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(54) **ANTI-CD14 ANTIBODY FUSION PROTEIN**

now Pat. No. 8,252,905, filed as application No. PCT/
JP2006/311255 on Jun. 5, 2006.

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(30) **Foreign Application Priority Data**

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Tokyo (JP)

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(52) **U.S. Cl.**
CPC **C07K 16/2896** (2013.01); **C07K 14/81**
(2013.01)
USPC **424/134.1**; 530/387.3

(21) Appl. No.: **13/972,778**

(22) Filed: **Aug. 21, 2013**

(57) **ABSTRACT**

Related U.S. Application Data

(62) Division of application No. 13/547,548, filed on Jul.
12, 2012, now Pat. No. 8,541,565, which is a division
of application No. 11/791,888, filed on May 30, 2007,

A protein comprising (I) an anti-CD14 antibody or its active
fragment, or a derivative thereof and (II) an inhibitor for a
protease, or its active fragment, or a derivative thereof is
provided.

FIG. 1

DNA sequence SEQ ID NO:123

PRT sequence SEQ ID NO:124

ATGGATTGGTTGTGGAACCTTGCTATTCCTGATGGTAGTTGCCCAAAGTGCTCAAGCACAG
METAspTrpLeuTrpAsnLeuLeuPheLeuMETValValAlaGlnSerAlaGlnAlaGln

ATCCAGTTGGTACAGTCTGGACCTGAACCTGAAGAAGCCTGGAGACTCAGTGAAGATCTCC
IleGlnLeuValGlnSerGlyProGluLeuLysLysProGlyGluSerValLysIleSer

TGCAAGGCTTCTGGGTATACCTTCACAGACTATGCAATGAACTGGGTGAAACAGGCTCCA
CysLysAlaSerGlyTyrThrPheThrAspTyrAlaMETAasnTrpValLysGlnAlaPro

GGAAATGGCTTGAAGTGGATGGGCTGGATCAACACCCAAACTGGAAAGCCAACATATGCG
GlyAsnGlyLeuLysTrpMETGlyTrpIleAsnThrGlnThrGlyLysProThrTyrAla

GATGATTTCAAACAACGGTTTGTCTTCTCTTGGAAACTTCTGCCAGCACTGCATACTTG
AspAspPheLysGlnArgPheValPheSerLeuGluThrSerAlaSerThrAlaTyrLeu

CAGATCAACAACCTCAATATTGAGGACACAGCTACATATTTCTGTACAAGATCCACTTTT
GlnIleAsnAsnLeuAsnIleGluAspThrAlaThrTyrPheCysThrArgSerThrPhe

TACTATAGCAGCTATATCTACGGGTGGTACTTTGACTTCTGGGGCCCAGGAACCATGGTC
TyrTyrSerSerTyrIleTyrGlyTrpTyrPheAspPheTrpGlyProGlyThrMETVal

ACCGTGTCTCTCAGCTGAAACAACA
ThrValSerSerAlaGluThrThr

FIG. 2

DNA sequence SEQ ID NO:125

PRT sequence SEQ ID NO:126

ATGGAGTCACATACTAGGGTCTTCATATTCCTGCTGCTCTGGTTGTCTGGTGCTGATGGG
METGluSerHisThrArgValPheIlePheLeuLeuLeuTrpLeuSerGlyAlaAspGly

GACATFGTGATGACTCAGTCTCCACATCCATTTCATATCAGTAGGAGAGAGGGTCACC
AspIleValMETThrGlnSerProThrSerIleSerIleSerValGlyGluArgValThr

ATGAACTGCAAGGCCAGTCAGAATGTGGGTTCTAATGTAGACTGGTACCAACAGAAAACA
METAsnCysLysAlaSerGlnAsnValGlySerAsnValAspTrpTyrGlnGlnLysThr

GGGCAGTCTCCTAAACTGCTTATCTACAAGGCATCCAACCGGTACACTGGCGTCCCTGAT
GlyGlnSerProLysLeuLeuIleTyrLysAlaSerAsnArgTyrThrGlyValProAsp

CGCTTCACAGGCAGTGGATCTGGAACAGATTTCACTTTCACCATCAGCAACATGCAGGCT
ArgPheThrGlySerGlySerGlyThrAspPheThrPheThrIleSerAsnMETGlnAla

GTGGACCTGGCTGTTTATTACTGTATGCAGTCTAACACCAATCCTCCGTGGACGTTCCGT
ValAspLeuAlaValTyrTyrCysMETGlnSerAsnThrAsnProProTrpThrPheGly

GGAGGCACCAAGCTGGAATTGAAACGGGCTGATGCTGCACCAACTGTATCT
GlyGlyThrLysLeuGluLeuLysArgAlaAspAlaAlaProThrValSer

FIG. 3

DNA sequence SEQ ID NO:127

PRT sequence SEQ ID NO:128

<u>tgaacacaga caactcacc atg</u> gaa tgt aac tgg ata ctt cct ttt att ctg	52
Met Glu Cys Asn Trp Ile Leu Pro Phe Ile Leu	
1 5 10	
tgg gta att tca gga gtc tac tca gag gtt cag ctc cag cag tct ggg	100
Ser Val Ile Ser Gly Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly	
15 20 25	
act gtg ctg gca agg cat ggg gct tcc gtg aag atg tcc tgc aag gct	148
Thr Val Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala	
30 35 40	
tct ggc tac agg tat acc aac tac tgg ttg cac tgg gta aaa cag agg	196
Ser Gly Tyr Arg Tyr Thr Asn Tyr Trp Leu His Trp Val Lys Gln Arg	
45 50 55	
cct gga cag ggt cta gag tgg att ggt gct att tat cct gga aat agt	244
Pro Gly Gln Gly Leu Gln Trp Ile Gly Ala Ile Tyr Pro Gly Asn Ser	
60 65 70 75	
gat tot agc tac aac cag aac ttc aag ggc aag gcc aaa ctg act gca	292
Asp Ser Ser Tyr Asn Gln Asn Phe Lys Gly Lys Ala Lys Leu Thr Ala	
80 85 90	
gtc aca tcc gcc agc act gcc tac atg gag ctc agc agc ctg aca aat	340
Val Thr Ser Ala Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Asn	
95 100 105	
gag gac tot gcg gtc tat tac tgt aca aga tgg ggc cct tat ggc atc	388
Gln Asp Ser Ala Val Tyr Tyr Cys Thr Arg Trp Gly Pro Tyr Gly Ile	
110 115 120	
tat gct atg gac tac tgg ggt caa gga acc tca gtc acc gtc tcc tca	436
Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser	
125 130 135	
gcc aaa aca aca ccc cca <u>tca gtc tat cca ctg gcc c</u>	473
Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala	
140 145 150	

FIG. 4

DNA sequence SEQ ID NO:129

PRT sequence SEQ ID NO:130

<u>gac atc gtg atg acc cag tct cca gct tct ttg gct gtg tct ctg ggg</u>	48
Asp Ile Val Met Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly	
1 5 10 15	
cag agg gcc acc atc tcc tgc aga gcc agc gaa agt gtt gat tat tct	96
Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Tyr Ser	
20 25 30	
ggc att agt ttt atg aac tgg ttc caa cag aaa cca gga cag cca ccc	144
Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro	
35 40 45	
aaa ctc ctc atc tat gct gca tcc aac caa gga tcc ggg gtc oct gcc	192
Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala	
50 55 60	
agg ttt agt ggc agt ggg tct ggg aca gac ttc agc ctc aac atc cat	240
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His	
65 70 75 80	
cct atg gag gag gat gat act gca atg tat ttc tgt cag cac agt aag	288
Pro Met Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys Gln His Ser Lys	
85 90 95	
gag ctt ccg tac acg ttc gga ggg ggg acc aag ctg gaa a	328
Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu	
100 105	

FIG. 5

DNA sequence SEQ ID NO:131

PRT sequence SEQ ID NO:132

<u>gaattcc atg gaa tgt aac tgg ata ctt cct ttt att ctg tcg gta att</u>	49
Met Glu Cys Asn Trp Ile Leu Pro Phe Ile Leu Ser Val Ile	
1 5 10	
tca gga gtc tac tca gag gtt cag ctc cag cag tct ggg act gtg ctg	97
Ser Gly Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu	
15 20 25 30	
gca agg cct ggg gct tcc gtg aag atg tcc tgc aag gct tct ggc tac	145
Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr	
35 40 45	
agg tat acc aac tac tgg ttg cac tgg gta aaa cag agg cct gga cag	193
Arg Tyr Thr Asn Tyr Trp Leu His Trp Val Lys Gln Arg Pro Gly Gln	
50 55 60	
ggt cta gag tgg att ggt gct att tat cct gga aat agt gat tct agc	241
Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Ser Asp Ser Ser	
65 70 75	
tac aac cag aac ttc aag ggc aag gcc aaa ctg act gca gtc aca tcc	289
Tyr Asn Gln Asn Phe Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser	
80 85 90	
gcc agc act gcc tac atg gag ctc agc agc ctg aca aat gag gac tct	337
Ala Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser	
95 100 105 110	
gcg gtc tat tac tgt aca aga tgg ggc cct tat ggc atc tat gct atg	385
Ala Val Tyr Tyr Cys Thr Arg Trp Gly Pro Tyr Gly Ile Tyr Ala Met	
115 120 125	
gac tac tgg ggt caa gga <u>acc tca gtc acc gtc tcc agc gct agc</u>	430
Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser	
130 135 140	

FIG. 6

DNA sequence SEQ ID NO:133

PRT sequence SEQ ID NO:134

gaattcc atg gag aca gac aca ctc ctg cta tgg gtc ctg ctt ctc tgg 49
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp
1 5 10

gtt cca ggt tcc aca ggt gac att gtg ctg acc caa tct cca gct tct 97
Val Pro Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser
15 20 25 30

ttg gct gtg tct ctg ggg cag agg gcc acc atc tcc tgc aga gcc agc 145
Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser
35 40 45

gaa agt gtt gat tat tct ggc att agt ttt atg aac tgg ttc caa cag 193
Glu Ser Val Asp Tyr Ser Gly Ile Ser Phe Met Asn Trp Phe Gln Gln
50 55 60

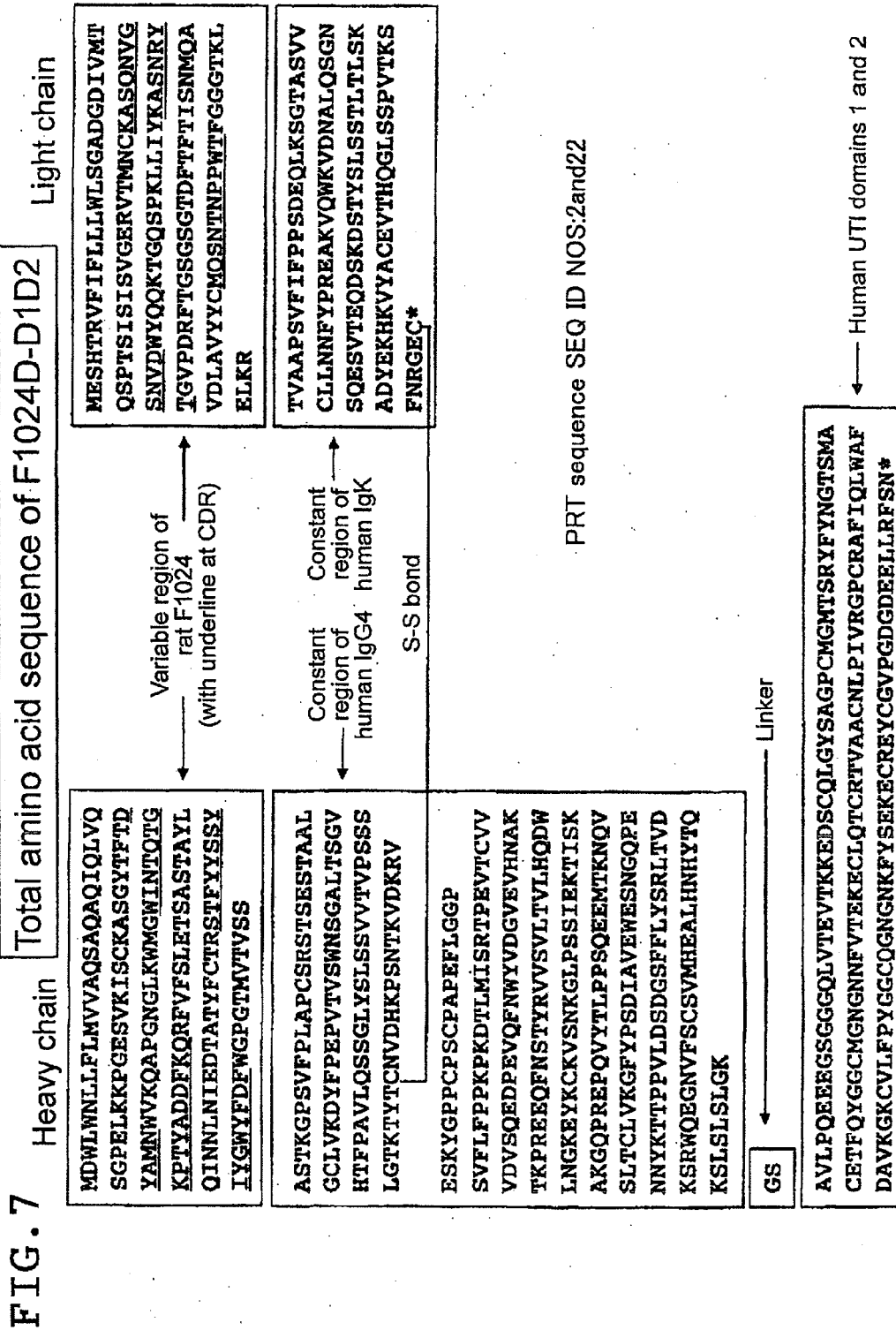
aaa cca gga cag cca ccc aaa ctc ctc atc tat gct gca tcc aac caa 241
Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln
65 70 75

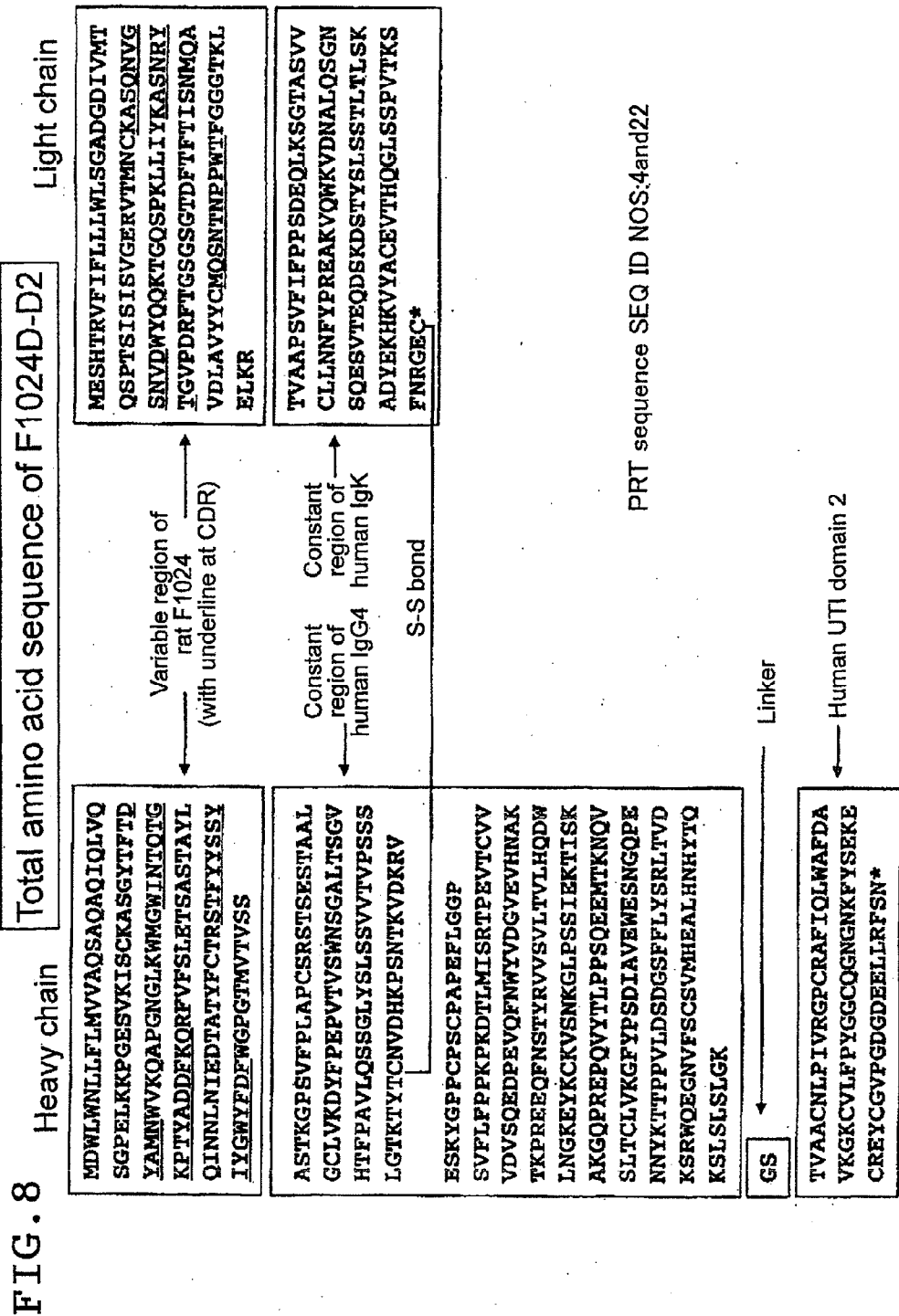
gga tcc ggg gtc cct gcc agg ttt agt ggc agt ggg tct ggg aca gac 289
Gly Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
80 85 90

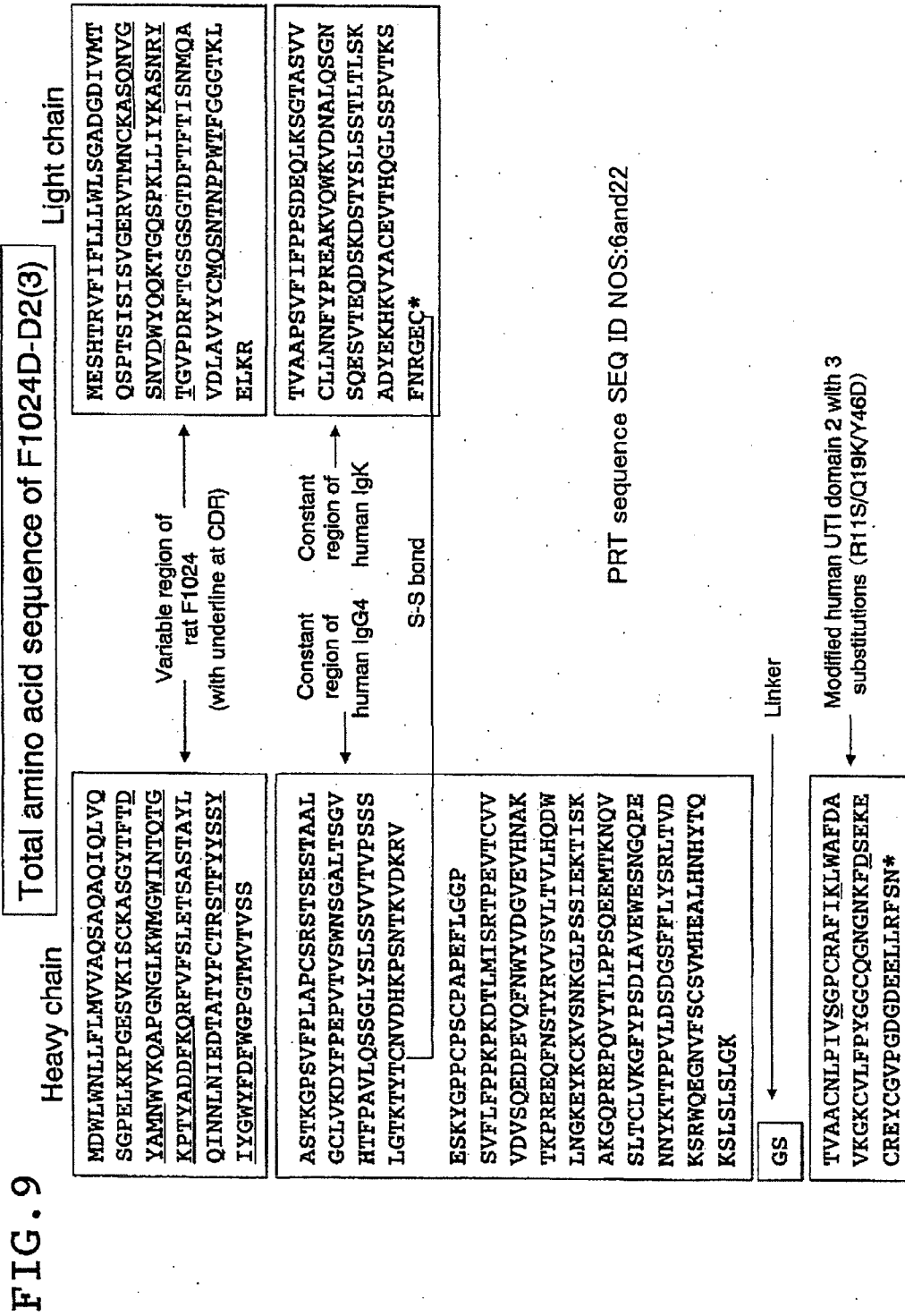
ttc agc ctc aac atc cat cct atg gag gag gat gat act gca atg tat 337
Phe Ser Leu Asn Ile His Pro Met Glu Glu Asp Asp Thr Ala Met Tyr
95 100 105 110

ttc tgt cag cac agt aag gag ctt cag tac acg ttc gga ggg ggg acc 385
Phe Cys Gln His Ser Lys Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr
115 120 125

aag ctg gaa atc aaa cgt acg 406
Lys Leu Glu Ile Lys Arg Thr
130







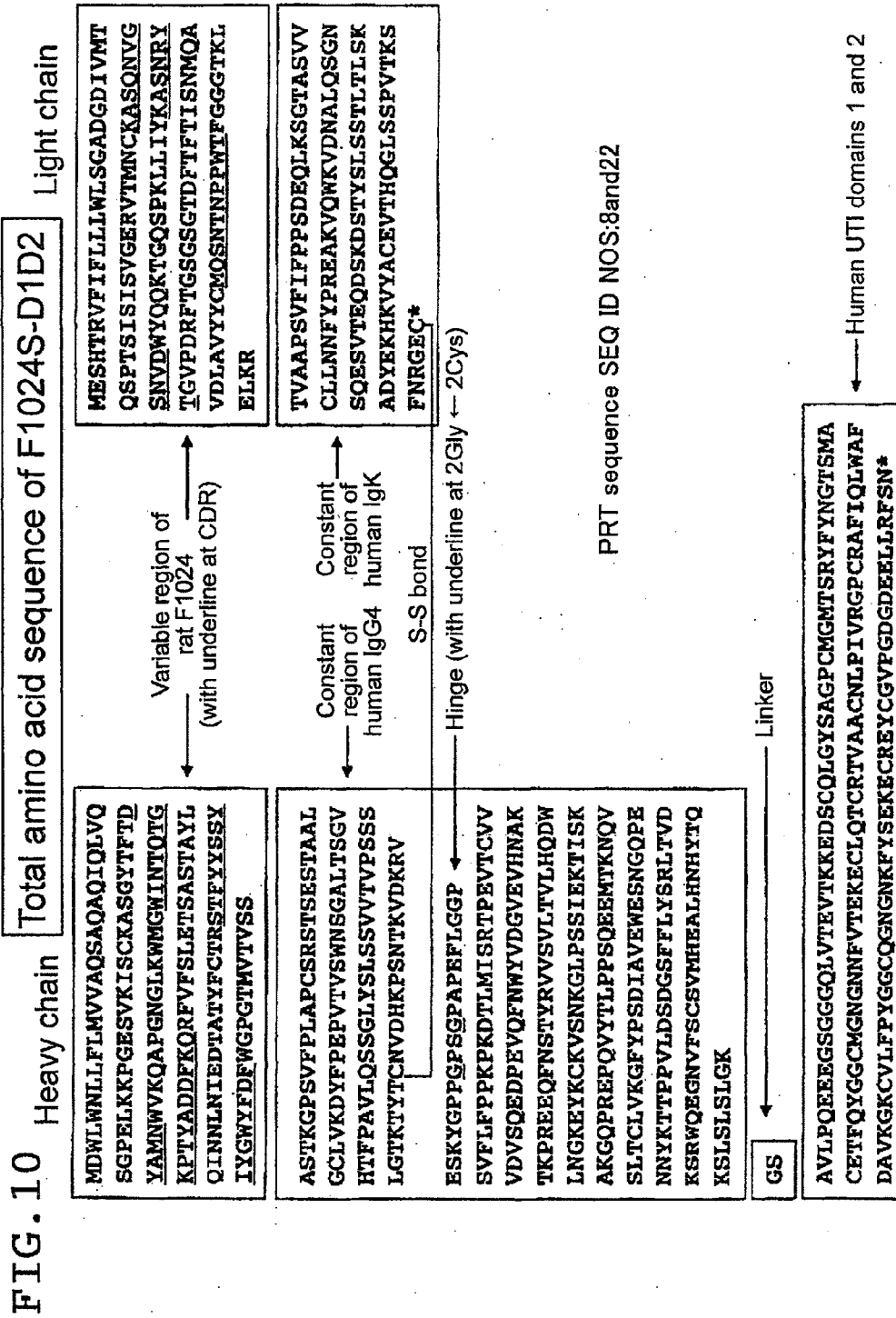


FIG. 11

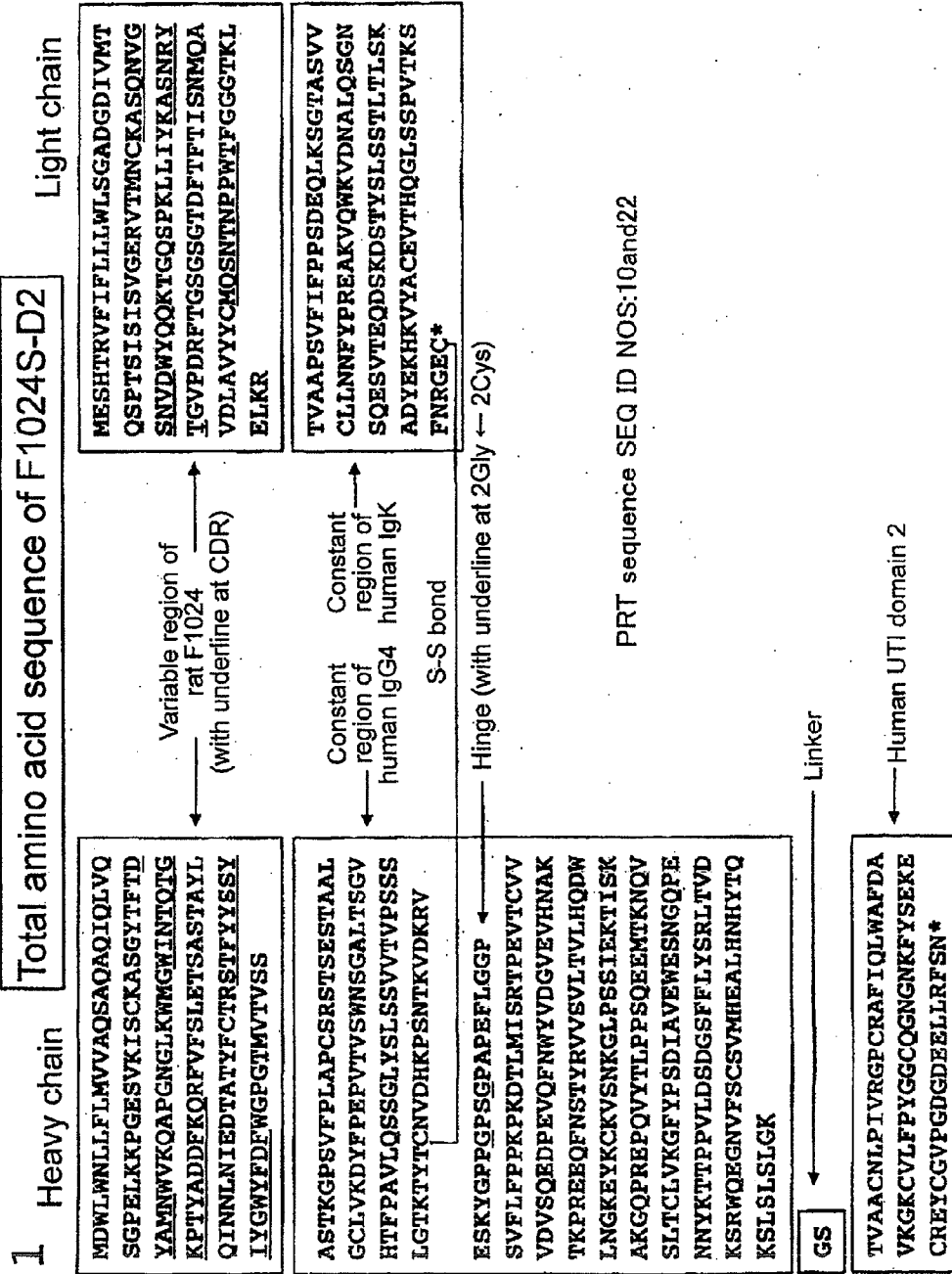
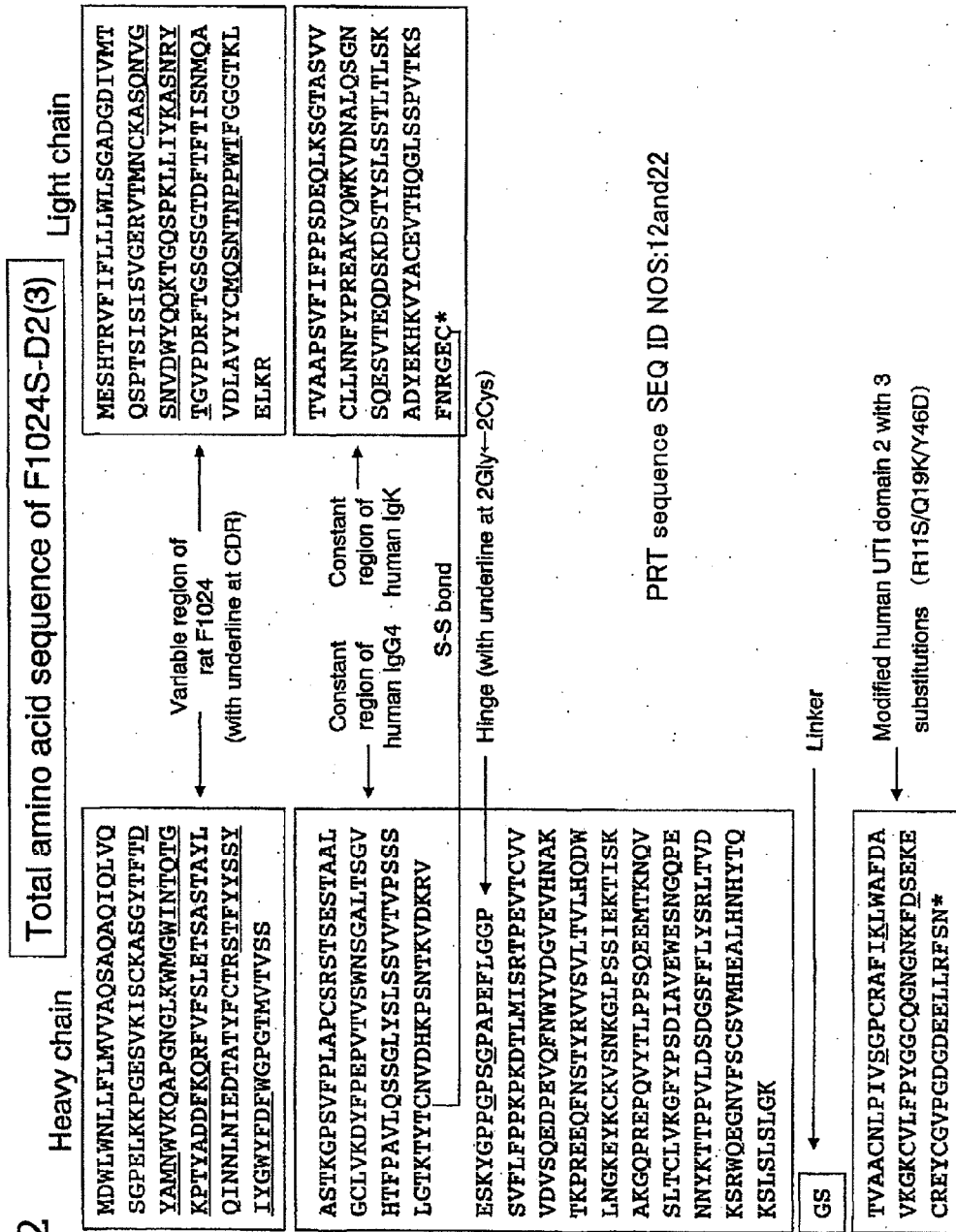
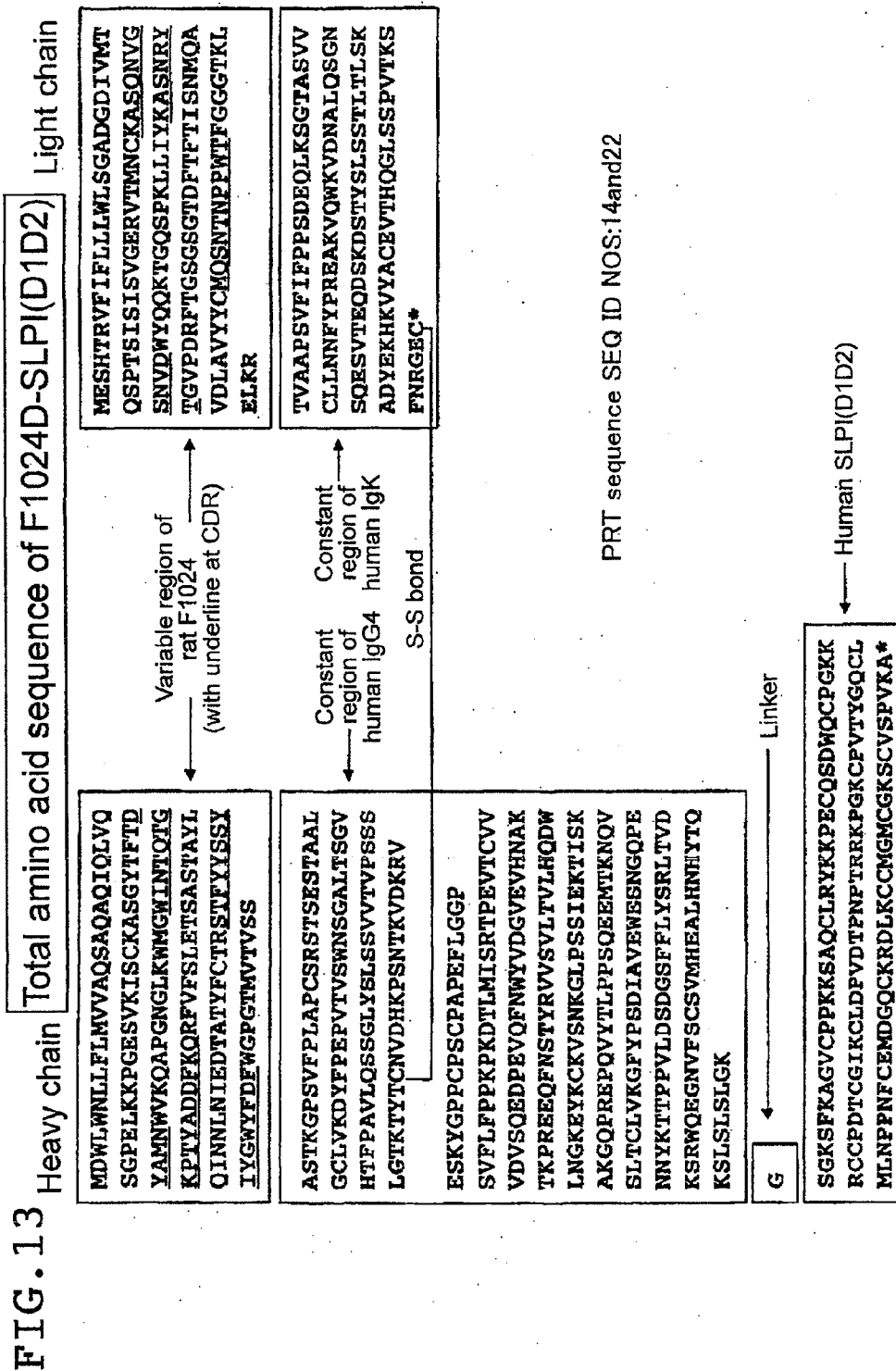


