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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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(22) Filed: **Oct. 7, 2020**

**Related U.S. Application Data**

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**Publication Classification**

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**A61P 37/00** (2006.01)  
**A61K 38/20** (2006.01)  
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(52) **U.S. Cl.**  
CPC ..... **C07K 14/55** (2013.01); **A61P 37/00** (2018.01); **A61K 38/2013** (2013.01); **C07K 16/246** (2013.01); **C07K 2317/21** (2013.01); **C07K 2319/30** (2013.01); **C07K 2317/524** (2013.01); **C07K 2317/76** (2013.01); **C07K 2317/92** (2013.01); **C07K 2317/94** (2013.01); **C07K 2317/41** (2013.01)

(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.**

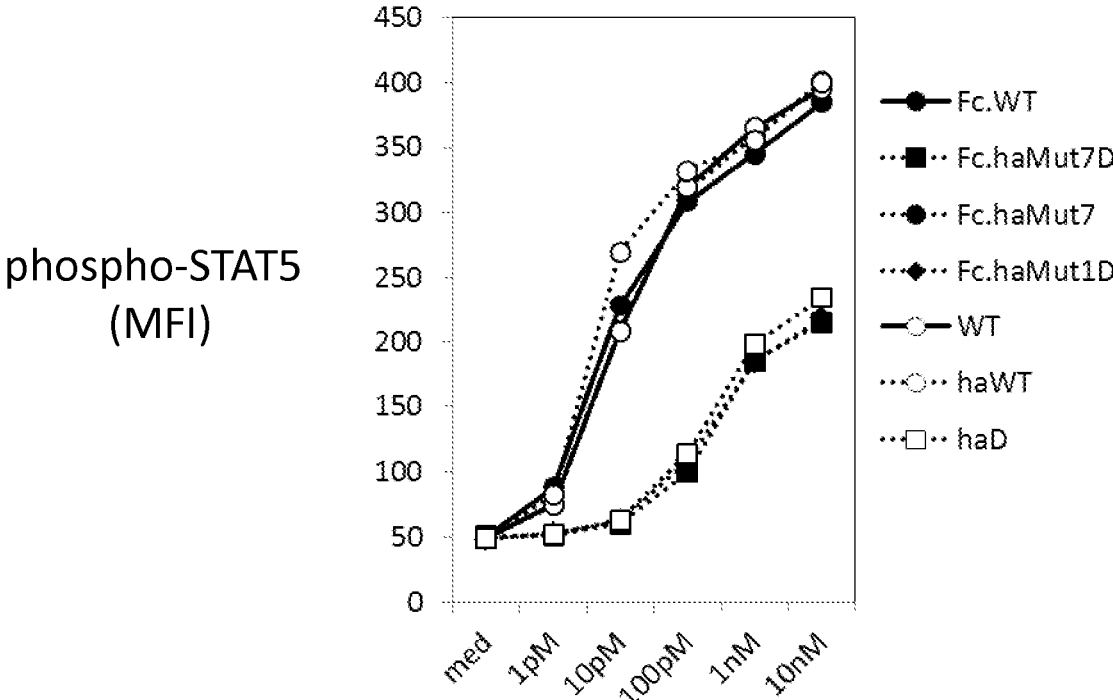


FIG. 1

FIG. 2A

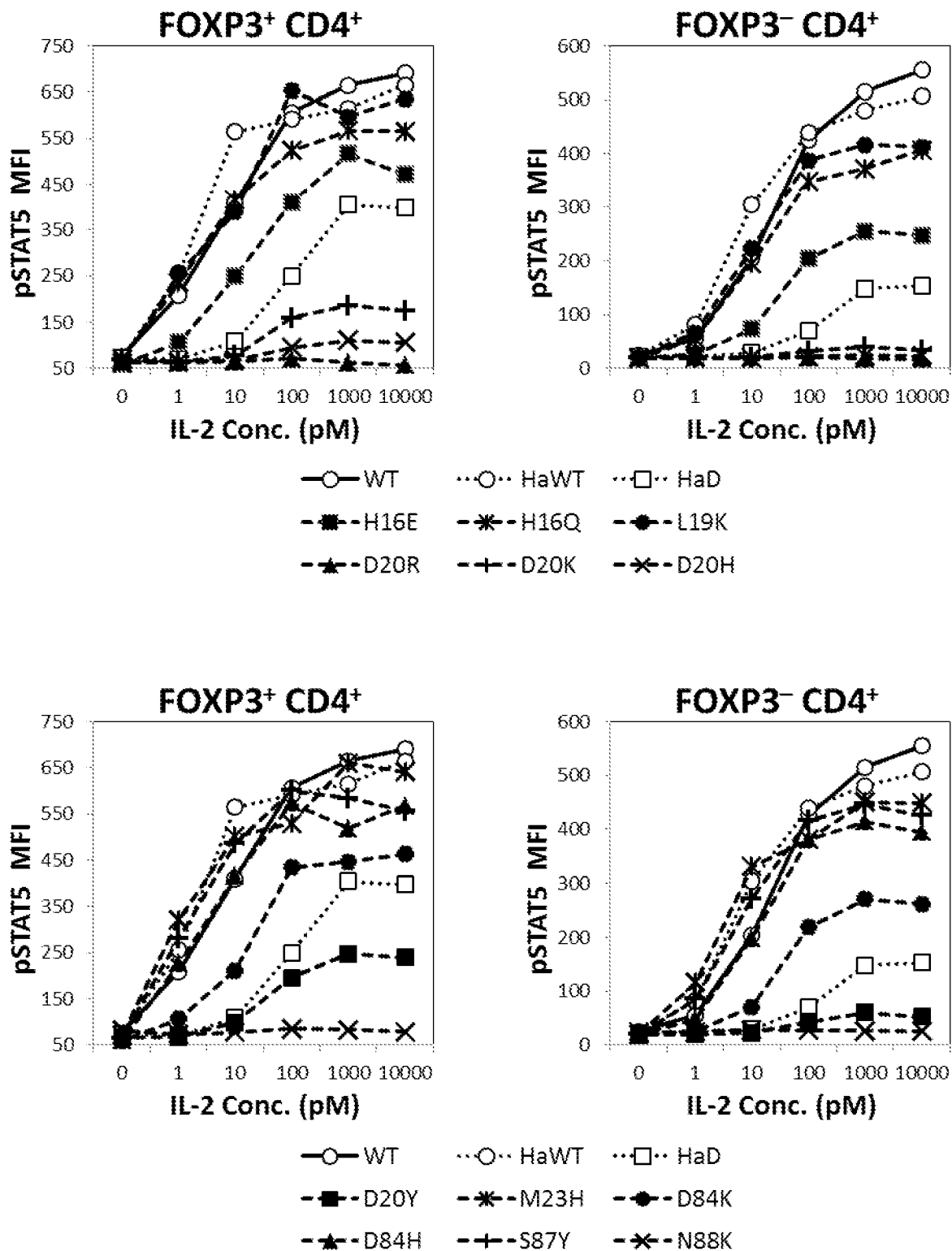
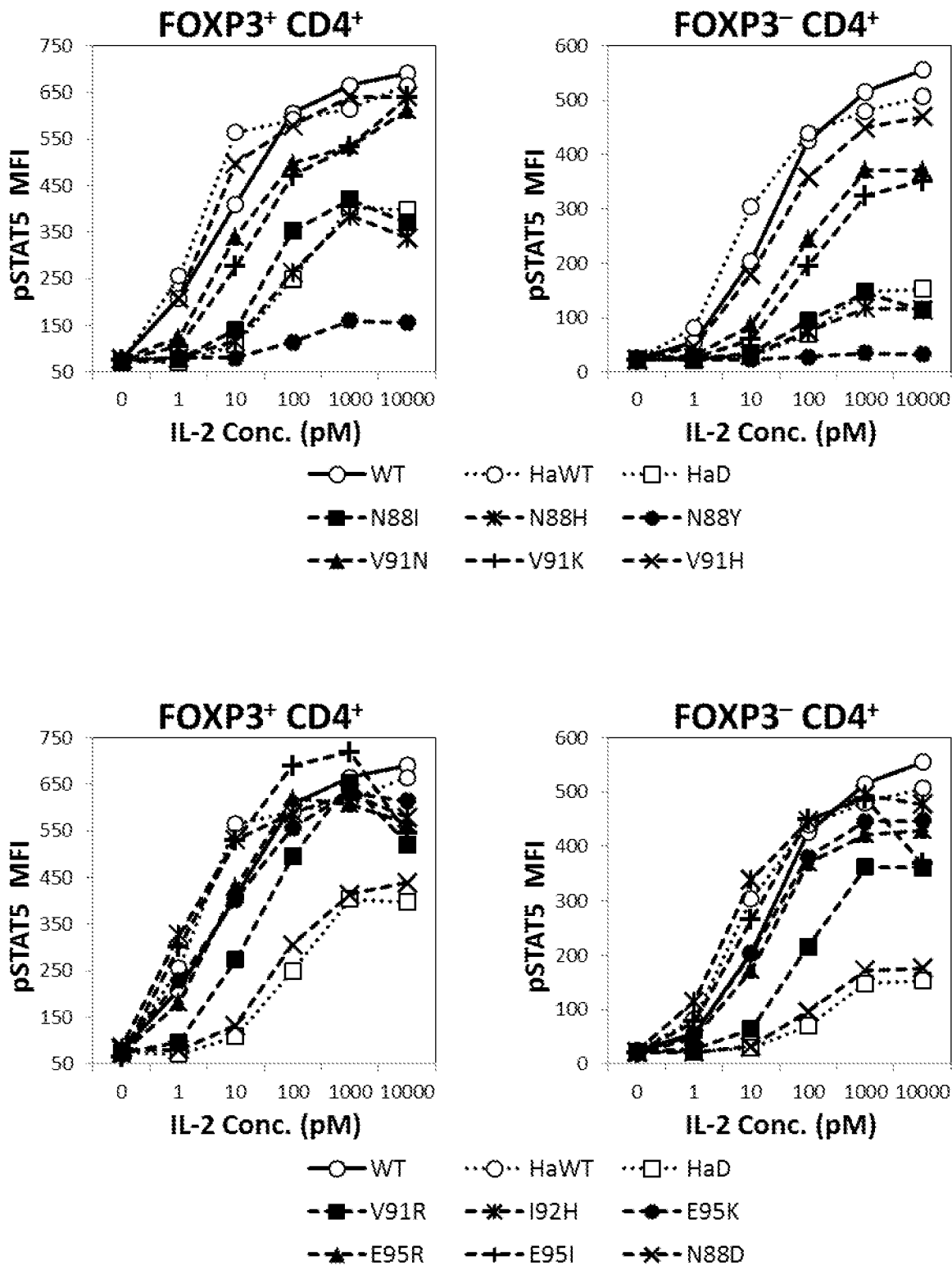


FIG. 2B



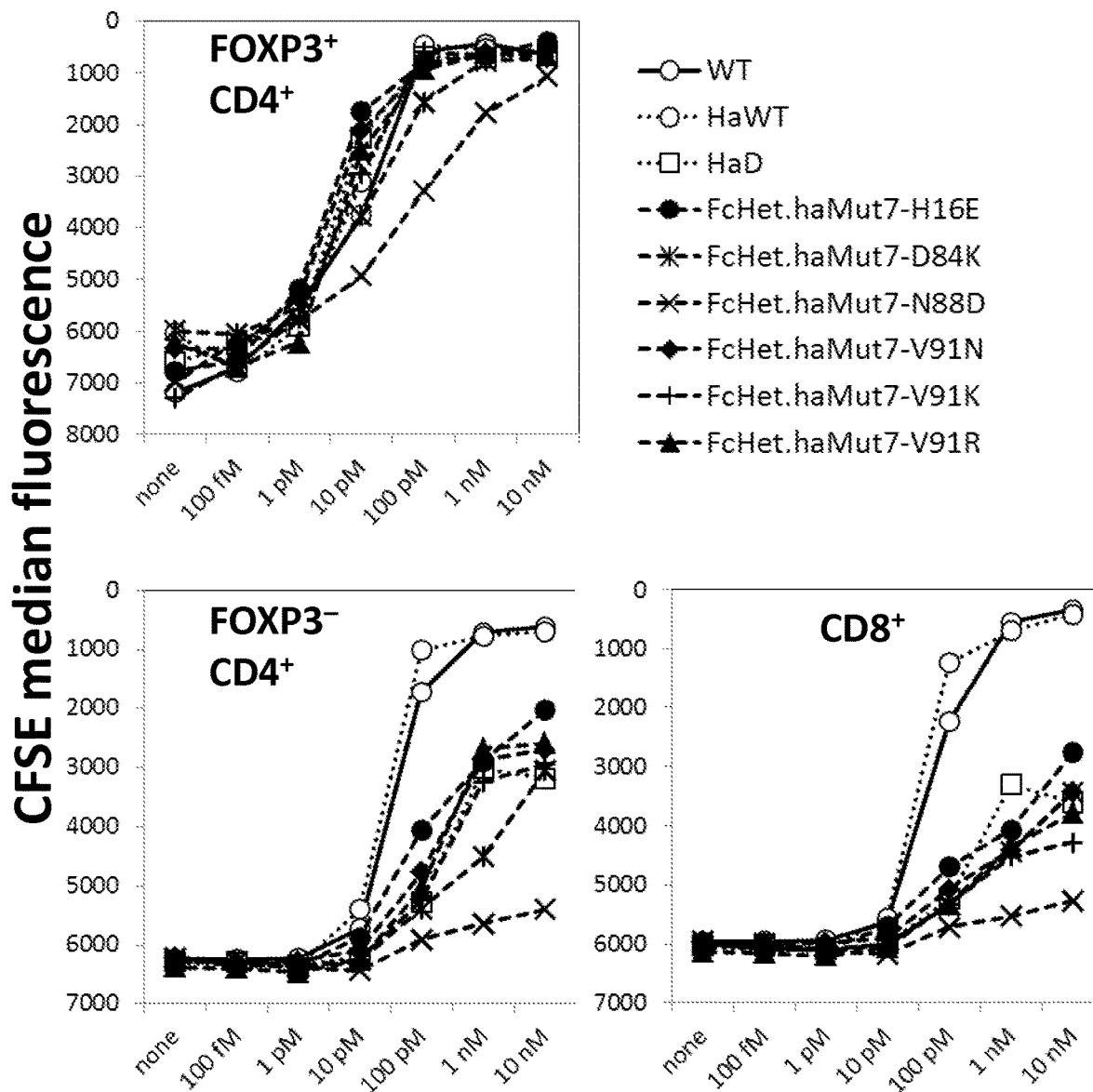


FIG. 3

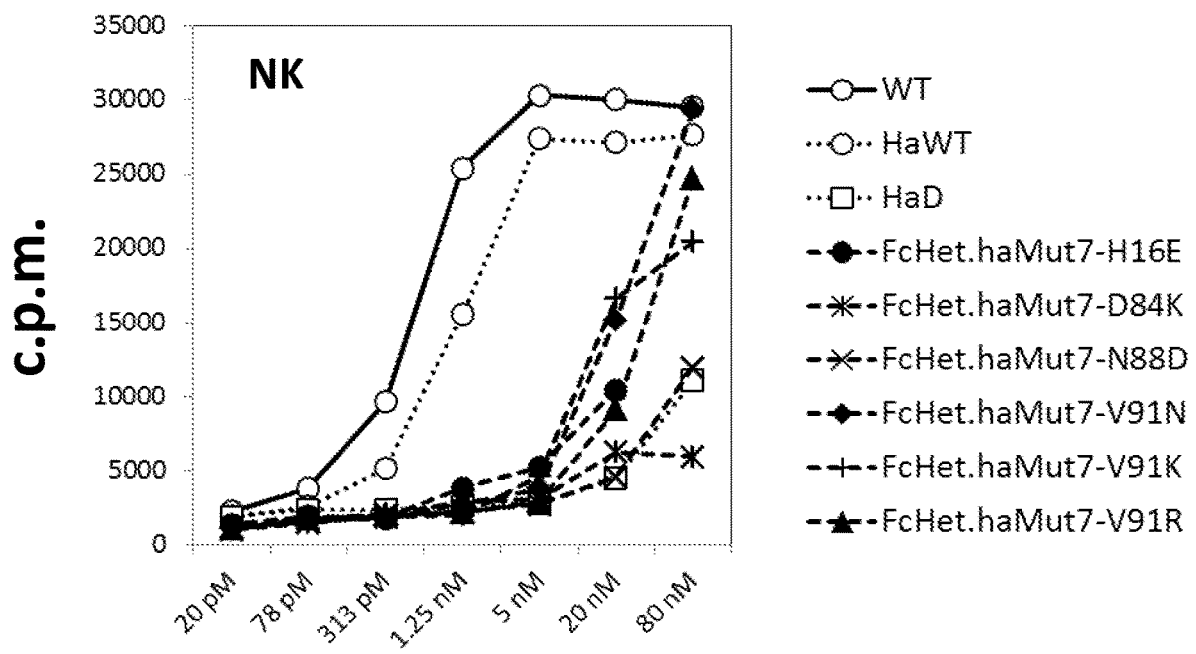


FIG. 4

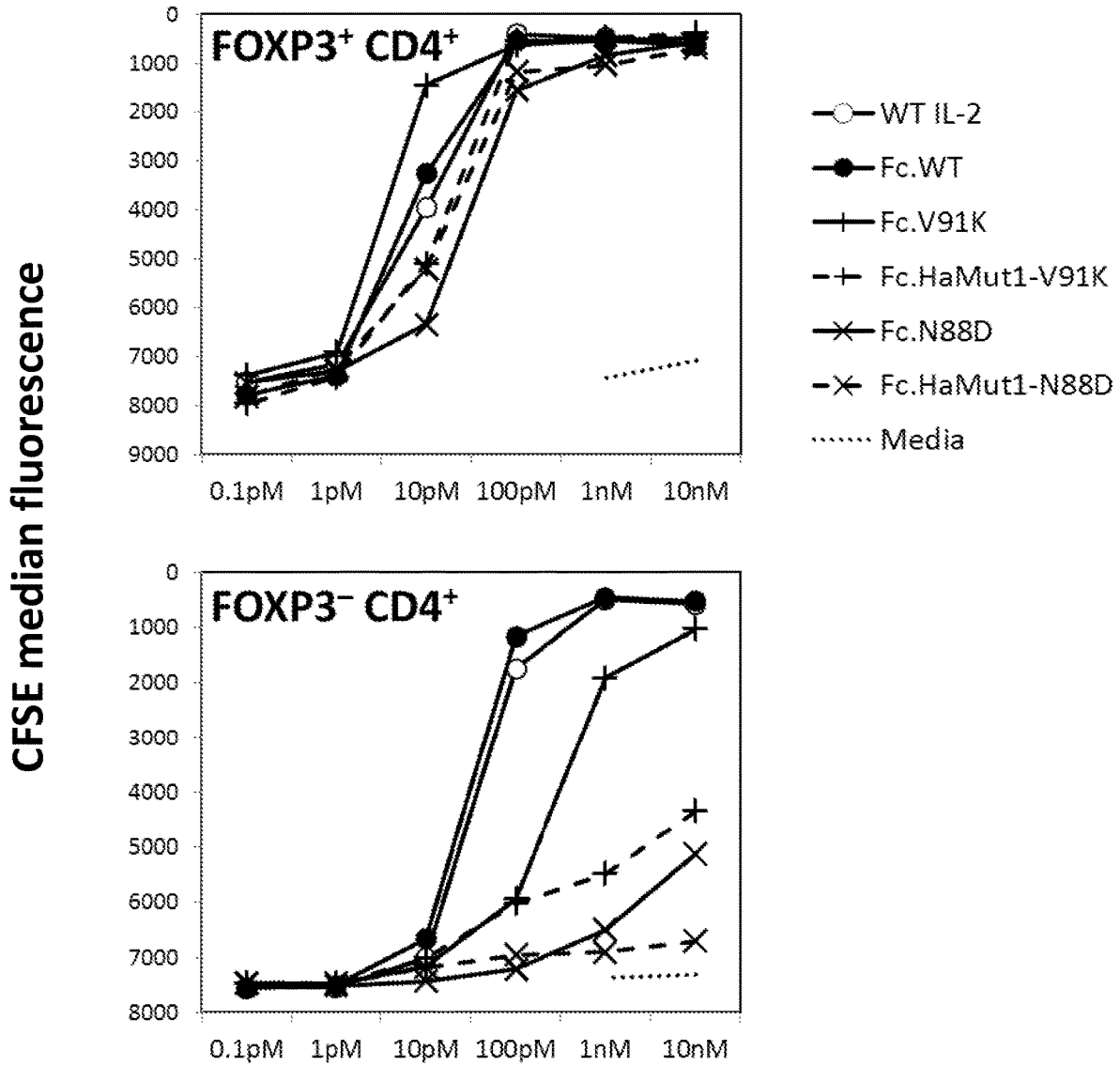


FIG. 5

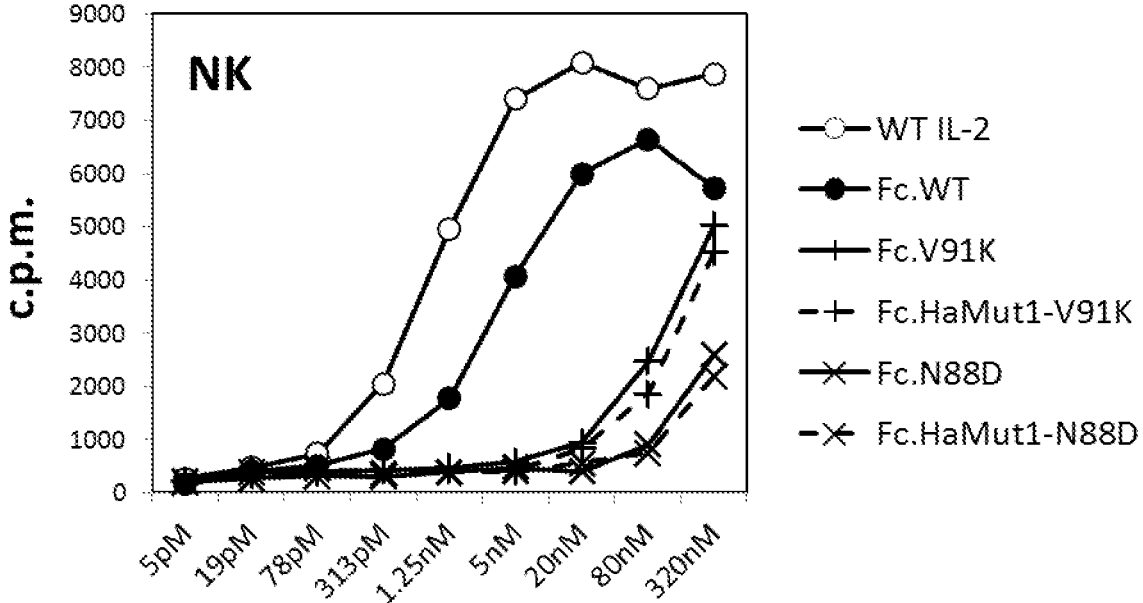


FIG. 6



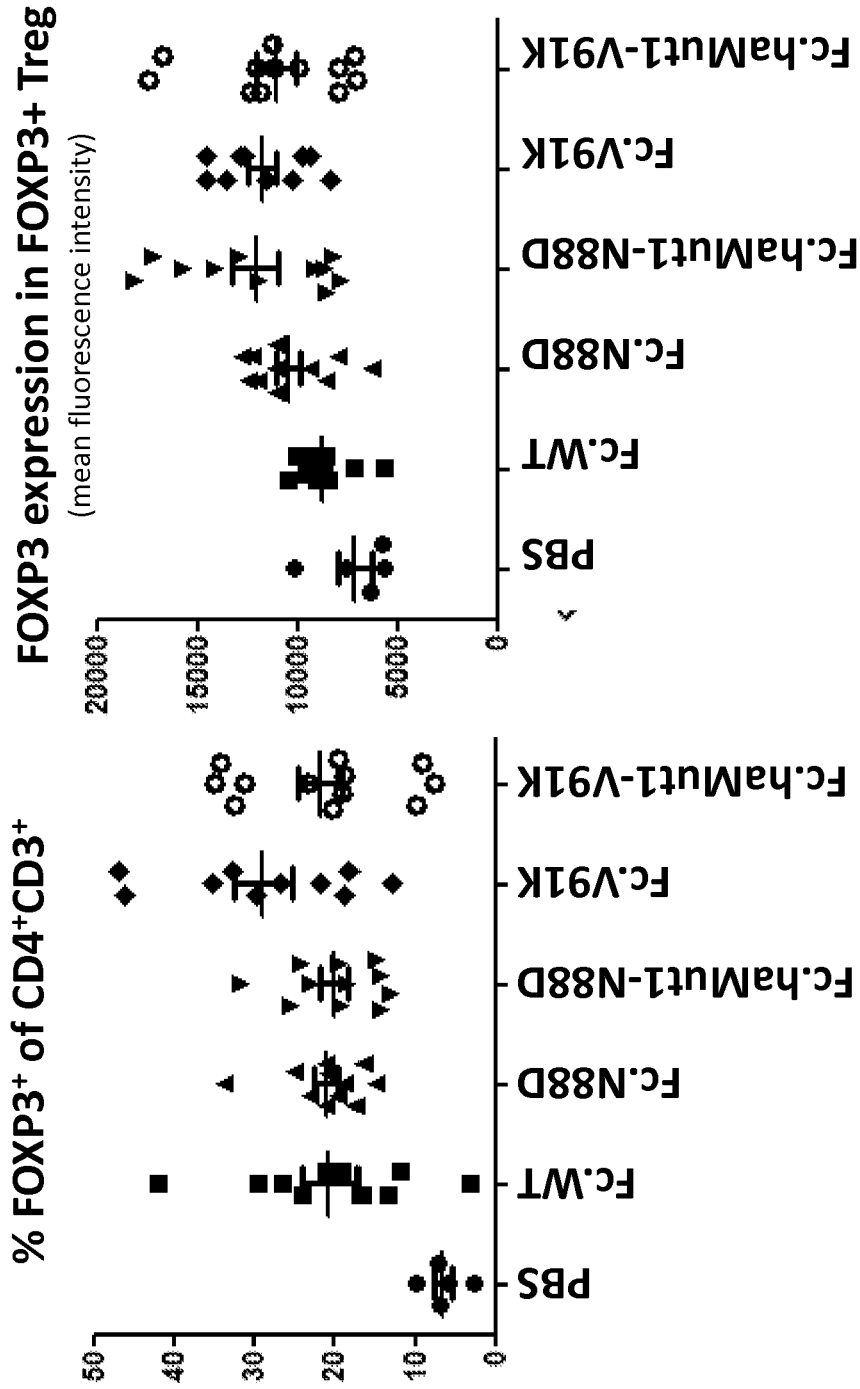


FIG. 7A

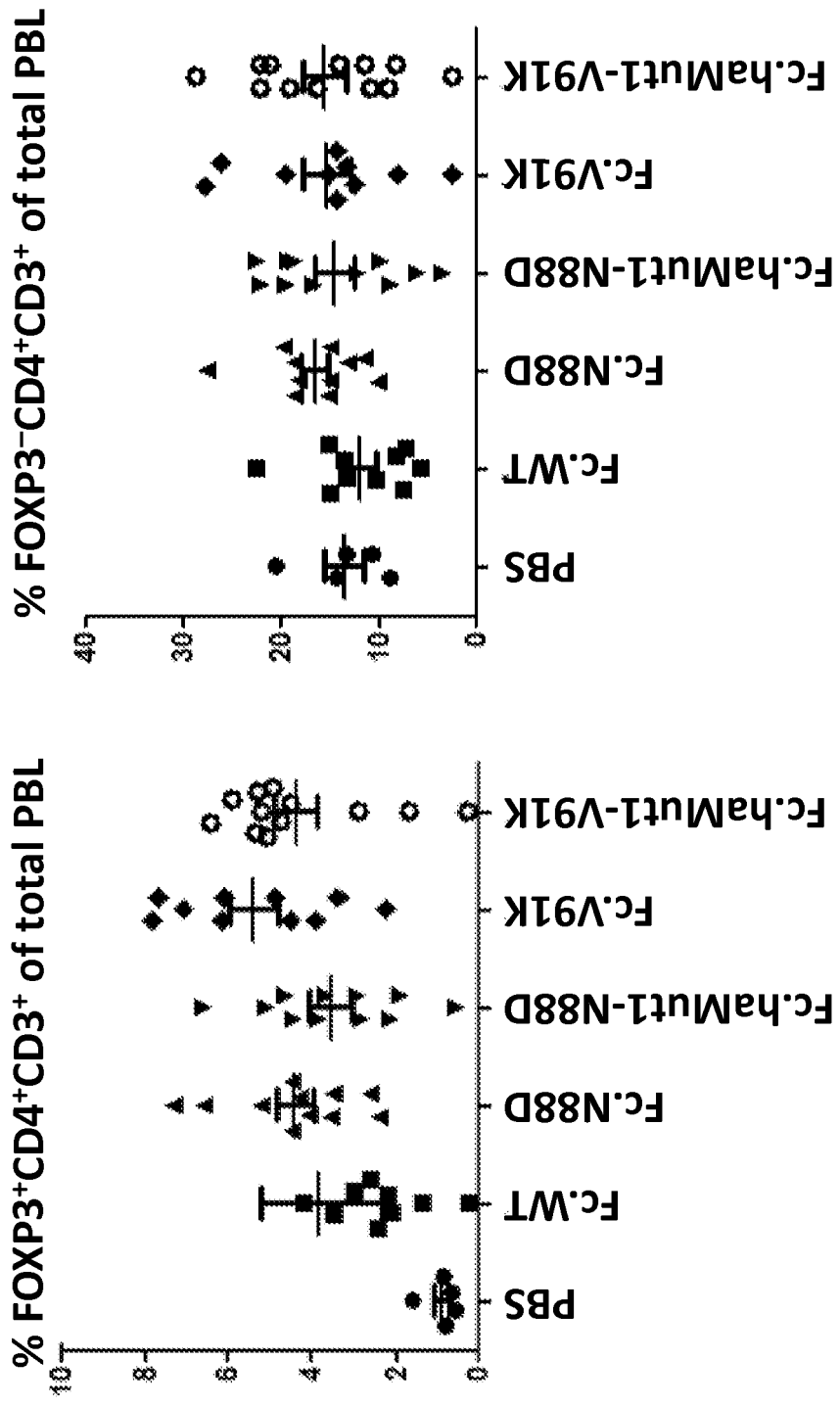


FIG. 7B

FIG. 8

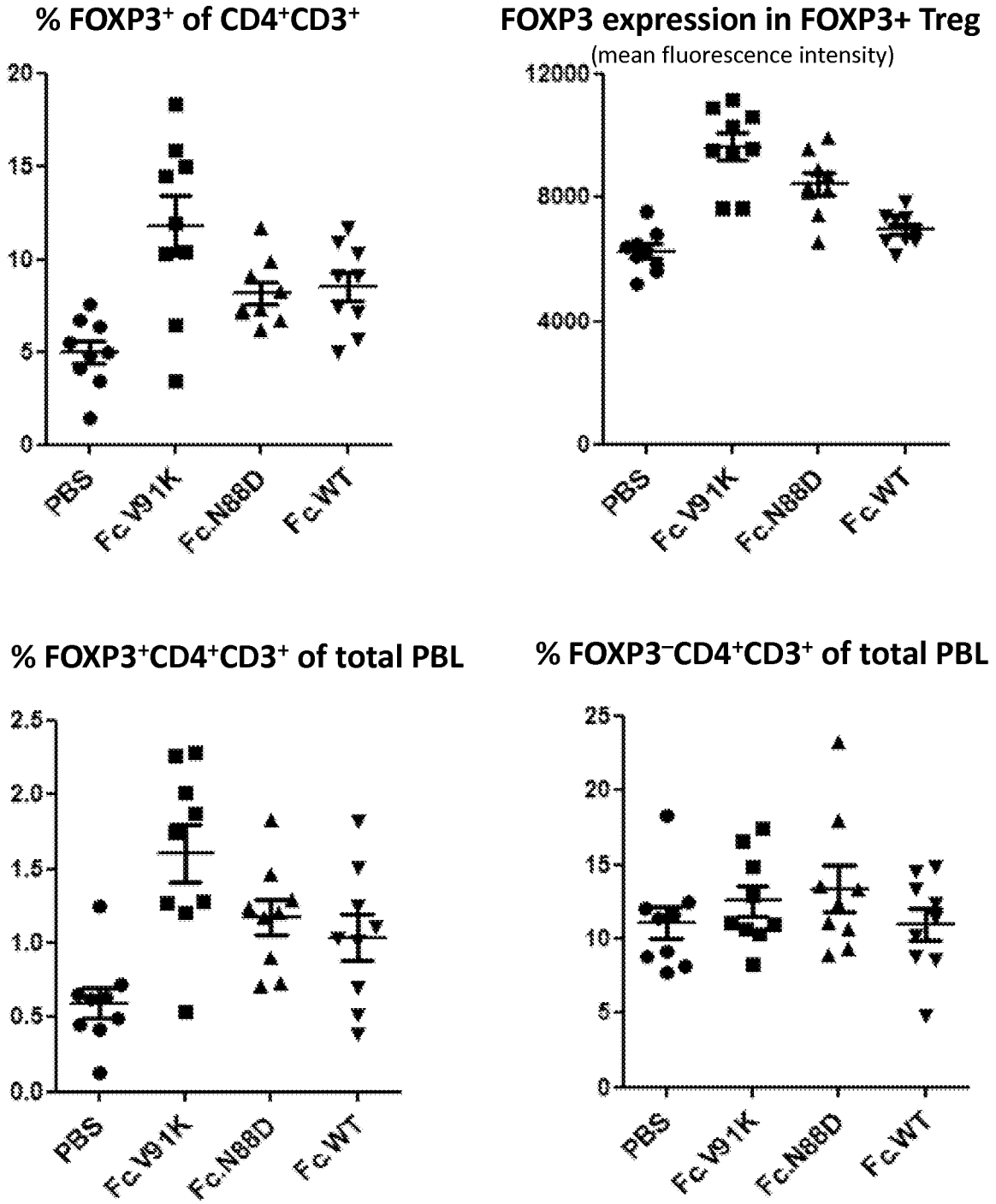




FIG. 9B

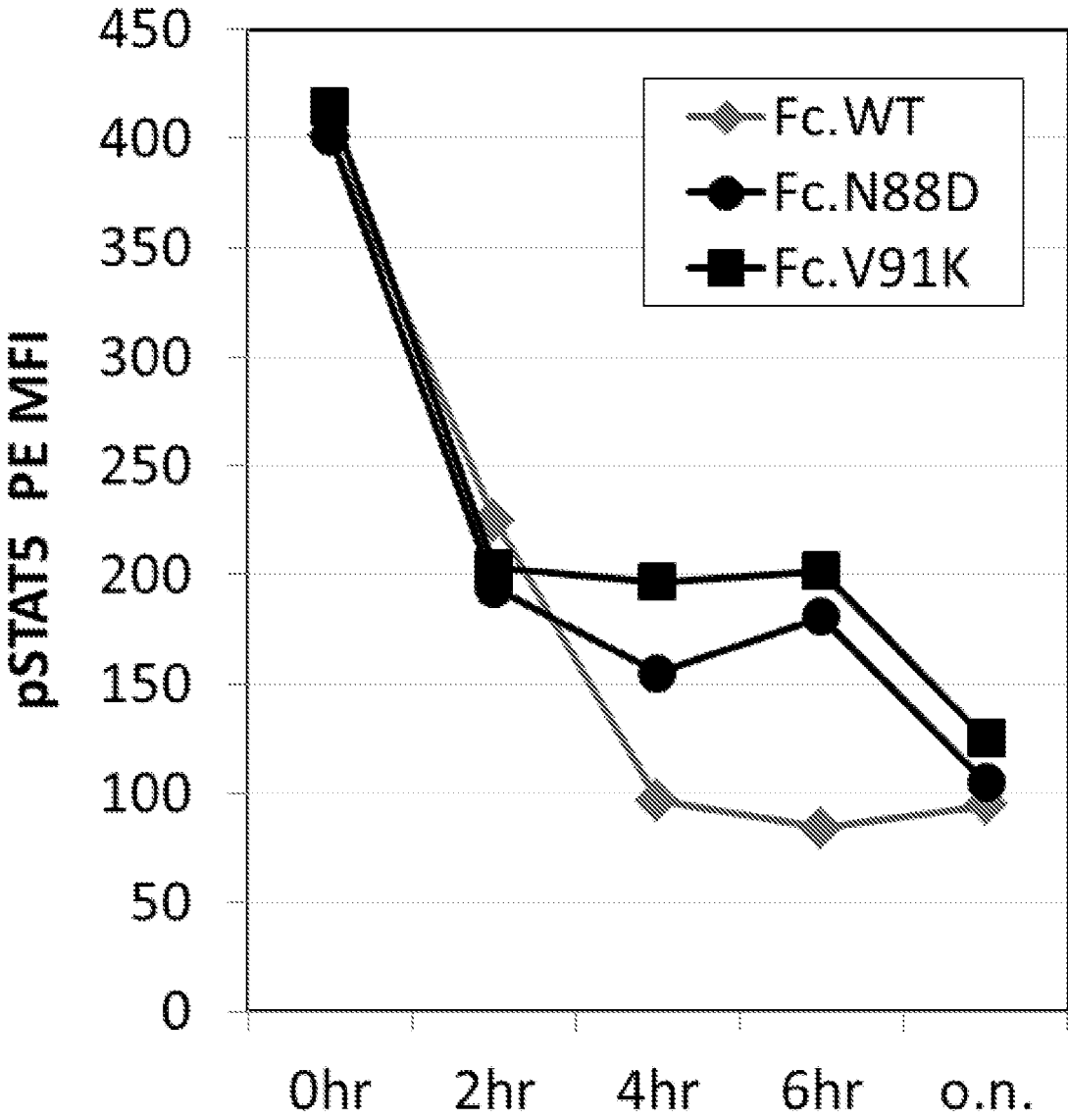
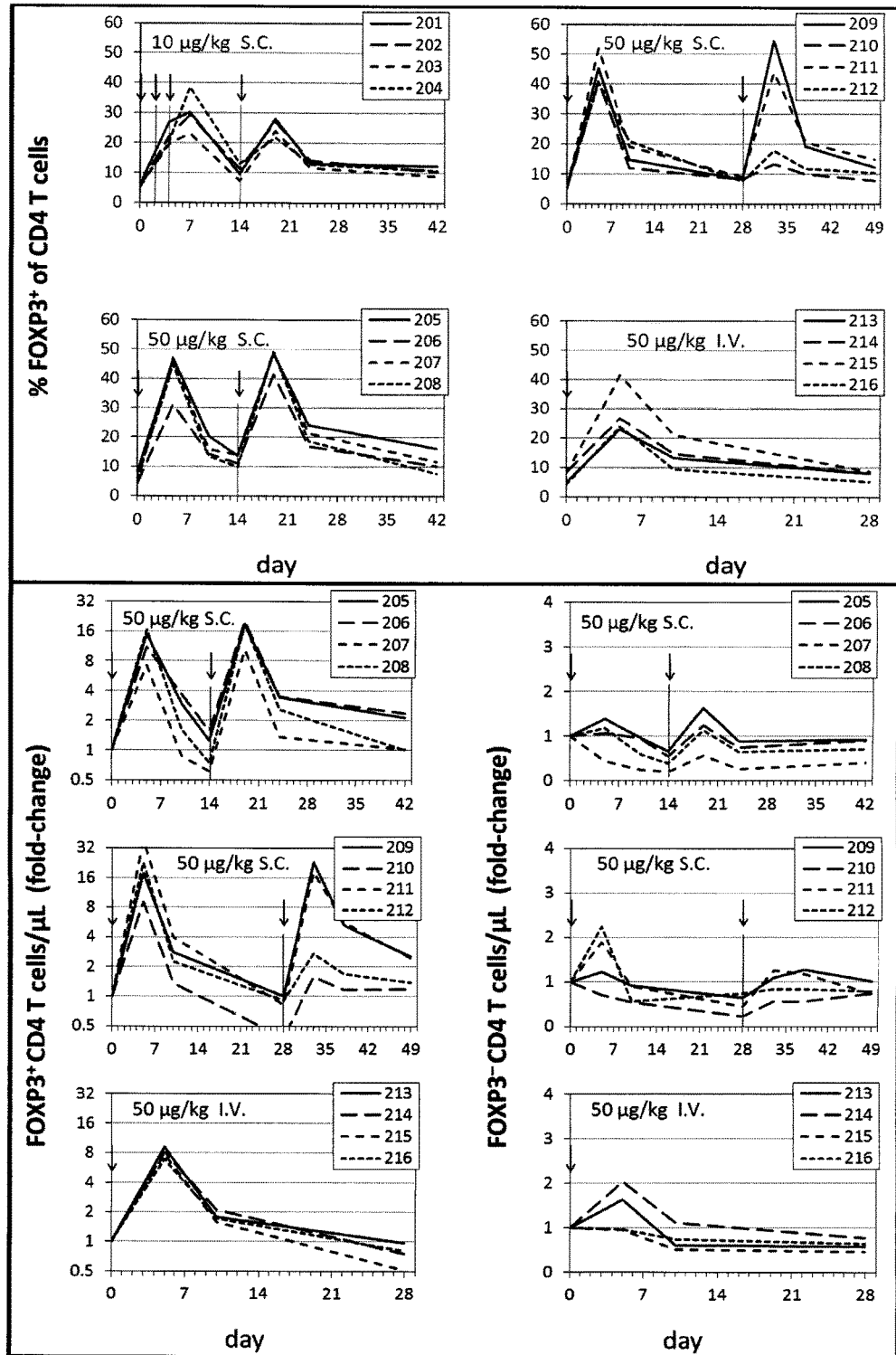


