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(54) **INTERLEUKIN-2 MUTEINS FOR THE EXPANSION OF T-REGULATORY CELLS**

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(73) Assignee: **Amgen Inc.**, Thousand Oaks, CA (US)

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A61P 37/00	(2006.01)
C07K 16/24	(2006.01)

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(57) **ABSTRACT**

Provided herein are IL-2 muteins, IL-2 mutein Fc-fusion molecules, anti-IL-2 antibodies, and complexes comprising an anti IL-2 antibody bound to an IL-2 cytokine that preferentially expand and activate T regulatory cells and are amenable to large scale production. Also provided herein are variant human IgG1 Fc molecules lacking or with highly reduced effector function and high stability despite lacking glycosylation at N297. Also provided herein are linker peptides that are glycosylated when expressed in mammalian cells. Also provided herein are methods of making and using the compositions of the present invention.

Specification includes a Sequence Listing.

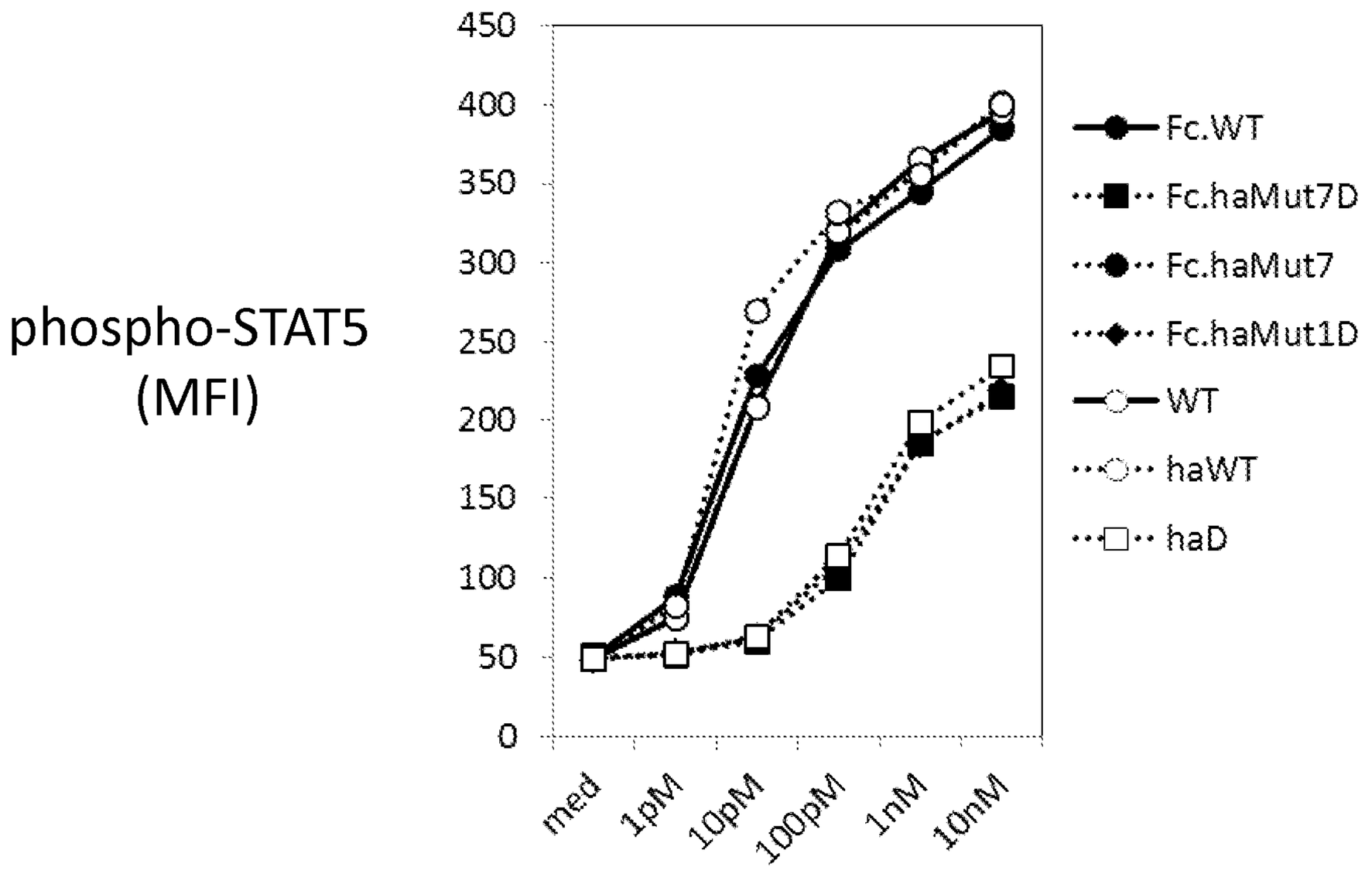

phospho-STAT5
(MFI)
450
400
350
300
250
200
150
100
50
0
med
1pM
10pM
100pM
1nM
10nM
Fc.WT
Fc.haMut7D
Fc.haMut7
Fc.haMut1D
WT
haWT
haD

FIG. 1

FIG. 2A

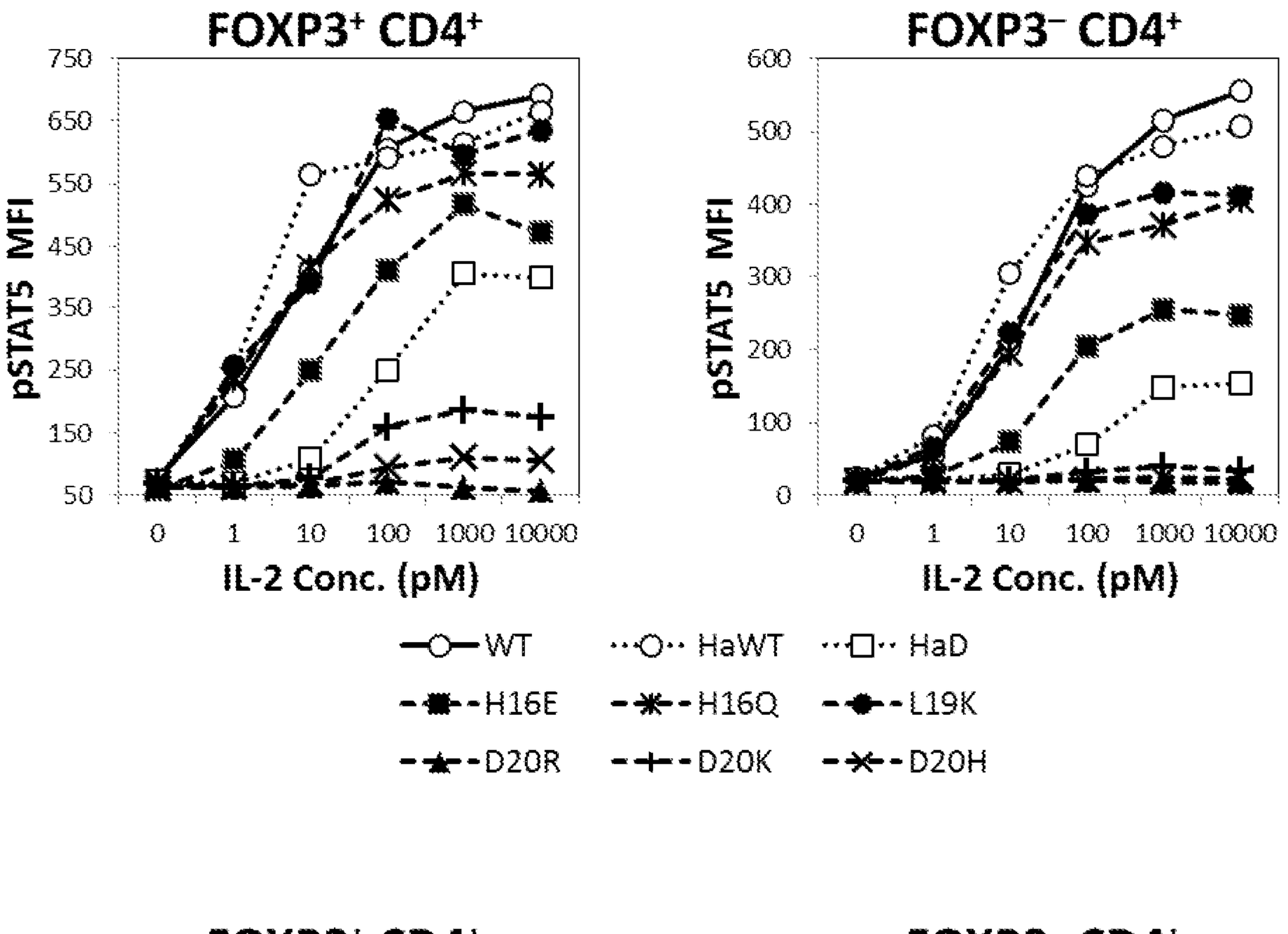
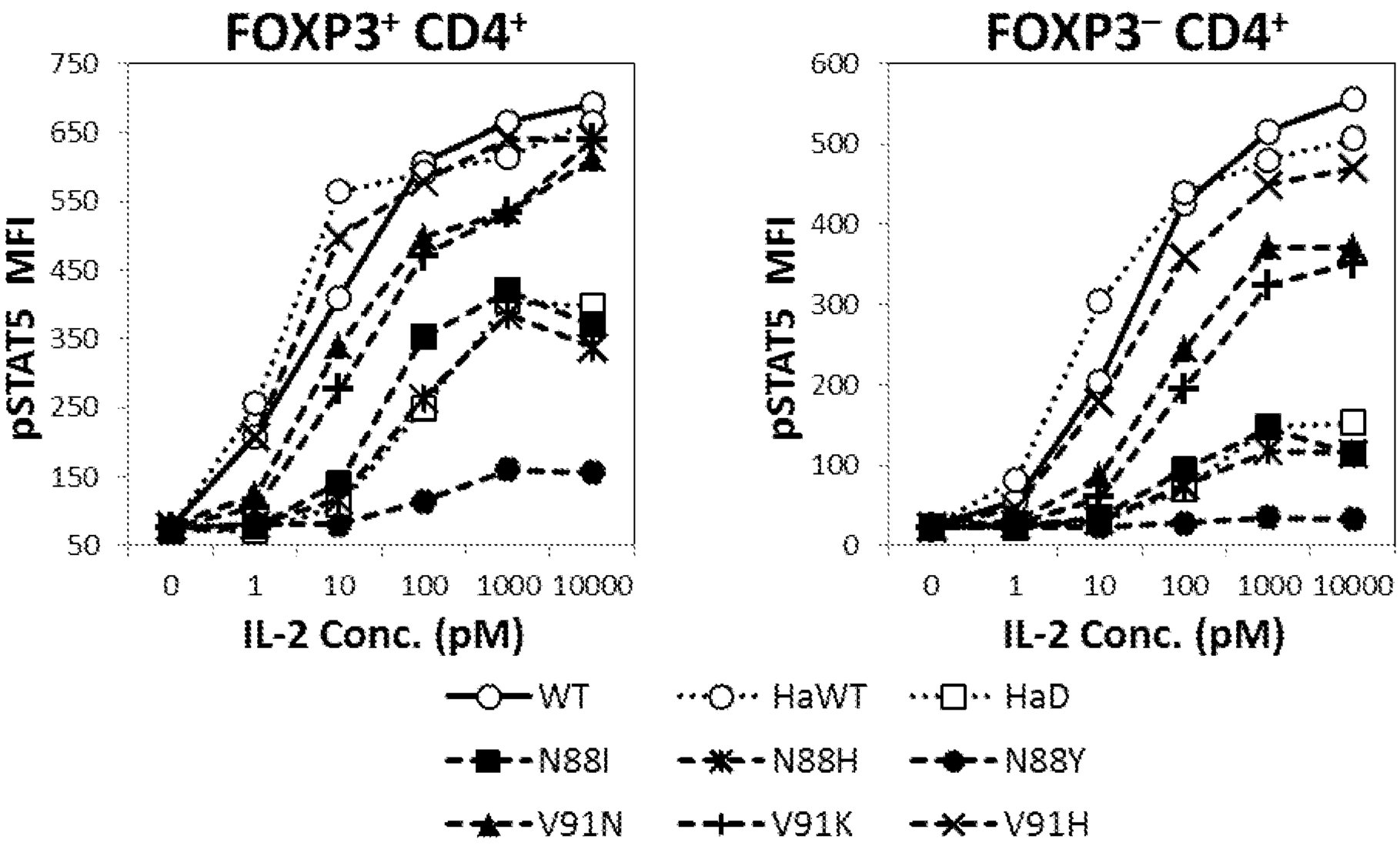
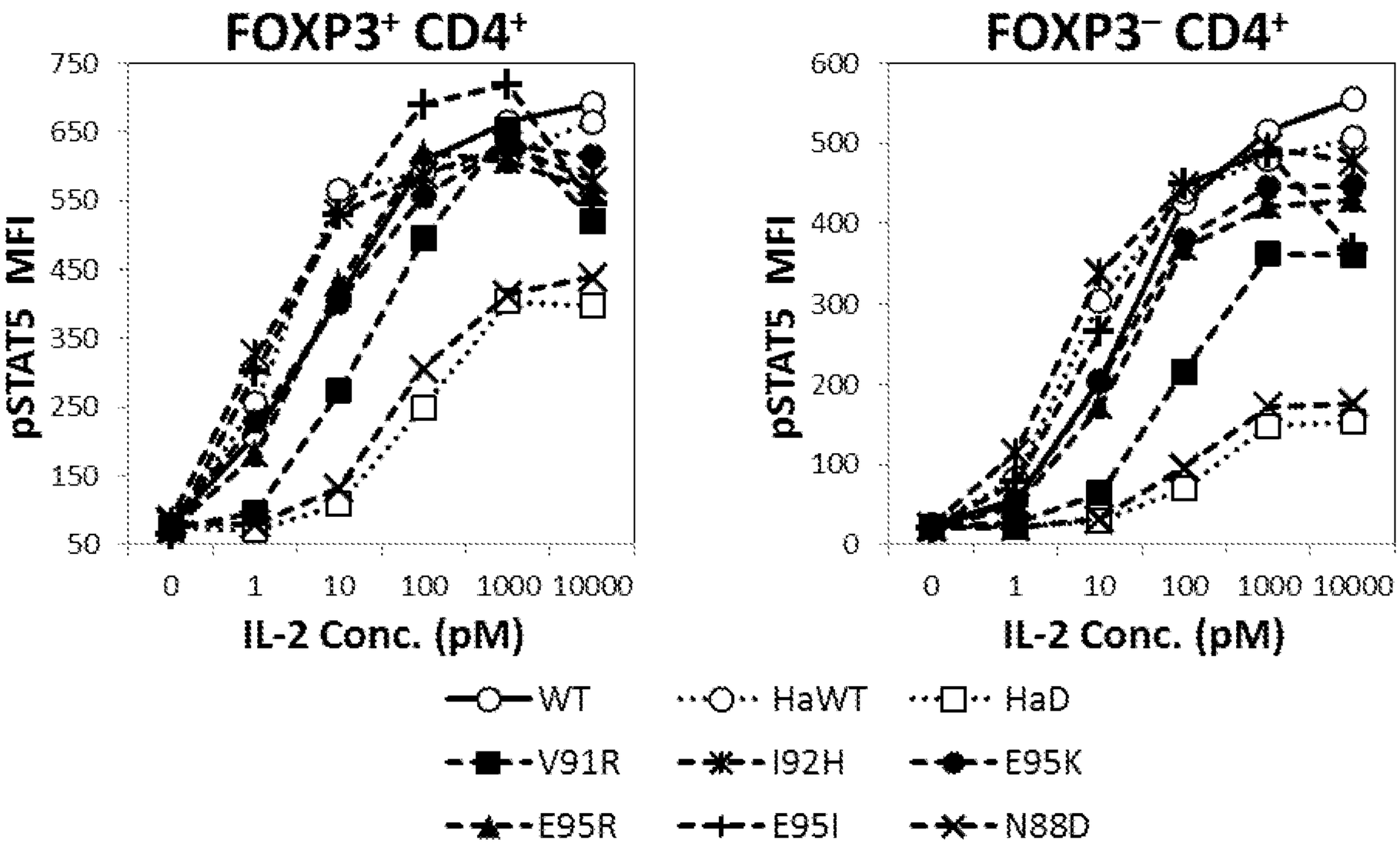

FOXP3+ CD4+
FOXP3− CD4+
pSTAT5 MFI
IL-2 Conc. (pM)
0
1
10
100
1000
10000
WT
HaWT
HaD
H16E
H16Q
L19K
D20R
D20K
D20H
D20Y
M23H
D84K
D84H
S87Y
N88K

FIG. 2B


FOXP3+ CD4+
FOXP3− CD4+
pSTAT5 MFI
IL-2 Conc. (pM)
0
1
10
100
1000
10000
WT
HaWT
HaD
N88I
N88H
N88Y
V91N
V91K
V91H


FOXP3+ CD4+
FOXP3− CD4+
pSTAT5 MFI
IL-2 Conc. (pM)
0
1
10
100
1000
10000
WT
HaWT
HaD
V91R
I92H
E95K
E95R
E95I
N88D

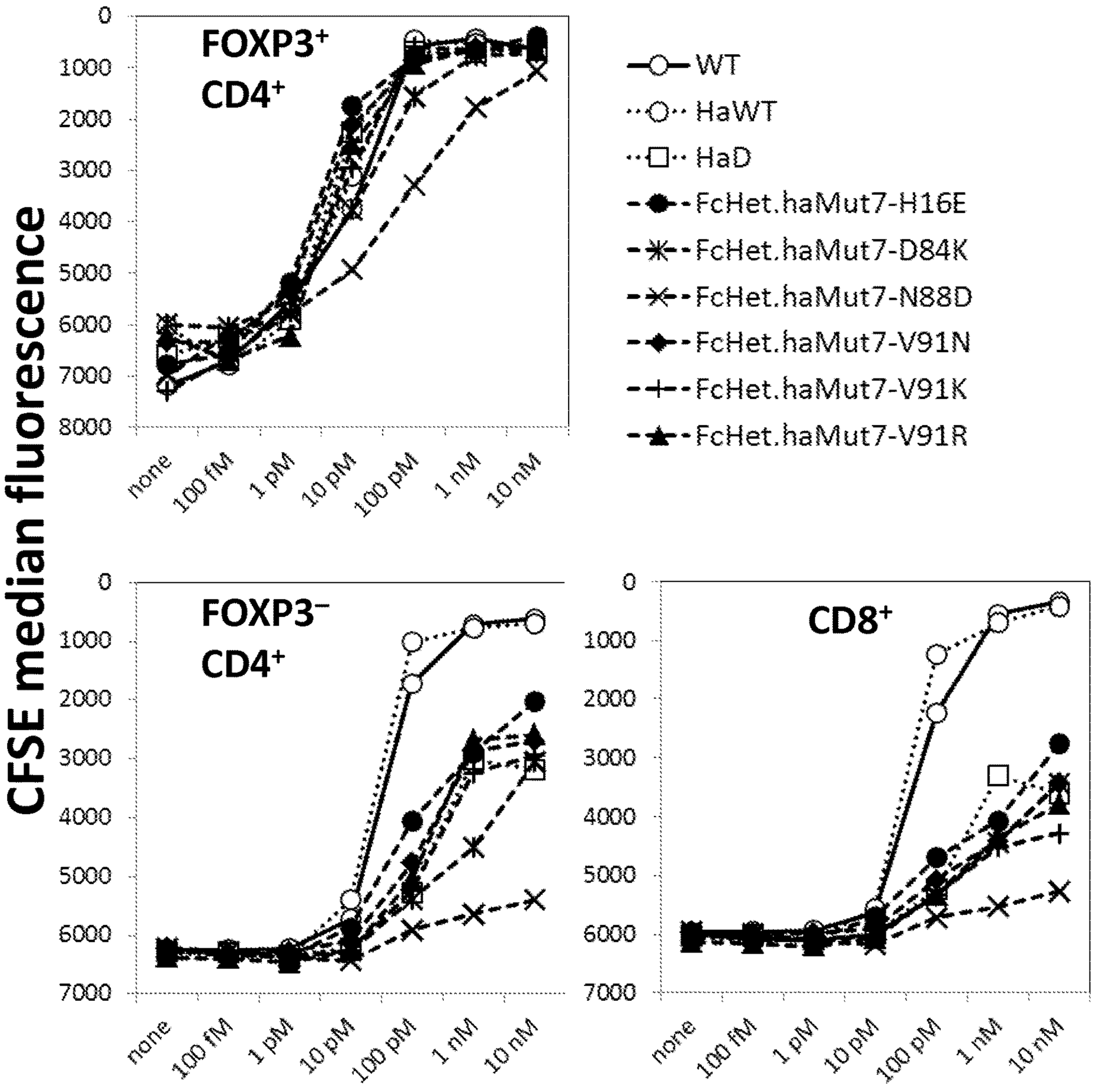

FOXP3+ CD4+
FOXP3− CD4+
CD8+
CFSE median fluorescence
0
1000
2000
3000
4000
5000
6000
7000
8000
none
100 fM
1 pM
10 pM
100 pM
1 nM
10 nM
WT
HaWT
HaD
FcHet.haMut7-H16E
FcHet.haMut7-D84K
FcHet.haMut7-N88D
FcHet.haMut7-V91N
FcHet.haMut7-V91K
FcHet.haMut7-V91R

FIG. 3

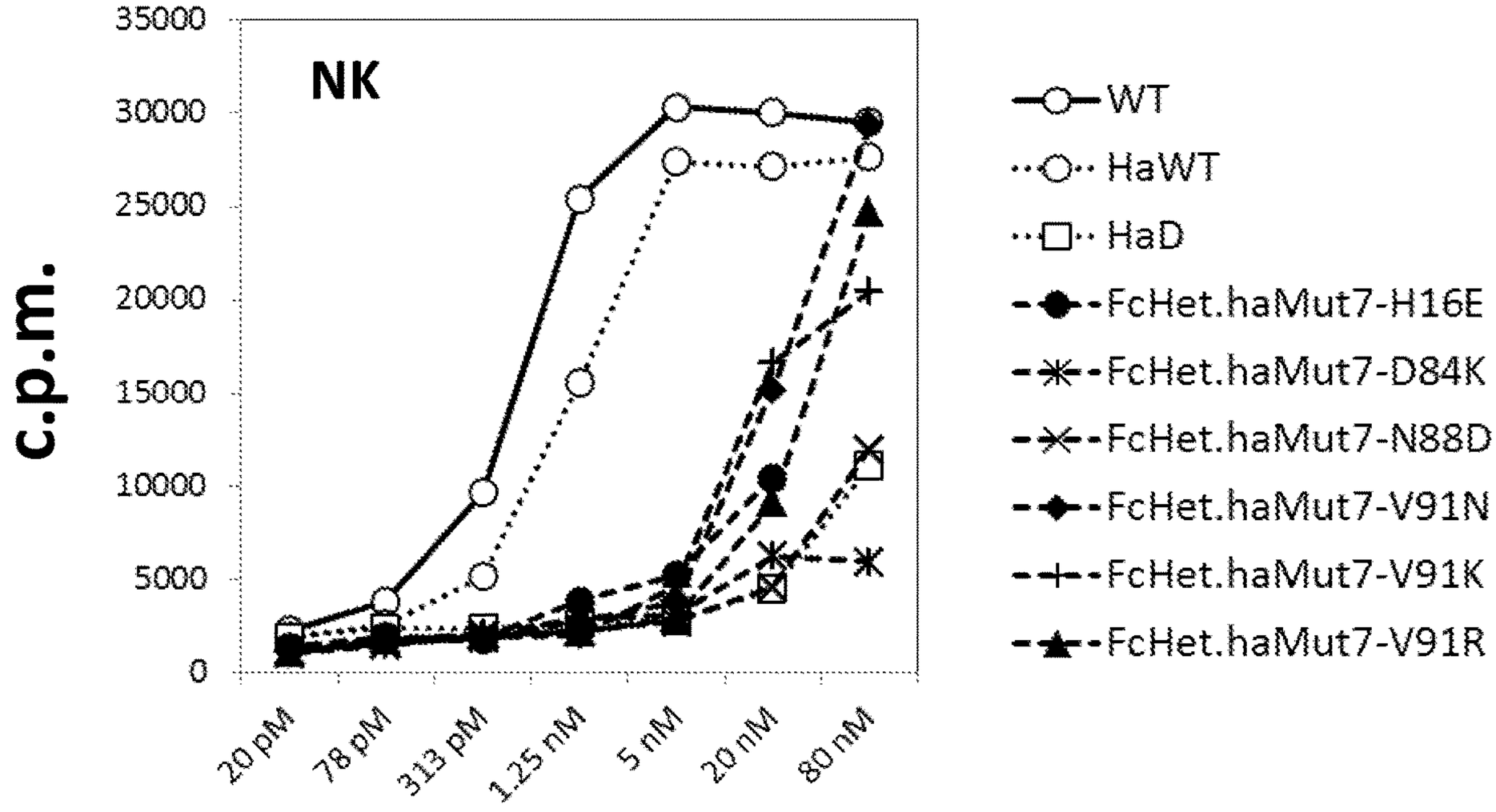

NK
c.p.m.
35000
30000
25000
20000
15000
10000
5000
0
20 pM
78 pM
313 pM
1.25 nM
5 nM
20 nM
80 nM
WT
HaWT
HaD
FcHet.haMut7-H16E
FcHet.haMut7-D84K
FcHet.haMut7-N88D
FcHet.haMut7-V91N
FcHet.haMut7-V91K
FcHet.haMut7-V91R

FIG. 4

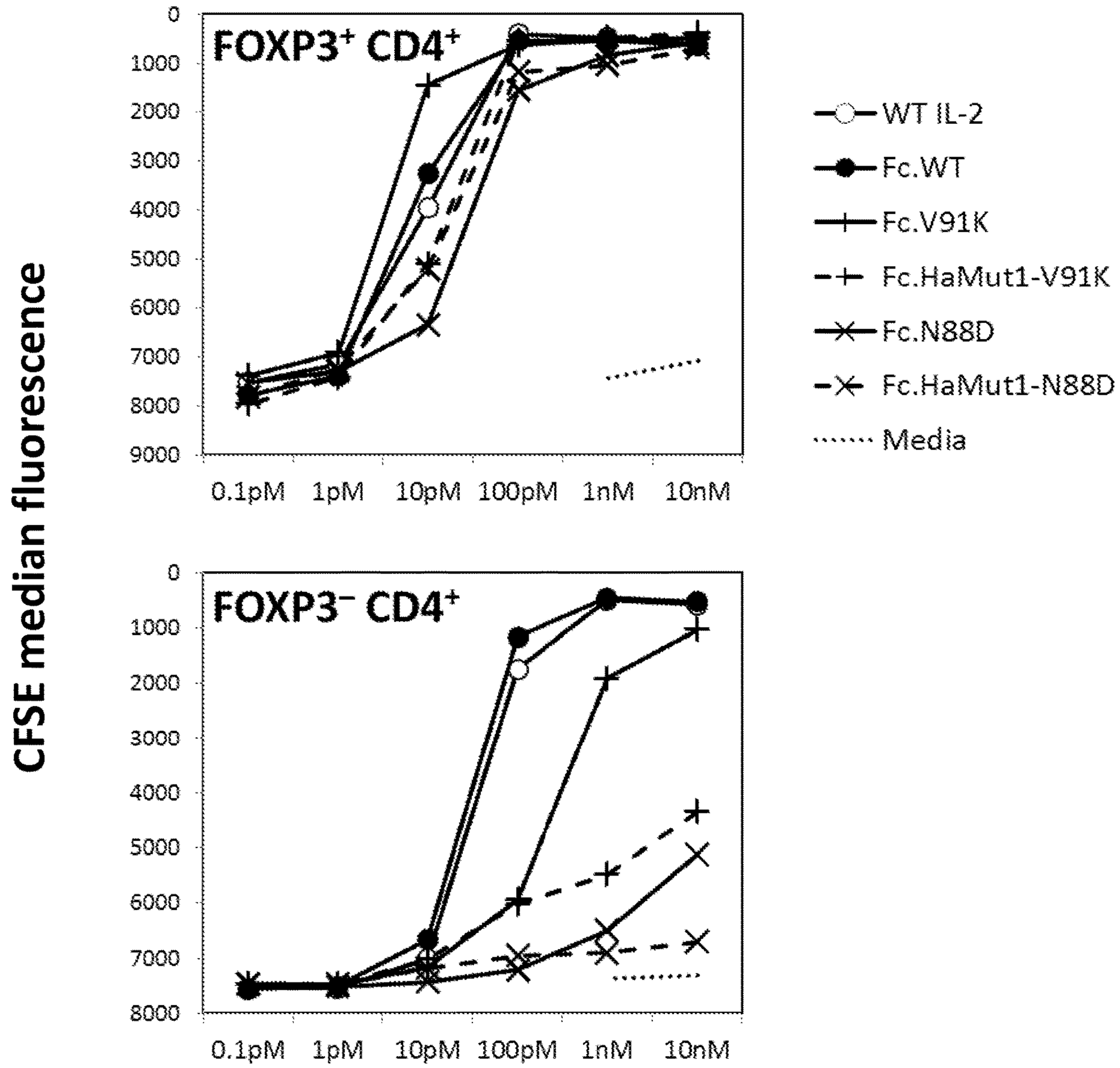

FOXP3+ CD4+
FOXP3− CD4+
CFSE median fluorescence
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
0.1pM
1pM
10pM
100pM
1nM
10nM
WT IL-2
Fc.WT
Fc.V91K
Fc.HaMut1-V91K
Fc.N88D
Fc.HaMut1-N88D
Media

FIG. 5

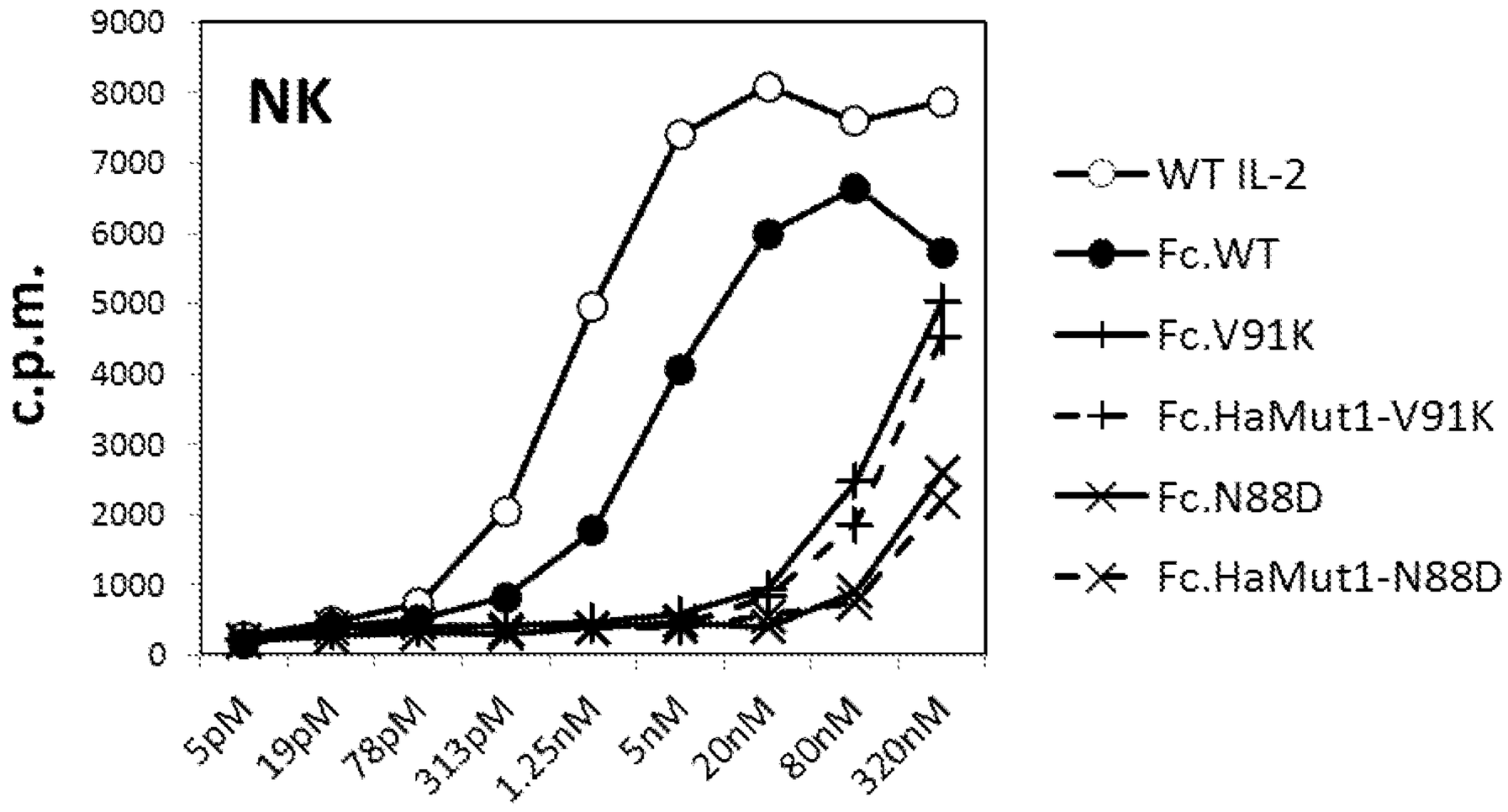

NK
c.p.m.
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5pM
19pM
78pM
313pM
1.25nM
5nM
20nM
80nM
320nM
WT IL-2
Fc.WT
Fc.V91K
Fc.HaMut1-V91K
Fc.N88D
Fc.HaMut1-N88D

FIG. 6

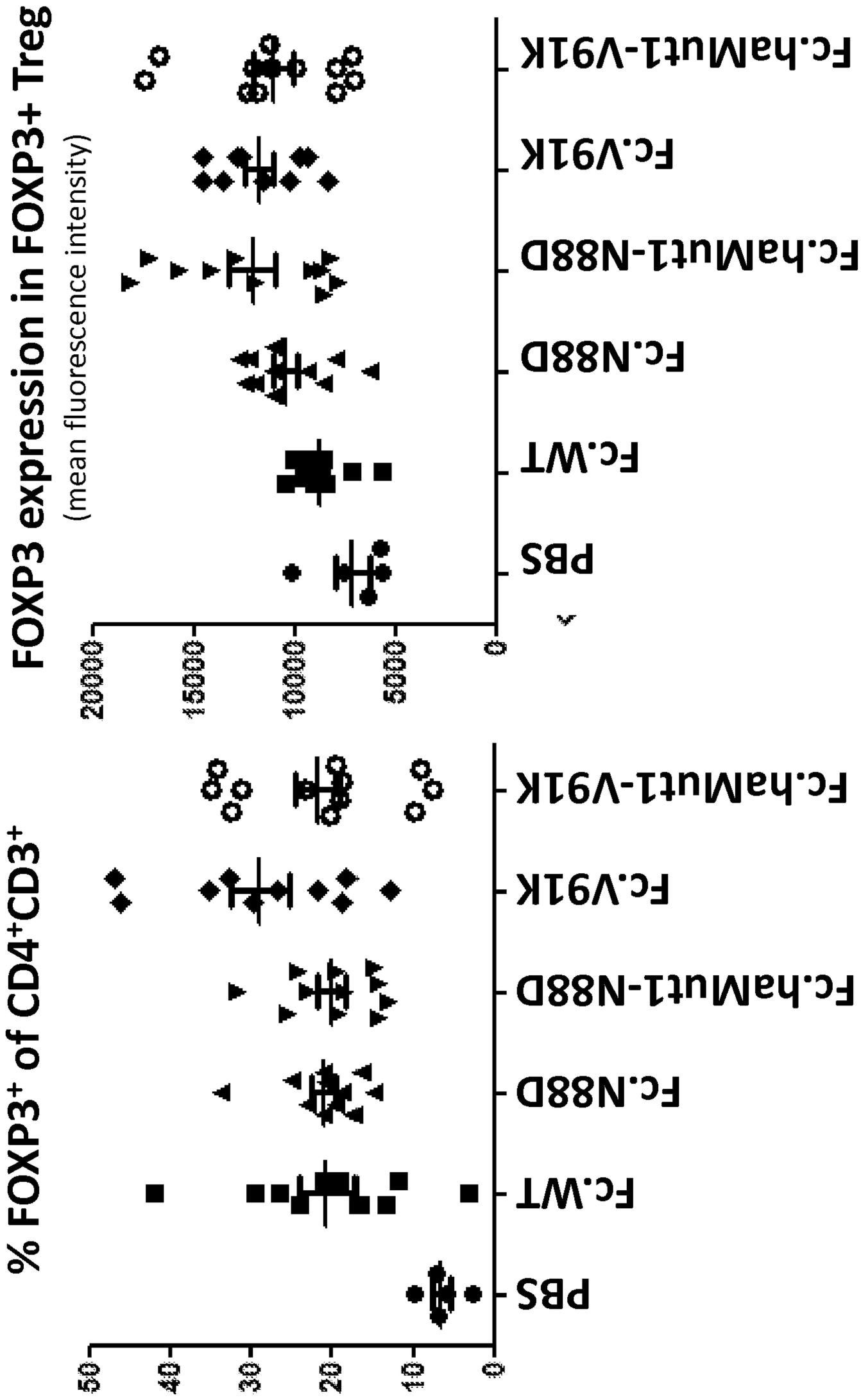

% FOXP3+ of CD4+CD3+
50
40
30
20
10
0
PBS
FC.WT
FC.N88D
FC.V91K
FC.haMut1-N88D
FC.haMut1-V91K
FOXP3 expression in FOXP3+ Treg
(mean fluorescence intensity)
20000
15000
10000
5000
0
PBS
FC.WT
FC.N88D
FC.V91K
FC.haMut1-N88D
FC.haMut1-V91K

FIG. 7A

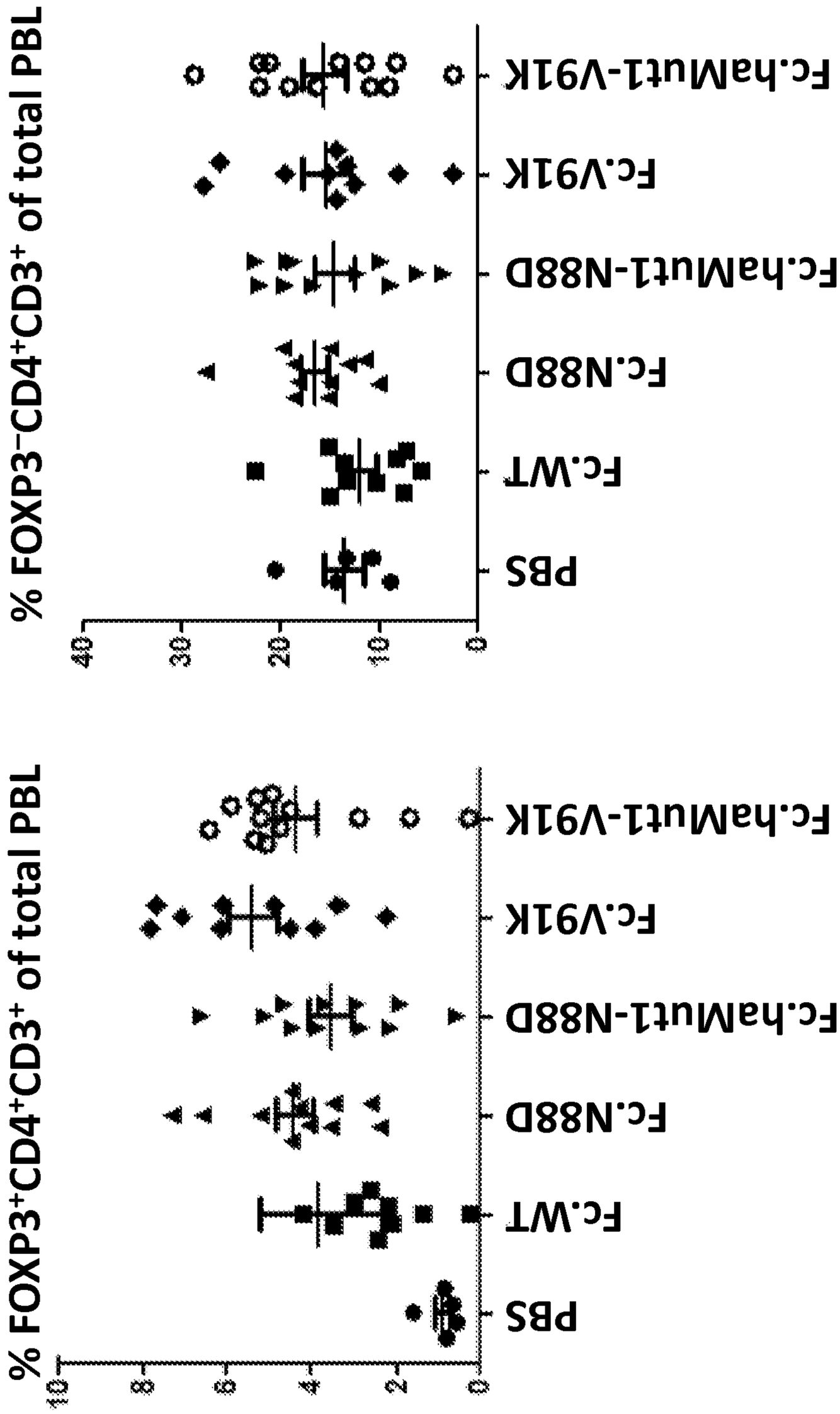
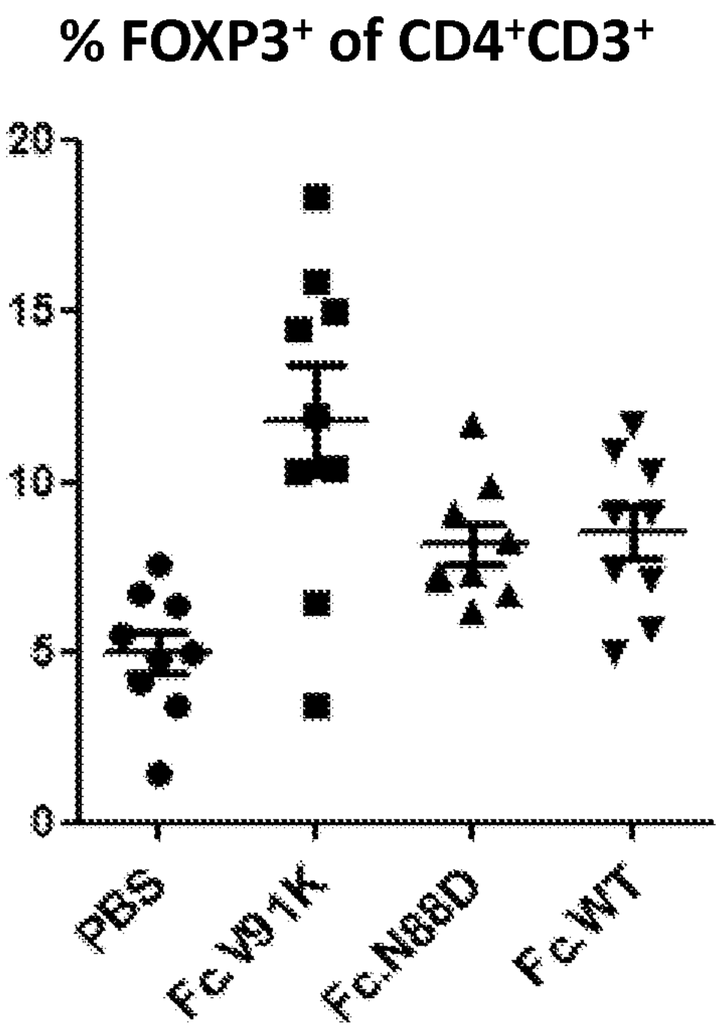
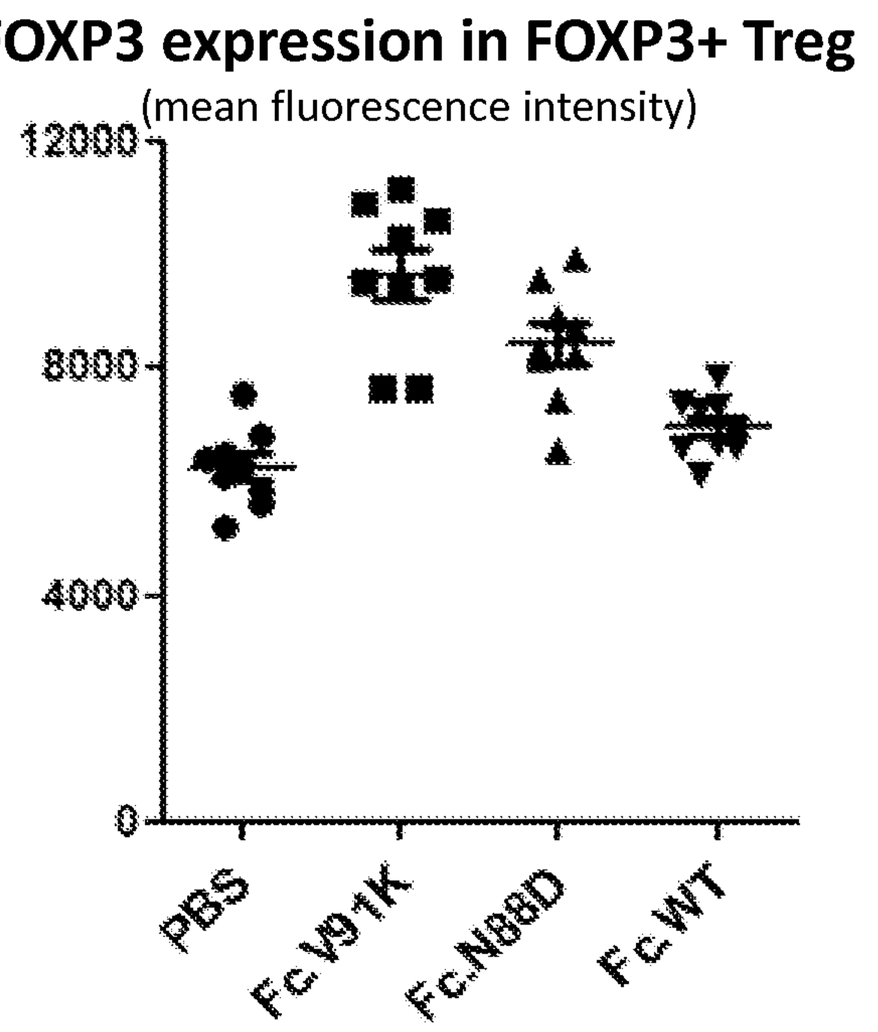
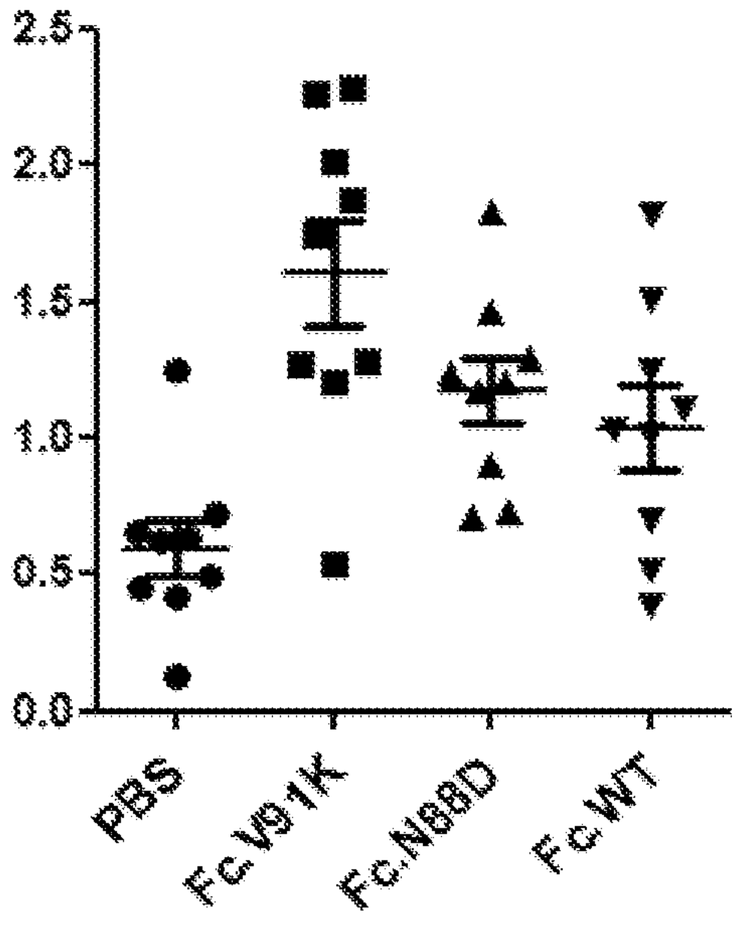

% FOXP3+CD4+CD3+ of total PBL
40
30
20
10
0
PBS
Fc.WT
Fc.N88D
Fc.V91K
Fc.haMut1-V91K
% FOXP3+CD4+CD3+ of total PBL
10
8
6
4
2
0
PBS
Fc.WT
Fc.N88D
Fc.V91K
Fc.haMut1-N88D
Fc.haMut1-V91K

FIG. 7B

FIG. 8


% FOXP3+ of CD4+CD3+
20
15
10
5
0
PBS
Fc.V91K
Fc.N88D
Fc.WT


FOXP3 expression in FOXP3+ Treg
(mean fluorescence intensity)
12000
8000
4000
0
PBS
Fc.V91K
Fc.N88D
Fc.WT


% FOXP3+CD4+CD3+ of total PBL
2.5
2.0
1.5
1.0
0.5
0.0
PBS
Fc.V91K
Fc.N88D
Fc.WT

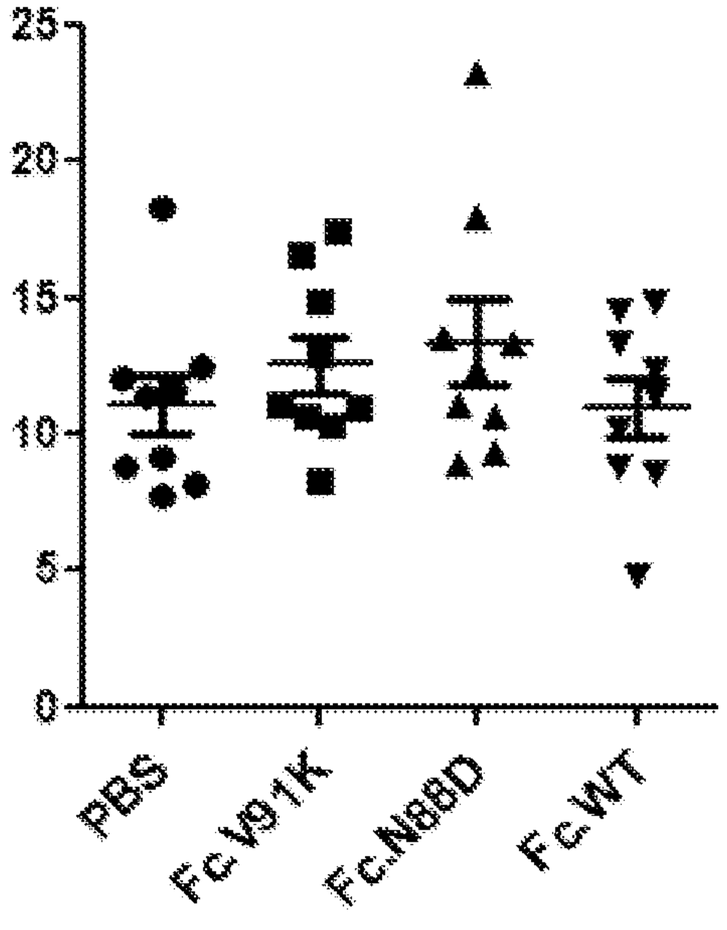

% FOXP3−CD4+CD3+ of total PBL
25
20
15
10
5
0
PBS
Fc.V91K
Fc.N88D
Fc.WT

FIG. 9A

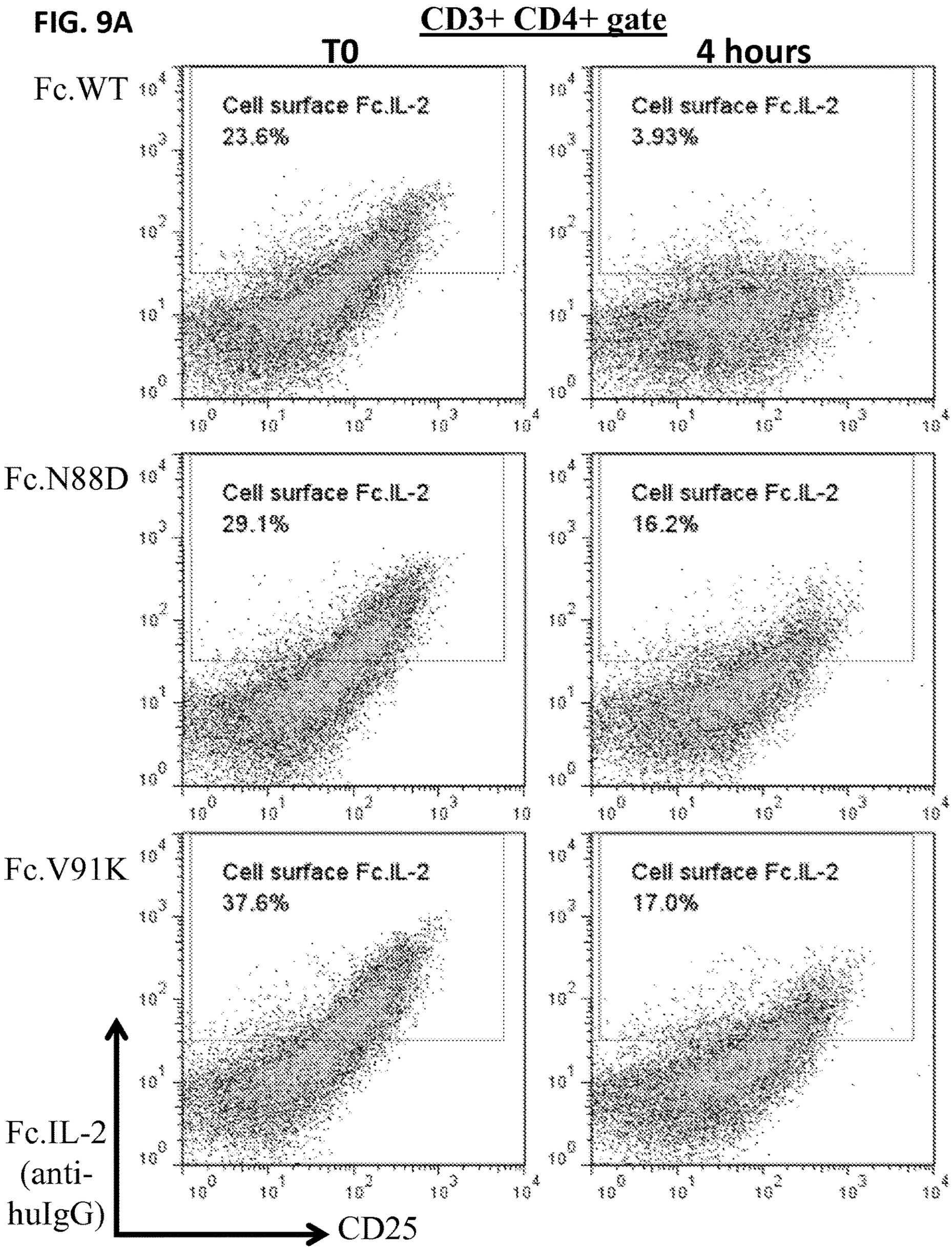

CD3+ CD4+ gate
T0
4 hours
Fc.WT
Fc.N88D
Fc.V91K
Cell surface Fc.IL-2
23.6%
3.93%
29.1%
16.2%
37.6%
17.0%
Fc.IL-2 (anti-huIgG)
CD25

FIG. 9B

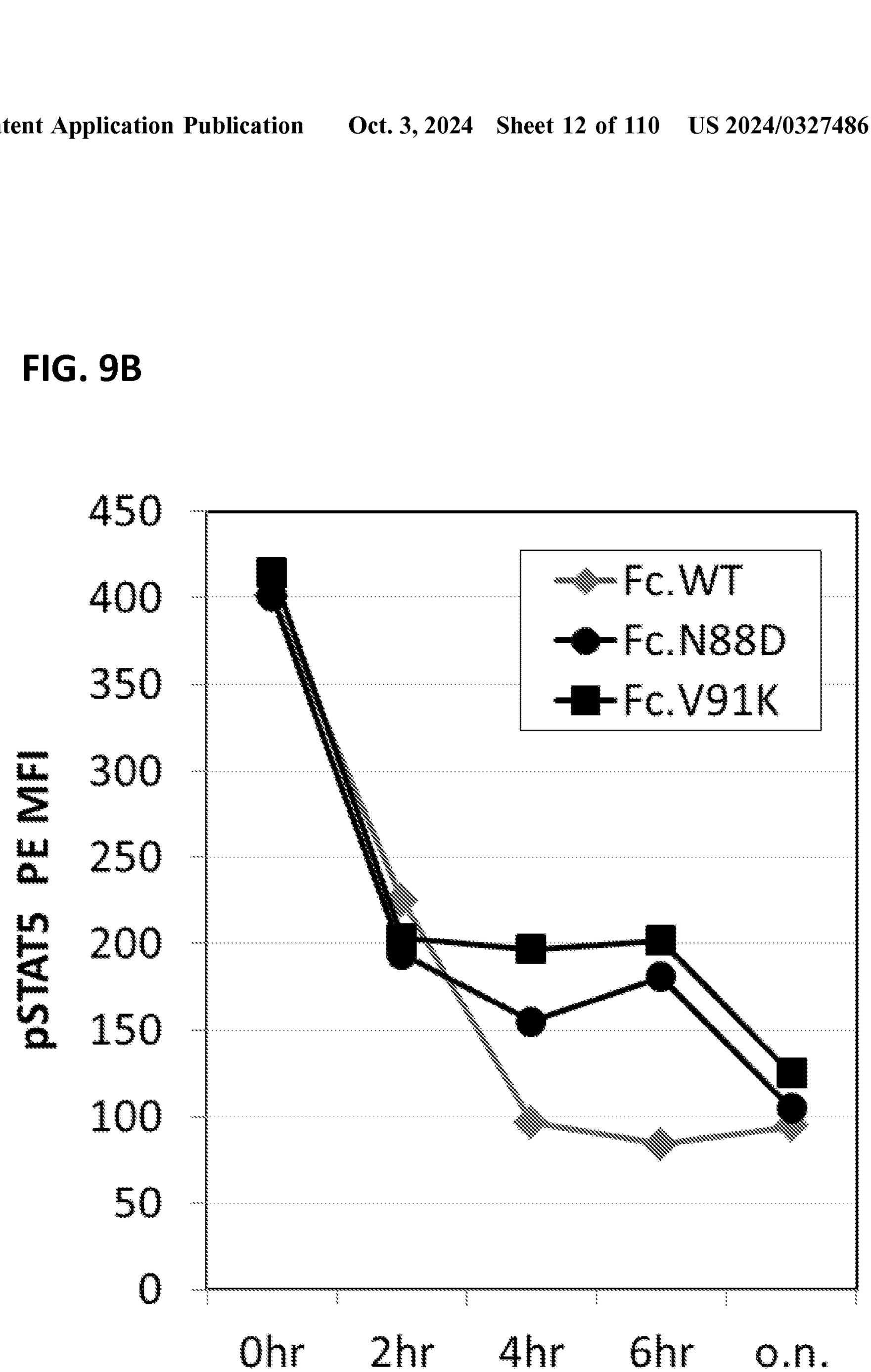
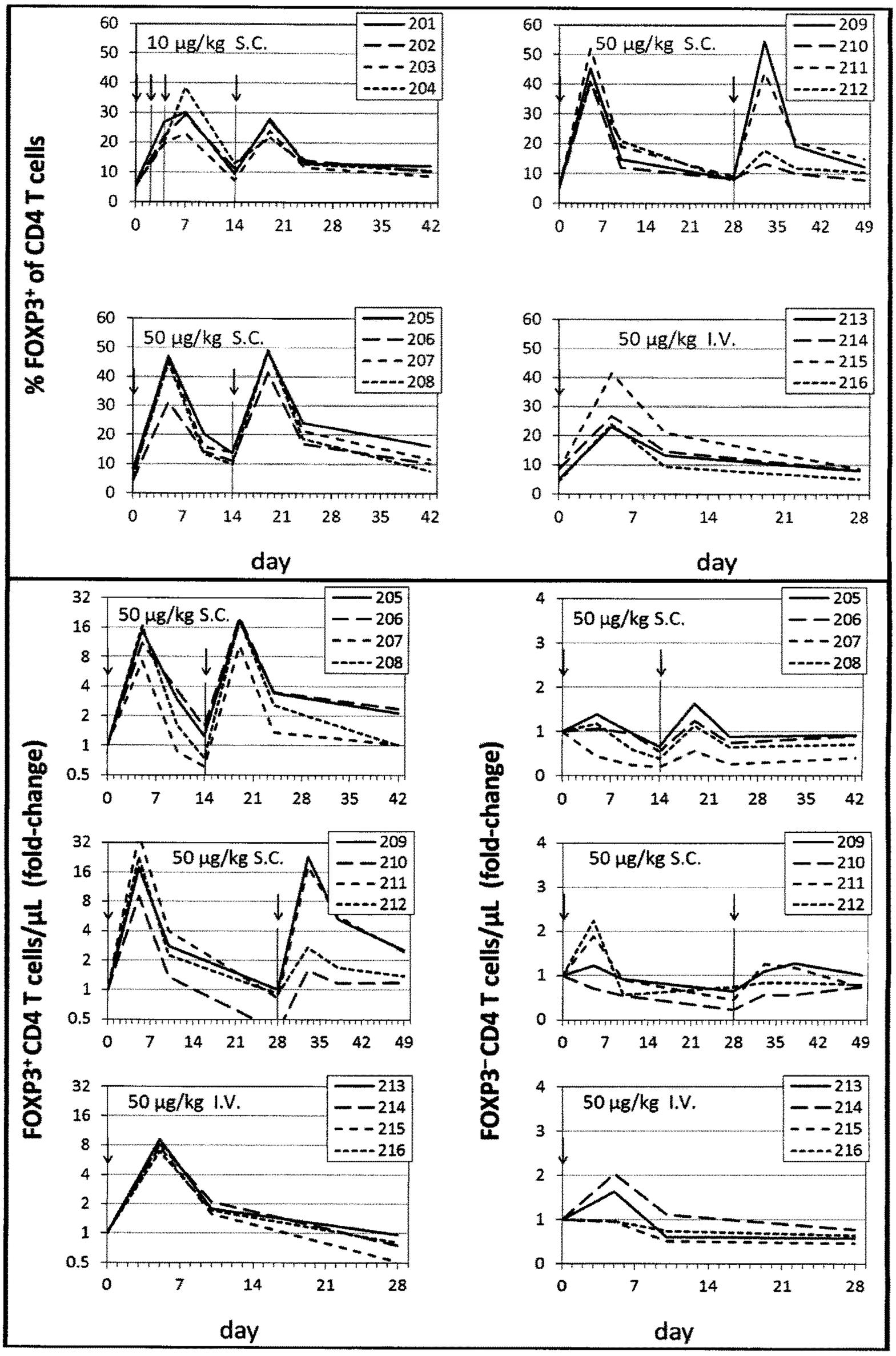

pSTAT5 PE MFI
450
400
350
300
250
200
150
100
50
0
0hr
2hr
4hr
6hr
o.n.
Fc.WT
Fc.N88D
Fc.V91K