FIG. 12





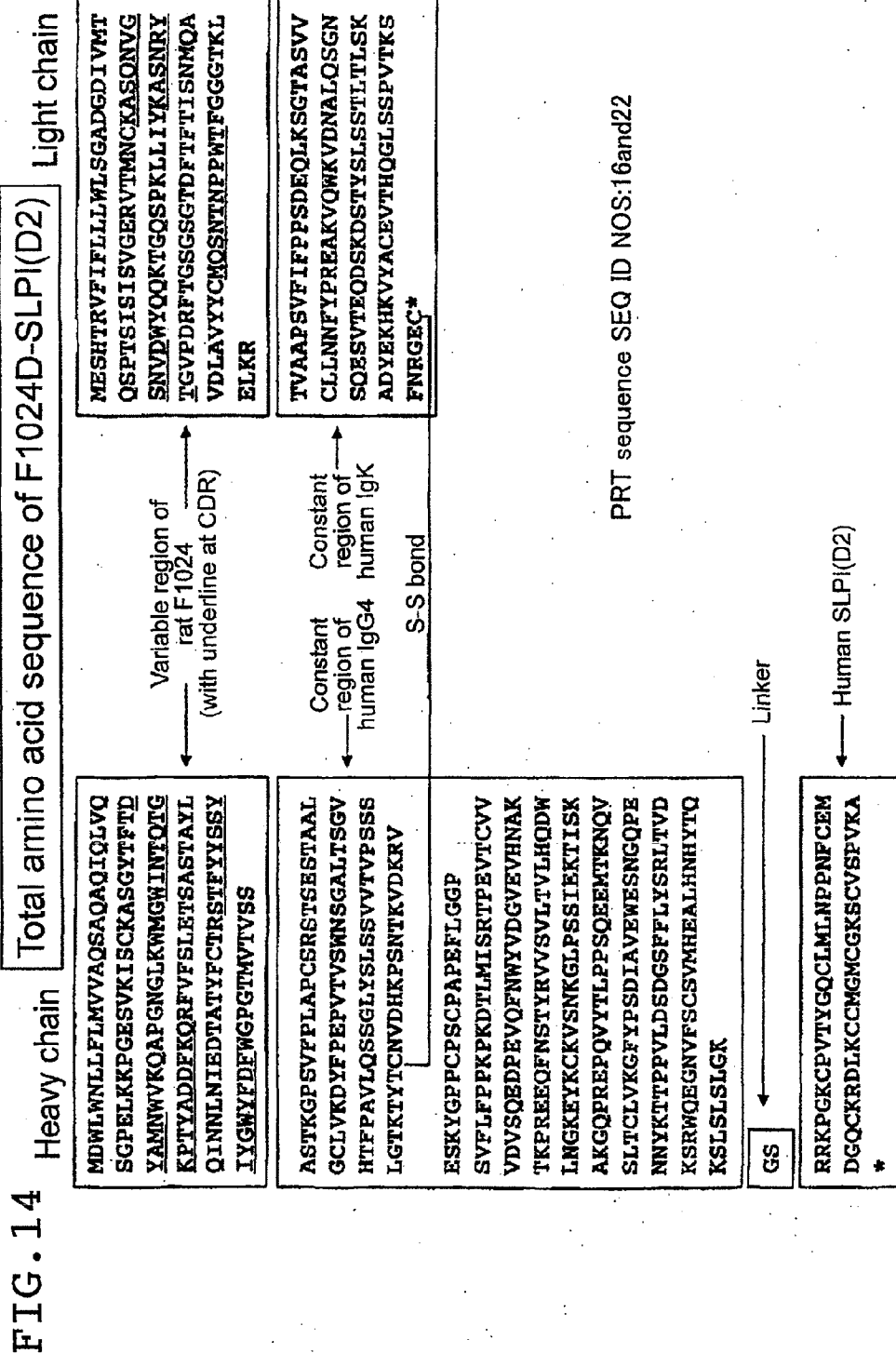


FIG. 15

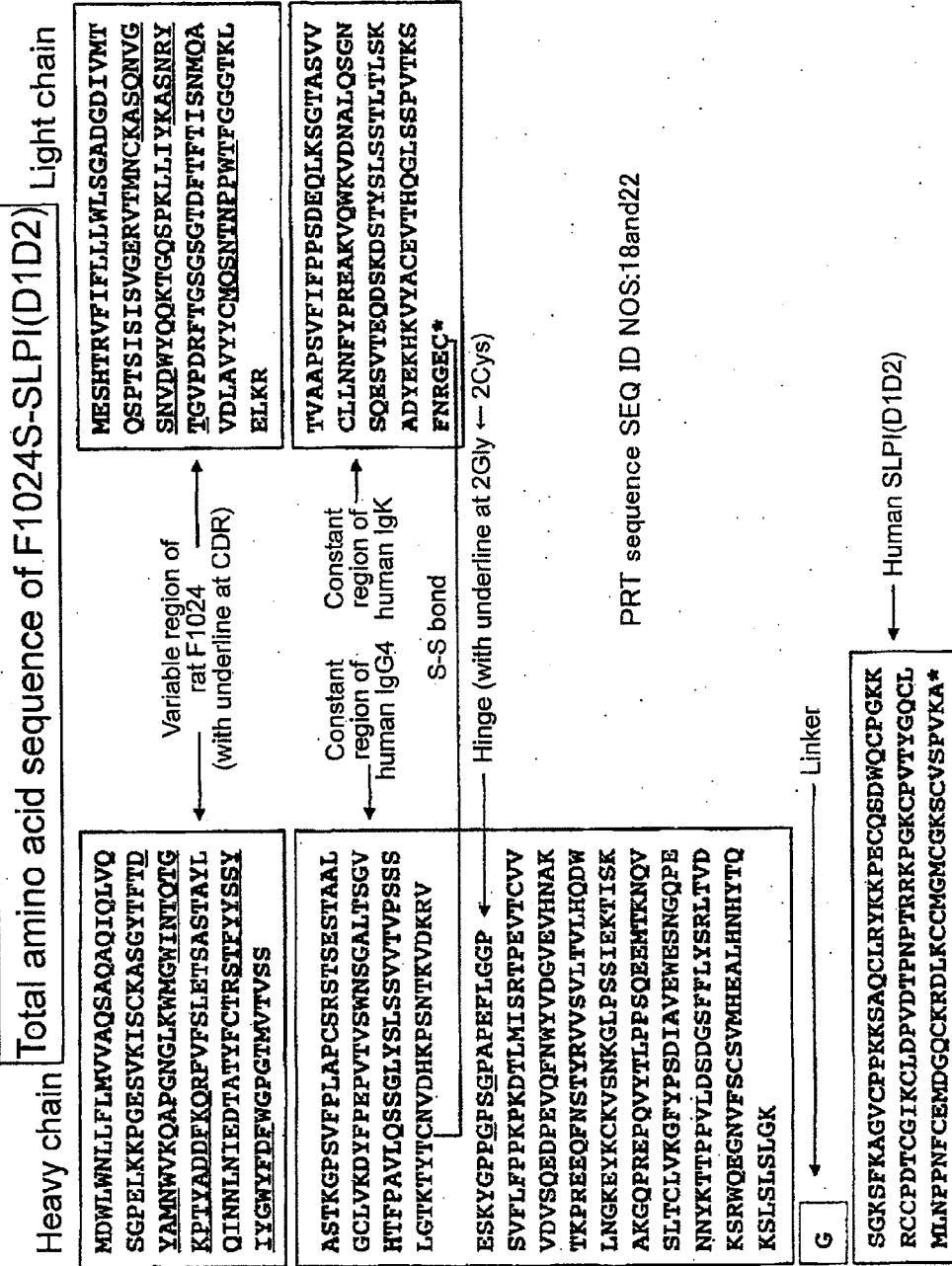


FIG. 16

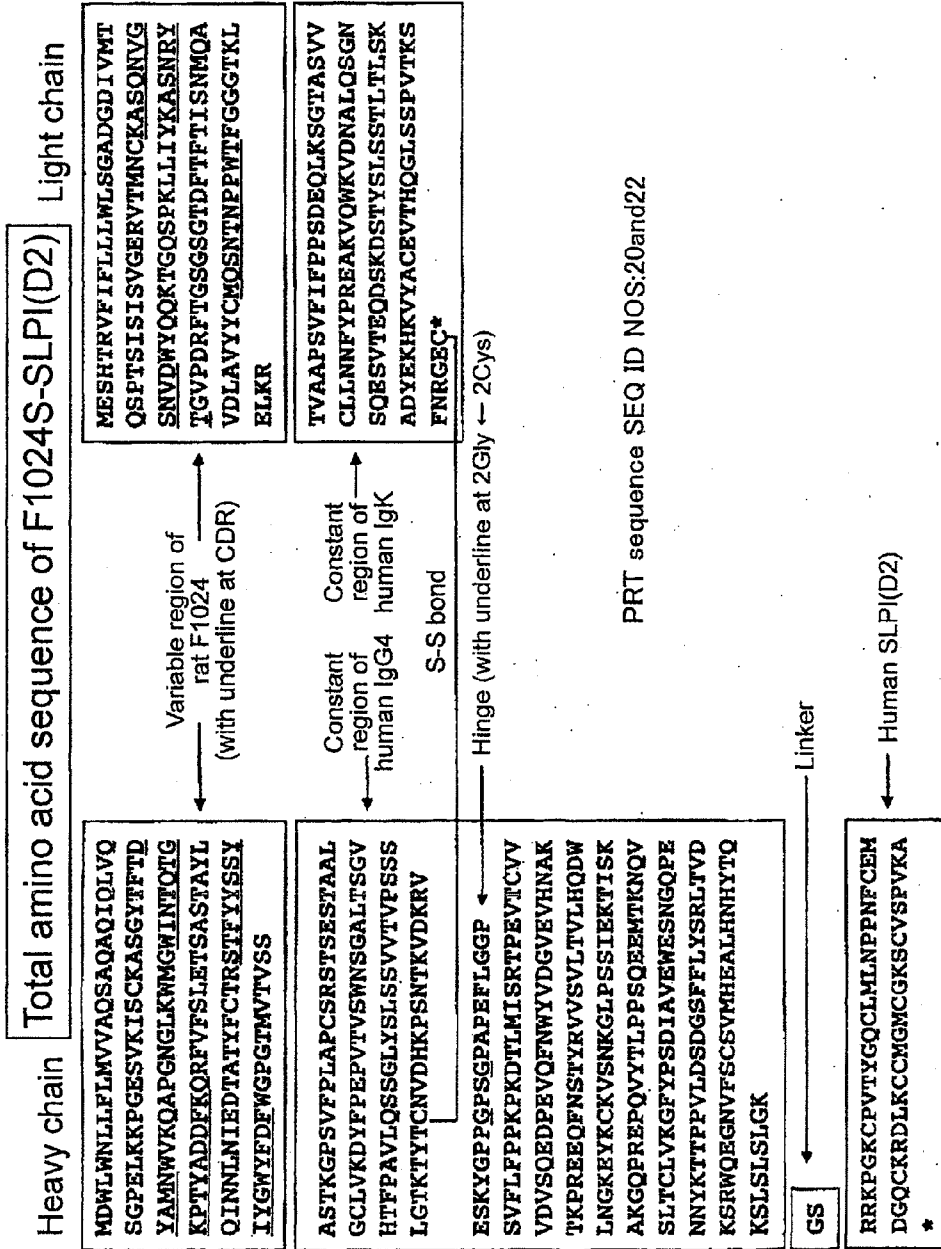


FIG. 17

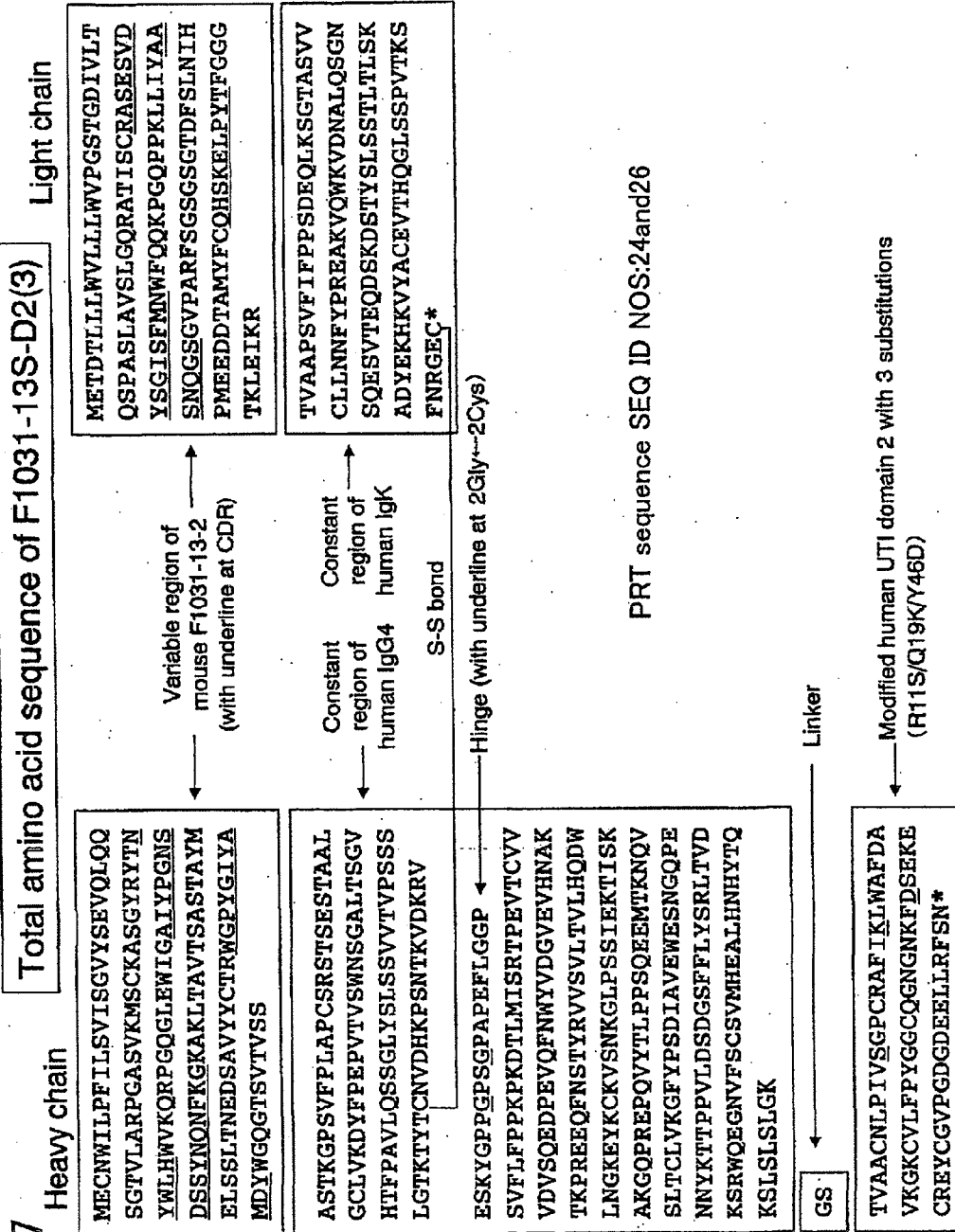


FIG. 18

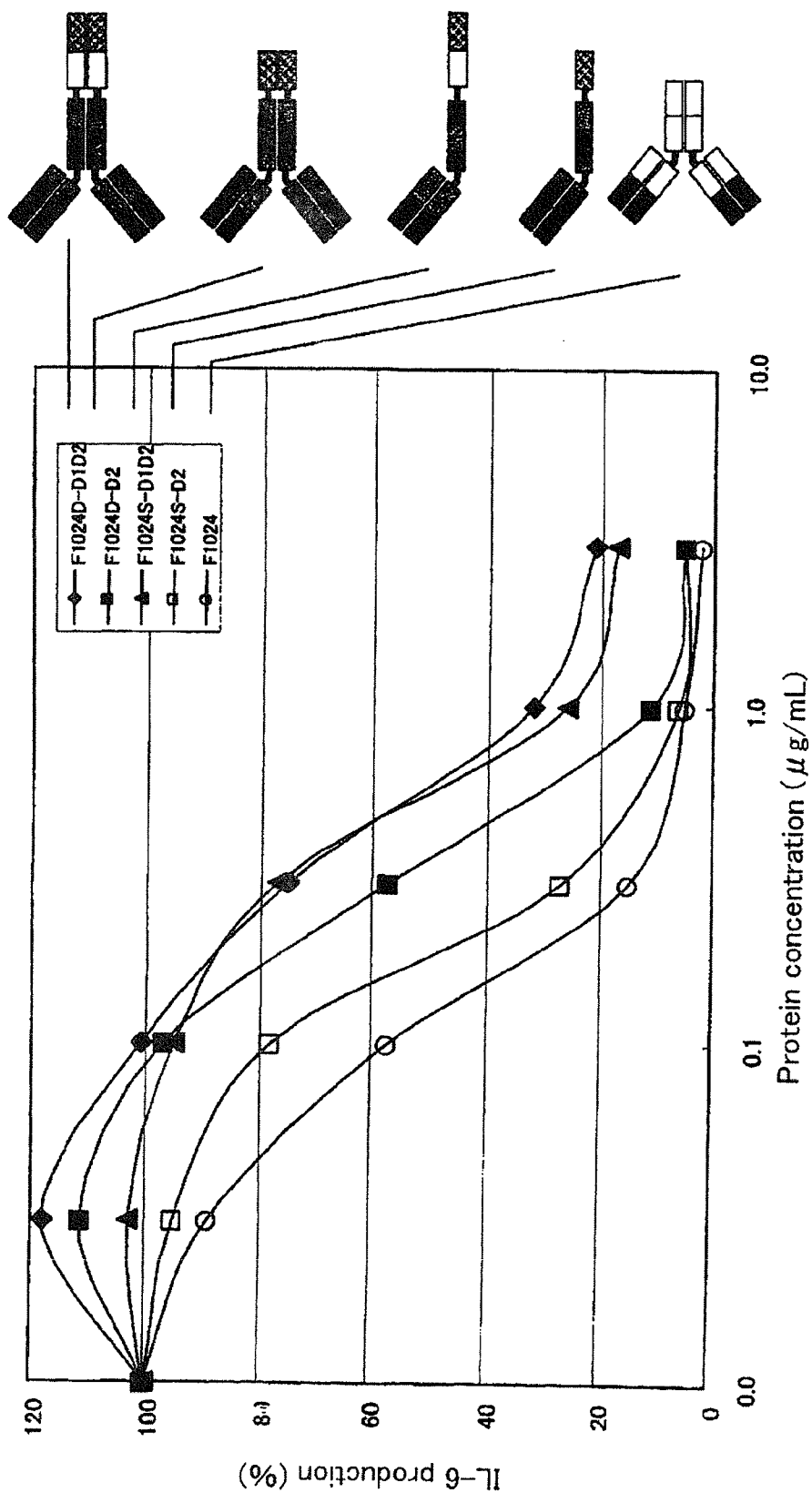


FIG. 19

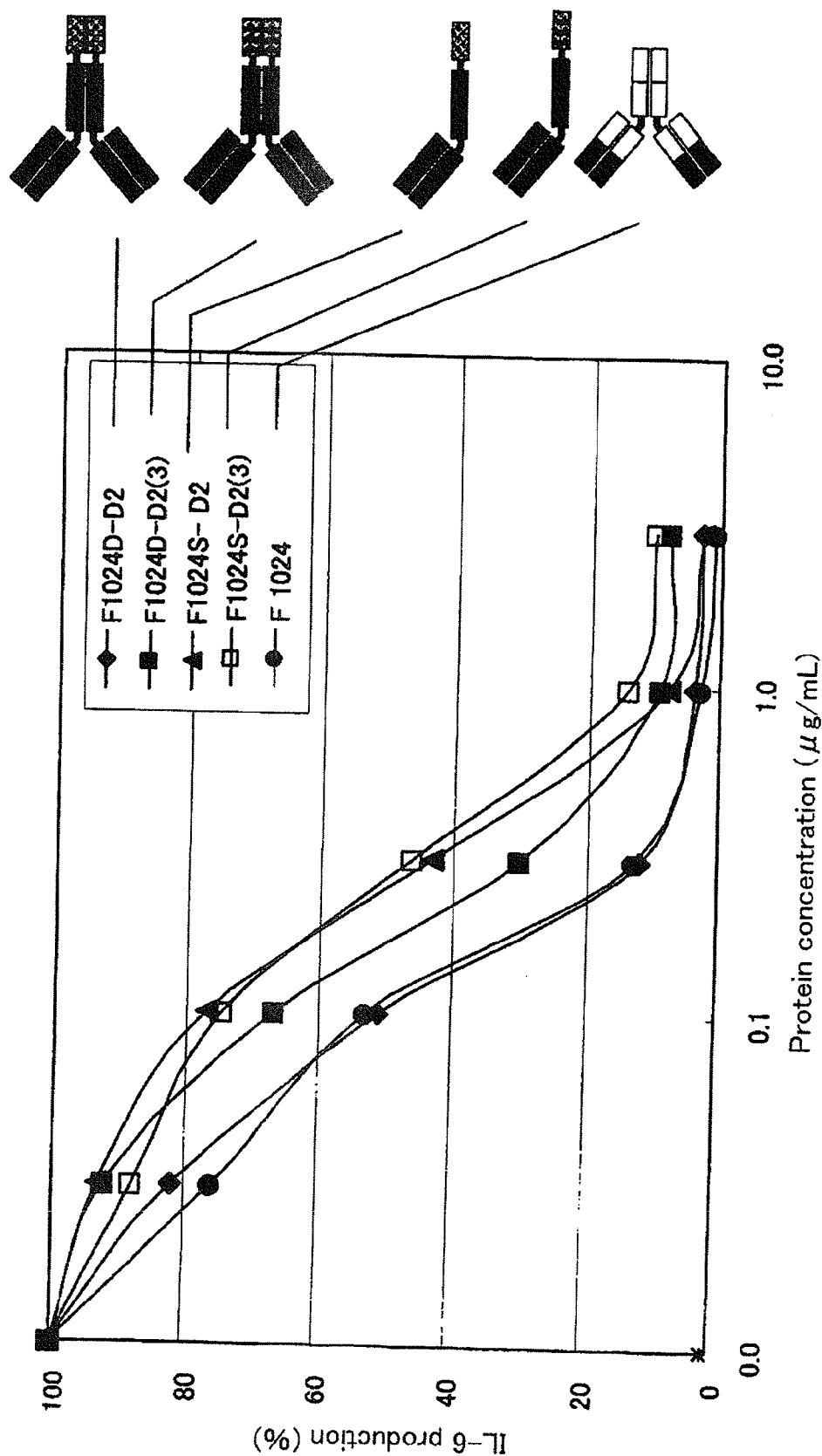


FIG. 20

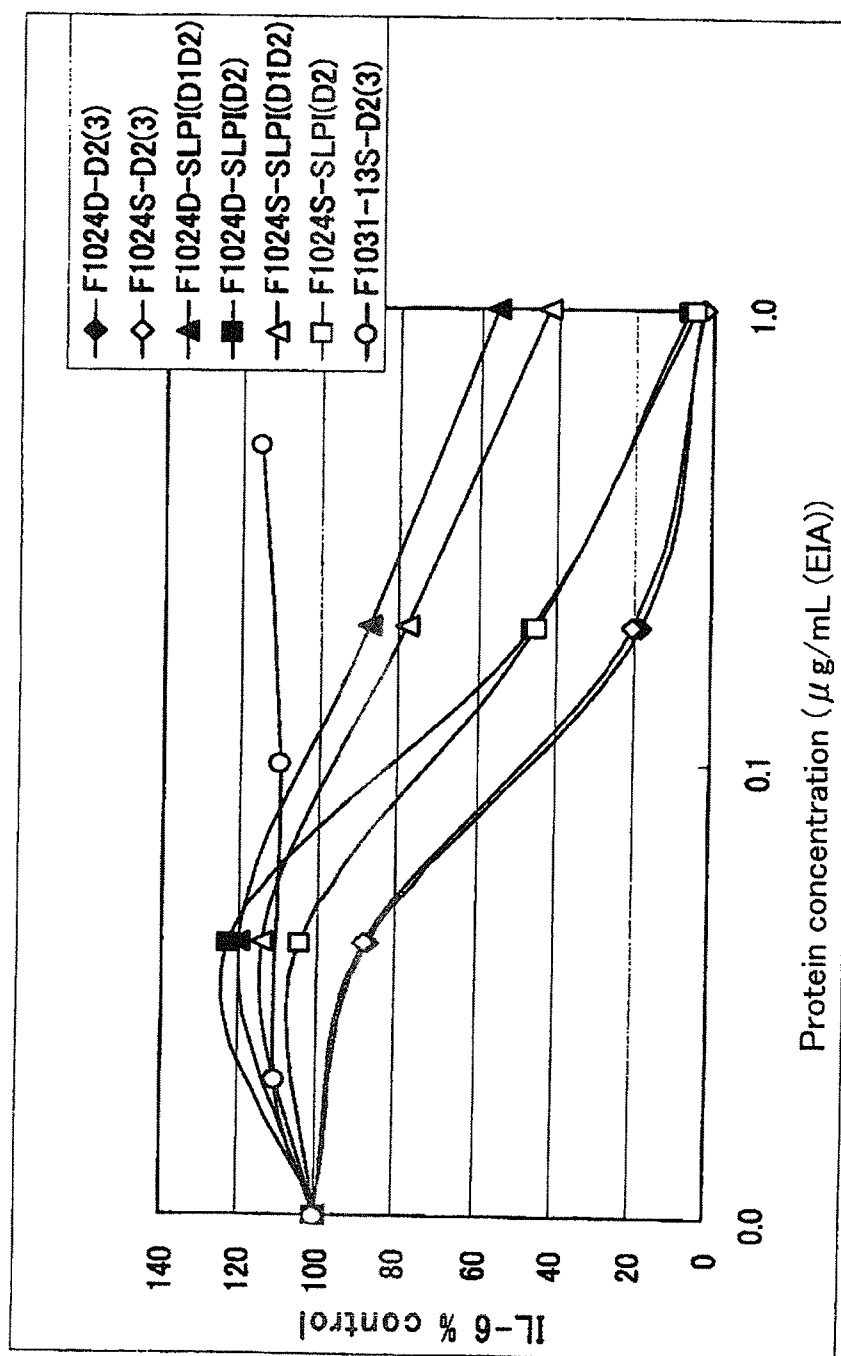


FIG. 21

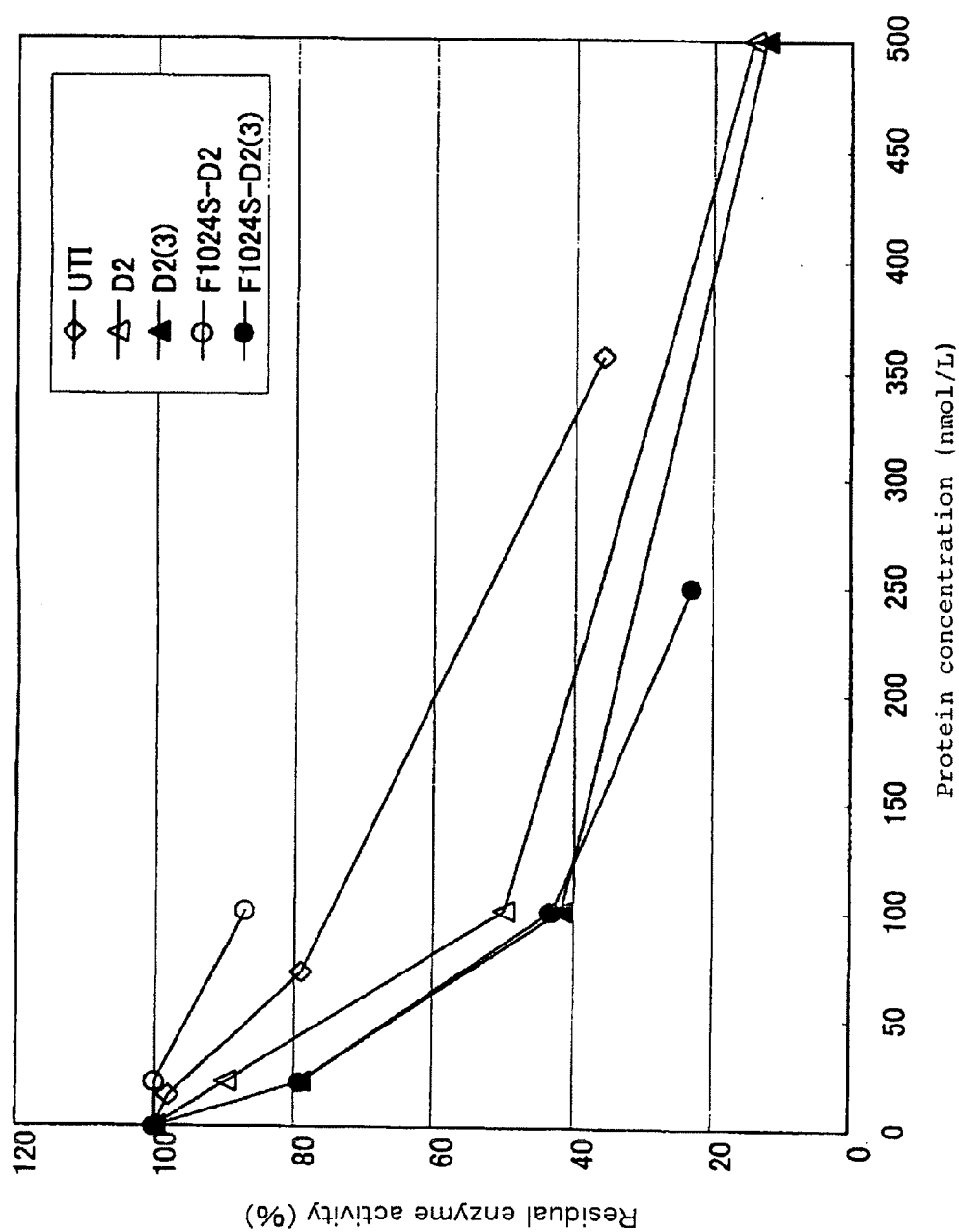


FIG. 22

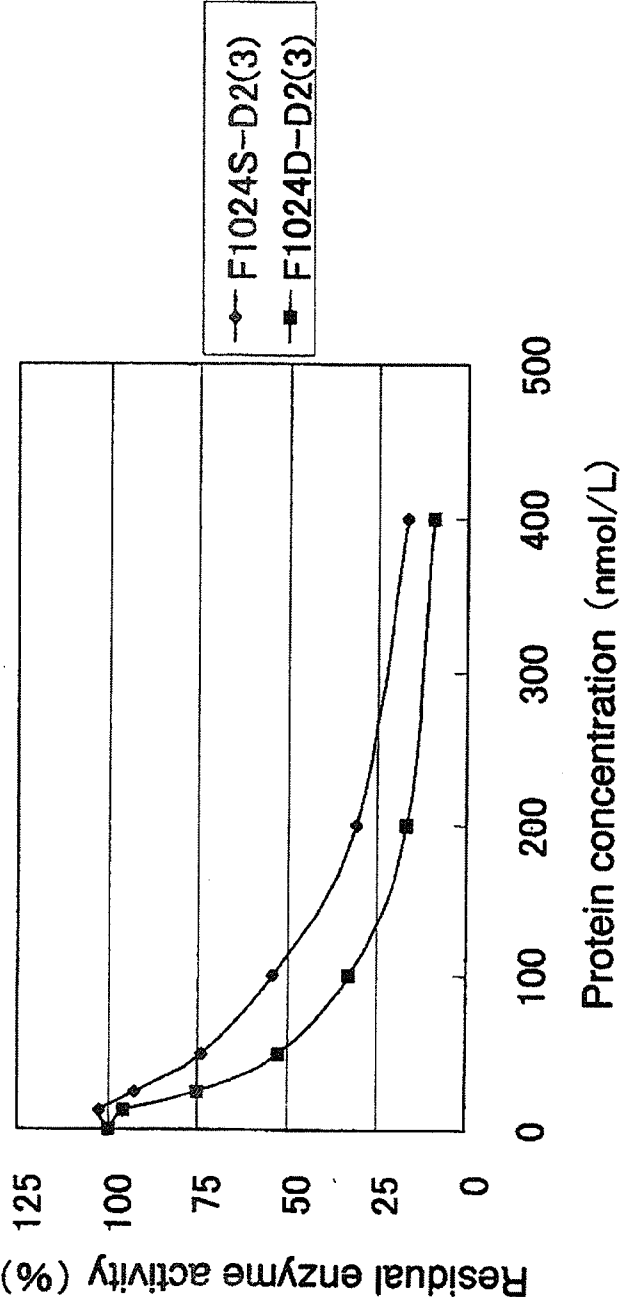


FIG. 23

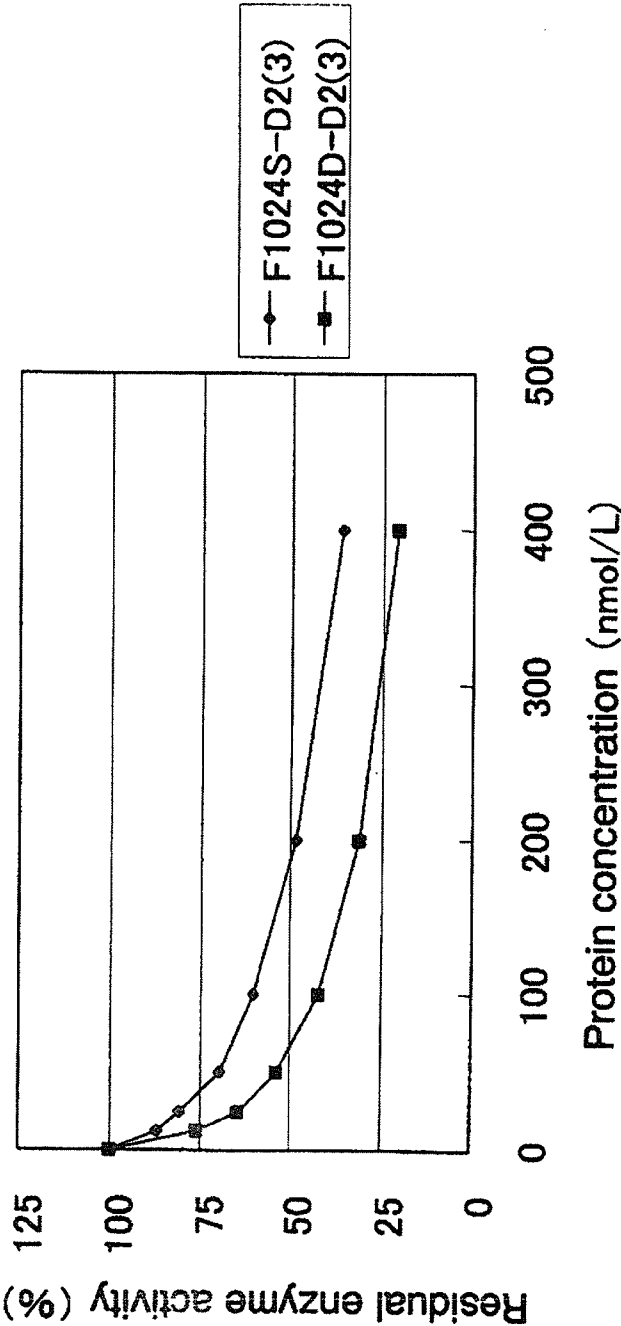


FIG. 24

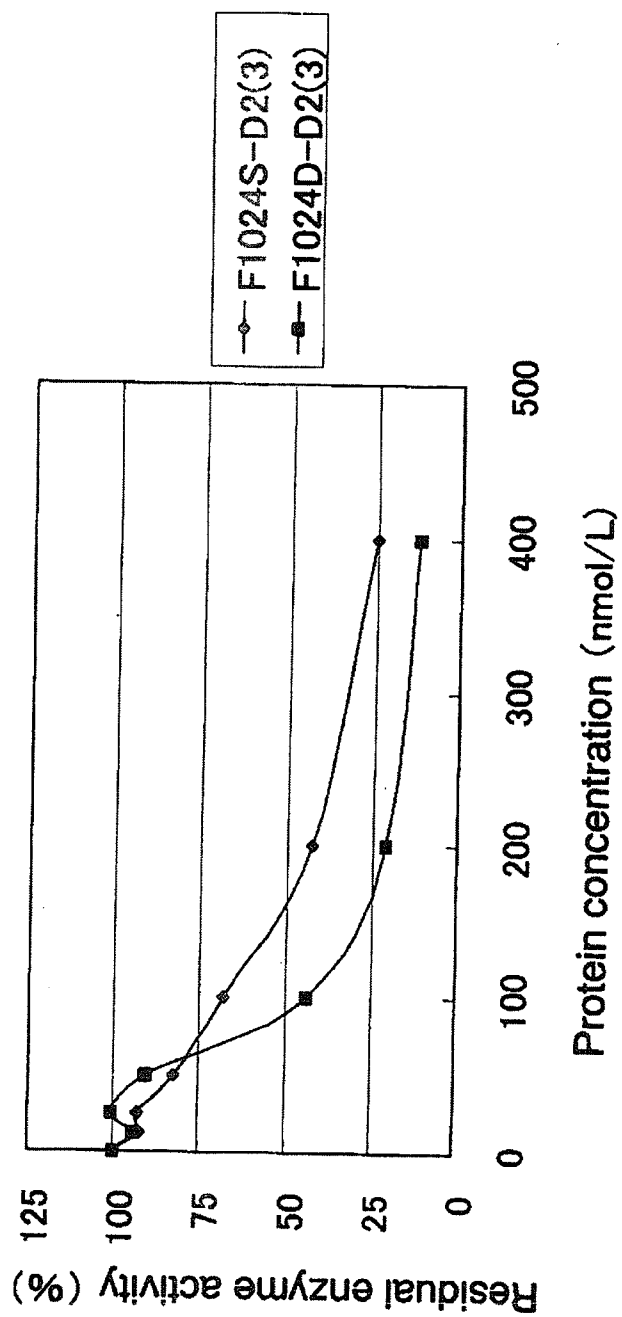


FIG. 25

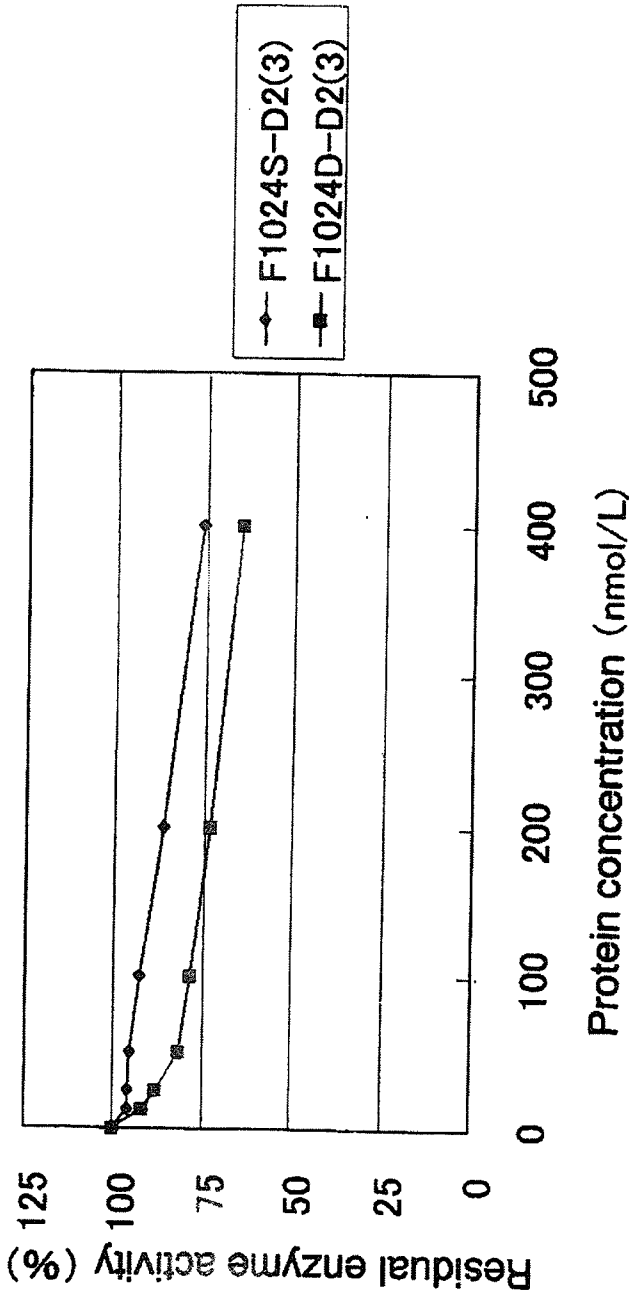


FIG. 26

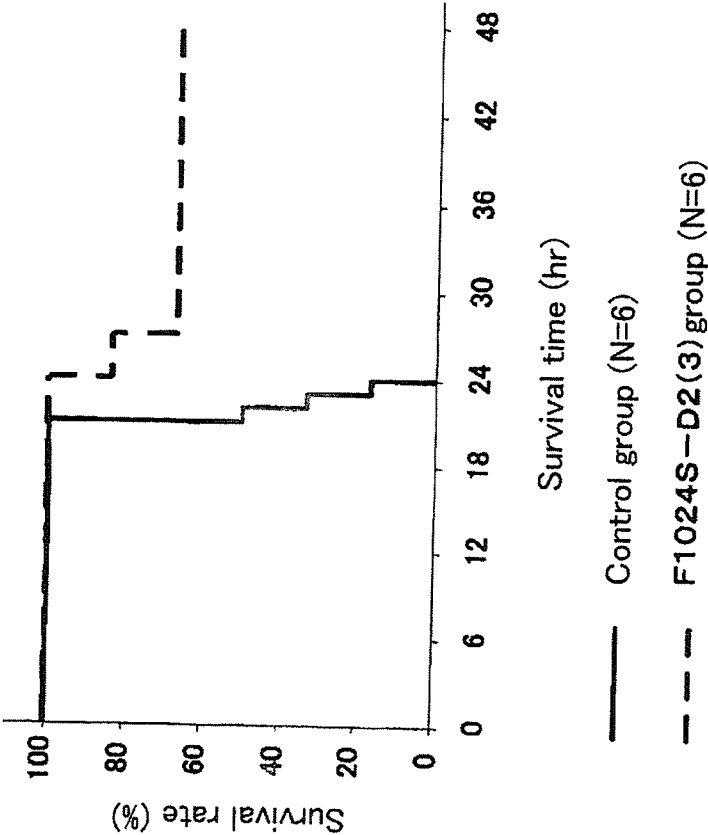


FIG. 27

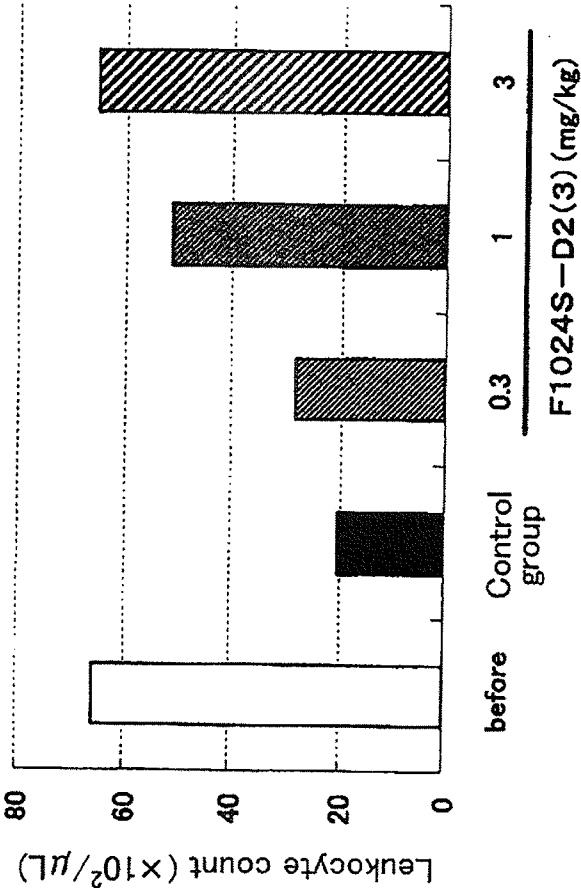


FIG. 28

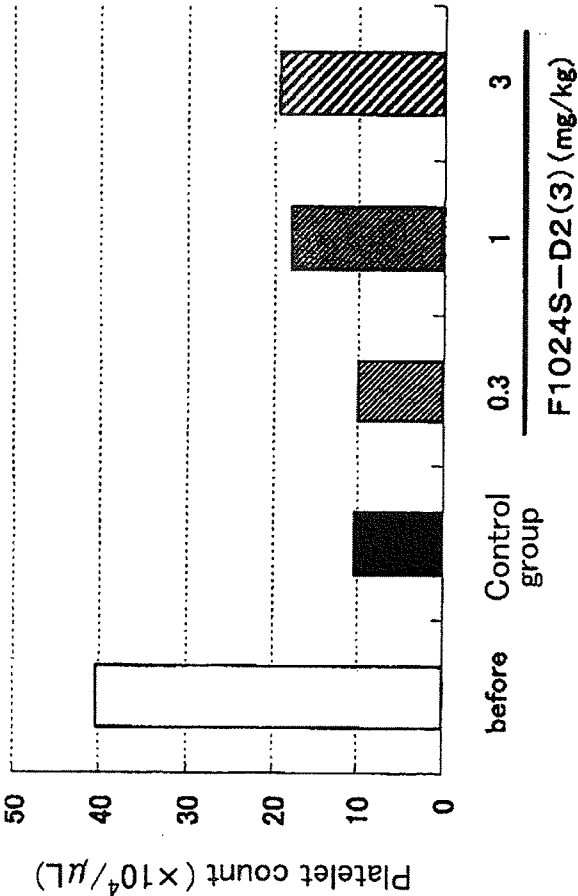


FIG. 29

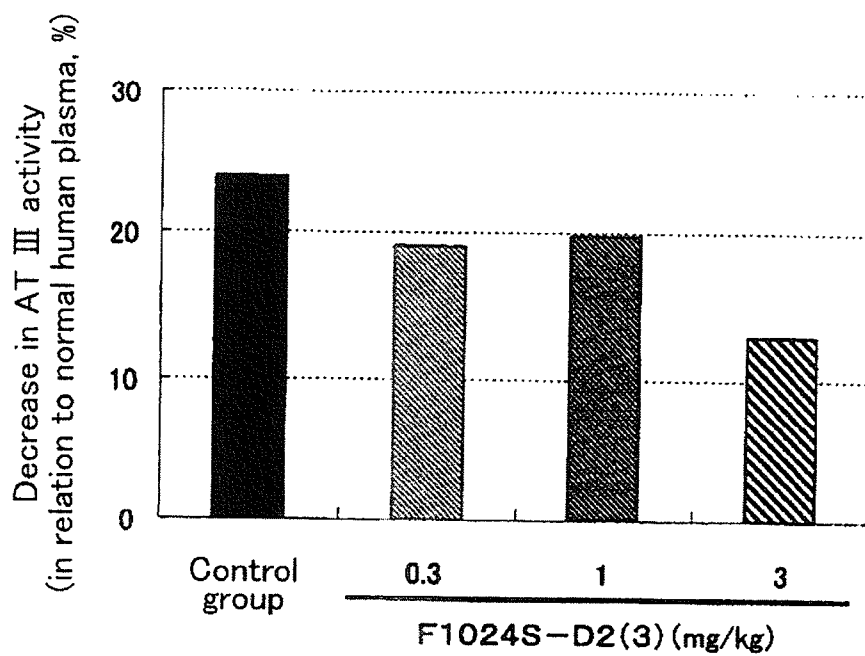


FIG. 30

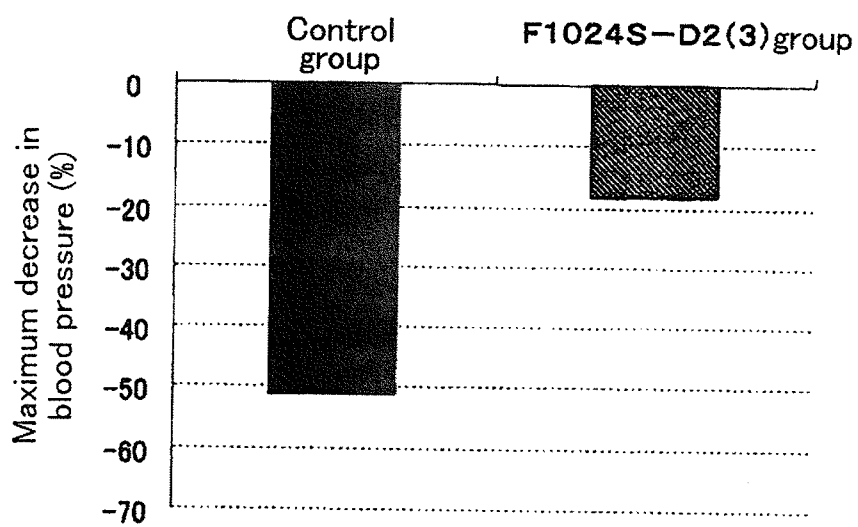


FIG. 31

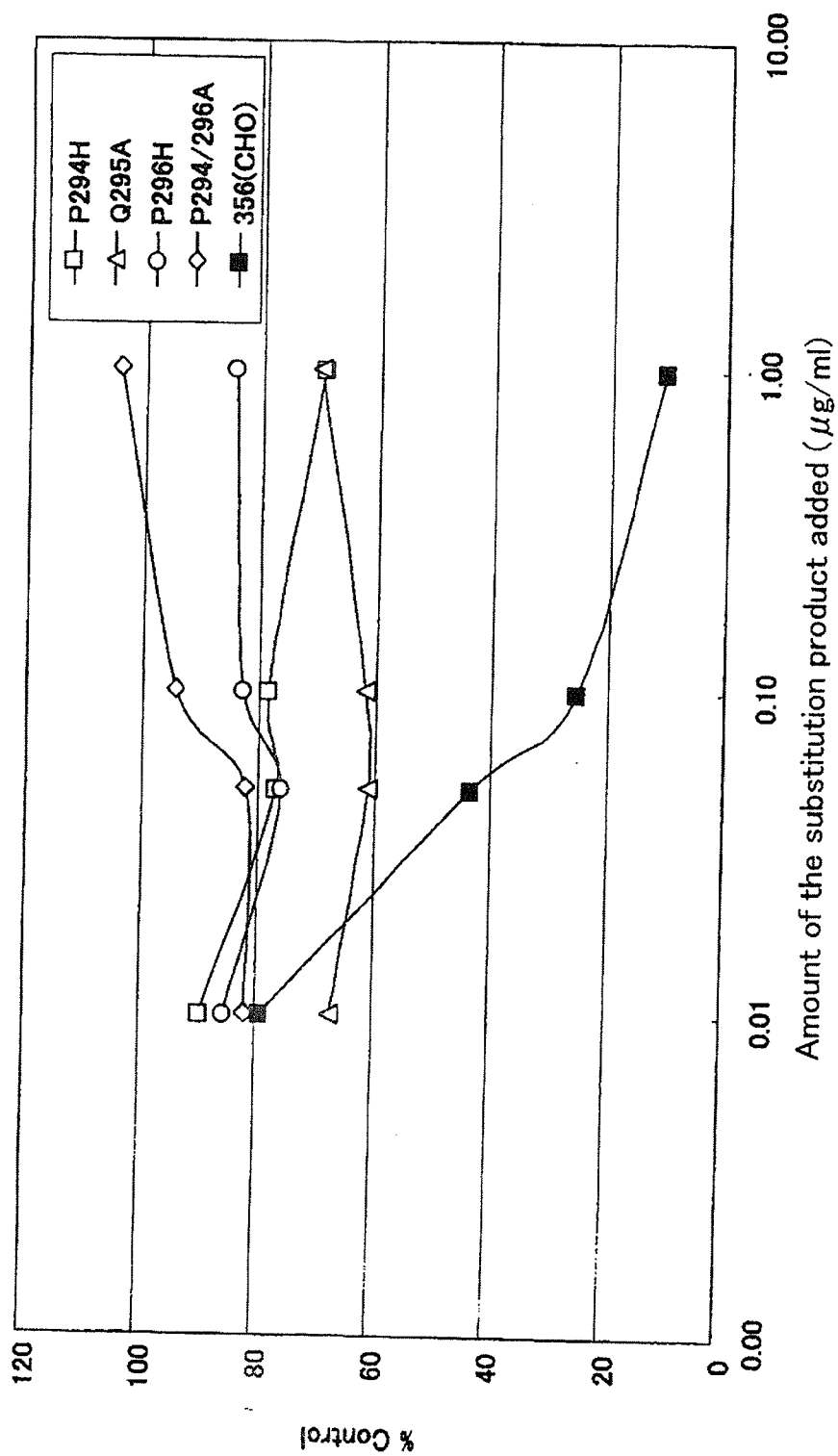


FIG. 32

PRT sequence SEQ ID NOS:10(residues 474-543),12(residues 474-543), 46 through 49, and 27 through 45)
1 10 20 30 40 50 60 70
PTK-2355 TVAACNLPIVRGPCRAFIQLWAFDAVKGKCVLFPYGGCQGNKGFYSEKECREYCGVPGDGEELLRFSN
PTK-2370S.....K.....D.....

PTK-2824S...I...K.....D.....
PTK-2825S...L...K.....D.....
PTK-2826S...T...K.....D.....
PTK-2827S...V...K.....D.....

PTK-2730A.....
PTK-2731C.....
PTK-2732D.....
PTK-2733E.....
PTK-2734F.....
PTK-2735G.....
PTK-2736H.....
PTK-2737I.....
PTK-2738K.....
PTK-2739L.....
PTK-2740M.....
PTK-2741N.....
PTK-2742P.....
PTK-2743Q.....
PTK-2744S.....
PTK-2745T.....
PTK-2746V.....
PTK-2747W.....
PTK-2748Y.....

FIG. 33

PRT sequence SEQ ID NOS:10(residues 474-543), 12(residues 474-543), 50 through 68)

	1	10	20	30	40	50	60	70
PTK-2355	T	V	A	A	C	N	L	P
PTK-2370	I	V	R	G	P	C	R	A
	F	I	Q	L	W	A	F	D
	A	V	K	G	C	V	L	F
	P	Y	G	G	C	Q	G	N
	K	F	Y	S	E	K	E	C
	R	E	Y	C	G	V	P	G
	D	E	E	L	L	R	F	S
	N							
PTK-2866	S	T	A					
PTK-2867	S	T	C					
PTK-2868	S	T	D					
PTK-2869	S	T	E					
PTK-2870	S	T	F					
PTK-2871	S	T	G					
PTK-2872	S	T	H					
PTK-2873	S	T	I					
PTK-2874	S	T	L					
PTK-2875	S	T	M					
PTK-2876	S	T	N					
PTK-2877	S	T	P					
PTK-2878	S	T						
PTK-2879	S	T	R					
PTK-2880	S	T	S					
PTK-2881	S	T	T					
PTK-2882	S	T	V					
PTK-2883	S	T	W					
PTK-2884	S	T	Y					

FIG. 34

PRT sequence SEQ ID NOS:10(residues 474-543), 12(residues 474-543), 69 through 87)

1	10	20	30	40	50	60	70
PTK-2355	TVAACNLPIVRGPCRAFIQLWAFDAVKGKCVLFPYGGCQGNKGFYSEKECREYCGVPGDGEELLRFSN						
PTK-2370	S.....K.....D.....						
PTK-2889	S...T.A.....D.....						
PTK-2890	S...T.C.....D.....						
PTK-2891	S...T.D.....D.....						
PTK-2892	S...T.E.....D.....						
PTK-2893	S...T.G.....D.....						
PTK-2894	S...T.H.....D.....						
PTK-2895	S...T.I.....D.....						
PTK-2896	S...T.K.....D.....						
PTK-2897	S...T.L.....D.....						
PTK-2898	S...T.M.....D.....						
PTK-2899	S...T.N.....D.....						
PTK-2900	S...T.P.....D.....						
PTK-2901	S...T.Q.....D.....						
PTK-2902	S...T.R.....D.....						
PTK-2903	S...T.S.....D.....						
PTK-2904	S...T.T.....D.....						
PTK-2905	S...T.V.....D.....						
PTK-2906	S...T.W.....D.....						
PTK-2907	S...T.Y.....D.....						

FIG. 35

PRT sequence SEQ ID NOS:10(residues 474-543), 12(residues 474-543), 88 through 106)

1 10 20 30 40 50 60 70
TVAACNLPIVRGPCRAFIQLWAFDAVKGKCVLFFYGGCQGNKFFYSEKECREYCGVPGDGEELLRFNS
.....S.....K.....D.....
.....A...T.....D.....
.....C...T.....D.....
.....D...T.....D.....
.....E...T.....D.....
.....F...T.....D.....
.....G...T.....D.....
.....H...T.....D.....
.....I...T.....D.....
.....K...T.....D.....
.....L...T.....D.....
.....M...T.....D.....
.....N...T.....D.....
.....P...T.....D.....
.....Q...T.....D.....
.....T...T.....D.....
.....V...T.....D.....
.....W...T.....D.....
.....Y...T.....D.....
pTK-2355
pTK-2370
pTK-2932
pTK-2933
pTK-2934
pTK-2935
pTK-2936
pTK-2937
pTK-2938
pTK-2939
pTK-2940
pTK-2941
pTK-2942
pTK-2943
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pTK-2945
pTK-2946
pTK-2947
pTK-2948
pTK-2949
pTK-2950

FIG. 36

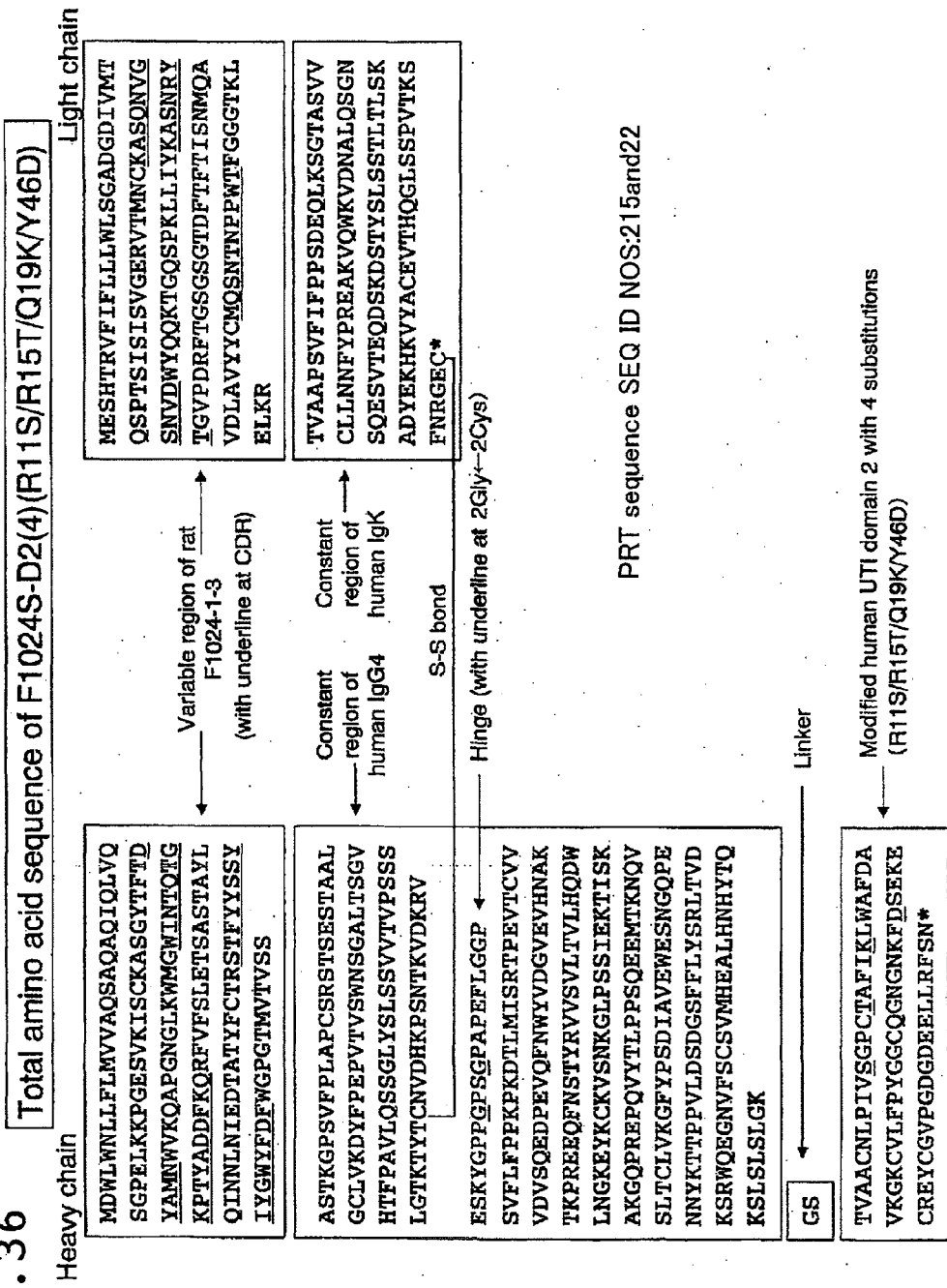


FIG. 37

PRT sequence SEQ ID NOS:107-108

F1024S-TM123456M
(pTK-2754)

CSVENGGEHACNAIPGAPRCQCPAGAAALQADGRSC
TASATQSCNDLCEHFCVPNPDPQPGSYSCMCETGYRLAADQHRC
EDVDDCILEPSPCPQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQMF
CNQTACPADCDPNTQASCECEPEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFFECICGPD¹⁰⁷SALARHIGTDC

F1024S-TM123456L
(pTK-2762)

CSVENGGEHACNAIPGAPRCQCPAGAAALQADGRSC
TASATQSCNDLCEHFCVPNPDPQPGSYSCMCETGYRLAADQHRC
EDVDDCILEPSPCPQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQ¹⁰⁸LF
CNQTACPADCDPNTQASCECEPEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFFECICGPD¹⁰⁸SALARHIGTDC

FIG. 38

PRT sequence SEQ ID NOS:109-110

F1024S-TM1234567M
(pTK-2755)

CSVENGGEHACNAIPGAPRCQCPAGALQADGRSC
TASATQSCNDLCEHFCVPNPDQPGSYSCMCETGYRLAADQHRC
EDVDDCILEPSPCPQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQMF
CNQTACPADCDPNTQASCECPEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFECICGPD~~S~~ALARHIGTDC
DSGKVDGGDSGSGEPPSPTPGSTLTTPPAVGLVHS

F1024S-TM1234567L
(pTK-2763)

CSVENGGEHACNAIPGAPRCQCPAGALQADGRSC
TASATQSCNDLCEHFCVPNPDQPGSYSCMCETGYRLAADQHRC
EDVDDCILEPSPCPQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQ~~L~~F
CNQTACPADCDPNTQASCECPEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFECICGPD~~S~~ALARHIGTDC
DSGKVDGGDSGSGEPPSPTPGSTLTTPPAVGLVHS

FIG. 39

PRT sequence SEQ ID NOS:111-112

F1024S-TM23456M

(pTK-2756)

TASATQSCNDLCEHFCVPNPDPQGSYS~~CM~~CETGYRLAADQHRC
EDVDDCILEPSPCQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDFCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQMF
CNQTACPADCDPNTQASCECEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFFECICGPD~~S~~ALARHIGTDC

F1024S-TM23456L

(pTK-2764)

TASATQSCNDLCEHFCVPNPDPQGSYS~~CM~~CETGYRLAADQHRC
EDVDDCILEPSPCQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDFCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQ~~LF~~
CNQTACPADCDPNTQASCECEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFFECICGPD~~S~~ALARHIGTDC

FIG. 40

PRT sequence SEQ ID NOS:113-114

F1024S-TM234567M
(pTK-2757)

TASATQSCNDLCEHFCVNPNDQPGSYSCMCETGYRLAADQHRC
EDVDDCILEPSPCQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDPFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQMF
CNQTACPADCDPNTQASCECEPEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFFECICGPD~~S~~ALARHIGTDC
DSGKVDGGDSGSGEPPSPTPGSTLTTPPAVGLVHS

F1024S-TM234567L
(pTK-2765)

TASATQSCNDLCEHFCVNPNDQPGSYSCMCETGYRLAADQHRC
EDVDDCILEPSPCQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDPFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQLF
CNQTACPADCDPNTQASCECEPEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFFECICGPD~~S~~ALARHIGTDC
DSGKVDGGDSGSGEPPSPTPGSTLTTPPAVGLVHS

FIG. 41

PRT sequence SEQ ID NOS:115-116

F1024S-TM3456M

(PTK-2758)

EDVDDCILEPSPCPQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQMF
CNQTACPADCDPNTQASCECEPEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFFECICGPD¹SALARHIGTDC

F1024S-TM3456L

(PTK-2766)

EDVDDCILEPSPCPQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQLF
CNQTACPADCDPNTQASCECEPEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFFECICGPD²SALARHIGTDC

FIG. 42

PRT sequence SEQ.ID NOS:117-118

F1024S-TM34567M

(pTK-2759)

EDVDDCILEPSPCQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQMF
CNQTACPADCDPNTQASCECEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFFECICGPD^SALARHIGTDC
DSGKVDGGDSGSGEPPSPPTPGSTLTTPPAVGLVHS

F1024S-TM34567L

(pTK-2767)

EDVDDCILEPSPCQRCVNTQGGFECHCYPNYDLVDGEC
VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQLF
CNQTACPADCDPNTQASCECEGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFFECICGPD^SALARHIGTDC
DSGKVDGGDSGSGEPPSPPTPGSTLTTPPAVGLVHS

FIG. 43

PRT sequence SEQ ID NOS:119-120

F1024S-TM456M

(PTK-2760)

VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQMF
CNOTACPADCDPNTQASCECEPGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFECICGPD~~S~~ALARHIGTDC

F1024S-TM456L

(PTK-2768)

VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQLF
CNOTACPADCDPNTQASCECEPGYILDDGFICTDIDE
CENGGFCSGVCHNLPGTFECICGPD~~S~~ALARHIGTDC

FIG. 44

PRT sequence SEQ ID NOS:121-122

F1024S-TM4567M (pTK-2761)	VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQMF CNQTACPADCDPNTQASCECEPEGYILDDGFICTDIDE CENGGFCSGVCHNLPGTFECICGPD ^S SALARHIGTDC DSGKVDGGDSGSGEPPSPTPGSTLTTPPAVGLVHS
------------------------------	--

F1024S-TM4567L (pTK-2769)	VEPVDPCFRANCEYQCQPLNQTSYLCVCAEGFAPIPHEPHRCQLF CNQTACPADCDPNTQASCECEPEGYILDDGFICTDIDE CENGGFCSGVCHNLPGTFECICGPD ^S SALARHIGTDC DSGKVDGGDSGSGEPPSPTPGSTLTTPPAVGLVHS
------------------------------	--

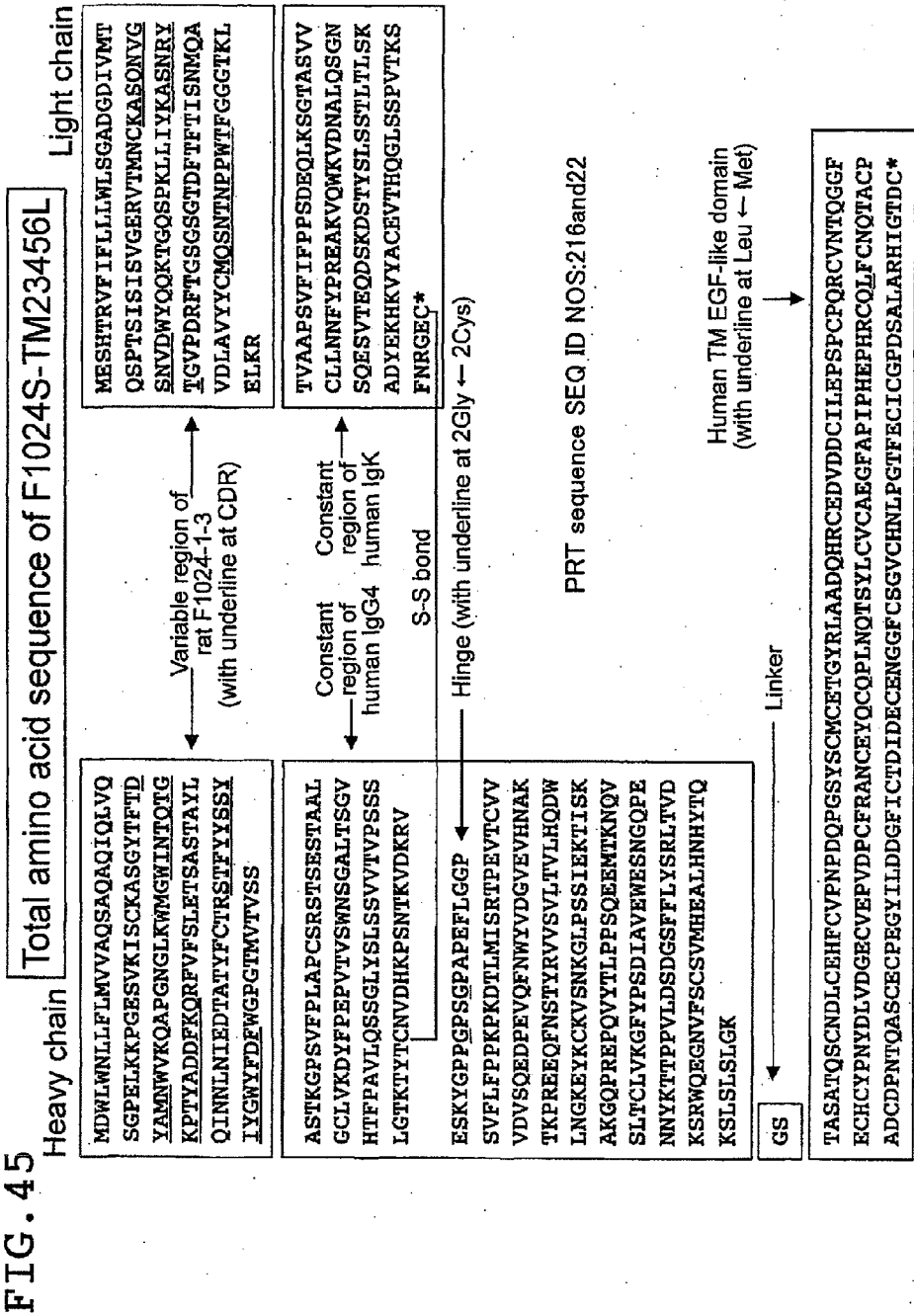
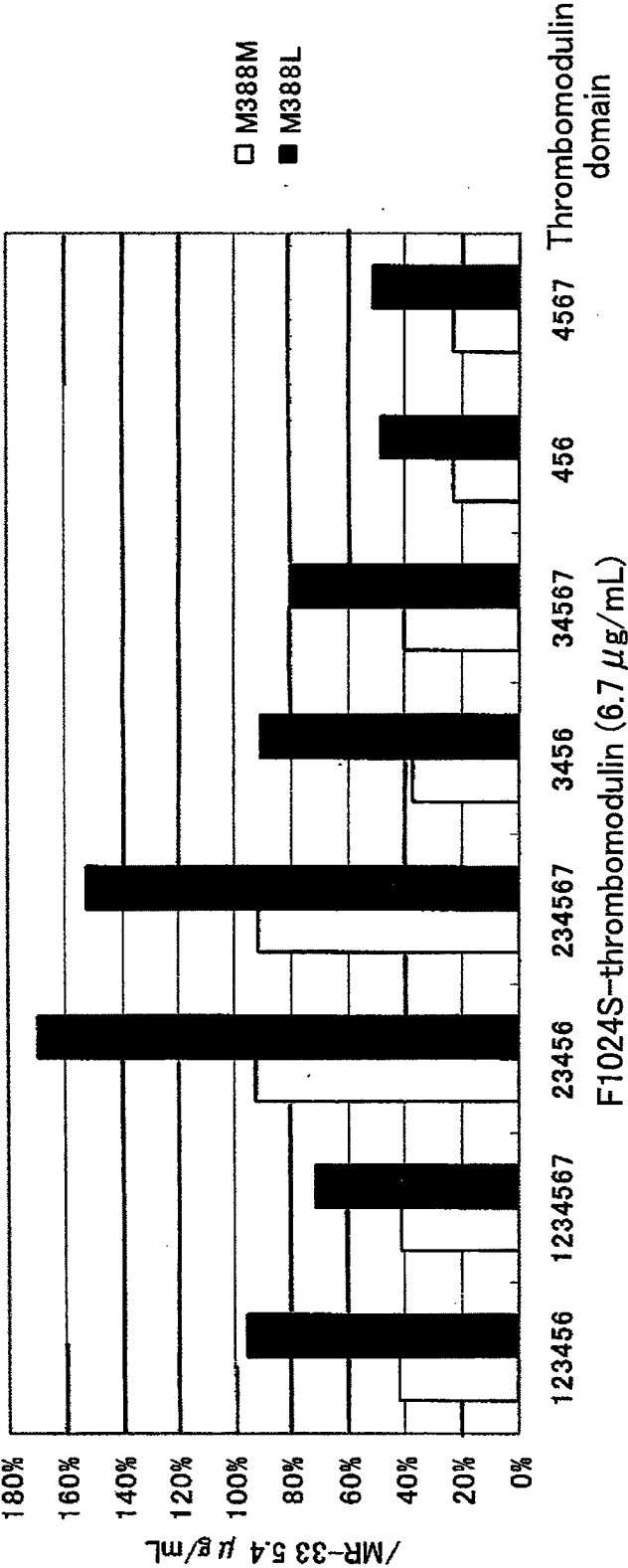


FIG. 46

Thrombomodulin activity
F1024-thrombomodulin/MR-33



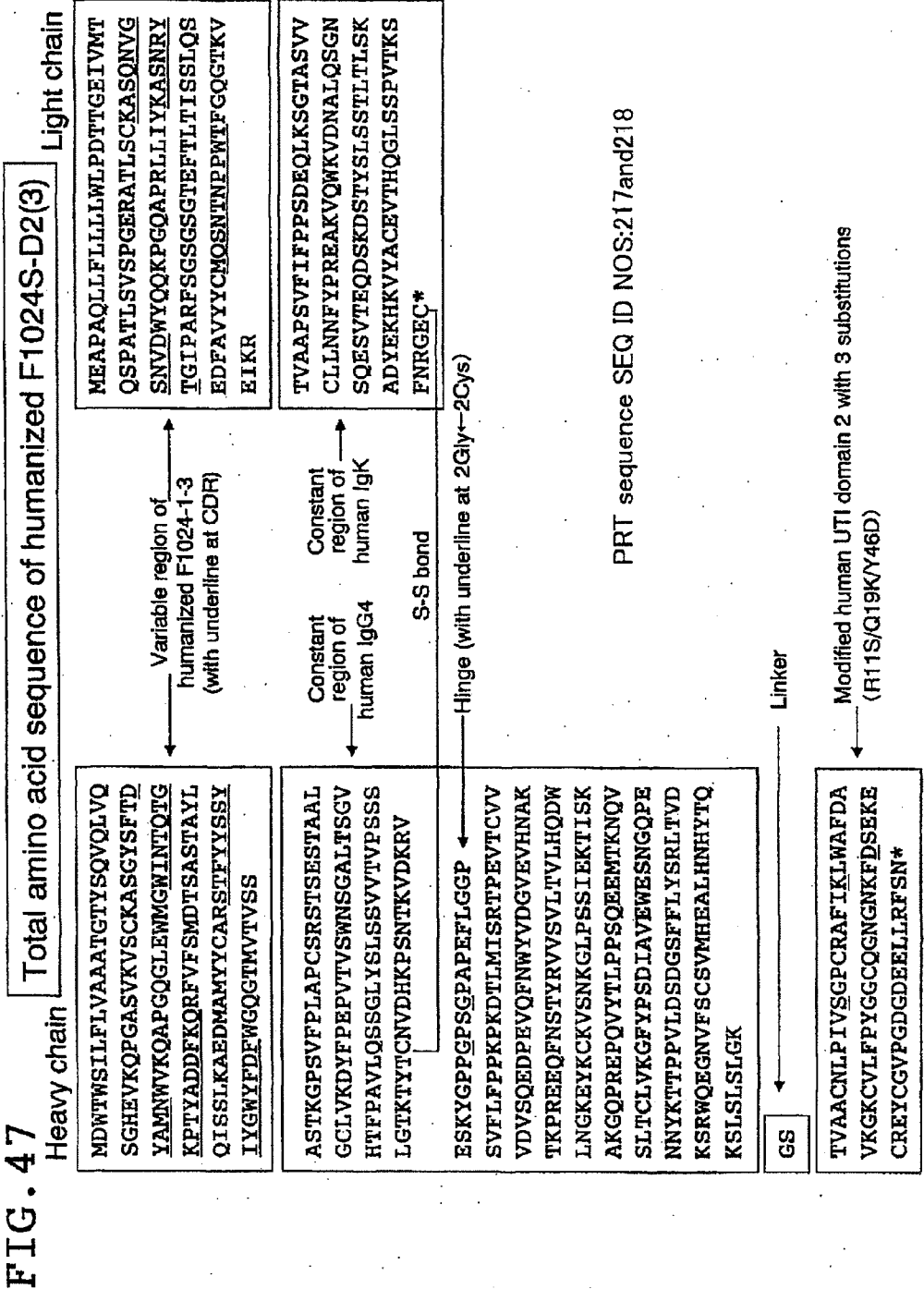


FIG. 48 PRT sequence (SEQ ID NOS:219), (SEQ ID NOS:223), (SEQ ID NOS:220-222), (SEQ ID NOS:224-226)**VH**

F1024-1-3 QIQLVQSGPELKKPGESVKISKASGYTFTDYAMNWKQAPGNGLKMMGWINTQTGKPTYAD
 IGHV7-81-HA V.....H.V.Q.A.A..V.....S.....P....Q..E.....
 NEW-HA .V..QE...G.VR.SQTLSLT.TV..S..S.....R.P..R..E..I.....
 Eu-HA .V.....A.V....S...V.....G..S.....R....Q..E.....

F1024-1-3 DFKQRFVFSLETSASTAYLQINNLIENIEDTATYFCTRSTFYSSYIYGWYDFWGPGETSVTVSS
 IGHV7-81-HAMD.....SS.KA..M.M.Y.A.....Q.....
 NEW-HAVTMLVD...KNQFS.RLSSVTAA...V.Y.A.....Q.SL.....
 Eu-HAVTITADE.TN...MELSS.RS....I.Y.A.....Q..L.....

VL

F1024-1-3 DIVMTQSPPTISISVGERVTMNCCKASQNVGSNVDWYQKQTGQSPKLLIYKASNRYT
 RF-KA E.....ATL.V.P...A.LS.....P..A.R.....
 REI-KA .Q.....S...A...D...IT.....P.KA.....
 Eu-KA .Q.....STL.A...D...IT.....P.KA...M.....

F1024-1-3 GVPDRFTGSGSGTDFFTTISNMQAVDLAVYYCMQSNTPNPPTFGGGTKLELKRT
 RF-KA .I.A..S.....E..L...SL.SE.F.....Q...V.I...
 REI-KA ...S..S.....SL.PE.I.T.....Q...V.I...
 Eu-KA ...S..I.....E..L...SL.PD.F.T.....Q...V.V...

FIG. 49

V_H PRT sequence SEQ ID NOS:219, 227-233

F1024-1-3 QIQLVQSGPELKPKGESVKISKASGYTFTDYAMNWKQAPGNGLKWMGWINTQTGKPTYAD

IGHV7-81-HA V.....H.V.Q.A..V.....S.....P....Q..E.....

IGHV7-81-HC V.....H.V.Q.A..V.....S.....K....N..K.....

IGHV7-81-HX V.....H.V.Q.A..V.....S.....K....Q..E.....

NEW-HA V..QE...G.VR.SQTLST.TV..S..S.....R.P..R..E.I.....

NEW-HB I..VQ...E..KK..GESVKIS..KA..S..S.....R.P..R..E.I.....

Eu-HA V.....A.V...S...V.....G..S.....R....Q..E.....

Eu-HB I.....P..L.....E...I.....Y..T.....R....Q..E.....

F1024-1-3 DFKQRFVFSLETSASTAYLQINNINIEDTATYFCTRSTFYSSYIYGWYDFWGPGETSVTVSS

IGHV7-81-HAMD.....SS.KA..M.M.Y.A.....Q.....

IGHV7-81-HCMD.....SS.KA..M.M.Y.A.....Q.....

IGHV7-81-HXMD.....SS.KA..M.M.Y.A.....Q.....

NEW-HAVTMLVD...KNQFS.RLSSVTAA...V.Y.A.....Q.SL.....

NEW-HBVTMLVD...KNQFS.RLSSVTAA...V.Y.A.....Q.SL.....

Eu-HAVTITADE.TN...MELSS.RS....I.Y.A.....Q..L.....

Eu-HBVTITADE.TN...MELSS.RS....I.Y.A.....Q..L.....