FIG. 10A



**FIG. 10B**

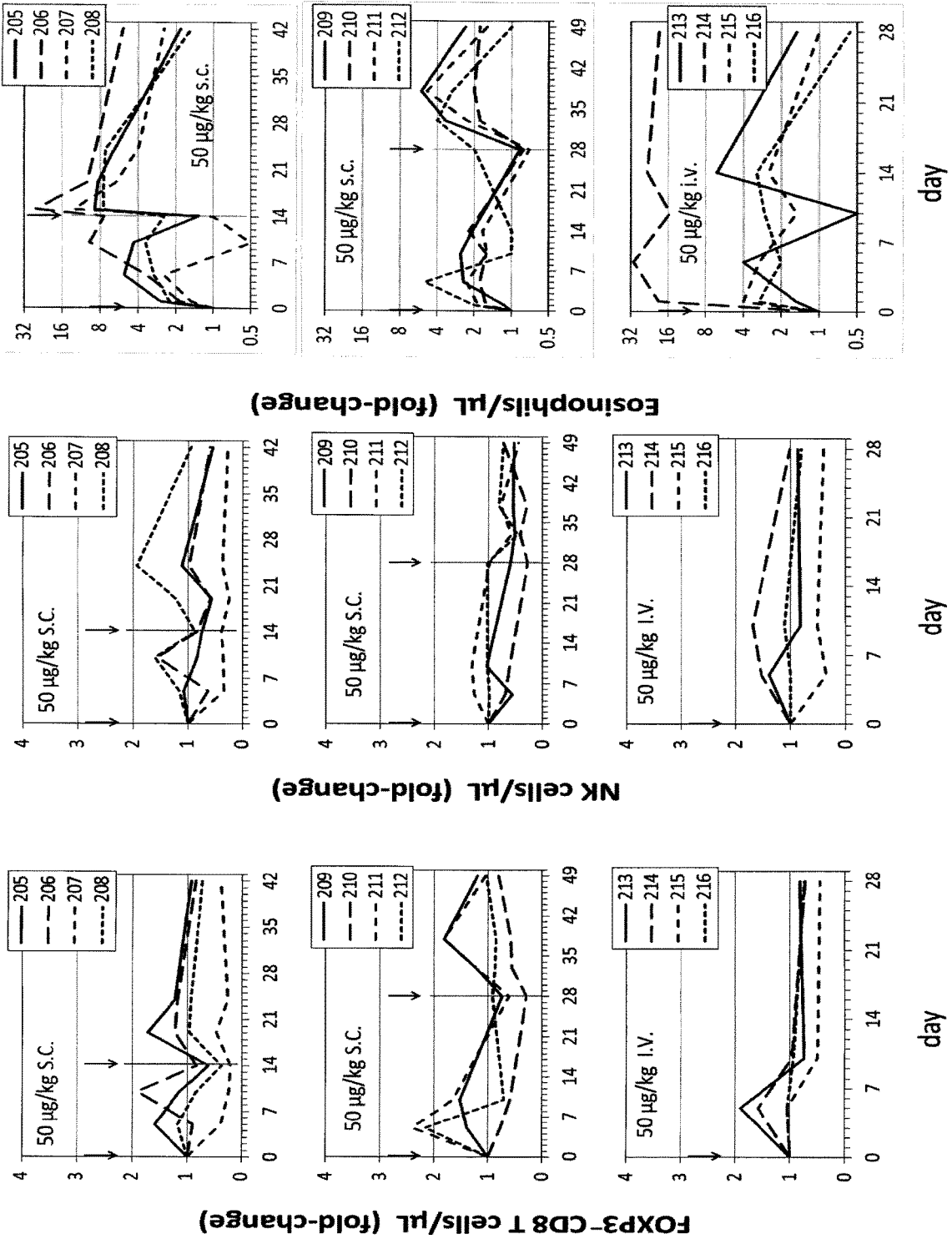


FIG. 11A

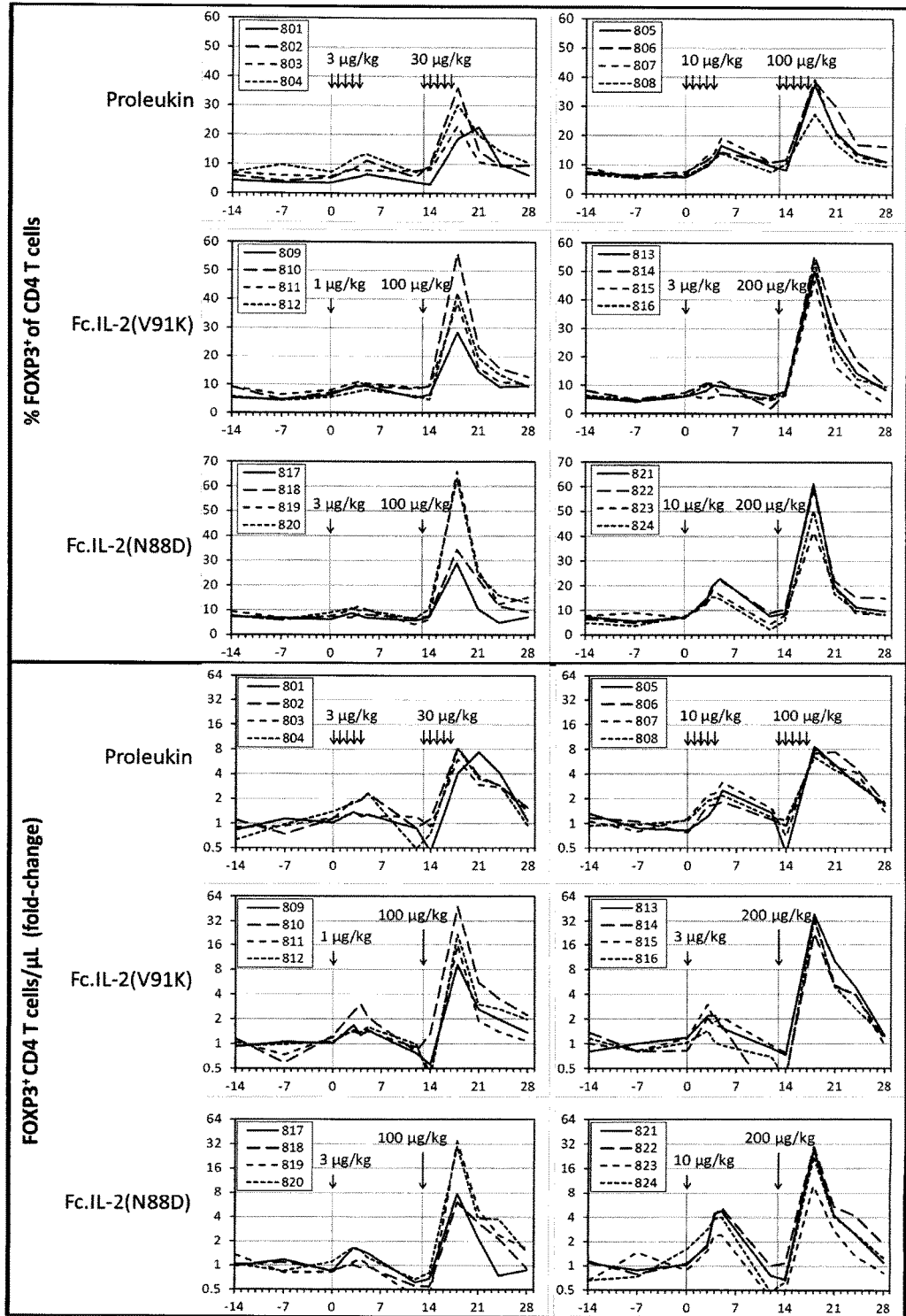




FIG. 11B

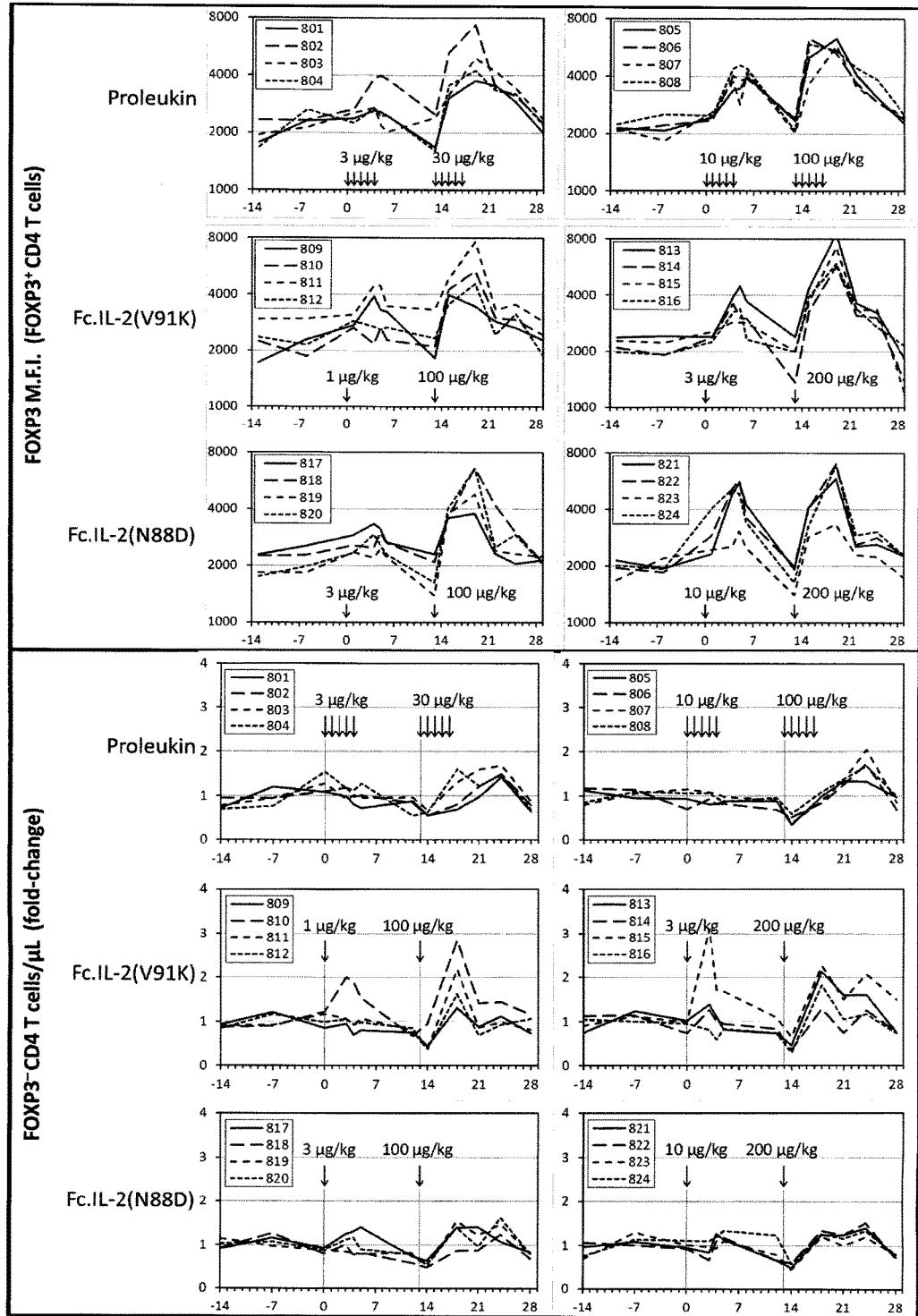


FIG. 11C

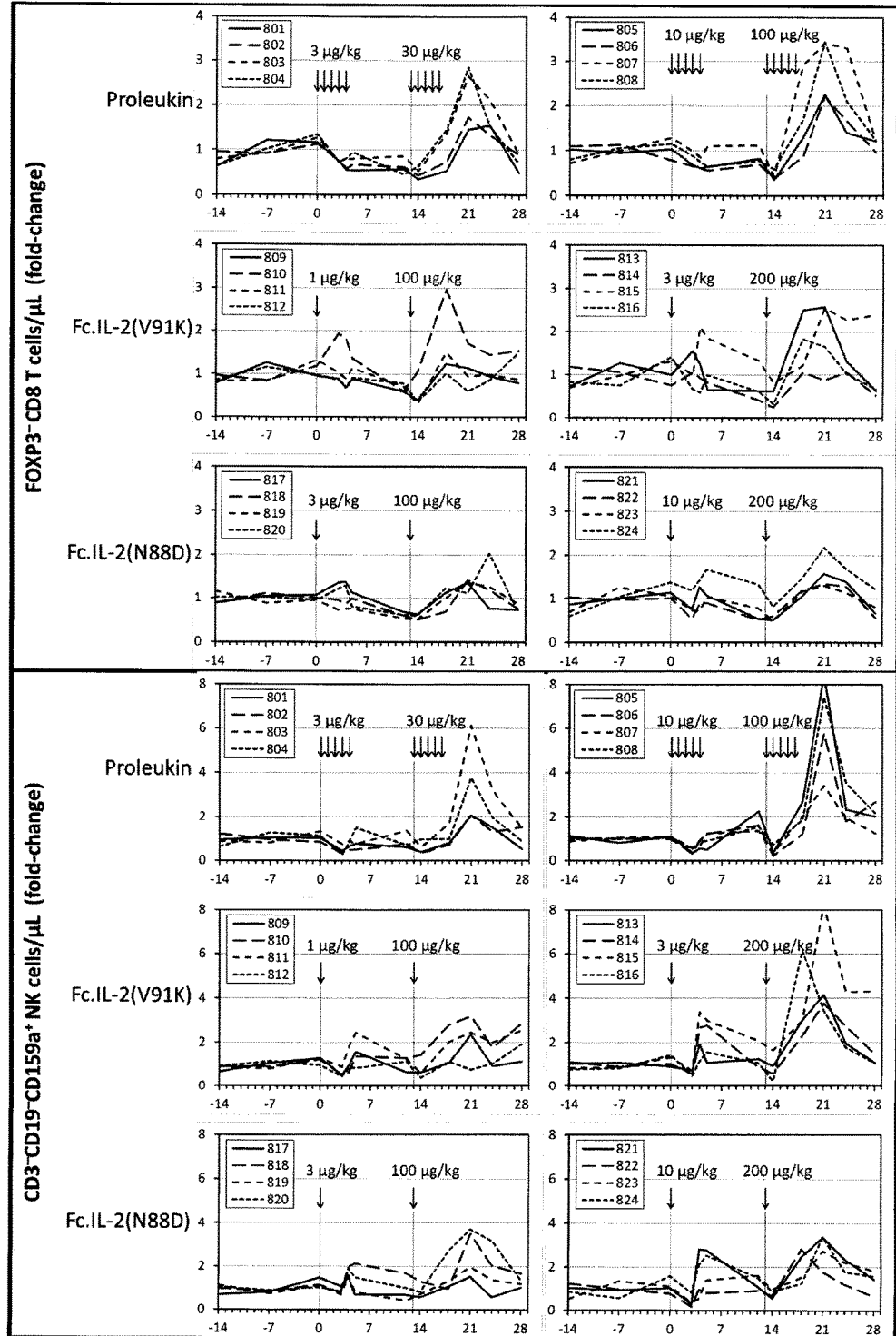
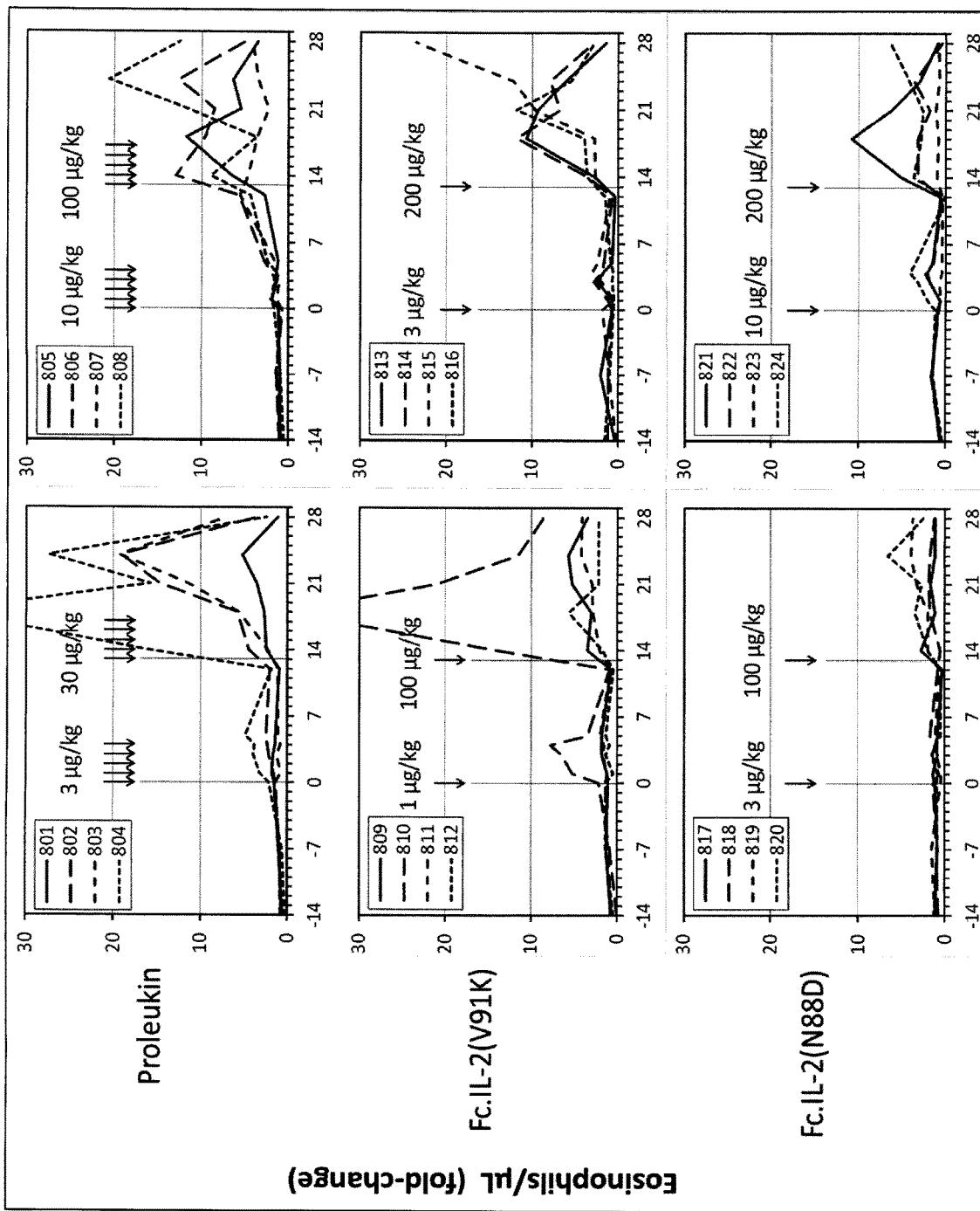


FIG. 11D



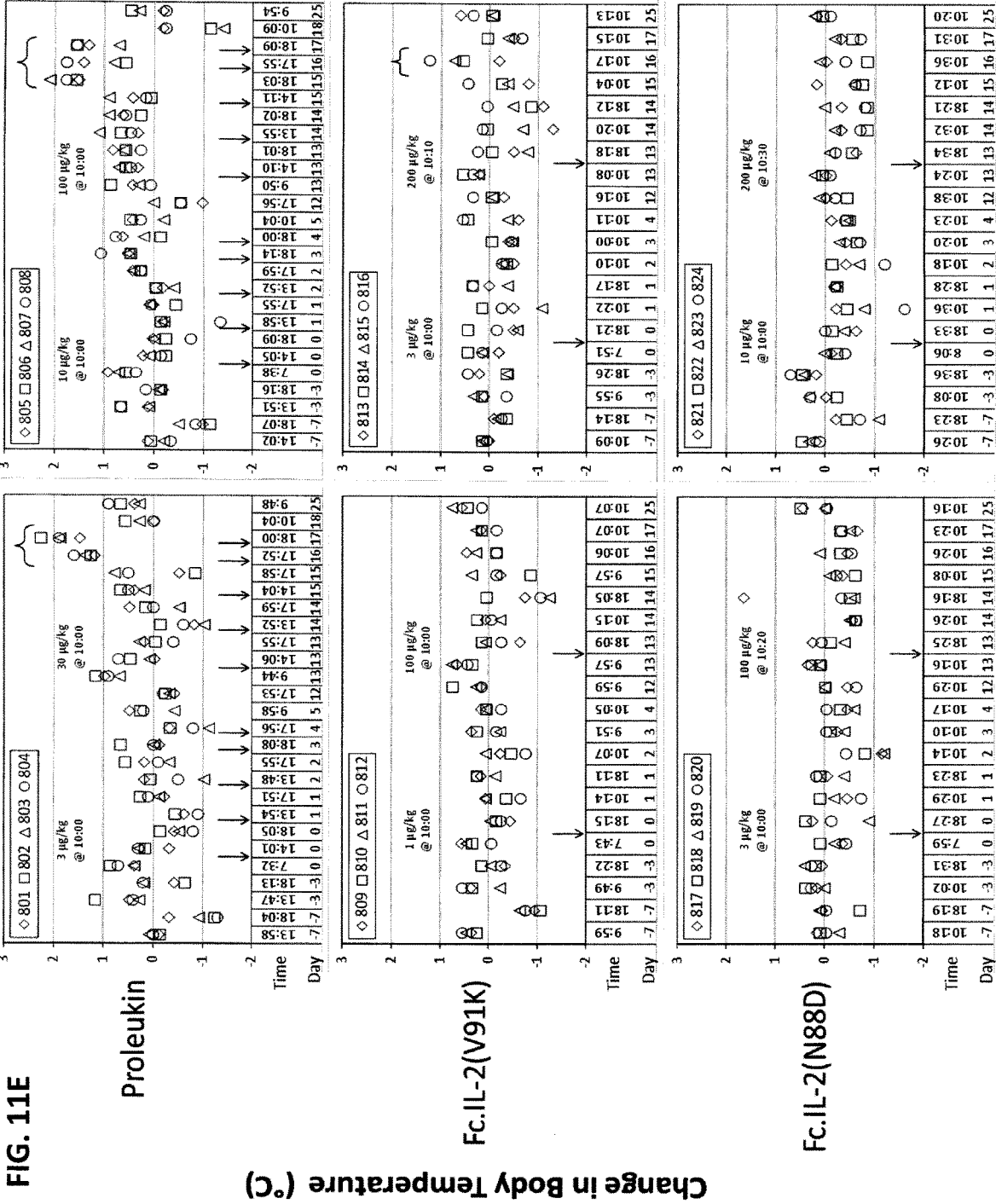


FIG. 11F

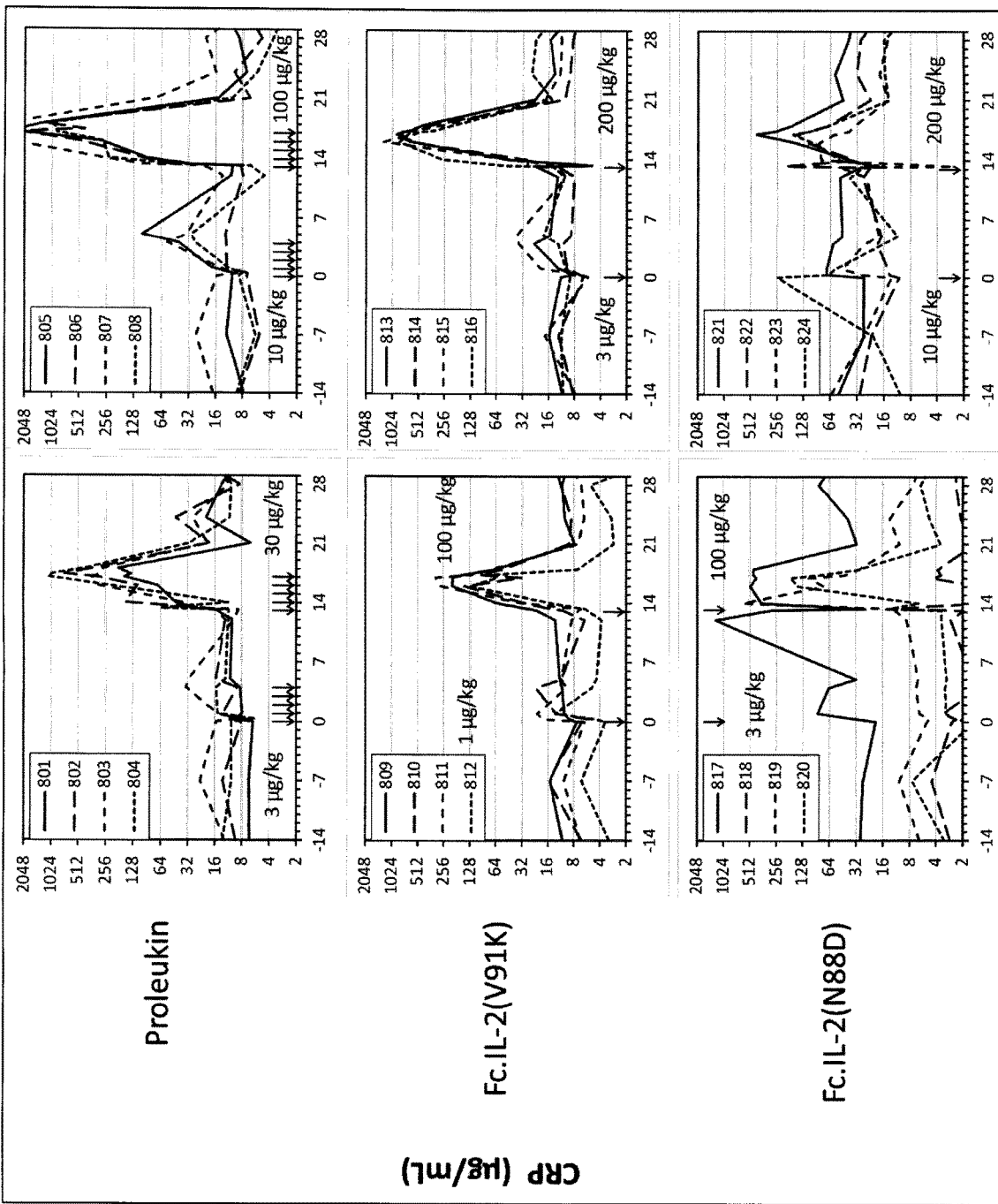


FIG. 12A

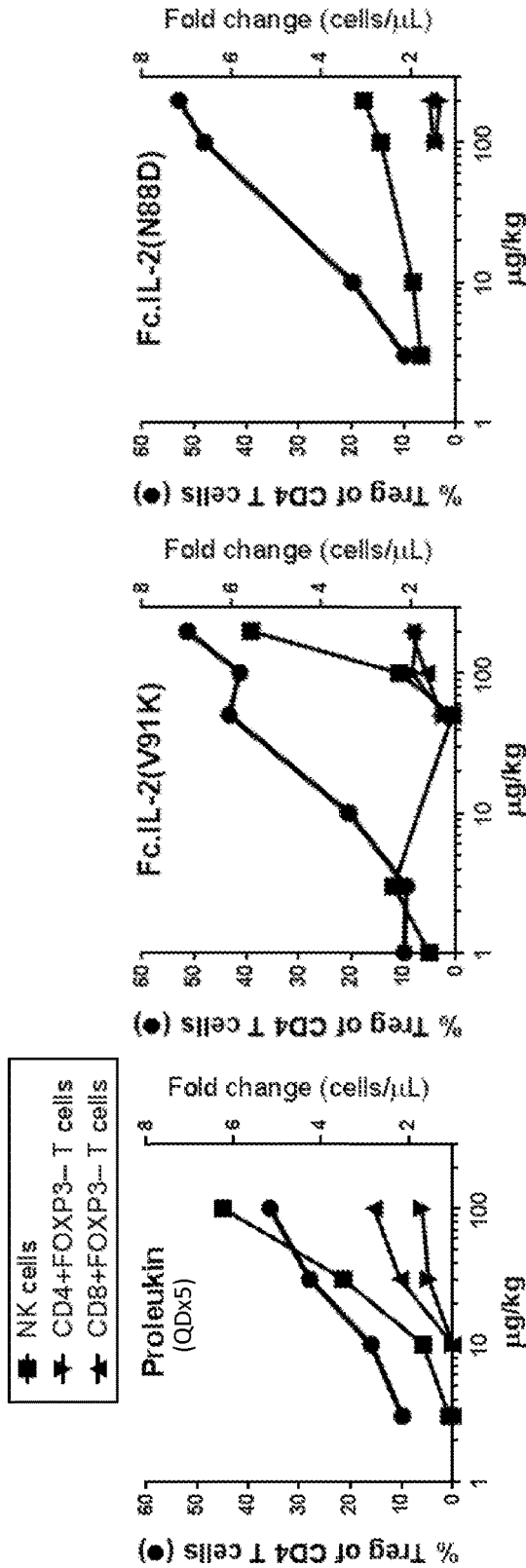


FIG. 12B

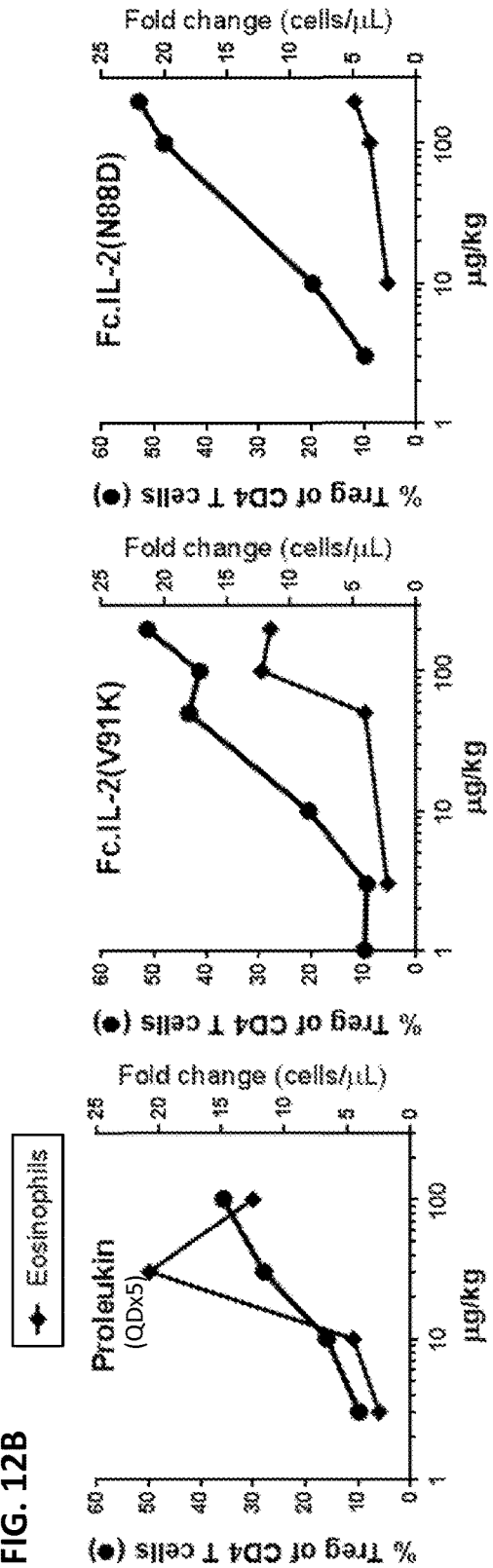


FIG. 12C

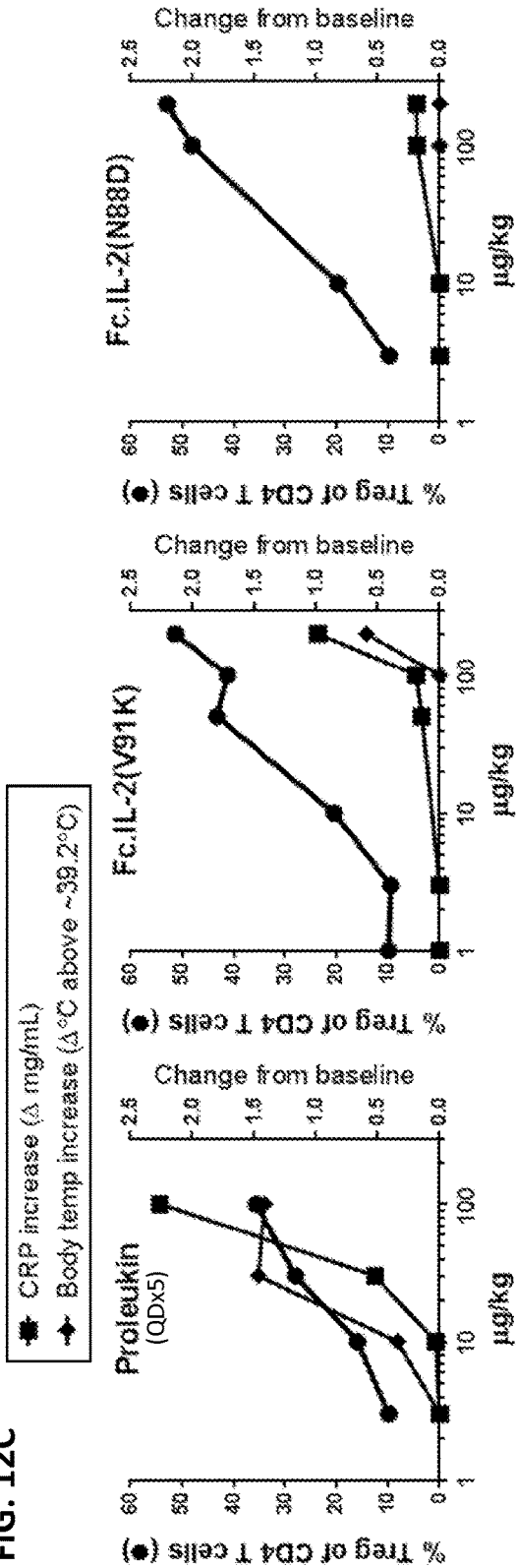


FIG. 12D

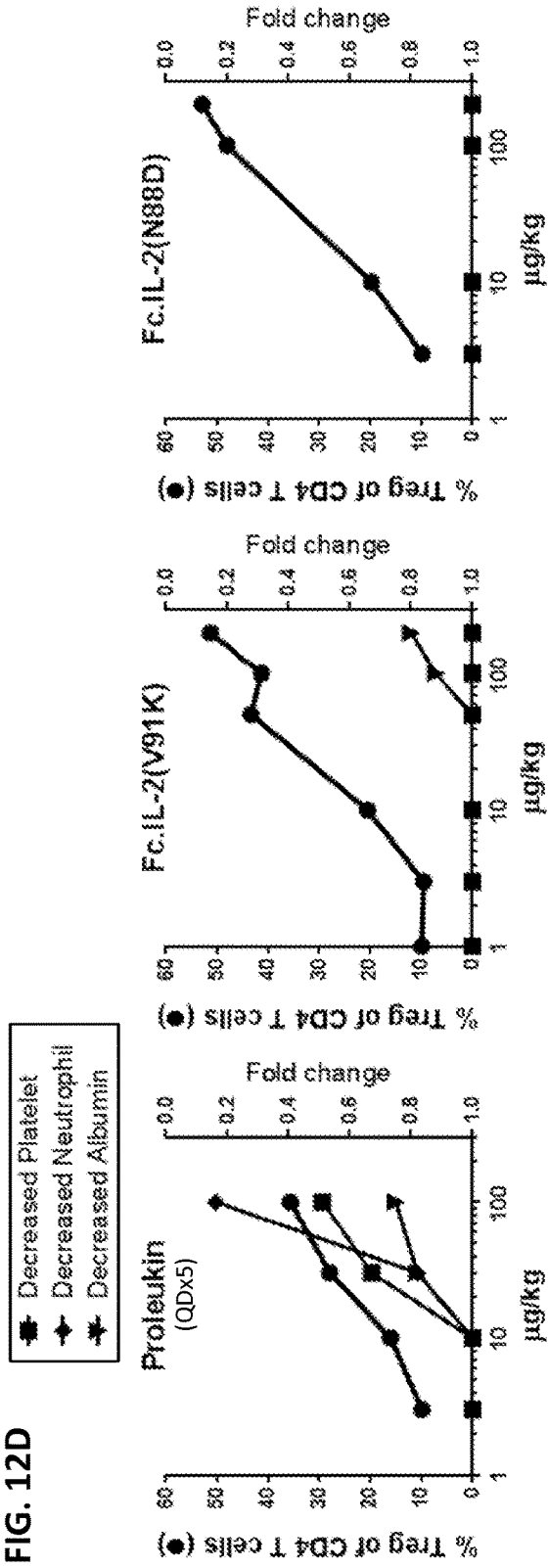
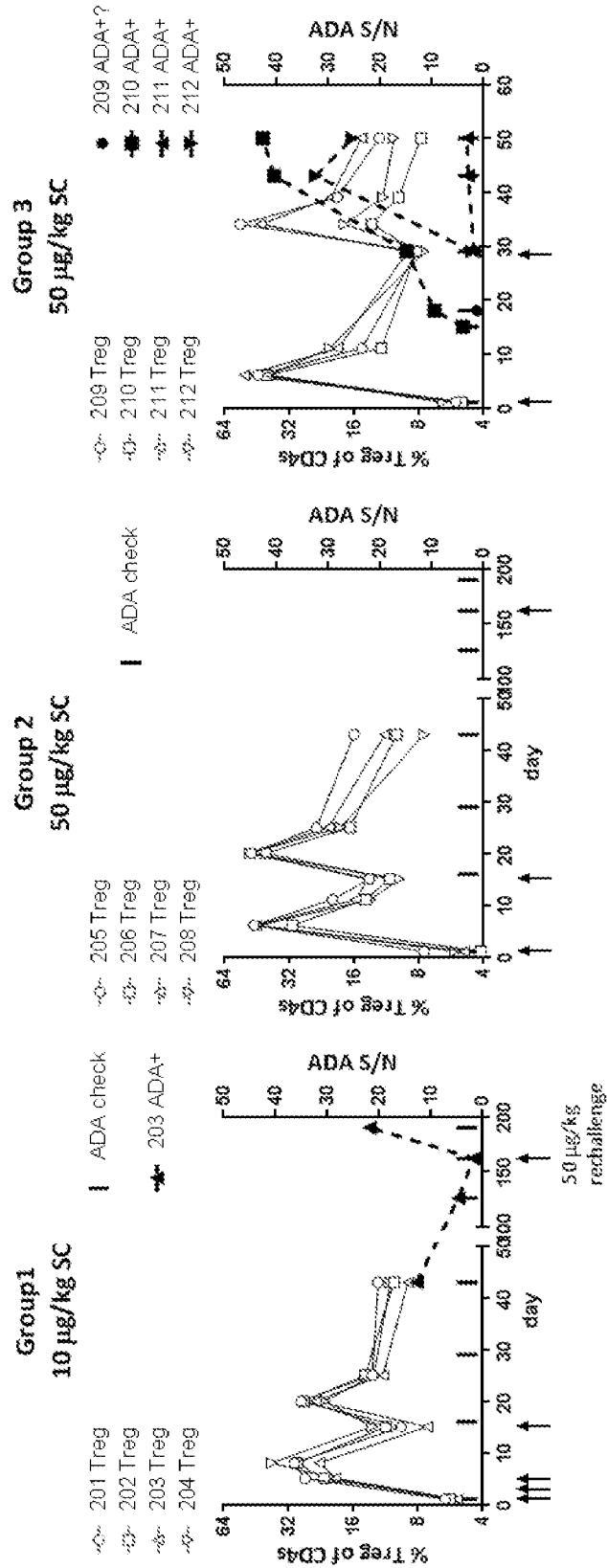


FIG. 13





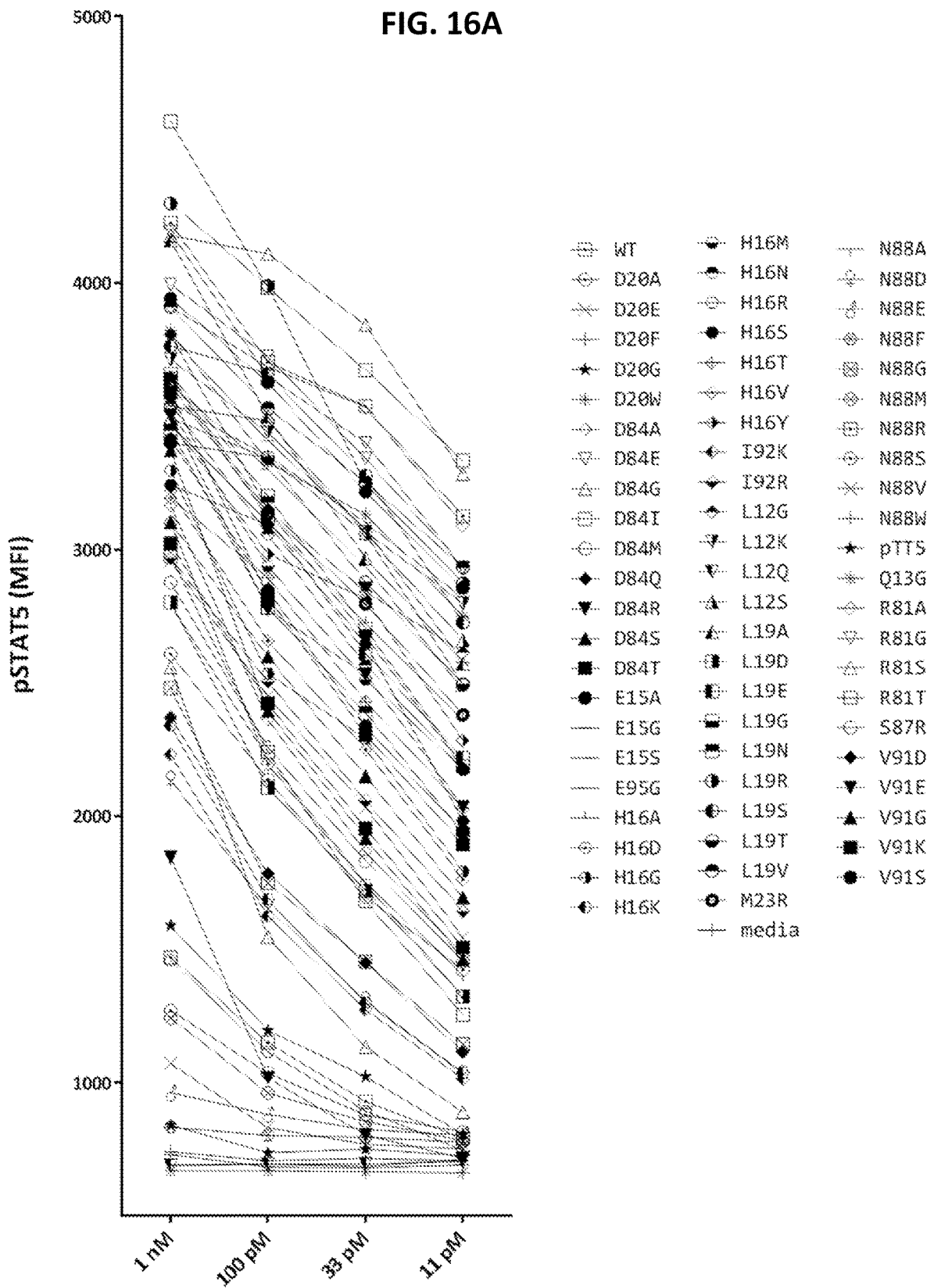
**FIG. 14**

	L12	Q13	E15	H16	L19	D20	M23	R81	D84	S87	N88	V91	I92	L94	E95
<b>A</b>	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
<b>D</b>	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
<b>E</b>	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
<b>F</b>	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
<b>G</b>	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
<b>H</b>	-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
<b>I</b>	-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
<b>K</b>	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
<b>L</b>	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
<b>M</b>	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
<b>N</b>	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
<b>P</b>	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
<b>Q</b>	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
<b>R</b>	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
<b>S</b>	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
<b>T</b>	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
<b>V</b>	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
<b>W</b>	-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
<b>Y</b>	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

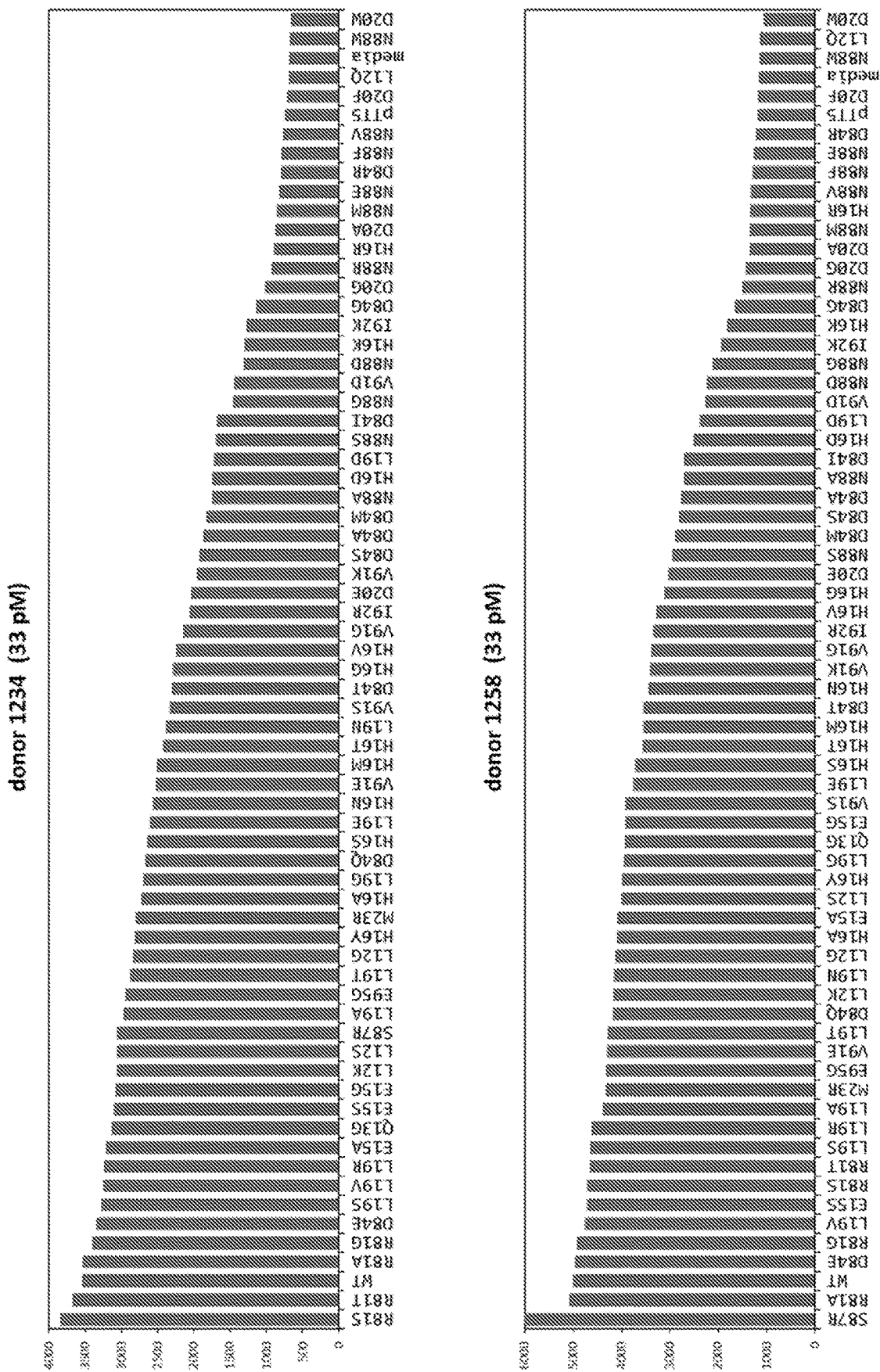
**FIG. 15**

	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	-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