FIG. 10A


% FOXP3+ of CD4 T cells
10 µg/kg S.C.
201
202
203
204
50 µg/kg S.C.
209
210
211
212
50 µg/kg S.C.
205
206
207
208
50 µg/kg I.V.
213
214
215
216
day
FOXP3+ CD4 T cells/µL (fold-change)
FOXP3− CD4 T cells/µL (fold-change)

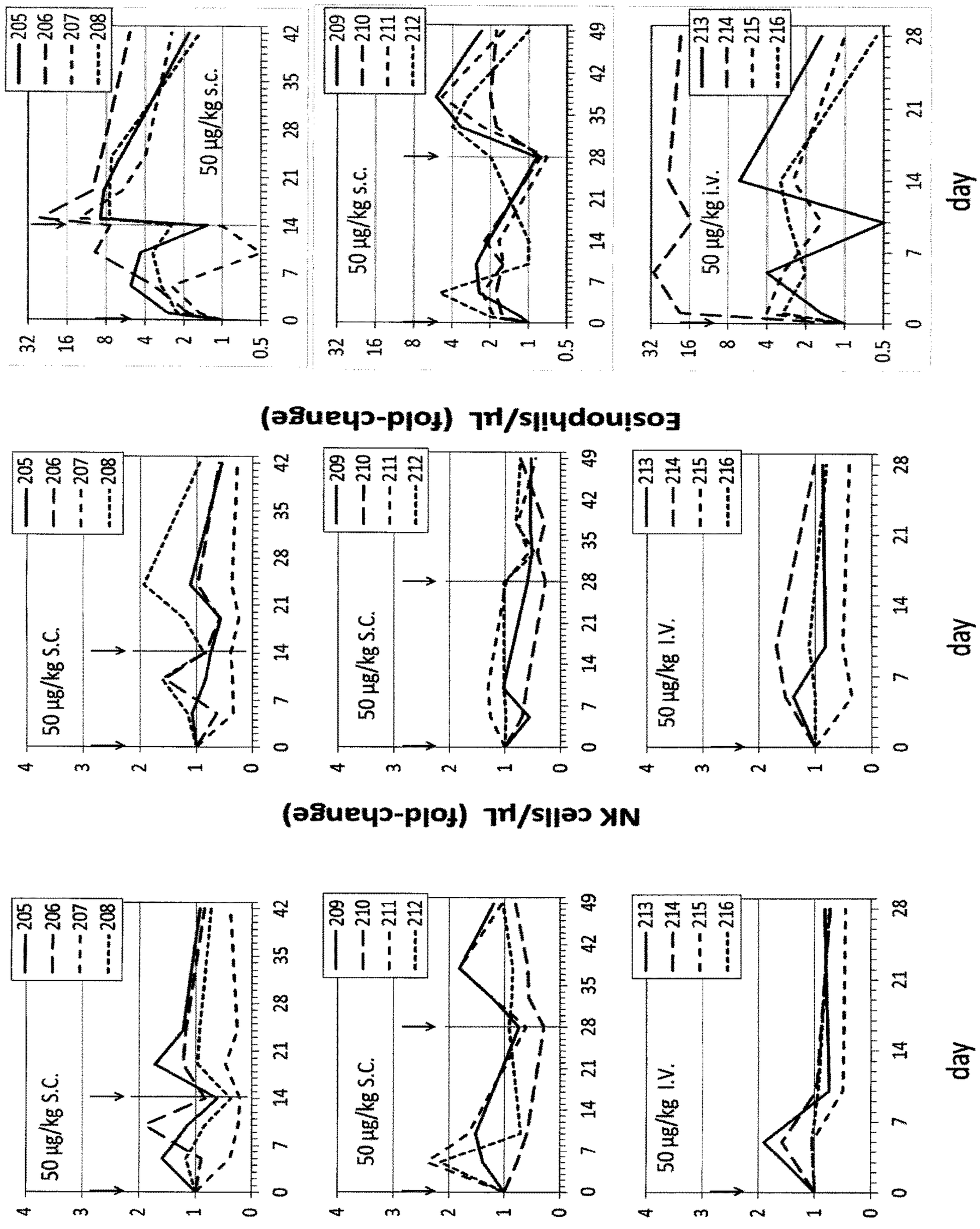

FOXP3⁻CD8 T cells/μL (fold-change)
NK cells/μL (fold-change)
Eosinophils/μL (fold-change)
205
206
207
208
209
210
211
212
213
214
215
216
50 μg/kg s.c.
50 μg/kg S.C.
50 μg/kg i.v.
50 μg/kg I.V.
day
0
7
14
21
28
35
42
49
0.5
1
2
4
8
16
32
3

FIG. 10B

FIG. 11A

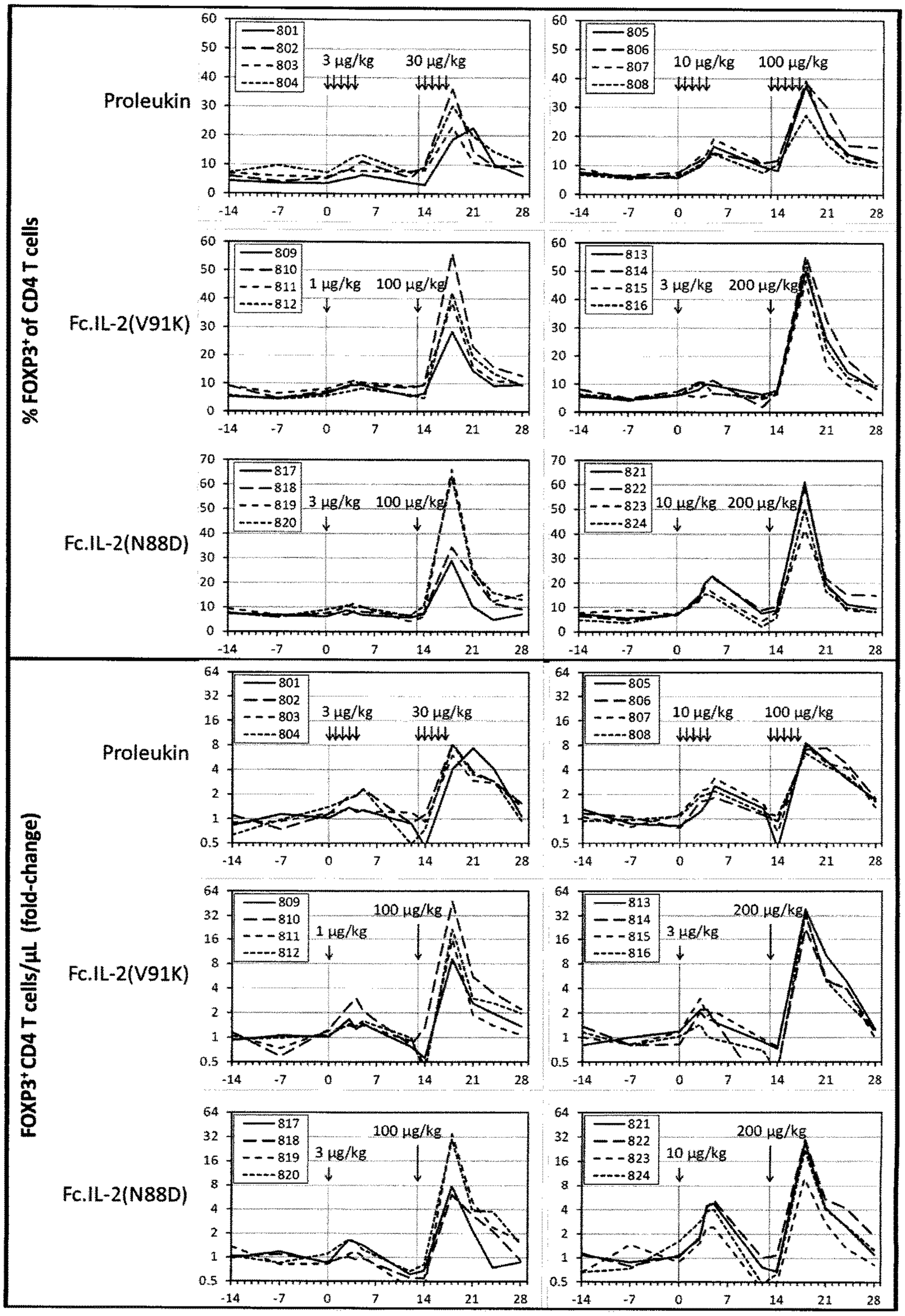

% FOXP3+ of CD4 T cells
FOXP3+ CD4 T cells/µL (fold-change)
Proleukin
Fc.IL-2(V91K)
Fc.IL-2(N88D)
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
3 µg/kg
30 µg/kg
10 µg/kg
100 µg/kg
1 µg/kg
200 µg/kg

FIG. 11B

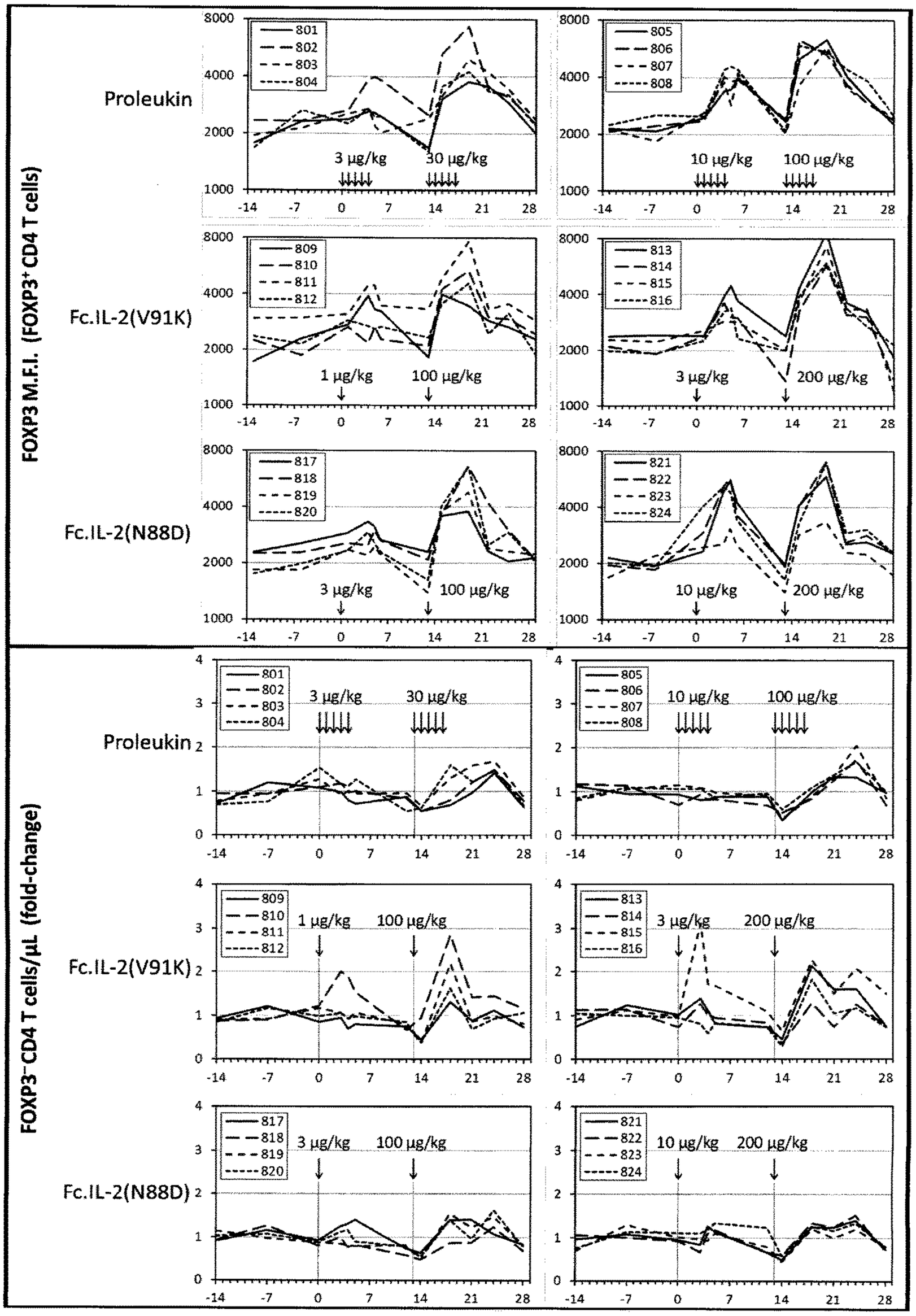
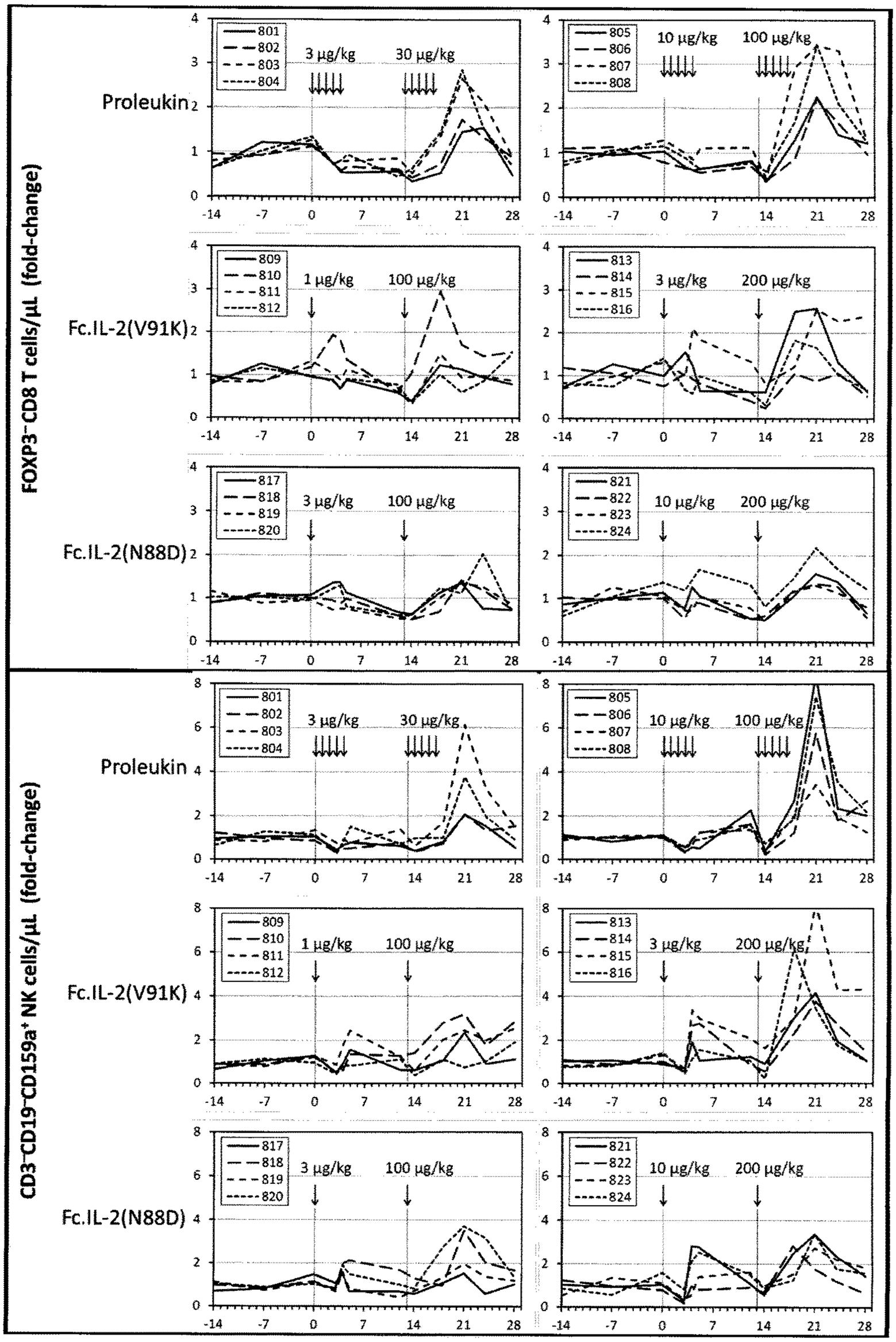

FOXP3 M.F.I. (FOXP3+ CD4 T cells)
FOXP3- CD4 T cells/μL (fold-change)
Proleukin
Fc.IL-2(V91K)
Fc.IL-2(N88D)
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
3 μg/kg
30 μg/kg
10 μg/kg
100 μg/kg
1 μg/kg
200 μg/kg
8000
4000
2000
1000
4
3
2
1
0
-14
-7
0
7
14
21
28

FIG. 11C


FOXP3⁻CD8 T cells/μL (fold-change)
CD3⁻CD19⁻CD159a⁺ NK cells/μL (fold-change)
Proleukin
Fc.IL-2(V91K)
Fc.IL-2(N88D)
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
3 μg/kg
30 μg/kg
10 μg/kg
100 μg/kg
1 μg/kg
200 μg/kg
-14
-7
0
7
14
21
28

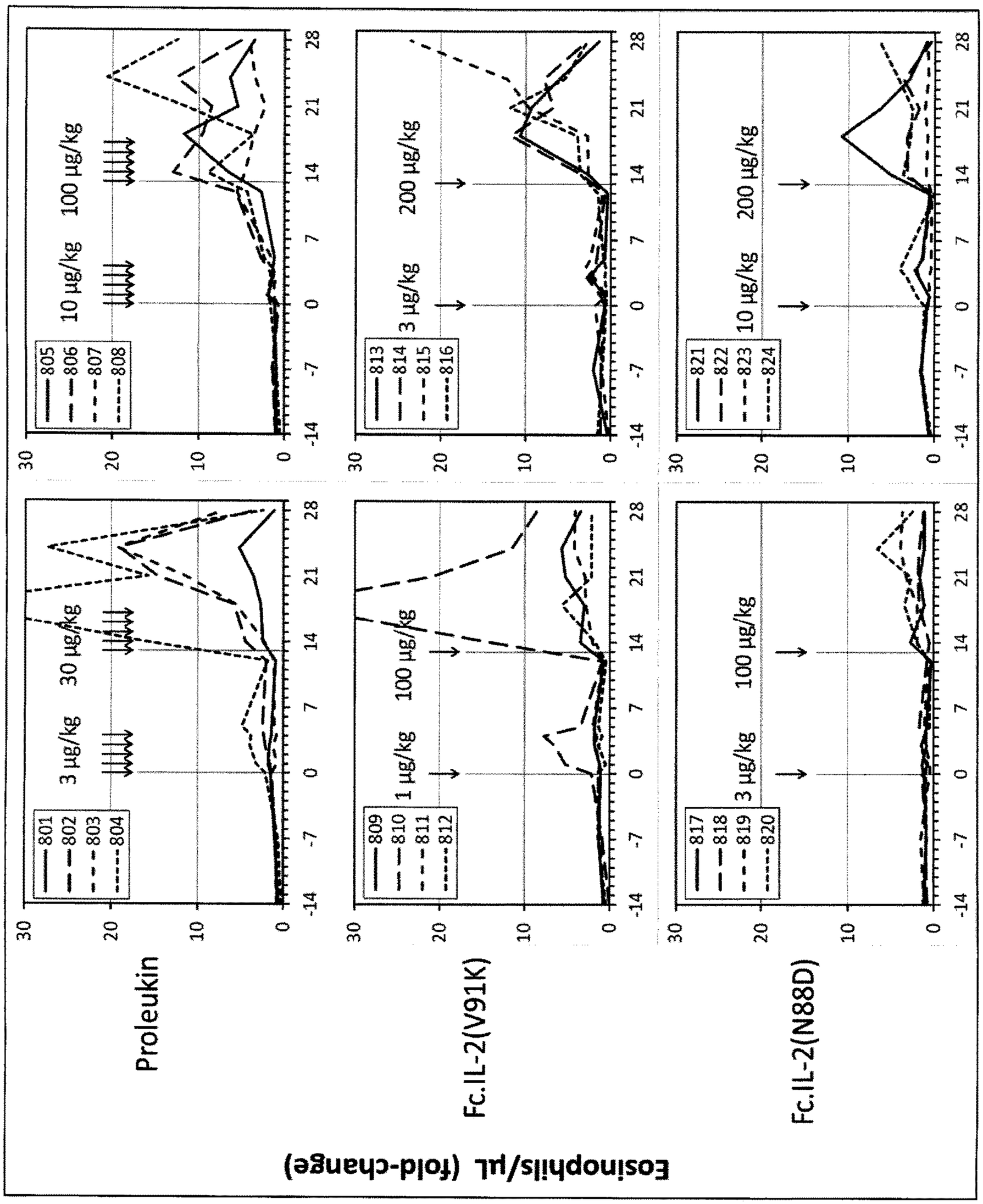
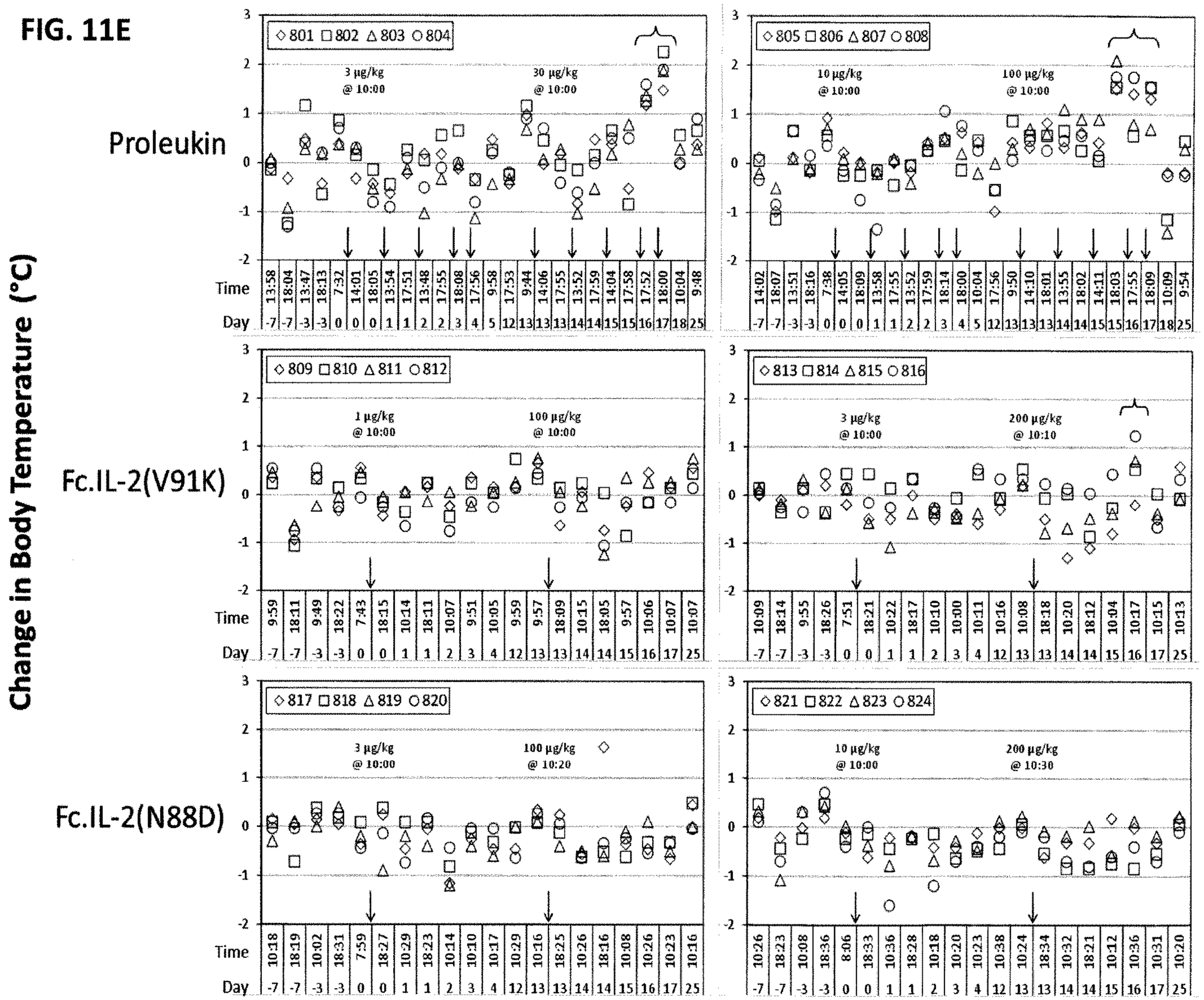

Proleukin
Fc.IL-2(V91K)
Fc.IL-2(N88D)
Eosinophils/µL (fold-change)
100 µg/kg
10 µg/kg
200 µg/kg
3 µg/kg
30 µg/kg
1 µg/kg
100 µg/kg
3 µg/kg
10 µg/kg
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
30
20
10
0
-14
-7
0
7
14
21
28

FIG. 11D

FIG. 11E


Change in Body Temperature (°C)
Proleukin
Fc.IL-2(V91K)
Fc.IL-2(N88D)
◇801 □802 △803 ○804
3 μg/kg @ 10:00
30 μg/kg @ 10:00
◇805 □806 △807 ○808
10 μg/kg @ 10:00
100 μg/kg @ 10:00
◇809 □810 △811 ○812
1 μg/kg @ 10:00
100 μg/kg @ 10:00
◇813 □814 △815 ○816
3 μg/kg @ 10:00
200 μg/kg @ 10:10
◇817 □818 △819 ○820
3 μg/kg @ 10:00
100 μg/kg @ 10:20
◇821 □822 △823 ○824
10 μg/kg @ 10:00
200 μg/kg @ 10:30
Time
Day

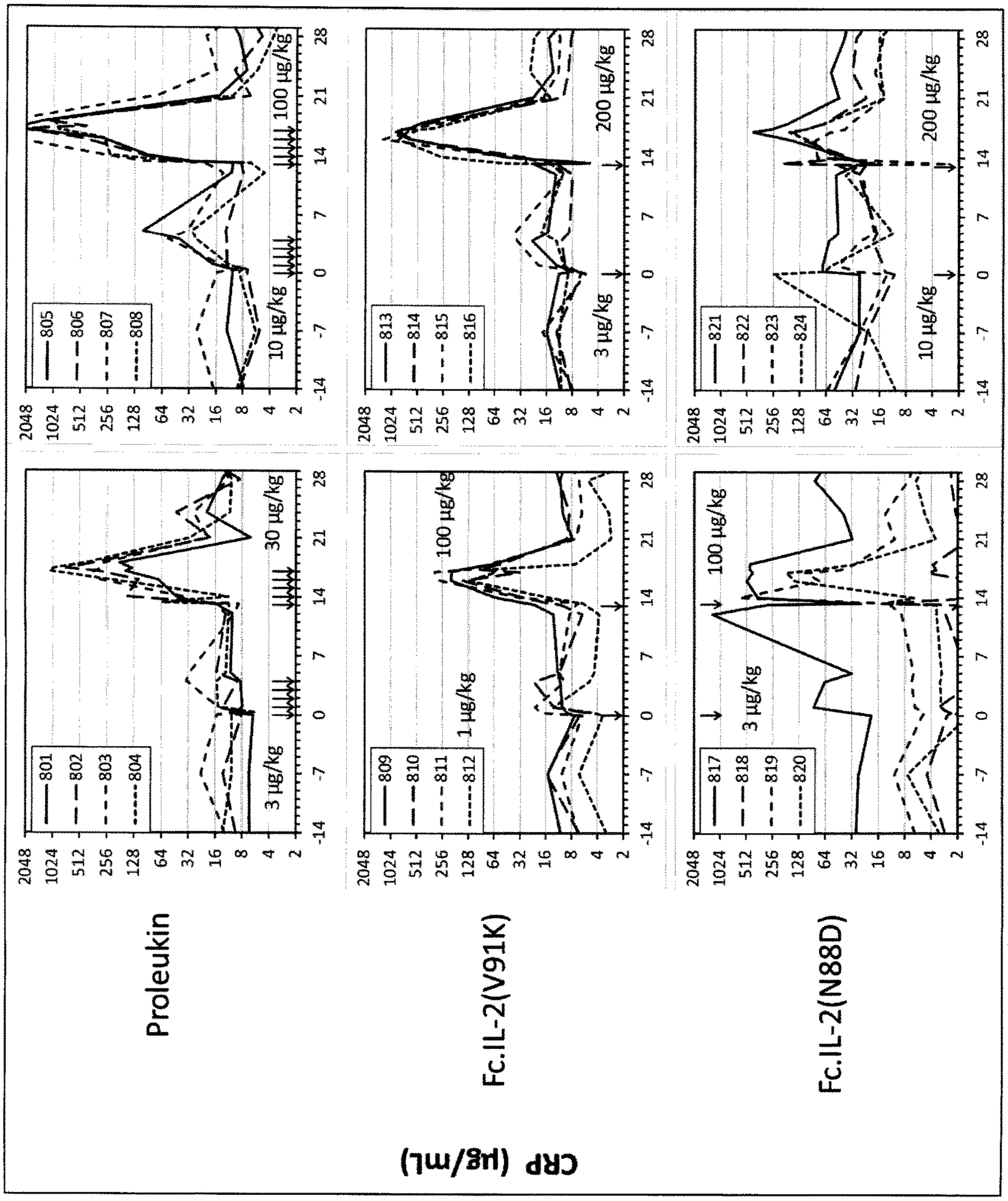

CRP (μg/mL)
Proleukin
Fc.IL-2(V91K)
Fc.IL-2(N88D)
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
3 μg/kg
10 μg/kg
30 μg/kg
100 μg/kg
200 μg/kg
1 μg/kg
2048
1024
512
256
128
64
32
16
8
4
2
-14
-7
0
7
14
21
28

FIG. 11F

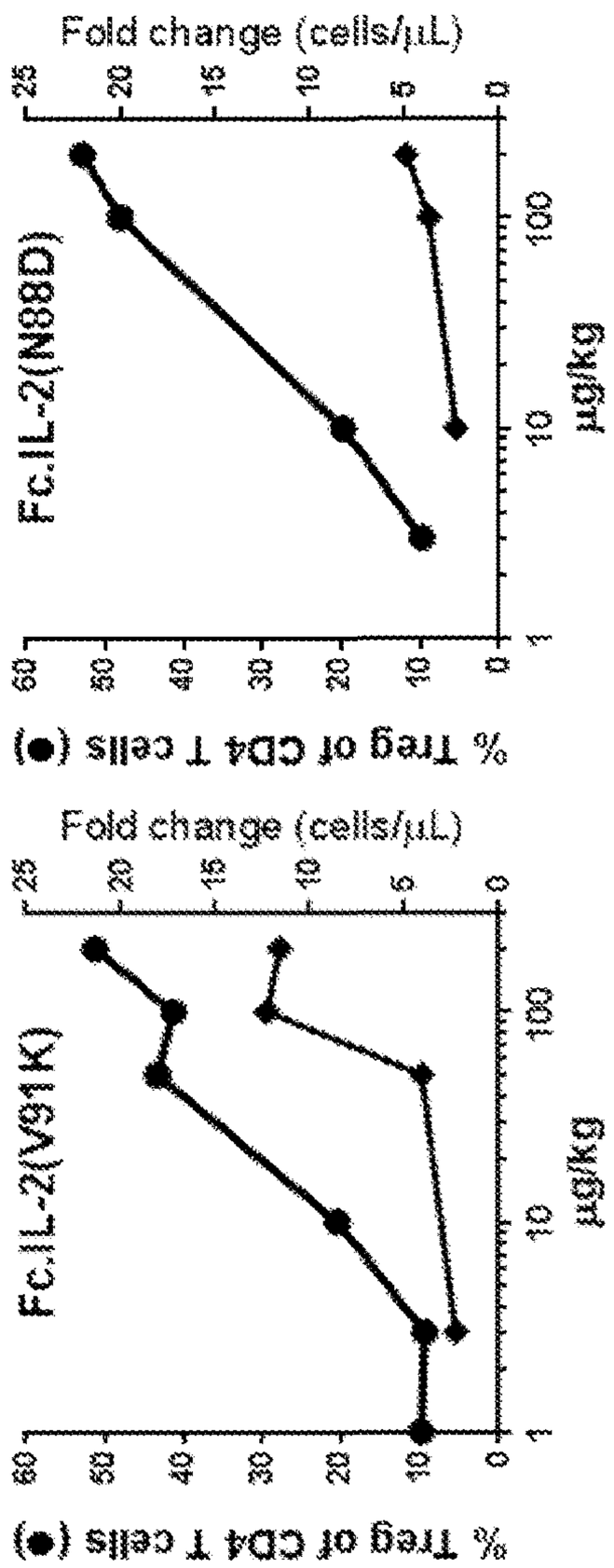


FIG. 12A

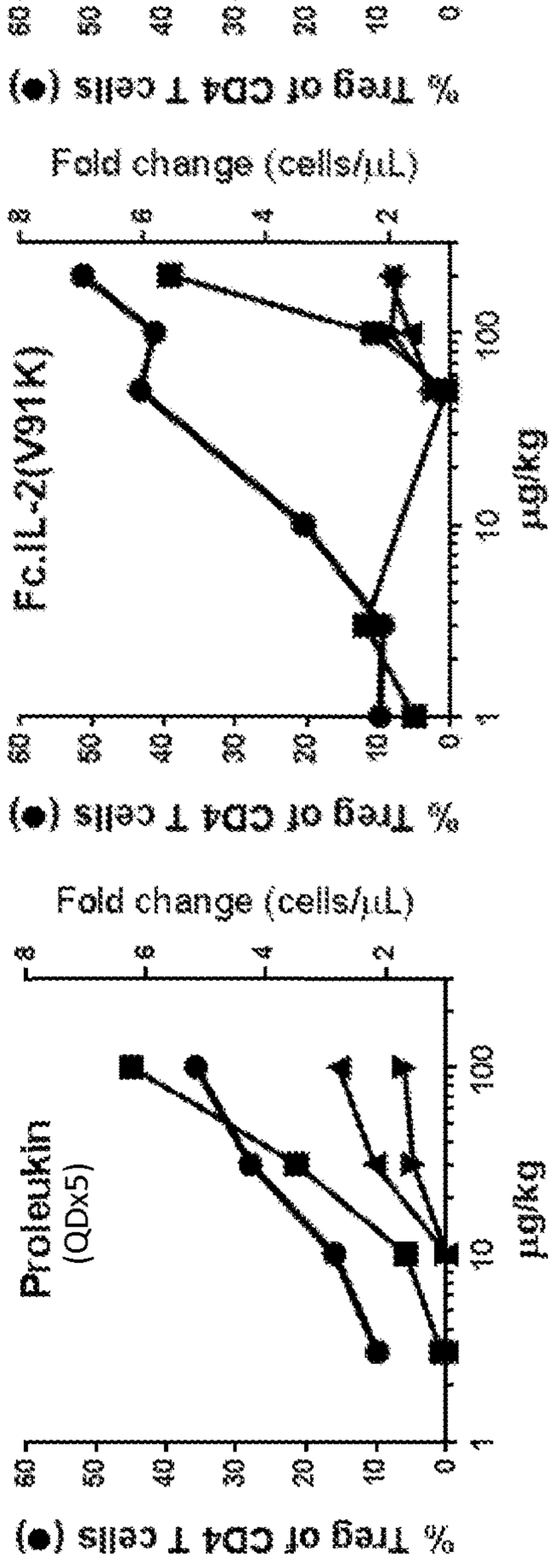
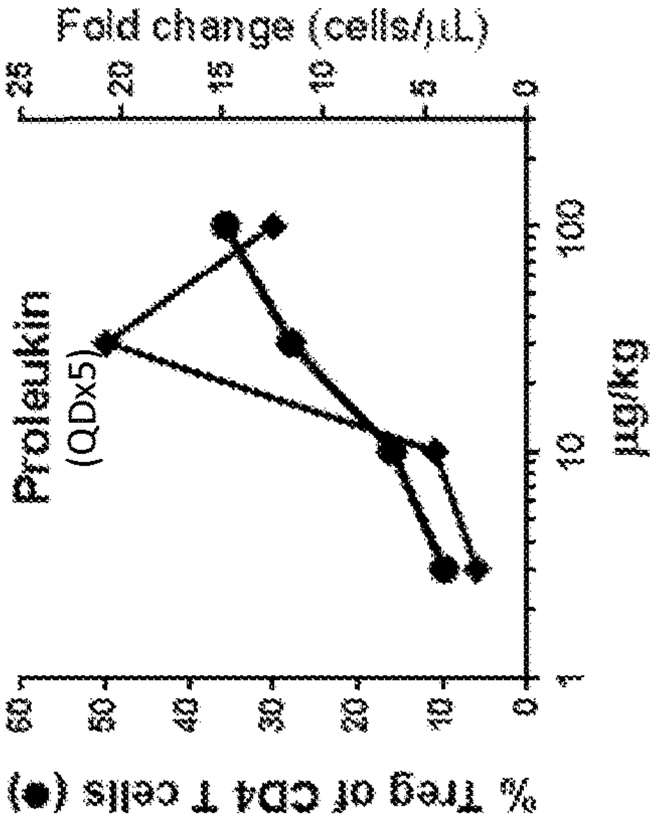


FIG. 12B



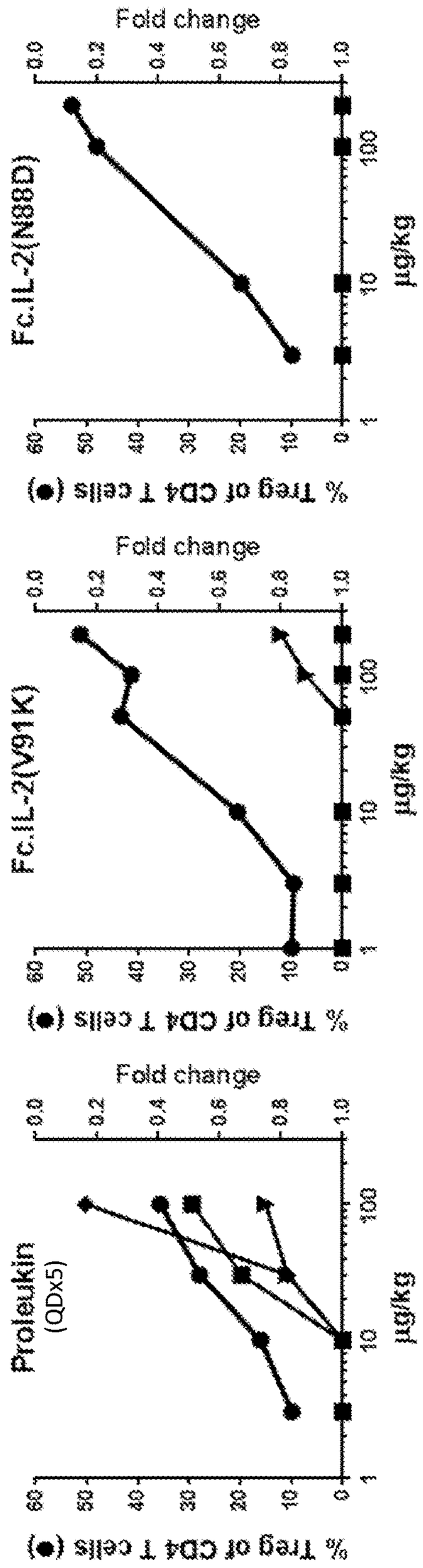


FIG. 12D

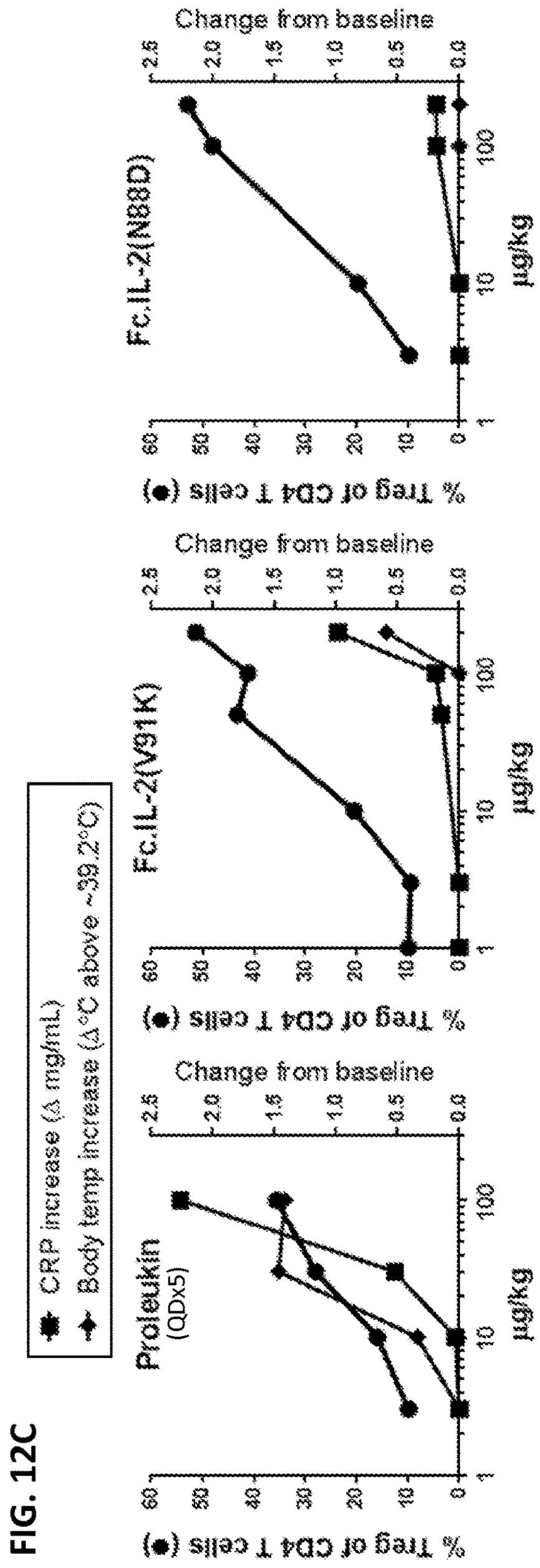


FIG. 12C

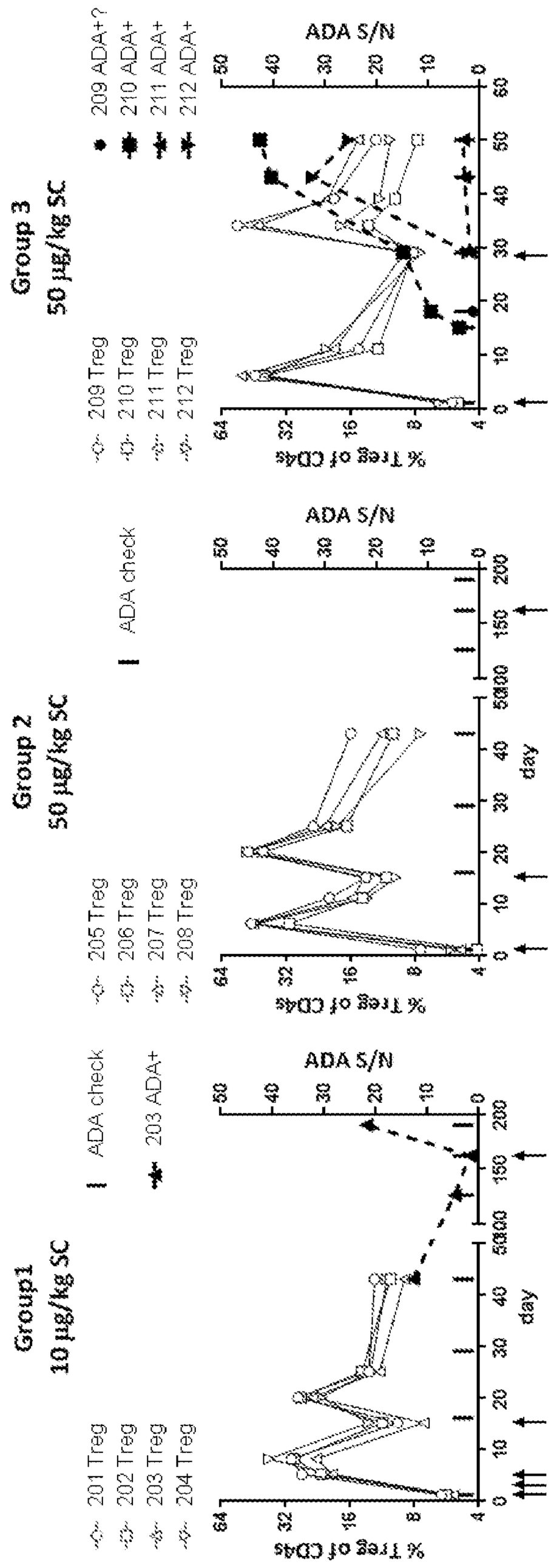

Group 3
50 µg/kg SC
209 Treg
210 Treg
211 Treg
212 Treg
209 ADA+?
210 ADA+
211 ADA+
212 ADA+
ADA S/N
% Treg of CD4s
Group 2
50 µg/kg SC
205 Treg
206 Treg
207 Treg
208 Treg
ADA check
day
Group1
10 µg/kg SC
201 Treg
202 Treg
203 Treg
204 Treg
ADA check
203 ADA+
50 µg/kg rechallenge

FIG. 13

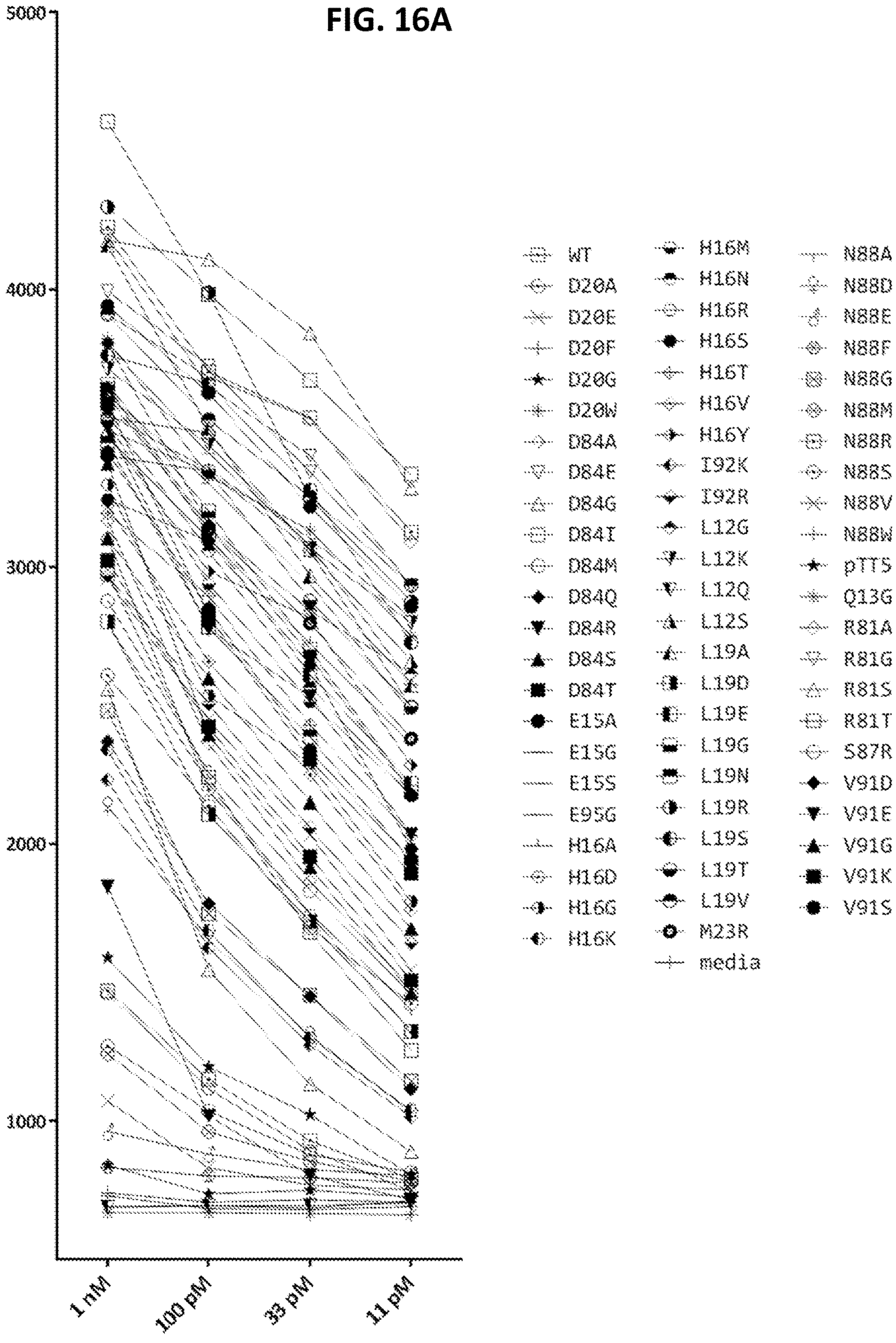
FIG. 14

	L12	Q13	E15	H16	L19	D20	M23	R81	D84	S87	N88	V91	I92	L94	E95
A	1.18	0.82	1.26	2.51	2.05	1.61	0.68	1.61	1.53	-0.1	2.13	1.22	1.04	0.21	0.68
D	0.49	0.81	0.99	2.39	1.7	0	0.41	1.19	0	-0.4	1.1	0.52	0.29	-0.2	0.15
E	0.93	-0.1	0	1.01	1.58	0.49	0.01	0.93	2.4	-0.4	2.15	1.89	0.75	-0.9	-0
F	0.1	0.86	-0.5	0.97	-0.9	1.6	0.2	-0	0.98	-1.5	1.3	-0.6	0.18	-0	-0.5
G	1.36	1.08	1.51	3.06	2.73	1.83	0.82	1.62	2.11	0.19	2.78	1.88	1.29	0.32	1.11
H	-0.1	-0	0.29	0.42	0.18	0.55	0.39	0.52	1.64	-0.3	1.69	0.5	-0.1	0.04	0.84
I	-0.1	0.45	0.06	0.91	0.73	0.74	-0.1	1.01	1.76	-0.9	0.25	0.98	0	-0.6	0.48
K	1.19	0.25	0.85	3.98	-0.3	1.56	0.22	1.04	2.66	0.01	3.72	2.7	1.57	0.59	0.73
L	0	0.33	-0.1	1.47	0	0.57	0.14	1.11	1.16	-0.8	0.29	0.74	-0.3	0	0.12
M	1.09	-0.1	0.41	1.86	1.2	0.96	0	0.9	2.04	-1	2.17	1.09	0.72	0.09	0.64
N	0.26	0.66	0.68	1.59	1.31	0.16	0.26	1.38	0.66	-0.5	0	0.32	0.89	-0.3	0.5
P	0.89	0.24	1.01	2.18	0.97	0.86	0.34	1.36	1.18	-0.5	0.89	0.28	0.33	-0.1	0.08
Q	1.27	-0	0.21	0.94	0.98	0.61	-0.2	1.11	2.41	-0.2	1.46	0.73	-0.3	0.08	0.51
R	1.04	-0.2	0.48	2.69	1.17	1.33	1.19	0	1.69	1.15	2.19	1.23	1.8	0.47	1.03
S	1.35	0.85	1.3	2.73	2.33	1.25	0.89	1.71	2.06	0	2.19	1.54	0.8	0.24	0.68
T	1.11	0.6	0.88	1.91	1.58	1.16	0.67	1.69	2.3	-0.2	1.17	0.72	0.53	0.07	0.6
V	0.77	0.75	0.45	1.76	1.64	1.22	0.28	1.34	0.69	-0.3	2.2	-0	0.54	-0.1	0.31
W	-1.4	0.47	-0.7	-0.6	-2.4	3.88	0.08	-0.7	0.33	-0	2.88	-0.5	-0.3	-0.2	-0.4
Y	0.25	0.62	-0.2	1.55	-1.8	0.96	0.06	-0.3	0.82	-0.6	1.07	-0.4	-0.3	-0	0.63

FIG. 15

	L12	Q13	E15	H16	L19	D20	M23	R81	D84	S87	N88	V91	I92	L94	E95
A	2.9	3.4	4.8	12.1	7.0	6.0	3.5	5.4	8.1	1.4	11.7	8.4	5.6	-0.3	6.5
D	5.9	8.2	8.6	21.0	17.8		5.6	6.9		-3.4	14.4	13.5	9.8	0.1	3.6
E	6.9	2.5		13.7	12.1	19.0	4.1	4.3	1.6	-0.4	20.4	4.4	8.6	-1.2	
F	-3.0	-1.5	0.0	-3.9	-0.2	13.4	2.0	3.3	2.3	-7.7	26.4	0.3	4.1	-0.2	3.4
G	3.2	4.8	6.4	15.1	9.8	6.8	3.8	5.5	9.8	2.1	13.5	12.8	7.5	-0.1	8.6
H	4.4	1.1	-2.2		5.9	12.3	3.2	3.3	4.9	-5.9	21.3	4.2	12.0	-0.2	2.8
I	1.2	3.9	2.2	2.9	1.9	4.6	0.9	2.5	6.0	-1.8	12.7	1.2		-0.2	4.1
K		2.0	7.9	8.1		25.8	1.6	3.7	14.4	4.7	24.1	9.3	-3.0	1.3	8.6
L	-4.2	-1.1	-3.5	3.1	-1.7	5.1	1.4	2.2	2.8	-2.3	1.9	0.5	-1.9		3.4
M	-1.5	-0.6	-4.7	-4.0	-3.2	4.0		-2.2	7.0	-6.0	-0.9	-4.6	-7.4	0.0	-2.4
N	-1.0	2.8	6.4	7.7	5.9	-0.4	2.3	5.3	4.7	-1.9		4.2	-1.8	-0.3	6.9
P	2.4	2.6	3.9	7.1	7.0	7.5	3.1	4.7	6.9	0.2	13.1	4.0	2.1	-0.2	5.9
Q	1.9	0.2	-2.2	1.1	4.4	3.1	0.5	0.8	8.7	-2.7	3.0	-0.5	-5.7	0.1	1.4
R	-14.9	2.2	-0.8	6.6	-7.4	16.6	3.4		10.9	3.4	5.4	4.0	-4.5	1.3	4.7
S	2.1	0.3	4.5	10.6	6.1	2.4	3.2	5.6	6.2		9.0	6.7	5.2	-0.3	6.5
T	0.9	0.1	2.3	5.1	7.3	5.0	2.3	4.6	4.9	0.1	8.2	4.3	3.9	-0.5	4.2
V	1.3	-2.1	2.1	7.8	3.9	4.2	2.0	4.8	5.9	0.4	5.6		1.4	-0.3	5.7
W	-0.5	-1.9	-7.8	8.9	3.6	39.6	2.9	3.6	-0.5	-13.1	36.8	-0.9	2.9	-4.7	-1.2
Y	-6.0		1.0	-3.2	4.9	37.4	1.7	2.0	4.4	-13.2	27.0	-0.6	-5.4	-0.2	3.7

FIG. 16A


pSTAT5 (MFI)
5000
4000
3000
2000
1000
1 nM
100 pM
33 pM
11 pM
WT
D20A
D20E
D20F
D20G
D20W
D84A
D84E
D84G
D84I
D84M
D84Q
D84R
D84S
D84T
E15A
E15G
E15S
E95G
H16A
H16D
H16G
H16K
H16M
H16N
H16R
H16S
H16T
H16V
H16Y
I92K
I92R
L12G
L12K
L12Q
L12S
L19A
L19D
L19E
L19G
L19N
L19R
L19S
L19T
L19V
M23R
media
N88A
N88D
N88E
N88F
N88G
N88M
N88R
N88S
N88V
N88W
pTTS
Q13G
R81A
R81G
R81S
R81T
S87R
V91D
V91E
V91G
V91K
V91S

