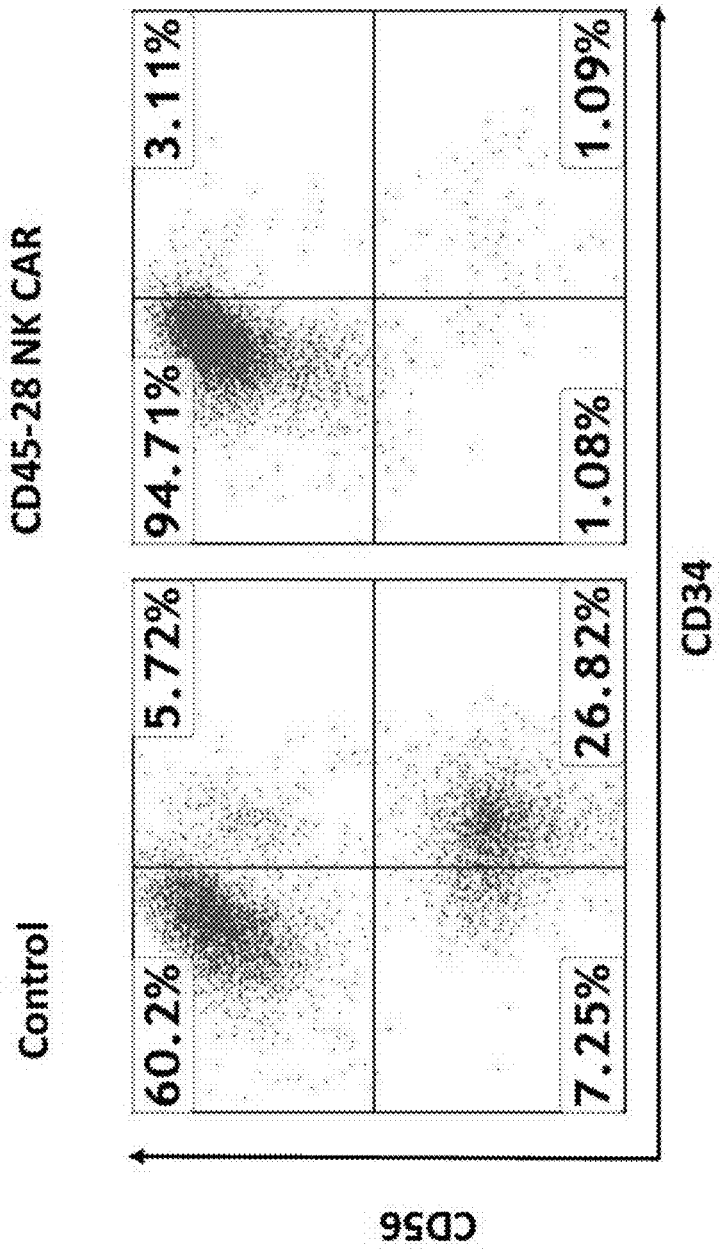

Control
CD45-28 NK CAR
60.2%
5.72%
7.25%
26.82%
94.71%
3.11%
1.08%
1.09%
CD56
CD34

FIGURE 57J

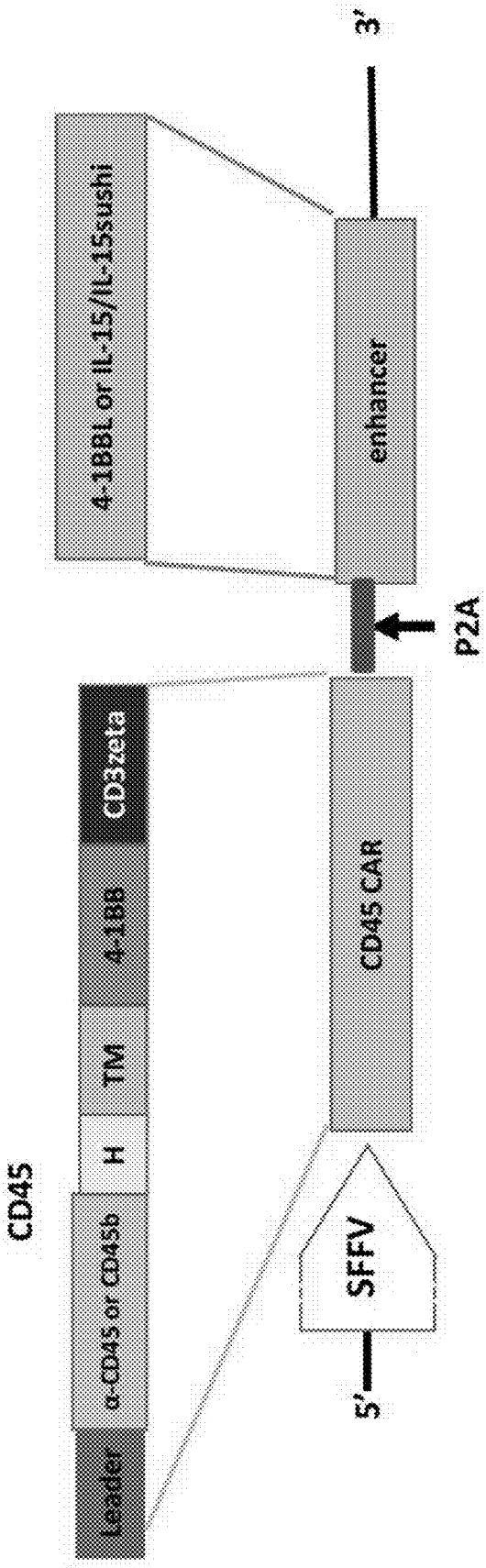

CD45
Leader
α-CD45 or CD45b
H
TM
4-1BB
CD3zeta
5'
SFFV
CD45 CAR
P2A
enhancer
4-1BBL or IL-15/IL-15sushi
3'

FIGURE 58A

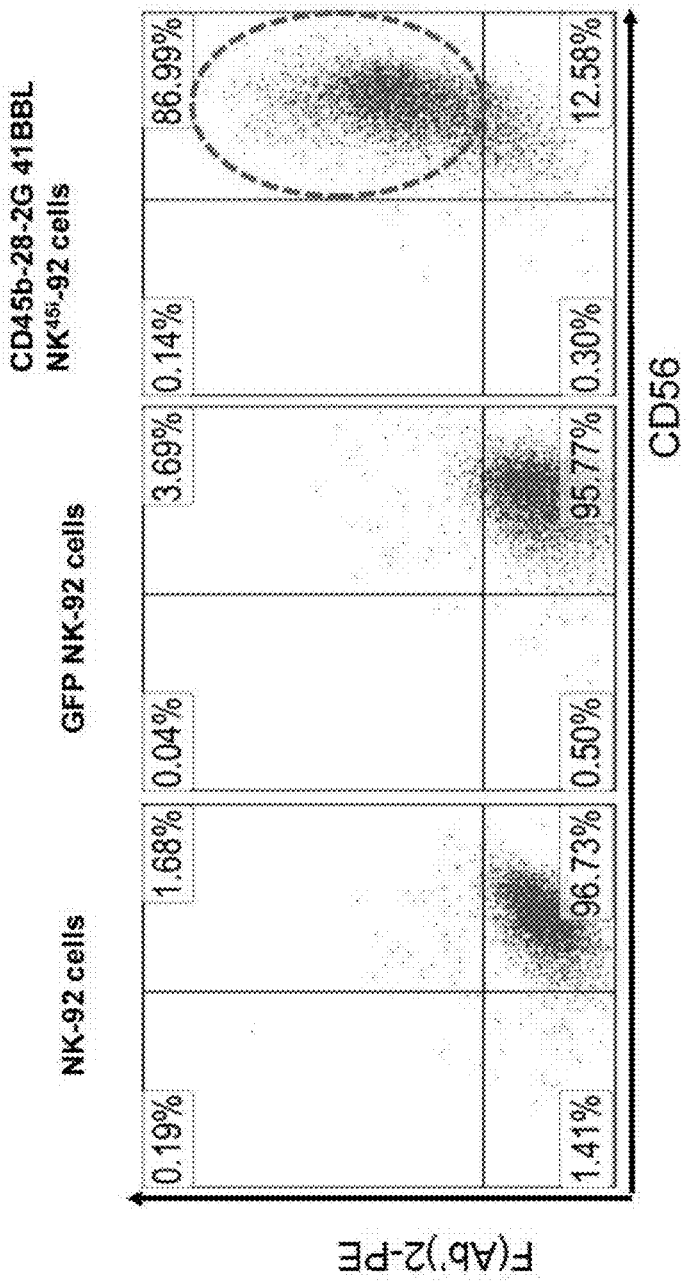

NK-92 cells
GFP NK-92 cells
CD45b-28-2G 41BBL
NK45-92 cells
0.19%
1.68%
0.04%
3.69%
0.14%
86.99%
1.41%
96.73%
0.50%
95.77%
0.30%
12.58%
F(Ab')2-PE
CD56

FIGURE 58B

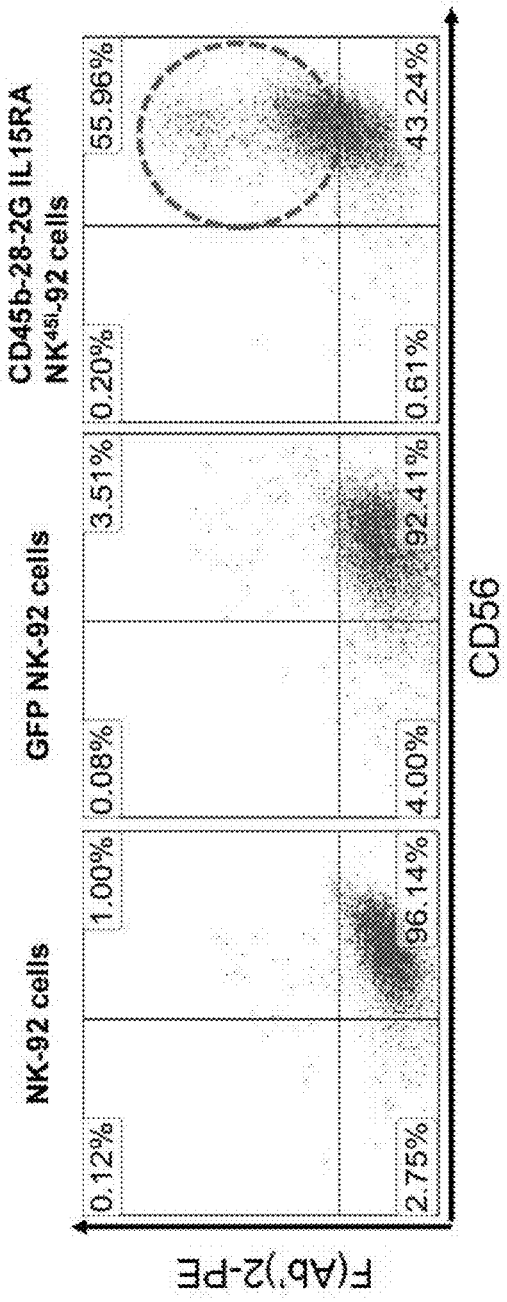

NK-92 cells
GFP NK-92 cells
CD45b-28-2G IL15RA
NK4SL-92 cells
0.12%
1.00%
0.08%
3.51%
0.20%
55.96%
2.75%
96.14%
4.00%
92.41%
0.61%
43.24%
F(Ab')2-PE
CD56

FIGURE 58C

FIGURE 59A

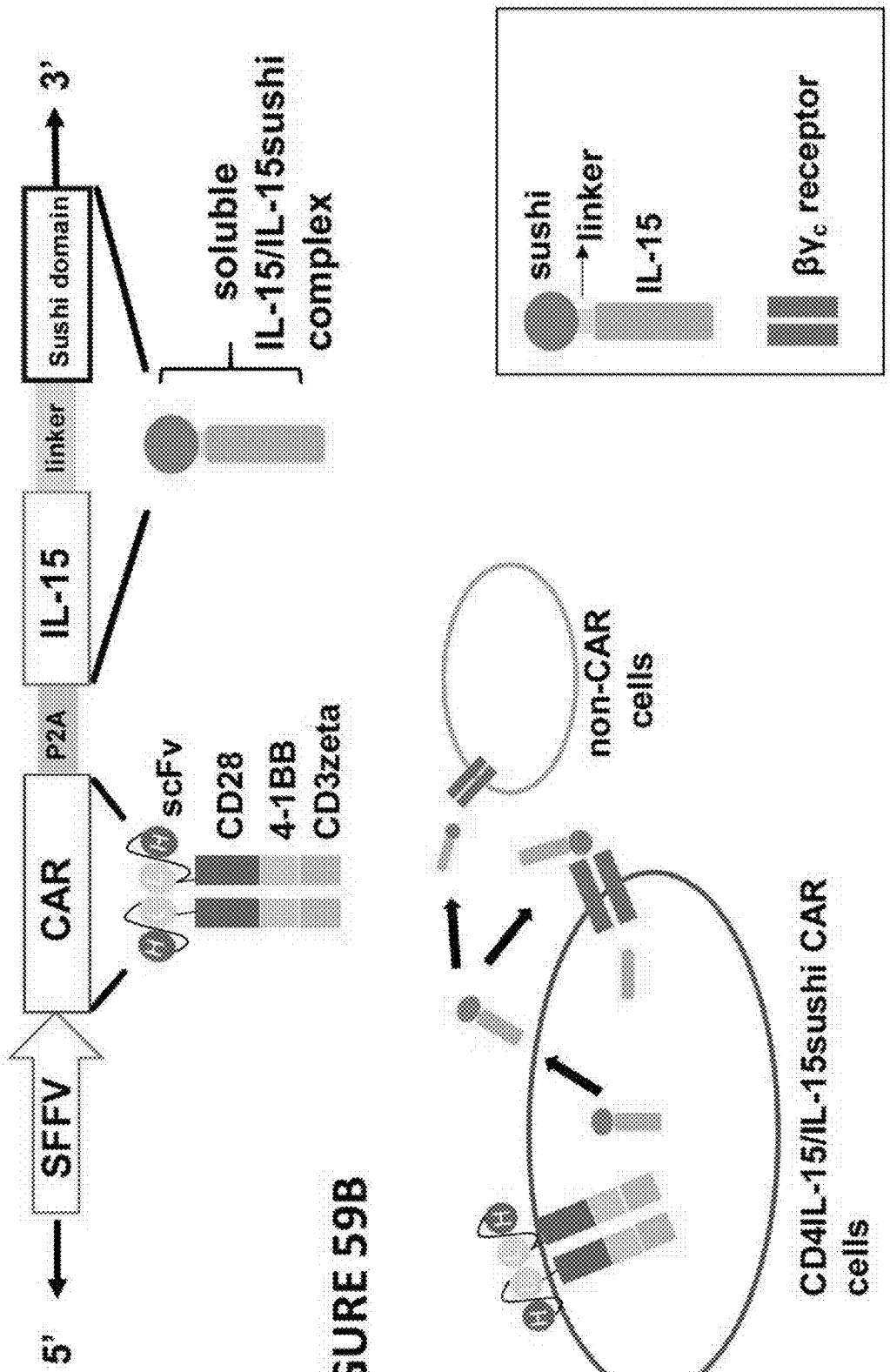


FIGURE 59B

FIGURE 60A

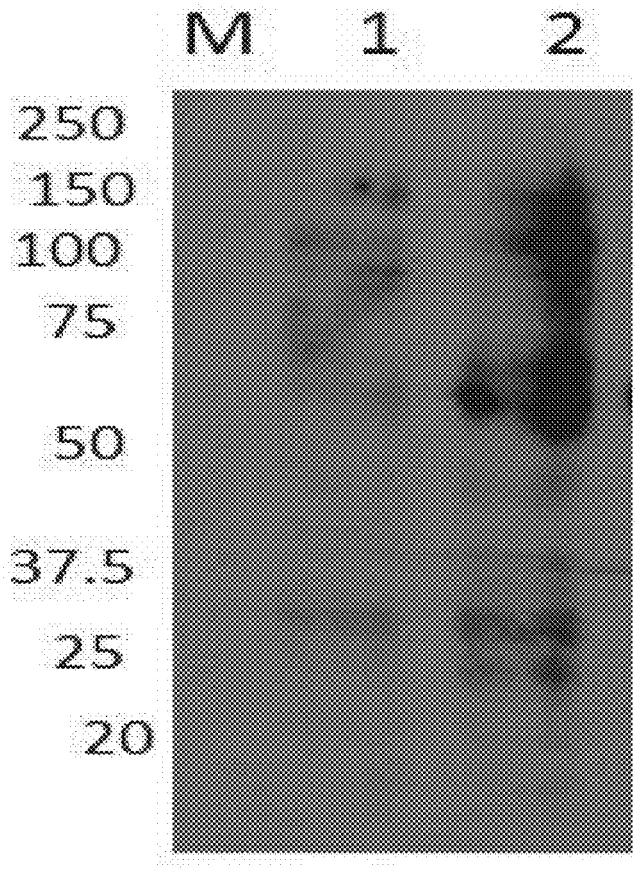


FIGURE 60B

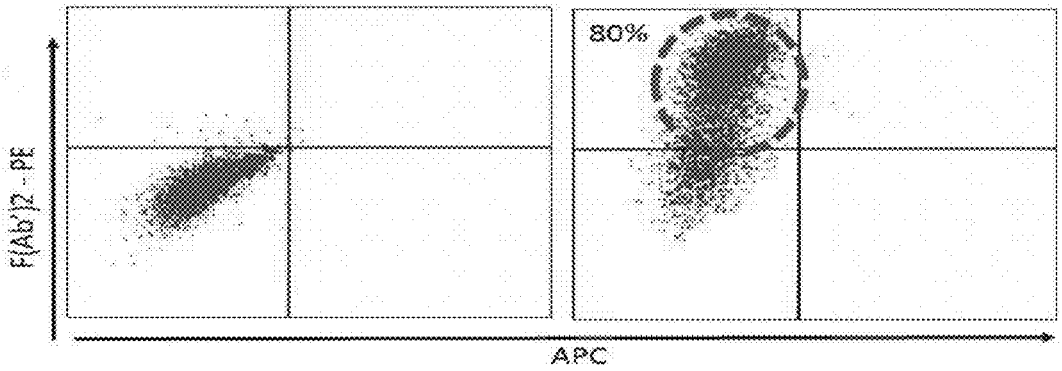


FIGURE 61

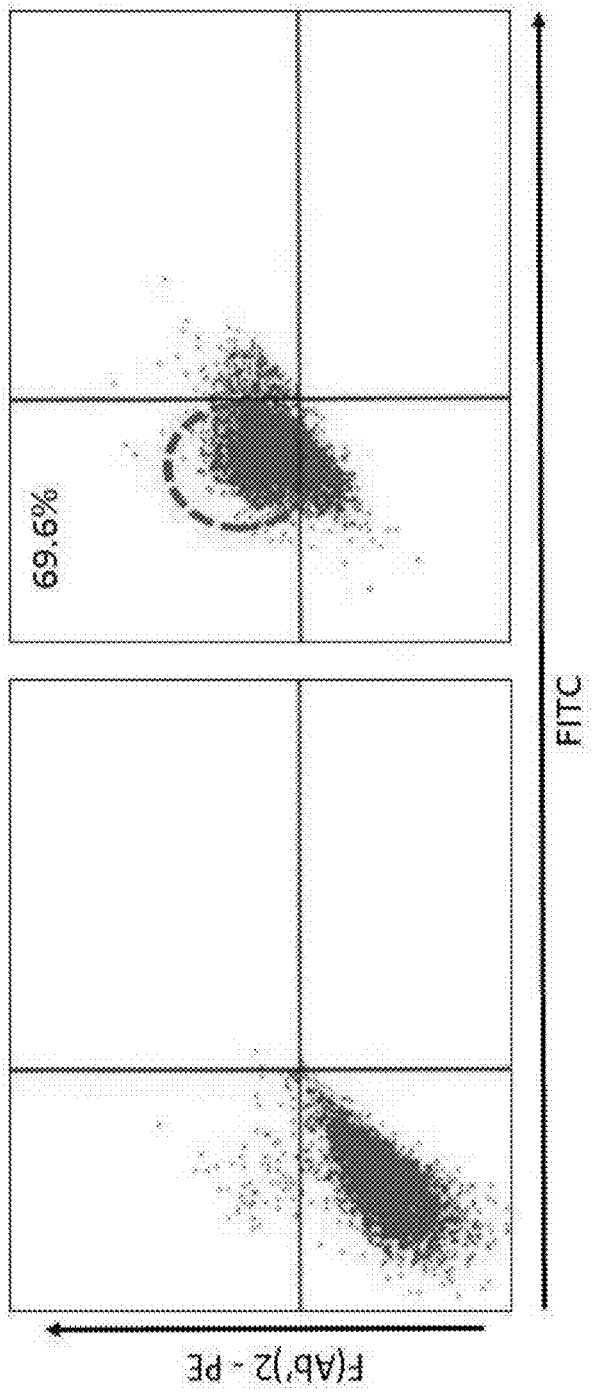


FIGURE 62

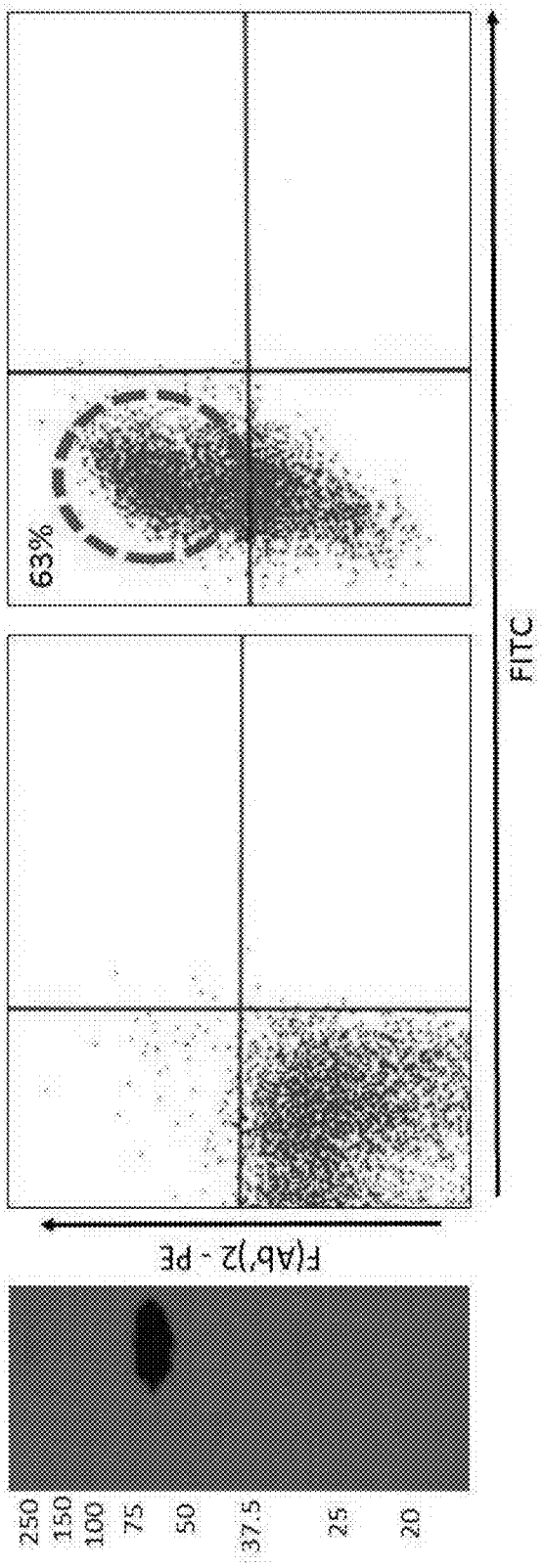
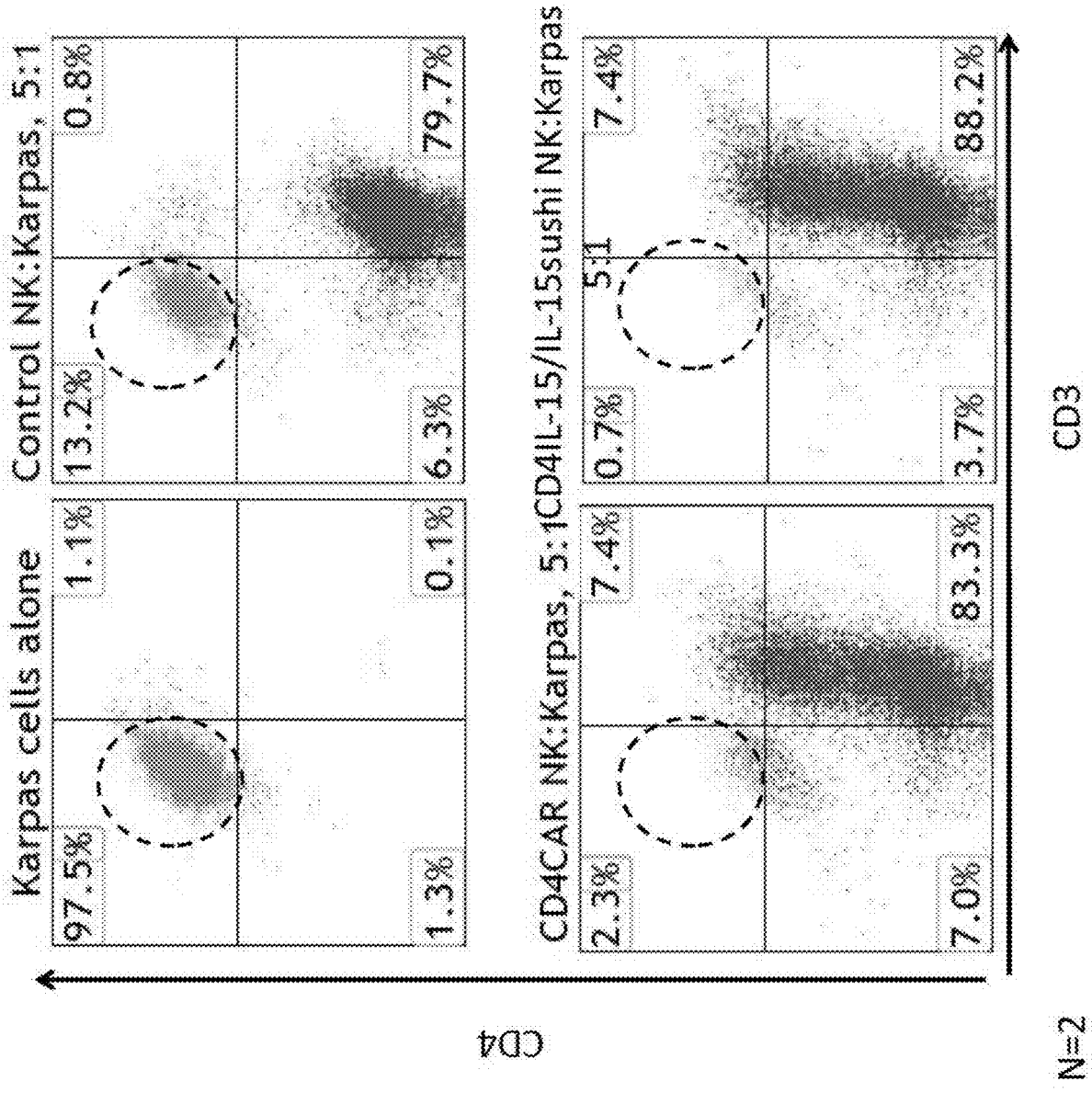


FIGURE 63A


Karpas cells alone
97.5%
1.1%
1.3%
0.1%
Control NK:Karpas, 5:1
13.2%
0.8%
6.3%
79.7%
CD4CAR NK:Karpas, 5:1
CD4IL-15/IL-15sushi NK:Karpas
2.3%
7.4%
7.0%
83.3%
5:1
0.7%
7.4%
3.7%
88.2%
CD4
CD3
N=2

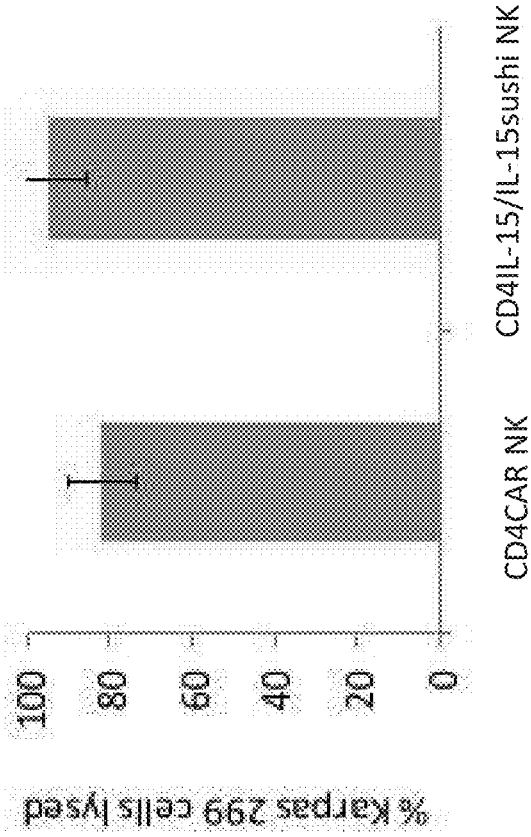

% Karpas 299 cells lysed
100
80
60
40
20
0
CD4CAR NK
CD4IL-15/IL-15sushi NK

FIGURE 63B

FIGURE 64

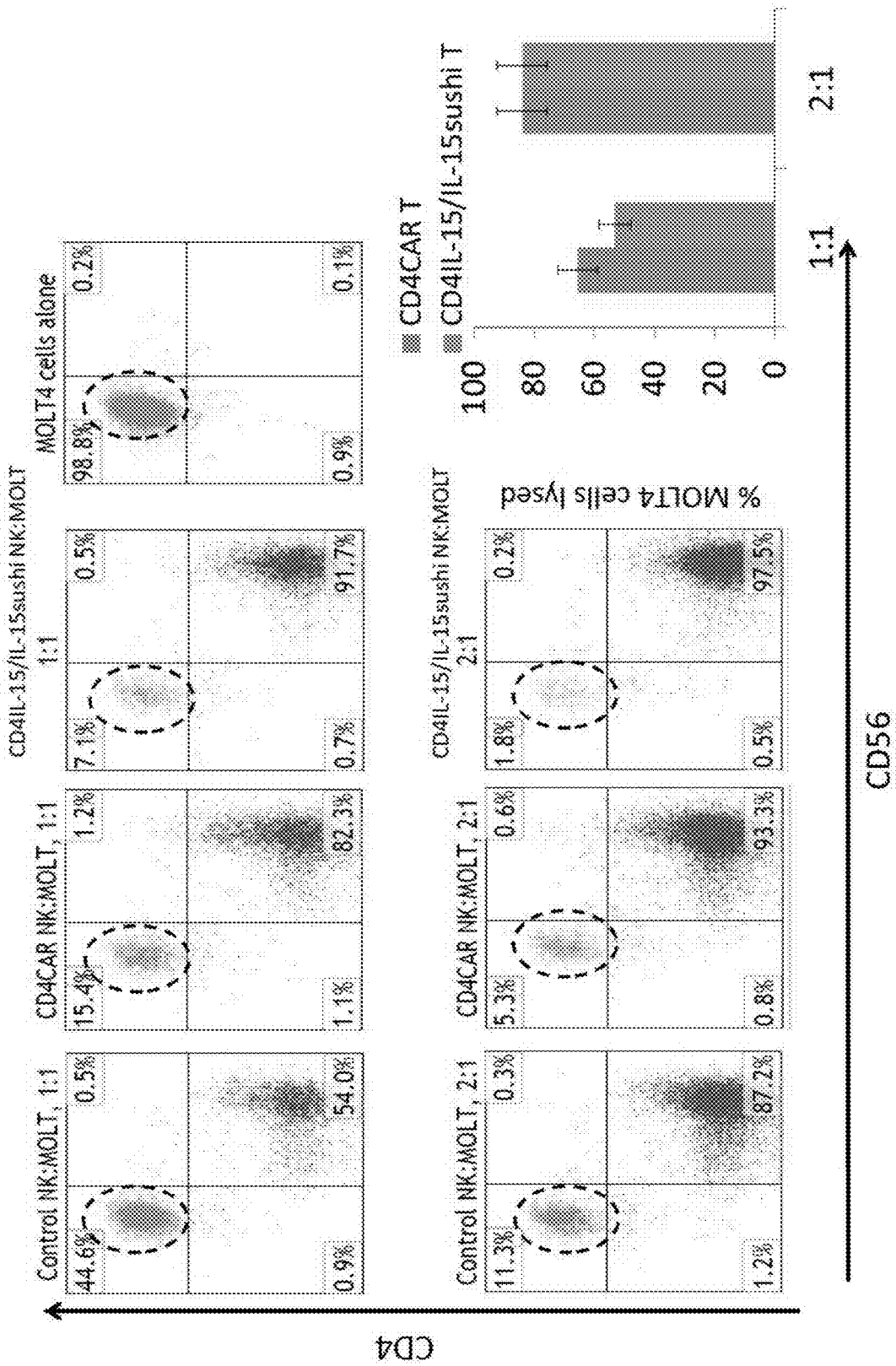
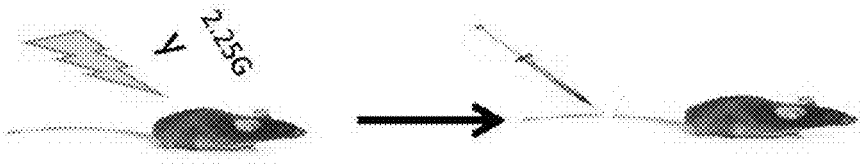

Control NK:MOLT, 1:1
44.6%
0.5%
0.9%
54.0%
CD4CAR NK:MOLT, 1:1
15.4%
1.2%
1.1%
82.3%
CD4IL-15/IL-15sushi NK:MOLT
1:1
7.1%
0.5%
0.7%
91.7%
MOLT4 cells alone
98.8%
0.2%
0.9%
0.1%
Control NK:MOLT, 2:1
11.3%
0.3%
1.2%
87.2%
CD4CAR NK:MOLT, 2:1
5.3%
0.6%
0.8%
93.3%
CD4IL-15/IL-15sushi NK:MOLT
2:1
1.8%
0.2%
0.5%
97.5%
CD4
CD56
CD4CAR T
CD4IL-15/IL-15sushi T
% MOLT4 cells lysed
100
80
60
40
20
0
1:1
2:1

FIGURE 65A



CD4 expression in AML (MOLM13) cells

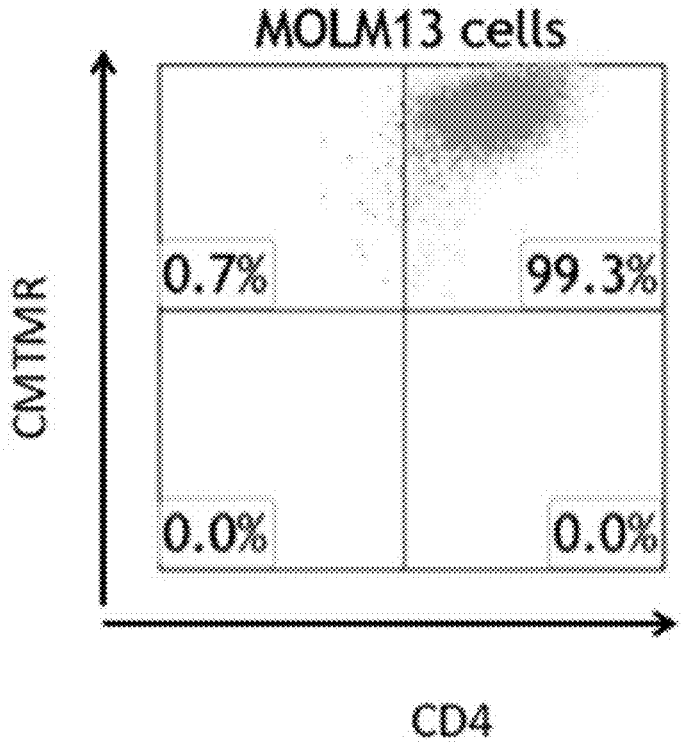


FIGURE 65B

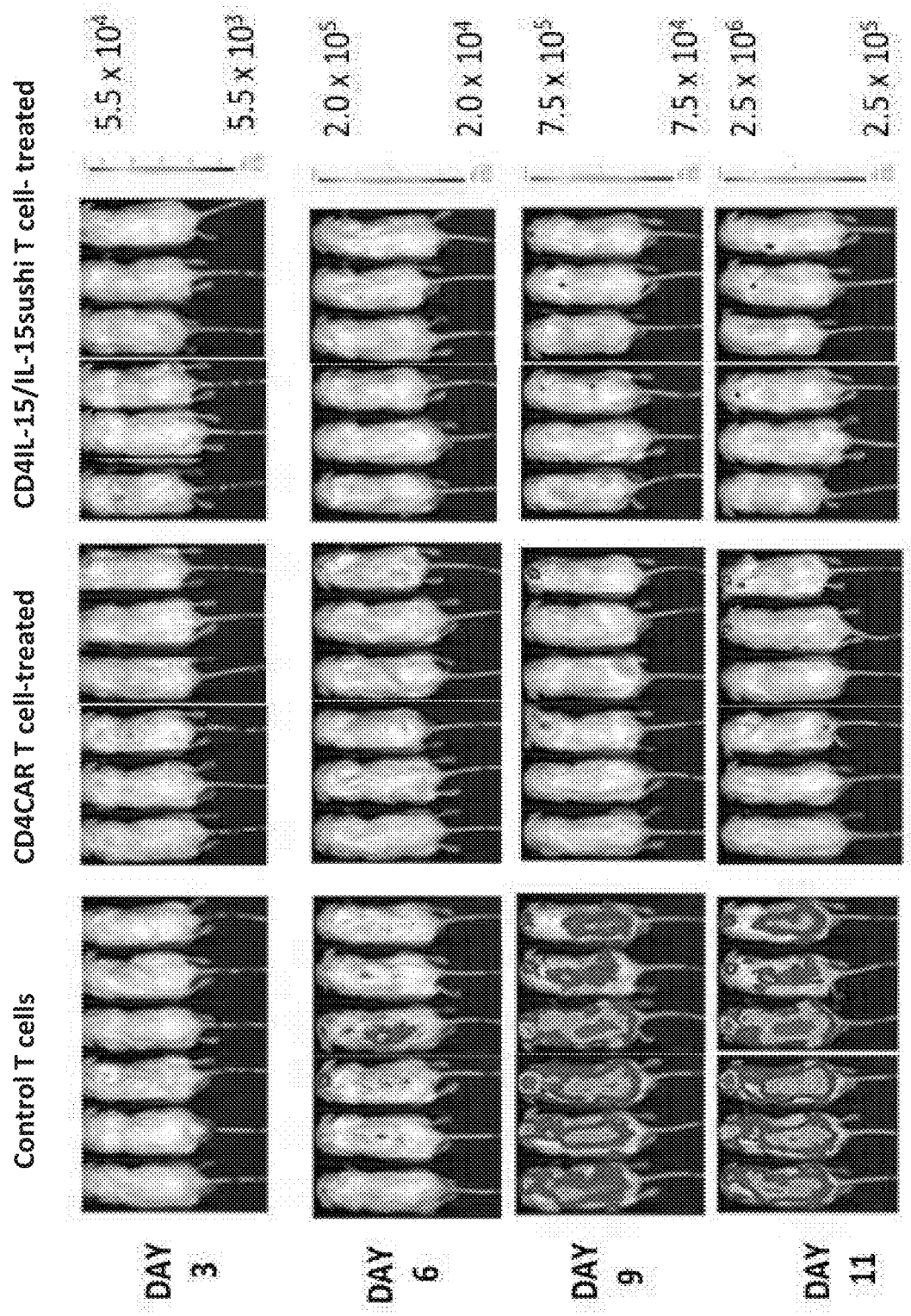

Control T cells
CD4CAR T cell-treated
CD4IL-15/IL-15sushi T cell- treated
DAY 3
DAY 6
DAY 9
DAY 11
5.5 x 10^4
5.5 x 10^3
2.0 x 10^5
2.0 x 10^4
7.5 x 10^5
7.5 x 10^4
2.5 x 10^6
2.5 x 10^5

FIGURE 65C

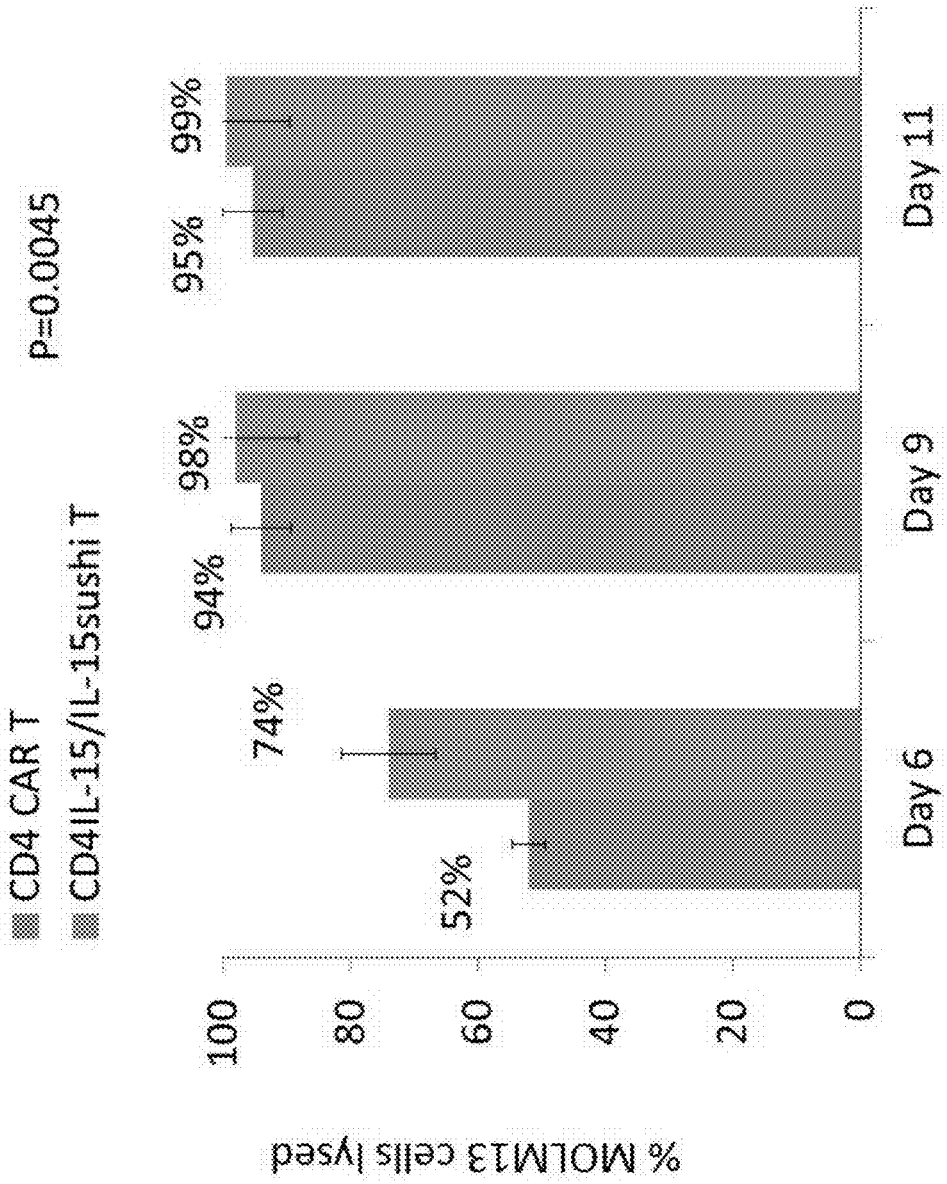

CD4 CAR T
CD4IL-15/IL-15sushi T
P=0.0045
% MOLM13 cells lysed
100
80
60
40
20
0
52%
74%
94%
98%
95%
99%
Day 6
Day 9
Day 11

FIGURE 65D

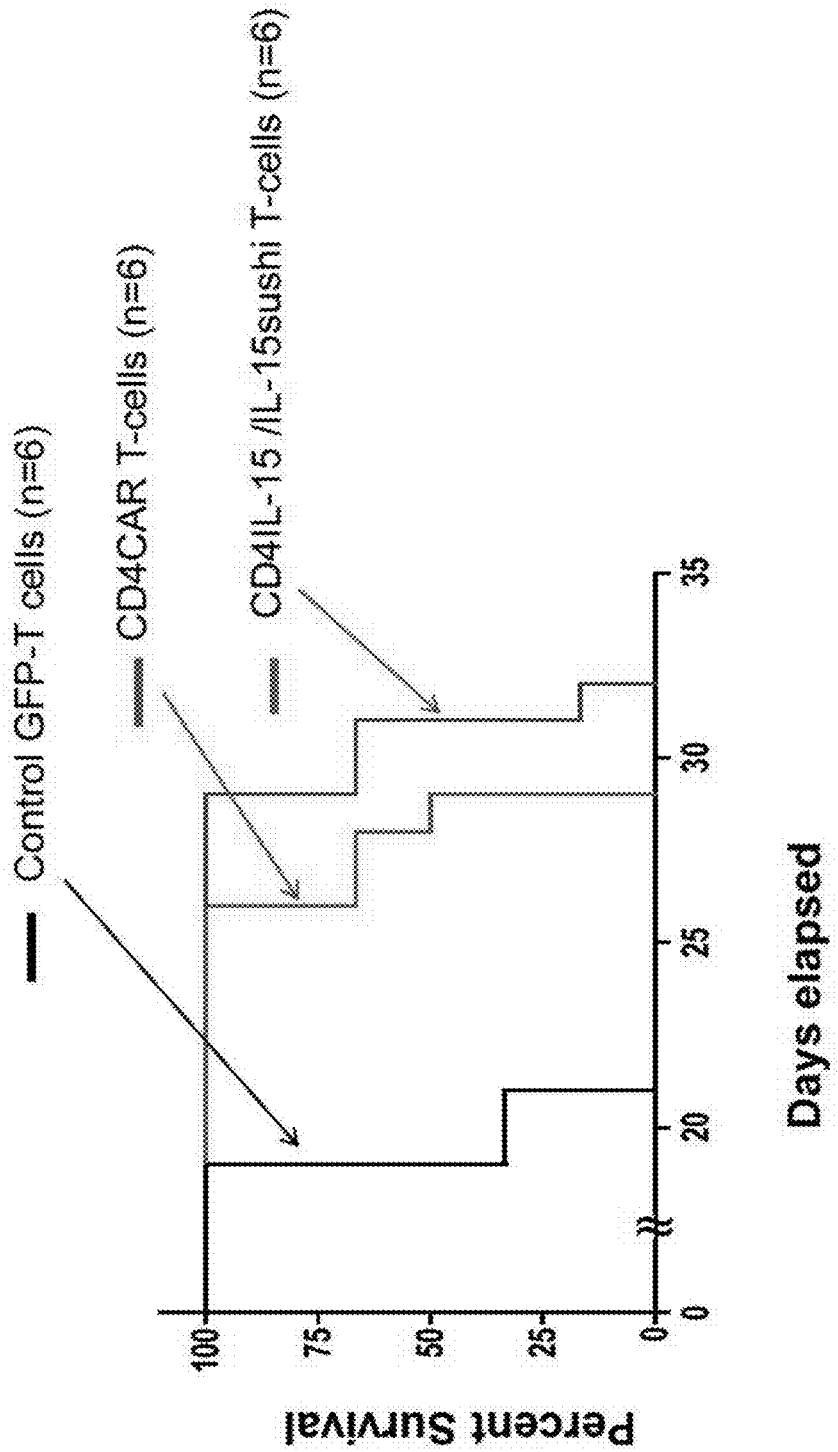

Control GFP-T cells (n=6)
CD4CAR T-cells (n=6)
CD4IL-15 /IL-15sushi T-cells (n=6)
Percent Survival
100
75
50
25
0
0
20
25
30
35
Days elapsed

FIGURE 66A

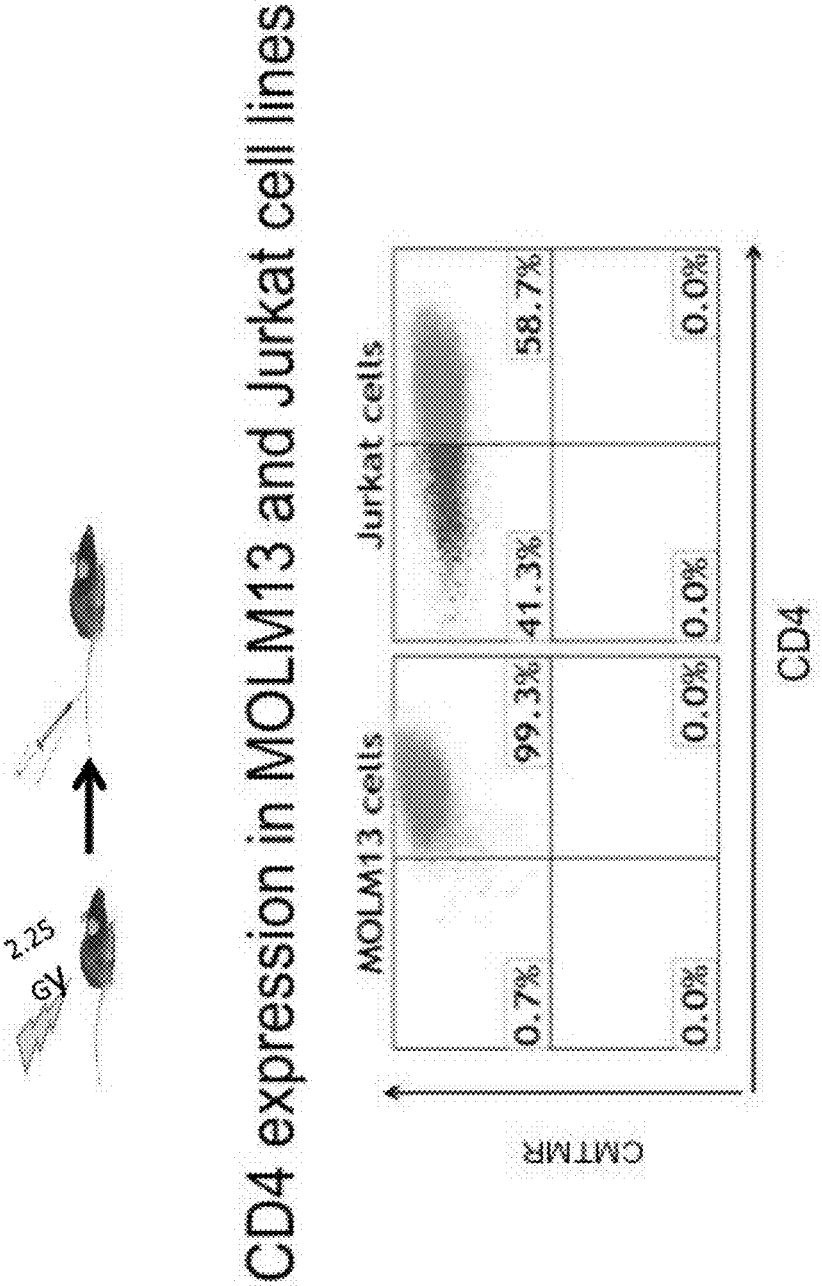

2.25
Gy
CD4 expression in MOLM13 and Jurkat cell lines
MOLM13 cells
Jurkat cells
0.7%
99.3%
0.0%
0.0%
41.3%
58.7%
0.0%
0.0%
CMTMR
CD4

FIGURE 66B

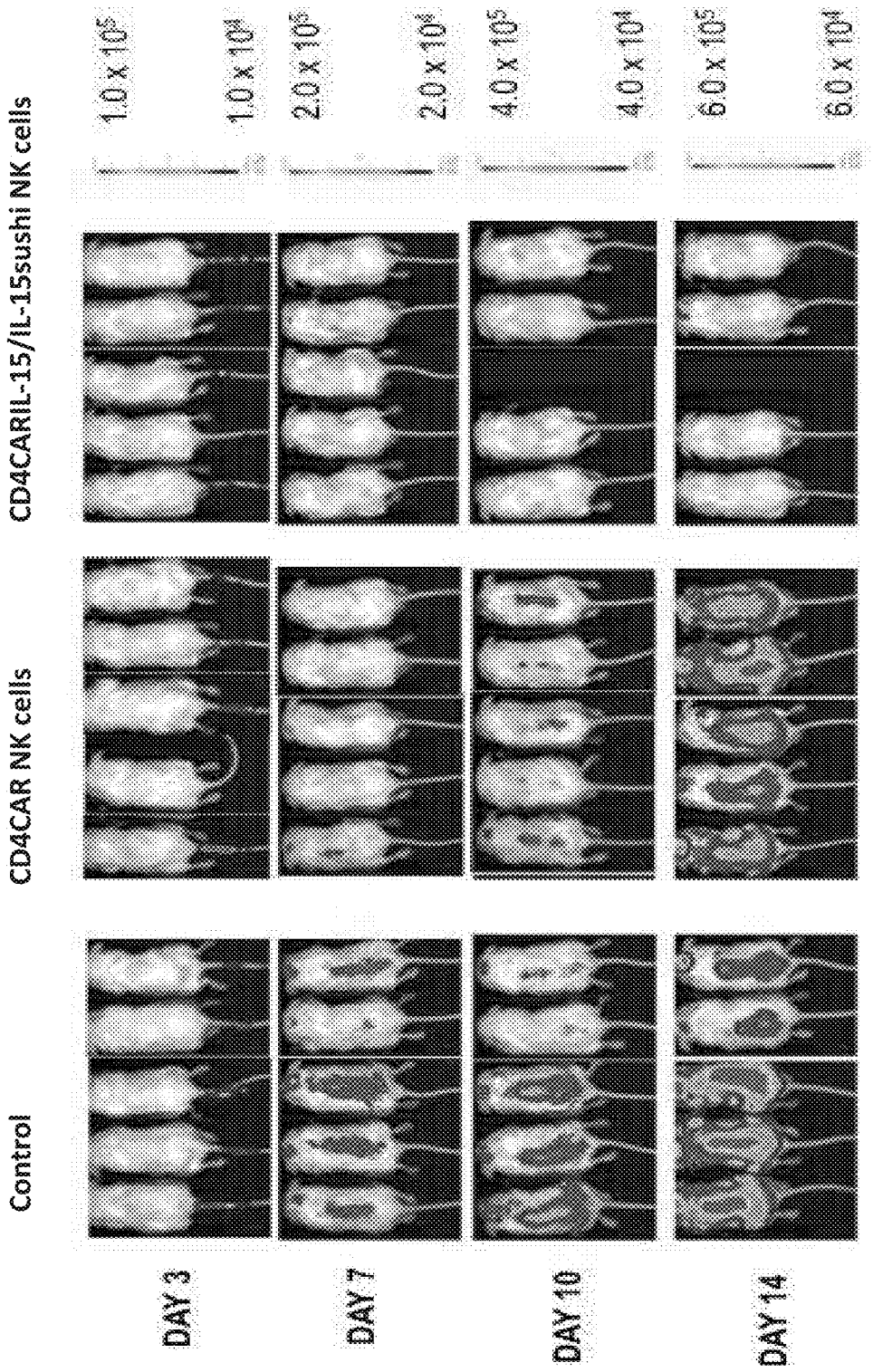

Control
CD4CAR NK cells
CD4CARIL-15/IL-15sushi NK cells
1.0 x 10^5
1.0 x 10^4
2.0 x 10^5
2.0 x 10^4
4.0 x 10^5
4.0 x 10^4
6.0 x 10^5
6.0 x 10^4
DAY 3
DAY 7
DAY 10
DAY 14

FIGURE 66C

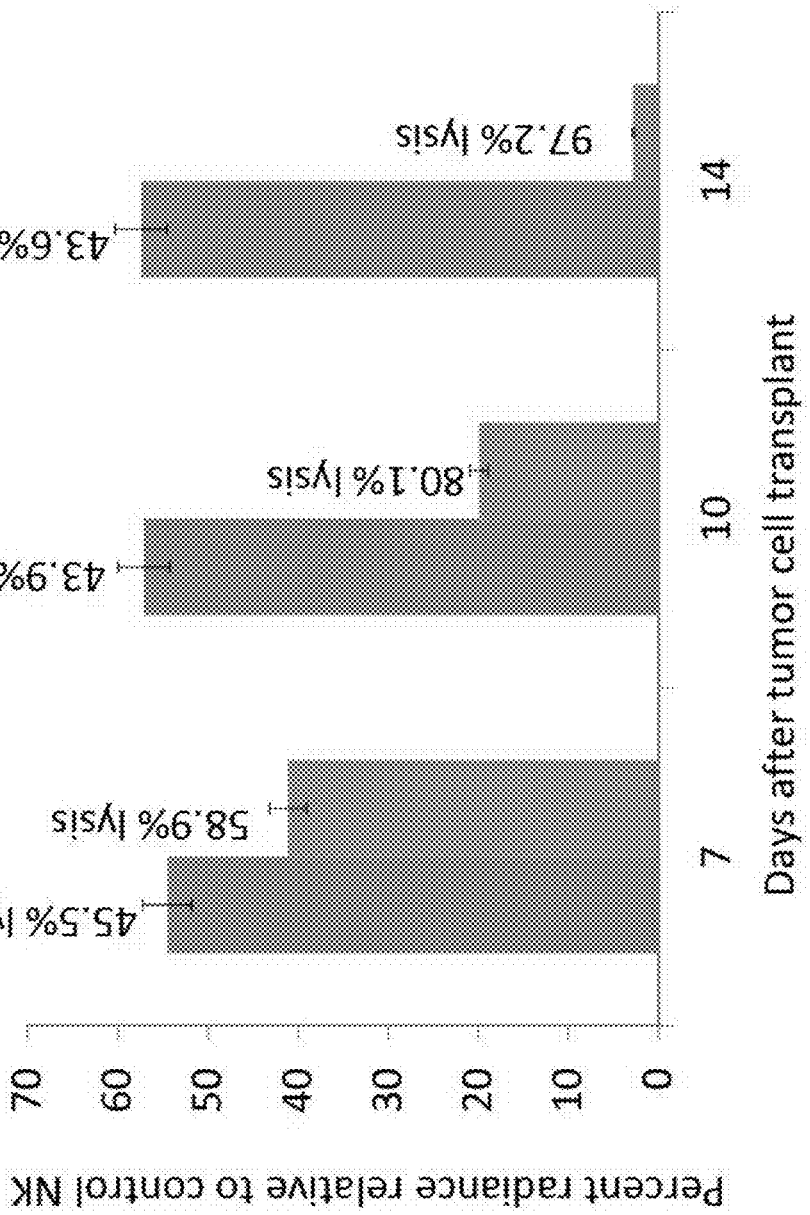

CD4CAR NK
CD4IL-15/IL-15sushi NK
45.5% lysis
58.9% lysis
43.9% lysis
80.1% lysis
43.6% lysis
97.2% lysis
Percent radiance relative to control NK
70
60
50
40
30
20
10
0
7
10
14
Days after tumor cell transplant

FIGURE 66D

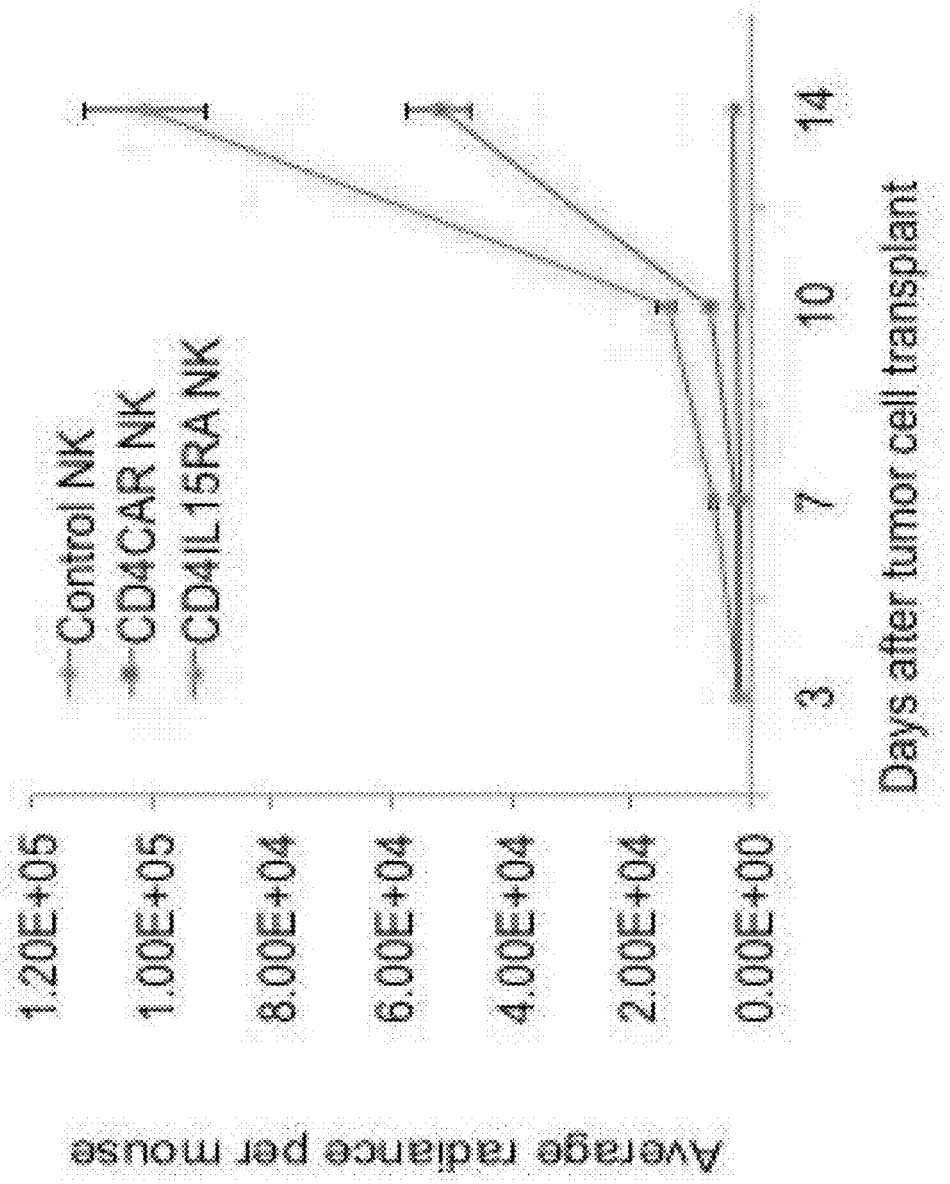

Control NK
CD4CAR NK
CD4IL15RA NK
1.20E+05
1.00E+05
8.00E+04
6.00E+04
4.00E+04
2.00E+04
0.00E+00
Average radiance per mouse
3
7
10
14
Days after tumor cell transplant

FIGURE 67A

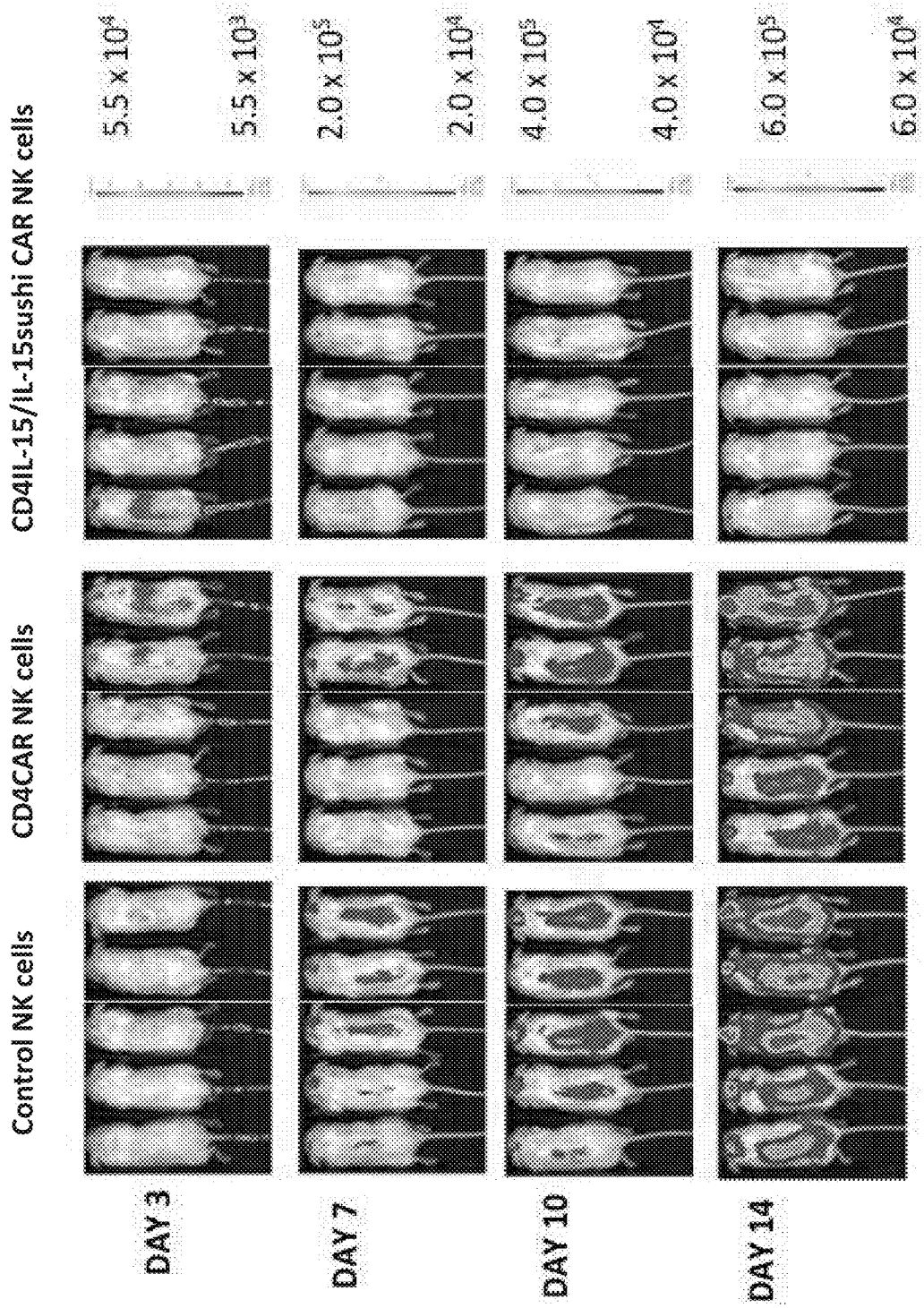

Control NK cells
CD4CAR NK cells
CD4IL-15/IL-15sushi CAR NK cells
DAY 3
DAY 7
DAY 10
DAY 14
5.5 x 10^4
5.5 x 10^3
2.0 x 10^5
2.0 x 10^4
4.0 x 10^5
4.0 x 10^4
6.0 x 10^5
6.0 x 10^4

FIGURE 67B

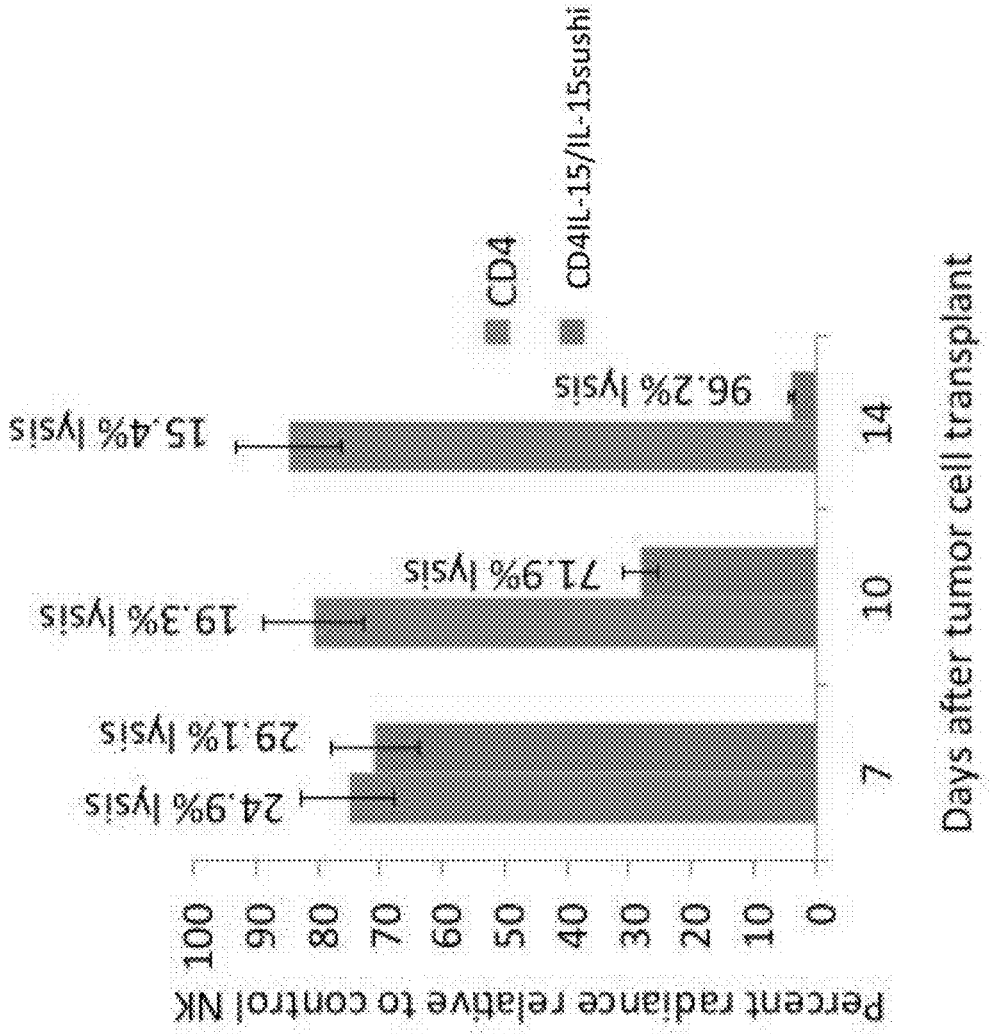

Percent radiance relative to control NK
100
90
80
70
60
50
40
30
20
10
0
24.9% lysis
29.1% lysis
19.3% lysis
71.9% lysis
15.4% lysis
96.2% lysis
7
10
14
Days after tumor cell transplant
CD4
CD4IL-15/IL-15sushi

FIGURE 68A

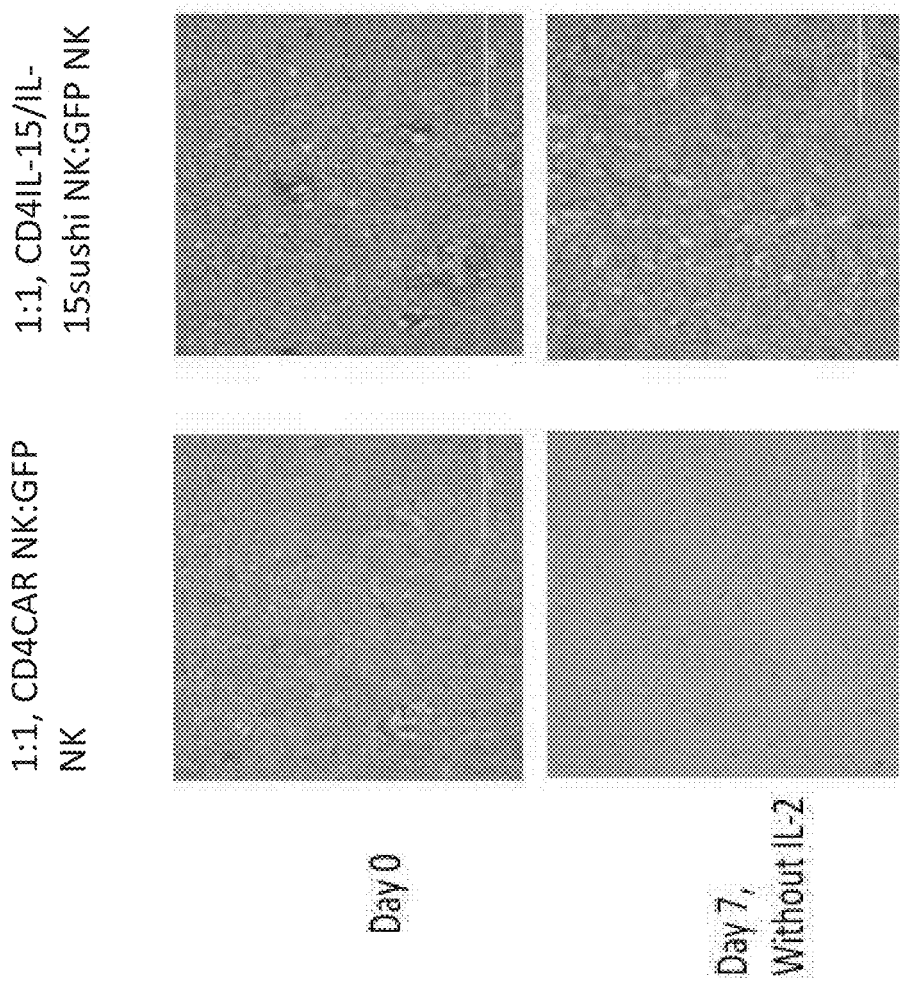

1:1, CD4CAR NK:GFP NK
1:1, CD4IL-15/IL-15sushi NK:GFP NK
Day 0
Day 7, Without IL-2

FIGURE 68B

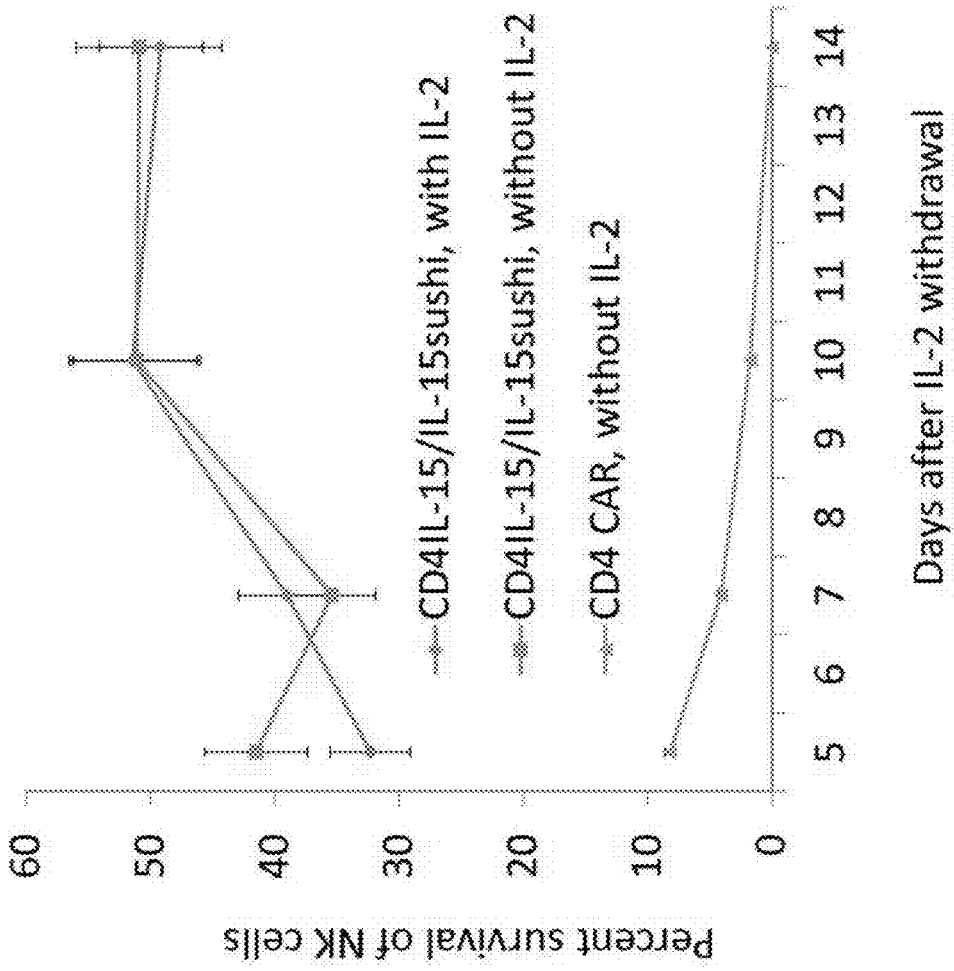

Percent survival of NK cells
60
50
40
30
20
10
0
5
6
7
8
9
10
11
12
13
14
Days after IL-2 withdrawal
CD4IL-15/IL-15sushi, with IL-2
CD4IL-15/IL-15sushi, without IL-2
CD4 CAR, without IL-2

FIGURE 69

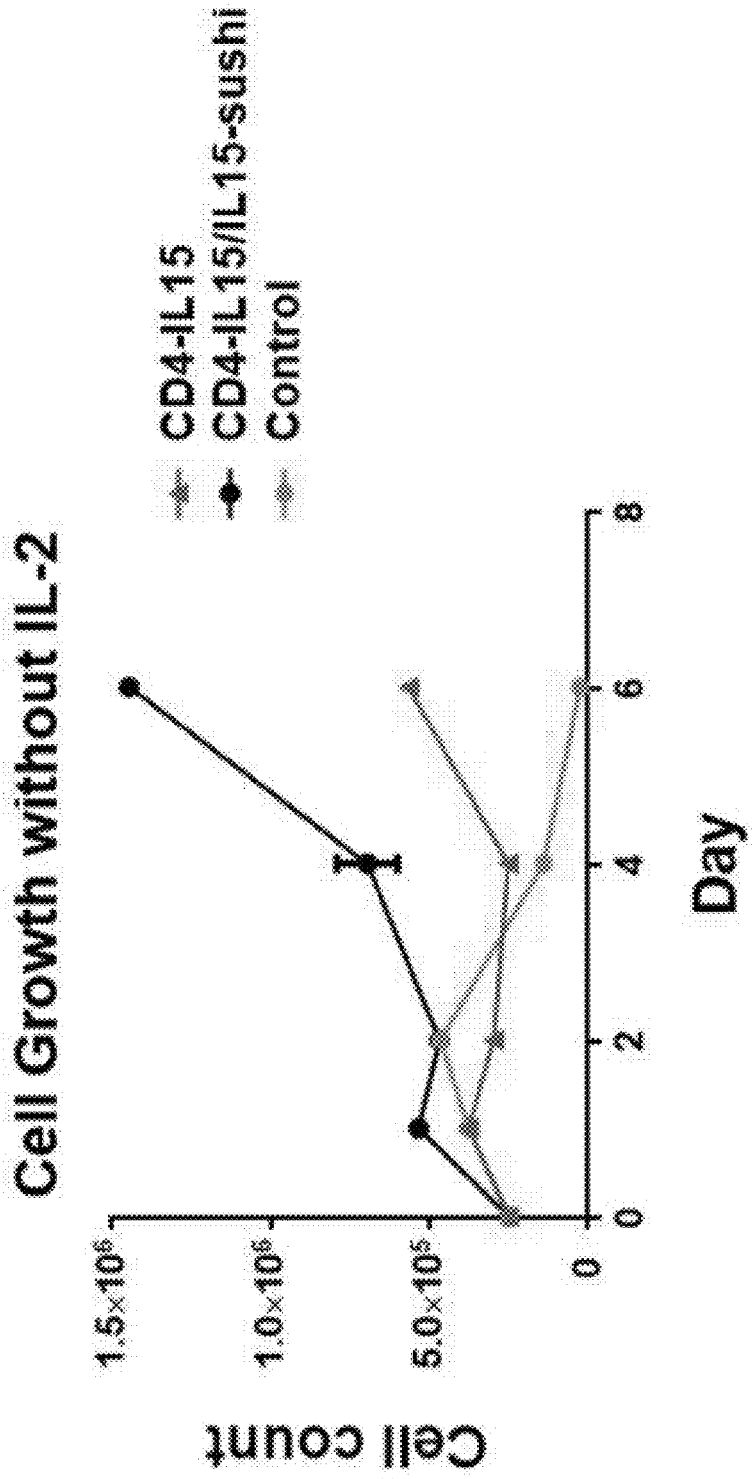

Cell Growth without IL-2
CD4-IL15
CD4-IL15/IL15-sushi
Control
Cell count
1.5×10^6
1.0×10^6
5.0×10^5
0
0
2
4
6
8
Day

FIGURE 70

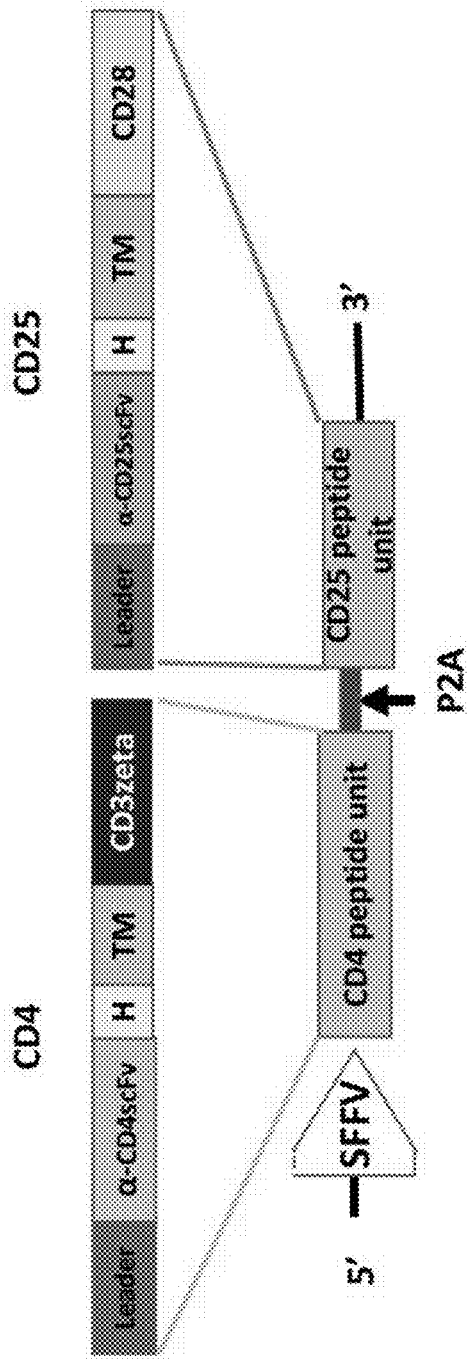

CD4
Leader
α-CD4scFv
H
TM
CD3zeta
CD25
Leader
α-CD25scFv
H
TM
CD28
5'
SFFV
CD4 peptide unit
P2A
CD25 peptide unit
3'

FIGURE 71A

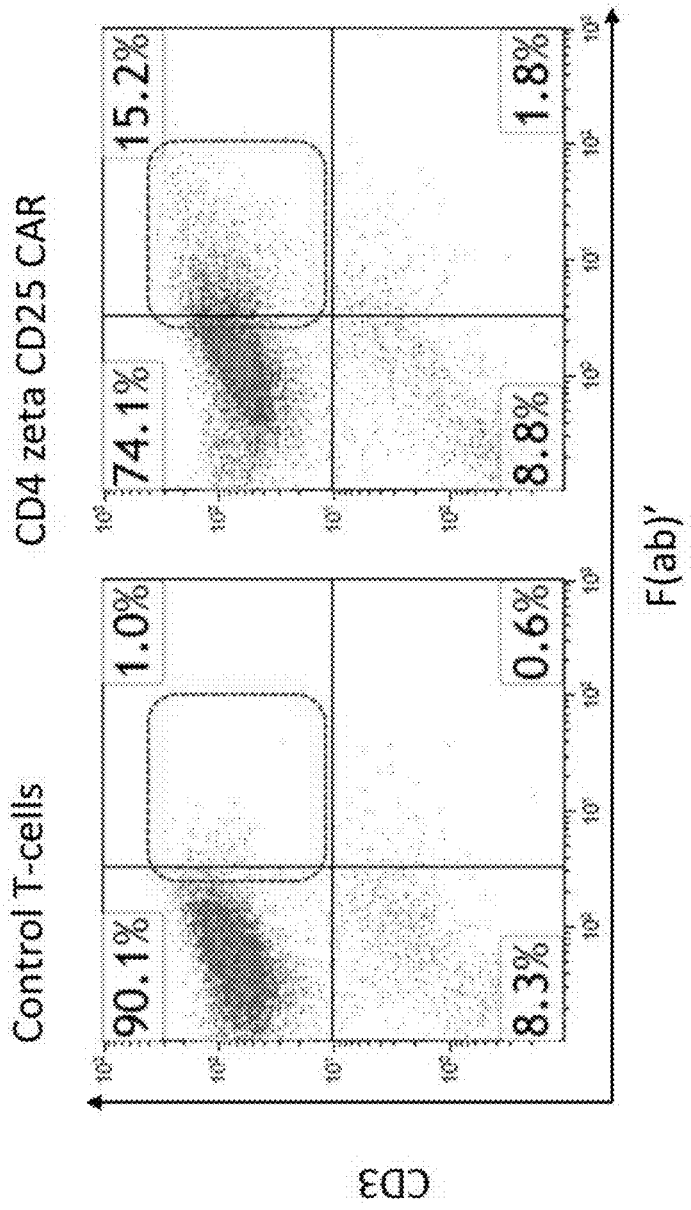
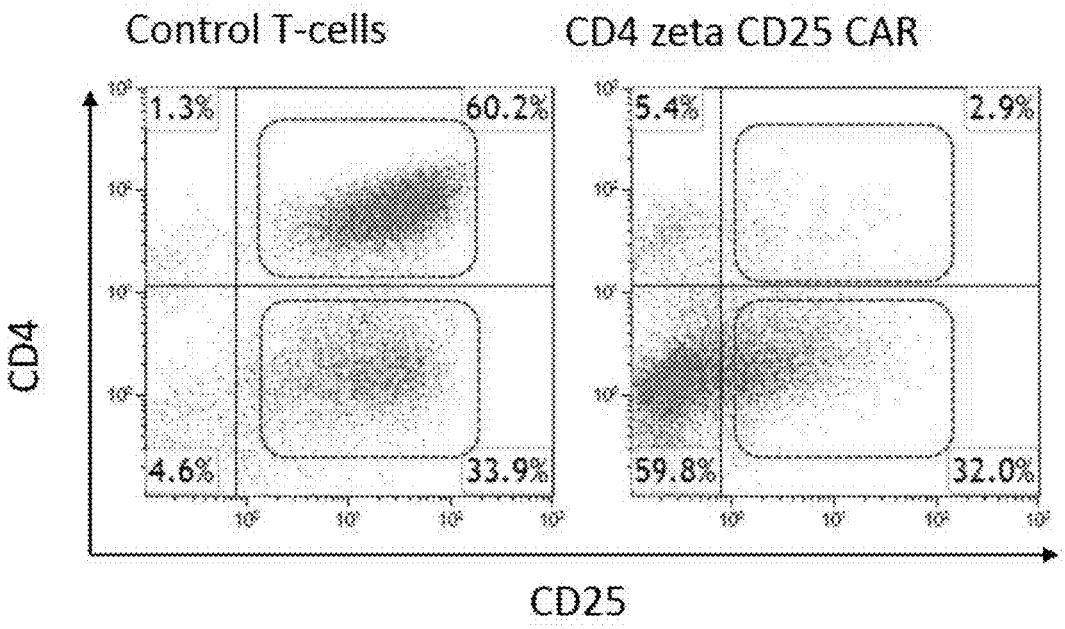
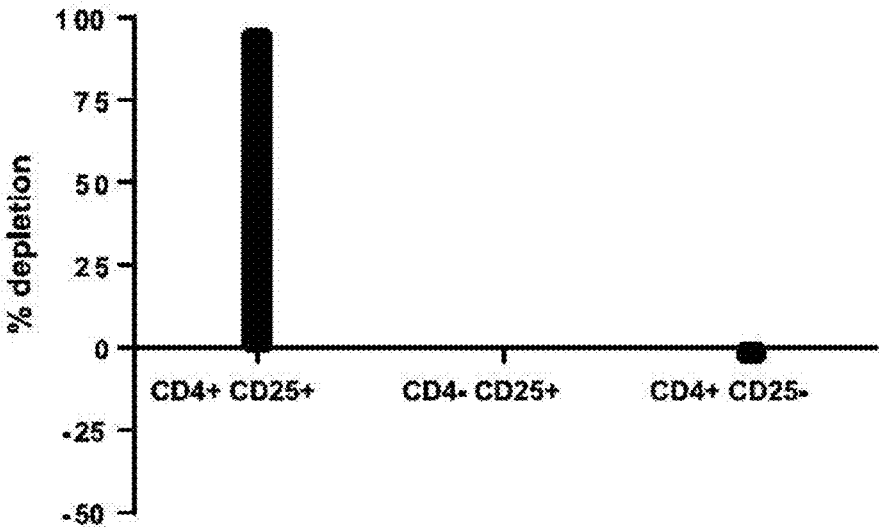

Control T-cells
CD4 zeta CD25 CAR
90.1%
1.0%
8.3%
0.6%
74.1%
15.2%
8.8%
1.8%
CD3
F(ab)'

FIGURE 71B


Control T-cells
CD4 zeta CD25 CAR
1.3%
60.2%
4.6%
33.9%
5.4%
2.9%
59.8%
32.0%
CD4
CD25


100
75
50
25
0
-25
-50
% depletion
CD4+ CD25+
CD4- CD25+
CD4+ CD25-

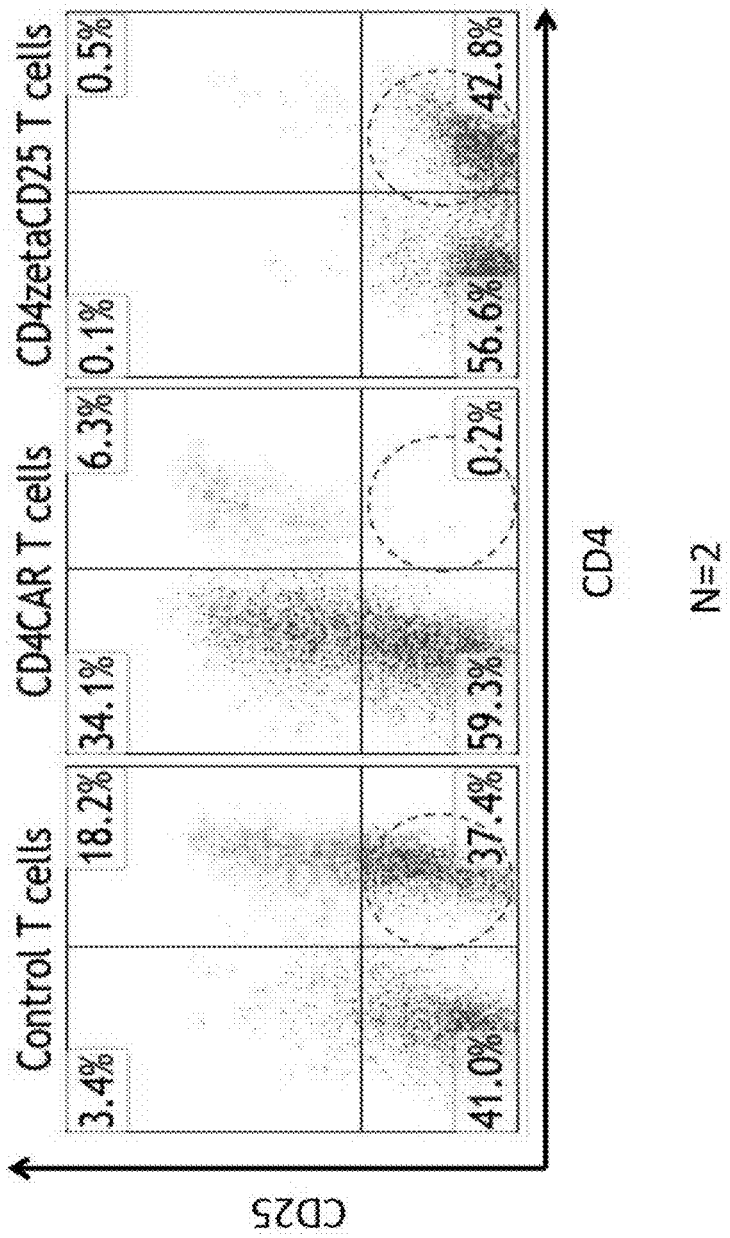

Control T cells
CD4CAR T cells
CD4zetaCD25 T cells
3.4%
18.2%
34.1%
6.3%
0.1%
0.5%
41.0%
37.4%
59.3%
0.2%
56.6%
42.8%
CD25
CD4
N=2