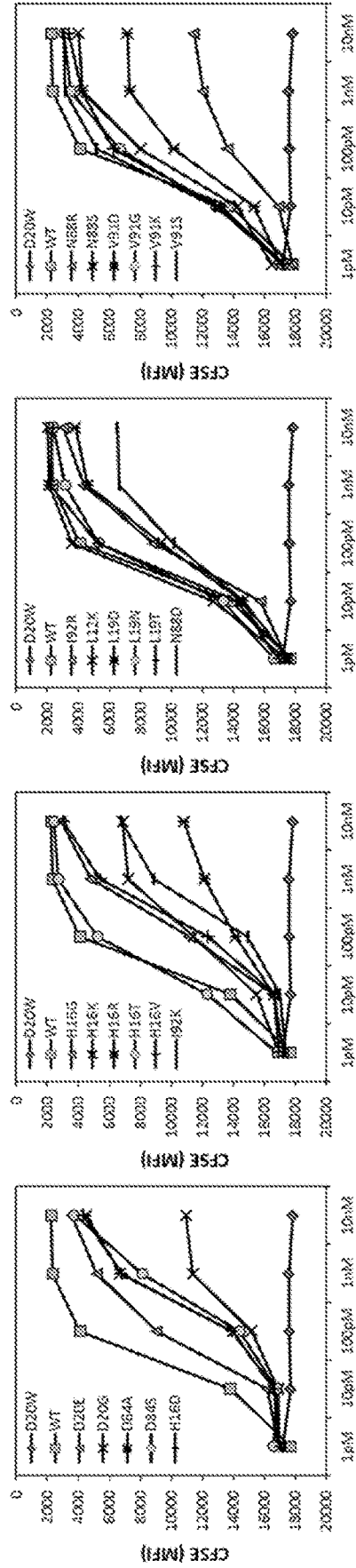
**FIG. 16B**





**FIG. 18A**

FOXP3<sup>-</sup> CD4<sup>+</sup> proliferation



**FIG. 18B**

FOXP3<sup>-</sup> CD8<sup>+</sup> proliferation

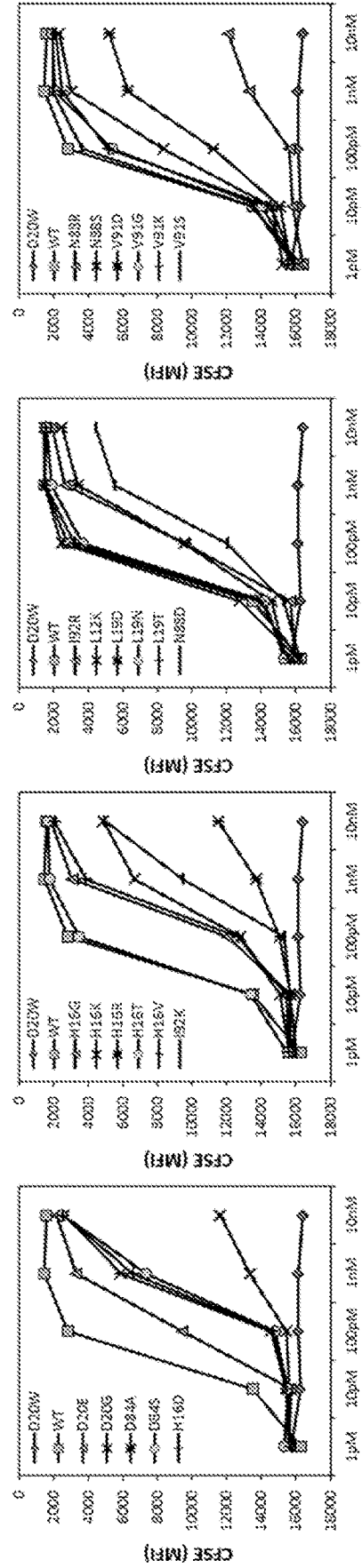
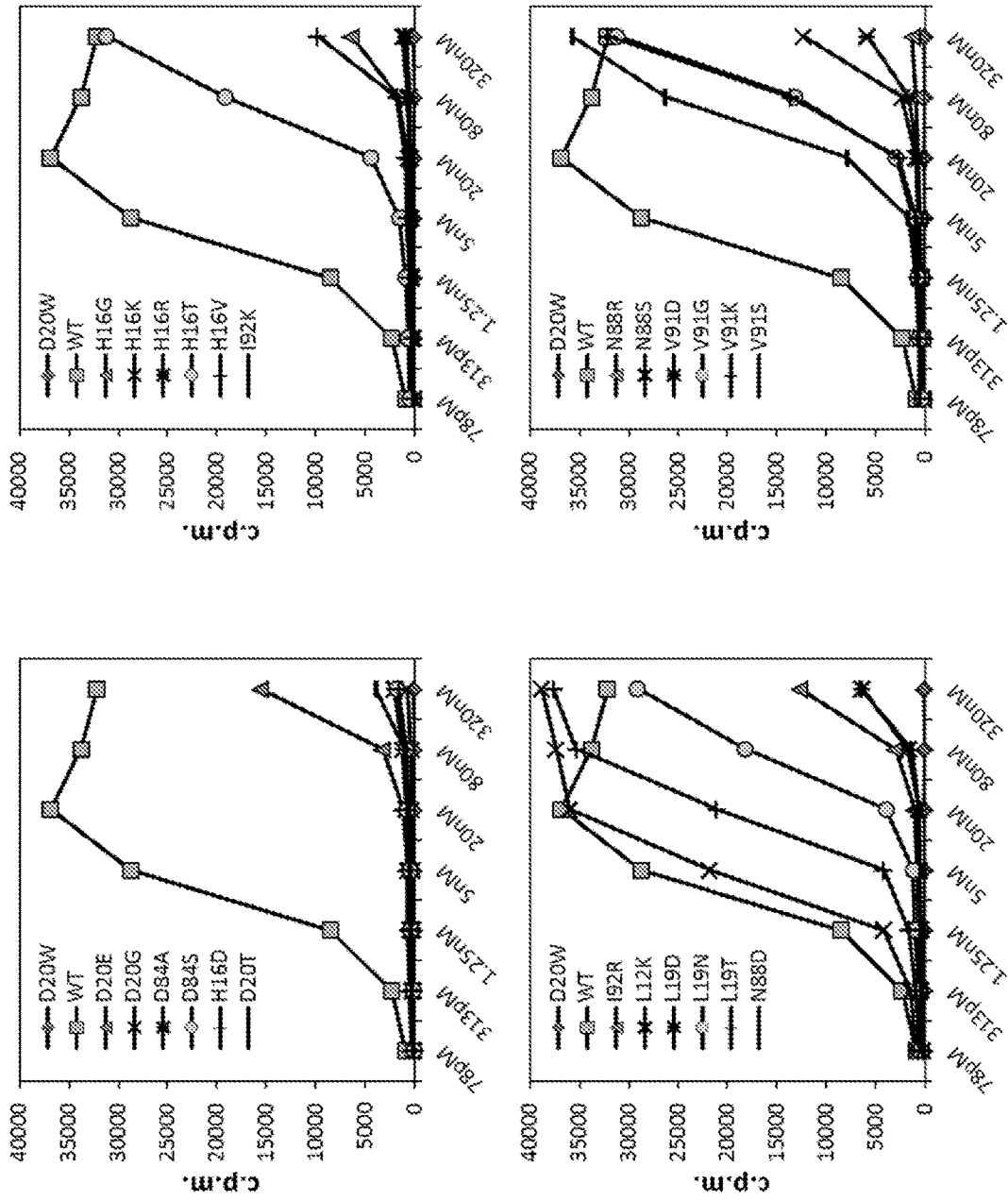




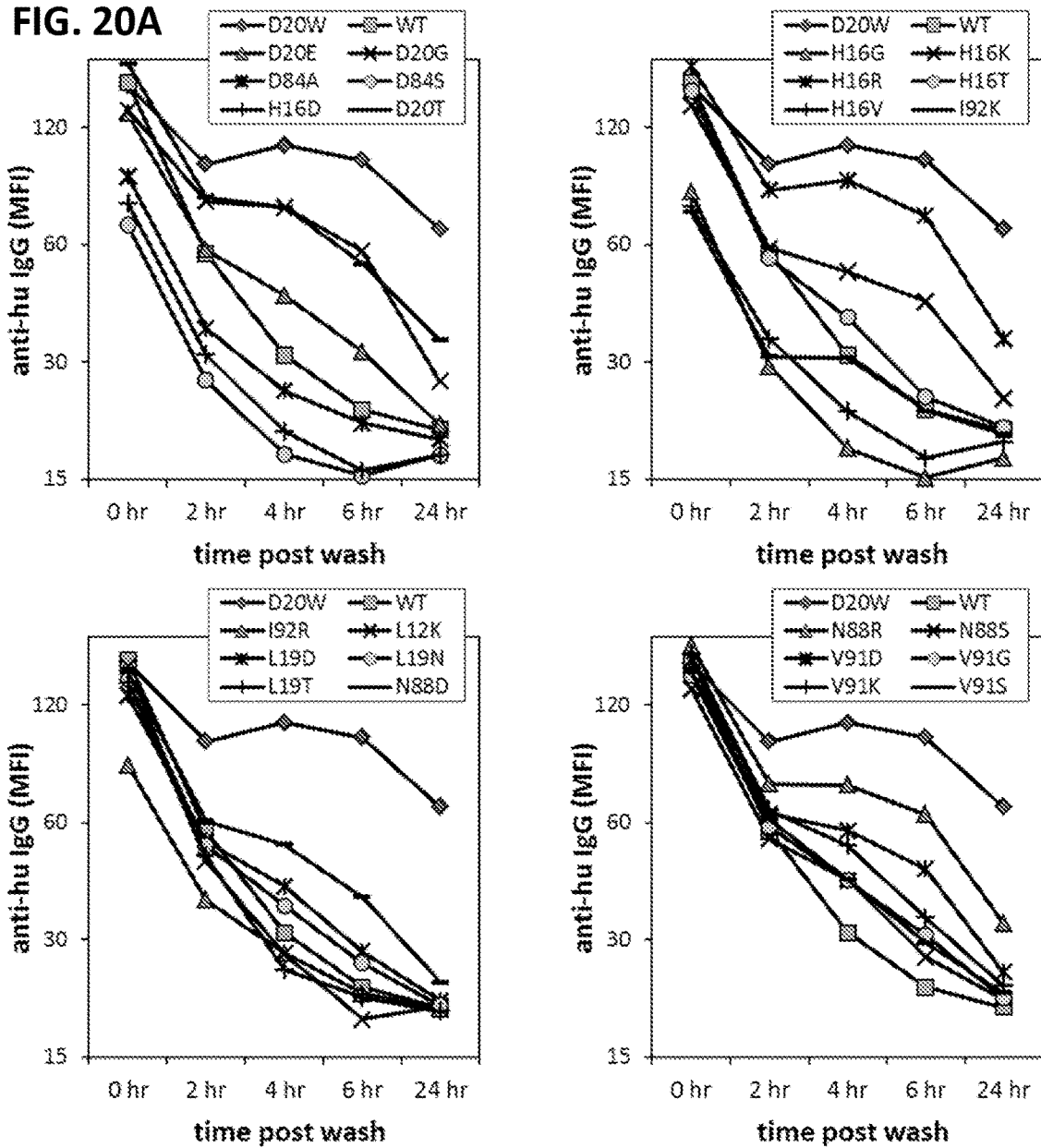
FIG. 19

NK proliferation





**FIG. 20A**



**FIG. 20B**

Sum of 4, 6, 24 hr timepoints  
Average of 2 donors

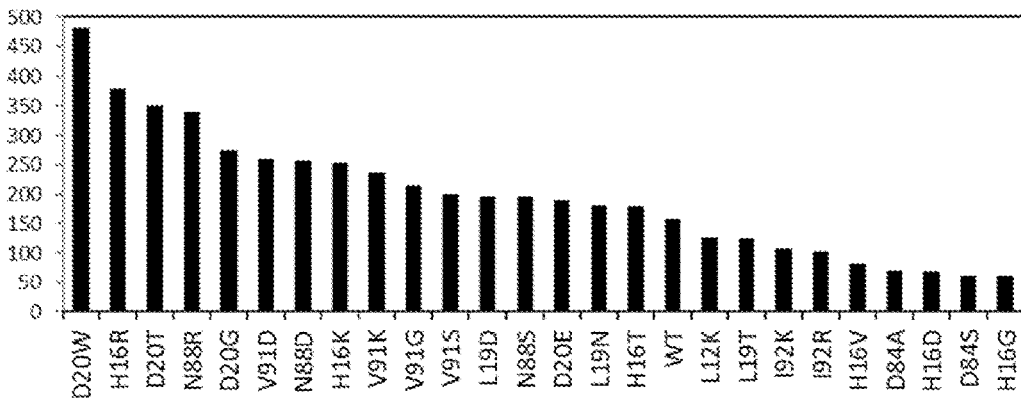
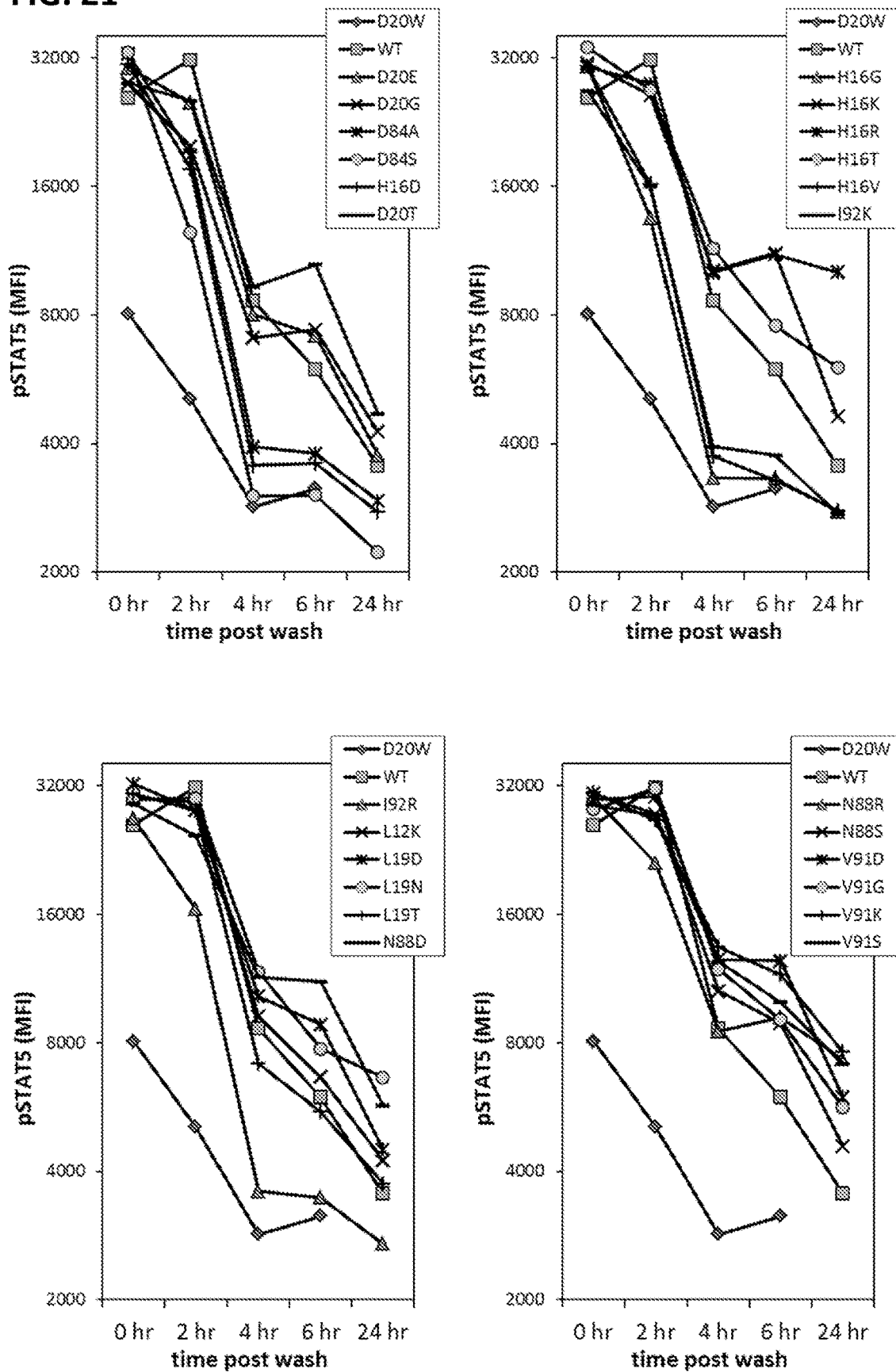


FIG. 21



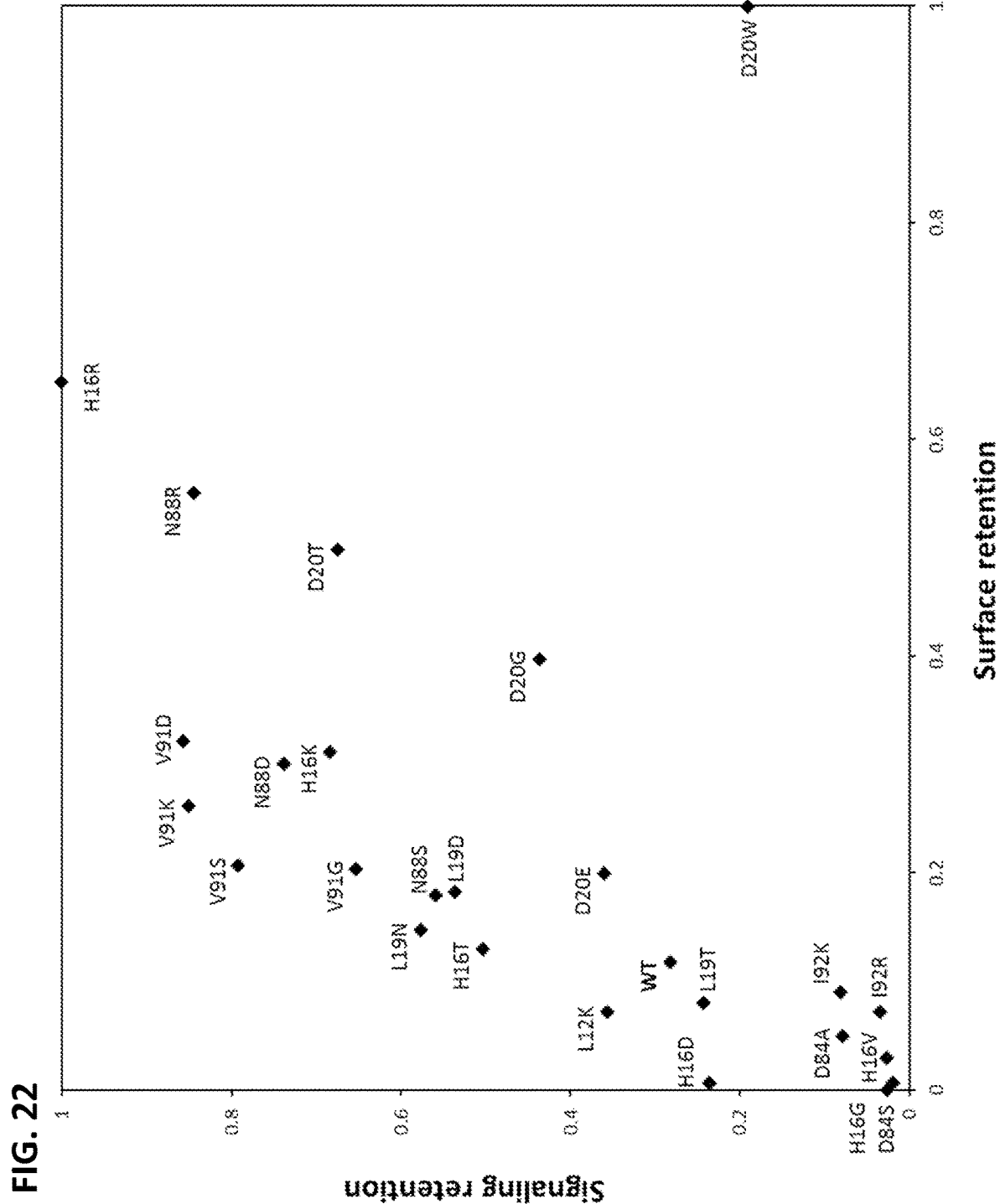


FIG. 23A

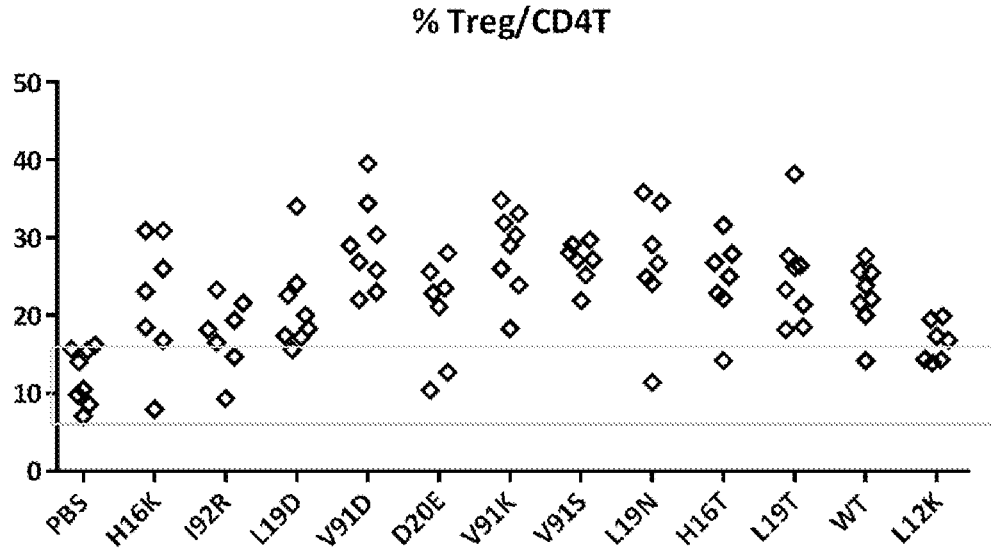
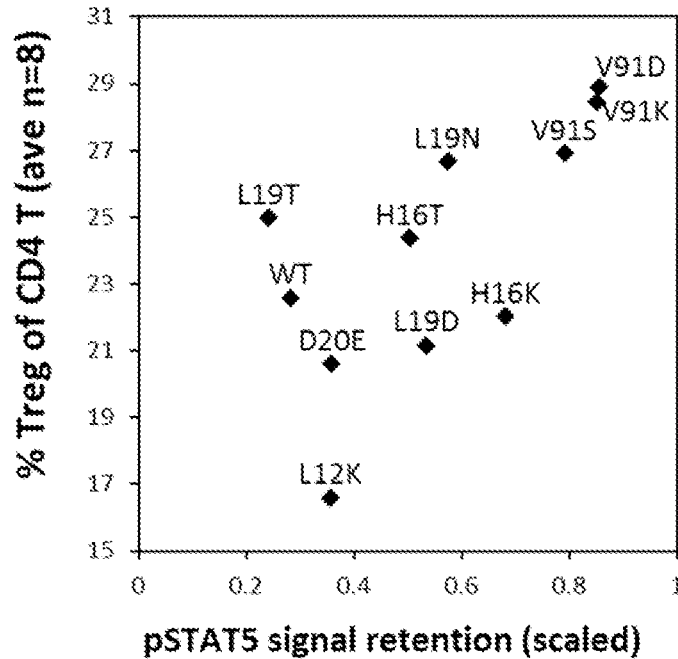


FIG. 23B



**FIG. 24A** Fc(N297G\_delK)::G4S::IL-2(L12G, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQGQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(L12K, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQKQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(L12Q, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQQQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(L12S, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQSQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

**FIG. 24B** IgG1Fc(N297G\_delK)::G4S::huIL-2(Q13G, C125A)

**MDMRVPAQLLGLLLLWLRGARC** DKTHTCPPCPAPPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLGLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISINIVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(E15A, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG GG  
GGSAPTSSSTKKTQLQLAHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISINIVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(E15G, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLGHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISINIVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(E15S, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLSHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISINIVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

**FIG. 24C** IgG1Fc(N297G\_delK)::G4S::huIL-2(H16A, C125A)

**MDMRVPAQLLGLLLLWLRGARC** DKTHTCPPCPAPPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEALLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISINIVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16D, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG GG  
GGSAPTSSSTKKTQLQLEDLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISINIVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16G, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEGLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISINIVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16K, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEKLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISINIVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

**FIG. 24D** IgG1Fc(N297G\_delK)::G4S::huIL-2(H16M, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GG*SAPTSSSTKKTQLQLEMLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16N, C125A)

**MDMRVPAQLLGLLLLWLRGARC** *DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GG*SAPTSSSTKKTQLQLENLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16R, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GG*SAPTSSSTKKTQLQLERLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16S, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GG*SAPTSSSTKKTQLQLESLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT



**FIG. 24E** IgG1Fc(N297G\_delK)::G4S::huL-2(H16T, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLETL~~LL~~DLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

IgG1Fc(N297G\_delK)::G4S::huL-2(H16V, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEVL~~LL~~DLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

IgG1Fc(N297G\_delK)::G4S::huL-2(H16Y, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLE~~Y~~LL~~LL~~DLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

IgG1Fc(N297G\_delK)::G4S::huL-2(L19A, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLADLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

**FIG. 24F** IgG1Fc(N297G\_delK)::G4S::huL-2(L19D, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(L19E, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(L19G, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(L19N, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

**FIG. 24G** IgG1Fc(N297G\_delK)::G4S::huL-2(L19R, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLRDLMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(L19S, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLSDLQMLNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(L19T, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLDLMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(L19V, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLVDLMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

**FIG. 24H** IgG1Fc(N297G\_delK)::G4S::huL-2(D20A, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLALQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(D20E, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLELQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(D20F, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLFLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(D20G, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLGLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

**FIG. 24I** IgG1Fc(N297G\_delK)::G4S::huL-2(D20W, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLWLMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

IgG1Fc(N297G\_delK)::G4S::huL-2(M23R, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQRIINGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

IgG1Fc(N297G\_delK)::G4S::huL-2(R81A, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMIINGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

IgG1Fc(N297G\_delK)::G4S::huL-2(R81G, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMIINGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISININVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

**FIG. 24J** IgG1Fc(N297G\_delK)::G4S::huIL-2(R81S, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLSRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(R81T, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLTPRDLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huIL-2(D84A, C125A)

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

IgG1Fc(N297G\_delK)::G4S::huIL-2(D84E, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRELISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

**FIG. 24K** IgG1Fc(N297G\_delK)::G4S::huL-2(D84G, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GG***SAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRGLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT**

IgG1Fc(N297G\_delK)::G4S::huL-2(D84I, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GG***SAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRILISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT**

IgG1Fc(N297G\_delK)::G4S::huL-2(D84M, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GG***SAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRMLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT**

IgG1Fc(N297G\_delK)::G4S::huL-2(D84Q, C125A)

**MDMRVPAQLLGLLLLWLRGARC***DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GG***SAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRQLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT**

**FIG. 24L** IgG1Fc(N297G\_delK)::G4S::huL-2(D84R, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRRLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(D84S, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRSLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(D84T, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRTLISNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(S87R, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLIRNINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT



**FIG. 24M** IgG1Fc(N297G\_delK)::G4S::huL-2(N88A, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISAINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(N88E, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISEINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(N88F, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISFINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(N88G, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISGINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

**FIG. 24N** IgG1Fc(N297G\_delK)::G4S::huL-2(N88M, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISMINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(N88S, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISSINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(N88V, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISVINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(N88W, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISWINVIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

**FIG. 240** IgG1Fc(N297G\_delK)::G4S::huL-2(V91D, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINDIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(V91E, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINEIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(V91G, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINGIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

IgG1Fc(N297G\_delK)::G4S::huL-2(V91S, C125A)

**MDMRVPAQLLGLLLLWLRGARC**DKTHTCPPCPAPELLGGPSVFLFPPKPK  
DTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS  
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV  
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL  
DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG  
GGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP  
KKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINSIVLELK  
GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT

**FIG. 24P** IgG1Fc(N297G\_delK)::G4S::huIL-2(I92K, C125A)

**MDMRVPAQLLGLLLLWLRGARCDKTHTCPPELGGPSVFLFPPKPK**  
*DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS*  
*TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV*  
*YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL*  
*DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG*  
GG*SAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP*  
*KKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINVKVLELK*  
*GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

IgG1Fc(N297G\_delK)::G4S::huIL-2(I92R, C125A)

**MDMRVPAQLLGLLLLWLRGARCDKTHTCPPELGGPSVFLFPPKPK**  
*DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS*  
*TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV*  
*YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL*  
*DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG*  
GG*SAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP*  
*KKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINVRVLELK*  
*GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

IgG1Fc(N297G\_delK)::G4S::huIL-2(E95G, C125A)

**MDMRVPAQLLGLLLLWLRGARCDKTHTCPPELGGPSVFLFPPKPK**  
*DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGS*  
*TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV*  
*YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL*  
*DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGGG*  
GG*SAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMP*  
*KKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINIVVGLK*  
*GSETTFMCEYADETATIVEFLNRWITFAQSIISTLT*

**FIG. 25A**

Fc(N297G\_delK)::G4S::IL-2(L12G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgcacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccagcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaaGGGcaatt  
ggagcacttggtggttgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaa  
ggttccgagactacttttatgtgtgagtagctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hull-2(L12K, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgcacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccagcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaaAAGcaatt

**FIG. 25B**

ggagcacttggttggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcggtggtatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(L12Q, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgaggaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccagcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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ggagcacttggttggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcggtggtatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(L12S, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgaggaggagcagtagcggcagc

**FIG. 25C**

acgtaccgtgtgggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgacctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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ggtggaagcgcctccaacttctcctccactaagaagactcaaTCGcaatt  
ggagcacttggttggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagttttgaaatcggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(Q13G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaaactcctggggggaccgtcagcttctcctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtgggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgacctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
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ggtggaagcgcctccaacttctcctccactaagaagactcaattgGGAtt  
ggagcacttggttggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagttttgaaatcggtggatcacttttgctcaatccatcatctcca  
ctttgact

**FIG. 25D**

IgG1Fc(N297G\_delK)::G4S::huIL-2(E15A, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgga  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
gGGCacttggtggttgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggagggttttgaatttggtcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(E15G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgga  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
gGGCacttggtggttgacttgcaaatgatcttgaatggtatcaataatt



**FIG. 25E**

acaagaatccaaagttgactcggatgttgacttttaagttttacatgccaa  
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtagcgtgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(E15S, C125A)

atggacatgagagtgctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccggaggagatgaccaagaaccaggtcagcct  
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ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
gTCGcacttggtggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatgttgacttttaagttttacatgccaa  
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtagcgtgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16A, C125A)

atggacatgagagtgctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa

**FIG. 25F**

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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gactccgacggctccttcttctctatagcaagctcacctgggacaagag  
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tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16D, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaactcctggggggaccgtcagctcttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
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acgtaccgtgtggtcagcgtcctcacctcctgcaccaggactggctgaa  
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tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccagcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcacctgggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
ggagGACTtggtggtggacttgcaaatgatcttgaatggtatcaataatt  
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aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

**FIG. 25G**

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
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ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagGGCttggttggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagtggaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16K, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagAAGttggttggacttgcaaatgatcttgaatggtatcaataatt

**FIG. 25H**

acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatgtttgaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16M, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttccctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttccctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtccttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttccctcctcactaagaagactcaattgcaatt  
ggagATGttggtggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatgtttgaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16N, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttccctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa

**FIG. 25I**

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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ggagAActtggttggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagttttgaaatcggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16R, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaaactcctgggggacggctcagtcttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
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tggaggtgcataatgccaaagacaaagccgcccggaggagcagtagcgc  
acgtaccgtggtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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ggagCGCttggttggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagttttgaaatcggtggatcacttttgctcaatccatcatctcca  
ctttgact

**FIG. 25J**

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16S, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
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tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagAGCttggtggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagtggaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16T, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
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acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
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tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
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ggagACCttggtggtggacttgcaaatgatcttgaatggtatcaataatt

**FIG. 25K**

acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16V, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttccctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
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tacaccctgccccatcccggaggagatgaccaagaaccaggtcagcct  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(H16Y, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttccctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa

**FIG. 25L**

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
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ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcc  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(L19A, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaactcctggggggaccgtcagctcttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
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acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
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agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
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ggagcacttgttgGCGgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcc  
ctttgact



**FIG. 25M**

IgG1Fc(N297G\_delK)::G4S::hulL-2(L19D, C125A)

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gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggacccctgaggtcacatgctggtggtgga  
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tggaggtgcataatgccaaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
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tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(L19E, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggacccctgaggtcacatgctggtggtgga  
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tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
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ggagcacttggtgGAGgacttgcaaatgatcttgaatggtatcaataatt

**FIG. 25N**

acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatgtttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(L19G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
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gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
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acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatgtttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(L19N, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcacctgctcaccaggactggctgaa

**FIG. 250**

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtgAATgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(L19R, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaaactcctggggggaccgtcagtccttcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgagggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcccggaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
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ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtgCGGgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

**FIG. 25P**

IgG1Fc(N297G\_delK)::G4S::hulL-2(L19S, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggacccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtgTCGgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(L19T, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggacccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtgACGgacttgcaaatgatcttgaatggtatcaataatt

**FIG. 25Q**

acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatgtttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtagctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(L19V, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgctggtcaaaggtctctatcccagcgacatcgccgtggagtggtg  
agagcaatgggcagccggagaacaactacaagaccagcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
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ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtgGTGgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatgtttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtagctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(D20A, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg

**FIG. 25R**

tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgcacatcgccgtggagtgagg  
agagcaatgggcagccggagaacaactacaagaccagcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgcctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtgGCCttgcaaagtatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(D20E, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgacgacaaaactcacacatgccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgaggaggagcagtcaggcagc  
acgtaccgtggtgagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgcacatcgccgtggagtgagg  
agagcaatgggcagccggagaacaactacaagaccagcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
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ggtggaagcgcctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtgGAGttgcaaagtatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcca  
ctttgact

## FIG. 25S

IgG1Fc(N297G\_delK)::G4S::huIL-2(D20F, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgacgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
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acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggtg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
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aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(D20G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgacgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggtg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtgGGCttgcaaatgatcttgaatggtatcaataatt

**FIG. 25T**

acaagaatccaaagttgactcggatggttgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(D20W, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggttctatcccagcgacatcgccgtggagtggtg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtccttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
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ggccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(M23R, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa



## FIG. 25U

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggttgacttgcaaAGGatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(R81A, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgctgccagcac  
ctgaaactcctggggggaccgtcagtccttcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
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tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggttgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
CGccacgggacttgatctccaatatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

**FIG. 25V**

IgG1Fc(N297G\_delK)::G4S::hulL-2(R81G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgagg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgG  
GGccacgggacttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(R81S, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgagg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtggacttgcaaatgatcttgaatggtatcaataatt

**FIG. 25W**

acaagaatccaaagttgactcggatggtgacttttaagttttacatgccaa  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttacttgT  
CGccacgggacttgatctccaatatcaatgtgatcgTTTTGGAGTTGAAG  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgTTGAGTTTTGAATCGGTGGATCACTTTTGCTCAATCCATCATCTCCA  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(R81T, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccggaggagatgaccaagaaccaggctcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtccttctcatgctccgtgatgcatgaggctc  
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ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgccaa  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttacttgA  
CGccacgggacttgatctccaatatcaatgtgatcgTTTTGGAGTTGAAG  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgTTGAGTTTTGAATCGGTGGATCACTTTTGCTCAATCCATCATCTCCA  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(D84A, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa

**FIG. 25X**

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggttgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacggGCCttgatctccaatatcaatgtgatcgttttggagttgaa  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(D84E, C125A)

atggacatgagagtgccctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccggtgccagcac  
ctgaaactcctggggggaccgtcagtccttcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgagggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcccggaggagcagtagcgcagc  
acgtaccgtggtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggttgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacggGAGttgatctccaatatcaatgtgatcgttttggagttgaa  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

**FIG. 25Y**

IgG1Fc(N297G\_delK)::G4S::hulL-2(D84G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacggGGCttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(D84I, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtggacttgcaaatgatcttgaatggtatcaataatt

**FIG. 25Z**

acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacggATCttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(D84M, C125A)

atggacatgagagtgccctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtccttctcatgctccgtgatgatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacggATGttgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(D84Q, C125A)

atggacatgagagtgccctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa

**FIG. 25AA**

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggttgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggtcaatccaagaattttcacttgc  
ggccacggCAGttgatctccaatatcaatgtgatcgttttggagttgaa  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagttttgaaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(D84R, C125A)

atggacatgagagtgccctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgagggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcccggaggagcagtagcgc  
acgtaccgtggtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggtcaatccaagaattttcacttgc  
ggccacggCGCttgatctccaatatcaatgtgatcgttttggagttgaa  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagttttgaaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

**FIG. 25BB**

IgG1Fc(N297G\_delK)::G4S::hulL-2(D84S, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggctcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggtg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacggAGCttgatctccaatatcaatgtgatcgttttggagttgaa  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(D84T, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggctcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggtg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtggacttgcaaatgatcttgaatggtatcaataatt



**FIG. 25CC**

acaagaatccaaagttgactcggatgttgacttttaagttttacatgccaa  
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacggACCTtgatctccaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtagcgtgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(S87R, C125A)

atggacatgagagtgacctgcacagctgctgggcctgctgctgctgtggct  
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ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
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acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
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tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggtg  
agagcaatgggcagccgggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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acaagaatccaaagttgactcggatgttgacttttaagttttacatgccaa  
aagaaggctactgagttgaagcacttgcaatgtttggaggaggagttgaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatcCGCaatatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtagcgtgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(N88A, C125A)

atggacatgagagtgacctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa

**FIG. 25DD**

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
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ggagcacttggtggttgacttgcaaatgatcttgaatggtatcaataatt  
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gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccGCTatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(N88E, C125A)

atggacatgagagtgccctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaaactcctggggggaccgtcagtccttcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgggaggagcagtacggcagc  
acgtaccgtggtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
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aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccGAGatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

**FIG. 25EE**

IgG1Fc(N297G\_delK)::G4S::huIL-2(N88F, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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ggagcacttggtggtgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagtggaa  
gccattggaggagggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccTTTatcaatgtgatcgtttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgcctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(N88G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
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tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtgacttgcaaatgatcttgaatggtatcaataatt

**FIG. 25FF**

acaagaatccaaagttgactcggatgttgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatgtttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttacttgc  
ggccacgggacttgatctccGGTatcaatgtgatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(N88M, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtagcggcagc  
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tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(N88S, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaagacaaagccgcgaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa

## FIG. 25GG

tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
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gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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ggagcacttggtggtggacttgcaaatgatcttgaatggtatcaataatt  
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ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagttttgaaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(N88V, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgagggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgaggaggagcagtagcgcagc  
acgtaccgtggtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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ggccacgggacttgatctccGTTatcaatgtgatcgttttggagttgaa  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagttttgaaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

**FIG. 25HH**

IgG1Fc(N297G\_delK)::G4S::huIL-2(N88W, C125A)

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gagagggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
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gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
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tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
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ggttccgagactacttttatgtgtgagtagcgtgacgagactgctactat  
cgttgagttttgaaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(V91D, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagagggcgccagatgcgacaaaactcacacatgcccaccgtgccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
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tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
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gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt

**FIG. 25II**

ggtggaagcgctccaacttcctcctccactaagaagactcaattgcaatt  
ggagcacttggtggttgacttgcaaatgatcttgaatgggatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatGATatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagttttgaaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(V91E, C125A)

atggacatgagagtgctgcacagctgctgggcctgctgctgctggtgct  
gagaggcgccagatgcgacaaaactcacacatgccaccgctgccagcac  
ctgaactcctggggggaccgctcagtcctcctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
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tacaccctgcccccatcccggaggagatgaccaagaaccaggtcagcct  
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ggagcacttggtggttgacttgcaaatgatcttgaatgggatcaataatt  
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aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
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ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagttttgaaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(V91G, C125A)

atggacatgagagtgctgcacagctgctgggcctgctgctgctggtgct  
gagaggcgccagatgcgacaaaactcacacatgccaccgctgccagcac  
ctgaactcctggggggaccgctcagtcctcctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg

**FIG. 25JJ**

tggaggtgcataatgccaaagacaaagccgcgaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccagggtcagcct  
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acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatGGGatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcggtggatcacttttgcctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(V91S, C125A)

atggacatgagagtgctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaactcctggggggaccgtcagcttctcctcttcccccaaaaaccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggagcagtagcggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccagcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggtggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatTCGatcgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat



**FIG. 25KK**

cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(I92K, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgcacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccgtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgtccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttgttgttgacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcca  
aagaaggctactgagttgaagcacttgcaatggttggaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgAAGgttttggagttgaag  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::hulL-2(I92R, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgcccaccgtgcccagcac  
ctgaactcctggggggaccgtcagtccttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgcacatcgccgtggagtggg  
agagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg

**FIG. 25LL**

gactccgacggctccttcttctctatagcaagctcaccggtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgcctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggttggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgAGAgttttggagttgaa  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

IgG1Fc(N297G\_delK)::G4S::huIL-2(E95G, C125A)

atggacatgagagtgcctgcacagctgctgggcctgctgctgctgtggct  
gagaggcgccagatgcgacaaaactcacacatgccaccgtgccagcac  
ctgaactcctggggggaccgtcagctcttctcttccccccaaaacccaag  
gacaccctcatgatctcccggaccctgaggtcacatgctggtggtgga  
cgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcg  
tggaggtgcataatgccaaagacaaagccgcgaggagcagtacggcagc  
acgtaccgtgtggtcagcgtcctcaccgctcctgcaccaggactggctgaa  
tggcaaggagtacaagtgaaggtctccaacaaagccctcccagccccca  
tcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtg  
tacaccctgcccccatcccgggaggagatgaccaagaaccagggtcagcct  
gacctgcctggtcaaaggcttctatcccagcgcacatcgccgtggagtggt  
agagcaatgggcagccggagaacaactacaagaccagcctcccgtgctg  
gactccgacggctccttcttctctatagcaagctcaccggtggacaagag  
caggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc  
tgcacaaccactacacgcagaagagcctctccctgtctccgggtggaggt  
ggtggaagcgcctccaacttctcctccactaagaagactcaattgcaatt  
ggagcacttggttggtggacttgcaaatgatcttgaatggtatcaataatt  
acaagaatccaaagttgactcggatggtgacttttaagttttacatgcc  
aagaaggctactgagttgaagcacttgcaatggttgaggaggagttgaa  
gccattggaggaggttttgaatttggctcaatccaagaattttcacttgc  
ggccacgggacttgatctccaatatcaatgtgatcgttttgGGGttgaa  
ggttccgagactacttttatgtgtgagtacgctgacgagactgctactat  
cgttgagtttttgaatcgggtggatcacttttgctcaatccatcatctcca  
ctttgact

FIG. 26 Light Chain Variable Domain Amino Acid Sequences

	FR1	FR2	CDR2	FR3	CDR3	FR4
9D6	DIVMTQTPLSPVTPGEPASISCRSSQSLDDEGNTYLDWYLQKPGQSPQLLIYTLISYRASGVPDRFSGTSDTFTLKISRVEAEDGYYCMQRIEFLTFGGGTKVEIKR					
2C3	EIVLTQSPGTLSPGERATLSCRASQSFSSYLWYQKPGQAPRLLIY <b>GASSRAUG</b> IPDRFGSGSGTDFLTISRLEPEDFAVYYC <b>QQYGS</b> SPLTFGGGTKVEIKR					
14C9	DIVLTQTPLSPVTLGQPASISCRSS <b>SHL</b> IHSDGNTYLSWLQRPQPPRLLIY <b>KISNRF</b> SVPDRFTSGTGTDFTLKISRVEAGDVGYV <b>CMQT</b> QFPTFGQGTKVEIKR					
8B12	DIVMTQTPSSPVTLGQPASISCRSSQNLVQSDGNTYLSWLHQRPGPPRLLIY <b>KISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQT</b> QFPTFGQGTKVEIKR					
16A4	DIVMTQTPSSPVTLGQPASISCRSSQILVNSDGNNTYLSWLHQRPGPPRLLIY <b>KISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQT</b> QFPTFGQGTKVEIKR					
16E1	DIVMTQTPSSPVTLGQPASISCRSSQSLVRSNGNTYLSWLHQRPGPPRLLIY <b>KISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQT</b> QFPTFGQGTKVEIKR					
13A1	DIVMTQTPSSPVTLGQPASISCRSSHSLVHSDGHTYLSWLQRPQPPRLLIY <b>KISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQT</b> QFPTFGGGTKVEIKR					
8F10	DIAMSQPLSPVTPGEPASMSCRSSQSLHNSGFNYLDWYLQKPGQSPQLLIY <b>HLSGDRAS</b> GVPDRFSGSGTDFTLKISRVEAEDGYY <b>CMQALQ</b> TPLTFGGGTKVEIKR					
12C4	DIVMTQSPPLSPVTPGEPASISCRSSQSLHNSGFNYLDWFLQKPGQSPQLLIY <b>LGSDRAS</b> GVPDRFSGSGTDFTLKISRVEAEDGYY <b>CMQALQ</b> TPLTFGGGTKVEIKR					
9B12	DIVMTQSPPLSPVTPGEPASISCRSSQSLHNSGFNYLDWYLQKPGQSPQLLIY <b>LGSDRAS</b> GVPDRFSGSGTDFTLKISRVEAEDGYYV <b>CMQALQ</b> TPLTFGGGTKVEIKR					
3H5	DIVMTQTPSSPVTLGQPASISCRSSQSLVNIIDGSTHLSWLQRPQPPRLLIY <b>KISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQT</b> QFPTFGQGTKVEIKR					
18A6	DIVMTQTPSSPVTLGQPASISCRSSQSLVQSDGITYLSWLQRPQPPRLLIY <b>KISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQT</b> QFPTFGQGTKVEIKR					
10A6	DIVMTQTPSSPVTLGQPASISCRSSQSLVNSDGNNTYLSWLQRPQPPRLLIY <b>KISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQATQ</b> FPTFGQGTKVEIKR					
10H7	DIVMTQTPSSPVTLGQPASISCRSSHNLVRSNGNTYLSWLQRPQPPRLLIY <b>KISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQATQ</b> FPTFGQGTKVEIKR					
15A10	NIVMTQTPSSPVTLGQPASISCRSSQSLVQSDGNTYLSWLQRPQPPRLLIY <b>KISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQT</b> QFPTFGQGTKVEIKR					
12D2	DIVMTQTPSSPVTLGQPASISCRSSHNLVRSNGNTYLSWLHQRPGPPRLLIY <b>KISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQT</b> QFPTFGQGTKVEIKR					
9B10	DIVMTQTPSSPVTLGQPASISCRSSHNLVRSNGNTYLSWLQRPQPPRLLIY <b>YEISNRF</b> SVPDRFSGSGAGTDFTLKISRVEAEDGYYV <b>CMQT</b> QFPTFGGGTKVEIKR					
17D3	EIVLTQSPGTLSPGERATLSCRASQSVSSYLAWYQKPGQAPRLLIY <b>GASSRAUG</b> IPDRFSGSGTDFLTISRLEPEDFAVYYC <b>QQVGS</b> SPLTFGGGTKVEIKR					
15G11	EIVLTQSPGTLSPGERATLSCRASQSVSSRYLAWYQKPGQAPRLLIY <b>HGPFRAUG</b> IPDRFSGSGTDFLTISRLEPEDFAVYYC <b>QQVGN</b> SSITFGQGTKVEIKR					
14D7	DIVMTQSPSSLSASVGDVRTITCRASQTISSYLNWYQKPKAPKPLIY <b>AASSRFQ</b> SGVPSRFSGSGTDFLTISRLEPEDFAVYYC <b>QQSHY</b> IPRTPFGQGTKVEIKR					
18F3	SYELTQPPSVSPGQTARIACSGDALPRKFAYWYQKSGQAPVLI <b>SEDSR</b> PSGIPERFSGSSGTEFTLTISGLQPEDFATY <b>YCS</b> FDSDSANHRVFGGGTKLVIG					
17D9	DIVMTQSPSSLSASVGDVRTITCRASQDIRNDLWYQKPGKAPKPLIY <b>AASSLQ</b> SGVPSRFSGSGTEFTLTISGLQPEDFATY <b>YCS</b> FDSDSANHRVFGGGTKVEIKR					
21F8	DIVMTQSPSSLSASVGDVRTITCRASQDIRDLGMYQKPGKAPKPLIY <b>IATSLQ</b> SGVPSRFSGSGTEFTLTISGLQPEDFATY <b>YCS</b> FDSDSANHRVFGGGTKVEIKR					
22B9	DIVMTQSPSSLSASVGDVRTITCRASQDIRDLGMYQKPGKAPKPLIY <b>VASSLQ</b> SGVPSRFSGSGTEFTLTISGLQPEDFATY <b>YCS</b> FDSDSANHRVFGGGTKVEIKR					
21D10	DIVMTQSPSSLSASVGDVRTITCRASQDIRDLGMYQKPGKAPKPLIY <b>VVSSLQ</b> SGVPSRFSGSGTEFTLTISGLQPEDFATY <b>YCS</b> FDSDSANHRVFGGGTKVEIKR					
14A6	DIVMTQSPSSLSASVGDVRTITCRASQIGIGDLDWYQKPGKAPKPLIY <b>SASSLPS</b> GVPSRFSGSGTEFTLTISGLQPEDFATY <b>YCS</b> FDSDSANHRVFGGGTKVEIKR					
11D6	DIVMTQSPSSLSASVGDVRTITCRASQDIEHDLGMYQKPGKAPKPLIY <b>AASTLPS</b> GVPSRFSGSGTEFTLTISGLQPEDFATY <b>YCS</b> FDSDSANHRVFGGGTKVEIKR					
10A9	DIVMTQTPSLPVTGEPASISCRSTQSLDGDGNTYLDWYLQKPGQSPQLLIY <b>YTLISYRAS</b> GVPDRFSGSGTDFTLKISRVEAEDGYYV <b>CMQRIE</b> FPLTFGGGTKVEIKR					
16E3	DIVMTQTPSLPVTGEPASISCRSSQSLDSDGNTYLDWYLQKPGQSPQLLIY <b>YTLISYRAS</b> GVPDRFSGSGTDFTLKISRVEAEDGYYV <b>CMQRIE</b> FPLTFGGGTKVEIKR					
14G7	DIVMTQSPSSLSASVGDVRTITCRASQDISNYLNWYQKPKAPKPLIY <b>DASNLET</b> GVPSRFSGSGTEFTLTISRLEPEDFAVYYC <b>QQYENL</b> PFTFGPGTKVDIKR					
5H3	SYELTQPPSVSPGQTARITCSGDALPRKYAYWYQKSGQAPVLIY <b>YEDSKR</b> PSGIPERFSGSSGTEFTLTISGLQPEDFATY <b>YCS</b> ADSDSGTYVFGGGTKLVIG					
2B12	SYELTQPPSVSPGQTARITCSGDALPRKYAYWYQKSGQAPVLIY <b>YEDSKR</b> PSGIPERFSGSSGTEFTLTISGLQPEDFATY <b>YCS</b> ADSDSGTYVFGGGTKLVIG					
26H7	DIVMTQSPSSLSASVGDVRTITCRASQDISNYLNWYQKPKAPKPLIY <b>DASNLET</b> GVPSRFSGSGTEFTLTISRLEPEDFAVYYC <b>QQDNDL</b> PFTFGPGTKVDIKR					
26C12	DIVMTQSPSSLSASVGDVRTITCRASQDISNYLNWYQKPKAPKPLIY <b>DASNLET</b> GVPSRFSGSGTEFTLTISRLEPEDFAVYYC <b>QQDNDL</b> PFTFGPGTKVDIKR					
2H11	SYELTQPPSVSPGQTARITCSGDALPRKFAYWYQKSGQAPVLIY <b>YEDKR</b> PSGIPERFSGSSGTEFTLTISGLQPEDFATY <b>YCS</b> YDSDSGHVVFGGGTKLVIG					
18H9	DIVMTQSPSSVSASVGDVRTITCRASQGISNMLVWYQKPKPKPLIY <b>YAASSLQ</b> NGVPSRFSGSGTDFLTISRLEPEDFAVYYC <b>QQALS</b> FVFWTFGPGTKVEYKR					