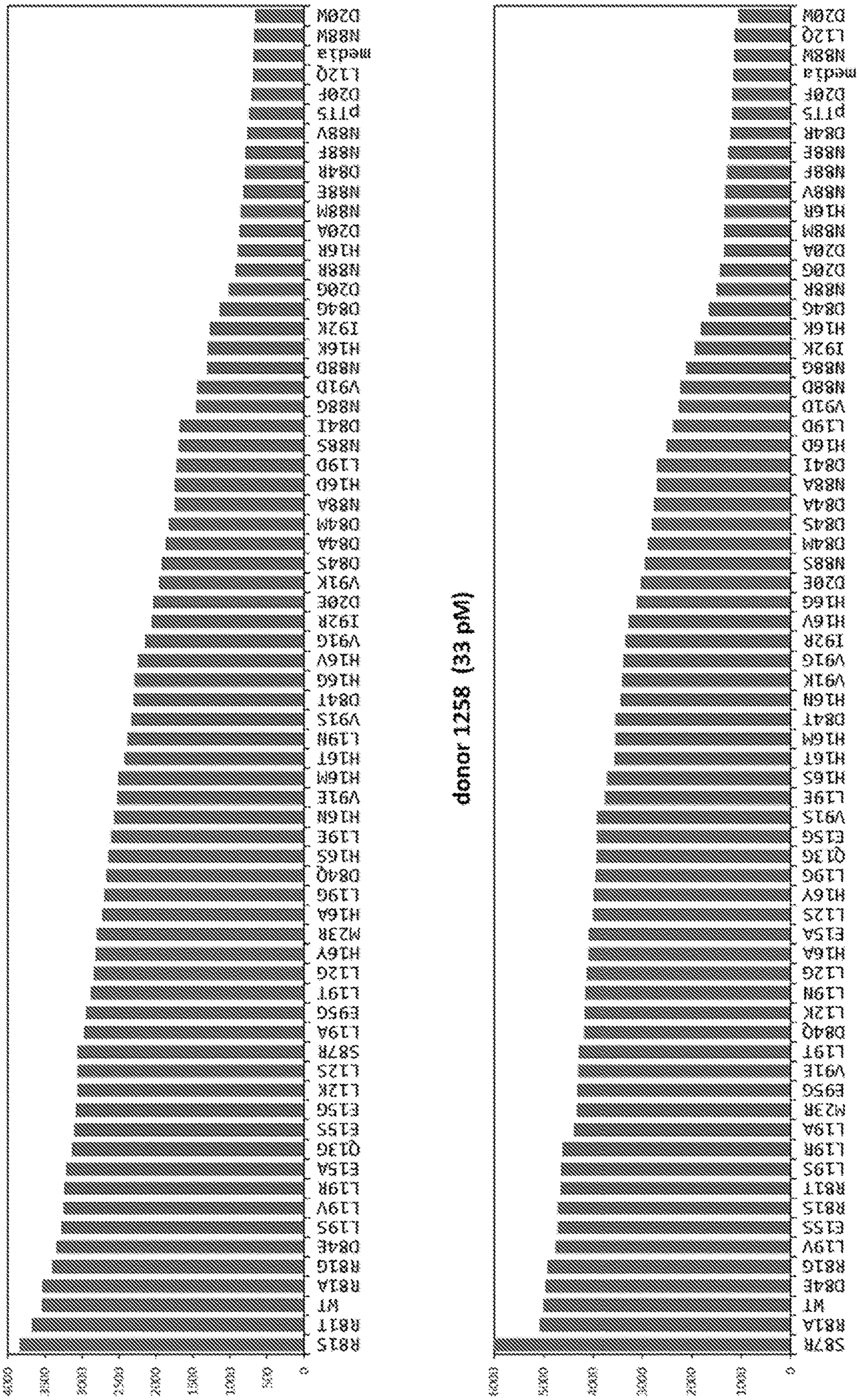

donor 1234 (33 pM)
R815
R813T
WT
R813A
R813G
D84E
L19S
L19V
L19R
E15A
Q13G
E15S
E15G
L12K
L12S
S87R
L19A
E95G
L19T
L12G
H16Y
M23R
H16A
E15G
L19G
H16V
L12S
H16S
L19E
H16N
V91E
H16T
H16M
L19N
V91S
D84T
H16G
V91G
H16V
D84Q
D84S
N88A
H16D
L19D
N88S
D84I
V91D
N88G
H16K
N88D
D84R
N88R
D20G
D20A
N88M
H16R
N88V
N88E
D84G
I92K
H16K
N88D
V91D
N88G
D84I
N88S
L19D
H16D
N88A
D84M
D84A
D84S
D84A
N88A
D84I
H16D
L19D
V91D
N88D
N88G
I92K
H16K
D84G
N88R
D20G
D20A
N88M
H16R
N88V
N88E
D84R
P113
D20F
L12Q
N88W
media
D20W
donor 1258 (33 pM)
S87R
R813A
WT
D84E
R813G
L19V
E15S
R813S
R813T
L19S
L19R
L19A
M23R
E95G
V91E
L19T
D84Q
L12K
L19N
L12G
H16A
E15A
L12S
H16Y
L19G
Q13G
E15S
V91S
L19E
H16S
H16T
H16M
D84T
H16N
V91K
V91G
I92R
H16V
H16G
D20E
N88S
D84M
D84S
D84A
N88A
D84I
H16D
L19D
N88D
N88G
I92K
H16K
D84G
N88R
D20G
D20A
N88M
H16R
N88V
N88E
D84R
P113
D20F
L12Q
N88W
media
D20W

FIG. 16B

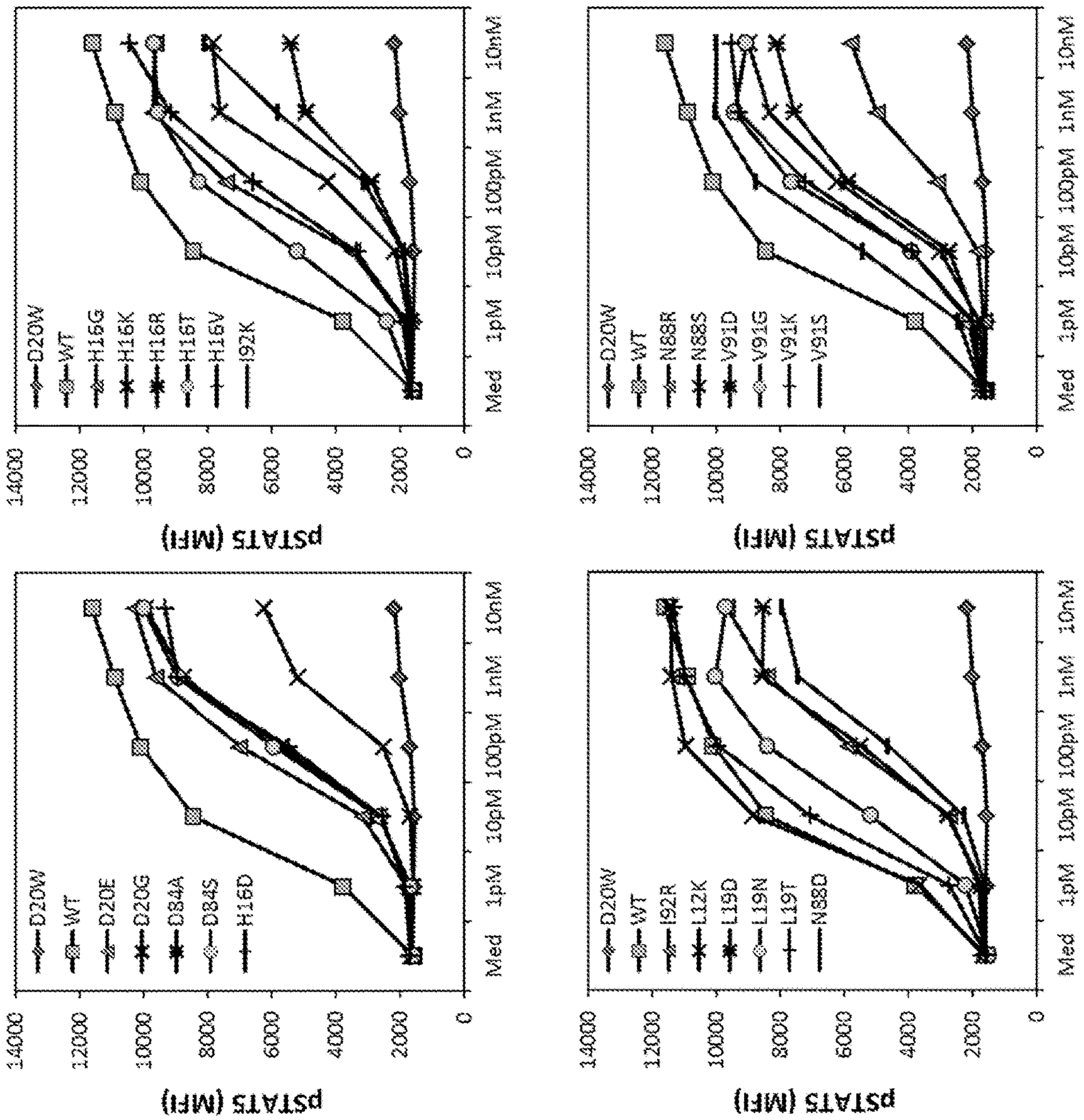

pSTAT5 (MFI)
0
2000
4000
6000
8000
10000
12000
14000
Med
1pM
10pM
100pM
1nM
10nM
D20W
WT
H15G
H16K
H16R
H16T
H16V
I92K
N88R
N88S
V91D
V91G
V91K
V91S
D20E
D20G
D84A
D84S
H16D
I92R
L12K
L19D
L19N
L19T
N88D

FIG. 17

FIG. 18A

FOXP3⁻ CD4⁺ proliferation

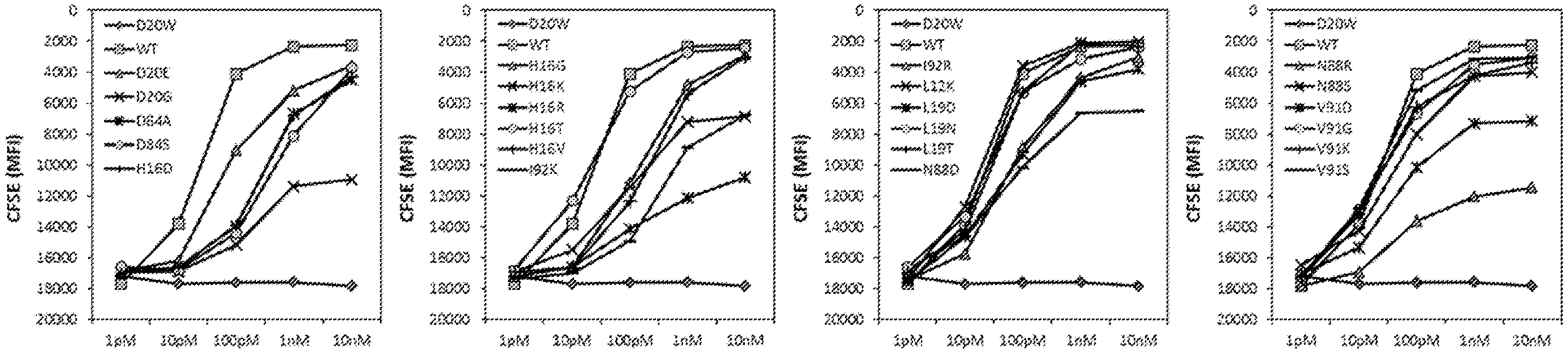


FIG. 18B

FOXP3⁻ CD8⁺ proliferation

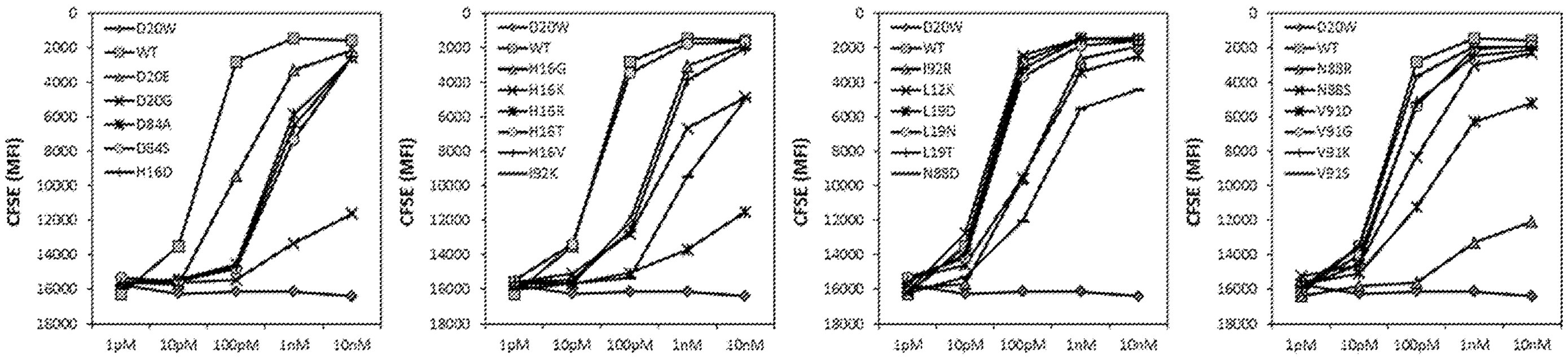


FIG. 18C

FOXP3$^+$ HELIOS$^+$ CD4$^+$ proliferation

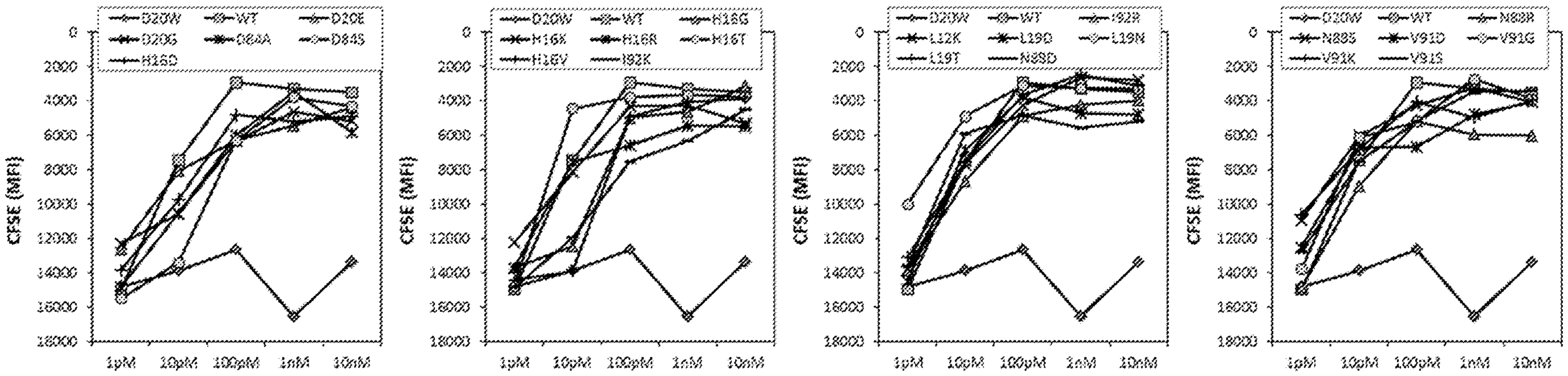


FIG. 18D

FOXP3 MFI in FOXP3$^+$ HELIOS$^+$ CD4$^+$

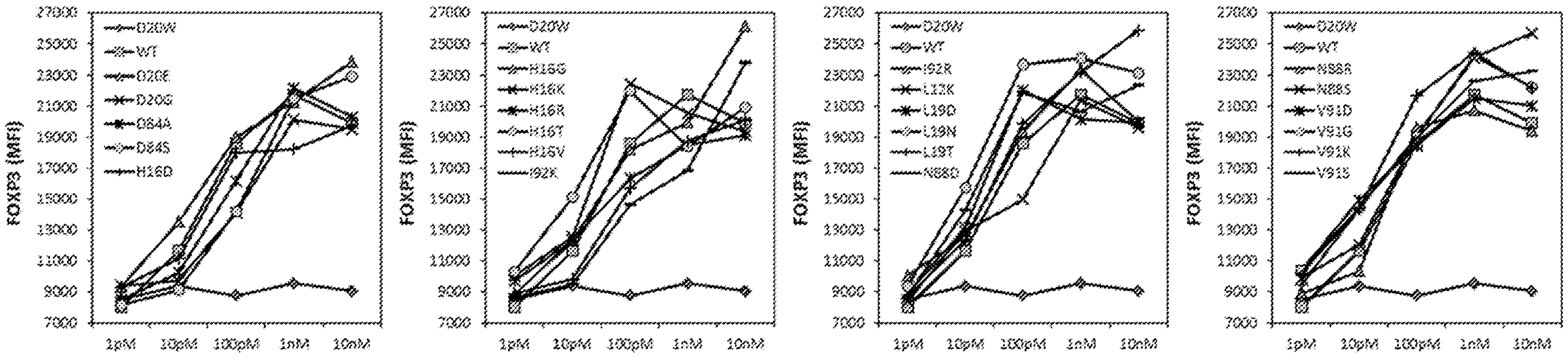


FIG. 19

NK proliferation

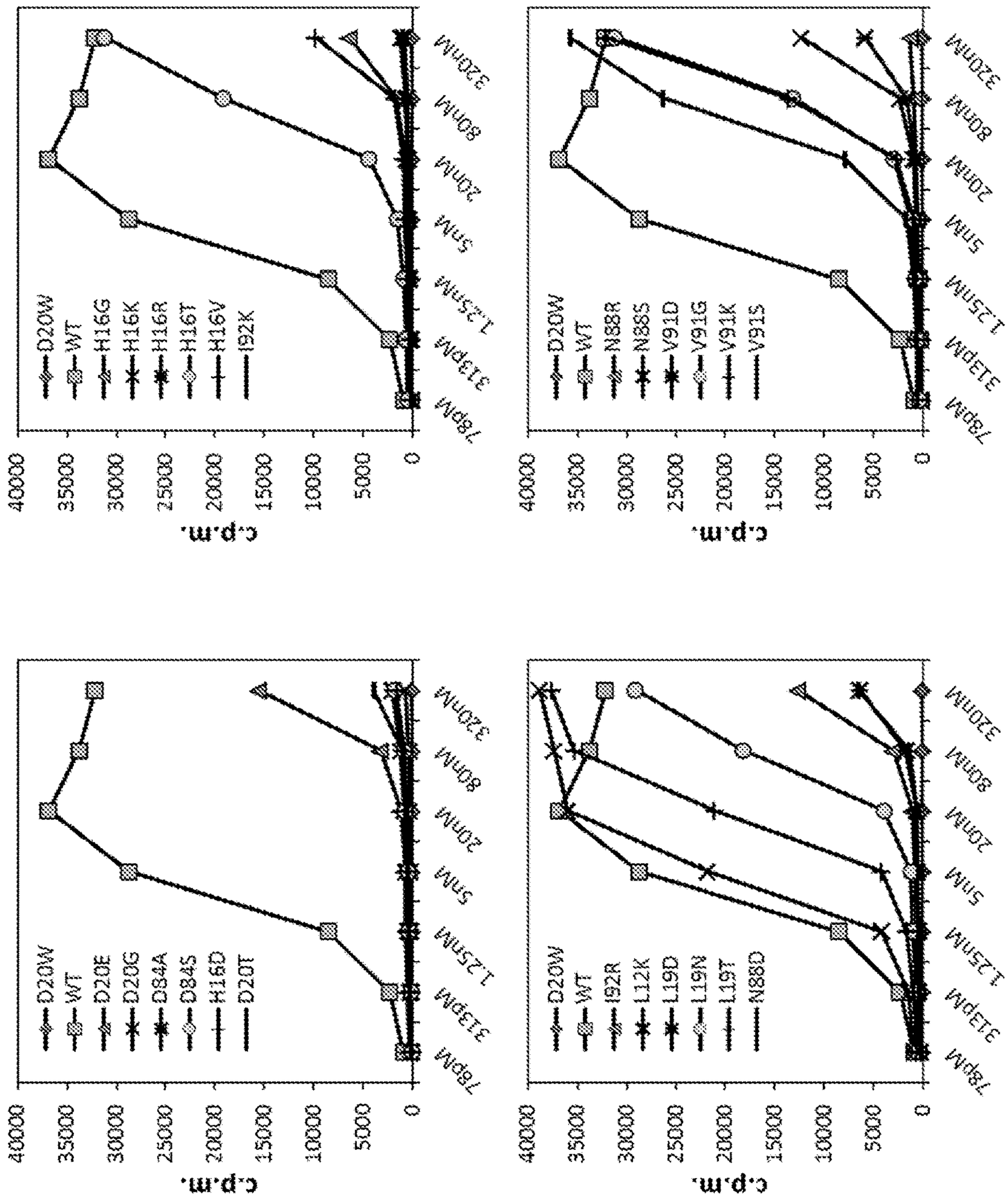
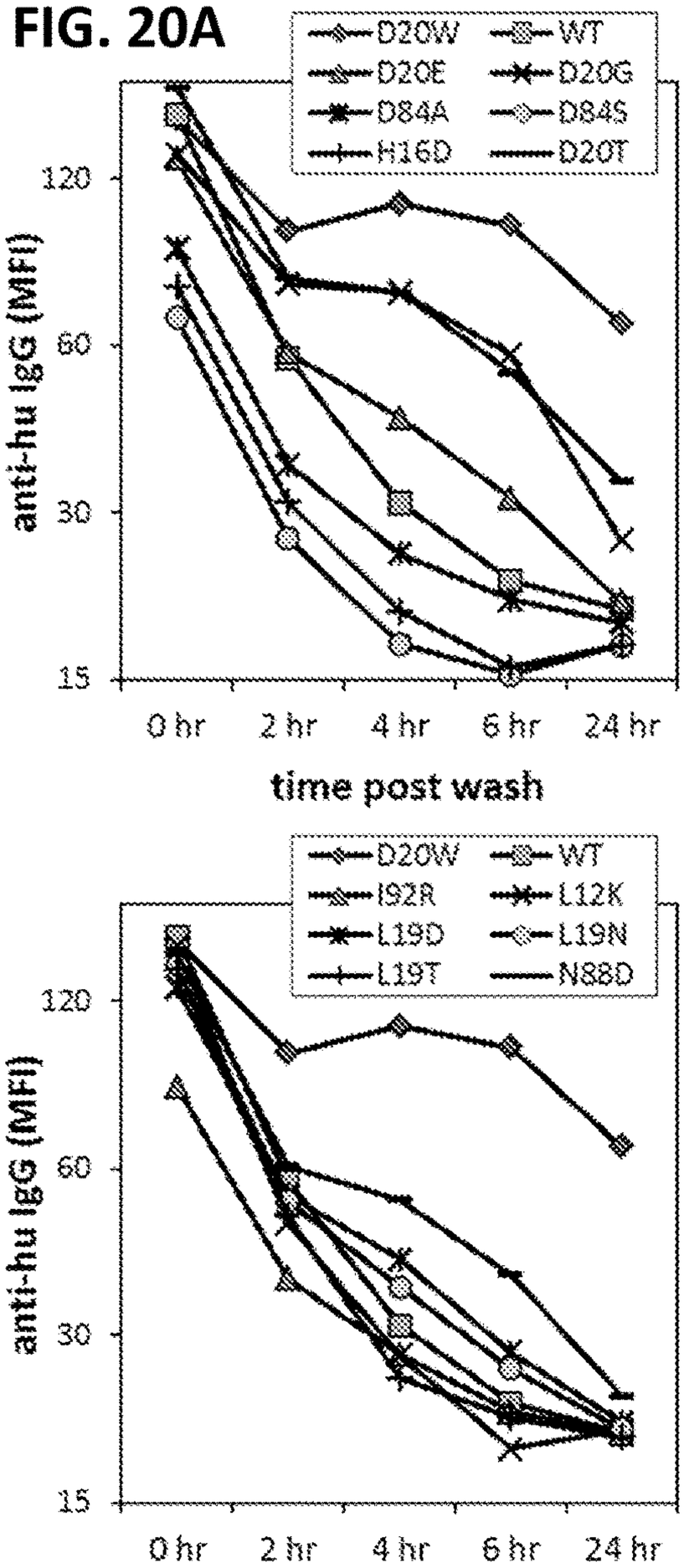


FIG. 20A



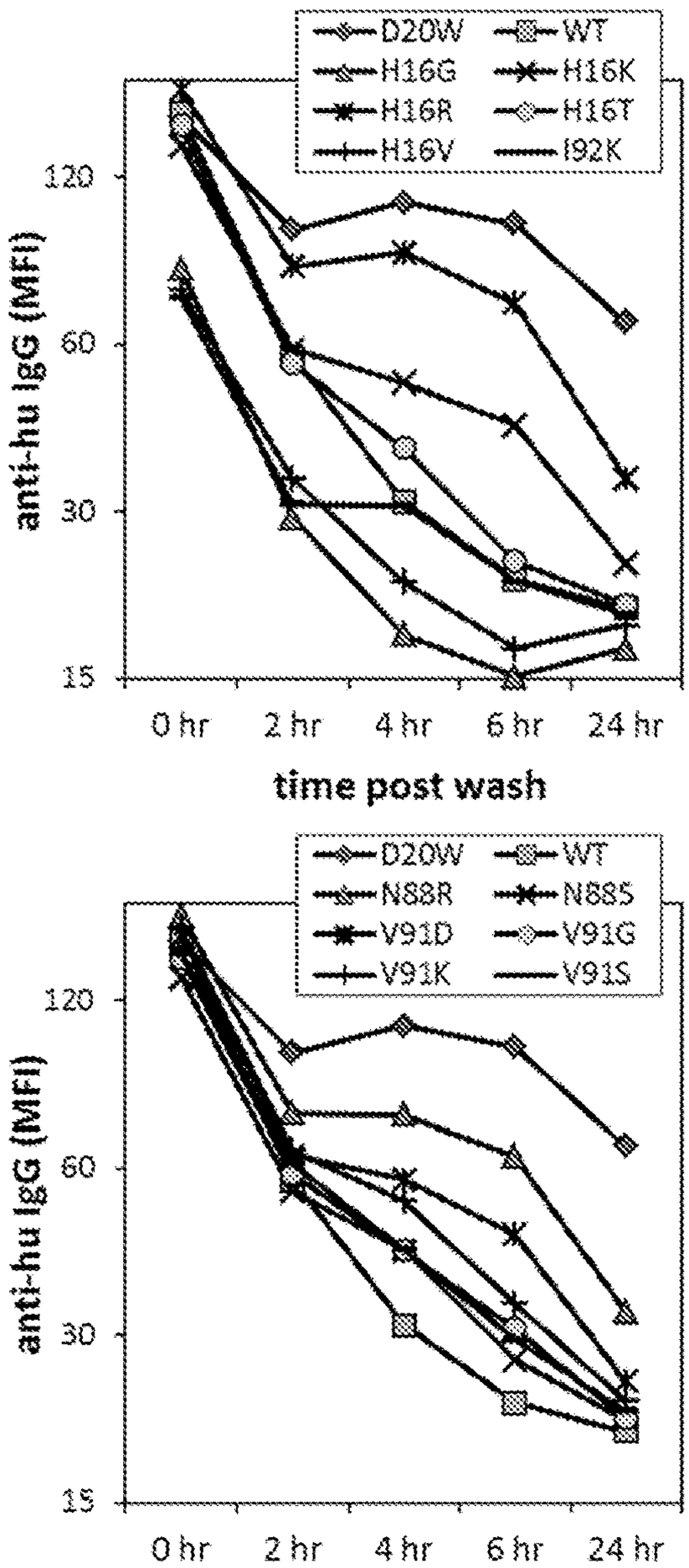


FIG. 20B

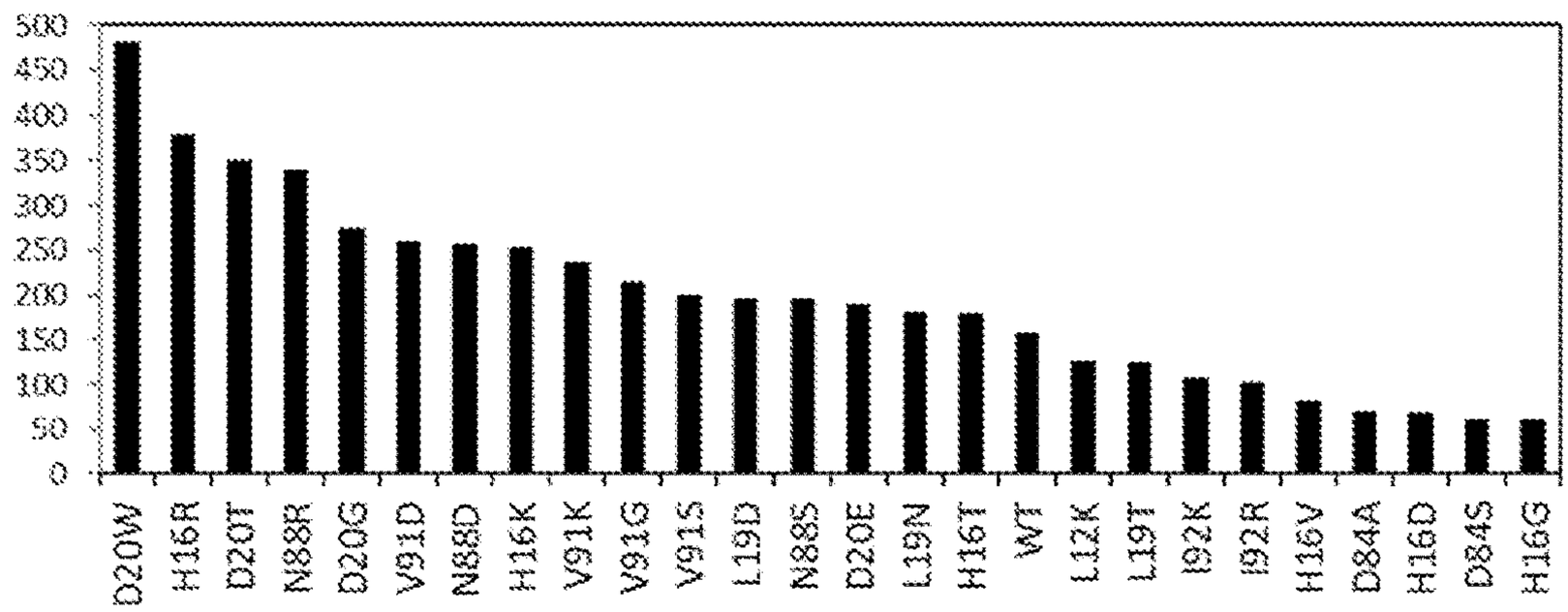
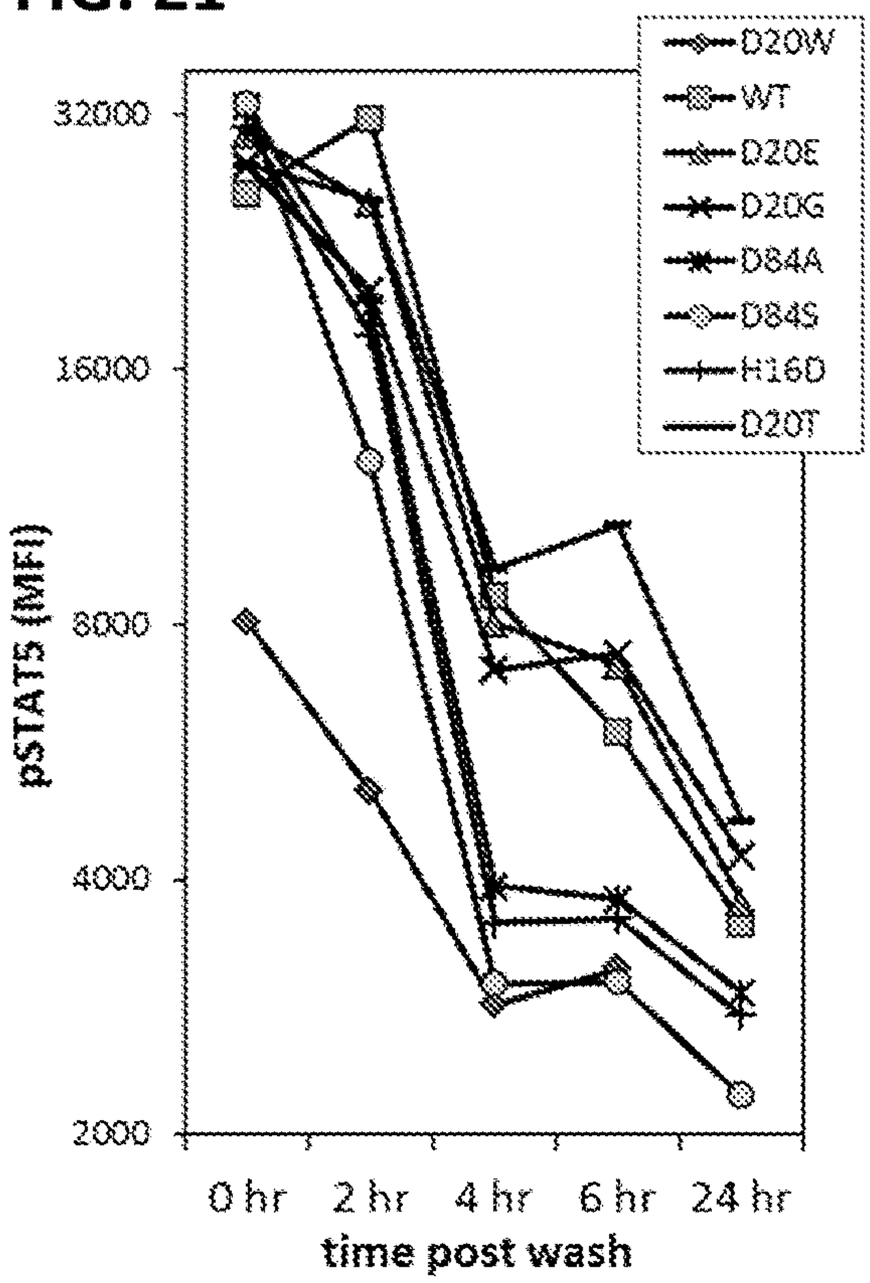
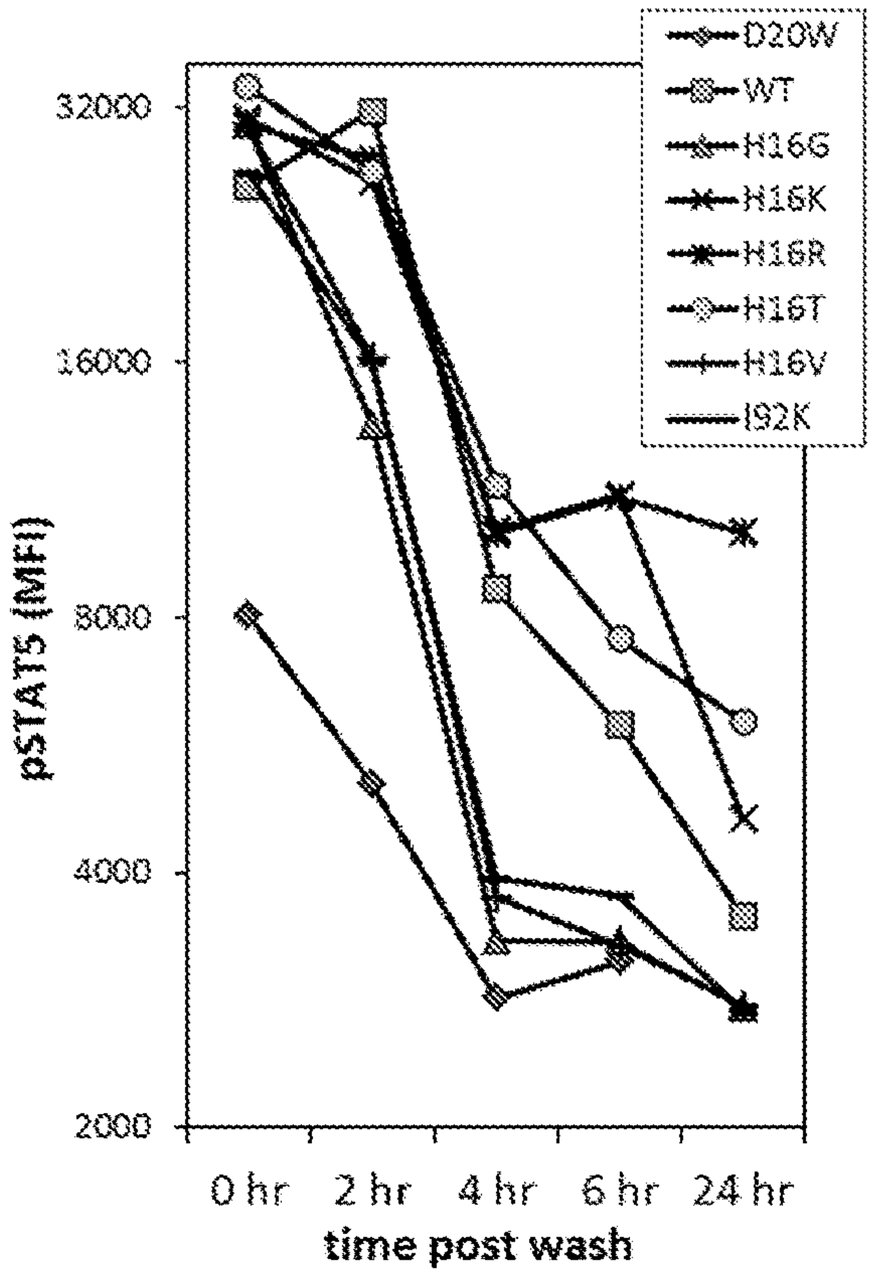
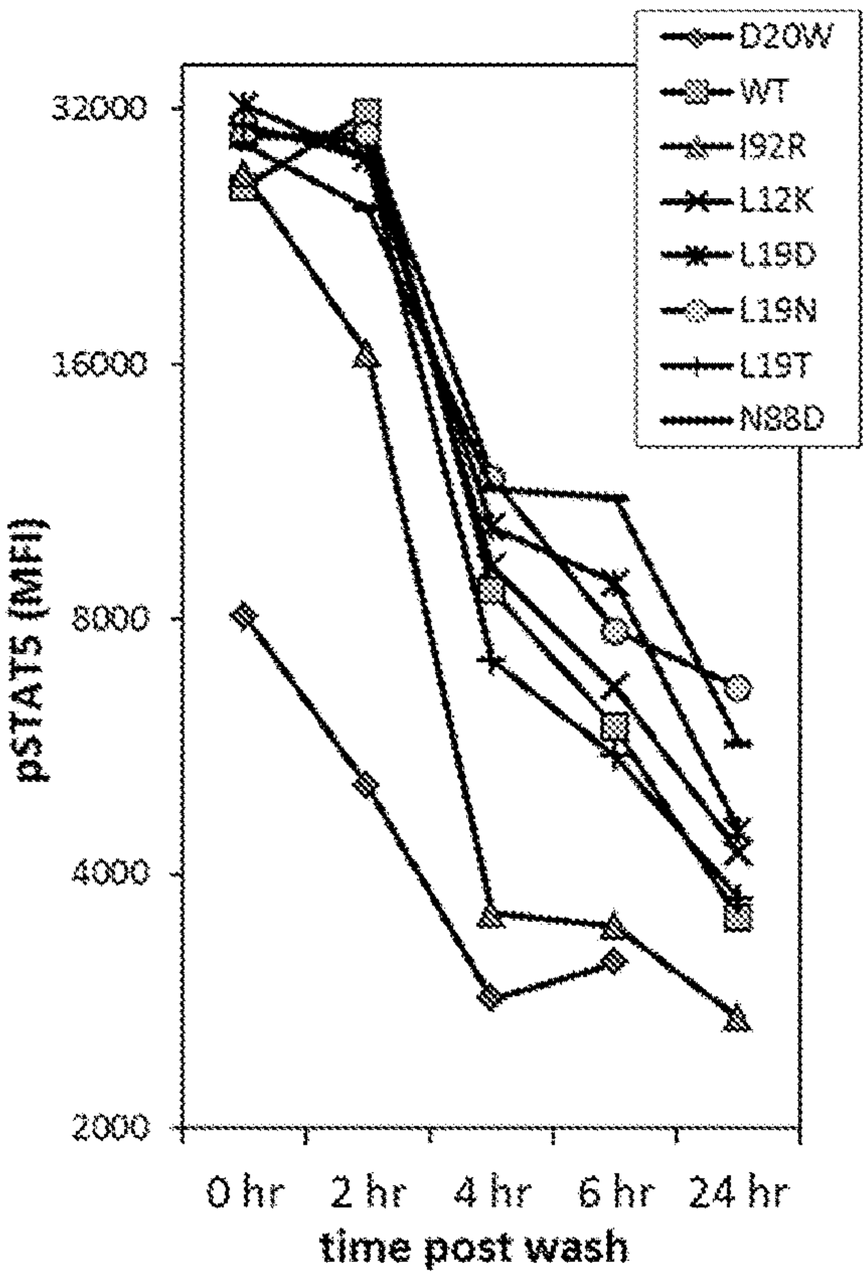
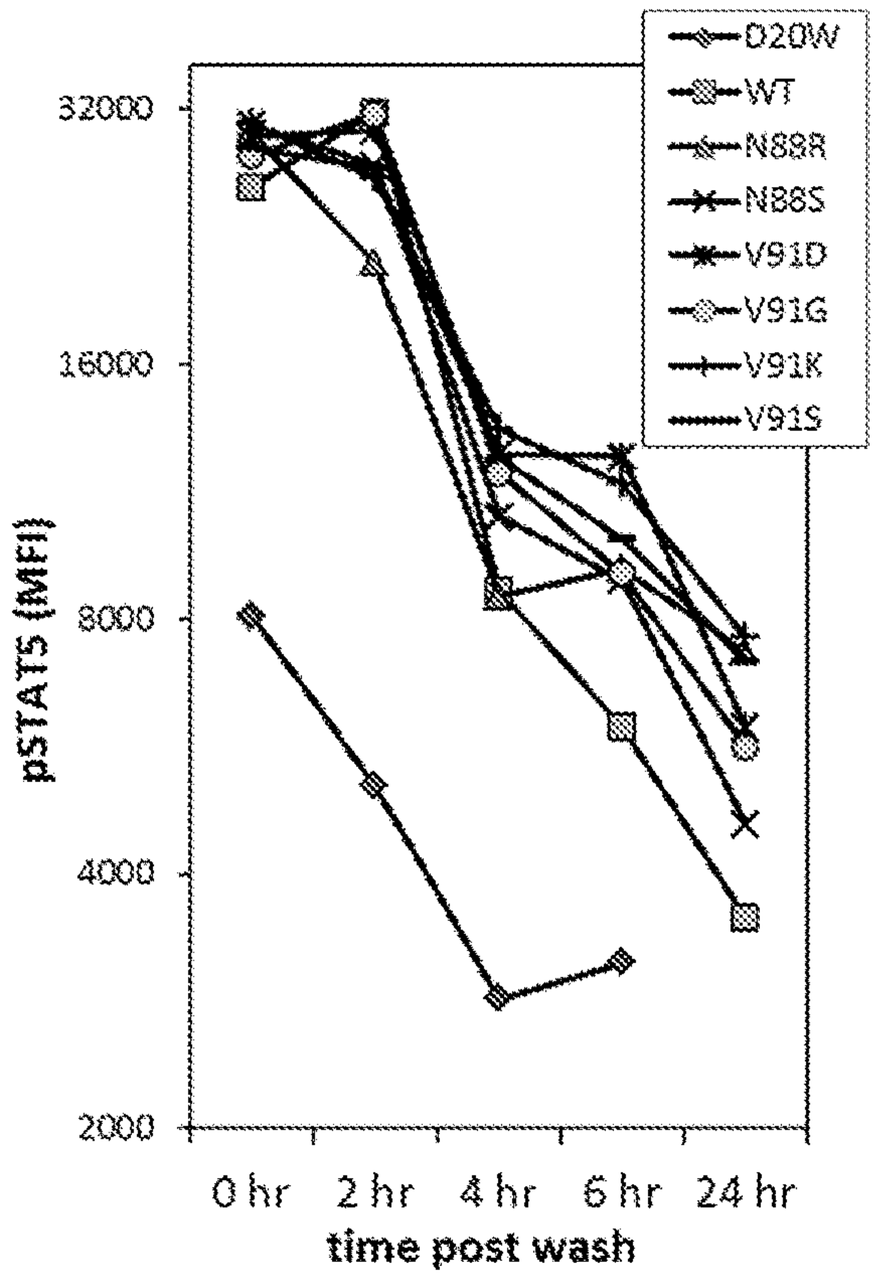


FIG. 21


D20W
WT
D20E
D20G
D84A
D84S
H16D
D20T
32000
16000
8000
4000
2000
pSTAT5 (MFI)
0 hr
2 hr
4 hr
6 hr
24 hr
time post wash


D20W
WT
H16G
H16K
H16R
H16T
H16V
I92K
32000
16000
8000
4000
2000
pSTAT5 (MFI)
0 hr
2 hr
4 hr
6 hr
24 hr
time post wash


D20W
WT
I92R
L12K
L19D
L19N
L19T
N88D
32000
16000
8000
4000
2000
pSTAT5 (MFI)
0 hr
2 hr
4 hr
6 hr
24 hr
time post wash


D20W
WT
N88R
N88S
V91D
V91G
V91K
V91S
32000
16000
8000
4000
2000
pSTAT5 (MFI)
0 hr
2 hr
4 hr
6 hr
24 hr
time post wash

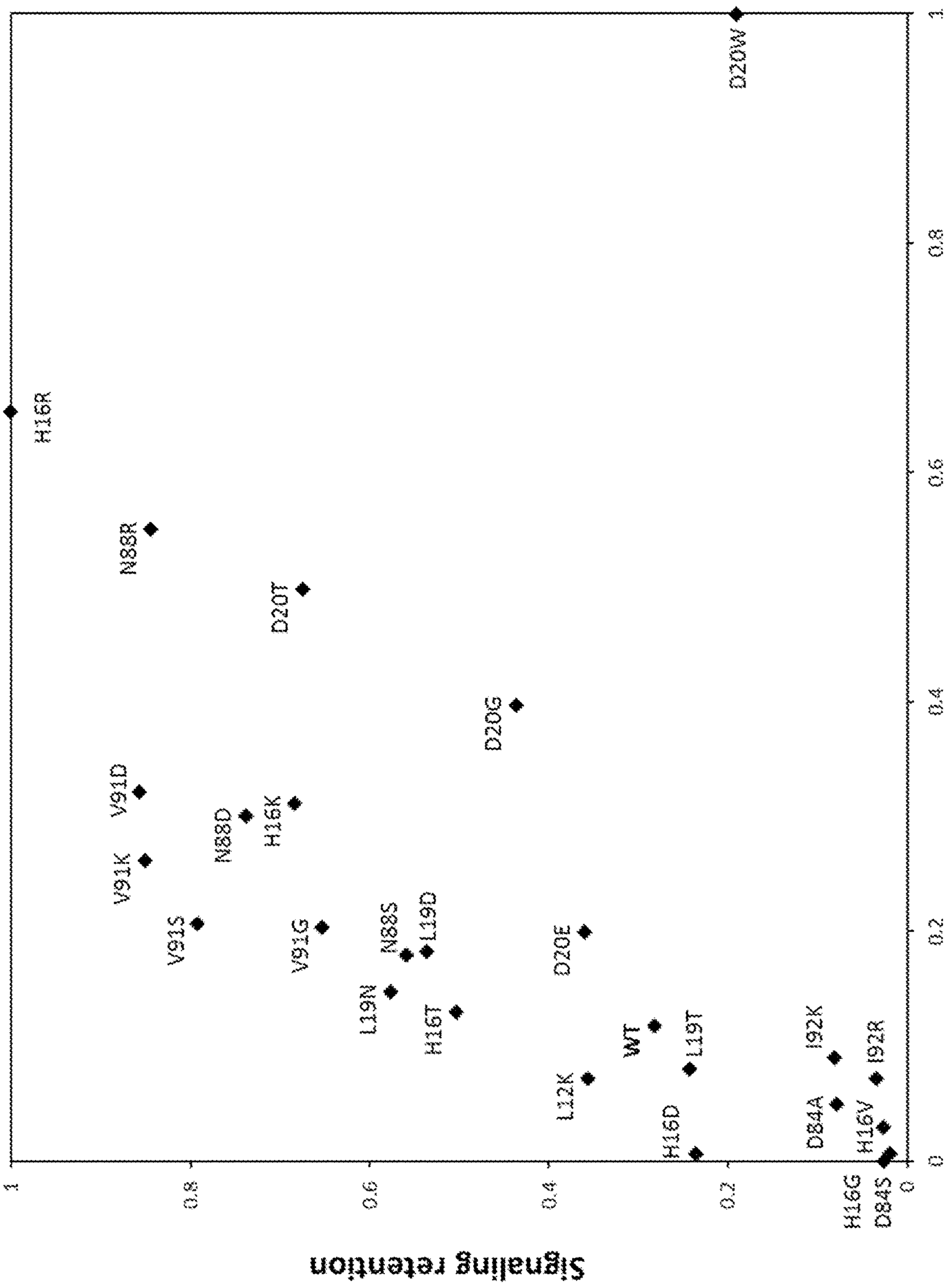

Signaling retention
Surface retention
0
0.2
0.4
0.6
0.8
1
H16R
N88R
D20T
D20G
V91D
V91K
N88D
H16K
V91S
V91G
L19N
N88S
L19D
H16T
D20E
L12K
WT
H16D
L19T
D84A
I92K
H16V
I92R
H16G
D84S

FIG. 22

FIG. 23A

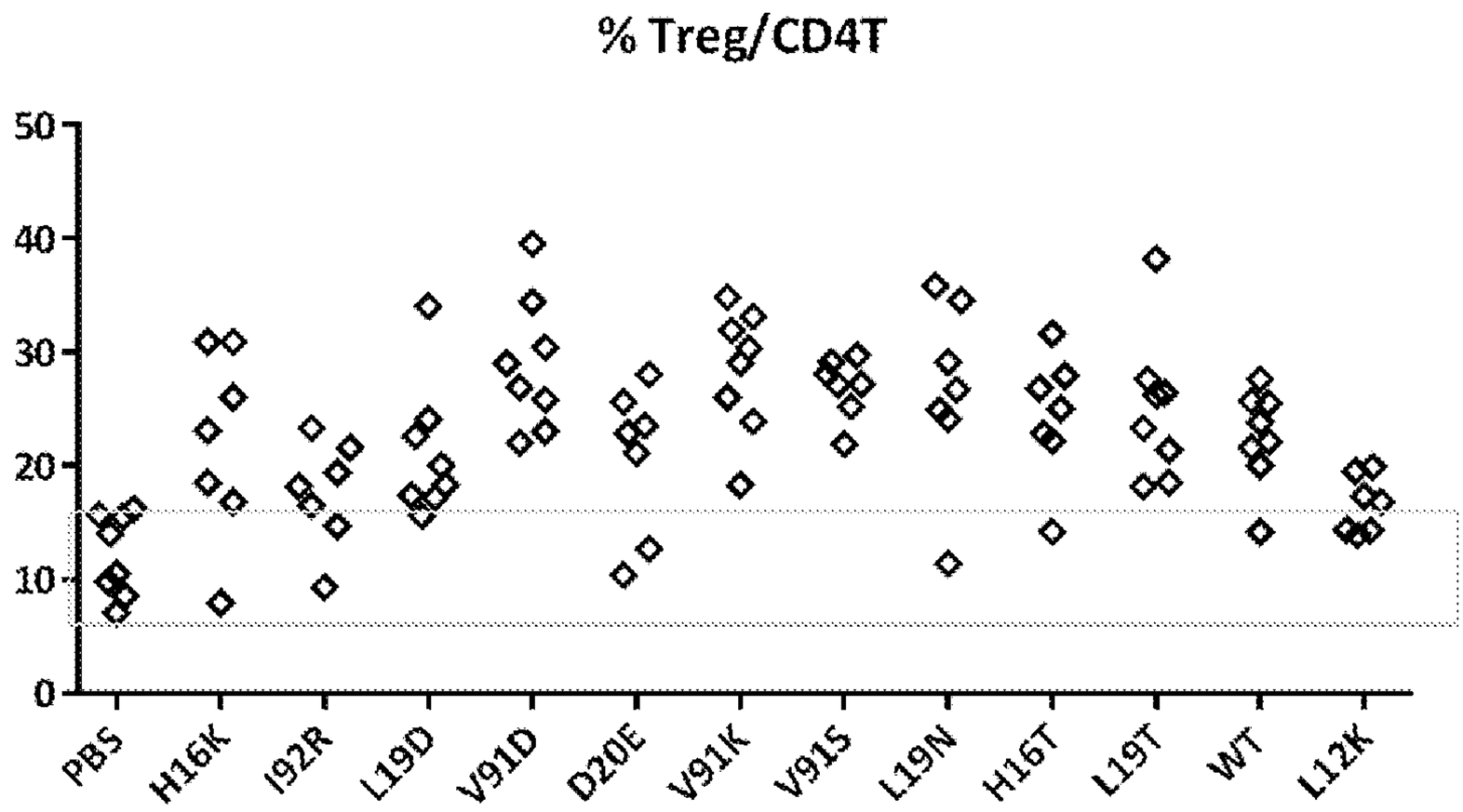


FIG. 23B

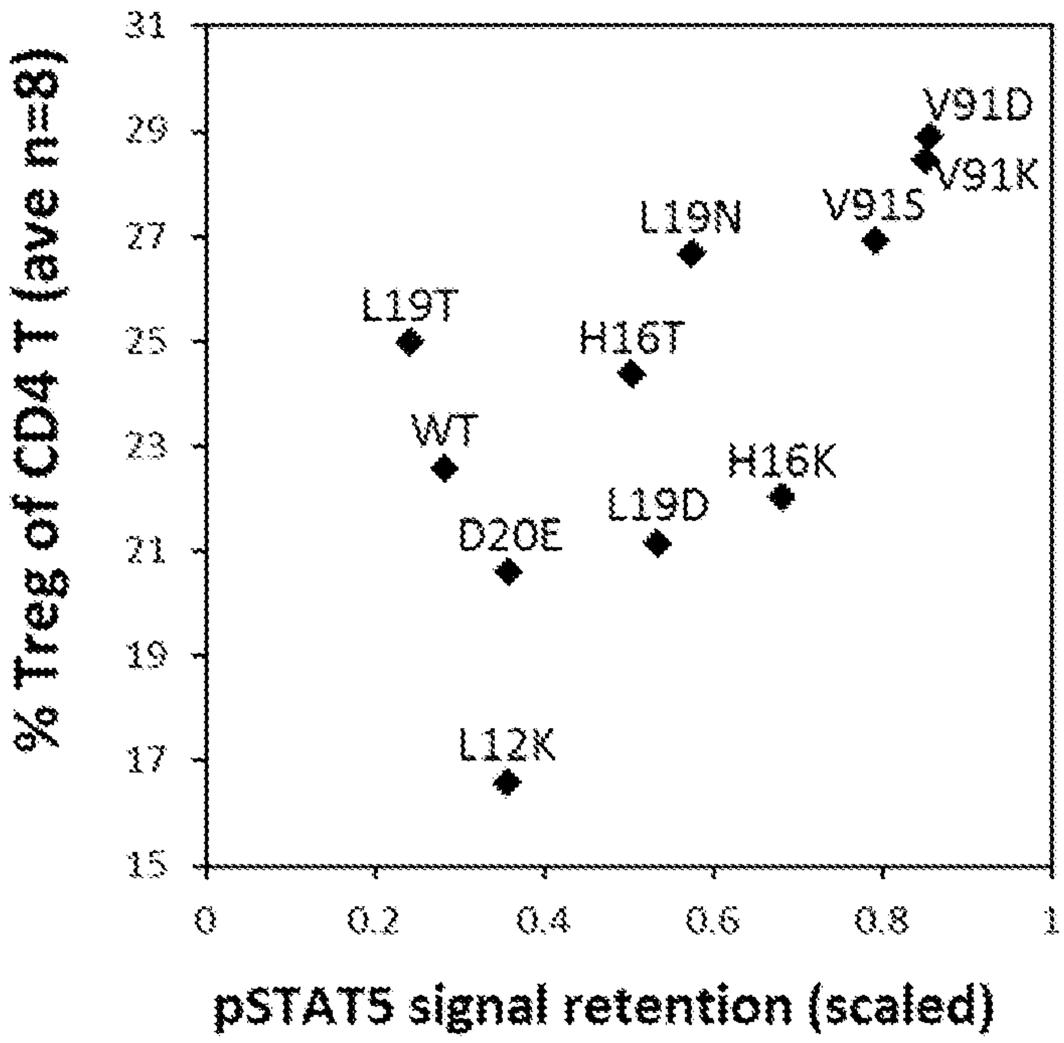


FIG. 24A Fc(N297G_delK)::G4S::IL-2(L12G, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQGQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(L12K, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQKQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(L12Q, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQQQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(L12S, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQSQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24B IgG1Fc(N297G_delK)::G4S::huIL-2(Q13G, C125A)

MDMRVPAQLLGLLLLWLRGARC *DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLGLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(E15A, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG GG
GGSAPTSSSTKKTQLQLAHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(E15G, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLGHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(E15S, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLSHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24C IgG1Fc(N297G_delK)::G4S::huIL-2(H16A, C125A)

MDMRVPAQLLGLLLLWLRGARC *DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEALLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(H16D, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG GG
GGSAPTSSSTKKTQLQLEDLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(H16G, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEGLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(H16K, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEKLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24D IgG1Fc(N297G_delK)::G4S::huIL-2(H16M, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEMLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(H16N, C125A)

MDMRVPAQLLGLLLLWLRGARC *DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLENLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(H16R, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLERLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(H16S, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLESLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24E IgG1Fc(N297G_delK)::G4S::huIL-2(H16T, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLETLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(H16V, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEVLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(H16Y, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEYLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(L19A, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLADLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24F IgG1Fc(N297G_delK)::G4S::huIL-2(L19D, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLDDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(L19E, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLEDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(L19G, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLGDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(L19N, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLNDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24G IgG1Fc(N297G_delK)::G4S::huIL-2(L19R, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLRDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(L19S, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLSDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(L19T, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLTDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(L19V, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLVDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24H IgG1Fc(N297G_delK)::G4S::huIL-2(D20A, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(D20E, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLELQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(D20F, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLFLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(D20G, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLGLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24I

IgG1Fc(N297G_delK)::G4S::huIL-2(D20W, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLWLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(M23R, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQRILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(R81A, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLAPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(R81G, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLGPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24J IgG1Fc(N297G_delK)::G4S::huIL-2(R81S, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLSPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(R81T, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLTPRDLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(D84A, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRALISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(D84E, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRELISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24K IgG1Fc(N297G_delK)::G4S::huIL-2(D84G, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRGLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(D84I, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRILISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(D84M, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRMLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(D84Q, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRQLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24L IgG1Fc(N297G_delK)::G4S::huIL-2(D84R, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRRLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(D84S, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRSLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(D84T, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRTLISNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(S87R, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLIRNINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24M IgG1Fc(N297G_delK)::G4S::huIL-2(N88A, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISAINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(N88E, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISEINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(N88F, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISFINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(N88G, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISGINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24N IgG1Fc(N297G_delK)::G4S::huIL-2(N88M, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISMINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(N88S, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISSINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(N88V, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISVINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(N88W, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISWINVIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24O IgG1Fc(N297G_delK)::G4S::huIL-2(V91D, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINDIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(V91E, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINEIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(V91G, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINGIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(V91S, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINSIVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 24P IgG1Fc(N297G_delK)::G4S::huIL-2(I92K, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVKVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(I92R, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVRVLELK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G_delK)::G4S::huIL-2(E95G, C125A)

MDMRVPAQLLGLLLLWLRGARC*DKTHTCPPCPAPELLGGPSVFLFPPKPK*
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
*DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*GG
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLGLK
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

FIG. 25A

Fc(N297G_delK)::G4S::IL-2(L12G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt
ggtggaagcgctccaacttcctcctccactaagaagactcaaGGGcaatt
ggagcacttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcacttttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(L12K, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt
ggtggaagcgctccaacttcctcctccactaagaagactcaaAAGcaatt

FIG. 25B

ggagcacttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(L12Q, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt
ggtggaagcgctccaacttcctcctccactaagaagactcaaCAGcaatt
ggagcacttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(L12S, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc

FIG. 25C

acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
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gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
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ggtggaagcgctccaacttcctcctccactaagaagactcaaTCGcaatt
ggagcacttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(Q13G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
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tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
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ggtggaagcgctccaacttcctcctccactaagaagactcaattgGGAtt
ggagcacttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

FIG. 25D

IgG1Fc(N297G_delK)::G4S::huIL-2(E15A, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
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ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
gGCGcacttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcacttttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(E15G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt
ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
gGGGcacttgttgttggacttgcaaatgatcttgaatggtatcaataatt

FIG. 25E

acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(E15S, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
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tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
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ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
gTCGcacttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(H16A, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa

FIG. 25F

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
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ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
ggagGCCttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(H16D, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
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agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
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ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
ggagGACttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

FIG. 25G

IgG1Fc(N297G_delK)::G4S::huIL-2(H16G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
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tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
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gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt
ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
ggagGGCttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(H16K, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
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acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
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tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
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gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
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tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt
ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
ggagAAGttgttgttggacttgcaaatgatcttgaatggtatcaataatt

FIG. 25H

acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcacttttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(H16M, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
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ctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
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tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
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tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
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ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
ggagATGttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcacttttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(H16N, C125A)

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gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
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gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
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FIG. 25I

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
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gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
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aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(H16R, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
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gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
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tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
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gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
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aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
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ctttgact

FIG. 25J

IgG1Fc(N297G_delK)::G4S::huIL-2(H16S, C125A)

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gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
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tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
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gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(H16T, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
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gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
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tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
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gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
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FIG. 25K

acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcacttttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(H16V, C125A)

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gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
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aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcacttttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(H16Y, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
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gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa

FIG. 25L

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
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gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
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aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(L19A, C125A)

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gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
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tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
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aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

FIG. 25M

IgG1Fc(N297G_delK)::G4S::huIL-2(L19D, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
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aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
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ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(L19E, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
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gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
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agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
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tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt
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ggagcacttgttgGAGgacttgcaaatgatcttgaatggtatcaataatt

FIG. 25N

acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcacttttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(L19G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
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gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
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IgG1Fc(N297G_delK)::G4S::huIL-2(L19N, C125A)

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gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa

FIG. 25O

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
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acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
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cgttgagttttttgaatcggtggatcacttttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(L19R, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
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ctttgact

FIG. 25P

IgG1Fc(N297G_delK)::G4S::huIL-2(L19S, C125A)

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acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
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tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
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agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
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ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
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aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
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ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(L19T, C125A)

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acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
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FIG. 25Q

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cgttgagttttgaatcggtggatcacttttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(L19V, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
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acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
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tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
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ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(D20A, C125A)

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acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
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FIG. 25R

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aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
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ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(D20E, C125A)

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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
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ctttgact

FIG. 25S

IgG1Fc(N297G_delK)::G4S::huIL-2(D20F, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(D20G, C125A)

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gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
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FIG. 25T

acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
ggttccgagactactttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(D20W, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
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ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(M23R, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
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gacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
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FIG. 25U

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
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cgttgagttttgaatcggtggatcacttttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(R81A, C125A)

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CGccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag
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FIG. 25V

IgG1Fc(N297G_delK)::G4S::huIL-2(R81G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
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IgG1Fc(N297G_delK)::G4S::huIL-2(R81S, C125A)

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FIG. 25W

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IgG1Fc(N297G_delK)::G4S::huIL-2(R81T, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(D84A, C125A)

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FIG. 25X

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IgG1Fc(N297G_delK)::G4S::huIL-2(D84E, C125A)

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FIG. 25Y

IgG1Fc(N297G_delK)::G4S::huIL-2(D84G, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(D84I, C125A)

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FIG. 25Z

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IgG1Fc(N297G_delK)::G4S::huIL-2(D84M, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(D84Q, C125A)

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FIG. 25AA

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IgG1Fc(N297G_delK)::G4S::huIL-2(D84R, C125A)

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FIG. 25BB

IgG1Fc(N297G_delK)::G4S::huIL-2(D84S, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(D84T, C125A)

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FIG. 25CC

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IgG1Fc(N297G_delK)::G4S::huIL-2(S87R, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(N88A, C125A)

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FIG. 25DD

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IgG1Fc(N297G_delK)::G4S::huIL-2(N88E, C125A)

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FIG. 25EE

IgG1Fc(N297G_delK)::G4S::huIL-2(N88F, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(N88G, C125A)

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FIG. 25FF

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IgG1Fc(N297G_delK)::G4S::huIL-2(N88M, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(N88S, C125A)

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FIG. 25GG

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IgG1Fc(N297G_delK)::G4S::huIL-2(N88V, C125A)

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FIG. 25HH

IgG1Fc(N297G_delK)::G4S::huIL-2(N88W, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(V91D, C125A)

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FIG. 25II

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IgG1Fc(N297G_delK)::G4S::huIL-2(V91E, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(V91G, C125A)

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FIG. 25JJ

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IgG1Fc(N297G_delK)::G4S::huIL-2(V91S, C125A)

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FIG. 25KK

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IgG1Fc(N297G_delK)::G4S::huIL-2(I92K, C125A)

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IgG1Fc(N297G_delK)::G4S::huIL-2(I92R, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg

FIG. 25LL

gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt
ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
ggagcacttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgAGAgttttggagttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

IgG1Fc(N297G_delK)::G4S::huIL-2(E95G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac
ctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaag
gacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtgga
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg
gactccgacggctccttcttcctctatagcaagctcaccgtggacaagag
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt
ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt
ggagcacttgttgttggacttgcaaatgatcttgaatggtatcaataatt
acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc
ggccacgggacttgatctccaatatcaatgtgatcgttttgGGGttgaag
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat
cgttgagttttgaatcggtggatcactttgctcaatccatcatctcca
ctttgact

FIG. 26 Light Chain Variable Domain Amino Acid Sequences

	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
9D6	DIVMTQTPLSLPVTPGEPASISC	RSSQSLLDSDEGNTYLD	WYLQKPGQSPQLLIY	TLSYRAS	GVPDRFSGTGSDTDFTLKISRVEAEDVGVYYC	MQRIEFPLT	FGGGTKVEIKR
2C3	EIVLTQSPGTLSLSPGERATLSC	RASQSFSSSYLV	WYQQKPGQAPRLLIY	GASSRAT	GIPDRFGGSGSGTDFTLTISRLEPEDFAVYYC	QQYGSSPLT	FGGGTKVEIKR
14C9	DIVLTQTPLSSPVTLGQPASISC	RSSHHLIHSDGNTYLS	WLQQRPGQPPRLLIY	KISNRFS	GVPDRFTGSGTGTDFTLKISRVEAGDVGVYYC	MQTTQFPT	FGQGTKVEIKR
8B12	DIVMTQTPLSSPVTLGQPASISC	RSSQNLVQSDGNTYLS	WLHQRPGQPPRLLIY	KISNRFS	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYFC	MQTTQFPT	FGQGTKVEIKR
16A4	DIVMTQTPLSSPVTLGQPASISC	RSSQILVNSDGNTYLS	WLHQRPGQPPRLLIY	KISNRFS	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC	MQTTQFPT	FGQGTKVEIKR
16E1	DIVMTQTPLSSPVTLGQPASISC	RSSQSLVRSDGNTYLS	WLHQRPGQPPRLLIY	KISNRFS	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC	MQTTQFPT	FGQGTKVEIKR
13A1	DIVMTQTPLSSPVTLGQPASISC	RSSHSLVHSDGHTYLS	WLQQRPGQPPRLLLY	KISNRFS	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC	MQTTQFPT	FGGGTKVEIKR
8F10	DIAMSQSPLSLPVTPGEPASMSC	RSSQSLLHSNGFNYLD	WYLQKPGQSPQVLIH	LGSDRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGIYYC	MQALQTPLT	FGGGTKVEIKR
12C4	DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGFNYLD	WFLQKPGQSPQPLIY	LGSDRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLT	FGGGTKVEIKR
9B12	DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGFNYLD	WYLQKPGQSPQLLIY	LGSDRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLT	FGGGTKVEIKR
3H5	DIVMTQTPLSSPVTLGQPASISC	RSSQSLVNIDGSTHLS	WLQQRPGQPPRLLIY	KISNRFS	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC	MQTTQFPT	FGQGTRLEIKR
18A6	EIVMTQTPLSSPVTLGQPASISC	RSSQSLVQSDGITYLS	WLQQRPGQPPRLLIY	KISNRFS	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC	MQTTQFPT	FGQGTKVEIKR
10A6	DIVMTQTPLSSPVTLGQPASISC	RSSQSLVNSDGNTYLN	WLQQRPGQPPRLLIY	KISNRFS	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC	MQATQFPT	FGQGTKVEIKR
10H7	DIVMTQTPLSSPVTLGQPASISC	RSSHNLVRSDGNTYLS	WLQQRPGQPPRLLIY	KISNRFS	GVPDRFSGSGAGTDFTLKISRVGAEDVGVYYC	MQATQFPT	FGQGTRLEIKR
15A10	NIVMTQTPLSSPVTLGQPASISC	RSSQSLVQTDGNTYLS	WLQQRPGQPPRPLIY	KISNRFS	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC	MQVTQFPT	FGQGTRLEIKR
12D2	DIVMTQTPLSSPVTLGQPASISC	RSSHNLIHSDGNTYLS	WLHQRPGQPPRLLIY	KISNRFS	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC	MQTSQFPT	FGGGTKVEIKR
9B10	DIVMTQTPLSSPVTLGQPASISC	RSSHNLLHSDGNTYLS	WLQQRPGQPPRLLIY	EISNRFS	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC	MQVTQFPT	FGGGTKVEIKR
17D3	EIVLTQSPGTLSLSPGERATLSC	RASQSVSSSYLA	WYQQKPGQAPRLLIY	GASSRAT	GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC	QQYGSSPLT	FGGGTKVEIKR
15G11	EIVLTQSPGTLSLSPGERATLSC	RASQSVSSRYLA	WYQQKPGQAPRLLIH	GPFSRAT	GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC	QQYGNSSIT	FGQGTRLEIKR
14D7	DIQMTQSPSSLSASVGDRVTITC	RASQTISSYLN	WYQQKPGKAPKVLIY	AASSFQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQSHYIPRT	FGQGTKVEIKR
18F3	SYELTQPPSVSVSPGQTARIAC	SGDALPRKFAY	WYQQKSGQAPVLVIS	EDSRRPS	GIPERFSGSSSGTMATLTISGAQVEDEADYYC	FSTDSSANHRV	FGGGTKLTVLG
17D9	DIQMTQSPSSLSASVGDRVTITC	RASQDIRNDLG	WYQQKPGKAPKRLIY	AASSLQS	GVPSRFSGSGSGTEFTLTIGSLQPEDFTTYYC	LQHNSYPLT	FGGGTKVEIKR
21F8	DIQMTQSPSSLSASVGDRVTITC	RASQGIRDDLG	WYQQKPGKAPKRLIY	IATSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHISYPWT	FGQGTKVEIKR
22B9	DIQMTQSPSSLSASVGDRVTITC	RASQDIRDDLG	WYQQKPGKAPKRLIY	VASSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHISYPWT	FGQGTKVEIKR
21D10	DIQMTQSPSSLSASVGDRVTITC	RASQDIRDDLG	WYQQKPGKAPKRLIY	VVSSLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNGYPWT	FGQGTKVEIKR
14A6	DIQMTQSPSSLSASVGDRVTITC	RASQGIGDDLG	WYQQKPGKAPQRLIY	SASSLPS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSYPRS	FGQGTKLEIRR
11D6	DIQMTQSPSSLSASVGDRVTITC	RASQDIEHDLG	WYQQKPGKAPKRLIY	AASTLPS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	LQHNSFPRS	FGQGTQLEIKR
10A9	DIVMTQTPLSLPVTPGEPASISC	RSTQSLLDGDDGNTLLD	WYLQKPGQSPQLLIY	TLSYRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQRLEFPLT	FGGGTKVEIKR
16E3	DIVMTQTPLSLPVTPGEPASISC	RSSQSLLDSDEGNTFLD	WYLQKPGQPPQLLIY	TLSYRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQRIEFPLT	FGGGTKVEIKR
14G7	DIQMTQSPSSLSASVGDRVTITC	QASQDISNYLN	WYQQKPGKAPKLLIY	DASNLET	GVPSRFSGSGSETDFTFTISSLQPEDIATYYC	QQYENLPFT	FGPGTKVDIKR
5H3	SYELTQPPSVSVSPGQTARITC	SGDALPRQYAY	WYQQKPGQAPMLVIY	KDSERPS	GIPERFSGSSSGTTVTLTISGVQAEDEADYYC	QSADSSGTYVV	FGGGTKLTVLG
2B12	SYELTQPPSVSVSPGQTARITC	SGDALPRKYAY	WYQQKSGQAPVLVIY	EDSKRPS	GIPERFSGSSSGTMATLTISGAQVEDEADYYC	YSTDSSGNHYV	FGTGTKVTVLG
26H7	DIQMTQSPSSLSASVGDRVTITC	QASQDISNYLN	WYQQKPGKAPKFLIY	DASNLET	GVPSRFSGSGSGTDFFFTISNLQPEDIATYFC	QQDDNLPFT	FGPGTKVDIKR
26C12	DIQMTQSPSSLSASVGDRVTITC	QASQDISNYLN	WYQQKPGKAPKLLIY	DASNLET	GVPSRFSGSGSGTDFTFTISSLQPEDIATFYC	QQYDNLPFT	FGPGTKVDIKR
2H11	SYELTQPPSVSVSPGQTARITC	SGDALPRKFAY	WYQQKSGQAPVLVIY	EDRKRPS	GIPERFSGSSSGTMATLTISGAQVEDEADYYC	YSTDRSGDHVV	FGGGTKLTVLG
18H9	DIQMTQSPSSVSASVGDRVTITC	RASQGISNWLV	WYQQKPGKPPKLLIY	AASSLQN	GVPSRFSGSGSGTDFTLTISSLQTEDFATYYC	QQALSFPWT	FGPGTKVEVKR

FIG. 27A

Light Chain Nucleic Acid Sequences

9D6

GATATTGTGATGACCCAGACTCCACTCTCCTTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAGAGCCTCTTAGATAGTGATGAGGGAAACACCTATTTGGACTGGTACCTGCAGAAGCCAGGGCAGTCTCCACA
GCTCCTGATCTATACGCTTTCCTATCGGGCCTCTGGAGTCCCAGACAGGTTCAGTGGCACTGGGTCAGACACTGAT
TTCACACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGAGTTTATTACTGCATGCAACGTATAGAGTTTCCTC
TCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

2C3

GAAATTGTATTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCA
GTCAGAGTTTTAGCAGCAGCTACTTAGTCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGG
TGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTCGGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCAT
CAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTAGCTCACCTCTCACTTTCGGCGGA
GGGACCAAGGTGGAGATCAAACGA

14C9

GATATTGTGCTGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCATCACCTCATACACAGTGATGGAAACACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACTC
CTAATTTATAAGATTTCTAACCGGTTCTCTGGGGTCCCAGACAGATTCACTGGCAGTGGGACAGGGACAGATTTCA
CACTGAAAATCAGCAGGGTGGAAGCTGGGGATGTCGGGGTTTATTACTGCATGCAAACTACACAATTTCCGACGT
TCGGCCAAGGGACCAAGGTGGAAATCAAACGA

8B12

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCCAG
TCAAAACCTCGTTCAAAGTGATGGAAACACCTACTTGAGTTGGCTTCACCAGAGGCCAGGCCAGCCTCCAAGACTC
CTAATTTATAAGATTTCTAACCGGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA
CACTGAAAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTTCTGCATGCAAACTACACAATTTCCGACGTT
CGGCCAAGGGACCAAGGTGGAAATCAAACGA

FIG. 27B

16A4

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATTTCCTGCAGGTCTAG
TCAAATCCTCGTAAACAGTGATGGAAACACCTACTTGAGTTGGCTTCACCAGAGGCCAGGCCAGCCTCCAAGACTC
CTAATTTATAAGATTTCTAACCGGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA
CACTGAAAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACTACACAATTTCCGACGT
TCGGCCAAGGGACCAAGGTGGAAATCAAACGA

16E1

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAAAGCCTCGTACGCAGTGATGGAAACACCTACTTGAGTTGGCTTCACCAGAGGCCAGGCCAGCCTCCAAGACT
CCTAATTTATAAGATTTCTAACCGGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTC
ACACTGAAAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACTACACAATTTCCGACG
TTCGGCCAAGGGACCAAGGTGGAAATCAAACGA

13A1

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCACAGCCTCGTACACAGTGATGGACACACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACTC
CTACTTTATAAGATTTCTAACCGGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA
CACTGAAAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACTACACAATTTCCCACTTT
CGGCGGAGGGACCAAGGTGGAGATCAAACGA

8F10

GATATTGCGATGAGTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATGTCATGCAGGTCTA
GTCAGAGCCTCCTGCATAGTAATGGATTCAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGGT
CCTGATCCATTTGGGTTCTGATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTT
ACATTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGAATTTATTACTGCATGCAAGCTCTACAAACTCCTCTCA
CTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

FIG. 27C

12C4

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAGAGCCTCCTACATAGTAATGGATTCAACTATTTGGATTGGTTCCTGCAGAAGCCAGGACAGTCTCCACAGCCC
CTGATCTATTTGGGTTCTGATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTA
CACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAAACTCCGCTCA
CTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

9B12

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAGAGCCTCCTGCATAGTAATGGATTCAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTC
CTGATCTATTTGGGTTCTGATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTA
CACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAAACTCCGCTCA
CTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

3H5

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATATCCTGCAGGTCCAG
TCAAAGCCTCGTAAACATTGATGGAAGTACCCACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACT
CCTAATTTATAAGATTTCTAACCGGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTC
ACACTGAAGATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACTACACAATTCCCCACC
TTCGGCCAAGGGACACGACTGGAGATTAAACGA

18A6

GAAATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATTTCCTGCAGGTCTAG
TCAAAGCCTCGTTCAGAGTGATGGAATCACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACTC
CTAATTTATAAGATTTCTAACCGGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA
CACTGAAAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACTACACAATTTCCGACGT
TCGGCCAAGGGACCAAGGTGGAAATCAAACGA

FIG. 27D

10A6

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAAAGCCTCGTAAACAGTGATGGAAACACCTACTTGAATTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACT
CCTAATTTATAAGATTTCTAACCGGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTC
ACACTGAAAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAGCTACACAATTTCCGACG
TTCGGCCAAGGGACCAAGGTGGAAATCAAACGA

10H7

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCCAG
TCACAACCTCGTACGCAGTGATGGAAACACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACT
CCTAATTTATAAGATTTCTAACCGGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTC
ACACTGAAAATCAGCAGGGTGGGAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAGCTACACAATTTCCCACC
TTCGGCCAAGGGACGCGACTGGAGATTAAACGA

15A10

AATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAAAGCCTCGTACAAACTGATGGAAACACATATTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACC
CCTAATTTATAAGATTTCTAACCGGTTTTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTC
ACACTGAAAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAGTAACACAATTTCCCACC
TTCGGCCAAGGGACACGACTGGAGATTAAACGA

12D2

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGTAGGTCTAG
TCATAACCTCATACACAGTGATGGAAACACCTACTTGAGTTGGCTTCACCAGAGGCCAGGCCAGCCTCCAAGACTC
CTAATTTATAAGATTTCTAACCGGTTCTCTGGGGTCCCGGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA
CACTGAAAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACTTCACAGTTTCCCACTTT
CGGCGGAGGGACCAAGGTGGAGATCAAACGA

FIG. 27E

9B10

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCATAACCTCCTACACAGTGATGGAAACACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACTC
CTAATTTATGAGATTTCTAACCGGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA
CACTGAAAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAGTTACACAATTTCCCACTTT
CGGCGGCGGGACCAAGGTGGAGATCAAACGA

17D3

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCA
GTCAGAGTGTTAGCAGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGG
TGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCAT
CAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTAGCTCACCGCTCACTTTCGGCGGA
GGGACCAAGGTGGAGATCAAACGA

15G11

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGTAGGGCCA
GTCAGAGTGTTAGCAGCAGGTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCCATG
GTCCATTCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCAT
CAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTAATTCATCGATCACCTTCGGCCAA
GGGACACGACTGGAGATTAAACGA

14D7

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA
GTCAGACCATTAGCAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGGTCCTGATCTATGCTGC
ATCCAGTTTCCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTCACTATATCCCTCGGACGTTCGGCCAAGGGA
CCAAGGTGGAAATCAAACGA

FIG. 27F

18F3

TCCTATGAGCTGACACAGCCACCCTCGGTGTCAGTGTCCCCAGGACAAACGGCCAGGATCGCCTGCTCTGGAGAT
GCATTGCCAAGAAAATTTGCTTATTGGTACCAGCAGAAGTCAGGCCAGGCCCCTGTGCTGGTCATCTCTGAGGACA
GCAGACGACCCTCCGGGATCCCTGAGAGATTCTCTGGCTCCAGCTCAGGGACAATGGCCACCTTGACTATCAGTG
GGGCCCAGGTGGAGGATGAAGCTGACTACTACTGTTTCTCAACAGACAGCAGTGCTAATCATAGGGTATTCGGCG
GAGGGACCAAGCTGACCGTCCTAGGT

17D9

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA
GTCAGGACATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTG
CATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAATCG
GCAGCCTGCAGCCTGAAGATTTTACAACTTATTACTGTCTACAGCATAATAGTTACCCGCTCACTTTCGGCGGAGG
GACCAAGGTGGAGATCAAACGA

21F8

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA
GTCAGGGCATTAGAGATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATATTG
CAACCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAATCA
GCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATATTAGTTACCCGTGGACGTTCGGCCAAGG
GACCAAGGTGGAAATCAAACGA

22B9

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA
GTCAGGACATCAGAGATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGTTG
CATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAATCA
GCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATATTAGTTACCCGTGGACGTTCGGCCAAGG
GACCAAGGTGGAAATCAAACGA

FIG. 27G

21D10

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA
GTCAGGACATTAGAGATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGTTG
TATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACAATCA
GCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATAATGGTTACCCGTGGACGTTCGGCCAAGG
GACCAAGGTGGAAATCAAACGA

14A6

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA
GTCAGGGCATTGGAGATGATTTAGGCTGGTATCAGCAGAAGCCAGGAAAAGCCCCTCAGCGCCTGATCTATTCTG
CATCCAGTTTGCCAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAATCA
GCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCTCGCAGTTTTGGCCAGGG
GACCAAGCTGGAGATCAGACGA

11D6

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA
GTCAGGACATTGAACATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTG
CATCCACTTTGCCAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAATCAG
CAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTTCCCTCGCAGTTTTGGCCAGGGGA
CCCAGCTGGAGATCAAACGA

10A9

GATATTGTGATGACCCAGACTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAC
TCAGAGCCTCTTGGATGGTGATGATGGAAACACCCTTTTGGACTGGTACCTGCAGAAGCCAGGGCAGTCTCCACA
GCTCCTGATCTATACGCTTTCCTATCGGGCCTCTGGAGTCCCAGACAGGTTCAGTGGCAGTGGGTCAGGCACTGAT
TTCACACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGAGTTTATTACTGCATGCAACGTTTAGAGTTTCCTC
TCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

FIG. 27H

16E3

GACATTGTGATGACCCAGACTCCACTCTCCTTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAGAGCCTCTTGGATAGTGATGAAGGAAACACCTTTTTGGATTGGTACCTGCAGAAGCCAGGGCAGCCTCCACA
GCTCCTGATCTATACGCTTTCCTATCGGGCCTCTGGAGTCCCAGACAGGTTCAGTGGCAGTGGGTCAGGCACTGAT
TTCACACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGAGTTTATTACTGCATGCAACGTATAGAGTTTCCTC
TCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

14G7

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCGA
GTCAGGACATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTACGATGC
ATCCAATTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGAGACAGATTTTACTTTCACCATCAGC
AGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAACAGTATGAAAATCTCCCATTCACTTTCGGCCCTGGGAC
CAAAGTGGATATCAAACGA

5H3

TCCTATGAGCTGACACAGCCACCCTCGGTGTCAGTGTCCCCAGGACAGACGGCCAGGATCACCTGCTCTGGAGAT
GCATTGCCAAGGCAATATGCTTATTGGTACCAGCAGAAGCCAGGCCAGGCCCCTATGCTGGTGATATATAAAGAC
AGTGAGAGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAGCTCAGGGACAACAGTCACGTTGACCATCAGT
GGAGTCCAGGCAGAAGACGAGGCTGACTATTACTGTCAATCAGCAGACAGCAGTGGTACTTATGTGGTATTCGGC
GGAGGGACCAAGCTGACCGTCCTAGGT

2B12

TCCTATGAGCTGACACAGCCACCCTCGGTGTCAGTGTCCCCAGGACAAACGGCCAGGATCACCTGCTCTGGAGAT
GCATTGCCAAGAAAATATGCTTATTGGTACCAGCAGAAGTCAGGCCAGGCCCCTGTGCTGGTCATCTATGAGGAC
AGCAAACGACCCTCCGGGATCCCTGAGAGATTCTCTGGCTCCAGCTCAGGGACAATGGCCACCTTGACTATCAGTG
GGGCCCAGGTGGAGGACGAAGCTGACTACTACTGTTACTCAACAGACAGCAGTGGTAATCATTATGTCTTCGGAA
CTGGGACCAAGGTCACCGTCCTAGGT

FIG. 27I

26H7

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCGA
GTCAGGACATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGTTCCTGATCTACGATGC
ATCCAATTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAGATTTTTTTTCACCATCAGC
AACCTGCAGCCTGAAGATATTGCAACATATTTCTGTCAACAGGATGATAATCTCCCATTCACTTTCGGCCCTGGGAC
CAAAGTGGATATCAAACGA

26C12

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCGA
GTCAGGACATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAACTCCTGATCTACGATGC
ATCCAATTTGGAAACAGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTCACCATCAGC
AGCCTGCAGCCTGAAGATATTGCAACATTTTACTGTCAACAGTATGATAATCTCCCATTCACTTTCGGCCCTGGGAC
CAAAGTGGATATCAAACGA

2H11

TCCTATGAGCTGACACAGCCACCCTCGGTGTCAGTGTCCCCAGGACAAACGGCCAGGATCACCTGCTCTGGAGAT
GCATTGCCAAGAAAATTTGCTTATTGGTACCAGCAGAAGTCAGGCCAGGCCCCTGTGCTGGTCATCTATGAGGAC
AGGAAACGACCCTCCGGGATCCCTGAGAGATTCTCTGGCTCCAGCTCAGGGACAATGGCCACCTTGACTATCAGT
GGGGCCCAGGTGGAGGATGAAGCTGACTACTACTGTTACTCAACAGACCGCAGTGGTGATCATGTGGTATTCGGC
GGAGGGACCAAGCTGACCGTCCTAGGT

18H9

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCGGGCGA
GTCAGGGTATTAGCAACTGGTTAGTCTGGTATCAGCAGAAACCAGGGAAACCCCCTAAACTCCTGATCTATGCTGC
ATCCAGTTTGCAAAATGGGGTCCCATCAAGATTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGACTGAAGATTTTGCAACTTACTATTGTCAACAGGCTCTCAGTTTCCCGTGGACGTTCGGCCCAGGGA
CCAAGGTGGAAGTCAAACGA

FIG. 28 Heavy Chain Variable Domain Amino Acid Sequences

	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
9D6	EVQLVQSGAEVKKPGESLKISCKGSGYRFT	SYWIG	WVRQMPGKGLEWMG	IIHPGDSDTRYSPSFQG	QVTISADKSISTAYLQWSSLKASDTAIYYCTR	QGRSFYYYGMDV	WGQGTTVTVSS
2C3	EVQLVQSGAEVKKPGESLKISCKGSGYRFT	SYWIG	WVRQMPGKGLEWMG	IIYPGDSDTRYSPSFQG	QVTISADKSISAAYLQWSSLKASDTAMYYCAR	QQVAGMLDY	WGQGTLVTVSS
14C9	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	IYGMH	WVRQAPGKGLEWVT	VIWYDGSNEYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EDFDSHYGMDV	WGQGTTVTVSS
8B12	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYGMH	WVRQAPGKGLEWVA	VIWYDGSNEYYADSVKG	RFTISRDNSKNTLYLQMHSLRAEDTAVYYCAR	EEWFGEADYGMDV	WGQGTTVTVSS
16A4	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYGMH	WVRQAPGKGLEWVA	VIWYDGSNEYYADSVKG	RFTISRDNSKNTLFLQMNSLRAEDTAVYYCAR	DDWFGEADYGMDV	WGQGTTVTVSS
16E1	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	NYGMH	WVRQAPGKGLEWVT	VIWNDGSNEYYADSVKG	RFTISRDNSKNTLFLQMNSLRAEDTAVYYCAR	EDWLGEADYGMDV	WGQGTTVTVSS
13A1	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EEWELEDYGMDV	WGQGTTVTVSS
8F10	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYGMY	WVRQAPGKGLEWVA	VIWYDGSNKYYVDSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GAVAGTGRDYYYYGMDV	WGQGTTVTVSS
12C4	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYGMY	WVRQAPGKGLEWVA	VIWYDGSNKYHGDSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	GAVAGTGRDYYYYGMDV	WGQGTTVTVSS
9B12	QVQLVESGGGVVQPGRSQRLSCAASGFTFS	SYGMY	WVRQAPGKGLEWVA	VIWYDGSNKNYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYHCAK	GTVAGTGRDYYYYGMDV	WGQGTTVTVSS
3H5	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SFGMH	WVRQAPGKGLEWVA	VIWFDGSNKYYVDSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DDFWSDYPFDY	WGQGTLVTVSS
18A6	QVQLVESGGGVVQPGRSLRLSCAASGFTFR	SYGMH	WVRQAPGKGLEWVA	VISDDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRPEDTAVYYCAR	DLYSSAWPFDY	WGQGTLVTVSS
10A6	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYDIH	WVRQAPGKGLEWVA	VIWNDGSIKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DGEQWRGFDY	WGQGTLVTVSS
10H7	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYDIH	WVRQAPGKGLEWVA	VIWYDGSIKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DQEQWLAFDY	WGQGTLVTVSS
15A10	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	TYGMH	WVRQAPDMGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDISKNTLYLEMNSLRAEDTAVYYCAR	DNWGSDAFDI	WGQGTMVTVSS
12D2	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	TYAMH	WVRQAPGKGLEWVA	VIWYDGINKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GSYYDSSGYYYGEDFDY	WGQGTLVTVSS
9B10	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYAMH	WVRQAPGKGLEWVA	VIWYDGINKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GSYYDSSGYYFGEDFDY	WGQGTLVTVSS
17D3	QVQLVESGGGLVKPGGSLRLSCAASGFTFS	DYYMS	WIRQAPGKGLEWVS	YISSSGSIIFYADSVKG	RFTMSRDNAKNSLYLQMNSLRAEDTAVYYCVR	RISITPFDY	WGQGTLVTVSS
15G11	QVTLKESGPVLVKPTETLTLTCTVSGFSLS	NARMGVS	WIRQPPGKALEWLA	HIFSNDEKSYSTSLKS	RLTISKDTSKSQVVLTMTNMDPVDTATYYCVR	IPRWLQPPYYYYGMDV	WGQGTTVTVSS
14D7	QVQLQESGPGLVKPSQTLSLTCTVSGGSIS	SGGYYWN	WIRQHPGKGLEWIG	YIYYSGNTHYNPSLKS	RVTISVDTSKNQFSLKLSSVIAADTAVYYCAR	DWGRDAFDI	WGQGTMVTVSS
18F3	QVQLQESGPGLVKPSQTLSLTCTVSGGSIS	SGGYYWS	WIRQHPGKGLEWIG	YIYYSGSTDYNPSLKS	RGIISGDTSKNQFSLKLNSVTAADTAVYYCAR	EGRFGELGSYYFDY	WGQGTLVTVSS
17D9	QVQLQESGPGLVKPSETLSLTCTVSGGSVS	SGGYYWS	WIRQPPGKGLEWIG	NTYYSGSTNYKPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCGR	DRGRAVGPFDY	WGQGTLVTVSS
21F8	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	NYDIN	WVRQATGQGLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	SRQWLVLDY	WGQGTLVTVSS
22B9	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	NYDIN	WVRQATGQGLEWMG	WMNPNSGNTGYVQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	SRQWLVLDY	WGQGTLVTVSS
21D10	QVQLVQSGAEVKKPGASVKVSCKASGYRFT	SYDIN	WVRQATGQGLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	SRQWLVLDY	WGQGTLVTVSS
14A6	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	TYDIN	WVRQATGQGLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	GRQWLGFDY	WGQGTLVTVSS
11D6	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	NYDIN	WVRQATGQGLEWMG	WMNPNSGNTGYAQKFQG	RVTMTRNTSINTAYMELSSLRSEDTAVYYCAR	GRQWLGFDY	WGQGTLVTVSS
10A9	EVQLVQSGAEVKKPGESLKISCKGSGYSFT	SQWIG	WVRQMPGKGLEWMG	IIFPGDSDTRYSPSFQG	QVTISADKSISTAYLQWSSLKASDTAMYYCAR	QGRSYHYYGMDV	WGQGTTVTVSS
16E3	EVQLVQSGAEVKKPGESLKISCKGSGYGFT	NYWIG	WVRQMPGKGLEWMG	TIYPGDSDTRYSPSFQG	QVTFSADKSISTAYLQWSSLKASDTAMYYCAR	QGRSYYYFGMDV	WGQGTTVTVSS
14G7	EVQLVQSGAEVKKPGESLKISCKGSGYSFT	DYWIG	WVRQMPGKGLEWMG	IIYPYDSDTRYSPSFQG	QVTLSADKSISTAYLRWSSLKASDTAMYYCAR	HRGGRSYYYGMDV	WGQGTTVTVSS
5H3	EVQLVQSGAEVKKPGESLKISCKGSGYSFT	SYWIG	WVRQMPGKGLEWMG	IIYPGDSDTTYSPSFQG	QVTISADKSINTAYLQWSSLKASDTAMYYCAR	EGFGESIHYGLDV	WGQGTTVTVSS
2B12	EVQLVQSGAEVKKPGESLKISCKGSGYNFT	NYWIG	WVRQMSGKGLEWMG	IIYPGDSETRYSPSFQG	QVTISADKSISTAYLQWSSLKASDTAMYYCAR	HGGGWSGWGMDV	WGQGTTVTVSS
26H7	EVQLVQSGAEVKKPGESLKISCKGSGYRFT	NYWIG	WVRQMPGKGLEWMG	IIYPGDSDTKYSPSFQG	QVTISADKSISTAYLQWSSLKASDTAMYYCAR	HGGYSGRSYYYGMDV	WGQGTAVTVSS
26C12	EVQLVQSGAEVKKPGESLKISCKGSGYRFT	SYWIG	WVRQMPGKGLEWMG	IIFPGDSDTRYSPSFQG	QVTISADKSITTAYLQWSSLKASDTAIYYCAR	HGHGSSSGRTYYYGLDV	WGQGTTVTVSS
2H11	EVQLVQSGAEVKKPGESLKISCKGSGYNFT	TYWIG	WVRQMPGKGLEWMG	IIYPGDSDTRYSPSFQG	QVTISADKSINTAYLQWSSLKASDTAIYYCAR	DTGYFDY	WGQGTLVTVSS
18H9	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	SYGMH	WVRQAPGKGLEWVA	VIWYDGSNKFYVDSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	PGSDYYFYYGMDV	WGQGTTVTVSS

FIG. 29A

Heavy Chain Nucleic Acid Sequences

9D6

GAGGTGCAGTTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC
TGGATACAGGTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGA
TCATCCATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCC
ATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACTGCCATATATTACTGTACGAGACAGGGT
AGAAGCTTCTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

2C3

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC
TGGATACAGGTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGA
TCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCC
ATCAGCGCCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACAACAA
GTGGCTGGTATGTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

14C9

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTATTTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGACAGT
TATATGGTATGATGGAAGTAATGAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGGA
CTTCGACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

8B12

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAG
TTATATGGTATGATGGAAGTAATGAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTC
CAAGAACACGCTGTATCTACAAATGCACAGCCTGAGAGCCGAGGACACGGCTGTGTATTATTGTGCGAGAGAAGA
ATGGTTCGGGGAGGCGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

FIG. 29B

16A4

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCAGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAG
TTATATGGTATGATGGAAGTAATGAATATTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTC
CAAGAACACGCTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATGA
TTGGTTCGGGGAGGCGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

16E1

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTAACTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGACAGT
TATATGGAATGATGGAAGTAATGAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAAGAT
TGGCTCGGGGAGGCGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

13A1

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAG
TTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTC
CAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAAG
AGTGGGAGCTAGAGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

8F10

CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTAGTTATGGCATGTACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT
TATATGGTATGATGGAAGTAATAAATACTATGTAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGC
AGTGGCTGGTACGGGACGGGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT
CCTCA

FIG. 29C

12C4

CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACGTTCAGTAGTTATGGCATGTACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAG
TTATATGGTATGATGGAAGTAATAAATACCATGGAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTC
CAAGAATACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAAAGGAGC
AGTGGCTGGTACGGGACGGGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT
CCTCA

9B12

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCAGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTTAGTAGTTATGGCATGTACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT
TATATGGTATGATGGAAGTAATAAAAACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAATACGTTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATCACTGTGCGAAAGGAACA
GTGGCTGGTACGGGACGGGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCT
TCA

3H5

CAGGTGCAACTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTAGCTTTGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT
TATTTGGTTTGATGGAAGTAATAAATACTATGTAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAATACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGCGGGACGAT
TTTTGGAGTGATTATCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

18A6

CAGGTGCAACTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCT
GGATTCACCTTCAGGAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT
TATATCAGATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGACCTGAGGACACGGCTGTGTATTACTGTGCGAGAGATCTC
TATAGCAGTGCCTGGCCCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

FIG. 29D

10A6

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTAGCTATGACATACACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT
TATATGGAATGATGGAAGTATTAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACGG
GGAGCAGTGGCGGGGCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

10H7

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTAGCTATGACATACACTGGGTCCGTCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT
TATATGGTATGATGGAAGTATTAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCAG
GAGCAGTGGCTGGCCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

15A10

CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTACCTATGGCATGCACTGGGTCCGCCAGGCTCCAGACATGGGGCTGGAGTGGGTGGCAGT
TATATGGTATGATGGAAGTAATAAATACTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACATTTCC
AAGAACACGCTGTATCTGGAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACAA
CTGGGGATCCGATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

12D2

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTACCTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT
TATATGGTATGATGGAATTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGAG
TTACTATGATAGTAGTGGTTATTACTACGGGGAGGACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC
TCA

FIG. 29E

9B10

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTAGCTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT
TATCTGGTATGATGGAATTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGAG
TTACTATGATAGTAGTGGTTATTACTTCGGGGAGGACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC
TCA

17D3

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCT
GGATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATAC
ATTAGTAGTAGTGGTAGTATCATTTTTTACGCAGACTCTGTGAAGGGCCGATTCACCATGTCCAGGGACAACGCCA
AGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTATTGTGTGAGAAGGATTA
GTATAACCCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

15G11

CAGGTCACCTTGAAGGAGTCTGGTCCTGTGCTGGTGAAACCCACAGAGACCCTCACGCTGACCTGCACCGTCTCTG
GGTTCTCACTCAGCAATGCTAGAATGGGTGTGAGCTGGATCCGTCAGCCCCCAGGGAAGGCCCTGGAGTGGCTTG
CACACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGCAGGCTCACCATCTCCAAGGACACCTCC
AAAAGCCAGGTGGTCCTTACCATGACCAACATGGACCCTGTGGACACAGCCACATATTACTGTGTACGGATACCGA
GATGGCTACAACCCCCCTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

14D7

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTCACCTGCACTGTCTCT
GGTGGCTCCATCAGCAGTGGTGGTTACTACTGGAACTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGAT
TGGGTACATCTATTACAGTGGGAACACCCACTACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACACG
TCTAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGATTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGACT
GGGGACGTGATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

FIG. 29F

18F3

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTCACCTGCACTGTCTCG
GGTGGCTCCATCAGCAGTGGTGGTTACTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGAT
TGGGTACATCTATTATAGTGGGAGCACCGACTACAACCCGTCCCTCAAGAGTCGAGGTATCATATCAGGAGACAC
GTCTAAGAACCAGTTCTCCCTGAAGCTGAACTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGA
GGGGAGGTTCGGGGAGTTAGGCTCCTACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

17D9

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCT
GGTGGCTCCGTCAGCAGTGGTGGTTACTACTGGAGCTGGATCCGGCAGCCCCCAGGGAAGGGACTGGAGTGGAT
TGGGAATACCTATTACAGTGGGAGCACCAACTACAAACCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACG
TCCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCTGCGGACACGGCCGTGTATTACTGTGGGAGAGAC
CGGGGTAGAGCAGTGGGTCCCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

21F8

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC
TGGATACACCTTCACCAATTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATG
GATGAACCCTAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACCTC
CATAAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAAGTA
GGCAGTGGCTGGTACTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

22B9

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC
TGGATACACCTTCACCAATTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATG
GATGAACCCTAACAGTGGTAACACAGGCTATGTACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACCTC
CATAAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAAGTA
GGCAGTGGCTGGTACTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

FIG. 29G

21D10

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC
TGGATACAGGTTCACCAGTTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGAT
GGATGAACCCAAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACC
TCCATAAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAAGT
AGGCAGTGGCTGGTACTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

14A6

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC
TGGATACACCTTCACCACTTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATG
GATGAACCCTAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACCTC
CATAAGCACAGCCTACATGGAGCTGAGCAGCCTAAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCC
GGCAGTGGCTGGGCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

11D6

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC
TGGATACACCTTCACCAATTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATG
GATGAACCCTAATAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACCTC
CATAAACACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCC
GGCAGTGGCTGGGCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

10A9

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC
TGGATACAGCTTTACCAGCCAGTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGA
TCATCTTTCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCC
ATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGCGACAGGGT
AGAAGTTACCACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

FIG. 29H

16E3

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC
TGGATACGGCTTTACCAACTACTGGATCGGCTGGGTGCGCCAGATGCCCGGAAAAGGCCTGGAGTGGATGGGGA
CCATCTATCCTGGTGACTCTGATACCAGATACAGTCCGTCCTTCCAAGGCCAGGTCACCTTCTCAGCCGACAAGTCC
ATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACAGGGT
AGAAGTTACTACTACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

14G7

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC
TGGATACAGCTTTACCGACTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAATGGATGGGGA
TCATCTATCCTTATGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCCTCTCAGCCGACAAGTCC
ATCAGCACCGCCTACCTGCGGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACATCGG
GGGGGGAGGTCCTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

5H3

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC
TGGATACAGCTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTAGAATGGATGGGGA
TCATCTATCCTGGTGACTCTGATACCACATACAGCCCGTCCTTCCAAGGCCAAGTCACCATCTCAGCCGACAAGTCC
ATCAACACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGAGAGGGT
TTCGGGGAGTCTATTCACTACGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

2B12

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC
TGGATACAATTTTACCAACTACTGGATCGGCTGGGTGCGCCAGATGTCCGGGAAAGGCCTGGAGTGGATGGGAA
TCATCTATCCTGGTGACTCTGAAACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTC
CATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACATGG
AGGGGGATGGAGTGGTTGGGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

FIG. 29I

26H7

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC
TGGATACAGGTTTACCAACTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGA
TCATCTATCCTGGTGACTCTGATACCAAATACAGCCCGTCCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCC
ATCAGTACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACATGGT
GGATATAGTGGCCGTTCCTACTACTACGGTATGGACGTCTGGGGCCAGGGGACCGCGGTCACCGTCTCCTCA

26C12

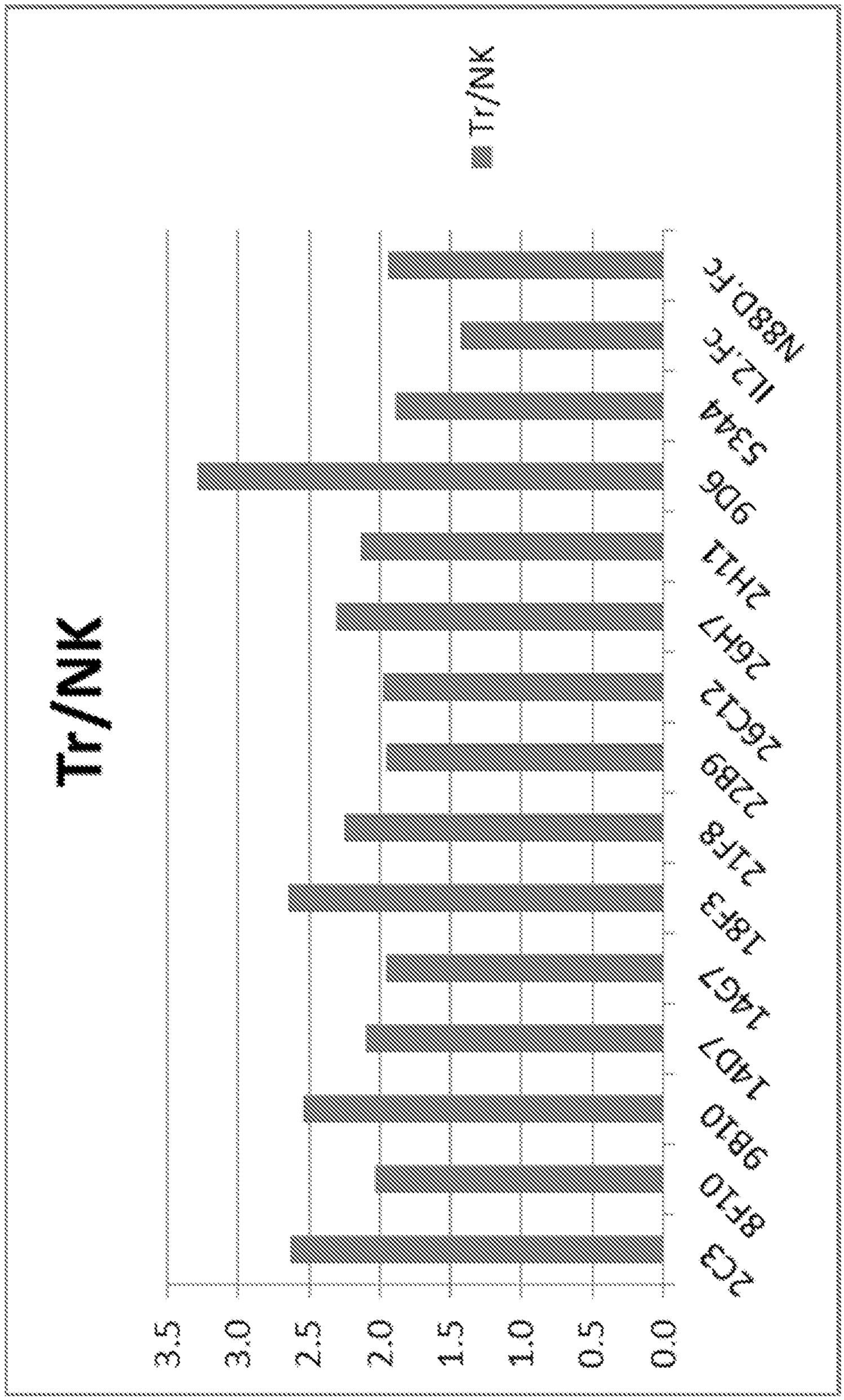
GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC
TGGATACAGGTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGA
TCATCTTTCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCC
ATCACCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATCTATTACTGTGCGCGACATGGG
CATGGCAGCTCGTCCGGGCGGACCTACTACTACGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC
TCA

2H11

GAGGTGCAGCTGGTGCAATCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC
TGGATACAACTTTACCACCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGA
TCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATTTCAGCCGACAAGTCC
ATCAACACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACAGCCATTTATTACTGTGCGAGAGACACA
GGATACTTTGACTACTGGGGCCAGGGCACCCTGGTCACCGTCTCCTCA

18H9

CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC
TGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGCCTGGAGTGGGTGGCAGT
TATCTGGTATGATGGAAGTAATAAATTCTATGTAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGACCCGG
GTCCGATTACTACTTCTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA


Tr/NK
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Tr/NK
FIG. 30

INTERLEUKIN-2 MUTEINS FOR THE EXPANSION OF T-REGULATORY CELLS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional of U.S. patent application Ser. No. 17/065,935, filed Oct. 7, 2020; which is a divisional of U.S. patent application Ser. No. 15/565,376, filed Oct. 9, 2017, now U.S. Pat. No. 10,851,144; which is a National Stage application under 35 U.S.C. § 371 of International Application No. PCT/US2016/030843, having an international filing date of May 4, 2016; which claims the benefit of U.S. Provisional Patent Application No. 62/146,136, filed Apr. 10, 2015; all of which are incorporated herein by reference in their entirety for all purposes.

REFERENCE TO THE SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as an XML file entitled "A-1935-US04-DIV_Sequence Listing", created Apr. 4, 2024, which is 518,234 bytes in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUND

[0003] IL-2 binds three transmembrane receptor subunits: IL-2Rβ and IL-2Rγ which together activate intracellular signaling events upon IL-2 binding, and CD25 (IL-2Rα) which serves to stabilize the interaction between IL-2 and IL-2Rβγ. The signals delivered by IL-2Rβ γ include those of the P13-kinase, Ras-MAP-kinase, and STAT5 pathways.

[0004] T cells require expression of CD25 to respond to the low concentrations of IL-2 that typically exist in tissues. T cells that express CD25 include both FOXP3+ regulatory T cells (Treg cells), which are essential for suppressing autoimmune inflammation, and FOXP3− T cells that have been activated to express CD25. FOXP3− CD25+T effector cells (Teff) may be either CD4+ or CD8+ cells, both of which may contribute to inflammation, autoimmunity, organ graft rejection, or graft-versus-host disease. IL-2-stimulated STAT5 signaling is crucial for normal T-reg cell growth and survival and for high FOXP3 expression.

[0005] In co-owned WO 2010/085495, we describe the use of IL-2 muteins to preferentially expand or stimulate Treg cells. When administered to a subject, the effect on Treg cells is useful for treating inflammatory and autoimmune diseases. Although the IL-2 muteins described therein are useful for expanding Treg over Teff cells in vivo, it was desirable to create IL-2 muteins that had optimal attributes for a human therapeutic.

SUMMARY

[0006] Described herein are IL-2 muteins, anti-IL-2 antibodies, and anti-IL-2 antibody/IL-2 complexes that are amenable to high-yield manufacturability and have pharmacological activity. In the effort to produce such molecules for use as human therapeutics, a number of unexpected and unpredictable observations occurred. The compositions and methods described herein resulted from that effort.

[0007] The IL-2 muteins described herein have a relatively low likelihood of creating an immune response against the IL-2 mutein and/or endogenous IL-2 and provide Treg preferential expansion and activation. Moreover, in certain embodiments, the IL-2 mutein is fused to a molecule, e.g. an antibody Fc, that increases the serum half-life when administered to a subject. IL-2 muteins have a short serum half-life (3 to 5 hrs for sub-cutaneous injection). Exemplary IL-2 mutein Fc fusions described herein have a half-life in humans of at least 1 day, at least 3 days, at least 5 days, at least 10 days, at least 15 days, at least 20 days, or at least 25 days. This effect on the pharmacokinetics of the IL-2 muteins allows for decreased or less frequent dosing of the IL-2 mutein therapeutic.

[0008] Moreover, when creating a pharmaceutical large molecule, consideration must be made for the ability to produce the large molecule in large quantities, while minimizing aggregation and maximizing the stability of the molecule. The IL-2 mutein Fc-fusion molecules demonstrate such attributes.

[0009] Additionally, in certain embodiments, the IL-2 mutein Fc-fusion protein contains an IgG1 Fc region. When it is desirable to abolish the effector functions of IgG1 (e.g., ADCC activity), it was found that mutation of the asparagine at position 297 to glycine (N297G; EU numbering scheme) provided greatly improved purification efficiency and biophysical properties over other mutations that lead to an aglycosylation IgG1 Fc. In preferred embodiments, cysteines are engineered into the Fc to allow disulfide bonds, which increased stability of the aglycosylated Fc-containing molecule. The usefulness of the aglycosylated Fc goes beyond the IL-2 mutein Fc-fusion context. Thus, provided herein are Fc-containing molecules, Fc-fusions and antibodies, comprising a N297G substitution and optionally substitution of one or more additional residues to cysteine.

[0010] In one aspect, the present invention provides a human interleukin-2 (IL-2) mutein comprising an amino acid sequence that is at least 90% identical to the amino acid sequence set forth in SEQ ID NO:1, wherein said IL-2 mutein has at least one mutation selected from L12G, L12K, L12Q, L12S, Q13G, E15A, E15G, E15S, H16A, H16D, H16G, H16K, H16M, H16N, H16R, H16S, H16T, H16V, H16Y, L19A, L19D, L19E, L19G, L19N, L19R, L19S, L19T, L19V, D20A, D20E, D20F, D20G, D20T, D20W, M23R, R81A, R81G, R81S, R81T, D84A, D84E, D84G, D841, D84M, D84Q, D84R, D84S, D84T, S87R, N88A, N88D, N88E, N88F, N88G, N88M, N88R, N88S, N88V, N88W, V91D, V91E, V91G, V91S, 192K, 192R, and E95G and preferentially stimulates T regulatory cells relative to other T cells or NK cells, both in in vitro assays and in humanized mice (NSG mice reconstituted with CD34+ hematopoietic stem cells). In one embodiment, said mutein is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:1. In another embodiment, said mutein is at least 97% identical to the amino acid sequence set forth in SEQ ID NO:1. In another embodiment, the amino acid sequence of said mutein differs from the amino acid sequence set forth in SEQ ID NO:1 only at C125A and at one position selected from L12G, L12K, L12Q, L12S, Q13G, E15A, E15G, E15S, H16A, H16D, H16G, H16K, H16M, H16N, H16R, H16S, H16T, H16V, H16Y, L19A, L19D, L19E, L19G, L19N, L19R, L19S, L19T, L19V, D20A, D20E, D20F, D20G, D20T, D20W, M23R, R81A, R81G, R81S, R81T, D84A, D84E, D84G, D841, D84M, D84Q, D84R, D84S, D84T, S87R, N88A, N88D, N88E, N88F, N88G, N88M, N88R, N88S, N88V, N88W, V91D, V91E, V91G, V91S, 192K, 192R, and E95G. In another embodi-

ment, the amino acid sequence of said mutein differs from the amino acid sequence set forth in SEQ ID NO:1 only at C125A and at one position selected from D20E, D20G, D20W, D84A, D84S, H16D, H16G, H16K, H16R, H16T, H16V, 192K, 192R, L12K, L19D, L19N, L19T, N88D, N88R, N88S, V91D, V91G, V91K, and V91S.

[0011] In another aspect, the present invention provides an Fc-fusion protein comprising an Fc and the human IL-2 mutein as described above. In one embodiment, the Fc is a human IgG1 Fc. In another embodiment, the human IgG1 Fc comprises one or more mutations altering effector function of said Fc. In another embodiment, the human IgG1 comprises a substitution at N297. In another embodiment, the substitution at N297 is N297G. In another embodiment, the Fc-fusion protein comprises a substitution or deletion of the C-terminal lysine of said human IgG Fc. In another embodiment, the C-terminal lysine of said human IgG Fc is deleted. In another embodiment, a linker connects the Fc and human IL-2 mutein portions of said protein. In another embodiment, the linker is GGGGS (SEQ ID NO: 5), GGNGT, or (SEQ ID NO: 6), and YGNGT (SEQ ID NO: 7). In another embodiment, the linker is GGGGS (SEQ ID NO: 5). In another embodiment, the IL-2 mutein further comprises an amino acid addition, substitution, or deletion altering glycosylation of said Fc-fusion protein when expressed in mammalian cells. In another embodiment, the IL-2 mutein comprises a T3 substitution. In another embodiment, the IL-2 mutein comprises a T3N or T3A substitution. In another embodiment, the IL-2 mutein comprises a T3N substitution. In another embodiment, the IL-2 mutein further comprises an S5 mutation. In another embodiment, the IL-2 mutein further comprises an S5T mutation. In another embodiment, said Fc-fusion protein comprises an Fc dimer. In another embodiment, said Fc-fusion protein comprises two IL-2 muteins. In another embodiment, said Fc-fusion protein comprises a single IL-2 mutein.

[0012] In another aspect, the present invention provides an isolated nucleic acid encoding a human IL-2 mutein as described above.

[0013] In another aspect, the present invention provides an isolated nucleic acid encoding an Fc portion of an antibody and a human IL-2 mutein as described above. In one embodiment, said Fc portion of an antibody and the human IL-2 mutein are encoded within a single open-reading frame. In another embodiment, the Fc is a human IgG1 Fc. In another embodiment, the human IgG1 Fc comprises one or more mutations altering effector function of said Fc. In another embodiment, the human IgG1 comprises a substitution at N297. In another embodiment, the substitution at N297 is N297G. In another embodiment, the nucleic acid encodes a substitution or deletion of the C-terminal lysine of said human IgG Fc. In another embodiment, the C-terminal lysine of said human IgG Fc is deleted. In another embodiment, the nucleic acid further encodes a linker connecting the Fc portion of an antibody and the human IL-2 mutein. In another embodiment, the linker is GGGGS (SEQ ID NO: 5), GGNGT, or (SEQ ID NO: 6), and YGNGT (SEQ ID NO: 7). In another embodiment, the linker is GGGGS (SEQ ID NO: 5). In another embodiment, the IL-2 mutein further comprises an amino acid addition, substitution, or deletion altering glycosylation of a protein comprising said IL-2 mutein when expressed in mammalian cells. In another embodiment, the IL-2 mutein comprises a T3 substitution. In another embodiment, the IL-2 mutein comprises a T3N or T3A substitution. In another embodiment, the IL-2 mutein comprises a T3N substitution. In another embodiment, the IL-2 mutein further comprises an S5 mutation. In another embodiment, the IL-2 mutein further comprises an S5T mutation.

[0014] In another aspect, the present invention provides an expression vector comprising an isolated nucleic acid described above operably linked to a promoter.

[0015] In another aspect, the present invention provides a host cell comprising an isolated nucleic acid described above. In one embodiment, the isolated nucleic acid is operably linked to a promoter. In another embodiment, said host cell is a prokaryotic cell. In another embodiment, the host cell is *E. coli*. In another embodiment, said host cell is a eukaryotic cell. In another embodiment, the host cell is a mammalian cell. In another embodiment, the host cell is a Chinese hamster ovary (CHO) cell line.

[0016] In another aspect, the present invention provides a method of making a human IL-2 mutein, comprising culturing a host cell as described above under conditions in which said promoter is expressed and harvesting the human IL-2 mutein from said culture.

[0017] In another aspect, the present invention provides a method of making a Fc-fusion protein, comprising culturing a host cell as described above under conditions in which said promoter is expressed and harvesting the Fc-fusion protein from said culture.

[0018] In another aspect, the present invention provides a method of increasing the ratio of regulatory T cells (Tregs) to non-regulatory T cells within a population of T cells, comprising contacting the population of T cells with an effective amount of a human IL-2 mutein as described above. In one embodiment, the ratio of CD3+FoxP3+ cells to CD3+FoxP3− increases. In another embodiment, the ratio of CD3+FoxP3+ cells to CD3+FoxP3− increases at least 50%.

[0019] In another aspect, the present invention provides a method of increasing the ratio of regulatory T cells (Tregs) to non-regulatory T cells within a population of T cells, comprising contacting the population of T cells with an effective amount of an Fc-fusion protein as described above. In one embodiment, the ratio of CD3+FoxP3+ cells to CD3+FoxP3− increases. In another embodiment, the ratio of CD3+FoxP3+ cells to CD3+FoxP3− increases at least 50%.

[0020] In another aspect, the present invention provides a method of increasing the ratio of regulatory T cells (Tregs) to non-regulatory T cells within peripheral blood of a subject, comprising administering an effective amount of a human IL-2 mutein as described above. In one embodiment, the ratio of CD3+FoxP3+ cells to CD3+FoxP3− increases. In another embodiment, the ratio of CD3+FoxP3+ cells to CD3+FoxP3− increases at least 50%.

[0021] In another aspect, the present invention provides a method of increasing the ratio of regulatory T cells (Tregs) to non-regulatory T cells within the peripheral blood of a subject, comprising administering an effective amount of an Fc-fusion protein as described above. In one embodiment, the ratio of CD3+FoxP3+ cells to CD3+FoxP3− increases. In another embodiment, the ratio of CD3+FoxP3+ cells to CD3+FoxP3− increases at least 50%.

[0022] In another aspect, the present invention provides a method of increasing the ratio of regulatory T cells (Tregs) to natural killer (NK) cells within the peripheral blood of a subject, comprising administering an effective amount of a

human IL-2 mutein as described above. In one embodiment, the ratio of CD3+FoxP3+ cells to CD3-CD19−lymphocytes expressing CD56 and/or CD16 increases. In another embodiment, the ratio of CD3+FoxP3+ cells to CD3-CD19−lymphocytes expressing CD56 and/or CD16 increases at least 50%.

[0023] In another aspect, the present invention provides a method of increasing the ratio of regulatory T cells (Tregs) to natural killer (NK) cells within the peripheral blood of a subject, comprising administering an effective amount of an Fc-fusion protein as described above. In one embodiment, the ratio of CD3+FoxP3+ cells to CD3-CD19−lymphocytes expressing CD56 and/or CD16 increases. In another embodiment, the ratio of CD3+FoxP3+ cells to CD3-CD19−lymphocytes expressing CD56 and/or CD16 increases at least 50%.

[0024] In another aspect, the present invention provides a method of treating a subject with an inflammatory or autoimmune disease, said method comprising administering to said subject a therapeutically effective amount of an IL-2 mutein as described above or a therapeutically effective amount of an Fc-fusion protein as described above. In one embodiment, administration causes reduction of at least one symptom of the disease. In another embodiment, the ratio of regulatory T cells (Tregs) to non-regulatory T cells within the peripheral blood of a subject increases after the administration. In another embodiment, the ratio of regulatory T cells (Tregs) to non-regulatory T cells within the peripheral blood of a subject remains essentially the same after the administration. In another embodiment, the inflammatory or autoimmune disease is lupus, graft-versus-host disease, hepatitis C-induced vasculitis, type I diabetes, type II diabetes, multiple sclerosis, rheumatoid arthritis, alopecia areata, atherosclerosis, psoriasis, organ transplant rejection, Sjögren's Syndrome, Behcet's disease, spontaneous loss of pregnancy, atopic diseases, asthma, or inflammatory bowel diseases.