FIGURE 72

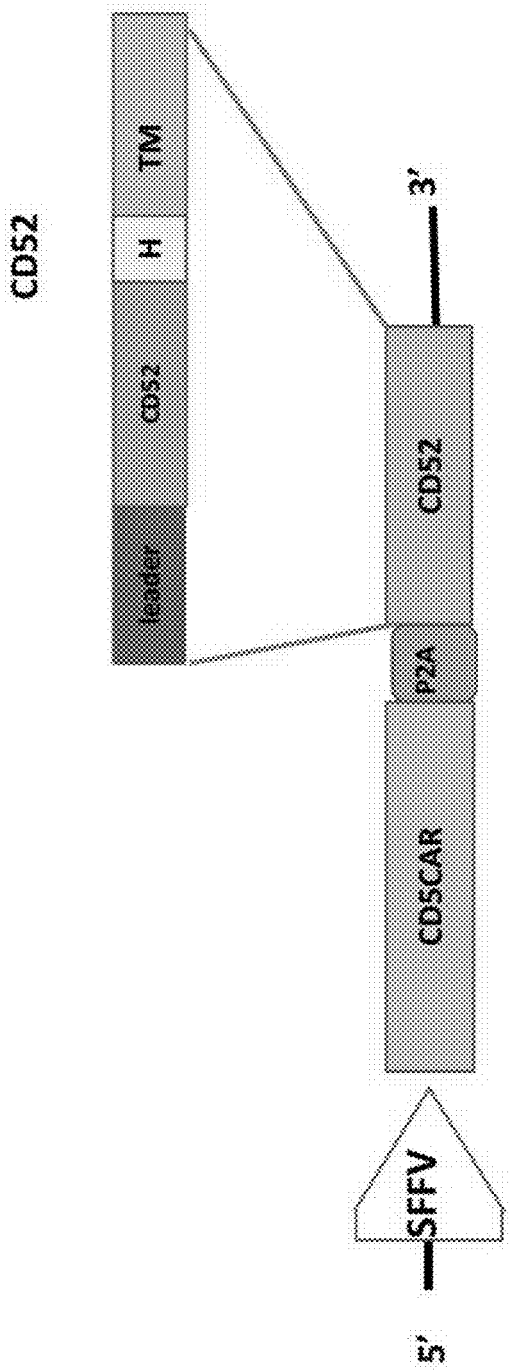


FIGURE 73A

FIGURE 73B

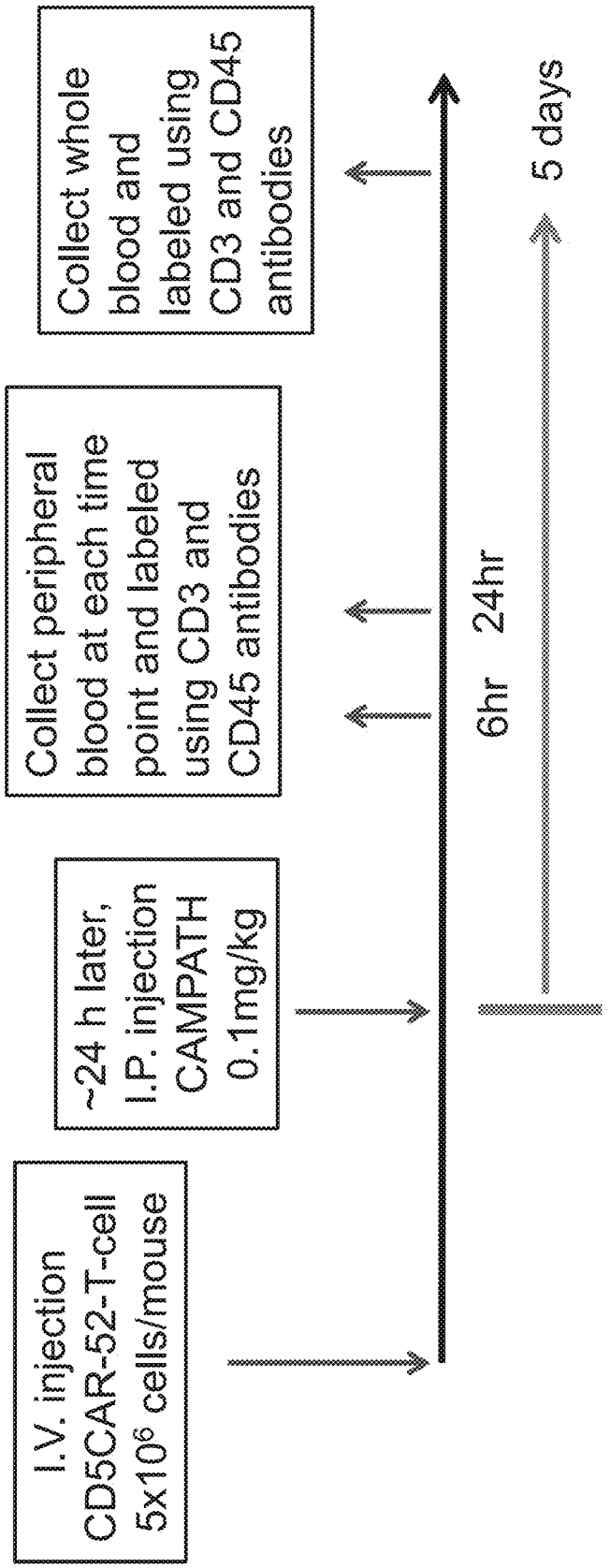

I.V. injection
CD5CAR-52-T-cell
5x10^6 cells/mouse
~24 h later,
I.P. injection
CAMPATH
0.1mg/kg
Collect peripheral
blood at each time
point and labeled
using CD3 and
CD45 antibodies
Collect whole
blood and
labeled using
CD3 and CD45
antibodies
6hr
24hr
5 days

FIGURE 73C

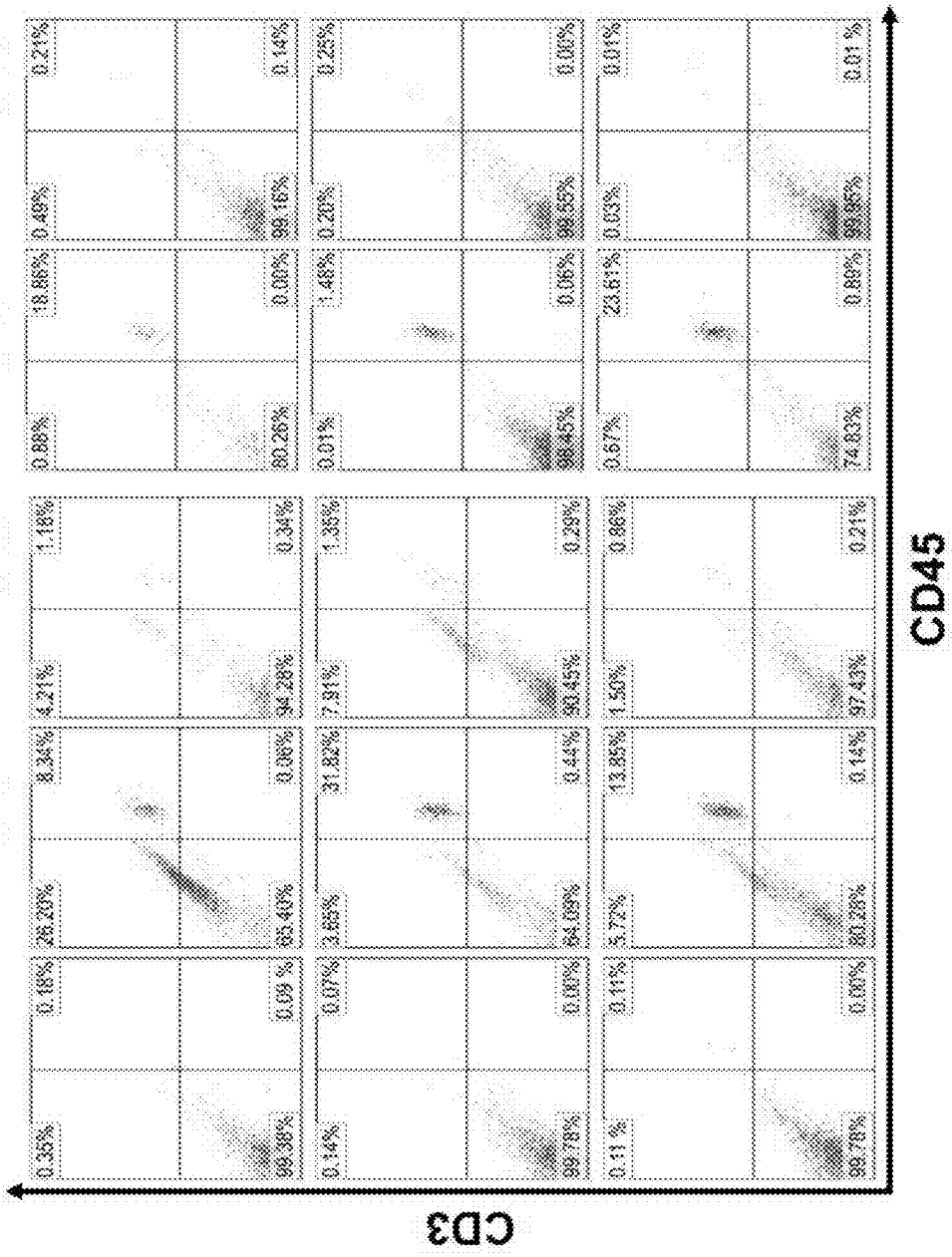

Uninfused CAR-T cells
6 h later CAMPATH 0 mg/kg
6 h later CAMPATH 0.1 mg/kg
24 h later CAMPATH 0 mg/kg
24 h later CAMPATH 0.1 mg/kg
0.35%
0.18%
28.20%
8.34%
4.21%
1.18%
0.88%
18.88%
0.49%
0.21%
99.36%
0.09 %
65.40%
0.06%
94.28%
0.34%
80.26%
0.00%
99.16%
0.14%
0.14%
0.07%
3.65%
31.82%
7.81%
1.35%
0.01%
1.48%
0.20%
0.25%
99.78%
0.00%
64.09%
0.44%
90.45%
0.29%
99.45%
0.06%
99.55%
0.00%
0.11 %
0.11%
5.72%
13.85%
1.50%
0.86%
0.67%
23.61%
0.03%
0.01%
99.78%
0.00%
80.28%
0.14%
97.43%
0.21%
74.83%
0.80%
99.86%
0.01 %
CD3
CD45

FIGURE 73D

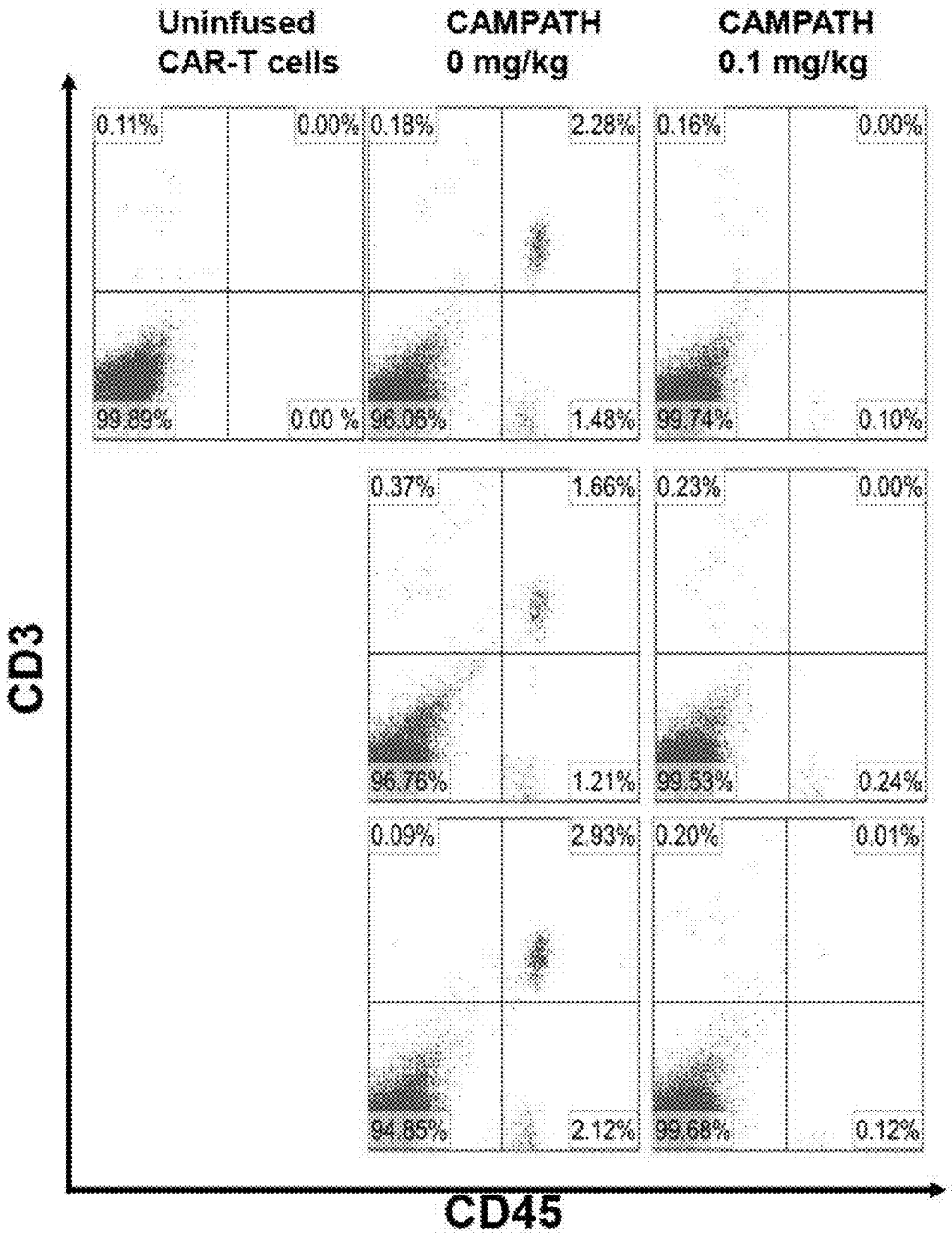
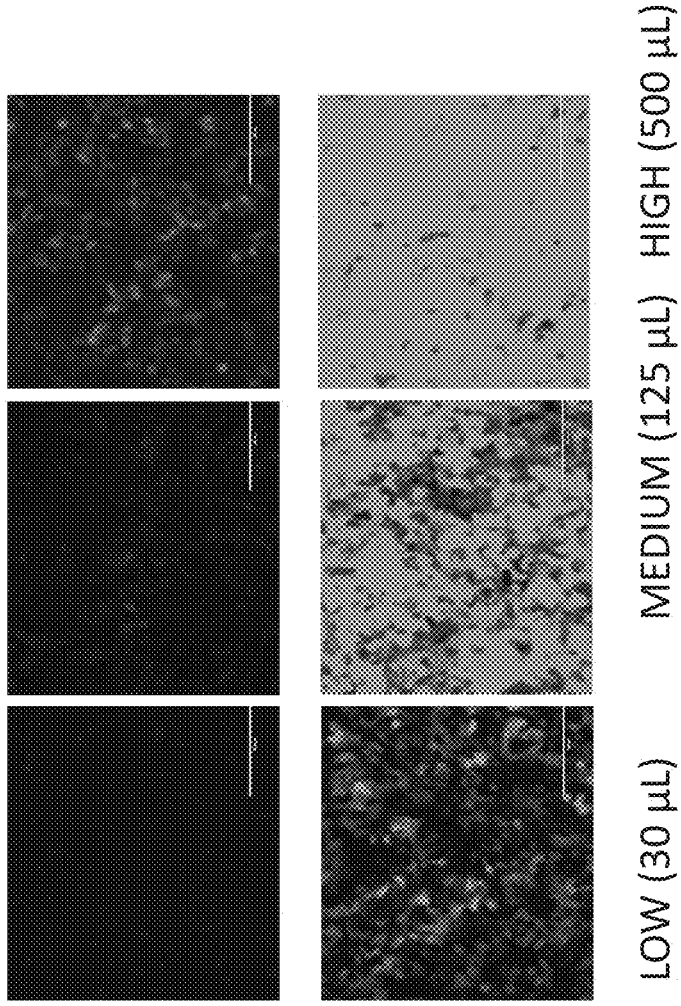

Uninfused CAR-T cells
CAMPATH 0 mg/kg
CAMPATH 0.1 mg/kg
0.11%
0.00%
99.89%
0.00 %
0.18%
2.28%
96.06%
1.48%
0.16%
0.00%
99.74%
0.10%
0.37%
1.66%
96.76%
1.21%
0.23%
0.00%
99.53%
0.24%
0.09%
2.93%
94.85%
2.12%
0.20%
0.01%
99.68%
0.12%
CD3
CD45

FIGURE 74


EF1 promoter
SFFV promoter
LOW (30 µL)
MEDIUM (125 µL)
HIGH (500 µL)

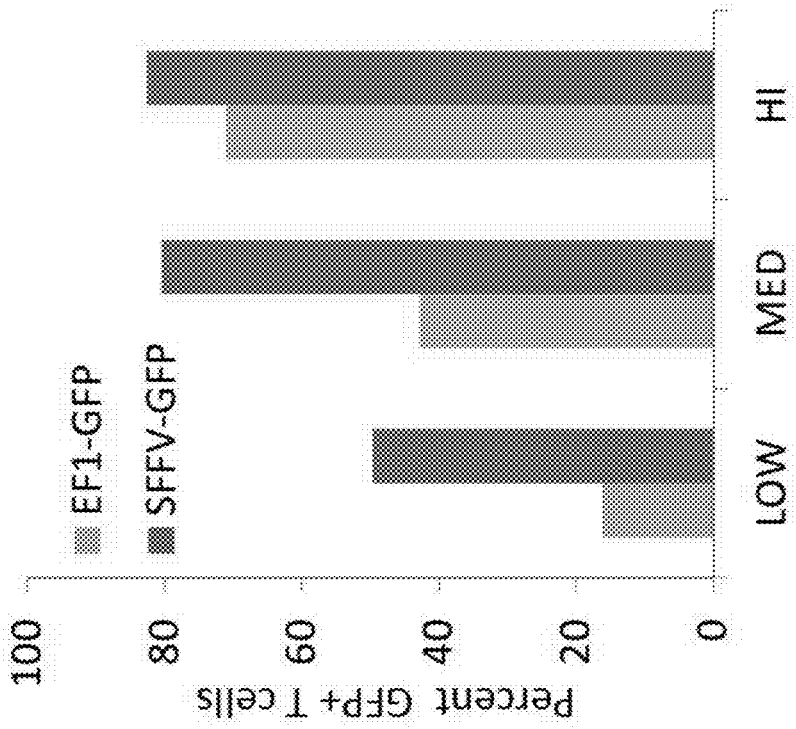


FIGURE 75

FIGURE 76A

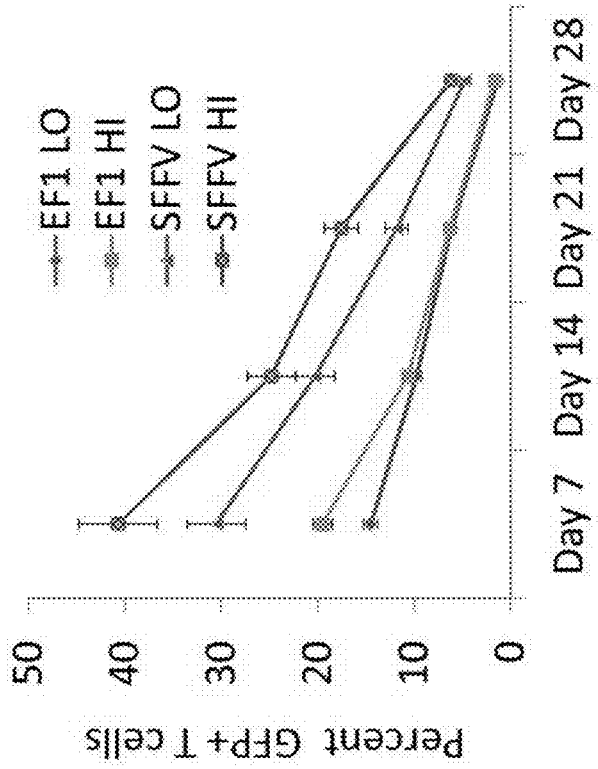


FIGURE 76B

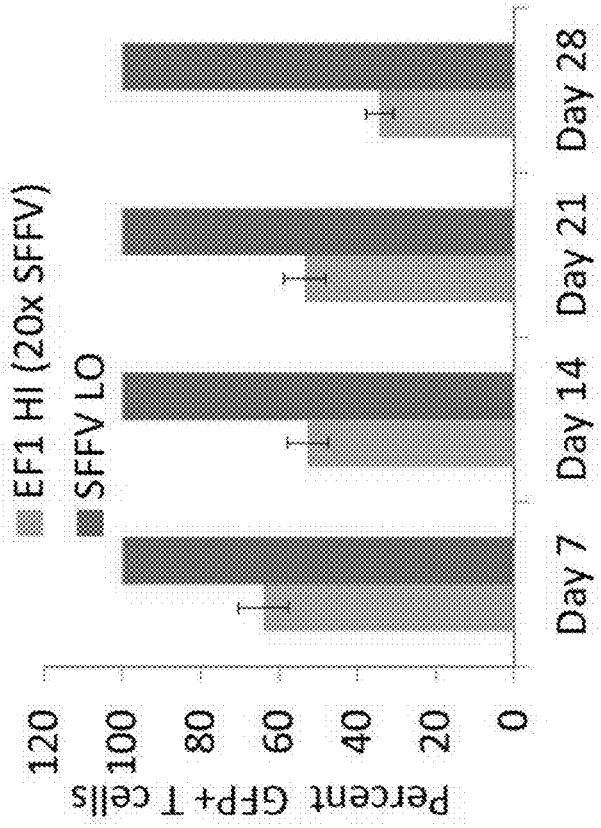
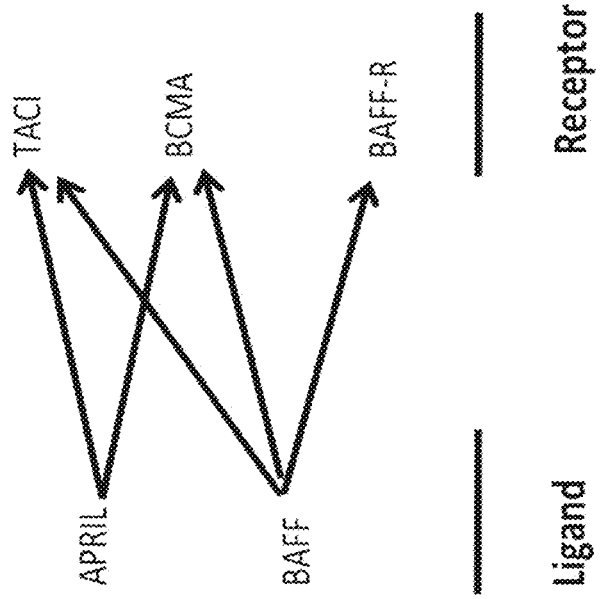


FIGURE 77



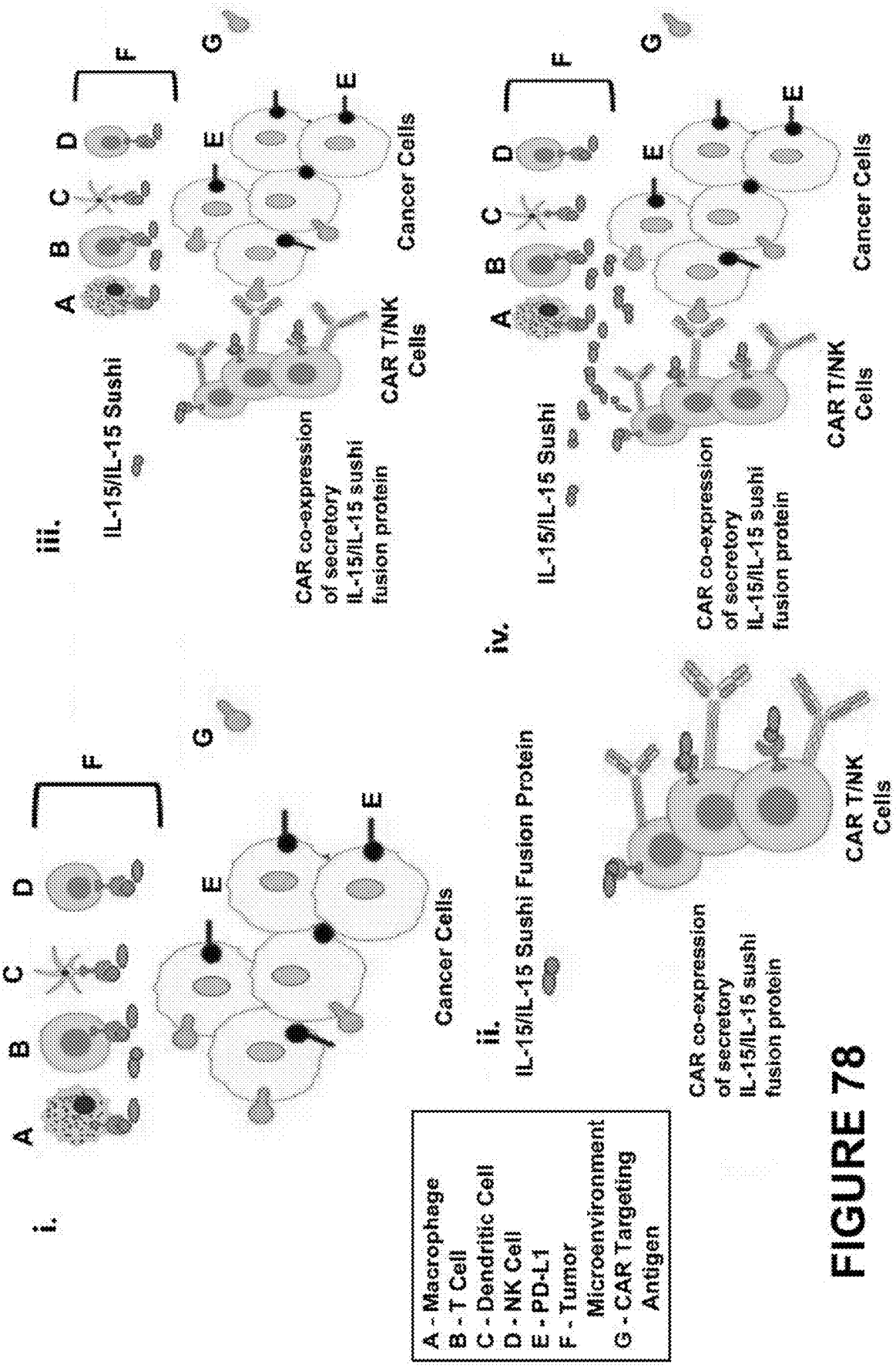

i.
A
B
C
D
F
E
E
G
Cancer Cells
ii.
IL-15/IL-15 Sushi Fusion Protein
CAR co-expression of secretory IL-15/IL-15 sushi fusion protein
CAR T/NK Cells
iii.
IL-15/IL-15 Sushi
CAR co-expression of secretory IL-15/IL-15 sushi fusion protein
CAR T/NK Cells
Cancer Cells
iv.
IL-15/IL-15 Sushi
CAR co-expression of secretory IL-15/IL-15 sushi fusion protein
CAR T/NK Cells
Cancer Cells
A - Macrophage
B - T Cell
C - Dendritic Cell
D - NK Cell
E - PD-L1
F - Tumor Microenvironment
G - CAR Targeting Antigen

FIGURE 78

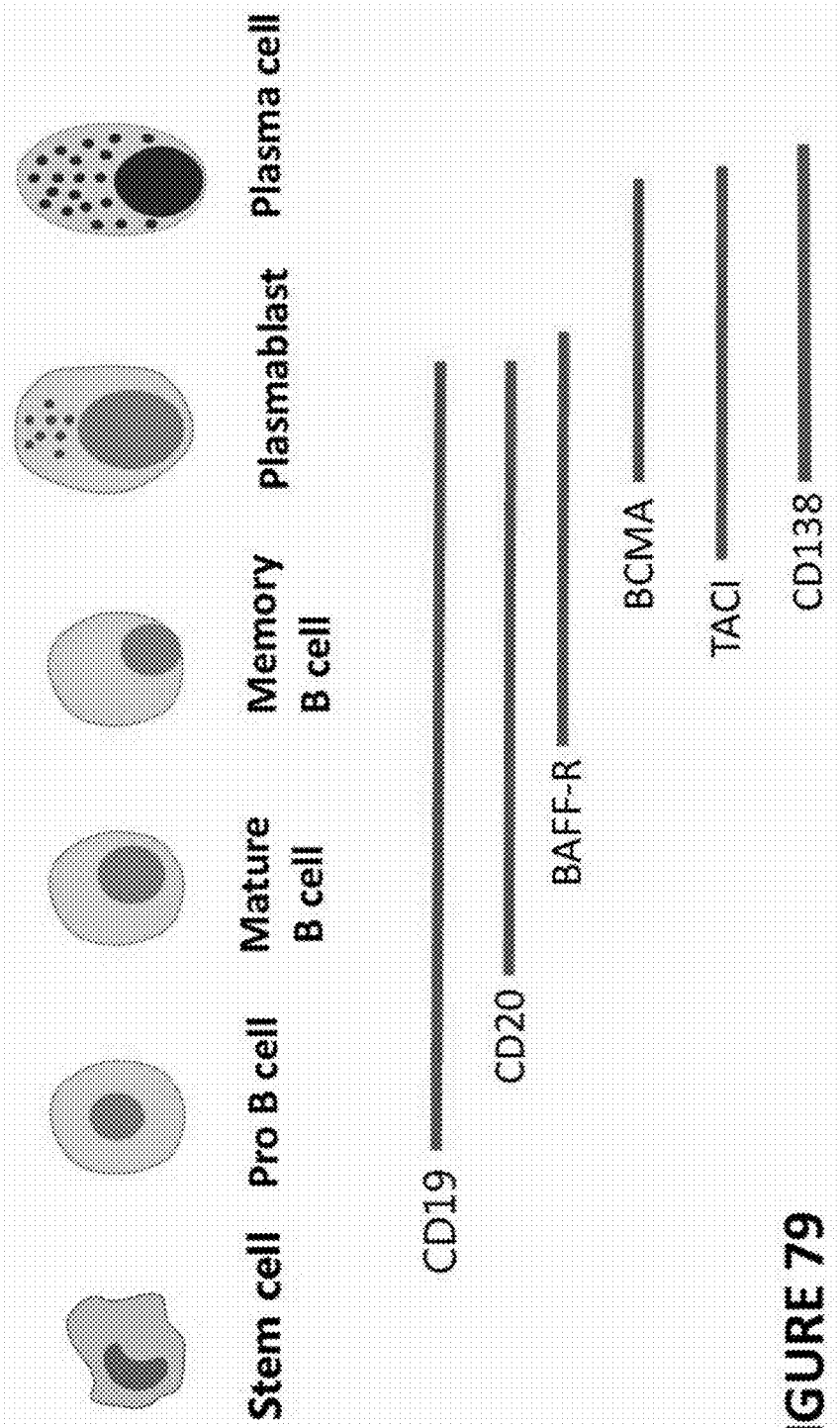

Stem cell
Pro B cell
Mature B cell
Memory B cell
Plasmablast
Plasma cell
CD19
CD20
BAFF-R
BCMA
TACI
CD138

FIGURE 79

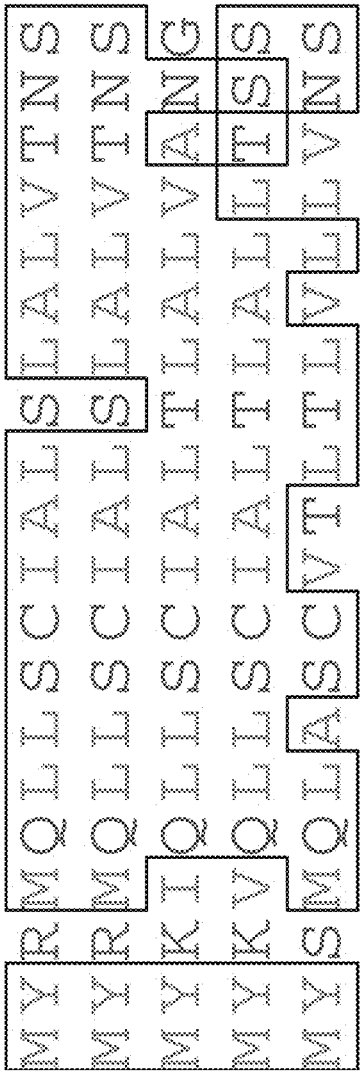

H. sapiens (human) MYRMQLLSCIALSLALVTNS
M. mulatta (rhesus) MYRMQLLSCIALSLALVTNS
B. taurus (bovine) MYKIQLLSCIALTLALVANG
O. cuniculus (rabbit) MYKVQLLSCIALTLALLTSS
M. musculus (mouse) MYSMQLASCVTLTLVLLVNS

FIGURE 80

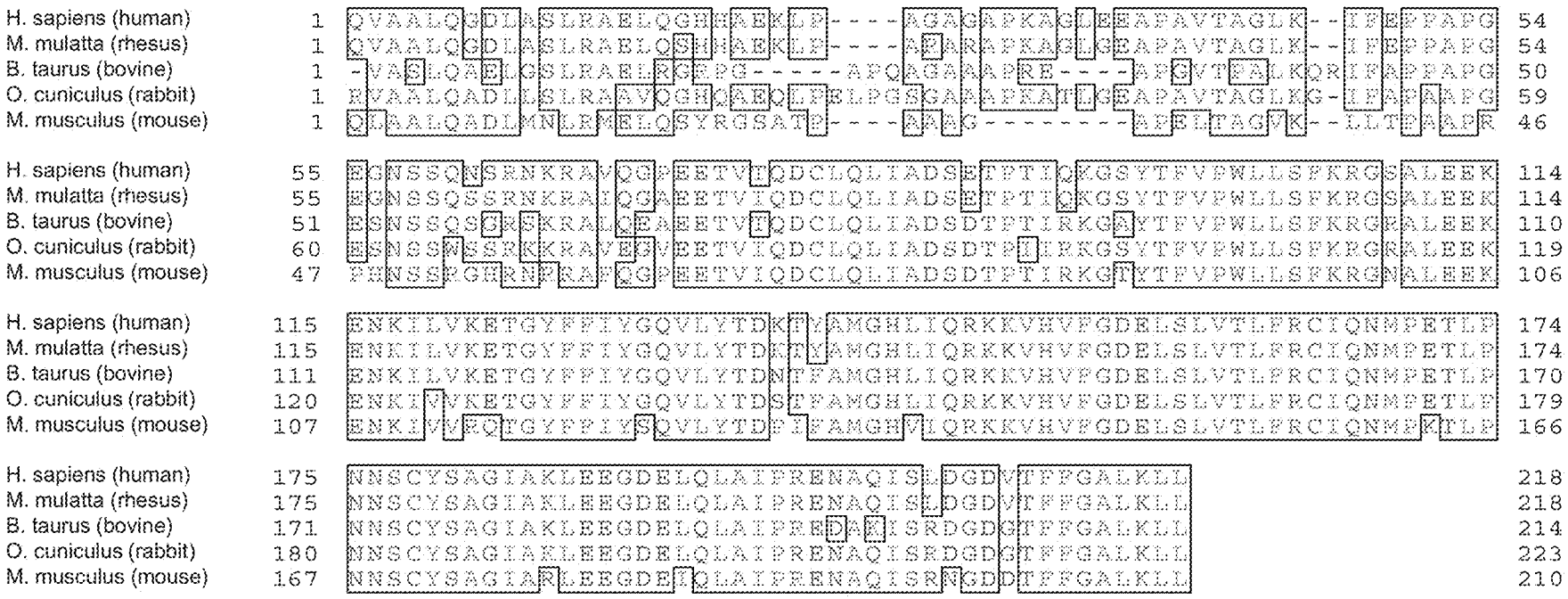

H. sapiens (human)
M. mulatta (rhesus)
B. taurus (bovine)
O. cuniculus (rabbit)
M. musculus (mouse)

FIGURE 81

CHIMERIC ANTIGEN RECEPTORS (CARS), COMPOSITIONS AND METHODS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is an International PCT Application claiming priority from International PCT Application No. PCT/US16/39306, filed on Jun. 24, 2016, and U.S. Provisional Application No. 62/369,004, filed on Jul. 29, 2016, the contents of which are incorporated herein by reference in its entirety.

BACKGROUND

[0002] T cells, a type of lymphocyte, play a central role in cell-mediated immunity. They are distinguished from other lymphocytes, such as B cells and natural killer cells (NK cells), by the presence of a T-cell receptor (TCR) on the cell surface. T helper cells, also called CD4+ T or CD4 T cells, express CD4 glycoprotein on their surface. Helper T cells are activated when exposed to peptide antigens presented by MHC (major histocompatibility complex) class II molecules. Once activated, these cells proliferate rapidly and secrete cytokines that regulate immune response. Cytotoxic T cells, also known as CD8+ T cells or CD8 T cells, express CD8 glycoprotein on the cell surface. The CD8+ T cells are activated when exposed to peptide antigens presented by MHC class I molecules. Memory T cells, a subset of T cells, persist long term and respond to their cognate antigen, thus providing the immune system with "memory" against past infections and/or tumor cells.

[0003] T cells can be genetically engineered to produce special receptors on their surface called chimeric antigen receptors (CARs). CARs are proteins that allow the T cells to recognize a specific protein (antigen) on tumor cells. These engineered CAR T cells are then grown in the laboratory until they number in the billions. The expanded population of CAR T cells is then infused into the patient.

[0004] Clinical trials to date have shown chimeric antigen receptor (CAR) T cells to have great promise in hematologic malignancies resistant to standard chemotherapies. Most notably, CD19-specific CAR (CD19CAR) T-cell therapies have had remarkable results including long-term remissions in B-cell malignancies (Kochenderfer, Wilson et al. 2010, Kalos, Levine et al. 2011, Porter, Levine et al. 2011, Davila, Riviere et al. 2013, Grupp, Frey et al. 2013, Grupp, Kalos et al. 2013, Kalos, Nazimuddin et al. 2013, Kochenderfer, Dudley et al. 2013, Kochenderfer, Dudley et al. 2013, Lee, Shah et al. 2013, Park, Riviere et al. 2013, Maude, Frey et al. 2014).

[0005] Despite the success of CAR therapy in B-cell leukemia and lymphoma, the application of CAR therapy to T-cell malignancies has not yet been well established. Given that T-cell malignancies are associated with dramatically poorer outcomes compared to those of B-cell malignancies (Abramson, Feldman et al. 2014), CAR therapy in this respect has the potential to further address a great clinical need.

[0006] To date, current efforts have focused on CAR T-cells demonstrating efficacy in various B-cell malignancies. While initial remission rates of approximately 90% are common in B-ALL using CD19CAR, most of these relapse within a year. The relapse is at least in part due to the antigen escape. Thus, more effective CAR T cell treatments in order to prevent the relapse is urgently needed. Target discovery and selection are the initial step as there are no general rules to ensure or guide CAR design that are efficacious.

[0007] There are some roadblocks that hinder the broader adoption of CAR therapeutic approach. Among the most general challenges are: (1) selection of antigen target and chimeric antigen receptor(s); (2) CAR design; (3) tumor heterogeneity, particularly the variance in the surface expression of tumor antigens. Targeting single antigen carries the risk of immune escape and this could be overcome by targeting multiple desired antigens; (4) immunosuppressive microenvironment. CAR T cells may be suppressed and de-activated on arrival at the tumor site.

[0008] Most CAR chimeric antigen receptors are scFvs derived from monoclonal antibodies and some of these monoclonal antibodies have been used in the clinical trials or treatment for diseases. However, they have limited efficacy, which suggests that alternative and more potent targeting approaches, such as CARs are required. scFvs are the most commonly used chimeric antigen receptor for CARs. However, CAR affinity binding and locations of the recognized epitope on the antigen could affect the function. Additionally the level of the surface CAR expression on the T cells or NK cells is affected by an appropriate leader sequence and promoter. Furthermore, overexpressed CAR proteins can be toxic to cells.

[0009] Therefore, there remains a need for improved chimeric antigen receptor-based therapies that allow for more effective, safe, and efficient targeting of T-cell associated malignancies.

SUMMARY OF THE INVENTION

[0010] In one embodiment, the present disclosure provides an engineered cell having a first chimeric antigen receptor polypeptide including a first antigen recognition domain, a first signal peptide, a first hinge region, a first transmembrane domain, a first co-stimulatory domain, and a first signaling domain; and a second chimeric antigen receptor polypeptide including a second antigen recognition domain, a second signal peptide, a second hinge region, a second transmembrane domain, a second co-stimulatory domain, and a second signaling domain; wherein the first antigen recognition domain is different than the second antigen recognition domain.

[0011] In another embodiment, the present disclosure provides an engineered polypeptide including a chimeric antigen receptor and an enhancer.

[0012] In another embodiment, the present disclosure provides an engineered polypeptide including a chimeric antigen receptor polypeptide and an enhancer.

[0013] In another embodiment, the present disclosure provides an engineered chimeric antigen receptor polypeptide, the polypeptide including: a signal peptide, a CD45 antigen recognition domain, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain. In another embodiment, the present disclosure provides a polynucleotide encoding for the aforementioned polypeptide.

[0014] In another embodiment, the present disclosure provides an engineered cell having the engineered polypeptide or polynucleotide described above.

[0015] In another embodiment, the present disclosure provides a method of reducing the number of target cells including the steps of (i.) contacting said target cells with an

effective amount of an engineered cell having at least one chimeric antigen receptor polypeptide, for engineered cells having multiple chimeric antigen receptor polypeptides, each chimeric antigen receptor polypeptide is independent; and (ii.) optionally, assaying for the reduction in the number of said cells. The target cells include at least one cell surface antigen selected from the group consisting of interleukin 6 receptor, NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BAFF-R, BAFF, APRIL, BCMA, TACI, LeY, CD5, CD13, CD14, CD15 CD19, CD20, CD22, CD33, CD41, CD45, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, and CS1.

[0016] In another embodiment, the present disclosure provides methods for treating B-cell lymphoma, T-cell lymphoma, multiple myeloma, chronic myeloid leukemia, B-cell acute lymphoblastic leukemia (B-ALL), and cell proliferative diseases by administering any of the engineered cells described above to a patient in need thereof.

BRIEF DESCRIPTION OF DRAWINGS

[0017] FIG. **1**. A schematic representation of cCAR construct (hereinafter, "multiple CAR or compound CAR"). Multiple or compound CAR targets multiple antigens (e.g. cell type 1 or cell type 2 or the same cell type). Multiple or cCAR T cell immunotherapies comprises individual component CAR comprising a different or same antigen recognition domain, a hinge region, a transmembrane domain, various co-stimulatory domain(s) and an intracellular signaling domain.

[0018] FIG. **2**A. A schematic representation of cCAR-T construct. The construct comprises a SFFV promoter driving the expression of-multiple modular units of CARs linked by a P2A peptide. Upon cleavage of the linker, the cCARs split and engage upon targets expressing CD33 and/or CD123. As a novel cCAR construct, the activation domains of the construct may include, but is not limited to, 4-1BB on the CD33 CAR segment and a CD28 region on the CD123 CAR.

[0019] FIG. **2**B. A Western blot depicting the expression of transduced CD33CD123 cCAR-T cells. The figure depicts expression of two different CAR proteins, i.e., CD33 CAR and CD123 CARs. The cCAR-T cells expressing both CD33 and CD123 CARs upon cleavage of the linker generate two distinct and consistently intense protein bands. Green Fluroscent Protein (GFP) is included as negative control.

[0020] FIG. **2**C. Flow cytometry representing the efficiency of transduction. Upper panel shows the lentiviral titer for CD33CD123 cCARs (also referred to as CD33CD123-2G-CAR) tested on 293FT HEK (human embryonic kidney) cells to gauge maximum transduction efficiency before usage on UCB (umbilical cord blood) and PB (peripheral blood) T-cells. Lower panel shows CD33CD123 cCAR (also referred to as CD33CD123-2G-CAR) T-cells transduced with lentiviral vectors comprising CD33CD123 cCAR construct and GFP-transduced cells as control Percentages indicated by yellow circles are proxies for transduction efficiency.

[0021] FIG. **3**. Schematic showing a method of generating a high-efficiency compound CAR (cCAR). HEK-293-FT cells are transfected with compound CAR plasmid DNA and lipofectamine 2000; viral supernatant collected at about 36 hr and at about 60 h; filtered and stored at −80° C. T cells are activated with anti-mouse CD3 antibody and IL-2 for at least 2 days. Activated T cells are transduced at least once with thawed lentivirus on retronectin-coated plates; After at least one overnight transductions at 0.3×106 T cells/mL for about 2 days, the number of T cells was reduced in order to increase transduction efficiency. After transduction, cells are washed and expanded; Flow analysis (F(Ab')2 labeling) is done to confirm CAR efficiency on day 3; total 5-7 day expansion. cCAR T cells are co-cultured with target cells in vitro and cCAR T cells killing efficacy of cancer cells is assessed in vivo (mice).

[0022] FIG. **4**. A co-culture assay representing the incubation of CD33CD123-2G CAR-T cells (cCAR) with the promyelocytic leukemia cell line HL60. cCAR-T cell (lower panel) is compared to control GFP transduced T-cell (upper panel). The efficacy of the killing is measured by the population of CD33+ cells that is left over after incubation for about 24 hours (enclosed in yellow circles).

[0023] FIG. **5**. A co-culture assay representing incubation of cCAR-T cells with the myelogenous leukemia cell line KG-1a, which expresses about 100% CD33 and about 50-80% CD123. cCAR-T cell (lower panel) is compared to control GFP transduced T-cell (upper panel). The efficacy of the killing is measured by the population of CD33+ cells that is left over after incubation for about 24 hours.

[0024] FIG. **6**. CD33CD123 cCAR-T cells co-cultures with AML-9 at 5:1. A co-culture assay representing incubation of cCAR-T cells with AML patient samples (here referred to as AML-9). The patient cells include mixed populations of cells, such as for example, leukemia cells, monocytes, and other types of blasts. CD33 acts as a marker for CAR-T action as well as CD34, a specific marker for leukemia cells. The CAR-T panel (right) is compared to control GFP transduced T-cells (middle). The efficacy of the killing is measured by the population of CD33+/CD34+ cells that is left over after incubation for at least 24 hours.

[0025] FIG. **7**. CD33CD123 cCAR-T cells co-cultures with Sp-BM-B6 at 5:1. A co-culture assay representing incubation of cCAR-T cells with B-ALL patient samples (here referred to as Sp-BM-B6). The patient cells include mixed populations of cells, such as, for example, leukemia cells, monocytes, and other types of blasts. CD34 acts as a specific marker for leukemia cells. The CAR-T panel (right) is compared to control GFP transduced T-cells (middle). The efficacy of the killing is measured by the population of CD34+ cells left over after incubation for at least 24 hours.

[0026] FIG. **8**. CD33CD123 cCAR expression in NK-92 cells. The CD33CD123 cCAR expression are detected using goat-anti-mouse antibody, F(ab)2.

[0027] FIG. **9**. A co-culture assay representing incubation of CD33CD123 cCAR NK-92 cells with HL-60. The cCAR NK-92 cells are compared with GFP transduced NK-92 cells. The efficacy of the killing is measured by the population of CD33+ cells left over after incubation for about 24 hours.

[0028] FIG. **10**. A co-culture assay representing incubation of cCAR NK-92 cells with KG1a. The cCAR NK cell panel is compared with GFP transduced NK-92 cells. The efficacy of the killing is measured by the population of CD33+ cells left over after incubation for about 24 hours.

[0029] FIG. **11**. Dose response of CD33CD123 cCAR (CAR-CD33/123) NK-92 cells with HL-60 or KG1a. The efficacy of the killing is measured by the population of CD33+ cells left over after incubation for about 24 hours.

[0030] FIG. **12**. A comparison of CD33CD123 cCAR NK-92 cell killing ability with control in two populations of

KG11 cells. Assays were performed at different ratios of CAR-CD33/123 (CD33CD123 cCAR NK-92 cells) and target cells, kG1a. The efficacy of the killing is measured by the population of CD33+CD123+ or CD33+CD123-cells left over after incubation for about 24 hours.

[0031] FIG. **13**A. Links by P2A and T2A schematic showing both cCAR-T and 4-1BBL in a single construct. The construct consists of a SFFV promoter driving the expression of two modular units of CARs A peptide and an enhancer, 4-1BBL. Upon cleavage of the linkers, the cCARs and 4-1BBL split and engage upon targets expressing CD33 and/or CD123 and 4-1BBL. Compound CAR, CD33CD123 CAR T cells received not only costimulation through the CD28 but also 4-1BB ligand (4-1BBL or CD137L). The CD3-zeta signaling domain complete the assembly of this CAR-T.

[0032] FIG. **13**B. Expression the CD33CD123-41BBL-2G construct in T-cells. T-cells derived from peripheral blood from healthy donors were transduced with the CD33CD123-4-1BBL-2G construct in 6-well plates incubated with 2 ml of virus supernatant. CAR expression was assayed with F(ab)' labeling for surface expression of the CAR protein and subsequently underwent FACS analysis. Transduced cells were compared to control T-cells labeled at the same time. Expression was determined and transduced population encircled on plot 1 day after end of transduction period.

[0033] FIG. **14**. Links by P2A and T2A schematic showing both cCAR-T and IL-15/IL-15sushi in a single construct. The construct consists of a SFFV promoter driving the expression of two modular units of CARs and an enhancer, IL-15/IL-15sushi. Upon cleavage of the linkers, the cCARs and IL-15/IL-15sushi split and engage upon targets expressing CD33 and/or CD123. The CD3-zeta signaling domain completes the assembly of this CAR-T. The enhancers include, but not limited to, IL-15/IL-15sushi on cCAR.

[0034] FIG. **15**. A schematic representation of cCAR. The construct comprises a SFFV promoter driving the expression of multiple modular units of CARs linked by a linker. Upon cleavage of the linker, the cCARs split and engage upon targets expressing combinations of various target antigens: CD19 and/or CD20, and/or CD22 and/or 138. Multiple cCARs utilize the same or different co-stimulatory domains, such as, without limiting 4-1BB (also labeled as 4-BB) and/or CD28.

[0035] FIG. **16**. Activated T cells transduced to make CD19CD20-2G, CD19CD22-2G CAR T cells (all are L8). (**16**A) Design of compound CARs. (**16**B) Western blot. HEK-293T cells were transfected with lentiviral plasmids for control vector (lane 1), CD19CD20-2G (lane 2), and CD19CD22-2G (lane 3). 48 hours after transfection, supernatant was removed, and cells were also harvested. Cells were lysed for Western blot and probed with mouse anti-human CD3z primary antibody, and goat anti-mouse HRP secondary antibody. (**16**C) PMBC buffy coat T cells were activated 3 days with anti-CD3 antibody. Cells were transduced with either control vector (left), CD19CD20-2G (middle), or CD19CD22-2G, (right) lentiviral supernatant. After 3 days of incubation, cells were harvested and incubated with goat anti-mouse Fab2 or goat IgG antibodies conjugated with biotin for 30 minutes. Cells were washed, suspended and stained with streptavidin-PE and mouse anti-human CD3-PerCp for 30 minutes. Cells were washed and suspended in 2% formalin, and analyzed by flow cytometry to determine CAR efficiency. (N=2).

[0036] FIG. **17**. Expression of compound CD19CD22CAR T cells using different leader sequences. PMBC buffy coat T cells were activated 3 days with anti-CD3 antibody. Cells were transduced with either control vector (left), L8-CD19CD22-2GCAR (middle left), L45-CD19CD22-2GCAR, (middle right) or CSF-CD19CD22-2GCAR (right) lentiviral supernatant. The supernatants were each 3× concentrated. After 3 days of incubation, cells were harvested and incubated with goat anti-mouse Fab2 or goat IgG antibodies conjugated with biotin for 30 minutes. Cells were washed, suspended and stained with streptavidin-PE and mouse anti-human CD3-PerCp for 30 minutes. Cells were washed and suspended in 2% formalin, and analyzed by flow cytometry to determine CAR efficiency. (N=2).

[0037] FIG. **18**. Comparison of transduction efficiency using concentrated vs unconcentrated L8-CD19CD22-2G or L8-CD19CD20-2G lentiviral supernatant. A. PMBC buffy coat T cells were activated 3 days with anti-CD3 antibody. Cells were transduced with either control vector (left), unconcentrated (middle) L8-CD19CD22-2GCAR or 3× concentrated L8-CD19CD22-2GCAR (right) lentiviral supernatant. After 3 days of incubation, cells were harvested and incubated with goat anti-mouse Fab2 or goat IgG antibodies conjugated with biotin for 30 minutes. Cells were washed, suspended and stained with streptavidin-PE and mouse anti-human CD3-PerCp for 30 minutes. Cells were washed and suspended in 2% formalin, and analyzed by flow cytometry to determine CAR efficiency. (N=2). B. The same experiment was used for constructs containing L8-CD19CD20-2G unconcentrated or 2.5× concentrated lentiviral vector.

[0038] FIG. **19**. L8-CD19CD22-2G CAR T cells lyse SP53 tumor cells in overnight co-culture. Activated PMBC T cells transduced with either control (top row), L8-CD19CD22-2G, or (bottom row) lentiviral supernatant were incubated with SP53 cells at the ratios of 1:1 (left) 2:1 (middle) and 5:1 (right), effector:target cells. After 24 hours of incubation at 37° C., samples were washed and stained with anti-human CD3-PerCp and anti-human CD19-APC, washed, and analyzed by flow cytometry. SP53 cells alone are shown on the far upper right, and a summary of percent lysis at each ratio is on the lower right. (N=2).

[0039] FIG. **20**. L8-CD19CD22-2G CAR T cells lyse JeKo-1 tumor cells in overnight co-culture. Activated PMBC T cells transduced with either control (left), or L8-CD19CD22-2G, (middle) 3× concentrated lentiviral supernatant were incubated with JeKo-1 cells at the ratios of 2:1 (top) and 5:1 (bottom), effector:target cells. After 24 hours of incubation at 37° C., samples were washed and stained with anti-human CD3-PerCp and anti-human CD19-APC, washed, and analyzed by flow cytometry. JeKo-1 cells alone and a summary of cell lysis are shown on the right. (N=2).

[0040] FIG. **21**. L8-CD19CD22-2G CAR T cells lyse AML patient cells in overnight co-culture. Activated PMBC T cells transduced with either control (left), or L8-CD19CD22-2G, (middle) 3× concentrated lentiviral supernatant were incubated with CMTMR-stained cells from a patient diagnosed with AML (PT1) at the ratios of 2:1 (top) and 5:1 (bottom), effector:target cells. After 24 hours of incubation at 37° C., samples were washed and stained

with anti-human CD3-PerCp and anti-human CD19-APC, washed, and analyzed by flow cytometry. Patient cells alone and a summary of cell lysis are shown on the right. (N=2).

[0041] FIG. **22**A. L8-CD19CD22-2G CAR T cells deplete CD19+B-ALL patient cells. Activated PMBC T cells transduced with either control (left), or L8-CD19CD22-2G, (middle) lentiviral supernatant were incubated with CMTMR-stained cells from a patient with B-ALL (PT2) at a 1:1 ratio for 4 days in the presence of 2.5% FBS and IL-2. Following this incubation at 37° C., samples were washed and stained with anti-human CD3-PerCp and anti-human CD19-APC, washed, and analyzed by flow cytometry. Prestained patient cells cultured alone for 4 days are shown on the right.

[0042] FIG. **22**B. L-8-CD19CD22-2G cCAR T-cells show effect on $CD22^+$ K562 cells. An artificial K562 expressing CD22 cell line (K562xp22) via transduction into wild-type K562 cells was generated. Subsequently, we tested the anti-tumor properties of the CD19CD22 cCAR to target the minor $CD22^+$ population of the K562 cells. A co-culture experiment at 1:1 ratio (effective:target) show a modest significant cytotoxic effect on K562 expressing CD22 population compared to the control. Co-cultures were stained with CD3, CD19 and CD22 to separate effector and target populations by flow cytometry. The result was graphed. Cytotoxicity results remain consistent with other numbers reported for anti-tumor activity against artificial antigen presenting cell lines.

[0043] FIG. **23**. Various transduction schemes for BC1cCAR lentivirus. (A) Method 1 consisting of a 2× transduction for 24 hours each time is a baseline transduction scheme. Scheme proceeds according to the figure. (B) Method 2 possesses the same methodology as Method 1, however, the second transduction is replaced by continued incubation. (C) Method 2 revised uses viral supernatant incubated with cells directly for 48 hours.

[0044] FIGS. **24**A-**24**C: CAR construct scheme and comparison of transduction methodologies. (**24**A) BC1cCAR's modular design consists of an anti-CD269 (BCMA) single-chain variable fragment (scFv) region fused to an anti-CD319 (CS1) scFv by a self-cleaving P2A peptide, CD8-derived hinge (H) and transmembrane (TM) regions, and tandem CD28 and 4-1BB co-activation domains linked to the CD3ζ signaling domain. A strong spleen focus forming virus promoter (SFFV) and a CD8 leader sequence were used for efficient expression of the CD3CAR molecule on the T-cell surface. (**24**B) BC1cCAR's expression was measured via flow cytometry against an isotype control. Population encircled represents transduced CAR cells. (**24**C) Transduction efficiency is improved by optimal methods.

[0045] FIG. **24**D. Protein expression of BC1cCAR and BCMA-CS1-2G in HEK-293FT cells. HEK-293FT cells were transfected with lentiviral plasmids for GFP (lane 1), BC1cCAR (lane 2) 48 hours after transfection, supernatant was removed, and cells were also removed. Cells were lysed for Western blot and probe with mouse anti-human CD3z antibody. C. Transduction efficiency is improved by optimal methods.

[0046] FIGS. **25**A-**25**C. in vitro evaluation of BC1cCAR T-cells against myeloma cell lines. (**25**A) BC1cCAR and control T-cells were cultured with highly BCMA positive MM1S and RPMI-8226 cells for 24 hours at E:T ratios of 2:1 and 5:1. Target MM1S and RPMI-8226 cells were stained by Cytotracker dye (CMTMR) to distinguish it from effector T-cells. Populations were gated by anti-BCMA (CD269) and anti-CS1 (CD319 antibodies) along with CMTMR-PE. Target U266 cells were labeled with Cytotracker (CMTMR) dye to distinguish it from effector T-cells. Encircled populations represent tumor cells. (**25**B) U266 target depletion. BC1cCAR and control T-cells were also incubated with U266 cells expressing BCMA and a subset of CS1. Target tumor cells were stained as described above and gating conditions applied similarly. Tumor populations are encircled. (**25**C) In vitro summary of BC1cCAR T activity against human myeloma cell lines. Graphical summary of BC1cCAR T-cell in vitro cytotoxicity against various myeloma cell lines at 2:1 and 5:1 E:T ratios.

[0047] FIGS. **26**A-**26**D. Characterization of BC1cCAR T-cell anti-tumor activity against primary myeloma tumor cells. (**26**A) Dose dependent effect on MM7-G primary double phenotype tumors. BC1cCAR and control T-cells were cultured against $BCMA^+$ $CS1^+$ primary myeloma cells MM7-G for 24 hours. Target cells were pre-stained with CMTMR and cultures were carried out in E:T ratios of 2:1, 5:1, and 10:1. Populations were gated by BCMA and CS1, along with CMTMR, and flow cytometry plots with populations encircled represent target tumor populations (left). Bar graph summarizing in vitro cytotoxicity is shown for clarity (right). (**26**B) Population specific depletion in MM10-G. Co-cultures with MM10-G primary tumor cells were carried out in similar conditions. When stained with anti-CS1 and anti-BCMA antibody, MM10-G reveal distinct populations. $BCMA^+$ $CS1^+$ double positive populations are colored purple whilst $CS1^+$ only populations are colored dark blue. BC1cCAR T-cell cytotoxicity against each population is summarized in the bar graph below. (**26**C) Dose dependent effect on CS1dim BCMAneg. MM11-G primary tumor. A third experiment using $BCMA^{dim}CS1^{dim}$ primary cells (MM11-G) further shows BC1cCAR cytotoxicity effects over a range of E:T dosages summarized. (**26**D) Summary panel graph showing BC1cCAR T-cell cytotoxicity against myeloma cell lines and primary tumor cells with a variety of BCMA and CS1 compositions.

[0048] FIGS. **27**A-**27**D. Functional validation of BC1cCAR antigenic specificity. (**27**A) We engineered a CML cell line, K562, to express either BCMA or CS1 independently. Wild-type K562 shows as a negative peak, while BCMA expressing K562 (BCMAxpK562) and CS1 expressing K562 (CS xpK562) show population shifts in their respective antigen expression ranges. (**27**B) Short term (4 hour-12 hour) cultures of BC1cCAR T-cells against either BCMAxpK562 or CS1 xpK562 show antigen specific cytotoxicity correlating with E:T dosage increase. Experiments against wild-type K562 were performed as a negative control. A CS1-specific single CAR was generated to compare efficacy with BC1cCAR against CS1xpK562 cells and are delineated with red bars in the respective plot. Anti-CS1 specific activity was also seen against $CS1^{dim}$ NK-92 cells after 24 hours of culture. (**27**C) Comparison between single antigen CARs and BC1 cCAR T in mixed cell assays. Long-term cultures were conducted over a 48 hour period with a 5:1 mixture of BCMAxpK562 cells and CS1xpK562 cells. BC1cCAR. CS1-CAR, BCM A-CAR, and control T-cells were added at a 5:1 E:T ratio to each treatment well and flow cytometry analyses acquired. Histogram plots showing residual populations of BCMA or CS1 cells are shown per treatment condition, with red lines demarcating T-cell or target tumor populations. Numerical values in

histogram plots represent residual gated populations of target tumor cells. (**27**D) BC1 cCAR T activity against CS1 subsets in primary bone-marrow aspirate. Further co-culture experiments were conducted using bone-marrow aspirate samples as CS1 expressing minority subsets. BC1 cCAR or control T-cells were added at 2:1 (left panel), 5:1 (middle panel), or 10:1 (right panel) ratios and encircled populations represent target CS1 expressing populations. Results are analyzed by flow cytometry (upper). Summary graph of anti-CS1 activity against bone marrow subsets (below).

[0049] FIGS. **28**A-**28**C: Long-term sequential killing assay and tumor re-challenge. (**28**A) Scheme for construction of long-term sequential killing assay. Assay was conducted over a period of 168 hours with no exogenous cytokines where the initial culture was set-up with a 1:1 E:T ratio of CAR cells or control cells mixed with MM1S tumor cells. After 48 hours, flow cytometry analysis was acquired for a small sample collection and MM1S cells re-introduced into each treatment well. Repeated until the 168 hour time-point. (**28**B) T-cell proliferation and response after 48 hours. Images were taken on day of flow cytometry acquisition and cells were stained with anti-BCMA, anti-CS1, and anti-CD3 antibodies MM1S cells express as highly $BCMA^+$ with a large $CS1^+$ proportion. Encircled populations represent the MM1S tumor presence, colored blue. (**28**C) CAR cell proliferation and antigen depletion after 108h. Similar image acquisition and flow cytometry analysis was performed at the 108 hour time mark.

[0050] FIG. **29**A-**29**C. BC1cCAR T-cells demonstrate anti-leukemic effects in vivo. (**29**A) IVIS imaging of MM1S Luc+ injected mouse model. NSG mice were sublethally irradiated and intravenously injected with luciferase-expressing MM1S multiple myeloma cells to induce measurable tumor formation. After 3 days, the mice were intravenously injected with 5×10^6 BC1cCAR T-cells or control GFP T-cells. On days 3, 6, 8 and 11, mice were injected subcutaneously with RediJect D-Luciferin and subjected to IVIS imaging. (**29**B) BC1cCAR T-cells control MM1S tumor growth. Average light intensity measured for the BC1cCAR T-cells injected mice was compared to that of GFP control T-cell injected mice. (**29**C) BC1cCAR T-cells improve murine survival outlook. Percent survival of mice was measured and compared between the two groups and log-rank mantel-cox test was conducted to calculate significance of improved survival outlook.

[0051] FIG. **29**D. BCMA-CAR and BC1 cCAR T-cells demonstrate a profound anti-leukemic effect on a mixture of K562 cells expressing BCMA and CS1 in xenograft mouse model. Luciferase positive K562 cells expressing BCMA are mixed with luciferase positive K562 cells expressing CS1 at a ratio of 4:1 BCMA to CS1 K562 cells. The mixed K562 cells (0.5×10^6 cells) were then injected intravenously (day 1) at 24 h later after sub-lethal irradiation. After day 3, a course of BCMA CAR T-cells, BC1cCAR T-cells or control T-cells were intravenously injected into each mouse (n=5 for each group). Dorsal side of tumor burden was measured using IVIS imaging system at days 3, 7, 10 and 12. At day 7 BCMA mouse #3 has large tumor. At day10 Dorsal BCMA vs control=47.7% less tumor, cCAR vs control=53.8% less tumor. At day 12 RESULTS (ventral view only) Dorsal BCMA vs control=43.8% less tumor, cCAR vs control=60. 7% less tumor

[0052] FIG. **29**E. BCMA and BC1 cCAR T-cells in vivo significant reduction of tumor burden. Percent reduction relative to control in mice treated with BCMA CAR T-cells or cCAR (BC1 cCAR) relative to control over time.

[0053] FIGS. **30**A-**30**B: BC1cCAR transduction into NK-92 cells. (**30**A) BC1cCAR's modular design is comprised as shown and described previously. (**30**B) CAR expression on NK-92 cell surface. The construct was transduced into NK-92 cells by incubating with viral supernatant for 48 hours and labeling with F(ab)' antibody detection for CAR protein surface expression. Transduced populations are encircled and compared to control NK-92 cells.

[0054] FIGS. **31**A-**31**B. Characterization of BC1cCAR NK-92 anti-tumor properties. (**31**A) BC1cCAR NK cells lyse myeloma cell lines and primary cells. BC1cCAR NK-92 cells were incubated against U266, RPMI-8226, and MM1S myeloma cell lines in addition to primary MM7-G tumor cells. Co-cultures were carried out over 2 hours at an E:T ratio of 5:1 and labeled with anti-CS1 and anti-BCMA antibodies to separate out populations. Tumor populations are encircled. MM7-G primary tumor cells were stained with cell cytotracker dye (CMTMR) to distinguish from NK-92 cells and are encircled. Summary bar graph of BC1cCAR NK-92 cytotoxic activity is presented as a visualization aid. (**31**B) BC1cCAR NK-92 cells were tested for antigen specific activity using artificially generated BCMA expressing K562 (BCMAxpK562) and CS1 expressing K562 (CS1xpK562) cells. Co-cultures were carried out over 4 hours at an E:T ratio of 5:1. K562 populations were previously stained with CMTMR and encircled in the flow cytometry plots. Bar graph summarizing anti-tumor activity to visualize.

[0055] FIGS. **32**A-**32**C. Generation and characterization of different BAFF-CAR constructs. (**32**A) L45-BAFF-28 CAR expression T-cell surface. L45-BAFF-28 CAR was transduced into T-cells and evaluated for surface expression using F(ab)' antibody. Gating was compared to controls. (**32**B) CAR expression dependence on leader sequence. BAFF-CAR constructs using different leader sequences were tested to determine if efficiency in transduction could be improved. Surface detection was evaluated using F(ab)' antibody and transduced populations encircled. (**32**C) CAR expression dependence on construct design. Additional BAFF-CAR constructs containing different leader sequences and construct designs (additional units) were validated and used to determine if CAR transduction could be improved. Transduced populations are encircled and gating compared to control T-cells. CSF-BAFF-28 41BBL is a BAFF CAR co-expressing 4-1BBL (41BBL) with a CSF leader sequence. CSF-BAFF-28 IL-15RA is a BAFF CAR co-expressing IL-15/IL-15sushi (IL-15RA) with a CSF leader.

[0056] FIG. **33**: Characterization of L45-BAFF-28 CAR T anti-tumor properties. (**33**A) L45-BAFF-28 CAR T-cells possess anti-tumor activity against MM1S tumor cells. L45-BAFF-28 CAR T-cells were cultured for 48 hours at an E:T ratio of 3:1 against MM1S myeloma cells. Duplicate samples are shown. Cytotoxic activity is summarized in the bar graph.

[0057] FIGS. **34**A-**34**B: Characterization of anti-tumor activity using different BAFF-CAR constructs and enhancements. (**34**A) BAFF-CAR constructs against MM1S cells. L8-BAFF-28IL-15/IL-15sushi and L8-BAFF-28-41BBL CARs were cultured for 24 hours against MM1S tumor cells at an E:T ratio of 5:1. Tumor populations are encircled. (**34**B) BAFF-CAR constructs against SP53 cells. Both

CARs and L45-BAFF-28 CAR were cultured against Sp53 tumor cells (B-lineage) at an E:T ratio of 5:1 for 24 hours. (**34**C) Summary bar graph of cytotoxic activity.

[0058] FIG. **35**. A schematic showing cCAR construct. The construct consists a SFFV promoter driving the expression of two modular units of CAR linked by a P2A peptide. Upon cleavage of this P2A peptide, the cCARs split and engage upon targets expressing BCMA and/or CD19. Two unit CARs use different or same co-stimulatory domain. A co-stimulatory domain could be, but limited to, 4-1BB or CD28.

[0059] FIGS. **36**A-**36**B. Characterization of the BCMA CAR unit. (**36**A) BCMA CAR effectively deplete BCMA+ MM1S cells. The BCMA CAR was transduced into T-cells and co-cultured with MM1S tumor cells. A CS1 CAR was also generated and used for robustness. MM1S cells are significantly dual positive for both BCMA and CS1. Co-cultures were conducted over 48 hours with BCMA and CS1 antibodies used to identify tumor centers. Encircled populations represent residual MM1S tumor cells after culture. (**36**B) BCMA CAR effectively lyses BCMA+ primary tumor cells. (**36**B) The BCMA CAR and CS1 CAR were also evaluated for its anti-tumor properties against primary MM7-G myeloma patient cells. The MM7-G population is a majority $BCMA^+$ CS1 population with minority but significant $CS1^+$ only populations as well. Both BCMA CAR and CS1 CAR were used in tandem to evaluate cytotoxicity with BCMA and cytotracker (CMTMR) used to differentiate tumor populations from CAR cells.

[0060] FIGS. **37**A-**37**C. Characterization of CD19 CARs. (**37**A) Design of CD19CAR unit. (**37**B) Western blot. HEK-293T cells were transfected with lentiviral plasmids for control vector (lane 1) and CD19-2G (lane 2). 48 hours after transfection, supernatant was removed, and cells were also harvested. Cells were lysed for Western blot and probed with mouse anti-human CD3z primary antibody, and goat anti-mouse HRP secondary antibody. C. PMBC buffy coat T cells were activated 3 days with anti-CD3 antibody. Cells were transduced with either control vector (left), L8-CD19-2G (middle left), L8-CD19CD20-2G, (middle right) or L8-CD19CD22-2GCAR (right) lentiviral supernatant. After 3 days of incubation, cells were harvested and incubated with goat anti-mouse Fab2 or goat IgG antibodies conjugated with biotin for 30 minutes. Cells were washed, suspended and stained with streptavidin-PE and mouse anti-human CD3-PerCp for 30 minutes. Cells were washed and suspended in 2% formalin, and analyzed by flow cytometry to determine CAR efficiency. (N=2)

[0061] FIGS. **38**A-**38**B. Expression of compound CD19CAR T cells using different leader sequences. (**38**A) CAR constructs were designed to express the fusion protein with different leader sequences. (**38**B) PMBC buffy coat T cells were activated 3 days with anti-CD3 antibody. Cells were transduced with either control vector (left), HA-CD19-2G (top middle), IL2-CD19-2G (top right), L8-CD19-2G (lower middle left), L45-CD19-2G, (lower middle right) or CSF-CD19-2GCAR (lower right) lentiviral supernatant. After 3 days of incubation, cells were harvested and incubated with goat anti-mouse Fab2 or goat IgG antibodies conjugated with biotin for 30 minutes. Cells were washed, suspended and stained with streptavidin-PE and mouse anti-human CD3-PerCp for 30 minutes. Cells were washed and suspended in 2% formalin, and analyzed by flow cytometry to determine CAR efficiency. (N=2)

[0062] FIGS. **39**A-**39**B. Expression of CD19CAR on T cells using different CD19 scFv sequences. (**39**A) CAR constructs were designed to express the fusion protein with different scFv sequences. (**39**B) PMBC buffy coat T cells were activated 3 days with anti-CD3 antibody. Cells were transduced with either control vector (left), L8-CD19-2G (middle), IL2-CD19-2G (top right), or L8-CD19b-BB-2G (right) lentiviral supernatant. After 3 days of incubation, cells were harvested and incubated with goat anti-mouse Fab2 or goat IgG antibodies conjugated with biotin for 30 minutes. Cells were washed, suspended and stained with streptavidin-PE and mouse anti-human CD3-PerCp for 30 minutes. Cells were washed and suspended in 2% formalin, and analyzed by flow cytometry to determine CAR efficiency. (N=2)

[0063] FIG. **40**. L8-CD19-2G and CD19b-BB CAR T cells lyse SP53 tumor cells in overnight co-culture. Activated PMBC T cells transduced with either control (left), L8-CD19-2G, (middle) or L8-CD19b-BB-2G (right) lentiviral supernatant were incubated with SP53 cells at the ratios of 2:1 (top) and 5:1 (bottom), effector:target cells. After 24 hours of incubation at 37° C., samples were washed and stained with anti-human CD3-PerCp and anti-human CD19-APC, washed, and analyzed by flow cytometry. SP53 cells alone and a summary of cell lysis are shown on the far right. (N=2)

[0064] FIG. **41**. L8-CD19-2G and CD19b-BB CAR T cells lyse JeKo-1 tumor cells in overnight co-culture. Activated PMBC T cells transduced with either control (left), L8-CD19-2G, (middle) or L8-CD19b-BB-2G (right) lentiviral supernatant were incubated with JeKo-1 cells at the ratios of 2:1 (top) and 5:1 (bottom), effector:target cells. After 24 hours of incubation at 37° C., samples were washed and stained with anti-human CD3-PerCp and anti-human CD19-APC, washed, and analyzed by flow cytometry. JeKo-1 cells alone and a summary of cell lysis are shown on the far right. (N=2).

[0065] FIG. **42**. L8-CD19-2G and L8-CD19b-BB-2G CAR T cells lyse AML patient cells in overnight co-culture. Activated PMBC T cells transduced with either control (left), L8-CD19-2G, (middle) or L8-CD19b-BB-2G (right) lentiviral supernatant were incubated with CMTMR-stained cells from a patient with AML at the ratios of 2:1 (top) and 5:1 (bottom), effector:target cells. After 24 hours of incubation at 37° C., samples were washed and stained with anti-human CD3-PerCp and anti-human CD19-APC, washed, and analyzed by flow cytometry. Prestained patient cells alone and a summary of cell lysis are shown on the far right. (N=2).

[0066] FIG. **43**. L8-CD19-2G and L8-CD19b-BB-2G CAR T cells deplete CD19+ patient cells. Activated PMBC T cells transduced with either control (left), L8-CD19-2G, (middle) or L8-CD19b-BB-2G (right) lentiviral supernatant were incubated with CMTMR-stained cells from a patient with B-ALL. L8-CD19-2G T cells were incubated with patient cells at a 1:1 ratio for overnight (top), while L8-CD19b-BB-2G T cells were incubated with patient cells at a 5:1 ratio for 40 hours (bottom). Following this incubation at 37° C., samples were washed and stained with anti-human CD3-PerCp and anti-human CD19-APC, washed, and analyzed by flow cytometry. Prestained patient cells alone are shown on the far right. (N=2).

[0067] FIG. **44**. A schematic showing cCAR construct. The construct consists a SFFV promoter driving the expres-

sion of two modular units of CAR linked by a P2A peptide. Upon cleavage of this P2A peptide, the cCARs split and engage upon targets expressing BCMA and/or CD19b. Two unit CARs use different or same co-stimulatory domain. A co-stimulatory domain could be 4-1BB or CD28.

[0068] FIGS. **45**A-**45**C. Generation and characterization of different BAFF-CAR constructs. (**45**A) L45-BAFF-28 CAR was transduced into T-cells and evaluated for surface expression using F(ab)' antibody. Gating was compared to controls. (**45**B) BAFF-CAR constructs using different leader sequences were tested to determine if efficiency in transduction could be improved. Surface detection was evaluated using F(ab)' antibody and transduced populations encircled. (**45**C) Additional BAFF-CAR constructs containing different leader sequences and construct designs (additional units) were validated and used to determine if CAR transduction could be improved. Transduced populations are encircled and gating compared to control T-cells. CSF-BAFF-28 41BBL is a BAFF CAR co-expressing 4-1BBL (41BBL) with a CSF leader sequence. CSF-BAFF-28IL-15/IL-15sushi—is a BAFF CAR co-expressing IL-15/IL-15sushi with a CSF leader.

[0069] FIGS. **46**A-**46**B: L45-BAFF-28 CAR T-cells possess anti-tumor activity against MM1S tumor cells. Characterization of L45-BAFF-28 CAR T anti-tumor properties. (**46**A) BAFF CAR cytotoxic activity in vitro summarized from (**46**B). (**46**B) L45-BAFF-28 CAR T-cells possess anti-tumor activity against MM1S tumor cells. L45-BAFF-28 CAR T-cells were cultured for 48 hours at an E:T ratio of 3:1 against MM1S myeloma cells. Duplicate samples are shown.

[0070] FIGS. **47**A-**47**B Characterization of anti-tumor activity using different BAFF-CAR constructs and enhancements. (**47**A) L8-BAFF-28IL-15/IL-15sushi and L8-BAFF-28 4-1BBL CARs were cultured for 24 hours against MM1S tumor cells at an E:T ratio of 5:1. Tumor populations are encircled. (**47**B) Both CARs and L45-BAFF-28 CAR were cultured against Sp53 tumor cells (B-lineage) at an E:T ratio of 5:1 for 24 hours.

[0071] FIG. **48**. CRISPR/Cas9 interference system. The expression of sgRNA and Cas9 puromycin is driven by the U6 and SFFV promoters, respectively. The Cas9 is linked with puromycin resistant gene by E2A self-cleaving sequences.

[0072] FIG. **49**A. Steps of generation of CAR T or NK cell targeting hematologic malignancies.

[0073] FIG. **49**B. Generation and cell sorting of stable CD45 knockdown NK-92 cells using CRISPR/Cas9 lentivirus system. Flow cytometry analysis indicated the CD45 expression levels on NK-92 cell surface (left panels). After transduced sgCD45B CRISPR into NK-92 cells, transduced cells were cultured in medium containing puromycin for a few weeks. CD45 negative NK-92 cells were determined using CD45 antibody and were sorted. The purity of stable NK^{45i}-92 (CD45 knockdown) NK-92 cells were determined by Flow cytometry analysis (right panel). This data showed that we we successfully generated and obtained NK^{45i}-92 cells.

[0074] FIG. **50**. Cell growth curve of wild type, GFP transduced NK-92 or NK^{45i}-92NK cells. To evaluate the effect for cell proliferation caused by CD45-knockdown (KD) in NK-92 cells, the number of cells of NK-92 (●), GFP-transduced NK-92(■) and NK^{45i}-92(▲) were counted at 48 h and 96 h after seeding into 24 well plates. IL-2 was added at 48 h time point. (n=3 independent experiments performed in duplicate). Data are mean±S.D. These data indicated that knockdown of CD45 receptor on NK-92 show similar cell growth curve compared to non-transduced NK-92 or GFP-transduced NK-92 cells. 24 well, duplicate, n=3 IL-2 was added at 48 hr time point.

[0075] FIGS. **51**A-**51**B. Co-culture assay with CCRF-CEM (target: T) and GFP NK-92 or GFP NK^{45i}-92 cells (effector: E) at 5:1 (E:T) ratio and 16 hour incubation. (**51**A) Flow cytometry analysis of CCRF-CEM only (blue dot in left panel), in co-culture with CCRF-CEM and control GFP transduced NK-92 cells (middle panel) or GFP NK^{45i}-92 cells (right panel). Blue dots in all of panels indicates the leftover target CCRF-CEM cells and red dots shows effector cells by co-culture assay. The majority of the blue dots are in the upper left square of each experiment. All of incubation time were 16 h and the ratio of effector T-cells:target cell is 5:1. All experiments were performed in duplicate. (**51**B) Bar graph indicates the percent of cell lysis by the GFP transduced NK^{45i}-92 cells compared to the control GFP transduced NK92 cells in co-culture assay with CCRF-CEM. These data suggest that knockdown of CD45 in NK-92 cells does not show a significant difference for killing activity against CCRF-CEM cells compared to GFP-control NK-92 cells in vitro co-culture assay.

[0076] FIGS. **52**A-**52**B. Co-culture assay with CCRF-CEM (target: T) and GFP NK-92, CD5CAR NK-92 or CD5CAR NK^{45i}-92 cells (effector: E) at 5:1 (E:T) ratio and 16 hour incubation. (**52**A) Flow cytometry analysis of CCRF-CEM only (left panel), in co-culture with CCRF-CEM and control GFP NK-92 cells (middle left panel), CD5CAR NK-92 cells (middle right panel), CD5CAR NK^{45i}-92 cells (right panel) from right to left. Blue dots in all of panels indicates the leftover target CCRF-CEM cells and red dots shows effector cells by co-culture assay. All of incubation time were 16 h and the ratio of effector T-cells: target cell is 5:1. All experiments were performed in duplicate. (**52**B) Bar graph indicates the percent of cell lysis by the CD5CAR NK-92 cells or CD5CAR NK^{45i}-92 cells cells compared to the control GFP NK92 cells in co-culture assay with CCRF-CEM. Data are mean±S.D. Both of CD5CAR NK-cells and CD5CAR NK^{45i}-92 cells shows near to 100% cell killing activity against CD5-potitive CCRF-CEM compared to control GFP NK-92 cells. These data suggest that CD5CAR NK-cells and CD5CAR NK^{45i}-92 cells can effectively lyse CCRF-CEM cells that express CD5 compared to GFP-control NK-92 cells in vitro co-culture assay and prof that knockdown of CD45 does not affect cell function for killing activity in NK-92 cells.

[0077] FIGS. **53**A-**53**B. Organization of the CD45CAR construct and its expression. (**53**A) Schematic representation of the CD45CAR lentiviral vector. The CD45CAR construct is a modularized signaling domain containing: a leader sequence, an anti-CD45scFv, a hinge domain (H), a transmembrane domain (TM), two co-stimulatory domains (CD28 and 4-1BB) that define the construct as a 3rd generation CAR, and the intracellular signaling domain CD3 zeta. (**53**B), HEK-293FT cells were transfected with lentiviral plasmids for GFP (lane 1) and CD45CAR (lane 2). 48 hours after transfection, supernatant was removed, and cells were also removed. Cells were lysed for Western blot and probe with mouse anti-human CD3z antibody.

[0078] FIG. **54**. Transduction of CD45CAR into NK^{45i}-92 cells and cell sorting of CD45CAR transduced cells. The

expression levels of CD45CAR on NK^{45i}-92 were determined by flow cytometry analysis (circled in blue at middle panel) compared to NK^{45i}-92 cells (left panel) after CD45CAR lentviruses were transduced into NK^{45i}-92 cells. CD45CAR expressed NK^{45i}-92 cells were sorted and CD45 expression levels on cell surface were determined by Flow cytometry analysis (right panel). About 87% of CD45CAR expression on cell surface was detected by flow cytometry analysis.

[0079] FIGS. **55**A-**55**B. Co-culture assay with CCRF-CEM (target: T) and GFP NK-92 or CD45CAR NK^{45i}-92 cells (effector: E) at 5:1 (E:T) ratio and 16 hour incubation. (**55**A) Flow cytometry analysis of in co-culture with CCRF-CEM and control GFP transduced NK-92 cells (left panel) or CD45CAR NK^{45i}-92 cells (right panel). Blue dots in all of panels indicates the leftover target CCRF-CEM cells and red dots shows effector NK-92 cells by co-culture assay. All of incubation time were 16 h and the ratio of effector T-cells:target cell is 5:1. All experiments were performed in duplicate. (**55**B) Bar graph indicates the percent of cell lysis by CD45CAR NK^{45i}-92 cells compared to the control GFP NK92 cells in co-culture assay with CCRF-CEM. Data are mean±S.D. CD45CAR NK^{45i}-92 cells shows about 70% cell lysis against CCRF-CEM cells compared to control GFP NK-92 cells. These data suggest that CD45CAR NK^{45i}-92 cells effectively lyse CCRF-CEM cells that express CD45 compared to GFP-control NK-92 cells in vitro co-culture assay.

[0080] FIGS. **56**A-**56**C. Co-culture assay with Jurkat cells (target: T) and GFP-control or CD45CAR NK^{45i}-92 cells (effector: E) at 5:1 or 2:1 (E:T) ratio and 6 hour incubation. (**56**A) Flow cytometry analysis was carried out after Jurkat cells were stained by CMTMR cell tracker dye. These data show that Jurkat cells are CD45 positive (left panels) and mostly CD56 negative cells (right panel). (**56**B) Flow cytometry analysis of co-culture assay with Jurkat cells (target: T) and control or CD45CAR NK^{45i}-92 cells (effector: E). The ratio of co-culture assay was performed in 5:1 or 2:1 (E:T). Left panels showed that in co-culture with control GFP or CD45CAR/CD45KD NK-92 cells in 5:1 (E:T) ratio and right panels indicated that in co-culture with control GFP or CD45CAR NK^{45i}-92 cells in 2:1 (E:T) ratio. Blue dots in panels indicate the leftover target Jurkat cells and red dots represent effector cells by co-culture assay. All of incubation time were 6 h. All experiments were performed in duplicate. (**56**C) Bar graph shows percent cell lysis by CD45CAR NK^{45i}-92 cells compared to control GFP NK92 cells at in 5:1 or 2:1 (E:T) ratio. Data are mean±S.D. CD45CAR NK^{45i}-92 cells shows about 60% cell lysis against Jurkat cells compared to control GFP NK-92 cells in both conditions. This data suggests that CD45CAR NK^{45i}-92 cells effectively lyse Jurkat cells that express CD45 on cell surface compared to GFP-control NK-92 cells in vitro co-culture assay.

[0081] FIG. **57**A-**57**C. Co-culture assay with GFP-NK-92 cells (target: T) and non-transduced NK-92 cells or CD45CAR NK^{45i}-92 cells (effector: E) at 5:1 or 2:1 (E:T) ratio, 6 hour incubation. (**57**A) Flow cytometry analysis was carried out using GFP control NK-92 cells. These data proof that GFP control NK-92 cells are about 99% GFP positive cells (green dots). (**57**B) Flow cytometry analysis of co-culture assay with GFP control NK-92 cells (target: T) and non-transduced or CD45CAR NK^{45i}-92 cells (effector: E). The ratio of co-culture assay was performed in 5:1 (**57**A) or 2:1 (E:T) (**57**C). Left panels showed that in co-culture with non-transduced or CD45CAR NK^{45i}-92 cells in 5:1 (E:T) ratio and right panels indicated that in co-culture with non-transduced or CD45CAR NK^{45i}-92 cells in 2:1 (E:T) ratio. Green dots in panels indicate the leftover target GFP NK-92 cells and red dots represent effector cells by co-culture assay. All of incubation times were 6 h. All experiments were performed in duplicate. (**57**C) Bar graph shows percent cell lysis of GFP NK-92 cells by CD45CAR NK^{45i}-92 cells compared to non-transduced NK-92 cells at in 5:1 or 2:1 (E:T) ratio. Data are mean±S.D. CD45CAR NK^{45i}-92 cells shows about 20% cell lysis in 2:1 (E:T) ratio and about 55% cell lysis in 5:1 (E:T) ratio against GFP NK-92 cells compared to non-transduced NK-92 cells. This data suggests that CD45CAR NK^{45i}-92 cells effectively lyse GFP NK-92 cells that express CD45 on cell surface compared to non-transduced NK-92 cells in vitro co-culture assay.

[0082] FIG. **57**D. Transduction of CD45b-BB or CD45b-28 into NK^{45i}-92 cells and cell sorting of CD45b-BB or CD45b-28 transduced NK^{45i}-92 cells. The co-stimulatory domain for CDb-BB is 4-1BB while co-stimulatory domain for CD45b-28 is CD28. The expression levels of CD45b-BB or CD45b-28 on NK^{45i}-92 were determined by flow cytometry analysis (circled in blue at middle panel) compared to NK^{45i}-92 cells (left panel) after CD45b-BB or CD45b-28 on lentviruses were transduced into NK^{45i}-92 cells. CD45b-BB or CD45b-28 on expressed NK^{45i}-92 cells were sorted and CD45b-BB or CD45b-28 on expression levels on cell surface were determined by Flow cytometry analysis (right panel). About 74% of CD45b-BB or 82% of CD45b-28 on expression on cell surface was detected by flow cytometry analysis.

[0083] FIG. **57**E. Co-culture assay with REH cells (target: T) and GFP NK-92 cells, CD45CAR NK^{45i}-92 cells, CD45b-BB NK^{45i}-92 cells or CD45b-28 NK^{45i}-92 cells at 5:1 (E:T) ratio and 20 hour incubation. Upper, Flow cytometry analysis of CREH cells only (left panel), in co-culture with with REH cells and control GFP transduced NK-92 cells (2nd left panel), CD45CAR NK^{45i}-92 cells (middle panel), CD45b-BB NK^{45i}-92 cells (4th from left panel) or CD45b-28 NK^{45i}-92 cells (right panel). Blue dots in all of panels indicates the leftover target REH cells and red dots shows effector GFP or CARs-NK-92 cells by co-culture assay. All of incubation time were 20h and the ratio of effector NK-cells:target cell is 5:1. All experiments were performed in duplicate. Lower, Bar graph indicates the percent of cell lysis by CD45CAR NK^{45i}-92 cells, CD45b-BB NK^{45i}-92 cells or CD45b-28 NK^{45i}-92 cells compared to the control GFP NK92 cells in co-culture assay with REH cells. Data are mean±S.D. CD45CAR NK^{45i}-92 cells shows about 76% cell lysis, CD45b-BB NK^{45i}-92 cells shows about 79% cell lysis and CD45b-28 NK^{45i}-92 shows 100% cell lysis against REH cells compared to control GFP NK-92 cells. These data suggest that these 3 of CD45CARs NK^{45i}-92 cells effectively lyse REH cells which characterized as B-cells expressing CD45 compared to GFP-control NK-92 cells in vitro co-culture assay.

[0084] FIGS. **57**FA-**57**FI. Co-culture assay with U937 cells (target: T) and GFP NK-92 cells or CD45b-28 NK^{45i}-92 cells. at 2:1 (E:T) ratio for 20 hours. FA, Flow cytometry analysis of U937 cells (monocytic leukemia cell line) only (left panel), in co-culture with U937 cells and control GFP transduced NK-92 cells (middle panel) or CD45b-28 NK^{45i}-92 cells (right panel). Blue dots in all of panels indicates the

leftover target U937 cells and red dots shows effector GFP or CD45b-28 NK^{45i}-92 cells by co-culture assay. All of incubation time were 6h and the ratio of effector NK-cells: target cell is 2:1. FB, Bar graph indicates the percent of cell lysis by CD45b-28 NK^{45i}-92 cells compared to the control GFP NK92 cells in co-culture assay with U937 cells. CD45b-28 NK^{45i}-92 shows about 81% cell lysis against U937 cells compared to control GFP NK-92 cells.

[0085] FIGS. **57**GA-**57**GB. Co-culture assay with MOLM-13 cells (target: T) and GFP NK-92 cells or CD45b-28 NK^{45i}-92 cells at 5:1 (E:T) ratio for 20 hours. GA, Flow cytometry analysis of MOLM13 cells (monocytic leukemic cell line) only (left panel), in co-culture with Molm13 cells and control GFP transduced NK-92 cells (middle panel) or CD45b-28 NK^{45i}-92 cells (right panel). Blue dots in all of panels indicates the leftover target MOLM13 cells and red dots shows effector GFP or CD45b-28 NK^{45i}-92 cells by co-culture assay. All of incubation time were 20h and the ratio of effector NK-cells:target cell is 5:1. GB, Bar graph indicates the percent of cell lysis by CD45b-28 NK^{45i}-92 cells compared to the control GFP NK92 cells in co-culture assay with MOLM13 cells. CD45b-28 NK^{45i}-92 shows about 91.6% cell lysis against Molm13 cells compared to control GFP NK-92 cells.

[0086] FIGS. **57**HA-**57**HB. Co-culture assay with Jeko-1 cells (target: T) and GFP NK-92 cells or CD45b-28 NK^{45i}-92 cells at 2:1 (E:T) ratio for 6 hours. HA, Flow cytometry analysis of Jeko-1 cells (T cell acute lymphoblastic cell line) only (left panel), in co-culture with Jeko-1 cells and control GFP transduced NK-92 cells (middle panel) or CD45b-28 NK^{45i}-92 cells (right panel). Blue dots in all of panels indicates the leftover target Jeko-1 cells and red dots shows effector GFP or CD45b-28 NK^{45i}-92 cells by co-culture assay. All of incubation time were 6h and the ratio of effector NK-cells:target cell is 2:1. HB. Bar graph indicates the percent of cell lysis by CD45b-28 NK^{45i}-92 cells compared to the control GFP NK92 cells in co-culture assay with Jeko-1 cells. CD45b-28 NK^{45i}-92 shows about 44.6% cell lysis against Jeko-1 cells compared to control GFP NK-92 cells.

[0087] FIGS. **57**IA-**57**IB. Co-culture assay with SP53 cells (target: T) and GFP NK-92 cells or CD45b-28 NK^{45i}-92 cells at 2:1 (E:T) ratio for 6 hour incubation. IA, Flow cytometry analysis of SP53 cells (mantle cell lymphoma cell line) only (left panel), in co-culture with Jeko-1 cells and control GFP transduced NK-92 cells (middle panel) or CD45b-28 NK^{45i}-92 cells (right panel). Blue dots in all of panels indicates the leftover target SP53 cells and red dots shows effector GFP or CD45b-28 NK^{45i}-92 cells by co-culture assay. All of incubation time were 6h and the ratio of effector NK-cells:target cell is 2:1. IB, Bar graph indicates the percent of cell lysis by CD45b-28 NK^{45i}-92 cells compared to the control GFP NK92 cells in co-culture assay with SP53 cells. CD45b-28 NK^{45i}-92 shows about 45% cell lysis against SP53 cells compared to control GFP NK-92 cells.

[0088] FIG. **57**J. Elimination of CD34(+) umbilical chord blood stem cells in 48 hr co-culture. CD34(+) stem cells derived from human umbilical cord blood were co-cultured with either Control or CD45b-28 CAR NK cells for 48 hr prior to labeling at a low ratio of 2:1 (effective:target). About 96% of CD34(+) cells were eliminated comparing to the control.

[0089] FIG. **58**A. A Link by P2A schematic showing both cCAR-T and 4-1BBL or IL-15/IL-15sushi in a single construct. The construct consists of a SFFV promoter driving the expression of CAR and an enhancer, 4-1BBL. Upon cleavage of the linkers, the CD45 CAR (or CD45b CAR) and 4-1BBL or IL-15/IL-15sush split and engage upon targets expressing CD45. CD45 CAR T cells received not only costimulation through the CD28 but also 4-1BB ligand (4-1BBL or CD137L) or IL-15/IL-15sushi. The CD3-zeta signaling domain completes the assembly of this CAR-T.

[0090] FIG. **58**B. Surface CD45b CAR expression levels on CD45b-28-2G-4-1BBL CAR transduced NK^{45i}-92 cells were determined using flow cytometry analysis. Left panel (NK92 cells) and middle panel (GFP-NK92) indicated negative control and right panel showed the surface expression of CD45b CAR which was labeled using goat anti-mouse F(AB')2-PE against ScFv region (circled in blue). Transduced cells expressed 86.99% of CD45b-CAR on the cell surface.

[0091] FIG. **58**C. Surface CD45b CAR expression levels on CD45b-28-2G-IL15/IL-15sushi CAR transduced NK45i-92 cells were determined using flow cytometry analysis. Left panel(NK92 cells) and middle panel (GFP-NK92) indicated negative control and right and right panel showed the surface expression of CD45b CAR which was labeled using goat anti-mouse F(AB')2-PE against ScFv region (circled in blue). CD45b-28-2G IL15RA virus transduced cells expressed 55.96% of CD45b-CAR on cells surface compared to negative control cells.