## FIG. 27A

### Light Chain Nucleic Acid Sequences

9D6

GATATTGTGATGACCCAGACTCCACTCTCCTTGCCCCTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG  
TCAGAGCCTCTTAGATAGTGATGAGGGAAACACCTATTTGGACTGGTACCTGCAGAAGCCAGGGCAGTCTCCACA  
GTCCTGATCTATACGCTTTCCTATCGGGCCTCTGGAGTCCCAGACAGGTTCAAGTGGCACTGGGTGAGACACTGAT  
TTCACACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGAGTTTATTACTGCATGCAACGTATAGAGTTTCCTC  
TCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

2C3

GAAATTGTATTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCA  
GTCAGAGTTTTAGCAGCAGCTACTTAGTCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGG  
TGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTTCGGTGGCAGTGGGTCTGGGACAGACTTCACTCTACCCAT  
CAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTAGCTCACCTCTCACTTTCGGCGGA  
GGGACCAAGGTGGAGATCAAACGA

14C9

GATATTGTGCTGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG  
TCATCACCTCATAACAGTGATGGAAACACCTACTTGAGTTGGCTTCCAGCAGAGGCCAGGCCAGCCTCCAAGACTC  
CTAATTTATAAGATTTCTAACCAGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGACAGGGACAGATTTCA  
CACTGAAAATCAGCAGGGTGGAAAGCTGGGGATGTCGGGGTTTATTACTGCATGCAAACACTACACAATTTCCGACGT  
TCGGCCAAGGGACCAAGGTGGAAATCAAACGA

8B12

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCCAG  
TCAAAACCTCGTTCAAAGTGATGGAAACACCTACTTGAGTTGGCTTCCAGCAGAGGCCAGGCCAGCCTCCAAGACTC  
CTAATTTATAAGATTTCTAACCAGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA  
CACTGAAAATCAGCAGGGTGGAAAGCTGAGGATGTCGGGGTTTATTTCTGCATGCAAACACTACACAATTTCCGACGT  
CGGCCAAGGGACCAAGGTGGAAATCAAACGA

**FIG. 27B**

16A4

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTACCCTTGGACAGCCGGCCTCCATTTCTGCAGGTCTAG  
TCAAATCCTCGTAAACAGTGATGGAAACACCTACTTGAGTTGGCTTCACCAGAGGCCAGGCCAGCCTCCAAGACTC  
CTAATTTATAAGATTTCTAACC GGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA  
CACTGAAAATCAGCAGGGTGGAAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACACTACACAATTTCCGACGT  
TCGGCCAAGGGACCAAGGTGGAAATCAAACGA

16E1

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG  
TCAAAGCCTCGTACGCAGTGATGGAAACACCTACTTGAGTTGGCTTCACCAGAGGCCAGGCCAGCCTCCAAGACT  
CCTAATTTATAAGATTTCTAACC GGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA  
AACTGAAAATCAGCAGGGTGGAAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACACTACACAATTTCCGACG  
TTCGGCCAAGGGACCAAGGTGGAAATCAAACGA

13A1

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG  
TCACAGCCTCGTACACAGTGATGGACACACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACTC  
CTACTTTATAAGATTTCTAACC GGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA  
CACTGAAAATCAGCAGGGTGGAAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACACTACACAATTTCCCACTTT  
CGGCGGAGGGACCAAGGTGGAGATCAAACGA

8F10

GATATTGCGATGAGTCAGTCTCCACTCTCCCTGCCCGTACCCTTGGAGAGCCGGCCTCCATGTCATGCAGGTCTA  
GTCAGAGCCTCCTGCATAGTAATGGATTCAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGGT  
CCTGATCCATTTGGGTTCTGATCGGGCCTCCGGGGTCCCTGACAGGTTTCAAGTGGCAGTGGATCAGGCACAGATTTT  
ACATTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGAATTTATTACTGCATGCAAGCTCTACAAACTCCTCTCA  
CTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

## FIG. 27C

12C4

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG  
TCAGAGCCTCCTACATAGTAATGGATTCAACTATTTGGATTGGTTCCTGCAGAAGCCAGGACAGTCTCCACAGCCC  
CTGATCTATTTGGGTTCTGATCGGGCCTCCGGGGTCCCTGACAGGTTTCAGTGGCAGTGGATCAGGCACAGATTTTA  
CACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAAACTCCGCTCA  
CTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

9B12

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG  
TCAGAGCCTCCTGCATAGTAATGGATTCAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTC  
CTGATCTATTTGGGTTCTGATCGGGCCTCCGGGGTCCCTGACAGGTTTCAGTGGCAGTGGATCAGGCACAGATTTTA  
CACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAAACTCCGCTCA  
CTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

3H5

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCCTGGACAGCCGGCCTCCATATCCTGCAGGTCCAG  
TCAAAGCCTCGTAAACATTGATGGAAGTACCCACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACT  
CCTAATTTATAAGATTTCTAACCGTTCTCTGGGGTCCCAGACAGATTTCAGTGGCAGTGGGGCAGGGACAGATTTCA  
AACTGAAGATCAGCAGGGTGGAAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACTACACAATTTCCCCACC  
TTCGGCCAAGGGACACGACTGGAGATTAACGA

18A6

GAAATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCCTGGACAGCCGGCCTCCATTTCTCCTGCAGGTCTAG  
TCAAAGCCTCGTTCAGAGTGATGGAATCACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACTC  
CTAATTTATAAGATTTCTAACCGTTCTCTGGGGTCCCAGACAGATTTCAGTGGCAGTGGGGCAGGGACAGATTTCA  
CACTGAAAATCAGCAGGGTGGAAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACTACACAATTTCCGACGT  
TCGGCCAAGGGACCAAGGTGGAAATCAAACGA

**FIG. 27D**

10A6

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG  
TCAAAGCCTCGTAAACAGTGATGGAAACACCTACTTGAATTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACT  
CCTAATTTATAAGATTTCTAACCGTTCTCTGGGGTCCCAGACAGATTTCAGTGGCAGTGGGGCAGGGACAGATTTT  
ACACTGAAAATCAGCAGGGTGGAAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAGCTACACAATTTCCGACG  
TTCGGCCAAGGGACCAAGGTGGAAATCAAACGA

10H7

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCCAG  
TCACAACCTCGTACGCAGTGATGGAAACACCTACTTGAATTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACT  
CCTAATTTATAAGATTTCTAACCGTTCTCTGGGGTCCCAGACAGATTTCAGTGGCAGTGGGGCAGGGACAGATTTT  
ACACTGAAAATCAGCAGGGTGGGAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAGCTACACAATTTCCCACC  
TTCGGCCAAGGGACGCGACTGGAGATTAACGA

15A10

AATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG  
TCAAAGCCTCGTACAAACTGATGGAAACACATATTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACC  
CCTAATTTATAAGATTTCTAACCGTTTTCTCTGGGGTCCCAGACAGATTTCAGTGGCAGTGGGGCAGGGACAGATTTT  
ACACTGAAAATCAGCAGGGTGGAAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAGTAAACACAATTTCCCACC  
TTCGGCCAAGGGACACGACTGGAGATTAACGA

12D2

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGTAGGTCTAG  
TCATAACCTCATAACAGTGATGGAAACACCTACTTGAATTGGCTTCACCAGAGGCCAGGCCAGCCTCCAAGACTC  
CTAATTTATAAGATTTCTAACCGTTCTCTGGGGTCCCGGACAGATTTCAGTGGCAGTGGGGCAGGGACAGATTTT  
CACTGAAAATCAGCAGGGTGGAAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAACTTCACAGTTTCCCCTTT  
CGGCGGAGGGACCAAGGTGGAGATCAAACGA

**FIG. 27E**

9B10

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCATCTCCTGCAGGTCTAG  
TCATAACCTCCTACACAGTGATGGAAACACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAGCCTCCAAGACTC  
CTAATTTATGAGATTTCTAACCGTTCTCTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACAGATTTCA  
CACTGAAAATCAGCAGGGTGGAAAGCTGAGGATGTCGGGGTTTATTACTGCATGCAAGTTACACAATTTCCCACTTT  
CGGCGGCGGGACCAAGGTGGAGATCAAACGA

17D3

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCA  
GTCAGAGTGTTAGCAGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGG  
TGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCAT  
CAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTAGCTCACCGCTCACTTTGCGCGGA  
GGGACCAAGGTGGAGATCAAACGA

15G11

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGTAGGGCCA  
GTCAGAGTGTTAGCAGCAGGTAAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCCATG  
GTCCATTAGCAGGGCCACTGGCATCCCAGACAGGTTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCAT  
CAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTAATTCATCGATCACCTTCGGCCAA  
GGGACACGACTGGAGATTAACGA

14D7

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA  
GTCAGACCATTAGCAGTTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGGTCCTGATCTATGCTGC  
ATCCAGTTTCAAAGTGGGGTCCCATCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC  
AGTCTGCAACCTGAAGATTTTGAACCTTACTACTGTCAACAGAGTCACTATATCCCTCGGACGTTTCGGCCAAGGGA  
CCAAGGTGGAAATCAAACGA



**FIG. 27F**

18F3

TCCTATGAGCTGACACAGCCACCCTCGGTGTCAGTGTCCCCAGGACAAACGGCCAGGATCGCCTGCTCTGGAGAT  
GCATTGCCAAGAAAATTTGCTTATTGGTACCAGCAGAAGTCAGGCCAGGCCCTGTGCTGGTCATCTCTGAGGACA  
GCAGACGACCCTCCGGGATCCCTGAGAGATTCTCTGGCTCCAGCTCAGGGACAATGGCCACCTTGACTATCAGTG  
GGGCCAGGTGGAGGATGAAGCTGACTACTACTGTTTCTCAACAGACAGCAGTGCTAATCATAGGGTATTCGGCG  
GAGGGACCAAGCTGACCGTCCTAGGT

17D9

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA  
GTCAGGACATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTG  
CATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTGAGCGGCAGTGGATCTGGGACAGAATTCACTCTACAATCG  
GCAGCCTGCAGCCTGAAGATTTTACAACCTTATTACTGTCTACAGCATAATAGTTACCCGCTCACTTTCGGCGGAGG  
GACCAAGGTGGAGATCAAACGA

21F8

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA  
GTCAGGGCATTAGAGATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATATTG  
CAACCAGTTTGCAAAGTGGGGTCCCATCAAGGTTGAGCGGCAGTGGATCTGGGACAGAATTCACTCTACAATCA  
GCAGCCTGCAGCCTGAAGATTTTGAACCTTATTACTGTCTACAGCATATTAGTTACCCGTGGACGTTTCGGCCAAGG  
GACCAAGGTGGAAATCAAACGA

22B9

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA  
GTCAGGACATCAGAGATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGTTG  
CATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTGAGCGGCAGTGGATCTGGGACAGAATTCACTCTACAATCA  
GCAGCCTGCAGCCTGAAGATTTTGAACCTTATTACTGTCTACAGCATATTAGTTACCCGTGGACGTTTCGGCCAAGG  
GACCAAGGTGGAAATCAAACGA

## FIG. 27G

21D10

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA  
GTCAGGACATTAGAGATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGTTG  
TATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTGAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACAAATCA  
GCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATAATGGTTACCCGTGGACGTTTCGGCCAAGG  
GACCAAGGTGGAAATCAAACGA

14A6

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA  
GTCAGGGCATTGGAGATGATTTAGGCTGGTATCAGCAGAAGCCAGGAAAAGCCCCTCAGCGCCTGATCTATTCTG  
CATCCAGTTTGCCAAGTGGGGTCCCATCAAGGTTGAGCGGCAGTGGATCTGGGACAGAATTCCTCTCACAAATCA  
GCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCCTCGCAGTTTTGGCCAGGG  
GACCAAGCTGGAGATCAGACGA

11D6

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAA  
GTCAGGACATTGAACATGATTTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTG  
CATCCACTTTGCCAAGTGGGGTCCCATCAAGGTTGAGCGGCAGTGGATCTGGGACAGAATTCCTCTCACAAATCAG  
CAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTTCCCTCGCAGTTTTGGCCAGGGGA  
CCCAGCTGGAGATCAAACGA

10A9

GATATTGTGATGACCCAGACTCCACTCTCCCTGCCCCTGACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAC  
TCAGAGCCTCTTGGATGGTATGATGAAACACCCTTTGGACTGGTACCTGCAGAAGCCAGGGCAGTCTCCACA  
GCTCCTGATCTATACGCTTTCCTATCGGGCCTCTGGAGTCCAGACAGGTTGAGTGGCAGTGGGTCAGGCACTGAT  
TTCACACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGAGTTTATTACTGCATGCAACGTTTAGAGTTTCCTC  
TCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

**FIG. 27H**

16E3

GACATTGTGATGACCCAGACTCCACTCTCCTTGCCCCTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG  
TCAGAGCCTCTTGGATAGTGATGAAGGAAACACCTTTTGGATTGGTACCTGCAGAAGCCAGGGCAGCCTCCACA  
GCTCCTGATCTATACGCTTTCCTATCGGGCCTCTGGAGTCCCAGACAGGTTCAAGTGGCAGTGGGTCAGGCACTGAT  
TTCACACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGAGTTTACTGCATGCAACGTATAGAGTTTCCTC  
TCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

14G7

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCGA  
GTCAGGACATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTACGATGC  
ATCCAATTTGGAAACAGGGTCCCATCAAGGTTCAAGTGGATCTGAGACAGATTTTACTTTCACCATCAGC  
AGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAACAGTATGAAAATCTCCATTCACTTTCGGCCCTGGGAC  
CAAAGTGGATATCAAACGA

5H3

TCCTATGAGCTGACACAGCCACCCTCGGTGTCAGTGTCCCCAGGACAGACGGCCAGGATCACCTGCTCTGGAGAT  
GCATTGCCAAGGCAATATGCTTATTGGTACCAGCAGAAGCCAGGCCAGGCCCTATGCTGGTATATATAAAGAC  
AGTGAGAGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAGCTCAGGGACAACAGTCACGTTGACCATCAGT  
GGAGTCCAGGCAGAAGACGAGGCTGACTATTACTGTCAATCAGCAGACAGCAGTGGTACTTATGTGGTATTCGGC  
GGAGGGACCAAGCTGACCGTCCTAGGT

2B12

TCCTATGAGCTGACACAGCCACCCTCGGTGTCAGTGTCCCCAGGACAAACGGCCAGGATCACCTGCTCTGGAGAT  
GCATTGCCAAGAAAATATGCTTATTGGTACCAGCAGAAGTCAGGCCAGGCCCTGTGCTGGTCATCTATGAGGAC  
AGCAAACGACCCTCCGGGATCCCTGAGAGATTCTCTGGCTCCAGCTCAGGGACAATGGCCACCTGACTATCAGTG  
GGGCCAGGTGGAGGACGAAGCTGACTACTACTGTTACTCAACAGACAGCAGTGGTAATCATTATGTCTTCGGAA  
CTGGGACCAAGGTACCGTCCTAGGT

**FIG. 271**

26H7

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCGA  
GTCAGGACATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGTTCCTGATCTACGATGC  
ATCCAATTTGGAAACAGGGGTCCCATCAAGGTTCAAGTGGATCTGGGACAGATTTTTTTTTTACCATCAGC  
AACCTGCAGCCTGAAGATATTGCAACATATTTCTGTCAACAGGATGATAATCTCCCATTCACTTTGGCCCTGGGAC  
CAAAGTGGATATCAAACGA

26C12

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGGCCGA  
GTCAGGACATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAACTCCTGATCTACGATGC  
ATCCAATTTGGAAACAGGGGTCCCATCAAGGTTCAAGTGGATCTGGGACAGATTTTACTTTCACCATCAGC  
AGCCTGCAGCCTGAAGATATTGCAACATTTTACTGTCAACAGTATGATAATCTCCCATTCACTTTGGCCCTGGGAC  
CAAAGTGGATATCAAACGA

2H11

TCCTATGAGCTGACACAGCCACCCTCGGTGTCAGTGTCCCCAGGACAAACGGCCAGGATCACCTGCTCTGGAGAT  
GCATTGCCAAGAAAATTTGCTTATTGGTACCAGCAGAAGTCAGGCCAGGCCCTGTGCTGGTCATCTATGAGGAC  
AGGAAACGACCCTCCGGGATCCCTGAGAGATTCTCTGGCTCCAGCTCAGGGACAATGGCCACCTTGACTATCAGT  
GGGGCCAGGTGGAGGATGAAGCTGACTACTACTGTTACTCAACAGACCCGAGTGGTGATCATGTGGTATTCGGC  
GGAGGGACCAAGCTGACCGTCCTAGGT

18H9

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCGGGCCGA  
GTCAGGGTATTAGCAACTGGTTAGTCTGGTATCAGCAGAAACCAGGGAAACCCCCTAAACTCCTGATCTATGCTGC  
ATCCAGTTTGCAAAATGGGGTCCCATCAAGATTCAGCGCAGTGGATCTGGGACAGATTTCACTCTACCATCAGC  
AGCCTGCAGACTGAAGATTTTGCAACTACTATTGTCAACAGGCTCTCAGTTTCCCCTGGACGTTTCGGCCCAGGGA  
CCAAGGTGGAAGTCAAACGA

FIG. 28 Heavy Chain Variable Domain Amino Acid Sequences

	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
9D6	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	<u>IHPGDS</u> TRYSFSFGQ	VTI	SADRSIS	TAIYLCY	CFR
2C3	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	<u>IHPGDS</u> TRYSFSFGQ	VTI	SADRSIS	AAIYQWSS	LKASDTAMYYCAR
14C9	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
8B12	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
16A4	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
16E1	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
13A1	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
8F10	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
12C4	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
9B12	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
3H5	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
18A6	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
10A6	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
10H7	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
15A10	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
12D2	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
9B10	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
17D3	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR
15G11	QVTLKESGFPVLVKKPTEITLTLCTVSGFSL	<u>SNARMGVS</u> WLRQPPGKALEWLA	<u>HIFSNDEK</u> SYSTSLKSR	LT	ISKDTSK	QVVL	TMTNMDPVD
14D7	QVQLQESGFPGLVKPSTLSLCTVSGGSI	<u>SSGGYYW</u> WLRQHPGKGLEW	<u>IGIYISGN</u> THYNP	SLKSR	VTI	SVDT	SKNQFSLKLSVAADTAVYYCAR
18F3	QVQLQESGFPGLVKPSTLSLCTVSGGSI	<u>SSGGYYW</u> WLRQHPGKGLEW	<u>IGIYISGN</u> THYNP	SLKSR	VTI	SVDT	SKNQFSLKLSVAADTAVYYCAR
17D9	QVQLQESGFPGLVKPSTLSLCTVSGGSI	<u>SSGGYYW</u> WLRQHPGKGLEW	<u>IGIYISGN</u> THYNP	SLKSR	VTI	SVDT	SKNQFSLKLSVAADTAVYYCAR
21F8	QVQLVQSGAEVVKKPCASVKVSCKASGYTFT	<u>NYD</u> INWVVRQATGQGLEW	<u>WMPN</u> SGNTGYAQR	<u>QKFG</u>	RV	TM	TRNTSIS
22B9	QVQLVQSGAEVVKKPCASVKVSCKASGYTFT	<u>NYD</u> INWVVRQATGQGLEW	<u>WMPN</u> SGNTGYAQR	<u>QKFG</u>	RV	TM	TRNTSIS
21D10	QVQLVQSGAEVVKKPCASVKVSCKASGYTFT	<u>NYD</u> INWVVRQATGQGLEW	<u>WMPN</u> SGNTGYAQR	<u>QKFG</u>	RV	TM	TRNTSIS
14A6	QVQLVQSGAEVVKKPCASVKVSCKASGYTFT	<u>NYD</u> INWVVRQATGQGLEW	<u>WMPN</u> SGNTGYAQR	<u>QKFG</u>	RV	TM	TRNTSIS
11D6	QVQLVQSGAEVVKKPCASVKVSCKASGYTFT	<u>NYD</u> INWVVRQATGQGLEW	<u>WMPN</u> SGNTGYAQR	<u>QKFG</u>	RV	TM	TRNTSIS
10A9	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	<u>IHPGDS</u> TRYSFSFGQ	VTI	SA	DRS	IS
16E3	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	<u>IHPGDS</u> TRYSFSFGQ	VTI	SA	DRS	IS
14G7	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	<u>IHPGDS</u> TRYSFSFGQ	VTI	SA	DRS	IS
5H3	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	<u>IHPGDS</u> TRYSFSFGQ	VTI	SA	DRS	IS
2B12	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	<u>IHPGDS</u> TRYSFSFGQ	VTI	SA	DRS	IS
26G7	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	<u>IHPGDS</u> TRYSFSFGQ	VTI	SA	DRS	IS
26G12	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	<u>IHPGDS</u> TRYSFSFGQ	VTI	SA	DRS	IS
2H11	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	<u>IHPGDS</u> TRYSFSFGQ	VTI	SA	DRS	IS
18H9	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMH</u> WVQAPGKGLIEWV	<u>VIWYDGS</u> NEYADSVKGR	FTI	SRDNSKNTLYL	QWSS	LKASDTAMYYCAR

FIG. 28 Heavy Chain Variable Domain Amino Acid Sequences

	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
9D6	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	IHPGDS	TRYS	PSFQ	QV	TI
2C3	EVQLVQSGAEVVKKPESELKTSCKGSGYRFT	<u>SYWIG</u> WVQMPGKGLIEWMG	IHPGDS	TRYS	PSFQ	QV	TI
14C9	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>YIGMHW</u> VRQAPGKGLIEWV	VIWYDGS	NEYAD	SVKGR	FT	I
8B12	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMHW</u> VRQAPGKGLIEWA	VIWYDGS	NEYAD	SVKGR	FT	I
16A4	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMHW</u> VRQAPGKGLIEWA	VIWYDGS	NEYAD	SVKGR	FT	I
16E1	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMHW</u> VRQAPGKGLIEWA	VIWYDGS	NEYAD	SVKGR	FT	I
13A1	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMHW</u> VRQAPGKGLIEWA	VIWYDGS	NEYAD	SVKGR	FT	I
8F10	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMHW</u> VRQAPGKGLIEWA	VIWYDGS	NEYAD	SVKGR	FT	I
12C4	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMHW</u> VRQAPGKGLIEWA	VIWYDGS	NEYAD	SVKGR	FT	I
9B12	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMHW</u> VRQAPGKGLIEWA	VIWYDGS	NEYAD	SVKGR	FT	I
3H5	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SFGMHW</u> VRQAPGKGLIEWA	VIWFDGS	NKYAD	SVKGR	FT	I
18A6	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMHW</u> VRQAPGKGLIEWA	VIWYDGS	NKYAD	SVKGR	FT	I
10A6	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYD</u> IHWVRQAPGKGLIEWA	VIWYDGS	LKYAD	SVKGR	FT	I
10H7	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYD</u> IHWVRQAPGKGLIEWA	VIWYDGS	LKYAD	SVKGR	FT	I
15A10	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>TYGMHW</u> VRQAPDMGLEWVA	VIWYDGS	NKYAD	SVKGR	FT	I
12D2	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>TYAMHW</u> VRQAPGKGLIEWA	VIWYDGS	NKYAD	SVKGR	FT	I
9B10	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>ZYAMHW</u> VRQAPGKGLIEWA	VIWYDGS	NKYAD	SVKGR	FT	I
17D3	QVQLVESGGGLVKPFGSLRLSCAASGFTFS	<u>DIYMS</u> WVRQAPGKGLIEWV	YISSGSI	LKYAD	SVKGR	FT	I
15G11	QVTLKESGFPVLVKKPTEITLTLCTVSGFSL	<u>SNARMGVS</u> WLRQPPKALEWLA	HIFSNDEK	SYSTSLK	SR	LT	IS
14D7	QVQLQESGFLVKPSTLTLCTVSGGSI	<u>SSGGYYW</u> WLRQHPKGLEWIG	YIYISG	NTNPN	SLKSR	VT	IS
18F3	QVQLQESGFLVKPSTLTLCTVSGGSI	<u>SSGGYYW</u> WLRQHPKGLEWIG	YIYISG	NTNPN	SLKSR	VT	IS
17D9	QVQLQESGFLVKPSTLTLCTVSGGSI	<u>SSGGYYW</u> WLRQHPKGLEWIG	YIYISG	NTNPN	SLKSR	VT	IS
21F8	QVQLVQSGAEVVKKPCASVKVSCKASGYTFT	<u>NYD</u> INWVRQATGQGLEWVG	WMPN	NSGNTGYA	QKFK	FQ	GR
22B9	QVQLVQSGAEVVKKPCASVKVSCKASGYTFT	<u>NYD</u> INWVRQATGQGLEWVG	WMPN	NSGNTGYA	QKFK	FQ	GR
21D10	QVQLVQSGAEVVKKPCASVKVSCKASGYTFT	<u>NYD</u> INWVRQATGQGLEWVG	WMPN	NSGNTGYA	QKFK	FQ	GR
14A6	QVQLVQSGAEVVKKPCASVKVSCKASGYTFT	<u>TYD</u> INWVRQATGQGLEWVG	WMPN	NSGNTGYA	QKFK	FQ	GR
11D6	QVQLVQSGAEVVKKPCASVKVSCKASGYTFT	<u>TYD</u> INWVRQATGQGLEWVG	WMPN	NSGNTGYA	QKFK	FQ	GR
10A9	EVQLVQSGAEVVKKPESELKTSCKGSGYGF	<u>TSQWIG</u> WVRQMPGKGLIEWMG	IIFPGD	SD	TRYS	PSFQ	QV
16E3	EVQLVQSGAEVVKKPESELKTSCKGSGYGF	<u>TSQWIG</u> WVRQMPGKGLIEWMG	IIFPGD	SD	TRYS	PSFQ	QV
14G7	EVQLVQSGAEVVKKPESELKTSCKGSGYGF	<u>TYWIG</u> WVRQMPGKGLIEWMG	IIPYD	SD	TRYS	PSFQ	QV
5H3	EVQLVQSGAEVVKKPESELKTSCKGSGYGF	<u>TYWIG</u> WVRQMPGKGLIEWMG	IIPYD	SD	TRYS	PSFQ	QV
2B12	EVQLVQSGAEVVKKPESELKTSCKGSGYGF	<u>TYWIG</u> WVRQMPGKGLIEWMG	IIPYD	SD	TRYS	PSFQ	QV
26H7	EVQLVQSGAEVVKKPESELKTSCKGSGYGF	<u>TYWIG</u> WVRQMPGKGLIEWMG	IIPYD	SD	TRYS	PSFQ	QV
26G12	EVQLVQSGAEVVKKPESELKTSCKGSGYGF	<u>TYWIG</u> WVRQMPGKGLIEWMG	IIPYD	SD	TRYS	PSFQ	QV
2H11	EVQLVQSGAEVVKKPESELKTSCKGSGYGF	<u>TYWIG</u> WVRQMPGKGLIEWMG	IIPYD	SD	TRYS	PSFQ	QV
18H9	QVQLVESGGGVVQVQGRSLRLSCAASGFTFS	<u>SYGMHW</u> VRQAPGKGLIEWA	VIWYDGS	NKYAD	SVKGR	FT	I

## FIG. 29A

### Heavy Chain Nucleic Acid Sequences

9D6

GAGGTGCAGTTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCAGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC  
TGGATACAGGTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGAAAGGCCTGGAGTGGATGGGGA  
TCATCCATCCTGGTGA CTCTGATACCAGATACAGCCCGTCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCC  
ATCAGCACCCGCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACTGCCATATATTACTGTACGAGACAGGGT  
AGAAGCTTCTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

2C3

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCAGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC  
TGGATACAGGTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGAAAGGCCTGGAGTGGATGGGGA  
TCATCTATCCTGGTGA CTCTGATACCAGATACAGCCCGTCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCC  
ATCAGCGCCGCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACAACAA  
GTGGCTGGTATGTTGGACTACTGGGGCCAGGGAAACCCTGGTCACCGTCTCCTCA

14C9

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATCACCTTCAGTATTTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGACAGT  
TATATGGTATGATGGAAGTAATGAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTC  
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGGA  
CTTCGACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

8B12

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAG  
TTATATGGTATGATGGAAGTAATGAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTC  
CAAGAACACGCTGTATCTACAAATGCACAGCCTGAGAGCCGAGGACACGGCTGTGTATTATTGTGCGAGAGAAGA  
ATGGTTCGGGGAGGCGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

## FIG. 29B

16A4

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCAGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAG  
TTATATGGTATGATGGAAGTAATGAATATTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTC  
CAAGAACACGCTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATGA  
TTGGTTCGGGGAGGCGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

16E1

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTCAGTAACTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGACAGT  
TATATGGAATGATGGAAGTAATGAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTC  
AAGAACACGCTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAAGAT  
TGGCTCGGGGAGGCGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

13A1

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAG  
TTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTC  
CAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAAG  
AGTGGGAGCTAGAGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

8F10

CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTCAGTAGTTATGGCATGTACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT  
TATATGGTATGATGGAAGTAATAAATACTATGTAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTC  
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGC  
AGTGGCTGGTACGGGACGGGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT  
CCTCA



## FIG. 29C

12C4

CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACGTTACAGTAGTTATGGCATGTACTGGGTCCGCCAGGCTCCAGGCAAGGGGGCTGGAGTGGGTGGCAG  
TTATATGGTATGATGGAAGTAATAAATACCATGGAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTC  
CAAGAATACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAAAGGAGC  
AGTGGCTGGTACGGGACGGGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT  
CCTCA

9B12

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCAGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTTAGTAGTTATGGCATGTACTGGGTCCGCCAGGCTCCAGGCAAGGGGGCTGGAGTGGGTGGCAGT  
TATATGGTATGATGGAAGTAATAAAAACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC  
AAGAATACGTTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATCACTGTGCGAAAGGAACA  
GTGGCTGGTACGGGACGGGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCT  
TCA

3H5

CAGGTGCAACTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTACAGTAGCTTTGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGGCTGGAGTGGGTGGCAGT  
TATTTGGTTTGATGGAAGTAATAAATACTATGTAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC  
AAGAATACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGCGGGACGAT  
TTTTGGAGTGATTATCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

18A6

CAGGTGCAACTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCTGAGACTCTCCTGTGCAGCCTCT  
GGATTCACCTTCAGGAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGGCTGGAGTGGGTGGCAGT  
TATATCAGATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC  
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGACTGAGGACACGGCTGTGTATTACTGTGCGAGAGATCTC  
TATAGCAGTGCCTGGCCCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

**FIG. 29D**

10A6

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTCAGTAGCTATGACATACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT  
TATATGGAATGATGGAAGTATTAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC  
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACGG  
GGAGCAGTGGCGGGGCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

10H7

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTCAGTAGCTATGACATACTGGGTCCGTGAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT  
TATATGGTATGATGGAAGTATTAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC  
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCAG  
GAGCAGTGGCTGGCCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

15A10

CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTCAGTACCTATGGCATGCACTGGGTCCGCCAGGCTCCAGACATGGGGCTGGAGTGGGTGGCAGT  
TATATGGTATGATGGAAGTAATAATACTATGCAGACTCTGTGAAGGGCCGATTACCATCTCCAGAGACATTTCC  
AAGAACACGCTGTATCTGGAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACAA  
CTGGGGATCCGATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

12D2

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTCAGTACCTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT  
TATATGGTATGATGGAATTAATAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC  
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGAG  
TTACTATGATAGTAGTGGTTATTACTACGGGGAGGACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC  
TCA

**FIG. 29E**

9B10

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATTCACCTTCAGTAGCTATGCCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGT  
TATCTGGTATGATGGAATTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC  
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGAG  
TACTATGATAGTAGTGGTTATTACTTCGGGGAGGACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC  
TCA

17D3

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCT  
GGATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATAC  
ATTAGTAGTAGTGGTAGTATCATTTTTTACGCAGACTCTGTGAAGGGCCGATTCACCATGTCCAGGGACAACGCCA  
AGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTATTGTGTGAGAAGGATTA  
GTATAACCCCTTTTACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

15G11

CAGGTACCTTGAAGGAGTCTGGTCCTGTGCTGGTGAACCCACAGAGACCCTCACGCTGACCTGCACCGTCTCTG  
GGTTCTCACTCAGCAATGCTAGAATGGGTGTGAGCTGGATCCGTCAGCCCCAGGGAAGGCCCTGGAGTGGCTTG  
CACACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGCAGGCTCACCATCTCCAAGGACACCTCC  
AAAAGCCAGGTGGTCCTTACCATGACCAACATGGACCCTGTGGACACAGCCACATATTACTGTGTACGGATAACCGA  
GATGGCTACAACCCCTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

14D7

CAGGTGCAGCTGCAGGAGTCGGGCCAGGACTGGTGAAGCCTTACAGACCCTGTCCCTCACCTGCACTGTCTCT  
GGTGGCTCCATCAGCAGTGGTGGTTACTACTGGAAGTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGAT  
TGGGTACATCTATTACAGTGGGAACCCACTACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACAG  
TCTAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGATTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGACT  
GGGGACGTGATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

**FIG. 29F**

18F3

CAGGTGCAGCTGCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTCACCTGCACTGTCTCG  
GGTGGCTCCATCAGCAGTGGTGGTTACTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGAT  
TGGGTACATCTATTATAGTGGGAGCACCGACTACAACCCGTCCCTCAAGAGTCGAGGTATCATATCAGGAGACAC  
GTCTAAGAACCAGTTCTCCCTGAAGCTGAACTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGA  
GGGGAGGTTCCGGGAGTTAGGCTCCTACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

17D9

CAGGTGCAGCTGCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCT  
GGTGGCTCCGTAGCAGTGGTGGTTACTACTGGAGCTGGATCCGGCAGCCCCAGGGAAGGGACTGGAGTGGAT  
TGGAATACCTATTACAGTGGGAGCACCAACTACAAACCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACG  
TCCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTGTGACCGCTGCGGACACGGCCGTGTATTACTGTGGGAGAGAC  
CGGGGTAGAGCAGTGGGTCCCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

21F8

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC  
TGGATACACCTTACCAATTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATG  
GATGAACCCTAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACCTC  
CATAAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAAGTA  
GGCAGTGGCTGGTACTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

22B9

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC  
TGGATACACCTTACCAATTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATG  
GATGAACCCTAACAGTGGTAACACAGGCTATGTACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACCTC  
CATAAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAAGTA  
GGCAGTGGCTGGTACTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

**FIG. 29G**

21D10

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC  
TGGATACAGGTTACCAGTTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGAT  
GGATGAACCCAAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACC  
TCCATAAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAAGT  
AGGCAGTGGCTGGTACTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

14A6

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC  
TGGATACACCTTACCACCTTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATG  
GATGAACCCCTAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACCTC  
CATAAGCACAGCCTACATGGAGCTGAGCAGCCTAAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCC  
GGCAGTGGCTGGGCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

11D6

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC  
TGGATACACCTTACCAATTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATG  
GATGAACCCCTAATAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACCTC  
CATAAACACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCC  
GGCAGTGGCTGGGCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

10A9

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC  
TGGATACAGCTTTACCAGCCAGTGGATCGGCTGGGTGCGCCAGATGCCCGGAAAGGCCTGGAGTGGATGGGGA  
TCATCTTTCTGGTGA CTCTGATACCAGATACAGCCCGTCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCC  
ATCAGCACCCGCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGCGACAGGGT  
AGAAGTTACCACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

**FIG. 29H**

16E3

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC  
TGGATACGGCTTTACCAACTACTGGATCGGCTGGGTGCGCCAGATGCCCGGAAAAGGCCTGGAGTGGATGGGGA  
CCATCTATCCTGGTGA CTCTGATACCAGATACAGTCCGTCCTTCCAAGGCCAGGTACCTTCTCAGCCGACAAGTCC  
ATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACAGGGT  
AGAAGTACTACTACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

14G7

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC  
TGGATACAGCTTTACCGACTACTGGATCGGCTGGGTGCGCCAGATGCCCGGAAAAGGCCTGGAATGGATGGGGA  
TCATCTATCCTTATGACTCTGATACCAGATACAGCCGTCCTTCCAAGGCCAGGTACCTTCTCAGCCGACAAGTCC  
ATCAGCACCGCCTACCTGCGGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACATCGG  
GGGGGGAGGTCTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

5H3

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC  
TGGATACAGCTTTACCGACTACTGGATCGGCTGGGTGCGCCAGATGCCCGGAAAAGGCCTAGAATGGATGGGGA  
TCATCTATCCTGGTGA CTCTGATACCACATACAGCCGTCCTTCCAAGGCCAAGTCACCATCTCAGCCGACAAGTCC  
ATCAACACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGAGAGGGT  
TTCGGGGAGTCTATTCACTACGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

2B12

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC  
TGGATACAATTTTACCAACTACTGGATCGGCTGGGTGCGCCAGATGTCCGGGAAAAGGCCTGGAGTGGATGGGAA  
TCATCTATCCTGGTGA CTCTGAAACCAGATACAGCCGTCCTTCCAAGGCCAGGTACCATCTCAGCCGACAAGTC  
CATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACATGG  
AGGGGGATGGAGTGGTTGGGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

**FIG. 29I**

26H7

GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC  
TGGATACAGGTTTACCAACTACTGGATCGGCTGGGTGCGCCAGATGCCCGGAAAGGCCTGGAGTGGATGGGGA  
TCATCTATCCTGGTGA CTCTGATACCAAATACAGCCCGTCCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCC  
ATCAGTACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGACATGGT  
GGATATAGTGGCCGTTCTACTACTACGGTATGGACGTCTGGGGCCAGGGGACCGCGGTACCGTCTCCTCA

26C12

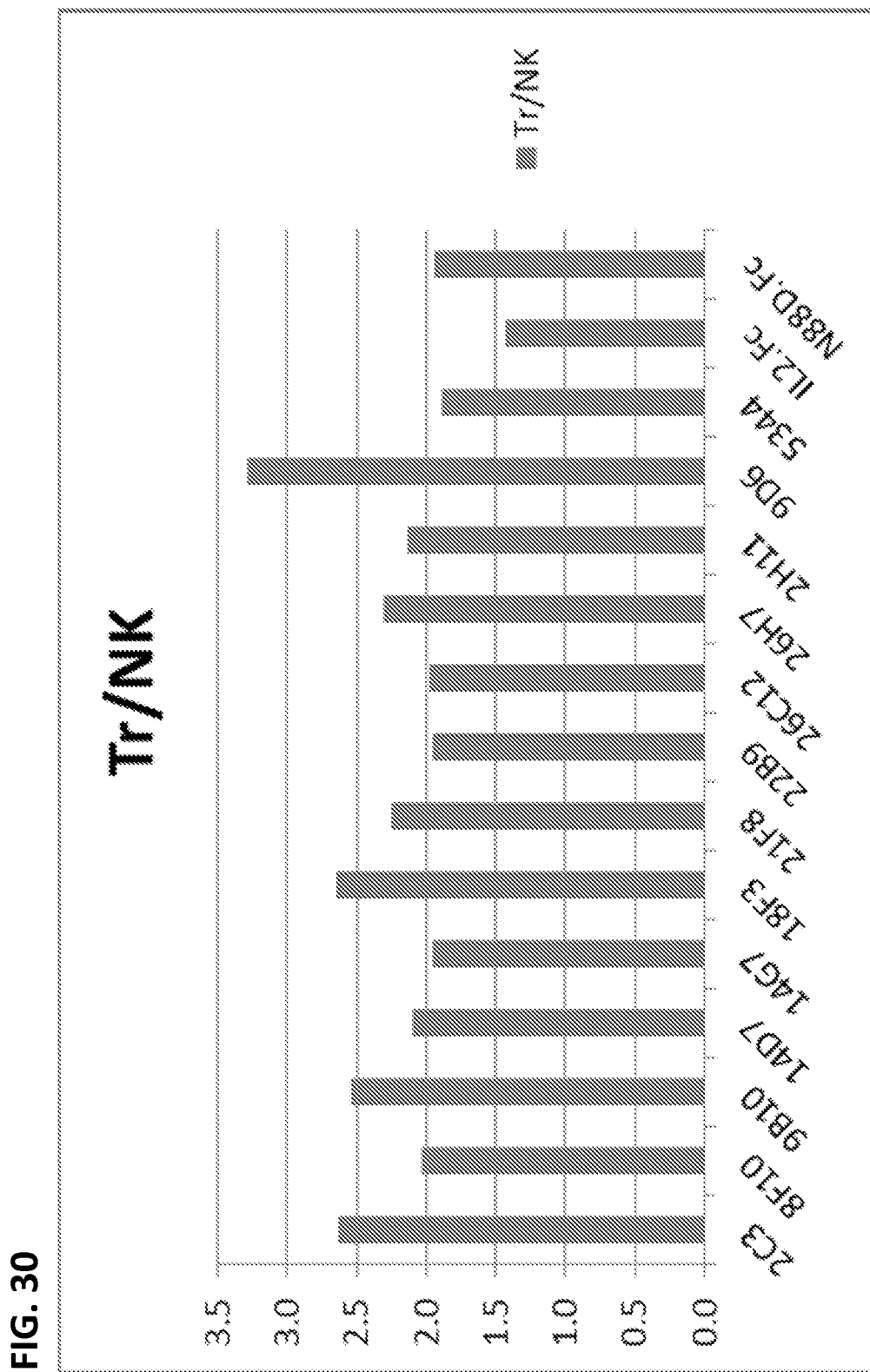
GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC  
TGGATACAGGTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGAAAGGCCTGGAGTGGATGGGGA  
TCATCTTTCCTGGTGA CTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCC  
ATCACCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATCTATTACTGTGCGGACATGGG  
CATGGCAGCTCGTCCGGGCGGACCTACTACTACGGTTTGGACGTCTGGGGCCAAGGGACCGTACCGTCTCC  
TCA

2H11

GAGGTGCAGCTGGTGC AATCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAGATCTCCTGTAAGGGTTC  
TGGATACA AACTTTACCACCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGAAAGGCCTGGAGTGGATGGGGA  
TCATCTATCCTGGTGA CTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATTTAGCCGACAAGTCC  
ATCAACACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACAGCCATTTATTACTGTGCGAGAGACACA  
GGATACTTTGACTACTGGGGCCAGGGCACCCCTGGTCACCGTCTCCTCA

18H9

CAGGTGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTC  
TGGATCACCTT CAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGCCTGGAGTGGGTGGCAGT  
TATCTGGTATGATGGAAGTAATAAATTCTATGTAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC  
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGACCCGG  
GTCGATTACTACTTCTACTACGGTATGGACGTCTGGGGCCAAGGGACCGTACCGTCTCCTCA





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

### CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims the benefit of U.S. Provisional Application No. 62/146,136 filed Apr. 10, 2015, which is incorporated in its entirety by reference herein.

### BACKGROUND

**[0002]** IL-2 binds three transmembrane receptor subunits: IL-2R $\beta$  and IL-2R $\gamma$  which together activate intracellular signaling events upon IL-2 binding, and CD25 (IL-2R $\alpha$ ) which serves to stabilize the interaction between IL-2 and IL-2R $\beta\gamma$ . The signals delivered by IL-2R $\beta\gamma$  include those of the PI3-kinase, Ras-MAP-kinase, and STAT5 pathways.

**[0003]** 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.

**[0004]** 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

**[0005]** 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.

**[0006]** 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.

**[0007]** Moreover, when creating a pharmaceutical large molecule, consideration must be made for the ability to produce the large molecule in large quantities, while mini-

mizing aggregation and maximizing the stability of the molecule. The IL-2 mutein Fc-fusion molecules demonstrate such attributes.