[0025] In another aspect, the present invention provides a polypeptide comprising an Fc region of a human IgG1 antibody wherein said Fc region comprises an N297G mutation and said Fc region of a human IgG1 comprises at least 90% identity to the amino acid sequence set forth in SEQ ID NO:3. In one embodiment, said Fc region of a human IgG1 comprises at least 95% identity to the amino acid sequence set forth in SEQ ID NO:3. In another embodiment, said Fc region of a human IgG1 comprises the amino acid sequence set forth in SEQ ID NO:3. In another embodiment, said Fc region of a human IgG1 further comprises one or more mutations to stabilize the polypeptide. In another embodiment, one or more amino acids set forth in SEQ ID NO:3 are substituted with cysteine. In another embodiment, V259, A287, R292, V302, L306, V323, or 1332 of the amino acid sequence set forth in SEQ ID NO:3 is substituted with cysteine. In another embodiment, said Fc region comprises an A287C and L306C substitution within the amino acid sequence set forth in SEQ ID NO:3. In another embodiment, said Fc region comprises an V259C and L306C substitution within the amino acid sequence set forth in SEQ ID NO:3. In another embodiment, said Fc region comprises an R292C and V302C substitution within the amino acid sequence set forth in SEQ ID NO:3. In another embodiment, said Fc region comprises an V323C and 1332C substitution within the amino acid sequence set forth in SEQ ID NO:3.

[0026] In another aspect, the present invention provides an antibody comprising an Fc region as described above.

[0027] In another aspect, the present invention provides an Fc-fusion protein comprising an Fc region as described above.

[0028] In another aspect, the present invention provides a polypeptide comprising a linker, wherein the linker is GGNGT (SEQ ID NO: 6) or YGNGT (SEQ ID NO: 7). In one embodiment, the linker comprises N-glycosylation. In another embodiment, the linker is inserted into or replaces a loop in the polypeptide structure.

[0029] In another aspect, the present invention provides a method of making an aglycosylated IgG1 Fc-containing molecule, said method comprising:

[0030] a) expressing a nucleic acid encoding a polypeptide as described above in a mammalian cell culture; and

[0031] b) harvesting the aglycosylated IgG1 Fc-containing molecule from said culture.

[0032] In another aspect, the present invention provides a method of making an IgG1 Fc-containing molecule aglycosylated when expressed in mammalian cells, said method comprising the step of mutating a codon for N297 in the Fc region to a glycine codon.

[0033] In another aspect, the present invention provides an Fc-fusion protein wherein the amino acid sequence of said Fc-fusion protein is at least 90% identical to the amino acid sequence of a human IL-2 mutein fusion protein illustrated in FIG. **24**. In one embodiment, the amino acid sequence of said Fc-fusion protein is at least 95% identical to the amino acid sequence of a human IL-2 mutein fusion protein illustrated in FIG. **24**. In another embodiment, the amino acid sequence of said Fc-fusion protein is at least 97% identical to the amino acid sequence of a human IL-2 mutein fusion protein illustrated in FIG. **24**. In another embodiment, the amino acid sequence of said Fc-fusion protein is at least 99% identical to the amino acid sequence of a human IL-2 mutein fusion protein illustrated in FIG. **24**. In another embodiment, the amino acid sequence of said Fc-fusion protein is identical to the amino acid sequence of a human IL-2 mutein fusion protein illustrated in FIG. **24**.

[0034] In another aspect, the present invention provides a nucleic acid encoding the Fc-fusion as described above.

[0035] In another aspect, the present invention provides a cell comprising the nucleic acid as described above.

[0036] In another aspect, the present invention provides a method of making an Fc-fusion protein comprising incubating the cell as described above under conditions allowing it to express said Fc-fusion protein.

[0037] In another aspect, the present invention provides a method of treating an inflammatory or auto-immune condition in a subject comprising administering an effective amount of the Fc-fusion protein as described above to said subject. In one embodiment, said inflammatory or auto-immune condition is lupus, graft-versus-host disease, hepatitis C-induced vasculitis, type I diabetes, type II diabetes, multiple sclerosis, rheumatoid arthritis, alopecia areata, atherosclerosis, psoriasis, organ transplant rejection, Sjögren's Syndrome, Behcet's disease, spontaneous loss of pregnancy, atopic diseases, asthma, or inflammatory bowel diseases.

[0038] In another aspect, the present invention provides a method of monitoring the response of a subject to treatment with the human interleukin-2 (IL-2) mutein as described above, the Fc-fusion protein as described above, or the

Fc-fusion protein as described above, comprising detecting a change in said subject, said change being: an increase in body temperature, an increase in CRP in said subject's peripheral blood, a decrease in platelets in said subject's peripheral blood, a decrease in neutrophils in said subject's peripheral blood, or a decrease in albumin in said subject's peripheral blood, wherein said treatment is terminated, suspended, reduced in dosing frequency, or reduced in dosing amount after said change is detected. In one embodiment, said change comprises: an increase in body temperature of at least 0.5° C., an increase in CRP in said subject's peripheral blood of at least 0.2 mg/mL, a decrease in platelets in said subject's peripheral blood of at least 0.8-fold, a decrease in neutrophils in said subject's peripheral blood of at least 0.8-fold, or a decrease in albumin in said subject's peripheral blood of at least 0.4-fold.

[0039] In another aspect, the present invention provides an isolated anti-human IL-2 antibody, wherein said antibody: comprises a heavy chain variable domain that is at least 90% identical to the heavy variable domain of a reference antibody, and a light chain variable domain that is at least 90% identical to the light chain variable domain of said reference antibody, wherein said reference antibody is 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 221D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9, and wherein the heavy chain variable domain and light chain variable domain of said reference antibody is as illustrated in FIG. **28** and FIG. **26**, respectively; or comprises a heavy chain variable domain that comprises CDR1, CDR2, and CDR3 of the heavy chain variable domain of a reference antibody, and a light chain variable domain that comprises CDR1, CDR2, and CDR3 of the light chain variable domain of said reference antibody, and wherein said heavy chain CDRs and said light chain CDRs are as illustrated in FIG. **28** and FIG. **26**, respectively; or cross-competes for binding to wild-type human IL-2 cytokine with a reference antibody, wherein said reference antibody is 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 221D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9. In one embodiment, said antibody comprises a heavy chain variable domain amino acid sequence that is at least 90% identical to the heavy chain variable domain amino acid sequence of a reference antibody, and a light chain variable domain amino acid sequence that is at least 90% identical to the light chain variable domain amino acid sequence of said reference antibody, wherein said reference antibody is 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 221D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9, and wherein the heavy chain variable domain amino acid sequence and light chain variable domain amino acid sequence of said reference antibody is as illustrated in FIG. **28** and FIG. **26**, respectively. In another embodiment, said antibody comprises a heavy chain variable domain amino acid sequence that is at least 95% identical to the heavy variable domain amino acid sequence of a reference antibody, and a light chain variable domain amino acid sequence that is at least 95% identical to the light chain variable domain amino acid sequence of said reference antibody, wherein said reference antibody is 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 221D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9, and wherein the heavy chain variable domain amino acid sequence and light chain variable domain amino acid sequence of said reference antibody is as illustrated in FIG. **28** and FIG. **26**, respectively. In another embodiment, said antibody comprises a heavy chain variable domain amino acid sequence that is at least 97% identical to the heavy variable domain amino acid sequence of a reference antibody, and a light chain variable domain amino acid sequence that is at least 97% identical to the light chain variable domain amino acid sequence of said reference antibody, wherein said reference antibody is 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 221D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9, and wherein the heavy chain variable domain amino acid sequence and light chain variable domain amino acid sequence of said reference antibody is as illustrated in FIG. **28** and FIG. **26**, respectively. In another embodiment, said antibody comprises a heavy chain variable domain amino acid sequence that is at least 99% identical to the heavy variable domain amino acid sequence of a reference antibody, and a light chain variable domain amino acid sequence that is at least 99% identical to the light chain variable domain amino acid sequence of said reference antibody, wherein said reference antibody is 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 221D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9, and wherein the heavy chain variable domain amino acid sequence and light chain variable domain amino acid sequence of said reference antibody is as illustrated in FIG. **28** and FIG. **26**, respectively. In another embodiment, said antibody comprises a heavy chain variable domain amino acid sequence of a reference antibody, and a light chain variable domain amino acid sequence of said reference antibody, wherein said reference antibody is 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 221D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9, and wherein the heavy chain variable domain amino acid sequence and light chain variable domain amino acid sequence of said reference antibody is as illustrated in FIG. **28** and FIG. **26**, respectively. In another embodiment, said isolated antibody is: a human antibody; a humanized antibody; a chimeric antibody; a monoclonal antibody; a polyclonal antibody; a recombinant antibody; an antigen-binding antibody fragment; a single chain antibody; a diabody; a triabody; a tetrabody; a Fab fragment; a F(ab')2 fragment; a domain antibody; an IgD antibody; an IgE antibody; an IgM antibody; an IgG1 antibody; an IgG2 antibody; an IgG3 antibody; an IgG4 antibody; or an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond. In another embodiment, said isolated antibody comprises a human IgG1 Fc. In another embodiment, said human IgG1 Fc has one or more mutations altering effector function of said Fc.

In another embodiment, said human IgG1 Fc comprises a substitution at N297. In another embodiment, said substitution at N297 is N297G. In another embodiment, the antibody comprises a substitution or deletion of the C-terminal lysine of said human IgG Fc. In another embodiment, the C-terminal lysine of said human IgG Fc is deleted. In another embodiment, said isolated antibody comprises a human IgG1 Fc. In another embodiment, said human IgG1 Fc has one or more mutations altering effector function of said Fc. In another embodiment, said human IgG1 Fc comprises a substitution at N297. In another embodiment, said substitution at N297 is N297G. In another embodiment, the antibody comprises a substitution or deletion of the C-terminal lysine of said human IgG Fc. In another embodiment, the C-terminal lysine of said human IgG Fc is deleted.

[0040] In another aspect, the present invention provides an isolated complex comprising an isolated anti-human IL-2 antibody as described above bound to a human IL-2 cytokine.

[0041] In another aspect, the present invention provides an isolated nucleic acid encoding the light chain, the heavy chain, or both the light chain and the heavy chain of the isolated anti-human IL-2 antibody as described above.

[0042] In another aspect, the present invention provides an expression vector comprising the isolated nucleic acid as described above operably linked to a promoter.

[0043] In another aspect, the present invention provides a host cell comprising the isolated nucleic acid as described above. In one embodiment, the isolated nucleic acid is operably linked to a promoter. In another embodiment, said host cell is a prokaryotic cell. In another embodiment, the host cell is *E. coli*.

[0044] In another embodiment, said host cell is a eukaryotic cell. In another embodiment, the host cell is a mammalian cell. In another embodiment, the host cell is a Chinese hamster ovary (CHO) cell line.

[0045] In another aspect, the present invention provides a method of making an anti-human IL-2 antibody, comprising culturing a host cell as described above under conditions in which said promoter is expressed and harvesting the human IL-2 mutein from said culture.

[0046] In another aspect, the present invention provides a method of treating an inflammatory or auto-immune condition in a subject comprising administering an effective amount of the anti-human IL-2 antibody or isolated complex comprising an isolated anti-human IL-2 antibody as described above to said subject. In one embodiment, said inflammatory or auto-immune condition is lupus, graft-versus-host disease, hepatitis C-induced vasculitis, type I diabetes, type II diabetes, multiple sclerosis, rheumatoid arthritis, alopecia areata, atherosclerosis, psoriasis, organ transplant rejection, Sjögren's Syndrome, Behcet's disease, spontaneous loss of pregnancy, atopic diseases, asthma, or inflammatory bowel diseases.

BRIEF DESCRIPTION OF THE FIGURES

[0047] FIG. **1** In a short term stimulation assay, homodimerization by fusion to the C-terminus of IgG-Fc does not alter the activity of IL-2 muteins with reduced potency and with high affinity for CD25.

[0048] FIG. **2**A and FIG. **2**B IL-2 muteins with the indicated mutations and fused to the C-terminus of one side of an Fc-heterodimer were tested for their ability to stimulate STAT5 phosphorylation in T cells. These muteins also contained three mutations conferring high affinity for CD25 (V69A, N71R, Q74P). Their activity was compared to three forms of IL-2 without Fc fusion (open symbols): WT IL-2, HaWT (high affinity for CD25) (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P), and HaD (high affinity for CD25 and reduced signaling activity) (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P, N88D). Phospho-STAT5 responses are shown for gated FOXP3+CD4+ and FOXP3−CD4+ T cells.

[0049] FIG. **3** Proliferation of T cell subsets in response to titrations of IL-2 muteins fused to Fc-heterodimer. Activity of fusion proteins was compared to three forms of IL-2 without Fc fusion (open symbols): WT IL-2, HaWT (high affinity for CD25) (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P), and HaD (high affinity for CD25 and reduced signaling activity) (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P, N88D)

[0050] FIG. **4** Proliferation of NK cells in response to titrations of IL-2 muteins fused to Fc-heterodimer. Activity of fusion proteins was compared to three forms of IL-2 without Fc fusion (open symbols): WT IL-2, HaWT (high affinity for CD25) (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P), and HaD (high affinity for CD25 and reduced signaling activity) (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P, N88D)

[0051] FIG. **5** Proliferation of T cell subsets in response to titrations of IL-2 muteins fused to Fc-homodimer N297G. Activity of Fc.muteins was compared to WT IL-2 (open circles) and Fc.WT (closed circles). Mutations that confer high affinity for CD25 (HaMut1) were V69A and Q74P.

[0052] FIG. **6** Proliferation of NK cells in response to titrations of IL-2 muteins fused to Fc-homodimer N297G. Activity of Fc.muteins was compared to WT IL-2 (open circles) and Fc.WT (closed circles).

[0053] FIG. **7**A and FIG. **7**B Fc.IL-2 muteins without mutations that confer high affinity for CD25 promote Treg expansion and FOXP3 upregulation in humanized mice.

[0054] FIG. **8** Low weekly doses (0.5 μg per animal) of Fc.IL-2 muteins promote Treg expansion and FOXP3 upregulation in humanized mice, with better activity observed for Fc.V91K relative to Fc.N88D and Fc.WT.

[0055] FIG. **9**A Fc.V91K and Fc.N88D persist on the surface of activated T cells through association with CD25.

[0056] FIG. **9**B Persistence of IL-2R signaling with Fc.V91K and Fc.N88D relative to Fc.WT.

[0057] FIGS. **10**A and B Comparison of two week and four week dosing intervals of Fc.V91K in cynomolgus monkeys, and comparison of IV and SC dosing routes.

[0058] FIG. **11**A-F Kinetics of cellular responses, body temperature, and serum CRP in cynomolgus monkeys treated with different dosing regimens of PROLEUKIN®, Fc.V91K, and Fc.N88D.

[0059] FIG. **12**A Effect of increasing dosages of PROLEUKIN®, Fc.V91K, or Fc.N88D on levels of Treg cells, NK cells, $CD4^+FOXP3-$ T cells, and $CD8^+FOXP3-$ T cells in cynomolgus monkeys. Each data point represents the average peak responses of four animals.

[0060] FIG. **12**B Effect of increasing dosages of PROLEUKIN®, Fc.V91K, or Fc.N88D on levels of Treg cells and eosinophils in cynomolgus monkeys. Each data point represents the average peak responses of four animals.

[0061] FIG. **12**C Effect of increasing dosages of PROLEUKIN®, Fc.V91K, or Fc.N88D on levels of Treg cells

and CRP and on body temperature in cynomolgus monkeys. Each data point represents the average peak responses of four animals.

[0062] FIG. **12**D Effect of increasing dosages of PROLEUKIN®, Fc.V91K, or Fc.N88D on levels of Treg cells, platelets, neutrophils, and albumin in cynomolgus monkeys. Each data point represents the average peak responses of four animals. The right y-axes are inverted to convey a fold-change decrease in platelets, neutrophils, or albumin relative to pre-dose samples.

[0063] FIG. **13** Kinetics of the development of anti-drug antibodies (ADA) in cynomolgus monkeys treated with Fc.V91K.

[0064] FIG. **14** Discovery Studio predicted $\Delta\Delta G_{binding}$ (kcal/mol) of IL-2:IL-2Rβ interaction for various IL-2 muteins. Positive value of $\Delta\Delta G_{binding}$ indicates a weaker binding of the mutein compared to the wild-type IL-2. $\Delta\Delta G_{binding}$ values for N88 and D20 mutants are likely to be under-predicted. The muteins shown in boxes were selected.

[0065] FIG. **15** Schrödinger predicted $\Delta\Delta G_{binding}$ (kcal/mol) of IL-2:IL-2Rβ interaction for various IL-2 mutants. Positive value of $\Delta\Delta G_{binding}$ indicates a weaker binding of the mutant compared to the WT. The muteins shown in boxes were selected.

[0066] FIG. **16**A and FIG. **16**B Primary human PBMCs were pre-activated with 100 ng/ml OKT3 for two days. Cells were then rested for three days after three washes to remove OKT3 antibody. The bioactivities of Fc.IL-2 mutein fusion proteins were tested by stimulating these rested pre-activated PBMCs with titrations (1 nM, 100 pM, 33 pM, 11 pM) of IL-2 muteins at 37° C. for 10 min followed by a standard PHOSFLOW™ (BD, Franklin Lakes, NJ) assay to detect phospho-STAT5 levels. The bioactivity of Fc.IL-2 muteins is presented as phospho-STAT5 mean fluorescence intensity (MFI) in gated CD4+ T cells. The muteins were assayed as supernatants of transfected 293-6E cells and the concentrations of Fc.IL-2 fusion proteins were determined by Protein A binding (OCTET Q SYSTEM®, Pall forteBIO Co., Menlo Park, CA). The "pTT5" sample represents the supernatant fraction from cells transfected with an empty DNA expression vector. A) Phospho-STAT5 responses to titrated Fc.IL-2 mutein fusion proteins, in T cells from one donor. B) Ranked pSTAT5 responses to 33 pM Fc.IL-2 muteins for two donors.

[0067] FIG. **17** Primary human PBMCs were pre-activated with 100 ng/ml OKT3 for two days. Cells were then rested for three days after three washes to remove OKT3 antibody. The bioactivity of IL-2 muteins was tested by stimulating these rested pre-activated PBMCs with titrations of IL-2 muteins at 37° C. for 10 min followed by a standard PHOSFLOW™ (BD, Franklin Lakes, NJ) assay to detect phospho-STAT5 levels. The bioactivity of IL-2 muteins is presented as phospho-STAT5 mean fluorescence intensity (MFI) in gated CD25highCD4$^+$ T cells. Fc.IL-2(D20W, C125A) did not activate pSTAT5, and this molecule and Fc.IL-2(WT, C125A) are shown in each plot as a positive and negative control. Consistent results were obtained for two different PBMC donors.

[0068] FIGS. **18**A-**18**D Total PBMCs were activated at 3 million/ml with 100 ng OKT3. On day two, cells were washed three times and rested in fresh media for five days. Cells were then labeled with CFSE and further cultured in a twenty-four well plate at 0.5 million/well in IL-2 containing media for seven days before FACS analysis. The proliferation of T cell subsets is presented as CFSE dilution (median CFSE fluorescence) for FOXP3$^-$CD4$^+$ cells (FIG. **18**A), FOXP3$^-$CD8$^+$ cells (FIG. **18**B), and HELIOS+FOXP3$^+$CD4$^+$ (FIG. **18**C). The capacity for muteins to upregulate FOXP3 in HELIOS+FOXP3$^+$CD4$^+$ cells is also shown (FIG. **18**D).

[0069] FIG. **19** MACS sorted CD16$^+$ NK cells were cultured with titrations of the indicated Fc.IL-2 muteins for three days at 0.1 million/well in ninety-six well plates. 0.5 μCi 3H-thymidine was added to each well during the final eighteen hours of incubation.

[0070] FIGS. **20**A and **20**B Primary human PBMCs were pre-stimulated for two days with 100 ng/ml OKT3. Cells were harvested, washed four times and rested overnight in medium. Cells were then pulsed with 400 pM Fc.IL-2 for 30 min at 37° C. After pulse, cells were either harvested for TO after one wash, or washed an additional three times in 12 ml of warm medium and cultured for the indicated times. To detect cell-associated Fc.IL-2, cells were stained with anti-human IgG-FITC (Jackson Immunoresearch, West Grove, PA) and anti-CD25-APC (FIG. **20**A). To rank the muteins for cell surface retention, the sum of the hu IgG MFI values for 4, 6, and 24 hr timepoints was averaged for two PBMC donors (FIG. **20**B).

[0071] FIG. **21** pSTAT5 signal retention after pulse-wash, as in FIGS. **20**A and **20**B, except cells were pulsed with 100 pM Fc.IL-2.

[0072] FIG. **22** Correlation of cell surface retention and IL-2R signaling retention. The scaled surface retention and pSTAT5 signal retention values were calculated by adding the hu-IgG MFI (surface) or the pSTAT5 MFI (signaling) values for the 6 and 24 hr time points, scaling the values from 0 to 1, and averaging the scaled values for two donors.

[0073] FIG. **23**A and FIG. **23**B Percent Treg of CD4 T cells in blood of humanized mice (NSG mice reconstituted with CD34$^+$ hematopoietic stem cells) on day four after subcutaneous dose of 1 pg Fc.IL-2 mutein at day zero. (B) Correlation of Treg enrichment with pSTAT5 signal retention. The scaled pSTAT5 signal retention values were calculated by adding the pSTAT5 MFI for the 6 and 24 hr timepoints, scaling the values from 0 to 1, and averaging the scaled values for two donors.

[0074] FIG. **24** (A)-(P) Amino acid sequences of the human IL-2 mutein fusion proteins created and tested according to Examples 13 and 14. Bold text=leader sequence; italics=Fc domain (comprising the N297G and delK mutations); underlined text=linker sequence; plain text=IL-2 (comprising C125A and the indicated mutations). Together, the Fc domain, linker sequence, and IL-2 comprise the mature form of the protein.

[0075] FIG. **25** (A)-(LL) Nucleic acid sequences of the human IL-2 mutein fusion proteins created and tested according to Examples 13 and 14.

[0076] FIG. **26** Amino acid sequences of the light chain variable domains of the antibodies isolated and tested according to Example 15. CDRs 1, 2, and 3 (defined according to Kabat) are indicated in bold and underlined; framework regions 1, 2, 3, and 4 are in plain text.

[0077] FIG. **27**(A)-(I) Nucleic acid sequences of the light chain variable domains of the antibodies isolated and tested according to Example 15.

[0078] FIG. **28** Amino acid sequences of the heavy chain variable domains of the antibodies isolated and tested according to Example 15. CDRs 1, 2, and 3 (defined

according to Kabat) are indicated in bold and underlined; framework regions 1, 2, 3, and 4 are in plain text.

[0079] FIG. **29**(A)-(I) Nucleic acid sequences of the heavy chain variable domains of the antibodies isolated and tested according to Example 15.

[0080] FIG. **30** Ratio of activation of Treg cells expansion to NK cell expansion in NSG SCID/Hu mice treated with a single injection of 8 pg of anti-IL-2 antibody complexed with 1.5 pg wild-type human IL-2) as described in Example 15.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0081] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All references cited within the body of this specification are expressly incorporated by reference in their entirety.

[0082] Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, tissue culture and transformation, protein purification, etc. Enzymatic reactions and purification techniques may be performed according to the manufacturer's specifications or as commonly accomplished in the art or as described herein. The following procedures and techniques may be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the specification. See, e.g., Sambrook et al., 2001, *Molecular Cloning: A Laboratory Manuel,* 3rd ed., Cold Spring Harbor Laboratory Press, cold Spring Harbor, N.Y., which is incorporated herein by reference for any purpose. Unless specific definitions are provided, the nomenclature used in connection with, and the laboratory procedures and techniques of, analytic chemistry, organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical synthesis, chemical analyses, pharmaceutical preparation, formulation, and delivery and treatment of patients.

IL-2

[0083] The IL-2 muteins described herein are variants of wild-type human IL-2. As used herein, "wild-type human IL-2," "wild-type IL-2," or "WT IL-2" shall mean the polypeptide having the following amino acid sequence:

(SEQ ID NO: 2)

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKA

TELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE

TTFMCEYADETATIVEFLNRWITFXQSIISTLT

Wherein X is C, S, V, or A

[0084] Variants may contain one or more substitutions, deletions, or insertions within the wild-type IL-2 amino acid sequence. Residues are designated herein by the one letter amino acid code followed by the IL-2 amino acid position, e.g., K35 is the lysine residue at position 35 of SEQ ID NO: 2. Substitutions are designated herein by the one letter amino acid code followed by the IL-2 amino acid position followed by the substituting one letter amino acid code, e.g., K35A is a substitution of the lysine residue at position 35 of SEQ ID NO:2 with an alanine residue.

IL-2 Muteins and anti-IL-2 Antibodies

[0085] Provided herein are human IL-2 muteins and anti-IL-2 antibodies that preferentially stimulate T regulatory (Treg) cells. As used herein "preferentially stimulates T regulatory cells" means the mutein or antibody promotes the proliferation, survival, activation and/or function of CD3+ FoxP3+ T cells over CD3+FoxP3− T cells. Methods of measuring the ability to preferentially stimulate Tregs can be measured by flow cytometry of peripheral blood leukocytes, in which there is an observed increase in the percentage of FOXP3+CD4+ T cells among total CD4+ T cells, an increase in percentage of FOXP3+CD8+ T cells among total CD8+ T cells, an increase in percentage of FOXP3+ T cells relative to NK cells, and/or a greater increase in the expression level of CD25 on the surface of FOXP3+ T cells relative to the increase of CD25 expression on other T cells. Preferential growth of Treg cells can also be detected as increased representation of demethylated FOXP3 promoter DNA (i.e. the Treg-specific demethylated region, or TSDR) relative to demethylated CD3 genes in DNA extracted from whole blood, as detected by sequencing of polymerase chain reaction (PCR) products from bisulfite-treated genomic DNA (J. Sehouli, et al. 2011. Epigenetics 6:2, 236-246).

[0086] IL-2 muteins or anti-IL-2 antibodies that preferentially stimulate Treg cells increase the ratio of CD3+FoxP3+ T cells over CD3+FoxP3− T cells in a subject or a peripheral blood sample at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 150%, at least 200%, at least 300%, at least 400%, at least 500%, at least 600%, at least 700%, at least 800%, at least 900%, or at least 1000%.

[0087] Examples of IL-2 muteins include, but are not limited to, IL-2 muteins comprising H16T, H16K, H16R, L19N, L19D, D20E, D20G, D20T, N88D, N88R, N88S, V91D, V91G, V91K, and/or V91S substitution(s) in the amino acid sequence set forth in SEQ ID NO:2. Exemplary IL-2 muteins are set forth in FIG. **24**. IL-2 muteins of the present invention optionally comprise a C125A substitution. Although it may be advantageous to reduce the number of further mutations to the wild-type IL-2 sequence, the invention includes IL-2 muteins also including truncations and/or additional insertions, deletions, and/or substitutions in addition to the H16T, H16K, H16R, L19N, L19D, D20E, D20G, D20T, N88D, N88R, N88S, V91D, V91G, V91K, and/or V91S substitution, provided that said muteins maintain the activity of preferentially simulating Tregs. Thus, embodiments include IL-2 muteins that preferentially stimulate Treg cells and comprise an amino acid sequence having a H16T, H16K, H16R, L19N, L19D, D20E, D20G, D20T, N88D, N88R, N88S, V91D, V91G, V91K, and/or V91S substitution and that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence set forth in SEQ ID NO:2. In particularly preferred embodiments, such IL-2 muteins comprise an amino acid sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequence set forth in SEQ ID NO:2.

[0088] For amino acid sequences, sequence identity and/or similarity is determined by using standard techniques known in the art, including, but not limited to, the local sequence

identity algorithm of Smith and Waterman, 1981, *Adv. Appl. Math.* 2:482, the sequence identity alignment algorithm of Needleman and Wunsch, 1970, *J. Mol. Biol.* 48:443, the search for similarity method of Pearson and Lipman, 1988, *Proc. Nat. Acad. Sci. U.S.A.* 85:2444, computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.), the Best Fit sequence program described by Devereux et al., 1984, *Nucl. Acid Res.* 12:387-395, preferably using the default settings, or by inspection. Preferably, percent identity is calculated by FastDB based upon the following parameters: mismatch penalty of 1; gap penalty of 1; gap size penalty of 0.33; and joining penalty of 30, "Current Methods in Sequence Comparison and Analysis," Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp 127-149 (1988), Alan R. Liss, Inc.

[0089] An example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments. It can also plot a tree showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng & Doolittle, 1987, *J. Mol. Evol.* 35:351-360; the method is similar to that described by Higgins and Sharp, 1989, *CABIOS* 5:151-153. Useful PILEUP parameters including a default gap weight of 3.00, a default gap length weight of 0.10, and weighted end gaps.

[0090] Another example of a useful algorithm is the BLAST algorithm, described in: Altschul et al., 1990, *J. Mol. Biol.* 215:403-410; Altschul et al., 1997, *Nucleic Acids Res.* 25:3389-3402; and Karin et al., 1993, *Proc. Natl. Acad. Sci. U.S.A.* 90:5873-5787. A particularly useful BLAST program is the WU-BLAST-2 program which was obtained from Altschul et al., 1996, *Methods in Enzymology* 266:460-480. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span=1, overlap fraction=0.125, word threshold (T)=II. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity.

[0091] An additional useful algorithm is gapped BLAST as reported by Altschul et al., 1993, *Nucl. Acids Res.* 25:3389-3402. Gapped BLAST uses BLOSUM-62 substitution scores; threshold T parameter set to 9; the two-hit method to trigger ungapped extensions, charges gap lengths of k a cost of 10+k; X_u set to 16, and X_g set to 40 for database search stage and to 67 for the output stage of the algorithms. Gapped alignments are triggered by a score corresponding to about 22 bits.

[0092] While the site or region for introducing an amino acid sequence variation may be predetermined, the mutation per se need not be predetermined. For example, in order to optimize the performance of a mutation at a given site, random mutagenesis may be conducted at the target codon or region and the expressed IL-2 mutein screened for the optimal combination of desired activity. Techniques for making substitution mutations at predetermined sites in DNA having a known sequence are well known, for example, M13 primer mutagenesis and PCR mutagenesis. Screening of the mutants may be done using assays described herein, for example.

[0093] Amino acid substitutions are typically of single residues; insertions usually will be on the order of from about one (1) to about twenty (20) amino acid residues, although considerably larger insertions may be tolerated. Deletions range from about one (1) to about twenty (20) amino acid residues, although in some cases deletions may be much larger.

[0094] Substitutions, deletions, insertions or any combination thereof may be used to arrive at a final derivative or variant. Generally these changes are done on a few amino acids to minimize the alteration of the molecule, particularly the immunogenicity and specificity of the antigen binding protein. However, larger changes may be tolerated in certain circumstances. Conservative substitutions are generally made in accordance with the following chart depicted as TABLE 1.

TABLE 1

Original Residue	Exemplary Substitutions
Ala	Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser, Ala
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn, Gln
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile
Phe	Met, Leu, Tyr, Trp
Ser	Thr
Thr	Ser
Trp	Tyr, Phe
Tyr	Trp, Phe
Val	Ile, Leu

Substantial changes in function or immunological identity are made by selecting substitutions that are less conservative than those shown in TABLE 1. For example, substitutions may be made which more significantly affect: the structure of the polypeptide backbone in the area of the alteration, for example the alpha-helical or beta-sheet structure; the charge or hydrophobicity of the molecule at the target site; or the bulk of the side chain. The substitutions which in general are expected to produce the greatest changes in the polypeptide's properties are those in which (a) a hydrophilic residue, e.g., seryl or threonyl, is substituted for (or by) a hydrophobic residue, e.g., leucyl, isoleucyl, phenylalanyl, valyl or alanyl; (b) a cysteine or proline is substituted for (or by) any other residue; (c) a residue having an electropositive side chain, e.g., lysyl, arginyl, or histidyl, is substituted for (or by) an electronegative residue, e.g., glutamyl or aspartyl; or (d) a residue having a bulky side chain, e.g., phenylalanine, is substituted for (or by) one not having a side chain, e.g., glycine.

[0095] The variants typically exhibit the same qualitative biological activity and will elicit the same immune response as the naturally-occurring analogue, although variants also are selected to modify the characteristics of the IL-2 mutein as needed. Alternatively, the variant may be designed such

that the biological activity of the IL-2 mutein is altered. For example, glycosylation sites may be altered or removed as discussed herein.

[0096] In another embodiment, the present invention provides an antibody comprising the heavy and light chain variable domains of one of the antibodies designated herein as 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 21D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, and 18H9.

[0097] In another embodiment, the present invention provides an anti-IL-2 antibody comprising a light chain variable domain comprising a sequence of amino acids that differs from the sequence of the light chain variable domain of 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 21D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9, only at 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 residue(s), wherein each such sequence difference is independently either a deletion, insertion, or substitution of one amino acid residue. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to the sequence of the light chain variable domain of 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 21D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a nucleotide sequence of FIG. **27**.

[0098] In another embodiment, the present invention provides an anti-IL-2 antibody comprising a heavy chain variable domain comprising a sequence of amino acids that differs from the sequence of the heavy chain variable domain of 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 21D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9, only at 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 residue(s), wherein each such sequence difference is independently either a deletion, insertion, or substitution of one amino acid residue. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to the sequence of the heavy chain variable domain of 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 21D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a nucleotide sequence of FIG. **29**.

[0099] In another embodiment, the present invention provides anti-IL-2 antibodies that comprise all three light chain CDR sequences and all three heavy chain CDR sequences of antibody 9D6, 2C3, 14C9, 8B12, 16A4, 16E1, 13A1, 8F10, 12C4, 9B12, 3H5, 18A6, 10A6, 10H7, 15A10, 12D2, 9B10, 17D3, 15G11, 14D7, 18F3, 17D9, 21F8, 22B9, 21D10, 14A6, 11D6, 10A9, 16E3, 14G7, 5H3, 2B12, 26H7, 26C12, 2H11, or 18H9.

[0100] In another embodiment, the present invention provides anti-IL-2 antibodies that cross-inhibit for binding to IL-2 as described in Example 15.

IL-2 Muteins and Anti-IL-2 Antibodies Having Extended Serum Half-Life

[0101] Because the IL-2 muteins provided herein preferentially expand Tregs over, for example Teff or NK cells, it is expected that the safety profile when administered to a patient will differ from that of wild-type IL-2 or PROLEUKIN® (aldesleukin; Novartis, Basel, Switzerland). Side-effects associated with wild-type IL-2 or PROLEUKIN® include flu-like symptoms, chills/rigor, arthralgia, fever, rash, pruritus, injection site reactions, hypotension, diarrhea, nausea, anxiety, confusion, and depression. The IL-2 muteins provided herein may be altered to include or fused to molecules that extend the serum half-life of the mutein without increasing the risk that such half-life extension would increase the likelihood or the intensity of a side-effect or adverse event in a patient. Subcutaneous dosing of such an extended serum half-life mutein may allow for prolonged target coverage with lower systemic maximal exposure (C_{max}). Extended serum half-life may allow a lower or less frequent dosing regimen of the mutein.

[0102] The serum half-life of the IL-2 muteins provided herein may be extended by essentially any method known in the art. Such methods include altering the sequence of the IL-2 mutein to include a peptide that binds to the neonatal Fcγ receptor or bind to a protein having extended serum half-life, e.g., IgG or human serum albumin. In other embodiments, the IL-2 mutein is fused to a polypeptide that confers extended half-life on the fusion molecule. Such polypeptides include an IgG Fc or other polypeptides that bind to the neonatal Fcγ receptor, human serum albumin, or polypeptides that bind to a protein having extended serum half-life. In preferred embodiments, the IL-2 mutein is fused to an IgG Fc molecule.

[0103] The IL-2 mutein may be fused to the N-terminus or the C-terminus of the IgG Fc region. As shown in the Examples, fusion to the C-terminus of the IgG Fc region maintains the IL-2 mutein activity to a greater extent than when fused to the N-terminus of the IgG Fc.

[0104] One embodiment of the present invention is directed to a dimer comprising two Fc-fusion polypeptides created by fusing an IL-2 mutein to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain bonds form between the Fc moieties to yield the dimer.

[0105] The term "Fc polypeptide" or "Fc region" as used herein includes native and mutein forms of polypeptides derived from the Fc region of an antibody and can be part of either the IL-2 mutein fusion proteins or the anti-IL-2 antibodies of the invention. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. In certain embodiments, the Fc region comprises an antibody CH2 and CH3 domain. Along with extended serum half-life, fusion proteins comprising Fc

moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns. Preferred Fc regions are derived from human IgG, which includes IgG1, IgG2, IgG3, and IgG4. Herein, specific residues within the Fc are identified by position. All Fc positions are based on the EU numbering scheme.

[0106] One of the functions of the Fc portion of an antibody is to communicate to the immune system when the antibody binds its target. This is considered "effector function." Communication leads to antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and/or complement dependent cytotoxicity (CDC). ADCC and ADCP are mediated through the binding of the Fc to Fc receptors on the surface of cells of the immune system. CDC is mediated through the binding of the Fc with proteins of the complement system, e.g., C1q.

[0107] The IgG subclasses vary in their ability to mediate effector functions. For example, IgG1 is much superior to IgG2 and IgG4 at mediating ADCC and CDC. Thus, in embodiments wherein effector function is undesirable, an IgG2 Fc would be preferred. IgG2 Fc-containing molecules, however, are known to be more difficult to manufacture and have less attractive biophysical properties, such as a shorter half-life, as compared to IgG1 Fc-containing molecules.

[0108] The effector function of an antibody can be increased, or decreased, by introducing one or more mutations into the Fc. Embodiments of the invention include IL-2 mutein Fc fusion proteins having an Fc engineered to increase effector function (U.S. Pat. No. 7,317,091 and Strohl, *Curr. Opin. Biotech.,* 20:685-691, 2009; both incorporated herein by reference in its entirety). Exemplary IgG1 Fc molecules having increased effector function include those having the following substitutions:

[0109] S239D/1332E
[0110] S239D/A330S/1332E
[0111] S239D/A330L/1332E
[0112] S298A/D333A/K334A
[0113] P2471/A339D
[0114] P2471/A339Q
[0115] D280H/K290S
[0116] D280H/K290S/S298D
[0117] D280H/K290S/S298V
[0118] F243L/R292P/Y300L
[0119] F243L/R292P/Y300L/P396L
[0120] F243L/R292P/Y300L/V3051/P396L
[0121] G236A/S239D/1332E
[0122] K326A/E333A
[0123] K326W/E333S
[0124] K290E/S298G/T299A
[0125] K290N/S298G/T299A
[0126] K290E/S298G/T299A/K326E
[0127] K290N/S298G/T299A/K326E

[0128] Another method of increasing effector function of IgG Fc-containing proteins is by reducing the fucosylation of the Fc. Removal of the core fucose from the biantennary complex-type oligosachharides attached to the Fc greatly increased ADCC effector function without altering antigen binding or CDC effector function. Several ways are known for reducing or abolishing fucosylation of Fc-containing molecules, e.g., antibodies. These include recombinant expression in certain mammalian cell lines including a FUT8 knockout cell line, variant CHO line Lec13, rat hybridoma cell line YB2/0, a cell line comprising a small interfering RNA specifically against the FUT8 gene, and a cell line coexpressing β-1,4-N-acetylglucosaminyltransferase 11 and Golgi α-mannosidase 11. Alternatively, the Fc-containing molecule may be expressed in a non-mammalian cell such as a plant cell, yeast, or prokaryotic cell, e.g., *E. coli.*

[0129] In certain embodiments, the IL-2 mutein Fc-fusion proteins or anti-IL-2 antibodies of the invention comprise an Fc engineered to decrease effector function. Exemplary Fc molecules having decreased effector function include those having the following substitutions:

[0130] N297A or N297Q (IgG1)
[0131] L234A/L235A (IgG1)
[0132] V234A/G237A (IgG2)
[0133] L235A/G237A/E318A (IgG4)
[0134] H268Q/V309L/A330S/A331S (IgG2)
[0135] C220S/C226S/C229S/P238S (IgG1)
[0136] C226S/C229S/E233P/L234V/L235A (IgG1)
[0137] L234F/L235E/P331S (IgG1)
[0138] S267E/L328F (IgG1)

[0139] It is known that human IgG1 has a glycosylation site at N297 (EU numbering system) and glycosylation contributes to the effector function of IgG1 antibodies. An exemplary IgG1 sequence is provided in SEQ ID NO:3:

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
1               5                  10

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
        15                  20

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
25                  30                  35

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                65                  70

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
        75                  80

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    110                 115                 120

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
                125                 130

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            160                 165

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
    170                 175                 180

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                185                 190
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-continued

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Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
205                 210                 215