FIG. 50

Human

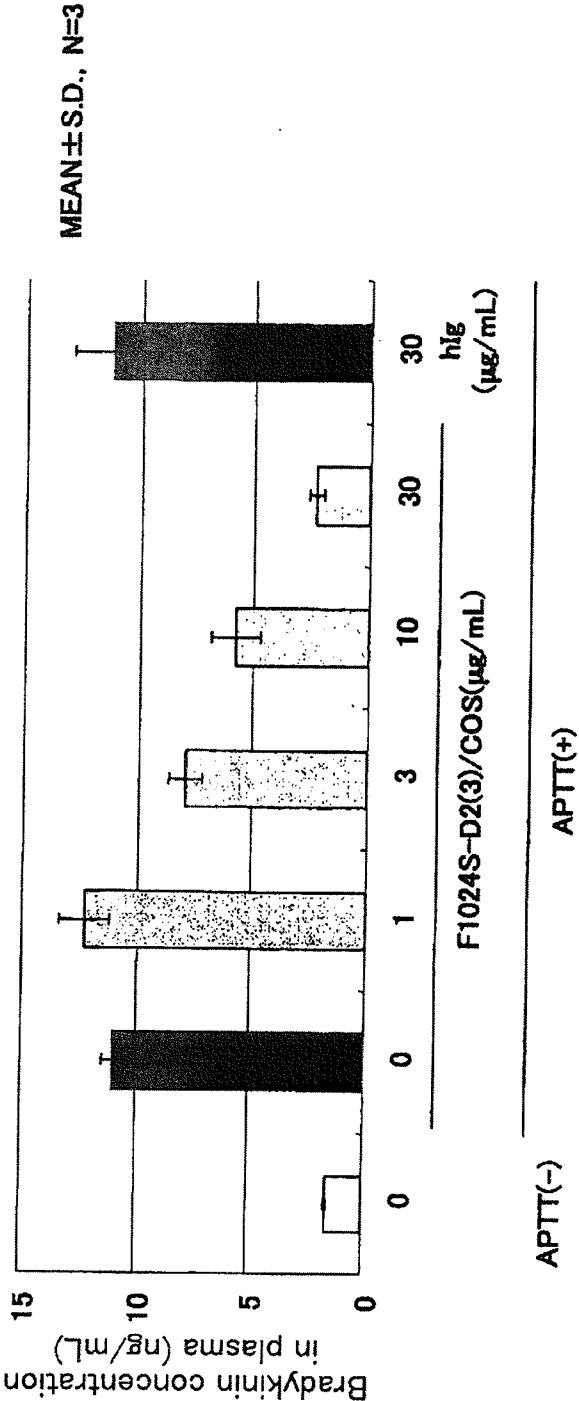


FIG. 51

Rabbit

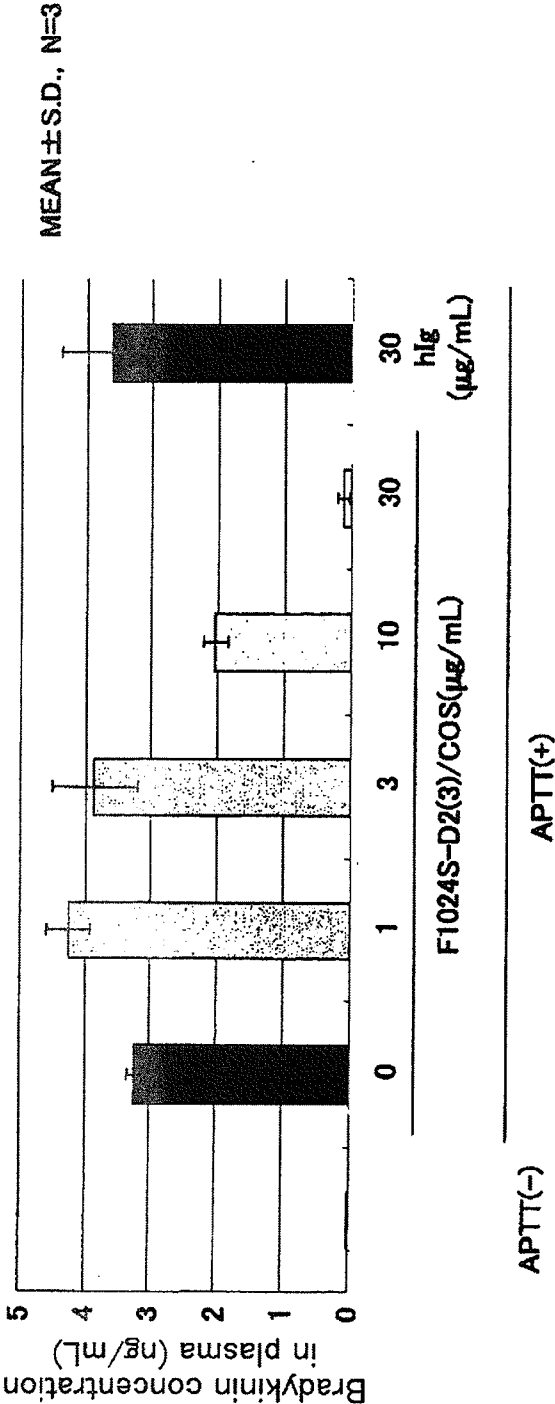


FIG. 52

Human

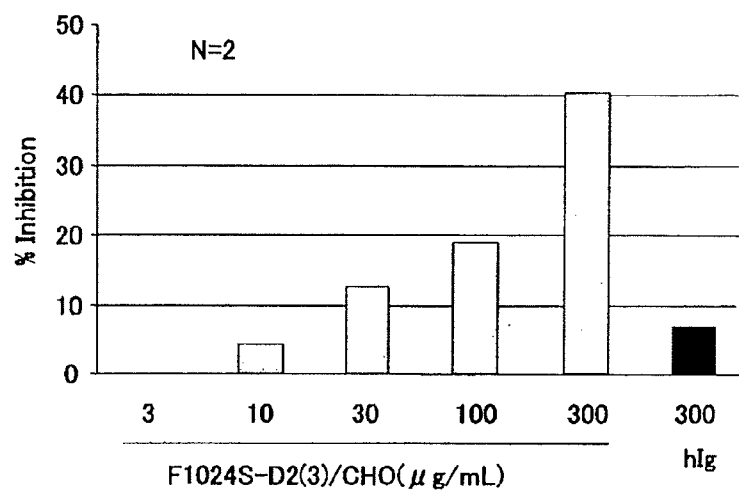


FIG. 53

Rabbit

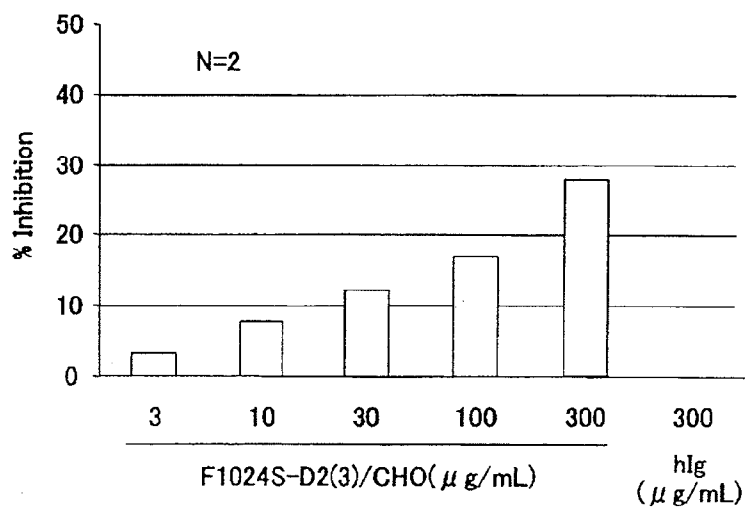


FIG. 54

Rabbit ex vivo test

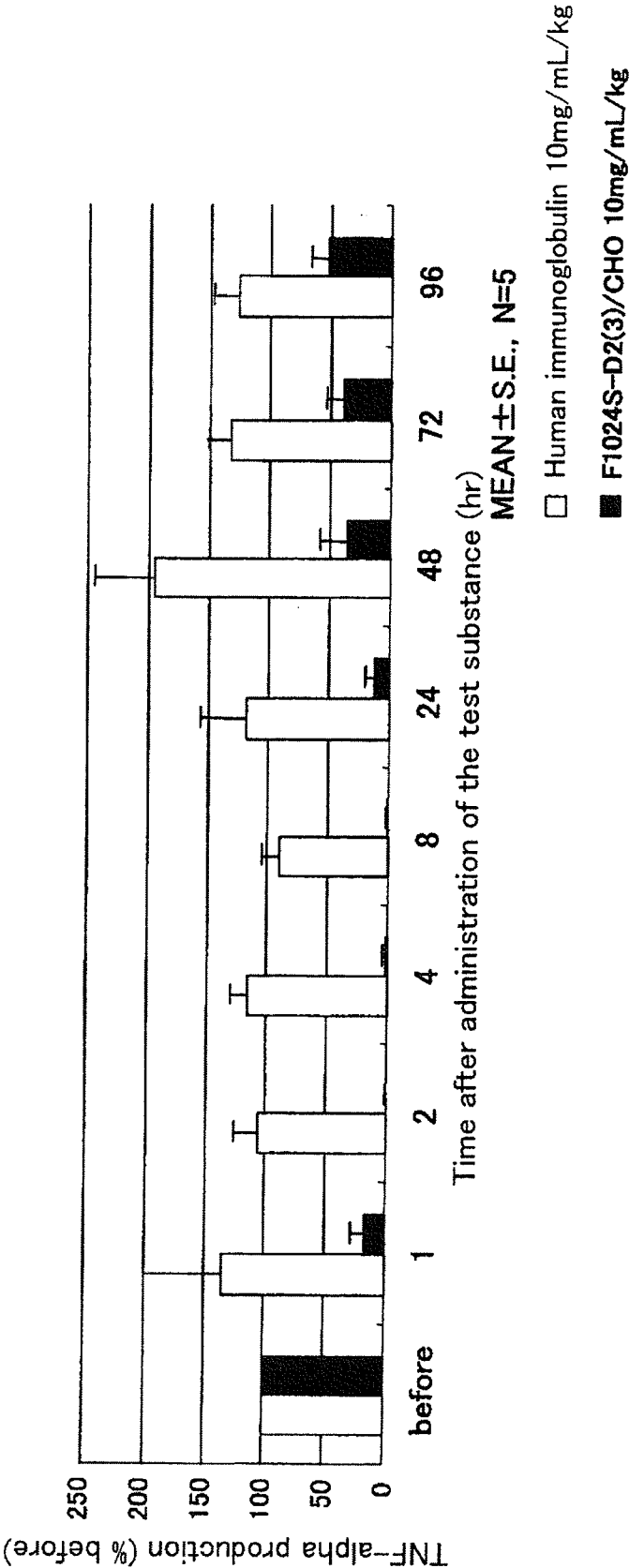


FIG. 55

Rabbit ex vivo test

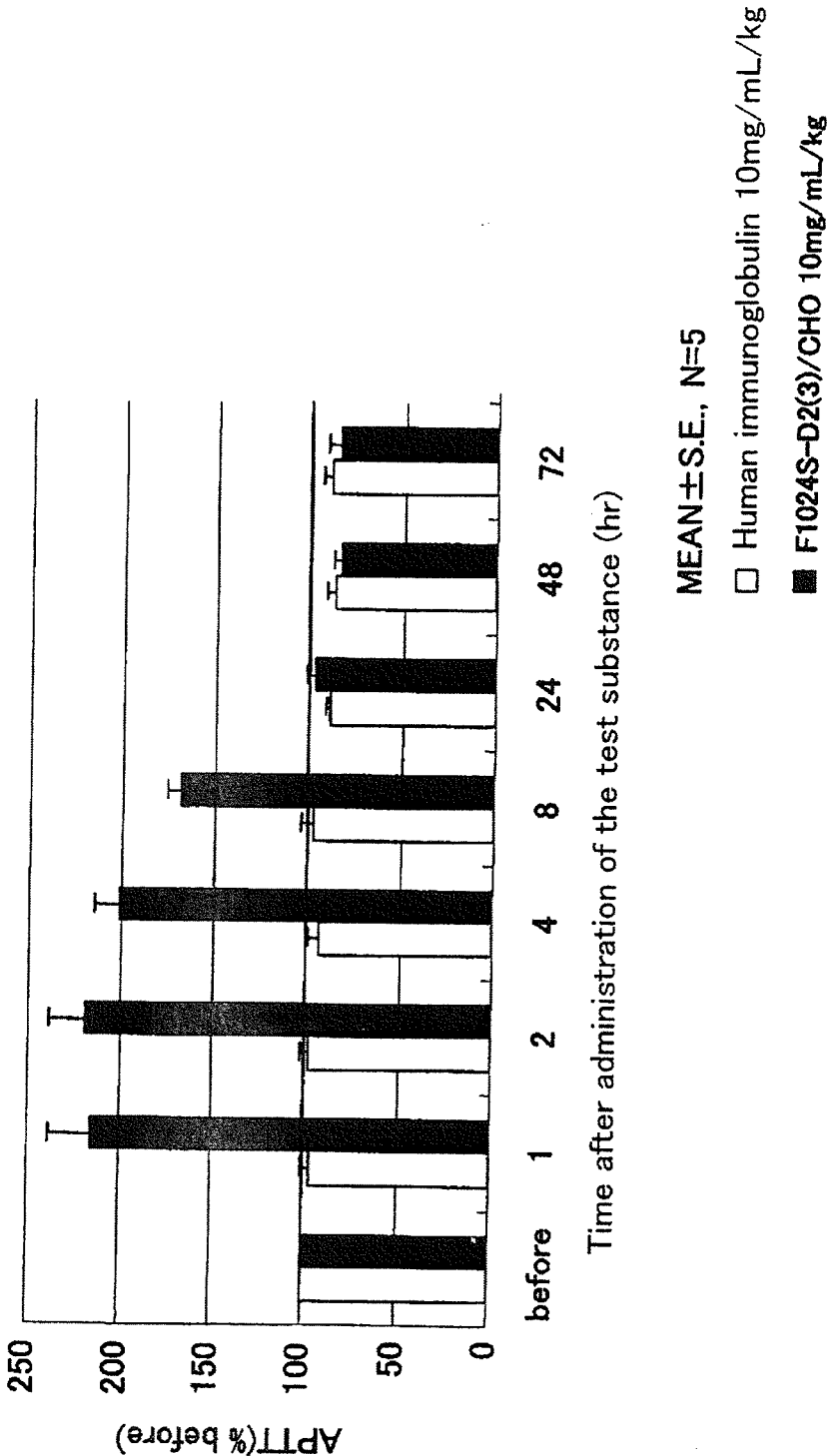


FIG. 56

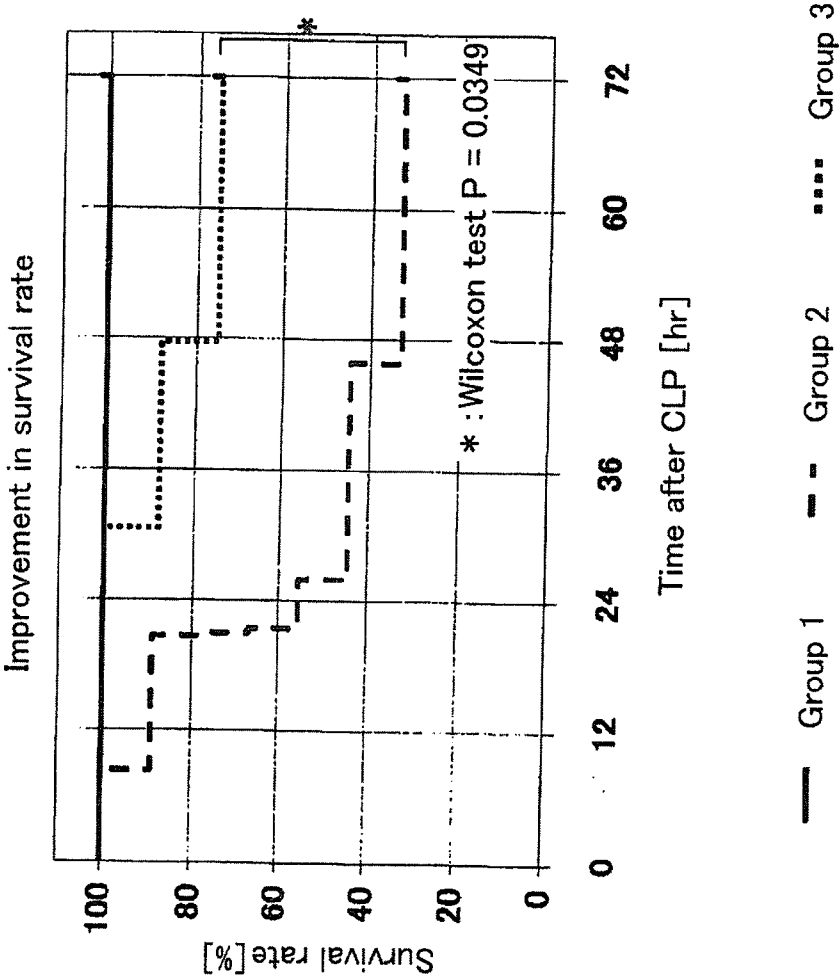


FIG. 57

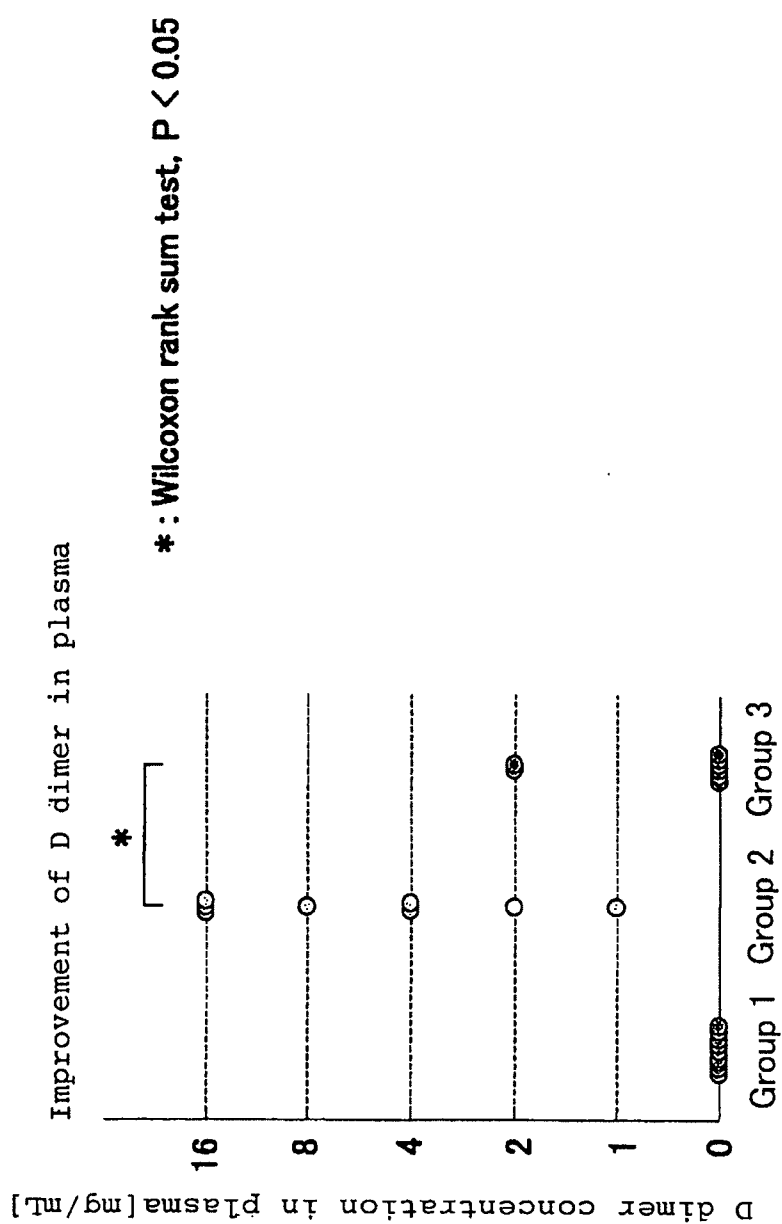


FIG. 58

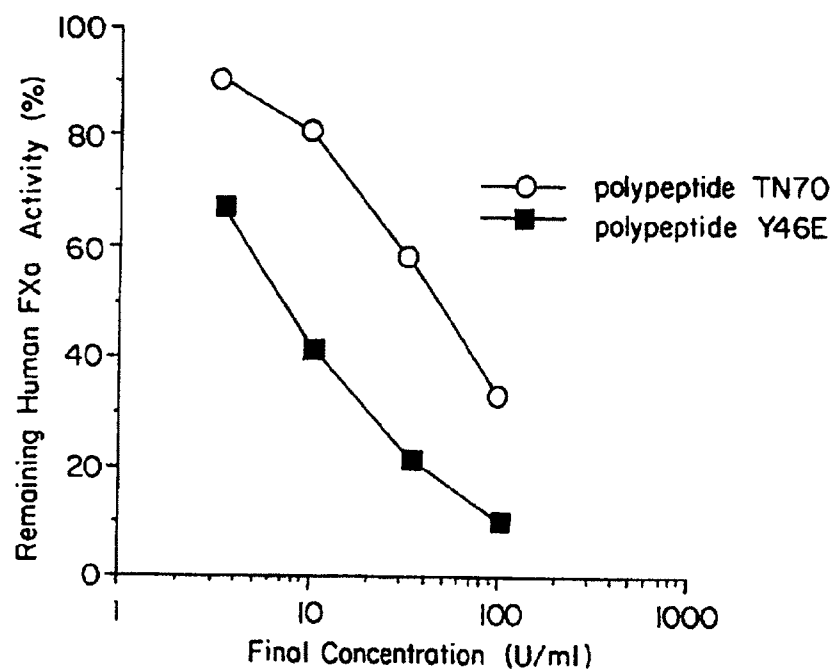


FIG. 59

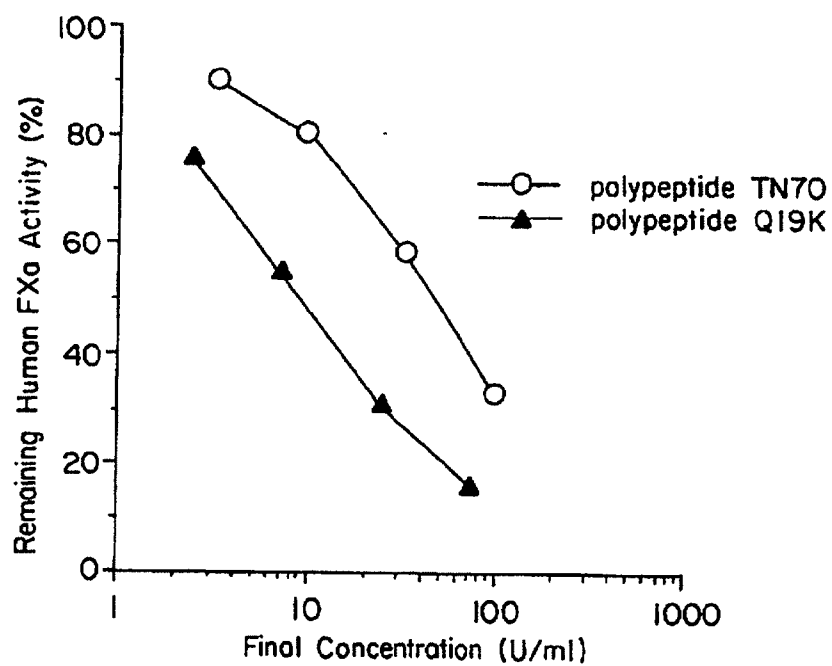


FIG. 60

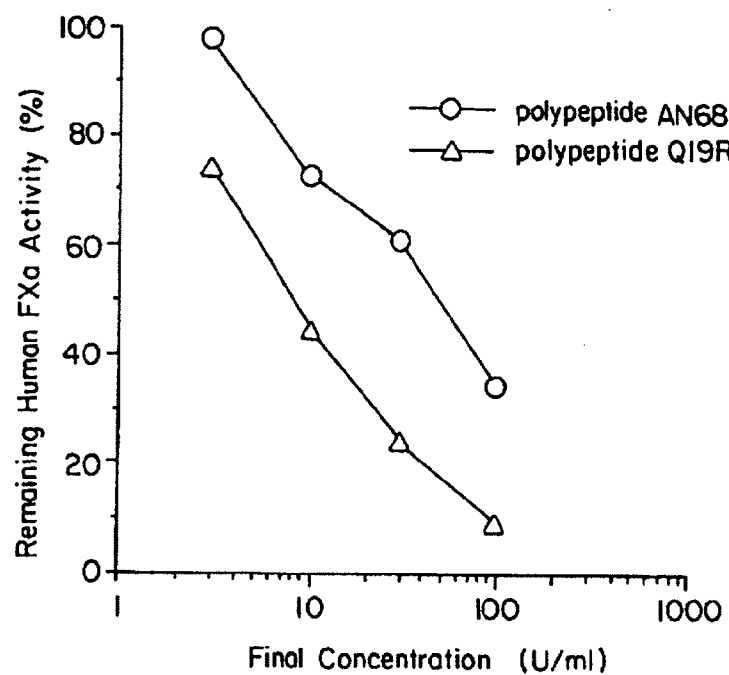


FIG. 61

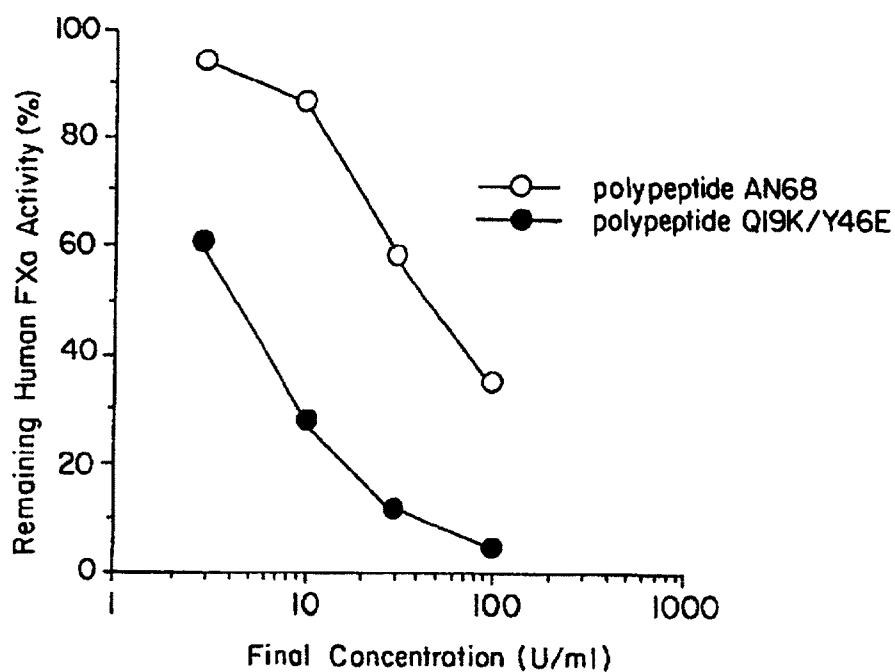


FIG. 62

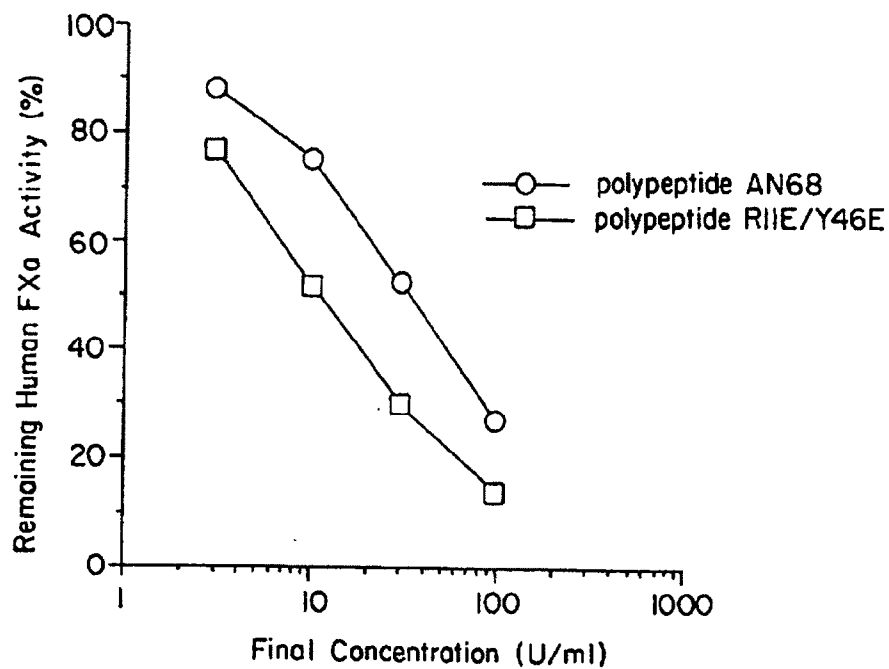


FIG. 63

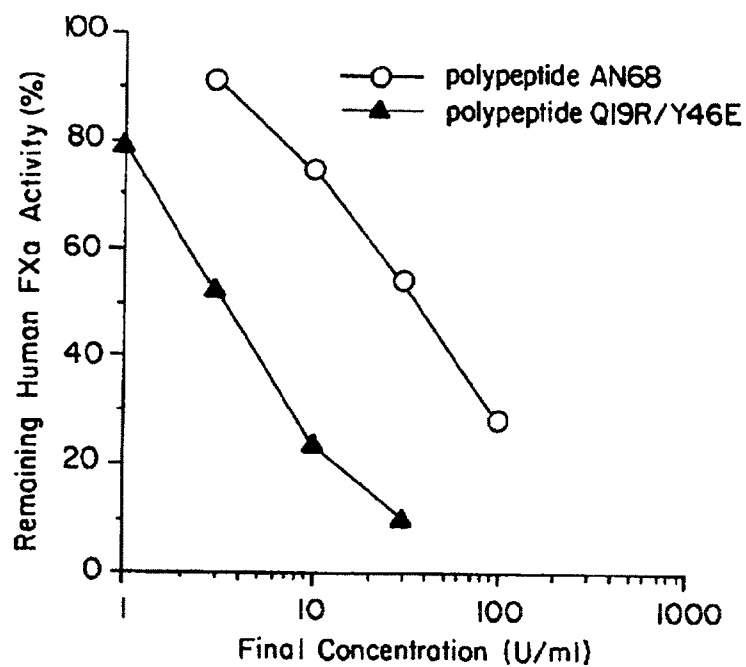


FIG. 64

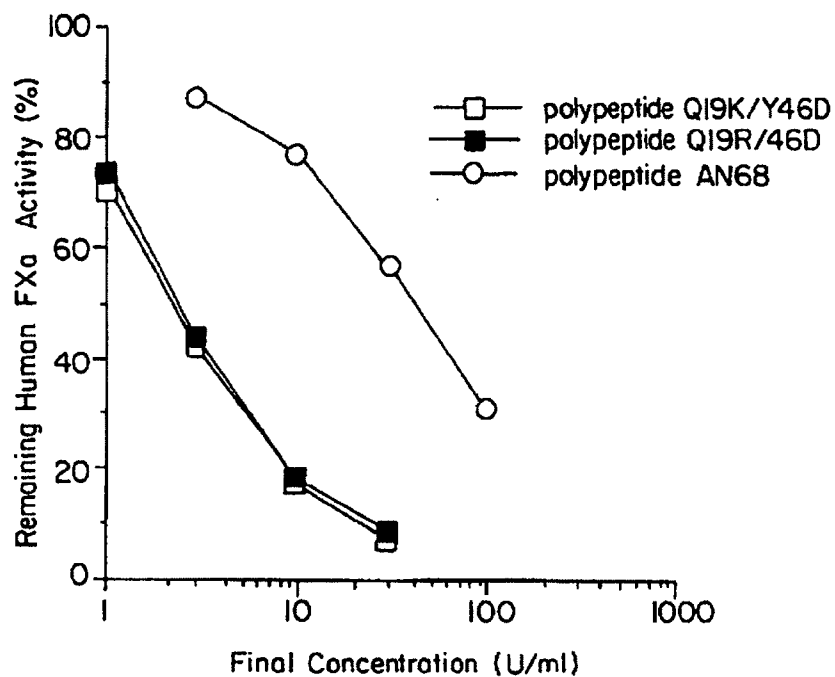


FIG. 65

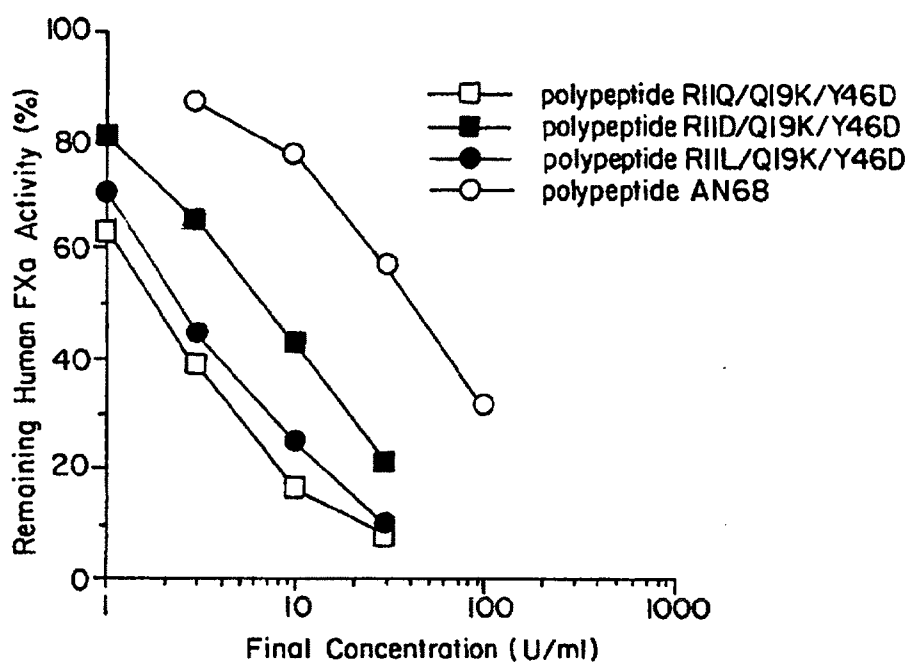
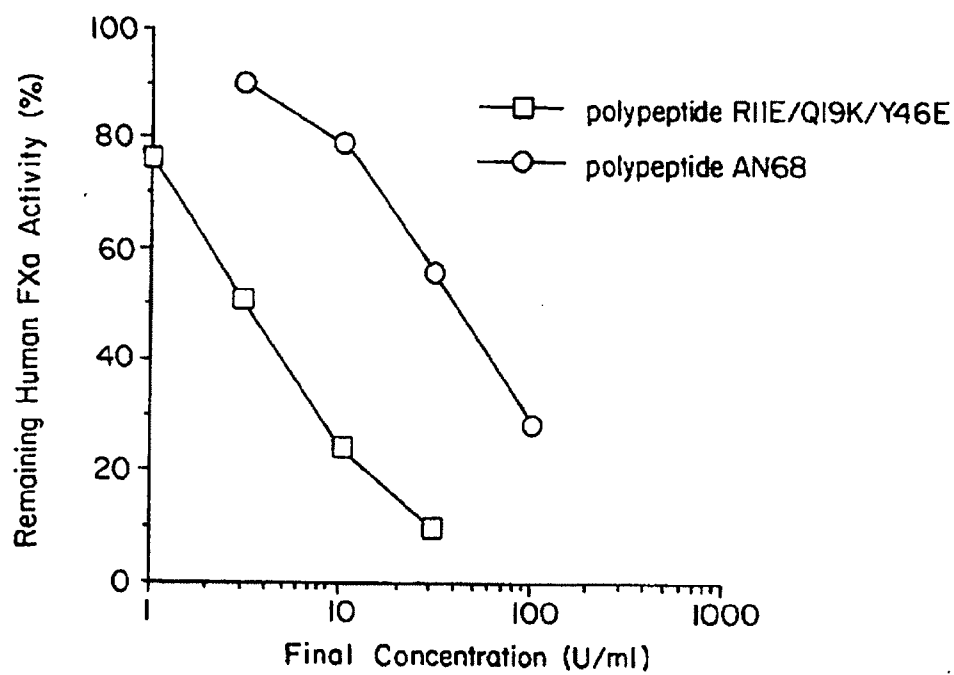


FIG. 66



ANTI-CD14 ANTIBODY FUSION PROTEIN

[0001] This application is a Divisional of U.S. application Ser. No. 13/547,548 filed Jul. 12, 2012, which is a Divisional of U.S. application Ser. No. 11/791,888, filed May 30, 2007, now U.S. Pat. No. 8,252,905, issued on Aug. 28, 2012, which is the National Phase of PCT/JP2006/311255 filed on Jun. 5, 2006. This application also claims priority under 35 U.S.C. 119(a) to Patent Application No. 2005-164901 filed in Japan on Jun. 3, 2005. The entire content of each of the above-identified applications is hereby incorporated by reference.

TECHNICAL FIELD

[0002] The present invention relates to a novel protein comprising an anti-CD14 antibody and a protease inhibitor; a polynucleotide coding for the novel protein; a method for producing the novel protein; and medical use of the novel protein for sepsis and the like.

BACKGROUND ART

[0003] Sepsis is defined as a disease which has infectious cause and which shows the pathology of systemic inflammatory response syndrome (SIRS) (see Non-Patent Document 1). Initial symptoms found include ague, sweating, fever, and decrease in the blood pressure, and when various inflammatory mediators and blood coagulation factors increase in the whole body, disturbance in the microcirculation occurs, and this results in the worsening of the pathological conditions including tissue and organ failures, which often lead to continuous onset of multiple organ failure or septic shock resulting in the death.

[0004] Onset of the sepsis is triggered by action of the components constituting the infectious bacteria, for example, lipopolysaccharide (LPS) of Gram-negative bacteria and lipoteichoic acid (LTA) in Gram-positive bacteria with leukocyte (monocyte/macrophage and neutrophil) or vascular endothelial cell, which in turn causes production of various inflammatory mediators. Recent studies revealed that CD14 which was first found as a differentiation antigen of leukocyte (see Non-Patent Document 2) and Toll-like-receptors (TLR) which are accepted to be pattern recognition molecules in the innate immune system (see Non-Patent Document 3) play an important role in such activation of the target cell by the bacterial constituent components.

[0005] CD14 is present in two forms, namely, in membrane-bound form and soluble form. The membrane-bound form CD14 is anchored to cell membrane by glycosylphosphatidyl-inositol, and the soluble form CD14 includes the one synthesized in liver and the one present in blood after cleavage on leukocyte by phosphatidylinositol-specific phospholipase (see Non-Patent Document 4). For example, activation of the target cell by LPS is caused by binding of the LPS to the CD14 promoted by catalytic action of LPS-binding protein (LBP) in blood and the subsequent binding to the TLR on the cell membrane which results in the transduction of the activation signal to the target cell. The target cell which has received the activation signal produces and expresses various mediators related to inflammatory response, for example, cytokines such as TNF- α , IL-1, IL-6, and IL-8 and tissue factors. The cytokine which is a typical mediator activates neutrophil and macrophage, and this causes adhesion to vascular endothelium, migration in the tissue, release of neutral proteases such as neutrophil elastase, and production of reactive oxygen species. Activation of the coagulation and fibrin-

olytic system, activation of the complement system, and activation of kallikrein also contribute for this process. As described above, a large number of mediator molecules and effector molecules are involved at the molecular level and the cell level with the formation of the pathology, and excessive promotion of these reactions results in the systemic damage, which leads worsening of the pathology from the microcirculatory disturbance to the tissue failure and organ failure as described above.

[0006] In order to cope with the sepsis exhibiting such complicated pathology, many studies have been conducted on the therapeutic agents. The approaches employed in developing the therapeutic agents may be divided into two major categories, namely, the approach of inhibiting the action of the bacterial constituent component which is the substance responsible for the onset of the sepsis, and the approach of inhibiting various factors which are expressed as the biological response to the signal of the substance responsible for the onset of the sepsis.

[0007] The therapeutic approaches of inhibiting the action of the endotoxin from Gram-negative bacteria include (1) the method using an anti-endotoxin antibody (see Non-Patent Documents 5 and 6); (2) the method using an endotoxin antagonist (see Non-Patent Document 7); (3) a method using polymixin B (see Non-Patent Document 8); and (4) a method using BPI (see Non-Patent Document 9). Endotoxin is a component constituting Gram-negative bacteria, which is not found in the Gram-positive bacteria and fungi which are responsible for the sepsis. Accordingly, sepsis agents targeting the endotoxin are associated with the problem that they cannot cope with the bacteria and fungi other than the Gram-negative bacteria.

[0008] A sepsis agent which targets on CD14 which functions as a receptor for LPS which is a substance constituting Gram-negative bacteria has also been proposed. Since CD14 has been found to be not only the receptor for the LPS but also a receptor for a bacterial constituent such as lipoteichoic acid and peptidoglycan which are the constituents of Gram-positive bacteria (see Non-Patent Document 10), it is indicated that the sepsis agent targeting the CD14 is applicable not only to the Gram-negative sepsis. The agents that have been proposed include anti-CD14 antibodies (See Patent Documents 1 and 2) and soluble CD14 (see Non-Patent Document 11 and Patent Documents 3 and 4). These agents, however, are not yet used in practice. The pathology of sepsis has been estimated to be sequential and complex development from the stage triggering the inflammatory response with the constituent of the pathogen to a more serious stage. The drawback of the CD14 targeting agents is that, since action of these agents focuses on the early triggering stage of the pathology formation, dubiousness remains on the effects on the more serious late stage of the pathology.

[0009] In the meanwhile, of the therapeutic approaches of targeting the excessively produced factors, the therapeutic methods of inhibiting a cytokine or other inflammatory mediators include (1) the method using an anti-TNF antibody (see Non-Patent Document 12), (2) the method using a soluble TNF receptor (see Non-Patent Document 13), (3) the method using an IL-1 receptor antagonist (see Non-Patent Document 14), (4) the method using an PAF inhibitor (see Non-Patent Document 15), and (5) the method using an NO inhibitor (see Non-Patent Document 16). Although these therapeutic methods have demonstrated their effectiveness in the stage of experimental animals or in small scale clinical

tests, their effectiveness and usefulness are not clearly revealed in the stage of large scale clinical test. As described above, cytokine and other inflammatory mediators each have a plurality of activities, and these mediators constitute a complicated network and various events occur in this network in which each mediator complements other mediators and induces the expression of other mediators. Therefore, it has been estimated that treatment made by inhibiting one factor has some limitation (see Non-Patent Document 17).

[0010] Also proposed is the therapeutic approach which targets blood coagulation factors whose production is enhanced in the process of the interaction of mediators associated with the generation of the pathology of the sepsis. The blood coagulation factors are believed to be included among the important targets of the therapeutic agent since enhancement of the blood coagulation invites disturbance in the blood microcirculation system, which in turn invites decrease in the amount of oxygen supplied to the peripheral tissue, tissue failure, and even multiple organ failure. Exemplary methods include (1) a therapeutic method using an activated protein C (see Non-Patent Document 18), (2) a therapeutic method using an antithrombin III (see Non-Patent Document 19), and (3) a therapeutic method using a TFPI (see Non-Patent Document 20). Among these, the treatment of severe sepsis using activated protein C has been demonstrated to have a significant therapeutic effect in a large scale clinical test (see Non-Patent Document 21), and this treatment has been offered for clinical use. However, this treatment has great clinical limitation that it is contraindicated for patients having bleeding tendency.

[0011] [Patent Document 1] JP 2744130 B

[0012] [Patent Document 2] WO 02/42333

[0013] [Patent Document 3] JP 10-512142 A

[0014] [Patent Document 4] WO 01/72993

[0015] [Non-Patent Document 1] The ACCP/SCCM Consensus Conference Committee. Chest, 1992, 101, 1644-1655.

[0016] [Non-Patent Document 2] Goyert S. M. and Ferrero E., in McMichael A. (ed.): Leukocyte Typing III. Oxford, Oxford University Press, 1987.

[0017] [Non-Patent Document 3] Zhang G. and Ghosh S., Endotoxin Res., 2000, 6, 453-457.

[0018] [Non-Patent Document 4] Stelter F., Structure/Function relationship of CD14; in Jack R. S. (ed.): CD14 in the Inflammatory Response. Chem. Immunol. Basel, Karger, 2000, 74, pp. 25-41.

[0019] [Non-Patent Document 5] Ziegler E. J., et al., New Engl. J. Med., 1991, 324, 429-436.

[0020] [Non-Patent Document 6] Greenman R. L. et al., JAMA, 1991, 266, 1097-1102.

[0021] [Non-Patent Document 7] Kawata T. et al., Prog Clin Biol Res., 1995, 392, 499-509.

[0022] [Non-Patent Document 8] Tani T. et al., Artif. Organs, 1998, 22, 1038-1045.

[0023] [Non-Patent Document 9] Lin Y. et al., Antimicrob. Agents Chemother., 1996, 40, 65-69.

[0024] [Non-Patent Document 10] Cleveland, Infect Immun., 1996, 64, 1906-1912.

[0025] [Non-Patent Document 11] Goyert S. M., J. Immunol., 1995, 154, 6529-6532.

[0026] [Non-Patent Document 12] Fischer C. J. et al., Crit. Care Med., 1993, 21, 318-327.

[0027] [Non-Patent Document 13] Fischer C. J. et al., N. Engl. J. Med., 1996, 334, 1697-1702.

[0028] [Non-Patent Document 14] Fischer C. J. et al., JAMA, 1994, 271, 1836-1843.

[0029] [Non-Patent Document 15] Dhainaut J. F. et al., Crit. Care Med., 1994, 22, 1720-1728.

[0030] [Non-Patent Document 16] Gachot B., Intensive Care Med., 1995, 21, 1027-1031.

[0031] [Non-Patent Document 17] Vincent J. L. et al., CID, 2002, 34, 1984-1093.

[0032] [Non-Patent Document 18] Rivard G. E. et al., J. Pediatr., 1995, 126, 646-652.

[0033] [Non-Patent Document 19] Fourrier F. et al., Chest, 1993, 104, 882-888.

[0034] [Non-Patent Document 20] Abraham E. et al., Crit. Care Med., 2000, 28, S31-33.

[0035] [Non-Patent Document 21] Bernard, G. R. et al., N. Engl. J. Med., 2001, 344, 699-709.

DISCLOSURE OF THE INVENTION

Problems to be Solved by the Invention

[0036] In view of such situation, the inventors of the present invention noticed that a novel protein produced by binding an anti-CD14 antibody and a protease inhibitor would solve the problems associated with prior art techniques, and confirmed its effectiveness by producing such novel protein. An object of the present invention is to provide a novel protein comprising an anti-CD14 antibody and a protease inhibitor; a polynucleotide coding for such novel protein; a method for producing such novel protein; a preventive and/or therapeutic agent for sepsis comprising such novel protein.

Means for Solving the Problems

[0037] Next, typical aspects of the present invention are described below. A first aspect of the present invention is a novel protein comprising (I) an anti-CD14 antibody or its active fragment, or a derivative thereof and (II) an inhibitor for a protease or its active fragment, or a derivative thereof. More specifically, the novel protein of this aspect is

(1) a protein comprising (I) an anti-CD14 antibody or its active fragment, or a derivative thereof and (II) an inhibitor for a protease, or its active fragment, or a derivative thereof, (2) the protein according to (1) wherein the inhibitor in (II) is a protein inhibitor,

(3) the protein according to (1) or (2) wherein the inhibitor in (II) is a multivalent enzyme inhibitor,

(4) the protein according to any one of (1) to (3) wherein the protease in (II) is a blood coagulation factor (a blood coagulation protease) or an inflammatory protease,

(5) the protein according to any one of (1) to (4) wherein the protease in (II) is FXa and/or FXIa,

(6) the protein according to any one of (1) to (4) wherein the protease in (II) is thrombin,

(7) the protein according to any one of (1) to (6) wherein the inhibitor in (II) is derived from UTI,

(8) the protein according to any one of (1) to (6) wherein the inhibitor in (II) is derived from thrombomodulin,

(9) the protein according to any one of (1) to (6) wherein the inhibitor in (II) is derived from UTI domain 2,

(10) the protein according to any one of (1) to (8) wherein the inhibitor in (II) is derived from functional domain, especially EGF-like domain, of thrombomodulin,

(11) the protein according to any one of (1) to (4) wherein the protease in (II) is elastase,

(12) the protein according to any one of (1) to (4) and (11) wherein the inhibitor in (II) is a secretory leukocyte protease inhibitor,

(13) the protein according to any one of (1) to (11) wherein the inhibitor in (II) is a mutant of UTI domain 2 with 1 to 4 amino acid substitutions,

(14) the protein according to any one of (1) to (13) wherein the anti-CD14 antibody in (I) is an antibody which has neutralizing activity,

(15) the protein according to any one of (1) to (14) wherein the anti-CD14 antibody in (I) is one which recognizes at least a part of amino acid Nos. 269-315 of human CD14,

(16) the protein according to any one of (1) to (15) wherein the anti-CD14 antibody in (I) is a chimeric antibody,

(17) the protein according to any one of (1) to (16) wherein the anti-CD14 antibody in (I) is a humanized antibody, or

(18) the protein according to any one of (1) to (17) wherein the anti-CD14 antibody in (I) is one comprising CDR1, CDR2, and CDR3 of the heavy chain described in Table 2 as the CDR1, CDR2, and CDR3 in the heavy chain variable region, or CDR1, CDR2, and CDR3 of the light chain described in Table 2 as the CDR1, CDR2, and CDR3 of the light chain variable region.

[0038] A second aspect of the present invention is a polynucleotide which codes for at least a part of the protein according to the first aspect. More specifically, the polynucleotide of this aspect is

(19) a polynucleotide which codes for at least a part of the protein according to any one of (1) to (18).

[0039] A third aspect of the present invention is a vector which comprises the polynucleotide according to the second aspect of the present invention. More specifically, the vector of this aspect is

(20) a vector which comprises the polynucleotide of (19).

[0040] A fourth aspect of the present invention is a cell which comprises the polynucleotide according to the second aspect of the present invention or the vector according to the third aspect of the present invention. More specifically, the cell of this aspect is

(21) a cell which comprises the polynucleotide of (19) or the vector of (20).

[0041] A fifth aspect of the present invention is a method for producing the protein according to the first aspect of the present invention which uses at least one of the polynucleotide according to the second aspect of the present invention, the vector according to the third aspect of the present invention, and the cell according to the fourth aspect of the present invention. More specifically, the method of this aspect is

(22) a method for producing the protein according to any one of (1) to (18) which uses at least one of the polynucleotide of (19), the vector of (20), and the cell of (21).

[0042] A sixth aspect of the present invention is a preventive and/or therapeutic agent for a disease comprising at least one of the protein according to the first aspect of the present invention, the polynucleotide according to the second aspect of the present invention, the vector according to the third aspect of the present invention, and the cell according to the fourth aspect of the present invention. More specifically, the preventive and/or therapeutic agent of this aspect is

(23) a preventive and/or therapeutic agent for a disease comprising at least one of the protein of any one of (1) to (18), the polynucleotide of (19), the vector of (20), and the cell of (21), or

(24) the preventive and/or therapeutic agent according to

(23) wherein the disease is sepsis, severe sepsis or septic shock, SIRS related disease, endotoxin shock, or ARDS.

Effects of the Invention

[0043] The novel protein of the present invention is effective for a disease or a pathology, or a specific symptom or therapeutic index associated with such disease or pathology, to which use of the anti-CD14 antibody or the protease inhibitor alone is ineffective or insufficiently effective. This protein simultaneously exhibits a stable in vivo anti-inflammatory action, anticoagulant action, and/or elastase inhibitory action, and therefore, it is useful as a preventive and/or therapeutic agent for sepsis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0044] FIG. 1 shows the DNA sequence (SEQ ID NO: 123) and the amino acid sequence (SEQ ID NO: 124) of the heavy chain variable region of antibody F1024.

[0045] FIG. 2 shows the DNA sequence (SEQ ID NO: 125) and the amino acid sequence (SEQ ID NO: 126) of the light chain variable region of antibody F1024.

[0046] FIG. 3 shows the DNA sequence (SEQ ID NO: 127) and the amino acid sequence (SEQ ID NO: 128) of the heavy chain variable region of antibody F1031-13-2.

[0047] FIG. 4 shows the DNA sequence (SEQ ID NO: 129) and the amino acid sequence (SEQ ID NO: 130) of the light chain variable region of antibody F1031-13-2.

[0048] FIG. 5 shows the DNA sequence (SEQ ID NO: 131) and the amino acid sequence (SEQ ID NO: 132) of the heavy chain variable region of antibody F1031-13-2.

[0049] FIG. 6 shows the DNA sequence (SEQ ID NO: 133) and the amino acid sequence (SEQ ID NO: 134) of the light chain variable region of antibody F1031-13-2.

[0050] FIG. 7 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 2 and 22) of fusion protein F1024D-D1D2.

[0051] FIG. 8 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 4 and 22) of fusion protein F1024D-D2.

[0052] FIG. 9 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 6 and 22) of fusion protein F1024D-D2(3).

[0053] FIG. 10 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 8 and 22) of fusion protein F1024S-D1D2.

[0054] FIG. 11 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 10 and 22) of fusion protein F1024S-D2.

[0055] FIG. 12 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 12 and 22) of fusion protein F1024S-D2(3).

[0056] FIG. 13 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 14 and 22) of fusion protein F1024D-SLP1(D1D2).

[0057] FIG. 14 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 16 and 22) of fusion protein F1024D-SLP1(D2).

[0058] FIG. 15 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 18 and 22) of fusion protein F1024S-SLP1(D1D2).

[0059] FIG. 16 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 20 and 22) of fusion protein F1024S-SLP1(D2).

[0060] FIG. 17 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 24 and 26) of fusion protein F1031-13S-D2(3).

[0061] FIG. 18 is a view showing suppressive activity of F1024 (anti-CD14 antibody) or antibody fusion proteins in the production of IL-6 by the LPS-stimulated U373MG cell.

[0062] FIG. 19 is a view showing suppressive activity of F1024 (anti-CD14 antibody) or antibody fusion proteins in the production of IL-6 by the LPS-stimulated U373MG cell.

[0063] FIG. 20 is a view showing suppressive activity of antibody fusion proteins in the production of IL-6.

[0064] FIG. 21 is a view showing trypsin inhibitory activity of the proteins derived from UTI and anti-CD14 antibody fusion proteins.

[0065] FIG. 22 is a view showing Factor Xa inhibitory activity of anti-CD14 antibody fusion proteins.

[0066] FIG. 23 is a view showing Factor XIa inhibitory activity of anti-CD14 antibody fusion proteins.

[0067] FIG. 24 is a view showing elastase inhibitory activity of anti-CD14 antibody fusion proteins.

[0068] FIG. 25 is a view showing plasma kallikrein inhibitory activity of anti-CD14 antibody fusion proteins.

[0069] FIG. 26 is a view showing the effect of fusion protein F1024S-D2(3) on improving the survival rate of the LPS-induced rabbit sepsis model.

[0070] FIG. 27 is a view showing the effect of fusion protein F1024S-D2(3) on leukocyte count in LPS-induced rabbit sepsis model (leukocyte count at 28 hours after the initial administration of the LPS in the LPS-induced rabbit sepsis model).

[0071] FIG. 28 is a view showing the effect of fusion protein F1024S-D2(3) on platelet count in LPS-induced rabbit sepsis model (platelet count at 26 hours after the initial administration of the LPS in the LPS-induced rabbit sepsis model).

[0072] FIG. 29 is a view showing the effect of fusion protein F1024S-D2(3) on decrease in antithrombin (AT)III activity in LPS-induced rabbit sepsis model (decrease in antithrombin (AT)III activity at 28 hours after the initial administration of the LPS in the LPS-induced rabbit sepsis model).

[0073] FIG. 30 is a view showing the improvement of decrease in blood pressure by the fusion protein F1024S-D2(3) in the LPS-induced rabbit sepsis model.

[0074] FIG. 31 is a view showing the experimental results of competitive binding to antibody F1024.

[0075] FIG. 32 shows the amino acid sequences (SEQ ID NOS: 10 (residues 474-543), 12 (residues 474-543), 46 through 49, and 27 through 45) of modified UTI domain 2 of fusion protein F1024-D2.

[0076] FIG. 33 shows the amino acid sequences (SEQ ID NOS: (residues 474-543), 12 (residues 474-543), 50 through 68) of modified UTI domain 2 of fusion protein F1024-D2.

[0077] FIG. 34 shows the amino acid sequences (SEQ ID NOS: 10 (residues 474-543), 12 (residues 474-543), 69 through 87) of modified UTI domain 2 of fusion protein F1024-D2.

[0078] FIG. 35 shows the amino acid sequences (SEQ ID NOS: 10 (residues 474-543), 12 (residues 474-543), 88 through 106) of modified UTI domain 2 of fusion protein F1024-D2.

[0079] FIG. 36 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 215 and 22) of fusion protein F1024S-D2(R4)(R11S/R15T/Q19K/Y46D).

[0080] FIG. 37 shows the amino acid sequences (SEQ ID NOS: 107-108) of modified functional domain of TM in fusion protein F1024-TM.

[0081] FIG. 38 shows the amino acid sequences (SEQ ID NOS: 109-110) of modified functional domain of TM in fusion protein F1024-TM.

[0082] FIG. 39 shows the amino acid sequences (SEQ ID NOS: 111-112) of modified functional domain of TM in fusion protein F1024-TM.

[0083] FIG. 40 shows the amino acid sequences (SEQ ID NOS: 113-114) of modified functional domain of TM in fusion protein F1024-TM.

[0084] FIG. 41 shows the amino acid sequences (SEQ ID NOS: 115-116) of modified functional domain of TM in fusion protein F1024-TM.

[0085] FIG. 42 shows the amino acid sequences (SEQ ID NOS: 117-118) of modified functional domain of TM in fusion protein F1024-TM.

[0086] FIG. 43 shows the amino acid sequences (SEQ ID NOS: 119-120) of modified functional domain of TM in fusion protein F1024-TM.

[0087] FIG. 44 shows the amino acid sequences (SEQ ID NOS: 121-122) of modified functional domain of TM in fusion protein F1024-TM.

[0088] FIG. 45 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 216 and 22) of fusion protein F1024S-TM23456L.

[0089] FIG. 46 is a view showing thrombomodulin activity of modified functional domains of TM in fusion protein F1024S-TM.

[0090] FIG. 47 is a view showing the structure of the total amino acid sequences (SEQ ID NOS: 217 and 218) of humanized F1024S-D2(3).

[0091] FIG. 48 is a view showing the amino acid sequences of the heavy (SEQ ID NO: 219) and light (SEQ ID NO: 223) chain variable regions of F1024-1-3 rat antibody; and the amino acid sequences of human antibodies having a high homology with the heavy (SEQ ID NOS: 220-222) and light (SEQ ID NOS: 224-226) chain variable regions of humanized F1024S-D2(3).

[0092] FIG. 49 is a view showing the amino acid sequences (SEQ ID NOS: 219, 227-233) which are capable of expressing the heavy chain of the humanized antibody and maintaining the binding activity.

[0093] FIG. 50 is a view showing the inhibition of bradykinin production in human plasma induced by APTT reagent.

[0094] FIG. 51 is a view showing the inhibition of bradykinin production in rabbit plasma induced by APTT reagent.

[0095] FIG. 52 is a view showing the inhibition of thrombin production in human plasma induced by thromboplastin.

[0096] FIG. 53 is a view showing the inhibition of thrombin production in rabbit plasma induced by thromboplastin.

[0097] FIG. 54 is a view showing time course of the inhibitory action of F1024S-D2(3) on the LPS-induced TNF- α production in rabbit whole blood after the administration of the F1024S-D2(3).

[0098] FIG. 55 is a view showing time course of APTT after administration of F1024S-D2(3) to the rabbit.

[0099] FIG. 56 is a view showing time course of survival rate after administration of F1024S-D2(3) to rabbit cecal ligation and puncture (CLP) model.

[0100] FIG. 57 is a view showing D dimer levels in plasma after administration of F1024S-D2(3) to rabbit cecal ligation and puncture (CLP) model.

[0101] FIG. 58 is a graph showing FXa-inhibiting activity of polypeptide Y46E of the present invention.

[0102] FIG. 59 is a graph showing FXa-inhibiting activity of polypeptide Q19K of the present invention.

[0103] FIG. 60 is a graph showing FXa-inhibiting activity of polypeptide Q19R of the present invention.

[0104] FIG. 61 is a graph showing FXa-inhibiting activity of polypeptide Q19K/Y46E of the present invention.

[0105] FIG. 62 is a graph showing FXa-inhibiting activity of polypeptide R11E/Y46E of the present invention.

[0106] FIG. 63 is a graph showing FXa-inhibiting activity of polypeptide Q19R/Y46E of the present invention.

[0107] FIG. 64 is a graph showing FXa-inhibiting activity of polypeptides Q19K/Y46D and Q19R/Y46D of the present invention.

[0108] FIG. 65 is a graph showing FXa-inhibiting activity of polypeptides R11Q/Q19K/Y46D, R11D/Q19K/Y46D and R11L/Q19K/Y46D of the present invention.

[0109] FIG. 66 is a graph showing FXa-inhibiting activity of polypeptide R11E/Q19K/Y46E of the present invention.

BEST MODE FOR CARRYING OUT THE INVENTION

[0110] Next, the present invention is described in further detail.

[0111] The protein according to the first aspect of the present invention is not particularly limited for its type. Exemplary proteins include simple protein (or polypeptide) and complex protein (for example, glycoprotein).

[0112] In the protein according to the first aspect of the present invention, the binding mode between (I) an anti-CD14 antibody or its active fragment, or a derivative thereof and (II) an inhibitor for a protease or its active fragment, or a derivative thereof is not particularly limited. Although (I) and (II) are generally linked by covalent bond, they may be linked, for example, by chemical means (chemical synthesis or chemical conjugation) or genetic engineering. The protein according to the first aspect of the present invention is preferably a fusion protein produced by genetic engineering.

[0113] The protease inhibitor (II) may be the one which binds to either one or both of the heavy chain and the light chain of the antibody. Typically, the protease inhibitor (II) is fused to the heavy chain, especially C terminal side of the heavy chain of the antibody. The number of protease inhibitor (II) molecules linked to the antibody is not particularly limited, and either one or two or more molecules may be linked to the antibody. If desired, the linkage may be accomplished by using an appropriate linker or spacer. Such method, the linker, the spacer, and the like are well known to those skilled in the art, and typical examples are described in the Examples.

[0114] In the protein of the present invention, active fragment of the anti-CD14 antibody (I) or the protease inhibitor (II) is a fragment which comprises a part which is capable of expressing or retaining at least one of the activities or functions inherent in the anti-CD14 antibody (I) or the protease inhibitor (II), and comprises the active region or functional domain. In the protein of the present invention, the derivative of the anti-CD14 antibody (I), the protease inhibitor (II), or the active fragment thereof is the anti-CD14 antibody (I), the protease inhibitor (II), or the active fragment thereof which includes some modification, mutation, or addition, for example, the one which comprises other chemical substance (such as polyethylene glycol), or the one which is associated with mutation such as addition, deletion, insertion or substi-

tution of at least one, and preferably one to several amino acids. In other words, the derivatives of (I), (II), and active fragments thereof include mutants, modified forms, and modification products of the (I), (II), and active fragments thereof, and they are capable of expressing or retaining at least one, and preferably all of the activities or functions inherent in the anti-CD14 antibody (I), the protease inhibitor, or the active fragment thereof.

[0115] The protein according to the first aspect of the present invention expresses or retains at least one, and preferably all of the activities inherent in each of the anti-CD14 antibody (I), and the protease inhibitor (II). Since the protein according to the first aspect of the present invention has at least one, and preferably all of the activities inherent in each of the anti-CD14 antibody (I), and the protease inhibitor (II), it is effective in the disease or the pathology, or the specific symptom or therapeutic index associated with such disease or pathology, to which use of the anti-CD14 antibody (I) or the protease inhibitor (II) alone is ineffective or insufficiently effective.

[0116] In the protein according to the first aspect of the present invention, the protease inhibitor (II) is not particularly limited, and it may be a nonprotein inhibitor or a low molecular weight compound. The protease inhibitor (II), however, is preferably a protein inhibitor.

[0117] Although the protease inhibitor (II) may also be the one which is specific to a particular enzyme, the protease inhibitor (II) is preferably a multivalent enzyme inhibitor which inhibits two or more enzymes. Exemplary substances having multivalent enzyme inhibitory action include Kunitz-type protease inhibitors such as urinary trypsin inhibitor (UTI), secretory leukocyte protease inhibitor (SLPI), tissue factor pathway inhibitor (TFPI), and aprotinin, among which the preferred are UTI, SLPI, and TFPI.

[0118] UTI is a protease inhibitor which is the same as bikunin or ulinastatin, and it is an inhibitor for proteases such as trypsin, plasmin, and neutrophil elastase.

[0119] SLPI is an inhibitor for proteases such as neutrophil elastase and cathepsin.

[0120] TFPI is a protease inhibitor which is also referred to as lipoprotein-associated coagulation inhibitor (LACI) or extrinsic pathway inhibitor (EPI). TFPI binds to blood coagulation factor Xa (FXa) to inhibit factor VIIa—tissue factor (factor III) complex to thereby suppress the initiation of the extrinsic blood coagulation.

[0121] Other multivalent enzyme inhibitors include α 2-macroglobulin (α 2-MG), antithrombin III (ATIII), and α 1-antitrypsin (α 1-AT). α 2-MG is a plasma protein with a huge molecular weight of about 770,000, and inhibits thrombin, FXa, plasmin, trypsin, chymotrypsin, elastase, and the like. ATIII forms a complex with a serine protease such as FXa or thrombin at a ratio of 1:1, to thereby control the coagulation. ATIII has a heparin binding domain at its N terminal and a reactive site with thrombin at its C terminal, and the anti-thrombin activity of the ATIII increases by a factor of about 1000 by binding to the heparin. α 1-AT is a glycoprotein comprising 394 amino acids, and the molecular weight is 51000. α 1-AT inhibits various serine proteases including thrombin, plasmin, trypsin, chymotrypsin, and elastase.

[0122] The protease inhibitor (II) in the protein of the present invention is preferably an inhibitor which has an inhibitory action for a blood coagulation factor (blood coagulation protease) including the factor which induces antico-

agulant action or bradykinin production, especially an inhibitory action for activated blood coagulation factor, or an anti-inflammatory action or an inhibitory action for inflammatory protease. Typical blood coagulation factors include kallikrein, thrombin, FVa, FVIIa, FVIIIa, FIXa, FXa, FXIa, FXIIa, and FXIIIa, and among these, kallikrein, thrombin, FVa, FVIIIa, FIXa, FXa, FXIa, and FXIIIa are the important factors, and thrombin, or FXa and FXIa are the most important target enzymes. Typical inflammatory proteases include elastase, trypsin, chymotrypsin, and cathepsin, and among these, elastase, and in particular, neutrophil elastase and pancreatic elastase, especially neutrophil elastase, are the important target enzymes. The protease inhibitory activity of the protein of the present invention or the inhibitor (II) in the protein of the present invention may be measured by various known materials and methods, and typical examples are described in the Examples.

[0123] The inhibitor having the anticoagulant action or the inhibitory action for a blood coagulation factor may be a substance known in the art. Examples include TFPI, ATIII, α 1-AT, and α 2-MG; and UTI and thrombomodulin (TM); their active fragments, and derivatives thereof, and the preferred are TM or UTI, their active fragments or derivatives thereof, and the more preferred are the functional domain of TM or the UTI domain 2 (UTI-D2) having inhibitory activity for FXa and/or FXIa, or their modified forms, especially the mutant with 3 amino acid substitutions (UTI-D2(3)). The amino acid sequences and the nucleotide sequences of the UTI, UTI-D2, and UTI-D2(3) and their production methods are described in JP 5-84083 A, JP 5-308988 A, JP 6-25289 A, and JP 6-321989 A, and they can be produced by referring to such documents.

[0124] Thrombomodulin (TM) is one of the anticoagulants produced by vascular endothelial cell, and when TM forms a complex with thrombin on the cell membrane, protein C will subsequently be activated and the blood coagulation will be suppressed. TM was discovered in 1981, and this substance which is present on the vascular endothelial cell converts thrombin from the coagulation enzyme to an anticoagulation enzyme. TM also directly inhibits the thrombin activity and promotes the activation of the protein C (PC), and the resulting activated protein C (APC) contributes for the negative feedback of the blood coagulation cascade by inactivating activated blood coagulation factor V (FVa) and factor VIII (FVIIIa) to thereby suppress the generation of the thrombin. In other words, TM inhibits both the coagulation activity and the fibrinolytic activity in a manner dependent on the thrombin. Since this action does not require antithrombin III in contrast to the case of heparin, this process is understood to involve less risk of promoting the bleeding tendency.

[0125] Since the amino acid sequence of the TM and the nucleotide sequence coding for such amino acid sequence, and the domain structure and the function of the TM are known (for example, Kurosawa, S, Supplementary volume of Progress in Medicine (in Japanese), "Blood Disease—State of Arts (Ver.2)", 1998, pp. 205-207), preparation of the TM, its active fragments and derivatives used in the present invention and evaluation of their activity may be carried out by referring to such publications as JP 1-6219 A and WO 88/5053. TM comprises 5 domains, namely, lectin-like domain, Epidermal growth factor (EGF)-like domain, O-linked glycosylation domain, transmembrane domain, and cytoplasmic domain from the extra-cellular N terminal (Kurosawa, S. et al., J. Biol. Chem., 263, 5993, 1988), and among

these, the EGF-like domain comprises 6 repeating units (this domain is sometimes also referred to as EGF1-6 or TM123456 in the present invention). The minimal active unit is assumed to be the fourth to sixth repeating units of the EGF-like domain, namely, the EGF4-6.

[0126] Examples of the preferable active fragments, the derivatives, and the functional domains of the TM include EGF-like domain; active fragments of TM comprising the EGF-like domain or their derivatives; active fragments of the EGF-like domain or their derivatives, which may preferably be EGF4-6, more preferably EGF3-6, and most preferably EGF2-6; active fragments of TM comprising such part or their derivatives, for example, active fragments of the TM or their derivatives prepared in the Examples, especially TM23456M, TM234567M, or their active fragments or derivatives. Preferable examples of the derivatives include a mutant (M388L) in which methionine at amino acid No. 388 of TM has been replaced with leucine, and these are TM23456L and TM234567L. The production and the evaluation of such derivatives may be accomplished by the methods known in the art, and typical examples are described in the Examples.

[0127] Various inhibitors are known to have anti-inflammatory action or inhibitory action for inflammatory protease. Although various known inhibitors may be used, the most preferred is elastase inhibitor. Typical examples include UTI, UTI-D2, SLPI, α 1-AT and α 2-MG and their active fragments or derivatives; and preferable examples are UTI, especially modified UTI domain 2 having elastase inhibitory activity, for example, a mutant of UTI-D2 with 3 amino acid substitutions, a mutant of UTI-D2 with 4 amino acid substitutions (also referred to as UTI-D2(4)), and SLPI, especially the downstream part of the SLPI (the polypeptide at the C terminal). The amino acid sequence, the nucleotide sequence, and the production method of SLPI and the downstream part (the polypeptide at the C terminal) are described in JP 6-80697 A, and the like, and the publication may be used as a reference.

[0128] Typical examples of the mutants of the UTI-D2 with 3 or 4 amino acid substitutions are shown in Table 9 of Example 7, and the most preferred is UTI-D2(4) (R11S/R15T/Q19K/Y46D).

[0129] The modified UTI domain 2 having the inhibitory activity for FXa and/or FXIa and the elastase inhibitory activity, specifically UTI-D2(3), is most preferred.

[0130] In the protein according to the first aspect of present invention, the anti-CD14 antibody is not particularly limited as long as it binds to CD14, and preferably, to human CD14. In the protein of the present invention, the anti-CD14 antibody (I) acts synergistically with the protease inhibitor, and improves the function or the effect of the protein or the inhibitor. The anti-CD14 antibody (I) in the protein according to the first aspect of present invention is not limited by the presence or the absence of the CD14 inhibitory action. However, the anti-CD14 antibody (I) is preferably an antibody which has the CD14 inhibitory action. The term "CD14 inhibitory action" used herein is the action of inhibiting at least one of the functions of the CD14, for example, binding ability with LPS, interaction with TLR, and activation of the TLR expressing cell, and more specifically, activation of NF- κ B, production of IL-8, or production of cytokine such as IL-6 by the endothelial cell; and preferably, the action of inhibiting the binding between the CD14 and the TLR, especially the binding between the CD14 and the TLR2 or the TLR4.

[0131] Exemplary preferable antibodies include known anti-CD14 antibodies, especially the antibodies disclosed in WO02/42333 or the like and those produced by a known method, for example, a method disclosed in WO02/42333 or the like. The chimeric antibody and the humanized antibody produced from such antibody are also included in the anti-CD14 antibody (I) of the protein of the present invention.

[0132] In the protein of the present invention, the anti-CD14 antibody (I) is not particularly limited for its recognition region or binding region as long as it binds to the CD14, and preferably, to the human CD14. However, the anti-CD14 antibody (I) is preferably the one which recognizes or binds to at least a part of the C terminal region of the human CD14, especially to amino acid Nos. 269 to 315, and more preferably amino acid Nos. 285 to 307, and most preferably to the amino acid Nos. 294 to 296. More specifically, the anti-CD14 antibody (I) is the antibody which recognizes or binds to the part of the CD14 or the antigenic determinant on the CD14. Among the CD14 amino acid substitution mutants of CD14 shown in Table 5 (hereinafter sometimes referred to as amino acid substitution product, amino acid substitution modified form, or an amino acid modified form), the preferred is the one which has significantly reduced binding ability to at least one and preferably all of P294H, Q295A, P296H, and P294/296A compared to the binding ability to the human CD14, and the more preferred is the antibody whose binding ability with other mutants has not substantially changed despite such reduced binding ability. The recognition region or the binding region of the anti-CD14 antibody (I) in the protein of the present invention can be confirmed by using the known material and method, for example, by using the material and method described in WO02/42333. The preferable example, however, is described in the Examples.

[0133] Furthermore, of the mutants described in Table 5, the anti-CD14 antibody having the CD14 inhibitory activity can be easily screened, identified, or prepared by using the significant reduction of the binding ability to at least one and preferably all of P294H, Q295A, P296H, and P294/296A compared to the binding ability to the human CD14 for the index, and more preferably, by using absence of the substantial change in the binding ability with other mutants in addition to such reduced binding ability with the said specified mutants for the index. The present invention also provides such method.

[0134] In the protein according to the first aspect of the present invention, the antibody (I) is preferably a monoclonal antibody although the antibody may be a polyclonal antibody, and its source is not limited to a particular species. In view of ease of preparing the antibody, the source is preferably a mouse or a rat. In view of constituting a pharmaceutical composition, the antibody is preferably a chimeric antibody, a CDR-grafted antibody, a humanized antibody, or human antibody. The human antibody also includes a human antibody prepared by immunizing a transgenic mouse expressing human antibody gene. Also included in the antibody of the present invention is a phage antibody or the like. The humanized antibody is a CDR-grafted antibody in which the constant region and the framework region (FR) are from human and the complementarity determining region (CDR) is from non-human, or an antibody which has further mutation introduced in its FR. The phage antibody is an antibody produced by fusing an antibody with the coat protein of a filamentous phage for presentation of the antibody on a phage particle, and single chain Fv (scFv) form or Fab form is mainly used.

The chimeric antibody is an antibody comprising the variable region of a monoclonal antibody from a mammal other than human, for example, a rat or a mouse and the constant region of a human antibody. In the protein according to the first aspect of the present invention, the antibody (I) is not particularly limited for its molecular species, and the antibody may be the one belonging to any class (for example, IgG, IgM, and IgA, especially IgG), subclass (for example, IgG1, IgG2, IgG3, and IgG4, especially IgG4) or isotype. With regard to the light chain of the antibody, either one of the kappa chain and the lambda chain may be used. Also included within the present invention are active fragments and derivatives, such as biologically active Fab (fragment of antigen binding), Fab', F(ab')₂, antibody active fragments linked by a linker or the like, such as a single chain antibody (single chain Fv: scFv) (Bird, R. E. et al., Science, 1988; 242: 423-426), a disulfide stabilized antibody (disulfide stabilized Fv: dsFv) (Reiter et al., Protein Engineering, 1994; 7: 697) and a diabody (Holliger P. et al., Proc Natl Acad Sci USA 1993; 90: 6444-8), a single domain antibody (dAb) (Ward E. S. et al., Nature., 1989; 341:544-6) and the like. These antibodies may be produced by techniques known in the art such as genetic engineering technique and treatment of an antibody with an appropriate protease.

[0135] The chimeric antibody is an antibody which has been typically produced by genetic engineering means in which the light chain gene and the heavy chain gene are constituted from the antibody gene segments belonging to different species. For example, the variable (V) segment in the gene from a rat or a mouse monoclonal antibody may be linked to a human constant (C) segment, for example, γ 1 and γ 4. Therefore, a typical chimeric antibody used for therapeutic purposes is a hybrid protein comprising a V or antigen-binding domain from a rat or a mouse antibody and a C or effector domain from human antibody although other mammalian species may be used.