**[0008]** 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.

**[0009]** 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, D84I, D84M, D84Q, D84R, D84S, D84T, S87R, N88A, N88D, N88E, N88F, N88G, N88M, N88R, N88S, N88V, N88W, V91D, V91E, V91G, V91S, I92K, I92R, 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, D84I, D84M, D84Q, D84R, D84S, D84T, S87R, N88A, N88D, N88E, N88F, N88G, N88M, N88R, N88S, N88V, N88W, V91D, V91E, V91G, V91S, I92K, I92R, and E95G. 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 D20E, D20G, D20W, D84A, D84S, H16D, H16G, H16K, H16R, H16T, H16V, I92K, I92R, L12K, L19D, L19N, L19T, N88D, N88R, N88S, V91D, V91G, V91K, and V91S.

**[0010]** 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.

**[0011]** In another aspect, the present invention provides an isolated nucleic acid encoding a human IL-2 mutein as described above.

**[0012]** 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.

**[0013]** In another aspect, the present invention provides an expression vector comprising an isolated nucleic acid described above operably linked to a promoter.

**[0014]** 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.

**[0015]** 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.

**[0016]** 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.

**[0017]** 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%.

**[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 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%.

**[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 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%.

**[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 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%.

**[0021]** 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%.

**[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 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%.

**[0023]** 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.

**[0024]** 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 I332 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 I332C substitution within the amino acid sequence set forth in SEQ ID NO:3.

**[0025]** In another aspect, the present invention provides an antibody comprising an Fc region as described above.

**[0026]** In another aspect, the present invention provides an Fc-fusion protein comprising an Fc region as described above.

**[0027]** 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.

**[0028]** In another aspect, the present invention provides a method of making an aglycosylated IgG1 Fc-containing molecule, said method comprising:

**[0029]** a) expressing a nucleic acid encoding a polypeptide as described above in a mammalian cell culture; and

**[0030]** b) harvesting the aglycosylated IgG1 Fc-containing molecule from said culture.

**[0031]** 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.

**[0032]** 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.

**[0033]** In another aspect, the present invention provides a nucleic acid encoding the Fc-fusion as described above.

**[0034]** In another aspect, the present invention provides a cell comprising the nucleic acid as described above.

**[0035]** 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.

**[0036]** In another aspect, the present invention provides a method of treating an inflammatory or autoimmune 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 autoimmune 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.

**[0037]** 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.

**[0038]** 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')<sub>2</sub> 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.

**[0039]** 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.

**[0040]** 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.

**[0041]** In another aspect, the present invention provides an expression vector comprising the isolated nucleic acid as described above operably linked to a promoter.

**[0042]** 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*. 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.

**[0043]** 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.

**[0044]** 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

**[0045]** 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.

**[0046]** FIG. 2A and FIG. 2B 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<sup>+</sup>CD4<sup>+</sup> and FOXP3<sup>-</sup>CD4<sup>+</sup> T cells.

**[0047]** 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)

**[0048]** 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)

**[0049]** 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.

**[0050]** 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).

**[0051]** FIG. 7A and FIG. 7B Fc.IL-2 muteins without mutations that confer high affinity for CD25 promote Treg expansion and FOXP3 upregulation in humanized mice.

**[0052]** 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.

**[0053]** FIG. 9A Fc.V91K and Fc.N88D persist on the surface of activated T cells through association with CD25.

**[0054]** FIG. 9B Persistence of IL-2R signaling with Fc.V91K and Fc.N88D relative to Fc.WT.

**[0055]** FIGS. 10A 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.

**[0056]** FIG. 11A-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.

**[0057]** FIG. 12A Effect of increasing dosages of PROLEUKIN®, Fc.V91K, or Fc.N88D on levels of Treg cells, NK cells, CD4<sup>+</sup>FOXP3<sup>-</sup> T cells, and CD8<sup>+</sup>FOXP3<sup>-</sup> T cells in cynomolgus monkeys. Each data point represents the average peak responses of four animals.

**[0058]** FIG. 12B 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.

**[0059]** FIG. 12C 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.

**[0060]** FIG. 12D 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.

**[0061]** FIG. 13 Kinetics of the development of anti-drug antibodies (ADA) in cynomolgus monkeys treated with Fc.V91K.

**[0062]** FIG. 14 Discovery Studio predicted  $\Delta\Delta G_{binding}$  (kcal/mol) of IL-2:IL-2R $\beta$  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.

**[0063]** FIG. 15 Schrödinger predicted  $\Delta\Delta G_{binding}$  (kcal/mol) of IL-2:IL-2R $\beta$  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.

**[0064]** FIG. 16A and FIG. 16B 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, N.J.) 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, Calif.). 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.

**[0065]** 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, N.J.) assay to detect phospho-STAT5 levels. The bioactivity of IL-2 muteins is presented as phospho-STAT5 mean fluorescence intensity (MFI) in gated CD25<sup>high</sup>CD4+ 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.

**[0066]** FIG. 18(A)-(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<sup>-</sup>CD4+ cells (FIG. 18A), FOXP3<sup>-</sup>CD8+ cells (FIG. 18B), and HELIOS<sup>+</sup>FOXP3<sup>+</sup>CD4+(FIG. 18C). The capacity for muteins to upregulate FOXP3 in HELIOS<sup>+</sup>FOXP3<sup>+</sup>CD4+ cells is also shown (FIG. 18D).

**[0067]** 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  $\mu$ Ci 3H-thymidine was added to each well during the final eighteen hours of incubation.

**[0068]** 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. 20A). 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. 20B).

**[0069]** FIG. 21 pSTAT5 signal retention after pulse-wash, as in FIG. 20, except cells were pulsed with 100 pM Fc:IL-2.

**[0070]** 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.

**[0071]** FIG. 23A and FIG. 23B 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  $\mu$ g 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.

**[0072]** 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.

**[0073]** FIG. 25 (A)-(LL) Nucleic acid sequences of the human IL-2 mutein fusion proteins created and tested according to Examples 13 and 14.

**[0074]** 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.

**[0075]** FIG. 27(A)-(I) Nucleic acid sequences of the light chain variable domains of the antibodies isolated and tested according to Example 15.

**[0076]** 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.

**[0077]** FIG. 29(A)-(I) Nucleic acid sequences of the heavy chain variable domains of the antibodies isolated and tested according to Example 15.

**[0078]** 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  $\mu$ g of anti-IL-2 antibody complexed with 1.5  $\mu$ g wild-type human IL-2) as described in Example 15.

#### DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

**[0079]** 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.

**[0080]** 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 Manual*, 3<sup>rd</sup> 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

**[0081]** 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: APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKL-TRMLTFKFFYMPKKATELKHLCLEELKPLEEVLN-LAQSKNFHLR PRDLISNINVIVLELKGSETTFMCEYA-DETATIVEFLNRWITFXQSIISLT

Wherein X is C, S, V, or A (SEQ ID NO:2).

**[0082]** 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

**[0083]** 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).

**[0084]** 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%.

**[0085]** 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 stimulating 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.

**[0086]** 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.

**[0087]** 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.

**[0088]** 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)=11. 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.

**[0089]** 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  $10+k$ ;  $X_n$  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.

**[0090]** 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.

**[0091]** 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.

**[0092]** 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.

**[0093]** 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.

**[0094]** 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.

**[0095]** 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.

**[0096]** 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.

**[0097]** 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, 8612, 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.

**[0098]** 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

**[0099]** 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, arthral-

gia, 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.

**[0100]** 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 Fc $\gamma$  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 Fc $\gamma$  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.

**[0101]** 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.

**[0102]** 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.

**[0103]** 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.

**[0104]** 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.

**[0105]** 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.

**[0106]** 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:

S239D/I332E

S239D/A330S/I332E

S239D/A330L/I332E

S298A/D333A/K334A

P247I/A339D

P247I/A339Q

D280H/K290S

D280H/K290S/S298D

D280H/K290S/S298V

F243L/R292P/Y300L

F243L/R292P/Y300L/P396L

F243L/R292P/Y300L/V305I/P396L

G236A/S239D/I332E

K326A/E333A

K326W/E333S

K290E/S298G/T299A

K290N/S298G/T299A

K290E/S298G/T299A/K326E

K290N/S298G/T299A/K326E

**[0107]** 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 oligosaccharides 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  $\beta$ -1,4-N-acetylglucosaminyltransferase III and Golgi  $\alpha$ -mannosidase II. 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*.

**[0108]** 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:

N297A or N297Q (IgG1)

L234A/L235A (IgG1)

V234A/G237A (IgG2)

L235A/G237A/E318A (IgG4)

H268Q/V309L/A330S/A331S (IgG2)

C220S/C226S/C229S/P238S (IgG1)

C226S/C229S/E233P/L234V/L235A (IgG1)

L234F/L235E/P331S (IgG1)

S267E/L328F (IgG1)

**[0109]** 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

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-continued

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		
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			

**[0110]** 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.

**[0111]** 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 aglycosylated Fc-fusion protein.

**[0112]** 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.

**[0113]** 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.

**[0114]** 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 I332 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 I332C.

**[0115]** Provided herein are Fc-containing molecules wherein one or more of residues V259, A287, R292, V302, L306, V323, or I332 are substituted with cysteine, examples of which include those comprising A287C and L306C, V259C and L306C, R292C and V302C, or V323C and I332C substitutions.

**[0116]** 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.

**[0117]** 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.

**[0118]** 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.

**[0119]** 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.

**[0120]** 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).

**[0121]** 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

**[0122]** 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.

**[0123]** Cysteinyll residues most commonly are reacted with  $\alpha$ -haloacetates (and corresponding amines), such as chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteinyll residues also are derivatized by reaction with bromotrifluoroacetone,  $\alpha$ -bromo- $\beta$ -(5-imidazolyl)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.

**[0124]** 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.

**[0125]** Lysinyll 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 lysinyll 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.

**[0126]** Arginyll 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.

**[0127]** 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-acetylimidazole 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.

**[0128]** 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-dimethyl pentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues are converted to asparaginyll and glutaminyll residues by reaction with ammonium ions.

**[0129]** 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-azidoalicyclic 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.

**[0130]** Glutaminyll and asparaginyll 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.

**[0131]** Other modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyll residues, methylation of the  $\alpha$ -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.

**[0132]** 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.

**[0133]** 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.

**[0134]** 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.

**[0135]** 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.

**[0136]** 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. 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.

**[0137]** 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. No. 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

**[0138]** 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.

**[0139]** 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).

**[0140]** 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, N.Y. (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.

**[0141]** The IL-2 muteins according to the invention are ordinarily prepared by site specific mutagenesis of nucleotides 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.

**[0142]** 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.

**[0143]** 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.

**[0144]** 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 (hemagglutinin 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.

**[0145]** 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.

**[0146]** 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.

**[0147]** 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, Calif.), 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.

**[0148]** 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, Mass.) is suitable for most gram-negative bacteria, and various viral origins (e.g., SV40, polyoma, adenovirus, vesicular stomatitis 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).

**[0149]** 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.

**[0150]** 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.

**[0151]** 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 thymidine 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.

**[0152]** 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.

**[0153]** 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.

**[0154]** 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.

**[0155]** 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.

**[0156]** 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 metallothionein 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-feto-protein 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).

**[0157]** 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.

**[0158]** 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.

**[0159]** 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.

**[0160]** 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*.

**[0161]** 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.

**[0162]** 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 CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (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.

**[0163]** 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.

**[0164]** 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".

**[0165]** 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, I92K, I92R, 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.

**[0166]** 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.

**[0167]** 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.

**[0168]** 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.

**[0169]** 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.

**[0170]** 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.

**[0171]** 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

**[0172]** 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.

**[0173]** 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.

**[0174]** 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 dextrans); 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 phar-

maceutical adjuvants. See, REMINGTON'S PHARMACEUTICAL SCIENCES, 18<sup>th</sup> Edition, (A. R. Genrmo, ed.), 1990, Mack Publishing Company.

**[0175]** 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, IL-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.

**[0176]** 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.

**[0177]** 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.

**[0178]** 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.

**[0179]** 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.

**[0180]** 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.

**[0181]** As discussed above, certain embodiments provide IL-2 mutein or anti-IL-2 antibody compositions, particularly pharmaceutical IL-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.

**[0182]** 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.

**[0183]** 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.

**[0184]** 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.

**[0185]** 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 denature 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.

**[0186]** 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.

**[0187]** 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.

**[0188]** 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 glycinate 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.

**[0189]** 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.

**[0190]** 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.

**[0191]** 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.

**[0192]** 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. 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.

**[0193]** 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.

**[0194]** 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.

**[0195]** 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. However, metal ions also catalyze physical and chemical processes that degrade proteins.

**[0196]** Magnesium ions (10-120 mM) can be used to inhibit isomerization of aspartic acid to isoaspartic acid.  $\text{Ca}^{+2}$  ions (up to 100 mM) can increase the stability of human deoxyribonuclease.  $\text{Mg}^{+2}$ ,  $\text{Mn}^{+2}$ , and  $\text{Zn}^{+2}$ , however, can destabilize rhDNase. Similarly,  $\text{Ca}^{+2}$  and  $\text{Sr}^{+2}$  can stabilize Factor VIII, it can be destabilized by  $\text{Mg}^{+2}$ ,  $\text{Mn}^{+2}$  and  $\text{Zn}^{+2}$ ,  $\text{Cu}^{+2}$  and  $\text{Fe}^{+2}$ , and its aggregation can be increased by  $\text{Al}^{+3}$  ions.

**[0197]** 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 Somatropin (Eli Lilly) is formulated with m-cresol.

**[0198]** 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.

**[0199]** 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.

**[0200]** 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.

**[0201]** 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, ophthalmically, rectally, and vaginally, and by parenteral routes, including intravenous and intraarterial injection, intramuscular injection, and subcutaneous injection.

**[0202]** 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.

**[0203]** 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  $\mu\text{g}/\text{kg}$  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  $\mu\text{g}/\text{kg}$  up to about 100  $\mu\text{g}/\text{kg}$ , optionally from 2.5  $\mu\text{g}/\text{kg}$  up to about 50  $\mu\text{g}/\text{kg}$ .

**[0204]** 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.

**[0205]** 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.

**[0206]** In one embodiment, a pharmaceutical composition is provided comprising

#### Methods of Treating Autoimmune or Inflammatory Disorders

**[0207]** 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.

**[0208]** 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 nodosa, 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 esophagitis, 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.

**[0209]** 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.

**[0210]** 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, appetite, 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°, 0.7°, 1°, 1.5°, 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<sup>-</sup> CD4 T cells, FOXP3<sup>+</sup> CD4 T cells, FOXP3<sup>-</sup> 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<sup>+</sup> cells in a sample of the patient's peripheral blood.

#### Methods of Expanding Treg Cells

**[0211]** 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.

**[0212]** 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-.

**[0213]** 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

**[0214]** 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

**[0215]** IL-2 muteins with elevated affinity for CD25 and reduced signaling strength through IL-2R $\beta$  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)  
APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKPYMP

KKATELKHLLQCLEEELKPLEEALNLPASKNFHLRPRDLISDINVIVL  
ELKGSETTFMCEYADETATIVEEFLNRWITFAQSIISTLT

HaMut2D (N30S, V69A, Q74P, N88D, C125A)  
(SEQ ID NO: 9)  
APTSSSTKKTQLQLEHLLLDLQMLNGINSYKNPKLTRMLTFKPYMP

KKATELKHLLQCLEEELKPLEEALNLPASKNFHLRPRDLISDINVIVL  
ELKGSETTFMCEYADETATIVEEFLNRWITFAQSIISTLT

HaMut3D (K35R, V69A, Q74P, N88D, C125A)  
(SEQ ID NO: 10)  
APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKPYMP

KKATELKHLLQCLEEELKPLEEALNLPASKNFHLRPRDLISDINVIVL  
ELKGSETTFMCEYADETATIVEEFLNRWITFAQSIISTLT

HaMut4D (T37A, V69A, Q74P, N88D, C125A)  
(SEQ ID NO: 11)  
APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLARMLTFKPYMP

KKATELKHLLQCLEEELKPLEEALNLPASKNFHLRPRDLISDINVIVL  
ELKGSETTFMCEYADETATIVEEFLNRWITFAQSIISTLT

HaMut5D (K48E, V69A, Q74P, N88D, C125A)  
(SEQ ID NO: 12)  
APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKPYMP

EKATELKHLLQCLEEELKPLEEALNLPASKNFHLRPRDLISDINVIVL  
ELKGSETTFMCEYADETATIVEEFLNRWITFAQSIISTLT

HaMut6D (E68D, V69A, Q74P, N88D, C125A)  
(SEQ ID NO: 13)  
APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKPYMP

KKATELKHLLQCLEEELKPLEDALNLPASKNFHLRPRDLISDINVIVL  
ELKGSETTFMCEYADETATIVEEFLNRWITFAQSIISTLT

HaMut7D (N71R, V69A, Q74P, N88D, C125A)  
(SEQ ID NO: 14)  
APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKPYMP

KKATELKHLLQCLEEELKPLEEALRLAPASKNFHLRPRDLISDINVIVL  
ELKGSETTFMCEYADETATIVEEFLNRWITFAQSIISTLT

HaMut8D (K35R, K48E, E68D, N88D, C125A)  
(SEQ ID NO: 15)  
APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKPYMP

EKATELKHLLQCLEEELKPLEEALNLAQSKNFHLRPRDLISDINVIVL  
ELKGSETTFMCEYADETATIVEEFLNRWITFAQSIISTLT

**[0216]** 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

**[0217]** 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.

**[0218]** 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.

**[0219]** 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.

**[0220]** 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 10x dose titration ranging from 1 pM to 10 nM at a final volume of 50  $\mu$ l. 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 1x BD phosflow perm buffer on ice before stained for CD4, CD25, FOXP3 and pSTAT5.

**[0221]** 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

**[0222]** 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-2R $\beta$ -interacting amino acids (crystal structure, PDB code—2B5I). Particular substitutions were selected based on predicted decrease in the binding free energy between the mutein and IL-2R $\beta$ . 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  $\Delta\Delta G_{mut} = \mu (\Delta G_{mut} - \Delta G_{wt})$ . Where,  $\mu$  ( $=0.1$ , 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 ( $\Delta G$ ) was defined as the energy difference between the complex ( $\Delta G_{bound}$ ) and free states ( $\Delta G_{free}$ ). The dissociation energy  $\Delta G_{mut}$  was calculated for each substitution.

**[0223]** A panel of IL-2 muteins with the following substitutions (H16E, H16Q, L19K, D20R, D20K, D20H, D20Y, M23H, D84K, D84H, S87Y, N88D, N88K, N88I, N88H, N88Y, V91N, V91K, V91H, V91R, I92H, E95K, E95R, or E95I) 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.

**[0224]** 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).

**[0225]** H16E, D84K, V91N, V91K, and V91R possessed activity less than wild type IL-2 and more than N88D.

**[0226]** Selected muteins were also tested in T cell and NK growth assays.

**[0227]** 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).

**[0228]** 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  $\mu$ Ci  $^3$ H-thymidine was added to each well during the final 18 hours of incubation. The results are shown in FIG. 4.

**[0229]** Mutants H16E, D84K, V91N, V91K, and V91R mutants were capable of stimulating Treg growth similar to WT IL-2 but were approximately 10x less potent on other T cells (FIG. 3), and approximately 100x less potent on NK cells (FIG. 4).

**[0230]** 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.

Fc.haMut7	Fc...TQKSLSPGKGGGSAPTSSSTKKTQLQLE HLLLDLQMLLN...haMut7 (SEQ ID NO: 22)
Trunc1	Fc...TQKSLSSSTKKTQLQLEHLLLDLQMI LN...haMut7 (SEQ ID NO: 23)
Trunc2	Fc...TQKSLSL- <u>STKKTQLQLEHLLLDLQMI</u> LN...haMut7 (SEQ ID NO: 24)
Trunc3	Fc...TQKSLSL-- <u>TKKTQLQLEHLLLDLQMI</u> LN...haMut7 (SEQ ID NO: 25)
Trunc4	Fc...TQKSLSL--- <u>KKTQLQLEHLLLDLQMI</u> LN...haMut7 (SEQ ID NO: 26)
Trunc5	Fc...TQKSLSL---- <u>KTQLQLEHLLLDLQMI</u> LN...haMut7 (SEQ ID NO: 27)
Trunc6	Fc...TQKSLSL----- <u>TQLQLEHLLLDLQMI</u> LN...haMut7 (SEQ ID NO: 28)
Trunc7	Fc...TQKSLSL----- <u>QLQLEHLLLDLQMI</u> LN...haMut7 (SEQ ID NO: 29)
Trunc8	Fc...TQKSLSL----- <u>QLQLEHLLLDLQMI</u> LN...haMut7 (SEQ ID NO: 30)

**[0231]** 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

**[0232]** 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 bioactivity. 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).

**[0233]** 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.II-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 µg 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 µg per animal, the high affinity mutations did not improve Treg expansion beyond that observed with the N88D or V91K mutations alone (FIG. 7).

**[0234]** Treg expansion was selective in that FOXP3<sup>-</sup>CD4<sup>+</sup> 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<sup>-</sup> 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\_de1K)::G4S::huIL-2 (C125A)  
(SEQ ID NO: 16)  
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSHE

DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE  
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPG

GGGG

APTSSSTKKTQLQLEHLLLDLQMI<sup>L</sup>NGINNYKNPKL<sup>R</sup>RLMT<sup>R</sup>FKFYMPKK  
ATELKH<sup>L</sup>QLCEEELKPLEEVLNLAQSKNFHLRPRDLISININIVLELKG  
SETTFMCEYADETATIVEFLNRWITFAQSIISTLT

Fc.haMut1V91K IgG1Fc (N297G\_de1K)::G4S::huIL-2  
(V69A, Q74P, V91K, C125A)  
(SEQ ID NO: 17)  
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSHE

DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE  
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPG

GGGG

APTSSSTKKTQLQLEHLLLDLQMI<sup>L</sup>NGINNYKNPKL<sup>R</sup>RLMT<sup>R</sup>FKFYMPKK  
ATELKH<sup>L</sup>QLCEEELKPLEEALNLAQSKNFHLRPRDLISININKIVLELKG  
SETTFMCEYADETATIVEFLNRWITFAQSIISTLT

Fc.V91K (or Fc.II-2 (V91K))  
IgG1Fc (N297G\_de1K)::G4S::huIL-2 (V91K, C125A)  
(SEQ ID NO: 18)  
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSHE

DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE  
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR



-continued

LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR  
WQQGNVFSCSVMEALHNHYTKSLSLSPG

GGGS

APTSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKPYMPKK  
ATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINKIVLELKG  
SETTFMCEYADETATIVEFLNRWITFAQSIISTLT

Fc.haMut1N88D\_IgG1Fc(N297G\_delK)::G4S::huIL-2  
(V69A, Q74P, N88D, C125A) (SEQ ID NO: 19)

DKHTHTPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH  
DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE  
YKCKVSNKALPAPIEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLT  
LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR  
WQQGNVFSCSVMEALHNHYTKSLSLSPG

GGGS

APTSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKPYMPKK  
ATELKHLCLEELKPLEEALNLAQSKNFHLRPRDLISDINIVLELKG  
SETTFMCEYADETATIVEFLNRWITFAQSIISTLT

Fc.N88D (or Fc.IL-2(N88D))  
IgG1Fc(N297G\_delK)::G4S::huIL-2(N88D, C125A)  
(SEQ ID NO: 20)

DKHTHTPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH  
DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE  
YKCKVSNKALPAPIEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLT  
LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR  
WQQGNVFSCSVMEALHNHYTKSLSLSPG

GGGS

APTSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKPYMPKK  
ATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISDINIVLELKG  
SETTFMCEYADETATIVEFLNRWITFAQSIISTLT

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

**[0235]** 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 µg/mouse (FIG. 7) and at a lower dose of 0.5 µg/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.

**[0236]** 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. 9A and B).

**[0237]** 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. 9A).

**[0238]** 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. 9B).

Example 6—Fusion Sequence Optimization

**[0239]** 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 proteolytic 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)  
...TQKSLSLSPGKGGGSAPTSSTKKTQLQ... ha7N88D

(N297G\_delK)\_G4S (SEQ ID NO: 32)  
...TQKSLSLSPG GGGGSAPTSSTKKTQLQ... ha1V91K

(N297G\_KtoA)\_AAPT (SEQ ID NO: 33)  
...TQKSLSLSPGA APTSSTKKTQLQ... ha1V91K

(N297G\_KtoA)\_AAPA (SEQ ID NO: 34)  
...TQKSLSLSPGA APASSSTKKTQLQ... ha1V91K

**[0240]** 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.

**[0241]** 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

#### Altered

IgG1Fc(N297G\_delK)::G4S::huIL-2(T3N,V91K,C125A)  
(SEQ ID NO: 35)

TQKSLSLSPGGGGGSAPFSSSTKKTQLQ

IgG1Fc(N297G\_delK)::G4S::huIL-2(T3N,S5T,V91K,C125A)  
(SEQ ID NO: 36)

TQKSLSLSPGGGGGSAPFSSSTKKTQLQ

IgG1Fc(N297G\_delK)::GGNGT::huIL-2(T3A,V91K,C125A)  
(SEQ ID NO: 37)

TQKSLSLSPGGGGGNGTAPFSSSTKKTQLQ

### Example 7—Cynomolgus Monkey PK/PD Determination

**[0242]** 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.

**[0243]** 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.

**[0244]** Pharmacokinetics (quantitative immunoassay for intact molecule and total human Fc), anti-drug antibodies, shed soluble CD25, and serum cytokines (IL-113, TNF- $\alpha$ , IFN- $\gamma$ , 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.

**[0245]** Pharmacodynamics (immunophenotyping 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.

**[0246]** 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:

**[0247]** leukocyte count (total and absolute differential)

**[0248]** erythrocyte count

**[0249]** hemoglobin

**[0250]** hematocrit

**[0251]** mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated)

**[0252]** absolute reticulocytes

**[0253]** platelet count

**[0254]** blood cell morphology

**[0255]** red cell distribution width

**[0256]** mean platelet volume

## Clinical Chemistry:

- [0257] alkaline phosphatase
- [0258] total bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dL)
- [0259] aspartate aminotransferase
- [0260] alanine aminotransferase
- [0261] gamma glutamyl transferase
- [0262] urea nitrogen
- [0263] creatinine
- [0264] total protein
- [0265] albumin
- [0266] globulin and A/G (albumin/globulin) ratio (calculated)
- [0267] glucose
- [0268] total cholesterol
- [0269] triglycerides
- [0270] electrolytes (sodium, potassium, chloride)
- [0271] calcium
- [0272] phosphorus

## Example 8—Aglycosylated IgG1 Fc

[0273] Naturally occurring IgG antibodies possess 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 aglycosylated molecules with better biophysical properties and manufacturability attributes (e.g., recovery during purification).

[0274] 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 adopt 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.

[0275] Mutating Asn297 with Gly leads to aglycosylated 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, 2 L scale run.

[0276] 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 Aglycosylated IgG1 Fc

[0277] 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 Fcγ 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.

[0278] 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-I332C). The criteria used included (i) positions within the CH2 domain, (ii) away from loops, turns and carbohydrates, (iii) away from Fcγ receptor and FcRn interaction sites, (iv) solvent accessibility (preferred buried positions), etc.

[0279] 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-I332C, 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-I332C 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.

[0280] 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

**[0281]** 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<sup>+</sup>CD25<sup>+</sup> 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<sup>-</sup> 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<sup>+</sup> 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

**[0282]** 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. 10A 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

**[0283]** 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 QD×5). 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 QD×5 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	1 <sup>st</sup> cycle treatment Treatment day: Dose (SC)	2 <sup>nd</sup> 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

**[0284]** In FIGS. 11A-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.

**[0285]** 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. 12A 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<sup>+</sup> innate lymphoid cells. CD4 and CD8 Teff growth occurred



**[0293]** 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.

**[0294]** The IL-2:IL-2R $\alpha$ :IL-2R $\beta$ : $\gamma$ c 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, N.Y.).

**[0295]** The following IL-2 residues in the IL-2: IL-2R $\beta$  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, I92, 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.

**[0296]** Using the predicted  $\Delta\Delta G_{binding}$ , variants were selected according to the following criteria: the selected mutation does not introduce a proline residue; 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).

**[0297]** Mutations D20E, V91D, and I92W 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, 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, 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.

**[0298]** 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. 16A, 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. 16B 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

**[0299]** 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, I92K, I92R, 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 (FIG. 18) and for their ability to stimulate NK cell proliferation (FIG. 19).

**[0300]** Fc:IL-2 muteins were tested for their ability to bind CD25 (IL-2R $\alpha$ ) on the surface of T cells and to remain bound to cell surface CD25 at various time points (FIG. 20). 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-2R $\beta$ γ was closely linked to receptor agonism potency.

**[0301]** In a parallel experiment, the persistence of pSTAT5 signaling was observed by intracellular immunodetection of phospho-STAT5 at different time points. Phospho-STAT5 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).

**[0302]** To determine how different Fc:IL-2 muteins increased Treg frequency in vivo, humanized mice (NSG mice reconstituted four months prior with CD34<sup>+</sup> hematopoietic stem cells) were dosed with the indicated muteins, and Treg enrichment was measured in blood on day four (FIG. 23A). The degree of Treg enrichment was found to correlate most closely with the capacity to deliver an extended pSTAT5 signal (FIG. 23B), and substitutions at position V91 were particularly effective at Treg enrichment in vivo and increasing IL-2R signaling retention in vitro.

#### Example 15

**[0303]** A series of human anti-human IL-2 antibodies was generated in XENOMOUSE® (Amgen Inc., Thousand Oaks, Calif.) 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.

**[0304]** These antibodies were screened for their ability to inhibit IL-2 responses by DERL-2 cells (IL-2 receptor  $\alpha/\beta/\gamma$  positive) and by NKL cells (IL-2 receptor  $\alpha/\beta/\gamma$  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 IL2R $\alpha$ , 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  $\alpha$  and Bin G was defined by control antibody 5344.111 (Cat. No. 555051, BD Biosciences, San Jose, Calif.). None of the tested XENOMOUSE® antibodies fell into Bin F or G.

**[0305]** 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).

**[0306]** 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

Antibody	Bin	Hu WB pSTAT5 $IC_{50}$ vs			
		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	HGGSSSG----- -----RTYYYGLDV	VK1   O18/JK3	B	270 pM	130 pM
26H7	G4	VH5   5-51/D5   5-24   RF3/JH6	HGGYSGR----- -----SYYGMDV	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----- -----YFGEFDPY	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

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 Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys  
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 Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Leu Lys  
 50 55 60  
 Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu  
 65 70 75 80  
 Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu  
 85 90 95  
 Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala  
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 Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile  
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 50 55 60  
 Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu  
 65 70 75 80  
 Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu  
 85 90 95  
 Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala  
 100 105 110  
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35          40          45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50          55          60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65          70          75          80
Arg Val Val Ser 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 Pro Ala Pro Ile
100         105         110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115        120        125
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130        135        140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145        150        155        160
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165        170        175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180        185        190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195        200        205
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35          40          45
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Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
			100					105					110		
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
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Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
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Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
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His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
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Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys
35          40          45
Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys
50          55          60
Pro Leu Glu Glu Ala Leu Asn Leu Ala Pro Ser Lys Asn Phe His Leu
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Arg Pro Arg Asp Leu Ile Ser Asp Ile Asn Val Ile Val Leu Glu Leu
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20          25          30
Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys
35          40          45
Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys
50          55          60
Pro Leu Glu Glu Ala Leu Asn Leu Ala Pro Ser Lys Asn Phe His Leu
65          70          75          80
Arg Pro Arg Asp Leu Ile Ser Asp Ile Asn Val Ile Val Leu Glu Leu
85          90          95
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 Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys  
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 65 70 75 80  
 Arg Pro Arg Asp Leu Ile Ser Asp Ile Asn Val Ile Val Leu Glu Leu  
 85 90 95  
 Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala  
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&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic Polypeptide

&lt;400&gt; SEQUENCE: 11

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 Asn Pro Lys Leu Ala Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys  
 35 40 45  
 Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys  
 50 55 60  
 Pro Leu Glu Glu Ala Leu Asn Leu Ala Pro Ser Lys Asn Phe His Leu  
 65 70 75 80  
 Arg Pro Arg Asp Leu Ile Ser Asp Ile Asn Val Ile Val Leu Glu Leu  
 85 90 95  
 Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala  
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 Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys  
 50 55 60  
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 Arg Pro Arg Asp Leu Ile Ser Asp Ile Asn Val Ile Val Leu Glu Leu  
 85 90 95  
 Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala  
 100 105 110  
 Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile  
 115 120 125  
 Ile Ser Thr Leu Thr  
 130

<210> SEQ ID NO 13  
 <211> LENGTH: 133  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 13

Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His  
 1 5 10 15  
 Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys  
 20 25 30  
 Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys  
 35 40 45  
 Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys  
 50 55 60  
 Pro Leu Glu Asp Ala Leu Asn Leu Ala Pro Ser Lys Asn Phe His Leu  
 65 70 75 80  
 Arg Pro Arg Asp Leu Ile Ser Asp Ile Asn Val Ile Val Leu Glu Leu  
 85 90 95  
 Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala  
 100 105 110  
 Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile  
 115 120 125  
 Ile Ser Thr Leu Thr  
 130

<210> SEQ ID NO 14  
 <211> LENGTH: 133  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 14

Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His

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1	5	10	15
Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys	20	25	30
Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys	35	40	45
Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys	50	55	60
Pro Leu Glu Glu Ala Leu Arg Leu Ala Pro Ser Lys Asn Phe His Leu	65	70	75
Arg Pro Arg Asp Leu Ile Ser Asp Ile Asn Val Ile Val Leu Glu Leu	85	90	95
Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala	100	105	110
Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile	115	120	125
Ile Ser Thr Leu Thr	130		

<210> SEQ ID NO 15  
 <211> LENGTH: 133  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 15

Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His	1	5	10	15
Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys	20	25	30	
Asn Pro Arg Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Glu	35	40	45	
Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys	50	55	60	
Pro Leu Glu Asp Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu	65	70	75	80
Arg Pro Arg Asp Leu Ile Ser Asp Ile Asn Val Ile Val Leu Glu Leu	85	90	95	
Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala	100	105	110	
Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile	115	120	125	
Ile Ser Thr Leu Thr	130			

<210> SEQ ID NO 16  
 <211> LENGTH: 364  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 16

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly	1	5	10	15
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Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met  
                   20                                  25                                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His  
                   35                                  40                                  45

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

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr  
                   65                                  70                                  75                                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly  
                   85                                  90

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile  
                   100                                  105                                  110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val  
                   115                                  120                                  125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser  
                   130                                  135                                  140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu  
                   145                                  150                                  155                                  160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro  
                   165                                  170                                  175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val  
                   180                                  185                                  190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met  
                   195                                  200                                  205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser  
                   210                                  215                                  220

Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys  
                   225                                  230                                  235                                  240

Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu  
                   245                                  250                                  255

Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr  
                   260                                  265                                  270

Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln  
                   275                                  280                                  285

Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala  
                   290                                  295                                  300

Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile  
                   305                                  310                                  315                                  320

Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys  
                   325                                  330                                  335

Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp  
                   340                                  345                                  350

Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr Leu Thr  
                   355                                  360

<210> SEQ ID NO 17  
 <211> LENGTH: 364  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic Polypeptide  
 <400> SEQUENCE: 17

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Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1      5      10      15
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
      20      25      30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
      35      40      45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
      50      55      60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
      65      70      75      80
Arg Val Val Ser 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 Pro Ala Pro Ile
      100      105      110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
      115      120      125
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
      130      135      140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
      145      150      155      160
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
      165      170      175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
      180      185      190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
      195      200      205
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
      210      215      220
Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys
      225      230      235      240
Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu
      245      250      255
Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr
      260      265      270
Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln
      275      280      285
Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Ala Leu Asn Leu Ala
      290      295      300
Pro Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile
      305      310      315
Asn Lys Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys
      325      330      335
Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp
      340      345      350
Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr Leu Thr
      355      360

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&lt;210&gt; SEQ ID NO 18

&lt;211&gt; LENGTH: 364

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic Polypeptide



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&lt;400&gt; SEQUENCE: 18

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly  
 1 5 10 15  
 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met  
 20 25 30  
 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His  
 35 40 45  
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val  
 50 55 60  
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr  
 65 70 75 80  
 Arg Val Val Ser 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 Pro Ala Pro Ile  
 100 105 110  
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val  
 115 120 125  
 Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser  
 130 135 140  
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu  
 145 150 155 160  
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro  
 165 170 175  
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val  
 180 185 190  
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met  
 195 200 205  
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser  
 210 215 220  
 Pro Gly Gly Gly Gly Lys Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys  
 225 230 235 240  
 Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu  
 245 250 255  
 Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr  
 260 265 270  
 Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln  
 275 280 285  
 Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala  
 290 295 300  
 Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile  
 305 310 315 320  
 Asn Lys Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys  
 325 330 335  
 Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp  
 340 345 350  
 Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr Leu Thr  
 355 360

&lt;210&gt; SEQ ID NO 19

&lt;211&gt; LENGTH: 364

&lt;212&gt; TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 19
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1          5          10          15
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20          25          30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35          40          45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50          55          60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
65          70          75          80
Arg Val Val Ser 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 Pro Ala Pro Ile
100         105         110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115         120
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130         135         140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145         150         155         160
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165         170         175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180         185         190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195         200         205
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210         215         220
Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys
225         230         235         240
Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu
245         250         255
Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr
260         265         270
Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln
275         280         285
Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Ala Leu Asn Leu Ala
290         295         300
Pro Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asp Ile
305         310         315         320
Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys
325         330         335
Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp
340         345         350
Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr Leu Thr
355         360

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<210> SEQ ID NO 20
<211> LENGTH: 364
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 20

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1      5      10      15
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20     25     30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35     40     45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50     55     60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
65     70     75     80
Arg Val Val Ser 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 Pro Ala Pro Ile
100    105   110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115    120   125
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130    135   140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145    150   155   160
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165    170   175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180    185   190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195    200   205
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210    215   220
Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys
225    230   235   240
Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu
245    250   255
Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr
260    265   270
Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln
275    280   285
Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala
290    295   300
Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asp Ile
305    310   315   320
Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys
325    330   335
Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp
340    345   350
Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr Leu Thr

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355                      360

<210> SEQ ID NO 21  
<211> LENGTH: 6  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 21

His His His His His His  
1    5

<210> SEQ ID NO 22  
<211> LENGTH: 42  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 22

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser  
1                                      5                                      10                                      15

Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His  
                                    20                                      25                                      30

Leu Leu Leu Asp Leu Gln Met Ile Leu Asn  
                                    35                                      40

<210> SEQ ID NO 23  
<211> LENGTH: 30  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 23

Thr Gln Lys Ser Leu Ser Leu Ser Ser Thr Lys Lys Thr Gln Leu  
1                                      5                                      10                                      15

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn  
                                    20                                      25                                      30

<210> SEQ ID NO 24  
<211> LENGTH: 29  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 24

Thr Gln Lys Ser Leu Ser Leu Ser Ser Thr Lys Lys Thr Gln Leu Gln  
1                                      5                                      10                                      15

Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn  
                                    20                                      25

<210> SEQ ID NO 25  
<211> LENGTH: 28  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 25

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Thr Gln Lys Ser Leu Ser Leu Ser Thr Lys Lys Thr Gln Leu Gln Leu  
1 5 10 15

Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn  
20 25

<210> SEQ ID NO 26  
<211> LENGTH: 27  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 26

Thr Gln Lys Ser Leu Ser Leu Ser Lys Lys Thr Gln Leu Gln Leu Glu  
1 5 10 15

His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn  
20 25

<210> SEQ ID NO 27  
<211> LENGTH: 26  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 27

Thr Gln Lys Ser Leu Ser Leu Ser Lys Thr Gln Leu Gln Leu Glu His  
1 5 10 15

Leu Leu Leu Asp Leu Gln Met Ile Leu Asn  
20 25

<210> SEQ ID NO 28  
<211> LENGTH: 25  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 28

Thr Gln Lys Ser Leu Ser Leu Ser Thr Gln Leu Gln Leu Glu His Leu  
1 5 10 15

Leu Leu Asp Leu Gln Met Ile Leu Asn  
20 25

<210> SEQ ID NO 29  
<211> LENGTH: 24  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 29

Thr Gln Lys Ser Leu Ser Leu Ser Gln Leu Gln Leu Glu His Leu Leu  
1 5 10 15

Leu Asp Leu Gln Met Ile Leu Asn  
20

<210> SEQ ID NO 30  
<211> LENGTH: 23  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 30

Thr Gln Lys Ser Leu Ser Leu Gln Leu Gln Leu Glu His Leu Leu Leu  
1 5 10 15

Asp Leu Gln Met Ile Leu Asn  
20

<210> SEQ ID NO 31

<211> LENGTH: 29

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 31

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser  
1 5 10 15

Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln  
20 25

<210> SEQ ID NO 32

<211> LENGTH: 28

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 32

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala  
1 5 10 15

Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln  
20 25

<210> SEQ ID NO 33

<211> LENGTH: 24

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 33

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala Ala Pro Thr Ser Ser  
1 5 10 15

Ser Thr Lys Lys Thr Gln Leu Gln  
20

<210> SEQ ID NO 34

<211> LENGTH: 24

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 34

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala Ala Pro Ala Ser Ser  
1 5 10 15

Ser Thr Lys Lys Thr Gln Leu Gln  
20

<210> SEQ ID NO 35

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<211> LENGTH: 28  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 35

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala  
 1                   5                   10                   15

Pro Asn Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln  
                   20                   25

<210> SEQ ID NO 36  
 <211> LENGTH: 28  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 36

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala  
 1                   5                   10                   15

Pro Asn Ser Thr Ser Thr Lys Lys Thr Gln Leu Gln  
                   20                   25

<210> SEQ ID NO 37  
 <211> LENGTH: 28  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 37

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Asn Gly Thr Ala  
 1                   5                   10                   15

Pro Ala Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln  
                   20                   25

<210> SEQ ID NO 38  
 <211> LENGTH: 28  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 38

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Tyr Gly Asn Gly Thr Ala  
 1                   5                   10                   15

Pro Ala Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln  
                   20                   25

<210> SEQ ID NO 39  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 39

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp  
 1                   5                   10                   15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro

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	20						25						30						
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys				
	35						40					45							
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val				
	50					55					60								
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr				
65					70					75					80				
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu				
				85					90					95					
Gln	Tyr	Gly	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His				
			100						105					110					
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys				
		115						120						125					
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln				
	130					135						140							
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met				
145					150						155				160				
Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro				
				165					170					175					
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn				
		180							185					190					
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu				
		195					200						205						
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val				
	210					215					220								
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln				
225					230						235				240				
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Gly	Gly	Gly	Gly	Ser	Ala	Pro	Thr				
				245					250					255					
Ser	Ser	Ser	Thr	Lys	Lys	Thr	Gln	Gly	Gln	Leu	Glu	His	Leu	Leu	Leu				
			260						265					270					
Asp	Leu	Gln	Met	Ile	Leu	Asn	Gly	Ile	Asn	Asn	Tyr	Lys	Asn	Pro	Lys				
		275						280						285					
Leu	Thr	Arg	Met	Leu	Thr	Phe	Lys	Phe	Tyr	Met	Pro	Lys	Lys	Ala	Thr				
	290					295					300								
Glu	Leu	Lys	His	Leu	Gln	Cys	Leu	Glu	Glu	Glu	Leu	Lys	Pro	Leu	Glu				
305					310						315				320				
Glu	Val	Leu	Asn	Leu	Ala	Gln	Ser	Lys	Asn	Phe	His	Leu	Arg	Pro	Arg				
				325						330				335					
Asp	Leu	Ile	Ser	Asn	Ile	Asn	Val	Ile	Val	Leu	Glu	Leu	Lys	Gly	Ser				
		340							345					350					
Glu	Thr	Thr	Phe	Met	Cys	Glu	Tyr	Ala	Asp	Glu	Thr	Ala	Thr	Ile	Val				
		355						360						365					
Glu	Phe	Leu	Asn	Arg	Trp	Ile	Thr	Phe	Ala	Gln	Ser	Ile	Ile	Ser	Thr				
	370					375						380							
Leu	Thr																		
	385																		

<210> SEQ ID NO 40  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence



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&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 40

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1           5           10           15
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20           25           30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35           40           45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50           55           60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65           70           75           80
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
85           90           95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100          105          110
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
115          120          125
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
130          135          140
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145          150          155          160
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
165          170          175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
180          185          190
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
195          200          205
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
210          215          220
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225          230          235          240
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
245          250          255
Ser Ser Ser Thr Lys Lys Thr Gln Lys Gln Leu Glu His Leu Leu Leu
260          265          270
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
275          280          285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
290          295          300
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305          310          315          320
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
325          330          335
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
340          345          350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
355          360          365
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
370          375          380

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Leu Thr  
385

<210> SEQ ID NO 41  
<211> LENGTH: 386  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 41

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1           5           10           15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20           25           30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35           40           45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50           55           60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65           70           75           80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
85           90           95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100          105          110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
115          120          125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
130          135          140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145          150          155          160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
165          170          175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
180          185          190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
195          200          205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
210          215          220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225          230          235          240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
245          250          255

Ser Ser Ser Thr Lys Lys Thr Gln Gln Gln Leu Glu His Leu Leu Leu
260          265          270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
275          280          285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
290          295          300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305          310          315          320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
325          330          335

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Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
    340                               345                               350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
    355                               360                               365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
    370                               375                               380

Leu Thr
385

<210> SEQ ID NO 42
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 42

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1      5      10      15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
 20     25     30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 35     40     45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 50     55     60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 65     70     75     80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 85     90     95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100    105    110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
115    120    125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
130    135    140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145    150    155    160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
165    170    175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
180    185    190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
195    200    205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
210    215    220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225    230    235    240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
245    250    255

Ser Ser Ser Thr Lys Lys Thr Gln Ser Gln Leu Glu His Leu Leu Leu
260    265    270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
275    280    285

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Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 43  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 43

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240

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Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
      245                        250                        255
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gly Leu Glu His Leu Leu Leu
      260                        265                        270
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
      275                        280                        285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
      290                        295                        300
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
      305                        310                        315                        320
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
      325                        330                        335
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
      340                        345                        350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
      355                        360                        365
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
      370                        375                        380

Leu Thr
385

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<210> SEQ ID NO 44
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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<400> SEQUENCE: 44
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1      5      10      15
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
 20     25     30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 35     40     45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 50     55     60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 65     70     75     80
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 85     90     95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100    105    110
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
115    120    125
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
130    135    140
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145    150    155    160
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
165    170    175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
180    185    190

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Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Ala His Leu Leu Leu  
 260 265 270  
 Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335  
 Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380  
 Leu Thr  
 385