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            220                 225
```

[0140] Groups have mutated N297 in an effort to make aglycosylated antibodies. The mutations have focuses on substituting N297 with amino acids that resemble asparagine in physiochemical nature such as glutamine (N297Q) or with alanine (N297A) which mimics asparagines without polar groups.

[0141] As used herein, "aglycosylated antibody" or "aglycosylated fc" refers to the glycosylation status of the residue at position 297 of the Fc. An antibody or other molecule may contain glycosylation at one or more other locations but may still be considered an aglycosylated antibody or aglcosylated Fc-fusion protein.

[0142] In the effort to make an effector functionless IgG1 Fc, it was discovered that mutation of amino acid N297 of human IgG1 to glycine, i.e., N297G, provides far superior purification efficiency and biophysical properties over other amino acid substitutions at that residue. See Example 8. Thus, in preferred embodiments, the IL-2 mutein Fc-fusion protein comprises a human IgG1 Fc having a N297G substitution. The Fc comprising the N297G substitution is useful in any context wherein a molecule comprises a human IgG1 Fc, and is not limited to use in the context of an IL-2 mutein Fc-fusion. In certain embodiments, an antibody comprises the Fc having a N297G substitution.

[0143] An Fc comprising a human IgG1 Fc having the N297G mutation may also comprise further insertions, deletions, and substitutions. In certain embodiments the human IgG1 Fc comprises the N297G substitution and is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the amino acid sequence set forth in SEQ ID NO:3. In a particularly preferred embodiment, the C-terminal lysine residue is substituted or deleted. The amino acid sequence of human IgG1 comprising the N297G substitution and deletion of the C-terminal lysine is set forth in SEQ ID NO:4.

[0144] A glycosylated IgG1 Fc-containing molecules were shown to be less stable than glycosylated IgG1 Fc-containing molecules. The Fc region may be further engineered to increase the stability of the aglycosylated molecule. In some embodiments, one or more amino acids are substituted to cysteine so to form di-sulfide bonds in the dimeric state. Residues V259, A287, R292, V302, L306, V323, or 1332 of the amino acid sequence set forth in SEQ ID NO:3 may be substituted with cysteine. In preferred embodiments, specific pairs of residues are substitution such that they preferentially form a di-sulfide bond with each other, thus limiting or preventing di-sulfide bond scrambling. Preferred pairs include, but are not limited to, A287C and L306C, V259C and L306C, R292C and V302C, and V323C and 1332C.

[0145] Provided herein are Fc-containing molecules wherein one or more of residues V259, A287, R292, V302, L306, V323, or 1332 are substituted with cysteine, examples of which include those comprising A287C and L306C, V259C and L306C, R292C and V302C, or V323C and 1332C substitutions.

[0146] Additional mutations that may be made to the IgG1 Fc include those facilitate heterodimer formation amongst Fc-containing polypeptides. In some embodiments, Fc region is engineering to create "knobs" and "holes" which facilitate heterodimer formation of two different Fc-containing polypeptide chains when co-expressed in a cell. U.S. Pat. No. 7,695,963. In other embodiments, the Fc region is altered to use electrostatic steering to encourage heterodimer formation while discouraging homodimer formation of two different Fc-containing polypeptide when co-expressed in a cell. WO 09/089,004, which is incorporated herein by reference in its entirety. Preferred heterodimeric Fc include those wherein one chain of the Fc comprises D399K and E356K substitutions and the other chain of the Fc comprises K409D and K392D substitutions. In other embodiments, one chain of the Fc comprises D399K, E356K, and E357K substitutions and the other chain of the Fc comprises K409D, K392D, and K370D substitutions.

[0147] In certain embodiments, it may be advantageous for the IL-2 mutein Fc-fusion protein to be monomeric, i.e., contain only a single IL-2 mutein molecule. Similarly, a bi-, tri, or tetra-specific antibody that can specifically bind one or more additional targets may be desired. In such embodiments, the Fc-region of the fusion protein or antibody may contain one or more mutations that facilitate heterodimer formation. The fusion protein or antibody is co-expressed with an Fc-region having reciprocal mutations to those in the IL-2 mutein Fc-fusion polypeptide but lacking an IL-2 mutein or anti-IL-2 heavy chain variable domain. When the heterodimer of the two Fc-containing polypeptides forms, the resulting protein comprises only a single IL-2 mutein or anti-IL-2 binding domain.

[0148] Another method of creating a monomeric IL-2 mutein Fc-fusion protein is fusing the IL-2 mutein to a monomeric Fc, i.e., an Fc region that does not dimerize. Stable monomeric Fcs comprise mutations that discourage dimerization and that stabilize the molecule in the monomeric form. Preferred monomeric Fcs are disclosed in WO 2011/063348, which is incorporated herein by reference in its entirety. In certain embodiments, IL-2 mutein Fc fusion proteins comprise an Fc comprising negatively charged amino acids at positions 392 and 409 along with a threonine substitution at Y349, L351, L368, V397, L398, F405, or Y407.

[0149] In certain embodiments, the IL-2 mutein Fc-fusion protein comprises a linker between the Fc and the IL-2 mutein. Many different linker polypeptides are known in the art and may be used in the context of an IL-2 mutein Fc-fusion protein. In preferred embodiments, the IL-2 mutein Fc-fusion protein comprises one or more copies of a peptide consisting of GGGGS (SEQ ID NO:5), GGNGT (SEQ ID NO: 6), or YGNGT (SEQ ID NO: 7) between the Fc and the IL-2 mutein. In some embodiments, the polypeptide region between the Fc region and the IL-2 mutein region comprises a single copy of GGGGS (SEQ ID NO: 5), GGNGT (SEQ ID NO: 6), or YGNGT (SEQ ID NO: 7). As shown herein, the linkers GGNGT (SEQ ID NO: 6) or YGNGT (SEQ ID NO: 7) are glycosylated when expressed in the appropriate cells and such glycosylation may help stabilize the protein in solution and/or when administered in vivo. Thus, in certain embodiments, an IL-2 mutein fusion

protein comprises a glycosylated linker between the Fc region and the IL-2 mutein region.

[0150] It is contemplated that the glycosylated linker may be useful when placed in the context of a polypeptide. Provided herein are polypeptides comprising GGNGT (SEQ ID NO: 6) or YGNGT (SEQ ID NO: 7) inserted into the amino acid sequence of the polypeptide or replacing one or more amino acids within the amino acid sequence of the polypeptide. In preferred embodiments, GGNGT (SEQ ID NO: 6) or YGNGT (SEQ ID NO: 7) is inserted into a loop of the polypeptides tertiary structure. In other embodiments, one or more amino acids of a loop are replaced with GGNGT (SEQ ID NO: 6) or YGNGT (SEQ ID NO: 7).

[0151] The C-terminal portion of the Fc and/or the amino terminal portion of the IL-2 mutein may contain one or more mutations that alter the glycosylation profile of the IL-2 mutein Fc-fusion protein when expressed in mammalian cells. In certain embodiments, the IL-2 mutein further comprises a T3 substitution, e.g., T3N or T3A. The IL-2 mutein may further comprise an S5 substitution, such as S5T

[0152] Covalent modifications of IL-2 mutein and IL-2 mutein Fc-fusion proteins and anti-IL-2 antibodies are included within the scope of this invention, and are generally, but not always, done post-translationally. For example, several types of covalent modifications are introduced into the molecule by reacting certain of its amino acid residues with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues.

[0153] Cysteinyl residues most commonly are reacted with α-haloacetates (and corresponding amines), such as chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteinyl residues also are derivatized by reaction with bromotrifluoroacetone, α-bromo-β-(5-imidozoyl)propionic acid, chloroacetyl phosphate, N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

[0154] Histidyl residues are derivatized by reaction with diethylpyrocarbonate at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain. Para-bromophenacyl bromide also is useful; the reaction is preferably performed in 0.1M sodium cacodylate at pH 6.0.

[0155] Lysinyl and amino terminal residues are reacted with succinic or other carboxylic acid anhydrides. Derivatization with these agents has the effect of reversing the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4-pentanedione; and transaminase-catalyzed reaction with glyoxylate.

[0156] Arginyl residues are modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pK_a of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

[0157] The specific modification of tyrosyl residues may be made, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidizole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively. Tyrosyl residues are iodinated using ^{125}I or ^{131}I to prepare labeled proteins for use in radioimmunoassay, the chloramine T method described above being suitable.

[0158] Carboxyl side groups (aspartyl or glutamyl) are selectively modified by reaction with carbodiimides (R'—N═C═N—R'), where R and R' are optionally different alkyl groups, such as 1-cyclohexyl-3-(2-morpholinyl-4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues are converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

[0159] Derivatization with bifunctional agents is useful for crosslinking antigen binding proteins to a water-insoluble support matrix or surface for use in a variety of methods. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis (succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

[0160] Glutaminyl and asparaginyl residues are frequently deamidated to the corresponding glutamyl and aspartyl residues, respectively. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

[0161] Other modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W. H. Freeman & Co., San Francisco, 1983, pp. 79-86), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

[0162] Another type of covalent modification of the IL-2 mutein, IL-2 mutein Fc-fusion, or anti-IL-2 antibody included within the scope of this invention comprises altering the glycosylation pattern of the protein. As is known in the art, glycosylation patterns can depend on both the sequence of the protein (e.g., the presence or absence of particular glycosylation amino acid residues, discussed below), or the host cell or organism in which the protein is produced. Particular expression systems are discussed below.

[0163] Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tri-peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tri-peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one

of the sugars N-acetylgalactosamine, galactose, or xylose, to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[0164] Addition of glycosylation sites to the IL-2 mutein, IL-2 mutein Fc-fusion, or anti-IL-2 antibody may be conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tri-peptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the starting sequence (for O-linked glycosylation sites). For ease, the IL-2 mutein, IL-2 mutein Fc-fusion, or anti-IL-2 antibody amino acid sequence is preferably altered through changes at the DNA level, particularly by mutating the DNA encoding the target polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

[0165] Another means of increasing the number of carbohydrate moieties on the IL-2 mutein, IL-2 mutein Fc-fusion, or anti-IL-2 antibody is by chemical or enzymatic coupling of glycosides to the protein. These procedures are advantageous in that they do not require production of the protein in a host cell that has glycosylation capabilities for N- and O-linked glycosylation. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO 87/05330 published Sep. 11, 1987, and in Aplin and Wriston, 1981, *CRC Crit. Rev. Biochem.*, pp. 259-306.

[0166] Removal of carbohydrate moieties present on the starting IL-2 mutein, IL-2 mutein Fc-fusion, or anti-IL-2 antibody may be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the protein to the compound trifluoromethanesulfonic acid, or an equivalent compound.

[0167] This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), while leaving the polypeptide intact. Chemical deglycosylation is described by Hakimuddin et al., 1987, *Arch. Biochem. Biophys.* 259:52 and by Edge et al., 1981, *Anal. Biochem.* 118:131. Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., 1987, *Meth. Enzymol.* 138:350. Glycosylation at potential glycosylation sites may be prevented by the use of the compound tunicamycin as described by Duskin et al., 1982, *J. Biol. Chem.* 257:3105. Tunicamycin blocks the formation of protein-N-glycoside linkages.

[0168] Another type of covalent modification of the IL-2 mutein, IL-2 mutein Fc-fusion, or anti-IL-2 antibody comprises linking the protein to various nonproteinaceous polymers, including, but not limited to, various polyols such as polyethylene glycol, polypropylene glycol or polyoxyalkylenes, in the manner set forth in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337. In addition, amino acid substitutions may be made in various positions within the IL-2 mutein, IL-2 mutein Fc-fusion, or anti-IL-2 antibody to facilitate the addition of polymers such as PEG. Thus, embodiments of the invention include PEGylated IL-2 mutein, IL-2 mutein Fc-fusion, or anti-IL-2 antibody. Such PEGylated proteins may have increased half-life and/or reduced immunogenicity over their non-PEGylated forms.

Polynucleotides Encoding IL-2 Muteins and IL-2 Mutein Fc-Fusion Proteins

[0169] Encompassed within the invention are nucleic acids encoding IL-2 muteins, IL-2 mutein Fc-fusions, or anti-IL-2 antibodies. Aspects of the invention include polynucleotide variants (e.g., due to degeneracy) that encode the amino acid sequences described herein.

[0170] Nucleotide sequences corresponding to the amino acid sequences described herein, to be used as probes or primers for the isolation of nucleic acids or as query sequences for database searches, can be obtained by "back-translation" from the amino acid sequences. The well-known polymerase chain reaction (PCR) procedure can be employed to isolate and amplify a DNA sequence encoding IL-2 muteins and IL-2 mutein Fc-fusion protein. Oligonucleotides that define the desired termini of the combination of DNA fragments are employed as 5' and 3' primers. The oligonucleotides can additionally contain recognition sites for restriction endonucleases, to facilitate insertion of the amplified combination of DNA fragments into an expression vector. PCR techniques are described in Saiki et al., *Science* 239:487 (1988); *Recombinant DNA Methodology*, Wu et al., eds., Academic Press, Inc., San Diego (1989), pp. 189-196; and *PCR Protocols: A Guide to Methods and Applications*, Innis et. al., eds., Academic Press, Inc. (1990).

[0171] Nucleic acid molecules of the invention include DNA and RNA in both single-stranded and double-stranded form, as well as the corresponding complementary sequences. An "isolated nucleic acid" is a nucleic acid that has been separated from adjacent genetic sequences present in the genome of the organism from which the nucleic acid was isolated, in the case of nucleic acids isolated from naturally-occurring sources. In the case of nucleic acids synthesized enzymatically from a template or chemically, such as PCR products, cDNA molecules, or oligonucleotides for example, it is understood that the nucleic acids resulting from such processes are isolated nucleic acids. An isolated nucleic acid molecule refers to a nucleic acid molecule in the form of a separate fragment or as a component of a larger nucleic acid construct. In one preferred embodiment, the nucleic acids are substantially free from contaminating endogenous material. The nucleic acid molecule has preferably been derived from DNA or RNA isolated at least once in substantially pure form and in a quantity or concentration enabling identification, manipulation, and recovery of its component nucleotide sequences by standard biochemical methods (such as those outlined in Sambrook et al., *Molecular Cloning: A Laboratory Manual,* 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989)). Such sequences are preferably provided and/or constructed in the form of an open reading frame uninterrupted by internal non-translated sequences, or introns, that are typically present in eukaryotic genes. Sequences of non-translated DNA can be present 5' or 3' from an open reading frame, where the same do not interfere with manipulation or expression of the coding region.

[0172] The IL-2 muteins according to the invention are ordinarily prepared by site specific mutagenesis of nucleo-

tides in the DNA encoding the IL-2 mutein or IL-2 mutein Fc-fusion protein, using cassette or PCR mutagenesis or other techniques well known in the art, to produce DNA encoding the variant, and thereafter expressing the recombinant DNA in cell culture as outlined herein. However, IL-2 muteins and IL-2 mutein Fc-fusion may be prepared by in vitro synthesis using established techniques. The variants typically exhibit the same qualitative biological activity as the naturally occurring analogue, e.g., Treg expansion, although variants can also be selected which have modified characteristics as will be more fully outlined below.

[0173] As will be appreciated by those in the art, due to the degeneracy of the genetic code, each IL-2 mutein, IL-2 mutein Fc-fusion, and anti-IL-2 antibody of the present invention is encoded by an extremely large number of nucleic acids, each of which is within the scope of the invention and can be made using standard techniques. Thus, having identified a particular amino acid sequence, those skilled in the art could make any number of different nucleic acids, by simply modifying the sequence of one or more codons in a way that does not change the amino acid sequence of the encoded protein.

[0174] The present invention also provides expression systems and constructs in the form of plasmids, expression vectors, transcription or expression cassettes which comprise at least one polynucleotide as above. In addition, the invention provides host cells comprising such expression systems or constructs. Typically, expression vectors used in any of the host cells will contain sequences for plasmid maintenance and for cloning and expression of exogenous nucleotide sequences. Such sequences, collectively referred to as "flanking sequences" in certain embodiments will typically include one or more of the following nucleotide sequences: a promoter, one or more enhancer sequences, an origin of replication, a transcriptional termination sequence, a complete intron sequence containing a donor and acceptor splice site, a sequence encoding a leader sequence for polypeptide secretion, a ribosome binding site, a polyadenylation sequence, a polylinker region for inserting the nucleic acid encoding the polypeptide to be expressed, and a selectable marker element. Each of these sequences is discussed below.

[0175] Optionally, the vector may contain a "tag"-encoding sequence, i.e., an oligonucleotide molecule located at the 5' or 3' end of the IL-2 mutein, IL-2 mutein Fc-fusion, or anti-IL-2 antibody-encoding sequence; the oligonucleotide sequence encodes polyHis (such as hexaHis (SEQ ID NO: 21)), or another "tag" such as FLAG, HA (hemaglutinin influenza virus), or myc, for which commercially available antibodies exist. This tag is typically fused to the polypeptide upon expression of the polypeptide, and can serve as a means for affinity purification or detection of it from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies against the tag as an affinity matrix. Optionally, the tag can subsequently be removed by various means such as using certain peptidases for cleavage.

[0176] Flanking sequences may be homologous (i.e., from the same species and/or strain as the host cell), heterologous (i.e., from a species other than the host cell species or strain), hybrid (i.e., a combination of flanking sequences from more than one source), synthetic or native. As such, the source of a flanking sequence may be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence is functional in, and can be activated by, the host cell machinery.

[0177] Flanking sequences useful in the vectors of this invention may be obtained by any of several methods well known in the art. Typically, flanking sequences useful herein will have been previously identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In some cases, the full nucleotide sequence of a flanking sequence may be known. Here, the flanking sequence may be synthesized using the methods described herein for nucleic acid synthesis or cloning.

[0178] Whether all or only a portion of the flanking sequence is known, it may be obtained using polymerase chain reaction (PCR) and/or by screening a genomic library with a suitable probe such as an oligonucleotide and/or flanking sequence fragment from the same or another species. Where the flanking sequence is not known, a fragment of DNA containing a flanking sequence may be isolated from a larger piece of DNA that may contain, for example, a coding sequence or even another gene or genes. Isolation may be accomplished by restriction endonuclease digestion to produce the proper DNA fragment followed by isolation using agarose gel purification, Qiagen® column chromatography (Chatsworth, CA), or other methods known to the skilled artisan. The selection of suitable enzymes to accomplish this purpose will be readily apparent to one of ordinary skill in the art.

[0179] An origin of replication is typically a part of those prokaryotic expression vectors purchased commercially, and the origin aids in the amplification of the vector in a host cell. If the vector of choice does not contain an origin of replication site, one may be chemically synthesized based on a known sequence, and ligated into the vector. For example, the origin of replication from the plasmid pBR322 (New England Biolabs, Beverly, MA) is suitable for most gram-negative bacteria, and various viral origins (e.g., SV40, polyoma, adenovirus, vesicular stomatitus virus (VSV), or papillomaviruses such as HPV or BPV) are useful for cloning vectors in mammalian cells. Generally, the origin of replication component is not needed for mammalian expression vectors (for example, the SV40 origin is often used only because it also contains the virus early promoter).

[0180] A transcription termination sequence is typically located 3' to the end of a polypeptide coding region and serves to terminate transcription. Usually, a transcription termination sequence in prokaryotic cells is a G-C rich fragment followed by a poly-T sequence. While the sequence is easily cloned from a library or even purchased commercially as part of a vector, it can also be readily synthesized using methods for nucleic acid synthesis such as those described herein.

[0181] A selectable marker gene encodes a protein necessary for the survival and growth of a host cell grown in a selective culture medium. Typical selection marker genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, tetracycline, or kanamycin for prokaryotic host cells; (b) complement auxotrophic deficiencies of the cell; or (c) supply critical nutrients not available from complex or defined media. Specific selectable markers are the kanamycin resistance gene, the ampicillin resistance gene, and the tetracycline resistance gene.

Advantageously, a neomycin resistance gene may also be used for selection in both prokaryotic and eukaryotic host cells.

[0182] Other selectable genes may be used to amplify the gene that will be expressed. Amplification is the process wherein genes that are required for production of a protein critical for growth or cell survival are reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples of suitable selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and promoterless thyrnidine kinase genes. Mammalian cell transformants are placed under selection pressure wherein only the transformants are uniquely adapted to survive by virtue of the selectable gene present in the vector. Selection pressure is imposed by culturing the transformed cells under conditions in which the concentration of selection agent in the medium is successively increased, thereby leading to the amplification of both the selectable gene and, consequently, of a gene that encodes a desired polypeptide, such as an IL-2 mutein, IL-2 mutein Fc-fusion, or the heavy and/or light chain of an anti-IL-2 antibody. As a result, increased quantities of the polypeptide are synthesized from the amplified DNA.

[0183] A ribosome-binding site is usually necessary for translation initiation of mRNA and is characterized by a Shine-Dalgarno sequence (prokaryotes) or a Kozak sequence (eukaryotes). The element is typically located 3' to the promoter and 5' to the coding sequence of the polypeptide to be expressed. In certain embodiments, one or more coding regions may be operably linked to an internal ribosome binding site (IRES), allowing translation of two open reading frames from a single RNA transcript.

[0184] In some cases, such as where glycosylation is desired in a eukaryotic host cell expression system, one may manipulate the various pre- or prosequences to improve glycosylation or yield. For example, one may alter the peptidase cleavage site of a particular signal peptide, or add prosequences, which also may affect glycosylation. The final protein product may have, in the −1 position (relative to the first amino acid of the mature protein) one or more additional amino acids incident to expression, which may not have been totally removed. For example, the final protein product may have one or two amino acid residues found in the peptidase cleavage site, attached to the amino-terminus. Alternatively, use of some enzyme cleavage sites may result in a slightly truncated form of the desired polypeptide, if the enzyme cuts at such area within the mature polypeptide.

[0185] Expression and cloning vectors of the invention will typically contain a promoter that is recognized by the host organism and operably linked to the molecule encoding the IL-2 mutein, IL-2 mutein Fc-fusion, or the heavy and/or light chain of an anti-IL-2 antibody. Promoters are untranscribed sequences located upstream (i.e., 5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control transcription of the structural gene. Promoters are conventionally grouped into one of two classes: inducible promoters and constitutive promoters. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, such as the presence or absence of a nutrient or a change in temperature. Constitutive promoters, on the other hand, uniformly transcribe gene to which they are operably linked, that is, with little or no control over gene expression. A large number of promoters, recognized by a variety of potential host cells, are well known.

[0186] Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable promoters for use with mammalian host cells are well known and include, but are not limited to, those obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, retroviruses, hepatitis-B virus and most preferably Simian Virus 40 (SV40). Other suitable mammalian promoters include heterologous mammalian promoters, for example, heat-shock promoters and the actin promoter.

[0187] Additional promoters which may be of interest include, but are not limited to: SV40 early promoter (Benoist and Chambon, 1981, *Nature* 290:304-310); CMV promoter (Thornsen et al., 1984, *Proc. Natl. Acad. U.S.A.* 81:659-663); the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., 1980, *Cell* 22:787-797); herpes thymidine kinase promoter (Wagner et al., 1981, *Proc. Natl. Acad. Sci. U.S.A.* 78:1444-1445); promoter and regulatory sequences from the metallothionine gene Prinster et al., 1982, *Nature* 296:39-42); and prokaryotic promoters such as the beta-lactamase promoter (Villa-Kamaroff et al., 1978, *Proc. Natl. Acad. Sci. U.S.A.* 75:3727-3731); or the tac promoter (DeBoer et al., 1983, *Proc. Natl. Acad. Sci. U.S.A.* 80:21-25). Also of interest are the following animal transcriptional control regions, which exhibit tissue specificity and have been utilized in transgenic animals: the elastase I gene control region that is active in pancreatic acinar cells (Swift et al., 1984, *Cell* 38:639-646; Ornitz et al., 1986, *Cold Spring Harbor Symp. Quant. Biol.* 50:399-409; MacDonald, 1987, *Hepatology* 7:425-515); the insulin gene control region that is active in pancreatic beta cells (Hanahan, 1985, *Nature* 315:115-122); the immunoglobulin gene control region that is active in lymphoid cells (Grosschedl et al., 1984, *Cell* 38:647-658; Adames et al., 1985, *Nature* 318:533-538; Alexander et al., 1987, *Mol. Cell. Biol.* 7:1436-1444); the mouse mammary tumor virus control region that is active in testicular, breast, lymphoid and mast cells (Leder et al., 1986, *Cell* 45:485-495); the albumin gene control region that is active in liver (Pinkert et al., 1987, *Genes and Devel.* 1:268-276); the alpha-fetoprotein gene control region that is active in liver (Krumlauf et al., 1985, *Mol. Cell. Biol.* 5:1639-1648; Hammer et al., 1987, *Science* 253:53-58); the alpha 1-antitrypsin gene control region that is active in liver (Kelsey et al., 1987, *Genes and Devel.* 1:161-171); the beta-globin gene control region that is active in myeloid cells (Mogram et al., 1985, *Nature* 315:338-340; Kollias et al., 1986, *Cell* 46:89-94); the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain (Readhead et al., 1987, *Cell* 48:703-712); the myosin light chain-2 gene control region that is active in skeletal muscle (Sani, 1985, *Nature* 314:283-286); and the gonadotropic releasing hormone gene control region that is active in the hypothalamus (Mason et al., 1986, *Science* 234:1372-1378).

[0188] An enhancer sequence may be inserted into the vector to increase transcription by higher eukaryotes. Enhancers are cis-acting elements of DNA, usually about 10-300 bp in length, that act on the promoter to increase transcription. Enhancers are relatively orientation and position independent, having been found at positions both 5' and 3' to the transcription unit. Several enhancer sequences

available from mammalian genes are known (e.g., globin, elastase, albumin, alpha-feto-protein and insulin). Typically, however, an enhancer from a virus is used. The SV40 enhancer, the cytomegalovirus early promoter enhancer, the polyoma enhancer, and adenovirus enhancers known in the art are exemplary enhancing elements for the activation of eukaryotic promoters. While an enhancer may be positioned in the vector either 5' or 3' to a coding sequence, it is typically located at a site 5' from the promoter. A sequence encoding an appropriate native or heterologous signal sequence (leader sequence or signal peptide) can be incorporated into an expression vector, to promote extracellular secretion of the IL-2 mutein, IL-2 mutein Fc-fusion, or heavy and/or light chain of an anti-IL-2 antibody. The choice of signal peptide or leader depends on the type of host cells in which the protein is to be produced, and a heterologous signal sequence can replace the native signal sequence. Examples of signal peptides that are functional in mammalian host cells include the following: the signal sequence for interleukin-7 (IL-7) described in U.S. Pat. No. 4,965,195; the signal sequence for interleukin-2 receptor described in Cosman et al., 1984, *Nature* 312:768; the interleukin-4 receptor signal peptide described in EP Patent No. 0367 566; the type I interleukin-1 receptor signal peptide described in U.S. Pat. No. 4,968,607; the type II interleukin-1 receptor signal peptide described in EP Patent No. 0 460 846. In one embodiment, IL-2 mutein Fc-fusions of the invention comprise a leader sequence as illustrated in FIG. **24**.

[0189] The vector may contain one or more elements that facilitate expression when the vector is integrated into the host cell genome. Examples include an EASE element (Aldrich et al. 2003 *Biotechnol Prog.* 19:1433-38) and a matrix attachment region (MAR). MARs mediate structural organization of the chromatin and may insulate the integrated vector from "position" effect. Thus, MARs are particularly useful when the vector is used to create stable transfectants. A number of natural and synthetic MAR-containing nucleic acids are known in the art, e.g., U.S. Pat. Nos. 6,239,328; 7,326,567; 6,177,612; 6,388,066; 6,245,974; 7,259,010; 6,037,525; 7,422,874; 7,129,062.

[0190] Expression vectors of the invention may be constructed from a starting vector such as a commercially available vector. Such vectors may or may not contain all of the desired flanking sequences. Where one or more of the flanking sequences described herein are not already present in the vector, they may be individually obtained and ligated into the vector. Methods used for obtaining each of the flanking sequences are well known to one skilled in the art.

[0191] After the vector has been constructed and a nucleic acid molecule encoding an IL-2 mutein, IL-2 mutein Fc-fusion, or the heavy and/or light chain of anti-IL-2 antibody has been inserted into the proper site of the vector, the completed vector may be inserted into a suitable host cell for amplification and/or polypeptide expression. The transformation of an expression vector into a selected host cell may be accomplished by well-known methods including transfection, infection, calcium phosphate co-precipitation, electroporation, microinjection, lipofection, DEAE-dextran mediated transfection, or other known techniques. The method selected will in part be a function of the type of host cell to be used. These methods and other suitable methods are well known to the skilled artisan, and are set forth, for example, in Sambrook et al., 2001, supra.

[0192] A host cell, when cultured under appropriate conditions, synthesizes an IL-2 mutein, IL-2 mutein Fc-fusion, or the heavy and/or light chain of an anti-IL-2 antibody that can subsequently be collected from the culture medium (if the host cell secretes it into the medium) or directly from the host cell producing it (if it is not secreted). The selection of an appropriate host cell will depend upon various factors, such as desired expression levels, polypeptide modifications that are desirable or necessary for activity (such as glycosylation or phosphorylation) and ease of folding into a biologically active molecule. A host cell may be eukaryotic or prokaryotic.

[0193] Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to, immortalized cell lines available from the American Type Culture Collection (ATCC) and any cell lines used in an expression system known in the art can be used to make the recombinant polypeptides of the invention. In general, host cells are transformed with a recombinant expression vector that comprises DNA encoding a desired IL-2 mutein, IL-2 mutein Fc-fusion, or anti-IL-2 antibody. Among the host cells that may be employed are prokaryotes, yeast or higher eukaryotic cells. Prokaryotes include gram negative or gram positive organisms, for example *E. coli* or bacilli. Higher eukaryotic cells include insect cells and established cell lines of mammalian origin. Examples of suitable mammalian host cell lines include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (Gluzman et al., 1981, Cell 23:175), L cells, 293 cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells, or their derivatives such as Veggie CHO and related cell lines which grow in serum-free media (Rasmussen et al., 1998, *Cytotechnology* 28: 31), HeLa cells, BHK (ATCC CRL 10) cell lines, and the CVI/EBNA cell line derived from the African green monkey kidney cell line CVI (ATCC CCL 70) as described by McMahan et al., 1991, EMBO J. 10: 2821, human embryonic kidney cells such as 293, 293 EBNA or MSR 293, human epidermal A431 cells, human Colo205 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HL-60, U937, HaK or Jurkat cells. Optionally, mammalian cell lines such as HepG2/3B, KB, NIH 3T3 or S49, for example, can be used for expression of the polypeptide when it is desirable to use the polypeptide in various signal transduction or reporter assays.

[0194] Alternatively, it is possible to produce the polypeptide in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Suitable yeasts include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces strains, Candida*, or any yeast strain capable of expressing heterologous polypeptides. Suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous polypeptides. If the polypeptide is made in yeast or bacteria, it may be desirable to modify the polypeptide produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional polypeptide. Such covalent attachments can be accomplished using known chemical or enzymatic methods.

[0195] The polypeptide can also be produced by operably linking the isolated nucleic acid of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are

commercially available in kit form from, e.g., Invitrogen, San Diego, Calif., U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), and Luckow and Summers, *Bio/Technology* 6:47 (1988). Cell-free translation systems could also be employed to produce polypeptides using RNAs derived from nucleic acid constructs disclosed herein. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (*Cloning Vectors: A Laboratory Manual, Elsevier*, New York, 1985). A host cell that comprises an isolated nucleic acid of the invention, preferably operably linked to at least one expression control sequence, is a "recombinant host cell".

[0196] In certain aspects, the invention includes an isolated nucleic acid encoding a human IL-2 mutein that preferentially stimulates T regulatory cells and comprises a D20E, D20G, D20W, D84A, D84S, H16D, H16G, H16K, H16R, H16T, H16V, 192K, 192R, L12K, L19D, L19N, L19T, N88D, N88R, N88S, V91D, V91G, V91K, and/or V91S substitution and an amino acid sequence at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO:1.

[0197] Also included are isolated nucleic acids encoding any of the exemplary IL-2 mutein Fc-fusion proteins described herein. In preferred embodiments, the Fc portion of an antibody and the human IL-2 mutein are encoded within a single open-reading frame, optionally with a linker encoded between the Fc region and the IL-2 mutein.

[0198] In another aspect, provided herein are expression vectors comprising the above IL-2 mutein- or IL-2 mutein Fc-fusion protein-encoding nucleic acids operably linked to a promoter.

[0199] In another aspect, provided herein are host cells comprising the isolated nucleic acids encoding the above IL-2 muteins, IL-2 mutein Fc-fusion proteins, or anti-IL-2 antibodies. The host cell may be a prokaryotic cell, such as *E. coli*, or may be a eukaryotic cell, such as a mammalian cell. In certain embodiments, the host cell is a Chinese hamster ovary (CHO) cell line.

[0200] In another aspect, provided herein are methods of making a human IL-2 mutein. The methods comprising culturing a host cell under conditions in which a promoter operably linked to a human IL-2 mutein is expressed. Subsequently, the human IL-2 mutein is harvested from said culture. The IL-2 mutein may be harvested from the culture media and/or host cell lysates.

[0201] In another aspect, provided herein are methods of making a human IL-2 mutein Fc-fusion protein. The methods comprising culturing a host cell under conditions in which a promoter operably linked to a human IL-2 mutein Fc-fusion protein is expressed. Subsequently, the human IL-2 mutein Fc-fusion protein is harvested from said culture. The human IL-2 mutein Fc-fusion protein may be harvested from the culture media and/or host cell lysates.

[0202] In another aspect, provided herein are methods of making an anti-IL-2 antibody. The methods comprising culturing a host cell under conditions in which promoters operably linked to the heavy and light chains of an anti-IL-2 antibody are expressed. Subsequently, the anti-IL-2 antibody is harvested from said culture. The anti-IL-2 antibody may be harvested from the culture media and/or host cell lysates.

Pharmaceutical Compositions

[0203] In some embodiments, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of an IL-2 mutein or anti-IL-2 antibody together with a pharmaceutically effective diluents, carrier, solubilizer, emulsifier, preservative, and/or adjuvant. In certain embodiments, the IL-2 mutein is within the context of an IL-2 mutein Fc-fusion protein. Pharmaceutical compositions of the invention include, but are not limited to, liquid, frozen, and lyophilized compositions.

[0204] Preferably, formulation materials are nontoxic to recipients at the dosages and concentrations employed. In specific embodiments, pharmaceutical compositions comprising a therapeutically effective amount of an IL-2 mutein containing therapeutic molecule, e.g., an IL-2 mutein Fc-fusion, are provided.

[0205] In certain embodiments, the pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine, proline, or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrins); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. See, REMINGTON'S PHARMACEUTICAL SCIENCES, 18" Edition, (A. R. Genrmo, ed.), 1990, Mack Publishing Company.

[0206] In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, supra. In certain embodiments, such compositions may influence the physical state, stability, rate of in vivo

release and rate of in vivo clearance of the antigen binding proteins of the invention. In certain embodiments, the primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In specific embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, and may further include sorbitol or a suitable substitute therefor. In certain embodiments of the invention, 11-2 mutein or anti-IL-2 antibody compositions may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (REMINGTON'S PHARMACEUTICAL SCIENCES, supra) in the form of a lyophilized cake or an aqueous solution. Further, in certain embodiments, the IL-2 mutein or anti-IL-2 antibody product may be formulated as a lyophilizate using appropriate excipients such as sucrose.

[0207] The pharmaceutical compositions of the invention can be selected for parenteral delivery. Alternatively, the compositions may be selected for inhalation or for delivery through the digestive tract, such as orally. Preparation of such pharmaceutically acceptable compositions is within the skill of the art. The formulation components are present preferably in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0208] When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be provided in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired IL-2 mutein or anti-IL-2 antibody composition in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the mutein or anti-IL-2 antibody composition is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that may provide controlled or sustained release of the product which can be delivered via depot injection. In certain embodiments, hyaluronic acid may also be used, having the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices may be used to introduce the IL-2 mutein or anti-IL-2 antibody composition.

[0209] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving IL-2 mutein or anti-IL-2 antibody compositions in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See, for example, International Patent Application No. PCT/US93/00829, which is incorporated by reference and describes controlled release of porous polymeric microparticles for delivery of pharmaceutical compositions. Sustained-release preparations may include semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides (as disclosed in U.S. Pat. No. 3,773,919 and European Patent Application Publication No. EP 058481, each of which is incorporated by reference), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., 1983, Biopolymers 2:547-556), poly (2-hydroxyethyl-methacrylate) (Langer et al., 1981, J. Biomed. Mater. Res. 15:167-277 and Langer, 1982, Chem. Tech. 12:98-105), ethylene vinyl acetate (Langer et al., 1981, supra) or poly-D(−)-3-hydroxybutyric acid (European Patent Application Publication No. EP 133,988). Sustained release compositions may also include liposomes that can be prepared by any of several methods known in the art. See, e.g., Eppstein et al., 1985, Proc. Natl. Acad. Sci. U.S.A. 82:3688-3692; European Patent Application Publication Nos. EP 036,676; EP 088,046 and EP 143,949, incorporated by reference.

[0210] Pharmaceutical compositions used for in vivo administration are typically provided as sterile preparations. Sterilization can be accomplished by filtration through sterile filtration membranes. When the composition is lyophilized, sterilization using this method may be conducted either prior to or following lyophilization and reconstitution. Compositions for parenteral administration can be stored in lyophilized form or in a solution. Parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0211] Aspects of the invention includes self-buffering IL-2 mutein or anti-IL-2 antibody formulations, which can be used as pharmaceutical compositions, as described in international patent application WO 06138181A2 (PCT/US2006/022599), which is incorporated by reference in its entirety herein.

[0212] As discussed above, certain embodiments provide IL-2 mutein or anti-IL-2 antibody compositions, particularly pharmaceutical 11-2 mutein Fc-fusion proteins, that comprise, in addition to the IL-2 mutein or anti-IL-2 antibody composition, one or more excipients such as those illustratively described in this section and elsewhere herein. Excipients can be used in the invention in this regard for a wide variety of purposes, such as adjusting physical, chemical, or biological properties of formulations, such as adjustment of viscosity, and or processes of the invention to improve effectiveness and or to stabilize such formulations and processes against degradation and spoilage due to, for instance, stresses that occur during manufacturing, shipping, storage, pre-use preparation, administration, and thereafter.

[0213] A variety of expositions are available on protein stabilization and formulation materials and methods useful in this regard, such as Arakawa et al., "Solvent interactions in pharmaceutical formulations," Pharm Res. 8(3): 285-91 (1991); Kendrick et al., "Physical stabilization of proteins in aqueous solution," in: RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS: THEORY AND PRACTICE, Carpenter and Manning, eds. Pharmaceutical Biotechnology. 13: 61-84 (2002), and Randolph et al., "Surfactant-protein interactions," Pharm Biotechnol. 13: 159-75 (2002), each of which is herein incorporated by reference in its entirety, particularly in parts pertinent to excipients and processes of the same for self-buffering protein formulations in accordance with the current invention, especially as to

protein pharmaceutical products and processes for veterinary and/or human medical uses.

[0214] Salts may be used in accordance with certain embodiments of the invention to, for example, adjust the ionic strength and/or the isotonicity of a formulation and/or to improve the solubility and/or physical stability of a protein or other ingredient of a composition in accordance with the invention.

[0215] As is well known, ions can stabilize the native state of proteins by binding to charged residues on the protein's surface and by shielding charged and polar groups in the protein and reducing the strength of their electrostatic interactions, attractive, and repulsive interactions. Ions also can stabilize the denatured state of a protein by binding to, in particular, the denatured peptide linkages (—CONH) of the protein. Furthermore, ionic interaction with charged and polar groups in a protein also can reduce intermolecular electrostatic interactions and, thereby, prevent or reduce protein aggregation and insolubility.

[0216] Ionic species differ significantly in their effects on proteins. A number of categorical rankings of ions and their effects on proteins have been developed that can be used in formulating pharmaceutical compositions in accordance with the invention. One example is the Hofmeister series, which ranks ionic and polar non-ionic solutes by their effect on the conformational stability of proteins in solution. Stabilizing solutes are referred to as "kosmotropic." Destabilizing solutes are referred to as "chaotropic." Kosmotropes commonly are used at high concentrations (e.g., >1 molar ammonium sulfate) to precipitate proteins from solution ("salting-out"). Chaotropes commonly are used to denture and/or to solubilize proteins ("salting-in"). The relative effectiveness of ions to "salt-in" and "salt-out" defines their position in the Hofmeister series.

[0217] Free amino acids can be used in IL-2 mutein or anti-IL-2 antibody formulations in accordance with various embodiments of the invention as bulking agents, stabilizers, and antioxidants, as well as other standard uses. Lysine, proline, serine, and alanine can be used for stabilizing proteins in a formulation. Glycine is useful in lyophilization to ensure correct cake structure and properties. Arginine may be useful to inhibit protein aggregation, in both liquid and lyophilized formulations. Methionine is useful as an antioxidant.

[0218] Polyols include sugars, e.g., mannitol, sucrose, and sorbitol and polyhydric alcohols such as, for instance, glycerol and propylene glycol, and, for purposes of discussion herein, polyethylene glycol (PEG) and related substances. Polyols are kosmotropic. They are useful stabilizing agents in both liquid and lyophilized formulations to protect proteins from physical and chemical degradation processes. Polyols also are useful for adjusting the tonicity of formulations.

[0219] Among polyols useful in select embodiments of the invention is mannitol, commonly used to ensure structural stability of the cake in lyophilized formulations. It ensures structural stability to the cake. It is generally used with a lyoprotectant, e.g., sucrose. Sorbitol and sucrose are among preferred agents for adjusting tonicity and as stabilizers to protect against freeze-thaw stresses during transport or the preparation of bulks during the manufacturing process. Reducing sugars (which contain free aldehyde or ketone groups), such as glucose and lactose, can glycate surface lysine and arginine residues. Therefore, they generally are not among preferred polyols for use in accordance with the invention. In addition, sugars that form such reactive species, such as sucrose, which is hydrolyzed to fructose and glucose under acidic conditions, and consequently engenders glycation, also is not among preferred polyols of the invention in this regard. PEG is useful to stabilize proteins and as a cryoprotectant and can be used in the invention in this regard.

[0220] Embodiments of IL-2 mutein and/or anti-IL-2 antibody formulations further comprise surfactants. Protein molecules may be susceptible to adsorption on surfaces and to denaturation and consequent aggregation at air-liquid, solid-liquid, and liquid-liquid interfaces. These effects generally scale inversely with protein concentration. These deleterious interactions generally scale inversely with protein concentration and typically are exacerbated by physical agitation, such as that generated during the shipping and handling of a product.

[0221] Surfactants routinely are used to prevent, minimize, or reduce surface adsorption. Useful surfactants in the invention in this regard include polysorbate 20, polysorbate 80, other fatty acid esters of sorbitan polyethoxylates, and poloxamer 188.

[0222] Surfactants also are commonly used to control protein conformational stability. The use of surfactants in this regard is protein-specific since, any given surfactant typically will stabilize some proteins and destabilize others.

[0223] Polysorbates are susceptible to oxidative degradation and often, as supplied, contain sufficient quantities of peroxides to cause oxidation of protein residue side-chains, especially methionine.

[0224] Consequently, polysorbates should be used carefully, and when used, should be employed at their lowest effective concentration. In this regard, polysorbates exemplify the general rule that excipients should be used in their lowest effective concentrations.

[0225] Embodiments of IL-2 mutein or anti-IL-2 antibody formulations further comprise one or more antioxidants. To some extent deleterious oxidation of proteins can be prevented in pharmaceutical formulations by maintaining proper levels of ambient oxygen and temperature and by avoiding exposure to light. Antioxidant excipients can be used as well to prevent oxidative degradation of proteins. Among useful antioxidants in this regard are reducing agents, oxygen/free-radical scavengers, and chelating agents. Antioxidants for use in therapeutic protein formulations in accordance with the invention preferably are water-soluble and maintain their activity throughout the shelf life of a product. EDTA is a preferred antioxidant in accordance with the invention in this regard.

[0226] Antioxidants can damage proteins. For instance, reducing agents, such as glutathione in particular, can disrupt intramolecular disulfide linkages. Thus, antioxidants for use in the invention are selected to, among other things, eliminate or sufficiently reduce the possibility of themselves damaging proteins in the formulation.

[0227] Formulations in accordance with the invention may include metal ions that are protein co-factors and that are necessary to form protein coordination complexes, such as zinc necessary to form certain insulin suspensions. Metal ions also can inhibit some processes that degrade proteins.

[0228] However, metal ions also catalyze physical and chemical processes that degrade proteins.

[0229] Magnesium ions (10-120 mM) can be used to inhibit isomerization of aspartic acid to isoaspartic acid. Ca^{+2} ions (up to 100 mM) can increase the stability of human deoxyribonuclease. Mg^{+2}, Mn^{+2}, and Zn^{+2}, however, can destabilize rhDNase. Similarly, Ca^{+2} and Sr^{+2} can stabilize Factor VIII, it can be destabilized by Mg^{+2}, Mn^{+2} and Zn^{+2}, Cu^{+2} and Fe^{+2}, and its aggregation can be increased by Al^{+3} ions.

[0230] Embodiments of IL-2 mutein or anti-IL-2 antibody formulations further comprise one or more preservatives. Preservatives are necessary when developing multi-dose parenteral formulations that involve more than one extraction from the same container. Their primary function is to inhibit microbial growth and ensure product sterility throughout the shelf-life or term of use of the drug product. Commonly used preservatives include benzyl alcohol, phenol and m-cresol. Although preservatives have a long history of use with small-molecule parenterals, the development of protein formulations that includes preservatives can be challenging. Preservatives almost always have a destabilizing effect (aggregation) on proteins, and this has become a major factor in limiting their use in multi-dose protein formulations. To date, most protein drugs have been formulated for single-use only. However, when multi-dose formulations are possible, they have the added advantage of enabling patient convenience, and increased marketability. A good example is that of human growth hormone (hGH) where the development of preserved formulations has led to commercialization of more convenient, multi-use injection pen presentations. At least four such pen devices containing preserved formulations of hGH are currently available on the market. Norditropin (liquid, Novo Nordisk), Nutropin AQ (liquid, Genentech) & Genotropin (lyophilized—dual chamber cartridge, Pharmacia & Upjohn) contain phenol while Somatrope (Eli Lilly) is formulated with m-cresol.

[0231] In one embodiment, an IL-2 mutein or Fc-fusion of an IL-2 mutein, such as, for example, Fc.IL-2(H16T), Fc.IL-2(H16K), Fc.IL-2(H16R), Fc.IL-2(L19N), Fc.IL-2(L19D), Fc.IL-2(D20E), Fc.IL-2(D20G), Fc.IL-2(D20T), Fc.IL-2 (N88D), Fc.IL-2(N88R), Fc.IL-2(N88S), Fc.IL-2(V91D), Fc.IL-2(V91G), Fc.IL-2(V91K), or Fc.IL-2(V91S), is formulated to 10 mg/mL in 10 mM L-Glutamic Acid, 3.0% (w/v) L-Proline, at pH 5.2. In another embodiment, an IL-2 mutein or Fc-fusion of an IL-2 mutein, such as, for example, Fc.IL-2(H16T), Fc.IL-2(H16K), Fc.IL-2(H16R), Fc.IL-2 (L19N), Fc.IL-2(L19D), Fc.IL-2(D20E), Fc.IL-2(D20G), Fc.IL-2(D20T), Fc.IL-2(N88D), Fc.IL-2(N88R), Fc.IL-2 (N88S), Fc.IL-2(V91D), Fc.IL-2(V91G), Fc.IL-2(V91K), or Fc.IL-2(V91S), is formulated in 10 mM KPi, 161 mM L-arginine, at pH 7.6.

[0232] Several aspects need to be considered during the formulation and development of preserved dosage forms. The effective preservative concentration in the drug product must be optimized. This requires testing a given preservative in the dosage form with concentration ranges that confer anti-microbial effectiveness without compromising protein stability.

[0233] In another aspect, the present invention provides IL-2 muteins, anti-IL-2 antibodies, or Fc-fusions of IL-2 muteins, in lyophilized formulations. Freeze-dried products can be lyophilized without the preservative and reconstituted with a preservative containing diluent at the time of use. This shortens the time for which a preservative is in contact with the protein, significantly minimizing the associated stability risks. With liquid formulations, preservative effectiveness and stability should be maintained over the entire product shelf-life (about 18 to 24 months). An important point to note is that preservative effectiveness should be demonstrated in the final formulation containing the active drug and all excipient components.

[0234] IL-2 mutein or anti-IL-2 antibody formulations generally will be designed for specific routes and methods of administration, for specific administration dosages and frequencies of administration, for specific treatments of specific diseases, with ranges of bio-availability and persistence, among other things. Formulations thus may be designed in accordance with the invention for delivery by any suitable route, including but not limited to orally, aurally, opthalmically, rectally, and vaginally, and by parenteral routes, including intravenous and intraarterial injection, intramuscular injection, and subcutaneous injection.

[0235] Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, crystal, or as a dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form or in a form (e.g., lyophilized) that is reconstituted prior to administration. The invention also provides kits for producing a single-dose administration unit. The kits of the invention may each contain both a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments of this invention, kits containing single and multi-chambered pre-filled syringes (e.g., liquid syringes and lyosyringes) are provided.

[0236] The therapeutically effective amount of an IL-2 mutein- or anti-IL-2 antibody-containing pharmaceutical composition to be employed will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will vary depending, in part, upon the molecule delivered, the indication for which the IL-2 mutein or anti-IL-2 antibody is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about 0.1 μg/kg to up to about 1 mg/kg or more, depending on the factors mentioned above. In specific embodiments, the dosage may range from 0.5 μg/kg up to about 100 μg/kg, optionally from 2.5 μg/kg up to about 50 μg/kg.

[0237] A therapeutic effective amount of an IL-2 mutein or anti-IL-2 antibody preferably results in a decrease in severity of disease symptoms, in an increase in frequency or duration of disease symptom-free periods, or in a prevention of impairment or disability due to the disease affliction.

[0238] Pharmaceutical compositions may be administered using a medical device. Examples of medical devices for administering pharmaceutical compositions are described in U.S. Pat. Nos. 4,475,196; 4,439,196; 4,447,224; 4,447, 233; 4,486,194; 4,487,603; 4,596,556; 4,790,824; 4,941,880; 5,064,413; 5,312,335; 5,312,335; 5,383,851; and 5,399,163, all incorporated by reference herein.

[0239] In one embodiment, a pharmaceutical composition is provided comprising

Methods of Treating Autoimmune or Inflammatory Disorders

[0240] In certain embodiments, an IL-2 mutein or anti-IL-2 antibody of the invention is used to treat an autoimmune or inflammatory disorder. In preferred embodiments, an IL-2 mutein Fc-fusion protein is used.

[0241] Disorders that are particularly amenable to treatment with IL-2 mutein or anti-IL-2 antibody disclosed herein include, but are not limited to, inflammation, autoimmune disease, atopic diseases, paraneoplastic autoimmune diseases, cartilage inflammation, arthritis, rheumatoid arthritis, juvenile arthritis, juvenile rheumatoid arthritis, pauciarticular juvenile rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, juvenile ankylosing spondylitis, juvenile enteropathic arthritis, juvenile reactive arthritis, juvenile Reiter's Syndrome, SEA Syndrome (Seronegativity, Enthesopathy, Arthropathy Syndrome), juvenile dermatomyositis, juvenile psoriatic arthritis, juvenile scleroderma, juvenile systemic lupus erythematosus, juvenile vasculitis, pauciarticular rheumatoid arthritis, polyarticular rheumatoid arthritis, systemic onset rheumatoid arthritis, ankylosing spondylitis, enteropathic arthritis, reactive arthritis, Reiter's Syndrome, SEA Syndrome (Seronegativity, Enthesopathy, Arthropathy Syndrome), dermatomyositis, psoriatic arthritis, scleroderma, vasculitis, myolitis, polymyolitis, dermatomyolitis, polyarteritis nodossa, Wegener's granulomatosis, arteritis, ploymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, Sjögren's syndrome, psoriasis, plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, dermatitis, atopic dermatitis, atherosclerosis, lupus, Still's disease, Systemic Lupus Erythematosus (SLE), myasthenia gravis, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, celiac disease, multiple sclerosis (MS), asthma, COPD, rhinosinusitis, rhinosinusitis with polyps, eosinophilic esophogitis, eosinophilic bronchitis, Guillain-Barre disease, Type I diabetes mellitus, thyroiditis(e.g., Graves' disease), Addison's disease, Raynaud's phenomenon, autoimmune hepatitis, GVHD, transplantation rejection, kidney damage, hepatitis C-induced vasculitis, spontaneous loss of pregnancy, and the like.

[0242] In preferred embodiments, the autoimmune or inflammatory disorder is lupus, graft-versus-host disease, hepatitis C-induced vasculitis, Type I diabetes, multiple sclerosis, spontaneous loss of pregnancy, atopic diseases, and inflammatory bowel diseases.

[0243] In another embodiment, a patient having or at risk for developing an autoimmune or inflammatory disorder is treated with an IL-2 mutein or anti-IL-2 antibody (for example, an IL-2 mutein disclosed herein, such as an IL-2 mutein Fc-fusion as disclosed herein, or another IL-2 mutein known in the art or wild-type IL-2, optionally as part of an Fc-fusion molecule of the type described herein) and the patient's response to the treatment is monitored. The patient's response that is monitored can be any detectable or measurable response of the patient to the treatment, or any combination of such responses. For example, the response can be a change in a physiological state of the patient, such as body temperature or fever, appetence, sweating, headache, nausea, fatigue, hunger, thirst, mental acuity, or the like. Alternatively, the response can be a change in the amount of a cell type or gene product (for example, a protein, peptide, or nucleic acid), for example, in a sample of peripheral blood taken from the patient. In one embodiment, the patient's treatment regimen is altered if the patient has a detectable or measurable response to the treatment, or if such response crosses a particular threshold. The alteration can be a reduction or increase in the frequency in dosing, or a reduction or increase in the amount of the IL-2 mutein or anti-IL-2 antibody administered per dose, or a "holiday" from dosing (i.e., a temporary cessation of treatment, either for a specified period of time, or until a treating physician determines that treatment should continue, or until a monitored response of the patient indicates that treatment should or can resume), or the termination of treatment. In one embodiment, the response is a change in the patient's temperature or CRP levels. For example, the response can be an increase in the patient's body temperature, or an increase of the CRP levels in a sample of peripheral blood, or both. In one particular embodiment, the patient's treatment is reduced, suspended, or terminated if the patient's body temperature increases during the course of treatment by at least 0.1°, 0.2°, 0.3°, 0.4°, 0.5°, 0.70, 1°, 1.50, 2°, or 2.5° C.. In another particular embodiment, the patient's treatment is reduced, suspended, or terminated if the concentration of CRP in a sample of the patient's peripheral blood increases during the course of treatment by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.7, 1, 1.5, or 2 mg/mL. Other patient reactions that can be monitored and used in deciding whether to modify, reduce, suspend, or terminate treatment include the development or worsening of capillary leak syndrome (hypotension and cardiovascular instability), impaired neutrophil function (for example, resulting in or detected the development or worsening of an infection), thrombocytopenia, thrombotic angiopathy, injection site reactions, vasculitis (such as Hepatitis C virus vasculitis), or inflammatory symptoms or diseases. Further patient reactions that can be monitored and used in deciding whether to modify, reduce, increase, suspend, or terminate treatment include an increase in the number of NK cells, Treg cells, $FOXP3^-$ CD4 T cells, $FOXP3^+$ CD4 T cells, $FOXP3^-$ CD8 T cells, or eosinophils. Increases of these cell types can be detected, for example, as an increase in the number of such cells per unit of peripheral blood (for example, expressed as an increase in cells per milliliter of blood) or as an increase in the percentage of such cell type compared to another type of cell or cells in the blood sample. Another patient reaction that can be monitored is an increase in the amount of cell surface-bound IL-2 mutein or anti-IL-2 antibody on CD25+ cells in a sample of the patient's peripheral blood.

Methods of Expanding Treg Cells

[0244] The IL-2 mutein, anti-IL-2 antibody, or IL-2 mutein Fc-fusion protein may be used to expand Treg cells within a subject or sample. Provided herein are methods of increasing the ratio of Tregs to non-regulatory T cells. The method comprises contacting a population of T cells with an effective amount of a human IL-2 mutein, anti-IL-2 antibody or IL-2 mutein Fc-fusion. The ratio may be measured by determining the ratio of CD3+FOXP3+ cells to CD3+ FOXP3– cells within the population of T cells. The typical Treg frequency in human blood is 5-10% of total CD4+ CD3+ T cells, however, in the diseases listed above this percentage may be lower or higher. In preferred embodiments, the percentage of Treg increases at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at

least 200%, at least 300%, at least 400%, at least 500%, at least 600%, at least 700%, at least 800%, at least 900%, or at least 1000%. Maximal fold increases in Treg may vary for particular diseases; however, a maximal Treg frequency that might be obtained through IL-2 mutein treatment is 50% or 60% of total CD4+CD3+ T cells. In certain embodiments, the IL-2 mutein, anti-IL-2 antibody, or IL-2 mutein Fc-fusion protein is administered to a subject and the ratio of regulatory T cells (Tregs) to non-regulatory T cells within peripheral blood of a subject increases.

[0245] Because the IL-2 mutein, anti-IL-2 antibody, and IL-2 mutein Fc-fusion proteins preferentially expand Tregs over other cell types, they also are useful for increasing the ratio of regulatory T cells (Tregs) to natural killer (NK) cells within the peripheral blood of a subject. The ratio may be measured by determining the ratio of CD3+FOXP3+ cells to CD16+ and/or CD56+ lymphocytes that are CD19− and CD3−.

[0246] It is contemplated that the IL-2 mutein, anti-IL-2 antibody, or IL-2 mutein Fc-fusion protein may have a therapeutic effect on a disease or disorder within a patient without significantly expanding the ratio of Tregs to non-regulatory T cells or NK cells within the peripheral blood of the patient. The therapeutic effect may be due to localized activity of the IL-2 mutein, anti-IL-2 antibody, or IL-2 mutein Fc-fusion protein at the site of inflammation or autoimmunity.

EXAMPLES

[0247] The following examples, both actual and prophetic, are provided for the purpose of illustrating specific embodiments or features of the present invention and are not intended to limit its scope.

Example 1—Reducing Number of Mutations that Confer High Affinity for CD25

[0248] IL-2 muteins with elevated affinity for CD25 and reduced signaling strength through IL-2Rβγ preferentially promote Treg growth and function. To reduce the potential immunogenicity, the minimum number of mutations required to achieve high affinity for CD25 was sought. The crystal structure of IL-2 in complex with its three receptors (PDB code—2B51) shows V69A and Q74P are located in the helical structure that interacts with CD25. This may explain why V69A and Q74P were frequently isolated in two independent IL-2 mutagenesis screens for high CD25 binding affinity (Rao et al. 2005; Thanos et al. 2006). This Example explores which of the other mutations in IL-2 mutein "2-4" identified in the screen of Rao et al. are most important to increase the affinity above that observed with V69A and Q74P alone. The following proteins were screened by flow cytometry for binding to CD25 on the surface of activated T cells. All constructs also included a C-terminal FLAG and poly-His tag for purification and detection. The specific mutations are provided in parenthesis.

HaMut1D (V69A, Q74P, N88D, C125A)
(SEQ ID NO: 8)
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEALNLAPSKNFHLRPRDLISDINVIVL
ELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

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HaMut2D (N30S, V69A, Q74P, N88D, C125A)
(SEQ ID NO: 9)
APTSSSTKKTQLQLEHLLLDLQMILNGINSYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEALNLAPSKNFHLRPRDLISDINVIVL
ELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

HaMut3D (K35R, V69A, Q74P, N88D, C125A)
(SEQ ID NO: 10)
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPRLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEALNLAPSKNFHLRPRDLISDINVIVL
ELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

HaMut4D (T37A, V69A, Q74P, N88D, C125A)
(SEQ ID NO: 11)
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLARMLTFKFYMP
KKATELKHLQCLEEELKPLEEALNLAPSKNFHLRPRDLISDINVIVL
ELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

HaMut5D (K48E, V69A, Q74P, N88D, C125A)
(SEQ ID NO: 12)
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
EKATELKHLQCLEEELKPLEEALNLAPSKNFHLRPRDLISDINVIVL
ELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

HaMut6D (E68D, V69A, Q74P, N88D, C125A)
(SEQ ID NO: 13)
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEDALNLAPSKNFHLRPRDLISDINVIVL
ELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

HaMut7D (N71R, V69A, Q74P, N88D, C125A)
(SEQ ID NO: 14)
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP
KKATELKHLQCLEEELKPLEEALRLAPSKNFHLRPRDLISDINVIVL
ELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

HaMut8D (K35R, K48E, E68D, N88D, C125A)
(SEQ ID NO: 15)
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPRLTRMLTFKFYMP
EKATELKHLQCLEEELKPLEDVLNLAQSKNFHLRPRDLISDINVIVL
ELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

[0249] HaMut7D bound CD25 with nearly the same affinity as the original isolate "2-4" (~200 pM), indicating that mutation N71R was capable of greatly increasing the affinity above that observed with V69A, Q74P alone (HaMut1D, ~2 nM). The other constructs possessed affinities similar to or slightly higher than HaMut1D, with the exception of HaMut8D whose affinity was only slightly higher than that of WT IL-2.

Example 2—IL-2 Muteins Fused to IgG1-Fc Domains for Improved Half-Life

[0250] To reduce the dosing frequency required to achieve Treg enrichment with an IL-2 mutein, various fusions between IL-2 and IgG1-Fc domains were evaluated. The Fc domains contained point mutations to abolish effector functions mediated by IgG1, such as target cell lysis. The Fc effector function mutations utilized were either A327Q, Ala Ala (L234A+L235A) or N297G. Because the Treg-selective IL-2 muteins have partial reduction in IL-2 potency, it was important to fuse IL-2 to Fc in such a way that did not significantly impact IL-2R signaling. Thus, IL-2 muteins were tested for IL-2R activation with and without Fc fusion.

[0251] To determine if IL-2 dimerization by Fc fusion would increase IL-2R signaling strength due to increased avidity for IL-2R, a weaker IL-2 mutein (haD5) (US20110274650) was fused to the amino terminus of Fc, separated by a GGGGS (SEQ ID NO: 5) linker sequence. This mutein possessed 3 mutations impacting IL-2R signaling (E15Q, H16N, N88D), 8 mutations to confer high

affinity for CD25 (N29S, Y31H, K35R, T37A, K48E, V69A, N71R, Q74P) (Rao et al. 2005), and C125S to prevent cysteine mispairing and aggregation. Fusion to Fc in this manner completely abrogated the biological activity of haD5, while its high-affinity binding to cell surface CD25 was enhanced, likely due to increased avidity from dimerization.

[0252] IL-2 muteins were also fused to either the N- or C-terminus of an Fc heterodimer, such that only one chain of the Fc dimer bore the IL-2 domain. Heterodimeric pairing between two asymmetric Fc chains was promoted by electrostatic interactions between introduced lysines on one Fc chain and introduced aspartic acids on the other Fc chain. IL-2 mutein haD6 was fused to the N-terminus of one Fc chain or the other, in the event that one configuration was preferred, resulting in two protein constructs termed haD6.FcDD and haD6.FcKK. Mutein haMut7D was also fused to the C-terminus of the Fc heterodimer with one or two GGGGS (SEQ ID NO: 5) linkers (FcKK(G4S)haMut7D, FcKK(G4S)2haMut7D). Fusion of the IL-2 mutein haD6 to the N-terminus of the Fc heterodimer resulted in a partial loss of activity relative to free haD6 in both pSTAT5 and T cell proliferation experiments. In contrast, fusion of haMut7D to the C-terminus of the Fc heterodimer with either one or two GGGGS (SEQ ID NO: 5) linkers did not alter the potency of haMut7D.

[0253] Fusion of an IL-2 mutein to the C-terminus of an Fc homodimer was also investigated. Total PBMC were activated in T75 tissue culture flasks at 300 million cells per 100 ml with 100 ng/ml anti-CD3 (OKT3). On day 3 of culture, cells were washed 3 times and rested in fresh media for 3 days. Cells were then stimulated with IL-2 variants at 10× dose titration ranging from 1 pM to 10 nM at a final volume of 50 μl. The level of STAT5 phosphorylation was measured using BD phosflow buffer kit. Briefly, 1 ml of BD lyse/fix phosflow buffer was added to stop stimulation. Cells were fixed for 20 min at 37° C. and permeabilized with 1× BD phosflow perm buffer on ice before stained for CD4, CD25, FOXP3 and pSTAT5.

[0254] As can be seen in FIG. **1**, the bioactivity of muteins haMut1D and haMut7D was not altered by fusion to the C-terminus of an Fc homodimer. Thus, fusion between the N-terminus of IL-2 and C-terminus of Fc did not compromise the agonist activity of the IL-2 muteins, even in the context of an Fc.IL-2 homodimer. In these constructs, the C125A mutation was used in place of C125S for improved manufacturing.

Example 3—Tuning IL-2 Mutein Potency to Achieve Preferential Treg Growth

[0255] The initial panel of IL-2 muteins contained N88D alone or with 1 or 2 additional mutations impacting IL-2R signaling. A second panel of muteins was designed, all with single point mutations, with the goal of identifying muteins with either similar or slightly more potent agonism than those of the N88D series. A panel of 24 signaling mutations was identified based on predicted IL-2Rβ-interacting amino acids (crystal structure, PDB code—2B51). Particular substitutions were selected based on predicted decrease in the binding free energy between the mutein and IL-2R1p. The binding free energy was calculated using EGAD computational algorithm (Handel's Laboratory, University of California at San Diego, USA). The binding free energy of a mutant is defined as $\Delta\Delta Gm_{mut}=\mu(\Delta G_{mut}-\Delta G_{wt})$. Where, μ(=0.1, in general) is the scaling factor used to normalize the predicted changes in binding affinity to have a slope of 1 when comparing with the experimental energies (Pokala and Handel 2005). The free energy of dissociation (ΔG) was defined as the energy difference between the complex (ΔG_{bound}) and free states (ΔG_{free}). The dissociation energy ΔG_{mut} was calculated for each substitution.

[0256] A panel of IL-2 muteins with the following substitutions (H16E, H16Q, L19K, D20R, D20K, D20H, D20Y, M23H, D84K, D84H, S87Y, N88D, N88K, N881, N88H, N88Y, V91N, V91K, V91H, V91R, 192H, E95K, E95R, or E951) was expressed as C-terminal fusions to the Fc heterodimer. These constructs also contained the haMut7 mutations for high CD25 binding affinity (V69A, N71R, Q74P) and C125A for efficient folding.

[0257] The panel was screened for potency in the T cell STAT5 phosphorylation assay of Example 2, and H16E, D84K, V91N, V91K, and V91R were found to possess activity less than wild type IL-2 and more than N88D (FIG. **2**).

[0258] H16E, D84K, V91N, V91K, and V91R possessed activity less than wild type IL-2 and more than N88D.

[0259] Selected muteins were also tested in T cell and NK growth assays.

[0260] For the T-cell assay, total PBMCs were activated at 3 million/ml with 100 ng OKT3. On day 2, cells were washed 3 times and rested in fresh media for 5 days. Cells were then labeled with CFSE and further cultured in a 24 well plate at 0.5 million/well in IL-2 containing media for 7 days before FACS analysis. The proliferation of T cell subsets is presented in FIG. **3** as CFSE dilution (median CFSE fluorescence).

[0261] For the NK-cell assay, MACS sorted CD16+NK cells were cultured in IL-2 containing media for 3 days at 0.1 million/well in 96 well plates. 0.5 μCi ^{3}H-thymidine was added to each well during the final 18 hours of incubation. The results are shown in FIG. **4**.

[0262] Mutants H16E, D84K, V91N, V91K, and V91R mutants were capable of stimulating Treg growth similar to WT IL-2 but were approximately 10× less potent on other T cells (FIG. **3**), and approximately 100× less potent on NK cells (FIG. **4**).

[0263] A separate panel of Fc.IL-2 fusion proteins was designed in which the distance between the Fc heterodimer and the mutein haMut7 (V69A, N71R, Q74P, C125A) was reduced by a series of individual amino acid truncations.

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Fc.haMut7
                                                    (SEQ ID NO: 22)
Fc...TQKSLSLSPGKGGGGSAPTSSSTKKTQLQLEHLLLDLQMILN...
haMut7

Trunc1
                                                    (SEQ ID NO: 23)
Fc...TQKSLSLSSSTKKTQLQLEHLLLDLQMILN...haMut7

Trunc2
                                                    (SEQ ID NO: 24)
Fc...TQKSLSLS-STKKTQLQLEHLLLDLQMILN...haMut7

Trunc3
                                                    (SEQ ID NO: 25)
Fc...TQKSLSLS--TKKTQLQLEHLLLDLQMILN...haMut7
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Trunc4
(SEQ ID NO: 26)
Fc...TQKSLSLS---KKTQLQLEHLLLDLQMILN...haMut7

Trunc5
(SEQ ID NO: 27)
Fc...TQKSLSLS----KTQLQLEHLLLDLQMILN...haMut7

Trunc6
(SEQ ID NO: 28)
Fc...TQKSLSLS-----TQLQLEHLLLDLQMILN...haMut7

Trunc7
(SEQ ID NO: 29)
Fc...TQKSLSLS------QLQLEHLLLDLQMILN...haMut7

Trunc8
(SEQ ID NO: 30)
Fc...TQKSLSL-------QLQLEHLLLDLQMILN...haMut7

[0264] Trunc1-Trunc4 possessed potency equal to the full length parent construct Fc.haMut7 as measured by STAT5 phosphorylation and by T cell and NK cell proliferation as described for FIGS. **2**, **3**, and **4**. Trunc5 and Trunc6 stimulated weaker responses yet stronger than those stimulated by the N88D mutation (haD and haMut7D) and very similar to those stimulated by V91K. Trunc7 was weaker than N88D muteins, and Trunc8 had very little activity. When tested on NK cells, however, Trunc5 and
Trunc6 were stronger agonists than V91K, indicating that Treg selectivity was more readily achieved with signaling mutations rather than steric hindrance by a proximal Fc domain.

Example 4—High CD25 Affinity Mutations in the Context of an Fc Homodimer

[0265] The mutations that conferred high CD25 binding affinity were considered advantageous because they increased tropism for CD25-high T cells, and because they promoted long term CD25::IL-2mutein association and prolonged signaling. However, reducing mutation number may reduce immunogenicity potential. The N88D or the V91K muteins, with and without the haMut1 high affinity mutations V69A and Q74P, were expressed as fusions to the C-terminus of an Fc homodimer and compared for bioactivty. In pSTAT5 stimulation assays, the homodimerization had no effect on signal strength relative to monomeric mutein. The reversion of the high affinity mutations V69A and Q74P also did not affect pSTAT5 signaling. In T cell growth assays, the high affinity mutations reduced activity on conventional CD4 T cells and CD8 T cells but not on regulatory T cells (FIG. **5**). The high affinity mutations also did not alter proliferative responses in NK cells (FIG. **6**).

[0266] To determine if the high affinity mutations impacted T cell responses in vivo, humanized mice (NOD.SCID.II2rg-null mice reconstituted with human $CD34^+$ hematopoietic stem cells) were dosed with the Fc.IL-2 mutein fusion proteins and monitored Treg expansion. Seven week old NOD.SCID.II2rg-null (NSG) mice (Jackson Labs, Bar Harbor, ME) were irradiated (180 rad) and reconstituted with 94,000 human fetal liver $CD34^+$ hematopoietic stem cells. At 21 weeks, mice were distributed into 6 groups based on equal distribution of percent chimerism (determined by flow cytometry of PBL) and were given 1 pg sub-cutaneous injections of the indicated Fc.mutein fusion proteins or PBS on day 0 and day 7. On day 11, T cell subset frequencies in blood were determined by flow cytometry. At the low dose of 1 pg per animal, the high affinity mutations did not improve Treg expansion beyond that observed with the N88D or V91K mutations alone (FIG. **7**).

[0267] Treg expansion was selective in that $FOXP3^-CD4^+$ T cells did not increase in abundance relative to total peripheral blood leukocytes (PBL) which includes a mixture of human B and T cells, and mouse myeloid cells. Furthermore, at higher doses, the high affinity mutations promoted an increase in $CD25^+FOXP3^-$ T cells, thus reducing Treg selectivity. Thus, in the context of the Fc homodimer, the high affinity mutations were not considered necessary for promoting preferential Treg growth.

Fc.WT IgG1Fc(N297G_delK)::G4S::hulL-2(C125A)
(SEQ ID NO: 16)
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG

GGGGS

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKK
ATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKG
SETTFMCEYADETATIVEFLNRWITFAQSIISTLT

Fc.haMut1V91K IgG1Fc(N297G_delK)::G4S::hulL-2
(V69A, Q74P, V91K, C125A)
(SEQ ID NO: 17)
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG

GGGGS

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKK
ATELKHLQCLEEELKPLEEALNLAPSKNFHLRPRDLISNINKIVLELKG
SETTFMCEYADETATIVEFLNRWITFAQSIISTLT

Fc.V91K (or Fc.IL-2(V91K))
IgG1Fc(N297G_delK)::G4S::hulL-2(V91K, C125A)
(SEQ ID NO: 18)
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG

GGGGS

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKK
ATELKHLQCLEEELKPLEEALNLAPSKNFHLRPRDLISNINKIVLELKG
SETTFMCEYADETATIVEFLNRWITFAQSIISTLT

Fc.haMut1N88D IgG1Fc(N297G_delK)::G4S::hulL-2
(V69A, Q74P, N88D, C125A)
(SEQ ID NO: 19)
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG

GGGGS

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKK
ATELKHLQCLEEELKPLEEALNLAPSKNFHLRPRDLISDINVIVLELKG
SETTFMCEYADETATIVEFLNRWITFAQSIISTLT

-continued

Fc.N88D (or Fc.IL-2(N88D))
IgG1Fc(N297G_delK)::G4S::hulL-2(N88D, C125A)
(SEQ ID NO: 20)

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG

GGGGS

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKK
ATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISDINVIVLELKG
SETTFMCEYADETATIVEFLNRWITFAQSIISTLT

Example 5—Prolonged Cell Surface CD25 Association of Fc.IL-2 Muteins

[0268] An unexpected result from the humanized mouse studies was that, despite their reduced signaling capacity, the muteins induced more robust Treg enrichment relative to Fc.WT IL-2. Greater Treg enrichment and FOXP3 upregulation relative to that seen with Fc.WT was observed at a dose of 1 ag/mouse (FIG. **7**) and at a lower dose of 0.5 ag/mouse (FIG. **8**). This increased potency in vivo may have resulted from reduced consumption by T cells, making more Fc.IL-2 mutein available for prolonged signaling.

[0269] In vitro and in vivo PK studies failed, however, to demonstrate significantly increased persistence of Fc.V91K or Fc.N88D relative to Fc.WT in supernatants from activated T cell cultures or serum from dosed mice. Because the Fc fusions bore two IL-2 mutein domains, increased endosomal recycling may result in prolonged cell surface association due to increased avidity for CD25. Indeed, it was found that Fc.V91K and Fc.N88D persisted more efficiently than Fc.WT on the surface of previously activated T cells following a brief exposure the fusion proteins (FIGS. **9**A and B).

[0270] Primary PBMCs were prestimulated for two days with 100 ng/ml OKT3. Cells were harvested, washed four times and rested for overnight in media. Cells were then pulsed with 400 pM Fc.IL-2 for 30 min at 37° C. After the pulse, cells were either harvested for TO after one wash, or washed an additional three times in 12 ml of warm media and cultured for four hours. To detect cell-associated Fc.IL-2, cells were stained with anti-human IgG-FITC (Jackson Immunoresearch, West Grove, PA) and anti-CD25-APC (FIG. **9**A).

[0271] The persistence of IL-2R signaling with Fc.V91K and Fc.N88D relative to Fc.WT was observed by intracellular immunodetection of phospho-STAT5 at the same time points. Phospho-STAT5 MFI for FOXP3+CD4+ T cells is shown (FIG. **9**B).

Example 6—Fusion Sequence Optimization

[0272] In preclinical studies in mice, the Fc.IL-2 muteins showed differential exposure when serum concentrations of the intact molecule were compared that of the human Fc portion only, indicative of circulating human Fc catabolite. To optimize the in vivo stability and pharmacokinetics of the Fc.IL-2 muteins, fusion sequence modifications were characterized for their impact on protoeolytic degradation of Fc.IL-2 muteins in systemic circulation and during recycling through the reticuloendothelial system. The following constructs were evaluated for proteolytic degradation in vitro and in vivo.

(Ala_Ala)_G4S
(SEQ ID NO: 31)
...TQKSLSLSPGGGGGSAPTSSSTKKTQLQ... ha7N88D

(N297G_delK)_G4S
(SEQ ID NO: 32)
...TQKSLSLSPG_GGGGSAPTSSSTKKTQLQ... ha1V91K

(N297G_KtoA)_AAPT
(SEQ ID NO: 33)
...TQKSLSLSPGA_____APTSSSTKKTQLQ... ha1V91K

(N297G_KtoA)_AAPA
(SEQ ID NO: 34)
...TQKSLSLSPGA_____APASSSTKKTQLQ... ha1V91K

[0273] Stability was measured by quantitative immunoassays comparing concentrations over time of total human Fc to that of intact Fc.IL-2 mutein. Proteolysis of Fc.IL-2 muteins was verified by western blot analysis utilizing anti-IL-2 and anti-human Fc antibodies, followed by immunocapture of catabolites and characterization by mass spectrometry. Characterization by mass spectrometry of catabolites of (Ala_Ala)_G4S from in vitro and in vivo samples identified the C-terminal Lys of the Fc domain as a proteolytic cleavage site. Deletion or mutation of the C-terminal lysine of the Fc domain ((N297G_delK)_G4S and (N297G_KtoA)_AAPT) resulted in prolonged in vitro stability in mouse serum at 37° C. compared to Fc constructs with the C-terminal lysine ((Ala_Ala)_G4S). This prolonged in vitro serum stability translated to greater exposure in mice as measured by the area under the Fc.IL-2 mutein serum concentration versus time curve (AUC). This prolonged stability of Fc.IL-2 muteins lacking the C-terminal Fc lysine was also observed in vitro in serum from cynomolgus monkeys and humans. Mutation of Thr-3 of IL-2 to Ala ((N297G_KtoA)_AAPA) resulted in decreased in vitro stability at 37° C. (compared to (N297G_KtoA)_AAPT) in mouse serum and in separate incubations with recombinant human cathepsin D and L. This decreased in vitro serum stability translated to lower exposure (AUC) in mice in vivo for (N297G_KtoA)_AAPA compared to (N297G_KtoA)_AAPT. Characterization of catabolites of (N297G_KtoA)_AAPA from in vitro and in vivo samples by mass spectrometry identified Lys 8 and Lys 9 of the IL-2 mutein domain as residues susceptible to proteolysis which was not observed for equivalent samples of (N297G_KtoA)_AAPT. Decreased stability at 37° C. of (N297G_KtoA)_AAPA to that of (N297G_KtoA)_AAPT was also observed in vitro in serum from cynomolgus monkeys and humans.

[0274] Because of the importance of glycosylation in this region, and to potentially improve upon the manufacturability of the fusion protein, the fusion sequences were altered to promote N-linked rather than O-linked glycosylation, as follows.

Original
IgG1Fc(N297G_delK)::G4S::huIL-2(V91K, C125A)
(SEQ ID NO: 32)
TQKSLSLSPGGGGGSAPTSSSTKKTQLQ

-continued

Altered
IgG1Fc(N297G_delK)::G4S::huIL-2(T3N, V91K, C125A)
(SEQ ID NO: 35)
TQKSLSLSPGGGGGSAPNSSSTKKTQLQ

IgG1Fc(N297G_delK)::G4S::huIL-2(T3N, S5T, V91K, C125A)
(SEQ ID NO: 36)
TQKSLSLSPGGGGGSAPNSTSTKKTQLQ

IgG1Fc(N297G_delK)::GGNGT::huIL-2(T3A, V91K, C125A)
(SEQ ID NO: 37)
TQKSLSLSPGGGNGTAPASSSTKKTQLQ n

IgG1Fc(N297G_delK)::YGNGT::huIL-2(T3A, V91K, C125A)
(SEQ ID NO: 38)
TQKSLSLSPGYGNGTAPASSSTKKTQLQ

Example 7—Cynomolgus Monkey PK/PD Determination

[0275] Standard IL-2 immune stimulating therapies require drug free holidays (no exposure) between dosing cycles to avoid undesirable side effects. In contrast, Treg expansion or stimulation therapies may require prolonged exposure with sustained trough drug levels (serum C_{min}) sufficient for Treg stimulation but with maximal exposures (serum C_{max}) below drug levels that lead to immune activation. This example demonstrates dosing strategies of half-life extended muteins in cynomolgus monkeys for extended target coverage (serum C_{min}) while maintaining maximal exposures (serum C_{max}) below drug levels contemplated to be necessary for proinflammatory immune activation.

[0276] Cynomolgus monkeys are dosed with Fc.V91K (IgG1Fc(N297G_delK)::G4S::huIL-2(V91K, C125A) in four groups (A-D), with three groups (A-C) dosed subcutaneously and one group (D) dosed intravenously. For each group, four biologically naïve male cynomolgus monkeys are dosed per the dosing strategy outlined below. Subcutaneous dosing of half-life extended muteins may allow for greater lymphatic absorption resulting in lower maximal exposure (serum C_{max}) and/or a more robust pharmacological response (Treg expansion). Dosing strategy for group A consists of three consecutive 10 microgram per kilogram doses on Day 0, 2, and 4 for cycle 1 and 10 microgram per kilogram on Day 14, allowing prolonged target coverage similar to a higher initial dose of 50 microgram per kilogram while maintaining a lower maximal exposure (C_{max}). The dosing strategy for group B is 50 microgram per kilogram dosed on Day 0 and 14 for comparison to Group A. The dosing strategy for group C is 50 microgram per kilogram dosed on Day 0 and 28. Allowing the determination of whether trough coverage is required for sustaining Treg enrichment or whether a drug free holiday is beneficial between dosing cycles. The dosing strategy for the intravenous dosing arm group D is 50 microgram per kilogram dosed on Day 0, allowing a comparison of maximal exposures (C_{max}) and Treg enrichment differences to that of subcutaneous dosing.

[0277] Pharmacokinetics (quantitative immunoassay for intact molecule and total human Fc), anti-drug antibodies, shed soluble CD25, and serum cytokines (IL-1p, TNF-α, IFN-γ, IL-10, IL-5, IL-4, and IL-13) are measured at the following time points for each dose group specified:

Group A: pre-dose (first cycle; dose 1), 48 (pre-dose first cycle; dose 2), 96 (pre-dose first cycle; dose 3), 100, 104, 120, 168, 216, 264, 336 (pre-dose second cycle), 340, 344, 360, 408, 456, 504, 576, 672, 744, 840, and 1008 hours.

Group B: pre-dose (first cycle), 4, 8, 24, 72, 120, 168, 240, 336 (pre-dose second cycle), 340, 344, 360, 408, 456, 504, 576, 672, 744, 840, and 1008 hours.

Group C: pre-dose (first cycle), 4, 8, 24, 72, 120, 168, 240, 336, 408, 504, 672 (pre-dose second cycle), 676, 680, 696, 744, 792, 840, 912, 1008, 1080, and 1176 hours.

Group D: pre-dose (first cycle), 0.25, 1, 4, 8, 24, 72, 120, 168, 240, 336, 408, 504, and 672 hours.

[0278] Pharmacodynamics (immunopheotyping and enumeration of peripheral blood Tregs, non-regulatory CD4 and CD8 T cells, and NK cells) is measured at the following time points for each dose group specified:

Group A: pre-dose (first cycle; dose 1), 96 (pre-dose first cycle; dose 3), 168, 336 (pre-dose second cycle), 456, and 576 hours.

Group B: pre-dose (first cycle), 120, 240, 336 (pre-dose second cycle), 456, and 576 hours.

Group C: pre-dose (first cycle), 120, 240, 672 (pre-dose second cycle), 792, and 912 hours.

Group D: pre-dose (first cycle), 120 and 240 hours.

[0279] Hematology and clinical chemistry are assessed for all animals and dose groups pre-dose and at 24 hours post initial dose per dose group. The following parameters are evaluated.

Hematology:

[0280] leukocyte count (total and absolute differential)

[0281] erythrocyte count

[0282] hemoglobin

[0283] hematocrit

[0284] mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated)

[0285] absolute reticulocytes

[0286] platelet count

[0287] blood cell morphology

[0288] red cell distribution width

[0289] mean platelet volume

Clinical Chemistry:

[0290] alkaline phosphatase

[0291] total bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dL)

[0292] aspartate aminotransferase

[0293] alanine aminotransferase

[0294] gamma glutamyl transferase

[0295] urea nitrogen

[0296] creatinine

[0297] total protein

[0298] albumin

[0299] globulin and A/G (albumin/globulin) ratio (calculated)

[0300] glucose

[0301] total cholesterol

[0302] triglycerides

[0303] electrolytes (sodium, potassium, chloride)

[0304] calcium

[0305] phosphorus

Example 8—Aglycosylated IgG1 Fc

[0306] Naturally occurring IgG antibodies posses a glycosylation site in the constant domain 2 of the heavy chain (CH2). For example, human IgG1 antibodies have a glycosylation site located at the position Asn297 (EU numbering). To date, the strategies for making aglycosylated antibodies involve replacing the Asn residue with an amino acid that resembles Asn in terms of physico-chemical properties (e.g., Gln) or with Ala residue which mimics the Asn side chain without the polar groups. This Example demonstrates the benefits of replacing Asn with Glycine (N297G). N297G Fc are aglcosylated molecules with better biophysical properties and manufacturability attributes (e.g., recovery during purification).

[0307] Examination of multiple known crystal structures of Fc fragments and IgG antibodies revealed considerable conformational flexibility around the glycosylated loop segment, particularly at the position Asn297 that is glycosylated. In many of the known crystal structures, Asn297 adapted positive backbone dihedral angles. Gly has high propensity to adapt positive backbone dihedral angle due to the lack of side chain atoms. Therefore, based on this conformation and structure reason, Gly may be a better replacement for Asn than N297Q or N297A.

[0308] Mutating Asn297 with Gly leads to aglcosylated molecules with much improved recovery (or efficiency) in the purification process and biophysical properties. For example, the percentage of recovery (final yield) from the protein A pool was 82.6% for the N297G mutation, compared to 45.6% for N297Q and 39.6% for N297A. SPHP column analysis revealed the lower percentage of recovery for the N297Q and N297A mutants was due to a tailing peak, which indicates high molecular weight aggregation and/or misfolded species. This result was re-confirmed at a larger, 2L scale run.

[0309] In the biopharmaceutical industry, molecules with potential need for large-scale production, e.g., potential to be sold as a drug, are assessed for a number of attributes to mitigate the risk that the molecule is not amenable to large-scale production and purification. In the manufacturability assessments, N297G revealed robustness to pH changes. N297G had no aggregation issue; whereas N297Q and N297A had 20% and 10% increase in aggregation, respectively. Although N297G had better manufacturability attributes, it was similar to N297Q and N297A in all the functional assays in which it was tested. For example, in ADCC assays, N297G lacked cytotoxicity similarly to N297Q and N297A.

Example 9—Stabilized Aglyosylated IgG1 Fc

[0310] This Example describes a method of improving stability of IgG antibody scaffolds by introducing engineered disulfide bond(s). Naturally occurring IgG antibodies are stable molecules. However, for some therapeutic applications, it may be necessary to make mutations or create aglycosylated molecules. For example, aglycosylated IgG molecules may be used in therapeutic indications where there is a need to avoid ADCC and binding to Fcgamma receptors. However, the aglycosylated IgG1 has much lower melting temperature (CH2 domain melting temperature decreases by about 10° C.; 70° C. to 60° C.) than the glycosylated IgG1. The observed lower melting temperature negatively impacts various biophysical properties of the aglycosylated IgG1. For example, aglycosylated IgG1 has increased level of aggregation at low pH compared to glycosylated IgG1.

[0311] In order to engineer disulfide bonds, a structure based method involving distance calculation between the C-alpha atoms was initially used to identify 54 residue pairs in the Fc region for mutation to Cys. These 54 sites were further narrowed down to 4 residue pairs (V259C-L306C, R292C-V302C, A287C-L306C, and V323C-1332C). The criteria used included (i) positions within the CH2 domain, (ii) away from loops, turns and carbohydrates, (iii) away from Fcgamma receptor and FcRn interaction sites, (iv) solvent accessibility (preferred buried positions), etc.

[0312] The paired cysteine substitutions were created in the context of the aglycosylated N297G Fc. Non-reduced peptide mapping analysis revealed that three of the four engineered sites formed disulfide bond as expected and designed in that context. The V259C-L306C mutation did not form disulfide bonds correctly and led to mis-pairing with the native disulfide already present in the CH2 domain. The other three designs, R292C-V302C, A287C-L306C, and V323C-1332C, formed disulfide bond correctly as predicted and designed. Adding the disulfide bond to the N297G mutation led to about 15° C. improvement in thermal stability over the N297G mutation alone. Of the R292C-V302C, A287C-L306C, and V323C-1332C disulfide variants, R292C-V302C and A287C-L306C had good pharmacokinetics when administered to rats ($t_{1/2}$ of eleven days and nine days, respectively). This is in contrast to the pharmacokinetics profile observed in rats for the previously published CH2 domain disulfide bond (Gong et al., *J. Biol. Chem.* 2009 284: 14203-14210), which had a $t_{1/2}$ of five days.

[0313] Engineering a disulfide bond in the CH2 domain improves the stability of the aglycosylated molecule on par with glycosylated IgG1 molecules (10° to 15° C. improvement in the melting temperature as determined by Differential Scanning Calorimetry). The engineered sites described herein do not lead to disulfide scrambling and the disulfides are formed as predicted in approximately 100% of the population. More importantly, unlike the published disulfide bond site in the CH2 domain, the disulfide bonds described herein do not impact the rat PK.

Example 10

[0314] The effects of the V91K and N88D mutations on responses in T and NK cells from cynomolgus monkeys and humans were compared in vitro. In the presence of CD25 ($CD4^+CD25^+$ gated T cells in whole blood pSTAT5 responses), the effect of the V91K mutation on cynomolgus IL-2R signaling was negligible compared to its reduced activity on human IL-2R. However, in the absence of CD25 (both $CD25^-$ gated T cells in whole blood pSTAT5 responses

and NK cell proliferation) the V91K mutation reduced cynomolgus IL-2R signaling more substantially. In contrast, Fc.N88D shows reduced signaling in CD25$^+$ T cells in cynomolgus whole blood which is more similar to the signaling effect of Fc.V91K in T cells in human whole blood. The in vitro data summarized in Table 2 suggest that the therapeutic window observed with the weaker agonist, Fc.N88D, in cynomolgus monkeys will be predictive of the effects of Fc.V91K in human subjects.

TABLE 2

Summary of effects of the V91K or N88D mutations on in vitro responses of human and cyno cells

	Whole blood pSTAT5		NK cell
	CD25+ T cells	CD25− T cells	proliferation
V91K on cyno	∅	↓	↓
V91K on human	↓	↓↓	↓↓
N88D on cyno	↓	↓↓	↓↓
N88D on human	↓↓	↓↓	↓↓↓

Example—11

[0315] Two in vivo studies were performed in cynomolgus monkeys. The first cynomolgus monkey study was designed to compare two week and four week dosing intervals of Fc.V91K to determine if a complete or partial pharmacokinetic (PK) and pharmacodynamic (PD) trough altered the magnitude of response to a second dose (FIGS. **10**A and B). A first dose, predicted to give a strong Treg response (50 μg/kg), and a second dose, to explore the lower limits of the therapeutic window (10 μg/kg), were used. Because it was not known whether 10 μg/kg was too low, doses were given on Days 1, 3, and 5 to increase the likelihood of a response. This dosing regimen gave the same exposure following Day 5 as achieved with the single 50 μg/kg subcutaneous (SC) dose, but with a lower C-max. A 50 μg/kg intravenous (IV) group was also included to investigate potential differences in PD depending on higher drug exposure in the lymph versus blood compartments. The results of this study established that each of the dose levels induced a strong Treg growth response without adverse events (AEs) or Teff or NK growth, and that responses to a second dose at either Day 14 or 28 were equivalent.

TABLE 3

Study Design for First Cynomolgus Monkey Study

Group	# animals	Dosing (days)	Dose Fc.V91K
1	4	1, 3, 5, 15	10 μg/kg SC
2	4	1, 15	50 μg/kg SC
3	4	1, 29	50 μg/kg SC
4	4	1	50 μg/kg IV

[0316] The second cynomolgus monkey study was designed to explore the margins of the therapeutic window with Fc.V91K doses of 1, 3, 100, 200 μg/kg (SC) and compare this with the weaker agonist Fc.N88D at doses of 3, 10, 100, 200 μg/kg (SC) and PROLEUKIN® at 3, 10, 30, 100 μg/kg (SC QDx5). PROLEUKIN® doses were selected based on published human and non-human primate studies (Hartemann et al., 2013, Lancet Diabetes Endocrin 1:295-305; Saadoun et al., 2011, NEJM 365:2067-77; Aoyama et al., 2012, Am J Transplantation 12:2532-37) and were administered QDx5 to mimic low-dose IL-2 clinical trials in HCV vasculitis and Type 1 diabetes (T1D).

TABLE 4

Study Design for Second Cynomolgus Monkey Study

Group	# animals	Test Article	1st cycle treatment Treatment day: Dose (SC)	2nd cycle treatment Treatment day: Dose (SC)
1	4	PROLEUKIN ®	Days 1-5: 3 μg/kg	Days 14-18: 30 μg/kg
2	4	PROLEUKIN ®	Days 1-5: 10 μg/kg	Days 14-18: 100 μg/kg
3	4	Fc.V91K	Day 1: 1 μg/kg	Day 14: 100 μg/kg
4	4	Fc.V91K	Day 1: 3 μg/kg	Day 14: 200 μg/kg
5	4	Fc.N88D	Day 1: 3 μg/kg	Day 14: 100 μg/kg
6	4	Fc.N88D	Day 1: 10 μg/kg	Day 14: 200 μg/kg

[0317] In FIGS. **11**A-F, the kinetics of cellular responses, body temperature, and serum CRP are shown. The timeline on the x-axis starts with Day 0 rather than Day 1 as the day of first dose.

[0318] In combination, the two cynomolgus monkey studies demonstrated that the IL-2 muteins induced greater Treg enrichment with a wider therapeutic window than achieved with PROLEUKIN® (FIGS. **12**A and B). With PROLEUKIN®, Treg enrichment paralleled NK and eosinophil growth. Without being bound to any particular theory, eosinophil growth is a well-known response to IL-2 therapy and is likely a result of IL-2-induced IL-5 from CD25' innate lymphoid cells. CD4 and CD8 Teff growth occurred at doses that increased Tregs to 25-35% of CD4 T cells. In contrast, Fc.V91K and Fc.N88D induced Treg growth with greater selectivity over NK cells and eosinophils, and doses that promoted Teff growth were above those that enriched Treg to >40% of CD4 T cells.

[0319] In low-dose IL-2 clinical trials reported in the literature, the first AEs that occurred were flu-like symptoms and fever. Thus, in addition to comparing therapeutic windows, a goal of this study was to discover a biomarker that preceded fever. As shown in FIG. **12**C, with the two higher doses of PROLEUKIN®, CRP levels were found to parallel body temperature. With Fc.V91K, a moderate elevation in body temperature was detected at the highest dose, and at the next lower dose a small increase in CRP was observed. Thus

CRP can be used to monitor a subject's response to treatment with a molecule of the present invention and/or to define the upper limit of dose escalation in a patient.

[0320] Certain toxicities were also observed in the PROLEUKIN®-treated animals that were either less pronounced or not present in the Fc.V91K- or Fc.N88D-treated animals (FIG. **12**D). Levels of platelets, neutrophils, and albumin were all found to be reduced by treatment with PROLEUKIN®, whereas doses of either Fc.V91K or Fc.N88D that resulted in similar or greater Treg enrichment produced little or no reductions in these parameters. Taken together, these data indicate that the therapeutic window for treatment of patients with either Fc.V91K- or Fc.N88D is expected to be significantly greater than with PROLEUKIN®.

Example—12

[0321] At selected time points, sera from the first cynomolgus study of Example 11 were tested for anti-drug antibodies (ADA) (FIG. **13**). ADA signal/noise data for samples where Fc.V91K specificity was confirmed by competition are shown. Time points where ADA were tested are shown with vertical lines above the x-axis. In Group 1, one animal generated ADA at least fifteen days after the last dose, in Group 2, no animals tested positive for ADA, and in Group 3, ADA consistently appeared in three animals fifteen or more days after the first dose. Upon repeat dosing of Groups 1 and 2 with 50 μg/kg on Day 162, no additional animals tested positive for ADA four weeks later (day 190). The two animals in Group 3 that generated the strongest ADA signals (210, 212) exhibited a reduced PD response, consistent with a reduced C-max observed after the second dose in these animals. No animals in a fourth group (50 μg/kg IV) tested positive for ADA. ADA were specific for both the IL-2 and Fc domains, which might be expected due to eight amino acid differences between cynomolgus IL-2 and human IL-2(V91K,C125A). Neutralizing activity of the ADA was not tested.

Example 13

[0322] This example illustrates that the principles of the present invention can be used to design and identify IL-2 muteins that induce IL-2R signaling to a desired level.

[0323] To discover IL-2 mutations that partially attenuate IL-2Rβ binding and IL-2R signaling strength, a computational algorithm was applied to determine the degree to which IL-2 mutations decrease the energy of association between IL-2 and IL-2R1P. The structure of the IL-2:IL-2Rα:IL-2Rβ:γc (PDB ID: 2B51 (Wang et al., 2005, Science 310(5751):1159-63)) was used as an input to computational algorithms to recommend sixty-four variants based on structure-guided computational energy calculations. In summary, the steps involve (i) preparing the structure of IL-2 in complex with its receptors for the energy calculations, (ii) identifying the interface residues at the IL-2:IL-2Rβ boundary for mutation to the other nineteen naturally-occurring amino acids, (iii) carrying out mutational energy calculations using two different computational algorithms, and (iv) selecting muteins using criteria that take advantage of the calculated energy values, conformation of amino acids, and previous experience and knowledge.

[0324] The IL-2:IL-2Rα:IL-2Rβ:γc structure was prepared via deletion of all water molecules, generation of coordinates of the missing atoms, and minimization of the energy of the complex structure in an implicit (GBIM) solvent model using CHARMm force field. The above steps were performed in the Discovery Studio software from ACCELRYS® (BIOVIA, San Diego, CA).

[0325] The following IL-2 residues at the IL-2: IL-2Rβ interface were identified from the complex structure and were chosen for in silico mutagenesis calculations: L12, Q13, E15, H16, L19, D20, M23, R81, D84, S87, N88, V91, 192, L94, and E95. The in silico mutagenesis was performed using the "Calculate Mutation Energy (Binding)" protocol of Discovery Studio software. This protocol computes the change in binding free energy, $\Delta\Delta G_{binding}$ (i.e. [binding free energy of mutant IL-2 to IL-2Rβ]-[binding free energy of wild-type IL-2 to IL-2Rβ]). The $\Delta\Delta G_{binding}$ values were calculated in an implicit solvent model (Generalized Born with Implicit Membrane). The numbering of residues within each mutein is relative to the sequence of wild-type human IL-2 (SEQ ID NO:1):