[0092] FIGS. **59**A-**59**B. Schematic diagram to elucidate the construct and its expression in T or NK cells. (**59**A) a combination of CAR, (third generation), and IL-15/sushi domain of the IL-15 alpha receptor, is assembled on an expression vector and their expression is driven by the SFFV promoter. CAR with IL-15/sushi is linked with the P2A self-cleaving sequence. The IL-15/sushi portion is composed of IL-2 signal peptide fused to IL-15 and linked to sushi domain via a 26-amino acid poly-proline linker. (**59**B) CAR and IL-15/sushi are present on the T or NK cells.

[0093] FIG. **59**C. Surface CD45b CAR expression levels on CD45b-28-2G-IL-15/IL-15sushi CAR transduced NK^{45i}-92 cells were determined using flow cytometry analysis. Left panel (NK92 cells) and middle panel (GFP-NK92) indicated negative control and right and right panel showed the surface expression of CD45b CAR which was labeled using goat anti-mouse F(AB')2-PE against ScFv region (circled in blue). CD45b-28-2G IL-15/IL-15sushi virus transduced cells expressed 55.96% of CD45b-CAR on cells surface compared to negative control cells. CD45b-28-2G-IL-15/IL-15sushi NK cells showed a robust functional activity.

[0094] FIGS. **60**A-**60**B. CD4IL-15/IL-15sushi expression. (**60**A) HEK-293FT cells were transfected with lentiviral plasmids for GFP (lane 1) and CD4IL-15/IL-15sushi CAR (lane 2). 48 hours after transfection, supernatant was removed, and cells were also removed for a Western blot with mouse anti-human CD3z antibody. (**60**B) HEK-293 cells were transduced with either GFP (left) or CD4IL-15/IL-15sushi-CAR(right) viral supernatant from transfected HEK-293FT cells. After 3 days incubation, cells were harvested, stained with goat-anti-mouse F(Ab')2 and analyzed by flow cytometry.

[0095] FIG. **61**. Transduction of NK cells with CD4IL-15/IL-15sushi CAR. NK-92 cells were transduced with either GFP (left) or CD4 IL-15/IL-15sushi CAR (right) viral supernatant from transfected HEK-293FT cells. A second

transduction was performed 24 hours after the first. 24 hours after the second transduction, cells were harvested, washed and moved to tissue culture plates with fresh media and IL-2. After 3 days incubation, cells were harvested and stained with goat-anti-mouse F(Ab')2 antibody or goat IgG (control) at 1:250 for 30 minutes. Cells were washed and stained with streptavidin-PE conjugate at 1:500, washed, suspended in 2% formalin, and analyzed by flow cytometry.

[0096] FIG. **62**. Transduction of T cells with CD4IL15RACAR. Left is the Western blot. HEK-293FT cells were transfected with lentiviral plasmids for GFP (lane 1) and CD4IL15RA-CAR (lane 2). 48 hours after transfection, supernatant was removed, and cells were also collected for a Western blot with mouse anti-human CD3zeta antibody. Right is CD4IL15RACAR expression. Activated T cells from cord blood buffy coat were transduced with either GFP (left) or concentrated CD4IL15RACAR (right) viral supernatant from transfected HEK-293FT cells. A second transduction was performed 24 hours after the first. 24 hours after the second transduction, cells were harvested, washed and moved to tissue culture plates with fresh media and IL-2. After 3 days incubation, cells were harvested and stained with goat-anti-mouse F(Ab') transduced with either GFP (left) or CD4IL15RA CAR (right). Cells were washed and stained with streptavidin-PE conjugate at 1:500, washed, suspended in 2% formalin, and analyzed by flow cytometry.

[0097] FIGS. **63**A-**63**B. CD4CAR NK-92 cells and CD4IL-15/IL-15sushi CAR NK-92 cells eliminate KARPAS 299 T leukemic cells in co-culture. (**63**A) NK-92 cells transduced with either GFP control (upper right), CD4CAR (lower left), or CD4IL-15/IL-15sushi (lower right) lentiviral supernatant were incubated with KARPAS 299 cells at a ratio of 5:1. After 4 hours co-culture, cells were stained with mouse-anti-human CD4 (APC) and CD3 (PerCp) antibodies and analyzed by flow cytometry (N=2). The upper left panel shows labeled Karpas 299 cells alone. The percentage of target cells lysed is shown in the graph (**63**B).

[0098] FIG. **64**. CD4CAR NK-92 cells and CD4IL-15/IL-15sushi CAR NK-92 cells eliminate MOLT4 T leukemic cells in co-culture. NK-92 cells transduced with either GFP control (left), CD4CAR (center), or CD4IL-15/IL-15sushi (second from right) lentiviral supernatant were incubated with MOLT4 cells at effector:target ratios of 1:1 or 2:1. After overnight co-culture, cells were stained with mouse-anti-human CD4 (APC) and CD56 (PerCp) antibodies and analyzed by flow cytometry (N=2). The upper right panel shows labeled MOLT4 cells alone. The percentage of target cells lysed is shown in the graph.

[0099] FIGS. **65**A and **65**B. CD4CAR and CD4IL-15/IL-15sushi CAR T cells demonstrate anti-leukemic effects in vivo. NSG mice were sublethally irradiated and intravenously (tail vein) injected the following day with luciferase-expressing MOLM13 cells to induce measurable tumor formation (**65**A). MOLM-13 cells are nearly 100% CD4+. After 3 days, the mice were intravenously injected with one course of 8×10^6 CD4CAR, or CD4IL-15/IL-15sushi CAR T cells, or vector control T control cells. On days 3, 6, 9, and 11, mice were injected subcutaneously with RediJect D-Luciferin and subjected to IVIS imaging (**65**B).

[0100] FIGS. **65**C and **65**D. (**65**C) Average light intensity measured for the CD4CAR and CD4IL-15/IL-15sushi CAR T injected mice was compared to that of vector control T injected mice, and correlated with remaining tumor burden to determine a percent lysis. (**65**D) Percent survival of mice was measured and compared between the three groups.

[0101] FIGS. **66**A and **66**B. CD4IL15/IL-15sushi CAR NK cells demonstrate robust anti-leukemic activity under stressful condition in vivo. NSG mice were sublethally irradiated and intravenously (tail vein) injected the following day with luciferase-expressing Jurkat cells to induce measurable tumor formation (**66**A). Jurkat cells are less than 60% CD4+. After 3 days, the mice were intravenously injected with one course of 8×10^6 CD4CAR, or CD4IL-15/IL-15sushi CAR NK cells, or vector control NK cells. On days 3, 7, 10, and 14, mice were injected subcutaneously with RediJect D-Luciferin and subjected to IVIS imaging (**66**B).

[0102] FIG. **66**C. Average light intensity measured for the CD4CAR and CD4IL-15/IL-15sushi NK injected mice was compared to that of vector control NK injected mice, and correlated with remaining tumor burden to determine a percent lysis.

[0103] FIG. **67**. Repeat of the in vivo experiment demonstrating robust lysis of Jurkat tumor cells by CD4I-15/IL-15sushi CAR NK cells showing similar results to those described in FIG. **66**.

[0104] FIGS. **68**A-**68**B. Effect of secreted IL-15/IL-15sushi on CAR and non-transduced neighboring cells. NK-92 cells stably expressing either CD4CAR or CD4IL15RA were mixed in a 50:50 ratio with NK-92 cells stably expressing GFP. These cells were co-cultured either with IL-2 added or no IL-2. (**68**A) Photographs taken on a fluorescent microscope at 20× on Day 0 (start of co-culture) and Day 7, without the addition of IL-2. (**68**B) Total cell counts calculated throughout the experiment (up to Day 14) for NK-92 cells co-cultured with or without IL-2.

[0105] FIG. **69**. Comparing the effect of secreted IL-15 and IL-15sushi on NK-92 cell growth. CD4IL-15/IL-15sushi, CD4 IL-15, and control transduced NK-92 cells were cultured from 250,000 cells in regular NK cell media but in the absence of IL-2 for up to 6 days. Both transduced cells had 10% surface CAR expression, while CD4IL15-IL15sushi transduced NK-92 cells were able to expand at a rate approximately 3-fold higher than the CD4 IL-15 transduced NK-92 cells on day 6. On day 4, the growth rate of CD4 IL-15 transduced NK-92 cells were slightly higher than the Control, but significantly below the CD4 IL-15/IL15sushi transduced NK-92 cells. This study pin-points the importance of co-expression functional complex of IL-15/IL-15sushi in promoting NK-92 cell growth.

[0106] FIG. **70**. A schematic showing the Treg CAR T construct targeting Tregs. The construct consists of a SFFV promoter driving the expression of two units of chimeric antigen receptors linked by a P2A peptide. Each unit contains a CD45 leader peptide sequence (signal peptide). Upon cleavage of the linker, two units of peptide are divided and engage upon targets expressing CD4 and CD25. The CD4 chimeric antigen receptor polypeptide unit comprises a signal peptide, a CD4 antigen recognition domain, a hinge region, a transmembrane domain and CD3 zeta chain; CD25 chimeric antigen receptor polypeptide unit comprises a signal peptide, a CD25 antigen recognition domain, a hinge region, a transmembrane domain, a co-stimulatory domain (s). The Treg CAR can potentiate the lysis activity of a cell co-expressing CD4 and CD25 while minimizing a cell bearing CD4 or CD25 antigen.

[0107] FIGS. **71**A-**71**B. Characterization of the CD4 zeta CD25 CAR. (**71**A) The CD4 zeta CD25 CAR was transduced into T-cells via viral incubation for 48 hours and stained with F(ab)' antibody to assay CAR surface expression. Encircled populations represent transduced cells. (**71**B) The C4-25z CAR was characterized using CD4 and CD25 antibodies to validate the construct function. Two most relevant populations are encircled: $CD4^+$ $CD25^+$ and $CD4^-$ $CD25^+$. The depletion of the double positive population and other phenotype groups are summarized in the bar graph adjacent.

[0108] FIG. **72**. CD4zetaCD25 CAR T cells target cells mainly co-expressing CD4 and CD25. 3 days after activation, PMBC buffy coat T cells transduced with either control vector (left), CD4CAR (middle) or CD4zetaCD25(right) lentiviral supernatant were harvested and incubated with mouse anti-human CD25-PE and mouse anti-human CD4-APC for 30 minutes. Cells were washed and suspended in 2% formalin, and analyzed by flow cytometry.

[0109] FIG. **73**A. A schematic showing the CD52-52 construct. The construct consists of a SFFV promoter driving the co-expression of CD5CAR and CD52 surface antigen. Upon cleavage of the linker of P2A. The CD5 chimeric antigen receptor polypeptide unit comprises a signal peptide, a CD5 antigen recognition domain, a hinge region, a transmembrane domain and CD3 zeta chain; CD5 peptide comprises a signal peptide, a CD52 antigen recognition domain, a hinge region, a transmembrane domain (derived from CD28).

[0110] FIG. **73**B. Experimental design to determine depletion of CD5CAR-52 T cells in blood. CD5CAR-52 T cells (5×10^6 cells) were injected intravenously into each NSG mouse after sublethally irradiation. After ~24 h later, PBS or 0.1 mg/kg of CAMPATH was injected via I.P. (intraperitoneal injection). N=3. After 6 h and 24 h later, peripheral blood was collected from each mouse and labeled using CD3 and CD45 antibodies to determine the depletion of CAR-T cells as acute phase response by CAMPATH treatment. After 5 days later, whole blood was collected from each mouse and labeled using CD3 and CD45 antibodies to determine the persistency of CAR-T cells as well. CAR-T-cells were determined using Flow cytometry analysis.

[0111] FIG. **73**C. Depletion of CD5CAR-52 T in peripheral blood after 6 h and 24 h later with or without CAMPATH treatment. Flow cytometry analysis shows persistence of CD5CAR-52 T-cells (Blue dots) in peripheral blood of mouse with or without CAMPATH treatment. Blood samples were labeled with CD3 and CD45 antibodies to detect CD5CAR-52 T-cells. Blood samples from un-infused CAR-T cells (left panels) did not show CD3 and CD45 positive cells (negative control). 0.1 mg/kg of CAMPATH injected mice indicate elimination of CD5CAR-52 T-cells at 6h (middle panels) and 24 h (right panels) later compared to CAMPATH untreated mouse at 6h (second panels from left) and 24 h (second panels from right) in blood samples. N=3. These results suggest that CAMPAT treatment can delete CAR-T cells from blood during short time.

[0112] FIG. **73**D. Depletion of CD5CAR-52 T in whole blood after 5 days later with or without CAMPATH treatment. Flow cytometry analysis shows persistence of CD5CAR-52 T-cells (Blue dots) in whole blood samples from mouse with or without CAMPATH treatment. Blood samples were labeled with CD3 and CD45 antibodies to detect CD5CAR-52 T-cells persistence. Blood samples from uninfused CAR-T cells (left panel) did not show CD3 and CD45 positive cells (negative control). 0.1 mg/kg of CAMPATH treated mice eliminate CD5CAR-52 T-cells (right panels) compared to CAMPATH uninjected mouse (middle panels) after 5 days later in whole blood samples. These results also suppose CAMPAT treatment can delete CAR-T cells from blood.

[0113] FIG. **74**. HEK 293 cells were transduced with either EF1-GFP or SFFV-GFP viral supernatant, using the volumes indicated, in DMEM with 10% FBS in a 6 well tissue culture plate. Culture media was changed the following morning. Forty-eight hours later, transduced cells were visualized on an EVOS fluorescent microscope using GFP at 10×.

[0114] FIG. **75**. HEK 293 cells transduced with either EF1-GFP or SFFV-GFP viral supernatant, using the volumes from the previous figure, were trypsinized, suspended in formalin, and subjected to flow cytometry analysis, using the FITC channel to determine the percentage of GFP+ cells.

[0115] FIGS. **76**A-**76**B. Activated cord blood buffy coat T cells transduced with either EF1-GFP or SFFV-GFP viral supernatant, with either low or high amounts of viral supernatant, were trypsinized, suspended in formalin, and subjected to flow cytometry analysis, using the FITC channel to determine the percentage of GFP+ cells, 7, 14, 21 and 28 days after transduction. (**76**A) Percent GFP+ T cells for cells transduced with either low or high amounts of supernatant. (**76**B) Percent of GFP+ T cells transduced with the high amount of EF1-GFP supernatant, relative to the percent GFP+ cells in the T cells transduced with the lower amount of SFFV-GFP supernatant. (50 μL of SFFV-GFP and 1 mL of EF1-GFP supernatant was used). (N=2).

[0116] FIG. **77**. Ligand receptor interactions in malignant plasma cells. The APRIL ligand binds TAC1 or BCMA. The BAFF ligand binds TAC1, BCMA, or BAFF-R.

[0117] FIG. **78**. Steps for elimination of tumor by CAR co-expressing secretory IL-15/IL-15sushi. I, tumor and its microenviroment. Macrophages, T cells, dendritic cells and NK cells are immune response cells against tumor in the tumor microenvironment and they secrete a low level of endogenous IL-15, which is unstable, which complexes with the soluble extracellular domain of IL-15RA. The complex forms a more stable molecule, which greatly enhances immune cell survival and expansion. In the tumor microenvironment, cancer cells express programmed death ligand 1 (PD-L1) as a transmembrane protein that has been considered to play a major role in suppressing the immune system during particular events including cancer. PD-L1 binds to its receptor, PD-1, found on activated T cells, B cells, and myeloid cells, to suppress these cell immune activities. II, CAR T or NK cells targeting tumor cells, could be a carrier to deliver an enhancer to the tumor microenvironment. CAR T or NK cells are engineered to co-express a secretory fusion protein, IL-15/IL-15sushi fusion. III, Engineered CAR T or NK cells bind to targeted tumor cells (either subset or all cells). IV, Engineered CAR T or NK cells in tumor microenvironment target tumor cells, binding to the CAR targeting antigen, and triggering lysis of tumor cells and massive secretion of soluble IL-15/IL-15sushi fusion from the expansion of CAR T or NK cells. The soluble IL-15/IL-15sushi fusion are stable and functions as an unexpected and powerful immunomodulatory for CAR T/NK cells and their neighbor tumor immune response cells. The secreted IL-15/IL-15sushi protein would be involved in trafficking of other

T cells, dendritic cells, macrophages and NK cells to the tumor microenvironment, which then also: 1) lyse the tumor cells by supplementing the defect that CAR T or NK cells are unable to eliminate non-targeting cancer cells; 2) enhance CAR T/NK cell persistency and anti-tumor activity. The overexpression of IL-15/IL-15sushi overwhelms the PD-L1 ability to suppress the immune response. Preferably, this CAR therapy could be used synergistically with administration of a checkpoint blockage including, but not limited to PD-L1, CTLA-4 inhibitor for even greater efficacy.

[0118] FIG. **79**. Surface markers during B cell and plasma cell development are shown. Both BAFF and APRIL binds to receptors, BCMA and TACI. BAFF also binds to BAFF-R receptor.

[0119] FIG. **80**. Protein sequence alignment of IL-2 signal peptide among different species.

[0120] FIG. **81**. Protein sequence alignment of BAFF extracellular domain among different species.

DETAILED DESCRIPTION

[0121] The disclosure provides chimeric antigen receptor (CAR) compositions, methods of making and using thereof.

[0122] A chimeric antigen receptor (CAR) polypeptide includes a signal peptide, an antigen recognition domain, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain.

[0123] First-generation CARs include CD3z as an intracellular signaling domain, whereas second-generation CARs include at least one single co-stimulatory domain derived from various proteins. Examples of co-stimulatory domains include, but are not limited to, CD28, CD2, 4-1BB (CD137, also referred to as "4-BB"), and OX-40 (CD124). Third generation CARs include two co-stimulatory domains, such as, but not limited to, CD28, 4-1BB, CD134 (OX-40), CD2, and/or CD137 (4-1BB).

[0124] As used herein, the terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound having amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can be included in a protein's or peptide's sequence. Polypeptides include any peptide or protein having two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides, and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, and fusion proteins, among others. The polypeptides include natural peptides, recombinant peptides, synthetic peptides, or a combination thereof.

[0125] A "signal peptide" includes a peptide sequence that directs the transport and localization of the peptide and any attached polypeptide within a cell, e.g. to a certain cell organelle (such as the endoplasmic reticulum) and/or the cell surface. As used herein, "signal peptide" and "leader sequence" are used interchangeably.

[0126] The signal peptide is a peptide of any secreted or transmembrane protein that directs the transport of the polypeptide of the disclosure to the cell membrane and cell surface, and provides correct localization of the polypeptide of the present disclosure. In particular, the signal peptide of the present disclosure directs the polypeptide of the present disclosure to the cellular membrane, wherein the extracellular portion of the polypeptide is displayed on the cell surface, the transmembrane portion spans the plasma membrane, and the active domain is in the cytoplasmic portion, or interior of the cell.

[0127] In one embodiment, the signal peptide is cleaved after passage through the endoplasmic reticulum (ER), i.e. is a cleavable signal peptide. In an embodiment, the signal peptide is human protein of type I, II, III, or IV. In an embodiment, the signal peptide includes an immunoglobulin heavy chain signal peptide.

[0128] In one embodiment, the signal peptide includes the signal peptide from human CD45. (UniProtKB/Swiss-Prot Accession Number P08575). The CD45 signal peptide is 23 amino acids in length (MYLWLKLLAFGFAFLDTEVFVTG). In some embodiments, the signal peptide may be a functional fragment of the CD45 signal peptide. A functional fragment includes a fragment of at least 10 amino acids of the CD45 signal peptide that directs the appended polypeptide to the cell membrane and cell surface. Examples of fragments of the human CD45 signal peptide include: MYLWLKLLAFG, FAFLDTEVFVTG, and LKLLAFGFAFLDTE.

[0129] Functional equivalents of the human CD45 signal peptide have also been contemplated. As used herein, "functional equivalents" are to be understood as mutants that exhibit, in at least one of the abovementioned sequence positions, an amino acid substitution other than the one mentioned specifically, but still lead to a mutant which show the same or similar properties with respect to the wild-type CD45 signal peptide. Functional equivalents include polypeptides having at least 80%, at least 85%, at least 90%, or at least 95% identity to the human CD45 signal peptide, functional fragments thereof, or functional equivalents thereof.

[0130] Functional equivalents also include CD45 signal peptides from homologous proteins from other species. Examples of these signal peptides include signal peptide from mouse CD45 (MGLWLKLLAFGFALLDTEVFVTG); signal peptide from rat CD45 (MYLWLKLLAFSLALLGPEVFVTG); signal peptide from sheep CD45 (MTMYLWLKLLAFGFAFLDTAVSVAG); signal peptide from chimpanzee CD45 (MYLWLKLLAFGFAFLDTEVFVTG); and signal peptide from monkey CD45 (MTMYLWLKLLAFGFAFLDTEVFVAG.

[0131] In another embodiment, the signal peptide includes the following sequence: $MX^1LWLKLLAF X^2X^3AX^4LX^5X^6X^7VX^8 VX^9G$; wherein X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, and X^9 are independently Y, G, S, F, L, D, P, T, E, or A. In one embodiment, X^1 is Y or G; X^2 is G or S; X^3 and X^4 are independently F or L; X^5 is D or G; X^6 is P or T; X^7 is E or A; X^8 is F or S; and X^9 is A or T.

[0132] In one embodiment, the signal peptide includes the signal peptide from human CD8a (MALPVTALLLPLALLLHAARP). In some embodiments, the signal peptide may be a functional fragment of the CD8a signal peptide. A functional fragment includes a fragment of at least 10 amino acids of the CD8a signal peptide that directs the appended polypeptide to the cell membrane and cell surface. Examples of fragments of the human CD8a signal

peptide include: MALPVTALLLPLALLLHAA, MALPVTALLLP, PVTALLLPLALL, and LLLPLALLL-HAARP.

[0133] In another embodiment, the signal peptide includes the signal peptide from human CD8b (MRPRLWLL-LAAQLTVLHGNSV). In some embodiments, the signal peptide may be a functional fragment of the CD8b signal peptide. A functional fragment includes a fragment of at least 10 amino acids of the CD8b signal peptide that directs the appended polypeptide to the cell membrane and cell surface. Examples of fragments of the human CD8b signal peptide include: MRPRLWLLLAAQ, RLWLLLAAQLTV-LHG, and LWLLLAAQLTVLHGNSV.

[0134] Functional equivalents of the human CD8a or CD8b signal peptide have also been contemplated. As used herein, "functional equivalents" are to be understood as mutants which exhibit, in at least one of the abovementioned sequence positions, an amino acid substitution other than the one mentioned specifically, but still lead to a mutant which show the same or similar properties with respect to the wild-type CD8a or CD8b signal peptide. Functional equivalents include polypeptides having at least 80%, at least 85%, at least 90%, or at least 95% identity to the human CD8 signal peptide, functional fragments thereof, or functional equivalents thereof.

[0135] Functional equivalents also include CD8a and CD8b signal peptides from homologous proteins from other species.

[0136] In one embodiment, the signal peptide includes the signal peptide from human IL-2. The IL-2 signal peptide is 23 amino acids in length (MYRMQLLSCIALSLALVTNS). In some embodiments, the signal peptide may be a functional fragment of the IL-2 signal peptide. A functional fragment includes a fragment of at least 10 amino acids of the IL-2 signal peptide that directs the appended polypeptide to the cell membrane and cell surface. Examples of fragments of the human IL-2 signal peptide include: MYRMQLLSCIAL, QLLSCIALSLAL, and SCIALSLA-LVTNS.

[0137] Functional equivalents of the human IL-2 signal peptide have also been contemplated. As used herein, "functional equivalents" are to be understood as mutants which exhibit, in at least one of the abovementioned sequence positions, an amino acid substitution other than the one mentioned specifically, but still lead to a mutant which show the same or similar properties with respect to the wild-type IL-2 signal peptide. Functional equivalents include polypeptides having at least 80%, at least 85%, at least 90%, or at least 95% identity to the human IL-2 signal peptide, functional fragments thereof, or functional equivalents thereof.

[0138] Functional equivalents also include IL-2 signal peptides from homologous proteins from other species. See for example FIG. **80**.

[0139] In another embodiment, the signal peptide includes the following sequence: $MYX^1X^2QLX^3SCX^4XLX^6LX^7LXX^9X^{10}X^{11}$; wherein X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, and X^{11} are independently R, K, S, M, I, V, L, A, I, T, N, S, or G. In one embodiment, X^1 is R, K, or S; X^2 is M, I, or V; X^3 is L or A; X^4 and X^5 are independently I, A, V, or T; X^6 is S or T; X^7 is A or V; X^8, X^9, X^{10}, and X^{11} are independently V, L, T, A, N, S, or G.

[0140] The "antigen recognition domain" includes a polypeptide that is selective for or targets an antigen, receptor, peptide ligand, or protein ligand of the target; or a polypeptide of the target.

[0141] The antigen recognition domain may be obtained from any of the wide variety of extracellular domains or secreted proteins associated with ligand binding and/or signal transduction. The antigen recognition domain may include a portion of Ig heavy chain linked with a portion of Ig light chain, constituting a single chain fragment variable (scFv) that binds specifically to a target antigen. The antibody may be monoclonal or polyclonal antibody or may be of any type that binds specifically to the target antigen. In another embodiment, the antigen recognition domain can be a receptor or ligand. In particular embodiments, the target antigen is specific for a specific disease condition and the disease condition may be of any kind as long as it has a cell surface antigen, which may be recognized by at least one of the chimeric receptor construct present in the compound CAR architecture. In a specific embodiment, the chimeric receptor may be for any cancer for which a specific monoclonal or polyclonal antibody exists or is capable of being generated. In particular, cancers such as neuroblastoma, small cell lung cancer, melanoma, ovarian cancer, renal cell carcinoma, colon cancer, Hodgkin's lymphoma, and childhood acute lymphoblastic leukemia have antigens specific for the chimeric receptors.

[0142] In some embodiments, antigen recognition domain can be non-antibody protein scaffolds, such as but not limited to, centyrins, non-antibody protein scaffolds that can be engineered to bind a variety of specific targets with high affinity. Centyrins are scaffold proteins based on human consensus tenascin FN3 domain, are usually smaller than scFv molecules CAR molecules.

[0143] The target specific antigen recognition domain preferably includes an antigen binding domain derived from an antibody against an antigen of the target, or a peptide binding an antigen of the target, or a peptide or protein binding an antibody that binds an antigen of the target, or a peptide or protein ligand (including but not limited to a growth factor, a cytokine, or a hormone) binding a receptor on the target, or a domain derived from a receptor (including but not limited to a growth factor receptor, a cytokine receptor or a hormone receptor) binding a peptide or protein ligand on the target.

[0144] In one embodiment, the antigen recognition domain includes the binding portion or variable region of a monoclonal or polyclonal antibody directed against (selective for) the target.

[0145] In another embodiment, the antigen recognition domain includes Camelid single domain antibody, or portions thereof. In one embodiment, Camelid single-domain antibodies include heavy-chain antibodies found in camelids, or VHH antibody. A VHH antibody of camelid (for example camel, dromedary, llama, and alpaca) refers to a variable fragment of a camelid single-chain antibody (See Nguyen et al, 2001; Muyldermans, 2001), and also includes an isolated VHH antibody of camelid, a recombinant VHH antibody of camelid, or a synthetic VHH antibody of camelid.

[0146] In another embodiment, the antigen recognition domain includes ligands that engage their cognate receptor. By way of example, APRIL is a ligand that binds the TAC1 receptor or the BCMA receptor. In accordance with the

present disclosure, the antigen recognition domain includes APRIL, or a fragment thereof. By way of further example, BAFF is a ligand that binds the BAFF-R receptor or the BCMA receptor. In accordance with the present disclosure, the antigen recognition domain includes BAFF, or a fragment thereof. In another embodiment, the antigen recognition domain is humanized.

[0147] It is understood that the antigen recognition domain may include some variability within its sequence and still be selective for the targets disclosed herein. Therefore, it is contemplated that the polypeptide of the antigen recognition domain may be at least 95%, at least 90%, at least 80%, or at least 70% identical to the antigen recognition domain polypeptide disclosed herein and still be selective for the targets described herein and be within the scope of the disclosure.

[0148] The target includes interleukin 6 receptor, NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BCMA, BAFF-R, TACI, LeY, CD13, CD14, CD15 CD19, CD20, CD22, CD33, CD41, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, CS1, CD45, ROR1, PSMA, MAGE A3, Glycolipid, glypican 3, F77, GD-2, WT1, CEA, HER-2/neu, MAGE-3, MAGE-4, MAGE-5, MAGE-6, alpha-fetoprotein, CA 19-9, CA 72-4, NY-ESO, FAP, ErbB, c-Met, MART-1, CD30, EGFRvIII, immunoglobin kappa and lambda, CD38, CD52, CD3, CD4, CD8, CD5, CD7, CD2, and CD138

[0149] In another embodiment, the target includes any portion interleukin 6 receptor, NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BCMA, BAFF-R, TACI, LeY, CD13, CD14, CD15 CD19, CD20, CD22, CD33, CD41, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, CS1, CD45, TACI, ROR1, PSMA, MAGE A3, Glycolipid, glypican 3, F77, GD-2, WT1, CEA, HER-2/neu, MAGE-3, MAGE-4, MAGE-5, MAGE-6, alpha-fetoprotein, CA 19-9, CA 72-4, NY-ESO, FAP, ErbB, c-Met, MART-1, CD30, EGFRvIII, immunoglobin kappa and lambda, CD38, CD52, CD3, CD4, CD8, CD5, CD7, CD2, and CD138.

[0150] In one embodiment, the target includes surface exposed portions of interleukin 6 receptor, NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BCMA, BAFF-R, TACI, LeY, CD13, CD14, CD15 CD19, CD20, CD22, CD33, CD41, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, CS1, CD45, TACI, ROR1, PSMA, MAGE A3, Glycolipid, glypican 3, F77, GD-2, WT1, CEA, HER-2/neu, MAGE-3, MAGE-4, MAGE-5, MAGE-6, alpha-fetoprotein, CA 19-9, CA 72-4, NY-ESO, FAP, ErbB, c-Met, MART-1, CD30, EGFRvIII, immunoglobin kappa and lambda, CD38, CD52, CD3, CD4, CD8, CD5, CD7, CD2, and CD138 polypeptides.

[0151] For example, the target includes the surface exposed regions of BAFF, as shown in FIG. **81**. The target may include a portion of the surface exposed regions of BAFF. For example, portions of BAFF include residues 1-200, 1-100, 50-150, or 100-200 of human BAFF.

[0152] In another embodiment, the target antigens include viral or fungal antigens, such as E6 and E7 from the human papillomavirus (HPV) or EBV (Epstein Barr virus) antigens; portions thereof; or surface exposed regions thereof.

[0153] In one embodiment, the TACI antigen recognition domain includes SEQ ID NO. 24.

[0154] In one embodiment, the BCMA antigen recognition domain includes SEQ ID NO. 25.

[0155] In one embodiment, the CS1 antigen recognition domain includes SEQ ID NO. 26.

[0156] In one embodiment, the BAFF-R antigen recognition domain includes SEQ ID NO. 27.

[0157] In one embodiment, the CD33 antigen recognition domain includes SEQ ID NO. 28.

[0158] In one embodiment, the CD123 antigen recognition domain includes SEQ ID NO. 29.

[0159] In one embodiment, the CD19 antigen recognition domain includes SEQ ID NO. 30.

[0160] In one embodiment, the CD20 antigen recognition domain includes SEQ ID NO. 31. In another embodiment, the CD20 antigen recognition domain includes SEQ ID NO. 32.

[0161] In one embodiment, the CD22 antigen recognition domain includes SEQ ID NO. 33.

[0162] In on embodiment, the CD45 antigen recognition domain includes SEQ ID NO. 34.

[0163] In on embodiment, the CD4 antigen recognition domain includes SEQ ID NO. 35

[0164] In on embodiment, the CD25 antigen recognition domain includes SEQ ID NO. 36

[0165] The hinge region is a sequence positioned between for example, including, but not limited to, the chimeric antigen receptor, and at least one co-stimulatory domain and a signaling domain. The hinge sequence may be obtained including, for example, from any suitable sequence from any genus, including human or a part thereof. Such hinge regions are known in the art. In one embodiment, the hinge region includes the hinge region of a human protein including CD-8 alpha, CD28, 4-1BB, OX40, CD3-zeta, T cell receptor a or 3 chain, a CD3 zeta chain, CD28, CD3c, CD45, CD4, CD5, CD8, CD8a, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, ICOS, CD154, functional derivatives thereof, and combinations thereof.

[0166] In one embodiment the hinge region includes the CD8 a hinge region.

[0167] In some embodiments, the hinge region includes one selected from, but not limited to, immunoglobulin (e.g. IgG1, IgG2, IgG3, IgG4, and IgD).

[0168] The transmembrane domain includes a hydrophobic polypeptide that spans the cellular membrane. In particular, the transmembrane domain spans from one side of a cell membrane (extracellular) through to the other side of the cell membrane (intracellular or cytoplasmic).

[0169] The transmembrane domain may be in the form of an alpha helix or a beta barrel, or combinations thereof. The transmembrane domain may include a polytopic protein, which has many transmembrane segments, each alpha-helical, beta sheets, or combinations thereof.

[0170] In one embodiment, the transmembrane domain that is naturally associated with one of the domains in the CAR is used. In another embodiment, the transmembrane domain is selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins to minimize interactions with other members of the receptor complex.

[0171] For example, a transmembrane domain includes a transmembrane domain of a T-cell receptor a or β chain, a CD3 zeta chain, CD28, CD3c, CD45, CD4, CD5, CD7, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD68, CD134, CD137, ICOS, CD41, CD154, functional derivatives thereof, and combinations thereof.

[0172] In one embodiment, the transmembrane domain is artificially designed so that more than 25%, more than 50% or more than 75% of the amino acid residues of the domain are hydrophobic residues such as leucine and valine. In one embodiment, a triplet of phenylalanine, tryptophan and valine is found at each end of the synthetic transmembrane domain.

[0173] In one embodiment, the transmembrane domain is the CD8 transmembrane domain. In another embodiment, the transmembrane domain is the CD28 transmembrane domain. Such transmembrane domains are known in the art.

[0174] The signaling domain and co-stimulatory domain include polypeptides that provide activation of an immune cell to stimulate or activate at least some aspect of the immune cell signaling pathway.

[0175] In an embodiment, the signaling domain includes the polypeptide of a functional signaling domain of CD3 zeta, common FcR gamma (FCER1G), Fc gamma R11a, FcR beta (Fc Epsilon Rib), CD3 gamma, CD3 delta, CD3 epsilon, CD79a, CD79b, DNAX-activating protein 10 (DAP10), DNAX-activating protein 12 (DAP12), active fragments thereof, functional derivatives thereof, and combinations thereof. Such signaling domains are known in the art.

[0176] In an embodiment, the CAR polypeptide further includes one or more co-stimulatory domains. In an embodiment, the co-stimulatory domain is a functional signaling domain from a protein including OX40; CD27; CD28; CD30; CD40; PD-1; CD2; CD7; CD258; Natural killer Group 2 member C (NKG2C); Natural killer Group 2 member D (NKG2D), B7-H3; a ligand that binds to at least one of CD83, ICAM-1, LFA-1 (CD11a/CD18), ICOS, and 4-1BB (CD137); CDS; ICAM-1; LFA-1 (CD1a/CD18); CD40; CD27; CD7; B7-H3; NKG2C; PD-1; ICOS; active fragments thereof; functional derivatives thereof; and combinations thereof.

[0177] As used herein, the at least one co-stimulatory domain and signaling domain may be collectively referred to as the intracellular domain. As used herein, the hinge region and the antigen recognition domain may be collectively referred to as the extracellular domain.

[0178] The present disclosure further provides a polynucleotide encoding the chimeric antigen receptor polypeptide described above.

[0179] The term "polynucleotide" as used herein is defined as a chain of nucleotides. Polynucleotide includes DNA and RNA. Furthermore, nucleic acids are polymers of nucleotides. Thus, nucleic acids and polynucleotides as used herein are interchangeable. One skilled in the art has the general knowledge that nucleic acids are polynucleotides, which can be hydrolyzed into the monomeric "nucleotides." The monomeric nucleotides can be hydrolyzed into nucleosides. As used herein polynucleotides include, but are not limited to, all nucleic acid sequences which are obtained by any means available in the art, including, without limitation, recombinant means, i.e., the cloning of nucleic acid sequences from a recombinant library or a cell genome, using ordinary cloning technology and polymerase chain reaction (PCR), and the like, and by synthetic means.

[0180] The polynucleotide encoding the CAR is easily prepared from an amino acid sequence of the specified CAR by any conventional method. A base sequence encoding an amino acid sequence can be obtained from the aforementioned NCBI RefSeq IDs or accession numbers of GenBank for an amino acid sequence of each domain, and the nucleic acid of the present disclosure can be prepared using a standard molecular biological and/or chemical procedure. For example, based on the base sequence, a polynucleotide can be synthesized, and the polynucleotide of the present disclosure can be prepared by combining DNA fragments which are obtained from a cDNA library using a polymerase chain reaction (PCR).

[0181] In one embodiment, the polynucleotide disclosed herein is part of a gene, or an expression or cloning cassette.

[0182] The polynucleotide described above can be cloned into a vector. A "vector" is a composition of matter which includes an isolated polynucleotide and which can be used to deliver the isolated polynucleotide to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, phagemid, cosmid, and viruses. Viruses include phages, phage derivatives. Thus, the term "vector" includes an autonomously replicating plasmid or a virus. The term should also be construed to include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, polylysine compounds, liposomes, and the like. Examples of viral vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like. In one embodiment, vectors include cloning vectors, expression vectors, replication vectors, probe generation vectors, integration vectors, and sequencing vectors.

[0183] In an embodiment, the vector is a viral vector. In an embodiment, the viral vector is a retroviral vector or a lentiviral vector. In an embodiment, the engineered cell is virally transduced to express the polynucleotide sequence.

[0184] A number of viral based systems have been developed for gene transfer into mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems. 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 cells of the patient either in vivo or ex vivo. A number of retroviral systems are known in the art. In some embodiments, adenovirus vectors are used. A number of adenovirus vectors are known in the art. In one embodiment, lentivirus vectors are used.

[0185] Viral vector technology is well known in the art and is described, for example, in Sambrook et al, (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York), and in other virology and molecular biology manuals. Viruses, which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient and unique restriction endonuclease sites, and one or more selectable markers, (e.g., WO 01/96584; WO 01/29058; and U.S. Pat. No. 6,326,193).

[0186] Lentiviral vectors have been well known for their capability of transferring genes into human T cells with high efficiency but expression of the vector-encoded genes is dependent on the internal promoter that drives their expression. A strong promoter is particularly important for the third or fourth generation of CARs that bear additional co-stimulatory domains or genes encoding proliferative cytokines as increased CAR body size does not guarantee equal

levels of expression. There are a wide range of promoters with different strength and cell-type specificity. Gene therapies using CAR T cells rely on the ability of T cells to express adequate CAR body and maintain expression over a long period of time. The EF-1α promoter has been commonly selected for the CAR expression.

[0187] The present disclosure provides an expression vector containing a strong promoter for high level gene expression in T cells or NK cells. In further embodiment, the inventor discloses a strong promoter useful for high level expression of CARs in T cells or NK cells. In particular embodiments, a strong promoter relates to the SFFV promoter, which is selectively introduced in an expression vector to obtain high levels of expression and maintain expression over a long period of time in T cells or NK cells. Expressed genes prefer CARs, T cell co-stimulatory factors and cytokines used for immunotherapy.

[0188] One example of a suitable promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of any polynucleotide sequence operatively linked thereto. Another example of a suitable promoter is Elongation Growth Factor-1 a (EF-1 a). However, other constitutive promoter sequences may also be used, including, but not limited to the simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter. Further, the disclosure should not be limited to the use of constitutive promoters, inducible promoters are also contemplated as part of the disclosure. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence, which is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metalothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

[0189] Expression of chimeric antigen receptor polynucleotide may be achieved using, for example, expression vectors including, but not limited to, at least one of a SFFV (spleen-focus forming virus) (for example, SEQ ID NO. 23) or human elongation factor 11α (EF) promoter, CAG (chicken beta-actin promoter with CMV enhancer) promoter human elongation factor 1α (EF) promoter. Examples of less-strong/lower-expressing promoters utilized may include, but is not limited to, the simian virus 40 (SV40) early promoter, cytomegalovirus (CMV) immediate-early promoter, Ubiquitin C (UBC) promoter, and the phosphoglycerate kinase 1 (PGK) promoter, or a part thereof. Inducible expression of chimeric antigen receptor may be achieved using, for example, a tetracycline responsive promoter, including, but not limited to, TRE3GV (Tet-response element, including all generations and preferably, the 3rd generation), inducible promoter (Clontech Laboratories, Mountain View, Calif.) or a part or a combination thereof.

[0190] In a preferred embodiment, the promoter is an SFFV promoter or a derivative thereof. It has been unexpectedly discovered that SFFV promoter provides stronger expression and greater persistence in the transduced cells in accordance with the present disclosure.

[0191] "Expression vector" refers to a vector including a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector includes sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an in vitro expression system. Expression vectors include all those known in the art, such as cosmids, plasmids (e.g., naked or contained in liposomes) and viruses (e.g., lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide. The expression vector may be a bicistronic or multicistronic expression vector. Bicistronic or multicistronic expression vectors may include (1) multiple promoters fused to each of the open reading frames; (2) insertion of splicing signals between genes; fusion of genes whose expressions are driven by a single promoter; (3) insertion of proteolytic cleavage sites between genes (self-cleavage peptide); and (iv) insertion of internal ribosomal entry sites (IRESs) between genes.

[0192] In one embodiment, the disclosure provides an engineered cell having at least one chimeric antigen receptor polypeptide or polynucleotide.

[0193] An "engineered cell" means any cell of any organism that is modified, transformed, or manipulated by addition or modification of a gene, a DNA or RNA sequence, or protein or polypeptide. Isolated cells, host cells, and genetically engineered cells of the present disclosure include isolated immune cells, such as NK cells and T cells that contain the DNA or RNA sequences encoding a chimeric antigen receptor or chimeric antigen receptor complex and express the chimeric receptor on the cell surface. Isolated host cells and engineered cells may be used, for example, for enhancing an NK cell activity or a T lymphocyte activity, treatment of cancer, and treatment of infectious diseases.

[0194] In an embodiment, the engineered cell includes immunoregulatory cells. Immunoregulatory cells include T-cells, such as CD4 T-cells (Helper T-cells), CD8 T-cells (Cytotoxic T-cells, CTLs), and memory T cells or memory stem cell T cells. In another embodiment, T-cells include Natural Killer T-cells (NK T-cells).

[0195] In an embodiment, the engineered cell includes Natural Killer cells. Natural killer cells are well known in the art. In one embodiment, natural killer cells include cell lines, such as NK-92 cells. Further examples of NK cell lines include NKG, YT, NK-YS, HANK-1, YTS cells, and NKL cells.

[0196] NK cells mediate anti-tumor effects without the risk of GvHD and are short-lived relative to T-cells. Accordingly, NK cells would be exhausted shortly after destroying cancer cells, decreasing the need for an inducible suicide gene on CAR constructs that would ablate the modified cells.

[0197] In accordance with the present disclosure, it was surprisingly found that NK cells provide a readily available cell to be engineered to contain and express the chimeric antigen receptor polypeptides disclosed herein.

[0198] Allogeneic or autologous NK cells induce a rapid immune response but disappear relatively rapidly from the circulation due to their limited lifespan. Thus, applicants surprisingly discovered that there is reduced concern of persisting side effects using CAR cell based therapy.

[0199] According to one aspect of the present disclosure, NK cells can be expanded and transfected with CAR polynucleotides in accordance to the present disclosure. NK cells can be derived from cord blood, peripheral blood, iPS cells and embryonic stem cells. According to one aspect of the present disclosure, NK-92 cells may be expanded and transfected with CAR. NK-92 is a continuously growing cell line that has features and characteristics of natural killer (NK) cells (Arai, Meagher et al. 2008). NK-92 cell line is IL-2 dependent and has been proven to be safe (Arai, Meagher et al. 2008) and feasible. CAR expressing NK-92 cells can be expanded in the serum free-medium with or without co-culturing with feeder cells. A pure population of NK-92 carrying the CAR of interest may be obtained by sorting.

[0200] In one embodiment, engineered cells include allogeneic T cells obtained from donors that are modified to inactivate components of TCR (T cell receptor) involved in MHC recognition. As a result, TCR deficient T cells would not cause graft versus host disease (GVHD).

[0201] In some embodiments, the engineered cell may be modified to prevent expression of cell surface antigens. For example, an engineered cell may be genetically modified to delete the native CD45 gene to prevent expression and cell surface display thereof.

[0202] In some embodiments, the engineered cell includes an inducible suicide gene ("safety switch") or a combination of safety switches, which may be assembled on a vector, such as, without limiting, a retroviral vector, lentiviral vector, adenoviral vector or plasmid. Introduction of a "safety switch" greatly increases safety profile and limits on-target or off-tumor toxicities of the compound CARs. The "safety switch" may be an inducible suicide gene, such as, without limiting, caspase 9 gene, thymidine kinase, cytosine deaminase (CD) or cytochrome P450. Other safety switches for elimination of unwanted modified T cells involve expression of CD20 or CD52 or CD19 or truncated epidermal growth factor receptor in T cells. All possible safety switches have been contemplated and are embodied in the present disclosure.

[0203] In some embodiments, the suicide gene is integrated into the engineered cell genome.

[0204] In one embodiment, the present disclosure provides an engineered cell having a CD45 chimeric antigen receptor polynucleotide. In one embodiment, the CD45 CAR polypeptide includes SEQ ID NO. 13 and corresponding polynucleotide sequence SEQ ID NO. 14. In another embodiment, the CD45 CAR polypeptide includes SEQ ID NO. 15, and corresponding polynucleotide sequence SEQ ID NO. 16. In another embodiment, the CD45 CAR polypeptide includes SEQ ID NO. 17, and corresponding polynucleotide sequence SEQ ID NO. 18.

[0205] In particular embodiments, the engineered cell includes CD45 CAR linked to IL15/IL-15sushi via the P2A cleavage sequence. A polypeptide providing this embodiment includes SEQ ID No. 43 and corresponding polynucleotide sequence SEQ ID No. 44.

[0206] In particular embodiments, the engineered cell includes CD45 CAR linked to 4-1BBL (CD137L) via the P2A cleavage sequence. A polypeptide providing this embodiment includes SEQ ID No. 41 and corresponding polynucleotide sequence SEQ ID No. 42.

Multiple CAR Units

[0207] In one embodiment, the present disclosure provides an engineered cell having at least two distinct or separate CAR units. The two CAR units may be complete CAR units or incomplete CAR units. As used herein, "distinct CAR polypeptide" and "distinct CAR polypeptide unit" are used interchangeably.

[0208] The present disclosure provides chimeric antigen receptor polypeptides having a signal peptide, antigen recognition domain, a hinge region, a transmembrane domain, a signaling domain, and at least one co-stimulatory domain, defining a CAR unit or a complete CAR unit. As used herein, an incomplete CAR unit includes a polypeptide having a signal peptide, antigen recognition domain, a hinge region, a transmembrane domain, and a signaling domain or at least one co-stimulatory domain. An incomplete CAR unit will not contain a signaling domain and at least one co-stimulatory domain, but one or the other.

[0209] In one embodiment, the present disclosure provides an engineered cell having a first chimeric antigen receptor polypeptide having a first antigen recognition domain and a co-stimulatory domain (first incomplete CAR unit); and a second chimeric antigen receptor polypeptide having a second antigen recognition domain and a signaling domain (second incomplete CAR unit); wherein the first antigen recognition domain is different than the second antigen recognition domain.

[0210] Therefore, an engineered cell having two incomplete CAR units will only be fully activated when both target antigens are bound to the antigen recognition domain. This strategy provides added specificity in that the engineered cells are not fully activated until targets are bound at the antigen recognition domain of each incomplete CAR unit.

[0211] Furthermore, in embodiments wherein an engineered cell includes two incomplete CAR units, one of the antigen recognition domains may be specific for and bind streptavidin, biotin, HIS, MYC, HA, agarose, V5, Maltose, GST, GFP, CD52, CD20, 4-1BB, or CD28.

[0212] As used herein, compound CAR (cCAR) or multiple CAR refers to an engineered cell having at least two complete and distinct chimeric antigen receptor polypeptides. As used herein, a "distinct chimeric antigen receptor polypeptide" has a unique antigen recognition domain, a signal peptide, a hinge region, a transmembrane domain, at least one costimulatory domain, and a signaling domain. Therefore, two unique chimeric antigen receptor polypeptides will have different antigen recognition domains. The signal peptide, hinge region, transmembrane domain, at least one costimulatory domain, and signaling domain may be the same or different between the two distinct chimeric antigen receptor polypeptides. As used herein, a chimeric antigen receptor (CAR) unit refers to a distinct chimeric antigen receptor polypeptide, or a polynucleotide encoding for the same.

[0213] As used herein, a unique antigen recognition domain is one that is specific for or targets a single target, or a single epitope of a target.

[0214] In some embodiments, the compound CAR targets the same antigen. For example, cCAR targets different epitopes or parts of a single antigen. In some embodiments, each of the CAR units present in the compound CAR targets different antigen specific to the same or different disease condition or side effects caused by a disease condition.

[0215] In some embodiments, the compound CAR targets two different antigens.

[0216] Creation of compound CARs bearing different CAR units can be quite challenging: (1) CAR-CAR interactions might have a deleterious effect and an appropriate CAR design is a key to offset this effect; (2) a compound CAR in a single construct could increase the length of the expression cassette, which may cause the reduction of the viral titer and level of protein expression; (3) an appropriate design to include various CAR body elements particularly to select a strategy to express multiple CARs in a single vector is required; (4) A strong promoter is particularly important for a compound CAR that bears additional units of CAR; (5) The hinge region in the CAR needs to be designed so that interaction of the hinge region between each CAR unit is avoided preferably; (6) two or more units of CARs expressing in a cell may cause toxic effects (CAR-CAR interaction). Applicants herein provide novel and surprising CAR compositions and methods to overcome these hurdles.

[0217] In one embodiment, the present disclosure provides an engineered cell having multiple CAR units. This allows a single engineered cell to target multiple antigens. Targeting multiple surface markers or antigens simultaneously with a multiple CAR unit prevents selection of resistant clones and reduces tumor recurrence. Multiple CAR T cell immunotherapies, with each individual component CAR comprising various domains and activation sites has not yet been developed for any malignancies.

[0218] In one aspect of the present disclosure, cCAR includes multiple CAR units. In some embodiments, cCAR includes at least two CAR units. In another embodiment, the cCAR includes at least three CAR units. In another embodiment, the cCAR includes at least four units.

[0219] In one embodiment, the present disclosure provides an engineered cell having at least two distinct chimeric antigen receptor polypeptides, each having a different antigen recognition domain.

[0220] In one embodiment, the engineered cell having at least two distinct chimeric antigen receptor polypeptides is a T-cell. The T-cell may be engineered so that it does not express a cell surface antigen. For example, a T-cell may be engineered so that it does not express a CD45 cell surface antigen.

[0221] In a preferred embodiment, the engineered cell having at least two distinct chimeric antigen receptor polypeptides is a primary NK cell isolated from the peripheral blood or cord blood and NK-92 cells, such that it is administered "off-the-shelf" to any mammal with a disease or cancer.

[0222] In one embodiment, the engineered cell includes (i.) a first chimeric antigen receptor polypeptide comprising a first antigen recognition domain, a first signal peptide, a first hinge region, a first transmembrane domain, a first co-stimulatory domain, and a first signaling domain; and (ii.) a second chimeric antigen receptor polypeptide comprising a second antigen recognition domain, a second signal peptide, a second hinge region, a second transmembrane domain, a second co-stimulatory domain, and a second signaling domain. The first antigen recognition domain is different from the second antigen recognition domain.

[0223] In a preferred embodiment, each engineered CAR unit polynucleotide have different nucleotide sequences in order to avoid homologous recombination.

[0224] In one embodiment, the target of the first antigen recognition domain is selected from the group consisting of interleukin 6 receptor, NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BAFF-R, BCMA, TACI, LeY, CD5, CD13, CD14, CD15 CD19, CD20, CD22, CD33, CD41, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, and CS1; and the target of the second recognition domain is selected from the group consisting of interleukin 6 receptor, NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BAFF-R, BCMA, TACI, LeY, CD5, CD13, CD14, CD15, CD19, CD20, CD22, CD33, CD41, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, and CS1.

[0225] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD19 antigen recognition domain and second chimeric antigen receptor polypeptide having a CD20 recognition domain. In one embodiment, this engineered cell includes a polypeptide of SEQ ID NO. 3 and corresponding polynucleotide of SEQ ID NO. 4.

[0226] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD19 antigen recognition domain and second chimeric antigen receptor polypeptide having a CD22 antigen recognition domain. In one embodiment, this engineered cell includes a polypeptide of SEQ ID NO. 5 and corresponding polynucleotide of SEQ ID NO. 6.

[0227] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD19 antigen recognition domain and second chimeric antigen receptor polypeptide having a CD123 antigen recognition domain. In one embodiment, this engineered cell includes a polypeptide of SEQ ID NO. 7 and corresponding polynucleotide of SEQ ID NO. 8.

[0228] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD33 antigen recognition domain and second chimeric antigen receptor polypeptide having a CD123 antigen recognition domain. In one embodiment, this engineered cell includes a polypeptide of SEQ ID NO. 9 and corresponding polynucleotide of SEQ ID NO. 10. In another embodiment, this engineered cell includes a polypeptide of SEQ ID NO. 11 and corresponding polynucleotide of SEQ ID NO. 12.

[0229] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a BAFF-R antigen recognition domain and second chimeric antigen receptor polypeptide having a CS lantigen recognition domain.

[0230] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD269 antigen recognition domain and second chimeric antigen receptor polypeptide having a CS1 antigen recognition domain. In one embodiment, the engineered cell includes a polypeptide including SEQ ID NO. 19 and corresponding polynucleotide SEQ ID NO. 20. In one embodiment, the engineered cell includes a polypeptide including SEQ ID NO. 21 and corresponding polynucleotide SEQ ID NO. 22.

[0231] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD33 antigen recognition domain and second chimeric antigen receptor polypeptide having a CD123 antigen recognition domain.

[0232] In one embodiment, each CAR unit includes the same or different hinge region. In another embodiment, each

CAR unit includes the same or different transmembrane region. In another embodiment, each CAR unit includes the same or different intracellular domain.

[0233] In one embodiment, each CAR unit includes the CD3 zeta chain signaling domain.

[0234] In one embodiment, each distinct CAR unit includes different co-stimulatory domains to avoid interaction. For example, the first chimeric antigen receptor polypeptide includes a 4-BB co-stimulatory domain; and the second chimeric antigen receptor polypeptide includes a CD28 co-stimulatory domain.

[0235] In another embodiment, the hinge region is designed to exclude amino acids that may cause undesired intra- or intermolecular interactions. For example, the hinge region may be designed to exclude or minimize cysteine residues to prevent formation of disulfide bonds. In another embodiment, the hinge region may be designed to exclude or minimize hydrophobic residues to prevent unwanted hydrophobic interactions.

[0236] Compound CAR can perform killing independently or in combination. Multiple or compound CAR comprises same or different hinge region, same or different transmembrane, same or different co-stimulatory and same or different intracellular domains. Preferably, the hinge region is selected to avoid the interaction site.

[0237] The compound CAR of the present disclosure may target same or different tumor populations in T or NK cells. The first CAR, for example, may target the bulky tumor population and the next or the second CAR, for example, may eradicate cancer or leukemic stem cells, to avoid cancer relapses.

[0238] In accordance with the present disclosure it was surprisingly found that the compound CAR in a T or NK cells targeting different or same tumor populations combat tumor factors causing cancer cells resistant to the CAR killing activity, thereby producing down regulation of the target antigen from the cancer cell surface. It was also surprisingly found that this enables the cancer cell to "hide" from the CAR therapy referred to as "antigen escape" and tumor heterogeneity, by which different tumor cells can exhibit distinct surface antigen expression profiles.

Engineered Cell Having CAR Polypeptide and Enhancer

[0239] In another embodiment, the present disclosure provides an engineered cell having at least one chimeric antigen receptor polypeptide and an enhancer.

[0240] In one embodiment, the present disclosure provides an engineered cell having at least two distinct chimeric antigen receptor polypeptides and an enhancer.

[0241] As used herein, an enhancer includes a biological molecule that promotes or enhances the activity of the engineered cell having the chimeric antigen receptor polypeptide. Enhancers include cytokines. In another embodiment, enhancers include IL-2, IL-7, IL-12, IL-15, IL-18, IL-21, PD-1, PD-L1, CSF1R, CTAL-4, TIM-3, and TGFR beta, receptors for the same, and functional fragments thereof.

[0242] Enhancers may be expressed by the engineered cell described herein and displayed on the surface of the engineered cell or the enhancer may be secreted into the surrounding extracellular space by the engineered cell. Methods of surface display and secretion are well known in the art. For example, the enhancer may be a fusion protein with a peptide that provides surface display or secretion into the extracellular space.

[0243] The effect of the enhancer may be complemented by additional factors such as enhancer receptors and functional fragments thereof. The additional factors may be co-expressed with the enhancer as a fusion protein, or expressed as a separate polypeptide and secreted into the extracellular space.

[0244] Enhancers can be cytokines secreted from engineered CAR cells and are designed to co-express with the CAR polypeptide. A massive release occurs upon CAR engagement of cognate antigen. Inflammatory cells surrounding tumor cells have a significant correlation with cancer cell progression and metastasis. Inflammatory cells could include T cells and innate immune response cells, such as NK cells, macrophages, and dendritic cells and their proliferation and anti-tumor activity are regulated by cytokines. CAR cells such as CAR T or NK cells bind to targeted cancer cells and trigger massive secretion of enhancers from the expansion of CAR T/NK cells. The secreted enhancers efficiently promote survival, differentiation and activation of immune response cells against cancer cells. The co-expression of an enhancer(s) with CAR can supplement the defect that CAR T or NK cells are unable to eliminate non-targeting cancer cells (FIG. **78**).

[0245] CAR cells can be a carrier of cytokines, and cytokines can be delivered to targeted cancer sites by CAR cells to reduce systemic toxicity with high-dose exogenous cytokines (FIG. **78**).

[0246] To improve sustained survival or long-lived persistence of CAR cells, a membrane bound enhancer (s) can be co-expressed with CAR to improve CAR persistency.

[0247] In one embodiment, the enhancer is IL-15. In this instance, the additional factor described above is the IL-15 receptor, and functional fragments thereof. Functional fragments include the IL-15 receptor, IL-15RA, and the sushi domain of IL-15RA (IL-15sushi). Soluble IL-15RA or IL15sushi profoundly potentiates IL-15 functional activity by prevention of IL-15 degradation. Soluble IL-15/IL-15RA or IL-15/IL-15sushi complexes are stable and much more stimulatory than IL-15 alone in vivo.

[0248] In one embodiment, IL-15 is co-expressed as a fusion protein with at least one of IL-15 receptor, IL-15RA, and the sushi domain of IL-15RA (IL-15sushi). In one embodiment, the IL-15 receptor, IL-15RA, or the sushi domain of IL-15RA (IL-15sushi) is at the N-terminus of IL-15. In another embodiment, the IL-15 receptor, IL-15RA, or the sushi domain of IL-15RA (IL-15sushi) is at the C-terminus of IL-15. As used herein, IL-15/IL-15 sushi denotes that IL-15 sushi is at the C-terminus of IL-15 in a fusion protein; and IL-15sushi/il-15 denotes that IL-15 sushi is at the N-terminus of IL-15 in a fusion protein.

[0249] In some embodiments, IL-15 and the IL-15 receptor or functional fragments thereof polypeptide is on a single polypeptide molecule and is separated by a peptide linker, the peptide linker may be 1-25 amino acid residues in length, 25-100 amino acid residues in length, or 50-200 amino acid residues in length. This linker may include a high efficiency cleavage site described herein.

[0250] An example of a suitable sushi domain includes a CAR construct, SEQ ID NO. 1. In accordance with the present disclosure, any chimeric antigen receptor polypep-

tide disclosed herein may be co-expressed with the Human Interleukin 15 with human interleukin 2 signal peptide SEQ ID NO. 2.

[0251] Interleukin (IL)-15 and its specific receptor chain, IL-15Rα (IL-15-RA) play a key functional role in various effector cells, including NK and CD8 T cells. CD8+ T cells can be modified to express autocrine growth factors including, but not limited to, IL-2, 11-7, IL21 or IL-15, to sustain survival following transfer in vivo. Without wishing to be bound by theory, it is believed that IL-15 overcomes the CD4 deficiency to induce primary and recall memory CD8T cells. Overexpression of IL-15-RA or an IL-15 IL-RA fusion on CD8 T cells significantly enhances its survival and proliferation in-vitro and in-vivo. In some embodiments, CD4CAR or any CAR is co-expressed with at least one of IL-15, IL15RA and IL-15/IL-15R or IL15-RA/IL-15, or a part or a combination thereof, to enhance survival or proliferation of CAR T or NK, and to improve expansion of memory CAR CD8+ T cells.

[0252] The present disclosure provides an engineered cell having a CAR polypeptide as described herein and at least one of IL-15, IL-15RA, IL-15sushi, IL-15/IL-15RA, IL15-RA/IL-15, IL-15/IL-15sushi, IL15sushi/IL-15, fragment thereof, a combination thereof, to enhance survival or persistence or proliferation of CAR T or NK for treating cancer in a patient.

[0253] In another embodiment, the present disclosure provides an engineered cell having at least one of recombinant IL-15, IL-15RA, IL-15sushi, IL-15/IL-15RA, IL15-RA/IL-15, IL-15/IL-15sushi, IL15sushi/IL-15, functional fragment thereof, and combination thereof; and at least one distinct CAR polypeptide wherein the antigen recognition domain includes NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BCMA, BAFF-R, BCMA, TACI, LeY, CD5, CD7, CD2, CD3, CD4, CD45, CD13, CD14, CD15, CD19, CD20, CD22, CD33, CD41, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, ROR1, PSMA, MAGE A3, Glycolipid, F77, GD-2, WT1, CEA, HER-2/neu, MAGE-3, MAGE-4, MAGE-5, MAGE-6, CA 19-9, CA 72-4, NY-ESO, FAP, ErbB, c-Met, MART-1, CD30, EGFRvIII, immunoglobin kappa and lambda, CD38 and CS1. The target antigens can also include viral or fungal antigens, such as E6 and E7 from the human papillomavirus (HPV) or EBV (Epstein Barr virus) antigens. In further embodiment, the antigen recognition polypeptides (scFv) and corresponding polynucleotides for CD2, CD3, CD5, CD7, and CD52 are described in more detail publications in PCT Application NO. PCT/US2016/39306, the contents of which are incorporated herein by reference.

[0254] Without wishing to be bound by theory, it is believed that IL-15/IL-15sushi and other types of IL-15 or IL-15RA proteins or protein fragments thereof provide synergistic efficacy of a CAR polypeptide when combined with checkpoint inhibitors or modulators (e.g. anti-PD-1).

[0255] In one embodiment, the disclosure provides a CD4 CAR engineered cell that includes IL-15/IL-15sushi (SEQ ID NO. 1), and corresponding polynucleotide (SEQ ID NO. 2). In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a CD4 CAR engineered cell that includes IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD4 CAR polypeptide provides long-term durable remission in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

[0256] In one embodiment, the present disclosure provides engineered cell having a CD45 chimeric antigen receptor polypeptide and IL-15/IL-15sushi (SEQ ID NO. 44), and corresponding nucleotides (SEQ ID NO. 43).

[0257] In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a CD45 CAR engineered cell that includes IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD45 CAR polypeptide provides long-term durable remission in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

[0258] In one embodiment, the engineered cell includes a CD45 chimeric antigen receptor polypeptide and 4-1BBL (SEQ ID NO. 74), and corresponding nucleotides (SEQ ID NO. 73).

[0259] In one embodiment, the present disclosure provides a method of providing long-term durable remission in patients suffering from cancer by administering a CD45 CAR engineered cell that co-expresses 4-1BBL to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of 4-1BBL with a CD45 CAR provides long-term durable remission in patients by increasing the persistence of CAR engineered cells.

[0260] In one embodiment, the engineered cell includes a CD19 chimeric antigen receptor polypeptide and IL-15/IL-15sushi (SEQ ID NO. 59), and corresponding polynucleotide (SEQ ID NO. 60). In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a CD19 CAR engineered cell that includes IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD19 CAR provides long-term durable remission in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

[0261] In one embodiment, the engineered cell includes a CD20 chimeric antigen receptor polypeptide and IL-15/IL-15sushi (SEQ ID NO. 58), and corresponding polynucleotide (SEQ ID NO. 57). In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a CD20 CAR engineered cell that includes IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD20 CAR provides long-term durable remission in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

[0262] In one embodiment, the engineered cell includes a CD22 chimeric antigen receptor polypeptide and IL-15/IL-15sushi (SEQ ID NO. 62), and corresponding polynucleotide (SEQ ID NO. 61). In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a CD22 CAR engineered cell that includes IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD22 CAR provides long-term durable remission in

patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

[0263] In one embodiment, the engineered cell includes a CD269 chimeric antigen receptor polypeptide and IL-15/IL-15sushi (SEQ ID NO. 44), and corresponding polynucleotide (SEQ ID NO. 45). In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a CD269 CAR engineered cell that includes IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD269 CAR provides long-term durable remission in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells as plasma cells or myeloma cells are usually dim CD269 (BCMA) positive.

[0264] In one embodiment, the engineered cell includes a CAR, CD4 polypeptide of SEQ ID NO. 90, and corresponding polynucleotide of SEQ ID NO. 89.

[0265] In one embodiment, the engineered cell includes a CD4 chimeric antigen receptor polypeptide and IL-15/IL-15sushi (SEQ ID NO. 96), and corresponding polynucleotide (SEQ ID NO. 95). In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a CD4 CAR engineered cell that includes IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD4 CAR provides long-term durable remission in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

[0266] In one embodiment, the engineered cell includes a CD4 chimeric antigen receptor polypeptide and IL-15/IL-15RA (membrane bound) (SEQ ID NO. 98), and corresponding polynucleotide (SEQ ID NO. 97). In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a CD4 CAR engineered cell that includes IL-15/IL-15RA to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15RA (membrane bound) with a CD4 CAR provides long-term durable remission in patients by increasing the persistence of CAR engineered cells.

[0267] In one embodiment, the engineered cell includes a compound CAR, CD33CD123 polypeptide and IL-15/IL-15sushi (SEQ ID NO. 40), and corresponding polynucleotide (SEQ ID NO. 39). In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a CD33CD123 compound CAR engineered cell that includes IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD33CD123 CAR provides long-term durable remission in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

[0268] In one embodiment, the engineered cell includes a compound CAR, CD33CD123 polypeptide and 4-1BBL (SEQ ID NO. 38), and corresponding polynucleotide (SEQ ID NO. 37). In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a CD33CD123 compound CAR engineered cell that co-expresses 4-1BBL to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of 4-1BBL with a CD33CD123 cCAR provides long-term durable remission in patients by increasing the persistency of cCAR engineered cells.

[0269] In one embodiment, the engineered cell includes a BAFF CAR polypeptide with a CD45 leader sequence (SEQ ID NO. 78) and corresponding polynucleotide sequence (SEQ ID NO. 77).

[0270] In one embodiment, the engineered cell includes BAFF CAR polypeptide with a CD8a leader sequence (includes SEQ ID NO. 80) and corresponding polynucleotide sequence (SEQ ID NO. 79).

[0271] In one embodiment, the engineered cell includes a BAFF CAR polypeptide and IL-15/IL-15sushi (SEQ ID NO. 84), and corresponding polynucleotide (SEQ ID NO. 83).

[0272] In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a BAFF CAR engineered cell that includes IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a BAFF CAR provides long-term durable remission in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells as BAFF receptor, CD269 (BCMA) is weakly expressed in plasma cells and myeloma cells.

[0273] In one embodiment, the engineered cell includes a BAFF CAR polypeptide and 4-1BBL (SEQ ID NO. 82), and corresponding polynucleotide (SEQ ID NO. 81). In one embodiment, the present disclosure provides a method of providing long-term durable remission in cancer patients by administering a BAFF CAR engineered cell co-expresses 4-1BBL to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of 4-1BBL with a BAFF CAR can provide long-term durable remission in patients by increasing the persistence of CAR engineered cells.

[0274] In one embodiment, the engineered cell includes a compound CAR, BAFF CD19b polypeptide of SEQ ID NO. 86 and corresponding polynucleotide of SEQ ID NO. 85.

[0275] In one embodiment, the present disclosure provides a method of treating an autoimmune disorder in a patients by administering a BAFF CD19b compound CAR engineered cell to a patient in need thereof. Without wishing to be bound by theory, it is believed that the BAFF CD19b compound CAR engineered cells provide a better therapeutic outcome for depletion of B-cells and plasma cells associated with autoimmune disorders.

[0276] In one embodiment, the engineered cell includes a APRIL CD19b compound CAR polypeptide of SEQ ID NO. 88 and corresponding polynucleotide of SEQ ID NO. 77.

[0277] In one embodiment, the present disclosure provides a method of depleting B-cells and plasma cells in a patient in need thereof by administering a APRIL CD19b compound CAR engineered cell to a patient in need thereof. Without wishing to be bound by theory, it is believed that the APRIL CD19b compound CAR engineered cell can provide a better therapeutic outcome for depletion of B-cells and plasma cells associated with autoimmune disorders.

[0278] In one embodiment, the engineered cell includes a compound CAR, CD269 CS1 polypeptide of SEQ ID NO. 48 and corresponding polynucleotide of SEQ ID NO. 47. In one embodiment, the present disclosure provides a method

of treating myeloma in a patient by administering a CD269CS1 compound CAR engineered cell to a patient in need thereof.

[0279] Without wishing to be bound by theory, it is believed that CD269 CS1 compound CAR engineered cells provide a better therapeutic outcome for patients with myeloma, and prevent antigen escape or disease relapse.

[0280] In one embodiment, the engineered cell includes a compound CAR, CD269 CD19b polypeptide of SEQ ID NO. 50 and corresponding polynucleotide of SEQ ID NO. 49.

[0281] In one embodiment, the present disclosure provides a method of depleting B-cells and plasma cells in patients by administering a CD269 CD19b compound CAR engineered cell to a patient in need thereof. Without wishing to be bound by theory, it is believed that CD269 CD19b compound CAR engineered cells provide a better therapeutic outcomes for patients suffering from an autoimmune disorder by depletion of B-cells and plasma cells associated with autoimmune disorders.

[0282] In one embodiment, the engineered cell includes another compound CAR, CD269 CD19 polypeptide of SEQ ID NO. 52 and corresponding polynucleotide of SEQ ID NO. 51. In one embodiment, the present disclosure provides a method of depleting B-cells and plasma cells in patients by administering a CD269 CD19 compound CAR engineered cell to a patient in need thereof. Without wishing to be bound by theory, it is believed that CD269 CD19 compound CAR engineered cells provide a better therapeutic outcomes in patients suffering from an autoimmune disorder by depletion of B-cells and plasma cells associated with autoimmune disorders.

[0283] In one embodiment, the present disclosure provides an engineered cell having a CD19 chimeric antigen receptor polynucleotide. In one embodiment, the CD19 CAR polypeptide includes SEQ ID NO. 54 and corresponding polynucleotide sequence SEQ ID NO. 53. In another embodiment, the CD19 CAR polypeptide includes SEQ ID NO. 56, and corresponding polynucleotide sequence SEQ ID NO. 55

[0284] In one embodiment, the engineered cell includes a CD30 CAR polypeptide, and IL-15/IL-15sushi polypeptide (SEQ ID NO. 100), and corresponding polynucleotide (SEQ ID NO. 99). The targeted disease is malignant Hodgkin lymphoma with cancer cells expressing CD30.

[0285] In one embodiment, the present disclosure provides a method of re-activating T-cell and innate immune cells in the tumor microenvironment patients by administering a CD30CAR engineered cell that secretes IL-15/IL-15 complexes to a patient in need thereof. Without wishing to be bound by theory, it is believed that IL-15/IL-15 complexes (e.g. IL-15/IL-15sushi complexes) secreted from engineered cells can re-activate T-cell and innate immune cells in the tumor microenvironment and then restore or augment their anti-tumor immune responses for Hodgkin lymphoma or anaplastic large cell lymphoma.

[0286] In one embodiment, the present disclosure provides a method of restoring or augmenting T-cell or innate immune cell activation or expansion including coexpression of IL-15/IL-15sushi with a CAR polypeptide disclosed herein.

[0287] In another embodiment, the disclosure provides a chimeric antigen receptor polypeptide having an antigen recognition domain specific for a CD30 antigen.

[0288] In one embodiment, the CD30CAR includes at least one-costimulatory domain. In another embodiment, the CD30CAR includes at least two co-stimulatory domains.

[0289] In some embodiments, the disclosure includes a method of co-expressing IL-15/IL-15sushi with CD30CAR. In further embodiments, massive secretion of stable, functional IL-15/IL-15sushi complexes occurs upon binding of CAR to target cells.

[0290] In another embodiment, the present disclosure provides a method of treating a patient suffering from Hodgkin's lymphoma or a cancer associated with a malignant cell expressing CD30 antigen by administering a CD30 CAR engineered cell to a patient in need thereof. An example of a malignant cells expressing CD30 includes anaplastic large cell lymphoma.

[0291] Malignant Hodgkin lymphoma bears CD30+ Reed-Sternberg or Reed-Sternberg like cells, which are surrounded by an overwhelming numbers of T cells and innate immune cells. These T or innate immune cells are immunologically tolerant as they fail to eliminate cancer cells. Therefore, one of critical aspects for treating Hodgkin lymphoma is to re-activate T-cell and innate immune cells in the tumor microenvironment and then restore or augment their anti-tumor immune responses.

[0292] In some embodiments, the present disclosure comprises a method of co-expression of IL-15/IL-15sushi with a CD30CAR. Engineered CD30CAR T or NK cells bind to targeted cancer cells, trigger massive secretion of IL-15/IL-15sushi from the expansion of CD30CAR T or NK cells, whereby secreting IL-15/IL-15sushi efficiently restore or augment T or innate immune cells against cancer cells to overcome immunosuppressive tumor microenvironment.

[0293] In one embodiment, the present disclosure provides a method of providing long-term durable remission in a cancer patient by administering a CD30 CAR engineered cell that co-express IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD30CAR provides long-term durable remission in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells against target cancer cells to overcome immunosuppressive tumor microenvironment.

[0294] In some embodiments, the present disclosure provides an engineered cell that co-expresses IL-15/IL-15sushi and a CD30CAR polypeptide. Without wishing to be bound by theory, it is believed that the combination of CD30CAR engineered cell with co-expression of IL-15/IL-15sushi provides synergistic efficacy when combined with checkpoint inhibitors or modulators (e.g. anti-PD-1).

[0295] In some embodiments, the present disclosure provides a method of treating Hodgkin's lymphoma in a patient by administering a CD30 CAR engineered cell that co-expresses IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, co-expression of CD30CAR polypeptide and IL-15/IL-15sushi provides better outcomes for treatment of Hodgkin's lymphoma or anaplastic large cells than CD30CAR alone as CD30 is not expressed in all cancer cells.

Steps for Elimination of Tumor by CAR Co-Expressing Secretory IL-15/IL-15Sushi (FIG. **78**)

[0296] In some embodiments, the present disclosure provides a method of provide long-term durable remission in a

cancer patient by administering a APRIL CAR engineered cell that co-expresses IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a APRIL CAR polypeptide provides long-term durable remissions in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate cells to cancer cells. APRIL receptor, CD269 (BCMA) is weakly expressed in plasma cells and myeloma cells.

[0297] In particular embodiments, the present disclosure provides a method for elimination of tumor cells including contacting said tumor cell with a CAR engineered cell that co-expresses IL-2 to destroy said tumor cell.

[0298] IL-15 was originally considered as an interleukin-2 (IL-2)-like factor for T and NK cells. Unlike IL-2, IL-15 is a survival factor for memory T cells.

[0299] In particular embodiments, elimination of tumor can be achieved by combination of at least one or more of the following steps:

(1) binding of an CAR engineered T cell or NK cell disclosed herein to a portion of tumor cells by targeting CAR or NK antigen(s);

(2) Triggering massive secretion of IL-15/IL-15sushi or IL-2 with a prolonged half-life from expansion of CAR T/NK cells, which co-express this molecule;

(3) Recruiting and stimulating a variety of innate and adaptive immune cells against tumor;

(4) Reducing tumor suppression that is present in tumor by administration of a checkpoint blockage such as PD-L1 and CTLA-4 inhibitor.

[0300] Without wishing to be bound by theory, it is believed that the combination of steps described above provide potent anti-tumor effects via a concerted innate and adaptive immune response.

[0301] The engineered cells and methods described herein are suitable for the treatment of any cancer wherein specific monoclonal or polyclonal antibodies exist or are capable of being generated in accordance with the current state of the art. In particular, the following cancers have been contemplated and are considered within the scope of the present disclosure, neuroblastoma, lung cancer, melanoma, ovarian cancer, renal cell carcinoma, colon cancer, brain cancer, Hodgkin's lymphoma, B cell lymphoma/leukemia and T cell lymphomalleukemia. All of which have cell surface antigens that may be targeted by the chimeric antigen receptor polypeptides and methods disclosed herein.

[0302] Many tumors escape the specific CAR T/NK killing due to the loss of targeted antigen(s) or CAR T or NK exhaustion. The present disclosure provides a method to overcome this escape. Without wishing to be bound by theory, the present disclosure provides a method of preventing tumor escape by administering a CAR engineered cell having an enhancer or cytokine as disclosed herein, in particular IL-15 or IL-2 to a tumor site by CAR engineered cell. It is believed that this directly stimulates innate and adaptive immune responses. Furthermore, it is believed that IL-15 and/or IL-2 secretion from CAR engineered cells promote the expansion of infused CAR T cells or CAR NK cells and infiltration of immune cells to the tumor site, which is believed to result in tumor destruction.

[0303] In embodiments, half-life extension and prolonged therapeutic activity can be established in the presence of the Fc domain, such IL-15Fc or IL-2Fc. For IL-15 cytokine, IL-15/IL-15sushi or IL-15/IL-15sushi Fc is preferred. Fc domain is referred to as the IgG Fc-domain fused to various effector molecules (so-called Fc-fusion proteins).

[0304] Single antigen-directed CAR immunotherapy, such as, but not limited to, CD19, CD20, CD22, CD2, CD3, CD4, CD5, CD7, CD33, CD30, CD123, CD45, BCMA, CS1, BAFF, TACI, and APRIL CAR, bears a risk of remission in patients due to the complete loss of target antigen or changes of target antigen expression. On this basis, the present disclosure provides a method of providing long-term durable remission in patients by administering an engineered cell having a CAR polypeptide disclosed herein and co-expression of IL-15/IL-15sushi to increase the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

[0305] The large volume of some solid tumors or lymphoma can be difficult for CAR T cells to eradicate the whole tumor. In addition, the immunosuppressive microenvironment needs to be overcome as CAR T cells may end up simply being inactivated or suppressed when contacting tumor.

[0306] In some embodiments, the present disclosure provides a method of co-expressing secretory IL-15/IL-15sushi and a chimeric antigen receptor polypeptide in an engineered cell.

[0307] In some embodiments, the present disclosure provides a method of increasing CAR engineered cell in vivo half life by co expressing secretory IL-15/IL-5sushi in said engineered cell. Without wishing to be bound by theory, it is believed that the secreted complexes of IL-15/1L-15sushi are functionally stable and efficiently promote survival of the CAR containing engineered cell.

[0308] In some embodiments, the present disclosure provides a method of delivering IL-15/IL-15sushi to targeted cancer sites using CAR as a carrier to promote the proliferation of innate immune response cells against cancer cells, prevent the tumor microenvironment suppression, and reduce systemic toxicity with high-dose exogenous cytokines.

[0309] In some embodiments, the present disclosure provides a method of delivering IL-15/IL-15sushi to targeted cancer sites using CAR as a carrier to recruit other effector immune cells to the site and help them to kill cancer cells.

[0310] In some embodiments, the present disclosure provides a method of delivering IL-15/IL-15sushi to targeted cancer sites using CAR as a carrier to activate bystander immunity to eradicate cancer cells that lose the antigen for CAR T/NK cells.

Methods of Generating Engineered Cells

[0311] Any of the polynucleotides disclosed herein may be introduced into an engineered cell by any method known in the art.

[0312] In one embodiment, CAR polynucleotides are delivered to the engineered cell by any viral vector as disclosed herein.

[0313] In one embodiment, to achieve enhanced safety profile or therapeutic index, the any of the engineered cells disclosed herein be constructed as a transient RNA-modified "biodegradable" version or derivatives, or a combination thereof. The RNA-modified CARs of the present disclosure may be electroporated into T cells or NK cells. The expression of the compound CAR may be gradually diminished over few days.

[0314] In some embodiments of the present disclosure, any of the engineered cells disclosed herein may be constructed in a transponson system (also called a "Sleeping Beauty"), which integrates the CAR DNA into the host genome without a viral vector.

Methods of Generating an Engineered Cell Having Multiple CAR Units

[0315] In another embodiment, the present disclosure provides a method making an engineered cell having at least two CAR units.

[0316] In some embodiments, multiple units of CAR are expressed in a T or NK cell using bicistronic or multicistronic expression vectors. There are several strategies which can be employed to construct bicistronic or multicistronic vectors including, but not limited to, (1) multiple promoters fused to the CARs' open reading frames; (2) insertion of splicing signals between units of CAR; fusion of CARs whose expressions are driven by a single promoter; (3) insertion of proteolytic cleavage sites between units of CAR (self-cleavage peptide); and (iv) insertion of internal ribosomal entry sites (IRESs).

[0317] In a preferred embodiment, multiple CAR units are expressed in a single open reading frame (ORF), thereby creating a single polypeptide having multiple CAR units. In this embodiment, an amino acid sequence or linker containing a high efficiency cleavage site is disposed between each CAR unit.

[0318] As used herein, high cleavage efficiency is defined as more than 50%, more than 70%, more than 80%, or more than 90% of the translated protein is cleaved. Cleavage efficiency may be measured by Western Blot analysis, as described by Kim 2011.

[0319] Furthermore, in a preferred embodiment, there are equal amounts of cleavage product, as shown on a Western Blot analysis.

[0320] Examples of high efficiency cleavage sites include porcine teschovirus-1 2A (P2A), FMDV 2A (abbreviated herein as F2A); equine rhinitis A virus (ERAV) 2A (E2A); and Thoseaasigna virus 2A (T2A), cytoplasmic polyhedrosis virus 2A (BmCPV2A) and flacherie Virus 2A (BmIFV2A), or a combination thereof. In a preferred embodiment, the high efficiency cleavage site is P2A. High efficiency cleavage sites are described in Kim J H, Lee S-R, Li L-H, Park H-J, Park J-H, Lee K Y, et al. (2011) High Cleavage Efficiency of a 2A Peptide Derived from Porcine Teschovirus-1 in Human Cell Lines, Zebrafish and Mice. PLoS ONE 6(4): e18556, the contents of which are incorporated herein by reference.

[0321] In embodiments wherein multiple CAR units are expressed in a single open reading frame (ORF), expression is under the control of a strong promoter. Examples of strong promoters include the SFFV promoter, and derivatives thereof.

Engineered Cell Having CAR Polypeptide and Enhancer

[0322] In another embodiment, the present disclosure provides a method making an engineered cell that expresses at least one CAR unit and an enhancer.

[0323] In some embodiments, at least one CAR unit and enhancer is expressed in a T or NK cell using bicistronic or multicistronic expression vectors. There are several strategies which can be employed to construct bicistronic or multicistronic vectors including, but not limited to, (1) multiple promoters fused to the CARs' open reading frames; (2) insertion of splicing signals between units of CAR; fusion of CARs whose expressions are driven by a single promoter; (3) insertion of proteolytic cleavage sites between units of CAR (self-cleavage peptide); and (4) insertion of internal ribosomal entry sites (IRESs).

[0324] In a preferred embodiment, at least one CAR unit and an enhancer are expressed in a single open reading frame (ORF), thereby creating a single polypeptide having at least one CAR unit and an enhancer. In this embodiment, an amino acid sequence or linker containing a high efficiency cleavage site is disposed between each CAR unit and between a CAR unit and enhancer. In this embodiment, the ORF is under the control of a strong promoter. Examples of strong promoters include the SFFV promoter, and derivatives thereof.

[0325] Furthermore, in a preferred embodiment, there are equal amounts of cleavage product, as shown on a Western Blot analysis.

Methods of Treatment Using the Compositions Disclosed Herein

[0326] In another embodiment, the present disclosure provides a method of targeting CD45 for conditioning prior to allogenic transplantation in cancer treatment. CD45 is also known as leukocyte common antigen (LCA) and is a tyrosine phosphatase expressed on virtually all cells of hematopoietic origin except erythrocytes and platelets. Most hematologic malignancies express CD45. For instance, 85% to 90% acute lymphoid and myeloid leukernias express CD45. (1CD45 is not found in non-hematopoietic origin. In addition, CD45 is expressed at a high density of an average copy number of approximately 200,000 molecules per cells on malignant cells and leukocytes. CD45 presents an ideal target for a variety of hematologic malignancies. H-lowever, CAR T and NK cells also express CD45. Without inactivation of endogenous CD45, CAR T or NK cells armed with CARs targeting CD45 may result in self-killing.

[0327] The association of CD45 with TCR complexes is essential in regulation of T-cell activation in response to antigen. The inability of CD45-deficient T cells to present antigen is due to reduced signaling through the T cell receptors (TCRs). TCRs are cell surface receptors that play an essential role in the activation of T cells in response to the presentation of antigen. The TCR is generally made from two chains, alpha and beta, which are associated with the transducing subunits, the CD3, to form the T-cell receptor complex present on the cell surface.

[0328] It was surprisingly found that multiple CARs (Compound CARs, cCAR) of the present disclosure combat a key mechanism by which cancer cells resist CAR activity, i.e., the downregulation or heterogeneous expression of the target antigen from the cancer cell surface. This mechanism allows the cancer cell to "hide" from the CAR therapy, a phenomenon referred to as 'antigen escape'. The present disclosure pre-empts cancer antigen escape by recognizing a combination of two or more antigens to rapidly eliminate the tumor.

[0329] The disclosure provides a method of simultaneous targeting of multi-antigens using a cCAR resulting in improved tumor control by minimizing the possibility of tumor selection on the basis of target antigen loss or downregulation.

[0330] The disclosed disclosure includes compound (multiple or compound) cCAR in a T or NK cell targeting different or same surface antigens present in tumor cells. The compound chimeric antigen receptors of the present disclosure comprise at least multiple chimeric receptor constructs linked by a linker and target of the same or different antigens. For example, each of the CAR construct present in the compound CAR (cCAR) construct includes an antigen recognition domain, an extracellular domain, a transmembrane domain and/or a cytoplasmic domain. The extracellular domain and transmembrane domain can be derived from any desired source for such domains. The multiple CAR constructs are linked by a linker. The expression of the compound CAR construct is driven by a promoter. The linker may be a peptide or a part of a protein, which is self-cleaved after a protein or peptide is generated (also called as a self-cleaving peptide).

[0331] In one embodiments, the compound CARs of the present disclosure target Myelodysplastic Syndrome and acute myeloid leukemia (AML) populations. Myelodysplastic Syndrome (MDS) remains an incurable hematopoietic stem cell malignancy that occurs most frequently among the elderly, with about 14,000 new cases each year in the USA. About 30-40% of MDS cases progress to AML. The incidence of MDS continues to increase as our population ages. Although MDS and AML have been studied intensely, no satisfactory treatments have been developed.

[0332] The compositions and methods of this disclosure can be used to generate a population of T lymphocyte or NK cells that deliver both primary and co-stimulatory signals for use in immunotherapy in the treatment of cancer, in particular, the treatment of lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, brain cancer, sarcoma, leukemia and lymphoma.

[0333] Immunotherapeutics generally rely on the use of immune effector cells and molecules to target and destroy cancer cells. The effector may be a lymphocyte carrying a surface molecule that interacts, either directly or indirectly, with a tumor cell target. Various effector cells include cytotoxic T cells, NK cells, and NK-92 cells. The compositions and methods described in the present disclosure may be utilized in conjunction with other types of therapy for cancer, such as chemotherapy, surgery, radiation, gene therapy, and so forth. The compositions and methods described in the present disclosure may be utilized in other disease conditions that rely on immune responses such as inflammation, immune diseases, and infectious diseases.

[0334] In some embodiments, the compound CAR of the present disclosure may act as a bridge to bone marrow transplant, by achieving complete remission for patients who have minimal residual disease and are no longer responding to chemotherapy. In other embodiments, the compound CAR eliminates leukemic cells followed by bone marrow stem cell rescue to support leukopenia.

[0335] In some embodiments, the compound CAR of the present disclosure can combat a key mechanism by which cancer cells resist CAR activity by the down-regulation of the target antigen. In another embodiment, the invented compound CAR can also combat the heterogeneity of cancer cells, which creates significant challenges in a regular CAR T/NK cell therapy. In a further embodiment, the disclosed compound CAR is designed that the first CAR targets the bulky tumor population and another eradicates cancer or leukemic stem cells to avoid cancer relapses.

[0336] In one embodiment, the present disclosure provides a method of destroying cells having a CD33 antigen or a CD123 antigen, or both by contacting said cells with an engineered cell having at least one of chimeric antigen receptor polypeptide having a CD33 antigen recognition domain and chimeric antigen receptor polypeptide having a CD23 antigen recognition domain. The engineered cell may be a T or NK cell.

[0337] Cells having at least one of the CD33 antigen and the CD123 antigen include acute myeloid leukemia, precursor acute lymphoblastic leukemia, chronic myeloproliferative neoplasms, chronic myeloid leukemia, myelodysplasia syndromes, blastic plasmocytoid dendritic neoplasms (BP-DCN), Hodgkin's lymphoma, mastocytosis, and hairy cell leukemia cells.

[0338] In another embodiment, the present disclosure provides a method of providing myeloblative conditioning regimens for hematopoietic stem cell transplantation. In this embodiment, a T or NK engineered cell having a CD33 unit and a CD123 unit is administered to a patient in need thereof.

[0339] In further embodiments, the present disclosure provides a method of eradicating or killing leukemic stem cells (LSCs) or bulk leukemic cells expressing CD123 or CD33, or both. In this embodiment, a T or NK engineered cell having a CD33 unit and a CD123 unit is administered to a patient in need thereof.

[0340] In further embodiments, the compound CAR in a T or NK cell may be used to eradicate or kill CD34+CD38− leukemic stem cells or bulk leukemic cells expressing CD123 or CD33 or both.

[0341] In some embodiments, a compound CAR targets cells expressing CD19 or CD20 antigens or both. In another embodiment, a compound CAR targets cells expressing CD19 or CD22 antigens or both. The targeted cells may be cancer cells, such as, without limiting, B-cell lymphomas or leukemias. In further embodiments, the target antigens can include at least one of this group, but not limited to, ROR1, PSMA, MAGE A3, Glycolipid, glypican 3, F77, GD-2, WT1, CEA, HER-2/neu, MAGE-3, MAGE-4, MAGE-5, MAGE-6, alpha-fetoprotein, CA 19-9, CA 72-4, NY-ESO, FAP, ErbB, c-Met, MART-1, CD30, EGFRvIII, immunoglobin kappa and lambda, CD38, CD52, CD3, CD4, CD8, CD5, CD7, CD2, and CD138. The target antigens can also include viral or fungal antigens, such as E6 and E7 from the human papillomavirus (HPV) or EBV (Epstein Barr virus) antigens.

[0342] In some embodiments, the compound CAR engineered cells target cells having cell surface CD19 antigen or cell surface CD123 antigen or both. The targeted cells are cancer cells, such as, without limiting, B-cell lymphomas or leukemias.

[0343] Clinical trials of CD19 CAR T cell therapy have shown that 80-94% of patients with B-ALL achieve complete remission, but a substantial proportion of patients eventually relapse. The prevalence of CD123 expression in B-ALL is high, and can be used as a CAR target for B-ALL.

[0344] In some embodiments, the compound CAR targets cells expressing CD19 or CD123 antigen or both. Without wishing to be bound by theory, it is believed that CD19 and/or CD123 compound CAR engineered cells offset tumor escape due to the loss of CD19 or CD123 antigen or prevent B-ALL or other type B-cell lymphoma/leukemia relapse.

[0345] In further embodiments, the CD19 and/or CD20 compound CAR engineered cells target cells having cell surface CD19 antigens and/or CD20 cell surface antigens. In another embodiment, the targeted cells are malignant B cell lymphoma/leukemia such as, without limiting, B-ALL, high grade B cell lymphoma, low grade B-cell lymphoma, diffuse large B cell lymphoma, Burkett lymphoma, mantle cell lymphoma, CLL, marginal zone B cell lymphoma and follicular lymphoma.

[0346] Without wishing to be bound by theory, it is believed that the CD19 and/or CD20 CAR engineered cells provide an effective safeguard against antigen escape and prevent disease relapse in adoptive T/NK-cell therapy for B-cell malignancies.

[0347] CAR target cells having at least one of the antigens CD19, CD20, CD22, and CD123, include precursor acute lymphoblastic leukemia, B-cell lymphoma/leukemia, chronic lymphocytic leukemia/lymphoma, mantle lymphoma, follicular lymphoma, marginal zone B cell lymphoma, diffuse large B cell lymphoma, Burkett lymphoma, blastic plasmocytoid dendritic neoplasms (BPDCN), Hodgkin's lymphoma, and hairy cell leukemia cells.

[0348] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD19 antigen recognition domain and second chimeric antigen receptor polypeptide having a CD22 antigen recognition domain. In one embodiment, this engineered cell includes a polypeptide of SEQ ID NO. 64 and corresponding polynucleotide of SEQ ID NO. 63.

[0349] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD19 antigen recognition domain and second chimeric antigen receptor polypeptide having a CD20 antigen recognition domain. In one embodiment, this engineered cell includes a polypeptide of SEQ ID NO. 66 and corresponding polynucleotide of SEQ ID NO. 65.

[0350] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD19 antigen recognition domain and second chimeric antigen receptor polypeptide having a CD123 antigen recognition domain. In one embodiment, this engineered cell includes a polypeptide of SEQ ID NO. 68 and corresponding polynucleotide of SEQ ID NO. 67.