<210> SEQ ID NO 45  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 45

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

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Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145          150          155          160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
          165          170          175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
          180          185          190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
          195          200          205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
          210          215          220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225          230          235          240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
          245          250          255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Gly His Leu Leu Leu
          260          265          270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
          275          280          285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
          290          295          300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305          310          315          320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
          325          330          335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
          340          345          350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
          355          360          365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
          370          375          380

Leu Thr
385

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<210> SEQ ID NO 46
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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<400> SEQUENCE: 46

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1          5          10          15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
          20          25          30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
          35          40          45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
          50          55          60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
          65          70          75          80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
          85          90          95

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Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Ser His Leu Leu Leu  
 260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 47  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 47

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45



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Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 50                               55                               60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 65                               70                               75                               80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
                               85                               90                               95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                               100                              105                              110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                               115                              120                              125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
                               130                              135                              140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145                               150                              155                              160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
                               165                              170                              175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                               180                              185                              190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                               195                              200                              205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
210                               215                              220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225                               230                              235                              240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
                               245                              250                              255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Ala Leu Leu Leu
260                               265                              270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
275                               280                              285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
290                               295                              300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305                               310                              315                              320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
325                               330                              335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
340                               345                              350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
355                               360                              365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
370                               375                              380

Leu Thr
385

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<210> SEQ ID NO 48
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 48

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Asp Leu Leu Leu  
 260 265 270  
 Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335  
 Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380  
 Leu Thr  
 385

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<210> SEQ ID NO 49
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 49

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1          5          10          15
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20          25          30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35          40          45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50          55          60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65          70          75          80
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
85          90          95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100         105         110
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
115         120         125
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
130         135         140
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145         150         155         160
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
165         170         175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
180         185         190
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
195         200         205
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
210         215         220
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225         230         235         240
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
245         250         255
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Gly Leu Leu Leu
260         265         270
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
275         280         285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
290         295         300
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305         310         315         320
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
325         330         335
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
340         345         350

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Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
           355                                  360                                  365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
       370                                  375                                  380

Leu Thr  
 385

<210> SEQ ID NO 50  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 50

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1                  5                                  10                                  15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
           20                                  25                                  30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
           35                                  40                                  45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
           50                                  55                                  60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65                                  70                                  75                                  80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
           85                                  90                                  95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
           100                                  105                                  110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
           115                                  120                                  125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
           130                                  135                                  140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145                                  150                                  155                                  160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
           165                                  170                                  175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
           180                                  185                                  190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
           195                                  200                                  205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
           210                                  215                                  220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225                                  230                                  235                                  240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
           245                                  250                                  255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Lys Leu Leu Leu  
           260                                  265                                  270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
           275                                  280                                  285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290                                  295                                  300

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Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
370 375 380

Leu Thr  
385

<210> SEQ ID NO 51  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 51

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
245 250 255

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Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Met Leu Leu Leu  
 260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 52  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 52

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

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Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Asn Leu Leu Leu  
 260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 53  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 53

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

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Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
      165                               170                               175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
      180                               185                               190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
      195                               200                               205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
      210                               215                               220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
      225                               230                               235                               240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
      245                               250                               255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Arg Leu Leu Leu
      260                               265                               270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
      275                               280                               285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
      290                               295                               300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
      305                               310                               315                               320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
      325                               330                               335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
      340                               345                               350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
      355                               360                               365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
      370                               375                               380

Leu Thr
385

<210> SEQ ID NO 54
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 54

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1      5      10      15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20     25     30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35     40     45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50     55     60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65     70     75     80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
85     90     95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100    105    110

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Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Ser Leu Leu Leu  
 260 265 270  
 Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335  
 Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380  
 Leu Thr  
 385

&lt;210&gt; SEQ ID NO 55

&lt;211&gt; LENGTH: 386

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 55

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp  
 1 5 10 15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

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Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Thr Leu Leu Leu  
260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
370 375 380

Leu Thr  
385

<210> SEQ ID NO 56  
<211> LENGTH: 386  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 56

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
1 5 10 15

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Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Val Leu Leu Leu  
260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
370 375 380

Leu Thr  
385

<210> SEQ ID NO 57  
<211> LENGTH: 386  
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 57

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1      5      10
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20     25     30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35     40     45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50     55     60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65     70     75     80
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
85     90     95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100    105    110
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
115    120    125
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
130    135    140
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145    150    155    160
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
165    170    175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
180    185    190
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
195    200    205
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
210    215    220
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225    230    235    240
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
245    250    255
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu Tyr Leu Leu Leu
260    265    270
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
275    280    285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
290    295    300
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305    310    315    320
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
325    330    335
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
340    345    350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
355    360    365
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr

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370	375	380													
Leu Thr															
385															
<210> SEQ ID NO 58															
<211> LENGTH: 386															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: synthetic polypeptide															
<400> SEQUENCE: 58															
Met	Asp	Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Trp	
1				5				10					15		
Leu	Arg	Gly	Ala	Arg	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
		20						25				30			
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
		35					40					45			
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
	50					55					60				
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
65					70					75					80
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
				85					90					95	
Gln	Tyr	Gly	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
			100					105					110		
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
		115					120					125			
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln
	130					135					140				
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met
145					150					155					160
Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro
				165					170					175	
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn
		180					185						190		
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu
		195					200					205			
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
	210					215					220				
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln
225					230					235					240
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Gly	Gly	Gly	Gly	Ser	Ala	Pro	Thr
				245					250					255	
Ser	Ser	Ser	Thr	Lys	Lys	Thr	Gln	Leu	Gln	Leu	Glu	His	Leu	Leu	Ala
			260				265						270		
Asp	Leu	Gln	Met	Ile	Leu	Asn	Gly	Ile	Asn	Asn	Tyr	Lys	Asn	Pro	Lys
	275					280						285			
Leu	Thr	Arg	Met	Leu	Thr	Phe	Lys	Phe	Tyr	Met	Pro	Lys	Lys	Ala	Thr
	290					295					300				
Glu	Leu	Lys	His	Leu	Gln	Cys	Leu	Glu	Glu	Glu	Leu	Lys	Pro	Leu	Glu
305				310						315					320
Glu	Val	Leu	Asn	Leu	Ala	Gln	Ser	Lys	Asn	Phe	His	Leu	Arg	Pro	Arg

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325	330	335
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser		
340	345	350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val		
355	360	365
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr		
370	375	380
Leu Thr		
385		
<210> SEQ ID NO 59		
<211> LENGTH: 386		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: synthetic polypeptide		
<400> SEQUENCE: 59		
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp		
1	5	10
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro		
20	25	30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys		
35	40	45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val		
50	55	60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr		
65	70	75
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu		
85	90	95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His		
100	105	110
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		
115	120	125
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln		
130	135	140
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met		
145	150	155
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
165	170	175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn		
180	185	190
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu		
195	200	205
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val		
210	215	220
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
225	230	235
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Pro Thr		
245	250	255
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Asp		
260	265	270
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys		

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      275                280                285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
 290                295                300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
 305                310                315                320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
      325                330                335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
      340                345                350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
      355                360                365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
      370                375                380

Leu Thr
 385

<210> SEQ ID NO 60
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 60
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1                5                10                15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
      20                25                30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
      35                40                45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
      50                55                60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
      65                70                75                80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
      85                90                95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
      100                105                110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
      115                120                125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
      130                135                140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
      145                150                155                160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
      165                170                175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
      180                185                190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
      195                200                205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
      210                215                220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln

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225                230                235                240
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
                245                250                255
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Glu
                260                265                270
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
                275                280                285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
                290                295                300
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305                310                315                320
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
                325                330                335
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
                340                345                350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
                355                360                365
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
                370                375                380
Leu Thr
385

<210> SEQ ID NO 61
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptides

<400> SEQUENCE: 61
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1                5                10                15
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                20                25                30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
                35                40                45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50                55                60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65                70                75                80
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
                85                90                95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                100                105                110
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                115                120                125
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
                130                135                140
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145                150                155                160
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
                165                170                175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn

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180					185					190					
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu
	195						200					205			
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
	210					215					220				
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln
	225					230					235				240
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Gly	Gly	Gly	Gly	Ser	Ala	Pro	Thr
				245					250					255	
Ser	Ser	Ser	Thr	Lys	Lys	Thr	Gln	Leu	Gln	Leu	Glu	His	Leu	Leu	Gly
			260					265						270	
Asp	Leu	Gln	Met	Ile	Leu	Asn	Gly	Ile	Asn	Asn	Tyr	Lys	Asn	Pro	Lys
	275						280					285			
Leu	Thr	Arg	Met	Leu	Thr	Phe	Lys	Phe	Tyr	Met	Pro	Lys	Lys	Ala	Thr
	290					295					300				
Glu	Leu	Lys	His	Leu	Gln	Cys	Leu	Glu	Glu	Glu	Leu	Lys	Pro	Leu	Glu
	305					310								320	
Glu	Val	Leu	Asn	Leu	Ala	Gln	Ser	Lys	Asn	Phe	His	Leu	Arg	Pro	Arg
				325					330					335	
Asp	Leu	Ile	Ser	Asn	Ile	Asn	Val	Ile	Val	Leu	Glu	Leu	Lys	Gly	Ser
		340						345						350	
Glu	Thr	Thr	Phe	Met	Cys	Glu	Tyr	Ala	Asp	Glu	Thr	Ala	Thr	Ile	Val
		355					360						365		
Glu	Phe	Leu	Asn	Arg	Trp	Ile	Thr	Phe	Ala	Gln	Ser	Ile	Ile	Ser	Thr
	370					375						380			
Leu	Thr														
	385														

<210> SEQ ID NO 62  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 62

Met	Asp	Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Trp	
1				5					10					15	
Leu	Arg	Gly	Ala	Arg	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
			20					25					30		
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Lys	
		35				40						45			
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
	50					55					60				
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
	65					70					75				80
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
			85						90					95	
Gln	Tyr	Gly	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
			100					105						110	
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
		115					120						125		
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln

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130          135          140
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145          150          155          160
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
165          170          175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
180          185          190
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
195          200          205
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
210          215          220
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225          230          235          240
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
245          250          255
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Asn
260          265          270
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
275          280          285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
290          295          300
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305          310          315          320
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
325          330          335
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
340          345          350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
355          360          365
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
370          375          380
Leu Thr
385

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<210> SEQ ID NO 63
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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<400> SEQUENCE: 63
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1          5          10          15
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20          25          30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35          40          45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50          55          60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65          70          75          80
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu

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85	90	95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His 100 105 110		
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys 115 120 125		
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln 130 135 140		
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met 145 150 155 160		
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro 165 170 175		
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn 180 185 190		
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu 195 200 205		
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val 210 215 220		
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln 225 230 235 240		
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr 245 250 255		
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Arg 260 265 270		
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys 275 280 285		
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr 290 295 300		
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu 305 310 315 320		
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg 325 330 335		
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser 340 345 350		
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val 355 360 365		
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr 370 375 380		
Leu Thr 385		

<210> SEQ ID NO 64  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 64

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp 1 5 10 15		
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro 20 25 30		
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys		

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35					40					45					
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
50						55					60				
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
65					70					75					80
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
				85					90					95	
Gln	Tyr	Gly	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
			100						105					110	
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
		115						120					125		
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln
130						135						140			
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met
145					150					155					160
Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro
				165					170						175
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn
			180						185					190	
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu
			195				200						205		
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
210						215					220				
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln
225						230					235				240
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Gly	Gly	Gly	Gly	Ser	Ala	Pro	Thr
				245						250					255
Ser	Ser	Ser	Thr	Lys	Lys	Thr	Gln	Leu	Gln	Leu	Glu	His	Leu	Leu	Ser
			260					265							270
Asp	Leu	Gln	Met	Ile	Leu	Asn	Gly	Ile	Asn	Asn	Tyr	Lys	Asn	Pro	Lys
		275					280						285		
Leu	Thr	Arg	Met	Leu	Thr	Phe	Lys	Phe	Tyr	Met	Pro	Lys	Lys	Ala	Thr
290						295					300				
Glu	Leu	Lys	His	Leu	Gln	Cys	Leu	Glu	Glu	Glu	Leu	Lys	Pro	Leu	Glu
305					310					315					320
Glu	Val	Leu	Asn	Leu	Ala	Gln	Ser	Lys	Asn	Phe	His	Leu	Arg	Pro	Arg
				325						330					335
Asp	Leu	Ile	Ser	Asn	Ile	Asn	Val	Ile	Val	Leu	Glu	Leu	Lys	Gly	Ser
			340					345						350	
Glu	Thr	Thr	Phe	Met	Cys	Glu	Tyr	Ala	Asp	Glu	Thr	Ala	Thr	Ile	Val
			355					360					365		
Glu	Phe	Leu	Asn	Arg	Trp	Ile	Thr	Phe	Ala	Gln	Ser	Ile	Ile	Ser	Thr
370						375									380
Leu	Thr														
385															

&lt;210&gt; SEQ ID NO 65

&lt;211&gt; LENGTH: 386

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

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&lt;400&gt; SEQUENCE: 65

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
1 5 10 15  
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
20 25 30  
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
35 40 45  
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
50 55 60  
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
65 70 75 80  
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
85 90 95  
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
100 105 110  
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
115 120 125  
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
130 135 140  
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
145 150 155 160  
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
165 170 175  
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
180 185 190  
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
195 200 205  
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
210 215 220  
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
225 230 235 240  
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
245 250 255  
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Thr  
260 265 270  
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
275 280 285  
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
290 295 300  
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
305 310 315 320  
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
325 330 335  
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
340 345 350  
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
355 360 365  
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
370 375 380  
Leu Thr  
385

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<210> SEQ ID NO 66
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 66

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1          5          10          15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20         25         30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35         40         45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50         55         60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65         70         75         80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
85         90         95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100        105        110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
115        120        125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
130        135        140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145        150        155        160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
165        170        175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
180        185        190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
195        200        205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
210        215        220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225        230        235        240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
245        250        255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Val
260        265        270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
275        280        285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
290        295        300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305        310        315        320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
325        330        335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
340        345        350

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Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
                   355                                  360                                  365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
           370                                  375                                  380

Leu Thr  
 385

<210> SEQ ID NO 67  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 67

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1                  5                                  10                                  15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
           20                                  25                                  30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
           35                                  40                                  45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
           50                                  55                                  60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
           65                                  70                                  75                                  80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
                   85                                  90                                  95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
           100                                  105                                  110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
           115                                  120                                  125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
           130                                  135                                  140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
           145                                  150                                  155                                  160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
                   165                                  170                                  175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
           180                                  185                                  190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
           195                                  200                                  205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
           210                                  215                                  220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
           225                                  230                                  235                                  240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
                   245                                  250                                  255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
           260                                  265                                  270

Ala Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
           275                                  280                                  285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
           290                                  295                                  300

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Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 68  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 68

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255



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Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270

Glu Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 69  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 69

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

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Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270  
 Phe Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335  
 Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380  
 Leu Thr  
 385  
  
 <210> SEQ ID NO 70  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide  
  
 <400> SEQUENCE: 70  
  
 Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

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Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
      165                               170                               175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
      180                               185                               190
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
      195                               200                               205
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
      210                               215                               220
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
      225                               230                               235                               240
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
      245                               250                               255
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu
      260                               265                               270
Gly Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
      275                               280                               285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
      290                               295                               300
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
      305                               310                               315                               320
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
      325                               330                               335
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
      340                               345                               350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
      355                               360                               365
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
      370                               375                               380
Leu Thr
      385

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<210> SEQ ID NO 71
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 71

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1      5      10      15
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
 20     25     30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 35     40     45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 50     55     60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 65     70     75     80
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 85     90     95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100    105    110

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Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270  
 Trp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335  
 Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380  
 Leu Thr  
 385

&lt;210&gt; SEQ ID NO 72

&lt;211&gt; LENGTH: 386

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 72

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp  
 1 5 10 15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

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Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
260 265 270

Asp Leu Gln Arg Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
370 375 380

Leu Thr  
385

<210> SEQ ID NO 73  
<211> LENGTH: 386  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 73

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
1 5 10 15



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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 74

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1          5          10          15
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
 20          25          30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 35          40          45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 50          55          60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 65          70          75          80
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 85          90          95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 100         105         110
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 115         120         125
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 130         135         140
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 145         150         155         160
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 165         170         175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 180         185         190
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
 195         200         205
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 210         215         220
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 225         230         235         240
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
 245         250         255
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu
 260         265         270
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
 275         280         285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
 290         295         300
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
 305         310         315         320
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Gly Pro Arg
 325         330         335
Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
 340         345         350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
 355         360         365

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Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 75  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 75

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270  
 Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320





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Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
           275                                  280                                  285  
  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
           290                                  295                                  300  
  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305                                  310                                  315                                  320  
  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Thr Pro Arg  
                                   325                                  330                                  335  
  
 Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
           340                                  345                                  350  
  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
           355                                  360                                  365  
  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
           370                                  375                                  380  
  
 Leu Thr  
 385

<210> SEQ ID NO 77  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 77

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1                  5                                  10                                  15  
  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
           20                                  25                                  30  
  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
           35                                  40                                  45  
  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
           50                                  55                                  60  
  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65                                  70                                  75                                  80  
  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
           85                                  90                                  95  
  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
           100                                  105                                  110  
  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
           115                                  120                                  125  
  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
           130                                  135                                  140  
  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145                                  150                                  155                                  160  
  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
                                   165                                  170                                  175  
  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
           180                                  185                                  190  
  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
           195                                  200                                  205  
  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
           210                                  215                                  220

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Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225                230                235                240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
                245                250                255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu
                260                265                270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
                275                280                285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
290                295                300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305                310                315

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
                325                330                335

Ala Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
                340                345                350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
                355                360                365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
370                375                380

Leu Thr
385

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<210> SEQ ID NO 78
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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<400> SEQUENCE: 78

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1          5          10          15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20        25        30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35        40        45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50        55        60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65        70        75        80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
85        90        95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100       105       110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
115       120       125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
130       135       140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145       150       155       160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
165       170       175

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Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
      180                      185                      190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
      195                      200                      205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
      210                      215                      220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
      225                      230                      235                      240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
      245                      250                      255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu
      260                      265                      270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
      275                      280                      285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
      290                      295                      300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
      305                      310                      315                      320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
      325                      330                      335

Glu Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
      340                      345                      350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
      355                      360                      365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
      370                      375                      380

Leu Thr
385

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<210> SEQ ID NO 79
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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<400> SEQUENCE: 79

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```

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1      5      10      15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
 20     25     30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 35     40     45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 50     55     60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 65     70     75     80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 85     90     95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100    105    110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
115    120    125

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Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Ile Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 81  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 81

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

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Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Met Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 82  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

-continued

&lt;400&gt; SEQUENCE: 82

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270  
 Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335  
 Gln Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380  
 Leu Thr



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385

<210> SEQ ID NO 83  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 83

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp  
 1 5 10 15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270  
 Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335  
 Arg Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser

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340	345	350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val 355 360 365		
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr 370 375 380		
Leu Thr 385		
<210> SEQ ID NO 84 <211> LENGTH: 386 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: synthetic polypeptide		
<400> SEQUENCE: 84		
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp 1 5 10 15		
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro 20 25 30		
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys 35 40 45		
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val 50 55 60		
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr 65 70 75 80		
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu 85 90 95		
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His 100 105 110		
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys 115 120 125		
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln 130 135 140		
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met 145 150 155 160		
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro 165 170 175		
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn 180 185 190		
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu 195 200 205		
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val 210 215 220		
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln 225 230 235 240		
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr 245 250 255		
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu 260 265 270		
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys 275 280 285		
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr		

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290                    295                    300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305                    310                    315                    320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
                          325                    330                    335  
 Ser Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
                          340                    345                    350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
                          355                    360                    365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
                          370                    375                    380  
 Leu Thr  
 385  
  
 <210> SEQ ID NO 85  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide  
  
 <400> SEQUENCE: 85  
 Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1                    5                    10                    15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
                          20                    25                    30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
                          35                    40                    45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
                          50                    55                    60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
                          65                    70                    75                    80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
                          85                    90                    95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
                          100                    105                    110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
                          115                    120                    125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
                          130                    135                    140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
                          145                    150                    155                    160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
                          165                    170                    175  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
                          180                    185                    190  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
                          195                    200                    205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
                          210                    215                    220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
                          225                    230                    235                    240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr



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195					200					205					
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
210						215					220				
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln
225					230					235					240
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Gly	Gly	Gly	Gly	Ser	Ala	Pro	Thr
				245					250					255	
Ser	Ser	Ser	Thr	Lys	Lys	Thr	Gln	Leu	Gln	Leu	Glu	His	Leu	Leu	Leu
			260					265					270		
Asp	Leu	Gln	Met	Ile	Leu	Asn	Gly	Ile	Asn	Asn	Tyr	Lys	Asn	Pro	Lys
	275						280					285			
Leu	Thr	Arg	Met	Leu	Thr	Phe	Lys	Phe	Tyr	Met	Pro	Lys	Lys	Ala	Thr
290						295					300				
Glu	Leu	Lys	His	Leu	Gln	Cys	Leu	Glu	Glu	Glu	Leu	Lys	Pro	Leu	Glu
305					310					315					320
Glu	Val	Leu	Asn	Leu	Ala	Gln	Ser	Lys	Asn	Phe	His	Leu	Arg	Pro	Arg
				325					330					335	
Asp	Leu	Ile	Arg	Asn	Ile	Asn	Val	Ile	Val	Leu	Glu	Leu	Lys	Gly	Ser
			340					345					350		
Glu	Thr	Thr	Phe	Met	Cys	Glu	Tyr	Ala	Asp	Glu	Thr	Ala	Thr	Ile	Val
			355				360					365			
Glu	Phe	Leu	Asn	Arg	Trp	Ile	Thr	Phe	Ala	Gln	Ser	Ile	Ile	Ser	Thr
370						375					380				
Leu	Thr														
385															

&lt;210&gt; SEQ ID NO 87

&lt;211&gt; LENGTH: 386

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 87

Met	Asp	Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Leu	Trp
1				5					10					15	
Leu	Arg	Gly	Ala	Arg	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
			20					25					30		
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
		35				40						45			
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
	50					55					60				
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
65					70					75					80
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
				85					90					95	
Gln	Tyr	Gly	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
				100				105					110		
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
		115					120					125			
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln
130						135						140			
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met

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145              150              155              160
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
      165              170              175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
      180              185              190
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
      195              200              205
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
      210              215              220
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
      225              230              235              240
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
      245              250              255
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu
      260              265              270
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
      275              280              285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
      290              295              300
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
      305              310              315              320
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
      325              330              335
Asp Leu Ile Ser Ala Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
      340              345              350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
      355              360              365
Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr
      370              375              380
Leu Thr
385

<210> SEQ ID NO 88
<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 88
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp
1      5      10      15
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20     25     30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35     40     45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50     55     60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65     70     75     80
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
85     90     95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His

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100				105				110							
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
	115						120					125			
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln
	130					135					140				
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met
	145				150					155					160
Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro
			165						170					175	
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn
		180							185					190	
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu
		195					200						205		
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
	210					215					220				
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln
	225				230					235					240
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Gly	Gly	Gly	Gly	Ser	Ala	Pro	Thr
			245						250					255	
Ser	Ser	Ser	Thr	Lys	Lys	Thr	Gln	Leu	Gln	Leu	Glu	His	Leu	Leu	Leu
			260						265					270	
Asp	Leu	Gln	Met	Ile	Leu	Asn	Gly	Ile	Asn	Asn	Tyr	Lys	Asn	Pro	Lys
	275						280						285		
Leu	Thr	Arg	Met	Leu	Thr	Phe	Lys	Phe	Tyr	Met	Pro	Lys	Lys	Ala	Thr
	290					295					300				
Glu	Leu	Lys	His	Leu	Gln	Cys	Leu	Glu	Glu	Glu	Leu	Lys	Pro	Leu	Glu
	305				310					315					320
Glu	Val	Leu	Asn	Leu	Ala	Gln	Ser	Lys	Asn	Phe	His	Leu	Arg	Pro	Arg
			325						330					335	
Asp	Leu	Ile	Ser	Glu	Ile	Asn	Val	Ile	Val	Leu	Glu	Leu	Lys	Gly	Ser
	340								345				350		
Glu	Thr	Thr	Phe	Met	Cys	Glu	Tyr	Ala	Asp	Glu	Thr	Ala	Thr	Ile	Val
		355					360						365		
Glu	Phe	Leu	Asn	Arg	Trp	Ile	Thr	Phe	Ala	Gln	Ser	Ile	Ile	Ser	Thr
	370					375					380				
Leu	Thr														
	385														

&lt;210&gt; SEQ ID NO 89

&lt;211&gt; LENGTH: 386

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 89

Met	Asp	Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Leu	Trp
	1				5					10				15	
Leu	Arg	Gly	Ala	Arg	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
		20							25					30	
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
		35					40						45		
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val

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50	55	60																	
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr				
65					70					75					80				
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu				
			85						90					95					
Gln	Tyr	Gly	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His				
			100						105					110					
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys				
			115						120					125					
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln				
	130					135					140								
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met				
145					150					155					160				
Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro				
			165						170					175					
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn				
			180						185					190					
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu				
			195						200					205					
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val				
			210			215					220								
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln				
225					230						235				240				
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Gly	Gly	Gly	Gly	Ser	Ala	Pro	Thr				
			245						250					255					
Ser	Ser	Ser	Thr	Lys	Lys	Thr	Gln	Leu	Gln	Leu	Glu	His	Leu	Leu	Leu				
			260						265					270					
Asp	Leu	Gln	Met	Ile	Leu	Asn	Gly	Ile	Asn	Asn	Tyr	Lys	Asn	Pro	Lys				
			275						280					285					
Leu	Thr	Arg	Met	Leu	Thr	Phe	Lys	Phe	Tyr	Met	Pro	Lys	Lys	Ala	Thr				
			290						295					300					
Glu	Leu	Lys	His	Leu	Gln	Cys	Leu	Glu	Glu	Glu	Leu	Lys	Pro	Leu	Glu				
305					310						315				320				
Glu	Val	Leu	Asn	Leu	Ala	Gln	Ser	Lys	Asn	Phe	His	Leu	Arg	Pro	Arg				
			325						330					335					
Asp	Leu	Ile	Ser	Phe	Ile	Asn	Val	Ile	Val	Leu	Glu	Leu	Lys	Gly	Ser				
			340						345					350					
Glu	Thr	Thr	Phe	Met	Cys	Glu	Tyr	Ala	Asp	Glu	Thr	Ala	Thr	Ile	Val				
			355						360					365					
Glu	Phe	Leu	Asn	Arg	Trp	Ile	Thr	Phe	Ala	Gln	Ser	Ile	Ile	Ser	Thr				
			370						375					380					
Leu	Thr																		
385																			

<210> SEQ ID NO 90  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: sythetic polypeptide  
  
 <400> SEQUENCE: 90  
 Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp



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1	5	10	15
Leu Arg Gly	Ala Arg Cys Asp Lys Thr His Thr	Cys Pro Pro Cys Pro	20 25 30
Ala Pro Glu	Leu Leu Gly Gly Pro Ser Val Phe Leu Phe	Pro Pro Lys	35 40 45
Pro Lys Asp	Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val	50 55 60	
Val Val Asp	Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr	65 70 75 80	
Val Asp Gly	Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu	85 90 95	
Gln Tyr Gly	Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His	100 105 110	
Gln Asp Trp	Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys	115 120 125	
Ala Leu Pro	Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln	130 135 140	
Pro Arg Glu	Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met	145 150 155 160	
Thr Lys Asn	Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro	165 170 175	
Ser Asp Ile	Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn	180 185 190	
Tyr Lys Thr	Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu	195 200 205	
Tyr Ser Lys	Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val	210 215 220	
Phe Ser Cys	Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln	225 230 235 240	
Lys Ser Leu	Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Pro Thr	245 250 255	
Ser Ser Ser	Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu	260 265 270	
Asp Leu Gln	Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys	275 280 285	
Leu Thr Arg	Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr	290 295 300	
Glu Leu Lys	His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu	305 310 315 320	
Glu Val Leu	Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg	325 330 335	
Asp Leu Ile	Ser Gly Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser	340 345 350	
Glu Thr Thr	Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val	355 360 365	
Glu Phe Leu	Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr	370 375 380	
Leu Thr		385	

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<211> LENGTH: 386
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 91
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1          5          10          15
Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
20          25          30
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
35          40          45
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
50          55          60
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65          70          75          80
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
85          90          95
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
100         105         110
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
115        120        125
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
130        135        140
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145        150        155        160
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
165        170        175
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
180        185        190
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
195        200        205
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
210        215        220
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225        230        235        240
Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
245        250        255
Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu
260        265        270
Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
275        280        285
Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
290        295        300
Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305        310        315        320
Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
325        330        335
Asp Leu Ile Ser Met Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser
340        345        350
Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val
355        360        365

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Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 92  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 92

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

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Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335  
 Asp Leu Ile Ser Ser Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380  
 Leu Thr  
 385

<210> SEQ ID NO 93  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 93

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270

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Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
           275                                  280                                  285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
           290                                  295                                  300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
           305                                  310                                  315                                  320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
                                   325                                  330                                  335  
 Asp Leu Ile Ser Val Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
                                   340                                  345                                  350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
                                   355                                  360                                  365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
           370                                  375                                  380  
 Leu Thr  
 385

<210> SEQ ID NO 94  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 94

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1                  5                                  10                                  15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
           20                                  25                                  30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
           35                                  40                                  45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
           50                                  55                                  60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
           65                                  70                                  75                                  80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
                                   85                                  90                                  95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
           100                                  105                                  110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
           115                                  120                                  125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
           130                                  135                                  140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
           145                                  150                                  155                                  160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
                                   165                                  170                                  175  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
                                   180                                  185                                  190  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
           195                                  200                                  205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
           210                                  215                                  220

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Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270  
 Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335  
 Asp Leu Ile Ser Trp Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380  
 Leu Thr  
 385

<210> SEQ ID NO 95  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 95

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15  
 Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30  
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

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Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Asp Leu Ile Ser Asn Ile Asn Asp Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

&lt;210&gt; SEQ ID NO 96

&lt;211&gt; LENGTH: 386

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 96

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

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Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Asp Leu Ile Ser Asn Ile Asn Glu Ile Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

&lt;210&gt; SEQ ID NO 97

&lt;211&gt; LENGTH: 386

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 97

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80



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Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
				85					90					95	
Gln	Tyr	Gly	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
			100					105					110		
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
		115					120					125			
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln
	130					135					140				
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met
145					150					155					160
Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro
				165					170					175	
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn
			180						185				190		
Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu
			195				200					205			
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
		210				215					220				
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln
225					230						235				240
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Gly	Gly	Gly	Gly	Ser	Ala	Pro	Thr
				245					250					255	
Ser	Ser	Ser	Thr	Lys	Lys	Thr	Gln	Leu	Gln	Leu	Glu	His	Leu	Leu	Leu
			260					265					270		
Asp	Leu	Gln	Met	Ile	Leu	Asn	Gly	Ile	Asn	Asn	Tyr	Lys	Asn	Pro	Lys
		275					280					285			
Leu	Thr	Arg	Met	Leu	Thr	Phe	Lys	Phe	Tyr	Met	Pro	Lys	Lys	Ala	Thr
		290				295					300				
Glu	Leu	Lys	His	Leu	Gln	Cys	Leu	Glu	Glu	Glu	Leu	Lys	Pro	Leu	Glu
305					310					315					320
Glu	Val	Leu	Asn	Leu	Ala	Gln	Ser	Lys	Asn	Phe	His	Leu	Arg	Pro	Arg
				325					330					335	
Asp	Leu	Ile	Ser	Asn	Ile	Asn	Gly	Ile	Val	Leu	Glu	Leu	Lys	Gly	Ser
			340					345						350	
Glu	Thr	Thr	Phe	Met	Cys	Glu	Tyr	Ala	Asp	Glu	Thr	Ala	Thr	Ile	Val
			355					360					365		
Glu	Phe	Leu	Asn	Arg	Trp	Ile	Thr	Phe	Ala	Gln	Ser	Ile	Ile	Ser	Thr
		370					375				380				
Leu	Thr														
385															

<210> SEQ ID NO 98  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 98

Met	Asp	Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Leu	Trp
1				5						10					15
Leu	Arg	Gly	Ala	Arg	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
			20					25						30	

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Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
           35                          40                          45  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
   50                          55                          60  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
   65                          70                          75                          80  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
                           85                          90                          95  
 Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
                           100                          105                          110  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
                           115                          120                          125  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
   130                          135                          140  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
   145                          150                          155                          160  
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
                           165                          170                          175  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
                           180                          185                          190  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
                           195                          200                          205  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
   210                          215                          220  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
   225                          230                          235                          240  
 Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
                           245                          250                          255  
 Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
                           260                          265                          270  
 Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
   275                          280                          285  
 Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
   290                          295                          300  
 Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
   305                          310                          315                          320  
 Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
                           325                          330                          335  
 Asp Leu Ile Ser Asn Ile Asn Ser Ile Val Leu Glu Leu Lys Gly Ser  
                           340                          345                          350  
 Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
   355                          360                          365  
 Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
   370                          375                          380  
 Leu Thr  
 385

&lt;210&gt; SEQ ID NO 99

&lt;211&gt; LENGTH: 386

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

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<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 99

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr  
245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
275 280 285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Lys Val Leu Glu Leu Lys Gly Ser  
340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
370 375 380

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 Leu Thr  
 385

<210> SEQ ID NO 100  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 100

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1           5           10           15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
           20           25           30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
           35           40           45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
           50           55           60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
65           70           75           80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
           85           90           95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
           100          105          110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
           115          120          125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
           130          135          140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
145          150          155          160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
           165          170          175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
           180          185          190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
195          200          205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
210          215          220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
225          230          235          240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Pro Thr
           245          250          255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu
           260          265          270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys
           275          280          285

Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr
290          295          300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu
305          310          315          320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg
           325          330          335
  
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Asp Leu Ile Ser Asn Ile Asn Val Arg Val Leu Glu Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 101  
 <211> LENGTH: 386  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 101

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp  
 1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
 20 25 30

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 35 40 45

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 50 55 60

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 65 70 75 80

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 85 90 95

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 100 105 110

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 115 120 125

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 130 135 140

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 145 150 155 160

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
 165 170 175

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 180 185 190

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 195 200 205

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 210 215 220

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 225 230 235 240

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Ala Pro Thr  
 245 250 255

Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu  
 260 265 270

Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys  
 275 280 285

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Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr  
 290 295 300

Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu  
 305 310 315 320

Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg  
 325 330 335

Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Gly Leu Lys Gly Ser  
 340 345 350

Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val  
 355 360 365

Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr  
 370 375 380

Leu Thr  
 385

<210> SEQ ID NO 102  
 <211> LENGTH: 1158  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 102

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atggacatga gagtgctgc acagctgctg gccctgctgc tgetgtggct gagagggcc 60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaaccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaa catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccg 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 ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aagggaatt ggagcacttg ttgttgact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttgagg aggagttgaa gccattggag 960
gaggttttga atttgctca atccaagaat tttcacttgc gggcacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 103  
 <211> LENGTH: 1158  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence

-continued

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 103

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atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaactcct ggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag      180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccctg tggtcagcgt cctcacogtc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa      420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg      480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc      540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg      600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag      660
caggggaacg tcttctcatg ctccgtgatg catgaggtc tgcacaacca ctacacgcag      720
aagagcctct ccctgtctcc ggtgaggtg ggtggaagcg ctccaacttc ctctccact      780
aagaagactc aaaagcaatt ggagcacttg ttgttgact tgcaaatgat cttgaatggt      840
atcaataatt acaagaatcc aaagttagc 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 ttgaatcggg ggatcaacttt tgctcaatcc     1140
atcatctcca ctttgact                                     1158

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&lt;210&gt; SEQ ID NO 104

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 104

```

atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaactcct ggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag      180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccctg tggtcagcgt cctcacogtc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa      420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg      480
accaagaacc aggtcagcct gacctgctg 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
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aacagcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga 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 ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 105
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 105

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atggacatga gagtgctgc acagctgctg gcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtggtga cgtgagccac gaagaccctg aggtcaaagt caactggtac 240
gtggacggcg tggaggtgca taatgccaaag acaaagcccg gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tgcagaaaaac catctccaaa 420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aatcgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga 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 ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 106
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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&lt;400&gt; SEQUENCE: 106

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atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag      180
gtcacatgcg tgggtgtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccgtg tggtcagcgt cctcacgctc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa      420
gccaagggcg agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg      480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc      540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg      600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag      660
caggggaacg tcttctcatg ctccgtgatg catgaggtc tgcacaacca ctacacgcag      720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact      780
aagaagactc aattgggatt 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 ttgaatcggg ggatcacttt tgctcaatcc     1140
atcatctcca ctttgact                                     1158

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&lt;210&gt; SEQ ID NO 107

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 107

```

atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct gggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag      180
gtcacatgcg tgggtgtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccgtg tggtcagcgt cctcacgctc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa      420
gccaagggcg agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg      480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc      540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg      600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag      660
caggggaacg tcttctcatg ctccgtgatg catgaggtc tgcacaacca ctacacgcag      720

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aagagcctct ccctgtctcc gggtaggagt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggcgcacttg ttgtaggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggtca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 108
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

```

```

<400> SEQUENCE: 108

```

```

atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgog tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaagggcg agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatgccc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tccogtgctg 600
gactccgacg gctcctctct cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgacg 720
aagagcctct ccctgtctcc gggtaggagt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggggcacttg ttgtaggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggtca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

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<210> SEQ ID NO 109
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 109

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atggacatga gagtgectgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tgggtgtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc 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 ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt gtcgcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggcacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgetcaatcc 1140
atcatctcca ctttgact 1158

```

&lt;210&gt; SEQ ID NO 110

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 110

```

atggacatga gagtgectgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tgggtgtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc 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 ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780

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aagaagactc aattgcaatt ggaggccttg ttggtggact tgcaaatgat cttgaatggt      840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca      900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag      960
gaggttttga atttggtca atccaagaat tttcacttgc ggccacggga cttgatctcc     1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac     1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc     1140
atcatctcca ctttgact                                     1158

```

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<210> SEQ ID NO 111
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

```

```

<400> SEQUENCE: 111

```

```

atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaaactcct ggggggaccg     120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag     180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac     240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc     300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag     360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaaa catctccaaa     420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc 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 ctacacgacg     720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact     780
aagaagactc aattgcaatt ggaggacttg ttggtggact tgcaaatgat cttgaatggt     840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca     900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag     960
gaggttttga atttggtca atccaagaat tttcacttgc ggccacggga cttgatctcc     1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac     1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc     1140
atcatctcca ctttgact                                     1158

```

```

<210> SEQ ID NO 112
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 112

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atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc      60

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agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgct 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggtgaggtt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagggcttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagtgtact 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 ttgaaatcggg ggatcaacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 113
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 113

```

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atggacatga gagtgctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgct 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggtgaggtt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagaagttg ttggtggact tgcaaatgat cttgaatggt 840

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atcaataatt acaagaatcc aaagttgact cggatggtga 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 ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 114
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

```

```

<400> SEQUENCE: 114

```

```

atggacatga gagtgctgc acagctgctg gcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacacccca tgatctccc gaccctgag 180
gtcacatgcg tgggtggtga cgtgagccac gaagaccctg aggtcaaagt caactggtac 240
gtggacggcg tggaggtgca taatgccaa acaaagccg gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaaccag actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaa catctccaaa 420
gccaaggggc agccccgaga accacaggtg tacacccctc ccccatccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccaagcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct cctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagatggtt ttggttgact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga 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 ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 115
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 115

```

```

atggacatga gagtgctgc acagctgctg gcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaaactcct ggggggaccg 120

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tcagtcttcc tcttcccccc aaaacccaag gacacccctca tgatctcccc gaccocctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacgctc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgctg 600
gactccgacg gctcctctct cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagaacttg 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 ttgaatcggg ggateacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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&lt;210&gt; SEQ ID NO 116

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 116

```

atggacatga gagtgctgac acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacacccctca tgatctcccc gaccocctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacgctc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgctg 600
gactccgacg gctcctctct cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcgtctg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900

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aagaaggcta ctgagttgaa gcacttgcaa tgtttgagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 117
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 117

```

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atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctccc gaccctgag 180
gtcacatgog tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtag 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccctg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatgccc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctctg 600
gactccgacg gctcctctct cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaaag tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagagcttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttgagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 118
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

```

```

<400> SEQUENCE: 118

```

```

atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctccc gaccctgag 180

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gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgocct gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgacg 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagaccttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc gggcacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgetcaatcc 1140
atcatctcca ctttgact 1158

```

&lt;210&gt; SEQ ID NO 119

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 119

```

atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgocct gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgacg 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggaggtcttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960

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gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgetcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 120
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

```

```

<400> SEQUENCE: 120

```

```

atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgog tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggog tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaaa catctccaaa 420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgacg 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagtacttg ttgttgact 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 tgetcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 121
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

```

```

<400> SEQUENCE: 121

```

```

atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgog tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240

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gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaaoc tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 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 ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

&lt;210&gt; SEQ ID NO 122

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 122

```

atggacatga gagtgctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtgggga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaaoc tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 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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```

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

```

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<210> SEQ ID NO 123
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: sythetic polynucleotide

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```

<400> SEQUENCE: 123

```

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atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtccttc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccctg tggtcagcgt cctcacctgc ctgcaaccag actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgct 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct cctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggaggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggtcga atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 124
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: sythetic polynucleotide

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<400> SEQUENCE: 124

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```

atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtccttc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300

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acgtaccgtg tggtcagcgt cctcacogtc ctgcaccagg actggctgaa tggcaaggag	360
tacaagtgca aggtctccaa caaagccctc ccagccccc tgcagaaaac catctccaaa	420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg	480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc	540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg	600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag	660
caggggaaag tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag	720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact	780
aagaagactc aattgcaatt ggagcacttg ttgggggact 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 ttgaatcggg ggateacttt tgctcaatcc	1140
atcatctcca ctttgact	1158

&lt;210&gt; SEQ ID NO 125

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 125

atggacatga gagtgctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc	60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg	120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag	180
gtcacatgcy tgggtggtgga cgtgagccac gaagaccctg aggtcaaagt caactggtac	240
gtggacggcg tggaggtgca taatgccaag acaaagcccg gggaggagca gtacggcagc	300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaccagg actggctgaa tggcaaggag	360
tacaagtgca aggtctccaa caaagccctc ccagccccc tgcagaaaac catctccaaa	420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg	480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc	540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg	600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag	660
caggggaaag tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag	720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact	780
aagaagactc aattgcaatt ggagcacttg ttgaatgact 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 ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 126
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

```

```

<400> SEQUENCE: 126

```

```

atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacgctc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagcctc ccagccccc tcgagaaaac catctccaaa 420
gccaaggggc agccccgaga accacaggtg tacaccctgc cccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatgccc 540
gtggagtggg agagcaatgg gcaccggag aacaactaca agaccacgcc tcccgctgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaaag tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttgctgggact 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 ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 127
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 127

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atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacgctc ctgcaccagg actggctgaa tggcaaggag 360

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tacaagtgca aggtctccaa caaagccctc ccagcccca tcgagaaaac catctccaaa	420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg	480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc	540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctctg	600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag	660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgacg	720
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact	780
aagaagactc aattgcaatt ggagcacttg ttgtcggact tgcaaatgat cttgaatggt	840
atcaataatt acaagaatcc aaagttgact cggatggtga 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

&lt;210&gt; SEQ ID NO 128

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 128

atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc	60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg	120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag	180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtag	240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc	300
acgtaccctg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag	360
tacaagtgca aggtctccaa caaagccctc ccagcccca tcgagaaaac catctccaaa	420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg	480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc	540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctctg	600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag	660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgacg	720
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact	780
aagaagactc aattgcaatt ggagcacttg ttgacggact tgcaaatgat cttgaatggt	840
atcaataatt acaagaatcc aaagttgact cggatggtga 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

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 atcatctcca ctttgact 1158

<210> SEQ ID NO 129  
 <211> LENGTH: 1158  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 129

atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60  
 agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120  
 tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccocctgag 180  
 gtcacatgcy tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240  
 gtggacggcg tggaggtgca taatgccaaag acaaagccgc gggaggagca gtacggcagc 300  
 acgtaccctg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360  
 tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaaac catctccaaa 420  
 gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480  
 accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 540  
 gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgce tcccgtgctg 600  
 gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660  
 caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgag 720  
 aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaaactc ctctccact 780  
 aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840  
 atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900  
 aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960  
 gaggttttga atttggctca atccaagaat tttcacttgc gggcacggga cttgatctcc 1020  
 aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080  
 gctgacgaga ctgctactat cgttgagttt ttgaaatcggg ggatcacttt tgetcaatcc 1140  
 atcatctcca ctttgact 1158

<210> SEQ ID NO 130  
 <211> LENGTH: 1158  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 130

atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60  
 agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120  
 tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccocctgag 180  
 gtcacatgcy tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240  
 gtggacggcg tggaggtgca taatgccaaag acaaagccgc gggaggagca gtacggcagc 300  
 acgtaccctg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360  
 tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaaac catctccaaa 420



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gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg	480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc	540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgctg	600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag	660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag	720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact	780
aagaagactc aattgcaatt ggagcacttg ttggtggcct tgcaaatgat cttgaatggt	840
atcaataatt acaagaatcc aaagttgact cggatggtga 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 ttgaatcggg ggatcacttt tgctcaatcc	1140
atcatctcca ctttgact	1158

<210> SEQ ID NO 131  
 <211> LENGTH: 1158  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 131

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agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaaactcct ggggggaccg	120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag	180
gtcacatgog tgggtgggga cgtgagccac gaagaccctg aggtcaagtt caactggtac	240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc	300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag	360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaaac catctccaaa	420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg	480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc	540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgctg	600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag	660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag	720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact	780
aagaagactc aattgcaatt ggagcacttg ttggtggagt tgcaaatgat cttgaatggt	840
atcaataatt acaagaatcc aaagttgact cggatggtga 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 ttgaatcggg ggatcacttt tgctcaatcc	1140
atcatctcca ctttgact	1158

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<210> SEQ ID NO 132
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 132
atggacatga gagtgctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag      180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccctg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa      420
gccaagggcg agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg      480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc      540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgctg      600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag      660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag      720
aagagcctct ccctgtctcc ggttgagggt ggtggaagcg ctccaacttc ctctccact      780
aagaagactc aattgcaatt ggagcacttg ttggtgttct 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 ttgaatcggg ggatcacttt tgctcaatcc      1140
atcatctcca ctttgact                                     1158

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<210> SEQ ID NO 133
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 133
atggacatga gagtgctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag      180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccctg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa      420
gccaagggcg agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg      480

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accaagaacc aggtcagcct gacctgctg 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 gggtgagggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtgggct tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga 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 ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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&lt;210&gt; SEQ ID NO 134

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 134

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atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct gggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcy tgggtgggga cgtgagccac gaagaccctg aggtcaaagt caactggtac 240
gtggacggcg tggaggtgca taatgccaaag acaaagcccg gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacctgc ctgcccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tgcagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg 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 gggtgagggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtgggct tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga 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 ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 135
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 135
atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag      180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa      420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg      480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc      540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctctg      600
gactccgacg gctcctctct cctctatagc aagctcaccg tggacaagag cagggtggcag      660
caggggaaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag      720
aagagcctct ccctgtctcc gggtgagggt ggtggaagcg ctccaacttc ctctccact      780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaaggat 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 ttgaatcggg ggateacttt tgctcaatcc      1140
atcatctcca ctttgact                                     1158

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<210> SEQ ID NO 136
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 136
atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag      180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa      420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg      480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc      540

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gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tccogtgctg   600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag   660
caggggaaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag   720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact   780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt   840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca   900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag   960
gaggttttga atttggtcga atccaagaat tttcacttgg gccacggga cttgatctcc  1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac  1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgetcaatcc  1140
atcatctcca ctttgact                                     1158

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<210> SEQ ID NO 137
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 137

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atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc   60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg   120
tcagtcttcc tcttcccccc aaaacccaag gacacoccca tgatctcccg gaccctgag   180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtag   240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc   300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaaccagg actggctgaa tggcaaggag   360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa   420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg   480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc   540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tccogtgctg   600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag   660
caggggaaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag   720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact   780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt   840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca   900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag   960
gaggttttga atttggtcga atccaagaat tttcacttgg gccacggga cttgatctcc  1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac  1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgetcaatcc  1140
atcatctcca ctttgact                                     1158

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<210> SEQ ID NO 138
<211> LENGTH: 1158

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 138
atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccocctgag      180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaa catctccaaa      420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg      480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc      540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg      600
gactccgaog gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag      660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag      720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaaette ctctccact      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 tttcacttgt cgccacggga cttgatctcc     1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac     1080
gctgacgaga ctgctactat cgttgagttt ttgaaatcggg ggatcacttt tgctcaatcc     1140
atcatctcca ctttgact                                     1158

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<210> SEQ ID NO 139
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 139
atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccocctgag      180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaa catctccaaa      420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg      480
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc      540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg      600

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gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttgttgact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggtca atccaagaat tttcacttga gcccacggga cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

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<210> SEQ ID NO 140
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 140

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atggacatga gagtgctgc acagctgctg ggcctgctgc tgctgtggct gagagggcc 60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaaccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgog tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaaa catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatccag cgacatgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttgttgact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggtca atccaagaat tttcacttgc gcccacgggc cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 141
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 141

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atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaactcct ggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctccc gaccctgag      180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccctg tggtcagcgt cctcacctgc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa      420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatccc ggaggagatg      480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatgccc      540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg      600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag      660
caggggaacg tcttctcatg ctccgtgatg catgaggtc tgcacaacca ctacacgcag      720
aagagcctct ccctgtctcc ggtgaggtg ggtggaagcg ctccaacttc ctctccact      780
aagaagactc aattgcaatt ggagcacttg ttgttgact tgcaaatgat cttgaatggt      840
atcaataatt acaagaatcc aaagttagc cggatgttga cttttaagtt ttacatgcca      900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag      960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga gttgatctcc     1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac     1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcaactt tgctcaatcc     1140
atcatctcca ctttgact                                     1158