```
Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln
1               5                   10

Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln
            15                  20

Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn
        25                  30

Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
    35                  40

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His
45                  50                  55

Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu
                60                  65

Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn
            70                  75

Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn
        80                  85

Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
    90                  95

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu
100                 105                 110

Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp
                115                 120

Ile Thr Phe Cys Gln Ser Ile Ile Ser Thr Leu
            125                 130

Thr
```

[0326] All of the selected IL-2 residues were mutated to the nineteen other amino acids leading to 299 single amino acid substitution variants. $\Delta\Delta G_{binding}$ for each of these variants was computed as described above. The calculated $\Delta\Delta G_{binding}$ are reported in FIG. **14**. Variants were selected such that the selected mutation leads to a $\Delta\Delta G_{binding}$ value>1.5 kcal/mol and does not introduce a proline residue. To increase diversity, for positions where no mutation led to $\Delta\Delta G_{binding}$>1.5 kcal/mol (e.g., L12), mutations were selected with $\Delta\Delta G_{binding}$>1.0 kcal/mol.

[0327] The IL-2:IL-2Rα:IL-2Rβ:γc structure was prepared via deletion of all water molecules from the structure, generating coordinates of the missing atoms and minimization of the structure using OPLS 2005 force field (Banks et

al., 2005, J Comp Chem 26:1752). The above steps were performed in BIOLUMINATE® software (Schrödinger, New York, NY).

[0328] The following IL-2 residues in the IL-2: IL-2Rβ interface were identified from the complex structure and were chosen for in silico mutagenesis calculations: L12, Q13, E15, H16, L19, D20, M23, R81, D84, S87, N88, V91, 192, L94, E95. The in silico mutagenesis was performed using the "Residue Scanning" feature of BIOLUMINATE®. The calculated $\Delta\Delta G_{binding}$ are reported in FIG. **15**.

[0329] Using the predicted $\Delta\Delta G_{binding}$, variants were selected according to the following criteria: the selected mutation does not introduce a proline reside; the selected mutation was not already recommended by the Discovery Studio software; the selected mutation leads to a $\Delta\Delta G_{binding}$ value>10 kcal/mol; the selected mutation does not introduce a histidine residue (the $\Delta\Delta G_{binding}$ values computed for mutation to histidine residues by BIOLUMINATE® were found to be unreliable).

[0330] Mutations D20E, V91D, and 192W were new variants suggested by BIOLUMINATE® and were added to the list of fifty-seven variants recommended by Discovery Studio software. Variants L12K, L12Q, L19R and L19N were also included in the final analysis, resulting in the following list: D20A, D20E, D20F, D20G, D20W, D84A, D84E, D84G, D841, D84M, D84Q, D84R, D84S, D84T, E15A, E15G, E15S, E95G, H16A, H16D, H16G, H16K, H16M, H16N, H16R, H16S, H16T, H16V, H16Y, 192K, 192R, L12G, L12K, L12Q, L12S, L19A, L19D, L19E, L19G, L19N, L19R, L19S, L19T, L19V, M23R, N88A, N88D, N88E, N88F, N88G, N88M, N88R, N88S, N88V, N88W, Q13G, R81A, R81G, R81S, R81T, S87R, V91D, V91E, V91G, V91K, and V91S. All IL-2 muteins also contained the C125A mutation for improved manufacturability.

[0331] A panel of sixty-six IL-2 muteins fused to the C-terminus of IgG1 Fc (N297G), separated by a G4S linker, was tested for IL-2R stimulation on pre-activated and rested human T cells (FIG. **16**). As shown in FIG. **16**A, 33 pM was a suboptimal concentration for all muteins, thus the activity of the muteins was ranked based on the pSTAT5 MFI at this concentration. This ranking is shown in FIG. **16**B for two PBMC donors. Because Treg respond preferentially to such attenuated IL-2 muteins, as shown above, this panel can be used to define the upper and lower limits of IL-2R signaling that result in optimal Treg selectivity.

Example 14

[0332] From the initial pSTAT5 signaling data obtained with the supernatant fractions, a smaller panel of constructs was selected for expression, purification, and further evaluation. Each of these molecules comprised Fc.IL-2-G4S linker-IL-2 mutein, wherein each mutein comprised C125A and one of the following mutations: D20E, D20G, D20W, D84A, D84S, H16D, H16G, H16K, H16R, H16T, H16V, 192K, 192R, L12K, L19D, L19N, L19T, N88D, N88R, N88S, V91D, V91G, V91K, V91S, or no additional mutation ("WT"). These purified molecules were tested for their ability to activate STAT5 phosphorylation in pre-stimulated and rested human T cells (FIG. **17**). The Fc.IL-2 muteins were also tested for their ability to stimulate proliferation of T cell subsets and to increase FOXP3 expression (FIGS. **18**A-**18**D) and for their ability to stimulate NK cell proliferation (FIG. **19**).

[0333] Fc.IL-2 muteins were tested for their ability to bind CD25 (IL-2Rα) on the surface of T cells and to remain bound to cell surface CD25 at various time points (FIGS. **20**A-**20**B). The degree to which Fc.IL-2 muteins stimulated STAT5 phosphorylation in T cells (FIG. **17**) bore a high negative correlation with cell surface retention (r=−0.87), indicating that the rate of internalization by signaling through IL-2Rβγ was closely linked to receptor agonism potency.

[0334] In a parallel experiment, the persistence of pSTAT5 signaling was observed by intracellular immunodetection of phospho-STATS at different time points. Phospho-STATS MFI for FOXP3+CD25+CD4+ T cells is shown in FIG. **21**. These results demonstrated that certain muteins with intermediate signaling strength were more effective than Fc.WT IL-2 at maintaining pSTAT5 signaling at later timepoints (e.g., H16T, H16K, H16R, L19N, L19D, D20T, N88D, N88R, N88S, V91D, V91G, V91K, V91S). With the exception of the antagonist mutein (D20W), IL-2R signaling retention tended to correlate with cell surface retention; however, certain weak muteins that exhibited high surface retention were not the most effective at maintaining IL-2R signaling (e.g., D20G and D20T) (FIG. **22**).

[0335] To determine how different Fc.IL-2 muteins increased Treg frequency in vivo, humanized mice (NSG mice reconstituted four months prior with $CD34^+$ hematopoietic stem cells) were dosed with the indicated muteins, and Treg enrichment was measured in blood on day four (FIG. **23**A). The degree of Treg enrichment was found to correlate most closely with the capacity to deliver an extended pSTAT5 signal (FIG. **23**B), and substitutions at position V91 were particularly effective at Treg enrichment in vivo and increasing IL-2R signaling retention in vitro.

Example 15

[0336] A series of human anti-human IL-2 antibodies was generated in XENOMOUSE® (Amgen Inc., Thousand Oaks, CA) mice and selected on the basis of their ability to bind both human and cynomolgus monkey IL-2 in an ELISA assay. Their light and heavy chain variable domain amino acid and nucleic acid sequences are shown in FIGS. **26**-**29**.

[0337] These antibodies were screened for their ability to inhibit IL-2 responses by DERL-2 cells (IL-2 receptor α/β/γ positive) and by NKL cells (IL-2 receptor α/β/γ positive). Antibodies that exhibited high inhibitory activity against DERL2 cells and moderate to low activity on NKL cells were selected for further analysis. Clones were sequenced to eliminate sister clones and those mAb that would be more difficult to manufacture satisfactorily. Binding cross-inhibition studies were conducted and antibodies were found to fall into eight bins. The tested XENOMOUSE® antibodies all fell into Bins A, B, C, D, E, and E.1. Antibodies in Bins B, C, E and E.1 were found to interfere with human IL-2 binding to human IL2Rα, while antibodies in Bins A and D did not. Bin F was defined by a control antibody whose binding to human IL-2 does not prevent the cytokine from binding to the IL-2 receptor α and Bin G was defined by control antibody 5344.111 (Cat. No. 555051, BD Biosciences, San Jose, CA). None of the tested XENOMOUSE® antibodies fell into Bin F or G.

[0338] The kinetic parameters K_D, k_{on} and k_{dis} were also defined for each of the antibodies using BIACORE® (GE Healthcare Bio-Sciences, Pittsburgh, PA) analysis. A subset of thirty-six antibodies was selected to represent a diversity of clones, including representatives of all of the Bins and a range of K_D and k_{dis} values. All of these clones were found to inhibit IL-2 signaling in human whole blood lymphocytes, generally with higher IC_{50} values in regulatory T cells (Treg) than in non-Treg CD4 T cells (nTr), CD8 T cells (CD8) or natural killer (NK) cells (where a higher IC_{50} indicates less effective inhibition).

[0339] All thirty-six antibodies were then tested as part of an anti-IL-2 antibody/hIL-2 immune complex (at a 1:2 molar ratio of antibody: hIL-2) in NSG SCID/Hu mice reconstituted with human stem cells for their ability to expand Treg vs nTr, NK and CD8 cells as compared to low dose wild type IL-2.Fc, a model IL-2 mutein N88D.Fc, 5344.111 mouse anti-human IL-2/hIL-2 complexes and PBS-treated control mice. Treg/NK and Tr/nTr ratios were used to assess the relative ability of the XENOMOUSE® antibodies to selectively expand Treg vs effector cells (ratios were normalized to the values observed for PBS-treated mice to allow comparability between and among the several runs needed to analyze all the antibodies). Twelve of the antibodies performed as well as or better than the 5344.111/IL-2 controls. Their properties are listed in Table 5 and shown in FIG. **30**.

TABLE 5

		Hu WB pSTAT5 IC_{50} vs			
Antibody	Bin	Treg	nonTreg CD4	CD8	NK
9B10	A	200	38	23	79
14G7	B	61	64	44	54
26C12	B	302	224	283	370
26H7	B	25	22	16	259
2H11	B	106	42	49	18
9D6	B	29	21	16	23
18F3	C	42	25	21	181
2C3	D	184	132	79	152
8F10	D	158	30	20	24
14D7	E	668	244	144	293
21F8	E	61	64	44	54
22B9	E.1	813	137	276	—

TABLE 6

Kinetic Properties of Anti-IL-2 Antibodies

Antibody ID	Iso-type	VH Germline	HC CDR3	VL Germline	Epitope Bin	~KD human	~KD cyno
14D7	G2	VH4|4-31/D7|7-27|RF3/JH3	DWGR----------DAFDI	VK1|O12/JK1	E	300 pM	140 pM
14G7	G4	VH5|5-51/D4|4-23|RF2/JH6	HRGGRS---------YYYGMDV	VK1|O18/JK3	B	280 pM	130 pM
18F3	G4	VH4|4-31/D3|3-3|RF1/JH4	EGRFGE---------LGSYYFDY	VL3|3p/JL2	C	50 pM*	50 pM*
21F8	G2	VH1|1-08/D2|2-21|RF1/JH4	SRQW----------LVLDY	VK1|A30/JK1	E	690 pM	500 pM
22B9	G2	VH1|1-08/D2|2-21|RF1/JH4	SRQW----------LVLDY	VK1|A30/JK1	E.1	450 pM	170 pM
26C12	G4	VH5|5-51/D3|3-10|RF2/JH6	HGHGSSSG-------RTYYYGLDV	VK1|O18/JK3	B	270 pM	130 pM
26H7	G4	VH5|5-51/D5|5-24|RF3/JH6	HGGYSGR--------SYYYGMDV	VK1|O18/JK3	B	1.3 nM	310 pM
2C3	G2	VH5|5-51/D4|4-11|RF3/JH4	QQVA----------GMLDY	VK3|A27/JK4	D	150 pM	1.2 nM
2H11	G2/G4	VH5|5-51/D4|4-17|RF2/JH4	DTG----------YFDY	VL3|3p/JL2	B	30 pM	8.0 pM
8F10	G2	VH3|3-33/D1|1-26|RF1/JH6	GAVAGTGR-------`------`	VK2|A19/JK4	D	1 pM*	460 pM*
9B10	G2	VH3|3-30.3/D5|5-18|RF3/JH4	GSYYDSSG-------YYFGEDFDY	VK2|A23/JK4	A	110 pM	160 pM
9D6	G2	VH5|5-51/D3|3-9|RF1/JH6	QGRSF----------YYYGMDV	VK2|O11/JK4;	B	41 pM	16 pM

SEQUENCE LISTING

Sequence total quantity: 308

SEQ ID NO: 1 moltype = AA length = 133
FEATURE Location/Qualifiers
source 1..133
mol_type = protein
organism = Homo sapiens
SEQUENCE: 1
APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLE 60
EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNR 120
WITFCQSIIS TLT 133

SEQ ID NO: 2 moltype = AA length = 133
FEATURE Location/Qualifiers
SITE 125
note = MISC_FEATURE - Wherein X is C, S, V, or A
source 1..133
mol_type = protein
organism = Homo sapiens
SEQUENCE: 2
APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLE 60
EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNR 120
WITFXQSIIS TLT 133

SEQ ID NO: 3 moltype = AA length = 227
FEATURE Location/Qualifiers
source 1..227
mol_type = protein
organism = Homo sapiens
SEQUENCE: 3
DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD 60
GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK 120
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 180
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK 227

SEQ ID NO: 4 moltype = AA length = 226
FEATURE Location/Qualifiers
REGION 1..226
note = Synthetic Polypeptide
source 1..226
mol_type = protein
organism = synthetic construct
SEQUENCE: 4
DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD 60
GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK 120
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 180
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG 226

SEQ ID NO: 5 moltype = AA length = 5
FEATURE Location/Qualifiers
REGION 1..5
note = Synthetic Polypeptide
source 1..5
mol_type = protein
organism = synthetic construct
SEQUENCE: 5
GGGGS 5

SEQ ID NO: 6 moltype = AA length = 5
FEATURE Location/Qualifiers
REGION 1..5
note = Synthetic Polypeptide
source 1..5
mol_type = protein
organism = synthetic construct
SEQUENCE: 6
GGNGT 5

SEQ ID NO: 7 moltype = AA length = 5
FEATURE Location/Qualifiers
REGION 1..5
note = Synthetic Polypeptide
source 1..5
mol_type = protein
organism = synthetic construct
SEQUENCE: 7

-continued

YGNGT 5

SEQ ID NO: 8 moltype = AA length = 133
FEATURE Location/Qualifiers
REGION 1..133
note = Synthetic Polypeptide
source 1..133
mol_type = protein
organism = synthetic construct
SEQUENCE: 8
APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLE 60
EELKPLEEAL NLAPSKNFHL RPRDLISDIN VIVLELKGSE TTFMCEYADE TATIVEFLNR 120
WITFAQSIIS TLT 133

SEQ ID NO: 9 moltype = AA length = 133
FEATURE Location/Qualifiers
REGION 1..133
note = Synthetic Polypeptide
source 1..133
mol_type = protein
organism = synthetic construct
SEQUENCE: 9
APTSSSTKKT QLQLEHLLLD LQMILNGINS YKNPKLTRML TFKFYMPKKA TELKHLQCLE 60
EELKPLEEAL NLAPSKNFHL RPRDLISDIN VIVLELKGSE TTFMCEYADE TATIVEFLNR 120
WITFAQSIIS TLT 133

SEQ ID NO: 10 moltype = AA length = 133
FEATURE Location/Qualifiers
REGION 1..133
note = Synthetic Polypeptide
source 1..133
mol_type = protein
organism = synthetic construct
SEQUENCE: 10
APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPRLTRML TFKFYMPKKA TELKHLQCLE 60
EELKPLEEAL NLAPSKNFHL RPRDLISDIN VIVLELKGSE TTFMCEYADE TATIVEFLNR 120
WITFAQSIIS TLT 133

SEQ ID NO: 11 moltype = AA length = 133
FEATURE Location/Qualifiers
REGION 1..133
note = Synthetic Polypeptide
source 1..133
mol_type = protein
organism = synthetic construct
SEQUENCE: 11
APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLARML TFKFYMPKKA TELKHLQCLE 60
EELKPLEEAL NLAPSKNFHL RPRDLISDIN VIVLELKGSE TTFMCEYADE TATIVEFLNR 120
WITFAQSIIS TLT 133

SEQ ID NO: 12 moltype = AA length = 133
FEATURE Location/Qualifiers
REGION 1..133
note = Synthetic Polypeptide
source 1..133
mol_type = protein
organism = synthetic construct
SEQUENCE: 12
APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPEKA TELKHLQCLE 60
EELKPLEEAL NLAPSKNFHL RPRDLISDIN VIVLELKGSE TTFMCEYADE TATIVEFLNR 120
WITFAQSIIS TLT 133

SEQ ID NO: 13 moltype = AA length = 133
FEATURE Location/Qualifiers
REGION 1..133
note = Synthetic Polypeptide
source 1..133
mol_type = protein
organism = synthetic construct
SEQUENCE: 13
APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLE 60
EELKPLEDAL NLAPSKNFHL RPRDLISDIN VIVLELKGSE TTFMCEYADE TATIVEFLNR 120
WITFAQSIIS TLT 133

SEQ ID NO: 14 moltype = AA length = 133
FEATURE Location/Qualifiers

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REGION 1..133
note = Synthetic Polypeptide
source 1..133
mol_type = protein
organism = synthetic construct
SEQUENCE: 14
APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLE 60
EELKPLEEAL RLAPSKNFHL RPRDLISDIN VIVLELKGSE TTFMCEYADE TATIVEFLNR 120
WITFAQSIIS TLT 133

SEQ ID NO: 15 moltype = AA length = 133
FEATURE Location/Qualifiers
REGION 1..133
note = Synthetic Polypeptide
source 1..133
mol_type = protein
organism = synthetic construct
SEQUENCE: 15
APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPRLTRML TFKFYMPEKA TELKHLQCLE 60
EELKPLEDVL NLAQSKNFHL RPRDLISDIN VIVLELKGSE TTFMCEYADE TATIVEFLNR 120
WITFAQSIIS TLT 133

SEQ ID NO: 16 moltype = AA length = 364
FEATURE Location/Qualifiers
REGION 1..364
note = Synthetic Polypeptide
source 1..364
mol_type = protein
organism = synthetic construct
SEQUENCE: 16
DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD 60
GVEVHNAKTK PREEQYGSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK 120
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 180
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGGGGG SAPTSSSTKK 240
TQLQLEHLLL DLQMILNGIN NYKNPKLTRM LTFKFYMPKK ATELKHLQCL EEELKPLEEV 300
LNLAQSKNFH LRPRDLISNI NVIVLELKGS ETTFMCEYAD ETATIVEFLN RWITFAQSII 360
STLT 364

SEQ ID NO: 17 moltype = AA length = 364
FEATURE Location/Qualifiers
REGION 1..364
note = Synthetic Polypeptide
source 1..364
mol_type = protein
organism = synthetic construct
SEQUENCE: 17
DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD 60
GVEVHNAKTK PREEQYGSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK 120
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 180
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGGGGG SAPTSSSTKK 240
TQLQLEHLLL DLQMILNGIN NYKNPKLTRM LTFKFYMPKK ATELKHLQCL EEELKPLEEA 300
LNLAPSKNFH LRPRDLISNI NKIVLELKGS ETTFMCEYAD ETATIVEFLN RWITFAQSII 360
STLT 364

SEQ ID NO: 18 moltype = AA length = 364
FEATURE Location/Qualifiers
REGION 1..364
note = Synthetic Polypeptide
source 1..364
mol_type = protein
organism = synthetic construct
SEQUENCE: 18
DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD 60
GVEVHNAKTK PREEQYGSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK 120
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 180
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGGGGG SAPTSSSTKK 240
TQLQLEHLLL DLQMILNGIN NYKNPKLTRM LTFKFYMPKK ATELKHLQCL EEELKPLEEV 300
LNLAQSKNFH LRPRDLISNI NKIVLELKGS ETTFMCEYAD ETATIVEFLN RWITFAQSII 360
STLT 364

SEQ ID NO: 19 moltype = AA length = 364
FEATURE Location/Qualifiers
REGION 1..364
note = Synthetic Polypeptide
source 1..364
mol_type = protein

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	organism = synthetic construct	
SEQUENCE: 19		
DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD		60
GVEVHNAKTK PREEQYGSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK		120
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS		180
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGGGGG SAPTSSSTKK		240
TQLQLEHLLL DLQMILNGIN NYKNPKLTRM LTFKFYMPKK ATELKHLQCL EEELKPLEEA		300
LNLAPSKNFH LRPRDLISDI NVIVLELKGS ETTFMCEYAD ETATIVEFLN RWITFAQSII		360
STLT		364
SEQ ID NO: 20	moltype = AA length = 364	
FEATURE	Location/Qualifiers	
REGION	1..364	
	note = Synthetic Polypeptide	
source	1..364	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 20		
DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD		60
GVEVHNAKTK PREEQYGSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK		120
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS		180
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGGGGG SAPTSSSTKK		240
TQLQLEHLLL DLQMILNGIN NYKNPKLTRM LTFKFYMPKK ATELKHLQCL EEELKPLEEV		300
LNLAQSKNFH LRPRDLISDI NVIVLELKGS ETTFMCEYAD ETATIVEFLN RWITFAQSII		360
STLT		364
SEQ ID NO: 21	moltype = AA length = 6	
FEATURE	Location/Qualifiers	
REGION	1..6	
	note = Synthetic Polypeptide	
source	1..6	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 21		
HHHHHH		6
SEQ ID NO: 22	moltype = AA length = 42	
FEATURE	Location/Qualifiers	
REGION	1..42	
	note = Synthetic Polypeptide	
source	1..42	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 22		
TQKSLSLSPG KGGGGSAPTS SSTKKTQLQL EHLLLDLQMI LN		42
SEQ ID NO: 23	moltype = AA length = 30	
FEATURE	Location/Qualifiers	
REGION	1..30	
	note = Synthetic Polypeptide	
source	1..30	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 23		
TQKSLSLSSS TKKTQLQLEH LLLDLQMILN		30
SEQ ID NO: 24	moltype = AA length = 29	
FEATURE	Location/Qualifiers	
REGION	1..29	
	note = Synthetic Polypeptide	
source	1..29	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 24		
TQKSLSLSST KKTQLQLEHL LLDLQMILN		29
SEQ ID NO: 25	moltype = AA length = 28	
FEATURE	Location/Qualifiers	
REGION	1..28	
	note = Synthetic Polypeptide	
source	1..28	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 25		
TQKSLSLSTK KTQLQLEHLL LDLQMILN		28

-continued

SEQ ID NO: 26 moltype = AA length = 27
FEATURE Location/Qualifiers
REGION 1..27
note = Synthetic Polypeptide
source 1..27
mol_type = protein
organism = synthetic construct
SEQUENCE: 26
TQKSLSLSKK TQLQLEHLLL DLQMILN 27

SEQ ID NO: 27 moltype = AA length = 26
FEATURE Location/Qualifiers
REGION 1..26
note = Synthetic Polypeptide
source 1..26
mol_type = protein
organism = synthetic construct
SEQUENCE: 27
TQKSLSLSKT QLQLEHLLLD LQMILN 26

SEQ ID NO: 28 moltype = AA length = 25
FEATURE Location/Qualifiers
REGION 1..25
note = Synthetic Polypeptide
source 1..25
mol_type = protein
organism = synthetic construct
SEQUENCE: 28
TQKSLSLSTQ LQLEHLLLDL QMILN 25

SEQ ID NO: 29 moltype = AA length = 24
FEATURE Location/Qualifiers
REGION 1..24
note = Synthetic Polypeptide
source 1..24
mol_type = protein
organism = synthetic construct
SEQUENCE: 29
TQKSLSLSQL QLEHLLLDLQ MILN 24

SEQ ID NO: 30 moltype = AA length = 23
FEATURE Location/Qualifiers
REGION 1..23
note = Synthetic Polypeptide
source 1..23
mol_type = protein
organism = synthetic construct
SEQUENCE: 30
TQKSLSLQLQ LEHLLLDLQM ILN 23

SEQ ID NO: 31 moltype = AA length = 29
FEATURE Location/Qualifiers
REGION 1..29
note = Synthetic Polypeptide
source 1..29
mol_type = protein
organism = synthetic construct
SEQUENCE: 31
TQKSLSLSPG KGGGGSAPTS SSTKKTQLQ 29

SEQ ID NO: 32 moltype = AA length = 28
FEATURE Location/Qualifiers
REGION 1..28
note = Synthetic Polypeptide
source 1..28
mol_type = protein
organism = synthetic construct
SEQUENCE: 32
TQKSLSLSPG GGGGSAPTSS STKKTQLQ 28

SEQ ID NO: 33 moltype = AA length = 24
FEATURE Location/Qualifiers
REGION 1..24
note = Synthetic Polypeptide
source 1..24
mol_type = protein

-continued

	organism = synthetic construct
SEQUENCE: 33	
TQKSLSLSPG AAPTSSSTKK TQLQ	24
SEQ ID NO: 34	moltype = AA length = 24
FEATURE	Location/Qualifiers
REGION	1..24
	note = Synthetic Polypeptide
source	1..24
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 34	
TQKSLSLSPG AAPASSSTKK TQLQ	24
SEQ ID NO: 35	moltype = AA length = 28
FEATURE	Location/Qualifiers
REGION	1..28
	note = Synthetic Polypeptide
source	1..28
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 35	
TQKSLSLSPG GGGGSAPNSS STKKTQLQ	28
SEQ ID NO: 36	moltype = AA length = 28
FEATURE	Location/Qualifiers
REGION	1..28
	note = Synthetic Polypeptide
source	1..28
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 36	
TQKSLSLSPG GGGGSAPNST STKKTQLQ	28
SEQ ID NO: 37	moltype = AA length = 28
FEATURE	Location/Qualifiers
REGION	1..28
	note = Synthetic Polypeptide
source	1..28
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 37	
TQKSLSLSPG GGNGTAPASS STKKTQLQ	28
SEQ ID NO: 38	moltype = AA length = 28
FEATURE	Location/Qualifiers
REGION	1..28
	note = Synthetic Polypeptide
source	1..28
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 38	
TQKSLSLSPG YGNGTAPASS STKKTQLQ	28
SEQ ID NO: 39	moltype = AA length = 386
FEATURE	Location/Qualifiers
REGION	1..386
	note = Synthetic polypeptide
source	1..386
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 39	
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE	60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE	120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA	180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ	240
KSLSLSPGGG GGSAPTSSST KKTQGQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP	300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY	360
ADETATIVEF LNRWITFAQS IISTLT	386
SEQ ID NO: 40	moltype = AA length = 386
FEATURE	Location/Qualifiers
REGION	1..386
	note = synthetic polypeptide
source	1..386
	mol_type = protein

-continued

organism = synthetic construct

SEQUENCE: 40

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQKQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 41 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 41

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQQQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 42 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 42

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQSQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 43 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 43

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLGLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 44 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 44

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLAHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 45 moltype = AA length = 386
FEATURE Location/Qualifiers

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REGION                  1..386
                        note = synthetic polypeptide
source                  1..386
                        mol_type = protein
                        organism = synthetic construct
SEQUENCE: 45
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLGHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 46           moltype = AA  length = 386
FEATURE                 Location/Qualifiers
REGION                  1..386
                        note = synthetic polypeptide
source                  1..386
                        mol_type = protein
                        organism = synthetic construct
SEQUENCE: 46
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLSHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 47           moltype = AA  length = 386
FEATURE                 Location/Qualifiers
REGION                  1..386
                        note = synthetic polypeptide
source                  1..386
                        mol_type = protein
                        organism = synthetic construct
SEQUENCE: 47
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEAL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 48           moltype = AA  length = 386
FEATURE                 Location/Qualifiers
REGION                  1..386
                        note = synthetic polypeptide
source                  1..386
                        mol_type = protein
                        organism = synthetic construct
SEQUENCE: 48
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEDL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 49           moltype = AA  length = 386
FEATURE                 Location/Qualifiers
REGION                  1..386
                        note = synthetic polypeptide
source                  1..386
                        mol_type = protein
                        organism = synthetic construct
SEQUENCE: 49
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEGL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY  360
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ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 50 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 50
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEKL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 51 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 51
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEML LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 52 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 52
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLENL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 53 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 53
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLERL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 54 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 54
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120

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YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLESL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 55 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 55
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLETL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 56 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 56
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEVL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 57 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 57
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEYL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 58 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 58
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LADLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 59 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein

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organism = synthetic construct

SEQUENCE: 59

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LDDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 60 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 60

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LEDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 61 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptides
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 61

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LGDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 62 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 62

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LNDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 63 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 63

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LRDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 64 moltype = AA length = 386
FEATURE Location/Qualifiers

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REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 64
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LSDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 65 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 65
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LTDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 66 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 66
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LVDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 67 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 67
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLALQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 68 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 68
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLELQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360

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ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 69 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 69
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLFLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 70 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 70
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLGLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 71 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 71
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLWLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 72 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 72
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQRILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 73 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 73
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120

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YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLAPRDLIS NINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 74          moltype = AA  length = 386
FEATURE                Location/Qualifiers
REGION                 1..386
                       note = synthetic polypeptide
source                 1..386
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 74
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLGPRDLIS NINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 75          moltype = AA  length = 386
FEATURE                Location/Qualifiers
REGION                 1..386
                       note = synthetic polypeptide
source                 1..386
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 75
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLSPRDLIS NINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 76          moltype = AA  length = 386
FEATURE                Location/Qualifiers
REGION                 1..386
                       note = synthetic polypeptide
source                 1..386
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 76
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLTPRDLIS NINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 77          moltype = AA  length = 386
FEATURE                Location/Qualifiers
REGION                 1..386
                       note = synthetic polypeptide
source                 1..386
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 77
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRALIS NINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 78          moltype = AA  length = 386
FEATURE                Location/Qualifiers
REGION                 1..386
                       note = synthetic polypeptide
source                 1..386
                       mol_type = protein
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organism = synthetic construct

SEQUENCE: 78

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRELIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 79 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 79

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRGLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 80 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 80

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRILIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 81 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 81

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRMLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 82 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 82

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRQLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 83 moltype = AA length = 386
FEATURE Location/Qualifiers

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REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 83
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRRLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 84 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 84
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRSLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 85 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 85
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRTLIS NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 86 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 86
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIR NINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 87 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 87
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS AINVIVLELK GSETTFMCEY 360

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ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 88 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 88
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS EINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 89 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 89
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS FINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 90 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = sythetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 90
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS GINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 91 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 91
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS MINVIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 92 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct
SEQUENCE: 92
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120

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YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS SINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 93          moltype = AA  length = 386
FEATURE                Location/Qualifiers
REGION                 1..386
                       note = synthetic polypeptide
source                 1..386
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 93
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS VINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 94          moltype = AA  length = 386
FEATURE                Location/Qualifiers
REGION                 1..386
                       note = synthetic polypeptide
source                 1..386
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 94
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS WINVIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 95          moltype = AA  length = 386
FEATURE                Location/Qualifiers
REGION                 1..386
                       note = synthetic polypeptide
source                 1..386
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 95
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINDIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 96          moltype = AA  length = 386
FEATURE                Location/Qualifiers
REGION                 1..386
                       note = synthetic polypeptide
source                 1..386
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 96
MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE  60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE  120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA  180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ  240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP  300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINEIVLELK GSETTFMCEY  360
ADETATIVEF LNRWITFAQS IISTLT                                       386

SEQ ID NO: 97          moltype = AA  length = 386
FEATURE                Location/Qualifiers
REGION                 1..386
                       note = synthetic polypeptide
source                 1..386
                       mol_type = protein
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organism = synthetic construct

SEQUENCE: 97

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINGIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 98 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 98

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINSIVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 99 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 99

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVKVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 100 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 100

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVRVLELK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 101 moltype = AA length = 386
FEATURE Location/Qualifiers
REGION 1..386
note = synthetic polypeptide
source 1..386
mol_type = protein
organism = synthetic construct

SEQUENCE: 101

MDMRVPAQLL GLLLLWLRGA RCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE 60
VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYGS TYRVVSVLTV LHQDWLNGKE 120
YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA 180
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ 240
KSLSLSPGGG GGSAPTSSST KKTQLQLEHL LLDLQMILNG INNYKNPKLT RMLTFKFYMP 300
KKATELKHLQ CLEEELKPLE EVLNLAQSKN FHLRPRDLIS NINVIVLGLK GSETTFMCEY 360
ADETATIVEF LNRWITFAQS IISTLT 386

SEQ ID NO: 102 moltype = DNA length = 1158
FEATURE Location/Qualifiers

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misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 102

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agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aagggcaatt ggagcacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 103 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 103

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agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aaaagcaatt ggagcacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 104 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 104

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agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720

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aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aacagcaatt ggagcacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 105 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 105
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agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aatcgcaatt ggagcacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 106 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 106
atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgggatt ggagcacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 107 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 107
atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60

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agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggcgcacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 108 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 108
atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggggcacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 109 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 109
atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt gtcgcacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
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SEQ ID NO: 110 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 110
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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggaggccttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 111 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 111
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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
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aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
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gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 112 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 112
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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480

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accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
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gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagggcttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 113 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 113
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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagaagttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
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aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 114 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 114
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gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
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tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagatgttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 115 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158

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mol_type = other DNA
organism = synthetic construct

SEQUENCE: 115

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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
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atcatctcca ctttgact 1158

SEQ ID NO: 116 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 116

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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
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gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
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gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 117 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 117

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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
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gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagagcttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900

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aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 118 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 118
atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
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tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
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gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 119 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 119
atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
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tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
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aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggaggtcttg ttgttggact tgcaaatgat cttgaatggt 840
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aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 120 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 120
atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240

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gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
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tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagtacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 121 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 121
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agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagcacttg ttggcggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 122 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 122
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agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagcacttg ttggatgact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
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gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 123 moltype = DNA length = 1158

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FEATURE Location/Qualifiers
misc_feature 1..1158
note = sythetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 123

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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagcacttg ttggaggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 124 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 124

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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagcacttg ttgggggact tgcaaatgat cttgaatggt 840
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aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 125 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 125

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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660

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caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag  720
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aagaagactc aattgcaatt ggagcacttg ttgaatgact tgcaaatgat cttgaatggt  840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca  900
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gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc  1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac  1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc  1140
atcatctcca ctttgact                                               1158

SEQ ID NO: 126          moltype = DNA  length = 1158
FEATURE                 Location/Qualifiers
misc_feature            1..1158
                        note = synthetic polynucleotide
source                  1..1158
                        mol_type = other DNA
                        organism = synthetic construct
SEQUENCE: 126
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agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg  120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag  180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac  240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc  300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag  360
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gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg  480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc  540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg  600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag  660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag  720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact  780
aagaagactc aattgcaatt ggagcacttg ttgcgggact tgcaaatgat cttgaatggt  840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca  900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag  960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc  1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac  1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc  1140
atcatctcca ctttgact                                               1158

SEQ ID NO: 127          moltype = DNA  length = 1158
FEATURE                 Location/Qualifiers
misc_feature            1..1158
                        note = synthetic polynucleotide
source                  1..1158
                        mol_type = other DNA
                        organism = synthetic construct
SEQUENCE: 127
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agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg  120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag  180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac  240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc  300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag  360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa  420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg  480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc  540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg  600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag  660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag  720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact  780
aagaagactc aattgcaatt ggagcacttg ttgtcggact tgcaaatgat cttgaatggt  840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca  900
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gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc  1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac  1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc  1140
atcatctcca ctttgact                                               1158

SEQ ID NO: 128          moltype = DNA  length = 1158
FEATURE                 Location/Qualifiers
misc_feature            1..1158
                        note = synthetic polynucleotide
source                  1..1158
                        mol_type = other DNA
                        organism = synthetic construct
SEQUENCE: 128
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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagcacttg ttgacggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 129 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 129
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agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 130 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 130
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tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagcacttg ttgttggcct tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080

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gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 131 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 131
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SEQ ID NO: 132 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 132
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SEQ ID NO: 133 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 133
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SEQ ID NO: 134 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 134
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SEQ ID NO: 135 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 135
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SEQ ID NO: 136 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide

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source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 136

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SEQ ID NO: 137 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 137

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atcatctcca ctttgact 1158

SEQ ID NO: 138 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 138

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gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 139 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 139
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SEQ ID NO: 140 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 140
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SEQ ID NO: 141 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 141
atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
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SEQ ID NO: 142 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 142
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SEQ ID NO: 143 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 143
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SEQ ID NO: 144 moltype = DNA length = 1158
FEATURE Location/Qualifiers
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note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 144
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SEQ ID NO: 145 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 145
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SEQ ID NO: 146 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 146
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accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
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atcatctcca ctttgact 1158

SEQ ID NO: 147 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 147
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SEQ ID NO: 148 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 148
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SEQ ID NO: 149 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct

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SEQUENCE: 149
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SEQ ID NO: 150 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 150
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atcatctcca ctttgact 1158

SEQ ID NO: 151 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 151
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atcatctcca ctttgact 1158

SEQ ID NO: 152 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 152
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SEQ ID NO: 153 moltype = DNA length = 1158
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note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 153
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SEQ ID NO: 154 moltype = DNA length = 1158
FEATURE Location/Qualifiers
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note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 154
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note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 155
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note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 156
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SEQ ID NO: 157 moltype = DNA length = 1158
FEATURE Location/Qualifiers
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source               1..1158
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SEQ ID NO: 158       moltype = DNA  length = 1158
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source               1..1158
                     mol_type = other DNA
                     organism = synthetic construct
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SEQ ID NO: 159       moltype = DNA  length = 1158
FEATURE              Location/Qualifiers
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source               1..1158
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SEQ ID NO: 160 moltype = DNA length = 1158
FEATURE Location/Qualifiers
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note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 160
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SEQ ID NO: 161 moltype = DNA length = 1158
FEATURE Location/Qualifiers
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note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 161
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SEQ ID NO: 162 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 162
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SEQ ID NO: 163 moltype = DNA length = 1158
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note = synthetic polynucleotide
source 1..1158
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organism = synthetic construct
SEQUENCE: 163
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gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagcacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgagagtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

SEQ ID NO: 164 moltype = DNA length = 1158
FEATURE Location/Qualifiers
misc_feature 1..1158
note = synthetic polynucleotide
source 1..1158
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 164
atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtggaggt ggtggaagcg ctccaacttc ctcctccact 780
aagaagactc aattgcaatt ggagcacttg ttgttggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggggttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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SEQ ID NO: 165 moltype = AA length = 114
FEATURE Location/Qualifiers
REGION 1..114
note = synthetic polypeptide
source 1..114
mol_type = protein
organism = synthetic construct
SEQUENCE: 165
DIVMTQTPLS LPVTPGEPAS ISCRSSQSLL DSDEGNTYLD WYLQKPGQSP QLLIYTLSYR 60
ASGVPDRFSG TGSDTDFTLK ISRVEAEDVG VYYCMQRIEF PLTFGGGTKV EIKR 114

SEQ ID NO: 166 moltype = AA length = 109
FEATURE Location/Qualifiers
REGION 1..109
note = synthetic polypeptide
source 1..109
mol_type = protein
organism = synthetic construct
SEQUENCE: 166
EIVLTQSPGT LSLSPGERAT LSCRASQSFS SSYLVWYQQK PGQAPRLLIY GASSRATGIP 60
DRFGGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPLTFG GGTKVEIKR 109

SEQ ID NO: 167 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 167
DIVLTQTPLS SPVTLGQPAS ISCRSSHHLI HSDGNTYLSW LQQRPGQPPR LLIYKISNRF 60
SGVPDRFTGS GTGTDFTLKI SRVEAGDVGV YYCMQTTQFP TFGQGTKVEI KR 112

SEQ ID NO: 168 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 168
DIVMTQTPLS SPVTLGQPAS ISCRSSQNLV QSDGNTYLSW LHQRPGQPPR LLIYKISNRF 60
SGVPDRFSGS GAGTDFTLKI SRVEAEDVGV YFCMQTTQFP TFGQGTKVEI KR 112

SEQ ID NO: 169 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 169
DIVMTQTPLS SPVTLGQPAS ISCRSSQILV NSDGNTYLSW LHQRPGQPPR LLIYKISNRF 60
SGVPDRFSGS GAGTDFTLKI SRVEAEDVGV YYCMQTTQFP TFGQGTKVEI KR 112

SEQ ID NO: 170 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 170
DIVMTQTPLS SPVTLGQPAS ISCRSSQSLV RSDGNTYLSW LHQRPGQPPR LLIYKISNRF 60
SGVPDRFSGS GAGTDFTLKI SRVEAEDVGV YYCMQTTQFP TFGQGTKVEI KR 112

SEQ ID NO: 171 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 171
DIVMTQTPLS SPVTLGQPAS ISCRSSHSLV HSDGHTYLSW LQQRPGQPPR LLLYKISNRF 60

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SGVPDRFSGS GAGTDFTLKI SRVEAEDVGV YYCMQTTQFP TFGGGTKVEI KR 112

SEQ ID NO: 172 moltype = AA length = 113
FEATURE Location/Qualifiers
REGION 1..113
note = synthetic polypeptide
source 1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 172
DIAMSQSPLS LPVTPGEPAS MSCRSSQSLL HSNGFNYLDW YLQKPGQSPQ VLIHLGSDRA 60
SGVPDRFSGS GSGTDFTLKI SRVEAEDVGI YYCMQALQTP LTFGGGTKVE IKR 113

SEQ ID NO: 173 moltype = AA length = 113
FEATURE Location/Qualifiers
REGION 1..113
note = synthetic polypeptide
source 1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 173
DIVMTQSPLS LPVTPGEPAS ISCRSSQSLL HSNGFNYLDW FLQKPGQSPQ PLIYLGSDRA 60
SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCMQALQTP LTFGGGTKVE IKR 113

SEQ ID NO: 174 moltype = AA length = 113
FEATURE Location/Qualifiers
REGION 1..113
note = synthetic polypeptide
source 1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 174
DIVMTQSPLS LPVTPGEPAS ISCRSSQSLL HSNGFNYLDW YLQKPGQSPQ LLIYLGSDRA 60
SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCMQALQTP LTFGGGTKVE IKR 113

SEQ ID NO: 175 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 175
DIVMTQTPLS SPVTLGQPAS ISCRSSQSLV NIDGSTHLSW LQQRPGQPPR LLIYKISNRF 60
SGVPDRFSGS GAGTDFTLKI SRVEAEDVGV YYCMQTTQFP TFGQGTRLEI KR 112

SEQ ID NO: 176 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 176
EIVMTQTPLS SPVTLGQPAS ISCRSSQSLV QSDGITYLSW LQQRPGQPPR LLIYKISNRF 60
SGVPDRFSGS GAGTDFTLKI SRVEAEDVGV YYCMQTTQFP TFGQGTKVEI KR 112

SEQ ID NO: 177 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 177
DIVMTQTPLS SPVTLGQPAS ISCRSSQSLV NSDGNTYLNW LQQRPGQPPR LLIYKISNRF 60
SGVPDRFSGS GAGTDFTLKI SRVEAEDVGV YYCMQATQFP TFGQGTKVEI KR 112

SEQ ID NO: 178 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 178

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DIVMTQTPLS SPVTLGQPAS ISCRSSHNLV RSDGNTYLSW LQQRPGQPPR LLIYKISNRF 60
SGVPDRFSGS GAGTDFTLKI SRVGAEDVGV YYCMQATQFP TFGQGTRLEI KR 112

SEQ ID NO: 179 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 179
NIVMTQTPLS SPVTLGQPAS ISCRSSQSLV QTDGNTYLSW LQQRPGQPPR PLIYKISNRF 60
SGVPDRFSGS GAGTDFTLKI SRVEAEDVGV YYCMQVTQFP TFGQGTRLEI KR 112

SEQ ID NO: 180 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 180
DIVMTQTPLS SPVTLGQPAS ISCRSSHNLI HSDGNTYLSW LHQRPGQPPR LLIYKISNRF 60
SGVPDRFSGS GAGTDFTLKI SRVEAEDVGV YYCMQTSQFP TFGGGTKVEI KR 112

SEQ ID NO: 181 moltype = AA length = 112
FEATURE Location/Qualifiers
REGION 1..112
note = synthetic polypeptide
source 1..112
mol_type = protein
organism = synthetic construct
SEQUENCE: 181
DIVMTQTPLS SPVTLGQPAS ISCRSSHNLL HSDGNTYLSW LQQRPGQPPR LLIYEISNRF 60
SGVPDRFSGS GAGTDFTLKI SRVEAEDVGV YYCMQVTQFP TFGGGTKVEI KR 112

SEQ ID NO: 182 moltype = AA length = 109
FEATURE Location/Qualifiers
REGION 1..109
note = synthetic polypeptide
source 1..109
mol_type = protein
organism = synthetic construct
SEQUENCE: 182
EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASSRATGIP 60
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPLTFG GGTKVEIKR 109

SEQ ID NO: 183 moltype = AA length = 109
FEATURE Location/Qualifiers
REGION 1..109
note = synthetic polypeptide
source 1..109
mol_type = protein
organism = synthetic construct
SEQUENCE: 183
EIVLTQSPGT LSLSPGERAT LSCRASQSVS SRYLAWYQQK PGQAPRLLIH GPFSRATGIP 60
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGNSSITFG QGTRLEIKR 109

SEQ ID NO: 184 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = synthetic polypeptide
source 1..108
mol_type = protein
organism = synthetic construct
SEQUENCE: 184
DIQMTQSPSS LSASVGDRVT ITCRASQTIS SYLNWYQQKP GKAPKVLIYA ASSFQSGVPS 60
RFSGSGSGTD FTLTISSLQP EDFATYYCQQ SHYIPRTFGQ GTKVEIKR 108

SEQ ID NO: 185 moltype = AA length = 109
FEATURE Location/Qualifiers
REGION 1..109
note = synthetic polypeptide
source 1..109
mol_type = protein
organism = synthetic construct

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SEQUENCE: 185
SYELTQPPSV SVSPGQTARI ACSGDALPRK FAYWYQQKSG QAPVLVISED SRRPSGIPER 60
FSGSSSGTMA TLTISGAQVE DEADYYCFST DSSANHRVFG GGTKLTVLG 109

SEQ ID NO: 186 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = synthetic polypeptide
source 1..108
mol_type = protein
organism = synthetic construct
SEQUENCE: 186
DIQMTQSPSS LSASVGDRVT ITCRASQDIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS 60
RFSGSGSGTE FTLTIGSLQP EDFTTYYCLQ HNSYPLTFGG GTKVEIKR 108

SEQ ID NO: 187 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = synthetic polypeptide
source 1..108
mol_type = protein
organism = synthetic construct
SEQUENCE: 187
DIQMTQSPSS LSASVGDRVT ITCRASQGIR DDLGWYQQKP GKAPKRLIYI ATSLQSGVPS 60
RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HISYPWTFGQ GTKVEIKR 108

SEQ ID NO: 188 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = synthetic polypeptide
source 1..108
mol_type = protein
organism = synthetic construct
SEQUENCE: 188
DIQMTQSPSS LSASVGDRVT ITCRASQDIR DDLGWYQQKP GKAPKRLIYV ASSLQSGVPS 60
RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HISYPWTFGQ GTKVEIKR 108

SEQ ID NO: 189 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = synthetic polypeptide
source 1..108
mol_type = protein
organism = synthetic construct
SEQUENCE: 189
DIQMTQSPSS LSASVGDRVT ITCRASQDIR DDLGWYQQKP GKAPKRLIYV VSSLQSGVPS 60
RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNGYPWTFGQ GTKVEIKR 108

SEQ ID NO: 190 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = synthetic polypeptide
source 1..108
mol_type = protein
organism = synthetic construct
SEQUENCE: 190
DIQMTQSPSS LSASVGDRVT ITCRASQGIG DDLGWYQQKP GKAPQRLIYS ASSLPSGVPS 60
RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNSYPRSFGQ GTKLEIRR 108

SEQ ID NO: 191 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = synthetic polypeptide
source 1..108
mol_type = protein
organism = synthetic construct
SEQUENCE: 191
DIQMTQSPSS LSASVGDRVT ITCRASQDIE HDLGWYQQKP GKAPKRLIYA ASTLPSGVPS 60
RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNSFPRSFGQ GTQLEIKR 108

SEQ ID NO: 192 moltype = AA length = 114
FEATURE Location/Qualifiers
REGION 1..114
note = synthetic polypeptide
source 1..114
mol_type = protein

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                     organism = synthetic construct
SEQUENCE: 192
DIVMTQTPLS LPVTPGEPAS ISCRSTQSLL DGDDGNTLLD WYLQKPGQSP QLLIYTLSYR  60
ASGVPDRFSG SGSGTDFTLK ISRVEAEDVG VYYCMQRLEF PLTFGGGTKV EIKR       114

SEQ ID NO: 193         moltype = AA  length = 114
FEATURE                Location/Qualifiers
REGION                 1..114
                       note = synthetic polypeptide
source                 1..114
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 193
DIVMTQTPLS LPVTPGEPAS ISCRSSQSLL DSDEGNTFLD WYLQKPGQPP QLLIYTLSYR  60
ASGVPDRFSG SGSGTDFTLK ISRVEAEDVG VYYCMQRIEF PLTFGGGTKV EIKR       114

SEQ ID NO: 194         moltype = AA  length = 108
FEATURE                Location/Qualifiers
REGION                 1..108
                       note = synthetic polypeptide
source                 1..108
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 194
DIQMTQSPSS LSASVGDRVT ITCQASQDIS NYLNWYQQKP GKAPKLLIYD ASNLETGVPS  60
RFSGSGSETD FTFTISSLQP EDIATYYCQQ YENLPFTFGP GTKVDIKR              108

SEQ ID NO: 195         moltype = AA  length = 109
FEATURE                Location/Qualifiers
REGION                 1..109
                       note = synthetic polypeptide
source                 1..109
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 195
SYELTQPPSV SVSPGQTARI TCSGDALPRQ YAYWYQQKPG QAPMLVIYKD SERPSGIPER  60
FSGSSSGTTV TLTISGVQAE DEADYYCQSA DSSGTYVVFG GGTKLTVLG             109

SEQ ID NO: 196         moltype = AA  length = 109
FEATURE                Location/Qualifiers
REGION                 1..109
                       note = synthetic polypeptide
source                 1..109
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 196
SYELTQPPSV SVSPGQTARI TCSGDALPRK YAYWYQQKSG QAPVLVIYED SKRPSGIPER  60
FSGSSSGTMA TLTISGAQVE DEADYYCYST DSSGNHYVFG TGTKVTVLG             109

SEQ ID NO: 197         moltype = AA  length = 108
FEATURE                Location/Qualifiers
REGION                 1..108
                       note = synthetic polypeptide
source                 1..108
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 197
DIQMTQSPSS LSASVGDRVT ITCQASQDIS NYLNWYQQKP GKAPKFLIYD ASNLETGVPS  60
RFSGSGSGTD FFFTISNLQP EDIATYFCQQ DDNLPFTFGP GTKVDIKR              108

SEQ ID NO: 198         moltype = AA  length = 108
FEATURE                Location/Qualifiers
REGION                 1..108
                       note = synthetic polypeptide
source                 1..108
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 198
DIQMTQSPSS LSASVGDRVT ITCQASQDIS NYLNWYQQKP GKAPKLLIYD ASNLETGVPS  60
RFSGSGSGTD FTFTISSLQP EDIATFYCQQ YDNLPFTFGP GTKVDIKR              108

SEQ ID NO: 199         moltype = AA  length = 109
FEATURE                Location/Qualifiers
REGION                 1..109
                       note = synthetic polypeptide
source                 1..109
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mol_type = protein
organism = synthetic construct

SEQUENCE: 199
SYELTQPPSV SVSPGQTARI TCSGDALPRK FAYWYQQKSG QAPVLVIYED RKRPSGIPER 60
FSGSSSGTMA TLTISGAQVE DEADYYCYST DRSGDHVVFG GGTKLTVLG 109

SEQ ID NO: 200 moltype = AA length = 108
FEATURE Location/Qualifiers
REGION 1..108
note = synthetic polypeptide
source 1..108
mol_type = protein
organism = synthetic construct
SEQUENCE: 200
DIQMTQSPSS VSASVGDRVT ITCRASQGIS NWLVWYQQKP GKPPKLLIYA ASSLQNGVPS 60
RFSGSGSGTD FTLTISSLQT EDFATYYCQQ ALSFPWTFGP GTKVEVKR 108

SEQ ID NO: 201 moltype = DNA length = 342
FEATURE Location/Qualifiers
misc_feature 1..342
note = nucleic acid
source 1..342
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 201
gatattgtga tgacccagac tccactctcc ttgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctctta gatagtgatg agggaaacac ctatttggac 120
tggtacctgc agaagccagg gcagtctcca cagctcctga tctatacgct ttcctatcgg 180
gcctctggag tcccagacag gttcagtggc actgggtcag acactgattt cacactgaaa 240
atcagcaggg tggaggctga ggatgttgga gtttattact gcatgcaacg tatagagttt 300
cctctcactt tcggcggagg gaccaaggtg gagatcaaac ga 342

SEQ ID NO: 202 moltype = DNA length = 327
FEATURE Location/Qualifiers
misc_feature 1..327
note = nucleic acid
source 1..327
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 202
gaaattgtat tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagttttagc agcagctact tagtctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttcg gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcacctct cactttcggc 300
ggagggacca aggtggagat caaacga 327

SEQ ID NO: 203 moltype = DNA length = 336
FEATURE Location/Qualifiers
misc_feature 1..336
note = nucleic acid
source 1..336
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 203
gatattgtgc tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atctcctgca ggtctagtca tcacctcata cacagtgatg gaaacaccta cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cactggcagt gggacaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgggga tgtcggggtt tattactgca tgcaaactac acaatttccg 300
acgttcggcc aagggaccaa ggtggaaatc aaacga 336

SEQ ID NO: 204 moltype = DNA length = 336
FEATURE Location/Qualifiers
misc_feature 1..336
note = nucleic acid
source 1..336
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 204
gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atctcctgca ggtccagtca aaacctcgtt caaagtgatg gaaacaccta cttgagttgg 120
cttcaccaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tatttctgca tgcaaactac acaatttccg 300
acgttcggcc aagggaccaa ggtggaaatc aaacga 336

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SEQ ID NO: 205 moltype = DNA length = 336
FEATURE Location/Qualifiers
misc_feature 1..336
note = nucleic acid
source 1..336
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 205
gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atttcctgca ggtctagtca aatcctcgta aacagtgatg gaaacaccta cttgagttgg 120
cttcaccaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaaactac acaatttccg 300
acgttcggcc aagggaccaa ggtggaaatc aaacga 336

SEQ ID NO: 206 moltype = DNA length = 336
FEATURE Location/Qualifiers
misc_feature 1..336
note = nucleic acid
source 1..336
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 206
gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atctcctgca ggtctagtca aagcctcgta cgcagtgatg gaaacaccta cttgagttgg 120
cttcaccaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaaactac acaatttccg 300
acgttcggcc aagggaccaa ggtggaaatc aaacga 336

SEQ ID NO: 207 moltype = DNA length = 336
FEATURE Location/Qualifiers
misc_feature 1..336
note = nucleic acid
source 1..336
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 207
gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atctcctgca ggtctagtca cagcctcgta cacagtgatg gacacaccta cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctcctacttt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaaactac acaatttccc 300
actttcggcg gagggaccaa ggtggagatc aaacga 336

SEQ ID NO: 208 moltype = DNA length = 339
FEATURE Location/Qualifiers
misc_feature 1..339
note = nucleic acid
source 1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 208
gatattgcga tgagtcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atgtcatgca ggtctagtca gagcctcctg catagtaatg gattcaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag gtcctgatcc atttgggttc tgatcgggcc 180
tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac attgaaaatc 240
agcagagtgg aggctgagga tgttggaatt tattactgca tgcaagctct acaaactcct 300
ctcactttcg gcggagggac caaggtggag atcaaacga 339

SEQ ID NO: 209 moltype = DNA length = 339
FEATURE Location/Qualifiers
misc_feature 1..339
note = nucleic acid
source 1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 209
gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctccta catagtaatg gattcaacta tttggattgg 120
ttcctgcaga agccaggaca gtctccacag cccctgatct atttgggttc tgatcgggcc 180
tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactccg 300
ctcactttcg gcggagggac caaggtggag atcaaacga 339

-continued

SEQ ID NO: 210 moltype = DNA length = 339
FEATURE Location/Qualifiers
misc_feature 1..339
note = nucleic acid
source 1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 210
gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctg catagtaatg gattcaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ctcctgatct atttgggttc tgatcgggcc 180
tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactccg 300
ctcactttcg gcggagggac caaggtggag atcaaacga 339

SEQ ID NO: 211 moltype = DNA length = 336
FEATURE Location/Qualifiers
misc_feature 1..336
note = nucleic acid
source 1..336
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 211
gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atatcctgca ggtccagtca aagcctcgta aacattgatg gaagtaccca cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaagatc 240
agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaaactac acaattcccc 300
accttcggcc aagggacacg actggagatt aaacga 336

SEQ ID NO: 212 moltype = DNA length = 336
FEATURE Location/Qualifiers
misc_feature 1..336
note = nucleic acid
source 1..336
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 212
gaaattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atttcctgca ggtctagtca aagcctcgtt cagagtgatg gaatcaccta cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaaactac acaatttccg 300
acgttcggcc aagggaccaa ggtggaaatc aaacga 336

SEQ ID NO: 213 moltype = DNA length = 336
FEATURE Location/Qualifiers
misc_feature 1..336
note = nucleic acid
source 1..336
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 213
gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atctcctgca ggtctagtca aagcctcgta aacagtgatg gaaacaccta cttgaattgg 120
cttcagcaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaagctac acaatttccg 300
acgttcggcc aagggaccaa ggtggaaatc aaacga 336

SEQ ID NO: 214 moltype = DNA length = 336
FEATURE Location/Qualifiers
misc_feature 1..336
note = nucleic acid
source 1..336
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 214
gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atctcctgca ggtccagtca caacctcgta cgcagtgatg gaaacaccta cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg gagctgagga tgtcggggtt tattactgca tgcaagctac acaatttccc 300
accttcggcc aagggacgcg actggagatt aaacga 336

SEQ ID NO: 215 moltype = DNA length = 336

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FEATURE	Location/Qualifiers
misc_feature	1..336
	note = nucleic acid
source	1..336
	mol_type = other DNA
	organism = synthetic construct

SEQUENCE: 215

aatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atctcctgca ggtctagtca aagcctcgta caaactgatg gaaacacata tttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga cccctaattt ataagatttc taaccggttt 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaagtaac acaatttccc 300
accttcggcc aagggacacg actggagatt aaacga 336

SEQ ID NO: 216 moltype = DNA length = 336

FEATURE	Location/Qualifiers
misc_feature	1..336
	note = nucleic acid
source	1..336
	mol_type = other DNA
	organism = synthetic construct

SEQUENCE: 216

gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atctcctgta ggtctagtca taacctcata cacagtgatg gaaacaccta cttgagttgg 120
cttcaccaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180
tctggggtcc cggacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaaacttc acagtttccc 300
actttcggcg gagggaccaa ggtggagatc aaacga 336

SEQ ID NO: 217 moltype = DNA length = 336

FEATURE	Location/Qualifiers
misc_feature	1..336
	note = nucleic acid
source	1..336
	mol_type = other DNA
	organism = synthetic construct

SEQUENCE: 217

gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atctcctgca ggtctagtca taacctccta cacagtgatg gaaacaccta cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctcctaattt atgagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaagttac acaatttccc 300
actttcggcg gcgggaccaa ggtggagatc aaacga 336

SEQ ID NO: 218 moltype = DNA length = 327

FEATURE	Location/Qualifiers
misc_feature	1..327
	note = nucleic acid
source	1..327
	mol_type = other DNA
	organism = synthetic construct

SEQUENCE: 218

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcaccgct cactttcggc 300
ggagggacca aggtggagat caaacga 327

SEQ ID NO: 219 moltype = DNA length = 327

FEATURE	Location/Qualifiers
misc_feature	1..327
	note = nucleic acid
source	1..327
	mol_type = other DNA
	organism = synthetic construct

SEQUENCE: 219

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgta gggccagtca gagtgttagc agcaggtact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatccat ggtccattca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gatttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta attcatcgat caccttcggc 300
caagggacac gactggagat taaacga 327

SEQ ID NO: 220 moltype = DNA length = 324

FEATURE	Location/Qualifiers

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misc_feature 1..324
note = nucleic acid
source 1..324
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 220
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gaccattagc agttatttaa attggtatca gcagaaacca 120
gggaaagccc ctaaggtcct gatctatgct gcatccagtt tccaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agtcactata tccctcggac gttcggccaa 300
gggaccaagg tggaaatcaa acga 324

SEQ ID NO: 221 moltype = DNA length = 327
FEATURE Location/Qualifiers
misc_feature 1..327
note = nucleic acid
source 1..327
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 221
tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacaaac ggccaggatc 60
gcctgctctg gagatgcatt gccaagaaaa tttgcttatt ggtaccagca gaagtcaggc 120
caggcccctg tgctggtcat ctctgaggac agcagacgac cctccgggat ccctgagaga 180
ttctctggct ccagctcagg gacaatggcc accttgacta tcagtggggc ccaggtggag 240
gatgaagctg actactactg tttctcaaca gacagcagtg ctaatcatag ggtattcggc 300
ggagggacca agctgaccgt cctaggt 327

SEQ ID NO: 222 moltype = DNA length = 324
FEATURE Location/Qualifiers
misc_feature 1..324
note = nucleic acid
source 1..324
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 222
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca ggacattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcggcag cctgcagcct 240
gaagatttta caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300
gggaccaagg tggagatcaa acga 324

SEQ ID NO: 223 moltype = DNA length = 324
FEATURE Location/Qualifiers
misc_feature 1..324
note = nucleic acid
source 1..324
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 223
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattaga gatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatatt gcaaccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag catattagtt acccgtggac gttcggccaa 300
gggaccaagg tggaaatcaa acga 324

SEQ ID NO: 224 moltype = DNA length = 324
FEATURE Location/Qualifiers
misc_feature 1..324
note = nucleic acid
source 1..324
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 224
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca ggacatcaga gatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagcgcct gatctatgtt gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag catattagtt acccgtggac gttcggccaa 300
gggaccaagg tggaaatcaa acga 324

SEQ ID NO: 225 moltype = DNA length = 324
FEATURE Location/Qualifiers
misc_feature 1..324

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```
                     note = nucleic acid
source               1..324
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 225
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc  60
atcacttgcc gggcaagtca ggacattaga gatgatttag gctggtatca gcagaaacca  120
gggaaagccc ctaagcgcct gatctatgtt gtatccagtt tgcaaagtgg ggtcccatca  180
aggttcagcg gcagtggatc tgggacagag ttcactctca caatcagcag cctgcagcct  240
gaagattttg caacttatta ctgtctacag cataatggtt acccgtggac gttcggccaa  300
gggaccaagg tggaaatcaa acga                                        324

SEQ ID NO: 226       moltype = DNA  length = 324
FEATURE              Location/Qualifiers
misc_feature         1..324
                     note = nucleic acid
source               1..324
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 226
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc  60
atcacttgcc gggcaagtca gggcattgga gatgatttag gctggtatca gcagaagcca  120
ggaaaagccc ctcagcgcct gatctattct gcatccagtt tgccaagtgg ggtcccatca  180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct  240
gaagattttg caacttatta ctgtctacag cataatagtt accctcgcag ttttggccag  300
gggaccaagc tggagatcag acga                                        324

SEQ ID NO: 227       moltype = DNA  length = 324
FEATURE              Location/Qualifiers
misc_feature         1..324
                     note = nucleic acid
source               1..324
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 227
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc  60
atcacttgcc gggcaagtca ggacattgaa catgatttag gctggtatca gcagaaacca  120
gggaaagccc ctaagcgcct gatctatgct gcatccactt tgccaagtgg ggtcccatca  180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct  240
gaagattttg caacttatta ctgtctacag cataatagtt tccctcgcag ttttggccag  300
gggacccagc tggagatcaa acga                                        324

SEQ ID NO: 228       moltype = DNA  length = 342
FEATURE              Location/Qualifiers
misc_feature         1..342
                     note = nucleic acid
source               1..342
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 228
gatattgtga tgacccagac tccactctcc ctgcccgtca cccctggaga gccggcctcc  60
atctcctgca ggtctactca gagcctcttg gatggtgatg atggaaacac ccttttggac  120
tggtacctgc agaagccagg gcagtctcca cagctcctga tctatacgct ttcctatcgg  180
gcctctggag tcccagacag gttcagtggc agtgggtcag gcactgattt cacactgaaa  240
atcagcaggg tggaggctga ggatgttgga gtttattact gcatgcaacg tttagagttt  300
cctctcactt tcggcggagg gaccaaggtg gagatcaaac ga                     342

SEQ ID NO: 229       moltype = DNA  length = 342
FEATURE              Location/Qualifiers
misc_feature         1..342
                     note = nucleic acid
source               1..342
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 229
gacattgtga tgacccagac tccactctcc ttgcccgtca cccctggaga gccggcctcc  60
atctcctgca ggtctagtca gagcctcttg gatagtgatg aaggaaacac ctttttggat  120
tggtacctgc agaagccagg gcagcctcca cagctcctga tctatacgct ttcctatcgg  180
gcctctggag tcccagacag gttcagtggc agtgggtcag gcactgattt cacactgaaa  240
atcagcaggg tggaggctga ggatgttgga gtttattact gcatgcaacg tatagagttt  300
cctctcactt tcggcggagg gaccaaggtg gagatcaaac ga                     342

SEQ ID NO: 230       moltype = DNA  length = 324
FEATURE              Location/Qualifiers
misc_feature         1..324
                     note = nucleic acid
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source 1..324
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 230
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180
aggttcagtg gaagtggatc tgagacagat tttactttca ccatcagcag cctgcagcct 240
gaagatattg caacatatta ctgtcaacag tatgaaaatc tcccattcac tttcggccct 300
gggaccaaag tggatatcaa acga 324

SEQ ID NO: 231 moltype = DNA length = 327
FEATURE Location/Qualifiers
misc_feature 1..327
note = nucleic acid
source 1..327
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 231
tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacagac ggccaggatc 60
acctgctctg gagatgcatt gccaaggcaa tatgcttatt ggtaccagca gaagccaggc 120
caggccccta tgctggtgat atataaagac agtgagaggc cctcagggat ccctgagcga 180
ttctctggct ccagctcagg gacaacagtc acgttgacca tcagtggagt ccaggcagaa 240
gacgaggctg actattactg tcaatcagca gacagcagtg gtacttatgt ggtattcggc 300
ggagggacca agctgaccgt cctaggt 327

SEQ ID NO: 232 moltype = DNA length = 327
FEATURE Location/Qualifiers
misc_feature 1..327
note = nucleic acid
source 1..327
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 232
tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacaaac ggccaggatc 60
acctgctctg gagatgcatt gccaagaaaa tatgcttatt ggtaccagca gaagtcaggc 120
caggcccctg tgctggtcat ctatgaggac agcaaacgac cctccgggat ccctgagaga 180
ttctctggct ccagctcagg gacaatggcc accttgacta tcagtggggc ccaggtggag 240
gacgaagctg actactactg ttactcaaca gacagcagtg gtaatcatta tgtcttcgga 300
actgggacca aggtcaccgt cctaggt 327

SEQ ID NO: 233 moltype = DNA length = 324
FEATURE Location/Qualifiers
misc_feature 1..324
note = nucleic acid
source 1..324
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 233
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagttcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180
aggttcagtg gaagtggatc tgggacagat ttttttttca ccatcagcaa cctgcagcct 240
gaagatattg caacatattt ctgtcaacag gatgataatc tcccattcac tttcggccct 300
gggaccaaag tggatatcaa acga 324

SEQ ID NO: 234 moltype = DNA length = 324
FEATURE Location/Qualifiers
misc_feature 1..324
note = nucleic acid
source 1..324
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 234
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120
gggaaagccc ctaaactcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180
aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240
gaagatattg caacatttta ctgtcaacag tatgataatc tcccattcac tttcggccct 300
gggaccaaag tggatatcaa acga 324

SEQ ID NO: 235 moltype = DNA length = 327
FEATURE Location/Qualifiers
misc_feature 1..327
note = nucleic acid
source 1..327

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```
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 235
tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacaaac ggccaggatc  60
acctgctctg gagatgcatt gccaagaaaa tttgcttatt ggtaccagca gaagtcaggc  120
caggcccctg tgctggtcat ctatgaggac aggaaacgac cctccgggat ccctgagaga  180
ttctctggct ccagctcagg gacaatggcc accttgacta tcagtggggc ccaggtggag  240
gatgaagctg actactactg ttactcaaca gaccgcagtg gtgatcatgt ggtattcggc  300
ggagggacca agctgaccgt cctaggt                                      327

SEQ ID NO: 236        moltype = DNA  length = 324
FEATURE               Location/Qualifiers
misc_feature          1..324
                      note = nucleic acid
source                1..324
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 236
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc  60
atcacttgtc gggcgagtca gggtattagc aactggttag tctggtatca gcagaaacca  120
gggaaacccc ctaaactcct gatctatgct gcatccagtt tgcaaaatgg ggtcccatca  180
agattcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagact  240
gaagattttg caacttacta ttgtcaacag gctctcagtt tcccgtggac gttcggccca  300
gggaccaagg tggaagtcaa acga                                         324

SEQ ID NO: 237        moltype = AA  length = 121
FEATURE               Location/Qualifiers
REGION                1..121
                      note = synthetic polypeptide
source                1..121
                      mol_type = protein
                      organism = synthetic construct
SEQUENCE: 237
EVQLVQSGAE VKKPGESLKI SCKGSGYRFT SYWIGWVRQM PGKGLEWMGI IHPGDSDTRY  60
SPSFQGQVTI SADKSISTAY LQWSSLKASD TAIYYCTRQG RSFYYYGMDV WGQGTTVTVS  120
S                                                                  121

SEQ ID NO: 238        moltype = AA  length = 118
FEATURE               Location/Qualifiers
REGION                1..118
                      note = synthetic polypeptide
source                1..118
                      mol_type = protein
                      organism = synthetic construct
SEQUENCE: 238
EVQLVQSGAE VKKPGESLKI SCKGSGYRFT SYWIGWVRQM PGKGLEWMGI IYPGDSDTRY  60
SPSFQGQVTI SADKSISAAY LQWSSLKASD TAMYYCARQQ VAGMLDYWGQ GTLVTVSS    118

SEQ ID NO: 239        moltype = AA  length = 120
FEATURE               Location/Qualifiers
REGION                1..120
                      note = synthetic polypeptide
source                1..120
                      mol_type = protein
                      organism = synthetic construct
SEQUENCE: 239
QVQLVESGGG VVQPGRSLRL SCAASGFTFS IYGMHWVRQA PGKGLEWVTV IWYDGSNEYY  60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARED FDSHYGMDVW GQGTTVTVSS  120

SEQ ID NO: 240        moltype = AA  length = 122
FEATURE               Location/Qualifiers
REGION                1..122
                      note = synthetic polypeptide
source                1..122
                      mol_type = protein
                      organism = synthetic construct
SEQUENCE: 240
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYDGSNEYY  60
ADSVKGRFTI SRDNSKNTLY LQMHSLRAED TAVYYCAREE WFGEADYGMD VWGQGTTVTV  120
SS                                                                 122

SEQ ID NO: 241        moltype = AA  length = 122
FEATURE               Location/Qualifiers
REGION                1..122
                      note = synthetic polypeptide
source                1..122
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```
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 241
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYDGSNEYY  60
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCARDD WFGEADYGMD VWGQGTTVTV  120
SS                                                                 122

SEQ ID NO: 242       moltype = AA  length = 122
FEATURE              Location/Qualifiers
REGION               1..122
                     note = synthetic polypeptide
source               1..122
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 242
QVQLVESGGG VVQPGRSLRL SCAASGFTFS NYGMHWVRQA PGKGLEWVTV IWNDGSNEYY  60
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCARED WLGEADYGMD VWGQGTTVTV  120
SS                                                                 122

SEQ ID NO: 243       moltype = AA  length = 121
FEATURE              Location/Qualifiers
REGION               1..121
                     note = synthetic polypeptide
source               1..121
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 243
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYDGSNKYY  60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAREE WELEDYGMDV WGQGTTVTVS  120
S                                                                  121

SEQ ID NO: 244       moltype = AA  length = 126
FEATURE              Location/Qualifiers
REGION               1..126
                     note = synthetic polypeptide
source               1..126
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 244
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMYWVRQA PGKGLEWVAV IWYDGSNKYY  60
VDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGA VAGTGRDYYY YGMDVWGQGT  120
TVTVSS                                                             126

SEQ ID NO: 245       moltype = AA  length = 126
FEATURE              Location/Qualifiers
REGION               1..126
                     note = synthetic polypeptide
source               1..126
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 245
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMYWVRQA PGKGLEWVAV IWYDGSNKYH  60
GDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKGA VAGTGRDYYY YGMDVWGQGT  120
TVTVSS                                                             126

SEQ ID NO: 246       moltype = AA  length = 126
FEATURE              Location/Qualifiers
REGION               1..126
                     note = synthetic polypeptide
source               1..126
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 246
QVQLVESGGG VVQPGRSQRL SCAASGFTFS SYGMYWVRQA PGKGLEWVAV IWYDGSNKNY  60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYHCAKGT VAGTGRDYYY YGMDVWGQGT  120
TVTVSS                                                             126

SEQ ID NO: 247       moltype = AA  length = 120
FEATURE              Location/Qualifiers
REGION               1..120
                     note = synthetic polypeptide
source               1..120
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 247
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SFGMHWVRQA PGKGLEWVAV IWFDGSNKYY  60
```