[0351] Multiple myeloma is an incurable disease exhibiting uncontrollable proliferation of plasma cells in the bone marrow. CS1 and BCMA are widely expressed on myeloma cells, but is not expressed in hematopoietic stem/progenitor cells. Therefore, BCMA and CS1 are ideal targets for CAR T/NK cell therapy.

[0352] In further embodiments, the present disclosure provides compound CAR engineered cell having a CS1 (SLAM7) antigen recognition domain and/or an antigen recognition domain that targets B-cell maturation antigens (BCMA). In another embodiment, the targeted cells are malignant plasma cells, such as, but not limited to, multiple myeloma.

[0353] Without wishing to be bound by theory, it is believed that a compound CAR engineered cell having at least one of CS1 and BCMA antigen recognition domain enhances functionality against multiple myeloma and offset antigen escape.

[0354] In some embodiments, a CAR targets cells expressing multiple antigens including, but not limited to, CS1, BCMA, CD267, BAFF-R, CD38, CD138, CD52, CD19, TACI, CD20, interleukin 6 receptor, and NY-ESO-1 antigens. In another embodiment, the targeted cells are plasma cells, B-cells, malignant plasma cells such as, without limiting, multiple myeloma.

[0355] In some embodiments, the compound CAR targets cells expressing multiple antigens including, but not limited to, CS1, BCMA, CD267, BAFF-R, CD38, CD138, CD52, CD19, TACI, CD20, interleukin 6 receptor, and NY-ESO-1 antigens. In another embodiment, the targeted cells are malignant plasma cells such as, without limiting, multiple myeloma.

[0356] In some embodiments, the compound CAR targets cells expressing multiple antigens including but not limited to, alpha fetoprotein (AFP) and Glypican-3 (GPC3). In another embodiment, the targeting cells are hepatocellular carcinoma, fibrolamellar carcinoma, hepatoblastoma, undifferentiated embryonal sarcoma and mesenchymal hamartoma of liver, lung-squamous cell carcinoma, testicular nonseminomatous germ cell tumors, liposarcoma, ovarian and extragonadal yolk sac tumors, ovarian choriocarcinoma, teratomas, ovarian clear cell carcinoma, and placental site trophoblastic tumor.

[0357] Without wishing to be bound by theory, the present disclosure provides compound CAR engineered T cells or NK cells that target different or the same antigens offset tumor escape and provides simultaneous targeting of tumor cells.

[0358] The T or NK host cells comprising compound CAR disclosed herein is embodied in the present disclosure. The nucleotide and polypeptide constructs, sequences, host cells, and vectors of the compound CAR are considered to be part of the present disclosure and is embodied herein.

[0359] In some embodiments, the compound CAR engineered cell is administrated in combination with any chemotherapy agents currently being developed or available in the market. In some embodiments, the compound CAR engineered cell is administrated as a first line treatment for diseases including, but not limited to, hematologic malignancies, cancers, non-hematologic malignances, inflammatory diseases, infectious diseases such as HIV and HTLV and others. In one embodiment, T cells expressing the compound CAR engineered cells are co-administrated with NK cells expressing the same or different compound CAR as an adaptive immunotherapy. Compound CAR NK cells provide rapid, innate activity targeting cells while compound T cells provide relative long-lasting adaptive immune activity.

[0360] In one embodiment, the compound CAR engineered cells are administrated as a bridge to bone marrow stem transplantation for mammals, e.g. patients who are resistant to chemotherapies and are not qualified for bone marrow stem cell transplantation.

[0361] In some embodiments, the compound CAR co-expresses a transgene and releases a transgenic product, such as IL-12 in the targeted tumor lesion and further modulates the tumor microenvironment.

[0362] In one embodiment, compound CAR engineered cells are administrated to a mammal for bone marrow myeloid ablation as a part of the treatment to a disease.

[0363] In a specific embodiment, the cells expressing a compound CAR can be T cells or NK cells, administrated to a mammal, e.g. human. The presented disclosure includes a method of treating a mammal having a disorder or disease by administration of a compound CAR. The targeted cells may

be cancer cells such as, or cells affected by any other disease condition, such as infectious diseases, inflammation, and autoimmune disorders.

[0364] The present disclosure is intended to include the use of fragments, mutants, or variants (e.g., modified forms) of the compound CAR or antigens that retain the ability to induce stimulation and proliferation of TINK cells. A "form of the protein" is intended to mean a protein that shares a significant homology with at least one CAR or antigen and is capable of effecting stimulation and proliferation of T/NK cells. The terms "biologically active" or "biologically active form of the protein," as used herein, are meant to include forms of the proteins or variants that are capable of effecting anti-tumor activity of the cells.

[0365] The compositions and methods of this disclosure can be used to generate a population of TINK cells that deliver both primary and co-stimulatory signals for use in immunotherapy in the treatment of cancer, in particular the treatment of lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma. The compositions and methods described in the present disclosure may be utilized in conjunction with other types of therapy for cancer, such as chemotherapy, surgery, radiation, gene therapy, and so forth.

[0366] 1) In some embodiments, the disclosure provides a method of depleting B cells, immature B cells, memory B cells, plasmablasts, long lived plasma cells, or plasma cells in patients with an autoimmune disease by administering to patients CAR or compound CAR T cells or NK cells. CAR targeted cells are B or plasma cells expressing one or two or all of the antigens, BCMA, TACI and BAFF-R. The autoinmmune diseases include systemic scleroderma, multiple sclerosis, psoriasis, dermatitis, inflammatory bowel diseases (such as Crohn's disease and ulcerative colitis), systemic lupus erythematosus, vasculitis, rheumatoid arthritis, Sjorgen's syndrome, polymyositis, pulmonary alveolar proteinosis, granulomatosis and vasculitis, Addison's disease, antigen-antibody complex mediated diseases, and anti-glomerular basement membrane disease.

[0367] Multiple extracellular cell markers are now being studied for value as tumor-associated antigens and thus potential targets for CAR T/NK cell therapy. However, expression of these antigens on healthy tissue leading to on-target, off-tumor adverse events remains a major safety concern in addition to off-target toxicities. Furthermore, a major limitation of CAR T/NK cell therapy is in the possibility of selecting for antigen escape variants when targeting molecules non-essential to tumorigenesis. Thus, malignant cells that persist with little or no expression of the target antigens may evade CAR T/NK cells, despite their high-affinity action.

[0368] In accordance with the present disclosure, natural killer (NK) cells represent alternative cytotoxic effectors for CAR driven killing. Unlike T-cells, NK cells do not need pre-activation and constitutively exhibit cytolytic functions. Further expression of cCARs in NK cells allow NK cells to effectively kill cancers, particularly cancer cells that are resistant to NK cell treatment.

[0369] Further, NK cells are known to mediate anti-cancer effects without the risk of inducing graft-versus-host disease (GvHD).

[0370] Studies have shown an aberrant overexpression of CD123 on CD34+CD38− AML cells, while the normal bone marrow counterpart CD34+CD38− does not express CD123 (Jordan, Upchurch et al. 2000). This population of CD123+, CD34+CD38− has been considered as LSCs as these cells are able to initiate and maintain the leukemic process in immunodeficient mice.

[0371] The number of CD34+/CD38−/CD123+ LSCs can be used to predict the clinical outcome for AML patients. The CD34+/CD38−/CD123+ cells, greater than 15% in AML patients, are associated with a lack of complete remission and unfavorable cytogenetic profiles. In addition, the presence of more than 1% of CD34+/CD38−/CD123+ cells could also have a negative impact on disease-free survival and overall survival.

[0372] At the present, therapies for MDS and AML have focused on the leukemic blast cells because they are very abundant and clearly represent the most immediate problem for patients. Importantly, leukemic stem cells (LSCs) are quite different from most of the other leukemia cells ("blast" cells), and they constitute a rare subpopulation. While killing blast cells can provide short-term relief, LSCs, if not destroyed, will always re-grow, causing the patient to relapse. It is imperative that LSCs be destroyed in order to achieve durable cures for MDS disease.

[0373] Unfortunately, standard drug regimens are not effective against MDS or AML LSCs. Therefore, it is critical to develop of new therapies that can specifically target both the leukemic stem cell population and the bulky leukemic population. The compound CAR disclosed in the present disclosure target both of these populations and is embodied herein.

[0374] In accordance to the present disclosure, it was surprisingly found that NK cells provide an off-the-shelf product that may be used as an allogeneic product for treatment. Thus, according to the present disclosure, cCAR cell therapy needs to be performed on a patient-specific basis as required by the current state of art. The applicants of the present disclosure have discovered a novel immunotherapy, where the patient's lymphocytes or tumor infiltrated lymphocytes need not be isolated for an effective CAR cell based therapy.

[0375] Allogeneic or autologous NK cells are expected to induce a rapid immune response but disappear relatively rapidly from the circulation due to their limited lifespan. Thus, applicants surprisingly discovered that there is reduced concern of persisting side effects using cCAR cell based therapy.

[0376] According to one aspect of the present disclosure, NK cells can be expanded and transfected with cCAR in accordance to the present disclosure. NK cells can be derived from cord blood, peripheral blood, iPS cells and embryonic stem cells. According to one aspect of the present disclosure, NK-92 cells may be expanded and transfected with cCAR. NK-92 is a continuously growing cell line that has features and characteristics of natural killer (NK) cells. NK-92 cell line is IL-2 dependent and has been proven to be safe and feasible. cCAR expressing NK-92 cells can be expanded in the serum free-medium with or without co-culturing with feeder cells. A pure population of NK-92 carrying the cCAR of interest may be obtained by sorting.

[0377] Identification of appropriate surface target antigens is a prerequisite for developing CAR T/NK cells in adaptive immune therapy.

[0378] In one aspect of the present disclosure, CD123 antigen is one of the targets for cCAR therapy. CD123, the alpha chain of the interleukin 3 receptor, is overexpressed on a variety of hematologic malignancies, including acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia (B-ALL), hairy cell leukemia, and blastic plasmocytoid dendritic neoplasms. CD123 is absent or minimally expressed on normal hematopoietic stem cells. More importantly, CD123 is expressed on a subset of leukemic cells related to leukemic stem cells (LSCs), the ablation of which is essential in preventing disease refractoriness and relapse.

[0379] In one aspect of the present disclosure, CD33 antigen is one of the targets for cCAR therapy. CD33 is a transmembrane receptor expressed on 90% of malignant cells in acute myeloid leukemia. Thus, according to the present disclosure, CD123 and CD33 target antigens are particularly attractive from a safety standpoint.

[0380] In accordance with the present disclosure, the compound CD33CD123 CARs may be highly effective for therapeutic treatment of chronic myeloid leukemia (CML) population. In chronic myeloid leukemia (CML), there is a rare subset of cells that are CD34+CD38-. This population is considered as comprised of LSCs. Increased number of LSCs is associated with the progression of the disease. A small-molecule Bcr-Abl tyrosine kinase inhibitor (TKI) is shown to significantly improve the overall survival in CP-CML patients. However, LSCs are thought to be resistant to TKI therapy. A novel therapy targeting CML resistant LSCs is urgently needed for treatment of CML and the novel therapy is embodied in the compound CD33CD123 CAR disclosed in the present disclosure. CD123 expression is high in the CD34+CD38-population. In accordance with the present disclosure, the compound CD33CD123 CARs is highly effective for therapeutic treatment of this population.

[0381] In one embodiment of the present disclosure, leukemic cells expressing both CD123 and CD33 in the cCAR is used as a therapeutic treatment. CD33 is expressed on cells of myeloid lineage, myeloid leukemic blasts, and mature monocytes but not normal pluripotent hematopoietic stem cells. CD33 is widely expressed in leukemic cells in CML, myeloproliferative neoplasms, and MDS.

[0382] Since a significant number of patients with acute myeloid leukemia (AML) are refractory to standard chemotherapy regimens or experience disease relapse following treatment (Burnett 2012), the development of CAR T cell immunotherapy for AML has the potential to address a great clinical need. In the majority of these patients, leukemic cells express both CD123 and CD33, giving broad clinical applicability to the compound CD33CD123 CAR disclosed herein. Thus, the present disclosure discloses a novel multiple cCAR T/NK cell construct comprising multiple CARs targeting multiple leukemia-associated antigens, thereby offsetting antigen escape mechanism, targeting leukemia cells, including leukemic stem cells, by synergistic effects of co-stimulatory domain activation, thereby providing a more potent, safe and effective therapy.

[0383] The present disclosure further discloses a compound CAR construct with enhanced potency of anti-tumor activity against cells co-expressing target antigens, and yet retains sensitivity to tumor cells only expressing one antigen. In addition, each CAR of the compound CAR includes one or two co-stimulatory domains and exhibits potent killing capability in the presence of the specific target.

[0384] In pre-clinical studies on dual specificity, trans-signaling CARs targeting solid tumors including breast cancer and epithelial ovarian cancer, a CD3 intracellular signaling domain, is separated from co-stimulatory domains from second generation of CARs. In other words, one CAR contains the first generation of CAR without any co-stimulatory domain, and another lacks a CD3 zeta intracellular domain. Therefore, the presence of both target antigens is required for T cell activation and potent killing. Thus, they were proposed as a way to decrease off-tumor toxicity caused by healthy tissue expression of one of the two target antigens, increasing target specificity, but at the expense of sensitivity. In one embodiment, the compound CAR is a compound CD123CD19 CAR. It has been shown that more than 90% of B-ALLs express CD123 in a subset of population. Like AML and MDS, it has been considered that a rare LSC population exists in B-ALL. Therefore, targeting both leukemic stem cell and bulky leukemic populations in accordance to the present disclosure, can be applied to B-ALLs. CD123 and CD19 surface antigens expressed in the B-ALLs may be targets as CD19 is widely expressed in different stages of B-cell lymphoid populations, in accordance with the present disclosure.

[0385] Multiple myeloma (MM) is the second most common hematologic malignancy in the US and is derived from clonal plasma cells accumulated in the bone marrow or extramedullary sites. MM is an incurable disease with a median survival of approximately 4.5 years. Anti-Myeloma CARs in Pre-clinical Development have been developed and CAR targets include CD38, CS1, and B cell maturation Antigen (BCMA). However, heterogeneity of surface antigen expression commonly occurs in malignant plasma cells, which makes it a difficult target for CARs. Malignant plasma cells also express low levels of CD19. Previously it has been shown that myeloma stem cells also express some B-cell markers including CD19. Targeting this population could be effective in the treatment of myeloma in conjunction with standard and other myeloma CAR therapies.

[0386] Multiple myeloma (MM) is a haematological malignancy with a clonal expansion of plasma cells. Despite important advances in the treatment, myeloma remains an incurable disease; thus novel therapeutic approaches are urgently needed.

[0387] CS1 (also called as CD319 or SLAMF7) is a protein encoded by the SLAMF7 gene. The surface antigen CS1 is a robust marker for normal plasma cells and myeloma cells (malignant plasma cells).

[0388] Tumour necrosis factor receptor superfamily, member 17 (TNFRSF17), also referred to as B-cell maturation antigen (BCMA) or CD269 is almost exclusively expressed at the terminal stages of plasma cells and malignant plasma cells. Its expression is absent other tissues, indicating the potential as a target for CAR T or NK cells.

[0389] Malignant plasma cells display variable degrees of antigenic heterogeneity for CD269 and CS1. A single CAR unit product targeting either CD269 or CS1 could target the majority of the cells in a bulk tumor resulting in an initial robust anti-tumor response. Subsequently residual rare non-targeted cells are expanded and cause a disease relapse. While multiple myeloma is particularly heterogeneous, this phenomena could certainty apply to other leukemias or tumors. A recent clinical trial at NIH using BCMA CAR T cells showed a promising result with a complete response in some patients with multiple myeloma. However, these

patients relapsed after 17 weeks, which may be due to the antigen escape. The antigen escape is also seen in CD19 CAR and NY-ESO1 CAR T cell treatments. Thus, there is an urgent need for more effective CAR T cell treatment in order to prevent the relapse.

[0390] In one aspect of the present disclosure, BCMA and CS1 are the targets for BCMACS1 CAR therapy.

[0391] In some embodiments, a compound CAR targets cells expressing BCMA or CS1 antigens or both. The targeted cells may be cancer cells, such as, without limiting, lymphomas, or leukemias or plasma cell neoplasms. In further embodiments, plasma cell neoplasms is selected from plasma cell leukemia, multiple myeloma, plasmacytoma, heavy chain diseases, amyloidosis, waldestrom's macroglobulinema, heavy chain diseases, solitary bone plasmacytoma, monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma.

[0392] In some embodiments, the present disclosure provides a compound CAR polypeptide engineered cell that targets cells expressing BCMA or CD19 antigens or both. The targeted cells may be cancer cells, such as, but not limited to, lymphomas, or leukemias or plasma cell neoplasms. In further embodiments, plasma cell neoplasms are selected from plasma cell leukemia, multiple myeloma, plasmacytoma, heavy chain diseases, amyloidosis, waldestrom's macroglobulinema, heavy chain diseases, solitary bone plamacytoma, monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma.

[0393] BAFF (B-cell-activation factor) and APRIL (a proliferation-induced ligand) are two TNF homologs that bind specifically TACI (also called as TNFRSF1 3B or CD267) and BCMA with high affinity. BAFF (also known as BLyS) binds BAFF-R and functionally involves in the enhancement of survival and proliferation of later stage of B cells. BAFF has been shown to involve some autoimmune disorders. APRIL plays an important role in the enhancement of antibody class switching. Both BAFF and APRIL have been implicated as growth and survival factors for malignant plasma cells.

[0394] Ligand-receptor interactions in the malignant plasma cells or normal plasma cells are described in FIGS. **77** and **79**.

[0395] In some embodiments, the present disclosure provides a compound CAR engineered cell that targets cells expressing TACI or CS1 antigens or both. In another embodiment, a compound CAR engineered cell that targets cells expressing TACI or CS1 antigens or both. The targeted cells may be cancer cells, such as, without limiting, lymphomas, or leukemias or plasma cell neoplasms. In further embodiments, plasma cell neoplasms is selected from plasma cell leukemia, multiple myeloma, plasmacytoma, heavy chain diseases, amyloidosis, waldestrom's macroglobulinema, heavy chain diseases, solitary bone plamacytoma, monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma. The target cells may also be one or two or multiple different cell types of B cells, immature B cells, naïve B cells, centroblasts, centrocytes, memory B cells, plasmablasts, long lived plasma cells, plasma cells. These cells involve autoimmune diseases include systemic scleroderma, multiple sclerosis, psoriasis, dermatitis, inflammatory bowel diseases (such as Crohn's disease and ulcerative colitis), systemic lupus erythematosus, vasculitis, rheumatoid arthritis, Sjorgen's syndrome, polymyositis, granulomatosis and vasculitis, Addison's disease, antigen-antibody complex mediated diseases, and anti-glomerular basement membrane disease.

[0396] In some embodiments, the present disclosure provides a compound CAR engineered cell that targets cells expressing BAFF-R or CS1 antigens or both. In another embodiment, a compound CAR engineered cell that targets cells expressing BAFF-R or CS1 antigens or both. The targeted cells may be cancer cells, such as, without limiting, lymphomas, or leukemias or plasma cell neoplasms. In further embodiments, plasma cell neoplasms is selected from plasma cell leukemia, multiple myeloma, plasmacytoma, heavy chain diseases, amyloidosis, waldestrom's macroglobulinema, heavy chain diseases, solitary bone plamacytoma, monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma.

[0397] Autoimmune disorders such as lupus erythematosus (SLE), pemphigus vulgaris and multiple sclerosis (MS) cause significant morbidity and disability. These diseases respond poorly to current therapies and frequent relapse during disease course is noted. B and plasma cells play a critical role in the pathogenesis of autoimmune disorders as they are the sources of autoantibody production. B and plasma cells may contribute to disease progression and relapse through antigen presentation, cytokine secretion, or antibody production. Deletion of B cells or plasma cells or both using CAR T/NK cell approaches can be a beneficial therapy.

[0398] An organ transplant represents a new life for a person and organs that can be transplanted could include the kidneys, heart, lungs, pancreas and intestine. However, many, patients are unable to receive a potentially life-saving organ because of pre-existing or developing donor-specific antibody against the donor's antigens such human leukocyte antigens (HLA). Thus, patients may lose the donated organ. Currently there are few treatment options available for antibody mediated rejection, and an enormous unmet need in the field for efficacious treatment of antibody mediated rejection. Deletion of B cells or plasma cells or both using CAR T/NK cell provide a therapy for antibody-mediated rejection.

[0399] The disclosed disclosure provides compositions and methods relating to CAR engineered cells that target cells expressing CD19 or CD20 that result in the deletion of B cells but spare long-lived plasma cells in patients with antibody mediated organ rejection or autoimmune disorders including, but not limited to, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and pemphigus vulgaris and multiple sclerosis (MS). The deletion of B cells by CAR is beneficial to the reduction of disease activity.

[0400] The present disclosure also provides compositions and methods relating to CAR engineered cells that target cells expressing BCMA or BAFF-R, TACI which results in the deletion of plasma cells in patients with antibody mediated organ rejection or autoimmune disorders including, but not limited to, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and pemphigus vulgaris and multiple sclerosis (MS). The deletion of plasma cells can contribute to the reduction of disease activity.

[0401] In some embodiments, he present disclosure provides compositions and methods relating to CAR engineered cells for CARs depleting mature, memory B cells, and short, long lived plasma cells for treatment of autoimmune disorders and organ antibody-mediated organ rejection. In one

embodiment, the present disclosure provides a method for depleting mature, memory B cells, and short, long lived plasma cells using one or more of the following strategies:

[0402] 1) Depletion of mature, memory B cells and short, long lived plasma cells by a contacting said cells with an CAR engineered cell having a scFv against CD19 or CD20 or CD22;

[0403] 2) Depletion of short- and long-lived plasma cells by contacting said cells with a CAR engineered cell having a scFv against BCMA or TACI or BAFF-R; or

[0404] 3) Depletion of short- and long-lived plasma cells by contacting said cells with a CAR engineered cell having having an antigen recognition domain including BCMA or TACI or BAFF-R binding domain (BAFF or APRIL);

[0405] 4) Deletion of mature, memory B cells, and short, long lived plasma cells contacting said cells with a compound CAR engineered cell targeting more than one different antigen to provide a reduction of disease activity for patients with antibody mediated organ rejection or autoimmune disorders.

[0406] 5) Deletion of mature, memory B cells, and short, long lived plasma cells by contacting a CAR engineered cells that target more than one different antigen selecting from CD19, CD20, CD22, BCMA, TACI, APRIL and BAFF.

[0407] In some embodiments, a compound CAR (cCAR) targets cells expressing one or two or all of BAFF-R, BCMA, TACI and CS1 antigens.

[0408] In some embodiments, a unit of CAR in a cCAR can comprise: 1) a scFv against either BAFF-R, BCMA, TACI and CS1; 2) a hinge region; 3) co-stimulatory domain (s) and intracellular signaling domain.

[0409] In some embodiments, BAFF CAR can be a unit of CAR in a cCAR comprises: 1) BCMA or TACI or BAFF-R binding domain; 2) a hinge region; 3) co-stimulatory domain (s) and intracellular signaling domain.

[0410] In some embodiments, APRIL CAR can be a unit of CAR in a cCAR comprises: 1) BCMA or TACI binding domain; 2) a hinge region; 3) co-stimulatory domain (s) and intracellular signaling domain.

[0411] In a further embodiment, BCMA or TAC1 or BAFF-R binding domain can be a part of or entire APRIL and BAFF molecules.

[0412] In some embodiments, a unit of CAR in a cCAR can comprise: 1) a scFv against BCMA or CS1; 2) a hinge region; 3) co-stimulatory domain (s) and intracellular signaling domain.

[0413] In some embodiments, a unit of CAR in a cCAR can comprise: 1) a scFv against BCMA or CD19; 2) a hinge region; 3) co-stimulatory domain (s) and intracellular signaling domain.

[0414] In some embodiments, a unit of CAR in a cCAR can comprise: 1) a scFv against BCMA or CD20; 2) a hinge region; 3) co-stimulatory domain (s) and intracellular signaling domain.

[0415] In some embodiments, a unit of CAR in a cCAR can comprise: 1) BAFF-R binding domain or a scFv against BCMA; 2) a hinge region; 3) co-stimulatory domain (s) and intracellular signaling domain.

[0416] In some embodiments, a unit of CAR in a cCAR can comprise: 1) BAFF-R binding domain or a scFv against CD19; 2) a hinge region; 3) co-stimulatory domain (s) and intracellular signaling domain.

[0417] In some embodiments, a unit of CAR in a cCAR can comprise: 1) BAFF-R binding domain or a scFv against CD20; 2) a hinge region; 3) co-stimulatory domain (s) and intracellular signaling domain.

[0418] It is unexpected that some myeloma cells are dim (weak) or negative for BCMA. To increase the sensitivity of CAR antigen recognition in myeloma cells, it is critical to target multiple antigens to cure this disease.

[0419] TACI, BCMA and BAFF-R are receptors for BAFF. It is also unexpected that some myeloma cells express TACI or BAFF-R over BCMA.

[0420] In some embodiments, the disclosure provides a method of comprising a BAFF CAR targeting a cell expressing at least one of receptors, BAFF-R, TACI and BCMA to improve therapeutic efficacy and reduce the risk of antigen disease escape.

[0421] The affinity for BAFF binding to BCMA is within the micromolar range, which is much lower than that of BAFF-R or TACI in the nanomolar range.

[0422] In some embodiments, the disclosure provides a method of generating a compound cCAR comprising BAFF and BCMA CARs to complement some of myeloma cells that cannot be eliminated by a BAFF CAR.

[0423] In further embodiments, cCAR can comprise one or two or multiple units of CAR. Each unit CAR could bear same or different hinge region and co-stimulatory domain.

[0424] In further embodiments, cCAR polypeptides two or more CAR polypeptide units. Each unit CAR could bear a different polynucleotide sequence to avoid a homologous recombination.

[0425] In some embodiments, targeting more than one different antigen can be achieved by pooled CAR engineered cells, which are generated by at least two separate CAR T or NK cells. As used herein, pooled CAR engineered cells include a population of engineered cells having more than one distinct CAR polypeptide unit. By way of example, pooled engineered cells include a population of engineered cells with a distinct CAR polypeptide and a population of engineered cells with a different and distinct CAR polypeptide. Furthermore, the pooled CAR engineered cells include engineered cells having cCAR polypeptides.

[0426] The pooled CAR T or NK cells can be completed by the following steps:

[0427] 1) Generate at least two separate constructs of CARs targeting different antigens;

[0428] 2) Transduce individual construct to T or NK cells and expand them ex vivo in a standard medium;

[0429] 3) Pool different expanded T or NK cells at an appropriate ratio; and

[0430] 4) Administer pooled CAR T or NK cells to a subject.

[0431] In the alternative, the different engineered cells may be individual expanded and independently or sequentially administered.

[0432] In further embodiments, the target antigens can include at least one of this group, but not limited to, ROR1, PSMA, MAGE A3, Glycolipid, glypican 3, F77, GD-2, WT1, CEA, HER-2/neu, MAGE-3, MAGE-4, MAGE-5, MAGE-6, alpha-fetoprotein, CA 19-9, CA 72-4, NY-ESO, FAP, ErbB, c-Met, MART-1, CD30, EGFRvIII, immunoglobin kappa and lambda, CD38, CD52, CD3, CD4, CD8, CD5, CD7, CD2, and CD138. The target antigens can also

include viral or fungal antigens, such as E6 and E7 from the human papillomavirus (HPV) or EBV (Epstein Barr virus) antigens.

[0433] In some embodiments, a cCAR engineered cell targets a cell expressing either CD19 or CD20 antigens or both of them. In another embedment, a cCAR engineered cells target a cell expressing either CD19 or CD22 antigens or both of them. The targeted cells are normal B cells associated with autoimmune disorders or cancer cells such as B-cell lymphomas or leukemias.

[0434] Acute graft-versus-host disease (GVHD) remains the most important cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation. In the effector phase of GVHD, T cell receptor (TCR), a heterodimer of alpha and beta chains, is expressed on the surface of T cells, TCR recognizes some antigens on the HLA molecule on host cells, enhances T cell proliferation, and releases cytotoxic agents that cause the damage on host cells. TCR gene inactivation is efficient at preventing potential graft-versus-host reaction. The inactivation of TCRs can result in the prevention of the TCR recognition of alloantigen and thus GVHD. The role of CD45 on NK cells is quite different from that of T cells. NK cells from CD45-defficient mice have normal cytotoxic activity against the prototypic tumor cell line, Yac-1. In addition, CD45-deficient NK cells proliferate normally and respond to IL-15 and IL-21. Therefore, CD45 disruption or deletion would not affect the NK cell killing and proliferation. The present disclosure includes methods of permanent deletion of CD45 in a T or NK cell with subsequent stable introduction of CD45-specific CARs. As a result, the engineered T cells display the desired properties of redirected specificity for CD45 without causing self-killing and response to presentation of antigen. In a further embodiment, the engineered T cells may have efficacy as an off-the-shelf therapy for treating malignancies or other diseases.

[0435] The present disclosure relates to a method where T-cells are engineered to allow proliferation when TCR signaling is reduced or lost through the inactivation or deletion of endogenous CD45.

[0436] The reduction or loss of TCR signaling could result in the prevention of GVHD.

[0437] In a further embodiment, T cells reducing or losing the TCR signaling by the inactivation of CD45 could be used as an "off the shelf" therapeutic product.

[0438] The present disclosure includes methods of modified T or NK cells, which comprises: (a) modifying T or NK cells by inactivating CD45; (b) expanding these modified cells; (c) sorting modified T or NK cells, which do not express CD45; (d) introducing CD45CAR.

In embodiments, the CD45CAR gene encodes a chimeric antigen receptor (CAR), wherein the CAR comprises at least one of an antigen recognition domain, a hinge region, a transmembrane domain, and T cell activation domains, and the antigen recognition domain is redirected against CD45 surface antigen present on a cell. The antigen recognition domain includes a monoclonal antibody or a polyclonal antibody directed against CD45 antigen. The antigen recognition domain includes the binding portion or a variable region of a monoclonal or a polyclonal antibody.

[0439] The present disclosure includes methods of improving CD45CAR T/NK cell expansion, persistency and anti-tumor activity by co-expressing secretory IL-15/IL-15sushi complexes. In a further embodiment, engineered CD45CAR T/NK cells comprise secretory IL-15/IL-15sushi complexes, which can promote expansion of specific CAR T/NK cells, and promote infiltrate of innate immune cells to the tumor sites resulting in tumor destruction.

[0440] The present disclosure provides an alternative strategy in which engineered CD45 CAR T cells receive not only costimulation through the CD28 pathway but also co-express the 4-1BB ligand (CD137L), which provide high therapeutic efficacy.

[0441] In some embodiments, the modified T cells are obtained from allogeneic donors and used as an "off-the-shelf product".

[0442] Targeting CD45 using CAR T or NK cells may cause self-killing as T and NK cells express this surface antigen. To overcome this drawback, the present disclosure provides engineered cells that are deficient in CD45. As used herein, an engineered cell is deficient for a particular gene when expression of the gene is reduced or eliminated. Reduction or elimination of expression can be accomplished by any genetic method known in the art. In one example, the CD45 gene may be inactivated by using engineered CRISPR/Cas9 system, zinc finger nuclease (ZFNs) and TALE nucleases (TALENs) and meganucleases. The loss of CD45 in T or NK cells is further transduced with CARs targeting neoplasms expressing CD45.

[0443] The disclosure includes methods for eliminating or reducing abnormal or malignant cells in bone marrow, blood and organs. In, B and some embodiments, malignant cells expressing CD45 are present in patients with acute leukemia, chronic leukemia T cell lymphomas, myeloid leukemia, Acute lymphoblastic lymphoma or leukemia, primary effusion lymphoma, Reticulohistiocytoma, transient myeloproliferative disorder of Down's syndrome, lymphocyte predominant Hodgkin's lymphoma, myeloid leukemia or sarcoma, dendrocytoma, histiocytic sarcoma, Giant cell tumor of tendon sheath, interdigitating dendritic cell sarcoma, post-transplant lymphoproliferative disorders, etc.

[0444] Hematopoietic stem cell transplantation (HSCT) has been widely used for the treatment of hematologic malignancies or non-hematologic diseases. Non-hematologic diseases include genetic disorders and immunodeficiencies and autoimmune disorders. Genetic disorders include, not limited to, sickle cell disease, thalassemia and lysosomal storage diseases. Before stem cell transplant, patients are required to undergo a conditional therapy to deplete hematopoietic stem/progenitor cells in the bone marrow niches to promote the donor stem cell engraftment and proliferation. High doses of chemotherapies and total body irradiation are used for conditional therapies, which cause severe toxicity and long-term complications particularly in non-hematopoietic organs such as severe intestinal mucositis. In addition, conventional conditional therapies could destruct bone marrow niches resulting hematopoietic cell recovery. The safety concerns represent a major obstacle in effort to expand HSCT to a variety of non-hematologic diseases. CD45 is expressed only on hematopoietic cells and targeting CD45 should minimize the toxicity to non-hematopoietic organs.

[0445] In some embodiments, CD45CAR cells are used to make space in the bone marrow for bone marrow stem cell transplant by removing hematopoietic cells, at the same time removing leukemic/lymphoma cells or immunologic cells capable of graft rejection.

[0446] In some embodiments, CD45CAR engineered cells are used to deplete hematopoietic stem/progenitor cells while the architecture and vasculature of the bone marrow are preserved, in contrast to the disruptive effects of total body irradiation on these tissues. Preservation of the architecture and vasculature of the bone marrow allows faster hematopoietic recovery after transient CD45CAR treatment.

[0447] In a further embodiment, CD45CAR cells may be used for pre-treatment of patients before their undergoing a bone marrow transplant to receive stem cells. In a further embodiment, CD45CAR can be used as myeloblative conditioning regimens for hematopoietic stem cell transplantation.

[0448] In a preferred embedment, CD45CAR engineered cell therapy is transient for allowing faster recovery of bone marrow and peripheral hematopoietic cells. Transient therapy may be accomplished by using short lived engineered cells or providing an engineered cell having the suicide system as described herein.

[0449] In some embodiments, the present disclosure comprises a method of selectively depleting or ablating an endogenous hematopoietic stem/progenitor population, where the endogenous hematopoietic stem/progenitor cells expressing CD45, by contacting said cells with CD45CAR engineered cell that specifically targets CD45 expressing hematopoietic stem/progenitor cells.

[0450] In some embodiment, CD45CAR cells are utilized for treating or preventing a residual disease after stem cell transplant and/or chemotherapy.

[0451] In some embodiments, the CD45CAR is part of an expressing gene or a cassette. In a preferred embodiment, the expressing gene or the cassette includes an accessory gene or a tag or a part thereof, in addition to the CD45CAR. The accessory gene may be an inducible suicide gene or a part thereof, including, but not limited to, caspase 9 gene, thymidine kinase, cytosine deaminase (CD) or cytochrome P450. The "suicide gene" ablation approach improves safety of the gene therapy and kills cells only when activated by a specific compound or a molecule. In some embodiments, the suicide gene is inducible and is activated using a specific chemical inducer of dimerization (CID).

[0452] In some embodiments, the safety switch can include the accessory tags are a c-myc tag, CD20, CD52 (Campath), truncated EGFR gene (EGFRt) or a part or a combination thereof. The accessory tag may be used as a nonimmunogenic selection tool or for tracking markers. In some embodiments, safety switch can include a 24-residue peptide that corresponds to residues 254-277 of the RSV F glycoprotein A2 strain (NSELLSLINDMPITNDQKKLMSNN). In some embodiments, a safety switch can include the amino acid sequence of TNF a bound by monoclonal anti-TNF a drugs.

IL-15 and its Receptor in Enhancing CAR T and NK Cell Functions

[0453] Recent studies have demonstrated that T cell persistence correlates well with CAR T cell therapeutic efficacy. Recent trials demonstrate that potent and persistent antitumor activity can be generated by an infused small number of CAR T cells indicative that quality rather than quantity of infused products is more important in contributing to the anti-tumor activity. Interleukin (IL)-15 is a cytokine that promotes the development and hemostasis of lymphocytes. Increased levels of IL-15 promote T-cell proliferation and enhance T cell effector response. Data from recent studies have shown that IL-15 is crucial for the generation and maintenance of memory CD8 T-cells, one of the key factors associated with anti-tumor activity. IL-15 binds the IL-15 receptor alpha chain (also called IL-15RA or RA) contributing to IL-15-mediated effects such as T-cell survival, proliferation and memory T cell generation.

[0454] IL-15RA binds the βγ complex in the surface of T cells and IL-15 signals by binding with this IL-15RA/βγ complex on the cell surface of T cells and other types of cells.

[0455] Transfection of IL-15 alone does not significantly influence T-cell function, transfection of IL-15/IL-15RA allows T cells to survive and proliferate autonomously.

[0456] The efficacy of administered IL-15 alone may be limited by the availability of free IL-15RA and its short half-life. Administration of soluble IL-15/RA complexes greatly enhanced II-15 half-life and bioavailability in vivo. Therefore, treatment of mice with this complex, but not with IL-15 alone results in robust proliferation and maintenance of memory CD8 T cells and NK cells. A portion of the extracellular region of IL-15RA called sushi domain (IL-15sushi) is required for its binding of IL-15 (WEI et al., J. Immunol., vol. 167(1), p:277-282, 2001). The IL-15/sushi fusion protein is also called IL-15/IL-15sushi containing the linker is more potent than IL-15 and soluble IL-15RA (IL-15sushi) alone. The combination of IL-15/RA (membrane bound form) or IL-15/sushi (soluble form) can maximize IL-15 activity. The membrane bound form, IL-15/RA would not release of free IL-15 by keeping IL-15 bound to IL-15RA on the surface of transduced cells.

[0457] In the present disclosure, it is unexpected to find that the soluble IL-15/IL-15sushi released from transduced cells are able to promote the expansion of transduced cells and their neighbor cells, and further stimulate them against tumor.

[0458] The present disclosure provides an engineered cell having both CAR and IL-15/IL-15sushi or IL-15/RA in a single construct. In some embodiments, the disclosure includes methods to generate higher virus titer and use a stronger promoter to drive both CAR and IL-15/RA or IL-15/IL-15sushi.

[0459] In some embodiments, the present disclosure provides an engineered cell having: (1) a CAR targeting an antigen including, but not limited to, CD4, CD2, CD3, CD7, CD5, CD45, CD20, CD19, CD33, CD123, CS1, and B-cell mature antigen (BCMA); and (2) IL-15; (3) IL-15RA (membrane bound) or sushi (IL-15/IL-15sushi. In further embodiments, CAR comprises chimeric antigen receptor, one or more of co-stimulatory endodomains including, but not limited to, CD28, CD2, 4-1BB, 4-1BBL (CD137L), B7-2/CD86, CTLA-4, B7-H1/PD-L1, ICOS, B7-H2, PD-1, B7-H3, PD-L2, B7-H4, CD40 Ligand/TNFSF5, DPPIV/CD26, DAP12 and OX40, and intracellular domain of CD3 zeta chain. In further embodiments, a strong promoter can be, but is not limited to, SFFV. CARs, IL-15/RA or sushi and inducible suicide gene ("safety switch"), or a combination can be assembled on a vector, such as a lentiviral vector, adenoviral vector and retroviral vector or a plasmid. The introduction of "safety switch" could significantly increase safety profile, and limit on-target or off-tumor toxicities of CARs.

[0460] In one embodiment, the engineered cell includes a CD2 chimeric antigen receptor polypeptide and IL-15/IL-

15sushi (SEQ ID NO. 102), and corresponding polynucleotide (SEQ ID NO. 101). Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD2 CAR provides long-term durable remissions in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

[0461] In one embodiment, the engineered cell includes a CD3 chimeric antigen receptor polypeptide and IL-15/IL-15sushi (SEQ ID NO. 104), and corresponding polynucleotide (SEQ ID NO. 103). Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD3 CAR provides long-term durable remissions in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate cells against target cancer cells.

[0462] In one embodiment, the engineered cell includes a CD7 chimeric antigen receptor polypeptide and IL-15/IL-15sushi (SEQ ID NO. 106), and corresponding polynucleotide (SEQ ID NO. 105). In some embodiments, the present disclosure provides a method of providing long-term durable remission in a cancer patient by administering a CD7 CAR engineered cell that co-expresses IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD7 CAR provides long-term durable remissions in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

[0463] In one embodiment, the engineered cell includes a CD5 chimeric antigen receptor polypeptide and IL-15/IL-15sushi (SEQ ID NO. 107), and corresponding polynucleotide (SEQ ID NO. 108). In some embodiments, the present disclosure provides a method of providing long-term durable remission in a cancer patient by administering a CD5 CAR engineered cell that co-expresses IL-15/IL-15sushi to a patient in need thereof. Without wishing to be bound by theory, it is believed that co-expression of IL-15/IL-15sushi with a CD5 CAR provides long-term durable remissions in patients by increasing the sensitivity of CAR recognition of target cancer cells or recruiting innate immune cells to cancer cells.

CAR Targeting CD4+CD25+ Regulatory T Cells

[0464] Regulatory T cells (Tregs), also called suppressor T cells, are a sub-population of T cells which regulate the immune system and maintain tolerance of self-antigens. Tregs constitute about 1-5% of total CD4+ T cells in blood with diverse clinical applications in transplantation, allergy, asthma, infectious diseases, graft versus host disease (GVHD), and autoimmunity. The biomarkers for Tregs are CD4, Foxp3 and CD25. Tregs are considered to be derived from Naïve CD4 cells.

[0465] In cancers, Tregs play an important role in suppressing tumor immunity and hindering the body's innate ability to control the growth of cancerous cells.

[0466] Tregs expand in patients with cancer and are often enriched in the tumor microenvironment. Tregs cab infiltrate tumors and limit antitumor immunity as well. Depletion of Treg can render mice capable of rejecting tumors that normally grow progressively.

[0467] Depletion of Tregs using antibodies targeting CD25 results in partial reduction of Tregs but anti-tumor activity is limited. A high-level of Treg depletion is required for a profound anti-tumor effect. In addition, there is a significant issue concerning specificity, as Tregs share CD25 expression with activated CD4+ and CD8+ lymphocytes as well as activated NK cells. In general, Tregs are very difficult to effectively discern from effector T cells and NK cells, making them difficult to study.

[0468] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD4 antigen recognition domain and second chimeric antigen receptor polypeptide having a CD25 antigen recognition domain. In one embodiment, this engineered cell includes a polypeptide of SEQ ID NO. 92 with a CD45 leader sequence and corresponding polynucleotide of SEQ ID NO. 91.

[0469] In one embodiment, the engineered cell includes a first chimeric antigen receptor polypeptide having a CD4 antigen recognition domain and second chimeric antigen receptor polypeptide having a CD25 antigen recognition domain. In one embodiment, this engineered cell includes a polypeptide of SEQ ID NO. 94 with a CD8a leader sequence and corresponding polynucleotide of SEQ ID NO. 93.

Specific Embodiments for T-Regulatory Cells

[0470] T lymphocytes (T cells) are a subtype of white blood cells that play a key role in cell-mediated immunity. T cells are divided into CD4 and CD8 cells. Natural killer cells (NK cells) are a type of cytotoxic cells critical to the innate immunity.

[0471] T-regulatory cells (Tregs) are a type of CD4+ cells mediating immune tolerance and suppression and are distinguished from helper T cells. Tregs express CD4, CD25 and Foxp3 (CD4CD25+ regulatory T cells).

[0472] Tregs are enriched in the tumor microenvironment and considered to be important for hindering antitumor immune responses and promoting cancer cell tolerance. Increased numbers of infiltrating Tregs in tumors have been associated poor survival in a variety of cancers including hematologic malignancies and solid tumors.

[0473] Tregs appear to be preferentially trafficked to the tumor microenvironment and play a critical role of immunosuppression (Ethan M. Shevach et al, Annual Review of Immunology, Vol. 18: 423-449, 2000).

[0474] A number of different methods are employed to delete Tregs for cancer treatments by targeting CD25, resulting in a partial reduction of Tregs. However, this could be problematic as: (1) CD25 is also expressed in activated CD4, CD8 and NK cells. CD25 expression can be seen in activated B cells, macrophages, osteoblasts, some thymocytes, some myeloid precursors and some oligodendocytes. (2) a very high-level of Treg depletion is required for efficacy (Xingrui Li et al, Eur. J. Immunol. 2010. 40: 3325-3335).

[0475] The CAR design is to redirect patient or donor immune cells against a specific "target" antigen in a major-histocompatibility complex (MHC)—independent manner. The CAR protein construct usually includes a number of modular components or regions integral to function. The module for "target" recognition is the extracellular single-chain variable fragment (scFv). This component is derived from a monoclonal antibody with specific direction against a carefully selected target antigen. A hinge region of appropriate length tandem to the scFv conveys mobility of the scFv region to allow for optimal binding to the target protein. The transmembrane domain region serves as a conduit between the extracellular binding regions and co-

activation domains' such as CD28 and/or 4-1BB. The final module includes the CD3 zeta intracellular signaling domain.

[0476] The present disclosure provides a method for a novel Treg CAR (also called CD4zetaCD25CAR or C4-25z CAR) construct targeting a cell co-expressing CD4 and CD25. The Treg CAR depletes Tregs specifically while sparing most of cells that do not co-express CD4 and CD25.

[0477] In some embodiments, T cell activation could be achieved upon simultaneous engagement of two scFv molecules against CD4 and CD25 in a Treg CAR. In a further embodiment, both T cell activation and co-stimulation signals are provided using two distinct/separate chimeric antigen receptor polypeptides.

[0478] In some embodiments, a TregCAR includes (1) a first chimeric antigen receptor polypeptide unit comprising a first signal peptide, a first antigen recognition domain, a first hinge region, a first transmembrane domain, and an intracellular signaling domain; and (2) a second chimeric antigen receptor polypeptide unit comprising a second signal peptide, a second antigen recognition domain, a second hinge region, a second transmembrane domain, and a co-stimulatory domain (s). Both the first chimeric antigen receptor polypeptide unit and the second chimeric engineered polypeptide unit are expressed on a single polypeptide molecule, and wherein an amino acid sequence comprising a high efficiency cleavage site is disposed between the first chimeric antigen receptor polypeptide unit and the second chimeric antigen receptor polypeptide unit.

[0479] In some embodiments, the Treg CAR potentiates the lysis activity of a cell co-expressing CD4 and CD25 while minimizing a cell bearing only CD4 or CD25 antigen.

[0480] In some embodiments, the nucleotide sequence of the first chimeric antigen receptor polypeptide unit is different from the second chimeric engineered polypeptide unit in order to avoid a homologous recombination

[0481] In some embodiments, the high efficiency cleavage site in Treg CAR is P2A.

[0482] In some embodiments, the target of the first antigen recognition domain is either CD4 or CD25 and the target of the second antigen recognition domain is either CD4 or CD25; wherein the first antigen recognition domain is different than the second antigen recognition domain.

[0483] In one embodiment, the antigen recognition domain includes the binding portion or variable region of a monoclonal or polyclonal antibody directed against (selective for) the target.

[0484] In a further embodiment, the target antigen is CD4 or CD25.

[0485] In some embodiments, the T or NK cell comprising Treg CARs targeting different or same antigens.

[0486] In some embodiments, the T or NK cell comprises Treg CARs targeting Tregs expressing CD4 and CD25 while sparing most of cells, which do not co-express CD4 and CD25.

[0487] In some embodiments, the T or NK cell comprises Treg CARs depleting Tegs.

[0488] In some embodiments, the present disclosure provides a method of generation of Treg CAR useful for treating or preventing a CD4+CD25+ Foxp3+ T regulatory cell (Treg) related disease in a subject is provided. In a further embodiment, the diseases treated with Treg CAR include, but not limiting to, cancers.

[0489] In some embodiments, the present disclosure provides a method of generation of Treg CAR useful for treating or preventing a CD4+CD25+ Foxp3+ T regulatory cell (Treg) related Cancers including, but not limited, hepatocellular carcinoma, fibrolamellar carcinoma, hepatoblastoma, undifferentiated embryonal sarcoma and mesenchymal hamartoma of liver, lung-squamous cell carcinoma, testicular nonseminomatous germ cell tumors, liposarcoma, ovarian and extragonadal yolk sac tumors, ovarian choriocarcinoma, teratomas, ovarian clear cell carcinoma, placental site trophoblastic tumor, lymphoma and leukemia.

[0490] In some embodiments, the present disclosure provides a method of generation of Treg CAR useful for inhibiting the growth of a tumor in a subject is provided.

[0491] In some embodiments, the Treg CAR is administrated in combination with any chemotherapy agents currently being developed or available in the market. In some embodiments, the Treg CAR is administrated as a first line treatment for diseases including, but not limited to, hematologic malignancies and cancers.

[0492] In some embodiments, the cells expressing a Treg CAR are co-administrated with immunomodulatory drugs, such as, but not limited to, CTLA-4 and PD-1/PD-L1 blockades, or cytokines, such as IL-2, IL-15 or IL-15/IL-15sushi or IL-15/RA, and IL-12 or inhibitors of colony stimulating factor-1 receptor (CSF1R) for better therapeutic outcomes.

[0493] In some embodiments, the cells expressing a Treg CAR are co-administrated with other immunomodulatory drugs or CAR-expressing cells to provide synergistic effects in a subject.

[0494] In a specific embodiment, the cells expressing a Treg CAR can be T cells or NK cells, administrated to a mammal, e.g. human.

[0495] In some embodiments, the Treg CAR is used in immunotherapy in the treatment of cancers. The cancers may be selected from the group consisting of lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, cervical cancer, head or neck cancer, stomach cancer, liver cancer, neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma. The compositions and methods described in the present disclosure may be utilized in conjunction with other types of therapy for cancer, such as chemotherapy, surgery, radiation, gene therapy, and so forth.

[0496] To achieve enhanced safety profile or therapeutic index, the Treg CAR of the present disclosure may be constructed as a transient RNA-modified "biodegradable" version or derivatives, or a combination thereof. The RNA-modified CARs of the present disclosure may be electroporated into T cells or NK cells. The expression of the Treg CAR may be gradually diminished over few days.

[0497] A method for treating cancers using Treg CAR in a subject is embodied in the present disclosure. The method comprises:

(1) Obtaining T/NK cells from a subject or donor(s).

(2) Culturing the lymphocytes/T cells or NK cells.

(3) Introducing an Treg CAR construct into the cultured T cells or NK cells.

(4) Expanding Treg CAR T cells or NK cells

(5) Treating the subject by administering a therapeutically effective amount thereto.

[0498] The ex vivo expansion of tumor-infiltrating lymphocytes (TILs) are successfully used in the current adoptive

cell therapy. In one embodiment, TILs are harvested and successfully expanded ex vivo.

[0499] In some embodiments, TILs can be obtained from a tumor tissue sample and expanding the number of TILs. Treg CAR T or NK cells were used to co-culture with TILs to deplete Treg population to enhance TIL responses to cancers, which is valuable to the disease therapies.

[0500] In some embodiments, CD4CAR bear a set of CAR body including an antigen recognition domain, a hinge region, a co-stimulatory domain (s) and an intracellular domain (CD3 zeta chain). In a further embodiment, CD4CAR depletes Tregs, and then enhances T-cell responses to cancer cells and improves therapeutic outcomes of anti-tumor activity.

[0501] In some embodiments, CD25CAR bear a set of CAR body including an antigen recognition domain, a hinge region, a co-stimulatory domain (s) and an intracellular domain (CD3 zeta chain). In a further embodiment, CD25CAR depletes Tregs, and then enhances T-cell responses to cancer cells and improves therapeutic outcomes of anti-tumor activity.

[0502] The present disclosure may be better understood with reference to the examples, set forth below. The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the disclosure

[0503] Administration of any of the engineered cells described herein may be supplemented with the co-administration of a CAR enhancing agent. Examples of CAR enhancing agents include immunomodulatory drugs that enhance CAR activities, such as, but not limited to agents that target immune-checkpoint pathways, inhibitors of colony stimulating factor-1 receptor (CSFIR) for better therapeutic outcomes. Agents that target immune-checkpoint pathways include small molecules, proteins, or antibodies that bind inhibitory immune receptors CTLA-4, PD-1, and PD-L1, and result in CTLA-4 and PD-1/PD-L1 blockades. As used herein, enhancing agent includes enhancer as described above.

[0504] As used herein, "patient" includes mammals. The mammal referred to herein can be any mammal. As used herein, the term "mammal" refers to any mammal, including, but not limited to, mammals of the order Rodentia, such as mice and hamsters, and mammals of the order Logomorpha, such as rabbits. The mammals may be from the order Carnivora, including Felines (cats) and Canines (dogs). The mammals may be from the order Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perssodactyla, including Equines (horses). The mammals may be of the order Primates, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). Preferably, the mammal is a human. A patient includes subject.

[0505] In certain embodiments, the patient is a human 0 to 6 months old, 6 to 12 months old, I to 5 years old, 5 to 10 years old, 5 to 12 years old, 10 to 15 years old, 15 to 20 years old, 13 to 19 years old, 20 to 25 years old, 25 to 30 years old, 20 to 65 years old, 30 to 35 years old, 35 to 40 years old, 40 to 45 years old, 45 to 50 years old, 50 to 55 years old, 55 to 60 years old, 60 to 65 years old, 65 to 70 years old, 70 to 75 years old, 75 to 80 years old, 80 to 85 years old, 85 to 90 years old, 90 to 95 years old or 95 to 100 years old.

[0506] The terms "effective amount" and "therapeutically effective amount" of an engineered cell as used herein mean a sufficient amount of the engineered cell to provide the desired therapeutic or physiological or effect or outcome. Such, an effect or outcome includes reduction or amelioration of the symptoms of cellular disease. Undesirable effects, e.g. side effects, are sometimes manifested along with the desired therapeutic effect; hence, a practitioner balances the potential benefits against the potential risks in determining what an appropriate "effective amount" is. The exact amount required will vary from patient to patient, depending on the species, age and general condition of the patient, mode of administration and the like. Thus, it may not be possible to specify an exact "effective amount". However, an appropriate "effective amount" in any individual case may be determined by one of ordinary skill in the art using only routine experimentation. Generally, the engineered cell or engineered cells is/are given in an amount and under conditions sufficient to reduce proliferation of target cells.

[0507] Following administration of the delivery system for treating, inhibiting, or preventing a cancer, the efficacy of the therapeutic engineered cell can be assessed in various ways well known to the skilled practitioner. For instance, one of ordinary skill in the art will understand that a therapeutic engineered cell delivered in conjunction with the chemo-adjuvant is efficacious in treating or inhibiting a cancer in a patient by observing that the therapeutic engineered cell reduces the cancer cell load or prevents a further increase in cancer cell load. Cancer cell loads can be measured by methods that are known in the art, for example, using polymerase chain reaction assays to detect the presence of certain cancer cell nucleic acids or identification of certain cancer cell markers in the blood using, for example, an antibody assay to detect the presence of the markers in a sample (e.g., but not limited to, blood) from a subject or patient, or by measuring the level of circulating cancer cell antibody levels in the patient.

[0508] Throughout this specification, quantities are defined by ranges, and by lower and upper boundaries of ranges. Each lower boundary can be combined with each upper boundary to define a range. The lower and upper boundaries should each be taken as a separate element.

[0509] Reference throughout this specification to "one embodiment," "an embodiment," "one example," or "an example" means that a particular feature, structure or characteristic described in connection with the embodiment or example is included in at least one embodiment of the present embodiments. Thus, appearances of the phrases "in one embodiment," "in an embodiment," "one example," or "an example" in various places throughout this specification are not necessarily all referring to the same embodiment or example. Furthermore, the particular features, structures or characteristics may be combined in any suitable combinations and/or sub-combinations in one or more embodiments or examples. In addition, it is appreciated that the figures provided herewith are for explanation purposes to persons ordinarily skilled in the art and that the drawings are not necessarily drawn to scale.

[0510] As used herein, the terms "comprises," "comprising," "includes," "including," "has," "having," or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a process, article, or apparatus that comprises a list of elements is not necessarily limited to only

those elements but may include other elements not expressly listed or inherent to such process, article, or apparatus.

[0511] Further, unless expressly stated to the contrary, "or" refers to an inclusive "or" and not to an exclusive "or". For example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

[0512] Additionally, any examples or illustrations given herein are not to be regarded in any way as restrictions on, limits to, or express definitions of any term or terms with which they are utilized. Instead, these examples or illustrations are to be regarded as being described with respect to one particular embodiment and as being illustrative only. Those of ordinary skill in the art will appreciate that any term or terms with which these examples or illustrations are utilized will encompass other embodiments which may or may not be given therewith or elsewhere in the specification and all such embodiments are intended to be included within the scope of that term or terms. Language designating such nonlimiting examples and illustrations includes, but is not limited to: "for example," "for instance," "e.g.," and "in one embodiment."

[0513] In this specification, groups of various parameters containing multiple members are described. Within a group of parameters, each member may be combined with any one or more of the other members to make additional sub-groups. For example, if the members of a group are a, b, c, d, and e, additional sub-groups specifically contemplated include any one, two, three, or four of the members, e.g., a and c; a, d, and e; b, c, d, and e; etc.

[0514] As used herein, a XXXX antigen recognition domain is a polypeptide that is selective for XXXX. "XXXX" denotes the target as discussed herein and above. For example, a CD38 antigen recognition domain is a polypeptide that is specific for CD38.

[0515] As used herein, CDXCAR refers to a chimeric antigen receptor having a CDX antigen recognition domain.

[0516] As used herein, a CAR engineered cell is an engineered cell as described herein that includes a chimeric antigen receptor polypeptide. By way of example, a CD45 engineered cell is an engineered cell having a CD45 chimeric antigen receptor polypeptide as disclosed herein.

[0517] As used herein, a compound CAR (cCAR) engineered cell is an engineered cell as described herein that includes at least two distinct chimeric antigen receptor polypeptides. By way of example, a CD19CD22 compound CAR engineered cell is an engineered cell as described herein that includes a first chimeric antigen receptor polypeptide having a CD19 antigen recognition domain, and a second chimeric antigen receptor polypeptide having a CD22 antigen recognition domain.

[0518] The present disclosure may be better understood with reference to the examples, set forth below. The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the disclosure.

EXAMPLES

[0519] Engineered cCAR Targets Cells Expressing CD33 or CD123 or Both Generation of compound CAR (cCAR)

[0520] The construction of the CD33CD123 cCAR follows the schematic in FIGS. **1** and **2**A. It includes SFFV (spleen focus-forming virus) promoter that drives the expression of the functional compound CAR (cCAR) bearing two different units of CARs. The antigen receptor head, a scFv (single-chain variable fragment) nucleotide sequence of the anti-CD33 and anti-CD123. A P2A peptide derived from picornavirus is utilized due to the highly efficient mechanism of its self-cleaving dynamics for bicistronic genetic constructs. The self-cleaving P2A peptide serves to link the two independent units of CARs, CD33CAR, and CD123CAR together during expression. The advantages of this approach over an internal ribosomal entry site (IRES), which is commonly used in the literature, include its small size and high cleavage efficiency between two unit proteins upstream and downstream of the 2A peptide. In addition, the use of self-cleaving P2A peptide can avoid a problem of differences in expression levels between gene before and after IRES when IRES is applied.

[0521] The modular unit, CD33CAR includes the CD33 scFv domain, a CD8a hinge region, a CD8a transmembrane domain, 4-BB co-stimulatory domain and an intracellular domain of CD3 zeta chain. The second modular CAR, CD123CAR bears the same hinge, transmembrane and intracellular signaling domains as CD33CAR but different scFv, and co-stimulatory domains. The CD33 CAR recognizes its corresponding antigen and the CD123 CAR binds to its corresponding antigen. The hinge region was designed such that sequences where disulfide interactions are avoided. Different co-stimulatory domains, 4-BB and CD28 were used. The CD33CD123 compound CAR was subcloned into a lentiviral plasmid.

Generation of a High-Efficiency Compound CAR (cCAR)

[0522] Compound CAR lentivirus was generated by transfection of HEK-293 FT cells with Lipofectamine 2000 according to manufacturer's directions, except with 2× the vector DNA due to a large size of insert, in order to increase titer as shown in FIG. **2**. After about 12-16 hours incubation, media containing Lipofectamine was removed and replaced with DMEM containing 10% FBS, 20 mM HEPES, 1 mM sodium pyruvate and 1 mM sodium butyrate. After about 24 hours, the supernatant was harvested and refrigerated, and replaced with fresh media. After about another 24 hours, this was collected and combined with the previous supernatant, and filtered through a 0.45 μM filter disc. Supernatant was split into aliquots, flash frozen with liquid nitrogen and stored at −80° C. HEK-293 FT cells were harvested, stored frozen, and lysed for subsequent electrophoresis and Western blotting (FIG. **2**B).

[0523] PB (peripheral blood) or CB (human umbilical cord blood) buffy coat cells were activated 2 days with anti-CD3 antibody and IL-2. cCAR lentiviral supernatant was spinoculated onto retronectin-coated multiwell plates. Activated T cells were transduced in multiple wells with lentiviral supernatant at a low concentration of about 0.3× 10^6 cells/mL to increase transduction efficiency (FIG. **3**).

[0524] Following the first overnight transduction, cells were added directly to a second virus-coated plate for a second transduction without washing, unless the cells did not look healthy. Following the second overnight transduction, cells were washed, combined and incubated in tissue culture treated plates. CAR T cells were allowed to expand for up to about 5 days prior to co-culture killing assays. After about 3 days of incubation, cells were incubated with goat

anti-mouse F(Ab')2 or goat IgG (isotype) antibodies conjugated with biotin, washed and followed by incubation with streptavidin-PE and conjugated anti-human CD3. After washing and suspension in 2% formalin, cells were then analyzed by flow cytometry to determine percent transduction efficiency.

Characterization of the CD33CD123 cCAR

[0525] Transfected CD33CD123 cCAR HEK293T cells were subjected to Western blot analysis in order to confirm the compound construct. Immunoblot with an anti-CD3ζ monoclonal antibody showed bands of predicted size for the compoundCAR CD3ζ fusion protein (FIG. **2**B). Importantly, two distinct bands of similar intensity were observed on the blot signaling the successful high cleavage action of the P2A peptide as expected. No CD3ζ expression was seen for the GFP control vector as expected. The surface expression of scFv was also tested on HEK 293 cells (FIG. **2**C) and primary T cells (FIG. **2**C).

[0526] The compound CD33CD23CAR lentivirus was tested for transduction efficiency in the HEK293 cell line and analyzed by flow cytometry (Beckman Coulter) (FIG. **2**C). Flow cytometry showed that about 67% of HEK cells expressed CD33CD123 CARs. Human peripheral blood (PB) is often used for autologous T cell therapy. Human PB buffy coat cells were activated with anti-CD3 antibody and IL-2, and transduced with either CD4CAR or control (GFP) lentiviruses. After transduction, flow cytometry analysis showed that about 22% of T-cells expressed the CD33CD123CAR (FIG. **2**C).

CD33CD123 cCAR T-Cells Derived from Umbilical Cord Blood (UCB) and Peripheral Blood (PB) Specifically Kill CD33-Expressing Tumor Cells

[0527] CD33CD123 cCAR T cells or GFP T cells (control) were incubated with target cells at ratios ranging from 0.5:1 from 50:1, preferably, at about 2:1, 5:1, 10:1, 20:1, 50:1, at about 100,000, 200,000, 500,000, about 1 million, or 2 million effector cells to about 50,000, 100,000, 200,000 target cells, respectively) in about 1-2 mL T cell culture media, without IL-2 for about 24h. Target cells were leukemic cell lines and leukemia cells from a patient with leukemia. After about 24 hours of co-culture, cells were stained with mouse anti-human CD33, CD123, CD34 and CD3 antibodies.

[0528] CD33CD123 cCAR T cells expressing the CD33CAR and CD123 CAR were generated and tested for anti-leukemic functions using the HL60 and KG-1a cell lines. The HL60 cell line is a promyelocytic leukemia cell line highly enriched for CD33. About 100% of its cell population is CD33+ with a small subset (<10%) of it being dim CD123+. In culture, this cell line was tested to determine the effectiveness of the CD33CD123 CAR with an emphasis on targeting CD33-expressing leukemic cells. Additionally, due to the strong expression of CD33 in HL60, it is CD33CD123 cCAR action may be profound. Indeed, during 24h co-culture conditions with various ratios of effector to target cells, the CD33CD123 cCAR exhibited significant leukemic cell killing properties (FIG. **4**). CB-derived CD33CD123 CAR T-cells were first tested for their ability to kill HL60 cells. At about 24h incubation and low effector:target (E:T) ratios ranging from about 0.5:1 to 50:1, preferably, 1:1 to about 5:1, more preferably about 2:1 to 4:1, CD33CD123 CAR cells eliminated about 55% of the CD33 expressing HL60 cells when compared to GFP control. At a ratio of about 5:1, the killing action rose to about 82%.

[0529] CD33CD123 CAR derived from peripheral blood mononuclear cells (PBMCs) were co-cultured with the myelogenous leukemia cell line KG1a, which also expresses about 100% CD33 at moderate levels compared to HL60 and 50-80% CD123. KG1a is, therefore, a relatively dual target cell population that is double positive for the antigens targeted by the CD33CD123 CAR. At about 24 hours of incubation and low effector:target (E:T) ratios ranging from about 0.5:1 to 50:1 were used. While at a low E:T ratio of about 2:1, the CD33CD123 CAR exhibited modest anti-leukemic activity about 26%, an increase in E:T ratio to 10:1 resulted in a killing of KG1a of about 62% compared to GFP control (FIG. **5**), signaling that the intensity of the CD33 marker may be an indicator for the efficacy of killing with HL60 presenting strongly and harnessing more CAR action than KG1a. These experiments provide evidence for the function of the whole CD33CD123 CAR against its relevant antigen presenting cell populations.

[0530] Additional compound CAR, CD33CD123-BB cCAR has been generated (data not shown). This compound CAR comprises two independent units of CARs, CD33 and CD123. The first CAR comprises scFv binding to CD33 and the second CAR bears a different scFv recognizing CD123. Both CARs contain the same hinge region, transmembrane, co-stimulatory and intracellular domains. CD33CD123-BB cCAR lentiviruses were produced and their killing ability was tested in KG-1a cells. As shown in FIG. **5**, there was substantial killing at a ratio of about 10:1 but it is less potent than that of CD33CD123 cCAR.

CD33CD123 cCAR Possesses Activity Against Patient Samples Expressing CD33 and/or CD123

[0531] In addition to cell line experiments, studies were also conducted on patient samples in order to test the function of each individual CAR unit. An aggressive acute myeloid leukemia (AML), AML-9 was used for testing efficacy of the CD33CD123 cCAR. Due to the heterogeneity of the patient cell population, which includes multiple cell types in the AML-9 sample, leukemic blasts were gated with CD34 and CD33, as they were positive for these two markers. The depletion of this CD33+CD34+ population of leukemic cells was observed to be 48% over the GFP control at a ratio of CAR T cell:target cell (FIG. **6**).

[0532] Leukemic cells that were CD123 positive and CD33 negative were also tested. For this purpose, human B cell acute lympoblastic leukemia (B-ALL) sample, Sp-BM-B6 was chosen. All leukemic blasts in this sample were CD34+CD33−, and more than about 50% positive for CD123. Depletion of the CD34+ leukemic cell population by CD33CD123 cCAR T cells was about 86% as compared to that of the GFP control (FIG. **7**). Based on the cell line and human sample studies, our data strongly suggest that the compound CD33CD123 CAR is able to target leukemic cells expressing CD33 or CD123 or both.

CD33CD123 cCAR NK Cells Targeting Leukemia Cells Expressing CD33 or CD23 or Both

[0533] Natural killer (NK) cells are CD56+CD3- and can efficiently kill infected and tumor cells like CD8+ T cells. Unlike CD8+ T cells, NK cells launch cytotoxicity against tumors without the requirement of activation to kill cells. NK cells are safer effector cells, as they may avoid the potentially lethal complications of cytokine storms. How-

ever, the use of either CD33 or CD123 or both CAR NK cells in killing leukemias is entirely unexplored.

Production of CD33CD123 cCAR NK Cells

[0534] NK-92 cells were transduced with CD33CD123 CAR lentiviral supernatant in two consecutive overnight transductions with a change of retronectin- and virus-coated plates in between. The transduced cells were expanded for 3 or 4 days and then analyzed by flow cytometry for CAR expression. Cells were harvested and incubated with goat anti-mouse F(Ab')2 at about 1:250 for about 30 minutes. Cells were washed, suspended and stained with streptavidin-PE for about 30 minutes. Cells were washed and suspended in 2% formalin, and analyzed by flow cytometry. NK-92 cells expressing CD33CD123 cCAR were then labeled as above and sorted on FACSAria, with the top 0.2% of F(Ab')2-expressing cells collected and cultured. Subsequent labeling of sorted, expanded cells showed about 89% of NK-92 cell positive for anti-mouse F(Ab')2 (FIG. **8**).

CD33CD123 cCAR NK Cells Efficiently Lyse or Eliminate Leukemic Cells

[0535] First, we tested the function of CD33CD123 cCAR NK-92 cells by assessing their ability to kill a HL-60 cancerous cell line in co-culture. Virtually all HL-60 cells highly express CD33 but CD123 expression in this cell line is only less than 10% (weak). Therefore, it is likely that the killing ability of CD33CD123cCAR is dependent on the ability for cCAR to properly targeting CD33.

[0536] CD33CD123 cCAR NK-92 cells were co-cultured with the HL-60 cells for about 24 hours in NK cell media without IL-2. After the incubation, the CD33CD123 cCAR NK-92 cells were labeled and compared to a control of non-CAR, GFP NK-92 cells. Dramatic killing of HL-60 cells by CD33CD123 cCAR NK-92 cells was observed as compared to the control, GFP NK-92 cells. Moreover, the killing ability of CD33CD123 cCAR NK-92 cells was dose-dependent, with a about 10 to 1 ratio of about 100% compared to the control (FIGS. **9** and **11**).

[0537] A second co-culture experiment using the myeloid leukemia cell line was performed using KG1a, which expresses CD33 in all cells but at a moderate level compared to that of HL-60. The CD123 antigen is expressed in about 50-80% of KG1a cells. The experimental design was similar to the first experiment of the HL-60 killing assay described above, with the same incubation time, effector:cancer cell ratios and GFP NK-92 cell controls. Results show a remarkable killing of KG1a cells by CD33CD123 cCAR NK-92 cells in a dose-dependent manner as compared to the GFP NK-92 cell control. At a ratio of effector:target of 10:1, killing of KG1a cells by CD33CD123 cCAR NK-92 cells was about 85% as compared to that of GFP control (FIGS. **10** and **11**).

[0538] Analysis of KG1a cells showed two different populations, CD33+CD123- and CD33+CD123-. FIG. **11** showed a dose dependent increase in cell killing seen in both populations. Surprisingly, the double positive population showed a higher efficient killing for each increased ratio, suggesting a possible synergistic effect of two modular CARs of CD33 and CD123 (FIG. **12**).

[0539] We also generated engineered CD33CD123 CAR T cells received not only costimulation through the CD28 but also co-express the 4-1BB ligand (4-1BBL or CD137L) in a single construct, which provide the better therapeutic efficacy (FIG. **13**A). T-cells derived from peripheral blood from healthy donors were transduced with the CD33CD123-4-1BBL-2G construct in 6-well plates incubated with 2 ml of virus supernatant. CAR expression was assayed with F(ab)' labeling for surface expression of the CAR protein and subsequently underwent FACS analysis. Transduced cells were compared to control T-cells labeled at the same time. Expression was determined and transduced population encircled on plot 1 day after the end of transduction period. The surface CD33CD123-41BBL-2G CAR expression on T cells was approximately 60% (FIG. **13**B). CD33CD123 CAR improves functional activates when 4-1BBL was included in the construct.

[0540] An enhancer, IL-15/IL-15sushi was also included in CD33CD123 CAR construct as an alternative approach. Both compound CAR, CD33CD123 and IL-15/IL-15sushi were in a single construct (FIG. **14**). IL-15/IL-15sushi is able to promote the expansion of CAR T/NK cells, and infiltrate of innate immune cells to the tumor site, which could result in better tumor destruction

Engineered cCAR Targets Cells Expressing: 1) CD19 or CD20 or Both; 2) CD19 or CD20 or Both; 3) CD19 or CD138 or Both

[0541] Generation of CD19CD20, CD19CD22, and CD19CD138 cCARs

[0542] The three cCARs have been generated (FIG. **15**) using the similar strategy to that of the CD33CD123 cCAR described above.

Generation of the Second Generation Compound CARs (CD19CD20 and CD19CD22)

[0543] The construction of the compound CAR (cCAR) follows the schematic in FIG. **16**A. It comprises of SFFV (spleen focus-forming virus) promoter that drives the expression of the functional cCAR bearing two different units of CARs. The first CAR is the complete L8-CD19-2G CAR (using human CD8a leader sequence, called L-8), linked to the complete second CAR (either CD20-2G or CD22-2G) by a high efficient P2A self-cleaving peptide, derived from picornavirus. The entire sequence is in frame as to result in initially one large fusion protein which is cleaved in half prior to cell surface expression. This method ensures equal expression levels of both CARs. The cCAR DNA molecules were subsequently sub-cloned into the same lentiviral plasmid as above.

Transduced T Cells Efficiently Express cCARs

[0544] Lentiviral vector supernatant was generated from HEK293T cells transfected with either CD19CD20-2G or CD19CD22-2G vector construct or control vector. After collection of lentiviral supernatant was collected, cells were harvested, lysed, and electrophoresed prior to Western blot transfer. Incubation of blot membrane with anti-human CD3zeta antibody resulted in two distinct bands representing each CAR unit after cleavage; the CD19CAR is slightly larger than the CD20 or CD22 CAR units (FIG. **18**B). Next, peripheral blood mononuclear buffy coat cells were activated for three days and transduced with concentrated CD19CD20-2G, CD19CD22-2G or control vector lentiviral supernatant on non-tissue culture plates coated with retronectin. The transduction procedure was repeated 24 hours after the first transduction. CAR expression on the T-cell surface was demonstrated three days after transduction by staining transduced T cells with goat anti-mouse F(Ab')2 antibody and mouse anti-human CD3.

[0545] FIG. **16** shows that 26.9% of cells transduced with concentrated L8-CD19CD20-2G lentiviral supernatant and 35.6% of T cells transduced with concentrated CD19CD22-2G lentiviral supernatant were positive for both F(Ab')2 and CD3 as determined by flow cytometry, when compared to the control transduction.

Transduced T Cells Express CD19CD22-2G at Different Levels Based on Leader Sequences

[0546] We then determined the leader sequence that would result in the highest level of cell surface expression of cCAR, three constructs were made that incorporated leader sequences for human CD8a (L8), CD45 (L45), and colony stimulating factor (CSF) (FIG. **17**). Following transduction of human peripheral blood T cells with lentiviral supernatant generated from each of these vectors, transduction efficiency for the T cells was determined using F(Ab')2 antibody as above. The L8 leader sequence again led to the highest transduction efficiency (43.8%), followed by L45 (9.8%) and CSF (1.3%). (FIG. **17**). This shows that the optimal design of a compound CAR, like a single CAR, depends in part on the leader sequence for surface CAR expression.

Concentration of Lentiviral Supernatant can Lead to Higher Transduction Efficiency for cCARs

[0547] To improve CAR efficiency in transduced T cells, lentiviral supernatant for CD19CD20-2G and CD19CD22-2G was centrifuged at 3,880×g for 24 hours. The resulting viral pellets were suspended in media at one third their original volume, making them 3× concentrated. This concentrate was used to transduce activated T cells in the same volume as non-concentrated virus. FIG. **10***a* shows that CAR efficiency for T cells transduced with 3× concentrated CD19CD22-2G lentiviral supernatant nearly tripled, while CAR efficiency for T cells transduced with 2.5× concentrated CD19CD20-2G lentiviral supernatant increased nearly 10-fold (FIG. **18**). This illustrates the importance of concentrating lentiviral vector for the longer cCAR constructs.

cCAR CAR T Cells Specifically Target CD19-Expressing Tumor Cell Lines

[0548] T cell co-culture killing assays were performed to determine the ability of L8-CD19CD22-2G and L8-CD19CD20-2G CAR T cells to effectively lyse the CD19+ cell lines, SP53 and JeKo-1 (both mantle cell lymphoma lines). Briefly, each target cell line was pre-labeled with CMTMR membrane dye, and then co-cultured with either vector control, L8-CD19CD22-2G or L8-CD19CD20-2G CAR T cells at ratios of 2:1 and 5:1 effector:target cells (200,000 or 500,000 effector cells to 100,000 target cells, in 1 mL T cell media without serum or IL-2). After overnight incubation, cells were labeled with anti-human CD3-PerCp and CD19-APC for 30 minutes, washed, and suspended in 2% formalin for analysis by flow cytometry. The L8-CD19CD22-2G CAR T cells demonstrated robust lysis of tumor cells (FIG. **19**), lysing 53.4% and 93% of the SP53 cells at 2:1 and 5:1 ratios, respectively. At the same ratios, the L8-CD19CD22-2G CAR T cells were able to lyse 69% and 97.3% of the JeKo-1 cells (FIG. **20**).

cCAR CAR T Cells Eliminate CD19+ Cells from AML and B-ALL Patient Samples

[0549] Studies were again conducted using patient samples. Buffy coat fractions of these primary cells were pre-labeled with CMTMR and co-cultured with either vector control, or L8-CD19CD22-2G CAR T cells in the same manner as the tumor cell lines. L8-CD19CD22-2G CAR T cells lysed 54.3% and 77% of the AML patient cells with aberrant expression of CD19 at 2:1 and 5:1 ratios, respectively, in an overnight co-culture, and lysed 84.3% of the B-ALL tumor cells at a 1:1 ratio in a four day co-culture with 2.5% FBS and IL-2 added to the media (FIGS. **21**, **22**A). As these AML patient cells only comprised 65% blasts and 75% of them expressed CD19, it was likely that L8-CD19CD22-2G CAR T cells were able to eliminate the entire CD19 positive blast population.

cCAR CAR T Cells Lyse K562 Cells Expressing CD22.

[0550] An artificial K562 expressing CD22 cell line (K562xp22) via transduction into wild-type K562 cells was generated. Subsequently, we tested the anti-tumor properties of the CD19CD22 cCAR to target the minor $CD22^+$ population of the K562 cells. A co-culture experiment at 1:1 ratio (effective:target) show a modest significant cytotoxic effect on K562 expressing CD22 population compared to the control. Cytotoxicity results remain consistent with other numbers reported for anti-tumor activity against artificial antigen presenting cell lines (FIG. **22**B).

Engineered cCAR Targets Cells Expressing BCMA and CS1

[0551] Generation of cCAR Including BCMA CS1 cCAR and BCMA CD19 cCAR for Treatment of Multiple Myeloma or Autoimmune Disorders

[0552] Pre-clinical studies have been developed for cCARs to target surface antigens including CD38, CS1, CD138, B cell maturation antigen (BCMA) and CD38. CD19 CAR has also demonstrated some efficacy for the treatment of multiple myeloma in a phase I clinical trial. However, given that the heterogeneity of surface antigen expression commonly occurs in malignant plasma cells, it is unlikely that a single target is sufficient to eliminate this disease. BCMA CS1 cCAR, BCMA CD19 cCAR, BCMA CD38 cCAR and BCMA CD138 cCAR were generated and the experimental design was similar to that of CD33CD123 cCAR as described above.

Generation of cCAR Including BCMA CS1 cCAR (BC1cCAR) for Treatment of Multiple Myeloma or Autoimmune Disorders

[0553] Generation and Characterization of BCMA-CS1 cCAR (BC1cCAR) Construct

[0554] We have observed that transduction of compound CAR constructs in general lack high efficiency gene transfer rates compared to single antigen CARs. Whether due to construct size or metabolic stress on effector cells or other factors, optimization of a transduction schema for compound CARs remain necessary. We compared 3 different protocols for transductions and major differences included whether incubation occurs within viral supernatant, transduction procedure frequency, and final cell density numbers per treatment. Method 1 was a 2× transduction for 24 hours each time and uses retronectin coated plates incubated with virus first, aspirated, then incubated with T-cells to a final concentration of 0.5×10^6 cells/ml. Method 2 used the same viral retronectin procedure, however, it exchanged the 2nd transduction period for continued incubation to a total of 48 hours of incubation with a final cell density of 0.3×10^6 cells/ml. Method 2 revised uses an incubation scheme where

viral supernatant was directly incubated with cells for 48 hours on a retronectin coated plate at a cell density of 0.3×10^6 cells/ml (FIG. **23**).

Transduction Protocol Optimizations Correlate to Improved BC1cCAR Surface Expression

[0555] BC1cCAR's modular design consists of an anti-CD269 (BCMA) single-chain variable fragment (scFv) region fused to an anti-CD319 (CS1) scFv by a self-cleaving P2A peptide, CD8-derived hinge (H) and transmembrane (TM) regions, and 4-1BB co-activation domains linked to the CD3ζ signaling domain (FIG. **24**A). A strong spleen focus forming virus promoter (SFFV) and a CD8 leader sequence were used for efficient expression of the BC1cCAR molecule on the T-cell surface. T-cells isolated from human peripheral blood buffy coats were transduced with BC1cCAR lentivirus after 2 days of activation. According to the different transduction schemas above, various transduction efficiencies are reported for each technique (FIG. **24**B). We find that, in general, cells incubated with viral supernatant for 48 hours at reduced cell densities (0.3×10^6 cells/ml) support the highest gene-transfer efficiencies (FIG. **24**B). Thus, as we improve our transduction schemes, we observe a correspondingly higher rate of gene transfer (FIG. **24**C).

[0556] Transfected BC1cCAR HEK293T cells were subjected to Western blot analysis in order to confirm the compound construct. Immunoblot with an anti-CD3ζ monoclonal antibody showed bands of predicted size for the compound CAR CD3ζ fusion protein (FIG. **24**D). Importantly, two distinct bands of similar intensity were observed on the blot signaling the successful high cleavage action of the P2A peptide as expected. No CD3ζ expression was seen for the GFP control vector as expected.

BC1cCAR T-Cells Specifically Lyse BCMA$^+$ and CS1$^+$ Myeloma Cell Lines

[0557] To assess the cytotoxicity ability of BC1cCAR T-cells, we conducted co-culture assays against myeloma cell lines: MM1S (BMCA$^+$ CS1$^+$), RPMI-8226 (BCMA$^+$ CS1$^-$), and U266 (BCMA$^+$ CS1^{dim}). The ability of the BC1cCAR T-cells to lyse the target cells was quantified by flow cytometry analysis, and target cells were stained with Cytotracker dye (CMTMR). In 24 hour co-cultures, the BC1cCAR exhibited virtually complete lysis of MM1S cells, with over 90% depletion of target cells at an E:T ratio of 2:1 and over 95% depletion at an E:T of 5:1 (FIGS. **25**A and **25**C). In RPMI-8226 cells, BC1cCAR lysed over 70% of BCMA$^+$ target cells at an E:T ratio of 2:1, and over 75% at an E:T of 5:1 (FIGS. **25**A and **25**C). In 24 hour co-culture with U266 target cells, BC1cCAR lysed 80% of BCMA$^+$ U266 cells at an E:T ratio of 2:1, reaching saturation (FIGS. **25**B and **25**C). As the myeloma cell lines are all mostly BCMA$^+$, these results suggest that largely BCMA targeting by BC1cCAR T-cells promotes effective cell lysis.

BC1cCAR T-Cells Specifically Target BCMA$^+$ and CS1$^+$ Populations in Primary Patient Myeloma Samples

[0558] We conducted co-cultures using BC1cCAR T cells against primary tumor cells to evaluate their ability to kill diverse primary myeloma cell types. Flow cytometry analysis of the MM10-G primary sample reveal distinct and consistent BCMA$^+$ and CS1$^+$ population subsets. MM7-G sample shows a complete BCMA$^+$ CS1$^+$ phenotype while MM11-G exhibits a noisy BCMA^{dim}CS1^{dim} phenotype likely attributable to its property of being a bone-marrow aspirate. BC1cCAR T-cells show robust dose-dependent ablation of the MM7-G primary patient sample, with over 75% lysis at an E:T ratio of 5:1, increasing to over 85% at 10:1 (FIG. **26**A).

[0559] BC1cCAR also show targeted and specific lysis ability, by significantly ablating both the BCMA$^+$ CS1$^+$ and the BCMA-CS1$^+$ population subsets in MM10-G co-cultures. At an E:T ratio of 2:1, BC1cCAR T-cells ablate over 60% of the BCMA$^+$ CS1$^+$ population, and 70% of the CS1$^+$ only population (FIG. **26**B). At an E:T ratio of 5:1, the ablation of CS1$^+$ only population increases to 80% (FIG. **26**B). Against the MM11-G (FIG. **26**C), BC1cCAR T-cells were also able to demonstrate cytotoxic activity in a dose-dependent manner as well (FIG. **26**C). In summary, BC1cCAR T cells exhibit robust anti-tumor activity against both myeloma cell lines and primary tumor cells presenting different combinations of BCMA and CS1 (FIG. **26**D)

Functional Evaluation of BC1cCAR Antigenic Specific Activity

[0560] To assess and characterize the biological properties of the BC1cCAR in terms of its antigenic targeting, we established a model that would allow us to test the BC1cCAR scFv functionality independently. Using a CML cell line negative for myeloma markers (K562), we established a stable CS1 expressing K562 cell line (CS1xpK562) by transducing CS1 cDNA into K562 cells and subsequently promoting stable expression through puromycin selection (FIG. **27**A). To test the BCMA scFv functionality, we obtained a BCMA expressing K562 cell line (BCMAxpK562) from the NIH (Kochenderfer Lab). After we confirmed the independent expression of each antigen for each antigen expressing cell line (FIG. **27**A), we used them in co-culture experiments to determine BC1cCAR T targeting functionality.

[0561] In short-term cultures (<24 hrs), BC1cCAR T-cells exhibited cytotoxic activity against BCMAxpK562 cells while showing no effect against wild-type K562 cells (FIG. **27**B). Next, short-term cultures against CS1xpK562 cells show similar responses against CS1 expressing target cells. Furthermore, BC1cCAR T-cells appeared to have a stronger cytotoxic effect than a CS1-specific CAR against CS1xpK562 cells (FIG. **27**B). Further validation of the anti-CS1 activity was performed on CS1^{dim} expressing NK-92 cells where cytotoxicity exhibited as a dose-dependent effect (FIG. **27**B).

[0562] To model antigen escape in potential clinical scenarios, we conducted combined co-culture experiments. We mixed BCMAxpK562 and CS1xpK562 in 1:1 ratios and looked for evidence of antigen residual populations that could lead to relapse in real world scenarios. Co-cultures were carried out over 48 hours to ensure antigen depletion. Next, histograms were constructed that represents populations of T-cells and target tumor cells. The numbers in each histogram plot represents the residual gated target tumor population. We found that compared to control T-cells, a BCMA-specific CAR and a CS1-specific CAR were able to deplete or have profound cytotoxic effects against their respective populations. However, a CS1-specific CAR left a significant residual BCMA$^+$ population, whereas a BCMA-specific CAR achieved a high degree of cytotoxicity but still left a small but definite CS1$^+$ population (FIG. **27**C). In contrast, the BC1cCAR T-cells effectively depleted both target populations (FIG. **27**C). We speculate that residual

tumor populations possessing 1 antigen may lead to relapse in patients that have undergone treatment using only a single antigen-specific CAR.

[0563] Since normal bone marrow expresses a small subset of plasma cells that can express CS1, there are concerns that a CS1 directed CAR could be adversely cytotoxic. While the CS1 population in bone marrow is indeed affected by the BC1cCAR in a dose-dependent manner (FIG. **27**D), the CS1 subset itself is small.

BC1cCAR T-Cells Exhibit Persistency and Sequential Killing Ability Even with Tumor Re-Challenge

[0564] We next investigated the ability of BC1cCAR T-cells to kill tumor cells in a sequential manner under unfavorable microenvironments caused by cell lysis, debris, and tumor re-challenge. Using the scheme in FIG. **28**A, we conducted long-term co-cultures using MM1S cells as a model myeloma tumor and periodically re-challenged BC1cCAR T-cells and other CAR constructs with fresh MM1S to simulate tumor expansion or relapse. The initial co-culture condition was done at an E:T ratio of 1:1. With no exogenous cytokines, we find that depletion of target antigens is accomplished by all CAR cells after 48 hours, with significant clustering and T-cell proliferation (FIG. **28**B). In contrast, control T-cells show no response and proliferation yielding a tumor population that has now expanded by twice its initial number. After re-challenging all treatment wells with fresh MM1S cells we find that all CARs still retain a high degree of cytotoxicity even without exogenous cytokines. By 108 hours, the newly inputted MM1S cells have been virtually depleted by both BCMA-CAR and the BC1cCAR with significant cytotoxicity still observed from the CS1-CAR. However, at this stage, flow cytometry show a diminished CS1-CAR population and a relative growth in the tumor antigen population to ~17% (FIG. **28**C), suggesting that the CS1-CAR T-cells may be faltering. At this time point, the control T-cells have been completely overgrown by tumor cells. All CAR tumor-lysis and cytotoxicity stopped after 168 hours, however, BCMA-CAR and BC1cCAR still show detectable minority T-cell populations while control T-cells and CS1-CAR T-cells have all virtually disappeared (data not shown).

BC1cCAR T-Cells Exhibit Significant Control and Reduction of Tumor In Vivo

[0565] In order to evaluate the in vivo anti-tumor activity of BC1cCAR T-cells, we developed a xenogeneic mouse model using NSG mice sublethally irradiated and intravenously injected with luciferase-expressing MM1S cells, a multiple myeloma cell line, to induce measurable tumor formation. Three days following tumor cell injection, mice were intravenously injected with 5×10^6 BC1cCAR T-cells or control GFP cells in a single dose. On days 3, 6, 8 and 11, mice were injected subcutaneously with RediJect D-Luciferin (Perkin Elmer) and subjected to IVIS imaging to measure tumor burden (FIG. **29**A). Average light intensity measured for the BC1cCAR T-cell injected mice was compared to that of GFP control mice in order to determine the control of tumor growth by BC1cCAR treatment (FIG. **29**B). Unpaired T test analysis revealed an extremely significant difference ($P<0.01$) between the two groups by Day 6 with less light intensity and thus less tumor burden in the BC1cCAR T-cell injected group compared to control (FIG. **29**B). Next, we compared mouse survival across the two groups (FIG. **29**C). All of the BC1cCAR T-cell injected mice survived past day 50 and over a quarter remained past day 65. P-value between control and treated mice is 0.0011 based on Long-Rank Mantel-Cox test. The percent survival of control T-cell injected mice started to decrease shortly by Day 50 and were deceased by Day 55. In summary, these in vivo data indicate that BC1cCAR T-cells significantly reduce tumor burden and prolong survival in MM1S-injected NSG mice when compared to control cells.

[0566] BC1cCAR T-cells exhibit improved cytotoxic effect in a mixed antigen xenogeneic mouse model.

[0567] To evaluate the dual targeting nature of the compound CAR that may preclude antigen escape, we designed a xenogeneic mouse model using NSG mice sublethally irradiated and intravenously injected with luciferase-expressing K562 cells expressing either stably transduced BCMA or CS1. BCMA and CS1 expressing K562 cells were further sorted for expression following puromycin selection and established as stable homogenous single antigen populations. BCMA and CS1 expressing K562 cells were then mixed at a 4:1 ratio respectively before injection to model potential antigen escape. Three days following tumor cell injection, mice were intravenously injected with a course 15×10^6 control T-cells, BCMA-specific CAR, or BC1cCAR T-cells. Two control mice died as a result of injection procedure as a result of technical issues during T-cell infusion and cell aggregation. On days 3, 7, 10 and 12, mice were injected subcutaneously with RediJect D-Luciferin (Perkin Elmer) and subjected to IVIS imaging to visualize tumor burden (FIG. **19**D). Average light intensity (signifying tumor burden) measured for the BC1cCAR T-cell injected mice was compared to that of a BCMA-specific CAR and GFP control injected mice in order to determine the control of tumor growth by treatment (FIG. **29**D). By day 10, both the BCMA-specific CAR and BC1cCAR T-cells exhibited over 47% tumor reduction compared to control. However, there was a 6% difference in the tumor burden reduction in favor of the BC1cCAR as early as day 10 on the dorsal side of the mice. By day 12, there was a 17% difference in tumor reduction in favor of BC1cCAR (FIGS. **19**D and E) on the dorsal side. This number approaches the percentage of CS1-K562 cells injected (20%) versus BCMA-K562 (80%). It is likely the result of CS1 expressing K562 cells surviving and proliferating as a model for antigen escape. In summary, these in vivo data indicate that BC1cCAR T-cells appeared to show improved tumor burden control for multiple antigen populations.

BC1cCAR Transduction and Validation of Anti-Tumor Properties in NK Cells

[0568] To further evaluate the robustness of BC1cCAR in different settings, we transduced the BC1cCAR construct into a model NK cell line, NK-92. The construct was successfully able to be transduced via lentiviral incubation for 48 hours into NK-92 cells and resulted in a surface expression profile of 62.1% after gene-transfer (FIGS. **30**A and **30**B). Maintenance of NK-92 cells at densities of $0.3\text{-}0.5\times10^6$ cells/ml resulted in stable populations. To test for BC1cCAR anti-tumor activity in vitro, we conducted co-cultures against myeloma cell lines and a primary patient sample. The BC1cCAR approached 80% lysis against MM1S, U266, and RPMI-8226 cell lines at E:T ratios of 5:1 in culture. It also successfully lysed over 60% of the primary MM7-G tumor (FIGS. **31**A and **31**B). These results are similar in terms of comparability with BC1cCAR T-cells.

Next, we assayed the antigen specificity of the BC1cCAR in its ability to lyse BCMA$^+$ or CS1$^+$ cell independently. Similar assays were carried out for BC1cCAR T-cells (FIG. **27**). In 4 hour cultures with either BCMA expressing K562 (BCMAxpK562) or CS1 expressing K562 (CS1xpK562 cells), we find that the BC1cCAR NK cells are able to have cytotoxic effects against either population (FIG. **31**B).

Generation of cCAR Including BCMA CD19 or BCMA CD19b for Treatment of Plasma Cell Myeloma or Autoimmune Disorders

[0569] Generation and Characterization of BCMA-CD19 cCAR or BCMA-CD19b cCAR Construct

[0570] BC1cCAR's modular design consists of an anti-CD269 (BCMA) single-chain variable fragment (scFv) region fused to an anti-CD319 (CS1) scFv by a self-cleaving P2A peptide, CD8-derived hinge (H) and transmembrane (TM) regions, and 4-1BB co-activation domains linked to the CD3ζ signaling domain (FIG. **35**). A strong spleen focus forming virus promoter (SFFV) and a CD8 leader sequence were used for efficient expression of the BC1cCAR molecule on the T-cell surface and anti-tumor activities in vitro and in vivo using a similar approach described above.