[0136] Preferable examples of the variable region sequence of the antibody (I) in the protein according to the first aspect of the present invention are shown in FIGS. 1 and 2 (SEQ ID NOS: 123 to 126), and the preferable examples of the fusion protein in which the antibody is a chimeric antibody are shown in FIGS. 7 to 17 and Examples.

[0137] While an antibody is typically polyvalent in the binding to an antigen (and divalent in the case of IgG), the antibody (I) in the protein of the present invention is preferably monovalent in some phase. A typical such antibody is a monovalent antibody produced by introducing an amino acid mutation in Fab, or in the constant region of an antibody, especially in the constant region of the heavy chain (CH), so that normal formation of the disulfide bond between the heavy chains is prevented, and typically, by substituting Cys residue, especially Cys residue in the hinge region of the antibody heavy chain, with another amino acid residue. Preferable examples are described in the Examples.

[0138] A plurality of definitions of the "complementarity determining region (CDR)" and methods for determining its location have been reported and any one may be employed in the present invention. Typical examples include definition by Kabat (Sequences of proteins of immunological interest, 5th ed., U.S. Department of Health and Human Services, 1991) and definition by Chothia (Chothia and Lesk, J. Mol. Biol., 1987; 196: 901-917). In the present invention, the preferable CDR is the one according to the definition of Kabat, while the CDR is not limited to such type. In some cases, the CDR may

be determined by considering both the definition of Kabat and the definition of Chothia. For example, the CDR may be an overlapping region of the CDR according to both the definitions or a region covering the CDR according to both the definitions. Typical example of such method is the method of Martin et al. (Proc. Natl. Acad. Sci. USA, 1989; 86: 9268-9272) using Oxford Molecular's AbM antibody modeling software, which is a compromise between the definition of Kabat and the definition of Chothia.

[0139] The "framework region" is a region in the light chain and heavy chain variable regions which is considerably conserved among various antibodies in a single species as in the case of the definition by Kabat et al (namely, the region other than the CDR). In the present invention, "human framework region" means the framework region which is substantially the same (with a homology of about 85% or higher) as the framework region of the naturally occurring human antibody or common sequence between some of such antibodies.

[0140] The "humanized antibody" is an antibody comprising human framework and at least one CDR derived from a non-human antibody, the constant region of the humanized antibody is substantially the same as the constant region of the human antibody, namely, with the homology at a level of at least about 85 to 90%, and preferably at least 95%. Accordingly, it is likely that the every part of the humanized antibody except the CDR is substantially the same as the corresponding part of at least one natural human antibody sequence. For example, the humanized antibody does not include chimeric antibody comprising the mouse variable region/human constant region.

[0141] Such humanized antibody, and more specifically, the antibody (I) of the present invention is a humanized antibody comprising at least one, preferably all (4) of one chain, and more preferably all (4 for each chain), of the framework regions (FRs) from the human acceptor antibodies, preferably from a single human acceptor antibody; and at least one, and preferably all (3 for each chain) of the complementarity determining regions (CDRs) from the antibody F1024. Such antibody may comprise 2 pairs of the light chain/heavy chain complexes, and at least one chain, especially the heavy chain, comprise at least one, and preferably all (3) of the complementarity determining regions from the donor antibody (for example, the rat or mouse antibody, and this applies to the following description) which are functionally linked to the human framework region segment. For example, the complementarity determining region of the donor may be introduced in the human framework region with or without the additional naturally accompanying donor amino acid residues. More illustratively, the humanized antibody of the present invention is the one comprising at least one, and preferably all (3 for each chain) of the CDRs comprising or consisting of any one of the amino acid sequences of the CDRs shown in Table 2. In the humanized antibody, each CDR and the framework are preferably located at positions corresponding to their positions in the original donor antibody.

[0142] The humanized antibody used as the antibody (I) of the present invention generally has a homology (percentage of the sequence consistency) of from 65% to 95%, and preferably 70% to 90% between the framework of the heavy chain variable region of the humanized antibody and the framework of the heavy chain variable region of the donor antibody. In the standard procedure, the framework sequences are derived from the heavy chain and the light chain of the same human antibody in order to reduce the risk of incompatibility in the

combination of the two chains. The framework sequences, however, may be derived from two or more different human antibodies.

[0143] With regard to the human framework region, the sequences are obtained by comparing the amino acid sequences of the frameworks or the variable regions of the non-human antibody from which the CDRs are obtained, with the corresponding sequences in the human antibody sequence collection, and selecting the sequences having a high homology. Preferably, the homology of the framework amino acid sequence is at least 60%, and more preferably at least 65%. In addition, the amino acid sequence of the heavy chain variable region of the acceptor antibody is selected from 5, and more preferably 3 sequences in a typical collection of the sequence of the heavy chain variable region of the human antibody which have the highest homology with the amino acid sequence of the heavy chain variable region of the donor antibody. The designing of the humanized antibody may be accomplished as described below.

[0144] 1) When the particular amino acid corresponds to the following categories (a) to (c), this particular amino acid in the framework of the human antibody (acceptor antibody) may be substituted with the amino acid from the non-human antibody (donor antibody).

[0145] (a) the particular amino acid in the human framework region of the acceptor antibody is rarely found at the position of the human antibody, while this corresponding amino acid in the donor antibody is typically found at the position of the human antibody;

[0146] (b) the particular amino acid is close or adjacent to one of the CDRs in the primary sequence; or

[0147] (c) the particular amino acid has an atom at a distance within about 5, preferably 4, and more preferably 3 angstroms in the three-dimensional model of the donor antibody or the humanized antibody (Co et al., Proc. Natl. Acad. Sci. USA, 1991; 88: 2869).

[0148] 2) When a particular amino acid in the human framework region of the acceptor antibody and the corresponding amino acid in the donor antibody are rare at the corresponding position of the human antibody, the amino acid is substituted with the amino acid which is typically found at the corresponding position of the human framework.

[0149] For detailed description of the production of the humanized antibody, Queen et al., Proc. Natl. Acad. Sci. USA, 1989; 86: 10029, WO90/07861, WO92/11018, Co et al., Proc. Natl. Acad. Sci. USA, 1991; 88: 2869, Co and Queen, Nature, 1991; 351: 501, and Co et al., J. Immunol., 1992; 148: 1149 may be referred to, which are herein incorporated by reference.

[0150] It is generally desirable that all or most of the amino acid substitutions fulfill the criteria as described above. However, since uncertainty is associated with the judgment whether the individual amino acid is actually consistent with the criteria as described above, and various antibodies produced include those with and without the substitution at the particular position, optimization of the CDR and the FR may be conducted by computer modeling.

[0151] When the V region of the human antibody having a high homology is found, the CDR sequences of the donor antibody, especially antibody F1024, are transplanted into the framework portion of such V region, and the conformation is simulated by computer molecular modeling. The programs used in this step include ABMOD and ENCAD (Biochemistry, 1990; 29: 10032). By this simulation of the conformation,

optimization is accomplished by substituting an amino acid in the FR near the CDR with another amino acid so that the amino acid arrangement of the CDR region will realize optimized binding activity with the CD14.

[0152] Alternatively, the optimization of the CDR and FR may be accomplished by using the amino acid sequence of a part of the FR of the donor antibody, especially antibody F1024, without any change in the sequence and transplanting such sequence into the V region of the human antibody. In this case, the sequence of a part of the CDR and the FR of the antibody F1024 is transplanted into the V region of the human antibody, and the conformation is simulated by computer molecular modeling. Exemplary programs which may be used in this step include Modeler and QUANTA/CHARMm (Molecular Simulations).

[0153] When 3 to 4 sites in the light chain and 7 to 8 sites in the heavy chain are replaced with the amino acids from a donor, for example rat, FR will have a structure resembling the rat antibody and the arrangement of the amino acids in the CDR region may facilitate optimization of the binding activity with the CD14.

[0154] As long as the binding activity as an anti-CD14 antibody is retained, deletion, substitution, insertion, or addition of a single or 2 or more amino acids may be conducted in the amino acids of the CDR region. In this case, binding activity as an anti-CD14 antibody is more likely to be retained when the substitution takes place between the amino acids classified as the same group, for example, between Gly and Ala; Val, Leu and Ile; Asn and Gln; Cys and Met; or Lys and Arg. In addition, the amino acids at some positions of the framework region are involved in the direct interaction with the antigen, for example, contact with the antigen in a non-covalent binding mode, and such positions are also subject to the substitution as described above. Especially, the amino acids at 26th to 30th of the heavy chain are described to be a part of the hypervariable loop in terms of the conformation (Chothia and Lesk, *J. Mol. Biol.*, 1987; 196: 901-917), and such region may also be transplanted as in the case of the CDR.

[0155] The humanized antibody is prepared based on the resulting amino acid sequence. For example, the nucleotide sequence of the humanized antibody may be determined from the thus determined amino acid sequence, and the gene coding for the humanized monoclonal antibody is thereby produced. More specifically, DNA coding for the CDR is deleted from the gene coding for the human V region, and instead, the DNA coding for the CDR from the donor such as the rat is inserted. According to the changed amino acid based on the results of the molecular modeling, the corresponding DNA sequence is altered, for example, by site-directed mutagenesis using PCR to thereby produce the recombinant human V gene. This gene is cloned into the vector comprising the C regions of the heavy chain and the light chain of the human antibody to produce the expression vector. By changing the sequence from the human used in this stage, antibodies of the desired subclass, for example, human IgG1 or IgG3, and preferably IgG4 and the like may be produced. The expression vector may be introduced and expressed in mouse myeloma cell Sp2-O-ag14 (ATCC CRL1581) or hamster ovary cell CHO.

[0156] The humanized antibody has at least three latent advantages when used for therapeutic treatment of human compared to the non-human antibody, for example, the mouse or rat antibody, and in some cases, chimeric antibody.

[0157] 1) Since the effector part is of human origin, the antibody undergoes better interaction with other parts of the human immune system (for example, a more efficient destruction of the target cell by complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC)).

[0158] 2) Human immune system does not recognize the framework or the C region of the humanized antibody as a foreign substance, and therefore, response by the antibody upon administration of the antibody is reduced compared to the mouse antibody which is totally foreign or the chimeric antibody which is partly foreign.

[0159] 3) Administered rat and mouse antibodies are reported to have an in vivo half life in the circulation in blood of human which is extremely shorter than the normal antibodies (Shaw, D. et al., *J. Immunol.*, 1987; 138: 4534-4538). The humanized antibody after the administration probably has a half life more or less resembling that of the naturally occurring human antibody, and effective administration will be accomplished by using a smaller amount or by administering at a lower frequency.

[0160] The anti-CD14 antibody (I) may include the antibodies, especially humanized antibodies, having at least one of the CDRs of the antibody described in the Examples, especially F1024, preferably having 3 CDRs in the heavy chain variable region (VH) or the light chain variable region (VL) of the antibody, and more preferably having all of the 6 CDRs of the antibody, positioned at the corresponding positions. More specifically, the anti-CD14 antibody (I) is an antibody, especially a humanized antibody, comprising the CDR1, CDR2, and CDR3 of the heavy chain described in Table 2 as the CDR1, CDR2, and CDR3 of the heavy chain variable region and/or the CDR1, CDR2, and CDR3 of the light chain described in Table 2 as the CDR1, CDR2, and CDR3 of the light chain variable region.

[0161] When the anti-CD14 antibody (I) is a human antibody, exemplary methods used in the production include a method in which a hybridoma is produced by using activation of human lymphocyte by in vitro immunization; a method carried out by using a human antibody phage library; and a method in which a hybridoma is produced by using a non-human animal having the recombinant human antibody gene, especially a transgenic mouse such as KM mouse (WO2002/070648 (JP 2005-504507 A) and WO2002/043478 (JP 2004-515230 A)).

[0162] The human antibody phage library is a library produced by inserting the antibody gene prepared from human B cell in a phage gene to promote expression of the active fragments of the antibody such as the Fab and the single chain antibody on the surface of the phage. The antibody of the present invention can also be obtained by screening such libraries. These and other methods are well known to those skilled in the art (Huse et al., *Science*, 246: 1275-1281 (1989), Winter and Harris, *Immunol. Today* 14: 243-246 (1993), Ward et al., *Nature* 341: 544-546 (1989), Harlow and Lane (1988), supra, Hilyard et al., *Protein Engineering: A practical approach* (IRL Press 1992), Borrabeck, *Antibody Engineering*, 2nd ed. (Oxford University Press 1995), Barbas, C. F. I., Burton, D. R., Scott, J. K., and Silverman, G. J. 2001. *Phage display: a laboratory manual*. Cold Spring Harbor Laboratory Press. Cold Spring Harbor, N.Y., USA. 736 pp.). A phage expressing the active fragment of the antibody having the desired antigen binding activity may be collected from the library by using the binding activity to a substrate having an

antigen immobilized thereto for the index. The active fragment of the antibody may also be converted to a human antibody molecule comprising two complete H chains and two complete L chains by genetic engineering.

[0163] The polynucleotide according to the second aspect of the present invention may be any molecular species including the nucleic acid. The polynucleotide may include DNA and RNA as well as polydeoxyribonucleotide and polyribonucleotide. The polynucleotide may be a mixture or a modification product thereof as long as it codes for at least a part of the protein according to the first aspect of the present invention. The polynucleotide according to the second aspect of the present invention can be produced from the cell producing the (I) and/or (II) as described above by a method known in the art, and particularly by genetic engineering. Typical examples are described in the Examples.

[0164] The second aspect of the present invention is a polynucleotide coding for the protein, preferably the fusion protein, and more specifically, the fusion protein comprising an antibody of the first aspect. However, since the antibody is a protein inherently comprising a plurality of polypeptide chains, the polynucleotide of the present invention includes the case in which the single molecule polynucleotide codes for the protein of the present invention and the case in which 2 or more molecules, for example, 2 or 3 molecules of polynucleotide codes for the protein of the present invention. Typical examples are described in the Examples. With regard to at least a part of the protein according to the first aspect of the present invention, typical polynucleotide is the polynucleotide coding for the heavy chain, especially the heavy chain variable region (VH) part of the antibody, or the heavy chain part and the inhibitor part, or preferably their fusion protein; or the polynucleotide coding for the light chain, especially the light chain variable region (VL) part of the antibody, or the light chain part and the inhibitor part, or preferably their fusion protein. Preferable examples of the polynucleotide include those shown by SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25 in the Sequence Listing.

[0165] The vector according to the third aspect of the present invention includes a case in which the polynucleotide according to the second aspect is present on a single vector, and a case in which the polynucleotide is present on 2 or more vectors, for example, 2 or 3 vectors. The vector according to the third aspect of the present invention may also include components required for replication of the vector and components required for controlling the expression of the polynucleotide according to the second aspect in addition to the polynucleotide according to the second aspect. Such additional components are well known to those skilled in the art.

[0166] The vector used for the incorporation of the polynucleotide according to the second aspect is not particularly limited. The vector, however, is preferably a vector which is generally used for the expression of a protein gene, especially a vector which is adapted for expression of an antibody or a fusion protein comprising an antibody, or a vector for over-expression. Exemplary preferable vectors include a vector comprising human elongation factor (EF) 1 α promoter and/or CMV enhancer, for example, pEF-BOS or the vector used in the Examples. While the general practice is such that an expression vector having incorporated therein a polynucleotide coding for the VH part, or the VH and the inhibitor part, and preferably, the fusion protein of the VH and the inhibitor part, and an expression vector having incorporated therein a polynucleotide coding for the VL part, or the VL part and the

inhibitor part, and preferably, the fusion protein of the VL part and the inhibitor part are separately prepared, and these vectors are cotransfected in a host cell, it is also possible to incorporate both polynucleotides in a single expression vector. The procedure as described above may be carried out by using known materials and methods, and typical examples are described in the Examples.

[0167] The cell according to the fourth aspect of the present invention can be prepared by introducing the vector according to the third aspect of the present invention in an adequate host cell by the method known in the art. Examples of such cells include hybridoma, transformant, and genetically modified cell having the polynucleotide or the vector of the present invention introduced therein. The host cell used is not particularly limited, and the preferred are those which are generally used in the expression of a protein gene or the like, especially the cells which are adapted for use in the expression of an antibody, a fusion protein comprising an antibody or the like. Exemplary host cells include bacteria (for example, *E. coli*), actinomycete, yeast, insect cell (for example, SF9), and mammalian cell (for example, COS-1, CHO, and myeloma cell), and the preferred is the mammalian cell. The procedure as described above may be carried out by using known materials and methods, and typical examples are described in the Examples.

[0168] The protein according to the first aspect of the present invention can be produced by the in vitro translation using the polynucleotide according to the second aspect or the vector according to the third aspect of the present invention, or by cultivating the cell according to the fourth aspect of the present invention under appropriate conditions (fifth aspect of the present invention). The protein produced may be isolated by combining appropriate known purification methods. Preferable examples are described in the Examples.

[0169] The preventive and/or therapeutic agent for a disease according to the sixth aspect of the present invention is a pharmaceutical composition comprising at least one of the protein according to the first aspect of the present invention, the polynucleotide according to the second aspect of the present invention, the vector according to the third aspect of the present invention, and the cell according to the fourth aspect of the present invention as its effective component, and the polynucleotide and the vector of the present invention can be used, for example, in gene therapy, and the transformant can be used in cell therapy with optional addition of pharmaceutically acceptable additives.

[0170] The preventive and/or therapeutic agent for a disease according to the sixth aspect of the present invention can be applied to various diseases or pathologies, or particular therapeutic indexes associated with such diseases or pathology. Although such disease, pathology, and therapeutic index are not limited to any particular types, they are preferably diseases related to distribution or function of the CD14, distribution or function of the protease, or bacterial infection. Accordingly, the preventive and/or therapeutic agent of the present invention may be used for sepsis and related diseases, systemic or cardiovascular disease, infectious disease, inflammatory disease, respiratory disease or respiratory failure, autoimmune disease, multiple organ dysfunction syndrome (MODS) or failure or dysfunction of individual organ. More specifically, the preventive and/or therapeutic agent of the present invention may be used for sepsis and related diseases such as severe sepsis, septic ARDS and septic shock; SIRS related disease; shocks such as endotoxin shock, exo-

toxin shock, hemorrhagic shock, and intraoperative or post-operative shock; systemic or cardiovascular diseases such as ischemic reperfusion organ failure, ischemic encephalopathy, acute ischemic stroke, acute stage cerebral thrombosis, acute coronary microvascular embolus, vascular embolus resulting from shock, disseminated intravascular coagulation (DIC), myocardial infarction and its aftereffect, and hypotension; infectious diseases such as periodontal disease, acute bacterial meningitis, invasive staphylococcal infection, infectious endocarditis, acute viral encephalitis, and AIDS; inflammatory diseases such as psoriasis, gastritis, peptic ulcer, pancreatitis, nephritis, myocarditis, pneumonia, hepatitis, liver cirrhosis, encephalitis, osteoarthritis, atopic dermatitis, allergic contact dermatitis, allergic rhinitis, reflux esophagitis, and ankylosing spondylitis; respiratory diseases or respiratory failures such as acute respiratory distress syndrome (ARDS), infantile respiratory distress syndrome (IRDS), chronic obstructive pulmonary disease (COPD), pulmonary emphysema, and asthma; autoimmune diseases such as chronic rheumatoid arthritis, intractable colitis, ulcerative colitis, Crohn's disease, glomerulonephritis, SLE, scleroderma, multiple sclerosis and Sjogren's syndrome; multiple organ failure; organ failure or rejection after organ transplantation; and individual organ dysfunctions such as cardiac failure, unstable angina, valvulitis, renal failure, cardiomyopathy, nephrotic syndrome, hepatic insufficiency, and fulminant hepatic failure.

[0171] Preferable diseases for application of the preventive and/or therapeutic agent are diseases such as sepsis, severe sepsis, septic ARDS or septic shock, SIRS, endotoxin shock, and ARDS.

[0172] The preventive and/or therapeutic agent of the present invention is also useful for improving or preventing the conditions associated with the increase in the inflammatory cytokine, especially increase in the blood TNF concentration. Furthermore, the agent of the present invention is expected to have therapeutic and preventive effects on Gram-negative bacterial infection in which LPS is involved, Gram-positive bacterial infection in which LTA or peptidoglycan is involved, and sepsis associated with mycoplasma infection, namely, therapeutic effects after emergence or progress of the conditions associated with such diseases as well as preventive effects for patients exhibiting high value of blood LPS, LTA, or mycoplasma, patients exhibiting high blood concentration of certain CD14 molecular species (see WO01/22085 and WO2004/44005), and those who are expected to develop such conditions.

[0173] Exemplary pharmaceutically acceptable additives which may be incorporated as desired include carrier, excipient, stabilizer, lubricant, colorant, disintegrant, antiseptic, isotonic agent, stabilizer, dispersant, antioxidant, buffer agent, preservative, suspending agent, emulsifier, appropriate solvents generally used in the art (for example, sterile water and vegetable oil), and physiologically acceptable solubilizer.

[0174] The pharmaceutical composition of the present invention may also comprise an antibiotic, steroid, various cytokine antibodies, or anticoagulants. These agents will exhibit additive effects or synergistic effects with the protein of the present invention, and the pharmaceutical composition will have an improved effectiveness.

[0175] The dose when the pharmaceutical composition of the present invention is administered as a agent is not particularly limited, and the dose may be adequately determined by

taking the conditions, body weight, age, sex, and the like of a patient into consideration. In a typical case of administering the protein of the present invention as the effective component, the dose is preferably at least 0.1 mg/kg, and more preferably 1 to 10 mg/kg.

[0176] The dosage form used in administering the pharmaceutical composition of the present invention as a agent is not particularly limited, and preferable dosage forms include tablet, injection, powder, suppository, inhalant, and the more preferred are injection and inhalant. While various administration routes are possible, the preferred is parenteral administration. Parenteral administration is commonly performed with an injection such as intravenous administration (bolus administration, continuous infusion, intermittent infusion), intraarterial administration, subcutaneous administration, and intramuscular administration, and inhalation is also preferably used. Other administration routes include intrarectal administration, percutaneous absorption, intraarticular administration, transnasal administration, and transmucosal administration. The administration method may include prophylactic administration, single administration, and continuous administration while actual timing and frequency of the administration depends on the conditions of the patient.

[0177] Also provided is a therapeutic method using the agent comprising the pharmaceutical composition of the present invention as its main ingredient for the disease or the pathology to which the preventive and/or therapeutic agent according to the sixth aspect of the present invention is applied.

EXAMPLES

[0178] Next, the present invention is described in further detail by referring to the Examples which by no means limit the scope of the present invention.

Example 1

Construction of Chimeric Antibody and Antibody Fusion Protein

[0179] 1-1) Construction of Chimeric Antibody and Antibody Fusion Protein (F1024)

[0180] (1) Materials

[0181] Major materials and apparatus used were as described below.

[0182] Primer: primers shown in Table 1 (synthesized by Sigma Genosys Japan, K.K.),

[0183] Enzyme for PCR: Ex Taq (TAKARA BIO INC.),

[0184] Restriction enzymes: EcoRI, BamHI, NotI, NheI, EcoRV, StuI, BglII, and others (TAKARA BIO INC.),

[0185] Genomic DNA: HeLa genome (lot. N34707-1, BD Biosciences Clontech),

[0186] PCR apparatus: DNA Engine (MJ RESEARCH, INC.),

[0187] Agarose electrophoresis gel: SeaKem GTG Agarose (TAKARA BIO INC.),

[0188] 50×TAE (2 mol/L Tris-acetate, 0.05 mol/L EDTA) (NIPPON GENE CO., LTD.),

[0189] Molecular weight marker (λ DNA fragment digested with StyI),

[0190] Kit used for extraction of DNA fragment from the gel (QIAEX II, QIAGEN K.K.),

[0191] Expression vector for mammalian cell: pEF2csw (a vector produced by improving pEF-BOS),

[0192] Plasmid comprising human IgG4 heavy chain constant region (C γ 4) gene: pIK-2232,

[0193] TA cloning vector: pT7BlueT (NOVAGEN) and ligation reagent: TaKaRa ligation Kit ver. 2 (TAKARA BIO INC.),

[0194] *E. coli* competent cell: JM109 (TAKARA BIO INC.),

[0195] Plasmid DNA and genomic DNA purification kit (QIAGEN K.K.),

[0196] Sequencing kit: DYEnamic ET Terminator Cycle Sequencing Premix Kit lot. 1767 (Amersham Biosciences) and analyzer: ABI3100 genetic analyzer (Applied Biosystems),

[0197] Total RNA isolation reagent: TRIzol (GIBCO BRL),

[0198] 5'RACE kit: 5'RACE system for Rapid Amplification of cDNA Ends, v.2.0 (Invitrogen Corporation),

[0199] Dulbecco's MEM (SIGMA),

[0200] Transfection reagent: FuGENE6 (Roche Diagnostics K.K.)

TABLE 1

Table 1: Sequence of primers		
Primer Name	Base Sequence	SEQ ID
M4	5'-GTTTCCAGTCACGACG-3'	135
T7	5'-CTGTTGTTTCAGCTGAGGACAC-3'	136
rIgH-b	5'-CTGTTGTTTCAGCTGAGGACAC-3'	137
rIgH-c	5'-AGGGTCACCATGGAGTTACTT-3'	138
rIgK-a	5'-AGATACAGTTGGTGCAGCATCAGC-3'	139
rIgK-b	5'-GACACTGATGTCCTCTGGGATAGA-3'	140
1024H-a	5'-GAATTCCATGGATTGGTTGTGGAAGT-3'	141
1024K-a	5'-GAATTCCATGGAGTCACATACTAG-3'	142
HchainEco47NheI	5'-CCCCCGCTAGCGCTGGAGACGGTGACC-3'	143
rIgK-BsiWI	5'-CGTACGTTTCAATTCCAGCTTGGT-3'	144
IgG4-m	5'-AGCGCTAGCACCAAGGGCCATCCGTCTTC-3'	145
IgG4-v	5'-GGATCCTTTACCCAGAGACAGGGA-3'	146
IgG4-s	5'-TTACCTGGGCCTGATGGCCCTGGGGACCA-3'	147
IgG4-r	5'-TGGTCCCCAGGCCCATCAGGCCAGGTAA-3'	148
IgK-e	5'-GCACTTCTCCCTCTAACA-3'	149
BsiWI-hIgK	5'-CGTACGGTGGCTGCACCATCTGTC-3'	150
UTI-a	5'-GGATCCGCTGTGCTACCCCAAGAA-3'	151
UTI-b	5'-GGATCCACTGTGGCGGCCTGCAAT-3'	152
UTI-c	5'-GCGGCCGCTCAGTTGGAGAAGCGCAGCAG-3'	153
UTI-f	5'-GATATCACCACCACCACCGTTGGAGAAGCGCAGCA-3'	154
UTI-g	5'-AGGCCTACCACCACCACCGTTGGAGAAGCGCAGCA-3'	155
UTI-h	5'-GATATCGGAGGAGGAGAGCTGTGCTACCCCAAGA-3'	156
UTI-i	5'-GATATCGGAGGAGGAGGAAGTGTGGCGCCTGCAA-3'	157
SLPI-a	5'-CAGAGTCACTCCTGCCTTCA-3'	158
SLPI-c	5'-AGATCTGGAAAGTCCTTCAAAGCTGGAGTC-3'	159
SLPI-d	5'-ACACCCCAAACCAACAAGGAGGAAGCCTG-3'	160
SLPI-e	5'-CAGGCTTCCTCCTTGTGGGTTTGGGGTGT-3'	161
SLPI-g	5'-GCGGCCGCTCAAGCTTTCACAGGGGAAACG-3'	162
1031H-a	5'-GGG GAA TTC CAT GGG ATG GAG CCG GAT C-3'	163
mIgG2b-c	5'-TGA ACA CAG ACC ACT CAC CAT G-3'	164

TABLE 1-continued

Table 1: Sequence of primers		
Primer Name	Base Sequence	SEQ ID
mIgG2b-a	5'-GGG CCA GTG GAT AGA CTG ATG-3'	165
IGKV4-1-a	5'-GCA TTG TGA ACT GAG CTA CAA C-3'	166
IgK-d	5'-GAC ATC GTG ATG ACC CAG TCT C-3'	167
rIgK-a	5'-AGA TAC AGT TGG TGC AGC ATC AGC-3'	168
13HcS-EcoR	5'-GGA ATT CCA TGG AAT GTA ACT GGA TAC TTC-3'	169
13HcA-Nhe	5'-CTA GCT AGC GCT GGA GAC GGT GAC TGA GGT-3'	170
13LcS-EcoR	5'-GGA ATT CCA TGG AGA CAG ACA CAC TCC TG-3'	171
13LcA-BsiW	5'-CAC CGT ACG TTT GAT TTC CAG CTT GGT CCC-3'	172

[0201] (2) Experimental Methods

[0202] Major experimental methods employed are as described below.

[0203] PCR

[0204] PCR was conducted according to the instruction manual of the enzyme.

[0205] Agarose Gel Electrophoresis

[0206] Agarose gel at a concentration of 0.8% was prepared, and this gel was placed in an electrophoresis tank filled with 1×TAE, and after applying 5 μL of the sample to the well, electrophoresis was conducted at 135 V for 15 minutes. After completion of the electrophoresis, the gel was stained with ethidium bromide, and the band was detected with UV.

[0207] Extraction of DNA Fragments from the Gel

[0208] The band of interest was cut with a razor, and the DNA fragment was extracted from the gel piece using QIAEX II kit according to the attached instruction manual. The thus extracted DNA fragment was dissolved in 20 μL sterile water.

[0209] Ligation Reaction

[0210] 1 μL of the extracted DNA fragment, 1 μL of the cloning vector (pT7BlueT), and 2 μL of I solution of the ligation kit ver.2 were mixed, and the mixture was allowed to stand at room temperature for 15 minutes to promote the ligation.

[0211] Transformation of *E. coli*

[0212] 50 μL of competent *E. coli* was allowed to thaw on ice, and 4 μL of the ligation product was added. After allowing to stand on ice for 30 minutes, heat shock was applied at 42° C. for 45 seconds, and the solution was coated on an ampicillin-containing LB plate (final concentration, 50 μg/mL), and the plate was incubated overnight at 37° C.

[0213] Purification of Plasmid and Sequencing Reaction The procedure was conducted according to the instruction manual attached to the kit.

[0214] Separation of Total RNA from Hybridoma and 5'RACE

[0215] The procedure was conducted according to the instruction manual attached to the kit. The number of hybridoma cells used was 5×10^7 .

[0216] Transfection

[0217] The transfection was conducted according to the instruction manual attached to the FuGENE6. In the case of

6-well plate, 2 mL of COS-1 cell was inoculated in each well at a density of 1.5×10^5 cells/mL on the day before the transfection. On the next day, 3 μL of FuGENE6 and 1 of the expression plasmid were added to 97 μL of Dulbecco's MEM, and after allowing the mixture to stand for at least 15 minutes, 2 mL of this mixture was added dropwise to the serum free Dulbecco's MEM. The transfection was accomplished by the replacement of the culture medium.

[0218] (3) Cloning of the Variable Region of the Hybridoma Antibody Gene and Determination of the Sequence (F1024)

[0219] The hybridoma F1024 (1×10^7 cells) produced by the method described in WO02/42333 was washed with PBS⁻ (SIGMA), and total RNA was extracted by using TRIzol (GIBCO BRL). Next, 5 μg of the total RNA was subjected to 5' RACE by using 5'RACE system for Rapid Amplification of cDNA Ends, ver. 2.0 (Invitrogen Corporation), and gene fragments coding for the heavy and light chain variable regions were respectively amplified. The procedure was conducted as described in the manual attached to the kit, and the heavy chain variable region was subjected to reverse transcription using rIgH-c primer, dC addition on the terminal using terminal deoxynucleotide transferase, and first PCR using the rIgH-c primer and AAP primer (attached to the kit). The light chain variable region was similarly subjected to the reverse transcription using rIgK-b primer, and first PCR using the rIgK-b primer and the AAP primer. Subsequently, second PCR was conducted using the reaction product for the template by using the rIgH-b primer and AUAP primer (attached to the kit) for the heavy chain variable region, and rIgH-a primer and AUAP primer (attached to the kit) for the light chain variable region, and each of the thus specifically amplified DNA fragments were confirmed by agarose gel electrophoresis. After extracting the DNA fragment from the gel, the nucleotide sequence was determined, and amino acid sequence of the corresponding region was also determined (FIGS. 1 and 2). The CDR sequences according to the definition of Kabat are shown in Table 2. The sequences shown in Table 2 are described in SEQ ID NOS: 173 to 178.

TABLE 2

Table 2: CDR amino acid sequence of antibody F1024			
F1024	CDR1	CDR2	CDR3
Heavy chain	DYAMN SEQ ID No: 173)	WINTQTGKPTYADDFKQ (SEQ ID No: 174)	STFYYSYIYGWYDFD (SEQ ID No: 175)
Light chain	KASQNVGS NVD (SEQ ID No: 176)	KASNRYT (SEQ ID No: 177)	MQSNTNPPWT (SEQ ID No: 178)

[0220] (4) Construction of Expression Plasmid of Chimeric Antibody Fusion Protein

[0221] Production of a chimeric antibody in which the variable region having the antigen binding activity is the one from the hybridoma antibody, namely, the one from the rat antibody and the constant region is the one from human antibody enables provision of an antibody with reduced antigenicity for human. A large number of chimeric antibodies have been developed since the report of Morrison et al. in 1984 (Proc. Natl. Acad. Sci. USA, 81: 6851, 1984).

[0222] 5' primers respectively having a recognition sequence for restriction enzyme EcoRI attached immediately upstream of the initiation codon of the variable region (1024H-a for the heavy chain, 1024K-a for the light chain) and 3' primers (HchainEco47NheI for the heavy chain and rIgK-BsiWI for the light chain) having attached thereto a restriction enzyme (NheI recognition sequence for the heavy chain and BsiWI recognition sequence for the light chain) which can be ligated with the human constant region without altering the amino acid sequence of the 3' side sequence of the variable region were designed. With these primers, PCR was conducted again by using the heavy chain and the light chain samples prepared in Example 1-1)-(3) after the reverse transcription for the template. The thus amplified PCR product was mixed with pT7BlueT vector (NOVAGEN), and ligation reaction was conducted using TaKaRa Ligation Kit ver. 2 (TAKARA BIO INC.) at room temperature for 15 minutes. Competent cell *E. coli* (JM109, TAKARA BIO INC.) was transformed by using the reaction solution.

[0223] The colony formed was picked up, and the insertion of the insert in the vector was confirmed by colony direct PCR by using Ex Taq polymerase (TAKARA BIO INC.), M4 primer, and T7 primer.

[0224] Next, the colony which had been confirmed for the insertion of the insert was cultivated overnight in LB medium, and the plasmid was purified by using QIAGEN plasmid midi kit (QIAGEN) (The plasmid having the gene fragment coding for the heavy chain variable region was designated pT7-1024H, and the plasmid having the gene fragment coding for the light chain variable region was designated pT7-1024K). The nucleotide sequence of the purified plasmid was checked by using the M4 primer and the T7 primer.

[0225] pT7-1024H was cleaved with restriction enzymes EcoRI and NheI to prepare gene fragment A coding for the heavy chain variable region. In a similar manner, pT7-1024K was cleaved with restriction enzymes EcoRI and BsiWI to prepare gene fragment B coding for the light chain variable region.

[0226] PCR was conducted by using plasmid pTK-2232 (see WO2005/7800) comprising the gene for human IgG4

heavy chain constant region (C γ 4) for the template and the primer pair (IgG4-m and IgG4-v) to amplify a gene fragment having the recognition sequence for restriction enzyme NheI at the 5' terminal of the C γ 4, and having the recognition sequence for restriction enzyme BamHI at the 3' terminal of the C γ 4 in place of the stop codon that had been deleted. This fragment was cleaved with restriction enzymes NheI and BamHI to prepare gene fragment C.

[0227] PCR was conducted by using pTK-2232 for the template and 2 primer pairs (IgG4-m and IgG4-s) and (IgG4-r and IgG4-v) to thereby amplify each gene fragment. These gene fragments were mixed for use as a template, and PCR was conducted again by using another primer pair (IgG4-m and IgG4-v) to amplify a gene fragment which has 2 cysteine residues required for the dimerization of the heavy chains replaced with glycine residues, and which has the recognition sequence for restriction enzyme NheI at the 5' terminal, and the recognition sequence for restriction enzyme BamHI at the 3' terminal in place of the stop codon. This fragment was cleaved with restriction enzymes NheI and BamHI to prepare gene fragment D.

[0228] PCR was conducted by using HeLa genomic DNA for the template and the primers (BsiWI-hIgK and IgK-e) to thereby amplify human light chain constant region (CK), and this amplification product was cloned into pT7BlueT vector to construct pT7-hIgK. Fragment E was then prepared by using adequate restriction enzymes (BsiWI and BamHI) which were capable of cleaving the human light chain constant region from the plasmid.

[0229] PCR was conducted by using plasmid pM1213 comprising human UTI domain 1 and domain 2 (D1D2) for the template and the primer pair (UTI-a and UTI-c) to amplify a gene fragment having the recognition sequence for restriction enzyme BamHI at the 5' terminal of the D1D2, and the recognition sequence for restriction enzyme NotI immediately downstream of the stop codon at the 3' terminal. This fragment was cleaved with restriction enzymes BamHI and NotI to prepare gene fragment F.

[0230] PCR was conducted by using pM1213 for the template and the primer pair (UTI-b and UTI-c) to amplify a gene fragment having the recognition sequence for the restriction enzyme BamHI at the 5' terminal of D2, and the recognition sequence for restriction enzyme NotI immediately downstream of the stop codon at the 3' terminal. This fragment was cleaved with restriction enzymes BamHI and NotI to prepare gene fragment G.

[0231] PCR was conducted by using plasmid pM765 comprising 3 amino acids modified form of human UTI domain 2 {D2(3)} (see JP 6-321989 A) for the template and the primer pair (UTI-b and UTI-c), and a gene fragment having the recognition sequence for restriction enzyme BamHI at the 5' terminal of D2(3), and the recognition sequence for restriction enzyme NotI immediately downstream of the stop codon at the 3' terminal. This fragment was cleaved with restriction enzymes BamHI and NotI to prepare gene fragment H.

[0232] PCR was conducted by using pM1213 for the template and the primer pair (UTI-a and UTI-f) to amplify a gene fragment having the recognition sequence for restriction enzyme BamHI at the 5' terminal of the D1D2, and having a linker comprising 4 glycine residues added after removing the stop codon at the 3' terminal and further having recognition sequence for restriction enzyme EcoRV immediately downstream of the linker. This fragment was cleaved with restriction enzymes BamHI and EcoRV to prepare gene fragment I.

[0233] PCR was conducted by using pM1213 for the template and the primer pair (UTI-b and UTI-f) to amplify a gene fragment having the recognition sequence for restriction enzyme BamHI at the 5' terminal of D2 and having a linker comprising 4 glycine residues added after removing the stop codon at the 3' terminal and further having recognition sequence for restriction enzyme EcoRV immediately downstream of the linker. This fragment was cleaved with restriction enzymes BamHI and EcoRV to prepare gene fragment J.

[0234] PCR was conducted by using pM1213 for the template and the primer pair (UTI-h and UTI-c) to amplify a gene fragment having a linker comprising 4 glycine residues added at the 5' terminal of D1D2 and having the recognition sequence for the restriction enzyme EcoRV immediately upstream of the linker, and having the recognition sequence for restriction enzyme NotI immediately downstream of the stop codon at the 3' terminal. This fragment was cleaved with restriction enzymes EcoRV and NotI to prepare gene fragment K.

[0235] PCR was conducted by using pM1213 for the template and the primer pair (UTI-i and UTI-c) to amplify a gene fragment having a linker comprising 4 glycine residues added at the 5' terminal of D2 and the recognition sequence for restriction enzyme EcoRV immediately before the linker, and having the recognition sequence for restriction enzyme NotI immediately downstream of the stop codon at the 3' terminal. This fragment was cleaved with restriction enzymes EcoRV and NotI to prepare gene fragment L.

[0236] PCR was conducted by using pM1213 for the template and the primer pair (UTI-h and UTI-g) to amplify a gene fragment having a linker comprising 4 glycine residues added at the 5' terminal of D1D2 and the recognition sequence for restriction enzyme EcoRV immediately before the linker, and having a linker comprising 4 glycine residues added after removing the stop codon at the 3' terminal and further having recognition sequence for restriction enzyme StuI immediately downstream of the linker. After cloning this fragment in pT7BlueT vector, the vector was cleaved with EcoRV and BamHI, and gene fragment I was ligated to construct an intermediate plasmid comprising D1D2D1D2 sequence. This plasmid was cleaved with BamHI and StuI to prepare gene fragment M.

[0237] PCR was conducted by using pM1213 for the template and the primer pair (UTI-i and UTI-g) to amplify a gene fragment having a linker comprising 4 glycine residues added at the 5' terminal of D2 and having the recognition sequence for restriction enzyme EcoRV immediately upstream of the linker, and having a linker comprising 4 glycine residues added after removing the stop codon at the 3' terminal and further having recognition sequence for restriction enzyme StuI immediately downstream of the linker. After cloning this fragment in pT7BlueT vector, the vector was cleaved with EcoRV and BamHI, and gene fragment J was ligated to construct an intermediate plasmid comprising D2D2 sequence. This plasmid was cleaved with BamHI and StuI to prepare gene fragment N.

[0238] PCR was conducted by using HeLa genomic DNA for the template and the following primer pair. As a consequence, PCR amplification product O was obtained by SLPI-c and SLPI-e, PCR amplification product P was obtained by SLPI-d and SLPI-g, and PCR amplification product R was obtained by SLPI-a and SLPI-g.

[0239] When PCR was conducted again by using a mixture of O and P for the template using primers SLPI-c and SLPI-g, amplification product Q, which is ligation product of both fragments was obtained.

[0240] The amplification products Q and R were respectively cloned in pT7BlueT vector, and Q and R were confirmed to be the sequences coding for Ser¹-Ala¹⁰⁷ of human SLPI (also referred to as SLPI(D1D2)) and Arg⁵⁸-Ala¹⁰⁷ of human SLPI (also referred to as SLPI(D2)), and they were designated pT7-SLPI(D1D2) and pT7-SLPI(D2), respectively. Both were constructed such that the recognition sequence for restriction enzyme BglII was located on the 5' side of the SLPI, NotI recognition sequence was located immediately downstream of the stop codon on the 3' side. These plasmids were respectively cleaved with restriction enzymes BglII and NotI, respectively, to prepare SLPI (D1D2) fragment S and SLPI(D2) fragment T.

[0241] The gene fragments as described above were ligated in the downstream of the EF1 α promoter of the expression vector pEF2caw prepared by cleaving with EcoRI and NotI, or EcoRI and BamHI in appropriate combinations to construct respective expression plasmids. The names of the expression plasmids and the names of the gene fragments incorporated in the vector are together shown in Table 3. The same plasmid pTK-2344 expressing the light chain of the chimeric antibody was used for all types of heavy chains. The structure, the nucleotide sequence, and the deduced amino acid sequence of each fusion protein are shown in FIGS. 7 to 17 and Sequence Listing (SEQ ID NOS: 1 to 26). In each of the amino acid sequences of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 24, Amino Acid Nos. 1 to 19 correspond to the signal peptide sequence, and in the amino acid sequences of SEQ ID NOS: 22 and 26, Amino Acid Nos. 1 to 20 correspond to the signal peptide sequence. Accordingly, the deduced amino acid sequence of the fusion protein of the present invention is the amino acid sequence from which the signal peptide has been excluded.

TABLE 3

chimeric antibody-heavy chain fusion protein and plasmid expressing light chain of the chimeric antibody				
Antibody Fusion Protein	Plasmid Name	Insert Fragment	FIG. No.	SEQ ID
F1024D-D1D2	pTK-2348	A + C + F	7	1 to 2
F1024D-D2	pTK-2349	A + C + G	8	3 to 4
F1024D-D2 (3)	pTK-2368	A + C + H	9	5 to 6
F1024S-D1D2	pTK-2354	A + D + F	10	7 to 8
F1024S-D2	pTK-2355	A + D + G	11	9 to 10
F1024S-D2 (3)	pTK-2370	A + D + H	12	11 to 12
F1024D-D1D2D1D2	pTK-2356	A + C + I + K	—	—
F1024D-D2D2	pTK-2357	A + C + J + L	—	—
F1024S-D1D2D1D2	pTK-2360	A + D + I + K	—	—
F1024S-D2D2	pTK-2361	A + D + J + L	—	—
F1024D-D1D2D1D2D2	pTK-2362	A + C + M + K	—	—
F1024D-D2D2D2	pTK-2363	A + C + N + L	—	—
F1024S-D1D2D1D2D2	pTK-2366	A + D + M + K	—	—
F1024S-D2D2D2	pTK-2367	A + D + N + L	—	—
F1024D-SLPI (D1D2)	pTK-2397	A + C + S	13	13 to 14
F1024D-SLPI (D2)	pTK-2394	A + C + T	14	15 to 16
F1024S-SLPI (D1D2)	pTK-2399	A + D + S	15	17 to 18
F1024S-SLPI (D2)	pTK-2396	A + D + T	16	19 to 20
F1024 light chain of chimeric antibody	pTK-2344	B + E	7 to 16	21 to 22

TABLE 3-continued

chimeric antibody-heavy chain fusion protein and plasmid expressing light chain of the chimeric antibody				
Antibody Fusion Protein	Plasmid Name	Insert Fragment	FIG. No.	SEQ ID
F1031-13S-D2 (3)	pF31-13HU		17	23 to 24
F1031-13 light chain of chimeric antibody	pF31-13L		17	25 to 26

[0242] (5) Expression of Each Fusion Protein in Small Scale and Purification of Expressed Fusion Protein

[0243] COS-1 cell was subcultured in Dulbecco's MEM supplemented with 10% fetal bovine serum, and on the day before the transfection, the cell was inoculated in the cultivation vessel at a density of 1.5×10^5 cells/mL. On the next day, light chain expression plasmid (pTK-2344) was mixed with each heavy chain expression plasmid at a weight ratio of 1:1, and then, with an adequate amount of the transfection reagent (FuGENE6, Rosch Diagnostics). This mixture was added dropwise to serum free Dulbecco's MEM, and the cell was transfected by replacing this medium with the culture medium. The cell was incubated in the presence of 5% CO₂ at 37° C. for 2 to 3 days, and the supernatant was collected. The purification was conducted using Prosep-A column (MILLIPORE), and after dialyzing with PBS (pH 7.4), concentration was calculated from the absorbance at 280 nm.

[0244] 1-2) Construction of Chimeric Antibody and Antibody Fusion Protein (F1031)

[0245] (1) Cloning of Variable Region of Hybridoma Antibody Gene and Determination of Sequence (F1031)

[0246] CDR sequence of antibody F1031-13-2 (mouse IgG2b/ κ) which is an anti-human CD14 antibody that binds to CD14 but that has no CD14 inhibitory activity was determined by the procedure as described below.

[0247] First, total RNA was prepared from the hybridoma expressing F1031-13-2 by using TRIzol, and single chain cDNA was synthesized by using SuperScript III First-Strand Synthesis System for RT-PCR (Invitrogen Corporation).

[0248] In the meanwhile, sense primers 1031H-a and mIgG2b-c and antisense primer mIgG2b-a were synthesized for use in the amplification of the variable region of the mouse IgG2b heavy chain, and sense primers IGKV4-1-a and IgK-d and antisense primer rIgK-a were synthesized for use in the amplification of the variable region of κ chain (see Table 1).

[0249] Next, PCR was conducted by using the thus synthesized single chain cDNA of the hybridoma for the template. The primers used were the combinations of 1031H-a and mIgG2b-a for heavy chain (i), mIgG2b-c and mIgG2b-a for heavy chain (ii), IGKV4-1-a and rIgK-a for light chain (i), and IgK-d and rIgK-a for light chain (ii). PCR was conducted by heating the reaction solution at 96° C. for 2 minutes and then repeating 25 cycles of heating at 96° C. for 30 seconds, 55° C. for 30 seconds, and 72° C. for 30 seconds.

[0250] The resulting products were directly determined for their sequence, and it was found that the heavy chains (i) (ii), and the light chains (i) (ii) respectively had the same sequence. With regard to the light chain, 5' terminal was incomplete, and the translation initiation codon could not be identified. Accordingly, sequence showing homology in the frame region was searched in the mouse κ chain whose sequence has already been reported. FIGS. 3 and 4 (SEQ ID NOS: 127 to 130) show sequences (the nucleotide sequence

and the amino acid sequence) of the heavy chain and the light chain of variable region of antibody F1031-13-2. In the sequence, the underlined part is the sequence from the primers.

[0251] (2) Construction of Plasmid Expressing Chimeric Antibody (F1031)

[0252] Plasmid expressing chimeric antibody F1031-13-2 was constructed by the method similar to that of Example 1-1) (construction of plasmid expressing F1024 chimeric antibody). More specifically, by referring to the sequence obtained in 1-2)(1), primers for constructing the heavy chain expressing plasmid, namely, primer 13HcS-EcoR of the 5' side having the recognition sequence for restriction enzyme EcoRI added immediately upstream of the initiation codon of the variable region, and primer 13HcA-Nhe of the 3' having the recognition site for restriction enzyme NheI which can be ligated to the human constant region added without altering the amino acid sequence of the 3' side of the variable region were synthesized. Although the sequence on the 5' side of the light chain was not identified, the sequence on the 5' terminal side was estimated by homology search, and primer 13LcS-EcoR of the 5' side having the recognition sequence for restriction enzyme EcoRI added immediately upstream of the initiation codon of the variable region, and primer 13LcA-BsiW of the 3' side having the recognition site for restriction enzyme BsiWI which can be ligated to the human constant region added without altering the amino acid sequence of the 3' side of the variable region were synthesized (see Table 1).

[0253] Next, PCR was conducted by using the single strand cDNA synthesized in 1-2)(1) for the template. The reaction was conducted by heating at 90° C. for 2 minutes, and then repeating 30 cycles of (1) heating at 94° C. for 30 seconds, (2) 50° C. for 30 seconds, and (3) 72° C. for 1 minute. The resulting PCR product for constructing the heavy chain was digested with EcoRI and NheI, and the PCR product for constructing the light chain was digested with EcoRI and BsiWI, and the fragments of about 0.4 kb were collected from the respective digestion products.

[0254] Next, the plasmid pTK-2370 for expressing the heavy chain and the plasmid pTK-2344 for expressing the light chain of the F1024 chimeric antibody constructed in Example 1-1) were digested with EcoRI and NheI, and EcoRI and BsiWI, respectively, to collect the fragments of about 5.7 kb and 4.8 kb. The fragments from the PCR product were then inserted in these fragments, and *E. coli* competent cell JM109 was transformed by the standard method to obtain plasmid pF31-13HU for expressing the heavy chain and plasmid pF31-13L for expressing the light chain of the F1031-13-2. Since the 5' terminal sequence of the light chain of the F1031-13-2 includes the sequence newly confirmed in the construction of the present invention, the sequences of the heavy chain variable region and the light chain variable region of the expression plasmid are shown again in FIGS. 5 and 6 (SEQ ID NOS: 131 to 134). In the sequence, the underlined part is the sequence from the construction primers.

[0255] (3) Confirmation of Expression of Chimeric Antibody Fusion Protein

[0256] The heavy chain expression plasmid and the light chain expression plasmid constructed in 1-2)(2) were introduced in COS-1 cells to confirm the expression of the chimeric antibody fusion protein.

[0257] First, COS-1 cells were inoculated in DMEM supplemented with 10% inactivated FBS in 6-well plate at 2.0 to 2.4×10^5 cells/well, and the cells were incubated overnight

at 37° C. and in the presence of 5% CO₂. On the next day, 6 µL of FuGENE6 was mixed with 1 µg of the heavy chain expression plasmid and 1 µg of the light chain expression plasmid, and the mixture was added dropwise to the COS-1 cells according to the protocol attached to the FuGENE6. In the procedure as described above, the following treatment was conducted before the dropwise addition of the FuGENE/plasmid mixture to the cells in order to prevent contamination of the immunoglobulin from FBS. Namely, after incubating the COS-1 cells overnight and removing the cell supernatant, the cells were washed twice with the production medium (Hybridoma-SFM (Invitrogen Corporation) or Cellgro Complete Serum Free Medium (Mediatech)), and subsequently, 2 mL/well of the production medium was added to the plate. The FuGENE/plasmid mixture was then added dropwise to the cells. After incubating the cells at 37° C. and in the presence 5% CO₂ for 3 to 4 days, the supernatant was recovered and the amount of the chimeric antibody fusion protein in the supernatant was confirmed by the procedure similar to the EIA procedure described in Example 2 except that the HRP-labeled antibody used in the detection was HRP-labeled anti human κ light chain antibody (DAKO) instead of the peroxidase-labeled UTI antibody. It was then found that the chimeric antibody was expressed at approximately 10-20 µg/mL. The culture supernatant produced in this experiment was used in the experiment examining inhibitory activity for IL-6 production in Example 1-3(1).

[0258] 1-3) Confirmation Tests of Activities

[0259] (1) Confirmation Test of IL-6 Production Inhibitory Activity

[0260] The following experiments were conducted to examine activity of the antibody functional domains of the antibody fusion proteins prepared in Examples 1-1) and 1-2).

[0261] Cell line U-373 MG from human glioma was inoculated in MEM (SIGMA) containing 2% inactivated FBS in a 96-well plate at 1×10⁴ cells/well, and the cells were incubated overnight at 37° C. and in the presence of 5% CO₂. The following solutions were prepared on the next day.

[0262] 1) Physiological saline (Otsuka Pharmaceutical Co., Ltd.) containing 0.2% human serum albumin (SIGMA) (hereinafter referred to as 0.2% HSA/physiological saline)

[0263] 2) MEM containing 0.2% human serum albumin (SIGMA) (hereinafter referred to as 0.2% HSA/MEM)

[0264] 3) A solution prepared by mixing 0.2% HSA/physiological saline and 0.2% HSA/MEM at a ratio of 1:1 (hereinafter referred to as 0.1% HSA/1/2MEM)

[0265] 4) MEM containing 4% human serum (hereinafter referred to as 4% HS/MEM)

[0266] 5) A solution prepared by diluting LPS (*E. coli* 0111:B4, SIGMA) with physiological saline to 1 mg/mL, sonicating for 10 minutes, and diluting with 0.2% HSA/MEM to 200 ng/mL (hereinafter referred to as 200 ng/mL LPS B4)

[0267] 6) A solution prepared by mixing 4% HS/MEM and 200 ng/mL LPS B4 at a ratio of 9:1 (hereinafter referred to as 2×(HS+LPS))

[0268] The analyte sample was diluted to twice the target concentration with 0.2% HSA/physiological saline to prepare the sample. Culture supernatant of the overnight culture of U-373MG cells was discarded, and the cells were washed twice with 0.1% HSA/1/2MEM. To these cells, 100 µL/well of a mixture of equal amounts of the analyte sample and 2×(HS+LPS) was added, and the cells were incubated in the presence of 5% CO₂ at 37° C. for about 18 hours. Amount of the IL-6 in the culture supernatant was then detected using

human IL-6 detection kit (Eli-PAIR hIL-6; Invitrogen Corporation). FIGS. 18 to 20 show typical test results.

[0269] It was then demonstrated that the antibody activity was maintained in the chimeric antibody fusion proteins in the case of the antibodies exhibiting the CD14 inhibitory activity, whereas the F1031-13-2 antibody exhibiting no CD14 inhibitory activity did not show the inhibitory activity when it was produced in the form of a chimeric antibody fusion protein. In FIG. 20, the results are shown in relation to the IL-6 production (100%) of the control having no sample added (IL-6% Control).

[0270] (2) Confirmation Test of Enzyme Inhibitory Activity

[0271] Trypsin inhibitory activity was measured in order to confirm the activity of the domain having the enzyme inhibitory function of the antibody fusion proteins produced in Examples 1-1) and 1-2).

[0272] The analyte sample was diluted to ten times the target concentration with 0.1 mol/L NaCl/5 mmol/L CaCl₂/20 mmol/L Tris-HCl (pH 7.4) (hereinafter referred to as dilution solution). In the meanwhile, 1 µg/mL of trypsin from human pancreas (Athens Research and Technology) was prepared with 0.1 w/v % BSA/1 mmol/L HCl, and synthetic substrate S2222 (TESTZYM, Daiichi Pure Chemicals Co., Ltd.) was diluted with water to 4 mmol/L.

[0273] After preparation of the reagents, 70 µL of the dilution solution, 10 µL of 1 µg/mL human trypsin solution, and 10 µL of analyte sample solution were placed in 96-well microtiter plate (Nunc), and the solution was incubated at 37° C. for 3 minutes. Next, 10 µL of synthetic substrate S2222 solution was added to the well, and the solution was incubated at 37° C. for another 60 minutes. The reaction was then terminated with 20 v/v % aqueous solution of acetic acid, and absorbance of the reaction solution at 405 nm was measured. FIG. 21 shows the typical results. It was then found that enzyme inhibitory activity was substantially retained in the chimeric antibody fusion protein.

Example 2

Mass Production of Antibody Fusion Protein

[0274] (1) Mass Production of F1024S-D2(3) and F1031-13S-D2 (3)

[0275] In order to conduct the mass production of F1024S-D2(3), transient expression system using COS-1 cell was employed. More specifically, 1700 mL of DMEM containing 10% inactivated FBS and 10 mM HEPES (pH 7.0 to 7.6) was added to CellsTACK-10 Chamber (Corning), and 21×10⁶ COS-1 cells were inoculated in this medium. The interior of the CellsTACK-10 Chamber was replaced with a gas mixture containing 5% CO₂, and after sealing the container, the medium was incubated at 37° C.

[0276] Transfection was conducted 4 days after the inoculation by the following procedure.

[0277] First, 2.12 mL of FuGENE6 transfection reagent (Rosch Diagnostics K.K.) was added to 63.6 mL of DMEM, and stirred. After 5 minutes, 530 µg each of the plasmid pTK2370 coding for the heavy chain and the plasmid pTK2344 coding for the light chain prepared in Example 1 were added, and after stirring, the culture was allowed to stand for 15 minutes at room temperature. In the meanwhile, the medium of the CellsTACK-10 Chamber was replaced with 1300 mL of Hybridoma-SFM (Invitrogen Corporation) containing 10 mM HEPES (pH 7.0-7.6) (hereinafter referred

to as production medium), and the thus prepared mixture of the transfection reagent and the plasmid was added. After incubating at 37° C. for 3 days, the production medium was collected. 1300 mL of new production medium was added to the CellsTACK-10 Chamber, and the production medium was again collected after 4 days.

[0278] Production of F1031-13S-D2(3) was similarly conducted by using the plasmid pF31-13HU coding for the heavy chain and the plasmid F31-13L coding for the light chain prepared in Example 1.

[0279] (2) Assay System (EIA) of F1024S-D2(3) and F1031-13S-D2(3)

[0280] Concentration of the F1024S-D2(3) was measured by sandwich EIA.

[0281] A sandwich EIA system was prepared by using a recombinant human CD14 comprising the full length 356 amino acids of the human CD14 prepared by the procedure similar to that in Example 6 for the immobilized protein, and peroxidase-labeled UTI antibody produced by the procedure described in JP 2002-14104 A for the labeled antibody.

[0282] F1024S-D2(3) prepared in Example 1 was used for the standard. More specifically, recombinant human CD14 was diluted with PBS (pH 7.4) to 4 µg/mL, and 50 µL was added to each well of NUNC-Immuno plate Maxisorp (NUNC). After allowing to react overnight at 4° C., the well was washed three times with 0.05% Tween 20/0.9% sodium chloride solution, and 100 µL of PBS (pH 7.4) containing 2% StabilGuard (SurModics, Inc.) was added to the well for blocking. Next, diluted specimens of the analytes and the standard were prepared by using PBS (pH 7.4) containing 0.1% BSA for the dilution solution. In the meanwhile, peroxidase-labeled UTI antibody diluted with PBS (pH 7.4) containing 10% rabbit serum was prepared. 25 µL of the diluted peroxidase-labeled antibody and 25 µL of the diluted specimen were added to the well, and the reaction was allowed to take place at 37° C. for 1 hour. After the termination of the reaction, the well was washed three times with 0.05% Tween 20/0.9% sodium chloride solution, and 50 µL of tetramethylbenzidine solution (BioFX) was added to each well. After allowing the reaction to take place at room temperature for about 20 minutes, the reaction was terminated by adding 50 µL of 1 mol/L hydrochloric acid solution, and absorbance at 450 nm was measured with a plate spectrophotometer.

[0283] The concentration was measured for F1031-13S-D2(3) in the same manner. In the measurement, F1031-13S-D2(3) having known concentration was used for the standard.

[0284] (3) Mass Purification of F1024S-D2(3)

[0285] Unless otherwise noted, the following procedure was conducted at 4° C.

[0286] The COS culture supernatant produced in Example 2(1) was applied to 1 µm capsule cartridge filter (Advantec Toyo Kaisha, Ltd.) connected to 0.22 µm Fluorodyne II DFLP Filter (Nihon Pall Ltd.) to thereby remove the insoluble content in the culture supernatant. The filtrate was applied to ProSep-vA column (Nihon Millipore K.K.) which had been preliminarily equilibrated with PBS (SIGMA), and the non-adsorbed contents were washed off with PBS. Then, non-specifically adsorbed contents were washed off with 10×PBS (SIGMA) and eluted with 25 mM Glycine-HCl (pH 2.5) to recover F1024S-D2(3). The resulting eluted fraction was adjusted to pH 5 by adding MacIlvaine buffer solution. The precipitate in the eluted fraction was removed by centrifugation, and the supernatant after the centrifugation was passed

through a dialysis tube (SPECTRUM) having a cut-off molecular weight of 10,000 for dialysis against physiological saline. The dialysate was used as the purified standard.

[0287] (4) Mass Purification of F1031-13S-D2(3)

[0288] Unless otherwise noted, the following procedure was conducted at 4° C.

[0289] The COS culture supernatant produced in Example 2(1) was applied to 1 µm capsule cartridge filter (Advantec Toyo Kaisha, Ltd.) connected to 0.22 µm Fluorodyne II DFLP Filter (Nihon Pall Ltd.) to thereby remove the insoluble content in the culture supernatant. The filtrate was applied to ProSep-vA column which had been preliminarily equilibrated with PBS (SIGMA), and the non-adsorbed contents were washed off with PBS. Then, non-specifically adsorbed contents were washed off with 1M sodium chloride solution and eluted with 100 mM Glycine-HCl (pH 2.7) to recover F1031-13S-D2(3). The resulting eluted fraction was neutralized by adding 1M Tris-hydrochloric acid (pH 8.0), and this solution was passed through a dialysis tube (SPECTRUM) having a cut-off molecular weight of 3,500 for dialysis against physiological saline. The dialysate was concentrated using YM10 ultrafiltration membrane (Nihon Millipore K.K.), and the concentrate was used as the purified standard.

Example 3

Evaluation of Efficacy (In Vitro)

[0290] 3-1) Confirmation of Antibody Activity

[0291] (1) Confirmation of Inhibitory Activity for LPS-Induced IL-6 Production in Human Vascular Endothelial Cell

[0292] Endothelial cells of the human umbilical cord vein (HUVEC, Sanko Junyaku Co., Ltd.) separated by PBS(−) containing 0.05% trypsin and 0.02% EDTA were suspended in RPMI 1640 medium (SIGMA) containing 10% of human serum (TENNESSEE BLOOD SERVICE CORPORATION), and inoculated in 96-well plate at 2×10⁴ cells/well. The cells were incubated overnight at 37° C. in the presence of 5% CO₂. After the incubation, LPS (*W. E. coli* 055:B5, DIFCO) was added to a final concentration of 10 ng/mL, and simultaneously, F1024S-D2(3) was added to final concentrations of 0.03, 0.1, 0.3, 1, 3, and 10 µg/mL. After incubating at 37° C. in the presence of 5% CO₂ for 6 hours, the IL-6 in the culture supernatant was measured by using human IL-6 EIA kit (Diacor Research) according to the attached protocol. IC₅₀ value for the inhibition of the IL-6 production by the F1024S-D2(3) was 0.38 µg/mL. This result revealed that F1024S-D2(3) inhibits cytokine production of the human vascular endothelial cell induced by LPS which is a component constituting the Gram-negative bacteria.

[0293] The inhibitory activity of the F1031-13S-D2(3) and F1024D-SLPI(D1D2), F1024D-SLPI(D2), F1024S-SLPI(D1D2), or F1024S-SLPI(D2) is evaluated by using a similar assay system.