```

&lt;210&gt; SEQ ID NO 142

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 142

```

atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc      60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaactcct ggggggaccg      120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctccc gaccctgag      180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac      240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc      300
acgtaccctg tggtcagcgt cctcacctgc ctgcaccagg actggctgaa tggcaaggag      360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa      420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatccc ggaggagatg      480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatgccc      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
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacgggg cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 143
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 143

```

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atggacatga gagtgctgc acagctgctg gcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtggtga cgtgagccac gaagaccctg aggtcaaagt caactggtac 240
gtggacggcg tggaggtgca taatgccaaag acaaagcccg gggaggagca gtacggcagc 300
acgtaccctg tggtcagcgt cctcacctgc ctgcaaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tgcagaaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg 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 ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggat cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

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<210> SEQ ID NO 144
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 144

```
atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc    60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg    120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag    180
gtcacatgcg tgggtgtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac    240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc    300
acgtaccgtg tggtcagcgt cctcacgctc ctgcaccagg actggctgaa tggcaaggag    360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa    420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg    480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc    540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg    600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag    660
caggggaacg tcttctcatg ctccgtgatg catgaggtc tgcacaacca ctacacgcag    720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact    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 ggccacggat gttgatctcc   1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac   1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc   1140
atcatctcca ctttgact                                     1158
```

<210> SEQ ID NO 145

<211> LENGTH: 1158

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 145

```
atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc    60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg    120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag    180
gtcacatgcg tgggtgtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac    240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc    300
acgtaccgtg tggtcagcgt cctcacgctc ctgcaccagg actggctgaa tggcaaggag    360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa    420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg    480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc    540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg    600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag    660
caggggaacg tcttctcatg ctccgtgatg catgaggtc tgcacaacca ctacacgcag    720
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```

aagagcctct ccctgtctcc gggtaggagt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttgtaggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggca gttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 146
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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```

<400> SEQUENCE: 146

```

```

atggacatga gactgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgag tggtagtggg cgtgagccac gaagaccctg aggtcaagtt caactggtag 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtagcgtt cctcacctgc ctgcaaccag actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccc aaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtagctg 600
gactccgacg gctcctctct cctctatagc aagctcaccg tggacaagag caggtaggag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgag 720
aagagcctct ccctgtctcc gggtaggagt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttgtaggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggcg cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 147
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 147

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```

atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacctgc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgacg 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggtca atccaagaat tttcacttgc ggcacggag cttgatctcc 1020
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgetcaatcc 1140
atcatctcca ctttgact 1158

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&lt;210&gt; SEQ ID NO 148

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 148

```

atggacatga gagtgctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacctgc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgacg 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780

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aagaagactc aattgcaatt ggagcacttg ttgttgact tgcaaatgat cttgaatggt 840  
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900  
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960  
gaggttttga atttggtca atccaagaat tttcacttgc ggccacggac cttgatctcc 1020  
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080  
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140  
atcatctcca ctttgact 1158

<210> SEQ ID NO 149  
<211> LENGTH: 1158  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 149

atggacatga gaggcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60  
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaaactcct ggggggaccg 120  
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180  
gtcacatgcy tgggtggtga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240  
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300  
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360  
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaaa catctccaaa 420  
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480  
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccg cgacatcgcc 540  
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600  
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660  
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgag 720  
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcy ctccaacttc ctctccact 780  
aagaagactc aattgcaatt ggagcacttg ttgttgact tgcaaatgat cttgaatggt 840  
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900  
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960  
gaggttttga atttggtca atccaagaat tttcacttgc ggccacggga cttgatccgc 1020  
aatatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080  
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140  
atcatctcca ctttgact 1158

<210> SEQ ID NO 150  
<211> LENGTH: 1158  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 150

atggacatga gaggcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60

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agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgct 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggtgaggtg ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagtgtact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
gctatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcaactt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

&lt;210&gt; SEQ ID NO 151

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 151

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atggacatga gagtgctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgct 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggtgaggtg ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840

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atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
gagatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

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<210> SEQ ID NO 152
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 152

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atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtccttc tcttcccccc aaaacccaag gacacccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaaagt caactggtac 240
gtggacggcg tggaggtgca taatgccaaag acaaagcccg gggaggagca gtacggcagc 300
acgtaccctg tggtcagcgt cctcacogtc ctgcaaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggcg agccccgaga accacaggtg tacacccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccaagcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct cctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggttgact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
tttatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 153
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 153

```

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atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120

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tcagtcttcc tcttcccccc aaaacccaag gacaccccca tgatctcccc gaccocctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacgctc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgctg 600
gactccgacg gctcctctct cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtgagggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
ggtatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

&lt;210&gt; SEQ ID NO 154

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 154

```

atggacatga gagtgctgac acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccccca tgatctcccc gaccocctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacgctc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgctg 600
gactccgacg gctcctctct cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc gggtgagggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900

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aagaaggcta ctgagttgaa gcacttgcaa tgtttgagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
atgatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 155
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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&lt;400&gt; SEQUENCE: 155

```

atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgog tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccctg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatgccc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctctg 600
gactccgacg gctcctctct cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaaag tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatgttga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttgagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
agtatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 156
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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&lt;400&gt; SEQUENCE: 156

```

atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180

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gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgocct gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgagc 720
aagagcctct ccctgtctcc gggtgagggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggtcga atccaagaat tttcacttgc gggcacggga cttgatctcc 1020
gttatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgetcaatcc 1140
atcatctcca ctttgact 1158

```

&lt;210&gt; SEQ ID NO 157

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 157

```

atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcacogtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc ggaggagatg 480
accaagaacc aggtcagcct gacctgocct gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgagc 720
aagagcctct ccctgtctcc gggtgagggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960

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```

gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
tggatcaatg tgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgetcaatcc 1140
atcatctcca ctttgact 1158

```

```

<210> SEQ ID NO 158
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

```

```

<400> SEQUENCE: 158

```

```

atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgog tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggog tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaaa catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccc 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 ctacacgacg 720
aagagcctct ccctgtctcc ggttggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttgttgact 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 atatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggt ggatcacttt tgetcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 159
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 159

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atggacatga gagtgcctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccc gaccctgag 180
gtcacatgog tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240

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gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaaoc tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatg agatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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&lt;210&gt; SEQ ID NO 160

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 160

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atggacatga gagtgctgc acagctgctg ggcctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtgggga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccc tcgagaaaac catctccaaa 420
gccaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaaoc tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtggaggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggtggact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggctca atccaagaat tttcacttgc ggccacggga cttgatctcc 1020

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aatatcaatg ggatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 161
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 161

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atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300
acgtaccctg tggtcagcgt cctcacctgc ctgcaaccag actggctgaa tggcaaggag 360
tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa 420
gccaaggggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatcgcc 540
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgct 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 660
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct cctctgtctc ggttgagggt ggtggaagcg ctccaacttc ctctccact 780
aagaagactc aattgcaatt ggagcacttg ttggttgact tgcaaatgat cttgaatggt 840
atcaataatt acaagaatcc aaagttgact cggatggtga cttttaagtt ttacatgcca 900
aagaaggcta ctgagttgaa gcacttgcaa tgtttggagg aggagttgaa gccattggag 960
gaggttttga atttggtcga atccaagaat tttcacttgc ggccacggga cttgatctcc 1020
aatatcaatt cgatcgtttt ggagttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 162
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

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<400> SEQUENCE: 162

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atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 240
gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacggcagc 300

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acgtaccgtg	tggtcagcgt	cctcacogtc	ctgcaccagg	actggctgaa	tggaaggag	360
tacaagtgca	aggtctccaa	caaagccctc	ccagccccc	tcgagaaaac	catctccaaa	420
gccaaggggc	agccccgaga	accacaggtg	tacaccctgc	ccccatcccc	ggaggagatg	480
accaagaacc	aggtcagcct	gacctgctg	gtcaaaggct	tctatcccag	cgacatcgcc	540
gtggagtggg	agagcaatgg	gcagccggag	aacaactaca	agaccacgcc	tcccgtgctg	600
gactccgacg	gctccttctt	cctctatagc	aagctcaccg	tggacaagag	caggtggcag	660
caggggaacg	tcttctcatg	ctccgtgatg	catgaggctc	tgcaacaacca	ctacacgcag	720
aagagcctct	ccctgtctcc	gggtggaggt	ggtggaagcg	ctccaacttc	ctcctccact	780
aagaagactc	aattgcaatt	ggagcacttg	ttggtggact	tgcaaatgat	cttgaatggt	840
atcaataatt	acaagaatcc	aaagttgact	cggatggtga	cttttaagtt	ttacatgcca	900
aagaaggcta	ctgagttgaa	gcacttgcaa	tgtttggagg	aggagttgaa	gccattggag	960
gaggttttga	atltggctca	atccaagaat	tttcacttgc	ggccacggga	cttgatctcc	1020
aatatcaatg	tgaagttttt	ggagttgaag	ggttccgaga	ctacttttat	gtgtgagtac	1080
gctgacgaga	ctgctactat	cgttgagttt	ttgaatcggg	ggatcacttt	tgctcaatcc	1140
atcatctcca	ctttgact					1158

&lt;210&gt; SEQ ID NO 163

&lt;211&gt; LENGTH: 1158

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polynucleotide

&lt;400&gt; SEQUENCE: 163

atggacatga	gagtgctg	acagctgctg	ggcctgctgc	tgctgtggct	gagaggcgcc	60
agatgcgaca	aaactcacac	atgcccaccg	tgcccagcac	ctgaaactcct	ggggggaccg	120
tcagtcttcc	tcttcccccc	aaaacccaag	gacaccctca	tgatctcccc	gaccctgag	180
gtcacatgcg	tggtgggtgga	cgtgagccac	gaagaccctg	aggtcaaagtt	caactggtac	240
gtggacggcg	tgagggtgca	taatgccaag	acaaagcccg	gggaggagca	gtacggcagc	300
acgtaccgtg	tggtcagcgt	cctcacogtc	ctgcaccagg	actggctgaa	tggaaggag	360
tacaagtgca	aggtctccaa	caaagccctc	ccagccccc	tcgagaaaac	catctccaaa	420
gccaaggggc	agccccgaga	accacaggtg	tacaccctgc	ccccatcccc	ggaggagatg	480
accaagaacc	aggtcagcct	gacctgctg	gtcaaaggct	tctatcccag	cgacatcgcc	540
gtggagtggg	agagcaatgg	gcagccggag	aacaactaca	agaccacgcc	tcccgtgctg	600
gactccgacg	gctccttctt	cctctatagc	aagctcaccg	tggacaagag	caggtggcag	660
caggggaacg	tcttctcatg	ctccgtgatg	catgaggctc	tgcaacaacca	ctacacgcag	720
aagagcctct	ccctgtctcc	gggtggaggt	ggtggaagcg	ctccaacttc	ctcctccact	780
aagaagactc	aattgcaatt	ggagcacttg	ttggtggact	tgcaaatgat	cttgaatggt	840
atcaataatt	acaagaatcc	aaagttgact	cggatggtga	cttttaagtt	ttacatgcca	900
aagaaggcta	ctgagttgaa	gcacttgcaa	tgtttggagg	aggagttgaa	gccattggag	960
gaggttttga	atltggctca	atccaagaat	tttcacttgc	ggccacggga	cttgatctcc	1020
aatatcaatg	tgaagttttt	ggagttgaag	ggttccgaga	ctacttttat	gtgtgagtac	1080

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gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

<210> SEQ ID NO 164
<211> LENGTH: 1158
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polynucleotide

<400> SEQUENCE: 164
atggacatga gagtgcctgc acagctgctg gccctgctgc tgctgtggct gagaggcgcc 60
agatgcgaca aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg 120
tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 180
gtcacatgcg tgggtggtgga 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
gccaagggcg agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 480
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatcccag cgacatgccc 540
gtggagtggg agagcaatgg gcaccggag aacaactaca agaccacgcc tcccgctgctg 600
gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag cagggtggcag 660
caggggaaag tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 720
aagagcctct ccctgtctcc ggggtgaggt ggtggaagcg ctccaacttc ctctccact 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 ggggttgaag ggttccgaga ctacttttat gtgtgagtac 1080
gctgacgaga ctgctactat cgttgagttt ttgaatcggg ggatcacttt tgctcaatcc 1140
atcatctcca ctttgact 1158

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<210> SEQ ID NO 165
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 165
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1           5           10          15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asp Ser
20          25          30
Asp Glu Gly Asn Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln
35          40          45
Ser Pro Gln Leu Leu Ile Tyr Thr Leu Ser Tyr Arg Ala Ser Gly Val
50          55          60

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Pro Asp Arg Phe Ser Gly Thr Gly Ser Asp Thr Asp Phe Thr Leu Lys  
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln  
85 90 95

Arg Ile Glu Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile  
100 105 110

Lys Arg

<210> SEQ ID NO 166  
<211> LENGTH: 109  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 166

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly  
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Ser  
20 25 30

Tyr Leu Val Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu  
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Gly  
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu  
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro  
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg  
100 105

<210> SEQ ID NO 167  
<211> LENGTH: 112  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 167

Asp Ile Val Leu Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly  
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser His His Leu Ile His Ser  
20 25 30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro  
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro  
50 55 60

Asp Arg Phe Thr Gly Ser Gly Thr Gly Thr Asp Phe Thr Leu Lys Ile  
65 70 75 80

Ser Arg Val Glu Ala Gly Asp Val Gly Val Tyr Tyr Cys Met Gln Thr  
85 90 95

Thr Gln Phe Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg  
100 105 110

<210> SEQ ID NO 168



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<211> LENGTH: 112  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 168

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly  
 1 5 10 15  
 Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Leu Val Gln Ser  
 20 25 30  
 Asp Gly Asn Thr Tyr Leu Ser Trp Leu His Gln Arg Pro Gly Gln Pro  
 35 40 45  
 Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro  
 50 55 60  
 Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Met Gln Thr  
 85 90 95  
 Thr Gln Phe Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg  
 100 105 110

<210> SEQ ID NO 169  
 <211> LENGTH: 112  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 169

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly  
 1 5 10 15  
 Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ile Leu Val Asn Ser  
 20 25 30  
 Asp Gly Asn Thr Tyr Leu Ser Trp Leu His Gln Arg Pro Gly Gln Pro  
 35 40 45  
 Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro  
 50 55 60  
 Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile  
 65 70 75 80  
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr  
 85 90 95  
 Thr Gln Phe Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg  
 100 105 110

<210> SEQ ID NO 170  
 <211> LENGTH: 112  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 170

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly  
 1 5 10 15  
 Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Arg Ser  
 20 25 30

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Asp Gly Asn Thr Tyr Leu Ser Trp Leu His Gln Arg Pro Gly Gln Pro
    35          40          45
Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
    50          55          60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
    65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
          85          90          95
Thr Gln Phe Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
    100          105          110

```

```

<210> SEQ ID NO 171
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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<400> SEQUENCE: 171

```

```

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
 1          5          10          15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser His Ser Leu Val His Ser
          20          25          30
Asp Gly His Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
          35          40          45
Pro Arg Leu Leu Leu Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
    50          55          60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
    65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
          85          90          95
Thr Gln Phe Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
    100          105          110

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```

<210> SEQ ID NO 172
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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```

<400> SEQUENCE: 172

```

```

Asp Ile Ala Met Ser Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1          5          10          15
Glu Pro Ala Ser Met Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
    20          25          30
Asn Gly Phe Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
    35          40          45
Pro Gln Val Leu Ile His Leu Gly Ser Asp Arg Ala Ser Gly Val Pro
    50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
    65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Ala
          85          90          95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
    100          105          110

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Arg

<210> SEQ ID NO 173  
 <211> LENGTH: 113  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 173

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Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1           5           10           15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20          25          30
Asn Gly Phe Asn Tyr Leu Asp Trp Phe Leu Gln Lys Pro Gly Gln Ser
35          40          45
Pro Gln Pro Leu Ile Tyr Leu Gly Ser Asp Arg Ala Ser Gly Val Pro
50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85          90          95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100         105         110

```

Arg

<210> SEQ ID NO 174  
 <211> LENGTH: 113  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 174

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1           5           10           15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20          25          30
Asn Gly Phe Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35          40          45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asp Arg Ala Ser Gly Val Pro
50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85          90          95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100         105         110

```

Arg

<210> SEQ ID NO 175  
 <211> LENGTH: 112  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

-continued

&lt;400&gt; SEQUENCE: 175

```

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1           5           10           15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Asn Ile
          20           25           30
Asp Gly Ser Thr His Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
          35           40           45
Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
          50           55           60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65           70           75           80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
          85           90           95
Thr Gln Phe Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
          100          105          110

```

&lt;210&gt; SEQ ID NO 176

&lt;211&gt; LENGTH: 112

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 176

```

Glu Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1           5           10           15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Gln Ser
          20           25           30
Asp Gly Ile Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
          35           40           45
Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
          50           55           60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65           70           75           80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
          85           90           95
Thr Gln Phe Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
          100          105          110

```

&lt;210&gt; SEQ ID NO 177

&lt;211&gt; LENGTH: 112

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 177

```

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1           5           10           15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Asn Ser
          20           25           30
Asp Gly Asn Thr Tyr Leu Asn Trp Leu Gln Gln Arg Pro Gly Gln Pro
          35           40           45
Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
          50           55           60

```

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```

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
          85          90          95

Thr Gln Phe Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100          105          110

```

```

<210> SEQ ID NO 178
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

```

```

<400> SEQUENCE: 178

```

```

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1          5          10          15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser His Asn Leu Val Arg Ser
20          25          30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
35          40          45

Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
50          55          60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80

Ser Arg Val Gly Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
          85          90          95

Thr Gln Phe Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
100          105          110

```

```

<210> SEQ ID NO 179
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

```

```

<400> SEQUENCE: 179

```

```

Asn Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1          5          10          15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Gln Thr
20          25          30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
35          40          45

Pro Arg Pro Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
50          55          60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Val
          85          90          95

Thr Gln Phe Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
100          105          110

```

```

<210> SEQ ID NO 180
<211> LENGTH: 112
<212> TYPE: PRT

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```

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 180
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1           5           10          15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser His Asn Leu Ile His Ser
          20          25          30
Asp Gly Asn Thr Tyr Leu Ser Trp Leu His Gln Arg Pro Gly Gln Pro
          35          40          45
Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
          50          55          60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
          85          90          95
Ser Gln Phe Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
          100         105         110

```

```

<210> SEQ ID NO 181
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 181
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1           5           10          15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser His Asn Leu Leu His Ser
          20          25          30
Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
          35          40          45
Pro Arg Leu Leu Ile Tyr Glu Ile Ser Asn Arg Phe Ser Gly Val Pro
          50          55          60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Val
          85          90          95
Thr Gln Phe Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
          100         105         110

```

```

<210> SEQ ID NO 182
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 182
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1           5           10          15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
          20          25          30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
          35          40          45

```

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Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50                               55                               60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                               70                               75                               80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
                               85                               90                               95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
 100                               105

```

```

<210> SEQ ID NO 183
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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```

<400> SEQUENCE: 183

```

```

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1                               5                               10                               15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Arg
 20                               25                               30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35                               40                               45

Ile His Gly Pro Phe Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50                               55                               60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                               70                               75                               80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Asn Ser Ser
 85                               90                               95

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
 100                               105

```

```

<210> SEQ ID NO 184
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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```

<400> SEQUENCE: 184

```

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1                               5                               10                               15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Ser Ser Tyr
 20                               25                               30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
 35                               40                               45

Tyr Ala Ala Ser Ser Phe Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50                               55                               60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                               70                               75                               80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Tyr Ile Pro Arg
 85                               90                               95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100                               105

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<210> SEQ ID NO 185  
 <211> LENGTH: 109  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 185

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln  
 1 5 10 15  
 Thr Ala Arg Ile Ala Cys Ser Gly Asp Ala Leu Pro Arg Lys Phe Ala  
 20 25 30  
 Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Ser  
 35 40 45  
 Glu Asp Ser Arg Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
 50 55 60  
 Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu  
 65 70 75 80  
 Asp Glu Ala Asp Tyr Tyr Cys Phe Ser Thr Asp Ser Ser Ala Asn His  
 85 90 95  
 Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly  
 100 105

<210> SEQ ID NO 186  
 <211> LENGTH: 108  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 186

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asp  
 20 25 30  
 Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile  
 35 40 45  
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
 50 55 60  
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Gly Ser Leu Gln Pro  
 65 70 75 80  
 Glu Asp Phe Thr Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu  
 85 90 95  
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg  
 100 105

<210> SEQ ID NO 187  
 <211> LENGTH: 108  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 187

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
 1 5 10 15  
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asp Asp  
 20 25 30



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Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile  
           35                          40                          45

Tyr Ile Ala Thr Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
       50                          55                          60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
   65                          70                          75                          80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Ile Ser Tyr Pro Trp  
                           85                          90                          95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg  
           100                          105

<210> SEQ ID NO 188  
 <211> LENGTH: 108  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 188

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
 1                  5                          10                          15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asp Asp  
           20                          25                          30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile  
       35                          40                          45

Tyr Val Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
   50                          55                          60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
   65                          70                          75                          80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Ile Ser Tyr Pro Trp  
                           85                          90                          95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg  
           100                          105

<210> SEQ ID NO 189  
 <211> LENGTH: 108  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 189

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
 1                  5                          10                          15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asp Asp  
           20                          25                          30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile  
       35                          40                          45

Tyr Val Val Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
   50                          55                          60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
   65                          70                          75                          80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Gly Tyr Pro Trp  
                           85                          90                          95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg

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100 105

<210> SEQ ID NO 190  
 <211> LENGTH: 108  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 190

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Gly Asp Asp  
 20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Gln Arg Leu Ile  
 35 40 45

Tyr Ser Ala Ser Ser Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Arg  
 85 90 95

Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Arg Arg  
 100 105

<210> SEQ ID NO 191  
 <211> LENGTH: 108  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 191

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Glu His Asp  
 20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile  
 35 40 45

Tyr Ala Ala Ser Thr Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Phe Pro Arg  
 85 90 95

Ser Phe Gly Gln Gly Thr Gln Leu Glu Ile Lys Arg  
 100 105

<210> SEQ ID NO 192  
 <211> LENGTH: 114  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 192

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1 5 10 15



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```

Ser Gly Ser Glu Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                               70                               75                               80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Glu Asn Leu Pro Phe
                               85                               90                               95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
        100                               105

```

```

<210> SEQ ID NO 195
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

```

&lt;400&gt; SEQUENCE: 195

```

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1      5      10      15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Arg Gln Tyr Ala
        20      25      30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Met Leu Val Ile Tyr
        35      40      45

Lys Asp Ser Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
        50      55      60

Ser Ser Gly Thr Thr Val Thr Leu Thr Ile Ser Gly Val Gln Ala Glu
65      70      75      80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Ala Asp Ser Ser Gly Thr Tyr
        85      90      95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
        100      105

```

```

<210> SEQ ID NO 196
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

```

&lt;400&gt; SEQUENCE: 196

```

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1      5      10      15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Arg Lys Tyr Ala
        20      25      30

Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr
        35      40      45

Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
        50      55      60

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
65      70      75      80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ser Ser Gly Asn His
        85      90      95

Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
        100      105

```

```

<210> SEQ ID NO 197
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

```

-continued

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 197

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20           25           30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
35           40           45
Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50           55           60
Ser Gly Ser Gly Thr Asp Phe Phe Phe Thr Ile Ser Asn Leu Gln Pro
65           70           75           80
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Asp Asn Leu Pro Phe
85           90           95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
100          105

```

&lt;210&gt; SEQ ID NO 198

&lt;211&gt; LENGTH: 108

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 198

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20           25           30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35           40           45
Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50           55           60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65           70           75           80
Glu Asp Ile Ala Thr Phe Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Phe
85           90           95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
100          105

```

&lt;210&gt; SEQ ID NO 199

&lt;211&gt; LENGTH: 109

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 199

```

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1           5           10           15
Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Arg Lys Phe Ala
20           25           30
Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr
35           40           45

```

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Glu Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser  
 50 55 60

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu  
 65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Arg Ser Gly Asp His  
 85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly  
 100 105

<210> SEQ ID NO 200  
 <211> LENGTH: 108  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 200

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly  
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Trp  
 20 25 30

Leu Val Trp Tyr Gln Gln Lys Pro Gly Lys Pro Pro Lys Leu Leu Ile  
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly  
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Thr  
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Leu Ser Phe Pro Trp  
 85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Glu Val Lys Arg  
 100 105

<210> SEQ ID NO 201  
 <211> LENGTH: 342  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 201

gatattgtga tgaccagac tccactctcc ttgcccgta cccctggaga gccggcctcc 60

atctcctgca ggtctagtc gagcctotta gatagtgatg agggaaacac ctatttggac 120

tggtacctgc agaagccagg gcagtctcca cagctcctga tctatacgct ttcctatcgg 180

gcctctggag tcccagacag gtccagtggc actgggtcag aactgattt cacactgaaa 240

atcagcaggg tggaggctga ggatgttga gtttattact gcatgcaacg tatagagttt 300

cctctcactt tcggcggagg gaccaaggtg gagatcaaac ga 342

<210> SEQ ID NO 202  
 <211> LENGTH: 327  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 202

gaaattgtat tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60

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```

ctctcctgca gggccagtc gagttttagc agcagctact tagtctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcaccca gcagggccac tggeatccca 180
gacaggttcg gtggcagtg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtga ttactgtcag cagtatggta gctcacctct cactttcggc 300
ggagggacca aggtggagat caaacga 327

```

```

<210> SEQ ID NO 203
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 203

```

```

gatattgtgc tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc 60
atctcctgca ggtctagtca tcacctcata cacagtgatg gaaacaccta cttgagttgg 120
cttcaccaga ggccaggcca gctccaaga ctctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cactggcagt gggacagga cagatttcac actgaaaatc 240
agcaggggtg aagctgggga tgtcgggggt tattactgca tgcaaaactac acaatttccg 300
acgttcggcc aagggaccaa ggtggaatc aaacga 336

```

```

<210> SEQ ID NO 204
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 204

```

```

gatattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc 60
atctcctgca ggtccagtca aaacctcgtt caaagtgatg gaaacaccta cttgagttgg 120
cttcaccaga ggccaggcca gctccaaga ctctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcagga cagatttcac actgaaaatc 240
agcaggggtg aagctgagga tgtcgggggt tatttctgca tgcaaaactac acaatttccg 300
acgttcggcc aagggaccaa ggtggaatc aaacga 336

```

```

<210> SEQ ID NO 205
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 205

```

```

gatattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc 60
atttcctgca ggtctagtca aatcctcgtt aacagtgatg gaaacaccta cttgagttgg 120
cttcaccaga ggccaggcca gctccaaga ctctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcagga cagatttcac actgaaaatc 240
agcaggggtg aagctgagga tgtcgggggt tattactgca tgcaaaactac acaatttccg 300
acgttcggcc aagggaccaa ggtggaatc aaacga 336

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<210> SEQ ID NO 206  
<211> LENGTH: 336  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 206

gatattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc	60
atctcctgca ggtctagta aagcctcgta cgcagtgatg gaaacaccta cttgagttgg	120
cttcaccaga ggccaggcca gcctccaaga ctcttaattt ataagatttc taaccggttc	180
tctggggctcc cagacagatt cagtggcagt ggggcagga cagatttcac actgaaaatc	240
agcaggggtgg aagctgagga tgtcgggggtt tattactgca tgcaaaactac acaatttccg	300
acgttcggcc aagggaacca ggtggaatc aaacga	336

<210> SEQ ID NO 207  
<211> LENGTH: 336  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 207

gatattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc	60
atctcctgca ggtctagta cagcctcgta cacagtgatg gacacaccta cttgagttgg	120
cttcagcaga ggccaggcca gcctccaaga ctctactttt ataagatttc taaccggttc	180
tctggggctcc cagacagatt cagtggcagt ggggcagga cagatttcac actgaaaatc	240
agcaggggtgg aagctgagga tgtcgggggtt tattactgca tgcaaaactac acaatttccc	300
actttcggcg gagggacca ggtggagatc aaacga	336

<210> SEQ ID NO 208  
<211> LENGTH: 339  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 208

gatattgcga tgaagtcagtc tccactctcc ctgcccgtca cccttgaga gccggcctcc	60
atgtcatgca ggtctagta gagcctcctg catagtaatg gattcaacta tttgagttgg	120
tacctgcaga agccaggcca gtctccacag gtctgatcc atttgggttc tgatcgggcc	180
tccggggctcc ctgacaggtt cagtggcagt ggatcaggca cagattttac attgaaaatc	240
agcagagtgagg aggtgagga tgttgaatt tattactgca tgcaagctct acaaaactcct	300
ctcactttcg gcgaggagac caaggtggag atcaaacga	339

<210> SEQ ID NO 209  
<211> LENGTH: 339  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 209



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```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtc gagcctocta catagtaatg gattcaacta tttggattgg 120
ttcctgcaga agccaggaca gtctccacag cccctgatct atttgggttc tgatcgggcc 180
tccgggttcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttgggtt tattactgca tgcaagctct acaaactccg 300
ctcactttcg gccgagggac caaggtggag atcaaacga 339

```

```

<210> SEQ ID NO 210
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 210

```

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtc gagcctoctg catagtaatg gattcaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ctccctgatct atttgggttc tgatcgggcc 180
tccgggttcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttgggtt tattactgca tgcaagctct acaaactccg 300
ctcactttcg gccgagggac caaggtggag atcaaacga 339

```

```

<210> SEQ ID NO 211
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 211

```

```

gatattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc 60
atatcctgca ggtccagtc aagcctcgt aacattgatg gaagtaccca cttgagttgg 120
cttcagcaga ggccaggcca gctccaaga ctccctaattt ataagatttc taaccggttc 180
tctgggttcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaagatc 240
agcaggttgg aagctgagga tgtcgggtt tattactgca tgcaaaactac acaattcccc 300
accttcggcc aaggacacg actggagatt aaacga 336

```

```

<210> SEQ ID NO 212
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 212

```

```

gaaattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc 60
atttcctgca ggtctagtc aagcctcgtt cagagtgatg gaatcaacta cttgagttgg 120
cttcagcaga ggccaggcca gctccaaga ctccctaattt ataagatttc taaccggttc 180
tctgggttcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcaggttgg aagctgagga tgtcgggtt tattactgca tgcaaaactac acaatttccg 300

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acgttcggcc aagggaacaa ggtggaatc aaacga 336

<210> SEQ ID NO 213  
<211> LENGTH: 336  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 213

gatattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc 60

atctcctgca ggtctagtca aagcctcgta aacagtgatg gaaacaccta cttgaattgg 120

cttcagcaga gccaggcca gcctccaaga ctccctaattt ataagatttc taaccggttc 180

tctgggtcc cagacagatt cagtggcagt ggggcagga cagatttcac actgaaaatc 240

agcagggtgg aagctgagga tgtcgggggtt tattactgca tgcaagctac acaatttccc 300

acgttcggcc aagggaacaa ggtggaatc aaacga 336

<210> SEQ ID NO 214  
<211> LENGTH: 336  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 214

gatattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc 60

atctcctgca ggtccagtca caacctcgta cgcagtgatg gaaacaccta cttgagttgg 120

cttcagcaga gccaggcca gcctccaaga ctccctaattt ataagatttc taaccggttc 180

tctgggtcc cagacagatt cagtggcagt ggggcagga cagatttcac actgaaaatc 240

agcagggtgg gagctgagga tgtcgggggtt tattactgca tgcaagctac acaatttccc 300

accttcggcc aagggaacgc actggagatt aaacga 336

<210> SEQ ID NO 215  
<211> LENGTH: 336  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 215

aatattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc 60

atctcctgca ggtctagtca aagcctcgta caaactgatg gaaacacata tttgagttgg 120

cttcagcaga gccaggcca gcctccaaga cccctaattt ataagatttc taaccggttt 180

tctgggtcc cagacagatt cagtggcagt ggggcagga cagatttcac actgaaaatc 240

agcagggtgg aagctgagga tgtcgggggtt tattactgca tgcaagtaac acaatttccc 300

accttcggcc aagggaacgc actggagatt aaacga 336

<210> SEQ ID NO 216  
<211> LENGTH: 336  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

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<400> SEQUENCE: 216

```
gatattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc    60
atctcctgta ggtctagtca taacctcata cacagtgatg gaaacaccta cttgagttgg    120
cttcaccaga ggccaggcca gcctccaaga ctccctaattt ataagatttc taaccggttc    180
tctggggctcc cggacagatt cagtggcagt ggggcagga cagatttcac actgaaaatc    240
agcaggggtgg aagctgagga tgtcgggggtt tattactgca tgcaaaacttc acagtttccc    300
actttcggcg gagggaccaa ggtggagatc aaacga                               336
```

<210> SEQ ID NO 217

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 217

```
gatattgtga tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc    60
atctcctgca ggtctagtca taacctcata cacagtgatg gaaacaccta cttgagttgg    120
cttcagcaga ggccaggcca gcctccaaga ctccctaattt atgagatttc taaccggttc    180
tctggggctcc cagacagatt cagtggcagt ggggcagga cagatttcac actgaaaatc    240
agcaggggtgg aagctgagga tgtcgggggtt tattactgca tgcaagttac acaatttccc    300
actttcggcg gcgggaccaa ggtggagatc aaacga                               336
```

<210> SEQ ID NO 218

<211> LENGTH: 327

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 218

```
gaaattgtgt tgaagcagtc tccaggcacc ctgtcttctg ctccagggga aagagccacc    60
ctctcctgca gggccagtc gagtgtagc agcagctact tagcctggta ccagcagaaa    120
cctggccagg ctcccaggct cctcatctat ggtgcattca gcagggccac tggcatccca    180
gacaggttca gtggcagtg gctctgggaca gacttcactc tcaccatcag cagactggag    240
cctgaagatt ttgacagtg ttactgtcag cagtatggta gctcaccgct cactttcggc    300
ggagggacca aggtggagat caaacga                                       327
```

<210> SEQ ID NO 219

<211> LENGTH: 327

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 219

```
gaaattgtgt tgaagcagtc tccaggcacc ctgtcttctg ctccagggga aagagccacc    60
ctctcctgta gggccagtc gagtgtagc agcaggtact tagcctggta ccagcagaaa    120
cctggccagg ctcccaggct cctcatccat ggtccattca gcagggccac tggcatccca    180
gacaggttca gtggcagtg gctctgggaca gatttcactc tcaccatcag cagactggag    240
```

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cctgaagatt ttgcagtgta ttactgtcag cagtatggta attcatcgat caccttoggc 300

caagggacac gactggagat taaacga 327

<210> SEQ ID NO 220

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> 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

<210> SEQ ID NO 221

<211> LENGTH: 327

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 221

tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacaaaac ggccaggatc 60

gcctgctctg gagatgcatt gccaaagaaa ttgcttatt ggtaccagca gaagtcaggc 120

caggccccctg tgctggatcct ctctgaggac agcagacgac cctccgggat ccctgagaga 180

ttctctggct ccagctcagg gacaatggcc accttgacta tcagtggggc ccaggtggag 240

gatgaagctg actactactg tttctcaaca gacagcagtg ctaatcatag ggtattcggc 300

ggagggacca agctgaccgt cctaggt 327

<210> SEQ ID NO 222

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 222

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca ggacattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcggcag cctgcagcct 240

gaagatttta caacttatta ctgtctacag cataatagtt acccgctcac tttcggcgga 300

gggaccaagg tggagatcaa acga 324

<210> SEQ ID NO 223

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

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<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 223

```
gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgcc gggcaagtca gggcattaga gatgatttag gctggtatca gcagaaacca    120
gggaaagccc ctaagcgct gatctatatt gcaaccagtt tgcaaagtgg ggtcccatca    180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct    240
gaagattttg caacttatta ctgtctacag catattagtt acccgtggac gttcggccaa    300
gggaccaagg tggaaatcaa acga                                           324
```

<210> SEQ ID NO 224

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 224

```
gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgcc gggcaagtca ggacatcaga gatgatttag gctggtatca gcagaaacca    120
gggaaagccc ctaagcgct gatctatggt gcatccagtt tgcaaagtgg ggtcccatca    180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct    240
gaagattttg caacttatta ctgtctacag catattagtt acccgtggac gttcggccaa    300
gggaccaagg tggaaatcaa acga                                           324
```

<210> SEQ ID NO 225

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 225

```
gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgcc gggcaagtca ggacattaga gatgatttag gctggtatca gcagaaacca    120
gggaaagccc ctaagcgct gatctatggt gtatccagtt tgcaaagtgg ggtcccatca    180
aggttcagcg gcagtggatc tgggacagag ttcactctca caatcagcag cctgcagcct    240
gaagattttg caacttatta ctgtctacag cataatggtt acccgtggac gttcggccaa    300
gggaccaagg tggaaatcaa acga                                           324
```

<210> SEQ ID NO 226

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 226

```
gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgcc gggcaagtca gggcattgga gatgatttag gctggtatca gcagaagcca    120
gggaaagccc ctcagcgct gatctattct gcatccagtt tgccaagtgg ggtcccatca    180
```

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```

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt accctcgcag ttttgccag 300
gggaccaagc tggagatcag acga 324

```

```

<210> SEQ ID NO 227
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 227

```

```

gacatccaga tgaccagtc tccatctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtc ggacattgaa catgatttag gctggatca gcagaaacca 120
gggaaagccc ctaagcgct gatctatgct gcaccactt tgccaagtgg ggtccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt tcctcgcag ttttgccag 300
gggaccagc tggagatcaa acga 324

```

```

<210> SEQ ID NO 228
<211> LENGTH: 342
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 228

```

```

gatattgtga tgaccagac tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctactca ggcctcttg gatggtgatg atggaaacac cttttggac 120
tggtaacctgc agaagccagg gcagtctcca cagctctga tctatacgt ttcctatcg 180
gcctctggag tcccagacag gttcagtggc agtgggtcag gcactgattt cacactgaaa 240
atcagcaggg tggaggctga ggatgttga gtttattact gcatgcaacg tttagagttt 300
cctctcactt tcggcggagg gaccaagtg gagatcaaac ga 342

```

```

<210> SEQ ID NO 229
<211> LENGTH: 342
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 229

```

```

gacattgtga tgaccagac tccactctcc ttgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca ggcctcttg gatagtgatg aaggaaacac cttttggat 120
tggtaacctgc agaagccagg gcagcctcca cagctctga tctatacgt ttcctatcg 180
gcctctggag tcccagacag gttcagtggc agtgggtcag gcactgattt cacactgaaa 240
atcagcaggg tggaggctga ggatgttga gtttattact gcatgcaacg tatagagttt 300
cctctcactt tcggcggagg gaccaagtg gagatcaaac ga 342

```

```

<210> SEQ ID NO 230
<211> LENGTH: 324

```

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```

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 230

gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca    120
gggaaagccc ctaagctcct gatctacgat gcaccaatt tggaaacagg ggtcccatca    180
aggttcagtg gaagtggatc tgagacagat tttactttca ccatcagcag cctgcagcct    240
gaagatattg caacatatta ctgtcaacag tatgaaaatc tcccattcac tttcggcct    300
gggaccaaag tggatatcaa acga                                           324

```

```

<210> SEQ ID NO 231
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 231

tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacagac ggccaggatc    60
acctgctctg gagatgcatt gccaaaggca tatgcttatt ggtaccagca gaagccaggc    120
caggccccta tgctggtgat atataagac agtgagaggc cctcagggat ccctgagcga    180
ttctctggct ccagctcagg gacaacagtc acgttgacca tcagtggagt ccaggcagaa    240
gacgaggctg actattactg tcaatcagca gacagcagtg gtacttatgt ggtattoggc    300
ggagggacca agctgaccgt cctaggt                                           327

```

```

<210> SEQ ID NO 232
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 232

tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacaaac ggccaggatc    60
acctgctctg gagatgcatt gccaaagaaa 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

```

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<210> SEQ ID NO 233
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 233

gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca    120

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gggaaagccc ctaagttcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180
aggttcagtg gaagtggatc tgggacagat ttttttttca ccatcagcaa cctgcagcct 240
gaagatattg caacatattt ctgtcaacag gatgataatc tcccattcac tttcggcct 300
gggaccaaaag tggatatcaa acga 324

```

```

<210> SEQ ID NO 234
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

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<400> SEQUENCE: 234

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gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc aggcgagtc ggacattagc aactatttaa attggtatca gcagaaacca 120
gggaaagccc ctaaaactcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180
aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240
gaagatattg caacatttta ctgtcaacag tatgataatc tcccattcac tttcggcct 300
gggaccaaaag tggatatcaa acga 324

```

```

<210> SEQ ID NO 235
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 235

```

```

tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacaaac ggccaggatc 60
acctgctctg gagatgcatt gccaaagaaa tttgcttatt ggtaccagca gaagtcaggc 120
caggcccctg tgctggatc ctatgaggac aggaaacgac cctccgggat ccctgagaga 180
ttctctggct ccagctcagg gacaatggcc accttgacta tcagtggggc ccaggtggag 240
gatgaagctg actactactg ttactcaaca gaccgcagtg gtgatcatgt ggtattcggc 300
ggagggacca agctgaccgt cctaggt 327

```

```

<210> SEQ ID NO 236
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 236

```