[0571] Each of units of CAR in the BCMA CD19 CAR will be tested for its anti-plasma cell or anti-B cell activity. We found that the BCMA CAR unit was able to potently lyse any BCMA$^+$ population. We first conducted co-cultures against the dual BCMA CS1 positive plasma cell line MM1S and used a CS1 CAR as a secondary measure for robustness. We observed that both BCMA and CS1 specific CARs were able to lyse MM1S targets at high efficiency (FIG. **36**A). Next, we cultured the BCMA CAR and CS1 CAR against a majority BCMA$^+$ primary myeloma sample MM7-G. We find that, with regard to BCMA expression, the BCMA CAR was able to virtually deplete all BCMA$^+$ cells. In contrast, the CS1 CAR left a residual BCMA$^+$ population (FIG. **36**B). These results suggest that a BCMA CAR achieves high potency and specificity in its cytotoxic effect.

[0572] We next tested the CD19 CAR unit for its anti-B cell activity. The single-chain variable fragment (scFv) nucleotide sequences of the anti-CD19 molecule was used for two different constructs, CD19-2G and CD19b-BB CAR. To improve signal transduction, the CD19CAR was designed with 4-1BB co-activation domain fused to the CD3zeta signaling domain, making it a second generation CAR (FIG. **37**A). CD19-targeting second generation CAR T-cells have previously been used in clinical trials. For efficient expression of the CD19CAR molecule on the T cell surface, a strong spleen focus-forming virus promoter (SFFV) was used and the leader sequence of CD8a was incorporated in the construct. For comparison, CD19CAR constructs using the leader sequences of CD45, CSF, human albumin (HA) or IL-2 were also made. The anti-CD19 scFv was separated from the intracellular signaling domains by CD-8 derived hinge (H) and transmembrane (TM) regions (FIG. **37**). The CD19CAR DNA molecules, with different leader sequences or different scFv sequences, were also subsequently sub-cloned into a lentiviral plasmid.

Transduced T Cells Efficiently Express CD19CAR

[0573] Lentiviral vector supernatant was generated from HEK293T cells transfected with CD19-2G vector construct and control vector. After collection of lentiviral supernatant was collected, cells were harvested, lysed, and electrophoresed prior to Western blot transfer. Incubation of blot membrane with anti-human CD3zeta antibody resulted in a ~56 kDa band in the lane containing lysate from cells transfected with CD19-2G, the predicted size for the expressed fusion protein (FIG. **37**B). Next, peripheral blood mononuclear buffy coat cells were activated for three days and transduced with L8-CD19-2G, or control vector lentiviral supernatant on non-tissue culture plates coated with retronectin. The transduction procedure was repeated 24 hours after the first transduction. CAR expression on the T-cell surface was demonstrated three days after transduction by staining transduced T cells with goat anti-mouse Fab antibody and mouse anti-human CD3. FIG. **37**C shows that 19.8% of cells transduced with the L8-CD19-2G virus were positive for both F(Ab')2 and CD3 as determined by flow cytometry, when compared to the control transduction.

Transduced T Cells Express CD19-2G at Different Levels Based on Leader Sequences

[0574] To determine the leader sequence that would result in the highest level of cell surface expression of CD19-2G CAR, several constructs were made that incorporated leader sequences for human CD8a (L8), CD45 (L45), colony stimulating factor (CSF), human albumin (HA), and IL2 (FIG. **38**A). Following transduction of human peripheral blood T cells with lentiviral supernatant generated from each of these vectors, transduction efficiency for the T cells was determined using F(Ab')2 antibody as above. Only the CD19-2G construct incorporating the L8 leader sequence resulted in any appreciable cell surface expression of CAR (32.5%), while the L45 leader sequence resulted in only 3.3% transduction efficiency, and CSF, HA and IL2 were below 1% (FIG. **38**B). This shows that the optimal design of CD19-2G CAR depends in part on the leader sequence used.

Transduced T Cells Express CD19-2G at Different Levels Based on scFv Sequences

[0575] To determine the scFv sequence of CD19 that would result in the highest level of cell surface expression of CD19-2G CAR, two different sequences were used in the design of CD19-2G CAR (FIG. **39**A), CD19 and CD19b. Both used the L8 leader sequence. Following transduction of human peripheral blood T cells with lentiviral supernatant generated from each of these vectors under the same condition, transduction efficiency for the T cells was determined using F(Ab')2 antibody as above. The CD19-2G construct resulted in 18.2% CAR cells, but the CD19b-BB-2G construct resulted in 54.7% CAR efficiency (FIG. **39***b*). This shows that the optimal design of CD19-2G CAR also depends in part on the sequence of the scFv used.

CD19-2G and CD19b-BB-2G CAR T Cells Specifically Target CD19-Expressing Cell Lines

[0576] T cell co-culture killing assays were performed to determine the ability of CD19-2G and CD19b-BB-2G CAR T cells to effectively lyse the CD19+ cell lines, SP53 and JeKo-1 (both mantle cell lymphoma lines). Briefly, each target cell line was pre-labeled with CMTMR membrane dye, and then co-cultured with either vector control, L8-CD19-2G or L8-CD19b-BB-2G CAR T cells at ratios of 2:1 and 5:1 effector:target cells (200,000 or 500,000 effector cells to 100,000 target cells, in 1 mL T cell media without serum or IL-2). After overnight incubation, cells were

labeled with anti-human CD3-PerCp and CD19-APC for 30 minutes, washed, and suspended in 2% formalin for analysis by flow cytometry. Both CD19-2G and CD19b 2G CAR T cells displayed robust lysis of B cell lines, SP53 and Jeko-1 (FIG. **41**).

[0577] CD19-2G and CD19b-BB-2G CAR T Cells Eliminate CD19+ Cells from AML and B-ALL Patient Samples

[0578] Studies were also conducted using patient samples. Two patients with CD19+ cells were used: one diagnosed as AML (aberrant expression of CD19), and one with B-ALL, were used in the study. The patients' blood contained 26.4% and 90% of CD19+ cells, respectively (FIGS. **41**A, **42**A). Buffy coat fractions of these primary cells were pre-labeled with CMTMR and co-cultured with either vector control, L8-CD19-2G or L8-CD19b-BB-2G T cells in the same manner and ratios as the tumor cell lines. Both L-8-CD19-2G CAR and L-8-CD19b-2G cells were able to complete eliminate the target cells expressing CD19 (FIGS. **42** and **43**).

[0579] Viral titers generally decrease as the size of insert increases and the sequence of CD19b scFv provided a higher titer for CD19b CAR (FIG. **39**). Therefore, CD19b scFv was used to generate the compound BCMA CD19b CAR (FIG. **44**). BCMA CD19b CAR.

An Alternative CAR Design for Myeloma and Plasma Cells

[0580] We designed a ligand expressing CAR that binds to various B-cell activation factor receptors. While it seems a logical leap to design CARs for any potential antigen or ligand factor that can be bound to a tumor population, technical troubleshooting in CAR technology is still a high and persistent barrier. Not all CAR constructs are able to achieve consistent or sufficient surface expression as a result of undefined molecular interactions or design problems. We were able to achieve surface expression of CD45 leader sequence BAFF-CAR with a CD28 intracellular signaling domain of around 21% (FIG. **45**A). However, BAFF-CARs with alternate leader sequences from CD8 or CSF did not achieve any meaningful expression (FIG. **45**B). Yet another factor was observed when CAR design was considered. We designed BAFF-CAR constructs using the 4-1BBL ligand binding domain as a supportive stimulatory pathway in one case. In another, we added an IL-15/IL-15sushi armor expressing arm to the construct. The CD8 leader sequence paired with the 4-1BBL or the IL-15/IL-15sushi both achieved higher surface expression than the CSF leader sequence in both cases (FIG. **45**C).

Anti-Plasma Cell Properties of the BAFF-CARs

[0581] We characterized the biological properties of the various BAFF-CARs by culturing them with either plasma cell myeloma cells (MM1S) or mantle (MCL) cells (SP53) that all express a component of the plasma cell marker CD138 to which BAFF is a ligand bound complex. The L45-BAFF-28 CAR was able to lyse MM1S tumor cells after 48 hours at an E:T ratio of 3:1 approaching 60% (FIG. **46**). Furthermore, the L8-BAFF-28 IL-15/IL-15sushi and L8-BAFF-28 4-1BBL CARs were also able to achieve comparable degrees of cytotoxicity (FIG. **47**A, **47**C). Co-culture with the B cell mantle cell line SP53 show a limited effect with around 25% cytotoxicity observed for the L8-BAFF-28 IL-15/IL-15 CAR only (FIG. **47**).

CD45 CAR Therapy

[0582] Three pairs of sgRNA are designed with CHOP-CHOP to target the gene of interest. Gene-specific sgRNAs are then cloned into the lentiviral vector (Lenti U6-sgRNA-SFFV-Cas9-puro-wpre) expressing a human Cas9 and puromycin resistance genes linked with an E2A self-cleaving linker. The U6-sgRNA cassette is in front of the Cas9 element. The expression of sgRNA and Cas9puro is driven by the U6 promoter and SFFV promoter, respectively (FIG. **48**).

[0583] The following gene-specific sgRNA sequences were used and constructed,

In a non-limiting embodiment of the disclosure, exemplary gene-specific sgRNAs have been designed and constructed as set forth below:

[0584] CD45 sgRNA construct:

```
Lenti-U6-sgCD45a-SFFV-Cas9-puro
GTGGTGTGAGTAGGTAA

Lenti-U6-sgCD45b-SFFV-Cas9-puro
GAGTTTTGCATTGGCGG

Lenti-U6-sgCD45c-SFFV-Cas9-puro
GAGGGTGGTTGTCAATG
```

FIG. **49**A shows steps of generation of CD45 CAR T or NK cell targeting hematologic malignancies.

CRISPR/Cas Nucleases Target to CD45 on NK Cells

[0585] Lentiviruses carried gene-specific sgRNAs were used to transduce NK-92 cells. The loss of CD45 expression on NK-92 cells was determined by flow cytometry analysis. The CD45 negative population of NK-92 cells was sorted and expanded (FIG. **49**B). The sorted and expanded CD45 negative NK-92 cells were used to generate CD45CAR NK cells. The resulting CD45CAR NK cells were used to test their ability of killing CD45+ cells.

Functional Characterization of CD45 Inactivated NK-92 Cells (NK^{45i}-92) after CRISPR/Cas Nucleases Target

[0586] We demonstrated that, following CRISPR/Cas nuclease inactivation of CD45, the growth of NK^{45i}-92 cells was similar to that of the wild NK-92 cells (FIG. **50**). Inactivation of CD45 did not significantly affect the cell proliferation of NK-92. In addition, we showed that the lysis ability of NK^{45i}-92 cells was compatible to that of wild type, NK-92 when cells were co-cultured with leukemic cells, CCRF (FIG. **51**).

[0587] To demonstrate that CD45-inactivated NK-92 was compatible with CAR lysis, NK^{45i}-92 cells and their wild type, NK-92 were transduced with lentiviruses expressing CD5CAR or GFP. The resulting CD5CAR NK^{45i}-92 cells and GFP NK^{45i}-92 were sorted by FACS, and used to compare their ability of killing targeted cells. CD5CAR NK^{45i}-92 cells displayed the ability of robustly killing CD5 target leukemic cells at ratios (E:T), 2:1 and 5:1 when they were co-cultured with CCRF-CEM cells. We showed that there was a similar efficacy of elimination of CCRF-CEM cells in vitro between CD5CAR NK^{45i}-92 and CD5 CAR NK-92 cells (FIG. **52**). This suggests that the loss of CD45 expression does not diminish the anti-tumor activity of CAR NK-cells.

Generation of CD45CAR Construct

[0588] We next investigate that CD45CAR in NK^{45i}-92 cells response to the CD45 antigen in leukemic cells. We generated CD45CAR. CD45CAR consists of an anti-CD45 single-chain variable fragment (scFv) region, CD8-derived hinge (H) and transmembrane (TM) regions, and tandem CD28 and 4-1BB co-activation domains linked to the CD3ζ signaling domain (FIG. **53**A). A strong spleen focus forming virus promoter (SFFV) and a CD8 leader sequence were used. CD45CAR protein was characterized by Western blot of HEK293-FT cells transfected with CD45CAR lentiviral plasmid with appropriate vector control. Additionally, anti-CD3zeta monoclonal antibody immunoblots revealed bands of predicted size for the CD45CAR protein with no bands observed in vector control (FIG. **53**B).

CD45CAR NK^{45i}-92 NK Cells

[0589] Following fluorescence-activated cell sorting (FACS) to enrich for NK^{45i}-92 cells, CD45CAR NK-92 transduction efficiency was determined to be 87%, as determined by flow cytometry (FIG. **54**) after sorting. After FACS collection of NK^{45i}-92 cells, CD45CAR expression levels remained consistently stable for at least 10 passages.

CD45CAR NK^{45i}-92 Cells Specifically Lyse CD45+ Leukemic Cells.

[0590] To assess CD45CAR NK^{45i}-92 anti-leukemic activity, we conducted co-culture assays using T-ALL cell lines, CCRF-CEM and Jurkat, and NK cell line and NK-92 cells since they all express CD45 (FIGS. **55**, **56** and **57**). We demonstrated that CD45CAR NK^{45i}-92 cells consistently displayed robust lysis of leukemic cells. Following 6-hour incubation at a low effective to target cell (E:T ratio 5:1), CD45CAR NK^{45i}-92 cells effectively lysed more than 60% of CCRF-CEMcells (FIG. **55**). After 6-hour co-culture, CD45CAR NK^{45i}-92 cells were also able to eliminate about 60% of Jurkat cells at a ratio of E:T, 2:1 or 5:1 (FIG. **56**). After 6 hours of co-culture, CD45CAR NK^{45i}-92 cells efficiently lysed 20% CD45 positive NK-92 cells at an E:T ratio of 2:1, with close to 60% lysis at an E:T of 5:1 (FIGS. **57**A-**57**C).

[0591] To further analyze the CD45 target for hematologic malignancies, we also generated additional two CARs: CD45-28 and CD45-BB, and the lentiviruses expressing CD45-28 or CD45-BB CAR were used to transduce NK45i-92 cells. CD45-28 and CD45-BB CARs contain a new anti-CD45 scFv, which is different from that of CD45CAR described above. CD45-28 CAR uses a CD28 co-stimulatory domain while the CD45-BB bears a 4-BB co-stimulatory domain. Both CARs use the CD8-derived hinge (H), transmembrane (TM) regions and CD3ζ signaling domain. CD45CARs displayed robust lysis of B acute lymphoblastic cell line, REH. CD45CAR NK45i-92 cells lysed about 76% REH cells. CD45b-BB CAR NK45i-92 cells and CD45b-28 CAR NK45i-92 cells showed about 79% and 100% lysis of REH cells, respectively compared to control GFP NK-92 cells (FIG. **57**D-**57**E). CD45b-28 CAR NK45i-92 cells exhibited the highest ability of lysis of REH cells (B-ALL cells).

[0592] We also investigated if CD4b-28CAR CD45b-28 CAR NK45i-92 cells could lyse other types of leukemic cells. As shown in FIG. **57**F, co-culture assay was performed with U937 cells (target: T) and GFP NK-92 cells or CD45b-28 NK^{45i}-92 cells (effector: E) at 2:1 (E:T) ratio for 20 hours, CD45b-28 NK^{45i}-92 cells exhibited a robust anti-leukemic activity with about 81% cell lysis against U937 cells compared to control GFP NK-92 cells. U937 is an acute myeloid leukemia cell line. A similar finding was seen when co-culture assay was done with MOLM-13 cells (target: T) and GFP NK-92 cells or CD45b-28 NK45i-92 cells (effector: E) at 5:1 (E:T) ratio for 20 hours (FIG. **57**G). MOLM-13 cells are derived from a patient with aggressive acute monocytic leukemia. The anti-leukemic activities were also examined in two mantle cell lines, SP53 and Jeko (FIGS. **57**H and I). CD45b-28 NK^{45i}-92 with a low ratio of 2:1 (E:T), were able to lyse more than 40% of SP53 cells or Jeko leukemic cells compared to control GFP NK-92 cells at a relative short co-culture period of time, 6 hours. These studies demonstrated that CD45b-28 NK^{45i}-92 had a remarkable anti-leukemic property against different types of malignant leukemias.

[0593] We further investigated if CD45b-28 NK^{45i}-92 cells could lyse CD34+ hematopoietic stem/progenitor cells. CD34(+) stem cells derived from human umbilical cord blood were co-cultured with either control or CD45b-28 CAR NK cells for 48 hr at a low ratio of 2:1 (effective: target). CD45b-28 NK^{45i}-92 cells nearly eliminate CD34+ hematopoietic precursor cells (FIG. **57**J) compared to the control.

An Alternative CAR Design to Enhance CD45 CAR Activity

[0594] We also generated engineered CD45 CAR cells received not only costimulation through the CD28 but also co-express the 4-1BB ligand (4-1BBL or CD137L) in a single construct, which provide the better therapeutic efficacy (FIG. **58**A) and their example is described below:

[0595] Example: CD45b-28-2G-4-1BBL was generated and the generated CD45b CAR cells could receive both co-stimulatory pathways, CD28 and 4-1BB. CD45b-28-2G-4-1BBL viruses were concentrated by 4 fold and used to transduce NK^{45i}-92 cells. Its CAR surface expression was about 87% (FIG. **58**B). CD45b-28-2G-4-1BBL viruses were concentrated by 4 fold and used for transduction. Anti-tumor activity of CD45b-2G CAR cells was significantly improved when 4-1BBL was included in the construct.

[0596] An enhancer, IL-15/IL-15sushi was also included in CD45 CAR construct as an alternative approach to enhance CD45 CAR anti-tumor activity. Both CD45 CAR and IL-15/IL-15sushi were in a single construct (FIG. **58**). Anti-tumor activity of CD45b-2G CAR cells is significantly improved when IL-15/IL-15sushi is included in the construct.

[0597] Example: CD45b-28-2G-IL-15/IL-15sushi NK cells was generated. Surface CD45b CAR expression were about 60%. (FIG. **58**C). Anti-tumor activity of CD45b-2G CAR cells was significantly improved when IL-15/IL-15sushi was included in the construct.

Characterization of CD4IL-15/IL-15Sushi CAR

[0598] The CD4IL-15/IL-15sushi-CAR has been generated and it contains the third generation of CD4CAR linked to IL-15/IL-15sushi (FIG. **59**). A combination of CAR, (third generation), sushi/IL-15 is assembled on an expression vector and their expression is driven by the SFFV promoter (FIG. **59**). CAR with IL-15/IL-15sushi is linked

with the P2A cleaving sequence. The IL-15/IL-15sushi portion is composed of IL-2 signal peptide fused to IL-15 linked to IL-15susi via a 26-amino acid poly-proline linker (FIG. **59**). The IL-2 signal peptide provide a better secreting signal. The stable, functional complexes of IL-15/IL-15sushi can be secreted from the transduced cells and the secretion is directed by IL-2 signal peptide.

[0599] To verify the CD4IL-15/IL-15sushi construct, HEK293FT cells were transfected with lentiviral plasmids for either GFP (control) or. CD4IL-15/IL-15sushi. Approximately 60 hours after transfection, both HEK-293FT cells and supernatant were collected. Cells were lysed in RIPA buffer containing protease inhibitor cocktail and electrophoresed. The gel was transferred to Immobilon FL blotting membrane, blocked, and probed with mouse anti-human CD3z antibody at 1:500. After washes, membrane was probed with goat anti-mouse HRP conjugate, washed, and exposed to film following treatment with HyGlo HRP substrate. The CD4IL-15/IL-15sushi was successfully expressed in HEK 293 cells (Lane 2, FIG. **60***a*). The CD4IL-15/IL-15sushi lentiviral supernatant was further examined by the transduction of fresh HEK-293 cells (FIG. **60**A). HEK-293 cells were transduced with either GFP or CD4IL-15/IL-15sushi CAR viral supernatant from transfected HEK-293FT cells. Polybrene was added to 4 μL/mL. Media was changed after 16 hours and replaced with media containing no viral supernatant or polybrene. Three days after transduction, cells were harvested and stained with goat-anti-mouse F(Ab')2 antibody at 1:250 for 30 minutes. Cells were washed and stained with streptavidin-PE conjugate at 1:500, washed, suspended in 2% formalin, and analyzed by flow cytometry. FIG. **60***b* shows that HEK-293 cells that were transduced with the CD4IL-15/IL-15sushi CAR lentivirus were 80% positive for F(Ab)2-PE (circled, FIG. **60**B), while transduction with GFP control lentivirus was minimal for F(Ab)2-PE (FIG. **60**).

Production of CD4IL-15/IL-15Sushi—CAR NK Cells

[0600] NK-92 cells were transduced with concentrated CD4IL-15/IL-15sushi-CAR lentiviral supernatant. After 5 days incubation, cells were harvested and incubated with goat anti-mouse F(Ab')2 at 1:250 for 30 minutes. Cells were washed, suspended and stained with streptavidin-PE for 30 minutes. Cells were washed and suspended in 2% formalin, and analyzed by flow cytometry, resulting in nearly 70% of the transduced cells expressing CD4IL-15/IL-15sushi-CAR (circled, FIG. **61**. Further experimental tests for CD4IL-15/IL-15sushi-CAR included leukemia/lymphoma killing assays in vitro and vivo, and comparison of target killing and proliferation rates with cells transduced with CD4CAR. The inventor also used the same strategy described above to generate CD19IL-15/IL-15sush CAR, CD20IL-15/IL-15sush CAR and CD22IL-15/IL-15sush CAR.

Production of CD4IL-15/IL-15Sushi-CAR T Cells

[0601] Human umbilical cord buffy coat cells were transduced with concentrated CD4IL-15/IL-15sushi-CAR lentiviral supernatant. After 5 days incubation, cells were harvested and incubated with goat anti-mouse F(Ab')2 at 1:250 for 30 minutes. Cells were washed, suspended and stained with streptavidin-PE for 30 minutes. Cells were washed and suspended in 2% formalin, and analyzed by flow cytometry, resulting in 63% of the transduced cells expressing CD4IL-15/IL-15sushi-CAR(circled, FIG. **62**). Further experimental tests for CD4IL-15/IL-15sushi-CAR will include leukemia/lymphoma killing assays in vitro and vivo, and comparison of target killing and proliferation rates with cells transduced with CD4CAR.

CD4IL-15/IL-15Sushi CAR NK Cells were Tested for Anti-Leukemic Activity Relative to CD4CAR NK Cells In Vitro by Co-Culturing them with the Following CD4 Positive Cell Lines: Karpas 299 and MOLT4.

[0602] The Karpas 299 cell line was derived from a patient with anaplastic large T cell lymphoma. The MOLT4 cell line expressing CD4 was established from the peripheral blood of a 19-year-old patient with acute lymphoblastic leukemia (T-ALL). During 4-hour co-culture experiments, CD4IL-15/IL-15sushi CAR NK cells showed profound killing (95%) of Karpas 299 cells at a 5:1 ratio of effector:target, at an even higher rate than that of CD4CAR NK cells (82%; FIG. **63**). Similarly, when co-cultured 1:1 with MOLT4 cells, CD4IL-15/IL-15sushi CAR NK cells lysed target cells at a higher rate (84% to 65%) than CD4CAR NK cells in an overnight assay (FIG. **64**). These results show that CD4IL-15/sushi CAR NK cells can ablate tumor cells.

Both CD4CAR and CD4IL-15/IL-15Sushi CAR T Cells Exhibit Significant Anti-Tumor Activity In Vivo

[0603] In order to evaluate the in vivo anti-tumor activity of CD4CAR and CD4IL-15/IL-15sushi CAR T cells, and to determine the possible increase in persistence of the CD4IL-15/IL-15sushi CAR T cells relative to the CD4CAR T cells, we developed a xenogeneic mouse model using NSG mice sublethally irradiated and intravenously injected with luciferase-expressing MOLM13 cells, an acute myeloid leukemia cell line that is 100% CD4+, to induce measurable tumor formation (FIG. **65**). Three days following tumor cell injection, 6 mice each were intravenously injected with a course of 8×10^6 CD4CAR, CD4IL-15/IL-15sushi T cells or vector control T cells. On days 3, 6, 9 and 11, mice were injected subcutaneously with RediJect D-Luciferin (Perkin Elmer) and subjected to IVIS imaging to measure tumor burden (FIG. **65**B). Average light intensity measured for the CD4CAR and CD4IL-15/IL-15sushi CAR T cell injected mice was compared to that of vector control T cell injected mice in order to determine the percentage of tumor cells in treated versus control mice (FIG. **65**C). CD4CAR T cell-treated mice had a 52% lower tumor burden relative to control on Day 6, whereas CD4IL-15/IL-15sushi CAR T cell-treated mice had a 74% lower tumor burden. On Day 11, nearly all tumor cells had been lysed in both of these groups. Unpaired T test analysis revealed a very significant difference (P=0.0045) between control and the two groups by day 9 with less light intensity and thus less tumor burden in the CD4CAR and CD4IL-15/IL-15sushi CAR T cells treated group compared to control. In summary, these in vivo data indicate that CD4CAR and CD4IL-15/IL-15sushi CAR T cells both significantly reduce tumor burden and in MOLM13-injected NSG mice when compared to vector control T cells.

[0604] Next, we compared mouse survival across the two groups (FIG. **65**D). All leukemic mice injected with CD4IL-15/IL-15sushi CAR T cell survived longer than that of CD4CAR T cells. In summary, these in vivo data indicate that CD4IL-15/IL-15sushi CAR T cells significantly reduce tumor burden and prolong survival in CD4IL-15/IL-15sush CAR T-injected NSG mice when compared to control cells.

CD4IL-15/IL-15Sushi CAR NK Cells Exhibit Robust and Persistent Anti-Tumor Activity in Vivo

[0605] In order to further evaluate the CD4IL-15/IL-15sushi CAR function, we created a stressful condition utilizing NK CAR cells and Jurkat tumor cells. The NK cells bear a short half-life property and leukemic Jurkat cells show less than 60% CD4+ phenotype (FIG. **66**A). In such a condition, it allows us to investigate how secretory soluble IL-15sushi affects the CAR functions in terms of its persistence and killing capability. We then used our xenogeneic NSG mouse model using NSG mice sublethally irradiated and intravenously injected with luciferase-expressing Jurkat cells to induce measurable tumor formation. In contrast with MOLM-13 cells, Jurkat cells show less than 60% CD4+ phenotype (FIG. **66**A**5**). Three days following Jurkat cell injection, mice were intravenously injected with a course of 10×10^6 either CD4CAR, CD4IL-15/IL-15sushi, or vector control NK cells. On day 3 (the day before treatment), 7, 10, and 14, mice were subjected to IVIS imaging to measure tumor burden (FIG. **66**B). Average light intensity measured for the CD4CAR and CD4IL-15/IL-15sushi NK injected mice was compared to that of vector control NK injected mice to determine percent lysis of Jurkat cells (FIG. **66**C). Although both conditions showed significant tumor cell lysis by Day 7, lysis percentage for CD4CAR NK cells stayed the same to Day 14 while CD4IL-15/IL-15sushi NK cells increased to over 97%. (FIG. **66**D). Unpaired T test analysis revealed an extremely significant difference ($P<0.0001$) between the two groups by Day 14. These results indicate that CD4CAR NK cell lysis of Jurkat tumor cells was not able to keep up with the expansion of CD4− Jurkat cells, whereas the continued expansion of NK CAR cells secreting IL-15/IL-15sushi effectively lysed. The co-expression of secretory IL-15/IL-15sushi with CAR could supplement the defect that CAR T or NK cells are unable to eliminate dim expressed cancer cells or non-targeting cancer cells. A repeat of experiments (FIG. **67**) showed similar results to those described in FIG. **66**.

Secreted IL-15/IL-15Sushi Substitutes for IL-2 in NK Cell Survival and Expansion.

[0606] The effect of IL-15/IL-15sushi-secreting NK cells on cell survival was determined. NK-92 cells stably transduced with either CD4CAR or CD4IL-15/IL-15sushi were cultured in the presence or absence of IL-2 to determine if IL-15/IL-15sushi secretion alone could lead to survival and expansion. CD4CAR-expressing NK cells cultured without IL-2 died by Day 7, while CD4IL-15/IL-15sushi-expressing NK cells cultured without IL-2 expanded at approximately the same rate as either CD4CAR or CD4IL-15/IL-15sushi cells cultured with IL-2 (FIG. **68**B), showing that secreted IL-15/IL-15sushi could substitute for IL-2. Furthermore, we were able to demonstrate that NK cells secreting IL-15/IL-15sushi could aid in the survival and expansion of non-transduced NK-92 cells in a co-culture. In this experiment, an equal ratio of NK GFP-expressing cells were cultured with either CD4CAR- or CD4IL-15/IL-15sushi-expressing NK cells, in the presence or absence of IL-2. Cells were counted every 2-3 days (FIG. **8**A). By Day 7, CD4CAR NK cells given no IL-2 had died, but CD4IL-15/IL-15sushi NK cells without IL-2 had survived and expanded at approximately the same rate as either CD4CAR or CD4IL-15/IL-15sushi cells cultured with IL-2. The number of GFP-expressing cells had risen along with the CD4IL-15/IL-15sushi NK cells (FIG. **68**B), indicating that the secreted IL-15/IL-15sushi had positively affected GFP NK cell survival. The percentage of GFP-positive cells had risen from 50% to over 70% over the course of the experiment (data not shown). In the second experiment (FIG. **69**), GFP NK and either control vector NK or CD4IL-15/IL-15sushi NK cells were mixed at a 10 to 1 ratio, with no IL-2. By Day 6, cells co-cultured with control cells had all died, but survival of cells cultured with NK cells secreting IL-15/IL-15sushi survived until Day 10.

[0607] To further determine if this effect was due to secreted protein alone, or an interaction between co-cultured cells, we devised an experiment in which the GFP NK cells were cultured in a chamber above the cultured CD4CAR or CD4IL-15/IL-15sushi NK cells, or non-transduced NK-92 cells. In this situation, only proteins and not cells could pass between the membrane separating the two cultures. Cells were incubated without IL-2, counted and split 1:1 every other day. While GFP NK cells in the upper chamber above NK-92 cells had died by Day 6, the GFP NK cells above the CD4IL-15/IL-15sushi NK cells had survived and expanded by Day 12 (FIG. **70**), thereby indicating that it was the IL-15/IL-15sushi protein secreted by the CD4IL-15/IL-15sushi NK cells which had kept them alive, and not direct cell-to-cell contact. In this model, the upper chamber represents the tumor microenvironment, in which the survival of T cells or NK cells is improved by the secretion of IL-15/IL-15sushi from the CD4IL-15/IL-15sushi NK cells.

Effect of Secreted IL-15/IL-15Sushi on CAR T and Non-Transduced Neighboring Cells.

[0608] We also compared the cell growth of CD4CAR and CD4IL-15/IL-15sushi transduced T cells in the presence or absence of IL-2. Total cell counts calculated throughout the experiment (up to Day 17) for transduced cells with or without IL-2. CD4IL-15/IL-15sushi transduced T cells appeared to be more tolerant to the absence of IL-2 than that of CD4CAR transduced T cells.

EXAMPLES

Generation of Treg CAR Target Treg Cells

[0609] Treg CAR (also called CD4zetaCD25CAR or C4-25z) followed the schematic in FIG. **70**. It comprises of SFFV (spleen focus-forming virus) promoter that drives the expression of two different units of incomplete CARs linked by a P2A cleavage peptide. The CD4 chimeric antigen receptor polypeptide unit comprises a CD45 signal peptide, a CD4 antigen recognition domain, a hinge region (derived CD8a), a transmembrane domain (CD8a) and CD3 zeta chain; CD25 chimeric antigen receptor polypeptide unit comprises a CD45 signal peptide, a CD25 antigen recognition domain, a hinge region (CD8a), a transmembrane domain (CD8a), a co-stimulatory domain (s), CD28. The Treg CAR can potentiate the lysis activity of a cell co-expressing CD4 and CD25 while minimizing a cell bearing CD4 or CD25 antigen alone.

[0610] The CD4zetaCD25CAR (C4-25z) (Treg CAR) was transduced in an assay. Compared to control T-cells, CD4zetaCD25CAR cells show ~15% surface expression and this was sufficient to observe the following phenotype validation of construct function (FIG. **70**A). CD4zetaCD25

CAR cells and control T-cells were both assayed with CD4 and CD25 antibody to look for logic gated behavior using flow cytometry analysis. Due to the construct design, the CD4zetaCD25CAR cell would potentiate the lysis activity for cells co-expressing both CD4 and CD25 antigens. Here, we showed depletion (~95%) of the CD4+CD25+ double positive population with little impact of off-logic events in the other phenotype cases. A bar graph summary shows that the logic gated CAR construct design only significantly impacts the double positive population (FIG. **70**B).

[0611] We further characterized CD4zetaCD25 CAR by comparing it with CD4 CAR. As expected, CD4CAR T cells had a profound lysis ability of cells expressing CD4 only while CD4zetaCD25CAR T cells had a limited killing ability on this population (FIG. **71**). CD4zetaCD25CAR T cells also showed virtually complete depletion of cells expressing both CD4 and CD25 antigens (FIG. **71**). These studies demonstrate that the robust CD4zetaCD25CAR targeting cells co-expressing both CD4 and CD25, has been established. Due to human-specific CD4 or CD25scFv in the construct, the functional properties of CD4zetaCD25CAR are difficult to test in animals.

[0612] In some embodiments, the disclosed disclosure also comprises methods of improving the CD4zetaCD25CAR therapeutic activity. The example is described below.

Example

[0613] An engineered CD4zetaCD25CAR cell was prepared in accordance with the present disclosure.

Cell Killing Assay is Performed

[0614] Targeted Cells killing by CD4zetaCD25CAR is improved when co-expressed with 4-1BBL or IL-15/IL-15sushi or IL-15/IL-15RA.

Safety Switch

[0615] Introduction of a "safety switch" greatly increases safety profile and the "safety switch" may be an inducible suicide gene, such as, without limiting, caspase 9 gene, thymidine kinase, cytosine deaminase (CD) or cytochrome P450. Other safety switches for elimination of unwanted modified T cells involve co-expression of CD20 or CD52 or CD19 or truncated epidermal growth factor receptor in T cells.

Example: Co-Expression of CD52 with CARs Using CD5CAR Targeting T-Cell Malignancies as an Example

[0616] For clinical treatment using CAR T-cells against T-cell malignancies, establishment of safety methods to eliminate CAR T-cells from patients may be necessary after tumor depletion or in emergency cases due to unexpected side effects caused by CAR therapy. T-cells and B-cells express CD52 on the cell surface and a CD52 specific antibody, CAMPATH (alemtuzumab), can eliminate CD52+ cells from circulation. We thus incorporated a human CD52 sequence into the CD5CAR vector construct (FIG. **72**A). This additional CD52 construct mechanically separates the signaling from native CD52. The aim was to preempt the possibility of native CD52 antigen escape on CAR T-cell surface after CAMPATH treatment. CD5CAR-CD52 lentiviral protein and expression were confirmed via western blot and flow cytometry analysis using CD52 antibody on transduced HEK293 cells. We also found that co-expressing CD52 would affect the CAR T cell functions.

In Vivo Depletion of Infused CD5CAR-CD52 T Cells Following Treatment with CAMPATH

[0617] To assess the effect of CAR elimination by CAMPATH (alemtuzumab) treatment, we conducted in vivo procedures as described (FIGS. **72**B and **72**C). We intravenously injected 5×10^6 CD5CAR-52 T-cells into irradiated mice. Next day, we added 0.1 mg/kg of CAMPATH or PBS via IP injection for 3 mice of each group. After 6 and 24 hours following CAMPATH treatment, we collected peripheral blood from the mouse tail and determined presence of CD5CAR-52 T-cells by FACS analysis. CAMPATH injection virtually completely deplete CD5CAR-CD52 T-cells in blood at both 6 h and 24 h (FIG. **72**C). Five days following CAMPATH administration, CD5CAR-CD52 cells were also completely depleted in both the bone marrow and spleen (FIG. **72**D). These findings support the use of CAMPATH as a useful strategy in acting as a safety trigger to deplete CAR-T cells from circulation and lymphoid organs.

[0618] In one embodiment, the engineered cell includes a CD5 chimeric antigen receptor polypeptide and an anchor CD52 (SEQ ID NO. 70), and corresponding polynucleotide (SEQ ID NO. 69). In some embodiments, CD52 is incorporated into CD5 CAR engineered cell or any CAR engineered cell and can be used as a "safety switch" for CAR therapy.

Promoter Testing Using the GFP Reporter

[0619] HEK293FT cells were transfected with lentiviral plasmids expressing GFP under the SFFV, EF1 or CAG promoters. Approximately 60 hours after transfection, supernatant was collected from each. Relative viral titer was determined by first transducing HEK293 cells with supernatant from each of the 3 promoters. HEK-293 cells were transduced with GFP viral supernatant from each of the 3 transfected HEK-293FT cells. Polybrene was added to 4 μL/mL. Media was changed after 16 hours and replaced with media containing no viral supernatant or polybrene. Three days after transduction, cells were harvested and washed, suspended in 2% formalin, and analyzed by flow cytometry for GFP expression (FITC). GFP expression was seen in each sample, but was highest for the cells transduced with virus made using the SFFV promoter.

[0620] Activated human umbilical cord buffy coat cells were transduced with GFP lentiviral supernatant (amount based on the results of the HEK293 transduction efficiency) from each of the promoters. After 5 days incubation, cells were harvested, washed and suspended in 2% formalin, and analyzed by flow cytometry for GFP expression. 43% of cells expressed GFP at high levels ($>10^3$) while GFP-expression for cells transduced with virus using promoters EF1 (15%) and CAG (3%) were considerably lower. Five days later, cells analyzed the same way showed nearly the same percentages for each (46%, 15% and 3%, respectively). These results indicate that SFFV promoter leads to stronger expression than EF1 or CAG promoters, and that the expression remains high for at least 10 days post-transduction. Further experimental tests will include longer incubation times for transduced cells beyond the 10-day window.

Functional Titer of Viral Vector Particles in Supernatants (the % GFP Cells as Determined by Flow Cytometry Allows for Proxy Viral Titer Adjustments as Higher Titer Virus Infiltrates More Cells, Leading to Higher % GFP Cell Populations).

[0621] To determine functional titer of viral vector particles in each of our supernatants, HEK 293 cells were transduced with either EF1-GFP or SFFV-GFP viral supernatant, with either 30 μL (low), 125 μL (medium), or 500 μL (high) per well of a 12 well tissue-culture treated plate. Culture media was changed the following morning to DMEM plus 10% FBS (FIG. **73**).

[0622] Transduced cells were then trypsinized, washed, and suspended in formalin and subjected to flow analysis. The percentage of GFP+ cells in each of the conditions was determined by flow cytometry using the FITC channel (FIG. **74**). In each case, the percentage of GFP+ was higher in cells transduced with SFFV-GFP than the cells transduced with the corresponding volume of EF1-GFP viral supernatant (50% to 18% for low, 80% to 40% for medium, and 82% to 70% for high). From this, we determined that using the highest volume of EF1-promoter virus was comparable to using the lowest volume of SFFV-promoter virus in terms of titer, and would allow for comparison of relative promoter strengths for the following transduction experiments

[0623] Transduced cells were also visualized on an EVOS fluorescent microscope using GFP at 20× at the same exposure conditions for each well (FIG. **73**). Cells transduced with SFFV-GFP viral supernatant were dramatically brighter than cells transduced with EF1-GFP. Furthermore, comparing the image of the EF1-promoter under high viral volume loads with the image of the SFFV-promoter using low viral volume loads show similar fluorescent intensity. This suggests that the SFFV promoter is a stronger driver of gene expression.

Comparison of Surface Expression and Persistence of Different Promoters in Primary T-Cells (the % GFP Cells as Determined by Flow Cytometry for T-Cell Transductions Show Expected Differences in GFP Cell Populations as Expected from the Prior Experiments on HEK293 Cells)

[0624] To determine promoter transduction efficiency and persistence of surface expression in primary T cells, activated cord blood buffy coat T cells were transduced with either 50 μL of SFFV-GFP or 1 mL of EF1-GFP EF1-GFP viral supernatant, in 12-well tissue culture-treated plates pre-coated with retronectin (Clontech). Following two overnight transductions, cells were cultured on T cell media with 300 IU/mL IL-2 (Peprotech) and maintained at $1.0\text{-}4.0\times10^6$/mL. Cells were washed, suspended in formalin, and subjected to flow cytometry analysis, using the FITC channel to determine the percentage of GFP+ cells, on 7, 14, 21 and 28 days after transduction. The percentage of GFP+ cells was consistently higher for T cells transduced with SFFV-GFP compared to EF1-GFP-transduced T cells (FIG. **75**A), even as the percentage of total GFP+ cells decreased over this period. A further comparison showed that T cells transduced with the higher (1 mL) amount of EF1-GFP supernatant actually decreased in percentage relative to the percent of GFP+ cells transduced with the lower amount (50 μL, or 20-fold less) of SFFV-GFP, between Day 7 and Day 28, from over 60% to under 40% (FIG. **75**B). This suggests that transduction using the SFFV promoter led to greater persistence of transduced cells.

[0625] Methods of generating the CAR gene including at least one of a T antigen recognition moiety (at least one of CD4, CD8, CD3, CD5, CD7, and CD2, or a part or a combination thereof), a hinge region and T-cell activation domains is provided.

[0626] Methods of generating multiple units of CARs (cCAR) targeting antigen (s) including at least one of CD33, CD123, CD19, CD20, CD22, CD269, CS1, CD38, CD52, ROR1, PSMA, BAFF, TACI, CD138, and GPC3, or a part or a combination of a hinge region and T-cell activation domains is provided.

[0627] The provided methods also include: 1) generating of the CAR T or NK cells targeting leukemias and lymphomas expressing CD45 and avoiding self-killing; 2) generation of "armored" CAR T or NK cells designed to both overcome the inhibitory tumor microenvironment and exhibit enhanced anti-tumor activity and long-term persistence.

[0628] The present disclosure is not limited to the embodiments described and exemplified above, but is capable of variation and modification within the scope of the disclosure and claims.

[0629] While there have been described what are presently believed to be the preferred embodiments of the present disclosure, those skilled in the art will realize that other and further changes and modifications may be made thereto without departing from the spirit of the disclosure, and it is intended to claim all such modifications and changes as come within the true scope of the disclosure.

[0630] Various terms relating to aspects of the disclosure are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art, unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definition provided herein.

INCORPORATION OF SEQUENCE LISTING

[0631] Incorporated herein by reference in its entirety is the Sequence Listing for the application. The Sequence Listing is disclosed on a computer-readable ASCII text file titled, "sequence_listing.txt", created on Dec. 22, 2016. The sequence-listing.txt file is 508 KB in size.

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acatctgggt gaagagctac agcctgtaca gcagagagag atacatctgc aacagcggct   2400

tcaagagaaa ggccggcacc agcagcctga ccgagtgcgt gctgaacaag gccaccaacg   2460

tggcccactg gaccaccccc agcctgaagt gcatcagata agtttaaac               2509
```

```
<210> SEQ ID NO 3
<211> LENGTH: 995
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 3

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu
            20                  25                  30

Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr
    50                  55                  60

Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
                85                  90                  95

Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220
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Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly
            420                 425                 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        435                 440                 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
    450                 455                 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465                 470                 475                 480

Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu
                485                 490                 495

Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Ala Leu
            500                 505                 510

Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu His Ala Ala
        515                 520                 525

Arg Pro Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser
    530                 535                 540

Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser
545                 550                 555                 560

Tyr Ile His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp
                565                 570                 575

Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser
            580                 585                 590

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu
        595                 600                 605

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro
    610                 615                 620
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Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly
625                 630                 635                 640

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln
                645                 650                 655

Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser
            660                 665                 670

Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val
        675                 680                 685

Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro
    690                 695                 700

Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr
705                 710                 715                 720

Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser
                725                 730                 735

Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser Thr Tyr
            740                 745                 750

Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly Ala Gly Thr Thr Val
        755                 760                 765

Thr Val Ser Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
    770                 775                 780

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
785                 790                 795                 800

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
                805                 810                 815

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
            820                 825                 830

Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu
        835                 840                 845

Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr
    850                 855                 860

Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr
865                 870                 875                 880

Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
                885                 890                 895

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
            900                 905                 910

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
        915                 920                 925

Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
    930                 935                 940

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
945                 950                 955                 960

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
                965                 970                 975

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
            980                 985                 990

Pro Pro Arg
        995
```

<210> SEQ ID NO 4
<211> LENGTH: 3004
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 4

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg 60

ccgccaggcc ggacatccag atgacacaga ctacatcctc cctgtctgcc tctctgggag 120

acagagtcac catcagttgc agggcaagtc aggacattag taaatattta aattggtatc 180

agcagaaacc agatggaact gttaaactcc tgatctacca tacatcaaga ttacactcag 240

gagtcccatc aaggttcagt ggcagtgggt ctggaacaga ttattctctc accattagca 300

acctggagca agaagatatt gccacttact tttgccaaca gggtaatacg cttccgtaca 360

cgttcggagg ggggaccaag ctggagatca caggtggcgg tggctcgggc ggtggtgggt 420

cgggtggcgg cggatctgag gtgaaactgc aggagtcagg acctggcctg gtggcgccct 480

cacagagcct gtccgtcaca tgcactgtct caggggtctc attacccgac tatggtgtaa 540

gctggattcg ccagcctcca cgaaagggtc tggagtggct gggagtaata tggggtagtg 600

aaaccacata ctataattca gctctcaaat ccagactgac catcatcaag gacaactcca 660

agagccaagt tttcttaaaa atgaacagtc tgcaaactga tgacacagcc atttactact 720

gtgccaaaca ttattactac ggtggtagct atgctatgga ctactggggc caaggaacct 780

cagtcaccgt ctcctcaacc acgacgccag cgccgcgacc accaacaccg gcgcccacca 840

tcgcgtcgca gcccctgtcc ctgcgcccag aggcgtgccg gccagcggcg gggggcgcag 900

tgcacacgag ggggctggac ttcgcctgtg atatctacat ctgggcgccc ttggccggga 960

cttgtggggt ccttctcctg tcactggtta tcacccttta ctgcaaacgg ggcagaaaga 1020

aactcctgta tatattcaaa caaccattta tgagaccagt acaaactact caagaggaag 1080

atggctgtag ctgccgattt ccagaagaag aagaaggagg atgtgaactg agagtgaagt 1140

tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc tataacgagc 1200

tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc cgggaccctg 1260

agatgggggg aaagccgcag agaaggaaga accctcagga aggcctgtac aatgaactgc 1320

agaaagataa gatggcggag gcctacagtg agattgggat gaaaggcgag cgccggaggg 1380

gcaaggggca cgatggcctt taccagggtc tcagtacagc caccaaggac acctacgacg 1440

cccttcacat gcaggccctg ccccctcgcg gaagcggagc caccaacttc agcctgctga 1500

agcaggccgg cgacgtggag gagaaccccg gccccatggc cttaccagtg accgccttgc 1560

tcctgccgct ggccttgctg ctccacgccg ccaggccgca gatcgtgctg agccagagcc 1620

ctgccatcct gtccgcaagc ccaggcgaga aggtgaccat gacctgtagg gccagcagct 1680

ccgtgagcta catccactgg tttcagcaga agcctggaag cagccctaag ccctggatct 1740

acgccacaag caatctggct agcggcgtgc ccgtgaggtt cagcggcagc gggagcggga 1800

ccagctacag cctgactatc agcagggtgg aggccgagga cgccgccaca tactactgcc 1860

aacagtggac ctccaaccca cccacctttg gaggagggac aaaactggag atcaaagggg 1920

gcggagggtc cggaggcggc ggaagcgggg gagggggaag ccaggtccaa ctgcaacagc 1980

ccggagcaga actggtcaaa ccaggcgcca gcgtgaagat gagctgcaag gccagcgggt 2040

acaccttcac ttcctataac atgcactggg tgaagcagac cccaggaagg ggcctggagt 2100

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ggatcggggc aatctatccc ggcaacggcg acacaagcta caaccagaag ttcaagggga   2160

aagccactct gaccgccgac aagtccagct ccaccgccta catgcagctg agctccctga   2220

ccagcgagga cagcgccgtg tactattgcg ccagaagcac ttattacgga ggggactggt   2280

acttcaacgt gtgggggca gggaccaccg tgaccgtgtc cgccaccacg acgccagcgc   2340

cgcgaccacc aacaccggcg cccaccatcg cgtcgcagcc cctgtccctg cgcccagagg   2400

cgtgccggcc agcggcgggg ggcgcagtgc acacgagggg gctggacttc gcctgtgata   2460

tctacatctg ggcgcccttg gccgggactt gtggggtcct tctcctgtca ctggttatca   2520

ccctttactg caggagtaag aggagcaggc tcctgcacag tgactacatg aacatgactc   2580

cccgccgccc cgggcccacc cgcaagcatt accagcccta tgccccacca cgcgacttcg   2640

cagcctatcg ctccagagtg aagttcagca ggagcgcaga cgcccccgcg taccagcagg   2700

gccagaacca gctctataac gagctcaatc taggacgaag agaggagtac gatgttttgg   2760

acaagagacg tggccgggac cctgagatgg ggggaaagcc gcagagaagg aagaaccctc   2820

aggaaggcct gtacaatgaa ctgcagaaag ataagatggc ggaggcctac agtgagattg   2880

ggatgaaagg cgagcgccgg aggggcaagg ggcacgatgg cctttaccag ggtctcagta   2940

cagccaccaa ggacacctac gacgcccttc acatgcaggc cctgccccct cgctaagttt   3000

aaac                                                                3004
```

<210> SEQ ID NO 5
<211> LENGTH: 1001
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 5

```
Asp Arg Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu
1               5                   10                  15

Leu Leu His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Thr Thr Ser
            20                  25                  30

Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala
        35                  40                  45

Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp
    50                  55                  60

Gly Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly
65                  70                  75                  80

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu
                85                  90                  95

Thr Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln
            100                 105                 110

Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu
        115                 120                 125

Ile Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140

Ser Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser
145                 150                 155                 160

Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp
                165                 170                 175

Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp
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            180                 185                 190

Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu
        195                 200                 205

Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe
    210                 215                 220

Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys
225                 230                 235                 240

Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly
                245                 250                 255

Gln Gly Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg
            260                 265                 270

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        275                 280                 285

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
    290                 295                 300

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305                 310                 315                 320

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
                325                 330                 335

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
            340                 345                 350

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
        355                 360                 365

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
    370                 375                 380

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
385                 390                 395                 400

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                405                 410                 415

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
            420                 425                 430

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
        435                 440                 445

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
    450                 455                 460

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
465                 470                 475                 480

His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser
                485                 490                 495

Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Ala
            500                 505                 510

Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu His Ala
        515                 520                 525

Ala Arg Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala
    530                 535                 540

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Ile
545                 550                 555                 560

Val His Ser Val Gly Asn Thr Phe Leu Glu Trp Tyr Gln Gln Lys Pro
                565                 570                 575

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser
            580                 585                 590
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```
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        595                 600                 605

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
    610                 615                 620

Phe Gln Gly Ser Gln Phe Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val
625                 630                 635                 640

Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                645                 650                 655

Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
            660                 665                 670

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Glu Phe Ser
        675                 680                 685

Arg Ser Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
    690                 695                 700

Trp Val Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Ser Gly
705                 710                 715                 720

Lys Phe Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr
                725                 730                 735

Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
            740                 745                 750

Tyr Cys Ala Arg Asp Gly Ser Ser Trp Asp Trp Tyr Phe Asp Val Trp
        755                 760                 765

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro
    770                 775                 780

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
785                 790                 795                 800

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
                805                 810                 815

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
            820                 825                 830

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
        835                 840                 845

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
    850                 855                 860

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
865                 870                 875                 880

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
                885                 890                 895

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
            900                 905                 910

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
        915                 920                 925

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
    930                 935                 940

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
945                 950                 955                 960

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
                965                 970                 975

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
            980                 985                 990
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Leu His Met Gln Ala Leu Pro Pro Arg
995 1000

<210> SEQ ID NO 6
<211> LENGTH: 3016
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 6

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg 60

ccgccaggcc ggacatccag atgacacaga ctacatcctc cctgtctgcc tctctgggag 120

acagagtcac catcagttgc agggcaagtc aggacattag taaatattta aattggtatc 180

agcagaaacc agatggaact gttaaactcc tgatctacca tacatcaaga ttacactcag 240

gagtcccatc aaggttcagt ggcagtgggt ctggaacaga ttattctctc accattagca 300

acctggagca agaagatatt gccacttact tttgccaaca gggtaatacg cttccgtaca 360

cgttcggagg ggggaccaag ctggagatca caggtggcgg tggctcgggc ggtggtgggt 420

cgggtggcgg cggatctgag gtgaaactgc aggagtcagg acctggcctg gtggcgccct 480

cacagagcct gtccgtcaca tgcactgtct caggggtctc attacccgac tatggtgtaa 540

gctggattcg ccagcctcca cgaaagggtc tggagtggct gggagtaata tggggtagtg 600

aaaccacata ctataattca gctctcaaat ccagactgac catcatcaag gacaactcca 660

agagccaagt tttcttaaaa atgaacagtc tgcaaactga tgacacagcc atttactact 720

gtgccaaaca ttattactac ggtggtagct atgctatgga ctactggggc caaggaacct 780

cagtcaccgt ctcctcaacc acgacgccag cgccgcgacc accaacaccg gcgcccacca 840

tcgcgtcgca gcccctgtcc ctgcgcccag aggcgtgccg gccagcggcg gggggcgcag 900

tgcacacgag ggggctggac ttcgcctgtg atatctacat ctgggcgccc ttggccggga 960

cttgtggggt ccttctcctg tcactggtta tcacccttta ctgcaaacgg ggcagaaaga 1020

aactcctgta tatattcaaa caaccattta tgagaccagt acaaactact caagaggaag 1080

atggctgtag ctgccgattt ccagaagaag aagaaggagg atgtgaactg agagtgaagt 1140

tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc tataacgagc 1200

tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc cgggaccctg 1260

agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat gaactgcaga 1320

aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc cggaggggca 1380

aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc tacgacgccc 1440

ttcacatgca ggccctgccc cctcgcggaa gcggagccac caacttcagc ctgctgaagc 1500

aggccggcga cgtggaggag aaccccggcc ccatggcctt accagtgacc gccttgctcc 1560

tgccgctggc cttgctgctc cacgccgcca ggccggatat ccagatgacc cagagcccca 1620

gctccctgtc cgcatccgtg ggcgacagag tgacaattac ctgtagaagc agccaaagca 1680

tcgtgcatag cgtcggcaac acttttctgg agtggtatca acagaagccc gggaaggccc 1740

ccaaactgct gatctacaag gtgagcaaca gattcagcgg ggtcccaagc agattctccg 1800

gcagcggctc cgggactgac ttcaccctga ccattagcag cctgcagcca gaggacttcg 1860

ccacatacta ctgcttccaa gggagccagt tcccctacac cttcggccaa ggcactaagg 1920

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tggagatcaa agggggggga ggaagcggcg gaggagggag cggaggcggg ggatccgaag   1980

tgcaactggt cgaatccgga ggggggctgg tccagcctgg agggtccctg agactgagct   2040

gcgccgcaag cggctacgag ttctccaggt cctggatgaa ctgggtgagg caggccccag   2100

gaaaagggct ggaatgggtg ggcaggatct accctggcga cggcgatacc aactactccg   2160

gaaagttcaa gggcaggttc actatcagcg ccgacactag caagaatacc gcctacctgc   2220

agatgaatag cctgagggcc gaggacaccg ccgtgtatta ctgcgctaga gacggcagca   2280

gctgggattg gtacttcgac gtgtggggcc agggcactct ggtgactgtg agcagcacca   2340

cgacgccagc gccgcgacca ccaacaccgg cgcccaccat cgcgtcgcag cccctgtccc   2400

tgcgcccaga ggcgtgccgg ccagcggcgg ggggcgcagt gcacacgagg gggctggact   2460

tcgcctgtga tatctacatc tgggcgccct tggccgggac ttgtggggtc cttctcctgt   2520

cactggttat cacccttttac tgcaaacggg gcagaaagaa actcctgtat atattcaaac   2580

aaccatttat gagaccagta caaactactc aagaggaaga tggctgtagc tgccgatttc   2640

cagaagaaga agaaggagga tgtgaactga gagtgaagtt cagcaggagc gcagacgccc   2700

ccgcgtacca gcagggccag aaccagctct ataacgagct caatctagga cgaagagagg   2760

agtacgatgt tttggacaag agacgtggcc gggaccctga gatgggggga aagccgagaa   2820

ggaagaaccc tcaggaaggc ctgtacaatg aactgcagaa agataagatg gcggaggcct   2880

acagtgagat tgggatgaaa ggcgagcgcc ggaggggcaa ggggcacgat ggcctttacc   2940

agggtctcag tacagccacc aaggacacct acgacgccct tcacatgcag gccctgcccc   3000

ctcgctaagt ttaaac                                                   3016
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<210> SEQ ID NO 7
<211> LENGTH: 990
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 7

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu
            20                  25                  30

Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr
    50                  55                  60

Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
                85                  90                  95

Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140
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Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly
            420                 425                 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        435                 440                 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
    450                 455                 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465                 470                 475                 480

Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu
                485                 490                 495

Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Ala Leu
            500                 505                 510

Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu His Ala Ala
        515                 520                 525

Arg Pro Asp Val Gln Ile Thr Gln Ser Pro Ser Tyr Leu Ala Ala Ser
    530                 535                 540

Pro Gly Glu Thr Ile Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser
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545                 550                 555                 560

Lys Asp Leu Ala Trp Tyr Gln Glu Lys Pro Gly Lys Thr Asn Lys Leu
                565                 570                 575

Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ser Arg Phe
            580                 585                 590

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
        595                 600                 605

Glu Pro Glu Asp Phe Ala Met Tyr Tyr Cys Gln Gln His Asn Lys Tyr
    610                 615                 620

Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly
625                 630                 635                 640

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu
                645                 650                 655

Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly Ala Ser Val Lys Leu
            660                 665                 670

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Trp Met Asn Trp
        675                 680                 685

Val Lys Gln Arg Pro Asp Gln Gly Leu Glu Trp Ile Gly Arg Ile Asp
    690                 695                 700

Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe Lys Asp Lys Ala
705                 710                 715                 720

Ile Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser
                725                 730                 735

Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Asn
            740                 745                 750

Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Thr
        755                 760                 765

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
    770                 775                 780

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
785                 790                 795                 800

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
                805                 810                 815

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
            820                 825                 830

Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
        835                 840                 845

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
    850                 855                 860

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys
865                 870                 875                 880

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
                885                 890                 895

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
            900                 905                 910

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg
        915                 920                 925

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
    930                 935                 940

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
945                 950                 955                 960
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Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
                965                 970                 975

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
            980                 985                 990


<210> SEQ ID NO 8
<211> LENGTH: 2989
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 8

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc ggacatccag atgacacaga ctacatcctc cctgtctgcc tctctgggag    120

acagagtcac catcagttgc agggcaagtc aggacattag taaatattta aattggtatc    180

agcagaaacc agatggaact gttaaactcc tgatctacca tacatcaaga ttacactcag    240

gagtcccatc aaggttcagt ggcagtgggt ctggaacaga ttattctctc accattagca    300

acctggagca agaagatatt gccacttact tttgccaaca gggtaatacg cttccgtaca    360

cgttcggagg ggggaccaag ctggagatca caggtggcgg tggctcgggc ggtggtgggt    420

cgggtggcgg cggatctgag gtgaaactgc aggagtcagg acctggcctg gtggcgccct    480

cacagagcct gtccgtcaca tgcactgtct caggggtctc attacccgac tatggtgtaa    540

gctggattcg ccagcctcca cgaaagggtc tggagtggct gggagtaata tggggtagtg    600

aaaccacata ctataattca gctctcaaat ccagactgac catcatcaag gacaactcca    660

agagccaagt tttcttaaaa atgaacagtc tgcaaactga tgacacagcc atttactact    720

gtgccaaaca ttattactac ggtggtagct atgctatgga ctactggggc caaggaacct    780

cagtcaccgt ctcctcaacc acgacgccag cgccgcgacc accaacaccg gcgcccacca    840

tcgcgtcgca gcccctgtcc ctgcgcccag aggcgtgccg gccagcggcg gggggcgcag    900

tgcacacgag ggggctggac ttcgcctgtg atatctacat ctgggcgccc ttggccggga    960

cttgtggggt ccttctcctg tcactggtta tcacccttta ctgcaaacgg ggcagaaaga   1020

aactcctgta tatattcaaa caaccattta tgagaccagt acaaactact caagaggaag   1080

atggctgtag ctgccgattt ccagaagaag aagaaggagg atgtgaactg agagtgaagt   1140

tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc tataacgagc   1200

tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc cgggaccctg   1260

agatgggggg aaagccgcag agaaggaaga accctcagga aggcctgtac aatgaactgc   1320

agaaagataa gatggcggag gcctacagtg agattgggat gaaaggcgag cgccggaggg   1380

gcaaggggca cgatggcctt taccagggtc tcagtacagc caccaaggac acctacgacg   1440

cccttcacat gcaggccctg ccccctcgcg gaagcggagc caccaacttc agcctgctga   1500

agcaggccgg cgacgtggag gagaaccccg gccccatggc cttaccagtg accgccttgc   1560

tcctgccgct ggccttgctg ctccacgccg ccaggccgga cgtgcagatc acccagagcc   1620

ccagctacct ggccgccagc cccggcgaga ccatcaccat caactgcaga gccagcaaga   1680

gcatcagcaa ggacctggcc tggtaccagg agaagcccgg caagaccaac aagctgctga   1740

tctacagcgg cagcaccctg cagagcggca tccccagcag attcagcggc agcggcagcg   1800
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gcaccgactt caccctgacc atcagcagcc tggagcccga ggacttcgcc atgtactact   1860

gccagcagca caacaagtac ccctacacct tcggcggcgg caccaagctg gagatcaagg   1920

gagggggggg atccggggga ggaggctccg gcggaggcgg aagccaggtg cagctgcagc   1980

agcccggcgc cgagctggtg agacccggcg ccagcgtgaa gctgagctgc aaggccagcg   2040

gctacacctt caccagctac tggatgaact gggtgaagca gagacccgac cagggcctgg   2100

agtggatcgg cagaatcgac ccctacgaca gcgagaccca ctacaaccag aagttcaagg   2160

acaaggccat cctgaccgtg gacaagagca gcagcaccgc ctacatgcag ctgagcagcc   2220

tgaccagcga ggacagcgcc gtgtactact gcgccagagg caactgggac gactactggg   2280

gccagggcac caccctgacc gtgagcagca ccacgacgcc agcgccgcga ccaccaacac   2340

cggcgcccac catcgcgtcg cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg   2400

cgggggcgc agtgcacacg agggggctgg acttcgcctg tgatatctac atctgggcgc   2460

ccttggccgg gacttgtggg gtccttctcc tgtcactggt tatcaccctt tactgcagga   2520

gtaagaggag caggctcctg cacagtgact acatgaacat gactccccgc cgccccgggc   2580

ccacccgcaa gcattaccag ccctatgccc caccacgcga cttcgcagcc tatcgctcca   2640

gagtgaagtt cagcaggagc gcagacgccc ccgcgtacca gcagggccag aaccagctct   2700

ataacgagct caatctagga cgaagagagg agtacgatgt tttggacaag agacgtggcc   2760

gggaccctga gatgggggga aagccgcaga gaaggaagaa ccctcaggaa ggcctgtaca   2820

atgaactgca gaaagataag atggcggagg cctacagtga gattgggatg aaaggcgagc   2880

gccggagggg caaggggcac gatggccttt accagggtct cagtacagcc accaaggaca   2940

cctacgacgc ccttcacatg caggccctgc cccctcgcta agtttaaac               2989
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<210> SEQ ID NO 9
<211> LENGTH: 1066
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 9

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met
            20                  25                  30

Ser Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser
        35                  40                  45

Ser Ile Ser Tyr Met His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro
    50                  55                  60

Lys Leu Trp Ile Tyr Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser
                85                  90                  95

Arg Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Arg Ser
            100                 105                 110

Thr Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Leu Lys Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
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    130                 135                 140

Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val
145                 150                 155                 160

Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met
                165                 170                 175

His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
            180                 185                 190

Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe Lys Asp
        195                 200                 205

Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln
    210                 215                 220

Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg
225                 230                 235                 240

Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
                245                 250                 255

Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
            260                 265                 270

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
        275                 280                 285

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
    290                 295                 300

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
305                 310                 315                 320

Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His
                325                 330                 335

Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys
            340                 345                 350

His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        355                 360                 365

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
    370                 375                 380

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
385                 390                 395                 400

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
                405                 410                 415

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
            420                 425                 430

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
        435                 440                 445

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
    450                 455                 460

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
465                 470                 475                 480

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
                485                 490                 495

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
            500                 505                 510

Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn
        515                 520                 525

Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro
    530                 535                 540
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Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
545                 550                 555                 560

His Ala Ala Arg Pro Asp Val Gln Ile Thr Gln Ser Pro Ser Tyr Leu
                565                 570                 575

Ala Ala Ser Pro Gly Glu Thr Ile Thr Ile Asn Cys Arg Ala Ser Lys
            580                 585                 590

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Glu Lys Pro Gly Lys Thr
        595                 600                 605

Asn Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro
    610                 615                 620

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
625                 630                 635                 640

Ser Ser Leu Glu Pro Glu Asp Phe Ala Met Tyr Tyr Cys Gln Gln His
                645                 650                 655

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            660                 665                 670

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
        675                 680                 685

Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly Ala Ser
    690                 695                 700

Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Trp
705                 710                 715                 720

Met Asn Trp Val Lys Gln Arg Pro Asp Gln Gly Leu Glu Trp Ile Gly
                725                 730                 735

Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe Lys
            740                 745                 750

Asp Lys Ala Ile Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met
        755                 760                 765

Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala
    770                 775                 780

Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
785                 790                 795                 800

Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
                805                 810                 815

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
            820                 825                 830

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
        835                 840                 845

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
    850                 855                 860

Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His
865                 870                 875                 880

Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys
                885                 890                 895

His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
            900                 905                 910

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
        915                 920                 925

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
    930                 935                 940
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Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
945                 950                 955                 960

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
                965                 970                 975

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
            980                 985                 990

Arg Gly Arg Asp Pro Glu Met Gly  Gly Lys Pro Arg Arg  Lys Asn Pro
        995                 1000                1005

Gln Glu  Gly Leu Tyr Asn Glu  Leu Gln Lys Asp Lys  Met Ala Glu
    1010                1015                1020

Ala Tyr  Ser Glu Ile Gly Met  Lys Gly Glu Arg Arg  Arg Gly Lys
    1025                1030                1035

Gly His  Asp Gly Leu Tyr Gln  Gly Leu Ser Thr Ala  Thr Lys Asp
    1040                1045                1050

Thr Tyr  Asp Ala Leu His Met  Gln Ala Leu Pro Pro  Arg
    1055                1060                1065


<210> SEQ ID NO 10
<211> LENGTH: 3217
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 10

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc gcagatcgtg ctgacccaga gccccgccat catgagcgcc agccccggcg    120

agaaggtgac catcacctgc agcgccagca gcagcatcag ctacatgcac tggttccagc    180

agaagcccgg caccagcccc aagctgtgga tctacaccac cagcaacctg gccagcggcg    240

tgcccgccag attcagcggc agcggcagcg gcaccagcta cagcctgacc atcagcagaa    300

tggaggccga ggacgccgcc acctactact gccaccagag aagcacctac cccctgacct    360

tcggcagcgg caccaagctg gagctgaagg gagggggggg atccggggga ggaggctccg    420

gcggaggcgg aagccaggtg cagctgcagc agagcggcgc cgagctggcc aagcccggcg    480

ccagcgtgaa gatgagctgc aaggccagcg gctacacctt caccagctac agaatgcact    540

gggtgaagca gagacccggc cagggcctgg agtggatcgg ctacatcaac cccagcaccg    600

gctacaccga gtacaaccag aagttcaagg acaaggccac cctgaccgcc gacaagagca    660

gcagcaccgc ctacatgcag ctgagcagcc tgaccttcga ggacagcgcc gtgtactact    720

gcgccagagg cggcggcgtg ttcgactact ggggccaggg caccaccctg accgtgagca    780

gcaccacgac gccagcgccg cgaccaccaa caccggcgcc caccatcgcg tcgcagcccc    840

tgtccctgcg cccagaggcg tgccggccag cggcgggggg cgcagtgcac acgagggggc    900

tggacttcgc ctgtgatatc tacatctggg cgcccttggc cgggacttgt ggggtccttc    960

tcctgtcact ggttatcacc ctttactgca ggagtaagag gagcaggctc ctgcacagtg   1020

actacatgaa catgactccc cgccgccccg ggcccacccg caagcattac cagccctatg   1080

ccccaccacg cgacttcgca gcctatcgct ccaaacgggg cagaaagaaa ctcctgtata   1140

tattcaaaca accatttatg agaccagtac aaactactca agaggaagat ggctgtagct   1200

gccgatttcc agaagaagaa gaaggaggat gtgaactgag agtgaagttc agcaggagcg   1260
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cagacgcccc cgcgtacaag cagggccaga accagctcta taacgagctc aatctaggac   1320
gaagagagga gtacgatgtt ttggacaaga gacgtggccg ggaccctgag atgggggaa   1380
agccgagaag gaagaaccct caggaaggcc tgtacaatga actgcagaaa gataagatgg   1440
cggaggccta cagtgagatt gggatgaaag gcgagcgccg gaggggcaag gggcacgatg   1500
gcctttacca gggtctcagt acagccacca aggacaccta cgacgccctt cacatgcagg   1560
ccctgccccc tcgcggaagc ggagctacta acttcagcct gctgaagcag gctggagacg   1620
tggaggagaa ccctggacct atggccttac cagtgaccgc cttgctcctg ccgctggcct   1680
tgctgctcca cgccgccagg ccggacgtgc agatcaccca gagccccagc tacctggccg   1740
ccagccccgg cgagaccatc accatcaact gcagagccag caagagcatc agcaaggacc   1800
tggcctggta ccaggagaag cccggcaaga ccaacaagct gctgatctac agcggcagca   1860
ccctgcagag cggcatcccc agcagattca gcggcagcgg cagcggcacc gacttcaccc   1920
tgaccatcag cagcctggag cccgaggact tcgccatgta ctactgccag cagcacaaca   1980
agtaccccta caccttcggc ggcggcacca agctggagat caagggaggg gggggatccg   2040
ggggaggagg ctccggcgga ggcggaagcc aggtgcagct gcagcagccc ggcgccgagc   2100
tggtgagacc cggcgccagc gtgaagctga gctgcaaggc cagcggctac accttcacca   2160
gctactggat gaactgggtg aagcagagac ccgaccaggg cctggagtgg atcggcagaa   2220
tcgaccccta cgacagcgag acccactaca accagaagtt caaggacaag gccatcctga   2280
ccgtggacaa gagcagcagc accgcctaca tgcagctgag cagcctgacc agcgaggaca   2340
gcgccgtgta ctactgcgcc agaggcaact gggacgacta ctggggccag ggcaccaccc   2400
tgaccgtgag cagcaccacg acgccagcgc cgcgaccacc aacaccggcg cccaccatcg   2460
cgtcgcagcc cctgtccctg cgcccagagg cgtgccggcc agcggcgggg ggcgcagtgc   2520
acacgagggg gctggacttc gcctgtgata tctacatctg ggcgcccttg gccgggactt   2580
gtggggtcct tctcctgtca ctggttatca ccctttactg caggagtaag aggagcaggc   2640
tcctgcacag tgactacatg aacatgactc cccgccgccc cgggcccacc cgcaagcatt   2700
accagcccta tgccccacca cgcgacttcg cagcctatcg ctccaaacgg ggcagaaaga   2760
aactcctgta tatattcaaa caaccattta tgagaccagt acaaactact caagaggaag   2820
atggctgtag ctgccgattt ccagaagaag aagaaggagg atgtgaactg agagtgaagt   2880
tcagcaggag cgcagacgcc cccgcgtaca agcagggcca gaaccagctc tataacgagc   2940
tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc cgggaccctg   3000
agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat gaactgcaga   3060
aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc cggaggggca   3120
aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc tacgacgccc   3180
ttcacatgca ggccctgccc cctcgctaag tttaaac                            3217
```

<210> SEQ ID NO 11
<211> LENGTH: 985
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 11

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```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met
            20                  25                  30

Ser Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser
        35                  40                  45

Ser Ile Ser Tyr Met His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro
    50                  55                  60

Lys Leu Trp Ile Tyr Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser
                85                  90                  95

Arg Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Arg Ser
            100                 105                 110

Thr Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Leu Lys Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
    130                 135                 140

Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val
145                 150                 155                 160

Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met
                165                 170                 175

His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
            180                 185                 190

Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe Lys Asp
        195                 200                 205

Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln
    210                 215                 220

Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg
225                 230                 235                 240

Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
                245                 250                 255

Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
            260                 265                 270

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
        275                 280                 285

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
    290                 295                 300

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
305                 310                 315                 320

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
                325                 330                 335

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
            340                 345                 350

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
        355                 360                 365

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
    370                 375                 380

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
385                 390                 395                 400

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
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                405                 410                 415

Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
            420                 425                 430

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
        435                 440                 445

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
    450                 455                 460

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465                 470                 475                 480

Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly
                485                 490                 495

Asp Val Glu Glu Asn Pro Gly Pro Met Ala Leu Pro Val Thr Ala Leu
            500                 505                 510

Leu Leu Pro Leu Ala Leu Leu Leu His Ala Ala Arg Pro Asp Val Gln
        515                 520                 525

Ile Thr Gln Ser Pro Ser Tyr Leu Ala Ala Ser Pro Gly Glu Thr Ile
    530                 535                 540

Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp
545                 550                 555                 560

Tyr Gln Glu Lys Pro Gly Lys Thr Asn Lys Leu Leu Ile Tyr Ser Gly
                565                 570                 575

Ser Thr Leu Gln Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser
            580                 585                 590

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe
        595                 600                 605

Ala Met Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly
    610                 615                 620

Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly
625                 630                 635                 640

Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Pro Gly Ala
                645                 650                 655

Glu Leu Val Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser
            660                 665                 670

Gly Tyr Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro
        675                 680                 685

Asp Gln Gly Leu Glu Trp Ile Gly Arg Ile Asp Pro Tyr Asp Ser Glu
    690                 695                 700

Thr His Tyr Asn Gln Lys Phe Lys Asp Lys Ala Ile Leu Thr Val Asp
705                 710                 715                 720

Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu
                725                 730                 735

Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp
            740                 745                 750

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Thr Thr Thr Pro Ala Pro
        755                 760                 765

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
    770                 775                 780

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
785                 790                 795                 800

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
                805                 810                 815
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Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg
            820                 825                 830

Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro
        835                 840                 845

Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
    850                 855                 860

Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala
865                 870                 875                 880

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
                885                 890                 895

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
            900                 905                 910

Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln
        915                 920                 925

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
    930                 935                 940

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
945                 950                 955                 960

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
                965                 970                 975

Leu His Met Gln Ala Leu Pro Pro Arg
            980                 985


<210> SEQ ID NO 12
<211> LENGTH: 2974
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 12

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc gcagatcgtg ctgacccaga gccccgccat catgagcgcc agccccggcg    120

agaaggtgac catcacctgc agcgccagca gcagcatcag ctacatgcac tggttccagc    180

agaagcccgg caccagcccc aagctgtgga tctacaccac cagcaacctg gccagcggcg    240

tgcccgccag attcagcggc agcggcagcg gcaccagcta cagcctgacc atcagcagaa    300

tggaggccga ggacgccgcc acctactact gccaccagag aagcacctac cccctgacct    360

tcggcagcgg caccaagctg gagctgaagg gagggggggg atccggggga ggaggctccg    420

gcggaggcgg aagccaggtg cagctgcagc agagcggcgc cgagctggcc aagcccggcg    480

ccagcgtgaa gatgagctgc aaggccagcg gctacacctt caccagctac agaatgcact    540

gggtgaagca gagacccggc cagggcctgg agtggatcgg ctacatcaac cccagcaccg    600

gctacaccga gtacaaccag aagttcaagg acaaggccac cctgaccgcc gacaagagca    660

gcagcaccgc ctacatgcag ctgagcagcc tgaccttcga ggacagcgcc gtgtactact    720

gcgccagagg cggcggcgtg ttcgactact ggggccaggg caccaccctg accgtgagca    780

gcaccacgac gccagcgccg cgaccaccaa caccggcgcc caccatcgcg tcgcagcccc    840

tgtccctgcg cccagaggcg tgccggccag cggcgggggg cgcagtgcac acgagggggc    900

tggacttcgc ctgtgatatc tacatctggg cgcccttggc cgggacttgt ggggtccttc    960
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tcctgtcact ggttatcacc ctttactgca aacggggcag aaagaaactc ctgtatatat   1020
tcaaacaacc atttatgaga ccagtacaaa ctactcaaga ggaagatggc tgtagctgcc   1080
gatttccaga agaagaagaa ggaggatgtg aactgagagt gaagttcagc aggagcgcag   1140
acgcccccgc gtaccagcag ggccagaacc agctctataa cgagctcaat ctaggacgaa   1200
gagaggagta cgatgttttg gacaagagac gtggccggga ccctgagatg gggggaaagc   1260
cgcagagaag gaagaaccct caggaaggcc tgtacaatga actgcagaaa gataagatgg   1320
cggaggccta cagtgagatt gggatgaaag gcgagcgccg gaggggcaag gggcacgatg   1380
gcctttacca gggtctcagt acagccacca aggacaccta cgacgccctt cacatgcagg   1440
ccctgccccc tcgcggaagc ggagctacta acttcagcct gctgaagcag gctggagacg   1500
tggaggagaa ccctggacct atggccttac cagtgaccgc cttgctcctg ccgctggcct   1560
tgctgctcca cgccgccagg ccggacgtgc agatcaccca gagccccagc tacctggccg   1620
ccagccccgg cgagaccatc accatcaact gcagagccag caagagcatc agcaaggacc   1680
tggcctggta ccaggagaag cccggcaaga ccaacaagct gctgatctac agcggcagca   1740
ccctgcagag cggcatcccc agcagattca gcggcagcgg cagcggcacc gacttcaccc   1800
tgaccatcag cagcctggag cccgaggact tcgccatgta ctactgccag cagcacaaca   1860
agtaccccta caccttcggc ggcggcacca agctggagat caagggaggg gggggatccg   1920
ggggaggagg ctccggcgga ggcggaagcc aggtgcagct gcagcagccc ggcgccgagc   1980
tggtgagacc cggcgccagc gtgaagctga gctgcaaggc cagcggctac accttcacca   2040
gctactggat gaactgggtg aagcagagac ccgaccaggg cctggagtgg atcggcagaa   2100
tcgaccccta cgacagcgag acccactaca accagaagtt caaggacaag gccatcctga   2160
ccgtggacaa gagcagcagc accgcctaca tgcagctgag cagcctgacc agcgaggaca   2220
gcgccgtgta ctactgcgcc agaggcaact gggacgacta ctggggccag ggcaccaccc   2280
tgaccgtgag cagcaccacg acgccagcgc cgcgaccacc aacaccggcg cccaccatcg   2340
cgtcgcagcc cctgtccctg cgcccagagg cgtgccggcc agcggcgggg ggcgcagtgc   2400
acacgagggg gctggacttc gcctgtgata tctacatctg ggcgcccttg gccgggactt   2460
gtggggtcct tctcctgtca ctggttatca ccctttactg caggagtaag aggagcaggc   2520
tcctgcacag tgactacatg aacatgactc cccgccgccc cgggcccacc cgcaagcatt   2580
accagcccta tgccccacca cgcgacttcg cagcctatcg ctccagagtg aagttcagca   2640
ggagcgcaga cgcccccgcg taccagcagg gccagaacca gctctataac gagctcaatc   2700
taggacgaag agaggagtac gatgttttgg acaagagacg tggccgggac cctgagatgg   2760
ggggaaagcc gcagagaagg aagaaccctc aggaaggcct gtacaatgaa ctgcagaaag   2820
ataagatggc ggaggcctac agtgagattg ggatgaaagg cgagcgccgg aggggcaagg   2880
ggcacgatgg cctttaccag ggtctcagta cagccaccaa ggacacctac gacgcccttc   2940
acatgcaggc cctgccccct cgctaagttt aaac                               2974
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<210> SEQ ID NO 13
<211> LENGTH: 546
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

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<400> SEQUENCE: 13

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Ser Asp Ile Val Leu Thr Gln Ser Pro Ala Ser
20 25 30

Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser
35 40 45

Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln
50 55 60

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu
65 70 75 80

Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
85 90 95

Phe Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr
100 105 110

Tyr Cys Gln His Ser Arg Glu Leu Pro Phe Thr Phe Gly Ser Gly Thr
115 120 125

Lys Leu Glu Ile Lys Lys Ile Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
165 170 175

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg
180 185 190

Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
195 200 205

Ile Gly Glu Ile Asn Pro Thr Ser Ser Thr Ile Asn Phe Thr Pro Ser
210 215 220

Leu Lys Asp Lys Val Phe Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu
225 230 235 240

Tyr Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr Ala Leu Tyr Tyr
245 250 255

Cys Ala Arg Gly Asn Tyr Tyr Arg Tyr Gly Asp Ala Met Asp Tyr Trp
260 265 270

Gly Gln Gly Thr Ser Val Thr Val Ser Thr Thr Thr Pro Ala Pro Arg
275 280 285

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
290 295 300

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
305 310 315 320

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
325 330 335

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser
340 345 350

Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
355 360 365

Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
370 375 380

Asp Phe Ala Ala Tyr Arg Ser Lys Arg Gly Arg Lys Lys Leu Leu Tyr
385 390 395 400

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Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
                405                 410                 415

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
            420                 425                 430

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
        435                 440                 445

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
    450                 455                 460

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
465                 470                 475                 480

Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
                485                 490                 495

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
            500                 505                 510

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
        515                 520                 525

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
    530                 535                 540

Pro Arg
545


<210> SEQ ID NO 14
<211> LENGTH: 1657
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 14

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc gagcgacatc gtgctgaccc agagccccgc cagcctggcc gtgagcctgg    120

gccagagagc caccatcagc tgcagagcca gcaagagcgt gagcaccagc ggctacagct    180

acctgcactg gtaccagcag aagcccggcc agccccccaa gctgctgatc tacctggcca    240

gcaacctgga gagcggcgtg cccgccagat tcagcggcag cggcagcggc accgacttca    300

ccctgaacat ccaccccgtg gaggaggagg acgccgccac ctactactgc cagcacagca    360

gagagctgcc cttcaccttc ggcagcggca ccaagctgga gatcaagaag atcagcggcg    420

gcggcggcag cggcggcggc ggcagcggcg gcggcggcag cggcggcggc ggcagcggcg    480

gcggcggcag ccaggtgcag ctggtggaga gcggcggcgg cctggtgcag cccggcggca    540

gcctgaagct gagctgcgcc gccagcggct tcgacttcag cagatactgg atgagctggg    600

tgagacaggc ccccggcaag ggcctggagt ggatcggcga gatcaacccc accagcagca    660

ccatcaactt cacccccagc ctgaaggaca aggtgttcat cagcagagac aacgccaaga    720

acaccctgta cctgcagatg agcaaggtga gaagcgagga caccgccctg tactactgcg    780

ccagaggcaa ctactacaga tacggcgacg ccatggacta ctggggccag ggcaccagcg    840

tgaccgtgag caccacgacg ccagcgccgc gaccaccaac accggcgccc accatcgcgt    900

cgcagcccct gtccctgcgc ccagaggcgt gccggccagc ggcgggggc gcagtgcaca    960

cgagggggct ggacttcgcc tgtgatatct acatctgggc gcccttggcc gggacttgtg   1020

gggtccttct cctgtcactg gttatcaccc tttactgcag gagtaagagg agcaggctcc   1080
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tgcacagtga ctacatgaac atgactcccc gccgccccgg gcccacccgc aagcattacc   1140

agccctatgc cccaccacgc gacttcgcag cctatcgctc caaacggggc agaaagaaac   1200

tcctgtatat attcaaacaa ccatttatga gaccagtaca aactactcaa gaggaagatg   1260

gctgtagctg ccgatttcca gaagaagaag aaggaggatg tgaactgaga gtgaagttca   1320

gcaggagcgc agacgccccc gcgtaccagc agggccagaa ccagctctat aacgagctca   1380

atctaggacg aagagaggag tacgatgttt tggacaagag acgtggccgg gaccctgaga   1440

tgggggggaaa gccgcagaga aggaagaacc ctcaggaagg cctgtacaat gaactgcaga   1500

aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc cggaggggca   1560

aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc tacgacgccc   1620

ttcacatgca ggccctgccc cctcgctaag tttaaac                            1657
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<210> SEQ ID NO 15
<211> LENGTH: 490
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 15

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
            20                  25                  30

Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys
        35                  40                  45

Ser Val Ser Thr Ser Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu
65                  70                  75                  80

Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr
            100                 105                 110

Cys Gln His Ser Arg Glu Leu Pro Phe Thr Phe Gly Ser Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
145                 150                 155                 160

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe
                165                 170                 175

Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
            180                 185                 190

Glu Trp Ile Gly Glu Ile Asn Pro Thr Ser Ser Thr Ile Asn Phe Thr
        195                 200                 205

Pro Ser Leu Lys Asp Lys Val Phe Ile Ser Arg Asp Asn Ala Lys Asn
    210                 215                 220

Thr Leu Tyr Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr Ala Leu
225                 230                 235                 240
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Tyr Tyr Cys Ala Arg Gly Asn Tyr Tyr Arg Tyr Gly Asp Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
            340                 345                 350

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
        355                 360                 365

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser
    370                 375                 380

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385                 390                 395                 400

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
                405                 410                 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> SEQ ID NO 16
<211> LENGTH: 1489
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 16

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg      60

ccgccaggcc ggacatcgtg ctgacccaga gccccgccag cctggccgtg agcctgggcc     120

agagggccac catcagctgc agggccagca agagcgtgag caccagcggc tacagctacc     180

tgcactggta ccagcagaag cccggccagc cccccaagct gctgatctac ctggccagca     240

acctggagag cggcgtgccc gccaggttca gcggcagcgg cagcggcacc gacttcaccc     300

tgaacatcca ccccgtggag gaggaggacg ccgccaccta ctactgccag cacagcaggg     360

agctgccctt caccttcggc agcggcacca agctggagat caagggaggg gggggatccg     420

ggggaggagg ctccggcgga ggcggaagcc aggtgcagct ggtggagagc ggcggcggcc     480

tggtgcagcc cggcggcagc ctgaagctga gctgcgccgc cagcggcttc gacttcagca     540
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ggtactggat gagctgggtg aggcaggccc ccggcaaggg cctggagtgg atcggcgaga    600

tcaaccccac cagcagcacc atcaacttca cccccagcct gaaggacaag gtgttcatca    660

gcagggacaa cgccaagaac accctgtacc tgcagatgag caaggtgagg agcgaggaca    720

ccgccctgta ctactgcgcc aggggcaact actacaggta cggcgacgcc atggactact    780

ggggccaggg caccagcgtg accgtgagca ccacgacgcc agcgccgcga ccaccaacac    840

cggcgcccac catcgcgtcg cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg    900

cgggggggcgc agtgcacacg agggggctgg acttcgcctg tgatatctac atctgggcgc    960

ccttggccgg gacttgtggg gtccttctcc tgtcactggt tatcaccctt tactgcagga   1020

gtaagaggag caggctcctg cacagtgact acatgaacat gactccccgc cgccccgggc   1080

ccacccgcaa gcattaccag ccctatgccc caccacgcga cttcgcagcc tatcgctcca   1140

gagtgaagtt cagcaggagc gcagacgccc ccgcgtacca gcagggccag aaccagctct   1200

ataacgagct caatctagga cgaagagagg agtacgatgt tttggacaag agacgtggcc   1260

gggaccctga gatgggggga aagccgcaga gaaggaagaa ccctcaggaa ggcctgtaca   1320

atgaactgca gaaagataag atggcggagg cctacagtga gattgggatg aaaggcgagc   1380

gccggagggg caaggggcac gatggccttt accagggtct cagtacagcc accaaggaca   1440

cctacgacgc ccttcacatg caggccctgc cccctcgcta agtttaaac               1489
```

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<210> SEQ ID NO 17
<211> LENGTH: 491
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 17

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
            20                  25                  30

Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys
        35                  40                  45

Ser Val Ser Thr Ser Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu
65                  70                  75                  80

Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr
            100                 105                 110

Cys Gln His Ser Arg Glu Leu Pro Phe Thr Phe Gly Ser Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
145                 150                 155                 160

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe
                165                 170                 175

Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
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            180                 185                 190

Glu Trp Ile Gly Glu Ile Asn Pro Thr Ser Ser Thr Ile Asn Phe Thr
        195                 200                 205

Pro Ser Leu Lys Asp Lys Val Phe Ile Ser Arg Asp Asn Ala Lys Asn
    210                 215                 220

Thr Leu Tyr Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr Ala Leu
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Gly Asn Tyr Tyr Arg Tyr Gly Asp Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> SEQ ID NO 18
<211> LENGTH: 1492
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 18

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg      60

ccgccaggcc ggacatcgtg ctgacccaga gccccgccag cctggccgtg agcctgggcc     120

agagggccac catcagctgc agggccagca agagcgtgag caccagcggc tacagctacc     180

tgcactggta ccagcagaag cccggccagc cccccaagct gctgatctac ctggccagca     240
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acctggagag cggcgtgccc gccaggttca gcggcagcgg cagcggcacc gacttcaccc    300

tgaacatcca ccccgtggag gaggaggacg ccgccaccta ctactgccag cacagcaggg    360

agctgccctt caccttcggc agcggcacca agctggagat caagggaggg gggggatccg    420

ggggaggagg ctccggcgga ggcggaagcc aggtgcagct ggtggagagc ggcggcggcc    480

tggtgcagcc cggcggcagc ctgaagctga gctgcgccgc cagcggcttc gacttcagca    540

ggtactggat gagctgggtg aggcaggccc ccggcaaggg cctggagtgg atcggcgaga    600

tcaaccccac cagcagcacc atcaacttca cccccagcct gaaggacaag gtgttcatca    660

gcagggacaa cgccaagaac accctgtacc tgcagatgag caaggtgagg agcgaggaca    720

ccgccctgta ctactgcgcc aggggcaact actacaggta cggcgacgcc atggactact    780

ggggccaggg caccagcgtg accgtgagca ccacgacgcc agcgccgcga ccaccaacac    840

cggcgcccac catcgcgtcg cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg    900

cgggggcgcc agtgcacacg agggggctgg acttcgcctg tgatatctac atctgggcgc    960

ccttggccgg gacttgtggg gtccttctcc tgtcactggt tatcaccctt tactgcaaac   1020

ggggcagaaa gaaactcctg tatatattca aacaaccatt tatgagacca gtacaaacta   1080

ctcaagagga agatggctgt agctgccgat ttccagaaga agaagaagga ggatgtgaac   1140

tgagagtgaa gttcagcagg agcgcagacg cccccgcgta ccagcagggc cagaaccagc   1200

tctataacga gctcaatcta ggacgaagag aggagtacga tgttttggac aagagacgtg   1260

gccgggaccc tgagatgggg ggaaagccgc agagaaggaa gaaccctcag gaaggcctgt   1320

acaatgaact gcagaaagat aagatggcgg aggcctacag tgagattggg atgaaaggcg   1380

agcgccggag gggcaagggg cacgatggcc tttaccaggg tctcagtaca gccaccaagg   1440

acacctacga cgcccttcac atgcaggccc tgccccctcg ctaagtttaa ac           1492
```

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<210> SEQ ID NO 19
<211> LENGTH: 997
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 19

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser His Arg Phe Met
            20                  25                  30

Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln
        35                  40                  45

Asp Val Asn Thr Ala Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser
    50                  55                  60

Pro Lys Leu Leu Ile Phe Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro
65                  70                  75                  80

Asp Arg Phe Thr Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125
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Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Ile Gln Leu Val Gln Ser Gly Pro Asp Leu Lys Lys Pro Gly Glu Thr
145                 150                 155                 160

Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Phe Gly
                165                 170                 175

Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Phe Lys Trp Met Ala
            180                 185                 190

Trp Ile Asn Thr Thr Arg Tyr Thr Gly Glu Ser Tyr Phe Ala Asp Asp
        195                 200                 205

Phe Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Thr Thr Ala
    210                 215                 220

Tyr Leu Gln Ile Asn Asn Leu Lys Thr Glu Asp Thr Ala Thr Tyr Phe
225                 230                 235                 240

Cys Ala Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Gly Gly Phe Ala Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr
                485                 490                 495

Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly
            500                 505                 510

Pro Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
        515                 520                 525
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His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
    530                 535                 540

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln
545                 550                 555                 560

Asp Val Gly Ile Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val
                565                 570                 575

Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro
            580                 585                 590

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
        595                 600                 605

Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr
    610                 615                 620

Ser Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
625                 630                 635                 640

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
                645                 650                 655

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
            660                 665                 670

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr Trp
        675                 680                 685

Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
    690                 695                 700

Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Ala Pro Ser Leu Lys
705                 710                 715                 720

Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
                725                 730                 735

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
            740                 745                 750

Arg Pro Asp Gly Asn Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr
        755                 760                 765

Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
    770                 775                 780

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
785                 790                 795                 800

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
                805                 810                 815

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
            820                 825                 830

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg Ser
        835                 840                 845

Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
    850                 855                 860

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
865                 870                 875                 880

Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
                885                 890                 895

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
            900                 905                 910

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
        915                 920                 925

Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
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    930                 935                 940

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
945                 950                 955                 960

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
                965                 970                 975

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
            980                 985                 990