[0294] (2) Confirmation of Inhibitory Activity for LPS-Induced Expression of E-Selectin in Human Vascular Endothelial Cell

[0295] Endothelial cells of human umbilical cord vein (HUVEC, Sanko Junyaku Co., Ltd.) were inoculated by the procedure described in Example 3-1)(1), and after incubation, LPS (*W. E. coli* 055:B5, DIFCO) was added to a final concentration of 10 ng/mL simultaneously with the addition of F1024S-D2(3) to final concentrations of 0.03, 0.1, 0.3, 1, 3, and 10 µg/mL. After incubating at 37° C. in the presence of 5% CO₂ for 6 hours, the culture medium was removed, and

the cells were washed twice with PBS(-). After drying with a dryer, 100 μ L/well of PBS(-) containing 2% paraformaldehyde was added. After incubating at room temperature for 20 minutes, the cells were washed three times with PBS(-), and 100 μ L/well of biotinylated anti-human E-Selectin antibody (Cosmo Bio Co., Ltd.) diluted with RPMI 1640 containing 1% human serum was added, and the cells were incubated at room temperature for 60 minutes. The cells were then washed 3 times with PBS(-), and after adding 100 μ L/well of peroxidase-labeled streptavidin solution (Dako Cytomation), the cells were incubated at room temperature for another 30 minutes. After washing, 100 μ L/well of chromogenic substrate (TMB) was added, and the reaction was allowed to proceed at room temperature for 30 minutes, and the reaction was terminated by adding 100 μ L/well of 2N sulfuric acid. Absorbance was measured at wavelengths of 450 nm and 650 nm, Δ OD (450 nm-650 nm) was used for the amount of E-Selectin expressed. IC_{50} value for the inhibition of the E-Selectin expression by the F1024S-D2(3) was 0.43 μ g/mL. This result revealed that LPS-induced expression of the adhesion molecule in the human vascular endothelial cell is inhibited by the F1024S-D2(3).

[0296] The inhibitory activity of the F1031-13S-D2(3) and F1024D-SLPI(D1D2), F1024D-SLPI(D2), F1024S-SLPI(D1D2) or F1024S-SLPI(D2) is evaluated by using a similar assay system.

[0297] (3) Confirmation of Inhibitory Activity for LPS Induced TNF- α Production in Human Peripheral Blood Mononuclear Cell

[0298] Normal human peripheral blood mononuclear cells (hPBMC, BioWhittaker Inc.) were suspended in RPMI 1640 containing 10% human serum and 25 mM HEPES (SIGMA), and inoculated in 96-well plate at 2.5×10^5 cells/well. F1024S-D2(3) was added to final concentrations of 0.1, 0.3, 1, 3, 10, and 30 μ g/mL, and after allowing to stand at room temperature for 20 minutes, LPS (*W. E. coli* 055:B5, DIFCO) was added to a final concentration of 0.1 ng/mL. After incubating at 37° C. in the presence of 5% CO₂ for 6 hours, TNF- α in the culture supernatant was measured using human TNF- α EIA kit (Diacalone Research) according to the protocol attached to the kit.

[0299] IC_{50} value for the inhibition of the TNF- α production by F1024S-D2(3) was 0.58 μ g/mL. This result revealed that LPS-induced cytokine production in the human leukocyte is inhibited by the F1024S-D2(3).

[0300] The inhibitory activity of the F1031-13S-D2(3) and F1024D-SLPI(D1D2), F1024D-SLPI(D2), F1024S-SLPI(D1D2) or F1024S-SLPI(D2) is evaluated by using a similar assay system.

[0301] (4) Confirmation of Inhibitory Activity for Enhancement of LPS-Induced Procoagulant Activity (PCA) in Human Peripheral Blood Mononuclear Cell

[0302] Mononuclear cells of normal human peripheral blood (hPBMC, BioWhittaker Inc.) were inoculated by the procedure described in Example 3-1(3), and F1024S-D2(3) was added to final concentrations of 0.1, 0.3, 1, 3, 10, and 30 μ g/mL, and after allowing the cells to stand at room temperature for 20 minutes, LPS (*W. E. coli* 055:B5, DIFCO) was added to a final concentration of 0.1 ng/mL. After incubating at 37° C. in the presence of 5% CO₂ for 6 hours, PCA of the cell suspension was measured by using normal human plasma (DADE BEHRING INC.). More specifically, after diluting the suspension 2.5 folds with 50 mM Tris-HCl (pH 7.4) solution containing 0.15M NaCl and 0.1% BSA, the cells

were lysed by ultrasonication (SIMAZU) for 20 seconds. This sample was placed in a coagulometer (AMAX CS190, MC Medical, Inc.). 20 μ L of the sample was collected from the coagulometer, and after adding 20 μ L of 25 mM CaCl₂, the sample was incubated at 37° C. for 3 minutes. Coagulation reaction was started by adding 90 μ L of normal human plasma, and coagulation time was measured. The IC_{50} value for the PCA inhibition by F1024S-D2(3) calculated from the coagulation time was 20.86 μ g/mL. This result revealed that F1024S-D2(3) inhibits enhancement of the LPS-induced PCA in human leucocyte.

[0303] The inhibitory activity of the F1031-13S-D2(3) and F1024D-SLPI(D1D2), F1024D-SLPI(D2), F1024S-SLPI(D1D2) or F1024S-SLPI(D2) is evaluated by using a similar assay system.

[0304] (5) Confirmation of Inhibitory Activity for LPS-Induced TNF- α Production in Rabbit Whole Blood

[0305] The blood was collected from auricular artery of male rabbit (New Zealand white, 3.4 kg, Kitayama Labes Co., Ltd.), and after adding 10 unit/mL of heparin (Mochida Pharmaceutical Co., Ltd.) to the collected whole blood, it was transferred to microtubes and F1024S-D2(3) was added to final concentrations of 0.3, 1, 3, 10, and 30 μ g/mL. After incubating at room temperature for 30 minutes, LPS (*W. E. coli* 055:B5, DIFCO) was added to a final concentration of 0.1 ng/mL.

[0306] After incubating at 37° C. for 6 hours, plasma was separated by centrifuging at 4° C. and at 8000 rpm (TOMY) for 10 minutes, and TNF- α in the plasma was measured by sandwich ELISA using anti-rabbit TNF- α antibody. More specifically, 100 μ L of plasma diluted with PBS(-) containing 1% BSA was moved to a plate having 4 μ g/mL of anti-rabbit TNF- α antibody (BD Biosciences) immobilized thereon, and the plate was incubated at room temperature for 2 hours. The well was washed three times with 400 μ L/well of PBS(-) containing 0.05% Tween 20, and 100 μ L/well of biotinylated anti-rabbit TNF- α antibody solution (2 μ g/mL, BD Biosciences) was added. After incubating at room temperature for 1 hour and washing, 100 μ L/well of peroxidase labeled streptavidin solution (Invitrogen Corporation) was added, and the well was incubated at room temperature for 30 minutes. After washing, 100 μ L/well of chromogenic substrate (TMB) was added, and the reaction was allowed to proceed at room temperature for 30 minutes and 100 μ L/well of 2N sulfuric acid was added to terminate the reaction. Absorbance was measured at 450 nm and 650 nm, and amount of the TNF- α produced in the sample was calculated. IC_{50} value for the inhibition of the TNF- α production by F1024S-D2(3) was 0.83 μ g/mL. This result revealed that LPS-induced cytokine production in the rabbit whole blood is inhibited by F1024S-D2(3).

[0307] The inhibitory activity of the F1031-13S-D2(3) and F1024D-SLPI(D1D2), F1024D-SLPI(D2), F1024S-SLPI(D1D2) or F1024S-SLPI(D2) is evaluated by using a similar assay system.

[0308] 3-2) Confirmation of Enzyme Inhibitory Activity

[0309] In order to confirm the activity of enzyme inhibitory functional domains of F1024S-D2(3) and F1024D-D2(3), inhibitory activities for various enzymes were measured as described below. In the assay system, the protein concentration of the analyte sample was measured by using bovine γ globulin (Nippon Bio-Rad Laboratories K.K.) for the standard and using protein assay staining solution (Nippon Bio-Rad Laboratories K.K.), and the molar concentration was

calculated from the deduced molecular weight of the antibody fusion protein. The test results are shown in FIGS. 22 to 25 in which the y axis represents the residual activity of the enzyme, and the x axis represents protein concentration of the analyte sample in the reaction solution.

[0310] (1) Inhibitory Activity for Factor Xa

[0311] F1024S-D2(3) and F1024D-D2(3) were serially diluted with a dilution solution prepared by mixing 0.14M sodium chloride/5 mM calcium chloride/20 mM Tris-hydrochloric acid buffer solution (pH 7.4) and 10% BSA at a ratio of 99:1 (this solution being hereinafter referred to as the dilution solution) to prepare the samples for measuring inhibitory activity. In the meanwhile, Human Factor Xa (Enzyme Research Laboratories Ltd.) was diluted with the dilution solution to 0.1 U/mL, and this solution was used as the Factor Xa solution. Synthetic substrate S-2222 (Daiichi Pure Chemicals Co., Ltd.) was also diluted with the dilution solution to 2 mM, and this solution was used as the S-2222 solution. After the preparation of the reagents, 10 μ L of sample for measuring the inhibitory activity, 50 μ L of the dilution solution, and 20 μ L of the Factor Xa solution were placed in the wells of 96-well microtiter plate (Nunc). After incubating at 37° C. for 5 minutes, the S-2222 solution was added in 20 μ L/well, and incubation at 37° C. was continued for another 30 minutes. The reaction was then terminated by adding 50 μ L of 20% solution of acetic acid to each well, and absorbance at a wavelength of 405 nm was measured.

[0312] The control was prepared by mixing 20 μ L of the Factor Xa solution with 60 μ L of the diluting solution, incubating the mixture at 37° C. for 5 minutes, adding 20 μ L of the S-2222 solution, incubating the mixture at 37° C. for 30 minutes, and adding 50 μ L of the 20% solution of acetic acid. The results shown in FIG. 22 confirmed retention of the FXa inhibitory activity.

[0313] Inhibitory activity of F1031-13S-D2(3) is evaluated by using a similar assay system.

[0314] (2) Inhibitory Activity for Factor XIa

[0315] F1024S-D2(3) and F1024D-D2(3) were serially diluted with the dilution solution (as described above) to prepare the samples for measuring inhibitory activity. In the meanwhile, Human Factor XIa (American Diagnostica Inc.) was diluted with the dilution solution to 750 ng/mL, and this solution was used as the Factor XIa solution. Synthetic substrate S-2366 (Daiichi Pure Chemicals Co., Ltd.) was also diluted with water to 5 mM, and this solution was used as the S-2366 solution.

[0316] After the preparation of the reagents, 10 μ L of the sample for inhibitory activity measurement, 60 μ L of the dilution solution, and 10 μ L of the Factor XIa solution were placed in the wells of 96-well microtiter plate (Nunc). After incubating at 37° C. for 5 minutes, 20 μ L of the S-2366 solution was added to the well, and incubation at 37° C. was continued for another 30 minutes. Next, the reaction was terminated by adding 100 μ L of 20% acetic acid solution to the well, and the reaction solution was measured for absorbance at a wavelength of 405 nm.

[0317] The control used was the one prepared by mixing 70 μ L of the dilution solution with 10 μ L of the Factor XIa solution, incubating the mixture at 37° C. for 5 minutes, adding 20 μ L of the S-2366 solution to the mixture, incubating at 37° C. for 30 minutes, and adding 100 μ L of 20% acetic acid solution.

[0318] The results shown in FIG. 23 reveal FXIa inhibitory activity of D2(3).

[0319] Inhibitory activity of F1031-13S-D2(3) is evaluated by using a similar assay system.

[0320] (3) Inhibitory Activity for Elastase

[0321] F1024S-D2(3) and F1024D-D2(3) were serially diluted with the dilution solution (as described above) to prepare the samples for measuring inhibitory activity. In the meanwhile, Elastase, Human Neutrophil (Athens Research & Technology) which has been dissolved in 500 mM sodium chloride/50 mM sodium acetate (pH 5.5) and cryopreserved was diluted with the dilution solution to 20 μ g/mL, and this solution was used as the elastase solution. Synthetic substrate S-2484 (Daiichi Pure Chemicals Co., Ltd.) was diluted with dimethylsulfoxide and stored at a low temperature, and diluted with water to 2 mM immediately before use as the S-2484 solution.

[0322] After the preparation of the reagents, 10 μ L of the sample for inhibitory activity measurement, 70 μ L of the dilution solution, and 10 μ L of the elastase solution were placed in the wells of 96-well microtiter plate (Nunc). After incubating at 37° C. for 3 minutes, 10 μ L of the S-2484 solution was added to the well, and incubation at 37° C. was continued for exactly 10 minutes. Next, the reaction was terminated by adding 50 μ L of 20% acetic acid solution to the well, and the reaction solution was measured for absorbance at a wavelength of 405 nm.

[0323] The control was prepared by mixing 10 μ L of the elastase solution with 80 μ L of the diluting solution, incubating the mixture at 37° C. for 3 minutes, adding 10 μ L of the S-2484 solution, incubating at 37° C. for exactly 10 minutes, and adding 50 μ L of 20% solution of acetic acid. The results shown in FIG. 24 confirmed retention of the elastase inhibitory activity.

[0324] Inhibitory activity of fusion proteins F1031-13S-D2(3) and F1024D-SLPI(D1D2), F1024D-SLPI(D2), F1024S-SLPI(D1D2), or F1024S-SLPI(D2) is evaluated by using a similar assay system.

[0325] (4) Plasma Kallikrein

[0326] F1024S-D2(3) and F1024D-D2(3) were serially diluted with the dilution solution (as described above) to prepare the samples for measuring inhibitory activity. In the meanwhile, Kallikrein from human plasma (Sigma-Aldrich Co.) was diluted with the dilution solution to 20 mU/mL, and this solution was used as the plasma kallikrein solution. Synthetic substrate S-2302 (Daiichi Pure Chemicals Co., Ltd.) was also diluted with water to 4 mM, and this solution was used as the S-2302 solution.

[0327] After the preparation of the reagents, 10 μ L of the sample for inhibitory activity measurement, 70 μ L of the dilution solution, and 10 μ L of the plasma kallikrein solution were placed in the wells of 96-well microtiter plate (Nunc). After incubating at 37° C. for 3 minutes, 10 μ L of the S-2302 solution was added to the well, and incubation at 37° C. was continued for another 30 minutes. Next, the reaction was terminated by adding 50 μ L of 20% acetic acid solution to the well, and the reaction solution was measured for absorbance at a wavelength of 405 nm.

[0328] The control was prepared by mixing 10 μ L of the plasma kallikrein solution with 80 μ L of the diluting solution, incubating at 37° C. for 3 minutes, adding 10 μ L of the S-2302 solution, incubating at 37° C. for 30 minutes, and adding 50 μ L of 20% solution of acetic acid. The results are shown in FIG. 25.

[0329] Inhibitory activity of F1031-13S-D2(3) is evaluated by using a similar assay system.

[0330] 3-3) Confirmation of Inhibitory Action for coagulation

[0331] (1) Confirmation of Extension of Activated Partial Thromboplastin Time (APTT) in Human and Rabbit

[0332] The normal human plasma used was Dade Ci-Trol Level 1 (DADE BEHRING INC.). The rabbit plasma was obtained by collecting blood from auricular artery of male rabbit (New Zealand white, 2.6 to 2.7 kg, Kitayama Labes Co., Ltd.) using a syringe containing $\frac{1}{10}$ volume of 3.8% sodium citrate (sodium citrate for measuring erythrocyte sedimentation rate, Iwaki Seiyaku Co., Ltd.), and centrifuging at 4° C. and at 3000 rpm (05PR-22, Hitachi) for 10 minutes.

[0333] To 113 μ L of human or rabbit plasma, 20 μ L of F1024S-D2(3) solution was added to final concentrations of 0, 1.56, 3.13, 6.25, 12.5, 25, 50, and 100 μ g/mL, and the plasma was placed in a coagulometer (AMAX CS190, MC Medical, Inc.). 50 μ L was collected from the coagulometer, and after addition of 50 μ L of APTT measurement reagent (DADE BEHRING INC.) and 2 minute incubation, 50 μ L of 25 mM CaCl_2 was added to measure the coagulation time. It was then found that F1024S-D2(3) extends the human and rabbit APTT in a concentration dependent manner, and extension of the human and rabbit APTT of 1.5 folds was attained at a concentration of 9.06 μ g/mL and 40.96 μ g/mL, respectively.

[0334] F1031-13S-D2(3) is evaluated for extension of APTT by using a similar assay system.

Example 4

Evaluation of In Vivo Effectiveness

[0335] 4-1) Effect of the Fusion Protein on Improving Survival Rate of LPS-Induced Rabbit Sepsis Model

[0336] LPS-induced rabbit sepsis fatal model was prepared, and improvement in the survival rate by post-administration of the fusion protein was examined.

[0337] The LPS-induced rabbit sepsis model was prepared according to the method of Schimke et al. (Proc. Natl. Acad. Sci. USA, 95: 13875, 1998) by administering LPS (Salmonella Minnesota Re595, SIGMA) to auricular vein of a rabbit (New Zealand white, 1.8 to 2.6 kg, Kitayama Labes Co., Ltd.) at a dose of 15 μ g/kg at 0, 5, and 24 hours. F1024S-D2(3) was administered to the auricular vein at a dose of 1 mg/kg at 2, 8, and 23 hours. Control group was administered with human immunoglobulin instead of the fusion protein. The survival was monitored until 48 hours after the administration, and Kaplan-Meier survival curve was depicted. It was then found that administration of F1024S-D2(3) improves the survival rate compared to the control group.

[0338] In the same assay system, administration of F1024D-SLPI(D1D2), F1024D-SLPI(D2), F1024S-SLPI(D1D2), and F1024S-SLPI(D2) also had the action of improving the survival rate.

[0339] 4-2) Effect of the Fusion Protein on Improving Inflammation and Coagulation Parameters of LPS-Induced Rabbit Sepsis Model

[0340] LPS-induced rabbit sepsis model was prepared, and the effect on inflammation and coagulation parameters by the post-administration of the fusion protein was examined.

[0341] The LPS-induced rabbit sepsis model was prepared according to the method of Schimke et al. (Proc. Natl. Acad. Sci. USA, 95: 13875, 1998) by administering LPS (Salmonella Minnesota Re595, SIGMA) to auricular vein of a rabbit

(New Zealand white, 1.8 to 2.6 kg, Kitayama Labes Co., Ltd.) at a dose of 10 μ g/kg at 0, 5, and 24 hours. F1024S-D2(3) was administered to the auricular vein at a dose of 0.3, 1, and 3 mg/kg at 2, 8, and 23 hours. Control group was administered with 3 mg/kg of human immunoglobulin instead of the fusion protein.

[0342] Blood was collected (with addition of citric acid) from auricular artery before the LPS administration and at 1.5, 25, 26, 28 hours post administration to measure the inflammatory parameters and the coagulation parameters.

[0343] The inflammatory parameters used were leukocyte count and plasma TNF concentration, and the coagulation parameter used were platelet count and plasma antithrombin III activity.

[0344] The leukocyte count was measured by Sysmex F-820 (Sysmex Corporation). The TNF- α concentration was measured by sandwich ELISA using Purified Goat Anti-rabbit TNF Polyclonal Antibody (BD Biosciences) and Biotinylated Mouse Anti-rabbit TNF- α Monoclonal Antibody (BD Biosciences).

[0345] The antithrombin III activity was measured by TESTZYM ATIII 2 kit (Daiichi Pure Chemicals Co., Ltd.).

[0346] The TNF- α concentration in plasma was evaluated "positive" when the concentration measured was equal to or higher than 0.4 ng/mL which is the detection limit of the sandwich ELISA, and "negative" when the measured value was less than 0.4 ng/mL. It was then found that the group administered with F1024S-D2(3) showed dose dependent improvement of the decrease of the leukocyte count (FIG. 27), increase of the TNF- α concentration in the plasma (Table 4), decrease of the platelet count (FIG. 28), and decrease of the antithrombin III activity (FIG. 29) compared to the control group. These results demonstrated improvement of the inflammation and coagulation parameters by the F1024S-D2(3).

[0347] In the same assay system, the group administered with the F1031-13S-D2(3) shows the effects of improving the decrease of the leukocyte count, increase of the TNF- α concentration in the plasma, decrease of the platelet count, and decrease of the antithrombin III activity compared to the control group.

TABLE 4

TNF- α concentration in plasma at 25 hours after the initial administration of LPS in LPS-induced rabbit sepsis model	
Dose of F1024S-D2 (3) (mg/kg)	Positive rate
Control group	4/6
0.3	3/6
1	1/6
3	0/6

[0348] 4-3) Effect of the Fusion Protein on Improving Decrease in Blood Pressure of LPS-Induced Rabbit Sepsis Model

[0349] LPS-induced rabbit sepsis model was prepared, and the effect of improving the decrease in blood pressure by the post-administration of the fusion protein was examined.

[0350] The LPS-induced rabbit sepsis model was prepared according to the method of Schimke et al. (Proc. Natl. Acad. Sci. USA, 95: 13875, 1998) by administering LPS (Salmonella Minnesota Re595, SIGMA) to auricular vein of a rabbit (New Zealand white, 1.8 to 2.6 kg, Kitayama Labes Co., Ltd.)

at a dose of 5 $\mu\text{g/kg}$ at 0 and 5 hours. F1024S-D2(3) was administered to the auricular vein at a dose of 1 mg/kg at 2 hours after the initial administration of the LPS. Control group was administered with 1 mg/kg of human immunoglobulin instead of the fusion protein.

[0351] Before the LPS administration and at 4, 6, and 8 hours post administration, a catheter inserted in the carotid artery was connected to a blood pressure transducer (DT-XX, Japan BD Medical Systems) to measure the average arterial blood pressure. It was then found that the group administered with F1024S-D2(3) showed improvement in the decrease of the blood pressure compared to the control group (FIG. 30).

[0352] In the same assay system, the group administered with the F1031-13S-D2(3) shows the effects of improving the decrease in the blood pressure compared to the control group.

Example 5

Establishment of Strain Stably Producing Antibody Fusion Protein

[0353] 5-1) Construction of Plasmid Expressing Strain Producing F1024S-D2(3) or F1024D-D2(3)

[0354] The expression plasmid used in establishing the strain which is capable of stably producing the F1024S-D2(3) or the F1024D-D2(3) was constructed by the procedure as described below.

[0355] The plasmid pTK-2370 expressing the heavy chain of F1024S-D2(3) and the plasmid pTK-2368 expressing the heavy chain of F1024D-D2(3) constructed in Example 1 were respectively digested with EcoRI and KpnI to recover the fragment of about 1.7 kb. The expression plasmid pM1103 having mouse DHFR expression unit and EF1 α promoter (see WO97/42319) was also digested with EcoRI and KpnI to recover the fragment having about 7.9 kb. The fragment obtained by digesting the plasmid expressing heavy chain and the fragment obtained by digesting pM1103 were ligated, and plasmid pEFD2370 expressing the heavy chain of F1024S-D2(3) and plasmid pEFD2368 expressing the heavy chain of F1024D-D2(3) for producing the production strain were produced by transforming JM109 competent cell by the method commonly used in the art. In the meanwhile, the light chain expression plasmid is common to F1024S-D2(3) and F1024D-D2(3), and this plasmid was constructed by the following procedure. Plasmid pTK-2344 for transient expression was digested by BamHI, and blunt-ended, and further digested with EcoRI to recover the fragment of 0.7 kb. pM1103 was digested with KpnI, and after blunt ending, it was digested with EcoRI to recover the fragment of about 7.9 kb. The fragment obtained by digesting pTK-2344 and the fragment obtained by digesting pM1103 were ligated, and plasmid pEFD2344 expressing the light chain for producing the production strain was produced by transforming JM109 competent cell by the method commonly used in the art.

[0356] 5-2) Establishment of Transformant Strain Producing F1024S-D2(3) and F1024D-D2(3)

[0357] The plasmids expressing the heavy chain and the light chain constructed in Example 5-1) were co-transfected in DHFR gene-deleted CHO cell to establish the CHO transformant producing the chimeric antibody fusion protein. More specifically, CHO DXB11 derived from the conditioned medium of EX-CELL 325 PF CHO (JRH Bioscience) containing HT media Supplement (50 $\times$) Hybri-Max (SIGMA, used at a final concentration of 1 $\times$) and 200 mM L-Glutamine (SIGMA, used at a final concentration of 4 mM)

was centrifuged on the day of the transfection, and inoculated in a flask at a concentration of 8×10^6 cells/150 Roux. 12.5 μg of the plasmid expressing the heavy chain and 12.5 of the plasmid expressing the light chain (namely, pEFD2370+pEFD2344, or pEFD2368+pEFD2344) were prepared according to the protocol attached to FuGENE6 by using 125 μL of FuGENE6 (Roche Diagnostics K.K.), and they were co-transfected in the CHO DXB11 as described above. After incubating at 37 $^\circ\text{C}$. in the presence of 5% CO_2 for 2 days, the cells were collected, and the cells were washed once with HT-free EX-CELL 325 PF CHO medium containing 4 mM L-Glutamine (hereinafter referred to as EX-CELL(HT-)), and then once with PBS-, and suspended again in EX-CELL(HT-). Next, the cells were newly inoculated in a 96-well plate at 3,000 to 48,000 cells/well, the cells were incubated at 37 $^\circ\text{C}$. in the presence of 5% CO_2 , and half of the medium was replaced with a new EX-CELL(HT-) at intervals of 3 days or 4 days. After incubating for about 1 month, the cells of the well in which the colony had formed were transferred to a new plate, and amount of the chimeric antibody in the culture supernatant was measured by the EIA procedure described in Example 2. The cell for which expression of the chimeric antibody in the supernatant had been confirmed was obtained as the transformant strain producing the chimeric antibody fusion protein.

[0358] 5-3) Gene Amplification Using Methotrexate

[0359] Gene amplification was conducted by selectively cultivating the CHO transformant strain expressing the chimeric antibody fusion protein produced in Example 5-2) on EX-CELL(HT-) medium containing methotrexate (hereinafter referred to as MTX) to select the clone producing the chimeric antibody fusion protein of interest at a high yield.

[0360] (1) Establishment of CHO-F1024SC93t3L1

[0361] The transformant strain producing F1024S-D2(3) produced in the above 5-2) was suspended in EX-CELL(HT-) medium containing 100 nM MTX, and inoculated in 96-well plate, and half of the medium was changed with a fresh EX-CELL(HT-) containing 100 nM MTX in every 3 or 4 days. Incubation was continued at 37 $^\circ\text{C}$. in the presence of 5% CO_2 until colonies were formed. The resulting colonies were evaluated by EIA for their expression, and the increasingly produced clones were selected. The selected clones were subsequently suspended in EX-CELL(HT-) medium containing 300 nM MTX, and inoculated in 96-well plate for selective cultivation. A process similar to the selective cultivation using 100 nM MTX was conducted to thereby obtain a transformant strain having an about 20 times higher production rate. Clones having even higher production rate can also be obtained by repeating the process of selective cultivation by using cultures having 3 to 10 times higher MTX concentration.

[0362] (2) Establishment of CHO-F1024DC78u1

[0363] The transformant strain producing the F1024D-D2(3) produced in the above 5-2) was treated by the procedure similar to that of Example 5-2) to produce a strain with high production rate. The selective cultivation using MTX was conducted first at the MTX concentration of 100 nM, and then at the concentration of 1000 nM to thereby obtain a clone which produces the F1024D-D2(3) at about 60 $\mu\text{g/mL}$ as measured by EIA.

Example 6

Analysis of Sequence Required for Binding to F1024 Antibody

[0364] 6-1) Construction of Plasmid Expressing Amino Acid-Substituted Soluble Human CD14

[0365] In order to analyze the region recognized by the F1024 antibody, 31 types of amino acid-substituted soluble human CD14 shown in Table 5 were prepared. It is to be noted that the 1 amino acid-substituted CD14 having the 263rd Asn calculated from N terminal of the soluble CD14 molecule substituted with Gln is designated "N263Q", and other 1 amino acid-substituted CD4 were designated in the same manner. In the meanwhile, the 2 amino acid-substituted CD14 having both the 294th Pro and the 296th Pro substituted with Ala is designated "P294/296A". The plasmid expressing these substituted CD14 was constructed by the procedure as described below.

[0366] First, the plasmids expressing the modified sCD14 (1-307) with amino acid substitution(s) were constructed by the method similar to that in the construction of the plasmid expressing the amino acid-substituted polypeptide described in WO02/42333 or US2004/0092712. For example, the plasmid expressing the modified sCD14(1-307) having the amino acid substitution P294H, P294/296A, Q295A, or P296H introduced therein was constructed by designing the primer set which was shown in Table 6 and coded for the amino acid substitution sequence, and using the primer set for the PCR. The codon coding for the amino acid-substituted part is shown in bold (underline) (Table 6).

[0367] Next, a DNA fragment having introduced therein an amino acid substitution (codon substitution) was produced by using recombinant PCR to construct a plasmid expressing soluble human amino acid-substituted CD14. More specifically, P294H, P294/296A, Q295A and P296H expression plasmids were constructed by the procedure as described below. Sense primer S1 (5'-GCG GCA GTA TGC TGA CAC GG-3'), SEQ ID NO: 209, sense primer S2 (5'-GAT AAC CTG ACA CTG GAC GGG AAT CCC TTC-3'), SEQ ID NO: 210, and sense primer S3 (5'-GCC ATC CAG AAT CTA GCG CT-3'); SEQ ID NO: 211, and antisense primer A1 (5'-GAA GGG ATT CCC GTC CAG TGT CAG GTT ATC-3'), SEQ ID NO: 212, antisense primer A2 (5'-ATT AGC CAG AAG TCA GAT GCT C-3'), SEQ ID NO: 213, and antisense primer A3 (5'-GGG CAT TGG CCA CAC CAG C-3'), SEQ ID NO: 214, were synthesized. PCR was conducted by using each of the above-mentioned plasmids expressing the amino acid-substituted modified sCD14(1-307) for the template and using sense primers S1 and A1. The amplification product was separated and purified by electrophoresis (PCR product A). PCR was also conducted by using pCAG356 for the template, and using sense primers S2 and A2, and the amplification product was separated and purified by electrophoresis (PCR product B). PCR was also conducted by using the mixture of PCR product A and PCR product B for the template and using sense primers S3 and A3, the PCR product was separated and purified by electrophoresis (PCR product C). Next, PCR product C was digested with PvuII and KpnI, and the fragment of about 0.2 kb was separated by electrophoresis and collected. In the meanwhile, pCAG356 was similarly digested with PvuII and KpnI, and the fragment of about 5.8 kb was collected by electrophoresis, and this fragment was ligated to the fragment of about 0.2 kb as described above. *E. coli* XL1-Blue (STRATGENE) was transformed by the

method commonly used in the art to produce the desired expression plasmid. It is to be noted that pCAG356 is a plasmid produced by inserting CD14 gene (having a mutation introduced at the GPI anchoring site) derived from sCD14 expression plasmid pM1656 described in WO02/42333 in pCAGGS (GENE, Vol. 15 (1989) pp. 269-277).

TABLE 5

Table 5: Amino acid-substituted soluble human CD4

Substituted human CD4	Substitution	
	Amino acid	Nucleotide (codon)
N263Q	263rd Asn → Gln	AAT → CAG
L269A	269th Leu → Ala	CTG → GCT
L276A	276th Leu → Ala	CTG → GCT
K279A	279th Lys → Ala	AAG → GCT
L280A	280th Leu → Ala	CTC → GCT
V282A	282nd Val → Ala	GTG → GCT
L283A	283rd Leu → Ala	CTC → GCT
D284A	284th Asp → Ala	GAT → GCT
L285A	285th Leu → Ala	CTC → GCT
S286C	286th Ser → Cys	AGC → TGT
C287A	287th Cys → Ala	TGC → GCT
N288A	288th Asn → Ala	AAC → GCT
R289A	289th Arg → Ala	AGA → GCT
L290A	290th Leu → Ala	CTG → GCT
N291A	291st Asn → Ala	AAC → GCT
R292A	292nd Arg → Ala	AGG → GCT
A293S	293rd Ala → Ser	GCG → AGC
P294H	294th Pro → His	CCG → CAC
P294/296A	294th and 296th Pro → Ala	CCG, CCT → GCG, GCT
Q295A	295th Gln → Ala	CAG → GCT
P296H	296th Pro → His	CCT → CAC
D297A	297th Asp → Ala	GAC → GCT
E298A	298th Glu → Ala	GAG → GCT
L299A	299th Leu → Ala	CTG → GCT
P300H	300th Pro → His	CCC → CAC
E301A	301st Glu → Ala	GAG → GCT
V302A	302nd Val → Ala	GTG → GCT
D303A	303rd Asp → Ala	GAT → GCT
N304A	304th Asn → Ala	AAC → GCT

TABLE 5-continued

Table 5: Amino acid-substituted soluble human CD4		
Substituted	Substitution	
human CD4	Amino acid	Nucleotide (codon)
L305A	305th Leu → Ala	CTG → GCT
L307A	307th Leu → Ala	CTG → GCT

TABLE 6

Table 6: Primer sequence				
Pro-duct		Primer	Sequence	SEQ ID
P294H	Sense	P294H-S1	5'-AGA CTG AAC AGG GCG CAC CAG CCT GAC GAG-3'	179
	Anti-sense	P294H-A1	5'-CAG CTC GTC AGG CTG GTG CGC CCT GTT CAG-3'	180
P294/ 296A	Sense	H1043Sdmt	5'-C AGG GCG GCG CAG GCT GAC GA-3'	181
	Anti-sense	H1043Admt	5'-TC GTC AGC CTG CGC CGC CCT G-3'	182
Q295A	Sense	Q295A-S1	5'-AGG GCG CCG GCT CCT GAC GAG CTG CCC GAG-3'	183
	Anti-sense	Q295A-A1	5'-CTC GTC AGG AGC CGG CGC CCT GTT CAG TCT-3'	184
P296H	Sense	P296H-S1	5'-AAC AGG GCG CCG CAG CAC GAC GAG CTG CCC-3'	185
	Anti-sense	P296H-A1	5'-CTC GGG CAG CTC GTC GTG CTG CGG CGC CCT-3'	186

[0368] 6-2) Expression of Amino Acid-Substituted Soluble Human CD14

[0369] The expression plasmid prepared in the above 7-1) was introduced in the COS-1 cell by the procedure as described below. 50 μ L of FuGENE6 (Roche Diagnostics K.K.) was mixed with 12.5 μ g of each plasmid DNA according to the attached protocol, and the mixture was added to the COS-1 cell grown to semiconfluency in 150 cm^2 flask. The cell was incubated for 3 to 4 days at 37° C. in the presence of 5% CO_2 for expression of the human amino acid-substituted CD14 in the supernatant. The expression was confirmed by EIA using the CD14 antibody described in WO02/42333. The expression was then confirmed for all of substitution products described in Table 5 except N263Q, L276A, L283A, N288A, and L290A.

[0370] 6-3) Purification of Amino Acid-Substituted Soluble Human CD14

[0371] The soluble human amino acid-substituted CD14 was purified by the procedure as described below. The culture supernatant produced in the above 6-2) was passed through an affinity purification column (NHS-activated Sepharose4 Fast Flow; Amersham Biosciences) having anti-human CD14 antibody (3C10) immobilized for selective adsorption, and the column was eluted with 10 mM HCl. The eluted fraction was immediately neutralized by adding 10 $\times$ PBS⁻ (SIGMA)

to a concentration twice higher than the final concentration. The solution was subsequently dialyzed against physiological saline, and the dialysate was used as the purified specimen.

[0372] 6-4) Competitive Experiment for F1024 Antibody

[0373] A competitive experiment was conducted by the following procedure to confirm the reactivity of each soluble human amino acid-substituted CD14 with the F1024 antibody. First, soluble CD14 molecule (356(CHO)); production method is described below in 6-5)) was diluted with PBS⁻ to 4 μ g/mL, and placed in 96-well plate (F8 MaxiSorp; NUNC) at 50 μ L/well. After allowing to stand overnight at 4° C. and washing 3 times with the PBS containing 0.05% Tween 20, 200 μ L/well of PBS⁻ containing 2% StabilGuard (SurModics, Inc.) was added to the well, and the solution was incubated at 37° C. for 30 minutes and stored at 4° C. In the meanwhile, amino acid-substituted soluble human CD14 that had been purified in Example 6-3) was diluted to 2 to 0.02 μ g/mL with PBS⁻ containing 0.1% BSA. HRP-labeled F1024 antibody was diluted to 2 μ g/mL with PBS⁻ containing 0.1% BSA, and the diluted HRP-labeled F1024 antibody was mixed with an equal amount of the human amino acid-substituted CD14 (25 μ L+25 μ L). Next, the solution was discarded from the wells of the plate having the soluble CD14 immobilized, and 50 μ L/well of a mixed solution of amino acid-substituted CD14 and HRP-labeled F1024 was added. After the incubation at 37° C. for 2 hours, the plate was washed 5 times with PBS⁻ containing 0.05% Tween 20, and 50 μ L/well of TMB solution (BioFX) was added to the well as the chromogenic substrate. The reaction was allowed to proceed at room temperature for 5 minutes, the reaction was terminated by adding 50 μ L/well of 1M hydrochloric acid solution. Absorbance at 450 nm was measured with a plate spectrophotometer.

[0374] The results are shown in FIG. 31 in relation to the absorbance without the addition of the amino acid-substituted CD-14 (100%). In FIG. 31, 356(CHO) shows the absorbance when the soluble CD14 molecule used for the immobilization was added.

[0375] The absorbance decreased in many cases of the amino acid-substituted CD14 in a manner dependent on the concentration, and this confirmed their binding with the F1024 antibody in a manner competitive with the 356(CHO). However, in the cases of P294H, P294/296A, Q295A, and P296H, decrease in the absorbance was not confirmed irrespective of their concentration, and it was determined that binding to the F1024 antibody had not occurred (FIG. 31). These results demonstrated that 294th, 295th, and 296th Pro, Gln, and Pro in the CD14 are the regions critical in the binding to the F1024 antibody.

[0376] 6-5) Preparation of Soluble Human CD14 Molecule (356(CHO))

[0377] Soluble human CD14 molecule (356(CHO)) was prepared by using CHO cell by the procedure as described below.

[0378] (1) Construction of Expression Plasmid

[0379] pM1656 described in WO02/42333 was digested with HindIII, and the fragment was blunt-ended with DNA Blunting Kit (TAKARA BIO INC.). It was digested with XbaI, and the fragment of about 1.4 kb was separated by electrophoresis and recovered. The expression plasmid pM1103 having mouse DHFR expression unit and EF1 α promoter was digested with NotI, and the fragment was blunt-ended with DNA Blunting Kit (TAKARA BIO INC.). This

fragment was subsequently digested with XbaI, and the fragment of about 8.0 kb was separated by electrophoresis and recovered. The fragment of about 1.4 kb from pM1656 was inserted for ligation in the fragment of about 8.0 kb, and the fragment was then used in transforming *E. coli* JM109 to thereby produce a plasmid expressing 356(CHO).

[0380] (2) Establishment of 356(CHO) Expressing Transformant Strain

[0381] This expression plasmid was introduced in DHFR gene-deleted CHO cell to establish the transformant strain expressing the 356(CHO). More specifically, 50 μ L of FuGENE6 (Roche Diagnostics K.K.) was mixed with 12.5 μ g of plasmid DNA according to the protocol attached to the FuGENE6, and the mixture was added to CHO DXB11 cell that had been grown by using Ham's F-12 medium (Invitrogen Corporation) containing 10% inactivated FBS to semi-confluency in 150 cm² flask. After incubating overnight at 37° C. in the presence of 5% CO₂, the cells were separated and recovered on the next day by using trypsin, and the cells were re-inoculated in the 96-well plate by using α -MEM containing 10% inactivated dialyzed FBS (not containing ribonucleoside or deoxyribonucleoside) (Invitrogen Corporation) (hereinafter referred to as selective medium). The incubation was continued at 37° C. in the presence of 5% CO₂, and half of the medium was replaced in every 3 or 4 days with a fresh selective medium. After continuing the incubation for 3 to 4 weeks, the cells in the well where colony development was observed was transferred to a new plate, and the amount of the soluble CD14 produced in the culture supernatant was assayed by EIA which used CD14 antibody described in WO02/42333. Clone No. P3 exhibiting high amount of expression was established as the soluble CD14-expressing strain.

[0382] (3) Gene Amplification Using Methotrexate (MTX)

[0383] In order to enhance expression of 356(CHO), selective cultivation of P3 clone was conducted in a selective medium containing MTX to thereby increase its production amount by gene amplification. More specifically, P3 clone produced in Example 6-5)(2) was suspended in the selective medium containing 15 nM MTX, and the cells were inoculated in 10 cm culture dish. Half of the medium was replaced in every 3 or 4 days with a fresh selective medium containing 15 nM MTX, and the incubation was continued at 37° C. in the presence of 5% CO₂ until colony formation was observed. The resulting colony was subcultured in the plate and the amount of 356(CHO) in the supernatant was confirmed by EIA to obtain clone P3-54 with an increase amount of expression.

[0384] (4) Production and Purification of 356(CHO)

[0385] The P3-54 clone produced in the above 6-5)(3) was incubated in a selective medium, and the 356(CHO) expressed in the supernatant was purified by repeating the procedure of Example 6-3).

Example 7

Modification of UTI Domain 2 of Antibody Fusion Protein (F1024S-D2)

[0386] 7-1) Preparation of Modified Forms of UTI Domain 2 of F1024S-D2

[0387] For example, in the case of replacing 15th arginine in UTI domain with alanine (indicated as R15A), primers

coding for about 10 amino acids at and near the part to which the mutation is to be introduced were designed and synthesized.

TABLE 7

Primer Name	Base Sequence	SEQ ID
Sense D2-R15A-s	5' GGC CCC TGC GCA GCC TTC ATC 187 CAG CTC 3'	
Anti- D2-R15A-a sense	5' GAT GAA GGC TGC GCA GGG GCC 188 CCG GAC 3'	

[0388] Next, PCR was conducted again by using pTK-2355 for the template and using each of the primer pairs [IgG4-w and D2-R15A-s] and [pEF2ce-27 and D2-R15A-a]. The resulting amplification products were mixed and again subjected to PCR using primer pair [IgG4-w and pEF2ce-27] (Table 8).

[0389] The amplification product was cleaved with restriction enzymes BamHI and NotI, and subjected to agarose gel electrophoresis. After extracting the fragments, they were ligated by T4 DNA ligase to the vector part of the pTK-2355 which had been similarly cleaved with the BamHI and NotI to thereby construct plasmid (pTK-2730) which was capable of expressing the heavy chain of modified F1024S-D2 having the R15A mutation introduced therein. This plasmid was cotransfected in COS-1 cell with the light chain expression plasmid (pTK-2344) for expression of modified F1024S-D2 (R15A) in the culture supernatant. After confirming the expression in the culture supernatant, the expressed product was purified by Prosep-A column.

[0390] By using a similar procedure, 80 modified forms of UTI domain 2 of the F1024S-D2 shown in Table 9 were prepared, and they were confirmed to retain their ability to bind to CD14 antigen. The amino acid sequences of the modified UTI domain 2 shown in Table 9 are shown in FIGS. 32 to 35.

TABLE 8

Primer Name	Base Sequence	SEQ ID
IgG4-w	5' AATGTCTTCTCATGCTCCGTG 3'	189
pEF2ce-27	5' CATCAATGTATCTTATCATCTCT 3'	190

TABLE 9

Modified UTI domain 2 of F1024S-D2	FIG. ID	SEQ ID
pTK-2730 (R15A)	32	27
pTK-2731 (R15C)	32	28
pTK-2732 (R15D)	32	29
pTK-2733 (R15E)	32	30
pTK-2734 (R15F)	32	31
pTK-2735 (R15G)	32	32
pTK-2736 (R15H)	32	33
pTK-2737 (R15I)	32	34
pTK-2738 (R15K)	32	35
pTK-2739 (R15L)	32	36
pTK-2740 (R15M)	32	37
pTK-2741 (R15N)	32	38
pTK-2742 (R15P)	32	39
pTK-2743 (R15Q)	32	40
pTK-2744 (R15S)	32	41

TABLE 9-continued

Modified UTI domain 2 of F1024S-D2	FIG. ID	SEQ ID
pTK-2745 (R15T)	32	42
pTK-2746 (R15V)	32	43
pTK-2747 (R15W)	32	44
pTK-2748 (R15Y)	32	45
pTK-2824 (R11S/R15I/Q19K/Y46D)	32	46
pTK-2825 (R11S/R15L/Q19K/Y46D)	32	47
pTK-2826 (R11S/R15T/Q19K/Y46D)	32	48
pTK-2827 (R11S/R15V/Q19K/Y46D)	32	49
pTK-2866 (R11S/R15T/Q19A/Y46D)	33	50
pTK-2867 (R11S/R15T/Q19C/Y46D)	33	51
pTK-2868 (R11S/R15T/Q19D/Y46D)	33	52
pTK-2869 (R11S/R15T/Q19E/Y46D)	33	53
pTK-2870 (R11S/R15T/Q19F/Y46D)	33	54
pTK-2871 (R11S/R15T/Q19G/Y46D)	33	55
pTK-2872 (R11S/R15T/Q19H/Y46D)	33	56
pTK-2873 (R11S/R15T/Q19I/Y46D)	33	57
pTK-2874 (R11S/R15T/Q19L/Y46D)	33	58
pTK-2875 (R11S/R15T/Q19M/Y46D)	33	59
pTK-2876 (R11S/R15T/Q19N/Y46D)	33	60
pTK-2877 (R11S/R15T/Q19P/Y46D)	33	61
pTK-2878 (R11S/R15T/Y46D)	33	62
pTK-2879 (R11S/R15T/Q19R/Y46D)	33	63
pTK-2880 (R11S/R15T/Q19S/Y46D)	33	64

TABLE 10

Modified UTI domain 2 of F1024S-D2	FIG. ID	SEQ ID
pTK-2881 (R11S/R15T/Q19T/Y46D)	33	65
pTK-2882 (R11S/R15T/Q19V/Y46D)	33	66
pTK-2883 (R11S/R15T/Q19W/Y46D)	33	67
pTK-2884 (R11S/R15T/Q19Y/Y46D)	33	68
pTK-2889 (R11S/R15T/F17A/Y46D)	34	69
pTK-2890 (R11S/R15T/F17C/Y46D)	34	70
pTK-2891 (R11S/R15T/F17D/Y46D)	34	71
pTK-2892 (R11S/R15T/F17E/Y46D)	34	72
pTK-2893 (R11S/R15T/F17G/Y46D)	34	73
pTK-2894 (R11S/R15T/F17H/Y46D)	34	74
pTK-2895 (R11S/R15T/F17I/Y46D)	34	75
pTK-2896 (R11S/R15T/F17K/Y46D)	34	76
pTK-2897 (R11S/R15T/F17L/Y46D)	34	77
pTK-2898 (R11S/R15T/F17M/Y46D)	34	78
pTK-2899 (R11S/R15T/F17N/Y46D)	34	79
pTK-2900 (R11S/R15T/F17P/Y46D)	34	80
pTK-2901 (R11S/R15T/F17Q/Y46D)	34	81
pTK-2902 (R11S/R15T/F17R/Y46D)	34	82
pTK-2903 (R11S/R15T/F17S/Y46D)	34	83
pTK-2904 (R11S/R15T/F17T/Y46D)	34	84
pTK-2905 (R11S/R15T/F17V/Y46D)	34	85
pTK-2906 (R11S/R15T/F17W/Y46D)	34	86
pTK-2907 (R11S/R15T/F17Y/Y46D)	34	87
pTK-2932 (R11A/R15T/Y46D)	35	88
pTK-2933 (R11C/R15T/Y46D)	35	89
pTK-2934 (R11D/R15T/Y46D)	35	90
pTK-2935 (R11E/R15T/Y46D)	35	91
pTK-2936 (R11F/R15T/Y46D)	35	92
pTK-2937 (R11G/R15T/Y46D)	35	93
pTK-2938 (R11H/R15T/Y46D)	35	94
pTK-2939 (R11I/R15T/Y46D)	35	95
pTK-2940 (R11K/R15T/Y46D)	35	96
pTK-2941 (R11L/R15T/Y46D)	35	97
pTK-2942 (R11M/R15T/Y46D)	35	98
pTK-2943 (R11N/R15T/Y46D)	35	99
pTK-2944 (R11P/R15T/Y46D)	35	100
pTK-2945 (R11Q/R15T/Y46D)	35	101
pTK-2946 (R15T/Y46D)	35	102
pTK-2947 (R11T/R15T/Y46D)	35	103
pTK-2948 (R11V/R15T/Y46D)	35	104
pTK-2949 (R11W/R15T/Y46D)	35	105
pTK-2950 (R11Y/R15T/Y46D)	35	106

[0391] 7-2) Elastase Inhibitory Activity of Modified F1024S-D2

[0392] The 80 modified forms of F1024S-D2 prepared as described above and F1024-D2(3) were evaluated for their elastase inhibitory activity by repeating the procedure of Example 3-2)(3) except that incubation was made for 5 minutes at 37° C. after the addition of the S-2484 solution. It was then confirmed that the fusion proteins (modified F1024S-D2) from the following expression plasmids exhibit elastase inhibitory activity equivalent to that of the F1024S-D2(3).

[0393] pTK-2730(R15A), pTK-2737(R15I), pTK-2739 (R15L), pTK-2740(R15M), pTK-2745(R15T), pTK-2746 (R15V), pTK-2866(R11S/R15T/Q19A/Y46D), pTK-2867 (R11S/R15T/Q19C/Y46D), pTK-2868(R11S/R15T/Q19D/Y46D), pTK-2869(R11S/R15T/Q19E/Y46D), pTK-2870 (R11S/R15T/Q19F/Y46D), pTK-2871(R11S/R15T/Q19G/Y46D), pTK-2872(R11S/R15T/Q19H/Y46D), pTK-2873 (R11S/R15T/Q19I/Y46D), pTK-2874(R11S/R15T/Q19L/Y46D), pTK-2875(R11S/R15T/Q19M/Y46D), pTK-2876 (R11S/R15T/Q19N/Y46D), pTK-2877(R11S/R15T/Q19P/Y46D), pTK-2878(R11S/R15T/Y46D), pTK-2879(R11S/R15T/Q19R/Y46D), pTK-2880(R11S/R15T/Q19S/Y46D), pTK-2881(R11S/R15T/Q19T/Y46D), pTK-2882(R11S/R15T/Q19V/Y46D), pTK-2883(R11S/R15T/Q19W/Y46D), pTK-2884(R11S/R15T/Q19Y/Y46D), pTK-2889(R11S/R15T/F17A/Y46D), pTK-2890(R11S/R15T/F17C/Y46D), pTK-2891(R11S/R15T/F17D/Y46D), pTK-2892(R11S/R15T/F17E/Y46D), pTK-2932(R11A/R15T/Y46D), pTK-2893(R11S/R15T/F17G/Y46D), pTK-2933(R11c/R15T/Y46D), pTK-2895(R11S/R15T/F17H/Y46D), pTK-2934 (R11D/R15T/Y46D), pTK-2896(R11S/R15T/F17I/Y46D), pTK-2935(R11E/R15T/Y46D), pTK-2897(R11S/R15T/F17L/Y46D), pTK-2936(R11F/R15T/Y46D), pTK-2898 (R11S/R15T/F17M/Y46D), pTK-2937(R11G/R15T/Y46D), pTK-2899(R11S/R15T/F17N/Y46D), pTK-2938 (R11H/R15T/Y46D), pTK-2900(R11S/R15T/F17P/Y46D), pTK-2939(R11I/R15T/Y46D), pTK-2901(R11S/R15T/F17Q/Y46D), pTK-2940(R11K/R15T/Y46D), pTK-2902 (R11S/R15T/F17R/Y46D), pTK-2941(R11L/R15T/Y46D), pTK-2903(R11S/R15T/F17S/Y46D), pTK-2942(R11M/R15T/Y46D), pTK-2904(R11S/R15T/F17T/Y46D), pTK-2943(R11N/R15T/Y46D), pTK-2905(R11S/R15T/F17V/Y46D), pTK-2944(R11P/R15T/Y46D), pTK-2906(R11S/R15T/F17W/Y46D), pTK-2945(R11Q/R15T/Y46D), pTK-2907(R11S/R15T/F17Y/Y46D), pTK-2946(R15T/Y46D), pTK-2947(R11T/R15T/Y46D), pTK-2948(R11V/R15T/Y46D), pTK-2949(R11W/R15T/Y46D), pTK-2950(R11Y/R15T/Y46D), pTK-2824(R11S/R15I/Q19K/Y46D), pTK-2825(R11S/R15L/Q19K/Y46D), pTK-2826(R11S/R15T/Q19K/Y46D), pTK-2827(R11S/R15V/Q19K/Y46D)

[0394] In particular, the fusion protein from the expression plasmid pTK-2826 (R11S/R15T/Q19K/Y46D) exhibited a 50% inhibitory concentration of 4.43 µg/mL in contrast to the 50% inhibitory concentration of F1024S-D2(3) which was 8.90 µg/mL, demonstrating the enhanced elastase inhibitory activity provided by the replacement of the 15th arginine of D2(3) portion with threonine.

[0395] FIG. 36 is a view explaining the total amino acid sequence of fusion protein F1024-D2(4) (R11S/R15T/Q19K/Y46D).

Example 8

Antibody Fusion Protein (F1024S-Thrombomodulin (TM) Functional Domain)

[0396] 8-1) Construction of F1024S-TM Expression Plasmid

[0397] In order to produce fusion proteins of anti-CD14 antibody (F1024S) with various functional domains of TM, PCR was conducted by using HeLa genomic DNA for the template and the primer pair (TM-b and TM-g) to amplify full gene length of the human thrombomodulin (hereinafter referred to as TM), and the amplification product was cloned in pT7-Blue vector by TA cloning. After confirming the sequence, this plasmid was designated pT7-TM.

[0398] Next, PCR was conducted by using pT7-TM for the template and the primer pair (TMD123456 and TM domain 2-NotI Bgl2), and after cleaving the thus amplified fragment with restriction enzymes BamHI and BglII and mixing with the preliminarily prepared vector (prepared by cleaving the pTK-2354 described in Example 1, Table 3 with restriction enzyme BamHI, followed by dephosphorylation), and the fragment was ligated using T4 DNA ligase to thereby produce plasmid pTK-2754 which was capable of expressing the heavy chain of fusion protein (designated F1024S-TM123456M) comprising F1024S having the region of 227th cysteine to 462nd cysteine (Cys²²⁷ to Cys⁴⁶²) in the amino acid sequence of TM added thereto. This procedure was repeated by using the primer pair (TMD123456 and TM domain 3-NotI Bgl2) to prepare a plasmid pTK-2755 which was capable of expressing the heavy chain of fusion protein (designated F1024S-TM123456M) comprising F1024S having the region of 227th cysteine to 497th serine (Cys²²⁷ to Ser⁴⁹⁷) of the amino acid sequence added thereto; by using the primer pair (TMD23456 and TM domain 2-NotI Bgl2) to prepare plasmid pTK-2756 which was capable of expressing the heavy chain of fusion protein (designated F1024S-TM23456M) having the region of 263rd threonine to 462nd cysteine (Thr²⁶³ to Cys⁴⁶²) of the amino acid sequence added thereto; by using the primer pair (TMD23456 and TM domain 3-NotI Bgl2) to prepare plasmid pTK-2757 which was capable of expressing the heavy chain of fusion protein (designated F1024S-TM23456M) having the region of 263rd threonine to 497th serine (Thr²⁶³ to Ser⁴⁹⁷) added thereto; by using the primer pair (TMD3456 and TM domain 2-NotI Bgl2) to prepare plasmid pTK-2758 which was capable of expressing the heavy chain of fusion protein (designated F1024S-TM3456M) having the region of 306th glutamine to 462nd cysteine (Glu³⁰⁶ to Cys⁴⁶²) added thereto; by using the primer pair (TMD3456 and TM domain 3-NotI Bgl2) to prepare plasmid pTK-2759 which was capable of expressing the heavy chain of fusion protein (designated F1024S-TM3456M) having the region of 306th glutamine to 497th serine (Glu³⁰⁶ to Ser⁴⁹⁷) added thereto; by using the primer pair (TMD456 and TM domain 2-NotI Bgl2) to prepare plasmid pTK-2760 which was capable of expressing the heavy chain of fusion protein (designated F1024S-TM456M) having the region of 345th valine to 462nd cysteine (Val³⁴⁵ to Cys⁴⁶²) added thereto; and by using the primer pair (TMD456 and TM domain 3-NotI Bgl2) to prepare plasmid pTK-2761 which was capable of expressing the heavy chain of fusion protein (designated F1024S-TM456M) having the region of 345th valine to 497th serine (Val³⁴⁵ to Ser⁴⁹⁷) added thereto.

[0399] In the meanwhile, in order to prevent decrease in the activity by the oxidation of TM, the mutant (M388L) in which

388th methionine (Met³⁸⁸) in the amino acid sequence has been substituted with leucine (Leu) was also produced by the procedure as described below (Clarke, J H. et al., J. Biol. Chem. 268, 6309-6315 (1993)), namely, by conducting PCR using pT7-TM for the template and each of the primer pairs [TMD123456 and TM(M388L)-a] and [TM domain 2-NotI Bgl2 and TM(M388L)-s], mixing each of the amplification products, and again conducting PCR using the primer pair (TMD123456 and TM domain 2-NotI Bgl2). The gene fragment coding for the region of 227th cysteine to 462nd cysteine (Cys²²⁷ to Cys⁴⁶²) which included the M388L mutation was thereby amplified. As in the case described above, this fragment was cleaved with restriction enzymes BamHI and BglII and ligated to the vector using a ligase to construct plasmid pTK-2762 which was capable of expressing the heavy chain of fusion protein (designated F1024S-TM123456L) comprising the antibody molecule F1024S having added thereto the region of the TM from 227th cysteine to 462nd cysteine (Cys²²⁷ to Cys⁴⁶²) including the M388L mutation. The plasmids finally constructed were pTK-2763 which was capable of expressing the heavy chain of the fusion protein (F1024S-TM123456L) including the mutation of M388L introduced in the pTK-2755; pTK-2764 which was capable of expressing the heavy chain of the fusion protein (designated F1024S-TM23456L) including the mutation of M388L introduced in the pTK-2756; pTK-2765 which was capable of expressing the heavy chain of the fusion protein (designated F1024S-TM23456L) including the mutation of M388L introduced in the pTK-2757; pTK-2766 which was capable of expressing the heavy chain of the fusion protein (designated F1024S-TM3456L) including the mutation of M388L introduced in the pTK-2758; pTK-2767 which was capable of expressing the heavy chain of the fusion protein (designated F1024S-TM3456L) including the mutation of M388L introduced in the pTK-2759; and pTK-2768 which was capable of expressing the heavy chain of the fusion protein (designated F1024S-TM456L) including the mutation of M388L introduced in the pTK-2760; and pTK-2769 which was capable of expressing the heavy chain of the fusion protein (designated F1024S-TM456L) including the mutation of M388L introduced in the pTK-2761.

[0400] The sequences of the primers used are shown in Table 10, and the fusion proteins of the anti-CD14 antibody (F1024S) and the expression plasmids are shown in Table 11.

[0401] The amino acid sequences of the fusion proteins of the anti-CD14 antibody (F1024S) are shown in FIGS. 37 to 44 and Sequence Listing.

[0402] FIG. 45 is a view explaining the total amino acid sequence of fusion protein F1024-TM23456L.

TABLE 11

Table 10		
Primer Name	Base Sequence	SEQ ID
TM-b	5' TTTCCCGCGCGCTGCACGC 3'	191
TM-g	5' TCCTGGACGGAGGCGCTCAG 3'	192
TMD123456	5' GGGATCCTGCACGCTGGAGAACGGCGGCT 3'	193
TMD23456	5' GGGATCCACCGCATCCGCGACGCAGTCCT 3'	194
TMD3456	5' GGGATCCGAGGACGTGGATGACTGCATAC 3'	195

TABLE 11-continued

Table 10			
Primer Name	Base Sequence	SEQ ID	
TMD456	5' GGGATCCGTGGAGCCCGTGGACCCGTGCT 3'	196	
TMdomain2-Not1Bg12	5' GGAGATCTGCGGCCGCTCAACAGTCGGTGCC AATG 3'	197	
TMdomain3-Not1Bg12	5' GGAGATCTGCGGCCGCTCACGAATGCACGAG CCCC 3'	198	
TM(M388L) - s	5' CCGCACAGGTGCCAGCTGTTTTTGCAACCAGA CT 3'	199	
TM(M388L) - a	5' AGTCTGGTTGCAAAACAGCTGGCACCTGTGC GG 3'	200	

TABLE 11

F1024S Fusion Protein Name	Plasmid Name	FIG. No.	SEQ ID
F1024S-TM123456M	pTK-2754	37	107
F1024S-TM123456L	pTK-2762	37	108
F1024S-TM1234567M	pTK-2755	38	109
F1024S-TM1234567L	pTK-2763	38	110
F1024S-TM23456M	pTK-2756	39	111
F1024S-TM23456L	pTK-2764	39	112
F1024S-TM234567M	pTK-2757	40	113
F1024S-TM234567L	pTK-2765	40	114
F1024S-TM3456M	pTK-2758	41	115
F1024S-TM3456L	pTK-2766	41	116
F1024S-TM34567M	pTK-2759	42	117
F1024S-TM34567L	pTK-2767	42	118
F1024S-TM456M	pTK-2760	43	119
F1024S-TM456L	pTK-2768	43	120
F1024S-TM4567M	pTK-2761	44	121
F1024S-TM4567L	pTK-2769	44	122

[0403] These plasmids were cotransfected in COS-1 cell with the light chain expression plasmid (pTK-2344) to express F1024S-TM in the culture supernatant. This supernatant was purified using Prosep-A column for use in the subsequent assay.

[0404] The binding test using EIA confirmed that the fusion proteins had the binding activity for the CD14 antigen.

[0405] 8-2) Measurement of Thrombomodulin (TM) Activity

[0406] TM activity was measured by using action of the thrombomodulin (TM) forming a complex with thrombin in blood to activate protein C which is the blood coagulation inhibitory factor for the index of the activity. The measurement was conducted as described below.

[0407] The reaction for the activity measurement was conducted in a multitube. The fusion protein was diluted with 25 mmol/L Tris-HCl buffer solution containing 0.14 mol/L sodium chloride, 10 mmol/L calcium chloride, and 1 mg/mL bovine serum albumin (pH 7.4). To 40 μ L of the specimen, 10 μ L of 6 U/mL human thrombin (SIGMA) was added and preincubation was conducted at 37° C. for 10 minutes. Next, 10 μ L of 24 μ g/mL protein C (American Diagnostica Inc.) was added, and the mixture was incubated at 37° C. for 5 minutes. 40 μ L of the mixture of 0.15 U/mL antithrombin III (Green Cross Corporation) and 15 U/mL heparin (Mochida Pharmaceutical Co., Ltd.) was added and the mixture was

incubated at 37° C. for 10 minutes. 100 μ L of 3.2 mmol/L activated protein C substrate S-2366 (Daiichi Pure Chemicals Co., Ltd.) was added, and after incubating the mixture at 37° C. for 10 minutes, the reaction was terminated by adding 200 μ L of 50% acetic acid. 300 μ L of the reaction solution was transferred to 96-well flat plate, and absorbance at 405 nm was measured using a plate reader (Molecular Devices Corporation). Human thrombomodulin MR-33 (Mochida Pharmaceutical Co., Ltd.) was used for the positive control. It was then found that all F1024S-TM fusion proteins have the activity of promoting the protein C activation, and F1024S-TM23456M, F1024S-TM234567M, F1024S-TM23456L, and F1024S-TM234567L have high activity for promoting the protein C activation. The M388L mutants also exhibited relatively high activity (FIG. 46).

Example 9

Alteration of Linker Portion in Antibody Fusion Protein (F1024S-SLPI)

[0408] 9-1) Construction of Expression Plasmid

[0409] Linker SG-4-s (5' pGATCTGGAGGTGGAG 3', SEQ ID NO: 201, with phosphorylated 5' terminal) and linker SG-4-a (5' pGATCCTCCACCTCCA 3', SEQ ID NO: 202, with phosphorylated 5' terminal) were mixed and, and the mixture was incubated at 96.degree ° C. for 2 minutes. The temperature was gradually reduced to room temperature for annealing. An adequate amount of the mixture was mixed with the preliminarily prepared vector fragment (which had been prepared by cleaving the pT7-SLPI(D2) described in Example 1 with restriction enzyme BglII, dephosphorylating, subjecting to agarose gel electrophoresis, and extracting the fragment from the gel), and the fragment was ligated with T4 DNA ligase. By this procedure, plasmid pTK-2729 comprising SLPI(D2) having 1 copy of GGGGS linker, SEQ ID NO: 203, added thereto was constructed. This pTK-2729 was cleaved with restriction enzyme BglII, and by repeating the procedure as described above, pTK-2749 comprising SLPI (D2) having 2 copies of GGGGS, SEQ ID NO: 203, linker added thereto, and pTK-2750 comprising SLPI(D2) having 3 copies of GGGGS, SEQ ID NO: 203, linker added thereto were constructed.