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VDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDD FWSDYPFDYW GQGTLVTVSS 120

SEQ ID NO: 248 moltype = AA length = 120
FEATURE Location/Qualifiers
REGION 1..120
note = synthetic polypeptide
source 1..120
mol_type = protein
organism = synthetic construct
SEQUENCE: 248
QVQLVESGGG VVQPGRSLRL SCAASGFTFR SYGMHWVRQA PGKGLEWVAV ISDDGSNKYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRPED TAVYYCARDL YSSAWPFDYW GQGTLVTVSS 120

SEQ ID NO: 249 moltype = AA length = 119
FEATURE Location/Qualifiers
REGION 1..119
note = synthetic polypeptide
source 1..119
mol_type = protein
organism = synthetic construct
SEQUENCE: 249
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYDIHWVRQA PGKGLEWVAV IWNDGSIKYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDG EQWRGFDYWG QGTLVTVSS 119

SEQ ID NO: 250 moltype = AA length = 119
FEATURE Location/Qualifiers
REGION 1..119
note = synthetic polypeptide
source 1..119
mol_type = protein
organism = synthetic construct
SEQUENCE: 250
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYDIHWVRQA PGKGLEWVAV IWYDGSIKYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDQ EQWLAFDYWG QGTLVTVSS 119

SEQ ID NO: 251 moltype = AA length = 119
FEATURE Location/Qualifiers
REGION 1..119
note = synthetic polypeptide
source 1..119
mol_type = protein
organism = synthetic construct
SEQUENCE: 251
QVQLVESGGG VVQPGRSLRL SCAASGFTFS TYGMHWVRQA PDMGLEWVAV IWYDGSNKYY 60
ADSVKGRFTI SRDISKNTLY LEMNSLRAED TAVYYCARDN WGSDAFDIWG QGTMVTVSS 119

SEQ ID NO: 252 moltype = AA length = 126
FEATURE Location/Qualifiers
REGION 1..126
note = synthetic polypeptide
source 1..126
mol_type = protein
organism = synthetic construct
SEQUENCE: 252
QVQLVESGGG VVQPGRSLRL SCAASGFTFS TYAMHWVRQA PGKGLEWVAV IWYDGINKYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGS YYDSSGYYYG EDFDYWGQGT 120
LVTVSS 126

SEQ ID NO: 253 moltype = AA length = 126
FEATURE Location/Qualifiers
REGION 1..126
note = synthetic polypeptide
source 1..126
mol_type = protein
organism = synthetic construct
SEQUENCE: 253
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYAMHWVRQA PGKGLEWVAV IWYDGINKYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGS YYDSSGYYFG EDFDYWGQGT 120
LVTVSS 126

SEQ ID NO: 254 moltype = AA length = 118
FEATURE Location/Qualifiers
REGION 1..118
note = synthetic polypeptide
source 1..118
mol_type = protein

-continued

organism = synthetic construct
SEQUENCE: 254
QVQLVESGGG LVKPGGSLRL SCAASGFTFS DYYMSWIRQA PGKGLEWVSY ISSSGSIIFY 60
ADSVKGRFTM SRDNAKNSLY LQMNSLRAED TAVYYCVRRI SITPFDYWGQ GTLVTVSS 118

SEQ ID NO: 255 moltype = AA length = 126
FEATURE Location/Qualifiers
REGION 1..126
note = synthetic polypeptide
source 1..126
mol_type = protein
organism = synthetic construct
SEQUENCE: 255
QVTLKESGPV LVKPTETLTL TCTVSGFSLS NARMGVSWIR QPPGKALEWL AHIFSNDEKS 60
YSTSLKSRLT ISKDTSKSQV VLTMTNMDPV DTATYYCVRI PRWLQPPYYY YGMDVWGQGT 120
TVTVSS 126

SEQ ID NO: 256 moltype = AA length = 119
FEATURE Location/Qualifiers
REGION 1..119
note = synthetic polypeptide
source 1..119
mol_type = protein
organism = synthetic construct
SEQUENCE: 256
QVQLQESGPG LVKPSQTLSL TCTVSGGSIS SGGYYWNWIR QHPGKGLEWI GYIYYSGNTH 60
YNPSLKSRVT ISVDTSKNQF SLKLSSVIAA DTAVYYCARD WGRDAFDIWG QGTMVTVSS 119

SEQ ID NO: 257 moltype = AA length = 124
FEATURE Location/Qualifiers
REGION 1..124
note = synthetic polypeptide
source 1..124
mol_type = protein
organism = synthetic construct
SEQUENCE: 257
QVQLQESGPG LVKPSQTLSL TCTVSGGSIS SGGYYWSWIR QHPGKGLEWI GYIYYSGSTD 60
YNPSLKSRGI ISGDTSKNQF SLKLNSVTAA DTAVYYCARE GRFGELGSYY FDYWGQGTLV 120
TVSS 124

SEQ ID NO: 258 moltype = AA length = 121
FEATURE Location/Qualifiers
REGION 1..121
note = synthetic polypeptide
source 1..121
mol_type = protein
organism = synthetic construct
SEQUENCE: 258
QVQLQESGPG LVKPSETLSL TCTVSGGSVS SGGYYWSWIR QPPGKGLEWI GNTYYSGSTN 60
YKPSLKSRVT ISVDTSKNQF SLKLSSVTAA DTAVYYCGRD RGRAVGPFDY WGQGTLVTVS 120
S 121

SEQ ID NO: 259 moltype = AA length = 118
FEATURE Location/Qualifiers
REGION 1..118
note = synthetic polypeptide
source 1..118
mol_type = protein
organism = synthetic construct
SEQUENCE: 259
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYDINWVRQA TGQGLEWMGW MNPNSGNTGY 60
AQKFQGRVTM TRNTSISTAY MELSSLRSED TAVYYCARSR QWLVLDYWGQ GTLVTVSS 118

SEQ ID NO: 260 moltype = AA length = 118
FEATURE Location/Qualifiers
REGION 1..118
note = synthetic polypeptide
source 1..118
mol_type = protein
organism = synthetic construct
SEQUENCE: 260
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYDINWVRQA TGQGLEWMGW MNPNSGNTGY 60
VQKFQGRVTM TRNTSISTAY MELSSLRSED TAVYYCARSR QWLVLDYWGQ GTLVTVSS 118

SEQ ID NO: 261 moltype = AA length = 118
FEATURE Location/Qualifiers

-continued

REGION 1..118
note = synthetic polypeptide
source 1..118
mol_type = protein
organism = synthetic construct
SEQUENCE: 261
QVQLVQSGAE VKKPGASVKV SCKASGYRFT SYDINWVRQA TGQGLEWMGW MNPNSGNTGY 60
AQKFQGRVTM TRNTSISTAY MELSSLRSED TAVYYCARSR QWLVLDYWGQ GTLVTVSS 118

SEQ ID NO: 262 moltype = AA length = 118
FEATURE Location/Qualifiers
REGION 1..118
note = synthetic polypeptide
source 1..118
mol_type = protein
organism = synthetic construct
SEQUENCE: 262
QVQLVQSGAE VKKPGASVKV SCKASGYTFT TYDINWVRQA TGQGLEWMGW MNPNSGNTGY 60
AQKFQGRVTM TRNTSISTAY MELSSLRSED TAVYYCARGR QWLGFDYWGQ GTLVTVSS 118

SEQ ID NO: 263 moltype = AA length = 118
FEATURE Location/Qualifiers
REGION 1..118
note = synthetic polypeptide
source 1..118
mol_type = protein
organism = synthetic construct
SEQUENCE: 263
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYDINWVRQA TGQGLEWMGW MNPNSGNTGY 60
AQKFQGRVTM TRNTSINTAY MELSSLRSED TAVYYCARGR QWLGFDYWGQ GTLVTVSS 118

SEQ ID NO: 264 moltype = AA length = 121
FEATURE Location/Qualifiers
REGION 1..121
note = synthetic polypeptide
source 1..121
mol_type = protein
organism = synthetic construct
SEQUENCE: 264
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT SQWIGWVRQM PGKGLEWMGI IFPGDSDTRY 60
SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARQG RSYHYYGMDV WGQGTTVTVS 120
S 121

SEQ ID NO: 265 moltype = AA length = 121
FEATURE Location/Qualifiers
REGION 1..121
note = synthetic polypeptide
source 1..121
mol_type = protein
organism = synthetic construct
SEQUENCE: 265
EVQLVQSGAE VKKPGESLKI SCKGSGYGFT NYWIGWVRQM PGKGLEWMGT IYPGDSDTRY 60
SPSFQGQVTF SADKSISTAY LQWSSLKASD TAMYYCARQG RSYYYFGMDV WGQGTTVTVS 120
S 121

SEQ ID NO: 266 moltype = AA length = 122
FEATURE Location/Qualifiers
REGION 1..122
note = synthetic polypeptide
source 1..122
mol_type = protein
organism = synthetic construct
SEQUENCE: 266
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT DYWIGWVRQM PGKGLEWMGI IYPYDSDTRY 60
SPSFQGQVTL SADKSISTAY LRWSSLKASD TAMYYCARHR GGRSYYYGMD VWGQGTTVTV 120
SS 122

SEQ ID NO: 267 moltype = AA length = 122
FEATURE Location/Qualifiers
REGION 1..122
note = synthetic polypeptide
source 1..122
mol_type = protein
organism = synthetic construct
SEQUENCE: 267
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT SYWIGWVRQM PGKGLEWMGI IYPGDSDTTY 60

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SPSFQGQVTI SADKSINTAY LQWSSLKASD TAMYYCAREG FGESIHYGLD VWGQGTTVTV 120
SS 122

SEQ ID NO: 268 moltype = AA length = 121
FEATURE Location/Qualifiers
REGION 1..121
note = synthetic polypeptide
source 1..121
mol_type = protein
organism = synthetic construct
SEQUENCE: 268
EVQLVQSGAE VKKPGESLKI SCKGSGYNFT NYWIGWVRQM SGKGLEWMGI IYPGDSETRY 60
SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARHG GGWSGWGMDV WGQGTTVTVS 120
S 121

SEQ ID NO: 269 moltype = AA length = 124
FEATURE Location/Qualifiers
REGION 1..124
note = synthetic polypeptide
source 1..124
mol_type = protein
organism = synthetic construct
SEQUENCE: 269
EVQLVQSGAE VKKPGESLKI SCKGSGYRFT NYWIGWVRQM PGKGLEWMGI IYPGDSDTKY 60
SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARHG GYSGRSYYYG MDVWGQGTAV 120
TVSS 124

SEQ ID NO: 270 moltype = AA length = 126
FEATURE Location/Qualifiers
REGION 1..126
note = synthetic polypeptide
source 1..126
mol_type = protein
organism = synthetic construct
SEQUENCE: 270
EVQLVQSGAE VKKPGESLKI SCKGSGYRFT SYWIGWVRQM PGKGLEWMGI IFPGDSDTRY 60
SPSFQGQVTI SADKSITTAY LQWSSLKASD TAIYYCARHG HGSSSGRTYY YGLDVWGQGT 120
TVTVSS 126

SEQ ID NO: 271 moltype = AA length = 116
FEATURE Location/Qualifiers
REGION 1..116
note = synthetic polypeptide
source 1..116
mol_type = protein
organism = synthetic construct
SEQUENCE: 271
EVQLVQSGAE VKKPGESLKI SCKGSGYNFT TYWIGWVRQM PGKGLEWMGI IYPGDSDTRY 60
SPSFQGQVTI SADKSINTAY LQWSSLKASD TAIYYCARDT GYFDYWGQGT LVTVSS 116

SEQ ID NO: 272 moltype = AA length = 122
FEATURE Location/Qualifiers
REGION 1..122
note = synthetic polypeptide
source 1..122
mol_type = protein
organism = synthetic construct
SEQUENCE: 272
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV IWYDGSNKFY 60
VDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARPG SDYYFYYGMD VWGQGTTVTV 120
SS 122

SEQ ID NO: 273 moltype = DNA length = 363
FEATURE Location/Qualifiers
misc_feature 1..363
note = nucleic acid
source 1..363
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 273
gaggtgcagt tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata caggtttacc agctactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atccatcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac actgccatat attactgtac gagacagggt 300
agaagcttct actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360

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tca 363

SEQ ID NO: 274 moltype = DNA length = 354
FEATURE Location/Qualifiers
misc_feature 1..354
note = nucleic acid
source 1..354
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 274
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata caggtttacc agctactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag cgccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagacaacaa 300
gtggctggta tgttggacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

SEQ ID NO: 275 moltype = DNA length = 360
FEATURE Location/Qualifiers
misc_feature 1..360
note = nucleic acid
source 1..360
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 275
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt atttatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtgacagtt atatggtatg atggaagtaa tgaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagaggac 300
ttcgactccc actacggtat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360

SEQ ID NO: 276 moltype = DNA length = 366
FEATURE Location/Qualifiers
misc_feature 1..366
note = nucleic acid
source 1..366
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 276
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa tgaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctacaaatgc acagcctgag agccgaggac acggctgtgt attattgtgc gagagaagaa 300
tggttcgggg aggcggacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

SEQ ID NO: 277 moltype = DNA length = 366
FEATURE Location/Qualifiers
misc_feature 1..366
note = nucleic acid
source 1..366
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 277
caggtgcagc tggtggagtc tgggggaggc gtggtccagc cagggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa tgaatattat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatgat 300
tggttcgggg aggcggacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

SEQ ID NO: 278 moltype = DNA length = 366
FEATURE Location/Qualifiers
misc_feature 1..366
note = nucleic acid
source 1..366
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 278
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtgacagtt atatggaatg atggaagtaa tgaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240

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ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagaagat 300
tggctcgggg aggcggacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

SEQ ID NO: 279 moltype = DNA length = 363
FEATURE Location/Qualifiers
misc_feature 1..363
note = nucleic acid
source 1..363
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 279
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagaagag 300
tgggagctag aggactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360
tca 363

SEQ ID NO: 280 moltype = DNA length = 378
FEATURE Location/Qualifiers
misc_feature 1..378
note = nucleic acid
source 1..378
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 280
caggtgcagt tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agttatggca tgtactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaggagca 300
gtggctggta cgggacggga ctactactac tacggtatgg acgtctgggg ccaagggacc 360
acggtcaccg tctcctca 378

SEQ ID NO: 281 moltype = DNA length = 378
FEATURE Location/Qualifiers
misc_feature 1..378
note = nucleic acid
source 1..378
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 281
caggtgcagt tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt cacgttcagt agttatggca tgtactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaataccat 180
ggagactccg tgaagggccg attcaccatc tccagagaca attccaagaa tacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gaaaggagca 300
gtggctggta cgggacggga ctactactac tacggtatgg acgtctgggg ccaagggacc 360
acggtcaccg tctcctca 378

SEQ ID NO: 282 moltype = DNA length = 378
FEATURE Location/Qualifiers
misc_feature 1..378
note = nucleic acid
source 1..378
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 282
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc ccagagactc 60
tcctgtgcag cgtctggatt caccttttagt agttatggca tgtactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaaaactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa tacgttgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt atcactgtgc gaaaggaaca 300
gtggctggta cgggacggga ctactactac tacggtatgg acgtctgggg ccaagggacc 360
acggtcaccg tctcttca 378

SEQ ID NO: 283 moltype = DNA length = 360
FEATURE Location/Qualifiers
misc_feature 1..360
note = nucleic acid
source 1..360
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 283

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caggtgcaac tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctttggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atttggtttg atggaagtaa taaatactat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa tacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gcgggacgat 300
ttttggagtg attatccttt tgactactgg ggccagggaa ccctggtcac cgtctcctca 360

SEQ ID NO: 284 moltype = DNA length = 360
FEATURE Location/Qualifiers
misc_feature 1..360
note = nucleic acid
source 1..360
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 284
caggtgcaac tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagg agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatcagatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag acctgaggac acggctgtgt attactgtgc gagagatctc 300
tatagcagtg cctggccctt tgactactgg ggccagggaa ccctggtcac cgtctcctca 360

SEQ ID NO: 285 moltype = DNA length = 357
FEATURE Location/Qualifiers
misc_feature 1..357
note = nucleic acid
source 1..357
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 285
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatgaca tacactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggaatg atggaagtat taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagacggg 300
gagcagtggc ggggctttga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

SEQ ID NO: 286 moltype = DNA length = 357
FEATURE Location/Qualifiers
misc_feature 1..357
note = nucleic acid
source 1..357
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 286
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatgaca tacactgggt ccgtcaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtat taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatcag 300
gagcagtggc tggcctttga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

SEQ ID NO: 287 moltype = DNA length = 357
FEATURE Location/Qualifiers
misc_feature 1..357
note = nucleic acid
source 1..357
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 287
caggtgcagt tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt acctatggca tgcactgggt ccgccaggct 120
ccagacatgg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
gcagactctg tgaagggccg attcaccatc tccagagaca tttccaagaa cacgctgtat 240
ctggaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagacaac 300
tggggatccg atgcttttga tatctggggc caagggacaa tggtcaccgt ctcttca 357

SEQ ID NO: 288 moltype = DNA length = 378
FEATURE Location/Qualifiers
misc_feature 1..378
note = nucleic acid
source 1..378
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 288
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

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tcctgtgcag cgtctggatt caccttcagt acctatgcca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaattaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagggagt 300
tactatgata gtagtggtta ttactacggg gaggactttg actactgggg ccagggaacc 360
ctggtcaccg tctcctca 378

SEQ ID NO: 289 moltype = DNA length = 378
FEATURE Location/Qualifiers
misc_feature 1..378
note = nucleic acid
source 1..378
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 289
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatgcca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atctggtatg atggaattaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagggagt 300
tactatgata gtagtggtta ttacttcggg gaggactttg actactgggg ccagggaacc 360
ctggtcaccg tctcctca 378

SEQ ID NO: 290 moltype = DNA length = 354
FEATURE Location/Qualifiers
misc_feature 1..354
note = nucleic acid
source 1..354
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 290
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attagtagta gtggtagtat catttttac 180
gcagactctg tgaagggccg attcaccatg tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attattgtgt gagaaggatt 300
agtataaccc cttttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

SEQ ID NO: 291 moltype = DNA length = 378
FEATURE Location/Qualifiers
misc_feature 1..378
note = nucleic acid
source 1..378
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 291
caggtcacct tgaaggagtc tggtcctgtg ctggtgaaac ccacagagac cctcacgctg 60
acctgcaccg tctctgggtt ctcactcagc aatgctagaa tgggtgtgag ctggatccgt 120
cagcccccag ggaaggccct ggagtggctt gcacacattt tttcgaatga cgaaaaatcc 180
tacagcacat ctctgaagag caggctcacc atctccaagg acacctccaa aagccaggtg 240
gtccttacca tgaccaacat ggaccctgtg gacacagcca catattactg tgtacggata 300
ccgagatggc tacaaccccc ctactactac tacggtatgg acgtctgggg ccaagggacc 360
acggtcaccg tctcctca 378

SEQ ID NO: 292 moltype = DNA length = 357
FEATURE Location/Qualifiers
misc_feature 1..357
note = nucleic acid
source 1..357
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 292
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggaa ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gaacacccac 180
tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc 240
tccctgaagc tgagctctgt gattgccgcg gacacggccg tgtattactg tgcgagagac 300
tggggacgtg atgcttttga tatctggggc caagggacaa tggtcaccgt ctcttca 357

SEQ ID NO: 293 moltype = DNA length = 372
FEATURE Location/Qualifiers
misc_feature 1..372
note = nucleic acid
source 1..372
mol_type = other DNA
organism = synthetic construct

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SEQUENCE: 293
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcactg tctcgggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt gggtacatct attatagtgg gagcaccgac 180
tacaacccgt ccctcaagag tcgaggtatc atatcaggag acacgtctaa gaaccagttc 240
tccctgaagc tgaactctgt gactgccgcg gacacggccg tgtattactg tgcgagagag 300
gggaggttcg gggagttagg ctcctactac tttgactact ggggccaggg aaccctggtc 360
accgtctcct ca 372

SEQ ID NO: 294 moltype = DNA length = 363
FEATURE Location/Qualifiers
misc_feature 1..363
note = nucleic acid
source 1..363
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 294
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccgtcagc agtggtggtt actactggag ctggatccgg 120
cagccccag ggaagggact ggagtggatt gggaatacct attacagtgg gagcaccaac 180
tacaaaccct ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagttc 240
tccctgaagc tgagttctgt gaccgctgcg gacacggccg tgtattactg tgggagagac 300
cggggtagag cagtgggtcc ctttgactac tggggccagg gaaccctggt caccgtctcc 360
tca 363

SEQ ID NO: 295 moltype = DNA length = 354
FEATURE Location/Qualifiers
misc_feature 1..354
note = nucleic acid
source 1..354
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 295
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc aattatgata tcaactgggt gcgacaggcc 120
actggacaag ggcttgagtg gatgggatgg atgaacccta acagtggtaa cacaggctat 180
gcacagaagt tccagggcag agtcaccatg accaggaaca cctccataag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaagtagg 300
cagtggctgg tacttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

SEQ ID NO: 296 moltype = DNA length = 354
FEATURE Location/Qualifiers
misc_feature 1..354
note = nucleic acid
source 1..354
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 296
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc aattatgata tcaactgggt gcgacaggcc 120
actggacaag ggcttgagtg gatgggatgg atgaacccta acagtggtaa cacaggctat 180
gtacagaagt tccagggcag agtcaccatg accaggaaca cctccataag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaagtagg 300
cagtggctgg tacttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

SEQ ID NO: 297 moltype = DNA length = 354
FEATURE Location/Qualifiers
misc_feature 1..354
note = nucleic acid
source 1..354
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 297
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caggttcacc agttatgata tcaactgggt gcgacaggcc 120
actggacaag ggcttgagtg gatgggatgg atgaacccaa acagtggtaa cacaggctat 180
gcacagaagt tccagggcag agtcaccatg accaggaaca cctccataag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaagtagg 300
cagtggctgg tacttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

SEQ ID NO: 298 moltype = DNA length = 354
FEATURE Location/Qualifiers
misc_feature 1..354
note = nucleic acid
source 1..354
mol_type = other DNA

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organism = synthetic construct

SEQUENCE: 298

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc acttatgata tcaactgggt gcgacaggcc 120
actggacaag ggcttgagtg gatgggatgg atgaacccta acagtggtaa cacaggctat 180
gcacagaagt tccagggcag agtcaccatg accaggaaca cctccataag cacagcctac 240
atggagctga gcagcctaag atctgaggac acggccgtgt attactgtgc gagaggccgg 300
cagtggctgg gctttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

SEQ ID NO: 299 moltype = DNA length = 354
FEATURE Location/Qualifiers
misc_feature 1..354
note = nucleic acid
source 1..354
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 299

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc aattatgata tcaactgggt gcgacaggcc 120
actggacaag ggcttgagtg gatgggatgg atgaacccta atagtggtaa cacaggctat 180
gcacagaagt tccagggcag agtcaccatg accaggaaca cctccataaa cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggccgg 300
cagtggctgg gctttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

SEQ ID NO: 300 moltype = DNA length = 363
FEATURE Location/Qualifiers
misc_feature 1..363
note = nucleic acid
source 1..363
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 300

gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata cagctttacc agccagtgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctttcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gcgacagggt 300
agaagttacc actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360
tca 363

SEQ ID NO: 301 moltype = DNA length = 363
FEATURE Location/Qualifiers
misc_feature 1..363
note = nucleic acid
source 1..363
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 301

gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata cggctttacc aactactgga tcggctgggt gcgccagatg 120
cccggaaaag gcctggagtg gatggggacc atctatcctg gtgactctga taccagatac 180
agtccgtcct tccaaggcca ggtcaccttc tcagccgaca agtccatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagacagggt 300
agaagttact actacttcgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360
tca 363

SEQ ID NO: 302 moltype = DNA length = 366
FEATURE Location/Qualifiers
misc_feature 1..366
note = nucleic acid
source 1..366
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 302

gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata cagctttacc gactactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggaatg gatggggatc atctatcctt atgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccctc tcagccgaca agtccatcag caccgcctac 240
ctgcggtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagacatcgg 300
ggggggaggt cctactacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

SEQ ID NO: 303 moltype = DNA length = 366
FEATURE Location/Qualifiers
misc_feature 1..366
note = nucleic acid

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source 1..366
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 303
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata cagctttacc agctactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctagaatg gatggggatc atctatcctg gtgactctga taccacatac 180
agcccgtcct tccaaggcca agtcaccatc tcagccgaca agtccatcaa caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagagagggt 300
ttcggggagt ctattcacta cggtttggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

SEQ ID NO: 304 moltype = DNA length = 363
FEATURE Location/Qualifiers
misc_feature 1..363
note = nucleic acid
source 1..363
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 304
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata caattttacc aactactgga tcggctgggt gcgccagatg 120
tccgggaaag gcctggagtg gatgggaatc atctatcctg gtgactctga aaccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagacatgga 300
gggggatgga gtggttgggg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360
tca 363

SEQ ID NO: 305 moltype = DNA length = 372
FEATURE Location/Qualifiers
misc_feature 1..372
note = nucleic acid
source 1..372
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 305
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata caggtttacc aactactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccaaatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag taccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagacatggt 300
ggatatagtg gccgttccta ctactacggt atggacgtct ggggccaggg gaccgcggtc 360
accgtctcct ca 372

SEQ ID NO: 306 moltype = DNA length = 378
FEATURE Location/Qualifiers
misc_feature 1..378
note = nucleic acid
source 1..378
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 306
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata caggtttacc agctactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctttcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcac caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatct attactgtgc gcgacatggg 300
catggcagct cgtccgggcg gacctactac tacggtttgg acgtctgggg ccaagggacc 360
acggtcaccg tctcctca 378

SEQ ID NO: 307 moltype = DNA length = 348
FEATURE Location/Qualifiers
misc_feature 1..348
note = nucleic acid
source 1..348
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 307
gaggtgcagc tggtgcaatc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata caactttacc acctactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatt tcagccgaca agtccatcaa caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac acagccattt attactgtgc gagagacaca 300
ggatactttg actactgggg ccagggcacc ctggtcaccg tctcctca 348

SEQ ID NO: 308 moltype = DNA length = 366

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FEATURE	Location/Qualifiers
misc_feature	1..366
	note = nucleic acid
source	1..366
	mol_type = other DNA
	organism = synthetic construct

SEQUENCE: 308

caggtgcagt tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg gcctggagtg ggtggcagtt atctggtatg atggaagtaa taaattctat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagacccggg 300
tccgattact acttctacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360
tcctca 366

1. A human interleukin-2 (IL-2) mutein comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:1, wherein the IL-2 mutein has at least one mutation selected from D20A D20E D20F, D20G, D20T, and D20W; and wherein the IL-2 mutein preferentially stimulates T regulatory cells relative to other T cells or NK cells.

2. (canceled)

3. (canceled)

4. The human IL-2 mutein of claim **1**, wherein the IL-2 mutein further comprises the mutation C125A.

5. (canceled)

6. An Fc-fusion protein comprising an Fc and the human IL-2 mutein of claim **1**.

7. The Fc-fusion protein of claim **6**, wherein the Fc is a human IgG1 Fc.

8. The Fc-fusion protein of claim **7**, wherein the human IgG1 Fc comprises one or more mutations altering effector function of said Fc.

9. The Fc-fusion protein of claim **8**, wherein the human IgG1 Fc comprises a substitution at N297, as numbered according to the EU numbering scheme.

10. The Fc-fusion protein of claim **9**, wherein the substitution at N297 is N297G.

11. The Fc-fusion protein of claim **7**, comprising a substitution or deletion of the C-terminal lysine of said human IgG Fc.

12. (canceled)

13. The Fc-fusion protein of claim **6**, wherein a linker connects the Fc and human IL-2 mutein portions of said protein.

14. The Fc-fusion protein of claim **13**, wherein the linker is GGGGS (SEQ ID NO: 5), GGNGT (SEQ ID NO: 6), or YGNGT (SEQ ID NO: 7).

15. The Fc-fusion protein of claim **14**, wherein the linker is GGGGS (SEQ ID NO: 5).

16. The Fc-fusion protein of claim **6**, wherein the IL-2 mutein further comprises an amino acid addition, substitution, or deletion altering glycosylation of said Fc-fusion protein when expressed in mammalian cells.

17. The Fc-fusion protein of claim **6**, wherein the IL-2 mutein further comprises a substitution at T3.

18. The Fc-fusion protein of claim **17**, wherein the IL-2 mutein comprises a T3N or T3A substitution.

19. The Fc-fusion protein of claim **18**, wherein the IL-2 mutein comprises a T3N substitution.

20. The Fc-fusion protein of claim **6**, wherein the IL-2 mutein further comprises a substitution at S5.

21. The Fc-fusion protein of claim **20**, wherein the IL-2 mutein comprises a S5T substitution.

22. The Fc-fusion protein of claim **6**, wherein said Fc-fusion protein comprises an Fc dimer.

23. The Fc-fusion protein of claim **22**, wherein the Fc-fusion protein comprises two IL-2 muteins.

24. The Fc-fusion protein of claim **22**, wherein the Fc-fusion protein comprises a single IL-2 mutein.

25-131. (canceled)

* * * * *