Ala Leu Pro Pro Arg
        995


<210> SEQ ID NO 20
<211> LENGTH: 2994
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 20

atggccttac cagtgaccgc cttgctcctg ccgctggcct tgctgctcca cgccgccagg     60

ccggatgtgg tgatgaccca gagccatcgc tttatgagca ccagcgtggg cgatcgcgtg    120

agcattacct gccgcgcgag ccaggatgtg aacaccgcgg tgagctggta tcagcagaaa    180

ccgggccaga gcccgaaact gctgattttt agcgcgagct atcgctatac cggcgtgccg    240

gatcgcttta ccggcagcgg cagcggcgcg gattttaccc tgaccattag cagcgtgcag    300

gcggaagatc tggcggtgta ttattgccag cagcattata gcaccccgtg gacctttggc    360

ggcggcacca aactggaaat taaaggaggg gggggatccg ggggaggagg ctccggcgga    420

ggcggaagcc agattcagct ggtgcagagc ggcccggatc tgaaaaaacc gggcgaaacc    480

gtgaaactga gctgcaaagc gagcggctat acctttacca actttggcat gaactgggtg    540

aaacaggcgc cgggcaaagg ctttaaatgg atggcgtgga ttaacaccac ccgctatacc    600

ggcgaaagct attttgcgga tgattttaaa ggccgctttg cgtttagcgt ggaaaccagc    660

gcgaccaccg cgtatctgca gattaacaac ctgaaaaccg aagataccgc gacctatttt    720

tgcgcgcgcg gcgaaattta ttatggctat gatggcggct ttgcgtattg gggccagggc    780

accctggtga ccgtgagcgc gaccacgacg ccagcgccgc gaccaccaac accggcgccc    840

accatcgcgt cgcagcccct gtccctgcgc ccagaggcgt gccggccagc ggcgggggc    900

gcagtgcaca cgagggggct ggacttcgcc tgtgatatct acatctgggc gcccttggcc    960

gggacttgtg gggtccttct cctgtcactg gttatcaccc tttactgcaa acggggcaga   1020

aagaaactcc tgtatatatt caaacaacca tttatgagac cagtacaaac tactcaagag   1080

gaagatggct gtagctgccg atttccagaa gaagaagaag gaggatgtga actgagagtg   1140

aagttcagca ggagcgcaga cgcccccgcg taccagcagg gccagaacca gctctataac   1200

gagctcaatc taggacgaag agaggagtac gatgttttgg acaagagacg tggccgggac   1260

cctgagatgg ggggaaagcc gcagagaagg aagaaccctc aggaaggcct gtacaatgaa   1320

ctgcagaaag ataagatggc ggaggcctac agtgagattg ggatgaaagg cgagcgccgg   1380

aggggcaagg ggcacgatgg cctttaccag ggtctcagta cagccaccaa ggacacctac   1440

gacgcccttc acatgcaggc cctgccccct cgcggaagcg gagccaccaa cttcagcctg   1500

ctgaagcagg ccggcgacgt ggaggagaac cccggccccg ccttaccagt gaccgccttg   1560
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ctcctgccgc tggccttgct gctccacgcc gccaggccgg atattcagat gacccagagc   1620

ccgagcagcc tgagcgcgag cgtgggcgat cgcgtgacca ttacctgcaa agcgagccag   1680

gatgtgggca ttgcggtggc gtggtatcag cagaaaccgg gcaaagtgcc gaaactgctg   1740

atttattggg cgagcacccg ccataccggc gtgccggatc gctttagcgg cagcggcagc   1800

ggcaccgatt ttaccctgac cattagcagc ctgcagccgg aagatgtggc gacctattat   1860

tgccagcagt atagcagcta tccgtatacc tttggccagg gcaccaaagt ggaaattaaa   1920

ggagggggg gatccggggg aggaggctcc ggcggaggcg gaagcgaagt gcagctggtg   1980

gaaagcggcg gcggcctggt gcagccgggc ggcagcctgc gcctgagctg cgcggcgagc   2040

ggctttgatt ttagccgcta ttggatgagc tgggtgcgcc aggcgccggg caaaggcctg   2100

gaatggattg gcgaaattaa cccggatagc agcaccatta actatgcgcc gagcctgaaa   2160

gataaattta ttattagccg cgataacgcg aaaaacagcc tgtatctgca gatgaacagc   2220

ctgcgcgcgg aagataccgc ggtgtattat tgcgcgcgcc cggatggcaa ctattggtat   2280

tttgatgtgt ggggccaggg caccctggtg accgtgagca gcaccacgac gccagcgccg   2340

cgaccaccaa caccggcgcc caccatcgcg tcgcagcccc tgtccctgcg cccagaggcg   2400

tgccggccag cggcgggggg cgcagtgcac acgagggggc tggacttcgc ctgtgatatc   2460

tacatctggg cgcccttggc cgggacttgt ggggtccttc tcctgtcact ggttatcacc   2520

ctttactgca ggagtaagag gagcaggctc ctgcacagtg actacatgaa catgactccc   2580

cgccgccccg ggcccacccg caagcattac cagccctatg ccccaccacg cgacttcgca   2640

gcctatcgct ccagagtgaa gttcagcagg agcgcagacg cccccgcgta ccagcagggc   2700

cagaaccagc tctataacga gctcaatcta ggacgaagag aggagtacga tgttttggac   2760

aagagacgtg gccgggaccc tgagatgggg ggaaagccgc agagaaggaa gaaccctcag   2820

gaaggcctgt acaatgaact gcagaaagat aagatggcgg aggcctacag tgagattggg   2880

atgaaaggcg agcgccggag gggcaagggg cacgatggcc tttaccaggg tctcagtaca   2940

gccaccaagg acacctacga cgcccttcac atgcaggccc tgccccctcg ctaa         2994
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<210> SEQ ID NO 21
<211> LENGTH: 997
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 21

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser His Arg Phe Met
            20                  25                  30

Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln
        35                  40                  45

Asp Val Asn Thr Ala Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser
    50                  55                  60

Pro Lys Leu Leu Ile Phe Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro
65                  70                  75                  80

Asp Arg Phe Thr Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
                85                  90                  95
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Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Ile Gln Leu Val Gln Ser Gly Pro Asp Leu Lys Lys Pro Gly Glu Thr
145                 150                 155                 160

Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Phe Gly
                165                 170                 175

Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Phe Lys Trp Met Ala
            180                 185                 190

Trp Ile Asn Thr Tyr Thr Gly Glu Ser Tyr Phe Ala Asp Asp Phe Lys
        195                 200                 205

Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Thr Thr Ala Tyr Leu
    210                 215                 220

Gln Ile Asn Asn Leu Lys Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
225                 230                 235                 240

Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Gly Gly Phe Ala Tyr Trp Gly
                245                 250                 255

Gln Gly Thr Leu Val Thr Val Ser Ala Thr Thr Thr Pro Ala Pro Arg
            260                 265                 270

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        275                 280                 285

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
    290                 295                 300

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305                 310                 315                 320

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
                325                 330                 335

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
            340                 345                 350

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
        355                 360                 365

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
    370                 375                 380

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
385                 390                 395                 400

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                405                 410                 415

Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln
            420                 425                 430

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
        435                 440                 445

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
    450                 455                 460

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
465                 470                 475                 480

Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe
                485                 490                 495

Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met
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            500                 505                 510

Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu His
        515                 520                 525

Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
    530                 535                 540

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp
545                 550                 555                 560

Val Gly Ile Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro
                565                 570                 575

Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp
            580                 585                 590

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        595                 600                 605

Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser
    610                 615                 620

Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly
625                 630                 635                 640

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val
                645                 650                 655

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
            660                 665                 670

Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr Trp Met
        675                 680                 685

Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly Glu
    690                 695                 700

Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Ala Pro Ser Leu Lys Asp
705                 710                 715                 720

Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln
                725                 730                 735

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
            740                 745                 750

Pro Asp Gly Asn Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu
        755                 760                 765

Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
    770                 775                 780

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
785                 790                 795                 800

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
                805                 810                 815

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
            820                 825                 830

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
        835                 840                 845

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
    850                 855                 860

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
865                 870                 875                 880

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
                885                 890                 895

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
            900                 905                 910
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Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
        915                 920                 925

Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
    930                 935                 940

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
945                 950                 955                 960

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
                965                 970                 975

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
            980                 985                 990

Ala Leu Pro Pro Arg
        995


<210> SEQ ID NO 22
<211> LENGTH: 3009
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 22

cgatcgcatg gccttaccag tgaccgcctt gctcctgccg ctggccttgc tgctccacgc     60

cgccaggccg gatgtggtga tgacccagag ccatcgcttt atgagcacca gcgtgggaga    120

tcgagtgagc attacctgcc gcgcgagcca ggatgtgaac accgcggtga gctggtatca    180

gcagaaaccg ggccagagcc cgaaactgct gatttttagc gcgagctatc gctataccgg    240

cgtgccggat cgctttaccg gcagcggcag cggcgcggat tttaccctga ccattagcag    300

cgtgcaggcg gaagatctgg cggtgtatta ttgccagcag cattatagca ccccgtggac    360

ctttggcggc ggcaccaaac tggatattaa aggagggggg ggatccgggg gaggaggctc    420

cggcggaggc ggaagccaga ttcagctggt gcagagcggc ccggatctga aaaaaccggg    480

cgaaaccgtg aaactgagct gcaaagcgag cggctatacc tttaccaact ttggcatgaa    540

ctgggtgaaa caggcgccgg gcaaaggctt taaatggatg gcgtggatta acacctatac    600

cggcgaaagc tattttgcgg atgattttaa aggccgcttt gcgtttagcg tggaaaccag    660

cgcgaccacc gcgtatctgc agattaacaa cctgaaaacc gaagataccg cgacctattt    720

ttgcgcgcgc ggcgaaattt attatggcta tgatggcggc tttgcgtatt ggggccaggg    780

caccctggtg accgtgagcg cgaccacgac gccagcgccg cgaccaccaa caccggcgcc    840

caccatcgcg tcgcagcccc tgtccctgcg cccagaggcg tgccggccag cggcgggggg    900

cgcagtgcac acgagggggc tggacttcgc ctgtgatatc tacatctggg cgcccttggc    960

cgggacttgt ggggtccttc tcctgtcact ggttatcacc ctttactgca aacggggcag   1020

aaagaaactc ctgtatatat tcaagcaacc atttatgaga ccagtacaaa ctactcaaga   1080

ggaagatggc tgtagctgcc gatttccaga agaagaagaa ggaggatgtg aactgagagt   1140

gaagttcagc aggagcgcag acgcccccgc gtaccagcag ggccagaacc agctctataa   1200

cgagctcaat ctaggacgaa gagaggagta cgatgttttg gacaagagac gtggccggga   1260

ccctgagatg gggggaaagc cgcagagaag gaagaaccct caggaaggcc tgtacaatga   1320

actgcagaaa gataagatgg cggaggccta cagtgagatt gggatgaaag gcgagcgccg   1380

gaggggcaag gggcacgatg gcctttacca gggtctcagt acagccacca aggacaccta   1440
```

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```
cgacgccctt cacatgcagg ccctgccccc tcgcggaagc ggagccacca acttcagcct   1500

gctgaagcag gccggcgacg tggaggagaa ccccggcccc atggccttac cagtgaccgc   1560

cttgctcctg ccgctggcct tgctgctcca cgccgccagg ccggatattc agatgaccca   1620

gagcccgagc agcctgagcg cgagcgtggg cgaccgcgtg accattacct gcaaagcgag   1680

ccaggatgtg ggcattgcgg tggcgtggta tcagcagaaa ccgggcaaag tgccgaaact   1740

gctgatttat tgggcgagca cccgccatac cggcgtgccg gatcgcttta gcggcagcgg   1800

cagcggcacc gattttaccc tgaccattag cagcctgcag ccggaagatg tggcgaccta   1860

ttattgccag cagtatagca gctatccgta tacctttggc cagggcacca aagtggaaat   1920

taaaggaggg gggggatccg ggggaggagg ctccggcgga ggcggaagcg aagtgcagct   1980

ggtggaaagc ggcggcggcc tggtgcagcc gggcggcagc ctgcgcctga gctgcgcggc   2040

gagcggcttt gattttagcc gctattggat gagctgggtg cgccaggcgc cgggcaaagg   2100

cctggaatgg attggcgaaa ttaacccgga tagcagcacc attaactatg cgccgagcct   2160

gaaagataaa tttattatta gccgcgataa cgcgaaaaac agcctgtatc tgcagatgaa   2220

cagcctgcgc gcggaagata ccgcggtgta ttattgcgcg cgcccggatg gcaactattg   2280

gtattttgat gtgtggggcc agggcaccct ggtgaccgtg agcagcacca cgacgccagc   2340

gccgcgacca ccaacaccgg cgcccaccat cgcgtcgcag cccctgtccc tgcgcccaga   2400

ggcgtgccgg ccagcggcgg ggggcgcagt gcacacgagg gggctggact tcgcctgtga   2460

tatctacatc tgggcgccct tggccgggac ttgtggggtc cttctcctgt cactggttat   2520

cacccttac tgcaaacggg gcagaaagaa actcctgtat atattcaagc aaccatttat   2580

gagaccagta caaactactc aagaggaaga tggctgtagc tgccgatttc cagaagaaga   2640

agaaggagga tgtgaactga gagtgaagtt cagcaggagc gcagacgccc ccgcgtacca   2700

gcagggccag aaccagctct ataacgagct caatctagga cgaagagagg agtacgatgt   2760

tttggacaag agacgtggcc gggaccctga gatgggggga aagccgcaga gaaggaagaa   2820

ccctcaggaa ggcctgtaca atgaactgca gaaagataag atggcggagg cctacagtga   2880

gattgggatg aaaggcgagc gccggagggg caaggggcac gatggccttt accagggtct   2940

cagtacagcc accaaggaca cctacgacgc ccttcacatg caggccctgc cccctcgcta   3000

agtttaaac                                                           3009
```

<210> SEQ ID NO 23
<211> LENGTH: 423
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 23

```
agctagctgc agtaacgcca ttttgcaagg catggaaaaa taccaaacca agaatagaga     60

agttcagatc aagggcgggt acatgaaaat agctaacgtt gggccaaaca ggatatctgc    120

ggtgagcagt ttcggccccg gcccggggcc aagaacagat ggtcaccgca gtttcggccc    180

cggcccgagg ccaagaacag atggtcccca gatatggccc aaccctcagc agtttcttaa    240

gacccatcag atgtttccag gctcccccaa ggacctgaaa tgaccctgcg ccttatttga    300

attaaccaat cagcctgctt ctcgcttctg ttcgcgcgct tctgcttccc gagctctata    360
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aaagagctca caacccctca ctcggcgcgc cagtcctccg acagactgag tcgcccgggt    420

acc                                                                  423


<210> SEQ ID NO 24
<211> LENGTH: 165
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 24

Met Ser Gly Leu Gly Arg Ser Arg Arg Gly Gly Arg Ser Arg Val Asp
1               5                   10                  15

Gln Glu Glu Arg Phe Pro Gln Gly Leu Trp Thr Gly Val Ala Met Arg
            20                  25                  30

Ser Cys Pro Glu Glu Gln Tyr Trp Asp Pro Leu Leu Gly Thr Cys Met
        35                  40                  45

Ser Cys Lys Thr Ile Cys Asn His Gln Ser Gln Arg Thr Cys Ala Ala
    50                  55                  60

Phe Cys Arg Ser Leu Ser Cys Arg Lys Glu Gln Gly Lys Phe Tyr Asp
65                  70                  75                  80

His Leu Leu Arg Asp Cys Ile Ser Cys Ala Ser Ile Cys Gly Gln His
                85                  90                  95

Pro Lys Gln Cys Ala Tyr Phe Cys Glu Asn Lys Leu Arg Ser Pro Val
            100                 105                 110

Asn Leu Pro Pro Glu Leu Arg Arg Gln Arg Ser Gly Glu Val Glu Asn
        115                 120                 125

Asn Ser Asp Asn Ser Gly Arg Tyr Gln Gly Leu Glu His Arg Gly Ser
    130                 135                 140

Glu Ala Ser Pro Ala Leu Pro Gly Leu Lys Leu Ser Ala Asp Gln Val
145                 150                 155                 160

Ala Leu Val Tyr Ser
                165


<210> SEQ ID NO 25
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 25

Met Leu Gln Met Ala Gly Gln Cys Ser Gln Asn Glu Tyr Phe Asp Ser
1               5                   10                  15

Leu Leu His Ala Cys Ile Pro Cys Gln Leu Arg Cys Ser Ser Asn Thr
            20                  25                  30

Pro Pro Leu Thr Cys Gln Arg Tyr Cys Asn Ala Ser Val Thr Asn Ser
        35                  40                  45

Val Lys Gly Thr Asn Ala
    50


<210> SEQ ID NO 26
<211> LENGTH: 204
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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-continued

<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 26

Ser Gly Pro Val Lys Glu Leu Val Gly Ser Val Gly Gly Ala Val Thr
1 5 10 15

Phe Pro Leu Lys Ser Lys Val Lys Gln Val Asp Ser Ile Val Trp Thr
20 25 30

Phe Asn Thr Thr Pro Leu Val Thr Ile Gln Pro Glu Gly Gly Thr Ile
35 40 45

Ile Val Thr Gln Asn Arg Asn Arg Glu Arg Val Asp Phe Pro Asp Gly
50 55 60

Gly Tyr Ser Leu Lys Leu Ser Lys Leu Lys Lys Asn Asp Ser Gly Ile
65 70 75 80

Tyr Tyr Val Gly Ile Tyr Ser Ser Ser Leu Gln Gln Pro Ser Thr Gln
85 90 95

Glu Tyr Val Leu His Val Tyr Glu His Leu Ser Lys Pro Lys Val Thr
100 105 110

Met Gly Leu Gln Ser Asn Lys Asn Gly Thr Cys Val Thr Asn Leu Thr
115 120 125

Cys Cys Met Glu His Gly Glu Glu Asp Val Ile Tyr Thr Trp Lys Ala
130 135 140

Leu Gly Gln Ala Ala Asn Glu Ser His Asn Gly Ser Ile Leu Pro Ile
145 150 155 160

Ser Trp Arg Trp Gly Glu Ser Asp Met Thr Phe Ile Cys Val Ala Arg
165 170 175

Asn Pro Val Ser Arg Asn Phe Ser Ser Pro Ile Leu Ala Arg Lys Leu
180 185 190

Cys Glu Gly Ala Ala Asp Asp Pro Asp Ser Ser Met
195 200

<210> SEQ ID NO 27
<211> LENGTH: 46
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 27

Met Asp Asp Ser Thr Glu Arg Glu Gln Ser Arg Leu Thr Ser Cys Leu
1 5 10 15

Lys Lys Arg Glu Glu Met Lys Leu Lys Glu Cys Val Ser Ile Leu Pro
20 25 30

Arg Lys Glu Ser Pro Ser Val Arg Ser Ser Lys Asp Gly Lys
35 40 45

<210> SEQ ID NO 28
<211> LENGTH: 242
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 28

Asp Pro Asn Phe Trp Leu Gln Val Gln Glu Ser Val Thr Val Gln Glu
1 5 10 15

Gly Leu Cys Val Leu Val Pro Cys Thr Phe Phe His Pro Ile Pro Tyr

-continued

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            20                  25                  30

Tyr Asp Lys Asn Ser Pro Val His Gly Tyr Trp Phe Arg Glu Gly Ala
        35                  40                  45

Ile Ile Ser Arg Asp Ser Pro Val Ala Thr Asn Lys Leu Asp Gln Glu
    50                  55                  60

Val Gln Glu Glu Thr Gln Gly Arg Phe Arg Leu Leu Gly Asp Pro Ser
65                  70                  75                  80

Arg Asn Asn Cys Ser Leu Ser Ile Val Asp Ala Arg Arg Arg Asp Asn
                85                  90                  95

Gly Ser Tyr Phe Phe Arg Met Glu Arg Gly Ser Thr Lys Tyr Ser Tyr
            100                 105                 110

Lys Ser Pro Gln Leu Ser Val His Val Thr Asp Leu Thr His Arg Pro
        115                 120                 125

Lys Ile Leu Ile Pro Gly Thr Leu Glu Pro Gly His Ser Lys Asn Leu
    130                 135                 140

Thr Cys Ser Val Ser Trp Ala Cys Glu Gln Gly Thr Pro Pro Ile Phe
145                 150                 155                 160

Ser Trp Leu Ser Ala Ala Pro Thr Ser Leu Gly Pro Arg Thr Thr His
                165                 170                 175

Ser Ser Val Leu Ile Ile Thr Pro Arg Pro Gln Asp His Gly Thr Asn
            180                 185                 190

Leu Thr Cys Gln Val Lys Phe Ala Gly Ala Gly Val Thr Thr Glu Arg
        195                 200                 205

Thr Ile Gln Leu Asn Val Thr Tyr Val Pro Gln Asn Pro Thr Thr Gly
    210                 215                 220

Ile Phe Pro Gly Asp Gly Ser Gly Lys Gln Glu Thr Arg Ala Gly Val
225                 230                 235                 240

Val His


<210> SEQ ID NO 29
<211> LENGTH: 287
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 29

Thr Lys Glu Asp Pro Asn Pro Pro Ile Thr Asn Leu Arg Met Lys Ala
1               5                   10                  15

Lys Ala Gln Gln Leu Thr Trp Asp Leu Asn Arg Asn Val Thr Asp Ile
            20                  25                  30

Glu Cys Val Lys Asp Ala Asp Tyr Ser Met Pro Ala Val Asn Asn Ser
        35                  40                  45

Tyr Cys Gln Phe Gly Ala Ile Ser Leu Cys Glu Val Thr Asn Tyr Thr
    50                  55                  60

Val Arg Val Ala Asn Pro Pro Phe Ser Thr Trp Ile Leu Phe Pro Glu
65                  70                  75                  80

Asn Ser Gly Lys Pro Trp Ala Gly Ala Glu Asn Leu Thr Cys Trp Ile
                85                  90                  95

His Asp Val Asp Phe Leu Ser Cys Ser Trp Ala Val Gly Pro Gly Ala
            100                 105                 110

Pro Ala Asp Val Gln Tyr Asp Leu Tyr Leu Asn Val Ala Asn Arg Arg
        115                 120                 125
```

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```
Gln Gln Tyr Glu Cys Leu His Tyr Lys Thr Asp Ala Gln Gly Thr Arg
    130                 135                 140

Ile Gly Cys Arg Phe Asp Asp Ile Ser Arg Leu Ser Ser Gly Ser Gln
145                 150                 155                 160

Ser Ser His Ile Leu Val Arg Gly Arg Ser Ala Ala Phe Gly Ile Pro
                165                 170                 175

Cys Thr Asp Lys Phe Val Val Phe Ser Gln Ile Glu Ile Leu Thr Pro
            180                 185                 190

Pro Asn Met Thr Ala Lys Cys Asn Lys Thr His Ser Phe Met His Trp
        195                 200                 205

Lys Met Arg Ser His Phe Asn Arg Lys Phe Arg Tyr Glu Leu Gln Ile
    210                 215                 220

Gln Lys Arg Met Gln Pro Val Ile Thr Glu Gln Val Arg Asp Arg Thr
225                 230                 235                 240

Ser Phe Gln Leu Leu Asn Pro Gly Thr Tyr Thr Val Gln Ile Arg Ala
                245                 250                 255

Arg Glu Arg Val Tyr Glu Phe Leu Ser Ala Trp Ser Thr Pro Gln Arg
            260                 265                 270

Phe Glu Cys Asp Gln Glu Glu Gly Ala Asn Thr Arg Ala Trp Arg
        275                 280                 285


<210> SEQ ID NO 30
<211> LENGTH: 272
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 30

Pro Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp Asn Ala Val
1               5                   10                  15

Leu Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln Gln Leu Thr
            20                  25                  30

Trp Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu Ser Leu Gly
        35                  40                  45

Leu Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile Trp Leu Phe
    50                  55                  60

Ile Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu Cys Gln Pro
65                  70                  75                  80

Gly Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr Val Asn Val
                85                  90                  95

Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp Leu Gly Gly
            100                 105                 110

Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro Ser Ser Pro
        115                 120                 125

Ser Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala Lys Asp Arg
    130                 135                 140

Pro Glu Ile Trp Glu Gly Glu Pro Pro Cys Leu Pro Pro Arg Asp Ser
145                 150                 155                 160

Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro Gly Ser Thr
                165                 170                 175

Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser Arg Gly Pro
            180                 185                 190
```

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```
Leu Ser Trp Thr His Val His Pro Lys Gly Pro Lys Ser Leu Leu Ser
        195                 200                 205

Leu Glu Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp Val Met Glu
    210                 215                 220

Thr Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala Gly Lys Tyr
225                 230                 235                 240

Tyr Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu Glu Ile Thr
                245                 250                 255

Ala Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly Gly Trp Lys
            260                 265                 270


<210> SEQ ID NO 31
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 31

Pro Ile Cys Val Thr Val
1               5


<210> SEQ ID NO 32
<211> LENGTH: 47
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 32

Lys Ile Ser His Phe Leu Lys Met Glu Ser Leu Asn Phe Ile Arg Ala
1               5                   10                  15

His Thr Pro Tyr Ile Asn Ile Tyr Asn Cys Glu Pro Ala Asn Pro Ser
            20                  25                  30

Glu Lys Asn Ser Pro Ser Thr Gln Tyr Cys Tyr Ser Ile Gln Ser
        35                  40                  45


<210> SEQ ID NO 33
<211> LENGTH: 480
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 33

Asp Ser Ser Lys Trp Val Phe Glu His Pro Glu Thr Leu Tyr Ala Trp
1               5                   10                  15

Glu Gly Ala Cys Val Trp Ile Pro Cys Thr Tyr Arg Ala Leu Asp Gly
            20                  25                  30

Asp Leu Glu Ser Phe Ile Leu Phe His Asn Pro Glu Tyr Asn Lys Asn
        35                  40                  45

Thr Ser Lys Phe Asp Gly Thr Arg Leu Tyr Glu Ser Thr Lys Asp Gly
    50                  55                  60

Lys Val Pro Ser Glu Gln Lys Arg Val Gln Phe Leu Gly Asp Lys Asn
65                  70                  75                  80

Lys Asn Cys Thr Leu Ser Ile His Pro Val His Leu Asn Asp Ser Gly
                85                  90                  95
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```
Gln Leu Gly Leu Arg Met Glu Ser Lys Thr Glu Lys Trp Met Glu Arg
            100                 105                 110

Ile His Leu Asn Val Ser Glu Arg Pro Phe Pro Pro His Ile Gln Leu
        115                 120                 125

Pro Pro Glu Ile Gln Glu Ser Gln Glu Val Thr Leu Thr Cys Leu Leu
    130                 135                 140

Asn Phe Ser Cys Tyr Gly Tyr Pro Ile Gln Leu Gln Trp Leu Leu Glu
145                 150                 155                 160

Gly Val Pro Met Arg Gln Ala Ala Val Thr Ser Thr Ser Leu Thr Ile
                165                 170                 175

Lys Ser Val Phe Thr Arg Ser Glu Leu Lys Phe Ser Pro Gln Trp Ser
            180                 185                 190

His His Gly Lys Ile Val Thr Cys Gln Leu Gln Asp Ala Asp Gly Lys
        195                 200                 205

Phe Leu Ser Asn Asp Thr Val Gln Leu Asn Val Lys His Thr Pro Lys
    210                 215                 220

Leu Glu Ile Lys Val Thr Pro Ser Asp Ala Ile Val Arg Glu Gly Asp
225                 230                 235                 240

Ser Val Thr Met Thr Cys Glu Val Ser Ser Ser Asn Pro Glu Tyr Thr
                245                 250                 255

Thr Val Ser Trp Leu Lys Asp Gly Thr Ser Leu Lys Lys Gln Asn Thr
            260                 265                 270

Phe Thr Leu Asn Leu Arg Glu Val Thr Lys Asp Gln Ser Gly Lys Tyr
        275                 280                 285

Cys Cys Gln Val Ser Asn Asp Val Gly Pro Gly Arg Ser Glu Glu Val
    290                 295                 300

Phe Leu Gln Val Gln Tyr Ala Pro Glu Pro Ser Thr Val Gln Ile Leu
305                 310                 315                 320

His Ser Pro Ala Val Glu Gly Ser Gln Val Glu Phe Leu Cys Met Ser
                325                 330                 335

Leu Ala Asn Pro Leu Pro Thr Asn Tyr Thr Trp Tyr His Asn Gly Lys
            340                 345                 350

Glu Met Gln Gly Arg Thr Glu Glu Lys Val His Ile Pro Lys Ile Leu
        355                 360                 365

Pro Trp His Ala Gly Thr Tyr Ser Cys Val Ala Glu Asn Ile Leu Gly
    370                 375                 380

Thr Gly Gln Arg Gly Pro Gly Ala Glu Leu Asp Val Gln Tyr Pro Pro
385                 390                 395                 400

Lys Lys Val Thr Thr Val Ile Gln Asn Pro Met Pro Ile Arg Glu Gly
                405                 410                 415

Asp Thr Val Thr Leu Ser Cys Asn Tyr Asn Ser Ser Asn Pro Ser Val
            420                 425                 430

Thr Arg Tyr Glu Trp Lys Pro His Gly Ala Trp Glu Glu Pro Ser Leu
        435                 440                 445

Gly Val Leu Lys Ile Gln Asn Val Gly Trp Asp Asn Thr Thr Ile Ala
    450                 455                 460

Cys Ala Ala Cys Asn Ser Trp Cys Ser Trp Ala Ser Pro Val Ala Leu
465                 470                 475                 480
```

<210> SEQ ID NO 34
<211> LENGTH: 480
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 34

Gln Ser Pro Thr Pro Ser Pro Thr Gly Leu Thr Thr Ala Lys Met Pro
1 5 10 15

Ser Val Pro Leu Ser Ser Asp Pro Leu Pro Thr His Thr Thr Ala Phe
20 25 30

Ser Pro Ala Ser Thr Phe Glu Arg Glu Asn Asp Phe Ser Glu Thr Thr
35 40 45

Thr Ser Leu Ser Pro Asp Asn Thr Ser Thr Gln Val Ser Pro Asp Ser
50 55 60

Leu Asp Asn Ala Ser Ala Phe Asn Thr Thr Gly Val Ser Ser Val Gln
65 70 75 80

Thr Pro His Leu Pro Thr His Ala Asp Ser Gln Thr Pro Ser Ala Gly
85 90 95

Thr Asp Thr Gln Thr Phe Ser Gly Ser Ala Ala Asn Ala Lys Leu Asn
100 105 110

Pro Thr Pro Gly Ser Asn Ala Ile Ser Asp Val Pro Gly Glu Arg Ser
115 120 125

Thr Ala Ser Thr Phe Pro Thr Asp Pro Val Ser Pro Leu Thr Thr Thr
130 135 140

Leu Ser Leu Ala His His Ser Ser Ala Ala Leu Pro Ala Arg Thr Ser
145 150 155 160

Asn Thr Thr Ile Thr Ala Asn Thr Ser Asp Ala Tyr Leu Asn Ala Ser
165 170 175

Glu Thr Thr Thr Leu Ser Pro Ser Gly Ser Ala Val Ile Ser Thr Thr
180 185 190

Thr Ile Ala Thr Thr Pro Ser Lys Pro Thr Cys Asp Glu Lys Tyr Ala
195 200 205

Asn Ile Thr Val Asp Tyr Leu Tyr Asn Lys Glu Thr Lys Leu Phe Thr
210 215 220

Ala Lys Leu Asn Val Asn Glu Asn Val Glu Cys Gly Asn Asn Thr Cys
225 230 235 240

Thr Asn Asn Glu Val His Asn Leu Thr Glu Cys Lys Asn Ala Ser Val
245 250 255

Ser Ile Ser His Asn Ser Cys Thr Ala Pro Asp Lys Thr Leu Ile Leu
260 265 270

Asp Val Pro Pro Gly Val Glu Lys Phe Gln Leu His Asp Cys Thr Gln
275 280 285

Val Glu Lys Ala Asp Thr Thr Ile Cys Leu Lys Trp Lys Asn Ile Glu
290 295 300

Thr Phe Thr Cys Asp Thr Gln Asn Ile Thr Tyr Arg Phe Gln Cys Gly
305 310 315 320

Asn Met Ile Phe Asp Asn Lys Glu Ile Lys Leu Glu Asn Leu Glu Pro
325 330 335

Glu His Glu Tyr Lys Cys Asp Ser Glu Ile Leu Tyr Asn Asn His Lys
340 345 350

Phe Thr Asn Ala Ser Lys Ile Ile Lys Thr Asp Phe Gly Ser Pro Gly
355 360 365

Glu Pro Gln Ile Ile Phe Cys Arg Ser Glu Ala Ala His Gln Gly Val

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    370                 375                 380

Ile Thr Trp Asn Pro Pro Gln Arg Ser Phe His Asn Phe Thr Leu Cys
385                 390                 395                 400

Tyr Ile Lys Glu Thr Glu Lys Asp Cys Leu Asn Leu Asp Lys Asn Leu
                405                 410                 415

Ile Lys Tyr Asp Leu Gln Asn Leu Lys Pro Tyr Thr Lys Tyr Val Leu
            420                 425                 430

Ser Leu His Ala Tyr Ile Ile Ala Lys Val Gln Arg Asn Gly Ser Ala
        435                 440                 445

Ala Met Cys His Phe Thr Thr Lys Ser Ala Pro Pro Ser Gln Val Trp
    450                 455                 460

Asn Met Thr Val Ser Met Thr Ser Asp Asn Ser Met His Val Lys Cys
465                 470                 475                 480


<210> SEQ ID NO 35
<211> LENGTH: 371
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 35

Lys Lys Val Val Leu Gly Lys Lys Gly Asp Thr Val Glu Leu Thr Cys
1               5                   10                  15

Thr Ala Ser Gln Lys Lys Ser Ile Gln Phe His Trp Lys Asn Ser Asn
            20                  25                  30

Gln Ile Lys Ile Leu Gly Asn Gln Gly Ser Phe Leu Thr Lys Gly Pro
        35                  40                  45

Ser Lys Leu Asn Asp Arg Ala Asp Ser Arg Arg Ser Leu Trp Asp Gln
    50                  55                  60

Gly Asn Phe Pro Leu Ile Ile Lys Asn Leu Lys Ile Glu Asp Ser Asp
65                  70                  75                  80

Thr Tyr Ile Cys Glu Val Glu Asp Gln Lys Glu Glu Val Gln Leu Leu
                85                  90                  95

Val Phe Gly Leu Thr Ala Asn Ser Asp Thr His Leu Leu Gln Gly Gln
            100                 105                 110

Ser Leu Thr Leu Thr Leu Glu Ser Pro Pro Gly Ser Ser Pro Ser Val
        115                 120                 125

Gln Cys Arg Ser Pro Arg Gly Lys Asn Ile Gln Gly Gly Lys Thr Leu
    130                 135                 140

Ser Val Ser Gln Leu Glu Leu Gln Asp Ser Gly Thr Trp Thr Cys Thr
145                 150                 155                 160

Val Leu Gln Asn Gln Lys Lys Val Glu Phe Lys Ile Asp Ile Val Val
                165                 170                 175

Leu Ala Phe Gln Lys Ala Ser Ser Ile Val Tyr Lys Lys Glu Gly Glu
            180                 185                 190

Gln Val Glu Phe Ser Phe Pro Leu Ala Phe Thr Val Glu Lys Leu Thr
        195                 200                 205

Gly Ser Gly Glu Leu Trp Trp Gln Ala Glu Arg Ala Ser Ser Ser Lys
    210                 215                 220

Ser Trp Ile Thr Phe Asp Leu Lys Asn Lys Glu Val Ser Val Lys Arg
225                 230                 235                 240

Val Thr Gln Asp Pro Lys Leu Gln Met Gly Lys Lys Leu Pro Leu His
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                245                 250                 255

Leu Thr Leu Pro Gln Ala Leu Pro Gln Tyr Ala Gly Ser Gly Asn Leu
            260                 265                 270

Thr Leu Ala Leu Glu Ala Lys Thr Gly Lys Leu His Gln Glu Val Asn
        275                 280                 285

Leu Val Val Met Arg Ala Thr Gln Leu Gln Lys Asn Leu Thr Cys Glu
    290                 295                 300

Val Trp Gly Pro Thr Ser Pro Lys Leu Met Leu Ser Leu Lys Leu Glu
305                 310                 315                 320

Asn Lys Glu Ala Lys Val Ser Lys Arg Glu Lys Ala Val Trp Val Leu
                325                 330                 335

Asn Pro Glu Ala Gly Met Trp Gln Cys Leu Leu Ser Asp Ser Gly Gln
            340                 345                 350

Val Leu Leu Glu Ser Asn Ile Lys Val Leu Pro Thr Trp Ser Thr Pro
        355                 360                 365

Val Gln Pro
    370


<210> SEQ ID NO 36
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 36

Glu Leu Cys Asp Asp Asp Pro Pro Glu Ile Pro His Ala Thr Phe Lys
1               5                   10                  15

Ala Met Ala Tyr Lys Glu Gly Thr Met Leu Asn Cys Glu Cys Lys Arg
            20                  25                  30

Gly Phe Arg Arg Ile Lys Ser Gly Ser Leu Tyr Met Leu Cys Thr Gly
        35                  40                  45

Asn Ser Ser His Ser Ser Trp Asp Asn Gln Cys Gln Cys Thr Ser Ser
    50                  55                  60

Ala Thr Arg Asn Thr Thr Lys Gln Val Thr Pro Gln Pro Glu Glu Gln
65                  70                  75                  80

Lys Glu Arg Lys Thr Thr Glu Met Gln Ser Pro Met Gln Pro Val Asp
                85                  90                  95

Gln Ala Ser Leu Pro Gly His Cys Arg Glu Pro Pro Pro Trp Glu Asn
            100                 105                 110

Glu Ala Thr Glu Arg Ile Tyr His Phe Val Val Gly Gln Met Val Tyr
        115                 120                 125

Tyr Gln Cys Val Gln Gly Tyr Arg Ala Leu His Arg Gly Pro Ala Glu
    130                 135                 140

Ser Val Cys Lys Met Thr His Gly Lys Thr Arg Trp Thr Gln Pro Gln
145                 150                 155                 160

Leu Ile Cys Thr Gly Glu Met Glu Thr Ser Gln Phe Pro Gly Glu Glu
                165                 170                 175

Lys Pro Gln Ala Ser Pro Glu Gly Arg Pro Glu Ser Glu Thr Ser Cys
            180                 185                 190

Leu Val Thr Thr Thr Asp Phe Gln Ile Gln Thr Glu Met Ala Ala Thr
        195                 200                 205

Met Glu Thr Ser Ile Phe Thr Thr Glu Tyr Gln
```

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210 215

<210> SEQ ID NO 37
<211> LENGTH: 3799
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 37

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg 60

ccgccaggcc gcagatcgtg ctgacccaga gccccgccat catgagcgcc agccccggcg 120

agaaggtgac catcacctgc agcgccagca gcagcatcag ctacatgcac tggttccagc 180

agaagcccgg caccagcccc aagctgtgga tctacaccac cagcaacctg gccagcggcg 240

tgcccgccag attcagcggc agcggcagcg gcaccagcta cagcctgacc atcagcagaa 300

tggaggccga ggacgccgcc acctactact gccaccagag aagcacctac cccctgacct 360

tcggcagcgg caccaagctg gagctgaagg gagggggggg atccggggga ggaggctccg 420

gcggaggcgg aagccaggtg cagctgcagc agagcggcgc cgagctggcc aagcccggcg 480

ccagcgtgaa gatgagctgc aaggccagcg gctacacctt caccagctac agaatgcact 540

gggtgaagca gagacccggc cagggcctgg agtggatcgg ctacatcaac cccagcaccg 600

gctacaccga gtacaaccag aagttcaagg acaaggccac cctgaccgcc gacaagagca 660

gcagcaccgc ctacatgcag ctgagcagcc tgaccttcga ggacagcgcc gtgtactact 720

gcgccagagg cggcggcgtg ttcgactact ggggccaggg caccaccctg accgtgagca 780

gcaccacgac gccagcgccg cgaccaccaa caccggcgcc caccatcgcg tcgcagcccc 840

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tggacttcgc ctgtgatatc tacatctggg cgcccttggc cgggacttgt ggggtccttc 960

tcctgtcact ggttatcacc ctttactgca aacggggcag aaagaaactc ctgtatatat 1020

tcaaacaacc atttatgaga ccagtacaaa ctactcaaga ggaagatggc tgtagctgcc 1080

gatttccaga agaagaagaa ggaggatgtg aactgagagt gaagttcagc aggagcgcag 1140

acgcccccgc gtaccagcag ggccagaacc agctctataa cgagctcaat ctaggacgaa 1200

gagaggagta cgatgttttg gacaagagac gtggccggga ccctgagatg gggggaaagc 1260

cgcagagaag gaagaaccct caggaaggcc tgtacaatga actgcagaaa gataagatgg 1320

cggaggccta cagtgagatt gggatgaaag gcgagcgccg gaggggcaag gggcacgatg 1380

gcctttacca gggtctcagt acagccacca aggacaccta cgacgccctt cacatgcagg 1440

ccctgccccc tcgcggaagc ggagctacta acttcagcct gctgaagcag gctggagacg 1500

tggaggagaa ccctggacct atggccttac cagtgaccgc cttgctcctg ccgctggcct 1560

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tgaccatcag cagcctggag cccgaggact tcgccatgta ctactgccag cagcacaaca 1860

agtaccccta caccttcggc ggcggcacca agctggagat caagggaggg gggggatccg 1920

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tggtgagacc cggcgccagc gtgaagctga gctgcaaggc cagcggctac accttcacca   2040
gctactggat gaactgggtg aagcagagac ccgaccaggg cctggagtgg atcggcagaa   2100
tcgaccccta cgacagcgag acccactaca accagaagtt caaggacaag gccatcctga   2160
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tgaccgtgag cagcaccacg acgccagcgc cgcgaccacc aacaccggcg cccaccatcg   2340
cgtcgcagcc cctgtccctg cgcccagagg cgtgccggcc agcggcgggg ggcgcagtgc   2400
acacgagggg gctggacttc gcctgtgata tctacatctg ggcgcccttg gccgggactt   2460
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tcctgcacag tgactacatg aacatgactc cccgccgccc cgggcccacc cgcaagcatt   2580
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ataagatggc ggaggcctac agtgagattg ggatgaaagg cgagcgccgg aggggcaagg   2880
ggcacgatgg cctttaccag ggtctcagta cagccaccaa ggacacctac gacgcccttc   2940
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gcgatgtgga agaaaacccg ggccccatgg aatacgcctc tgacgcttca ctggaccccg   3060
aagccccgtg gcctcccgcg ccccgcgctc gcgcctgccg cgtactgcct tgggccctgg   3120
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cctgggccgt gtccggggct cgcgcctcgc ccggctccgc ggccagcccg agactccgcg   3240
agggtcccga gctttcgccc gacgatcccg ccggcctctt ggacctgcgg cagggcatgt   3300
ttgcgcagct ggtggcccaa aatgttctgc tgatcgatgg gcccctgagc tggtacagtg   3360
acccaggcct ggcaggcgtg tccctgacgg ggggcctgag ctacaaagag gacacgaagg   3420
agctggtggt ggccaaggct ggagtctact atgtcttctt tcaactagag ctgcggcgcg   3480
tggtggccgg cgagggctca ggctccgttt cacttgcgct gcacctgcag ccactgcgct   3540
ctgctgctgg ggccgccgcc ctggctttga ccgtggacct gccacccgcc tcctccgagg   3600
ctcggaactc ggccttcggt ttccagggcc gcttgctgca cctgagtgcc ggccagcgcc   3660
tgggcgtcca tcttcacact gaggccaggg cacgccatgc ctggcagctt acccagggcg   3720
ccacagtctt gggactcttc cgggtgaccc ccgaaatccc agccggactc ccttcaccga   3780
ggtcggaata agtttaaac                                                3799
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<210> SEQ ID NO 38
<211> LENGTH: 1260
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 38

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15
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His Ala Ala Arg Pro Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met
            20                  25                  30

Ser Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser
        35                  40                  45

Ser Ile Ser Tyr Met His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro
    50                  55                  60

Lys Leu Trp Ile Tyr Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser
                85                  90                  95

Arg Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Arg Ser
            100                 105                 110

Thr Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Leu Lys Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
    130                 135                 140

Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val
145                 150                 155                 160

Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met
                165                 170                 175

His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
            180                 185                 190

Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe Lys Asp
        195                 200                 205

Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln
    210                 215                 220

Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg
225                 230                 235                 240

Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
                245                 250                 255

Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
            260                 265                 270

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
        275                 280                 285

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
    290                 295                 300

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
305                 310                 315                 320

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
                325                 330                 335

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
            340                 345                 350

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
        355                 360                 365

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
    370                 375                 380

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
385                 390                 395                 400

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
                405                 410                 415
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Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
            420                 425                 430

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
        435                 440                 445

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
    450                 455                 460

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465                 470                 475                 480

Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly
                485                 490                 495

Asp Val Glu Glu Asn Pro Gly Pro Met Ala Leu Pro Val Thr Ala Leu
            500                 505                 510

Leu Leu Pro Leu Ala Leu Leu Leu His Ala Ala Arg Pro Asp Val Gln
        515                 520                 525

Ile Thr Gln Ser Pro Ser Tyr Leu Ala Ala Ser Pro Gly Glu Thr Ile
    530                 535                 540

Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp
545                 550                 555                 560

Tyr Gln Glu Lys Pro Gly Lys Thr Asn Lys Leu Leu Ile Tyr Ser Gly
                565                 570                 575

Ser Thr Leu Gln Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser
            580                 585                 590

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe
        595                 600                 605

Ala Met Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly
    610                 615                 620

Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly
625                 630                 635                 640

Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Pro Gly Ala
                645                 650                 655

Glu Leu Val Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser
            660                 665                 670

Gly Tyr Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro
        675                 680                 685

Asp Gln Gly Leu Glu Trp Ile Gly Arg Ile Asp Pro Tyr Asp Ser Glu
    690                 695                 700

Thr His Tyr Asn Gln Lys Phe Lys Asp Lys Ala Ile Leu Thr Val Asp
705                 710                 715                 720

Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu
                725                 730                 735

Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp
            740                 745                 750

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Thr Thr Thr Pro Ala Pro
        755                 760                 765

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
    770                 775                 780

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
785                 790                 795                 800

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
                805                 810                 815

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg
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            820                 825                 830

Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro
        835                 840                 845

Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
    850                 855                 860

Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala
865                 870                 875                 880

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
                885                 890                 895

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
            900                 905                 910

Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln
        915                 920                 925

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
    930                 935                 940

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
945                 950                 955                 960

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
                965                 970                 975

Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Glu Gly Arg Gly
            980                 985                 990

Ser Leu Leu Thr Cys Gly Asp Val  Glu Glu Asn Pro Gly  Pro Met Glu
        995                 1000                1005

Tyr Ala  Ser Asp Ala Ser Leu  Asp Pro Glu Ala Pro  Trp Pro Pro
    1010                1015                1020

Ala Pro  Arg Ala Arg Ala Cys  Arg Val Leu Pro Trp  Ala Leu Val
    1025                1030                1035

Ala Gly  Leu Leu Leu Leu Leu  Leu Leu Ala Ala Ala  Cys Ala Val
    1040                1045                1050

Phe Leu  Ala Cys Pro Trp Ala  Val Ser Gly Ala Arg  Ala Ser Pro
    1055                1060                1065

Gly Ser  Ala Ala Ser Pro Arg  Leu Arg Glu Gly Pro  Glu Leu Ser
    1070                1075                1080

Pro Asp  Asp Pro Ala Gly Leu  Leu Asp Leu Arg Gln  Gly Met Phe
    1085                1090                1095

Ala Gln  Leu Val Ala Gln Asn  Val Leu Leu Ile Asp  Gly Pro Leu
    1100                1105                1110

Ser Trp  Tyr Ser Asp Pro Gly  Leu Ala Gly Val Ser  Leu Thr Gly
    1115                1120                1125

Gly Leu  Ser Tyr Lys Glu Asp  Thr Lys Glu Leu Val  Val Ala Lys
    1130                1135                1140

Ala Gly  Val Tyr Tyr Val Phe  Phe Gln Leu Glu Leu  Arg Arg Val
    1145                1150                1155

Val Ala  Gly Glu Gly Ser Gly  Ser Val Ser Leu Ala  Leu His Leu
    1160                1165                1170

Gln Pro  Leu Arg Ser Ala Ala  Gly Ala Ala Ala Leu  Ala Leu Thr
    1175                1180                1185

Val Asp  Leu Pro Pro Ala Ser  Ser Glu Ala Arg Asn  Ser Ala Phe
    1190                1195                1200

Gly Phe  Gln Gly Arg Leu Leu  His Leu Ser Ala Gly  Gln Arg Leu
    1205                1210                1215
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Gly Val  His Leu His Thr Glu  Ala Arg Ala Arg His  Ala Trp Gln
    1220                 1225                 1230

Leu Thr  Gln Gly Ala Thr Val  Leu Gly Leu Phe Arg  Val Thr Pro
    1235                 1240                 1245

Glu Ile  Pro Ala Gly Leu Pro  Ser Pro Arg Ser Glu
    1250                 1255                 1260


<210> SEQ ID NO 39
<211> LENGTH: 3856
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 39

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ccgccaggcc gcagatcgtg ctgacccaga gccccgccat catgagcgcc agccccggcg    120

agaaggtgac catcacctgc agcgccagca gcagcatcag ctacatgcac tggttccagc    180

agaagcccgg caccagcccc aagctgtgga tctacaccac cagcaacctg gccagcggcg    240

tgcccgccag attcagcggc agcggcagcg gcaccagcta cagcctgacc atcagcagaa    300

tggaggccga ggacgccgcc acctactact gccaccagag aagcacctac cccctgacct    360

tcggcagcgg caccaagctg gagctgaagg gagggggggg atccggggga ggaggctccg    420

gcggaggcgg aagccaggtg cagctgcagc agagcggcgc cgagctggcc aagcccggcg    480

ccagcgtgaa gatgagctgc aaggccagcg gctacacctt caccagctac agaatgcact    540

gggtgaagca gagacccggc cagggcctgg agtggatcgg ctacatcaac cccagcaccg    600

gctacaccga gtacaaccag aagttcaagg acaaggccac cctgaccgcc gacaagagca    660

gcagcaccgc ctacatgcag ctgagcagcc tgaccttcga ggacagcgcc gtgtactact    720

gcgccagagg cggcggcgtg ttcgactact ggggccaggg caccaccctg accgtgagca    780

gcaccacgac gccagcgccg cgaccaccaa caccggcgcc caccatcgcg tcgcagcccc    840

tgtccctgcg cccagaggcg tgccggccag cggcgggggg cgcagtgcac acgagggggc    900

tggacttcgc ctgtgatatc tacatctggg cgcccttggc cgggacttgt ggggtccttc    960

tcctgtcact ggttatcacc ctttactgca aacggggcag aaagaaactc ctgtatatat   1020

tcaaacaacc atttatgaga ccagtacaaa ctactcaaga ggaagatggc tgtagctgcc   1080

gatttccaga agaagaagaa ggaggatgtg aactgagagt gaagttcagc aggagcgcag   1140

acgcccccgc gtaccagcag ggccagaacc agctctataa cgagctcaat ctaggacgaa   1200

gagaggagta cgatgttttg gacaagagac gtggccggga ccctgagatg gggggaaagc   1260

cgcagagaag gaagaaccct caggaaggcc tgtacaatga actgcagaaa gataagatgg   1320

cggaggccta cagtgagatt gggatgaaag gcgagcgccg gaggggcaag gggcacgatg   1380

gcctttacca gggtctcagt acagccacca aggacaccta cgacgccctt cacatgcagg   1440

ccctgccccc tcgcggaagc ggagctacta acttcagcct gctgaagcag gctggagacg   1500

tggaggagaa ccctggacct atggccttac cagtgaccgc cttgctcctg ccgctggcct   1560

tgctgctcca cgccgccagg ccggacgtgc agatcaccca gagccccagc tacctggccg   1620

ccagccccgg cgagaccatc accatcaact gcagagccag caagagcatc agcaaggacc   1680
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tggtgagacc cggcgccagc gtgaagctga gctgcaaggc cagcggctac accttcacca   2040
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aggacctgat ccagagcatg cacatcgacg ccaccctgta caccgagagc gacgtgcacc   3240
ccagctgcaa ggtgaccgcc atgaagtgct tcctgctgga gctgcaggtg atcagcctgg   3300
agagcggcga cgccagcatc cacgacaccg tggagaacct gatcatcctg gccaacaaca   3360
gcctgagcag caacggcaac gtgaccgaga gcggctgcaa ggagtgcgag gagctggagg   3420
agaagaacat caaggagttc ctgcagagct tcgtgcacat cgtgcagatg ttcatcaaca   3480
ccagctccgg cggcggctcc ggcggcggcg gctccggcgg cggcggctcc ggcggcggcg   3540
gctccggcgg cggctccctg caggccccca gaagagccag aggctgcaga accctgggcc   3600
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cccccccat gagcgtggag cacgccgaca tctgggtgaa gagctacagc ctgtacagca   3720
gagagagata catctgcaac agcggcttca agagaaaggc cggcaccagc agcctgaccg   3780
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tcagataagt ttaaac                                                   3856
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<210> SEQ ID NO 40

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<211> LENGTH: 1279
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 40

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met
20 25 30

Ser Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser
35 40 45

Ser Ile Ser Tyr Met His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro
50 55 60

Lys Leu Trp Ile Tyr Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser
85 90 95

Arg Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Arg Ser
100 105 110

Thr Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Leu Lys Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
130 135 140

Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val
145 150 155 160

Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met
165 170 175

His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
180 185 190

Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe Lys Asp
195 200 205

Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln
210 215 220

Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg
225 230 235 240

Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
245 250 255

Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
260 265 270

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
275 280 285

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
290 295 300

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
305 310 315 320

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
325 330 335

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
340 345 350

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
355 360 365

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Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
    370                 375                 380

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
385                 390                 395                 400

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
                405                 410                 415

Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
            420                 425                 430

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
        435                 440                 445

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
    450                 455                 460

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465                 470                 475                 480

Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly
                485                 490                 495

Asp Val Glu Glu Asn Pro Gly Pro Met Ala Leu Pro Val Thr Ala Leu
            500                 505                 510

Leu Leu Pro Leu Ala Leu Leu Leu His Ala Ala Arg Pro Asp Val Gln
        515                 520                 525

Ile Thr Gln Ser Pro Ser Tyr Leu Ala Ala Ser Pro Gly Glu Thr Ile
    530                 535                 540

Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp
545                 550                 555                 560

Tyr Gln Glu Lys Pro Gly Lys Thr Asn Lys Leu Leu Ile Tyr Ser Gly
                565                 570                 575

Ser Thr Leu Gln Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser
            580                 585                 590

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe
        595                 600                 605

Ala Met Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly
    610                 615                 620

Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly
625                 630                 635                 640

Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Pro Gly Ala
                645                 650                 655

Glu Leu Val Arg Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser
            660                 665                 670

Gly Tyr Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro
        675                 680                 685

Asp Gln Gly Leu Glu Trp Ile Gly Arg Ile Asp Pro Tyr Asp Ser Glu
    690                 695                 700

Thr His Tyr Asn Gln Lys Phe Lys Asp Lys Ala Ile Leu Thr Val Asp
705                 710                 715                 720

Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu
                725                 730                 735

Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp
            740                 745                 750

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Thr Thr Thr Pro Ala Pro
        755                 760                 765
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Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
    770                 775                 780

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
785                 790                 795                 800

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
                805                 810                 815

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg
            820                 825                 830

Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro
        835                 840                 845

Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro
    850                 855                 860

Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala
865                 870                 875                 880

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
                885                 890                 895

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
            900                 905                 910

Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln
        915                 920                 925

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
    930                 935                 940

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
945                 950                 955                 960

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
                965                 970                 975

Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Glu Gly Arg Gly
            980                 985                 990

Ser Leu Leu Thr Cys Gly Asp Val  Glu Glu Asn Pro Gly  Pro Met Tyr
        995                 1000                1005

Arg Met  Gln Leu Leu Ser Cys  Ile Ala Leu Ser Leu  Ala Leu Val
    1010                1015                1020

Thr Asn  Ser Gly Ile His Val  Phe Ile Leu Gly Cys  Phe Ser Ala
    1025                1030                1035

Gly Leu  Pro Lys Thr Glu Ala  Asn Trp Val Asn Val  Ile Ser Asp
    1040                1045                1050

Leu Lys  Lys Ile Glu Asp Leu  Ile Gln Ser Met His  Ile Asp Ala
    1055                1060                1065

Thr Leu  Tyr Thr Glu Ser Asp  Val His Pro Ser Cys  Lys Val Thr
    1070                1075                1080

Ala Met  Lys Cys Phe Leu Leu  Glu Leu Gln Val Ile  Ser Leu Glu
    1085                1090                1095

Ser Gly  Asp Ala Ser Ile His  Asp Thr Val Glu Asn  Leu Ile Ile
    1100                1105                1110

Leu Ala  Asn Asn Ser Leu Ser  Ser Asn Gly Asn Val  Thr Glu Ser
    1115                1120                1125

Gly Cys  Lys Glu Cys Glu Glu  Leu Glu Glu Lys Asn  Ile Lys Glu
    1130                1135                1140

Phe Leu  Gln Ser Phe Val His  Ile Val Gln Met Phe  Ile Asn Thr
    1145                1150                1155

Ser Ser  Gly Gly Gly Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Gly
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    1160                1165                1170

Ser Gly  Gly Gly Gly Ser Gly  Gly Gly Ser Leu Gln  Ala Pro Arg
    1175                1180                1185

Arg Ala  Arg Gly Cys Arg Thr  Leu Gly Leu Pro Ala  Leu Leu Leu
    1190                1195                1200

Leu Leu  Leu Leu Arg Pro Pro  Ala Thr Arg Gly Ile  Thr Cys Pro
    1205                1210                1215

Pro Pro  Met Ser Val Glu His  Ala Asp Ile Trp Val  Lys Ser Tyr
    1220                1225                1230

Ser Leu  Tyr Ser Arg Glu Arg  Tyr Ile Cys Asn Ser  Gly Phe Lys
    1235                1240                1245

Arg Lys  Ala Gly Thr Ser Ser  Leu Thr Glu Cys Val  Leu Asn Lys
    1250                1255                1260

Ala Thr  Asn Val Ala His Trp  Thr Thr Pro Ser Leu  Lys Cys Ile
    1265                1270                1275

Arg


<210> SEQ ID NO 41
<211> LENGTH: 2314
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 41

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc ggacatcgtg ctgacccaga gccccgccag cctggccgtg agcctgggcc    120

agagggccac catcagctgc agggccagca agagcgtgag caccagcggc tacagctacc    180

tgcactggta ccagcagaag cccggccagc cccccaagct gctgatctac ctggccagca    240

acctggagag cggcgtgccc gccaggttca gcggcagcgg cagcggcacc gacttcaccc    300

tgaacatcca ccccgtggag gaggaggacg ccgccaccta ctactgccag cacagcaggg    360

agctgccctt caccttcggc agcggcacca agctggagat caagggaggg gggggatccg    420

ggggaggagg ctccggcgga ggcggaagcc aggtgcagct ggtggagagc ggcggcggcc    480

tggtgcagcc cggcggcagc ctgaagctga gctgcgccgc cagcggcttc gacttcagca    540

ggtactggat gagctgggtg aggcaggccc ccggcaaggg cctggagtgg atcggcgaga    600

tcaaccccac cagcagcacc atcaacttca cccccagcct gaaggacaag gtgttcatca    660

gcagggacaa cgccaagaac accctgtacc tgcagatgag caaggtgagg agcgaggaca    720

ccgccctgta ctactgcgcc aggggcaact actacaggta cggcgacgcc atggactact    780

ggggccaggg caccagcgtg accgtgagca ccacgacgcc agcgccgcga ccaccaacac    840

cggcgcccac catcgcgtcg cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg    900

cgggggcgc agtgcacacg agggggctgg acttcgcctg tgatatctac atctgggcgc    960

ccttggccgg gacttgtggg gtccttctcc tgtcactggt tatcaccctt tactgcagga   1020

gtaagaggag caggctcctg cacagtgact acatgaacat gactccccgc cgccccgggc   1080

ccacccgcaa gcattaccag ccctatgccc caccacgcga cttcgcagcc tatcgctcca   1140

gagtgaagtt cagcaggagc gcagacgccc ccgcgtacca gcagggccag aaccagctct   1200

ataacgagct caatctagga cgaagagagg agtacgatgt tttggacaag agacgtggcc   1260
```

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gggaccctga gatgggggga aagccgcaga gaaggaagaa ccctcaggaa ggcctgtaca   1320

atgaactgca gaaagataag atggcggagg cctacagtga gattgggatg aaaggcgagc   1380

gccggagggg caaggggcac gatggccttt accagggtct cagtacagcc accaaggaca   1440

cctacgacgc ccttcacatg caggccctgc cccctcgcgg cagcggcgaa ggccgcggca   1500

gcctgctgac ctgcggcgat gtggaagaaa acccgggccc catggaatac gcctctgacg   1560

cttcactgga ccccgaagcc ccgtggcctc ccgcgccccg cgctcgcgcc tgccgcgtac   1620

tgccttgggc cctggtcgcg gggctgctgc tgctgctgct gctcgctgcc gcctgcgccg   1680

tcttcctcgc ctgcccctgg gccgtgtccg gggctcgcgc ctcgcccggc tccgcggcca   1740

gcccgagact ccgcgagggt cccgagcttt cgcccgacga tcccgccggc ctcttggacc   1800

tgcggcaggg catgtttgcg cagctggtgg cccaaaatgt tctgctgatc gatgggcccc   1860

tgagctggta cagtgaccca ggcctggcag gcgtgtccct gacgggggc ctgagctaca   1920

aagaggacac gaaggagctg gtggtggcca aggctggagt ctactatgtc ttctttcaac   1980

tagagctgcg gcgcgtggtg gccggcgagg gctcaggctc cgtttcactt gcgctgcacc   2040

tgcagccact gcgctctgct gctggggccg ccgccctggc tttgaccgtg gacctgccac   2100

ccgcctcctc cgaggctcgg aactcggcct tcggtttcca gggccgcttg ctgcacctga   2160

gtgccggcca gcgcctgggc gtccatcttc acactgaggc cagggcacgc catgcctggc   2220

agcttaccca gggcgccaca gtcttgggac tcttccgggt gaccccgaa atcccagccg   2280

gactcccttc accgaggtcg gaataagttt aaac                               2314
```

```
<210> SEQ ID NO 42
<211> LENGTH: 765
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 42

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
            20                  25                  30

Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys
        35                  40                  45

Ser Val Ser Thr Ser Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu
65                  70                  75                  80

Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr
            100                 105                 110

Cys Gln His Ser Arg Glu Leu Pro Phe Thr Phe Gly Ser Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
145                 150                 155                 160
```

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```
Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe
                165                 170                 175

Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
            180                 185                 190

Glu Trp Ile Gly Glu Ile Asn Pro Thr Ser Ser Thr Ile Asn Phe Thr
        195                 200                 205

Pro Ser Leu Lys Asp Lys Val Phe Ile Ser Arg Asp Asn Ala Lys Asn
    210                 215                 220

Thr Leu Tyr Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr Ala Leu
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Gly Asn Tyr Tyr Arg Tyr Gly Asp Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
            340                 345                 350

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
        355                 360                 365

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser
    370                 375                 380

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385                 390                 395                 400

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
                405                 410                 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Glu Gly Arg
                485                 490                 495

Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met
            500                 505                 510

Glu Tyr Ala Ser Asp Ala Ser Leu Asp Pro Glu Ala Pro Trp Pro Pro
        515                 520                 525

Ala Pro Arg Ala Arg Ala Cys Arg Val Leu Pro Trp Ala Leu Val Ala
    530                 535                 540

Gly Leu Leu Leu Leu Leu Leu Leu Ala Ala Ala Cys Ala Val Phe Leu
545                 550                 555                 560
```

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```
Ala Cys Pro Trp Ala Val Ser Gly Ala Arg Ala Ser Pro Gly Ser Ala
                565                 570                 575

Ala Ser Pro Arg Leu Arg Glu Gly Pro Glu Leu Ser Pro Asp Asp Pro
            580                 585                 590

Ala Gly Leu Leu Asp Leu Arg Gln Gly Met Phe Ala Gln Leu Val Ala
        595                 600                 605

Gln Asn Val Leu Leu Ile Asp Gly Pro Leu Ser Trp Tyr Ser Asp Pro
    610                 615                 620

Gly Leu Ala Gly Val Ser Leu Thr Gly Gly Leu Ser Tyr Lys Glu Asp
625                 630                 635                 640

Thr Lys Glu Leu Val Val Ala Lys Ala Gly Val Tyr Tyr Val Phe Phe
                645                 650                 655

Gln Leu Glu Leu Arg Arg Val Val Ala Gly Glu Gly Ser Gly Ser Val
            660                 665                 670

Ser Leu Ala Leu His Leu Gln Pro Leu Arg Ser Ala Ala Gly Ala Ala
        675                 680                 685

Ala Leu Ala Leu Thr Val Asp Leu Pro Pro Ala Ser Ser Glu Ala Arg
    690                 695                 700

Asn Ser Ala Phe Gly Phe Gln Gly Arg Leu Leu His Leu Ser Ala Gly
705                 710                 715                 720

Gln Arg Leu Gly Val His Leu His Thr Glu Ala Arg Ala Arg His Ala
                725                 730                 735

Trp Gln Leu Thr Gln Gly Ala Thr Val Leu Gly Leu Phe Arg Val Thr
            740                 745                 750

Pro Glu Ile Pro Ala Gly Leu Pro Ser Pro Arg Ser Glu
        755                 760                 765


<210> SEQ ID NO 43
<211> LENGTH: 2371
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 43

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc ggacatcgtg ctgacccaga gccccgccag cctggccgtg agcctgggcc    120

agagggccac catcagctgc agggccagca agagcgtgag caccagcggc tacagctacc    180

tgcactggta ccagcagaag cccggccagc cccccaagct gctgatctac ctggccagca    240

acctggagag cggcgtgccc gccaggttca gcggcagcgg cagcggcacc gacttcaccc    300

tgaacatcca ccccgtggag gaggaggacg ccgccaccta ctactgccag cacagcaggg    360

agctgccctt caccttcggc agcggcacca agctggagat caagggaggg gggggatccg    420

ggggaggagg ctccggcgga ggcggaagcc aggtgcagct ggtggagagc ggcggcggcc    480

tggtgcagcc cggcggcagc ctgaagctga gctgcgccgc cagcggcttc gacttcagca    540

ggtactggat gagctgggtg aggcaggccc ccggcaaggg cctggagtgg atcggcgaga    600

tcaaccccac cagcagcacc atcaacttca cccccagcct gaaggacaag gtgttcatca    660

gcagggacaa cgccaagaac accctgtacc tgcagatgag caaggtgagg agcgaggaca    720

ccgccctgta ctactgcgcc aggggcaact actacaggta cggcgacgcc atggactact    780

ggggccaggg caccagcgtg accgtgagca ccacgacgcc agcgccgcga ccaccaacac    840
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cggcgcccac catcgcgtcg cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg    900

cgggggcgc agtgcacacg agggggctgg acttcgcctg tgatatctac atctgggcgc    960

ccttggccgg gacttgtggg gtccttctcc tgtcactggt tatcaccctt tactgcagga   1020

gtaagaggag caggctcctg cacagtgact acatgaacat gactccccgc cgccccgggc   1080

ccacccgcaa gcattaccag ccctatgccc caccacgcga cttcgcagcc tatcgctcca   1140

gagtgaagtt cagcaggagc gcagacgccc ccgcgtacca gcagggccag aaccagctct   1200

ataacgagct caatctagga cgaagagagg agtacgatgt tttggacaag agacgtggcc   1260

gggaccctga gatgggggga aagccgcaga gaaggaagaa ccctcaggaa ggcctgtaca   1320

atgaactgca gaaagataag atggcggagg cctacagtga gattgggatg aaaggcgagc   1380

gccggagggg caaggggcac gatggccttt accagggtct cagtacagcc accaaggaca   1440

cctacgacgc ccttcacatg caggccctgc cccctcgcgg cagcggcgaa ggccgcggca   1500

gcctgctgac ctgcggcgat gtggaagaaa acccgggccc catgtacaga atgcagctgc   1560

tgagctgcat cgccctgagc ctggccctgg tgaccaacag cggcatccac gtgttcatcc   1620

tgggctgctt cagcgccggc ctgcccaaga ccgaggccaa ctgggtgaac gtgatcagcg   1680

acctgaagaa gatcgaggac ctgatccaga gcatgcacat cgacgccacc ctgtacaccg   1740

agagcgacgt gcaccccagc tgcaaggtga ccgccatgaa gtgcttcctg ctggagctgc   1800

aggtgatcag cctggagagc ggcgacgcca gcatccacga caccgtggag aacctgatca   1860

tcctggccaa caacagcctg agcagcaacg gcaacgtgac cgagagcggc tgcaaggagt   1920

gcgaggagct ggaggagaag aacatcaagg agttcctgca gagcttcgtg cacatcgtgc   1980

agatgttcat caacaccagc tccggcggcg gctccggcgg cggcggctcc ggcggcggcg   2040

gctccggcgg cggcggctcc ggcggcggct ccctgcaggc ccccagaaga gccagaggct   2100

gcagaaccct gggcctgccc gccctgctgc tgctgctgct gctgagaccc cccgccacca   2160

gaggcatcac ctgcccccc cccatgagcg tggagcacgc cgacatctgg gtgaagagct   2220

acagcctgta cagcagagag agatacatct gcaacagcgg cttcaagaga aaggccggca   2280

ccagcagcct gaccgagtgc gtgctgaaca aggccaccaa cgtggcccac tggaccaccc   2340

ccagcctgaa gtgcatcaga taagtttaaa c                                  2371
```

<210> SEQ ID NO 44
<211> LENGTH: 784
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 44

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
            20                  25                  30

Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys
        35                  40                  45

Ser Val Ser Thr Ser Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu
```

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```
65                  70                  75                  80

Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr
            100                 105                 110

Cys Gln His Ser Arg Glu Leu Pro Phe Thr Phe Gly Ser Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
145                 150                 155                 160

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe
                165                 170                 175

Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
            180                 185                 190

Glu Trp Ile Gly Glu Ile Asn Pro Thr Ser Ser Thr Ile Asn Phe Thr
        195                 200                 205

Pro Ser Leu Lys Asp Lys Val Phe Ile Ser Arg Asp Asn Ala Lys Asn
    210                 215                 220

Thr Leu Tyr Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr Ala Leu
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Gly Asn Tyr Tyr Arg Tyr Gly Asp Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
            340                 345                 350

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
        355                 360                 365

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser
    370                 375                 380

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385                 390                 395                 400

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
                405                 410                 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480
```

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```
Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Glu Gly Arg
                485                 490                 495

Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met
            500                 505                 510

Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu Val
        515                 520                 525

Thr Asn Ser Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly
    530                 535                 540

Leu Pro Lys Thr Glu Ala Asn Trp Val Asn Val Ile Ser Asp Leu Lys
545                 550                 555                 560

Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr
                565                 570                 575

Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys
            580                 585                 590

Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser
        595                 600                 605

Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu
    610                 615                 620

Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu
625                 630                 635                 640

Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile
                645                 650                 655

Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly
            660                 665                 670

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser
        675                 680                 685

Leu Gln Ala Pro Arg Arg Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro
    690                 695                 700

Ala Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro Ala Thr Arg Gly Ile
705                 710                 715                 720

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
                725                 730                 735

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
            740                 745                 750

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
        755                 760                 765

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
    770                 775                 780


<210> SEQ ID NO 45
<211> LENGTH: 2369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 45

atggccttac cagtgaccgc cttgctcctg ccgctggcct tgctgctcca cgccgccagg      60

ccggatgtgg tgatgaccca gagccatcgc tttatgagca ccagcgtggg cgaccgagtg     120

agcattacct gccgcgcgag ccaggatgtg aacaccgcgg tgagctggta tcagcagaaa     180

ccgggccaga gcccgaaact gctgattttt agcgcgagct atcgctatac cggcgtgccg     240
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gatcgcttta ccggcagcgg cagcggcgcg gattttaccc tgaccattag cagcgtgcag    300
gcggaagatc tggcggtgta ttattgccag cagcattata gcaccccgtg gacctttggc    360
ggcggcacca aactggacat taaaggaggg gggggatccg ggggaggagg ctccggcgga    420
ggcggaagcc agattcagct ggtgcagagc ggcccggatc tgaaaaaacc gggcgaaacc    480
gtgaaactga gctgcaaagc gagcggctat acctttacca actttggcat gaactgggtg    540
aaacaggcgc cgggcaaagg ctttaaatgg atggcgtgga ttaacaccac ccgctatacc    600
ggcgaaagct attttgcgga tgattttaaa ggccgctttg cgtttagcgt ggaaaccagc    660
gcgaccaccg cgtatctgca gattaacaac ctgaaaaccg aagataccgc gacctatttt    720
tgcgcgcgcg gcgaaattta ttatggctat gatggcggct ttgcgtattg gggccagggc    780
accctggtga ccgtgagcgc gaccacgacg ccagcgccgc gaccaccaac accggcgccc    840
accatcgcgt cgcagcccct gtccctgcgc ccagaggcgt gccggccagc ggcgggggc    900
gcagtgcaca cgagggggct ggacttcgcc tgtgatatct acatctgggc gcccttggcc    960
gggacttgtg gggtccttct cctgtcactg gttatcaccc tttactgcaa acggggcaga   1020
aagaaactcc tgtatatatt caaacaacca tttatgagac cagtacaaac tactcaagag   1080
gaagatggct gtagctgccg atttccagaa gaagaagaag gaggatgtga actgagagtg   1140
aagttcagca ggagcgcaga cgcccccgcg taccagcagg gccagaacca gctctataac   1200
gagctcaatc taggacgaag agaggagtac gatgttttgg acaagagacg tggccgggac   1260
cctgagatgg ggggaaagcc gcagagaagg aagaaccctc aggaaggcct gtacaatgaa   1320
ctgcagaaag ataagatggc ggaggcctac agtgagattg ggatgaaagg cgagcgccgg   1380
aggggcaagg ggcacgatgg cctttaccag ggtctcagta cagccaccaa ggacacctac   1440
gacgcccttc acatgcaggc cctgcccccct cgcggaagcg gagccaccaa cttcagcctg   1500
ctgaagcagg ccggcgacgt ggaggagaac cccggcccca tgtacagaat gcagctgctg   1560
agctgcatcg ccctgagcct ggccctggtg accaacagcg gcatccacgt gttcatcctg   1620
ggctgcttca gcgccggcct gcccaagacc gaggccaact gggtgaacgt gatcagcgac   1680
ctgaagaaga tcgaggacct gatccagagc atgcacatcg acgccaccct gtacaccgag   1740
agcgacgtgc accccagctg caaggtgacc gccatgaagt gcttcctgct ggagctgcag   1800
gtgatcagcc tggagagcgg cgacgccagc atccacgaca ccgtggagaa cctgatcatc   1860
ctggccaaca acagcctgag cagcaacggc aacgtgaccg agagcggctg caaggagtgc   1920
gaggagctgg aggagaagaa catcaaggag ttcctgcaga gcttcgtgca catcgtgcag   1980
atgttcatca acaccagctc cggcggcggc tccggcggcg gcggctccgg cggcggcggc   2040
tccggcggcg gcggctccgg cggcggctcc ctgcaggccc ccagaagagc cagaggctgc   2100
agaaccctgg gcctgcccgc cctgctgctg ctgctgctgc tgagaccccc cgccaccaga   2160
ggcatcacct gcccccccc catgagcgtg gagcacgccg acatctgggt gaagagctac   2220
agcctgtaca gcagagagag atacatctgc aacagcggct tcaagagaaa ggccggcacc   2280
agcagcctga ccgagtgcgt gctgaacaag gccaccaacg tggcccactg gaccaccccc   2340
agcctgaagt gcatcagata agtttaaac                                     2369
```

<210> SEQ ID NO 46
<211> LENGTH: 786
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 46

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser His Arg Phe Met
20 25 30

Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln
35 40 45

Asp Val Asn Thr Ala Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser
50 55 60

Pro Lys Leu Leu Ile Phe Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro
65 70 75 80

Asp Arg Phe Thr Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
85 90 95

Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His
100 105 110

Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
130 135 140

Ile Gln Leu Val Gln Ser Gly Pro Asp Leu Lys Lys Pro Gly Glu Thr
145 150 155 160

Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Phe Gly
165 170 175

Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Phe Lys Trp Met Ala
180 185 190

Trp Ile Asn Thr Thr Arg Tyr Thr Gly Glu Ser Tyr Phe Ala Asp Asp
195 200 205

Phe Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Thr Thr Ala
210 215 220

Tyr Leu Gln Ile Asn Asn Leu Lys Thr Glu Asp Thr Ala Thr Tyr Phe
225 230 235 240

Cys Ala Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Gly Gly Phe Ala Tyr
245 250 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Thr Thr Thr Pro Ala
260 265 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
275 280 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
290 295 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305 310 315 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
325 330 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
340 345 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
355 360 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg

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    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr
                485                 490                 495

Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly
            500                 505                 510

Pro Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala
        515                 520                 525

Leu Val Thr Asn Ser Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser
    530                 535                 540

Ala Gly Leu Pro Lys Thr Glu Ala Asn Trp Val Asn Val Ile Ser Asp
545                 550                 555                 560

Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr
                565                 570                 575

Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met
            580                 585                 590

Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp
        595                 600                 605

Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn
    610                 615                 620

Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys
625                 630                 635                 640

Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val
                645                 650                 655

His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly
            660                 665                 670

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        675                 680                 685

Gly Ser Leu Gln Ala Pro Arg Arg Ala Arg Gly Cys Arg Thr Leu Gly
    690                 695                 700

Leu Pro Ala Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro Ala Thr Arg
705                 710                 715                 720

Gly Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp
                725                 730                 735

Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser
            740                 745                 750

Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu
        755                 760                 765

Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys
    770                 775                 780
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Ile Arg
785

<210> SEQ ID NO 47
<211> LENGTH: 3019
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 47

gcgatcgcac catggcctta ccagtgaccg ccttgctcct gccgctggcc ttgctgctcc 60

acgccgccag gccggatgtg gtgatgaccc agagccatcg ctttatgagc accagcgtgg 120

gcgaccgagt gagcattacc tgccgcgcga gccaggatgt gaacaccgcg gtgagctggt 180

atcagcagaa accgggccag agcccgaaac tgctgatttt tagcgcgagc tatcgctata 240

ccggcgtgcc ggatcgcttt accggcagcg gcagcggcgc ggattttacc ctgaccatta 300

gcagcgtgca ggcggaagat ctggcggtgt attattgcca gcagcattat agcaccccgt 360

ggacctttgg cggcggcacc aaactggaca ttaaaggagg ggggggatcc gggggaggag 420

gctccggcgg aggcggaagc cagattcagc tggtgcagag cggcccggat ctgaaaaaac 480

cgggcgaaac cgtgaaactg agctgcaaag cgagcggcta tacctttacc aactttggca 540

tgaactgggt gaaacaggcg ccgggcaaag gctttaaatg gatggcgtgg attaacacca 600

cccgctatac cggcgaaagc tattttgcgg atgattttaa aggccgcttt gcgtttagcg 660

tggaaaccag cgcgaccacc gcgtatctgc agattaacaa cctgaaaacc gaagataccg 720

cgacctattt ttgcgcgcgc ggcgaaattt attatggcta tgatggcggc tttgcgtatt 780

ggggccaggg caccctggtg accgtgagcg cgaccacgac gccagcgccg cgaccaccaa 840

caccggcgcc caccatcgcg tcgcagcccc tgtccctgcg cccagaggcg tgccggccag 900

cggcgggggg cgcagtgcac acgagggggc tggacttcgc ctgtgatatc tacatctggg 960

cgcccttggc cgggacttgt ggggtccttc tcctgtcact ggttatcacc ctttactgca 1020

aacggggcag aaagaaactc ctgtatatat tcaaacaacc atttatgaga ccagtacaaa 1080

ctactcaaga ggaagatggc tgtagctgcc gatttccaga agaagaagaa ggaggatgtg 1140

aactgagagt gaagttcagc aggagcgcag acgcccccgc gtaccagcag ggccagaacc 1200

agctctataa cgagctcaat ctaggacgaa gagaggagta cgatgttttg gacaagagac 1260

gtggccggga ccctgagatg gggggaaagc cgcagagaag gaagaaccct caggaaggcc 1320

tgtacaatga actgcagaaa gataagatgg cggaggccta cagtgagatt gggatgaaag 1380

gcgagcgccg gaggggcaag gggcacgatg gcctttacca gggtctcagt acagccacca 1440

aggacaccta cgacgccctt cacatgcagg ccctgccccc tcgcggaagc ggagccacca 1500

acttcagcct gctgaagcag gccggcgacg tggaggagaa ccccggcccc atggccctgc 1560

ccgtgaccgc cctgctgctg cccctggccc tgctgctgca cgccgccagg cccgatattc 1620

agatgaccca gagcccgagc agcctgagcg cgagcgtggg cgaccgggtg accattacct 1680

gcaaagcgag ccaggatgtg ggcattgcgg tggcgtggta tcagcagaaa ccgggcaaag 1740

tgccgaaact gctgatttat tgggcgagca cccgccatac cggcgtgccg gatcgcttta 1800

gcggcagcgg cagcggcacc gattttaccc tgaccattag cagcctgcag ccggaagatg 1860

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tggcgaccta ttattgccag cagtatagca gctatccgta tacctttggc cagggcacca   1920

aagtggaaat taaaggaggg gggggatccg ggggaggagg ctccggcgga ggcggaagcg   1980

aagtgcagct ggtggaaagc ggcggcggcc tggtgcagcc gggcggcagc ctgcgcctga   2040

gctgcgcggc gagcggcttt gattttagcc gctattggat gagctgggtg cgccaggcgc   2100

cgggcaaagg cctggaatgg attggcgaaa ttaacccgga tagcagcacc attaactatg   2160

cgccgagcct gaaagataaa tttattatta gccgcgataa cgcgaaaaac agcctgtatc   2220

tgcagatgaa cagcctgcgc gcggaagata ccgcggtgta ttattgcgcg cgcccggatg   2280

gcaactattg gtattttgat gtgtggggcc agggcaccct ggtgaccgtg agcagcacca   2340

ccacccccgc ccccaggccc cccacccccg cccccaccat cgccagccag cccctgagcc   2400

tgaggcccga ggcctgcagg cccgccgccg gcggcgccgt gcacaccagg ggcctggact   2460

tcgcctgcga catctacatc tgggcccccc tggccggcac ctgcggcgtg ctgctgctga   2520

gcctggtgat caccctgtac tgcaagaggg gcaggaagaa gctgctgtac atcttcaagc   2580

agcccttcat gaggcccgtg cagaccaccc aggaggagga cggctgcagc tgcaggttcc   2640

ccgaggagga ggagggcggc tgcgagctga gggtgaagtt cagcaggagc gccgacgccc   2700

ccgcctacca gcagggccag aaccagctgt acaacgagct gaacctgggc aggagggagg   2760

agtacgacgt gctggacaag aggaggggca gggaccccga gatgggcggc aagccccaga   2820

ggaggaagaa cccccaggag ggcctgtaca acgagctgca gaaggacaag atggccgagg   2880

cctacagcga gatcggcatg aagggcgaga ggaggagggg caagggccac gacggcctgt   2940

accagggcct gagcaccgcc accaaggaca cctacgacgc cctgcacatg caggccctgc   3000

cccccaggta agtttaaac                                                3019
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<210> SEQ ID NO 48
<211> LENGTH: 999
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 48

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser His Arg Phe Met
            20                  25                  30

Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln
        35                  40                  45

Asp Val Asn Thr Ala Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser
    50                  55                  60

Pro Lys Leu Leu Ile Phe Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro
65                  70                  75                  80

Asp Arg Phe Thr Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140
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Ile Gln Leu Val Gln Ser Gly Pro Asp Leu Lys Lys Pro Gly Glu Thr
145                 150                 155                 160

Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Phe Gly
                165                 170                 175

Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Phe Lys Trp Met Ala
            180                 185                 190

Trp Ile Asn Thr Thr Arg Tyr Thr Gly Glu Ser Tyr Phe Ala Asp Asp
        195                 200                 205

Phe Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Thr Thr Ala
    210                 215                 220

Tyr Leu Gln Ile Asn Asn Leu Lys Thr Glu Asp Thr Ala Thr Tyr Phe
225                 230                 235                 240

Cys Ala Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Gly Gly Phe Ala Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr
                485                 490                 495

Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly
            500                 505                 510

Pro Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu
        515                 520                 525

Leu His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
    530                 535                 540
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Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
545                 550                 555                 560

Gln Asp Val Gly Ile Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
                565                 570                 575

Val Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg His Thr Gly Val
            580                 585                 590

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        595                 600                 605

Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln
    610                 615                 620

Tyr Ser Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
625                 630                 635                 640

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
                645                 650                 655

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
            660                 665                 670

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
        675                 680                 685

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
    690                 695                 700

Gly Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Ala Pro Ser Leu
705                 710                 715                 720

Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
                725                 730                 735

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
            740                 745                 750

Ala Arg Pro Asp Gly Asn Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly
        755                 760                 765

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
    770                 775                 780

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
785                 790                 795                 800

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
                805                 810                 815

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
            820                 825                 830

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
        835                 840                 845

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
    850                 855                 860

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
865                 870                 875                 880

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
                885                 890                 895

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
            900                 905                 910

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
        915                 920                 925

Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly
    930                 935                 940

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
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945 950 955 960

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
965 970 975

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
980 985 990

Met Gln Ala Leu Pro Pro Arg
995

<210> SEQ ID NO 49
<211> LENGTH: 3040
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 49

gcgatcgcac catggcctta ccagtgaccg ccttgctcct gccgctggcc ttgctgctcc 60

acgccgccag gccggatgtg gtgatgaccc agagccatcg ctttatgagc accagcgtgg 120

gcgaccgagt gagcattacc tgccgcgcga gccaggatgt gaacaccgcg gtgagctggt 180

atcagcagaa accgggccag agcccgaaac tgctgatttt tagcgcgagc tatcgctata 240

ccggcgtgcc ggatcgcttt accggcagcg gcagcggcgc ggattttacc ctgaccatta 300

gcagcgtgca ggcggaagat ctggcggtgt attattgcca gcagcattat agcaccccgt 360

ggacctttgg cggcggcacc aaactggaca ttaaaggagg ggggggatcc gggggaggag 420

gctccggcgg aggcggaagc cagattcagc tggtgcagag cggcccggat ctgaaaaaac 480

cgggcgaaac cgtgaaactg agctgcaaag cgagcggcta tacctttacc aactttggca 540

tgaactgggt gaaacaggcg ccgggcaaag gctttaaatg gatggcgtgg attaacacca 600

cccgctatac cggcgaaagc tattttgcgg atgattttaa aggccgcttt gcgtttagcg 660

tggaaaccag cgcgaccacc gcgtatctgc agattaacaa cctgaaaacc gaagataccg 720

cgacctattt ttgcgcgcgc ggcgaaattt attatggcta tgatggcggc tttgcgtatt 780

ggggccaggg caccctggtg accgtgagcg cgaccacgac gccagcgccg cgaccaccaa 840

caccggcgcc caccatcgcg tcgcagcccc tgtccctgcg cccagaggcg tgccggccag 900

cggcgggggg cgcagtgcac acgagggggc tggacttcgc ctgtgatatc tacatctggg 960

cgcccttggc cgggacttgt ggggtccttc tcctgtcact ggttatcacc ctttactgca 1020

aacggggcag aaagaaactc ctgtatatat tcaaacaacc atttatgaga ccagtacaaa 1080

ctactcaaga ggaagatggc tgtagctgcc gatttccaga agaagaagaa ggaggatgtg 1140

aactgagagt gaagttcagc aggagcgcag acgcccccgc gtaccagcag ggccagaacc 1200

agctctataa cgagctcaat ctaggacgaa gagaggagta cgatgttttg gacaagagac 1260

gtggccggga ccctgagatg gggggaaagc cgcagagaag gaagaaccct caggaaggcc 1320

tgtacaatga actgcagaaa gataagatgg cggaggccta cagtgagatt gggatgaaag 1380

gcgagcgccg gaggggcaag gggcacgatg gcctttacca gggtctcagt acagccacca 1440

aggacaccta cgacgccctt cacatgcagg ccctgccccc tcgcggaagc ggagccacca 1500

acttcagcct gctgaagcag gccggcgacg tggaggagaa ccccggcccc atggccctgc 1560

ccgtgaccgc cctgctgctg cccctggccc tgctgctgca cgccgccagg cccgaggtcc 1620

agctgcagca gtctggacct gagctgataa agcctggggc ttcagtgaag atgtcctgca 1680

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aggcttctgg atacacattc actagctatg ttatgcactg ggtgaagcag aagcctgggc   1740

agggccttga gtggattgga tatattaatc cttacaatga tggtactaag tacaatgaga   1800

agttcaaagg caaggccaca ctgacttcag acaaatcctc cagcacagcc tacatggagc   1860

tcagcagcct gacctctgag gactctgcgg tctattactg tgcaagaggg acttattact   1920

acggtagtag ggtatttgac tactggggcc aaggcaccac tctcacagtc tcctcaggtg   1980

gagggggctc aggcggaggt ggctctgggg gtggaggctc ggacattgtg atgactcagg   2040

ctgcaccctc tatacctgtc actcctggag agtcagtatc catctcctgc aggtctagta   2100

agagtctcct gaatagtaat ggcaacactt acttgtattg gttcctgcag aggccaggcc   2160

agtctcctca gctcctgata tatcggatgt ccaaccttgc ctcaggagtc ccagacaggt   2220

tcagtggcag tgggtcagga actgctttca cactgagaat cagtagagtg gaggctgagg   2280

atgtgggtgt ttattactgt atgcaacatc tagaatatcc gttcacgttc ggtgctggga   2340

ccaagctgga gctgaaacgg accaccaccc ccgcccccag gccccccacc cccgccccca   2400

ccatcgccag ccagcccctg agcctgaggc ccgaggcctg caggcccgcc gccggcggcg   2460

ccgtgcacac caggggcctg gacttcgcct gcgacatcta catctgggcc cccctggccg   2520

gcacctgcgg cgtgctgctg ctgagcctgg tgatcaccct gtactgcagg agtaagagga   2580

gcaggctcct gcacagtgac tacatgaaca tgactccccg ccgccccggg cccacccgca   2640

agcattacca gccctatgcc ccaccacgcg acttcgcagc ctatcgctcc agggtgaagt   2700

tcagcaggag cgccgacgcc cccgcctacc agcagggcca gaaccagctg tacaacgagc   2760

tgaacctggg caggagggag gagtacgacg tgctggacaa gaggaggggc agggaccccg   2820

agatgggcgg caagccccag aggaggaaga acccccagga gggcctgtac aacgagctgc   2880

agaaggacaa gatggccgag gcctacagcg agatcggcat gaagggcgag aggaggaggg   2940

gcaagggcca cgacggcctg taccagggcc tgagcaccgc caccaaggac acctacgacg   3000

ccctgcacat gcaggccctg ccccccaggt aagtttaaac                         3040
```

```
<210> SEQ ID NO 50
<211> LENGTH: 1006
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 50

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser His Arg Phe Met
            20                  25                  30

Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln
        35                  40                  45

Asp Val Asn Thr Ala Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser
    50                  55                  60

Pro Lys Leu Leu Ile Phe Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro
65                  70                  75                  80

Asp Arg Phe Thr Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His
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            100                 105                 110

Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Ile Gln Leu Val Gln Ser Gly Pro Asp Leu Lys Lys Pro Gly Glu Thr
145                 150                 155                 160

Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Phe Gly
                165                 170                 175

Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Phe Lys Trp Met Ala
            180                 185                 190

Trp Ile Asn Thr Thr Arg Tyr Thr Gly Glu Ser Tyr Phe Ala Asp Asp
        195                 200                 205

Phe Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Thr Thr Ala
    210                 215                 220

Tyr Leu Gln Ile Asn Asn Leu Lys Thr Glu Asp Thr Ala Thr Tyr Phe
225                 230                 235                 240

Cys Ala Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Gly Gly Phe Ala Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr
                485                 490                 495

Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly
            500                 505                 510
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Pro Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu
        515                 520                 525

Leu His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Glu
    530                 535                 540

Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly
545                 550                 555                 560

Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly
                565                 570                 575

Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr
            580                 585                 590

Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys
        595                 600                 605

Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp
    610                 615                 620

Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg
625                 630                 635                 640

Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly
                645                 650                 655

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
            660                 665                 670

Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser
        675                 680                 685

Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly
    690                 695                 700

Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln
705                 710                 715                 720

Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg
                725                 730                 735

Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg
            740                 745                 750

Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu
        755                 760                 765

Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr
    770                 775                 780

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
785                 790                 795                 800

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
                805                 810                 815

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
            820                 825                 830

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
        835                 840                 845

Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
    850                 855                 860

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
865                 870                 875                 880

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys
                885                 890                 895

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
            900                 905                 910
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Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
        915                 920                 925

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg
    930                 935                 940

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
945                 950                 955                 960

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
                965                 970                 975

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
            980                 985                 990

Asp Thr Tyr Asp Ala Leu His Met  Gln Ala Leu Pro Pro  Arg
        995                 1000                1005