[0410] Next, pTK-2729, pTK-2749, and pTK-2750 were cleaved with restriction enzymes BglII and NotI to prepare gene fragments coding for the part of the linker plus SLPI (D2) (The resulting fragments are respectively designated fragment 1, fragment 2, and fragment 3). As in the case of the construction of the pTK-2396 in Example 1 (Table 3), the gene fragments A and D were ligated with each fragment by T4 DNA ligase to construct plasmids expressing heavy chain of the F1024S-SLPI(D2) with modified linker respectively having linkers GSGGGGS, SEQ ID NO: 204, GSGGGGS GSGGGGS, SEQ ID NO: 205, and GSGGGGS GSGGGGS GSGGGGS, SEQ ID NO: 206, between the antibody molecule and the SLPI(D2) (respectively designated pTK-2751, pTK-2752, and pTK-2753).

[0411] These plasmids were cotransfected in COS-1 cell with the light chain expression plasmid (pTK-2344) to express F1024S-SLPI(D2) with modified linker in the culture supernatant, and the supernatant was purified by Prosep-A column.

[0412] All purification products were confirmed to have the binding activity for the CD14 antigen.

[0413] Tables 12 and 13 show SEQ ID NOS of the primers and the linkers.

TABLE 13

Table 12		
Primer Name	Base Sequence	SEQ ID
LinkerSG-4-s	5' pGATCTGGAGGTGGAG 3'	201
LinkerSG-4-a	5' pGATCTCCACCTCCA 3'	202

TABLE 14

Table 13	
Linker Base Sequence	SEQ ID
GGGGS	203
GSGGGGS	204
GSGGGSGGGGS	205
GSGGGSGGGSGGGGS	206

[0414] 9-2) Elastase Inhibitory Activity of F1024S-SLPI

[0415] 1024D-SLPI(D1D2), F1024D-SLPI(D2), F1024S-SLPI(D1D2), and F1024S-SLPI(D2), and furthermore, the fusion protein of SLPI(D2) having 1, 2, or 3 copies of GGGGS linker added thereto were evaluated for their elastase inhibitory activity by repeating the procedure of Example 3-2(3) except that the incubation at 37° C. after the addition of the S-2484 solution was conducted for 5 minutes.

[0416] The control was prepared by mixing 10 μ L of the elastase solution to 80 μ L of the diluting solution, incubating at 37° C. for 3 minutes, adding 10 μ L of the S-2484 solution, and incubating at 37° C. for exactly 5 minutes, and thereafter adding 50 μ L of 20% acetic acid solution. The 50% inhibitory concentrations of F1024S-SLPI(D1D2) and F1024S-SLPI(D2) were 22.5 μ g/mL and 26.9 μ g/mL, respectively, and the 50% inhibitory concentrations of the fusion proteins of SLPI(D2) having 1, 2, and 3 copies of GGGGS linker added thereto were 11.6 μ g/mL, 11.9 μ g/mL, and 11.6 μ g/mL, respectively.

Example 10

Preparation of Humanized Antibody (hF1024S-D2(3))

[0417] The amino acid sequences of the heavy chain and the light chain variable regions of the rat antibody F1024-1-3 were searched on the data base, and these sequences were respectively determined to have high homology with human antibodies IGHV7-81 (BC032733) and HUMIGRFFM (L48242). Accordingly, humanization was conducted by transplanting the 3 complementarity determining regions (CDRs) of both chains of the antibody F1024 to each framework (FR) of (1) IGHV7-81 and HUMIGRFFM (hereinafter referred to as RF) or (2) NEW, Eu, and REI which have been thoroughly analyzed by crystal structure analysis (see FIG. 47). The nucleotide sequence was designed based on each amino acid sequence (FIG. 48), and all of the 6 gene fragments were prepared by dividing the nucleotide sequence into several parts and synthesizing them. Each fragment was replaced with the variable region of the heavy chain pTK-

2370 and the light chain pTK-2344 to construct the expression plasmid (heavy chain: pTK-2887 for IGHV7-81-HA, pTK-2679 for NEW-HA, and pTK-2685 for Eu-HA; light chain: pTK-2955 for RF-KA, pTK-2680 for REI-KA, and pTK-2681 for Eu-KA). COS-1 cell was cotransfected with various combinations of such plasmids and the chimeric antibody expression plasmids (pTK-2370 for heavy chain and pTK-2344 for light chain), and the antibodies secreted in the supernatant were compared for their binding activity to GPVI antigen.

[0418] With regard to the heavy chain, significant decrease in the amount of the expression by the humanization was found in all cases. In view of such situation, various mutations were introduced in the FR, and the results were examined. In the meanwhile, expression and binding activity were confirmed for the light chain.

[0419] For three humanized heavy chain expression plasmids, the sequences maintaining the expression and the binding activity (pTK-2909 for IGHV7-81-HC, pTK-3007 for IGHV7-81-HX, pTK-2803 for NEW-HB, and pTK-2811 for Eu-HB) could be finally obtained by constructing a large number of mutants in which part of the human-specific sequence in FR was returned to the sequence from the rat and precisely analyzing such constructs (FIG. 49 shows the amino acid sequence).

[0420] Finally, combinations of the humanized heavy chain and the humanized light chain were examined, and the combination exhibiting the highest expression and binding activity was the combination of IGHV7-81-HX with RF-KA or other light chain.

[0421] The antibody portion of other antibody fusion proteins are humanized by a similar procedure.

Example 11

Production of Strain which is Capable of Stably Producing Antibody Fusion Protein F1024S-D2(3) at High Yield

[0422] 1-1 Production of Plasmid (pTK-2671) which is Capable of Stably Expressing F1024S-D2(3) at High Yield

[0423] PCR was conducted by using a transient expression plasmid (pTK-2370, described in Example 1) for expressing heavy chain of F1024S-D2(3) for the template and using the primer pair (F1024H-kozak, IgG4-1) shown in Table 14. The amplification product was cleaved with restriction enzymes EcoRI and NheI, and after the agarose gel electrophoresis, the gene fragment (fragment U) comprising the heavy chain variable region of the antibody F1024 was extracted. SEQ ID NOS of the primers used are shown in Table 14.

TABLE 15

Table 14		
Primer Name	Base Sequence	SEQ ID
F1024H-kozak	5' GGGGAATTCCGCCACCATGGATTGG TTGTGGAA 3'	207
IgG4-1	5' GCTGTGCTCTCGGAGGTGCT 3'	208

[0424] pTK-2370 was cleaved with restriction enzymes NheI and Sse8387I, and after agarose gel electrophoresis, gene fragment (fragment V) comprising the heavy chain constant region of the F1024S-D2(3), the gene sequence coding

for the D2(3), and SV40 polyA signal was extracted. Plasmid (pTK-2344 described in Example 1) expressing the light chain of F1024 was cleaved with restriction enzymes BsiWI and NcoI, and after agarose gel electrophoresis, the gene fragment (fragment W) comprising the light chain variable region of the antibody F1024 was extracted.

[0425] Plasmid (pTK-2577) comprising EF promoter, human light chain constant region, and mouse DHFR expression unit (comprising SV40 promoter (not including enhancer region) as promoter, and polyA signal from SV40) was cleaved with restriction enzymes BsiWI and EcoRI, and after agarose gel electrophoresis, the vector fragment (fragment X) of interest was extracted. In the meanwhile, this plasmid was also cleaved with Sse8387I and NcoI, and after the agarose gel electrophoresis, gene fragment (fragment Y) comprising EF promoter region was extracted.

[0426] The gene fragments U to Y were ligated into one fragment using T4 DNA ligase (TAKARA BIO INC.) to construct plasmid (pTK-2671) for stable expression which was capable of simultaneously expressing the heavy chain and the light chain of the F1024S-D2(3), and which contained mouse DHFR expression unit serving as a marker in the cell into which the plasmid was to be introduced.

[0427] By using a similar procedure, plasmids capable of stable expression at a high yield are also constructed for other antibody fusion proteins.

Example 12

Evaluation of Efficacy (In Vitro)

[0428] 12-1) Confirmation of Inhibitory Action for Bradykinin Production

[0429] (1) Confirmation of Inhibitory Action for Bradykinin Production in Human and Rabbit Plasmas Induced by APTT Reagent

[0430] The normal human plasma used was Dade Ci-Trol Level 1 (DADE BEHRING INC.). The rabbit plasma was prepared by collecting blood from auricular artery of male rabbit (New Zealand white, Kitayama Labes Co., Ltd.) using a syringe containing $\frac{1}{10}$ volume of 3.8% sodium citrate (sodium citrate for measuring erythrocyte sedimentation rate, Iwaki Seiyaku Co., Ltd.), and centrifuging the blood for 10 minutes at 4° C. and 3000 rpm (05PR-22, Hitachi). After adding o-phenanthroline solution to 80 μ L of human or rabbit plasma, F1024S-D2(3) solution which had been serially diluted with the diluting solution was added to final concentrations of 0, 1, 3, 10, and 30 μ g/mL, or human immunoglobulin (hIg) was added to a final concentration of 30 μ g/mL. After stirring, the plasma was incubated at 37° C. for 10 minutes. 80 μ L of APTT reagent diluted with Milli-Q Water was added, and the plasma was further incubated at 37° C. for 10 minutes. 100 μ L of the plasma was collected, and 20 μ L of deproteinizing agent attached to the bradykinin measurement kit (Markit-M bradykinin, Dainippon Pharmaceutical Co., Ltd.) was added, and this plasma was centrifuged at 4° C. and 10000 rpm (MRX-150, TOMY) for 10 minutes. The resulting supernatant was measured for bradykinin concentration by using the bradykinin measurement kit. It was then found that F1024S-D2(3) inhibits bradykinin production in human and rabbit plasmas induced by APTT reagent in a concentration dependent manner (FIGS. 50 and 51).

[0431] 12-2) Confirmation of Coagulation Inhibitory Action

[0432] (1) Confirmation of Inhibitory Action for (Factor XI Dependent) Thrombin Production in Human Plasma Induced by Thromboplastin

[0433] To each of the human plasma containing human platelet at $3 \times 10^5/\mu$ L and the rabbit plasma containing rabbit platelet at $3 \times 10^5/\mu$ L, the F1024S-D2(3) solution was added to final concentrations of 0, 3, 10, 30, 100, and 300 μ g/mL, or human immunoglobulin (hIg) was added to a final concentration of 300 μ g/mL. The plasma was then pre-incubated at 37° C. for 10 minutes. Incubation was started at 37° C. after adding a solution of thromboplastin (Simplastin Exel, BIOMERIEUX, INC.) diluted 8000 folds with 25 mmol/L CaCl₂ solution. 5 μ L of the incubated solution was collected before the addition of the thromboplastin solution and with time after the addition of the thromboplastin solution, and added to a mixture of 100 μ L of Buffer B (50 mmol/L Tris-HCl buffer solution (pH 7.9) containing 0.5 mg/mL BSA, 0.1 mol/L NaCl, and 20 mmol/L EDTA) and 25 μ L of 2 mmol/L S-2238, and the mixture was incubated at 37° C. for 10 minutes. After adding 100 μ L of 50 vol % acetic acid, the reaction solution was added to a 96-well plate at 200 μ L/well, and the absorbance at 405 nm was measured by a plate reader (Thermomax microplate reader, Molecular Devices Corporation). It was then found that F1024S-D2(3) inhibits thrombin production in human and rabbit plasmas induced by thromboplastin in a concentration dependent manner (FIGS. 52 to 53).

[0434] 12-3) Confirmation of Coagulation Inhibitory Action

[0435] (1) Confirmation of Human APTT Extending Action

[0436] APTT extending actions of F1024S-TM23456M, F1024S-TM23456L, F1024S-TM234567M and F1024S-TM234567L prepared in Example 8 were respectively evaluated at final concentrations of 2.00, 2.00, 1.95, and 2.29 μ g/mL by the procedure similar to that of Example 3-3) (1) using human normal human plasma. As a consequence, APTT was extended by 26, 32, 42, and 57% by the 4 fusion proteins, respectively.

Example 13

Evaluation of Effectiveness in Ex Vivo Test

[0437] 13-1) Confirmation of Antiinflammatory Action of F1024S-D2(3)

[0438] 10 mg/kg of F1024S-D2(3) was administered to rabbit (New Zealand white, 1.8 to 2.6 kg, Kitayama Labes Co., Ltd.) from auricular vein, and the blood was collected with time with addition of citric acid. LPS (W E. coli 055:B5, DIFCO) was added to the collected blood to a final concentration of 1 ng/mL, and the blood was incubated at 37° C. for 4 hours. The blood was centrifuged at 4° C. and 10000 rpm (MRX-150, TOMY) for 10 minutes, and the resulting plasma was measured for its TNF- α concentration by ELISA using anti-rabbit TNF- α antibody. It was then found that production of TNF- α was suppressed in the LPS-stimulated blood until 24 hours after the administration of the F1024S-D2(3) (FIG. 54).

[0439] 13-2) Confirmation of Anticoagulant Action of F1024S-D2 (3)

[0440] The plasma obtained by centrifugation immediately after the blood collection in Example 13-1) was used for the

measurement of activated partial thromboplastin time (APTT). The measurement of the APTT was conducted by repeating the procedure of Example 3-3). Extension of APTT was found until 8 hours after the administration of the F1024S-D2(3) (FIG. 55).

Example 14

Evaluation of In Vivo Effectiveness

[0441] 14-1) Rabbit CLP (Cecal Ligation and Puncture) Model

[0442] Rabbit CLP (cecal ligation and puncture) peritonitis model was produced, and improvement in the survival rate and coagulation parameter after the administration of the F1024S-D2(3) was confirmed.

[0443] The rabbit peritonitis model by cecal ligation and puncture was produced by the method of Keith, A. et al. (Journal of Surgical Research, 29: 189, 1980) by puncturing cecum of a rabbit (New Zealand white, 1.8 to 2.6 kg, Kitayama Labes Co., Ltd.) under anesthesia, and sprinkling the content of the cecum in the abdominal cavity. After 2 hours, 10 mg/kg of F1024S-D2(3) was administered to auricular vein, and after this, F1024S-D2(3) was administered twice a day for 3 days. The control group was administered with human immunoglobulin (hIg) instead of the F1024S-D2(3). The survival was monitored and recorded for 72 hours to depict Kaplan-Meier survival curve. At 8 hours after the cecal ligation and puncture, blood was collected with addition of citric acid, and D dimer was measured as coagulation parameter of the plasma. It was then found that both the survival rate (FIG. 56) and the D dimer (FIG. 57) were improved in the group administered with the F1024S-D2(3) compared to the control group.

[0444] The overview of the control group of FIGS. 56 and 57 is shown in Table 15.

TABLE 15

Group	Treatment	Anti-biotic	Test substance	Dose	Number of cases
1	Sham	60 mg/kg	Human	10	9
2	Cecal ligation and puncture		Immunoglobulin preparation	mg/kg, twice, 3 days	9
3	peritonitis		FR1024S-D2 (3)		8

Example 15

[0445] A polypeptide, Y46E, having an amino acid sequence derived from the formula 1 amino acid sequence by substituting Glu for the position 42 Tyr of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 2 of JP 6-25289 A to Morishita et al.

Formula 1 (amino acids 478-528) of
SEQ ID NO: 10
Cys Asn Leu Pro Ile Val Arg Gly Pro Cys
Arg Ala Phe Ile Gln Leu Trp Ala Phe Asp
Ala Val Lys Gly Lys Cys Val Leu Phe Pro

-continued

Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys

Phe Tyr Ser Glu Lys Glu Cys Arg Glu Tyr

Cys

[0446] It was confirmed that the purified polypeptide sample obtained was the polypeptide of interest Y46E (amino acids 1-70 of SEQ ID NO: 234).

[0447] A polypeptide, Q19K, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Lys for the position 15 Gln of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 3 of JP 6-25289 A to Morishita et al.

[0448] It was confirmed that the purified polypeptide sample obtained was the polypeptide Q19K of the present invention (amino acids 1-70 of SEQ ID NO: 235).

[0449] A polypeptide, Q19R, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Arg for the position 15 Gln of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 4 of JP 6-25289 A to Morishita et al.

[0450] It was thus confirmed that the purified polypeptide sample obtained is the polypeptide Q19R of the present invention (amino acids 1-68 of SEQ ID NO: 236).

[0451] A polypeptide, Q19K/Y46E, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Lys for the position 15 Gln, as well as Glu for position 42 Tyr, of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 5 of JP 6-25289 A to Morishita et al.

[0452] It was confirmed that the purified polypeptide sample obtained is the polypeptide Q19K/Y46E of the present invention (amino acids 1-68 of SEQ ID NO: 237).

[0453] A polypeptide, R11E/Y46E, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Glu for the position 7 Arg, as well as Glu for the position 42 Tyr, of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 6 of JP 6-25289 A to Morishita et al.

[0454] It was confirmed that the purified polypeptide sample obtained is the desired polypeptide R11E/Y46E of the present invention (amino acids 1-68 of SEQ ID NO: 238).

[0455] A polypeptide, Y46E-AN, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Glu for the position 42 Tyr of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 7 of JP 6-25289 A to Morishita et al.

[0456] It was confirmed that the purified polypeptide sample obtained is the desired polypeptide Y46E-AN of the present invention (amino acids 1-68 of SEQ ID NO: 250).

[0457] A polypeptide, Q19K-AN, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Lys for the position 15 Gln of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 8 of JP 6-25289 A to Morishita et al.

[0458] It was confirmed that the purified polypeptide sample obtained is the polypeptide Q19K-AN of the present invention (amino acids 1-68 of SEQ ID NO: 251).

[0459] A polypeptide, Q19R/Y46E, having an amino acid sequence derived from the aforementioned formula 1 amino

acid sequence by substituting Arg for the position 15 Gln, as well as Glu for the position 42 Tyr, of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 9 of JP 6-25289 A to Morishita et al.

[0460] It was confirmed that the purified polypeptide sample is the polypeptide Q19R/Y46E (amino acids 1-68 of SEQ ID NO: 239).

[0461] A polypeptide, Q19K/Y46D, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Lys for the position 15 Gln, as well as Asp for the position 42 Tyr, of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 10 of JP 6-25289 A to Morishita et al.

[0462] It was confirmed that the purified sample is the polypeptide Q19K/Y46D of the present invention (amino acids 1-68 of SEQ ID NO: 240).

[0463] A polypeptide, Q19R/Y46D, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Arg for the position 15 Gln, as well as Asp for the position 42 Tyr, of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 11 of JP 6-25289 A to Morishita et al.

[0464] It was confirmed that the purified polypeptide sample obtained is the polypeptide Q19R/Y46D of the present invention (amino acids 1-68 of SEQ ID NO: 241).

[0465] A polypeptide, R11Q/Q19K/Y46D, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Gln for the position 7 Arg, Lys for the position 15 Gln, as well as Asp for the position 42 Tyr, of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 12 of JP 6-25289 A to Morishita et al.

[0466] It was confirmed that the purified polypeptide sample obtained is the polypeptide R11Q/Q19K/Y46D of the present invention (amino acids 1-68 of SEQ ID NO: 242).

[0467] A polypeptide, R11D/Q19K/Y46D, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Asp for the position 7 Arg, Lys for the position 15 Gln, as well as Asp for the position 42 Tyr, of the formula 1 sequence, counting from its N-terminus, side was prepared as described in Example 13 of JP 6-25289 A to Morishita et al.

[0468] It was confirmed that the purified polypeptide sample obtained is the polypeptide R11D/Q19K/Y46D of the present invention (amino acids 1-68 of SEQ ID NO: 243).

[0469] A polypeptide, R11L/Q19K/Y46D, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Leu for the position 7 Arg, Lys for the position 15 Gln, as well as Asp for the position 42 Tyr, of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 14 of JP 6-25289 A to Morishita et al.

[0470] It was confirmed that the purified polypeptide sample obtained is the polypeptide R11L/Q19K/Y46D of the present invention (amino acids 1-68 of SEQ ID NO: 244).

[0471] A polypeptide, R11E/Q19K/Y46E, having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Glu for the 7 position Arg, Lys for the position 15 Gln, as well as Glu for the position 42 Tyr, of the formula 1 sequence, counting from its N-terminus, was prepared as described in Example 15 of JP 6-25289 A to Morishita et al.

[0472] It was confirmed that the purified polypeptide sample is the desired polypeptide R11E/Q19K/Y46E of the present invention (amino acids 1-68 of SEQ ID NO: 245).

[0473] Polypeptides R11N/Q19K/Y46D (SEQ ID NO: 248), R11S/Q19K/Y46D (SEQ ID NO: 246) and R11A/Q19K/Y46D (SEQ ID NO: 249) having an amino acid sequence derived from the aforementioned formula 1 amino acid sequence by substituting Asn, Ser and Ala for the position 7 Arg, respectively, in addition to substituting Lys for the position 15 Gln and Asp for the position 42 Tyr of the formula 1 sequence, counting from its N-terminus, were prepared as described in Example 16 of JP 6-25289 A to Morishita et al.

[0474] FXa-inhibiting activities of the polypeptide of the present invention were measured in the following manner, using polypeptide samples Y46E, Q19K, Q19R, Q19K/Y46E, R11E/Y46E, Y46E-AN, Q19K-AN, Q19R/Y46E, Q19K/Y46D, Q19R/Y46D, R11Q/Q19K/Y46D, R11D/Q19K/Y46D, R11L/Q19K/Y46D, R11E/Q19K/Y46E, R11N/Q19K/Y46D, R11S/Q19K/Y46D and R11A/Q19K/Y46D.

[0475] The purified polypeptide of the present invention was dissolved in 100 μ l of distilled water. Polypeptide concentration of this solution was determined based on its bovine trypsin-inhibiting activity using the aforementioned UTI as a standard as described in Example 17(1) of JP 6-25289 A to Morishita et al. The thus prepared solution was then diluted to various concentration levels with 0.1% BSA/150 mM NaCl/5 mM CaCl_2 /50 mM Tris-HCl buffer (pH 8.3) for use in the activity measurement. On the other hand, the purified polypeptide TN70 and AN68 were diluted to various concentration levels to be used as a control solution. In this case a polypeptide TN70 (cf. Japanese Patent Application No. 3-325220) was purified respectively in accordance with the procedure of Example 2(4) in JP 6-25289 A to Morishita et al. from a culture supernatant of *E. coli* JE5505(pM552) (deposit No., FERM BP-3561) and polypeptide AN68 was purified in accordance with the procedure of Example 2(4) in JP 6-25289 A to Morishita et al. from a culture supernatant of *E. coli* JE5505(pM594) obtained by transforming *E. coli* JE5505 with the aforementioned plasmid pM594 obtained as described in Example 4 of JP 6-25289 A to Morishita et al.

[0476] The amino acid sequence of polypeptide TN 70 and AN68 are represented below.

Polypeptide TN70
(amino acids 474-543 of SEQ ID NO: 10)
Thr Val Ala Ala Cys Asn Leu Pro Ile Val
Arg Gly Pro Cys Arg Ala Phe Ile Gln Leu
Trp Ala Phe Asp Ala Val Lys Gly Lys Cys
Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly
Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu
Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp
Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn
Polypeptide An68
(amino acids 476-543 of SEQ ID NO: 10)
Ala Ala Cys Asn Leu Pro Ile Val Arg Gly
Pro Cys Arg Ala Phe Ile Gln Leu Trp Ala
Phe Asp Ala Val Lys Gly Lys Cys Val Leu

-continued

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly
 Asn Lys Phe Tyr Ser Glu Lys Glu Cys Arg
 Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp
 Glu Glu Leu Leu Arg Phe Ser Asn

[0477] Using a synthetic compound S-2222 (Daiichi Pure Chemicals Co., Ltd.) as a substrate, FXa-inhibiting activities in the thus prepared test sample solution and control solution were measured in accordance with the method of Ohno et al. (Ohno H. et al., *Thromb. Res.*, vol. 19, pp. 579-588, 1980) as follows. First, human FXa (American Diagnostica Inc.) was dissolved in distilled water to a final concentration of 10 PEU/ml and the solution was further diluted with the aforementioned 0.1% BSA/150 mM NaCl/5 mM CaCl_2 /50 mM Tris-HCl buffer (pH 8.3) to prepare 0.1 PEU/ml of FXa solution. Separately from this, a 4 mM solution of S-2222 was prepared by dissolving it in distilled water and the solution was further diluted with the 0.1% BSA/150 mM NaCl/5 mM CaCl_2 /50 mM Tris-HCl buffer (pH 8.3) to obtain a 2 mM solution of S-2222.

[0478] Next, 25 μl of the test sample or control solution was mixed with 100 μl of the 0.1% BSA/150 mM NaCl/5 mM CaCl_2 /50 mM Tris-HCl buffer (pH 8.3) and 25 μl of the FXa solution. After incubating statically at 37° C. for 10 minutes, 100 μl of the S-2222 solution was added to start the reaction. The reaction was carried out at 37° C. for 30 minutes and then stopped by adding 50 μl of 50% acetic acid solution to the reaction mixture. Thereafter, absorbance at a wavelength of 405 nm was measured using a spectrophotometer. In this instance, in order to eliminate absorbancy of various contents in the reaction mixture other than the reaction product, a blank solution was prepared by mixing 25 μl of the FXa solution with 50 μl of 50% acetic acid and then with 25 μl of each test sample or the control solution, 100 μl of the 0.1% BSA/150 mM NaCl/5 mM CaCl_2 /50 mM Tris-HCl buffer (pH 8.3) and with 100 μl of the S-2222 solution.

[0479] The results are shown in FIG. 58-66. In these figures, polypeptide concentration in the reaction solution was expressed as its bovine trypsin-inhibiting activity. Also, residual human FXa activity was expressed by percentage based on the absorbance of a control reaction mixture in which 25 μl of the 0.1% BSA/150 mM NaCl/5 mM CaCl_2 /50 mM Tris-HCl buffer (pH 8.3) was used instead of the test sample.

[0480] FIG. 58 shows the polypeptide Y46E of the present invention has significantly high FXa-inhibiting activity in comparison with the polypeptide TN70 used as a control. In

other words, it has an FXa-inhibiting activity which is about seven times higher than that of the polypeptide TN70.

[0481] FIG. 59 shows the polypeptide Q19K of the present invention has significantly high FXa-inhibiting activity in comparison with the polypeptide TN70 used as a control. In other words, it has an FXa-inhibiting activity which is about five times higher than that of the polypeptide TN70.

[0482] FIG. 60 shows the polypeptide Q19R of the present invention has significantly high FXa-inhibiting activity in comparison with the polypeptide AN68 used as a control. In other words, it has an FXa-inhibiting activity which is about six times higher than that of the polypeptide AN68.

[0483] FIG. 61 shows the polypeptide Q19K/Y46E of the present invention has significantly high FXa-inhibiting activity in comparison with the polypeptide AN68 used as a control. In other words, it has an FXa-inhibiting activity which is about ten times higher than that of the polypeptide AN68.

[0484] FIG. 62 shows the polypeptide R11E/Y46E of the present invention has significantly high FXa-inhibiting activity in comparison with the polypeptide AN68 used as a control. In other words, it has an FXa-inhibiting activity which is about three times higher than that of the polypeptide AN68.

[0485] FIG. 63 shows the polypeptide Q19R/Y46E of the present invention has an FXa-inhibiting activity which is about ten times higher than that of the polypeptide AN68.

[0486] FIG. 64 shows the polypeptides Q19K/Y46D and Q19R/Y46D of the present invention have significantly high FXa-inhibiting activity in comparison with the polypeptide AN68 used as a control. In other words, polypeptide Q19K/Y46D has an FXa-inhibiting activity which is about twenty times higher than that of the polypeptide AN68. Polypeptide Q19R/Y46D has an FXa-inhibiting activity which is about 18 times higher than that of the polypeptide AN68.

[0487] FIG. 65 shows the polypeptides R11Q/Q19K/Y46D, R11L/Q19K/Y46D, R11D/Q19K/Y46D of the present invention have significantly high FXa-inhibiting activity in comparison with the polypeptide AN68 used as a control. In other words, polypeptide R11Q/Q19K/Y46D of the present invention has an FXa-inhibiting activity which is about twenty times higher than that of the polypeptide AN68. The polypeptide R11D/Q19K/Y46D has an FXa-inhibiting activity which is about 5 times higher than that of the polypeptide AN68. The polypeptide R11L/Q19K/Y46D has an FXa-inhibiting activity which is about 16 times higher than that of the polypeptide AN68.

[0488] FIG. 66 shows the polypeptides R11E/Q19K/Y46E of the present invention has significantly high FXa-inhibiting activity in comparison with the polypeptide AN68 used as a control. In other words, polypeptide R11E/Q19K/Y46E has an FXa-inhibiting activity which is about 13 times higher than that of the polypeptide AN68.

SEQUENCE LISTING

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<210> SEQ ID NO 1

<211> LENGTH: 1860

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024D-D1D2

<220> FEATURE:

<221> NAME/KEY: CDS

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1 5 10 15	
gct caa gca cag atc cag ttg gta cag tct gga cct gaa ctg aag aag	96
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys	
20 25 30	
cct gga gag tca gtg aag atc tcc tgc aag gct tct ggg tat acc ttc	144
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe	
35 40 45	
aca gac tat gca atg aac tgg gtg aaa cag gct cca gga aat ggc ttg	192
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu	
50 55 60	
aag tgg atg ggc tgg atc aac acc caa act gga aag cca aca tat gcg	240
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala	
65 70 75 80	
gat gat ttc aaa caa cgg ttt gtc ttc tct ttg gaa act tct gcc agc	288
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	
85 90 95	
act gca tac ttg cag atc aac aac ctc aat att gag gac aca gct aca	336
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr	
100 105 110	
tat ttc tgt aca aga tcc act ttt tac tat agc agc tat atc tac ggg	384
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly	
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Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser	
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg	
145 150 155 160	
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Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr	
165 170 175	
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Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser	
180 185 190	
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Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser	
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Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr	
210 215 220	
tac acc tgc aac gta gat cac aag ccc agc aac acc aag gtg gac aag	720
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys	
225 230 235 240	
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Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro	
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Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys	
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-continued

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Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	
305					310					315					320	
aac	agc	acg	tac	cgt	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	1008
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
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tgg	ctg	aac	ggc	aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	aaa	ggc	ctc	1056
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	
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ccg	tcc	tcc	atc	gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggg	cag	ccc	cga	1104
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
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gag	cca	cag	gtg	tac	acc	ctg	ccc	cca	tcc	cag	gag	gag	atg	acc	aag	1152
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	
	370					375				380						
aac	cag	gtc	agc	ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tac	ccc	agc	gac	1200
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	
385					390					395					400	
atc	gcc	gtg	gag	tgg	gag	agc	aat	ggg	cag	ccg	gag	aac	aac	tac	aag	1248
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	
			405						410					415		
acc	acg	cct	ccc	gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	tac	agc	1296
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	
			420					425					430			
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Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	
			435				440					445				
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Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	
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ctc	tcc	ctg	tct	ctg	ggc	aaa	gga	tcc	gct	gtg	cta	ccc	caa	gaa	gag	1440
Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Ser	Ala	Val	Leu	Pro	Gln	Glu	Glu	
					470					475					480	
gaa	gga	tca	ggg	ggc	ggg	caa	ctg	gta	act	gaa	gtc	acc	aag	aaa	gaa	1488
Glu	Gly	Ser	Gly	Gly	Gln	Leu	Val	Thr	Glu	Val	Thr	Lys	Lys	Glu		
			485						490				495			
gat	tcc	tgc	cag	ctg	ggc	tac	tgc	gcc	ggc	ccc	tgc	atg	gga	atg	acc	1536
Asp	Ser	Cys	Gln	Leu	Gly	Tyr	Ser	Ala	Gly	Pro	Cys	Met	Gly	Met	Thr	
			500					505					510			
agc	agg	tat	ttc	tat	aat	ggc	aca	tcc	atg	gcc	tgt	gag	act	ttc	cag	1584
Ser	Arg	Tyr	Phe	Tyr	Asn	Gly	Thr	Ser	Met	Ala	Cys	Glu	Thr	Phe	Gln	
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Tyr	Gly	Gly	Cys	Met	Gly	Asn	Gly	Asn	Asn	Phe	Val	Thr	Glu	Lys	Glu	
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tgt	ctg	cag	acc	tgc	cga	act	gtg	gcg	gcc	tgc	aat	ctc	ccc	ata	gtc	1680
Cys	Leu	Gln	Thr	Cys	Arg	Thr	Val	Ala	Ala	Cys	Asn	Leu	Pro	Ile	Val	
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Arg	Gly	Pro	Cys	Arg	Ala	Phe	Ile	Gln	Leu	Trp	Ala	Phe	Asp	Ala	Val	
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aag	ggg	aag	tgc	gtc	ctc	ttc	ccc	tac	ggg	ggc	tgc	cag	ggc	aac	ggg	1776
Lys	Gly	Lys	Cys	Val	Leu	Phe	Pro	Tyr	Gly	Gly	Cys	Gln	Gly	Asn	Gly	
			580					585					590			
aac	aag	ttc	tac	tca	gag	aag	gag	tgc	aga	gag	tac	tgc	ggc	gtc	cct	1824
Asn	Lys	Phe	Tyr	Ser	Glu	Lys	Glu	Cys	Arg	Glu	Tyr	Cys	Gly	Val	Pro	

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595	600	605	
ggt gat ggt gat gag gag ctg ctg cgc ttc tcc aac			1860
Gly Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn			
610	615	620	

<210> SEQ ID NO 2
 <211> LENGTH: 620
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024D-D1D2

<400> SEQUENCE: 2

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

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325					330					335					
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu
			340					345					350		
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg
			355				360					365			
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys
	370					375					380				
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp
	385					390					395				400
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
			405					410						415	
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser
			420					425					430		
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser
			435				440					445			
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser
	450					455					460				
Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Ser	Ala	Val	Leu	Pro	Gln	Glu	Glu
	465					470					475				480
Glu	Gly	Ser	Gly	Gly	Gly	Gln	Leu	Val	Thr	Glu	Val	Thr	Lys	Lys	Glu
			485					490						495	
Asp	Ser	Cys	Gln	Leu	Gly	Tyr	Ser	Ala	Gly	Pro	Cys	Met	Gly	Met	Thr
			500					505					510		
Ser	Arg	Tyr	Phe	Tyr	Asn	Gly	Thr	Ser	Met	Ala	Cys	Glu	Thr	Phe	Gln
			515				520					525			
Tyr	Gly	Gly	Cys	Met	Gly	Asn	Gly	Asn	Asn	Phe	Val	Thr	Glu	Lys	Glu
	530					535					540				
Cys	Leu	Gln	Thr	Cys	Arg	Thr	Val	Ala	Ala	Cys	Asn	Leu	Pro	Ile	Val
	545					550					555				560
Arg	Gly	Pro	Cys	Arg	Ala	Phe	Ile	Gln	Leu	Trp	Ala	Phe	Asp	Ala	Val
			565					570						575	
Lys	Gly	Lys	Cys	Val	Leu	Phe	Pro	Tyr	Gly	Gly	Cys	Gln	Gly	Asn	Gly
			580				585						590		
Asn	Lys	Phe	Tyr	Ser	Glu	Lys	Glu	Cys	Arg	Glu	Tyr	Cys	Gly	Val	Pro
	595					600						605			
Gly	Asp	Gly	Asp	Glu	Glu	Leu	Leu	Arg	Phe	Ser	Asn				
	610					615					620				

<210> SEQ ID NO 3
 <211> LENGTH: 1629
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024D-D2
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(1629)

<400> SEQUENCE: 3

atg	gat	tgg	tgg	aac	ttg	cta	ttc	ctg	atg	gta	ggt	gcc	caa	agt	48	
Met	Asp	Trp	Leu	Trp	Asn	Leu	Leu	Phe	Leu	Met	Val	Val	Ala	Gln	Ser	
1			5					10					15			
gct	caa	gca	cag	atc	cag	ttg	gta	cag	tct	gga	cct	gaa	ctg	aag	aag	96
Ala	Gln	Ala	Gln	Ile	Gln	Leu	Val	Gln	Ser	Gly	Pro	Glu	Leu	Lys	Lys	
			20					25					30			

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cct gga gag tca gtg aag atc tcc tgc aag gct tct ggg tat acc ttc	144
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe	
35 40 45	
aca gac tat gca atg aac tgg gtg aaa cag gct cca gga aat ggc ttg	192
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu	
50 55 60	
aag tgg atg ggc tgg atc aac acc caa act gga aag cca aca tat gcg	240
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala	
65 70 75 80	
gat gat ttc aaa caa cgg ttt gtc ttc tct ttg gaa act tct gcc agc	288
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	
85 90 95	
act gca tac ttg cag atc aac aac ctc aat att gag gac aca gct aca	336
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr	
100 105 110	
tat ttc tgt aca aga tcc act ttt tac tat agc agc tat atc tac ggg	384
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly	
115 120 125	
tgg tac ttt gac ttc tgg ggc cca gga acc atg gtc acc gtc tcc agc	432
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser	
130 135 140	
gct agc acc aag ggc cca tcc gtc ttc ccc ctg ggc ccc tgc tcc agg	480
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg	
145 150 155 160	
agc acc tcc gag agc aca gcc gcc ctg ggc tgc ctg gtc aag gac tat	528
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr	
165 170 175	
ttc ccc gaa ccg gtg acg gtg tcg tgg aac tca ggt gcc ctg acc agc	576
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser	
180 185 190	
ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc	624
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser	
195 200 205	
ctc agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acg aag acc	672
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr	
210 215 220	
tac acc tgc aac gta gat cac aag ccc agc aac acc aag gtg gac aag	720
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys	
225 230 235 240	
aga gtt gag tcc aaa tat ggt ccc cca tgc cca tca tgc cca gca cct	768
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro	
245 250 255	
gag ttc ctg ggg gga cca tca gtc ttc ctg ttc ccc cca aaa ccc aag	816
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys	
260 265 270	
gac act ctc atg atc tcc cgg acc cct gag gtc acg tgc gtg gtg gtg	864
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val	
275 280 285	
gac gtg agc cag gaa gac ccc gag gtc cag ttc aac tgg tac gtg gat	912
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp	
290 295 300	
ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag ttc	960
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe	
305 310 315 320	
aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac	1008
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp	
325 330 335	
tgg ctg aac ggc aag gag tac aag tgc aag gtc tcc aac aaa ggc ctc	1056

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Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu		
			340					345					350				
ccg	tcc	tcc	atc	gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggg	cag	ccc	cga	1104	
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg		
		355					360					365					
gag	cca	cag	gtg	tac	acc	ctg	ccc	cca	tcc	cag	gag	gag	atg	acc	aag	1152	
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys		
	370					375				380							
aac	cag	gtc	agc	ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tac	ccc	agc	gac	1200	
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp		
385				390				395						400			
atc	gcc	gtg	gag	tgg	gag	agc	aat	ggg	cag	ccg	gag	aac	aac	tac	aag	1248	
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys		
			405					410						415			
acc	acg	cct	ccc	gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	tac	agc	1296	
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser		
		420						425					430				
agg	cta	acc	gtg	gac	aag	agc	agg	tgg	cag	gag	ggg	aat	gtc	ttc	tca	1344	
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser		
		435					440					445					
tgc	tcc	gtg	atg	cat	gag	gct	ctg	cac	aac	cac	tac	aca	cag	aag	agc	1392	
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser		
		450				455					460						
ctc	tcc	ctg	tct	ctg	ggg	aaa	gga	tcc	act	gtg	ggc	gcc	tgc	aat	ctc	1440	
Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Ser	Thr	Val	Ala	Ala	Cys	Asn	Leu		
465				470					475					480			
ccc	ata	gtc	cgg	ggc	ccc	tgc	cga	gcc	ttc	atc	cag	ctc	tgg	gca	ttt	1488	
Pro	Ile	Val	Arg	Gly	Pro	Cys	Arg	Ala	Phe	Ile	Gln	Leu	Trp	Ala	Phe		
			485					490					495				
gat	gct	gtc	aag	ggg	aag	tgc	gtc	ctc	ttc	ccc	tac	ggg	ggc	tgc	cag	1536	
Asp	Ala	Val	Lys	Gly	Lys	Cys	Val	Leu	Phe	Pro	Tyr	Gly	Gly	Cys	Gln		
		500						505					510				
ggc	aac	ggg	aac	aag	ttc	tac	tca	gag	aag	gag	tgc	aga	gag	tac	tgc	1584	
Gly	Asn	Gly	Asn	Lys	Phe	Tyr	Ser	Glu	Lys	Glu	Cys	Arg	Glu	Tyr	Cys		
		515					520				525						
ggg	gtc	cct	ggg	gat	ggg	gat	gag	gag	ctg	ctg	cgc	ttc	tcc	aac		1629	
Gly	Val	Pro	Gly	Asp	Gly	Asp	Glu	Glu	Leu	Leu	Arg	Phe	Ser	Asn			
		530				535					540						

<210> SEQ ID NO 4

<211> LENGTH: 543

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024D-D2

<400> SEQUENCE: 4

Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser
 1 5 10 15

Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
 20 25 30

Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
 35 40 45

Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu
 50 55 60

Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala
 65 70 75 80

Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser

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85								90					95				
Thr	Ala	Tyr	Leu	Gln	Ile	Asn	Asn	Leu	Asn	Ile	Glu	Asp	Thr	Ala	Thr		
			100					105					110				
Tyr	Phe	Cys	Thr	Arg	Ser	Thr	Phe	Tyr	Tyr	Ser	Ser	Tyr	Ile	Tyr	Gly		
		115					120					125					
Trp	Tyr	Phe	Asp	Phe	Trp	Gly	Pro	Gly	Thr	Met	Val	Thr	Val	Ser	Ser		
		130				135					140						
Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg		
145					150					155					160		
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr		
			165						170					175			
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser		
		180						185					190				
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser		
		195					200					205					
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr		
	210					215					220						
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys		
225					230					235					240		
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Ser	Cys	Pro	Ala	Pro		
			245						250					255			
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys		
		260						265					270				
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val		
		275					280					285					
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp		
	290					295					300						
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe		
305					310					315					320		
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp		
			325						330					335			
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu		
		340						345					350				
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg		
		355					360					365					
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys		
	370					375					380						
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp		
385					390					395					400		
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys		
			405						410					415			
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser		
		420						425					430				
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser		
		435					440					445					
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser		
	450					455					460						
Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Ser	Thr	Val	Ala	Ala	Cys	Asn	Leu		
465					470					475					480		
Pro	Ile	Val	Arg	Gly	Pro	Cys	Arg	Ala	Phe	Ile	Gln	Leu	Trp	Ala	Phe		
			485						490					495			

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Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln
500 505 510

Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys Arg Glu Tyr Cys
515 520 525

Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn
530 535 540

<210> SEQ ID NO 5

<211> LENGTH: 1629

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024D-D2(3)

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(1629)

<400> SEQUENCE: 5

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Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser
1 5 10 15

gct caa gca cag atc cag ttg gta cag tct gga cct gaa ctg aag aag 96
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
20 25 30

cct gga gag tca gtg aag atc tcc tgc aag gct tct ggg tat acc ttc 144
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

aca gac tat gca atg aac tgg gtg aaa cag gct cca gga aat ggc ttg 192
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu
50 55 60

aag tgg atg ggc tgg atc aac acc caa act gga aag cca aca tat gcg 240
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala
65 70 75 80

gat gat ttc aaa caa cgg ttt gtc ttc tct ttg gaa act tct gcc agc 288
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser
85 90 95

act gca tac ttg cag atc aac aac ctc aat att gag gac aca gct aca 336
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr
100 105 110

tat ttc tgt aca aga tcc act ttt tac tat agc agc tat atc tac ggg 384
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly
115 120 125

tgg tac ttt gac ttc tgg ggc cca gga acc atg gtc acc gtc tcc agc 432
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser
130 135 140

gct agc acc aag ggc cca tcc gtc ttc ccc ctg gcg ccc tgc tcc agg 480
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145 150 155 160

agc acc tcc gag agc aca gcc gcc ctg ggc tgc ctg gtc aag gac tat 528
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
165 170 175

ttc ccc gaa ccg gtg acg gtg tgg tgg aac tca ggt gcc ctg acc agc 576
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
180 185 190

ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc 624
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
195 200 205

ctc agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acg aag acc 672
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
210 215 220

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tac acc tgc aac gta gat cac aag ccc agc aac acc aag gtg gac aag Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys 225 230 235 240	720
aga gtt gag tcc aaa tat ggt ccc cca tgc cca tca tgc cca gca cct Arg Val Glu Ser Lys Tyr Gly Pro Cys Pro Ser Cys Pro Ala Pro 245 250 255	768
gag ttc ctg ggg gga cca tca gtc ttc ctg ttc ccc cca aaa ccc aag Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys 260 265 270	816
gac act ctc atg atc tcc cgg acc cct gag gtc acg tgc gtg gtg gtg Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val 275 280 285	864
gac gtg agc cag gaa gac ccc gag gtc cag ttc aac tgg tac gtg gat Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp 290 295 300	912
ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag ttc Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 305 310 315 320	960
aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp 325 330 335	1008
tgg ctg aac ggc aag gag tac aag tgc aag gtc tcc aac aaa ggc ctc Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu 340 345 350	1056
ccg tcc tcc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg 355 360 365	1104
gag cca cag gtg tac acc ctg ccc cca tcc cag gag gag atg acc aag Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys 370 375 380	1152
aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tac ccc agc gac Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp 385 390 395 400	1200
atc gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys 405 410 415	1248
acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser 420 425 430	1296
agg cta acc gtg gac aag agc agg tgg cag gag ggg aat gtc ttc tca Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser 435 440 445	1344
tgc tcc gtg atg cat gag gct ctg cac aac cac tac aca cag aag agc Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser 450 455 460	1392
ctc tcc ctg tct ctg ggt aaa gga tcc act gtg gcg gcc tgc aat cta Leu Ser Leu Ser Leu Gly Lys Gly Ser Thr Val Ala Ala Cys Asn Leu 465 470 475 480	1440
cca ata gtc agc ggc ccc tgc cga gcc ttc atc aag ctc tgg gca ttt Pro Ile Val Ser Gly Pro Cys Arg Ala Phe Ile Lys Leu Trp Ala Phe 485 490 495	1488
gat gct gtc aag ggg aag tgc gtc ctc ttc ccc tac ggg ggc tgc cag Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln 500 505 510	1536
ggc aac ggg aac aag ttc gac tca gag aag gag tgc aga gag tac tgc Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys Glu Cys Arg Glu Tyr Cys 515 520 525	1584

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ggg gtc cct ggt gat ggt gat gag gag ctg ctg cgc ttc tcc aac      1629
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<210> SEQ ID NO 6
<211> LENGTH: 543
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024D-D2(3)

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<400> SEQUENCE: 6

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Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
                20                      25                      30

Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
    35                      40                      45

Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu
    50                      55                      60

Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala
    65                      70                      75                      80

Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser
                85                      90                      95

Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr
    100                      105                      110

Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly
    115                      120                      125

Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser
    130                      135                      140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
    145                      150                      155                      160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
                165                      170                      175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
    180                      185                      190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    195                      200                      205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
    210                      215                      220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
    225                      230                      235                      240

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
                245                      250                      255

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    260                      265                      270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    275                      280                      285

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
    290                      295                      300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
    305                      310                      315                      320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                325                      330                      335

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Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
340 345 350

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
355 360 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385 390 395 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
405 410 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
435 440 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
450 455 460

Leu Ser Leu Ser Leu Gly Lys Gly Ser Thr Val Ala Ala Cys Asn Leu
465 470 475 480

Pro Ile Val Ser Gly Pro Cys Arg Ala Phe Ile Lys Leu Trp Ala Phe
485 490 495

Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln
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Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys Glu Cys Arg Glu Tyr Cys
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Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn
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<210> SEQ ID NO 7
<211> LENGTH: 1860
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024S-D1D2
<220> FEATURE:
<221> NAME/KEY: CDS
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<400> SEQUENCE: 7

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gct caa gca cag atc cag ttg gta cag tct gga cct gaa ctg aag aag	96
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys	
20 25 30	
cct gga gag tca gtg aag atc tcc tgc aag gct tct ggg tat acc ttc	144
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe	
35 40 45	
aca gac tat gca atg aac tgg gtg aaa cag gct cca gga aat ggc ttg	192
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu	
50 55 60	
aag tgg atg ggc tgg atc aac acc caa act gga aag cca aca tat gcg	240
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala	
65 70 75 80	
gat gat ttc aaa caa cgg ttt gtc ttc tct ttg gaa act tct gcc agc	288
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	
85 90 95	
act gca tac ttg cag atc aac aac ctc aat att gag gac aca gct aca	336

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tat	ttc	tgt	aca	aga	tcc	act	ttt	tac	tat	agc	agc	tat	atc	tac	ggg	384
Tyr	Phe	Cys	Thr	Arg	Ser	Thr	Phe	Tyr	Tyr	Ser	Ser	Tyr	Ile	Tyr	Gly	
		115					120					125				
tgg	tac	ttt	gac	ttc	tgg	ggc	cca	gga	acc	atg	gtc	acc	gtc	tcc	agc	432
Trp	Tyr	Phe	Asp	Phe	Trp	Gly	Pro	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	
	130					135					140					
gct	agc	acc	aag	ggc	cca	tcc	gtc	ttc	ccc	ctg	gcg	ccc	tgc	tcc	agg	480
Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	
145					150				155					160		
agc	acc	tcc	gag	agc	aca	gcc	gcc	ctg	ggc	tgc	ctg	gtc	aag	gac	tat	528
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	
			165					170					175			
ttc	ccc	gaa	ccg	gtg	acg	gtg	tcg	tgg	aac	tca	ggg	gcc	ctg	acc	agc	576
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	
		180					185					190				
ggc	gtg	cac	acc	ttc	ccg	gct	gtc	cta	cag	tcc	tca	gga	ctc	tac	tcc	624
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	
	195					200					205					
ctc	agc	agc	gtg	gtg	acc	gtg	ccc	tcc	agc	agc	ttg	ggc	acg	aag	acc	672
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	
	210					215					220					
tac	acc	tgc	aac	gta	gat	cac	aag	ccc	agc	aac	acc	aag	gtg	gac	aag	720
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	
225					230				235					240		
aga	gtt	gag	tcc	aaa	tat	ggg	ccc	cca	ggc	cca	tca	ggc	cca	gca	cct	768
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Gly	Pro	Ser	Gly	Pro	Ala	Pro	
			245					250					255			
gag	ttc	ctg	ggg	gga	cca	tca	gtc	ttc	ctg	ttc	ccc	cca	aaa	ccc	aag	816
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	
	260						265					270				
gac	act	ctc	atg	atc	tcc	cgg	acc	cct	gag	gtc	acg	tgc	gtg	gtg	gtg	864
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	
	275						280					285				
gac	gtg	agc	cag	gaa	gac	ccc	gag	gtc	cag	ttc	aac	tgg	tac	gtg	gat	912
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	
	290					295					300					
ggc	gtg	gag	gtg	cat	aat	gcc	aag	aca	aag	ccg	cgg	gag	gag	cag	ttc	960
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	
305					310					315				320		
aac	agc	acg	tac	cgt	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	1008
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
			325						330				335			
tgg	ctg	aac	ggc	aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	aaa	ggc	ctc	1056
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	
	340						345					350				
ccg	tcc	tcc	atc	gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggg	cag	ccc	cga	1104
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
	355					360						365				
gag	cca	cag	gtg	tac	acc	ctg	ccc	cca	tcc	cag	gag	gag	atg	acc	aag	1152
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	
	370					375					380					
aac	cag	gtc	agc	ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tac	ccc	agc	gac	1200
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	
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atc	gcc	gtg	gag	tgg	gag	agc	aat	ggg	cag	ccg	gag	aac	aac	tac	aag	1248
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	

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acc	acg	cct	ccc	gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	tac	agc	1296																		
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser																			
420																425						430												
agg	cta	acc	gtg	gac	aag	agc	agg	tgg	cag	gag	ggg	aat	gtc	ttc	tca	1344																		
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser																			
435																440						445												
tgc	tcc	gtg	atg	cat	gag	gct	ctg	cac	aac	cac	tac	aca	cag	aag	agc	1392																		
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser																			
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ctc	tcc	ctg	tct	ctg	ggc	aaa	gga	tcc	gct	gtg	cta	ccc	caa	gaa	gag	1440																		
Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Ser	Ala	Val	Leu	Pro	Gln	Glu	Glu																			
465																470						475						480						
gaa	gga	tca	ggg	ggc	ggg	caa	ctg	gta	act	gaa	gtc	acc	aag	aaa	gaa	1488																		
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gat	tcc	tgc	cag	ctg	ggc	tac	tcg	gcc	ggc	ccc	tgc	atg	gga	atg	acc	1536																		
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Ser	Arg	Tyr	Phe	Tyr	Asn	Gly	Thr	Ser	Met	Ala	Cys	Glu	Thr	Phe	Gln																			
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tac	ggc	ggc	tgc	atg	ggc	aac	ggc	aac	aac	ttc	gtc	aca	gaa	aag	gag	1632																		
Tyr	Gly	Gly	Cys	Met	Gly	Asn	Gly	Asn	Asn	Phe	Val	Thr	Glu	Lys	Glu																			
530																535						540												
tgt	ctg	cag	acc	tgc	cga	act	gtg	gcg	gcc	tgc	aat	ctc	ccc	ata	gtc	1680																		
Cys	Leu	Gln	Thr	Cys	Arg	Thr	Val	Ala	Ala	Cys	Asn	Leu	Pro	Ile	Val																			
545																550						555						560						
cgg	ggc	ccc	tgc	cga	gcc	ttc	atc	cag	ctc	tgg	gca	ttt	gat	gct	gtc	1728																		
Arg	Gly	Pro	Cys	Arg	Ala	Phe	Ile	Gln	Leu	Trp	Ala	Phe	Asp	Ala	Val																			
565																570						575												
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Lys	Gly	Lys	Cys	Val	Leu	Phe	Pro	Tyr	Gly	Gly	Cys	Gln	Gly	Asn	Gly																			
580																585						590												
aac	aag	ttc	tac	tca	gag	aag	gag	tgc	aga	gag	tac	tgc	ggc	gtc	cct	1824																		
Asn	Lys	Phe	Tyr	Ser	Glu	Lys	Glu	Cys	Arg	Glu	Tyr	Cys	Gly	Val	Pro																			
595																600						605												
ggc	gat	ggc	gat	gag	gag	ctg	ctg	cgc	ttc	tcc	aac						1860																	
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Ala	Gln	Ala	Gln	Ile	Gln	Leu	Val	Gln	Ser	Gly	Pro	Glu	Leu	Lys	Lys																			
20																25						30												
Pro	Gly	Glu	Ser	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe																			
35																40						45												
Thr	Asp	Tyr	Ala	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Asn	Gly	Leu																			
50																55						60												
Lys	Trp	Met	Gly	Trp	Ile	Asn	Thr	Gln	Thr	Gly	Lys	Pro	Thr	Tyr	Ala																			

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65	70				75				80			
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	85				90				95			
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr	100				105				110			
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly	115				120				125			
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser	130				135				140			
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg	145				150				155			
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr	165				170				175			
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser	180				185				190			
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser	195				200				205			
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr	210				215				220			
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys	225				230				235			
Arg Val Glu Ser Lys Tyr Gly Pro Pro Gly Pro Ser Gly Pro Ala Pro	245				250				255			
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys	260				265				270			
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val	275				280				285			
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp	290				295				300			
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe	305				310				315			
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp	325				330				335			
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu	340				345				350			
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg	355				360				365			
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys	370				375				380			
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp	385				390				395			
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys	405				410				415			
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser	420				425				430			
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser	435				440				445			
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser	450				455				460			
Leu Ser Leu Ser Leu Gly Lys Gly Ser Ala Val Leu Pro Gln Glu Glu	465				470				475			

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Glu	Gly	Ser	Gly	Gly	Gly	Gln	Leu	Val	Thr	Glu	Val	Thr	Lys	Lys	Glu
			485						490					495	
Asp	Ser	Cys	Gln	Leu	Gly	Tyr	Ser	Ala	Gly	Pro	Cys	Met	Gly	Met	Thr
			500					505					510		
Ser	Arg	Tyr	Phe	Tyr	Asn	Gly	Thr	Ser	Met	Ala	Cys	Glu	Thr	Phe	Gln
		515					520					525			
Tyr	Gly	Gly	Cys	Met	Gly	Asn	Gly	Asn	Asn	Phe	Val	Thr	Glu	Lys	Glu
	530					535					540				
Cys	Leu	Gln	Thr	Cys	Arg	Thr	Val	Ala	Ala	Cys	Asn	Leu	Pro	Ile	Val
545					550					555					560
Arg	Gly	Pro	Cys	Arg	Ala	Phe	Ile	Gln	Leu	Trp	Ala	Phe	Asp	Ala	Val
				565					570					575	
Lys	Gly	Lys	Cys	Val	Leu	Phe	Pro	Tyr	Gly	Gly	Cys	Gln	Gly	Asn	Gly
			580					585					590		
Asn	Lys	Phe	Tyr	Ser	Glu	Lys	Glu	Cys	Arg	Glu	Tyr	Cys	Gly	Val	Pro
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Gly	Asp	Gly	Asp	Glu	Glu	Leu	Leu	Arg	Phe	Ser	Asn				
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<210> SEQ ID NO 9
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 <213> ORGANISM: Artificial Sequence
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 <223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024S-D2
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 <221> NAME/KEY: CDS
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gct caa gca cag atc cag ttg gta cag tct gga cct gaa ctg aag aag	96
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys	
20 25 30	
cct gga gag tca gtg aag atc tcc tgc aag gct tct ggg tat acc ttc	144
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe	
35 40 45	
aca gac tat gca atg aac tgg gtg aaa cag gct cca gga aat ggc ttg	192
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu	
50 55 60	
aag tgg atg ggc tgg atc aac acc caa act gga aag cca aca tat gcg	240
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala	
65 70 75 80	
gat gat ttc aaa caa cgg ttt gtc ttc tct ttg gaa act tct gcc agc	288
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	
85 90 95	
act gca tac ttg cag atc aac aac ctc aat att gag gac aca gct aca	336
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr	
100 105 110	
tat ttc tgt aca aga tcc act ttt tac tat agc agc tat atc tac ggg	384
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly	
115 120 125	
tgg tac ttt gac ttc tgg ggc cca gga acc atg gtc acc gtc tcc agc	432
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser	
130 135 140	
gct agc acc aag ggc cca tcc gtc ttc ccc ctg gcg ccc tgc tcc agg	480

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Ala 145	Ser	Thr	Lys	Gly	Pro 150	Ser	Val	Phe	Pro	Leu 155	Ala	Pro	Cys	Ser	Arg 160	
agc	acc	tcc	gag	agc	aca	gcc	gcc	ctg	ggc	tgc	ctg	gtc	aag	gac	tat	528
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	
				165					170					175		
ttc	ccc	gaa	ccg	gtg	acg	gtg	tcg	tgg	aac	tca	ggc	gtc	acc	agc		576
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	
			180					185					190			
ggc	gtg	cac	acc	ttc	ccg	gct	gtc	cta	cag	tcc	tca	gga	ctc	tac	tcc	624
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	
			195				200					205				
ctc	agc	agc	gtg	gtg	acc	gtg	ccc	tcc	agc	agc	ttg	ggc	acg	aag	acc	672
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	
	210					215					220					
tac	acc	tgc	aac	gta	gat	cac	aag	ccc	agc	aac	acc	aag	gtg	gac	aag	720
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	
	225				230				235					240		
aga	gtt	gag	tcc	aaa	tat	ggc	ccc	cca	ggc	cca	tca	ggc	cca	gca	cct	768
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Gly	Pro	Ser	Gly	Pro	Ala	Pro	
				245				250						255		
gag	ttc	ctg	ggg	gga	cca	tca	gtc	ttc	ctg	ttc	ccc	cca	aaa	ccc	aag	816
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	
			260				265						270			
gac	act	ctc	atg	atc	tcc	cgg	acc	cct	gag	gtc	acg	tgc	gtg	gtg	gtg	864
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	
	275					280						285				
gac	gtg	agc	cag	gaa	gac	ccc	gag	gtc	cag	ttc	aac	tgg	tac	gtg	gat	912
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	
	290					295					300					
ggc	gtg	gag	gtg	cat	aat	gcc	aag	aca	aag	ccg	cgg	gag	gag	cag	ttc	960
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	
	305				310					315				320		
aac	agc	acg	tac	cgt	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	1008
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
				325				330						335		
tgg	ctg	aac	ggc	aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	aaa	ggc	ctc	1056
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	
			340				345						350			
ccg	tcc	tcc	atc	gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggg	cag	ccc	cga	1104
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
			355				360					365				
gag	cca	cag	gtg	tac	acc	ctg	ccc	cca	tcc	cag	gag	gag	atg	acc	aag	1152
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	
	370					375					380					
aac	cag	gtc	agc	ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tac	ccc	agc	gac	1200
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	
	385				390				395					400		
atc	gcc	gtg	gag	tgg	gag	agc	aat	ggg	cag	ccg	gag	aac	aac	tac	aag	1248
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	
			405					410						415		
acc	acg	cct	ccc	gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	tac	agc	1296
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	
			420					425					430			
agg	cta	acc	gtg	gac	aag	agc	agg	tgg	cag	gag	ggg	aac	gtc	ttc	tca	1344
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	
			435				440					445				
tgc	tcc	gtg	atg	cat	gag	gct	ctg	cac	aac	cac	tac	aca	cag	aag	agc	1392
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	

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450	455	460	
ctc tcc ctg tct ctg ggt aaa gga tcc act gtg gcg gcc tgc aat ctc			1440
Leu Ser Leu Ser Leu Gly Lys Gly Ser Thr Val Ala Ala Cys Asn Leu			
465	470	475	480
ccc ata gtc cgg ggc ccc tgc cga gcc ttc atc cag ctc tgg gca ttt			1488
Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile Gln Leu Trp Ala Phe			
	485	490	495
gat gct gtc aag ggg aag tgc gtc ctc ttc ccc tac ggg ggc tgc cag			1536
Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln			
	500	505	510
ggc aac ggg aac aag ttc tac tca gag aag gag tgc aga gag tac tgc			1584
Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys Arg Glu Tyr Cys			
	515	520	525
ggg gtc cct ggt gat ggt gat gag gag ctg ctg cgc ttc tcc aac			1629
Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn			
	530	535	540

<210> SEQ ID NO 10

<211> LENGTH: 543

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024S-D2

<400> SEQUENCE: 10

Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser		
1	5	15
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys		
	20	30
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe		
	35	45
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu		
	50	60
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala		
	65	80
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser		
	85	95
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr		
	100	110
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly		
	115	125
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser		
	130	140
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg		
	145	160
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr		
	165	175
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser		
	180	190
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser		
	195	205
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr		
	210	220
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys		
	225	240

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<210> SEQ ID NO 11
<211> LENGTH: 1629
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024S-D2(3)
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1) .. (1629)

<400> SEQUENCE: 11
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atg	gat	tgg	tgt	tgg	aac	ttg	cta	ttc	ctg	atg	gta	ggt	gcc	caa	agt	48
Met	Asp	Trp	Leu	Trp	Asn	Leu	Leu	Phe	Leu	Met	Val	Val	Ala	Gln	Ser	
1				5					10					15		
gct	caa	gca	cag	atc	cag	ttg	gta	cag	tct	gga	cct	gaa	ctg	aag	aag	96
Ala	Gln	Ala	Gln	Ile	Gln	Leu	Val	Gln	Ser	Gly	Pro	Glu	Leu	Lys	Lys	
			20					25					30			

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cct gga gag tca gtg aag atc tcc tgc aag gct tct ggg tat acc ttc	144
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe	
35 40 45	
aca gac tat gca atg aac tgg gtg aaa cag gct cca gga aat ggc ttg	192
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu	
50 55 60	
aag tgg atg ggc tgg atc aac acc caa act gga aag cca aca tat gcg	240
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala	
65 70 75 80	
gat gat ttc aaa caa cgg ttt gtc ttc tct ttg gaa act tct gcc agc	288
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	
85 90 95	
act gca tac ttg cag atc aac aac ctg aat att gag gac aca gct aca	336
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr	
100 105 110	
tat ttc tgt aca aga tcc act ttt tac tat agc agc tat atc tac ggg	384
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly	
115 120 125	
tgg tac ttt gac ttc tgg ggc cca gga acc atg gtc acc gtc tcc agc	432
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser	
130 135 140	
gct agc acc aag ggc cca tcc gtc ttc ccc ctg gcg ccc tgc tcc agg	480
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg	
145 150 155 160	
agc acc tcc gag agc aca gcc gcc ctg ggc tgc ctg gtc aag gac tat	528
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr	
165 170 175	
ttc ccc gaa ccg gtg acg gtg tcg tgg aac tca ggt gcc ctg acc agc	576
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser	
180 185 190	
ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctg tac tcc	624
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser	
195 200 205	
ctc agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acg aag acc	672
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr	
210 215 220	
tac acc tgc aac gta gat cac aag ccc agc aac acc aag gtg gac aag	720
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys	
225 230 235 240	
aga gtt gag tcc aaa tat ggt ccc cca ggc cca tca ggc cca gca cct	768
Arg Val Glu Ser Lys Tyr Gly Pro Pro Gly Pro Ser Gly Pro Ala Pro	
245 250 255	
gag ttc ctg ggg gga cca tca gtc ttc ctg ttc ccc cca aaa ccc aag	816
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys	
260 265 270	
gac act ctg atg atc tcc cgg acc cct gag gtc acg tgc gtg gtg gtg	864
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val	
275 280 285	
gac gtg agc cag gaa gac ccc gag gtc cag ttc aac tgg tac gtg gat	912
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp	
290 295 300	
ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag ttc	960
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe	
305 310 315 320	
aac agc acg tac cgt gtg gtc agc gtc ctg acc gtc ctg cac cag gac	1008
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp	
325 330 335	