```

gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc ggcgagtc gggattagc aactggtag tctggtatca gcagaaacca 120
gggaaacccc ctaaaactcct gatctatgct gcatccagtt tgcaaaatgg ggtcccatca 180
agattcagcg gcagtggatc tgggacagat ttcacttca ccatcagcag cctgcagact 240
gaagattttg caacttaacta ttgtcaacag gctctcagtt tcccgtaggac gttcggccca 300
gggaccaagg tggaaagtcac acga 324

```



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<210> SEQ ID NO 237  
 <211> LENGTH: 121  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 237

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu  
 1 5 10 15  
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr  
 20 25 30  
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met  
 35 40 45  
 Gly Ile Ile His Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe  
 50 55 60  
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr  
 65 70 75 80  
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Ile Tyr Tyr Cys  
 85 90 95  
 Thr Arg Gln Gly Arg Ser Phe Tyr Tyr Tyr Gly Met Asp Val Trp Gly  
 100 105 110  
 Gln Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> SEQ ID NO 238  
 <211> LENGTH: 118  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 238

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu  
 1 5 10 15  
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr  
 20 25 30  
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met  
 35 40 45  
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe  
 50 55 60  
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Ala Ala Tyr  
 65 70 75 80  
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys  
 85 90 95  
 Ala Arg Gln Gln Val Ala Gly Met Leu Asp Tyr Trp Gly Gln Gly Thr  
 100 105 110  
 Leu Val Thr Val Ser Ser  
 115

<210> SEQ ID NO 239  
 <211> LENGTH: 120  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 239

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ile Tyr  
 20 25 30  
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Thr Val Ile Trp Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Glu Asp Phe Asp Ser His Tyr Gly Met Asp Val Trp Gly Gln  
 100 105 110  
 Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> SEQ ID NO 240  
 <211> LENGTH: 122  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 240

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30  
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Ala Val Ile Trp Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 Leu Gln Met His Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Glu Glu Trp Phe Gly Glu Ala Asp Tyr Gly Met Asp Val Trp  
 100 105 110  
 Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> SEQ ID NO 241  
 <211> LENGTH: 122  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 241

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30  
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

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35	40	45																		
Ala	Val	Ile	Trp	Tyr	Asp	Gly	Ser	Asn	Glu	Tyr	Tyr	Ala	Asp	Ser	Val					
50						55						60								
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Phe					
65				70					75					80						
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys					
			85						90					95						
Ala	Arg	Asp	Asp	Trp	Phe	Gly	Glu	Ala	Asp	Tyr	Gly	Met	Asp	Val	Trp					
		100						105						110						
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser											
	115						120													

<210> SEQ ID NO 242  
 <211> LENGTH: 122  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 242

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg					
1			5					10						15						
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asn	Tyr					
			20					25					30							
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val					
		35				40						45								
Thr	Val	Ile	Trp	Asn	Asp	Gly	Ser	Asn	Glu	Tyr	Tyr	Ala	Asp	Ser	Val					
	50					55					60									
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Phe					
65				70					75					80						
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys					
			85						90					95						
Ala	Arg	Glu	Asp	Trp	Leu	Gly	Glu	Ala	Asp	Tyr	Gly	Met	Asp	Val	Trp					
		100						105						110						
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser											
	115						120													

<210> SEQ ID NO 243  
 <211> LENGTH: 121  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 243

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg					
1			5					10						15						
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr					
			20					25					30							
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val					
		35				40						45								
Ala	Val	Ile	Trp	Tyr	Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val					
	50					55					60									
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr					
65				70					75					80						

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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
                                   85                                  90                                  95

Ala Arg Glu Glu Trp Glu Leu Glu Asp Tyr Gly Met Asp Val Trp Gly  
                                   100                                  105                                  110

Gln Gly Thr Thr Val Thr Val Ser Ser  
                                   115                                  120

<210> SEQ ID NO 244  
 <211> LENGTH: 126  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 244

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1                                  5                                  10                                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
                                   20                                  25                                  30

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
                                   35                                  40                                  45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val  
                                   50                                  55                                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65                                  70                                  75                                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
                                   85                                  90                                  95

Ala Arg Gly Ala Val Ala Gly Thr Gly Arg Asp Tyr Tyr Tyr Tyr Gly  
                                   100                                  105                                  110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
                                   115                                  120                                  125

<210> SEQ ID NO 245  
 <211> LENGTH: 126  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 245

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1                                  5                                  10                                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
                                   20                                  25                                  30

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
                                   35                                  40                                  45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr His Gly Asp Ser Val  
                                   50                                  55                                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65                                  70                                  75                                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
                                   85                                  90                                  95

Ala Lys Gly Ala Val Ala Gly Thr Gly Arg Asp Tyr Tyr Tyr Tyr Gly  
                                   100                                  105                                  110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
                                   115                                  120                                  125

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<210> SEQ ID NO 246  
 <211> LENGTH: 126  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 246

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15  
 Ser Gln Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30  
 Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Asn Tyr Ala Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr His Cys  
 85 90 95  
 Ala Lys Gly Thr Val Ala Gly Thr Gly Arg Asp Tyr Tyr Tyr Tyr Gly  
 100 105 110  
 Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
 115 120 125

<210> SEQ ID NO 247  
 <211> LENGTH: 120  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 247

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe  
 20 25 30  
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Ala Val Ile Trp Phe Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Asp Asp Phe Trp Ser Asp Tyr Pro Phe Asp Tyr Trp Gly Gln  
 100 105 110  
 Gly Thr Leu Val Thr Val Ser Ser  
 115 120

<210> SEQ ID NO 248  
 <211> LENGTH: 120  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

-continued

&lt;400&gt; SEQUENCE: 248

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Tyr  
 20 25 30  
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Ala Val Ile Ser Asp Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Asp Leu Tyr Ser Ser Ala Trp Pro Phe Asp Tyr Trp Gly Gln  
 100 105 110  
 Gly Thr Leu Val Thr Val Ser Ser  
 115 120

&lt;210&gt; SEQ ID NO 249

&lt;211&gt; LENGTH: 119

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 249

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30  
 Asp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Ala Val Ile Trp Asn Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
 65 70 75 80  
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95  
 Ala Arg Asp Gly Glu Gln Trp Arg Gly Phe Asp Tyr Trp Gly Gln Gly  
 100 105 110  
 Thr Leu Val Thr Val Ser Ser  
 115

&lt;210&gt; SEQ ID NO 250

&lt;211&gt; LENGTH: 119

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 250

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
 1 5 10 15  
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

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Asp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35                               40           45
Ala Val Ile Trp Tyr Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val
      50                               55           60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
      65                               70           75           80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85                               90           95
Ala Arg Asp Gln Glu Gln Trp Leu Ala Phe Asp Tyr Trp Gly Gln Gly
      100                              105           110
Thr Leu Val Thr Val Ser Ser
      115

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<210> SEQ ID NO 251
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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<400> SEQUENCE: 251

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
 20     25     30
Gly Met His Trp Val Arg Gln Ala Pro Asp Met Gly Leu Glu Trp Val
 35     40     45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
 50     55     60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr
 65     70     75     80
Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85     90     95
Ala Arg Asp Asn Trp Gly Ser Asp Ala Phe Asp Ile Trp Gly Gln Gly
 100    105    110
Thr Met Val Thr Val Ser Ser
 115

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<210> SEQ ID NO 252
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic polypeptide

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<400> SEQUENCE: 252

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
 20     25     30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35     40     45
Ala Val Ile Trp Tyr Asp Gly Ile Asn Lys Tyr Tyr Ala Asp Ser Val
 50     55     60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

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65	70	75	80
Leu Gln Met Asn Ser	Leu Arg Ala Glu Asp Thr	Ala Val Tyr Tyr Cys	
	85	90	95
Ala Arg Gly Ser Tyr Tyr Asp Ser Ser Gly Tyr Tyr Tyr Gly Glu Asp		105	110
	100		
Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser		120	125
	115		

<210> SEQ ID NO 253  
 <211> LENGTH: 126  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 253

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg			
1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr		25	30
	20		
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val		40	45
	35		
Ala Val Ile Trp Tyr Asp Gly Ile Asn Lys Tyr Tyr Ala Asp Ser Val		55	60
	50		
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr		70	75
	65		80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys		90	95
	85		
Ala Arg Gly Ser Tyr Tyr Asp Ser Ser Gly Tyr Tyr Phe Gly Glu Asp		105	110
	100		
Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser		120	125
	115		

<210> SEQ ID NO 254  
 <211> LENGTH: 118  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 254

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly			
1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr		25	30
	20		
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val		40	45
	35		
Ser Tyr Ile Ser Ser Ser Gly Ser Ile Ile Phe Tyr Ala Asp Ser Val		55	60
	50		
Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr		70	75
	65		80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys		90	95
	85		
Val Arg Arg Ile Ser Ile Thr Pro Phe Asp Tyr Trp Gly Gln Gly Thr		105	110
	100		



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Leu Val Thr Val Ser Ser  
115

<210> SEQ ID NO 255  
 <211> LENGTH: 126  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 255

Gln Val Thr Leu Lys Glu Ser Gly Pro Val Leu Val Lys Pro Thr Glu  
 1 5 10 15  
 Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Asn Ala  
 20 25 30  
 Arg Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu  
 35 40 45  
 Trp Leu Ala His Ile Phe Ser Asn Asp Glu Lys Ser Tyr Ser Thr Ser  
 50 55 60  
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Ser Gln Val  
 65 70 75 80  
 Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr  
 85 90 95  
 Cys Val Arg Ile Pro Arg Trp Leu Gln Pro Pro Tyr Tyr Tyr Tyr Gly  
 100 105 110  
 Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
 115 120 125

<210> SEQ ID NO 256  
 <211> LENGTH: 119  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 256

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln  
 1 5 10 15  
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly  
 20 25 30  
 Gly Tyr Tyr Trp Asn Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu  
 35 40 45  
 Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Asn Thr His Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe  
 65 70 75 80  
 Ser Leu Lys Leu Ser Ser Val Ile Ala Ala Asp Thr Ala Val Tyr Tyr  
 85 90 95  
 Cys Ala Arg Asp Trp Gly Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly  
 100 105 110  
 Thr Met Val Thr Val Ser Ser  
 115

<210> SEQ ID NO 257  
 <211> LENGTH: 124  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence

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&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 257

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln  
 1 5 10 15  
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly  
 20 25 30  
 Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu  
 35 40 45  
 Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asp Tyr Asn Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Gly Ile Ile Ser Gly Asp Thr Ser Lys Asn Gln Phe  
 65 70 75 80  
 Ser Leu Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr  
 85 90 95  
 Cys Ala Arg Glu Gly Arg Phe Gly Glu Leu Gly Ser Tyr Tyr Phe Asp  
 100 105 110  
 Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 115 120

&lt;210&gt; SEQ ID NO 258

&lt;211&gt; LENGTH: 121

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 258

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
 1 5 10 15  
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Val Ser Ser Gly  
 20 25 30  
 Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu  
 35 40 45  
 Trp Ile Gly Asn Thr Tyr Tyr Ser Gly Ser Thr Asn Tyr Lys Pro Ser  
 50 55 60  
 Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe  
 65 70 75 80  
 Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr  
 85 90 95  
 Cys Gly Arg Asp Arg Gly Arg Ala Val Gly Pro Phe Asp Tyr Trp Gly  
 100 105 110  
 Gln Gly Thr Leu Val Thr Val Ser Ser  
 115 120

&lt;210&gt; SEQ ID NO 259

&lt;211&gt; LENGTH: 118

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: synthetic polypeptide

&lt;400&gt; SEQUENCE: 259

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15



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Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr  
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Ser Arg Gln Trp Leu Val Leu Asp Tyr Trp Gly Gln Gly Thr  
 100 105 110

Leu Val Thr Val Ser Ser  
 115

<210> SEQ ID NO 262  
 <211> LENGTH: 118  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 262

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr  
 20 25 30

Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr  
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Gly Arg Gln Trp Leu Gly Phe Asp Tyr Trp Gly Gln Gly Thr  
 100 105 110

Leu Val Thr Val Ser Ser  
 115

<210> SEQ ID NO 263  
 <211> LENGTH: 118  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 263

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr  
 20 25 30

Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met  
 35 40 45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe  
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Asn Thr Ala Tyr  
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys  
 85 90 95

Ala Arg Gly Arg Gln Trp Leu Gly Phe Asp Tyr Trp Gly Gln Gly Thr

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100	105	110
Leu Val Thr Val Ser Ser		
115		
<210> SEQ ID NO 264		
<211> LENGTH: 121		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: synthetic polypeptide		
<400> SEQUENCE: 264		
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu		
1	5	10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Gln		
20	25	30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met		
35	40	45
Gly Ile Ile Phe Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe		
50	55	60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr		
65	70	75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys		
85	90	95
Ala Arg Gln Gly Arg Ser Tyr His Tyr Tyr Gly Met Asp Val Trp Gly		
100	105	110
Gln Gly Thr Thr Val Thr Val Ser Ser		
115	120	

<210> SEQ ID NO 265		
<211> LENGTH: 121		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: synthetic polypeptide		
<400> SEQUENCE: 265		
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu		
1	5	10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Gly Phe Thr Asn Tyr		
20	25	30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met		
35	40	45
Gly Thr Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe		
50	55	60
Gln Gly Gln Val Thr Phe Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr		
65	70	75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys		
85	90	95
Ala Arg Gln Gly Arg Ser Tyr Tyr Tyr Phe Gly Met Asp Val Trp Gly		
100	105	110
Gln Gly Thr Thr Val Thr Val Ser Ser		
115	120	

<210> SEQ ID NO 266  
 <211> LENGTH: 122

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<212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide  
  
 <400> SEQUENCE: 266  
  
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu  
 1 5 10 15  
  
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asp Tyr  
 20 25 30  
  
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met  
 35 40 45  
  
 Gly Ile Ile Tyr Pro Tyr Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe  
 50 55 60  
  
 Gln Gly Gln Val Thr Leu Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr  
 65 70 75 80  
  
 Leu Arg Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys  
 85 90 95  
  
 Ala Arg His Arg Gly Gly Arg Ser Tyr Tyr Tyr Gly Met Asp Val Trp  
 100 105 110  
  
 Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> SEQ ID NO 267  
 <211> LENGTH: 122  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide  
  
 <400> SEQUENCE: 267  
  
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu  
 1 5 10 15  
  
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr  
 20 25 30  
  
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met  
 35 40 45  
  
 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Thr Tyr Ser Pro Ser Phe  
 50 55 60  
  
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Asn Thr Ala Tyr  
 65 70 75 80  
  
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys  
 85 90 95  
  
 Ala Arg Glu Gly Phe Gly Glu Ser Ile His Tyr Gly Leu Asp Val Trp  
 100 105 110  
  
 Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> SEQ ID NO 268  
 <211> LENGTH: 121  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide  
  
 <400> SEQUENCE: 268  
  
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

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1	5	10	15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Asn Phe Thr Asn Tyr	20	25	30
Trp Ile Gly Trp Val Arg Gln Met Ser Gly Lys Gly Leu Glu Trp Met	35	40	45
Gly Ile Ile Tyr Pro Gly Asp Ser Glu Thr Arg Tyr Ser Pro Ser Phe	50	55	60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr	65	70	75
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys	85	90	95
Ala Arg His Gly Gly Gly Trp Ser Gly Trp Gly Met Asp Val Trp Gly	100	105	110
Gln Gly Thr Thr Val Thr Val Ser Ser	115	120	

<210> SEQ ID NO 269  
 <211> LENGTH: 124  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 269

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu	5	10	15
1			
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Asn Tyr	20	25	30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met	35	40	45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Lys Tyr Ser Pro Ser Phe	50	55	60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr	65	70	75
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys	85	90	95
Ala Arg His Gly Gly Tyr Ser Gly Arg Ser Tyr Tyr Tyr Gly Met Asp	100	105	110
Val Trp Gly Gln Gly Thr Ala Val Thr Val Ser Ser	115	120	

<210> SEQ ID NO 270  
 <211> LENGTH: 126  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 270

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu	5	10	15
1			
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr	20	25	30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met	35	40	45

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Gly Ile Ile Phe Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe  
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Thr Thr Ala Tyr  
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Ile Tyr Tyr Cys  
85 90 95

Ala Arg His Gly His Gly Ser Ser Ser Gly Arg Thr Tyr Tyr Tyr Gly  
100 105 110

Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
115 120 125

<210> SEQ ID NO 271  
 <211> LENGTH: 116  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 271

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu  
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Asn Phe Thr Thr Tyr  
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met  
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe  
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Asn Thr Ala Tyr  
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Ile Tyr Tyr Cys  
85 90 95

Ala Arg Asp Thr Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val  
100 105 110

Thr Val Ser Ser  
115

<210> SEQ ID NO 272  
 <211> LENGTH: 122  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: synthetic polypeptide

<400> SEQUENCE: 272

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr  
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Phe Tyr Val Asp Ser Val  
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr  
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys  
85 90 95



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Ala Arg Pro Gly Ser Asp Tyr Tyr Phe Tyr Tyr Gly Met Asp Val Trp  
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
 115 120

<210> SEQ ID NO 273  
 <211> LENGTH: 363  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 273

```
gaggtgcagt tgggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc    60
tctctgtaagg gttctggata caggtttacc agctactgga tgggctgggt gcgccagatg    120
cccgggaaaag gcctggagtg gatggggatc atccatcctg gtgactctga taccagatac    180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac    240
ctgcagtgga gcagcctgaa ggctcggac actgccatat attactgtac gagacaggtt    300
agaagcttct actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc    360
tca                                                                    363
```

<210> SEQ ID NO 274  
 <211> LENGTH: 354  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 274

```
gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc    60
tctctgtaagg gttctggata caggtttacc agctactgga tgggctgggt gcgccagatg    120
cccgggaaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac    180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag cgccgcctac    240
ctgcagtgga gcagcctgaa ggctcggac accgccatgt attactgtgc gagacaacaa    300
gtggctggta tgttggaacta ctggggccag ggaaccctgg tcaccgtctc ctca      354
```

<210> SEQ ID NO 275  
 <211> LENGTH: 360  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 275

```
caggtgcagc tgggtggagtc tgggggaggc gtgggtccagc ctgggaggtc cctgagactc    60
tctctgtcag cgtctggatt caccttcagt atttatggca tgcactgggt ccgccaggct    120
ccaggcaagg ggctggagtg ggtgacagtt atatggtatg atggaagtaa tgaatactat    180
gcagactccg tgaagggccg atccaccatc tccagagaca attccaagaa cacgctgtat    240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagaggac    300
ttcgactccc actacggtat ggacgtctgg ggccaagga ccacggtcac cgtctcctca    360
```

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<210> SEQ ID NO 276  
<211> LENGTH: 366  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 276

caggtgcagc tgggtggagtc 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
tctca	366

<210> SEQ ID NO 277  
<211> LENGTH: 366  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 277

caggtgcagc tgggtggagtc 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
tctca	366

<210> SEQ ID NO 278  
<211> LENGTH: 366  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 278

caggtgcagc tgggtggagtc 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
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagaagat	300
tggctcgggg aggcggacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc	360
tctca	366

<210> SEQ ID NO 279  
<211> LENGTH: 363  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 279

```
caggtgcagc tggtaggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc    60
tctctgtcag cgtctggatt caccttcagt agctatggca tgcaactgggt cgcaccaggt    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
```

<210> SEQ ID NO 280

<211> LENGTH: 378

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 280

```
caggtgcagt tggtaggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc    60
tctctgtcag cgtctggatt caccttcagt agttatggca tgtaactgggt cgcaccaggt    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
```

<210> SEQ ID NO 281

<211> LENGTH: 378

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 281

```
caggtgcagt tggtaggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc    60
tctctgtcag cgtctggatt cacgttcagt agttatggca tgtaactgggt cgcaccaggt    120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaataccat    180
gggactccg tgaagggccg attcaccatc tccagagaca attccaagaa tacgctgtat    240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gaaaggagca    300
gtggctggta cgggacggga ctactactac tacggtatgg acgtctgggg ccaagggacc    360
acggtcaccg tctcctca                                                                    378
```

<210> SEQ ID NO 282

<211> LENGTH: 378

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 282

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```

caggtgcagc tggtaggagtc tgggggaggc gtggtccagc ctgggaggtc ccagagactc   60
tcctgtgcag cgtctggatt caccttagt agttatggca tgtactgggt ccgccaggct   120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaaaactat   180
gcagactccg tgaagggccg atccaccatc tccagagaca attccaagaa tacgttgtat   240
ctgcaaatga acagcctgag agccgaggac acggctgtgt atcactgtgc gaaaggaaca   300
gtggctggta cgggacggga ctactactac tacggtatgg acgtctgggg ccaagggacc   360
acggtcaccg tctcttca                                     378

```

```

<210> SEQ ID NO 283
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 283

```

```

caggtgcaac tggtaggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc   60
tcctgtgcag cgtctggatt caccttcagt agctttggca tgcactgggt ccgccaggct   120
ccaggcaagg ggctggagtg ggtggcagtt atttggtttg atggaagtaa taaatactat   180
gtagactccg tgaagggccg atccaccatc tccagagaca attccaagaa tacgctgtat   240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gcgggacgat   300
ttttggagtg attatccttt tgactactgg ggcagggaa ccctggtcac cgtctctca   360

```

```

<210> SEQ ID NO 284
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 284

```

```

caggtgcaac tggtaggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc   60
tcctgtgcag cctctggatt caccttcagg agctatggca tgcactgggt ccgccaggct   120
ccaggcaagg ggctggagtg ggtggcagtt atatcagatg atggaagtaa taaatactat   180
gcagactccg tgaagggccg atccaccatc tccagagaca attccaagaa cacgctgtat   240
ctgcaaatga acagcctgag acctgaggac acggctgtgt attactgtgc gagagatctc   300
tatagcagtg cctggccctt tgactactgg ggcagggaa ccctggtcac cgtctctca   360

```

```

<210> SEQ ID NO 285
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 285

```

```

caggtgcagc tggtaggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc   60
tcctgtgcag cgtctggatt caccttcagt agctatgaca tacactgggt ccgccaggct   120
ccaggcaagg ggctggagtg ggtggcagtt atatggaatg atggaagtat taaatactat   180
gcagactccg tgaagggccg atccaccatc tccagagaca attccaagaa cacgctgtat   240

```

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 ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagacggg 300

gagcagtggc ggggcttga ctactggggc cagggaaacc tggtcaccgt ctctca 357

&lt;210&gt; SEQ ID NO 286

&lt;211&gt; LENGTH: 357

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: nucleic acid

&lt;400&gt; SEQUENCE: 286

caggtgcagc tgggtggagtc tgggggaggc gtgggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatgaca tacactgggt ccgtcaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtat taaatactat 180

gcagactcgc tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatcag 300

gagcagtggc tggccttga ctactggggc cagggaaacc tggtcaccgt ctctca 357

&lt;210&gt; SEQ ID NO 287

&lt;211&gt; LENGTH: 357

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: nucleic acid

&lt;400&gt; SEQUENCE: 287

caggtgcagt tgggtggagtc tgggggaggc gtgggtccagc 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 ctctca 357

&lt;210&gt; SEQ ID NO 288

&lt;211&gt; LENGTH: 378

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: nucleic acid

&lt;400&gt; SEQUENCE: 288

caggtgcagc tgggtggagtc tgggggaggc gtgggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt acctatgcca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaattaa taaatactat 180

gcagactcgc tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagggagt 300

tactatgata gtagtggta ttactacggg gaggactttg actactgggg ccagggaaacc 360

ctggtcaccg tctctca 378

&lt;210&gt; SEQ ID NO 289

&lt;211&gt; LENGTH: 378

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```

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 289

caggtgcagc tggtaggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc   60
tcctgtgcag cgtctggatt caccttcagt agctatgccca tgcaactgggt ccgccaggct   120
ccaggcaagg ggctggagtg ggtggcagtt atctggtagt atggaattaa taaatactat   180
gcagactccg tgaagggcgc attcaccatc tccagagaca attccaagaa cacgctgtat   240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagggagt   300
tactatgata gtagtgggta ttacttcogg gaggactttg actactgggg ccaggaacc   360
ctggtcaccg tctcctca                               378

```

```

<210> SEQ ID NO 290
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 290

caggtgcagc tggtaggagtc tgggggaggc ttggtcaagc ctgggaggtc cctgagactc   60
tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct   120
ccagggaagg ggctggagtg ggtttcatac attagtagta gtgtagtat ctttttttac   180
gcagactctg tgaagggcgc attcaccatg tccagggaca acgccaagaa ctcactgtat   240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attattgtgt gagaaggatt   300
agtataaacc cttttgacta ctggggccag ggaaccctgg tcaccgtctc ctca   354

```

```

<210> SEQ ID NO 291
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 291

caggtcacct tgaaggagtc tggctctgtg ctggtgaaac ccacagagac cctcacgctg   60
acctgcaccg tctctggggt ctcactcagc aatgctagaa tgggtgtgag ctggatccgt   120
cagcccccag ggaaggccct ggagtggcct gcacacattt tttcgaatga cgaaaaatcc   180
tacagccatc ctctgaagag caggctcacc atctccaagg acacctcaa aagccagggtg   240
gtccttacca tgaccaacat ggaccctgtg gacacagcca catattactg tgtacggata   300
ccgagatggc tacaaccccc ctactactac tacggtatgg acgtctgggg ccaagggacc   360
acggtcaccg tctcctca                               378

```

```

<210> SEQ ID NO 292
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 292

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caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc   60
acctgcactg tctctggtgg ctccatcagc agtgggtggtt actactggaa ctggatccgc   120
cagcaccagc ggaagggcct ggagtggatt gggtagatct attacagtgg gaacaccacc   180
tacaaccctg ccctcaagag tcgagttacc atatacagtag acacgtctaa gaaccagttc   240
tccctgaagc tgagctctgt gattgcccgc gacacggccg tgtattactg tgcgagagac   300
tggggacgtg atgcttttga tatctggggc caagggacaa tggtcaccgt ctcttca    357

```

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<210> SEQ ID NO 293
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

&lt;400&gt; SEQUENCE: 293

```

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc   60
acctgcactg tctcgggtgg ctccatcagc agtgggtggtt actactggag ctggatccgc   120
cagcaccagc ggaagggcct ggagtggatt gggtagatct attatagtgg gagcaccgac   180
tacaaccctg ccctcaagag tcgaggtatc atatacaggag acacgtctaa gaaccagttc   240
tccctgaagc tgaactctgt gactgcccgc gacacggccg tgtattactg tgcgagagag   300
gggaggttcg gggagttagg ctctactac tttgactact ggggccaggg aaccctggtc   360
accgtctcct ca                               372

```

```

<210> SEQ ID NO 294
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

&lt;400&gt; SEQUENCE: 294

```

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc   60
acctgcactg tctctggtgg ctccgtcagc agtgggtggtt actactggag ctggatccgg   120
cagcccccag ggaagggact ggagtggatt ggaataacct attacagtgg gagcaccac   180
tacaaacctc ccctcaagag tcgagtccac atatacagtag acacgtccaa gaaccagttc   240
tccctgaagc tgagtctctg gaccgtctgc gacacggccg tgtattactg tgggagagac   300
cggggtagag cagtgggtcc ctttgactac tggggccagg gaaccctggt caccgtctcc   360
tca                                           363

```

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<210> SEQ ID NO 295
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

&lt;400&gt; SEQUENCE: 295

```

caggtgcagc tgggtgcagc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc   60
tcttgcaagg cttctggata caccttcacc aattatgata tcaactgggt gcgacaggcc   120
actggacaag ggcttgagtg gatgggatgg atgaacccta acagtggtaa cacaggctat   180

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gcacagaagt tccagggcag agtcaccatg accaggaaca cctccataag cacagcctac 240  
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaagtagg 300  
cagtggtctgg tacttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> SEQ ID NO 296  
<211> LENGTH: 354  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 296

caggtgcagc tgggtcagtc 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  
cagtggtctgg tacttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> SEQ ID NO 297  
<211> LENGTH: 354  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 297

caggtgcagc tgggtcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60  
tcctgcaagg cttctggata caggttcacc agttatgata tcaactgggt gcgacaggcc 120  
actggacaag ggcttgagtg gatgggatgg atgaacccta acagtggtaa cacaggctat 180  
gcacagaagt tccagggcag agtcaccatg accaggaaca cctccataag cacagcctac 240  
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaagtagg 300  
cagtggtctgg tacttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> SEQ ID NO 298  
<211> LENGTH: 354  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 298

caggtgcagc tgggtcagtc 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  
cagtggtctgg gctttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> SEQ ID NO 299  
<211> LENGTH: 354



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<212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 299

caggtgcagc tgggtgcagtc 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
cagtggtctg gctttgacta ctggggccag ggaaccctgg tcaccgtctc ctca	354

<210> SEQ ID NO 300  
 <211> LENGTH: 363  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 300

gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc	60
tcctgtaagg gttctggata cagctttacc agccagtgga tcggctgggt gcgccagatg	120
cccgggaaag gcctggagtg gatggggatc atctttcctg gtgactctga taccagatac	180
agcccgtcct tccaaggcca ggtcacctc tcagccgaca agtccatcag caccgcctac	240
ctgcagtgga gcagcctgaa ggctcggac accgccatgt attactgtgc gcgacagggt	300
agaagttacc actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc	360
tca	363

<210> SEQ ID NO 301  
 <211> LENGTH: 363  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 301

gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc	60
tcctgtaagg gttctggata cggctttacc aactactgga tcggctgggt gcgccagatg	120
cccgggaaag gcctggagtg gatggggacc atctatcctg gtgactctga taccagatac	180
agtccgtcct tccaaggcca ggtcaccttc tcagccgaca agtccatcag caccgcctac	240
ctgcagtgga gcagcctgaa ggctcggac accgccatgt attactgtgc gagacagggt	300
agaagttact actactcgg tatggacgtc tggggccaag ggaccacggt caccgtctcc	360
tca	363

<210> SEQ ID NO 302  
 <211> LENGTH: 366  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: nucleic acid

<400> SEQUENCE: 302

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gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc cgggggagtc tctgaagatc    60
tctgttaagg gttctggata cagctttacc gactactgga tcggttgggt gcgccagatg    120
cccgggaaag gcctggaatg gatggggatc atctatcctt atgactctga taccagatac    180
agcccgctct tccaaggcca ggtcaccctc tcagccgaca agtccatcag caccgcctac    240
ctgcggtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagacatcgg    300
ggggggaggt cctactacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc    360
tctca                                           366

```

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<210> SEQ ID NO 303
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

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<400> SEQUENCE: 303

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gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc cgggggagtc tctgaagatc    60
tctgttaagg gttctggata cagctttacc agctactgga tcggttgggt gcgccagatg    120
cccgggaaag gcctggaatg gatggggatc atctatcctg gtgactctga taccacatac    180
agcccgctct tccaaggcca agtcaccctc tcagccgaca agtccatcaa caccgcctac    240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagagaggggt    300
ttcggggagt ctattcacta cggtttggac gtctggggcc aagggaccac ggtcaccgtc    360
tctca                                           366

```

```

<210> SEQ ID NO 304
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

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<400> SEQUENCE: 304

```

```

gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc cgggggagtc tctgaagatc    60
tctgttaagg gttctggata caattttacc aactactgga tcggttgggt gcgccagatg    120
tccgggaaag gcctggagtg gatgggaatc atctatcctg gtgactctga aaccagatac    180
agcccgctct tccaaggcca ggtcaccctc tcagccgaca agtccatcag caccgcctac    240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagacatgga    300
gggggatgga gtggttgggg tatggacgtc tggggccaag ggaccacgggt caccgtctcc    360
tca                                           363

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<210> SEQ ID NO 305
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

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<400> SEQUENCE: 305

```

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gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc cgggggagtc tctgaagatc    60
tctgttaagg gttctggata caggtttacc aactactgga tcggttgggt gcgccagatg    120

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cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccaaatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag tacccgctac 240
ctgcagtggg gcagcctgaa ggccctggac accgccatgt attactgtgc gagacatggt 300
ggatatagtg gccgttccta ctactacggt atggacgtct ggggccaggg gaccgcggtc 360
accgtctcct ca 372

```

```

<210> SEQ ID NO 306
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

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<400> SEQUENCE: 306

```

```

gaggtgcagc tgggtcagtc tggagcagag gtgaaaaagc cgggggagtc tctgaagatc 60
tcctgtaagg gttctggata caggtttacc agctactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctttcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcac caccgctac 240
ctgcagtggg gcagcctgaa ggccctggac accgccatct attactgtgc gcgacatggg 300
catggcagct cgtccggggc gacctactac tacggtttgg acgtctgggg ccaagggacc 360
acggtcaccg tctcctca 378

```

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<210> SEQ ID NO 307
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

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<400> SEQUENCE: 307

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```

gaggtgcagc tgggtgcaatc tggagcagag gtgaaaaagc cgggggagtc tctgaagatc 60
tcctgtaagg gttctggata caactttacc acctactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatt tcagccgaca agtccatcaa caccgctac 240
ctgcagtggg gcagcctgaa ggccctggac acagccattt attactgtgc gagagacaca 300
ggatactttg actactgggg ccagggcacc ctggtcaccg tctcctca 348

```

```

<210> SEQ ID NO 308
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleic acid

```

```

<400> SEQUENCE: 308

```

```

caggtgcagt tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg gcctggagtg ggtggcagtt atctggatg atggaagtaa taaattctat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaccgggg 300

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tccgattact acttctacta cggatggac gtctggggcc aagggaccac ggtcacogtc 360

tctctca 366

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What is claimed is:

**1.** 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, D84I, D84M, D84Q, D84R, D84S, D84T, S87R, N88A, N88D, N88E, N88F, N88G, N88M, N88R, N88S, N88V, N88W, V91D, V91E, V91G, V91S, I92K, I92R, 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).

**2.** The human IL-2 mutein of claim 1, wherein said mutein is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:1.

**3.** The human IL-2 mutein of claim 1, wherein said mutein is at least 97% identical to the amino acid sequence set forth in SEQ ID NO:1.

**4.** The human IL-2 mutein of claim 1, claim 2, or claim 3, wherein 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 LUG, 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, D84I, D84M, D84Q, D84R, D84S, D84T, S87R, N88A, N88D, N88E, N88F, N88G, N88M, N88R, N88S, N88V, N88W, V91D, V91E, V91G, V91S, I92K, I92R, and E95G.

**5.** The human IL-2 mutein of claim 4 wherein 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, I92K, I92R, L12K, L19D, L19N, L19T, N88D, N88R, N88S, V91D, V91G, V91K, and V91S.

**6.** An Fc-fusion protein comprising an Fc and the human IL-2 mutein of any of claims 1-5.

**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 comprises a substitution at N297.

**10.** The Fc-fusion protein of claim 9, wherein the substitution at N297 is N297G.

**11.** The Fc-fusion protein of any of claims 7-10, comprising a substitution or deletion of the C-terminal lysine of said human IgG Fc.

**12.** The Fc-fusion protein of claim 11, wherein the C-terminal lysine of said human IgG Fc is deleted.

**13.** The Fc-fusion protein of any of claims 6-12, 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, or (SEQ ID NO: 6), and 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 any of claims 6-15, 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 16, wherein the IL-2 mutein comprises a T3 substitution.

**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 19, wherein the IL-2 mutein further comprises an S5 mutation.

**21.** The Fc-fusion protein of claim 20, wherein the IL-2 mutein further comprises an S5T mutation.

**22.** The Fc-fusion protein of any of claim 6-21, wherein said Fc-fusion protein comprises an Fc dimer.

**23.** The Fc-fusion protein of claim 22, wherein said Fc-fusion protein comprises two IL-2 muteins.

**24.** The Fc-fusion protein of claim 22, wherein said Fc-fusion protein comprises a single IL-2 mutein.

**25.** An isolated nucleic acid encoding the human IL-2 mutein of any of claims 1-5.

**26.** An isolated nucleic acid encoding an Fc portion of an antibody and the human IL-2 muteins of any of claims 1-5.

**27.** The isolated nucleic acid of claim 26, wherein said Fc portion of an antibody and the human IL-2 mutein are encoded within a single open-reading frame.

**28.** The isolated nucleic acid of claim 26 or 27, wherein the Fc is a human IgG1 Fc.

**29.** The isolated nucleic acid of claim 28, wherein the human IgG1 Fc comprises one or more mutations altering effector function of said Fc.

**30.** The isolated nucleic acid of claim 29, wherein the human IgG1 comprises a substitution at N297.

**31.** The isolated nucleic acid of claim 28, wherein the substitution at N297 is N297G.

**32.** The isolated nucleic acid of any of claims 28-31 encoding a substitution or deletion of the C-terminal lysine of said human IgG Fc.

**33.** The isolated nucleic acid of claim 32, wherein the C-terminal lysine of said human IgG Fc is deleted.

**34.** The isolated nucleic acid of any of claims 26-33, further encoding a linker connecting the Fc portion of an antibody and the human IL-2 mutein.

**35.** The isolated nucleic acid of claim 34, wherein the linker is GGGGS (SEQ ID NO: 5), GGNGT, or (SEQ ID NO: 6), and YGNGT (SEQ ID NO: 7).

36. The isolated nucleic acid of claim 35, wherein the linker is GGGGS (SEQ ID NO: 5).

37. The isolated nucleic acid of any of claims 26-36, wherein 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.

38. The isolated nucleic acid of claim 37, wherein the IL-2 mutein comprises a T3 substitution.

39. The isolated nucleic acid of claim 38, wherein the IL-2 mutein comprises a T3N or T3A substitution.

40. The isolated nucleic acid of claim 39, wherein the IL-2 mutein comprises a T3N substitution.

41. The isolated nucleic acid of claim 40, wherein the IL-2 mutein further comprises an S5 mutation.

42. The isolated nucleic acid of claim 41, wherein the IL-2 mutein further comprises an S5T mutation.

43. An expression vector comprising the isolated nucleic acid of any of claims 25-42 operably linked to a promoter.

44. A host cell comprising the isolated nucleic acid of any of claims 25-42.

45. The host cell of claim 44, wherein the isolated nucleic acid is operably linked to a promoter.

46. The host cell of claim 44 or 45, wherein said host cell is a prokaryotic cell.

47. The host cell of claim 46, wherein the host cell is *E. coli*.

48. The host cell of claim 44 or 45, wherein said host cell is a eukaryotic cell.

49. The host cell of claim 48, wherein the host cell is a mammalian cell.

50. The host cell of claim 49, wherein the host cell is a Chinese hamster ovary (CHO) cell line.

51. A method of making a human IL-2 mutein, comprising culturing a host cell of any of claims 45 to 50 under conditions in which said promoter is expressed and harvesting the human IL-2 mutein from said culture.

52. A method of making a Fc-fusion protein, comprising culturing a host cell of any of claims 45 to 50 under conditions in which said promoter is expressed and harvesting the Fc-fusion protein from said culture.

53. 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 of any of claims 1-5.

54. The method of claim 53, wherein the ratio of CD3+FoxP3+ cells to CD3+FoxP3- increases.

55. The method of claim 54, wherein the ratio of CD3+FoxP3+ cells to CD3+FoxP3- increases at least 50%.

56. 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 of any of claims 6-24.

57. The method of claim 56, wherein the ratio of CD3+FoxP3+ cells to CD3+FoxP3- increases.

58. The method of claim 57, wherein the ratio of CD3+FoxP3+ cells to CD3+FoxP3- increases at least 50%.

59. 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 of any of claims 1-5.

60. The method of claim 59, wherein the ratio of CD3+FoxP3+ cells to CD3+FoxP3- increases.

61. The method of claim 60, wherein the ratio of CD3+FoxP3+ cells to CD3+FoxP3- increases at least 50%.

62. 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 of any of claims 6-24.

63. The method of claim 62, wherein the ratio of CD3+FoxP3+ cells to CD3+FoxP3- increases.

64. The method of claim 63, wherein the ratio of CD3+FoxP3+ cells to CD3+FoxP3- increases at least 50%.

65. 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 of any of claims 1-5.

66. The method of claim 65, wherein the ratio of CD3+FoxP3+ cells to CD3-CD19- lymphocytes expressing CD56 and/or CD16 increases.

67. The method of claim 66, wherein the ratio of CD3+FoxP3+ cells to CD3-CD19- lymphocytes expressing CD56 and/or CD16 increases at least 50%.

68. 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 of any of claims 6-24.

69. The method of claim 68, wherein the ratio of CD3+FoxP3+ cells to CD3-CD19- lymphocytes expressing CD56 and/or CD16 increases.

70. The method of claim 63, wherein the ratio of CD3+FoxP3+ cells to CD3-CD19- lymphocytes expressing CD56 and/or CD16 increases at least 50%.

71. 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 of any of claims 1-5.

72. 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 Fc-fusion protein of any of claims 6-21.

73. The method of treating a subject with an inflammatory or autoimmune disease of claim 71 or 72, wherein administration causes reduction of at least one symptom of the disease.

74. The method of claim 73, wherein the ratio of regulatory T cells (Tregs) to non-regulatory T cells within the peripheral blood of a subject increases after the administration.

75. The method of claim 73, wherein 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.

76. The method of any of claims 71-75, wherein 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.

77. 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.

**78.** The polypeptide of claim **77**, wherein said Fc region of a human IgG1 comprises at least 95% identity to the amino acid sequence set forth in SEQ ID NO:3.

**79.** The polypeptide of claim **77**, wherein said Fc region of a human IgG1 comprises the amino acid sequence set forth in SEQ ID NO:3.

**80.** The polypeptide of claim **77**, wherein said Fc region of a human IgG1 further comprises one or more mutations to stabilize the polypeptide.

**81.** The polypeptide of claim **80**, wherein one or more amino acids set forth in SEQ ID NO:3 are substituted with cysteine.

**82.** The polypeptide of claim **81**, wherein V259, A287, R292, V302, L306, V323, or I332 of the amino acid sequence set forth in SEQ ID NO:3 is substituted with cysteine.

**83.** The polypeptide of claim **82**, wherein said Fc region comprises an A287C and L306C substitution within the amino acid sequence set forth in SEQ ID NO:3.

**84.** The polypeptide of claim **82**, wherein said Fc region comprises an V259C and L306C substitution within the amino acid sequence set forth in SEQ ID NO:3.

**85.** The polypeptide of claim **82**, wherein said Fc region comprises an R292C and V302C substitution within the amino acid sequence set forth in SEQ ID NO:3.

**86.** The polypeptide of claim **82**, wherein said Fc region comprises an V323C and I332C substitution within the amino acid sequence set forth in SEQ ID NO:3.

**87.** An antibody comprising an Fc region of any of claims **77-86**.

**88.** An Fc-fusion protein comprising the Fc region of any of claims **77-86**.

**89.** A polypeptide comprising a linker, wherein the linker is GGNGT (SEQ ID NO: 6) or YGNGT (SEQ ID NO: 7).

**90.** The polypeptide of claim **89**, wherein the linker comprises N-glycosylation.

**91.** The polypeptide of claim **89**, wherein the linker is inserted into or replaces a loop in the polypeptide structure.

**92.** A method of making an aglycosylated IgG1 Fc-containing molecule, said method comprising:

- a) expressing a nucleic acid encoding a polypeptide of any of claims **77-86** in a mammalian cell culture; and
- b) harvesting the aglycosylated IgG1 Fc-containing molecule from said culture.

**93.** 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.

**94.** 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**.

**95.** The Fc-fusion protein of claim **94**, wherein 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**.

**96.** The Fc-fusion protein of claim **94**, wherein 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**.

**97.** The Fc-fusion protein of claim **94**, wherein 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**.

**98.** The Fc-fusion protein of claim **94**, wherein 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**.

**99.** A nucleic acid encoding the Fc-fusion of claim **94**.

**100.** A cell comprising the nucleic acid of claim **99**.

**101.** A method of making an Fc-fusion protein comprising incubating the cell of claim **100** under conditions allowing it to express said Fc-fusion protein.

**102.** A method of treating an inflammatory or autoimmune condition in a subject comprising administering an effective amount of the Fc-fusion protein of claim **94** to said subject.

**103.** The method of claim **102** wherein said inflammatory or autoimmune 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.

**104.** A method of monitoring the response of a subject to treatment with the human interleukin-2 (IL-2) mutein of claim **1**, the Fc-fusion protein of claim **6**, or the Fc-fusion protein of claim **94**, comprising detecting a change in said subject, said change being:

- a) an increase in body temperature,
- b) an increase in CRP in said subject's peripheral blood,
- c) a decrease in platelets in said subject's peripheral blood,
- d) a decrease in neutrophils in said subject's peripheral blood, or
- e) 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.

**105.** The method of claim **104**, wherein said change comprises:

- a) an increase in body temperature of at least 0.5° C.,
- b) an increase in CRP in said subject's peripheral blood of at least 0.2 mg/mL,
- c) a decrease in platelets in said subject's peripheral blood of at least 0.8-fold,
- d) a decrease in neutrophils in said subject's peripheral blood of at least 0.8-fold, or
- e) a decrease in albumin in said subject's peripheral blood of at least 0.4-fold.

**106.** An isolated anti-human IL-2 antibody, wherein said antibody:

- a) 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

- b) 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
- c) 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.

**107.** The isolated anti-human IL-2 antibody of claim 106, wherein 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.

**108.** The isolated anti-human IL-2 antibody of claim 106, wherein said antibody comprises a heavy chain variable domain amino acid sequence that is at least 95% 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 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.

**109.** The isolated anti-human IL-2 antibody of claim 106, wherein said antibody comprises a heavy chain variable domain amino acid sequence that is at least 97% 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 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.

**110.** The isolated anti-human IL-2 antibody of claim 106, wherein said antibody comprises a heavy chain variable domain amino acid sequence that is at least 99% 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 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.

**111.** The isolated anti-human IL-2 antibody of claim 106, wherein 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.

**112.** The isolated anti-human IL-2 antibody of claim 106, wherein said isolated antibody is:

- a) a human antibody;
- b) a humanized antibody;
- c) a chimeric antibody;
- d) a monoclonal antibody;
- e) a polyclonal antibody;
- f) a recombinant antibody;
- g) an antigen-binding antibody fragment;
- h) a single chain antibody;
- i) a diabody;
- j) a triabody;
- k) a tetraabody;
- l) a Fab fragment;
- m) a F(ab')<sub>2</sub> fragment;
- n) a domain antibody;
- o) an IgD antibody;
- p) an IgE antibody;
- q) an IgM antibody;
- r) an IgG1 antibody;
- s) an IgG2 antibody;
- t) an IgG3 antibody;
- u) an IgG4 antibody; or
- v) an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.

**113.** An isolated complex comprising an isolated anti-human IL-2 antibody of claim 106 bound to a human IL-2 cytokine.

**114.** The isolated anti-human IL-2 antibody of claim 106, wherein said isolated antibody comprises a human IgG1 Fc.

**115.** The isolated anti-human IL-2 antibody of claim **114**, wherein said human IgG1 Fc has one or more mutations altering effector function of said Fc.

**116.** The isolated anti-human IL-2 antibody of claim **115**, wherein said human IgG1 Fc comprises a substitution at N297.

**117.** The isolated anti-human IL-2 antibody of claim **116**, wherein said substitution at N297 is N297G.

**118.** The isolated anti-human IL-2 antibody of claim **114**, comprising a substitution or deletion of the C-terminal lysine of said human IgG Fc.

**119.** The isolated anti-human IL-2 antibody of claim **118**, wherein the C-terminal lysine of said human IgG Fc is deleted.

**120.** 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 of claim **106**.

**121.** An expression vector comprising the isolated nucleic acid of claim **120** operably linked to a promoter.

**122.** A host cell comprising the isolated nucleic acid of claim **120** or **121**.

**123.** The host cell of claim **122**, wherein the isolated nucleic acid is operably linked to a promoter.

**124.** The host cell of claim **122**, wherein said host cell is a prokaryotic cell.

**125.** The host cell of claim **124**, wherein the host cell is *E. coli*.

**126.** The host cell of claim **122**, wherein said host cell is a eukaryotic cell.

**127.** The host cell of claim **126**, wherein the host cell is a mammalian cell.

**128.** The host cell of claim **127**, wherein the host cell is a Chinese hamster ovary (CHO) cell line.

**129.** A method of making an anti-human IL-2 antibody, comprising culturing a host cell of any of claims **122** to **128** under conditions in which said promoter is expressed and harvesting the human IL-2 mutein from said culture.

**130.** 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 of claim **106** or the isolated complex comprising an isolated anti-human IL-2 antibody of claim **113** to said subject.

**131.** The method of claim **130** wherein 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.

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