<210> SEQ ID NO 51
<211> LENGTH: 3022
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 51

gcgatcgcac catggcctta ccagtgaccg ccttgctcct gccgctggcc ttgctgctcc     60

acgccgccag gccggatgtg gtgatgaccc agagccatcg ctttatgagc accagcgtgg    120

gcgaccgagt gagcattacc tgccgcgcga gccaggatgt gaacaccgcg gtgagctggt    180

atcagcagaa accgggccag agcccgaaac tgctgatttt tagcgcgagc tatcgctata    240

ccggcgtgcc ggatcgcttt accggcagcg gcagcggcgc ggattttacc ctgaccatta    300

gcagcgtgca ggcggaagat ctggcggtgt attattgcca gcagcattat agcaccccgt    360

ggacctttgg cggcggcacc aaactggaca ttaaaggagg ggggggatcc gggggaggag    420

gctccggcgg aggcggaagc cagattcagc tggtgcagag cggcccggat ctgaaaaaac    480

cgggcgaaac cgtgaaactg agctgcaaag cgagcggcta tacctttacc aactttggca    540

tgaactgggt gaaacaggcg ccgggcaaag gctttaaatg gatggcgtgg attaacacca    600

cccgctatac cggcgaaagc tattttgcgg atgattttaa aggccgcttt gcgtttagcg    660

tggaaaccag cgcgaccacc gcgtatctgc agattaacaa cctgaaaacc gaagataccg    720

cgacctattt ttgcgcgcgc ggcgaaattt attatggcta tgatggcggc tttgcgtatt    780

ggggccaggg caccctggtg accgtgagcg cgaccacgac gccagcgccg cgaccaccaa    840

caccggcgcc caccatcgcg tcgcagcccc tgtccctgcg cccagaggcg tgccggccag    900

cggcgggggg cgcagtgcac acgagggggc tggacttcgc ctgtgatatc tacatctggg    960

cgcccttggc cgggacttgt ggggtccttc tcctgtcact ggttatcacc ctttactgca   1020

aacggggcag aaagaaactc ctgtatatat tcaaacaacc atttatgaga ccagtacaaa   1080

ctactcaaga ggaagatggc tgtagctgcc gatttccaga agaagaagaa ggaggatgtg   1140

aactgagagt gaagttcagc aggagcgcag acgcccccgc gtaccagcag ggccagaacc   1200

agctctataa cgagctcaat ctaggacgaa gagaggagta cgatgttttg gacaagagac   1260

gtggccggga ccctgagatg gggggaaagc cgcagagaag gaagaaccct caggaaggcc   1320

tgtacaatga actgcagaaa gataagatgg cggaggccta cagtgagatt gggatgaaag   1380

gcgagcgccg gaggggcaag gggcacgatg gcctttacca gggtctcagt acagccacca   1440
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aggacaccta cgacgccctt cacatgcagg ccctgccccc tcgcggaagc ggagccacca   1500

acttcagcct gctgaagcag gccggcgacg tggaggagaa ccccggcccc atggccctgc   1560

ccgtgaccgc cctgctgctg cccctggccc tgctgctgca cgccgccagg cccgacatcc   1620

agatgacaca gactacatcc tccctgtctg cctctctggg agacagagtc accatcagtt   1680

gcagggcaag tcaggacatt agtaaatatt taaattggta tcagcagaaa ccagatggaa   1740

ctgttaaact cctgatctac catacatcaa gattacactc aggagtccca tcaaggttca   1800

gtggcagtgg gtctggaaca gattattctc tcaccattag caacctggag caagaagata   1860

ttgccactta cttttgccaa cagggtaata cgcttccgta cacgttcgga ggggggacca   1920

agctggagat cacaggtggc ggtggctcgg gcggtggtgg gtcgggtggc ggcggatctg   1980

aggtgaaact gcaggagtca ggacctggcc tggtggcgcc ctcacagagc ctgtccgtca   2040

catgcactgt ctcaggggtc tcattacccg actatggtgt aagctggatt cgccagcctc   2100

cacgaaaggg tctggagtgg ctgggagtaa tatggggtag tgaaaccaca tactataatt   2160

cagctctcaa atccagactg accatcatca aggacaactc caagagccaa gttttcttaa   2220

aaatgaacag tctgcaaact gatgacacag ccatttacta ctgtgccaaa cattattact   2280

acggtggtag ctatgctatg gactactggg gccaaggaac ctcagtcacc gtctcctcaa   2340

ccaccacccc cgcccccagg ccccccaccc ccgcccccac catcgccagc cagcccctga   2400

gcctgaggcc cgaggcctgc aggcccgccg ccggcggcgc cgtgcacacc aggggcctgg   2460

acttcgcctg cgacatctac atctgggccc ccctggccgg cacctgcggc gtgctgctgc   2520

tgagcctggt gatcaccctg tactgcaaga ggggcaggaa gaagctgctg tacatcttca   2580

agcagccctt catgaggccc gtgcagacca cccaggagga ggacggctgc agctgcaggt   2640

tccccgagga ggaggagggc ggctgcgagc tgagggtgaa gttcagcagg agcgccgacg   2700

cccccgccta ccagcagggc cagaaccagc tgtacaacga gctgaacctg ggcaggaggg   2760

aggagtacga cgtgctggac aagaggaggg gcagggaccc cgagatgggc ggcaagcccc   2820

agaggaggaa gaacccccag gagggcctgt acaacgagct gcagaaggac aagatggccg   2880

aggcctacag cgagatcggc atgaagggcg agaggaggag gggcaagggc cacgacggcc   2940

tgtaccaggg cctgagcacc gccaccaagg acacctacga cgccctgcac atgcaggccc   3000

tgcccccccag gtaagtttaa ac                                           3022
```

<210> SEQ ID NO 52
<211> LENGTH: 1000
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 52

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser His Arg Phe Met
            20                  25                  30

Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln
        35                  40                  45

Asp Val Asn Thr Ala Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser
    50                  55                  60
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Pro Lys Leu Leu Ile Phe Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro
65                  70                  75                  80

Asp Arg Phe Thr Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Ile Gln Leu Val Gln Ser Gly Pro Asp Leu Lys Lys Pro Gly Glu Thr
145                 150                 155                 160

Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Phe Gly
                165                 170                 175

Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Phe Lys Trp Met Ala
            180                 185                 190

Trp Ile Asn Thr Thr Arg Tyr Thr Gly Glu Ser Tyr Phe Ala Asp Asp
        195                 200                 205

Phe Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Thr Thr Ala
    210                 215                 220

Tyr Leu Gln Ile Asn Asn Leu Lys Thr Glu Asp Thr Ala Thr Tyr Phe
225                 230                 235                 240

Cys Ala Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Gly Gly Phe Ala Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
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465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr
                485                 490                 495

Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly
            500                 505                 510

Pro Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu
        515                 520                 525

Leu His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
    530                 535                 540

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
545                 550                 555                 560

Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
                565                 570                 575

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
            580                 585                 590

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
        595                 600                 605

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
    610                 615                 620

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
625                 630                 635                 640

Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
                645                 650                 655

Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
            660                 665                 670

Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr
        675                 680                 685

Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu
    690                 695                 700

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
705                 710                 715                 720

Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
                725                 730                 735

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala
            740                 745                 750

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
        755                 760                 765

Gly Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro
    770                 775                 780

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
785                 790                 795                 800

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
                805                 810                 815

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
            820                 825                 830

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
        835                 840                 845

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
    850                 855                 860

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
865                 870                 875                 880
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Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
                885                 890                 895

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
            900                 905                 910

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
        915                 920                 925

Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu
    930                 935                 940

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
945                 950                 955                 960

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
                965                 970                 975

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
            980                 985                 990

His Met Gln Ala Leu Pro Pro Arg
        995                 1000


<210> SEQ ID NO 53
<211> LENGTH: 1483
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 53

gcgatcgcac catggccctg cccgtgaccg ccctgctgct gcccctggcc ctgctgctgc     60

acgccgccag gcccgacatc cagatgacac agactacatc ctccctgtct gcctctctgg    120

gagacagagt caccatcagt tgcagggcaa gtcaggacat tagtaaatat ttaaattggt    180

atcagcagaa accagatgga actgttaaac tcctgatcta ccatacatca agattacact    240

caggagtccc atcaaggttc agtggcagtg ggtctggaac agattattct ctcaccatta    300

gcaacctgga gcaagaagat attgccactt acttttgcca acagggtaat acgcttccgt    360

acacgttcgg agggggggacc aagctggaga tcacaggtgg cggtggctcg ggcggtggtg    420

ggtcgggtgg cggcggatct gaggtgaaac tgcaggagtc aggacctggc ctggtggcgc    480

cctcacagag cctgtccgtc acatgcactg tctcaggggt ctcattaccc gactatggtg    540

taagctggat tcgccagcct ccacgaaagg gtctggagtg gctgggagta atatggggta    600

gtgaaaccac atactataat tcagctctca aatccagact gaccatcatc aaggacaact    660

ccaagagcca agttttctta aaaatgaaca gtctgcaaac tgatgacaca gccatttact    720

actgtgccaa acattattac tacggtggta gctatgctat ggactactgg ggccaaggaa    780

cctcagtcac cgtctcctca accacgacgc cagcgccgcg accaccaaca ccggcgccca    840

ccatcgcgtc gcagcccctg tccctgcgcc cagaggcgtg ccggccagcg gcgggggggcg    900

cagtgcacac gagggggctg gacttcgcct gtgatatcta catctgggcg cccttggccg    960

ggacttgtgg ggtccttctc ctgtcactgg ttatcaccct ttactgcaaa cggggcagaa   1020

agaaactcct gtatatattc aaacaaccat ttatgagacc agtacaaact actcaagagg   1080

aagatggctg tagctgccga tttccagaag aagaagaagg aggatgtgaa ctgagagtga   1140

agttcagcag gagcgcagac gcccccgcgt accagcaggg ccagaaccag ctctataacg   1200

agctcaatct aggacgaaga gaggagtacg atgttttgga caagagacgt ggccgggacc   1260
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ctgagatggg gggaaagccg cagagaagga agaaccctca ggaaggcctg tacaatgaac   1320

tgcagaaaga taagatggcg gaggcctaca gtgagattgg gatgaaaggc gagcgccgga   1380

ggggcaaggg gcacgatggc ctttaccagg gtctcagtac agccaccaag gacacctacg   1440

acgcccttca catgcaggcc ctgccccctc gctaagttta aac                     1483


<210> SEQ ID NO 54
<211> LENGTH: 487
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 54

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu
            20                  25                  30

Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr
    50                  55                  60

Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
                85                  90                  95

Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300
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Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly
            420                 425                 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        435                 440                 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
    450                 455                 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465                 470                 475                 480

Met Gln Ala Leu Pro Pro Arg
                485


<210> SEQ ID NO 55
<211> LENGTH: 1501
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 55

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg      60

ccgccaggcc ggaggtccag ctgcagcagt ctggacctga gctgataaag cctggggctt     120

cagtgaagat gtcctgcaag gcttctggat acacattcac tagctatgtt atgcactggg     180

tgaagcagaa gcctgggcag ggccttgagt ggattggata tattaatcct tacaatgatg     240

gtactaagta caatgagaag ttcaaaggca aggccacact gacttcagac aaatcctcca     300

gcacagccta catggagctc agcagcctga cctctgagga ctctgcggtc tattactgtg     360

caagagggac ttattactac ggtagtaggg tatttgacta ctggggccaa ggcaccactc     420

tcacagtctc ctcaggtgga gggggctcag gcggaggtgg ctctgggggt ggaggctcgg     480

acattgtgat gactcaggct gcaccctcta tacctgtcac tcctggagag tcagtatcca     540

tctcctgcag gtctagtaag agtctcctga atagtaatgg caacacttac ttgtattggt     600

tcctgcagag gccaggccag tctcctcagc tcctgatata tcggatgtcc aaccttgcct     660

caggagtccc agacaggttc agtggcagtg ggtcaggaac tgctttcaca ctgagaatca     720

gtagagtgga ggctgaggat gtgggtgttt attactgtat gcaacatcta gaatatccgt     780

tcacgttcgg tgctgggacc aagctggagc tgaaacggac cacgacgcca gcgccgcgac     840

caccaacacc ggcgcccacc atcgcgtcgc agcccctgtc cctgcgccca gaggcgtgcc     900
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ggccagcggc ggggggcgca gtgcacacga gggggctgga cttcgcctgt gatatctaca    960

tctgggcgcc cttggccggg acttgtgggg tccttctcct gtcactggtt atcacccttt   1020

actgcaaacg gggcagaaag aaactcctgt atatattcaa acaaccattt atgagaccag   1080

tacaaactac tcaagaggaa gatggctgta gctgccgatt tccagaagaa gaagaaggag   1140

gatgtgaact gagagtgaag ttcagcagga gcgcagacgc ccccgcgtac cagcagggcc   1200

agaaccagct ctataacgag ctcaatctag gacgaagaga ggagtacgat gttttggaca   1260

agagacgtgg ccgggaccct gagatggggg gaaagccgca gagaaggaag aaccctcagg   1320

aaggcctgta caatgaactg cagaaagata agatggcgga ggcctacagt gagattggga   1380

tgaaaggcga gcgccggagg ggcaaggggc acgatggcct ttaccagggt ctcagtacag   1440

ccaccaagga cacctacgac gcccttcaca tgcaggccct gccccctcgc taagtttaaa   1500

c                                                                   1501


<210> SEQ ID NO 56
<211> LENGTH: 494
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 56

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
            20                  25                  30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65                  70                  75                  80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
                85                  90                  95

Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145                 150                 155                 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
            180                 185                 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225                 230                 235                 240
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```
Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
                245                 250                 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Thr
            260                 265                 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
        275                 280                 285

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
    290                 295                 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305                 310                 315                 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
                325                 330                 335

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
            340                 345                 350

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
        355                 360                 365

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
    370                 375                 380

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
385                 390                 395                 400

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                405                 410                 415

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> SEQ ID NO 57
<211> LENGTH: 2293
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 57

gcgatcgcac catggccctg cccgtgaccg ccctgctgct gcccctggcc ctgctgctgc      60

acgccgccag gcccgacatt cagctgaccc agtctccagc aatcctttct gcatctccag     120

gggagaaggt cacaatgact tgcagggcca gctcaagttt aagtttcatg cactggtacc     180

agcagaagcc aggatcctcc cccaaaccct ggatttatgc cacatccaac ctggcttctg     240

gagtccctgc tcgcttcagt ggcagtgggt ctgggacctc ttactctctc acaatcagca     300

cagtggaggc tgaagatgct gcctcttatt tctgccatca gtggagtagt aacccgctca     360

cgttcggtgc tgggaccaag ctggagatca gctcgggcgg cggcggctcg ggcggcggcg     420

gctccggaga cgtcatgggg gtggattctg ggggaggctt agtgcagcct ggagggtccc     480

ggaaactctc ctgtgcagcc cctggattca ctttcagtag ctttgggatg cactgggttc     540
```

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```
gtcaggctcc agagaagggg ttggagtggg tcgcatacat tagtagtccc agtagtaccc    600
tccactatgc agacagagtg aagggccgat tcaccatctc cagagacaat cccaagaaca    660
ccctgttcct gcaaatgaaa ctaccctcac tatgctatgg actactgggg ccaagggacc    720
acgttcacac caccaccccc gcccccaggc cccccacccc cgcccccacc atcgccagcc    780
agcccctgag cctgaggccc gaggcctgca ggcccgccgc cggcggcgcc gtgcacacca    840
ggggcctgga cttcgcctgc gacatctaca tctgggcccc cctggccggc acctgcggcg    900
tgctgctgct gagcctggtg atcaccctgt actgcaggag taagaggagc aggctcctgc    960
acagtgacta catgaacatg actccccgcc gccccgggcc cacccgcaag cattaccagc   1020
cctatgcccc accacgcgac ttcgcagcct atcgctccag ggtgaagttc agcaggagcg   1080
ccgacgcccc cgcctaccag cagggccaga accagctgta caacgagctg aacctgggca   1140
ggagggagga gtacgacgtg ctggacaaga ggaggggcag ggaccccgag atgggcggca   1200
agccccagag gaggaagaac ccccaggagg gcctgtacaa cgagctgcag aaggacaaga   1260
tggccgaggc ctacagcgag atcggcatga agggcgagag gaggaggggc aagggccacg   1320
acggcctgta ccagggcctg agcaccgcca ccaaggacac ctacgacgcc ctgcacatgc   1380
aggccctgcc ccccagggga agcggagcca ccaacttcag cctgctgaag caggccggcg   1440
acgtggagga gaaccccggc cccatgtaca gaatgcagct gctgagctgc atcgccctga   1500
gcctggccct ggtgaccaac agcggcatcc acgtgttcat cctgggctgc ttcagcgccg   1560
gcctgcccaa gaccgaggcc aactgggtga acgtgatcag cgacctgaag aagatcgagg   1620
acctgatcca gagcatgcac atcgacgcca ccctgtacac cgagagcgac gtgcacccca   1680
gctgcaaggt gaccgccatg aagtgcttcc tgctggagct gcaggtgatc agcctggaga   1740
gcggcgacgc cagcatccac gacaccgtgg agaacctgat catcctggcc aacaacagcc   1800
tgagcagcaa cggcaacgtg accgagagcg gctgcaagga gtgcgaggag ctggaggaga   1860
agaacatcaa ggagttcctg cagagcttcg tgcacatcgt gcagatgttc atcaacacca   1920
gctccggcgg cggctccggc ggcggcggct ccggcggcgg cggctccggc ggcggcggct   1980
ccggcggcgg ctccctgcag gcccccagaa gagccagagg ctgcagaacc ctgggcctgc   2040
ccgccctgct gctgctgctg ctgctgagac cccccgccac cagaggcatc acctgccccc   2100
cccccatgag cgtggagcac gccgacatct gggtgaagag ctacagcctg tacagcagag   2160
agagatacat ctgcaacagc ggcttcaaga gaaaggccgg caccagcagc ctgaccgagt   2220
gcgtgctgaa caaggccacc aacgtggccc actggaccac ccccagcctg aagtgcatca   2280
gataagttta aac                                                      2293
```

<210> SEQ ID NO 58
<211> LENGTH: 757
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 58

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Gln Leu Thr Gln Ser Pro Ala Ile Leu
            20                  25                  30
```

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```
Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser
        35                  40                  45

Ser Leu Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro
    50                  55                  60

Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Ala
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser
                85                  90                  95

Thr Val Glu Ala Glu Asp Ala Ala Ser Tyr Phe Cys His Gln Trp Ser
            100                 105                 110

Ser Asn Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Ser Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Asp Val Met Gly Val
    130                 135                 140

Asp Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Arg Lys Leu Ser
145                 150                 155                 160

Cys Ala Ala Pro Gly Phe Thr Phe Ser Ser Phe Gly Met His Trp Val
                165                 170                 175

Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ala Tyr Ile Ser Ser
            180                 185                 190

Pro Ser Ser Thr Leu His Tyr Ala Asp Arg Val Lys Gly Arg Phe Thr
        195                 200                 205

Ile Ser Arg Asp Asn Pro Lys Asn Thr Leu Phe Leu Gln Met Lys Leu
    210                 215                 220

Pro Ser Leu Cys Tyr Gly Leu Leu Gly Pro Arg Asp His Val His Thr
225                 230                 235                 240

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
                245                 250                 255

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
            260                 265                 270

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
        275                 280                 285

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
    290                 295                 300

Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
305                 310                 315                 320

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
                325                 330                 335

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys
            340                 345                 350

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
        355                 360                 365

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
    370                 375                 380

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg
385                 390                 395                 400

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
                405                 410                 415

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
            420                 425                 430
```

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```
Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
        435                 440                 445

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser
    450                 455                 460

Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu
465                 470                 475                 480

Asn Pro Gly Pro Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu
                485                 490                 495

Ser Leu Ala Leu Val Thr Asn Ser Gly Ile His Val Phe Ile Leu Gly
            500                 505                 510

Cys Phe Ser Ala Gly Leu Pro Lys Thr Glu Ala Asn Trp Val Asn Val
        515                 520                 525

Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile
    530                 535                 540

Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val
545                 550                 555                 560

Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu
                565                 570                 575

Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu
            580                 585                 590

Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys
        595                 600                 605

Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln
    610                 615                 620

Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly
625                 630                 635                 640

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                645                 650                 655

Ser Gly Gly Gly Ser Leu Gln Ala Pro Arg Arg Ala Arg Gly Cys Arg
            660                 665                 670

Thr Leu Gly Leu Pro Ala Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro
        675                 680                 685

Ala Thr Arg Gly Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala
    690                 695                 700

Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile
705                 710                 715                 720

Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu
                725                 730                 735

Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser
            740                 745                 750

Leu Lys Cys Ile Arg
        755


<210> SEQ ID NO 59
<211> LENGTH: 2389
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 59

gcgatcgcac catggcctta ccagtgaccg ccttgctcct gccgctggcc ttgctgctcc      60

acgccgccag gccggaggtc cagctgcagc agtctggacc tgagctgata aagcctgggg     120
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cttcagtgaa gatgtcctgc aaggcttctg gatacacatt cactagctat gttatgcact    180
gggtgaagca gaagcctggg cagggccttg agtggattgg atatattaat ccttacaatg    240
atggtactaa gtacaatgag aagttcaaag gcaaggccac actgacttca gacaaatcct    300
ccagcacagc ctacatggag ctcagcagcc tgacctctga ggactctgcg gtctattact    360
gtgcaagagg gacttattac tacggtagta gggtatttga ctactggggc caaggcacca    420
ctctcacagt ctcctcaggt ggagggggct caggcggagg tggctctggg ggtggaggct    480
cggacattgt gatgactcag gctgcaccct ctatacctgt cactcctgga gagtcagtat    540
ccatctcctg caggtctagt aagagtctcc tgaatagtaa tggcaacact tacttgtatt    600
ggttcctgca gaggccaggc cagtctcctc agctcctgat atatcggatg tccaaccttg    660
cctcaggagt cccagacagg ttcagtggca gtgggtcagg aactgctttc acactgagaa    720
tcagtagagt ggaggctgag gatgtgggtg tttattactg tatgcaacat ctagaatatc    780
cgttcacgtt cggtgctggg accaagctgg agctgaaacg gaccacgacg ccagcgccgc    840
gaccaccaac accggcgccc accatcgcgt cgcagcccct gtccctgcgc ccagaggcgt    900
gccggccagc ggcgggggc gcagtgcaca cgagggggct ggacttcgcc tgtgatatct    960
acatctgggc gcccttggcc gggacttgtg gggtccttct cctgtcactg gttatcaccc   1020
tttactgcaa acggggcaga aagaaactcc tgtatatatt caaacaacca tttatgagac   1080
cagtacaaac tactcaagag gaagatggct gtagctgccg atttccagaa gaagaagaag   1140
gaggatgtga actgagagtg aagttcagca ggagcgcaga cgcccccgcg taccagcagg   1200
gccagaacca gctctataac gagctcaatc taggacgaag agaggagtac gatgttttgg   1260
acaagagacg tggccgggac cctgagatgg ggggaaagcc gcagagaagg aagaaccctc   1320
aggaaggcct gtacaatgaa ctgcagaaag ataagatggc ggaggcctac agtgagattg   1380
ggatgaaagg cgagcgccgg aggggcaagg ggcacgatgg cctttaccag ggtctcagta   1440
cagccaccaa ggacacctac gacgcccttc acatgcaggc cctgccccct cgcggaagcg   1500
gagccaccaa cttcagcctg ctgaagcagg ccggcgacgt ggaggagaac cccggcccca   1560
tgtacagaat gcagctgctg agctgcatcg ccctgagcct ggccctggtg accaacagcg   1620
gcatccacgt gttcatcctg ggctgcttca gcgccggcct gcccaagacc gaggccaact   1680
gggtgaacgt gatcagcgac ctgaagaaga tcgaggacct gatccagagc atgcacatcg   1740
acgccaccct gtacaccgag agcgacgtgc accccagctg caaggtgacc gccatgaagt   1800
gcttcctgct ggagctgcag gtgatcagcc tggagagcgg cgacgccagc atccacgaca   1860
ccgtggagaa cctgatcatc ctggccaaca acagcctgag cagcaacggc aacgtgaccg   1920
agagcggctg caaggagtgc gaggagctgg aggagaagaa catcaaggag ttcctgcaga   1980
gcttcgtgca catcgtgcag atgttcatca acaccagctc cggcggcggc tccggcggcg   2040
gcggctccgg cggcggcggc tccggcggcg gcggctccgg cggcggctcc ctgcaggccc   2100
ccagaagagc cagaggctgc agaaccctgg gcctgcccgc cctgctgctg ctgctgctgc   2160
tgagaccccc cgccaccaga ggcatcacct gcccccccc catgagcgtg gagcacgccg   2220
acatctgggt gaagagctac agcctgtaca gcagagagag atacatctgc aacagcggct   2280
tcaagagaaa ggccggcacc agcagcctga ccgagtgcgt gctgaacaag gccaccaacg   2340
tggcccactg gaccaccccc agcctgaagt gcatcagata agtttaaac               2389
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<210> SEQ ID NO 60
<211> LENGTH: 789
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 60

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
20 25 30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65 70 75 80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
85 90 95

Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
115 120 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145 150 155 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
165 170 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
180 185 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
195 200 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
210 215 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225 230 235 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
245 250 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Thr
260 265 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
275 280 285

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
290 295 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305 310 315 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
325 330 335

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
340 345 350

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Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
        355                 360                 365

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
    370                 375                 380

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
385                 390                 395                 400

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                405                 410                 415

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser
                485                 490                 495

Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu
            500                 505                 510

Asn Pro Gly Pro Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu
        515                 520                 525

Ser Leu Ala Leu Val Thr Asn Ser Gly Ile His Val Phe Ile Leu Gly
    530                 535                 540

Cys Phe Ser Ala Gly Leu Pro Lys Thr Glu Ala Asn Trp Val Asn Val
545                 550                 555                 560

Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile
                565                 570                 575

Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val
            580                 585                 590

Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu
        595                 600                 605

Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu
    610                 615                 620

Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys
625                 630                 635                 640

Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln
                645                 650                 655

Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly
            660                 665                 670

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        675                 680                 685

Ser Gly Gly Gly Ser Leu Gln Ala Pro Arg Arg Ala Arg Gly Cys Arg
    690                 695                 700

Thr Leu Gly Leu Pro Ala Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro
705                 710                 715                 720

Ala Thr Arg Gly Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala
                725                 730                 735

Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile
            740                 745                 750
```

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```
Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu
        755                 760                 765

Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser
    770                 775                 780

Leu Lys Cys Ile Arg
785


<210> SEQ ID NO 61
<211> LENGTH: 2389
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 61

gcgatcgcac catggccctg cccgtgaccg ccctgctgct gcccctggcc ctgctgctgc     60

acgccgccag gcccgatatc cagatgaccc agagccccag ctccctgtcc gcatccgtgg    120

gcgacagagt gacaattacc tgtagaagca gccaaagcat cgtgcatagc gtcggcaaca    180

cttttctgga gtggtatcaa cagaagcccg ggaaggcccc caaactgctg atctacaagg    240

tgagcaacag attcagcggg gtcccaagca gattctccgg cagcggctcc gggactgact    300

tcaccctgac cattagcagc ctgcagccag aggacttcgc cacatactac tgcttccaag    360

ggagccagtt cccctacacc ttcggccaag gcactaaggt ggagatcaaa gggggggag    420

gaagcggcgg aggagggagc ggaggcgggg gatccgaagt gcaactggtc gaatccggag    480

gggggctggt ccagcctgga gggtccctga gactgagctg cgccgcaagc ggctacgagt    540

tctccaggtc ctggatgaac tgggtgaggc aggccccagg aaaagggctg gaatgggtgg    600

gcaggatcta ccctggcgac ggcgatacca actactccgg aaagttcaag ggcaggttca    660

ctatcagcgc cgacactagc aagaataccg cctacctgca gatgaatagc ctgagggccg    720

aggacaccgc cgtgtattac tgcgctagag acggcagcag ctgggattgg tacttcgacg    780

tgtggggcca gggcactctg gtgactgtga gcagcaccac cacccccgcc cccaggcccc    840

ccacccccgc ccccaccatc gccagccagc ccctgagcct gaggcccgag gcctgcaggc    900

ccgccgccgg cggcgccgtg cacaccaggg gcctggactt cgcctgcgac ttttgggtgc    960

tggtggtggt tggtggagtc ctggcttgct atagcttgct agtaacagtg gcctttatta   1020

ttttctgggt gaggagtaag aggagcaggc tcctgcacag tgactacatg aacatgactc   1080

cccgccgccc cgggcccacc cgcaagcatt accagcccta tgccccacca cgcgacttcg   1140

cagcctatcg ctccagggtg aagttcagca ggagcgccga cgcccccgcc taccagcagg   1200

gccagaacca gctgtacaac gagctgaacc tgggcaggag ggaggagtac gacgtgctgg   1260

acaagaggag gggcagggac cccgagatgg gcggcaagcc ccagaggagg aagaaccccc   1320

aggagggcct gtacaacgag ctgcagaagg acaagatggc cgaggcctac agcgagatcg   1380

gcatgaaggg cgagaggagg aggggcaagg gccacgacgg cctgtaccag ggcctgagca   1440

ccgccaccaa ggacacctac gacgccctgc acatgcaggc cctgcccccc aggggaagcg   1500

gagccaccaa cttcagcctg ctgaagcagg ccggcgacgt ggaggagaac cccggcccca   1560

tgtacagaat gcagctgctg agctgcatcg ccctgagcct ggccctggtg accaacagcg   1620

gcatccacgt gttcatcctg ggctgcttca gcgccggcct gcccaagacc gaggccaact   1680

gggtgaacgt gatcagcgac ctgaagaaga tcgaggacct gatccagagc atgcacatcg   1740
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acgccaccct gtacaccgag agcgacgtgc accccagctg caaggtgacc gccatgaagt   1800

gcttcctgct ggagctgcag gtgatcagcc tggagagcgg cgacgccagc atccacgaca   1860

ccgtggagaa cctgatcatc ctggccaaca acagcctgag cagcaacggc aacgtgaccg   1920

agagcggctg caaggagtgc gaggagctgg aggagaagaa catcaaggag ttcctgcaga   1980

gcttcgtgca catcgtgcag atgttcatca acaccagctc cggcggcggc tccggcggcg   2040

gcggctccgg cggcggcggc tccggcggcg gcggctccgg cggcggctcc ctgcaggccc   2100

ccagaagagc cagaggctgc agaaccctgg gcctgcccgc cctgctgctg ctgctgctgc   2160

tgagaccccc cgccaccaga ggcatcacct gcccccccc catgagcgtg gagcacgccg   2220

acatctgggt gaagagctac agcctgtaca gcagagagag atacatctgc aacagcggct   2280

tcaagagaaa ggccggcacc agcagcctga ccgagtgcgt gctgaacaag gccaccaacg   2340

tggcccactg gaccaccccc agcctgaagt gcatcagata agtttaaac               2389
```

```
<210> SEQ ID NO 62
<211> LENGTH: 789
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 62

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
            20                  25                  30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln
        35                  40                  45

Ser Ile Val His Ser Val Gly Asn Thr Phe Leu Glu Trp Tyr Gln Gln
    50                  55                  60

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg
65                  70                  75                  80

Phe Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
                85                  90                  95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
            100                 105                 110

Tyr Cys Phe Gln Gly Ser Gln Phe Pro Tyr Thr Phe Gly Gln Gly Thr
        115                 120                 125

Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
145                 150                 155                 160

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Glu
                165                 170                 175

Phe Ser Arg Ser Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Val Gly Arg Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr
        195                 200                 205

Ser Gly Lys Phe Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys
    210                 215                 220

Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
```

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225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Asp Gly Ser Ser Trp Asp Trp Tyr Phe Asp
                245                 250                 255

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Trp Val Leu Val Val Val
305                 310                 315                 320

Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile
                325                 330                 335

Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
            340                 345                 350

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
        355                 360                 365

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys
    370                 375                 380

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
385                 390                 395                 400

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                405                 410                 415

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser
                485                 490                 495

Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu
            500                 505                 510

Asn Pro Gly Pro Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu
        515                 520                 525

Ser Leu Ala Leu Val Thr Asn Ser Gly Ile His Val Phe Ile Leu Gly
    530                 535                 540

Cys Phe Ser Ala Gly Leu Pro Lys Thr Glu Ala Asn Trp Val Asn Val
545                 550                 555                 560

Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile
                565                 570                 575

Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val
            580                 585                 590

Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu
        595                 600                 605

Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu
    610                 615                 620

Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys
625                 630                 635                 640
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Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln
                645                 650                 655

Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly
            660                 665                 670

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        675                 680                 685

Ser Gly Gly Gly Ser Leu Gln Ala Pro Arg Arg Ala Arg Gly Cys Arg
    690                 695                 700

Thr Leu Gly Leu Pro Ala Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro
705                 710                 715                 720

Ala Thr Arg Gly Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala
                725                 730                 735

Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile
            740                 745                 750

Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu
        755                 760                 765

Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser
    770                 775                 780

Leu Lys Cys Ile Arg
785


<210> SEQ ID NO 63
<211> LENGTH: 3049
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 63

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc ggaggtccag ctgcagcagt ctggacctga gctgataaag cctggggctt    120

cagtgaagat gtcctgcaag gcttctggat acacattcac tagctatgtt atgcactggg    180

tgaagcagaa gcctgggcag ggccttgagt ggattggata tattaatcct tacaatgatg    240

gtactaagta caatgagaag ttcaaaggca aggccacact gacttcagac aaatcctcca    300

gcacagccta catggagctc agcagcctga cctctgagga ctctgcggtc tattactgtg    360

caagagggac ttattactac ggtagtaggg tatttgacta ctggggccaa ggcaccactc    420

tcacagtctc ctcaggtgga gggggctcag gcggaggtgg ctctgggggt ggaggctcgg    480

acattgtgat gactcaggct gcaccctcta tacctgtcac tcctggagag tcagtatcca    540

tctcctgcag gtctagtaag agtctcctga atagtaatgg caacacttac ttgtattggt    600

tcctgcagag gccaggccag tctcctcagc tcctgatata tcggatgtcc aaccttgcct    660

caggagtccc agacaggttc agtggcagtg ggtcaggaac tgctttcaca ctgagaatca    720

gtagagtgga ggctgaggat gtgggtgttt attactgtat gcaacatcta gaatatccgt    780

tcacgttcgg tgctgggacc aagctggagc tgaaacggac cacgacgcca gcgccgcgac    840

caccaacacc ggcgcccacc atcgcgtcgc agcccctgtc cctgcgccca gaggcgtgcc    900

ggccagcggc ggggggcgca gtgcacacga gggggctgga cttcgcctgt gatatctaca    960

tctgggcgcc cttggccggg acttgtgggg tccttctcct gtcactggtt atcacccttt   1020

actgcaaacg gggcagaaag aaactcctgt atatattcaa acaaccattt atgagaccag   1080
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tacaaactac tcaagaggaa gatggctgta gctgccgatt tccagaagaa gaagaaggag   1140
gatgtgaact gagagtgaag ttcagcagga gcgcagacgc ccccgcgtac cagcagggcc   1200
agaaccagct ctataacgag ctcaatctag gacgaagaga ggagtacgat gttttggaca   1260
agagacgtgg ccgggaccct gagatggggg gaaagccgca gagaaggaag aaccctcagg   1320
aaggcctgta caatgaactg cagaaagata agatggcgga ggcctacagt gagattggga   1380
tgaaaggcga gcgccggagg ggcaaggggc acgatggcct ttaccagggt ctcagtacag   1440
ccaccaagga cacctacgac gcccttcaca tgcaggccct gccccctcgc ggaagcggag   1500
ccaccaactt cagcctgctg aagcaggccg gcgacgtgga ggagaacccc ggccccatgg   1560
ccctgcccgt gaccgccctg ctgctgcccc tggccctgct gctgcacgcc gccaggcccg   1620
atatccagat gacccagagc cccagctccc tgtccgcatc cgtgggcgac agagtgacaa   1680
ttacctgtag aagcagccaa agcatcgtgc atagcgtcgg caacactttt ctggagtggt   1740
atcaacagaa gcccgggaag gcccccaaac tgctgatcta caaggtgagc aacagattca   1800
gcggggtccc aagcagattc tccggcagcg gctccgggac tgacttcacc ctgaccatta   1860
gcagcctgca gccagaggac ttcgccacat actactgctt ccaagggagc cagttcccct   1920
acaccttcgg ccaaggcact aaggtggaga tcaaaggggg gggaggaagc ggcggaggag   1980
ggagcggagg cgggggatcc gaagtgcaac tggtcgaatc cggagggggg ctggtccagc   2040
ctggagggtc cctgagactg agctgcgccg caagcggcta cgagttctcc aggtcctgga   2100
tgaactgggt gaggcaggcc ccaggaaaag ggctggaatg ggtgggcagg atctaccctg   2160
gcgacggcga taccaactac tccggaaagt tcaagggcag gttcactatc agcgccgaca   2220
ctagcaagaa taccgcctac ctgcagatga atagcctgag ggccgaggac accgccgtgt   2280
attactgcgc tagagacggc agcagctggg attggtactt cgacgtgtgg ggccagggca   2340
ctctggtgac tgtgagcagc accaccaccc ccgcccccag gcccccccacc cccgccccca   2400
ccatcgccag ccagcccctg agcctgaggc ccgaggcctg caggcccgcc gccggcggcg   2460
ccgtgcacac caggggcctg gacttcgcct gcgacttttg ggtgctggtg gtggttggtg   2520
gagtcctggc ttgctatagc ttgctagtaa cagtggcctt tattattttc tgggtgagga   2580
gtaagaggag caggctcctg cacagtgact acatgaacat gactccccgc cgccccgggc   2640
ccacccgcaa gcattaccag ccctatgccc caccacgcga cttcgcagcc tatcgctcca   2700
gggtgaagtt cagcaggagc gccgacgccc ccgcctacca gcagggccag aaccagctgt   2760
acaacgagct gaacctgggc aggagggagg agtacgacgt gctggacaag aggaggggca   2820
gggaccccga gatgggcggc aagccccaga ggaggaagaa cccccaggag ggcctgtaca   2880
acgagctgca gaaggacaag atggccgagg cctacagcga gatcggcatg aagggcgaga   2940
ggaggagggg caagggccac gacggcctgt accagggcct gagcaccgcc accaaggaca   3000
cctacgacgc cctgcacatg caggccctgc cccccaggta agtttaaac               3049
```

<210> SEQ ID NO 64
<211> LENGTH: 1010
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 64

-continued

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
            20                  25                  30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65                  70                  75                  80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
                85                  90                  95

Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145                 150                 155                 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
            180                 185                 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225                 230                 235                 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
                245                 250                 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Thr
            260                 265                 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
        275                 280                 285

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
    290                 295                 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305                 310                 315                 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
                325                 330                 335

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
            340                 345                 350

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
        355                 360                 365

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
    370                 375                 380

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
385                 390                 395                 400
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```
Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                405                 410                 415

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser
                485                 490                 495

Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu
            500                 505                 510

Asn Pro Gly Pro Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu
        515                 520                 525

Ala Leu Leu Leu His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Ser
    530                 535                 540

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
545                 550                 555                 560

Arg Ser Ser Gln Ser Ile Val His Ser Val Gly Asn Thr Phe Leu Glu
                565                 570                 575

Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys
            580                 585                 590

Val Ser Asn Arg Phe Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly
        595                 600                 605

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp
    610                 615                 620

Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gln Phe Pro Tyr Thr Phe
625                 630                 635                 640

Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly
                645                 650                 655

Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
            660                 665                 670

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
        675                 680                 685

Ser Gly Tyr Glu Phe Ser Arg Ser Trp Met Asn Trp Val Arg Gln Ala
    690                 695                 700

Pro Gly Lys Gly Leu Glu Trp Val Gly Arg Ile Tyr Pro Gly Asp Gly
705                 710                 715                 720

Asp Thr Asn Tyr Ser Gly Lys Phe Lys Gly Arg Phe Thr Ile Ser Ala
                725                 730                 735

Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala
            740                 745                 750

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Gly Ser Ser Trp Asp
        755                 760                 765

Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    770                 775                 780

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
785                 790                 795                 800

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
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                805                 810                 815

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Trp Val
            820                 825                 830

Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr
        835                 840                 845

Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu
    850                 855                 860

His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
865                 870                 875                 880

Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
                885                 890                 895

Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
            900                 905                 910

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
        915                 920                 925

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
    930                 935                 940

Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
945                 950                 955                 960

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
                965                 970                 975

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
            980                 985                 990

Thr Ala Thr Lys Asp Thr Tyr Asp  Ala Leu His Met Gln  Ala Leu Pro
        995                 1000                1005

Pro Arg
    1010


<210> SEQ ID NO 65
<211> LENGTH: 2953
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 65

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc ggaggtccag ctgcagcagt ctggacctga gctgataaag cctggggctt    120

cagtgaagat gtcctgcaag gcttctggat acacattcac tagctatgtt atgcactggg    180

tgaagcagaa gcctgggcag ggccttgagt ggattggata tattaatcct tacaatgatg    240

gtactaagta caatgagaag ttcaaaggca aggccacact gacttcagac aaatcctcca    300

gcacagccta catggagctc agcagcctga cctctgagga ctctgcggtc tattactgtg    360

caagagggac ttattactac ggtagtaggg tatttgacta ctggggccaa ggcaccactc    420

tcacagtctc ctcaggtgga gggggctcag gcggaggtgg ctctgggggt ggaggctcgg    480

acattgtgat gactcaggct gcaccctcta tacctgtcac tcctggagag tcagtatcca    540

tctcctgcag gtctagtaag agtctcctga atagtaatgg caacacttac ttgtattggt    600

tcctgcagag gccaggccag tctcctcagc tcctgatata tcggatgtcc aaccttgcct    660

caggagtccc agacaggttc agtggcagtg ggtcaggaac tgctttcaca ctgagaatca    720

gtagagtgga ggctgaggat gtgggtgttt attactgtat gcaacatcta gaatatccgt    780
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tcacgttcgg tgctgggacc aagctggagc tgaaacggac cacgacgcca gcgccgcgac    840
caccaacacc ggcgcccacc atcgcgtcgc agcccctgtc cctgcgccca gaggcgtgcc    900
ggccagcggc ggggggcgca gtgcacacga gggggctgga cttcgcctgt gatatctaca    960
tctgggcgcc cttggccggg acttgtgggg tccttctcct gtcactggtt atcacccttt   1020
actgcaaacg gggcagaaag aaactcctgt atatattcaa acaaccattt atgagaccag   1080
tacaaactac tcaagaggaa gatggctgta gctgccgatt tccagaagaa gaagaaggag   1140
gatgtgaact gagagtgaag ttcagcagga gcgcagacgc ccccgcgtac cagcagggcc   1200
agaaccagct ctataacgag ctcaatctag gacgaagaga ggagtacgat gttttggaca   1260
agagacgtgg ccgggaccct gagatggggg gaaagccgca gagaaggaag aaccctcagg   1320
aaggcctgta caatgaactg cagaaagata agatggcgga ggcctacagt gagattggga   1380
tgaaaggcga gcgccggagg ggcaaggggc acgatggcct ttaccagggt ctcagtacag   1440
ccaccaagga cacctacgac gcccttcaca tgcaggccct gccccctcgc ggaagcggag   1500
ccaccaactt cagcctgctg aagcaggccg gcgacgtgga ggagaacccc ggccccatgg   1560
ccctgcccgt gaccgccctg ctgctgcccc tggccctgct gctgcacgcc gccaggcccg   1620
acattcagct gacccagtct ccagcaatcc tttctgcatc tccaggggag aaggtcacaa   1680
tgacttgcag ggccagctca agtttaagtt tcatgcactg gtaccagcag aagccaggat   1740
cctcccccaa accctggatt tatgccacat ccaacctggc ttctggagtc cctgctcgct   1800
tcagtggcag tgggtctggg acctcttact ctctcacaat cagcacagtg gaggctgaag   1860
atgctgcctc ttatttctgc catcagtgga gtagtaaccc gctcacgttc ggtgctggga   1920
ccaagctgga gatcagctcg ggcggcggcg gctcgggcgg cggcggctcc ggagacgtca   1980
tgggggtgga ttctgggggga ggcttagtgc agcctggagg gtcccggaaa ctctcctgtg   2040
cagcccctgg attcactttc agtagctttg ggatgcactg ggttcgtcag gctccagaga   2100
aggggttgga gtgggtcgca tacattagta gtcccagtag taccctccac tatgcagaca   2160
gagtgaaggg ccgattcacc atctccagag acaatcccaa gaacaccctg ttcctgcaaa   2220
tgaaactacc ctcactatgc tatggactac tggggccaag ggaccacgtt cacaccacca   2280
cccccgcccc caggcccccc acccccgccc ccaccatcgc cagccagccc ctgagcctga   2340
ggcccgaggc ctgcaggccc gccgccggcg gcgccgtgca caccaggggc ctggacttcg   2400
cctgcgacat ctacatctgg gcccccctgg ccggcacctg cggcgtgctg ctgctgagcc   2460
tggtgatcac cctgtactgc aggagtaaga ggagcaggct cctgcacagt gactacatga   2520
acatgactcc ccgccgcccc gggcccaccc gcaagcatta ccagccctat gccccaccac   2580
gcgacttcgc agcctatcgc tccagggtga agttcagcag gagcgccgac gcccccgcct   2640
accagcaggg ccagaaccag ctgtacaacg agctgaacct gggcaggagg gaggagtacg   2700
acgtgctgga caagaggagg ggcagggacc ccgagatggg cggcaagccc cagaggagga   2760
agaacccccca ggagggcctg tacaacgagc tgcagaagga caagatggcc gaggcctaca   2820
gcgagatcgg catgaagggc gagaggagga ggggcaaggg ccacgacggc ctgtaccagg   2880
gcctgagcac cgccaccaag gacacctacg acgccctgca catgcaggcc ctgcccccca   2940
ggtaagttta aac                                                      2953
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<210> SEQ ID NO 66
<211> LENGTH: 978
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 66

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
20 25 30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
50 55 60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65 70 75 80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
85 90 95

Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
115 120 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145 150 155 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
165 170 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
180 185 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
195 200 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
210 215 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225 230 235 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
245 250 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Thr
260 265 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
275 280 285

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
290 295 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305 310 315 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
325 330 335

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
340 345 350

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser

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        355                 360                 365

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
    370                 375                 380

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
385                 390                 395                 400

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                405                 410                 415

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser
                485                 490                 495

Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu
            500                 505                 510

Asn Pro Gly Pro Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu
        515                 520                 525

Ala Leu Leu Leu His Ala Ala Arg Pro Asp Ile Gln Leu Thr Gln Ser
    530                 535                 540

Pro Ala Ile Leu Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys
545                 550                 555                 560

Arg Ala Ser Ser Ser Leu Ser Phe Met His Trp Tyr Gln Gln Lys Pro
                565                 570                 575

Gly Ser Ser Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser
            580                 585                 590

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser
        595                 600                 605

Leu Thr Ile Ser Thr Val Glu Ala Glu Asp Ala Ala Ser Tyr Phe Cys
    610                 615                 620

His Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu
625                 630                 635                 640

Glu Ile Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Asp
                645                 650                 655

Val Met Gly Val Asp Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
            660                 665                 670

Arg Lys Leu Ser Cys Ala Ala Pro Gly Phe Thr Phe Ser Ser Phe Gly
        675                 680                 685

Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ala
    690                 695                 700

Tyr Ile Ser Ser Pro Ser Ser Thr Leu His Tyr Ala Asp Arg Val Lys
705                 710                 715                 720

Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Asn Thr Leu Phe Leu
                725                 730                 735

Gln Met Lys Leu Pro Ser Leu Cys Tyr Gly Leu Leu Gly Pro Arg Asp
            740                 745                 750

His Val His Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
        755                 760                 765
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Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
    770                 775                 780

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
785                 790                 795                 800

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
                805                 810                 815

Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu
            820                 825                 830

His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
        835                 840                 845

Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
    850                 855                 860

Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
865                 870                 875                 880

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
                885                 890                 895

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
            900                 905                 910

Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
        915                 920                 925

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
    930                 935                 940

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
945                 950                 955                 960

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
                965                 970                 975

Pro Arg


<210> SEQ ID NO 67
<211> LENGTH: 3010
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 67

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg      60

ccgccaggcc ggaggtccag ctgcagcagt ctggacctga gctgataaag cctggggctt     120

cagtgaagat gtcctgcaag gcttctggat acacattcac tagctatgtt atgcactggg     180

tgaagcagaa gcctgggcag ggccttgagt ggattggata tattaatcct tacaatgatg     240

gtactaagta caatgagaag ttcaaaggca aggccacact gacttcagac aaatcctcca     300

gcacagccta catggagctc agcagcctga cctctgagga ctctgcggtc tattactgtg     360

caagagggac ttattactac ggtagtaggg tatttgacta ctggggccaa ggcaccactc     420

tcacagtctc ctcaggtgga gggggctcag gcggaggtgg ctctgggggt ggaggctcgg     480

acattgtgat gactcaggct gcaccctcta tacctgtcac tcctggagag tcagtatcca     540

tctcctgcag gtctagtaag agtctcctga atagtaatgg caacacttac ttgtattggt     600

tcctgcagag gccaggccag tctcctcagc tcctgatata tcggatgtcc aaccttgcct     660

caggagtccc agacaggttc agtggcagtg ggtcaggaac tgctttcaca ctgagaatca     720
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gtagagtgga ggctgaggat gtgggtgttt attactgtat gcaacatcta gaatatccgt    780
tcacgttcgg tgctgggacc aagctggagc tgaaacggac cacgacgcca gcgccgcgac    840
caccaacacc ggcgcccacc atcgcgtcgc agcccctgtc cctgcgccca gaggcgtgcc    900
ggccagcggc ggggggcgca gtgcacacga gggggctgga cttcgcctgt gatatctaca    960
tctgggcgcc cttggccggg acttgtgggg tccttctcct gtcactggtt atcacccttt   1020
actgcaaacg gggcagaaag aaactcctgt atatattcaa acaaccattt atgagaccag   1080
tacaaactac tcaagaggaa gatggctgta gctgccgatt tccagaagaa gaagaaggag   1140
gatgtgaact gagagtgaag ttcagcagga gcgcagacgc ccccgcgtac cagcagggcc   1200
agaaccagct ctataacgag ctcaatctag gacgaagaga ggagtacgat gttttggaca   1260
agagacgtgg ccgggaccct gagatggggg gaaagccgca gagaaggaag aaccctcagg   1320
aaggcctgta caatgaactg cagaaagata agatggcgga ggcctacagt gagattggga   1380
tgaaaggcga gcgccggagg ggcaaggggc acgatggcct ttaccagggt ctcagtacag   1440
ccaccaagga cacctacgac gcccttcaca tgcaggccct gccccctcgc ggaagcggag   1500
ccaccaactt cagcctgctg aagcaggccg gcgacgtgga ggagaacccc ggccccatgg   1560
ccctgcccgt gaccgccctg ctgctgcccc tggccctgct gctgcacgcc gccaggcccg   1620
acgtgcagat cacccagagc cccagctacc tggccgccag ccccggcgag accatcacca   1680
tcaactgcag agccagcaag agcatcagca aggacctggc ctggtaccag gagaagcccg   1740
gcaagaccaa caagctgctg atctacagcg gcagcaccct gcagagcggc atccccagca   1800
gattcagcgg cagcggcagc ggcaccgact tcaccctgac catcagcagc ctggagcccg   1860
aggacttcgc catgtactac tgccagcagc acaacaagta cccctacacc ttcggcggcg   1920
gcaccaagct ggagatcaag ggagggggg gatccggggg aggaggctcc ggcggaggcg   1980
gaagccaggt gcagctgcag cagcccggcg ccgagctggt gagacccggc gccagcgtga   2040
agctgagctg caaggccagc ggctacacct tcaccagcta ctggatgaac tgggtgaagc   2100
agagacccga ccagggcctg gagtggatcg gcagaatcga cccctacgac agcgagaccc   2160
actacaacca gaagttcaag gacaaggcca tcctgaccgt ggacaagagc agcagcaccg   2220
cctacatgca gctgagcagc ctgaccagcg aggacagcgc cgtgtactac tgcgccagag   2280
gcaactggga cgactactgg ggccagggca ccaccctgac cgtgagcagc accaccaccc   2340
ccgcccccag gcccccccacc cccgccccca ccatcgccag ccagcccctg agcctgaggc   2400
ccgaggcctg caggcccgcc gccggcggcg ccgtgcacac caggggcctg gacttcgcct   2460
gcgacatcta catctgggcc cccctggccg gcacctgcgg cgtgctgctg ctgagcctgg   2520
tgatcaccct gtactgcagg agtaagagga gcaggctcct gcacagtgac tacatgaaca   2580
tgactccccg ccgccccggg cccacccgca agcattacca gccctatgcc ccaccacgcg   2640
acttcgcagc ctatcgctcc agggtgaagt tcagcaggag cgccgacgcc cccgcctacc   2700
agcagggcca gaaccagctg tacaacgagc tgaacctggg caggagggag gagtacgacg   2760
tgctggacaa gaggaggggc agggaccccg agatgggcgg caagccccag aggaggaaga   2820
acccccagga gggcctgtac aacgagctgc agaaggacaa gatggccgag gcctacagcg   2880
agatcggcat gaagggcgag aggaggaggg gcaagggcca cgacggcctg taccagggcc   2940
tgagcaccgc caccaaggac acctacgacg ccctgcacat gcaggccctg ccccccaggt   3000
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aagtttaaac                                                          3010


<210> SEQ ID NO 68
<211> LENGTH: 997
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 68

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
            20                  25                  30

Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys
65                  70                  75                  80

Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser
                85                  90                  95

Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
145                 150                 155                 160

Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser Val
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn
            180                 185                 190

Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg Val
225                 230                 235                 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu Tyr
                245                 250                 255

Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Thr
            260                 265                 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
        275                 280                 285

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
    290                 295                 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305                 310                 315                 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
                325                 330                 335

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
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            340                 345                 350

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
        355                 360                 365

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
    370                 375                 380

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
385                 390                 395                 400

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                405                 410                 415

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser
                485                 490                 495

Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu
            500                 505                 510

Asn Pro Gly Pro Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu
        515                 520                 525

Ala Leu Leu Leu His Ala Ala Arg Pro Asp Val Gln Ile Thr Gln Ser
    530                 535                 540

Pro Ser Tyr Leu Ala Ala Ser Pro Gly Glu Thr Ile Thr Ile Asn Cys
545                 550                 555                 560

Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Glu Lys
                565                 570                 575

Pro Gly Lys Thr Asn Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln
            580                 585                 590

Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
        595                 600                 605

Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Met Tyr Tyr
    610                 615                 620

Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys
625                 630                 635                 640

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
                645                 650                 655

Gly Gly Ser Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg
            660                 665                 670

Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        675                 680                 685

Thr Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Asp Gln Gly Leu
    690                 695                 700

Glu Trp Ile Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn
705                 710                 715                 720

Gln Lys Phe Lys Asp Lys Ala Ile Leu Thr Val Asp Lys Ser Ser Ser
                725                 730                 735

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
            740                 745                 750
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Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr
        755                 760                 765

Thr Leu Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
    770                 775                 780

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
785                 790                 795                 800

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
                805                 810                 815

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
            820                 825                 830

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg Ser
        835                 840                 845

Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
    850                 855                 860

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
865                 870                 875                 880

Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
                885                 890                 895

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
            900                 905                 910

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
        915                 920                 925

Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
    930                 935                 940

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
945                 950                 955                 960

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
                965                 970                 975

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
            980                 985                 990

Ala Leu Pro Pro Arg
        995


<210> SEQ ID NO 69
<211> LENGTH: 1767
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 69

gcgatcgctg acctctagaa tgtatttgtg gcttaaactc ttggcatttg gctttgcctt      60

tctggacaca gaagtatttg tgacagggga catccaggtg acccagagcc ccagcagcct     120

gagcgccagc ctgggcgaga gaatcagcct gacctgcaga accagccagg acatcagcaa     180

ctacctgaac tggttccagc agaagcccga cggcaccttc aagagactga tctacgccac     240

cagcagcctg gacagcggcg tgcccaagag attcagcggc agcggcagcg gcagcgacta     300

cagcctgacc atcagcagcc tggagagcga ggacttcgcc gactactact gcctgcagta     360

cgccagctac cccttcacct tcggcagcgg caccaagctg gagatcaagg gagggggggg     420

atccggggga ggaggctccg gcggaggcgg aagcgaggtg cagctgcagg agagcggccc     480

cggcctggtg aagcccagcc agaccctgag cctgacctgc agcgtgaccg gctacagcat     540
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caccagcggc tactactggc actggatcag acagttcccc ggcaacaagc tgcagtggat    600

gggctacatc agctacagcg gcttcaccaa ctacaagacc agcctgatca acagaatcag    660

catcacccac gacaccagcg agaaccagtt cttcctgaac ctgaacagcg tgaccaccga    720

ggacaccgcc acctactact gcgccggcga cagaaccggc agctggttcg cctactgggg    780

ccagggcacc ctggtgaccg tgagcgccac cacgacgcca gcgccgcgac caccaacacc    840

ggcgcccacc atcgcgtcgc agcccctgtc cctgcgccca gaggcgtgcc ggccagcggc    900

ggggggcgca gtgcacacga gggggctgga cttcgcctgt gatatctaca tctgggcgcc    960

cttggccggg acttgtgggg tccttctcct gtcactggtt atcacccttt actgcaggag   1020

taagaggagc aggctcctgc acagtgacta catgaacatg actccccgcc gccccgggcc   1080

cacccgcaag cattaccagc cctatgcccc accacgcgac ttcgcagcct atcgctccag   1140

agtgaagttc agcaggagcg cagacgcccc cgcgtaccag cagggccaga accagctcta   1200

taacgagctc aatctaggac gaagagagga gtacgatgtt ttggacaaga gacgtggccg   1260

ggaccctgag atgggggaa agccgcagag aaggaagaac cctcaggaag gcctgtacaa   1320

tgaactgcag aaagataaga tggcggaggc ctacagtgag attgggatga aaggcgagcg   1380

ccggaggggc aaggggcacg atggccttta ccagggtctc agtacagcca ccaaggacac   1440

ctacgacgcc cttcacatgc aggccctgcc ccctcgcggc agcggcgaag gccgcggcag   1500

cctgctgacc tgcggcgatg tggaagaaaa cccgggcccc atgtacctgt ggctgaagct   1560

gctggccttc ggcttcgcct tcctggacac cgaggtgttc gtgaccggcg gccagaacga   1620

caccagccag accagcagcc ccagcagccc gctgtttccg ggcccgagca aaccgttttg   1680

ggtgctggtg gtggtgggcg gcgtgctggc gtgctatagc ctgctggtga ccgtggcgtt   1740

tattattttt tgggtgtaag tttaaac                                       1767
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<210> SEQ ID NO 70
<211> LENGTH: 579
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 70

```
Met Tyr Leu Trp Leu Lys Leu Leu Ala Phe Gly Phe Ala Phe Leu Asp
1               5                   10                  15

Thr Glu Val Phe Val Thr Gly Asp Ile Gln Val Thr Gln Ser Pro Ser
            20                  25                  30

Ser Leu Ser Ala Ser Leu Gly Glu Arg Ile Ser Leu Thr Cys Arg Thr
        35                  40                  45

Ser Gln Asp Ile Ser Asn Tyr Leu Asn Trp Phe Gln Gln Lys Pro Asp
    50                  55                  60

Gly Thr Phe Lys Arg Leu Ile Tyr Ala Thr Ser Ser Leu Asp Ser Gly
65                  70                  75                  80

Val Pro Lys Arg Phe Ser Gly Ser Gly Ser Gly Ser Asp Tyr Ser Leu
                85                  90                  95

Thr Ile Ser Ser Leu Glu Ser Glu Asp Phe Ala Asp Tyr Tyr Cys Leu
            100                 105                 110

Gln Tyr Ala Ser Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu
        115                 120                 125
```

-continued

```
Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140

Ser Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser
145                 150                 155                 160

Gln Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser
                165                 170                 175

Gly Tyr Tyr Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Gln
            180                 185                 190

Trp Met Gly Tyr Ile Ser Tyr Ser Gly Phe Thr Asn Tyr Lys Thr Ser
        195                 200                 205

Leu Ile Asn Arg Ile Ser Ile Thr His Asp Thr Ser Glu Asn Gln Phe
    210                 215                 220

Phe Leu Asn Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr
225                 230                 235                 240

Cys Ala Gly Asp Arg Thr Gly Ser Trp Phe Ala Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg
                325                 330                 335

Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
            340                 345                 350

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
        355                 360                 365

Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
    370                 375                 380

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
385                 390                 395                 400

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
                405                 410                 415

Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu
                485                 490                 495

Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met Tyr Leu Trp Leu
            500                 505                 510

Lys Leu Leu Ala Phe Gly Phe Ala Phe Leu Asp Thr Glu Val Phe Val
        515                 520                 525
```

-continued

```
Thr Gly Gly Gln Asn Asp Thr Ser Gln Thr Ser Ser Pro Ser Ser Pro
    530                 535                 540

Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly
545                 550                 555                 560

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
                565                 570                 575

Phe Trp Val


<210> SEQ ID NO 71
<211> LENGTH: 1880
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 71

atgtacctgt ggctgaagct gctggccttc ggcttcgcct tcctggacac cgaggtgttc     60

gtgaccggcg acatccaggt gacccagagc cccagcagcc tgagcgccag cctgggcgag    120

agaatcagcc tgacctgcag aaccagccag gacatcagca actacctgaa ctggttccag    180

cagaagcccg acggcacctt caagagactg atctacgcca ccagcagcct ggacagcggc    240

gtgcccaaga gattcagcgg cagcggcagc ggcagcgact acagcctgac catcagcagc    300

ctggagagcg aggacttcgc cgactactac tgcctgcagt acgccagcta ccccttcacc    360

ttcggcagcg gcaccaagct ggagatcaag ggagggggg gatccggggg aggaggctcc    420

ggcggaggcg gaagcgaggt gcagctgcag gagagcggcc ccggcctggt gaagcccagc    480

cagaccctga gcctgacctg cagcgtgacc ggctacagca tcaccagcgg ctactactgg    540

cactggatca gacagttccc cggcaacaag ctgcagtgga tgggctacat cagctacagc    600

ggcttcacca actacaagac cagcctgatc aacagaatca gcatcaccca cgacaccagc    660

gagaaccagt tcttcctgaa cctgaacagc gtgaccaccg aggacaccgc cacctactac    720

tgcgccggcg acagaaccgg cagctggttc gcctactggg gccagggcac cctggtgacc    780

gtgagcgcca ccacgacgcc agcgccgcga ccaccaacac cggcgcccac catcgcgtcg    840

cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg cgggggcgc agtgcacacg    900

agggggctgg acttcgcctg tgatatctac atctgggcgc ccttggccgg gacttgtggg    960

gtccttctcc tgtcactggt tatcaccctt tactgcagga gtaagaggag caggctcctg   1020

cacagtgact acatgaacat gactccccgc cgccccgggc ccacccgcaa gcattaccag   1080

ccctatgccc caccacgcga cttcgcagcc tatcgctcca aacggggcag aaagaaactc   1140

ctgtatatat tcaaacaacc atttatgaga ccagtacaaa ctactcaaga ggaagatggc   1200

tgtagctgcc gatttccaga agaagaagaa ggaggatgtg aactgagagt gaagttcagc   1260

aggagcgcag acgcccccgc gtaccagcag ggccagaacc agctctataa cgagctcaat   1320

ctaggacgaa gagaggagta cgatgttttg gacaagagac gtggccggga ccctgagatg   1380

gggggaaagc cgcagagaag gaagaaccct caggaaggcc tgtacaatga actgcagaaa   1440

gataagatgg cggaggccta cagtgagatt gggatgaaag gcgagcgccg gaggggcaag   1500

gggcacgatg gcctttacca gggtctcagt acagccacca aggacaccta cgacgccctt   1560

cacatgcagg ccctgccccc tcgcatcgat ggcagcggcg agggcagggg cagcctgctg   1620

acctgcggcg acgtggagga gaaccccggc cccatggcct taccagtgac cgccttgctc   1680
```

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```
ctgccgctgg ccttgctgct ccacgccgcc aggccgggcc agaacgacac cagccagacc   1740

agcagcccca gcagcccccct gttccccggc cccagcaagc ccttctgggt gctggtggtg   1800

gtgggcggcg tgctggcctg ctacagcctg ctggtgaccg tggccttcat catcttctgg   1860

gtgaggagct aagtttaaac                                                1880
```

<210> SEQ ID NO 72
<211> LENGTH: 623
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 72

```
Met Tyr Leu Trp Leu Lys Leu Leu Ala Phe Gly Phe Ala Phe Leu Asp
1               5                   10                  15

Thr Glu Val Phe Val Thr Gly Asp Ile Gln Val Thr Gln Ser Pro Ser
            20                  25                  30

Ser Leu Ser Ala Ser Leu Gly Glu Arg Ile Ser Leu Thr Cys Arg Thr
        35                  40                  45

Ser Gln Asp Ile Ser Asn Tyr Leu Asn Trp Phe Gln Gln Lys Pro Asp
    50                  55                  60

Gly Thr Phe Lys Arg Leu Ile Tyr Ala Thr Ser Ser Leu Asp Ser Gly
65                  70                  75                  80

Val Pro Lys Arg Phe Ser Gly Ser Gly Ser Gly Ser Asp Tyr Ser Leu
                85                  90                  95

Thr Ile Ser Ser Leu Glu Ser Glu Asp Phe Ala Asp Tyr Tyr Cys Leu
            100                 105                 110

Gln Tyr Ala Ser Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu
        115                 120                 125

Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140

Ser Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser
145                 150                 155                 160

Gln Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser
                165                 170                 175

Gly Tyr Tyr Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Gln
            180                 185                 190

Trp Met Gly Tyr Ile Ser Tyr Ser Gly Phe Thr Asn Tyr Lys Thr Ser
        195                 200                 205

Leu Ile Asn Arg Ile Ser Ile Thr His Asp Thr Ser Glu Asn Gln Phe
    210                 215                 220

Phe Leu Asn Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr
225                 230                 235                 240

Cys Ala Gly Asp Arg Thr Gly Ser Trp Phe Ala Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300
```

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```
Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg
                325                 330                 335

Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
            340                 345                 350

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
        355                 360                 365

Ala Ala Tyr Arg Ser Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
    370                 375                 380

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
385                 390                 395                 400

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
                405                 410                 415

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
            420                 425                 430

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
        435                 440                 445

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
    450                 455                 460

Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
465                 470                 475                 480

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
                485                 490                 495

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
            500                 505                 510

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
        515                 520                 525

Ile Asp Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp
    530                 535                 540

Val Glu Glu Asn Pro Gly Pro Met Ala Leu Pro Val Thr Ala Leu Leu
545                 550                 555                 560

Leu Pro Leu Ala Leu Leu Leu His Ala Ala Arg Pro Gly Gln Asn Asp
                565                 570                 575

Thr Ser Gln Thr Ser Ser Pro Ser Ser Pro Leu Phe Pro Gly Pro Ser
            580                 585                 590

Lys Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr
        595                 600                 605

Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser
    610                 615                 620
```

<210> SEQ ID NO 73
<211> LENGTH: 2314
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 73

```
gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg      60

ccgccaggcc ggacatcgtg ctgacccaga gccccgccag cctggccgtg agcctgggcc     120

agagggccac catcagctgc agggccagca agagcgtgag caccagcggc tacagctacc     180
```

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```
tgcactggta ccagcagaag cccggccagc cccccaagct gctgatctac ctggccagca    240
acctggagag cggcgtgccc gccaggttca gcggcagcgg cagcggcacc gacttcaccc    300
tgaacatcca ccccgtggag gaggaggacg ccgccaccta ctactgccag cacagcaggg    360
agctgccctt caccttcggc agcggcacca agctggagat caagggaggg gggggatccg    420
ggggaggagg ctccggcgga ggcggaagcc aggtgcagct ggtggagagc ggcggcggcc    480
tggtgcagcc cggcggcagc ctgaagctga gctgcgccgc cagcggcttc gacttcagca    540
ggtactggat gagctgggtg aggcaggccc ccggcaaggg cctggagtgg atcggcgaga    600
tcaaccccac cagcagcacc atcaacttca cccccagcct gaaggacaag gtgttcatca    660
gcagggacaa cgccaagaac accctgtacc tgcagatgag caaggtgagg agcgaggaca    720
ccgccctgta ctactgcgcc aggggcaact actacaggta cggcgacgcc atggactact    780
ggggccaggg caccagcgtg accgtgagca ccacgacgcc agcgccgcga ccaccaacac    840
cggcgcccac catcgcgtcg cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg    900
cgggggcgc agtgcacacg agggggctgg acttcgcctg tgatatctac atctgggcgc    960
ccttggccgg gacttgtggg gtccttctcc tgtcactggt tatcaccctt tactgcagga   1020
gtaagaggag caggctcctg cacagtgact acatgaacat gactccccgc cgccccgggc   1080
ccacccgcaa gcattaccag ccctatgccc caccacgcga cttcgcagcc tatcgctcca   1140
gagtgaagtt cagcaggagc gcagacgccc ccgcgtacca gcagggccag aaccagctct   1200
ataacgagct caatctagga cgaagagagg agtacgatgt tttggacaag agacgtggcc   1260
gggaccctga gatgggggga aagccgcaga gaaggaagaa ccctcaggaa ggcctgtaca   1320
atgaactgca gaaagataag atggcggagg cctacagtga gattgggatg aaaggcgagc   1380
gccggagggg caaggggcac gatggccttt accagggtct cagtacagcc accaaggaca   1440
cctacgacgc ccttcacatg caggccctgc cccctcgcgg cagcggcgaa ggccgcggca   1500
gcctgctgac ctgcggcgat gtggaagaaa acccgggccc catggaatac gcctctgacg   1560
cttcactgga ccccgaagcc ccgtggcctc ccgcgccccg cgctcgcgcc tgccgcgtac   1620
tgccttgggc cctggtcgcg gggctgctgc tgctgctgct gctcgctgcc gcctgcgccg   1680
tcttcctcgc ctgcccctgg gccgtgtccg gggctcgcgc ctcgcccggc tccgcggcca   1740
gcccgagact ccgcgagggt cccgagcttt cgcccgacga tcccgccggc ctcttggacc   1800
tgcggcaggg catgtttgcg cagctggtgg cccaaaatgt tctgctgatc gatgggcccc   1860
tgagctggta cagtgaccca ggcctggcag gcgtgtccct gacgggggc ctgagctaca   1920
aagaggacac gaaggagctg gtggtggcca aggctggagt ctactatgtc ttctttcaac   1980
tagagctgcg gcgcgtggtg gccggcgagg gctcaggctc cgtttcactt gcgctgcacc   2040
tgcagccact gcgctctgct gctggggccg ccgccctggc tttgaccgtg gacctgccac   2100
ccgcctcctc cgaggctcgg aactcggcct tcggtttcca gggccgcttg ctgcacctga   2160
gtgccggcca gcgcctgggc gtccatcttc acactgaggc cagggcacgc catgcctggc   2220
agcttaccca gggcgccaca gtcttgggac tcttccgggt gacccccgaa atcccagccg   2280
gactcccttc accgaggtcg gaataagttt aaac                               2314
```

<210> SEQ ID NO 74
<211> LENGTH: 765
<212> TYPE: PRT

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 74

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
20 25 30

Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys
35 40 45

Ser Val Ser Thr Ser Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys
50 55 60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu
65 70 75 80

Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr
100 105 110

Cys Gln His Ser Arg Glu Leu Pro Phe Thr Phe Gly Ser Gly Thr Lys
115 120 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
145 150 155 160

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe
165 170 175

Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
180 185 190

Glu Trp Ile Gly Glu Ile Asn Pro Thr Ser Ser Thr Ile Asn Phe Thr
195 200 205

Pro Ser Leu Lys Asp Lys Val Phe Ile Ser Arg Asp Asn Ala Lys Asn
210 215 220

Thr Leu Tyr Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr Ala Leu
225 230 235 240

Tyr Tyr Cys Ala Arg Gly Asn Tyr Tyr Arg Tyr Gly Asp Ala Met Asp
245 250 255

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Thr Thr Thr Pro Ala
260 265 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
275 280 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
290 295 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305 310 315 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
325 330 335

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
340 345 350

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
355 360 365

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser

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    370                 375                 380

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385                 390                 395                 400

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
                405                 410                 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Glu Gly Arg
                485                 490                 495

Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met
            500                 505                 510

Glu Tyr Ala Ser Asp Ala Ser Leu Asp Pro Glu Ala Pro Trp Pro Pro
        515                 520                 525

Ala Pro Arg Ala Arg Ala Cys Arg Val Leu Pro Trp Ala Leu Val Ala
    530                 535                 540

Gly Leu Leu Leu Leu Leu Leu Leu Ala Ala Ala Cys Ala Val Phe Leu
545                 550                 555                 560

Ala Cys Pro Trp Ala Val Ser Gly Ala Arg Ala Ser Pro Gly Ser Ala
                565                 570                 575

Ala Ser Pro Arg Leu Arg Glu Gly Pro Glu Leu Ser Pro Asp Asp Pro
            580                 585                 590

Ala Gly Leu Leu Asp Leu Arg Gln Gly Met Phe Ala Gln Leu Val Ala
        595                 600                 605

Gln Asn Val Leu Leu Ile Asp Gly Pro Leu Ser Trp Tyr Ser Asp Pro
    610                 615                 620

Gly Leu Ala Gly Val Ser Leu Thr Gly Gly Leu Ser Tyr Lys Glu Asp
625                 630                 635                 640

Thr Lys Glu Leu Val Val Ala Lys Ala Gly Val Tyr Tyr Val Phe Phe
                645                 650                 655

Gln Leu Glu Leu Arg Arg Val Val Ala Gly Glu Gly Ser Gly Ser Val
            660                 665                 670

Ser Leu Ala Leu His Leu Gln Pro Leu Arg Ser Ala Ala Gly Ala Ala
        675                 680                 685

Ala Leu Ala Leu Thr Val Asp Leu Pro Pro Ala Ser Ser Glu Ala Arg
    690                 695                 700

Asn Ser Ala Phe Gly Phe Gln Gly Arg Leu Leu His Leu Ser Ala Gly
705                 710                 715                 720

Gln Arg Leu Gly Val His Leu His Thr Glu Ala Arg Ala Arg His Ala
                725                 730                 735

Trp Gln Leu Thr Gln Gly Ala Thr Val Leu Gly Leu Phe Arg Val Thr
            740                 745                 750

Pro Glu Ile Pro Ala Gly Leu Pro Ser Pro Arg Ser Glu
        755                 760                 765
```

<210> SEQ ID NO 75

-continued

<211> LENGTH: 2371
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 75

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg 60

ccgccaggcc ggacatcgtg ctgacccaga gccccgccag cctggccgtg agcctgggcc 120

agagggccac catcagctgc agggccagca agagcgtgag caccagcggc tacagctacc 180

tgcactggta ccagcagaag cccggccagc cccccaagct gctgatctac ctggccagca 240

acctggagag cggcgtgccc gccaggttca gcggcagcgg cagcggcacc gacttcaccc 300

tgaacatcca ccccgtggag gaggaggacg ccgccaccta ctactgccag cacagcaggg 360

agctgccctt caccttcggc agcggcacca agctggagat caagggaggg gggggatccg 420

ggggaggagg ctccggcgga ggcggaagcc aggtgcagct ggtggagagc ggcggcggcc 480

tggtgcagcc cggcggcagc ctgaagctga gctgcgccgc cagcggcttc gacttcagca 540

ggtactggat gagctgggtg aggcaggccc ccggcaaggg cctggagtgg atcggcgaga 600

tcaaccccac cagcagcacc atcaacttca cccccagcct gaaggacaag gtgttcatca 660

gcagggacaa cgccaagaac accctgtacc tgcagatgag caaggtgagg agcgaggaca 720

ccgccctgta ctactgcgcc aggggcaact actacaggta cggcgacgcc atggactact 780

ggggccaggg caccagcgtg accgtgagca ccacgacgcc agcgccgcga ccaccaacac 840

cggcgcccac catcgcgtcg cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg 900

cgggggcgc agtgcacacg agggggctgg acttcgcctg tgatatctac atctgggcgc 960

ccttggccgg gacttgtggg gtccttctcc tgtcactggt tatcaccctt tactgcagga 1020

gtaagaggag caggctcctg cacagtgact acatgaacat gactccccgc cgccccgggc 1080

ccacccgcaa gcattaccag ccctatgccc caccacgcga cttcgcagcc tatcgctcca 1140

gagtgaagtt cagcaggagc gcagacgccc ccgcgtacca gcagggccag aaccagctct 1200

ataacgagct caatctagga cgaagagagg agtacgatgt tttggacaag agacgtggcc 1260

gggaccctga gatgggggga aagccgcaga gaaggaagaa ccctcaggaa ggcctgtaca 1320

atgaactgca gaaagataag atggcggagg cctacagtga gattgggatg aaaggcgagc 1380

gccggagggg caaggggcac gatggccttt accagggtct cagtacagcc accaaggaca 1440

cctacgacgc ccttcacatg caggccctgc cccctcgcgg cagcggcgaa ggccgcggca 1500

gcctgctgac ctgcggcgat gtggaagaaa acccgggccc catgtacaga atgcagctgc 1560

tgagctgcat cgccctgagc ctggccctgg tgaccaacag cggcatccac gtgttcatcc 1620

tgggctgctt cagcgccggc ctgcccaaga ccgaggccaa ctgggtgaac gtgatcagcg 1680

acctgaagaa gatcgaggac ctgatccaga gcatgcacat cgacgccacc ctgtacaccg 1740

agagcgacgt gcaccccagc tgcaaggtga ccgccatgaa gtgcttcctg ctggagctgc 1800

aggtgatcag cctggagagc ggcgacgcca gcatccacga caccgtggag aacctgatca 1860

tcctggccaa caacagcctg agcagcaacg gcaacgtgac cgagagcggc tgcaaggagt 1920

gcgaggagct ggaggagaag aacatcaagg agttcctgca gagcttcgtg cacatcgtgc 1980

agatgttcat caacaccagc tccggcggcg gctccggcgg cggcggctcc ggcggcggcg 2040

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```
gctccggcgg cggcggctcc ggcggcggct ccctgcaggc ccccagaaga gccagaggct   2100

gcagaaccct gggcctgccc gccctgctgc tgctgctgct gctgagaccc cccgccacca   2160

gaggcatcac ctgcccccc cccatgagcg tggagcacgc cgacatctgg gtgaagagct   2220

acagcctgta cagcagagag agatacatct gcaacagcgg cttcaagaga aaggccggca   2280

ccagcagcct gaccgagtgc gtgctgaaca aggccaccaa cgtggcccac tggaccaccc   2340

ccagcctgaa gtgcatcaga taagtttaaa c                                  2371
```

<210> SEQ ID NO 76
<211> LENGTH: 784
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 76

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
            20                  25                  30

Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys
        35                  40                  45

Ser Val Ser Thr Ser Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu
65                  70                  75                  80

Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr
            100                 105                 110

Cys Gln His Ser Arg Glu Leu Pro Phe Thr Phe Gly Ser Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
145                 150                 155                 160

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe
                165                 170                 175

Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
            180                 185                 190

Glu Trp Ile Gly Glu Ile Asn Pro Thr Ser Ser Thr Ile Asn Phe Thr
        195                 200                 205

Pro Ser Leu Lys Asp Lys Val Phe Ile Ser Arg Asp Asn Ala Lys Asn
    210                 215                 220

Thr Leu Tyr Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr Ala Leu
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Gly Asn Tyr Tyr Arg Tyr Gly Asp Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285
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Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
            340                 345                 350

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
        355                 360                 365

Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser
    370                 375                 380

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385                 390                 395                 400

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
                405                 410                 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Glu Gly Arg
                485                 490                 495

Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met
            500                 505                 510

Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu Val
        515                 520                 525

Thr Asn Ser Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly
    530                 535                 540

Leu Pro Lys Thr Glu Ala Asn Trp Val Asn Val Ile Ser Asp Leu Lys
545                 550                 555                 560

Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr
                565                 570                 575

Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys
            580                 585                 590

Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser
        595                 600                 605

Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu
    610                 615                 620

Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu
625                 630                 635                 640

Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile
                645                 650                 655

Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly
            660                 665                 670

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser
        675                 680                 685

Leu Gln Ala Pro Arg Arg Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro
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    690                 695                 700

Ala Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro Ala Thr Arg Gly Ile
705                 710                 715                 720

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
                725                 730                 735

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
            740                 745                 750

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
        755                 760                 765

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
    770                 775                 780


<210> SEQ ID NO 77
<211> LENGTH: 1223
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 77

gcgatcgctg ccatcgatac catgtatttg tggcttaaac tcttggcatt tggctttgcc     60

tttctggaca cagaagtatt tgtgacaggg gccgttcagg gtccagaaga aacagtcact    120

caagactgct tgcaactgat tgcagacagt gaaacaccaa ctatacaaaa aggatcttac    180

acatttgttc catggcttct cagctttaaa aggggaagtg ccctagaaga aaaagagaat    240

aaaatattgg tcaaagaaac tggttacttt tttatatatg gtcaggtttt atatactgat    300

aagacctacg ccatgggaca tctaattcag aggaagaagg tccatgtctt tggggatgaa    360

ttgagtctgg tgactttgtt tcgatgtatt caaaatatgc ctgaaacact acccaataat    420

tcctgctatt cagctggcat tgcaaaactg gaagaaggag atgaactcca acttgcaata    480

ccaagagaaa atgcacaaat atcactggat ggagatgtca catttttgg tgcattgaaa    540

ctgctgacca cgacgccagc gccgcgacca ccaacaccgg cgcccaccat cgcgtcgcag    600

cccctgtccc tgcgcccaga ggcgtgccgg ccagcggcgg ggggcgcagt gcacacgagg    660

gggctggact tcgcctgtga tatctacatc tgggcgccct tggccgggac ttgtggggtc    720

cttctcctgt cactggttat cacccttac tgcaggagta agaggagcag gctcctgcac    780

agtgactaca tgaacatgac tccccgccgc cccgggccca cccgcaagca ttaccagccc    840

tatgccccac cacgcgactt cgcagcctat cgctccagag tgaagttcag caggagcgca    900

gacgcccccg cgtaccagca gggccagaac cagctctata acgagctcaa tctaggacga    960

agagaggagt acgatgtttt ggacaagaga cgtggccggg accctgagat ggggggaaag   1020

ccgagaagga agaaccctca ggaaggcctg tacaatgaac tgcagaaaga taagatggcg   1080

gaggcctaca gtgagattgg gatgaaaggc gagcgccgga ggggcaaggg gcacgatggc   1140

ctttaccagg gtctcagtac agccaccaag gacacctacg acgcccttca catgcaggcc   1200

ctgccccctc gctaagttta aac                                           1223


<210> SEQ ID NO 78
<211> LENGTH: 397
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence
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<400> SEQUENCE: 78

Met Tyr Leu Trp Leu Lys Leu Leu Ala Phe Gly Phe Ala Phe Leu Asp
1 5 10 15

Thr Glu Val Phe Val Thr Gly Ala Val Gln Gly Pro Glu Glu Thr Val
20 25 30

Thr Gln Asp Cys Leu Gln Leu Ile Ala Asp Ser Glu Thr Pro Thr Ile
35 40 45

Gln Lys Gly Ser Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg
50 55 60

Gly Ser Ala Leu Glu Glu Lys Glu Asn Lys Ile Leu Val Lys Glu Thr
65 70 75 80

Gly Tyr Phe Phe Ile Tyr Gly Gln Val Leu Tyr Thr Asp Lys Thr Tyr
85 90 95

Ala Met Gly His Leu Ile Gln Arg Lys Lys Val His Val Phe Gly Asp
100 105 110

Glu Leu Ser Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Glu
115 120 125

Thr Leu Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu
130 135 140

Glu Gly Asp Glu Leu Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile
145 150 155 160

Ser Leu Asp Gly Asp Val Thr Phe Phe Gly Ala Leu Lys Leu Leu Thr
165 170 175

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
180 185 190

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
195 200 205

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
210 215 220

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
225 230 235 240

Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
245 250 255

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
260 265 270

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys
275 280 285

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
290 295 300

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
305 310 315 320

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
325 330 335

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
340 345 350

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
355 360 365

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
370 375 380

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg

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385 390 395

<210> SEQ ID NO 79
<211> LENGTH: 1214
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 79

gcgatcgctg ccatcgatac catggcctta ccagtgaccg ccttgctcct gccgctggcc 60

ttgctgctcc acgccgccag gccggttcag ggtccagaag aaacagtcac tcaagactgc 120

ttgcaactga ttgcagacag tgaaacacca actatacaaa aaggatctta cacatttgtt 180

ccatggcttc tcagctttaa aaggggaagt gccctagaag aaaaagagaa taaaatattg 240

gtcaaagaaa ctggttactt ttttatatat ggtcaggttt tatatactga taagacctac 300

gccatgggac atctaattca gaggaagaag gtccatgtct ttggggatga attgagtctg 360

gtgactttgt ttcgatgtat tcaaaatatg cctgaaacac tacccaataa ttcctgctat 420

tcagctggca ttgcaaaact ggaagaagga gatgaactcc aacttgcaat accaagagaa 480

aatgcacaaa tatcactgga tggagatgtc acatttttg gtgcattgaa actgctgacc 540

acgacgccag cgccgcgacc accaacaccg gcgcccacca tcgcgtcgca gcccctgtcc 600

ctgcgcccag aggcgtgccg gccagcggcg gggggcgcag tgcacacgag ggggctggac 660

ttcgcctgtg atatctacat ctgggcgccc ttggccggga cttgtggggt ccttctcctg 720

tcactggtta tcacccttta ctgcaggagt aagaggagca ggctcctgca cagtgactac 780

atgaacatga ctccccgccg ccccgggccc acccgcaagc attaccagcc ctatgcccca 840

ccacgcgact tcgcagccta tcgctccaga gtgaagttca gcaggagcgc agacgccccc 900

gcgtaccagc agggccagaa ccagctctat aacgagctca atctaggacg aagagaggag 960

tacgatgttt tggacaagag acgtggccgg gaccctgaga tgggggaaa gccgagaagg 1020

aagaaccctc aggaaggcct gtacaatgaa ctgcagaaag ataagatggc ggaggcctac 1080

agtgagattg ggatgaaagg cgagcgccgg aggggcaagg ggcacgatgg cctttaccag 1140

ggtctcagta cagccaccaa ggacacctac gacgcccttc acatgcaggc cctgcccccct 1200

cgctaagttt aaac 1214

<210> SEQ ID NO 80
<211> LENGTH: 394
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 80

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Val Gln Gly Pro Glu Glu Thr Val Thr Gln Asp
20 25 30

Cys Leu Gln Leu Ile Ala Asp Ser Glu Thr Pro Thr Ile Gln Lys Gly
35 40 45

Ser Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Ser Ala
50 55 60

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Leu Glu Glu Lys Glu Asn Lys Ile Leu Val Lys Glu Thr Gly Tyr Phe
65                  70                  75                  80

Phe Ile Tyr Gly Gln Val Leu Tyr Thr Asp Lys Thr Tyr Ala Met Gly
                85                  90                  95

His Leu Ile Gln Arg Lys Lys Val His Val Phe Gly Asp Glu Leu Ser
            100                 105                 110

Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Glu Thr Leu Pro
        115                 120                 125

Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly Asp
    130                 135                 140

Glu Leu Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Leu Asp
145                 150                 155                 160

Gly Asp Val Thr Phe Phe Gly Ala Leu Lys Leu Leu Thr Thr Thr Pro
                165                 170                 175

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
            180                 185                 190

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
        195                 200                 205

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
    210                 215                 220

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
225                 230                 235                 240

Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
                245                 250                 255

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
            260                 265                 270

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg
        275                 280                 285

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
    290                 295                 300

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
305                 310                 315                 320

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
                325                 330                 335

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
            340                 345                 350

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
        355                 360                 365

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
    370                 375                 380

Ala Leu His Met Gln Ala Leu Pro Pro Arg
385                 390


<210> SEQ ID NO 81
<211> LENGTH: 2039
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 81

gcgatcgctg ccatcgatac catggcctta ccagtgaccg ccttgctcct gccgctggcc      60

ttgctgctcc acgccgccag gccggttcag ggtccagaag aaacagtcac tcaagactgc     120
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ttgcaactga ttgcagacag tgaaacacca actatacaaa aaggatctta cacatttgtt    180
ccatggcttc tcagctttaa aaggggaagt gccctagaag aaaaagagaa taaaatattg    240
gtcaaagaaa ctggttactt ttttatatat ggtcaggttt tatatactga taagacctac    300
gccatgggac atctaattca gaggaagaag gtccatgtct ttggggatga attgagtctg    360
gtgactttgt ttcgatgtat tcaaaatatg cctgaaacac tacccaataa ttcctgctat    420
tcagctggca ttgcaaaact ggaagaagga gatgaactcc aacttgcaat accaagagaa    480
aatgcacaaa tatcactgga tggagatgtc acattttttg gtgcattgaa actgctgacc    540
acgacgccag cgccgcgacc accaacaccg gcgcccacca tcgcgtcgca gcccctgtcc    600
ctgcgcccag aggcgtgccg gccagcggcg gggggcgcag tgcacacgag ggggctggac    660
ttcgcctgtg atatctacat ctgggcgccc ttggccggga cttgtggggt ccttctcctg    720
tcactggtta tcacccttta ctgcaggagt aagaggagca ggctcctgca cagtgactac    780
atgaacatga ctccccgccg ccccgggccc acccgcaagc attaccagcc ctatgcccca    840
ccacgcgact tcgcagccta tcgctccaga gtgaagttca gcaggagcgc agacgccccc    900
gcgtaccagc agggccagaa ccagctctat aacgagctca atctaggacg aagagaggag    960
tacgatgttt tggacaagag acgtggccgg gaccctgaga tgggggggaaa gccgagaagg   1020
aagaaccctc aggaaggcct gtacaatgaa ctgcagaaag ataagatggc ggaggcctac   1080
agtgagattg ggatgaaagg cgagcgccgg aggggcaagg ggcacgatgg cctttaccag   1140
ggtctcagta cagccaccaa ggacacctac gacgcccttc acatgcaggc cctgcccccct   1200
cgcggcagcg gcgaaggccg cggcagcctg ctgacctgcg gcgatgtgga agaaaacccg   1260
ggccccatgg aatacgcctc tgacgcttca ctggaccccg aagccccgtg gcctcccgcg   1320
ccccgcgctc gcgcctgccg cgtactgcct tgggccctgg tcgcggggct gctgctgctg   1380
ctgctgctcg ctgccgcctg cgccgtcttc ctcgcctgcc cctgggccgt gtccggggct   1440
cgcgcctcgc ccggctccgc ggccagcccg agactccgcg agggtcccga gctttcgccc   1500
gacgatcccg ccggcctctt ggacctgcgg cagggcatgt ttgcgcagct ggtggcccaa   1560
aatgttctgc tgatcgatgg gcccctgagc tggtacagtg acccaggcct ggcaggcgtg   1620
tccctgacgg ggggcctgag ctacaaagag gacacgaagg agctggtggt ggccaaggct   1680
ggagtctact atgtcttctt tcaactagag ctgcggcgcg tggtggccgg cgagggctca   1740
ggctccgttt cacttgcgct gcacctgcag ccactgcgct ctgctgctgg ggccgccgcc   1800
ctggctttga ccgtggacct gccacccgcc tcctccgagg ctcggaactc ggccttcggt   1860
ttccagggcc gcttgctgca cctgagtgcc ggccagcgcc tgggcgtcca tcttcacact   1920
gaggccaggg cacgccatgc ctggcagctt acccagggcg ccacagtctt gggactcttc   1980
cgggtgaccc ccgaaatccc agccggactc ccttcaccga ggtcggaata agtttaaac    2039
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<210> SEQ ID NO 82
<211> LENGTH: 669
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 82

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu

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1               5                   10                  15

His Ala Ala Arg Pro Val Gln Gly Pro Glu Glu Thr Val Thr Gln Asp
            20                  25                  30

Cys Leu Gln Leu Ile Ala Asp Ser Glu Thr Pro Thr Ile Gln Lys Gly
        35                  40                  45

Ser Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Ser Ala
    50                  55                  60

Leu Glu Glu Lys Glu Asn Lys Ile Leu Val Lys Glu Thr Gly Tyr Phe
65                  70                  75                  80

Phe Ile Tyr Gly Gln Val Leu Tyr Thr Asp Lys Thr Tyr Ala Met Gly
                85                  90                  95

His Leu Ile Gln Arg Lys Lys Val His Val Phe Gly Asp Glu Leu Ser
            100                 105                 110

Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Glu Thr Leu Pro
        115                 120                 125

Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly Asp
    130                 135                 140

Glu Leu Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Leu Asp
145                 150                 155                 160

Gly Asp Val Thr Phe Phe Gly Ala Leu Lys Leu Leu Thr Thr Thr Pro
                165                 170                 175

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
            180                 185                 190

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
        195                 200                 205

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
    210                 215                 220

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
225                 230                 235                 240

Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
                245                 250                 255

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
            260                 265                 270

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg
        275                 280                 285

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
    290                 295                 300

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
305                 310                 315                 320

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
                325                 330                 335

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
            340                 345                 350

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
        355                 360                 365

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
    370                 375                 380

Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Glu Gly Arg
385                 390                 395                 400

Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met
                405                 410                 415
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Glu Tyr Ala Ser Asp Ala Ser Leu Asp Pro Glu Ala Pro Trp Pro Pro
            420                 425                 430

Ala Pro Arg Ala Arg Ala Cys Arg Val Leu Pro Trp Ala Leu Val Ala
        435                 440                 445

Gly Leu Leu Leu Leu Leu Leu Leu Ala Ala Ala Cys Ala Val Phe Leu
    450                 455                 460

Ala Cys Pro Trp Ala Val Ser Gly Ala Arg Ala Ser Pro Gly Ser Ala
465                 470                 475                 480

Ala Ser Pro Arg Leu Arg Glu Gly Pro Glu Leu Ser Pro Asp Asp Pro
                485                 490                 495

Ala Gly Leu Leu Asp Leu Arg Gln Gly Met Phe Ala Gln Leu Val Ala
            500                 505                 510

Gln Asn Val Leu Leu Ile Asp Gly Pro Leu Ser Trp Tyr Ser Asp Pro
        515                 520                 525

Gly Leu Ala Gly Val Ser Leu Thr Gly Gly Leu Ser Tyr Lys Glu Asp
    530                 535                 540

Thr Lys Glu Leu Val Val Ala Lys Ala Gly Val Tyr Tyr Val Phe Phe
545                 550                 555                 560

Gln Leu Glu Leu Arg Arg Val Val Ala Gly Glu Gly Ser Gly Ser Val
                565                 570                 575

Ser Leu Ala Leu His Leu Gln Pro Leu Arg Ser Ala Ala Gly Ala Ala
            580                 585                 590

Ala Leu Ala Leu Thr Val Asp Leu Pro Pro Ala Ser Ser Glu Ala Arg
        595                 600                 605

Asn Ser Ala Phe Gly Phe Gln Gly Arg Leu Leu His Leu Ser Ala Gly
    610                 615                 620

Gln Arg Leu Gly Val His Leu His Thr Glu Ala Arg Ala Arg His Ala
625                 630                 635                 640

Trp Gln Leu Thr Gln Gly Ala Thr Val Leu Gly Leu Phe Arg Val Thr
                645                 650                 655

Pro Glu Ile Pro Ala Gly Leu Pro Ser Pro Arg Ser Glu
            660                 665


<210> SEQ ID NO 83
<211> LENGTH: 2096
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 83

gcgatcgctg ccatcgatac catggcctta ccagtgaccg ccttgctcct gccgctggcc      60

ttgctgctcc acgccgccag gccggttcag ggtccagaag aaacagtcac tcaagactgc     120

ttgcaactga ttgcagacag tgaaacacca actatacaaa aaggatctta cacatttgtt     180

ccatggcttc tcagctttaa aaggggaagt gccctagaag aaaaagagaa taaaatattg     240

gtcaaagaaa ctggttactt ttttatatat ggtcaggttt tatatactga taagacctac     300

gccatgggac atctaattca gaggaagaag gtccatgtct ttggggatga attgagtctg     360

gtgactttgt ttcgatgtat tcaaaatatg cctgaaacac tacccaataa ttcctgctat     420

tcagctggca ttgcaaaact ggaagaagga gatgaactcc aacttgcaat accaagagaa     480

aatgcacaaa tatcactgga tggagatgtc acattttttg gtgcattgaa actgctgacc     540
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acgacgccag cgccgcgacc accaacaccg gcgcccacca tcgcgtcgca gcccctgtcc    600

ctgcgcccag aggcgtgccg gccagcggcg gggggcgcag tgcacacgag ggggctggac    660

ttcgcctgtg atatctacat ctgggcgccc ttggccggga cttgtggggt ccttctcctg    720

tcactggtta tcacccttta ctgcaggagt aagaggagca ggctcctgca cagtgactac    780

atgaacatga ctccccgccg ccccgggccc acccgcaagc attaccagcc ctatgcccca    840

ccacgcgact tcgcagccta tcgctccaga gtgaagttca gcaggagcgc agacgccccc    900

gcgtaccagc agggccagaa ccagctctat aacgagctca atctaggacg aagagaggag    960

tacgatgttt tggacaagag acgtggccgg gaccctgaga tgggggggaaa gccgagaagg   1020

aagaaccctc aggaaggcct gtacaatgaa ctgcagaaag ataagatggc ggaggcctac   1080

agtgagattg ggatgaaagg cgagcgccgg aggggcaagg ggcacgatgg cctttaccag   1140

ggtctcagta cagccaccaa ggacacctac gacgcccttc acatgcaggc cctgcccccct   1200

cgcggcagcg gcgaaggccg cggcagcctg ctgacctgcg gcgatgtgga agaaaacccg   1260

ggccccatgt acagaatgca gctgctgagc tgcatcgccc tgagcctggc cctggtgacc   1320

aacagcggca tccacgtgtt catcctgggc tgcttcagcg ccggcctgcc caagaccgag   1380

gccaactggg tgaacgtgat cagcgacctg aagaagatcg aggacctgat ccagagcatg   1440

cacatcgacg ccaccctgta caccgagagc gacgtgcacc ccagctgcaa ggtgaccgcc   1500

atgaagtgct tcctgctgga gctgcaggtg atcagcctgg agagcggcga cgccagcatc   1560

cacgacaccg tggagaacct gatcatcctg gccaacaaca gcctgagcag caacggcaac   1620

gtgaccgaga gcggctgcaa ggagtgcgag gagctggagg agaagaacat caaggagttc   1680

ctgcagagct tcgtgcacat cgtgcagatg ttcatcaaca ccagctccgg cggcggctcc   1740

ggcggcggcg gctccggcgg cggcggctcc ggcggcggcg gctccggcgg cggctccctg   1800

caggccccca gaagagccag aggctgcaga accctgggcc tgcccgccct gctgctgctg   1860

ctgctgctga gaccccccgc caccagaggc atcacctgcc cccccccat gagcgtggag   1920

cacgccgaca tctgggtgaa gagctacagc ctgtacagca gagagagata catctgcaac   1980

agcggcttca agagaaaggc cggcaccagc agcctgaccg agtgcgtgct gaacaaggcc   2040

accaacgtgg cccactggac cacccccagc ctgaagtgca tcagataagt ttaaac       2096
```

```
<210> SEQ ID NO 84
<211> LENGTH: 688
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 84

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Val Gln Gly Pro Glu Glu Thr Val Thr Gln Asp
            20                  25                  30

Cys Leu Gln Leu Ile Ala Asp Ser Glu Thr Pro Thr Ile Gln Lys Gly
        35                  40                  45

Ser Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Ser Ala
    50                  55                  60

Leu Glu Glu Lys Glu Asn Lys Ile Leu Val Lys Glu Thr Gly Tyr Phe
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65                  70                  75                  80

Phe Ile Tyr Gly Gln Val Leu Tyr Thr Asp Lys Thr Tyr Ala Met Gly
                85                  90                  95

His Leu Ile Gln Arg Lys Lys Val His Val Phe Gly Asp Glu Leu Ser
            100                 105                 110

Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Glu Thr Leu Pro
        115                 120                 125

Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly Asp
    130                 135                 140

Glu Leu Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Leu Asp
145                 150                 155                 160

Gly Asp Val Thr Phe Phe Gly Ala Leu Lys Leu Leu Thr Thr Thr Pro
                165                 170                 175

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
            180                 185                 190

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
        195                 200                 205

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
    210                 215                 220

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
225                 230                 235                 240

Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met
                245                 250                 255

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
            260                 265                 270

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg
        275                 280                 285

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
    290                 295                 300

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
305                 310                 315                 320

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
                325                 330                 335

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
            340                 345                 350

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
        355                 360                 365

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
    370                 375                 380

Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Glu Gly Arg
385                 390                 395                 400

Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Met
                405                 410                 415

Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu Val
            420                 425                 430

Thr Asn Ser Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly
        435                 440                 445

Leu Pro Lys Thr Glu Ala Asn Trp Val Asn Val Ile Ser Asp Leu Lys
    450                 455                 460

Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr
465                 470                 475                 480
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Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys
                485                 490                 495

Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser
            500                 505                 510

Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu
        515                 520                 525

Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu
    530                 535                 540

Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile
545                 550                 555                 560

Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly
                565                 570                 575

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser
            580                 585                 590

Leu Gln Ala Pro Arg Arg Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro
        595                 600                 605

Ala Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro Ala Thr Arg Gly Ile
    610                 615                 620

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
625                 630                 635                 640

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
                645                 650                 655

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
            660                 665                 670

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
        675                 680                 685


<210> SEQ ID NO 85
<211> LENGTH: 2755
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 85

gcgatcgcac catggccctg cccgtgaccg ccctgctgct gcccctggcc ctgctgctgc      60

acgccgccag gcccgccgtt cagggtccag aagaaacagt cactcaagac tgcttgcaac     120

tgattgcaga cagtgaaaca ccaactatac aaaaaggatc ttacacattt gttccatggc     180

ttctcagctt taaaagggga agtgccctag aagaaaaaga gaataaaata ttggtcaaag     240

aaactggtta ctttttata tatggtcagg ttttatatac tgataagacc tacgccatgg     300

gacatctaat tcagaggaag aaggtccatg tctttgggga tgaattgagt ctggtgactt     360

tgtttcgatg tattcaaaat atgcctgaaa cactacccaa taattcctgc tattcagctg     420

gcattgcaaa actggaagaa ggagatgaac tccaacttgc aataccaaga gaaaatgcac     480

aaatatcact ggatggagat gtcacatttt ttggtgcatt gaaactgctg accacgacgc     540

cagcgccgcg accaccaaca ccggcgccca ccatcgcgtc gcagcccctg tccctgcgcc     600

cagaggcgtg ccggccagcg gcgggggcg cagtgcacac gagggggctg gacttcgcct     660

gtgatatcta catctgggcg cccttggccg ggacttgtgg ggtccttctc ctgtcactgg     720

ttatcaccct ttactgcagg agtaagagga gcaggctcct gcacagtgac tacatgaaca     780
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tgactccccg ccgccccggg cccacccgca agcattacca gccctatgcc ccaccacgcg    840
acttcgcagc ctatcgctcc agagtgaagt tcagcaggag cgcagacgcc cccgcgtacc    900
agcagggcca gaaccagctc tataacgagc tcaatctagg acgaagagag gagtacgatg    960
ttttggacaa gagacgtggc cgggaccctg agatgggggg aaagccgaga aggaagaacc   1020
ctcaggaagg cctgtacaat gaactgcaga aagataagat ggcggaggcc tacagtgaga   1080
ttgggatgaa aggcgagcgc cggaggggca aggggcacga tggcctttac cagggtctca   1140
gtacagccac caaggacacc tacgacgccc ttcacatgca ggccctgccc cctcgcggaa   1200
gcggagccac caacttcagc ctgctgaagc aggccggcga cgtggaggag aaccccggcc   1260
ccatggcctt accagtgacc gccttgctcc tgccgctggc cttgctgctc cacgccgcca   1320
ggccggaggt ccagctgcag cagtctggac ctgagctgat aaagcctggg gcttcagtga   1380
agatgtcctg caaggcttct ggatacacat tcactagcta tgttatgcac tgggtgaagc   1440
agaagcctgg gcagggcctt gagtggattg gatatattaa tccttacaat gatggtacta   1500
agtacaatga gaagttcaaa ggcaaggcca cactgacttc agacaaatcc tccagcacag   1560
cctacatgga gctcagcagc ctgacctctg aggactctgc ggtctattac tgtgcaagag   1620
ggacttatta ctacggtagt agggtatttg actactgggg ccaaggcacc actctcacag   1680
tctcctcagg tggagggggc tcaggcggag gtggctctgg gggtggaggc tcggacattg   1740
tgatgactca ggctgcaccc tctatacctg tcactcctgg agagtcagta tccatctcct   1800
gcaggtctag taagagtctc ctgaatagta atggcaacac ttacttgtat tggttcctgc   1860
agaggccagg ccagtctcct cagctcctga tatatcggat gtccaacctt gcctcaggag   1920
tcccagacag gttcagtggc agtgggtcag gaactgcttt cacactgaga atcagtagag   1980
tggaggctga ggatgtgggt gtttattact gtatgcaaca tctagaatat ccgttcacgt   2040
tcggtgctgg gaccaagctg gagctgaaac ggaccacgac gccagcgccg cgaccaccaa   2100
caccggcgcc caccatcgcg tcgcagcccc tgtccctgcg cccagaggcg tgccggccag   2160
cggcgggggg cgcagtgcac acgagggggc tggacttcgc ctgtgatatc tacatctggg   2220
cgcccttggc cgggacttgt ggggtccttc tcctgtcact ggttatcacc ctttactgca   2280
aacggggcag aaagaaactc ctgtatatat tcaaacaacc atttatgaga ccagtacaaa   2340
ctactcaaga ggaagatggc tgtagctgcc gatttccaga agaagaagaa ggaggatgtg   2400
aactgagagt gaagttcagc aggagcgcag acgcccccgc gtaccagcag ggccagaacc   2460
agctctataa cgagctcaat ctaggacgaa gagaggagta cgatgttttg gacaagagac   2520
gtggccggga ccctgagatg gggggaaagc cgcagagaag gaagaaccct caggaaggcc   2580
tgtacaatga actgcagaaa gataagatgg cggaggccta cagtgagatt gggatgaaag   2640
gcgagcgccg gaggggcaag gggcacgatg gcctttacca gggtctcagt acagccacca   2700
aggacaccta cgacgccctt cacatgcagg ccctgccccc tcgctaagtt taaac        2755
```