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tgg ctg aac ggc aag gag tac aag tgc aag gtc tcc aac aaa ggc ctc Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu 340 345 350	1056
ccg tcc tcc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg 355 360 365	1104
gag cca cag gtg tac acc ctg ccc cca tcc cag gag gag atg acc aag Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys 370 375 380	1152
aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tac ccc agc gac Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp 385 390 395 400	1200
atc gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys 405 410 415	1248
acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser 420 425 430	1296
agg cta acc gtg gac aag agc agg tgg cag gag ggg aat gtc ttc tca Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser 435 440 445	1344
tgc tcc gtg atg cat gag gct ctg cac aac cac tac aca cag aag agc Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser 450 455 460	1392
ctc tcc ctg tct ctg ggt aaa gga tcc act gtg gcg gcc tgc aat cta Leu Ser Leu Ser Leu Gly Lys Gly Ser Thr Val Ala Ala Cys Asn Leu 465 470 475 480	1440
cca ata gtc agc ggc ccc tgc cga gcc ttc atc aag ctc tgg gca ttt Pro Ile Val Ser Gly Pro Cys Arg Ala Phe Ile Lys Leu Trp Ala Phe 485 490 495	1488
gat gct gtc aag ggg aag tgc gtc ctc ttc ccc tac ggg ggc tgc cag Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln 500 505 510	1536
ggc aac ggg aac aag ttc gac tca gag aag gag tgc aga gag tac tgc Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys Glu Cys Arg Glu Tyr Cys 515 520 525	1584
ggt gtc cct ggt gat ggt gat gag gag ctg ctg cgc ttc tcc aac Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn 530 535 540	1629

<210> SEQ ID NO 12

<211> LENGTH: 543

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein F1024S-D2(3)

<400> SEQUENCE: 12

Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser 1 5 10 15
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys 20 25 30
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe 35 40 45
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu 50 55 60
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala 65 70 75 80

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Asp	Asp	Phe	Lys	Gln	Arg	Phe	Val	Phe	Ser	Leu	Glu	Thr	Ser	Ala	Ser	
			85						90					95		
Thr	Ala	Tyr	Leu	Gln	Ile	Asn	Asn	Leu	Asn	Ile	Glu	Asp	Thr	Ala	Thr	
			100					105					110			
Tyr	Phe	Cys	Thr	Arg	Ser	Thr	Phe	Tyr	Tyr	Ser	Ser	Tyr	Ile	Tyr	Gly	
		115					120					125				
Trp	Tyr	Phe	Asp	Phe	Trp	Gly	Pro	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	
	130					135					140					
Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	
145					150					155					160	
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	
			165						170					175		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	
		180						185					190			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	
		195					200					205				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	
	210					215					220					
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	
225					230					235				240		
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Gly	Pro	Ser	Gly	Pro	Ala	Pro	
				245					250					255		
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	
		260						265					270			
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	
		275					280					285				
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	
	290					295					300					
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	
305					310					315				320		
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
				325					330					335		
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	
		340						345					350			
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
		355					360					365				
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	
	370					375					380					
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	
385					390					395				400		
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	
			405						410					415		
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	
		420						425					430			
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	
		435					440					445				
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	
	450					455					460					
Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Ser	Thr	Val	Ala	Ala	Cys	Asn	Leu	
465					470					475				480		
Pro	Ile	Val	Ser	Gly	Pro	Cys	Arg	Ala	Phe	Ile	Lys	Leu	Trp	Ala	Phe	
				485					490					495		

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Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln
500 505 510

Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys Glu Cys Arg Glu Tyr Cys
515 520 525

Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn
530 535 540

<210> SEQ ID NO 13

<211> LENGTH: 1737

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein
F1024D-SLPI (D1D2)

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1) .. (1737)

<400> SEQUENCE: 13

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1 5 10 15	
gct caa gca cag atc cag ttg gta cag tct gga cct gaa ctg aag aag	96
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys	
20 25 30	
cct gga gag tca gtg aag atc tcc tgc aag gct tct ggg tat acc ttc	144
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe	
35 40 45	
aca gac tat gca atg aac tgg gtg aaa cag gct cca gga aat ggc ttg	192
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu	
50 55 60	
aag tgg atg ggc tgg atc aac acc caa act gga aag cca aca tat gcg	240
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala	
65 70 75 80	
gat gat ttc aaa caa cgg ttt gtc ttc tct ttg gaa act tct gcc agc	288
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	
85 90 95	
act gca tac ttg cag atc aac aac ctc aat att gag gac aca gct aca	336
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr	
100 105 110	
tat ttc tgt aca aga tcc act ttt tac tat agc agc tat atc tac ggg	384
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly	
115 120 125	
tgg tac ttt gac ttc tgg ggc cca gga acc atg gtc acc gtc tcc agc	432
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser	
130 135 140	
gct agc acc aag ggc cca tcc gtc ttc ccc ctg gcg ccc tgc tcc agg	480
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg	
145 150 155 160	
agc acc tcc gag agc aca gcc gcc ctg ggc tgc ctg gtc aag gac tat	528
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr	
165 170 175	
ttc ccc gaa ccg gtg acg gtg tgg aac tca ggt gcc ctg acc agc	576
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser	
180 185 190	
ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc	624
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser	
195 200 205	
ctc agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acg aag acc	672

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Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	
210						215					220					
tac	acc	tgc	aac	gta	gat	cac	aag	ccc	agc	aac	acc	aag	gtg	gac	aag	720
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	
225					230					235					240	
aga	gtt	gag	tcc	aaa	tat	ggg	ccc	cca	tgc	cca	tca	tgc	cca	gca	cct	768
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Ser	Cys	Pro	Ala	Pro	
			245						250					255		
gag	ttc	ctg	ggg	gga	cca	tca	gtc	ttc	ctg	ttc	ccc	cca	aaa	ccc	aag	816
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	
			260					265					270			
gac	act	ctc	atg	atc	tcc	cgg	acc	cct	gag	gtc	acg	tgc	gtg	gtg	gtg	864
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	
		275					280					285				
gac	gtg	agc	cag	gaa	gac	ccc	gag	gtc	cag	ttc	aac	tgg	tac	gtg	gat	912
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	
	290					295					300					
ggc	gtg	gag	gtg	cat	aat	gcc	aag	aca	aag	ccg	cgg	gag	gag	cag	ttc	960
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	
305					310					315					320	
aac	agc	acg	tac	cgt	gtg	gtc	agc	gtc	ctc	acc	gtc	ctg	cac	cag	gac	1008
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
				325					330					335		
tgg	ctg	aac	ggc	aag	gag	tac	aag	tgc	aag	gtc	tcc	aac	aaa	ggc	ctc	1056
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	
			340					345					350			
ccg	tcc	tcc	atc	gag	aaa	acc	atc	tcc	aaa	gcc	aaa	ggg	cag	ccc	cga	1104
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
			355				360					365				
gag	cca	cag	gtg	tac	acc	ctg	ccc	cca	tcc	cag	gag	gag	atg	acc	aag	1152
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	
	370					375						380				
aac	cag	gtc	agc	ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tac	ccc	agc	gac	1200
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	
	385				390					395					400	
atc	gcc	gtg	gag	tgg	gag	agc	aat	ggg	cag	ccg	gag	aac	aac	tac	aag	1248
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	
				405				410						415		
acc	acg	cct	ccc	gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	tac	agc	1296
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	
			420					425					430			
agg	cta	acc	gtg	gac	aag	agc	agg	tgg	cag	gag	ggg	aat	gtc	ttc	tca	1344
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	
			435				440					445				
tgc	tcc	gtg	atg	cat	gag	gct	ctg	cac	aac	cac	tac	aca	cag	aag	agc	1392
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	
			450			455					460					
ctc	tcc	ctg	tct	ctg	ggg	aaa	gga	tct	gga	aag	tcc	ttc	aaa	gct	gga	1440
Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Ser	Gly	Lys	Ser	Phe	Lys	Ala	Gly	
				465		470				475				480		
gtc	tgt	cct	cct	aag	aaa	tct	gcc	cag	tgc	ctt	aga	tac	aag	aaa	cct	1488
Val	Cys	Pro	Pro	Lys	Lys	Ser	Ala	Gln	Cys	Leu	Arg	Tyr	Lys	Lys	Pro	
				485					490					495		
gag	tgc	cag	agt	gac	tgg	cag	tgt	cca	ggg	aag	aag	aga	tgt	tgt	cct	1536
Glu	Cys	Gln	Ser	Asp	Trp	Gln	Cys	Pro	Gly	Lys	Lys	Arg	Cys	Cys	Pro	
			500					505					510			
gac	act	tgt	ggc	atc	aaa	tgc	ctg	gat	cct	gtt	gac	acc	cca	aac	cca	1584
Asp	Thr	Cys	Gly	Ile	Lys	Cys	Leu	Asp	Pro	Val	Asp	Thr	Pro	Asn	Pro	

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515	520	525	
aca agg agg aag cct ggg aag tgc cca gtg act tat ggc caa tgt ttg			1632
Thr Arg Arg Lys Pro Gly Lys Cys Pro Val Thr Tyr Gly Gln Cys Leu			
530	535	540	
atg ctt aac ccc ccc aat ttc tgt gag atg gat ggc cag tgc aag cgt			1680
Met Leu Asn Pro Pro Asn Phe Cys Glu Met Asp Gly Gln Cys Lys Arg			
545	550	555	560
gac ttg aag tgt tgc atg ggc atg tgt ggg aaa tcc tgc gtt tcc cct			1728
Asp Leu Lys Cys Cys Met Gly Met Cys Gly Lys Ser Cys Val Ser Pro			
	565	570	575
gtg aaa gct			1737
Val Lys Ala			

<210> SEQ ID NO 14

<211> LENGTH: 579

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein
F1024D-SLPI (D1D2)

<400> SEQUENCE: 14

Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser			
1	5	10	15
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys			
	20	25	30
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe			
	35	40	45
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu			
	50	55	60
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala			
	65	70	75
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser			
	85	90	95
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr			
	100	105	110
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly			
	115	120	125
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser			
	130	135	140
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg			
	145	150	155
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr			
	165	170	175
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser			
	180	185	190
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser			
	195	200	205
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr			
	210	215	220
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys			
	225	230	235
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro			
	245	250	255
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys			

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260					265					270					
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val
275							280					285			
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp
290						295					300				
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe
305						310					315				320
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp
				325					330					335	
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu
			340					345					350		
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg
			355				360					365			
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys
	370					375					380				
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp
385						390					395				400
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
			405						410					415	
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser
			420					425					430		
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser
			435				440					445			
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser
			450			455					460				
Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Ser	Gly	Lys	Ser	Phe	Lys	Ala	Gly
465						470					475				480
Val	Cys	Pro	Pro	Lys	Lys	Ser	Ala	Gln	Cys	Leu	Arg	Tyr	Lys	Lys	Pro
				485					490					495	
Glu	Cys	Gln	Ser	Asp	Trp	Gln	Cys	Pro	Gly	Lys	Lys	Arg	Cys	Cys	Pro
			500					505					510		
Asp	Thr	Cys	Gly	Ile	Lys	Cys	Leu	Asp	Pro	Val	Asp	Thr	Pro	Asn	Pro
			515				520					525			
Thr	Arg	Arg	Lys	Pro	Gly	Lys	Cys	Pro	Val	Thr	Tyr	Gly	Gln	Cys	Leu
			530				535					540			
Met	Leu	Asn	Pro	Pro	Asn	Phe	Cys	Glu	Met	Asp	Gly	Gln	Cys	Lys	Arg
545						550					555				560
Asp	Leu	Lys	Cys	Cys	Met	Gly	Met	Cys	Gly	Lys	Ser	Cys	Val	Ser	Pro
				565					570					575	
Val	Lys	Ala													

<210> SEQ ID NO 15
 <211> LENGTH: 1569
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic Antibody fusion protein
 F1024D-SLPI(D2)
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (1)..(1569)
 <400> SEQUENCE: 15

atg gat tgg ttg tgg aac ttg cta ttc ctg atg gta gtt gcc caa agt
 Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser

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1	5	10	15	
gct caa gca cag atc cag ttg gta cag tct gga cct gaa ctg aag aag				96
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys				
	20	25	30	
cct gga gag tca gtg aag atc tcc tgc aag gct tct ggg tat acc ttc				144
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe				
	35	40	45	
aca gac tat gca atg aac tgg gtg aaa cag gct cca gga aat ggc ttg				192
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu				
	50	55	60	
aag tgg atg ggc tgg atc aac acc caa act gga aag cca aca tat gcg				240
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala				
	65	70	75	80
gat gat ttc aaa caa cgg ttt gtc ttc tct ttg gaa act tct gcc agc				288
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser				
	85	90	95	
act gca tac ttg cag atc aac aac ctg aat att gag gac aca gct aca				336
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr				
	100	105	110	
tat ttc tgt aca aga tcc act ttt tac tat agc agc tat atc tac ggg				384
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly				
	115	120	125	
tggtac ttt gac ttc tgg ggc cca gga acc atg gtc acc gtc tcc agc				432
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser				
	130	135	140	
gct agc acc aag ggc cca tcc gtc ttc ccc ctg ggc ccc tgc tcc agg				480
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg				
	145	150	155	160
agc acc tcc gag agc aca gcc gcc ctg ggc tgc ctg gtc aag gac tat				528
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr				
	165	170	175	
ttc ccc gaa ccg gtg acg gtg tgg tgg aac tca ggt gcc ctg acc agc				576
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser				
	180	185	190	
ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctg tac tcc				624
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser				
	195	200	205	
ctc agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acg aag acc				672
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr				
	210	215	220	
tac acc tgc aac gta gat cac aag ccc agc aac acc aag gtg gac aag				720
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys				
	225	230	235	240
aga gtt gag tcc aaa tat ggt ccc cca tgc cca tca tgc cca gca cct				768
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro				
	245	250	255	
gag ttc ctg ggg gga cca tca gtc ttc ctg ttc ccc cca aaa ccc aag				816
Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys				
	260	265	270	
gac act ctg atg atc tcc cgg acc cct gag gtc acg tgc gtg gtg gtg				864
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val				
	275	280	285	
gac gtg agc cag gaa gac ccc gag gtc cag ttc aac tgg tac gtg gat				912
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp				
	290	295	300	
ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag ttc				960
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe				
	305	310	315	320

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aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp 325 330 335	1008
tgg ctg aac ggc aag gag tac aag tgc aag gtc tcc aac aaa ggc ctc Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu 340 345 350	1056
ccg tcc tcc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg 355 360 365	1104
gag cca cag gtg tac acc ctg ccc cca tcc cag gag gag atg acc aag Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys 370 375 380	1152
aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tac ccc agc gac Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp 385 390 395 400	1200
atc gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys 405 410 415	1248
acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser 420 425 430	1296
agg cta acc gtg gac aag agc agg tgg cag gag ggg aat gtc ttc tca Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser 435 440 445	1344
tgc tcc gtg atg cat gag gct ctg cac aac cac tac aca cag aag agc Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser 450 455 460	1392
ctc tcc ctg tct ctg ggt aaa gga tct agg agg aag cct ggg aag tgc Leu Ser Leu Ser Leu Gly Lys Gly Ser Arg Arg Lys Pro Gly Lys Cys 465 470 475 480	1440
cca gtg act tat ggc caa tgt ttg atg ctt aac ccc ccc aat ttc tgt Pro Val Thr Tyr Gly Gln Cys Leu Met Leu Asn Pro Pro Asn Phe Cys 485 490 495	1488
gag atg gat ggc cag tgc aag cgt gac ttg aag tgt tgc atg ggc atg Glu Met Asp Gly Gln Cys Lys Arg Asp Leu Lys Cys Cys Met Gly Met 500 505 510	1536
tgt ggg aaa tcc tgc gtt tcc cct gtg aaa gct Cys Gly Lys Ser Cys Val Ser Pro Val Lys Ala 515 520	1569

<210> SEQ ID NO 16

<211> LENGTH: 523

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein
F1024D-SLPI (D2)

<400> SEQUENCE: 16

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

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65	70	75	80
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	85	90	95
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr	100	105	110
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly	115	120	125
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser	130	135	140
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg	145	150	155
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr	165	170	175
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser	180	185	190
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser	195	200	205
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr	210	215	220
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys	225	230	235
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro	245	250	255
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys	260	265	270
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val	275	280	285
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp	290	295	300
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe	305	310	315
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp	325	330	335
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu	340	345	350
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg	355	360	365
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys	370	375	380
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp	385	390	395
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys	405	410	415
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser	420	425	430
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser	435	440	445
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser	450	455	460
Leu Ser Leu Ser Leu Gly Lys Gly Ser Arg Arg Lys Pro Gly Lys Cys	465	470	475
			480

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<210> SEQ ID NO 17
<211> LENGTH: 1737
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Antibody fusion protein
      F1024S-SLPI (D1D2)
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1737)
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5																
gct Ala	caa Gln	gca Ala	cag Gln	atc Ile	cag Gln	ttg Leu	gta Val	cag Gln	tct Ser	gga Gly	cct Pro	gaa Glu	ctg Leu	aag Lys	aag Lys	96
20																
cct Pro	gga Gly	gag Glu	tca Ser	gtg Val	aag Lys	atc Ile	tcc Ser	tgc Cys	aag Lys	gct Ala	tct Ser	ggg Gly	tat Tyr	acc Thr	ttc Phe	144
35																
aca Thr	gac Asp	tat Tyr	gca Ala	atg Met	aac Asn	tgg Trp	gtg Val	aaa Lys	cag Gln	gct Ala	cca Pro	gga Gly	aat Asn	ggc Gly	ttg Leu	192
50																
aag Lys	tgg Trp	atg Met	ggc Gly	tgg Trp	atc Ile	aac Asn	acc Thr	caa Gln	act Thr	gga Gly	aag Lys	cca Pro	aca Thr	tat Tyr	gcg Ala	240
65																
gat Asp	gat Asp	ttc Phe	aaa Lys	caa Gln	cgg Arg	ttt Phe	gtc Val	ttc Phe	tct Ser	ttg Leu	gaa Glu	act Thr	tct Ser	gcc Ala	agc Ser	288
85																
act Thr	gca Ala	tac Tyr	ttg Leu	cag Gln	atc Ile	aac Asn	aac Asn	ctc Leu	aat Asn	att Ile	gag Glu	gac Asp	aca Thr	gct Ala	aca Thr	336
100																
tat Tyr	ttc Phe	tgt Cys	aca Thr	aga Arg	tcc Ser	act Thr	ttt Phe	tac Tyr	tat Tyr	agc Ser	agc Ser	tat Tyr	atc Ile	tac Tyr	ggg Gly	384
115																
tgg Trp	tac Tyr	ttt Phe	gac Asp	ttc Phe	tgg Trp	ggc Gly	cca Pro	gga Gly	acc Thr	atg Met	gtc Val	acc Thr	gtc Val	tcc Ser	agc Ser	432
130																
135																
gct Ala	agc Ser	acc Thr	aag Lys	ggc Gly	cca Pro	tcc Ser	gtc Val	ttc Phe	ccc Pro	ctg Leu	gcg Ala	ccc Pro	tgc Cys	tcc Ser	agg Arg	480
145																
agc Ser	acc Thr	tcc Ser	gag Glu	agc Ser	aca Thr	gcc Ala	gcc Ala	leu Leu	ggc Gly	tgc Cys	ctg Leu	gtc Val	aag Lys	gac Thr	tat Tyr	528
165																
ttc Phe	ccc Pro	gaa Glu	ccg Pro	gtg Val	acg Thr	gtg Val	tcg Ser	tgg Trp	aac Asn	tca Ser	ggt Gly	gcc Ala	ctg Leu	acc Thr	agc Ser	576
180																
185																
ggc Gly	gtg Val	cac His	acc Thr	ttc Phe	ccg Pro	gct Ala	gtc Val	cta Leu	cag Gln	tcc Ser	tca Ser	gga Gly	ctc Leu	tac Tyr	tcc Ser	624
195																
200																
ctc Leu	agc Ser	agc Ser	gtg Val	gtg Val	acc Thr	gtg Val	ccc Ser	tcc Ser	agc Ser	agc Ser	ttg Leu	ggc Gly	acg Thr	aag Lys	acc Thr	672

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210	215	220	
tac acc tgc aac gta gat cac aag ccc agc aac acc aag gtg gac aag			720
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys			
225	230	235	240
aga gtt gag tcc aaa tat ggt ccc cca ggc cca tca ggc cca gca cct			768
Arg Val Glu Ser Lys Tyr Gly Pro Pro Gly Pro Ser Gly Pro Ala Pro			
	245	250	255
gag ttc ctg ggg gga cca tca gtc ttc ctg ttc ccc cca aaa ccc aag			816
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys			
	260	265	270
gac act ctc atg atc tcc cgg acc cct gag gtc acg tgc gtg gtg gtg			864
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val			
	275	280	285
gac gtg agc cag gaa gac ccc gag gtc cag ttc aac tgg tac gtg gat			912
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp			
	290	295	300
ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag ttc			960
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe			
	305	310	315
aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac			1008
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp			
	325	330	335
tgg ctg aac ggc aag gag tac aag tgc aag gtc tcc aac aaa ggc ctc			1056
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu			
	340	345	350
ccg tcc tcc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga			1104
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg			
	355	360	365
gag cca cag gtg tac acc ctg ccc cca tcc cag gag gag atg acc aag			1152
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys			
	370	375	380
aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tac ccc agc gac			1200
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp			
	385	390	400
atc gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag			1248
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys			
	405	410	415
acc acg cct ccc gtg ctg gac tcc gag ggc tcc ttc ttc ctc tac agc			1296
Thr Thr Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser			
	420	425	430
agg cta acc gtg gac aag agc agg tgg cag gag ggg aat gtc ttc tca			1344
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser			
	435	440	445
tgc tcc gtg atg cat gag gct ctg cac aac cac tac aca cag aag agc			1392
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser			
	450	455	460
ctc tcc ctg tct ctg ggt aaa gga tct gga aag tcc ttc aaa gct gga			1440
Leu Ser Leu Ser Leu Gly Lys Gly Ser Gly Lys Ser Phe Lys Ala Gly			
	465	470	475
gtc tgt cct cct aag aaa tct gcc cag tgc ctt aga tac aag aaa cct			1488
Val Cys Pro Pro Lys Lys Ser Ala Gln Cys Leu Arg Tyr Lys Lys Pro			
	485	490	495
gag tgc cag agt gac tgg cag tgt cca ggg aag aag aga tgt tgt cct			1536
Glu Cys Gln Ser Asp Trp Gln Cys Pro Gly Lys Lys Arg Cys Cys Pro			
	500	505	510
gac act tgt ggc atc aaa tgc ctg gat cct gtt gac acc cca aac cca			1584
Asp Thr Cys Gly Ile Lys Cys Leu Asp Pro Val Asp Thr Pro Asn Pro			
	515	520	525

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aca agg agg aag cct ggg aag tgc cca gtg act tat ggc caa tgt ttg      1632
Thr Arg Arg Lys Pro Gly Lys Cys Pro Val Thr Tyr Gly Gln Cys Leu
    530                535                540

atg ctt aac ccc ccc aat ttc tgt gag atg gat ggc cag tgc aag cgt      1680
Met Leu Asn Pro Pro Asn Phe Cys Glu Met Asp Gly Gln Cys Lys Arg
    545                550                555                560

gac ttg aag tgt tgc atg ggc atg tgt ggg aaa tcc tgc gtt tcc cct      1728
Asp Leu Lys Cys Cys Met Gly Met Cys Gly Lys Ser Cys Val Ser Pro
                565                570                575

gtg aaa gct      1737
Val Lys Ala

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<210> SEQ ID NO 18
<211> LENGTH: 579
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Antibody fusion protein
      F1024S-SLPI (D1D2)

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<400> SEQUENCE: 18

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Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser
1          5          10          15

Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
          20          25          30

Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
          35          40          45

Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu
          50          55          60

Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala
65          70          75          80

Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser
          85          90          95

Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr
          100          105          110

Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly
          115          120          125

Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser
          130          135          140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
          145          150          155          160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
          165          170          175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
          180          185          190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
          195          200          205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
          210          215          220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
          225          230          235          240

Arg Val Glu Ser Lys Tyr Gly Pro Pro Gly Pro Ser Gly Pro Ala Pro
          245          250          255

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
          260          265          270

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Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    275                      280                      285

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
    290                      295                      300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
    305                      310                      315                      320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
    325                      330                      335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
    340                      345                      350

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    355                      360                      365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
    370                      375                      380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    385                      390                      395                      400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
    405                      410                      415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
    420                      425                      430

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    435                      440                      445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    450                      455                      460

Leu Ser Leu Ser Leu Gly Lys Gly Ser Gly Lys Ser Phe Lys Ala Gly
    465                      470                      475                      480

Val Cys Pro Pro Lys Lys Ser Ala Gln Cys Leu Arg Tyr Lys Lys Pro
    485                      490                      495

Glu Cys Gln Ser Asp Trp Gln Cys Pro Gly Lys Lys Arg Cys Cys Pro
    500                      505                      510

Asp Thr Cys Gly Ile Lys Cys Leu Asp Pro Val Asp Thr Pro Asn Pro
    515                      520                      525

Thr Arg Arg Lys Pro Gly Lys Cys Pro Val Thr Tyr Gly Gln Cys Leu
    530                      535                      540

Met Leu Asn Pro Pro Asn Phe Cys Glu Met Asp Gly Gln Cys Lys Arg
    545                      550                      555                      560

Asp Leu Lys Cys Cys Met Gly Met Cys Gly Lys Ser Cys Val Ser Pro
    565                      570                      575

Val Lys Ala

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<210> SEQ ID NO 19
<211> LENGTH: 1569
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Antibody fusion protein
    F1024S-SLPI (D2)
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1) .. (1569)

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<400> SEQUENCE: 19

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```

atg gat tgg ttg tgg aac ttg cta ttc ctg atg gta gtt gcc caa agt
Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser
1          5          10          15

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48

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gct caa gca cag atc cag ttg gta cag tct gga cct gaa ctg aag aag	96
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys	
20 25 30	
cct gga gag tca gtg aag atc tcc tgc aag gct tct ggg tat acc ttc	144
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe	
35 40 45	
aca gac tat gca atg aac tgg gtg aaa cag gct cca gga aat ggc ttg	192
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu	
50 55 60	
aag tgg atg ggc tgg atc aac acc caa act gga aag cca aca tat gcg	240
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala	
65 70 75 80	
gat gat ttc aaa caa cgg ttt gtc ttc tct ttg gaa act tct gcc agc	288
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	
85 90 95	
act gca tac ttg cag atc aac aac ctc aat att gag gac aca gct aca	336
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr	
100 105 110	
tat ttc tgt aca aga tcc act ttt tac tat agc agc tat atc tac ggg	384
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly	
115 120 125	
tgg tac ttt gac ttc tgg ggc cca gga acc atg gtc acc gtc tcc agc	432
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser	
130 135 140	
gct agc acc aag ggc cca tcc gtc ttc ccc ctg gcg ccc tgc tcc agg	480
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg	
145 150 155 160	
agc acc tcc gag agc aca gcc gcc ctg ggc tgc ctg gtc aag gac tat	528
Ser Thr Ser Glu Pro Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr	
165 170 175	
ttc ccc gaa ccg gtg acg gtg tcg tgg aac tca ggt gcc ctg acc agc	576
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser	
180 185 190	
ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc	624
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser	
195 200 205	
ctc agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acg aag acc	672
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr	
210 215 220	
tac acc tgc aac gta gat cac aag ccc agc aac acc aag gtg gac aag	720
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys	
225 230 235 240	
aga gtt gag tcc aaa tat ggt ccc cca ggc cca tca ggc cca gca cct	768
Arg Val Glu Ser Lys Tyr Gly Pro Pro Gly Pro Ser Gly Pro Ala Pro	
245 250 255	
gag ttc ctg ggg gga cca tca gtc ttc ctg ttc ccc cca aaa ccc aag	816
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys	
260 265 270	
gac act ctc atg atc tcc cgg acc cct gag gtc acg tgc gtg gtg gtg	864
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val	
275 280 285	
gac gtg agc cag gaa gac ccc gag gtc cag ttc aac tgg tac gtg gat	912
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp	
290 295 300	
ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag ttc	960
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe	
305 310 315 320	

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aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp 325 330 335	1008
tgg ctg aac ggc aag gag tac aag tgc aag gtc tcc aac aaa ggc ctc Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu 340 345 350	1056
ccg tcc tcc atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg 355 360 365	1104
gag cca cag gtg tac acc ctg ccc cca tcc cag gag gag atg acc aag Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys 370 375 380	1152
aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tac ccc agc gac Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp 385 390 395 400	1200
atc gcc gtg gag tgg gag agc aat ggg cag ccg gag aac aac tac aag Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys 405 410 415	1248
acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser 420 425 430	1296
agg cta acc gtg gac aag agc agg tgg cag gag ggg aat gtc ttc tca Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser 435 440 445	1344
tgc tcc gtg atg cat gag gct ctg cac aac cac tac aca cag aag agc Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser 450 455 460	1392
ctc tcc ctg tct ctg ggt aaa gga tct agg agg aag cct ggg aag tgc Leu Ser Leu Ser Leu Gly Lys Gly Ser Arg Arg Lys Pro Gly Lys Cys 465 470 475 480	1440
cca gtg act tat ggc caa tgt ttg atg ctt aac ccc ccc aat ttc tgt Pro Val Thr Tyr Gly Gln Cys Leu Met Leu Asn Pro Pro Asn Phe Cys 485 490 495	1488
gag atg gat ggc cag tgc aag cgt gac ttg aag tgt tgc atg ggc atg Glu Met Asp Gly Gln Cys Lys Arg Asp Leu Lys Cys Cys Met Gly Met 500 505 510	1536
tgt ggg aaa tcc tgc gtt tcc cct gtg aaa gct Cys Gly Lys Ser Cys Val Ser Pro Val Lys Ala 515 520	1569

<210> SEQ ID NO 20

<211> LENGTH: 523

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein
F1024S-SLPI (D2)

<400> SEQUENCE: 20

Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser
1 5 10 15Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
20 25 30Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu
50 55 60Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala
65 70 75 80

Asp	Asp	Phe	Lys	Gln	Arg	Phe	Val	Phe	Ser	Leu	Glu	Thr	Ser	Ala	Ser
			85												
Thr	Ala	Tyr	Leu	Gln	Ile	Asn	Asn	Leu	Asn	Ile	Glu	Asp	Thr	Ala	Thr
			100												
Tyr	Phe	Cys	Thr	Arg	Ser	Thr	Phe	Tyr	Tyr	Ser	Ser	Tyr	Ile	Tyr	Gly
			115												
Trp	Tyr	Phe	Asp	Phe	Trp	Gly	Pro	Gly	Thr	Met	Val	Thr	Val	Ser	Ser
			130												
Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg
			145												
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
			165												
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
			180												
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
			195												
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr
			210												
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			225												
Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Gly	Pro	Ser	Gly	Pro	Ala	Pro
			245												
Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys
			260												
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val
			275												
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp
			290												
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe
			305												
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp
			325												
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu
			340												
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg
			355												
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys
			370												
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp
			385												
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
			405												
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser
			420												
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser
			435												
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser
			450												
Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Ser	Arg	Arg	Lys	Pro	Gly	Lys	Cys
			465												
Pro	Val	Thr	Tyr	Gly	Gln	Cys	Leu	Met	Leu	Asn	Pro	Pro	Asn	Phe	Cys
			480												

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485										490					495					
Glu	Met	Asp	Gly	Gln	Cys	Lys	Arg	Asp	Leu	Lys	Cys	Cys	Met	Gly	Met					
			500						505					510						
Cys	Gly	Lys	Ser	Cys	Val	Ser	Pro	Val	Lys	Ala										
		515					520													
<210> SEQ ID NO 21																				
<211> LENGTH: 705																				
<212> TYPE: DNA																				
<213> ORGANISM: Artificial Sequence																				
<220> FEATURE:																				
<223> OTHER INFORMATION: Synthetic Antibody fusion protein, F1024 chimeric antibody light chain																				
<220> FEATURE:																				
<221> NAME/KEY: CDS																				
<222> LOCATION: (1)..(705)																				
<400> SEQUENCE: 21																				
atg	gag	tca	cat	act	agg	gtc	ttc	ata	ttc	ctg	ctg	ctc	tgg	ttg	tct	48				
Met	Glu	Ser	His	Thr	Arg	Val	Phe	Ile	Phe	Leu	Leu	Leu	Trp	Leu	Ser					
1				5				10						15						
ggt	gct	gat	ggg	gac	att	gtg	atg	act	cag	tct	ccc	aca	tcc	att	tcc	96				
Gly	Ala	Asp	Gly	Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Thr	Ser	Ile	Ser					
			20				25						30							
ata	tca	gta	gga	gag	agg	gtc	acc	atg	aac	tgc	aag	gcc	agt	cag	aat	144				
Ile	Ser	Val	Gly	Glu	Arg	Val	Thr	Met	Asn	Cys	Lys	Ala	Ser	Gln	Asn					
		35				40						45								
gtg	ggt	tct	aat	gta	gac	tgg	tac	caa	cag	aaa	aca	ggg	cag	tct	cct	192				
Val	Gly	Ser	Asn	Val	Asp	Trp	Tyr	Gln	Gln	Lys	Thr	Gly	Gln	Ser	Pro					
		50				55					60									
aaa	ctg	ctt	atc	tac	aag	gca	tcc	aac	cgg	tac	act	ggc	gtc	cct	gat	240				
Lys	Leu	Leu	Ile	Tyr	Lys	Ala	Ser	Asn	Arg	Tyr	Thr	Gly	Val	Pro	Asp					
		65			70				75				80							
cgc	ttc	aca	ggc	agt	gga	tct	gga	aca	gat	ttc	act	ttc	acc	atc	agc	288				
Arg	Phe	Thr	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser					
			85				90						95							
aac	atg	cag	gct	gtg	gac	ctg	gct	gtt	tat	tac	tgt	atg	cag	tct	aac	336				
Asn	Met	Gln	Ala	Val	Asp	Leu	Ala	Val	Tyr	Tyr	Cys	Met	Gln	Ser	Asn					
		100					105						110							
acc	aat	cct	ccg	tgg	acg	ttc	ggt	gga	ggc	acc	aag	ctg	gaa	ttg	aaa	384				
Thr	Asn	Pro	Pro	Trp	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Leu	Lys					
		115				120						125								
cgt	acg	gtg	gct	gca	cca	tct	gtc	ttc	atc	ttc	ccg	cca	tct	gat	gag	432				
Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu					
		130				135						140								
cag	ttg	aaa	tct	gga	act	gcc	tct	gtt	gtg	tgc	ctg	ctg	aat	aac	ttc	480				
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe					
		145			150				155					160						
tat	ccc	aga	gag	gcc	aaa	gta	cag	tgg	aag	gtg	gat	aac	gcc	ctc	caa	528				
Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln					
			165					170						175						
tcg	ggt	aac	tcc	cag	gag	agt	gtc	aca	gag	cag	gac	agc	aag	gac	agc	576				
Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser					
		180					185						190							
acc	tac	agc	ctc	agc	agc	acc	ctg	acg	ctg	agc	aaa	gca	gac	tac	gag	624				
Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu					
		195				200						205								
aaa	cac	aaa	gtc	tac	gcc	tgc	gaa	gtc	acc	cat	cag	ggc	ctg	agc	tcg	672				
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser					
		210				215						220								

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ccc gtc aca aag agc ttc aac agg gga gag tgt
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225          230          235

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705

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<210> SEQ ID NO 22
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Antibody fusion protein, F1024
        chimeric antibody light chain

```

<400> SEQUENCE: 22

```

Met Glu Ser His Thr Arg Val Phe Ile Phe Leu Leu Leu Trp Leu Ser
1          5          10          15
Gly Ala Asp Gly Asp Ile Val Met Thr Gln Ser Pro Thr Ser Ile Ser
20          25          30
Ile Ser Val Gly Glu Arg Val Thr Met Asn Cys Lys Ala Ser Gln Asn
35          40          45
Val Gly Ser Asn Val Asp Trp Tyr Gln Gln Lys Thr Gly Gln Ser Pro
50          55          60
Lys Leu Leu Ile Tyr Lys Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp
65          70          75          80
Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser
85          90          95
Asn Met Gln Ala Val Asp Leu Ala Val Tyr Tyr Cys Met Gln Ser Asn
100         105         110
Thr Asn Pro Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
115         120         125
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130         135         140
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145         150         155         160
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165         170         175
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180         185         190
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195         200         205
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
210         215         220
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225          230          235

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<210> SEQ ID NO 23
<211> LENGTH: 1614
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Antibody fusion protein
        F1031-13S-D2(3)
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(1614)

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<400> SEQUENCE: 23

```

atg gaa tgt aac tgg ata ctt cct ttt att ctg tgc gta att tca gga
Met Glu Cys Asn Trp Ile Leu Pro Phe Ile Leu Ser Val Ile Ser Gly

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48

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1	5	10	15	
gtc tac tca gag gtt cag ctc cag cag tct ggg act gtg ctg gca agg				96
Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg				
	20	25	30	
cct ggg gct tcc gtg aag atg tcc tgc aag gct tct ggc tac agg tat				144
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Arg Tyr				
	35	40	45	
acc aac tac tgg ttg cac tgg gta aaa cag agg cct gga cag ggt cta				192
Thr Asn Tyr Trp Leu His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu				
	50	55	60	
gag tgg att ggt gct att tat cct gga aat agt gat tct agc tac aac				240
Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Ser Asp Ser Ser Tyr Asn				
	65	70	75	80
cag aac ttc aag ggc aag gcc aaa ctg act gca gtc aca tcc gcc agc				288
Gln Asn Phe Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser				
	85	90	95	
act gcc tac atg gag ctc agc agc ctg aca aat gag gac tct gcg gtc				336
Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val				
	100	105	110	
tat tac tgt aca aga tgg ggc cct tat ggc atc tat gct atg gac tac				384
Tyr Tyr Cys Thr Arg Trp Gly Pro Tyr Gly Ile Tyr Ala Met Asp Tyr				
	115	120	125	
tgg ggt caa gga acc tca gtc acc gtc tcc agc gct agc acc aag ggc				432
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly				
	130	135	140	
cca tcc gtc ttc ccc ctg gcg ccc tgc tcc agg agc acc tcc gag agc				480
Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser				
	145	150	155	160
aca gcc gcc ctg ggc tgc ctg gtc aag gac tat ttc ccc gaa ccg gtg				528
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val				
	165	170	175	
acg gtg tgc tgg aac tca ggt gcc ctg acc agc ggc gtg cac acc ttc				576
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe				
	180	185	190	
ccg gct gtc cta cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg				624
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val				
	195	200	205	
acc gtg ccc tcc agc agc ttg ggc acg aag acc tac acc tgc aac gta				672
Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val				
	210	215	220	
gat cac aag ccc agc aac acc aag gtg gac aag aga gtt gag tcc aaa				720
Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys				
	225	230	235	240
tat ggt ccc cca ggc cca tca ggc cca gca cct gag ttc ctg ggg gga				768
Tyr Gly Pro Pro Gly Pro Ser Gly Pro Ala Pro Glu Phe Leu Gly Gly				
	245	250	255	
cca tca gtc ttc ctg ttc ccc cca aaa ccc aag gac act ctc atg atc				816
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile				
	260	265	270	
tcc cgg acc cct gag gtc acg tgc gtg gtg gtg gac gtg agc cag gaa				864
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu				
	275	280	285	
gac ccc gag gtc cag ttc aac tgg tac gtg gat ggc gtg gag gtg cat				912
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His				
	290	295	300	
aat gcc aag aca aag ccg cgg gag gag cag ttc aac agc acg tac cgt				960
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg				
	305	310	315	320

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gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aac ggc aag	1008
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys	
325 330 335	
gag tac aag tgc aag gtc tcc aac aaa ggc ctc ccg tcc tcc atc gag	1056
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu	
340 345 350	
aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gag cca cag gtg tac	1104
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr	
355 360 365	
acc ctg ccc cca tcc cag gag gag atg acc aag aac cag gtc agc ctg	1152
Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu	
370 375 380	
acc tgc ctg gtc aaa ggc ttc tac ccc agc gac atc gcc gtg gag tgg	1200
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp	
385 390 395 400	
gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct ccc gtg	1248
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val	
405 410 415	
ctg gac tcc gac ggc tcc ttc ttc ctc tac agc agg cta acc gtg gac	1296
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp	
420 425 430	
aag agc agg tgg cag gag ggg aat gtc ttc tca tgc tcc gtg atg cat	1344
Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His	
435 440 445	
gag gct ctg cac aac cac tac aca cag aag agc ctc tcc ctg tct ctg	1392
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu	
450 455 460	
ggg aaa gga tcc act gtg ggc gcc tgc aat cta cca ata gtc agc ggc	1440
Gly Lys Gly Ser Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly	
465 470 475 480	
ccc tgc cga gcc ttc atc aag ctc tgg gca ttt gat gct gtc aag ggg	1488
Pro Cys Arg Ala Phe Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly	
485 490 495	
aag tgc gtc ctc ttc ccc tac ggg ggc tgc cag gcc aac ggg aac aag	1536
Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys	
500 505 510	
ttc gac tca gag aag gag tgc aga gag tac tgc ggt gtc cct ggt gat	1584
Phe Asp Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp	
515 520 525	
ggg gat gag gag ctg ctg cgc ttc tcc aac	1614
Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn	
530 535	

<210> SEQ ID NO 24

<211> LENGTH: 538

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein
F1031-13S-D2(3)

<400> SEQUENCE: 24

Met Glu Cys Asn Trp Ile Leu Pro Phe Ile Leu Ser Val Ile Ser Gly
1 5 10 15Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg
20 25 30Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Arg Tyr
35 40 45

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Thr	Asn	Tyr	Trp	Leu	His	Trp	Val	Lys	Gln	Arg	Pro	Gly	Gln	Gly	Leu
50						55					60				
Glu	Trp	Ile	Gly	Ala	Ile	Tyr	Pro	Gly	Asn	Ser	Asp	Ser	Ser	Tyr	Asn
65					70					75					80
Gln	Asn	Phe	Lys	Gly	Lys	Ala	Lys	Leu	Thr	Ala	Val	Thr	Ser	Ala	Ser
				85					90					95	
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Thr	Asn	Glu	Asp	Ser	Ala	Val
			100					105					110		
Tyr	Tyr	Cys	Thr	Arg	Trp	Gly	Pro	Tyr	Gly	Ile	Tyr	Ala	Met	Asp	Tyr
		115					120					125			
Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly
	130					135					140				
Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser
145					150					155					160
Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val
			165						170					175	
Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe
			180					185					190		
Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val
		195					200					205			
Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val
	210					215					220				
Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys
225					230					235					240
Tyr	Gly	Pro	Pro	Gly	Pro	Ser	Gly	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly
				245					250					255	
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
			260					265					270		
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu
		275					280					285			
Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
	290					295					300				
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg
305					310					315					320
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
				325					330					335	
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu
		340						345					350		
Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
		355					360					365			
Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu
	370					375					380				
Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
385					390					395					400
Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val
				405					410					415	
Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp
			420					425					430		
Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His
		435					440					445			
Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu
	450					455					460				

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Gly Lys Gly Ser Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly
465 470 475 480

Pro Cys Arg Ala Phe Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly
485 490 495

Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys
500 505 510

Phe Asp Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp
515 520 525

Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn
530 535

<210> SEQ ID NO 25

<211> LENGTH: 714

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Antibody fusion protein, F1031-13
chimeric antibody light chain

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(714)

<400> SEQUENCE: 25

atg gag aca gac aca ctc ctg cta tgg gtc ctg ctt ctc tgg gtt cca 48
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

ggg tcc aca ggt gac att gtg ctg acc caa tct cca gct tct ttg gct 96
Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
20 25 30

gtg tct ctg ggg cag agg gcc acc atc tcc tgc aga gcc agc gaa agt 144
Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
35 40 45

gtt gat tat tct ggc att agt ttt atg aac tgg ttc caa cag aaa cca 192
Val Asp Tyr Ser Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro
50 55 60

gga cag cca ccc aaa ctc ctc atc tat gct gca tcc aac caa gga tcc 240
Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser
65 70 75 80

ggg gtc cct gcc agg ttt agt ggc agt ggg tct ggg aca gac ttc agc 288
Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser
85 90 95

ctc aac atc cat cct atg gag gag gat gat act gca atg tat ttc tgt 336
Leu Asn Ile His Pro Met Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys
100 105 110

cag cac agt aag gag ctt ccg tac acg ttc gga ggg ggg acc aag ctg 384
Gln His Ser Lys Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu
115 120 125

gaa atc aaa cgt acg gtg gct gca cca tct gtc ttc atc ttc ccg cca 432
Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
130 135 140

tct gat gag cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg 480
Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
145 150 155 160

aat aac ttc tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac 528
Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
165 170 175

gcc ctc caa tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc 576
Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
180 185 190

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aag gac agc acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca      624
Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
      195                200                205

gac tac gag aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc      672
Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
      210                215                220

ctg agc tcg ccc gtc aca aag agc ttc aac agg gga gag tgt      714
Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
      225                230                235

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<210> SEQ ID NO 26
<211> LENGTH: 238
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Antibody fusion protein, F1031-13
      chimeric antibody light chain

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<400> SEQUENCE: 26

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Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
 1              5              10              15

Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
      20              25              30

Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
      35              40              45

Val Asp Tyr Ser Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro
      50              55              60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser
      65              70              75              80

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser
      85              90              95

Leu Asn Ile His Pro Met Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys
      100             105             110

Gln His Ser Lys Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu
      115             120             125

Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
      130             135             140

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
      145             150             155             160

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
      165             170             175

Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
      180             185             190

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
      195             200             205

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
      210             215             220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
      225             230             235

```

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<210> SEQ ID NO 27
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15A)

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-continued

<400> SEQUENCE: 27

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Ala Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 28

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15C)

<400> SEQUENCE: 28

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Cys Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 29

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15D)

<400> SEQUENCE: 29

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Asp Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 30

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15E)

<400> SEQUENCE: 30

-continued

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Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Glu Ala
1           5           10           15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
           20           25           30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
           35           40           45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
           50           55           60
Leu Leu Arg Phe Ser Asn
65           70

```

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<210> SEQ ID NO 31
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2(R15F)

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<400> SEQUENCE: 31

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Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Phe Ala
1           5           10           15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
           20           25           30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
           35           40           45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
           50           55           60
Leu Leu Arg Phe Ser Asn
65           70

```

```

<210> SEQ ID NO 32
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024F-D2(R15G)

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<400> SEQUENCE: 32

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```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Gly Ala
1           5           10           15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
           20           25           30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
           35           40           45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
           50           55           60
Leu Leu Arg Phe Ser Asn
65           70

```

```

<210> SEQ ID NO 33
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024-D2(R15H)

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<400> SEQUENCE: 33

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Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys His Ala
1           5           10           15

```

-continued

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 34
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024-D2 (R15I)

<400> SEQUENCE: 34

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Ile Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 35
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15K)

<400> SEQUENCE: 35

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Lys Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 36
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15L)

<400> SEQUENCE: 36

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Leu Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Pro Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

-continued

```

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
   35                                40                                45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
   50                                55                                60

Leu Leu Arg Phe Ser Asn
  65                                70

```

```

<210> SEQ ID NO 40
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15Q)

```

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<400> SEQUENCE: 40

```

```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Gln Ala
 1           5           10           15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
 20           25           30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
 35           40           45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
 50           55           60

Leu Leu Arg Phe Ser Asn
 65           70

```

```

<210> SEQ ID NO 41
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15S)

```

```

<400> SEQUENCE: 41

```

```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Ser Ala
 1           5           10           15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
 20           25           30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
 35           40           45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
 50           55           60

Leu Leu Arg Phe Ser Asn
 65           70

```

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<210> SEQ ID NO 42
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15T)

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<400> SEQUENCE: 42

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Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Thr Ala
 1           5           10           15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
 20           25           30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
 35           40           45

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-continued

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 43
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15V)

<400> SEQUENCE: 43

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Val Ala
1 5 10 15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 44
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15W)

<400> SEQUENCE: 44

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Trp Ala
1 5 10 15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 45
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15Y)

<400> SEQUENCE: 45

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Tyr Ala
1 5 10 15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu

-continued

50	55	60
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Leu Leu Arg Phe Ser Asn
 65 70

<210> SEQ ID NO 46
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide
 F1024S-D2(R11S/R15I/Q19K/Y46D)

<400> SEQUENCE: 46

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Ile Ala
1 5 10 15
Phe Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 47
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15L/Q19K/Y46D)

<400> SEQUENCE: 47

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Leu Ala
1 5 10 15
Phe Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 48
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2(R11S/R15T/Q19K
 /Y46D)

<400> SEQUENCE: 48

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45

-continued

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 49
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2(R11S/R15V/Q19K/Y46D)

<400> SEQUENCE: 49

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Val Ala
1 5 10 15

Phe Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 50
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide
 F1024S-D2(R11S/R15T/Q19A/Y46D)

<400> SEQUENCE: 50

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15

Phe Ile Ala Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 51
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15T/Q19C/Y46D)

<400> SEQUENCE: 51

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15

Phe Ile Cys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45

-continued

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 52
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
(R11S/R15T/Q19D/Y46D)

<400> SEQUENCE: 52

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15

Phe Ile Asp Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 53
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
F1024S-D2(R11S/R15T/Q19E/Y46D)

<400> SEQUENCE: 53

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15

Phe Ile Glu Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 54
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
(R11S/R15T/Q19F/Y46D)

<400> SEQUENCE: 54

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15

Phe Ile Phe Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu

-continued

35	40	45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu		
50	55	60
Leu Leu Arg Phe Ser Asn		
65	70	

<210> SEQ ID NO 55
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15T/Q19G/Y46D)

<400> SEQUENCE: 55

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala		
1	5	10
Phe Ile Gly Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu		
20	25	30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu		
35	40	45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu		
50	55	60
Leu Leu Arg Phe Ser Asn		
65	70	

<210> SEQ ID NO 56
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide
 F1024S-D2(R11S/R15T/Q19H/Y46D)

<400> SEQUENCE: 56

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala		
1	5	10
Phe Ile His Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu		
20	25	30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu		
35	40	45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu		
50	55	60
Leu Leu Arg Phe Ser Asn		
65	70	

<210> SEQ ID NO 57
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15T/Q19I/Y46D)

<400> SEQUENCE: 57

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala		
1	5	10
Phe Ile Ile Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu		
20	25	30

-continued

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Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
   35                               40                               45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
   50                               55                               60

Leu Leu Arg Phe Ser Asn
65                               70

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<210> SEQ ID NO 58
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
      F1024S-D2(R11S/R15T/Q19L/Y46D)

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<400> SEQUENCE: 58

```

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Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1           5           10           15

Phe Ile Leu Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
   20           25           30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
   35           40           45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
   50           55           60

Leu Leu Arg Phe Ser Asn
65           70

```

```

<210> SEQ ID NO 59
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
      (R11S/R15T/Q19M/Y46D)

```

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<400> SEQUENCE: 59

```

```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1           5           10           15

Phe Ile Met Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
   20           25           30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
   35           40           45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
   50           55           60

Leu Leu Arg Phe Ser Asn
65           70

```

```

<210> SEQ ID NO 60
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
      (R11S/R15T/Q19N/Y46D)

```

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<400> SEQUENCE: 60

```

```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1           5           10           15

Phe Ile Asn Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
   20           25           30

```

-continued

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 61
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
F1024S-D2(R11S/R15T/Q19P/Y46D)

<400> SEQUENCE: 61

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Pro Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 62
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2(R11S/R15T/Y46D)

<400> SEQUENCE: 62

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 63
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
(R11S/R15T/Q19R/Y46D)

<400> SEQUENCE: 63

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Arg Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

-continued

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 64
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
(R11S/R15T/Q19S/Y46D)

<400> SEQUENCE: 64

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Ser Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 65
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
(R11S/R15T/Q19T/Y46D)

<400> SEQUENCE: 65

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Thr Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 66
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
(R11S/R15T/Q19V/Y46D)

<400> SEQUENCE: 66

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Val Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu

-continued

	20		25		30										
Phe	Pro	Tyr	Gly	Gly	Cys	Gln	Gly	Asn	Gly	Asn	Lys	Phe	Asp	Ser	Glu
	35						40					45			
Lys	Glu	Cys	Arg	Glu	Tyr	Cys	Gly	Val	Pro	Gly	Asp	Gly	Asp	Glu	Glu
	50					55				60					
Leu	Leu	Arg	Phe	Ser	Asn										
65					70										

<210> SEQ ID NO 67
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide
 F1024S-D2 (R11S/R15T/Q19W/Y46D)

<400> SEQUENCE: 67

Thr	Val	Ala	Ala	Cys	Asn	Leu	Pro	Ile	Val	Ser	Gly	Pro	Cys	Thr	Ala
1				5					10					15	
Phe	Ile	Trp	Leu	Trp	Ala	Phe	Asp	Ala	Val	Lys	Gly	Lys	Cys	Val	Leu
	20				25								30		
Phe	Pro	Tyr	Gly	Gly	Cys	Gln	Gly	Asn	Gly	Asn	Lys	Phe	Asp	Ser	Glu
	35					40						45			
Lys	Glu	Cys	Arg	Glu	Tyr	Cys	Gly	Val	Pro	Gly	Asp	Gly	Asp	Glu	Glu
	50					55				60					
Leu	Leu	Arg	Phe	Ser	Asn										
65					70										

<210> SEQ ID NO 68
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15T/Q19Y/Y46D)

<400> SEQUENCE: 68

Thr	Val	Ala	Ala	Cys	Asn	Leu	Pro	Ile	Val	Ser	Gly	Pro	Cys	Thr	Ala
1				5					10					15	
Phe	Ile	Tyr	Leu	Trp	Ala	Phe	Asp	Ala	Val	Lys	Gly	Lys	Cys	Val	Leu
	20				25								30		
Phe	Pro	Tyr	Gly	Gly	Cys	Gln	Gly	Asn	Gly	Asn	Lys	Phe	Asp	Ser	Glu
	35					40						45			
Lys	Glu	Cys	Arg	Glu	Tyr	Cys	Gly	Val	Pro	Gly	Asp	Gly	Asp	Glu	Glu
	50					55				60					
Leu	Leu	Arg	Phe	Ser	Asn										
65					70										

<210> SEQ ID NO 69
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15T/F17A/Y46D)

<400> SEQUENCE: 69

Thr	Val	Ala	Ala	Cys	Asn	Leu	Pro	Ile	Val	Ser	Gly	Pro	Cys	Thr	Ala
1				5					10					15	

-continued

Ala	Ile	Gln	Leu	Trp	Ala	Phe	Asp	Ala	Val	Lys	Gly	Lys	Cys	Val	Leu
			20					25					30		
Phe	Pro	Tyr	Gly	Gly	Cys	Gln	Gly	Asn	Gly	Asn	Lys	Phe	Asp	Ser	Glu
		35					40					45			
Lys	Glu	Cys	Arg	Glu	Tyr	Cys	Gly	Val	Pro	Gly	Asp	Gly	Asp	Glu	Glu
	50					55					60				
Leu	Leu	Arg	Phe	Ser	Asn										
65					70										

<210> SEQ ID NO 70
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15T/F17C/Y46D)

<400> SEQUENCE: 70

Thr	Val	Ala	Ala	Cys	Asn	Leu	Pro	Ile	Val	Ser	Gly	Pro	Cys	Thr	Ala
1				5					10					15	
Cys	Ile	Gln	Leu	Trp	Ala	Phe	Asp	Ala	Val	Lys	Gly	Lys	Cys	Val	Leu
		20						25					30		
Phe	Pro	Tyr	Gly	Gly	Cys	Gln	Gly	Asn	Gly	Asn	Lys	Phe	Asp	Ser	Glu
		35					40					45			
Lys	Glu	Cys	Arg	Glu	Tyr	Cys	Gly	Val	Pro	Gly	Asp	Gly	Asp	Glu	Glu
	50					55					60				
Leu	Leu	Arg	Phe	Ser	Asn										
65					70										

<210> SEQ ID NO 71
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15T/F17D/Y46D)

<400> SEQUENCE: 71

Thr	Val	Ala	Ala	Cys	Asn	Leu	Pro	Ile	Val	Ser	Gly	Pro	Cys	Thr	Ala
1				5					10					15	
Asp	Ile	Gln	Leu	Trp	Ala	Phe	Asp	Ala	Val	Lys	Gly	Lys	Cys	Val	Leu
		20						25					30		
Phe	Pro	Tyr	Gly	Gly	Cys	Gln	Gly	Asn	Gly	Asn	Lys	Phe	Asp	Ser	Glu
		35					40					45			
Lys	Glu	Cys	Arg	Glu	Tyr	Cys	Gly	Val	Pro	Gly	Asp	Gly	Asp	Glu	Glu
	50					55					60				
Leu	Leu	Arg	Phe	Ser	Asn										
65					70										

<210> SEQ ID NO 72
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15T/F17E/Y46D)

<400> SEQUENCE: 72

Thr	Val	Ala	Ala	Cys	Asn	Leu	Pro	Ile	Val	Ser	Gly	Pro	Cys	Thr	Ala
1				5					10					15	

-continued

Glu Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 73
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
F1024S-D2(R11S/R15T/F17G/Y46D)

<400> SEQUENCE: 73

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Gly Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 74
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
F1024S-D2(R11S/R15T/F17H/Y46D)

<400> SEQUENCE: 74

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
His Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 75
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
F1024S-D2(R11S/R15T/F17I/Y46D)

<400> SEQUENCE: 75

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala

-continued

1	5	10	15
Ile Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu			
	20	25	30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu			
	35	40	45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu			
	50	55	60
Leu Leu Arg Phe Ser Asn			
65	70		

<210> SEQ ID NO 76
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide
 F1024S-D2 (R11S/R15T/F17K/Y46D)

<400> SEQUENCE: 76

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala			
1	5	10	15
Lys Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu			
	20	25	30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu			
	35	40	45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu			
	50	55	60
Leu Leu Arg Phe Ser Asn			
65	70		

<210> SEQ ID NO 77
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15T/F17L/Y46D)

<400> SEQUENCE: 77

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala			
1	5	10	15
Leu Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu			
	20	25	30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu			
	35	40	45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu			
	50	55	60
Leu Leu Arg Phe Ser Asn			
65	70		

<210> SEQ ID NO 78
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2
 (R11S/R15T/F17M/Y46D)

<400> SEQUENCE: 78

-continued

```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1           5           10           15
Met Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
           20           25           30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
           35           40           45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
           50           55           60
Leu Leu Arg Phe Ser Asn
65           70

```

```

<210> SEQ ID NO 79
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
      F1024S-D2(R11S/R15T/F17N/Y46D)

```

<400> SEQUENCE: 79

```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1           5           10           15
Asn Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
           20           25           30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
           35           40           45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
           50           55           60
Leu Leu Arg Phe Ser Asn
65           70

```

```

<210> SEQ ID NO 80
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
      F1024S-D2(R11S/R15T/F17P/Y46D)

```

<400> SEQUENCE: 80

```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1           5           10           15
Pro Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
           20           25           30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
           35           40           45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
           50           55           60
Leu Leu Arg Phe Ser Asn
65           70

```

```

<210> SEQ ID NO 81
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
      (R11S/R15T/F17Q/Y46D)

```

<400> SEQUENCE: 81

-continued

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Gln Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 82
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
(R11S/R15T/F17R/Y46D)

<400> SEQUENCE: 82

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Arg Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 83
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
F1024S-D2(R11S/R15T/F17S/Y46D)

<400> SEQUENCE: 83

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Ser Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 84
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
F1024S-D2(R11S/R15T/F17T/Y46D)

-continued

<400> SEQUENCE: 84

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Thr Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 85

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
(R11S/R15T/F17V/Y46D)

<400> SEQUENCE: 85

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Val Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 86

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2
(R11S/R15T/F17W/Y46D)

<400> SEQUENCE: 86

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Trp Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 87

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide
F1024S-D2(R11S/R15T/F17Y/Y46D)

-continued

<400> SEQUENCE: 87

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Thr Ala
1 5 10 15
Tyr Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 88

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11A/R15T/Y46D)

<400> SEQUENCE: 88

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ala Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 89

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11C/R15T/Y46D)

<400> SEQUENCE: 89

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Cys Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 90

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11D/R15T/Y46D)

<400> SEQUENCE: 90

-continued

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Asp Gly Pro Cys Thr Ala
1 5 10 15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 91

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11E/R15T/Y46D)

<400> SEQUENCE: 91

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Glu Gly Pro Cys Thr Ala
1 5 10 15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 92

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11F/R15T/Y46D)

<400> SEQUENCE: 92

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Phe Gly Pro Cys Thr Ala
1 5 10 15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 93

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11G/R15T/Y46D)

<400> SEQUENCE: 93

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Gly Gly Pro Cys Thr Ala

-continued

1	5	10	15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu			
	20	25	30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu			
	35	40	45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu			
	50	55	60
Leu Leu Arg Phe Ser Asn			
65	70		

<210> SEQ ID NO 94
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11H/R15T/Y46D)

<400> SEQUENCE: 94

Thr Val Ala Ala Cys Asn Leu Pro Ile Val His Gly Pro Cys Thr Ala			
1	5	10	15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu			
	20	25	30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu			
	35	40	45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu			
	50	55	60
Leu Leu Arg Phe Ser Asn			
65	70		

<210> SEQ ID NO 95
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11I/R15T/Y46D)

<400> SEQUENCE: 95

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Ile Gly Pro Cys Thr Ala			
1	5	10	15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu			
	20	25	30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu			
	35	40	45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu			
	50	55	60
Leu Leu Arg Phe Ser Asn			
65	70		

<210> SEQ ID NO 96
 <211> LENGTH: 70
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11K/R15T/Y46D)

<400> SEQUENCE: 96

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Lys Gly Pro Cys Thr Ala			
1	5	10	15

-continued

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Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
      20              25              30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
      35              40              45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
      50              55              60

Leu Leu Arg Phe Ser Asn
65              70

```

```

<210> SEQ ID NO 97
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11L/R15T/Y46D)

<400> SEQUENCE: 97

```

```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Leu Gly Pro Cys Thr Ala
1              5              10              15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
      20              25              30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
      35              40              45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
      50              55              60

Leu Leu Arg Phe Ser Asn
65              70

```

```

<210> SEQ ID NO 98
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11M/R15T/Y46D)

<400> SEQUENCE: 98

```

```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Met Gly Pro Cys Thr Ala
1              5              10              15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
      20              25              30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
      35              40              45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
      50              55              60

Leu Leu Arg Phe Ser Asn
65              70

```

```

<210> SEQ ID NO 99
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11N/R15T/Y46D)

<400> SEQUENCE: 99

```

```

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Asn Gly Pro Cys Thr Ala
1              5              10              15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
      20              25              30

```

-continued

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 100
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11P/R15T/Y46D)

<400> SEQUENCE: 100

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Pro Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 101
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11Q/R15T/Y46D)

<400> SEQUENCE: 101

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Gln Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60
Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 102
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R15T/Y46D)

<400> SEQUENCE: 102

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Thr Ala
1 5 10 15
Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30
Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu

-continued

```

      35              40              45
Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
  50              55              60

Leu Leu Arg Phe Ser Asn
  65              70

<210> SEQ ID NO 103
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11T/R15T/Y46D)

<400> SEQUENCE: 103

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Thr Gly Pro Cys Thr Ala
  1              5              10              15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
      20              25              30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
      35              40              45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
  50              55              60

Leu Leu Arg Phe Ser Asn
  65              70

<210> SEQ ID NO 104
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11V/R15T/Y46D)

<400> SEQUENCE: 104

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Val Gly Pro Cys Thr Ala
  1              5              10              15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
      20              25              30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
      35              40              45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
  50              55              60

Leu Leu Arg Phe Ser Asn
  65              70

<210> SEQ ID NO 105
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11W/R15T/Y46D)

<400> SEQUENCE: 105

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Trp Gly Pro Cys Thr Ala
  1              5              10              15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
      20              25              30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
      35              40              45

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Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 106

<211> LENGTH: 70

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-D2 (R11Y/R15T/Y46D)

<400> SEQUENCE: 106

Thr Val Ala Ala Cys Asn Leu Pro Ile Val Tyr Gly Pro Cys Thr Ala
1 5 10 15

Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu
20 25 30

Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu
35 40 45

Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu
50 55 60

Leu Leu Arg Phe Ser Asn
65 70

<210> SEQ ID NO 107

<211> LENGTH: 236

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-TM123456M

<400> SEQUENCE: 107

Cys Ser Val Glu Asn Gly Gly Cys Glu His Ala Cys Asn Ala Ile Pro
1 5 10 15

Gly Ala Pro Arg Cys Gln Cys Pro Ala Gly Ala Ala Leu Gln Ala Asp
20 25 30

Gly Arg Ser Cys Thr Ala Ser Ala Thr Gln Ser Cys Asn Asp Leu Cys
35 40 45

Glu His Phe Cys Val Pro Asn Pro Asp Gln Pro Gly Ser Tyr Ser Cys
50 55 60

Met Cys Glu Thr Gly Tyr Arg Leu Ala Ala Asp Gln His Arg Cys Glu
65 70 75 80

Asp Val Asp Asp Cys Ile Leu Glu Pro Ser Pro Cys Pro Gln Arg Cys
85 90 95

Val Asn Thr Gln Gly Gly Phe Glu Cys His Cys Tyr Pro Asn Tyr Asp
100 105 110

Leu Val Asp Gly Glu Cys Val Glu Pro Val Asp Pro Cys Phe Arg Ala
115 120 125

Asn Cys Glu Tyr Gln Cys Gln Pro Leu Asn Gln Thr Ser Tyr Leu Cys
130 135 140

Val Cys Ala Glu Gly Phe Ala Pro Ile Pro His Glu Pro His Arg Cys
145 150 155 160

Gln Met Phe Cys Asn Gln Thr Ala Cys Pro Ala Asp Cys Asp Pro Asn
165 170 175

Thr Gln Ala Ser Cys Glu Cys Pro Glu Gly Tyr Ile Leu Asp Asp Gly
180 185 190

Cys Ser Val Glu Asn Gly Gly Cys Glu His Ala Cys Asn Ala Ile Pro
1 5 10 15

```

<210> SEQ ID NO 110
<211> LENGTH: 271
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-TM1234567L

<400> SEQUENCE: 110

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

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100					105					110						
Leu	Val	Asp	Gly	Glu	Cys	Val	Glu	Pro	Val	Asp	Pro	Cys	Phe	Arg	Ala	
115					120					125						
Asn	Cys	Glu	Tyr	Gln	Cys	Gln	Pro	Leu	Asn	Gln	Thr	Ser	Tyr	Leu	Cys	
130					135					140						
Val	Cys	Ala	Glu	Gly	Phe	Ala	Pro	Ile	Pro	His	Glu	Pro	His	Arg	Cys	
145					150					155					160	
Gln	Leu	Phe	Cys	Asn	Gln	Thr	Ala	Cys	Pro	Ala	Asp	Cys	Asp	Pro	Asn	
165					170					175						
Thr	Gln	Ala	Ser	Cys	Glu	Cys	Pro	Glu	Gly	Tyr	Ile	Leu	Asp	Asp	Gly	
180					185					190						
Phe	Ile	Cys	Thr	Asp	Ile	Asp	Glu	Cys	Glu	Asn	Gly	Gly	Phe	Cys	Ser	
195					200					205						
Gly	Val	Cys	His	Asn	Leu	Pro	Gly	Thr	Phe	Glu	Cys	Ile	Cys	Gly	Pro	
210					215					220						
Asp	Ser	Ala	Leu	Ala	Arg	His	Ile	Gly	Thr	Asp	Cys	Asp	Ser	Gly	Lys	
225					230					235					240	
Val	Asp	Gly	Gly	Asp	Ser	Gly	Ser	Gly	Glu	Pro	Pro	Pro	Ser	Pro	Thr	
245					250					255						
Pro	Gly	Ser	Thr	Leu	Thr	Pro	Pro	Ala	Val	Gly	Leu	Val	His	Ser		
260					265					270						

<210> SEQ ID NO 111

<211> LENGTH: 200

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024S-TM23456M

<400> SEQUENCE: 111

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

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Ala Arg His Ile Gly Thr Asp Cys
195 200

<210> SEQ ID NO 112
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-TM23456L

<400> SEQUENCE: 112

Thr Ala Ser Ala Thr Gln Ser Cys Asn Asp Leu Cys Glu His Phe Cys
1 5 10 15
Val Pro Asn Pro Asp Gln Pro Gly Ser Tyr Ser Cys Met Cys Glu Thr
20 25 30
Gly Tyr Arg Leu Ala Ala Asp Gln His Arg Cys Glu Asp Val Asp Asp
35 40 45
Cys Ile Leu Glu Pro Ser Pro Cys Pro Gln Arg Cys Val Asn Thr Gln
50 55 60
Gly Gly Phe Glu Cys His Cys Tyr Pro Asn Tyr Asp Leu Val Asp Gly
65 70 75 80
Glu Cys Val Glu Pro Val Asp Pro Cys Phe Arg Ala Asn Cys Glu Tyr
85 90 95
Gln Cys Gln Pro Leu Asn Gln Thr Ser Tyr Leu Cys Val Cys Ala Glu
100 105 110
Gly Phe Ala Pro Ile Pro His Glu Pro His Arg Cys Gln Leu Phe Cys
115 120 125
Asn Gln Thr Ala Cys Pro Ala Asp Cys Asp Pro Asn Thr Gln Ala Ser
130 135 140
Cys Glu Cys Pro Glu Gly Tyr Ile Leu Asp Asp Gly Phe Ile Cys Thr
145 150 155 160
Asp Ile Asp Glu Cys Glu Asn Gly Gly Phe Cys Ser Gly Val Cys His
165 170 175
Asn Leu Pro Gly Thr Phe Glu Cys Ile Cys Gly Pro Asp Ser Ala Leu
180 185 190
Ala Arg His Ile Gly Thr Asp Cys
195 200

<210> SEQ ID NO 113
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-TM234567M

<400> SEQUENCE: 113

Thr Ala Ser Ala Thr Gln Ser Cys Asn Asp Leu Cys Glu His Phe Cys
1 5 10 15
Val Pro Asn Pro Asp Gln Pro Gly Ser Tyr Ser Cys Met Cys Glu Thr
20 25 30
Gly Tyr Arg Leu Ala Ala Asp Gln His Arg Cys Glu Asp Val Asp Asp
35 40 45
Cys Ile Leu Glu Pro Ser Pro Cys Pro Gln Arg Cys Val Asn Thr Gln
50 55 60
Gly Gly Phe Glu Cys His Cys Tyr Pro Asn Tyr Asp Leu Val Asp Gly
65 70 75 80

<400> SEQUENCE: 114

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

-continued

Ala Arg His Ile Gly Thr Asp Cys Asp Ser Gly Lys Val Asp Gly Gly
 195 200 205

Asp Ser Gly Ser Gly Glu Pro Pro Pro Ser Pro Thr Pro Gly Ser Thr
 210 215 220

Leu Thr Pro Pro Ala Val Gly Leu Val His Ser
 225 230 235

<210> SEQ ID NO 115
 <211> LENGTH: 157
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-TM3456M

<400> SEQUENCE: 115

Glu Asp Val Asp Asp Cys Ile Leu Glu Pro Ser Pro Cys Pro Gln Arg
 1 5 10 15

Cys Val Asn Thr Gln Gly Gly Phe Glu Cys His Cys Tyr Pro Asn Tyr
 20 25 30

Asp Leu Val Asp Gly Glu Cys Val Glu Pro Val Asp Pro Cys Phe Arg
 35 40 45

Ala Asn Cys Glu Tyr Gln Cys Gln Pro Leu Asn Gln Thr Ser Tyr Leu
 50 55 60

Cys Val Cys Ala Glu Gly Phe Ala Pro Ile Pro His Glu Pro His Arg
 65 70 75 80

Cys Gln Met Phe Cys Asn Gln Thr Ala Cys Pro Ala Asp Cys Asp Pro
 85 90 95

Asn Thr Gln Ala Ser Cys Glu Cys Pro Glu Gly Tyr Ile Leu Asp Asp
 100 105 110

Gly Phe Ile Cys Thr Asp Ile Asp Glu Cys Glu Asn Gly Gly Phe Cys
 115 120 125

Ser Gly Val Cys His Asn Leu Pro Gly Thr Phe Glu Cys Ile Cys Gly
 130 135 140

Pro Asp Ser Ala Leu Ala Arg His Ile Gly Thr Asp Cys
 145 150 155

<210> SEQ ID NO 116
 <211> LENGTH: 157
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-TM3456L

<400> SEQUENCE: 116

Glu Asp Val Asp Asp Cys Ile Leu Glu Pro Ser Pro Cys Pro Gln Arg
 1 5 10 15

Cys Val Asn Thr Gln Gly Gly Phe Glu Cys His Cys Tyr Pro Asn Tyr
 20 25 30

Asp Leu Val Asp Gly Glu Cys Val Glu Pro Val Asp Pro Cys Phe Arg
 35 40 45

Ala Asn Cys Glu Tyr Gln Cys Gln Pro Leu Asn Gln Thr Ser Tyr Leu
 50 55 60

Cys Val Cys Ala Glu Gly Phe Ala Pro Ile Pro His Glu Pro His Arg
 65 70 75 80

Cys Gln Leu Phe Cys Asn Gln Thr Ala Cys Pro Ala Asp Cys Asp Pro
 85 90 95

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Asn Thr Gln Ala Ser Cys Glu Cys Pro Glu Gly Tyr Ile Leu Asp Asp
      100                      105                      110

Gly Phe Ile Cys Thr Asp Ile Asp Glu Cys Glu Asn Gly Gly Phe Cys
      115                      120                      125

Ser Gly Val Cys His Asn Leu Pro Gly Thr Phe Glu Cys Ile Cys Gly
      130                      135                      140

Pro Asp Ser Ala Leu Ala Arg His Ile Gly Thr Asp Cys
145                      150                      155

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<210> SEQ ID NO 117
<211> LENGTH: 192
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-TM34567M

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<400> SEQUENCE: 117

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Glu Asp Val Asp Asp Cys Ile Leu Glu Pro Ser Pro Cys Pro Gln Arg
1      5      10      15

Cys Val Asn Thr Gln Gly Gly Phe Glu Cys His Cys Tyr Pro Asn Tyr
      20      25      30

Asp Leu Val Asp Gly Glu Cys Val Glu Pro Val Asp Pro Cys Phe Arg
      35      40      45

Ala Asn Cys Glu Tyr Gln Cys Gln Pro Leu Asn Gln Thr Ser Tyr Leu
      50      55      60

Cys Val Cys Ala Glu Gly Phe Ala Pro Ile Pro His Glu Pro His Arg
      65      70      75      80

Cys Gln Met Phe Cys Asn Gln Thr Ala Cys Pro Ala Asp Cys Asp Pro
      85      90      95

Asn Thr Gln Ala Ser Cys Glu Cys Pro Glu Gly Tyr Ile Leu Asp Asp
      100     105     110

Gly Phe Ile Cys Thr Asp Ile Asp Glu Cys Glu Asn Gly Gly Phe Cys
      115     120     125

Ser Gly Val Cys His Asn Leu Pro Gly Thr Phe Glu Cys Ile Cys Gly
      130     135     140

Pro Asp Ser Ala Leu Ala Arg His Ile Gly Thr Asp Cys Asp Ser Gly
145     150     155     160

Lys Val Asp Gly Gly Asp Ser Gly Ser Gly Glu Pro Pro Pro Ser Pro
      165     170     175

Thr Pro Gly Ser Thr Leu Thr Pro Pro Ala Val Gly Leu Val His Ser
      180     185     190

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<210> SEQ ID NO 118
<211> LENGTH: 192
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide F1024S-TM34567L

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<400> SEQUENCE: 118

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Glu Asp Val Asp Asp Cys Ile Leu Glu Pro Ser Pro Cys Pro Gln Arg
1      5      10      15

Cys Val Asn Thr Gln Gly Gly Phe Glu Cys His Cys Tyr Pro Asn Tyr
      20      25      30

Asp Leu Val Asp Gly Glu Cys Val Glu Pro Val Asp Pro Cys Phe Arg
      35      40      45

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Ala	Asn	Cys	Glu	Tyr	Gln	Cys	Gln	Pro	Leu	Asn	Gln	Thr	Ser	Tyr	Leu
	50					55					60				
Cys	Val	Cys	Ala	Glu	Gly	Phe	Ala	Pro	Ile	Pro	His	Glu	Pro	His	Arg
65					70					75					80
Cys	Gln	Leu	Phe	Cys	Asn	Gln	Thr	Ala	Cys	Pro	Ala	Asp	Cys	Asp	Pro
				85					90					95	
Asn	Thr	Gln	Ala	Ser	Cys	Glu	Cys	Pro	Glu	Gly	Tyr	Ile	Leu	Asp	Asp
			100					105					110		
Gly	Phe	Ile	Cys	Thr	Asp	Ile	Asp	Glu	Cys	Glu	Asn	Gly	Gly	Phe	Cys
		115					120					125			
Ser	Gly	Val	Cys	His	Asn	Leu	Pro	Gly	Thr	Phe	Glu	Cys	Ile	Cys	Gly
	130					135					140				
Pro	Asp	Ser	Ala	Leu	Ala	Arg	His	Ile	Gly	Thr	Asp	Cys	Asp	Ser	Gly
145					150					155					160
Lys	Val	Asp	Gly	Gly	Asp	Ser	Gly	Ser	Gly	Glu	Pro	Pro	Pro	Ser	Pro
			165					170						175	
Thr	Pro	Gly	Ser	Thr	Leu	Thr	Pro	Pro	Ala	Val	Gly	Leu	Val	His	Ser
			180				185					190			

<210> SEQ ID NO 119
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-TM456M

<400> SEQUENCE: 119

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

<210> SEQ ID NO 120
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-TM456L

<400> SEQUENCE: 120

Val	Glu	Pro	Val	Asp	Pro	Cys	Phe	Arg	Ala	Asn	Cys	Glu	Tyr	Gln	Cys
1				5					10					15	
Gln	Pro	Leu	Asn	Gln	Thr	Ser	Tyr	Leu	Cys	Val	Cys	Ala	Glu	Gly	Phe
		20					25						30		

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

<210> SEQ ID NO 121
 <211> LENGTH: 153
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-TM4567M

<400> SEQUENCE: 121

Val	Glu	Pro	Val	Asp	Pro	Cys	Phe	Arg	Ala	Asn	Cys	Glu	Tyr	Gln	Cys
1			5					10					15		
Gln	Pro	Leu	Asn	Gln	Thr	Ser	Tyr	Leu	Cys	Val	Cys	Ala	Glu	Gly	Phe
		20				25						30			
Ala	Pro	Ile	Pro	His	Glu	Pro	His	Arg	Cys	Gln	Met	Phe	Cys	Asn	Gln
		35				40					45				
Thr	Ala	Cys	Pro	Ala	Asp	Cys	Asp	Pro	Asn	Thr	Gln	Ala	Ser	Cys	Glu
	50				55					60					
Cys	Pro	Glu	Gly	Tyr	Ile	Leu	Asp	Asp	Gly	Phe	Ile	Cys	Thr	Asp	Ile
65				70					75					80	
Asp	Glu	Cys	Glu	Asn	Gly	Gly	Phe	Cys	Ser	Gly	Val	Cys	His	Asn	Leu
			85					90						95	
Pro	Gly	Thr	Phe	Glu	Cys	Ile	Cys	Gly	Pro	Asp	Ser	Ala	Leu	Ala	Arg
		100					105						110		
His	Ile	Gly	Thr	Asp	Cys	Asp	Ser	Gly	Lys	Val	Asp	Gly	Gly	Asp	Ser
		115				120					125				
Gly	Ser	Gly	Glu	Pro	Pro	Pro	Ser	Pro	Thr	Pro	Gly	Ser	Thr	Leu	Thr
	130					135				140					
Pro	Pro	Ala	Val	Gly	Leu	Val	His	Ser							
145					150										

<210> SEQ ID NO 122
 <211> LENGTH: 153
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide F1024S-TM4567L

<400> SEQUENCE: 122

Val	Glu	Pro	Val	Asp	Pro	Cys	Phe	Arg	Ala	Asn	Cys	Glu	Tyr	Gln	Cys
1			5					10					15		
Gln	Pro	Leu	Asn	Gln	Thr	Ser	Tyr	Leu	Cys	Val	Cys	Ala	Glu	Gly	Phe
		20				25						30			
Ala	Pro	Ile	Pro	His	Glu	Pro	His	Arg	Cys	Gln	Leu	Phe	Cys	Asn	Gln
		35				40					45				

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Thr Ala Cys Pro Ala Asp Cys Asp Pro Asn Thr Gln Ala Ser Cys Glu
50 55 60

Cys Pro Glu Gly Tyr Ile Leu Asp Asp Gly Phe Ile Cys Thr Asp Ile
65 70 75 80

Asp Glu Cys Glu Asn Gly Gly Phe Cys Ser Gly Val Cys His Asn Leu
85 90 95

Pro Gly Thr Phe Glu Cys Ile Cys Gly Pro Asp Ser Ala Leu Ala Arg
100 105 110

His Ile Gly Thr Asp Cys Asp Ser Gly Lys Val Asp Gly Gly Asp Ser
115 120 125

Gly Ser Gly Glu Pro Pro Pro Ser Pro Thr Pro Gly Ser Thr Leu Thr
130 135 140

Pro Pro Ala Val Gly Leu Val His Ser
145 150

<210> SEQ ID NO 123
<211> LENGTH: 444
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic F1024 Antibody Heavy Chain variable
region
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1) .. (444)

<400> SEQUENCE: 123

atg gat tgg ttg tgg aac ttg cta ttc ctg atg gta gtt gcc caa agt	48
Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser	
1 5 10 15	
gct caa gca cag atc cag ttg gta cag tct gga cct gaa ctg aag aag	96
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys	
20 25 30	
cct gga gag tca gtg aag atc tcc tgc aag gct tct ggg tat acc ttc	144
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe	
35 40 45	
aca gac tat gca atg aac tgg gtg aaa cag gct cca gga aat ggc ttg	192
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu	
50 55 60	
aag tgg atg ggc tgg atc aac acc caa act gga aag cca aca tat gcg	240
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala	
65 70 75 80	
gat gat ttc aaa caa cgg ttt gtc ttc tct ttg gaa act tct gcc agc	288
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	
85 90 95	
act gca tac ttg cag atc aac aac ctc aat att gag gac aca gct aca	336
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr	
100 105 110	
tat ttc tgt aca aga tcc act ttt tac tat agc agc tat atc tac ggg	384
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly	
115 120 125	
tggtac ttt gac ttc tgg ggc cca gga acc atg gtc acc gtg tcc tca	432
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser	
130 135 140	
gct gaa aca aca	444
Ala Glu Thr Thr	
145	

<210> SEQ ID NO 124

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<211> LENGTH: 148
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic F1024 Antibody Heavy Chain variable
region

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<400> SEQUENCE: 124

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Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser
1           5           10           15

Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
           20           25           30

Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
           35           40           45

Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu
           50           55           60

Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala
65           70           75           80

Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser
           85           90           95

Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr
           100          105          110

Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly
           115          120          125

Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser
           130          135          140

Ala Glu Thr Thr
145

```

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<210> SEQ ID NO 125
<211> LENGTH: 411
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic F1024 Antibody Light Chain variable
region
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(411)

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<400> SEQUENCE: 125

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```

atg gag tca cat act agg gtc ttc ata ttc ctg ctg ctc tgg ttg tct      48
Met Glu Ser His Thr Arg Val Phe Ile Phe Leu Leu Leu Trp Leu Ser
1           5           10           15

ggg gct gat ggg gac att gtg atg act cag tct ccc aca tcc att tcc      96
Gly Ala Asp Gly Asp Ile Val Met Thr Gln Ser Pro Thr Ser Ile Ser
           20           25           30

ata tca gta gga gag agg gtc acc atg aac tgc aag gcc agt cag aat     144
Ile Ser Val Gly Glu Arg Val Thr Met Asn Cys Lys Ala Ser Gln Asn
           35           40           45

gtg ggt tct aat gta gac tgg tac caa cag aaa aca ggg cag tct cct     192
Val Gly Ser Asn Val Asp Trp Tyr Gln Gln Lys Thr Gly Gln Ser Pro
           50           55           60

aaa ctg ctt atc tac aag gca tcc aac cgg tac act ggc gtc cct gat     240
Lys Leu Leu Ile Tyr Lys Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp
           65           70           75           80

cgc ttc aca ggc agt gga tct gga aca gat ttc act ttc acc atc agc     288
Arg Phe Thr Gly Ser Gly Ser Gly Asp Phe Thr Phe Thr Ile Ser
           85           90           95

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aac atg cag gct gtg gac ctg gct gtt tat tac tgt atg cag tct aac      336
Asn Met Gln Ala Val Asp Leu Ala Val Tyr Tyr Cys Met Gln Ser Asn
          100                      105                      110

```

```

acc aat cct ccg tgg acg ttc ggt gga ggc acc aag ctg gaa ttg aaa      384
Thr Asn Pro Pro Trp Thr Phe Gly Gly Thr Lys Leu Glu Leu Lys
          115                      120                      125

```

```

cgg gct gat gct gca cca act gta tct      411
Arg Ala Asp Ala Ala Pro Thr Val Ser
          130                      135

```

<210> SEQ ID NO 126

<211> LENGTH: 137

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic F1024 Antibody Light Chain variable region

<400> SEQUENCE: 126

```

Met Glu Ser His Thr Arg Val Phe Ile Phe Leu Leu Leu Trp Leu Ser
1          5          10          15

```

```

Gly Ala Asp Gly Asp Ile Val Met Thr Gln Ser Pro Thr Ser Ile Ser
          20          25          30

```

```

Ile Ser Val Gly Glu Arg Val Thr Met Asn Cys Lys Ala Ser Gln Asn
          35          40          45

```

```

Val Gly Ser Asn Val Asp Trp Tyr Gln Gln Lys Thr Gly Gln Ser Pro
          50          55          60

```

```

Lys Leu Leu Ile Tyr Lys Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp
65          70          75          80

```

```

Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser
          85          90          95

```

```

Asn Met Gln Ala Val Asp Leu Ala Val Tyr Tyr Cys Met Gln Ser Asn
          100          105          110

```

```

Thr Asn Pro Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
          115          120          125

```

```

Arg Ala Asp Ala Ala Pro Thr Val Ser
          130          135

```

<210> SEQ ID NO 127

<211> LENGTH: 473

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic F1031-13-2 heavy chain variable region

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (20)..(472)

<400> SEQUENCE: 127

```

tgaacacaga ccactcacc atg gaa tgt aac tgg ata ctt cct ttt att ctg      52
Met Glu Cys Asn Trp Ile Leu Pro Phe Ile Leu
          1          5          10

```

```

tcg gta att tca gga gtc tac tca gag gtt cag ctc cag cag tct ggg      100
Ser Val Ile Ser Gly Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly
          15          20          25

```

```

act gtg ctg gca agg cct ggg gct tcc gtg aag atg tcc tgc aag gct      148
Thr Val Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala
          30          35          40

```

```

tct ggc tac agg tat acc aac tac tgg ttg cac tgg gta aaa cag agg      196

```

-continued

Ser	Gly	Tyr	Arg	Tyr	Thr	Asn	Tyr	Trp	Leu	His	Trp	Val	Lys	Gln	Arg	
45						50					55					
cct	gga	cag	ggt	cta	gag	tgg	att	ggt	gct	att	tat	cct	gga	aat	agt	244
Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile	Gly	Ala	Ile	Tyr	Pro	Gly	Asn	Ser	
60					65				70					75		
gat	tct	agc	tac	aac	cag	aac	ttc	aag	ggc	aag	gcc	aaa	ctg	act	gca	292
Asp	Ser	Ser	Tyr	Asn	Gln	Asn	Phe	Lys	Gly	Lys	Ala	Lys	Leu	Thr	Ala	
			80					85					90			
gtc	aca	tcc	gcc	agc	act	gcc	tac	atg	gag	ctc	agc	agc	ctg	aca	aat	340
Val	Thr	Ser	Ala	Ser	Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Thr	Asn	
			95					100					105			
gag	gac	tct	gcg	gtc	tat	tac	tgt	aca	aga	tgg	ggc	cct	tat	ggc	atc	388
Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys	Thr	Arg	Trp	Gly	Pro	Tyr	Gly	Ile	
	110						115					120				
tat	gct	atg	gac	tac	tgg	ggt	caa	gga	acc	tca	gtc	acc	gtc	tcc	tca	436
Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	
	125					130					135					
gcc	aaa	aca	aca	ccc	cca	tca	gtc	tat	cca	ctg	gcc	c				473
Ala	Lys	Thr	Thr	Pro	Pro	Ser	Val	Tyr	Pro	Leu	Ala					
140					145				150							

<210> SEQ ID NO 128
 <211> LENGTH: 151
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic F1031-13-2 heavy chain variable region

<400> SEQUENCE: 128

Met	Glu	Cys	Asn	Trp	Ile	Leu	Pro	Phe	Ile	Leu	Ser	Val	Ile	Ser	Gly	
1			5						10					15		
Val	Tyr	Ser	Glu	Val	Gln	Leu	Gln	Gln	Ser	Gly	Thr	Val	Leu	Ala	Arg	
			20					25					30			
Pro	Gly	Ala	Ser	Val	Lys	Met	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Arg	Tyr	
		35				40						45				
Thr	Asn	Tyr	Trp	Leu	His	Trp	Val	Lys	Gln	Arg	Pro	Gly	Gln	Gly	Leu	
	50				55						60					
Glu	Trp	Ile	Gly	Ala	Ile	Tyr	Pro	Gly	Asn	Ser	Asp	Ser	Ser	Tyr	Asn	
65				70					75					80		
Gln	Asn	Phe	Lys	Gly	Lys	Ala	Lys	Leu	Thr	Ala	Val	Thr	Ser	Ala	Ser	
			85					90						95		
Thr	Ala	Tyr	Met	Glu	Leu	Ser	Ser	Leu	Thr	Asn	Glu	Asp	Ser	Ala	Val	
			100					105					110			
Tyr	Tyr	Cys	Thr	Arg	Trp	Gly	Pro	Tyr	Gly	Ile	Tyr	Ala	Met	Asp	Tyr	
	115					120						125				
Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser	Ala	Lys	Thr	Thr	Pro	
	130					135					140					
Pro	Ser	Val	Tyr	Pro	Leu	Ala										
145					150											

<210> SEQ ID NO 129
 <211> LENGTH: 328
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic F1031-13-2 light chain variable region
 <220> FEATURE:

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<221> NAME/KEY: CDS
<222> LOCATION: (1) .. (327)

<400> SEQUENCE: 129

gac atc gtg atg acc cag tct cca gct tct ttg gct gtg tct ctg ggg      48
Asp Ile Val Met Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1       5              10              15

cag agg gcc acc atc tcc tgc aga gcc agc gaa agt gtt gat tat tct      96
Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Tyr Ser
                20              25              30

ggc att agt ttt atg aac tgg ttc caa cag aaa cca gga cag cca ccc      144
Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
          35              40              45

aaa ctc ctc atc tat gct gca tcc aac caa gga tcc ggg gtc cct gcc      192
Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
          50              55              60

agg ttt agt ggc agt ggg tct ggg aca gac ttc agc ctc aac atc cat      240
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His
65              70              75              80

cct atg gag gag gat gat act gca atg tat ttc tgt cag cac agt aag      288
Pro Met Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys Gln His Ser Lys
                85              90              95

gag ctt ccg tac acg ttc gga ggg ggg acc aag ctg gaa a      328
Glu Leu Pro Tyr Thr Phe Gly Gly Thr Lys Leu Glu
          100              105

<210> SEQ ID NO 130
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic F1031-13-2 light chain variable
region

<400> SEQUENCE: 130

Asp Ile Val Met Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1       5              10              15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Tyr Ser
                20              25              30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
          35              40              45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
          50              55              60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His
65              70              75              80

Pro Met Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys Gln His Ser Lys
                85              90              95

Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu
          100              105

<210> SEQ ID NO 131
<211> LENGTH: 430
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic F1031-13-2 heavy chain variable
region
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (8) .. (430)

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-continued

<400> SEQUENCE: 131

```

gaattcc atg gaa tgt aac tgg ata ctt cct ttt att ctg tgc gta att      49
    Met Glu Cys Asn Trp Ile Leu Pro Phe Ile Leu Ser Val Ile
      1              5              10

tca gga gtc tac tca gag gtt cag ctc cag cag tct ggg act gtg ctg      97
Ser Gly Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu
15              20              25              30

gca agg cct ggg gct tcc gtg aag atg tcc tgc aag gct tct ggc tac      145
Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr
              35              40              45

agg tat acc aac tac tgg ttg cac tgg gta aaa cag agg cct gga cag      193
Arg Tyr Thr Asn Tyr Trp Leu His Trp Val Lys Gln Arg Pro Gly Gln
              50              55              60

ggg cta gag tgg att ggt gct att tat cct gga aat agt gat tct agc      241
Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Ser Asp Ser Ser
65              70              75

tac aac cag aac ttc aag ggc aag gcc aaa ctg act gca gtc aca tcc      289
Tyr Asn Gln Asn Phe Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser
80              85              90

gcc agc act gcc tac atg gag ctc agc agc ctg aca aat gag gac tct      337
Ala Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser
95              100              105              110

gcg gtc tat tac tgt aca aga tgg ggc cct tat ggc atc tat gct atg      385
Ala Val Tyr Tyr Cys Thr Arg Trp Gly Pro Tyr Gly Ile Tyr Ala Met
115              120              125

gac tac tgg ggt caa gga acc tca gtc acc gtc tcc agc gct agc      430
Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser
130              135              140

```

<210> SEQ ID NO 132

<211> LENGTH: 141

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic F1031-13-2 heavy chain variable region

<400> SEQUENCE: 132

```

Met Glu Cys Asn Trp Ile Leu Pro Phe Ile Leu Ser Val Ile Ser Gly
1              5              10              15

Val Tyr Ser Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg
20              25              30

Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Arg Tyr
35              40              45

Thr Asn Tyr Trp Leu His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu
50              55              60

Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Ser Asp Ser Ser Tyr Asn
65              70              75              80

Gln Asn Phe Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser
85              90              95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val
100              105              110

Tyr Tyr Cys Thr Arg Trp Gly Pro Tyr Gly Ile Tyr Ala Met Asp Tyr
115              120              125

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser
130              135              140

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<210> SEQ ID NO 133
<211> LENGTH: 406
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic F1031-13-2 light chain variable
region
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (8)..(406)

<400> SEQUENCE: 133

gaattcc atg gag aca gac aca ctc ctg cta tgg gtc ctg ctt ctc tgg      49
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp
1 5 10

gtt cca ggt tcc aca ggt gac att gtg ctg acc caa tct cca gct tct      97
Val Pro Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser
15 20 25 30

ttg gct gtg tct ctg ggg cag agg gcc acc atc tcc tgc aga gcc agc      145
Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser
35 40 45

gaa agt gtt gat tat tct ggc att agt ttt atg aac tgg ttc caa cag      193
Glu Ser Val Asp Tyr Ser Gly Ile Ser Phe Met Asn Trp Phe Gln Gln
50 55 60

aaa cca gga cag cca ccc aaa ctc ctc atc tat gct gca tcc aac caa      241
Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln
65 70 75

gga tcc ggg gtc cct gcc agg ttt agt ggc agt ggg tct ggg aca gac      289
Gly Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
80 85 90

ttc agc ctc aac atc cat cct atg gag gag gat gat act gca atg tat      337
Phe Ser Leu Asn Ile His Pro Met Glu Glu Asp Asp Thr Ala Met Tyr
95 100 105 110

ttc tgt cag cac agt aag gag ctt cgg tac acg ttc gga ggg ggg acc      385
Phe Cys Gln His Ser Lys Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr
115 120 125

aag ctg gaa atc aaa cgt acg      406
Lys Leu Glu Ile Lys Arg Thr
130

<210> SEQ ID NO 134
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic F1031-13-2 light chain variable
region

<400> SEQUENCE: 134

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
20 25 30

Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
35 40 45

Val Asp Tyr Ser Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro
50 55 60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser
65 70 75 80

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser
85 90 95

```

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Leu Asn Ile His Pro Met Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys
100 105 110

Gln His Ser Lys Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu
115 120 125

Glu Ile Lys Arg Thr
130

<210> SEQ ID NO 135
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: M4 synthetic primer

<400> SEQUENCE: 135

gttttcccag tcacgacg 18

<210> SEQ ID NO 136
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: T7 synthetic primer

<400> SEQUENCE: 136

ctgttggttc agctgaggac ac 22

<210> SEQ ID NO 137
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: rIgH-b synthetic primer

<400> SEQUENCE: 137

ctgttggttc agctgaggac ac 22

<210> SEQ ID NO 138
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: rIgH-c synthetic primer

<400> SEQUENCE: 138

agggtcacca tggagttact t 21

<210> SEQ ID NO 139
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: rIgK-a synthetic primer

<400> SEQUENCE: 139

agatacagtt ggtgcagcat cagc 24

<210> SEQ ID NO 140
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: rIgK-b synthetic primer

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<400> SEQUENCE: 140

gacactgatg tctctgggat aga 23

<210> SEQ ID NO 141

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 1024H-a synthetic primer

<400> SEQUENCE: 141

gaattccatg gattggttgt ggaactt 27

<210> SEQ ID NO 142

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 1024K-a synthetic primer

<400> SEQUENCE: 142

gaattccatg gagtcacata ctg 24

<210> SEQ ID NO 143

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: HchainEco47NheI synthetic primer

<400> SEQUENCE: 143

cccccgctag cgctggagac ggtgacc 27

<210> SEQ ID NO 144

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: rIgK-BsiWI synthetic primer

<400> SEQUENCE: 144

cgtacgtttc aattccagct tgg 24

<210> SEQ ID NO 145

<211> LENGTH: 30

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: IgG4-m synthetic primer

<400> SEQUENCE: 145

agcgctagca ccaagggccc atccgtcttc 30

<210> SEQ ID NO 146

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: IgG4-v synthetic primer

<400> SEQUENCE: 146

ggatccttta cccagagaca ggga 24

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<210> SEQ ID NO 147
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgG4-s synthetic primer

<400> SEQUENCE: 147
ttacctgggc ctgatgggcc tgggggacca 30

<210> SEQ ID NO 148
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgG4-r synthetic primer

<400> SEQUENCE: 148
tgggtccccc ggcccatcag gcccggtaa 30

<210> SEQ ID NO 149
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgK-e synthetic primer

<400> SEQUENCE: 149
gcacttctcc ctctaact 20

<210> SEQ ID NO 150
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: BsiWI-hIgK synthetic primer

<400> SEQUENCE: 150
cgtacggtgg ctgcaccatc tgtc 24

<210> SEQ ID NO 151
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: UTI-a synthetic primer

<400> SEQUENCE: 151
ggatccgctg tgctaccca agaa 24

<210> SEQ ID NO 152
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: UTI-b synthetic primer

<400> SEQUENCE: 152
ggatccactg tggcggcctg caat 24

<210> SEQ ID NO 153
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: UTI-c synthetic primer

<400> SEQUENCE: 153

gcggccgctc agttggagaa ggcgcagcag 29

<210> SEQ ID NO 154
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: UTI-f synthetic primer

<400> SEQUENCE: 154

gatatacaca ccaccaccgt tggagaagcg cagca 35

<210> SEQ ID NO 155
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: UTI-g synthetic primer

<400> SEQUENCE: 155

aggcctacca ccaccaccgt tggagaagcg cagca 35

<210> SEQ ID NO 156
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: UTI-h synthetic primer

<400> SEQUENCE: 156

gatatcggag gaggaggagc tgtgctaccc caaga 35

<210> SEQ ID NO 157
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: UTI-i synthetic primer

<400> SEQUENCE: 157

gatatcggag gaggaggaac tgtggcggcc tgcaa 35

<210> SEQ ID NO 158
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: SLPI-a synthetic primer

<400> SEQUENCE: 158

cagagtcact cctgccttca 20

<210> SEQ ID NO 159
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: SLPI-c synthetic primer

<400> SEQUENCE: 159

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agatctggaa agtccttcaa agctggagtc 30

<210> SEQ ID NO 160
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: SLPI-d synthetic primer

<400> SEQUENCE: 160

acaccccaaa cccaacaagg aggaagcctg 30

<210> SEQ ID NO 161
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: SLPI-e synthetic primer

<400> SEQUENCE: 161

caggcttcct ccttggtggg tttggggtgt 30

<210> SEQ ID NO 162
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: SLPI-g synthetic primer

<400> SEQUENCE: 162

gcggccgctc aagctttcac aggggaaacg 30

<210> SEQ ID NO 163
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 1031H-a synthetic primer

<400> SEQUENCE: 163

ggggaattcc atgggatgga gccggatc 28

<210> SEQ ID NO 164
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mIgG2b-c synthetic primer

<400> SEQUENCE: 164

tgaacacaga ccactcacca tg 22

<210> SEQ ID NO 165
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mIgG2b-a synthetic primer

<400> SEQUENCE: 165

gggccagtgg atagactgat g 21

<210> SEQ ID NO 166
<211> LENGTH: 22

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IGKV4-1-a synthetic primer

<400> SEQUENCE: 166

gcattgtgaa ctgagctaca ac 22

<210> SEQ ID NO 167
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgK-d synthetic primer

<400> SEQUENCE: 167

gacatcgtga tgaccagtc tc 22

<210> SEQ ID NO 168
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: rIgK-a synthetic primer

<400> SEQUENCE: 168

agatacagtt ggtgcagcat cagc 24

<210> SEQ ID NO 169
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 13HcS-EcoR synthetic primer

<400> SEQUENCE: 169

ggaattccat ggaatgtaac tggatacttc 30

<210> SEQ ID NO 170
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 13HcA-Nhe synthetic primer

<400> SEQUENCE: 170

ctagctagcg ctggagacgg tgactgaggt 30

<210> SEQ ID NO 171
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 13LcS-EcoR synthetic primer

<400> SEQUENCE: 171

ggaattccat ggagacagac acactcctg 29

<210> SEQ ID NO 172
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 13LcA-BsiW synthetic primer

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<400> SEQUENCE: 172

cacggtacgt ttgatttcca gcttggtccc

30

<210> SEQ ID NO 173

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024 Heavy chain CDR1

<400> SEQUENCE: 173

Asp Tyr Ala Met Asn
1 5

<210> SEQ ID NO 174

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024 Heavy chain CDR2

<400> SEQUENCE: 174

Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gln

<210> SEQ ID NO 175

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024 Heavy chain CDR3

<400> SEQUENCE: 175

Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly Trp Tyr Phe Asp Phe
1 5 10 15

<210> SEQ ID NO 176

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024 light chain CDR1

<400> SEQUENCE: 176

Lys Ala Ser Gln Asn Val Gly Ser Asn Val Asp
1 5 10

<210> SEQ ID NO 177

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide F1024 light chain CDR2

<400> SEQUENCE: 177

Lys Ala Ser Asn Arg Tyr Thr
1 5

<210> SEQ ID NO 178

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic peptide F1024 light chain CDR3

<400> SEQUENCE: 178

Met Gln Ser Asn Thr Asn Pro Pro Trp Thr
1 5 10

<210> SEQ ID NO 179

<211> LENGTH: 30

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: P294H-S1 synthetic primer

<400> SEQUENCE: 179

agactgaaca gggcgaccca gcctgacgag 30

<210> SEQ ID NO 180

<211> LENGTH: 30

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: P294H-A1 synthetic primer

<400> SEQUENCE: 180

cagctcgtea ggctggtgcg cctgttcag 30

<210> SEQ ID NO 181

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: H1043Sdmt synthetic primer

<400> SEQUENCE: 181

cagggcgggcg caggctgacg a 21

<210> SEQ ID NO 182

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: H1043Admt synthetic primer

<400> SEQUENCE: 182

tcgtcagcct gcgcgcacct g 21

<210> SEQ ID NO 183

<211> LENGTH: 30

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Q295A-S1 synthetic primer

<400> SEQUENCE: 183

agggcgccgg ctcttgacga gctgcccag 30

<210> SEQ ID NO 184

<211> LENGTH: 30

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Q295A-A1 synthetic primer

<400> SEQUENCE: 184

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ctcgtcagga gccggcgccc tgttcagtct 30

<210> SEQ ID NO 185
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: P296H-S1 synthetic primer

<400> SEQUENCE: 185

aacagggcgc cgcagcacga cgagctgccc 30

<210> SEQ ID NO 186
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: P296H-A1 Synthetic primer

<400> SEQUENCE: 186

ctcgggcagc tcgtcgtgct gcggcgccct 30

<210> SEQ ID NO 187
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D2-R15A-s synthetic primer

<400> SEQUENCE: 187

ggcccctgcg cagccttcat ccagctc 27

<210> SEQ ID NO 188
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D2-R15A-a synthetic primer

<400> SEQUENCE: 188

gatgaaggct gcgcaggggc cccggac 27

<210> SEQ ID NO 189
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgG4-w synthetic primer

<400> SEQUENCE: 189

aatgtcttct catgctccgt g 21

<210> SEQ ID NO 190
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: pEF2ce-27 synthetic primer

<400> SEQUENCE: 190

catcaatgta tcttatcatc tct 23

<210> SEQ ID NO 191
<211> LENGTH: 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TM-b synthetic primer

<400> SEQUENCE: 191

tttccccggc gcctgcacgc 20

<210> SEQ ID NO 192
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TM-g synthetic primer

<400> SEQUENCE: 192

tcctggacgg aggccgctca g 21

<210> SEQ ID NO 193
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TMD 123456 synthetic primer

<400> SEQUENCE: 193

gggatcctgc agcgtggaga acggcggct 29

<210> SEQ ID NO 194
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TMD23456

<400> SEQUENCE: 194

gggatccacc gcatccgcga cgcagtcct 29

<210> SEQ ID NO 195
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TMD 3456 synthetic primer

<400> SEQUENCE: 195

gggatccgag gacgtggatg actgcatac 29

<210> SEQ ID NO 196
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TMD456 synthetic primer

<400> SEQUENCE: 196

gggatccgtg gagcccgtag acccgtagct 29

<210> SEQ ID NO 197
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TMdomain2-Not1Bg12 synthetic primer

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<400> SEQUENCE: 197

ggagatctgc ggccgctcaa cagtcggtgc caatg

35

<210> SEQ ID NO 198

<211> LENGTH: 35

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: TMdomain3-Not1Bg12 synthetic primer

<400> SEQUENCE: 198

ggagatctgc ggccgctcac gaatgcacga gcccc

35

<210> SEQ ID NO 199

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: TM(M388L)-s synthetic primer

<400> SEQUENCE: 199

ccgcacaggt gccagctggt ttgcaaccag act

33

<210> SEQ ID NO 200

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: TM(M388L)-a synthetic primer

<400> SEQUENCE: 200

agtcctggttg caaaacagct ggcacctgtg cgg

33

<210> SEQ ID NO 201

<211> LENGTH: 15

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: LinkerSG-4-s synthetic primer

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (1)..(1)

<223> OTHER INFORMATION: phosphorylation

<400> SEQUENCE: 201

gatctggagg tggag

15

<210> SEQ ID NO 202

<211> LENGTH: 15

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: LinkerSG-4-a synthetic primer

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (1)..(1)

<223> OTHER INFORMATION: phosphorylation

<400> SEQUENCE: 202

gattcctccac ctcca

15

<210> SEQ ID NO 203

<211> LENGTH: 5

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Linker

<400> SEQUENCE: 203

ggggg

5

<210> SEQ ID NO 204
<211> LENGTH: 7
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Linker

<400> SEQUENCE: 204

gsgggg

7

<210> SEQ ID NO 205
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Linker

<400> SEQUENCE: 205

gsgggsggg g

12

<210> SEQ ID NO 206
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Linker

<400> SEQUENCE: 206

gsgggsggg gsgggg

17

<210> SEQ ID NO 207
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: F1024H-kozak synthetic primer

<400> SEQUENCE: 207

ggggaattcg ccgccacat ggattggttg tggaa

35

<210> SEQ ID NO 208
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgG4-1 synthetic primer

<400> SEQUENCE: 208

gctgtgctct cggaggtgct

20

<210> SEQ ID NO 209
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Primer

<400> SEQUENCE: 209

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gcggcagtat gctgacacgg 20

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

<400> SEQUENCE: 210

gataacctga cactggacgg gaatcccttc 30

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

<400> SEQUENCE: 211

gccatccaga atctagcgct 20

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

<400> SEQUENCE: 212

gaagggattc ccgtccagtg tcaggttattc 30

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

<400> SEQUENCE: 213

attagccaga agtcagatgc tc 22

<210> SEQ ID NO 214
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Primer

<400> SEQUENCE: 214

gggcattggc cacaccagg 19

<210> SEQ ID NO 215
<211> LENGTH: 543
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic fusion protein F1024S-D2(4)

<400> SEQUENCE: 215

Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser
1 5 10 15

Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
20 25 30

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

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435	440	445
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser		
450	455	460
Leu Ser Leu Ser Leu Gly Lys Gly Ser Thr Val Ala Ala Cys Asn Leu		
465	470	475
Pro Ile Val Ser Gly Pro Cys Thr Ala Phe Ile Lys Leu Trp Ala Phe		
485	490	495
Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln		
500	505	510
Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys Glu Cys Arg Glu Tyr Cys		
515	520	525
Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn		
530	535	540

<210> SEQ ID NO 216
 <211> LENGTH: 673
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic fusion protein F1024S-TM23456L

<400> SEQUENCE: 216

Met Asp Trp Leu Trp Asn Leu Leu Phe Leu Met Val Val Ala Gln Ser	
1	15
Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys	
20	30
Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe	
35	45
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Asn Gly Leu	
50	60
Lys Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala	
65	80
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser	
85	95
Thr Ala Tyr Leu Gln Ile Asn Asn Leu Asn Ile Glu Asp Thr Ala Thr	
100	110
Tyr Phe Cys Thr Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly	
115	125
Trp Tyr Phe Asp Phe Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser	
130	140
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg	
145	160
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr	
165	175
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser	
180	190
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser	
195	205
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr	
210	220
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys	
225	240
Arg Val Glu Ser Lys Tyr Gly Pro Pro Gly Pro Ser Gly Pro Ala Pro	
245	255

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Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	260	265	270
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	275	280	285
Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	290	295	300
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	305	310	315
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	325	330	335
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	340	345	350
Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	355	360	365
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	370	375	380
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	385	390	395
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	405	410	415
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	420	425	430
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	435	440	445
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	450	455	460
Leu	Ser	Leu	Ser	Leu	Gly	Lys	Gly	Ser	Thr	Ala	Ser	Ala	Thr	Gln	Ser	465	470	475
Cys	Asn	Asp	Leu	Cys	Glu	His	Phe	Cys	Val	Pro	Asn	Pro	Asp	Gln	Pro	485	490	495
Gly	Ser	Tyr	Ser	Cys	Met	Cys	Glu	Thr	Gly	Tyr	Arg	Leu	Ala	Ala	Asp	500	505	510
Gln	His	Arg	Cys	Glu	Asp	Val	Asp	Asp	Cys	Ile	Leu	Glu	Pro	Ser	Pro	515	520	525
Cys	Pro	Gln	Arg	Cys	Val	Asn	Thr	Gln	Gly	Gly	Phe	Glu	Cys	His	Cys	530	535	540
Tyr	Pro	Asn	Tyr	Asp	Leu	Val	Asp	Gly	Glu	Cys	Val	Glu	Pro	Val	Asp	545	550	555
Pro	Cys	Phe	Arg	Ala	Asn	Cys	Glu	Tyr	Gln	Cys	Gln	Pro	Leu	Asn	Gln	565	570	575
Thr	Ser	Tyr	Leu	Cys	Val	Cys	Ala	Glu	Gly	Phe	Ala	Pro	Ile	Pro	His	580	585	590
Glu	Pro	His	Arg	Cys	Gln	Leu	Phe	Cys	Asn	Gln	Thr	Ala	Cys	Pro	Ala	595	600	605
Asp	Cys	Asp	Pro	Asn	Thr	Gln	Ala	Ser	Cys	Glu	Cys	Pro	Glu	Gly	Tyr	610	615	620
Ile	Leu	Asp	Asp	Gly	Phe	Ile	Cys	Thr	Asp	Ile	Asp	Glu	Cys	Glu	Asn	625	630	635
Gly	Gly	Phe	Cys	Ser	Gly	Val	Cys	His	Asn	Leu	Pro	Gly	Thr	Phe	Glu	645	650	655
Cys	Ile	Cys	Gly	Pro	Asp	Ser	Ala	Leu	Ala	Arg	His	Ile	Gly	Thr	Asp			

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660	665	670
Cys		
<210> SEQ ID NO 217		
<211> LENGTH: 543		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: Synthetic humanized F1024S-D2(3)		
<400> SEQUENCE: 217		
Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Ala Thr Gly		
1 5 10 15		
Thr Tyr Ser Gln Val Gln Leu Val Gln Ser Gly His Glu Val Lys Gln		
20 25 30		
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe		
35 40 45		
Thr Asp Tyr Ala Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu		
50 55 60		
Glu Trp Met Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala		
65 70 75 80		
Asp Asp Phe Lys Gln Arg Phe Val Phe Ser Met Asp Thr Ser Ala Ser		
85 90 95		
Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Met Ala Met		
100 105 110		
Tyr Tyr Cys Ala Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly		
115 120 125		
Trp Tyr Phe Asp Phe Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser		
130 135 140		
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg		
145 150 155 160		
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr		
165 170 175		
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser		
180 185 190		
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser		
195 200 205		
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr		
210 215 220		
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys		
225 230 235 240		
Arg Val Glu Ser Lys Tyr Gly Pro Pro Gly Pro Ser Gly Pro Ala Pro		
245 250 255		
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys		
260 265 270		
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val		
275 280 285		
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp		
290 295 300		
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe		
305 310 315 320		
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
325 330 335		

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Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
 340 345 350
 Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 355 360 365
 Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
 370 375 380
 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 385 390 395 400
 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 405 410 415
 Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 420 425 430
 Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
 435 440 445
 Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 450 455 460
 Leu Ser Leu Ser Leu Gly Lys Gly Ser Thr Val Ala Ala Cys Asn Leu
 465 470 475 480
 Pro Ile Val Ser Gly Pro Cys Arg Ala Phe Ile Lys Leu Trp Ala Phe
 485 490 495
 Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln
 500 505 510
 Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys Glu Cys Arg Glu Tyr Cys
 515 520 525
 Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn
 530 535 540

<210> SEQ ID NO 218

<211> LENGTH: 235

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic humanized F1024S-D2(3)

<400> SEQUENCE: 218

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

-continued

145	150	155	160
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln	165	170	175
Ser Gly Asn Ser Glu Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser	180	185	190
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu	195	200	205
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser	210	215	220
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys	225	230	235

<210> SEQ ID NO 219
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 219

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

<210> SEQ ID NO 220
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 220

Gln Val Gln Leu Val Gln Ser Gly His Glu Val Lys Gln Pro Gly Ala	1	5	10	15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr	20	25	30	
Ala Met Asn Trp Val Pro Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	35	40	45	
Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala Asp Asp Phe	50	55	60	
Lys Gln Arg Phe Val Phe Ser Met Asp Thr Ser Ala Ser Thr Ala Tyr	65	70	75	80
Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Met Ala Met Tyr Tyr Cys				

-continued

85										90					95				
Ala	Arg	Ser	Thr	Phe	Tyr	Tyr	Ser	Ser	Tyr	Ile	Tyr	Gly	Trp	Tyr	Phe				
100										105					110				
Asp	Phe	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	Ser							
115										120					125				

<210> SEQ ID NO 221
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 221

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

<210> SEQ ID NO 222
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 222

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

-continued

<210> SEQ ID NO 223
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 223

Asp Ile Val Met Thr Gln Ser Pro Thr Ser Ile Ser Ile Ser Val Gly
1 5 10 15

Glu Arg Val Thr Met Asn Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30

Val Asp Trp Tyr Gln Gln Lys Thr Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Asn Met Gln Ala
65 70 75 80

Val Asp Leu Ala Val Tyr Tyr Cys Met Gln Ser Asn Thr Asn Pro Pro
85 90 95

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg Thr
100 105 110

<210> SEQ ID NO 224
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 224

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30

Val Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Arg Tyr Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Met Gln Ser Asn Thr Asn Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> SEQ ID NO 225
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 225

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Ile Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Ser Asn
20 25 30

-continued

Val	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
	35						40					45			
Tyr	Lys	Ala	Ser	Asn	Arg	Tyr	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	Tyr	Tyr	Cys	Met	Gln	Ser	Asn	Thr	Asn	Pro	Pro
				85					90					95	
Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr		
		100						105					110		

<210> SEQ ID NO 226
 <211> LENGTH: 110
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 226

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

<210> SEQ ID NO 227
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 227

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

-continued

Asp Phe Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 228
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 228

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

<210> SEQ ID NO 229
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 229

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

<210> SEQ ID NO 230
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 230

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

<210> SEQ ID NO 231

<211> LENGTH: 125

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 231

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

<210> SEQ ID NO 232

<211> LENGTH: 125

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 232

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

-continued

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala Asp Asp Phe
 50 55 60

Lys Gln Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95

Ala Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly Trp Tyr Phe
 100 105 110

Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 233
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 233

Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
 1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asn Thr Gln Thr Gly Lys Pro Thr Tyr Ala Asp Asp Phe
 50 55 60

Lys Gln Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95

Ala Arg Ser Thr Phe Tyr Tyr Ser Ser Tyr Ile Tyr Gly Trp Tyr Phe
 100 105 110

Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 234
 <211> LENGTH: 91
 <212> TYPE: PRT
 <213> ORGANISM: Eschericia coli
 <220> FEATURE:
 <221> NAME/KEY: mat_peptide
 <222> LOCATION: (22)..(91)

<400> SEQUENCE: 234

Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
 -20 -15 -10

Pro Val Thr Lys Ala Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg
 -5 -1 1 5 10

Gly Pro Cys Arg Ala Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys
 15 20 25

Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn
 30 35 40

Lys Phe Glu Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly

-continued

45	50	55
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Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn
60 65 70

<210> SEQ ID NO 235
<211> LENGTH: 91
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (22)..(91)

<400> SEQUENCE: 235

Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
-20 -15 -10

Pro Val Thr Lys Ala Asp Asp Ala Ala Cys Asn Leu Pro Ile Val Arg
-5 -1 1 5 10

Gly Pro Cys Arg Ala Phe Ile Lys Leu Trp Ala Phe Asp Ala Val Lys
15 20 25

Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn
30 35 40

Lys Phe Tyr Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly
45 50 55

Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn
60 65 70

<210> SEQ ID NO 236
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (22)..(89)

<400> SEQUENCE: 236

Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
-20 -15 -10

Pro Val Thr Lys Ala Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro
-5 -1 1 5 10

Cys Arg Ala Phe Ile Arg Leu Trp Ala Phe Asp Ala Val Lys Gly Lys
15 20 25

Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe
30 35 40

Tyr Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly
45 50 55

Asp Glu Glu Leu Leu Arg Phe Ser Asn
60 65

<210> SEQ ID NO 237
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (22)..(89)

<400> SEQUENCE: 237

Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
-20 -15 -10

-continued

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Pro Val Thr Lys Ala Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro
-5          -1 1          5          10

Cys Arg Ala Phe Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys
          15          20          25

Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe
          30          35          40

Glu Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly
          45          50          55

Asp Glu Glu Leu Leu Arg Phe Ser Asn
60          65

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<210> SEQ ID NO 238
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (22)..(89)

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<400> SEQUENCE: 238

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Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
-20          -15          -10

Pro Val Thr Lys Ala Ala Ala Cys Asn Leu Pro Ile Val Glu Gly Pro
-5          -1 1          5          10

Cys Arg Ala Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys
          15          20          25

Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe
          30          35          40

Glu Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly
          45          50          55

Asp Glu Glu Leu Leu Arg Phe Ser Asn
60          65

```

```

<210> SEQ ID NO 239
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (22)..(89)

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<400> SEQUENCE: 239

```

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Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
-20          -15          -10

Pro Val Thr Lys Ala Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro
-5          -1 1          5          10

Cys Arg Ala Phe Ile Arg Leu Trp Ala Phe Asp Ala Val Lys Gly Lys
          15          20          25

Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe
          30          35          40

Glu Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly
          45          50          55

Asp Glu Glu Leu Leu Arg Phe Ser Asn
60          65

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<210> SEQ ID NO 240
<211> LENGTH: 101
<212> TYPE: PRT

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-continued

<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (34)..(101)

<400> SEQUENCE: 240

Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
-30 -25 -20
Pro Val Thr Lys Ala Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly
-15 -10 -5
Met Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe
-1 1 5 10 15
Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe
20 25 30
Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys
35 40 45
Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu
50 55 60
Leu Arg Phe Ser Asn
65

<210> SEQ ID NO 241
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (34)..(101)

<400> SEQUENCE: 241

Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
-30 -25 -20
Pro Val Thr Lys Ala Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly
-15 -10 -5
Met Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe
-1 1 5 10 15
Ile Arg Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe
20 25 30
Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys
35 40 45
Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu
50 55 60
Leu Arg Phe Ser Asn
65

<210> SEQ ID NO 242
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (34)..(101)

<400> SEQUENCE: 242

Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
-30 -25 -20
Pro Val Thr Lys Ala Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly
-15 -10 -5

-continued

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Met Ala Ala Cys Asn Leu Pro Ile Val Gln Gly Pro Cys Arg Ala Phe
-1 1 5 10 15
Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe
20 25 30
Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys
35 40 45
Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu
50 55 60
Leu Arg Phe Ser Asn
65

```

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<210> SEQ ID NO 243
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (34)..(101)

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<400> SEQUENCE: 243

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Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
-30 -25 -20
Pro Val Thr Lys Ala Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly
-15 -10 -5
Met Ala Ala Cys Asn Leu Pro Ile Val Asp Gly Pro Cys Arg Ala Phe
-1 1 5 10 15
Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe
20 25 30
Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys
35 40 45
Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu
50 55 60
Leu Arg Phe Ser Asn
65

```

```

<210> SEQ ID NO 244
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (34)..(101)

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<400> SEQUENCE: 244

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

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-continued

65

<210> SEQ ID NO 245
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (34)..(101)

<400> SEQUENCE: 245
Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
-30 -25 -20
Pro Val Thr Lys Ala Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly
-15 -10 -5
Met Ala Ala Cys Asn Leu Pro Ile Val Glu Gly Pro Cys Arg Ala Phe
-1 1 5 10 15
Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe
20 25 30
Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Glu Ser Glu Lys
35 40 45
Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu
50 55 60
Leu Arg Phe Ser Asn
65

<210> SEQ ID NO 246
<211> LENGTH: 68
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (34)..(68)

<400> SEQUENCE: 246
Ala Ala Cys Asn Leu Pro Ile Val Ser Gly Pro Cys Arg Ala Phe Ile
-30 -25 -20
Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro
-15 -10 -5
Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys Glu
-1 1 5 10 15
Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu
20 25 30
Arg Phe Ser Asn
35

<210> SEQ ID NO 247
<211> LENGTH: 68
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: AN68 polypeptide

<400> SEQUENCE: 247
Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile
1 5 10 15
Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro
20 25 30

-continued

Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu
 35 40 45

Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu
 50 55 60

Arg Phe Ser Asn
 65

<210> SEQ ID NO 248
 <211> LENGTH: 68
 <212> TYPE: PRT
 <213> ORGANISM: Eschericia coli
 <220> FEATURE:
 <221> NAME/KEY: mat_peptide
 <222> LOCATION: (34)..(68)

<400> SEQUENCE: 248

Ala Ala Cys Asn Leu Pro Ile Val Asn Gly Pro Cys Arg Ala Phe Ile
 -30 -25 -20

Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro
 -15 -10 -5

Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys Glu
 -1 1 5 10 15

Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu
 20 25 30

Arg Phe Ser Asn
 35

<210> SEQ ID NO 249
 <211> LENGTH: 68
 <212> TYPE: PRT
 <213> ORGANISM: Eschericia coli
 <220> FEATURE:
 <221> NAME/KEY: mat_peptide
 <222> LOCATION: (34)..(68)

<400> SEQUENCE: 249

Ala Ala Cys Asn Leu Pro Ile Val Ala Gly Pro Cys Arg Ala Phe Ile
 -30 -25 -20

Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro
 -15 -10 -5

Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Asp Ser Glu Lys Glu
 -1 1 5 10 15

Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu
 20 25 30

Arg Phe Ser Asn
 35

<210> SEQ ID NO 250
 <211> LENGTH: 89
 <212> TYPE: PRT
 <213> ORGANISM: Eschericia coli
 <220> FEATURE:
 <221> NAME/KEY: mat_peptide
 <222> LOCATION: (22)..(89)

<400> SEQUENCE: 250

Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
 -20 -15 -10

Pro Val Thr Lys Ala Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro
 -5 -1 1 5 10

-continued

```

Cys Arg Ala Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly Lys
      15              20              25
Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe
      30              35              40
Glu Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly
      45              50              55
Asp Glu Glu Leu Leu Arg Phe Ser Asn
60              65

```

```

<210> SEQ ID NO 251
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Eschericia coli
<220> FEATURE:
<221> NAME/KEY: mat_peptide
<222> LOCATION: (22)..(89)

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```

<400> SEQUENCE: 251

```

```

Met Lys Gln Ser Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr
      -20              -15              -10
Pro Val Thr Lys Ala Ala Ala Cys Asn Leu Pro Ile Val Arg Gly Pro
      -5              -1 1              5              10
Cys Arg Ala Phe Ile Lys Leu Trp Ala Phe Asp Ala Val Lys Gly Lys
      15              20              25
Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe
      30              35              40
Tyr Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly
      45              50              55
Asp Glu Glu Leu Leu Arg Phe Ser Asn
60              65

```

1. A fusion protein comprising:

- (I) an anti-CD14 antibody or its CD14 binding fragment, wherein said antibody or the fragment has an antigen binding activity and an inhibitory activity for LPS-induced IL-6 production in a TLR expressing cell and
- (II) an inhibitor for a protease consisting of any one of an amino acid sequence selected from the group consisting of the amino acid sequences of the mutant UTI domain 2 of SEQ ID NOS: 27-106.

2. A fusion protein comprising:

- (I) an anti-CD14 antibody or its CD14 binding fragment, wherein said antibody or the fragment has an antigen binding activity and an inhibitory activity for LPS-induced IL-6 production in a TLR expressing cell, and
- (II) an inhibitor for a protease selected from a mutant of 4 amino acid substitutions (hereinafter referred to "UTI-D2(4)") (R11S/R15I/Q19K/Y46D) represented by the amino acid sequence of SEQ ID NO:46,
 UTI-D2(4) (R11S/R15L/Q19K/Y46D) represented by the amino acid sequence of SEQ ID NO: 47,
 UTI-D2(4) (R11S/R15T/Q19/Y46D) represented by the amino acid sequence of SEQ ID NO: 48, or
 UTI-D2 (4) (R11S/R15V/Q19K/Y46D) represented by the amino acid sequence of SEQ ID NO: 49.

3. The fusion protein according to claim 1, wherein the protein has an inhibitory activity for LPS-induced IL-6 pro-

duction in a TLR expressing cell, and an anti-inflammatory action or an inhibitory action for inflammatory protease.

4. The fusion protein according to claim 1, wherein the protein has an elastase inhibitory action or TNF- α production inhibitory action.

5. The fusion protein according to claim 1, wherein said fusion protein has the action of inhibiting the binding between CD14 and the TLR.

6. The fusion protein according to claim 1, wherein said anti-CD14 antibody or its CD14 binding fragment in (I) has the action of inhibiting the binding between CD14 and the TLR.

7. The fusion protein according to claim 1, wherein the anti CD14 antibody or its CD14 binding fragment in (I) recognizes at least a part of the region represented by from 269th to 315th amino acid residues of the amino acid sequence of human CD14.

8. The fusion protein according to claim 1, wherein the anti CD14 antibody or its CD14 binding fragment in (I) recognizes at least a part of the region represented by from 294th to 296th amino acid residues of the amino acid sequence of human CD14.

9. The fusion protein according to claim 1, wherein the anti CD14 antibody or its CD14 binding fragment in (I) comprises CDR1 consisting of SEQ ID NO: 173, CDR2 consisting of SEQ ID NO: 174, and CDR3 consisting of SEQ ID NO: 175

of the heavy chain as the CDR1, CDR2, and CDR3 in the heavy chain variable region, and

CDR1 consisting of SEQ ID NO: 176, CDR2 consisting of SEQ ID NO: 177, CDR3 consisting of SEQ ID NO: 178 of the light chain as the CDR1, CDR2, and CDR3 in the light chain variable region.

10. The fusion protein according to claim **1**, wherein the anti-CD14 antibody or its CD14 binding fragment in (I) a chimeric antibody.

11. The fusion protein according to claim **1**, wherein the anti-CD14 antibody or its CD14 binding fragment in (I) is a humanized antibody.

12. The fusion protein according to claim **1**, wherein the anti-CD14 antibody or its CD14 binding fragment in (I) is monovalent.

13. The fusion protein according to claim **1**, wherein the anti-CD14 antibody or its CD14 binding fragment in (I) is divalent.

14. The fusion protein according to claim **1**, wherein the protease inhibitor in (II) is fused to the C terminal side of the heavy chain of an anti-CD14 antibody or its CD14 binding fragment in (I).

15. A pharmaceutical composition comprising the fusion protein of claim **1** as an active ingredient and a pharmaceutically acceptable additive.

16. The pharmaceutical composition according to claim **15** for sepsis, severe sepsis, septic ARDS, septic shock, SIRS related disease, endotoxin shock or ARDS.

17. A therapeutic agent comprising the fusion protein of claim **1** for sepsis, severe sepsis, septic ARDS, septic shock, SIRS related disease, endotoxin shock or ARDS.

* * * * *