<210> SEQ ID NO 86
<211> LENGTH: 911
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 86

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```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Ala Val Gln Gly Pro Glu Glu Thr Val Thr Gln
            20                  25                  30

Asp Cys Leu Gln Leu Ile Ala Asp Ser Glu Thr Pro Thr Ile Gln Lys
        35                  40                  45

Gly Ser Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Ser
    50                  55                  60

Ala Leu Glu Glu Lys Glu Asn Lys Ile Leu Val Lys Glu Thr Gly Tyr
65                  70                  75                  80

Phe Phe Ile Tyr Gly Gln Val Leu Tyr Thr Asp Lys Thr Tyr Ala Met
                85                  90                  95

Gly His Leu Ile Gln Arg Lys Lys Val His Val Phe Gly Asp Glu Leu
            100                 105                 110

Ser Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Glu Thr Leu
        115                 120                 125

Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly
    130                 135                 140

Asp Glu Leu Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Leu
145                 150                 155                 160

Asp Gly Asp Val Thr Phe Phe Gly Ala Leu Lys Leu Leu Thr Thr Thr
                165                 170                 175

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
            180                 185                 190

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
        195                 200                 205

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
    210                 215                 220

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
225                 230                 235                 240

Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn
                245                 250                 255

Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
            260                 265                 270

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser
        275                 280                 285

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
    290                 295                 300

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
305                 310                 315                 320

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
                325                 330                 335

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
            340                 345                 350

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
        355                 360                 365

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
    370                 375                 380

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr
385                 390                 395                 400

Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly
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                405                 410                 415

Pro Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu
            420                 425                 430

Leu His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Glu
        435                 440                 445

Leu Ile Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly
    450                 455                 460

Tyr Thr Phe Thr Ser Tyr Val Met His Trp Val Lys Gln Lys Pro Gly
465                 470                 475                 480

Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr
                485                 490                 495

Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys
            500                 505                 510

Ser Ser Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp
        515                 520                 525

Ser Ala Val Tyr Tyr Cys Ala Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg
    530                 535                 540

Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly
545                 550                 555                 560

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
                565                 570                 575

Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly Glu Ser
            580                 585                 590

Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asn Ser Asn Gly
        595                 600                 605

Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln
    610                 615                 620

Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro Asp Arg
625                 630                 635                 640

Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile Ser Arg
                645                 650                 655

Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His Leu Glu
            660                 665                 670

Tyr Pro Phe Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr
        675                 680                 685

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
    690                 695                 700

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
705                 710                 715                 720

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
                725                 730                 735

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
            740                 745                 750

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
        755                 760                 765

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
    770                 775                 780

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
785                 790                 795                 800

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
                805                 810                 815
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Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
            820                 825                 830

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln
        835                 840                 845

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
    850                 855                 860

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
865                 870                 875                 880

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
                885                 890                 895

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
            900                 905                 910


<210> SEQ ID NO 87
<211> LENGTH: 2734
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 87

gcgatcgcac catggcctta ccagtgaccg ccttgctcct gccgctggcc ttgctgctcc     60

acgccgccag gccggtgctc acccaaaaac agaagaagca gcactctgtc ctgcacctgg    120

ttcccattaa cgccacctcc aaggatgact ccgatgtgac agaggtgatg tggcaaccag    180

ctcttaggcg tgggagaggc ctacaggccc aaggatatgg tgtccgaatc caggatgctg    240

gagtttatct gctgtatagc caggtcctgt ttcaagacgt gactttcacc atgggtcagg    300

tggtgtctcg agaaggccaa ggaaggcagg agactctatt ccgatgtata agaagtatgc    360

cctcccaccc ggaccgggcc tacaacagct gctatagcgc aggtgtcttc catttacacc    420

aaggggatat tctgagtgtc ataattcccc gggcaagggc gaaacttaac ctctctccac    480

atggaacctt cctggggttt gtgaaactga ccacgacgcc agcgccgcga ccaccaacac    540

cggcgcccac catcgcgtcg cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg    600

cgggggcgc agtgcacacg agggggctgg acttcgcctg tgatatctac atctgggcgc    660

ccttggccgg gacttgtggg gtccttctcc tgtcactggt tatcaccctt tactgcagga    720

gtaagaggag caggctcctg cacagtgact acatgaacat gactccccgc cgccccgggc    780

ccacccgcaa gcattaccag ccctatgccc caccacgcga cttcgcagcc tatcgctcca    840

gagtgaagtt cagcaggagc gcagacgccc ccgcgtacca gcagggccag aaccagctct    900

ataacgagct caatctagga cgaagagagg agtacgatgt tttggacaag agacgtggcc    960

gggaccctga gatgggggga aagccgagaa ggaagaaccc tcaggaaggc ctgtacaatg   1020

aactgcagaa agataagatg gcggaggcct acagtgagat tgggatgaaa ggcgagcgcc   1080

ggaggggcaa ggggcacgat ggcctttacc agggtctcag tacagccacc aaggacacct   1140

acgacgccct tcacatgcag gccctgcccc ctcgcggaag cggagccacc aacttcagcc   1200

tgctgaagca ggccggcgac gtggaggaga accccggccc catggcctta ccagtgaccg   1260

ccttgctcct gccgctggcc ttgctgctcc acgccgccag gccggaggtc cagctgcagc   1320

agtctggacc tgagctgata aagcctgggg cttcagtgaa gatgtcctgc aaggcttctg   1380

gatacacatt cactagctat gttatgcact gggtgaagca gaagcctggg cagggccttg   1440
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agtggattgg atatattaat ccttacaatg atggtactaa gtacaatgag aagttcaaag   1500

gcaaggccac actgacttca gacaaatcct ccagcacagc ctacatggag ctcagcagcc   1560

tgacctctga ggactctgcg gtctattact gtgcaagagg gacttattac tacggtagta   1620

gggtatttga ctactggggc caaggcacca ctctcacagt ctcctcaggt ggagggggct   1680

caggcggagg tggctctggg ggtggaggct cggacattgt gatgactcag gctgcaccct   1740

ctatacctgt cactcctgga gagtcagtat ccatctcctg caggtctagt aagagtctcc   1800

tgaatagtaa tggcaacact tacttgtatt ggttcctgca gaggccaggc cagtctcctc   1860

agctcctgat atatcggatg tccaaccttg cctcaggagt cccagacagg ttcagtggca   1920

gtgggtcagg aactgctttc acactgagaa tcagtagagt ggaggctgag gatgtgggtg   1980

tttattactg tatgcaacat ctagaatatc cgttcacgtt cggtgctggg accaagctgg   2040

agctgaaacg gaccacgacg ccagcgccgc gaccaccaac accggcgccc accatcgcgt   2100

cgcagcccct gtccctgcgc ccagaggcgt gccggccagc ggcgggggc gcagtgcaca   2160

cgagggggct ggacttcgcc tgtgatatct acatctgggc gcccttggcc gggacttgtg   2220

gggtccttct cctgtcactg gttatcaccc tttactgcaa acggggcaga aagaaactcc   2280

tgtatatatt caaacaacca tttatgagac cagtacaaac tactcaagag gaagatggct   2340

gtagctgccg atttccagaa gaagaagaag gaggatgtga actgagagtg aagttcagca   2400

ggagcgcaga cgcccccgcg taccagcagg gccagaacca gctctataac gagctcaatc   2460

taggacgaag agaggagtac gatgttttgg acaagagacg tggccgggac cctgagatgg   2520

ggggaaagcc gcagagaagg aagaaccctc aggaaggcct gtacaatgaa ctgcagaaag   2580

ataagatggc ggaggcctac agtgagattg ggatgaaagg cgagcgccgg aggggcaagg   2640

ggcacgatgg cctttaccag ggtctcagta cagccaccaa ggacacctac gacgcccttc   2700

acatgcaggc cctgcccccct cgctaagttt aaac                              2734
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<210> SEQ ID NO 88
<211> LENGTH: 904
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 88

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Val Leu Thr Gln Lys Gln Lys Lys Gln His Ser
            20                  25                  30

Val Leu His Leu Val Pro Ile Asn Ala Thr Ser Lys Asp Asp Ser Asp
        35                  40                  45

Val Thr Glu Val Met Trp Gln Pro Ala Leu Arg Arg Gly Arg Gly Leu
    50                  55                  60

Gln Ala Gln Gly Tyr Gly Val Arg Ile Gln Asp Ala Gly Val Tyr Leu
65                  70                  75                  80

Leu Tyr Ser Gln Val Leu Phe Gln Asp Val Thr Phe Thr Met Gly Gln
                85                  90                  95

Val Val Ser Arg Glu Gly Gln Gly Arg Gln Glu Thr Leu Phe Arg Cys
            100                 105                 110
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Ile Arg Ser Met Pro Ser His Pro Asp Arg Ala Tyr Asn Ser Cys Tyr
        115                 120                 125

Ser Ala Gly Val Phe His Leu His Gln Gly Asp Ile Leu Ser Val Ile
    130                 135                 140

Ile Pro Arg Ala Arg Ala Lys Leu Asn Leu Ser Pro His Gly Thr Phe
145                 150                 155                 160

Leu Gly Phe Val Lys Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
                165                 170                 175

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
            180                 185                 190

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
        195                 200                 205

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
    210                 215                 220

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg Ser
225                 230                 235                 240

Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
                245                 250                 255

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
            260                 265                 270

Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
        275                 280                 285

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
    290                 295                 300

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
305                 310                 315                 320

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
                325                 330                 335

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
            340                 345                 350

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
        355                 360                 365

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
    370                 375                 380

Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln
385                 390                 395                 400

Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Ala Leu Pro Val Thr
                405                 410                 415

Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu His Ala Ala Arg Pro Glu
            420                 425                 430

Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Ile Lys Pro Gly Ala Ser
        435                 440                 445

Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Val
    450                 455                 460

Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly
465                 470                 475                 480

Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys
                485                 490                 495

Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr Met
            500                 505                 510

Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala
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        515                 520                 525

Arg Gly Thr Tyr Tyr Tyr Gly Ser Arg Val Phe Asp Tyr Trp Gly Gln
    530                 535                 540

Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
545                 550                 555                 560

Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ala Ala Pro
                565                 570                 575

Ser Ile Pro Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Arg Ser
            580                 585                 590

Ser Lys Ser Leu Leu Asn Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe
        595                 600                 605

Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser
    610                 615                 620

Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
625                 630                 635                 640

Thr Ala Phe Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly
                645                 650                 655

Val Tyr Tyr Cys Met Gln His Leu Glu Tyr Pro Phe Thr Phe Gly Ala
            660                 665                 670

Gly Thr Lys Leu Glu Leu Lys Arg Thr Thr Thr Pro Ala Pro Arg Pro
        675                 680                 685

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
    690                 695                 700

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
705                 710                 715                 720

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
                725                 730                 735

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
            740                 745                 750

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
        755                 760                 765

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
    770                 775                 780

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
785                 790                 795                 800

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
                805                 810                 815

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
            820                 825                 830

Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu
        835                 840                 845

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
    850                 855                 860

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
865                 870                 875                 880

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
                885                 890                 895

His Met Gln Ala Leu Pro Pro Arg
            900
```

<210> SEQ ID NO 89

-continued

<211> LENGTH: 1498
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 89

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg 60

ccgccaggcc ggacatcgtg atgacccaaa gccccgacag cctggccgtg agcctgggcg 120

agagggtgac catgaactgc aaaagcagcc agtccctgct gtactccacc aaccagaaga 180

actacctggc ttggtatcaa cagaagcccg gacagagccc caagctgctg atctattggg 240

ccagcactag ggaaagcggc gtgcccgata ggttcagcgg cagcgggagc ggcacagact 300

tcactctgac cattagcagc gtgcaggctg aggatgtggc cgtctactac tgccagcagt 360

actacagcta caggaccttt gggggcggaa ctaagctgga gatcaaggga gggggggat 420

ccgggggagg aggctccggc ggaggcggaa gccaagtgca actgcagcag agcggcccag 480

aggtggtcaa acctggggca agcgtgaaga tgagctgcaa ggctagcggc tataccttca 540

ccagctatgt gatccactgg gtgaggcaga aaccaggaca gggcctggac tggatcggct 600

acatcaaccc ctacaatgac ggcaccgatt atgacgaaaa attcaagggg aaggccaccc 660

tgaccagcga caccagcaca agcaccgcct acatggagct gtccagcctg aggtccgagg 720

acaccgccgt gtattactgt gccagggaga aggacaatta cgccaccggc gcttggttcg 780

cctactgggg ccagggcaca ctggtgacag tgagcagcac cacgacgcca gcgccgcgac 840

caccaacacc ggcgcccacc atcgcgtcgc agcccctgtc cctgcgccca gaggcgtgcc 900

ggccagcggc ggggggcgca gtgcacacga gggggctgga cttcgcctgt gatatctaca 960

tctgggcgcc cttggccggg acttgtgggg tccttctcct gtcactggtt atcacccttt 1020

actgcaggag taagaggagc aggctcctgc acagtgacta catgaacatg actccccgcc 1080

gccccgggcc cacccgcaag cattaccagc cctatgcccc accacgcgac ttcgcagcct 1140

atcgctccag agtgaagttc agcaggagcg cagacgcccc cgcgtaccag cagggccaga 1200

accagctcta taacgagctc aatctaggac gaagagagga gtacgatgtt ttggacaaga 1260

gacgtggccg ggaccctgag atgggggaa agccgcagag aaggaagaac cctcaggaag 1320

gcctgtacaa tgaactgcag aaagataaga tggcggaggc ctacagtgag attgggatga 1380

aaggcgagcg ccggaggggc aaggggcacg atggccttta ccagggtctc agtacagcca 1440

ccaaggacac ctacgacgcc cttcacatgc aggccctgcc ccctcgctaa gtttaaac 1498

<210> SEQ ID NO 90
<211> LENGTH: 493
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 90

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu
20 25 30

Ala Val Ser Leu Gly Glu Arg Val Thr Met Asn Cys Lys Ser Ser Gln
35 40 45

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Ser Leu Leu Tyr Ser Thr Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
65                  70                  75                  80

Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val
            100                 105                 110

Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Arg Thr Phe Gly Gly Gly Thr
        115                 120                 125

Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Val Val
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Val Ile His Trp Val Arg Gln Lys Pro Gly Gln Gly
            180                 185                 190

Leu Asp Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Asp Tyr
        195                 200                 205

Asp Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Thr Ser Thr
    210                 215                 220

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Glu Lys Asp Asn Tyr Ala Thr Gly Ala Trp
                245                 250                 255

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr
            260                 265                 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
        275                 280                 285

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
    290                 295                 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305                 310                 315                 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
                325                 330                 335

Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
            340                 345                 350

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
        355                 360                 365

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
385                 390                 395                 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg
            420                 425                 430

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
        435                 440                 445
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Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
    450                 455                 460

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
465                 470                 475                 480

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> SEQ ID NO 91
<211> LENGTH: 2560
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 91

gcgatcgcat gtatttgtgg cttaaactct tggcatttgg ctttgccttt ctggacacag     60

aagtatttgt gacaggggac atcgtgatga cccaaagccc cgacagcctg gccgtgagcc    120

tgggcgagag ggtgaccatg aactgcaaaa gcagccagtc cctgctgtac tccaccaacc    180

agaagaacta cctggcttgg tatcaacaga agcccggaca gagccccaag ctgctgatct    240

attgggccag cactagggaa agcggcgtgc ccgataggtt cagcggcagc gggagcggca    300

cagacttcac tctgaccatt agcagcgtgc aggctgagga tgtggccgtc tactactgcc    360

agcagtacta cagctacagg acctttgggg gcggaactaa gctggagatc aagggagggg    420

ggggatccgg gggaggaggc tccggcggag gcggaagcca agtgcaactg cagcagagcg    480

gcccagaggt ggtcaaacct ggggcaagcg tgaagatgag ctgcaaggct agcggctata    540

ccttcaccag ctatgtgatc cactgggtga ggcagaaacc aggacagggc ctggactgga    600

tcggctacat caacccctac aatgacggca ccgattatga cgaaaaattc aaggggaagg    660

ccaccctgac cagcgacacc agcacaagca ccgcctacat ggagctgtcc agcctgaggt    720

ccgaggacac cgccgtgtat tactgtgcca gggagaagga caattacgcc accggcgctt    780

ggttcgccta ctggggccag ggcacactgg tgacagtgag cagcaccacg acgccagcgc    840

cgcgaccacc aacaccggcg cccaccatcg cgtcgcagcc cctgtccctg cgcccagagg    900

cgtgccggcc agcggcgggg ggcgcagtgc acacgagggg gctggacttc gcctgtgata    960

tctacatctg ggcgcccttg gccgggactt gtggggtcct tctcctgtca ctggttatca   1020

ccctttactg cagagtgaag ttcagcagga gcgcagacgc ccccgcgtac cagcagggcc   1080

agaaccagct ctataacgag ctcaatctag gacgaagaga ggagtacgat gttttggaca   1140

agagacgtgg ccgggaccct gagatggggg gaaagccgag aaggaagaac cctcaggaag   1200

gcctgtacaa tgaactgcag aaagataaga tggcggaggc ctacagtgag attgggatga   1260

aaggcgagcg ccggaggggc aaggggcacg atggccttta ccagggtctc agtacagcca   1320

ccaaggacac ctacgacgcc cttcacatgc aggccctgcc ccctcgcgga agcggagcca   1380

ccaacttcag cctgctgaag caggccggcg acgtggagga gaaccccggc ccctacctgt   1440

ggctgaagct gctggccttc ggcttcgcct tcctggacac cgaggtgttc gtgaccggcg   1500

acatccagat gacccagagc cccagcaccc tgagcgccag cgtgggcgac agggtgacca   1560

tcacctgcag cgccagcagc agcatcagct acatgcactg gtaccagcag aagcccggca   1620

aggcccccaa gctgctgatc tacaccacca gcaacctggc cagcggcgtg cccgccaggt   1680

tcagcggcag cggcagcggc accgagttca ccctgaccat cagcagcctg cagcccgacg   1740
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acttcgccac ctactactgc caccagagga gcacctaccc cctgaccttc ggccagggca   1800

ccaaggtgga ggtgaagggc ggcggcggca gcggcggcgg cggcagcggc ggcggcggca   1860

gccaggtgca gctggtgcag agcggcgccg aggtgaagaa gcccggcagc agcgtgaagg   1920

tgagctgcaa ggccagcggc tacaccttca ccagctacag gatgcactgg gtgaggcagg   1980

cccccggcca gggcctggag tggatcggct acatcaaccc cagcaccggc tacaccgagt   2040

acaaccagaa gttcaaggac aaggccacca tcaccgccga cgagagcacc aacaccgcct   2100

acatggagct gagcagcctg aggagcgagg acaccgccgt gtactactgc gccaggggcg   2160

gcggcgtgtt cgactactgg ggccagggca ccctggtgac cgtgagcagc accaccaccc   2220

ccgcccccag gcccccccacc cccgccccca ccatcgccag ccagcccctg agcctgaggc   2280

ccgaggcctg caggcccgcc gccggcggcg ccgtgcacac caggggcctg gacttcgcct   2340

gcgacttttg ggtgctggtg gtggttggtg gagtcctggc ttgctatagc ttgctagtaa   2400

cagtggcctt tattattttc tgggtgagga gtaagaggag caggctcctg cacagtgact   2460

acatgaacat gactccccgc cgccccgggc ccacccgcaa gcattaccag ccctatgccc   2520

caccacgcga cttcgcagcc tatcgctcct aagtttaaac                         2560
```

<210> SEQ ID NO 92
<211> LENGTH: 847
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 92

```
Met Tyr Leu Trp Leu Lys Leu Leu Ala Phe Gly Phe Ala Phe Leu Asp
1               5                   10                  15

Thr Glu Val Phe Val Thr Gly Asp Ile Val Met Thr Gln Ser Pro Asp
            20                  25                  30

Ser Leu Ala Val Ser Leu Gly Glu Arg Val Thr Met Asn Cys Lys Ser
        35                  40                  45

Ser Gln Ser Leu Leu Tyr Ser Thr Asn Gln Lys Asn Tyr Leu Ala Trp
    50                  55                  60

Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala
65                  70                  75                  80

Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
                85                  90                  95

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Val
            100                 105                 110

Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Arg Thr Phe Gly Gly
        115                 120                 125

Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu
145                 150                 155                 160

Val Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly
                165                 170                 175

Tyr Thr Phe Thr Ser Tyr Val Ile His Trp Val Arg Gln Lys Pro Gly
            180                 185                 190

Gln Gly Leu Asp Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr
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        195                 200                 205

Asp Tyr Asp Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Thr
    210                 215                 220

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
225                 230                 235                 240

Thr Ala Val Tyr Tyr Cys Ala Arg Glu Lys Asp Asn Tyr Ala Thr Gly
                245                 250                 255

Ala Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
            340                 345                 350

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
        355                 360                 365

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
    370                 375                 380

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
385                 390                 395                 400

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
                405                 410                 415

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
            420                 425                 430

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
        435                 440                 445

Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys
    450                 455                 460

Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Tyr Leu Trp Leu Lys
465                 470                 475                 480

Leu Leu Ala Phe Gly Phe Ala Phe Leu Asp Thr Glu Val Phe Val Thr
                485                 490                 495

Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val
            500                 505                 510

Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr
        515                 520                 525

Met His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
    530                 535                 540

Tyr Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly
545                 550                 555                 560

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
                565                 570                 575

Asp Asp Phe Ala Thr Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu
            580                 585                 590

Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys Gly Gly Gly Gly Ser
        595                 600                 605
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Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Gln
    610                 615                 620

Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys
625                 630                 635                 640

Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met His Trp Val Arg
                645                 650                 655

Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
            660                 665                 670

Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Ile
        675                 680                 685

Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr Met Glu Leu Ser Ser Leu
    690                 695                 700

Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Gly Gly Val
705                 710                 715                 720

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr
                725                 730                 735

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
            740                 745                 750

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
        755                 760                 765

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Phe Trp Val Leu Val
    770                 775                 780

Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala
785                 790                 795                 800

Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser
                805                 810                 815

Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His
            820                 825                 830

Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        835                 840                 845


<210> SEQ ID NO 93
<211> LENGTH: 2551
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 93

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc ggacatcgtg atgacccaaa gccccgacag cctggccgtg agcctgggcg    120

agagggtgac catgaactgc aaaagcagcc agtccctgct gtactccacc aaccagaaga    180

actacctggc ttggtatcaa cagaagcccg gacagagccc caagctgctg atctattggg    240

ccagcactag ggaaagcggc gtgcccgata ggttcagcgg cagcgggagc ggcacagact    300

tcactctgac cattagcagc gtgcaggctg aggatgtggc cgtctactac tgccagcagt    360

actacagcta caggaccttt gggggcggaa ctaagctgga gatcaaggga gggggggat    420

ccgggggagg aggctccggc ggaggcggaa gccaagtgca actgcagcag agcggcccag    480

aggtggtcaa acctggggca agcgtgaaga tgagctgcaa ggctagcggc tataccttca    540

ccagctatgt gatccactgg gtgaggcaga aaccaggaca gggcctggac tggatcggct    600
```

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acatcaaccc ctacaatgac ggcaccgatt atgacgaaaa attcaagggg aaggccaccc    660
tgaccagcga caccagcaca agcaccgcct acatggagct gtccagcctg aggtccgagg    720
acaccgccgt gtattactgt gccagggaga aggacaatta cgccaccggc gcttggttcg    780
cctactgggg ccagggcaca ctggtgacag tgagcagcac cacgacgcca gcgccgcgac    840
caccaacacc ggcgcccacc atcgcgtcgc agcccctgtc cctgcgccca gaggcgtgcc    900
ggccagcggc ggggggcgca gtgcacacga gggggctgga cttcgcctgt gatatctaca    960
tctgggcgcc cttggccggg acttgtgggg tccttctcct gtcactggtt atcacccttt   1020
actgcagagt gaagttcagc aggagcgcag acgcccccgc gtaccagcag ggccagaacc   1080
agctctataa cgagctcaat ctaggacgaa gagaggagta cgatgttttg gacaagagac   1140
gtggccggga ccctgagatg gggggaaagc cgagaaggaa gaaccctcag gaaggcctgt   1200
acaatgaact gcagaaagat aagatggcgg aggcctacag tgagattggg atgaaaggcg   1260
agcgccggag gggcaagggg cacgatggcc tttaccaggg tctcagtaca gccaccaagg   1320
acacctacga cgcccttcac atgcaggccc tgccccctcg cggaagcgga gccaccaact   1380
tcagcctgct gaagcaggcc ggcgacgtgg aggagaaccc cggccccatg gccctgcccg   1440
tgaccgccct gctgctgccc ctggccctgc tgctgcacgc cgccaggccc gacatccaga   1500
tgacccagag ccccagcacc ctgagcgcca gcgtgggcga cagggtgacc atcacctgca   1560
gcgccagcag cagcatcagc tacatgcact ggtaccagca gaagcccggc aaggccccca   1620
agctgctgat ctacaccacc agcaacctgg ccagcggcgt gcccgccagg ttcagcggca   1680
gcggcagcgg caccgagttc accctgacca tcagcagcct gcagcccgac gacttcgcca   1740
cctactactg ccaccagagg agcacctacc ccctgacctt cggccagggc accaaggtgg   1800
aggtgaaggg cggcggcggc agcggcggcg gcggcagcgg cggcggcggc agccaggtgc   1860
agctggtgca gagcggcgcc gaggtgaaga agcccggcag cagcgtgaag gtgagctgca   1920
aggccagcgg ctacaccttc accagctaca ggatgcactg ggtgaggcag gcccccggcc   1980
agggcctgga gtggatcggc tacatcaacc ccagcaccgg ctacaccgag tacaaccaga   2040
agttcaagga caaggccacc atcaccgccg acgagagcac caacaccgcc tacatggagc   2100
tgagcagcct gaggagcgag gacaccgccg tgtactactg cgccaggggc ggcggcgtgt   2160
tcgactactg gggccagggc accctggtga ccgtgagcag caccaccacc cccgccccca   2220
ggcccccccac ccccgccccc accatcgcca gccagcccct gagcctgagg cccgaggcct   2280
gcaggcccgc cgccggcggc gccgtgcaca ccaggggcct ggacttcgcc tgcgactttt   2340
gggtgctggt ggtggttggt ggagtcctgg cttgctatag cttgctagta acagtggcct   2400
ttattatttt ctgggtgagg agtaagagga gcaggctcct gcacagtgac tacatgaaca   2460
tgactccccg ccgccccggg cccacccgca agcattacca gccctatgcc ccaccacgcg   2520
acttcgcagc ctatcgctcc taagtttaaa c                                  2551
```

<210> SEQ ID NO 94
<211> LENGTH: 844
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 94

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```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu
            20                  25                  30

Ala Val Ser Leu Gly Glu Arg Val Thr Met Asn Cys Lys Ser Ser Gln
        35                  40                  45

Ser Leu Leu Tyr Ser Thr Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
65                  70                  75                  80

Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val
            100                 105                 110

Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Arg Thr Phe Gly Gly Gly Thr
        115                 120                 125

Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Val Val
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Val Ile His Trp Val Arg Gln Lys Pro Gly Gln Gly
            180                 185                 190

Leu Asp Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Asp Tyr
        195                 200                 205

Asp Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Thr Ser Thr
    210                 215                 220

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Glu Lys Asp Asn Tyr Ala Thr Gly Ala Trp
                245                 250                 255

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr
            260                 265                 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
        275                 280                 285

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
    290                 295                 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305                 310                 315                 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
                325                 330                 335

Leu Tyr Cys Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
            340                 345                 350

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
        355                 360                 365

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
    370                 375                 380

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
385                 390                 395                 400

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
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                405                 410                 415

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
            420                 425                 430

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
        435                 440                 445

Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala
    450                 455                 460

Gly Asp Val Glu Glu Asn Pro Gly Pro Met Ala Leu Pro Val Thr Ala
465                 470                 475                 480

Leu Leu Leu Pro Leu Ala Leu Leu Leu His Ala Ala Arg Pro Asp Ile
                485                 490                 495

Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg
            500                 505                 510

Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr Met His Trp
        515                 520                 525

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Thr Thr
    530                 535                 540

Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser
545                 550                 555                 560

Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe
                565                 570                 575

Ala Thr Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr Phe Gly
            580                 585                 590

Gln Gly Thr Lys Val Glu Val Lys Gly Gly Gly Gly Ser Gly Gly Gly
        595                 600                 605

Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala
    610                 615                 620

Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser
625                 630                 635                 640

Gly Tyr Thr Phe Thr Ser Tyr Arg Met His Trp Val Arg Gln Ala Pro
                645                 650                 655

Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Thr Gly Tyr
            660                 665                 670

Thr Glu Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Ile Thr Ala Asp
        675                 680                 685

Glu Ser Thr Asn Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu
    690                 695                 700

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Gly Gly Val Phe Asp Tyr
705                 710                 715                 720

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala
                725                 730                 735

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
            740                 745                 750

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
        755                 760                 765

Arg Gly Leu Asp Phe Ala Cys Asp Phe Trp Val Leu Val Val Val Gly
    770                 775                 780

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
785                 790                 795                 800

Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
                805                 810                 815
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Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
            820                 825                 830

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        835                 840


<210> SEQ ID NO 95
<211> LENGTH: 2149
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 95

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc ggacatcgtg atgacccaaa gccccgacag cctggccgtg agcctgggcg    120

agagggtgac catgaactgc aaaagcagcc agtccctgct gtactccacc aaccagaaga    180

actacctggc ttggtatcaa cagaagcccg gacagagccc caagctgctg atctattggg    240

ccagcactag ggaaagcggc gtgcccgata ggttcagcgg cagcgggagc ggcacagact    300

tcactctgac cattagcagc gtgcaggctg aggatgtggc cgtctactac tgccagcagt    360

actacagcta caggaccttt gggggcggaa ctaagctgga gatcaaggga gggggggat    420

ccgggggagg aggctccggc ggaggcggaa gccaagtgca actgcagcag agcggcccag    480

aggtggtcaa acctggggca agcgtgaaga tgagctgcaa ggctagcggc tataccttca    540

ccagctatgt gatccactgg gtgaggcaga aaccaggaca gggcctggac tggatcggct    600

acatcaaccc ctacaatgac ggcaccgatt atgacgaaaa attcaagggg aaggccaccc    660

tgaccagcga caccagcaca agcaccgcct acatggagct gtccagcctg aggtccgagg    720

acaccgccgt gtattactgt gccagggaga aggacaatta cgccaccggc gcttggttcg    780

cctactgggg ccagggcaca ctggtgacag tgagcagcac cacgacgcca gcgccgcgac    840

caccaacacc ggcgcccacc atcgcgtcgc agcccctgtc cctgcgccca gaggcgtgcc    900

ggccagcggc ggggggcgca gtgcacacga gggggctgga cttcgcctgt gatatctaca    960

tctgggcgcc cttggccggg acttgtgggg tccttctcct gtcactggtt atcacccttt   1020

actgcaggag taagaggagc aggctcctgc acagtgacta catgaacatg actccccgcc   1080

gccccgggcc cacccgcaag cattaccagc cctatgcccc accacgcgac ttcgcagcct   1140

atcgctccaa acggggcaga aagaaactcc tgtatatatt caaacaacca tttatgagac   1200

cagtacaaac tactcaagag gaagatggct gtagctgccg atttccagaa gaagaagaag   1260

gaggatgtga actgagagtg aagttcagca ggagcgcaga cgcccccgcg taccagcagg   1320

gccagaacca gctctataac gagctcaatc taggacgaag agaggagtac gatgttttgg   1380

acaagagacg tggccgggac cctgagatgg ggggaaagcc gcagagaagg aagaaccctc   1440

aggaaggcct gtacaatgaa ctgcagaaag ataagatggc ggaggcctac agtgagattg   1500

ggatgaaagg cgagcgccgg aggggcaagg ggcacgatgg cctttaccag ggtctcagta   1560

cagccaccaa ggacacctac gacgcccttc acatgcaggc cctgccccct cgcggaagcg   1620

gagccaccaa cttcagcctg ctgaagcagg ccggcgacgt ggaggagaac cccggcccca   1680

tgtacagaat gcagctgctg agctgcatcg ccctgagcct ggccctggtg accaacagcg   1740

gcatccacgt gttcatcctg ggctgcttca gcgccggcct gcccaagacc gaggccaact   1800
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gggtgaacgt gatcagcgac ctgaagaaga tcgaggacct gatccagagc atgcacatcg   1860

acgccaccct gtacaccgag agcgacgtgc accccagctg caaggtgacc gccatgaagt   1920

gcttcctgct ggagctgcag gtgatcagcc tggagagcgg cgacgccagc atccacgaca   1980

ccgtggagaa cctgatcatc ctggccaaca acagcctgag cagcaacggc aacgtgaccg   2040

agagcggctg caaggagtgc gaggagctgg aggagaagaa catcaaggag ttcctgcaga   2100

gcttcgtgca catcgtgcag atgttcatca acaccagcta agtttaaac               2149
```

<210> SEQ ID NO 96
<211> LENGTH: 710
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 96

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu
            20                  25                  30

Ala Val Ser Leu Gly Glu Arg Val Thr Met Asn Cys Lys Ser Ser Gln
        35                  40                  45

Ser Leu Leu Tyr Ser Thr Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
65                  70                  75                  80

Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val
            100                 105                 110

Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Arg Thr Phe Gly Gly Gly Thr
        115                 120                 125

Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Val Val
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Val Ile His Trp Val Arg Gln Lys Pro Gly Gln Gly
            180                 185                 190

Leu Asp Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Asp Tyr
        195                 200                 205

Asp Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Thr Ser Thr
    210                 215                 220

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Glu Lys Asp Asn Tyr Ala Thr Gly Ala Trp
                245                 250                 255

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr
            260                 265                 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
        275                 280                 285
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```
Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
    290                 295                 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305                 310                 315                 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
                325                 330                 335

Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
            340                 345                 350

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
        355                 360                 365

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Lys Arg Gly Arg
    370                 375                 380

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
385                 390                 395                 400

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
                405                 410                 415

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
            420                 425                 430

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
        435                 440                 445

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
    450                 455                 460

Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly
465                 470                 475                 480

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
                485                 490                 495

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
            500                 505                 510

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
        515                 520                 525

Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu
    530                 535                 540

Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Tyr Arg
545                 550                 555                 560

Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu Val Thr Asn
                565                 570                 575

Ser Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu Pro
            580                 585                 590

Lys Thr Glu Ala Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile
        595                 600                 605

Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu
    610                 615                 620

Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu
625                 630                 635                 640

Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His
                645                 650                 655

Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser
            660                 665                 670

Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu
        675                 680                 685
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Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln
    690                 695                 700

Met Phe Ile Asn Thr Ser
705                 710


<210> SEQ ID NO 97
<211> LENGTH: 2623
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 97

gcgatcgcat ggccttacca gtgaccgcct tgctcctgcc gctggccttg ctgctccacg     60

ccgccaggcc ggacatcgtg atgacccaaa gccccgacag cctggccgtg agcctgggcg    120

agagggtgac catgaactgc aaaagcagcc agtccctgct gtactccacc aaccagaaga    180

actacctggc ttggtatcaa cagaagcccg gacagagccc caagctgctg atctattggg    240

ccagcactag ggaaagcggc gtgcccgata ggttcagcgg cagcgggagc ggcacagact    300

tcactctgac cattagcagc gtgcaggctg aggatgtggc cgtctactac tgccagcagt    360

actacagcta caggaccttt gggggcggaa ctaagctgga gatcaaggga gggggggat    420

ccgggggagg aggctccggc ggaggcggaa gccaagtgca actgcagcag agcggcccag    480

aggtggtcaa acctggggca agcgtgaaga tgagctgcaa ggctagcggc tataccttca    540

ccagctatgt gatccactgg gtgaggcaga aaccaggaca gggcctggac tggatcggct    600

acatcaaccc ctacaatgac ggcaccgatt atgacgaaaa attcaagggg aaggccaccc    660

tgaccagcga caccagcaca agcaccgcct acatggagct gtccagcctg aggtccgagg    720

acaccgccgt gtattactgt gccagggaga aggacaatta cgccaccggc gcttggttcg    780

cctactgggg ccagggcaca ctggtgacag tgagcagcac cacgacgcca gcgccgcgac    840

caccaacacc ggcgcccacc atcgcgtcgc agcccctgtc cctgcgccca gaggcgtgcc    900

ggccagcggc ggggggcgca gtgcacacga gggggctgga cttcgcctgt gatatctaca    960

tctgggcgcc cttggccggg acttgtgggg tccttctcct gtcactggtt atcacccttt   1020

actgcaggag taagaggagc aggctcctgc acagtgacta catgaacatg actccccgcc   1080

gccccgggcc cacccgcaag cattaccagc cctatgcccc accacgcgac ttcgcagcct   1140

atcgctccaa acggggcaga aagaaactcc tgtatatatt caaacaacca tttatgagac   1200

cagtacaaac tactcaagag gaagatggct gtagctgccg atttccagaa gaagaagaag   1260

gaggatgtga actgagagtg aagttcagca ggagcgcaga cgcccccgcg taccagcagg   1320

gccagaacca gctctataac gagctcaatc taggacgaag agaggagtac gatgttttgg   1380

acaagagacg tggccgggac cctgagatgg ggggaaagcc gcagagaagg aagaaccctc   1440

aggaaggcct gtacaatgaa ctgcagaaag ataagatggc ggaggcctac agtgagattg   1500

ggatgaaagg cgagcgccgg aggggcaagg ggcacgatgg cctttaccag ggtctcagta   1560

cagccaccaa ggacacctac gacgcccttc acatgcaggc cctgcccccct cgcggaagcg   1620

gagccaccaa cttcagcctg ctgaagcagg ccggcgacgt ggaggagaac cccggcccca   1680

tgtacagaat gcagctgctg agctgcatcg ccctgagcct ggccctggtg accaacagcg   1740

gcatccacgt gttcatcctg ggctgcttca gcgccggcct gcccaagacc gaggccaact   1800
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gggtgaacgt gatcagcgac ctgaagaaga tcgaggacct gatccagagc atgcacatcg   1860

acgccaccct gtacaccgag agcgacgtgc accccagctg caaggtgacc gccatgaagt   1920

gcttcctgct ggagctgcag gtgatcagcc tggagagcgg cgacgccagc atccacgaca   1980

ccgtggagaa cctgatcatc ctggccaaca acagcctgag cagcaacggc aacgtgaccg   2040

agagcggctg caaggagtgc gaggagctgg aggagaagaa catcaaggag ttcctgcaga   2100

gcttcgtgca catcgtgcag atgttcatca acaccagctc cggcggcggc tccggcggcg   2160

gcggctccgg cggcggcggc tccggcggcg gcggctccgg cggcggctcc ctgcagatca   2220

cctgcccccc ccccatgagc gtggagcacg ccgacatctg ggtgaagagc tacagcctgt   2280

acagcagaga gagatacatc tgcaacagcg gcttcaagag aaaggccggc accagcagcc   2340

tgaccgagtg cgtgctgaac aaggccacca acgtggccca ctggaccacc cccagcctga   2400

agtgcatcag aaccaccacc cccgccccca ggcccccccac ccccgccccc accatcgcca   2460

gccagcccct gagcctgagg cccgaggcct gcaggcccgc cgccggcggc gccgtgcaca   2520

ccaggggcct ggacttcgcc tgcgacgtgg ctatctccac gtccactgtc ctgctgtgtg   2580

ggctgagcgc tgtgtctctc ctggcatgct actaagttta aac                     2623
```

```
<210> SEQ ID NO 98
<211> LENGTH: 868
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 98

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu
            20                  25                  30

Ala Val Ser Leu Gly Glu Arg Val Thr Met Asn Cys Lys Ser Ser Gln
        35                  40                  45

Ser Leu Leu Tyr Ser Thr Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
65                  70                  75                  80

Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val
            100                 105                 110

Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Arg Thr Phe Gly Gly Gly Thr
        115                 120                 125

Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Val Val
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Val Ile His Trp Val Arg Gln Lys Pro Gly Gln Gly
            180                 185                 190

Leu Asp Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Asp Tyr
        195                 200                 205
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Asp Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Thr Ser Thr
    210                 215                 220

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Glu Lys Asp Asn Tyr Ala Thr Gly Ala Trp
                245                 250                 255

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr
            260                 265                 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
        275                 280                 285

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
    290                 295                 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305                 310                 315                 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
                325                 330                 335

Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
            340                 345                 350

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
        355                 360                 365

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Lys Arg Gly Arg
    370                 375                 380

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
385                 390                 395                 400

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
                405                 410                 415

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
            420                 425                 430

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
        435                 440                 445

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
    450                 455                 460

Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly
465                 470                 475                 480

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
                485                 490                 495

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
            500                 505                 510

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
        515                 520                 525

Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu
    530                 535                 540

Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Tyr Arg
545                 550                 555                 560

Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu Val Thr Asn
                565                 570                 575

Ser Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu Pro
            580                 585                 590

Lys Thr Glu Ala Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile
        595                 600                 605
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```
Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu
    610                 615                 620

Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu
625                 630                 635                 640

Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His
                645                 650                 655

Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser
            660                 665                 670

Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu
        675                 680                 685

Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln
    690                 695                 700

Met Phe Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser
705                 710                 715                 720

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln
                725                 730                 735

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
            740                 745                 750

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
        755                 760                 765

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
    770                 775                 780

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
785                 790                 795                 800

Arg Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
                805                 810                 815

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
            820                 825                 830

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Val Ala
        835                 840                 845

Ile Ser Thr Ser Thr Val Leu Leu Cys Gly Leu Ser Ala Val Ser Leu
    850                 855                 860

Leu Ala Cys Tyr
865


<210> SEQ ID NO 99
<211> LENGTH: 2389
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 99

gcgatcgcac catggcctta ccagtgaccg ccttgctcct gccgctggcc ttgctgctcc      60

acgccgccag gccggacatc gtgatgagcc agagccccag cagcctggcc gtgagcgtgg     120

gcgagaagtt caccgtgaac tgcaagagca gccagagcct gctgtacagc agcaaccaga     180

agaacttcct ggcctggtac cagcagaagc ccggccagag ccccaagctg ctgatctact     240

gggccagcac cagagagagc ggcgtgcccg acagattcat cggcagcggc agcggcaccg     300

acttcaccct gaccatcagc agcgtgaagg ccgaggacct ggccgtgtac tactgccagc     360

agcactacag ataccccctgg accttcggcg gcggcaccaa gctggagatc aagagagcca     420

gaggaggggg gggatccggg ggaggaggct ccggcggagg cggaagccag gtgaccctga     480
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```
aggagagcgg ccccggcatc ctgcagccca gccagaccct gagcctgacc tgcagcttca    540
gcggcttcag cctgaacacc agcggcgtgg gcgtgggctg gatcagacag cccagcggca    600
agggcctgga gtggctggcc cacatctggt gggacgacga cgagagatac aaccccgtgc    660
tgaagagcag actgaccatc agcaaggaca ccagcagcaa ccaggtgttc ctgaagatcg    720
ccaacgtgga caccgccgac agcgccacct actactgcgt gagaagcatg gtggcctggt    780
tcttccccta ctggggcaga ggcaccctgg tgaccgtgag cgccaccacg acgccagcgc    840
cgcgaccacc aacaccggcg cccaccatcg cgtcgcagcc cctgtccctg cgcccagagg    900
cgtgccggcc agcggcgggg ggcgcagtgc acacgagggg gctggacttc gcctgtgata    960
tctacatctg ggcgcccttg gccgggactt gtggggtcct tctcctgtca ctggttatca   1020
ccctttactg caggagtaag aggagcaggc tcctgcacag tgactacatg aacatgactc   1080
cccgccgccc cgggcccacc cgcaagcatt accagcccta tgccccacca cgcgacttcg   1140
cagcctatcg ctccagggtg aagttcagca ggagcgccga cgcccccgcc taccagcagg   1200
gccagaacca gctgtacaac gagctgaacc tgggcaggag ggaggagtac gacgtgctgg   1260
acaagaggag gggcagggac cccgagatgg gcggcaagcc ccagaggagg aagaaccccc   1320
aggagggcct gtacaacgag ctgcagaagg acaagatggc cgaggcctac agcgagatcg   1380
gcatgaaggg cgagaggagg aggggcaagg gccacgacgg cctgtaccag ggcctgagca   1440
ccgccaccaa ggacacctac gacgccctgc acatgcaggc cctgcccccc aggggaagcg   1500
gagccaccaa cttcagcctg ctgaagcagg ccggcgacgt ggaggagaac cccggcccca   1560
tgtacagaat gcagctgctg agctgcatcg ccctgagcct ggccctggtg accaacagcg   1620
gcatccacgt gttcatcctg ggctgcttca gcgccggcct gcccaagacc gaggccaact   1680
gggtgaacgt gatcagcgac ctgaagaaga tcgaggacct gatccagagc atgcacatcg   1740
acgccaccct gtacaccgag agcgacgtgc accccagctg caaggtgacc gccatgaagt   1800
gcttcctgct ggagctgcag gtgatcagcc tggagagcgg cgacgccagc atccacgaca   1860
ccgtggagaa cctgatcatc ctggccaaca acagcctgag cagcaacggc aacgtgaccg   1920
agagcggctg caaggagtgc gaggagctgg aggagaagaa catcaaggag ttcctgcaga   1980
gcttcgtgca catcgtgcag atgttcatca acaccagctc cggcggcggc tccggcggcg   2040
gcggctccgg cggcggcggc tccggcggcg gcggctccgg cggcggctcc ctgcaggccc   2100
ccagaagagc cagaggctgc agaaccctgg gcctgcccgc cctgctgctg ctgctgctgc   2160
tgagaccccc cgccaccaga ggcatcacct gcccccccc catgagcgtg gagcacgccg   2220
acatctgggt gaagagctac agcctgtaca gcagagagag atacatctgc aacagcggct   2280
tcaagagaaa ggccggcacc agcagcctga ccgagtgcgt gctgaacaag gccaccaacg   2340
tggcccactg gaccaccccc agcctgaagt gcatcagata agtttaaac               2389
```

<210> SEQ ID NO 100
<211> LENGTH: 789
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 100

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu

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```
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu
            20                  25                  30

Ala Val Ser Val Gly Glu Lys Phe Thr Val Asn Cys Lys Ser Ser Gln
        35                  40                  45

Ser Leu Leu Tyr Ser Ser Asn Gln Lys Asn Phe Leu Ala Trp Tyr Gln
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
65                  70                  75                  80

Arg Glu Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Thr Ile Ser Ser Val Lys Ala Glu Asp Leu Ala Val
            100                 105                 110

Tyr Tyr Cys Gln Gln His Tyr Arg Tyr Pro Trp Thr Phe Gly Gly Gly
        115                 120                 125

Thr Lys Leu Glu Ile Lys Arg Ala Arg Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Thr Leu Lys Glu Ser Gly
145                 150                 155                 160

Pro Gly Ile Leu Gln Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe
                165                 170                 175

Ser Gly Phe Ser Leu Asn Thr Ser Gly Val Gly Val Gly Trp Ile Arg
            180                 185                 190

Gln Pro Ser Gly Lys Gly Leu Glu Trp Leu Ala His Ile Trp Trp Asp
        195                 200                 205

Asp Asp Glu Arg Tyr Asn Pro Val Leu Lys Ser Arg Leu Thr Ile Ser
    210                 215                 220

Lys Asp Thr Ser Ser Asn Gln Val Phe Leu Lys Ile Ala Asn Val Asp
225                 230                 235                 240

Thr Ala Asp Ser Ala Thr Tyr Tyr Cys Val Arg Ser Met Val Ala Trp
                245                 250                 255

Phe Phe Pro Tyr Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ala Thr
            260                 265                 270

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
        275                 280                 285

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
    290                 295                 300

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
305                 310                 315                 320

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
                325                 330                 335

Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr
            340                 345                 350

Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln
        355                 360                 365

Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys
    370                 375                 380

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
385                 390                 395                 400

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                405                 410                 415
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Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Gly Ser
                485                 490                 495

Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu
            500                 505                 510

Asn Pro Gly Pro Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu
        515                 520                 525

Ser Leu Ala Leu Val Thr Asn Ser Gly Ile His Val Phe Ile Leu Gly
    530                 535                 540

Cys Phe Ser Ala Gly Leu Pro Lys Thr Glu Ala Asn Trp Val Asn Val
545                 550                 555                 560

Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile
                565                 570                 575

Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val
            580                 585                 590

Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu
        595                 600                 605

Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu
    610                 615                 620

Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys
625                 630                 635                 640

Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln
                645                 650                 655

Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly
            660                 665                 670

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        675                 680                 685

Ser Gly Gly Gly Ser Leu Gln Ala Pro Arg Arg Ala Arg Gly Cys Arg
    690                 695                 700

Thr Leu Gly Leu Pro Ala Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro
705                 710                 715                 720

Ala Thr Arg Gly Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala
                725                 730                 735

Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile
            740                 745                 750

Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu
        755                 760                 765

Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser
    770                 775                 780

Leu Lys Cys Ile Arg
785
```

<210> SEQ ID NO 101
<211> LENGTH: 2371

-continued

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 101

gcgatcgcac catggcctta ccagtgaccg ccttgctcct gccgctggcc ttgctgctcc 60

acgccgccag gccggacatt atgatgacac agtcgccatc atctctggct gtgtctgcag 120

gagaaaaggt cactatgacc tgtaagtcca gtcaaagtgt tttatacagt tcaaatcaga 180

agaactactt ggcctggtac cagcagaaac cagggcagtc tcctaaacta ctgatctact 240

gggcatccac tagggaatct ggtgtccctg atcgcttcac aggcagtgga tctgggacag 300

attttactct taccatcagc agtgtgcaac ctgaagacct ggcagtttat tactgtcatc 360

aatacctctc ctcgcacacg ttcggagggg ggaccaagct ggaaataaaa cggggtggcg 420

gtggctcggg cggtggtggg tcgggtggcg gcggatctca actgcagcag cctggggctg 480

agctggtgag gcctgggtct tcagtgaagc tgtcctgcaa ggcttctggc tacaccttca 540

ccaggtactg gatacattgg gtgaagcaga ggcctataca aggccttgaa tggattggta 600

acattgatcc ttctgatagt gaaactcact acaatcaaaa gttcaaggac aaggccacat 660

tgactgtaga caaatcctcc ggcacagcct acatgcagct cagcagcctg acatctgagg 720

actctgcggt ctattactgt gcaacagagg atctttacta tgctatggag tactggggtc 780

aaggaacctc agtcaccgtc tcctctacca cgacgccagc gccgcgacca ccaacaccgg 840

cgcccaccat cgcgtcgcag cccctgtccc tgcgcccaga ggcgtgccgg ccagcggcgg 900

ggggcgcagt gcacacgagg gggctggact tcgcctgtga tatctacatc tgggcgccct 960

tggccgggac ttgtggggtc cttctcctgt cactggttat cacccttac tgcaggagta 1020

agaggagcag gctcctgcac agtgactaca tgaacatgac tccccgccgc cccgggccca 1080

cccgcaagca ttaccagccc tatgccccac cacgcgactt cgcagcctat cgctccagag 1140

tgaagttcag caggagcgca gacgcccccg cgtaccagca gggccagaac cagctctata 1200

acgagctcaa tctaggacga agagaggagt acgatgtttt ggacaagaga cgtggccggg 1260

accctgagat ggggggaaag ccgcagagaa ggaagaaccc tcaggaaggc ctgtacaatg 1320

aactgcagaa agataagatg gcggaggcct acagtgagat tgggatgaaa ggcgagcgcc 1380

ggaggggcaa ggggcacgat ggcctttacc agggtctcag tacagccacc aaggacacct 1440

acgacgccct tcacatgcag gccctgcccc ctcgcggaag cggagccacc aacttcagcc 1500

tgctgaagca ggccggcgac gtggaggaga accccggccc catgtacaga atgcagctgc 1560

tgagctgcat cgccctgagc ctggccctgg tgaccaacag cggcatccac gtgttcatcc 1620

tgggctgctt cagcgccggc ctgcccaaga ccgaggccaa ctgggtgaac gtgatcagcg 1680

acctgaagaa gatcgaggac ctgatccaga gcatgcacat cgacgccacc ctgtacaccg 1740

agagcgacgt gcaccccagc tgcaaggtga ccgccatgaa gtgcttcctg ctggagctgc 1800

aggtgatcag cctggagagc ggcgacgcca gcatccacga caccgtggag aacctgatca 1860

tcctggccaa caacagcctg agcagcaacg gcaacgtgac cgagagcggc tgcaaggagt 1920

gcgaggagct ggaggagaag aacatcaagg agttcctgca gagcttcgtg cacatcgtgc 1980

agatgttcat caacaccagc tccggcggcg gctccggcgg cggcggctcc ggcggcggcg 2040

gctccggcgg cggcggctcc ggcggcggct ccctgcaggc ccccagaaga gccagaggct 2100

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gcagaaccct gggcctgccc gccctgctgc tgctgctgct gctgagaccc cccgccacca   2160

gaggcatcac ctgccccccc cccatgagcg tggagcacgc cgacatctgg gtgaagagct   2220

acagcctgta cagcagagag agatacatct gcaacagcgg cttcaagaga aaggccggca   2280

ccagcagcct gaccgagtgc gtgctgaaca aggccaccaa cgtggcccac tggaccaccc   2340

ccagcctgaa gtgcatcaga taagtttaaa c                                  2371


<210> SEQ ID NO 102
<211> LENGTH: 783
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 102

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Met Met Thr Gln Ser Pro Ser Ser Leu
            20                  25                  30

Ala Val Ser Ala Gly Glu Lys Val Thr Met Thr Cys Lys Ser Ser Gln
        35                  40                  45

Ser Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
65                  70                  75                  80

Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Pro Glu Asp Leu Ala Val
            100                 105                 110

Tyr Tyr Cys His Gln Tyr Leu Ser Ser His Thr Phe Gly Gly Gly Thr
        115                 120                 125

Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg
145                 150                 155                 160

Pro Gly Ser Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe
                165                 170                 175

Thr Arg Tyr Trp Ile His Trp Val Lys Gln Arg Pro Ile Gln Gly Leu
            180                 185                 190

Glu Trp Ile Gly Asn Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn
        195                 200                 205

Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Gly
    210                 215                 220

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Thr Glu Asp Leu Tyr Tyr Ala Met Glu Tyr Trp Gly
                245                 250                 255

Gln Gly Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg
            260                 265                 270

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        275                 280                 285

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
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    290                 295                 300

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305                 310                 315                 320

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser
                325                 330                 335

Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg
            340                 345                 350

Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg
        355                 360                 365

Asp Phe Ala Ala Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp
    370                 375                 380

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385                 390                 395                 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
                405                 410                 415

Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu
            420                 425                 430

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
        435                 440                 445

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
    450                 455                 460

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
465                 470                 475                 480

His Met Gln Ala Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser
                485                 490                 495

Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Tyr
            500                 505                 510

Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu Val Thr
        515                 520                 525

Asn Ser Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu
    530                 535                 540

Pro Lys Thr Glu Ala Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys
545                 550                 555                 560

Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr
                565                 570                 575

Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe
            580                 585                 590

Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile
        595                 600                 605

His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser
    610                 615                 620

Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu
625                 630                 635                 640

Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val
                645                 650                 655

Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly
            660                 665                 670

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu
        675                 680                 685

Gln Ala Pro Arg Arg Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro Ala
    690                 695                 700
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Leu Leu Leu Leu Leu Leu Leu Arg Pro Pro Ala Thr Arg Gly Ile Thr
705                 710                 715                 720

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
                725                 730                 735

Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys
            740                 745                 750

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
        755                 760                 765

Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
    770                 775                 780


<210> SEQ ID NO 103
<211> LENGTH: 2356
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 103

gcgatcgcac catggcctta ccagtgaccg ccttgctcct gccgctggcc ttgctgctcc     60

acgccgccag gccggacatc cagatgaccc agagccccag cagcctgagc gccagcgtgg    120

gcgacagagt gaccatcacc tgcagcgcca gcagcagcgt gagctacatg aactggtacc    180

agcagacccc cggcaaggcc cccaagagat ggatctacga caccagcaag ctggccagcg    240

gcgtgcccag cagattcagc ggcagcggca gcggcaccga ctacaccttc accatcagca    300

gcctgcagcc cgaggacatc gccacctact actgccagca gtggagcagc aacccccttca    360

ccttcggcca gggcaccaag ctgcagatcg gcggcggcgg cagcggcggc ggcggcagcg    420

gcggcggcgg cagccaggtg cagctggtgc agagcggcgg cggcgtggtg cagcccggca    480

gaagcctgag actgagctgc aaggccagcg gctacacctt caccagatac accatgcact    540

gggtgagaca ggcccccggc aagggcctgg agtggatcgg ctacatcaac cccagcagag    600

gctacaccaa ctacaaccag aaggtgaagg acagattcac catcagcaga gacaacagca    660

agaacaccgc cttcctgcag atggacagcc tgagacccga ggacaccggc gtgtacttct    720

gcgccagata ctacgacgac cactactgcc tggactactg gggccagggc acccccgtga    780

ccgtgagcag caccacgacg ccagcgccgc gaccaccaac accggcgccc accatcgcgt    840

cgcagcccct gtccctgcgc ccagaggcgt gccggccagc ggcgggggc gcagtgcaca    900

cgagggggct ggacttcgcc tgtgatatct acatctgggc gcccttggcc gggacttgtg    960

gggtccttct cctgtcactg gttatcaccc tttactgcag gagtaagagg agcaggctcc   1020

tgcacagtga ctacatgaac atgactcccc gccgccccgg gcccacccgc aagcattacc   1080

agccctatgc cccaccacgc gacttcgcag cctatcgctc cagagtgaag ttcagcagga   1140

gcgcagacgc ccccgcgtac cagcagggcc agaaccagct ctataacgag ctcaatctag   1200

gacgaagaga ggagtacgat gttttggaca agagacgtgg ccgggaccct gagatggggg   1260

gaaagccgca gagaaggaag aaccctcagg aaggcctgta caatgaactg cagaaagata   1320

agatggcgga ggcctacagt gagattggga tgaaaggcga gcgccggagg ggcaaggggc   1380

acgatggcct ttaccagggt ctcagtacag ccaccaagga cacctacgac gcccttcaca   1440

tgcaggccct gccccctcgc ggaagcggag ccaccaactt cagcctgctg aagcaggccg   1500
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gcgacgtgga ggagaacccc ggccccatgt acagaatgca gctgctgagc tgcatcgccc   1560

tgagcctggc cctggtgacc aacagcggca tccacgtgtt catcctgggc tgcttcagcg   1620

ccggcctgcc caagaccgag gccaactggg tgaacgtgat cagcgacctg aagaagatcg   1680

aggacctgat ccagagcatg cacatcgacg ccaccctgta caccgagagc gacgtgcacc   1740

ccagctgcaa ggtgaccgcc atgaagtgct tcctgctgga gctgcaggtg atcagcctgg   1800

agagcggcga cgccagcatc cacgacaccg tggagaacct gatcatcctg gccaacaaca   1860

gcctgagcag caacggcaac gtgaccgaga gcggctgcaa ggagtgcgag gagctggagg   1920

agaagaacat caaggagttc ctgcagagct tcgtgcacat cgtgcagatg ttcatcaaca   1980

ccagctccgg cggcggctcc ggcggcggcg gctccggcgg cggcggctcc ggcggcggcg   2040

gctccggcgg cggctccctg caggccccca gaagagccag aggctgcaga accctgggcc   2100

tgcccgccct gctgctgctg ctgctgctga gaccccccgc caccagaggc atcacctgcc   2160

cccccccat gagcgtggag cacgccgaca tctgggtgaa gagctacagc ctgtacagca   2220

gagagagata catctgcaac agcggcttca agagaaaggc cggcaccagc agcctgaccg   2280

agtgcgtgct gaacaaggcc accaacgtgg cccactggac cacccccagc ctgaagtgca   2340

tcagataagt ttaaac                                                   2356
```

<210> SEQ ID NO 104
<211> LENGTH: 777
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 104

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
            20                  25                  30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser
        35                  40                  45

Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Thr Pro Gly Lys Ala Pro
    50                  55                  60

Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser
                85                  90                  95

Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Trp Ser
            100                 105                 110

Ser Asn Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Gln Ile Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln
    130                 135                 140

Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg
145                 150                 155                 160

Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His
                165                 170                 175

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile
            180                 185                 190
```

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```
Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Val Lys Asp Arg
        195                 200                 205

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Ala Phe Leu Gln Met
    210                 215                 220

Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys Ala Arg Tyr
225                 230                 235                 240

Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Pro Val
                245                 250                 255

Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
            260                 265                 270

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
        275                 280                 285

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
    290                 295                 300

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
305                 310                 315                 320

Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu
                325                 330                 335

Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr
            340                 345                 350

Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr
        355                 360                 365

Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
    370                 375                 380

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
385                 390                 395                 400

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
                405                 410                 415

Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
            420                 425                 430

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
        435                 440                 445

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
    450                 455                 460

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
465                 470                 475                 480

Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala
                485                 490                 495

Gly Asp Val Glu Glu Asn Pro Gly Pro Met Tyr Arg Met Gln Leu Leu
            500                 505                 510

Ser Cys Ile Ala Leu Ser Leu Ala Leu Val Thr Asn Ser Gly Ile His
        515                 520                 525

Val Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu Pro Lys Thr Glu Ala
    530                 535                 540

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
545                 550                 555                 560

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
                565                 570                 575

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
            580                 585                 590

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
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        595                 600                 605

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
    610                 615                 620

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
625                 630                 635                 640

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
                645                 650                 655

Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            660                 665                 670

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ala Pro Arg Arg
        675                 680                 685

Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro Ala Leu Leu Leu Leu Leu
    690                 695                 700

Leu Leu Arg Pro Pro Ala Thr Arg Gly Ile Thr Cys Pro Pro Pro Met
705                 710                 715                 720

Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser
                725                 730                 735

Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr
            740                 745                 750

Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His
        755                 760                 765

Trp Thr Thr Pro Ser Leu Lys Cys Ile
    770                 775


<210> SEQ ID NO 105
<211> LENGTH: 2401
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 105

gcgatcgcac catggcctta ccagtgaccg ccttgctcct gccgctggcc ttgctgctcc      60

acgccgccag gccgggcgcc cagcccgcca tggccgccta caaggacatc cagatgaccc     120

agaccaccag cagcctgagc gccagcctgg gcgacagagt gaccatcagc tgcagcgcca     180

gccagggcat cagcaactac ctgaactggt accagcagaa gcccgacggc accaacaagc     240

tgctgatcta ctacaccagc agcctgcaca gcggcgtgcc cagcagattc agcggcagcg     300

gcagcggcac cgactacagc ctgcacagca acctggagcc cgaggacatc gccacctact     360

actgccagca gtacagcaag ctgccctaca ccttcggcgg cggcaccaag ctggagatca     420

agagaggcgg cggcggcagc ggcggcggcg gcagcggcgg cggcggcagc ggcggcggcg     480

gcagcgaggt gcagctggtg gagagcggcg gcggcctggt gaagcccggc ggcagcctga     540

agctgagctg cgccgccagc ggcctgacct tcagcagcta cgccatgagc tggaacagac     600

agacccccga gaagagactg gagtgggtgg ccagcatcag cagcggcggc ttcacctact     660

accccgacag caacaagggc agattcacca tcagcagaga caacgccaga aacatcctgt     720

acctgcagat gagcagcctg agaagcgagg acaccgccat gtactactgc gccagagacg     780

aggtgagagg ctacctggac gtgtggggcg ccggcaccac cgtgaccgtg agcagcacca     840

cgacgccagc gccgcgacca ccaacaccgg cgcccaccat cgcgtcgcag cccctgtccc     900

tgcgcccaga ggcgtgccgg ccagcggcgg ggggcgcagt gcacacgagg gggctggact     960
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tcgcctgtga tatctacatc tgggcgccct tggccgggac ttgtggggtc cttctcctgt   1020
cactggttat cacccttac tgcaggagta agaggagcag gctcctgcac agtgactaca   1080
tgaacatgac tccccgccgc cccgggccca cccgcaagca ttaccagccc tatgccccac   1140
cacgcgactt cgcagcctat cgctccagag tgaagttcag caggagcgca gacgcccccg   1200
cgtaccagca gggccagaac cagctctata acgagctcaa tctaggacga agagaggagt   1260
acgatgtttt ggacaagaga cgtggccggg accctgagat ggggggaaag ccgcagagaa   1320
ggaagaaccc tcaggaaggc ctgtacaatg aactgcagaa agataagatg gcggaggcct   1380
acagtgagat tgggatgaaa ggcgagcgcc ggaggggcaa ggggcacgat ggcctttacc   1440
agggtctcag tacagccacc aaggacacct acgacgccct tcacatgcag gccctgcccc   1500
ctcgcggaag cggagccacc aacttcagcc tgctgaagca ggccggcgac gtggaggaga   1560
accccggccc catgtacaga atgcagctgc tgagctgcat cgccctgagc ctggccctgg   1620
tgaccaacag cggcatccac gtgttcatcc tgggctgctt cagcgccggc ctgcccaaga   1680
ccgaggccaa ctgggtgaac gtgatcagcg acctgaagaa gatcgaggac ctgatccaga   1740
gcatgcacat cgacgccacc ctgtacaccg agagcgacgt gcaccccagc tgcaaggtga   1800
ccgccatgaa gtgcttcctg ctggagctgc aggtgatcag cctggagagc ggcgacgcca   1860
gcatccacga caccgtggag aacctgatca tcctggccaa caacagcctg agcagcaacg   1920
gcaacgtgac cgagagcggc tgcaaggagt gcgaggagct ggaggagaag aacatcaagg   1980
agttcctgca gagcttcgtg cacatcgtgc agatgttcat caacaccagc tccggcggcg   2040
gctccggcgg cggcggctcc ggcggcggcg gctccggcgg cggcggctcc ggcggcggct   2100
ccctgcaggc ccccagaaga gccagaggct gcagaaccct gggcctgccc gccctgctgc   2160
tgctgctgct gctgagaccc cccgccacca gaggcatcac ctgcccccc cccatgagcg   2220
tggagcacgc cgacatctgg gtgaagagct acagcctgta cagcagagag agatacatct   2280
gcaacagcgg cttcaagaga aaggccggca ccagcagcct gaccgagtgc gtgctgaaca   2340
aggccaccaa cgtggcccac tggaccaccc ccagcctgaa gtgcatcaga taagtttaaa   2400
c                                                                   2401
```

<210> SEQ ID NO 106
<211> LENGTH: 793
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 106

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gly Ala Gln Pro Ala Met Ala Ala Tyr Lys Asp
            20                  25                  30

Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp
        35                  40                  45

Arg Val Thr Ile Ser Cys Ser Ala Ser Gln Gly Ile Ser Asn Tyr Leu
    50                  55                  60

Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Asn Lys Leu Leu Ile Tyr
65                  70                  75                  80
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Tyr Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
                85                  90                  95

Gly Ser Gly Thr Asp Tyr Ser Leu His Ser Asn Leu Glu Pro Glu Asp
            100                 105                 110

Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Lys Leu Pro Tyr Thr Phe
        115                 120                 125

Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val
145                 150                 155                 160

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser Leu
                165                 170                 175

Lys Leu Ser Cys Ala Ala Ser Gly Leu Thr Phe Ser Ser Tyr Ala Met
            180                 185                 190

Ser Trp Asn Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val Ala Ser
        195                 200                 205

Ile Ser Ser Gly Gly Phe Thr Tyr Tyr Pro Asp Ser Asn Lys Gly Arg
    210                 215                 220

Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu Gln Met
225                 230                 235                 240

Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala Arg Asp
                245                 250                 255

Glu Val Arg Gly Tyr Leu Asp Val Trp Gly Ala Gly Thr Thr Val Thr
            260                 265                 270

Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
        275                 280                 285

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
    290                 295                 300

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
305                 310                 315                 320

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
                325                 330                 335

Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg Leu Leu
            340                 345                 350

His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
        355                 360                 365

Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
    370                 375                 380

Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
385                 390                 395                 400

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
                405                 410                 415

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
            420                 425                 430

Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
        435                 440                 445

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
    450                 455                 460

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
465                 470                 475                 480

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
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                485                 490                 495

Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly
            500                 505                 510

Asp Val Glu Glu Asn Pro Gly Pro Met Tyr Arg Met Gln Leu Leu Ser
        515                 520                 525

Cys Ile Ala Leu Ser Leu Ala Leu Val Thr Asn Ser Gly Ile His Val
    530                 535                 540

Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu Pro Lys Thr Glu Ala Asn
545                 550                 555                 560

Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln
                565                 570                 575

Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro
            580                 585                 590

Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val
        595                 600                 605

Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn
    610                 615                 620

Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr
625                 630                 635                 640

Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys
                645                 650                 655

Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr
            660                 665                 670

Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        675                 680                 685

Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ala Pro Arg Arg Ala
    690                 695                 700

Arg Gly Cys Arg Thr Leu Gly Leu Pro Ala Leu Leu Leu Leu Leu Leu
705                 710                 715                 720

Leu Arg Pro Pro Ala Thr Arg Gly Ile Thr Cys Pro Pro Pro Met Ser
                725                 730                 735

Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg
            740                 745                 750

Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser
        755                 760                 765

Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp
    770                 775                 780

Thr Thr Pro Ser Leu Lys Cys Ile Arg
785                 790


<210> SEQ ID NO 107
<211> LENGTH: 2359
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 107

gcgatcgcac catggcctta ccagtgaccg ccttgctcct gccgctggcc ttgctgctcc      60

acgccgccag gccggacatc caggtgaccc agagccccag cagcctgagc gccagcctgg     120

gcgagagaat cagcctgacc tgcagaacca gccaggacat cagcaactac ctgaactggt     180

tccagcagaa gcccgacggc accttcaaga gactgatcta cgccaccagc agcctggaca     240
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gcggcgtgcc caagagattc agcggcagcg gcagcggcag cgactacagc ctgaccatca    300
gcagcctgga gagcgaggac ttcgccgact actactgcct gcagtacgcc agctacccct    360
tcaccttcgg cagcggcacc aagctggaga tcaagggagg ggggggatcc gggggaggag    420
gctccggcgg aggcggaagc gaggtgcagc tgcaggagag cggccccggc ctggtgaagc    480
ccagccagac cctgagcctg acctgcagcg tgaccggcta cagcatcacc agcggctact    540
actggcactg gatcagacag ttccccggca acaagctgca gtggatgggc tacatcagct    600
acagcggctt caccaactac aagaccagcc tgatcaacag aatcagcatc acccacgaca    660
ccagcgagaa ccagttcttc ctgaacctga acagcgtgac caccgaggac accgccacct    720
actactgcgc cggcgacaga accggcagct ggttcgccta ctggggccag ggcaccctgg    780
tgaccgtgag cgccaccacg acgccagcgc cgcgaccacc aacaccggcg cccaccatcg    840
cgtcgcagcc cctgtccctg cgcccagagg cgtgccggcc agcggcgggg ggcgcagtgc    900
acacgagggg gctggacttc gcctgtgata tctacatctg ggcgcccttg gccgggactt    960
gtggggtcct tctcctgtca ctggttatca ccctttactg caggagtaag aggagcaggc   1020
tcctgcacag tgactacatg aacatgactc cccgccgccc cgggcccacc cgcaagcatt   1080
accagcccta tgccccacca cgcgacttcg cagcctatcg ctccagagtg aagttcagca   1140
ggagcgcaga cgcccccgcg taccagcagg gccagaacca gctctataac gagctcaatc   1200
taggacgaag agaggagtac gatgttttgg acaagagacg tggccgggac cctgagatgg   1260
ggggaaagcc gcagagaagg aagaaccctc aggaaggcct gtacaatgaa ctgcagaaag   1320
ataagatggc ggaggcctac agtgagattg ggatgaaagg cgagcgccgg aggggcaagg   1380
ggcacgatgg cctttaccag ggtctcagta cagccaccaa ggacacctac gacgcccttc   1440
acatgcaggc cctgccccct cgcggaagcg gagccaccaa cttcagcctg ctgaagcagg   1500
ccggcgacgt ggaggagaac cccggcccca tgtacagaat gcagctgctg agctgcatcg   1560
ccctgagcct ggccctggtg accaacagcg gcatccacgt gttcatcctg ggctgcttca   1620
gcgccggcct gcccaagacc gaggccaact gggtgaacgt gatcagcgac ctgaagaaga   1680
tcgaggacct gatccagagc atgcacatcg acgccaccct gtacaccgag agcgacgtgc   1740
accccagctg caaggtgacc gccatgaagt gcttcctgct ggagctgcag gtgatcagcc   1800
tggagagcgg cgacgccagc atccacgaca ccgtggagaa cctgatcatc ctggccaaca   1860
acagcctgag cagcaacggc aacgtgaccg agagcggctg caaggagtgc gaggagctgg   1920
aggagaagaa catcaaggag ttcctgcaga gcttcgtgca catcgtgcag atgttcatca   1980
acaccagctc cggcggcggc tccggcggcg gcggctccgg cggcggcggc tccggcggcg   2040
gcggctccgg cggcggctcc ctgcaggccc ccagaagagc cagaggctgc agaaccctgg   2100
gcctgcccgc cctgctgctg ctgctgctgc tgagaccccc cgccaccaga ggcatcacct   2160
gcccccccc catgagcgtg gagcacgccg acatctgggt gaagagctac agcctgtaca   2220
gcagagagag atacatctgc aacagcggct tcaagagaaa ggccggcacc agcagcctga   2280
ccgagtgcgt gctgaacaag gccaccaacg tggcccactg gaccaccccc agcctgaagt   2340
gcatcagata agtttaaac                                                2359
```

<210> SEQ ID NO 108
<211> LENGTH: 779

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 108

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Ile Gln Val Thr Gln Ser Pro Ser Ser Leu
20 25 30

Ser Ala Ser Leu Gly Glu Arg Ile Ser Leu Thr Cys Arg Thr Ser Gln
35 40 45

Asp Ile Ser Asn Tyr Leu Asn Trp Phe Gln Gln Lys Pro Asp Gly Thr
50 55 60

Phe Lys Arg Leu Ile Tyr Ala Thr Ser Ser Leu Asp Ser Gly Val Pro
65 70 75 80

Lys Arg Phe Ser Gly Ser Gly Ser Gly Ser Asp Tyr Ser Leu Thr Ile
85 90 95

Ser Ser Leu Glu Ser Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr
100 105 110

Ala Ser Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
130 135 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln Thr
145 150 155 160

Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser Gly Tyr
165 170 175

Tyr Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Gln Trp Met
180 185 190

Gly Tyr Ile Ser Tyr Ser Gly Phe Thr Asn Tyr Lys Thr Ser Leu Ile
195 200 205

Asn Arg Ile Ser Ile Thr His Asp Thr Ser Glu Asn Gln Phe Phe Leu
210 215 220

Asn Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
225 230 235 240

Gly Asp Arg Thr Gly Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu
245 250 255

Val Thr Val Ser Ala Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
260 265 270

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
275 280 285

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
290 295 300

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
305 310 315 320

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Arg Ser Lys Arg Ser Arg
325 330 335

Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro
340 345 350

Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala
355 360 365

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```
Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
    370                 375                 380

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
385                 390                 395                 400

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
                405                 410                 415

Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
            420                 425                 430

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
        435                 440                 445

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
    450                 455                 460

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
465                 470                 475                 480

Leu Pro Pro Arg Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln
                485                 490                 495

Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Tyr Arg Met Gln Leu
            500                 505                 510

Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu Val Thr Asn Ser Gly Ile
        515                 520                 525

His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu Pro Lys Thr Glu
    530                 535                 540

Ala Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
545                 550                 555                 560

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
                565                 570                 575

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
            580                 585                 590

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
        595                 600                 605

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
    610                 615                 620

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
625                 630                 635                 640

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
                645                 650                 655

Asn Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            660                 665                 670

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln Ala Pro Arg
        675                 680                 685

Arg Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro Ala Leu Leu Leu Leu
    690                 695                 700

Leu Leu Leu Arg Pro Pro Ala Thr Arg Gly Ile Thr Cys Pro Pro Pro
705                 710                 715                 720

Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr
                725                 730                 735

Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly
            740                 745                 750

Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala
        755                 760                 765

His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
```

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770 775

<210> SEQ ID NO 109
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 109

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro
20

<210> SEQ ID NO 110
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 110

Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Val Gly
1 5 10 15

Glu Lys Phe Thr Val Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Ser Asn Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Lys Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85 90 95

His Tyr Arg Tyr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys Arg Ala Arg
115

<210> SEQ ID NO 111
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 111

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> SEQ ID NO 112
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 112

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln

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```
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Asn Thr Ser
            20                  25                  30

Gly Val Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45

Trp Leu Ala His Ile Trp Trp Asp Asp Asp Glu Arg Tyr Asn Pro Val
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
65                  70                  75                  80

Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Ser Ala Thr Tyr Tyr
                85                  90                  95

Cys Val Arg Ser Met Val Ala Trp Phe Phe Pro Tyr Trp Gly Arg Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ala
        115


<210> SEQ ID NO 113
<211> LENGTH: 45
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 113

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1               5                   10                  15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
            20                  25                  30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
        35                  40                  45


<210> SEQ ID NO 114
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 114

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1               5                   10                  15

Ser Leu Val Ile Thr Leu Tyr Cys
            20


<210> SEQ ID NO 115
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 115

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
1               5                   10                  15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
            20                  25                  30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        35                  40
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<210> SEQ ID NO 116
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 116

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
50 55 60

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
65 70 75 80

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
85 90 95

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
100 105 110

Arg

<210> SEQ ID NO 117
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 117

Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val
1 5 10 15

Glu Glu Asn Pro Gly Pro
20

<210> SEQ ID NO 118
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 118

Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser
20

<210> SEQ ID NO 119
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 119

-continued

```
Gly Ile His Val Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu Pro Lys
1               5                   10                  15

Thr Glu Ala Asn Trp
            20


<210> SEQ ID NO 120
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 120

Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser
1               5                   10                  15

Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
            20                  25                  30

Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
        35                  40                  45

Ser Leu
    50


<210> SEQ ID NO 121
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 121

Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile
1               5                   10                  15

Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly
            20                  25                  30

Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu
        35                  40                  45

Gln Ser
    50


<210> SEQ ID NO 122
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 122

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
1               5                   10


<210> SEQ ID NO 123
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 123

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15
```

-continued

```
Gly Gly Gly Ser Gly Gly Gly Ser Leu Gln
            20                  25


<210> SEQ ID NO 124
<211> LENGTH: 29
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 124

Ala Pro Arg Arg Ala Arg Gly Cys Arg Thr Leu Gly Leu Pro Ala Leu
1               5                   10                  15

Leu Leu Leu Leu Leu Leu Arg Pro Pro Ala Thr Arg Gly
            20                  25


<210> SEQ ID NO 125
<211> LENGTH: 65
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Sequence

<400> SEQUENCE: 125

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg
65
```

1.-**105**. (canceled)

106. An engineered cell comprising:

(i) a first chimeric antigen receptor polypeptide comprising a first antigen recognition domain, a first signal peptide, a first hinge region, a first transmembrane domain, a first co-stimulatory domain, and a first signaling domain;

(ii) a second chimeric antigen receptor polypeptide comprising a second antigen recognition domain, a second signal peptide, a second hinge region, a second transmembrane domain, a second co-stimulatory domain, and a second signaling domain; and

wherein

the first antigen recognition domain is selective for one of interleukin 6 receptor, NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BCMA, BAFF, BAFF-R, BCMA, TACI, LeY, CD4, CD25, CD38, CD5, CD13, CD14, CD15 CD19, CD20, CD22, CD33, CD41, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, APRIL, and CS1; and

the second antigen recognition domain is selective for one of interleukin 6 receptor, NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BCMA, BAFF, BAFF-R, BCMA, TACI, LeY, CD4, CD25, CD38, CD5, CD13, CD14, CD15 CD19, CD20, CD22, CD33, CD41, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, APRIL, and CS1;

the first antigen recognition domain and the second antigen recognition domain are different;

the first chimeric antigen receptor polypeptide and the second chimeric antigen receptor polypeptide each consist of a single antigen recognition domain; and

the first antigen recognition domain and second antigen recognition domain are expressed on the surface of the engineered cell.

107. The engineered cell according to claim **106**, wherein the first chimeric antigen receptor polypeptide and the second chimeric engineered polypeptide are on a single polypeptide molecule, and wherein an amino acid sequence comprising a high efficiency cleavage site is disposed between the first chimeric antigen receptor polypeptide and the second chimeric antigen receptor polypeptide, and wherein high efficiency cleavage site is defined as a polypeptide sequence that results in greater than 80% self cleavage.

108. The engineered cell according to claim **107**, wherein the high efficiency cleavage site is selected from the group consisting of P2A, T2A, E2A, and F2A.

109. The engineered cell according to claim **106** wherein the first co-stimulatory domain and the second co-stimulatory domain are different.

110. The engineered cell according to claim **106**, wherein the first co-stimulatory domain comprises CD28, and the second co-stimulatory domain comprises 4-1BB.

111. The engineered cell according to claim **106**, wherein the first antigen recognition domain is selective for TACI or CD269; and the second antigen recognition domain is selective for one of CD19, CD38, CD138, CD138, and CS1.

112. The engineered cell according to claim **106**, wherein the first antigen recognition domain is selective for CD19; and the second antigen recognition domain is selective for one of CD20, CD22, CD33, CD123, TACI, CD269, CD38, and CS1.

113. The engineered cell according to claim **106**, wherein the first antigen recognition domain is selective for CD33; and the second antigen recognition domain is selective for LeY or CD123.

114. The engineered cell according to claim **106**, wherein the first antigen recognition domain is selective for BCMA; and the second antigen recognition domain is selective for one of CS1, CD19, CD20, CD22, CD38, CD138, and CS1.

115. The engineered cell according to claim **106**, wherein the first antigen recognition domain is selective for CD19; and the second antigen recognition domain is selective for BCMA.

116. The engineered cell according to claim **106**, wherein the engineered cell is a T cell, NK cell, NK T cell, or NK-92 cell.

117. The engineered cell according to claim **106**, wherein the engineered cell further comprises a heterologously expressed enhancer.

118. The engineered cell according to claim **117**, wherein said enhancer is selected from the group consisting of PD-1, PD-L1, CSFIR, CTAL-4, TIM-3, TGFR beta, IL-2, IL-15/IL-15 sushi, IL-6, IL-7, IL-12, IL-15, IL-17, IL-18 IL-21, functional fragments thereof, and combinations thereof.

119. The engineered cell according to claim **106**, wherein the first antigen recognition domain is selective for one of CD19, CD33, and CD269; and the second antigen recognition domain is selective for CD123 or CS1.

120. The engineered cell according to claim **106**, wherein TAC1 antigen recognition domain comprises the APRIL ligand or the BAFF ligand or a portion thereof.

121. The engineered cell according to claim **106**, wherein the BCMA antigen recognition domain comprises APRIL ligand or BAFF ligand or a portion thereof.

122. The engineered cell according to claim **106**, wherein the BAFF-R antigen recognition domain comprises the BAFF ligand or a portion thereof.

123. The engineered cell according to claim **106**, wherein the first co-stimulatory domain and the second co-stimulatory domain comprise 4-1BB co-stimulatory domain.

124. A method of treating a cell proliferative disease in a patient, said method comprising:

administering to the patient an engineered cell that expresses:

(i) a first chimeric antigen receptor polypeptide comprising a first antigen recognition domain, a first signal peptide, a first hinge region, a first transmembrane domain, a first co-stimulatory domain, and a first signaling domain;

(ii) a second chimeric antigen receptor polypeptide comprising a second antigen recognition domain, a second signal peptide, a second hinge region, a second transmembrane domain, a second co-stimulatory domain, and a second signaling domain; and

reducing the tumor burden of cell proliferative disease cells;

wherein

the first antigen recognition domain is selective for one of interleukin 6 receptor, NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BCMA, BAFF, BAFF-R, BCMA, TACI, LeY, CD4, CD25, CD38, CD5, CD13, CD14, CD15 CD19, CD20, CD22, CD33, CD41, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, APRIL, and CS1; and

the second antigen recognition domain is selective for one of interleukin 6 receptor, NY-ESO-1, alpha fetoprotein (AFP), glypican-3 (GPC3), BCMA, BAFF, BAFF-R, BCMA, TACI, LeY, CD4, CD25, CD38, CD5, CD13, CD14, CD15 CD19, CD20, CD22, CD33, CD41, CD61, CD64, CD68, CD117, CD123, CD138, CD267, CD269, CD38, Flt3 receptor, APRIL, and CS1;

the first antigen recognition domain and the second antigen recognition domain are different;

the first chimeric antigen receptor polypeptide and the second chimeric antigen receptor polypeptide each consist of a single antigen recognition domain; and

the first antigen recognition domain and second antigen recognition domain are expressed on the surface of the engineered cell.

125. The method according to claim **124**, wherein the engineered cell comprises T cells, NK cells, NK T cells, or NK-92 cells.

126. The method according to claim **124**, wherein the cell proliferative disease is selected from the group consisting of: B-cell lymphoma, T-cell lymphoma, multiple myeloma, chronic myeloid leukemia, B-cell acute lymphoblastic leukemia (B-ALL), and plasma cell neoplasms.

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